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**New Opportunities for Four-Membered Heterocycles:  
From Synthetic Studies to Unique Applications in Drug Discovery**

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# Publications & Presentations

## Publications

T. Schmid, J. Burkhard, B.-S. Yeo, W. Zhang, R. Zenobi

**Towards chemical analysis of nanostructures in biofilms I: imaging of biological nanostructures.**  
*Anal. Bioanal. Chem.* **2008**, *391*, 1899-1905.

J. Burkhard, E. M. Carreira

**2,6-Diazaspiro[3.3]heptanes: Synthesis and Application in Pd-Catalyzed Aryl Amination Reactions.**

*Org. Lett.* **2008**, *10*, 3525-3526.

C. Eberle, J. A. Burkhard, B. Stump, M. Kaiser, R. Brun, R. L. Krauth-Siegel, F. Diederich  
**Synthesis, Inhibition Potency, Binding Mode, and Antiprotozoal Activities of Fluorescent Inhibitors of Trypanothione Reductase Based on Mepacrine-Conjugated Diaryl Sulfide Scaffolds.**

*ChemMedChem* **2009**, *4*, 2034-2044.

J. A. Burkhard, C. Guérot, H. Knust, M. Rogers-Evans, E. M. Carreira

**Synthesis and Structural Analysis of a New Class of Azaspiro[3.3]heptanes as Building Blocks for Medicinal Chemistry.**

*Org. Lett.* **2010**, *12*, 1944-1947.

J. A. Burkhard, B. Wagner, H. Fischer, F. Schuler, K. Müller, E. M. Carreira

**Synthesis of Azaspirocycles and their Evaluation in Drug Discovery.**

*Angew. Chem. Int. Ed.* **2010**, *49*, 3524-3527.

J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira

**Oxetanes as Versatile Elements in Drug Discovery and Synthesis.**

*Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira

**Cascade Formation of Isoxazoles: Facile Base-Mediated Rearrangement of Substituted Oxetanes.**

*Angew. Chem. Int. Ed.* **2011**, *50*, 5379-5382.

**Poster and Oral Presentations**

**17<sup>th</sup> European Symposium on Organic Chemistry (ESOC).**

July 2011, Chersonissos, Crete, Greece. Poster presentation.

**3<sup>rd</sup> Symposium of the Scholarship Funds of the Swiss Chemical Industry (SSCI).**

November 2010, ETH Zürich, Switzerland. Poster presentation.

**F. Hoffmann-La Roche AG.**

October 2010, Basel, Switzerland. Oral presentation.

**2<sup>nd</sup> Symposium of the Scholarship Funds of the Swiss Chemical Industry (SSCI).**

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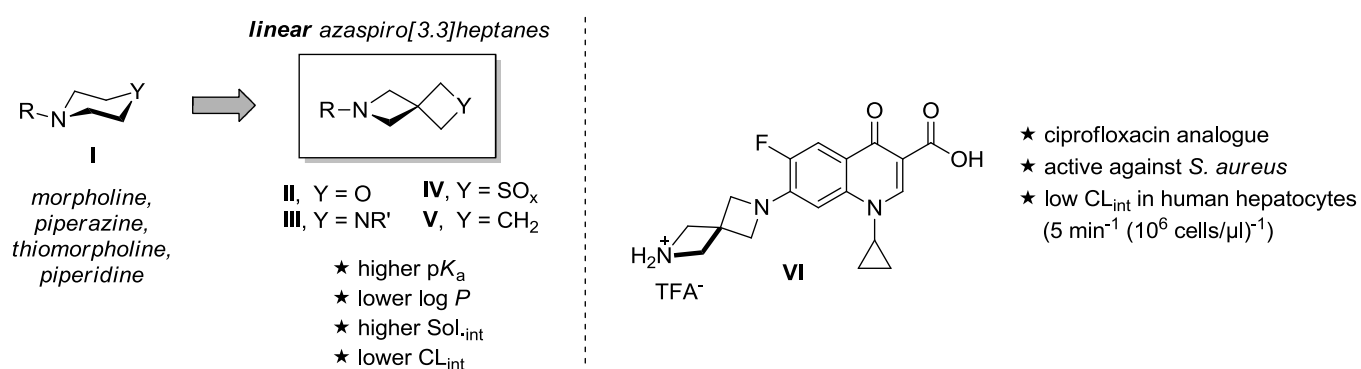
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# Abstract

Traditionally, four-membered heterocycles have found only limited use in organic chemistry and drug discovery. Earlier work by WUITSCHIK *et al.* from our laboratory indicated that oxetanes are intriguing units for the modulation of the pharmacokinetic profile of the underlying scaffold. In particular, 2-oxa-6-azaspiro[3.3]heptane **II** was discovered as a viable alternative for morpholine.

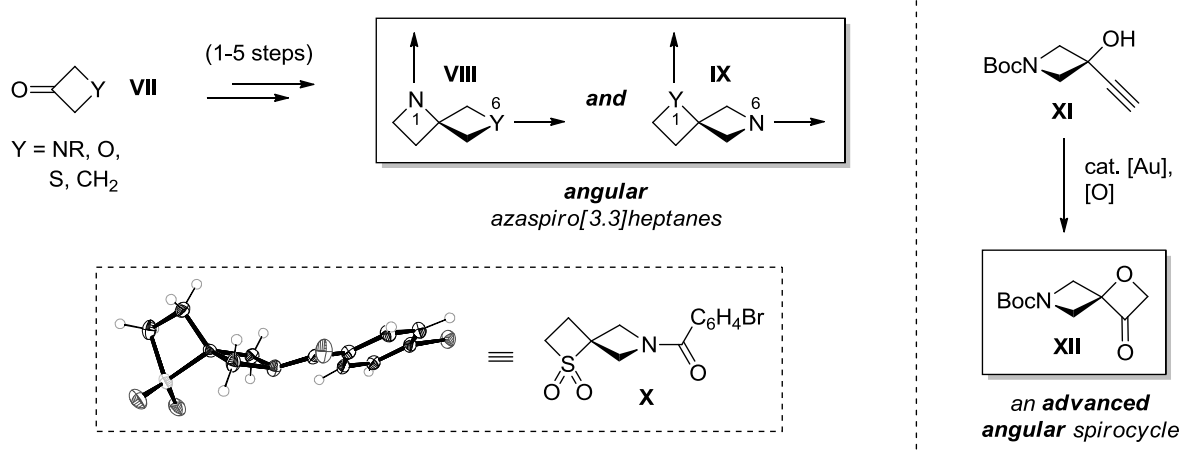
Consequently, we turned our attention to other members of the spiro[3.3]heptane family and synthesized *homospirropiperazines III*, *homospirothiomorpholines IV*, and a *homospirropiperidine V* (Figure I). These model compounds all bearing a piperonyl group were subsequently tested in collaboration with *F. Hoffmann-La Roche* (Basel) for their basicity, lipophilicity, aqueous solubility, and metabolic clearance rates. These analyses revealed highly desirable properties of the spirocycles, as they were in general less lipophilic, more soluble in an aqueous phosphate buffer, and metabolically more inert than the corresponding traditionally employed six-membered monocyclic counterparts **I** (piperazines, thiomorpholines, and a piperidine). Moreover, it was found that the 2,6-diaza- or the 2-oxa-6-aza-spiro[3.3]heptane unit can be mounted on the aromatic scaffold of the fluoroquinolones to produce antibiotically active ciprofloxacin analogues (such as **VI**) with an increased metabolic resistance.



**Figure I.** 2-Azaspiro[3.3]heptanes as valuable alternatives to azacyclohexanes.

By going from linear to angular spiro[3.3]heptanes, we were able to grant access to deeper chemical space. The 1,6-heteroatom-substituted azaspirocycles **VIII** and **IX** were efficiently synthesized in few steps from simple cyclic ketones **VII** (Figure II). Their analogy to six-membered monocyclic compounds having heteroatoms in a 1,3-relationship unveiled their potency as chemically stable surrogates. Structural information gathered through X-ray diffraction analyses (such as for **X**) can be useful for future modeling studies in drug discovery pro-

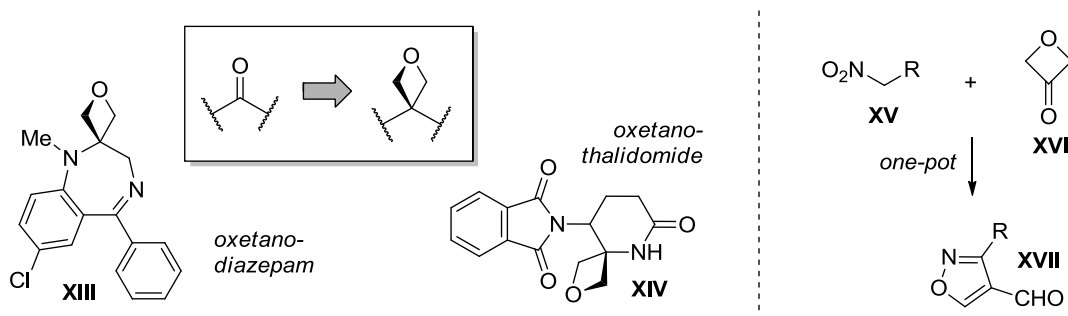
grams employing these building blocks. To showcase the versatility of the spiro[3.3]heptane core, we were interested in adding substituents on the carbon atoms of the linear or angular spirocycles. The resulting advanced angular spirocycles were successfully synthesized in few steps, as exemplified in the conversion of propargylic alcohol **XI** to spirocyclic oxetan-3-one **XII**.



**Figure II.** Angular and advanced angular azaspiro[3.3]heptanes.

The implementation of the oxetane as a surrogate for a carbonyl group was probed for diazepam and thalidomide, active substances of marketed drugs (Figure III). Whereas oxetano-diazepam (**XIII**) was inactive in binding to GABA<sub>A</sub> receptor subtypes, the oxetane analogue of thalidomide, **XIV**, showed promising anti-angiogenic properties. This result prompted us to synthesize larger quantities of **XIV** as well as of oxetano-lenalidomide in both racemic and enantiomerically pure form for additional biological studies (results are pending).

Oxetane in the form of oxetan-3-one (**XVI**) was found valuable for the synthesis of isoxazoles **XVII** from primary nitro compounds **XV**. A one-pot operation was developed, which granted access to isoxazole-4-carbaldehydes in 58-91% yield. Isoxazoles **XVII** were formed by a base-mediated rearrangement of intermediate substituted (nitromethylene)oxetanes.



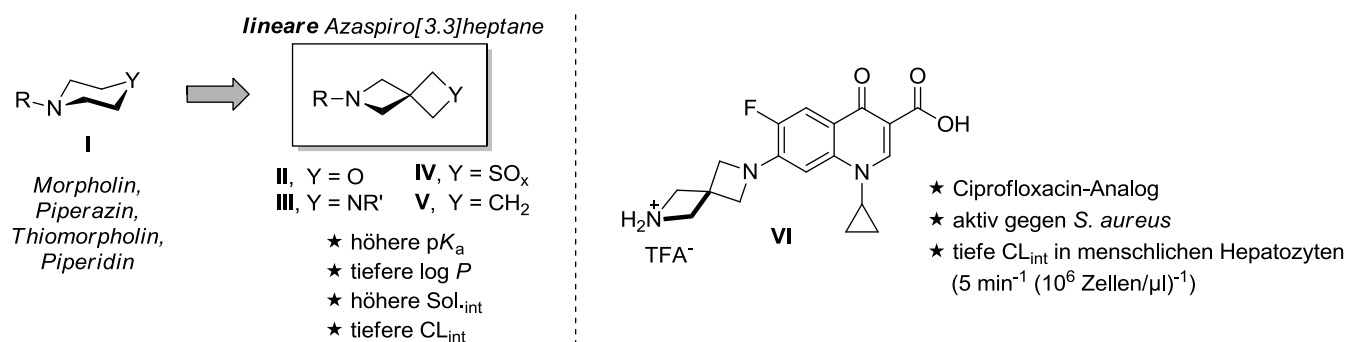
**Figure III.** Oxetane as a carbonyl surrogate or as a reagent for the synthesis of isoxazoles.



# Zusammenfassung

Traditionsgemäss wurden viergliedrige Heterocyklen nur spärlich in der organischen Chemie und der Wirkstoffforschung eingesetzt. Frühere Arbeiten von WUITSCHIK *et al.* aus unserem Laboratorium haben hingegen gezeigt, dass Oxetane faszinierende Einheiten für die Regulierung des pharmakokinetischen Profils einer Grundstruktur sein können. Insbesondere wurde 2-Oxa-6-azaspiro[3.3]heptan **II** als brauchbare Alternative für Morpholin entdeckt.

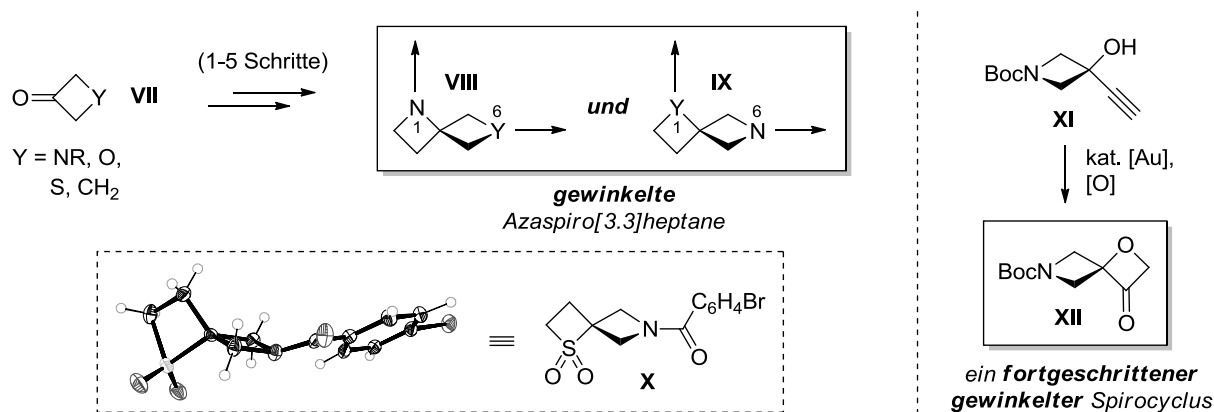
Infolgedessen haben wir uns weiteren Vertretern der Spiro[3.3]heptanfamilie zugewandt und stellten *Homospiropiperazine III*, *Homospiromorpholine IV* und ein *Homospiropiperidin V* her (Abbildung I). Diese Modellsysteme, welche alle eine Piperonylgruppe besitzen, wurden daraufhin in Zusammenarbeit mit *F. Hoffmann-La Roche* (Basel) auf deren Basizität, Lipophilie, wässrige Löslichkeit und metabolische Abbauraten getestet. Hervorragende Eigenschaften der Spirocyclen gingen aus diesen Analysen hervor, da die untersuchten Moleküle im Allgemeinen weniger lipophil, besser löslich in einem wässrigen Phosphatpuffer und metabolisch inerte als ihre entsprechenden traditionell eingesetzten sechsgliedrigen monocyclischen Pendanten **I** (Piperazine, Thiomorpholine und ein Piperidin) waren. Eine weitere Studie hat gezeigt, dass die 2,6-Diaza- oder die 2-Oxa-6-aza-Spiro[3.3]heptaneinheit am aromatischen Gerüst der Fluorchinolone angebracht werden kann und dabei antibiotisch aktive Ciprofloxacin-Derivate (wie z.B. **VI**) mit einer erhöhten metabolischen Resistenz gebildet werden.



**Abbildung I.** 2-Azaspiro[3.3]heptane als wertvolle Alternativen zu Azacyclohexanen.

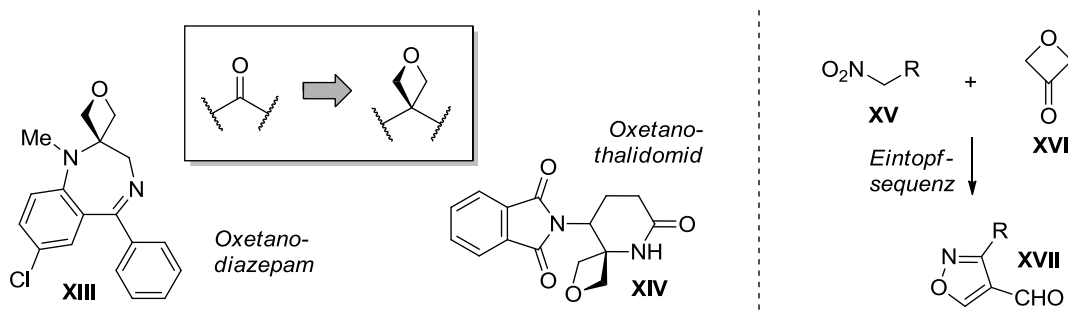
Der Gang von linearen zu gewinkelten Spiro[3.3]heptanen ermöglichte uns erweiterten Zugang zu neuem chemischen Raum. Die 1,6-heteroatom-substituierten Azaspirocyclen **VIII** und **IX** wurden in wenigen Schritten aus den einfachen cyclischen Ketonen **VII** hergestellt (Abbildung II). Die Analogie zu sechsgliedrigen Monocyclen mit einer heteroatomaren 1,3-Verwandtschaft brachte den Einsatz von **VIII** oder **IX** als chemisch stabile Surrogate hervor. Durch Röntgenstrukturanalyse gewonnene Information (wie z.B. für **X**) kann für zukünftige Modellierungsstudien in der Wirkstoffforschung nützlich sein, sollten diese Bausteine

verwendet werden. Um die Vielfalt des Spiro[3.3]heptankerns zu verdeutlichen, beabsichtigten wir, weitere Substituenten an Kohlenstoffatome der linearen oder gewinkelten Spirocyclen hinzuzufügen. Die daraus resultierenden fortgeschrittenen gewinkelten Spirocyclen wurden erfolgreich in wenigen Schritten synthetisiert, wie am Beispiel der Umwandlung von Propargylalkohol **XI** zu spirocyclischem Oxetan-3-on **XII** gezeigt wird.



**Abbildung II.** Gewinkelte und fortgeschrittene gewinkelte Azaspiro[3.3]heptane.

Der Einsatz eines Oxetans als Carbonylgruppenerersatz wurde untersucht am Beispiel von Diazepam und Thalidomid, zweier aktiver Substanzen in verkauften Medikamenten (Abbildung III). Während Oxetano-Diazepam (**XIII**) inaktiv in der Bindung zu GABA<sub>A</sub> Rezeptorsubtypen war, konnten vielversprechende anti-angiogenische Eigenschaften des Oxetananaloges von Thalidomid, **XIV**, beobachtet werden. Daher stellten wir grössere Mengen von **XIV** und Oxetano-Lenalidomid in racemischer und enantiomerenreiner Form für weitreichendere biologische Studien her (Resultate sind ausstehend). Oxetan in der Gestalt von Oxetan-3-on (**XVI**) erwies sich als nützlich in der Synthese von Isoxazolen **XVII** ausgehend von primären Nitroverbindungen **XV**. Ein Eintopf-Arbeitsablauf wurde ausgearbeitet, der den Zugang zu Isoxazol-4-carbaldehyden in 58-91% Ausbeute gewährte. Die Isoxazole **XVII** wurden durch eine basenvermittelte Umlagerung intermediärer substituierter (Nitromethylen)oxetane gebildet.



**Abbildung III.** Oxetan als Carbonylsurrogat oder als Reagenz für die Synthese von Isoxazolen.

# List of Abbreviations, Acronyms, and Symbols

$[\alpha]_{\text{D}}^{\text{T}}$	specific rotation at temperature T at the sodium D line
Å	Ångström, $10^{-10}$ m
ADME(T)	absorption, distribution, metabolism, excretion, (toxicity)
AIBN	2,2'-azobis(2-methylpropionitrile)
aq.	aqueous
atm	atmosphere, $1.01325 \cdot 10^5$ Pa
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
br	broad
CA	cycloaddition
<i>ca.</i>	<i>circa</i> , approximately
CAN	cerium ammonium nitrate
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
$\text{CL}_{\text{int}}$	intrinsic clearance rate
cod	cycloocta-1,5-diene
$\text{Cp}^*$	pentamethylcyclopentadienyl
Cy	cyclohexyl
CYP	cytochrome P450
$\delta$	NMR chemical shift in ppm downfield of a standard
$\Delta$	difference; heating
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	( <i>E,E</i> )-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIAD	diisopropyl diazene-1,2-dicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	<i>N,N</i> -dimethylpyridin-4-amine

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DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereoisomeric ratio
<i>E.</i>	<i>Escherichia</i>
<i>e.e.</i>	enantiomeric excess
EI	electron impact ionization
<i>ent</i>	inversion of all stereogenic centers
<i>Enteroc.</i>	<i>Enterococcus</i>
equiv	equivalents
ESI	electron spray ionization
<i>et al.</i>	<i>et alii</i> , and others
ETH	<i>Eidgenössische Technische Hochschule</i>
eV	electron volt, <i>ca.</i> $1.602 \cdot 10^{-19}$ J
FC	flash column chromatography
FT	FOURIER transformation
<i>gem</i>	geminal
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz, s <sup>-1</sup>
<i>i</i>	<i>iso</i>
IBX	2-iodoxybenzoic acid
IC <sub>50</sub>	half maximal (50%) inhibitory concentration
IR	infrared
<i>J</i>	coupling constant
kcal	kilocalorie, 4.184 kJ
<i>K<sub>D</sub></i>	dissociation constant
LC/MS	liquid chromatography/mass spectrometry
log <i>D</i>	logarithm of the 1-octanol/H <sub>2</sub> O distribution coefficient
log <i>P</i>	logarithm of the 1-octanol/H <sub>2</sub> O partition coefficient
m	multiplet
M	molecular ion
M	molar

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MALDI	matrix-assisted laser desorption ionization
<i>m</i> -CPBA	3-chlorobenzoperoxoic acid
MIC	minimum inhibitory concentration
Ms	methanesulfonyl
MS	molecular sieves; mass spectrometry
MW	microwave
<i>Mycobact.</i>	<i>Mycobacterium</i>
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear OVERHAUSER effect
OL	oxetano-lenalidomide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OT	oxetano-thalidomide
<i>P.</i>	<i>Pseudomonas</i>
PG	protecting group
pH	negative logarithm of proton concentration, $-\log_{10}([\text{H}^+])$
Pip	piperonyl, benzo[ <i>d</i> ][1,3]dioxol-5-ylmethyl
$\text{p}K_{\text{a}}$	negative logarithm of the acid dissociation constant
PM3	Parameterized Model number 3
PMB	4-methoxybenzyl
ppm	parts per million
q	quartet
quant.	quantitative
quint	quintet
rac	racemic
$R_f$	retention factor
RT	room temperature, <i>ca.</i> 23 °C
s	singlet
<i>S.</i>	<i>Staphylococcus</i>
Sol.	solubility
<i>t</i>	<i>tert</i>
$t_{1/2}$	half-life
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
THP	tetrahydro-2 <i>H</i> -pyran-2-yl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethane-1,2-diamine
TMS	trimethylsilyl
Ts	tosyl, 4-methylbenzenesulfonyl
UV	ultraviolet
VEGF	vascular endothelial growth factor

# 1

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# Introduction

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## 1.1 Drug Discovery Today

Advances in all areas of scientific research have revolutionized the processes of drug discovery within the last two decades.<sup>1</sup> Among other things, the availability of novel analytical techniques, the understanding of certain biological processes, and the automation of practices in scientific discovery have led to techniques such as high-throughput screening for the identification of active lead compounds. This way, new hit structures were generated at low cost from a large number of compounds in a library. Even though some of these new leads show high potency against a specific target, they may fail as a drug.<sup>2</sup> In order to reach the market, a drug molecule has to pass a number of hurdles. Safety issues such as cell toxicity or the undesired inhibition/activation of other enzymes have to be addressed. In addition, the drug molecule needs to be chemically stable and be able to survive in an organism for a given amount of time. And, importantly, the compound has to have the biophysical properties required to be adequately administered, to be able to reach the target, and to be excreted in the end. These pharmacokinetic properties are often classified under the terms absorption, distribution, metabolism, and excretion (ADME).

### 1.1.1 Drug Absorption

Drug absorption refers to the route or method by which the compound reaches the blood supply. After oral administration, the most desirable and also most applied administrative method, the drug molecule will reach the gastrointestinal tract. Here it needs to survive the harsh acidic conditions in the stomach and afterwards various digestive enzymes in the upper intestine. If the substance survives, it will pass between the cells in the gut wall to reach the blood supply. Not only are chemically labile groups in most cases undesirable in such a compound, but the latter must also obey certain rules. The molecule may not be too polar nor too apolar; it has to be soluble in the aqueous environment, but also needs to cross cellular membranes and other lipophilic areas. CHRISTOPHER LIPINSKI (*Pfizer Inc.*) derived rules (today known as LIPINSKI's rule of five) for assessing the oral bioavailability of drug compounds from an analysis of compounds listed in the World Drug Index database.<sup>3</sup> According to these, compounds should:

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<sup>1</sup> a) G. L. Patrick, *An Introduction to Medicinal Chemistry*, 4th ed., Oxford University Press, New York, **2009**; b) C. G. Wermuth, *The Practice of Medicinal Chemistry*, 3rd ed., Academic Press, New York, **2008**.

<sup>2</sup> K. H. Bleicher, H. J. Bohm, K. Müller, A. I. Alanine, *Nat. Rev. Drug Discov.* **2003**, *2*, 369-378.

<sup>3</sup> C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25.



- have a molecular weight less than 500 g mol<sup>-1</sup>
- contain no more than 5 hydrogen bond donor groups
- contain no more than 10 hydrogen bond acceptor groups
- have a calculated lipophilicity value (<sup>c</sup>log *P*) of less than +5

Most orally administered drugs obey these rules, but there are some exceptions.<sup>4</sup> Accordingly, further refinements were made and other rules were defined. For example, VEBER *et al.* (*GlaxoSmithKline*) demonstrated that the molecular flexibility can have a large influence on the oral bioavailability<sup>5</sup> and therefore created their own set of guidelines for what makes a good drug compound which should:

- have a polar surface area  $\leq 140 \text{ \AA}^2$  and contain  $\leq 10$  freely rotatable bonds
- or
- have  $\leq 12$  hydrogen bond donors and acceptors in total and at the same time have  $\leq 10$  rotatable bonds

### 1.1.2 Drug Distribution

Once an active substance has reached the blood distribution system it is transported to all parts of the body within one minute. Then it has to exit the arteries, veins, and capillaries and find its way to the tissues. There are pores in the walls of the capillaries that are 90-150 Å in diameter, large enough for most drugs to pass these and enter the aqueous fluid surrounding the various tissues and organs of the body. Most of the time the target does not sit in the cell membrane; consequently, the compound has to cross the cell membrane. Unless it is transported into the cell by carrier proteins or is taken up by pinocytosis, the drug must be lipophilic enough to be able to pass the membrane. For these reasons, most drugs that target intracellular machinery lack strongly ionizing groups such as basic sites with  $\text{p}K_{\text{a}} > 10$  (e.g. a guanidine) or acidic groups with  $\text{p}K_{\text{a}} < 5$  (e.g. carboxylic acids).

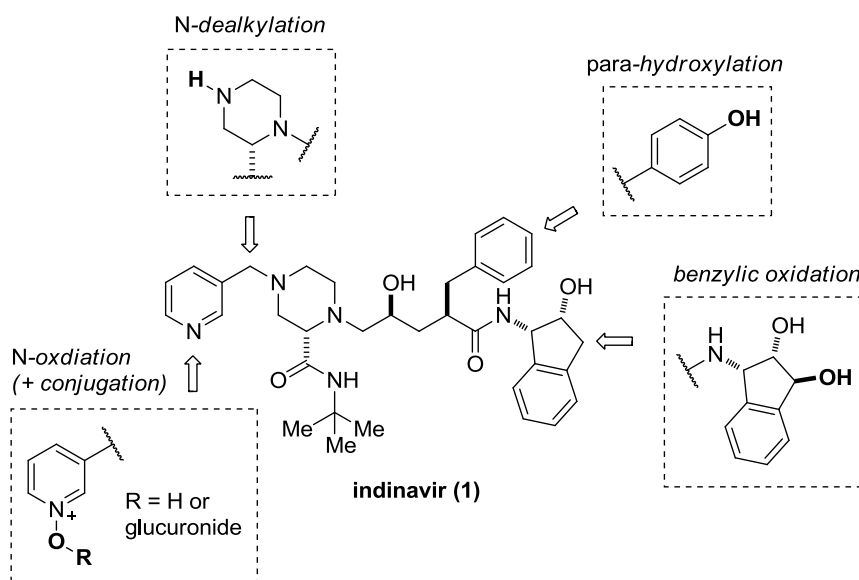
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<sup>4</sup> Among orally administered launched drugs that do not obey the rule are e.g.: atazanavir (MW = 705 g mol<sup>-1</sup>), fondaparinux sodium (5 H-bond donor), erythromycin (14 H-bond acceptors), telmisartan (<sup>c</sup>log *P* = 7.5).

<sup>5</sup> D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward, K. D. Kopple, *J. Med. Chem.* **2002**, *45*, 2615-2623.

### 1.1.3 Drug Metabolism and Excretion

Once a compound enters the body it is subject to attack from a range of metabolic enzymes. These have the task to modify the foreign molecule for it to be rapidly excreted again. In general, there are two major pathways by which the body deals with substances and makes them more polar for enhanced excretion rates. In phase I reactions, non-specific enzymes (particularly cytochrome P450 enzymes, CYP, in the liver) add polar groups to compounds by means of oxidation, reduction, or hydrolysis. Phase II involves the attachment of polar molecules to afford conjugates of high polarity. A selection of processes is highlighted in Figure 4, where the major metabolic transformations are indicated for *Merck's* antiviral agent *indinavir* (**1**).<sup>6</sup>

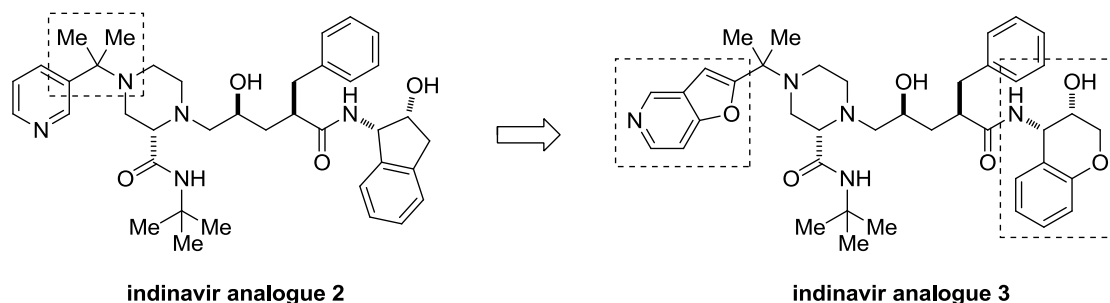


**Figure 4.** Major metabolites of the antiviral compound indinavir (**1**).

As shown in the above figure, phase I metabolism often leads to oxidized compounds, where heteroatoms as well as activated C—H bonds (e.g. benzylic or aryl bonds, or  $\alpha$ -positions to a heteroatom) are affected. This process can also lead to dealkylations, when for instance intermediate hemiaminals collapse (above: formation of terminal piperazine and nicotinic acid). In phase II polar groups such as glucuronate, sulfate or the tripeptide glutathione are attached to suitable handles that are either already present at the beginning or were introduced by CYPs in phase I. A number of other metabolic pathways known, but the examples mentioned above are responsible for the majority of observed metabolites. In general, fast metabolism is a highly un-

<sup>6</sup> Example taken from ref. 1. Additional information on the metabolism of **1** can be found in: a) T. Koudriakova, E. Iatsimirskaia, I. Utkin, E. Gangl, P. Vouros, E. Storozhuk, D. Orza, J. Marinina, N. Gerber, *Drug Metab. Dispos.* **1998**, *26*, 552-561; b) G. C. Williams, P. J. Sinko, *Adv. Drug Deliv. Rev.* **1999**, *39*, 211-238; c) M. Chiba, M. Hensleigh, J. A. Nishime, S. K. Balani, J. H. Lin, *Drug Metab. Dispos.* **1996**, *24*, 307-314.

desired process, since the action of the drug is limited (in certain cases specific metabolism like enzymatic hydrolysis of an ester or an amide can be desired and is used to release the active compound from a previously masked prodrug). Therefore, compounds are designed in order to be more robust. A geminal dimethyl group analogue of indinavir, compound **2**, exemplifies this by retaining a large portion of the activity ( $IC_{50} = 1.16$  nM; indinavir:  $IC_{50} = 0.59$  nM), but reducing the formation of dealkylated metabolites ( $t_{1/2}$  for **2** is more than twice as long in rats and dogs).<sup>7</sup> The HIV protease inhibitor **3** that came out of the same study replaces two other sites of significant metabolism (pyridine, dihydroindene) with furo[3,2-*c*]pyridine and chroman moieties, respectively. While the pharmacokinetic profile is improved, the potency is also increased leading to a highly active compound with an  $IC_{50}$  value of 0.075 nM.



**Figure 5.** Optimization of the pharmacokinetic and -dynamic profile of indinavir.

While it is of great importance to find novel biologically active molecules, it is equally important to optimize the new lead structures to fulfill all or most of the pharmacokinetic and -dynamic requirements as well as safety regulations. In this context, only the modulation of biophysical properties and the fine-tuning of structural elements of a given lead will provide novel useful drugs with reduced side-effects and enhanced activity and time of action.

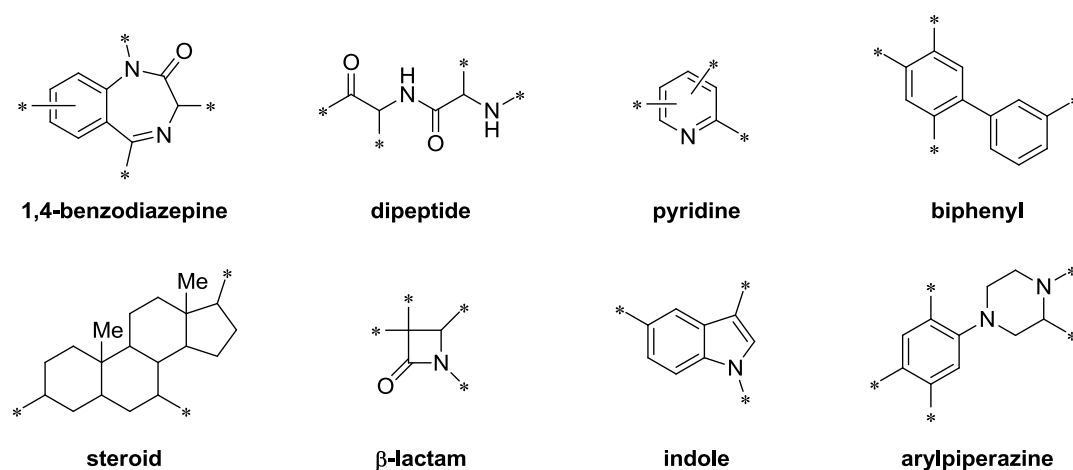
<sup>7</sup> Y. Cheng, F. Zhang, T. A. Rano, Z. Lu, W. A. Schleif, L. Gabryelski, D. B. Olsen, M. Stahlhut, C. A. Rutkowski, J. H. Lin, L. Jin, E. A. Emini, K. T. Chapman, J. R. Tata, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2419-2422.

## 1.2 Privileged Scaffolds

Browsing through the structures of marketed drugs or through the thousands of pharmaceutically active compounds it becomes clear that certain structural elements appear much more often than others. These substructures are called privileged scaffolds (or privileged structures)<sup>8</sup> and are characterized by a number of properties, such as:

- capability of a versatile pharmacophore
- pronounced chemical stability and controllable metabolism
- structural element that can be efficiently derivatized with functional groups
- predictable preferred conformations
- analogues readily synthesized

Such frameworks that allow for vast diversification and permit access to defined chemical space are predominantly cyclic, but can also be linear (oligopeptides). Both systems should have predictable conformations and enable the uniform decoration of the surrounding space.<sup>1,9</sup> Examples that fulfill most of these requirements can be called privileged and a selection of these is illustrated in Figure 6.



**Figure 6.** A selection of privileged scaffolds in drug discovery. The asterisks denote possible points for the attachment of vectors.

Interestingly, many of these privileged structural elements are also commonly found in natural products. Especially those that are found in biologically active natural products have certainly inspired their application in drug discovery (key examples are the use of β-lactams as an-

<sup>8</sup> D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.

<sup>9</sup> M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

tibiotics<sup>10</sup> or  $\beta$ -lactones in the irreversible inhibition of pancreatic lipase<sup>11</sup>). Although a large number of structural elements have already been termed privileged structures, the list is by far not complete and an intrusion into novel chemical space<sup>12</sup> yielding previously unknown frameworks that eventually could be termed privileged is highly desirable and will certainly have a high impact in drug discovery.

### 1.3 Six-Membered Aliphatic Heterocycles

The medicinal chemist needs not only privileged scaffolds, but also suitable building blocks that can be attached to those. In Figure 6 of the preceding section, one of the designated examples of a privileged scaffold was an arylpiperazine.<sup>13</sup> In fact, this entity is a merger between two building blocks, one of them being an aryl group and the other being a piperazine. A benzene ring is probably the most used building block in all branches of organic chemistry, but the piperazine unit has also found applications in agricultural and medicinal chemistry. Its defined structural characteristics, as well as its polarity and capacity as hydrogen bond donor or acceptor, have contributed to its widespread use. The moiety can either be employed as a terminal or a central scaffold with substituents being attached to the nitrogen (most common substitution pattern) or carbon atoms. Many variants are commercially available, and a multitude of synthetic pathways are known for the construction of substituted piperazines.

Nearly equally important are the other members of the 6-membered aza-ring family: piperidine, morpholine, thiomorpholine. A search in the *Thomson Reuters Integrity* database<sup>14</sup> for active substances confirms this, and the results are summarized in Table 1.

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<sup>10</sup> D. J. Waxman, J. L. Strominger, *Ann. Rev. Biochem.* **1983**, *52*, 825-869.

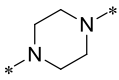


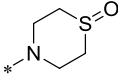
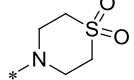

<sup>11</sup> P. Hadváry, H. Lengsfeld, H. Wolfer, *Biochem. J.* **1988**, *256*, 357-361.

<sup>12</sup> C. M. Dobson, *Nature* **2004**, *432*, 824-828.

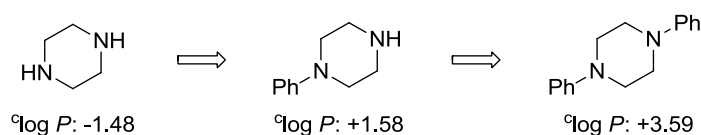
<sup>13</sup> See ref. 8 and references therein. A few examples are found e.g. in a) Y. Torisawa, T. Nishi, J. Minamikawa, *Bioorg. Med. Chem.* **2002**, *10*, 4023-4027; b) F. Kerrigan, C. Martin, G. H. Thomas, *Tetrahedron Lett.* **1998**, *39*, 2219-2222; c) M. Lee, J. B. Rangisetty, M. R. Pullagurla, M. Dukat, V. Setola, B. L. Roth, R. A. Glennon, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1707-1711.

<sup>14</sup> Search performed on July 18<sup>th</sup> 2011.

**Table 1.** Number of hits for nitrogen containing 6-membered monocyclic aliphatic rings in the *Thomson Reuters Integrity* database. Substructure search for substituents on the nitrogen atom(s) only for compounds with "Highest Phase" being either "Launched", "Phase III", "Phase II", "Phase I", or "Biological Testing". Numbers in parentheses refer to substructures with substituents allowed on nitrogen *and* carbon atoms.

Highest Phase						
Launched	93 (115)	22	0	0	0	21 (203)
Phase III	38 (45)	3	0	0	0	12 (69)
Phase II	117 (142)	29	0	0	0	21 (217)
Phase I	70 (91)	40	1	1	1	18 (184)
Biological Testing	17 129 (21 660)	6 158	247	30	161	3 581 (39 159)

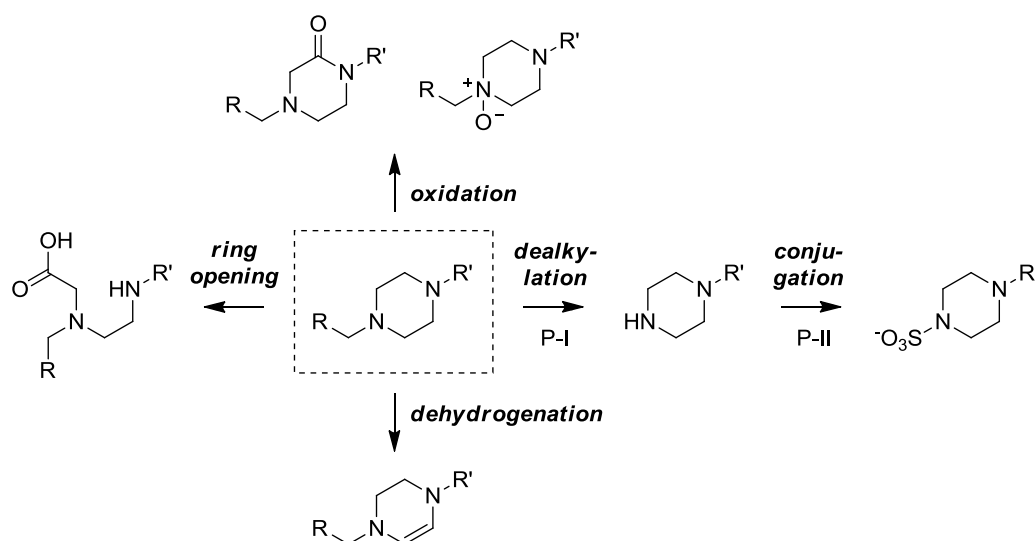
Evidently, piperazines and piperidines have a big impact in drug discovery, whereas the thiomorpholines, surprisingly, have only little precedence. A reason for this might be the tendency of thiomorpholines for metabolic liability (oxidations, reductions at sulfur; ring-opening to form thiodiglycolate<sup>15</sup>), the extraordinary synthetic effort required for their introduction, or the loss of reasonable amine basicity in thiomorpholines with an oxidized sulfur atom. Even though sulfoxides are known to be excellent hydrogen bond acceptors and the overall high polarity of the heterocycle would certainly help solubilize certain nonpolar frameworks, the aforementioned drawbacks might account for the reduced impact of thiomorpholine-*S*-oxides.



**Figure 7.** Change in lipophilicity on going from piperazine to phenyl- and diphenylpiperazine. Calculation was performed using the integrated method in *ChemBioDraw Ultra 12.0* (Cambridgesoft).

Even though piperazines, piperidines, and morpholines offer great possibilities for the medicinal chemist, these ring systems have some problematic pharmacokinetic properties that are associated with them. Lipophilicities, for instance, can rapidly increase when piperazines are arylated on the nitrogen atoms. Figure 7 shows that addition of one phenyl group leads to an increase of 3 logarithmic units, and when the other nitrogen is phenylated as well, the calculated  $\log P$  ( $\text{clog } P$ ) rises by an additional two orders of magnitude.

<sup>15</sup> a) B. Combourieu, P. Poupin, P. Besse, M. Sancelme, H. Veschambre, N. Truffaut, A.-M. Delort, *Biodegradation* **1998**, *9*, 433-442; b) B. Combourieu, P. Besse, M. Sancelme, J.-P. Godin, A. Monteil, H. Veschambre, A.-M. Delort, *Appl. Environ. Microbiol.* **2000**, *66*, 3187-3193.



**Figure 8.** Common metabolic pathways observed for piperazines.

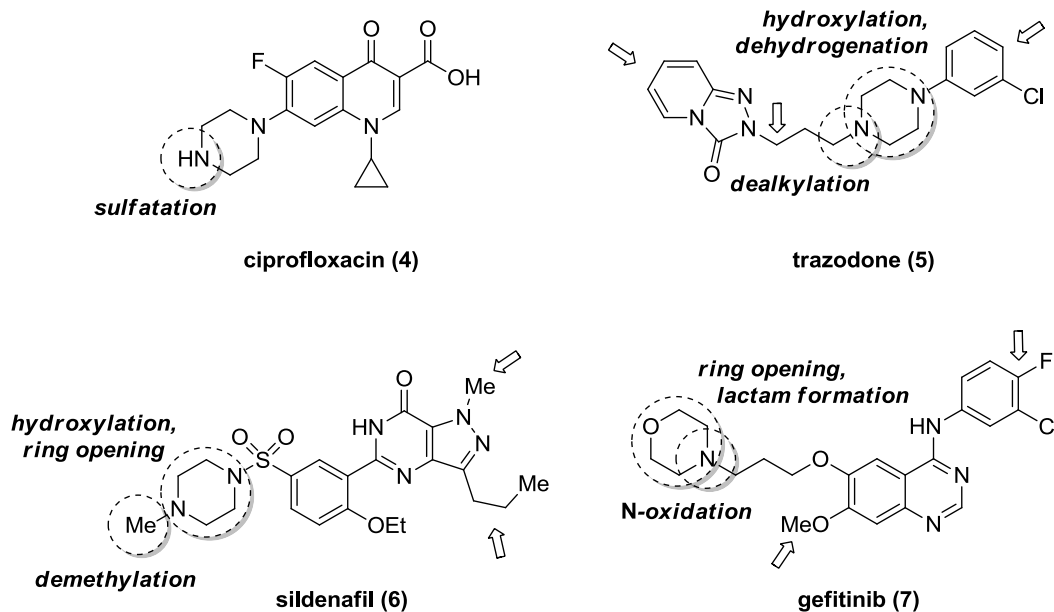
Furthermore, CYP enzymes are known to attack the piperazine scaffold and will produce a number of metabolites. Among these are dealkylated products, ring-opened fragments, oxidized compounds, and conjugates (Figure 8). These pathways account for the formation of major metabolites of a number of marketed drugs. Selected examples are depicted in Figure 9. *Bayer's* antibiotic ciprofloxacin (**4**) has a high degree of metabolic stability, and the only reported major metabolic site is at the terminal nitrogen atom of the piperazine ring, where phase-II conjugation leads to the attachment of a sulfate group.<sup>16</sup> Many metabolic transformations are known for trazodone (**5**), which belongs to the antidepressant of the serotonin antagonist and reuptake inhibitor class.<sup>17</sup> Its piperazine ring is affected by reactions leading to hydroxylated, dehydrogenated, and dealkylated intermediates or products. *Pfizer's* famous sildenafil (**6**, *Viagra*<sup>®</sup>) suffers from metabolism at the sulfonylated piperazine.<sup>18</sup> Major metabolites include demethylated, hydroxylated, and ring-opened compounds. Some oxidation is also observed at the other methyl and the propyl group of the pyrazole. Finally, the morpholine unit of *AstraZeneca's* anticancer agent gefitinib (**7**) is prone to metabolism, since formation of *N*-oxides, lactams, and ring-opened products was reported.<sup>19</sup>

<sup>16</sup> L. Senggunprai, K. Yoshinari, Y. Yamazoe, *Drug Metab. Dispos.* **2009**, *37*, 1711-1717.

<sup>17</sup> a) R. F. Staack, H. H. Maurer, *J. Anal. Toxicol.* **2003**, *27*, 560-568; b) B. Wen, L. Ma, A. D. Rodrigues, M. Zhu, *Drug Metab. Dispos.* **2008**, *36*, 841-850.

<sup>18</sup> a) M. G. Lee, S. H. Bae, S. K. Bae, *J. Pharm. Pharmacol.* **2009**, *61*, 1637-1642; b) J. S. Warrington, R. I. Shader, L. L. von Moltke, D. J. Greenblatt, *Drug Metab. Dispos.* **2000**, *28*, 392-397; c) G. J. Muirhead, D. J. Rance, D. K. Walker, P. Wastall, *Brit. J. Clin. Pharmacol.* **2002**, *53*, 13S-20S.

<sup>19</sup> D. McKillop, M. Hutchison, E. A. Partridge, N. Bushby, C. M. F. Cooper, J. A. Clarkson-Jones, W. Herron, H. C. Swaisland, *Xenobiotica* **2004**, *34*, 917-934.



**Figure 9.** Major metabolites formed around a piperazine or a morpholine ring in marketed drugs. Arrows indicate other sites of metabolism.

Overall, the compounds shown above and many other piperazine, morpholine, and piperidine compounds are metabolically labile at the ring system. All carbon centers in a piperazine or a morpholine are activated by virtue of the adjacent heteroatom. In general, it is difficult to block these sites by the introduction of bulky groups (*gem*-dimethyl) or fluorine atoms (or other halides). With the former, the system becomes much more lipophilic<sup>20</sup> and in terms of chemical synthesis the introduction of these groups is not straightforward.<sup>21</sup> The second option will produce compounds that are chemically unstable, since according to the ERLNMEYER rule,<sup>22</sup> the formation of iminium or oxonium ions after elimination of the halide is very well possible.

## 1.4 Four-Membered Heterocycles

It was shown in the preceding chapter that despite metabolic issues are found in aliphatic six-membered rings, they are abundantly used in drug discovery and various areas of applied organic chemistry. Not only six-membered rings but also their higher and lower homologues have found widespread use. In striking contrast, the number of four-membered rings found in the appropriate database is much smaller. One can speculate about the reasons, but their associ-

<sup>20</sup> Estimated increase in log *P* per methyl group is ~0.5.

<sup>21</sup> *gem*-Dimethyl piperazine is commonly synthesized from a lactam compound by reduction of the carbonyl group. Whereas the attachment of substituents is straightforward at the sterically less demanding amine, it becomes difficult and low-yielding at the other end.

<sup>22</sup> Seminal paper on the instability of geminal diols: E. Erlenmeyer, *Annalen der Chemie und Pharmacie* **1866**, 139, 211-234.







ated ring strain has probably frightened medicinal chemists to use them in their programs.<sup>23</sup> Furthermore, the scarcity of suitable building blocks and lengthy synthesis plans for their introduction has contributed to a reduced usage of four-membered rings. The aim of this work is to demonstrate that certain compounds of this family have extraordinary properties and should be considered for future applications in medicinal chemistry.

### 1.4.1 Oxetane, Azetidine, Thietane

The simplest members, oxetane, azetidine and thietane, were first synthesized in the late 19<sup>th</sup> century. Oxetane (or: trimethylene oxide) was first prepared by REBOUL in 1878 by base-mediated ring-closure of 3-chloropropanol.<sup>24</sup> GABRIEL was able to isolate azetidine from 3-bromopropylamine in 1888,<sup>25</sup> and the formation of thietane was postulated by WOLFF in 1899,<sup>26</sup> although this product was not characterized at that time.<sup>27</sup> Interestingly, the simplest organic four-membered ring, cyclobutane, was synthesized and characterized by WILLSTÄTTER only in 1907.<sup>28</sup> Ring strain energies have been reported for all of the above mentioned rings<sup>29</sup> and are summarized in Table 2. Whereas strain energies are similar in oxetane, azetidine, and cyclobutane, thietane is significantly less strained due to the prolonged C—S bonds and associated differences in bond angles.

**Table 2.** Characteristics of some simple four-membered ring compounds.

				
Compound	oxetane	azetidine	thietane	cyclobutane
First report	1878	1888	1899	1907
Physical appearance	colorless liquid	colorless liquid	colorless liquid	colorless gas
Boiling point	48 °C	62 °C	94 °C	12 °C
Ring strain / kcal mol <sup>-1</sup>	24.7	25.2	19.7	26.5

<sup>23</sup> On the other hand, even epoxides are found in launched drugs, the most prominent compound being an epothilone (ixabepilone, an anti-cancer agent from *Bristol-Myers-Squibb*).

<sup>24</sup> M. Reboul, *Ann. Chim.* **1878**, *14*, 496.

<sup>25</sup> S. Gabriel, J. Weiner, *Ber.* **1888**, *21*, 2669–2679.

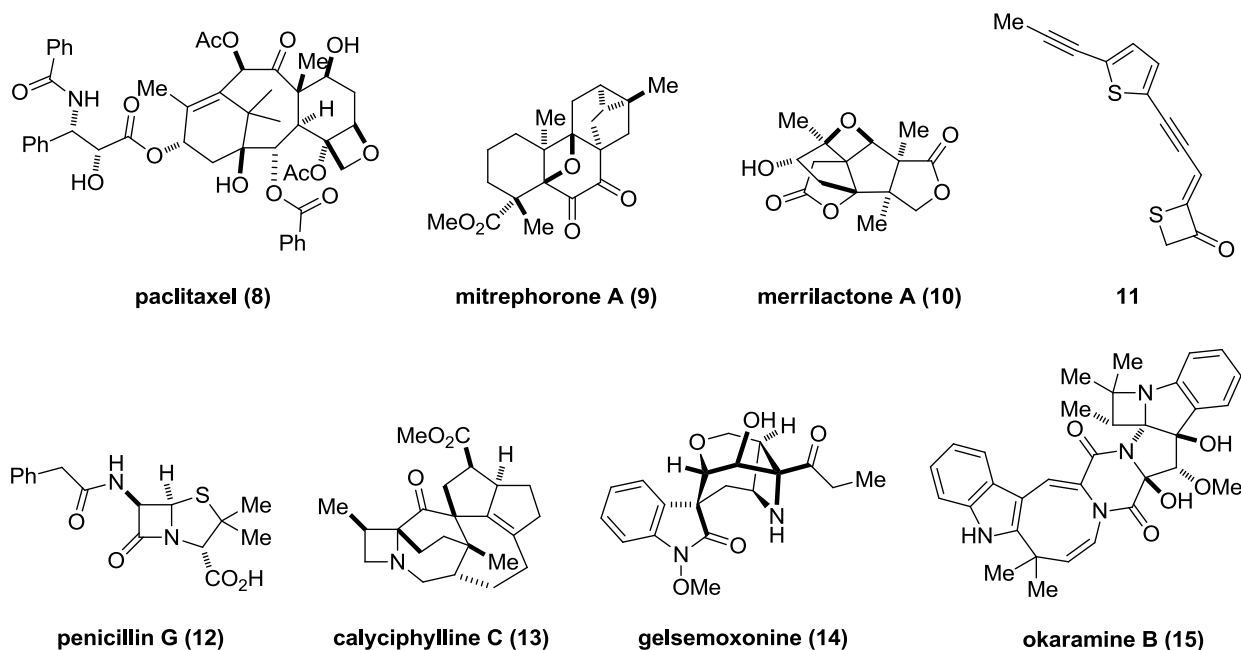
<sup>26</sup> W. Autenrieth, K. Wolff, *Ber.* **1899**, *32*, 1368–1375.

<sup>27</sup> The first report about the isolation and characterization of pure trimethylene sulfide appeared in 1927: G. M. Bennett, A. L. Hock, *J. Chem. Soc. (Res.)* **1927**, 2496–2499.

<sup>28</sup> R. Willstätter, J. Bruce, *Ber.* **1907**, *40*, 3979–3999.

<sup>29</sup> a) T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450–4458; b) W. Ried, B. Heinz, in *Advances in Heterocyclic Chemistry*, Vol. 35 (Ed.: A. R. Katritzky), Academic Press, **1984**, pp. 199–279.

## 1.4.2 Occurrence in Natural Products



**Figure 10.** Selected examples of isolated natural products containing four-membered heterocycles.

The four-membered heterocycles are found embedded in a number of natural products. The oxetane ring appears in 430 isolated natural products (out of which 82 are  $\beta$ -lactones).<sup>30</sup> Selected examples are shown in Figure 10. Paclitaxel (**8**, Taxol<sup>®</sup>) was isolated from the bark of *Taxus brevifolia* (western yew)<sup>31</sup> and due to its anticancer properties (interference in the normal breakdown of microtubules during cell division<sup>32</sup>) was introduced to the market by *Bristol-Myers-Squibb* in 1993. There has been some dispute about the role of the oxetane in Taxol, but computational studies indicate an overall rigidification<sup>33</sup> of the structure and postulate the oxetane to act as a hydrogen bond acceptor for a proximal threonine-OH in the putative binding site.<sup>34</sup> The hexacyclic *ent*-trachylobane diterpenoid mitrephorone A (**9**) was isolated from *Mitrephora glabra* and was found to have promising anticancer activity.<sup>35</sup> The intriguing structural framework of

<sup>30</sup> Number of appearances obtained by searching for substructures containing the heterocycle and the property „Isolation from Natural Product Available” in the *Reaxys* database (www.reaxys.com). Search performed on July 21<sup>st</sup> 2011.

<sup>31</sup> M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

<sup>32</sup> V. Farina, *The Chemistry and Pharmacology of Taxol and its Derivatives*, Elsevier Science B.V., Amsterdam, **1995**.

<sup>33</sup> T. C. Boge, M. Hepperle, D. G. Vander Velde, C. W. Gunn, G. L. Grunewald, G. I. Georg, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3041-3046.

<sup>34</sup> M. Wang, B. Cornett, J. Nettles, D. C. Liotta, J. P. Snyder, *J. Org. Chem.* **2000**, *65*, 1059-1068.

<sup>35</sup> C. Li, D. Lee, T. N. Graf, S. S. Phifer, Y. Nakanishi, J. P. Burgess, S. Riswan, F. M. Setyowati, A. M. Saribi, D. D. Soejarto, N. R. Farnsworth, J. O. Falkinham, D. J. Kroll, A. D. Kinghorn, M. C. Wani, N. H. Oberlies, *Org. Lett.* **2005**, *7*, 5709-5712.

the oxetane containing compound merrilactone A (**10**), isolated from *Illicium merrillianum*,<sup>36</sup> triggered a number of total syntheses.<sup>37</sup>

The majority of azetidine containing natural products have the substructure embedded in the form of a  $\beta$ -lactam (102 out of 139 isolates). Pharmaceutically important representatives are the penicillins (e.g. penicillin G, **12**) which have found tremendous use as antibiotics.<sup>38</sup> Out of the few azetidines that contain a basic amine, calyciphylline C (**13**), isolated from *Daphniphyllum calycinum*,<sup>39</sup> has probably the most intriguing polycyclic structure. Gelsemoxonine (**14**) belongs to the large family of *Gelsemium* alkaloids and was first isolated from *Gelsemium elegans* in 1991.<sup>40</sup> The initially proposed structure was later corrected in favor of a structure with an azetidine instead of an amino-epoxide.<sup>41</sup> Okaramine B (**15**), the only member in the okaramine family containing an azetidine ring, was isolated from *Penidllium simplidssimum* in 1989.<sup>42</sup> Its insecticidal activity was tested against the larvae of the silkworm, whereby in comparison with the other family members a significant increase in activity was observed and 100% of the larvae were killed under the assay conditions (concentration 0.03 ppm) within 24 h. So far only other okaramines have been synthesized,<sup>43</sup> and a total synthesis of this member is yet to be achieved.

One of the four reported natural products containing a thietane ring is the acetylenic compound **11**, which was isolated from *Berkheya barbata*.<sup>44</sup> The somewhat unusual structure was confirmed by synthesis, but no information is available about its biological function or activity.

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<sup>36</sup> J. M. Huang, R. Yokoyama, C. S. Yang, Y. Fukuyama, *Tetrahedron Lett.* **2000**, *41*, 6111-6114.

<sup>37</sup> Completed syntheses: a) V. B. Birman, S. J. Danishefsky, *J. Am. Chem. Soc.* **2002**, *124*, 2080-2081; b) M. Inoue, T. Sato, M. Hirama, *J. Am. Chem. Soc.* **2003**, *125*, 10772-10773; c) G. Mehta, S. R. Singh, *Angew. Chem. Int. Ed.* **2006**, *45*, 953-955; d) M. Inoue, T. Sato, M. Hirama, *Angew. Chem. Int. Ed.* **2006**, *45*, 4843-4848; e) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2007**, *129*, 498-499; f) L. Shi, K. Meyer, M. F. Greaney, *Angew. Chem. Int. Ed.* **2010**, *49*, 9250-9253.

<sup>38</sup> W. Sneader, in *Drug Discovery: A History*, John Wiley & Sons, Ltd, **2006**, pp. 287-318.

<sup>39</sup> S. Saito, T. Kubota, E. Fukushi, J. Kawabata, H. Zhang, J. Kobayashi, *Tetrahedron Lett.* **2007**, *48*, 1587-1589.

<sup>40</sup> L.-Z. Lin, G. A. Cordell, C.-Z. Ni, J. Clardy, *Phytochemistry* **1991**, *30*, 1311-1315.

<sup>41</sup> M. Kitajima, N. Kogure, K. Yamaguchi, H. Takayama, N. Aimi, *Org. Lett.* **2003**, *5*, 2075-2078.

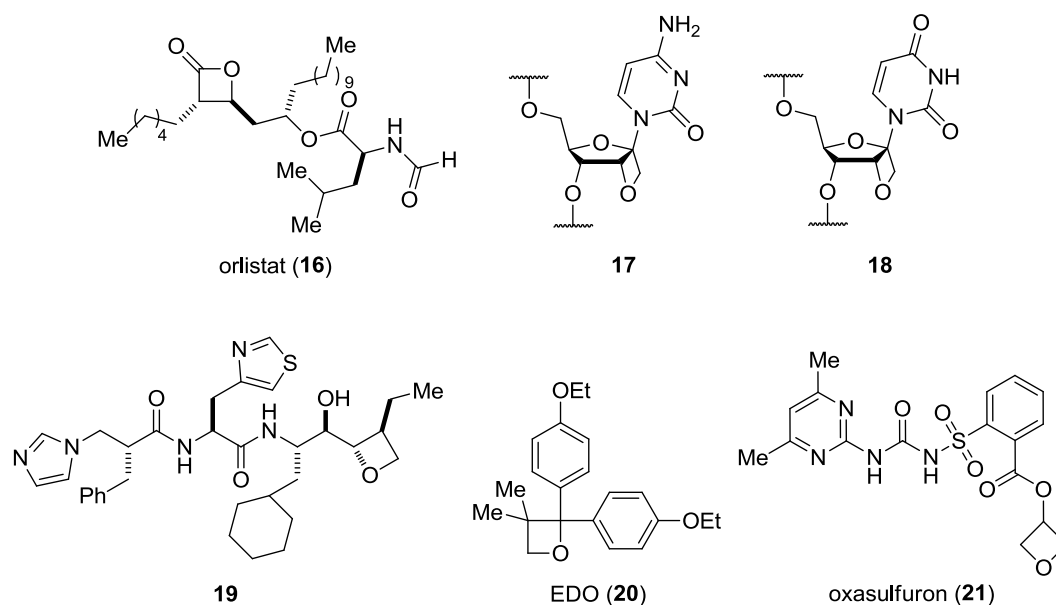
<sup>42</sup> H. Hayashi, K. Takiuchi, S. Murao, M. Arai, *Agr. Biol. Chem.* **1989**, *53*, 461-469.

<sup>43</sup> Okaramine N: P. S. Baran, C. A. Guerrero, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629; okaramine J: J. M. Roe, R. A. B. Webster, A. Ganesan, *Org. Lett.* **2003**, *5*, 2825-2827; okaramine C: P. R. Hewitt, E. Cleator, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 2415-2417; okaramine M: T. Iizuka, S. Takiguchi, Y.-s. Kumakura, N. Tsukioka, K. Higuchi, T. Kawasaki, *Tetrahedron Lett.* **2010**, *51*, 6003-6005.

<sup>44</sup> F. Bohlmann, W. Skuballa, *Chem. Ber.* **1973**, *106*, 497-504.

### 1.4.3 Manifestations in Active Compounds

Paclitaxel (**8**) and its close analogues, docetaxel and cabazitaxel,<sup>45</sup> are the only oxetane compounds that are being marketed as pharmaceuticals, unless the  $\beta$ -lactone orlistat (**16**) is included, which was developed as an anti-obesity drug and was launched by *F. Hoffmann-La Roche* in 1998. A number of other applications have been described in the literature. For example, the conformationally restricted oxetane derivatives of cytidine **17** and thymidine **18** have been examined for their use in antisense oligonucleotides, and the corresponding RNA-heterodimers displayed increased stability toward degradation by nucleases.<sup>46</sup> The oxetane compound **19**, a transition-state mimic for the aspartate protease inhibitor renin, showed 1.2 nM activity ( $IC_{50}$ ) and proved to be better than the corresponding tetrahydrofuran or hydroxy compounds.<sup>47</sup>



**Figure 11.** Selected examples of oxetane compounds with useful properties.

Among oxetane compounds outside of the pharmaceutical sector are the insecticide EDO (**20**) and the herbicide oxasulfuron (**21**). In contrast to the notorious environmentally persistent DDT, EDO is biodegradable and at the same time showed a 25-fold increase in potency.<sup>48</sup> Before its production was stopped in 2007 due to increased resistance, oxasulfuron was marketed

<sup>45</sup> In contrast to paclitaxel, docetaxel has a Boc group on the amine and the  $\alpha$ -hydroxy ketone is not acylated. Additionally, in cabazitaxel both “northern” hydroxy groups are methylated.

<sup>46</sup> a) P. I. Pradeepkumar, J. Chattopadhyaya, *J. Chem. Soc., Perkin Trans. 2* **2001**, 2074–2083; b) P. I. Pradeepkumar, N. V. Amirkhanov, J. Chattopadhyaya, *Org. Biomol. Chem.* **2003**, *1*, 81–92.

<sup>47</sup> S. H. Rosenberg, K. P. Spina, H. Stein, J. Cohen, W. R. Baker, H. D. Kleinert, *Bioorg. Med. Chem.* **1994**, *2*, 927–937.

<sup>48</sup> G. Holan, *Nature* **1971**, *232*, 644–647.

by *Syngenta* and was used to keep weeds under control, for instance in the cultivation of soybeans.<sup>49</sup>

Azetidine in the form of a  $\beta$ -lactam is embedded in numerous active compounds and defines the class of  $\beta$ -lactam antibiotics that include the penicillins (e.g. penicillin G, **12**), cephalosporins, monobactams, and carbapenems. A few  $\beta$ -lactam compounds have found other uses with *Merck's* ezetimibe (**22**) being the most prominent one. This blockbuster molecule<sup>50</sup> is a potent inhibitor of cholesterol uptake from the intestines and hepatocytes and acts by binding to Niemann-Pick C1-Like 1 (NPC1L1).<sup>51</sup> Binding constants were determined for ezetimibe glucuronide, the major metabolic conjugate that is rapidly formed when the compound is orally administered, and the  $K_D$  values indicate a strong binding for mouse (40 nM) and human NPC1L1 (220 nM). It has been shown as well that **22** no longer binds to membranes from NPC1L1 knockout mice, a strong indication that this enzyme is indeed the molecular target for ezetimibe.

A few other azetidine compounds have been commercialized as pharmaceuticals. *Daiichi Sankyo* and *Ube* have developed the calcium channel blocker azelnidipine (**23**) for the treatment of hypertension.<sup>52</sup> Its structure is characterized by a dihydropyridine linked via an ester group to a benzhydryl substituted azetidine. Another example is *Pfizer's* (Japan; marketed by *Meiji Seika*) tebipenem pivoxil (**24**), an oral carbapenem prodrug that was launched in Japan in 2009 for the treatment of bacterial infections.

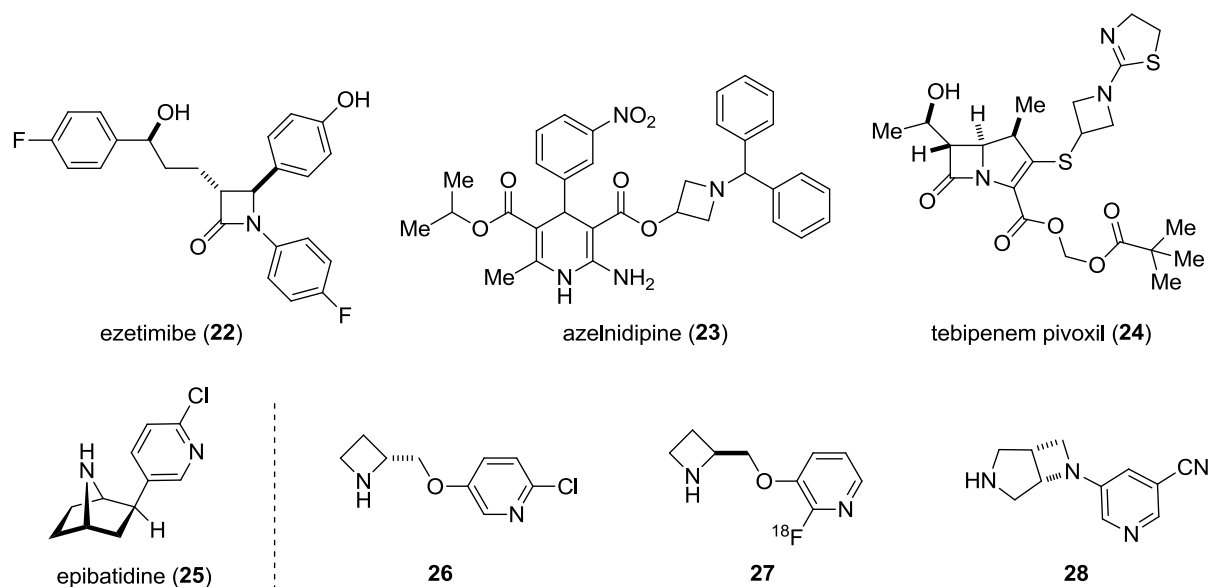
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<sup>49</sup> a) W. Meyer (Ciba-Geigy AG), EP 92-810027, **1992**; b) M. K. Koeppe, H. M. Brown, *Agro Food Ind. Hi-Tech* **1995**, 6, 9-14.

<sup>50</sup> Ranked #31 in sales in 2010 (Zetia®; data obtained from [www.drugs.com/top200.html](http://www.drugs.com/top200.html), July 22<sup>nd</sup> 2011). Also marketed in the form of a mixture with simvastatin as Vytorin®, ranked #33 in sales in 2010.

<sup>51</sup> M. Garcia-Calvo, J. Lisnock, H. G. Bull, B. E. Hawes, D. A. Burnett, M. P. Braun, J. H. Crona, H. R. Davis, D. C. Dean, P. A. Detmers, M. P. Graziano, M. Hughes, D. E. MacIntyre, A. Ogawa, K. A. O'Neill, S. P. N. Iyer, D. E. Shevell, M. M. Smith, Y. S. Tang, A. M. Makarewicz, F. Ujjainwalla, S. W. Altmann, K. T. Chapman, N. A. Thornberry, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, 102, 8132-8137.

<sup>52</sup> H. Koike, M. Yoshimoto, H. Nishino (Sankyo Company Limited), EP 0266922, **1988**.



**Figure 12.** Top row: pharmaceuticals containing an azetidinium ring. Bottom row: epibatidine and a few azetidines analogues.

Epibatidine (**25**) was isolated in 1991 from the skins of the Ecuadorian frog *Epipedobates tricolor* following an expedition of DALY and co-workers as part of their research program focusing on the identification of novel alkaloids from endangered frog species found in the rainforests of northern South America.<sup>53</sup> It was found to be a very potent analgesic of the non-opioid class. The structural novelty and its intriguing biological function have triggered a number of total syntheses (including a stereocontrolled synthesis of both enantiomers by COREY<sup>54</sup>) and an enormous amount of research publications.<sup>55</sup> Unfortunately, epibatidine is not a very selective analgesic and proved to have a high toxicity.<sup>56</sup> Many analogues were prepared in the search for more selective drugs.<sup>57</sup> Among these are also a few azetidines compounds, such as **26**, **27**, and **28**. Azetidines **26** was found to be as potent as epibatidine (200 times more active than morphine) in its function as a selective ligand for the human nicotinic acetylcholine receptor (nAChR) subtype.<sup>58</sup> While this compound reached phase II trials as an analgesic, it was discontin-

<sup>53</sup> T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475-3478.

<sup>54</sup> E. J. Corey, T. P. Loh, S. AchyuthaRao, D. C. Daley, S. Sarshar, *J. Org. Chem.* **1993**, *58*, 5600-5602.

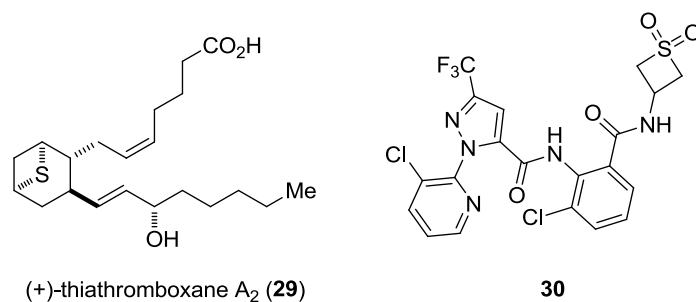
<sup>55</sup> A search in the Web of Knowledge® (*Thomson Reuters*) with "epibatidine" in the title affords 449 hits. Search performed on July 22<sup>nd</sup> 2011.

<sup>56</sup> For a review, see: a) J. W. Daly, H. Martin Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan, M. Williams, *Nat. Prod. Rep.* **2000**, *17*, 131-135; b) H. M. Garraffo, T. F. Spande, M. Williams, *Heterocycles* **2009**, *79*, 207-217.

<sup>57</sup> A review: F. I. Carroll, *Heterocycles* **2009**, *79*, 99-120.

<sup>58</sup> a) M. W. Holladay, J. T. Wasicak, N.-H. Lin, Y. He, K. B. Ryther, A. W. Bannon, M. J. Buckley, D. J. B. Kim, M. W. Decker, D. J. Anderson, J. E. Campbell, T. A. Kuntzweiler, D. L. Donnelly-Roberts, M. Piattoni-Kaplan, C. A. Briggs, M. Williams, S. P. Arneric, *J. Med. Chem.* **1998**, *41*, 407-412; b) A. W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon, D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz, A. H. Dickenson, R. D. Porsolt, M. Williams, S. P. Arneric, *Science* **1998**, *279*, 77-80.

ued due to side-effect liabilities including emesis and nausea (insufficient selectivity). Fluorine-18 labeled compounds have been used in positron emission tomography (PET) to study the *in vivo* distribution of appropriately labeled compounds. Labeled epibatidine analogue **27** was efficiently synthesized and subsequently used in PET studies that revealed the lack of binding to  $\alpha 7$  nicotinic or  $5\text{HT}_3$  receptors in rodents.<sup>59</sup> In further optimization studies, the diazabicycloheptane **28** was discovered as a potent analgesic agent with a reduced incidence of emesis.<sup>60</sup>



**Figure 13.** Selected examples of active thietane compounds.

Thromboxane A<sub>2</sub>, produced by thromboxane-A synthase from prostaglandin H<sub>2</sub>, facilitates platelet aggregation and thus is a vasoconstrictor as well as a potent hypertensive agent.<sup>61</sup> Unfortunately, its short half-life of about 30 s in H<sub>2</sub>O (pH 7.4) significantly reduces its biological potency. In search for better agents, analogues such as the thietane **29** and similar compounds<sup>62</sup> were prepared and in many cases showed comparable activity with a significantly prolonged time of action.

Oxidized thietane compound **30** and many similar anthranilamides containing thietanes, oxetanes, and azetidines were described by *Syngenta* as powerful insecticides.<sup>63</sup> Thus, **30** showed significantly increased insecticidal activity against *S. littoralis* larvae than an analogous compound bearing a cyclobutane ring in place of the thietane.<sup>64</sup> At 3 ppm concentration, 55% of the larvae were killed after 4 days and a 100% reduction in larvae growth was observed (for cyclobutane derivative: 0% in both cases at the same concentration).

<sup>59</sup> F. Dollé, L. Dolci, H. Valette, F. Hinnen, F. Vaufrey, I. Guenther, C. Fuseau, C. Coulon, M. Bottlaender, C. Crouzel, *J. Med. Chem.* **1999**, *42*, 2251-2259.

<sup>60</sup> J. Ji, M. R. Schrimpf, K. B. Sippy, W. H. Bunnelle, T. Li, D. J. Anderson, C. Faltynek, C. S. Surowy, T. Dyhring, P. K. Ahring, M. D. Meyer, *J. Med. Chem.* **2007**, *50*, 5493-5508.

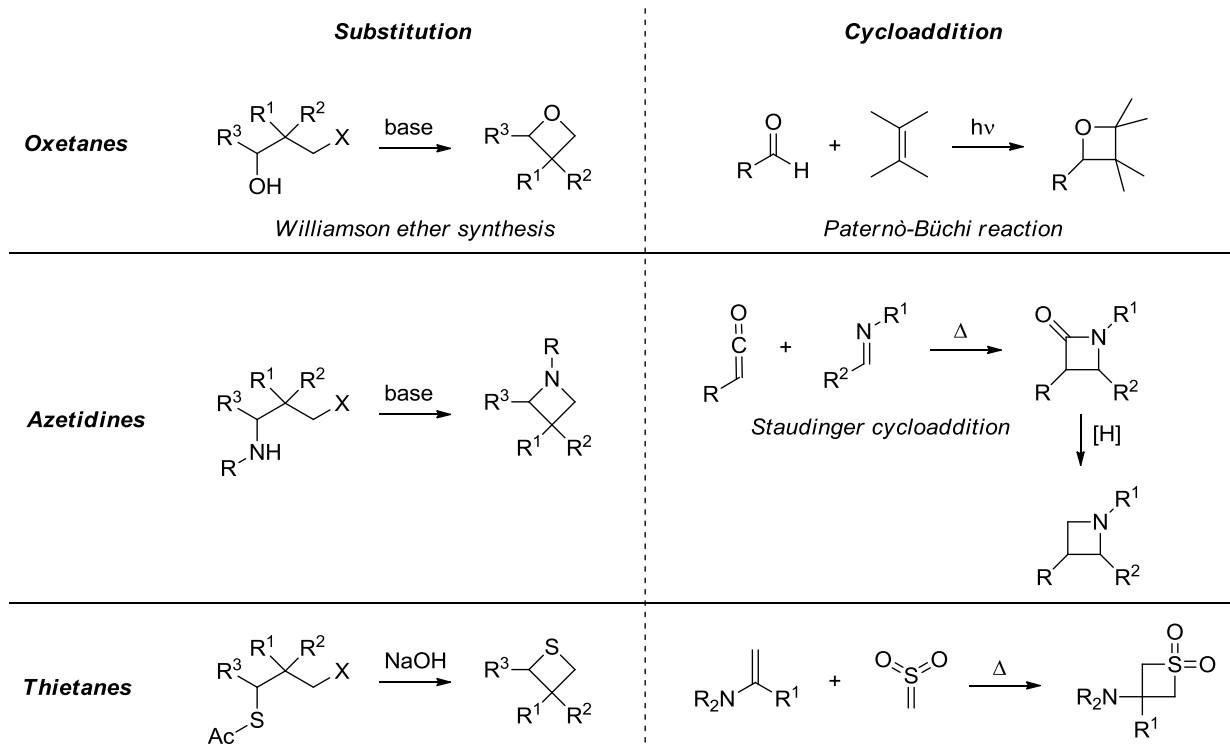
<sup>61</sup> B. Samuelsson, M. Goldyne, E. Granstrom, M. Hamberg, S. Hammarstrom, C. Malmsten, *Ann. Rev. Biochem.* **1978**, *47*, 997-1029.

<sup>62</sup> a) S. Ohuchida, N. Hamanaka, M. Hayashi, *Tetrahedron Lett.* **1981**, *22*, 1349-1352; b) S. Ohuchida, N. Hamanaka, M. Hayashi, *Tetrahedron* **1983**, *39*, 4257-4261; c) S. Ohuchida, N. Hamanaka, M. Hayashi, *Tetrahedron* **1983**, *39*, 4263-4268; d) S. Ohuchida, N. Hamanaka, M. Hayashi, *Tetrahedron* **1983**, *39*, 4269-4272.

<sup>63</sup> M. Muehlebach, A. Jeanguenat, R. G. Hall (Syngenta AG), WO 2007080131, **2008**.

<sup>64</sup> Cyclobutane derivative described herein: G. P. Lahm, S. F. McCann, K. M. Patel, T. P. Selby, T. M. Stevenson (Du Pont), WO 2003015518, **2003**.

## 1.4.4 Preparation



**Figure 14.** Common synthetic pathways for the formation of four-membered heterocycles.

Previous sections have indicated that a number of compounds with embedded four-membered heterocycles have remarkable properties and structural characteristics. Convenient and reliable methods are required for their efficient synthesis. In general, there are two major classes of reactions for accessing these heterocycles: intramolecular substitution reactions and cycloaddition reactions (Figure 14).

Oxetanes are commonly formed by an intramolecular variant of the WILLIAMSON ether synthesis<sup>65</sup> or by light-mediated PATERNÒ-BÜCHI cycloaddition reactions.<sup>66</sup> 2-Mono- or 2,2-disubstituted oxetanes can also be uncovered by a variant of the COREY-CHAYKOVSKY reaction involving double methylenation of carbonyl groups or ring-expansion of epoxides.<sup>67</sup> The synthesis of azetidines follows the same principles.<sup>68</sup> Intramolecular substitution reactions or in-

<sup>65</sup> Older reviews on the synthesis of oxetanes: a) S. Searles, in *The Chemistry of Heterocyclic Compounds, Vol. 19-2* (Ed.: A. Weissberger), Wiley-Interscience, New York, **1964**, pp. 983-1068; b) S. Searles, in *Comprehensive Heterocyclic Chemistry, Vol. 7* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, **1984**, pp. 363-402.

<sup>66</sup> Selected reviews: J. A. Porco, S. L. Schreiber, in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 151-192; b) T. Bach, *Synthesis* **1998**, *1998*, 683-703.

<sup>67</sup> See for example, a) K. Okuma, Y. Tanaka, S. Kaji, H. Ohta, *J. Org. Chem.* **1983**, *48*, 5133-5134; A. O. Fitton, J. Hill, D. E. Jane, R. Millar, *Synthesis* **1987**, *1987*, 1140-1142. An enantioselective variant: T. Sone, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 1677-1680.

<sup>68</sup> For comprehensive reviews, see: a) A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988-4035; b) G. S. Singh, M. D'Hooghe, N. De Kimpe, in *Comprehensive Heterocyclic Chemistry III* (Eds.: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), Elsevier, Oxford, **2008**, pp. 1-110.



termolecular versions with a primary amine and e.g. a 1,3-dibromide will furnish azetidines, whereas the STAUDINGER cycloaddition reaction<sup>69</sup> produces  $\beta$ -lactams, which after reduction (metal hydrides; thiolactam formation and subsequent desulfurization) will also give rise to substituted azetidines. In addition to the standard procedures, intramolecular hydroamination of aminoallenes or intramolecular N—H insertion reactions of metallocarbenes are also known, leading to the corresponding azetidines.<sup>70</sup> Common preparative methods for the construction of thietanes predominantly involve substitution reactions (often double nucleophilic displacement reactions of 1,3-electrophiles with sodium sulfide or an analogous reagent), but also  $[2+2]$ -cycloadditions of electron-rich alkenes with sulfene (generated from methanesulfonyl chloride with base). The former strategy leads to thietanes, whereas the latter affords thietane-*S,S*-dioxides. Rearrangement of 2-(chloromethyl)thiiranes in the presence of suitable nucleophilic species is known to afford 3-substituted thietanes.<sup>71</sup>

### 1.4.5 Commercial Availability

Although most of the compounds with four-membered heterocycles are best constructed using the methods described above, it can be of great advantage to use building blocks that already contain the heterocyclic unit for the construction of certain target compounds. For example, the synthesis of starting materials for the ring-closing step can require multiple linear steps; furthermore, cycloaddition reactions might deliver products with low regio-, diastereo-, or enantioselectivity. These obstacles can be circumvented by using suitable building blocks in the synthesis of moderately substituted heterocycles.<sup>72</sup> The recent interest in four-membered heterocycles has also led to increased commercial availability of oxetane, azetidine, and thietane building blocks. At the time of writing, a total of 424 compounds containing an oxetane were commercially available as building blocks or reagents. Azetidines appear in 1985 commercial substances, and 91 thietane compounds can be purchased on the market.<sup>73</sup>

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<sup>69</sup> A recent review: G. S. Singh, *Tetrahedron* **2003**, *59*, 7631-7649.


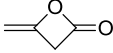
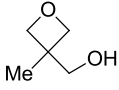


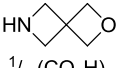
<sup>70</sup> See ref. 68b for details and further methods.

<sup>71</sup> For an overview about thietane syntheses, see: S. Lesniak, W. J. Kinart, J. Lewkowski, in *Comprehensive Heterocyclic Chemistry III* (Eds.: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), Elsevier, Oxford, **2008**, pp. 389-428.

<sup>72</sup> If the heterocycles are highly substituted (> 2- or 3-fold), cycloaddition reactions are to be considered first in most cases.

<sup>73</sup> For comparison: cyclobutane yields 2674 hits. Numbers taken from a search in *Reaxys* (www.reaxys.com) on July 25<sup>th</sup> 2011. Search criteria: substructure with filter "Availability" = "product for purchase". Other databases like *Scifinder Web* (scifinder.cas.org) or *DiscoveryGate* (www.discoverygate.com) deliver more results, but certain hits seem unreliable or refer to screening compounds.

**Table 3.** Selected commercial oxetane products. [a] From *DiscoveryGate* (www.discoverygate.com); July 25<sup>th</sup> 2011. [b] Freely chosen supplier, prices in US dollar for American market.

Compound						
	<b>31</b>	<b>32</b>	<b>33</b>	<b>34</b>	<b>35</b>	<b>36</b>
Amount of suppliers <sup>[a]</sup>	31	41	72	59	23	15
Price <sup>[a,b]</sup>	\$306/10 g (Aldrich)	\$40/500 ml (TCI America)	\$40/10 g (Aldrich)	\$65/500 mg (Aldrich)	\$380/1 g (Synthonix)	\$440/1 g (Synthonix)

A selection of commercial oxetane products is shown in Table 3. Oxetane (**31**) is available from multiple sources at a relatively high price. Traditional reagents like diketene (**32**) or COREY's oxetane reagent **33** for the preparation of OBO-protected carboxylic acids<sup>74</sup> are available in larger quantities at moderate prices. Oxetan-3-one (**34**) is nowadays available from many suppliers including global distributors like *Aldrich*, an indication for its industrial need. Other simple building blocks like 3-iodooxetane (**35**) and spirocycle **36** are still rather expensive.

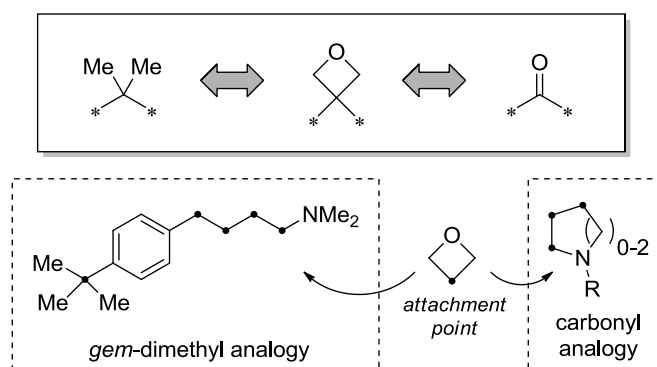
## 1.5 Oxetanes

The introduction of a geminal dimethyl group at a metabolically labile methylene unit (e.g. benzylic or in  $\alpha$ -position to a heteroatom) is common practice in drug discovery programs.<sup>75</sup> By doing this, metabolism should in most cases be reduced or directed to other parts of the molecule. However, the *gem*-dimethyl unit is metabolically at risk,<sup>76</sup> and, importantly, the molecule becomes much more lipophilic with an estimated  $\Delta\log P = +1.0$ . As discussed earlier in the chapter, a higher lipophilicity in general leads to more undesired pharmacokinetic properties. By analogy to the influence of the ethereal oxygen in THF on lipophilicity ( $\Delta\log P = -2.5$  in comparison with cyclopentane) an oxetane should have similar or even reduced lipophilicity compared to a methylene group. Thus, an oxetane unit is derived by bridging the *gem*-dimethyl group with an ethereal oxygen atom, and it can be seen as a liponeutral bulk-increasing group.

<sup>74</sup> E. J. Corey, N. Raju, *Tetrahedron Lett.* **1983**, *24*, 5571-5574.

<sup>75</sup> For examples, see: a) J. L. Duffy, T. A. Rano, N. J. Kevin, K. T. Chapman, W. A. Schleif, D. B. Olsen, M. Stahlhut, C. A. Rutkowski, L. C. Kuo, L. X. Jin, J. H. Lin, E. A. Emini, J. R. Tata, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2569-2572; b) S. Ahmad, L. M. Doweyko, S. Dugar, N. Grazier, K. Ngu, S. C. Wu, K. J. Yost, B. C. Chen, J. Z. Gougoutas, J. D. DiMarco, S. J. Lan, B. J. Gavin, A. Y. Chen, C. R. Dorso, R. Serafino, M. Kirby, K. S. Atwal, *J. Med. Chem.* **2001**, *44*, 3302-3310.

<sup>76</sup> Cytochrome P450 enzymes have a preference for lipophilic molecules: a) K. A. S. Al-Gailany, J. B. Houston, J. W. Bridges, *Biochem. Pharmacol.* **1978**, *27*, 783-788; b) D. A. Smith, K. Brown, M. G. Neale, *Drug Metab. Rev.* **1985**, *16*, 365-388; c) B. Testa, P. Crivori, M. Reist, P.-A. Carrupt, *Perspect. Drug Discovery Des.* **2000**, *19*, 179-211. For a review on CYPs: F. J. Gonzalez, D. W. Nebert, *Trends Gen.* **1990**, *6*, 182-186.



**Figure 15.** Short summary of studies with oxetanes within the CARREIRA research group.

Research carried out by WUITSCHIK, CARREIRA, ROGERS-EVANS, MÜLLER, and co-workers at *ETH Zürich* and *F. Hoffmann-La Roche AG* has revealed that oxetanes indeed function as a bulky but polar group with low lipophilicity (Figure 15).<sup>77</sup> Furthermore, their influence on amine basicity, solubility in aqueous media, and metabolism has been investigated. These studies uncovered a trend for higher solubility and lower metabolic clearance than in the corresponding methylene compounds. Moreover, a comparison of VAN'T HOFF's and PAULING's description of the carbonyl group<sup>78</sup> with the shape and polarization of the oxetane unit reveals matching properties and supports the identification of a 3,3-disubstituted oxetane as a possible surrogate for a carbonyl group.

Not only were oxetanes described as good modulators of pharmacokinetic properties, but their introduction on drug-like scaffolds was straightforward and the targeted oxetane compounds were chemically stable. Their synthesis was achieved by using suitable building blocks and by taking advantage of inherent reactivity displayed by strained heterocycles.<sup>79</sup> In conclusion, these specifications render oxetanes intriguing elements in drug discovery and beyond.<sup>80</sup>

### 1.5.1 Recent Advances in the Preparation of Oxetanes

While oxetanes have received more and more attention in drug discovery programs at pharmaceutical companies, their efficient incorporation into drug-like molecules became crucial.

<sup>77</sup> For details, see: a) G. Wuitschik, PhD Thesis, ETH Zurich (Zurich), **2008**; b) G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem. Int. Ed.* **2006**, *45*, 7736-7739; c) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Marki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4512-4515; d) G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227-3246.

<sup>78</sup> Landmark publication: L. Pauling, *J. Am. Chem. Soc.* **1931**, *53*, 1367-1400.

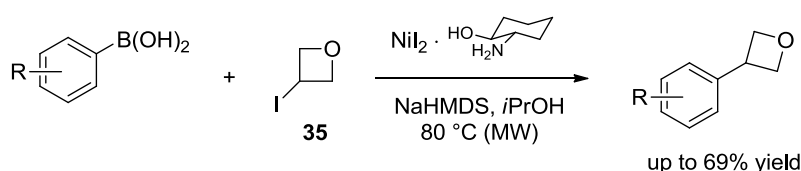
<sup>79</sup> An account of this work: G. Wuitschik, E. M. Carreira, M. Rogers-Evans, K. Müller, in *Process Chemistry in the Pharmaceutical Industry* (Eds.: K. Gadamasetti, T. Braish), CRC Press LLC, Boca Raton, **2008**, pp. 217-229.

<sup>80</sup> A recent review on oxetanes: J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

Within this context, several recent publications from industrial laboratories disclosed novel methods for the generation of oxetane compounds. Important advances that will not be discussed in later chapters are highlighted here.

DUNCTON and co-workers (*Evotec*, USA) were interested in the preparation of 3-aryl or 3-heteroaryl oxetanes as part of their medicinal chemistry programs. In search for an alternative to the cyclization of 2-aryl-propan-1,3-diols<sup>81</sup> or to additions to oxetan-3-one (**34**) with subsequent reductive deoxygenation,<sup>77b</sup> these researchers investigated the option of a nickel-catalyzed Suzuki coupling.<sup>82</sup> After optimization of reaction conditions, they found that a variety of arylboronic acids reacted with 3-iodooxetane (**35**) in the presence of  $\text{NiI}_2$ /*trans*-1,2-aminocyclohexanol and NaHMDS under microwave irradiation to afford the desired products in moderate to good yields (Scheme 1).<sup>83</sup>

**Evotec (2008):**



**Evotec (2009):**



**Scheme 1.** Preparation of aryl and heteroaryl oxetanes.

For certain heteroarylboronic acids poor conversions were observed, and in a few cases no desired product was obtained. To circumvent this problem, DUNCTON *et al.* discovered the rarely used MINISCI reaction<sup>84</sup> to be compatible with **35**. Using a heteroaromatic substrate such as quinoline **37** as starting material and iodide **35** (2 equiv), iron(II)sulfate ( $3 \times 0.3$  equiv), hydrogen peroxide ( $2 \times 3$  equiv), and sulfuric acid (2 equiv) as reagents they were able to obtain the

<sup>81</sup> See for example: B. Delmond, J. C. Pommier, J. Valade, *Tetrahedron Lett.* **1969**, 10, 2089-2090.

<sup>82</sup> FU and co-workers have pioneered in this field. Relevant references: a) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2004**, 126, 1340-1341; b) F. Gonzalez-Bobes, G. C. Fu, *J. Am. Chem. Soc.* **2006**, 128, 5360-5361; c) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2007**, 129, 9602-9603.

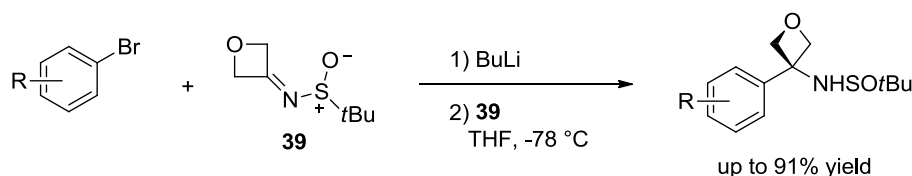
<sup>83</sup> M. A. J. Duncton, M. A. Estiarte, D. Tan, C. Kaub, D. J. R. O'Mahony, R. J. Johnson, M. Cox, W. T. Edwards, M. Wan, J. Kincaid, M. G. Kelly, *Org. Lett.* **2008**, 10, 3259-3262.

<sup>84</sup> For a review on this type of reaction, see: D. C. Harrowven, B. J. Sutton, in *Progress in Heterocyclic Chemistry*, Vol. Volume 16 (Eds.: W. Gribble Gordon, A. Joule John), Elsevier, **2005**, pp. 27-53.

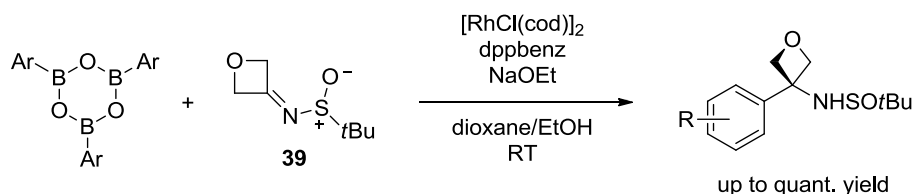
desired oxetanes (like **38**), albeit in moderate yield (~30-40%).<sup>85</sup> In both methods, not only 3-iodooxetane, but also Boc-protected 3-iodoazetidone can be used as starting material for the attachment onto an aromatic scaffold.

The 3-aminooxetane motif resembles an amide group according to the analogy introduced earlier in this chapter. Aryl amides are among the most extensively used structural elements in drug discovery and thus their analogous motif might be of great potential, too. The addition of a hard nucleophile onto a 3-iminooxetane would deliver straightforward access. The identification of **39**<sup>86</sup> as a good intermediate and suitable electrophile prompted a group at *Merck* to study its reactivity toward lithiated nucleophiles. To their delight, lithiated aromatics and heteroaromatics as well as acetylides, an alkene, and an enolate served as excellent nucleophiles and afforded the corresponding products in good to excellent yields (Scheme 2).<sup>87</sup> Furthermore, a COREY-CHAYKOVSKY reaction on **39** gave the corresponding aziridine, which could be opened with different nucleophiles to afford homologated 3-aminooxetanes.

**Merck (2010):**



**Ellman and co-workers (2011):**



**Scheme 2.** Recent advances in the synthesis of substituted 3-aminooxetanes. cod = cycloocta-1,5-diene; dppbenz = 1,2-bis(diphenylphosphino)benzene.

An even broader substrate scope for the generation of analogous 3-aminooxetanes was recently defined by ELLMAN and co-workers by using Rh(I) catalysis. Thus, a variety of arylboroxines<sup>88</sup> added smoothly and habitually in excellent yield to imine **39** by application of  $[\text{RhCl}(\text{cod})]_2$  (2 mol %)/dppbenz (4 mol %), sodium ethoxide (1.2 equiv) in THF/EtOH at

<sup>85</sup> M. A. J. Dunston, M. A. Estiarte, R. J. Johnson, M. Cox, D. J. R. O'Mahony, W. T. Edwards, M. G. Kelly, *J. Org. Chem.* **2009**, *74*, 6354-6357.

<sup>86</sup> First reported by *Novartis*: R. Albert, N. G. Cooke, F. Zecri, I. Lewis (Novartis AG), WO 2009068682, **2009**.

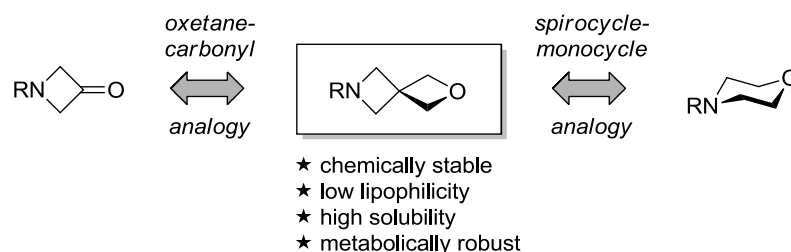
<sup>87</sup> P. J. Hamzik, J. D. Brubaker, *Org. Lett.* **2010**, *12*, 1116-1119.

<sup>88</sup> Arylboroxines proved better than corresponding arylboronic acids due to reduced water-content in the reaction mixture that is responsible for hydrolyzing the starting sulfinyl imine.

RT.<sup>89</sup> In contrast to the procedure developed by the group at *Merck*, products could contain phenyl groups decorated with halogens, unprotected hydroxy groups, ketones, and amides. In addition to substituted oxetanes, also 3-amino-3-aryl azetidines were accessible following this protocol and Boc-protected 3-(*tert*-butylsulfinimino)azetidine as starting point.

## 1.6 Spirocycles

As part of a series of oxetane-spirocyclic compounds, WUITSCHIK and co-workers synthesized the oxetane analogue of azetidin-3-one yielding a compound based on the 2-oxa-6-azaspiro[3.3]heptane construct.<sup>77c</sup> Surprisingly, this compound (specifically the *N*-piperonyl substituted version) exhibited extraordinary properties. While it was chemically stable (in contrast to *N*-piperonyl azetidine, which readily decomposes upon storage), it also exhibited a highly desirable pharmacokinetic profile:  $pK_a$  of amine = 8.0,  $\log P = 1.2$ , Sol. = 100 000  $\mu\text{mol ml}^{-1}$ ,  $hCL_{\text{int}} = 3 \text{ min}^{-1} \text{ mg}^{-1} \mu\text{l}$ . These properties alone render this building block attractive for its use in medicinal chemistry. But what makes the structural entity even more eye-catching is its resemblance to the ubiquitously used morpholine ring.



**Figure 16.** 2-Oxa-6-azaspiro[3.3]heptane, a new building block for drug discovery.

Even though the *homospirormorpholine* system has been known for quite some time,<sup>90</sup> only two patents with structures that contained this framework were filed before 2008.<sup>91</sup> Since that time, 19 patents from a number of pharmaceutical companies (e.g., *Roche*, *Genentech*, *AstraZeneca*, *Pfizer*, *Janssen*, *Gilead*) have appeared.

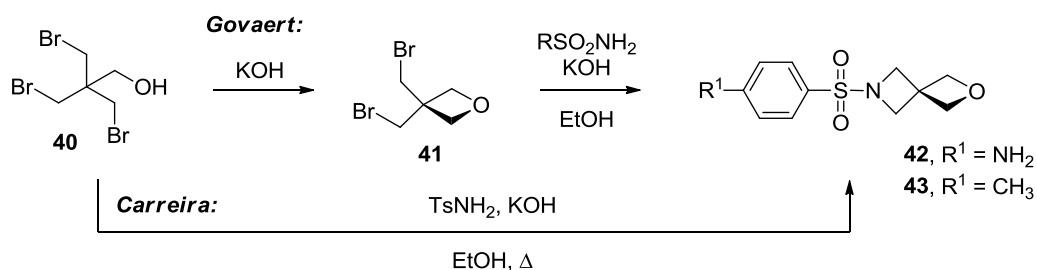
The original synthesis of this spirocycle reported by HOSTE and GOVÆRT makes use of tri-bromopentaerythritol as starting material and delivers the target compound **42** in 2 steps

<sup>89</sup> H. H. Jung, A. W. Buesking, J. A. Ellman, *Org. Lett.* **2011**, *13*, 3912-3915.

<sup>90</sup> a) J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 16-27; b) J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 157-166.

<sup>91</sup> a) D. Miller, P. Clark, T. Melton (Beecham Group Ltd.), GB 1169027, **1969**; b) C. G. Krespan (C. G. Krespan), US 3952015, **1976**.

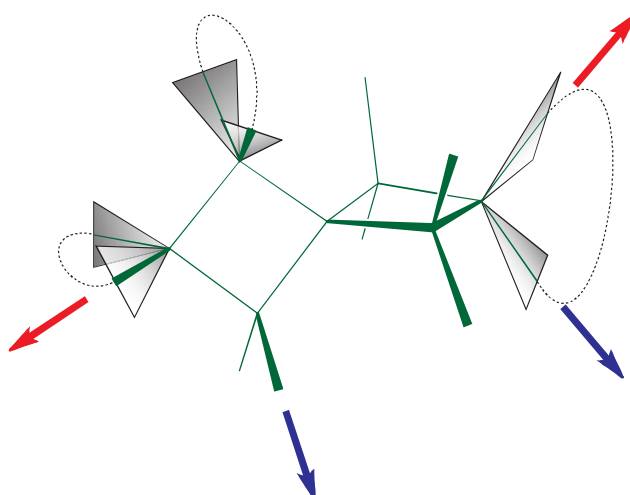
(Scheme 3). The improved protocol from our group makes the isolation of the dibromide intermediate **41** superfluous, and converts **40** directly into **43** by treatment with  $\text{TsNH}_2$  and excess base (58% yield).<sup>77c</sup>



**Scheme 3.** Syntheses of sulfonylated 2-oxa-6-azaspiro[3.3]heptanes.

Subsequently, the tosyl group was removed ( $\text{Mg}$ ,  $\text{MeOH}$ ) and the resulting amine trapped in the form of an ammonium oxalate salt. This compound served as an ideal building block for the introduction of a terminal polar group onto a pharmacophore.

The lack of precedence in the literature and the encouraging properties of the homospiro-morpholine system led us to consider the exploration of other members of this family. By looking at the basic framework, spiro[3.3]heptane, one can identify characteristic features of this scaffold. The molecule itself is achiral and also a significant amount of substituted versions remain achiral. A large portion of the surrounding space can be reached by the attachment of vectors to the core structure. This property is highlighted in Figure 17.

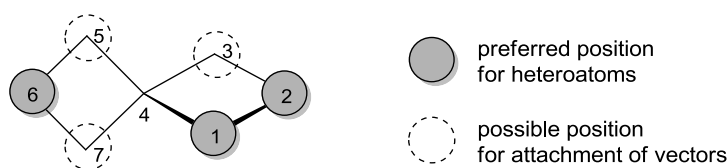


**Figure 17.** Illustrative picture of the spiro[3.3]heptane core. PM3-optimized structure that avoids puckered conformations (ChemBio3D 12.0; CambridgeSoft).

At selected positions, the available vectorial space is indicated with gradient triangles and dotted curves. The colored arrows display two possible situations, where clearly distinct portions of the surrounding sphere can be reached with appropriate head groups. Red arrows stand

for vectors that reach roughly opposite sides of the sphere, whereas the blue arrows point in the same octant. By choosing appropriate chemical entities, essentially the entire surrounding space is accessible from the same scaffold. Even though the spiro[3.3]heptane core may seem rigid, it does not have unique conformational locks (low-lying energetic minima) and thus can adopt a number of similarly populated conformations independently on both sides of the ring system. This behavior differs significantly from cyclohexanes that adopt chair- or boat-like conformations, but rarely want to deviate from those energetic minima. A more detailed analysis of these conformational aspects is discussed in Chapter 2, section 2.6.

The picture shown in Figure 17 illustrates the situation for the carbocyclic framework, but due to their polarity heteroatom-substituted systems (like in **43**) would be more desirable in a medicinal chemistry environment. Furthermore, their synthesis is envisaged to be more easily achieved due to the nucleophilic nature of heteroatoms in combination with appropriate synthetic building blocks. Moreover, heteroatoms such as oxygen, nitrogen and sulfur (in most cases) cannot form a stereogenic center and thus enantiomeric or diastereomeric product mixtures can be excluded.



**Figure 18.** Preferred positions for heteroatoms and vectors.

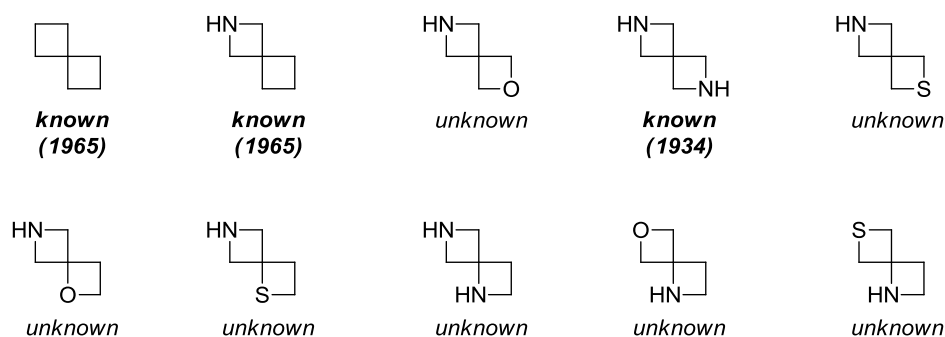
Heteroatoms are best situated at positions 2 (or 1) and/or 6; accordingly, the so obtained structures are achiral, should be chemically stable, and their synthesis should not require lengthy sequences. Investigations would be necessary to find out whether in this system neighboring (e.g., positions 1 & 2) or geminal (1 & 7) heteroatomic relationships would be allowed. The remaining carbon atoms (except for the fully substituted spirocenter 4) give the opportunity to decorate with suitable vectors.

By the appropriate selection of mounting positions the spiro[3.3]heptane framework can be used as a terminal or internal construction element for the creation of designed drug candidates. Its versatility in terms of structural features (orientation of exit vectors, distinct patterns for heteroatoms possible) and conformational aspects (can adopt a number of predictable conformations) would be the basis for its use as a novel privileged scaffold (see section 1.2).



## 1.7 Reaching Novel Chemical Space

By virtue of the unimaginable number of theoretically possible organic molecules, chemical space can be viewed analogous to the universe, where, instead of molecules, stars populate the available space. In accordance with the statement by LIPINSKI and HOPKINS in a key review article<sup>92</sup> that “chemical space is for all practical purposes infinite and limited only by the chemist’s imagination” is the fact that spirocyclic building blocks have been ignored by the pharmaceutical community for many years. Given the apparent low molecular complexity and the equally small molecular weight of systems based on the spiro[3.3]heptane construct, one would have predicted to find these members fully disclosed in the appropriate literature 180 years after WÖHLER’s landmark synthesis of urea,<sup>93</sup> a molecule that is only approximately a third smaller in molecular weight than 2-oxa-6-azaspiro[3.3]heptane. Quite the contrast; before the year 2000 out of 10 simple spiro[3.3]heptanes with permutations of heteroatoms in reasonable positions, only 3 were known (Figure 19)!<sup>94</sup> It is envisioned that an amplitude of chemical space can and will be conquered by exploring the galaxy of spiro[3.3]heptanes, and research will show whether some ‘chemical planets’ even allow for a settlement of medicinal chemistry.



**Figure 19.** Precedence for simple members of the spiro[3.3]heptane family by the year 2000.

<sup>92</sup> C. Lipinski, A. Hopkins, *Nature* **2004**, 432, 855-861.

<sup>93</sup> F. Wöhler, *Annalen der Physik* **1828**, 88, 253-256.

<sup>94</sup> *Reaxys* (www.reaxys.com) search for these compounds not including substructures. Search performed on July 27<sup>th</sup> 2011.



**2**

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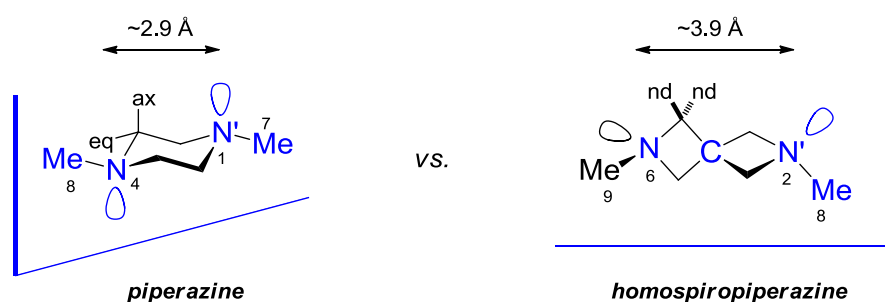
**Linear Spirocycles**

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## 2.1 2,6-Diazaspiro[3.3]heptanes

### 2.1.1 Introduction

The analogy of 2-oxa-6-azaspiro[3.3]heptane to the morpholine ring system (see introduction chapter) triggered us to look at 2,6-diazaspiro[3.3]heptanes as surrogates for the ubiquitously employed piperazines (Figure 20). Due to the obvious similarities of these building blocks (cyclic diamines, four methylene groups, nitrogens placed on opposite sides of the framework, overall shape) and the extra carbon of the spirocycle we call the latter *homospiropiperazine*. Apart from the structural similarities there are also a few striking differences between the two fragments. The N-N' distance in piperazine is approximately 2.9 Å,<sup>95</sup> whereas in the homospiropiperazine the nitrogen atoms are roughly 3.9 Å apart. Furthermore, the arrangement of substituents on the carbon framework as well as on the terminal nitrogen atoms is vastly different. In the piperazine unit substituents on the nitrogen atoms (e.g., methyl groups) are usually pseudo-equatorially oriented and would both be in the same plane defined by C(8)-N-N'. In contrast, in the spirocycle the other substituent bearing C(9), clearly sticks out of the imaginary plane defined through C(8)-N-N' (in disregard of possible ring puckering). Moreover, there are no distinct axial or equatorial arrangements of substituents on the carbon skeleton of the homospiropiperazine. Unique conformational aspects of the spirocyclic framework will be discussed later in the chapter (section 2.6).



**Figure 20.** Structural comparison of piperazine with its homospiro surrogate (eq: equatorial, ax: axial, nd: not defined).

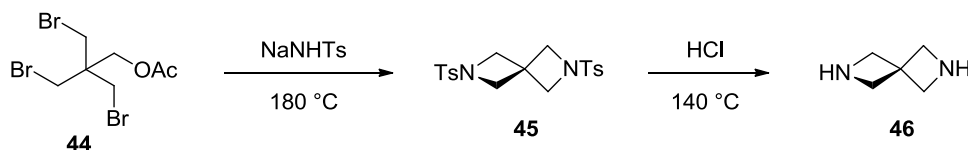
Although the existence of the parent 2,6-diazaspiro[3.3]heptane has been known since a report by LITHERLAND and MANN in 1938,<sup>96</sup> it has been largely neglected by the chemical com-

<sup>95</sup> Calculated using *CambridgeSoft ChemBio3D Ultra 11.0*.

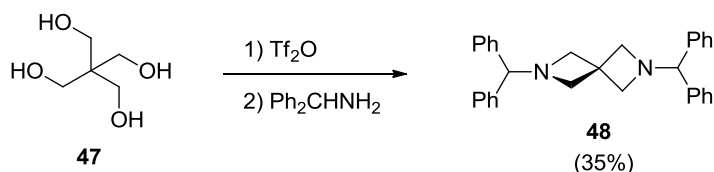
<sup>96</sup> a) F. G. Mann, A. Litherland, *Nature* **1938**, *141*, 789-790; b) A. Litherland, F. G. Mann, *J. Chem. Soc.* **1938**, 1588-1595.

munity.<sup>97</sup> Only after the year 2000 did the unusual looking framework gain new attention, when papers about novel derivatives were published by groups at *Merck & Co.*<sup>98</sup> and *AstraZeneca*.<sup>99</sup> The syntheses generally rely on pentaerythritol starting materials (Scheme 4). LITHERLAND and MANN treated tribromopentaerythritol acetate (**44**) with sodium *p*-toluenesulfonamide to arrive at the bis(sulfonamide) intermediate **45**, which was subsequently hydrolyzed with hydrochloric acid to give the free diamine **46**.

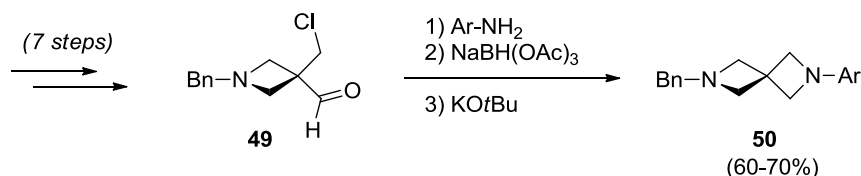
**Litherland and Mann (1938):**



**Merck & Co. (2006):**



**AstraZeneca (2007):**



**Scheme 4.** Previous reports of syntheses of 2,6-diazaspiro[3.3]heptanes.

The research group at *Merck & Co* was able to obtain bis(benzhydryl)-protected homospiperazine **48** following tetratriflation of pentaerythritol (**47**) and displacement reactions with diphenylmethanamine in an overall yield of 35%. The first synthesis of differentiated 2,6-diazaspiro[3.3]heptanes was reported by a group at *AstraZeneca*. Their route involved seven synthetic steps to arrive at the crucial chloroaldehyde intermediate **49**, which was condensed with anilines, and the products subsequently reduced and ring-closed to afford the targeted compounds in 60-70% yield. Although these approaches gave access to the spirocyclic frame-

<sup>97</sup> Two of the few other reports: a) J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 157-166; b) W. Engel, W. Eberlein, G. Trummilitz, G. Mihm, H. Doods, N. Mayer, A. de Jonge (Dr. Karl Thomae GmbH), EP 0417631 A2, **1990**.

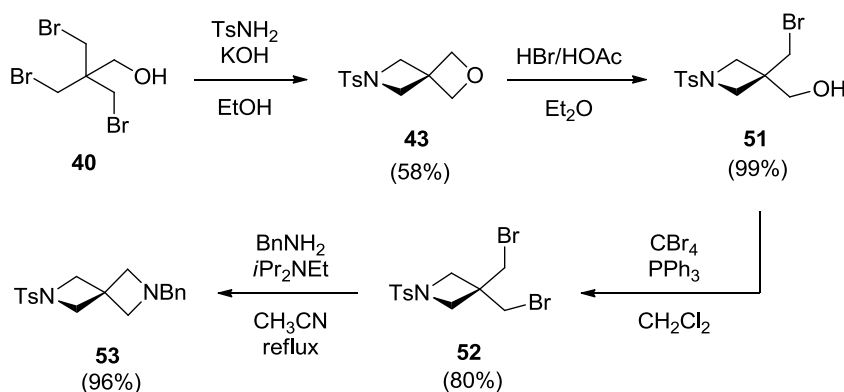
<sup>98</sup> M. C. Hillier, C. Y. Chen, *J. Org. Chem.* **2006**, *71*, 7885-7887.

<sup>99</sup> a) M. J. Stocks, D. Hamza, G. Pairaudeau, J. P. Stonehouse, P. V. Thorne, *Synlett* **2007**, 2587-2589; b) D. Hamza, M. J. Stocks, A. Decor, G. Pairaudeau, J. P. Stonehouse, *Synlett* **2007**, 2584-2586; c) M. J. Stocks, G. R. H. Wilden, G. Pairaudeau, M. W. D. Perry, J. Steele, J. P. Stonehouse, *ChemMedChem* **2009**, *4*, 800-808.

work, the preparative procedures that were characterized in part by harsh conditions, expensive reagents, lengthy sequences, or low yields would require modification, so that the spirocyclic system could be employed as a useful building block.

### 2.1.2 2,6-Diazaspiro[3.3]heptane as a New Building Block

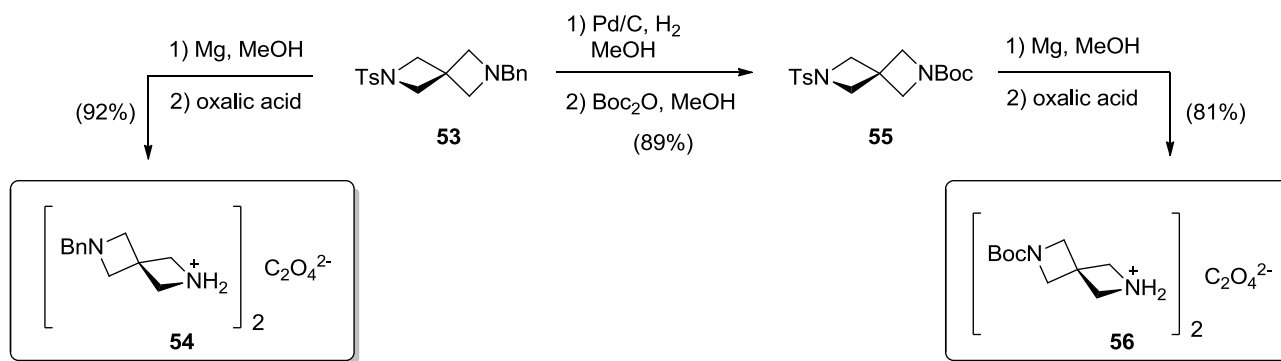
It had previously been shown in our group that tosyl-protected 2-oxa-6-azaspiro[3.3]heptane (**43**) is available in one step from tribromopentaerythritol (**40**), a compound that is used as a flame retardant and thus is available in bulk quantities.<sup>100</sup> HOSTE and GOVÆRT have shown that a similar oxetane can be opened with hydrobromic acid to afford a bromoalcohol. Indeed, when oxetane **43** was treated with a solution of HBr in acetic acid, the desired alcohol **51** was obtained in almost quantitative yield and did not require any further purification after work-up (Scheme 5). The alcohol was subsequently converted to a bromide using APPEL's conditions ( $\text{CBr}_4$ ,  $\text{PPh}_3$ ) affording the crucial dibromide **52**. Finally, treatment with benzylamine and  $i\text{Pr}_2\text{NEt}$  in acetonitrile at elevated temperatures gave differentially protected 2,6-diazaspiro[3.3]heptane **53** in good overall yield. This sequence can be run in multi-gram quantities without noticeable complications.



**Scheme 5.** Synthesis of differentially protected 2,6-diazaspiro[3.3]heptane **53**.

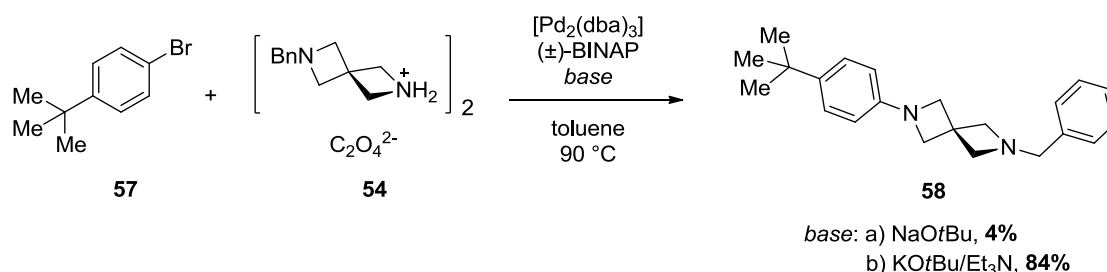
In order to arrive at a convenient building block that can be used in any standard amine functionalization reaction it was decided to have one amine end free (or trapped in the form of an ammonium salt) and to have the other protected with an easily removable group such as a benzyl or *tert*-butoxycarbonyl (Boc) group. Tosyl amide **53** can thus be converted either into the ammonium oxalate **54** or, after a protecting group exchange, to the synthetically most convenient compound, **56** (Scheme 6).

<sup>100</sup> See for example: J.-N. B. Bertrand (Labofina S.A.), US 4699943, **1987**. The best reported price for this compound (*eMolecules*, July 2011) is US\$ 500.-/25 kg (*BetaPharma*).



**Scheme 6.** Formation of homospiropiperazine building blocks.

This oxalate salt **56** (colorless fluffy solid, non-hygroscopic) can be stored at room temperature for years without any noticeable change. Furthermore, it can be applied with ease in most amine functionalization reactions. To demonstrate its utility, we studied its reactivity profile in arene amination reactions,<sup>101</sup> a setting that is commonly observed for piperazines in drug discovery.<sup>102</sup> Application of fairly standard conditions for a BUCHWALD-HARTWIG amination with a secondary amine (aryl bromide,  $[\text{Pd}_2(\text{dba})_3]$ , ( $\pm$ )-BINAP,  $\text{NaOtBu}$ , toluene, 90 °C) afforded the desired coupling product **58**, albeit in very low yield. Changing the base to a mixture of  $\text{KOtBu}$  (3.0 equiv) and triethylamine (a few drops; *ca.* 0.5 equiv) then afforded the aniline in a dramatically increased yield under otherwise unchanged conditions (Scheme 7).



**Scheme 7.** Screening for optimal conditions in arene amination reactions with ammonium oxalate **54**.

This protocol was slightly altered (110 °C instead of 90 °C) for its use in aminations with the Boc-protected oxalate salt **56**; and subsequently, a scope was defined for a variety of aryl bromides (Table 4). Electronically neutral arenes such as 2-bromotoluene or 1-bromo-4-(*tert*-butyl)benzene gave the coupling products in highest yields (91-97%; entries 1 and 2), but also a variety of electron-rich, electron-poor, and sterically encumbered arenes afforded the anilines in

<sup>101</sup> For recent reviews, see: a) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, 576, 125-146; b) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, 219, 131-209. Consider also a recent “user’s guide” for Buchwald-Hartwig aminations: D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, 2, 27-50.

<sup>102</sup> a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, 103, 893-930, and references therein; b) F. Kerrigan, C. Martin, G. H. Thomas, *Tetrahedron Lett.* **1998**, 39, 2219-2222; c) S. H. Zhao, A. K. Miller, J. Berger, L. A. Flippin, *Tetrahedron Lett.* **1996**, 37, 4463-4466.

useful quantities (63–89%; entries 3–8). The most difficult substrates under these conditions were 2-bromobenzonitrile (61%; entry 9), ethyl 4-bromobenzoate (56%; entry 10), and 3-bromopyridine (34%; entry 11).

**Table 4.** BUCHWALD-HARTWIG amination reactions with building block **56**.<sup>[a]</sup>

Ar-Br +  $\left[ \text{BocN} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{NH}_2^+ \right]_2 \text{C}_2\text{O}_4^{2-}$   $\xrightarrow[\text{toluene, 110 }^\circ\text{C}]{[\text{Pd}_2(\text{dba})_3], (\pm)\text{-BINAP}, \text{KOtBu/Et}_3\text{N}}$  Ar-N  $\begin{array}{c} \diagup \\ \diagdown \end{array}$  NBoc

**56** **59a-k**

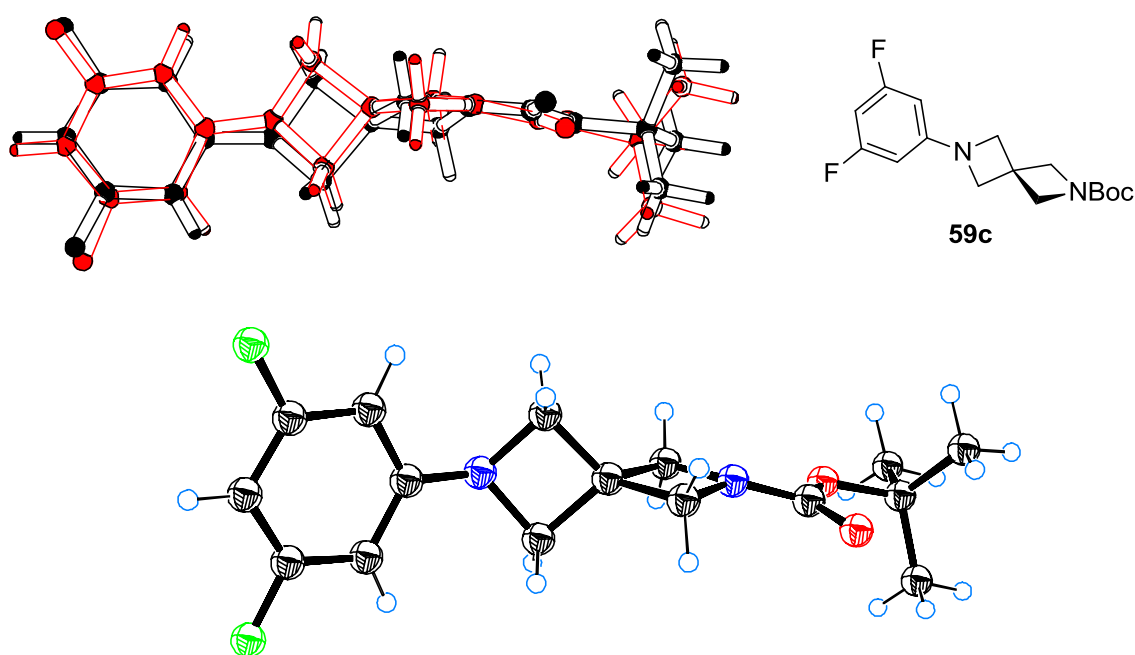
entry	aryl bromide	time	mol % Pd	yield
1		21 h	2	97%
2		17 h	2	91%
3		22 h	2	89%
4		13 h	5	83%
5		13 h	2	77%
6		22 h	4	64%
7		21 h	5	63%
8		21 h	2	63%
9		12 h	2	61%
10 <sup>[b]</sup>		46 h	4	56%
11		22 h	5	34%

[a] Typical reaction conditions: aryl bromide (0.4 mmol, 1.0 equiv), **56** (0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (1–2.5 mol %), (±)-BINAP (1.5/Pd), KOtBu (3.0 equiv), Et<sub>3</sub>N (0.5 equiv), toluene (5 ml), 110 °C, 12–46 h.

[b] Cs<sub>2</sub>CO<sub>3</sub> used as base instead of KOtBu.



The observation that all coupling products were crystalline solids motivated the preparation of single crystals of **59c** that were suitable for analysis by X-ray crystallography. The obtained structure is represented in Figure 21. A few notes on the structure: the unit cell consists of two unidentical (but very similar, see overlay in Figure 21) conformations of the molecule, the distance between the two nitrogen atoms is 4.20 Å, the aniline nitrogen is pyramidal with a hinge angle of 36.4°, whereas the carbamate nitrogen shows less pyramidalization (14.5°), and the azetidine rings are only slightly puckered (9.5° and 3.1°).



**Figure 21.** Top: overlay of the two conformations; bottom: ORTEP representation of 2,6-diazaspiro[3.3]heptane **59c** with ellipsoids at 50% probability.

## 2.2 Evaluation of Azaspiro[3.3]heptanes

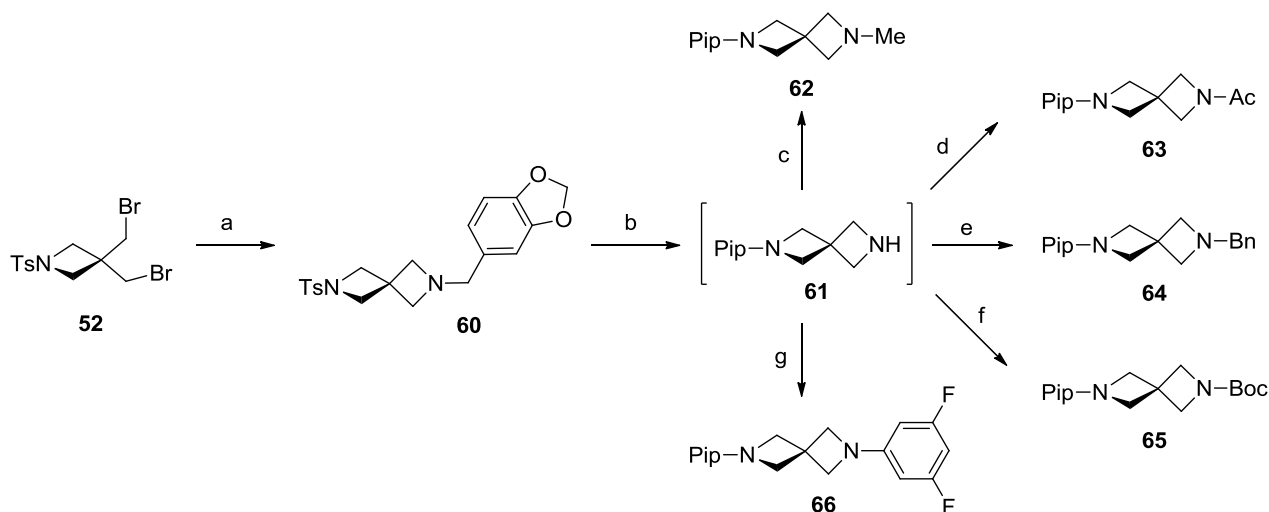
### 2.2.1 Synthesis

With a reliable synthetic route in hand for the synthesis of 2,6-diazaspiro[3.3]heptane building blocks we became interested in defining their properties relevant to drug discovery. These ADME properties include amine basicities ( $pK_a$ ), lipophilicities ( $\log D$ ), solubilities (Sol.), and metabolic clearance rates ( $CL_{int}$ ). For comparison reasons<sup>103</sup> and in order to facilitate analytical measurements carried out at *F. Hoffmann-La Roche*, Basel, we chose to tag all model compounds

<sup>103</sup> See the work by WUITSCHIK, ref. 77.

with a common piperonyl residue. The compounds were chosen in a way that common groups found in drug discovery (aryl sulfonamide, alkyl, benzyl, aryl, carbamate, amide) would populate the other amine of the homospirropiperazine and that compounds would fill a wide range of expected lipophilicities. Furthermore, we targeted also azaspirocycles with CH<sub>2</sub>, S, SO or SO<sub>2</sub> in place of the adjacent amine. These compounds would be compared with the respective monocyclic counterparts (piperazine, piperidine, and thiomorpholine).

Dibromide **52** seemed to be the optimal starting point for the synthesis of various derivatives (Scheme 8). Treatment of **52** with piperonylamine and *i*Pr<sub>2</sub>NEt in refluxing acetonitrile gave the first target compound **60** in 90% yield. In a first step the tosyl group was removed using excess Mg powder in MeOH (with activation by ultrasonication), and the free amine was subsequently decorated with common amine residues in a second step. Amine **61** was methylated in a reductive amination with aqueous formaldehyde to give methylamine **62** (71% yield). Acetamide **63** was obtained following treatment of **61** with acetic anhydride and triethylamine. Reductive amination of **61** with benzaldehyde and sodium triacetoxyborohydride afforded benzylamine **64** in 62%. Treatment of the intermediate **61** with Boc<sub>2</sub>O gave *tert*-butyl carbamate **65**, and aniline **66** was synthesized in a BUCHWALD-HARTWIG amination of **61** with 2,5-difluorobromobenzene.



**Scheme 8.** Synthesis of various 2,6-diazaspiro[3.3]heptane model systems. Pip = piperonyl. Reagents and conditions: a) piperonylamine, *i*Pr<sub>2</sub>NEt, CH<sub>3</sub>CN, reflux, 90%; b) Mg, MeOH, ultrasound; c) CH<sub>2</sub>O, NaBH(OAc)<sub>3</sub>, 71% (2 steps); d) Ac<sub>2</sub>O, Et<sub>3</sub>N, 71% (2 steps); e) PhCHO, NaBH(OAc)<sub>3</sub>, 62% (2 steps); f) Boc<sub>2</sub>O, Et<sub>3</sub>N, 66% (2 steps); g) 1-Br-3,5-F<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, (±)-BINAP, [Pd<sub>2</sub>(dba)<sub>3</sub>], KOtBu, 69% (2 steps).

The straightforward introduction of substituents on the carbon framework of the homospirropiperazine building block would be highly desirable. Since these carbon-centered positions are  $\alpha$  to an amine, directed lithiations with subsequent treatment with an electrophile could generate

the desired substituted azetidines starting from an unsubstituted, achiral 2,6-diazaspiro[3.3]heptane. Using suitable directing groups, such as a *tert*-butyl carbamate or a pivalamide, with conditions developed by BEAK,<sup>104</sup> SEEBACH,<sup>105</sup> and others,<sup>106</sup> the synthesis of substituted azetidines seemed viable. Furthermore, reports of enantioselective deprotonations and functionalizations of cyclic amines<sup>107</sup> would make a stereoselective substitution on the spirocycles possible. At the time of consideration only one example with an azetidine (activating group: triphenylacetamide) had been reported,<sup>105</sup> although many examples were known for the derivatization of piperidines and pyrrolidines.

**Table 5.** Selected examples for the attempted lithiation-electrophilic substitution sequence on spirocycles.

entry	X	R	base / conditions	electrophile / conditions	result
1	N- <i>t</i> Bu	O- <i>t</i> Bu	<i>sec</i> -BuLi, TMEDA THF, -78 °C	TMSCl -78 °C → RT	decomposition
2	N- <i>t</i> Bu	CPh <sub>3</sub>	<i>t</i> BuLi, THF -40 °C → -10 °C	TMSCl -40 °C → -10 °C	some starting material recovered
3	N-Bn	<i>t</i> Bu	<i>sec</i> -BuLi, TMEDA Et <sub>2</sub> O, -78 °C	PhCHO -78 °C → RT	decomposition
4	O	O- <i>t</i> Bu	<i>sec</i> -BuLi, TMEDA THF, -78 °C	CD <sub>3</sub> OD -78 °C → RT	53% starting material recovered

A few simple starting materials were prepared (*cf.* Chapter 9, Experimental Part for details) and subjected to the conditions that were reported for the functionalization of pyrrolidines. Table 5 summarizes some of the efforts. Unfortunately, the spirocycles were reluctant to undergo directed lithiations and electrophilic trapping: either starting materials could be reisolated, or decomposition was observed. Thus, an attempted lithiation of a *tert*-butyl-substituted and Boc-protected diazaspiro[3.3]heptane using *sec*-BuLi and TMEDA at low temperature with subsequent treatment with TMSCl afforded only decomposition products (entry 1). The directing group was changed to a triphenylacetyl group, and lithiation was conducted using *t*BuLi, but a similar outcome was observed (entry 2). A substrate bearing a benzyl group on one end and a pivaloyl group on the other was first treated with *sec*-BuLi and TMEDA in Et<sub>2</sub>O, and then with

<sup>104</sup> P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109-1117.

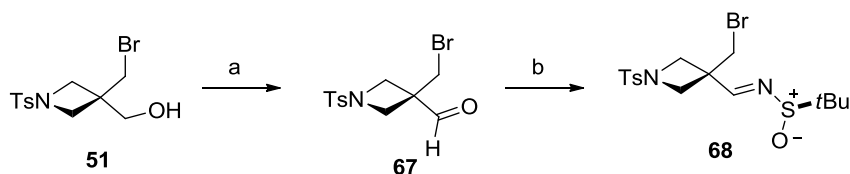
<sup>105</sup> W. Wykypiel, J. J. Lohmann, D. Seebach, *Helv. Chim. Acta* **1981**, *64*, 1337-1346.

<sup>106</sup> For a review, see: P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984**, *84*, 471-523.

<sup>107</sup> Review on enantioselective deprotonations: D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2283-2316.

PhCHO, but again decomposition products were seen by  $^1\text{H}$  NMR spectroscopy of the unpurified reaction product (entry 3). Also a Boc-protected homospirromorpholine was reluctant to undergo any lithiation/electrophilic trapping, as a significant amount of starting material was recovered (entry 4). Not even small quantities of the desired product could be isolated in any of the attempted functionalization reactions. In 2010, HODGSON and KLOESGES published their successful  $\alpha$ -functionalization of *N*-thiopivaloylazetidione.<sup>108</sup> It remains yet to be investigated, whether this directing group could be used for the lithiation-electrophilic substitution of spirocyclic systems.

Since the above mentioned strategy was not successful, an alternative route to the same spirocycles was considered. ELLMAN and co-workers have disclosed in a number of papers the generation of chiral amines from *tert*-butanesulfinyl imines.<sup>109</sup> Their strategy would serve us to introduce one substituent along the general pathway towards homospirropiperazines. For this reason, bromoalcohol **51** was oxidized to the corresponding aldehyde **67** using SWERN's conditions (DMSO, oxalyl chloride,  $\text{Et}_3\text{N}$ ; 91% yield of the aldehyde), and subsequent condensation with the (*R*)-ELLMAN-auxiliary using  $\text{Ti}(\text{OEt})_4$  in THF<sup>110</sup> gave sulfinyl imine **68** in good overall yield (Scheme 9).



**Scheme 9.** Formation of sulfinyl imine **68**. Reagents and conditions: a) DMSO,  $(\text{COCl})_2$ ,  $\text{Et}_3\text{N}$ , 91%; b) (*R*)-*t*Bu-S(O)NH<sub>2</sub>,  $\text{Ti}(\text{OEt})_4$ , THF, 79%.

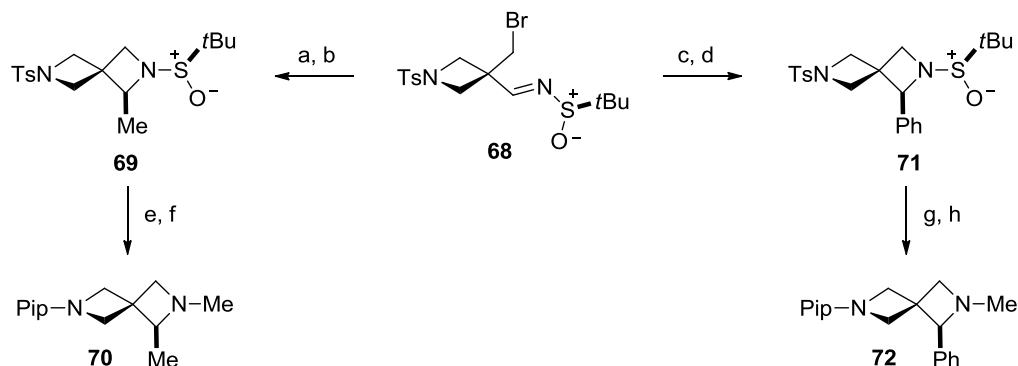
Lithiated nucleophiles such as MeLi or PhLi readily added to the electrophile **68** at low temperatures to give the addition products in high yields but modest diastereoselectivities (52:48 d.r. and 73:27 d.r., respectively) (Scheme 10). Fortunately though, diastereomers were separable either by column chromatography or recrystallization. Therefore, after ring closure promoted by  $\text{KO}^t\text{Bu}$  in THF at 0 °C, the diastereomerically pure substituted homospirropiperazines **69** and **71** were isolated in overall yields of 40% (Me) and 73% (Ph). These compounds were then converted to the piperonyl- and methyl-decorated target compounds **70** and **72** in a four-step sequence: (1) removal of the tosyl group with Mg powder in MeOH, (2) reductive amination of

<sup>108</sup> D. M. Hodgson, J. Kloesges, *Angew. Chem. Int. Ed.* **2010**, *49*, 2900-2903.

<sup>109</sup> For a comprehensive review, see: M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.

<sup>110</sup> G. C. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278-1284.

piperonal with the formed amine using sodium triacetoxyborohydride, (3) removal of the *tert*-butanesulfinyl group with anhydrous HCl, and (4) methylation of the released amine using aqueous formaldehyde and NaBH(OAc)<sub>3</sub>.



**Scheme 10.** Synthesis of C-substituted diazaspiro[3.3]heptanes. Pip = piperonyl. Reagents and conditions: a) MeLi, THF,  $-78\text{ }^{\circ}\text{C}$ , 52:48 d.r., 93% (combined); b) KOtBu, THF,  $0\text{ }^{\circ}\text{C}$ , 84% (40% over 2 steps); c) PhLi, THF,  $-78\text{ }^{\circ}\text{C}$ , 73:27 d.r.; d) KOtBu, THF,  $0\text{ }^{\circ}\text{C}$ , 73% (2 steps; combined yield of both diastereomers over the 2 steps: quantitative); e) Mg powder, MeOH, ultrasound, then piperonal, NaBH(OAc)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 71% (2 steps); f) HCl, THF, then CH<sub>2</sub>O, Et<sub>3</sub>N, NaBH(OAc)<sub>3</sub>, 59% (2 steps); g) see (e), 66% (2 steps); h) see (f), 70% (2 steps).

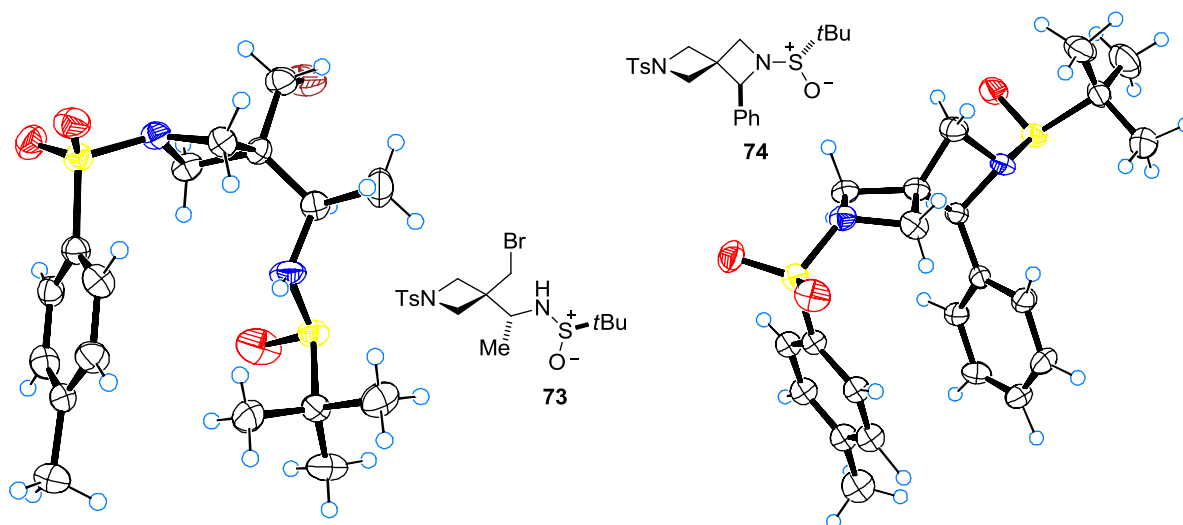
It is worth noting that in contrast to lithiated nucleophiles (MeLi, PhLi, BuLi, TMSCLi, 2-furyllithium), methylmagnesium bromide (with BF<sub>3</sub>·OEt<sub>2</sub>) failed to add to the sterically hindered electrophile ( $-78\text{ }^{\circ}\text{C} \rightarrow 40\text{ }^{\circ}\text{C}$ ),<sup>111</sup> and only starting material was reisolated. Only with forcing conditions employing AlMe<sub>3</sub> ( $-78\text{ }^{\circ}\text{C} \rightarrow \text{RT}$ ) some of the addition product ( $\sim 40\%$ ; diastereomeric mixture of addition product and ring-closed product, as determined by <sup>1</sup>H NMR spectroscopy of the unpurified reaction product) was formed.

It was attempted to improve the diastereomeric selectivity in the addition of methyllithium to the ELLMAN imine using additives (BF<sub>3</sub>·OEt<sub>2</sub>, TMEDA, sparteine), a different solvent (toluene), or by going to lower temperatures ( $-100\text{ }^{\circ}\text{C}$ ), but a significant improvement was not achieved (d.r. between 45:55 and 55:45 without a clear trend; d.r. determined by <sup>1</sup>H NMR analysis of the unpurified reaction products).

The absolute and relative stereochemistry of the products from the nucleophilic addition to the sulfinyl imine **68** was defined using X-ray crystallography. Samples of the first eluting compound during flash chromatography after addition of MeLi to **68** were recrystallized to give suitable crystals for X-ray analysis. For phenyl-substitution, suitable crystals were obtained

<sup>111</sup> For a similar steric environment, see: Z. X. Han, D. Krishnamurthy, D. Pflum, P. Grover, S. A. Wald, C. H. Senanayake, *Org. Lett.* **2002**, *4*, 4025–4028.

from the minor diastereomer after ring closure, corresponding to the structure **74**.<sup>112</sup> The results are shown in Figure 22.



**Figure 22.** ORTEP-representations (ellipsoids at 50% probability) of X-ray structures of addition products.

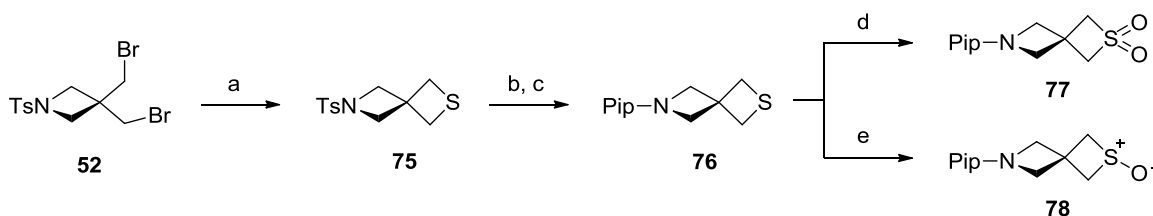
Whereas the obtained structural data from **73** does not reveal significant surprises, the situation for **74** is much more interesting. In spirocycle **74**, the distance between the two nitrogen atoms is 4.19 Å and the phenyl-bearing ring is puckered by 26.5°. Interestingly, the other azetidine ring can be considered nearly flat (puckering 11.1°), even though the nitrogen shows significant pyramidalization. The observed preferred sulfonamide conformation leads to an intriguing alignment of aryl substituents. These conceivable pharmacophores display an almost parallel orientation along the same direction, and ring centroids are separated by 4.06 Å.

Access to azathiaspirocycles was granted from the common dibromide **52**. It was converted to the corresponding thietane **75** (86%) by treatment with sodium sulfide trihydrate in a mixture of CH<sub>3</sub>CN and H<sub>2</sub>O (10:1) at 50 °C for 3 h (Scheme 11). This solvent system gave better results than the use of only CH<sub>3</sub>CN or DMF, which both gave lower yields and more (possibly polymeric) side products. The tosyl group was removed (Mg, MeOH) and the amine was tagged with a piperonyl residue (piperonal, NaBH(OAc)<sub>3</sub>) to afford *homospirothiomorpholine* **76** in 70% over three steps. Conversion to the sulfone **77** (99%) was best achieved using potassium osmate dihydrate (5 mol %) and *N*-methylmorpholine-*N*-oxide (NMO; 2.5 equiv).<sup>113</sup> More standard conditions for the conversion of sulfides into the corresponding sulfones in the presence of a

<sup>112</sup> The product shown here was obtained after addition of PhLi to the (*S*)-enantiomer of the ELLMAN imine (i.e., to *ent*-**68**) and subsequent ring-closure with KO<sup>t</sup>Bu, following analogous procedures as described for the (*R*)-enantiomer.

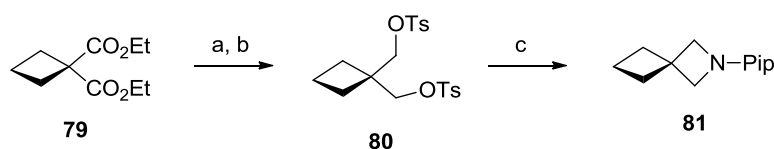
<sup>113</sup> For a similar procedure, see: J. A. Dodge, S. A. Frank, C. W. Hummel (Eli Lilly Co.), WO 2005073206, **2005**.

basic amine, i.e. tetrapropylammonium perruthenate (5 mol %) with NMO (3.0 equiv)<sup>114</sup> or H<sub>2</sub>O<sub>2</sub> (3.0 equiv) in acetic acid at 50 °C,<sup>115</sup> gave yields between 50% and 60%, in part due to substantial debenzoylation of the amine (formation of some piperonal was observed). Homospirothiomorpholine-*S*-oxide **78** was prepared by oxidizing **76** with aqueous H<sub>2</sub>O<sub>2</sub> (1.1 equiv) in AcOH.



**Scheme 11.** Synthesis of azathiaspirocycles. Pip = piperonyl. Reagents and conditions: a) Na<sub>2</sub>S, CH<sub>3</sub>CN/H<sub>2</sub>O (10:1), 50 °C, 86%; b) Mg powder, MeOH, ultrasound, then oxalic acid, 79%; c) piperonal, NaBH(OAc)<sub>3</sub>, Et<sub>3</sub>N, 89%; d) K<sub>2</sub>OsO<sub>4</sub>·2 H<sub>2</sub>O, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 99%; e) H<sub>2</sub>O<sub>2</sub>, AcOH, 68%.

The piperidine surrogate, 2-azaspiro[3.3]heptane, was envisioned to be made from a cyclobutane starting material. According to literature procedures, commercially available cyclobutane-1,1-diethyl dicarboxylate was reduced (LiAlH<sub>4</sub>) to the corresponding diol, which was subsequently treated with TsCl in pyridine to afford the known bis(tosylate) **80** (Scheme 12).<sup>116</sup> Ring closure was achieved under conditions similar to those described above for other azetidines (piperonylamine, *i*Pr<sub>2</sub>NEt, CH<sub>3</sub>CN) to afford the *homospirropiperidine* **81** in 69% yield.<sup>117</sup>



**Scheme 12.** Synthesis of azaspiro[3.3]heptane **81**. Pip = piperonyl. Reagents and conditions: a) LiAlH<sub>4</sub>, THF, 94%; b) TsCl, pyridine, 81%; c) piperonylamine, *i*Pr<sub>2</sub>NEt, CH<sub>3</sub>CN, reflux, 69%.

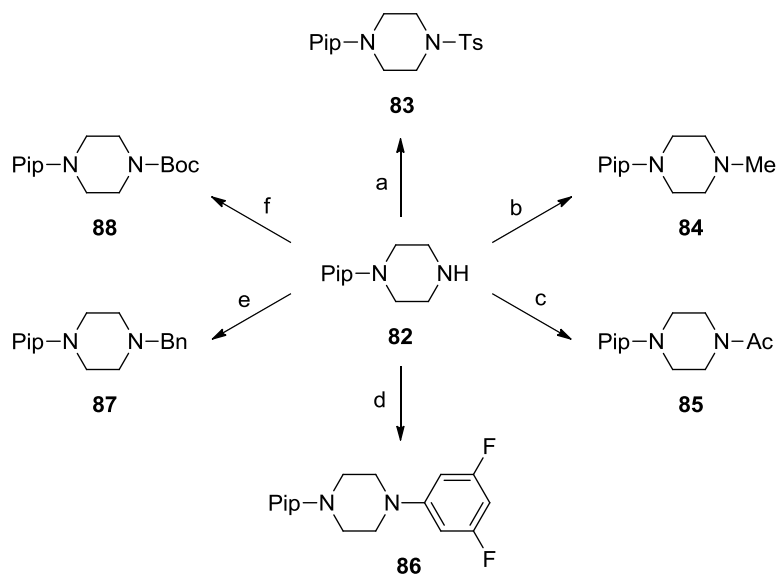
<sup>114</sup> R. K. Haynes, B. Fugmann, J. Stetter, K. Rieckmann, H. D. Heilmann, H. W. Chan, M. K. Cheung, W. L. Lam, H. N. Wong, S. L. Croft, L. Vivas, L. Rattray, L. Stewart, W. Peters, B. L. Robinson, M. D. Edstein, B. Kotecka, D. E. Kyle, B. Beckermann, M. Gerisch, M. Radtke, G. Schmuck, W. Steinke, U. Wollborn, K. Schmeer, A. Romer, *Angew. Chem. Int. Ed.* **2006**, *45*, 2082-2088.

<sup>115</sup> See for example: J. Zhou, R. He, K. M. Johnson, Y. P. Ye, A. P. Kozikowski, *J. Med. Chem.* **2004**, *47*, 5821-5824.

<sup>116</sup> J. Foos, F. Steel, S. Q. A. Rizvi, G. Fraenkel, *J. Org. Chem.* **1979**, *44*, 2522-2529.

<sup>117</sup> For other uses of 2-azaspiro[3.3]heptanes, see: a) T. A. Blizzard, F. DiNinno, J. D. Morgan, H. Y. Chen, J. Y. Wu, C. Gude, S. Kim, W. D. Chan, E. T. Birzin, Y. T. Yang, L. Y. Pai, Z. P. Zhang, E. C. Hayes, C. A. DaSilva, W. Tang, S. P. Rohrer, J. M. Schaeffer, M. L. Hammond, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3861-3864; b) M. Altman, M. Christopher, J. B. Grimm, A. Haidle, K. Konrad, J. Lim, R. N. Maccoss, M. Machacek, E. Osimboni, R. D. Otte, T. Siu, K. Spencer, B. Taoka, P. Tempest, K. Wilson, H. C. Woo, J. Young, A. Zabierek (Merck & Co., Inc., USA), WO 2008156726, **2008**. For the report of a similar building block, see: c) M. J. Meyers, I. Muizebelt, J. v. Wiltenburg, D. L. Brown, A. Thorarensen, *Org. Lett.* **2009**, *11*, 3523-3525.

The synthesis of the monocyclic counterparts (piperazines, piperidine and thiomorpholines) was required in order to compare the properties of the spirocycles with those of the traditional ring systems. Commercially available piperonyl piperazine (**82**) was converted to the desired piperazines **83–88** using standard protocols as described below (Scheme 13). Thus, commercially available piperonyl piperazine was treated with tosyl chloride and Et<sub>3</sub>N to afford tosyl amide **83** almost quantitatively. Methylation of the secondary amine in **82** was achieved under conditions for reductive amination (aqueous CH<sub>2</sub>O, NaBH(OAc)<sub>3</sub>; 92% yield of **84**). The acetamide **85** was obtained in 94% yield following treatment of **82** with acetic anhydride and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub>. A BUCHWALD-HARTWIG amination of 3,5-difluorobromobenzene with **82** gave aniline **86** in 42% (unoptimized). Finally, piperazine **82** was converted to the corresponding benzylamine **87** (BnBr, Et<sub>3</sub>N, CH<sub>3</sub>CN; 91% yield) and *tert*-butyl carbamate **88** (Boc<sub>2</sub>O, MeOH; 99% yield).



**Scheme 13.** Synthesis of simple piperazines. Reagents and conditions: a) TsCl, Et<sub>3</sub>N, THF, 99%; b) CH<sub>2</sub>O, NaBH(OAc)<sub>3</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 92%; c) Ac<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 94%; d) 1-Br-3,5-F<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, [Pd<sub>2</sub>(dba)<sub>3</sub>], (±)-BINAP, KOtBu, toluene, 110 °C, 42%; e) BnBr, Et<sub>3</sub>N, CH<sub>3</sub>CN, 91%; f) Boc<sub>2</sub>O, MeOH, 99%.

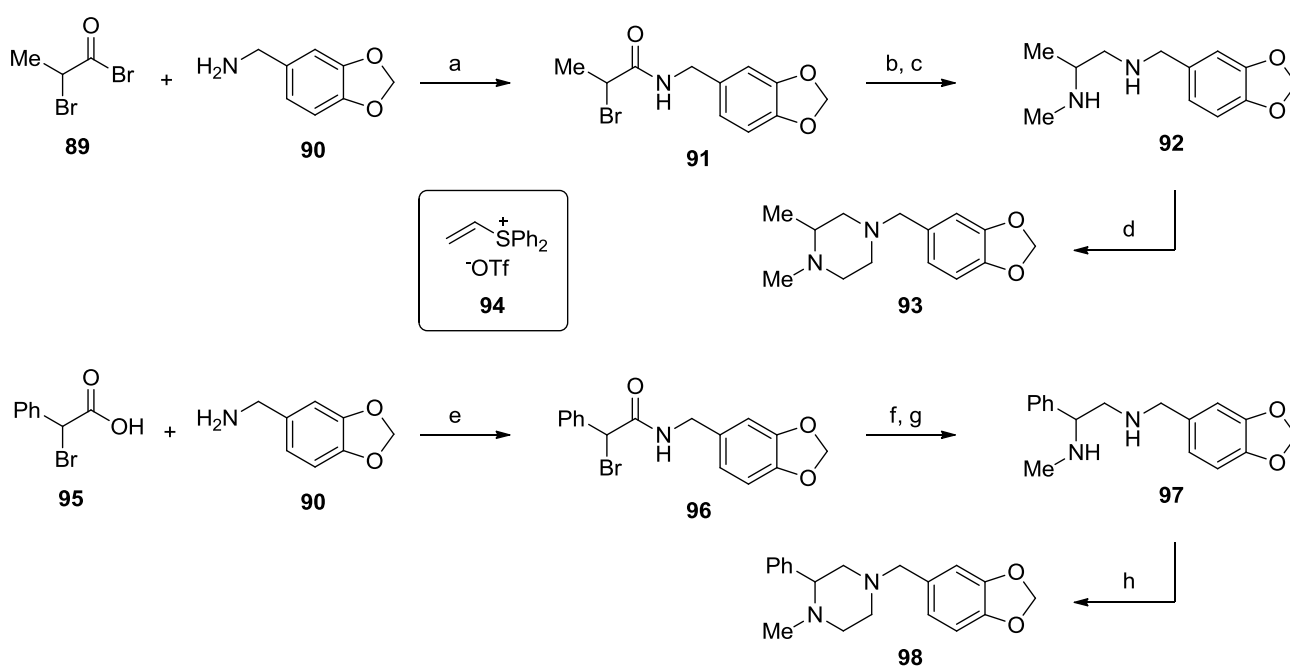
Me- and Ph-substituted piperazines were synthesized in racemic form (Scheme 14). Bromopropionyl bromide (**89**) and piperonylamine (**90**) were linked to give amide **91**. Displacement of the bromide with methylamine in the presence of Ag<sub>2</sub>O and ultrasound<sup>118</sup> afforded an intermediate, which was reduced to the diamine **92** using LiAlH<sub>4</sub> at 50 °C. Application of AGGARWAL's method for the construction of an ethylene bridge between two heteroatoms<sup>119</sup> gave access to

<sup>118</sup> F. D'Angeli, P. Marchetti, G. Cavicchioni, V. Bertolasi, F. Maran, *Tetrahedron: Asymmetry* **1991**, *2*, 1111-1121.

<sup>119</sup> M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2008**, *47*, 3784-3786. See also a more recent improved protocol: M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 257-260.

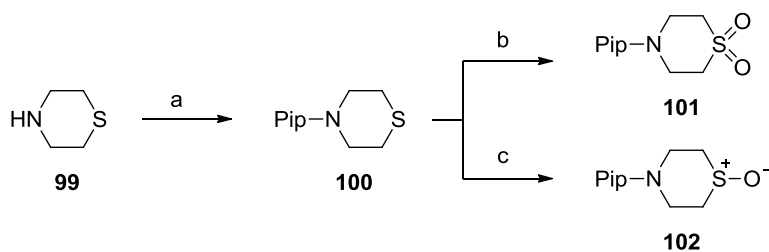


the desired methyl-piperazine **93**. Specifically, **92** was treated with sulfonium triflate **94** (prepared in three steps from 2-bromoethanol) and Et<sub>3</sub>N at RT to afford the cyclized product **93** in 76% yield over two steps. Similar conversions were used in the synthesis of phenyl-piperazine **98**. Consequently, carboxylic acid **95** was converted to the corresponding acid chloride (oxalyl chloride, substoichiometric DMF), which was reacted with piperonylamine (**90**) to afford amide **96** in 84% yield. A two-step protocol involving Ag<sub>2</sub>O-assisted displacement of bromide with methylamine and subsequent amide reduction (LiAlH<sub>4</sub>) yielded diamine **97** in 51%. Its treatment with the sulfonium salt **94** and a base resulted in the formation of the desired piperazine **98** (83% yield).



**Scheme 14.** Synthesis of methyl- and phenyl-substituted piperazines. Reagents and conditions: a) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 41%; b) CH<sub>3</sub>NH<sub>2</sub>, Ag<sub>2</sub>O, toluene, ultrasound, 75%; c) LiAlH<sub>4</sub>, THF, 50 °C; d) sulfonium triflate **94**, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 76% (2 steps); e) 95, (COCl)<sub>2</sub>, DMF, CH<sub>2</sub>Cl<sub>2</sub>, then 90, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 84%; f) CH<sub>3</sub>NH<sub>2</sub>, Ag<sub>2</sub>O, toluene, ultrasound, 79%; g) LiAlH<sub>4</sub>, THF, 50 °C, 65%; h) sulfonium triflate **94**, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 83%.

Finally, the thiomorpholines **100**, **101**, and **102** were constructed from thiomorpholine (**99**) with piperonal and NaBH(OAc)<sub>3</sub> and subsequent oxidation steps (Scheme 15). The use of catalytic amounts of potassium osmate and superstoichiometric NMO effected sulfur oxidation to give sulfone **101** in 80% yield. The analogous sulfoxide **102** was obtained by treatment of piperonyl thiomorpholine **100** with aqueous H<sub>2</sub>O<sub>2</sub> in acetic acid (92% yield).



**Scheme 15.** Synthesis of thiomorpholines. Pip = piperonyl. Reagents and conditions: a) piperonylamine,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 92%; b)  $\text{K}_2\text{OsO}_4 \cdot 2 \text{H}_2\text{O}$ , NMO,  $\text{CH}_2\text{Cl}_2$ , 80%; c)  $\text{H}_2\text{O}_2$ ,  $\text{AcOH}$ , 92%.

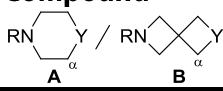
## 2.2.2 Properties

The synthesized spirocycles and their respective monocyclic counterparts were then tested in collaboration with KLAUS MÜLLER, BJÖRN WAGNER, HOLGER FISCHER, and FRANZ SCHULER (*F. Hoffmann-La Roche*, Basel) for their lipophilicities, aqueous solubilities, metabolic stabilities, and amine basicities (see the Experimental Part for details). The results are summarized in Table 6.

By looking at the determined  $\text{p}K_{\text{a}}$  values it becomes obvious that the amine of the spirocycle is generally more basic. On average over the entire series the  $\text{p}K_{\text{a}}$  of the spirocycle is 8.2, whereas the one of the monocyclic rings is 6.9 ( $\Delta\text{p}K_{\text{a}} = 1.3$ ). Pronounced differences can be observed in sulfone and sulfoxide pairs, where the  $\Delta\text{p}K_{\text{a}}$  are 2.7 and 1.7, respectively. Even though these values seem quite large, they fit nicely into an observed behavior. The decrease in basicity as a consequence of Y (the  $\sigma$  acceptor) is typically by a factor of 0.5-0.6 lower relative to the corresponding members of the six-membered monocyclic series. This observation is illustrated in Figure 23, where the common references are piperidine **103** and homospirpiperidine **81**, which have identical basicity. The observed regularity in basicity decrements holds true for the whole range of  $\text{p}K_{\text{a}}$  values, and is consistent with the fact that the  $\sigma$  acceptor exerts its influence through two paths of three  $\sigma$  bonds in the six-membered monocyclic series,<sup>120</sup> but through four  $\sigma$  bonds in the spirocyclic series. These data indicate a clear trend for the attenuation of the basicity by a neutral nitrogen functionality in  $\beta$ -position to an amine. Although differences in  $\text{p}K_{\text{a}}$  reductions are not dramatic, they are distinct and parallel chemical intuition (NTs > NAc > NBoc > NAryl). They are in agreement with previously assigned basicity reducing factors, as obtained from a few acyclic and cyclic amines,<sup>120</sup> as well as with recently reported data on

<sup>120</sup> M. Morgenthaler, E. Schweizer, A. Hoffmann-Roder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100-1115.

**Table 6.** Measured physicochemical and biochemical properties.

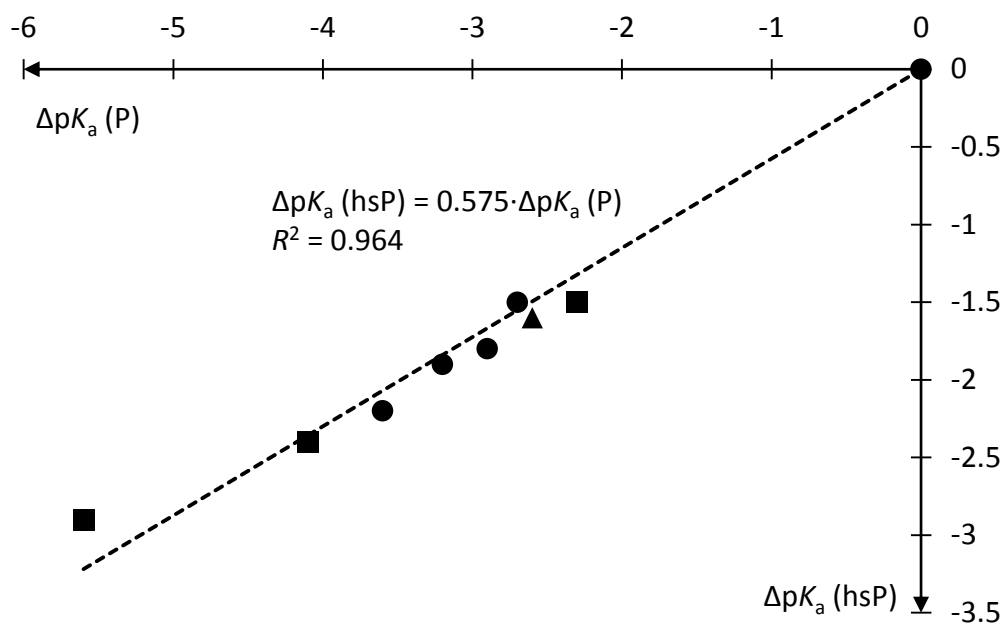
Compound <sup>[a]</sup> 		log <i>D</i> <sup>[b]</sup> (log <i>P</i> ) <sup>[c]</sup>	Sol. <sup>[d]</sup>	CL <sub>int</sub> (h/m) <sup>[e]</sup>	p <i>K</i> <sub>a</sub> <sup>[f]</sup>
<b>A</b> , Y = NTs	<b>83</b>	3.4 (3.4)	13	310/586	6.0
<b>B</b> , Y = NTs	<b>60</b>	2.5 (2.8)	23	25/114	7.4
<b>A</b> , Y = NMe	<b>84</b>	0.5 (1.1)	>59800	18/21	7.9
<b>B</b> , Y = NMe	<b>62</b>	-0.5 (1.6)	26800	12/4	9.5
<b>A</b> , Y = NAc	<b>85</b>	0.9 (1.0)	>14900	13/39	6.4
<b>B</b> , Y = NAc	<b>63</b>	0.0 (0.5)	>10600	6/10	7.7
<b>A</b> , Y = NBn	<b>87</b>	2.8 (3.2)	n.d. <sup>[g]</sup>	26/156	7.6
<b>B</b> , Y = NBn	<b>64</b>	1.6 (2.7)	n.d. <sup>[g]</sup>	6/41	8.4
<b>A</b> , Y = NBoc	<b>88</b>	3.1 (3.1)	287	32/1150	6.7
<b>B</b> , Y = NBoc	<b>65</b>	2.2 (2.8)	2620	2/35	7.8
<b>A</b> , Y = NAr <sup>[h]</sup>	<b>86</b>	>3.7 (>3.8)	12	184/495	6.9
<b>B</b> , Y = NAr <sup>[h]</sup>	<b>66</b>	>3.0 (>3.8)	12	29/241	8.1
<b>A</b> , Y = S	<b>100</b>	2.2 (2.4)	1740	28/2300	7.3
<b>B</b> , Y = S	<b>76</b>	1.6 (2.3)	4560	18/330	8.1
<b>A</b> , Y = SO <sub>2</sub>	<b>101</b>	0.1 (0.1)	1440	7/100	4.0
<b>B</b> , Y = SO <sub>2</sub>	<b>77</b>	0.5 (0.6)	4930	21/30	6.7
<b>A</b> , Y = SO	<b>102</b>	0.5 (0.5)	>33000	0/6	5.5
<b>B</b> , Y = SO	<b>78</b>	0.1 (0.3)	>32000	9/0	7.2
<b>A</b> , Y = CH <sub>2</sub>	<b>103</b>	0.9 (3.1)	2060	8/18	9.6
<b>B</b> , Y = CH <sub>2</sub>	<b>81</b>	1.0 (3.2)	3280	9/26	9.6
<b>A</b> , Y = O	<b>104</b>	1.5 (1.6)	36300	9/8	7.0
<b>B</b> , Y = O	<b>105</b>	0.5 (1.2)	100000	3/7	8.0
<b>A</b> , Y = NMe;α-Me	<b>93</b>	n.d. <sup>[g]</sup>	n.d. <sup>[g]</sup>	0/23	7.9
<b>B</b> , Y = NMe;α-Me	<b>70</b>	n.d. <sup>[g]</sup>	n.d. <sup>[g]</sup>	9/39	9.3
<b>A</b> , Y = NMe;α-Ph	<b>98</b>	2.9 (3.1)	796	16/91	7.1
<b>B</b> , Y = NMe;α-Ph	<b>72</b>	2.0 (3.1)	2490	16/67	8.4

[a] R = piperonyl. [b] Log *n*-octanol/water distribution coefficient at pH 7.4. [c] Intrinsic lipophilicity of neutral base according to  $\log P = \log D + \log_{10}(1+10^{(pK_a-pH)})$ . [d] Intrinsic molar solubility of the neutral base. Values obtained from the experimental thermodynamic solubility [ $\mu\text{mol l}^{-1}$ ] in phosphate buffer (50 mM) at pH 9.9 and  $22.5 \pm 1^\circ\text{C}$ , and corrected for p*K*<sub>a</sub>. [e] Intrinsic clearance rates in  $\text{min}^{-1}/(\text{mg}(\text{protein})/\mu\text{l})$  measured in human (h) and mouse (m) liver microsomes. [f] Amine basicity in H<sub>2</sub>O measured spectrophotometrically at 24 °C; for details, see the Experimental Part. [g] n.d. = not determined. [h] Ar = 3,5-difluorophenyl.

*N*-propyl-*N'*-arylpiperazine derivatives.<sup>121</sup> Dibasic compounds are excluded in this correlation, as their p*K*<sub>a</sub> values cannot be assigned unambiguously to specific protonation sites. The values obtained for amines with sulfones in β- or γ-position are in agreement with previously reported data on acyclic phenylsulfonyl-alkylamines.<sup>122</sup>

<sup>121</sup> E. Lacivita, M. Leopoldo, P. De Giorgio, F. Berardi, R. Perrone, *Bioorg. Med. Chem.* **2009**, *17*, 1339-1344.

<sup>122</sup> R. E. Martin, B. Plançq, O. Gavelle, B. Wagner, H. Fischer, S. Bendels, K. Müller, *ChemMedChem* **2007**, *2*, 285-287.



**Figure 23.** Correlation of  $pK_a$  decrements in the homospirocyclic series,  $\Delta pK_a$  (hsP), against the six-membered monocyclic series,  $\Delta pK_a$  (P), relative to the reference compounds **81** and **103**, respectively, containing no heterofunctionality ( $Y = CH_2$ , see Table 6). The round, square, and triangular dots refer to  $Y = NR$ ,  $S(O)_x$  ( $x = 0-2$ ), and  $O$  functionalities, respectively.

The azaspirocycles generally exhibit lower lipophilicities than their monocyclic partners. The average difference in lipophilicity,  $\Delta \log D$ , is  $-0.75$ . Interestingly, their neutral bases are also more polar, as can be seen from their  $\log P$  values (average  $\Delta \log P = -0.21$ ). One notable exception is sulfone **77**, which has higher lipophilicity than its thiomorpholine counterpart **101**, but it is still by a factor of 3.4 more soluble in aqueous phosphate buffer. Most of the spirocyclic compounds have a higher intrinsic solubility at pH 9.9 in 50 mM phosphate, even for substances that have very similar  $\log P$  values (for example, **76** and **100**, or **81** and **103**), or when  $\Delta \log P > 0$  (**77** and **101**). The differences are in certain cases remarkable – *tert*-butyl carbamates **65** and **88** show a solubility difference of almost an order of magnitude ( $2620 \mu\text{mol l}^{-1}$  vs.  $287 \mu\text{mol l}^{-1}$ ). For the whole series the average factor is 1.8 by which solubility is increased for the spirocycles.

The obtained data for metabolic clearance rates shows that most azaspiro[3.3]heptanes were oxidatively degraded at lower rates than the six-membered monocyclic analogues both in human (h) and mouse (m) liver microsomes. Even though metabolic susceptibility is dependent on the structural context and cannot be attributed on a given structural subunit of interest, striking differences were observed especially for the more lipophilic pairs. In particular, carbamate **65**, sulfonamide **60**, and aniline **66** display pronounced greater metabolic stability than their monocyclic counterparts. This finding suggests that the higher aqueous solubility may result in the more polar compounds having fewer interactions with cytochromes P450 and other membrane-bound oxidizing enzymes, thereby avoiding metabolism. Only in a few cases the spirocyclic

cles show similar or slightly higher clearance rates than the monocycles, which, in these cases, also possess a high metabolic robustness.

In conclusion, the data displayed in Table 6 propose that in terms of ADME properties, the concept of replacing a six-membered heterocyclic unit in a drug candidate by a corresponding spiro[3.3]heptane surrogate is worth realizing. Important aspects of the pharmacokinetic profile may significantly be improved by increasing the aqueous solubility and reducing both lipophilicity and metabolic degradation.

## 2.3 Ciprofloxacin Analogues

The above presented and discussed data suggests that implementation of a spiro[3.3]heptane motif into a drug candidate can lead to compounds with advantageous ADME properties. Unfortunately, the replacement of a monocyclic system with a spirocycle for property reasons does not automatically make the compound a better drug. By changing the physical properties of the drug candidate, its interactions with a specific target are likely to be altered as well. Therefore, evaluation of the binding site is required in order to estimate whether the substitution would be worth implementing.

From the large number of marketed drugs containing a piperazine ring, the antibacterial compound ciprofloxacin was an excellent case to investigate the potential of replacing a piperazine unit. Among the reasons were:

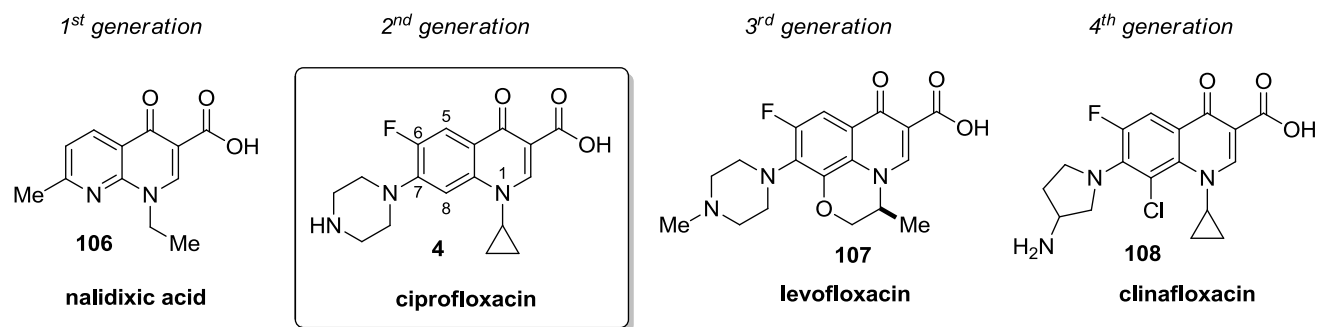
- terminal piperazine moiety is part of the pharmacophore, and is not just used as a linker or solubilizing residue
- availability of assays to evaluate the potency of the target compounds
- *Bayer's* ciprofloxacin patent<sup>123</sup> expired in 2003
- some of the major metabolism is observed at the piperazine ring<sup>124</sup>
- commercial availability of a precursor

Ciprofloxacin was first patented by *Bayer* in 1982 and then introduced to the market in 1987. Ever since it has been used for the treatment of a variety of bacterial infections, being one of the most used prescription drugs. It is sold under a multitude of brand names, among which are *Cipro*<sup>®</sup>, *Ciproxin*<sup>®</sup>, or *Proquin*<sup>®</sup>. Today it is also available in generic form from a number of pharmaceutical companies.

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<sup>123</sup> K. Grohe, H.-J. Zeiler, K. G. Metzger (Bayer AG), EP 0049355, 1982.

<sup>124</sup> L. Senggunprai, K. Yoshinari, Y. Yamazoe, *Drug Metab. Dispos.* 2009, 37, 1711-1717.



**Figure 24.** Ciprofloxacin (**4**) and other representatives of the fluoroquinolone class of antibiotics.

Ciprofloxacin belongs to the family of fluoroquinolone antibiotics and is considered a second-generation drug (Figure 24).<sup>125</sup> The first marketed compound of this class of synthetic antibacterial agents was nalidixic acid (**106**), which was mainly used for the treatment of urinary tract infections. The second generation of quinolone compounds is defined by the introduction of a fluorine substituent at position 6 and a piperazine ring at position 7. These modifications allowed for the treatment of a wide range of infections involving Gram-positive and Gram-negative bacteria. Furthermore, the pharmacokinetic profile was improved, and these new compounds exhibited a high ability to penetrate through bacterial cell walls and at the same time were well absorbed from the gastrointestinal tract. Even higher activities resulted from bridging N(1) and C(8) in the third generation of fluoroquinolones exemplified by levofloxacin (**107**). Clinafloxacin (**108**) as a member of the fourth generation drugs has high activity against many Gram-positive cocci as well as an improved activity against anaerobes. Minimal inhibitory concentrations (MIC) against *Streptococcus pneumoniae* (a significant pathogen for humans causing pneumonia) showcase the improvements made in quinolone antibiotics. Nalidixic acid has an MIC<sub>50</sub> value of 128 mg l<sup>-1</sup> against *Streptococcus pneumoniae*, but later developed compounds (ciprofloxacin: 1–2 mg l<sup>-1</sup>, levofloxacin: 1 mg l<sup>-1</sup>, clinafloxacin: 0.06 mg l<sup>-1</sup>) behave much better. Overall, the fluoroquinolones represent an important class of agents against bacterial infections and compete very well with the penicillins and the macrolides.

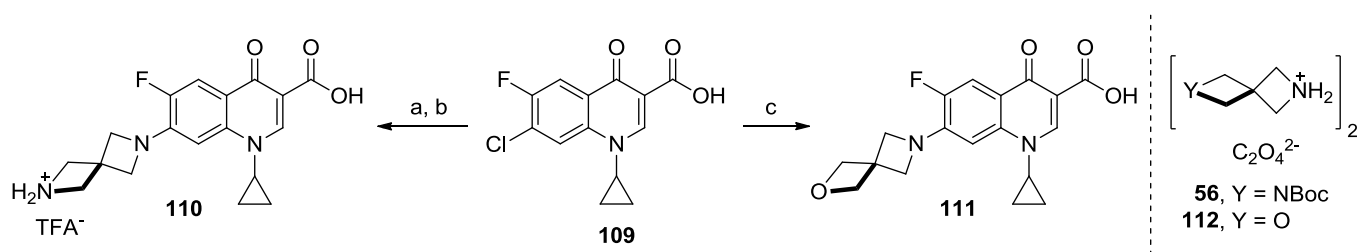
The mode of action for all these compounds is believed to be inhibition of bacterial DNA gyrase that supercoils relaxed closed circular DNA.<sup>126</sup> By doing this, DNA replication and protein synthesis is stopped and bacterial cells are prone to die. Structure-activity relationships (SAR) were defined for the fluoroquinolones:<sup>125</sup> position 1 (quinolone nitrogen) should be substituted

<sup>125</sup> For an overview of ciprofloxacin and other fluoroquinolones, see: a) P. C. Appelbaum, P. A. Hunter, *Int. J. Antimicrob. Agents* **2000**, *16*, 5–15; b) D. T. W. Chu, P. B. Fernandes, *Antimicrob. Agents Chemother.* **1989**, *33*, 131–135.

<sup>126</sup> a) D. M. Benbrook, R. V. Miller, *Antimicrob. Agents Chemother.* **1986**, *29*, 1–6; b) N. R. Cozzarelli, *Science* **1980**, *207*, 953–960.

with a medium-sized group for good activity, position 5 does not allow large substituents (best: H; tolerated are CH<sub>3</sub>, NH<sub>2</sub>), a diamine similar to piperazine at position 7 is responsible for broad activity and cell wall permeability, and substitution at C(8) affects *in vivo* properties and activities against anaerobic species.

Data found in the literature<sup>127</sup> show that a variety of amine-type substituents are tolerated at the C(7) position of the fluoroquinolone scaffold with piperazines and aminopyrrolidines being the most competitive diamine scaffolds. Therefore, a replacement with a homospirropiperazine unit could indeed provide an active analogue. To gain access to this, commercially available aryl chloride **109** was treated with Boc-protected ammonium oxalate salt **56** and potassium *tert*-butoxide in DMSO at elevated temperatures (130 °C), whereby the spirocycle underwent a nucleophilic aromatic displacement reaction to afford the product in 62% yield (Scheme 16). Subsequent removal of the protecting group with excess TFA in CH<sub>2</sub>Cl<sub>2</sub> gave the trifluoroacetate salt of the spirocyclic analogue, compound **110**, in quantitative manner. For comparison reasons, the homospirromorpholine system was also attached to the fluoroquinolone scaffold under identical conditions (KO<sup>t</sup>Bu, DMSO, 130 °C) affording **111** in 68% yield. Conversions were in general quantitative, but purifications turned out to be cumbersome, for the fluoroquinolones exhibiting low solubilities in many common organic solvents.



**Scheme 16.** Synthesis of ciprofloxacin analogues. Reagents and conditions: a) **56**, KO<sup>t</sup>Bu, DMSO, 130 °C, 62%; b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 99%; c) **112**, KO<sup>t</sup>Bu, DMSO, 130 °C, 68%.

Subsequent to their synthesis, analogues **110** and **111**, as well as commercial ciprofloxacin (**4**), were tested in collaboration with SVEN HOBBIÉ and E. C. BÖTTGER (*University of Zürich*) against a representative selection of clinical isolates of bacterial strains. In general, the activity of the homospirropiperazinyl compound was within the range of ciprofloxacin, but always slightly reduced (Table 7). Good activities were found against strains of *E. coli*, *S. aureus*, and problematic *P. aeruginosa*. Not surprisingly, homospirromorpholine-decorated fluoroquinolone **111**

<sup>127</sup> a) J. P. Sanchez, J. M. Domagala, C. L. Heifetz, S. R. Priebe, J. A. Sesnie, A. K. Trehan, *J. Med. Chem.* **1992**, 35, 1764–1773; b) J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez, M. Solomon, *J. Med. Chem.* **1986**, 29, 394–404; c) H. Koga, A. Itoh, S. Murayama, S. Suzue, T. Irikura, *J. Med. Chem.* **1980**, 23, 1358–1363.

turned out to be inactive against many strains (*Mycobact. smegmatis*, *Enteroc. faecalis*, *P. aeruginosa*), but gave good results for the inhibition of *E. coli* and a particular strain of *S. aureus* (AG011).

**Table 7.** Minimal inhibitory concentrations (MIC) against a representative selection of clinical isolates.

species	strain	MIC ( $\mu\text{g ml}^{-1}$ )		
		azetidine 110	oxetane 111	ciprofloxacin (4)
<i>Mycobact. smegmatis</i>	SZ380	8 - 16	> 512	0.25 - 0.50
<i>E. coli</i>	AG001	0.5	1.0	$\leq 0.0625$
<i>E. coli</i>	AG003	0.5 - 1.0	1 - 2	$\leq 0.0625$
<i>S. aureus</i>	AG011	0.5 - 1.0	0.125	0.125
<i>S. aureus</i>	AG013	128	> 512	32
<i>Enteroc. faecalis</i>	AG017	16	$\geq 128$	2
<i>Enteroc. faecalis</i>	AG018	16	$\geq 128$	2
<i>P. aeruginosa</i>	AG020	64	> 512	4
<i>P. aeruginosa</i>	AG022	8	> 512	1

The results obtained for minimal inhibitory concentrations indicate that the homospirropiperazine unit can be considered as an alternative to piperazines in lead optimization. In addition, inhibitory properties may be retained with refinement of pharmacokinetic and -dynamic properties leading to an improvement in overall efficacy. Thus, both azetidine **110** and oxetane **111** gave high metabolic stabilities, with no observable degradation in human microsomal assays, whereas ciprofloxacin trifluoroacetate showed slight metabolic clearance (Table 8). Their stability was also confirmed in a more complex whole-cell human hepatocyte assay, where both analogues were degraded at lower rates than ciprofloxacin.

**Table 8.** Metabolic stability of ciprofloxacin and its analogues.

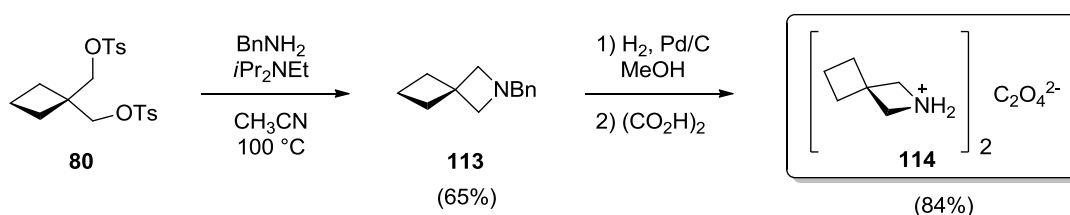
compound	CL <sub>int</sub> (human)	
	microsomal [min <sup>-1</sup> (mg <sub>protein</sub> /μl) <sup>-1</sup> ]	hepatocytes [min <sup>-1</sup> (10 <sup>6</sup> cells/μl) <sup>-1</sup> ]
azetidine <b>110</b>	0	5
oxetane <b>111</b>	0	1
ciprofloxacin ( <b>4</b> )	5	7



## 2.4 Further Linear Spirocyclic Building Blocks

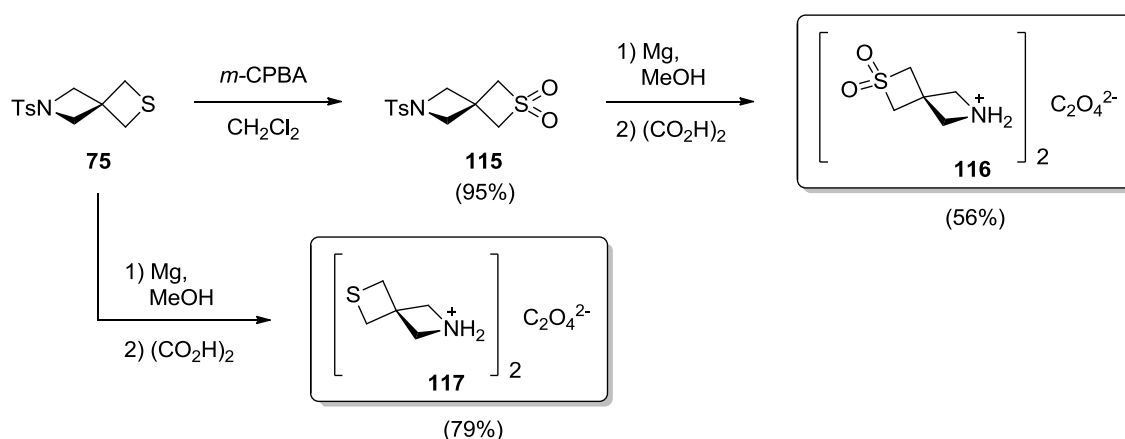
In section 2.2.1 the synthesis of various azaspiro[3.3]heptanes was described as part of their subsequent analysis for key pharmacokinetic properties. Within that context, compounds were prepared that carried a piperonyl residue on the amine. Generally, though, for applications in drug discovery programs, the frameworks should be prepared in a way that they can be used as readily functionalizable building blocks.

According to these considerations, we envisioned preparing similar compounds like the described 2,6-diazaspiro[3.3]heptane units **54** and **56** or the homospirromorpholine building block **112**. Thus, in order to arrive at a useful homospirropiperidine compound, bis(tosylate) **80** was treated with benzylamine (2 equiv) and *i*Pr<sub>2</sub>NEt (3 equiv) in refluxing acetonitrile to afford *N*-benzyl 2-azaspiro[3.3]heptane (**113**) in acceptable yield (65%). Following a catalytic hydrogenation (H<sub>2</sub>, Pd/C, MeOH), the resulting amine was converted to its oxalate salt, thereby yielding the building block **114** (purity ~95% acc. to <sup>1</sup>H NMR) in 84% over the two manipulations (Scheme 17).



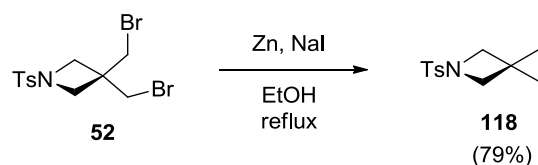
**Scheme 17.** Generation of a homospirropiperidine building block.

The logical extension of building blocks would be those that contained the homospiriothiomorpholine unit. Naturally, thietane **115** could be deprotected (Mg powder/MeOH) and the amine protonated to provide azetidine-thietane construct **117** in 79% over the two steps (Scheme 18). Its oxidized counterpart, ammonium oxalate **116**, was synthesized by first oxidizing **75** to sulfone **115** with *m*-CPBA (95% yield) and subsequent deprotection-salt formation (56%). All of the above mentioned ammonium oxalate salts were colorless solids that could be stored at RT for several months without noticeable change, therefore being convenient substances for any amine functionalization reactions.



**Scheme 18.** Formation of thietane- and thietane dioxide-containing building blocks.

Dibromide **52**, an important intermediate in the synthesis of spiro[3.3]heptane units, inspired us to synthesize a member of the spiro[2.3]hexane class, namely *N*-tosyl 5-azaspiro[2.3]hexane (**118**). Following a procedure by SAKUMA and TOGO for the construction of cyclopropanes from 1,3-dihalides,<sup>128</sup> dibromide **52** was treated with Zn dust (4 equiv) and sodium iodide (3 equiv) in refluxing EtOH to afford cyclopropane **118** in good yield (79%) (Scheme 19).<sup>129</sup>



**Scheme 19.** Construction of an azetidine-cyclopropane spirocycle.

Interestingly, also this spirocycle lacks precedence in the literature. There are no reports found about 5-azaspiro[2.3]hexanes that have substituents on the nitrogen only, but NAKAMURA and co-workers have developed a silver-salt-catalyzed [2+2]-cycloaddition of imines to (alkoxymethylene)cyclopropanes,<sup>130</sup> a method that delivers substituted versions of **118**.

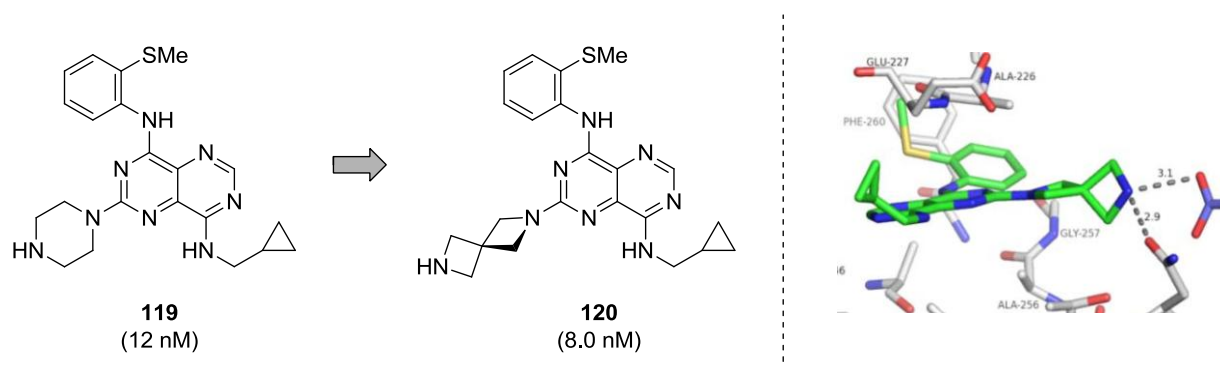
<sup>128</sup> D. Sakuma, H. Togo, *Tetrahedron* **2005**, *61*, 10138-10145.

<sup>129</sup> Initial attempts to cleave the tosyl amide using Mg/MeOH were not encouraging. Although full conversion of the starting material was observed, the desired amine could not be isolated in pure form and calculated yields were low.

<sup>130</sup> I. Nakamura, T. Nemoto, Y. Yamamoto, A. de Meijere, *Angew. Chem. Int. Ed.* **2006**, *45*, 5176-5179.

## 2.5 Industrial Impact

Following our investigations and disclosures on spiro[3.3]heptane units,<sup>131</sup> these building blocks have generated interest in the chemical industry. For example, since 2009, the 2,6-diazaspiro[3.3]heptane moiety appeared in synthesized structures of 12 patents from a variety of pharmaceutical companies including *Merck*, *Janssen*, *Novartis*, and *Roche*. Moreover, we were asked by a number of individuals from industry and academia to provide samples of synthesized compounds. Following our supply with material, MARYANOFF and co-workers (*Johnson & Johnson*) were able to implement the homospirropiperazine unit to afford active inhibitors of ketohexokinase (KHK), a target for the potential treatment of diabetes and obesity.<sup>132</sup> In a series of compounds, piperazine **119** and homospirropiperazine **120** displayed excellent inhibition properties ( $IC_{50}$  values are 12 nM and 8 nM, respectively) (Figure 25). Moreover, an X-ray crystallographic image of **120**·KHK reveals remarkable hydrogen bonding of the terminal azetidine to Asp-27B (3.1 Å) and Asn-107 (2.9 Å).



**Figure 25.** Ketokinase inhibitors **119** and **120**. Right: snapshot of a crystal structure of inhibitor **120** in the putative active site (image taken from ref. 132).

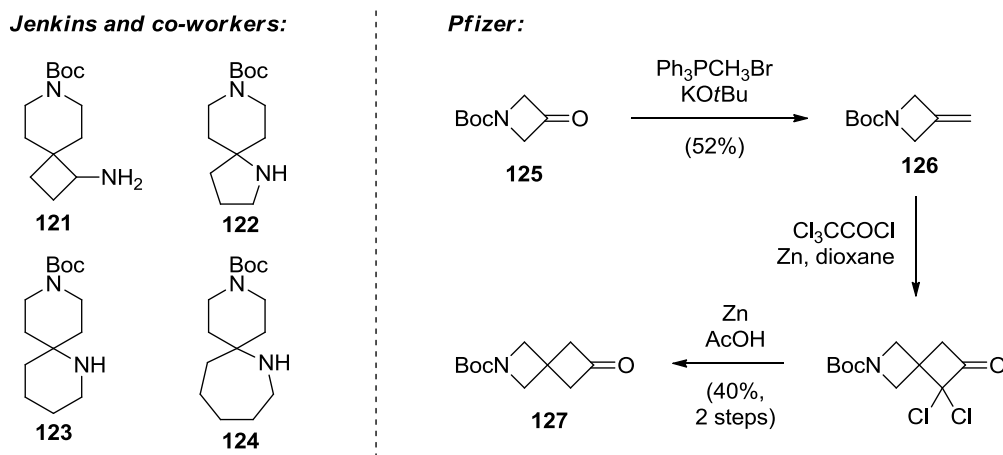
Other companies have also started programs for the introduction and generation of novel spirocyclic building blocks. JENKINS and co-workers (*Griffith University*, Australia in collaboration with *AstraZeneca*, UK) disclosed the preparation of natural product inspired spirocyclic diamine scaffolds **121-124** (Scheme 20).<sup>133</sup> To name a second published example, MEYERS and co-workers (*Pfizer*) synthesized an intriguing compound of the spiro[3.3]heptane family, namely

<sup>131</sup> a) J. Burkhard, E. M. Carreira, *Org. Lett.* **2008**, *10*, 3525-3526; b) J. A. Burkhard, B. Wagner, H. Fischer, F. Schuler, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 3524-3527.

<sup>132</sup> B. E. Maryanoff, J. C. O'Neill, D. F. McComsey, S. C. Yabut, D. K. Luci, A. D. Jordan, J. A. Masucci, W. J. Jones, M. C. Abad, A. C. Gibbs, I. Petrounia, *ACS Med. Chem. Lett.* **2011**, *2*, 538-543.

<sup>133</sup> I. D. Jenkins, F. Lacrampe, J. Ripper, L. Alcaraz, P. Van Le, G. Nikolakopoulos, P. D. Leone, R. H. White, R. J. Quinn, *J. Org. Chem.* **2009**, *74*, 1304-1313.

cyclobutanone **127**.<sup>134</sup> Their shortest route started with *N*-Boc azetidion-3-one (**125**) and by using a [2+2]-cycloaddition as a key step they were able to synthesize **127** in 3 steps and 21% yield from **126**.



**Scheme 20.** Related published examples on the use of spirocyclic systems in drug discovery.

## 2.6 Unique Conformational Properties

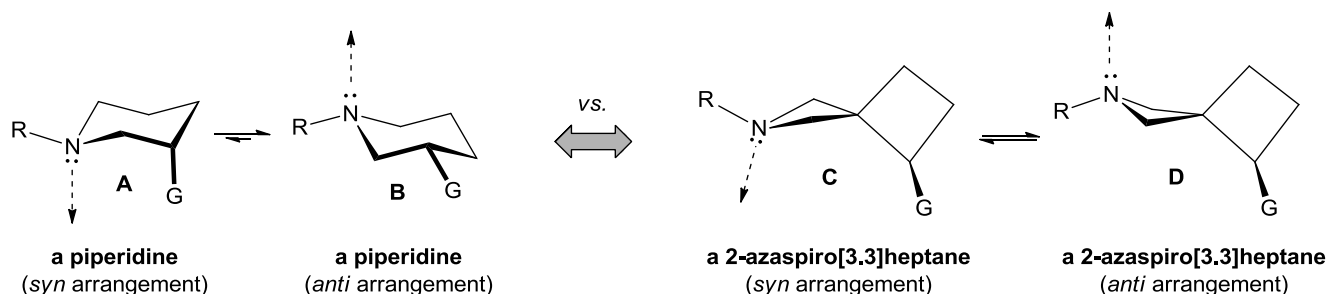
The rigidification of compounds to improve their oral bioavailability or their pharmacokinetic and -dynamic profile is an important concept in drug discovery.<sup>1,135</sup> In this respect, open-chain compounds or linker moieties are often locked into active conformations by the introduction of ring systems or other units that do not have freely rotatable bonds. Spirocycles like those discussed in this chapter certainly fulfill many aspects of a unit with conformational restraint.<sup>136</sup> However, it is important to note that spiro[3.3]heptanes do not necessarily function as more rigid cyclohexanes, as one might contemplate at first. In fact, their conformational behavior is quite different from six-membered monocyclic systems. Whereas a substituent on the carbon skeleton of a piperidine (e.g., a methyl group) determines, and in many cases, locks the piperidine conformation, a substituent on one side of the 2-azaspiro[3.3]heptane system does not lock the overall conformation of the unit. These characteristic behaviors are illustrated in Figure 26. A piperidine that has an alkyl substituent (R) on the nitrogen atom and another substituent (G) at C(3) will preferentially adapt the conformation as shown for structure **B**. Con-

<sup>134</sup> M. J. Meyers, I. Muizebelt, J. v. Wiltenburg, D. L. Brown, A. Thorarensen, *Org. Lett.* **2009**, *11*, 3523-3525.

<sup>135</sup> A. R. Khan, J. C. Parrish, M. E. Fraser, W. W. Smith, P. A. Bartlett, M. N. G. James, *Biochemistry* **1998**, *37*, 16839-16845.

<sup>136</sup> D. S. Radchenko, S. O. Pavlenko, O. O. Grygorenko, D. M. Volochnyuk, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *J. Org. Chem.* **2010**, *75*, 5941-5952.

former **A**, which is derived from **B** by a ring flip and concomitant nitrogen inversion, suffers from  $A_{1,3}$ -strain of the axially oriented substituent **G** with appropriately positioned H-atoms (of also a protonated amine). Hence, the equilibrium is strongly shifted toward the energetically lower lying conformer **B** having an *anti* arrangement of the nitrogen lone pair and the exit vector on C(3).

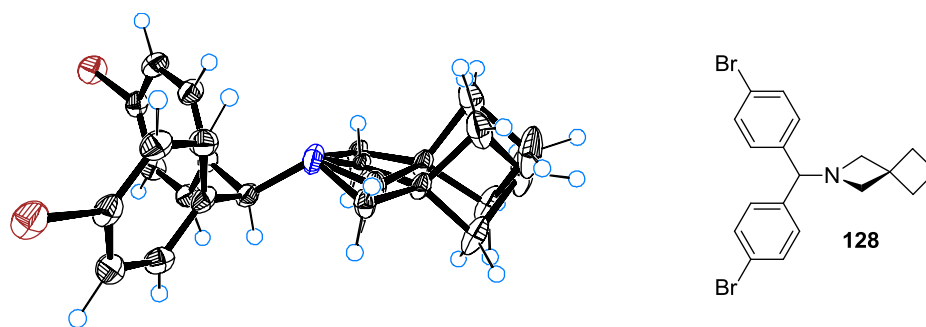


**Figure 26.** Conformational differences between piperidines and homospiripiperidines.

In a 2-azaspiro[3.3]heptane, which is similarly substituted like the aforementioned piperidine, the situation changes significantly. The conformational liberty of the azetidine is not constrained by the substituent in the cyclobutane ring. Energy calculations carried out at *F. Hoffmann-La Roche* reveal that when **R** and **G** are methyl groups, structures **C** and **D** as well as their cyclobutane puckering isomers all reside at the same energy level.<sup>137</sup> Hence, the spirocyclic carbon uncouples the two sides of the ring system and allows for an increased conformational freedom as compared to the piperidine. Solid-state structural evidence for this peculiarity was obtained for an *N*-substituted homospiripiperidine (Figure 27). Thus, X-ray diffraction analysis of dibromobenzhydryl amine **128**<sup>138</sup> revealed the almost uniform appearance of two conformers. Future work directed toward solid-state structures of protonated derivatives of **128** or of *C*-substituted analogues (bearing Me or Ph groups) will deliver further insights.

<sup>137</sup> Calculations were performed by BERND KUHN and KLAUS MÜLLER at the B3LYP/cc-pVDZ++ level of theory.

<sup>138</sup> Prepared by CAROLINE ROUSSEAU from bis(tosylate) **80** and bis(4-bromophenyl)methanamine with *i*Pr<sub>2</sub>NEt in refluxing CH<sub>3</sub>CN for 2 d; 20% yield. Crystals were obtained by slow evaporation from a solution in diethyl ether and hexane.



**Figure 27.** X-ray crystallographic image of azaspiro[3.3]heptane **128**. Ellipsoids at 50% probability.

**3**

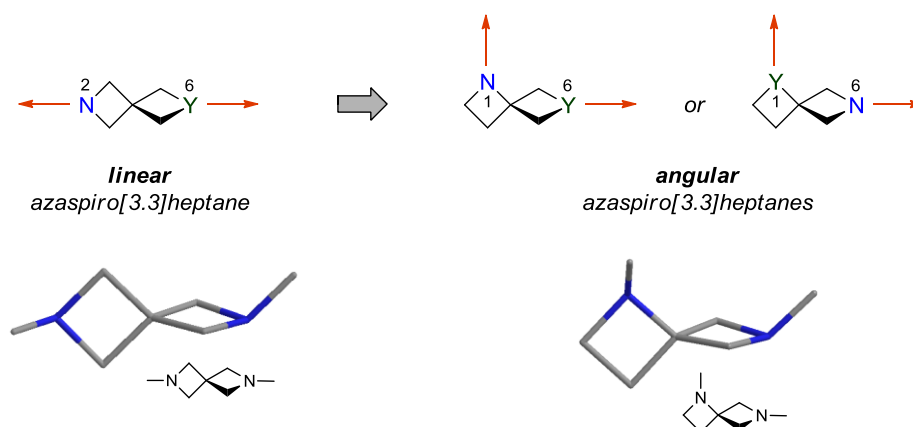
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**Angular Spirocycles**

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### 3.1 Conceptual Idea

In the preceding chapter it was described how azaspiro[3.3]heptanes are readily prepared and serve as excellent building blocks for medicinal chemistry purposes. Their advantages are accompanied also by a few limitations, such as the laborious introduction of vectors on the carbon skeleton, or the *linear* arrangement of heteroatoms and exit vectors. The latter characteristic is exemplified in homospiripiperazines, where substituents on the nitrogen atoms, the terminal positions of the framework, are roughly pointing in opposite directions in space. On the other hand, by moving the nitrogen atom from position 2 of the spiro[3.3]heptane core to position 1, the situation becomes quite different. Now, the modified orientation of heteroatomic units makes an *angular* arrangement of exit vectors possible and a heteroatomic substituent can be positioned at an internal point of the scaffold. The transition from linear to angular systems (terminology by us, KNUST, MÜLLER, and ROGERS-EVANS) and consequences for the orientation of amine substituents in diazaspino[3.3]heptanes are displayed in Figure 28.

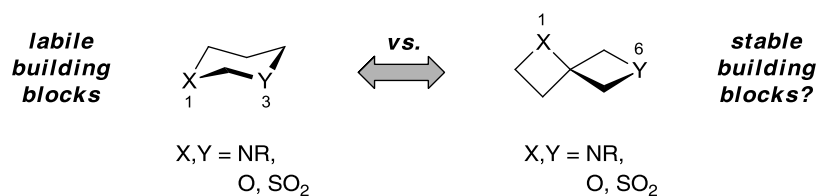


**Figure 28.** From linear to angular azaspiro[3.3]heptanes. Y: Heteroatomic unit.

Again, much like the linear spirocycles, the angular systems can form a central unit or they can be placed at the terminus of a compound framework. In the former case, Y (see Figure 28) would preferably be a substituted amine (i.e., an N–R unit), and in the latter, Y would consist of either a polar group (O, S, SO, or SO<sub>2</sub>) or a methylene group. Either way, two distinct configurations become available. Either the linking nitrogen atom is at the terminal position (position 6) or at an internal site (position 1). These compound pairs have a similar angular arrangement of heteroatoms, but their embedding in the framework is slightly different. The affiliated consequences should be taken into account when fine-tuning the pharmacokinetic profile of an active compound.



If we reverse the gedankenexperiment of Chapter 2, where the transition was made from cyclohexanes to spirocycles, by going from a 1,6-heteroatom-substituted spiro[3.3]heptane back to a monocyclic system, then the analogous structures would be characterized by a 1,3 relationship between the heteroatoms. According to ERLLENMEYER's rule, these systems are in general not stable in an acidic aqueous environment and tend to be hydrolyzed to open-chained compounds.<sup>139</sup> For this reason, compounds of that type are hardly seen in the context of drug discovery.<sup>140</sup> To overcome the associated pharmacokinetic issues, angular spiro[3.3]heptane systems might provide an intriguing alternative (Figure 29). Their heteroatomic relationship should render them stable under the above-mentioned conditions, but experiments would have to confirm the expected robustness of the connected four-membered heterocycles.

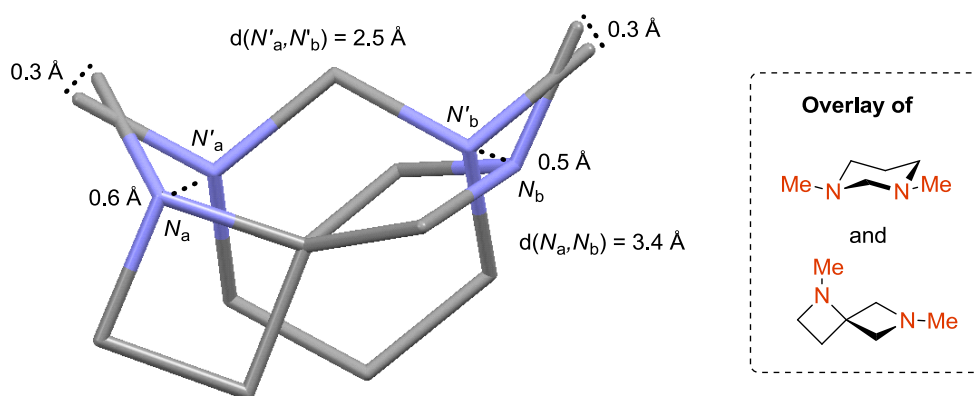


**Figure 29.** 1,6-Heteroatom-substituted spiro[3.3]heptanes as an alternative to 1,3-heteroatomic cyclohexanes.

To illustrate whether a spirocyclic system would serve as a viable mimic for a system exemplified by hexahydropyrimidine, an overlay of minimized structures was prepared. Figure 30 shows *N,N'*-dimethyl-1,6-diazaspiro[3.3]heptane together with *N,N'*-dimethyl hexahydropyrimidine, aligned in a way that distances between corresponding methyl groups and nitrogen atoms are minimal. These distances are also indicated in the picture. While corresponding nitrogen atoms are relatively far apart (0.5–0.6 Å), the attached methyl groups have a better match (*ca.* 0.3 Å). This result is remarkable, knowing that the spirocyclic system is considerably longer than the monocyclic analogue (nitrogen interatomic distances are 3.4 Å and 2.5 Å, respectively).

<sup>139</sup> Exceptions are known, e.g. certain spirocyclic acetals appear in a number of isolated natural products and are often thermodynamically more favored than the respective open-chained hydrolysis products.

<sup>140</sup> Nevertheless, a handful of patents involving hexahydropyrimidines, hemiaminal compounds or thioaminals have been published. For hexahydropyrimidines, consider a) V. Kodumuru (Xenon Pharmaceuticals, Inc.), WO 2007046867, **2007**; b) N. E. Faucher, P. Martres, S. Meunier (Smithkline Beecham Corp.), WO 2009047240, **2009**. For hemiaminals: c) C. J. Aquino, P. Y. Chong, M. Duan, W. M. Kazmierski (Smithkline Beecham Corp.), WO 2004055011, **2004**; d) J. E. G. Guillemont, E. T. J. Pasquier (Janssen Pharmaceuticals), WO 2005070924, **2005**; e) H. Ballhause, G. Engelhardt, C. A. Landgraf, N. Mayer, W. Roth, K. Schumacher, A. Prox (Dr. Karl Thomae GmbH), EP 0413302, **1991**; f) M. Schriewer, K. Grohe, A. Krebs, U. Petersen, T. Schenke, I. Haller, K. G. Metzger, R. Endermann, H.-J. Zeiler (Bayer AG), EP 0391132, **1990**. For thioaminals: g) J. H. Bateson, M. L. Gilpin (Smithkline Beecham PLC), WO 9839311, **1998**.



**Figure 30.** Overlay of minimized (PM3 using *CambridgeSoft ChemBio3D 12.0*) structures. Overlay generated with *Mercury CSD 2.4.6* by minimizing distances of atoms (groups) shown in red. Hydrogen atoms are omitted for clarity.

Even though there are significant structural discrepancies (overall shape, length of system, no overlap of ring carbon atoms), the observed proximity and orientation of corresponding vectors (here: methyl groups) can motivate the medicinal chemist to look at the unusual framework as a replacement for chemically unstable structures. With respect to this topological match of exit vectors or heteroatomic units, the concept of scaffold hopping,<sup>141</sup> i.e. the identification of isofunctional molecular structures with significantly different molecular architectures, could be very well realized in drug discovery programs for these systems.

## 3.2 Synthesis

Having identified a substantial interest in angular spiro[3.3]heptanes, we embarked on the synthesis of all family members, i.e. of all reasonable combinations of X and Y, indicated in Figure 29. The targeted azaspiro[3.3]heptanes were essentially unknown<sup>142</sup> and required the design of a novel access route.

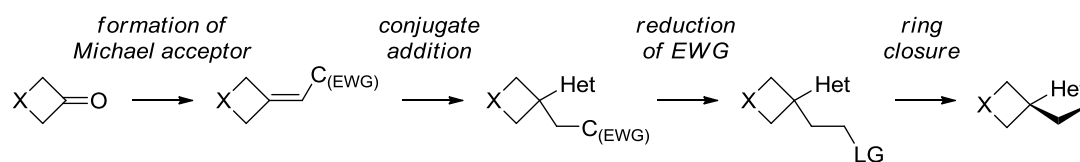
We identified that it was most convenient to begin with a starting material that would contain one of the four-membered rings, and build the second ring around it. The cyclic ketones oxetan-3-one, azetidin-3-one and thietan-3-one<sup>143</sup> seemed optimal and the general strategy would follow the lines of converting the ketone into a MICHAEL acceptor, adding a heteroatom-

<sup>141</sup> For a seminal publication, see: a) G. Schneider, W. Neidhart, T. Giller, G. Schmid, *Angew. Chem. Int. Ed.* **1999**, *38*, 2894–2896. Reviews on the topic: b) G. Schneider, P. Schneider, S. Renner, *QSAR Comb. Sci.* **2006**, *25*, 1162–1171; c) G. Schneider, U. Fechner, *Nat. Rev. Drug Discov.* **2005**, *4*, 649–663.

<sup>142</sup> The only example in the literature is a piperonyl decorated azetidine-oxetane spirocycle that had previously been prepared in our group, see ref. 77c.

<sup>143</sup> The chemistry of these ketones has been reviewed: Y. Dejaegher, N. M. Kuz'menok, A. M. Zvonok, N. De Kimpe, *Chem. Rev.* **2002**, *102*, 29–60.

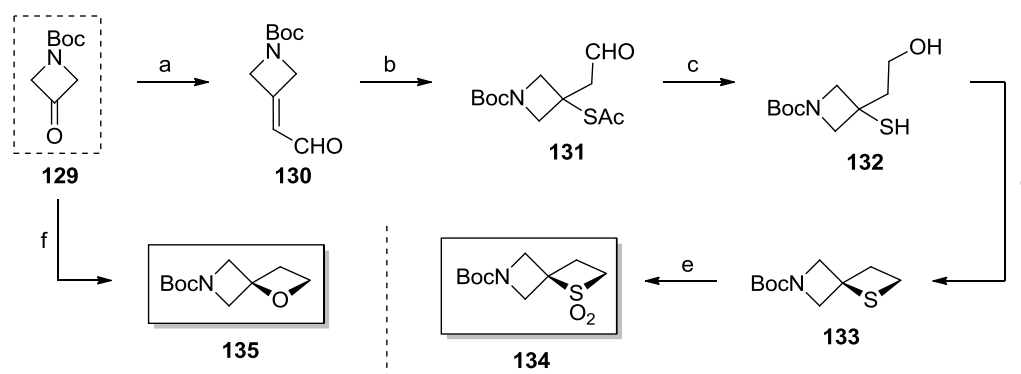
ic nucleophile in a conjugate addition, reducing the electron-withdrawing group, activating the formed alcohol, and finally performing a ring-closing reaction to arrive at the angular spirocycle (Scheme 21). This sequence should be scalable and give quick access to a number of family members.



**Scheme 21.** General strategy for the synthesis of angular spirocycles. EWG: electron-withdrawing group, Het: heteroatomic unit, LG: leaving group.

### 1-Thia-6-azaspiro[3.3]heptane & 1-Oxa-6-azaspiro[3.3]heptane

The synthesis of a 1-thia-6-azaspiro[3.3]heptane building block (Scheme 22) started with *N*-Boc-azetidin-3-one (**129**), a commercially available compound<sup>144</sup> that can also be readily prepared in two steps from azetidin-3-ol hydrochloride<sup>145</sup> (Boc<sub>2</sub>O; then IBX, Δ). Wittig olefination with (formylmethylene)triphenylphosphorane (40 °C, 5 h) gave α,β-unsaturated aldehyde **130** in excellent yield. Following a procedure for the conjugate addition of thioacetic acid to enals,<sup>146</sup> aldehyde **131** was obtained in 84% yield after subjecting **130** to conditions of iminium catalysis (AcSH (1.5 equiv), piperidine (0.07 equiv), THF, RT, 6 h). Concomitant reduction of the aldehyde and the thioester in **131** with LiAlH<sub>4</sub> gave thiol alcohol **132** in essentially quantitative yield.<sup>147</sup>



**Scheme 22.** Synthesis of azetidine-oxetane and azetidine-thietane spirocycles. Reagents and conditions: a) Ph<sub>3</sub>P=CHCHO, CH<sub>2</sub>Cl<sub>2</sub>, 94%; b) AcSH, piperidine, THF, 84%; c) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 99%; d) Ph<sub>3</sub>P(OEt)<sub>2</sub>, toluene, 60%; e) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 96%; f) Me<sub>3</sub>SO<sup>+</sup>Tf, KOtBu, *t*BuOH, 50 °C, 41%.

<sup>144</sup> Available from many different suppliers, e.g. from *Combi-Blocks* for US\$ 280.-/25 g.

<sup>145</sup> For comparison: available from *Combi-Blocks* for US\$ 65.-/25 g.

<sup>146</sup> M. Granvogel, M. Christlbauer, P. Schieberle, *J. Agric. Food Chem.* **2004**, *52*, 2797-2802.

<sup>147</sup> For a similar reduction in the context of thietanes, see: B. M. Trost, W. L. Schinski, F. Chen, I. B. Mantz, *J. Am. Chem. Soc.* **1971**, *93*, 676-684.

**Table 9.** Selected experiments in the attempted thietane-forming step.

entry	conditions	result
1	PPh <sub>3</sub> , CBr <sub>4</sub> , Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , RT	decomposition of starting material
2	PPh <sub>3</sub> (1.5 equiv), CBr <sub>4</sub> (1.5 equiv), CH <sub>2</sub> Cl <sub>2</sub> , RT, 2.5 h	49% of disulfide <b>136</b> isolated, otherwise decomposition products observed
3	Ph <sub>3</sub> PCl <sub>2</sub> (1.0 equiv), Et <sub>3</sub> N (2.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , RT → 40 °C	decomposition products; formation of <b>136</b> not observed
4	Ph <sub>3</sub> P(OEt) <sub>2</sub> (1.2 equiv), toluene, -30 °C → RT	60% of thietane <b>133</b> isolated; formation of <b>136</b> not observed

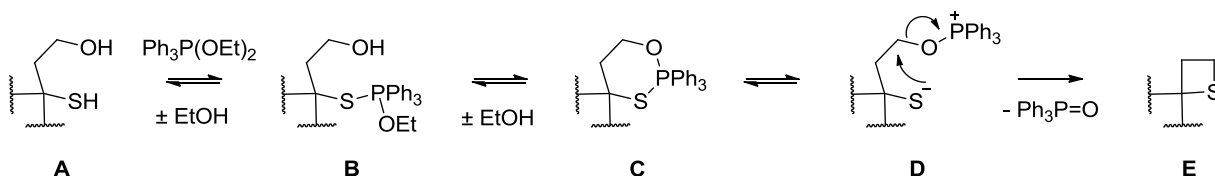
The subsequent ring-closing step turned out to be non-trivial. Standard conditions for AP-PEL type reactions (using PPh<sub>3</sub>, CBr<sub>4</sub>) failed to deliver the desired thietane (Table 9, entry 1). Interestingly, when **132** was treated with CBr<sub>4</sub> and PPh<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>, a compound was isolated that exhibited similar NMR spectral properties that were expected for the targeted thietane (entry 2). Only mass analysis revealed that a different compound had formed, as the major peak indicated the presence of two bromine atoms in the molecule. Thus, analytical data supported the formation of dimeric disulfide structure **136**. This was later chemically confirmed, when disulfide **136** was treated with NaBH<sub>4</sub>, a reagent that is known to cleave S—S bonds, and the desired thietane **133** was isolated (quantitative conversion).<sup>148</sup> This experiment revealed that a thiol (or thiolate) is indeed able to form the thietane ring once a suitable leaving group is installed at the primary position. It was thus necessary to selectively activate the alcohol in the presence of the thiol.<sup>149</sup> The initial attempt with a harder phosphorus electrophile than Ph<sub>3</sub>P<sup>+</sup>—Br by using Ph<sub>3</sub>PCl<sub>2</sub> prevented the formation of the disulfide side product, but nevertheless did not afford the thietane product (entry 3). Only conversion to a multitude of unidentified products was observed. EVANS and co-workers have described the use of diethoxytriphenylphosphorane (DTPP) as a cyclodehydrating agent for the formation of cyclic ethers, amines, and sulfides.<sup>150</sup> Ph<sub>3</sub>P(OEt)<sub>2</sub> is prepared in two steps by either reacting triphenylphosphine with bro-

<sup>148</sup> Reduction was performed according to: A. L. Braga, H. R. Appelt, P. H. Schneider, C. C. Silveira, L. A. Wessjohann, *Tetrahedron: Asymmetry* **1999**, *10*, 1733–1738.

<sup>149</sup> When only the aldehyde functionality in **131** is reduced to the alcohol (NaBH<sub>4</sub>), a concomitant transesterification is observed, where the acetate group is transferred from the thiol to the newly formed alcohol.

<sup>150</sup> a) P. L. Robinson, C. N. Barry, J. W. Kelly, S. A. Evans, *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219; b) J. W. Kelly, N. L. Anderson, S. A. Evans, *J. Org. Chem.* **1986**, *51*, 95–97; c) I. Mathieu-Pelta, S. A. Evans, *J. Org. Chem.* **1994**, *59*, 2234–2237.

mine and subsequently the formed phosphonium bromide salt with sodium ethoxide (the reagent is isolated as a solid) or by the treatment of triphenylphosphine with diethyl peroxide (the reagent is preferably stored as a toluene solution). Application of EVANS' conditions for the formation of thietane rings (thiol alcohol, DTPP, toluene,  $-30\text{ }^{\circ}\text{C} \rightarrow \text{RT}$ )<sup>151</sup> then afforded spirocycle **133** from thiol alcohol **132** in 60% yield (entry 4).



**Scheme 23.** Possible mechanistic pathway for the formation of thietanes from mercaptoalcohols using DTPP.

EVANS' proposed mechanism involves an initial attack of thiol **A** at phosphorus to give **B** and subsequent loss of ethanol to arrive at a 1,3,2-oxathiaphosphinane **C**, which in turn can equilibrate to activated alcohol **D** and upon loss of triphenylphosphine oxide undergo ring-closure to yield thietane **E** (Scheme 23). Whereas structures **A-D** lie between equilibria, the formation of triphenylphosphine oxide and thietane **E** is the thermodynamic sink and at the same time the driving force of the reaction.

To terminate the synthesis of the targeted building block, thietane **133** was treated with *m*-CPBA to afford conveniently protected sulfone **134**. In summary, building block **134** is available in five steps from ketone **129** in a good overall yield of 45%.

The COREY-CHAYKOVSKY reaction is widely used for the conversion of ketones to corresponding epoxides.<sup>152</sup> Interestingly, only a limited number of reports are available on the further homologation to oxetane compounds.<sup>153</sup> Quite recently, SHIBASAKI and co-workers have reported the enantioselective construction of oxetanes from methyl ketones.<sup>154</sup> These disclosures let us consider synthesizing target building block **135** directly in one step from common azetidin-3-one **129**. Initial attempts with “double-COREY-CHAYKOVSKY” reactions employing dimethylsulfoxonium methylide or sulfoximine ylides were discouraging, when either no or only very little oxetane product was formed (Table 10, entries 1-3). Since starting material was

<sup>151</sup> P. L. Robinson, J. W. Kelly, S. A. Evans, *Phosphorus, Sulfur Silicon Relat. Elem.* **1987**, *31*, 59-70.

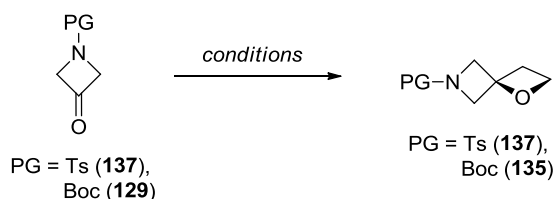
<sup>152</sup> Seminal publications: a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1962**, *84*, 867-868; b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364. Review on catalytic asymmetric methods involving sulfur ylides: A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341-2372.

<sup>153</sup> See for example: a) S. C. Welch, A. S. C. P. Rao, *J. Am. Chem. Soc.* **1979**, *101*, 6135-6136; b) S. C. Welch, A. S. C. P. Rao, J. T. Lyon, J. M. Assercq, *J. Am. Chem. Soc.* **1983**, *105*, 252-257; c) K. Okuma, Y. Tanaka, S. Kaji, H. Ohta, *J. Org. Chem.* **1983**, *48*, 5133-5134; d) A. O. Fitton, J. Hill, D. E. Jane, R. Millar, *Synthesis* **1987**, *1987*, 1140-1142.

<sup>154</sup> T. Sone, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 1677-1680.

fully consumed it was suspected that either starting material, epoxide intermediate, or oxetane product might be unstable under the reaction conditions and might collapse to unidentified decomposition products. Therefore, we changed the protecting group on the amine to a *tert*-butyl carbamate. Surprisingly, the yield increased by a factor of four, and the desired product was obtained in 20% yield (entry 4). Lowering the amount of reagents from eight equivalents to 3.5 equiv had little impact on the outcome (entry 5). Since starting material was still fully consumed and no byproducts could be isolated or identified, we reasoned that excess reagent might still open the formed oxetane ring and lead to polymerized material that would be lost during work-up. Consequently, only 2.5 equiv of both trimethylsulfoxonium iodide and base (KO*t*Bu) were added to the reaction mixture, which was stirred for 2 d. Following work-up and purification, the desired product was obtained in 41% yield (entry 6). Unfortunately, any other attempts at optimizing the reaction (different amounts of reagents, altered work-up protocols, or sequential addition of reagents) were unfruitful.

**Table 10.** Optimization of the “double-COREY-CHAYKOVSKY” reaction.



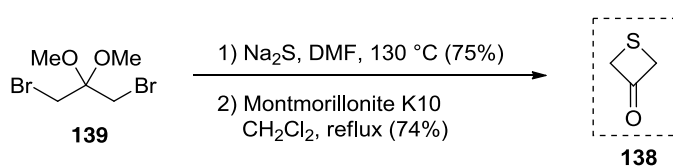
entry	PG	conditions	yield
1	Ts	Me <sub>2</sub> S(O)NTs (3.3 equiv), NaH (3 equiv), DMSO, 50 °C	traces of <b>137</b>
2	Ts	Me <sub>3</sub> SOI (8 equiv), KO <i>t</i> Bu (8 equiv), <i>t</i> BuOH, 50 °C, 3 d	5% of <b>137</b>
3	Ts	Me <sub>3</sub> SOI (5 equiv), KO <i>t</i> Bu (5 equiv), <i>t</i> BuOH, 50 °C, 16 h	5% of <b>137</b>
4	Boc	Me <sub>3</sub> SOI (8 equiv), KO <i>t</i> Bu (8 equiv), <i>t</i> BuOH, 50 °C, 26 h	20% of <b>135</b>
5	Boc	Me <sub>3</sub> SOI (3.5 equiv), KO <i>t</i> Bu (3.5 equiv), <i>t</i> BuOH, 50 °C, 13 h	19% of <b>135</b>
6	Boc	Me <sub>3</sub> SOI (2.5 equiv), KO <i>t</i> Bu (2.5 equiv), <i>t</i> BuOH, 50 °C, 48 h	41% of <b>135</b>

Although the yield of the reaction was moderate, the desired 2-oxa-6-azaspiro[3.3]heptane building block **135** was readily synthesized from commercially available starting material, thus making this route attractive for the preparation of this compound. It is also worth mentioning that the building block carries a conveniently removable protecting group and is therefore valuable for applications in medicinal chemistry.

### 1-Aza-6-thiaspiro[3.3]heptane

Thietan-3-one (**138**) was chosen as starting material for the synthesis of the 1-aza-6-thiaspiro[3.3]heptane building block and therefore required its preparation. The off-white solid with a garlic-like smell was first synthesized by MAYER and FUNK in 1961.<sup>155</sup> Their preparation of **138** started with the treatment of 1,3-dibromoacetone dimethyl ketal (**139**) with sodium sulfide in hot aqueous EtOH (150 °C) to give the dimethyl ketal of **138**. The acetal was cleaved with aqueous acid to afford the desired ketone. Other described routes involve the use of epichlorohydrin to give thiacyclobutan-3-ol that required selective oxidation to the ketone (pyridinium dichromate)<sup>156</sup> or irradiation of 1,3-dithiacyclohexan-5-one or derivatives to directly give thietan-3-one.<sup>157</sup> Since all of these methods were impractical on larger scale or proved difficult to reproduce, we chose to optimize MAYER's route for convenience.

It was found that the first step, i.e. the ring closure using sodium sulfide, was sluggish in ethanolic solution, but was complete in DMF within 24 h at 130 °C (Scheme 24). A simple water-Et<sub>2</sub>O extraction gave thietan-3-one dimethyl ketal in good purity following drying with MgSO<sub>4</sub> and concentration *in vacuo* (75% yield). Refluxing a CH<sub>2</sub>Cl<sub>2</sub>-solution of the newly formed product in the presence of montmorillonite K10 clay gave, after filtration and concentration, the desired ketone **138**, which could be purified by recrystallization from pentane (74% yield). It is advisable to minimize drying of thietan-3-one under vacuum, since it readily sublimates under reduced pressure. 3-Thiacyclobutanone was regularly synthesized on multi-gram scale and could be stored in the refrigerator for several months without noticeable change.



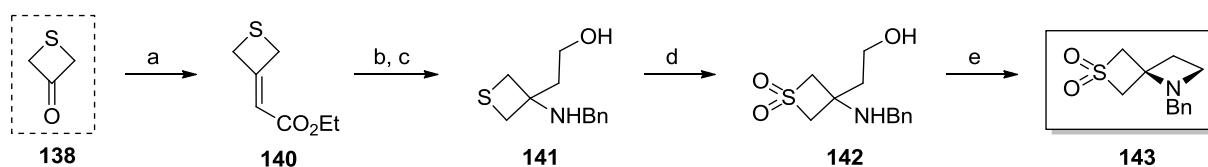
**Scheme 24.** Improved procedure for the large-scale synthesis of thietan-3-one (**138**).

With the material in hand, we initiated the synthesis of the targeted spirocycle. Accordingly, thietan-3-one (**138**) was converted to  $\alpha,\beta$ -unsaturated ester **140** in high yield using a WITTIG olefination (Scheme 25). Under forcing conditions (neat at RT, then in THF at 60 °C for several hours) benzylamine added 1,4 to the electrophile (71% yield after purification). The formed product was afterwards reduced with LiAlH<sub>4</sub> to give aminoalcohol **141** (91% yield).

<sup>155</sup> R. Mayer, K. F. Funk, *Angew. Chem.* **1961**, *73*, 578–579.

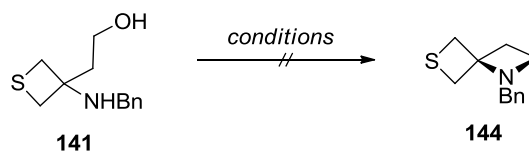
<sup>156</sup> A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783–784.

<sup>157</sup> K. K. Maheshwari, G. A. Berchtold, *J. Chem. Soc. D - Chem. Comm.* **1969**, 13.



**Scheme 25.** Synthetic sequence for the formation of thietane-azetidine building block. Reagents and conditions: a)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ,  $\text{CH}_2\text{Cl}_2$ , 95%; b)  $\text{BnNH}_2$ ; c)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , 67% (2 steps); d)  $\text{H}_2\text{O}_2$ ,  $\text{Ti}(\text{O}i\text{Pr})_4$ ,  $\text{CH}_2\text{Cl}_2$ , 94%; e)  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{CH}_3\text{CN}$ , then addition of  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$  and heating to  $60\text{ }^\circ\text{C}$ , 75%.

Unfortunately, any attempts in the ring closure of **141** that would deliver *N*-benzyl azetidine **144** were unsuccessful (Scheme 26). The use of APPEL type conditions ( $\text{PPh}_3$ ,  $\text{CBr}_4$  in  $\text{CH}_2\text{Cl}_2$ , or  $\text{PPh}_3$ ,  $\text{CBr}_4$ , then aqueous  $\text{K}_2\text{CO}_3$  in  $\text{CH}_3\text{CN}$ ) or MITSUNOBU conditions ( $\text{PPh}_3$ , DIAD, toluene) afforded new, defined compounds in reasonable amounts, but did not give the azetidine. Furthermore, also DTPP failed to give any product, as no conversion was seen even at  $100\text{ }^\circ\text{C}$ .



**Scheme 26.** Attempts to close the azetidine ring in the presence of a sulfur atom in the sulfide oxidation state.

By looking at NMR spectra, it became clear that characteristic thietane signals were missing, suggesting that a rearrangement had occurred. Since these were likely initiated by a nucleophilic attack of the sulfide, it was decided to oxidize the sulfur prior to ring-closure. As a result, **141** was treated with aqueous hydrogen peroxide in the presence of  $\text{Ti}(\text{O}i\text{Pr})_4$ <sup>158</sup> in  $\text{CH}_2\text{Cl}_2$  to give the desired sulfone **142** in 94% yield. We were then pleased to see that the ring-closure occurred uneventfully using  $\text{PPh}_3/\text{CBr}_4$  followed by addition of base, and the targeted building block **143** was isolated in 75% yield.

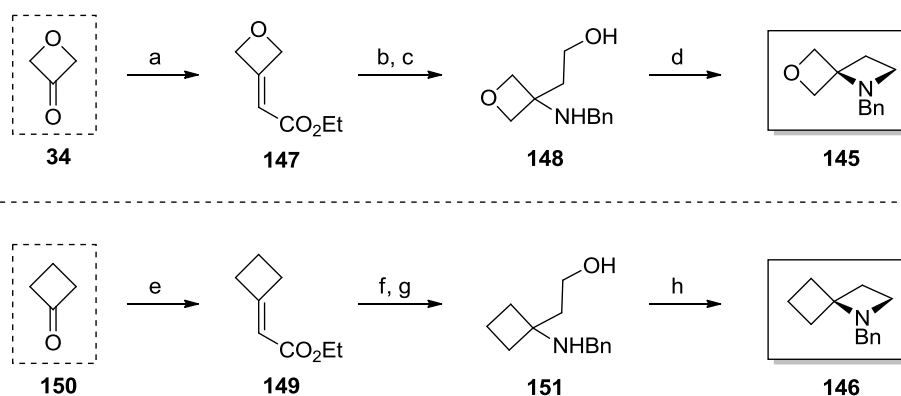
### 1-Aza-6-oxaspiro[3.3]heptane & 1-Azaspiro[3.3]heptane

The same strategic pathway as for the synthesis of thietane **143** was chosen for the preparation of oxetane **145** and cyclobutane **146** (Scheme 27). Thus, oxetan-3-one was converted to **147**, which served as an electrophile in the addition of benzylamine to give, after  $\text{LiAlH}_4$ -mediated reduction, aminoalcohol **148** in good overall yield. Standard conditions for ring-closure gave rise to benzyl-protected angular homospiromorpholine **145** (82% yield). For the corresponding cyclobutane compound, cyclobutanone was converted into  $\alpha,\beta$ -unsaturated

<sup>158</sup> C. A. Hutton, R. Jaber, M. Otaegui, J. J. Turner, P. Turner, J. M. White, G. B. Bacskey, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1066-1071.



ethylcarboxylate **149** following a literature procedure.<sup>159</sup> Analogous steps afforded angular homospiriperidine **146** in 51% overall yield. It is noteworthy that conjugate addition to **149** proved more difficult than in the other four-membered ring systems, as it was required to heat the neat mixture of amine and ester at 60 °C for two days to secure high conversion.



**Scheme 27.** Synthesis of oxetane-azetidines and cyclobutane-azetidines building blocks. Reagents and conditions: a)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ,  $\text{CH}_2\text{Cl}_2$ <sup>77b</sup>; b)  $\text{BnNH}_2$ ; c)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , 75% (2 steps); d)  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{CH}_3\text{CN}$ , then addition of  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$  and heating to 60 °C, 82%; e)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ ,  $\text{NaH}$ <sup>159</sup>; f)  $\text{BnNH}_2$ ; g)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ , 69% (2 steps); h)  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{CH}_3\text{CN}$ , then addition of  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$  and heating to 60 °C, 74%.

### 1,6-Diazaspiro[3.3]heptane

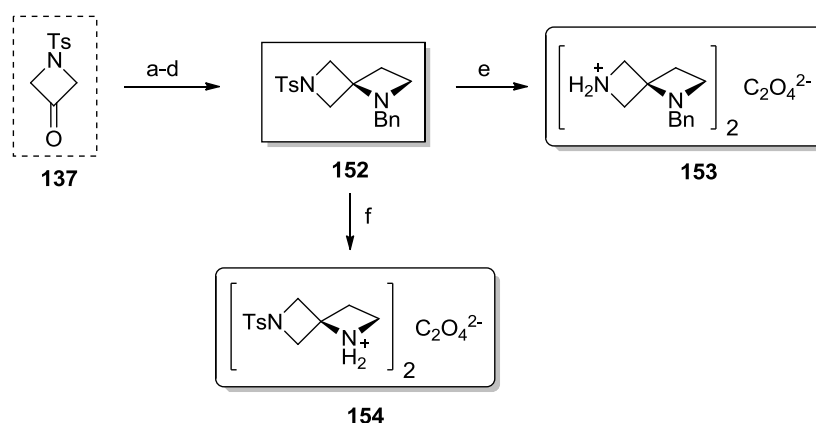
The remaining building block of the series is the angular version of the homospiriperazines, i.e. suitably protected 1,6-diazaspiro[3.3]heptane (Scheme 28).<sup>160</sup> *N*-Tosyl azetidin-3-one (**137**)<sup>161</sup> served as starting material and conversions are similar to those described above. WITIG olefination with (ethoxycarbonylmethylene)triphenylphosphorane, then conjugate addition of benzylamine, and  $\text{LiAlH}_4$ -reduction gave an aminoalcohol, which was cyclized to the azetidines **152** with  $\text{PPh}_3/\text{CBr}_4/\text{Et}_3\text{N}$  (59% overall yield from ketone). This differentially protected material was converted into more convenient building blocks **153** and **154** by removing either the tosyl or the benzyl group and trapping the appropriate amine as an ammonium oxalate salt. Similar to the particular salts described in Chapter 2, these compounds were bench-stable solids

<sup>159</sup> M. Afzal, J. C. Walton, *J. Chem. Soc., Perkin Trans. 2* **1999**, 937-945.

<sup>160</sup> Theoretical planning and experimental work was carried out by Dr. CARINE GUÉROT. For the purpose of completeness, the results are summarized herein.

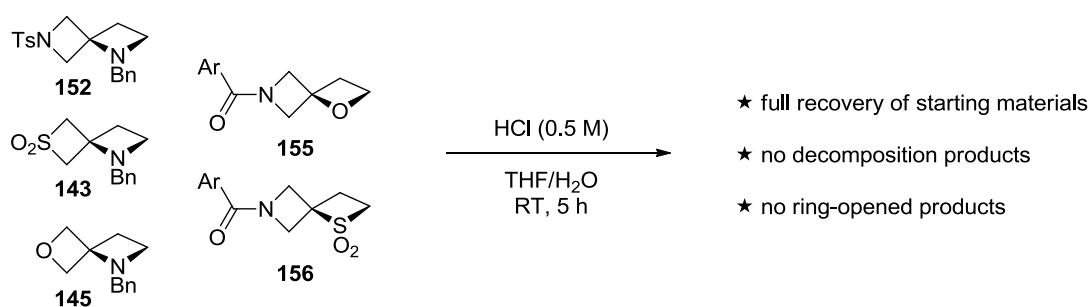
<sup>161</sup> a) A. R. Katritzky, D. J. Cundy, J. Chen, *J. Heterocyclic Chem.* **1994**, 31, 271-275; b) T. Axenrod, C. Watnick, H. Yazdekhasti, P. R. Dave, *J. Org. Chem.* **1995**, 60, 1959-1964; c) A. Singh, N. Sikder, A. K. Sikder, *Indian J. Chem. B* **2005**, 44, 2560-2563.

that could be stored at RT without noticeable change, and employed in a variety of amine functionalization reactions including BUCHWALD-HARTWIG aminations.<sup>162</sup>



**Scheme 28.** GUÉROT's synthesis of angular homospirropiperazine **152** and subsequent generation of ammonium oxalate salts **153** and **154**. Reagents and conditions: a)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ; b)  $\text{BnNH}_2$ ; c)  $\text{LiAlH}_4$ ; d)  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_3\text{CN}$ ; e)  $\text{Mg}$ ,  $\text{MeOH}$ , then oxalic acid; f)  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ , then oxalic acid.

To ascertain their stability towards acidic aqueous media, representatives of the angular spirocycles were subjected to aqueous HCl in THF (total: 0.5 M HCl) at RT for 5 h in individual experiments (Scheme 29). Then the reactions were worked up (aq.  $\text{NaHCO}_3/\text{CH}_2\text{Cl}_2$ ), and the isolated material was weighed and analyzed by  $^1\text{H}$  NMR. It can be said that, within the analytical and experimental error bars,<sup>163</sup> complete recovery of the starting materials was achieved.



**Scheme 29.** Experiments to probe the stability of angular spirocyclic compounds. Ar = 4-Br- $\text{C}_6\text{H}_4$ .

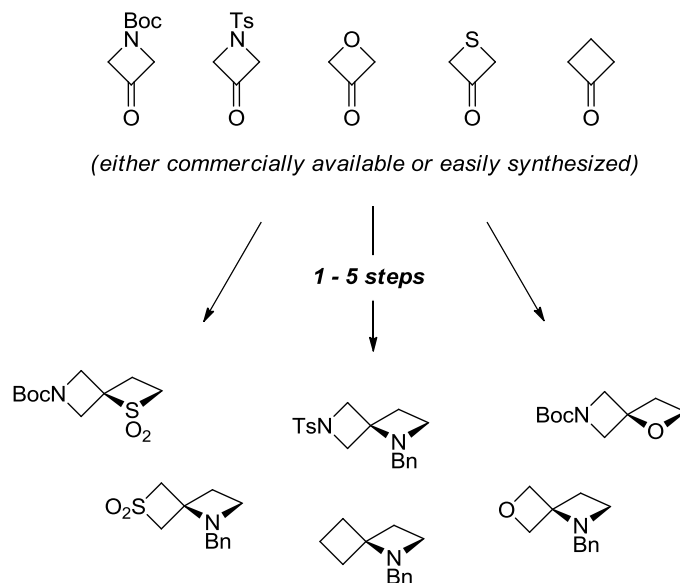
In summary, the novel spirocyclic building blocks were readily synthesized from the cyclic ketones azetidin-3-one, oxetan-3-one, thietan-3-one, and cyclobutanone (Figure 31). Their syntheses required one to five steps and the obtained compounds (or representatives thereof<sup>164</sup>)

<sup>162</sup> C. Guérot, unpublished results.

<sup>163</sup> For an interesting account on this topic, see: M. Wernerova, T. Hudlicky, *Synlett* **2010**, 2701-2707.

<sup>164</sup> Due to the general acid-lability of *tert*-butyl carbamates, it was decided to use amide derivatives of the Boc-protected building blocks in these experiments.

proved to be stable in diluted aqueous hydrochloric acid, thus making these systems intriguing alternatives to 1,3-heteroatom-substituted cyclohexanes.

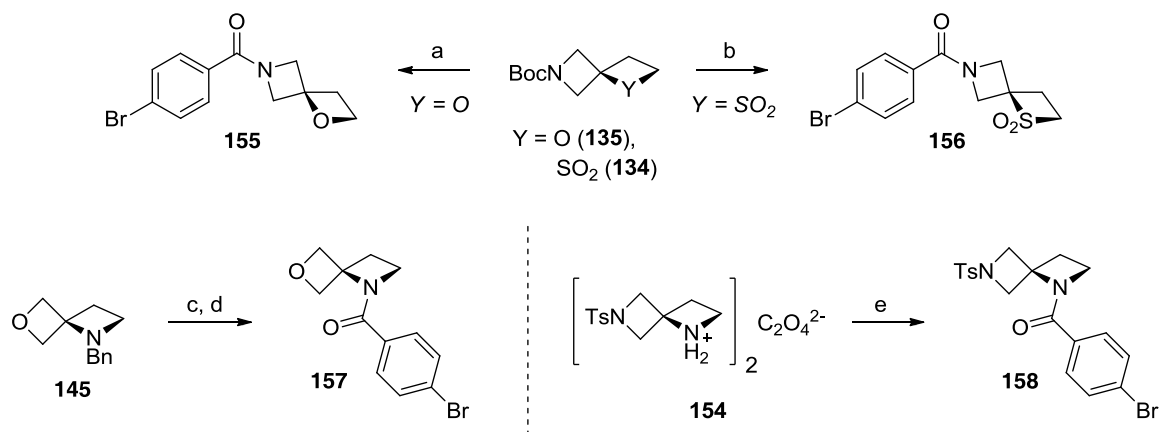


**Figure 31.** Summary of the synthesis of angular spirocycles from cyclic ketones.

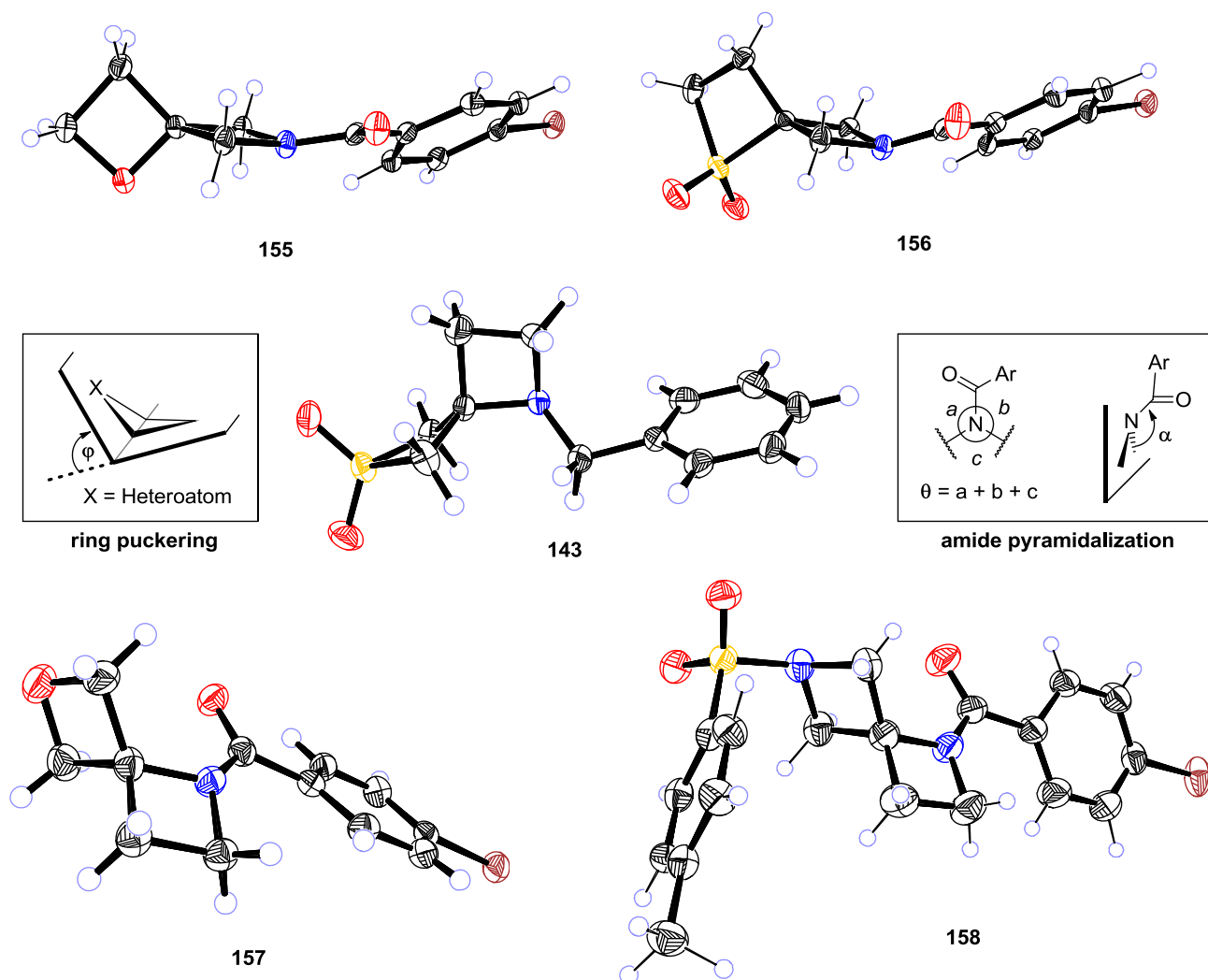
### 3.3 Structural Analysis

With reliable synthetic procedures in hand for the construction of angular spirocycles, we became interested in defining their structural characteristics by means of X-ray crystallography. The expected results would enable the medicinal chemist to better predict the conformational behavior of these spirocycles in modeling studies involving substrate-to-enzyme interactions. Thus, we embarked on the preparation of derivatives that could be crystallized for analysis.

*N*-Benzyl protected sulfone **143** solidified upon standing and recrystallization from  $\text{CH}_2\text{Cl}_2$ /hexanes afforded suitable crystals for analysis. Other building blocks required derivatization to give crystalline solids. Consequently, as outlined in Scheme 30, protecting groups were removed, and the resulting free amines were functionalized with a 4-bromobenzoyl group. Generally, the obtained compounds crystallized from a  $\text{CH}_2\text{Cl}_2$ /hexanes solution, and the formed crystals could be used for analysis by X-ray crystallography.



**Scheme 30.** Formation of crystalline derivatives for the analysis by X-ray crystallography. Reagents and conditions: a) TFA, CH<sub>2</sub>Cl<sub>2</sub>, then *p*-Br-C<sub>6</sub>H<sub>4</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 58% (2 steps); b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, then *p*-Br-C<sub>6</sub>H<sub>4</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 99% (2 steps); c) Pd/C, H<sub>2</sub>, MeOH; d) *p*-Br-C<sub>6</sub>H<sub>4</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 48% (2 steps); e) *p*-Br-C<sub>6</sub>H<sub>4</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 68%.



**Figure 32.** Obtained crystal structures of angular spiro[3.3]heptanes (ORTEP representation with ellipsoids at 50% probability). Indicated is also how conformational parameters (puckering angle  $\varphi$ , sum of the three valence angles around amide nitrogen  $\theta$ , and hinge angle  $\alpha$ ) are defined.

The obtained crystal structures of spirocycles **143** and **155-158** are illustrated in Figure 32. Pronounced ring puckering was found for the azetidine ring in **143** ( $\varphi = 27^\circ$ ) and the dioxothietane rings of **143** ( $\varphi = 28^\circ$ ) and **156** ( $\varphi = 21^\circ$ ). All other four-membered rings appear to be flat (ring puckering  $< 7^\circ$ ).

Previous studies have revealed that carboxamides of azetidines tend to be pyramidalized,<sup>165</sup> a trend that is also observed in the solid-state structures of **155** and **156**. In the case of sulfone **156**, the sum of the three valence angles around the nitrogen atom ( $\theta$ ) is  $344.7^\circ$ , a noticeable divergence from  $360^\circ$  for the ideal planar amide. The hinge angle  $\alpha$ , defined as the angle between the C—N—C plane and the N—C(carbonyl) bond, was calculated for **156** to be  $148.4^\circ$ , also greatly differing from the ideal  $180^\circ$  for planar carboxamides. The amide group geometry in oxetane **155** follows the same tendency with  $\theta = 354.2^\circ$  and  $\alpha = 160.9^\circ$ . Interestingly, if the amide is situated in the 1-position of the spiro[3.3]heptane scaffold, twisting to a much lesser extent is observed (for oxetane **157**:  $\theta = 357.7^\circ$ ,  $\alpha = 168.1^\circ$ ; for azetidine **158**:  $\theta = 359.8^\circ$ ,  $\alpha = 176.5^\circ$ ).

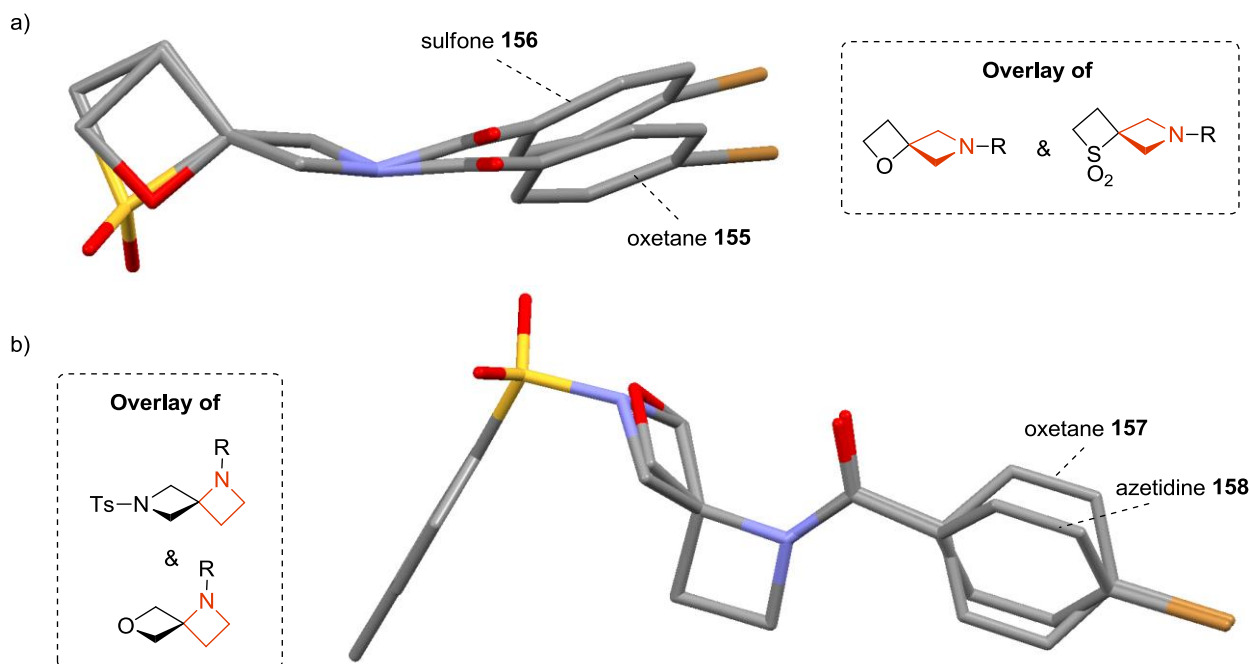
The conformational preferences of sulfonamides are quite different from carboxamides. In sulfonamides, the nitrogen typically adopts a pyramidal conformation with its lone pair bisecting the S=O bonds in the neighboring SO<sub>2</sub> unit. This behavior often leads to a *gauche* conformation of sulfonamide groups, whereas corresponding carboxamides would preferentially adopt an *anti*-type conformation. In the crystal structure of azetidine **158** we observe the typical conformation of a sulfonamide with a pronounced pyramidalization of the nitrogen atom ( $\theta = 333.3^\circ$ ,  $\alpha = 137.3^\circ$ ). This strongly pyramidal conformation of an azetidine sulfonamide follows previous findings by OHWADA *et al.*, who have studied nitrogen atom conformations in *N*-tosyl aziridine ( $\theta = 291.2^\circ$ ,  $\alpha = 120.5^\circ$ ) and *N*-tosyl azetidine ( $\theta = 338.8^\circ$ ,  $\alpha = 142.8^\circ$ ).<sup>166</sup>

To compare molecular conformations in compound pairs **155/156** and **157/158**, structural overlays were prepared by minimizing interatomic distances of common azetidine rings. Figure 33a illustrates the overlay of sulfone **156** with oxetane **155**. The respective azetidine rings are nearly flat and overlap very well. The thietane ring is puckered, and its size and shape differs from the corresponding oxetane, because C—S bonds are longer than C—O bonds (here: C(spiro)—S: 1.81 Å, C(spiro)—O: 1.45 Å). Therefore, the heteroatoms of the spirocycle are further apart in thietane **156** than in oxetane **155** (N—S: 3.58 Å *vs.* N—O: 3.19 Å). Due to differ-

<sup>165</sup> See for example: a) Y. Otani, O. Nagae, Y. Naruse, S. Inagaki, M. Ohno, K. Yamaguchi, G. Yamamoto, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.* **2003**, *125*, 15191-15199. For a general discussion about non-planar amides, consider: b) F. K. Winkler, J. D. Dunitz, *J. Mol. Biol.* **1971**, *59*, 169-182.

<sup>166</sup> T. Ohwada, I. Okamoto, K. Shudo, K. Yamaguchi, *Tetrahedron Lett.* **1998**, *39*, 7877-7880.

ent degrees of pyramidalization in the amide nitrogen, 4-bromophenyl groups do not overlap, and their ring centroids are spaced out by 0.72 Å.



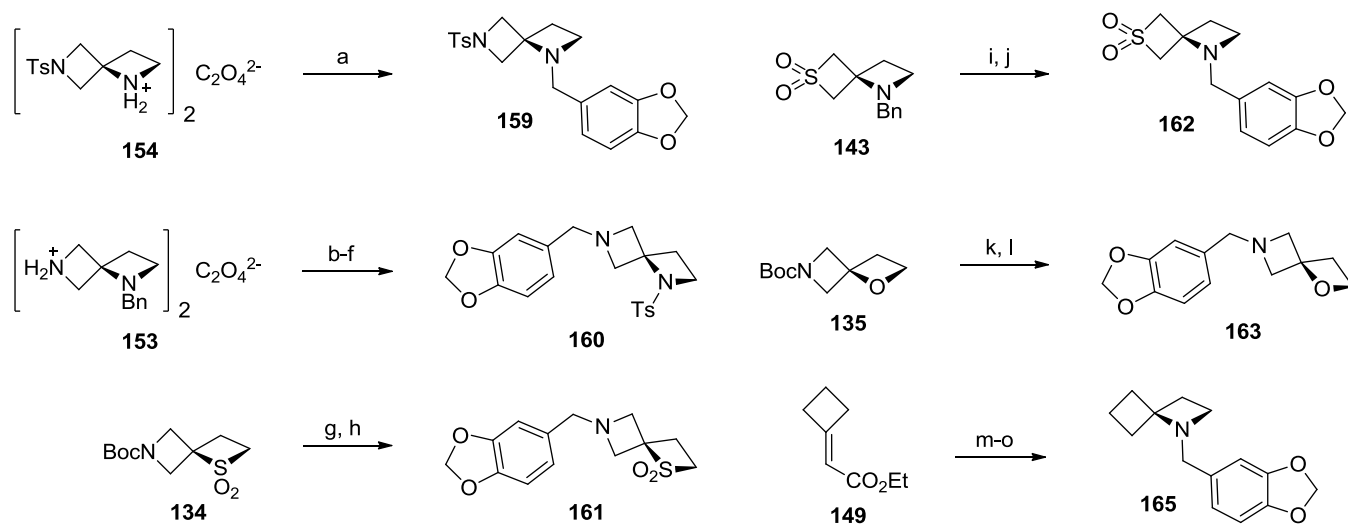
**Figure 33.** Overlay of crystallographic structures of **155** & **156**, and **157** & **158**, respectively. Hydrogen atoms are omitted for clarity. R = *p*-Br-C<sub>6</sub>H<sub>4</sub>C(O)—.

As illustrated in Figure 33b, the respective azetidine rings of the two spirocyclic compounds **157** and **158** nicely overlap, too. All displayed four-membered rings are nearly flat and besides the slightly different orientation of the 4-bromobenzoyl groups, the overlap is excellent. Distances between matching positions are minimal (O(oxetane)—N(Ts): 0.31 Å, phenyl ring centroids: 0.45 Å), and the interatomic distances between the heteroatoms in the spiro[3.3]heptane units are roughly equal (N—N = 3.39 Å *vs.* N—O = 3.35 Å).

### 3.4 Evaluation in Drug Discovery

Similarly to compounds described in Chapter 2, it was our aim to evaluate the physical- and biochemical properties of the angular spirocycles. For the ease of analysis and for comparison reasons, azetidines of this series were tagged with piperonyl residues. The preparation of these compounds is summarized below (Scheme 31). Following standard protocols, the piperonyl group was placed on either nitrogen of the 1,6-diazaspiro[3.3]heptane unit. Oxalate salt **154** was thus treated with piperonal, base, and NaBH(OAc)<sub>3</sub> to afford piperonylamine **159** in 85% yield. Its inversely substituted congener, compound **160**, was obtained via a five-step sequence (Boc-protection, Bn-deprotection, tosylation, Boc-deprotection, and reductive amination of pip-

eronal). Sulfone **134** was deprotected using TFA in  $\text{CH}_2\text{Cl}_2$ , and the resulting amine was functionalized with a piperonyl group to afford sulfone **161** in 83% yield. Deprotection of the *N*-benzyl group in **143** using catalytic hydrogenation and subsequent reductive amination with piperonal afforded angular sulfone **162**. Careful removal of the Boc group in **135** using TFA and then treatment with piperonal,  $\text{Et}_3\text{N}$ , and  $\text{NaBH}(\text{OAc})_3$  resulted in the formation of oxetane **163**. The inverse angular oxetane **164** has previously been made and analyzed.<sup>167</sup> Analogous procedures as described for the preparation of benzylamine **146** were followed in the synthesis of piperonyl-tagged angular homospirropiperidine **165** (conjugate addition of piperonylamine, reduction of the ester group using  $\text{LiAlH}_4$ , and ring-closure under APPEL conditions; 30% yield overall).




**Scheme 31.** Synthesis of piperonyl-tagged angular spirocycles. Reagents and conditions: a) piperonal,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 85%; b)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{MeOH}$ ; c)  $\text{Pd}/\text{C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ ; d)  $\text{TsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 35% (3 steps); e)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ; f) piperonal,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 81% (2 steps; 28% over 5 steps); g)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ; h) piperonal,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 83% (2 steps); i)  $\text{Pd}/\text{C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ ; j) piperonal,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{CH}_2\text{Cl}_2$ , 30% (2 steps); k)  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ; l) piperonal,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 89% (2 steps); m) piperonylamine,  $60^\circ\text{C}$ , 52%; n)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; o)  $\text{PPh}_3$ ,  $\text{CBr}_4$ ,  $\text{CH}_3\text{CN}$ , then addition of  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$  and heating to  $60^\circ\text{C}$ , 58% (2 steps; 30% over 3 steps).

The synthesized model compounds were tested for amine basicity ( $\text{p}K_a$ ), lipophilicity ( $\log P$ ), aqueous solubility ( $\text{Sol.}$ ), and metabolic stability ( $\text{CL}_{\text{int}}$ ) at *F. Hoffmann-La Roche AG* in collaboration with KLAUS MÜLLER, BJÖRN WAGNER ( $\text{p}K_a$ ,  $\log P$ ), HOLGER FISCHER ( $\text{p}K_a$ ,  $\log P$ ), STEPHEN FOWLER ( $\text{CL}_{\text{int}}$ ), and ISABELLE PARRILLA ( $\text{Sol.}$ ). The obtained results are summarized in Table 11. Type A compounds have the piperonyl amine at position 6 (terminal site), whereas isomeric structures with the piperonyl amine group placed at position 1 are categorized as type B compounds.

<sup>167</sup> See the work by WUITSCHIK, ref. 77c.

Since the electron-withdrawing group in type A compounds can exert its influence on the basicity of the proximal amine through one  $\beta$ -pathway only, these compounds are typically more basic than the isomeric compounds of type B, where the influence is transmitted through two  $\beta$ -pathways. This behavior is very consistent for all measured compounds. Furthermore, as the slightly reduced basicity of type B homospirropiperidine ( $pK_a$  (**165**) = 9.3 *vs.* 9.6 for **81**) indicates, the neighboring fully substituted carbon center might attenuate the basicity of amines in this position even more. Although for open-chain aliphatic amines double  $\alpha$ -substitution leads to an increase in  $pK_a$  value,<sup>168</sup> in our case the conformational constraint of the spirocyclic system might lead to unfavorable 1,4-interactions in the protonated form<sup>169</sup> and would thus disfavor protonation. Moreover, hampered solvation of the protonated amine similar to the situation with neopentyl amines can lower the basicity.

**Table 11.** Measured physicochemical and biochemical properties of angular spirocycles.

Compound <sup>[a]</sup> 			$\log D$ <sup>[a]</sup> ( $\log P$ ) <sup>[b]</sup>	Sol. <sup>[c]</sup>	CL <sub>int</sub> <sup>[d]</sup> (h/m)	$pK_a$ <sup>[e]</sup>	
X =		Y =					
Type A	NPip	O	<b>163</b>	1.3 (1.7)	16 300	1/10	7.6
	NPip	SO <sub>2</sub>	<b>161</b>	0.6 (0.6)	3 920	2/28	6.0
	NPip	NTs	<b>160</b>	3.0 (3.1)	18	50/592	6.9
	NPip	CH <sub>2</sub>	<b>81</b>	1.0 (3.2)	3 280	9/26	9.6
Type B	O	NPip	<b>164</b>	1.3 (1.3)	6 000	21/26	6.2
	SO <sub>2</sub>	NPip	<b>162</b>	0.7 (0.7)	149	8/115	4.5
	NTs	NPip	<b>159</b>	3.2 (3.2)	26	110/527	5.4
	CH <sub>2</sub>	NPip	<b>165</b>	1.2 (3.1)	3 410	8/14	9.3

[a] Log *n*-octanol/water distribution coefficient at pH 7.4. [b] Intrinsic lipophilicity of neutral base according to  $\log P = \log D + \log_{10}(1 + 10^{(pK_a - pH)})$ . [c] Intrinsic molar solubility of the neutral base. Values obtained from the experimental thermodynamic solubility [ $\mu\text{mol l}^{-1}$ ] in phosphate buffer (50 mM) at pH 9.9 and  $22.5 \pm 1$  °C, and corrected for  $pK_a$ . [d] Intrinsic clearance rates in  $\text{min}^{-1} / (\text{mg}(\text{protein})/\mu\text{l})$  measured in human (h) and mouse (m) liver microsomes. [e] Amine basicity in H<sub>2</sub>O measured spectrophotometrically at 24 °C; for details, see the Experimental Part. Pip = piperonyl.

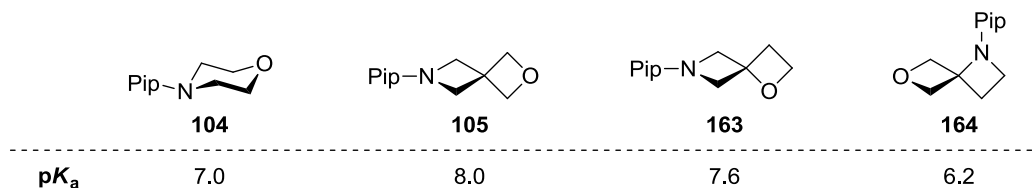
To illustrate a trend that is observed for the entire series,  $pK_a$  values are shown for corresponding ether compounds (Figure 34). Most basic is the linear spirocycle **105** (2  $\gamma$ -pathways) with a  $pK_a$  of 8.0, while reduced basicities are observed for angular spirocycle of type A (**163**; 1  $\beta$ -pathway), morpholine **104** (2  $\beta$ -pathways), and angular spirocycle of type B (**164**; 2  $\beta$ -

<sup>168</sup> M. Morgenthaler, E. Schweizer, A. Hoffmann-Roder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100-1115.

<sup>169</sup> Possible unfavorable eclipsing interactions include H(protonated amine)  $\leftrightarrow$  H(methylene unit of neighboring ring) or H( $\alpha$ , amine substituent)  $\leftrightarrow$  H(methylene unit of neighboring ring).

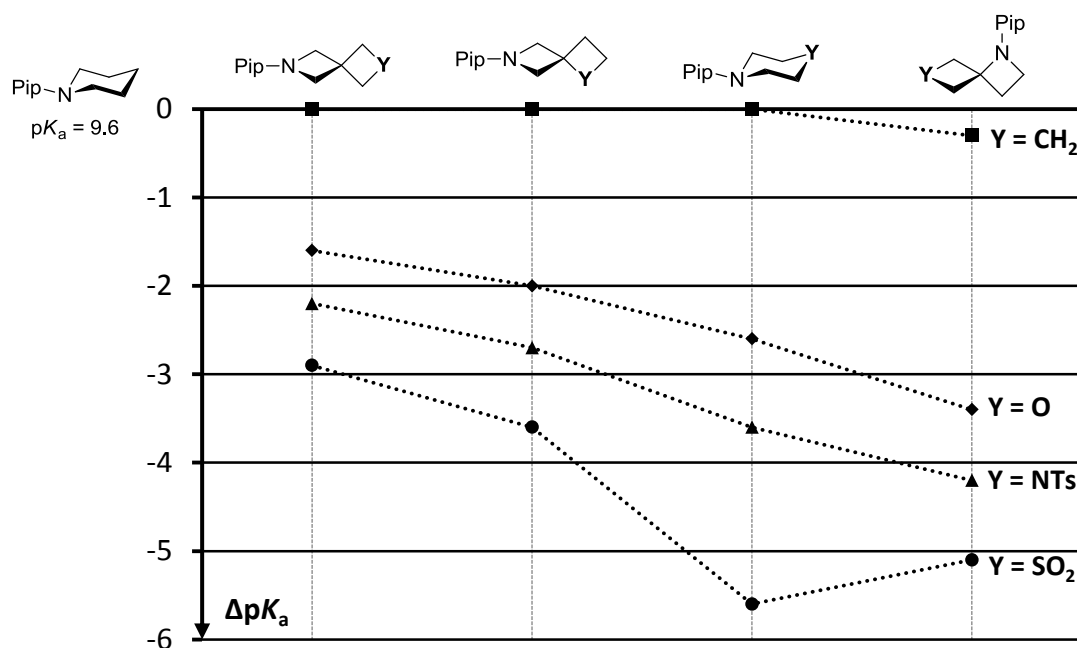


pathways) with a  $pK_a$  of 6.2. Thus, by choosing the proper mono- or spirocyclic etheral unit attached to the nitrogen, its basicity can be modulated over roughly two orders of magnitude.



**Figure 34.** Comparison of amine basicity for morpholine and the various homospirromorpholines.

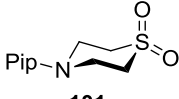
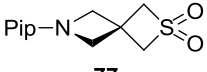
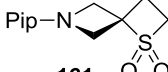
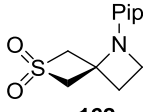
This general behavior of the morpholine/spirocyclic oxetanes series holds true for the majority of the measured compounds. The observed  $pK_a$  decrements in investigated piperonyl amines with respect to the reference compounds piperonyl piperidine **103** and piperonyl 2-azaspiro[3.3]heptane **81**, both with identical basicity ( $pK_a = 9.6$ ), are shown in Figure 35. Typically, basicity increases from type B spirocycle *via* monocycle and type A spirocycle to the linear spirocycle. The only exception is angular homospirithiomorpholine dioxide of type B (compound **162**) that has a higher basicity than its monocyclic counterpart thiomorpholine dioxide **101**.



**Figure 35.** Observed decrements in  $pK_a$  for corresponding spirocyclic and monocyclic compounds. Reference compounds are piperonyl piperidine **103** and piperonyl 2-azaspiro[3.3]heptane **81** that have identical basicity ( $pK_a = 9.6$ ).

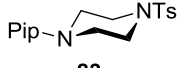
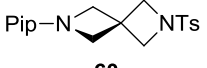
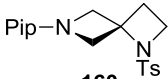
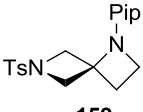
Whereas clear trends are observed for amine basicities, the type of angular scaffold does not have a big influence on the lipophilicity of the investigated compounds. For instance, this is seen

in compound pairs **160/159** and **81/165** that have almost identical log *P*s (in both cases either 3.1 or 3.2). The same behavior is also illustrated in Figure 36 with sulfone compounds. Interestingly, also linear spirocycle **77** has just about the same log *P* as the corresponding angular versions.<sup>170</sup>

				
<b>log <i>P</i></b>	0.1	0.6	0.6	0.7
<b>Sol.</b>	1440	4930	3920	149

**Figure 36.** Comparison of lipophilicity (log *P*) and intrinsic solubility (Sol. in [ $\mu\text{mol l}^{-1}$ ]) for thiomorpholine dioxide **101** and the respective spirocyclic systems.

High aqueous solubilities were found for oxetane spirocycles, homospirropiperidine **165**, and type A angular sulfone **161**; but isomeric angular sulfone **162** turned out to be only moderately soluble in water (more than one order of magnitude lower solubility; see Figure 36). Highly lipophilic tosyl amides **160** and **159** were about as much soluble as the linear version **60**. Although the statistical error bars are large, we observe that angular spirocycles generally are better soluble than monocyclic analogues, but behave slightly worse than 2,6-heteroatomic spiro[3.3]heptanes.

				
<b>hCL<sub>int</sub></b>	310	25	50	110

**Figure 37.** Comparison of intrinsic clearance rates for tosyl piperazine **83** and the corresponding homospirropiperazines in human liver microsomes (hCL<sub>int</sub> in [ $\mu\text{l min}^{-1} \text{mg}_{\text{protein}}^{-1}$ ]).

Following the general trend observed for linear spiro[3.3]heptanes, the angular systems also display a high metabolic robustness. Especially oxetane compounds, but also the sulfones and cyclobutanes have low intrinsic clearance rates in human liver microsomes. Faster metabolic degradation is observed in mouse liver microsomes, but for type A oxetane **163** and type B cyclobutane **165** the determined values are surprisingly low with hardly any observable metabolism (mCL<sub>int</sub> for **163** and **165** are 10 and 14  $\mu\text{l min}^{-1} \text{mg}_{\text{protein}}^{-1}$ , respectively). The more lipophilic tosyl amides **160** and **159** are metabolically at risk, but in comparison with tosyl piperazine **83**, they are still significantly more robust (Figure 37). In accord with the general high

<sup>170</sup> Generally though, the linear spirocycles tend to have lower lipophilicities than the angular analogues. But, since the amount of collected data on this matter is statistically insufficient, we cannot generalize this principle.

robustness of linear azaspiro[3.3]heptanes, tosyl amide **60** performs better than the angular versions.

### 3.5 Conclusion

Convenient synthetic protocols were developed for the construction of angular spiro[3.3]heptanes having generally two heteroatoms at positions 1 and 6 of the ring system. Simple cyclic ketones (azetidin-3-one, oxetan-3-one, thietan-3-one, and cyclobutanone) served as suitable starting materials for the preparation of all members in one to five steps. With reliable synthetic procedures in hand, we prepared a number of derivatives being substituted on a nitrogen atom with a piperonyl group. The analysis of these model systems for their key pharmacokinetic properties revealed in general low lipophilicities, good water-solubilities, and a high metabolic resistance toward human and mouse liver microsomes. Even though these characteristics were not as striking as those of the linear analogues, the angular spirocyclic building blocks are worth implementing in drug discovery programs, as they allow the access to novel chemical and biological space. If this opportunity is taken, then structural information gathered for selected representatives will be of use in enzyme inhibition modeling studies. Due to their ease of access and their remarkable stability and versatility, we expect the angular spirocycles to have an impact on academic and industrial research laboratories.



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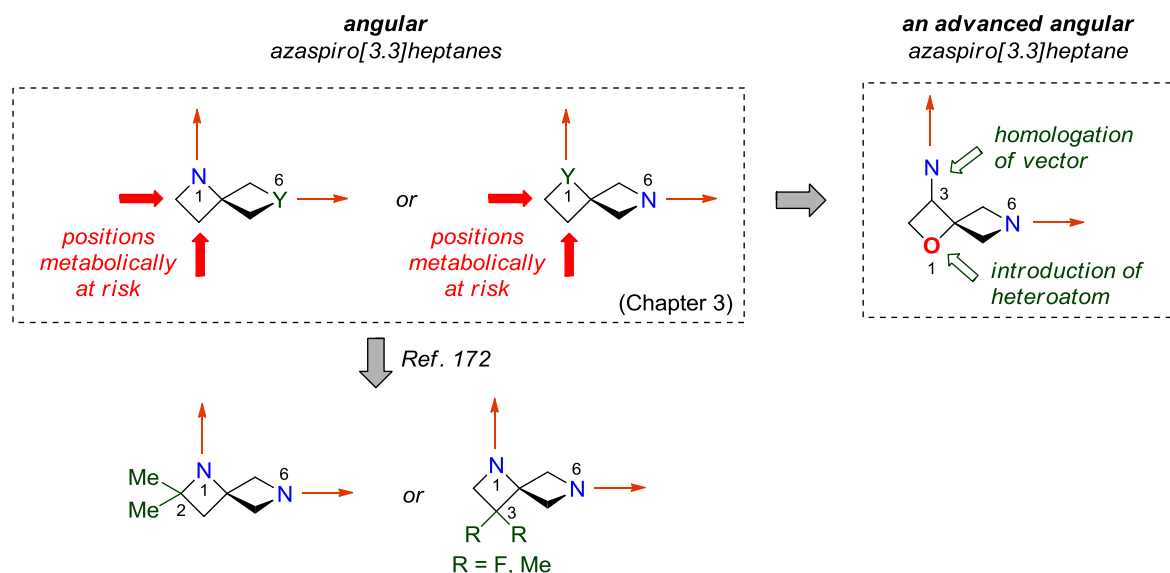
**Advanced Angular  
Spirocycles**

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## 4.1 Conceptual Idea

Previous chapters have shown that spirocyclic four-membered rings have good to exceptional pharmacokinetic properties: they are well soluble in aqueous media, they have low lipophilicities, and they are metabolically robust. Moreover, their preparation required only a few steps from simple starting materials. These assets render them intriguing building blocks and property modulators in drug discovery.

During our studies we have observed that linear azaspiro[3.3]heptanes are particularly metabolically inert, but that angular family members may contain centers that are metabolically at risk (Figure 38). Recent studies by GUÉROT, KNUST, and CARREIRA have indicated that in angular spirocycles, positions at C(2) and/or C(3) are prone to metabolic attack.<sup>171</sup> This was postulated after results from the identification of metabolites (MetID) showed metabolism at the central spiro[3.3]heptane scaffold, and not only peripheral metabolism on attached moieties like *p*-tolyl groups. In part due to this observation, but also with the aim of expanding chemical space, GUÉROT *et al.* have synthesized *gem*-dimethyl and *gem*-difluoro variants of 1,6-diazaspiro[3.3]heptane.<sup>172</sup> The newly introduced geminal groups were believed to hamper metabolic attack on the scaffold.<sup>173</sup>



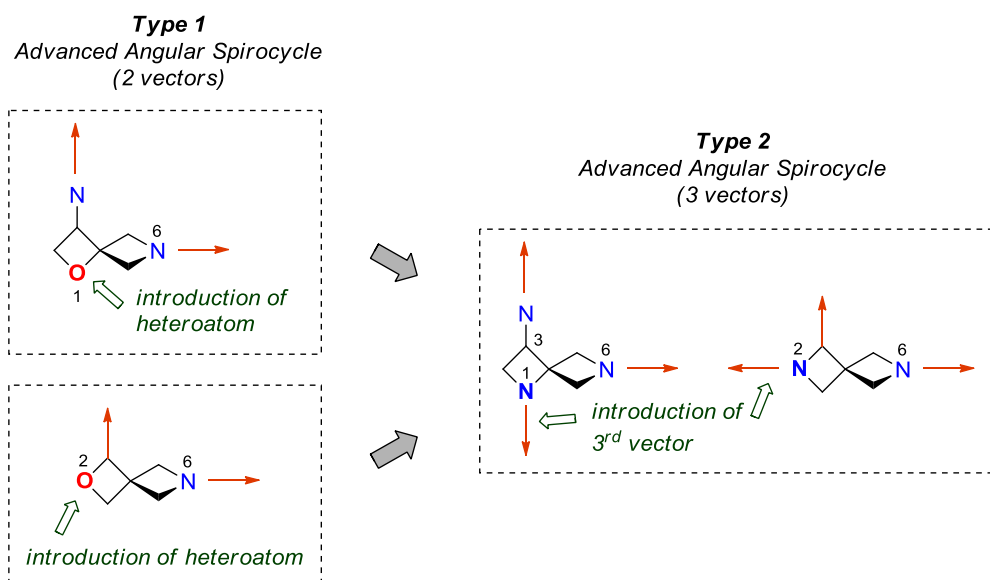
**Figure 38.** From angular to advanced angular systems: a strategy to reduce metabolism in the ring.

<sup>171</sup> C. Guérot, H. Knust, E. M. Carreira, unpublished work.

<sup>172</sup> C. Guérot, B. H. Tchitchanov, H. Knust, E. M. Carreira, *Org. Lett.* **2011**, *13*, 780–783.

<sup>173</sup> These results are pending.

A different entry into the field would involve the implementation of a heteroatom at either one of the two labile positions. As shown in the figure above, an ethereal oxygen at site 1 could minimize metabolic oxidation in the ring, since of all four-membered rings, oxetanes have thus far shown lowest metabolic clearance rates. By introducing this oxygen atom, the opposite position in the ring, originally populated with a heteroatom, would need modification to avoid an unstable aminal.<sup>174</sup> Thus, an amine attached to C(3) could constitute a viable vectorial replacement. If the ethereal oxygen is moved from position 1 to the terminal site 2 of the ring system, a heteroatom-containing vector at C(2) would need a further homologation to circumvent the aminal problem. These two new building blocks are classified in the following as type 1 advanced angular spirocycles (Figure 39, left), as they both have two exit vectors on an oxazaspiro[3.3]heptane skeleton.



**Figure 39.** Definition of type 1 (two exit vectors) and type 2 (three vectors) advanced angular spirocycles.

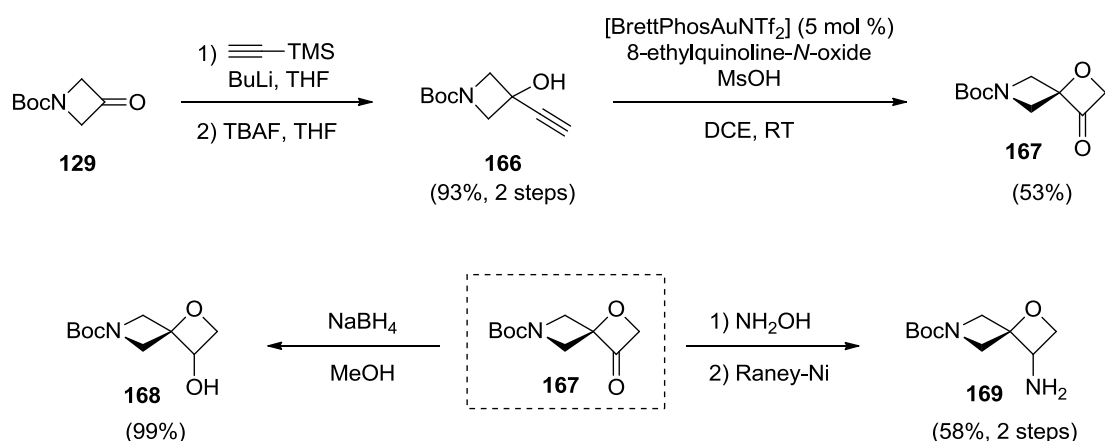
Type 2 advanced angular spirocyclic building blocks are characterized by having three exit vectors on the spiro[3.3]heptane scaffold. As shown in the figure above (right), these constructs are either built on 1,6-diazaspiro[3.3]heptane with an attached amino group at C(3), or on 2,6-diazaspiro[3.3]heptane with a carbon-based vector at C(3). Those building blocks are envisaged to be of high interest to the medicinal chemist as a three-dimensional central scaffold. In contrast to a planar unit such as an aryl or a heteroaryl group, a large portion of the surrounding space is accessible with suitable vectors on a type 2 system (*cf.* Figure 17, Chapter 1).

<sup>174</sup> A heteroatom at this position renders the system chemically unstable toward slightly acidic aqueous solutions, as C(2) is now geminally substituted with two heteroatoms (hydrolysis of an aminal).

## 4.2 Synthesis

### 1-Oxa-6-azaspiro[3.3]heptan-3-one

What was valid for previously described spirocyclic systems, still holds true for the advanced systems: their synthesis is to be achieved in a short fashion in order to make the compounds attractive for their use in drug discovery. This task is increasingly challenging with such densely functionalized systems. Hence, for the first member of type 1 advanced spirocycles, quick access to a suitably *N*-protected 1-oxa-6-azaspiro[3.3]heptan-3-one was desired. ZHANG's work on the synthesis of substituted oxetan-3-ones (*vide infra*) inspired us to prepare the building block *via* Au-catalyzed ring closure (Scheme 32). Boc-protected azetidin-3-one (**129**) was treated with lithiated ethynyltrimethylsilane at low temperature followed by TBAF in THF at 0 °C to afford propargylic alcohol **166**<sup>175</sup> in 93% yield over two steps. Subsequently, to a CH<sub>2</sub>Cl<sub>2</sub>-solution of acetylenic alcohol **166** was added a catalytic amount of [BrettPhosAuNTf<sub>2</sub>], two equivalents of 8-ethylquinoline-*N*-oxide,<sup>176</sup> and 1.5 equiv MsOH giving after 3 h of reaction time, work-up, and purification, oxetan-3-one **167** in 53% yield. This crucial ketone was converted to the corresponding alcohol **168** (NaBH<sub>4</sub>; 99% yield) and amine **169** (*via* a two-step procedure: hydroxylamine hydrochloride, sodium acetate; then RANEY-nickel, H<sub>2</sub>, ethanol) in 58% yield over two steps (unoptimized). In summary, compounds **167–169** were efficiently synthesized in 3–4 steps from commercially available azetidin-3-one **129**.



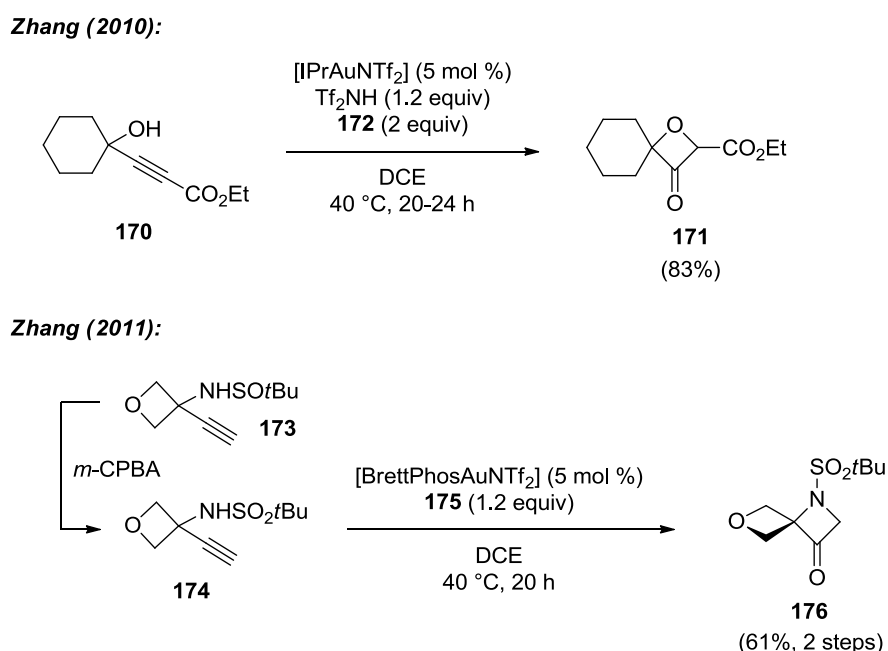
**Scheme 32.** Synthesis of oxetanone **167** and its conversion to corresponding alcohols and amines.

<sup>175</sup> D. A. Claremon, K. Leftheris, S. B. Singh, C. M. Tice, Y. Ye, L. Zhuang, W. Zhao (Vitae Pharmaceuticals Inc.), WO 2011002910, **2011**.

<sup>176</sup> Prepared according to ZHANG and co-workers (B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 14070–14072) in two steps (1. SKRAUP quinoline synthesis, 2. *m*-CPBA-mediated oxidation).



As briefly mentioned above, the synthesis of these building blocks profoundly relied on a recently disclosed method by ZHANG and co-workers (Scheme 33). Based on their findings in the synthesis of dihydrofuran-3-ones from homopropargylic alcohols,<sup>177</sup> they were able to cyclize propargylic alcohols into oxetan-3-ones using a gold(I) catalyst and a pyridine-*N*-oxide as oxidant. As exemplified below, electron-deficient propargylic alcohol **170** underwent oxidative cyclization to give trisubstituted oxetanone **171** in 83% yield.<sup>178</sup> Key to success was the use of [IPrAuNTf<sub>2</sub>], a gold(I) complex with an *N*-heterocyclic carbene as ligand, 4-acetylpyridine-*N*-oxide (2 equiv), and 1.2 equivalents of acid additive (Tf<sub>2</sub>NH). Whereas monosubstituted propargylic alcohols were easily cyclized into the corresponding monosubstituted oxetan-3-ones, electron-deficient alkynes were essential for disubstituted propargylic alcohols (such as **170**) to undergo cyclization.



**Scheme 33.** ZHANG's Au-catalyzed synthesis of oxetan-3-ones and azetidin-3-ones.

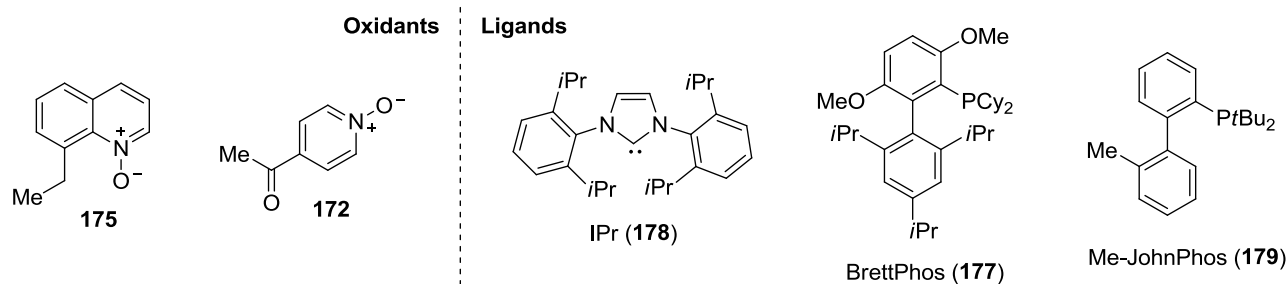
In 2011, ZHANG and co-workers disclosed an expansion of the aforementioned method, as they were now able to cyclize propargylic *tert*-butyl sulfonamides to give substituted azetidin-3-ones.<sup>179</sup> Thus, for instance, alkyne **173** (prepared from the addition of TMSCLi to the ELLMAN imine) was first oxidized with *m*-CPBA to the corresponding sulfonamide **174**, which in turn was treated with [BrettPhosAuNTf<sub>2</sub>] and 8-ethylquinoline-*N*-oxide (**175**) in warm DCE to afford spirocyclic ketone **176** in 61% over 2 steps. In their study, the researchers tested

<sup>177</sup> L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259.

<sup>178</sup> L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.

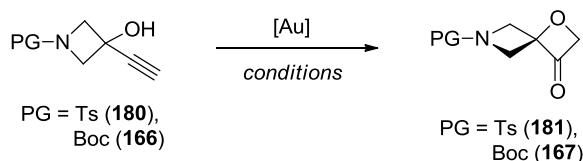
<sup>179</sup> L. Ye, W. He, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3236–3239.

a number of catalysts with different ligated phosphines, and they found BrettPhos (**177**, see Figure 40), initially developed by BUCHWALD and co-workers as a ligand for palladium in the highly efficient arylation of primary amines,<sup>180</sup> to be optimal. In most cases, the use of a sterically demanding pyridine-*N*-oxide (based on 2,6-dibromopyridine or 8-ethylquinoline) allowed the omission of the acid additive.



**Figure 40.** Oxidants and ligands used in the Au-catalyzed oxetan-3-one formation.

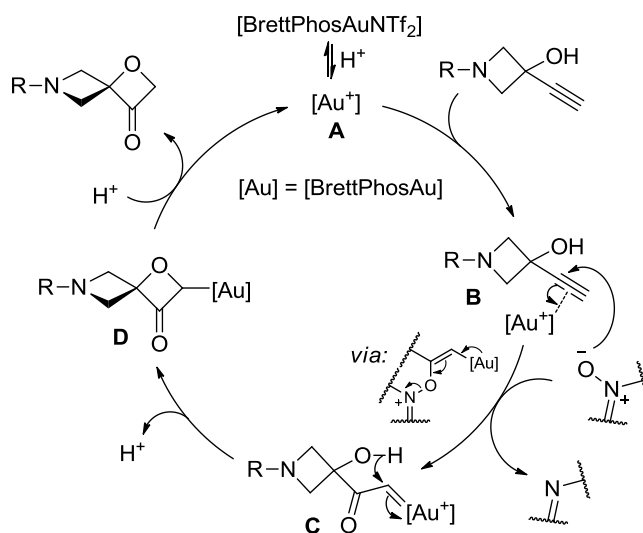
**Table 12.** Optimization of the gold-mediated cyclization to give substituted oxetan-3-ones.



entry	PG	[Au]	conditions	yield
1	Boc	[IPrAuNTf <sub>2</sub> ] (5 mol %)	<b>172</b> (1.2 equiv), HNTf <sub>2</sub> (1.2 equiv), DCE, 40 °C, 20 h	traces of <b>167</b>
2	Ts	[IPrAuNTf <sub>2</sub> ] (5 mol %)	<b>172</b> (1.2 equiv), HNTf <sub>2</sub> (1.2 equiv), DCE, 40 °C, 20 h	16% of <b>181</b>
3	Ts	[BrettPhosAuNTf <sub>2</sub> ] (7 mol %)	<b>175</b> (2.5 equiv) DCE, 40 °C, 23 h	28% of <b>181</b>
4	Ts	[Me-JohnPhosAuNTf <sub>2</sub> ] (7 mol %)	<b>172</b> (1.4 equiv), Tf <sub>2</sub> NH (1.4 equiv) DCE, RT, 13 h	28% of <b>181</b>
5	Ts	[BrettPhosAuNTf <sub>2</sub> ] (7 mol %)	<b>172</b> (1.4 equiv), MsOH (1.4 equiv) DCE, RT, 16 h	31% of <b>181</b>
6	Ts	[BrettPhosAuNTf <sub>2</sub> ] (5 mol %)	<b>172</b> (1.3 equiv), Tf <sub>2</sub> NH (1.3 equiv) DCE, RT, 18 h	32% of <b>181</b>
7	Ts	[BrettPhosAuNTf <sub>2</sub> ] (7 mol %)	<b>175</b> (1.5 equiv), Tf <sub>2</sub> NH (1.4 equiv) DCE, 40 °C, 2.6 h	37% of <b>181</b>
8	Boc	[BrettPhosAuNTf <sub>2</sub> ] (5 mol %)	<b>175</b> (2 equiv), MsOH (1.5 equiv) DCE, RT, 3 h	53% of <b>167</b>
9	Boc	[BrettPhosAuNTf <sub>2</sub> ] (8 mol %)	<b>175</b> (2 equiv), MsOH (1.5 equiv) DCE, RT, 4 h	53% of <b>167</b>

<sup>180</sup> B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.

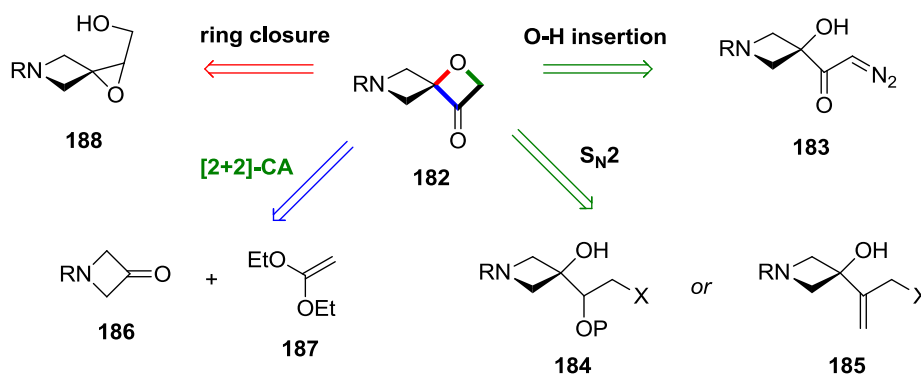
By combining the results that were published in the two papers by ZHANG, it seemed reasonable to investigate this method for the synthesis of building block **167**. Although application of either one of ZHANG's optimized conditions led to unsatisfactory results, the successful isolation of the desired product called for optimization (Table 12, entries 1-3). Interestingly, changing the ligand on gold, the nature of the oxidant, or acid additive had little impact on the yield of isolated products, which varied between 28% and 32% (entries 4-6). Heating significantly reduced the reaction time to below three hours, and a slightly higher catalyst loading as well as somewhat increased amounts of oxidant and acid additive were responsible for a marginally increased yield (entry 7). Even though initially the Boc protecting group was a poor choice (entries 1 *vs.* 2), the newly developed conditions were tested again on substrate **166**. To our surprise, the reaction was much faster and the yield increased by 16%, as target compound **167** was isolated in 53% after 3 h at RT. No further optimization was realized by raising the catalyst loading to 8 mol %, as exactly the same percentaged outcome was observed. It is worth noting that in all experiments from entries 3-9 starting material was fully consumed, and in many cases the  $^1\text{H}$  NMR analysis of unpurified product mixtures revealed the predominant existence of target material.<sup>181</sup>



**Scheme 34.** Proposed catalytic cycle for the Au-mediated cyclization to give oxetan-3-one **167** or **181**.

<sup>181</sup> It is unclear at the moment what happened to the rest of the material. In rare cases where MsOH was employed as the acid additive, some product was observed that contained an  $\alpha$ -OMs ketone without occurring cyclization (intermolecular *vs.* intramolecular O—H insertion of the Au-carbene, see also Scheme 34). No other byproducts could be isolated or identified.

A catalytic cycle is proposed based on the aforementioned results and literature precedence for gold-catalyzed intra- or intermolecular oxidations of alkynes (Scheme 34).<sup>182</sup> The loosely coordinated NTf<sub>2</sub><sup>-</sup> in [BrettPhosAuNTf<sub>2</sub>] is likely to dissociate in the presence of acid, and cationic gold catalyst **A** is released. The carbophilic nature of **A** in combination with the alkynyl substrate will give coordinated complex **B**. The external oxidant, here a pyridine-*N*-oxide, attacks at the internal carbon of the alkyne (similar to the attack of oxidant in *Wacker*-type oxidations), and *via* the intermediacy of a vinylgold(I) species the  $\alpha$ -oxo gold carbene **C** is formed. The nearby alcohol can perform a nucleophilic attack at the metal carbene and yield cyclized intermediate **D**.<sup>183</sup> The presence of acid in the reaction medium will protonate the carbon-bound gold enolate upon release of the product and reconstitution of the gold catalyst.



**Figure 41.** Unsuccessful approaches toward oxetan-3-one building block **182**.

A few other approaches toward the desired 1-oxa-6-azaspiro[3.3]heptan-3-one building block were considered before the solution *via* gold catalysis. Although most of them were unfruitful, they are briefly discussed herein (Figure 41). Initially, an intramolecular O—H insertion of an  $\alpha$ -diazo ketone **183** was considered that founded on similar reports by ZWANENBURG<sup>184</sup> or ROSNATI.<sup>185</sup> Unfortunately, this key step could not be tried because problems arose in the formation of the diazo ketone. Upon treatment of the corresponding carboxylic acid with SOCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> or oxalyl chloride/DMF in CH<sub>2</sub>Cl<sub>2</sub>, protecting groups on the amine were touched, leading to decomposition products when R = Boc and to unidentified side products and

<sup>182</sup> Selected examples from the literature; intramolecular: a) G. Li, L. Zhang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5156–5159; b) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161; c) H.-S. Yeom, J.-E. Lee, S. Shin, *Angew. Chem. Int. Ed.* **2008**, *47*, 7040–7043; intermolecular: d) C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung, R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9891–9894; e) P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2011**, *47*, 379–381.

<sup>183</sup> Also imaginable is the direct C—H insertion of the Au-carbene that would directly deliver the product and rebuild the catalyst.

<sup>184</sup> L. Thijs, P. J. M. Cillissen, B. Zwanenburg, *Tetrahedron* **1992**, *48*, 9985–9990.

<sup>185</sup> A. Pusino, V. Rosnati, C. Solinas, U. Vettori, *Tetrahedron* **1983**, *39*, 2259–2263.

*p*-toluenesulfonyl chloride in the case where the nitrogen was tosyl-protected. The approach was abandoned due to these discouraging results.

The S<sub>N</sub>2 reaction was then considered as the key reaction toward oxetanone **182**, and possible precursors were protected alcohol **184**<sup>186</sup> or alkene **185**<sup>187</sup> (X = leaving group). The latter with X being OTs or Br gave, upon treatment with base, primarily a dimeric product (presumably a dioxacyclooctane), and none of the desired methyleneoxetane was observed. The ring closure with **184** (R = Ts, X = Ts, P = Bn) was successful, but the sequence to the final compound suffered from too many steps and some low yields. An equally direct approach as with gold catalysis was a [2+2]-cycloaddition between an azetidin-3-one **186** and diethyl ketene acetal (**187**),<sup>188</sup> but no oxetane product was formed.<sup>189</sup> A somewhat exotic approach involved a reaction that can be classified as a homo-PAYNE rearrangement.<sup>190</sup> Thus, epoxide **188** would be protonated and might be in equilibrium with the tertiary carbocation that in turn could be trapped by the pendant alcohol functionality.<sup>191</sup> Although differences in energy are presumably not large, the so-formed oxetane would probably be the thermodynamically most stable constitutional isomer. Unfortunately, these theoretical considerations could not be endorsed, since experimentation revealed that the postulated carbocation is either not formed or rapidly leads to decomposition products. When acids with moderately nucleophilic conjugate bases (MsOH, CF<sub>3</sub>CO<sub>2</sub>H) were employed, attack of the anion at the secondary position was observed. Rapid decompositions were noted when triflic acid or HBF<sub>4</sub>·OMe<sub>2</sub> were used.

## **2-Oxa-6-azaspiro[3.3]heptane-1-carboxylic acid**

The second building block of type 1 advanced angular spirocycles is identical with a homospirromorpholine that has a carboxylic acid attached to C(1). Using a similar approach as when substituents were introduced  $\alpha$  to an amine in 2,6-diazaspiro[3.3]heptanes (see Chapter 2), the carboxylate would be introduced masked as a 2-furyl group (Scheme 35). Accordingly, aldehyde **67** was treated with 2-furyllithium (prepared from BuLi and furan in THF) to give

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<sup>186</sup> Key step in its synthesis: TfOH-mediated epoxide opening with benzyl alcohol (see for instance: H. S. Byun, R. Bittman, *Tetrahedron Lett.* **1989**, 30, 2751-2754).

<sup>187</sup> Prepared by the addition of lithiated 2-iodoprop-2-en-1-ol to the corresponding ketone (for a similar reaction: see A. Sakakura, Y. Takayanagi, H. Shimogawa, H. Kigoshi, *Tetrahedron* **2004**, 60, 7067-7075).

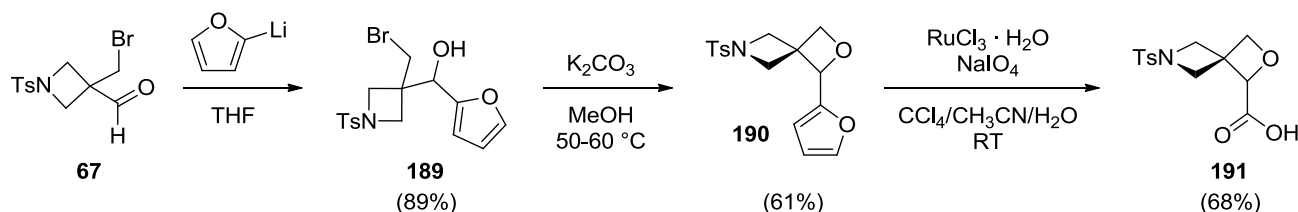
<sup>188</sup> The only example found in the literature, where this selectivity is observed: Y. Araki, J. Nagasawa, Y. Ishido, *Carbohydr. Res.* **1981**, 91, 77-84.

<sup>189</sup> A single reaction was conducted with blue light (maximum wavelength around 450 nm). This route was abandoned due to the successful implementation of Au-catalysis and lack of precedence in the literature for the intended transformation.

<sup>190</sup> The PAYNE rearrangement normally is run under basic conditions. Application of these here would probably favor the formation of epoxides over oxetanes.

<sup>191</sup> For a related precedence, see: T. Prangé, M. S. Rodríguez, E. Suárez, *J. Org. Chem.* **2003**, 68, 4422-4431.

carbinol **189** in good yield (89%). After some experimentation (*vide infra*),  $K_2CO_3$  in hot methanol was found to induce cyclization into oxetane **190** (61% yield). Application of catalytic ruthenium(III)chloride (*ca.* 5 mol %) and superstoichiometric sodium periodate (10 equiv) in a common solvent mixture ( $CCl_4/CH_3CN/H_2O$ ) gave the desired carboxylic acid **191** that could be purified by chromatography.



**Scheme 35.** Synthesis of carboxylic acid **191**.

As briefly mentioned above, ring-closure of bromoalcohol **189** was not straightforward. None of the desired oxetane could be isolated when initially  $KOtBu$  was used in anhydrous THF (Table 13), and instead 3-methylene-1-tosylazetidine (**192**) was obtained in 53% yield. This product is most likely formed in a GROB-type fragmentation (see Scheme 36), as similar observations had been made earlier by SEARLES *et al.*,<sup>192</sup> and the presence of furfural (**193**) was seen in the  $^1H$  NMR analysis of the unpurified reaction mixture. Only starting material was left after the treatment of **189** with either DBU in  $CH_2Cl_2$ <sup>193</sup> or  $Ag_2O$  in  $Et_2O$  (entries 2 and 3). Consumption of starting material and formation of the desired oxetane resulted from the treatment of **189** with sodium hydroxide and tetrabutylammonium hydrogensulfate in a biphasic solvent mixture ( $CH_2Cl_2/H_2O$ ).<sup>194</sup> At best, the pure product was isolated in 51% yield (entry 4). Issues with reproducibility and isolation of pure material (several side products had similar retention times on silica gel) prompted us to continue searching for alternative conditions. Finally, potassium carbonate in hot methanol<sup>195</sup> gave clean conversion to the oxetane, and no fragmented byproducts were observed (entry 5).<sup>196</sup>

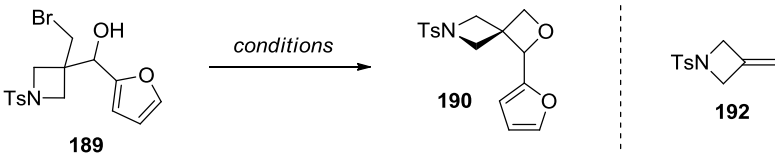
<sup>192</sup> S. Searles, R. G. Nickerson, W. K. Witsiepe, *J. Org. Chem.* **1959**, *24*, 1839–1844.

<sup>193</sup> E. Ciganek, J. C. Calabrese, *J. Org. Chem.* **1995**, *60*, 4439–4443.

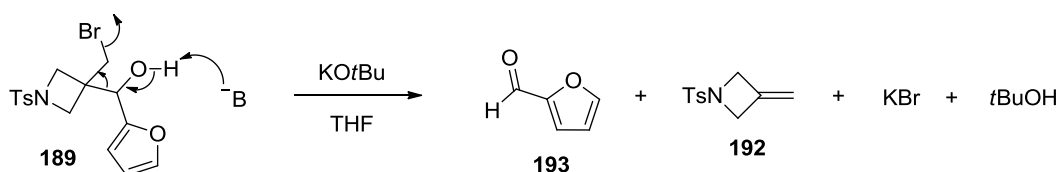
<sup>194</sup> H. Xianming, R. M. Kellogg, *Synthesis* **1995**, 533–538.

<sup>195</sup> Inspired by: E. A. Couladouros, V. P. Vidali, *Chem.–Eur. J.* **2004**, *10*, 3822–3835.

<sup>196</sup> The somewhat reduced yield can be explained by the fact that **190** is, to a certain extent, unstable on  $SiO_2$ . Its purification should be therefore performed as fast as possible.

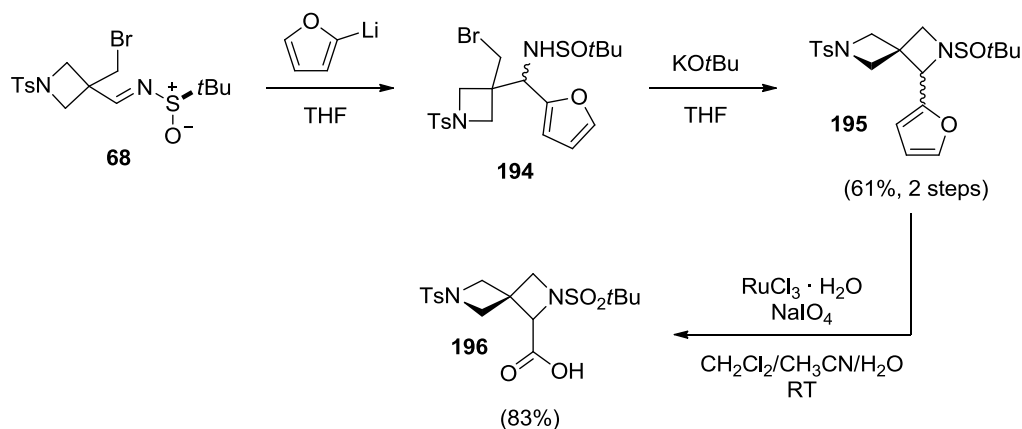
**Table 13.** Probing conditions for the oxetane formation in **190**.


entry	conditions	result
1	KOtBu (3 equiv) THF, 0 °C, 30 min	53% of side product <b>192</b>
2	DBU (2 equiv) CH <sub>2</sub> Cl <sub>2</sub> , 0 °C → RT, 22 h	only starting material
3	Ag <sub>2</sub> O (6 equiv), Et <sub>3</sub> N (0-2 equiv) Et <sub>2</sub> O, RT → reflux, several days	starting material and traces of other decomp. products
4	NaOH (17 equiv), Bu <sub>4</sub> NHSO <sub>4</sub> (0.3 equiv) CH <sub>2</sub> Cl <sub>2</sub> /H <sub>2</sub> O, 0 °C → RT, 1.5 h	51% of oxetane <b>190</b>
5	K <sub>2</sub> CO <sub>3</sub> (5 equiv) MeOH, 50-60 °C, 19 h	61% of oxetane <b>190</b>

**Scheme 36.** Explanation for the formation of observed byproducts.

### 2,6-Diazaspiro[3.3]heptane-1-carboxylic acid

The first building block of type 2 advanced angular spirocycles is a homospirropiperazine with a carboxylic acid  $\alpha$  to one of the amines, in other words an  $\alpha$ -amino acid. Its synthesis would be conducted similarly like  $\alpha$ -substituted homospirropiperazines (see Chapter 2) or like 2-oxa-6-azaspiro[3.3]heptane-1-carboxylic acid (see above). The substituted ring should be prepared by adding a CO<sub>2</sub>H-surrogate to an imine with subsequent ring-closure and unmasking of the carboxylic acid.



**Scheme 37.** Synthesis of carboxylic acid **196**.

This strategy was elaborated as shown in Scheme 37. Lithiated furan was added to *tert*-butylsulfinyl imine **68** (see Chapter 2) to afford the addition product **194** in almost quantitative yield, but no diastereoselectivity (d. r. = 1:1). Since the final material was targeted in racemic form, diastereoisomers were not separated, and the unpurified reaction product was used in the subsequent step. In contrast to the oxetane-forming step described above, treatment of **194** with KOtBu in THF cleanly led to the azetidine product **195** (61% over 2 steps) without observation of fragmentation products. Oxidative cleavage of the furan ring in presence of a *tert*-butanesulfinamide yielded the free carboxylic acid **196** under concomitant oxidation of the sulfur atom to give a sulfonamide functionality.<sup>197</sup> Although the SO<sub>2</sub>*t*Bu-group (also known as the Bus protecting group) requires harsher conditions for its removal than the analogous SO*t*Bu-unit, ELLMAN<sup>197a</sup>, WEINREB, and other researchers<sup>198</sup> have shown that it can be conveniently removed from a nitrogen atom with TfOH in CH<sub>2</sub>Cl<sub>2</sub>.

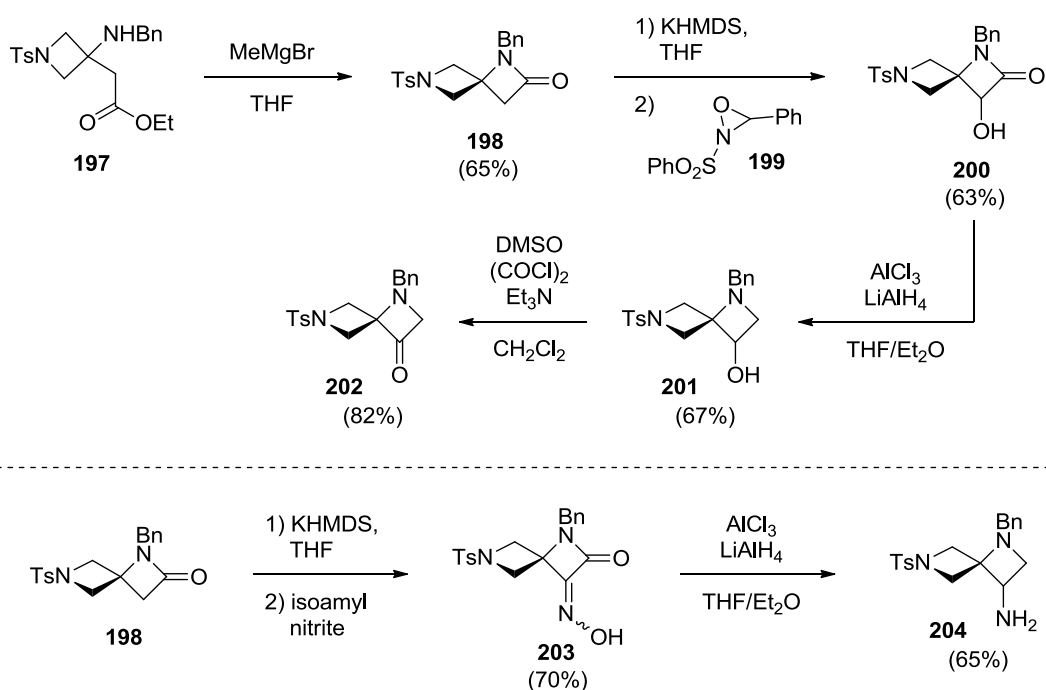
<sup>197</sup> a) G. Borg, M. Chino, J. A. Ellman, *Tetrahedron Lett.* **2001**, *42*, 1433-1435; b) Y.-C. Luo, H.-H. Zhang, P.-F. Xu, *Synlett* **2009**, 833-837; c) Y.-C. Luo, H.-H. Zhang, Y.-Z. Liu, R.-L. Cheng, P.-F. Xu, *Tetrahedron: Asymmetry* **2009**, *20*, 1174-1180.

<sup>198</sup> Selected examples from the literature: a) P. Sun, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1997**, *62*, 8604-8608; b) S. Hanessian, X. Wang, *Synlett* **2009**, 2803-2808; c) S.-S. Jin, M.-H. Xu, *Adv. Synth. Catal.* **2010**, *352*, 3136-3140.



**1,6-Diazaspiro[3.3]heptan-3-one**

While GUÉROT planned and executed the synthesis of the remaining building block of the series, the results are summarized herein for reasons of comprehensiveness (Scheme 38). Methylmagnesium bromide-mediated cyclization<sup>199</sup> of **197** afforded  $\beta$ -lactam **198** in 65% yield. The lactam was enolized using KHMDS, and the formed enolate trapped with DAVIS' oxaziridine **199**<sup>200</sup> to give  $\alpha$ -hydroxylated compound **200** in good yield. The lactam was reduced to the corresponding amine ( $\text{LiAlH}_4/\text{AlCl}_3$ ),<sup>201</sup> revealing the first target compound (**201**) in 67% yield. Alcohol **201** could be oxidized to the corresponding ketone **202** using SWERN's conditions (82% yield).



**Scheme 38.** GUÉROT's synthesis of alcohol **201**, ketone **202**, and triamine **204**.

The targeted triamine compound **204** was also successfully synthesized starting from  $\beta$ -lactam **198**. Using the same conditions for enolization as described above (KHMDS in THF), and by trapping the formed enolate with isoamyl nitrite,<sup>202</sup> an isomeric mixture of oximes **203** was isolated in 70% yield (the oxime is likely to be produced by the tautomerization of the ini-

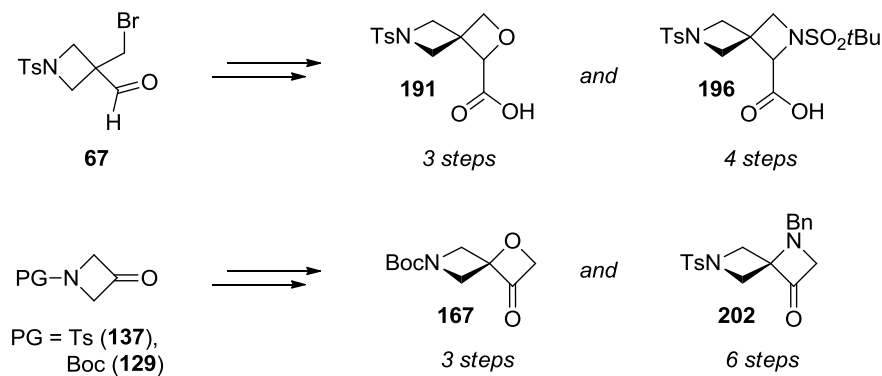
<sup>199</sup> S. G. Davies, D. R. Fenwick, *J. Chem. Soc., Chem. Commun.* **1995**, 1109-1110.

<sup>200</sup> Seminal work by DAVIS: F. A. Davis, L. C. Vishwakarma, J. G. Billmers, J. Finn, *J. Org. Chem.* **1984**, *49*, 3241-3243. A related review: F. A. Davis, A. C. Sheppard, *Tetrahedron* **1989**, *45*, 5703-5742.

<sup>201</sup> Seminal work on  $\beta$ -lactams by MANDER: a) M. Jackson, L. Mander, T. Spotswood, *Aust. J. Chem.* **1983**, *36*, 779-788. See also b) I. Ojima, M. Zhao, T. Yamato, K. Nakahashi, M. Yamashita, R. Abe, *J. Org. Chem.* **1991**, *56*, 5263-5277.

<sup>202</sup> Related publications on  $\beta$ -lactams: a) Y. Takahashi, H. Yamashita, S. Kobayashi, M. Ohno, *Chem. Pharm. Bull.* **1986**, *34*, 2732-2742; b) H. Yamashita, N. Minami, K. Sakakibara, S. Kobayashi, M. Ohno, *Chem. Pharm. Bull.* **1988**, *36*, 469-480; c) J. J. Folmer, C. Acero, D. L. Thai, H. Rapoport, *J. Org. Chem.* **1998**, *63*, 8170-8182.

tially formed nitroso compound). Reduction of both the lactam and the oxime functionalities occurred when **203** was treated with  $\text{LiAlH}_4/\text{AlCl}_3$  in hot THF/ $\text{Et}_2\text{O}$ , and differentially protected triamine **204** was obtained in good yield.



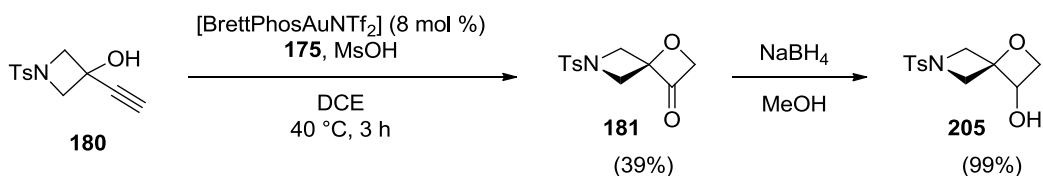
**Scheme 39.** Summary of the synthesis of advanced angular spiro[3.3]heptanes.

In conclusion, the heteroatom-rich and densely functionalized angular spirocyclic systems were prepared in short sequences from commercially available or previously easily prepared starting materials (Scheme 39). In addition to established synthetic techniques the application of recently discovered metal-catalyzed transformations enabled quick access to some of the spirocycles. Due to their ease of synthesis, their synthetic versatility (conveniently protected amines, free carboxylic acids, reactive ketones), and their defined spatial arrangement of vector substituents, we believe that these spirocyclic systems will have a similarly high impact in drug discovery as previously described linear and angular systems.<sup>203</sup>

### 4.3 Structural Analysis

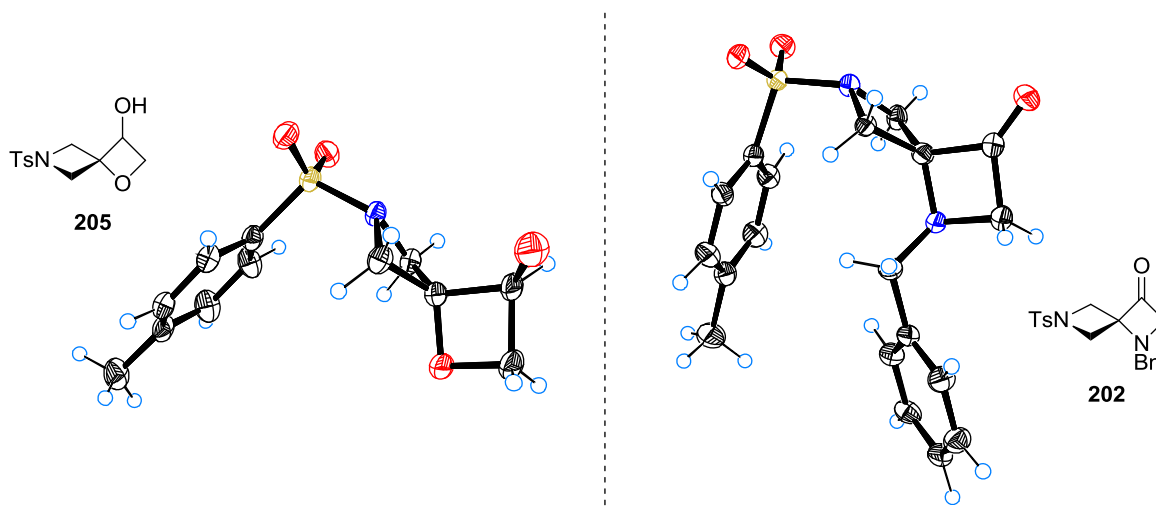
For comparison purposes and for the sake of a precise structural description of advanced angular spirocyclic building blocks, we obtained X-ray crystallographic structures of two illustrative compounds. While key ketone **202** gave suitable crystals for analysis, its analogous oxetane derivatives bearing a Boc protecting group on the amine were all oils. Therefore, tosyl protected derivatives **181** (39% yield) and **205** (99% yield) were prepared in equivalent transformations (Scheme 40), and oxetanol **205** afforded good quality crystals for subsequent X-ray crystallography.

<sup>203</sup> Angular spirocycles: J. A. Burkhard, C. Guérot, H. Knust, M. Rogers-Evans, E. M. Carreira, *Org. Lett.* **2010**, *12*, 1944–1947. A manuscript describing the synthesis of the advanced angular spirocycles is in preparation.



**Scheme 40.** Synthesis of a crystalline derivative of a type 1 advanced angular spirocycle.

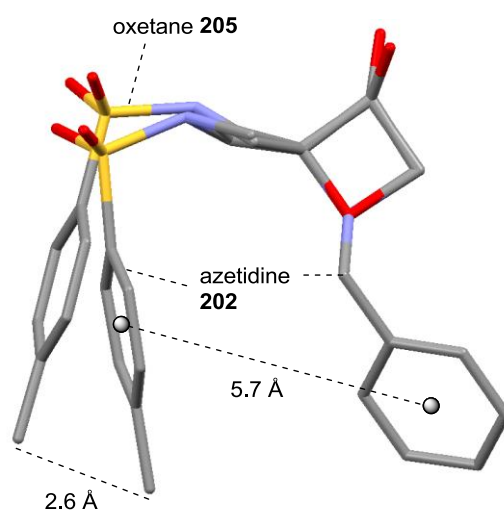
The crystal structures of oxetanol **205** and azetidinone **202** are shown in Figure 42. While there are no major structural surprises, it is worth noting that in both structures the aromatic moiety of the tosyl group is oriented on the same side as the heteroatom in the other four-membered ring, and the heteroatomic vector (CH—OH or C=O) is pointing in the other half of the surrounding imaginary sphere. In oxetane **205** the interatomic distance between the two heteroatoms of the spiro[3.3]heptane core is 3.38 Å, while the N—N distance in **202** is 3.43 Å.



**Figure 42.** Crystal structures of alcohol **205** and ketone **202** (ORTEP format with ellipsoids at 50% probability).

Of all the four-membered rings present in both structures, only the azetidine ring in **205** displays notable ring puckering with  $\varphi = 27^\circ$  (other rings:  $\varphi < 12^\circ$ ).<sup>204</sup> All nitrogens are pyramidalized. The benzyl-protected nitrogen in **202** is most pyramidalized ( $\theta = 328.0^\circ$ ,  $\alpha = 132.1^\circ$ ), but also sulfonamide nitrogens show regularly pronounced pyramidalization:  $\theta = 332.9^\circ$ ,  $\alpha = 136.8^\circ$  in azaspirocycle **202**, and  $\theta = 337.4^\circ$ ,  $\alpha = 141.4^\circ$  in oxaspirocycle **205**.

<sup>204</sup> For the definition of  $\varphi$ ,  $\theta$ , and  $\alpha$ , see Chapter 3.

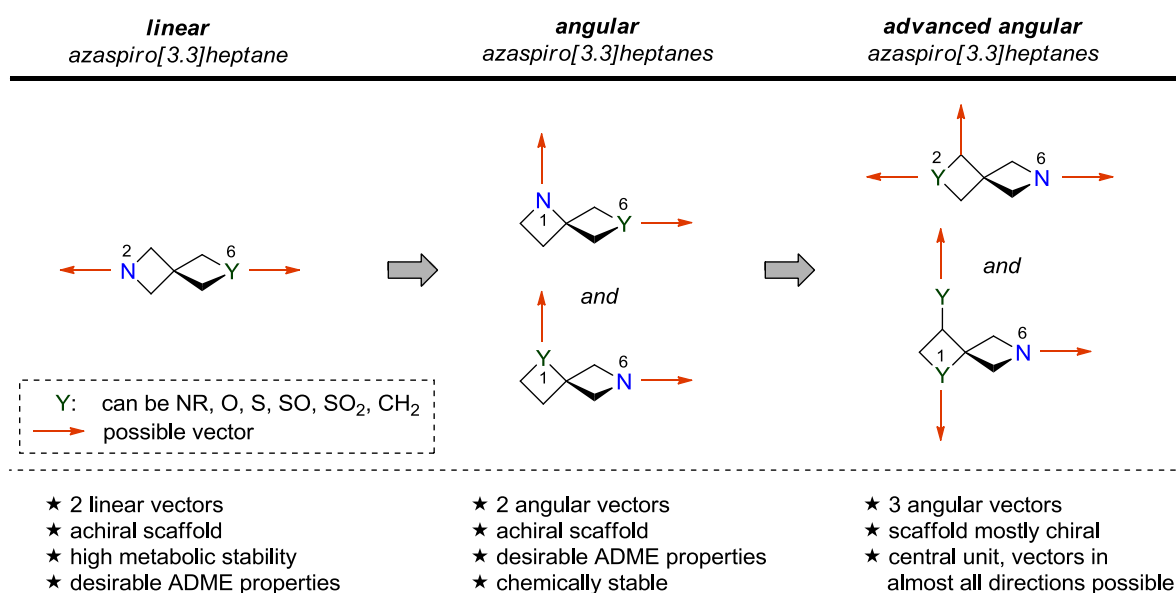


**Figure 43.** Structural overlay of oxetane **205** and azetidine **202** with minimized distances of corresponding atoms in the right four-membered ring. H-atoms are omitted for clarity.

Even though one of the compounds is a ketone and the other is an alcohol, a structural overlay of oxacycle **205** and azacycle **202** was prepared by minimizing distances of corresponding atoms in the right rings (Figure 43). While the overlay is almost perfect for the right rings, discrepancies (primarily in ring puckering) between the tosyl azetidines lead to noticeable differences in the orientation of the tosyl groups. Thus, in the overlay the corresponding methyl groups are 2.6 Å apart. Worth noting is also that both aromatic systems in **202** are oriented in roughly the same direction and could serve as intriguing pharmacophoric vectors in certain binding situations (ring centroids are 5.7 Å apart).

## 4.4 From Linear to Advanced Spirocyclic Building Blocks: Summary & Outlook

A number of different considerations influenced the definition and creation of novel building blocks, but important factors were always the pharmacokinetic properties of the parental compounds (e.g. for linear system: oxetanes), a reasonable structural simplicity (preferably an a-chiral scaffold), and an estimated straightforward synthetic access (small number of scalable steps from commercially available material). Naturally, these building blocks should be chemically stable and due to their unprecedented nature allow the pharmaceutical industry to enter novel chemical and intellectual property space.

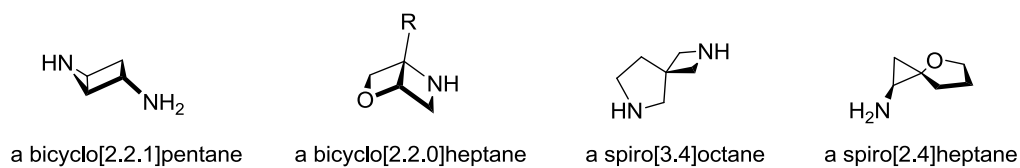


**Figure 44.** From linear to advanced angular spirocycles: an overview.

As shown in Chapters 2-4, many of the aforementioned goals were realized (Figure 44). The linear spirocycles displayed excellent pharmacokinetic properties and in many cases were superior to traditionally used heterocycles like piperazine, piperidine, and morpholine. Moreover, they were synthesized in only a few steps and proved to be chemically stable, too. These remarkable characteristics guided the journey toward angular scaffolds that would expand the vectorial space around the spiro[3.3]heptane unit. In addition, these surrogates for inherently unstable 1,3-heteroatomic cyclohexanes were easily accessible and turned out to possess a desirable pharmacokinetic profile. While the building blocks had at most two sites for the direct attachment of vectors so far, the leap toward advanced angular azaspiro[3.3]heptanes enabled the decoration with up to three exit vectors. This feature turns the spirocyclic unit from a largely terminal into a central scaffold. With this step, the system is no more only a property modulator, but is ready to be considered as a privileged structure, as many distinct requirements are fulfilled. The possibility to attach vectors at multiple positions in an array of orientations makes these building blocks attractive in drug discovery programs, and they should unquestionably be considered in the context of scaffold hopping.

Future directions should include the evaluation of the pharmacokinetic profile of advanced spirocycles as well as their application as a key scaffold in a defined inhibition project. With respect to this, it is expected that with the unique opportunities that this framework can provide, extraordinary compound-to-enzyme binding situations can be discovered and rendered useful for advances in the treatment of diseases. Moreover, these building blocks can inspire the creation of novel bi- or spirocyclic systems (e.g. bicyclo[2.1.0]pentanes, bicyclo[2.2.0]hexanes, spi-

ro[3.4]octanes, spiro[2.4]heptanes) that may populate uncharted chemical space and provide countless possibilities in medicinal chemistry (Figure 45).<sup>205</sup>



**Figure 45.** Selected examples of novel hypothetical building blocks.

<sup>205</sup> C. M. Marson, *Chem. Soc. Rev.* **2011**, *40*, doi: 10.1039/c1cs15119c.

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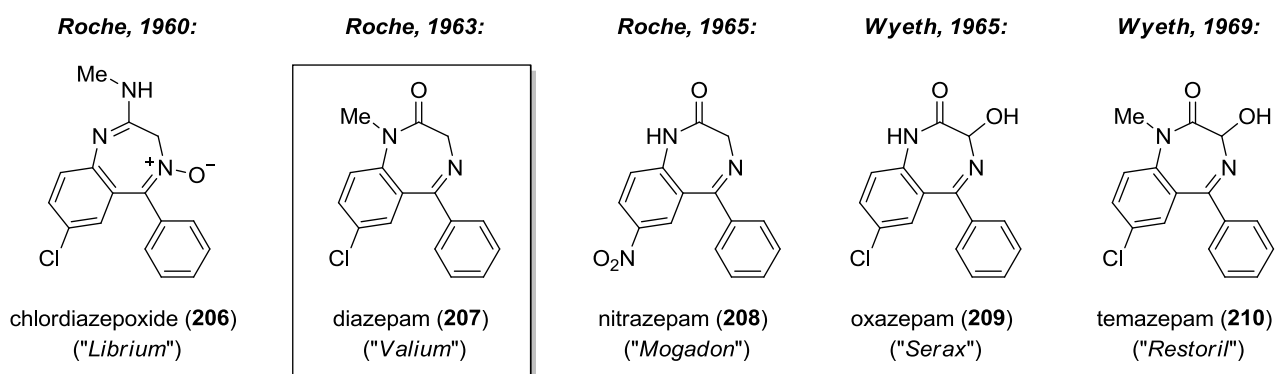
## Drug Analogues

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## 5.1 Oxetano-Diazepam

### 5.1.1 Diazepam

In the mid-1950s people initiated a program at *F. Hoffmann-La Roche Inc.* (site in Nutley, NJ) to search for improved tranquilizing agents. A team around LEO STERNBACH decided to look for a class of compounds that would “(1) be relatively unexplored, (2) be readily accessible, (3) give the possibility of a multitude of variations and transformations, (4) offer some challenging chemical problems, and (5) ‘look’ as if it could lead to biologically active products”.<sup>206</sup> Stimulated by STERNBACH’s postdoctoral work, they started to look at benzo[*d*][1,2,6]oxadiazepines as possible druglike molecules. In their work, the researchers found that in fact, many of the synthesized compounds did not belong to that class of molecules, but were instead quinazoline-3-oxides. Unfortunately, biological tests did not reveal a lead compound until a “forgotten sample” led to a breakthrough. Subsequent studies in STERNBACH’s laboratory with this compound showed that a structural rearrangement had occurred, and the active substance was identified as a 1,4-benzodiazepine-*N*-oxide. Interestingly, this compound was the best in its class and was successfully launched as a novel anxiolytic agent within 2.5 years after the first biological testing.<sup>207</sup> *Librium* (or: chlordiazepoxide, **206**) was thus the start of *Roche’s* success story with tranquilizers (Figure 46).



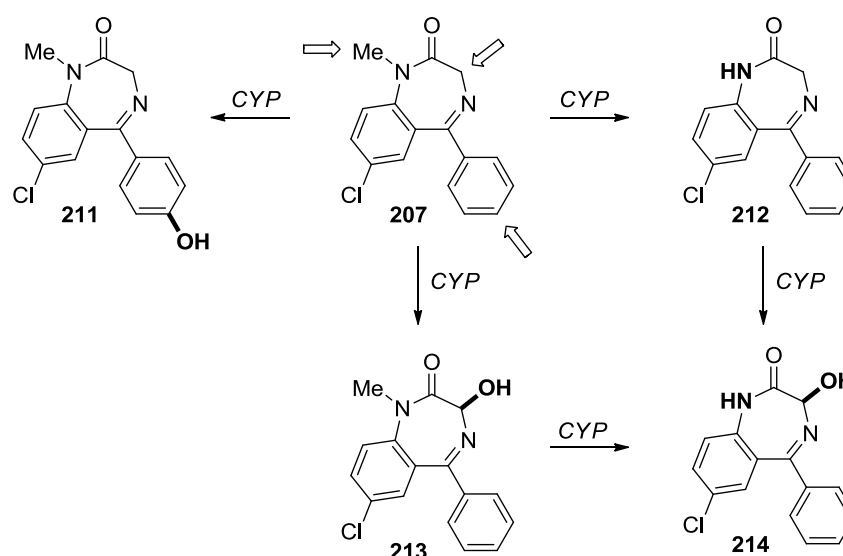
**Figure 46.** Diazepam (**207**) and other early benzodiazepines.

<sup>206</sup> An inspiring personal account by STERNBACH on the discovery of benzodiazepines: L. H. Sternbach, *J. Med. Chem.* **1979**, *22*, 1-7.

<sup>207</sup> a) L. H. Sternbach (F. Hoffmann-La Roche Inc.), US 2893992, **1959**; b) L. H. Sternbach, E. Reeder, O. Keller, W. Metlesics, *J. Org. Chem.* **1961**, *26*, 4488-4497.



Although chlordiazepoxide was a major advance in the field, researchers at *Roche* were not fully satisfied<sup>208</sup> and were looking for other active alternatives. A key discovery was that the amidine functionality in **206** was prone to hydrolysis, affording an also active lactam hydrolysis product. Moreover, it was shown that the *N*-oxide was not essential, as the corresponding imine was equally active. By combining these two findings, STERNBACH and co-workers synthesized diazepam (**207**).<sup>209</sup> This material was highly active and exhibited an optimal pharmacokinetic profile as assessed by subsequent biological and pharmacological measurements.<sup>210</sup> Still today this compound, which is primarily marketed under the trade name *Valium*, serves as an excellent drug for the treatment of anxiety, insomnia, epileptic seizures, muscle spasms, restless legs syndrome, alcohol withdrawal, and other indications. Its mode of action involves allosteric modulation of the GABA<sub>A</sub> receptor, thus enhancing the effect of the neurotransmitter  $\gamma$ -aminobutyric acid (GABA) and decreasing the neuronal activity.<sup>211</sup> Besides diazepam, there are many other benzodiazepines on the market; among these are *Roche's* nitrazepam (**208**), as well as *Wyeth's* (nowadays: *Pfizer*) oxazepam (**209**)<sup>212</sup> and temazepam (**210**).



**Scheme 41.** Major metabolites found for diazepam.

Diazepam (**207**) has a high overall chemical and metabolic stability and thus is a long-acting drug. But eventually, cytochromes P450 will degrade **207** by oxidative pathways leading to ei-

<sup>208</sup> For instance, it was difficult to find a suitable formulation of the drug for pediatric or geriatric use, as the compound was very bitter.

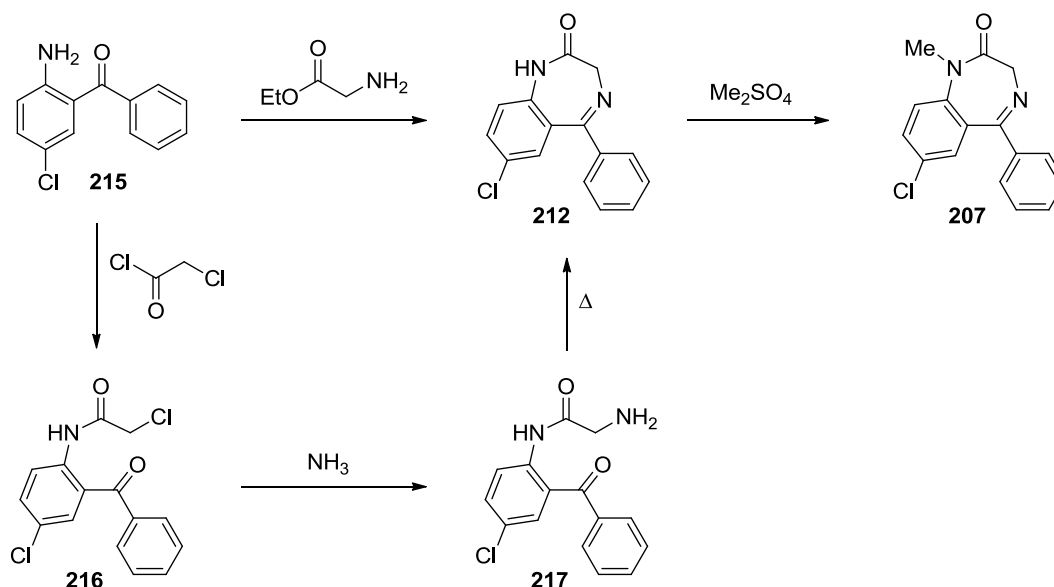
<sup>209</sup> L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, A. Stempel, *J. Org. Chem.* **1962**, *27*, 3788-3796.

<sup>210</sup> E. Reeder, L. H. Sternbach (F. Hoffmann-La Roche Inc.), US 3136815, **1964**.

<sup>211</sup> For reviews, see: a) J. Riss, J. Cloyd, J. Gates, S. Collins, *Acta Neurol. Scand.* **2008**, *118*, 69-86; b) J. R. Atack, *Exp. Opin. Investig. Drugs* **2005**, *14*, 601-618.

<sup>212</sup> S. C. Bell, S. J. Childress, *J. Org. Chem.* **1962**, *27*, 1691-1695.

ther hydroxylated or demethylated compounds (Scheme 41).<sup>213</sup> Among the major metabolites is phenol **211**, which is further glucuronated and excreted. More important are the other major metabolites ( $\alpha$ -hydroxy amide **213**, demethylated compound **212**, and doubly modified **214**) that all represent active substances and two of them are being marketed (originally by *Wyeth*, see Figure 46).



**Scheme 42.** Syntheses of diazepam (**207**).

Numerous approaches for the preparation of benzodiazepines are known,<sup>214</sup> but the original *Roche* routes that are indicated in Scheme 42 served best for the synthesis of diazepam and the other approximately 4000 analogues in *Roche's* large library.<sup>206,209</sup> The general route started with a 2-aminobenzophenone such as **215**, and construction of the seven-membered ring occurred either in one step using an esterified  $\alpha$ -amino acid or in a three-step procedure using an acyl chloride (*via* intermediates such as **216** and **217**). Modification of the 1-position was commonly achieved in the last step, e.g. methylation of **212** to give **207**.

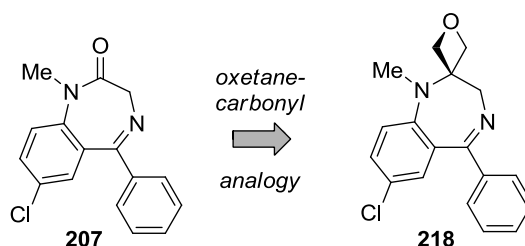
<sup>213</sup> a) T. Seddon, I. Michelle, R. J. Chenery, *Biochem. Pharmacol.* **1989**, *38*, 1657-1665; b) C. F. Neville, N. Shin-ichi, S. Noriaki, K. Tetsuya, I. Susumu, F. Yoshihiko, *Biochem. Pharmacol.* **1993**, *45*, 59-65.

<sup>214</sup> A. Walser, R. I. Fryer, in *Chemistry of Heterocyclic Compounds*, John Wiley & Sons, Inc., **1991**, pp. 431-543.

### 5.1.2 Oxetane Analogue

Oxetanes, in particular 3,3-disubstituted members, were introduced to drug discovery as a property modulating group having extraordinary effects on lipophilicity, aqueous solubility, and metabolic degradation.<sup>215</sup> While they exhibited superb qualities as a replacement for geminal dimethyl groups or carbonyl moieties in model systems, the substitution of a particular subunit in a biologically active compound with an oxetane has not yet been reported. For this reason it was decided to explore the influence of the oxetane on binding affinity and biological activity (collaboration with MÜLLER, ROGERS-EVANS, and WUITSCHIK).

Diazepam (**207**) seemed to be a good compound to probe its carbonyl substitution with a 3,3-disubstituted oxetane (Figure 47). As introduced in the previous section, various active benzodiazepines possess the crucial amide group in the seven-membered ring, which also significantly contributes to the overall three-dimensional structure (conformationally speaking, it is like a cycloheptatriene system).<sup>216</sup> By going to the oxetane analogue, the seven-membered ring should formally behave like a cycloheptadiene ring (in terms of conformation). This issue and the extra steric bulk associated with the oxetane will be key points for discussion.

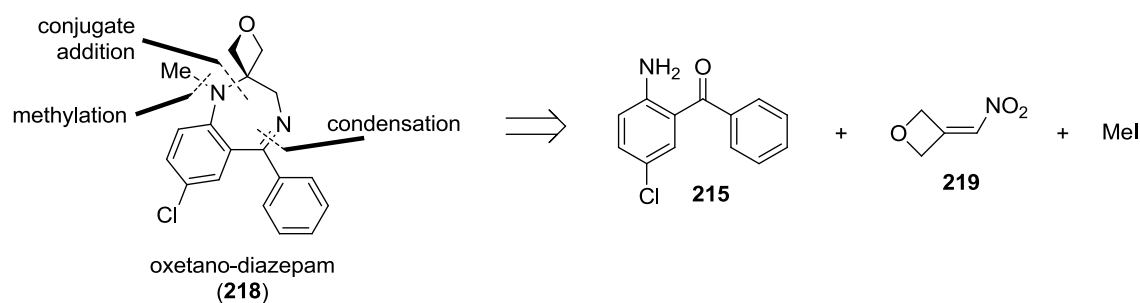


**Figure 47.** Transition from diazepam (**207**) to oxetano-diazepam (**218**).

Inspired by the classical synthetic approach toward diazepam and other benzodiazepines (*vide supra*), we decided to retrosynthetically cleave the target molecule at three distinct sites that would lead to benzophenone **215**, nitromethyleneoxetane **219**, and an electrophilic methyl group as fragments (Figure 48). Thus, conjugate addition of the aniline onto MICHAEL acceptor **219** followed by reduction of the nitro group should after spontaneous condensation provide the benzodiazepine system, which would only require amide methylation to complete the target.

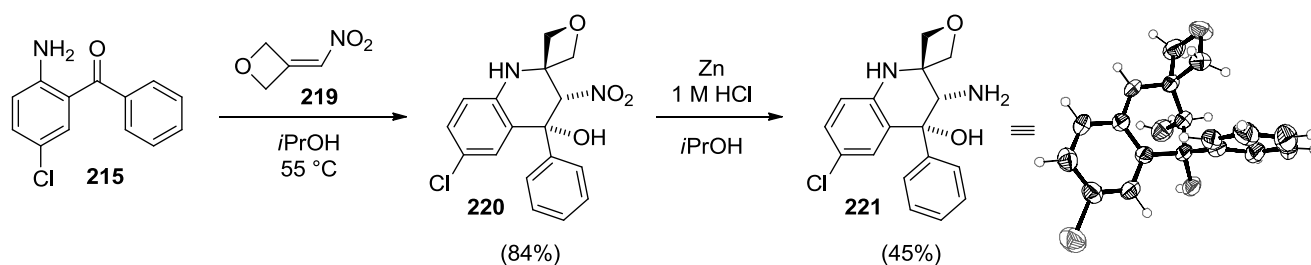
<sup>215</sup> See Chapter 1 and ref. 77.

<sup>216</sup> Klaus Müller, *Topics in Structure-Based Molecular Design in Drug Discovery*, lecture course held at ETH Zürich, spring semester, **2011**.



**Figure 48.** Retrosynthetic analysis for oxetano-diazepam.

Conjugate addition of **215** onto **219** in THF at 60 °C provided only minor amounts of the desired product, but delivered instead tertiary alcohol **220** (Scheme 43). The use of different solvents (DMF, *i*PrOH, *i*PrOH/H<sub>2</sub>O) or the use of acidic additives (SiO<sub>2</sub>, diluted aqueous HCl) did not prevent the HENRY-like cyclization from occurring. The desired material was observed by <sup>1</sup>H NMR, but all attempted purifications were unsuccessful. The relative configuration of the nitroalcohol was determined after its reduction to the aminoalcohol **221** (Zn, 1 M HCl) that delivered suitable crystals for X-ray crystallographic analysis (see Scheme 43, right).

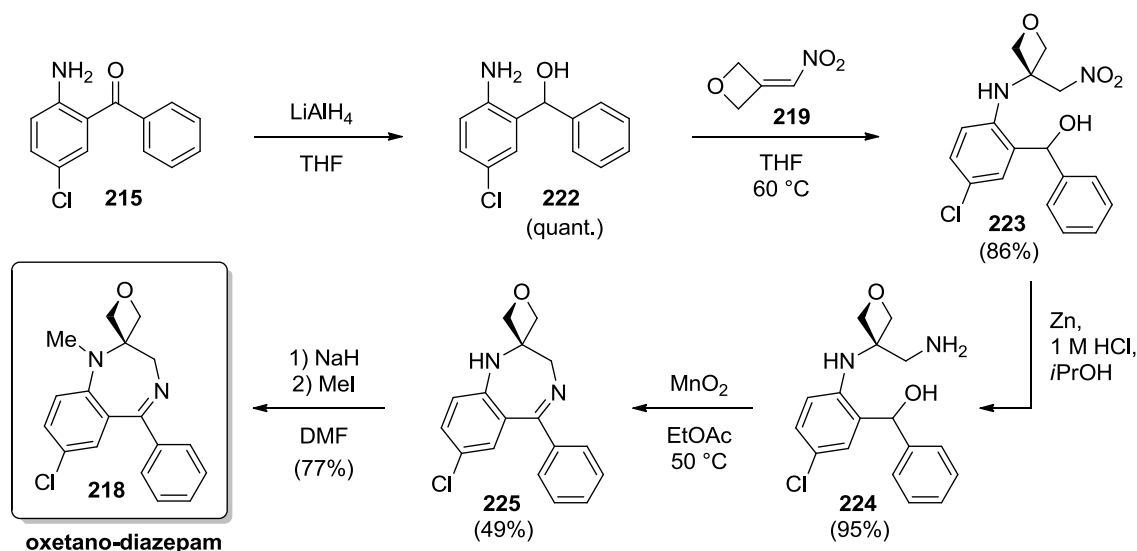


**Scheme 43.** Conjugate addition of benzophenone **215** to nitromethyleneoxetane **219**.

Since it was impossible to prevent the intramolecular HENRY-addition, it was decided to mask the ketone in the form of a carbinol. For this reason, benzophenone **215** was treated with LiAlH<sub>4</sub> in THF at 0 °C to give the corresponding alcohol **222** in quantitative yield (Scheme 44). Subsequent smooth conjugate addition to oxetane building block **219** (in THF, 60 °C) gave the adduct **223** in 86% yield. The nitro group was reduced with zinc powder in acidic aqueous *i*PrOH to afford aminoalcohol **224** in 95% yield. This material was taken forward without purifications and subjected to excess MnO<sub>2</sub> in EtOAc,<sup>217</sup> which would promote benzylic oxidation with concomitant condensation to the benzodiazepine **225**. Indeed, the desired compound could be isolated in 49% yield after chromatography. The aniline was deprotonated with sodium hy-

<sup>217</sup> F. Leroux, E. Castagnetti, M. Schlosser, *J. Org. Chem.* **2003**, 68, 4693–4699.

dride in DMF (formation of a deeply red solution), and then treated with methyl iodide.<sup>218</sup> The pure oxetane analogue of diazepam (**218**) was obtained in 77% yield after chromatographic purification. Thus, oxetano-diazepam was obtained in five steps from commercially available benzophenone **215** in an overall yield of 31%.



**Scheme 44.** Synthesis of oxetano-diazepam (**218**).

Synthesized compounds **218** and amine **225** represented formal analogues of diazepam and nordiazepam and were then submitted to biological tests to probe their activity. In a *3H*-flumazenil binding assay, **218** and **225** as well as diazepam and flumazenil as a control were tested for binding constants for different GABA<sub>A</sub> receptor subtypes. The results are shown in Table 14. Surprisingly, the oxetane analogues were essentially inactive, as no binding was observed up to a maximum concentration of 3160 nM. In contrast, diazepam and flumazenil both showed activities in the expected range.

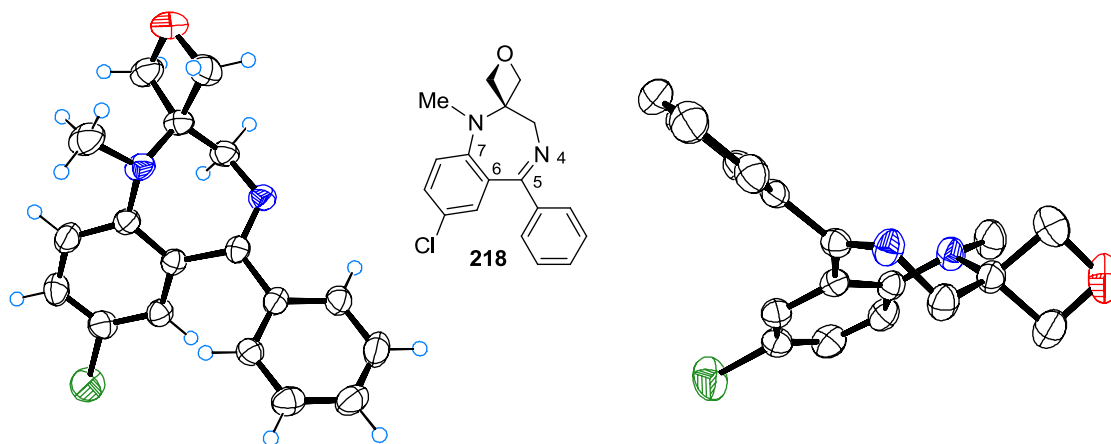
**Table 14.** Results from the *3H*-flumazenil binding assay. Maximal concentration tested was 3160 nM.

compound	<i>K<sub>i</sub></i> (nM) for GABA <sub>A</sub> Receptor Subtype			
	h a1b3g2	h a2b3g2	h a3b3g2	h a5b3g2
oxetano-diazepam ( <b>218</b> )	>3160	>3160	>3160	>3160
oxetano-nordiazepam ( <b>225</b> )	>3160	>3160	>3160	>3160
diazepam ( <b>207</b> )	14.69	10.99	45.06	8.52
flumazenil	1.23	2.21	2.08	0.33

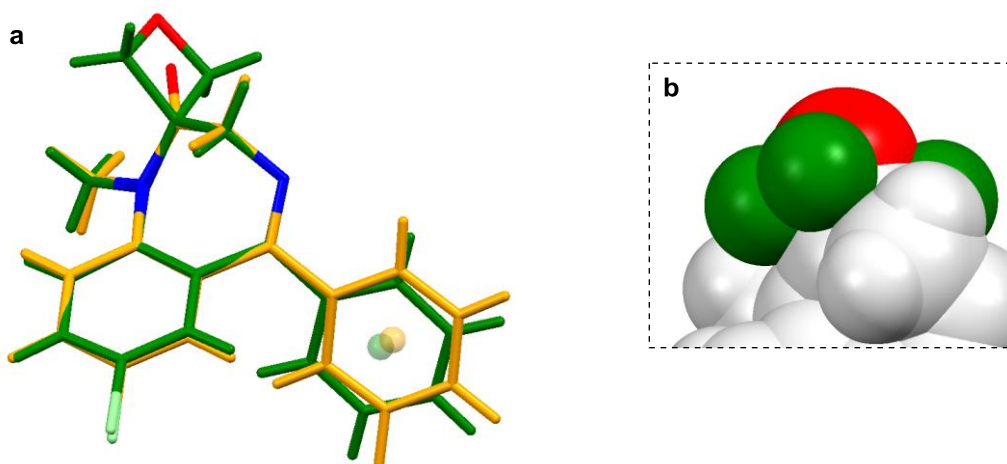
Puzzled by the disappointing results from biological testing, we were looking for details that would explain the differences. Accordingly, a solid-state structure of the oxetane analogue **218**

<sup>218</sup> M. E. Van Dort, B. J. Ciliax, D. L. Gildersleeve, P. S. Sherman, K. C. Rosenspire, A. B. Young, L. Junck, D. M. Wieland, *J. Med. Chem.* **1988**, *31*, 2081-2086.

could give further insights, as it can be compared with the available crystal structure of diazepam.<sup>219</sup> We were glad to obtain suitable crystals for analysis after slow evaporation of a solution of **218** in CH<sub>2</sub>Cl<sub>2</sub>/hexanes. The results from X-ray crystallography are shown in Figure 49.



**Figure 49.** Crystal structure of **218** in two different perspectives (ORTEP representation with ellipsoids at 50% probability). Right structure: H-atoms omitted for clarity.



**Figure 50. a)** Structural overlay of oxetano-diazepam (**218**; green structure) with diazepam (**207**; yellow structure). Distances between corresponding atoms of the seven-membered rings are minimized. **b)** Close-up of the overlay in the oxetane/carbonyl region. The spacefill model (100% VAN-DER-WAALS radii) should demonstrate the additional bulk of the oxetane fragment (colored) versus the corresponding carbonyl group in diazepam (grayscale).

The X-ray structure of **218** confirms the connectivity and displays a number of characteristic elements. For instance, the seven-membered ring exhibits the typical twist conformation that in general is the lowest-energy conformation of a conjugated cycloheptadiene-type molecule (double bond equivalents are here the N(4)=C(5) imine and the C(6)=C(7) aromatic bond). This fea-

<sup>219</sup> A. Camerman, N. Camerman, *J. Am. Chem. Soc.* **1972**, *94*, 268-272.

ture is best viewed from one side as displayed in Figure 49, right. Another distinct property that can be seen in the same display is the pseudo-equatorial orientation of the methyl group. It seems like the previously described “*gauche*-driving” effect of the oxetane<sup>77</sup> is not strong enough to force the methyl group into a pseudo-axial conformation.

An overlay of the solid-state structures of oxetano-diazepam and diazepam was created by minimizing the interatomic distances of corresponding atoms in the seven-membered ring (Figure 50a). Overall, the superposition is remarkably close fitting. Despite the substitution of an amide group with a 3-aminooxetane unit, the diazepine rings have nearly the same conformation, as evidenced by the proximity of corresponding methyl groups (0.14 Å distance) and even the distant chlorides (0.30 Å distance). However, the splaying of the N-Me and the iminophenyl units is more marked in the oxetane analogue than in diazepam, which leads to a slightly increased distance between the two corresponding phenyl ring centroids (0.50 Å). On the other hand, the oxetane oxygen atom is oriented exactly in the same direction as the carbonyl oxygen in diazepam. What distinguishes it from the parent compound is its extended length (corresponding oxygen atoms are distanced by 0.99 Å) and surrounding bulk (methylene groups). This feature is presented in detail in Figure 50b. Evidently, the oxetane compound requires significantly more space (see colored VAN-DER-WAALS atoms that stick out of the grayscale image of diazepam). From the structural point of view this discrepancy can account for the observed loss of activity of **218** and **225**. It also matches the observation that larger groups than H or Me on N(1) lead to considerably decreased activities.<sup>220</sup> Naturally, differences in electronics (e.g. reduced ability of the oxetane to form hydrogen bonds<sup>221</sup>) or in solubility, permeation or binding mode can also contribute to the reduced activity and further studies could shed light on these aspects.

In conclusion, this project revealed that it is possible to synthesize an oxetane analogue of a marketed drug in few steps not requiring any advanced synthetic techniques or specialized knowledge about oxetane chemistry. Although the desired activity was not attained, structural information revealed that an amide group can be replaced by a 3-aminooxetanyl unit with retention of the overall molecular conformation. A more comprehensive analysis will be essential to show whether this is generally the case also for open-chain compounds.

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<sup>220</sup> A *tert*-butyl derivative of diazepam is essentially inactive. See N. W. Gilman, L. H. Sternbach, *J. Heterocyclic Chem.* **1971**, *8*, 297-300, ref. 206, and additional references therein.

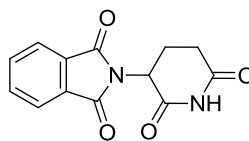
<sup>221</sup> a) M. Brandon, M. Tamres, S. Searles, *J. Am. Chem. Soc.* **1960**, *82*, 2129-2134. For related studies with carbonyl compounds, see: b) F. Besseau, M. Lucon, C. Laurence, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1998**, 101-107; c) F. Besseau, C. Laurence, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1994**, 485-489; d) J. Y. Lequestel, C. Laurence, A. Lachkar, M. Helbert, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091-2094.

## 5.2 Oxetano-Thalidomide and Oxetano-Lenalidomide

### 5.2.1 Thalidomide: History and Background

Thalidomide (**226**) is a drug with a multifarious history.<sup>222</sup> It was first discovered in the 1950s at *Chemie Grünenthal* and was brought to the market under the trade name “*Contergan*” as a “safe” (nontoxic) sedative in 1956 (Figure 51). Within a few years it had become a very popular sedative and was marketed worldwide by the end of the 1950s.<sup>223</sup> Not much thereafter, the drug’s positive effects were overshadowed by emerging reports about birth defects resulting from women that took as little as one dose of thalidomide during gestation.<sup>224</sup> The highest risk for teratogenicity was observed when the drug was taken 3-8 weeks after conception. In total more than 10,000 infants were born with severe malformations worldwide, which led to the withdrawal of thalidomide from numerous countries in Europe and elsewhere in the early 1960s.

*Grünenthal (1956):*



thalidomide (**226**)  
("Contergan")

**Figure 51.** The structure of thalidomide.

As a consequence of these tragic events, thalidomide had been of no use for many years. Only for the treatment of HANSEN’S disease, a rare but painful inflammatory dermatological reaction of lepromatous leprosy, thalidomide could be obtained as a regulated prescription drug. It was then redefined following a key finding from FOLKMAN’S laboratory, which suggested that thalidomide-linked malformations were the result of the drug’s interference with vasculogenesis, and that a similar mechanism might prevent the growth of blood vessels in solid tumors.<sup>225</sup> These studies revealed that thalidomide is a potent angiogenesis inhibitor *in vivo*, but no effect

<sup>222</sup> For a detailed description, see: a) W. Lenz, *Teratology* **1988**, *38*, 203-215; b) R. Brynner, T. Stephens, *Dark Remedy: The Impact of Thalidomide and Its Revival As a Vital Medicine*, Basic Books, **2001**.

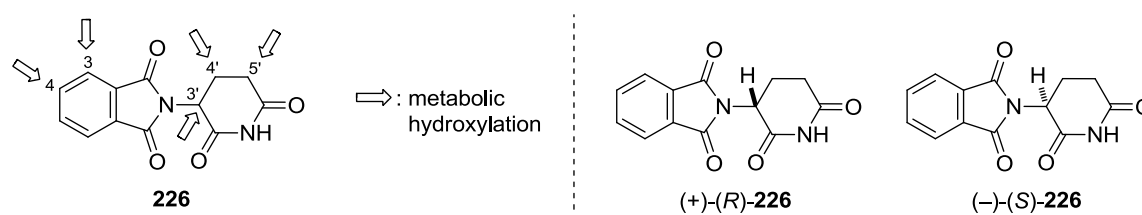
<sup>223</sup> A brief review about thalidomide and its derivatives: C. H. Chau, W. Dahut, W. D. Figg, in *Angiogenesis* (Eds.: W. D. Figg, J. Folkman), Springer US, **2008**, pp. 387-394.

<sup>224</sup> a) W. G. McBride, *Lancet* **1961**, *278*, 1358-1358; b) W. Lenz, R. A. Pfeiffer, W. Kosenow, D. J. Hayman, *Lancet* **1962**, *279*, 45-46; c) G. W. Mellin, M. Katzenstein, *N. Engl. J. Med.* **1962**, *267*, 1184-1193; d) G. W. Mellin, M. Katzenstein, *N. Engl. J. Med.* **1962**, *267*, 1238-1244.

<sup>225</sup> R. J. D’Amato, M. S. Loughnan, E. Flynn, J. Folkman, *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4082-4085.



was observed on the proliferation of endothelial cells in culture. The authors thus postulated that a thalidomide metabolite might be the active agent. This was later confirmed by other investigators, who found that the addition of human liver microsomes was essential to see an anti-angiogenic effect of thalidomide in *ex vivo* studies.<sup>226</sup> FIGG and co-workers identified several major metabolites of thalidomide (Figure 52), but these probably do not account for the observed effect. Their postulation that it is rather a metabolic intermediate such as an epoxide that is responsible for the anti-angiogenic property of thalidomide, has so far not been confirmed. Little is known today about the exact mechanism by which thalidomide acts,<sup>227</sup> but there was a positive correlation observed between the teratogenic and the anti-angiogenic effect of the drug (results based on the investigation of close configurationally fixed analogues of thalidomide). Furthermore, the sedative function was associated with (+)-(*R*)-thalidomide,<sup>228</sup> whereas the (-)-(*S*)-enantiomer was believed to act as an immunomodulatory agent that can intercalate in the major groove of DNA at purine sites.<sup>229</sup> Since these compounds rapidly epimerize *in vivo*,<sup>230</sup> the administration of only one enantiomer for the treatment of a particular indication does not serve its purpose. A recent disclosure by ITO *et al.* describes the identification of a primary target of thalidomide teratogenicity.<sup>231</sup> It is shown that thalidomide binds to cereblon (CRBN), a protein that forms an E3 ubiquitin ligase complex with damaged DNA protein 1 and Cul4A, which is important for limb outgrowth and the expression of fibroblast growth factor Fgf8 in zebrafish and chicks. By binding to CRBN, thalidomide thus inhibits the associated ubiquitin ligase activity and initiates the teratogenic pathway.



**Figure 52.** Main metabolic sites for thalidomide (**226**); thalidomide enantiomers.

<sup>226</sup> a) K. S. Bauer, S. C. Dixon, W. D. Figg, *Biochem. Pharmacol.* **1998**, *55*, 1827-1834; b) K. Fujita, Y. Asami, E. Murata, M. Akita, K. Kaneko, *Okajimas Folia Anat. Jpn.* **2002**, *79*, 101-106.

<sup>227</sup> S. K. Teo, W. A. Colburn, W. G. Tracewell, K. A. Kook, D. I. Stirling, M. S. Jaworsky, M. A. Scheffler, S. D. Thomas, O. L. Laskin, *Clin. Pharmacokin.* **2004**, *43*, 311-327.

<sup>228</sup> P. Höglund, T. Eriksson, S. Björkman, *J. Pharmacokin. Biopharm.* **1998**, *26*, 363-383.

<sup>229</sup> a) P. H. T. Huang, W. G. McBride, *Teratogen. Carcinogen. Mutagen.* **1997**, *17*, 1-5; b) T. D. Stephens, C. J. W. Bunde, B. J. Fillmore, *Biochem. Pharmacol.* **2000**, *59*, 1489-1499.

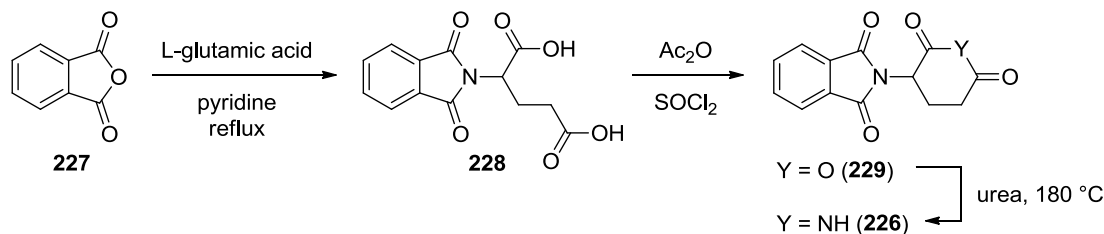
<sup>230</sup> Serum albumin is believed to catalyze the epimerization *in vivo*: a) M. Reist, P.-A. Carrupt, E. Francotte, B. Testa, *Chem. Res. Toxicol.* **1998**, *11*, 1521-1528; b) T. Eriksson, S. Björkman, B. Roth, Å. Fyge, P. Höglund, *Chirality* **1998**, *10*, 223-228.

<sup>231</sup> T. Ito, H. Ando, T. Suzuki, T. Ogura, K. Hotta, Y. Imamura, Y. Yamaguchi, H. Handa, *Science* **2010**, *327*, 1345-1350.

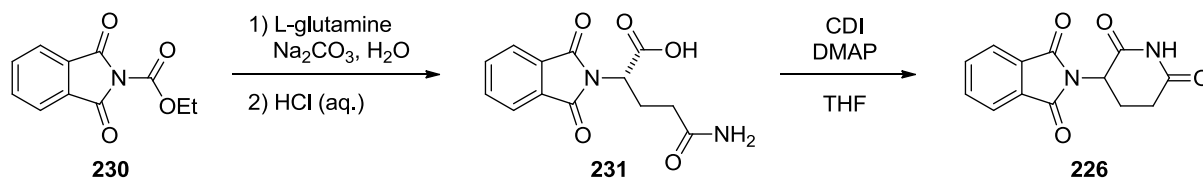
Currently, thalidomide is marketed by *Celgene* for the treatment of multiple myeloma (in combination with dexamethasone) and leprosy.<sup>232</sup> It is also in phase II or III trials for the treatment of a variety of other indications, including lung cancer, prostate cancer, and leukemia.<sup>233</sup> In selected countries thalidomide has the status of an orphan drug for the treatment of certain diseases.<sup>234</sup>

The original synthesis of thalidomide by *Chemie Grünenthal* started with phthalic anhydride (**227**), which was condensed with L-glutamic acid to afford phthalimide **228** (Scheme 45).<sup>235</sup> The six-membered cyclic anhydride **229** was formed using a combination of neat acetic anhydride and thionyl chloride. This compound was reacted with molten urea at 180 °C to afford the corresponding imide, thalidomide (**226**), which is a colorless powder with a relatively low solubility in water (<0.1 g/l at neutral pH and at RT) and other common solvents.<sup>236</sup> A modified synthetic route, as described by researchers at *Celgene*, uses *N*-carbethoxyphthalimide (**230**) as starting point.<sup>237</sup> This compound is treated with L-glutamine and upon acidification during work-up amide **231** precipitates as the product. Upon treatment of this intermediate with CDI and DMAP in THF, thalidomide (**226**) is formed, while the material isomerizes *in situ*.

**Grünenthal (1950s):**



**Celgene (1999):**



**Scheme 45.** Industrial syntheses of racemic thalidomide (**226**).

<sup>232</sup> Because of its teratogenicity, the marketing and use of thalidomide in the United States is restricted through the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program.

<sup>233</sup> S. K. Teo, D. I. Stirling, J. B. Zeldis, *Drug Discov. Today* **2005**, *10*, 107-114.

<sup>234</sup> See [www.orfa.net](http://www.orfa.net).

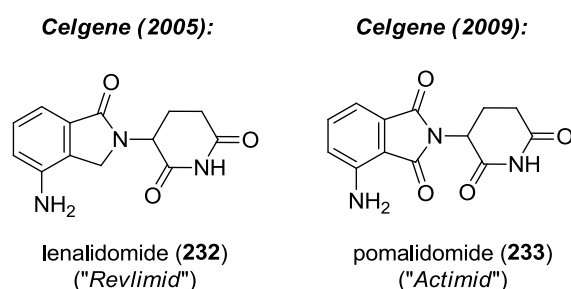
<sup>235</sup> H. Keller, W. Kunz (Chemie Grünenthal GmbH), GB 768821, **1957**.

<sup>236</sup> C. Goosen, T. J. Laing, J. du Plessis, T. C. Goosen, G. L. Flynn, *Pharm. Res.* **2002**, *19*, 13-19.

<sup>237</sup> G. W. Muller, W. E. Konnecke, A. M. Smith, V. D. Khetani, *Org. Proc. Res. Dev.* **1999**, *3*, 139-140.

## 5.2.2 Lenalidomide

Along with the new interest in the effects of thalidomide (see section 5.2.1) came also the need for novel structural analogues that would be safe and could match or even improve the desired anti-angiogenic effects. Celgene's drug discovery program led to the identification of lenalidomide (**232**) as a potent immunomodulatory and anti-angiogenic agent (Figure 53).<sup>238</sup> The compound exhibited an extraordinary efficacy in myelodysplastic syndromes.<sup>239</sup> It acts by the inhibition of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and tumor necrosis factor- $\alpha$ -(TNF- $\alpha$ )-induced endothelial cell migration.<sup>240</sup> Lenalidomide (by Celgene) is approved for the treatment of myelodysplasia and multiple myeloma (in combination with dexamethasone),<sup>241</sup> and its close analogue pomalidomide (**233**) is an orphan drug in Europe for the treatment of multiple myeloma. Although no clear evidence is reported, lenalidomide, which also racemizes *in vivo* and is therefore sold in the form of a racemate, is treated as a potentially teratogenic agent.



**Figure 53.** Structures of lenalidomide and pomalidomide.

As shown in Scheme 46, lenalidomide is synthesized in four steps from commercially available Cbz-protected glutamine (**234**).<sup>238a</sup> This material is treated with CDI in refluxing THF to promote imide formation, and the Cbz group is removed from the intermediate by a catalytic hydrogenation. The resulting primary amine is trapped in the form of a hydrochloride salt to give **235**. Lenalidomide's isoindolinone system is generated by the treatment of **235** with benzyl

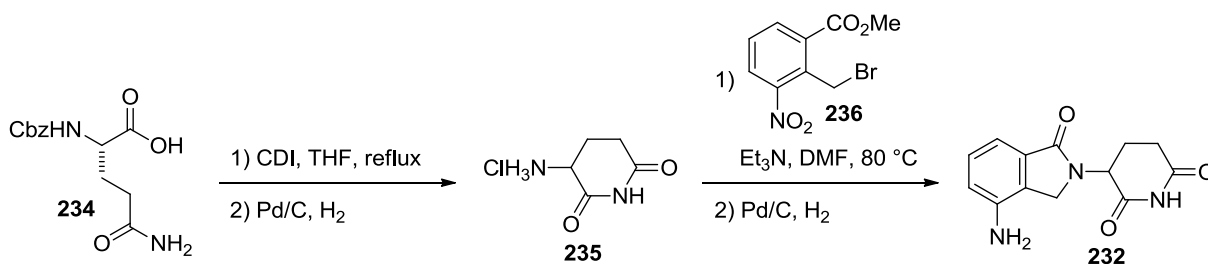
<sup>238</sup> a) G. W. Muller, R. Chen, S.-Y. Huang, L. G. Corral, L. M. Wong, R. T. Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1625-1630; b) G. W. Muller, D. I. Stirling, R. S.-C. Chen (Celgene Corp.), US 6335349, **2002**.

<sup>239</sup> A. List, S. Kurtin, D. J. Roe, A. Buresh, D. Mahadevan, D. Fuchs, L. Rimsza, R. Heaton, R. Knight, J. B. Zeldis, *N. Engl. J. Med.* **2005**, *352*, 549-557.

<sup>240</sup> a) K. Dredge, R. Horsfall, S. P. Robinson, L.-H. Zhang, L. Lu, Y. Tang, M. A. Shirley, G. Muller, P. Schafer, D. Stirling, A. G. Dalgleish, J. B. Bartlett, *Microvasc. Res.* **2005**, *69*, 56-63. For a brief review about lenalidomide, see: R. Dreicer, *Curr. Oncol. Rep.* **2007**, *9*, 120-123.

<sup>241</sup> Launches in 2005 and 2006, respectively.

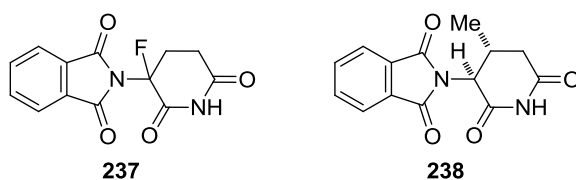
bromide **236** and base in hot DMF. Finally, hydrogen and Pd/C reduce the nitro group to the corresponding amine, and lenalidomide (**232**) is formed.



**Scheme 46.** Celgene's synthesis of lenalidomide (**232**).

### 5.2.3 Oxetane Analogues

The serious issues associated with thalidomide (*vide supra*) and the dispute about which enantiomer can be made responsible for the observed effects have triggered syntheses of a large number of thalidomide analogues.<sup>222,223</sup> Among the reported compounds are configurationally stable close analogues of thalidomide like fluoro-thalidomide **237** and methyl-substituted analogue **238** (Figure 54). The groups of TAKEUCHI and SHIBATA have reported a racemic synthesis (with separation of the enantiomers by chiral HPLC)<sup>242</sup> and later also an enantioselective synthesis of fluoro analogue **237**.<sup>243</sup> This work generated significant interest in the community, and many biological experiments are ongoing.<sup>244</sup> OHFUNE and co-workers have reported methyl (**238**) and phenyl analogues of thalidomide that were configurationally stable in neutral or slightly acidic aqueous environments, but suffered from epimerization at higher pH.<sup>245</sup>



**Figure 54.** Selected thalidomide analogues.

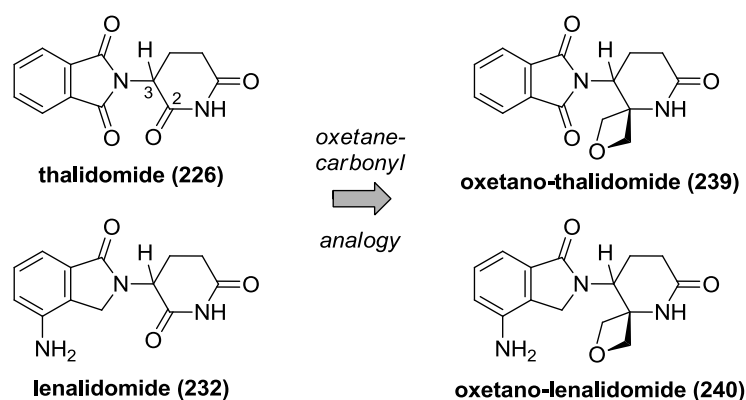
<sup>242</sup> Y. Takeuchi, T. Shiragami, K. Kimura, E. Suzuki, N. Shibata, *Org. Lett.* **1999**, *1*, 1571-1573.

<sup>243</sup> T. Yamamoto, Y. Suzuki, E. Ito, E. Tokunaga, N. Shibata, *Org. Lett.* **2010**, *13*, 470-473, and references therein.

<sup>244</sup> Celgene is investigating fluorine analogues as drugs, see for example: H.-W. Man, L. G. Corral, D. I. Stirling, G. W. Muller, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3415-3417.

<sup>245</sup> T. Yamada, T. Okada, K. Sakaguchi, Y. Ohfuné, H. Ueki, V. A. Soloshonok, *Org. Lett.* **2006**, *8*, 5625-5628.

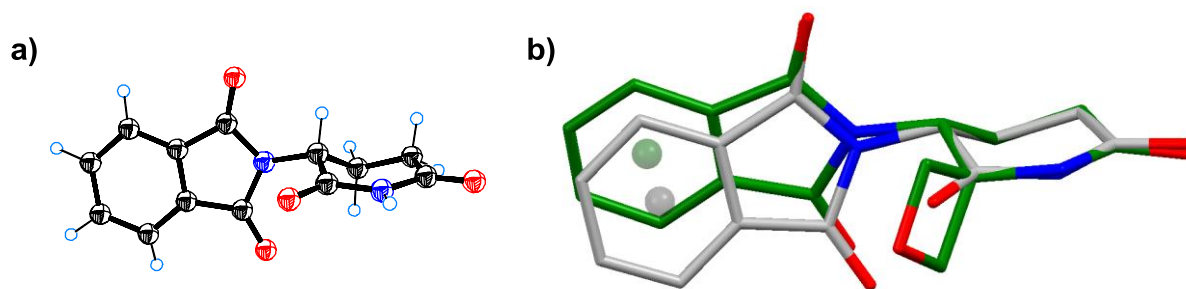
Our continued interest in oxetanes as a surrogate for carbonyl groups (see section 5.1.2 or Chapter 1) guided us to consider oxetane analogues of thalidomide and lenalidomide (Figure 55; collaboration with MÜLLER, ROGERS-EVANS, and WUITSCHIK). The replacement of the carbonyl group at C(2) with a 3,3-oxetanyl unit would address two issues: (1) the resulting compounds would not racemize under physiological conditions, and (2) hydrolysis of these substituted amides is expected to be slower than of the corresponding imide compounds. Moreover, the biological evaluation of the analogue compounds serves us to deeper understand the effects an oxetane has on the underlying scaffold when carbonyl groups are replaced by oxetanyl units.



**Figure 55.** Oxetane analogues of thalidomide and lenalidomide.

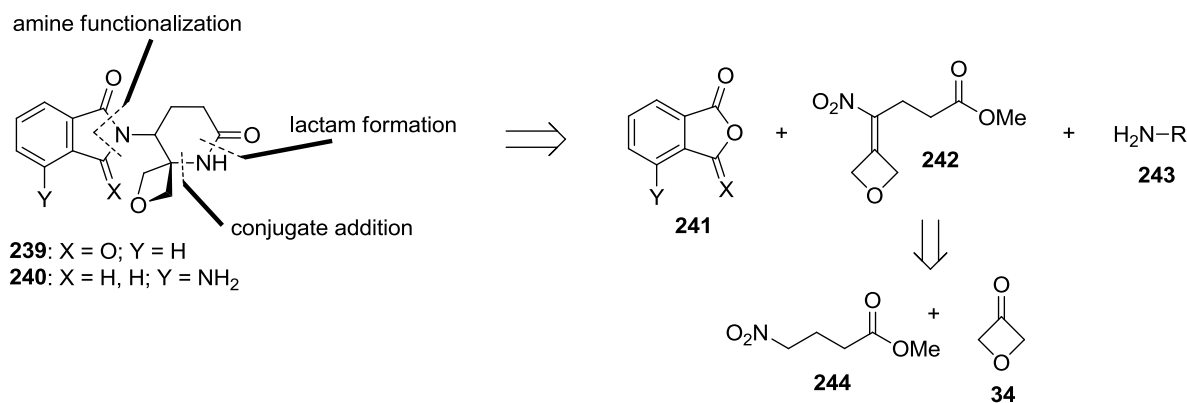
The solid state structure of thalidomide was determined in the 1970s (Figure 56a).<sup>246</sup> By superimposing this structure with an energy-minimized structure of oxetano-thalidomide it becomes apparent that the conformation of the six-membered ring (imide or lactam) is mostly retained (Figure 56b). The major difference is of course the extra bulk coming from the oxetane methylene groups and the prolonged C(2)—O distance (2.15 Å vs. 1.20 Å). The corresponding carbonyl groups of the six-membered rings are only 0.17 Å apart in the superimposed picture. In contrast, some differences are observed in the phthalimido unit. Whereas the overall orientation is comparable, slightly different bond angles at C(2) lead to small differences in the facial alignment of the phthalimides. Benzene ring centroids are distanced by 1.15 Å, and also the carbonyl oxygen atoms do not perfectly overlap (top O—O: 0.40 Å, bottom O—O: 1.36 Å). Overall, the structural correlation seems satisfactory and from this point of view, the synthesis of thalidomide analogues is worth executing.

<sup>246</sup> a) F. H. Allen, J. Trotter, *J. Chem. Soc. B* **1971**, 1073-1079. For a more recent analysis, see: J. C. Reepmeyer, M. O. Rhodes, D. C. Cox, J. V. Silvertown, *J. Chem. Soc., Perkin Trans. 2* **1994**, 2063-2067.



**Figure 56.** **a)** X-ray structure of thalidomide. **b)** Superimposition of the crystal structure of **226** (gray) with minimized (PM3-level; *Cambridgesoft*, ChemBio3D 12.0) structure of oxetano-thalidomide (green).

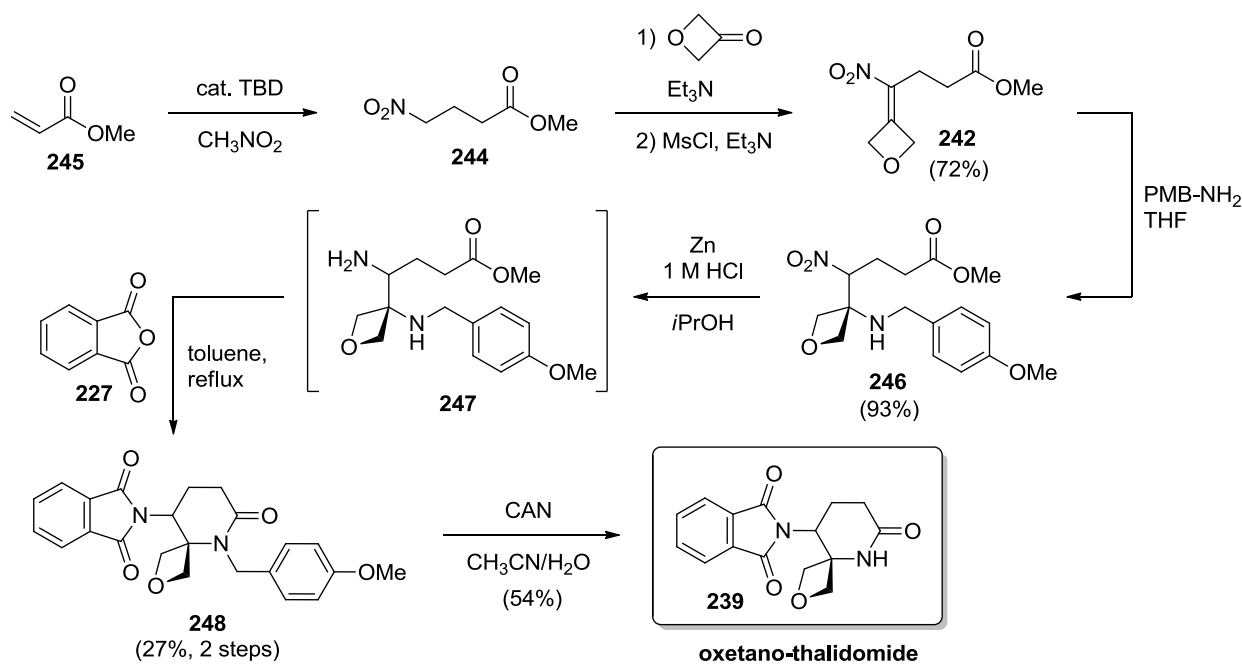
Figure 57 displays the general strategy toward oxetane analogues of thalidomide and lenalidomide. Major disconnections as indicated below will lead to building blocks of type **241** ( $X = O, CH_2$ ;  $Y = H, NO_2$ ), to a component like **242** that will be used to introduce the oxetane ring, and to an amine **243** that would undergo a conjugate addition onto nitroalkene **242**. The latter would be obtained from a condensation reaction of primary nitro compound **244** and oxetan-3-one (**34**). The following paragraphs describe the synthetic endeavors toward the isolation of small quantities (first generation synthesis) and larger amounts (second generation synthesis) of the desired compounds.



**Figure 57.** Retrosynthetic analysis for oxetane analogues of thalidomide and lenalidomide.

### First Generation Syntheses of Oxetano-Thalidomide and -Lenalidomide

The initial goal of the project was to obtain enough material of the target compounds for preliminary biological tests, i.e. the synthesis of *ca.* 5 mg of **239** would be sufficient. With this goal in mind, the synthetic route was carried out on the basis of the eventual successful isolation of some of the final product, and intermediate low yields would initially be neglected. The first generation synthesis is outlined in Scheme 47.



**Scheme 47.** First generation synthesis of oxetano-thalidomide (**239**). TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

In a first step, a MICHAEL-type addition of nitromethane onto methyl acrylate (**245**), mediated by bicyclic guanidine base TBD, afforded methyl  $\gamma$ -nitrobutanoate (**244**).<sup>247</sup> The reported yield in the literature for this reaction is 95%, but in our case, the product was obtained in 20–40% yield on a regular basis along with double and triple addition products. Changing the conditions (order of addition; higher or lower dilution;  $\text{KF}\cdot\text{Al}_2\text{O}_3$ ,<sup>248</sup>  $\text{Et}_3\text{N}$ , or  $\text{DBU}$ <sup>249</sup> as base; biphasic mixture  $\text{CH}_2\text{Cl}_2/\text{basic H}_2\text{O}$ <sup>250</sup>) did not have a big influence on the outcome. Since pure material was easily obtained after chromatographic purification, it was decided to move on. HENRY addition to oxetan-3-one delivered the oxetanyl alcohol, which was treated *in situ* with  $\text{MsCl}$  and  $\text{Et}_3\text{N}$  at  $-78^\circ\text{C}$ , and warming up of the reaction mixture promoted elimination of the mesylate to afford nitroalkene **242**. The optimized yield for this reaction is 72%, but in first attempts yields from 40–60% were more often obtained. Major side products were remaining mesylate and a rearranged isoxazole compound (*cf.* Chapter 6). Nitroalkene **242** served as an excellent MICHAEL acceptor, as 4-methoxybenzylamine could be added to it within 30 min at RT (regularly at 0.1–0.2 M in THF), and the product was obtained in almost quantitative fashion (93%). The next two tasks were to form the 6-membered PMB-protected lactam and to reduce the nitro group to the corresponding amine. Unfortunately, all attempts to close the lactam at this stage led to decomposition of the starting material. Therefore the nitro group was reduced

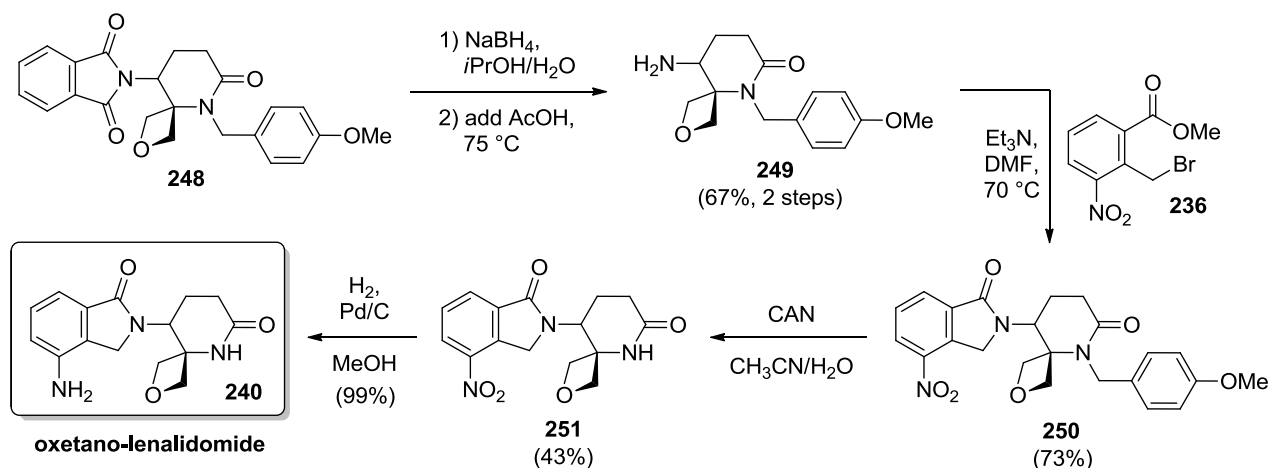
<sup>247</sup> D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607–1610.

<sup>248</sup> R. Shakirov, N. Yarmukhamedov, L. Vlasova, N. Baibulatova, R. Khisamutdinova, S. Gabdrakhmanova, L. Karachurina, N. Baschenko, *Pharm. Chem. J.* **2006**, *40*, 29–31.

<sup>249</sup> P. Yu, T. Wang, J. Li, J. M. Cook, *J. Org. Chem.* **2000**, *65*, 3173–3191.

<sup>250</sup> N. Ono, H. Katayama, S. Nisyyama, T. Ogawa, *J. Heterocyclic Chem.* **1994**, *31*, 707–710.

first. Rapid reduction occurred with Zn powder in acidic isopropyl alcohol,<sup>251</sup> but the amine **247** could not be isolated in pure form. Since also other methods for the reduction of nitro groups were unsatisfying (methods tried: SnCl<sub>2</sub>,<sup>252</sup> NiCl<sub>2</sub>/NaBH<sub>4</sub>,<sup>253</sup> Zn/NH<sub>4</sub>HCO<sub>2</sub>,<sup>254</sup> Fe/HCl, RANEY-Ni/H<sub>2</sub>, Pd-C/H<sub>2</sub><sup>255</sup>), it was decided to use the unpurified reaction product in a subsequent step with phthalic anhydride. By heating the crude amine **247** with phthalic anhydride (**227**) in toluene (110 °C), we were able to isolate desired phthalimido-lactam **248** in 27% over two steps. This material was only a deprotection step away from oxetano-thalidomide, and when PMB-protected lactam **248** was treated with cerium(IV) ammonium nitrate in an acetonitrile/water mixture,<sup>256</sup> the desired target material **239** was obtained in 54% yield. Initially obtained quantities (ca. 20 mg) were sufficient for preliminary tests.



**Scheme 48.** First generation synthesis of oxetano-lenalidomide (**240**).

The oxetane analogue of lenalidomide was the next immediate target. Its preparation was attempted from unpurified amine **247**, but all attempts to arrive at an intermediate like PMB-protected lactam **250** were unsuccessful. Therefore it was decided to start from previously synthesized phthalimide **248** and convert this to the corresponding amine (Scheme 48). The most common way to deprotect phthalimides is to use hydrazine,<sup>257</sup> but when **248** was treated with hydrazine in hot EtOH, only a 2-(hydrazinecarbonyl)benzamide was obtained. Consequently,

<sup>251</sup> a) R. P. Wurz, A. B. Charette, *J. Org. Chem.* **2004**, *69*, 1262-1269; b) B. Moreau, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 18014-18015.

<sup>252</sup> S. Batra, V. Singh, S. Kanojija, *Tetrahedron* **2006**, *62*, 10100-10110.

<sup>253</sup> S. Handa, V. Gnanadesikan, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 4900-4901.

<sup>254</sup> D. Gowda, B. Mahesh, G. Shankare, *Indian J. Chem. B* **2001**, *40*, 75-77.

<sup>255</sup> K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2001**, *57*, 4817-4824.

<sup>256</sup> a) M. Y. Chang, S. T. Chen, N. C. Chang, *Synth. Commun.* **2003**, *33*, 1375-1382. For an account on deprotections with CAN, see: N. Maulide, J.-C. Vanherck, A. Gautier, I. E. Markó, *Acc. Chem. Res.* **2007**, *40*, 381-392.

<sup>257</sup> P. G. M. Wuts, T. W. Greene, in *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., **2006**, pp. 696-926.



GANEM's two-step protocol involving a partial reduction followed by hydrolysis was considered.<sup>258</sup> Phthalimide **248** was thus treated with sodium borohydride in aqueous isopropyl alcohol, and when full conversion was observed (as judged by TLC), acetic acid was added, and the mixture was heated to 75 °C overnight. Free amine **249** was obtained in 67% yield and good purity and was used as such in the following step. The reaction of amine **249** with benzyl bromide **236** (prepared from corresponding toluene in a radical bromination: NBS, AIBN,  $\Delta$ <sup>259</sup>) and base in hot DMF afforded the desired isoindolin-1-one **250** in 73% yield.<sup>260</sup> Deprotection of the PMB group was effected with CAN in aqueous acetonitrile to give **251** in mediocre yield (43%). Ultimately, the nitro group was reduced (Pd/C, H<sub>2</sub>; 99% yield) and oxetano-lenalidomide (**240**) was obtained in sufficient quantities for initial biological tests.

### Biological Evaluation of Oxetane Analogues

As introduced in sections 5.2.1 and 5.2.2, thalidomide and lenalidomide were both found to have antiangiogenic activities and therefore have become attractive for the treatment of cancer. In order to be able to compare the potency of the oxetane analogues with the parent compounds, oxetano-thalidomide (**239**, OT) and oxetano-lenalidomide (**240**, OL) were subjected to an *in vitro* angiogenesis test ("AngioKit" by TCS CellWorks).<sup>261</sup> The cell lines were stimulated by the addition of 2 ng/ml vascular endothelial growth factor (VEGF, a signal protein that stimulates vasculogenesis and angiogenesis) two hours before treatment on day 1, 4, 7, and 9 of the test. On day 11, vascular tubes were visualized by staining of endothelial cells using CD31-PE antibody.

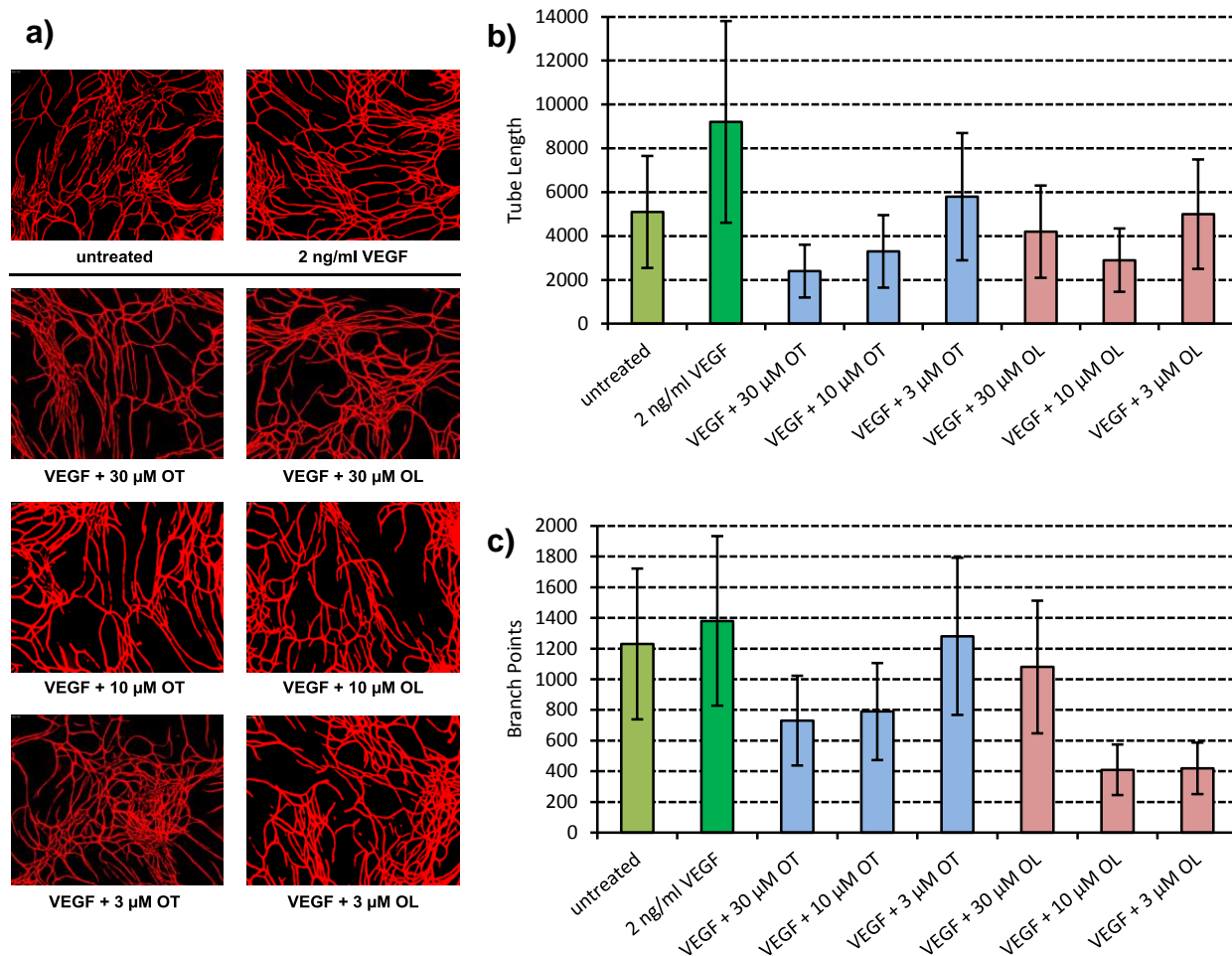
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<sup>258</sup> J. O. Osby, M. G. Martin, B. Ganem, *Tetrahedron Lett.* **1984**, 25, 2093-2096.

<sup>259</sup> S. Röhrig, M. Jeske, E. Prezborn, M. J. Gnoth (Bayer Healthcare AG), US 2010010060, **2010**.

<sup>260</sup> This transformation is frequently used in the synthesis of lenalidomide and its analogues. Selected references: a) G. W. Muller, R. Chen, S.-Y. Huang, L. G. Corral, L. M. Wong, R. T. Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett.* **1999**, 9, 1625-1630; b) G. W. Muller, D. I. Stirling, R. S.-C. Chen (Celgene Corp.), US 6335349, **2002**; c) H. Fujimoto, T. Noguchi, H. Kobayashi, H. Miyachi, Y. Hashimoto, *Chem. Pharm. Bull.* **2006**, 54, 855-860.

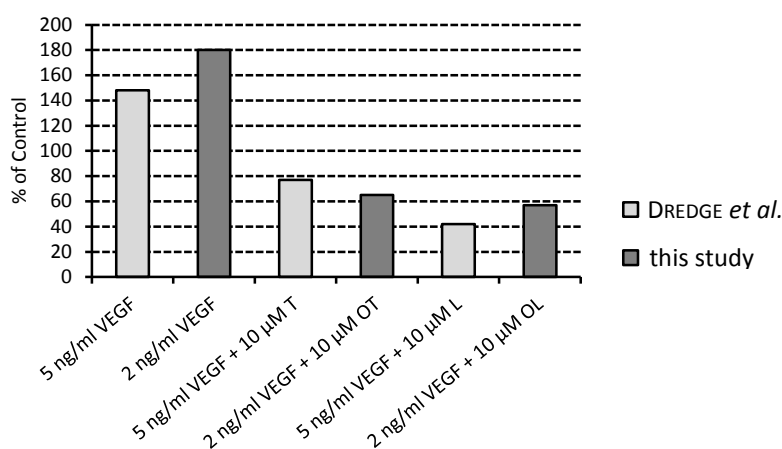
<sup>261</sup> This work was carried out by Dr. CHRISTIAN KLEIN at Roche, Penzberg (Germany).



**Figure 58.** Results from angiogenesis tests. **a)** Vascular tubes after 11 days, magnification:  $4\times$  objective. **b)** Determined tube lengths, approximate error bars at 50%. **c)** Counted branch points, approximate error bars at 40%. The exact values and standard deviations were calculated by duplicates and the analysis of four pictures per specimen.

The results from the angiogenesis test are shown in Figure 58. It is evident that both OT (**239**) and OL (**240**) show an inhibition of tubules formation in the range of 3–30  $\mu$ M. The controls are untreated specimen (light green) and specimen treated with VEGF (2 ng/ml) only (darker green). Whereas oxetano-thalidomide displayed a consistent pattern for tube lengths and the number of branch points (two major indications for tubules growth), results for the lenalidomide analogue were not entirely consistent. By comparison with the controls, tube lengths and branch points were significantly reduced for OL-treated specimen, but on the other hand, a higher number of branch points was obtained for the treatment with a higher concentration of the agent. This observation is counterintuitive and raises the question whether experimental errors or a non-specific stimulation at higher concentrations can account for the measured values. More reliable values would certainly be expected by repeating this assay or by the use of advanced (*in vivo*) biological tests. Comparing the values obtained in this study for OT and OL with the values for thalidomide (T) and lenalidomide (L) in a similar assay by DREDGE

*et al.*<sup>262</sup> encourages further measurements, since the oxetane analogues show comparable or even better results (Figure 59).



**Figure 59.** Comparison of results obtained by us with those reported by DREDGE *et al.* for thalidomide and lenalidomide. Visualized is the effect (DREDGE *et al.*: “tubule development”; this study: tube length) in % of the untreated control specimen.

A small amount of material is required for re-running the *AngioKit* assay, but advanced studies would necessitate larger quantities (>100 mg). To assess teratogenicity, it would be desirable to have access to both enantiomers of the target compounds. The synthetic route described above (5.2.3, First Generation Syntheses) does not qualify for the generation of larger quantities of the target material, and therefore some strategic adjustments need to be made and different tactics should be evaluated.

## Second Generation Syntheses

The central problem in the first generation synthesis of oxetano-thalidomide and oxetano-lenalidomide was the inefficient preparation of crucial amine **249**. If access to this compound is granted in a few scalable steps, then target compounds should become available in sufficient quantities for subsequent biological testing. With this in mind and the desire to preserve the overall strategy a modified route was worked out.

Two major issues encountered in the original OT synthesis were (1) the reluctance of nitro group containing **246** to undergo cyclization to the corresponding lactam, and (2) the unsatisfactory reduction of the nitro functionality in **246**. It seemed that using the nitro group as a precursor to the functionalized amine might not be the best option. But, on the other hand, ad-

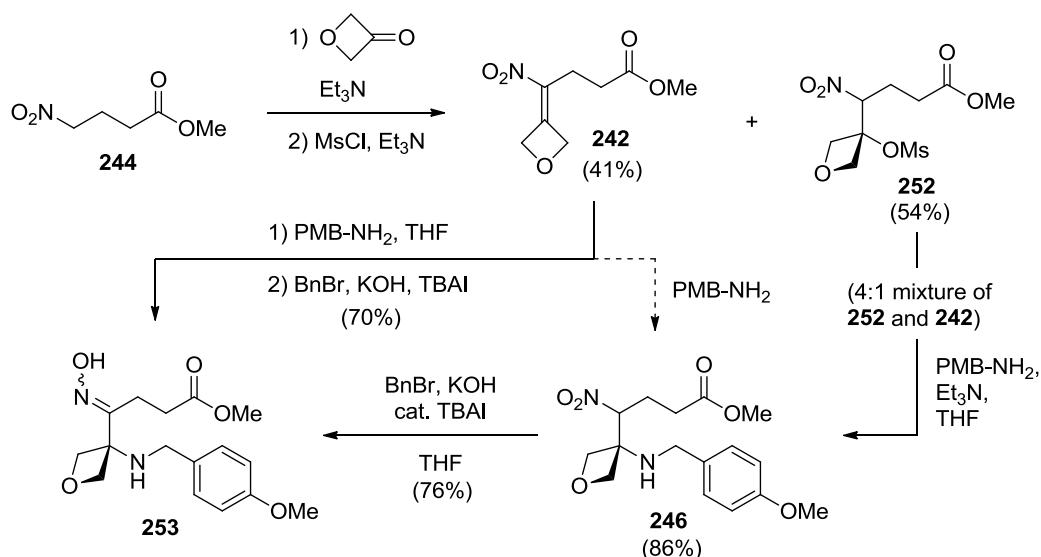
<sup>262</sup> K. Dredge, J. B. Marriott, C. D. Macdonald, H. W. Man, R. Chen, G. W. Muller, D. Stirling, A. G. Dalglish, *Brit. J. Cancer* **2002**, 87, 1166-1172.

dition of a benzylamine to MICHAEL acceptor **242** occurred in a highly desirable manner, and additions to any other electron-deficient alkene were believed to be much more difficult. As a consequence, we aimed for a synthesis that would contain the nitro group at first, but then a controlled reduction/cyclization sequence should afford the desired amine **249**.

Methyl  $\gamma$ -nitrobutanoate (**244**) was again chosen as starting point, and the sequence of HENRY addition, then activation and elimination gave on larger scale (1-10 g of **244**) a mixture of nitroalkene **242** and mesylate **252** (Scheme 49). The nitroalkene was isolated in 35% to 72% yield after one chromatographic purification and used for the next step. The remaining material, usually a varying mixture of **242** and **252** (total yield of useful material: 78-95%), was independently pushed forward: the use of benzylamine and triethylamine in THF promoted MsOH-elimination followed by addition of 4-methoxybenzyl amine, and nitro compound **246** could be isolated in 77-86%. This material was previously also obtained by addition of PMB—NH<sub>2</sub> to nitroalkene **242** (*vide supra*). At this point, we sought for a controlled reduction of the nitro group. A synthetic method developed earlier in the group by CZEKELIUS<sup>263</sup> inspired the conversion to the corresponding oxime (i.e., a partial reduction of the nitro group). Although the original work comprised the conversion of primary nitro groups to the corresponding aldoximes, we desired the partial reduction of **246**, which contains a secondary nitro group. In an initial attempt, **246** was subjected to the reported conditions (1.1 equiv BnBr, 1.05 equiv KOH, 0.05 equiv TBAI) and indeed, the desired oxime **253** was obtained in 65% yield as an inconsequential mixture of (*E*)- and (*Z*)-isomers (easily separable by chromatography). Starting material was reisolated in 10%. By slightly increasing the reagent amounts to 1.2 equiv of BnBr and KOH, the reaction went to full conversion and the oximes were isolated in 76% yield (900 mg scale). These oximes were also obtained in a one-pot operation from nitroalkene **242**. When full addition of 4-methoxybenzyl amine to **242** was observed (TLC analysis), TBAI, BnBr, and KOH were added, and the oximes **253** were obtained in 70% yield over the two steps (*ca.* 5 g scale).

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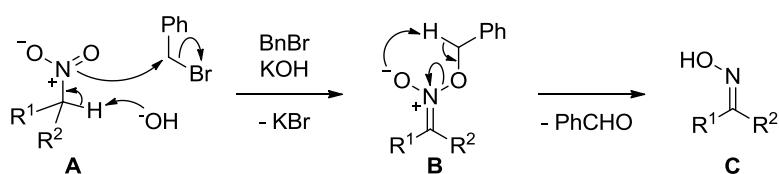
<sup>263</sup> a) C. Czekelius, E. M. Carreira, *Angew. Chem. Int. Ed.* **2005**, *44*, 612-615; b) C. O. Czekelius, Diss. ETH Nr. 15687, ETH Zürich (Zürich), **2004**.



**Scheme 49.** First part of the second generation synthesis of oxetano-thalidomide and -lenalidomide.

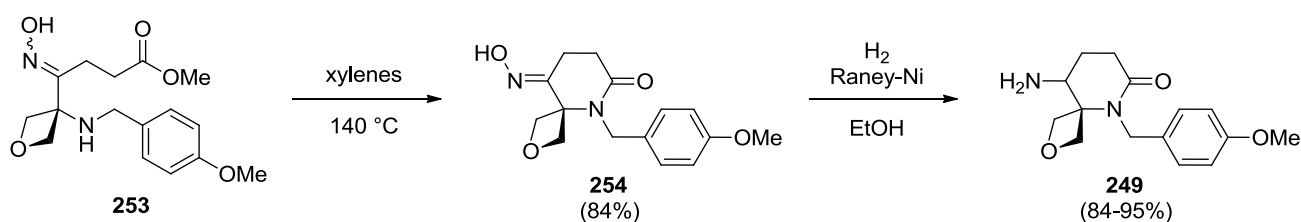
In general, the conversion of nitro groups to the corresponding oximes using benzyl bromide and base was reliable and easily scalable up to 5 g of starting material. However, it is interesting to note, that on one occasion, when 10.6 g of **246** was used under the same conditions, absolutely no conversion was observed by TLC after 3 h. Gentle heating ( $50\text{ }^\circ\text{C}$ ), accelerated stirring, or the addition of more  $\text{KOH}$  (*ca.* 0.2 equiv) did not have an impact on the reaction, and the only visible spots on TLC could be assigned to  $\text{BnBr}$  and remaining starting material. After a total time of 7 h it was decided to add a small amount of water (*ca.* 0.2 ml) to initiate the reaction. Indeed, monitoring of the reaction by TLC after 30 min revealed full conversion of the starting material and the presence of spots that could be associated with the oximes. Subsequent standard work-up and purification afforded 57% of the desired oximes **253**. The reasoning and explanation for the addition and influence of water is the following: on smaller scales the employed (freshly) powdered  $\text{KOH}$  probably contained a larger percentage of water (hygroscopic nature of  $\text{KOH}$ ), which could be influential to the reaction. On a larger scale, though, not enough water would be taken up from the powdered  $\text{KOH}$  to have the same hypothetical influence. The exact role of water in this reaction is unclear at present, but a likely process would be its function in solubilizing  $\text{KOH}$ <sup>264</sup> and thus promoting the deprotonation of the secondary nitro group.

<sup>264</sup> No numbers were found for the solubility of  $\text{KOH}$  in THF. Whereas its solubility in  $\text{H}_2\text{O}$  is enormous (more than 50% w/w at RT), only  $\sim 200\text{ mg/l}$  dissolve in DMF at  $20\text{ }^\circ\text{C}$  (Z. P. Dobronevskaya, S. V. Demin, G. D. Klinskii, Y. M. Udachin, *Russ. J. Inorg. Chem. (Transl. of Zhurnal Neorganicheskoi Khimii)* **1979**, *24*, 1746-1747).



**Scheme 50.** Mechanistic explanation for the formation of oximes from nitro groups.

This intriguing transformation of a nitro group is from the reagent point of view a KORNBLUM-type oxidation (Scheme 50).<sup>265</sup> The first step probably involves a deprotonation/*O*-alkylation sequence leading to nitronate **B**. Intramolecular proton transfer initiates the release of benzaldehyde and the formation of the oxime **C**.<sup>266</sup>



**Scheme 51.** Synthesis of common intermediate amine **249**.

At this point, it would be optimal to achieve lactam formation followed by oxime reduction, a process that would deliver the desired amine **249**. Since previous studies have shown that cyclization can occur at elevated temperatures, a toluene solution of **253** was heated to reflux. We were glad to observe the formation of the desired product (*ca.* 46% yield after 9 h at 110 °C), but an equal amount of starting material was still present. As a consequence, methyl ester **253** was taken up in xylenes and the solution was stirred for 1 day at 140 °C. Full conversion was achieved, and lactam **254** was isolated in 84% yield. Surprisingly, the product obtained was in the form of a single oxime isomer. <sup>1</sup>H NMR analysis of the unpurified reaction product did not reveal the presence of the isomeric product either. Due to the thermal instability of the oxime configuration,<sup>267</sup> it is likely that an isomerization of the starting material occurs at 140 °C, and one isomer is faster converting to the lactam product. When isomers were separated prior to the cyclization reaction, it was observed that they interconvert (new spot on TLC, <sup>1</sup>H NMR analysis of reaction aliquots), and finally cyclize to the same product. Isomerization might also

<sup>265</sup> For the oxidation of benzyl bromides to aldehydes with 2-nitropropane, see the seminal papers by HASS and BENDER: a) H. B. Hass, M. L. Bender, *J. Am. Chem. Soc.* **1949**, *71*, 1767-1769; b) H. B. Hass, M. L. Bender, *J. Am. Chem. Soc.* **1949**, *71*, 3482-3485.

<sup>266</sup> For the conversion of phenylnitromethane to benzaldehyde oxime with benzyl bromides, see L. Weisler, R. W. Helmkamp, *J. Am. Chem. Soc.* **1945**, *67*, 1167-1171.

<sup>267</sup> The activation barrier for a simple ketoxime in benzene solution is  $\Delta H^\ddagger = 16.5$  kcal/mol, see R. E. Gawley, T. Garcia-Pons, *Tetrahedron Lett.* **1986**, *27*, 5185-5188.

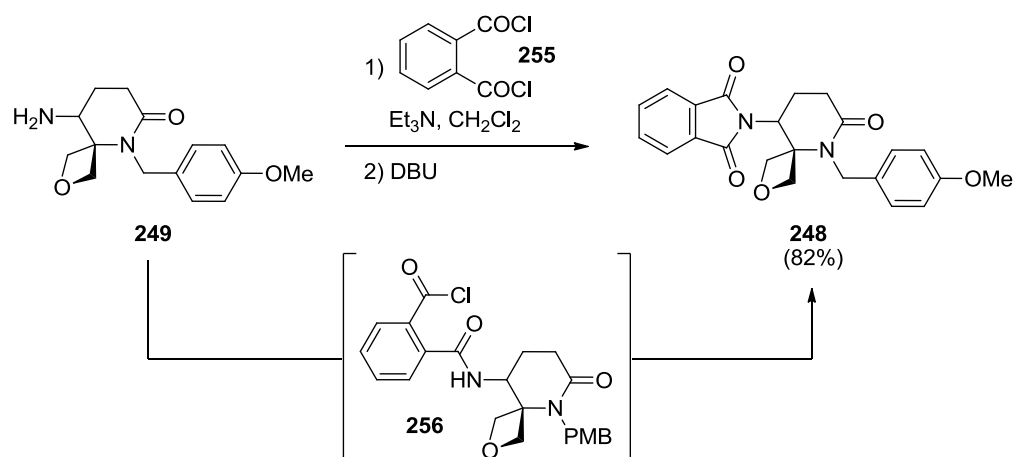
occur in the product, but since repeatedly only one isomer was isolated, one can postulate that this particular isomer is thermodynamically much more favored than the other. Unfortunately it was not possible to determine the absolute configuration of the oximes in either starting materials or the product, as these compounds did not form crystals for an eventual X-ray crystallographic analysis. Moreover,  $^1\text{H}$  NMR NOE experiments with either stereoisomer of **253** were also not instructive (the oxime protons were irradiated in  $\text{DMSO}-d_6$  solution, but no meaningful responses from close by oxetane or alkyl protons were observed). The cyclized product **254** is drawn with the oxime in (*E*)-configuration, as unfavorable pseudoallylic 1,3-interactions between the oxime OH and oxetane methylene groups would disadvantage the (*Z*)-configured product.

The remaining task was to efficiently reduce the oxime **254** to the corresponding primary amine **249**. Palladium on activated charcoal and  $\text{H}_2$  (1 atm) or zinc powder in acidic aqueous isopropyl alcohol were ineffective, and starting material was recovered from the reactions. However, the use of RANEY-nickel in ethanol under an atmosphere of hydrogen cleanly led to the desired product, which could be isolated in up to 95% yield not requiring chromatographic purification.<sup>268</sup> Commercial RANEY-Ni (50% slurry in  $\text{H}_2\text{O}$ ) was washed three times with ethanol prior to use, and the application of excess reagent (*ca.* 1 ml/100 mg of starting material) effected complete reduction within 6-9 hours. This reaction was routinely conducted on scales >1 g (largest batch: 3.7 g of starting material). At this point, 4.8 g of racemic **249** were subjected to preparative chiral HPLC, and (+)-**249** and (-)-**249** were obtained in 37% and 35% yield, respectively.<sup>269</sup>

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<sup>268</sup> RANEY-nickel and other impurities were removed by two filtrations over a plug of celite (1<sup>st</sup>: reaction solution in EtOH, 2<sup>nd</sup>: a solution of the crude product in  $\text{CH}_2\text{Cl}_2$ ).

<sup>269</sup> Work was done by DANIEL ZIMMERLI (*Roche*, Basel). Results from previous analytical studies suggested that separation at this stage was most effective. Oxetane analogues of thalidomide and lenalidomide proved troublesome in their separation by chiral HPLC due to issues of solubility and separability. For details, see the Experimental Part. Until now, the absolute configuration of (+)-**249** and (-)-**249** could not be determined by X-ray crystallography of appropriate derivatives.



**Scheme 52.** Synthesis of PMB-protected oxetano-thalidomide from amine **249**.

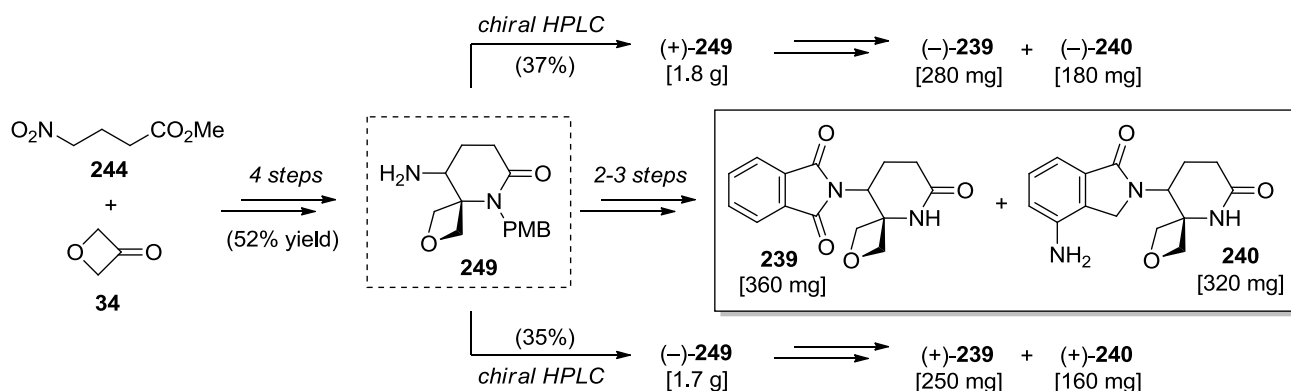
While it was shown earlier that amine **249** can be converted to oxetano-lenalidomide (*vide supra*), experimental studies had to demonstrate also its conversion to oxetano-thalidomide. Surprisingly, when **249** was treated with phthalic anhydride (1.5 equiv) in refluxing toluene, only trace amounts of the desired phthalimide were observed after 10 h. The use of the more reactive phthaloyl chloride (**255**) in presence of triethylamine led to full conversion of starting material, but the desired phthalimide **248** was not formed. Instead, intermediate amide **256** was isolated (42% yield). This material showed good stability in chromatographic purifications, but mass spectrometry of the compound always revealed major peaks for presumably the cyclized product and its adducts with  $\text{H}^+$  and  $\text{Na}^+$ . This finding suggested that imide formation should be feasible from this intermediate by the application of slightly harsher conditions. As a result, **256** was dissolved in toluene and DBU (3 equiv) was added, and the mixture was heated at 75 °C for 2 h, upon which TLC indicated complete conversion of the starting material. The desired phthalimide was isolated in 98% yield after chromatographic purification.

Although the targeted material was successfully obtained in two steps from amine **249**, it would be more desirable to turn this sequence into a single step. Thus, DBU (2.2 equiv) and phthaloyl chloride were sequentially added to a solution of amine **249** in toluene. Upon addition of the electrophile the reaction mixture turned immediately yellow and the formation of a precipitate was observed. Nonetheless, the mixture was heated to 75 °C, which led to the formation of a green, mostly insoluble material.<sup>270</sup> These indications arouse the suspicion that the desired product would probably not be formed – an assumption which was later confirmed by  $^1\text{H}$  NMR analysis of the unpurified reaction product. Instead, decomposition products along with unreacted starting material were observed. Independent experiments showed that DBU is incompatible with phthaloyl chloride, since a greenish product is formed by mixing the two components

<sup>270</sup> Similar observations were made by MYERS, GIN, and ROGERS; see ref. 271b for details.



at RT in toluene or  $\text{CH}_2\text{Cl}_2$ . Consequently, it was decided to conduct the reaction sequence in one pot, but two steps, employing triethylamine in the first and DBU at elevated temperatures in the second.<sup>271</sup> Amine **249** was thereupon first treated with phthaloyl chloride (1 equiv) and  $\text{Et}_3\text{N}$  (3 equiv) in THF at  $0\text{ }^\circ\text{C}\rightarrow\text{RT}$  (2 h), and then with DBU (3 equiv) at  $75\text{ }^\circ\text{C}$ . After heating for two hours, the product formed and was isolated after purification by FC in 82% yield.



**Scheme 53.** Summary of the larger scale synthesis of oxetano-thalidomide (**239**) and -lenalidomide (**240**).

With the improved route to common amine intermediate **249** it was possible to prepare multi-gram quantities of the material ( $>10.5$  g were prepared). Its separation into the enantiomers and subsequent analogous reactions as in the racemic route gave access to both enantiomers of oxetano-thalidomide ( $>250$  mg) and oxetano-lenalidomide ( $>160$  mg) (Scheme 53). In the racemic route, a total amount of 360 mg of OT and 320 mg of OL were prepared. As can be seen in the scheme above, a significant amount of material is lost from amine **249** to the final products. This is largely due to the deprotection step, where the 4-methoxybenzyl group is cleaved using CAN in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  in relatively low yields (see Scheme 47 and Scheme 48). Since alternative methods for the cleavage of a PMB group from an amide<sup>257</sup> were not applicable to this problem,<sup>272</sup> we attempted to optimize the reaction conditions for the CAN-mediated deprotection. It was found that for the PMB-removal from **248**, best and most consistent results were obtained by adding a solution of CAN (2 equiv) in  $\text{H}_2\text{O}$  to a solution of the substrate in acetonitrile at  $0\text{ }^\circ\text{C}$ , then letting the reaction slowly warm to RT, adding an additional 0.5 equiv of CAN after 1.5 hours, and letting the mixture stir for another hour at RT. Importantly, during aqueous work-up the use of half-saturated aqueous NaCl and large quantities of ethyl acetate

<sup>271</sup> A similar procedure was necessary for MYERS *et al.*: a) A. G. Myers, D. Y. Gin, D. H. Rogers, *J. Am. Chem. Soc.* **1993**, *115*, 2036–2038; b) A. G. Myers, D. Y. Gin, D. H. Rogers, *J. Am. Chem. Soc.* **1994**, *116*, 4697–4718.

<sup>272</sup> Other methods include the use of *t*BuLi and  $\text{O}_2$ , Pd- $\text{H}_2$  (no turnover observed with 1 atm  $\text{H}_2$ ),  $\text{AlCl}_3$  and anisole, or TFA/reflux (decomposition of starting material observed). The oxetane moiety was believed to be incompatible with most deprotection methods.

was necessary to recover the scarcely soluble product in good yield from the organic phase.<sup>273</sup> When this protocol was followed, the desired product could be regularly isolated in 45-60% yield. However, when the whole amount of CAN was added from the beginning or when the reaction was conducted throughout at RT, markedly reduced yields varying from 20% to 40% were obtained together with an inconstant purity of the final product.

To complicate matters, the aforementioned optimized conditions led to impure product in low yield when **250** was used as a substrate. Some experimentation revealed that as soon as the reaction mixture was warmed to RT new spots appeared on the TLC-plate during reaction monitoring. Therefore, an aqueous solution of CAN (3 equiv) was added to a solution of substrate **250** in CH<sub>3</sub>CN, and the mixture was stirred at 0 °C for 2 hours. Work-up as described above and subsequent purification by FC afforded the desired material in good purity and 35-45% yield.

Due to a discouraging result with 400 mg of **250** (impurities impeded the isolation of pure product), it was decided to run the deprotections in multiple small batches (200 mg in OL syntheses and 300 mg in OT syntheses). This observation along with the other challenges described above render the PMB a problematic protecting group in these syntheses. Although there are not many protecting groups that fulfill the requirements for this synthesis (1. nucleophilic nature during introduction, 2. readily cleavable from amide nitrogen, 3. compatibility with nearby oxetane), the choice of a different group<sup>274</sup> might have led to the isolation of more of the desired target material.

Nevertheless, the synthetic route delineated above served its purpose for the generation of suitable quantities of the oxetane analogues for their testing in advanced biological studies. These include a human umbilical vein endothelial cell (HUVEC) proliferation and migration assay,<sup>275</sup> an *in vivo* cornea pocket assay,<sup>276</sup> and a zebrafish teratogenicity study.<sup>277</sup> These experiments will be carried out within *F. Hoffmann-La Roche* in the future and results will be reported as they become available.

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<sup>273</sup> The use of CH<sub>2</sub>Cl<sub>2</sub> resulted in more difficult phase separations during work-up and lower yields of the isolated product.

<sup>274</sup> Reasonable alternatives for PMB-NH<sub>2</sub> include: allylamine, *tert*-butylamine, dimethoxybenzylamine.

<sup>275</sup> R. Auerbach, in *Angiogenesis* (Eds.: W. D. Figg, J. Folkman), Springer US, New York, **2008**, pp. 299-312.

<sup>276</sup> a) M. Ziche, L. Morbidelli, in *Methods in Molecular Biology*, Vol. 467 (Eds.: C. Murray, S. Martin), Humana Press, **2009**, pp. 319-329; b) M. Ziche, in *Methods in Molecular Medicine*, Vol. 46 (Ed.: J. C. Murray), Humana Press, **2001**, pp. 131-142; c) A. M. Jousen, T. Germann, B. Kirchhof, *Graefe's Arch. Clin. Exp. Ophthalmol.* **1999**, *237*, 952-961.

<sup>277</sup> K. C. Brannen, J. M. Panzica-Kelly, T. L. Danberry, K. A. Augustine-Rauch, *Birth Defects Res. B* **2010**, *89*, 66-77.

# 6

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## Isoxazoles

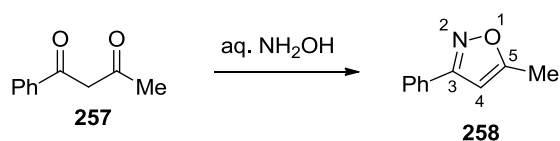
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## 6.1 Isoxazoles: Syntheses, Occurrences, Applications

### 6.1.1 Synthetic Approaches

The formation of an isoxazole compound was first described by CLAISEN and LOWMAN in 1888, when a condensation reaction between benzoyl acetone (**257**) and hydroxylamine produced isoxazole **258** (Scheme 54).<sup>278</sup> Ever since, a multitude of methods has been developed for the creation of isoxazoles and other azoles.<sup>279</sup> Isoxazoles belong to the class of heteroaromatic compounds and may undergo a variety of electrophilic aromatic substitution reactions, especially at position C(4). Nucleophilic aromatic substitutions are also possible at electrophilic centers C(3) and C(5). On the other hand, the compounds possess a comparably weak nitrogen-oxygen bond, which renders them susceptible toward fragmentations and reductive ring opening reactions. As a matter of fact, isoxazoles can first be modified appropriately and then, if desired, cleaved to afford highly functionalized open-chain compounds.

Claisen (1888):



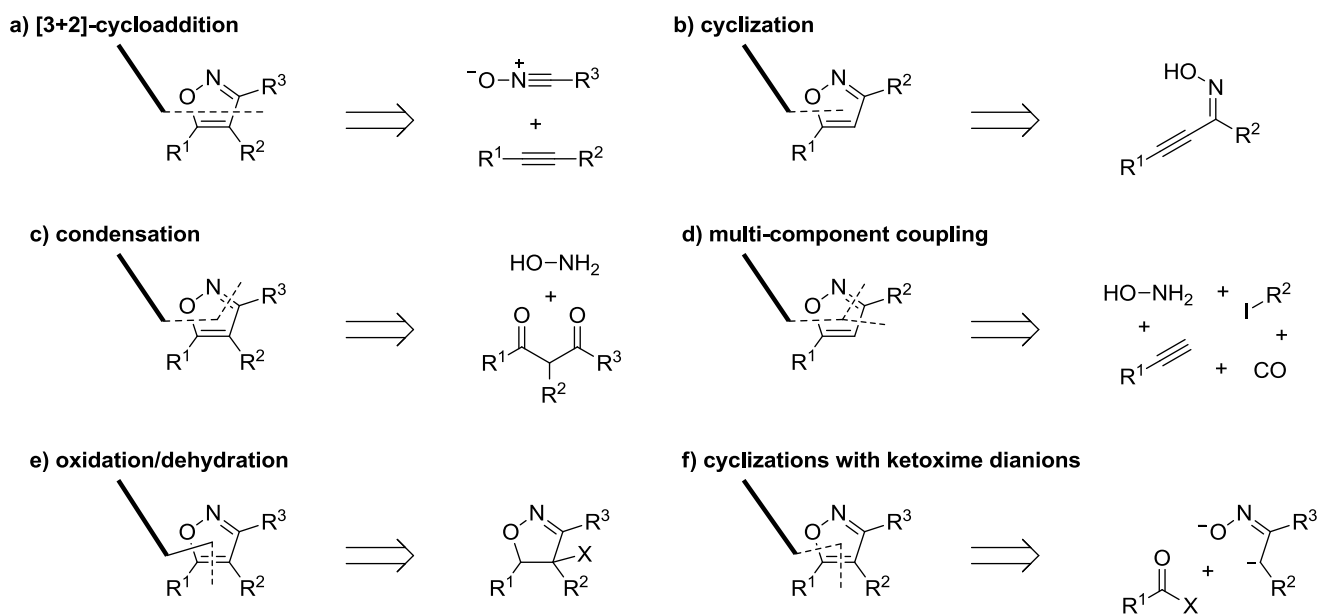
**Scheme 54.** Seminal work on isoxazoles by CLAISEN and LOWMAN.

Common synthetic access routes are summarized in Figure 60 and include: (a) dipolar cycloaddition reactions, (b) intramolecular cyclizations, (c) condensation processes, (d) multi-component assemblies, (e) oxidation or dehydration reactions, and (f) preparations involving ketoxime dianions. A few selected examples of the most useful preparative methods are discussed herein. The most desirable method in chemical research is arguably the [3+2]-cycloaddition between a nitrile oxide and an alkyne to afford the isoxazole. The possibility to join two independent fragments by a controlled cycloaddition reaction is certainly the advantage of this method, as it allows the efficient synthesis of compound libraries. Unfortunately,

<sup>278</sup> a) L. Claisen, O. Lowman, *Ber.* **1888**, *21*, 1149-1157. Earlier report of the same reaction: b) M. Ceresole, *Ber.* **1884**, *17*, 812-817.

<sup>279</sup> For reviews about isoxazoles, see: a) B. J. Wakefield, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, Vol. 11 (Ed.: E. Schaumann), Georg Thieme, Stuttgart, **2001**, pp. 229-288; b) L. Carlsen, D. Döpp, H. Döpp, F. Duus, H. Hartmann, S. Lang-Fugmann, B. Schulze, R. K. Smalley, B. J. Wakefield, in *Houben-Weyl Methods in Organic Chemistry*, Vol. E8a (Ed.: E. Schaumann), Georg Thieme, Stuttgart, **1992**, pp. 45-204; c) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.* **2005**, *9*, 925-958.

the direct thermal cycloaddition reaction suffers from reactivity, chemoselectivity, and regioselectivity issues, as nitrile oxides tend to dimerize and reactions with internal alkynes often lead to the formation of two products with low regioselectivity. Copper-catalyzed HUISGEN cycloadditions as popularized by SHARPLESS<sup>280</sup> in the context of click chemistry,<sup>281</sup> have, however, enabled the selective and efficient synthesis of isoxazoles.<sup>282</sup>



**Figure 60.** Common synthetic strategies toward isoxazole compounds.

As depicted in Scheme 55, FOKIN and co-workers established a one-pot procedure for the synthesis of isoxazoles, where aldehydes (such as **259**) were converted to the corresponding oximes, hydroximoyl chlorides, and to nitrile oxides, which then underwent Cu-catalyzed cycloadditions to afford 3,5-disubstituted isoxazoles such as **260**. Even though this process served well for the construction of isoxazoles, it was not possible to selectively make 3,4-disubstituted isoxazoles in an intermolecular cycloaddition reaction.<sup>283</sup> This challenge was later addressed by GRECIAN and FOKIN, who found ruthenium(II)-based cycloadditions to selectively give the op-

<sup>280</sup> Seminal publication: a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599. See also the work by MELDAL and co-workers: b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064.

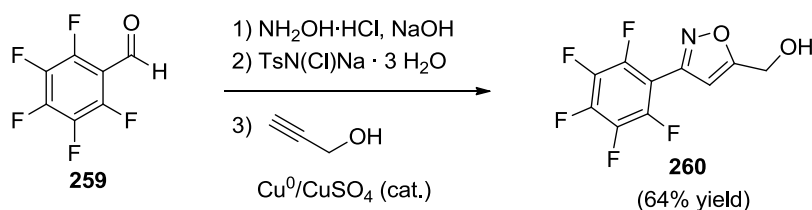
<sup>281</sup> H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

<sup>282</sup> a) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2004**, *127*, 210-216; b) T. V. Hansen, P. Wu, V. V. Fokin, *J. Org. Chem.* **2005**, *70*, 7761-7764.

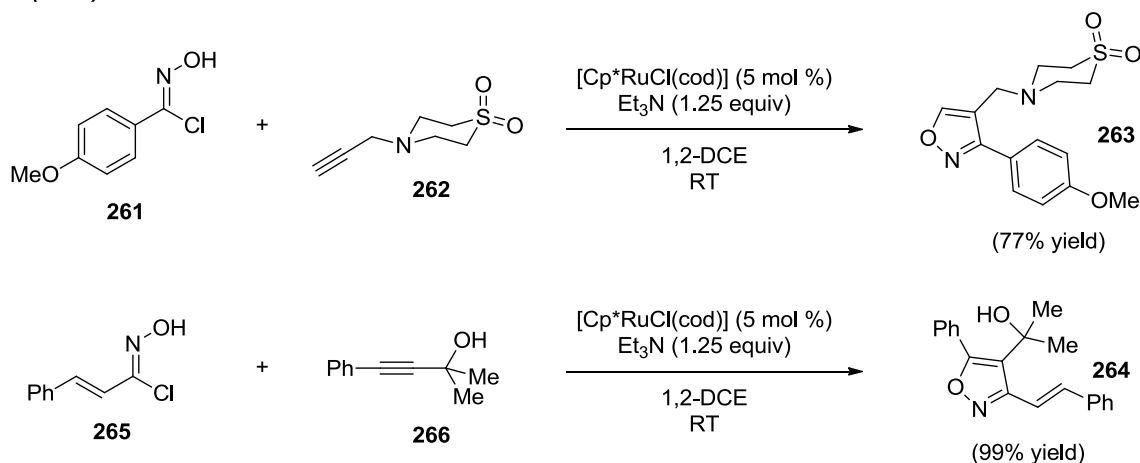
<sup>283</sup> Selective constructions of 4,5-disubstituted isoxazoles usually involve an intramolecular cycloaddition reaction: a) A. Hassner, K. S. K. Murthy, A. Padwa, U. Chiacchio, D. C. Dean, A. M. Schoffstall, *J. Org. Chem.* **1989**, *54*, 5277-5286; b) J. L. Duffy, M. J. Kurth, *J. Org. Chem.* **1994**, *59*, 3783-3785; c) G. L'Abbé, S. Emmers, W. Dehaen, L. K. Dyllal, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2553-2558. Intermolecular dipolar cycloadditions usually afford isomeric product mixtures: d) M. W. Davies, R. A. J. Wybrow, C. N. Johnson, J. P. A. Harrity, *Chem. Commun.* **2001**, 1558-1559; e) C. K. Y. Lee, C. J. Easton, M. Gebara-Coghlan, L. Radom, A. P. Scott, G. W. Simpson, A. C. Willis, *J. Chem. Soc., Perkin Trans. 2* **2002**, 2031-2038.

posite selectivity.<sup>284</sup> Hydroximoyl chlorides (e.g., **261**) reacted conveniently with terminal alkynes (e.g., **262**) in the presence of triethylamine (generation of nitrile oxides) and  $[\text{Cp}^*\text{RuCl}(\text{cod})]$  to afford isoxazoles like **263** in generally good yields. Moreover, it was feasible to use internal alkynes and in certain cases exceptional selectivity was observed (**264** was the only product from the reaction of **265** with **266**).

**Fokin (2005):**



**Fokin (2008):**



**Scheme 55.** FOKIN's copper- and ruthenium-catalyzed cycloadditions affording isoxazoles.

Apart from recent advances in dipolar cycloaddition reactions,<sup>285</sup> other particular methods for the construction of isoxazoles are worth mentioning. Since condensations of 1,3-diketones with hydroxylamine may lead to regioisomeric mixtures when the starting material is not symmetrical, an alternative method was needed. BEAM *et al.* first solved this issue by reacting ketoxime dianions with benzoic acid esters.<sup>286</sup> An extension to aliphatic compounds was published by HE and LIN (Scheme 56).<sup>287</sup> As exemplified below, the reaction tolerates the use of fairly functionalized electrophiles like dichlorocyclopropane **267**.

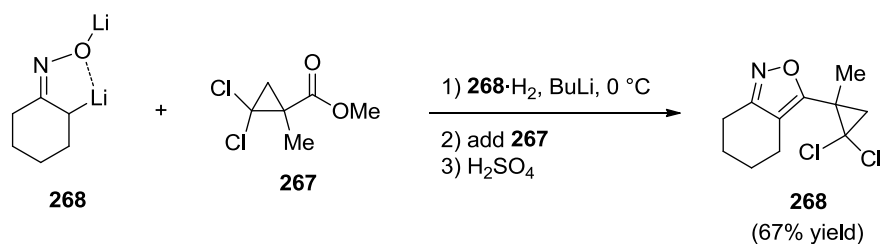
<sup>284</sup> S. Grecian, V. V. Fokin, *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287.

<sup>285</sup> Diketones may also serve as dipolarophiles: a) K. B. Umesh, K. A. Kumar, K. M. L. Rai, *Synth. Commun.* **2002**, *32*, 1841–1846; b) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 3555–3558; c) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Org. Lett.* **2003**, *5*, 391–394.

<sup>286</sup> C. F. Beam, M. C. D. Dyer, R. A. Schwarz, C. R. Hauser, *J. Org. Chem.* **1970**, *35*, 1806–1810.

<sup>287</sup> Y. He, N.-H. Lin, *Synthesis* **1994**, 989–992.

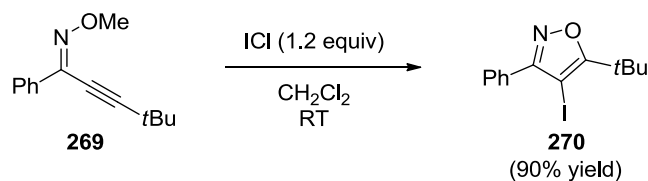
Lin (1994):



**Scheme 56.** Formation of an isoxazole through the condensation of a ketoxime dianion with a carboxylic acid derivative.

An intriguing variant of the cyclization of propargylic oximes to give isoxazoles was disclosed by WALDO and LAROCK in 2005 (Scheme 57).<sup>288</sup> Treatment of an oxime ether (e.g., **269**) with 1.2 equivalents of iodine monochloride in CH<sub>2</sub>Cl<sub>2</sub> gave an iodinated isoxazole product (e.g., **270**) in good yield. The products could be used in SUZUKI coupling reactions to further functionalize the isoxazole core.

Larock (2005):



**Scheme 57.** LAROCK'S synthesis of halogenated isoxazoles.

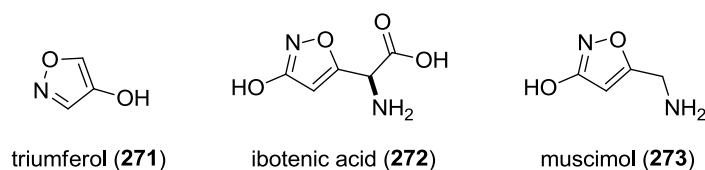
## 6.1.2 Isoxazole Natural Products

Isoxazoles are almost entirely of artificial origin and only a handful of isoxazole-containing compounds were isolated from natural sources. The simplest isoxazole isolated from nature is 4-hydroxyisoxazole (or: triumferol, **271**), which was obtained from East African folk medicinal plant *Triumfetta rhomboidea* and was found to exhibit antigermination activity against lettuce seeds (Figure 61).<sup>289</sup> Of more importance is ibotenic acid (**272**), the active substance in *Amanita muscaria*. It was isolated in the 1960s from the distinctive poisonous fly Amanita and due to its

<sup>288</sup> a) J. P. Waldo, R. C. Larock, *Org. Lett.* **2005**, 7, 5203-5205. See also b) J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2007**, 72, 9643-9647.

<sup>289</sup> T. Kusumi, C. C. Chang, M. Wheeler, I. Kubo, K. Nakanishi, H. Naoki, *Tetrahedron Lett.* **1981**, 22, 3451-3454.

potency as a neurotoxin patented by *Geigy*.<sup>290</sup> Its decarboxylated partner muscimol (**273**), found in the same fungus, is also a powerful psychoactive substance.<sup>291</sup>



**Figure 61.** Isolated isoxazole compounds from natural sources.

### 6.1.3 Applications Involving Isoxazole Compounds

Isoxazoles have been used as intermediates in the synthesis of natural products,<sup>292</sup> but their major impact is arguably in the medicinal chemistry environment. 19 drugs containing the isoxazole moiety have found the way to the market.<sup>293</sup> Among these are mainly drugs for the treatment of bacterial infections (penicillin analogues), schizophrenia, depression, and psychosis. Selected examples are shown below in Figure 62. The first isoxazole compound to be launched as a drug was isocarboxazid (**274**), which originated from the laboratories of *F. Hoffmann-La Roche* (site in Nutley, NJ).<sup>294</sup> It is still being used as a last resort drug for the treatment of depression. Leflunomide (**275**) was developed by *Aventis Pharma* (today *Sanofi*) and launched in 1998 for the treatment of adult patients with active rheumatoid arthritis. Its isoxazole is rapidly metabolized to give a 3-hydroxyacrylonitrile (cleavage of the N—O bond),<sup>295</sup> an active substance, which is currently under clinical development (name: teriflunomide). *Pfizer's* non-steroidal anti-inflammatory drug valdecoxib (**276**) was withdrawn from the market three years after its launch, as an increased risk of rare but serious skin reactions was perceived.<sup>296</sup>

<sup>290</sup> A. Gagneux, F. Hafliger, C. Eugster (*Geigy Chemical Corporation*), US 3459862, **1969**.

<sup>291</sup> D. Michelot, L. M. Melendez-Howell, *Mycol. Res.* **2003**, *107*, 131-146.

<sup>292</sup> P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, D. Simoni, *Synthesis* **1987**, 857-869.

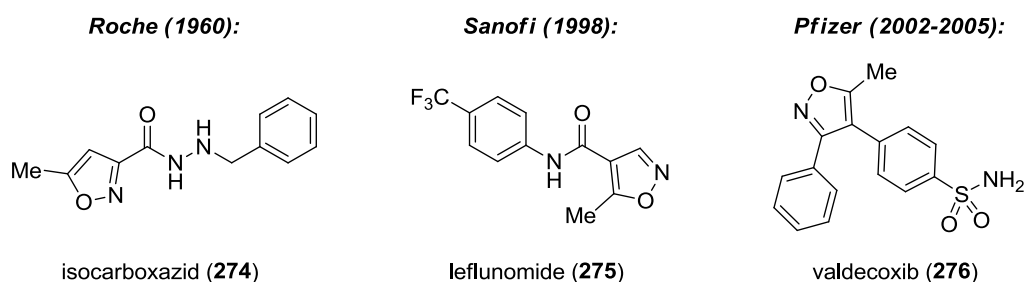
<sup>293</sup> Search in Thomson Reuters Integrity database for substituted isoxazoles with highest phase = "launched" or "withdrawn". Search performed on September 1<sup>st</sup> 2011.

<sup>294</sup> T. S. Gardner, E. Wenis, J. Lee, *J. Med. Pharm. Chem.* **1960**, *2*, 133-145.

<sup>295</sup> A. S. Kalgutkar, H. T. Nguyen, A. D. N. Vaz, A. Doan, D. K. Dalvie, D. G. McLeod, J. C. Murray, *Drug Metab. Dispos.* **2003**, *31*, 1240-1250.

<sup>296</sup> There was also an increased risk for heart attack and stroke. Valdecoxib (**276**) is a close analogue of *Merck's* rofecoxib (*Vioxx*), which was involved in a scandal in the mid-2000s (see <http://en.wikipedia.org/wiki/Rofecoxib>, September 2011 and following key papers: a) (original paper) C. Bombardier, L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M. B. Ferraz, C. J. Hawkey, M. C. Hochberg, T. K. Kvien, T. J. Schnitzer, *N. Engl. J. Med.* **2000**, *343*, 1520-1528; b) (editorial expression of concern) G. D. Curfinan, S. Morrissey, J. M. Drazen, *N. Engl. J. Med.* **2005**, *353*, 2813-2814.

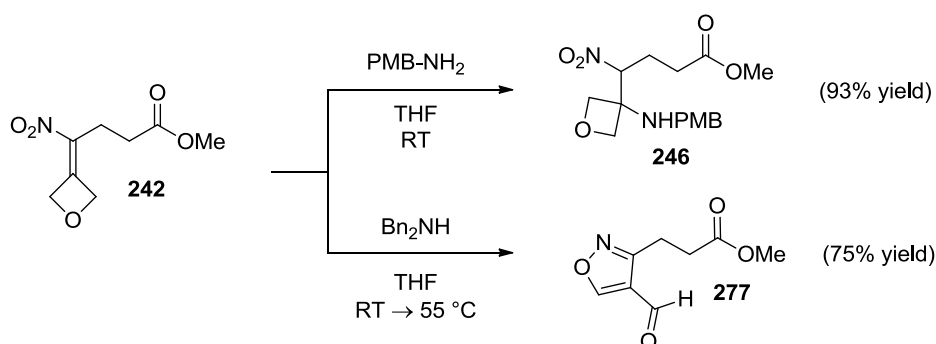




**Figure 62.** Isoxazoles found in marketed drugs (selection).

## 6.2 Isoxazoles from Nitro Compounds and Oxetan-3-one<sup>297</sup>

### 6.2.1 Initial Discovery and Optimization

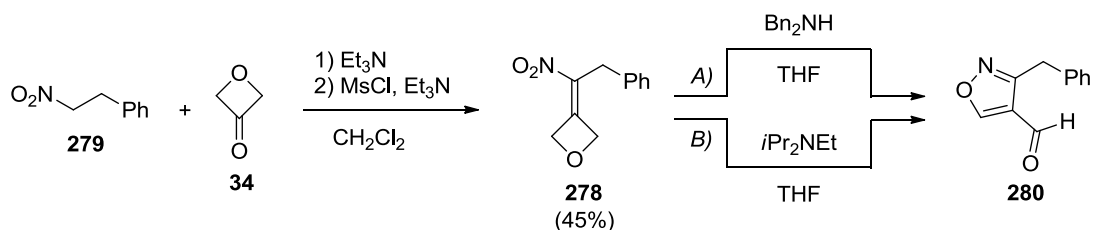


**Scheme 58.** Initial discovery of the rearrangement.

As shown in the synthesis of oxetano-thalidomide and oxetano-lenalidomide (*cf.* Chapter 5), oxetanyl nitroalkene **242** served as an excellent MICHAEL acceptor for the conjugate addition of 4-methoxybenzylamine, affording adduct **246** in 93% yield. It came with a surprise that when dibenzylamine was added to a solution of nitroalkene **242**, none of the desired 1,4-addition product was formed. Instead isoxazole-4-carbaldehyde **277** was isolated after chromatographic purification in 75% yield (Scheme 58). Characteristic signals in the <sup>1</sup>H NMR (singlets at 9.98 ppm and 8.87 ppm; measured in CDCl<sub>3</sub>) as well as other spectral data, in particular EI-MS and elemental analyses, supported the structural assignment.

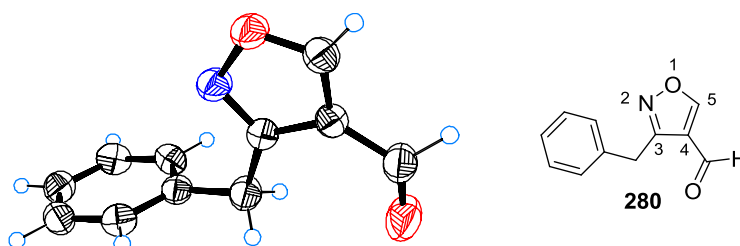
<sup>297</sup> The work described in this section is a combination of results from experiments carried out by the author of this doctoral thesis (J. A. B.) and experiments carried out by BORIS H. TCHITCHANOV in the course of his Master Thesis (see: B. H. Tchitchanov, *Synthesis of Substituted Isoxazoles from Nitroalkanes and Oxetan-3-one*, Master Thesis, ETH Zürich, 2009). All experiments mentioned herein were conceived and analyzed by J. A. B.

To investigate the generality of the rearrangement and its characteristics, benzyl-substituted nitromethyleneoxetane **278** was chosen as a standard substrate for further investigations. It was prepared by condensing (2-nitroethyl)benzene (**279**)<sup>298</sup> with oxetan-3-one (**34**), using triethylamine in the HENRY addition and MsCl, Et<sub>3</sub>N in chilled CH<sub>2</sub>Cl<sub>2</sub> (−78 °C → −20 °C) for the subsequent elimination step (Scheme 59). The product was isolated as an inseparable 22:1 mixture of nitroalkene **278** and already cyclized **280**. When this material was treated with dibenzylamine in THF, a 48% conversion to the isoxazole **280** was observed within 24 h at RT. The suspicion that dibenzylamine operates as base and not as a nucleophile was supported by the fact that when **278** was subjected to one equivalent of HÜNIG's base in THF, the same isoxazole **280** was produced (82% conversion after 22 h; 73% NMR yield).



**Scheme 59.** Synthesis of benzyl-substituted isoxazole-4-carbaldehyde.

Although analytical data as well as chemical intuition supported the structure of **280**, final proof was gained from an X-ray crystallographic study. Suitable single crystals were obtained by slowly evaporating a solution of **280** in CH<sub>2</sub>Cl<sub>2</sub>/hexanes. The resulting crystal structure, which unambiguously determines the structure of **280**, is shown in Figure 63. The phenyl ring and the isoxazole are in nearly orthogonal planes (85.1° angle) and respective ring centroids are separated by 4.70 Å. The bond lengths in the isoxazole are as follows: O(1)—N(2) = 1.43 Å, N(2)—C(3) = 1.30 Å, C(3)—C(4) = 1.43 Å, C(4)—C(5) = 1.35 Å, and C(5)—O(1) = 1.34 Å.<sup>299</sup>



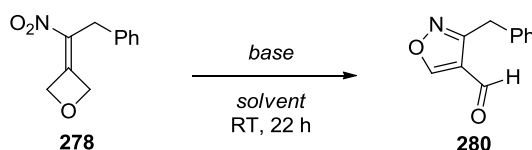
**Figure 63.** Solid state structure of **280**. ORTEP representations with ellipsoids at 50% probability.

<sup>298</sup> Prepared according to a literature procedure from nitromethane and benzaldehyde (a. condensation, b. reduction of the nitroalkene): a) R. P. K. Kodukulla, G. K. Trivedi, J. D. Vora, H. H. Mathur, *Synth. Commun.* **1994**, *24*, 819–832; b) A. K. Sinhababu, R. T. Borchardt, *Tetrahedron Lett.* **1983**, *24*, 227–230.

<sup>299</sup> In general accordance with literature values for isoxazole: O. L. Stiefvater, P. Nösberger, J. Sheridan, *Chem. Phys.* **1975**, *9*, 435–444.

The standard substrate **278** was used for the exploration of optimal conditions for the rearrangement step. Since the rearrangement conveniently occurred also at RT, the focus was on different bases and solvents. Thus, screening experiments were conducted on a 0.1 mmol scale, and yields and conversions were determined by  $^1\text{H}$  NMR after work-up using tetralin as an internal standard. The results are shown in Table 15.

**Table 15.** Screening of conditions for the rearrangement step. [a] Conversions and yields were determined by  $^1\text{H}$  NMR after 22 h of reaction time and following extractive work-up ( $\text{Et}_2\text{O}$ /half-saturated aqueous  $\text{NH}_4\text{Cl}$ ) using tetralin as an internal standard.

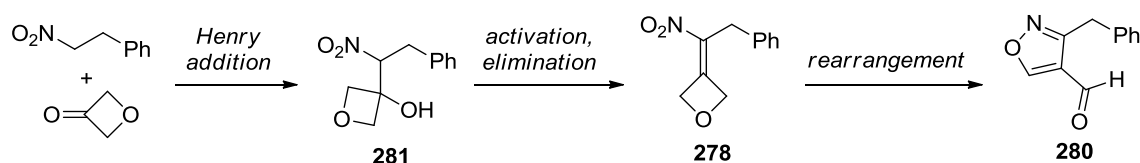


entry	base	solvent	conversion [%] <sup>[a]</sup>	yield [%] <sup>[a]</sup>
1	$\text{Cs}_2\text{CO}_3$	THF	100	18
2	LiHMDS	THF	95	10
3	$\text{Et}_3\text{N}$	THF	100	69
4	$i\text{Pr}_2\text{NEt}$	THF	82	73
5	$i\text{Pr}_2\text{NEt}$ (2 equiv)	THF	96	77
6	DABCO (0.5 equiv)	THF	100	50
7	none	THF	0	0
8	$i\text{Pr}_2\text{NEt}$	toluene	68	47
9	$i\text{Pr}_2\text{NEt}$	$\text{CH}_3\text{CN}$	100	30
10	$i\text{Pr}_2\text{NEt}$	$\text{CHCl}_3$	100	51
11	pyridine	pyridine	100	18
12	NaOMe	MeOH	100	0

Generally high conversions of starting material was observed for any base in THF as solvent (entries 1-6), but yields were greatly improved when amine bases were employed (entries 3-6), as cesium carbonate or LiHMDS gave primarily decomposition products (yield of desired **280** <20%). Of all amine bases tested,  $i\text{Pr}_2\text{NEt}$  proved best, as high conversions and yields above 70% were obtained. The slightly less hindered triethylamine led to a faster conversion, but due to the formation of putative polymerized side products the yield for the desired isoxazole was reduced. When the base was omitted, no conversion was observed (entry 7). Since HÜNIG's base performed best in THF, it was next tested in other solvents (entries 8-10). Solvents of higher polarity led to a faster conversion, but in the case of acetonitrile, the yield was dramatically reduced (30%). Since  $^1\text{H}$  NMR analysis of the unpurified reaction product revealed predominantly the formation of the isoxazole, it is presumed that the remaining material was consumed in polymerization or decomposition processes. These dominated even more by going to systems of

higher polarity like pyridine or methanol, and in the case of sodium methoxide in methanol, none of the desired isoxazole was obtained (entries 11-12). In general, optimal conditions involved the use of a non-nucleophilic tertiary amine base and a moderately polar solvent.

Although the use of amine bases in THF served well for the rearrangement and the desired product could be isolated in high yields, the overall process called for optimization, since the isolation of the nitroalkene intermediate **278** was difficult and low-yielding. Frequently the elimination of mesylated **281** was incomplete, but at the same time some rearrangement product could also be observed in the unpurified reaction product. Moreover, the separation of these three components turned out to be difficult by column chromatography. For these reasons and for the fact that amine bases are usually employed in all steps of the overall sequence (HENRY addition, alcohol activation, elimination, rearrangement; see Scheme 60), we reasoned a one-pot operation might be able to solve some of the problems and, in the optimal case, would make the sequence attractive for the preparation of isoxazole-4-carbaldehydes.



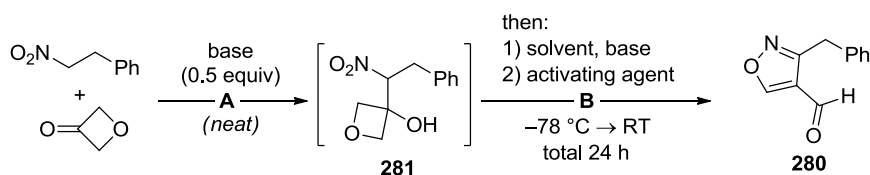
**Scheme 60.** Sequence from nitroalkanes and oxetan-3-one to isoxazole-4-carbaldehydes.

Hence, conditions were tested for the HENRY addition and the subsequent sequence giving the isoxazole **280**. Quantitative formation of the oxetanyl alcohol **281** was achieved when (2-nitroethyl)benzene was stirred with oxetan-3-one (1.3 equiv) and substoichiometric amounts of base (0.5 equiv of Et<sub>3</sub>N was optimal) without the use of an additional solvent.<sup>300</sup> The reaction was usually completed in 1.5 to 2 hours (0 °C → RT), and the product precipitated out of the reaction mixture. At this point, the mixture was diluted with the appropriate solvent, cooled to -78 °C, and base was added followed by alcohol activating agent. The reaction was allowed to slowly warm to RT and stirring was continued for a total of 24 h. The conditions tested in a one-pot operation are summarized in Table 16. Undesirable results were obtained when step B was conducted in CH<sub>2</sub>Cl<sub>2</sub> with TFAA or in CH<sub>3</sub>CN with MsCl, as mostly the formation of decomposition or polymerized products was observed (entries 1-2). The use of DBU led directly to the desired isoxazole, but the yield (50%) was unsatisfactory (entry 3). Using potassium fluoride on alumina, DABCO, or Et<sub>3</sub>N as base in CH<sub>2</sub>Cl<sub>2</sub> with MsCl as the activating agent led to

<sup>300</sup> Using CH<sub>2</sub>Cl<sub>2</sub> or THF as solvents also led to the formation of the HENRY adduct, but reaction rates were significantly reduced.

the isolation of nitroalkene **278** in useful yields (entries 4-6). The best yield of nitroalkene **278** was obtained by going to THF as solvent (entry 7). To our surprise, when the intermediate oxetanyl alcohol was activated with Tf<sub>2</sub>O, none of nitroalkene **278** nor of isoxazole **280** could be observed; instead most of the material remained at the stage of the activated alcohol (55% yield; entry 8).

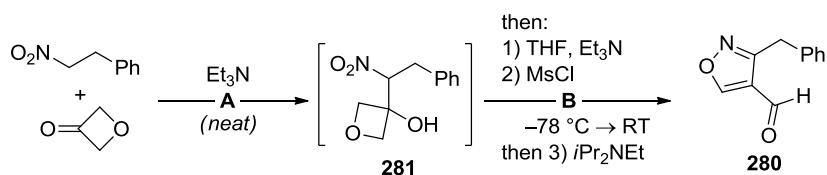
**Table 16.** Initial screening for the one-pot operation. [a] Isolated yields.



entry	base in step A	solvent	base in step B (2.5 equiv)	activating agent (2.5 equiv)	result <sup>[a]</sup>
1	Et <sub>3</sub> N	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	TFAA	traces of <b>280</b>
2	Et <sub>3</sub> N	CH <sub>3</sub> CN	Et <sub>3</sub> N	MsCl	decomposition
3	DBU	CH <sub>2</sub> Cl <sub>2</sub>	DBU	MsCl	50% <b>280</b>
4	KF-Al <sub>2</sub> O <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	KF-Al <sub>2</sub> O <sub>3</sub>	MsCl	33% <b>278</b>
5	DABCO	CH <sub>2</sub> Cl <sub>2</sub>	DABCO	MsCl	62% <b>278</b>
6	Et <sub>3</sub> N	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	MsCl	67% <b>278</b>
7	Et <sub>3</sub> N	THF	Et <sub>3</sub> N	MsCl	70% <b>278</b>
8	Et <sub>3</sub> N	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	Tf <sub>2</sub> O	55% activated <b>281</b>

The most promising result from this initial screening (Table 16, entry 7) suggested that a one-pot operation might be possible, but that the amount of base in the reaction mixture was not sufficient to provoke rearrangement of the nitroalkene. For this reason the amount of activating agent was reduced and an additional equivalent of HÜNIG's base was added at the time the reaction mixture had reached RT, and stirring was continued overnight (12 hours). As shown below in Table 17, entry 1; 56% of the desired isoxazole was successfully isolated using these conditions. By increasing the amount of *i*Pr<sub>2</sub>NEt to 1.5 equivalents, 74% of **280** was isolated (entry 2). The yield was slightly higher when less base was added and the total reaction time was increased (entry 3). <sup>1</sup>H NMR analysis of the unpurified reaction mixture revealed that minor amounts of intermediate mesylate were still present. For this reason 1.0 equivalent of *i*Pr<sub>2</sub>NEt was employed,<sup>301</sup> and the desired product was obtained in 82% yield (entry 4). These conditions were found to deliver the isoxazole-4-carbaldehyde in highest yield.

<sup>301</sup> Independently it was found that the first step required only 0.2 equiv of base, but the mesylation-elimination sequence was best carried out with 2 equiv of Et<sub>3</sub>N. Hence, these conditions were applied in here.

**Table 17.** Fine-tuning of the reagent amounts. [a] Isolated yields. [b] Rearrangement step required 15 h instead of 12 h.

entry	Et <sub>3</sub> N in step A	Et <sub>3</sub> N in step B	MsCl	iPr <sub>2</sub> NEt	yield <sup>[a]</sup>
1	0.5 equiv	2.0 equiv	1.1 equiv	1.0 equiv	56%
2	0.5 equiv	1.7 equiv	1.1 equiv	1.5 equiv	74%
3	0.5 equiv	1.7 equiv	1.1 equiv	0.5 equiv	79% <sup>[b]</sup>
4	0.2 equiv	2.0 equiv	1.1 equiv	1.0 equiv	82%

In conclusion, the optimized protocol was: (1) mixing of (2-nitroethyl)benzene with oxetan-3-one (1.3 equiv) and 0.2 equiv Et<sub>3</sub>N at 0 °C and letting the mixture reach RT over the course of 2 h; (2) diluting the reaction mixture with THF (0.1 M concentration), adding Et<sub>3</sub>N (2.0 equiv), cooling to -78 °C, adding MsCl (1.1 equiv), and letting the mixture warm to RT; then (3) adding iPr<sub>2</sub>NEt (1.0 equiv) and stirring the mixture for 12 h. To investigate whether it was possible to expand this protocol to the synthesis of other isoxazole-4-carbaldehydes, a scope was defined for the reaction (see section 6.2.2).

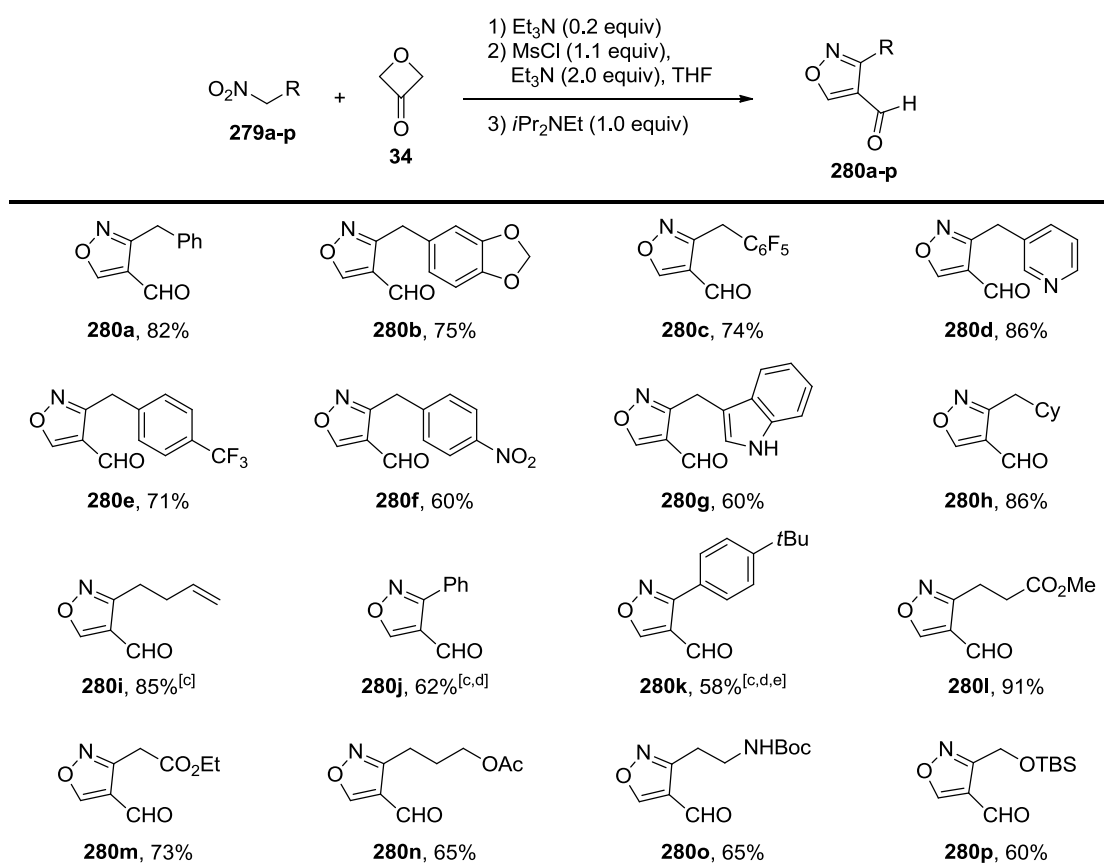
## 6.2.2 Scope of the Rearrangement

It was decided to test a number of functionalized primary nitro compounds under the optimal reaction conditions as defined above to determine how broad the applicability of the one-pot rearrangement sequence could be. Hence, nitroalkanes bearing aromatic systems, alkenes, ester groups and other functionalities were prepared (*vide infra*) and reacted with oxetan-3-one (1.3 equiv), Et<sub>3</sub>N (0.2 equiv), then MsCl (1.1 equiv) and Et<sub>3</sub>N (2.0 equiv), followed by iPr<sub>2</sub>NEt (1.0 equiv). Generally 0.75 mmol of the substrate was used and the reactions were monitored by TLC and stopped 12 h after the addition of HÜNIG's base, or later when TLC analyses indicated incomplete conversion. The results are summarized in Table 18.

Replacement of the standard phenyl substituent with electron-rich (piperonyl) and -deficient (pentafluoro-, *p*-CF<sub>3</sub>-, *p*-NO<sub>2</sub>-phenyl) aromatic and heteroaromatic (3-pyridyl, 3-indolyl) entities resulted in comparable yields (see products **280b-280g**, 60-86% yield). An aliphatic substrate bearing a cyclohexane ring also delivered the corresponding isoxazole **280h** in 86% yield. A terminal alkene was tolerated, but the rearrangement required more time (48 h; 85% yield of isoxazole **280i**). Moreover, the synthesis of isoxazoles that had directly attached aromatic

groups at position C(5) was successful, as the corresponding substituted nitromethanes afforded products **280j** and **280k** in 60% and 58% yield, respectively. These substrates also needed prolonged reaction times, since some starting material was still observed by TLC after 12 h. The slightly reduced yield for these transformations can be explained by the difficulties in the HENRY addition to reach full conversion, as uniform mixing of the neat mixture became difficult due to early precipitation of the intermediate product.<sup>302</sup> Remotely positioned ester groups were very well tolerated and the corresponding products **280l-280n** were isolated in 65-91% yield. Starting materials containing a Boc-protected primary amine or a TBS-protected primary alcohol afforded the functionalized isoxazoles **280o** and **280p** in useful yields. The high tolerance for functional groups renders this process attractive for any future applications. Likewise, the unveiled aldehyde group serves as a convenient handle for further functionalization (nucleophilic additions, condensations, reduction, oxidation, *etc.*).

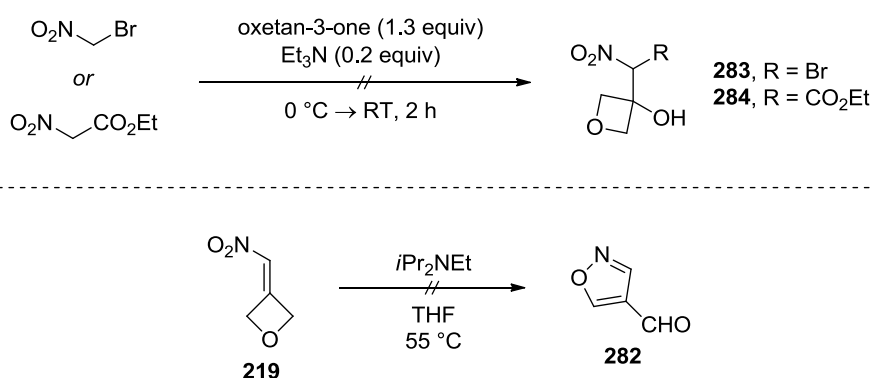
**Table 18.** Scope of the rearrangement.<sup>[a,b]</sup>



[a] General procedure: nitro compound **279** (0.75 mmol, 1.0 equiv), oxetan-3-one (**34**; 0.98 mmol, 1.3 equiv), THF (0.1 M). [b] Yields of isolated products are given. [c] Rearrangement required 48 h. [d] CH<sub>2</sub>Cl<sub>2</sub> (*ca.* 0.2 ml) was added in the first step. [e] 0.65 mmol of substrate was used.

<sup>302</sup> To circumvent this problem, minor amounts of CH<sub>2</sub>Cl<sub>2</sub> (*ca.* 0.2 ml) were added to dissolve the reaction mixture and assure good mixing.

Although the substrate scope for the rearrangement was found to be broad, some limitations were observed (Scheme 61). When activated nitromethanes such as bromonitromethane or ethyl 2-nitroacetate were subjected to standard conditions of the HENRY addition to oxetan-3-one, the reactions generally darkened and  $^1\text{H}$  NMR analysis of the mixture revealed that the desired oxetan-3-ols were not formed; instead spectral data suggested the formation of several undefined decomposition products. The exact same outcome was observed when 3-(nitromethylene)oxetane (**219**) was treated with  $i\text{Pr}_2\text{NEt}$  in warm THF, as only trace amounts of the monosubstituted isoxazole **282** were found among multiple ill-defined side products and polymerized material. Milder conditions or other bases were not investigated.

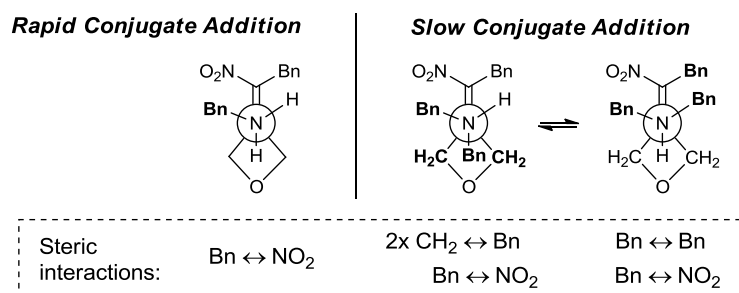


**Scheme 61.** Unsuccessful attempts for the synthesis of isoxazole-4-carbaldehydes.

### 6.2.3 Reaction Mechanism

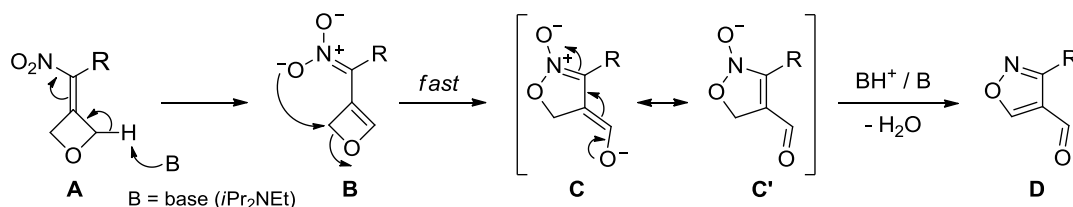
The initial discovery that benzylamine rapidly adds to the nitroalkene electrophile, but fails to take part in a conjugate addition reaction (described in section 6.2.1) can be explained by using NEWMAN projections. As shown in Figure 64 benzylamine can be placed with respect to the electrophile in a way that steric interactions are minimized, and the nucleophile may add to the nitroalkene. The rate of addition is significantly reduced when dibenzylamine is employed, as unfavorable steric interactions come into play. In Figure 64 (right) the two approaches involving least steric hindrance are displayed in a NEWMAN projection. Both situations suffer from steric clashes either between the benzyl group of  $\text{Bn}_2\text{NH}$  and the methylene units in the oxetane or between the benzyl groups of both starting materials. Thus an alternative process may take place when the nitroalkene is treated with basic dibenzylamine.





**Figure 64.** Increased steric interactions prevent dibenzylamine from adding to the nitroalkene.

Based on the above-mentioned results and those discussed in sections 6.2.1 and 6.2.2, we propose a reaction mechanism for the observed rearrangement from (nitromethylene)oxetanes to isoxazole-4-carbaldehydes. The suggested sequence is outlined in Scheme 62. Substituted (nitromethylene)oxetane **A** contains a moderately acidic methylene group,<sup>303</sup> which can be deprotonated by an amine base (here: B = HÜNIG's base). The formed nitronate is expected to initiate a rapid *5-exo-tet* opening of strained oxete in **B**. The hereby formed structure **C** is a mesomeric structure of  $\alpha,\beta$ -unsaturated aldehyde **C'**. Energy calculations reveal that the process from **B** to **C/C'** is considerably favored, since intermediate **C** is estimated to reside *ca.* 24 kcal mol<sup>-1</sup> lower in energy than the strained oxetene **B**.<sup>304</sup> A series of proton transfers ultimately lead to dehydrative generation of isoxazole-4-carbaldehyde **D**, the thermodynamic sink of the process.



**Scheme 62.** Working model for the rearrangement of nitroalkene **A** to give isoxazole **D**.

Upon deprotonation in the oxetane ring and formation of the oxetene (structure **B**), an alternative pathway may also lead to the isoxazole in **D**. As shown in Scheme 63, the oxetene might participate in an electrocyclic ring opening reaction, which would deliver enal **E**. Similar to a step in the DORNOW-WIEHLER isoxazole synthesis,<sup>305</sup> **E** may undergo a *5-endo-trig* cyclization

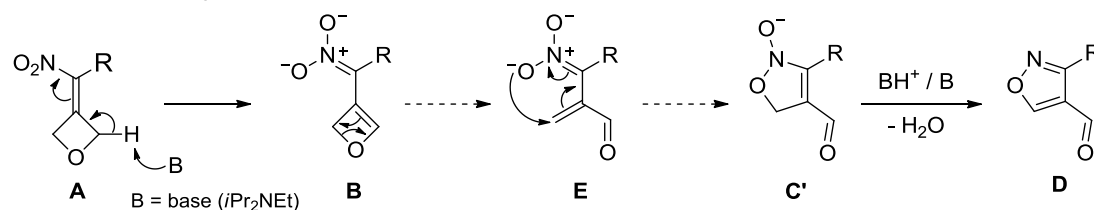
<sup>303</sup> Expected value:  $10 < \text{p}K_{\text{a}} < 15$ .

<sup>304</sup> Determined difference in energy: 24.29 kcal mol<sup>-1</sup>. Structures were optimized by PABLO RIVERA FUENTES (*ETH Zürich*) at the B3LYP/6-311G (d,p) level of theory using *Gaussian09*: Gaussian09, Revision A.1, M. J. Frisch, et al., Gaussian, Inc., Wallingford CT, 2009.

<sup>305</sup> a) A. Dornow, G. Wiehler, *Justus Liebigs Ann. Chem.* **1952**, 578, 113–121; b) A. Dornow, A. Frese, *Justus Liebigs Ann. Chem.* **1952**, 578, 122–136. See also: c) W. M. Best, E. L. Ghisalberti, M. Powell, *J. Chem. Res. Synop.* **1998**, 388–389.

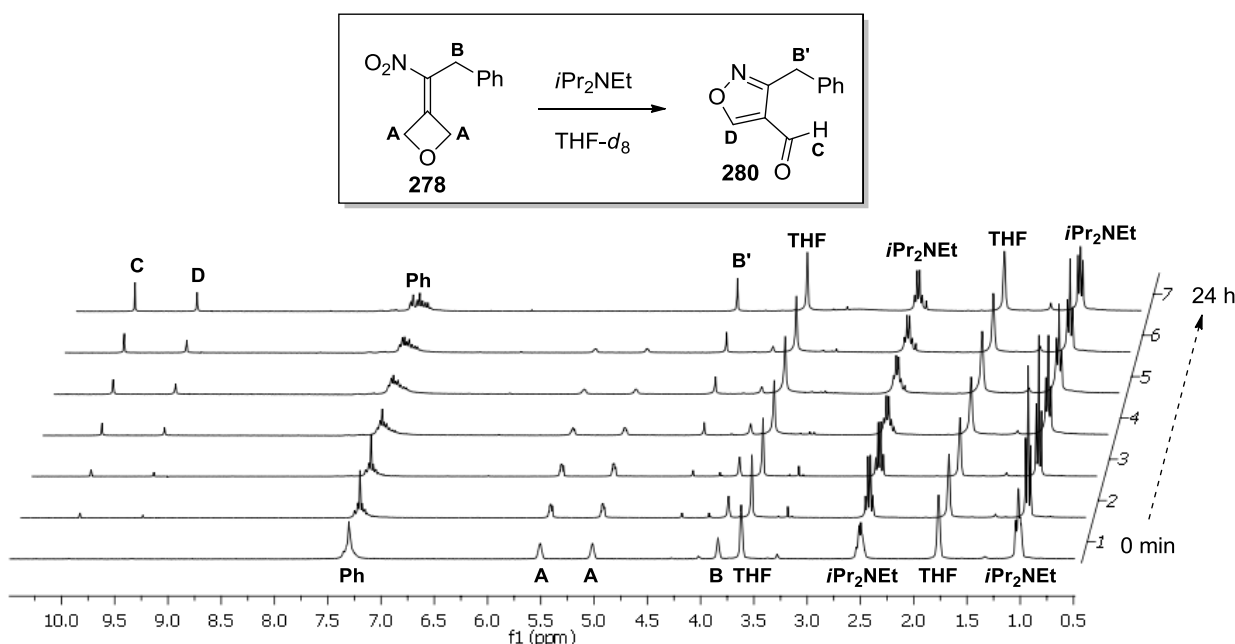
to give **C'**, an intermediate also obtained in the other pathway. Again, a series of protonations and deprotonations would afford isoxazole **D** after loss of water.

**Alternative pathway:**



**Scheme 63.** Alternative mechanistic explanation for the rearrangement step.

Since 2-unsubstituted oxetenes were found to possess half-lives of several hours in solution,<sup>306</sup> we would expect intermediates such as **B** or corresponding  $\alpha$ -NO<sub>2</sub> protonated species to accumulate during the reaction. However, by observation of the reaction progress with <sup>1</sup>H NMR spectroscopy it was not possible to identify any intermediates that would correspond to oxetene compounds (expected shifts in the 3-substituted oxetene:<sup>306b</sup>  $\delta(\text{CH}_2) \sim 5.3$  ppm,  $\delta(\text{CH}) \sim 6.7$  ppm).

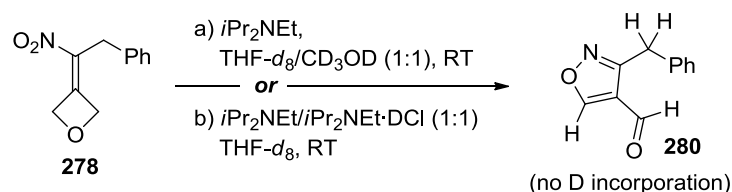


**Figure 65.** Monitoring of the rearrangement by <sup>1</sup>H NMR.

<sup>306</sup> a) L. E. Friedrich, P. Y.-S. Lam, *J. Org. Chem.* **1981**, *46*, 306-311; b) P. C. Martino, P. B. Shevlin, *J. Am. Chem. Soc.* **1980**, *102*, 5429-5430. For the synthesis of stable oxetenes, see: c) M. Longchar, U. Bora, R. C. Boruah, J. S. Sandhu, *Synth. Commun.* **2002**, *32*, 3611-3616; d) B. Alcaide, P. Almendros, T. M. del Campo, I. Fernandez, *Chem. Commun.* **2011**, *47*, 9054-9056.

In fact, the rearrangement turned out to be very clean, and starting material converted smoothly to product, while other  $^1\text{H}$  NMR signals could be assigned to  $i\text{Pr}_2\text{NH}$  and residual non-deuterated solvent (THF). The progress over 24 hours is shown in Figure 65, where seven successively recorded spectra visualize the conversion. It is worthy to repeat that all major signals can be assigned to starting material, product, base, solvent, or water; and minor signals do not indicate the presence of any oxetene intermediates.

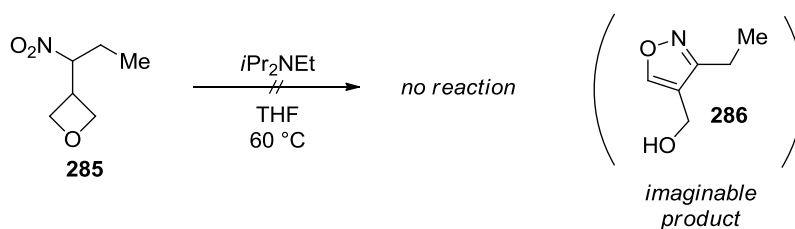
When the standard reaction from nitroolefin **278** to isoxazole **280** was run with either (a)  $i\text{Pr}_2\text{NEt}$  in a 1:1 mixture of  $\text{THF-}d_8$  and  $\text{CD}_3\text{OD}$  or with (b) a mixture of  $i\text{Pr}_2\text{NEt}$  and deuterated base (1:1) in  $\text{THF-}d_8$ , no incorporation of a deuterium atom could be observed, as concluded from the NMR analysis of the formed product (Scheme 64). These findings suggest that the individual steps in the rearrangement proceed quickly and probably irreversibly. The latter statement is difficult to prove for the intermediate steps, but certainly holds true for the first and the last step, i.e. for the initial deprotonation in the oxetane ring (no deuteration was observed in the oxetane at incomplete conversions nor at C(5) or the aldehyde in **280**) and the dehydration to afford the isoxazole.



**Scheme 64.** Running the rearrangement in deuterated solvents or with deuterated bases.

A control reaction involving a reduced starting material was conducted to investigate the necessity of the nitroalkene system (Scheme 65). Thus, 3-(1-nitropropyl)oxetane (**285**)<sup>307</sup> was treated with HÜNIG's base (1.0 equiv) in THF at 60 °C for 24 h, when the reaction mixture was concentrated *in vacuo* and the residue analyzed by  $^1\text{H}$  NMR. Essentially pure starting material was recovered, and no other signals were found that would have supported formation of isoxazole **286** (a mechanistically reasonable product if ring opening occurs).

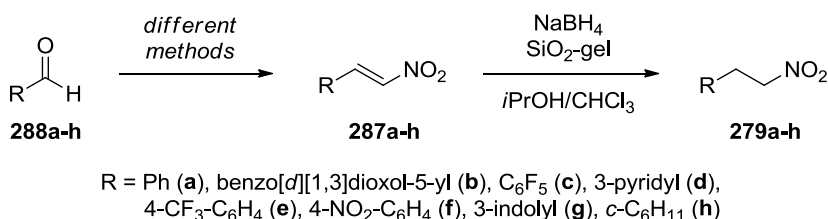
<sup>307</sup> Synthesized from the corresponding nitroalkene by treatment with  $\text{NaBH}_4$  (2 equiv) in  $\text{THF}/\text{MeOH}$  (1:1), 0 °C  $\rightarrow$  RT, 15 min, quantitative yield.



**Scheme 65.** Control reaction using a reduced starting material.

## 6.2.4 Preparation of Starting Materials

Some compounds having primary nitro groups are commercially available, but many of the above-mentioned starting materials required preparation. Substrates **279a-h** are  $\beta$ -monosubstituted nitroethanes, which are preferably made by HENRY condensation of an aldehyde with nitromethane and subsequent conjugate reduction of the formed nitroalkene. Whereas different literature methods were used for the preparation of the nitroalkenes **287a-h** (*vide infra*), their reduction was performed in a mixture of isopropyl alcohol and chloroform using sodium borohydride and silica gel (Scheme 66).<sup>298b</sup> The use of  $\text{SiO}_2$ -gel in  $\text{CHCl}_3$ /*i*PrOH avoids the formation of undesired di- or oligomeric byproducts (arising from the MICHAEL addition of a nitroenolate onto a not yet reduced nitroalkene), as these conditions lead to a rapid protonation of the *in situ* formed nitroenolates. It was found that vigorous stirring of the inhomogeneous reaction mixtures was essential in order to achieve fast conversions to the desired products.



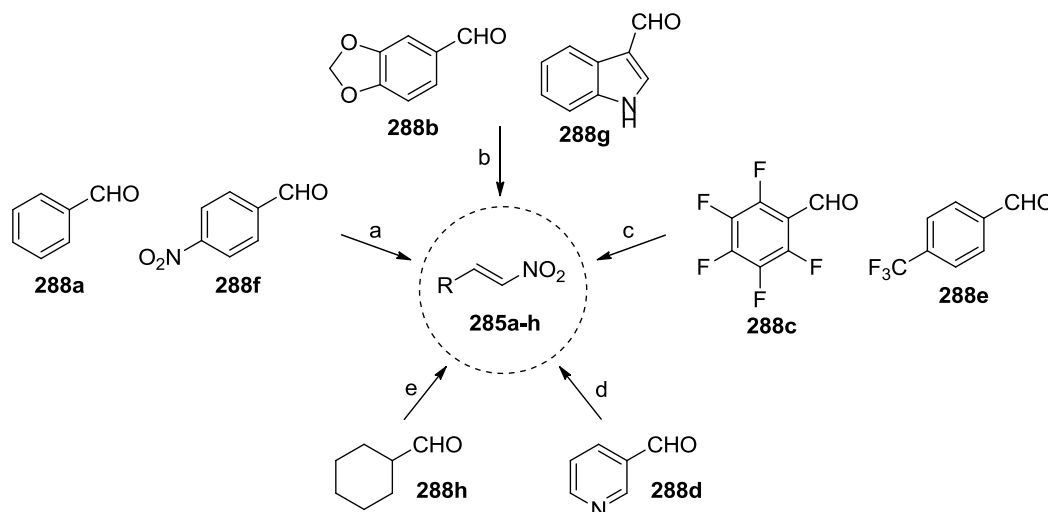
**Scheme 66.** Preparation of substrates **279a-h**.

The  $\beta$ -substituted nitroalkenes **287a-h** were synthesized from the corresponding commercially available aldehydes **288a-h**. As outlined in Scheme 67, five different literature procedures were used. Compounds **287a** and **287f** were prepared by sodium hydroxide-mediated HENRY addition with a subsequent acidic aqueous workup that triggered dehydration to give the nitroalkenes.<sup>298b,308</sup> A direct KNOEVENAGEL-type reaction could be implemented for the synthesis of nitroalkenes bearing benzo[*d*][1,3]dioxol-5-yl and 3-indolyl groups.<sup>309</sup> The carbinol inter-

<sup>308</sup> R. P. K. Kodukulla, G. K. Trivedi, J. D. Vora, H. H. Mathur, *Synth. Commun.* **1994**, *24*, 819-832.

<sup>309</sup> J. McNulty, J. A. Steere, S. Wolf, *Tetrahedron Lett.* **1998**, *39*, 8013-8016.

mediate was isolated, and the elimination reaction was carried out using MsCl and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> for substrates **288c** and **288e**.<sup>310</sup> Nicotinaldehyde (**288d**) was first treated with nitromethane and KOtBu in *tert*-butyl alcohol and THF, and the formed HENRY adduct was dehydrated using acetic anhydride.<sup>311</sup> Nitromethane was added to cyclohexane carbaldehyde (**288h**) under the same conditions as above, but the elimination was effected using TFAA and triethylamine in CH<sub>2</sub>Cl<sub>2</sub>.<sup>312</sup>



**Scheme 67.** Synthesis of nitroalkene intermediates. Reagents and conditions: a) 1. CH<sub>3</sub>NO<sub>2</sub>, aq. NaOH, MeOH, 2. aq. HCl; b) CH<sub>3</sub>NO<sub>2</sub>, NH<sub>4</sub>OAc; c) 1. CH<sub>3</sub>NO<sub>2</sub>, aq. NaOH, MeOH, 2. MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; d) 1. CH<sub>3</sub>NO<sub>2</sub>, KOtBu, *t*BuOH, THF, 2. Ac<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; e) 1. CH<sub>3</sub>NO<sub>2</sub>, KOtBu, *t*BuOH, THF, 2. TFAA, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>.

The synthesis of substrates containing olefins, ester groups, protected amines and protected alcohols is summarized in Scheme 68. 5-Bromopentene (**289**) was treated with sodium nitrite in DMSO with added urea to afford the corresponding nitro compound **279i**.<sup>313</sup> As described in Chapter 5 in the synthesis of thalidomide analogues, compound **244** was prepared from methyl acrylate (**245**) and nitromethane. Commercial 3-nitropropionic acid (**290**) was esterified *via* the corresponding acid chloride (oxalyl chloride, DMF; then EtOH, Et<sub>3</sub>N) to afford **279m**. Following a literature protocol, THF (**291**) was opened with AcCl and NaI to give open-chain primary iodide, which was subsequently substituted with AgNO<sub>2</sub> to give the corresponding nitro compound **279n**.<sup>314</sup> **279o** was prepared in a two-step procedure from commercially available Boc-protected 3-aminopropanol (**292**) (APPEL reaction to give primary iodide and subsequent displacement reaction using NaNO<sub>2</sub>/urea). Finally, TBS-protected nitroethanol (**279p**) was made

<sup>310</sup> See the Experimental Part for details.

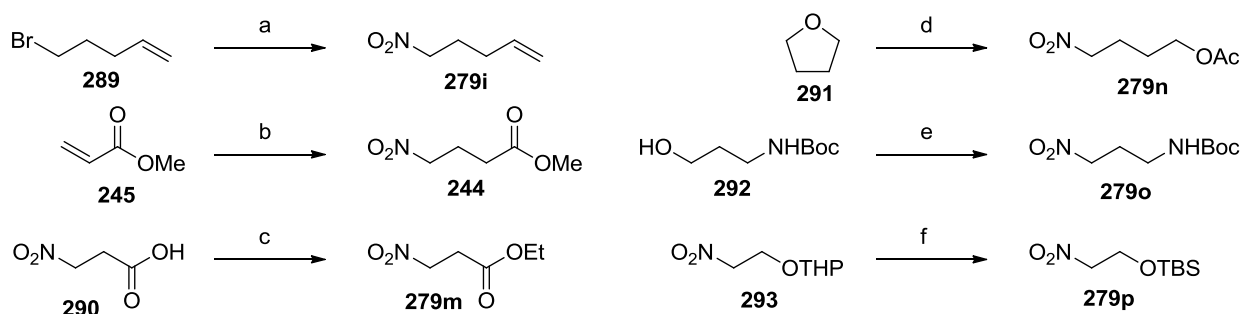
<sup>311</sup> G. J. T. Kuster, R. H. J. Steeghs, H. W. Scheeren, *Eur. J. Org. Chem.* **2001**, 553–560.

<sup>312</sup> S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1993**, *58*, 3850–3856.

<sup>313</sup> A. Kjær, S. R. Jensen, *Acta Chem. Scand.* **1968**, *22*, 3324–3326.

<sup>314</sup> a) S. D. Cho, J. W. Chung, W. Y. Choi, S. K. Kim, Y. J. Yoon, *J. Heterocyclic Chem.* **1994**, *31*, 1199–1208; b) R. Ballini, L. Barboni, G. Giarlo, *J. Org. Chem.* **2004**, *69*, 6907–6908.

via 2-nitroethanol from the corresponding THP-protected starting material **293** using standard literature procedures.<sup>315</sup>



**Scheme 68.** Preparation of starting materials. Reagents and conditions: a)  $\text{NaNO}_2$ , urea, DMSO; b)  $\text{CH}_3\text{NO}_2$ , TBD, THF; c) 1.  $(\text{COCl})_2$ , DMF,  $\text{CH}_2\text{Cl}_2$ , 2. EtOH,  $\text{Et}_3\text{N}$ ; d) 1. AcCl, NaI,  $\text{CH}_3\text{CN}$ , 2.  $\text{AgNO}_2$ ,  $\text{H}_2\text{O}$ ; e) 1.  $\text{I}_2$ ,  $\text{PPh}_3$ , imidazole,  $\text{CH}_2\text{Cl}_2$ , 2.  $\text{NaNO}_2$ , urea, DMSO; f) 1. *p*-TsOH, MeOH, 2. TBSCl, imidazole, DMF.

A number of methods are known for the construction of aryl nitromethanes.<sup>316</sup> The most studied approach is a nucleophilic substitution reaction with nitrite from corresponding benzyl halides (see Scheme 69, left). Commonly employed reagents in this transformation are silver nitrite in aprotic solvents or water<sup>317</sup> as well as sodium nitrite and urea in DMSO or DMF.<sup>318</sup> Although in many cases the desired product is formed in acceptable yields (40–80%), the reaction has some limitations. For instance,  $\text{AgNO}_2$  needs to be used in excess and the reaction is preferably run in the dark. When less expensive  $\text{NaNO}_2$  is used in combination with urea, yields are usually not high, and benzyl nitrites represent frequent side products that are difficult to separate from the desired nitro compounds. In certain cases, the only isolable material is the nitrite product, as observed, when 4-fluorobenzyl bromide was treated with  $\text{AgNO}_2$  in benzene (32% yield of 4-fluorobenzyl nitrite). A literature example with 4-*tert*-butylbenzyl bromide as starting material and  $\text{AgNO}_2$  (1.3 equiv) with CaH (5 mol %) as reagents in diethyl ether (0 °C, 26 h) describes the concomitant formation of 4-*tert*-butyl- $\alpha$ -nitrotoluene (**279k**) and corresponding 4-(*tert*-butyl)benzyl nitrite (**294**, R = 4-*tert*-butyl) (43:57 ratio).<sup>319</sup> Chromatographic purification afforded 35% of the desired nitro compound. Since oxidative approaches (Scheme 69, bottom) *via* benzaldoximes **293** seemed inefficient (low yields reported in the literature) and risky (used reagents are often peracetic acid, peroxymonosulfuric acid, or urea-hydrogen perox-

<sup>315</sup> C. W. Holzappel, K. Bischofberger, J. Olivier, *Synth. Commun.* **1994**, *24*, 3197–3211.

<sup>316</sup> For an overview, see: N. Ono, in *The Nitro Group in Organic Synthesis*, John Wiley & Sons, Inc., **2002**, pp. 3–29.

<sup>317</sup> N. Kornblum, L. Fishbein, R. A. Smiley, *J. Am. Chem. Soc.* **1955**, *77*, 6261–6266.

<sup>318</sup> N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, G. E. Graham, *J. Am. Chem. Soc.* **1956**, *78*, 1497–1501.

<sup>319</sup> L. Barr, C. J. Easton, K. Lee, S. F. Lincoln, *Org. Biomol. Chem.* **2005**, *3*, 2990–2993.



This positive result guided us to investigate, whether this procedure could be adapted for other aryl bromides as well. As listed in Table 19, nitromethane was also successfully coupled with other bromoarenes, albeit with limitations. 2-Bromotoluene afforded an excellent yield of 84% for the coupled product (entry 1), but either electron-rich (4-bromoanisidine) or electron-deficient (4-fluorobromobenzene) gave the corresponding aryl nitromethanes in low yield (35% and 17%, respectively; entries 2 and 5). 2-Bromonaphthalene also afforded a disappointing yield of 35% for the coupling under standard conditions (entry 4). On the other hand, when more palladium (2.5 mol %  $[\text{Pd}_2(\text{dba})_3]$ ) and ligand (10 mol % **179**) were employed, the coupling turned out to be more efficient, as now 70% of 1-methoxy-4-(nitromethyl)benzene (**296**, R = *p*-OMe) was isolated after chromatographic purification (entry 3). At this point the reactivity was not further investigated, but screening of different ligands, catalyst precursors, bases, and solvents may further improve this reaction.

**Table 19.** Scope for the arylation of nitromethane.

entry	aryl bromide	reaction time	isolated yield
1	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> Br	20 h	84%
2	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> Br	20 h	35%
3	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> Br	22 h	70% <sup>[a]</sup>
4	2-Br-naphthalene	18 h	35%
5	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> Br	18 h	17%

[a] 2.5 mol %  $[\text{Pd}_2(\text{dba})_3]$  and 10 mol % **179** used.



## 6.3 Conclusion

In summary, the above described novel synthesis of isoxazole-4-carbaldehydes from primary nitro compounds and oxetan-3-one provides a viable synthetic alternative to access 3,4-disubstituted isoxazoles.<sup>322</sup> Previously reported methods that generally relied on dipolar cycloaddition reactions afforded similar products in low yield only.<sup>323</sup> Moreover, the process delineates a unique reactivity of activated oxetane intermediates that could also be harnessed for the discovery of other pathways leading to novel compounds.

Thus far, oxetan-3-one (**34**) has generally been a good building block for the introduction of oxetanes onto molecular scaffolds. In this case, however, oxetane-3-one behaves more like a reagent. Future work directed at the exploration of the reactivity of this small heterocycle and its congeners may lead to unprecedented and efficient syntheses of higher building blocks. Even though oxetan-3-one has been known for more than 50 years,<sup>324</sup> its chemical space is still wide open.

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<sup>322</sup> For a summary of the work, see: J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 5379-5382.

<sup>323</sup> a) P. Caramella, E. Cereda, *Synthesis* **1971**, 433-434; b) L. Toma, P. Quadrelli, G. Perrini, R. Gandolfi, C. Di Valentin, A. Corsaro, P. Caramella, *Tetrahedron* **2000**, *56*, 4299-4309; c) A. Balsamo, I. Coletta, A. Guglielmotti, C. Landolfi, F. Mancini, A. Martinelli, C. Milanese, F. Minutolo, S. Nencetti, E. Orlandini, M. Pinza, S. Rapposelli, A. Rossello, *Eur. J. Med. Chem.* **2003**, *38*, 157-168; d) W. Zheng, A. Degterev, E. Hsu, J. Yuan, C. Yuan, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4932-4935; e) W. R. Ewing, J. Li, R. B. Sulsky, A. S. Hernandez (Bristol-Myers-Squibb), US 20060079562, **2006**.

<sup>324</sup> J. R. Marshall, J. Walker, *J. Chem. Soc.* **1952**, 467-475.



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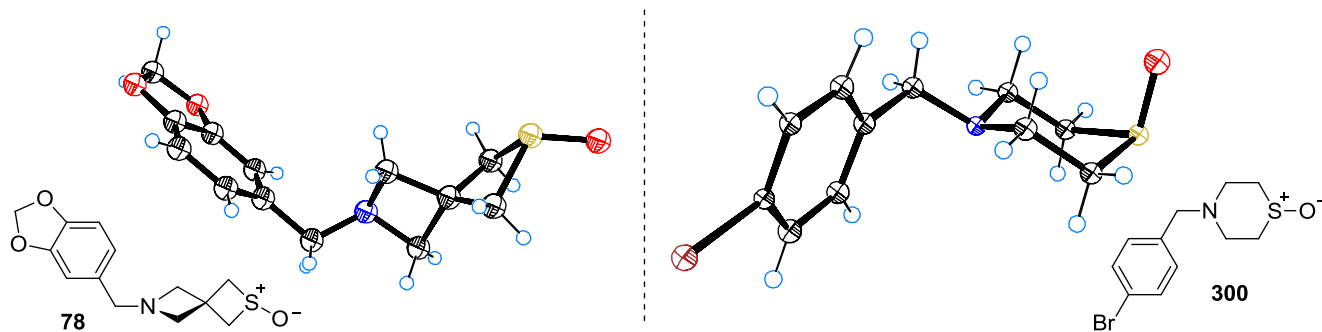
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# Thietanes

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## 7.1 Homospirothiomorpholine-Oxides and -Dioxides

Chapter 2 described the synthesis of a number of linear azaspiro[3.3]heptanes and their evaluation for properties relevant to the drug discovery process. Among the compounds synthesized were piperonyl-tagged 2-thia-6-azaspiro[3.3]heptane-*S*-oxide and -*S,S*-dioxide (compounds **78** and **77**) as well as their thiomorpholine analogues (sulfoxide **102** and sulfone **101**). By analyzing the data shown in Table 6, it becomes apparent that metabolic clearance rates of these compounds are generally low and exceptionally low for the sulfoxide compounds. To a certain extent this is surprising, since sulfoxides are known to be metabolized *via* either oxidative or reductive pathways.<sup>325</sup> In addition, we also observed comparatively low lipophilicity values (all four compounds have log *D* and log *P* values clearly <1.0). We thus became interested in analyzing the possible dependence of the rate of metabolic clearance on lipophilicity,<sup>326</sup> and also in explaining measured values on the basis of structural information.



**Figure 66.** Solid-state structures of two sulfoxide compounds.

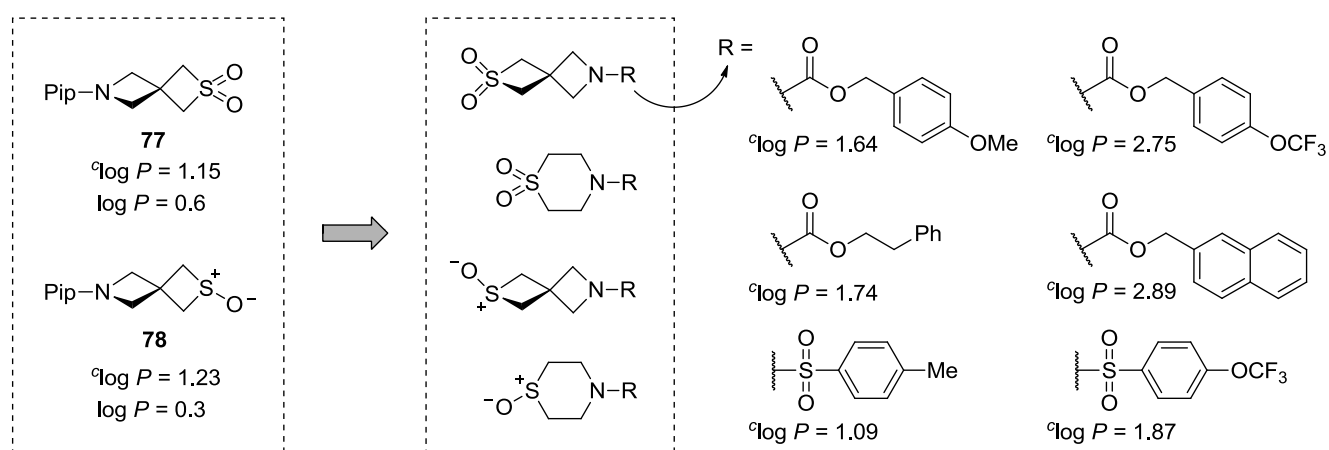
The latter is usually best acquired by X-ray diffraction analysis of suitable crystals. For this reason, it was attempted to obtain single crystals of a homospirothiomorpholine-*S*-oxide and of a similar thiomorpholine compound. To our delight, spirocyclic sulfoxide **78** afforded good quality crystals and was later appropriately analyzed. The corresponding thiomorpholine-*S*-oxide compound did not crystallize, which prompted us to prepare a similar compound that eventually would form crystals. 4-Bromobenzyl derivative **300**, prepared in two steps from thiomorpholine and 4-bromobenzyl bromide,<sup>327</sup> afforded material that could be analyzed by crystallographic techniques. The results obtained by ANDRÉ ALKER (*F. Hoffmann-La Roche*, Basel)

<sup>325</sup> B. Testa, S. D. Krämer, *Chem. Biodiv.* **2006**, *3*, 1053–1101.

<sup>326</sup> B. Testa, P. Crivori, M. Reist, P.-A. Carrupt, *Perspect. Drug Discovery Des.* **2000**, *19*, 179–211.

<sup>327</sup> 1. 4-Bromobenzyl bromide (1 equiv), thiomorpholine (2 equiv), Et<sub>3</sub>N (1.5 equiv), THF, RT, 94% yield (see H. J. Dyke, C. Ellwood, E. Gancia, L. J. Gazzard, S. C. Goodacre, S. S. Kintz, J. P. Lyssikatos, C. Macleod, K. Williams (Genentech, Inc.), WO 2009151598, **2009**). 2. H<sub>2</sub>O<sub>2</sub> (1.1 equiv), AcOH, RT, quantitative yield.

are shown in Figure 66. The sulfoxide in the spirocyclic thietane is pseudo-equatorially oriented, and valence angles around the sulfur atom are  $113^\circ$  (both O—S—C) and  $76^\circ$  (C—S—C). The distance between the sulfur and the oxygen atom is 1.49 Å. In monocyclic **300**, the sulfur-oxygen bond adopts an axial orientation, which is in agreement with observations by HUTTON and co-workers, who found that direct oxidants such as H<sub>2</sub>O<sub>2</sub> preferentially oxidize in the axial position.<sup>328</sup> While crystal structures of other thiomorpholine-*S*-oxides also confirm the preferred axial orientation,<sup>329</sup> the example illustrated in Figure 66 (right) is, to our knowledge, the first documented structure of a C-unsubstituted thiomorpholine-*S*-oxide. The valence angles around the sulfur atom are  $107^\circ$  (O—S—C),  $95^\circ$  (C—S—C), and  $106^\circ$  (C—S—O), and the sulfur-oxygen bond is 1.50 Å long. Due to the reduced possibility of solvation for the axial sulfoxide *vs.* the equatorial sulfoxide, the molecule is less polar (higher log *P* value) than the corresponding sulfone. On the other hand, the spirocyclic congener is more polar than its sulfone partner, as the sulfoxide resides in a solvent-accessible pseudo-equatorial position (log *P* is reduced by 0.3 units).



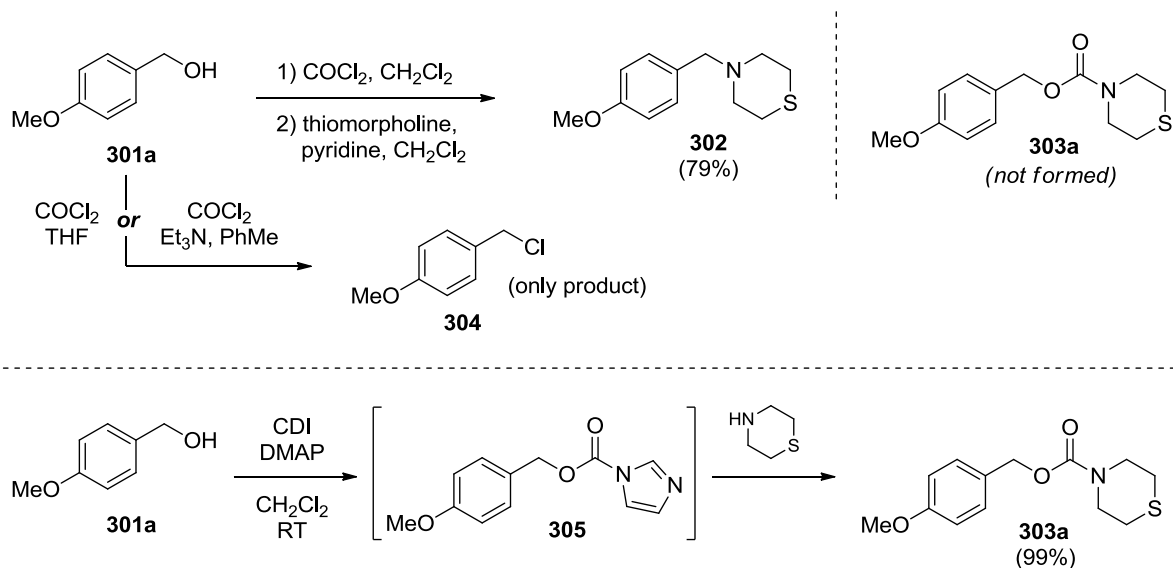
**Figure 67.** From systems of low lipophilicity to sulfoxides and sulfones with calculated log *P* values between 1 and 3. Numbers indicated are <sup>9</sup>log *P* values for homospirothiomorpholine-*S,S*-dioxides.

Since the spirocyclic sulfoxides and sulfones investigated were extraordinarily robust toward metabolism, we reasoned that their inherent polarity and associated hydrophilicity led to a reduced exposure to membrane-bound CYP450 enzymes, which would explain the observed low clearance rates. To obtain more experimental evidence on this matter, it became necessary to

<sup>328</sup> C. A. Hutton, R. Jaber, M. Otaegui, J. J. Turner, P. Turner, J. M. White, G. B. Bacskay, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1066–1071.

<sup>329</sup> a) K. J. Palmer, K. S. Lee, *Acta Cryst.* **1966**, *20*, 790–795 (*Cambridge Structural Database* code: CALHCL); b) K. J. Palmer, K. S. Lee, R. Y. Wong, J. F. Carson, *Acta Cryst. B* **1972**, *28*, 2789–2793 (CHONDR); c) A. Furusaki, Y. Tomiie, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 726–733 (CUYUNT); d) S. B. Sanni, M. De Wolf, A. T. H. Lenstra, C. Van der Auwera, M. J. Anteunis, *Acta Cryst. C* **1984**, *40*, 1624–1626 (CIRZUY).

synthesize similar compounds of higher lipophilicity. These compounds, within a range of calculated log *P* values between 1.0 and 3.0, would subsequently be used for the determination of the experimental lipophilicity value and later subjected to metabolic clearance assays. We chose to investigate model systems bearing aromatic systems linked through carbamates or sulfonamides, as these compounds would be easily accessible through synthesis and would lie in the desired lipophilicity range (Figure 67).



**Scheme 71.** Synthesis of 4-methoxybenzyl carbamates.

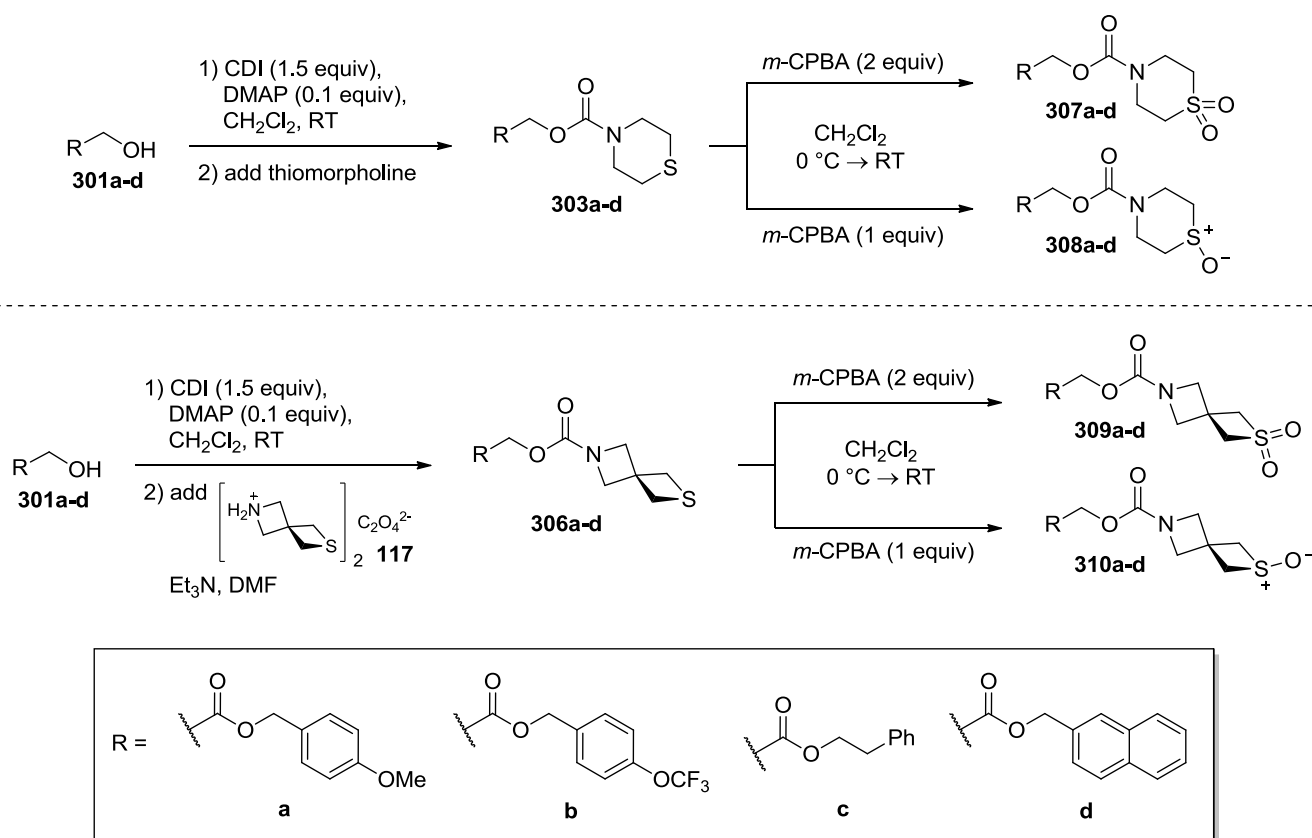
During the search for the optimal protocol for synthesizing carbamates from amines and alcohols, 4-methoxybenzyl alcohol (**301a**) was treated with a toluene solution of phosgene in  $\text{CH}_2\text{Cl}_2$ , and when TLC analysis indicated complete consumption of the starting material, thiomorpholine and pyridine were added (Scheme 71). Analysis of the purified product revealed that instead of the desired carbamate **303a**, benzylamine **302** had formed. Changing conditions in the first step (chloroformate formation) to  $\text{COCl}_2$  in  $\text{THF}$ <sup>330</sup> or to  $\text{COCl}_2$  with  $\text{Et}_3\text{N}$  in toluene,<sup>331</sup> it was not possible to change the outcome of the reaction, as still benzyl chloride **304** was produced. To circumvent this, it was decided to use carbonyl diimidazole as the linking agent (imidazole is less nucleophilic than chloride). Thus, 4-methoxybenzyl alcohol was treated with CDI (1.5 equiv) and catalytic amounts of DMAP (0.1 equiv) in  $\text{CH}_2\text{Cl}_2$  at RT<sup>332</sup> to afford after 30 min full conversion to the imidazole-carbamate **305**. Then, thiomorpholine (2 equiv) was added, and after stirring at RT overnight, work-up, and purification, the desired carbamate

<sup>330</sup> B. Zacharie, L. Gagnon, G. Attardo, T. P. Connolly, Y. St-Denis, C. L. Penney, *J. Med. Chem.* **1997**, *40*, 2883–2894.

<sup>331</sup> T. Pohl, H. Waldmann, *J. Am. Chem. Soc.* **1997**, *119*, 6702–6710.

<sup>332</sup> J. A. Duimstra, F. J. Femia, T. J. Meade, *J. Am. Chem. Soc.* **2005**, *127*, 12847–12855.

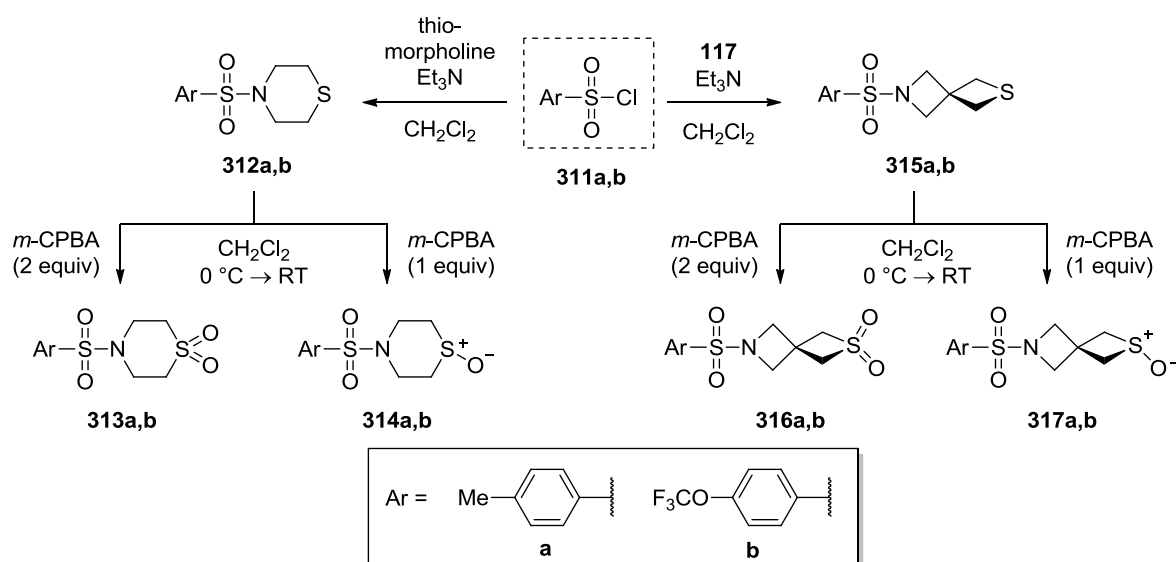
**303a** could be isolated in almost quantitative yield. Since this protocol proved convenient and reliable, it was used for the synthesis of the remaining carbamates (Scheme 72). The strategy remained the same for carbamates with the homospirothiomorpholine unit (compounds **306a-d**), but the procedure was slightly modified in the second step. The addition of ammonium oxalate salt **117** required the co-addition of triethylamine (deprotonation of the ammonium salt) and DMF (in order to solubilize salt **117**). Moreover, the amount of amine nucleophile was reduced to 1.2 equivalents (0.6 equiv of **117**). Accordingly, carbamates **303a-d** and **306a-d** were obtained in good yields (72-99%).<sup>333</sup> The corresponding sulfones and sulfoxides were prepared by *m*-CPBA-mediated oxidation using 2 equivalents and 1 equivalent of reagent in CH<sub>2</sub>Cl<sub>2</sub>, respectively. All target compounds were isolated in yields greater than 75%.



**Scheme 72.** Synthesis of thiomorpholine and homospirothiomorpholine carbamates.

Commercially available arylsulfonyl chlorides served as starting material for the construction of sulfonamide model systems (Scheme 73). Thiomorpholine and azetidinium oxalate **117** were reacted with ArSO<sub>2</sub>Cl (**311a,b**) and Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> to afford the corresponding sulfonamides in good yields. The remaining target materials were again obtained in excellent yield by oxidation with *m*-CPBA (1 equiv for sulfoxides, 2 equiv for sulfones) in CH<sub>2</sub>Cl<sub>2</sub>.<sup>333</sup>

<sup>333</sup> For individual yields, see Table 20 or the Experimental Part.



**Scheme 73.** Synthesis of thiomorpholine and homospirothiomorpholine aryl sulfonamides.

**Table 20.** Yields and lipophilicities of thiomorpholines (A) and homospirothiomorpholines (B).

compound			isolated yield for sulfide <sup>[b]</sup>	isolated yield <sup>[c]</sup>	<sup>o</sup> log P <sup>[d]</sup>	log P <sup>[e]</sup>
residue on amine	class, <sup>[a]</sup> SO <sub>x</sub>	307a-317b				
	A, SO <sub>2</sub>	<b>307a</b>	99%	97%	1.46	0.8
	A, SO	<b>308a</b>				
	B, SO <sub>2</sub>	<b>309a</b>				
	B, SO	<b>310a</b>				
	A, SO <sub>2</sub>	<b>307b</b>	85%	95%	2.57	2.2
	A, SO	<b>308b</b>				
	B, SO <sub>2</sub>	<b>309b</b>				
	B, SO	<b>310b</b>				
	A, SO <sub>2</sub>	<b>307c</b>	90%	75%	1.47	n.d. <sup>[f]</sup>
	A, SO	<b>308c</b>				
	B, SO <sub>2</sub>	<b>309c</b>				
	B, SO	<b>310c</b>				
	A, SO <sub>2</sub>	<b>307d</b>	86%	90%	2.71	2.0
	A, SO	<b>308d</b>				
	B, SO <sub>2</sub>	<b>309d</b>				
	B, SO	<b>310d</b>				
	A, SO <sub>2</sub>	<b>313a</b>	89%	96%	0.82	0.9
	A, SO	<b>314a</b>				
	B, SO <sub>2</sub>	<b>316a</b>				
	B, SO	<b>317a</b>				
	A, SO <sub>2</sub>	<b>313b</b>	94%	97%	1.60	1.5
	A, SO	<b>314b</b>				
	B, SO <sub>2</sub>	<b>316b</b>				
	B, SO	<b>317b</b>				

[a] A: thiomorpholine, B: 2-thia-6-azaspiro[3.3]heptane. [b] In the carbamate or sulfonamide forming step. [c] In the oxidation step. [d] Calculated using ChemBioDraw 12.0 (CambridgeSoft). [e] Measured values using CAMDIS. [f] Not determined. [g] Prepared by carbamate formation, see the Experimental Part. [h] Prepared differently, see Chapter 2.



The compounds were subsequently submitted to *F. Hoffmann-La Roche* in Basel for the determination of lipophilicities<sup>334</sup> and metabolic clearance rates. Yields for the compounds, along with their calculated and determined log *P* values are listed in Table 20. The measured lipophilicity values are generally lower than the predicted numbers. The differences are often large with many values differing by roughly one logarithmic unit. The predictions for spirocyclic compounds were generally worse than for the thiomorpholines. While there does not appear to be a clear trend toward lower lipophilicity of the spirocyclic systems, the values are on average 0.14 units lower than for corresponding monocyclic compounds. Interestingly, we do not observe significant differences between sulfone and sulfoxide compounds, as lipophilicity values are at most 0.4 units apart (on average sulfoxides are 0.1 logarithmic units less lipophilic than the sulfone equivalents; the same trend is found for mono- and spirocyclic compounds).

Results from metabolic clearance measurements were not available at the time of writing. Therefore, it is not possible to discuss the effect of more lipophilic compounds on the rate of metabolism. The results will be reported as they become available. In addition to the sulfoxides and sulfones, corresponding piperidines **318** and 2-azaspiro[3.3]heptanes **319** (see Figure 68) were prepared for use as reference compounds.<sup>335</sup> These will be analyzed for the same parameters and compared with the more polar substrates.



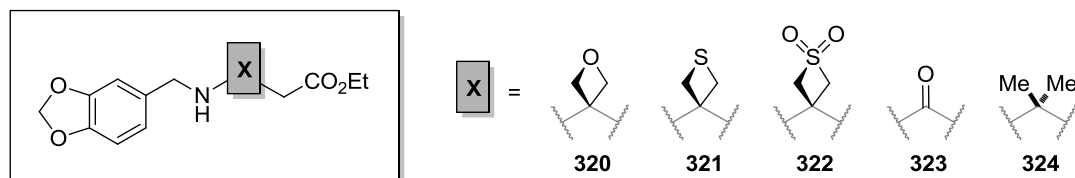
**Figure 68.** Piperidines and homospirropiperidines as reference compounds.

## 7.2 Other Thietanes and Thiete Dioxides

Results presented in Chapters 2 and 3 indicated that thietane compounds can possess desirable ADME properties. To investigate their effects on simple open-chain compounds, we prepared a small series of compounds that contained either an oxetane (compound **320**), a thietane (**321**), a dioxothietane (**322**), a ketone (**323**), or a geminal dimethyl group (**324**) at a particular site (Figure 69).

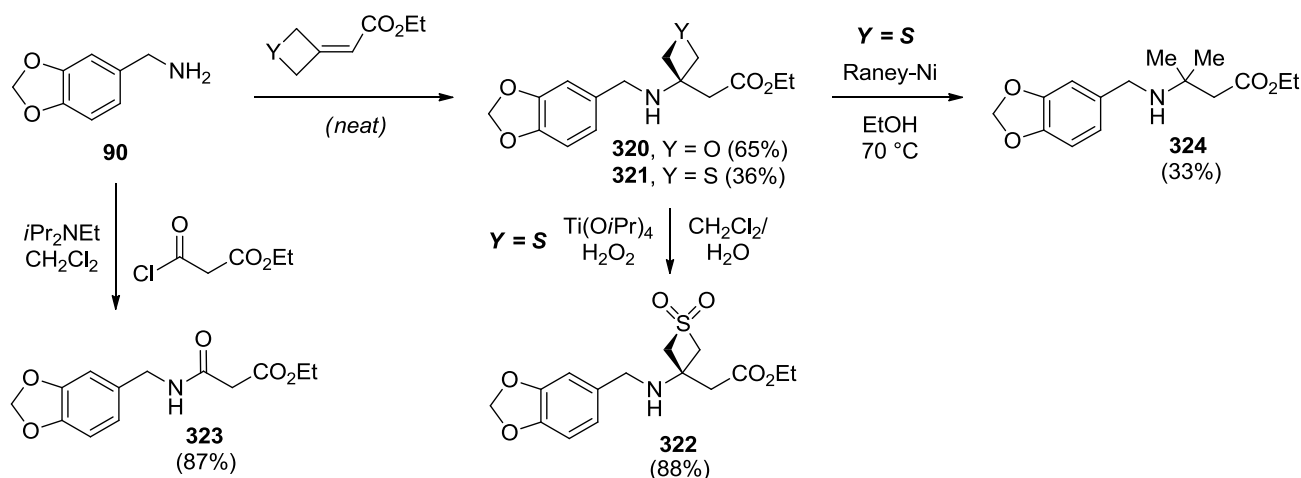
<sup>334</sup> Measurements were carried out by HOLGER FISCHER.

<sup>335</sup> These compounds were prepared by GUIDO MÖLLER, *ETH Zürich*.



**Figure 69.** Model system for the comparison of different related subunits.

The preparation of these compounds is delineated in Scheme 74. Piperonylamine (**90**) was treated with ethyl 2-(oxetan-3-ylidene)acetate to afford oxetane **320** in 65% yield. Similarly, thietane **321** was obtained in 36% yield by stirring piperonylamine with ethyl 2-(thietan-3-ylidene)acetate. The corresponding sulfone **322** was obtained in 88% yield after treatment of thietane **321** with  $\text{Ti}(\text{O}i\text{Pr})_4$  and hydrogen peroxide in a mixture of  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ .<sup>158</sup> The same thietane **321** was also used to synthesize *gem*-dimethyl compound **324**. Exposure to RANEY-Ni in EtOH at 70 °C<sup>336</sup> effected reductive cleavage of the carbon-sulfur bonds, and amine **324** was isolated in 33%. The carbonyl analogue **323** was synthesized in 87% yield by reacting piperonylamine (**90**) with ethyl malonyl chloride and HÜNIG's base in  $\text{CH}_2\text{Cl}_2$ .



**Scheme 74.** Synthesis of model compounds.

Following preparative efforts, these compounds were submitted to *F. Hoffmann-La Roche*, Basel for basicity and lipophilicity testing. As assembled in Table 21,  $\text{p}K_{\text{a}}$  values for the piperonylamine are largely dependent on the adjacent group. The reduction in basicity from the *gem*-dimethyl reference compound is significant, but least pronounced when a thietane was incorporated ( $\Delta\text{p}K_{\text{a}} = -2.4$ ). Greater reductions were obtained for the oxetane compound ( $\Delta\text{p}K_{\text{a}} = -3.0$ ) and especially for the dioxothietane derivative ( $\Delta\text{p}K_{\text{a}} = -4.8$ ). These values correlate very well with the results from Type B angular spirocycles (*cf.* Chapter 3, Table 11). Furthermore,  $\log P$

<sup>336</sup> S. Karlsson, H.-E. Högberg, *Org. Lett.* **1999**, *1*, 1667-1669.

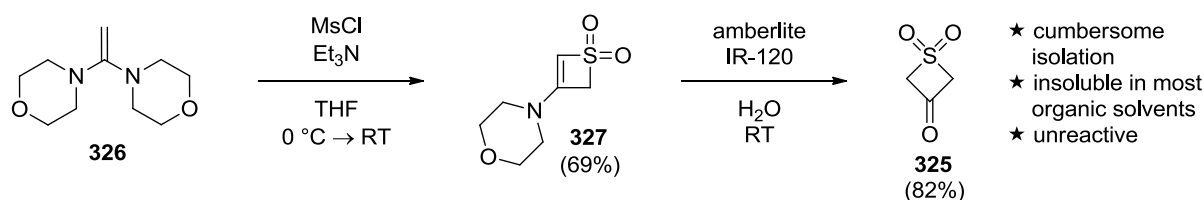
values follow the same trend that was seen in the angular spirocycles, although the correlation is not quite as pronounced. Whereas the thietane compound is approximately as lipophilic as the corresponding *gem*-dimethyl reference compound ( $\Delta\log P = +0.1$ ), lipophilicities are distinctively reduced for oxetane ( $\Delta\log P = -1.1$ ), dioxothietane ( $\Delta\log P = -1.3$ ), and carbonyl derivatives ( $\Delta\log P = -1.3$ ). In terms of amine basicity as well as lipophilicity, the dioxothietan-3-amine moiety is the best surrogate for an amide. Solubility and metabolic clearance tests will deliver further insights, to the extent as to which such correlations can be made.

**Table 21.** Basicity and lipophilicity values for compounds **320-324**.

					
$pK_a$	5.6	6.2	3.8	n.d. <sup>[a]</sup>	8.6
$\log D^{[b]}$	1.4	2.6	1.2	1.2	1.4
$\log P^{[c]}$	1.4	2.6	1.2	1.2	2.5

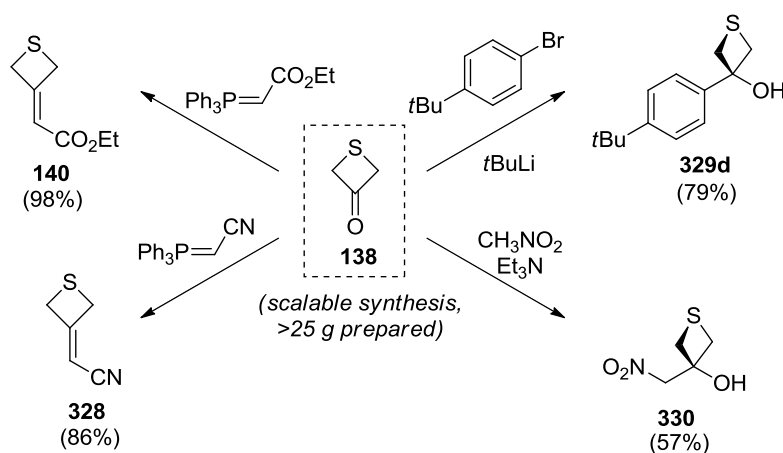
[a] Not determined (non-basic amine). [b] Measured at pH = 7.4. [c] According to  $\log P = \log D + \log_{10}(1 + 10^{(pK_a-pH)})$ .

Since the thietanes and the corresponding sulfones were found to have intriguing properties in the drug discovery setting, we sought to further explore their chemistry. Oxetan-3-one (**34**) was generally the preferred building block for the introduction of oxetane subunits onto molecular frameworks. Likewise, dioxothietan-3-one (**325**) was believed to serve as an equally potent building block for the introduction of the thietan-*S,S*-dioxide unit. Its preparation was carried out according to a literature procedure (Scheme 75).<sup>337</sup> 1,1-Bis(morpholino)ethylene (**326**) was treated with methanesulfonyl chloride and triethylamine (*in situ* formation of sulfene) to afford 3-morpholino-thiete-*S,S*-dioxide (**327**) in 69% yield. Subsequent hydrolysis of the enamine was effected using acidic amberlite IR-120 in water; the desired dioxothietan-3-one (**325**) was obtained after filtering and lyophilizing the reaction mixture. The isolated compound was purified by bulb-to-bulb sublimation to afford pure product in 82% yield.



**Scheme 75.** Synthesis of dioxothietan-3-one.

Dioxathietan-3-one (**325**) is a colorless solid with a melting point of 119–121 °C.<sup>338</sup> Its protons are very acidic (in water,  $pK_a = 4.1$ ), but HASEK *et al.* did not find the tautomeric enol form when measuring IR or <sup>1</sup>H NMR in D<sub>2</sub>O, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>, or DMSO-*d*<sub>6</sub>. What was reported by TRUCE and NORELL already in 1963 was confirmed by the author of this Thesis: the compound was poorly soluble in most organic solvents, which significantly impeded synthetic endeavors. Moreover, forcing conditions were required to achieve any reaction. Due to these drawbacks and the cumbersome and expensive<sup>339</sup> preparation of **325**, we decided to use its sulfide analogue, i.e. thietan-3-one (**138**), for future preparative purposes. Thietan-3-one can be accessed efficiently and on large scale, as >25 g of the compound were prepared in our laboratory (*cf.* Chapter 3).



**Scheme 76.** Reactions with thietan-3-one.

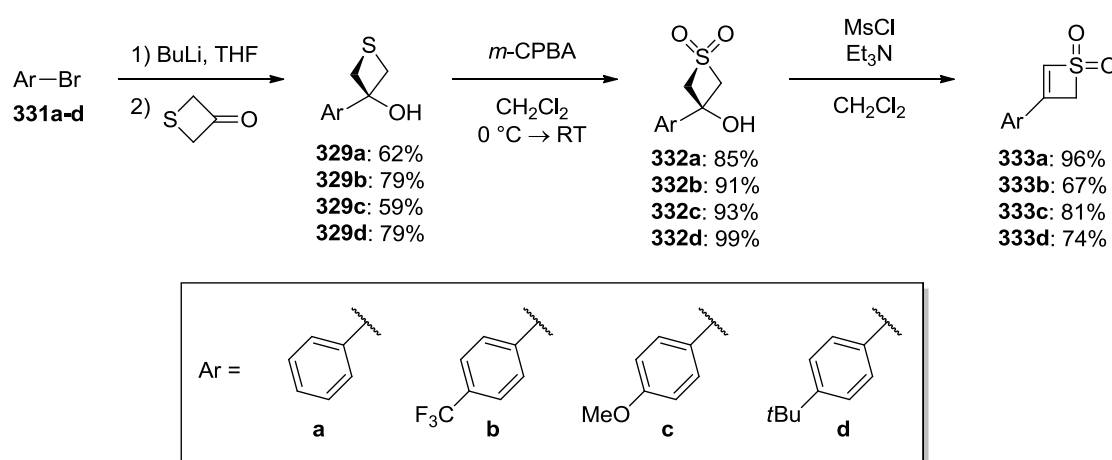
Thietan-3-one (**138**) is significantly more useful than its sulfone counterpart for synthetic purposes. As illustrated by the four examples in Scheme 76, it participated in many addition reactions. Although the desired compounds were successfully synthesized, the carbonyl group in thietan-3-one (**138**) was considerably less reactive than in oxetan-3-one (**34**). Whereas the carbonyl group in oxetanone in many cases behaves like an aldehyde carbonyl group, the thietanone C=O displays reactivity of a regular ketone. Nevertheless, WITTIG olefinations with ethyl 2-(triphenylphosphoranylidene)acetate (RT, 22 h) or 2-(triphenylphosphoranylidene)acetonitrile (100 °C, 14 h) were possible, and the  $\alpha,\beta$ -unsaturated ester (**140**) and nitrile (**328**) were formed in 98% and 86% yield, respectively. Additions of lithiated nucleophiles afforded the desired substituted thietan-3-ols in acceptable yields (79% yield of **329d** in the addition using preformed 4-*t*Bu-C<sub>6</sub>H<sub>4</sub>Li). Although HENRY addition of nitromethane to thietan-3-one delivered

<sup>338</sup> a) R. H. Hasek, P. G. Gott, R. H. Meen, J. C. Martin, *J. Org. Chem.* **1963**, *28*, 2496–2498; b) W. E. Truce, J. R. Norell, *J. Am. Chem. Soc.* **1963**, *85*, 3236–3239.

<sup>339</sup> 1,1-Bis(morpholino)ethylene: CHF 312.-/10 g (ABCR) or CHF 193.-/10 g (TCI Deutschland).

the nitroalcohol product **330** in 57% yield, all attempts at its dehydration to the corresponding nitroalkene failed (conditions tried: MsCl/Et<sub>3</sub>N, BURGESS reagent/ $\Delta$ ,<sup>340</sup> TsCl/DMAP/*i*Pr<sub>2</sub>NEt, Ac<sub>2</sub>O/DMAP<sup>341</sup>).

We became more interested in the products from the addition of lithiated arenes to thietan-3-one (Scheme 77). Accordingly, the corresponding sulfones were prepared by using *m*-CPBA in CH<sub>2</sub>Cl<sub>2</sub> (yields >85%). Literature precedent indicated that 3-substituted thiete-*S,S*-dioxides are accessible from respective starting materials bearing a leaving group at C(3) of the dioxothietane.<sup>342</sup> To our delight, mesylation with subsequent elimination (MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>) gave the desired 3-aryl-thiete-*S,S*-dioxides **333a-d** in good to excellent yields.



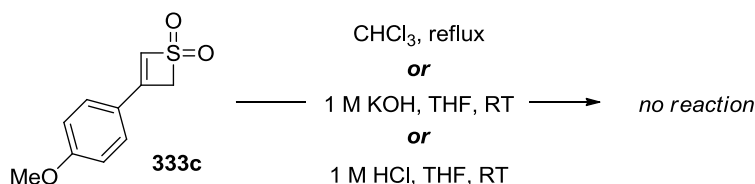
**Scheme 77.** Synthesis of 3-aryl-thiete-*S,S*-dioxides.

To test the stability of these unusual molecules, 4-methoxyphenyl-substituted substrate **333c** was subjected to three different conditions: (a) heating at 80 °C of a 0.014 M solution of **333c** in CHCl<sub>3</sub> for 5 h, (b) stirring of **333c** with 1 M KOH (35 equiv) in THF at RT for 15 h, and (c) stirring of **333c** with 1 M HCl (23 equiv) in THF at RT for 15 h (Scheme 78). The starting material was quantitatively recovered from all these test reactions. This important observation renders a 3-substituted thiete-*S,S*-oxide an intriguing unit for its potential use in material, agricultural, and pharmaceutical science.

<sup>340</sup> a) G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745; b) E. M. Burgess, H. R. Penton, E. A. Taylor, *J. Am. Chem. Soc.* **1970**, *92*, 5224–5226.

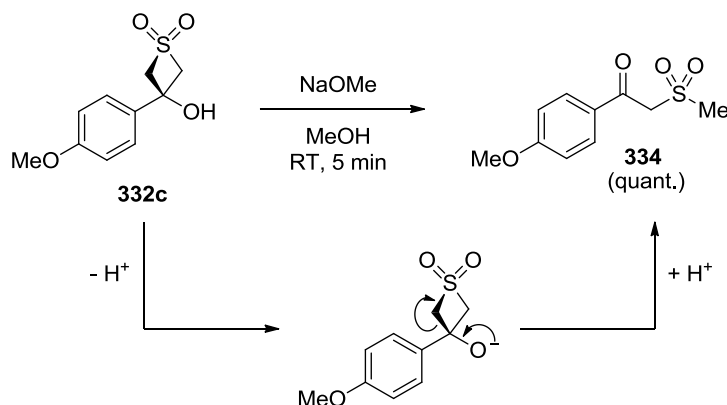
<sup>341</sup> Corresponding *O*-acetate was formed. Treatment with base (KOH/CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, *i*Pr<sub>2</sub>NEt/CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>/MeOH, Et<sub>3</sub>N/THF) did not afford the nitroalkene, either.

<sup>342</sup> a) F. S. Abbott, K. Haya, *Can. J. Chem.* **1978**, *56*, 71–79; b) D. C. Dittmer, B. H. Patwardhan, J. T. Bartholomew, *Org. Magn. Resonance* **1982**, *18*, 82–86; c) T. C. Sedergran, M. Yokoyama, D. C. Dittmer, *J. Org. Chem.* **1984**, *49*, 2408–2412.



**Scheme 78.** Stability tests with **333c**.

Unlike 3-aryl-thiete-*S,S*-dioxides like **333c**, their precursor alcohols did not exhibit extraordinary stability. For instance, when **332c** was treated with sodium methoxide (2 equiv) in methanol at RT, rapid ring-opening was observed and  $\beta$ -ketosulfone **334** was obtained in quantitative yield after a reaction time of just 5 min (Scheme 79). It is suggested that the tertiary alcohol is deprotonated, and as soon as the alkoxide is formed, it opens the thietane ring in a retro-aldol-type reaction to give a deprotonated methylsulfone, which quickly takes up a proton from the solvent. This behavior of 3-hydroxy-dioxothietanes was previously observed by TRUCE and NORELL in 1963<sup>338b</sup> and by YOUNG and STIRLING in 1987.<sup>343</sup>



**Scheme 79.** Rapid ring-opening of substituted dioxothietan-3-ols.

Exploratory experiments with **332c** have revealed that (a) it can be deoxyfluorinated using DAST at low temperatures in  $\text{CH}_2\text{Cl}_2$  to afford the corresponding benzyl fluoride,<sup>344</sup> and (b) reductive dehydroxylation is possible using Pd/C,  $\text{H}_2$ , MsOH in ethyl acetate,<sup>345</sup> affording 3-(4-methoxyphenyl)thietane 1,1-dioxide. The same product is formed by catalytic hydrogenation of the thiete **333c**, but conversions are slow with 1 atm  $\text{H}_2$ .

<sup>343</sup> D. J. Young, C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.* **1987**, 552–553.

<sup>344</sup> G. C. B. Harriman, J. Shao, J. R. Luly, *Tetrahedron Lett.* **2000**, 41, 8853–8856.

<sup>345</sup> V. J. Chebny, C. Gwengo, J. R. Gardinier, R. Rathore, *Tetrahedron Lett.* **2008**, 49, 4869–4872.

## 7.3 Conclusion & Outlook

Thietanes and their oxidized congeners have largely been neglected in the chemical industry and in the academic environment, and only a few preparative methods and applications are known (*cf.* Chapter 1). The various results presented in this Thesis suggest that it may be worth implementing thietanes in future research projects. The majority of thietanes (especially dioxothietanes) mentioned herein exhibit outstanding chemical stability. The compounds analyzed for basicity, lipophilicity, aqueous solubility, and metabolic stability revealed generally desirable properties. The superb metabolic stability of linear and angular azaspirocycles containing an SO<sub>2</sub> or SO unit is particularly worth mentioning here.

Preliminary conclusions from the synthetic efforts toward thietane compounds show that the most convenient building block is thietan-3-one, a solid compound that can efficiently be synthesized on large scale. It is the starting point for granting access to 3-substituted thiete dioxides, an underrepresented class of compounds that could have a major impact in agricultural or medicinal chemistry. The current synthesis of these molecules involves multiple steps – an approach involving a dioxothiete building block that can be mounted on various scaffolds by using for instance Pd-catalyzed cross-coupling reactions would be more desirable. 3-Aryl dioxothietes were found to be chemically inert, but future research is required to assure their compatibility in areas such as drug discovery (ADMET profile).

The properties of thietanes, thietan-*S*-oxides, and thietan-*S,S*-dioxides have been studied only to a limited extent. Exploration of their reactivity might lead to unprecedented reactions, in which thietanes are used as intermediates or reagents. In addition, novel synthetic protocols are required for the generation of certain desired thietane compounds; an important criterion that eventually makes these units attractive for future applications.





# 8

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## **Conclusion & Outlook**

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Among small aliphatic heterocyclic ring systems, four-membered cycles have traditionally attracted the least interest in the various areas of organic chemistry. This work, however, describes the intriguing opportunities for oxetanes, azetidines, thietanes, and cyclobutanes in synthetic and drug discovery-related applications. Their fundamental physical and biochemical properties were studied, and their use as surrogates for commonly employed structural units enabled the discovery of novel biologically active compounds. Moreover, oxetan-3-one was found to be a useful reagent in the synthesis of isoxazoles from nitro compounds.

The merger of azetidines with other four-membered rings resulted in 2-azaspiro[3.3]heptanes that can be viewed as structural analogues to azacyclohexanes. These systems, which were termed *homospiropiperazine*, *homospiro(thio)morpholine* and *homospiropiperidine*, were found to possess highly desirable pharmacokinetic properties. The analysis of a series of model compounds revealed a general trend toward higher basicity, lower lipophilicity, higher aqueous solubility, and reduced metabolic clearance rates when compared with their monocyclic structural counterparts.

The chemical space was further expanded by going from linear azaspiro[3.3]heptanes to angular units having a 1,6-relationship between the heteroatoms (spiro[3.3]heptane numbering). These modules can be regarded as surrogates for chemically inherently unstable 1,3-heteroatom-substituted cyclohexanes, which are readily cleaved in an acidic aqueous environment. The angular spirocycles were constructed in few steps and good yields from simple cyclic ketones (cyclobutanone, azetidin-3-one, oxetan-3-one, and thietan-3-one). Their chemical stability was confirmed, and their ADME properties were assessed by the analysis of piperonyl-substituted members.

To make the spiro[3.3]heptane scaffold even more attractive for future applications, we sought to prepare representatives with two or three exit vectors attached. Several of these topologically unique advanced angular spirocycles were then efficiently prepared by the adaption of recently developed synthetic protocols (e.g., ZHANG's Au-catalyzed cyclization of propargylic alcohols or ELLMAN's imine as an intermediate for the synthesis of  $\alpha$ -amino acids). X-ray structural information acquired for two building blocks will permit their application in modeling studies directed at the discovery of novel enzyme inhibitors.

In addition to the creation of unprecedented drug-like building blocks, this work was also focused on the application of four-membered heterocycles in selected drug discovery programs. It was shown that the homospiropiperazine or -morpholine unit can be mounted on the aromatic framework of the fluoroquinolones to provide novel antibiotic compounds with an increased metabolic resistance. Since a 3,3-disubstituted oxetane can be seen as a carbonyl group surro-

gate, we were intrigued to define its potency as a replacement for the C=O moiety in active substances of launched drugs. While the results were disappointing in the case of a diazepam analogue, we were glad to observe good activity of oxetane analogues of thalidomide and lenalidomide. Due to the associated issues with the latter (*in vivo* racemization; one enantiomer is teratogenic), the oxetane compounds may have a significant impact as anti-angiogenic agents, as the newly introduced oxetane unit presumably prevents racemization of the compound. Ongoing experiments involving an *in vivo* cornea pocket assay and a zebrafish teratogenicity study will shed more light on the potency of oxetano-thalidomide and oxetano-lenalidomide, and results will be disclosed as they become available.

This and earlier work from our laboratory outline the benefits of implementing the oxetane unit in drug discovery programs. Herein, it is shown that oxetan-3-one can also serve as a synthetic building block. In this respect, oxetanone underwent condensation with primary nitro compounds, and the resulting substituted (nitromethylene)oxetanes participated in a rearrangement reaction to produce isoxazole-4-carbaldehydes. A one-pot operation was developed that allowed the isolation of isoxazole compounds in 58-91% yield starting from a primary nitro compound, oxetan-3-one, and inexpensive reagents ( $\text{Et}_3\text{N}$ ,  $\text{MsCl}$ ,  $i\text{Pr}_2\text{NEt}$ ). To the best of our knowledge, this is the first example, where oxetan-3-one was used as a synthetic building block or reagent and not as a module to introduce the oxetane unit.

The results presented herein are expected to motivate other scientists to employ four-membered heterocycles in their research programs. Whether it is for the creation of novel biologically active compounds, the implementation in advanced materials, or the discovery of new chemical reactions, oxetanes, azetidines, and thietanes provide countless opportunities for future innovations. We thus envision these systems to propel science forward and appear in many forthcoming scientific disclosures.



# 9

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## Experimental Part

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## 9.1 General Methods

All non-aqueous reactions were carried out using oven-dried (90 °C) or heat gun dried glassware under a positive pressure of dry argon unless otherwise noted. Acetonitrile, dichloromethane, diethyl ether, tetrahydrofuran, and toluene were purified by passage over activated alumina under an argon atmosphere ( $\text{H}_2\text{O}$  content < 30 ppm, KARL-FISCHER titration). Triethylamine was distilled from KOH under an atmosphere of dry nitrogen. All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using *Merck* Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate, potassium permanganate, vanillin, 4-methoxybenzaldehyde, or ninhydrin stain. Chromatographic purification of products (flash chromatography) was performed on *Brunschwig* or *Fluka* silica 32-63, 60 Å using a forced flow of eluent at 0.3-0.5 bar. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

**Melting points:** measured on a *Büchi* SMP-20 or B-545 apparatus. All melting points were measured in open capillaries and are uncorrected.

**NMR spectra:** NMR spectra were recorded on a *Varian* Mercury 300 spectrometer operating at 300 MHz and 75 MHz for  $^1\text{H}$  and  $^{13}\text{C}$  acquisitions, respectively, or on *Bruker* DRX400 (or AV400) spectrometers operating at 400 MHz ( $^1\text{H}$ ) and 101 MHz ( $^{13}\text{C}$ ). Chemical shifts ( $\delta$ ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform ( $\delta = 7.26$ ) or methanol ( $\delta = 3.31$ ) for  $^1\text{H}$ , and chloroform ( $\delta = 77.0$ ) or methanol ( $\delta = 49.0$ ) for  $^{13}\text{C}$ . All  $^{13}\text{C}$  spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal; coupling constants in Hz.

**IR spectra:** recorded on a *Perkin Elmer* Spectrum RX-I FT-IR (as thin film) or *Perkin Elmer* Spectrum BX FT-IR (neat) spectrometer. Absorptions are given in wavenumbers ( $\text{cm}^{-1}$ ).

**Mass spectra:** recorded by the MS service at *ETH Zürich*. EI-MS ( $m/z$ ): *Waters* Micromass AutoSpec Ultima spectrometer. ESI-MS ( $m/z$ ): *Bruker* Daltonics maXis spectrometer. MALDI-MS ( $m/z$ ): *Bruker* Daltonics UltraFlex II spectrometer.

**Chemical names:** generated with ChemBioDraw Ultra 11.0 or 12.0 (*Cambridgesoft*) and modified where appropriate.

**Determination of solubility at thermodynamic equilibrium.** For each compound, a sample of approximately 2 mg was added to *ca.* 150  $\mu\text{L}$  of a 50 mM aqueous phosphate buffer and transferred to a standard 96-well plate at room temperature ( $22.5 \pm 1$  °C). The pH of each compound suspension was adjusted to pH 10 by using a concentrated NaOH solution and the 96-well plate was placed on a plate shaker which agitated the suspensions over night. At the next day the samples were filtered with a micronic filter plate (MSGVN2250) to separate the solid material from the solution. After confirming unchanged pH of the solutions by way of micro-pH-meter measurements, the solution concentrations were determined by calibrated HPLC. The calibrations were obtained by HPLC analysis of different concentrations of each compound in DMSO.

**Determination of lipophilicity ( $\log D^{\text{pH}=7.4}$ ).** The high-throughput assay method is derived from the conventional 'shake flask' method: The compound of interest is distributed between a 50 mM aqueous TAPSO buffer at pH 7.4 and 1-octanol. The distribution coefficient is then calculated from the difference in concentration in the aqueous phase before and after partitioning and the volume ratio of the two phases. To measure  $\log D$  values within the range of -1 to 3.5, it is necessary to carry out the procedure at four different octanol/water ratios. The "one-phase-analysis" experiment starts with 2 or 9  $\mu\text{L}$  of a pure DMSO-solution of the compound, which is dispensed into 38 or 171  $\mu\text{L}$  of the aqueous buffer solution, bringing the compound concentration to approximately  $c = 0.5$  mM. A small part of this solution is then analyzed by UV. The observed optical density corresponds to the concentration of the substance before partitioning. To a measured aliquot of the aqueous solution a matching aliquot of 1-octanol is added, and the mixture is incubated by quiet shaking for 2 hours at  $23 \pm 1$  °C. The emulsion is allowed to stand overnight at the same temperature to ensure that the partition equilibrium is reached. Then, thorough centrifugation at 3000 rpm for 10 min is applied to separate the layers, and the concentration of the compound in the aqueous phase is determined again by measuring the UV-absorption under the same conditions as the reference.

**Determination of lipophilicity ( $\log D$ ; CAMDIS method).** Distribution coefficients are determined using the CAMDIS<sup>®</sup> (CARRIER MEDIATED DISTRIBUTION SYSTEM, EP2005102211A)<sup>346</sup>

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<sup>346</sup> H. Fischer, M. Kansy, B. Wagner (F. Hoffmann-La Roche AG), EP 1705474, 2006.

method, which is derived from the conventional 'shake flask' method. CAMDIS<sup>®</sup> is carried out in 96-well microtiterplates in combination with DIFI<sup>®</sup>-tubes (*Weidmann Plastics Technology AG*, Rapperswil, Switzerland), which provide a hydrophobic layer for the 1-octanol phase. The hydrophobic layer (0.45  $\mu\text{m}$  PVDF membranes) fixed on the bottom of each DIFI<sup>®</sup>-tube is coated (Microfluidic Dispenser BioRAPTR, *Bechman Coulter*) with 1.0  $\mu\text{l}$  of 1-octanol. Next, the filter membranes are dipped into a 96-well plate which has been prefilled with 150  $\mu\text{l}$  of aqueous buffer solution (25 mM phosphate, pH 7.4) containing the compound of interest at a starting concentration of 100  $\mu\text{M}$ . The plate is sealed and shaken for 24 h at room temperature (23  $^{\circ}\text{C}$ ) to ensure that the partition equilibrium is reached. On the next day, the DIFI<sup>®</sup>-tubes are removed from the 96-well plate and an aliquote of the aqueous solution is analyzed by LC/MS. The distribution coefficient is calculated from a control experiment without 1-octanol and the remaining compound concentration in the aqueous phase with was in equilibrium with 1-octanol. Sample preparation is carried out using a TECAN robotic system (RSP 100, 8 channels).

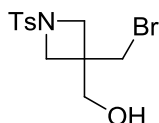
**High-throughput measurement of ionization constants ( $\text{p}K_{\text{a}}$ ).** Ionization constants are determined at  $23 \pm 1$   $^{\circ}\text{C}$  by spectrophotometry using a *Profiler.SGA* SIRIUS instrument in buffered water solution at an ionic strength of 150 mM. To this end the UV-spectrum of a compound is measured at different pH values. The solution of the sample is injected at constant flow rate into a flowing pH gradient. Changes in UV absorbance are monitored as a function of the pH gradient. The  $\text{p}K_{\text{a}}$  values are found and determined where the rate of change of absorbance is at a maximum. The pH gradient is established by proportionally mixing two flowing buffer solutions. The buffer solutions contain mixtures of weak acids and bases that are UV-spectroscopically transparent above 240 nm. It is necessary to calibrate the gradient in order to know exactly the pH at any given time. This is achieved by introducing standard compounds with known  $\text{p}K_{\text{a}}$  values.

**Determination of metabolic stability in liver microsomes.** Microsomal incubations were carried out in 96-well plates in 200  $\mu\text{l}$  of liver microsome incubation medium containing potassium phosphate buffer (50 mM, pH 7.4),  $\text{MgCl}_2$  (10 mM), EDTA (1 mM),  $\text{NADP}^+$  (2 mM), glucose-6-phosphate  $\cdot 2 \text{H}_2\text{O}$  (20 mM), glucose-6-phosphate dehydrogenase (4 units/ml) with 0.1 mg of liver microsomal protein per ml. Test compounds were incubated at 2  $\mu\text{M}$  for up to 30 min at 37  $^{\circ}\text{C}$  under vortexing at 800 rpm. The reaction was stopped by transferring 30  $\mu\text{L}$  incubation aliquots to 90  $\mu\text{l}$  of ice-cold methanol. Levels of non-metabolized drug were determined by high-performance liquid chromatography (HPLC) coupled with tandem-mass spectrometry (LC/MS/MS). The system consisted of a *Shimadzu* binary gradient HPLC system, a



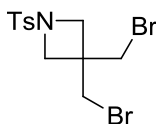
Waters XTerra® MS C18 column (1 mm·50 mm) and a Sciex API 2000 mass spectrometer. A two-component mobile phase, pumped at 0.15 ml/min, contained the following solvents: solvent A (1% aqueous formic acid and MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. The intrinsic clearance ( $CL_{int}$ ) was determined in semi-logarithmic plots of compound concentrations *versus* time.

## 9.2 Linear Spirocycles



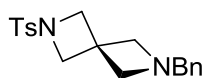
**(3-(Bromomethyl)-1-(*p*-toluenesulfonyl)azetidino-3-yl)methanol (51).** To a suspension of 6-(*p*-toluenesulfonyl)-2-oxa-6-azaspiro[3.3]heptane (7.99 g, 31.5 mmol, 1.0 equiv) in Et<sub>2</sub>O (300 ml) at 0 °C was dropwise added over a period of 15 min a solution of hydrobromic acid (*ca.* 33% in AcOH; 6 ml, *ca.* 34.7 mmol, *ca.* 1.1 equiv) in Et<sub>2</sub>O (40 ml). The resulting mixture was warmed to RT and stirred for 30 min. TLC-analysis of the reaction mixture indicated some unreacted starting material, therefore was dropwise added a solution of hydrobromic acid (*ca.* 33% in AcOH; 0.55 ml, *ca.* 3.15 mmol, *ca.* 0.1 equiv) in Et<sub>2</sub>O (15 ml). The resulting colorless solution was stirred at RT for 15 min, when it was poured into a saturated aqueous solution of NaHCO<sub>3</sub> (300 ml). The phases were separated and the aqueous phase was extracted with Et<sub>2</sub>O (100 ml). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford the title compound as a colorless solid. This product was pure enough for further transformations. Yield: 10.43 g (31.2 mmol, 99%). Colorless crystalline solid. An analytical sample can be obtained after FC (SiO<sub>2</sub>; hexanes : EtOAc : CH<sub>2</sub>Cl<sub>2</sub> 1:1:2).

**TLC:**  $R_f = 0.41$  (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 85-88 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.69$  (d,  $J = 8.1$ , 2 H), 7.37 (d,  $J = 8.1$ , 2 H), 3.67-3.55 (m, 4 H), 3.50 (d,  $J = 8.5$ , 2 H), 3.39 (s, 2 H), 2.48 (t,  $J = 4.9$ , 1 H), 2.44 (s, 3 H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 144.3$ , 130.8, 129.7, 128.1, 63.9, 55.9, 39.2, 36.1, 21.7; **IR** (thin film): 3521, 2949, 2878, 1597, 1340, 1162, 1090, 1059, 913, 816, 733, 671 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>BrNO<sub>3</sub>S (M<sup>+</sup>), 333.0029; found 333.0034.



**3,3-Bis(bromomethyl)-1-(*p*-toluenesulfonyl)azetidine (52).** Unpurified bromoalcohol **51** (22.07 g, 60.05 mmol, 1.0 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (200 ml) and  $\text{CBr}_4$  (33.20 g, 100.10 mmol, 1.67 equiv) was added in one portion. The resulting colorless solution was cooled to 0 °C and  $\text{PPh}_3$  (26.26 g, 100.10 mmol, 1.67 equiv) was added in one portion. The reaction mixture turned to a dark orange solution, which was stirred at 0 °C for 1.5 h, then warmed to RT and stirred for further 4 h.  $\text{Et}_2\text{O}$  (*ca.* 200 ml) was added, and the formed slightly yellow precipitate was filtered. The filtrate was concentrated under reduced pressure to afford a dark orange oil, which was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to give the pure title compound. Yield: 19.11 g (48.12 mmol, 80%). Colorless crystals.

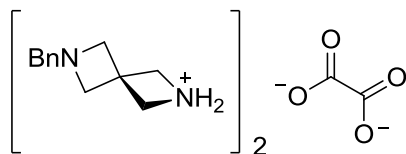
**TLC:**  $R_f = 0.45$  (pentane :  $\text{Et}_2\text{O}$  2:1; UV,  $\text{KMnO}_4$ ); **Melting Point:** 104–105 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.73$  (d,  $J = 8.1$ , 2 H), 7.39 (d,  $J = 8.1$ , 2 H), 3.59 (s, 4 H), 3.52 (s, 4 H), 2.47 (s, 3 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.6$ , 131.1, 129.9, 128.3, 57.2, 39.1, 36.7, 21.6; **IR** (thin film): 3029, 2961, 2877, 1597, 1430, 1348, 1240, 1207, 1164, 1092, 1042, 889, 816, 727, 670, 606  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{15}\text{Br}_2\text{NO}_2\text{S}$  ( $\text{M}^+$ ), 394.9185; found 394.9191.



**2-Benzyl-6-(*p*-toluenesulfonyl)-2,6-diazaspiro[3.3]heptane (53).** Dibromide **52** (14.41 g, 36.29 mmol, 1.0 equiv) was dissolved in  $\text{CH}_3\text{CN}$  (220 ml). Benzylamine (7.93 ml, 72.57 mmol, 2.0 equiv) and DIPEA (31.60 ml, 181.42 mmol, 5.0 equiv) were added, and the reaction mixture was heated to reflux for 3 d. The now yellowish solution was cooled to room temperature and concentrated to about  $1/6$  of the initial volume. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (200 ml) and NaOH (1 M in  $\text{H}_2\text{O}$ ; 140 ml). The phases were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (50 ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1  $\rightarrow$  33:66:1 gradient) to afford the title compound. Yield: 11.89 g (34.72 mmol, 96%). Colorless solid.

**TLC:**  $R_f = 0.25$  (EtOAc : hexanes 2:1; UV,  $\text{KMnO}_4$ ); **Melting Point:** 86–87 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.69$  (d,  $J = 8.2$ , 2 H), 7.34 (d,  $J = 8.2$ , 2 H), 7.32–7.11 (m, 5 H), 3.82 (s, 4 H), 3.47 (s, 2 H), 3.13 (s, 4 H), 2.44 (s, 3 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 143.9$ , 137.2,

131.2, 129.6, 128.2 (2 C), 128.1, 127.1, 63.7, 63.3, 60.3, 33.2, 21.7; **IR** (thin film): 3029, 2942, 2867, 2820, 1597, 1495, 1452, 1344, 1164, 1092, 1049, 913, 817, 743, 678, 631  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$  ( $[\text{M}-\text{H}]^+$ ), 341.1319; found 341.1318.



**6-Benzyl-2,6-diazaspiro[3.3]heptan-2-ium oxalate (54).** A mixture of tosyl amide **53** (2.53 g, 7.38 mmol, 1.0 equiv) and Mg powder (1.08 g, 44.3 mmol, 6.0 equiv) in MeOH (30 ml) was sonicated for 1 h. At this point the mixture was concentrated *in vacuo* and the residue was treated with  $\text{Et}_2\text{O}$  (120 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (a few spatulas), and the grayish suspension was vigorously stirred at RT for 30 min. Then it was filtered and the filtrate was dried ( $\text{Na}_2\text{SO}_4$ ) and filtered again. To the filtrate was added a solution of oxalic acid (0.33 g, 3.69 mmol, 0.5 equiv) in EtOH (0.7 ml), upon which a colorless precipitate formed immediately. The solid was collected by filtration to afford the title compound in good purity. Yield: 1.58 g (3.40 mmol, 92%). Colorless solid.

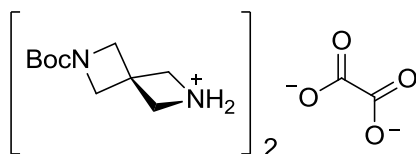
**TLC:**  $R_f = 0.0$  (EtOAc; UV, ninhydrin); **Melting Point:** 168-170  $^\circ\text{C}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 7.43 - 7.15$  (m, 5H), 4.90 (s, 2H), 4.13 (s, 4H), 3.69 (s, 2H), 3.56 (s, 4H);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 172.8, 136.6, 129.6, 129.2, 128.5, 63.4, 62.5, 55.7, 37.4$ ; **IR** (neat): 2933, 2832, 2467, 1591, 1363, 1299, 1230, 949, 756, 725, 697  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{17}\text{N}_2$  ( $\text{M}^+$ ), 189.1386; found 189.1387.



**tert-Butyl 6-(p-toluenesulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (55).** Benzyl azetidene **53** (2.70 g, 7.88 mmol, 1.0 equiv) was dissolved in MeOH (40 ml), and Pd (10% on charcoal; 0.42 g, 0.39 mmol, 0.05 equiv) was added. A hydrogen atmosphere (balloon) was built up and the mixture was heated to 45  $^\circ\text{C}$  and stirred at this temperature for 29 h. TLC-analysis of the reaction mixture indicated still some unreacted starting material. Therefore, an argon atmosphere was formed, the mixture was cooled to RT, and more Pd (10% on charcoal; 0.21 g, 0.20 mmol, 0.025 equiv) was added. Again a hydrogen atmosphere was built up and the mixture was heated to 45  $^\circ\text{C}$  and stirred at this temperature for further 24 h. At this point the reaction mixture was cooled to RT and an argon atmosphere was formed. The suspension was filtered

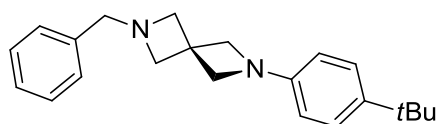
over celite and the filter cake thoroughly washed with MeOH ( $2 \times 20$  ml). To the solution of the intermediate free azetidone in MeOH (*ca.* 80 ml) was added  $\text{Boc}_2\text{O}$  (1.77 g, 7.88 mmol, 1 equiv). The resulting solution was stirred at RT for 1 h, when it was concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:1 to 1:2 gradient) to furnish the pure title compound. Yield: 2.47 g (7.01 mmol, 89%). Colorless crystals.

**TLC:**  $R_f = 0.52$  (EtOAc : hexanes 1:1; UV, CAM); **Melting Point:** 169-170 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.70$  (d,  $J = 8.2$ , 2 H), 7.36 (d,  $J = 8.2$ , 2 H), 3.84 (s, 4 H), 3.83 (s, 4 H), 2.45 (s, 3 H), 1.38 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.7$ , 144.4, 131.2, 129.8, 128.3, 79.9, 60.1, 58.9 (br), 32.0, 28.2, 21.6; **IR** (thin film): 2977, 2863, 1691, 1597, 1414, 1364, 1341, 1156, 1111, 1051, 913, 822, 742, 685  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$  ( $\text{M}^+$ ), 352.1457; found 352.1454.



**6-(*tert*-Butoxycarbonyl)-6-aza-2-azoniaspiro[3.3]heptane oxalate (56).** Tosyl amide **55** (2.31 g, 6.55 mmol, 1.0 equiv) was dissolved in MeOH (70 ml). Mg powder (1.27 g, 52.43 mmol, 8 equiv) was added, and the mixture was sonicated for 45 min. The mixture was concentrated *in vacuo* to afford a dark gray solid. This was suspended in  $\text{Et}_2\text{O}$  (170 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 20 g) was added. The suspension was vigorously stirred at room temperature for 1 h, then filtered, the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), and filtered. To the filtrate was added under stirring a solution of anhydrous oxalic acid (0.295 g, 3.28 mmol, 0.5 equiv) in EtOH (0.7 ml), upon which immediately a colorless precipitate formed. The solid was filtered and dried under reduced pressure to give the pure title compound. Yield: 1.28 g (2.64 mmol, 81%). Amorphous colorless solid.

**TLC:**  $R_f = 0.0$  (EtOAc; ninhydrin); **Melting Point:** 206-209 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 4.90$  (s, 2 H), 4.20 (s, 4 H), 4.09 (s, 4 H), 1.42 (s, 9 H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 168.9$ , 157.7, 81.3, 59.9 (br), 56.3, 36.7, 28.6; **IR** (neat): 3243, 2967, 2879, 2689, 2497, 1759, 1692, 1634, 1596, 1400, 1364, 1332, 1255, 1164, 1146, 1092, 856, 764, 721  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{19}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 199.1441; found 199.1442.

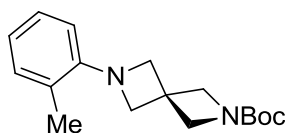


**2-Benzyl-6-(4-(*tert*-butyl)phenyl)-2,6-diazaspiro[3.3]heptane (58).** To degassed toluene (3× freeze-pump-thaw; 3 ml) was added sequentially oxalate salt **54** (66 mg, 0.14 mmol, 0.6 equiv), KO*t*Bu (68 mg, 0.71 mmol, 3.0 equiv), Et<sub>3</sub>N (8 drops), 1-bromo-4-(*tert*-butyl)benzene (41 μl, 0.24 mmol, 1.0 equiv), [Pd<sub>2</sub>(dba)<sub>3</sub>] (5 mg, 0.006 mmol, 0.05 equiv), and (±)-BINAP (11 mg, 0.018 mmol, 0.08 equiv). The mixture was heated to 90 °C and stirred at that temperature for 43 h. It was cooled to RT, diluted with EtOAc (15 ml), filtered over celite, and the filtrate was concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; hexanes : EtOAc 2:1 → 1:1 → 1:2 gradient) afforded the pure title compound as a colorless oil that slowly solidifies over time.

**TLC:** *R<sub>f</sub>* = 0.35 (EtOAc : hexanes 1:2; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ 7.43 – 7.18 (m, 7H), 6.43 (d, *J*=8.7, 2H), 3.94 (s, 4H), 3.61 (s, 2H), 3.40 (s, 4H), 1.30 (s, 9H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ 149.2, 140.2, 137.8, 128.3, 128.2, 127.0, 125.6, 111.3, 64.5, 63.7, 62.5, 34.8, 34.0, 31.6; **IR** (thin film): 3030, 2952, 2903, 2824, 1611, 1517, 1469, 1363, 1326, 1130, 819, 696, 553 cm<sup>-1</sup>; **HRMS** (MALDI): exact mass calculated for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub> ([M+H]<sup>+</sup>), 321.2325; found 321.2325.

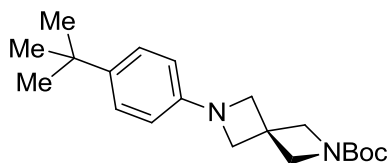
### General Procedure for Buchwald-Hartwig Amination Reactions (GP1)

In a Schlenk flask was added to degassed (freeze-pump-thaw technique, 3×) toluene (5 ml) in the following order the aryl bromide (0.4 mmol, 1.0 equiv), oxalate salt **56** (1.1 equiv of the amine), [Pd<sub>2</sub>(dba)<sub>3</sub>] (1–2.5 mol %), (±)-BINAP (1.5/Pd), Et<sub>3</sub>N (5 drops, ~30 μl, ~0.5 equiv), and KO*t*Bu (3.0 equiv). The resulting dark red mixture was heated to 110 °C (bath temperature) and stirred at this temperature for the appropriate time. Once TLC indicated complete consumption of the aryl bromide or no further turnover, the now brownish mixture was cooled to room temperature, then filtered over a thin layer of celite, and the filter cake was thoroughly washed with EtOAc (typically about 30 ml). The filtrate was concentrated *in vacuo* and the residue purified by FC using mixtures of hexanes and EtOAc as eluents.



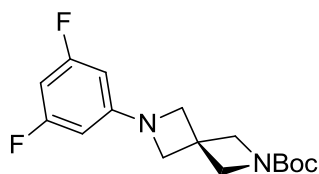
**tert-Butyl 6-*o*-tolyl-2,6-diazaspiro[3.3]heptane-2-carboxylate (59a).** Heated for 21 h according to GP1, using 1-bromo-2-methylbenzene (48  $\mu$ l, 0.40 mmol, 1.0 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}^t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 112 mg (0.39 mmol, 97%). Colorless crystals.

**TLC:**  $R_f$  = 0.36 (EtOAc : hexanes 1:4; UV, CAM); **Melting Point:** 86-87  $^\circ\text{C}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.11 (dt,  $J$  = 7.5, 1.1, 1 H), 7.12 (d,  $J$  = 8.0, 1 H), 6.79 (dt,  $J$  = 7.5, 1.1, 1 H), 6.47 (d,  $J$  = 8.0, 1 H), 4.09 (s, 4 H), 3.99 (s, 4 H), 2.22 (s, 3 H), 1.46 (s, 9 H);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.8, 149.2, 131.3, 126.3, 124.9, 119.7, 112.8, 79.6, 63.3, 59.4 (br), 33.2, 28.4, 19.5; **IR** (thin film): 2974, 2948, 2872, 2841, 1703, 1600, 1495, 1405, 1366, 1315, 1175, 1131, 1104, 1068, 933, 862, 752  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 288.1832; found 288.1834.



**tert-Butyl 6-(4-*tert*-butylphenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59b).** Heated for 17 h according to GP1, using 1-bromo-4-*tert*-butylbenzene (70  $\mu$ l, 0.40 mmol, 1.0 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}^t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) to afford the pure title compound. Yield: 120 mg (0.36 mmol, 91%). Colorless crystals.

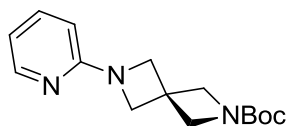
**TLC:**  $R_f$  = 0.17 (EtOAc : hexanes 1:6; UV, CAM); **Melting Point:** 146-147  $^\circ\text{C}$ ;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.25 (d,  $J$  = 8.7, 2 H), 6.42 (d,  $J$  = 8.7, 2 H), 4.07 (s, 4 H), 3.95 (s, 4 H), 1.45 (s, 9 H), 1.28 (s, 9 H);  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.8, 148.9, 140.7, 125.7, 111.4, 79.6, 62.4, 59.6 (br), 34.0, 33.5, 31.6, 28.4; **IR** (thin film): 2961, 2904, 2872, 1704, 1612, 1518, 1475, 1403, 1366, 1323, 1175, 1129, 1104, 912, 821, 732  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{20}\text{H}_{31}\text{N}_2\text{O}_2$  ( $[\text{M}+\text{H}]^+$ ), 331.2380; found 331.2386.



**tert-Butyl 6-(3,5-difluorophenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59c).**

Heated for 22 h according to GP1, using 1-bromo-3,5-difluorobenzene (47  $\mu$ l, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) to afford the pure title compound. Yield: 110 mg (0.35 mmol, 89%). Colorless crystalline solid.

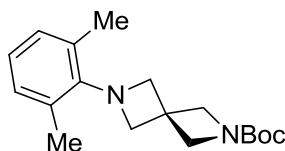
**TLC:**  $R_f = 0.27$  (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 137-138  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.55$  (tt,  $J_{\text{H,F}} = 9.2$ ,  $J = 2.2$ , 1 H), 6.01-5.75 (m, 2 H), 4.08 (s, 4 H), 3.94 (s, 4 H), 1.44 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 163.7$  (dd,  $J_{\text{C,F}} = 244.8$ , 15.5), 155.7, 152.7 (t,  $J_{\text{C,F}} = 12.7$ ), 94.4 (dd,  $J_{\text{C,F}} = 28.0$ , 3.9), 92.9 (t,  $J_{\text{C,F}} = 26.1$ ), 79.8, 61.9, 59.4 (br), 33.2, 28.4;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -109.56$  (t,  $J = 9.2$ ); **IR** (thin film): 2977, 2935, 2875, 1702, 1630, 1587, 1472, 1408, 1367, 1329, 1237, 1170, 1113, 983, 913, 861, 817, 772, 734  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{16}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 310.1487; found 310.1487.



**tert-Butyl 6-(pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59d).**

Heated for 13 h according to GP1, using 2-bromopyridine (39  $\mu$ l, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (9 mg, 0.010 mmol, 0.025 equiv), ( $\pm$ )-BINAP (19 mg, 0.030 mmol, 0.075 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:2) to afford the pure title compound. Yield: 91 mg (33 mmol, 83%). Off-white solid.

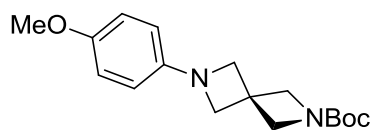
**TLC:**  $R_f = 0.41$  (EtOAc; UV, CAM); **Melting Point:** 146-147  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.13$  (ddd,  $J = 5.1$ , 1.9, 0.9, 1 H), 7.44 (ddd,  $J = 8.4$ , 7.2, 1.9, 1 H), 6.61 (ddd,  $J = 7.2$ , 5.1, 0.9, 1 H), 6.27 (td,  $J = 8.4$ , 0.9, 1 H), 4.10 (s, 4 H), 4.09 (s, 4 H), 1.43 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 160.1$ , 155.8, 148.0, 137.0, 113.3, 106.0, 79.7, 60.8, 59.5 (br), 33.4, 28.4; **IR** (thin film): 2974, 2933, 2869, 1698, 1596, 1560, 1491, 1440, 1406, 1324, 1175, 1151, 1105, 773, 734  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2$  ( $\text{M}^+$ ), 275.1628; found 275.1630.



**tert-Butyl 6-(2,6-dimethylphenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59e).**

Heated for 13 h according to GP1, using 2-bromo-1,3-dimethylbenzene (55  $\mu$ l, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 7:2) to afford the pure title compound. Yield: 93 mg (31  $\mu$ mol, 77%). Colorless solid.

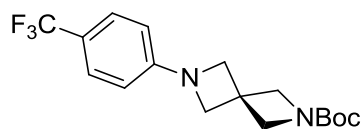
**TLC:**  $R_f = 0.22$  (hexanes : EtOAc 3:1; UV, CAM); **Melting Point:** 129-130  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.87$  (d,  $J = 7.5$ , 2 H), 6.70 (t,  $J = 7.5$ , 1 H), 4.22 (s, 4 H), 4.06 (s, 4 H), 2.28 (s, 6 H), 1.45 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.8$ , 148.9, 130.1, 125.7, 120.2, 79.6, 66.4, 59.4 (br), 33.3, 28.4, 21.1; **IR** (thin film): 2967, 2877, 1683, 1592, 1480, 1455, 1423, 1365, 1280, 1162, 1124, 1108, 912, 762, 732  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 302.1989; found 302.1991.



**tert-Butyl 6-(4-methoxyphenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59f).** Heated for 22 h according to GP1, using 1-bromo-4-methoxybenzene (52  $\mu$ l, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (8 mg, 0.008 mmol, 0.02 equiv), ( $\pm$ )-BINAP (14 mg, 0.024 mmol, 0.06 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to afford the pure title compound. Yield: 78 mg (0.26 mmol, 64%). Colorless solid.

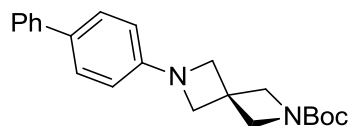
**TLC:**  $R_f = 0.19$  (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 138-139  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.81$  (d,  $J = 9.0$ , 2 H), 6.42 (d,  $J = 9.0$ , 2 H), 4.07 (s, 4 H), 3.89 (s, 4 H), 3.74 (s, 3 H), 1.45 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.9$ , 152.4, 145.7, 114.5, 112.9, 79.6, 62.7, 59.5 (br), 55.8 (appears as 2 signals), 33.5, 28.4; **IR** (thin film): 2970, 2932, 2829, 1687, 1514, 1405, 1366, 1240, 1182, 1131, 1046, 913, 825  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ), 304.1781; found 304.1781.





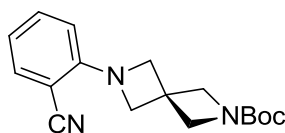
**tert-Butyl 6-(4-(trifluoromethyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59g).** Heated for 21 h according to GP1, using 1-bromo-4-(trifluoromethyl)benzene (55  $\mu$ l, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (9 mg, 0.004 mmol, 0.025 equiv), ( $\pm$ )-BINAP (19 mg, 0.012 mmol, 0.075 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) to afford the pure title compound. Yield: 86 mg (0.25 mmol, 63%). Colorless crystals.

**TLC:**  $R_f$  = 0.36 (hexanes : EtOAc 3:1; UV, CAM); **Melting Point:** 136–137 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.43 (d,  $J$  = 8.3, 2 H), 6.43 (d,  $J$  = 8.3, 2 H), 4.11 (s, 4 H), 4.03 (s, 4 H), 1.46 (s, 9 H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.0, 152.9, 126.3 (q,  $J_{\text{C,F}}$  = 2.0), 124.9 (q,  $J_{\text{C,F}}$  = 271.2), 119.5 (q,  $J_{\text{C,F}}$  = 32.6), 110.8, 79.8, 61.9, 59.5 (br), 33.4, 28.3;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -60.85 (s); **IR** (thin film): 2977, 2936, 2875, 1702, 1613, 1529, 1405, 1322, 1179, 1109, 1066, 824  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 342.1550; found 342.1551.



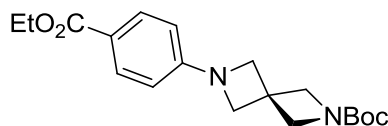
**tert-Butyl 6-(biphenyl-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59h).** Heated for 21 h according to GP1, using 4-bromobiphenyl (93 mg, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) to afford the pure title compound. Yield: 88 mg (0.25 mmol, 63%). Colorless solid.

**TLC:**  $R_f$  = 0.25 (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 149–150 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.59–7.52 (m, 2 H), 7.49 (d,  $J$  = 8.7, 2 H), 7.40 (t,  $J$  = 7.5, 2 H), 7.28 (t,  $J$  = 7.5, 1 H), 6.54 (d,  $J$  = 8.7, 2 H), 4.11 (s, 4 H), 4.01 (s, 4 H), 1.47 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.7, 150.2, 140.8, 130.8, 128.4, 127.5, 126.2, 126.0, 111.9, 79.7, 62.3, 59.5 (br), 33.6, 28.5; **IR** (thin film): 2980, 2943, 2873, 2838, 2249, 1678, 1609, 1430, 1366, 1326, 1178, 1127, 914, 826, 760, 733, 694  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 350.1989; found 350.1991.



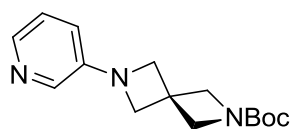
**tert-Butyl 6-(2-cyanophenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59i).** Heated for 12 h according to GP1, using 2-bromobenzonitrile (74 mg, 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4 mg, 0.004 mmol, 0.01 equiv), ( $\pm$ )-BINAP (7 mg, 0.012 mmol, 0.03 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{KO}^t\text{Bu}$  (135 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  3:1) to afford the pure title compound. Yield: 73 mg (0.24 mmol, 61%). Colorless crystals.

**TLC:**  $R_f$  = 0.17 (hexanes :  $\text{EtOAc}$  4:1; UV, CAM); **Melting Point:** 153-154 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.43-7.29 (m, 2 H), 6.73 (dt,  $J$  = 7.7, 1.0, 1 H), 6.41 (d,  $J$  = 8.2, 1 H), 4.27 (s, 4 H), 4.10 (s, 4 H), 1.44 (s, 9 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.7, 152.3, 134.2, 133.3, 119.0, 117.7, 112.7, 94.7, 79.8, 62.9, 59.3 (br), 33.2, 28.4; **IR** (thin film): 2976, 2937, 2873, 2212, 1702, 1601, 1562, 1496, 1451, 1406, 1366, 1327, 1302, 1277, 1258, 1168, 1107, 990, 914, 860, 751, 733  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_2$  ( $\text{M}^+$ ), 299.1628; found 299.1628.



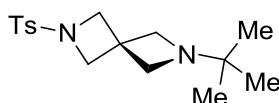
**tert-Butyl 6-(4-(ethoxycarbonyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59j).** Heated for 46 h according to GP1, using ethyl 4-bromobenzoate (65  $\mu\text{l}$ , 0.40 mmol, 1 equiv), oxalate salt **56** (103 mg, 0.22 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (8 mg, 0.008 mmol, 0.02 equiv), ( $\pm$ )-BINAP (14 mg, 0.024 mmol, 0.06 equiv),  $\text{Et}_3\text{N}$  (5 drops), and  $\text{Cs}_2\text{CO}_3$  (391 mg, 1.20 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  3:1) to afford the pure title compound. Yield: 78 mg (0.23 mmol, 56%). Off-white solid.

**TLC:**  $R_f$  = 0.19 (hexanes :  $\text{EtOAc}$  3:1; UV, CAM); **Melting Point:** 143-144 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.89 (d,  $J$  = 8.7, 2 H), 6.36 (d,  $J$  = 8.7, 2 H), 4.30 (q,  $J$  = 7.1, 2 H), 4.10 (s, 4 H), 4.04 (s, 4 H), 1.44 (s, 9 H), 1.35 (t,  $J$  = 7.1, 3 H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 166.6, 155.8, 153.3, 130.9, 119.1, 110.1, 79.8, 61.6, 60.3, 59.5 (br), 33.4, 28.4, 14.5; **IR** (thin film): 2978, 2936, 2874, 1702, 1606, 1521, 1404, 1275, 1172, 1105, 914, 741  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ), 346.1887; found 346.1889.



**tert-Butyl 6-(pyridin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (59k).** Heated at 90 °C for 22 h according to GP1, using 3-bromopyridine (12  $\mu$ l, 0.13 mmol, 1 equiv), oxalate salt **56** (32 mg, 0.07 mmol, 0.55 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (3 mg, 0.003 mmol, 0.025 equiv), ( $\pm$ )-BINAP (6 mg, 0.009 mmol, 0.075 equiv),  $\text{Et}_3\text{N}$  (3 drops), and  $\text{KO}t\text{Bu}$  (43 mg, 0.38 mmol, 3.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc) to afford the pure title compound. Yield: 12 mg (0.044 mmol, 34%). Colorless solid.

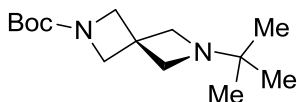
**TLC:**  $R_f = 0.22$  (EtOAc; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.03$  (dd,  $J=4.7, 1.3$ , 1H), 7.85 (d,  $J=2.8$ , 1H), 7.10 (ddd,  $J=8.3, 4.7, 0.6$ , 1H), 6.72 (ddd,  $J=8.3, 2.8, 1.3$ , 1H), 4.10 (s, 4H), 4.01 (s, 4H), 1.44 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.8, 146.6, 139.2, 134.2, 123.3, 118.3, 79.8, 62.3, 59.4$  (br), 34.1, 28.4; **IR** (thin film): 2975, 2934, 2874, 1699, 1584, 1485, 1427, 1404, 1366, 1324, 1172, 1110, 731, 708  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2$  ( $\text{M}^+$ ), 275.1628; found 275.1628.



**2-(tert-Butyl)-6-tosyl-2,6-diazaspiro[3.3]heptane.** To a solution of dibromide **52** (1.02 g, 2.57 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (8 ml) was added  $i\text{Pr}_2\text{NEt}$  (2.24 ml, 12.9 mmol, 5.0 equiv) and  $t\text{BuNH}_2$  (1.89 ml, 18.0 mmol, 7.0 equiv), and the mixture was heated at 50 °C for 24 h. Since TLC analysis of the reaction mixture indicated still the presence of starting material, more  $t\text{BuNH}_2$  (0.81 ml, 7.71 mmol, 3.0 equiv) was added and heating at 50 °C was continued for another 24 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between  $\text{CH}_2\text{Cl}_2$  (30 ml) and  $\text{NaOH}$  (1 M in  $\text{H}_2\text{O}$ ; 20 ml). The phases were separated and the organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* (mixture of starting material and product, ca. 2:1 ratio according to  $^1\text{H NMR}$  analysis of the residue). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1  $\rightarrow$  0:100:1 gradient) to give the pure title compound. Yield: 242 mg (0.79 mmol, 31%; 83% based on recovered starting material). Colorless crystals.

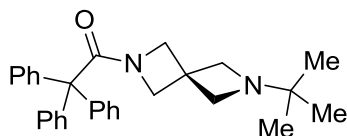
**TLC:**  $R_f = 0.17$  (EtOAc; UV, CAM); **Melting Point:** 118-119 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.70$  (d,  $J=8.1$ , 2H), 7.35 (d,  $J=8.1$ , 2H), 3.81 (s, 4H), 3.10 (s, 4H), 2.45 (s, 3H), 0.84 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 143.9, 131.4, 129.6, 128.2, 60.5, 56.1, 51.6, 31.3, 23.8$ ,

21.7; **IR** (thin film): 2964, 2868, 1344, 1246, 1163, 1092, 1037, 686, 612, 550  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$  ( $\text{M}^+$ ), 308.1553; found 308.1554.



**tert-Butyl 6-(tert-butyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate.** A mixture of 2-(tert-butyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (185 mg, 0.60 mmol, 1.0 equiv) and Mg powder (87 mg, 3.60 mmol, 6.0 equiv) in MeOH (5 ml) was ultrasonicated at RT for 40 min, then concentrated *in vacuo*.  $\text{Et}_2\text{O}$  (20 ml) and sodium sulfate decahydrate (3 spatulas) were added, and the mixture was vigorously stirred for 30 min. Then it was filtered, the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered again, and the filtrate concentrated *in vacuo*. The residue (colorless oil) was dissolved in MeOH (5 ml),  $\text{Boc}_2\text{O}$  (148 mg, 0.66 mmol, 1.1 equiv) was added, and the mixture was sonicated for 1 h, then stirred at RT for another hour. The solvent was evaporated, and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (15 ml) and NaOH (1 M in  $\text{H}_2\text{O}$ ; 8 ml). The layers were separated, and the organic phase was dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc : MeOH :  $\text{Et}_3\text{N}$  50:50:0:1  $\rightarrow$  0:100:0:1  $\rightarrow$  0:100:10:1 gradient) to afford the pure title compound. Yield: 59 mg (0.23 mmol, 39%). Colorless solid.

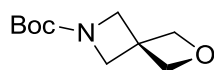
**TLC:**  $R_f = ca.$  0.10 (hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1;  $\text{KMnO}_4$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.95$  (s, 4H), 3.27 (s, 4H), 1.41 (s, 9H), 0.90 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.9$ , 79.3, 59.6 (br), 56.5, 51.6, 31.4, 28.4, 23.9; **IR** (thin film): 2960, 2861, 1692, 1414, 1362, 1219, 1110, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 254.1989; found 254.1990.



**1-(6-(tert-butyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2,2,2-triphenylethanone.** A mixture of 2-(tert-butyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (180 mg, 0.58 mmol, 1.0 equiv) and Mg powder (113 mg, 4.67 mmol, 8.0 equiv) in MeOH (5 ml) was ultrasonicated at RT for 30 min, then concentrated *in vacuo*.  $\text{Et}_2\text{O}$  (20 ml) and sodium sulfate decahydrate (3 spatulas) were added, and the mixture was vigorously stirred for 20 min. Then it was filtered, the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered again, and the filtrate concentrated *in vacuo*. The residue (colorless oil) was dissolved in THF (2 ml), and  $\text{Et}_3\text{N}$  (118  $\mu\text{l}$ , 0.85 mmol, 1.45 equiv) was added followed by dropwise addition

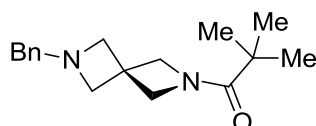
of a solution of 2,2,2-triphenylacetyl chloride (179 mg, 0.58 mmol, 1.0 equiv) in THF (2 ml). The resulting suspension was stirred at RT for 6 h. H<sub>2</sub>O (2 ml), NaOH (1 M in H<sub>2</sub>O; 5 ml), and CH<sub>2</sub>Cl<sub>2</sub> (15 ml) were added, and the phases were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml), and the combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by multiple chromatographic separations (FC on SiO<sub>2</sub> with hexanes/EtOAc/Et<sub>3</sub>N or CH<sub>2</sub>Cl<sub>2</sub>/MeOH as eluent mixtures) to afford the pure title compound. Yield: 45 mg (0.11 mmol, 18%). Colorless foam.

**TLC:**  $R_f = 0.32$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 10:1; UV, KMnO<sub>4</sub>); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.43 - 7.01$  (m, 15H), 4.12 (s, 2H), 3.22 (d,  $J=7.4$ , 2H), 3.13 (s, 2H), 3.02 (d,  $J=7.4$ , 2H), 0.85 (s, 9H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 172.0, 142.3, 130.3, 127.6, 126.6, 66.1, 63.3, 58.8, 56.3, 51.6, 31.6, 23.9$ ; **HRMS** (MALDI): exact mass calculated for C<sub>29</sub>H<sub>33</sub>N<sub>2</sub>O ( $[M+H]^+$ ), 425.2587; found 425.2584.



**tert-Butyl 2-oxa-6-azaspiro[3.3]heptane-6-carboxylate.** A mixture of tosyl amide **43** (240 mg, 0.95 mmol, 1.0 equiv) and Mg powder (184 mg, 7.58 mmol, 8.0 equiv) in MeOH (5 ml) was ultrasonicated at RT for 15 min, then filtered over celite. The filter cake was thoroughly washed with MeOH (10 ml). To the filtrate was added Boc<sub>2</sub>O (234 mg, 1.04 mmol, 1.1 equiv), and the mixture was sonicated at RT for 1 h. The solvent was evaporated, and the residue purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford the pure title compound. Yield: 69 mg (0.35 mmol, 37%). Colorless solid.

**TLC:**  $R_f = 0.28$  (hexanes : EtOAc 1:1; KMnO<sub>4</sub>, ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 4.73$  (s, 4H), 4.04 (s, 4H), 1.40 (s, 9H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 155.7, 80.9, 79.6, 58.8$  (br), 37.7, 28.3; **IR** (thin film): 2934, 2868, 1690, 1425, 1365, 1220, 1110, 976, 772 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub> (M<sup>+</sup>), 199.1203; found 199.1200.



**1-(6-Benzyl-2,6-diazaspiro[3.3]heptan-2-yl)-2,2-dimethylpropan-1-one.** To a suspension of oxalate salt **54** (285 mg, 0.61 mmol, 0.5 equiv) in CH<sub>3</sub>CN (10 ml) was added Et<sub>3</sub>N (1.02 ml, 7.33 mmol, 6.0 equiv). The uniform suspension was cooled to 0 °C, and pivaloyl chloride (0.15 ml, 1.22 mmol, 1.0 equiv) was added dropwise. Stirring at RT was continued for 14 h,

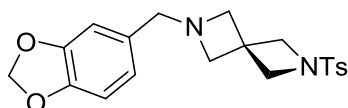
when the mixture was concentrated *in vacuo*. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (15 ml) and  $\text{NaOH}$  (0.2 M in  $\text{H}_2\text{O}$ ; 5 ml) and the phases were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml), and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by FC ( $\text{SiO}_2$ ;  $\text{EtOAc} : \text{MeOH} : \text{Et}_3\text{N}$  50:1:0  $\rightarrow$  100:2:1 gradient) afforded the pure title compound. Yield: 177 mg (0.65 mmol, 53%). Colorless solid.

**TLC:**  $R_f = 0.19$  ( $\text{EtOAc} : \text{MeOH}$  100:3; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.37 - 7.16$  (m, 5H), 4.38 (br s, 2H), 4.00 (br s, 2H), 3.53 (s, 2H), 3.30 (br s, 4H), 1.14 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 177.2, 137.4, 128.2, 128.1, 126.9, 64.1, 63.4, 58.6$  (br), 38.5, 33.8, 27.1; **IR** (thin film): 2954, 2869, 2818, 1627, 1481, 1419, 1364, 1331, 1250, 1150, 982, 726, 698  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}$  ( $\text{M}^+$ ), 272.1883; found 272.1882.



**tert-Butyl 6-benzyl-2,6-diazaspiro[3.3]heptane-2-carboxylate.** A mixture of tosyl amide **53** (0.30 g, 0.89 mmol, 1.0 equiv) and Mg powder (0.11 g, 4.44 mmol, 5.0 equiv) in MeOH (3 ml) was sonicated for 30 min. At this point the mixture was filtered over celite, and to the filtrate was added triethylamine (0.25 ml, 1.78 mmol, 2.0 equiv) and  $\text{Boc}_2\text{O}$  (0.22 g, 0.98 mmol, 1.1 equiv) and the mixture was stirred at RT for 2.5 h. Then the reaction mixture was concentrated *in vacuo* and the residue purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc} : \text{Et}_3\text{N}$  25:75:1) to afford the pure title compound. Yield: 0.19 g (0.67 mmol, 76%). Colorless oil.

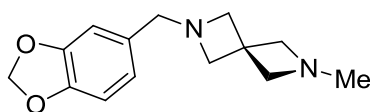
**TLC:**  $R_f = 0.18$  (hexanes :  $\text{EtOAc}$  1:3; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.41 - 7.14$  (m, 5H), 3.98 (s, 4H), 3.55 (s, 2H), 3.31 (s, 4H), 1.42 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.9, 137.6, 128.3, 128.2, 127.0, 79.4, 64.2, 63.5, 59.3$  (br), 33.5, 28.4; **IR** (thin film): 2975, 2934, 2872, 2815, 1702, 1403, 1365, 1330, 1150, 1116, 725  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 288.1832; found 189.1831.



**2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (60).** To a solution of dibromide **52** (1.00 g, 2.52 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (15 ml) was added piperonylamine (0.65 ml, 5.04 mmol, 2.0 equiv) followed by  $i\text{Pr}_2\text{NEt}$  (2.19 ml, 12.59 mmol, 5 equiv), and the mixture was heated to reflux and stirred for 2 days. Then it was cooled to RT and the mix-

ture was concentrated to about  $1/3$  of initial volume. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (40 ml) and NaOH (1 M in  $\text{H}_2\text{O}$ ; 30 ml). The phases were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml). The combined organic layers were washed with NaOH (1 M in  $\text{H}_2\text{O}$ ; 10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1  $\rightarrow$  34:66:1 gradient) to afford the pure title compound. Yield: 878 mg (2.72 mmol, 90%). Colorless crystalline solid.

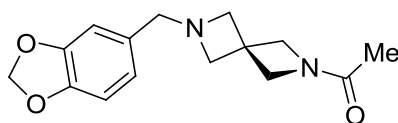
**TLC:**  $R_f = 0.33$  (EtOAc; UV, CAM); **Melting Point:** 129–130 °C;  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ): 7.69 (d,  $J=8.4$ , 2H), 7.34 (dd,  $J=0.6$ , 8.4, 2H), 6.71–6.68 (m, 2H), 6.61 (dd,  $J=1.7$ , 7.8, 1H), 5.91 (s, 2H), 3.81 (s, 4H), 3.37 (s, 2H), 3.09 (s, 4H), 2.44 (s, 3H);  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.7, 146.7, 144.1, 131.7, 131.3, 129.7, 128.3, 121.5, 108.8, 108.0, 100.9, 63.5, 63.0, 60.3, 33.2, 21.6$ ; **IR** (thin film): 2940, 2821, 1490, 1442, 1343, 1247, 1163, 1091, 1038, 925, 814, 679, 551  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$  ( $\text{M}^+$ ), 386.1295; found 386.1297.



**2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-methyl-2,6-diazaspiro[3.3]heptane (62).** A mixture of tosyl amide **60** (99 mg, 0.26 mmol, 1 equiv) and Mg powder (50 mg, 2.05 mmol, 8 equiv) in MeOH (5 ml) was sonicated for 60 min. Methanol was removed *in vacuo*, and to the solid residue was added  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (ca. 2.5 g), and the mixture was thoroughly stirred for 40 min. Then it was filtered, and the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml) and  $\text{Et}_3\text{N}$  (72  $\mu\text{l}$ , 0.51 mmol, 2 equiv), formaldehyde solution (ca. 35% in  $\text{H}_2\text{O}$ ; 109  $\mu\text{l}$ , ca. 1.28 mmol, ca. 5 equiv), and  $\text{NaBH}(\text{OAc})_3$  (136 mg, 0.64 mmol, 2.5 equiv) were sequentially added. The mixture was stirred at RT for 20 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated, and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification by FC ( $\text{SiO}_2$ ; EtOAc : MeOH :  $\text{Et}_3\text{N}$  50:5:1) afforded the pure title compound. Yield: 45 mg (0.18 mmol, 71% over 2 steps). Colorless oil.

**TLC:**  $R_f = 0.11$  (MeOH; UV, CAM);  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.81\text{--}6.60$  (m, 3H), 5.91 (s, 2H), 3.43 (s, 2H), 3.25 (s, 8H), 2.25 (s, 3H);  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.6, 146.5, 132.1, 121.5, 108.9, 108.0, 100.8, 66.4, 64.1, 63.4, 45.9, 34.4$ ; **IR** (thin film): 2936, 2823,

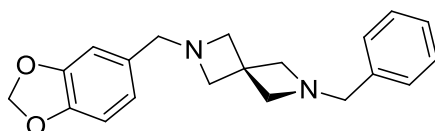
1503, 1490, 1442, 1247, 1181, 1102, 1038, 914, 744  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 246.1363; found 246.1362.



**1-(6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2,6-diazaspiro[3.3]heptan-2-yl)ethanone (63).**

A mixture of tosyl amide **60** (98 mg, 0.25 mmol, 1 equiv) and Mg powder (49 mg, 2.03 mmol, 8 equiv) in MeOH (5 ml) was sonicated for 40 min. Methanol was removed *in vacuo* and to the solid residue was added  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 2.5 g), and the mixture was thoroughly stirred for 40 min. Then it was filtered, and the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml), and to the colorless solution was added  $\text{Et}_3\text{N}$  (71  $\mu\text{l}$ , 0.51 mmol, 2 equiv) followed by dropwise addition of  $\text{Ac}_2\text{O}$  (29  $\mu\text{l}$ , 0.30 mmol, 1.2 equiv). The reaction mixture was stirred at RT for 1 h, then it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched by adding saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{EtOAc} : \text{MeOH} : \text{Et}_3\text{N}$  100:5:1  $\rightarrow$  100:10:1 gradient). Yield: 50 mg (0.18 mmol, 71% over 2 steps). Colorless oil.

**TLC:**  $R_f = 0.40$  (MeOH; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.81\text{--}6.62$  (m, 3H), 5.92 (s, 2H), 4.17 (s, 2H), 4.01 (s, 2H), 3.47 (s, 2H), 3.32 (q,  $J=8.3$ , 4H), 1.82 (s, 3H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.3$ , 147.7, 146.8, 131.0, 121.6, 108.9, 108.1, 100.9, 63.7, 63.0, 60.7, 57.5, 33.0, 18.7; **IR** (thin film): 2941, 2872, 2831, 1630, 1490, 1442, 1247, 1037, 925, 812  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ), 274.1312; found 274.1313.

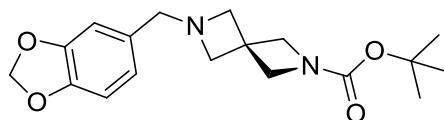


**2-(6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-benzyl-2,6-diazaspiro[3.3]heptane (64).** A mixture of tosyl amide **60** (99 mg, 0.26 mmol, 1 equiv) and Mg powder (50 mg, 2.05 mmol, 8 equiv) in MeOH (5 ml) was sonicated for 30 min. Methanol was removed *in vacuo* and to the solid residue was added  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 5 g), and the mixture was thoroughly stirred for 40 min. Then it was filtered, and the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml), benzaldehyde



(34  $\mu$ l, 0.33 mmol, 1.3 equiv) and  $\text{NaBH}(\text{OAc})_3$  (136 mg, 0.64 mmol, 2.5 equiv) were sequentially added, and the mixture was stirred at RT for 19 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated, and the aqueous phase extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc : MeOH :  $\text{Et}_3\text{N}$  33:66:5:1  $\rightarrow$  0:100:5:1 gradient) to give the pure title compound. Yield: 51 mg (0.16 mmol, 62% over 2 steps). Colorless oil.

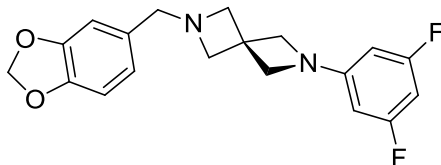
**TLC:**  $R_f$  = 0.24 (EtOAc : MeOH 1:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.41–7.14 (m, 5H), 6.83–6.61 (m, 3H), 5.92 (s, 2H), 3.55 (s, 2H), 3.44 (s, 2H), 3.31 (s, 4H), 3.28 (s, 4H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 147.4, 146.4, 137.9, 131.8, 128.3, 128.2, 126.9, 121.4, 108.8, 107.9, 100.8, 64.5, 64.3, 63.7, 63.4, 34.7; **IR** (thin film): 2899, 2813, 1502, 1490, 1442, 1364, 1248, 1039, 927, 811  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 322.1676; found 322.1674.



**tert-Butyl 6-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (65).** A mixture of tosyl amide **60** (100 mg, 0.26 mmol, 1 equiv) and Mg powder (50 mg, 2.07 mmol, 8 equiv) in MeOH (5 ml) was sonicated for 40 min. Methanol was removed *in vacuo* and to the solid residue was added  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 5 g), and the mixture was thoroughly stirred for 40 min. Then it was filtered, and the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was dissolved in MeOH (4 ml),  $\text{Boc}_2\text{O}$  (62 mg, 0.29 mmol, 1.1 equiv) was added, and the mixture was stirred at RT for 1 h. Then was added  $\text{Et}_3\text{N}$  (36  $\mu$ l, 0.26 mmol, 1 equiv) in order to accelerate the reaction. The mixture was stirred at RT for another 30 min, then concentrated *in vacuo* and partitioned between EtOAc (25 ml) and saturated aqueous  $\text{NaHCO}_3$  (20 ml). The phases were separated, and the aqueous layer extracted with EtOAc (25 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to give a colorless oil. The pure product was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  34:66:1). Yield: 57 mg (0.17 mmol, 66% over 2 steps). Colorless oil.

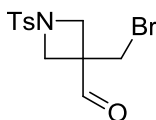
**TLC:**  $R_f$  = 0.46 (EtOAc : MeOH 1:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.85–6.57 (m, 3H), 5.92 (s, 2H), 3.97 (s, 4H), 3.44 (s, 2H), 3.28 (s, 4H), 1.42 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.9, 147.5, 146.5, 131.5, 121.4, 108.8, 108.0, 100.8, 79.4, 64.1, 63.3, 59.4 (br), 33.4,

28.4; **IR** (thin film): 2937, 2874, 2814, 1701, 1490, 1441, 1404, 1247, 1152, 1113, 1038, 914, 745  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_4$  ( $[\text{M}+\text{H}]^+$ ), 333.1809; found 333.1809.



**2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-(3,5-difluorophenyl)-2,6-diazaspiro[3.3]heptane (66).** A mixture of tosyl amide **60** (99 mg, 0.26 mmol, 1 equiv) and Mg powder (50 mg, 2.05 mmol, 8 equiv) in MeOH (5 ml) was sonicated for 40 min. Methanol was removed *in vacuo* and to the solid residue was added  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 5 g), and the mixture was thoroughly stirred for 40 min. Then it was filtered, and the filtrate dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue (slightly yellowish oil) was dissolved in toluene (3 ml). 1-Bromo-3,5-difluorobenzene (33  $\mu\text{l}$ , 0.28 mmol, 1.1 equiv), ( $\pm$ )-BINAP (9.6 mg, 0.015 mmol, 0.06 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (4.7 mg, 0.005 mmol, 0.02 equiv), and  $\text{KO}t\text{Bu}$  (58 mg, 0.51 mmol, 2 equiv) were sequentially added, and the mixture was heated to 110  $^\circ\text{C}$  and stirred for 20 h. Then it was cooled to RT, filtered over celite, and thoroughly washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  80:20:1) to give the pure title compound. Yield: 61 mg (0.18 mmol, 69% over 2 steps). Colorless solid.

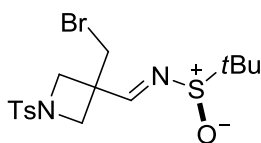
**TLC:**  $R_f = 0.23$  (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 47-48  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.82\text{--}6.67$  (m, 3H), 6.14 (tt,  $J=2.3, 9.3$ , 1H), 5.94 (s, 2H), 5.90–5.84 (m, 2H), 3.92 (s, 4H), 3.50 (s, 2H), 3.37 (s, 4H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.0$  (dd,  $J_{\text{C,F}}=14.2, 244.9$ ), 153.1 (t,  $J_{\text{C,F}}=14.2$ ), 147.7, 146.8, 131.5, 121.6, 108.9, 108.1, 100.9, 94.3 (d,  $J_{\text{C,F}}=27.1$ ), 92.6 (t,  $J_{\text{C,F}}=27.1$ ), 64.1, 63.3, 61.9, 34.5;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -109.70$  (t,  $J=9.3$ ); **IR** (thin film): 2904, 2840, 1631, 1585, 1490, 1441, 1246, 1112, 1039, 914, 811, 744  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 344.1331; found 344.1333.



**3-(Bromomethyl)-1-tosylazetidene-3-carbaldehyde (67).** A solution of oxalyl chloride (3.60 ml, 41.3 mmol, 2.3 equiv) in  $\text{CH}_2\text{Cl}_2$  (160 ml) was cooled to  $-78$   $^\circ\text{C}$ , and DMSO (5.87 ml, 82.6 mmol, 4.6 equiv) was dropwise added over 15 min. The solution was stirred at  $-78$   $^\circ\text{C}$  for

15 min, then was added a solution of alcohol **51** (6.00 g, 18.0 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (23 ml) over a period of 20 min. The mixture was stirred at -78 °C for 1 h, then was added Et<sub>3</sub>N (13.01 ml, 93.3 mmol, 5.2 equiv) over 10 min. Stirring was continued at -78 °C for another 30 min, and then it was warmed to RT over approximately 30 min. At this point, it was poured into saturated aqueous NH<sub>4</sub>Cl (300 ml), and CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added. The phases were separated, and the organic phase was washed with saturated aqueous NaCl (50 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc : CH<sub>2</sub>Cl<sub>2</sub> = 1:1:2) to afford the pure aldehyde. Yield: 5.44 g (16.4 mmol, 91%). Colorless solid.

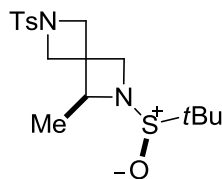
**TLC:**  $R_f$  = 0.47 (EtOAc : hexanes 1:1; UV, CAM); **Melting Point:** 89-90 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.56 (s, 1H), 7.74 (d,  $J$ =8.1, 2H), 7.40 (d,  $J$ =8.1, 2H), 3.93 (d,  $J$ =8.9, 2H), 3.73 (d,  $J$ =8.9, 2H), 3.60 (s, 2H), 2.48 (s, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 196.8, 144.6, 130.6, 129.8, 128.2, 54.4, 46.4, 31.5, 21.7; **IR** (thin film): 2951, 2876, 1730, 1246, 1164, 1089, 1040, 739, 674, 550 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>3</sub>S ([M-Br]<sup>+</sup>), 252.0689; found 252.0689.



**(E)-N-((3-(Bromomethyl)-1-tosylazetid-3-yl)methylene)-2-methylpropane-2-sulfinamide (68).** To a solution of aldehyde **67** (0.83 g, 2.50 mmol, 1.0 equiv) in THF (20 ml) was added Ti(OEt)<sub>4</sub> (technical grade; 2.07 ml) followed by (*R*)-*tert*-butylsulfinyl amine (0.32 g, 2.62 mmol, 1.05 equiv). The mixture was stirred at RT for 22 h. At this point, the mixture was poured into saturated aqueous NaCl (50 ml) and EtOAc (50 ml). The mixture was filtered through celite and the filter cake thoroughly washed with EtOAc (50 ml). The phases were separated, and the organic phase was washed with saturated aqueous NaCl (20 ml). The aqueous phase was extracted with EtOAc (15 ml), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford almost pure title compound. Yield: 0.86 g (1.97 mmol, 79%). Colorless solid. An analytical sample can be obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc : CH<sub>2</sub>Cl<sub>2</sub> 3:2:2).

**TLC:**  $R_f$  = 0.81 (EtOAc; UV, CAM); **Melting Point:** 119-120 °C; **Optical rotation:**  $[\alpha]_D^{25}$  -102.4 (c = 0.99, CHCl<sub>3</sub>); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.87 (s, 1H), 7.73 (d,  $J$ =8.2, 2H), 7.38 (d,  $J$ =8.2, 2H), 3.91 (t,  $J$ =8.5, 2H), 3.78 (t,  $J$ =8.5, 2H), 3.68 (dd,  $J$ =10.5, 22.0, 2H), 2.47 (s, 3H), 1.13 (s, 9H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 165.8, 144.5, 130.8, 129.9, 128.3, 57.6, 56.8, 56.7, 42.9, 34.7, 22.5, 21.8; **IR** (thin film): 2962, 2072, 1622, 1455, 1348, 1165, 1088, 914, 742,

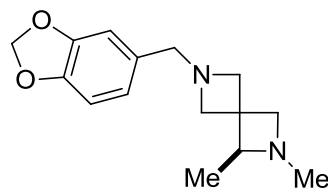
671, 610, 550  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{O}_3\text{S}_2$  ( $[\text{M}-\text{C}_4\text{H}_8]^+$ ), 377.9702; found 377.9706.



**(1S)-2-(tert-Butylsulfinyl)-1-methyl-6-tosyl-2,6-diazaspiro[3.3]heptane (69).** To a solution of sulfinyl imine **68** (0.51 g, 1.17 mmol, 1.0 equiv) in THF (20 ml), cooled to  $-78\text{ }^\circ\text{C}$ , was dropwise added over a period of 10 min MeLi (1.6 M in  $\text{Et}_2\text{O}$ ; 1.53 ml, 2.45 mmol, 2.1 equiv). The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 10 min, then it was quenched by rapid addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (20 ml). The mixture was diluted with EtOAc (20 ml) and  $\text{H}_2\text{O}$  (10 ml), and the phases were separated. The organic phase was washed with saturated aqueous NaCl (20 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to give an almost pure mixture of diastereomers. The residue was then purified by FC ( $\text{SiO}_2$ ;  $\text{Et}_2\text{O} : \text{CH}_2\text{Cl}_2 : \text{MeOH}$  2:1:0  $\rightarrow$  1:1:0  $\rightarrow$  50:50:1  $\rightarrow$  20:20:1 gradient) to afford *N*-((*R*)-1-(3-(bromomethyl)-1-tosylazetid-3-yl)ethyl)-2-methylpropane-2-sulfinamide (240 mg, 0.53 mmol, 45% yield) and *N*-((*S*)-1-(3-(bromomethyl)-1-tosylazetid-3-yl)ethyl)-2-methylpropane-2-sulfinamide (253 mg, 0.56 mmol, 48% yield). The relative and absolute stereochemistry was determined by X-ray crystallographic analysis of the first eluting compound. Ring-closing step: To a solution of *N*-((*S*)-1-(3-(bromomethyl)-1-tosylazetid-3-yl)ethyl)-2-methylpropane-2-sulfinamide (151 mg, 0.33 mmol, 1.0 equiv) in THF (10 ml), cooled to  $0\text{ }^\circ\text{C}$ , was added in one portion KO $t$ Bu (78 mg, 0.70 mmol, 1.4 equiv), and the mixture was held at  $0\text{ }^\circ\text{C}$  for 20 min. At this point the reaction was quenched by addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (10 ml). EtOAc (25 ml) and  $\text{H}_2\text{O}$  (10 ml) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (10 ml), and the combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1  $\rightarrow$  0:1 gradient) to afford the pure title compound. Yield: 104 mg (0.28 mmol, 84%; 40% over the 2 steps). Colorless solid.

**TLC:**  $R_f = 0.64$  (EtOAc : MeOH 1:1; UV, CAM); **Melting Point:**  $122\text{--}123\text{ }^\circ\text{C}$ ; **Optical rotation:**  $[\alpha]_{\text{D}}^{25} -100.3$  ( $c = 0.47$ ,  $\text{CHCl}_3$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.70$  (d,  $J=8.1$ , 2H), 7.36 (d,  $J=8.1$ , 2H), 4.08 (q,  $J=6.8$ , 1H), 4.02 (d,  $J=9.2$ , 1H), 3.93–3.74 (m, 3H), 3.62 (d,  $J=9.1$ , 1H), 3.46 (d,  $J=9.1$ , 1H), 2.45 (s, 3H), 1.23 (d,  $J=6.8$ , 3H), 1.07 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.2$ , 130.9, 129.7, 128.3, 64.0, 60.6, 56.6, 56.0, 55.8, 38.3, 23.2, 21.7, 16.5; **IR** (thin

film): 2964, 2869, 1597, 1454, 1345, 1165, 1063, 997, 685, 603, 551  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3\text{S}_2\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 393.1277; found 393.1276.

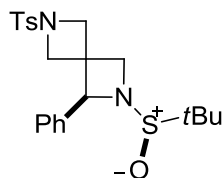


**(S)-6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1,2-dimethyl-2,6-diazaspiro[3.3]heptane**

**(70)**. Tosyl amide **69** (102 mg, 0.28 mmol, 1.0 equiv) was suspended in MeOH (5 ml), Mg powder (80 mg, 3.30 mmol, 12 equiv) was added, and the mixture was sonicated at RT for 30 min. Then it was concentrated *in vacuo*,  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 5 g) were added and the mixture was vigorously stirred for 30 min. Then it was filtered and the filtrate was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue (colorless solidifying oil) was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 ml), piperonal (54 mg, 0.36 mmol, 1.3 equiv) was added followed by addition of  $\text{NaBH}(\text{OAc})_3$  (146 mg, 0.69 mmol, 2.5 equiv), and the mixture was stirred at RT for 14 h. At that point it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched by addition of saturated aqueous  $\text{NaHCO}_3$  (15 ml). The phases were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{EtOAc} : \text{MeOH} : \text{Et}_3\text{N}$  98:1:1) to afford the pure piperonyl amine (68 mg, 0.19 mmol, 71% yield over 2 steps) ( $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.81–6.59 (m, 3H), 5.91 (d,  $J=0.4$ , 2H), 4.30–4.09 (m, 2H), 3.61 (d,  $J=8.7$ , 1H), 3.42 (d,  $J=1.8$ , 2H), 3.34 (d,  $J=7.8$ , 1H), 3.24 (t,  $J=8.2$ , 2H), 3.08 (d,  $J=7.8$ , 1H), 1.42 (d,  $J=6.7$ , 3H), 1.11 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 147.6, 146.6, 131.7, 121.5, 108.9, 108.0, 100.8, 65.0, 64.8, 63.3, 59.6, 56.7, 56.5, 39.9, 23.3, 16.7). Cleavage of the *tert*-butylsulfinamide: To a solution of the sulfinamide (50 mg, 0.14 mmol, 1.0 equiv) in THF (2.5 ml) was added HCl (2 M in  $\text{Et}_2\text{O}$ ; 0.43 ml, 0.86 mmol, 6 equiv), and the mixture was stirred at RT for 30 min. The formed suspension was concentrated *in vacuo* and the remaining white solid was suspended in  $\text{CH}_2\text{Cl}_2$  (2.5 ml) and  $\text{Et}_3\text{N}$  (40  $\mu\text{l}$ , 0.29 mmol, 2 equiv) was added, upon which the suspension turned into a yellowish solution. Then was added aqueous formaldehyde (*ca.* 35% in  $\text{H}_2\text{O}$ ; 61  $\mu\text{l}$ , *ca.* 0.71 mmol, *ca.* 5 equiv) and  $\text{NaBH}(\text{OAc})_3$  (76 mg, 0.36 mmol, 2.5 equiv). The reaction mixture was stirred at RT for 14 h, then diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was

purified by FC (SiO<sub>2</sub>; EtOAc : MeOH : Et<sub>3</sub>N 90:10:1 → 85:15:1 gradient) to give the pure title compound. Yield: 22 mg (0.09 mmol, 59% over 2 steps; 42% over the 4 steps). Colorless oil.

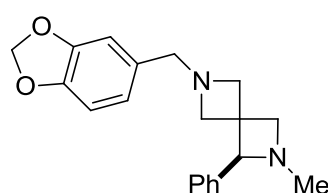
**TLC:**  $R_f = 0.16$  (MeOH; UV, CAM); **Optical rotation:**  $[\alpha]_{D^{25}} -4.4$  ( $c = 0.64$ , CHCl<sub>3</sub>); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 6.80\text{--}6.65$  (m, 3H), 5.92 (s, 2H), 3.59 (d,  $J=7.7$ , 1H), 3.49–3.37 (m, 2H), 3.35 (d,  $J=7.7$ , 1H), 3.24 (d,  $J=7.7$ , 1H), 3.17 (d,  $J=7.8$ , 1H), 2.97 (d,  $J=7.8$ , 1H), 2.84 (d,  $J=7.3$ , 2H), 2.25 (s, 3H), 1.15 (d,  $J=6.3$ , 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 147.6$ , 146.5, 132.2, 121.4, 108.9, 108.0, 100.8, 69.0, 64.7, 63.5, 62.2, 60.0, 43.7, 38.6, 16.0; **IR** (thin film): 2932, 2822, 1503, 1490, 1442, 1356, 1247, 1039, 914, 811, 744 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>), 260.1520; found 260.1523.



**(1S)-2-(*tert*-Butylsulfinyl)-1-phenyl-6-tosyl-2,6-diazaspiro[3.3]heptane (71).** To a solution of sulfinyl imine **68** (500 mg, 1.15 mmol, 1.0 equiv) in THF (20 ml), cooled to  $-78$  °C, was added dropwise over 3 min a solution of PhLi (2 M in Bu<sub>2</sub>O; 0.86 ml, 1.72 mmol, 1.5 equiv), and the reaction mixture was held at  $-78$  °C for 15 min. It was quenched by rapid addition of saturated aqueous NH<sub>4</sub>Cl (20 ml). EtOAc (30 ml) and H<sub>2</sub>O (15 ml) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (20 ml), and the combined organic layers were washed with saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue (colorless solid; mixture of diastereomers, d.r. 73:27) was directly used for the next step without further purifications. Ring-closing step: To a solution of the crude addition product (590 mg, 1.149 mmol, 1.0 equiv) in THF (20 ml), cooled to 0 °C, was added KO<sup>*t*</sup>Bu (155 mg, 1.38 mmol, 1.2 equiv) in one portion, when the mixture turned yellowish and turned over time into a yellowish suspension. The mixture was stirred at 0 °C for 8 min, then it was quenched by addition of saturated aqueous NH<sub>4</sub>Cl (20 ml). EtOAc (30 ml) and H<sub>2</sub>O (10 ml) were added, and the phases were separated. The organic phase was washed with saturated aqueous NaCl (20 ml), and the combined aqueous layers were extracted with EtOAc (20 ml). The unified organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford a colorless solid, which is essentially a clean mixture of diastereomers (499 mg, 1.15 mmol, quant.). The diastereomers can be separated by recrystallization from Et<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> (1:1; ~50 ml). Filtration of the initially insoluble material afforded the pure title compound (major diastereomer; 173 mg). More product is obtained after multiple recrystallization steps. The rel-

ative and absolute stereochemistry was determined by X-ray crystallographic analysis of the major diastereomer. Yield: 362 mg (0.84 mmol, 73% over 2 steps). Colorless solid.

**TLC:**  $R_f = 0.72$  (EtOAc; UV, CAM); **Melting Point:** 239–240 °C; **Optical rotation:**  $[\alpha]_D^{25} -174.4$  ( $c = 1.00$ ,  $\text{CHCl}_3$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.51$  (d,  $J=7.8$ , 2H), 7.35–7.16 (m, 5H), 6.99 (d,  $J=6.7$ , 2H), 4.81 (s, 1H), 4.34 (d,  $J=8.9$ , 1H), 3.87 (d,  $J=8.9$ , 1H), 3.65 (dd,  $J=8.8$ , 18.3, 2H), 3.27 (dd,  $J=8.8$ , 18.3, 2H), 2.47 (s, 3H), 1.17 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 143.9$ , 136.2, 130.3, 129.6, 128.6, 128.2, 128.2, 126.3, 70.6, 58.8, 57.4, 57.2, 50.7, 39.6, 23.5, 21.7; **IR** (thin film): 2938, 2872, 1598, 1450, 1342, 1162, 1136, 1066, 978, 811, 665, 550  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{S}_2\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 455.1434; found 455.1430.



**(S)-6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-methyl-1-phenyl-2,6-diazaspiro[3.3]heptane (72).** Tosyl amide **71** (200 mg, 0.46 mmol, 1.0 equiv) was suspended in MeOH (10 ml), Mg powder (135 mg, 5.55 mmol, 12 equiv) was added, and the mixture was sonicated at RT for 60 min, when it was concentrated *in vacuo*.  $\text{Et}_2\text{O}$  (25 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (*ca.* 5 g) were added and the mixture was vigorously stirred for 30 min. Then it was filtered and the filtrate was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue (colorless solidifying oil) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 ml), piperonal (90 mg, 0.60 mmol, 1.3 equiv) was added followed by addition of  $\text{NaBH}(\text{OAc})_3$  (245 mg, 1.16 mmol, 2.5 equiv), and the mixture was stirred at RT for 2 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched by addition of saturated aqueous  $\text{NaHCO}_3$  (15 ml). The phases were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc : MeOH :  $\text{Et}_3\text{N}$  98:1:1  $\rightarrow$  94:5:1 gradient) to afford the pure title compound (126 mg, 0.31 mmol, 66% yield over 2 steps) ( $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.46$ –7.27 (m, 5H), 6.65 (dd,  $J=4.6$ , 9.3, 2H), 6.56 (dd,  $J=1.7$ , 7.9, 1H), 5.89 (s, 2H), 4.97 (s, 1H), 4.46 (d,  $J=8.3$ , 1H), 3.43 (t,  $J=8.6$ , 2H), 3.36–3.21 (m, 2H), 3.16 (d,  $J=7.8$ , 1H), 3.07 (d,  $J=8.0$ , 1H), 2.63 (d,  $J=7.8$ , 1H), 1.19 (s, 9H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.6$ , 146.5, 138.0, 131.7, 128.5, 128.0, 127.0, 121.3, 108.7, 107.9, 100.8, 71.3, 62.9, 62.5, 61.1, 57.0, 51.8, 41.7, 23.5). Cleavage of the *tert*-butylsulfonamide: To a solution of the sulfonamide (64 mg, 0.16 mmol, 1.0 equiv) in THF (2.5 ml) was added HCl (2 M in  $\text{Et}_2\text{O}$ ; 0.50 ml, 1.00 mmol, 6.5 equiv), and the mixture was stirred at RT for 1 h. Then the suspension was concentrated *in vac-*

uo and the remaining pale white solid was suspended in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) and Et<sub>3</sub>N (44 μl, 0.31 mmol, 2.0 equiv) was added, upon which the suspension turned into a yellowish solution. Then was added aqueous formaldehyde (ca. 35% in H<sub>2</sub>O; 67 μl, ca. 0.78 mmol, ca. 5 equiv) and NaBH(OAc)<sub>3</sub> (82 mg, 0.39 mmol, 2.5 equiv). The reaction mixture was stirred at RT for 1 h, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and quenched with saturated aqueous NaHCO<sub>3</sub> (15 ml). The phases were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; EtOAc : MeOH : Et<sub>3</sub>N 98:1:1 → 94:5:1 gradient) to give the pure title compound. Yield: 35 mg (0.11 mmol, 70% over 2 steps; 46% over the 4 steps). Colorless oil.

**TLC:**  $R_f = 0.35$  (EtOAc : MeOH 1:1; UV, CAM); **Optical rotation:**  $[\alpha]_D^{25} -38.0$  ( $c = 1.10$ , CHCl<sub>3</sub>); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.46-7.27$  (m, 5H), 6.75–6.64 (m, 2H), 6.58 (dd,  $J=1.6$ , 7.8, 1H), 5.90 (s, 2H), 3.78 (s, 1H), 3.73 (d,  $J=7.0$ , 1H), 3.36 (d,  $J=7.9$ , 1H), 3.29 (s, 2H), 3.24 (d,  $J=7.9$ , 1H), 3.06 (d,  $J=7.8$ , 1H), 3.02 (d,  $J=7.0$ , 1H), 2.73 (d,  $J=7.8$ , 1H), 2.32 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 147.5, 146.5, 139.3, 131.9, 128.4, 127.4, 127.0, 121.4, 108.8, 107.9, 100.8, 77.3, 77.2, 77.0, 77.0, 76.7, 64.4, 62.9, 61.8, 60.6, 44.2, 40.5$ ; **IR** (thin film): 2933, 2821, 1502, 1490, 1442, 1376, 1246, 1039, 914, 811, 744, 699 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>), 322.1676; found 322.1680.



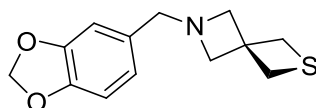
**6-Tosyl-2-thia-6-azaspiro[3.3]heptane (75).** Dibromide **52** (8.00 g, 20.14 mmol, 1 equiv) was dissolved in a mixture of CH<sub>3</sub>CN (200 ml) and H<sub>2</sub>O (20 ml). To the resulting colorless solution was added Na<sub>2</sub>S (~ trihydrate; 5.32 g, ca. 40.30 mmol, ca. 2 equiv) and the reaction mixture was stirred at 50 °C for 3 h, then it was cooled to RT and concentrated to about 1/3 of the initial volume. EtOAc (200 ml) and H<sub>2</sub>O (100 ml) were added, and the phases were separated. The organic phase was washed with saturated aqueous NaCl (50 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1) to give the title compound. Yield: 4.68 g (17.37 mmol, 86%). Colorless solid.

**TLC:**  $R_f = 0.55$  (hexanes : EtOAc 2:1; UV); **Melting Point:** 117–118 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.70$  (d,  $J=8.2$ , 2H), 7.36 (d,  $J=8.2$ , 2H), 3.78 (s, 4H), 3.13 (s, 4H), 2.45 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 144.3, 131.6, 129.8, 128.3, 77.3, 77.0, 76.7, 63.3, 41.9, 36.3, 21.6$ ; **IR** (thin film): 2933, 1448, 1338, 1220, 1150, 1086, 1008, 773, 691 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>2</sub>S ([M–SH]<sup>+</sup>), 236.0740; found 236.0743.



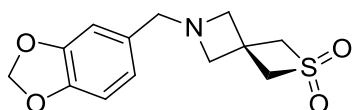
This compound can be converted to the free amine and subsequently to its ammonium oxalate salt **117** according to the following procedures. Tosyl amide **75** (500 mg, 1.86 mmol, 1.0 equiv) was dissolved in MeOH (25 ml). To the resulting colorless solution was added Mg powder (361 mg, 14.85 mmol, 8.0 equiv), and the reaction mixture was sonicated for 40 min. At this point the reaction mixture was concentrated *in vacuo*. The residue was suspended in Et<sub>2</sub>O (50 ml) and Na<sub>2</sub>SO<sub>4</sub> · 10 H<sub>2</sub>O (10 spatulas) was added, and the suspension was vigorously stirred at RT for 50 min. Then it was filtered, and the filtrate was dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered again. To the filtrate was added a solution of oxalic acid (84 mg, 0.93 mmol, 0.5 equiv) in EtOH (0.35 ml), upon which immediately a colorless precipitate formed. This solid was collected by filtration and subsequently dried under high vacuum to afford the pure oxalate salt. Yield: 235 mg (0.73 mmol, 79%). Colorless solid.

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ = 4.22 (d, *J*=1.7, 4H), 3.47 (d, *J*=1.7, 4H); <sup>13</sup>C NMR (101 MHz, D<sub>2</sub>O): δ 173.4, 58.2, 44.7, 35.5.



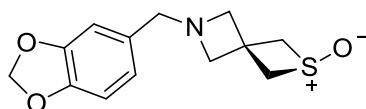
**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-thia-6-azaspiro[3.3]heptane (76)**. Oxalate salt **117** (60 mg, 0.19 mmol, 0.5 equiv) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (5 ml). To the resulting colorless suspension was added Et<sub>3</sub>N (79 μl, 0.56 mmol, 1.5 equiv), piperonal (73 mg, 0.49 mmol, 1.3 equiv), and NaBH(OAc)<sub>3</sub> (209 mg, 0.94 mmol, 2.5 equiv), and the reaction mixture was stirred at RT for 3 h. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and quenched with saturated aqueous NaHCO<sub>3</sub> (40 ml). The phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc : Et<sub>3</sub>N 17:83:1) to afford the pure title compound. Yield: 83 mg (0.33 mmol, 70% over 2 steps). Colorless oil.

**TLC**: *R<sub>f</sub>* = 0.11 (EtOAc; UV, CAM); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 6.80–6.61 (m, 3H), 5.92 (s, 2H), 3.42 (s, 2H), 3.30 (s, 4H), 3.22 (s, 4H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 147.4, 146.4, 131.5, 121.4, 108.9, 108.7, 107.9, 100.8, 67.5, 63.1, 43.5, 36.9; **IR** (thin film): 2929, 2814, 1637, 1501, 1489, 1441, 1245, 1175, 1038, 925, 811 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>13</sub>H<sub>15</sub>NO<sub>2</sub>S (M<sup>+</sup>), 249.0818; found 249.0819.



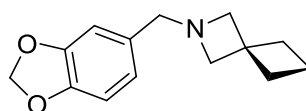
**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2,2-dioxo-2-thia-6-azaspiro[3.3]heptane (77).** To a solution of sulfide **76** (24 mg, 0.097 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 ml) was added at RT *N*-methyl morpholine *N*-oxide (28 mg, 0.24 mmol, 2.5 equiv), followed by potassium osmate dihydrate (1.8 mg, 5 μmol, 0.05 equiv), and the mixture was stirred at RT for 7 h. At this point it was concentrated *in vacuo* and the residue purified by FC (SiO<sub>2</sub>; EtOAc : hexanes : Et<sub>3</sub>N 75:25:1) to afford the pure product as a slowly solidifying oil. Yield: 26.9 mg (0.096 mmol, 99%). Colorless solid.

**TLC:** *R<sub>f</sub>* = 0.45 (EtOAc; UV, CAM); **Melting Point:** 97-98 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.83–6.59 (m, 3H), 5.94 (s, 2H), 4.22 (s, 4H), 3.50 (s, 2H), 3.38 (s, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.8, 146.9, 130.8, 121.6, 108.9, 108.1, 101.0, 73.9, 64.6, 62.8, 24.9; **IR** (thin film): 2954, 2906, 2826, 1502, 1490, 1442, 1320, 1248, 1193, 1146, 1114, 1036, 924, 811 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>13</sub>H<sub>15</sub>NO<sub>4</sub>S (M<sup>+</sup>), 281.0717; found 281.0718.



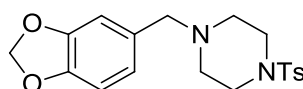
**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-oxo-2-thia-6-azaspiro[3.3]heptane (78).** To a solution of sulfide **76** (61 mg, 0.25 mmol, 1 equiv) in AcOH (2 ml) was added at RT H<sub>2</sub>O<sub>2</sub> (*ca.* 30% in H<sub>2</sub>O; 27 μl, *ca.* 0.27 mmol, *ca.* 1.1 equiv), and the mixture was stirred at RT for 14 h. The mixture was concentrated *in vacuo* and the residue partitioned between saturated aqueous NaHCO<sub>3</sub> (40 ml) and CH<sub>2</sub>Cl<sub>2</sub> (40 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; EtOAc : MeOH : Et<sub>3</sub>N 90:10:1) to furnish the pure title compound. Yield: 44 mg (0.17 mmol, 68%). Colorless solid.

**TLC:** *R<sub>f</sub>* = 0.1 (EtOAc : MeOH 1:1; UV, CAM); **Melting Point:** 95-96 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.78–6.60 (m, 3H), 5.92 (s, 2H), 3.80 (dq, *J*=2.9, 6.1, 2H), 3.44 (s, 2H), 3.29 (dq, *J*=2.9, 6.1, 2H), 3.20 (d, *J*=7.2, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.5, 146.6, 130.9, 121.4, 108.8, 108.0, 100.8, 65.3, 62.9, 62.3, 62.0, 29.8; **IR** (thin film): 2900, 2825, 1503, 1490, 1442, 1249, 1223, 1102, 1063, 1036, 914, 774 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>S (M<sup>+</sup>), 265.0768; found 265.0768.



**2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-azaspiro[3.3]heptane (81).** To a solution of bis(tosylate) **80**<sup>347</sup> (1.00 g, 2.36 mmol, 1.0 equiv) in CH<sub>3</sub>CN (20 ml) was added *i*Pr<sub>2</sub>NEt (1.23 ml, 7.07 mmol, 3.0 equiv) and piperonyl amine (0.61 ml, 4.71 mmol, 2.0 equiv), and the mixture was heated to 110 °C and stirred for 2 days. The mixture was cooled to RT and concentrated to about 1/4 of the initial volume. Then it was partitioned between EtOAc (40 ml) and saturated aqueous NaHCO<sub>3</sub> (40 ml). The phases were separated, and the aqueous phase extracted with EtOAc (30 ml). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc : Et<sub>3</sub>N 50:50:1). Yield: 377 mg (1.63 mmol, 69%). Colorless oil.

**TLC:** *R<sub>f</sub>* = 0.5 (EtOAc : MeOH 1:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.86–6.62 (m, 3H), 5.90 (s, 2H), 3.43 (s, 2H), 3.15 (s, 4H), 2.08 (t, *J*=7.5, 4H), 1.77 (quint, *J*=7.5, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.5, 146.3, 132.3, 121.5, 108.9, 107.9, 100.7, 66.6, 63.6, 38.9, 33.0, 16.7; **IR** (thin film): 2934, 2804, 1503, 1489, 1441, 1375, 1274, 1244, 1040, 938, 811 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> (M<sup>+</sup>), 231.1254; found 231.1254.

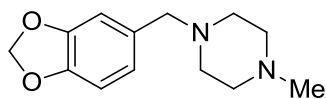


**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-tosylpiperazine (83).** To a solution of piperonyl piperazine (200 mg, 0.88 mmol, 1 equiv) in THF (6 ml) was added Et<sub>3</sub>N (0.25 ml, 1.76 mmol, 2 equiv) followed by TsCl (190 mg, 0.97 mmol, 1.1 equiv). The suspension was stirred at RT for 4.5 h, then it was diluted with EtOAc (20 ml) and H<sub>2</sub>O (15 ml). The phases were separated, and the organic phase washed with saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 2:1 to 1:1 gradient) to afford the pure title compound. Yield: 326 mg (0.87 mmol, 99%). Colorless solid.

**TLC:** *R<sub>f</sub>* = 0.34 (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 146–147 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.61 (d, *J*=8.2, 2H), 7.31 (d, *J*=8.2, 2H), 6.77–6.57 (m, 3H), 5.89 (s, 2H), 3.36 (s, 2H), 2.99 (br s, 4H), 2.48 (t, *J*=6.0, 4H), 2.42 (s, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.4, 146.5, 143.4, 132.1, 131.2, 129.4, 127.7, 122.0, 109.1, 107.7, 100.8, 62.2, 51.9, 46.1, 21.5;

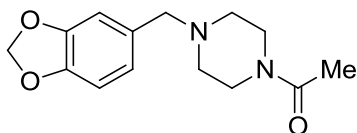
<sup>347</sup> J. Foos, F. Steel, S. Q. A. Rizvi, G. Fraenkel, *J. Org. Chem.* **1979**, *44*, 2522–2529.

**IR** (thin film): 2892, 2817, 2777, 1490, 1442, 1349, 1249, 1167, 1039, 944, 734  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$  ( $\text{M}^+$ ), 374.1295; found 374.1291.



**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methylpiperazine (84)**. To a solution of piperonyl piperazine (200 mg, 0.88 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (6 ml) was added  $\text{Et}_3\text{N}$  (0.25 ml, 1.76 mmol, 2 equiv) followed by  $\text{CH}_2\text{O}$  (~35% in  $\text{H}_2\text{O}$ ; 0.35 ml, *ca.* 4.40 mmol, *ca.* 5 equiv) and  $\text{NaBH}(\text{OAc})_3$  (589 mg, 2.64 mmol, 3 equiv). The resulting turbid mixture was stirred at RT for 16.5 h, then it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and saturated aqueous  $\text{Na}_2\text{CO}_3$  (15 ml). The phases were separated, and the organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{EtOAc} : \text{MeOH} : \text{Et}_3\text{N}$  100:5:1) to afford the pure title compound. Yield: 189 mg (0.81 mmol, 92%). Colorless oil.

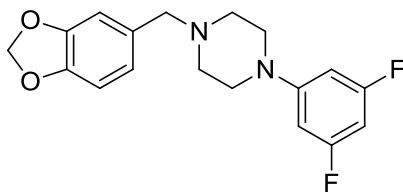
**TLC**:  $R_f = 0.11$  ( $\text{EtOAc} : \text{MeOH}$  10:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.82$  (s, 1H), 6.71 (d,  $J=0.9$ , 2H), 5.89 (s, 2H), 3.38 (s, 2H), 2.42 (br s, 8H), 2.25 (s, 3H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.5$ , 146.4, 132.1, 122.1, 109.4, 107.7, 100.7, 62.6, 55.1, 52.9, 46.0; **IR** (thin film): 2937, 2879, 2796, 1502, 1457, 1442, 1281, 1240, 1164, 1040, 1012, 934, 811  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 234.1363; found 234.1362.



**1-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperazin-1-yl)ethanone (85)**. To a solution of piperonyl piperazine (200 mg, 0.88 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (6 ml) was added  $\text{Et}_3\text{N}$  (0.25 ml, 1.76 mmol, 2 equiv) followed by dropwise addition of  $\text{Ac}_2\text{O}$  (0.17 ml, 1.76 mmol, 2 equiv). The solution was stirred at RT for 13 h, then it was diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and saturated aqueous  $\text{Na}_2\text{CO}_3$  (15 ml). The phases were separated, and the organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{EtOAc} : \text{MeOH} : \text{Et}_3\text{N}$  100:5:1) to afford the pure title compound. Yield: 218 mg (0.83 mmol, 94%). Colorless oil, which solidifies upon standing.

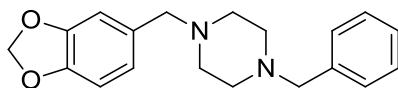
**TLC**:  $R_f = 0.27$  ( $\text{EtOAc} : \text{MeOH}$  95:5; UV, CAM); **Melting Point**: 79–80  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.82$  (d,  $J=0.6$ , 1H), 6.78–6.63 (m, 2H), 5.91 (s, 2H), 3.67–3.52 (m, 2H), 3.50–3.31 (m, 4H), 2.38 (dd,  $J=5.5$ , 10.4, 4H), 2.05 (s, 3H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta =$

168.8, 147.6, 146.6, 131.4, 122.0, 109.2, 107.8, 100.8, 62.5, 52.8, 52.4, 46.2, 41.3, 21.2; **IR** (thin film): 2900, 2813, 2774, 1643, 1490, 1442, 1250, 1038, 999, 931, 810, 730  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ), 262.1312; found 262.1313.



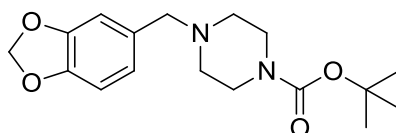
**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(3,5-difluorophenyl)piperazine (86).** In a Schlenk flask was added to degassed toluene (5 ml) in the following order piperonyl piperazine (127 mg, 0.56 mmol, 1.1 equiv), bromo-3,5-difluorobenzene (60  $\mu\text{l}$ , 0.51 mmol, 1 equiv),  $[\text{Pd}_2(\text{dba})_3]$  (5 mg, 0.005 mmol, 0.01 equiv), ( $\pm$ )-BINAP (9 mg, 0.015 mmol, 0.03 equiv), and  $\text{KO}^t\text{Bu}$  (85 mg, 0.76 mmol, 1.5 equiv). The mixture was heated to 110  $^\circ\text{C}$  and stirred for 19 h. It was cooled to RT, filtered over celite, and the filter cake thoroughly washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to yield the pure title compound. Yield: 71 mg (0.21 mmol, 42%). Slightly yellowish oil.

**TLC:**  $R_f = 0.25$  (hexanes : EtOAc 3:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.88$  (s, 1H), 6.76 (d,  $J=0.9$ , 2H), 6.45–6.29 (m, 2H), 6.24 (tt,  $J=2.2$ , 8.9, 1H), 5.95 (d,  $J=0.5$ , 2H), 3.46 (s, 2H), 3.28–3.05 (m, 4H), 2.65–2.44 (m, 4H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.0$  (dd,  $J_{\text{C,F}}=16.0$ , 243.7), 153.2 (t,  $J_{\text{C,F}}=12.4$ ), 147.7, 146.7, 131.7, 122.2, 109.4, 107.9, 100.9, 97.8 (d,  $J_{\text{C,F}}=28.2$ ), 93.84 (t,  $J_{\text{C,F}}=26.2$ ), 62.6, 52.5, 48.1;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -109.53$  (dd,  $J=8.8$ , 10.5); **IR** (thin film): 2884, 2821, 2777, 1633, 1586, 1488, 1441, 1246, 1196, 1113, 1040, 1005, 821  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{18}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 332.1331; found 332.1330.



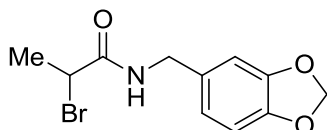
**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-benzylpiperazine (87).** To a solution of piperonyl piperazine (200 mg, 0.88 mmol, 1 equiv) in  $\text{CH}_3\text{CN}$  (6 ml) was added  $\text{Et}_3\text{N}$  (0.25 ml, 1.76 mmol, 2 equiv) followed by benzyl bromide (0.21 ml, 1.76 mmol, 2 equiv). The solution was stirred at RT for 18.5 h, then it was concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1) to afford the pure title compound. Yield: 249 mg (0.80 mmol, 91%). Colorless oil, which solidifies upon standing.

**TLC:**  $R_f = 0.27$  (EtOAc : MeOH 10:1; UV, CAM); **Melting Point:** 70-71 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.44\text{--}7.12$  (m, 5H), 6.86 (s, 1H), 6.75 (d,  $J=0.9$ , 2H), 5.93 (s, 2H), 3.52 (s, 2H), 3.43 (s, 2H), 2.48 (br s, 8H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.3$ , 146.3, 137.9, 131.9, 129.0, 128.0, 126.8, 122.0, 109.4, 107.7, 100.7, 63.0, 62.7, 53.0, 52.9; **IR** (thin film): 2936, 2809, 2771, 1502, 1441, 1243, 1136, 1040, 1010, 935, 812, 739, 699  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 310.1676; found 310.1675.



**tert-Butyl 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperazine-1-carboxylate (88).** To a solution of piperonyl piperazine (200 mg, 0.88 mmol, 1 equiv) in MeOH (6 ml) was added  $\text{Boc}_2\text{O}$  (218 mg, 0.97 mmol, 1.1 equiv). The clear solution was stirred at RT for 1.5 h, then it was concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1) to afford the pure title compound. Yield: 280 mg (0.87 mmol, 99%). Colorless oil, which solidifies upon standing.

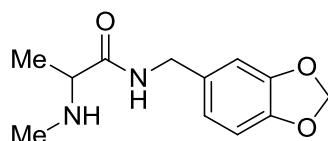
**TLC:**  $R_f = 0.46$  (hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1; UV, CAM); **Melting Point:** 55-56 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.81$  (s, 1H), 6.70 (d,  $J=0.6$ , 2H), 5.90 (s, 2H), 3.50-3.26 (m, 6H), 2.33 (t,  $J=6.0$ , 4H), 1.43 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.4$ , 147.4, 146.4, 131.5, 121.9, 109.2, 107.7, 100.7, 79.4, 62.7, 52.6, 43.2, 28.4; **IR** (thin film): 2976, 2898, 2773, 1694, 1489, 1442, 1366, 1247, 1173, 1040, 868, 733  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ), 320.1731; found 320.1731.



***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-bromopropanamide (91).** To a cooled (0 °C) solution of 2-bromopropionyl bromide (2.43 ml, 23.16 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (50 ml) was added  $\text{Et}_3\text{N}$  (3.23 ml, 23.16 mmol, 1.0 equiv) followed by piperonyl amine (2.98 ml, 23.16 mmol, 1.0 equiv), and the mixture was stirred at 0 °C for 10 min, then it was allowed to warm to RT over 2 h. At this point it was poured into saturated aqueous  $\text{NH}_4\text{Cl}$  (50 ml), the phases were separated, and the organic phase dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue

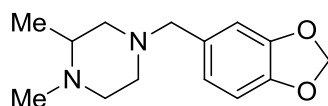
was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1 → 2:1 gradient) to afford the pure title compound. Yield: 2.68 g (9.38 mmol, 41%). Colorless solid.

**TLC:**  $R_f = 0.52$  (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 119–120 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 6.85\text{--}6.67$  (m, 3H), 6.62 (br s, 1H), 5.95 (s, 2H), 4.44 (q,  $J=7.1$ , 1H), 4.36 (d,  $J=5.7$ , 2H), 1.90 (d,  $J=7.1$ , 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 169.1, 148.0, 147.2, 131.3, 121.1, 108.4, 108.3, 101.1, 45.2, 44.0, 23.2$ ; **IR** (thin film): 3275, 3072, 2898, 1648, 1545, 1504, 1444, 1255, 1192, 1040, 930, 809 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>11</sub>H<sub>12</sub>BrNO<sub>3</sub> (M<sup>+</sup>), 284.9995; found 284.9994.



***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(methylamino)propanamide.** To a solution of bromide **91** (0.546 g, 1.91 mmol, 1.0 equiv) in toluene (20 ml) was added methylamine (2 M in THF; 3.82 ml, 7.63 mmol, 4 equiv) followed by Ag<sub>2</sub>O (0.442 g, 1.91 mmol, 1.0 equiv). The resulting suspension was sonicated at RT for 3 h, then it was filtered over celite, and the filtrate concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; EtOAc : MeOH : Et<sub>3</sub>N 1:0:0 → 86:14:1) to afford the pure title compound. Yield: 0.336 g (1.42 mmol, 75%). Colorless oil.

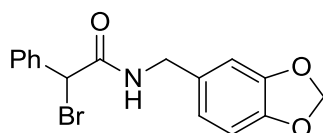
**TLC:**  $R_f = 0.11$  (EtOAc : MeOH 10:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.45$  (br s, 1H), 6.88–6.63 (m, 3H), 5.93 (s, 2H), 4.34 (d,  $J=6.0$ , 2H), 3.09 (q,  $J=6.9$ , 1H), 2.36 (s, 3H), 1.38 (br s, 1H), 1.31 (d,  $J=6.9$ , 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 174.7, 147.9, 146.9, 132.5, 120.9, 108.3, 108.2, 101.0, 60.4, 42.8, 35.2, 19.6$ ; **IR** (thin film): 3314, 2974, 2894, 1652, 1527, 1503, 1491, 1444, 1251, 1039, 926, 809 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>), 236.1156; found 236.1154.



**4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1,2-dimethylpiperazine (93).** To a solution of *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(methylamino)propanamide (226 mg, 0.96 mmol, 1.0 equiv) in THF (10 ml) was added LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 1.67 ml, 6.70 mmol, 7.0 equiv), and the mixture was heated to 50 °C and stirred for 11 h. At this point it was gradually cooled to 0 °C and carefully quenched with a combination of H<sub>2</sub>O (1.5 ml), then NaOH (15% in H<sub>2</sub>O; 1.5 ml), and again H<sub>2</sub>O (4.5 ml). The mixture was allowed to warm to RT and the formed precipitate

was filtered and thoroughly washed with Et<sub>2</sub>O. The filtrate was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give the almost pure intermediate (180 mg, *ca.* 85% yield). A fraction of this product (115 mg, 0.52 mmol, 1.0 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (13 ml) and Et<sub>3</sub>N (144 μl, 1.04 mmol, 2.0 equiv) was added, when the mixture was cooled to 0 °C. At this temperature, a solution of diphenyl(vinyl)sulfonium trifluoromethanesulfonate<sup>348</sup> (94% pure; 209 mg, 0.54 mmol, 1.05 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was dropwise added over 2 min. The mixture was stirred at 0 °C for 1.5 h, then at RT for further 20 h. At this point, the mixture was poured into 1 M HCl (5 ml), H<sub>2</sub>O (5 ml) was added, and the phases were separated. The aqueous phase was made alkaline by adding 1 M NaOH (*ca.* 15 ml), and it was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 ml). Those combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH : Et<sub>3</sub>N 95:5:1). Yield: 97 mg (0.39 mmol, 76% over 2 steps). Colorless oil.

**TLC:** *R*<sub>f</sub> = 0.33 (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 9:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.83 (s, 1H), 6.72 (d, *J*=1.0, 2H), 5.91 (s, 2H), 3.36 (s, 2H), 2.81–2.57 (m, 3H), 2.25 (s, 3H), 2.40–2.00 (m, 3H), 1.87–1.77 (m, 1H), 1.00 (d, *J*=6.3, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.5, 146.5, 132.0, 122.1, 109.4, 107.8, 100.8, 62.6, 60.4, 57.6, 55.7, 53.2, 42.4, 17.4; **IR** (thin film): 2936, 2791, 1503, 1490, 1441, 1339, 1241, 1040, 929, 807 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>), 248.1520; found 248.1517.

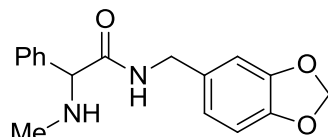


***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-bromo-2-phenylacetamide (96).** To a solution of 2-bromo-2-phenylacetic acid (1.00 g, 4.65 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (25 ml) was added oxalyl chloride (1.20 ml, 13.95 mmol, 3.0 equiv) followed by DMF (10 drops), upon which gas formation was observed. The mixture was stirred at RT for 1 h, then it was concentrated and dried *in vacuo*. The crude acid chloride was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 ml), and piperonyl amine (0.60 ml, 5.65 mmol, 1.0 equiv) was added. Et<sub>3</sub>N (1.43 ml, 10.23 mmol, 2.2 equiv) was added, and the mixture was aged at RT for 2.5 h. At this point it was quenched by addition of saturated aqueous NaHCO<sub>3</sub> (20 ml), the phases were separated, and the organic phase dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The yellow oil was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1 → 2:1 gradient) to afford the pure title compound. Yield: 1.36 g (3.91 mmol, 84%). Colorless solid.

<sup>348</sup> M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2008**, *47*, 3784–3786.

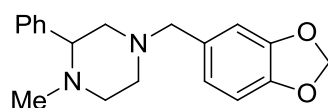


**TLC:**  $R_f = 0.45$  (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 110–111 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.54\text{--}7.31$  (m, 5H), 6.93 (br d,  $J=25.6$ , 1H), 6.82–6.67 (m, 3H), 5.96 (s, 2H), 5.43 (d,  $J=15.6$ , 1H), 4.40 (d,  $J=5.7$ , 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{DMSO-}d_6$ , 80 °C):  $\delta = 166.3$  (d), 146.8, 145.8, 136.9, 132.0, 128.1 (d), 127.9, 127.4, 120.1, 107.5 (d), 100.4, 59.6, 49.2, 42.3 (d); **IR** (thin film): 3294, 3067, 2892, 1656, 1502, 1490, 1445, 1252, 1220, 1039, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{16}\text{H}_{14}\text{NO}_3$  ( $[\text{M}-\text{Br}]^+$ ), 268.0968; found 268.0967.



***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(methylamino)-2-phenylacetamide.** To a solution of bromide **96** (1.35 g, 3.89 mmol, 1.0 equiv) in toluene (50 ml) was added methylamine (2 M in THF; 9.72 ml, 19.44 mmol, 5 equiv) followed by  $\text{Ag}_2\text{O}$  (1.35 g, 5.83 mmol, 1.5 equiv). The resulting suspension was sonicated at RT for 3 h, then it was filtered over celite, the filter cake thoroughly washed with EtOAc, and the filtrate concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc :  $\text{Et}_3\text{N} = 100:1$ ) to give the pure title compound. Yield: 0.92 g (3.08 mmol, 79%). Colorless oil.

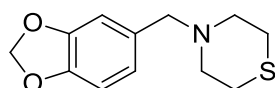
**TLC:**  $R_f = 0.21$  (EtOAc; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.49\text{--}7.26$  (m, 6H), 6.81–6.60 (m, 3H), 5.93 (s, 2H), 4.35 (dd,  $J=2.8, 5.9$ , 2H), 4.08 (s, 1H), 2.42 (s, 3H), 1.68 (s, 1H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.5, 147.6, 146.6, 139.0, 132.0, 128.6, 127.9, 126.9, 120.7, 108.1$  (2C), 100.9, 69.9, 43.1, 35.6; **IR** (thin film): 3312, 3058, 2890, 1652, 1503, 1490, 1444, 1251, 1100, 1038, 914, 744  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_3$  ( $[\text{M}+\text{H}]^+$ ), 298.1312; found 298.1316.



**4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-methyl-2-phenylpiperazine (98).** To a solution of *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-(methylamino)-2-phenylacetamide (296 mg, 0.99 mmol, 1.0 equiv) in THF (10 ml) was added  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 1.74 ml, 6.94 mmol, 7.0 equiv), and the mixture was heated to 50 °C and stirred for 11 h. At this point it was gradually cooled to 0 °C and carefully quenched with a combination of  $\text{H}_2\text{O}$  (1.5 ml), then NaOH (15% in  $\text{H}_2\text{O}$ ; 1.5 ml), and again  $\text{H}_2\text{O}$  (4.5 ml). The mixture was allowed to warm to RT and the formed precipitate was filtered and thoroughly washed with  $\text{Et}_2\text{O}$ . The filtrate was dried ( $\text{MgSO}_4$ ), filtered,

and concentrated *in vacuo*. The pure intermediate (184 mg, 0.65 mmol, 65% yield) was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH : Et<sub>3</sub>N 90:10:1). A fraction of this diamine (93 mg, 0.33 mmol, 1.0 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and Et<sub>3</sub>N (91 μl, 0.65 mmol, 2.0 equiv) was added, and the mixture was cooled to 0 °C. At this temperature, a solution of diphenyl(vinyl)sulfonium trifluoromethanesulfonate<sup>348</sup> (94% pure; 135 mg, 0.35 mmol, 1.07 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was dropwise added over 2 min. The mixture was stirred at 0 °C for 1 h, then at RT for further 30 min. At this point, the mixture was poured into HCl (1 M in H<sub>2</sub>O; 8 ml), and the phases were separated. The aqueous phase was made alkaline by adding NaOH (1 M in H<sub>2</sub>O; *ca.* 10 ml), and it was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 ml). Those combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH : Et<sub>3</sub>N 100:1:1). Yield: 84 mg (0.27 mmol, 83%; 54% over the 2 steps). Colorless oil.

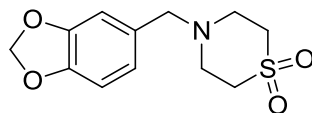
**TLC:**  $R_f = 0.47$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 9:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.44\text{--}7.16$  (m, 5H), 6.86 (s, 1H), 6.72 (d,  $J=0.9$ , 2H), 5.93 (d,  $J=1.5$ , 2H), 3.42 (s, 2H), 3.07 (dd,  $J=2.8$ , 10.4, 1H), 3.01–2.68 (m, 3H), 2.36 (dtd,  $J=2.8$ , 11.7, 22.4, 2H), 2.17–1.96 (m, 2H), 2.04 (s, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 147.5$ , 146.5, 141.6, 131.9, 128.3, 127.9, 127.4, 122.2, 109.4, 107.8, 100.8, 69.1, 62.6, 61.1, 55.7, 53.1, 43.4; **IR** (thin film): 2940, 2791, 1502, 1489, 1440, 1337, 1241, 1132, 1039, 931, 806, 702 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>), 310.1676; found 310.1675.



**4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)thiomorpholine (100).** Thiomorpholine (0.70 ml, 7.23 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (35 ml). To the resulting colorless solution was added piperonal (1.09 g, 7.23 mmol, 1 equiv), Et<sub>3</sub>N (1.02 ml, 7.23 mmol, 1 equiv) and NaBH(OAc)<sub>3</sub> (3.41 g, 14.47 mmol, 2 equiv), and the colorless suspension was stirred at RT for 17.5 h. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (20 ml). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml) and saturated aqueous NaHCO<sub>3</sub> (70 ml), and the phases were separated. The organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a colorless oil. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc : Et<sub>3</sub>N 80:20:1). Yield: 1.57 g (6.62 mmol, 92%). Colorless oil.

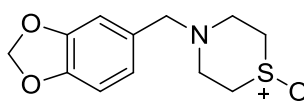
**TLC:**  $R_f = 0.33$  (hexanes : EtOAc : Et<sub>3</sub>N 80:20:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 6.83$  (dd,  $J=0.6$ , 1.3, 1H), 6.78–6.63 (m, 2H), 5.93 (s, 2H), 3.41 (s, 2H), 2.66 (s, 8H); **<sup>13</sup>C NMR**

(100 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.7, 146.6, 132.0, 122.1, 109.3, 107.8, 100.9, 63.4, 54.8, 28.0$ ; **IR** (thin film): 2908, 2807, 1502, 1488, 1440, 1241, 1039, 935, 809, 775  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{S}$  ( $\text{M}^+$ ), 237.0818; found 237.0819.



**2,2-Dioxo-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)thiomorpholine (101).** To a solution of thiomorpholine **100** (93 mg, 0.39 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (4 ml) was added at RT *N*-methylmorpholine *N*-oxide (115 mg, 0.98 mmol, 2.5 equiv) followed by potassium osmate dihydrate (7.2 mg, 0.02 mmol, 0.05 equiv), and the mixture was held at RT for 18 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (30 ml) and washed with saturated aqueous  $\text{NaHCO}_3$  (15 ml). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml), and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1). Yield: 84 mg (0.31 mmol, 80%). Colorless solid.

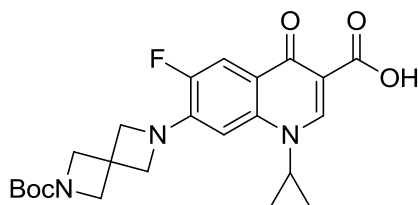
**TLC:**  $R_f = 0.56$  (EtOAc : hexanes :  $\text{Et}_3\text{N}$  75:25:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.82$  (d,  $J=1.1$ , 1H), 6.79–6.67 (m, 2H), 5.95 (s, 2H), 3.54 (s, 2H), 3.15–3.00 (m, 4H), 3.00–2.90 (m, 4H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.9, 147.1, 131.1, 122.0, 108.9, 108.0, 101.0, 61.2, 51.5, 50.4$ ; **IR** (thin film): 2917, 2826, 1489, 1442, 1300, 1243, 1125, 1037, 928  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{15}\text{NO}_4\text{S}$  ( $\text{M}^+$ ), 269.0717; found 269.0720.



**1-Oxo-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)thiomorpholine (102).** To a solution of thiomorpholine **100** (171 mg, 0.72 mmol, 1 equiv) in AcOH (5 ml) was added at RT  $\text{H}_2\text{O}_2$  (30% in  $\text{H}_2\text{O}$ ; 81  $\mu\text{l}$ , 0.79 mmol, 1.1 equiv), and the mixture was stirred at RT for 19 h. Then it was concentrated *in vacuo* and the residue taken up in  $\text{CH}_2\text{Cl}_2$  (30 ml). It was washed with saturated aqueous  $\text{Na}_2\text{CO}_3$  (20 ml), and the aqueous phase (pH  $\sim 12$ ) was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc : MeOH :  $\text{Et}_3\text{N}$  95:5:1) to yield the pure title compound. Yield: 168 mg (0.66 mmol, 92%). Colorless oil, which solidifies upon standing.

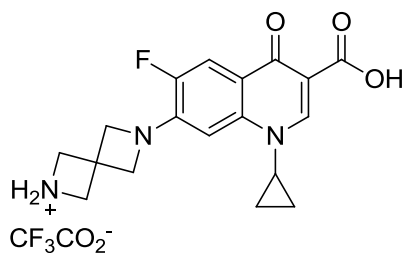
**TLC:**  $R_f = 0.27$  (EtOAc : MeOH 9:1; UV, CAM); **Melting Point:** 59–60  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.83$  (s, 1H), 6.78–6.66 (m, 2H), 5.94 (s, 2H), 3.49 (s, 2H), 3.13–2.95 (m,

2H), 2.95–2.75 (m, 4H), 2.75–2.59 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 147.4, 146.5, 130.9, 121.9, 109.0, 108.9, 107.8, 100.8, 62.4, 46.7, 44.1; **IR** (thin film): 2901, 2821, 1502, 1490, 1442, 1242, 1057, 1034, 925, 774  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_8\text{H}_7\text{O}_2$  ( $[\text{M}-(\text{thiomorpholine-S-oxide})]^+$ ), 135.0446; found 135.0444.



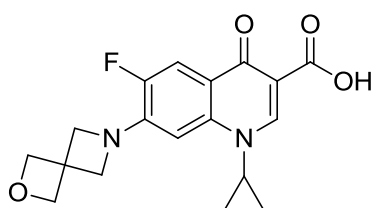
**7-(6-(*tert*-Butoxycarbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.** *KOtBu* (191 mg, 1.70 mmol, 2.4 equiv) was dissolved in DMSO (20 ml), azetidinium oxalate **56** (276 mg, 0.568 mmol, 0.8 equiv) was added, and the mixture was stirred at RT for 15 min, then was added 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**109**) (200 mg, 0.71 mmol, 1.0 equiv), and the now yellow mixture was heated to 130 °C and stirred for 5.5 h. Then it was cooled to RT and poured into  $\text{H}_2\text{O}$  (100 ml). The precipitate was filtered and dried overnight upon standing. Then it was suspended in MeOH (10 ml) and stirred at RT for 30 min, when the suspension was filtered, and the solid residue was dried *in vacuo* to give the pure title compound. Concentration of the filtrate yielded further fractions of the pure material. Yield: 194 mg (0.44 mmol, 62%). Faint yellowish amorphous solid.

**TLC:**  $R_f$  = ~0.1 (EtOAc; UV, CAM); **Melting Point:** >250 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.16 (s, 1H), 8.45 (s, 1H), 7.71 (d,  $J=12.3$ , 1H), 6.58 (d,  $J=7.4$ , 1H), 4.38 (s, 4H), 4.19 (s, 4H), 3.49 (br s, 1H), 1.46 (s, 9H), 1.33 (d,  $J=6.7$ , 2H), 1.16 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 176.4, 167.0, 156.0, 150.9 (d,  $^1J_{\text{C,F}}=247.9$ ), 146.6, 143.5 (d,  $^2J_{\text{C,F}}=13.8$ ), 139.5, 116.3 (d,  $^3J_{\text{C,F}}=6.6$ ), 111.1 (d,  $^2J_{\text{C,F}}=20.2$ ), 107.4, 98.1 (d,  $^3J_{\text{C,F}}=5.2$ ), 79.9, 63.2, 59.6, 35.2, 34.0, 28.4, 8.1;  $^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -132.7; **IR** (thin film): 2950, 2880, 1700, 1632, 1511, 1473, 1412, 1327, 1242, 1173, 913, 816, 745  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{23}\text{H}_{27}\text{FN}_3\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ), 444.1929; found 444.1922.



**6-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)-6-aza-2-azoniaspiro[3.3]heptane 2,2,2-trifluoroacetate (110).** 7-(6-(*tert*-Butoxycarbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17 mg, 0.038 mmol, 1.0 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml), and trifluoroacetic acid (1.5 ml) was added, upon which the solution turned bright yellow. After stirring at RT for 1 h, the mixture was concentrated *in vacuo* and the residue triturated with EtOAc (3 ml) to give a precipitate, which was filtered and dried *in vacuo* to give the pure title compound. Yield: 18 mg (0.038 mmol, 99%). Off-white to faint yellowish amorphous solid.

**TLC:**  $R_f = \sim 0.02$  (MeOH : EtOAc 1:2; UV); **Melting Point:**  $>250\text{ }^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 15.38$  (s, 1H), 8.72 (s, 2H), 8.55 (s, 1H), 7.78 (d,  $J=12.6$ , 1H), 6.87 (s, 1H), 4.40 (s, 4H), 4.22 (s, 4H), 3.72 (s, 1H), 1.28 (s, 2H), 1.14 (s, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 176.0$ , 166.0, 158.2 (d,  $J_{\text{C,F}}=30.8$ ), 150.3 (d,  $J_{\text{C,F}}=246.0$ ), 147.4, 143.2 (d,  $J_{\text{C,F}}=13.5$ ), 139.6, 115.4, 110.2 (d,  $J_{\text{C,F}}=20.5$ ), 99.4, 62.3, 54.7, 36.5, 35.8, 7.5;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{D}_2\text{O}$ ):  $\delta = -73.95$ ,  $-130.47$ ; **IR** (neat): 2970, 1685, 1632, 1520, 1408, 1337, 1189, 1123, 818  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{18}\text{H}_{19}\text{FN}_3\text{O}_3$  ( $[\text{M}-\text{CF}_3\text{CO}_2]^+$ ), 344.1405; found 344.1406.



**1-Cyclopropyl-6-fluoro-4-oxo-7-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-1,4-dihydroquinoline-3-carboxylic acid (111).**  $\text{KO}t\text{Bu}$  (191 mg, 1.70 mmol, 2.4 equiv) was dissolved in DMSO (20 ml), azetidinium oxalate **112**<sup>77</sup> (164 mg, 0.568 mmol, 0.8 equiv) was added, and the mixture was stirred at RT for 10 min, then was added 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**109**) (200 mg, 0.71 mmol, 1.0 equiv), and the now yellow mixture was heated to  $130\text{ }^\circ\text{C}$  and stirred for 5.5 h. Then it was cooled to RT and poured into  $\text{H}_2\text{O}$  (75 ml). The precipitate was filtered and dried overnight upon standing. The crude product was purified by suspending in hot  $\text{CHCl}_3$ , and cooling the mixture to RT, when it

was filtered, and the residue dried *in vacuo* to afford the pure title compound. Yield: 166 mg (0.48 mmol, 68%). Pale yellowish amorphous solid.

**TLC:**  $R_f = \sim 0.15$  (EtOAc : AcOH 19:1; UV); **Melting Point:**  $>250$  °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$  with a few drops of TFA):  $\delta = 12.78\text{--}12.48$  (br s, 1H), 8.99 (s, 1H), 7.94 (d,  $J=11.8$ , 1H), 6.85 (d,  $J=7.2$ , 1H), 5.13 (s, 4H), 4.65 (s, 4H), 3.86–3.68 (m, 1H), 1.61–1.40 (m,  $J=6.3$ , 2H), 1.37–1.14 (m, 2H);  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$  with a few drops of TFA):  $\delta = -126.33$ ; **IR** (neat): 3030, 2945, 1722, 1631, 1519, 1471, 1401, 1235, 1128, 967, 815  $\text{cm}^{-1}$ ; **HRMS** (MALDI): exact mass calculated for  $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_4$  ( $[\text{M}+\text{H}]^+$ ), 345.1245; found 345.1246.

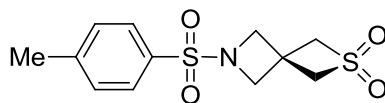


**2-Benzyl-2-azaspiro[3.3]heptane (113).** To a solution of bis(tosylate) **80** (1.05 g, 2.48 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (20 ml) was added  $i\text{Pr}_2\text{NEt}$  (1.30 ml, 7.45 mmol, 3.0 equiv) and benzylamine (0.54 ml, 4.97 mmol, 2.0 equiv), and the mixture was heated to 100 °C and stirred for 2 d, when it was cooled to RT and concentrated to about  $1/3$  of the initial volume. The residue was partitioned between saturated aqueous  $\text{NaHCO}_3$  (40 ml) and  $\text{CH}_2\text{Cl}_2$  (50 ml). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc :  $\text{Et}_3\text{N}$  50:50:1). Yield: 302 mg (1.61 mmol, 65%). Colorless oil.

**TLC:**  $R_f = 0.50$  (EtOAc : MeOH 1:1; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.39\text{--}7.13$  (m, 5H), 3.57 (s, 2H), 3.21 (s, 4H), 2.11 (t,  $J=7.5$ , 4H), 1.90 – 1.71 (m, 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 138.3, 128.3, 128.0, 126.6, 66.8, 63.9, 39.0, 33.1, 16.8$ ; **IR** (thin film): 2970, 2935, 2803, 1946, 1870, 1808, 1745, 1495, 1453, 1360, 1275, 1028, 725, 697  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{17}\text{N}$  ( $\text{M}^+$ ), 187.1356; found 187.1347.

This compound can be converted to the free amine and subsequently to its ammonium oxalate salt according to the following procedures. To a solution of benzylamine **113** (52 mg, 0.28 mmol, 1.0 equiv) in MeOH (5 ml) was added palladium (10% on carbon; 30 mg, 0.03 mmol, 0.1 equiv), and a hydrogen atmosphere was built up. The reaction mixture was stirred at RT for 20.5 h. At this point it was filtered over celite, thoroughly rinsed with MeOH, and concentrated to about  $2/3$  of the initial volume. Then was added oxalic acid (15 mg, 0.17 mmol, 0.6 equiv), and the mixture was concentrated *in vacuo*.  $\text{Et}_2\text{O}$  (5 ml) was added, and the solid residue was removed and filtered (rinsed with  $\text{Et}_2\text{O}$ ) to yield the oxalate salt **114** in good purity ( $>95\%$  by  $^1\text{H NMR}$ ). Yield: 33 mg (0.12 mmol, 84%). Off-white solid.

$^1\text{H NMR}$  (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 4.02$  (s, 4H), 2.26 (t,  $J=7.7$ , 4H), 1.94 – 1.71 (m, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 170.6, 58.8, 42.2, 33.3, 16.4$ .

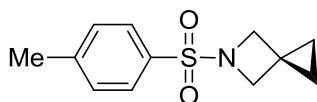


**6-Tosyl-2-thia-6-azaspiro[3.3]heptane 2,2-dioxide (115).** To a solution of sulfide **75** (102 mg, 0.38 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was added *m*-CPBA (77%; 205 mg, 0.83 mmol, 2.2 equiv), and the reaction mixture was stirred at RT for 2.3 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (25 ml) and saturated aqueous  $\text{NaHCO}_3$  (20 ml). The phases were separated, and the organic layer was washed with saturated aqueous  $\text{NaCl}$  (15 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:1). Yield: 108 mg (0.36 mmol, 95%). Colorless solid.

**TLC:**  $R_f = 0.54$  (hexanes : EtOAc 1:2; UV); **Melting Point:** 182–183 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.72$  (d,  $J=8.2$ , 2H), 7.39 (d,  $J=8.2$ , 2H), 4.11 (s, 4H), 3.96 (s, 4H), 2.47 (s, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 145.0, 131.2, 130.0, 128.4, 73.8, 60.5, 24.2, 21.6$ ; **IR** (thin film): 3012, 2944, 1598, 1338, 1314, 1168, 1153, 1100, 813, 695, 622, 552  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{15}\text{NO}_4\text{S}_2$  ( $\text{M}^+$ ), 301.0437; found 301.0437.

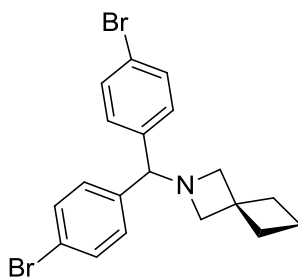
This compound can be converted to the free amine and subsequently to its ammonium oxalate salt (**116**) according to the following procedures. Tosyl amide **115** (200 mg, 0.63 mmol, 1.0 equiv) was suspended in MeOH (15 ml). To the resulting colorless suspension was added Mg powder (123 mg, 5.04 mmol, 8.0 equiv), and the reaction mixture was sonicated for 2 h. Then was added more Mg powder (123 mg, 5.04 mmol, 8.0 equiv) and MeOH (5 ml). The mixture was further sonicated for 30 min, when TLC analysis indicated complete consumption of the starting material. At this point the reaction mixture was concentrated *in vacuo*. The residue was suspended in  $\text{Et}_2\text{O}$  (40 ml) and  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$  (6 spatulas) was added, and the suspension was vigorously stirred at RT for 30 min. Then it was filtered, and the filtrate was dried ( $\text{Na}_2\text{SO}_4$ ) and filtered again. To the filtrate was added a solution of oxalic acid (28 mg, 0.32 mmol, 0.5 equiv) in EtOH (0.20 ml), upon which immediately a colorless precipitate formed. This solid was collected by filtration and subsequently dried under high vacuum to afford the pure oxalate salt. Yield: 68 mg (0.18 mmol, 56%). Colorless solid.

$^1\text{H NMR}$  (300 MHz,  $\text{D}_2\text{O}$ ):  $\delta = 4.64$  (s, 4H), 4.47 (s, 4H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{D}_2\text{O}$ ):  $\delta = 167.4, 73.4, 55.3, 27.2$ .



**5-Tosyl-5-azaspiro[2.3]hexane (118).** A solution of dibromide **52** (1.69 g, 4.26 mmol, 1.0 equiv) in EtOH (50 ml) was heated to reflux, when a mixture of Zn powder (1.11 g, 17.0 mmol, 4.0 equiv) and sodium iodide (1.91 g, 12.8 mmol, 3.0 equiv) was added in one portion. Heating was continued for 1 h, when the reaction mixture was allowed to cool to RT. At this point it was partitioned between H<sub>2</sub>O (250 ml) and EtOAc (500 ml), and filtered over celite. The phases were separated, and the organic phase was washed with saturated aqueous NaCl (250 ml), then dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 5:1) to afford the pure title compound, which can also be recrystallized from hexanes-EtOAc (9:1). Yield: 0.80 g (3.37 mmol, 79%). Colorless solid.

**TLC:**  $R_f = 0.25$  (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 128-129 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.75$  (d,  $J=8.2$ , 2H), 7.37 (d,  $J=8.2$ , 2H), 3.86 (s, 4H), 2.47 (s, 3H), 0.50 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 143.9$ , 132.2, 129.7, 128.3, 58.3, 21.6, 14.5, 9.6; **IR** (neat): 2975, 2870, 1596, 1333, 1153, 1113, 1049, 964, 814, 680 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>S (M<sup>+</sup>), 237.0818; found 237.0816.



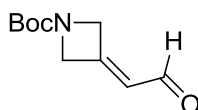
**2-(Bis(4-bromophenyl)methyl)-2-azaspiro[3.3]heptane (128).** To a solution of bis(tosylate) **80** (0.43 g, 1.00 mmol, 1.0 equiv) and bis(4-bromophenyl)methanamine<sup>349</sup> (0.68 g, 2.00 mmol, 2.0 equiv) in CH<sub>3</sub>CN (10 ml) was added *i*Pr<sub>2</sub>NEt (0.52 ml, 3.00 mmol, 3.0 equiv), and the reaction mixture was heated to reflux and stirred for 2 d. Then it was cooled to RT, and partitioned between half-saturated aqueous NaHCO<sub>3</sub> (15 ml) and EtOAc (30 ml). The phases were separated, and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 7:1) to afford the pure title compound. Yield: 85 mg (0.20 mmol, 20%). Colorless crystals.

<sup>349</sup> Y. Zhang, Z. Lu, A. Desai, W. D. Wulff, *Org. Lett.* **2008**, *10*, 5429-5432.



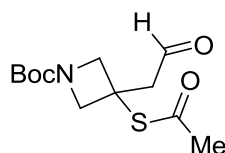
**TLC:**  $R_f = 0.61$  (hexanes : EtOAc 7:1; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.41 - 7.35$  (m, 4H), 7.26 – 7.20 (m, 4H), 4.17 (s, 1H), 3.07 (s, 4H), 2.12 – 2.04 (m, 4H), 1.84 – 1.71 (m, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 141.2, 131.6, 129.1, 120.9, 77.2, 65.9, 38.1, 33.2, 16.7$ ; **IR** (neat): 2927, 2813, 1907, 1588, 1482, 1403, 1339, 1285, 1265, 1240, 1204, 1095, 1069, 1009, 869, 798, 726, 689, 660, 626  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{19}\text{H}_{20}\text{Br}_2\text{N}$  ( $[\text{M}+\text{H}]^+$ ), 419.9957; found 419.9960.

### 9.3 Angular Spirocycles



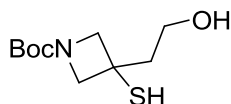
***tert*-Butyl 3-(2-oxoethylidene)azetidine-1-carboxylate (130).** To a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (680 mg, 3.97 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (14.6 ml) was added at RT (formylmethylene)triphenyl-phosphorane (1370 mg, 4.37 mmol, 1.1 equiv), and the reaction mixture was stirred at 40 °C for 5 h, when it was concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) to afford the pure title compound. Yield: 735 mg (3.73 mmol, 94%). Colorless oil.

**TLC:**  $R_f = 0.35$  (hexanes : EtOAc 2:1; UV,  $\text{KMnO}_4$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.60$  (d,  $J=6.4$ , 1H), 6.13–5.95 (m, 1H), 5.00–4.84 (m, 2H), 4.80–4.61 (m, 2H), 1.47 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 188.7, 157.0, 156.0, 122.5, 80.5, 58.8$  (br), 28.3; **IR** (thin film): 2978, 2932, 1697, 1391, 1367, 1155, 1119, 914, 744  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{15}\text{NNaO}_3$  ( $[\text{M}+\text{Na}]^+$ ), 220.0944; found 220.0939.



***tert*-Butyl 3-(acetylthio)-3-(2-oxoethyl)azetidine-1-carboxylate (131).** To a solution of  $\alpha,\beta$ -unsaturated aldehyde **130** (57 mg, 0.29 mmol, 1.0 equiv) in THF (0.2 ml) was added piperidine (2  $\mu\text{l}$ , 0.02 mmol, 0.07 equiv), when the solution turned slightly yellow. Thioacetic acid (31  $\mu\text{l}$ , 0.43 mmol, 1.5 equiv) was added and the mixture was stirred at RT for 6 h. At this point, the mixture was directly purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) to afford the title compound. Yield: 66 mg (0.24 mmol, 84%). Colorless oil.

**TLC:**  $R_f = 0.32$  (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.67$  (t,  $J=0.8$ , 1H), 4.06 (q,  $J=10.0$ , 4H), 3.29 (s, 2H), 2.29 (s, 3H), 1.42 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 198.4, 195.3, 155.8, 80.1, 61.2$  (br), 50.8, 41.4, 30.6, 28.3; **IR** (thin film): 2977, 2887, 1698, 1393, 1367, 1151, 1124, 1087, 633  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$  ( $[\text{M}+\text{NH}_4]^+$ ), 291.1373; found 291.1373.



**tert-Butyl 3-(2-hydroxyethyl)-3-mercaptoazetidino-1-carboxylate (132).** To a solution of aldehyde **131** (73 mg, 0.25 mmol, 1.0 equiv) in  $\text{Et}_2\text{O}$  (4 ml) was added dropwise  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 73  $\mu\text{l}$ , 0.29 mmol, 1.15 equiv), upon which the mixture immediately turned to a colorless suspension. The mixture was stirred at RT for 25 min, then it was diluted with  $\text{Et}_2\text{O}$  (10 ml) and quenched by addition of saturated aqueous  $\text{NaHCO}_3$  (10 ml). The organic phase was diluted with EtOAc (20 ml) and to the aqueous phase was added a saturated aqueous solution of ROCHELLE's salt (5 ml), and the phases were separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 59 mg (0.25 mmol, quantitative). Colorless oil.

**TLC:**  $R_f = 0.16$  (hexanes : EtOAc 1:1;  $\text{KMnO}_4$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.08$  (d,  $J=8.6$ , 2H), 3.92 (d,  $J=8.6$ , 2H), 3.86 (t,  $J=6.2$ , 2H), 2.22 (s, 1H), 2.10 (t,  $J=6.2$ , 2H), 2.11-2.01 (m, 1H), 1.43 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.2, 79.9, 64.9$  (br), 59.7, 43.2, 40.7, 28.3; **IR** (thin film): 3416, 2977, 2880, 2543, 1685, 1478, 1416, 1367, 1255, 1155, 914, 744  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{10}\text{H}_{20}\text{NO}_3\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 234.1158; found 234.1155.

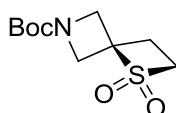


**tert-Butyl 1-thia-6-azaspiro[3.3]heptane-6-carboxylate (133).** To a solution of diethoxytriphenylphosphorane<sup>350</sup> (59 mg, 0.10 mmol, 1.2 equiv) in toluene (1 ml) was added at  $-30\text{ }^\circ\text{C}$  a solution of the alcohol **132** (20 mg, 0.09 mmol, 1.0 equiv) in toluene (1 ml), and the

<sup>350</sup> Prepared from  $\text{PPh}_3$ ,  $\text{Br}_2$ , then  $\text{NaOEt}$ ; slightly lower yields were obtained when a toluene solution of  $\text{PPh}_3(\text{OEt})_2$ , generated from  $\text{PPh}_3$  and diethyl peroxide, was used. References: a) P. L. Robinson, J. W. Kelly, S. A. Evans, *Phosphorus, Sulfur Silicon Relat. Elem.* **1987**, *31*, 59-70; b) P. L. Robinson, C. N. Barry, J. W. Kelly, S. A. Evans, *J. Am. Chem. Soc.* **1985**, *107*, 5210-5219.

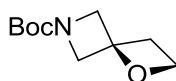
mixture was stirred at  $-30\text{ }^{\circ}\text{C}$  for 1 h, then it was allowed to slowly warm to RT overnight. After stirring for 13 h, the mixture was diluted with EtOAc (20 ml) and quenched with saturated aqueous NaCl (15 ml). The phases were separated and the organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:1). Yield: 11 mg (0.05 mmol, 60%). Colorless oil.

**TLC:**  $R_f = 0.42$  (hexanes : EtOAc 3:1;  $\text{KMnO}_4$ );  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.20\text{--}4.01$  (m, 4H), 3.21–2.96 (m, 4H), 1.51–1.32 (m, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.9, 79.7, 65.3$  (br), 44.4, 39.7, 28.3, 19.3; **IR** (thin film): 3005, 2857, 1702, 1392, 1366, 1172, 913, 773, 744  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{10}\text{NO}_2\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 216.1053; found 216.1049.



**tert-Butyl 1,1-dioxo-1-thia-6-azaspiro[3.3]heptane-6-carboxylate (134).** To a solution of thioether **133** (30 mg, 0.14 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added at  $0\text{ }^{\circ}\text{C}$  *m*-CPBA (77%; 66 mg, 0.29 mmol, 2.1 equiv), and the mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 15 min, when it was allowed to warm to RT, and stirring was continued for 3.5 h. It was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and saturated aqueous  $\text{NaHCO}_3$  (15 ml) was added. The phases were separated, and the organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure sulfone was obtained after FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:3). Yield: 33 mg (0.13 mmol, 96%). Colorless solid.

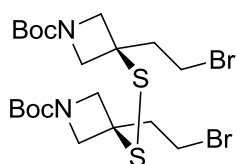
**TLC:**  $R_f = 0.24$  (hexanes : EtOAc 1:1; ninhydrin); **Melting Point:**  $143\text{--}144\text{ }^{\circ}\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.55$  (dd,  $J=10.3, 1.3, 2\text{H}$ ), 4.15–3.91 (m, 4H), 2.49–2.26 (m, 2H), 1.43 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.6, 80.6, 75.6, 62.5, 55.5$  (br), 28.2, 19.6; **IR** (thin film): 2975, 2877, 1701, 1387, 1316, 1201, 1166, 1146, 783  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{18}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 248.0951; found 248.0948.



**tert-Butyl 1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (135).** To a suspension of trimethylsulfoxonium iodide (0.643 g, 2.92 mmol, 2.5 equiv) in dry *t*BuOH (12 ml) was added at  $50\text{ }^{\circ}\text{C}$  potassium *tert*-butoxide (0.328 g, 2.92 mmol, 2.5 equiv), upon which the mixture turned to a cloudy suspension. The mixture was stirred at that temperature for 1.5 h, then was added *tert*-butyl 3-oxoazetidine-1-carboxylate (0.200 g, 1.17 mmol, 1.0 equiv). The suspension was

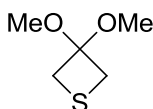
stirred at 50 °C for 48 h. It was cooled to RT and the mixture was partitioned between saturated aqueous  $\text{NH}_4\text{Cl}$  (30 ml) and EtOAc (50 ml). The phases were separated and the aqueous phase was extracted with EtOAc (50 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1  $\rightarrow$  0:1 gradient). Yield: 95 mg (0.48 mmol, 41%). Colorless oil.

**TLC:**  $R_f = 0.23$  (hexanes : EtOAc 2:1; ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.49$  (t,  $J=7.5$ , 2H), 4.07 (q,  $J=10.9$ , 4H), 2.80 (t,  $J=7.5$ , 2H), 1.40 (s, 9H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.0, 82.5, 79.5, 66.2, 63.8$  (br), 31.7, 28.2; **IR** (thin film): 2976, 2893, 1705, 1400, 1366, 1171, 1095, 978, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_6\text{H}_9\text{NO}_3$  ( $[\text{M}-\text{C}_4\text{H}_8]^+$ ), 143.0577; found 143.0578.



**Di-tert-butyl 3,3'-disulfanediyldis(3-(2-bromoethyl)azetidino-1-carboxylate) (136).** To a solution of thiol **132** (26 mg, 0.11 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (2.5 ml) was added  $\text{CBr}_4$  (55 mg, 0.17 mmol, 1.5 equiv) and triphenylphosphine (44 mg, 0.17 mmol, 1.5 equiv), and the mixture was stirred at RT for 2.5 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) gave the pure title compound. Yield: 14 mg (0.03 mmol, 49%). Colorless oil.

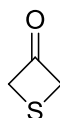
**TLC:**  $R_f = 0.35$  (hexanes : EtOAc 3:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.98$  (d,  $J=9.4$ , 2H), 3.87 (d,  $J=9.4$ , 2H), 3.40 (t,  $J=7.5$ , 2H), 2.55 (t,  $J=7.5$ , 2H), 1.45 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 155.8, 80.5, 60.7$  (br), 48.2, 39.8, 28.3, 26.6; **IR** (thin film): 1700, 1393, 1219, 1165, 913, 772, 668  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{20}\text{H}_{35}\text{Br}_2\text{N}_2\text{O}_4\text{S}_2$  ( $[\text{M}+\text{H}]^+$ ), 591.0379; found 591.0385.



**3,3-Dimethoxythietane.** To a solution of 1,3-dibromo-2,2-dimethoxypropane (10.2 g, 38.9 mmol, 1.0 equiv) in DMF (120 ml) was added sodium sulfide (about trihydrate; 6.68 g, *ca.*

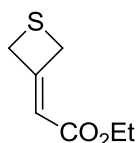
50.6 mmol, *ca.* 1.3 equiv), and the mixture was heated to 130 °C and stirred for 24 h (shortly after heating started, the mixture turned dark-brown to black). Then it was cooled to RT and Et<sub>2</sub>O (200 ml) was added, upon which a colorless precipitate formed, which was filtered. The filtrate was washed with H<sub>2</sub>O (150 ml). The Et<sub>2</sub>O-phase was washed with H<sub>2</sub>O (2 × 100 ml), saturated aqueous NaCl (50 ml), then dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give product as yellowish oil (3.54 g). The H<sub>2</sub>O/DMF phase from the first washing was extracted with Et<sub>2</sub>O (150 ml). The organic phase was washed with H<sub>2</sub>O (2 × 80 ml) and saturated aqueous NaCl (50 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give more product (0.37 g). The title compound was obtained in good purity, requiring no further purification. Yield: 3.91 g (29.1 mmol, 75%). Slightly yellowish and low viscous oil.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 3.34–3.31 (m, 4H), 3.18–3.15 (m, 6H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 102.3, 48.0, 47.9, 37.1; **IR** (thin film): 2949, 2831, 1437, 1253, 1192, 1114, 1040, 964 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>5</sub>H<sub>10</sub>O<sub>2</sub>S (M<sup>+</sup>), 134.0396; found 134.0397.



**Thietan-3-one (138).** To a solution of 3,3-dimethoxythietane (10.6 g, 79.0 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (590 ml) was added montmorillonite K10 clay (46.7 g), and the mixture was heated to 55 °C and stirred for 3 h. It was cooled to RT, and the solids were filtered. The filtrate was concentrated *in vacuo* to give the crude title compound as a light yellow solid. The pure title compound was obtained after recrystallization from pentane. *Important: The title compound sublimes readily under reduced pressure, therefore it is recommended to minimize drying under vacuum.* Yield: 5.15 g (58.5 mmol, 74%). Slightly yellowish crystals.

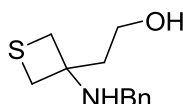
**Melting Point:** 63–64 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 4.30 (s, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 194.7, 55.2; **IR** (thin film): 1761, 1220, 773 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>3</sub>H<sub>4</sub>OS (M<sup>+</sup>), 87.9978; found 87.9977.



**Ethyl 2-(thietan-3-ylidene)acetate (140).** To a solution of thietan-3-one (**138**) (1.00 g, 11.35 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) was added at RT in portions (carbethoxymethylene)triphenylphosphorane (4.35 g, 12.48 mmol), and the mixture was stirred at RT for 21.5 h,

when it was concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 8:1) to afford the pure title compound. Yield: 1.71 g (10.81 mmol, 95%). Colorless oil.

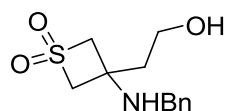
**TLC:**  $R_f = 0.60$  (hexanes : EtOAc 3:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 5.48$  (quint,  $J=2.5$ , 1H), 4.35 (dd,  $J=5.6, 2.5$ , 2H), 4.14 (q,  $J=7.1$ , 2H), 4.03-3.94 (m, 2H), 1.26 (t,  $J=7.1$ , 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 165.3, 159.0, 114.7, 60.0, 37.9, 35.4, 14.2$ ; **IR** (thin film): 2984, 2925, 1713, 1669, 1337, 1216, 1162, 1108, 1036, 773 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>7</sub>H<sub>10</sub>O<sub>2</sub>S (M<sup>+</sup>), 158.0396; found 158.0398.



**2-(3-(Benzylamino)thietan-3-yl)ethanol (141).** Ethyl 2-(thietan-3-ylidene)acetate **140** (438 mg, 2.77 mmol, 1.0 equiv) and benzylamine (317  $\mu$ l, 2.91 mmol, 1.05 equiv) were mixed, and the oil was stirred at RT for 2 d. <sup>1</sup>H NMR analysis of an aliquot of the reaction mixture showed incomplete conversion, therefore the oil was dissolved in THF (2 ml) and the solution was heated to 60 °C for 1 d. This mixture was directly purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 7:1) to afford pure ethyl 2-(3-(benzylamino)thietan-3-yl)acetate (524 mg, 1.98 mmol; 71% yield), which was directly used for the next step.

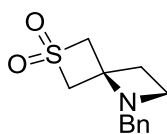
To a solution of ethyl 2-(3-(benzylamino)thietan-3-yl)acetate (524 mg, 1.98 mmol, 1.0 equiv) in Et<sub>2</sub>O (25 ml), cooled to 0 °C, was added LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 1.98 ml, 7.90 mmol), and the reaction mixture was stirred at 0 °C for 15 min. At this point, the reaction was quenched by careful addition of H<sub>2</sub>O (0.5 ml), NaOH (15% in H<sub>2</sub>O; 0.5 ml), and H<sub>2</sub>O (1.5 ml). The resulting colorless suspension was thoroughly stirred at RT for 10 min, when the solids were filtered off and the filter cake was thoroughly washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* to yield the pure title compound. Yield: 400 mg (1.79 mmol, 91%; 67% over the 2 steps). Colorless oil.

**TLC:**  $R_f = 0.18$  (hexanes : EtOAc 1:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.47-7.15$  (m, 5H), 3.95-3.83 (m, 2H), 3.80 (s, 2H), 3.33 (d,  $J=10.2$ , 2H), 3.10 (d,  $J=10.2$ , 2H), 2.27-2.10 (m, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 138.7, 128.5, 128.0, 127.2, 64.3, 58.8, 45.9, 37.1, 36.5$ ; **IR** (thin film): 3290, 2399, 2849, 1453, 1175, 1088, 1055, 913, 744 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>18</sub>NOS ([M+H]<sup>+</sup>), 224.1104; found 224.1099.



**2-(3-(Benzylamino)(S,S-dioxo-thietan)-3-yl)ethanol (142).** To a solution of thioether **141** (32 mg, 0.14 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.5 ml), cooled to 0 °C, was added titanium(IV)isopropoxide (42  $\mu\text{l}$ , 0.14 mmol, 1.0 equiv) followed by hydrogen peroxide (30% in  $\text{H}_2\text{O}$ ; 58  $\mu\text{l}$ , 0.56 mmol, 4 equiv), and the solution was stirred at 0 °C for 15 min. The ice-bath was removed and stirring was continued at RT for 1 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and quenched by addition of  $\text{H}_2\text{O}$  (10 ml). The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and  $\text{H}_2\text{O}$  (10 ml), the phases were separated, and the aqueous phase extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  10 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford a colorless oil, which represented almost pure title compound that can be used for further transformations without purification. Yield: 34 mg (0.13 mmol, 94%). Colorless oil. An analytically pure sample can be obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:2  $\rightarrow$  0:1 gradient).

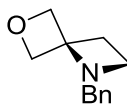
**TLC:**  $R_f = 0.23$  (hexanes : EtOAc 1:2; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.46\text{--}7.23$  (m, 5H), 4.08 (s, 4H), 3.85 (t,  $J=5.5$ , 2H), 3.74 (s, 2H), 2.16 (t,  $J=5.5$ , 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 137.7, 128.7, 128.1, 127.7, 72.9, 59.7, 48.2, 47.9, 37.7$ ; **IR** (thin film): 3528, 3322, 3028, 2949, 2876, 1454, 1392, 1311, 1202, 1106, 1074, 742  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 256.1002; found 256.1002.



**1-Benzyl-6,6-dioxo-6-thia-1-azaspiro[3.3]heptane (143).** To a solution of alcohol **142** (63 mg, 0.25 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (5 ml) was added triphenylphosphine (97 mg, 0.37 mmol, 1.5 equiv) and carbon tetrabromide (123 mg, 0.37 mmol, 1.5 equiv), and the mixture was stirred at RT for 1.5 h.  $\text{H}_2\text{O}$  (1 ml) was added followed by potassium carbonate (68 mg, 0.49 mmol, 2.0 equiv), and the colorless mixture was heated to 60 °C and stirred for 18 h. The mixture was cooled to RT and concentrated to  $1/4$  of the initial volume. The residue was partitioned between EtOAc (20 ml) and saturated aqueous  $\text{NaHCO}_3$  (10 ml), and the phases were separated. The organic phase was washed with saturated aqueous  $\text{NaHCO}_3$  (5 ml), then dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purifi-

cation by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2). Yield: 44 mg (0.19 mmol, 75%). Colorless crystalline solid.

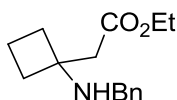
**TLC:**  $R_f = 0.16$  (hexanes : EtOAc 2:1; UV, ninhydrin); **Melting Point:** 86-88 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.43-7.19$  (m, 5H), 4.53-4.32 (m, 2H), 4.21-3.99 (m, 2H), 3.68 (s, 2H), 3.16 (t,  $J=6.8$ , 2H), 2.47 (t,  $J=6.8$ , 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 136.3, 128.4, 128.3, 127.4, 71.8, 55.8, 55.5, 50.1, 32.0$ ; **IR** (thin film): 2950, 2833, 1389, 1316, 1219, 1189, 1086, 772 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>NO<sub>2</sub>S ([M+H]<sup>+</sup>), 238.0896; found 238.0895.



**1-Benzyl-6-oxa-1-azaspiro[3.3]heptane (145).** To a solution of alcohol **148** (116 mg, 0.560 mmol, 1.0 equiv) in CH<sub>3</sub>CN (6 ml) was added at RT triphenylphosphine (220 mg, 0.839 mmol, 1.5 equiv) followed by carbon tetrabromide (278 mg, 0.839 mmol, 1.5 equiv), and the colorless solution was stirred at RT for 2 h. H<sub>2</sub>O (1.2 ml) was added followed by potassium carbonate (155 mg, 1.12 mmol, 2.0 equiv). The solution was heated to 60 °C and stirred for 3.75 h, when it was concentrated to 1/4 of the initial volume. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and saturated aqueous NaHCO<sub>3</sub> (10 ml). The phases were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 8 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2) to give the pure title compound. Yield: 87 mg (0.46 mmol, 82%). Colorless oil.

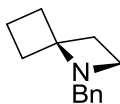
**TLC:**  $R_f = 0.19$  (hexanes : EtOAc 2:1; UV, ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.44-7.16$  (m, 5H), 5.00 (dd,  $J=7.5, 0.7$ , 2H), 4.64 (dd,  $J=7.5, 0.7$ , 2H), 3.82 (s, 2H), 3.06 (t,  $J=6.8$ , 2H), 2.38 (t,  $J=6.8$ , 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 137.9, 128.5, 128.4, 127.1, 81.4, 69.2, 56.3, 49.8, 29.4$ ; **IR** (thin film): 2944, 2861, 1495, 1453, 1362, 1215, 1120, 974, 913, 746, 696 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>16</sub>NO ([M+H]<sup>+</sup>), 190.1226; found 190.1227.





**Ethyl 2-(1-(benzylamino)cyclobutyl)acetate.** A mixture of ethyl 2-cyclobutylideneacetate<sup>351</sup> (162 mg, 1.16 mmol) and benzylamine (253  $\mu$ l, 2.32 mmol) was heated to 60 °C and stirred for 2 d. At this point the oil was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to give the pure title compound. Yield: 203 mg (0.82 mmol, 71%). Colorless oil.

**TLC:**  $R_f$  = 0.17 (hexanes : EtOAc 5:1; UV, ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.10 (m, 5H), 4.15 (q,  $J$ =7.1, 2H), 3.70 (s, 2H), 2.72 (s, 2H), 2.20-1.67 (m, 7H), 1.26 (t,  $J$ =7.1, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.8, 141.0, 128.3, 128.2, 126.7, 60.1, 58.7, 46.8, 41.5, 32.4, 14.3, 13.8; **IR** (thin film): 3028, 2981, 2936, 1729, 1454, 1368, 1245, 1193, 1114, 1029, 699 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub> ( $[M+H]^+$ ), 248.1645; found 248.1643.



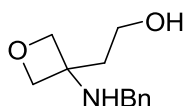
**1-Benzyl-1-azaspiro[3.3]heptane (146).** To a solution of ethyl 2-(1-(benzylamino)cyclobutyl)acetate (173 mg, 0.70 mmol, 1.0 equiv) in Et<sub>2</sub>O (8 ml), cooled to 0 °C, was added LiAlH<sub>4</sub> (4 M in Et<sub>2</sub>O; 0.70 ml, 2.80 mmol, 4.0 equiv), and the reaction mixture was stirred at 0 °C for 15 min. The reaction was quenched by addition of H<sub>2</sub>O (0.11 ml), NaOH (15% in H<sub>2</sub>O; 0.11 ml), and H<sub>2</sub>O (0.33 ml). The resulting colorless suspension was thoroughly stirred at RT for 15 min, when the solids were filtered off and the filter cake was thoroughly washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* to give the pure alcohol **151** (140 mg, 0.68 mmol; 97%), which was directly used for next step without purification.

To a solution of the alcohol **151** (140 mg, 0.68 mmol, 1.0 equiv) in CH<sub>3</sub>CN (10 ml) was added triphenylphosphine (268 mg, 1.02 mmol, 1.5 equiv) and carbon tetrabromide (339 mg, 1.02 mmol, 1.5 equiv), and the mixture was stirred at RT for 1.5 h. H<sub>2</sub>O (2 ml) was added followed by potassium carbonate (188 mg, 1.36 mmol, 2.0 equiv), and the colorless mixture was heated to 60 °C and stirred for 16.5 h. The reaction mixture was cooled to RT and concentrated to 1/4 of the initial volume. The residue was partitioned between EtOAc (20 ml) and HCl (1 M in H<sub>2</sub>O; 20 ml) and the phases were separated. To the aqueous phase was added EtOAc (30 ml) and the aqueous layer was basified with KOH (6 M in H<sub>2</sub>O) until the pH was basic. The phases

<sup>351</sup> M. Afzal, J. C. Walton, *J. Chem. Soc., Perkin Trans. 2* **1999**, 937-945.

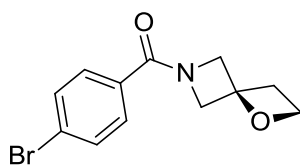
were separated, and the aqueous layer was extracted with EtOAc (10 ml). The combined organic phases from the basic extraction were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 95:5). Yield: 95 mg (0.51 mmol, 74%; 72% over the two steps). Colorless oil.

**TLC:**  $R_f$  = 0.09 ( $\text{CH}_2\text{Cl}_2$  : MeOH 95:5; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.48-7.11 (m, 5H), 3.65 (s, 2H), 3.12 (t,  $J=6.9$ , 2H), 2.43-2.21 (m, 2H), 2.22 (t,  $J=6.9$ , 2H), 2.09-1.85 (m, 2H), 1.77-1.49 (m, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 138.0, 128.8, 128.3, 126.9, 69.6, 56.1, 49.6, 32.4, 31.5, 13.4; **IR** (thin film): 3027, 2977, 2955, 2823, 1454, 1360, 1273, 1114, 725, 697  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{18}\text{N}$  ( $[\text{M}+\text{H}]^+$ ), 188.1434; found 188.1435.



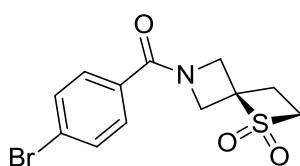
**2-(3-(Benzylamino)oxetan-3-yl)ethanol (148).** To ethyl 2-(oxetan-3-ylidene)acetate<sup>77b</sup> (1.47 g, 10.3 mmol, 1.0 equiv) was added benzylamine (1.19 ml, 10.9 mmol, 1.05 equiv), and the now slightly yellowish liquid was stirred at RT for 20 h, then it was heated to 40 °C for 30 min to assure complete conversion. The oil was now dissolved in  $\text{Et}_2\text{O}$  (80 ml) and the mixture was cooled to 0 °C.  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 10.34 ml, 41.4 mmol, 4.0 equiv) was dropwise added, when after  $4/5$  of the addition a yellowish precipitate formed. When the addition was completed, THF (20 ml) was added to redissolve the precipitate. The slightly yellowish suspension was further stirred at 0 °C for 30 min. At this point the reaction was carefully quenched with  $\text{H}_2\text{O}$  (1.57 ml), NaOH (15% in  $\text{H}_2\text{O}$ ; 1.57 ml), and  $\text{H}_2\text{O}$  ( $3 \times 1.57$  ml). The resulting mixture was thoroughly stirred at RT for 10 min, when the precipitate was filtered, and the filter cake was thoroughly washed with EtOAc and  $\text{Et}_2\text{O}$ . The filtrate was concentrated *in vacuo*. The title compound was obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 95:5). Yield: 1.60 g (7.72 mmol, 75%). Colorless oil.

**TLC:**  $R_f$  = 0.14 ( $\text{CH}_2\text{Cl}_2$  : MeOH 96:5; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.48-7.11 (m, 5H), 4.55 (d,  $J=6.8$ , 2H), 4.48 (d,  $J=6.8$ , 2H), 3.89-3.70 (m, 2H), 3.79 (s, 2H), 3.21 (br s, 2H), 2.23-2.03 (m, 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 138.8, 128.5, 128.0, 127.3, 81.2, 60.9, 59.3, 47.1, 35.2; **IR** (thin film): 3396, 3305, 2941, 2870, 1454, 1052, 974, 913, 744, 701  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{18}\text{NO}_2$  ( $[\text{M}+\text{H}]^+$ ), 208.1332; found 208.1332.



**(4-Bromophenyl)(1-oxa-6-azaspiro[3.3]heptan-6-yl)methanone (155).** To a solution of *tert*-butyl carbamate **135** (17.0 mg, 0.085 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added at 0 °C trifluoroacetic acid (0.4 ml), and the mixture was stirred at 0 °C for 15 min, when the volatiles were removed *in vacuo*. The residue (colorless oil) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 ml), and triethylamine (24 μl, 0.171 mmol, 2.0 equiv) followed by 4-bromobenzoyl chloride (22.5 mg, 0.102 mmol, 1.2 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then it was allowed to warm to RT and stirring was continued for 16 h. At this point, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (25 ml) and quenched by addition of saturated aqueous NaHCO<sub>3</sub> (10 ml). The phases were separated and the organic phase was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; EtOAc : hexanes 2:1). Yield: 14.0 mg (0.050 mmol, 58%). Colorless crystalline solid.

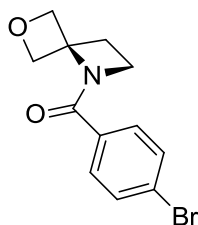
**TLC:**  $R_f = 0.19$  (hexanes : EtOAc 1:2; UV); **Melting Point:** 157–158 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.68\text{--}7.36$  (m, 4H), 4.71–4.18 (m, 6H), 2.87 (dd,  $J=13.8, 6.4, 2\text{H}$ ); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 169.1, 132.0, 131.7, 129.5, 125.7, 82.8, 67.6$  (br), 66.3, 63.5 (br), 31.8; **IR** (thin film): 2931, 2891, 1638, 1418, 958, 913, 748 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>13</sub>BrNO<sub>2</sub> ( $[\text{M}+\text{H}]^+$ ), 282.0124; found 282.0125.



**(4-Bromophenyl)(1,1-dioxo-1-thia-6-azaspiro[3.3]heptan-6-yl)methanone (156).** To a solution of *tert*-butyl carbamate **134** (20 mg, 0.08 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added at RT trifluoroacetic acid (0.2 ml), and the colorless solution was stirred at RT for 20 min. The volatiles were removed *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 ml), triethylamine (23 μl, 0.16 mmol, 2.0 equiv) was added followed by 4-bromobenzoyl chloride (20 mg, 0.09 mmol, 1.1 equiv), and the mixture was stirred at RT for 3 h. The mixture was directly purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:3 → 0:1 gradient) to give the pure title compound. Yield: 26.5 mg (0.080 mmol, 99%). Colorless crystalline solid.

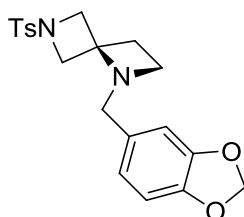
**TLC:**  $R_f = 0.13$  (hexanes : EtOAc 1:2; UV); **Melting Point:** 180–182 °C; **<sup>1</sup>H NMR**  $\delta = 7.71\text{--}7.39$  (m, 4H), 4.84 (d,  $J=10.4, 2\text{H}$ ), 4.34 (d,  $J=10.4, 2\text{H}$ ), 4.07 (t,  $J=8.7, 2\text{H}$ ), 2.42 (t,  $J=8.7, 2\text{H}$ );

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 169.7, 131.9, 130.9, 129.5, 126.4, 75.8, 62.7, 58.6$  (br),  $55.1$  (br),  $19.7$ ; IR (thin film):  $2940, 2872, 1638, 1589, 1415, 1313, 1206, 1122, 1011, 913, 748$   $\text{cm}^{-1}$ ; HRMS (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{13}\text{BrNO}_3\text{S}$  ( $[\text{M}+\text{H}]^+$ ),  $329.9794$ ; found  $329.9788$ .



**(4-Bromophenyl)(6-oxa-1-azaspiro[3.3]heptan-1-yl)methanone (157).** To a solution of benzyl amine **145** (79 mg, 0.42 mmol, 1.0 equiv) in MeOH (4 ml) was added palladium (10% on carbon; 89 mg, 0.083 mmol, 0.2 equiv), and a  $\text{H}_2$  atmosphere was built up. The mixture was stirred at RT for 36 h. At this point the mixture was filtered over celite and thoroughly washed with MeOH. The filtrate was co-evaporated with  $\text{CHCl}_3$  multiple times and briefly dried under high vacuum. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 ml), when triethylamine (88  $\mu\text{l}$ , 0.63 mmol, 1.5 equiv) was added followed by 4-bromobenzoyl chloride (101 mg, 0.46 mmol, 1.1 equiv), and the mixture was stirred at RT for 18.5 h. It was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (10 ml). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; EtOAc). Yield: 56 mg (0.20 mmol, 48%). Colorless crystalline solid.

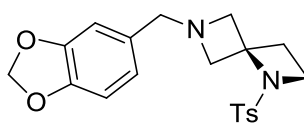
**TLC:**  $R_f = 0.31$  (EtOAc; UV, DNP); **Melting Point:**  $158\text{--}159$   $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.71\text{--}7.35$  (m, 4H),  $5.61$  (br s, 2H),  $4.63$  (d,  $J=7.2$ , 2H),  $4.11$  (t,  $J=7.5$ , 2H),  $2.61$  (d,  $J=7.5$ , 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 167.9, 132.6, 131.4, 128.8, 125.2, 80.6, 68.5, 49.5, 29.1$ ; IR (thin film):  $2962, 2870, 1619, 1558, 1416, 970, 913, 851, 748$   $\text{cm}^{-1}$ ; HRMS (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{13}\text{BrNO}_2$  ( $[\text{M}+\text{H}]^+$ ),  $282.0124$ ; found  $282.0125$ .



**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-tosyl-1,6-diazaspiro[3.3]heptane (159).** To a suspension of ammonium oxalate **154** (35 mg, 0.06 mmol, 0.5 equiv) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added at RT triethylamine (18  $\mu\text{l}$ , 0.128 mmol, 1.1 equiv), followed by piperonal (26 mg, 0.17 mmol,

1.5 equiv) and sodium triacetoxyborohydride (49 mg, 0.23 mmol, 2.0 equiv), and the mixture (which slowly cleared up) was stirred at RT for 3.5 h. Then it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and quenched with saturated aqueous NaHCO<sub>3</sub> (20 ml). The phases were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 2:1). Yield: 38 mg (0.10 mmol, 85%). Colorless oil, that solidifies upon standing.

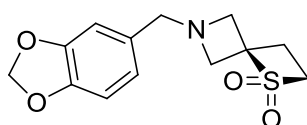
**TLC:**  $R_f$  = 0.18 (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 105–107 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.72 (d,  $J$ =8.1, 2H), 7.35 (d,  $J$ =8.1, 2H), 6.77 – 6.60 (m, 2H), 6.55 (dd,  $J$ =7.9, 1.6, 1H), 5.91 (s, 2H), 3.94 (d,  $J$ =9.7, 2H), 3.78 (d,  $J$ =9.7, 2H), 3.17 (s, 2H), 2.98 (t,  $J$ =6.8, 2H), 2.42 (s, 3H), 2.19 (t,  $J$ =6.8, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 147.7, 146.6, 144.1, 131.4, 131.2, 129.7, 128.4, 121.2, 108.6, 108.0, 100.9, 63.5, 60.0, 55.2, 49.6, 29.9, 21.5; **IR** (thin film): 2960, 2864, 1502, 1489, 1442, 1342, 1246, 1163, 1037, 927, 772, 676, 549 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S ([M+H]<sup>+</sup>), 387.1373; found 387.1370.



**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-tosyl-1,6-diazaspiro[3.3]heptane (160).** To a solution of ammonium oxalate **153** (100 mg, 0.21 mmol, 0.5 equiv) in MeOH (5 ml) was added triethylamine (0.12 ml, 0.86 mmol, 2.0 equiv) followed by di-*tert*-butyl dicarbonate (103 mg, 0.47 mmol, 1.1 equiv), and the solution was stirred at RT for 1.5 h. At this point TLC analysis indicated complete consumption of the starting material, therefore palladium (10% on carbon; 46 mg, 0.04 mmol, 0.1 equiv) was added and a H<sub>2</sub> atmosphere was built up. The mixture was stirred at RT for 24 h. At this point it was filtered over celite and the filter cake was thoroughly washed with MeOH. The filtrate was concentrated *in vacuo* and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml), and triethylamine (0.12 ml, 0.86 mmol, 2.0 equiv) was added followed by TsCl (90 mg, 0.47 mmol, 1.1 equiv). The mixture was stirred at RT for 30 min, when the clear solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and washed with HCl (0.1 M in H<sub>2</sub>O; 15 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (15 ml), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; hexanes : EtOAc : Et<sub>3</sub>N 66:33:1) afforded the pure Boc-protected intermediate. Yield: 53 mg (0.15 mmol, 35%). Colorless oil. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.75 (d,  $J$ =8.5, 2H), 7.32 (d,  $J$ =8.5, 2H), 4.54 (br d,  $J$ =9.9, 2H), 3.88 (d,  $J$ =9.9, 2H), 3.74 (br t,  $J$ =7.2, 2H), 2.44 (s, 3H), 2.40 (d,  $J$ =7.2,

2H), 1.44 (s, 9H). A fraction of this intermediate (35 mg, 0.10 mmol, 1.0 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 ml), and trifluoroacetic acid (0.4 ml, 5.2 mmol, 52 equiv) was added. The mixture was stirred at RT for 45 min, when it was concentrated *in vacuo* and the residue dried under high vacuum. Then the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 ml). Triethylamine (15  $\mu\text{l}$ , 0.109 mmol, 1.1 equiv) was added followed by piperonal (22 mg, 0.149 mmol, 1.5 equiv) and sodium triacetoxyborohydride (42 mg, 0.20 mmol, 2.0 equiv), and the mixture was stirred at RT for 14 h. Then it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and washed with saturated aqueous  $\text{NaHCO}_3$  (15 ml). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml), and the combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc) to afford the pure title compound. Yield: 31 mg (0.08 mmol, 81%; 28% over 5 chemical steps). Colorless solid.

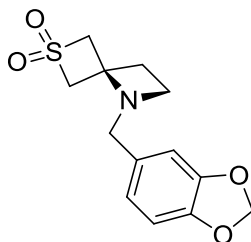
**TLC:**  $R_f = 0.19$  (EtOAc; UV, CAM); **Melting Point:** 115–116 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.74$  (d,  $J=8.3$ , 2H), 7.32 (d,  $J=8.3$ , 2H), 6.81 – 6.64 (m, 3H), 5.93 (s, 2H), 3.72 (t,  $J=7.4$ , 2H), 3.62 (dd,  $J=6.7$ , 2.2, 2H), 3.55 (s, 2H), 3.40 (dd,  $J=6.7$ , 2.2, 2H), 2.45 (t,  $J=7.4$ , 2H), 2.43 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.6$ , 146.6, 143.7, 136.1, 131.9, 129.7, 127.7, 121.6, 108.9, 108.0, 100.9, 66.3, 65.2, 63.1, 47.0, 29.9, 21.5; **IR** (thin film): 2940, 2889, 1502, 1489, 1441, 1340, 1245, 1219, 1158, 1038, 772, 673, 610, 548  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 387.1373; found 387.1371.



**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-thia-6-azaspiro[3.3]heptane 1,1-dioxide (161).**

To a solution of Boc-protected amine **134** (59 mg, 0.23 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (3 ml) was added at RT trifluoroacetic acid (0.6 ml, 7.8 mmol, 34.4 equiv), and the colorless solution was stirred at RT for 20 min. At this point the volatiles were removed *in vacuo* and the residue was dried in high vacuum. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml), and piperonal (51 mg, 0.34 mmol, 1.5 equiv) and sodium triacetoxyborohydride (96 mg, 0.45 mmol, 2.0 equiv) were added followed by triethylamine (0.064 ml, 0.453 mmol, 2.0 equiv). The mixture was stirred at RT for 14 h, when it was diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and washed with saturated aqueous  $\text{NaHCO}_3$  (15 ml). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml), and the combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc) to afford the pure title compound. Yield: 53 mg (0.19 mmol, 83%). Colorless oil.

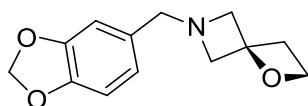
**TLC:**  $R_f = 0.24$  (EtOAc; UV, CAM);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.83 - 6.63$  (m, 3H), 5.93 (s, 2H), 4.01 – 3.91 (m, 2H), 3.88 (dd,  $J=8.2, 1.7$ , 2H), 3.51 (s, 2H), 3.30 (d,  $J=9.8$ , 2H), 2.37 – 2.19 (m, 2H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.6, 146.7, 130.6, 121.5, 108.8, 108.0, 100.9, 77.6, 62.5, 62.0, 59.6, 19.4$ ; **IR** (thin film): 2896, 2827, 1502, 1490, 1442, 1308, 1246, 1208, 1153, 1121, 1036, 923, 810, 737  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{16}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 282.0795; found 282.0788.



**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-6-thia-1-azaspiro[3.3]heptane 6,6-dioxide (162).**

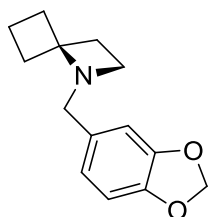
To a solution of benzylamine **143** (51 mg, 0.22 mmol, 1.0 equiv) in MeOH (3 ml) was added palladium (10% on carbon; 46 mg, 0.04 mmol, 0.2 equiv), and a hydrogen atmosphere was built up. The mixture was stirred at RT for 43 h. At this point an Ar atmosphere was formed, and the mixture was filtered over celite and the filter cake thoroughly washed with MeOH. The filtrate was co-evaporated with multiple portions of  $\text{CHCl}_3$ , then it was shortly (1 min) dried in high vacuum. The residue was partially dissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml), and piperonal (65 mg, 0.43 mmol, 2.0 equiv) was added followed by sodium triacetoxyborohydride (114 mg, 0.54 mmol, 2.5 equiv). The mixture was vigorously stirred at RT for 3.5 h, when it was partitioned between  $\text{CH}_2\text{Cl}_2$  (25 ml) and saturated aqueous  $\text{NaHCO}_3$  (15 ml). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:1). Yield: 18 mg (0.06 mmol, 30%). Colorless solid.

**TLC:**  $R_f = 0.33$  (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 161-162 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.91 - 6.66$  (m, 3H), 5.95 (s, 2H), 4.42 (d,  $J=15.1$ , 2H), 4.10 (d,  $J=15.1$ , 2H), 3.59 (s, 2H), 3.14 (t,  $J=6.8$ , 2H), 2.46 (t,  $J=6.8$ , 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.9, 147.0, 130.3, 121.6, 108.8, 108.2, 101.0, 71.9, 55.6, 55.5, 50.0, 32.0$ ; **IR** (thin film): 2960, 2831, 1502, 1490, 1442, 1315, 1248, 1190, 1084, 1037, 913, 744  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{16}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 282.0795; found 282.0791.



**6-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-oxa-6-azaspiro[3.3]heptane (163).** To a solution of Boc-protected amine **135** (54 mg, 0.27 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added at RT trifluoroacetic acid (0.6 ml, 7.8 mmol, 28.7 equiv), and the colorless solution was stirred at RT for 20 min. At this point the volatiles were removed *in vacuo* and the residue was dried in high vacuum. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 ml), and piperonal (61 mg, 0.41 mmol, 1.5 equiv) and sodium triacetoxyborohydride (115 mg, 0.54 mmol, 2.0 equiv) were added followed by triethylamine (0.08 ml, 0.54 mmol, 2.0 equiv). The mixture was stirred at RT for 7 h, when it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and washed with saturated aqueous NaHCO<sub>3</sub> (15 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc : Et<sub>3</sub>N 66:33:1 → 50:50:1 gradient) to afford the pure title compound. Yield: 56 mg (0.24 mmol, 89%). Colorless oil.

**TLC:** *R<sub>f</sub>* = 0.13 (EtOAc; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.81 – 6.63 (m, 3H), 5.92 (s, 2H), 4.49 (t, *J*=7.6, 2H), 3.59 (dd, *J*=7.3, 2.5, 2H), 3.48 (s, 2H), 3.14 (dd, *J*=7.3, 2.5, 2H), 2.83 (t, *J*=7.6, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 147.6, 146.6, 131.9, 121.6, 108.9, 108.0, 100.8, 82.9, 68.1, 66.7, 63.4, 32.3; **IR** (thin film): 2936, 2888, 2821, 1502, 1489, 1243, 1184, 1038, 935, 838, 810, 773 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>13</sub>H<sub>16</sub>NO<sub>3</sub> ([*M*+H]<sup>+</sup>), 234.1125; found 234.1126.



**1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-azaspiro[3.3]heptane (165).** A mixture of ethyl 2-cyclobutylideneacetate (95% purity; 198 mg, 1.34 mmol, 1.0 equiv) and piperonylamine (0.33 ml, 2.68 mmol, 2.0 equiv) was heated to 60 °C and stirring was continued for 26 h. At this point the mixture was allowed to cool to RT and then directly purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford the pure addition product. Yield: 202 mg (0.69 mmol, 52%). Colorless oil. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 6.87 (dd, *J*=1.0, 0.5, 1H), 6.84 – 6.69 (m, 2H), 5.92 (s, 2H), 4.15 (q, *J*=7.1, 2H), 3.60 (s, 2H), 2.69 (s, 2H), 2.16 – 1.63 (m, 7H), 1.26 (t, *J*=7.1, 3H). This material (202 mg, 0.69 mmol, 1.0 equiv) was dissolved in Et<sub>2</sub>O (9 ml) and the solution was cooled to



0 °C.  $\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 0.69 mmol, 4.0 equiv) was added, and the mixture was stirred at 0 °C for 15 min. At this point the reaction was quenched by addition of  $\text{H}_2\text{O}$  (0.11 ml),  $\text{NaOH}$  (15% in  $\text{H}_2\text{O}$ ; 0.11 ml), and  $\text{H}_2\text{O}$  (0.33 ml). The resulting colorless suspension was thoroughly stirred at RT for 15 min, when the solids were filtered off and the filter cake was thoroughly washed with  $\text{Et}_2\text{O}$ . The filtrate was concentrated *in vacuo* and the residue was directly used for next step by dissolving it in  $\text{CH}_3\text{CN}$  (10 ml). Then was added triphenylphosphine (0.27 g, 1.04 mmol, 1.5 equiv) and carbon tetrabromide (0.34 g, 1.04 mmol, 1.5 equiv), and the mixture was stirred at RT for 45 min. At this point was added  $\text{H}_2\text{O}$  (2 ml), followed by potassium carbonate (0.19 g, 1.38 mmol, 2.0 equiv), and the colorless mixture was heated to 60 °C and stirred for 14 h. The reaction mixture was then cooled to RT and concentrated to  $1/5$  of the initial volume. The residue was partitioned between  $\text{EtOAc}$  (30 ml) and saturated aqueous  $\text{NaHCO}_3$  (15 ml). The phases were separated, and the aqueous layer was extracted with  $\text{EtOAc}$  (10 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure product was obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  :  $\text{MeOH}$  96:4). Yield: 92 mg (0.40 mmol, 58% over 2 steps; 30% over 3 steps). Colorless oil.

**TLC:**  $R_f = 0.25$  ( $\text{CH}_2\text{Cl}_2$  :  $\text{MeOH}$  95:5; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.89 - 6.82$  (m, 1H),  $6.82 - 6.67$  (m, 2H),  $5.92$  (s, 2H),  $3.54$  (s, 2H),  $3.08$  (t,  $J=6.9$ , 2H),  $2.36 - 2.23$  (m, 2H),  $2.19$  (t,  $J=6.9$ , 2H),  $2.05 - 1.85$  (m, 2H),  $1.70 - 1.51$  (m, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.5, 146.3, 132.8, 121.6, 109.2, 107.9, 100.8, 69.3, 56.1, 49.7, 32.5, 31.6, 13.4$ ; **IR** (thin film): 2954, 2823, 1502, 1489, 1441, 1249, 1040, 937, 809, 743  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$  ( $[\text{M}+\text{H}]^+$ ), 232.1332; found 232.1328.

## 9.4 Advanced Angular Spirocycles

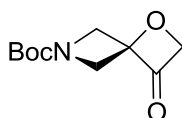


***tert*-Butyl 3-ethynyl-3-hydroxyazetidino-1-carboxylate (166).** To a solution of ethynyl-trimethylsilane (0.24 ml, 1.74 mmol, 1.5 equiv) in THF (13 ml) was added at  $-78$  °C  $\text{BuLi}$  (1.6 M in hexanes; 1.05 ml, 1.68 mmol, 1.45 equiv), and the mixture was stirred at  $-78$  °C for 15 min, when a solution of *tert*-butyl 3-oxoazetidino-1-carboxylate (199 mg, 1.16 mmol, 1.0 equiv) in THF (2 ml; rinsed with 0.3 ml) was added over 2 min. The reaction mixture was stirred at  $-78$  °C for 15 min, when it was allowed to warm to  $-20$  °C over 60 min. At this point it was quenched with half-saturated aqueous  $\text{NaCl}$  (15 ml) and diluted with  $\text{EtOAc}$  (20 ml). The phases

were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was directly used for the next step.

To a solution of *tert*-butyl 3-hydroxy-3-((trimethylsilyl)ethynyl)azetidine-1-carboxylate (313 mg, 1.16 mmol, 1.0 equiv) in THF (13 ml) was added at 0 °C TBAF (1 M in THF; 1.39 ml, 1.39 mmol, 1.2 equiv), and the mixture was stirred at 0 °C for 15 min. At this point was added half-saturated aqueous  $\text{NH}_4\text{Cl}$  (15 ml) followed by EtOAc (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to afford the pure title compound. Yield: 213 mg (1.08 mmol, 93% over 2 steps). Colorless oil.

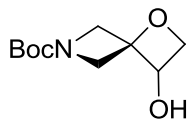
**TLC:**  $R_f = 0.61$  (hexanes : EtOAc 1:1; CAM, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.19$  (d,  $J=9.1$ , 2H), 4.02 (d,  $J=9.1$ , 2H), 3.63 (br s, 1H), 2.67 (s, 1H), 1.44 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.2$ , 83.8, 80.2, 74.1, 63.9, 61.9, 28.3; **IR** (neat): 3294, 2979, 1672, 1418, 1367, 1156, 1080, 646  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{15}\text{NNaO}_3$  ( $[\text{M}+\text{Na}]^+$ ), 220.0944; found 220.0946.



***tert*-Butyl 3-oxo-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (167).** To a solution of *tert*-butyl 3-ethynyl-3-hydroxyazetidine-1-carboxylate (**166**) (81 mg, 0.41 mmol, 1.0 equiv), 8-ethylquinoline 1-oxide (142 mg, 0.82 mmol, 2.0 equiv), and  $[\text{BrettPhosAuNTf}_2]$  (20.8 mg, 0.021 mmol, 0.05 equiv) in DCE (10 ml) was added at RT methanesulfonic acid (0.04 ml, 0.62 mmol), and the mixture was stirred at RT for 3 h. At this point the mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  (30 ml) and HCl (1 M in  $\text{H}_2\text{O}$ ; 10 ml). The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml). The combined organic phases were washed with saturated aqueous NaCl (15 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) to afford the pure title compound. Yield: 46 mg (0.22 mmol, 53%). Slightly yellowish oil.

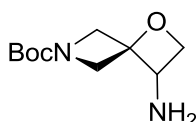
**TLC:**  $R_f = 0.21$  (hexanes : EtOAc 2:1; CAM, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.28$  (s, 2H), 4.35 (dd,  $J=10.6$ , 1.5, 2H), 4.24 (dd,  $J=10.6$ , 1.5, 2H), 1.44 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 199.3$ , 155.7, 99.9, 89.2, 80.4, 58.9, 28.3; **IR** (thin film): 2974, 2937, 1826,

1705, 1393, 1369, 1243, 1169, 950, 913, 745  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{15}\text{NNaO}_4$  ( $[\text{M}+\text{Na}]^+$ ), 236.0893; found 236.0889.



**tert-Butyl 3-hydroxy-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (168).** To a solution of ketone **167** (10.5 mg, 0.049 mmol, 1.0 equiv) in MeOH (1 ml), cooled to 0 °C, was added sodium borohydride (3.6 mg, 0.09 mmol, 1.9 equiv) and the mixture was stirred at 0 °C for 20 min, when it was allowed to warm to RT and stirring was continued for another 20 min. At this point it was partitioned between EtOAc (20 ml) and  $\text{H}_2\text{O}$  (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 10.5 mg (0.049 mmol, 99%). Colorless oil.

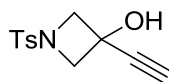
**TLC:**  $R_f = 0.23$  (hexanes : EtOAc 1:1; CAM, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.74$  (dd,  $J=11.5, 5.7$ , 1H), 4.63 (t,  $J=6.7$ , 1H), 4.49 (d,  $J=11.5$ , 1H), 4.33 (dd,  $J=6.7, 5.7$ , 1H), 4.05 (q,  $J=10.6$ , 2H), 3.93 (d,  $J=10.6$ , 1H), 3.43 (br s, 1H), 1.43 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.4, 87.5, 80.0, 76.1, 69.7, 61.2, 57.0, 28.3$ ; **IR** (thin film): 3397, 2978, 2941, 2876, 1674, 1423, 1367, 1167, 1097, 957, 855  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{10}\text{H}_{18}\text{NO}_4$  ( $[\text{M}+\text{H}]^+$ ), 216.1230; found 216.1237.



**tert-Butyl 3-amino-1-oxa-6-azaspiro[3.3]heptane-6-carboxylate (169).** To a solution of ketone **167** (23.4 mg, 0.110 mmol, 1.0 equiv) in EtOH (1 ml) and  $\text{H}_2\text{O}$  (1 ml) was added hydroxylamine hydrochloride (11.4 mg, 0.165 mmol, 1.5 equiv) and sodium acetate (22.5 mg, 0.274 mmol, 2.5 equiv), and the mixture was placed in a preheated oil bath (80 °C), and stirring at that temperature was continued for 5.5 h. Then it was cooled to RT and stirred over night. At this point it was partitioned between EtOAc (20 ml) and  $\text{H}_2\text{O}$  (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (20 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford the crude product (25 mg) as a slightly yellowish oil (*ca.* 14:11 ratio of oxime isomers). This material was pure enough for the next step.

Raney nickel (50% slurry in H<sub>2</sub>O; ca. 100 mg) was placed in a flask equipped with a stir bar under Ar. It was washed with EtOH (3 × 1 ml). The residue was suspended in EtOH (1 ml) and a solution of the above mentioned mixture of oxime isomers (25 mg, 0.11 mmol, 1.0 equiv) in EtOH (1.4 ml) was added. A hydrogen atmosphere was built up, and the mixture was vigorously stirred at RT for 3.5 h. At this point the atmosphere was changed to nitrogen, and the mixture was filtered over celite and thoroughly washed with MeOH. The filtrate was concentrated *in vacuo* and the residue filtered again over a small pad of celite using CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The filtrate was concentrated *in vacuo* to afford the title compound in good purity. Purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2 → 95:5 → 90:10 gradient) afforded the pure title compound. Yield: 13.5 mg (0.063 mmol, 58% over 2 steps). Colorless oil.

**TLC:**  $R_f$  = 0.30 (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5; ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.69 (dd,  $J$ =7.3, 6.3, 1H), 4.37 (dd,  $J$ =10.3, 1.4, 1H), 4.19 – 4.06 (m, 2H), 4.06 – 3.95 (m, 2H), 3.89 (dd,  $J$ =10.3, 1.4, 1H), 1.57 (br s, 2H), 1.44 (s, 9H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.2, 87.7, 79.7, 76.7, 61.9, 56.9, 53.3, 28.3; **IR** (thin film): 3366, 2974, 2872, 1695, 1411, 1216, 1174, 1090, 960, 913, 773 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>3</sub> ([M+Na]<sup>+</sup>), 237.1210; found 237.1209.

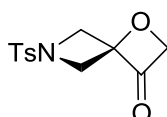


**3-Ethynyl-1-tosylazetididin-3-ol (180).** To a solution of ethynyltrimethylsilane (0.092 ml, 0.666 mmol, 1.5 equiv) in THF (5 ml) was added at –78 °C BuLi (1.6 M in hexanes; 0.40 ml, 0.64 mmol, 1.45 equiv), and the mixture was stirred at –78 °C for 15 min, when a solution of ketone **137** (100 mg, 0.44 mmol, 1.0 equiv) in THF (2 ml; rinsed with 0.3 ml) was added over 2 min. The mixture was stirred at –78 °C for 15 min, then it was allowed to warm to –20 °C over 60 min. At this point it was quenched with half-saturated aqueous NaCl (15 ml) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue did not require any further purification and was used as such for the next step.

To a solution of this material (138 mg, 0.43 mmol, 1.0 equiv) in THF (5 ml) was added at 0 °C TBAF (1 M in THF; 0.51 ml, 0.51 mmol, 1.2 equiv), and the mixture was stirred at 0 °C for 15 min. At this point was added half-saturated aqueous NH<sub>4</sub>Cl (15 ml) followed by EtOAc (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure

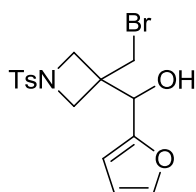
product was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 2:1). Yield: 83 mg (0.33 mmol, 74% over 2 steps). Colorless solid.

**TLC:**  $R_f = 0.15$  (hexanes : EtOAc 2:1; CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.73$  (d,  $J=8.1$ , 2H), 7.37 (d,  $J=8.1$ , 2H), 4.07 (dd,  $J=8.0$ , 1.3, 2H), 3.83 (dd,  $J=8.0$ , 1.3, 2H), 2.61 (s, 1H), 2.58 (s, 1H), 2.46 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 144.4$ , 131.4, 129.8, 128.4, 82.6, 74.7, 64.6, 61.2, 21.6; **IR** (thin film): 3461, 3334, 1597, 1445, 1301, 1293, 1160, 1090, 914 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>), 252.0689; found 252.0690.



**6-Tosyl-1-oxa-6-azaspiro[3.3]heptan-3-one (181).** To a solution of 3-ethynyl-1-tosylazetid-3-ol (102 mg, 0.406 mmol, 1.0 equiv), 8-ethylquinoline 1-oxide (141 mg, 0.812 mmol, 2.0 equiv), and [BrettPhosAuNTf<sub>2</sub>] (33 mg, 0.03 mmol, 0.08 equiv) in DCE (13 ml) was added at RT methanesulfonic acid (0.040 ml, 0.609 mmol, 1.5 equiv), and the flask was immersed into an oil bath preheated to 40 °C. Heating was continued for 3 h. At this point the mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and HCl (1 M in H<sub>2</sub>O; 15 ml). The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2). Yield: 42 mg (0.16 mmol, 39%). Slightly yellowish oil that solidifies upon standing.

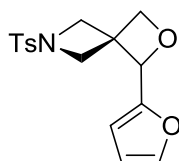
**TLC:**  $R_f = 0.27$  (hexanes : EtOAc 1:1; CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.72$  (d,  $J=8.1$ , 2H), 7.39 (d,  $J=8.1$ , 2H), 5.21 (s, 2H), 4.20 (dd,  $J=9.2$ , 1.9, 2H), 4.07 (dd,  $J=9.2$ , 1.9, 2H), 2.48 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 197.7$ , 144.7, 131.3, 130.0, 128.4, 98.0, 89.4, 59.6, 21.6; **IR** (neat): 2925, 1827, 1597, 1342, 1158, 1090, 1038, 947, 679 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>4</sub>S ([M+H]<sup>+</sup>), 268.0638; found 268.0628.



**(3-(Bromomethyl)-1-tosylazetid-3-yl)(furan-2-yl)methanol (189).** To a solution of freshly distilled furan (0.27 ml, 3.63 mmol, 6.0 equiv) in THF (8 ml), cooled to -78 °C, was added over 3 min BuLi (1.6 M in hexanes; 1.51 ml, 2.42 mmol, 4.0 equiv), and the resulting solution

was allowed to warm to  $-10\text{ }^{\circ}\text{C}$  over 60 min, when it was cooled again to  $-78\text{ }^{\circ}\text{C}$ . At this point was added a solution of aldehyde **67** (201 mg, 0.61 mmol, 1.0 equiv) in THF (1.5 ml; rinsed with 0.5 ml) over 5 min. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min, when it was quenched with  $\text{H}_2\text{O}$  (5 ml) and diluted with EtOAc (20 ml) and half-saturated aqueous NaCl (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (25 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:2). Yield: 215 mg (0.54 mmol, 89%). Colorless oil.

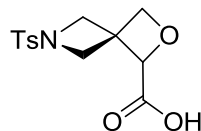
**TLC:**  $R_f = 0.32$  (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.72$  (d,  $J=8.1$ , 2H), 7.35 (d,  $J=8.1$ , 2H), 7.31 – 7.28 (m, 1H), 6.35 – 6.21 (m, 2H), 4.85 (d,  $J=4.6$ , 1H), 4.02 (dd,  $J=14.3$ , 8.4, 2H), 3.64 (dd,  $J=14.3$ , 10.0, 2H), 3.53 (d,  $J=8.4$ , 1H), 3.14 (d,  $J=10.0$ , 1H), 2.45 (s, 3H), 2.02 (d,  $J=4.6$ , 1H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.2$ , 144.0, 142.9, 131.7, 129.7, 128.4, 110.3, 109.0, 67.4, 54.9, 54.4, 42.1, 36.7, 21.6; **IR** (thin film): 3498, 2952, 2878, 1598, 1340, 1161, 1089, 914, 816, 744, 672, 550  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{16}\text{H}_{19}\text{BrNO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 400.0213; found 400.0210.



**1-(Furan-2-yl)-6-tosyl-2-oxa-6-azaspiro[3.3]heptane (190).** The bromoalcohol **189** (202 mg, 0.51 mmol, 1.0 equiv) was dissolved in MeOH (15 ml) and potassium carbonate (349 mg, 2.52 mmol, 5.0 equiv) was added, and the suspension was heated to  $60\text{ }^{\circ}\text{C}$  and the resulting solution was stirred at that temperature for 5 h and subsequently was held at  $50\text{ }^{\circ}\text{C}$  for 14 h. At this point the mixture was concentrated to approximately  $1/5$  of the initial volume, after which it was partitioned between EtOAc (30 ml) and half-saturated aqueous NaCl (15 ml). The phases were separated, and the organic phase was washed with saturated aqueous NaCl (10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The title compound was obtained in good purity ( $>95\%$  by  $^1\text{H NMR}$ ) after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1). Yield: 98 mg (0.31 mmol, 61%).

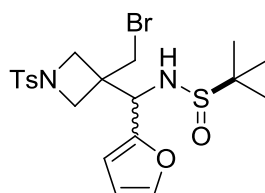
**TLC:**  $R_f = 0.21$  (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:**  $132\text{--}133\text{ }^{\circ}\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.63$  (d,  $J=8.2$ , 2H), 7.48 – 7.40 (m, 1H), 7.31 (d,  $J=8.2$ , 2H), 6.34 (dd,  $J=3.3$ , 1.8, 1H), 6.26 – 6.20 (m, 1H), 5.31 (s, 1H), 4.71 (d,  $J=6.9$ , 1H), 4.57 (d,  $J=6.9$ , 1H), 3.97 (q,  $J=9.1$ , 2H), 3.81 (d,  $J=9.5$ , 1H), 3.60 (d,  $J=9.5$ , 1H), 2.44 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,

$\text{CDCl}_3$ ):  $\delta = 150.8, 144.1, 143.8, 130.9, 129.6, 128.1, 110.4, 110.3, 82.2, 78.4, 59.2, 57.4, 42.0, 21.7$ ; **IR** (thin film): 2939, 2882, 1335, 1162, 1044, 964, 813, 749, 709, 675  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{16}\text{H}_{18}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 320.0951; found 320.0961.



**6-Tosyl-2-oxa-6-azaspiro[3.3]heptane-1-carboxylic acid (191).** To a mixture of furan **190** (35 mg, 0.11 mmol, 1.0 equiv) and sodium periodate (234 mg, 1.10 mmol, 10.0 equiv) in  $\text{CCl}_4$  (0.8 ml)/ $\text{CH}_3\text{CN}$  (0.8 ml)/ $\text{H}_2\text{O}$  (1.0 ml) was added at RT  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$  (1.2 mg, 5.5  $\mu\text{mol}$ , 0.05 equiv), and the now dark brown mixture was vigorously stirred at RT for 40 min. Then it was diluted with EtOAc (10 ml) and filtered over celite (thoroughly washed with EtOAc). Then was added  $\text{H}_2\text{O}$  (10 ml) and HCl (1 M in  $\text{H}_2\text{O}$ ; 5 ml), and the phases were separated. The aqueous layer was extracted with EtOAc (15 ml), and the combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH : AcOH 95:4:1) to afford the pure title compound. Yield: 22 mg (0.07 mmol, 68%). Colorless amorphous solid.

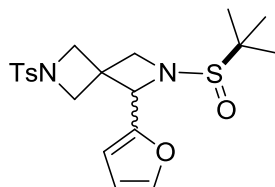
**TLC:**  $R_f = 0.24$  ( $\text{CH}_2\text{Cl}_2$  : MeOH : AcOH 95:4:1; UV, CAM);  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$  :  $\text{CD}_3\text{OD}$  7:2):  $\delta = 7.59$  (d,  $J=8.0$ , 2H), 7.29 (d,  $J=8.0$ , 2H), 4.82 (s, 1H), 4.50 (s, 2H), 4.00 – 3.51 (m, 4H), 2.36 (s, 3H);  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$  :  $\text{CD}_3\text{OD}$  7:2):  $\delta = 170.8, 144.6, 130.6, 129.7, 128.1, 83.9, 79.1, 59.1, 56.7, 39.6, 21.3$ ; **IR** (neat): 3498, 2955, 2924, 2885, 1719, 1615, 1598, 1338, 1156, 1090, 957, 814, 678  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{16}\text{NO}_5\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 298.0744; found 298.0752.



**(R)-N-((3-(Bromomethyl)-1-tosylazetididin-3-yl)(furan-2-yl)methyl)-2-methylpropane-2-sulfonamide (194).** To a solution of freshly distilled furan (0.30 ml, 4.13 mmol, 6.0 equiv) in THF (5 ml), cooled to  $-78$   $^\circ\text{C}$ , was added over 5 min BuLi (1.6 M in hexanes; 1.72 ml, 2.76 mmol, 4.0 equiv), and the resulting solution was allowed to warm to  $-50$   $^\circ\text{C}$  over 60 min, when it was cooled again to  $-78$   $^\circ\text{C}$ . At this point was added a solution of imine **68** (300 mg, 0.69 mmol, 1.0 equiv) in THF (2.5 ml; rinsed with 0.3 ml) over 5 min. The mixture was stirred

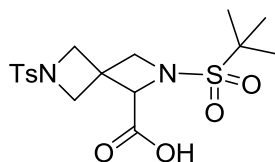
at  $-78\text{ }^{\circ}\text{C}$  for 15 min, when it was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (3 ml) and diluted with EtOAc (25 ml) and water (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*.  $^1\text{H}$  NMR analysis of the residue revealed an almost pure mixture of diastereomeric addition products (d.r.  $\sim 1:1$ ). Yield: 348 mg (0.69 mmol, quantitative). This material was used for the next step without further purifications.

**TLC:**  $R_f = 0.37$  (hexanes : EtOAc 1:2; UV, CAM) and 0.31 (hexanes : EtOAc 1:2; UV, CAM).



**(*R*)-2-(*tert*-Butylsulfinyl)-1-(furan-2-yl)-6-tosyl-2,6-diazaspiro[3.3]heptane (195).** To a solution of unpurified sulfinamide **194** (348 mg, 0.69 mmol, 1.0 equiv) in THF (15 ml), cooled to  $0\text{ }^{\circ}\text{C}$ , was added in one portion  $\text{KO}t\text{Bu}$  (171 mg, 1.52 mmol, 2.2 equiv). The now brown solution was stirred at  $0\text{ }^{\circ}\text{C}$  for 30 min, when it was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (5 ml). The mixture was diluted with EtOAc (40 ml) and  $\text{H}_2\text{O}$  (20 ml), and the phases were separated. The aqueous phase was extracted with EtOAc (20 ml), and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to afford the crude product as a brownish solid. The title compound (as a mixture of diastereomers) was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:3  $\rightarrow$  1:2 gradient). Yield: 179 mg (0.42 mmol, 61% over 2 steps). Colorless solid.

**TLC:**  $R_f = 0.35$  (hexanes : EtOAc 1:1; UV, CAM) and 0.29 (hexanes : EtOAc 1:1; UV, CAM).

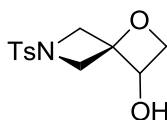


**2-(*tert*-Butylsulfonyl)-6-tosyl-2,6-diazaspiro[3.3]heptane-1-carboxylic acid (196).**  $\text{RuCl}_3 \cdot \text{H}_2\text{O}$  (1.0 mg, 3.0  $\mu\text{mol}$ , 0.05 equiv) was added to a mixture of  $\text{NaIO}_4$  (0.17 g, 0.78 mmol, 15.0 equiv),  $\text{CH}_2\text{Cl}_2$  (1 ml),  $\text{CH}_3\text{CN}$  (0.04 ml), and  $\text{H}_2\text{O}$  (0.7 ml). The now brownish mixture was stirred at RT for 1 h. At this point was added more  $\text{H}_2\text{O}$  (0.7 ml) and then in one portion a solution of furan **195** (mixture of diastereomers; 22 mg, 0.05 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1 ml). The now dark brown to black mixture was vigorously stirred at RT for 12 h. Then it was diluted



with  $\text{CH}_2\text{Cl}_2$  (5 ml), acidified to pH  $\sim 1$  with  $\text{NaHSO}_4$  (1 M in  $\text{H}_2\text{O}$ ), and the mixture was filtered over celite (rinsed with  $\text{CH}_2\text{Cl}_2$ ). The phases were then separated, and the organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford the title compound in good purity. Yield: 18 mg (0.04 mmol, 83%). An analytically pure sample can be obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH : AcOH 100:1:1). Colorless solid.

**TLC:**  $R_f = \sim 0.35$  ( $\text{CH}_2\text{Cl}_2$  : MeOH 9:1; UV, CAM); **Melting Point:** 197-199 °C (decomp.);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$  :  $\text{CD}_3\text{OD}$  6:1):  $\delta = 7.59$  (d,  $J=8.2$ , 2H), 7.29 (d,  $J=8.2$ , 2H), 4.60 (s, 1H), 4.08 (d,  $J=8.5$ , 1H), 3.91 – 3.59 (m, 4H), 3.53 (d,  $J=8.5$ , 1H), 2.36 (s, 3H), 1.25 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$  :  $\text{CD}_3\text{OD}$  6:1):  $\delta = 169.0$ , 144.7, 130.4, 129.8, 128.1, 66.3, 60.1, 59.8, 59.1, 57.5, 34.0, 23.4, 21.3; **IR** (neat): 3340, 3265, 2928, 1756, 1330, 1311, 1150, 1124, 1087, 1030, 812, 674  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_6\text{S}_2$  ( $[\text{M}+\text{H}]^+$ ), 417.1149; found 417.1151.

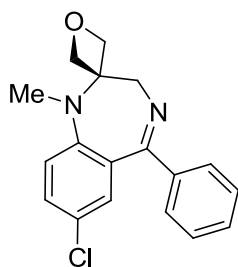


**6-Tosyl-1-oxa-6-azaspiro[3.3]heptan-3-ol (205).** To a solution of ketone **181** (10.0 mg, 0.04 mmol, 1.0 equiv) in MeOH (1 ml), cooled to 0 °C, was added sodium borohydride (3.0 mg, 0.08 mmol, 2.0 equiv) and the mixture was stirred at 0 °C for 15 min, when it was allowed to warm to RT and stirring was continued for another 60 min. At this point it was partitioned between EtOAc (20 ml) and  $\text{H}_2\text{O}$  (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (10 ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 10.0 mg (0.04 mmol, quantitative). Colorless oil.

**TLC:**  $R_f = 0.08$  (hexanes : EtOAc 3:2; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.73$  (d,  $J=8.1$ , 2H), 7.38 (d,  $J=8.1$ , 2H), 4.76 (dd,  $J=12.1$ , 5.6, 1H), 4.54 (t,  $J=6.7$ , 1H), 4.47 (dt,  $J=9.6$ , 1.4, 1H), 4.24 (dd,  $J=6.7$ , 5.6, 1H), 4.03 (dt,  $J=9.6$ , 1.4, 1H), 3.77 (dd,  $J=9.6$ , 1.0, 1H), 3.61 (dd,  $J=9.6$ , 1.0, 1H), 3.05 (d,  $J=5.6$ , 1H), 2.46 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.6$ , 130.7, 129.9, 128.5, 86.0, 75.9, 69.5, 62.3, 58.3, 21.6; **IR** (thin film): 3480, 2966, 2881, 1597, 1342, 1160, 1092, 959, 817, 709, 675, 552  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{12}\text{H}_{16}\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 270.0795; found 270.0794.

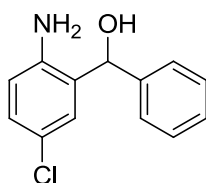
## 9.5 Drug Analogues

### Diazepam Analogue



**7-Chloro-1-methyl-5-phenyl-1,3-dihydrospiro[benzo[*e*][1,4]diazepine-2,3'-oxetane]** (**218**). To a cooled (0 °C) solution of aniline **225** (73 mg, 0.24 mmol, 1.0 equiv) in DMF (4 ml) was added in one portion NaH (60% in mineral oil; 50 mg, 1.22 mmol, 5.0 equiv), upon which the solution turned intense red. The mixture was allowed to warm to RT and stirring was continued for 30 min. At this point was added dropwise iodomethane (76  $\mu$ l, 1.22 mmol, 5.0 equiv), and the mixture was stirred at RT for 45 min, when another portion of CH<sub>3</sub>I (30 ml, 0.49 mmol, 2.0 equiv) was added. After stirring for 10 min the mixture was concentrated *in vacuo*. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NaCl and the phases were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic phases were washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : EtOAc 1:1) yielded the pure title compound. Yield: 59 mg (0.19 mmol, 77%). Slightly yellowish foam.

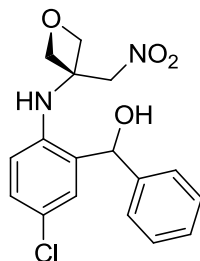
**TLC:**  $R_f$  = 0.15 (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 120–121 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.61 – 7.50 (m, 2H), 7.50 – 7.28 (m, 4H), 7.03 (d,  $J$ =8.8, 1H), 6.99 (d,  $J$ =2.6, 1H), 5.03 (d,  $J$ =7.3, 2H), 4.59 (d,  $J$ =7.3, 2H), 4.04 (s, 2H), 3.16 (s, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.6, 147.4, 139.0, 130.5, 130.2, 129.9, 129.8, 129.0, 128.1, 126.1, 120.3, 78.7, 74.3, 58.5, 34.5; **IR** (thin film): 2872, 1615, 1478, 1306, 1220, 978, 772, 699, 668 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>18</sub>H<sub>17</sub>ClN<sub>2</sub>O (M<sup>+</sup>), 312.1024; found 312.1020.



**(2-Amino-5-chlorophenyl)(phenyl)methanol** (**222**). To a cooled (0 °C) solution of 2-amino-5-chlorobenzophenone (1.00 g, 4.31 mmol, 1.0 equiv) in THF (8 ml) was dropwise added

$\text{LiAlH}_4$  (4 M in  $\text{Et}_2\text{O}$ ; 0.54 ml, 2.16 mmol, 0.5 equiv). The mixture was stirred at 0 °C for 45 min, when it was quenched by the addition of saturated aqueous sodium potassium tartrate (20 ml). The organic phase was diluted with  $\text{Et}_2\text{O}$  (40 ml) and the mixture was vigorously stirred at RT for 20 min. At this point the phases were separated, and the organic phase was washed with saturated aqueous NaCl, then dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue consisted of spectroscopically pure title compound and the spectral data was in agreement with literature values.<sup>352</sup> Yield: 1.01 g (4.31 mmol, quantitative).

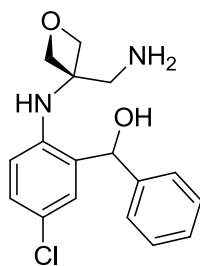
**TLC:**  $R_f = 0.37$  (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.46 - 7.27$  (m, 5H), 7.14 – 6.97 (m, 2H), 6.59 (d,  $J=8.1$ , 1H), 5.78 (d,  $J=3.1$ , 1H), 3.94 (br s, 2H), 2.61 (d,  $J=3.1$ , 1H).



**(5-Chloro-2-((3-(nitromethyl)oxetan-3-yl)amino)phenyl)(phenyl)methanol (223).** Amine **222** (0.62 g, 2.65 mmol, 1.0 equiv) and 3-(nitromethylene)oxetane (0.31 g, 2.65 mmol, 1.0 equiv) were dissolved in THF (30 ml), and the mixture was heated to 60 °C for 13 h. Then it was cooled to RT and concentrated *in vacuo*. Purification of the residue by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : EtOAc 20:1 → 10:1 gradient) afforded the pure title compound. Yield: 0.80 g (2.29 mmol, 86%). Slightly yellowish foam.

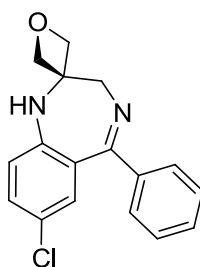
**TLC:**  $R_f = 0.61$  (hexanes : EtOAc 1:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.49 - 7.28$  (m, 5H), 7.12 (dd,  $J=8.5, 2.4$ , 1H), 7.02 (d,  $J=2.4$ , 1H), 5.86 (d,  $J=8.6$ , 1H), 5.79 (d,  $J=3.8$ , 1H), 5.53 (s, 1H), 5.10 – 4.90 (m, 2H), 4.81 – 4.58 (m, 4H), 2.41 (s, 1H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 140.4, 140.3, 129.8, 129.5, 128.7, 128.5, 128.2, 126.3, 123.3, 112.3, 78.5, 75.8, 74.7, 56.3$ ; **IR** (thin film): 3372, 2882, 1553, 1504, 1220, 987, 772, 702  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{O}_4$  ( $\text{M}^+$ ), 348.0871; found 348.0872.

<sup>352</sup> C. M. Martínez-Vituro, D. Domínguez, *Tetrahedron Lett.* **2007**, 48, 1023–1026.



**(2-((3-(Aminomethyl)oxetan-3-yl)amino)-5-chlorophenyl)(phenyl)methanol (224).** To a solution of nitro compound **223** (0.60 g, 1.71 mmol, 1.0 equiv) in *i*PrOH (50 ml) was added HCl (1 M in H<sub>2</sub>O; 17 ml) and the mixture was stirred at RT for 10 min, when Zn powder (2.23 g, 34.2 mmol, 20.0 equiv) was added in one portion under vigorous stirring. After stirring at RT for 9 min, the reaction was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (100 ml). The formed mixture was stirred for 20 min, then filtered over celite (rinsed with CH<sub>2</sub>Cl<sub>2</sub>). Subsequently, the phases were separated, and the organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue consisted of almost pure title compound that was used for the next transformation without any further purification. Yield: 0.52 g (1.62 mmol, 95%). Colorless foam.

**TLC:**  $R_f = 0.03$  (EtOAc; UV, ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.44 - 7.27$  (m, 5H), 7.06 (dd,  $J=8.5, 2.5$ , 1H), 7.00 (d,  $J=2.5$ , 1H), 5.94 (d,  $J=8.6$ , 1H), 5.70 (s, 1H), 5.15 (s, 1H), 4.53 (dd,  $J=9.6, 6.2$ , 2H), 4.47 - 4.35 (m, 2H), 3.03 (q,  $J=13.1$ , 2H), 2.32 (br s, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 141.5, 141.3, 130.0, 129.4, 128.6, 128.4, 127.9, 126.2, 122.5, 114.2, 79.7, 79.3, 74.7, 58.4, 43.8$ .

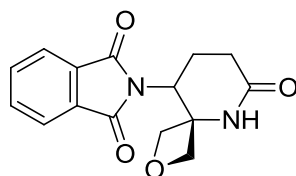


**7-Chloro-5-phenyl-1,3-dihydrospiro[benzo[*e*][1,4]diazepine-2,3'-oxetane] (225).** To a solution of unpurified amine **224** (119 mg, 0.37 mmol, 1.0 equiv) in EtOAc (10 ml) was added MnO<sub>2</sub> (0.16 g, 1.87 mmol, 5.0 equiv), and the mixture was heated to 50 °C for 1 h. Then was added more MnO<sub>2</sub> (0.32 g, 3.73 mmol, 10.0 equiv) and stirring was continued at 50 °C for 90 min. TLC indicated that still starting material was present, therefore was added more MnO<sub>2</sub> (0.16 g, 1.87 mmol, 5.0 equiv) and heating was continued for another 30 min. At this point, the mixture was cooled to RT and filtered over celite (rinsed with EtOAc). H<sub>2</sub>O (15 ml) was added

and the phases were separated. The organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc) to afford the pure title compound. Yield: 55 mg (0.18 mmol, 49%). Slightly yellowish solid.

**TLC:**  $R_f = 0.08$  (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 179-182 °C (decomp.);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.58 - 7.31$  (m, 5H), 7.23 (dd,  $J=8.6, 2.5$ , 1H), 7.03 (d,  $J=2.5$ , 1H), 6.75 (d,  $J=8.6$ , 1H), 4.72 (d,  $J=7.2$ , 2H), 4.58 (d,  $J=7.2$ , 2H), 4.35 (s, 1H), 4.09 (s, 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.4, 143.8, 139.8, 131.1, 131.1, 130.0, 129.1, 128.1, 124.9, 124.7, 120.6, 85.2, 69.7, 56.1$ ; **IR** (thin film): 3303, 3068, 2852, 1710, 1613, 1478, 1220, 969, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{17}\text{H}_{14}\text{ClN}_2\text{O}$  ( $[\text{M}-\text{H}]^+$ ), 297.0790; found 297.0790.

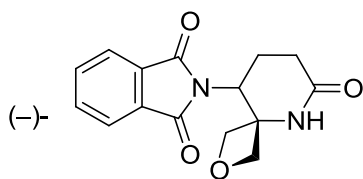
### Thalidomide & Lenalidomide Analogues



**2-(6-Oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione (239).** To a solution of phthalimide **248** (100 mg, 0.246 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (3.5 ml), cooled to 0 °C, was added a solution of CAN (270 mg, 0.492 mmol, 2.0 equiv) in  $\text{H}_2\text{O}$  (1.2 ml), and the yellow clear solution was stirred at 0 °C for 30 min. It was allowed to warm to RT and stirring was continued for 45 min, when more CAN (67 mg, 0.143 mmol, 0.5 equiv) was added in one portion. Stirring was continued for another hour. At this point the mixture was partitioned between EtOAc (20 ml) and half-saturated aqueous NaCl (20 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (20 ml), then with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The residue was dissolved in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (ca. 3:1) and silica gel was added, and the mixture was concentrated. The product on silica was added to a column and purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 100:2  $\rightarrow$  100:3) to afford the pure title compound. Yield: 38 mg (0.133 mmol, 54%). Colorless powder.

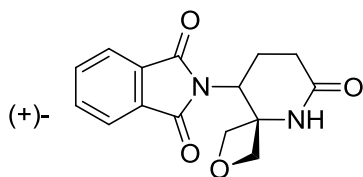
**TLC:**  $R_f = 0.21$  (EtOAc; UV); **Melting Point:**  $>250$  °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$  :  $\text{CD}_3\text{OD}$  5:2):  $\delta = 7.78 - 7.67$  (m, 2H), 7.67 - 7.54 (m, 2H), 4.80 (d,  $J=7.4$ , 1H), 4.59 - 4.35 (m, 4H), 2.79 - 2.52 (m, 1H), 2.42 - 2.11 (m, 2H), 1.91 - 1.72 (m, 1H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 169.9, 168.8, 134.5, 131.3, 123.6, 81.6, 81.3, 60.8, 50.9, 30.8, 22.2$ ; **IR** (thin film): 3183, 3080,

2884, 1713, 1672, 1394, 1374, 1220, 966, 773, 719  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{NaO}_4$  ( $[\text{M}+\text{Na}]^+$ ), 309.0846; found 309.0844.



**(-)-2-(6-Oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione** [(-)-**239**]. To a solution of 4-methoxybenzyl-protected amide (-)-**248** (300 mg, 0.738 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (10 ml), cooled to 0  $^\circ\text{C}$ , was added a solution of CAN (809 mg, 1.48 mmol, 2.0 equiv) in  $\text{H}_2\text{O}$  (3.3 ml), and the yellow clear solution was stirred at 0  $^\circ\text{C}$  for 30 min, then it was allowed to warm to RT and stirring was continued for 45 min, when more CAN (202 mg, 0.369 mmol, 0.5 equiv) was added in one portion. Stirring was continued for another hour. Then it was partitioned between EtOAc (50 ml) and half-saturated aqueous NaCl (50 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (60 ml), then with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 60$  ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 100:2  $\rightarrow$  100:3 gradient). Yield: 104 mg (0.363 mmol, 49%). Colorless powder.

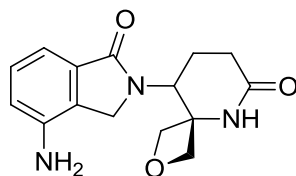
**Optical rotation:**  $[\alpha]_{\text{D}}^{23.0} -49.9$  ( $c = 0.5$ ,  $\text{CHCl}_3$  : MeOH 4:1); **Melting Point:**  $>200$   $^\circ\text{C}$ .



**(+)-2-(6-Oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione** [(+)-**239**]. To a solution of 4-methoxybenzyl-protected amide (+)-**248** (350 mg, 0.861 mmol, 1.0 equiv) in  $\text{CH}_3\text{CN}$  (11.6 ml), cooled to 0  $^\circ\text{C}$ , was added a solution of CAN (944 mg, 1.72 mmol, 2.0 equiv) in  $\text{H}_2\text{O}$  (3.9 ml), and the yellow clear solution was stirred at 0  $^\circ\text{C}$  for 30 min, then it was allowed to warm to RT and stirring was continued for 45 min, when more CAN (237 mg, 0.431 mmol, 0.5 equiv) was added in one portion. Stirring was continued for another hour. Then it was partitioned between EtOAc (50 ml) and half-saturated aqueous NaCl (50 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (60 ml), then with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 60$  ml). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure

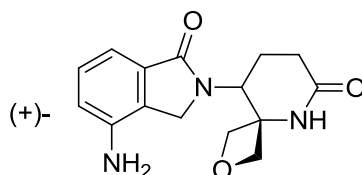
title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 100:2 → 100:3 gradient). Yield: 152 mg (0.531 mmol, 62%). Colorless powder.

**Optical rotation:**  $[\alpha]_{\text{D}}^{23.6} +47.4$  ( $c = 0.51$ , CHCl<sub>3</sub> : MeOH 4:1); **Melting Point:** >200 °C.



**9-(4-Amino-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one (240).** To a solution of lactam **251** (69 mg, 0.22 mmol, 1.0 equiv) in MeOH (5 ml)/CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added at RT palladium (10% on carbon; 43 mg, 0.04 mmol, 0.18 equiv), and a hydrogen atmosphere was built up (balloon). The mixture was stirred at RT for 50 min, when TLC analysis indicated full conversion of the starting material. An argon atmosphere was reinstalled, and the mixture was filtered over celite (washed with a 1:1 mixture of MeOH/CH<sub>2</sub>Cl<sub>2</sub>), and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5 → 92:8 gradient) to afford the pure title compound. Yield: 62 mg (0.22 mmol, 99%). Colorless powder.

**TLC:**  $R_f = 0.17$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 10:1; UV, ninhydrin); **Melting Point:** >200 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub> : CD<sub>3</sub>OD 5:2):  $\delta = 7.25 - 7.14$  (m, 2H), 6.79 (dd,  $J=6.7, 2.1$ , 1H), 5.00 (dd,  $J=6.1, 3.8$ , 1H), 4.67 (d,  $J=6.9$ , 1H), 4.63 – 4.52 (m, 3H), 4.19 (q,  $J=16.5$ , 2H), 2.40 (dd,  $J=8.1, 6.2$ , 2H), 2.22 – 1.90 (m, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> : CD<sub>3</sub>OD 3:1):  $\delta = 171.7, 170.9, 141.6, 131.3, 129.3, 125.8, 117.8, 112.8, 82.2, 79.2, 59.2, 49.6, 47.4, 28.1, 21.8$ ; **IR** (neat): 3442, 3349, 3178, 2956, 2892, 1677, 1657, 1607, 1487, 1393, 1311, 1232, 1154, 986, 819, 742 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>15</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub> ( $[\text{M}+\text{H}]^+$ ), 288.1343; found 288.1344.

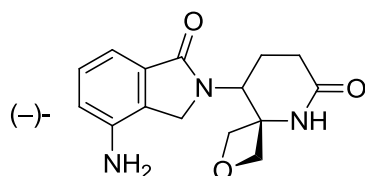


**(+)-9-(4-Amino-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(+)-240].**

To a solution of lactam (–)-**251** (212 mg, 0.668 mmol, 1.0 equiv) in MeOH (10 ml)/CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added at RT palladium (10% on carbon; 142 mg, 0.134 mmol, 0.2 equiv), and a hydrogen atmosphere was built up (balloon). The mixture was stirred at RT for 60 min, when TLC analysis indicated full conversion of the starting material. An argon atmosphere was reinstalled, and the mixture was filtered over celite (washed with a 1:1 mixture of MeOH/CH<sub>2</sub>Cl<sub>2</sub>),

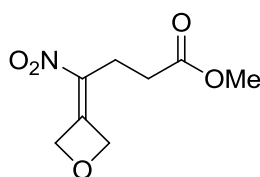
and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5 → 92:8 gradient) to afford the pure title compound. Yield: 182 mg (0.633 mmol, 95%). Colorless powder.

**Optical rotation:**  $[\alpha]_{\text{D}}^{21.9} +3.4$  (c = 0.5, CHCl<sub>3</sub> : MeOH 4:1); **Melting Point:** 182 °C (decomp.).



**(-)-9-(4-Amino-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(-)-240].** To a solution of lactam (+)-**251** (222 mg, 0.700 mmol, 1.0 equiv) in MeOH (10 ml)/CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added at RT palladium (10% on carbon; 149 mg, 0.140 mmol, 0.2 equiv), and a hydrogen atmosphere was built up (balloon). The mixture was stirred at RT for 90 min, when TLC analysis indicated full conversion of the starting material. An argon atmosphere was reinstalled, and the mixture was filtered over celite (washed with a 1:1 mixture of MeOH/CH<sub>2</sub>Cl<sub>2</sub>), and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5 → 92:8 gradient) to afford the pure title compound. Yield: 183 mg (0.637 mmol, 91%). Colorless powder.

**Optical rotation:**  $[\alpha]_{\text{D}}^{22.7} -5.8$  (c = 0.5, CHCl<sub>3</sub> : MeOH 4:1); **Melting Point:** 182 °C (decomp.).

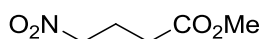


**Methyl 4-nitro-4-(oxetan-3-ylidene)butanoate (242).** To methyl 4-nitrobutanoate (1.03 g, 6.97 mmol, 1.0 equiv) was added oxetan-3-one (653 mg, 9.07 mmol, 1.3 equiv) and Et<sub>3</sub>N (0.19 ml, 1.40 mmol, 0.2 equiv), and the slightly yellowish mixture was stirred at RT for 75 min. Then it was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and the solution was cooled to -78 °C. Et<sub>3</sub>N (2.94 ml, 20.9 mmol, 3.0 equiv) was added followed by MsCl (1.36 ml, 17.4 mmol, 2.5 equiv), and the mixture was stirred at -78 °C for 30 min, when it was allowed to warm to -25 °C over *ca.* 45 min. After stirring at RT for 20 min, it was quenched with HCl (0.1 M in H<sub>2</sub>O; 50 ml). The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml), and the phases were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic layers were dried



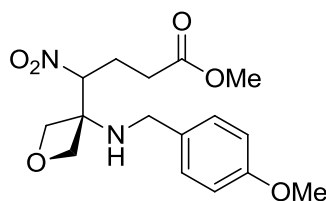
(MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1 → 2:1 → 3:2 gradient) afforded the pure title compound. Yield: 1.00 g (4.99 mmol, 72%). Colorless oil.

**TLC:**  $R_f = 0.26$  (hexanes : EtOAc 3:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 5.62 - 5.52$  (m, 2H), 5.46 – 5.34 (m, 2H), 3.69 (s, 3H), 2.70 – 2.57 (m, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 172.3, 152.1, 139.2, 79.4, 75.9, 51.9, 30.6, 22.6$ .



**Methyl 4-nitrobutanoate (244).** The compound was prepared according to a literature procedure<sup>353</sup> and the spectral data were in agreement with literature values.

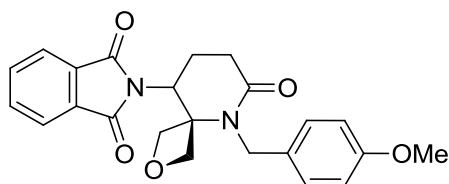
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 4.46$  (t,  $J=6.6$ , 2H), 3.68 (s, 3H), 2.46 (t,  $J=7.5$ , 2H), 2.30 (tt,  $J=7.5, 6.6$ , 2H).



**Methyl 4-(3-((4-methoxybenzyl)amino)oxetan-3-yl)-4-nitrobutanoate (246).** To a cooled (0 °C) solution of nitro compound **242** (2.78 g, 13.8 mmol, 1.0 equiv) in THF (110 ml) was added 4-methoxybenzylamine (1.80 ml, 13.8 mmol, 1.0 equiv), and the mixture was stirred at 0 °C for 30 min. Then it was allowed to warm to RT and stirring was continued for another 10 min. At this point the mixture was concentrated *in vacuo* and the residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2 → 1:1 gradient) to afford the title compound in good purity (>95% by <sup>1</sup>H NMR). Yield: 4.34 g (12.8 mmol, 93%). Colorless oil.

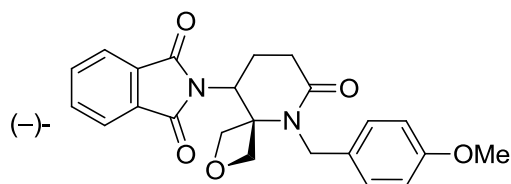
**TLC:**  $R_f = 0.49$  (hexanes : EtOAc 1:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.24$  (d,  $J=8.6$ , 2H), 6.86 (d,  $J=8.6$ , 2H), 5.06 (dd,  $J=10.4, 2.2$ , 1H), 4.76 (dd,  $J=7.4, 4.6$ , 2H), 4.61 (t,  $J=7.1$ , 2H), 3.95 – 3.79 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 2.70 – 2.23 (m, 4H), 1.79 (s, 1H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 172.4, 158.9, 131.4, 129.1, 113.9, 89.6, 77.0, 62.4, 55.2, 52.0, 46.3, 30.0, 23.8$ ; **IR** (thin film): 3323, 2953, 2891, 2833, 1736, 1552, 1513, 1440, 1369, 1247, 1220, 1175, 1033, 983, 773 cm<sup>-1</sup>; **HRMS** (MALDI): exact mass calculated for C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub> ([M+H]<sup>+</sup>), 339.1551; found 339.1550.

<sup>353</sup> D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607-1610.



**2-(5-(4-Methoxybenzyl)-6-oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione (248).** To a cooled (0 °C) solution of amine **249** (578 mg, 2.09 mmol, 1.0 equiv) in THF (17 ml) was added triethylamine (0.88 ml, 6.28 mmol, 3.0 equiv) followed by dropwise addition of phthaloyl chloride (0.30 ml, 2.09 mmol, 1.0 equiv). Formation of a colorless precipitate was observed. The mixture was stirred at 0 °C for 15 min, then it was allowed to warm to RT and stirring was continued for 2 h. The suspension was diluted with THF (7 ml) and DBU (0.97 ml, 6.28 mmol, 3.0 equiv) was added. The mixture was heated at 75 °C for 2 h. Then it was cooled to RT and concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and washed with saturated aqueous NH<sub>4</sub>Cl (20 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:2 → 1:3 → 0:1 gradient) to afford the pure title compound. Yield: 700 mg (1.72 mmol, 82%). Colorless solid.

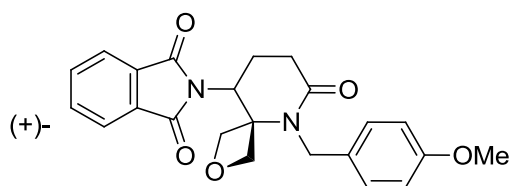
**TLC:**  $R_f = 0.45$  (EtOAc; UV, CAM); **Melting Point:** 155-157 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.94 - 7.82$  (m, 2H),  $7.82 - 7.71$  (m, 2H), 7.16 (d,  $J=8.7$ , 2H), 6.84 (d,  $J=8.7$ , 2H), 5.34 (d,  $J=15.9$ , 1H), 5.09 (d,  $J=8.0$ , 1H), 4.90 - 4.60 (m, 4H), 4.42 (d,  $J=8.0$ , 1H), 3.78 (s, 3H), 2.98 - 2.46 (m, 3H), 2.16 - 1.96 (m, 1H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 169.3$ , 168.7, 158.5, 134.4, 131.2, 130.0, 127.5, 123.6, 114.1, 78.2, 77.7, 65.2, 55.3, 52.3, 45.8, 31.7, 21.6; **IR** (thin film): 2999, 1712, 1658, 1513, 1370, 1220, 1033, 773, 674 cm<sup>-1</sup>; **HRMS** (MALDI): exact mass calculated for C<sub>23</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> ( $[M+H]^+$ ), 407.1602; found 407.1608.



**(-)-2-(5-(4-Methoxybenzyl)-6-oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione [(-)-248].** To a cooled (0 °C) solution of amine (+)-**249** (0.88 g, 3.19 mmol, 1.0 equiv) in THF (23 ml) was added triethylamine (1.35 ml, 9.58 mmol, 3.0 equiv) followed by dropwise addition of phthaloyl chloride (0.46 ml, 3.19 mmol, 1.0 equiv). Formation of a colorless precipitate was observed. The mixture was stirred at 0 °C for 15 min, then it was allowed to warm to RT and stirring was continued for 2 h. Then the suspension was diluted with THF (10 ml) and

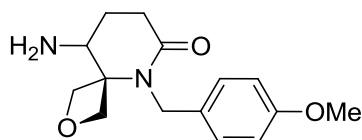
DBU (1.47 ml, 9.58 mmol, 3.0 equiv) was added. The mixture was heated at 75 °C for 2 h. Then it was cooled to RT and concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and washed with saturated aqueous NH<sub>4</sub>Cl (20 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:2 → 1:3 → 0:1 gradient). Yield: 1.18 g (2.91 mmol, 91%). Colorless foam.

**Optical rotation:**  $[\alpha]_{\text{D}}^{21.0} -14.8$  (c = 0.99, CHCl<sub>3</sub>).



**(+)-2-(5-(4-Methoxybenzyl)-6-oxo-2-oxa-5-azaspiro[3.5]nonan-9-yl)isoindoline-1,3-dione [(+)-248].** To a cooled (0 °C) solution of amine (–)-**249** (0.84 g, 3.05 mmol, 1.0 equiv) in THF (23 ml) was added triethylamine (1.29 ml, 9.14 mmol, 3.0 equiv) followed by dropwise addition of phthaloyl chloride (0.44 ml, 3.05 mmol, 1.0 equiv). Formation of a colorless precipitate was observed. The mixture was stirred at 0 °C for 15 min, then it was allowed to warm to RT and stirring was continued for 2 h. Then the suspension was diluted with THF (10 ml) and DBU (1.41 ml, 9.14 mmol, 3.0 equiv) was added. The mixture was heated at 75 °C for 2 h. Then it was cooled to RT and concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and washed with saturated aqueous NH<sub>4</sub>Cl (20 ml). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:2 → 1:3 → 0:1 gradient). Yield: 1.15 g (2.83 mmol, 93%). Colorless foam.

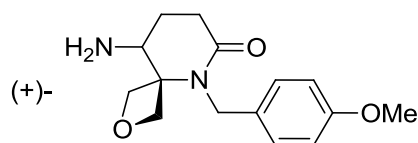
**Optical rotation:**  $[\alpha]_{\text{D}}^{27.0} +15.0$  (c = 0.98, CHCl<sub>3</sub>).



**9-Amino-5-(4-methoxybenzyl)-2-oxa-5-azaspiro[3.5]nonan-6-one (249).** RANEY-Ni (50% slurry in H<sub>2</sub>O; 15 ml, 5.7 mmol) was washed with EtOH (3 × 15 ml), then was added a solution of oxime **254** (1.65 g, 5.68 mmol, 1.0 equiv) in EtOH (60 ml), and the mixture was diluted with EtOH (60 ml). A hydrogen atmosphere (balloon) was built up, and the mixture was

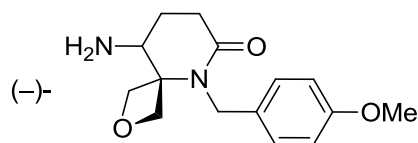
vigorously stirred at RT for 9 h. Then the atmosphere was changed to N<sub>2</sub> and the mixture was filtered over celite and washed with MeOH (*Caution*: new H<sub>2</sub>-saturated Raney-Ni is very active – never leave it dry!). The filtrate was then concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and filtered again over celite. The filtrate was concentrated *in vacuo* to afford the pure title compound. Yield: 1.45 g (5.3 mmol, 93%). Colorless foam.

**TLC:**  $R_f$  = 0.68 (MeOH; UV, CAM, ninhydrin); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.13 (d,  $J$ =8.6, 2H), 6.83 (d,  $J$ =8.6, 2H), 5.16 (d,  $J$ =16.0, 1H), 4.82 (d,  $J$ =16.0, 1H), 4.75 (d,  $J$ =7.3, 2H), 4.63 (d,  $J$ =7.3, 1H), 4.48 (d,  $J$ =7.3, 1H), 3.77 (s, 3H), 3.52 (dd,  $J$ =6.2, 2.9, 1H), 2.81 – 2.58 (m, 1H), 2.58 – 2.36 (m, 1H), 2.05 – 1.85 (m, 1H), 1.85 – 1.62 (m, 1H), 1.37 (br s, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.4, 158.2, 130.3, 127.1, 114.0, 79.4, 77.4, 65.5, 55.3, 51.2, 45.5, 28.3, 24.6; **IR** (neat): 3550, 2951, 2837, 1630, 1511, 1403, 1243, 1176, 1029, 979, 812 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>15</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> ( $[M+H]^+$ ), 277.1547; found 277.1539.



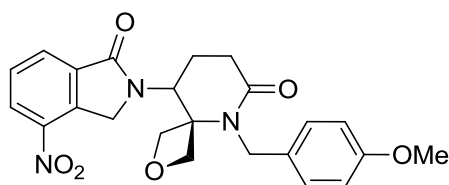
**(+)-9-Amino-5-(4-methoxybenzyl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(+)-249]**. This compound was obtained from the racemate (4.87 g, 17.6 mmol) using preparative chiral HPLC (Chiralpak AD, 220 nm, 40% *i*PrOH in heptane, flow rate: 35 ml/min at 18 bar,  $t_R$ : 71 min). Yield: 1.80 g (6.5 mmol, 37%). Colorless foam.

**Optical rotation:**  $[\alpha]_D^{24.4} +41.4$  ( $c$  = 1.0, CHCl<sub>3</sub>).



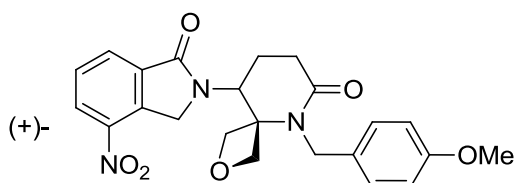
**(-)-9-Amino-5-(4-methoxybenzyl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(-)-249]**. This compound was obtained from the racemate (4.87 g, 17.6 mmol) using preparative chiral HPLC (Chiralpak AD, 220 nm, 40% *i*PrOH in heptane, flow rate: 35 ml/min at 18 bar,  $t_R$ : 86 min). Yield: 1.70 g (6.2 mmol, 35%). Colorless foam.

**Optical rotation:**  $[\alpha]_D^{25.3} -38.0$  ( $c$  = 1.0, CHCl<sub>3</sub>).



**5-(4-Methoxybenzyl)-9-(4-nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one (250).** To a solution of amine **249** (0.79 g, 2.84 mmol, 1.0 equiv) and methyl 2-(bromomethyl)-3-nitrobenzoate (**236**) (1.39 g, 3.69 mmol, 1.3 equiv) in DMF (30 ml) was added triethylamine (1.20 ml, 8.52 mmol, 3.0 equiv), and the mixture was heated to 75 °C and stirred at that temperature for 20 h. Then it was cooled to RT and poured into LiCl (5% in H<sub>2</sub>O; 70 ml). The mixture was extracted with EtOAc (2 × 60 ml), and the combined organic phases were washed with LiCl (5% in H<sub>2</sub>O; 3 × 15 ml) and saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; EtOAc : MeOH 1:0 → 20:1 gradient) and extraction (50 ml EtOAc / 2 × 20 ml 5% aqueous LiCl; to remove residual DMF). Yield: 0.90 g (2.07 mmol, 73%). Slightly yellowish foam.

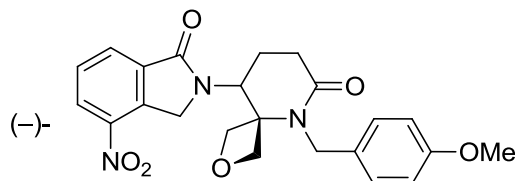
**TLC:**  $R_f = 0.28$  (EtOAc; UV); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.41$  (dd,  $J=7.9.2$ , 1.0, 1H), 8.20 (dd,  $J=7.9$ , 1.0, 1H), 7.72 (t,  $J=7.9$ , 1H), 7.29 (d,  $J=8.7$ , 2H), 6.88 (d,  $J=8.7$ , 2H), 5.29 – 5.12 (m, 2H), 5.04 – 4.82 (m, 4H), 4.73 (d,  $J=19.1$ , 1H), 4.64 (d,  $J=7.4$ , 1H), 4.58 (d,  $J=7.8$ , 1H), 3.77 (s, 3H), 2.69 (t,  $J=7.3$ , 2H), 2.38 – 2.05 (m, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 169.4$ , 167.2, 158.9, 143.4, 136.7, 134.6, 130.1, 130.0, 128.4, 127.2, 114.5, 79.9, 77.1, 64.3, 55.4, 52.4, 50.2, 46.0, 29.7, 22.0; **IR** (thin film): 2956, 1694, 1650, 1532, 1513, 1399, 1347, 1247, 1220, 1177, 1032, 985, 771, 733 cm<sup>-1</sup>; **HRMS** (MALDI): exact mass calculated for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>NaO<sub>6</sub> ([M+Na]<sup>+</sup>), 460.1479; found 460.1483.



**(+)-5-(4-Methoxybenzyl)-9-(4-nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(+)-250].** To a solution of amine (+)-**249** (0.79 g, 2.84 mmol, 1.0 equiv) and methyl 2-(bromomethyl)-3-nitrobenzoate (**236**) (1.39 g, 3.69 mmol, 1.3 equiv) in DMF (30 ml) was added triethylamine (1.20 ml, 8.52 mmol, 3.0 equiv), and the mixture was heated to 75 °C and stirred for 20 h. Then it was cooled to RT and poured into LiCl (5% in H<sub>2</sub>O; 70 ml). It was extracted with EtOAc (2 × 60 ml), and the combined organic phases were

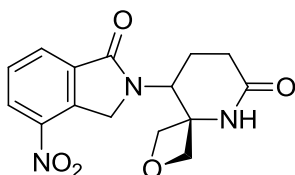
washed with LiCl (5% in H<sub>2</sub>O; 3 × 15 ml) and saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; EtOAc : MeOH 1:0 → 20:1 gradient) and extraction (50 ml EtOAc / 2 × 20 ml 5% aqueous LiCl; to remove residual DMF). Yield: 1.16 g (2.65 mmol, 93%). Slightly yellowish foam.

**Optical rotation:**  $[\alpha]_{\text{D}}^{21.0} +88.4$  (c = 1.03, CHCl<sub>3</sub>).



**(-)-5-(4-Methoxybenzyl)-9-(4-nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one [(-)-250].** To a solution of amine (-)-249 (0.86 g, 3.12 mmol, 1.0 equiv) and methyl 2-(bromomethyl)-3-nitrobenzoate (**236**) (1.52 g, 4.06 mmol, 1.3 equiv) in DMF (30 ml) was added triethylamine (1.32 ml, 9.37 mmol, 3.0 equiv), and the mixture was heated to 75 °C and stirred for 20 h. Then it was cooled to RT and poured into LiCl (5% in H<sub>2</sub>O; 70 ml). It was extracted with EtOAc (2 × 60 ml), and the combined organic phases were washed with LiCl (5% in H<sub>2</sub>O; 3 × 15 ml) and saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; EtOAc : MeOH 1:0 → 20:1 gradient) and extraction (50 ml EtOAc / 2 × 20 ml 5% aqueous LiCl; to remove residual DMF). Yield: 1.36 g (2.90 mmol, 93%). Slightly yellowish foam.

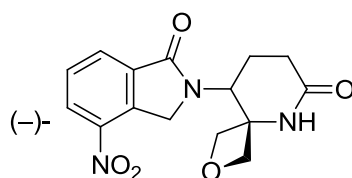
**Optical rotation:**  $[\alpha]_{\text{D}}^{21.0} -89.9$  (c = 1.0, CHCl<sub>3</sub>).



**9-(4-Nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one (251).** To a solution of 4-methoxybenzyl-protected amide **250** (221 mg, 0.505 mmol, 1.0 equiv) in CH<sub>3</sub>CN (8.5 ml), cooled to 0 °C, was added a solution of CAN (831 mg, 1.516 mmol, 3.0 equiv) in H<sub>2</sub>O (2.8 ml), and the yellow clear solution was stirred at 0 °C for 2 h. Then it was diluted with EtOAc and quenched with half-saturated aqueous NaCl (10 ml) and diluted with EtOAc (50 ml) and H<sub>2</sub>O (10 ml). The phases were separated, and the aqueous phase was extracted with EtOAc

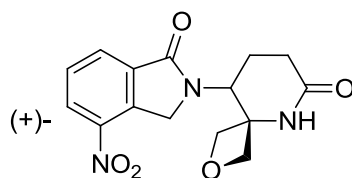
(2 × 30 ml) and CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 100:3 → 100:5 gradient). Yield: 69 mg (0.217 mmol, 43%). Colorless powder.

**TLC:**  $R_f = 0.44$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 3:1; UV); **Melting Point:** ~240 °C (decomp.); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub> : CD<sub>3</sub>OD 5:2):  $\delta = 8.32$  (dd,  $J=7.9, 0.9$ , 1H), 8.09 (d,  $J=7.9$ , 1H), 7.64 (t,  $J=7.9$ , 1H), 4.87 (s, 2H), 4.82 (dd,  $J=8.6, 3.6$ , 1H), 4.68 – 4.47 (m, 4H), 2.38 (t,  $J=6.9$ , 2H), 2.24 – 2.05 (m, 1H), 2.05 – 1.85 (m, 1H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> : CD<sub>3</sub>OD 3:1):  $\delta = 171.1, 167.7, 143.1, 136.6, 134.2, 129.9, 129.7, 127.0, 81.4, 79.4, 59.4, 50.5, 50.0, 28.5, 21.7$ ; **IR** (neat): 3349, 2953, 2891, 1694, 1670, 1532, 1391, 1344, 1234, 977, 827, 735 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>), 318.1084; found 318.1080.



**(-)-9-(4-Nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one** [(**-**)-**251**]. To a solution of 4-methoxybenzyl-protected amide (**+**)-**250** (200 mg, 0.457 mmol, 1.0 equiv) in CH<sub>3</sub>CN (6.7 ml), cooled to 0 °C, was added a solution of CAN (752 mg, 1.37 mmol, 3.0 equiv) in H<sub>2</sub>O (2.23 ml), and the yellow clear solution was stirred at 0 °C for 2 h. Then it was partitioned between EtOAc (50 ml) and half-saturated aqueous NaCl (50 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (60 ml), then CH<sub>2</sub>Cl<sub>2</sub> (2 × 60 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification of the residue together with the residue of a second equivalent batch by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 100:3 → 100:5 gradient). Yield: 130 mg (0.41 mmol, 45%). Colorless powder.

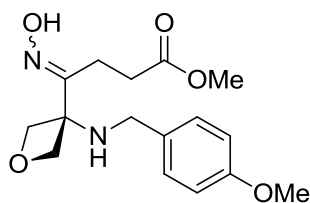
**Optical rotation:**  $[\alpha]_D^{21.1} -0.3$  (c = 0.51, CHCl<sub>3</sub> : MeOH 4:1).



**(+)-9-(4-Nitro-1-oxoisindolin-2-yl)-2-oxa-5-azaspiro[3.5]nonan-6-one** [(**+**)-**251**]. To a solution of 4-methoxybenzyl-protected amide (**-**)-**250** (200 mg, 0.457 mmol, 1.0 equiv) in CH<sub>3</sub>CN (6.7 ml), cooled to 0 °C, was added a solution of CAN (752 mg, 1.37 mmol, 3.0 equiv) in

H<sub>2</sub>O (2.23 ml), and the yellow clear solution was stirred at 0 °C for 2 h. Then it was partitioned between EtOAc (50 ml) and half-saturated aqueous NaCl (50 ml). The phases were separated, and the aqueous phase was extracted with EtOAc (60 ml), then CH<sub>2</sub>Cl<sub>2</sub> (2 × 60 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification of the residue together with the residue of a second equivalent batch by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 100:3 → 100:5 gradient). Yield: 102 mg (0.32 mmol, 35%). Colorless powder.

**Optical rotation:**  $[\alpha]_{\text{D}}^{21.1} + 1.9$  (c = 0.5, CHCl<sub>3</sub> : MeOH 4:1).



**Methyl 4-(hydroxyimino)-4-(3-((4-methoxybenzyl)amino)oxetan-3-yl)butanoate (253).**

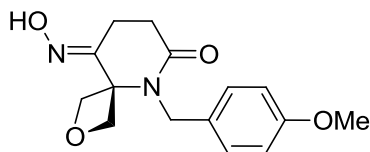
To a solution of nitro compound **246** (901 mg, 2.66 mmol, 1.0 equiv) in THF (20 ml) was added at RT tetrabutylammonium iodide (49 mg, 0.13 mmol, 0.05 equiv), benzyl bromide (0.39 ml, 3.20 mmol, 1.2 equiv), and potassium hydroxide (179 mg, 3.20 mmol, 1.2 equiv). The mixture was stirred at RT for 3.5 h. Then it was diluted with Et<sub>2</sub>O (40 ml) and washed with saturated aqueous NaCl (20 ml). Then it was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound as a mixture of oxime isomers (ratio: 1:1.65) was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1). Yield: 652 mg (2.02 mmol, 76%). Colorless solid. Oxime isomers can also be separated by FC.

*Isomer 1:* Colorless oil. **TLC:**  $R_f = 0.15$  (hexanes : EtOAc 3:2; UV, CAM); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.40$  (br s, 1H), 7.23 (d,  $J=8.7$ , 2H), 6.86 (d,  $J=8.7$ , 2H), 4.91 (d,  $J=6.7$ , 2H), 4.49 (d,  $J=6.7$ , 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.52 (s, 2H), 2.79 – 2.53 (m, 4H), 1.95 (s, 1H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 173.2$ , 158.9, 158.0, 131.5, 129.3, 113.9, 79.3, 64.0, 55.3, 51.8, 47.1, 30.1, 20.8; **IR** (neat): 3240, 2949, 2876, 1731, 1612, 1512, 1439, 1244, 1175, 1029, 977, 824 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> ( $[\text{M}+\text{H}]^+$ ), 323.1601; found 323.1600.

*Isomer 2:* Colorless solid. **TLC:**  $R_f = 0.10$  (hexanes : EtOAc 3:2; UV, CAM); **Melting Point:** 118–119 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.90$  (br s, 1H), 7.27 (d,  $J=8.2$ , 2H), 6.84 (d,  $J=8.2$ , 2H), 4.87 (d,  $J=7.4$ , 2H), 4.60 (d,  $J=7.4$ , 2H), 3.78 (s, 3H), 3.67 (s, 5H), 2.62 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 173.1$ , 158.8, 157.8, 131.7, 129.5, 113.9, 79.0, 62.7, 55.3, 51.8, 47.4, 29.7,



27.0; **IR** (neat): 3254, 3052, 2950, 2841, 1734, 1512, 1460, 1244, 1174, 1027, 976, 831  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ), 323.1601; found 323.1604.

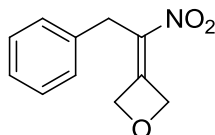


**(E)-9-(Hydroxyimino)-5-(4-methoxybenzyl)-2-oxa-5-azaspiro[3.5]nonan-6-one (254).**

A solution of methyl ester **253** (mixture of oxime isomers; 366 mg, 1.14 mmol, 1.0 equiv) in xylenes (38 ml) was heated to 140 °C and stirred at that temperature for 23 h. Then it was cooled to RT and concentrated *in vacuo* (bath temperature: 60 °C). (On larger batches, upon cooling the solution to RT the title compound will precipitate as an off-white solid that can be collected and dried *in vacuo* to afford pure material.) The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:2  $\rightarrow$  1:5 gradient) to afford the pure title compound as one oxime isomer. Yield: 276 mg (0.95 mmol, 84%). Off-white solid.

**TLC:**  $R_f$  = 0.09 (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 154 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.72 (br s, 1H), 7.07 (d,  $J=8.8$ , 2H), 6.83 (d,  $J=8.8$ , 2H), 4.97 (s, 2H), 4.93 (d,  $J=7.1$ , 2H), 4.81 (d,  $J=7.1$ , 2H), 3.78 (s, 3H), 2.86 (t,  $J=7.2$ , 2H), 2.47 (t,  $J=7.2$ , 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.4, 158.8, 154.9, 129.5, 127.6, 114.2, 78.2, 62.6, 55.2, 45.2, 29.7, 19.9; **IR** (neat): 3203, 3102, 2960, 2873, 1635, 1514, 1427, 1301, 1253, 1178, 991, 962, 809  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_4$  ( $[\text{M}+\text{Na}]^+$ ), 313.1159; found 313.1156.

## 9.6 Isoxazoles



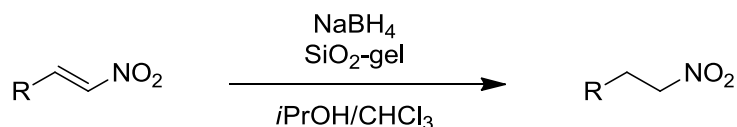
**3-(1-Nitro-2-phenylethylidene)oxetane (278).** To (2-nitroethyl)benzene (**279a**) (409 mg, 2.71 mmol, 1.0 equiv) was added oxetan-3-one (0.223 ml, 3.52 mmol, 1.3 equiv) and  $\text{Et}_3\text{N}$  (0.075 ml, 0.541 mmol, 0.2 equiv) and the slightly yellowish mixture was stirred at RT for 90 min. Then it was dissolved in  $\text{CH}_2\text{Cl}_2$  (16 ml) and cooled to  $-78$  °C. At this temperature was added  $\text{Et}_3\text{N}$  (1.14 ml, 8.12 mmol, 3.0 equiv), followed by  $\text{MsCl}$  (0.232 ml, 2.98 mmol, 1.1 equiv), and the mixture was stirred at  $-78$  °C for 30 min, then it was allowed to warm to  $-20$  °C over

1 h, when it was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 ml). It was diluted with  $\text{CH}_2\text{Cl}_2$  (30 ml) and water (10 ml) and the phases were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml), and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. After purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) the title compound was obtained as an inseparable ~22:1 mixture along with its rearrangement product 3-benzylisoxazole-4-carbaldehyde (**280a**). Yield: 250 mg (1.21 mmol, 45%). Colorless oil.

**TLC:**  $R_f = 0.40$  ( $\text{CH}_2\text{Cl}_2$  : hexanes 2:1; UV, DNP);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.48$ – $7.11$  (m, 5H), 5.73–5.46 (m, 2H), 5.01–4.77 (m, 2H), 3.82 (s, 2H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 151.0$ , 139.7, 134.5, 128.9, 128.7, 127.4, 79.8, 75.4, 33.9.

### Preparation of Nitro Compounds

Primary nitro compounds were prepared according to literature procedures. For substrates **279a-h** nitroalkanes were prepared from their corresponding nitroalkene precursors by reduction with  $\text{NaBH}_4$ ,  $\text{SiO}_2$  in  $i\text{PrOH}/\text{CHCl}_3$ <sup>354</sup> and the spectral data matched those of the literature values:



**(2-Nitroethyl)benzene (279a)**. Spectra were in agreement with literature values.<sup>355</sup>

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.26$  (m, 5H), 4.62 (t,  $J=7.3$ , 2H), 3.32 (t,  $J=7.3$ , 2H).

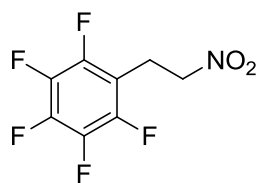
**5-(2-Nitroethyl)benzo[*d*][1,3]dioxole (279b)**. Spectra were in agreement with literature values.<sup>356</sup>

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 6.75$  (d,  $J=7.8$ , 1H), 6.70–6.62 (m, 2H), 5.95 (s, 2H), 4.56 (t,  $J=7.3$ , 2H), 3.23 (t,  $J=7.3$ , 2H).

<sup>354</sup> A. K. Sinhababu, R. T. Borchardt, *Tetrahedron Lett.* **1983**, 24, 227–230.

<sup>355</sup> Y. Motoyama, K. Kamo, H. Nagashima, *Org. Lett.* **2009**, 11, 1345–1348.

<sup>356</sup> A. Bhattacharjya, R. Mukhopadhyay, S. C. Pakrashi, *Synthesis* **1985**, 886–887.



**1,2,3,4,5-Pentafluoro-6-(2-nitroethyl)benzene (279c).** Nitromethane (0.106 ml, 1.96 mmol, 1.0 equiv) and pentafluorobenzaldehyde (0.37 ml, 1.96 mmol, 1.0 equiv) were dissolved in MeOH (2 ml) and the solution was cooled to 0 °C. NaOH (1 M in H<sub>2</sub>O; 2.20 ml, 2.20 mmol, 1.13 equiv) was added dropwise over 10 min and the reaction mixture was stirred for further 45 min at 0 °C - 5 °C. The mixture was then poured into HCl (10% in H<sub>2</sub>O; 20 ml) and the mixture was thoroughly stirred. The emulsion was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml) and the organic phase was washed with H<sub>2</sub>O (50 ml), saturated aqueous NaCl (50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The crude product (2-nitro-1-(perfluorophenyl)ethanol, 320 mg) was directly used for the next step without purification.

2-Nitro-1-(perfluorophenyl)ethanol (320 mg, 1.24 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (6.2 ml), the solution cooled to -20 °C and Et<sub>3</sub>N (0.53 ml, 3.73 mmol, 3.0 equiv) was added. MsCl (0.291 ml, 3.73 mmol, 3.0 equiv) was added dropwise and the reaction mixture was stirred at -20 °C for 1 h, and then quenched with H<sub>2</sub>O (10 ml). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and the organic phase was washed with H<sub>2</sub>O (2 × 10 ml), saturated aqueous NaCl (10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The unpurified 6-(2-nitrovinyl)-1,2,3,4,5-pentafluorobenzene (298 mg) was directly used for the next step without further purification.

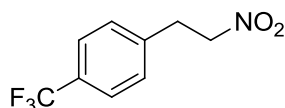
6-(2-Nitrovinyl)-1,2,3,4,5-pentafluorobenzene (**285c**) (298 mg, 1.24 mmol, 1.0 equiv) and silica gel (1.84 g) were suspended in chloroform (14.7 ml) and 2-propanol (2.8 ml). The mixture was vigorously stirred and sodium borohydride (189 mg, 4.99 mmol, 4 equiv) was added in portions over 30 min. The reaction mixture was stirred for 15 h. The excess of borohydride was then quenched with aqueous HCl (1 M; 10 ml). The reaction mixture was filtered and the filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The organic phase was washed with water (15 ml), saturated aqueous NaCl (15 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 10:1) to afford the pure title compound. Yield: 245 mg (1.01 mmol, 51% over 3 steps). Pale yellow oil.

**TLC:**  $R_f$  = 0.69 (hexanes : EtOAc 4:1; UV, KMnO<sub>4</sub>); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.63 (t,  $J$ =7.1, 1H), 3.43 (t,  $J$ =7.1, 1H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 147.6–143.0 (m), 142.6–139.0 (m), 139.2–135.4 (m), 109.1 (t,  $J$ =16.0), 72.7, 20.5; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -142.09 (dd,  $J$ =21.1, 7.8), -153.33 (t,  $J$ =21.1), -160.00 - -160.81 (m); **IR** (neat): 2926, 2849, 1659, 1557,

1523, 1500, 1379, 1126, 1070, 973, 955, 903  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_8\text{H}_3\text{F}_5$  ( $[\text{M}-\text{HNO}_2]^+$ ), 194.0149; found 194.0145.

**3-(2-Nitroethyl)pyridine (279d)**. Spectra were in agreement with literature values.<sup>357</sup>

**<sup>1</sup>H NMR** ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.65–8.40 (m, 2H), 7.61–7.47 (m, 1H), 7.34–7.17 (m, 1H), 4.63 (td,  $J=7.1, 0.9$ , 2H), 3.32 (t,  $J=7.1$ , 2H).



**1-(2-Nitroethyl)-4-(trifluoromethyl)benzene (279e)**. Nitromethane (0.341 ml, 6.32 mmol, 1.0 equiv) and 4-trifluoromethylbenzaldehyde (1.04 ml, 6.32 mmol, 1.0 equiv) were dissolved in MeOH (6 ml) and the mixture was cooled to 0 °C. NaOH (1 M in  $\text{H}_2\text{O}$ ; 7.11 ml, 7.11 mmol, 1.13 equiv) was added dropwise over 30 min and the reaction mixture was stirred for further 40 min at 0 °C - 5 °C. The mixture was then poured into HCl (10% in  $\text{H}_2\text{O}$ ; 60 ml) and the resulting mixture was stirred thoroughly. The emulsion was extracted with  $\text{CH}_2\text{Cl}_2$  (60 ml) and the organic phase was washed with  $\text{H}_2\text{O}$  (50 ml), saturated aqueous NaCl (50 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The crude product (2-nitro-1-(4-trifluoromethylphenyl)ethanol) was directly used for the next step without purification.

2-Nitro-1-(4-trifluoromethylphenyl)ethanol (1.486 g, 6.32 mmol, 1 equiv) was dissolved in  $\text{CH}_2\text{Cl}_2$  (32 ml), and the mixture was cooled to -20 °C, and  $\text{Et}_3\text{N}$  (2.66 ml, 19.0 mmol, 3.0 equiv) was added. MsCl (1.48 ml, 19.0 mmol, 3.0 equiv) was added dropwise and the reaction mixture was stirred at -20 °C for 1 h, then it was quenched with  $\text{H}_2\text{O}$  (10 ml). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (40 ml), the organic phase was washed with  $\text{H}_2\text{O}$  ( $2 \times 20$  ml), saturated aqueous NaCl (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated *in vacuo*. The crude product (4-trifluoromethyl-1-(2-nitrovinyl)benzene) was directly used for the next step without purification.

4-Trifluoromethyl-1-(2-nitrovinyl)benzene (**285e**) (1.40 g, 6.32 mmol, 1.0 equiv) and silica gel (9.52 g) were suspended in  $\text{CHCl}_3$  (70 ml) and 2-propanol (13 ml). The mixture was stirred vigorously and  $\text{NaBH}_4$  (906 mg, 25.4 mmol, 4 equiv) was added over 30 min. The reaction mixture was stirred at RT for 15 h. The excess of borohydride was then quenched with HCl (1 M in  $\text{H}_2\text{O}$ ; 5 ml). The mixture was filtered, and the filtrate was extracted with  $\text{CH}_2\text{Cl}_2$  (40 ml). The organic phase was washed with  $\text{H}_2\text{O}$  (20 ml), saturated aqueous NaCl (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ),

<sup>357</sup> T. Trefouel, P. Tintillier, G. Dupas, J. Bourguignon, G. Queguiner, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4492-4494.

filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 16:1) to afford the pure title compound. Yield: 737 mg (3.36 mmol, 53% over 3 steps). Pale yellow oil.

**TLC:**  $R_f = 0.20$  (hexanes : EtOAc 16:1; UV); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.53$  (d,  $J=8.0$ , 2H), 7.27 (d,  $J=8.0$ , 2H), 4.57 (t,  $J=7.2$ , 2H), 3.32 (t,  $J=7.2$ , 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 139.7$ , 129.7, 128.9, 125.9 (q,  $J=3.8$ ), 125.3, 122.6, 75.6, 33.0; **<sup>19</sup>F-NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta = -62.68$ ; **IR** (neat): 2980, 1621, 1558, 1380, 1327, 1168, 1068 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>NNaO<sub>2</sub> ( $[\text{M}+\text{Na}]^+$ ), 242.0399; found 242.0397.

**1-Nitro-4-(2-nitroethyl)benzene (279f).** Spectra were in agreement with literature values.<sup>358</sup>

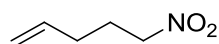
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 300 MHz):  $\delta = 8.20$  (d,  $J=8.7$ , 2H), 7.40 (d,  $J=8.7$ , 2H), 4.68 (t,  $J=7.0$ , 2H), 3.44 (t,  $J=7.0$ , 2H).

**3-(2-Nitroethyl)-1H-indole (279g).** Spectra were in agreement with literature values.<sup>359</sup>

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 300 MHz):  $\delta = 8.06$  (s, 1H), 7.61–7.51 (m, 1H), 7.41–7.33 (m, 1H), 7.26–7.02 (m, 3H), 4.67 (t,  $J=7.4$ , 2H), 3.50 (t,  $J=7.4$ , 2H).

**(2-Nitroethyl)cyclohexane (279h).** Spectra were in agreement with literature values.<sup>360</sup>

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 300 MHz):  $\delta = 4.41$  (td,  $J=7.4$ , 1.3, 2H), 1.91 (td,  $J=7.4$ , 1.3, 2H), 1.84–1.59 (m, 5H), 1.47–1.07 (m, 4H), 1.05–0.81 (m, 2H).



**5-Nitropent-1-ene (279i).** The compound was prepared according to a literature procedure<sup>361</sup> and the spectral data were in agreement with literature values.

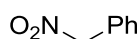
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 5.84$ –5.64 (m, 1H), 5.22–4.94 (m, 2H), 4.38 (dd,  $J=9.9$ , 3.8, 2H), 2.31–1.91 (m, 4H).

<sup>358</sup> R. Ballini, L. Barboni, G. Giarlo, *J. Org. Chem.* **2004**, 69, 6907–6908.

<sup>359</sup> C. C. Lin, J. M. Hsu, M. N. V. Sastry, H. L. Fang, Z. J. Tu, J. T. Liu, C. F. Yao, *Tetrahedron* **2005**, 61, 11751–11757.

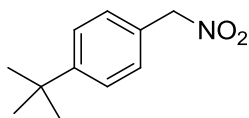
<sup>360</sup> Z. G. Zhang, P. R. Schreiner, *Synthesis* **2007**, 2559–2564.

<sup>361</sup> A. Kjær, S. R. Jensen, *Acta Chem. Scand.* **1968**, 22, 3324–3326.



**(Nitromethyl)benzene (279j).** The compound was prepared according to a literature procedure<sup>358</sup> and the spectral data were in agreement with literature values.

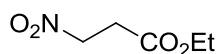
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.45 (m, 5H), 5.42 (s, 2H).



**1-tert-Butyl-4-(nitromethyl)benzene (279k).** The compound was prepared by a modified literature procedure<sup>362</sup>: In a dry Schlenk flask was placed under argon di-*tert*-butyl(2'-methylbiphenyl-2-yl)phosphine (18 mg, 0.056 mmol, 6 mol %), 1-bromo-4-*tert*-butylbenzene (0.163 ml, 0.938 mmol, 1.0 equiv), [Pd<sub>2</sub>(dba)<sub>3</sub>] (13 mg, 0.014 mmol, 3 mol %), and cesium carbonate (0.336 g, 1.03 mmol, 1.1 equiv). The flask was evacuated and flooded with argon (3 ×), then was added dry DME (5 ml) and nitromethane (0.506 ml, 9.38 mmol, 10 equiv), and the flask was placed in a preheated oil bath (50 °C) and stirring at this temperature was continued for 16.5 h. Then it was cooled to RT and saturated aqueous NH<sub>4</sub>Cl (20 ml) was added followed by Et<sub>2</sub>O (30 ml). The phases were separated and the aqueous layer was extracted with Et<sub>2</sub>O (20 ml). The combined organic phases were washed with saturated aqueous NaCl (15 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc = 40:1). Yield: 135 mg (0.699 mmol, 74%). Colorless oil.

**TLC:** *R*<sub>f</sub> = 0.36 (hexanes : EtOAc 9:1; UV, DNP); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.46 (d, *J*=8.6, 2H), 7.40 (d, *J*=8.6, 2H), 5.42 (s, 2H), 1.34 (s, 9H).

Spectral data were in agreement with literature values.<sup>363</sup>



**Ethyl 3-nitropropanoate (279m).** 3-Nitropropionic acid (500 mg, 4.07 mmol, 1.0 equiv) and oxalyl chloride (1.04 ml, 12.2 mmol, 3.0 equiv) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) at 0 °C and DMF (one drop) was added. The mixture was warmed to RT and stirred for 1 h, then volatile components were removed *in vacuo* and the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 ml). Ethanol (0.285 ml, 4.89 mmol, 1.2 equiv) was added, the solution was stirred for 5 min and then

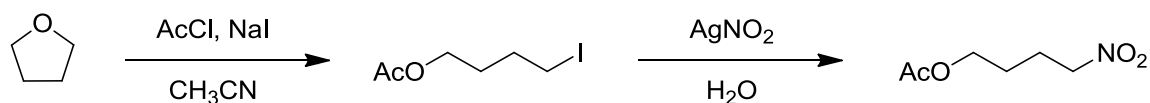
<sup>362</sup> E. M. Vogl, S. L. Buchwald, *J. Org. Chem.* **2002**, 67, 106-111.

<sup>363</sup> L. Barr, C. J. Easton, K. Lee, S. F. Lincoln, *Org. Biomol. Chem.* **2005**, 3, 2990-2993.

Et<sub>3</sub>N (1.26 ml, 8.96 mmol, 2.2 equiv) was added dropwise. After 2 h the mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (10 ml), and the phases were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and the combined organic phases were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 33:1) to afford the pure title compound. Yield: 240 mg (4.07 mmol, 40%). Colorless oil.

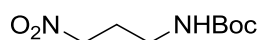
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 4.65 (t, *J*=6.1, 2H), 4.19 (q, *J*=7.2, 2H), 2.96 (t, *J*=6.1, 2H), 1.27 (t, *J*=7.2, 3H).

The spectral data were in agreement with literature values.<sup>364</sup>



**4-Nitrobutyl acetate (279n).** The compound was prepared according to a literature procedure<sup>365,358</sup> and the spectral data were in agreement with literature values.<sup>358</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 4.43 (t, *J*=6.9, 2H), 4.11 (m, 2H), 2.12 (m, 2H), 2.07 (s, 3H), 1.75 (m, 2H).



**tert-Butyl 3-nitropropylcarbamate (279o).** Iodine (3.90 g, 15.5 mmol, 1.2 equiv) was added in portions to a solution of 1*H*-imidazole (1.05 g, 15.5 mmol, 1.2 equiv) and PPh<sub>3</sub> (4.04 g, 15.5 mmol, 1.2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (75 ml) at 0 °C. The resulting deep-yellow suspension was warmed to RT before a solution of *tert*-butyl (3-hydroxypropyl)carbamate (2.25 g, 12.9 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) was added. The mixture was stirred at RT for 3.5 h, filtered over celite, and washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5% in H<sub>2</sub>O; 2 × 10 ml). The combined aqueous phases were extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and the combined organic layers were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Pure *tert*-butyl (3-iodopropyl)carbamate (2.70 g, 13.5 mmol, 81%) was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1).

Sodium nitrite (0.920 g, 13.3 mmol, 1.9 equiv) and urea (0.893 g, 14.9 mmol, 2.1 equiv) were dissolved in DMSO (7 ml). *tert*-Butyl (3-iodopropyl)carbamate (2.00 g, 7.01 mmol, 1.0 equiv), dissolved in DMSO (2 ml), was added and the reaction mixture was stirred at 0 °C for 1 h and at RT for further 1 h. The mixture turned initially orange, then brown and finally pale yellow.

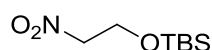
<sup>364</sup> J. K. Addo, P. Teesdale-Spittle, J. O. Hoberg, *Synthesis* **2005**, 2005, 1923-1925.

<sup>365</sup> S. D. Cho, J. W. Chung, W. Y. Choi, S. K. Kim, Y. J. Yoon, *J. Heterocyclic Chem.* **1994**, 31, 1199-1208.

The solution was then poured into water (10 ml) and extracted with methyl *tert*-butyl ether (3 × 20 ml). The organic phases were washed with water (5 × 10 ml), dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 86:14). Yield: 630 mg (3.08 mmol, 44%). Pale yellow crystals.

$R_f$  = 0.21 (SiO<sub>2</sub>; hexanes : EtOAc 6:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.60 (br s, 1H), 4.38 (t, *J*=6.8, 2H), 3.18 (q, *J*=6.4, 2H), 2.21–2.08 (m, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 156.0, 76.7, 73.0, 37.5, 28.3, 27.8; IR (neat): 3369, 2979, 2942, 1681, 1553, 1526, 1427, 1370, 1250, 1161, 1046, 1027, 948, 879, 808, 779, 637 cm<sup>-1</sup>; HRMS (ESI): exact mass calculated for C<sub>8</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup>), 205.1188; found 205.1183.

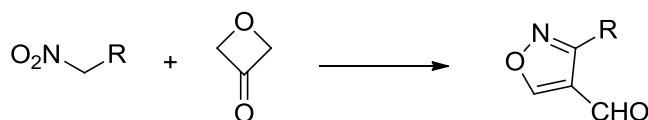
Spectral data were in agreement with literature values.<sup>366</sup>



***tert*-Butyldimethyl(2-nitroethoxy)silane (279p)**. The compound was prepared according to a literature procedure<sup>367</sup> and the spectral data were in agreement with literature values.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.39 (m, 2H), 4.08 (m, 2H), 0.80 (s, 9H), 0.00 (s, 6H).

### General Procedure for the One-Pot Synthesis of Isoxazoles (GP2)



In a 10 ml oven-dried cone-shaped flask were mixed under Ar the nitro compound (0.75 mmol, 1.0 equiv) and oxetan-3-one (0.98 mmol, 1.3 equiv), and the mixture was cooled to 0 °C. Et<sub>3</sub>N (0.15 mmol, 0.2 equiv) was added, and the reaction mixture was stirred at 0 °C for 10 min, warmed to RT and stirred for 90 min. In most cases formation of a solid was observed. The reaction mixture was diluted with THF (7.5 ml). Et<sub>3</sub>N (1.5 mmol, 2.0 equiv) was added and the solution was cooled to -78 °C. MsCl (0.83 mmol, 1.1 equiv) was added dropwise and the mixture was stirred at -78 °C for 30 min, then allowed to slowly warm to RT over 60 min. *i*Pr<sub>2</sub>NEt (0.75 mmol, 1.0 equiv) was added and the mixture was stirred at RT for 12 h. It was

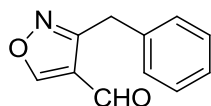
<sup>366</sup> T. Nagano, H. Kinoshita, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1605-1613.

<sup>367</sup> C. W. Holzapfel, K. Bischofberger, J. Olivier, *Synth. Commun.* **1994**, *24*, 3197-3211.



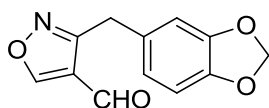
diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml), quenched with  $\text{H}_2\text{O}$  (5 ml) and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  ml). The combined organic phases were washed with saturated aqueous  $\text{NaCl}$  (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. The pure product was obtained after purification by flash column chromatography on silica gel.

### Preparation of Isoxazole-4-carbaldehydes



**3-Benzylisoxazole-4-carbaldehyde (280a).** Following the general procedure (GP2) using (2-nitroethyl)benzene (113 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  8:1) to afford the pure title compound. Yield: 112 mg (0.60 mmol, 80%). Colorless oil.

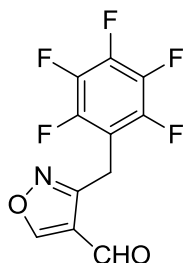
**TLC:**  $R_f = 0.34$  (hexanes :  $\text{EtOAc}$  4:1; UV, DNP);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.92$  (s, 1H), 8.91 (s, 1H), 7.52–6.91 (m, 5H), 4.29 (s, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.7, 165.5, 160.5, 136.2, 129.4, 129.0, 127.4, 121.4, 31.4$ ; **IR** (neat): 3099, 3039, 1689, 1575, 1455, 1421, 1392, 1129, 874, 744, 720, 694, 671  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{11}\text{H}_9\text{NO}_2$  ( $\text{M}^+$ ), 187.0628; found 187.0629.



**3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)isoxazole-4-carbaldehyde (280b).** Following the general procedure (GP2) using 5-(2-nitroethyl)benzo[*d*][1,3]dioxole (146 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  5:1) to afford the pure title compound. Yield: 130 mg (0.56 mmol, 75%). Pale yellow crystals.

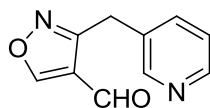
**TLC:**  $R_f = 0.20$  (hexanes :  $\text{EtOAc}$  5:1; UV, DNP); **Melting Point:** 56  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.87$  (s, 1H), 8.84 (s, 1H), 6.91–6.42 (m, 3H), 5.85 (s, 2H), 4.13 (s, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.3, 165.2, 160.2, 147.8, 146.6, 129.5, 122.2, 121.0, 109.5,$

108.3, 101.0, 30.8; **IR** (neat): 3098, 2912, 2830, 1682, 1577, 1502, 1485, 1444, 1421, 1383, 1284, 1186, 1120, 1037, 922, 869, 813, 779, 741, 760, 615  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_9\text{NO}_4$  ( $\text{M}^+$ ), 231.0526; found 231.0529.



**3-(Perfluorobenzyl)isoxazole-4-carbaldehyde (280c).** Following the general procedure (GP2) using 1,2,3,4,5-pentafluoro-6-(2-nitroethyl)benzene (181 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  5:1) to afford the pure title compound. Yield: 154 mg (0.56 mmol, 74%). Yellow crystals.

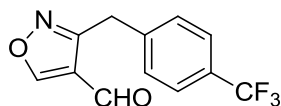
**TLC:**  $R_f = 0.25$  (hexanes :  $\text{EtOAc}$  5:1; UV, DNP); **Melting Point:** 53  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 10.09$  (s, 1H), 9.00 (s, 1H), 4.36 (s, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.4$ , 165.64, 157.3, 145.3 (dddd,  $J=19.4$ , 15.9, 8.1, 4.0), 142.3–139.1 (m), 139.0–138.5 (m), 120.8, 109.2 (td,  $J=18.4$ , 4.0);  **$^{19}\text{F-NMR}$**  (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -142.1$  (dd,  $J=21.7$ , 7.8),  $-155.3$  (t,  $J=20.8$ ),  $-162.2$  (td,  $J=21.5$ , 7.8); **IR** (neat): 3101, 1692, 1586, 1504, 1434, 1390, 1325, 1214, 1124, 1007, 969, 907, 883, 793, 744, 701, 791, 649  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{11}\text{H}_4\text{FNO}_2$  ( $\text{M}^+$ ), 277.0157; found 277.0155.



**3-(Pyridin-3-ylmethyl)isoxazole-4-carbaldehyde (280d).** Following the general procedure (GP2) using 3-(2-nitroethyl)pyridine (114 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  :  $\text{EtOAc}$  2:1) to afford the pure title compound. Yield: 125 mg (0.65 mmol, 86%). Colorless crystals.

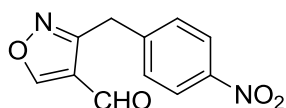
**TLC:**  $R_f = 0.20$  ( $\text{CH}_2\text{Cl}_2$  :  $\text{EtOAc}$  2:1; UV, DNP); **Melting Point:** 64  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.98$  (s, 1H), 8.95 (s, 1H), 8.61 (s, 1H), 8.49 (d,  $J=4.6$ , 1H), 7.66 (d,  $J=6.2$ , 1H), 7.38–

7.11 (m, 1H), 4.30 (s, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.1, 165.7, 159.3, 150.3, 148.4, 136.7, 131.6, 123.4, 120.9, 28.6$ ; **IR** (neat): 3089, 2847, 2761, 2363, 1686, 1575, 1477, 1434, 1396, 1307, 1128, 1026, 892, 873, 831, 770, 714, 657  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 188.0581; found 188.0580.



**3-(4-(Trifluoromethyl)benzyl)isoxazole-4-carbaldehyde (280e).** Following the general procedure (GP2) using 1-(2-nitroethyl)-4-(trifluoromethyl)benzene (164 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 136 mg (0.53 mmol, 71%). Yellow oil.

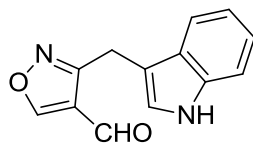
**TLC:**  $R_f = 0.25$  (hexanes : EtOAc 5:1; UV, DNP);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.90$  (s, 1H), 8.87 (t,  $J=0.5$ , 1H), 7.43 (dd,  $J=40.2, 8.1$ , 4H), 4.28 (s, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.1, 165.6, 159.3, 139.84, 129.4, 125.5$  (q,  $J=3.8$ ), 122.7, 120.9, 77.1, 30.9;  $^{19}\text{F-NMR}$  (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -62.59$ ; **IR** (neat): 3110, 1695, 1580, 1431, 1325, 1165, 1125, 1067, 1020, 865, 760  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_2$  ( $\text{M}^+$ ), 255.0502; found 255.0504.



**3-(4-Nitrobenzyl)isoxazole-4-carbaldehyde (280f).** Following the general procedure (GP2) using 1-nitro-4-(2-nitroethyl)benzene (147 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 104 mg (0.45 mmol, 60%). Yellow crystals.

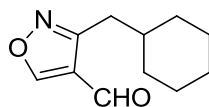
**TLC:**  $R_f = 0.15$  (hexanes : EtOAc 5:1; UV, DNP); **Melting Point:** 110-111  $^\circ\text{C}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.92$  (s, 1H), 8.91 (s, 1H), 8.09 (ddd,  $J=8.9, 2.4, 2.0$  2H), 7.44 (ddd,  $J=8.9, 2.4, 2.0$ , 2H), 4.32 (s, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.1, 165.8, 158.8, 147.1, 143.2, 130.0, 123.8, 120.8, 31.0$ ; **IR** (neat): 3161, 3107, 2862, 1681, 1604, 1579, 1475, 1435, 1402,

1350, 1319, 1301, 1136, 110, 1015, 915, 885, 861, 810, 781, 749, 771, 657, 642  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_4$  ( $\text{M}^+$ ), 232.0479; found 232.0479.



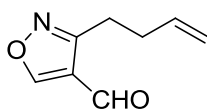
**3-((1H-Indol-3-yl)methyl)isoxazole-4-carbaldehyde (280g)**. Following the general procedure (GP2) using 3-(2-nitroethyl)-1H-indole (147 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  :  $\text{EtOAc}$  2:1) to afford the pure title compound. Yield: 102 mg (0.45 mmol, 60%). Slightly yellowish oil.

**TLC**:  $R_f = 0.25$  ( $\text{CH}_2\text{Cl}_2$  :  $\text{EtOAc}$  2:1; UV, DNP);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.70$  (s, 1H), 8.63 (s, 1H), 8.00 (bs, 1H), 7.65–7.50 (m, 1H), 7.27–6.82 (m, 4H), 4.29 (s, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.8, 165.1, 160.3, 136.2, 127.0, 123.3, 122.3, 121.1, 119.7, 118.9, 111.3, 110.0, 21.5$ ; **IR** (neat): 3112, 2844, 1678, 1578, 1506, 1390, 1310, 1127, 1101, 787, 739, 656  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ), 226.0742; found 226.0738.



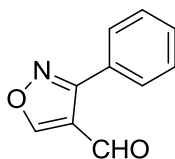
**3-(Cyclohexylmethyl)isoxazole-4-carbaldehyde (280h)**. Following the general procedure (GP2) using (2-nitroethyl)cyclohexane (118 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 48 h. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  5:1) to afford the pure title compound. Yield: 125 mg (0.65 mmol, 86%). Colorless oil.

**TLC**:  $R_f = 0.3$  (hexanes :  $\text{EtOAc}$  5:1; UV, DNP);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.95$  (s, 1H), 8.85 (s, 1H), 2.75 (d,  $J=6.7$ , 2H), 1.89–1.33 (m, 7H), 1.33–0.49 (m, 6H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.6, 165.1, 160.1, 121.5, 36.5, 33.0, 32.4, 26.1, 26.0$ ; **IR** (neat): 3114, 2924, 2851, 1682, 1579, 1452, 1422, 1388, 1120, 1070, 879, 819, 751, 736, 685  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{11}\text{H}_{14}\text{NO}_2$  ( $[\text{M}-\text{H}]^+$ ), 192.1019; found 192.1017.



**3-(But-3-enyl)isoxazole-4-carbaldehyde (280i).** Following the general procedure (GP2) using 5-nitropent-1-ene (86 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv), Et<sub>3</sub>N (21  $\mu$ l, 0.15 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.21 ml, 1.5 mmol, 2.0 equiv), MsCl (64  $\mu$ l, 0.83 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (130  $\mu$ l, 0.75 mmol, 1.0 equiv). The reaction mixture was stirred for 48 h. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 7:1) to afford the pure title compound. Yield: 103 mg (0.64 mmol, 85%). Colorless oil.

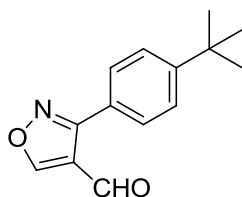
**TLC:**  $R_f$  = 0.25 (hexanes : EtOAc 7:1; UV, DNP); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.96 (s, 1H), 8.86 (s, 1H), 5.79 (ddt,  $J$ =17.1, 10.2, 6.6, 1H), 5.00 (ddd,  $J$ =17.1, 1.5, 1H), 4.95 (ddd,  $J$ =10.2, 2.9, 1.5, 1H), 3.05 – 2.86 (m, 2H), 2.50–2.35 (m, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 182.5, 165.4, 160.6, 136.5, 121.3, 116.0, 31.3, 24.9; **IR** (neat): 3106, 2978, 2848, 2749, 1689, 1579, 1390, 1132, 998, 917, 847, 780, 755 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub> (M<sup>+</sup>), 150.0550; found 150.0548.



**3-Phenylisoxazole-4-carbaldehyde (280j).** Following the general procedure (GP2) using (nitromethyl)benzene (103 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv), Et<sub>3</sub>N (21  $\mu$ l, 0.15 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.21 ml, 1.5 mmol, 2.0 equiv), MsCl (64  $\mu$ l, 0.83 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (130  $\mu$ l, 0.75 mmol, 1.0 equiv). CH<sub>2</sub>Cl<sub>2</sub> (*ca.* 0.2 ml) was added in the HENRY addition step. The reaction mixture was stirred for 48 h. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 6:1) to afford the pure title compound. Yield: 81 mg (0.47 mmol, 62%). Colorless crystals.

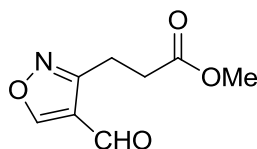
**TLC:**  $R_f$  = 0.25 (hexanes : EtOAc 6:1; UV, DNP); **Melting Point:** 41–42 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.96 (s, 1H), 9.02 (s, 1H), 7.83–7.61 (m, 2H), 7.57–7.30 (m, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 182.7, 165.2, 160.6, 130.8, 129.0, 129.0, 126.8, 121.0; **IR** (thin film): 2858, 2771, 1686, 1553, 1506, 1439, 1377, 1185, 1140, 969, 871, 820, 756, 685 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>10</sub>H<sub>7</sub>NO<sub>2</sub> (M<sup>+</sup>), 173.0471; found 173.0471.

The spectral data is in accordance with previously reported data.<sup>368</sup>



**3-(4-*tert*-Butylphenyl)isoxazole-4-carbaldehyde (280k).** Following the general procedure (GP2) using 1-*tert*-butyl-4-(nitromethyl)benzene (125 mg, 0.65 mmol, 1.0 equiv), oxetan-3-one (63 mg, 0.84 mmol, 1.3 equiv), Et<sub>3</sub>N (18  $\mu$ l, 0.13 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.18 ml, 1.29 mmol, 2.0 equiv), MsCl (55  $\mu$ l, 0.71 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (113  $\mu$ l, 0.65 mmol, 1.0 equiv). CH<sub>2</sub>Cl<sub>2</sub> (*ca.* 0.2 ml) was added in the HENRY addition step. The reaction mixture was stirred for 48 h. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 86 mg (0.38 mmol, 58%). Colorless oil.

**TLC:**  $R_f$  = 0.30 (hexanes : EtOAc 4:1; UV, DNP); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.02 (s, 1H), 9.07 (s, 1H), 7.74 (d,  $J$ =8.3, 2H), 7.54 (d,  $J$ =8.3, 2H), 1.36 (s, 9H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 182.9, 165.2, 160.4, 154.1, 128.7, 125.9, 123.7, 120.9, 34.9, 31.1; **IR** (neat): 2964, 2868, 1695, 1579, 1553, 1426, 1377, 1134, 765, 631 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>15</sub>NO<sub>2</sub> (M<sup>+</sup>), 229.1098; found 229.1098.

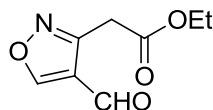


**Methyl 3-(4-formylisoxazol-3-yl)propanoate (280l).** Following the general procedure (GP2) using methyl 4-nitrobutanoate (110 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv), Et<sub>3</sub>N (21  $\mu$ l, 0.15 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.21 ml, 1.5 mmol, 2.0 equiv), MsCl (64  $\mu$ l, 0.83 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (130  $\mu$ l, 0.75 mmol, 1.0 equiv). The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 115 mg (0.68 mmol, 91%). Colorless oil.

**TLC:**  $R_f$  = 0.15 (hexanes : EtOAc 5:1; UV, DNP); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.98 (s, 1H), 8.87 (s, 1H), 3.63 (s, 3H), 3.20 (t,  $J$ =7.4, 2H), 2.75 (t,  $J$ =7.4, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 182.5, 172.4, 165.3, 163.2, 159.8, 121.2, 51.8, 30.9, 21.1; **IR** (neat): 3107, 2956, 2848,

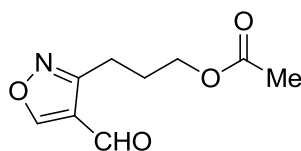
<sup>368</sup> P. Caramella, E. Cereda, *Synthesis* **1971**, 433-434.

1730, 1667, 1580, 1485, 1438, 1369, 1200, 11370, 1131, 990, 851, 767  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_8\text{H}_9\text{NO}_4$  ( $\text{M}^+$ ), 152.0343; found 152.0344.



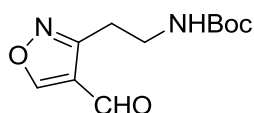
**Ethyl 2-(4-formylisoxazol-3-yl)acetate (280m).** Following the general procedure (GP2) using ethyl 3-nitropropanoate (110 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  5:1) to afford the pure title compound. Yield: 100 mg (0.55 mmol, 73%). Colorless oil.

**TLC:**  $R_f$  = 0.10 (hexanes :  $\text{EtOAc}$  5:1; UV, DNP);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.95 (s, 1H), 8.90 (s, 1H), 4.14 (q,  $J=7.1$ , 2H), 3.91 (s, 2H), 1.21 (t,  $J=7.1$ , 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 182.3, 168.0, 164.8, 155.1, 121.5, 61.6, 31.2, 14.1; **IR** (neat): 3111, 2986, 1733, 1687, 1585, 1433, 1336, 1200, 1179, 1128, 1027, 850, 753, 657  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_8\text{H}_9\text{NO}_4$  ( $\text{M}^+$ ), 183.0526; found 183.0524.



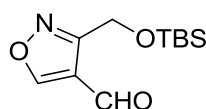
**3-(4-Formylisoxazol-3-yl)propyl acetate (280n).** Following the general procedure (GP2) using 4-nitrobutyl acetate (121 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv),  $\text{Et}_3\text{N}$  (21  $\mu\text{l}$ , 0.15 mmol, 0.2 equiv), then  $\text{Et}_3\text{N}$  (0.21 ml, 1.5 mmol, 2.0 equiv),  $\text{MsCl}$  (64  $\mu\text{l}$ , 0.83 mmol, 1.1 equiv), and  $i\text{Pr}_2\text{NEt}$  (130  $\mu\text{l}$ , 0.75 mmol, 1.0 equiv). The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  5:1) to afford the pure title compound. Yield: 96 mg (0.49 mmol, 65%). Colorless oil.

**TLC:**  $R_f$  = 0.10 (hexanes :  $\text{EtOAc}$  5:1; UV, DNP);  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.97 (s, 1H), 8.87 (s, 1H), 4.08 (t,  $J=6.3$ , 2H), 3.00–2.94 (m, 2H), 2.02 (dd,  $J=8.1$ , 6.9, 2H), 1.99 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 182.4, 171.0, 165.5, 160.3, 121.2, 63.3, 26.2, 22.3, 20.9; **IR** (neat): 3105, 2966, 1716, 1692, 1580, 1243, 1133, 1043, 876  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_9\text{H}_{11}\text{NO}_4$  ( $\text{M}^+$ ), 197.0688; found 197.0681.



**tert-Butyl 2-(4-formylisoxazol-3-yl)ethylcarbamate (280o).** Following the general procedure (GP2) using *tert*-butyl 3-nitropropylcarbamate (153 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv), Et<sub>3</sub>N (21 μl, 0.15 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.21 ml, 1.5 mmol, 2.0 equiv), MsCl (64 μl, 0.83 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (130 μl, 0.75 mmol, 1.0 equiv). The residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : EtOAc 6:1) to afford the pure title compound. Yield: 90 mg (0.49 mmol, 65%). Colorless crystals.

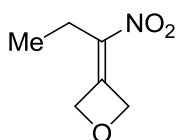
**TLC:**  $R_f = 0.25$  (CH<sub>2</sub>Cl<sub>2</sub> : EtOAc 6:1; UV, DNP); **Melting Point:** 69-70 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 9.97 (s, 1H), 8.87 (s, 1H), 4.78 (bs, 1H), 3.48 (t,  $J=6.3$ , 2H), 3.07 (t,  $J=6.3$ , 2H), 1.34 (s, 9H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 181.6, 164.2, 158.1, 154.8, 120.4, 78.4, 36.9, 27.3, 25.6; **IR** (neat): 3406, 3111, 2977, 2935, 2856, 2362, 1686, 1582, 1509, 1423, 1366, 1270, 1246, 1169, 1128, 1058, 991, 952, 934, 883, 856, 841, 781, 756, 695 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub> ( $[M-C_4H_9]^+$ ), 184.0479; found 184.0479.



**3-((tert-Butyldimethylsilyloxy)methyl)isoxazole-4-carbaldehyde (280p).** Following the general procedure (GP2) using *tert*-butyldimethyl(2-nitroethoxy)silane (154 mg, 0.75 mmol, 1.0 equiv), oxetan-3-one (70 mg, 0.98 mmol, 1.3 equiv), Et<sub>3</sub>N (21 μl, 0.15 mmol, 0.2 equiv), then Et<sub>3</sub>N (0.21 ml, 1.5 mmol, 2.0 equiv), MsCl (64 μl, 0.83 mmol, 1.1 equiv), and *i*Pr<sub>2</sub>NEt (130 μl, 0.75 mmol, 1.0 equiv). The residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>) to afford the pure title compound. Yield: 83 mg (0.45 mmol, 60%). Colorless oil.

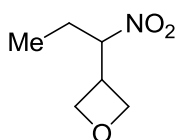
**TLC:**  $R_f = 0.10$  (CH<sub>2</sub>Cl<sub>2</sub>; UV, DNP); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 9.94 (s, 1H), 8.81 (s, 1H), 4.95-4.78 (m, 2H), 0.78 (s, 9H), 0.00 (s, 6H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 183.2 163.5, 160.9, 121.3, 57.2, 25.7, 18.2, -5.5; **IR** (neat): 2954, 2930, 2858, 1691, 1579, 1472, 1255, 1126, 1096, 1006, 833, 777, 747, 700, 664 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>7</sub>H<sub>10</sub>NO<sub>3</sub>Si ( $[M-C_4H_9]^+$ ), 184.0425; found 184.0424.





**3-(1-Nitropropylidene)oxetane.** Nitropropane (1.01 ml, 11.1 mmol, 1.0 equiv) and oxetan-3-one (0.90 g, 12.2 mmol, 1.1 equiv) were mixed and the mixture cooled to 0 °C. Et<sub>3</sub>N (0.78 ml, 5.53 mmol, 0.5 equiv) was dropwise added over 5 min, and the mixture was warmed to RT and stirred for 40 min. Then it was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 ml), and Et<sub>3</sub>N (3.88 ml, 27.6 mmol, 2.5 equiv) was added, and the colorless solution was cooled to -78 °C. Then was slowly added MsCl (2.15 ml, 27.6 mmol, 2.5 equiv) over 10 min, when a colorless precipitate formed and stirring became difficult. More Et<sub>3</sub>N (0.78 ml, 5.53 mmol, 0.5 equiv) was added. The colorless mixture was stirred at -78 °C for 30 min, then slowly warmed to RT over 30 min. At this point, it was quenched by pouring the mixture into H<sub>2</sub>O (75 ml). The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1) to afford the title compound in ~95% purity (<sup>1</sup>H NMR; impurity = 3-ethylisoxazole-4-carbaldehyde). Yield: 770 mg (5.38 mmol, 49%). Colorless oil.

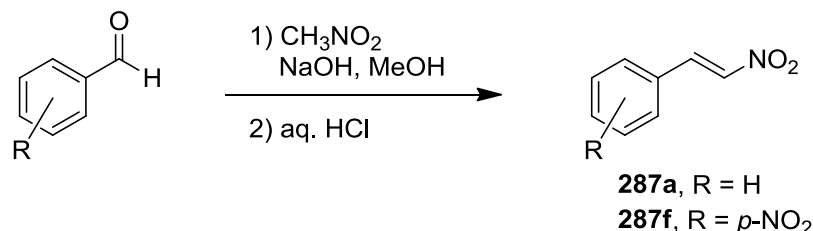
**TLC:**  $R_f$  = 0.20 (hexanes : EtOAc 3:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.64 – 5.48 (m, 2H), 5.40 – 5.25 (m, 2H), 2.52 – 2.35 (m, 2H), 1.14 (t,  $J$ =7.5, 3H).



**3-(1-Nitropropyl)oxetane (285).** To a solution of 3-(1-nitropropylidene)oxetane (81 mg, 0.57 mmol, 1.0 equiv) in MeOH (2.5 ml), cooled to 0 °C, was added NaBH<sub>4</sub> (43 mg, 1.13 mmol, 2.0 equiv), and the solution was stirred at 0 °C for 5 min. Then it was allowed to warm to RT, and stirring was continued for 10 min. The mixture was diluted with saturated aqueous NH<sub>4</sub>Cl (5 ml), H<sub>2</sub>O (5 ml), and Et<sub>2</sub>O (30 ml). The phases were separated, and the organic layer was washed with saturated aqueous NaCl (10 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 82 mg (0.57 mmol, quantitative). Colorless oil.

**TLC:**  $R_f$  = 0.27 (hexanes : EtOAc 3:1; CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.89 – 4.70 (m, 3H), 4.49 (t,  $J$ =6.4, 1H), 4.40 (t,  $J$ =6.4, 1H), 3.62 – 3.39 (m, 1H), 2.06 – 1.66 (m, 2H), 0.97 (t,  $J$ =7.4, 3H).

The nitroalkene intermediates were prepared by base-mediated HENRY additions of  $\text{CH}_3\text{NO}_2$  to the respective aldehydes followed by dehydration under acidic or basic (after activation of the alcohol) conditions. The aldehydes were commercially available and used as received.

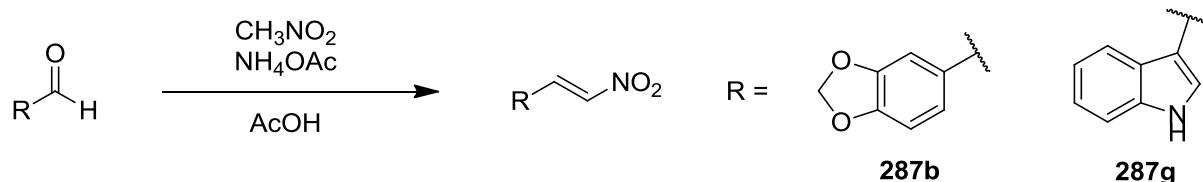


**(E)-(2-Nitrovinyl)benzene (287a).** The compound was prepared according to a literature procedure<sup>369</sup> and the spectral data were in agreement with literature values.<sup>370</sup>

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.00$  (d,  $J=13.7$ , 1H), 7.58 (d,  $J=13.7$ , 1H), 7.55–7.35 (m, 5H).

**(E)-1-Nitro-4-(2-nitrovinyl)benzene (287f).** The compound was prepared according to a literature procedure<sup>369</sup> and the spectral data were in agreement with literature values.<sup>371</sup>

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.32$  (d,  $J=8.6$ , 2H), 8.04 (d,  $J=13.8$ , 1H), 7.74 (d,  $J=8.6$ , 2H), 7.64 (d,  $J=13.8$ , 1H).



**(E)-5-(2-Nitrovinyl)benzo[*d*][1,3]dioxole (287b).** The compound was prepared according to a literature procedure<sup>372</sup> and the spectral data were in agreement with literature values.<sup>373</sup>

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92$  (d,  $J=13.6$ , 1H), 7.47 (d,  $J=13.6$ , 1H), 7.08 (dd,  $J=8.0$ , 1.6, 1H), 7.00 (d,  $J=1.6$ , 1H), 6.87 (d,  $J=8.0$ , 1H), 6.06 (s, 2H).

<sup>369</sup> R. P. K. Kodukulla, G. K. Trivedi, J. D. Vora, H. H. Mathur, *Synth. Commun.* **1994**, *24*, 819-832.

<sup>370</sup> S. E. Denmark, B. S. Kesler, Y. C. Moon, *J. Org. Chem.* **1992**, *57*, 4912-4924.

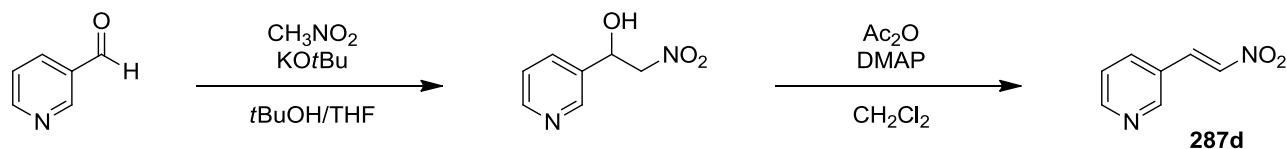
<sup>371</sup> H. K. Oh, J. H. Yang, D. D. Sung, I. Lee, *J. Chem. Soc., Perkin Trans. 2* **2000**, 101-105.

<sup>372</sup> J. McNulty, J. A. Steere, S. Wolf, *Tetrahedron Lett.* **1998**, *39*, 8013-8016.

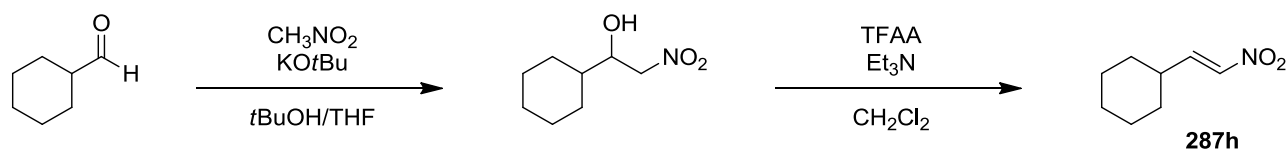
<sup>373</sup> G. Revial, S. Lim, B. Viossat, P. Lemoine, A. Tomas, A. F. Duprat, M. Pfau, *J. Org. Chem.* **2000**, *65*, 4593-4600.

**(*E*)-3-(2-Nitrovinyl)-1*H*-indole (287g).** The compound was prepared according to a literature procedure<sup>372</sup> and the spectral data were in agreement with literature values.<sup>374</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 9.00 (bs, 1H), 8.30 (d, *J*=13.5, 1H), 7.80 (d, *J*=13.5, 1H), 7.82–7.77 (m, 1H), 7.68 (d, *J*=3.0, 1H), 7.52–7.43 (m, 1H), 7.40–7.29 (m, 2H).



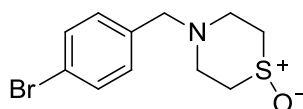
**(*E*)-3-(2-Nitrovinyl)pyridine (287d).** The compound was prepared according to a literature procedure<sup>374</sup> and the spectral data were in agreement with literature values.



**(*E*)-(2-Nitrovinyl)cyclohexane (287h).** The compound was prepared according to a literature procedure<sup>375</sup> and the spectral data were in agreement with literature values.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.19 (dd, *J*=13.5, 7.2, 1H), 6.90 (dd, *J*=13.5, 1.4, 1H), 2.36–2.08 (m, 1H), 1.88–1.58 (m, 5H), 1.44–1.00 (m, 5H).

## 9.7 Thietanes



**4-(4-Bromobenzyl)thiomorpholine 1-oxide (300).** To a solution of 4-(4-bromobenzyl)thiomorpholine (205 mg, 0.75 mmol, 1.0 equiv) in AcOH (6 ml) was added at RT H<sub>2</sub>O<sub>2</sub> (30% in H<sub>2</sub>O; 85 μl, 0.83 mmol, 1.1 equiv), and the mixture was stirred at RT for 16 h. Then it was concentrated *in vacuo* and the residue (*ca.* 0.5 ml) was poured into saturated aqueous NaHCO<sub>3</sub> (20 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 216 mg (0.75 mmol, quantitative). Colorless solid.

<sup>374</sup> G. J. T. Kuster, R. H. J. Steeghs, H. W. Scheeren, *Eur. J. Org. Chem.* **2001**, 553–560.

<sup>375</sup> S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1993**, 58, 3850–3856.

**TLC:**  $R_f = 0.03$  (hexanes : EtOAc 1:1; UV, CAM);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.52 - 7.39$  (m, 2H), 7.25 – 7.14 (m, 2H), 3.52 (s, 2H), 3.05 (ddd,  $J=12.6, 9.7, 3.0$ , 2H), 2.94 – 2.75 (m, 4H), 2.75 – 2.59 (m, 2H).

### **General Procedure for the Oxidation of Sulfides to Sulfones (GP3)**

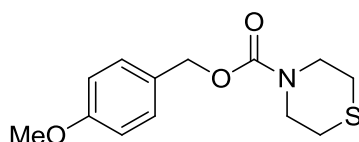
To a solution of the starting material (1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (~0.1 M), cooled to 0 °C, was added *m*-chloroperbenzoic acid (2.0 equiv). The mixture was stirred at 0 °C for *ca.* 1 h, then it was allowed to warm to RT and stirring was continued for a few hours. At this point the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with saturated aqueous  $\text{NaHCO}_3$ . The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. If necessary, purification of the residue was done chromatographically.

### **General Procedure for the Oxidation of Sulfides to Sulfoxides (GP4)**

To a solution of the starting material (1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (~0.1 M), cooled to 0 °C, was added *m*-chloroperbenzoic acid (1.0 equiv). The mixture was stirred at 0 °C for *ca.* 2 h, then it was allowed to warm to RT and stirring was continued for a few hours. At this point the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with saturated aqueous  $\text{NaHCO}_3$ . The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. If necessary, purification of the residue was done chromatographically.

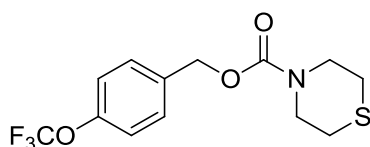
### **General Procedure for the Synthesis of Carbamates (GP5)**

To a solution of the alcohol (1.0 equiv) and DMAP (0.1 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.2 M) was added at RT CDI (1.5 equiv) and the mixture was stirred at RT until TLC indicated complete conversion of the starting material. At this point was added the amine (2.0 equiv), and the mixture was stirred at RT until TLC indicated full conversion. Then the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and saturated aqueous  $\text{NH}_4\text{Cl}$ . The phases were separated and the organic layer was washed with saturated aqueous  $\text{NaCl}$ , dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC to afford the pure desired compound.



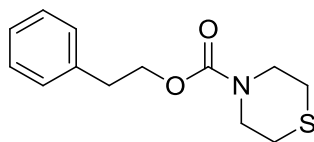
**4-Methoxybenzyl thiomorpholine-4-carboxylate (303a).** According to GP5 using 4-methoxybenzyl alcohol (0.10 ml, 0.80 mmol, 1.0 equiv), CDI (195 mg, 1.21 mmol, 1.5 equiv), DMAP (9.8 mg, 0.08 mmol, 0.1 equiv) and thiomorpholine (0.15 ml, 1.61 mmol, 2.0 equiv) for 30 min (1<sup>st</sup> step) and 13 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1) to afford pure title compound. Yield: 212 mg (0.79 mmol, 99%). Colorless solid.

**TLC:**  $R_f = 0.59$  (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 54–56 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.28$  (d,  $J=8.3$ , 2H), 6.88 (d,  $J=8.3$ , 2H), 5.06 (s, 2H), 3.80 (s, 3H), 3.78 – 3.62 (m, 4H), 2.56 (br s, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 159.3$ , 154.8, 129.6, 128.4, 113.7, 67.1, 55.2, 46.3, 27.3; **IR** (neat): 2908, 1684, 1512, 1459, 1430, 1246, 1209, 1086, 1027, 817 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>S (M<sup>+</sup>), 267.0924; found 267.0925.



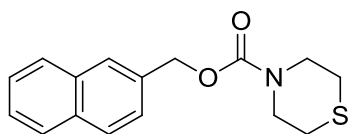
**4-(Trifluoromethoxy)benzyl thiomorpholine-4-carboxylate (303b).** According to GP5 using 4-(trifluoromethoxy)phenylmethanol (0.10 ml, 0.67 mmol, 1.0 equiv), CDI (130 mg, 0.80 mmol, 1.2 equiv), DMAP (8.2 mg, 0.07 mmol, 0.1 equiv) and thiomorpholine (0.13 ml, 1.34 mmol, 2.0 equiv) for 2.5 h (1<sup>st</sup> step) and 19 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 7:1) to afford pure title compound. Yield: 183 mg (0.57 mmol, 85%). Colorless oil.

**TLC:**  $R_f = 0.64$  (hexanes : EtOAc 2:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.37$  (d,  $J=8.8$ , 2H), 7.20 (d,  $J=8.8$ , 2H), 5.12 (s, 2H), 3.83 – 3.67 (m, 4H), 2.58 (br s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 154.7$ , 148.9, 135.3, 129.4, 121.0, 120.4 (q,  $^1J_{C,F}=257.3$ ), 66.3, 46.4, 27.2; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta = -57.7$ ; **IR** (neat): 2962, 2908, 1696, 1510, 1461, 1428, 1253, 1196, 1155, 1094, 956, 840, 764 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>13</sub>H<sub>14</sub>F<sub>3</sub>NNaO<sub>3</sub>S ([M+Na]<sup>+</sup>), 322.0719; found 322.0717.



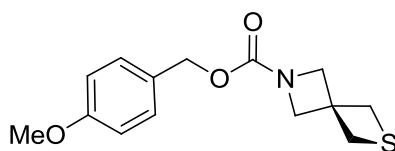
**Phenethyl thiomorpholine-4-carboxylate (303c).** According to GP5 using 2-phenylethanol (0.12 ml, 1.00 mmol, 1.0 equiv), CDI (244 mg, 1.50 mmol, 1.5 equiv), DMAP (12 mg, 0.10 mmol, 0.1 equiv) and thiomorpholine (0.19 ml, 2.00 mmol, 2.0 equiv) for 1 h (1<sup>st</sup> step) and 22 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 8:1) to afford pure title compound. Yield: 226 mg (0.90 mmol, 90%). Colorless oil.

**TLC:**  $R_f$  = 0.43 (hexanes : EtOAc 4:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.40 – 7.13 (m, 5H), 4.31 (t,  $J$ =6.9, 2H), 3.69 (br s, 4H), 2.95 (t,  $J$ =6.9, 2H), 2.53 (br s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 154.9, 138.0, 128.8, 128.4, 126.4, 65.9, 46.3 (br), 35.5, 27.1; **IR** (neat): 2957, 2909, 1692, 1457, 1423, 1296, 1220, 1199, 1099, 957, 749, 699 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>S (M<sup>+</sup>), 251.0975; found 251.0978.



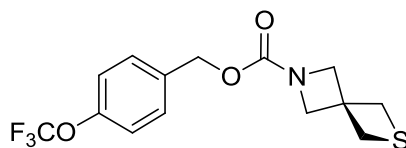
**Naphthalen-2-ylmethyl thiomorpholine-4-carboxylate (303d).** According to GP5 using naphthalen-2-ylmethanol (100 mg, 0.63 mmol, 1.0 equiv), CDI (154 mg, 0.95 mmol, 1.5 equiv), DMAP (7.7 mg, 0.06 mmol, 0.1 equiv) and thiomorpholine (0.12 ml, 1.26 mmol, 2.0 equiv) for 1.5 h (1<sup>st</sup> step) and 2 d (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford pure title compound. Yield: 157 mg (0.55 mmol, 86%). Colorless solid.

**TLC:**  $R_f$  = 0.26 (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 70-73 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 – 7.70 (m, 4H), 7.59 – 7.36 (m, 3H), 5.31 (s, 2H), 3.90 – 3.65 (m, 4H), 2.60 (br s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.0, 133.9, 133.2, 133.1, 128.3, 127.9, 127.7, 127.1, 126.2, 126.2, 125.7, 67.5, 46.4, 27.3; **IR** (neat): 2906, 1690, 1423, 1297, 1224, 1197, 1092, 993, 959, 817, 748 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub>S (M<sup>+</sup>), 287.0975; found 287.0974.



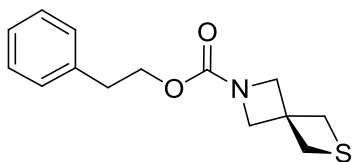
**4-Methoxybenzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate (306a).** According to GP5 using 4-methoxybenzyl alcohol (0.10 ml, 0.80 mmol, 1.0 equiv), CDI (156 mg, 0.96 mmol, 1.2 equiv), DMAP (9.8 mg, 0.08 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium oxalate (**117**) (0.15 mg, 0.48 mmol, 0.6 equiv) with triethylamine (0.34 ml, 2.41 mmol, 3.0 equiv) and DMF (1.5 ml) for 3.5 h (1<sup>st</sup> step) and 15 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:1) to afford pure title compound. Yield: 188 mg (0.67 mmol, 84%). Colorless oil.

**TLC:**  $R_f$  = 0.40 (hexanes : EtOAc 2:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.28 (d,  $J$ =8.8, 2H), 6.87 (d,  $J$ =8.8, 2H), 5.01 (s, 2H), 4.01 (s, 4H), 3.80 (s, 3H), 3.31 (s, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.3, 156.1, 129.8, 128.5, 113.7, 66.6, 62.7, 55.3, 42.7, 36.9; **IR** (neat): 3001, 2959, 1705, 1515, 1414, 1247, 1175, 1026, 823 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>S (M<sup>+</sup>), 279.0924; found 279.0925.



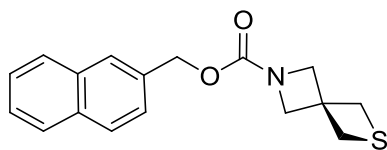
**4-(Trifluoromethoxy)benzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate (306b).** According to GP5 using (4-(trifluoromethoxy)phenyl)methanol (0.10 ml, 0.67 mmol, 1.0 equiv), CDI (141 mg, 0.87 mmol, 1.3 equiv), DMAP (8.2 mg, 0.067 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium oxalate (**117**) (161 mg, 0.50 mmol, 0.75 equiv) with triethylamine (0.28 ml, 2.01 mmol, 3.0 equiv) and DMF (2 ml) for 4 h (1<sup>st</sup> step) and 20 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford pure title compound. Yield: 196 mg (0.59 mmol, 88%). Colorless oil.

**TLC:**  $R_f$  = 0.38 (hexanes : EtOAc 2:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.37 (d,  $J$ =8.4, 2H), 7.19 (d,  $J$ =8.4, 2H), 5.06 (s, 2H), 4.03 (s, 4H), 3.32 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.9, 148.9, 135.3, 129.5, 120.9, 120.4 (q,  $^1J_{C,F}$ =257.2), 65.7, 62.8, 42.7, 36.8; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -57.7; **IR** (neat): 2945, 2876, 1702, 1510, 1408, 1248, 1217, 1152, 1081, 972, 840, 766 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>NNaO<sub>3</sub>S ([M+Na]<sup>+</sup>), 334.0719; found 334.0719.



**Phenethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate (306c).** According to GP5 using 2-phenylethanol (0.04 ml, 0.33 mmol, 1.0 equiv), CDI (65 mg, 0.40 mmol, 1.2 equiv), DMAP (4.1 mg, 0.033 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium oxalate (**117**) (64 mg, 0.20 mmol, 0.6 equiv) with triethylamine (0.141 ml, 1.002 mmol, 3.0 equiv) and DMF (1 ml) for 3 h (1<sup>st</sup> step) and 25 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford pure title compound. Yield: 79 mg (0.30 mmol, 90%). Colorless solid.

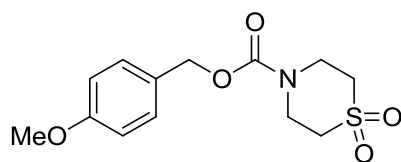
**TLC:**  $R_f$  = 0.29 (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 55-56 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.39 – 7.14 (m, 5H), 4.24 (t,  $J=7.0$ , 2H), 3.98 (s, 4H), 3.32 (s, 4H), 2.92 (t,  $J=7.0$ , 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.4, 137.9, 128.9, 128.4, 126.5, 65.5, 62.7 (br), 42.7, 36.8, 35.5; **IR** (neat): 2946, 2871, 1695, 1421, 1369, 1169, 1132, 1077, 968, 751, 700 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>18</sub>NO<sub>2</sub>S ([M+H]<sup>+</sup>), 264.1053; found 264.1058.



**Naphthalen-2-ylmethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate (306d).** According to GP5 using naphthalen-2-ylmethanol (29.5 mg, 0.186 mmol, 1.0 equiv), CDI (33 mg, 0.21 mmol, 1.1 equiv), DMAP (2.3 mg, 0.019 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium oxalate (**117**) (36 mg, 0.11 mmol, 0.6 equiv) with triethylamine (0.079 ml, 0.559 mmol, 3.0 equiv) and DMF (1 ml) for 2.5 h (1<sup>st</sup> step) and 23 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford pure title compound. Yield: 40 mg (0.13 mmol, 72%). Colorless solid.

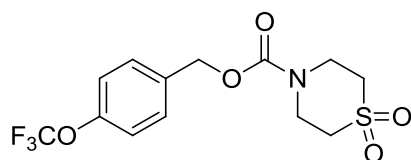
**TLC:**  $R_f$  = 0.38 (hexanes : EtOAc 3:1; UV, CAM); **Melting Point:** 104-105 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.94 – 7.74 (m, 4H), 7.57 – 7.39 (m, 3H), 5.25 (s, 2H), 4.05 (s, 4H), 3.33 (s, 4H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.9, 133.6, 132.9, 132.8, 128.0, 127.7, 127.4, 126.9, 126.0, 126.0, 125.6, 66.9, 62.9 (br), 42.8, 37.0; **IR** (neat): 3007, 2953, 1692, 1411, 1350, 1144, 1079, 945, 862, 830, 758 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>S (M<sup>+</sup>), 299.0975; found 299.0975.





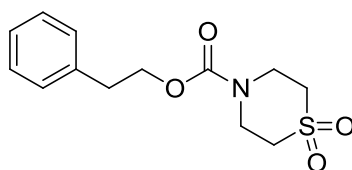
**4-Methoxybenzyl thiomorpholine-4-carboxylate 1,1-dioxide (307a).** According to GP3 using sulfide **303a** (38.5 mg, 0.144 mmol, 1.0 equiv) and *m*-CPBA (77%; 64.5 mg, 0.288 mmol, 2.0 equiv) for 4 h. Purification of the residue was not necessary. Yield: 42 mg (0.14 mmol, 97%). Colorless foam.

**TLC:**  $R_f = 0.10$  (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.29$  (d,  $J=8.7$ , 2H), 6.90 (d,  $J=8.7$ , 2H), 5.09 (s, 2H), 4.02 (br s, 4H), 3.81 (s, 3H), 3.00 (br s, 4H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 159.9$ , 154.6, 130.2, 127.8, 114.1, 68.1, 55.3, 51.9, 42.7; **IR** (neat): 2939, 1699, 1513, 1431, 1282, 1223, 1187, 1099, 1029, 818, 761  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{17}\text{NO}_5\text{S}$  ( $\text{M}^+$ ), 299.0822; found 299.0823.



**4-(Trifluoromethoxy)benzyl thiomorpholine-4-carboxylate 1,1-dioxide (307b).** According to GP3 using sulfide **303b** (44 mg, 0.14 mmol, 1.0 equiv) and *m*-CPBA (77%; 61 mg, 0.27 mmol, 2.0 equiv) for 3 h. Residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:2) to afford pure title compound. Yield: 46 mg (0.13 mmol, 95%). Colorless solid.

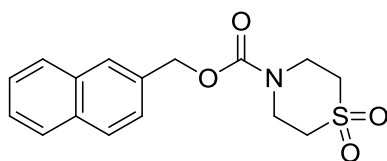
**TLC:**  $R_f = 0.29$  (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 97-98  $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.39$  (d,  $J=8.4$ , 2H), 7.22 (d,  $J=8.4$ , 2H), 5.15 (s, 2H), 4.12 – 3.86 (m, 4H), 3.02 (br s, 4H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.3$ , 149.3, 134.4, 129.8, 121.2, 120.4 (q,  $^1J_{\text{C,F}}=257.6$ ), 67.3, 51.9, 42.7;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -57.7$ ; **IR** (neat): 2990, 2937, 1700, 1512, 1431, 1271, 1219, 1183, 1124, 1092, 951, 869, 762, 710  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NNaO}_5\text{S}$  ( $[\text{M}+\text{Na}]^+$ ), 376.0437; found 376.0423.



**Phenethyl thiomorpholine-4-carboxylate 1,1-dioxide (307c).** According to GP3 using sulfide **303c** (37 mg, 0.15 mmol, 1.0 equiv) and *m*-CPBA (77%; 65 mg, 0.29 mmol, 2.0 equiv) for

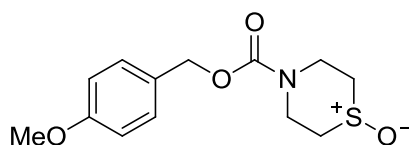
7 h. Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2) to afford pure title compound. Yield: 31 mg (0.11 mmol, 75%). Colorless solid.

**TLC:**  $R_f$  = 0.17 (hexanes : EtOAc 2:1; UV, CAM); **Melting Point:** 84–85 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.25 – 7.06 (m, 5H), 4.30 (t,  $J$ =6.8, 2H), 3.83 (br s, 4H), 2.90 (t,  $J$ =6.8, 2H), 2.78 (br s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 154.4, 137.5, 128.8, 128.6, 126.8, 66.6, 51.8, 42.6, 35.3; **IR** (neat): 2959, 2901, 1692, 1457, 1428, 1282, 1187, 1103, 1007, 874, 698 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>13</sub>H<sub>18</sub>NO<sub>4</sub>S ([M+H]<sup>+</sup>), 284.0951; found 284.0959.



**Naphthalen-2-ylmethyl thiomorpholine-4-carboxylate 1,1-dioxide (307d).** According to GP3 using sulfide **303d** (39 mg, 0.14 mmol, 1.0 equiv) and *m*-CPBA (77%; 61 mg, 0.27 mmol, 2.0 equiv) for 2.5 h. Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 39 mg (0.12 mmol, 90%). Colorless solid.

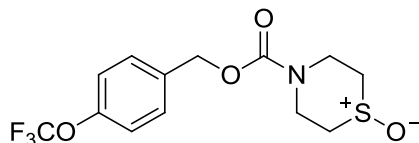
**TLC:**  $R_f$  = 0.34 (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 128–130 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.97 – 7.73 (m, 4H), 7.61 – 7.37 (m, 3H), 5.32 (s, 2H), 4.13 – 3.87 (m, 4H), 3.02 (br s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 154.5, 133.2, 133.1, 133.0, 128.6, 128.0, 127.8, 127.7, 126.5, 126.5, 125.8, 68.5, 51.9, 42.7; **IR** (neat): 2985, 2934, 1691, 1469, 1431, 1316, 1284, 1104, 953, 870, 813 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>S (M<sup>+</sup>), 319.0873; found 319.0874.



**4-Methoxybenzyl thiomorpholine-4-carboxylate 1-oxide (308a).** According to GP4 using sulfide **303a** (43.7 mg, 0.163 mmol, 1.0 equiv) and *m*-CPBA (~85%; 33 mg, 0.16 mmol, 1.0 equiv) for 4.5 h. Purification of the residue was not necessary. Yield: 45 mg (0.16 mmol, 97%). Colorless solid.

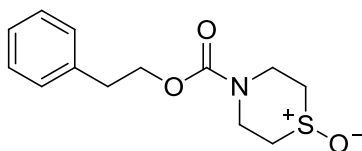
**TLC:**  $R_f$  = 0.21 (EtOAc; UV, CAM); **Melting Point:** 142–144 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.29 (d,  $J$ =8.7, 2H), 6.88 (d,  $J$ =8.7, 2H), 5.07 (s, 2H), 4.21 – 3.82 (m, 4H), 3.80 (s, 3H), 2.89 – 2.42 (m, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.7, 155.0, 130.0, 128.2, 114.0,

67.6, 55.2, 45.4, 35.2; **IR** (neat): 2908, 1690, 1512, 1422, 1245, 1190, 1081, 1010, 945, 818, 760  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{17}\text{NO}_4\text{S}$  ( $\text{M}^+$ ), 283.0873; found 283.0874.



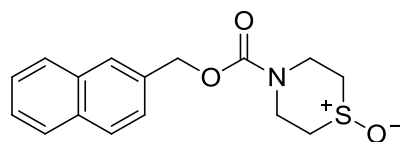
**4-(Trifluoromethoxy)benzyl thiomorpholine-4-carboxylate 1-oxide (308b)**. According to GP4 using sulfide **303b** (39 mg, 0.12 mmol, 1.0 equiv) and *m*-CPBA (~85%; 24.5 mg, 0.12 mmol, 1.0 equiv) for 3 h. Residue was purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 100:2) to afford pure title compound. Yield: 38 mg (0.11 mmol, 93%). Colorless solid.

**TLC**:  $R_f = 0.15$  (EtOAc; UV, CAM); **Melting Point**: 93-94 °C;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.39$  (d,  $J=8.3$ , 2H), 7.21 (d,  $J=8.3$ , 2H), 5.14 (s, 2H), 4.27 – 3.77 (br m, 4H), 2.92 – 2.53 (br m, 4H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.7$ , 149.1, 134.8, 129.6, 121.1, 120.4 (q,  $^1J_{\text{C,F}}=257.5$ ), 66.8, 45.4, 35.2;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -57.7$ ; **IR** (neat): 2924, 1688, 1511, 1464, 1427, 1269, 1217, 1159, 1087, 1007, 948, 850, 763  $\text{cm}^{-1}$ ; **HRMS** (ESI): exact mass calculated for  $\text{C}_{13}\text{H}_{15}\text{F}_3\text{NO}_4\text{S}$  ( $[\text{M}+\text{H}]^+$ ), 338.0668; found 338.0672.



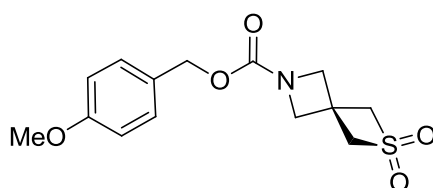
**Phenethyl thiomorpholine-4-carboxylate 1-oxide (308c)**. According to GP4 using sulfide **303c** (35 mg, 0.14 mmol, 1.0 equiv) and *m*-CPBA (~85%; 28 mg, 0.14 mmol, 1.0 equiv) for 7 h. Residue was purified by FC ( $\text{SiO}_2$ ;  $\text{CH}_2\text{Cl}_2$  : MeOH 100:2) to afford pure title compound. Yield: 28 mg (0.11 mmol, 76%). Colorless solid.

**TLC**:  $R_f = 0.17$  (EtOAc; UV, CAM); **Melting Point**: 82-83 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.37 - 7.15$  (m, 5H), 4.35 (t,  $J=6.8$ , 2H), 4.19 – 3.74 (br m, 4H), 2.97 (t,  $J=6.8$ , 2H), 2.90 – 2.28 (br m, 4H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.9$ , 137.8, 128.9, 128.5, 126.6, 66.3, 45.3, 35.4, 35.2; **IR** (neat): 2923, 1693, 1424, 1296, 1225, 1190, 1093, 1008, 947, 748, 695  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{17}\text{NO}_3\text{S}$  ( $\text{M}^+$ ), 267.0924; found 267.0921.



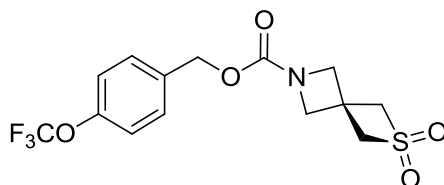
**Naphthalen-2-ylmethyl thiomorpholine-4-carboxylate 1-oxide (308d).** According to GP4 using sulfide **303d** (35 mg, 0.12 mmol, 1.0 equiv) and *m*-CPBA (~85%; 25 mg, 0.12 mmol, 1.0 equiv) for 3 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 100:3) to afford pure title compound. Yield: 33 mg (0.11 mmol, 89%). Colorless solid.

**TLC:**  $R_f$  = 0.14 (EtOAc; UV, CAM); **Melting Point:** 121-123 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.95 – 7.75 (m, 4H), 7.59 – 7.39 (m, 3H), 5.31 (s, 2H), 4.29 – 3.75 (br m, 4H), 2.96 – 2.49 (br m, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 154.9, 133.5, 133.2, 133.2, 128.5, 128.0, 127.7, 127.4, 126.4, 126.4, 125.8, 68.0, 45.4, 35.3; **IR** (neat): 3051, 2923, 1688, 1462, 1424, 1297, 1225, 1087, 1006, 948, 746 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>S (M<sup>+</sup>), 303.0924; found 303.0923.



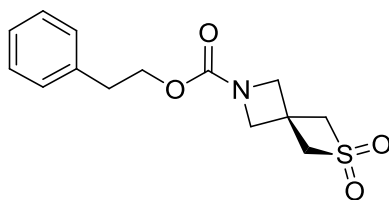
**4-Methoxybenzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2,2-dioxide (309a).** According to GP3 using sulfide **306a** (37.5 mg, 0.134 mmol, 1.0 equiv) and *m*-CPBA (77%; 60.2 mg, 0.268 mmol, 2.0 equiv) for 3 h. Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 39 mg (0.13 mmol, 93%). Colorless solid.

**TLC:**  $R_f$  = 0.18 (hexanes : EtOAc 1:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.28 (d,  $J$ =8.8, 2H), 6.88 (d,  $J$ =8.8, 2H), 5.03 (s, 2H), 4.29 (s, 4H), 4.21 (s, 4H), 3.81 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.7, 156.1, 130.1, 128.2, 113.9, 74.3, 67.0, 60.4 (br), 55.3, 24.7; **IR** (neat): 3022, 2964, 1693, 1515, 1434, 1355, 1297, 1254, 1181, 1073, 1024, 822, 748 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>5</sub>S (M<sup>+</sup>), 311.0822; found 311.0828.



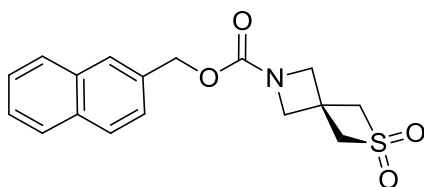
4-(Trifluoromethoxy)benzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2,2-dioxide (**309b**). According to GP3 using sulfide **306b** (45 mg, 0.14 mmol, 1.0 equiv) and *m*-CPBA (77%; 61 mg, 0.27 mmol, 2.0 equiv) for 3.5 h. Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 45 mg (0.12 mmol, 91%). Colorless solid.

**TLC:**  $R_f$  = 0.21 (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 125-126 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.37 (d,  $J=8.5$ , 2H), 7.20 (d,  $J=8.5$ , 2H), 5.08 (s, 2H), 4.30 (s, 4H), 4.24 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.6, 149.1, 134.8, 129.7, 121.0, 120.4 (q,  $^1J_{C,F}=257.4$ ), 74.3, 66.2, 60.4, 24.8; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -57.9; **IR** (neat): 2967, 2894, 1699, 1438, 1411, 1314, 1259, 1217, 1172, 1142, 1076, 760 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>NNaO<sub>5</sub>S ([M+Na]<sup>+</sup>), 388.0437; found 388.0434.



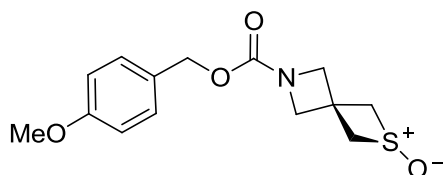
Phenethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2,2-dioxide (**309c**). According to GP5 using 2-phenylethanol (0.04 ml, 0.33 mmol, 1.0 equiv), CDI (81 mg, 0.50 mmol, 1.5 equiv), DMAP (4.1 mg, 0.033 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium 2,2-dioxide oxalate (**117**) (96 mg, 0.25 mmol, 0.75 equiv) with triethylamine (0.14 ml, 1.00 mmol, 3.0 equiv) and DMF (1.5 ml) for 1 h (1<sup>st</sup> step) and 2 d (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 62 mg (0.21 mmol, 63%). Colorless solid.

**TLC:**  $R_f$  = 0.27 (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 163 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.39 – 7.14 (m, 5H), 4.28 (s, 4H), 4.27 (t,  $J=6.9$ , 2H), 4.16 (s, 4H), 2.93 (t,  $J=6.9$ , 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.9, 137.5, 128.8, 128.4, 126.5, 74.3, 65.9, 60.3 (br), 35.5, 24.7; **IR** (neat): 3029, 2952, 1698, 1423, 1322, 1181, 1068, 967, 752, 702 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>18</sub>NO<sub>4</sub>S ([M+H]<sup>+</sup>), 296.0951; found 296.0948.



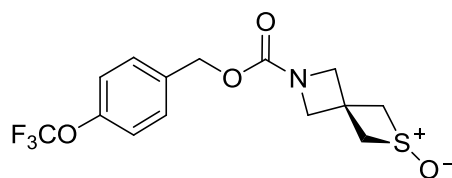
**Naphthalen-2-ylmethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2,2-dioxide (309d).** According to GP5 using naphthalen-2-ylmethanol (25 mg, 0.16 mmol, 1.0 equiv), CDI (38 mg, 0.24 mmol, 1.5 equiv), DMAP (1.9 mg, 0.016 mmol, 0.1 equiv) and 2-thia-6-azaspiro[3.3]heptan-6-ium 2,2-dioxide oxalate (**116**) (46 mg, 0.12 mmol, 0.75 equiv) with triethylamine (0.11 ml, 0.79 mmol, 5.0 equiv) and DMF (1 ml) for 2.5 h (1<sup>st</sup> step) and 23 h (2<sup>nd</sup> step). Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 32 mg (0.10 mmol, 61%). Colorless solid.

**TLC:**  $R_f$  = 0.21 (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 169-170 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 – 7.75 (m, 4H), 7.57 – 7.39 (m, 3H), 5.26 (s, 2H), 4.29 (s, 4H), 4.24 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.9, 133.4, 133.2, 128.4, 128.0, 127.7, 127.5, 126.4, 125.9, 74.3, 67.4, 60.4 (br), 24.7; **IR** (neat): 2957, 1700, 1417, 1287, 1177, 1071, 816, 751 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>17</sub>H<sub>17</sub>NNaO<sub>4</sub>S ([M+Na]<sup>+</sup>), 354.0770; found 354.0759.



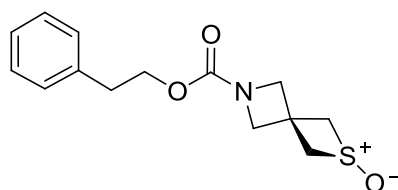
**4-Methoxybenzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2-oxide (310a).** According to GP3 using sulfide **306a** (39 mg, 0.14 mmol, 1.0 equiv) and *m*-CPBA (~85%; 28 mg, 0.14 mmol, 1.0 equiv) for 3.5 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 97:3) to afford pure title compound. Yield: 40 mg (0.14 mmol, 97%). Colorless foam.

**TLC:**  $R_f$  = 0.19 (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.26 (d,  $J$ =8.6, 2H), 6.87 (d,  $J$ =8.6, 2H), 5.00 (s, 2H), 4.03 (s, 2H), 4.01 (s, 2H), 3.83 (dt,  $J$ =12.4, 3.0, 2H), 3.80 (s, 3H), 3.34 (dt,  $J$ =12.4, 3.0, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.4, 155.8, 129.9, 128.1, 113.8, 66.8, 62.1, 61.2, 60.8, 55.3, 29.2; **IR** (neat): 2949, 2874, 1696, 1421, 1359, 1244, 1132, 1059, 968, 751 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub>S (M<sup>+</sup>), 295.0873; found 295.0875.



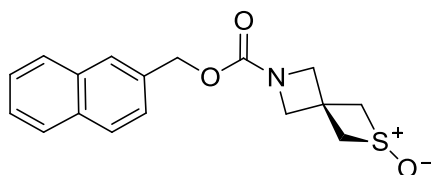
**4-(Trifluoromethoxy)benzyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2-oxide (310b).** According to GP4 using sulfide **306b** (42 mg, 0.13 mmol, 1.0 equiv) and *m*-CPBA (~85%; 25 mg, 0.13 mmol, 1.0 equiv) for 4.5 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2) to afford pure title compound. Yield: 39 mg (0.11 mmol, 89%). Colorless foam.

**TLC:**  $R_f = 0.14$  (EtOAc; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.36$  (d,  $J=8.3$ , 2H), 7.19 (d,  $J=8.3$ , 2H), 5.06 (s, 2H), 4.07 (s, 2H), 4.04 (s, 2H), 3.86 (dq,  $J=6.2$ , 2.9, 2H), 3.36 (dq,  $J=6.2$ , 2.9, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 155.6$ , 149.0, 134.9, 129.6, 121.0, 120.4 (q,  $^1J_{C,F}=257.3$ ), 66.0, 62.1, 61.3, 29.4; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta = -57.9$ ; **IR** (neat): 2956, 2885, 1701, 1510, 1435, 1408, 1254, 1216, 1144, 1055, 978, 841, 764 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>NNaO<sub>4</sub>S ([M+Na]<sup>+</sup>), 372.0488; found 372.0491.



**Phenethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2-oxide (310c).** According to GP4 using sulfide **306c** (44 mg, 0.17 mmol, 1.0 equiv) and *m*-CPBA (~85%; 34 mg, 0.17 mmol, 1.0 equiv) for 7 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2) to afford pure title compound. Yield: 43 mg (0.15 mmol, 92%). Colorless solid.

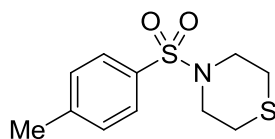
**TLC:**  $R_f = 0.13$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 96:4; UV, CAM); **Melting Point:** 83-84 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.41 - 7.10$  (m, 5H), 4.24 (t,  $J=6.9$ , 2H), 3.99 (s, 2H), 3.96 (s, 2H), 3.83 (dq,  $J=6.2$ , 2.9, 2H), 3.34 (dq,  $J=6.2$ , 2.9, 2H), 2.91 (t,  $J=6.9$ , 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 155.9$ , 137.6, 128.8, 128.3, 126.4, 65.8, 62.2, 61.2 (br), 35.5, 29.3; **IR** (neat): 2954, 2881, 1693, 1423, 1360, 1245, 1135, 1059, 988, 747, 696 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>14</sub>H<sub>18</sub>NO<sub>3</sub>S ([M+H]<sup>+</sup>), 280.1002; found 280.1010.



**Naphthalen-2-ylmethyl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2-oxide (310d).**

According to GP4 using sulfide **306d** (22 mg, 0.07 mmol, 1.0 equiv) and *m*-CPBA (~85%; 15 mg, 0.07 mmol, 1.0 equiv) for 6 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2) to afford pure title compound. Yield: 21 mg (0.07 mmol, 91%). Colorless solid.

**TLC:** *R<sub>f</sub>* = 0.29 (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5; UV, CAM); **Melting Point:** 149-150 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.94 – 7.71 (m, 4H), 7.59 – 7.36 (m, 3H), 5.24 (s, 2H), 4.08 (s, 2H), 4.05 (s, 2H), 3.85 (dq, *J*=6.2, 2.9, 2H), 3.36 (dq, *J*=6.2, 2.9, 2H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 155.9, 133.6, 133.2, 133.1, 128.3, 128.0, 127.7, 127.3, 126.3, 126.3, 125.8, 67.2, 62.2, 61.3 (br), 29.4; **IR** (neat): 2947, 2876, 1689, 1417, 1350, 1249, 1127, 1058, 981, 829, 747 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>17</sub>H<sub>18</sub>NO<sub>3</sub>S ([*M*+*H*]<sup>+</sup>), 316.1002; found 316.1005.



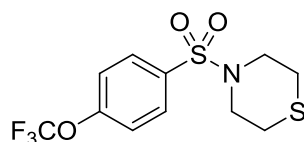
**4-Tosylthiomorpholine (312a).** To a solution of thiomorpholine (1.00 ml, 10.6 mmol, 1.0 equiv) in THF (10 ml) was added at RT triethylamine (2.97 ml, 21.1 mmol, 2.0 equiv), followed by *p*-toluenesulfonyl chloride (2.22 g, 11.6 mmol, 1.1 equiv), upon which the mixture warmed up quickly. The mixture was stirred at RT for 5 h, then was added EtOAc (40 ml) and H<sub>2</sub>O (40 ml). The phases were separated, and the organic layer was washed with saturated aqueous NaCl (20 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 9:1 → 5:1 → 2:1 gradient). Yield: 2.42 g (9.39 mmol, 89%). Colorless crystalline solid.

**Melting Point:** 125-126 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.62 (d, *J*=8.1, 2H), 7.33 (d, *J*=8.1, 2H), 3.42 – 3.18 (m, 4H), 2.79 – 2.57 (m, 4H), 2.44 (s, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 143.7, 133.6, 129.7, 127.4, 47.8, 27.2, 21.5; **IR** (neat): 2968, 2845, 1594, 1446, 1335, 1284, 1161, 1091, 967, 892, 814, 714 cm<sup>-1</sup>.

Analytical data matched the reported values.<sup>376</sup>

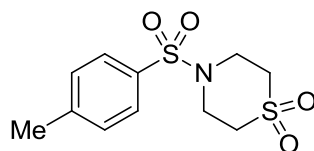
<sup>376</sup> C. J. M. Stirling, *J. Chem. Soc. (Res.)* **1962**, 3676-3685.





**4-((4-(Trifluoromethoxy)phenyl)sulfonyl)thiomorpholine (312b).** To a solution of thiomorpholine (60  $\mu$ l, 0.621 mmol, 1.0 equiv) in THF (3 ml), cooled to 0 °C, was added triethylamine (175  $\mu$ l, 1.24 mmol, 2.0 equiv), followed by 4-(trifluoromethoxy)benzene-1-sulfonyl chloride (**311b**) (118  $\mu$ l, 0.68 mmol, 1.1 equiv), upon which immediately a colorless precipitate formed. The suspension was stirred at 0 °C for 10 min, then it was allowed to warm to RT and stirring was continued for 17 h. At this point was added EtOAc (20 ml) and H<sub>2</sub>O (15 ml). The phases were separated, and the organic layer was washed with saturated aqueous NaCl (10 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 6:1) to afford the pure title compound. Yield: 191 mg (0.58 mmol, 94%). Colorless solid.

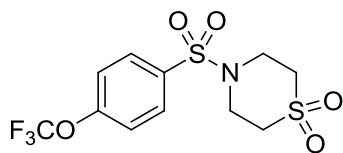
**TLC:**  $R_f$  = 0.48 (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 120–121 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.79 (d,  $J$ =8.8, 2H), 7.36 (d,  $J$ =8.8, 2H), 3.49 – 3.16 (m, 4H), 2.84 – 2.58 (m, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.3, 135.4, 129.5, 121.0, 120.2 (q,  $^1J_{C,F}$ =259.6), 47.8, 27.3; **<sup>19</sup>F-NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$  = –57.7; **IR** (neat): 2904, 1590, 1340, 1269, 1211, 1153, 1093, 970, 898, 717 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>11</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>3</sub>S<sub>2</sub> (M<sup>+</sup>), 327.0206; found 327.0204.



**4-Tosylthiomorpholine 1,1-dioxide (313a).** According to GP3 using sulfide **312a** (40 mg, 0.16 mmol, 1.0 equiv) and *m*-CPBA (77%; 70 mg, 0.31 mmol, 2.0 equiv) for 15 h. Purification of the residue was not necessary. Yield: 43 mg (0.15 mmol, 96%). Colorless solid.

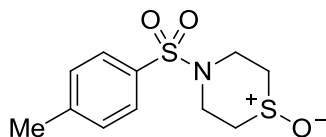
**Melting Point:** 202–203 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.65 (d,  $J$ =8.2, 2H), 7.35 (d,  $J$ =8.2, 2H), 3.65 (br s, 4H), 3.26 – 2.95 (m, 4H), 2.45 (s, 3H); **IR** (neat): 2997, 1460, 1304, 1162, 1125, 1027, 897, 716 cm<sup>-1</sup>.

Analytical data matched the reported values.<sup>376</sup>



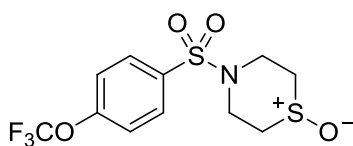
**4-((4-(Trifluoromethoxy)phenyl)sulfonyl)thiomorpholine 1,1-dioxide (313b).** According to GP3 using sulfide **312b** (30 mg, 0.09 mmol, 1.0 equiv) and *m*-CPBA (77%; 42 mg, 0.19 mmol, 2.0 equiv) for 8 h. Purification of the residue was not necessary. Yield: 32 mg (0.09 mmol, 97%). Colorless solid.

**TLC:**  $R_f = 0.60$  (hexanes : EtOAc 1:1; UV); **Melting Point:** 212–213 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92 - 7.77$  (m, 2H), 7.47 – 7.33 (m, 2H), 3.84 – 3.52 (m, 4H), 3.29 – 3.03 (m, 4H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.8, 135.3, 129.5, 121.3, 120.2$  (q,  $^1J_{\text{C,F}}=260.2$ ), 51.5, 44.8;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -57.5$ ; **IR** (neat): 2948, 1590, 1492, 1273, 1215, 1157, 1125, 1030, 901, 831, 719  $\text{cm}^{-1}$ ; **HRMS** (EI): exact masses calculated for  $\text{C}_7\text{H}_4\text{F}_3\text{O}_3\text{S}$  ( $[\text{arylsulfone fragment}]^+$ ), 224.9833; found 224.9826, and for  $\text{C}_4\text{H}_8\text{NO}_2\text{S}$  ( $[\text{thiomorpholine fragment}]^+$ ), 134.0276; found 134.0273.



**4-Tosylthiomorpholine 1-oxide (314a).** According to GP4 using sulfide **312a** (40 mg, 0.16 mmol, 1.0 equiv) and *m*-CPBA (~85%; 31 mg, 0.16 mmol, 1.0 equiv) for 16 h. The residue was purified by FC ( $\text{SiO}_2$ ; EtOAc : MeOH 99:1  $\rightarrow$  95:5 gradient) to give the pure title compound. Yield: 33 mg (0.12 mmol, 78%). Colorless solid.

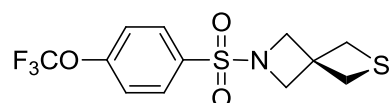
**TLC:**  $R_f = 0.17$  (EtOAc; UV); **Melting Point:** 186–187 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.66$  (d,  $J=8.3$ , 2H), 7.34 (d,  $J=8.3$ , 2H), 3.79 (d,  $J=13.3$ , 2H), 3.34 (t,  $J=13.3$ , 2H), 2.99 – 2.72 (m, 4H), 2.44 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.3, 133.3, 130.1, 127.5, 44.9, 36.4, 21.5$ ; **IR** (neat): 2998, 2900, 1701, 1320, 1287, 1161, 1026, 898, 714  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{S}_2$  ( $\text{M}^+$ ), 273.0488; found 273.0490.



**4-((4-(Trifluoromethoxy)phenyl)sulfonyl)thiomorpholine 1-oxide (314b).** According to GP4 using sulfide **312b** (37 mg, 0.11 mmol, 1.0 equiv) and *m*-CPBA (~85%; 23.2 mg,

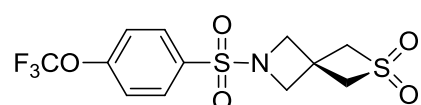
0.11 mmol, 1.0 equiv) for 8 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2) to afford pure title compound. Yield: 31 mg (0.09 mmol, 80%). Colorless solid.

**TLC:**  $R_f = 0.25$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2; UV, CAM); **Melting Point:** 196–197 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.77$  (d,  $J=8.5$ , 2H), 7.31 (d,  $J=8.5$ , 2H), 3.76 (dt,  $J=13.1, 2.5$ , 2H), 3.36 (td,  $J=13.1, 2.5$ , 2H), 3.03 – 2.68 (m, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 152.7, 134.9, 129.6, 121.2, 120.2$  (q,  $^1J_{C,F}=259.9$ ), 44.8, 36.3; **<sup>19</sup>F-NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta = -57.7$ ; **IR** (neat): 2974, 2922, 1592, 1495, 1273, 1209, 1154, 1096, 1011, 909, 740, 701 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>11</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>4</sub>S<sub>2</sub> (M<sup>+</sup>), 343.0155; found 343.0153.



**6-((4-(Trifluoromethoxy)phenyl)sulfonyl)-2-thia-6-azaspiro[3.3]heptane (315b).** To a suspension of 2-thia-6-azaspiro[3.3]heptan-6-ium oxalate (**117**) (100 mg, 0.31 mmol, 0.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added triethylamine (0.26 ml, 1.87 mmol, 3.0 equiv), followed by 4-(trifluoromethoxy)benzene-1-sulfonyl chloride (**311b**) (0.11 ml, 0.66 mmol, 1.05 equiv). The reaction mixture, which slightly warmed up during reagent addition, was stirred at RT for 1 h, when TLC indicated complete consumption of starting material. At this point was added CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and H<sub>2</sub>O (15 ml). The phases were separated, and the organic layer was washed with saturated aqueous NaCl (10 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 6:1). Yield: 141 mg (0.42 mmol, 67%). Colorless solid.

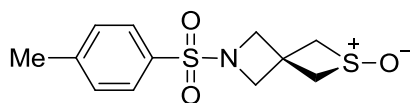
**TLC:**  $R_f = 0.41$  (hexanes : EtOAc 4:1; UV, CAM); **Melting Point:** 94–96 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.81$  (d,  $J=8.9$ , 2H), 7.32 (d,  $J=8.9$ , 2H), 3.76 (s, 4H), 3.11 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 152.7, 133.4, 130.3, 120.9, 120.2$  (q,  $^1J_{C,F}=259.7$ ), 63.3, 41.8, 36.3; **<sup>19</sup>F-NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta = -57.7$ ; **IR** (neat): 3024, 2946, 1589, 1494, 1254, 1203, 1151, 927, 837, 690 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub>S<sub>2</sub> ([M+H]<sup>+</sup>), 340.0283; found 340.0288.



**6-((4-(Trifluoromethoxy)phenyl)sulfonyl)-2-thia-6-azaspiro[3.3]heptane 2,2-dioxide (316b).** According to GP3 using sulfide **315b** (36 mg, 0.11 mmol, 1.0 equiv) and *m*-CPBA (77%;

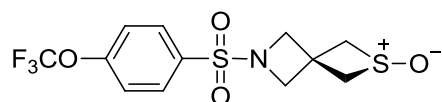
48 mg, 0.21 mmol, 2.0 equiv) for 5 h. Residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) to afford pure title compound. Yield: 37 mg (0.10 mmol, 94%). Colorless solid.

**TLC:**  $R_f = 0.39$  (hexanes : EtOAc 1:1; UV, CAM); **Melting Point:** 168 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.89$  (d,  $J=8.4$ , 2H), 7.41 (d,  $J=8.4$ , 2H), 4.18 (s, 4H), 4.01 (s, 4H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta = 153.0$ , 133.1, 130.4, 121.1, 120.2 (q,  $^1J_{C,F}=259.6$ ), 73.8, 60.5, 24.3; **<sup>19</sup>F-NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta = -57.7$ ; **IR** (neat): 3010, 2952, 1588, 1492, 1340, 1246, 1215, 1165, 1101, 1011, 843, 697 cm<sup>-1</sup>; **HRMS** (ESI): exact mass calculated for C<sub>12</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>5</sub>S<sub>2</sub> ( $[M+H]^+$ ), 372.0182; found 372.0175.



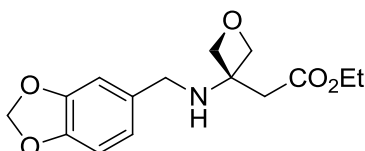
**6-Tosyl-2-thia-6-azaspiro[3.3]heptane 2-oxide (317a).** To a solution of sulfide **75** (200 mg, 0.74 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added *m*-CPBA (70%; 183 mg, 0.74 mmol, 1.0 equiv), and the reaction mixture was stirred at RT for 40 min. The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and washed with saturated aqueous NaHCO<sub>3</sub> (2 × 40 ml). The organic layer was dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a colorless solid. The residue was purified by FC (SiO<sub>2</sub>; EtOAc : MeOH 1:0 → 5:1) to afford the pure title compound. Yield: 186 mg (0.65 mmol, 88%). Colorless solid.

**TLC:**  $R_f = 0.29$  (CH<sub>2</sub>Cl<sub>2</sub> : MeOH 20:1; UV, CAM); **Melting Point:** 137 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.70$  (d,  $J=8.4$ , 2H), 7.38 (d,  $J=8.4$ , 2H), 3.81 (s, 2H), 3.78 (s, 2H), 3.65 (dt,  $J=12.8$ , 3.0, 2H), 3.21 (dt,  $J=12.8$ , 3.0, 2H), 2.47 (s, 3H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 144.5$ , 130.8, 129.8, 128.2, 61.5, 61.5, 61.5, 61.4, 29.0, 21.7; **IR** (neat): 2976, 2934, 1451, 1333, 1149, 1069, 982, 807, 682 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>S<sub>2</sub> (M<sup>+</sup>), 285.0488; found 285.0488.



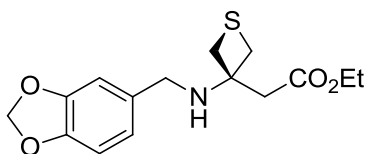
**6-((4-(Trifluoromethoxy)phenyl)sulfonyl)-2-thia-6-azaspiro[3.3]heptane 2-oxide (317b).** According to GP4 using sulfide **315b** (35 mg, 0.10 mmol, 1.0 equiv) and *m*-CPBA (~85%; 21 mg, 0.10 mmol, 1.0 equiv) for 6 h. Residue was purified by FC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> : MeOH 98:2) to afford pure title compound. Yield: 34 mg (0.10 mmol, 93%). Colorless foam.

**TLC:**  $R_f = 0.35$  ( $\text{CH}_2\text{Cl}_2$  : MeOH 95:5; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.87$  (d,  $J=8.9$ , 2H), 7.40 (d,  $J=8.9$ , 2H), 3.86 (s, 2H), 3.82 (s, 2H), 3.71 (dt,  $J=12.8$ , 3.0, 2H), 3.25 (dt,  $J=12.8$ , 3.0, 2H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.8$ , 133.2, 130.3, 121.0, 120.2 (q,  $^1J_{\text{C,F}}=259.9$ ), 61.6, 61.4, 29.2;  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -57.5$ ; **IR** (neat): 2997, 2938, 1589, 1493, 1305, 1258, 1206, 1161, 1067, 979, 839, 720  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_4\text{S}_2$  ( $\text{M}^+$ ), 355.0155; found 355.0159.



**Ethyl 2-(3-((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)oxetan-3-yl)acetate (320).** A mixture of ethyl 2-(oxetan-3-ylidene)acetate (184 mg, 1.27 mmol, 1.0 equiv) and piperonylamine (0.20 ml, 1.55 mmol, 1.2 equiv) was stirred at RT for 20 h, after which it was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1  $\rightarrow$  1:2 gradient) to afford the pure title compound. Yield: 240 mg (0.82 mmol, 65%). Colorless oil.

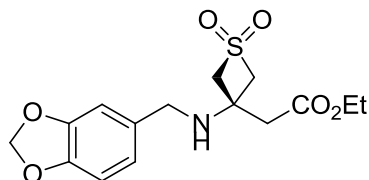
**TLC:**  $R_f = 0.12$  (hexanes : EtOAc 2:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.90 - 6.82$  (m, 1H), 6.82 – 6.69 (m, 2H), 5.93 (s, 2H), 4.65 (d,  $J=6.9$ , 2H), 4.52 (d,  $J=6.9$ , 2H), 4.15 (q,  $J=7.1$ , 2H), 3.74 (s, 2H), 2.94 (s, 2H), 1.95 (br s, 1H), 1.26 (t,  $J=7.1$ , 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.9$ , 147.8, 146.7, 134.1, 121.0, 108.7, 108.1, 100.9, 80.7, 60.6, 58.7, 47.2, 40.9, 14.2; **IR** (thin film): 2943, 2874, 1728, 1503, 1490, 1442, 1248, 1192, 1037, 977, 927, 809  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$  ( $[\text{M}-\text{CH}_2\text{O}]^+$ ), 263.1152; found 263.1153.



**Ethyl 2-(3-((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)thietan-3-yl)acetate (321).** A mixture of ethyl 2-(thietan-3-ylidene)acetate (**140**) (344 mg, 2.17 mmol, 1.0 equiv) and piperonylamine (0.34 ml, 2.65 mmol, 1.2 equiv) was stirred at RT for 14 h, after which it was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 4:1) to give the pure title compound. Yield: 242 mg (0.78 mmol, 36%). Colorless oil.

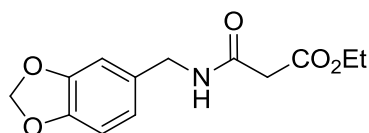
**TLC:**  $R_f = 0.32$  (hexanes : EtOAc 3:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.83$  (d,  $J=0.9$ , 1H), 6.80 – 6.67 (m, 2H), 5.90 (s, 2H), 4.14 (q,  $J=7.1$ , 2H), 3.70 (s, 2H), 3.46 (d,  $J=10.2$ , 2H), 3.03 (d,  $J=10.2$ , 2H), 2.99 (s, 2H), 2.08 (br s, 1H), 1.25 (t,  $J=7.1$ , 3H);  **$^{13}\text{C NMR}$**  (75 MHz,

CDCl<sub>3</sub>):  $\delta$  = 170.9, 147.6, 146.4, 134.0, 120.9, 108.5, 108.0, 100.8, 62.3, 60.4, 46.0, 42.1, 36.8, 14.1; **IR** (thin film): 2979, 2938, 2899, 1727, 1502, 1489, 1442, 1370, 1247, 1184, 1098, 1038, 929, 809 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>S (M<sup>+</sup>), 309.1029; found 309.1017.



**Ethyl 2-(3-((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-1,1-dioxidothietan-3-yl)acetate (322).** To a solution of thietane **321** (36 mg, 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added titanium(IV) isopropoxide (36  $\mu$ l, 0.12 mmol, 1.0 equiv), and the solution was cooled to 0 °C. At this point H<sub>2</sub>O<sub>2</sub> (30% in H<sub>2</sub>O; 36  $\mu$ l, 0.35 mmol, 3.0 equiv) was added, upon which yellow solids formed. The mixture was vigorously stirred at 0 °C for 40 min, when more H<sub>2</sub>O<sub>2</sub> (30% in H<sub>2</sub>O; 12  $\mu$ l, 0.12 mmol, 1.0 equiv) was added. The mixture was stirred for 10 min, when the ice-bath was removed and the mixture was stirred for another 10 min at RT. H<sub>2</sub>O (15 ml) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4  $\times$  15 ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2). Yield: 35 mg (0.10 mmol, 88%). Colorless solid.

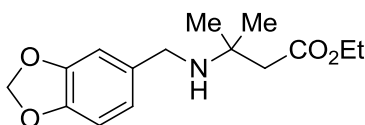
**TLC:**  $R_f$  = 0.21 (hexanes : EtOAc 2:1; UV, ninhydrin); **Melting Point:** 118–119 °C; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.83 (s, 1H), 6.80 – 6.69 (m, 2H), 5.94 (s, 2H), 4.18 (q,  $J$ =7.1, 2H), 4.14 – 4.08 (m, 4H), 3.61 (s, 2H), 2.99 (s, 2H), 2.23 (br s, 1H), 1.28 (t,  $J$ =7.1, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.9, 147.9, 147.0, 132.6, 121.1, 108.6, 108.2, 101.0, 73.6, 61.2, 47.6, 46.1, 41.1, 14.2; **IR** (thin film): 3328, 2982, 2903, 1726, 1503, 1490, 1443, 1317, 1249, 1207, 1037, 926, 809 cm<sup>-1</sup>; **HRMS** (EI): exact mass calculated for C<sub>15</sub>H<sub>19</sub>NO<sub>6</sub>S (M<sup>+</sup>), 341.0928; found 341.0929.



**Ethyl 3-((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-3-oxopropanoate (323).** A solution of piperonylamine (0.18 ml, 1.48 mmol, 1.0 equiv) and *i*Pr<sub>2</sub>NEt (0.26 ml, 1.48 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (7 ml) was cooled to 0 °C, and ethyl malonyl chloride (0.20 ml, 1.48 mmol, 1.0 equiv) was dropwise added. The mixture was stirred at 0 °C for 3 h, when it was quenched by pouring it into saturated aqueous NaHCO<sub>3</sub> (30 ml). CH<sub>2</sub>Cl<sub>2</sub> (40 ml) was added, and the phases were sep-

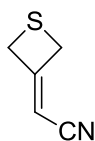
arated. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo* to afford a slightly yellowish solid. Purification of the residue by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 1:1  $\rightarrow$  0:1 gradient) afforded the pure title compound. Yield: 341 mg (1.29 mmol, 87%). Colorless solid.

**TLC:**  $R_f = 0.47$  (hexanes : EtOAc 1:2; UV, CAM); **Melting Point:** 85–86 °C;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.44$  (br s, 1H), 6.80 – 6.66 (m, 3H), 5.91 (s, 2H), 4.33 (d,  $J=5.7$ , 2H), 4.16 (q,  $J=7.1$ , 2H), 3.30 (s, 2H), 1.25 (t,  $J=7.1$ , 3H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 169.3$ , 164.8, 147.8, 146.8, 131.7, 120.9, 108.2, 108.2, 101.0, 61.5, 43.3, 41.1, 13.9; **IR** (thin film): 3291, 3074, 2985, 2905, 1786, 1650, 1550, 1503, 1490, 1445, 1252, 1037, 924, 808, 744  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{15}\text{NO}_5$  ( $\text{M}^+$ ), 265.0945; found 265.0945.



**Ethyl 3-((benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-3-methylbutanoate (324).** To a slurry of RANEY-Ni (*ca.* 50% in  $\text{H}_2\text{O}$ ; ~0.58 g) was added a solution of thietane **321** (30 mg, 0.10 mmol, 1.0 equiv) in EtOH (1 ml, rinsed with 0.5 ml), and the mixture was heated to 70 °C and stirred for 1.25 h. Then it was cooled to RT, filtered over celite, thoroughly washed with  $\text{CH}_2\text{Cl}_2$ , then the filtrate was washed with saturated aqueous  $\text{NaHCO}_3$  (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated *in vacuo*. Purification of the residue by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1) afforded the pure title compound. Yield: 9 mg (0.03 mmol, 33%). Colorless oil.

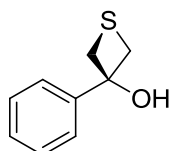
**TLC:**  $R_f = 0.22$  (hexanes : EtOAc 1:1; UV, ninhydrin);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.87$  (d,  $J=1.6$ , 1H), 6.84 – 6.70 (m, 2H), 5.92 (s, 2H), 4.14 (q,  $J=7.1$ , 2H), 3.62 (s, 2H), 2.49 (s, 2H), 1.70 (br s, 1H), 1.26 (t,  $J=7.1$ , 3H), 1.22 (s, 6H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.9$ , 147.6, 146.4, 121.2, 109.0, 108.1, 100.8, 60.1, 52.6, 46.7, 44.3, 27.5, 14.3; **IR** (thin film): 2971, 1726, 1489, 1442, 1247, 1219, 1038, 932, 772  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{14}\text{H}_{18}\text{NO}_4$  ( $[\text{M}-\text{CH}_3]^+$ ), 264.1231; found 264.1234.



**2-(Thietan-3-ylidene)acetonitrile (328).** To a solution of thietan-3-one (557 mg, 5.69 mmol, 1.0 equiv) in toluene (20 ml) was added ethyl 2-(triphenylphosphoranylidene)acetate (1.71 g, 5.69 mmol, 1.0 equiv), and the mixture was heated to 100 °C and stirred for 13.5 h. It

was cooled to RT and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 4:1) to afford the title compound in ~97% purity (<sup>1</sup>H NMR). Yield: 559 mg (4.88 mmol, 86%). Slightly yellowish oil.

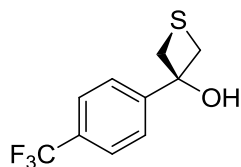
**TLC:**  $R_f = 0.41$  (hexanes : EtOAc 3:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 5.08$  (p,  $J=2.3$ , 1H), 4.14 – 4.06 (m, 2H), 4.04 – 3.96 (m, 2H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta = 162.9$ , 114.2, 94.0, 35.8, 35.5.



**3-Phenylthietan-3-ol (329a).** Thietan-3-one (245 mg, 2.50 mmol, 1.0 equiv) was dissolved in THF (12 ml) and the solution was cooled to  $-78$  °C. A solution of PhLi (2 M in Bu<sub>2</sub>O; 1.90 ml, 3.80 mmol, 1.5 equiv) was added dropwise, and the reaction mixture was stirred at  $-78$  °C for 15 min. The reaction was quenched at  $-78$  °C with saturated aqueous NH<sub>4</sub>Cl (5 ml), diluted with water (15 ml) and Et<sub>2</sub>O (40 ml), and the phases were separated. The aqueous phase was extracted with Et<sub>2</sub>O (10 ml), and the combined organic phases were washed with saturated aqueous NaCl (10 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. The residue was purified by FC (SiO<sub>2</sub>; hexanes : EtOAc 5:1) to afford the pure title compound. Yield: 256 mg (1.54 mmol, 62%). Colorless oil.

**TLC:**  $R_f = 0.33$  (hexanes : EtOAc 4:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.76$  – 7.57 (m, 2H), 7.51 – 7.29 (m, 3H), 3.67 (d,  $J=10.3$ , 2H), 3.59 (d,  $J=10.3$ , 2H), 2.84 (s, 1H).

Analytical data matched the literature values.<sup>377</sup>



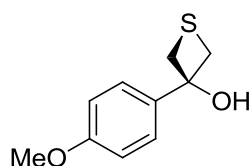
**3-(4-(Trifluoromethyl)phenyl)thietan-3-ol (329b).** To a solution of 4-trifluoromethylphenyl bromide (0.2 ml, 1.43 mmol, 1.0 equiv) in THF (8 ml) was added at  $-78$  °C *t*BuLi (1.7 M in pentane; 1.68 ml, 2.86 mmol, 2.0 equiv), and the now yellowish solution was stirred at  $-78$  °C for 35 min. A turbid solution of thietan-3-one (140 mg, 1.43 mmol, 1.0 equiv) in THF (2 ml) was added dropwise, and the mixture was stirred at  $-78$  °C for 1 h, then at

<sup>377</sup> F. S. Abbott, K. Haya, *Can. J. Chem.* **1978**, *56*, 71-79.



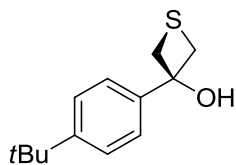
RT for 5 min, when it was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 ml). The mixture was diluted with  $\text{Et}_2\text{O}$  (20 ml) and  $\text{H}_2\text{O}$  (10 ml), and the phases were separated. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (10 ml), and the combined organic phases were washed with saturated aqueous  $\text{NaCl}$  (15 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  3:1). Yield: 264 mg (1.13 mmol, 79%). Colorless oil.

**TLC:**  $R_f = 0.32$  (hexanes :  $\text{EtOAc}$  3:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.82$  (d,  $J=8.2$ , 2H), 7.66 (d,  $J=8.2$ , 2H), 3.70 – 3.52 (m, 4H), 3.25 (s, 1H);  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -62.4$ .



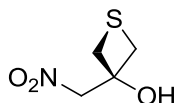
**3-(4-Methoxyphenyl)thietan-3-ol (329c).** To a solution of bromoanisole **331c** (0.50 ml, 3.86 mmol, 1.0 equiv) in THF (20 ml) was added at  $-78\text{ }^\circ\text{C}$  BuLi (1.6 M in hexanes; 2.66 ml, 4.25 mmol, 1.1 equiv), and the now slightly yellowish solution was stirred at  $-78\text{ }^\circ\text{C}$  for 1 h. Then was dropwise added a solution of thietan-3-one (378 mg, 3.86 mmol, 1.0 equiv) in THF (5 ml; rinsed with another 2 ml) and the mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 15 min. The reaction mixture was quenched by addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (10 ml), then it was diluted with  $\text{Et}_2\text{O}$  (40 ml) and  $\text{H}_2\text{O}$  (20 ml), and the phases were separated. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (15 ml), and the combined organic phases were washed with  $\text{H}_2\text{O}$  (15 ml), saturated aqueous  $\text{NaCl}$  (15 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes :  $\text{EtOAc}$  4:1) to afford the title compound in  $\sim 98\%$  purity ( $^1\text{H NMR}$ ). Yield: 455 mg (2.27 mmol, 59%). Slightly yellowish oil.

**TLC:**  $R_f = 0.32$  (hexanes :  $\text{EtOAc}$  3:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.62 - 7.46$  (m, 2H), 6.99 – 6.82 (m, 2H), 3.81 (s, 3H), 3.60 (d,  $J=9.4$ , 2H), 3.55 (d,  $J=9.4$ , 2H), 3.14 (s, 1H);  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 158.9, 136.6, 125.5, 113.7, 78.7, 55.3, 42.6$ ; **IR** (thin film): 3400, 2937, 2835, 1611, 1513, 1303, 1251, 1179, 1032, 813  $\text{cm}^{-1}$ .



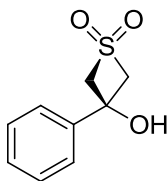
**3-(4-(*tert*-Butyl)phenyl)thietan-3-ol (329d).** A solution of 1-bromo-4-(*tert*-butyl)benzene (80  $\mu$ l, 0.47 mmol, 1.0 equiv) in THF (5 ml) was cooled to  $-78$   $^{\circ}$ C and *t*BuLi (1.7 M in pentane; 0.55 ml, 0.94 mmol, 2.0 equiv) was added dropwise over 5 min. The mixture was stirred at  $-78$   $^{\circ}$ C for 15 min, when thietan-3-one (41 mg, 0.47 mmol, 1.0 equiv) in THF (1 ml) was added. The mixture was stirred for 2 h, when it was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (10 ml). It was diluted with EtOAc (25 ml), and the phases were separated. The organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. Purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 10:1) afforded the pure title compound. Yield: 83 mg (0.37 mmol, 79%). Colorless oil.

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.58 (d,  $J=8.6$ , 2H), 7.44 (d,  $J=8.6$ , 2H), 3.67 (d,  $J=10.4$ , 2H), 3.59 (d,  $J=10.4$ , 2H), 2.73 (s, 1H), 1.35 (s, 9H).



**3-(Nitromethyl)thietan-3-ol (330).** To a solution of thietan-3-one (220 mg, 2.25 mmol, 1.0 equiv) in  $\text{MeNO}_2$  (2 ml) was dropwise added  $\text{Et}_3\text{N}$  (63  $\mu$ l, 0.45 mmol, 0.2 equiv). The solution immediately turned yellow and was stirred at RT for 13 h. It was concentrated *in vacuo* to afford a thick brown oil. This residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to afford the pure title compound. Yield: 191 mg (1.28 mmol, 57%). Slightly brownish oil.

**TLC:**  $R_f$  = 0.23 (hexanes : EtOAc 3:1; UV, CAM);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.91 (s, 2H), 3.60 (s, 1H), 3.56 (dd,  $J=10.0$ , 1.3, 2H), 3.19 – 3.04 (m, 2H).

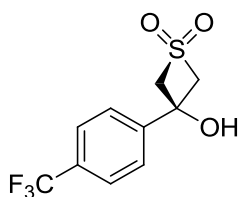


**3-Hydroxy-3-phenylthietane 1,1-dioxide (332a).** To a solution of thietane **329a** (216 mg, 1.30 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 ml), cooled to  $0$   $^{\circ}$ C, was added in portions *m*-CPBA (*ca.* 77%; 582 mg, 2.60 mmol, 2.0 equiv), and the colorless suspension was stirred at  $0$   $^{\circ}$ C for 5 min, when it was allowed to warm to RT. Stirring was continued at RT for 3.5 h. The reaction was

diluted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and quenched with saturated aqueous  $\text{NaHCO}_3$  (20 ml). The phases were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml). The combined organic layers were washed with saturated aqueous  $\text{NaCl}$  (20 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1  $\rightarrow$  1:1 gradient). Yield: 218 mg (1.10 mmol, 85%). Colorless solid.

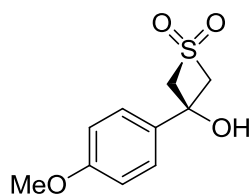
**TLC:**  $R_f = 0.45$  (hexanes : EtOAc 1:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.60 - 7.30$  (m, 5H), 4.72 – 4.52 (m, 2H), 4.52 – 4.30 (m, 2H), 3.59 (s, 1H).

Analytical data matched the literature values.<sup>377</sup>



**3-Hydroxy-3-(4-(trifluoromethyl)phenyl)thietane 1,1-dioxide (332b).** To a solution of thietane **329b** (78 mg, 0.33 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (4 ml), cooled to 0 °C, was added *m*-CPBA (*ca.* 77%; 164 mg, 0.73 mmol, 2.2 equiv), and the colorless suspension was stirred at 0 °C for 15 min. It was allowed to warm to RT and stirring was continued for 1.5 h. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (5 ml) and diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and  $\text{H}_2\text{O}$  (5 ml). The phases were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic phases were washed with saturated aqueous  $\text{NaCl}$  (10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1  $\rightarrow$  1:1 gradient) to afford the pure title compound. Yield: 81 mg (0.30 mmol, 91%). Colorless solid.

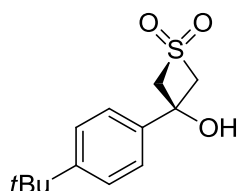
**TLC:**  $R_f = 0.27$  (hexanes : EtOAc 3:1; UV);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.71$  (s, 4H), 4.73 – 4.55 (m, 2H), 4.55 – 4.37 (m, 2H);  **$^{19}\text{F-NMR}$**  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -62.6$ .



**3-Hydroxy-3-(4-methoxyphenyl)thietane 1,1-dioxide (332c).** To a solution of thietane **329c** (261 mg, 1.30 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 ml), cooled to 0 °C, was added in portions *m*-CPBA (*ca.* 77%; 584 mg, 2.61 mmol, 2.0 equiv), and the colorless suspension was stirred at

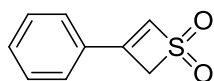
0 °C for 5 min, when it was allowed to warm to RT, and stirring was continued for 3.5 h. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (20 ml) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 ml). The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (15 ml). The combined organic layers were washed with saturated aqueous NaCl (20 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; hexanes : EtOAc 3:2) afforded the title compound. Yield: 282 mg (1.21 mmol, 93%). Colorless solid.

**TLC:**  $R_f$  = 0.35 (hexanes : EtOAc 1:1; UV, CAM); **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.41 (d,  $J$ =8.7, 2H), 6.94 (d,  $J$ =8.7, 2H), 4.69 – 4.52 (m, 2H), 4.49 – 4.32 (m, 2H), 3.83 (s, 3H), 3.29 (br s, 1H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.6, 133.1, 126.1, 114.3, 78.2, 64.5, 55.5; **HRMS** (EI): exact mass calculated for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub>S (M<sup>+</sup>), 228.0451; found 228.0454.



**3-(4-(*tert*-Butyl)phenyl)-3-hydroxythietane 1,1-dioxide (332d).** To a solution of thietane **329d** (63 mg, 0.28 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml), cooled to 0 °C, was added *m*-CPBA (*ca.* 77%; 132 mg, 0.59 mmol, 2.1 equiv), and the colorless suspension was stirred at 0 °C for 5 min, when it was allowed to warm to RT, and stirring was continued for 14 h. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (10 ml) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The combined organic layers were washed with saturated aqueous NaCl (10 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Purification of the residue by FC (SiO<sub>2</sub>; hexanes : EtOAc 1:1) afforded the title compound. Yield: 71 mg (0.28 mmol, 99%). Colorless solid.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53 – 7.34 (m, 4H), 4.73 – 4.57 (m, 2H), 4.52 – 4.31 (m, 2H), 3.20 (s, 1H), 1.33 (s, 9H).

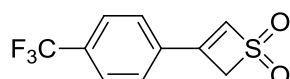


**3-Phenyl-2H-thiete 1,1-dioxide (333a).** To a solution of alcohol **332a** (73 mg, 0.37 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (4 ml) was added triethylamine (0.16 ml, 1.11 mmol, 3.0 equiv) followed by dropwise addition of MsCl (86  $\mu$ l, 1.11 mmol, 3.0 equiv), and the mixture was stirred at RT for 45 min. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 ml) and quenched by the addition of H<sub>2</sub>O (10 ml). The phases were separated, and the organic phase was washed with saturated aqueous

NaCl (10 ml), then dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The residue was purified by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1) to afford the title compound in ~98% purity ( $^1\text{H NMR}$ ). Yield: 65 mg (0.35 mmol, 96%). Colorless solid.

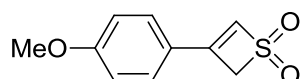
**TLC:**  $R_f = 0.24$  (hexanes : EtOAc 3:1; UV, CAM);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.61 - 7.39$  (m, 5H), 6.95 (s, 1H), 4.80 (s, 2H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.2, 136.6, 132.2, 129.2, 128.8, 127.4, 69.9$ .

Analytical data matched the literature values.<sup>378</sup>



**3-(4-(Trifluoromethyl)phenyl)-2H-thiete 1,1-dioxide (333b).** To a solution of alcohol **332b** (22.5 mg, 0.085 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.4 ml) was added triethylamine (36  $\mu\text{l}$ , 0.25 mmol, 3.0 equiv). MsCl (20  $\mu\text{l}$ , 0.25 mmol, 3.0 equiv) was added dropwise, and the mixture was stirred at RT for 12.5 h. More triethylamine (12  $\mu\text{l}$ , 0.085 mmol, 1.0 equiv) and MsCl (7  $\mu\text{l}$ , 0.085 mmol, 1.0 equiv) were added, and stirring was continued for 30 min, when the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (5 ml) and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 ml). It was further diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and  $\text{H}_2\text{O}$  (5 ml), and the phases were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml), and the combined organic layers were washed with saturated aqueous NaCl (10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 5:2). Yield: 14 mg (0.056 mmol, 67%). Colorless solid.

**TLC:**  $R_f = 0.40$  (hexanes : EtOAc 2:1; UV,  $\text{KMnO}_4$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.75$  (d,  $J=8.1$ , 2H), 7.59 (d,  $J=8.1$ , 2H), 7.08 (s, 1H), 4.85 (s, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 145.7, 139.4, 133.7$  (q,  $J_{\text{C,F}} = 33.1$ ), 132.2, 127.8, 126.3 (q,  $J_{\text{C,F}} = 3.8$ ), 123.4 (q,  $J_{\text{C,F}} = 272.6$ ), 70.1;  $^{19}\text{F-NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -63.0$ .

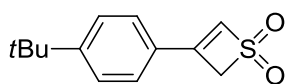


**3-(4-Methoxyphenyl)-2H-thiete 1,1-dioxide (333c).** To a solution of alcohol **332c** (30 mg, 0.13 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added triethylamine (54  $\mu\text{l}$ , 0.37 mmol, 3.0 equiv), then was dropwise added MsCl (30  $\mu\text{l}$ , 0.37 mmol, 3.0 equiv), and the mixture was stirred at RT

<sup>378</sup> D. C. Dittmer, B. H. Patwardhan, J. T. Bartholomew, *Org. Magn. Resonance* **1982**, 18, 82-86.

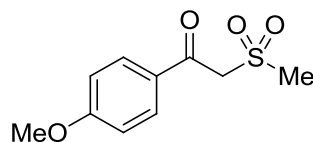
for 3 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (5 ml) and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 ml). It was further diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and  $\text{H}_2\text{O}$  (5 ml), and the phases were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (10 ml), and the combined organic layers were washed with saturated aqueous  $\text{NaCl}$  (10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification of the residue by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 2:1). Yield: 22 mg (0.11 mmol, 81%). Colorless solid.

**TLC:**  $R_f = 0.45$  (hexanes : EtOAc 1:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.47 - 7.34$  (m, 2H), 7.03 – 6.89 (m, 2H), 6.80 (s, 1H), 4.76 (s, 2H), 3.88 (s, 3H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.8, 146.7, 134.0, 129.4, 121.5, 114.6, 69.8, 55.5$ ; **IR** (thin film): 3078, 2998, 1607, 1508, 1279, 1253, 1207, 1186, 1124, 1029, 841, 782  $\text{cm}^{-1}$ .



**3-(4-(*tert*-Butyl)phenyl)-2H-thiete 1,1-dioxide (333d).** To a solution of alcohol **332d** (71 mg, 0.21 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (4.2 ml) was added triethylamine (117  $\mu\text{l}$ , 0.84 mmol, 3.0 equiv), then was dropwise added  $\text{MsCl}$  (65  $\mu\text{l}$ , 0.84 mmol, 3.0 equiv), and the mixture was stirred at RT for 6 h. At this point was added more  $\text{Et}_3\text{N}$  (39  $\mu\text{l}$ , 0.28 mmol, 1.0 equiv), and the mixture was stirred at RT for 14 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml) and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 ml). It was further diluted with  $\text{CH}_2\text{Cl}_2$  (15 ml) and  $\text{H}_2\text{O}$  (10 ml), and the phases were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (15 ml), and the combined organic layers were washed with saturated aqueous  $\text{NaCl}$  (10 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo*. The pure title compound was obtained after purification of the residue by FC ( $\text{SiO}_2$ ; hexanes : EtOAc 3:1). Yield: 49 mg (0.21 mmol, 74%). Colorless solid.

**TLC:**  $R_f = 0.43$  (hexanes : EtOAc 2:1; UV,  $\text{KMnO}_4$ ); **Melting Point:**  $>220$   $^\circ\text{C}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.49$  (d,  $J=8.7$ , 2H), 7.39 (d,  $J=8.7$ , 2H), 6.90 (s, 1H), 4.79 (s, 2H), 1.35 (s, 9H);  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.2, 147.1, 135.7, 127.3, 126.2, 126.1, 69.9, 35.2, 31.0$ ; **IR** (neat): 3104, 2961, 2807, 1606, 1503, 1365, 1292, 1202, 1130, 1102, 840, 796, 743  $\text{cm}^{-1}$ ; **HRMS** (EI): exact mass calculated for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$  ( $\text{M}^+$ ), 236.0866; found 236.0873.



**1-(4-Methoxyphenyl)-2-(methylsulfonyl)ethanone (334).** To a colorless solution of dioxothietan-3-ol **332c** (11 mg, 47  $\mu\text{mol}$ , 1.0 equiv) in MeOH (1 ml) was added NaOMe (5.1 mg, 94  $\mu\text{mol}$ , 2.0 equiv), and the mixture turned purple after *ca.* 30 s. After 5 min, the reaction mixture was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (5 ml), upon which the mixture turned colorless again. EtOAc (20 ml) and  $\text{H}_2\text{O}$  (10 ml) were added, and the phases were separated. The organic phase was washed with saturated aqueous NaCl (5 ml), dried ( $\text{MgSO}_4$ ), filtered, and concentrated *in vacuo* to afford the pure title compound. Yield: 11 mg (47  $\mu\text{mol}$ , quantitative). Colorless solid.

**TLC:**  $R_f = 0.56$  ( $\text{CH}_2\text{Cl}_2$  : EtOAc 10:1; UV, CAM);  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.07 - 7.90$  (m, 2H), 7.06 – 6.89 (m, 2H), 4.55 (s, 2H), 3.90 (s, 3H), 3.14 (s, 3H).

Analytical data matched the reported literature values.<sup>379</sup>

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<sup>379</sup> N. Kamigata, K. Udodaira, T. Shimizu, *J. Chem. Soc., Perkin Trans. 1* **1997**, 783–786.





# Curriculum Vitae

Born March 18<sup>th</sup> 1983 in Zürich, Switzerland.

- 04/2007 – present**      Doctoral studies in the group of Prof. Dr. ERICK M. CARREIRA, *ETH Zürich*, Switzerland.  
Title: *New Opportunities for Four-Membered Heterocycles: From Synthetic Studies to Unique Applications in Drug Discovery.*
- November 16<sup>th</sup> 2006**      M.Sc. ETH in Chemistry.
- 03/2006 – 08/2006**      Master thesis in the group of Prof. Dr. FRANÇOIS DIEDERICH, *ETH Zürich*, Switzerland.  
Title: *Synthesis of Mepacrine-Diarylsulfide Conjugates as New Trypanothione Reductase Inhibitors.*
- 10/2005 – 10/2006**      Master studies in chemistry, *ETH Zürich*, Switzerland.
- April 21<sup>st</sup> 2006**      B.Sc. ETH in Chemistry.
- 10/2002 – 03/2006**      Bachelor studies in chemistry, *ETH Zürich*, Switzerland.
- 02/2002 – 05/2002**      Mandatory service in the Swiss military.
- 08/1997 – 01/2002**      Kantonsschule Limmattal, Urdorf, Switzerland.
- 08/1995 – 08/1997**      Sekundarschule Ennetgraben, Affoltern am Albis, Switzerland.
- 08/1989 – 08/1995**      Primarschule, Zwillikon, Switzerland.

## Awards and Fellowships

- 05/2011**      2011 *SCNAT/SCS* Chemistry Travel Award.
- 04/2009 – 04/2010**      Scholarship from the *Roche Research Foundation.*
- 04/2008 – 04/2009**      *Novartis* Graduate Fellowship.

During my doctoral studies, I was once head assistant and twice teaching assistant for an introductory-level organic chemistry laboratory course, four times teaching assistant for organic chemistry exercises and lectures, responsible for six undergraduate students in the context of their research projects, and responsible for the supervision of an apprentice (chemistry technician) during three years.