Oxetanes in Drug Discovery

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# Table of Contents

Abstract .................................................................................................................. ix

Zusammenfassung ................................................................................................... xii

List of Abbreviations and Acronyms .................................................................... xv

1 *Introduction* ....................................................................................................... 1
  1.1 Structural Properties of Oxetanes: ................................................................. 3
  1.2 Ring-Opening Reactions of Oxetanes ............................................................ 6
  1.3 Tendency of Oxetane to Form Radicals ....................................................... 8
  1.4 Preparation of Oxetanes ............................................................................... 10
  1.5 Pharmacologically Relevant Oxetanes ......................................................... 12

2 *Idea and Theoretical Concept* ........................................................................ 19
  2.1 Oxetanes as Lipo-Neutral Bulk Increase ..................................................... 19
  2.2 Oxetanes as Carbonyl Analogues ................................................................. 24
  2.3 Spirocyclic Oxetanes as a Mimic for Oxa-Heterocycles ............................. 28
  2.4 Synthetic Access to Oxetanes ....................................................................... 31

3 *Main Part, Chemistry* ..................................................................................... 39
  3.1 Preparation of Oxetan-3-one ........................................................................ 39
    3.1.1 Route via Ketal Cleavage ........................................................................ 41
    3.1.2 Oxidation of Oxetan-3-ol ....................................................................... 45
  3.2 Additions to Oxetan-3-one ........................................................................... 50
    3.2.1 3-Aryloxetan-3-ols ................................................................................ 50
    3.2.2 3-Fluoro-oxetanes ................................................................................. 52
    3.2.3 3-Aryloxetanes ..................................................................................... 54
    3.2.4 3-Aminooxetanes .................................................................................. 57
  3.3 Oxetanes Bearing a Quaternary Center ......................................................... 59
  3.4 1,4-Addition to Michael Acceptors ................................................................ 60
    3.4.1 Preparation of Acceptors ....................................................................... 61
    3.4.2 Conjugate Additions .............................................................................. 62
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>Chemistry starting with Tribromopentaerythritol</td>
<td>67</td>
</tr>
<tr>
<td>3.6</td>
<td>Selective Opening of 2,6-dioxaspiro[3.3]heptane</td>
<td>71</td>
</tr>
<tr>
<td>3.7</td>
<td>Follow-up Reactions</td>
<td>74</td>
</tr>
<tr>
<td>3.7.1</td>
<td>Compounds of the Open Chain-Series</td>
<td>74</td>
</tr>
<tr>
<td>3.7.2</td>
<td>Oxetane-Analogues of Sibutramine</td>
<td>77</td>
</tr>
<tr>
<td>3.7.3</td>
<td>Spirocyclic Oxetanes</td>
<td>79</td>
</tr>
<tr>
<td>3.7.4</td>
<td>Reactions of Sulfone 93</td>
<td>83</td>
</tr>
<tr>
<td>3.8</td>
<td>Reagent Compatibility of Oxetanes</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Physicochemical and Pharmacological Profile of Oxetanes</td>
<td>87</td>
</tr>
<tr>
<td>4.1</td>
<td>Measured Properties</td>
<td>90</td>
</tr>
<tr>
<td>4.1.1</td>
<td>Structural Considerations</td>
<td>90</td>
</tr>
<tr>
<td>4.1.2</td>
<td>Acid Dissociation Constant $\text{pK}_a$</td>
<td>95</td>
</tr>
<tr>
<td>4.1.3</td>
<td>Lipophilicity</td>
<td>98</td>
</tr>
<tr>
<td>4.1.4</td>
<td>Aqueous Solubility</td>
<td>100</td>
</tr>
<tr>
<td>4.1.5</td>
<td>Metabolic Stability</td>
<td>102</td>
</tr>
<tr>
<td>4.1.6</td>
<td>Chemical Stability</td>
<td>105</td>
</tr>
<tr>
<td>4.2</td>
<td>Oxetanes as gem-dimethyl Analogues</td>
<td>105</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Structural Considerations</td>
<td>106</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Aqueous Solubility and Lipophilicity</td>
<td>107</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Metabolic stability</td>
<td>109</td>
</tr>
<tr>
<td>4.2.4</td>
<td>hERG-Channel</td>
<td>110</td>
</tr>
<tr>
<td>4.2.5</td>
<td>Amphiphilicity and Phospholipidosis</td>
<td>112</td>
</tr>
<tr>
<td>4.3</td>
<td>Oxetanes as Carbonyl Analogues</td>
<td>114</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Structural Considerations</td>
<td>114</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Influence on $\text{pK}_a$</td>
<td>116</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Lipophilicity and Aqueous Solubility</td>
<td>117</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Metabolic and Chemical Stability</td>
<td>119</td>
</tr>
<tr>
<td>4.4</td>
<td>Spirocyclic Oxetanes as Morpholine Analogues</td>
<td>120</td>
</tr>
<tr>
<td>4.4.1</td>
<td>Structural Considerations</td>
<td>121</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Influence on $\text{pK}_a$</td>
<td>122</td>
</tr>
<tr>
<td>4.4.3</td>
<td>Solubility and Lipophilicity</td>
<td>122</td>
</tr>
<tr>
<td>4.4.4</td>
<td>Metabolic stability</td>
<td>124</td>
</tr>
<tr>
<td>4.5</td>
<td>Applications</td>
<td>125</td>
</tr>
</tbody>
</table>
Abstract

Many drug candidates that display in vitro activity also share undesired features such as high lipophilicity or metabolic liabilities that rule out their further development. In many cases, these problems can be traced back to the presence of certain functional groups that are known to have a detrimental influence on the solubility, chemical or metabolic stability of a given scaffold. We reasoned that oxetanes might be able to substitute some of these.

From a structural point of view, 3,3-disubstituted oxetanes can be described as a combination of steric bulk exhibited by its methylene groups and the polarity introduced by the ethereal oxygen. Therefore, an oxetane poses a more hydrophilic alternative to bulky functionalities such as gem-dimethyl groups. Molecules containing carbonyl groups in turn often display undesirable chemical reactivity at or in proximity to the carbonyl function. An oxetane, being less electrophilic and lacking the ability to stabilize adjacent negative charges can be an alternative. Furthermore, a class of spirocyclic oxetanes might be able to replace morpholine, an oft encountered heterocycle in medicinal chemistry by virtue of their structural and physicochemical similarity. Interestingly, neither of these potential applications of oxetanes had been investigated before, nor is there much precedence for their use in medicinal chemistry.

We reasoned that in order to be practically relevant, the oxetane motif had to be easily accessible in various structural contexts. A building block strategy was pursued to achieve this goal. Starting from oxetan-3-one, a wide range of oxetane-containing compounds could be made. This structural diversity is a result of the flexibility, inherent to the chemistry of oxetan-3-one and even more to the Michael acceptors derived from it.
These routes allowed us to prepare two distinct series of molecules in which the oxetane was embedded at different positions of the scaffold. The compounds shown below on the left were compared with their gem-dimethyl counterparts.
The members of the spirocyclic series on the right were in addition to that also matched with the respective carbonyl and morpholine analogues. The aqueous solubility, lipophilicity, metabolic stability and other parameters were measured then for all these compounds at F. Hoffmann-La Roche.

The results clearly show that the integration of an oxetane can have a dramatic influence on the physico- and biochemical properties of the underlying scaffold. When compared with their gem-dimethyl counterparts, oxetanes are less lipophilic, more soluble and in most cases also metabolically more stable. The replacement of a carbonyl group with an oxetane can lead to significant changes in the conformational preference, basicity, lipophilicity and metabolic stability of the underlying scaffold. This replacement seems to be attractive in situations where the carbonyl compound shows chemical or metabolic instability, undesirable reactivity or when a nonplanar conformation is desired. Some of the spirocyclic oxetanes seem to even exceed morpholine in their ability to solubilize a given scaffold while at the same time being less prone to metabolic degradation.

The results of this work have not only been successfully applied to various projects of F. Hoffmann-La Roche, but also by several other pharmaceutical companies. Taken together our data make a case for a more general use of this under-represented structural motif in drug discovery and beyond.

We are deeply indebted to F. Hoffmann-La Roche, Basel for its commitment to initiate and support this project.
Zusammenfassung

Viele Verbindungen, welche Aktivität in vitro zeigen, weisen Eigenschaften wie hohe Lipophilie oder metabolische Instabilität auf, die eine Weiterentwicklung unmöglich machen. In vielen Fällen lassen sich diese Probleme auf das Vorhandensein bestimmter funktioneller Gruppen zurückführen, deren abträglicher Einfluss auf die wässrige Löslichkeit und metabolische Stabilität bekannt ist. Oxetane könnten einige dieser Gruppen ersetzen.


Die Ergebnisse dieser Untersuchungen zeigen deutlich, dass die Integration eines Oxetans dramatische Auswirkungen auf die physiko- wie auch biochemischen Parameter des zugrundeliegenden Molekülerüsts haben kann. Im Vergleich mit ihren geminalen Dimethylpendants sind Oxetane weniger lipophil, besser wasserlöslich und in den meisten Fällen auch metabolisch stabiler. Der Austausch einer Carbonylgruppe gegen ein Oxetan führt in der Regel zu signifikanten Änderungen der Konformation, der Basizität, der Lipophilie und der metabolischen Stabilität. Diese Substitution kommt infrage für Fälle, in denen die Carbonylverbindung instabil, oder wenn eine Änderung der Konformation erwünscht ist. Einige spirozyklische Oxetane andererseits, scheinen mehr noch als Morpholin in der Lage zu sein, die Wasserlöslichkeit einer Verbindung zu erhöhen bei gleichzeitig verringelter Anfälligkeit zu metabolischem Abbau.

Die Resultate dieser Arbeit wurden nicht nur in verschiedenen Projekten bei F. Hoffmann La-Roche, sondern auch von mehreren anderen Firmen erfolgreich angewandt. Unsere Ergebnisse legen den Grundstein für eine breitere Anwendung dieser unterrepräsentierten Substanzklasse in der Medizinalchemie und darüber hinaus.

Wir sind F. Hoffmann-La Roche, Basel für das grosse Engagement, das für Initiierung und vor allem die Durchführung dieses Projektes unerlässlich war zu grossem Dank verpflichtet.
List of Abbreviations and Acronyms

°  degree
Å  Ångstrom
Ac  acetyl
AIBN  2,2'‐azobisisobutyronitrile
aq.  aqueous
atm  atmosphere
Bn  benzyl
bp  boiling point
br  broad
Bu  butyl
Bz  benzoyl
°C  degree centigrade
calcd  calculated
CAM  ceric ammonium molybdate
cat.  catalytic
Cl_{int}  internal metabolic clearance
cm^{−1}  reciprocal centimeters
cod  cyclooctadiene
Cy  cyclohexyl
δ  NMR chemical shift in ppm downfield from a standard
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition/Description</th>
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<tbody>
<tr>
<td>d</td>
<td>day, doublet</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N')-dimethylamino pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppa</td>
<td>diphenylphosphoryl azide</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>ent</td>
<td>reversal of stereocenters</td>
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<tr>
<td>equiv.</td>
<td>equivalent</td>
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<tr>
<td>ESI</td>
<td>electron spray ionization</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>et al.</td>
<td>and others</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transformation</td>
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<tr>
<td>g</td>
<td>gram</td>
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<tr>
<td>gem</td>
<td>geminal</td>
</tr>
<tr>
<td>h</td>
<td>hour, human</td>
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<tr>
<td>hERG</td>
<td>human-Ether-a-go-go Related Gene</td>
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<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<tr>
<td>HR</td>
<td>high resolution</td>
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<tr>
<td>Symbol</td>
<td>Definition</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant, Joule</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium 1,1,1,3,3,3-hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>LiDBB</td>
<td>lithium Di-tert-butylbiphenyl</td>
</tr>
<tr>
<td>logD</td>
<td>intrinsic lipophilicity</td>
</tr>
<tr>
<td>logP</td>
<td>lipophilicity</td>
</tr>
<tr>
<td>m</td>
<td>multiplet, mouse</td>
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<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>M</td>
<td>molecule ion</td>
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<tr>
<td>m</td>
<td>molar</td>
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<td>mbar</td>
<td>millibar</td>
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<td>Me</td>
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<td>mg</td>
<td>milligram</td>
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<tr>
<td>MHz</td>
<td>megahertz</td>
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<td>min</td>
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<td>ml</td>
<td>milliliter</td>
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<tr>
<td>Symbol</td>
<td>Description</td>
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<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>( m_p )</td>
<td>melting point</td>
</tr>
<tr>
<td>( \mu l )</td>
<td>microliter</td>
</tr>
<tr>
<td>( \text{mmol} )</td>
<td>millimole</td>
</tr>
<tr>
<td>( \mu m )</td>
<td>micromole</td>
</tr>
<tr>
<td>( \text{mol}% )</td>
<td>mole per cent</td>
</tr>
<tr>
<td>( \text{Ms} )</td>
<td>methylsulfonyl</td>
</tr>
<tr>
<td>( \text{MS} )</td>
<td>molecular sieves, mass spectrometry</td>
</tr>
<tr>
<td>( n\text{Al}_2\text{O}_3 )</td>
<td>neutral aluminum oxide</td>
</tr>
<tr>
<td>( \text{NMO} )</td>
<td>( N )-methyl morpholine ( N )-oxide</td>
</tr>
<tr>
<td>( \text{NMR} )</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>( \nu )</td>
<td>vibration frequency in ( \text{cm}^{-1} )</td>
</tr>
<tr>
<td>( o )</td>
<td>ortho</td>
</tr>
<tr>
<td>( p )</td>
<td>para</td>
</tr>
<tr>
<td>( \text{PCC} )</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>( \text{pH} )</td>
<td>negative decadic logarithm of hydrogen ion concentration</td>
</tr>
<tr>
<td>( \text{Ph} )</td>
<td>phenyl</td>
</tr>
<tr>
<td>( \text{pK}_a )</td>
<td>negative decadic logarithm of the acid dissociation constant</td>
</tr>
<tr>
<td>( \text{ppm} )</td>
<td>parts per million</td>
</tr>
<tr>
<td>( \text{Pr} )</td>
<td>propyl</td>
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<tr>
<td>( \text{pyr} )</td>
<td>pyridine</td>
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<tr>
<td>( q )</td>
<td>quartet</td>
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quant. quantitative
R$f$ retention factor
rt room temperature
s singlet, second
t triplet
t $t$ tert
T temperature, tesla
TBAB tetra-$n$-butylammonium bromide
TBAF tetra-$n$-butylammonium fluoride
TEMPO $2,2,6,6$-tetramethylpiperidine $1$-oxyl radical
TES triethylsilyl
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl
Ts 4-methylphenylsulfonyl
TPAP tetra-$n$-propylammonium perruthenate
UV ultraviolet
w% weight per cent
Z benzyloxycarbonyl
1 Introduction

For an active compound to become a drug, affinity to its target is a prerequisite, but not by itself sufficient. Factors like aqueous solubility, lipophilicity, membrane permeability, metabolic stability, toxicity and side effects determine the fate of a compound much more than mere binding constants.

Picture 1: Drug candidate facing resistance on the way to the market.¹

The acceptable ranges for these properties are tight, because of the attrition risk a deviation poses for the clinical development of a drug candidate. As clinical studies and registration absorb the majority of costs in the drug discovery and development process it is critical to anticipate which compounds are worth the effort of clinical studies and reject others beforehand.²

Thus, physicochemical and pharmacokinetic properties are profiled on a routine basis early in the discovery process, and are optimized together with target affinity. As a result,

¹ Drawing by Dr. Simona Ceccarelli, F. Hoffmann-La Roche Basel.
the percentage to which pharmacokinetics and bioavailability are responsible for attrition of a compound in clinical development has declined from 39% in 1991 to 10% in 2000.\(^3\) In a given structural context, problems like low solubility, chemical or metabolic instability, or side effects can often be traced back to the presence of certain functional groups.

![Diagram](https://example.com/diagram.png)

*Picture 2: Selection of functional groups that can have detrimental effects on properties relevant to medicinal chemistry.*\(^4\)

For such functionalities it would be desirable to have alternatives at one’s disposal that relieve the individual problem whilst retaining the essential structural features of the re-

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\(^4\) In terms of chemical stability, Picture 2 lists functionalities that because of their inherent reactivity are to be avoided. Esters can be saponified and sulfur-containing functionalities oxidized. In many cases the presence of epoxides, acylating/alkylating agents, Michael acceptors, aldehydes makes a molecule susceptible towards nucleophilic attack. Stereocenters next to a carbonyl function can undergo epimerization, inter-converting for example in the case of thalidomide its two enantiomers one of which is extremely teratogenic. Linked to chemical stability is the susceptibility of some functional groups to undergo oxidative metabolic degradation, noteworthy in this respect being electron-rich aromatic rings, aliphatic groups and amines. Other members of this group can be enzymatically hydrolyzed. Nonpolar functionalities summarized in the bottom right not only decrease aqueous solubility, more lipophilic molecules were also shown to be more prone to metabolic degradation (K. A. S. Algailany, J. B. Houston, J. W. Bridges, *Biochem. Pharmacol.* **1978**, *27*, 783.). Side effects often result from inherent chemical reactivity, the formation of reactive metabolites (electron-rich aromatics), amphiphilicity or the presence of photochemically sensitive groups.
spective molecular entity. This would make it easier to optimize activity and pharmacokinetic properties concurrently.

Despite the need for a reservoir of functional groups to avoid the problems shown in Picture 2, the number of commonly used structural moieties is small. A recent study found that among the 800,000 different frameworks found for the compounds recorded in the CAS registry, half of them can be assigned to 143 different frameworks. This shows how narrowly focused scientific interest is to a small number of scaffolds. An analysis of a commercial drug database points in the same direction; here, half of the 5120 drugs could be described by the 32 most frequently occurring frameworks. This lack of structural diversity among test compounds has already been identified earlier as a potential bottleneck in the drug discovery process.

Oxetanes are clearly one of the neglected frameworks of organic, but also medicinal chemistry. Although earlier lack of interest itself was not the justification for our research, the previously reported physical and structural properties of oxetanes made us believe that 3,3-disubstituted oxetanes could help address specific recurring problems in drug discovery, pertinent to some of the functional groups shown in Picture 2. It was far from clear, however whether the physicochemical properties, the chemical reactivity and synthetic accessibility of oxetanes would warrant their extensive use in drug discovery.

1.1 Structural Properties of Oxetanes

For oxetanes to be useful for medicinal chemistry, their structural impact and property modulation effects need to be well defined and predictable. Furthermore, it is important to know how polar this structural motif is and what consequences the small ring size has on the polarity of the ethereal oxygen and its ability to form hydrogen bonds.

Analysis of the structure of oxetanes reveals some interesting features. In contrast to what is observed with cyclobutane, the ring is essentially planar as determined by micro-

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8 7,727 articles found in Scifinder Scholar contain the “concept” oxetanes, 377,866 epoxides and 65,197 (Search done with Scifinder Scholar, May 2, 2008).
wave-spectroscopy.\textsuperscript{9} The replacement of a methylene unit by an oxygen atom reduces the otherwise unfavorable eclipsing interactions which are minimized by out-of-plane distortion in cyclobutane. More recent crystallographic studies showed that oxetane is puckered at low temperatures (Figure 1) in the crystalline state ($10.7^\circ$ (90 K data) and $8.7^\circ$ (140 K data) respectively).\textsuperscript{10} Introduction of substituents increases eclipsing interactions and therefore also often leads to puckered structures.\textsuperscript{11} As the C-O bonds (1.45 Å) are shorter than the C-C bonds (1.55 Å), the bond-angles are smaller (C-C-C 85°) and bigger (O-C-C 92°, C-O-C 92°) than 90° in oxetane.\textsuperscript{12}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1}
\caption{Comparison of the puckering angles between cyclobutane\textsuperscript{13} and oxetane.}
\end{figure}

Several observations indicate that among cyclic ethers, oxetanes display the most Lewis-basic oxygen. The equilibrium constant of hydrogen-bond formation was determined by measuring IR-spectra of mixtures of the respective ether and 4-fluorophenol.\textsuperscript{14}


\textsuperscript{12} S. I. Chan, W. D. Gwinn, J. Zinn, \textit{J. Chem. Phys.} \textbf{1961}, 34, 1319. The structural data in this publication was obtained by microwave spectroscopy, differences from X-ray data (puckered oxetane, see Ref. 10) are small.


Diagram 1: Strength of association with 4-fluorophenol and iodine in cyclic ethers against ring-size.\textsuperscript{14,17}

The maximum of hydrogen-bonding strength among cyclic ethers results from two competing effects. With smaller ring size, the C-O-C angle diminishes, exposing the oxygen lone pairs more to potential acceptors; consequently the ability for hydrogen bonding increases.\textsuperscript{15} For small rings, the s-character in the hybridization of the oxygen lone pairs increases, making them less available for hydrogen bonding. Several studies suggest, however that only for three-membered rings a significant change in hybridization of the oxygen lone pairs occurs, thus making oxetanes the best acceptors for hydrogen bonds in the series.\textsuperscript{16}

Oxetane also forms complexes with iodine\textsuperscript{17} and with dinitrogen pentoxide\textsuperscript{18}. In case of iodine, a comparison of the binding constants (Diagram 1) of oxetane with propylene oxide and tetrahydrofuran reveals that the difference in binding strength is more pronounced than in case of hydrogen bonds. This might be a result of the higher steric demand of iodine compared to a proton, highlighting the accessibility of the electron pairs in oxetane. A study conducted on the aqueous solubility of isomeric cyclic ethers showed that among tetrahydropyran and 1-, or 2-methyltetrahydrofuran, 3,3-dimethyl-oxetane was the most soluble compound.\textsuperscript{19} The outstanding ability of oxetanes to form hydrogen bonds and donate electron density is of interest for pharmaceutical applications, as the incorporation of an oxetane might make the underlying scaffold more water soluble.

\textsuperscript{17} M. Brandon, M. Tamres, S. Searles, \textit{J. Am. Chem. Soc.} \textbf{1960}, \textit{82}, 2129. In Diagram 1 the point for iodine with \( n = 0 \) refers to propylene oxide.
1.2 Ring-Opening Reactions of Oxetanes

It is far from clear whether oxetanes are chemically stable enough to be practically useful in medicinal chemistry. As small saturated heterocycles, oxetanes display chemical as well as physical characteristics whose origins can be traced back to their inherent ring strain. In oxetane itself, the strain energy has been determined to be 106 kJ/mol, only 1 kJ/mol less than for oxirane and 20 kJ/mol more than tetrahydrofuran.

Oxetanes undergo polymerization in solvents such as chloromethane catalyzed by a variety of Lewis acids, forming polyethers of high molecular weight. The polymer of 3,3-bis(chloromethyl)oxetane has found wide application under the brand names “Pentaplast” or “Penton”.20

Oxetane undergoes hydrolysis catalyzed by sulphuric or perchloric acid in aqueous dioxane almost as rapidly as ethylene oxide. In the presence of base, however, ring opening of trimethylene oxide is very slow: Oxirane hydrolyses three orders of magnitude faster than oxetane under alkaline conditions.21 Theoretical studies carried out on the origin of this reactivity difference put forward different possible explanations. Hoz et al. conclude that in case of three-membered oxirane more strain is released in the transition state leading to a lower activation energy than in four-membered rings.22 For the closely related case of cyclopropane vs. cyclobutane, Houk et al. point out that for three-membered rings the transition state has aromatic character stabilizing it compared to four-membered rings displaying a transition state with antiaromatic character.23

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Scheme 1: Ring-opening reaction of oxetanes.\(^{24}\) a) LiO(\(\text{Bu}O\))C=CH\(_2\), BF\(_3\)·OEt\(_2\); b) RC=CLi, BF\(_3\)·OEt\(_2\); c) ArH, AlCl\(_3\); d) RLi or RMgX; e) TMSCN, ZnI\(_2\); f) RHC=CHAlR\(_3\)Li, BF\(_3\)·OEt\(_2\) or H\(_2\)C=CHMgX; g) allylTMS, TiCl\(_4\); h) i. Li, cat DBB, 2. RCHO; i) LiAlH\(_4\); j) R\(_2\)NH or R\(_2\)NMgX; k) HX; l) ROH, cat. H\(_2\)SO\(_4\); m) BF\(_3\)·OEt\(_2\), BF\(_3\), AlCl\(_3\) or PCl\(_3\); n) RCOCl

Due to this reactivity difference towards nucleophiles, ring opening reactions of oxetanes often require the use of strong Lewis acids (see Scheme 1) or high temperatures to occur. Additionally, oxetanes with substitution at the 3-position display reduced susceptibility to ring opening, because any ring cleavage via nucleophilic displacement reaction would suffer from unfavorable non-bonded interactions that are analogous to those observed at neopentyllic centers.

Being kinetically more stable than epoxides toward nucleophilic ring opening, oxetanes should also be less prone to react with endogenous nucleophiles like glutathione (GSH)\textsuperscript{25} or amines. Oxetanes should also be more compatible with chemical reagents and synthetic procedures than epoxides. Although not much is known about the proclivity of substituted oxetanes to undergo acid-induced ring opening, strongly acidic conditions might be problematic despite the fact that substitution lowers ring strain\textsuperscript{26} and shields the oxetane sterically\textsuperscript{24i} from attack.

### 1.3 Tendency of Oxetane to Form Radicals

Oxidative primary metabolism relies mainly on the cytochrome P450 (CYP) enzyme family.\textsuperscript{27} Members of this family share heme-bound iron-oxo complexes as common oxidant in their active sites. It has been suggested that in many cases the initial and often rate-limiting step of metabolism is the abstraction of H\textsuperscript{+} to form a radical, making positions in molecules that give rise to more stable radicals more susceptible towards metabolism.\textsuperscript{28} By virtue of the stabilizing interaction of an electron pair on the ether oxygen with an unpaired electron in alpha-position, the homolytic bond dissociation energy is reduced and radicals are formed more easily.\textsuperscript{29} Therefore cyclic ethers should be good substrates for CYPs.\textsuperscript{30} Among the few examples however, where metabolic data on oxetane-containing compounds has been published, none documents oxidative attack on the 2-position of the oxetane ring.\textsuperscript{31} Oxetane was found to react under thermal conditions with dimethyl azodicarboxylate via a proposed radical intermediate:\textsuperscript{32}

\textsuperscript{25} For a review on GSH-adducts, see: I. A. Blair, \textit{Current Drug Metabolism} \textbf{2006}, 7, 853.

\textsuperscript{26} B. Ringner, S. Sunner, H. Watanabe, \textit{Acta Chem. Scand.} \textbf{1971}, 25, 141. This is probably a result of reduced steric repulsion between substituents at the 3-position themselves, and between them and the methylene groups in the ring.

\textsuperscript{27} For a review about the P450 gene superfamily and their evolution, see: F. J. Gonzalez, D. W. Nebert, \textit{Trends Genet.} \textbf{1990}, 6, 182.


\textsuperscript{29} One prominent consequence is the formation of peroxides in many cyclic as well as acyclic ethers under the influence of oxygen and light.


\textsuperscript{31} Search done in MDL\textsuperscript{4} Drug Metabolite Database on May 12 2008. Hits where the oxetane ring was cleaved, can mainly be attributed to hydrolysis.

OXETANES IN DRUG DISCOVERY

Introduction

Scheme 2: Hydrazination of oxetane under thermal conditions.\textsuperscript{32}

Studies comparing the relative rates with which different cyclic ethers participate in radical reactions yield different results depending on the type of reaction and analytical technique employed.

Diagram 2: Relative reaction rates of a variety of substrates standardized for oxetane.\textsuperscript{33}

For the reaction with oxygen the rate of oxygen consumption was measured irrespective of the different reaction pathways.\textsuperscript{34} It has furthermore been suggested that the initial step in the photooxidation of ethers is the absorption of light by a charge-transfer complex of molecular oxygen with ether. The formation of this charge-transfer complex would then depend on the donor ability of the respective ether.\textsuperscript{35} Therefore the rate would not be solely determined by the stability of the ether radical.

\textsuperscript{33} Oxygen-uptake in case of epoxides refers to propylene oxide.

\textsuperscript{34} N. Kulevsky, C. T. Wang, V. I. Stenberg, J. Org. Chem. 1969, 34, 1345. 5 mL of the respective ether were saturated with oxygen and the amount of oxygen absorbed calculated from the pressure above the ether. No error-margins are given and the authors do not state whether the pressure above the liquid refers to the partial pressure of oxygen or the total pressure (in which case corrections would have to be made for the different partial ether pressures).

In case of the chlorination, the formation of the particular α-chloro ether was measured,\(^{36}\) whereas for the reaction with \(\text{SO}_4^–\) the time-dependent consumption of the radical was photometrically monitored.\(^{37}\) Here, the oxetane was found to be less reactive than tetrahydrofuran and tetrahydropyran.\(^{38}\)

The rate with which cyclic ethers participate in a radical chain reaction depends largely on the reaction chosen, and seemingly does not allow for ranking their propensity to form radicals. From this data it is therefore not clear, how likely the oxetane in a given molecule will be a target of metabolic oxidation, not least as factors other than radical stability seem to play an important role.

1.4 Preparation of Oxetanes

Only a small number of oxetanes is commercially available (see Picture 6) which reflects the limited use these compounds have found in the different fields of chemistry.\(^8\) Lacking commercial supplies, resilient synthetic access routes towards a host of functionalized oxetanes have to be provided for a widespread use in drug discovery.

Oxetane, the parent heterocycle has first been reported by Reboul in 1878, who prepared it by reaction of 3-chloropropanol with aqueous base.\(^{39}\) This class of saturated oxygen heterocycles has been made in a variety of different ways. Those that have found repeated use in the literature include intramolecular versions of the Williamson ether synthesis, the addition of sulfonium ylids to aldehydes, and the Paterno-Büchi cycloaddition.

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\(^{38}\) The authors also provide calculated C-H bond dissociation energies (oxetane: 387.4 kJ/mol, THF: 388.2 kJ/mol, THP: 390.4 kJ/mol), but cannot explain the discrepancy between the calculation (AM1) and the experimental findings.

Introduction

Scheme 3: Common ways to prepare oxetanes.

Among these, the Williamson ether synthesis is the most general.\textsuperscript{40} It is interesting to note that the rate of closure of different β- and γ-chloroalcohols in aqueous base differs considerably, with epoxide formation from β-chlorohydrin favored by two orders of magnitude over the homolog.\textsuperscript{41} It is often the case that formation of byproducts as well as a variety of intermolecular reactions effectively compete with the desired ring formation, thus lowering the yield.\textsuperscript{42} One notable side reaction is the Grob fragmentation of the γ-haloalcoxide into an aldehyde and an alkene that depending on the substrate can completely disrupt the formation of the corresponding oxetane:\textsuperscript{43}

\[ \text{Scheme 4: Grob fragmentation as side reaction competing with ring closure.} \textsuperscript{44} \]

\textsuperscript{40} S. Searles, Jr., \textit{Chem. Heterocyclic Compds.} (Arnold Weissberger, editor. Interscience) 1964, 19, 983.
\textsuperscript{41} G. Forsberg, \textit{Acta Chem. Scand.} 1954, 8, 135.
\textsuperscript{44} S. Searles, R. G. Nickerson, W. K. Witsiepe, \textit{J. Org. Chem.} 1959, 24, 1839. S. Searles, M. J. Gortatowski, \textit{J. Am. Chem. Soc.} 1953, 75, 3030. The authors claim that the rate of fragmentation correlates with the thermodynamic stability of the alkene formed, thus \( k_1/k_2: \text{Ph} > \text{Alkyl} > \text{H} \).
The one-pot conversion of aldehydes or ketones with sulfoxonium ylides to give 2-substituted oxetanes provides an alternate route.\textsuperscript{45} This reaction is considered to proceed \textit{via} an epoxide intermediate that subsequently undergoes ring opening by a second equivalent of the ylide. The resulting \(\gamma\)-alkoxy sulfonium ylide then participates in an intramolecular displacement reaction to furnish a 2-substituted oxetane (Scheme 3).\textsuperscript{46} The same class of substituted oxetanes can be accessed \textit{via} the Paterno-Büchi reaction.\textsuperscript{47} This cycloaddition reaction between an aldehyde or a ketone and an electron-rich alkene affords regioselectively the corresponding oxetanes in good yield.\textsuperscript{48} An important difference between the various approaches is that in the Williamson ether synthesis stereochemical issues are addressed separately from the ring-closing event. By contrast, in the processes which commence with carbonyl substrates control must be exercised over the generation of stereocenters during the ring-closure step.

The latter two methods necessarily lead to oxetanes that incorporate substitution at C-2 and are therefore not suitable for the preparation of 3,3-disubstituted oxetanes, the focus of this project. Although the remaining approach involving intramolecular Williamson ether synthesis provides access to 3,3-disubstitued oxetanes, its efficiency is highly substrate-dependant which is problematic for the \textit{de novo} construction of the oxetane ring on an existing scaffold.

\subsection*{1.5 Pharmacologically Relevant Oxetanes}

Like every functional group newly introduced to drug discovery, oxetanes face the risk of unknown general incompatibilities, for example with respect to metabolism or toxic effects. Any precedence of oxetanes in pharmacological applications therefore helps to reduce this risk. Not much is known, however about the pharmacological properties of oxetanes.

Introduction

Early studies in rats involving 3,3-diethylxetane and other simple oxetanes revealed their anesthetic, sedative and anticonvulsant properties.\(^{49}\) Conformationally restrained oxetane derivatives of cytidine 1 and thymidine 2 have been investigated for their use as part of antisense oligonucleotides (AON).

\[ \text{Scheme } 5: \text{ Oxetane analogues (1,2) of Cytidine and Thymidine used for Antisense oligonucleotides}\]^{50}

The resulting AON-RNA hetero-dimers were only slightly less stable as measured by their melting temperature \( (T_m) \). While the AON-RNA hetero-dimers still were substrates of RNAase H, they showed increased stability towards degradation by nucleases.\(^{50}\) Oxetanes also have been used as transition-state mimics for Renin, an aspartate protease important in blood pressure regulation.\(^{51}\)

\[ \text{Scheme 6: Oxetanes as transition-state analogues for Renin, an aspartate protease}\]^{51}


In case of the dihydroxy isoster 3 it is believed that the diol interacts with both aspartate residues in the active site. The authors, however do not provide a rational for the increased binding affinity of oxetane 5 compared to tetrahydrofuran 4.

All marketed drugs containing the oxetane ring are derived from one family of natural products. Taxol® (6, first commercially developed by Bristol-Myers-Squibb) was isolated from the bark of the western yew (Taxus brevifolia) and is, together with the structurally related Docetaxel (7, first marketed by Chugai Pharmaceuticals as Taxotere®), presently used in cancer chemotherapy.

**Scheme 7: Marketed drugs containing oxetanes**

Both compounds act by interfering with normal microtubule breakdown during cell division. The structural consequences of the oxetane in Taxol was subject of a computational study, from which it was concluded that the oxetane leads to the rigidification of the overall structure and acts as a hydrogen-bond acceptor partner for a threonine-OH in the putative binding pocket. Replacement of the oxetane in taxol with azetidine,

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53 Prous Science Integrity, Search on May 6 2008
Introduction

thietane, and selenetane invariably resulted in lower activity. However, the role of the oxetane moiety remains controversial regarding the bioactivity of Taxol (6).

Oxetanes are found embedded only in a few natural products, many of them being terpenoids (Figure 2). Oxetanocin A (8) was first isolated from the soil-bacterium *Bacillus megaterium* NK84-0218. It inhibits the reverse transcriptase of HIV by mimicking adenosine which triggered considerable commercial and synthetic interest. Thromboxane A2 (9) is a compound predominantly synthesized by platelets and promotes vasoconstriction, platelet aggregation, and bronchoconstriction. It has a plasma half-life of only 30 seconds, before the oxetane ring hydrolyses to give inactive Thromboxane B2. Merrilactone A (10) was first isolated from *Illicium merrillianum.* It stimulates the growth of rat neurons and because of that and its complex, condensed polycyclic structure several total syntheses have been published in recent years.

Mitrephorone A (12) has been isolated from *Mitrephora glabra* and was found to be cytotoxic for a variety of cancer cell lines. Oxetin (11) has been isolated from the fermentation broth of *Streptomyces* sp. OM-2317 and was found to have herbicidal as well as antibacterial effects; further investigation of its biological activity is ongoing.

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Maoyecrystal I (13) was isolated from *Isidon japonicus* and shows cytotoxic properties.\(^6^6\) Dictyoxetane (14) is a diterpenoid first isolated from the brown algae *Dictyoata dichotoma*.\(^6^7\) Its polycyclic ether core has triggered considerable synthetic interest.\(^6^8\) Bradyoxetin (15) was found to be an important chemical signal for *Bradyrhizobium japonicum* involved in symbiotic gene regulation.\(^6^9\)

There are anthropogenic small molecules (Figure 3) that also incorporate oxetane rings both as scaffold (EDO) and sidechain (oxasulfuron). The insecticide EDO (16, 2,2-bis(4-ethoxyphenyl)-3,3-dimethyloxetane) is 25 times more potent than DDT, and also active against DDT-resistant strains of *Musca domestica*. In contrast to the notorious environmentally persistent DDT, EDO (16) is biodegradable.\(^7^0\)

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Introduction

Figure 3: Oxetane-containing pesticides

Oxasulfuron (17)\textsuperscript{71} acts by inhibiting the biosynthesis of valine and isoleucine in cells. It is used, for example, in the cultivation of soybeans to keep weeds under control. This agrochemical is effective because crop rapidly metabolizes.\textsuperscript{72} At the end of 2007 its production was stopped due to resistance development in the targeted weeds.\textsuperscript{73} Norbornane 18 was found to be a potent herbicide and plant growth regulator.\textsuperscript{74}

Apart from using an oxetane, because it accidentally fits the structural binding requirements of a given target best, oxetanes might be beneficial in a broader context. What makes oxetanes potentially attractive for drug discovery is their high polarity and outstanding ability among cyclic ethers to act as an acceptor for hydrogen bonds and donate electron density.\textsuperscript{14, 17} Oxetanes are not as prone toward ring opening as epoxides, often requiring activation by acid. Not much can be predicted, however for the susceptibility of oxetanes toward oxidative metabolic degradation and it is not clear whether they are metabolically and chemically stable enough. Furthermore, the current state of synthetic methodology for the preparation of oxetanes does not allow for a widespread use of oxetanes in drug discovery.

\textsuperscript{72} M. K. Koepp, H. M. Brown, \textit{Agro Food Ind. Hi-Tech} 1995, 6, 9.
\textsuperscript{73} personal communication, Syngenta AG, 2008
2 Idea and Theoretical Concept

Oxetanes are not well precedented in medicinal chemistry and systematic studies on their physicochemical and pharmacological properties have, to the best of our knowledge, not been undertaken so far. As a consequence, oxetane derivatives are usually not covered by patent claims. This neglect of oxetane chemistry might be due to the paucity of synthetic methods for their efficient preparation, but is nevertheless surprising. Even more so, as their polarity and outstanding ability among cyclic ethers to donate electron density are well documented.

Equation 1: An oxetane is the sum of its bulky and polar nature.

Oxetanes can be seen as a combination of two characteristics; they unite steric bulk with polarity. Therefore, certain sterically demanding functionalities might be replaceable by an oxetane. While its methylene groups provide steric bulk, the presence of the polar oxygen and its ability to accept hydrogen bonds could render the oxetane an alternative for commonly used more lipophilic bulky groups.

Some oft encountered polar functionalities, on the other hand display inherent chemical reactivity that is undesirable in the context of drug discovery. The relative inertness of the oxetane scaffold may help to remedy the shortcomings of these more widely used functional groups.

2.1 Oxetanes as Lipo-Neutral Bulk Increase

In medicinal chemistry, steric bulk fulfills different purposes. It is often utilized to fill receptor pockets in the form of t-butyl and isopropyl groups. Both can be subsumed
under the term gem-dimethyl groups. More than 10% of all launched drugs contain at least one gem-dimethyl group, highlighting its relevance for drug discovery.\textsuperscript{75} By that, gem-dimethyl groups are slightly more common than carboxylic esters.\textsuperscript{76}

**Diagram 3: Launched drugs containing different forms of gem-dimethyl groups.**\textsuperscript{77}

The presence of a geminally substituted center in a chain increases the rate of cyclization compared to what is found for the unsubstituted molecule. This observation is commonly referred to as the Thorpe-Ingold effect.\textsuperscript{78} For the formation of three- or four-membered rings, the main contribution to this effect stems from the steric repulsion between the geminal substituents, which leads to a compression of the bond angle between the remaining substituents.\textsuperscript{80} In larger rings, the contribution of this was found to be small,\textsuperscript{81} here the effect predominantly stems from a change in the conformational distribution of the open-chain form.\textsuperscript{82}

\textsuperscript{75} Prous Science Integrity®, May 16 2008: Search for all compounds having „Launched“ as development status associated with it. Total number of launched compounds is 3094.
\textsuperscript{76} Prous Science Integrity®, May 16 2008: Search for all compounds having „Launched“ as development status and containing the substructure of a carboxylic ester. Number of compounds found: 333
\textsuperscript{77} Prous Science Integrity®, May 16 2008: Substructure search for all compounds with the given motif which have „launched“ as development status.
\textsuperscript{80} In small ring systems this accordingly decreases the ring strain. For a theoretical study with cyclobutanes, see: A. L. Ringer, D. H. Magers, *J. Org. Chem.* 2007, 72, 2533. An experimental determination of ring strain in oxetanes was reported by Ringner et al. (B. Ringner, S. Sunner, H. Watanabe, *Acta Chem. Scand.* 1971, 25, 141.).
\textsuperscript{82} This explanation for the Thorpe-Ingold effect was first suggested by Bruice and Pandit, and recently advanced by Jung et al. a) T. C. Bruice, U. K. Pandit, *J. Am. Chem. Soc.* 1960, 82, 5858. b) M. E. Jung, M. Kiankarimi, *J. Org. Chem.* 1998, 63, 2968. (also see Ref. 81)
Figure 4: Effect of geminal substitution on the distribution between antiperiplanar (± ap) and synclinal (+sc, -sc) conformations.\textsuperscript{83}

In case of cyclization reactions this leads to a higher relative population of reactive conformations, in which R’ and R” reside close to each other. For a drug candidate the presence of a geminally substituted center within a chain results in equipopulated conformations with respect to rotation around the bonds connecting to the geminally substituted carbon.

The introduction of steric hindrance often blocks chemical\textsuperscript{84} or metabolic\textsuperscript{85} liabilities of nearby functional groups. Also in case of metabolically unstable methylene groups it is common practice to block them by the introduction of a gem-dimethyl unit.\textsuperscript{86}

\textsuperscript{83} Calculated for 298.15 K, assuming the gauche-interaction between R’ and R” to be equivalent to 0.9 kcal/mol (R’ = R” = Me).


However, for a typical small molecule in medicinal chemistry the replacement of hydrogens by methyl groups leads to a significant increase of its lipophilicity which in turn may adversely affect its physicochemical and pharmacokinetic properties.\textsuperscript{87} Moreover, the \textit{gem}-dimethyl group can become a target of metabolic degradation itself.\textsuperscript{88} A search in the MDL\textsuperscript{8} Metabolite Database reveals how prevalent oxidative attack on \textit{gem}-dimethyl groups is:\textsuperscript{89}

\begin{equation*}
\begin{array}{c}
\text{H}_3\text{C} - \text{CH}_3 \quad \text{H}_3\text{C} - \text{CH}_3 \\
\text{R} \quad \text{R} \\
\text{H} \\
\text{H}_3\text{C} - \text{CH}_3 \\
\text{R} \quad \text{R}' \\
\text{R} \quad \text{R} '
\end{array}
\end{equation*}

\begin{center}
\begin{tabular}{c|c}
 & \text{531 hits} \\
\hline
H & 3 \quad \text{99} \\
\hline
\text{F} & 298 hits \\
\text{OH} & 105 hits \\
\text{Me} & 253 hits \\
\text{H} & 176 hits \\
\hline
\end{tabular}
\end{center}

\textit{Diagram 4: Hydroxylation of \textit{gem}-dimethyl containing compounds.}\textsuperscript{89}

All these applications of steric bulk currently rely on a pool of functionalities that – like the \textit{gem}-dimethyl group – have high lipophilicity as a common characteristic. It is not inescapable, however that the introduction of steric bulk comes along with increased lipophilicity and thus reduced aqueous solubility. Quite the contrary, high lipophilicity is undesirable in most cases.\textsuperscript{87} Therefore, a stable, small, and less lipophilic molecular module with reduced susceptibility to metabolic attack would be a very interesting alternative.

The oxetane might be able to fill this role, replacing a \textit{gem}-dimethyl group. An oxetane might thus introduce steric bulk and at the same time reduce lipophilicity.


\textsuperscript{89} MDL\textsuperscript{8} Metabolite Database, July 2006: Substructure search for metabolic oxidation as shown in Diagram 4.
**Figure 5: Oxetanes as a replacement for gem-dimethyl groups.**

Thinking of the oxetane as an oxygen-bridged gem-dimethyl group is an apparent analogy. In addition to that, the van-der-Waals calculated volumes of oxetane and propane are almost identical. This is in line with the experimental finding that the partial molar volumes of oxetane (61.4 cm$^3$mol$^{-1}$) in water is even smaller than that of propane (70.7 cm$^3$mol$^{-1}$).

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**Picture 3: Replacement of a methylene group with an oxetane is expected to lead to a decrease in logP.**

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In terms of lipophilicity, substitution of a methylene unit with a gem-dimethyl group typically leads to an increase of about 1 logP-unit. One can dissect the replacement into two discrete steps and add the accompanying changes in logP in order to estimate the influence the insertion of the ethereal oxygen would have.

The introduction of a cyclobutyl group may be expected to lead to an increase of lipophilicity by 1.5 units. If the replacement of a methylene group in cyclobutane by oxygen has the same impact as in cyclopentane (ΔlogP = -2.5), then on this basis the effect of the oxygen introduction can be estimated. Indeed, this would predict that the replacement of a methylene group with an oxetane would lower lipophilicity while increasing steric bulk.

2.2 Oxetanes as Carbonyl Analogues

Urea was one of the first organic compounds to be made without the help of “vital force” that is to say the metabolic apparatus of a living organism. Carbonyl compounds, urea being one of the simplest, are indispensable for the existence of the biology we know of. Not only are their electronic properties responsible for the structure of nucleic acids and proteins, but their reactivity makes them cornerstones of metabolic processes in nature. This also turns them into one of the workhorses of organic chemistry. Their proclivity towards nucleophilic attack as well as their ability to stabilize α-carbanions triggered early milestones in organic synthesis and tremendous scientific interest in their chemistry thereafter. With ample methods available to make and manipulate carbonyl compounds, they became routine constituents of anthropogenic products from polymers to drugs. Some incarnations of carbonyl groups like aldehydes, sterically accessible Michael-acceptors or acyl halides, however are rarely or not found in drug discovery because of their inherent reactivity. But even with more stable functionalities like esters, amides or ketones there are liabilities associated that are rooted in their ubiquity in nature.

92 V. Grignard, C. R. Hebd. Séances Acad. Sci. 1900, 130, 1322.
93 S. Reformatsky, Ber. 1887, 20, 1210.
94 Vinyl substituted carbonyl compounds like acryl amides are not present in marketed drugs (Prous Science Integrity®, May 17 2008).
Diagram 5: Prevalence of carbonyl groups in marketed drugs.95

Because of their widespread presence, organisms have developed enzymes that can hydrolyze esters and amides or reduce ketones which are part of drug molecules. While sometimes desired, for example for the release of the active compound from a prodrug, these transformations often lead to faster degradation in the body and thus to lower exposure of the target to the drug. Moreover, the relative ease of α-deprotonation in carbonyl compounds renders stereogenic centers at this position sensitive towards epimerization (refer to Diagram 5 for the commonness of epimerizable stereogenic centers alpha to the respective carbonyl functionality).

Van’t Hoff provided a very influential rational for the stereochemistry of organic compounds by postulating a tetrahedral coordination sphere for carbon in all its compounds, also the ones containing multiple bonds.96 The atom would be represented by a tetrahedron with its substituents attached to its vertices. Atoms, connected through a double bond would share two vertices or one edge, respectively.

---

95 Prous Science Integrity®, May 17 2008: Compounds were searched as substructures with highest development status being „Launched“. Chiral compounds additionally required a hydrogen alpha to the carbonyl functionality and the carbon atom to be a stereogenic center with defined configuration.

96 J. H. van’t Hoff, Arch. Neerl. Sci. Exactes Nat. 1874, 9, 445
While nowadays multiple bonds are rationalized differently,\(^9^8\) better accounting for the spectroscopic characteristics of these molecules, van’t Hoff’s and Pauling’s ‘bent bond’ model\(^9^9\) are revealing in how one can think of carbonyl compounds as related to oxetanes. If the two vertices shared by the tetrahedra of oxygen and carbon in Picture 4 are replaced by methylene groups, the van’t Hoff representation of the carbonyl becomes an oxetane.

\[ \text{Picture 4: Van’t Hoff representation of a carbonyl group.}^{9^7} \]

A side-by-side comparison of the two functionalities reveals the similar C-C-C bond angles and the identical relative spatial orientation of the oxygen lone pairs. The main difference between an oxetane and a carbonyl group consists in the distance they place the oxygen atom away from the chain. This will lead to incompatibility with some targets that

\[ \text{Picture 5: Structural comparison of a carbonyl group with an oxetane.}^{1^0^0} \]

\(^{9^7}\) Picture adapted from ref. 99a.

\(^{9^8}\) E. Hückel, Z. Physik, 1930, 60, 423.


\(^{1^0^0}\) The bond angles shown may vary with the substitution pattern. Models were generated using ChemBio3D 11.0 Ultra and optimized using MM2-forcefield algorithm.
do not tolerate the spatial requirements of an oxetane. In other cases larger volume occupancy and deeper oxygen placement might be advantageous at a receptor pocket.\textsuperscript{101}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{oxetanes.png}
\caption{Affinity to act as an acceptor for hydrogen bonds for oxetane and different carbonyl compounds.\textsuperscript{102}}
\end{figure}

A comparison of the hydrogen bonding avidity of oxetane with different carbonyl compounds shows that only electron-rich amides are better acceptors for hydrogen bonds.\textsuperscript{103} The examples shown in Figure 6 highlight the different benefits an oxetane might have when replacing a carbonyl group. Acetyl choline (19)\textsuperscript{104}, cocaine (20)\textsuperscript{105} or peptides can undergo enzymatic cleavage; the corresponding oxetane analogues however would be stable towards hydrolysis and might offer longer half-life times while retaining potency.

\textsuperscript{101} The conformational aspects of a carbonyl with its attendant substituents and an oxetane have to be cautiously examined. This is particularly evident in the case of esters, lactones, amides, or lactams, where the replacement of the carbonyl group by an oxetane unit eliminates the $\pi$-conjugation in the former and may result in substantially non-planar arrangements in the latter.

\textsuperscript{102} Data taken from Ref. 103. For a definition of log$K_{HB}$, see Diagram 1. For a description of the method used to determine log$K_{HB}$, see Ref. 14.


\textsuperscript{104} Acetyl choline is an important neurotransmitter. After release into the synaptic cleft it is saponified by acetylcholinesterase. The oxetane version might maintain the ability to function as a neurotransmitter stable towards acetylcholinesterase, or compete with the natural substrate for binding to the enzyme and thus prolong the life time of natural acetylcholine.

\textsuperscript{105} Cocaine is mainly metabolized by hydrolysis of the methyl ester into benzoylecgonine which is then excreted via the urine.
Figure 6: Possible applications for oxetanes as a carbonyl surrogate.

Pyruvate (22) is a central intermediate in energy metabolism and either undergoes decarboxylation or reduction of the keto group. In the case of thymine (23), switching to an oxetane might have an impact for its recognition as a substrate by DNA-polymerase or its ability to support proper base pairing when integrated into a DNA strand. Oxetanes may therefore not only be considered as a surrogate for a carbonyl group in de novo structural design of drug candidates, but also in marketed drugs or naturally occurring compounds, where attack on or around the carbonyl moiety is important for degradation.

2.3 Spiro cyclic Oxetanes as a Mimic for Oxa-Heterocycles

Morpholine has found widespread use as a building block in medicinal chemistry. It is often used to raise aqueous solubility of the underlying scaffold. The morpholine ring, however, is regularly target of oxidative metabolism. There are 17 marketed drugs substances that contain the morpholine subunit. For 4 of these no metabolic data has been published, of the residual 13 compounds 8 show oxidative degradation of the morpholine ring.106

Scheme 8: Marketed drugs containing a morpholine liable to metabolic oxidation.\textsuperscript{106}

A more detailed analysis shows that in the discovery process morpholine-containing compounds are underrepresented in marketed drugs and compounds in the clinic. Whereas 1.8% of all molecules in biological testing contain a morpholine, only 0.6% of all launched drugs share this moiety.

Diagram 7: Ratio of drug candidates containing a morpholine in the substructure and all compounds.\textsuperscript{107}

\textsuperscript{107} Prous Science Integrity\textsuperscript{®}, May 21 2008 on highest phase reached with morpholine as substructure or not.
It can be seen that especially before entering clinical studies a disproportionate number of morpholine-containing compounds is rejected. Drawing conclusions however from this data is not straightforward. Although morpholine is liable towards metabolic degradation and this might be the cause of rejection in some cases, it does not prove that morpholine is a risk factor for drug candidates.

As the population of molecules in biological testing for which the integration of a morpholine is considered, is probably biased towards molecules with scaffolds that have high lipophilicity and/or clearance, this group would have had a higher attrition risk anyway. But even with this caveat morpholine-containing compounds face a disproportionally high risk of attrition before entering the clinic and therefore an alternative – structurally similar, if possible – would be desirable. A whole range of spirocyclic oxetanes might be suited for this purpose.

**Scheme 9: Spirocyclic oxetanes (R = piperonyl) as a substitute for morpholine.**

These spiro-oxetanes position the oxygen atom in the molecular symmetry plane at an extended distance from the nitrogen atom (24, 25) with similar (25) or decreased lateral

---

bulk (24). Others (26-30) place the oxygen at a reclined angle from the symmetry plane of the parent morpholine, resulting in a reduction of symmetry without introducing chirality.

All spirocycles pit the hydrophilic oxetane against the 6-membered ring ether in morpholine and the potential advantage of the oxetane might partially compensate for the lipophilicity introduced by additional methylene groups in compounds (26, 27, 29-31). Additionally, whereas the hydrogen bonding ability of the oxygen in morpholine is dampened by the presence of the electron-withdrawing nitrogen atom, compounds 24 to 27 might benefit from the additional bond separation of the two electronegative atoms. All spirocyclic systems are not reported in the literature except for some 2-oxa-6-azaspiro[3.3]heptanes\(^{109}\) as well as a derivative of 2-oxa-7-azaspiro[3.5]nonane,\(^{110}\) but no systematic elucidation of the properties of these compounds has emerged.

### 2.4 Synthetic Access to Oxetanes

Practical access routes are imperative for possible application of oxetanes. Even if oxetanes showed great potential as surrogates for morpholine, \textit{gem}-dimethyl groups, or carbonyl-functionalities, oxetanes will not be used if they are not sufficiently convenient to prepare. Good routes must allow for oxetanes to be grafted on a variety of structurally diverse chemical surroundings in short sequences, high yield and with broad functional group tolerance. Among common synthetic methods, however only the Williamson ether synthesis is suited to provide oxetanes without substitution alpha to the ring oxygen.\(^{111}\)

Side reactions, highly substrate-dependant yields make the application of this method difficult in the setting of drug discovery which is characterized by structurally diverse contexts.

There are two strategically distinct approaches to make oxetanes. One relies on a precursor that does not contain an oxetane. This could be any cyclic as well as acyclic


\(^{111}\) See chapter 1.4.
intermediate, but for reasons outlined in chapter 1.4, it would likely be a substrate of the Williamson ether synthesis. For this approach to work, substantial improvements of synthetic methodology have to be accomplished, increasing its yield and breadth. This can, but need not happen within the frame of the Williamson ether synthesis.

If the precursor already contains an oxetane, the problem of ring closure might be solved for the particular case, or deferrable to a commercial supplier. A small set of oxetanes would then be used as building blocks that, once attached to a scaffold, would be amenable to synthetic modification.

![Diagram](image)

*Scheme 10: Building-block approach (top) in comparison with methodology involving late-stage cyclization.*

We reasoned that the *de novo* development of a new, broadly applicable ring-closing methodology has low chances of success, moreover as not only the ring closing event itself has to be controlled, but also as routes to suitable precursors have to be established. For the building-block approach, however suitably substituted oxetanes have to be identified, prepared in useful quantity and efficiency, and methodology for their functionalization developed. This approach has the important advantage to potentially reduce the work load for the applying chemist down to the integration and modification of an off-the-shelf reagent. Additionally, as the modification of the oxetane happens at the end of the synthetic sequence, chemical diversity is easier to generate than in the other approach.
Commercially available oxetanes are one potential source of building blocks. There are however not many oxetanes commercially available and most which are derived from a small set of structurally similar compounds.

Picture 6: Commercially available oxetanes by December 2006.¹¹²

Only a few of these compounds, highlighted in Picture 6, might be used as building blocks. These however will not provide access to the wide spectrum of oxetanes, necessary for the broad aim of this study.

Among the oxetanes known in the literature, oxetan-3-one seemed to be a good candidate for a building block. As a ketone, it reacts with a variety of nucleophiles, and the addition products are amenable to further functionalization.

¹¹² Scifinder® Scholar. Substructure search for oxetanes bearing no substituents in 2- and 4-position.
Literature precedent, albeit sparse, indicates that the ketone functionality is amenable to functionalization without opening of the oxetane ring and that at least under certain conditions the addition products can be manipulated further. Therefore, oxetan-3-one was chosen to be investigated first as a building block.

Several syntheses of oxetan-3-one (33) have been reported in the literature. Oxetan-3-one was first isolated by Marshall et al. in 1952 from a complex mixture as its 2,4-dinitrophenyl hydrazone.\textsuperscript{114}
The first synthesis of oxetan-3-one in pure form and significant quantities was reported in a patent from DuPont, wherein oxetan-3-one was investigated as a potential solvent for cyanoethyl cellulose.\textsuperscript{115}

![Scheme 11: DuPont route to oxetan-3-one.\textsuperscript{115}](image)

This synthesis of oxetan-3-one commences with the Diels-Alder adduct 41 of diethyl methylenemalonate and anthracene. Diester reduction, generation of the bis-sulfonate 42, followed by ring closure furnished oxetane 43. In a subsequent step, oxetane 43 undergoes retro-Diels-Alder reaction at 340-355 °C to release 3-methylene oxetane (44). This low-boiling liquid can be distilled from the reaction mixture. The authors highlighted the fact that 3-methylene oxetane needs to be handled under inert gas atmosphere, because it very easily undergoes autoxidation to form a peroxide.\textsuperscript{116} The safety issues along with the number and nature of the steps required in this sequence render in our estimation the approach unsuitable for the production of preparative amounts of oxetan-3-one. A different route to oxetan-3-one relies on the oxidation of oxetan-3-ol:

\textsuperscript{115} G. H. Berezin, US 3297719, 1967.

Scheme 12: Oxidation of oxetan-3-ol (45).\textsuperscript{117}

Whereas the oxidation of oxetan-3-ol (45) with Collins reagent ($\text{CrO}_3 \cdot \text{py}_2$) was done on a preparative scale, the formation of oxetan-3-one (33) was the unexpected product of the attempted preparation of oxet-2-ene from the tosylate of oxetan-3-ol (45). In both cases the authors had to resort to preparative GC to purify the compound, as the distillative separation from pyridine was found to be not possible in the first case. Oppenauer oxidation failed to give product, as well as dichromate- or permanganate-based methods.\textsuperscript{117a} Oxidation with pyridinium chlorochromate (PCC) also furnishes oxetan-3-one (33).\textsuperscript{118}

At the outset of the project, oxetan-3-ol was not available commercially in significant quantities.\textsuperscript{119} Therefore, when pondering different routes to oxetan-3-one, the preparation of oxetan-3-ol has to be taken into account. A procedure published by Baum et al.\textsuperscript{120} laid the foundation for the optimized route used by Syngenta\textsuperscript{121} to prepare oxetan-3-ol as part of the synthesis of the herbicide Oxasulfuron (see Chapter 1.5).

\textsuperscript{118}Ref. 117b. No supporting information is provided. Under the conditions reported, pyridine should be released into the reaction mixture and thus distillative purification of the product might face the same problems reported in ref. 117a.
\textsuperscript{119}Indicated through search for commercially available chemicals in Scifinder® Scholar. Oxetan-3-ol is now commercially available from a variety of suppliers.
\textsuperscript{121}W. Stutz, R. Waditschatka, K. Winter, M. Von Frielings, R. Gressly, B. Jau, S. Buerki, EP 751136, \textbf{1997}. 
Scheme 13: Preparation of oxetan-3-ol (45) on industrial scale.\textsuperscript{121}

The procedure starts with the opening of epichlorohydrine (47) with 2-ethylbutyric acid, followed by acetalization of the resulting secondary alcohol 48. Chloroester 49 can then be cyclized by treatment with base. Cleavage of the protecting group furnishes oxetan-3-ol in an overall yield of 70.5%.

Whereas adequate supply routes of oxetan-3-one might be mandatory for future applications of oxetanes in the drug discovery process, all efforts spent to develop a scalable synthesis might be rendered worthless, if these essential questions were not answered in the affirmative before:

1. Does the integration of an oxetane have a positive influence on the lipophilicity and solubility of the underlying scaffold?
2. Are oxetanes chemically and metabolically sufficiently stable?
3. Is oxetan-3-one the right starting point to make substituted oxetanes?

A negative answer to the first two questions would probably have stopped the project immediately. Therefore, first priority had to be the preparation of a few prototypic oxetanes from oxetan-3-one and measurement of their properties.
3 Main Part, Chemistry

In order to test the hypotheses regarding structural analogies of oxetanes, a number of compounds have to be made. Ideally, their preparation would not only deliver the respective oxetane in sufficient quantities, but also help explore the chemistry of oxetan-3-one and demonstrate its usefulness and versatility. We envisioned two principal paths leading to substituted oxetanes (Figure 8):

![Figure 8: Proposed buildup of oxetanes starting from oxetan-3-one](image)

Direct nucleophilic attack on oxetan-3-one would provide oxetan-3-ols which after activation could be further functionalized by nucleophilic substitution. In a second approach, the ketone would be transformed into a Michael acceptor that could then be a substrate for 1,4-additions of appropriate nucleophiles.

Both routes carry potentially problematic steps that lack precedence. Therefore, the preparation of oxetan-3-one should be capable of providing significant quantities to explore its usefulness as a starting material. But until this is established, the synthesis chosen need not be amenable to scale-up or optimized with respect to cost.

3.1 Preparation of Oxetan-3-one

We felt that the existing routes to oxetan-3-one discussed in chapter 2.4 were not practical for our purposes. The procedure by DuPont\textsuperscript{115} involved 6 steps, included 3-methyleneoxetane as an unstable intermediate\textsuperscript{116} and a retro-Diels-Alder reaction that seemed difficult to accomplish with standard laboratory equipment.
Further attempts to prepare oxetan-3-ol (45) as described by Baum et al.\textsuperscript{120} did not provide significant quantities of this material. Ring closure to oxetane 53 resulted in variable yields, complex product mixtures, and produced large volumes of an aqueous salt solution that made scale-up difficult.

The oxidation of oxetan-3-ol was known to fail with various methods other than Cr(VI)-based reagents, and the procedure with Collins reagent\textsuperscript{122} necessitates separation of the

product from co-distilling pyridine by preparative GC. The identification of a better oxidation procedure, the optimization of its reaction conditions and subsequent workup would have to rely on the availability of larger quantities of oxetan-3-ol. As those seemed difficult to obtain, we decided to investigate a shorter route which would not involve oxidation.

### 3.1.1 Route via Ketal Cleavage

Starting from known dihydroxyacetone dimethylketal (55), a one-pot ring closure, precedent for the preparation of 3,3-disubstituted oxetanes, would lead to 3,3-dimethoxyoxetane (56). This would yield oxetan-3-one upon deprotection.

\[
\begin{align*}
\text{54} & \xrightarrow{\text{HC(OMe)}_3, \rho\text{TsOH, MeOH, rt}} \text{55} \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

\[
\text{Scheme 16: Proposed synthesis of oxetan-3-one starting from commercial dihydroxyacetone dimer (54).}
\]

This synthesis would have the advantage of providing access to oxetan-3-one (33) in three steps from cheap commercial starting materials. The yields reported for the ring closure by Picard et al. range from 68 to 84%. Literature precedence existed for the cleavage of steroidal ketal 57 to give the corresponding oxetan-3-one 58 with dilute sulfuric acid.

---

124 It was expected that due to the hydrophilicity and volatility (bp 106 °C, ref. 123) of oxetan-3-one, only low-boiling solvents and non-aqueous workup were permissible. Distillation would then be used for purification.
127 The closest example reported, a 3,3-dialkyl oxetane was prepared in 72% yield (ref. 126).
Equation 3: Proposed cleavage of dioxolane 57 to give oxetan-3-one 58.\textsuperscript{128}

Based on its infrared spectrum, however other authors proposed a different structure for 58 in which the oxetane ring rearranged under the acidic reaction conditions.\textsuperscript{129} Therefore, it remained to be explored whether oxetan-3-one itself is stable under the acidic conditions employed to cleave the ketal in 3,3-dimethoxyoxetane.

Following the literature procedure,\textsuperscript{125} dihydroxyacetone dimethylketal (55) was prepared in quantitative yield from commercial dihydroxyacetone dimer. Initial attempts to prepare 3,3-dimethoxyoxetane showed that the ring closure is slow under the conditions of the general procedure reported by Picard et al.\textsuperscript{126}

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OH} & \quad \text{OH} \\
\text{THF} & \quad \text{1 equiv } \text{nBuLi} \\
55 & \quad \text{2 equiv } \text{pTsCl} \\
\rightarrow & \quad 59 \\
\rightarrow & \quad 60 \\
\rightarrow & \quad \text{slow} \\
60 & \quad \text{60} \\
\text{60} & \quad \text{MeO} \\
\text{OMe} & \quad \text{OMe} \\
\end{align*}
\]

Figure 9: Slow ring closure of γ-tosylatolithioxide 60.

After heating at 60 °C for 4 h, the reaction yielded product 56 and monotosylate 59 in a ratio of 1/1 upon workup. We reasoned that cyclization of the corresponding sodium alkoxide would be faster. If however only the second portion of \textsuperscript{7}BuLi is replaced with sodium hydride, the reaction does not significantly accelerate.\textsuperscript{130} When \textsuperscript{7}BuLi is substituted with sodium hydride in both deprotonation steps, the selectivity for the formation


\textsuperscript{130} This is probably due to a salt metathesis: The initially formed sodium alkoxide reacts with lithium tosylate present in the mixture to give the thermodynamically more stable, but less reactive lithium alkoxide and sodium tosylate.
of monotosylate 59 is reduced. Therefore 9BuLi has to be employed to prepare monotosylate 59. Simple aqueous workup removes lithium salts and sets the stage for the cyclization of monotosylate 59. Upon addition of sodium hydride 3,3-dimethoxyoxetane (56) is obtained in 37% yield after distillation. With this compound in hand, the ketal cleavage could be examined. It was found that 3,3-dimethoxyoxetane (56) is stable under a variety of acidic conditions.

Table 1: Screening of conditions for ketal cleavage.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1134</td>
<td>aq. H2SO4, CH2Cl2, 0 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>aq. H2SO4, acetone, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>aq. H2SO4, THF, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>4128</td>
<td>aq. H2SO4, MeOH, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>aq. H2SO4, acetone, reflux</td>
<td>traces of product</td>
</tr>
<tr>
<td>6</td>
<td>aq. H2SO4, THF, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>2.5 equiv pTSA·H2O, 25 equiv glyoxalic acid·H2O, CH2Cl2, rt</td>
<td>7% conversion</td>
</tr>
<tr>
<td>7135</td>
<td>Amberlyst 15, acetone/H2O, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>8136</td>
<td>15% H2SO4 on SiO2, CH2Cl2, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>9137</td>
<td>Montmorillon–ite K10, CH2Cl2, rt</td>
<td>7% conversion</td>
</tr>
<tr>
<td>10</td>
<td>Montmorillonite K10, CH2Cl2, reflux, 26 h, 0.08 M</td>
<td>12% conversion</td>
</tr>
<tr>
<td>11137</td>
<td>Montmorillonite K10, CH2Cl2, reflux, 26 h, 0.03 M</td>
<td>44% conversion</td>
</tr>
</tbody>
</table>

131 If 9BuLi is used for the first deprotonation, almost no bistosylate is formed on small scale which is in line with the observations made in ref. 126. If sodium hydride is used instead, the ratio of bistosylate to monotosylate is approximately 4/5.

132 Based on dihydroxyacetone dimer. Typically, one batch delivers 45 g of 3,3-dimethoxyoxetane. In total, 476 g of 3,3-dimethoxyoxetane were prepared.

133 The oxonium species that are formed as intermediates during the ketal cleavage are destabilized the electron-withdrawing effect of the ring oxygen. Formation of a sp2-center at the 3-position of the oxetane in intermediates as well as the product also increases ring strain (see page 60 for further explanation).

Aqueous acid in various solvents and at different temperatures resulted only in one case in traces of oxetan-3-one as determined by $^1$H NMR analysis of the crude products. Using montmorillonite K10$^{138}$ as an acid catalyst however gave some conversion after prolonged refluxing in methylene chloride. Further optimization of this lead result showed that neither the amount$^{139}$ nor the type of clay$^{140}$ used had an influence on the conversion. The reaction in tetralin (bp 207 °C) at 80 °C stopped at 54% conversion, complete extraction of oxetan-3-one from the solvent by distillation failed and significant decomposition occurred. In acetone, no conversion was observed. Therefore, it was decided to stick with methylene chloride as a low-boiling solvent.

The progress of the reaction can be followed by $^1$H NMR,$^{141}$ and it was found that maximum conversion is reached usually after 60 to 70 h of reflux. Increase of substrate concentration from 0.02 M to 0.1 M resulted in a drop of conversion from 92% to 26%. Addition of 0.5 equivalents of water led to decreased conversion, probably by partially deactivating the montmorillonite clay. Addition of 5 Å molecular sieves also did not allow us to increase concentration without reduced conversion.$^{142}$ On larger scale and upon further optimizations regarding workup and distillation protocol, the ketal cleavage provides 62% isolated yield of oxetan-3-one.

The overall yield over 4 steps is 23% with distillation of 3,3-dimethoxyoxetane (56) and oxetan-3-one as the only purification steps. In our laboratories more than 108 g of oxetan-3-one were produced with this route. One of the commercial suppliers is now using this route on a scale larger than 100 g.$^{143}$

$^{138}$ Montmorillonite K10 is a layered silicate that is activated by calcination and washing with mineral acid. It finds wide use as a solid Brønsted acid catalyst. For a review, see: A. Cornelis, P. Laszlo, Synlett 1994, 155. or P. Laszlo, Acc. Chem. Res. 1986, 19, 121.

$^{139}$ Increasing the amount of Montmorillonite K10 from 0.3 g/mmol to 1.5 g/mmol substrate did not bring significant improvement of conversion (59% instead of 50 – 57%).

$^{140}$ Montmorillonite K10 can act as an ion exchanger and intercalate cations like Fe$^{3+}$ or Ti$^{4+}$. The resulting clays are often observed to be more acidic than the parent Montmorillonite K10 and also found use for cleaving unreactive ketals (T. Kawabata, M. Kato, T. Mizugaki, K. Ebitani, K. Kaneda, Chem. Lett. 2003, 32, 648. P. Laszlo, A. Mathy, Helv. Chim. Acta 1987, 70, 577.). When used for the preparation of oxetan-3-one, however these showed approximately the same conversion as non-modified Montmorillonite K10.

$^{141}$ samples taken directly from the reaction mixture, no evaporation, $^1$H-NMR, 64 scans, line-broadening 0.3 to 0.5 as window function.

$^{142}$ Dry as well as hydrated molecular sieves were tried with no effect.

$^{143}$ Private communication, Dr. Mark Rogers-Evans. For the other suppliers, see ref. 172.
**Scheme 17: Preparation of oxetan-3-one (33) from dihydroxy acetone dimer (54).**

Despite that, the large amounts of methylene chloride needed in the last step make the preparation of oxetan-3-one via this route laborious and difficult, which may obstruct the application of oxetanes in drug discovery. A different approach had to be developed after the initial route via the ketal cleavage had provided enough oxetan-3-one to validate its usefulness as a building block.

### 3.1.2 Oxidation of Oxetan-3-ol

The main reason not to investigate alternative methods for the oxidation of oxetan-3-ol was the difficult preparation of this compound. The situation changed however upon publication of our initial study on oxetanes,\(^{144}\) when Syngenta showed interest in applying the chemistry to their projects. As Syngenta produced large amounts of oxetan-3-ol in the synthesis of their herbicide oxasulfuron, they supplied considerable amounts of oxetan-3-ol to investigate an improved oxidation procedure.

Syngenta chemists unsuccessfully tried Dess–Martin\(^{145}\) and Swern\(^{146}\) oxidations beforehand, facing problems in the isolation of oxetan-3-one. Its polar nature and volatility contribute significantly to the criteria a good oxidation procedure leading to oxetan-3-one should fulfill:

---


• Only low-boiling solvents are permissible.
• Aqueous workup should be avoided as well as expensive, toxic or explosive reagents.
• The reaction should be high-yielding and easy to execute.

It was found that oxetan-3-ol is oxidized under a number of conditions\textsuperscript{147}. Purification and isolation of oxetan-3-one, however, was a recurrent problem.

Table 2: Screening of conditions for the oxidation of oxetan-3-ol to oxetan-3-one.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (NMR)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{148}</td>
<td>CrO\textsubscript{3}/Et\textsubscript{2}O, 0 °C to rt\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>no completion, sluggish</td>
</tr>
<tr>
<td>2\textsuperscript{149}</td>
<td>CrO\textsubscript{3}, TBAC, KCl\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>slow, sluggish</td>
</tr>
<tr>
<td>3\textsuperscript{149}</td>
<td>CrO\textsubscript{3}, TBAC, NaOAc\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>no completion, slow</td>
</tr>
<tr>
<td>4\textsuperscript{150}</td>
<td>PCC, 4 Å-MS, rt\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>fast (15 min), clean, difficult purification</td>
</tr>
<tr>
<td>5\textsuperscript{150}</td>
<td>PCC, n-Al\textsubscript{2}O\textsubscript{3}\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>slow</td>
</tr>
<tr>
<td>6\textsuperscript{150}</td>
<td>PCC, Celite\textsuperscript{a}</td>
<td>n.d.\textsuperscript{b}</td>
<td>slow</td>
</tr>
<tr>
<td>7\textsuperscript{151}</td>
<td>TPAP, NMO (1.5 equiv)\textsuperscript{a}</td>
<td>47%\textsuperscript{c}</td>
<td>fast (5 min), side reactions</td>
</tr>
<tr>
<td>8\textsuperscript{152}</td>
<td>TPAP, O\textsubscript{2}\textsuperscript{a}</td>
<td>~34% (10 h)\textsuperscript{c}</td>
<td>slow, catalyst dies</td>
</tr>
<tr>
<td>9\textsuperscript{153}</td>
<td>TEMPO, H\textsubscript{5}IO\textsubscript{6}\textsuperscript{a}</td>
<td>0%\textsuperscript{c}</td>
<td>decomposition</td>
</tr>
<tr>
<td>10\textsuperscript{154}</td>
<td>TEMPO, Oxone, TBAB\textsuperscript{a}</td>
<td>0%\textsuperscript{c}</td>
<td>no reaction</td>
</tr>
<tr>
<td>11\textsuperscript{155}</td>
<td>IBX, EtOAc, reflux</td>
<td>89% (3 d)\textsuperscript{c}</td>
<td>slow, high-boiling solvent</td>
</tr>
<tr>
<td>12\textsuperscript{155}</td>
<td>IBX, rt\textsuperscript{a}</td>
<td>34% (3 d)\textsuperscript{c}</td>
<td>very slow</td>
</tr>
<tr>
<td>13\textsuperscript{155}</td>
<td>IBX, reflux\textsuperscript{a}</td>
<td>85%, (64 h)\textsuperscript{c}</td>
<td>very slow</td>
</tr>
<tr>
<td>14\textsuperscript{155}</td>
<td>IBX, acetone, reflux</td>
<td>83% (3 d)\textsuperscript{c}</td>
<td>slow</td>
</tr>
<tr>
<td>15\textsuperscript{156}</td>
<td>DMSO, P\textsubscript{4}O\textsubscript{10}, NEt\textsubscript{3}, −5 °C\textsuperscript{a}</td>
<td>63% (45 min)\textsuperscript{c}</td>
<td>fast, cheap</td>
</tr>
</tbody>
</table>

\textsuperscript{a} CH\textsubscript{2}Cl\textsubscript{2} used as solvent. \textsuperscript{b} broad signals in the NMR, probably due to the presence of Cr-species. \textsuperscript{c} Yield of product in the reaction mixture was determined by comparing the integrals of oxetan-3-one with tetralin which was added as an internal standard.

Chromium-based reagents were investigated first as they are closest to the literature precedence (Table 2, entries 1–6).\textsuperscript{157} Whereas chromium(VI) oxide in different variations led to slow reactions and the formation of byproducts, pyridinium chlorochromate\textsuperscript{158} when combined with 4 Å molecular sieves as a catalyst\textsuperscript{150} gave very fast and clean conversion to product. Removal of the chromium salts produced as a byproduct proved to be difficult however. Attempts to bind the chromium salts to Celite or by filtration through silica gel did not completely eliminate chromium from the crude product. The presence of high-valency chromium in the crude product would pose a fire hazard when attempting to perform distillation of this material at larger scale. Additionally, hexavalent chromium is toxic and has been found to be carcinogenic.\textsuperscript{159}

In the case of the Ley oxidation,\textsuperscript{151} use of \textit{N}-methyl morpholine \textit{N}-oxide (NMO) as a stoichiometric cooxidant resulted in a rapid reaction, but the yield was low as judged from the crude NMR. Furthermore, \textit{N}-methyl morpholine (bp\textsuperscript{115} 115 °C), produced in stoichiometric amounts as a byproduct would probably be difficult to separate from the product (bp\textsuperscript{116} 106 °C) without aqueous workup. Replacement of NMO with oxygen resulted in a slow reaction which stopped at 30% conversion.

Reaction of oxetan-3-ol with IBX (o-iodoxybenzoic acid) (Table 2, entries 11-14), albeit slow, furnishes clean product upon simple filtration and evaporation due to the virtual insolubility of IBX in the reaction media. This advantage however is balanced with serious drawbacks of IBX as an oxidant on larger scale. IBX behaves as an explosive with properties similar to TNT.\textsuperscript{160} The sensitivity of IBX towards detonation on impact or heat greatly depends on its purity.\textsuperscript{161} This makes preparation and handling of larger quantities dangerous, especially when procedures like in this case would envision refluxing for at least 3 days in the presence of 1.5 equivalents of IBX.\textsuperscript{162}

\textsuperscript{157} a) Oxidation with PCC: A. P. Kozikowski, A. H. Fauq, Synlett 1991, 783. b) Oxidation with Collins reagent (CrO\textsubscript{3}·2 C\textsubscript{6}H\textsubscript{5}N): I. A. Wojtowicz, R. J. Polak, J. Org. Chem. 1973, 38, 2061.
\textsuperscript{159} For an excellent overview, see: D. Michaels, C. Monforton, P. Lurie, Environ. Health 2006, 5, 5.
\textsuperscript{162} On a 1 mole scale, 420 g of IBX would be needed to perform the reaction.
Among the numerous other methods found in the literature for oxidizing a secondary alcohol to a ketone, a DMSO-based method caught our attention that could potentially fulfill all the conditions previously highlighted. A variety of dehydrating agents can be used to activate DMSO, the most well known probably being dicyclohexylcarbodiimide (DCC) in the Pfitzner–Moffatt oxidation and oxalyl chloride in the Swern modification of the Pfitzner–Moffat oxidation. Much less used in that respect is phosphorous pentoxide, first proposed by Onodera et al. (later modification by Taber et al.). Application of the original conditions described in the paper gave oxetan-3-one in a clean reaction and reasonable yield as judged by comparison with an internal standard in the $^1$H NMR. This approach was pursued further not only because of the cheap and rather innocuous starting material, but also because of the ease of implementation, avoiding low temperatures and special equipment.

The original procedure had to be adapted in several respects to fit the special requirements of oxetan-3-ol as a substrate. Without needing a mechanical stirrer, the molarity of the reaction can be increased from 0.2 M to 1.7 M in oxetan-3-ol. In order to facilitate distillation, low-boiling solvents should be used and components such as triethylamine with similar boiling points as oxetan-3-one eliminated before distillation.

---

165 Often also referred to as the Swern oxidation (K. Omura, D. Swern, Tetrahedron 1978, 34, 1651.).
167 D. F. Taber, J. C. Amedio, K. Y. Jung, J. Org. Chem. 1987, 52, 5621. The main difference to the work of Onodera is the introduction of a base, triethylamine that speeds up the reaction significantly.
168 Further increase in concentration might be possible, but mechanical stirring might be necessary as viscosity of the reaction mixture increases and thereby heat release to the surrounding ice bath becomes slow. Higher concentrations are important, because the amounts of solvents handled, distilled and disposed of become smaller, improving yield and practicability.
Equation 4: Optimization of reagent stoichiometry leads to a reduction of starting materials in the crude product.

Therefore, the amount of reagents needed to be optimized to reduce the presence of excess triethylamine and DMSO in the reaction medium. The optimized ratios reflect more closely the theoretical stoichiometry of the reaction as given in Equation 4. More importantly, neither triethylamine nor DMSO is found in the crude product after workup.

Due to the hydrophilicity of oxetan-3-one, an anhydrous workup procedure had to be developed. It was found that upon diluting the reaction mixture with an equal volume of diethylether, the ammonium phosphates produced separate from the organic phase which can be decanted and filtered through a plug of silica gel. The filtrate is then distilled without further purification to yield oxetan-3-one in 48% isolated yield.

More than 190 g of oxetan-3-one have been prepared via this route, usually in batches of one mol. Oxetan-3-one can be stored in the freezer without noticeable decomposition. Oxetan-3-one is now commercially available from several companies, which should facilitate its use in drug discovery and spur the exploration of its chemistry.

Interestingly, the amount of phosphorous pentoxide is more than twice as high as predicted for the case shown in Equation 4 when all but one of the available phosphorous anhydride bonds are used to propel the reaction. As the energy released upon cleavage of the anhydride bond depends on the chemical nature of the given polyphosphate (see different hydrolysis enthalpies in ATP), this result may indicate that only a certain extent of the anhydride bonds contained in $P_2O_{15}$ can support the reaction. Normal aqueous workup under acidic conditions was reported in ref. 167.

Reaction monitoring and workup by NMR with an internal standard reveals that the loss of material largely happens during the reaction. Between end of the reaction and beginning of distillation yield drops by four percentage points (two different internal standards used, one added to the reaction mixture and one after filtration). During distillation three percentage points of the total yield are lost compared with the isolated yield of oxetan-3-one. It is important to use appropriate columns and avoid bath temperatures higher than 56 °C in the distillation to prevent product from distilling over.

At the start of the project, oxetan-3-one was not commercially available (Scifinder Scholar). It was first introduced to the market by Molbridge in February 2007. Since then Chemgenx, Parkway Scientific and Research Support International also started offering oxetan-3-one commercially.
3.2 Additions to Oxetan-3-one

According to literature precedence, oxetan-3-one shares many of the chemical features of less strained and less electron-deficient ketones (see Figure 7). It can be hydrogenated to oxetan-3-ol\(^{173}\), adds Grignard reagents,\(^{174}\) its oxime is known\(^{173}\) as well as the stable 2,4-dinitrophenyl hydrazone\(^{175}\) and a Strecker adduct.\(^{176}\) This precedence laid the foundation for our own efforts.

3.2.1 3-Aryloxetan-3-ols

Grignard reagents as well as aryl lithium compounds cleanly add to oxetan-3-one (33) to give the respective oxetan-3-ols in good yields. While oxetan-3-ols might be useful themselves in supplanting their gem-dimethyl counterparts or carboxylic acids, the hydroxy function serves as a convenient handle for further reactions.

![Scheme 18: Oxetan-3-ols, structural analogues and starting points for further derivatization.](image)

Table 3 summarizes the oxetan-3-ols made by addition of organometallic species to oxetan-3-one. The products are usually crystalline solids that can be stored at room temperature without noticeable decomposition.

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\(^{173}\) G. H. Berezin, US 3449369, 1969. In this patent the hydrogenation of oxetan-3-one oxime to 3-amino oxetane is reported.


**Table 3: 3-Aryloxetan-3-ols made by addition of organometal reagents to oxetan-3-one.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RM</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhLi</td>
<td>62</td>
<td>87%</td>
</tr>
<tr>
<td>2(^{177})</td>
<td>3-pyrMgCl·LiCl</td>
<td>63</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOPhMgBr</td>
<td>64</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>4-BrPhMgBr</td>
<td>65</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>PhMe₂MgBr</td>
<td>66</td>
<td>quant.</td>
</tr>
<tr>
<td>6</td>
<td>'BuPhMgBr</td>
<td>67</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>PhPhLi</td>
<td>68</td>
<td>68%</td>
</tr>
<tr>
<td>8</td>
<td>MeO₂PhLi</td>
<td>69</td>
<td>80%</td>
</tr>
<tr>
<td>9</td>
<td>Me₂N⁺PhLi</td>
<td>70</td>
<td>71%</td>
</tr>
<tr>
<td>10</td>
<td>Li₃Me₂Ph</td>
<td>71</td>
<td>73%</td>
</tr>
</tbody>
</table>

The free alcohol functionality in these compounds can then be used for substitution reactions. A number of compound classes are accessible this way, including 3-fluoro oxetanes, 3-chlorooxetanes, 3-alkoxyoxetanes.

### 3.2.2 3-Fluoro-oxetanes

Replacement of the tertiary alcohol with a fluorine atom results in 3-fluorooxetanes. This class of compounds could serve as a polar group with a steric demand between t-butyl and isopropyl groups.\(^{178}\)

\[
\text{ArCH}_2\text{OH} \xrightarrow{\text{DAST}} \text{ArCH}_2\text{F} \quad \text{CH}_2\text{Cl}_2, -78 \ ^\circ\text{C} \\
\]

*Scheme 19: Significance of 3-fluorooxetanes and their preparation of oxetan-3-ols by treatment with DAST.*

Diethylaminosulfur trifluoride (DAST) and bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) are standard reagents for the conversion of alcohols, ketones and carboxylic acids into their fluorinated counterparts.\(^{179}\) Although substitution reactions at the 3-position of the oxetane were expected to be difficult because of steric hindrance, ring strain and electron deficiency of the oxetane, this reaction went to completion after less than 1 minute at −78 °C in the presence of one equivalent of DAST (Table 4, entry 1).

---

\(^{178}\) *gem*-dimethyl groups and an oxetane have similar steric demand, as estimated by their van-der-Waals volumes and partial molar volumes in water (see ref. 309). If one assigns \(\Delta V\) to be the change in steric demand upon replacement of a hydrogen with a methyl group, then the replacement of a hydrogen with a fluorine atom results in a change of \(1/3 \Delta V\).

Table 4: Conversion of 3-aryloxetan-3-ols into the corresponding fluorinated compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image 1" /></td>
<td><img src="image2" alt="Image 2" /></td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image 3" /></td>
<td><img src="image4" alt="Image 4" /></td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image 5" /></td>
<td><img src="image6" alt="Image 6" /></td>
<td>43%</td>
</tr>
</tbody>
</table>

The consistently low yield can only be explained by losses during the reaction to a very polar byproduct that cannot be extracted into the organic phase, as the crude NMR in all cases shows product of good purity. Evidence collected at Roche however suggests that the efficiency of the reaction increases with the ability of the aryl substituent to donate electron density.\(^{180}\)

\(^{180}\) If the aryl substituent is a Boc-protected aniline, almost quantitative yields of the corresponding fluoro oxetanes were obtained.
Equation 5: Preparation of 3-chloro-3-phenyloxetane (75) and formation of 2-phenylpropenal\textsuperscript{181} as byproduct.

In a similar reaction\textsuperscript{182}, 3-phenyloxetan-3-ol (62) was converted into 3-chloro-3-phenyloxetane (75). At elevated temperatures and in the presence of an amine base, the intermediate mesylate or the product could undergo elimination to give 3-phenyloxet-2-ene which then undergoes electrocyclic ring opening leading to the observed 2-phenylpropenal (76).

3.2.3 3-Aryloxetanes

Dehydroxylation of 3-aryloxetan-3-ols would provide 3-aryl oxetanes, analogues of isopropyl groups, a very common functionality in medicinal chemistry. Following a known\textsuperscript{183} procedure for the dehydroxylation of benzylic alcohols under acidic conditions in the presence of triethylsilane as a hydride donor, 3-(p-methoxyphenyl)oxetan-3-ol (64) could be reduced in good yield without accompanying ring opening.

Equation 6: Dehydroxylation of 3-(p-methoxyphenyl)oxetan-3-ol (64).

This initial positive result for the electron-donating p-anisyl residue could however not be generalized to other substrates\textsuperscript{184}. For less electron-rich aryl substituents, no reaction occurs or decomposition upon prolonged exposure or heating. Therefore, conditions were screened to find an alternative procedure.

\textsuperscript{181} This compound was identified by comparison of its NMR spectrum with literature data (R. H. Newman-Evans, R. J. Simon, B. K. Carpenter, J. Org. Chem. 1990, 55, 695.)


\textsuperscript{184} Neither 3-phenyloxetan-3-ol, nor 3-(2,4-dimethylphenyl)oxetan-3-ol gave any product under above conditions.
Table 5: Screening of conditions for the hydro-dehydroxylation of 3-phenyloxetan-3-ol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>Pd/C, H₂, EtOH, 4 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>Pd/C, HCO₂H, EtOH, 4 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>Pd(OH)₂/C, H₂, HCO₂H, EtOH, 2 d</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>Pd/C, H₂, AcOH, 70 °C, 15 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>OC(S)SMe</td>
<td>Lauroyl peroxide, 'PrOH, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Bu₃SnH, AIBN, PhMe, reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>Pd(OH)₂/C, H₂, MeOH, 12 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>OH</td>
<td>5% InCl₃, Ph₂SiHCl, 80 °C or rt, 1 d</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>OC(O)CO₂Me</td>
<td>Bu₃SnH, AIBN, PhMe, reflux</td>
<td>alcohol recovered</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td>LiAlH₄, rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>11</td>
<td>OH</td>
<td>Pd(OH)₂/C, H₂, TFAA, THF, 2 d</td>
<td>decomposition</td>
</tr>
<tr>
<td>12</td>
<td>OH</td>
<td>1. NaI, TMSCl, 2. AcOH, Zn</td>
<td>H₂C=CH(CPh)CH₂OH (34%)</td>
</tr>
<tr>
<td>13</td>
<td>OH</td>
<td>Et₃SiH, TFA, rt, 4 d</td>
<td>decomposition</td>
</tr>
<tr>
<td>14</td>
<td>OH</td>
<td>Et₃SiH, F₃CSO₂H, CH₂Cl₂</td>
<td>decomposition</td>
</tr>
<tr>
<td>15</td>
<td>OH</td>
<td>Pd/C, cyclohexene, AlCl₃, 75 °C, 60 h</td>
<td>rec. sm, decomposition</td>
</tr>
<tr>
<td>16</td>
<td>OTs (78)</td>
<td>Pd(OH)₂/C, H₂, EtOAc, 4 d</td>
<td>decomposition</td>
</tr>
<tr>
<td>17</td>
<td>OH</td>
<td>P₃I₄, PhMe, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>18</td>
<td>OTs (78)</td>
<td>LiAlH₄, 0 °C, Et₂O, 45 min</td>
<td>68%</td>
</tr>
<tr>
<td>19</td>
<td>OH</td>
<td>1. NaH 2. pTsCl, 3. LiAlH₄, THF, 0 °C</td>
<td>27%, 22%</td>
</tr>
<tr>
<td>20</td>
<td>OH</td>
<td>1. NaH 2. pTsCl (3. LiAlH₄) Et₂O, 0 °C</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

---

196 Compound 79 is fully characterized and the result was reproduced. The analogous 4-Bromobutyl ether was obtained upon treatment of tosylate 78 with MeMgBr in THF.
197 Reaction to the tosylate did not proceed in diethyl ether.
The vast majority of methods known for the deoxygenation of a benzylic alcohol failed to give product and resulted either in recovery of starting material or decomposition. Treatment of tosylate 78 with lithium aluminum hydride in diethylether at 0 °C however gave the reduced product in acceptable yield (Table 5, entry 18). As tosylate 78 was made by sequential treatment of the alcohol with sodium hydride and pTsCl in THF, it seemed obvious to try a one-pot deoxygenation of alcohol 62. When the sequence was performed in diethylether, no formation of tosylate 78 was observed, probably due to insolubility of the sodium alkoxide of 62 in diethyl ether.198

Equation 7: Formation of n-butyl ether 79 suggests SN1-pathway for the hydrodetosylation of 78.

When the solvent for the reduction was changed to THF, however n-butyl ether 79 was formed as a byproduct.196 This indicated that upon treatment of tosylate 78 with lithium aluminum hydride which acted as a Lewis acid, heterolytic bond cleavage occurred to form carbocation 80. This was then trapped by Lewis-basic THF or quenched by LiAlH4. When the less basic diethylether was used in place of THF, the corresponding oxonium ion was probably formed to a lesser extent.199 This sequence has been applied to the preparation of 3-aryloxetane 81.

198 For other, more lipophilic oxetanols (vide infra), the tosylation also proceeded in diethyl ether.
199 Additionally, the oxonium ion derived from diethylether is sterically more hindered, so that its trapping with LiAlH4 might result in formation of product rather than hydride attack on diethylether.
Equation 8: One-pot preparation of 3-aryloxetane 81 from its corresponding alcohol 70.

In this case, tosylate formation in diethylether succeeds\(^\text{200}\) and the reduction proceeds smoothly at \(-78^\circ\text{C}\). At higher temperatures and prolonged reaction times, opening of the oxetane ring in the product resulted in lower yields. The substrate dependency of this sequence leaves room for the application of other methods or building blocks that offer more reliable access to this class of compounds.

### 3.2.4 3-Aminooxetanes

Benzylic amines and benzamides are common motifs among marketed drugs.\(^\text{201}\) Given their prevalence in medicinal chemistry it would be desirable to have a method available for the preparation of their oxetane analogues from oxetan-3-one (33).

![Scheme 20: 3-Amino-3-aryloxetanes, structural analogues and starting points for further derivatization.](image)

Two approaches to this compound class were selected to be examined first, nucleophilic displacement and addition to a C=N double bond. Several attempts to displace a

\(^{200}\) The intermediary tosylate could not be isolated as it hydrolyzed immediately during aqueous workup to the alcohol 70.

\(^{201}\) 5.2\% of all drugs on the market (163 total) contain a benzylic amine and 3.2\% (100 total) a benzamide. (Prous Science Integrity®, June 2008: Search for all compounds containing the respective substructure and having „Launched“ as development status associated with it. Total found: 3114)
leaving group with sodium indolamidate invariably led to decomposition.\textsuperscript{202} Addition reactions of phenyl lithium to oxetan-3-one \textit{N,N}-dimethylhydrazone also yielded no product.\textsuperscript{203}

The known preparation of amino acid \textbf{36}\textsuperscript{204} (see Figure 7) from oxetan-3-one (\textbf{33}) inspired us to use \(\alpha\)-amino nitriles derived from oxetan-3-one as precursors for 3-aminooxetanes. In the so-called Bruylants’ reaction, arylmagnesium halides react with \(\alpha\)-amino nitriles to give the corresponding aryl amine.\textsuperscript{205}

\begin{equation}
\begin{aligned}
\text{O} & \xrightarrow{\text{Br}_2\text{NH, TMSCN, AcOH}} \text{Bn}_2\text{N} \text{CN} \\
\text{O} & \xrightarrow{\text{ArMgX}} \text{Bn}_2\text{N} \text{Ar} \\
\text{O} & \xrightarrow{\text{ArMgX}} \text{Bn}_2\text{N} \text{Ar} \\
\text{O} & \xrightarrow{\text{ArMgX}} \text{Bn}_2\text{N} \text{Ar} \\
\end{aligned}
\end{equation}

\textit{Equation 9: Preparation of 3-amino-3-aryloxetanes from aminonitriles.}

Aminonitrile \textbf{82} can be prepared in high yield by treatment of oxetan-3-one with di-benzyamine and trimethylsilyl cyanide in acetic acid. A procedure published for structurally similar azetidines was used as a starting point for the optimization of the reaction conditions.\textsuperscript{206} High concentration of the Grignard reagent as well as a switch from diethyl ether to THF is important for the reaction to proceed to completion. A high concentration of Lewis acidic Grignard reagent might help the formation of the intermediary iminium ion. High salt concentrations in the solution also raise its dielectric constant, promoting the heterolytic C–CN bond cleavage by stabilizing the resulting ion pair.\textsuperscript{207}

\textsuperscript{202} The leaving groups tried were chloride and tosylate in THF or DMF as solvents. As seen in Equation 5, the amide base probably rather led to elimination than substitution on the sterically hindered center.


\textsuperscript{207} Attempts to preform the iminium ion by treating the aminonitrile \textbf{82} with AgBF\textsubscript{4} (C. Agami, F. Couty, G. Evano, \textit{Org. Lett.} 2000, 2, 2085.) prior to the addition of PhMgBr invariably led to incomplete conversion and complex reaction mixtures.
Equation 10: Bruylants’ reaction of aminonitrile 82 and hydrogenolytic deprotection to give 3-amino-3-phenyloxetane (84).

The resulting amine 83 could then be debenzylated easily to give 3-amino-3-phenyloxetane (84). No reduction to 3-phenyloxetane was not observed.

### 3.3 Oxetanes Bearing a Quaternary Center

Oxetanes would be confined to a small niche in drug discovery, if their synthetic presence was limited to terminal positions (3-hydro- or 3-fluorooxetanes) or dependent on heteroatom linkages (3-hydroxy or 3-aminooxetanes). True flexibility and competitiveness would only arise from the potential ability to substitute any methylene, gem-dimethyl or carbonyl group by an oxetane. In many cases, this implies introduction of the oxetane unit at internal locations of a molecular structure, rendering the development of methodology to access oxetanes bearing a quaternary center important.

Different approaches were considered to prepare this compound class. A direct way would be the substitution of a leaving group X in compound 85 with a carbon nucleophile. As an alternative, nucleophilic addition reaction might be performed on Michael acceptors like compound 87.

Figure 10: Preparation of quaternary centers by substitution or conjugate addition.

---

208 See Table 5 for the stability of 3-phenyloxetan-3-ol under towards hydrogenolysis. Examples for hydrogenolytic cleavage of benzylc amines with substitution analogous to oxetane 84 could not be found in the literature (search in Beilstein and Scifinder Scholar, July 2008).
Efforts to react a variety of electrophiles 85 with different carbon nucleophiles did not result in the formation of appreciable amounts of substitution product.\textsuperscript{209} Therefore, it was decided to pursue the route via conjugate addition to 3-alkylideneoxetanes 87.

### 3.4 1,4-Addition to Michael Acceptors

A recurrent challenge in the chemistry of 3-substituted oxetanes seems to be their reluctance to undergo nucleophilic substitution. The transition state of a nucleophilic substitution (Picture 7, left) is characterized by steric hindrance, electron deficiency and increased ring strain.

*Picture 7: Comparison of the transition state of a nucleophilic substitution with conjugate addition onto a Michael acceptor.*

These impediments that render nucleophilic substitutions difficult foster the conjugate addition to compounds of the type shown in Picture 7 on the right. Here, the strained planar geometry which raises the energy of the S\textsubscript{N}-transition state is preformed in the reagent. The sp\textsuperscript{2}-hybridized 3-position of the oxetane suffers from a bond angle contraction of approximately 30° imposed by the small ring. Attack on the 3-position of the oxetane changes the hybridization to sp\textsuperscript{3}, reducing the deviation from the preferred bond angle to approximately 20°.\textsuperscript{210} The inductive effect of the oxetane oxygen which obstructs the buildup of partial positive charge in the S\textsubscript{N}-transition state promotes the 1,4-addition to alkylidene oxetanes, making the 3-position in oxetanes more electrophilic.

\textsuperscript{209} Neither Ruppert’s reagent (TMS-CF\textsubscript{3}/CsF) nor methylmagnesium iodide gave any product. Cyanide as a nucleophile only yielded small amounts of mixtures of nitrile and isonitrile. Attempts to lithiate 3-chloro-3-phenyloxetane with LiDBB only resulted in the formation β-elimination product H\textsubscript{2}C=C(Ph)CH\textsubscript{2}OH\textsuperscript{193}.

\textsuperscript{210} This positive approximation to the preferred bond geometry is balanced by additional eclipsing interactions between the substituents on the 3-position of the oxetane and its adjacent methylene groups.
3.4.1 Preparation of Acceptors

Precedence for the preparation of this compound class from oxetan-3-one (33) is sparse. The preparation of ester 39 via Horner–Wadsworth–Emmons reaction indicated however that their synthesis was possible.\textsuperscript{211}

\[ \text{Equation 11: Preparation of the } \alpha,\beta\text{-unsaturated ester 39 by HWE-reaction.}\textsuperscript{211} \]

It was found that a number of different members of this compound class can easily be prepared. Commercially available, resonance-stabilized ylides react cleanly to give the corresponding unsaturated ester 89, aldehyde 90, methyl ketone 91 and nitrile 92 in good yield.\textsuperscript{212} Horner–Wadsworth–Emmons reaction provides access to the phenylsulfone 93, ketone 94 and phosphonate 95. Condensation of oxetan-3-one with nitromethane yields the corresponding nitro alkene 96.

\textsuperscript{211} M. D. T. Moldes, G. Costantino, M. Marinozzi, R. Pellicciari, \textit{Farmaco} \textbf{2001}, 56, 609.
\textsuperscript{212} Workup was performed by filtering the reaction mixtures through a plug of silica gel.
Figure 11: Michael-acceptors prepared from oxetan-3-one.

All compounds show no signs of decomposition when stored in the freezer. Only in one case, vigorous and spontaneous decomposition of an impure sample of aldehyde 90 was observed.

3.4.2 Conjugate Additions

The compounds shown above react with a broad variety of heteroatom as well as carbon nucleophiles. Often, complete selectivity of 1,4 over 1,2-addition is seen. A comparison of ester 89 with the corresponding 3,3-dimethyl acrylate 98 highlights the reactivity of this compound class.

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213 Sulfone 93 is stable also at ambient temperature.
214 Traces of base present in the material which had been recovered from a reaction mixture might have triggered polymerization.
Equation 12: Conjugate addition of nitromethane to ester 89 and its gem-dimethyl analogue 98.$^{215}$

This reactivity towards nucleophilic addition allows for the preparation of a wide range of products. Being able to vary both electrophile and nucleophile provides flexible routes towards oxetanes with quaternary substitution. Comprehensive exploration of this vast uncharted area of chemical space is not within the grasp of this project and has not been its goal. We focused rather on harnessing the power of this methodology for the preparation of specific structures and thereby demonstrating its value and practical relevance. The following schemes contain an overview of the different nucleophiles explored. Many of the products were then used to prepare the prototypic analogues, the physico- and biochemical properties of which were profiled thereafter.

---

Scheme 21: Addition products derived from ester 89.

The compounds shown in Scheme 21 include a variety of functional groups and structural motives. Carbon and heteroatom, neutral and anionic nucleophiles add across the double bond often in high yield. The ability to utilize aryl- and vinylboronic acids as a carbon nucleophile in a simple procedure\textsuperscript{216} and thereby tap into the vast reservoir of commercially available boronic acids should make the preparation of this type of oxetanes also amenable to parallel synthesis.

Scheme 22: Addition products derived from nitro compound 96.

Scheme 23: Addition products derived from aldehyde 90.\textsuperscript{217}

\textsuperscript{217} The aldehyde group in particular possesses inherent reactivity that makes it necessary to quench the addition products of amines in situ either by reduction or olefination. It is known that β-amino aldehydes
These schemes highlight the structural diversity that emerges from the selected acceptors. A grouping by product instead of starting material better visualizes the different classes of oxetanes accessible through this pathway.

*Picture 8: Selection of addition products accessible through oxetan-3-one.*

The different classes of oxetanes that can be made from oxetan-3-one are grouped in Picture 8 according to the distance of the closest heteroatom to the oxetane core. Some of the target structures we envisioned to prepare however can be made more efficiently from a different set of starting materials. The compound classes accessible through them complement the chemistry shown so far.

3.5 Chemistry starting with Tribromopentaerythritol

An article by Hoste and Govaert appeared in 1949, detailing on the preparation 2-oxa-6-azaspiro[3.3]heptane derivatives from 3,3-bis(bromomethyl)oxetane (119). Other articles followed that also used nucleophilic displacement in 3,3-bis(halomethyl)oxetanes to build up this class of spirocycles.

![Scheme 24](image)

Scheme 24: Preparation of substituted 2-oxa-6-azaspiro[3.3]heptanes from 3,3-bis(halomethyl)oxetanes.

Azetidine 24 belongs to this group of spirocycles and it was therefore decided to build it up using chemistry related to the one shown in Scheme 24. It would be advantageous to have the unsubstituted 2-oxa-6-azaspiro[3.3]heptane (124) available as a building block in order to circumvent applying the harsh conditions of its preparation to the actual scaffolds of interest.

---


Therefore, conditions\textsuperscript{220} that were reported to yield 1-alkylazetidines from a primary amine and 1,3-dibromopropane were probed for their efficiency with the sterically more hindered 3,3-bis(bromomethyl)oxetane (119)\textsuperscript{221}. In all cases, the reactions were found to be slow\textsuperscript{222} and the products could be isolated only in small yield.

Scheme 26: Screening of conditions for the preparation of 2-oxa-6-azaspiro[3.3]heptanes.\textsuperscript{220}


\textsuperscript{221} This material was prepared from commercial tribromopentaerythritol (123): C. G. Overberger, Y. Okamoto, V. Bulacovski, Macromolecules 1975, 8, 31.

\textsuperscript{222} All reactions tried showed residual 3,3-bis(bromomethyl)oxetane even after refluxing/heating for several days.
Hydrogenolytic deprotection of either compound 125 or 126 was planned to give rise to the free amine. As variation of the parameters for the ring closure did not result in substantial improvements of yields, it was decided to use the high-yielding preparation of sulfonamide 120 as a starting point and investigate the cleavage of the sulfonamide bond.

\[
\begin{align*}
\text{Scheme 27: Preparation of tosyl amide 129 from commercial tribromopentaerythritol.}^{225} \\
\text{Instead of sulfanil amide, } p \text{-tosyl amide was chosen as a nucleophile, as most cases of sulfonamide cleavages in the literature refer to this protecting group. The initially employed two-step synthesis for the preparation of tosyl amide 129 could be turned into a one-pot procedure by virtue of the similarity of the reaction conditions of the two steps involved. The pure product 129 is simply isolated by evaporation of ethanol, followed by stirring with aqueous KOH in which excess } p \text{-tosyl amide dissolves.}
\end{align*}
\]

Common conditions for the deprotection of tosyl amides include boiling in strong mineral acid or the reductive cleavage with an alkali metal. A more recent study found that } N \text{-tosylaziridines can be deprotected with magnesium in methanol.}^{228} This method

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\begin{itemize}
\item \(^{223}\) Increase in time and reaction temperature did not give any improvement.
\item \(^{224}\) This work was carried out by Andreas Buckl as part of his Semesterarbeit.
\end{itemize}
was investigated first because of its simplicity and the potential benefits with respect to scale-up and purification. Indeed, initial attempts showed conversion to product which was trapped and isolated from the reaction mixture by benzylation. This proof-of-concept cleared the way to optimize both the reaction conditions and the isolation of the product. Its polarity and volatility as well as the production of magnesium salts during the reaction presented a challenge for the development of the simple and scalable isolation and purification of the product.

**Scheme 28: Optimized procedure for the preparation of oxalate 130 from tosyl amide 129.**

Several additives were screened to precipitate the magnesium salts from the reaction so that the crude mixture can be filtered. Only Na₂SO₄·10H₂O however was successful in providing filterable precipitates. This simple method involves only filtrations as purification steps and is amenable to scale-up. The synthesis has been reproduced successfully in the laboratories of Roche Basel and Novartis.

Oxalate 130 can also be utilized directly in acylation, alkylation and Buchwald–Hartwig reactions. In all cases, the free amine is liberated *in situ* by the presence of base. This stable salt 130 thereby represents a convenient source 2-oxa-6-azaspiro[3.3]heptane (124).

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229 Tartaric acid, oxalic acid and different salts of EDTA were tried without success to obtain precipitates that were filterable.


231 2-oxa-6-azaspiro[3.3]heptane can be isolated and characterized, but decomposes upon storage at ambient temperature.
Scheme 29: Use of oxalate 130 as a reagent in the amination of benzoyl chloride, benzyl halides and an aryl bromide.

3.6 Selective Opening of 2,6-Dioxaspiro[3.3]heptane

A molecule closely related to 2-oxa-6-azaspiro[3.3]heptane (124) is 2,6-dioxaspiro[3.3]heptane (140). This spirocyclic oxetane has first been obtained by Backer and Keuning\textsuperscript{232} in 1934 by treatment of dibromopentaerythritol (139)\textsuperscript{233} with base in hot ethanol.


Scheme 30: Preparation of 2,6-dioxaspiro[3.3]heptane (140) from dibromopentaerythritol (139).\textsuperscript{232}

We reasoned that there might be the possibility to attack selectively one of the two rings with a nucleophile and thereby use 2,6-dioxaspiro[3.3]heptane (140) as a building block for the preparation of oxetanes. Interestingly, this compound is crystalline and crystals suitable for single-crystal x-ray analysis were obtained.\textsuperscript{234}

![X-ray structure of 2,6-dioxaspiro[3.3]heptane (140).](image)

Picture 9: x-ray structure of 2,6-dioxaspiro[3.3]heptane (140).

Both oxetane rings are planar and the C–C–C–valence angle is 85° which is similar to what is observed in other oxetanes.\textsuperscript{235} In solution, 2,6-dioxaspiro[3.3]heptane (140) has a dipole moment of 0.79 D\textsuperscript{236} on the basis of which a puckering angle of 22° was predicted for both rings.\textsuperscript{237} The only explanation for the measured dipole moment might be a fundamental change in structural preference upon solvation.\textsuperscript{238}

---

\textsuperscript{234} Being comparable in structure to 1,4-dioxane which is a liquid at standard conditions and having neither a resulting dipole moment in the solid state nor the possibility to form hydrogen bonds, it is not clear why 2,6-dioxaspiro[3.3]heptane (140) is a solid (m\textsubscript{p} 89–90 °C, ref. 232) rather than a liquid.

\textsuperscript{235} Refer to Picture 11 for comparison.


\textsuperscript{238} This would mean that ceteris paribus and based on the calculation in ref. 237, in solution a puckering angle of approximately 22° in both rings should be found.
Shown in Picture 10 on the left is the view along the likely trajectory along which a nucleophile would attack. The picture on the right reflects the situation after opening of one of the two rings. In the conformation which is likely adopted, the methyl group and the newly formed alcohol shield the remaining oxetane from further attack. Therefore, selectivity should increase with increasing bulk of the nucleophile being used.

Scheme 31: Comparison of selectivities observed using an allyl cuprate versus a ester lithium enolate.

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239 Structure of 3-ethyl-3-(hydroxymethyl)oxetane (141) was calculated using the semiempiric AM1 algorithm of the Gamess Plugin in Chem3D 11.0.

240 For an explanation, why this conformation is likely to be adopted and not the one where the methyl group and the alcohol come to rest between the two arms of the oxetane, refer to Diagram 9.

241 In the reaction mixture, the alcohol is bound to metal part of the former nucleophile and its solvate shell. Therefore, the steric demand of a hydroxyl group insufficiently reflects the situation and merely poses a lower boundary for the true steric bulk.

242 A bigger nucleophile would not only be more selective for the sterically less hindered spirocycle 140, but also lend more steric hindrance to the mono-opened product.

243 Adapted from a procedure published for oxetane: C. Huynh, F. Derguinboumehal, G. L instrumelle, Tetrahedron Lett. 1979, 1503. When the reaction was stopped after 24 h, NMR of the crude material showed the presence of starting material in a ratio of p/sm ≈ 2/1.
The difference in nucleophilicity and size\(^{245}\) might help explain the different selectivities observed in both reactions in addition to the higher temperatures in the first example and the presence of a Lewis acid in the second. Other nucleophiles like aryl lithium compounds might also be suited. The compound classes thereby accessible offer convenient handles for their further functionalization and are complementary to what can be made by conjugate addition.

### 3.7 Follow-up Reactions

Although the sole availability of methodology to prepare oxetanes is sufficient for them to be applied in drug discovery, it is important to relate their properties to the functional groups they are planned to replace. A comparison between specific examples of oxetanes and their gem-dimethyl, carbonyl or morpholine counterparts had therefore to be performed. In order to achieve that, a number of discrete compounds were made and their properties measured. The routes leading to these do not necessarily expand the knowledge of oxetane chemistry, but demonstrate its applicability.

#### 3.7.1 Compounds of the Open-Chain Series

Shown in Figure 12 is the scaffold onto which the oxetane unit should be grafted. The synthesis of all of these compounds relies on conjugate additions to Michael acceptors and was the driving force to develop their chemistry.

\[\text{Figure 12: Locations in which the oxetane should be integrated in the initial series.}\]


\(^{245}\) Although the t-butyl group seems to be far away from the reaction center, it is plausible that the lithium alkoxide of 144 present in the reaction mixture places the t-butyl group close to the incoming nucleophile allowing the carbonyl of the ester to coordinate to the lithium.
The difficulty in case of compound 145 was to introduce the methyl group. Initial
1,4-addition to ester 89 gives compound 146 in good yield. Removal of the ester is
accomplished by reduction followed by decarboxylation\textsuperscript{246} with Wilkinson’s catalyst.

\textit{Scheme 32: Preparation of 3-aryl-3-methyloxetane 145.}

The necessity however to use stoichiometric amounts of Wilkinson’s catalyst renders
this method unattractive on larger scale. Therefore, a method developed by O’Connor \textit{et al.} in which the rhodium catalyst is regenerated by reaction with dppa was tried for a
simpler substrate.\textsuperscript{247}

\textit{Scheme 33: Decarboxylation of aldehyde 114 with catalytic amounts of Wilkinson’s
catalyst.}\textsuperscript{247}

Aldehyde 114 was prepared by conjugate addition to acrolein 90 and was also used in
the synthesis of compound 148. There it was condensed with nitromethane;\textsuperscript{248} the resulting
nitroolefin was then reduced and reductively alkylated to give compound 148 in 20% yield over 4 steps.

\textit{Scheme 34: Preparation of compound 148.}

\textsuperscript{248} Adapted from a literature procedure: C. Palomo, J. M. Aizpurua, F. P. Cossio, J. M. Garcia, M. C. Lopez, M.
Conjugate addition of a cuprate to acrylate 89 provided ester 101. Reduction to the corresponding aldehyde and reductive amination then gave the final product.

Scheme 35: Preparation of compound 149.

Compound 150 carries a nitrogen beta to the oxetane, so nitroolefin 96 was chosen to be the starting point for its preparation. Conjugate addition of styrylboronic acid 151 provides the nitro compound 152 which is then hydrogenated and reductively alkylated.

Scheme 36: Preparation of compound 150.

The preparation of compound 153 involves the conjugate addition of dimethylamine to acrolein 90. The intermediary β-aminoaldehyde 113 is then trapped with phosphorous ylide 154 and the resulting styrene hydrogenated to give the final product.

Scheme 37: Preparation of compound 153.

The sole purpose in all cases was the preparation of sufficient amounts of pure compound for the measurement of key properties relevant in drug discovery. Therefore, the


yields of these transformations were not optimized. In none of the reactions above, by-products resulting from opening of the oxetane ring were found.

3.7.2 Oxetane Analogues of Sibutramine

Sibutramine (155) and its metabolites belong to a class of compounds called serotonine reuptake inhibitors (SNRI). Sibutramine enhances both satiety and metabolism.\textsuperscript{252} It represents an interesting target for the introduction of an oxetane, because of its reported sites of metabolic oxidation.\textsuperscript{253}

![Figure 13: Sibutramine (sites of metabolic attack are marked with arrows) and proposed oxetane analogues 156 and 157.](image)

It was envisioned to replace either the cyclobutane or the isopropyl group with an oxetane and test these compounds for their metabolic stability and activity in vitro. The synthesis of compound 156 commenced with the addition p-chlorophenyl lithium to nitroolefin 96 in 35% yield (see Scheme 22).

![Scheme 38: Preparation of compound 156.\textsuperscript{254}](image)


\textsuperscript{254} This work was done by Roman Marty as part of his Semesterarbeit. It builds up on work done by Luzi Barandun during his SiRop-work.
Nitro compound 110 could be transformed into nitrile 158 applying known methodology.\textsuperscript{255} Subsequent treatment of nitrile 158 with isobutylmagnesium bromide at elevated temperature in toluene and reduction of the addition product \textit{in situ} with sodium borohydride provided primary amine 159 in good yield.\textsuperscript{256}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme39.png}
\caption{Attempted preparation of compound 157.\textsuperscript{257}}
\end{figure}

For the synthesis of compound 157, ketone 94 was prepared from oxetan-3-one (see Figure 11) via Horner–Wadsworth–Emmons reaction. After hydrogenation of the double bond, it was envisioned to introduce the amine by reductive amination\textsuperscript{258} or by nucleophilic displacement (shown in Scheme 39). Both approaches failed however to give product. Since the activity and metabolic stability of compound 156 were both poor, it was decided not to follow up on compound 157.

The chemistry \textit{en route} to these molecules nevertheless includes several interesting transformations. The class of 3-aryl-3-cyanooxetanes for example might serve as a surrogate for t-butyl groups and is useful as a building block for addition reactions. The same is true for the preparation of 3-alkyloxetanes like alcohol 160 through hydrogenation and their stability towards sodium borohydride.

3.7.3 Spirocyclic Oxetanes

Whereas the series of compounds described above were merely made for the purpose of measurement, the spirocyclic oxetanes shown below were also intended to serve as building blocks in the future. This has consequences for the synthetic efficiencies and the step count that should be achieved in their preparation. Contrary to the open-chain case, with these compounds it would be possible to study conformationally locked oxetanes. The piperonyl group was chosen as a substituent to facilitate spectroscopic readout. These compounds may be categorized in different manners, but from a synthetic point of view it makes most sense to group them according to the distance between the ring nitrogen and the oxetane. Hence, compounds bearing the nitrogen alpha to the oxetane all derive from conjugate additions of an amine nucleophile to appropriate Michael acceptors.

\[ \text{Scheme 40: Preparation of azetidine 28.}^{259} \]

Conjugate addition of piperonylamine to acrylate 89, followed by reduction furnishes aminoalcohol 106. Appel reaction\(^{260}\) then yields azetidine 28.\(^{261}\)

\[ \text{Scheme 41: Preparation of pyrrolidine 29.} \]

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\(^{259}\) This route was developed as part of the Semesterarbeit of Maurizio Bernasconi.


\(^{261}\) Attempts to build up the 6-oxa-1-azaspiro[3.3]heptane system by conjugate addition of azide to acrolein 90 were not successful.
Pyrrolidine 29 was prepared in a similar manner by 1,4-addition of piperonylamine to acrolein 90. The intermediary β-amino aldehyde was trapped by reacting it with methylentriphenylphosphorane (163).251 The low yield probably stems from competing 1,2-addition of piperonylamine to the aldehyde and concomitant side reactions of the resulting hemiaminal or imine.262 Homoallylic amine 115 then underwent mercury-mediated hydroamination to give the final product in low yield.263

**Scheme 42: Preparation of piperidine 30.**

Contrary to what was seen for piperonylamine and in accordance with the observation in case of dimethylamine264, N-allyl-piperonylamine (164) added cleanly to acrolein 90.265 Subsequent trapping with methylentriphenylphosphorane (163) yielded diene 165.251

---

262 A byproduct could be isolated in 2% yield from this reaction that most likely stems from the rearrangement of the N-piperonyl imine of acrolein 90:


264 Refer to Scheme 37 for details.

265 The increase in reaction time from 50 min for dimethyl amine to 5 d in case of N-allyl-piperonylamine (164) likely stems from increased steric demand and reduced nucleophilicity of the latter.
Ring-closing metathesis executed on the \textit{in situ} protonated amine 165 then gave 3,4-dehydropiperidine 166 which was hydrogenated to the final product 30. Interestingly, significant amounts of secondary amine 167 were formed as well.267

Spirocycles in this series that contain the oxetane in beta-position to the nitrogen are only partially derived from oxetan-3-one. In two out of three cases, other approaches yielded the respective product more easily.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme43.png}
\end{center}

\textit{Scheme 43: Preparation of compound 24.}268

With the availability of oxalate salt 130 in large quantities (see chapter 3.5), azetidine 24 could be prepared by reductive alkylation with piperonal (168).269

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267 It is not clear by what mechanism the side product is formed. It might result from the insertion of rhodium into the C–N bond (facilitated by traces of acid) to give an allyl-rhodium species which is then hydrogenated.


Scheme 44: Preparation of pyrrolidine 26.

Conjugate addition of nitromethane to acrylate 89 gave nitroester 103 in excellent yield. This compound was then reduced to the corresponding aldehyde which was reductively cyclized to give crude spiropyrrrolidine 169. Reductive alkylation then furnished the final product 26.

Scheme 45: Preparation of piperidine 27.

The preparation of hydroxyester 144 through selective ring opening of spirooxetane 140 has been discussed extensively on page 71. Reduction, mesylation and amination of ester 144 then results in piperidine 27.

---

270 This aldehyde can also be obtained from the reaction of acetaldehyde with nitroolefin 96 in the presence of catalytic amounts of pyrrolidine in 46% yield. Due to side reactions, however the yields in this reaction are not very reproducible and the product is difficult to isolate.
Scheme 46: Preparation of compound 25.

Piperidine 25 in which the oxetane is positioned gamma to the nitrogen was made in a five-step sequence that did not require any purification of intermediates. The route commenced with the conjugate addition of dimethyl malonate (170) to acrylate 89, followed by Krapcho demethoxycarbonylation. Subsequent reduction, mesylation and amination yielded the product 25.

3.7.4 Reactions of Sulfone 93.

The α,β-unsaturated sulfone 93 has the potential to become a very powerful building block. There is abundant methodology known that provides ways to reductively cleave the sulfone under mild conditions. Moreover, it might be used as a handle for the Julia olefination and its variations.

Figure 14: Nucleophilic additions to α,β-unsaturated sulfone 93 and follow-up reactions.

---

A few preliminary results indicate that carbon as well as heteroatom nucleophiles can add to α,β-unsaturated sulfone 93. Desulfonation by stirring with magnesium in methanol then gave the corresponding 3-methyloxetanes. While 3-aryl-3-methyloxetanes are also accessible by decarbonylation of the respective aldehydes with Wilkinson’s catalyst (see page 74), the possibility to prepare 3-amino-3-methyloxetanes in one pot constitutes a very simple method for the introduction of an oxetane onto a scaffold.

Scheme 47: Additions to α,β-unsaturated sulfone 93 and consecutive reductive sulfone cleavage.

For addition products like 181 and 183, decomposition was observed under these conditions, maybe due to elimination. Further experiments might solve this problem by adding catalytic amounts of mercury(II) salts to the reaction or by switching to Raney Nickel as a reductant. Attempts to use sulfone 172 in order to couple it with

---

274 The experiments in which decomposition was observed have nucleophiles in common that are relatively good leaving groups.
piperonal (168) in a Julia reaction, failed to give product. A likely solution to this could be to use 2-pyridylsulfone 184 as an acceptor.

Scheme 48: Addition products of 2-pyridylsulfone 184 and their proposed ability to undergo Julia–Kocienski olefination.

This type of sulfones has been reported to undergo rhodium-catalyzed conjugate additions of arylboronic acids and also one-step olefinations, following the Julia–Kocienski protocol.

3.8 Reagent Compatibility of Oxetanes

Many of the reagents used in the course of this work could in principle pose a threat to the integrity of the oxetane ring by their inherent acidity and/or nucleophilicity. Therefore, it is important to know which reaction conditions are tolerated by the oxetane moiety. The following table contains a compilation of conditions that were found to be tolerated or lead to decomposition in one or several cases.

Table 6: Compatibility of oxetanes to different reaction conditions.

<table>
<thead>
<tr>
<th>Reagent Conditions</th>
<th>Tolerated Conditions</th>
<th>Not Tolerated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>RMgX, NaOH, RNH₂, AcOH, Krapcho</td>
<td>LiAlH₄, TFA/Et₃SiH, H₃PO₄ (often)</td>
</tr>
<tr>
<td>rt</td>
<td>NaBH₄, BH₃·THF, aqueous acid</td>
<td>NaBH₄, BH₃·THF</td>
</tr>
<tr>
<td>0 °C</td>
<td>LiAlH₄, TFA/Et₃SiH, H₃PO₄ (often)</td>
<td>sometimes: TFA/Et₃SiH, H₃PO₄</td>
</tr>
<tr>
<td>Reflux</td>
<td>aqueous HCl</td>
<td>intramolecular nucleophiles⁵⁷¹</td>
</tr>
<tr>
<td>rt</td>
<td></td>
<td>HCl in dioxane</td>
</tr>
<tr>
<td>0 °C</td>
<td>intramolecular nucleophiles⁵⁷¹</td>
<td>often: TFA/Et₃SiH, H₃PO₄</td>
</tr>
<tr>
<td>−78 °C</td>
<td></td>
<td>LiAlH₄ (slow opening)</td>
</tr>
</tbody>
</table>

⁵⁷¹ alkoxides or carboxylates, if they are adequately positioned to form a five-membered ring

277 Only conditions are listed that might cause concern of ring opening because of the acidity or nucleophilicity of the reagents involved.
3,3-Disubstituted oxetanes are in general more resistant to decomposition than mono-substituted ones. Strong anhydrous acid is problematic for both groups and can lead to decomposition for example when trying to cleave a Boc group. Other commonly used reagents like strong base or reducing agents are well tolerated.

The initial concerns that oxetanes would be too unstable to withstand commonly used synthetic methods can thereby be dispelled. The synthetic data collected clearly show that the building block approach for the preparation of oxetanes is viable, that a broad variety of compound classes can be generated, and that these can be further elaborated to more complex structures.
4 Physicochemical and Pharmacological Profile of Oxetanes

A broad range of properties was measured for a number of oxetanes at F. Hoffmann-La Roche AG in Basel. For some of them, the respective gem-dimethyl or carbonyl compounds were also submitted in order to shed light on the hypothesized analogies with oxetanes. Initially, a series of compounds was investigated in which the oxetane moiety was integrated at different positions of the scaffold shown in Scheme 49.

![Scheme 49: Linear scaffold of which oxetane and gem-dimethyl derivatives were prepared (indicated by the arrows).](image)

A metabolite determination at Roche for compound 185 showed that its main metabolites are the corresponding N-oxide, a benzylic alcohol and a primary alcohol resulting from attack on the t-butyl group.

278 A metabolite determination at Roche for compound 185 showed that its main metabolites are the corresponding N-oxide, a benzylic alcohol and a primary alcohol resulting from attack on the t-butyl group.

279 For the detailed discussion of amphiphilicity and its relevance to drug discovery, refer to Chapter 4.2.4.

280 For the detailed discussion of the hERG-receptor and its relevance to drug discovery, refer to Chapter 4.2.4.

<table>
<thead>
<tr>
<th></th>
<th>(\omega)</th>
<th>(\delta)</th>
<th>(\gamma)</th>
<th>(\beta)</th>
<th>(\alpha)</th>
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<tr>
<td><strong>gem-Me</strong></td>
<td>185</td>
<td>186</td>
<td>187</td>
<td>188</td>
<td>189</td>
</tr>
<tr>
<td><strong>Oxetane</strong></td>
<td>145</td>
<td>148</td>
<td>149</td>
<td>150</td>
<td>153</td>
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</table>

Many of the problems encountered in drug discovery cumulate in the scaffold shown in Scheme 49. It is highly lipophilic, poorly soluble and features different positions for metabolic attack. Additionally, the combination of a terminal basic amine and the lipophilic arylated chain should render the molecule amphiphilic and a substrate of the hERG-receptor. By that, this scaffold represents a group of molecules for which the integration of an oxetane might be considered. The respective oxetane derivatives would
highlight the ability of the oxetane to influence these properties depending on the structural context.

Scheme 50: Cyclic scaffolds for which oxetane, gem-dimethyl and carbonyl derivatives were prepared (indicated by the arrows).

The series of spirocyclic oxetanes shown in Scheme 50 was chosen to serve several purposes. A comparison of the oxetanes with the corresponding carbonyl compounds would give an indication as to whether the analogy on paper translates into similar physicochemical properties. Additionally, these spirocyclic oxetanes are related to morpholine 32. The piperonyl group was selected in order to facilitate the measurements that depend on UV-absorption for signal readout. In case their properties were promising, the spirocyclic oxetanes of this series could – contrary to the first linear scaffold – directly serve as building blocks themselves, easily attachable to real-life examples.

Table 7: Compilation of the physicochemical and biochemical properties measured.281

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>LogD[a] (LogP) [b]</th>
<th>Sol. [c]</th>
<th>Cl [d] (h/m)</th>
<th>pKa [e]</th>
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<tr>
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<td>9.5</td>
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<tr>
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<td>2100</td>
<td>5 / 190</td>
<td>-</td>
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</tbody>
</table>

281 Measurements performed at F. Hoffmann-La Roche, Basel by: Dr. Manfred Kansy, Pia Warga, Isabelle Parrilla, Dr. Stefanie Bendels, Dr. Holger Fischer, Frank Senner, Björn Wagner and Dr. Franz Schuler.
## Physicochemical and Pharmacological Profile of Oxetanes

<table>
<thead>
<tr>
<th>No.</th>
<th>LogD$^{[a]}$</th>
<th>Sol.$^{[c]}$</th>
<th>Cl$^{[d]}$ (h/m)</th>
<th>pKa$^{[e]}$</th>
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<td>-</td>
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<td></td>
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<tr>
<td>153</td>
<td>3.3 (3.6)</td>
<td>57</td>
<td>57 / 13</td>
<td>7.2</td>
</tr>
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</table>

R = piperonyl; $^{[a]}$ logarithmic n-octanol/water distribution coefficient at pH 7.4; $^{[b]}$ intrinsic lipophilicity of the neutral base, according to logP = logD + log($1+10^{(pK_{a}-pH)}$); $^{[c]}$ intrinsic solubility of the neutral base, obtained from the experimental thermodynamic solubility (µg/mL) in 50 mM phosphate buffer at pH 9.9 and 22.5 ± 1 °C, and corrected for pK$_{a}$; $^{[d]}$ intrinsic clearance rates in min$^{-1}$ mg$^{-1}$ µL measured in human (hCl int) and mouse (mCl int) liver microsomes; $^{[e]}$ amine basicity in H$_{2}$O measured spectrophotometrically at 24 °C; for details, see supplementary material; $^{[f]}$ data not determined due to insufficient stability of compound 205; $^{[g]}$ not determined due to insufficient UV-absorption.
Table 7 combines the properties of all compounds measured. A discussion of absolute numbers, however would not provide insight in whether the substitution of some functional group for an oxetane made sense. Therefore, in the following, pairs of values are compared and their implications for a given substitution discussed.

4.1 Measured Properties

The changes seen upon incorporation of an oxetane to the investigated scaffolds can largely be attributed to the polarity of the cyclic ether and its electron-withdrawing nature as a substituent. A very important role, however also plays the three-dimensional structure of oxetanes to support or reject the hypotheses drawn about structural analogies.

4.1.1 Structural Considerations

The Cambridge Structural Database (CSD) contains x-ray structures of 14 oxetanes solely substituted on the 3-position. This group however is structurally very homogeneous.

Scheme 51: Oxetanes registered in the Cambridge Structural Database (CSD).282

The disproportional occurrence of 212 as a structural motif reflects the ease with which those compounds are synthetically accessible.283 It was therefore necessary to obtain x-ray structures that would be more representative for the envisioned applications in drug discovery.

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283 See page 67 for their preparation.
Physicochemical and Pharmacological Profile of Oxetanes

Scheme 52: Compounds of which x-ray structures were prepared.\textsuperscript{284}

All these compounds, with the exception of 2,6-dioxaspiro[3.3]heptane (140) and sulfone 93 which were measured only to elucidate their reactivity, were bundled in a database that allows to perform statistical analyses in combination with the CSD.\textsuperscript{285} This helped to define more precisely the structure of the oxetanes that are subject of this study.

Diagram 8: Histogram showing the distribution of puckering angles.\textsuperscript{286}

\textsuperscript{284} X-ray structures were prepared by Dr. W. B. Schweizer (ETH Zürich) and André Alker (Roche).
\textsuperscript{285} The program \textit{Prequest} was used to combine x-ray structure files into a database that can then be read by the data retrieval program \textit{Conquest} which is used to search the CSD.
\textsuperscript{286} The data was retrieved from CSD and the database of oxetanes described in Ref. 285 using the programs \textit{Conquest} and \textit{Vista}. 
The introduction of substitution at the 3-position increases eclipsing interactions with the adjacent methylene groups. Therefore, the oxetane ring is puckered in many of these structures. The average (7.9°) as well as the highest (21°) puckering angle in this sample are still much smaller than in cyclobutane (35°). This low propensity for puckering is important, as the structural analogy to carbonyl and gem-dimethyl groups fits best for planar oxetanes.

![Averaged structural parameters of 3-substituted oxetanes](image)

*Picture 11: Averaged structural parameters of 3-substituted oxetanes.*

A more detailed analysis reveals the effect, the steric bulk of an oxetane has on the conformational preferences of its substituents. Shown in Diagram 9 is the change in conformation that occurs when a methylene group is replaced with an oxetane in the substructure \( R-CH_2-CH_2-R' \) (\( R, R' \neq H \)).

![Diagram 9: The introduction of an oxetane leads to a preferred gauche relationship of \( R \) and \( R' \).](image)

*Diagram 9: The introduction of an oxetane leads to a preferred gauche relationship of \( R \) and \( R' \).*

---

2-oxa-6-azaspiro[3.3]heptanes 216 and 126 were excluded for the determination of the exocyclic bond angles as the spirocyclic ring system limits this angle to ~87°.
For R–CH$_2$–CH$_2$–R’ the antiperiplanar arrangement of R and R’ forms an energetic minimum (τ = 0°). In the oxetane case, this conformation is rarely found; instead the synclinal arrangement (τ ≈ 120°) dominates. In most of the surveyed structures R consists at least of a monosubstituted methylene group which has a steric demand similar to the methylene groups of an oxetane. Therefore one could expect equal distribution between the antiperiplanar and the synclinal conformations. In contrast, Diagram 9 shows only two examples where the antiperiplanar conformation is realized. This is likely a result of the small oxetane-C-C-C bond angle (~ 84°) that leads to a concentration of steric bulk between the two methylene groups of the oxetane. Hence, the antiperiplanar conformation is disfavored. In the x-ray structure of piperidine 30, this effect forces the piperonyl substituent into the axial position.

Equation 13: Axial orientation of the piperonyl substituent in piperidine 30 in the protonated state (left, NMR) and in the free base (right, x-ray).

Determination of the conformation of protonated piperidine 30 in aqueous solution by NMR confirms this result, showing only signals of the axial conformer. In the protonated state, the piperonyl group is significantly shielded due to its axial orientation. This effect is not observed in the free base form, where the steric demand of the piperonyl group is minimized.

---

289 Derived from the combined data base of 3-substituted oxetanes for the substructure R–CH$_2$–CH$\ddot{\text{e}}$–R’, R, R’≠H.

290 It might be expected that H-C-H bond angle in oxetanes is widened, as seen for the 3-position in case it carries substituents. This would lead to higher steric demand of the oxetane in the direction of R’. The H-C-H bond angles found however do not deviate significantly from what is expected for a H-C(sp$^3$)-H center. This is also the case for the subset of structures, where the position of hydrogens is determined from the electron density distribution and not calculated with a force field method.

291 Antiperiplanar conformations are found in 3,3-bis(methylnitraminomethyl)oxetane (DUMPAC, C. George, R. Gilardi, Acta Crystallogr., Sect. C: Cryst. Struct. Commun. 1986, 42, 1161.) and in aminooxetane 215 (see Picture 12 top right for a pictorial representation). In DUMPAC the almost planar methylnitraminomethyl substituent seems to be able to orient itself in a way to avoid steric interactions with the oxetane ring. For aminooxetane 215 potential double-gauche pentane interactions with the sterically demanding branched N,N-dimethylamino substituent R seem to be the reason why the methylene group is forced into the antiperiplanar orientation.

292 Based on these results one would predict that ring closures leading to spirocyclic oxetanes are faster than for their gem-dimethyl analogues.

293 2D-NOSY experiment done by Dr. Josef Schneider (Roche, Basel). See Experimental for details.
nated state, partial cancellation of the dipole moments also helps to stabilize the axial conformation which in turn has implications on pKₐ.

![Diagram of hydrogen bonding and dipolar interactions of oxetanes](image)

**Picture 12**: Examples for hydrogen bonding (top left and bottom row) and dipolar (top row) interactions of oxetanes.²⁹⁴

The ability of the oxetane to act as a hydrogen bond acceptor and to donate electron density is reflected in several x-ray structures. The examples in Picture 12 highlight how accessible the oxygen is for hydrogen bonding and dipolar interactions. In the top left example, the oxetane even accommodates two ligands. Another example for a dipolar interaction of an oxetane with a nitro group was found in the x-ray structure of compound 215 (top right) in which the oxetane orients itself almost perpendicularly to the plane of the nitro group at a N-O distance of 2.82 Å.

For 3-substituted oxetanes, ring puckering is small in most cases, despite the increased eclipsing interactions. The presence of an oxetane in a molecule has profound conse-

quences for its conformation. Alkyl chains usually reside in an all-anti conformation, steric repulsion disfavoring the gauche orientation. Upon integration of an oxetane, functionalities beta to it prefer to be gauche, the anti conformer being rarely observed in x-ray structures. This gauche-directing effect differentiates an oxetane from a gem-dimethyl group which leads to approximately equal population of anti and gauche. Also found in x-ray structures are hydrogen bonds to oxetanes, documenting the availability of the oxygen lone pairs to donate electron density and participate in dipolar interactions.

4.1.2 Acid Dissociation Constant $pK_a$

Ionized molecules are more soluble in water than neutral ones. Because aqueous solubility is critical for oral bioavailability, most drugs contain ionizable groups. Electrostatic attraction of ionized functionalities is also an important contributor to target binding.

$\text{Diagram 10: Most drugs contain ionizable functionalities.}^{295}$

The extent to which a compound is ionized in solution is measured by the $pK_a$. It is defined as the negative decadic logarithm of the heterolytic dissociation constant.

$$ HA \leftrightarrow H^+ + A^- \quad K_a = \frac{[H^+] \cdot [A^-]}{[HA]} \quad pK_a = -\log (K_a) $$

$\text{Equation 14: Definition of } pK_a$

Consequently, strong acids have a low $pK_a$ and are more ionized at a given pH. Strong bases have a high $pK_a$, as their conjugate acids are weak. Although high solubility is desir-

---

able and correlated with ionization, ionized compounds have difficulties permeating through lipid-bilayer membranes.\textsuperscript{296} Therefore it is often necessary to fine-tune pK\textsubscript{a} in order to balance solubility and permeability.

The electron-withdrawing nature of the oxetane can be used to temper the basicity of a proximal amine. The decrease in pK\textsubscript{a} depends on the topological distance between the two. Diagram 11 shows how the introduction of an oxetane changes the basicity of an amine.

\begin{center}
\includegraphics[width=0.5\textwidth]{Diagram11.png}
\end{center}

\textit{Diagram 11: Change in pK\textsubscript{a} depending on the distance to an oxetane.}\textsuperscript{297}

There are several discrepancies between the numbers for open chain and cyclic compounds. It can be argued that in the cyclic cases, the amine experiences the electron-withdrawing effect of the oxetane via two substituents. One would expect that the effect of the oxetane on the pK\textsubscript{a} of the cyclic amines should be stronger than in the open chain case. Moreover, \textit{ceteris paribus} the effect should become more pronounced with decreasing ring size, as for the second substituent the distance between oxetane and amine becomes smaller. This would account for the piperidine case in which the oxetane is positioned gamma to the amine and where ΔpK\textsubscript{a} is approximately twice as big as in the open chain case.

For the β-case however, the opposite trend is found. The shifts for the cyclic systems are consistently smaller than in the open chain and decrease from piperidine to azetidines.

\textsuperscript{296} Low membrane permeability does not only affect permeation through cell membranes, but also hampers intestinal uptake and thus reduces oral bioavailability.

\textsuperscript{297} Difference of pK\textsubscript{a} between the unsubstituted scaffold and the one that contains an oxetane.
Whereas in the open chain and also in the 6-membered ring staggered conformations dominate, in smaller rings eclipsing interactions become prevalent (Picture 13).

In a related study, it was found that the fluorine-induced pKₐ shifts are much smaller in pyrrolidines than in piperidines. This was explained on the basis of the conformational dependence of pKₐ-shifts and the different conformational preferences in cyclic systems. The authors state that more experiments are necessary to elucidate the origin of these results. It seems likely that in the oxetane case the same effects are responsible for the decreased pKₐ-shifts.

In case where the oxetane is located alpha to the amine, a marked decrease in basicity is found for pyrrolidine 29 and azetidine 28. As shown in Equation 13, the piperonyl substituent adopts an axial conformation owing to the steric requirements of the bulky oxetane unit. This steric congestion is alleviated partially in the five- and four-membered rings as a result of the increased spatial separation between vicinal groups.

---

298 Compared to what were to be expected based on the pKₐ-shifts in the open chain, the extent to which this calculated decrease is realised is in piperidine 27 77%, in pyrrolidine 26 62% and in azetidine 24 39% of the theoretical value. Theoretical values were calculated by adding the appropriate pKₐ-shifts of the open chain, e.g. for piperidine 27: ΔpKₐ(8) + ΔpKₐ(6).

299 Piperidine 27 was optimized using ChemBio3D 11 (Gamess-Plugin, AM1). The structure of azetidine 126 was determined by x-ray crystallography (benzhydryl group omitted for clarity).

This is reflected in the different conformational preference of pyrrolidine 29. Upon protonation, a conformation would result in which the dipole moments of the oxetane and the protonated nitrogen are partially aligned. This energetic cost renders the pyrrolidine 29 and azetidine 28 less basic than the piperidine, in which the proton resides in equatorial position and the dipole moments cancel each other out partially (Equation 13).  

4.1.3 Lipophilicity

The lipophilicity of a compound has a major impact on its aqueous solubility, absorption and metabolic stability. The lipophilicity is defined as the affinity of a molecule for a lipophilic environment. It was traditionally measured by determining the partitioning of a compound between octan-1-ol and aqueous buffer. The resulting partition coefficient then is used to define the numeric representations of lipophilicity, LogP and LogD.

\[
\text{LogD} = \log \left( \frac{[HB^+]_{\text{Oct}} + [B]_{\text{Oct}}}{[B]_{aq} + [HB^+]_{aq}} \right)
\]

\[
\text{LogP} = \log \left( \frac{[B]_{\text{Oct}}}{[B]_{aq}} \right)
\]

Equation 15: Definition of LogD and LogP as logarithmic partition coefficients for a basic compound.

301 NMR-analysis of the protonated pyrrolidine 29 didn’t give a clear picture as to what the preferred conformation is. This is probably due to the high conformational flexibility of five-membered rings.
303 The definition for an acid is analogous. The concentration of ionized compound [HB]_{Oct} in the octanol layer is small in many cases.
LogD and LogP are not identical, unless the compound is not ionized at the pH of the measurement. The LogD-value is dependent on the pKₐ of the compound and the pH of the medium, as the concentration of charged molecules is part of the definition of LogD.

\[
\text{LogP} = \text{LogD} + \log \left(1 + 10^{(pK_a-pH)}\right)
\]

*Equation 16: Correlation of LogP and LogD.*

The presence of an oxetane influences both, the lipophilicity of a scaffold as well as the pKₐ of a proximal amine. Therefore, it makes sense to treat both effects independently and look at the change in LogP to assess the influence of the oxetane on lipophilicity.

*Diagram 12: Change in lipophilicity upon integration of an oxetane.*

The exchange of a methylene group for an oxetane results for all molecules tested in a reduction of LogP. Therefore the polarity of the oxetane oxygen overcompensates the lipophilicity of the two additional methylene groups. The extent of this effect depends on
the topological distance between the oxetane and the amine. Additionally, an oscillation is seen in the open chain case, with the effect of the oxetane being less pronounced in the beta and the delta case. Whereas it is not clear what the origin of the oscillative lipophilicity in the open chain case is, the decrease in lipophilicity for compounds with separated polar groups can be attributed to several factors. As each polar group builds up its own hydration sphere through hydrogen bonding or electrostatic interactions, the vicinity of two polar groups leads to an overlap of hydration spheres and thus to less solvation. Through the close proximity of two polar groups, both act as electron-withdrawing groups on each other. That means the oxetanes reduces the electron density on the amine (as evidenced by its influence on the pKa), but also the amine acts as an electron-withdrawing group on the oxetane and makes the oxygen less prone to act as an electron donor.304

The oxetane leads overall to a reduction in LogP of the underlying scaffold, even when replacing a methylene group. Changes in LogD merely reflect the different pKa values of the compounds measured. They show however that the replacement of a methylene group far away from a basic center has the highest impact on LogD. These observations have consequences for the aqueous solubility of oxetanes, as this property is closely related to lipophilicity.

4.1.4 Aqueous Solubility

Aqueous solubility is one of the most important properties in medicinal chemistry. Low solubility of a compound usually leads to low absorption and low oral bioavailability. During lead optimization, solubility problems can intensify, as lipophilic groups are often added to the scaffold of a lead compound scaffold to improve target binding.305 For this study, the thermodynamic solubility of the respective compound was measured in an aqueous buffer at pH 9.9. At this pH almost no protonation of the basic centers occurs, so the solubility measured is not influenced by changes in pKa of the respective amine or the formation of micelles.

304 Electron density that is withdrawn from one group ends up on the other and vice versa. So overall there is no net loss of electron density, rather a reduced gain, as proximity of two polar groups makes them share the same pool of electron-donating (alkyl) groups.
Diagram 13: Factor by which aqueous solubility at pH 9.9 increases upon replacement of a methylene group with an oxetane.

Diagram 13 highlights how strong the influence of an oxetane can be on the solubility of a compound, if the underlying scaffold is highly lipophilic as in case of the linear chain. There, compounds with an oxetane instead of a methylene group are between 25 to 4,000 times more soluble.

For the series of spirocyclic oxetanes, the factors by which solubility increases are less pronounced, probably because the scaffold itself is more polar. But still, some of the oxetane derivatives show impressive gains in solubility. Remarkable in this respect is the azetidine 24 with the oxetane in β-position. Its solubility of 24,000 μg/mL almost reaches the limit of what can be measured reliably. This compound probably benefits from the concurrence of two factors:

1. The partially eclipsed conformation of the azetidine ring insulates the basic amine from the electron-withdrawing effect of the oxetane and vice versa. This is evidenced also by the unexpectedly low pKₐ shift the oxetane induces in this structure (see Diagram 11).

2. As the two substituents of the oxetane ring are tethered together to form the spirocyclic azetidine, the oxetane oxygen atom becomes sterically more accessible for solvation.

This might explain the significant solubility difference to the α-oxetanyl compound 28, the only compound that was found to be less soluble than its methylene counterpart.
In this molecule, the amine, being alpha to the oxetane, experiences the strong electron-withdrawing effect of the oxetane, manifested in its pKₐ shift of 3.3 units. Additionally, the steric bulk of the oxetane might shield the amine lone pair from solvation and reduce pyramidality of the amine in order to avoid eclipsing interactions between the piperonyl residue and the oxetane.

The replacement of a methylene group with an oxetane leads in almost all cases to a significant increase in solubility. If the underlying scaffold is apolar, this effect can be dramatic. Therefore, compounds with very low solubility seem to benefit most from the integration of an oxetane.

4.1.5 Metabolic Stability

Many promising lead scaffolds do not reach the clinical phase because of their metabolic instability. Several biological pathways are subsumed under the term metabolic degradation. Apart from enzymatic hydrolysis reactions that can happen in the gut or in the blood plasma, two distinct types of chemical modifications that can occur to a molecule in the body are to be differentiated.

Phase I metabolism modifies a molecule either oxidatively or reductively. Oxidations are often conferred by the cytochrome P450 family of enzymes (CYPs). Isoforms of this family are ubiquitous in the body and found in high abundance in liver hepatocytes. CYPs contain heme-bound iron in their active site and transfer an oxygen atom onto their substrates.³⁰⁶

\[ \text{R}^-\text{H} + \text{O}_2 + \text{NADPH} + \text{H}^+ \xrightarrow{\text{CYP450}} \text{R}^-\text{OH} + \text{NADP}^+ + \text{H}_2\text{O} \]

*Equation 17: NADPH- and oxygen-dependent oxidation of substrates by CYP450 enzymes.*

Over 400 isozymes are known in the CYP family, differing in their substrate specificities. In general, site and rate of metabolism is determined by the affinity of a compound to the given enzyme and the reactivity of the positions brought in close proximity of the

active site. Main purpose of oxidative metabolism is to make molecules more water soluble for excretion. Therefore, these enzymes have an evolutionary preference for lipophilic molecules. This correlation is also found for the oxetane-containing compounds measured in this study.

![Diagram 14: Correlation of LogD and hCl_int for the oxetanes in this study.](image)

Phase II metabolism covalently attaches a polar group such as glucuronic acid or sulfate to a scaffold. The greatly reduced lipophilicity of the resulting conjugates facilitates their elimination from the body.

All the compounds tested for this study were subjected to preparations of human, rat or mouse liver microsomes and the remaining material determined after 2 h of incubation. This test measures phase I metabolism and yields a decay constant. Its number indicates how many microliters of the 2 μM substrate solution are completely cleared from the substrate per minute and per mg metabolizing enzyme present.

The decay constants of the oxetane-containing compounds can be compared with the unsubstituted case and reveal that placing an oxetane in the vicinity of an amine decreases metabolic stability. The reason for this might be the reduced basicity of the amine and thus the increased LogD at pH 7.4 where the assay is carried out.

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Diagram 15: Change in intrinsic clearance upon exchange of a methylene group with an oxetane.

When placed further away, however the electron-withdrawing effect of the oxetane is not felt by the amine, so that a net reduction of metabolic degradation is seen. For compound 148, where the oxetane resides delta to the amine, this leads to complete silencing of metabolic degradation in human. The same trend is visible in the mouse. Due to the more aggressive enzymes in mice, differences between the compounds become more pronounced.

Metabolic liability is dependent upon the molecular environment and thus cannot be quantitatively transferred to other structural contexts. This is particularly relevant when considering incorporation into drug candidates by N-acylation or sulfonylation. There, a proximal oxetane might benefit amides, as these are not basic and thus the polar nature of the oxetane could outweigh its inductive effect.
4.1.6 Chemical Stability

Their proclivity to undergo acid-catalyzed ring opening reactions was one of the major concerns for the practical use of oxetanes. It was questionable whether they would be stable at low pH. Therefore, their chemical stability was measured at pH 1, 4, 6, 8 and 10. After 2 h at 37 °C, the amount of unchanged compound was determined. A compound is classified as „chemically unstable“ if less than 90% can be recovered. All oxetanes but one were found to be stable at every pH studied. Only the sterically less shielded 3-monosubstituted oxetane 81 was not stable at pH 1, although 83% could be recovered.

These results show that the concerns regarding chemical stability under biologically relevant conditions seem to be unfounded at least for 3,3-disubstituted oxetanes. Seemingly, double substitution at the 3-position shields the oxetane from nucleophilic attack, even in a strongly acidic media.

The presence of an oxetane changes the physicochemical properties of the underlying scaffold in many ways. When compared with a methylene group, in most cases, the oxetane effects a decrease in intrinsic lipophilicity and often a dramatic increase in aqueous solubility. Attention should be paid to the structural context. The strong electron-withdrawing nature of the oxetane not only tempers the pKₐ of vicinal amines, but also seems to increase oxidative metabolic degradation when positioned alpha or beta to the amine. Especially however when applied in apolar environments, the resulting oxetanes are found to be metabolically much more stable than the original methylene compound. In these contexts – for example when replacing other sterically demanding functionality – an oxetane could be very beneficial.

4.2 Oxetanes as gem-dimethyl Analogues

Considering an oxetane for the replacement of a gem-dimethyl group, one would expect the conformational changes to be small. At the same time, the improvements in solubility, lipophilicity and metabolic stability need to be documented for the different structural environments.
4.2.1 Structural Considerations

The van der Waals volume of an oxetane is approximately the same as a gem-dimethyl group. The partial molar volumes of propane and oxetane in water are similar as well.\(^\text{309}\) The x-ray structure of spirocycle 217 allows a side-by-side comparison of the oxetane and the gem-dimethyl moiety.

![Diagram](image-url)

*Picture 15: Structure of spirocycle 217 (left), overlay of the oxetane and the gem-dimethyl portion from different perspectives (right).*

The overlay of oxetane and gem-dimethyl substructures highlights the similarity of the two. This superimposition also reveals that as a result of the decreased C–C–C bond angle, the methylene groups of the oxetane are closer together than the corresponding methyl residues of the gem-dimethyl group. Consequently, steric bulk in the oxetane is more concentrated and by virtue of the oxygen atom expanded further out.

The different spatial distribution of steric bulk has implications for the preferred conformations of oxetanes in comparison with gem-dimethyl groups. As shown in Diagram 16, a substituent \( R' \) beta to the oxetane strongly favors an arrangement synclinal to the second substituent \( R \) of the oxetane avoiding the antiperiplanar conformation. In case of a gem-dimethyl group however, the antiperiplanar and the two synclinal conformations are almost equally populated.

Diagram 16: Arrangements of \(CH_2-R'\) relative to an oxetane or a gem-dimethyl.\(^{310}\)

Whereas antiperiplanar conformations are favored in an unsubstituted chain, a chain becomes more flexible upon integration of a gem-dimethyl group by the equal population of synclinal and antiperiplanar conformations. In case of the oxetane, the energies of the different arrangements seem to be different, and the preferred conformation switches from antiperiplanar to synclinal. If the oxetane resides in the middle of an alkyl chain it thereby introduces a kink into this chain.\(^{311}\)

### 4.2.2 Aqueous Solubility and Lipophilicity

As a gem-dimethyl group is more lipophilic than a methylene group, its introduction usually leads to decreased aqueous solubility. As shown in Diagram 13, aqueous solubility goes up when a methylene group is replaced with an oxetane. Therefore the direct comparison of oxetanes with their gem-dimethyl counterparts should show an even more pronounced increase in solubility.

\(^{310}\) Derived from CSD version 5.29a and a combined data base (see Refs. 285, 286) of 3-substituted oxetanes for the substructure \(\text{CH}_3R'\), \(R, R' \neq H\).

\(^{311}\) The respective substituents on the \(\text{CH}_2\)-groups alpha to the oxetane will seek to avoid double gauche pentane interactions with each other and thereby both assume the respective (+)- or (-)-synclinal arrangement relative to the oxetane.
Diagram 17: Increase in solubility when replacing a gem-dimethyl group with an oxetane.

The replacement of a gem-dimethyl group with an oxetane leads to a pronounced improvement in aqueous solubility for all the compounds studied. The increase spans from a factor of 3.7 for the oxetane alpha to an azetidine (28) to a factor of 4100 of the oxetane gamma to an acyclic amine (149). The median factor by which solubility goes up is 51. As expected, this is also reflected in a strong reduction of lipophilicity.

Diagram 18: Change in lipophilicity LogP upon replacement of a gem-dimethyl group with an oxetane.\(^{312}\)

\(^{312}\) The UV-absorption of the gem-dimethyl compounds in the open chain was not sufficient to determine their lipophilicities. Instead the lipophilicity of the compound with the methylene group was used for this
As seen in Diagram 12, the decrease in lipophilicity seems to become more pronounced with increasing distance between the oxetane and the amine. Overall, the oxetane performs very well as a substitute for a gem-dimethyl group in terms of solubility and lipophilicity.

4.2.3 Metabolic stability

Higher aqueous solubility and the decrease in lipophilicity should make the oxetane derivatives less prone to metabolic oxidation than their gem-dimethyl counterparts. Oxetanes in the vicinity of a basic amine are expected to lead to a decrease in LogD and the polarity of the amine because of their electron-withdrawing effect.

Diagram 19: Change in the rate of metabolic degradation upon replacement of a gem-dimethyl group with an oxetane. *(gem-dimethyl compound was completely degraded in assay)*

This turns the value displayed into a lower boundary for the change in lipophilicity. As the replacement of a methylene group usually results in an increase of lipophilicity by 1 Log unit, shifts calculated on that basis are also shown in the diagram.
Although the exchange of a gem-dimethyl group alpha to an amine with an oxetane is predicted to improve solubility and intrinsic lipophilicity, it often reduces metabolic stability. Thus, the replacement of a gem-dimethyl group alpha to an amine with an oxetane in many cases leads to higher metabolic clearance. Almost all cases where the oxetane is positioned further away, however show significantly reduced metabolic liability.\textsuperscript{313}

4.2.4 hERG-Channel

The human Ether-a-go-go Related Gene (hERG) is a gene that encodes for a potassium ion channel that is expressed mainly in heart muscle cells. Compounds that block this channel can lead to a prolongation of the QT-interval in the electrocardiogram (ECG).\textsuperscript{314} This can together with other risk factors cause life-threatening torsades de pointes (TdP) arrhythmia.\textsuperscript{315}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{normal_prolonged_TdP.png}
\caption{Normal ECG (left), an ECG showing a prolonged QT-interval (middle) and an ECG of torsades de pointes arrhythmia (right).\textsuperscript{316}}
\end{figure}

Drug candidates that block the hERG channel require large clinical trials with many patients to demonstrate their safety, as arrhythmia caused by hERG channel blockage is a rare event. Therefore screening for hERG blockage has become part of the discovery phase to avoid the high costs for proving the safety of a compound which has a potential hERG liability. Upon elucidation of the connection between hERG and torsades de pointes

\begin{footnotesize}
\begin{enumerate}
\item In the case of the beta-substituted azetidine, the gem-dimethyl compound shows no metabolic degradation. The oxetane is not significantly faster degraded with a clearance rate of \(3 \text{ min}^{-1}\text{mg}^{-1}\mu\text{L.}\)
\item Taken from Ref. 314 with permission.
\end{enumerate}
\end{footnotesize}
arrhythmia, hERG blocking has become one of the leading causes for market withdrawal or use restrictions imposed by the FDA.\textsuperscript{317}

![Figure 15: Drugs that were withdrawn or experienced major labeling restrictions due to hERG blocking.](image)

TdP arrhythmia has been reported to occur in about 1 patient in 50,000 for the antihistamine terfenadine.\textsuperscript{318} Many compounds that interact with the hERG channel share structural features such as a basic amine (pK\textsubscript{a} > 7.3), high lipophilicity (LogP > 3.7), the absence of negatively ionizable groups or the absence of oxygen hydrogen bond acceptors.\textsuperscript{319}

The open chain model system shares all these features and should therefore show some hERG binding. As an oxetane can reduce lipophilicity of the underlying scaffold and introduces a hydrogen bond acceptor, the introduction of an oxetane could lead to reduced hERG liability.


\textsuperscript{319} see Ref. 317 and Ref. 315
As shown in Picture 17, the introduction of an oxetane leads to a marked decrease in affinity to the hERG channel. The introduction of the polar oxetane in the lipophilic part of the molecule and its ability to accept hydrogen bonds might be the cause for this observation. Therefore, an oxetane might serve as a tool to reduce hERG-liability.

4.2.5 Amphiphilicity and Phospholipidosis

Molecules that combine a large nonpolar residue with a highly hydrophilic, often charged tail are termed amphiphilic. Cationic amphiphilic drugs can induce the accumulation of phospholipids in lysosomes; an event that has been connected to cell toxicity. Different mechanisms have been proposed to account for this effect. A recent study found a strong correlation between the ability of a compound to induce phospholipidosis and the strength of the compound–phospholipid interaction. The association of compound and phospholipids would then prevent their metabolic degradation and lead to their enrichment within the membrane. The amphiphilicity of a given compound can be correlated to the ability of a compound to support micelle formation and its influence on surface tension.

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320 Measurement was performed at F. Hoffmann-La Roche, Basel by Dr. Liudmila Polonchuk.
321 As the testing of compounds for hERG binding is expensive, this pair of compounds was the only one studied. Therefore, general conclusions should not be drawn from this result.
324 For a detailed description, refer to: H. Fischer, M. Kansi, D. Bur, Chimia 2000, 54, 640.
ΔΔG_{amph} = ΔG_{awi-w} - ΔG_{mc-w}

Equation 18: ΔΔG_{amph} as a measure for amphiphilicity and its calculation from ΔG_{awi-w} (free energy needed to transfer the compound from the aqueous solution to the air-water interface) and ΔG_{mc-w} (free energy needed to transfer the compound from the aqueous solution to micelles).324

A compound carries a liability towards phospholipidosis if its ΔΔG_{amph} is smaller than -6 kJ/mol and has a pK_a greater than 7. The amphiphilic properties of amine 34 were one of the reasons, why its scaffold was chosen initially for the investigation of oxetanes.

![Diagram](image)

pK_a 9.9 9.2 9.9
ΔΔG_{amph} -8.3 kJ/mol -7.7 kJ/mol -3.2 kJ/mol
amphillic amphillic not amphillic

Picture 18: Introduction of an oxetane in the lipophilic part of the molecule reduces ΔΔG_{amph} below the critical threshold.325

Whereas amine 185 is highly amphiphilic, ΔΔG_{amph} of oxetane 145 is above the critical threshold and thereby not amphiphilic. This compound therefore also does not carry a liability to induce phospholipidosis. An oxetane as in oxetane 149, however that is located away from the lipophilic core does not improve ΔΔG_{amph} significantly. These results indicate again that the oxetane can be an alternative to a gem-dimethyl group especially when dealing with very lipophilic scaffolds.

Taken together, the data suggests that the oxetane moiety can be used as an isosteric, less lipophilic, more soluble and metabolically more stable surrogate for a gem-dimethyl group. Moreover, in the isolated cases tested, the oxetane was also able to address specific problems such as hERG-binding and amphiphilicity. The oxetane is predestined to introduce steric bulk and polarity to lipophilic environments, a combination other sterically demanding alkyl or cycloalkyl functionalities do not offer.

325 Measurement was performed at F. Hoffmann-La Roche, Basel by Dr. Holger Fischer.
4.3 Oxetanes as Carbonyl Analogues

The presence of a carbonyl group has fundamental consequences for the structure, the physicochemical properties, and the reactivity of a molecule. Two characteristics are responsible for this; a polar oxygen that can accept hydrogen bonds and the ability of the C=O double bond to be conjugated with neighboring π-systems and absorb electron density from them. The question is whether the oxetane, featuring a polar oxygen but not supporting conjugation, can fill this role.

4.3.1 Structural Considerations

The analogy of an oxetane with a gem-dimethyl group draws on a very close structural resemblance, where an oxetane is viewed as a ‚bridged‘ gem-dimethyl group. The introduction of the oxygen only serves the purpose of making the molecule as a whole more polar. For the carbonyl analogy, the roles are inverted. The structural analogy is represented solely by the oxygen atom, its polarity and location in space. The methylene groups only hold the oxygen in place and supplant the double bond in that function.

One has to separate two effects when considering the structural changes the replacement of a carbonyl with an oxetane confers. One is the immediate surroundings, in which the oxetane places the oxygen further away from the chain than a carbonyl and where it adds steric bulk by virtue of its two methylene groups. The other pertains to the different influence an oxetane and a carbonyl have on the conformation and relative arrangement of their substituents.

An oxetane is sterically more demanding than a carbonyl by virtue of its additional methylene groups. In oxetanes, beta substituents should therefore be directed away from the oxetane. In case of carbonyl compounds however, beta substituents reside in plane with the carbonyl reflecting its smaller steric demand.
Diagram 20: Arrangements of CH₂–R’ relative to an oxetane or a carbonyl.326

The distribution of conformations found in the crystal structure confirms this, showing a very strong preference for R’ to reside in plane with the carbonyl. In the crystal structures documented for oxetanes however, R’ is pushed towards R, the other substituent on the oxetane.

Diagram 21: Rotative arrangement of a phenyl ring with respect to a carbonyl and oxetane 213.327

326 Derived from CSD version 5.29a and a combined data base (see Refs. 285, 286) of 3-substituted oxetanes for the substructure , R, R’ ≠ H.

327 Derived from CSD version 5.29a substructure search with R ≠ H and excluding compounds in which the carbonyl is part of a ring.
The stabilizing interaction of a carbonyl group with other π-systems like phenyl groups leads to a planarization (Diagram 21) which is not observed in the corresponding oxetane 213. Similarly, the conformation of amides differs significantly from the one found in the oxetane analogue 215. Almost all x-ray structures of N,N-dimethylamides registered in CSD feature planar arrangements of carbonyl and amine portions.\textsuperscript{328}

\textbf{Diagram 22: Conformational preference for rotation around an amide bond and what is found in oxetane analogue 215.}\textsuperscript{329}

In aminooxetane 215 however, the torsional angle C–N–C–O amounts to 116° and the amine is pyramidalized with an angle of 29°. A similar conformation will likely be observed in other cases of 3-aminooxetanes. These examples highlight that the conformational aspects of a carbonyl with its attendant substituents and an oxetane have to be cautiously examined. This is particularly evident in cases where the replacement of the carbonyl group by an oxetane unit eliminates the π-conjugation in the former and may result in substantially non-planar arrangements in the latter.

\subsection*{4.3.2 Influence on pK\textsubscript{a}}

A carbonyl group and an oxetane both lower the pK\textsubscript{a} of a proximal amine. The change in pK\textsubscript{a} upon replacement of a carbonyl group with an oxetane for different environments highlights similarities and differences in their electron-withdrawing effects.

\textsuperscript{328} Nonplanar amides have been made and shown to be very unstable when not protonated (K. Tani, B. M. Stoltz, \textit{Nature} 2006, 441, 731.).

\textsuperscript{329} Derived from CSD version 5.29a, substructure search. While the amide is planar, the amine in the oxetane analogue shows pyramidalization of 29°, allowing the C–N–C–O torsion to exceed 90°.
Diagram 23: Change in pKₐ upon replacement of a carbonyl group with an oxetane. *shown is the pKₐ of the oxetane; **Azetidin-3-one 205 was not sufficiently stable to be purified and measured.

Diagram 23 shows that the reduction of pKₐ by an oxetane is smaller in all cases than by the corresponding carbonyl compound. The difference between the two is biggest for the comparison of amides and 3-aminooxetanes, where in case of the amide the electron pair is in conjugation with the carbonyl group and not available for protonation. While 3-aminooxetanes lack a π-system and therefore still retain some basicity, they are only protonated to a small extent with a pKₐ of 7 or less at physiological pH. In case of beta or gamma substitution, the replacement of a carbonyl group with an oxetane leads to a similar pKₐ.

4.3.3 Lipophilicity and Aqueous Solubility

One of the most important differences from a lipophilicity point of view between an oxetane and a carbonyl are the additional methylene groups present in the oxetane. This explains why the intrinsic lipophilicity logP goes up upon replacement of a carbonyl group with an oxetane.

330 Protonation of amides typically occurs on the oxygen, so a direct comparison is not possible. Protonated aliphatic amides, however typically have a pKₐ between -1 and 0 (H. M. Grant, P. Mctigue, D. G. Ward, Aust. J. Chem. 1983, 36, 2211.), so the value shown is a lower boundary for the pKₐ-change to be expected when replacing an amide with an aminooxetane.
Physicochemical and Pharmacological Profile of Oxetanes

Diagram 24: Change in LogP and LogD upon replacement of a carbonyl group with an oxetane. *Azetidin-3-one 205 was not sufficiently stable to be purified and measured.

The same trend is seen for LogD, where 3-piperidone 208 is found to be slightly less lipophilic than its oxetane counterpart. Interestingly, both measures of lipophilicity show that in β-position the increase in lipophilicity is strongest as a result of the very low lipophilicities of the β-amine ketones measured.331

Diagram 25: Change in solubility upon replacement of a carbonyl group with an oxetane. * Azetidin-3-one 205 was not sufficiently stable to be purified and measured.

The same general trend is seen when looking at aqueous solubilities. The change in lipophilicity however is not fully translated into solubility, probably because of the differ-

331 In these, lipophilicities are on average 1 log unit lower than the corresponding amides or 3-piperidone 208. The reason for this decrease in lipophilicity is not clear, but maybe under the conditions of the assay partial hydration of these electron-poor ketones occurs, leading to a more polar hydrate or tautomerization giving the corresponding enaminols.
ent melting points and therefore different crystal lattice energies. Several polyaromatic compounds have high crystal lattice energies, because of highly planar conformations and the resulting stabilizing stacking effects. Here the replacement of an aromatic ketone, amide or ester with the corresponding oxetane would lead to nonplanar conformations and therefore could, despite higher lipophilicity, result in improved solubilities.

4.3.4 Metabolic and Chemical Stability

Oxetanes measured in this study display dramatically higher metabolic stabilities than their ketone counterparts. This is because these beta or gamma amino ketones show very high clearance in both human and mouse liver microsomes.

\[ \log(S) = 0.8 - \log(P) - 0.01(m_p - 25) \]

Higher melting points lead to lower solubility, because the crystal lattice energy that has to be spent for solubilization increases with the melting point.

Diagram 26: Change in rate of metabolic degradation upon replacement of a carbonyl group with an oxetane. * Azetidin-3-one 205 was not sufficiently stable to be purified and measured.

Yalkowsky and Banerjee (S. Yalkowsky, S. Banerjee, Aqueous solubility: Methods of estimation for organic compounds. 1992 New York, NY: Marcel Dekker) developed an empiric formula for the prediction of the solubility S of a compound from its LogP and melting point \(m_p\): \(\log(S) = 0.8 - \log(P) - 0.01(m_p - 25)\) Higher melting points lead to lower solubility, because the crystal lattice energy that has to be spent for solubilization increases with the melting point.
Oxetane analogues of lactams showed slightly higher metabolic clearance rates. Interestingly, the strained β-lactam 209 displays little metabolism in human, but is degraded very quickly in mouse liver microsomes. Although none of the carbonyl compounds in this study shows decomposition upon exposure to buffers of different pH at 37 °C for 2 h, both β-amino ketones tend to decompose into insoluble products upon storage in the refrigerator.\footnote{At ambient temperature, decomposition occurs in less than one day.}

The replacement of a carbonyl group with an oxetane can lead to significant changes in the conformational preference, basicity, lipophilicity and metabolic stability of the underlying scaffold. The introduction of an oxetane in place of a carbonyl group seems to be attractive in situations where the carbonyl compound shows chemical or metabolic instability, undesirable reactivity or when a nonplanar conformation is desired.

### 4.4 Spirocyclic Oxetanes as Morpholine Analogues

A gem-dimethyl group can be replaced by an oxetane because of its similar steric demand. The oxygen and its polarity are the cause for the improvements seen in many physicochemical properties, but do not contribute to the structural analogy. When a carbonyl group is replaced by an oxetane, the similar placement of its polar oxygen provides the rationale behind this transformation. The methylene groups help to position the oxygen correctly and replace the C=O double bond, but they do not contribute to the structural analogy themselves and are responsible for many of the differences seen between the properties of oxetanes and their carbonyl counterparts.

The analogy drawn between this group of spirocyclic oxetanes and morpholine aims at making use of both of the characteristics of oxetanes, polarity and steric demand. Important for this purpose is to what extent oxetanes are able to meet the high standard of morpholine as a solubilizing group without displaying its metabolic liability. In cases where morpholine contributes to the binding energy, structural aspects come into play as well.
The analogues in Picture 19 comprise a subset of spiro-oxetanes which position the oxygen atom in the molecular symmetry plane at an extended distance from the nitrogen atom (24, 25) with similar or decreased lateral bulk (24). Others (25–30) place the oxygen at a reclined angle from the symmetry plane of the parent morpholine, resulting in a reduction of symmetry without introducing chirality.

### 4.4.1 Structural Considerations

Morpholine has one very important function in drug discovery and that is to make compounds more water soluble and less lipophilic. Therefore, in many instances structural similarity between morpholine and a surrogate is not of major importance, because the morpholine does not contribute to target binding, but merely serves as an anchor for solvation. Especially in cases however, where the morpholine is rigidly linked to the respective scaffold, for example as an amide or aniline, it might interact with the target.

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Then the diverse structures of the spirocycles shown in Picture 19 could serve as a toolbox for building blocks with different steric demand and dipole orientation.

### 4.4.2 Influence on $pK_a$

All oxetanes studied are more basic than morpholine with the exception of those compounds where the amine is alpha to the oxetane. This correlates well with the increasing number of bonds that separate the amine from the electron-withdrawing oxygen.

![Diagram 27: Change in $pK_a$ upon replacement of morpholine 32 with an oxetane.](image)

In pyrrolidine 29 and azetidine 28, the amine is separated from the oxygen by two carbon atoms, as in morpholine. Still, these compounds are significantly less basic while the corresponding piperidine shows the same $pK_a$ as morpholine. This discrepancy is rooted in different conformations these compounds adopt in the protonated state.\(^{335}\) The slightly increased $pK_a$ of tetracycle 31 seems to indicate that the small ring size of an oxetane does not increase the inductive effect of the oxygen.

### 4.4.3 Solubility and Lipophilicity

The change in intrinsic lipophilicity LogP correlates very well with the different number of methylene groups between morpholine and the respective spirocycle, ranking piperidines before pyrrolidines and azetidines. Additionally, as seen before, accumulation of polar groups within close distance leads to an increase in LogP.\(^{336}\)

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\(^{335}\) See chapter 4.1.2 for detailed treatment.

\(^{336}\) See chapter 4.1.3 and footnote 304 for detailed treatment.
Physicochemical and Pharmacological Profile of Oxetanes

Diagram 28: Change in lipophilicity upon replacement of morpholine 32 with an oxetane.

For LogD, pKₐ becomes a third factor, favoring the more basic amines of the oxetanes positioned beta or gamma to the nitrogen. By virtue of its two polar atoms, the morpholine unit has a big influence on the solubility of the scaffold it is attached to. Consequently, the piperonyl morpholine has the highest solubility (8,000 μg/mL) of all compounds measured in this study that do not contain an oxetane.

Diagram 29: Change in aqueous solubility at pH 9.9 upon replacement of morpholine 32 with an oxetane.

When morpholine 32 is compared with its spirocyclic analogues, it is found to be more than twice as soluble. There is one exception however, the substituted 2-oxa-6-azaspiro[3.3]heptane 24. It has a solubility of 24,000 μg/mL which is three times higher than morpholine 32.337

337 It is not clear which the closely related pyrrolidine 26 which has similar lipophilicity and only one methylene group more possesses less than 3% of the solubility of azetidine 24. Both compounds are oils at room temperature, so different melting points should not play a role (see ref. 332).
Several arguments help explain why this spirocyclic oxetane has this prominent position. Both its LogP and LogD are substantially lower than that of morpholine 32. Additionally, its lipophilic parts are concentrated around the central quaternary carbon while both its oxygen and nitrogen are exposed to the solvent.

### 4.4.4 Metabolic stability

Morpholine 32 shows only small internal clearance both in human and in mouse liver microsomes which is probably a result of its high solubility and low lipophilicity. Still, metabolic liability is reduced in the most polar spirocyclic oxetanes.

*Diagram 30: Change in internal clearance upon replacement of morpholine with a spirocyclic oxetane.*

Pyrrolidine 26 and 2-oxa-6-azaspiro[3.3]heptane 24 are almost not metabolized. The more lipophilic piperidines and oxetanes alpha to the amine show higher, but still low internal clearance. These results together with its ease of preparation make compound 24 a very promising candidate for replacing morpholine as a solubilizing group.
4.5 Applications

Oxetanes have been applied to several projects within and outside of Roche. Most of the applications have not been published, making it difficult to quantify the impact oxetanes had so far on medicinal chemistry.338

Diagram 31: Number of compounds that contain a 3-substituted oxetane within the global Roche database.339

While it is not possible to detail on individual compounds or for which projects these were made, the number of oxetanes in the global Roche database shown in Diagram 31 provides an overview. The first paper340 together with presentations in front of Roche chemists led to a surge of requests by mail concerning oxetane chemistry and registration


339 Private communication from Dr. Mark Rogers-Evans.

of the resulting compounds in the database. The second paper\textsuperscript{341} might foster this trend, as it provides routes to compounds that can be directly used as building blocks.

It is difficult to estimate how often the oxetane chemistry has been applied so far outside of Roche, but there is evidence for its use in several companies. Requests by outsourcing companies for experimental details in the preparation of oxetan-3-one can serve as an indication as well as the commercial availability of oxetan-3-one through several companies after the publication of the first paper.\textsuperscript{342}

*Picture 20: Companies that have shown interest in and/or applied the oxetane chemistry in projects.*\textsuperscript{343}

Oxetanes have also been applied by Anna Hirsch from the group of Prof. Diederich in the design of inhibitors of 4-diphosphocytidyl-2C-methyl-D-erythritol kinase (IspE), an enzyme of central importance to the isoprenoid biosynthesis via the non-mevalonate pathway in human pathogens such as *Plasmodium falciparum* or *Mycobacterium tuberculosis*.\textsuperscript{344}


\textsuperscript{342} Oxetan-3-one is now commercially available through MolBridge, Research Support International Ltd. and Parkway Scientific.

\textsuperscript{343} Collected from e-mail requests of scientists of the respective companies. Bayer, Novartis, Genentech, Syngenta and Schering-Plough confirmed upon inquiry the application of oxetanes. No replies to these requests were obtained from GSK and Dompé. A recent publication by Evotec specifically deals with the preparation of 3-Aryloxetanes for their use in medicinal chemistry by coupling of arylboronic acids with 3-iodo oxetane (M. A. J. Duncon, 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).

Physicochemical and Pharmacological Profile of Oxetanes

Picture 21: Oxetane 219 cocrystallized with Aquifex aeolicus IspE

The authors state that the oxetane was used to improve solubility and it was found to be “particularly successful” in that respect among the compounds investigated. Picture 21 shows a crystal structure of oxetane 219 bound to IspE.

No solubility data is provided. Oxetane 219 was made by conjugate addition of the amine corresponding to 219 to acrylate 89. For a detailed procedure, see ref. 344.
5 Conclusion and Outlook

In this work we established the utility of oxetanes to medicinal chemistry. We could demonstrate that based on oxetan-3-one as a central building block, a broad spectrum of oxetanes can be prepared from it. A central role for that plays a class of Michael acceptors to which a variety of nucleophiles can be added. The oxetanes obtained are amenable to further functionalization and were used to prepare the members of two prototypic series of compounds on which the property changes imparted by the oxetane were studied.

We could show that oxetanes can be used to introduce steric bulk without increasing lipophilicity and thereby can replace the commonly found gem-dimethyl group. The versatility of oxetanes as a functional group was also demonstrated when they were related to carbonyl compounds. An oxetane can pose a real alternative, if the presence of a carbonyl group inflicts chemical or metabolic instability on a given scaffold. We could also show that some spirocyclic oxetanes can be used to substitute morpholine as a solubilizing group also as a structural motif.

Contrary to what was suspected before it could be shown that 3,3-disubstituted oxetanes are chemically relatively inert towards ring opening under various synthetically and physiologically relevant conditions. They are also often resistant to metabolic degradation and at the same time increase aqueous solubility when replacing a methylene or a gem-dimethyl group.

These findings have consequences not only for the development of new drugs, but might also be applied to compounds already on the market. Oxetane versions of existing drugs might not only have improved pharmacokinetic properties, but will also often not be covered by the original patent. Some of these are currently being investigated in our laboratories. This research will add examples for the application of established methodology, and will add substrate scope and consolidate the chemistry described in this work. But it will certainly also provide access to new classes of oxetanes.
The concepts developed in this work are not limited to oxetanes. Other heterocycles such as 3,3-disubstituted 1,1-dioxothietanes might prove to be even bulkier and more hydrophilic than oxetanes, posing yet another alternative to gem-dimethyl groups. Spiro[3.3]heptanes could also mimic other six-membered rings commonly encountered in medicinal chemistry such as tetrahydropyranes, piperazines, piperidines or cyclohexanes.

The feedback received for this work has demonstrated that there is a need for further exploration. A demand that can only be satisfied in close cooperation with a partner like Roche, able and willing to carry out the measurements and propagate their results.
6 Experimental Section

6.1 General Methods

All non-aqueous reactions were carried out using oven-dried or flame-dried glassware under a positive pressure of dry argon or nitrogen unless otherwise stated. Tetrahydrofuran, acetonitrile, toluene, diethylether and methylene chloride were dried by passage over two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; Macherey und Nagel; activated under a flow of nitrogen at 300 °C over night; solvent drying system) under an argon atmosphere (H₂O content < 30 ppm as determined by Karl-Fischer titration). Et₂O was distilled from a mixture of FeSO₄·7 H₂O and Na₂SO₄ prior to drying. Benzene was distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen. MeOH was distilled from magnesium turnings under an atmosphere of dry nitrogen. NEt₃, diisopropylamine and pyridine were distilled from potassium hydroxide under an atmosphere of dry nitrogen. Ethyldiisopropylamine (Hünig’s base) was distilled from sodium hydride under an atmosphere of dry nitrogen. Trimethylchlorosilane and BF₃·OEt₂ were distilled from calcium hydride prior to use. All chemicals were purchased from Acros, Aldrich, Fluka, Merck, Lancaster, ABCR or TCI and used as such unless otherwise stated. Deuterated solvents were obtained from Armar Chemicals, Döttingen, Switzerland in the indicated purity grade.

Reactions were magnetically stirred if not indicated otherwise and monitored by thin layer chromatography using Merck silica gel 60 F₂₅₄ TLC glass plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with ceric ammonium molybdate (CAM).

Chromatographic purification was performed as flash chromatography on Brunschwig silica 32-63, 60 Å using a forced flow of eluant at 0.3 bar. Technical grade solvents were employed, which were distilled prior to use. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified com-

pounds were further dried for 12 – 48 h under high vacuum (0.01 – 0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise.

**Melting points**: Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries and are uncorrected.

**NMR spectra**: NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for $^1$H and $^{13}$C acquisitions, respectively. Chemical shifts ($\delta$) are reported in ppm with the solvent resonance as the internal standard relative to chloroform ($\delta$ 7.26 ppm for $^1$H and 77.0 ppm for $^{13}$C). All $^{13}$C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constants in Hz, integration.

**IR spectra**: IR spectra were recorded on a Perkin Elmer Spectrum RX-I FT-IR as thin film. Absorptions are given in wavenumbers (cm$^{-1}$).

**Mass spectra**: Mass spectra were recorded by the MS service at ETH Zürich. EI-MS ($m/z$): EI-HIRES Micromass Autospel-ULTIMA spectrometer at 70 eV. ESI-MS ($m/z$): IONSPEC Ultima ESI-FT-ICR spectrometer at 4.7 T.

**Elemental analyses**: Elemental analyses were performed by the Mikrolabor der ETH Zürich.

**Chemical names**: generated with AutoNom 2.02 (Beilstein Informationssysteme GmbH) or ChemDraw Ultra 11.0 (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 µL of a 50 mM aqueous phosphate buffer and transferred to a standard 96-well plate at room temperature (22.5±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 con-
centrations were determined by calibrated HPLC. The calibrations were obtained by HPLC analysis of different concentrations of each compound in DMSO.

**Determination of lipophilicity (logD\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 logD 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 µL of a pure DMSO-solution of the compound, which is dispensed into, respectively, 38 or 171 µL 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 h at 23±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.

**High-throughput measurement of ionization constants (pK\text{a})**

**ProfilerSGA**

Ionization constants are determined at 23±1 °C by spectrophotometry using a ProfilerSGA 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 pK\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 \( pK_a \) values. In cases where the \( pK_a \) could not be measured with the ProfilerSGA system due to an insufficient UV absorption of the compound the \( pK_a \) values were measured by potentiometric titration (GLpKa). Internal validation studies (data not shown) proved that the difference between the \( pK_a \) values measured with both instruments were within the experimental error of the individual experiments.

**GLpKa**

\( pK_a \) values with low UV absorption were determined by potentiometric titration (SI-RIUS GLpKa Analyzer) in aqueous solution, containing 0.15 M KCl to adjust ionic strength. To measure \( pK_a \) of substances by the pH metric technique, a certain amount of sample was dissolved in the background electrolyte solution and acidified to pH 2 by addition of 0.5 M HCl. The solution was then titrated with standardized base (0.5 M KOH) to pH 12 at constant temperature (23°C) under an atmosphere of argon to minimize absorption of atmospheric CO₂. The \( pK_a \) values were then calculated by shape analysis of the titration curve in comparison to the blank titration curve.

**Determination of metabolic stability in liver microsomes**: Microsomal incubations were carried out in 96-well plates in 200 µL of liver microsome incubation medium containing potassium phosphate buffer (50 mM, pH 7.4), MgCl₂ (10 mM), EDTA (1 mM), NADP⁺ (2 mM), glucose-6-phosphate:2 H₂O (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 µM for up to 30 min at 37 °C under vortexing at 800 rpm. The reaction was stopped by transferring 30 µL incubation aliquots to 90 µL of ice-cold MeOH. 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 X Terra® 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.

**Determination of chemical stability in aqueous solutions:** The chemical stability of a given compound is determined in aqueous solutions at pH 1, 4, 6, 8, 10. Commercially available buffer systems from Merck KGaA, Darmstadt (Catalog numbers 109881, 109884, 109886, 109888, 109890) are used. An aqueous stock solution of 10 mM of each sample is prepared and diluted at a ratio of 1:20 (v/v) with buffer solution before they are shaken for 10 min at 37 °C. The solutions are then transferred to a filter plate (Millipore MSGVN2250, pore size 0.22 µm) and filtrated into V-bottom plates (from ABGene, AB-0800) that are heat-sealed prior to analysis by HPLC. Samples are taken at time points 0 h and 2 h and analyzed by HPLC. The percentage of recovered unchanged compound is determined by calibrated HPLC. A compound is classified as “chemically unstable” if after 2 h less than 90% of the initial concentration is detected.

**Measurement of amphiphilicity via the measurement of surface tension:** An aqueous solution of the compound of known concentration at the limit of its solubility is diluted 1:1 (v/v) with aqueous MOPS0 buffer 11 times in sequence. Samples of 5 µL of compound solution are taken at each dilution step and transferred to a 96-well plate containing 45 µL pure aqueous MOPS0 buffer in each well. This plate is then placed into a MULTI PI WS1 instrument of KIBRON Inc. The determination of amphiphilicity involves (i) the measurement of the surface tension of the compound solution at different concentrations based on the well known Du Nouy maximum pull force method, and (ii) the determination of the critical micelle concentration (CMC) which is obtained at the intersection of two experimental lines, the first being the correlation line of decreasing surface tension with increasing sample concentration, the second being the plateau line where the surface tension no longer changes with increasing sample concentration. All measurements are done at 22.5±1 °C. From the experimental data, the free energies of transfer from
aqueous solution to the air-water interface and from aqueous solution to micelles are obtained. The difference of free energies is taken as a measure of amphiphilicity.  

**Automated patch clamp procedure for the hERG current measurement at Patch-Xpress 7000A:** Electrophysiological recordings of $K^+$ currents ($I_{K_{hERG}}$) were conducted at room temperature (22-25 °C) using Aviva Bioscience SealChip™ (Molecular Devices Corporation, Cat SealChip™16). CHO cells stably expressing hERG $K^+$ channels (Roche Palo Alto, USA) were added by the integrated Cavro robot to each well of the sealchip. Cells were held at a resting voltage of $-80 \text{ mV}$ and they were stimulated by a voltage pattern to activate hERG channels and conduct outward $I_{K_{hERG}}$ current (Figure 1) at a stimulation frequency of 0.1 Hz (6 bpm). Cell health and membrane parameters (access resistance ($R_a$), membrane resistance ($R_m$) and membrane capacitance ($C_m$)) were monitored on-line. After the cells stabilized and the currents were steady, the amplitude and kinetics of $I_{K_{hERG}}$ were recorded under control conditions. Thereafter, the solution of the test compound in the extracellular buffer (NaCl 150 mM, KCl 4 mM, CaCl$_2$ 1.2 mM, MgCl$_2$ 1 mM, HEPES 10 mM, pH 7.4 with NaOH, 300-310 mOsm) was directly added by the robot to each well at increasing concentrations. Double addition of each compound concentration was performed at 1 min interval to ensure the full exchange of the solution in the well. Currents were monitored continuously during the exposure to compounds.

Offline analysis of the peak tail current was performed using DataXpress2 software (Molecular Devices Corporation, USA). The amplitude and kinetics of $I_{K_{hERG}}$ were recorded in each concentration of drug and they were compared to the control values (taken as 100%) to define fractional blocks. The hERG current was measured as the average current from 10 sweeps collected at the end of vehicle or compound addition. Data were expressed as mean±SEM. Concentration-response curves were fitted by non-linear regression analysis and the IC$_{50}$ values were reported.

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NMR spectroscopic analysis of N-piperonyl-piperidine 30

1) Oxetane 30

The free base is not sufficiently soluble in water for good NMR-spectroscopic analysis. $^1$H-NMR spectra in DMSO-$d_6$ and CDCl$_3$ show nearly the same chemical shifts and couplings. The signals for the methylene piperidine protons show typical averaged signal multiplets of protons due to fast ring/nitrogen inversion of the piperidine ring:

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 1.34 (m, 2 h, H-4) 1.48 (m, 2 h, H-5) 1.81 (t, $J = 6.2$ Hz, 2 h, H-3) 2.30 (t, $J = 5.5$ Hz, 2 h, H-6) 3.65 (s, 2 h, H-10) 4.23 (d, $J = 6.3$ Hz, 2 h, H-7'/9') 4.59 (d, $J = 6.3$ Hz, 2 h, H-7'/9') 5.98 (s, 2 H- H-18) 6.80 (dd, $J = 7.9$, 1.5 Hz, 1 h, H-16) 6.84 (d, $J = 7.9$ Hz, 1 h, H-18) 6.90 (d, $J = 1.5$ Hz, 1 h, H-12)

2) DCl salt of Oxetane 30

The DCl salt form of 30 was produced by dissolving 30 in a mixture of D$_2$O and DCl (0.4 mL D$_2$O and 0.1 mL 1 N DCl; pH = 1). Assignment of the signals was achieved on the basis of 2D $^1$H,$^1$H-COSY and 2D $^1$H,$^{13}$C-HSQC experiments.

By contrast to the free base, the $^1$H-NMR spectrum of the deuterated salt shows signals for diastereotopic methylene protons at 25 °C. Even the methylene protons of the

These spectra were taken and analyzed by Dr. Josef Schneider at F. Hoffmann-La Roche, Basel.
piperonyl O-CH$_2$-O group (C-18) at 6.04 ppm are split into a weak AB system. The benzylic protons (CH$_2$-10) at 4.39 ppm give rise to a pronounced AB system. The diastereotopic nature of these methylene protons arise from the chiral quaternary nitrogen center of the deuterated piperidine. All signals of the piperidine ring methylene groups are diasterotopic and show the typical coupling constants of a chair conformation of a six-membered ring. The signals of the axial protons at C-3, C-5 and C-6 were identified unambiguously on the basis of their multiplets (large diaxial h,H couplings and/or multiplet width).

\[
\begin{align*}
\text{Structure of deuterated oxetane 30 and stereochemical assignments of protons based on observed NOE's (green: NOE's identifying the oxetane protons; red: NOE's determining the axial orientation of the piperonyl group; red dotted: observed NOE's that do not allow a distinction between equatorial or axial position of the piperonyl group).}
\end{align*}
\]

$^1$H NMR (400 MHz, D$_2$O/DCl; $d_4$-TSP = 0 ppm) $\delta$ ppm 1.62 (m, 1 h, H-4ax) 1.68 (m, 1 h, H-5equiv) 1.84 (m, 1 h, H-4equiv) 2.00 (m, 1 h, H-5ax) 2.29 (dt, $J$ = 15.0, 4.3 Hz, 1 h, H-3equiv) 2.36 (td, $J$ = 15.0, 1.3 Hz, 1 h, H-3ax) 3.09 (ddd, $J$ = 13.7, 11.6, 3.5 Hz, 1 h, H-6ax) 3.14 (dt, $J$ = 13.7, 3.5 Hz, 1 h, H-6equiv) 4.39 (AB, 2 h, H-10) 4.54 (d, $J$ = 8.3 Hz, 1 h, H-7’’) 4.72 (d, $J$ = 8.1 Hz, 1 h, H-9’’) 4.88 (d, $J$ = 8.3 Hz, 1 h, H-7’) 5.01 (d, $J$ = 8.1 Hz, 1 h, H-9’) 6.04 (AB, 2 h, H-18) 6.97 (m, 1 h, H15) 7.05 (m, 2 h, H-12, H-16)
Assignments of the oxetane protons:

Based on HSQC experiments, the signals at 5.01, 4.88, 4.72, and 4.54 ppm can be assigned to the diastereotopic methylene protons of the oxetane moiety. The signal at 4.72 is assigned to one of the axial methylene oxetane protons, H-9”, based on the strong NOE to H-4ax and a significant NOE to H-3equiv. A strong NOE between H-6ax and the signal at 5.01 ppm defines H-9’. The proton H-7” (4.54 ppm) is determined by a significant NOE to H-3equiv.

Assignments of the spatial orientation of the piperonyl group:

The 2D-NOESY spectrum shows 4 cross peaks (cf. red arrows) for the benzylic protons (C-10). The two cross peaks between CH₂-10 and H-7’ and H-6eq are ambiguous (red dotted arrows) with respect to the stereochemistry. Both, axial or equatorial orientations of the piperonyl group are compatible with the occurrence of these NOE’s. The two other cross peaks are dipolar couplings between CH₂-10 and H-3ax and H-5ax respectively. These two NOE’s (cf. red solid arrows) determine unambiguously the axial orientation of the piperonyl group at the piperidine ring.

The observation of only one set of ¹H-signals in the NMR-spectrum of deuterated oxetane 30 with well separated and sharp signals for the equatorial and axial protons is clear evidence for the predominance of the chair conformation with an axial N-piperonyl substituent. Furthermore, the clear differentiation into axial and equatorial piperidine ring protons as well as the absence of NOE’s between the benzylic protons and H-6ax excludes
a rapid equilibrium at 25 °C between enantiomeric N-deuterated chair forms with the N-
piperonyl group axial via a sequence of rapid de-deuteration, ring- and N-inversion, and
re-deuteration processes.

6.2 Preparation of Oxetan-3-one

6.2.1 Preparation of Oxetan-3-one via 3,3-Dimethoxyoxetane

3,3-dimethoxyoxetane. To a mixture of dihydroxyacetone dimer (94.2 g, 0.522 mol,
1.00 equiv and trimethyl orthoformate (111 g, 1.05 mol, 2.00 equiv, Acros) in 1.5 L MeOH
(bottle, Fluka puriss., p.a. ACS, >99.8% (GC)) was added pTSA (377 mg, 1.98 mmol,
0.00375 equiv) at room temperature.

Picture 22: Clarification of mixture upon addition of pTSA. It is important that the solution
becomes clear. Undissolved material or turbidity indicates that the quality of the di-
hydroxyacetone dimer used is not good and problems might result in the following
step.
After stirring for 10 h, the reaction was quenched by addition of 20.7 g Ambersep 900 OH ion exchanger (not dried). After stirring for 15 min, the ion exchanger resin was filtered off and the filtrate concentrated in vacuo. The residual slightly yellow oil was dried under high vacuum for further 16 h to give crude dihydroxyacetone dimethylketal as a white solid which was used without further purification.  

*Picture 23: This is how the material should look like. It takes ~2 h at high vacuum, before crystallization starts. Shaking is important to spread the crystal mass across the inner surface of the flask. Usually the mass does not become fully crystalline, but ends up in a semisolid state like the one shown above.*

This material was dissolved in 1.5 L of a 2/1 mixture of THF (Acros, p.a.) and Et₂O (Fluka, puriss.) and cooled to 0 °C. A 2.5 M solution of nBuLi in hexanes (400 mL, 1.00 mol, 1.91 equiv, Acros) was added slowly over 45 min using a transfer cannula.
The solution of the dihydroxyacetone dimethyl ketal in THF should be clear. Upon addition of nBuLi, the lithium alkoxide precipitates.

After stirring for further 30 min, a solution of p-toluenesulfonyl chloride (151 g, 0.791 mol, 1.51 equiv, Acros 99+%) in 500 mL THF was added dropwise over 1 h.

During the addition of the solution of tosyl chloride, partial clarification will occur together with some darkening. If the addition is too fast and/or the time after the addition is too short, more of the undesired bistosylate will be formed.
After stirring for 40 min in the ice bath, the mixture was taken out of the ice bath and stirred for 1 h, before it was concentrated in vacuo (bath-temperature <35 °C) to a volume of approximately 500 mL and dissolved in 500 mL Et₂O.

Brine was added and the aqueous phase extracted with Et₂O (400 mL) twice. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo until all Et₂O was removed and the residue dissolved in THF to give 2.5 L of a clear slightly yellowish solution. This solution was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil, 45.0 g, 1.13 mol, 2.16 equiv) was added in small portions.

*Picture 26: The addition of the first portions of NaH results in vigorous H₂-evolution. The first 3 portions should be added very cautiously and not exceed 3 g.*

After stirring for 30 min at 0 °C, the mixture was heated to 50 °C over night. (Alternatively one can also stir at room temperature for 72 h.)
The mixture adopts the consistence of mud and should be shaken with ether remove it from the flask.

The viscous mass was diluted with 500 mL Et$_2$O and poured on ice. The aqueous phase was saturated with NaCl and extracted with Et$_2$O (400 mL) three times. The combined organic phases were dried over MgSO$_4$ for 20 min, filtered, concentrated in vacuo (bath temperature 30 °C, 150 mbar) and the residue distilled (20 mbar, b$_p$ = 40 °C) to give 47.96 g product (38.9%, calculated on the amount of dihydroxy acetone dimer used) as a clear colorless liquid together with 1.33 g THF (2.7w%). This material can be used without further purification.

The following procedure works well for the distillation. The residual THF is removed at ambient pressure with an oil-bath temperature of 83 °C. Vigorous stirring and the addition of boiling chips are important. When no more THF comes over, the pressure is slowly reduced to 150 mbar. When this pressure is reached, a middle fraction is taken in which the pressure is slowly reduced to 100 mbar. Once this pressure is reached, fractions are changed and the pressure further reduced to approximately 20 mbar while the temperature is raised to 93 °C. Never heat the mixture above 95 °C! Spontaneous and very vigorous decomposition has been observed at temperatures above 95 °C. It is advisable to immerse the flask in which the fraction is collected in an ice bath. When no more product comes over, the heating is removed before the vacuum. The residue of the distillation...
Experimental Section

consists mainly of bistosylate and mineral oil. The mineral oil can be decanted off and the bistosylate crystallized by stirring it with approximately 70 mL Et₂O over night.

\[ R_f = 0.41 \text{ (hexane/EtOAc 2:1).} \]  

\[ ^1H \text{ NMR } (300 \text{ MHz, CDCl}_3): \delta 4.55 (s, 4H), 3.21 (s, 6H); ^{13}C \text{ NMR } (75 \text{ MHz, CDCl}_3): \delta 100.6, 79.8, 49.4; \text{ IR (thin film) } \nu 2954, 2878, 2835, 1473, 1716, 1453, 1352, 1204, 1134, 1044, 980 \text{ cm}^{-1}; \text{ Anal. calcd for C}_9\text{H}_{10}\text{O}_3: C, 50.84; H, 8.53. \text{ Found: C, 51.07; H, 8.45; } \]

\[ \text{Oxetan-3-one: 3,3-dimethoxyoxetane (15.8 g, 0.134 mol) was dissolved in 7 L CH}_2\text{Cl}_2 \text{ (technical quality, distilled once via big rotovaper) and 99.1 g Montmorillonite K10 clay (Fluka) was added.} \]

![Picture 28: Two apparati for the refluxing step. Bumping will occur, but is usually no problem for the reaction.](image-url)
Experimental Section

The mixture was refluxed for 70 h, cooled to room temperature, filtered through a plug of celite and thoroughly washed with 3x 150 mL CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was removed from the filtrate by distillation employing a 30 cm Vigreux column to prevent product from distilling over.

The residue was transferred to a 500 mL flask and distilled under reduced pressure (b$_p$ = 49 °C, 117 mbar, bath temperature = 65 °C) to give 5.96 g (62% yield) product in 2 fractions. One containing 5.37 g product (~90% pure) being a clear slightly yellowish liquid, another containing 0.59 g product (30w%) together with CH$_2$Cl$_2$. The material should be stored in the freezer, where the neat compound solidifies (mp = ~–5 °C). Safety tests at Roche indicate that Oxetan-3-one should not be heated over 80 °C due to an exothermic
autocatalytic decomposition pathway. For longer processes (> 72 h) the maximum temperature was determined to be 60 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.40 (s, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$.199.74, 92.61

The proton NMR of oxetan-3-one found is identical with the one precedent in the literature.$^{117a}$

For the distillation (carried out with a 14 cm Vigreux-column-shortpath combination), the following procedure works well:

The material coming from the bulk distillation should not exceed 400 mL, as the separation with the Vigreux-column used is not perfect. Most of the residual CH$_2$Cl$_2$ is removed at ambient pressure with vigorous stirring and boiling chips added in an oil-bath of 62 °C. Once no more CH$_2$Cl$_2$ comes over, fractions are changed and the pressure is slowly lowered to 100 mbar. If this pressure is reached, fractions are changed again and the product is collected while reducing the pressure further to ~25 mbar and heating the oil-bath to 74 °C. The flask with which the material is collected should be immersed in an ice bath.

### 6.2.2 Preparation of Oxetan-3-one by Oxidation of Oxetan-3-ol

Phosphorous pentoxide (184.5 g, 1.300 moles, 1.300 equiv) was suspended in 600 mL CH$_2$Cl$_2$. Glassware need not be previously dried, the reaction is not air-sensitive. This suspension was cooled in an ice/salt-bath to a temperature below 0 °C, before DMSO (106 mL, 1.50 moles, 1.50 equiv) was added followed by oxetan-3-ol (45, 74.1 g, 1.00 moles, 1.00 equiv). The white dispersion was vigorously stirred and once the temperature inside reached −5 °C, the addition of NEt$_3$ was started (307 mL, 2.20 moles, 2.20 equiv).

The temperature should stay around 0 °C, but not exceed 5 °C. Usually the addition takes 3 h to 3.5 h. During the addition the mixture turned orange and became homogenous. After the addition is finished the mixture is stirred for 5 min, before 600 mL Et$_2$O are added. A phase separation occurred, the top phase containing the product.
The two phases should be stirred for approximately 5 min. The top phase was then filtered using vacuum (~700 mbar) through a plug of silica gel (h = 7 cm, d = 13 cm) of which the top 2 cm were wetted with Et₂O. The bottom phase of the reaction mixture was thoroughly washed with five times 100 mL of diethyl ether, becoming very viscous. These were then also filtered through the plug, resulting in a total volume of filtrate of approximately 1.5 L. The filtrate was then transferred to a flask equipped with a stir bar and boiling chips, and the solvent distilled off through a column filled with wire helices (joint 29, h 28 cm).

The temperature of the oil bath should not exceed 60 °C. Once no more solvent was coming over, the column was replaced with a short path distillation apparatus and stirring at ambient pressure was continued until no more solvent came over. Then fractions were changed with the receiving flask being cooled with ice, the temperature of the oil-bath was raised to 75 °C and at the same time the pressure was slowly reduced to 100 mbar (~2 min from ambient pressure to 180 mbars, ~30 seconds from 180 mbar to 100 mbar). Once this pressure was reached, fractions were changed and pure product came over with less than 2 w% CH₂Cl₂. The pressure was further lowered slowly to 30 mbar and the distillation stopped when no more product came over. The intermediate fraction and the main fraction together contained 34.77 g oxetan-3-one (48% yield). The oxetan-3-one should be stored in the freezer, where it solidifies.

6.3 Preparation of Michael Acceptors

Oxetan-3-ylidene-acetic acid ethyl ester: To a solution of oxetan-3-one (33, 0.22 g, 3.0 mmol, 1.0 equiv) in 6 mL dry CH₂Cl₂ was added Carboethoxymethylene triphenylphosphorane (1.2 g, 3.3 mmol, 1.1 equiv) at 0 °C. The solution was allowed to warm to room temperature and after stirring for 15 min filtered through silica gel (2/1 cyclohexane/EtOAc) to give 388 mg (89% yield) product (97 w% by NMR) as a colorless oil.
R_f = 0.33 (SiO_2, 2/1 cyclohexane/EtOAc); ^1H NMR (300 MHz, CDCl_3): δ 5.60 (m, 1H), 5.47 (m, 2H), 5.27 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz); ^13C NMR (75 MHz, CDCl_3): δ 165.4, 159.3, 111.3, 81.2, 78.6, 60.5, 14.4; IR (thin film) ν 2983, 2927, 2858, 1722, 1698, 1446, 1372, 1346, 1298, 1266, 1206, 1100, 1038, 961, 870, 833 cm^{-1}; Anal. calcd for C_7H_10O_3: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98.

Oxetan-3-ylidene-acetaldehyde: To a solution of oxetan-3-one (33, 441 mg, 6.12 mmol, 1.00 equiv) in 8 mL dry CH_2Cl_2 was added formylmethylene triphenylphosphorane (2.6 g, 8.6 mmol, 1.4 equiv) at room temperature. The solution was stirred overnight and filtered through silica gel (1/1 pentane/Et_2O) to give 537 mg product (~90 w% by NMR) as an orange oil (yield 81% assuming 90% purity).

R_f = 0.33 (SiO_2, 2/1 cyclohexane/EtOAc); ^1H NMR (300 MHz, CDCl_3): δ 9.52 (d, 1H, J = 5.8 Hz), 5.92 (m, 1H), 5.58 (m, 2H), 5.38 (m, 2H); ^13C NMR (75 MHz, CDCl_3): δ 188.6, 163.4, 119.8, 80.0, 79.7; IR (thin film) ν 2918, 2856, 2747, 1693, 1650, 1149, 962, 865 cm^{-1}; HRMS (El) calcd for C_5H_6O_2 [M]^+ 98.0368. Found: 98.0359

3-Nitromethylene-oxetane: To a solution of oxetan-3-one (33, 188 mg, 2.61 mmol, 1.00 equiv) in 3 mL nitro methane was added a catalytic amount of NEt_3 (6 drops) at room temperature. After stirring for 20 min, the mixture was concentrated in vacuo and the
residue dissolved in 10 mL dry CH₂Cl₂. The mixture was cooled to −78 °C, NEt₃ (1.6 mL, 12 mmol, 4.4 equiv) was added followed by dropwise addition of mesyl chloride (600 µL, 7.75 mmol, 3.00 equiv) over 10 min (pink color). After stirring for 20 min, the mixture was directly put on a column packed with silica gel and eluted with Et₂O/pentane = 1/1 to give 243 mg (81% yield) of product as a white solid (m_p = 41-43 °C).

R_f = 0.28 (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃): δ 6.92 (m, 1H), 5.66 (m, 2H), 5.38 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ 155.9, 130.0, 79.6, 75.5; IR (thin film) ν 3092, 2925, 2848, 1698, 1525, 1421, 1350, 1319, 1186, 1125, 960, 947, 904, 828, 777, 725 cm⁻¹; HRMS (EI) calcd for C₄H₅NO₃ [M-H]⁺ 114.0186. Found: 114.0184.

![1-Oxetan-3-ylidene-propan-2-one:](image)

1-Oxetan-3-ylidene-propan-2-one: To a solution of oxetan-3-one (33, 63 mg, 0.87 mmol, 1.0 equiv) in 8 mL dry CH₂Cl₂ was added acetylmethylene triphenylphosphorane (0.33 g, 1.0 mmol, 1.3 equiv) at room temperature. The solution was stirred over night and filtered through silica gel (4/1 to 2/1 pentane/Et₂O) to give 75 mg pure product as a colorless oil in 77% yield.

R_f = 0.16 (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃): δ 5.98 (m, 1H), 5.49 (m, 2H), 5.27 (m, 2H), 2.14 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ 196.4, 158.3, 118.0, 82.0, 78.9, 30.4; IR (thin film) ν 2923, 2855, 1724, 1709, 1694, 1672, 1651, 1431, 1366, 1198, 954 cm⁻¹; HRMS (EI) calcd for C₆H₈O₂ [M]⁺ 112.0524. Found: 112.0519.
1-[1-(4-Chloro-phenyl)-cyclobutyl]-2-oxetan-3-ylidene-ethanone: To a solution of ketophosphonate 220 (see page 211 for its preparation; 0.95 g, 3.0 mmol, 1.0 equiv) in 10 mL dry THF was added sodium hydride (60% dispersion in mineral oil, 0.12 g, 3.0 mmol, 1.0 equiv) at 0 °C. After stirring for 20 min, a solution of oxetan-3-one (33) (0.22 g, 3.0 mmol, 1.0 equiv) in 1 mL dry THF was added and the solution stirred at 0 °C for 30 min. The solvent was concentrated in vacuo partially, toluene was added and the mixture put on a column (SiO₂, 20/1 to 4/1 cyclohexane/EtOAc) to give 750 mg pure product (95% yield) as a colorless oil. The product is not stable at ambient temperature and rearranges to (5-(1-(4-chlorophenyl)cyclobutyl)furan-3-yl)methanol.

R_f = 0.48 (SiO₂, 2/1 cyclohexane/EtOAc); ^1H NMR (300 MHz, CDCl₃): δ 7.32 (d, 2H, J = 8.6 Hz), 7.14 (d, 2H, J = 8.6 Hz), 5.88 (p, 1H, J = 2.3 Hz), 5.55 (m, 2H), 5.22 (m, 2H), 2.74 (m, 2H), 2.38 (m, 2H), 1.90 (m, 2H); ^13C NMR (75 MHz, CDCl₃): δ 197.7, 160.3, 141.0, 132.7, 128.8, 127.6, 113.5, 82.4, 79.0, 57.6, 30.3, 15.9; IR (thin film) ν 2926, 2852, 2360, 1706, 1649, 1492, 1351, 1180, 1093, 1013, 953 cm⁻¹; HRMS (EI) calcd for C₁₅H₁₅ClO₂ [M]^⁺ 262.0756. Found: 262.0752

3-Benzenesulfonylmethylene-oxetane: To a solution methylphenylsulfone (5.0 g, 32 mmol, 1.0 equiv) in 150 mL dry THF was added nBuLi (2.5 M in hexanes, 28 mL, 71 mmol, 2.2 equiv) at 0 °C over the course of 10 min. After stirring for 30 min, chlorodiethylphosphonate (5.6 mL, 38 mmol, 1.2 equiv) was added dropwise and stirring was continued for 30 min, before the mixture was cooled to −78 °C and oxetan-3-one (33, 3.25 g, 351 Procedure adapted from: A. D. Briggs, R. F. W. Jackson, P. A. Brown, J. Chem. Soc. Perkin Trans. 1 1998, 4097.

351
45.1 mmol, 1.41 equiv) was added as a solution in 5 mL dry Et₂O. After stirring for 1.5 h, the mixture was filtered through a plug of silica gel to give 5.08 g pure product (76% yield) as a colorless solid (mp = 51-53 °C).

\[ R_f = 0.25 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 7.88 \text{ (d, 2H, } J = 7.8 \text{ Hz), 7.66 (m, 1H), 7.57 (t, 2H, } J = 7.3 \text{ Hz), 6.12 (m, 1H), 5.64 (m, 2H), 5.28 (m, 2H); } ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 156.2, 140.6, 133.7, 129.3, 127.2, 119.9, 79.6, 77.9; \text{ IR (thin film) } \nu 3057, 2923, 2856, 1692, 1445, 1324, 1303, 1147, 1085, 960, 872, 821, 755 \text{ cm}^{-1}; \text{ HRMS (EI) calcd for C}_{10}\text{H}_{10}\text{O}_3\text{S} [\text{M}]^+ 210.0351. \text{ Found: 210.0345}\]

**Oxetan-3-ylidene-acetonitrile:** To a solution of oxetan-3-one (33, 0.21 g, 3.0 mmol, 1.0 equiv) in 10 mL dry CH₂Cl₂ ways added cyanomethylenetriphenylphosphonium ylide (0.90 g, 3.0 mmol, 1.0 equiv) at room temperature. After stirring for 6 h, the solvent was partially concentrated *in vacuo* and the mixture filtered through a plug of silica gel (2/1 to 1/1 pentane/Et₂O) to give 235 mg pure product (82% yield) as slightly yellow crystals (mp = 56-58 °C).

\[ R_f = 0.30 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 5.39 \text{ (m, 2H), 5.30 (m, 2H), 5.25 (td, 1H, } J = 2.5 \text{ Hz, } J = 5.0 \text{ Hz}; } ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 163.3, 114.0, 90.8, 78.6, 78.4; \text{ IR (thin film) } \nu 3065, 3015, 3940, 2220, 1696, 1445, 1328, 1219, 943 \text{ cm}^{-1}; \text{ HRMS (EI) calcd for C}_{5}\text{H}_{5}\text{NO} [\text{M}]^+ 95.0371. \text{ Found: 95.0365}\]
**Diethyl oxetan-3-ylidenemethylphosphonate:** To a suspension of sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol, 1.0 equiv) in 30 mL dry THF was added a solution of tetraethyl methylenediphosphonate (5.0 mL, 20 mmol, 1.0 equiv) in 10 mL dry THF dropwise at room temperature. After stirring for 5 min, a solution of oxetan-3-one (33, 1.4 g, 20 mmol, 1.0 equiv) in 5 mL dry THF was added slowly. After stirring for 2 h, the solvent was partially concentrated *in vacuo*, Et₂O and water were added and the aqueous phase extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO₂, cyclohexane to remove mineral oil then elute with EtOAc) to give 2.77 g pure product (67% yield) as a colorless oil.

R_f = 0.16 (SiO₂, 2/1 cyclohexane/EtOAc); \(^1^H\) NMR (300 MHz, CDCl₃): δ 5.49 – 5.35 (m, 3H), 5.29 – 5.21 (m, 2H), 4.14 – 3.97 (m, 4H), 1.37 – 1.26 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ 161.1, 106.9 (d, J = 189.3 Hz), 80.8 (d, J = 10.0 Hz), 79.5 (d, J = 27.6 Hz), 61.7 (d, J = 5.5 Hz), 16.3; \(^{31}\)P NMR (121 MHz, CDCl₃): δ 15.8; IR (thin film) ν 3466, 2985, 1699, 1480, 1444, 1393, 1317, 1221, 1164, 1026, 871, 770 cm\(^{-1}\); HRMS (El) calcd for C₈H₁₅O₄P [M-H]\(^+\) = 205.0625. Found: 205.0624

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6.4 Preparation of Oxetanes of the Open-Chain Scaffold

[4-(4-Bromo-phenyl)-butyl]-dimethyl-amine: To a suspension of the hydrobromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide\(^{353}\) (12.2 g, 24.0 mmol, 1.00 equiv) in 150 mL dry THF was added \(^{6}\)BuLi (1.6 M in hexanes, 17 mL, 43 mmol, 1.8 equiv) at 0 °C. After stirring for 40 min at 0 °C, a solution of \(p\)-bromobenzaldehyde (5.3 g, 29 mmol, 1.2 equiv) in 15 mL dry THF was added slowly. The mixture was stirred at 60 °C over night, cooled to 0 °C; water was added, followed by concentrated aqueous HCl. The clear yellowish solution was freed from THF by evaporation and washed twice with 50 mL toluene. The aqueous phase was extracted five times with 40 mL chloroform. The combined chloroform phases were dried over MgSO\(_4\), concentrated in vacuo and the residue dissolved in 100 mL MeOH. After addition of 540 mg Rh/C (5 w%), hydrogen was bubbled through the solution for 45 min and the mixture vigorously stirred for 19 h. The mixture was filtered through a pad of celite, the filtrate concentrated in vacuo and the residue taken up in 25 mL water. Et\(_2\)O (50 mL) was added, followed by excess sodium hydroxide (with cooling) to free the amine. The aqueous phase was extracted three times with Et\(_2\)O, the combined organic phases were dried over MgSO\(_4\), filtered, the filtrate concentrated in vacuo and the residue distilled (bp 98 °C at 0.5 mm) to give 5.15 g (84% yield) pure product as a colorless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.38 (d, 2H, \(J = 8.4\) Hz), 7.05 (d, 2H, \(J = 8.3\) Hz), 2.63 (m, 2H), 2.27 (m, 2H), 2.21 (s, 6H), 1.55 (m, 4H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 141.3, 131.2, 130.1, 119.3, 59.6, 45.6, 35.3, 29.2, 27.4; IR (thin film) \(\nu\) 2937, 2858, 2818, 2762, 1488, 1462, 1072, 1011 cm\(^{-1}\); HRMS (EI) calcd for C\(_{12}\)H\(_{18}\)BrN [M]+, 255.0613. Found, 255.0614.

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3-[4-(4-Dimethylamino-butyl)-phenyl]-oxetan-3-ol: To a solution of [4-(4-Bromophenyl)-butyl]-dimethyl-amine (221, 0.89 g, 3.5 mmol, 1.3 equiv.) in 10 mL dry THF was added a solution of nBuLi (2.5 M in hexanes, 1.4 mL, 3.5 mmol, 1.3 equiv) at –78 °C. After stirring for 10 min, a solution of oxetan-3-one (193 mg, 2.68 mmol, 1.0 equiv.) in 4 mL dry THF was added dropwise. The mixture was stirred for 10 min, before it was allowed to warm to room temperature. Water was added and the aqueous phase extracted three times with EtOAc. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂; 10% to 40% MeOH in CH₂Cl₂, 0.1% NEt₃) to give 480 mg pure product (71% yield) as a viscous colorless oil which solidified upon cooling (mp=57-58 °C).

Rᵣ = 0.17 (SiO₂, 40% MeOH in CH₂Cl₂, 0.1% NEt₃); ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.2 Hz), 4.92 (d, 2H, J = 6.9 Hz), 4.89 (d, 2H, J = 6.9 Hz), 2.65 (m, 2H), 2.26 (m, 2H), 2.20 (s, 6H), 1.56 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 142.1, 139.9, 128.5, 124.4, 85.5, 75.5, 59.6, 45.4, 35.4, 29.3, 27.3; IR (thin film) ν 3373, 2940, 2859, 2780, 1467, 1175, 981 cm⁻¹; Anal. calcd for C₁₅H₂₃NO₂: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.13; H, 9.30; N, 5.54; HRMS (EI) calcd for C₁₅H₂₃NO₂ [M]+, 249.1729. Found, 249.1723

Dimethyl-[4-(4-oxetan-3-yl-phenyl)-butyl]-amine: To a solution of tertiary alcohol 70 (135 mg, 0.54 mmol, 1.00 equiv) in 8 mL dry Et₂O was added NaH (60% dispersion in mineral oil, 45 mg, 1.1 mmol, 2.1 equiv) at 0 °C. After stirring for 1 h at room temperature, pTosCl (0.14 g, 0.71 mmol, 1.3 equiv.) was added at 0 °C. After stirring for 1 h at 0 °C, the
mixture was cooled to −78 °C and a solution of lithium aluminum hydride (1.0 mL, 4.0 mmol, 7.4 equiv, 4.0 M solution in Et₂O) was added slowly. After stirring for 1 h, the reaction was quenched at this temperature by dropwise addition of 2 M aqueous NaOH. The aqueous phase was extracted three times with Et₂O. The combined organic phases were washed once with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al₂O₃; 20/1 to 1/1 cyclohexane/EtOAc) to give 73 mg (58% yield) pure product as a colorless oil.

\[
R_f = 0.44 \text{ (Al}_2\text{O}_3, 2/1 \text{ cyclohexane/EtOAc)}; \quad ^1\text{H NMR (300 MHz, CDCl}_3): \delta 7.30 (d, 2H, J = 8.1 Hz), 7.18 (d, 2H, J = 8.0 Hz), 5.05 (dd, 2H, J = 8.4 Hz), 4.77 (dd, 2H, J = 6.1 Hz, J = 6.7 Hz), 4.20 (m, 1H), 2.63 (m, 2H), 2.26 (m, 2H), 2.20 (s, 6H), 1.63 (m, 2H), 1.50 (m, 2H); \quad ^{13}\text{C NMR (75 MHz, CDCl}_3): \delta 141.2, 138.7, 128.7, 126.6, 79.1, 59.8, 45.7, 40.1, 35.5, 29.4, 27.6; \quad \text{IR (thin film) } \nu 2937, 2868, 2813, 2763, 1515, 1463, 983 \text{ cm}^{-1}; \quad \text{Anal. calcd for } \text{C}_{15}\text{H}_{23}\text{NO: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98; HRMS (EI) calcd for } \text{C}_{15}\text{H}_{23}\text{NO [M]}^+, 233.1775. \quad \text{Found, 233.1776.}
\]

[4-[4-(3-Fluoro-oxetan-3-yl)-phenyl]-butyl]-dimethyl-amine: To a solution of tertiary alcohol 70 (135 mg, 0.54 mmol, 1.00 equiv) in 8 mL dry CH₂Cl₂ was added DAST (86 μL, 0.65 mmol, 1.2 equiv) at −78 °C. The mixture was allowed to warm to 0 °C over 2 h and quenched by adding 1 M aqueous NaOH at −5 °C. The aqueous phase was extracted three times with Et₂O. The combined organic phases were washed once with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al₂O₃; 20/1 to 1/1 cyclohexane/EtOAc) to give 54 mg (40% yield) pure product as a colorless oil.
Experimental Section

\[ R_f = 0.43 \ (\text{Al}_2\text{O}_3, \ 2/1 \ \text{cyclohexane/EtOAc}) \]

\[^1\text{H} \ \text{NMR} \ (300 \ \text{MHz, CDCl}_3): \ \delta \ 7.44 \ (d, \ 2\text{H}, \ J = 8.0 \ \text{Hz}), \ 7.25 \ (d, \ 2\text{H}, \ J = 8.0 \ \text{Hz}), \ 5.08 \ (\text{ddd}, \ 2\text{H}, \ J = 1.1 \ \text{Hz}, \ J = 7.8 \ \text{Hz}, \ J = 21.2 \ \text{Hz}), \ 4.88 \ (\text{ddd}, \ 2\text{H}, \ J = 1.1 \ \text{Hz}, \ J = 7.8 \ \text{Hz}, \ J = 21.5 \ \text{Hz}), \ 2.65 \ (t, \ 2\text{H}, \ J = 7.5 \ \text{Hz}), \ 2.26 \ (m, \ 2\text{H}), \ 2.20 \ (s, \ 6\text{H}), \ 1.64 \ (m, \ 2\text{H}), \ 1.49 \ (m, \ 2\text{H}); \ ^{13}\text{C} \ \text{NMR} \ (75 \ \text{MHz, CDCl}_3): \ \delta \ 143.0, \ 135.6 \ (d, \ J = 23.8 \ \text{Hz}), \ 128.6, \ 124.0 \ (d, \ J = 8.2 \ \text{Hz}), \ 83.2 \ (d, \ J = 25.5 \ \text{Hz}), \ 95.2 \ (d, \ J = 206.3 \ \text{Hz}), \ 59.72, \ 45.64, \ 35.6, \ 29.30, \ 27.5; \ ^{19}\text{F} \ \text{NMR} (282 \ \text{MHz, CDCl}_3): \ \delta \ 147.8; \ \text{IR} \ (\text{thin film}) \ \nu \ 1940, \ 2858, \ 2814, \ 2764, \ 1518, \ 1460, \ 1299, \ 1174, \ 982, \ 820 \ \text{cm}^{-1}; \ \text{Anal. calcd for } C_{15}H_{22}FNO: \ C, \ 71.68; \ H, \ 8.82; \ N, \ 5.57. \ \text{Found: } C, \ 71.44; \ H, \ 8.93; \ N, \ 5.77; \ \text{HRMS (EI) calcd for } C_{15}H_{22}FNO [M]^+: \ 251.1680. \ \text{Found, 251.1682}

![Image of chemical structure](image)

\(2-\{(4-\{(\text{dimethylamino})\text{butyl}\})\text{phenyl}\} \ \text{boronic acid:} \) To a solution of [4-\{(4-Bromo-phenyl)-butyl\}-dimethyl-amine (221, 0.97 g, 3.8 mmol, 1.0 equiv) in 30 mL of a 1/1-mixture of Et\(_2\)O and THF was slowly added \(\text{nBuLi} \ (1.6 \ \text{M in hexanes, 3.0 mL, 4.8 mmol, 1.3 equiv)} \) at \(-78 \ ^\circ\text{C}. \) After stirring for 45 min, freshly distilled triisopropyl borate (1.5 mL, 6.0 mmol, 1.6 equiv) was added and the mixture was allowed to warm to room temperature over night. 6 mL 2 M aqueous HCl were added and the mixture vigorously stirred for 20 min. The mixture was basified with 5 M aqueous NaOH and the aqueous phase was washed twice with Et\(_2\)O. The pH was adjusted to 9-10 with aqueous HCl. The aqueous phase was saturated with sodium chloride and extracted 5 times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue (white foam) used without further purification.

\[^1\text{H} \ \text{NMR} \ (300 \ \text{MHz, CDCl}_3): \ \delta \ 7.91 \ (d, \ 2\text{H}, \ J = 7.7 \ \text{Hz}), \ 7.22 \ (d, \ 2\text{H}, \ J = 7.9 \ \text{Hz}), \ 2.68 \ (t, \ 2\text{H}, \ J = 6.7 \ \text{Hz}), \ 2.43 \ (m, \ 2\text{H}), \ 2.28 \ (s, \ 6\text{H}), \ 1.62 \ (m, \ 4\text{H}).\)
Ethyl 2-(3-(4-(4-(dimethylamino)butyl)phenyl)oxetan-3-yl)acetate: To a solution of [Rh(cod)Cl]₂ (25 mg, 50 μmol, 0.050 equiv) in 3 mL dry dioxane was added aqueous KOH (1.5 M, 0.9 mL, 1.3 mmol, 1.3 equiv), followed by the α,β-unsaturated ester 89 (137 mg, 0.96 mmol, 1.00 equiv) and a solution of 2-(4-(4-(dimethylamino)butyl)phenyl)boronic acid (147, 320 mg, 1.45 mmol, 1.50 equiv) in 5 mL dry dioxane. After stirring for 6 h, Et₂O and brine were added. The aqueous phase was extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al₂O₃; 8/1 to 2/1 cyclohexane/EtOAc) to give 256 mg (83% yield) pure product as a colorless oil.

Rᵣ = 0.29 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 7.14 (d, 2H, J = 8.2 Hz), 7.06 (d, 2H, 8.2 Hz), 4.99 (d, 2H, J = 6.1 Hz), 4.84 (d, 2H, J = 6.1 Hz), 3.99 (q, 2H, J = 7.1 Hz), 3.08 (s, 2H), 2.60 (m, 2H), 2.25 (m, 2H), 2.19 (s, 6H), 1.52 (m, 4H), 1.10 (t, 3H, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 170.9, 141.1, 128.7, 125.8, 82.2, 60.5, 59.9, 45.7, 45.3, 45.0, 35.6, 29.4, 27.6, 14.2; IR (thin film) ν 2933, 2867, 2762, 1798, 1463, 1372, 1191, 1029, 989 cm⁻¹; HRMS (MALDI) calcd for C₁₉H₂₉NO₃ [M]⁺ 319.2142. Found: 319.2142.

N,N-dimethyl-4-(4-(3-methyloxetan-3-yl)phenyl)butan-1-amine: To a solution of Ethyl 2-(3-(4-(4-(dimethylamino)butyl)phenyl)oxetan-3-yl)acetate (146, 0.23 g, 0.73 mmol, 1.0 equiv) in 10 mL Et₂O was added a solution of DIBAL-H (20 w% in hexanes, 2.2 mL,
2.2 mmol, 3.0 equiv) at −78 °C over 45 min. After stirring for 1 h at this temperature, the solution was poured into ice cold 1 N HCl. The aqueous phase was basified with KOH (cooling) and extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was dissolved in 30 mL toluene. [(Ph₃P)₃RhCl] (2.0 g, 2.2 mmol, 3.0 equiv) were added and the mixture stirred at 105 °C for 16 h. After cooling to room temperature, the mixture was filtered, washed with Et₂O and 2 M aqueous NaOH. The aqueous phase was extracted three times with EtOAc, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (Al₂O₃; 20/1 to 4/1 cyclohexane/EtOAc) to give 66 mg (33% yield) pure product as colorless oil.

R_f = 0.45 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 7.16 (d, 2H, J = 8.2 Hz), 7.10 (d, 2H, J = 8.3 Hz), 4.95 (d, 2H, J = 5.5 Hz), 4.61 (d, 2H, J = 5.5 Hz), 2.61 (m, 2H), 2.27 (m, 2H), 2.21 (s, 6H), 1.71 (s, 3H), 1.56 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 143.9, 140.7, 128.7, 125.1, 84.1, 59.9, 45.8, 43.3, 35.6, 29.5, 28.0, 27.7; IR (thin film) ν 2935, 2865, 2814, 2763, 1517, 1461, 1041, 985, 821 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₅NO [M]⁺ 247.1931. Found: 247.1933.

[3-{4-tert-Butyl-phenyl}-oxetan-3-yl]-acetaldehyde: A catalytic amount (~2 mg, ~0.004 mmol, 0.01 equiv) of [Rh(cod)Cl]₂ was dissolved in 1.6 mL dry dioxane within 10 min. 1.5 M aqueous KOH (0.17 mL, 0.25 mmol, 0.5 equiv) was added and the mixture was stirred for 5 min before p-²Bu-phenylboronic acid (198 mg, 1.11 mmol, 2.00 equiv) was added. A solution of α,β-unsaturated aldehyde 90 (49 mg, 0.5 mmol, 1.0 equiv) in 0.6 mL dry dioxane was added and the mixture stirred for 20 min at room temperature.
Another 170 mg of \( p \)-tBu-phenylboronic acid (0.96 mmol, 1.9 equiv) were added to drive the reaction to completion. After further stirring for 1 h, Et\(_2\)O (20 mL) and water was added. The aqueous phase was extracted three times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (SiO\(_2\); 8/1 to 2/1 cyclohexane/EtOAc) to give 90 mg (78% yield) pure product as a white solid (mp = 66-67 °C).

\[ \text{R_f} = 0.35 \,(\text{SiO}_2,\, 2/1 \text{cyclohexane/EtOAc}); \] \[ ^1\text{H NMR} \,(300 \,\text{MHz, CDCl}_3): \delta \,9.71 \,(\text{t,} \,1\text{H,} \,J = 1.7 \,\text{Hz), 7.38} \,(\text{d,} \,2\text{H,} \,J = 8.6 \,\text{Hz), 7.10} \,(\text{d,} \,2\text{H,} \,J = 6.2 \,\text{Hz), 4.77} \,(m, \,2\text{H), 3.25} \,(d, \,2\text{H,} \,J = 1.7 \,\text{Hz), 1.32} \,(s, \,9\text{H);} \] \[ ^{13}\text{C NMR} \,(75 \,\text{MHz,} \,\text{CDCl}_3): \delta \,200.1, \,149.7, \,140.2, \,125.5, \,125.4, \,82.0, \,53.3, \,44.6, \,34.6, \,31.4; \] \[ \text{IR (thin film)} \,\nu \,3092, \,2925, \,2848, \,1698, \,1525, \,1421, \,1350, \,1319, \,1186, \,1125, \,960, \,947, \,904, \,828, \,777, \,725 \,\text{cm}^{-1}; \] \[ \text{Anal. calcd for C}_{15}\text{H}_{20}\text{O}_2: \text{C,} \,77.55; \text{H,} \,8.68. \text{Found: C,} \,77.60; \text{H,} \,8.72. \]

3-(4-\text{tert-Butyl-phenyl})-3-(3-nitro-allyl)-\textit{oxetane:} To a solution of [3-(4-\text{tert-Butyl-phenyl})-oxetan-3-yl]-acetaldehyde (114, 90 mg, 0.4 mmol), 1.0 equiv) in 4 mL nitromethane was added NEt\(_3\) (8.0 µL, 58 µmol, 0.2 equiv). After stirring for 3 h, the solvent was concentrated \textit{in vacuo}, the residue dissolved in 10 mL dry CH\(_2\)Cl\(_2\) and cooled to \(-78 \,^\circ\text{C}. \) NEt\(_3\) (162 µL, 1.16 mmol, 3.00 equiv) was added, followed by mesyl chloride (90 µL, 1.2 mmol, 3.0 equiv). After stirring for 30 min at \(-78 \,^\circ\text{C}, \) NEt\(_3\) (162 µL, 1.16 mmol, 3.00 equiv) was added and the mixture slowly allowed to warm to 0 °C. This solution was added to cold brine and the aqueous phase was extracted three times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (SiO\(_2\); 8/1 to 4/1 cyclohexane/EtOAc) to give 62 mg almost pure product (58% yield) as a yellowish oil that solidified in the freezer (mp = 69-72 °C).
Experimental Section

R_f = 0.40 (SiO_2, 2/1 cyclohexane/EtOAc); ^1^H NMR (300 MHz, CDCl_3): δ 7.39 (d, 2H, J = 8.4 Hz), 7.06 (m, 2H), 6.93 (d, 2H, J = 8.5 Hz), 5.01 (d, 2H, J = 6.1 Hz), 4.63 (d, 2H, J = 6.2 Hz), 3.00 (d, 2H, J = 7.5 Hz), 1.32 (s, 9H); ^1^C NMR (75 MHz, CDCl_3): δ 150.0, 141.3, 139.4, 137.4, 125.7, 125.1, 80.8, 46.6, 39.4, 34.6, 31.4; IR (thin film) ν 3098, 2963, 2906, 2872, 1912, 1650, 1526, 1464, 1396, 1352, 1270, 1202, 1116, 982, 835, 736 cm⁻¹; Anal. calcd for C_{16}H_{21}NO_3: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.00; H, 7.68; N, 4.91.

![Image](148)

[3-[3-(4-tert-Butyl-phenyl)-oxetan-3-yl]-propyl]-dimethyl-amine: To a solution of nitro 3-(4-tert-Butyl-phenyl)-3-(3-nitro-allyl)-oxetane (222, 250 mg, 0.91 mmol, 1.00 equiv) in 15 mL MeOH was added Pd(OH)_2/C (20 w%, 600 mg). Hydrogen was bubbled through this mixture for 45 min under vigorous stirring, before formaldehyde (37 w% in water, 1.7 mL, 21 mmol, 23 equiv) and AcOH (0.2 mL) were added. After stirring for 72 h, the mixture was filtered through a pad of celite, the filtrate concentrated in vacuo, treated with aqueous NaOH and extracted three times with Et_2O. The combined organic phases were dried over MgSO_4, filtered, concentrated in vacuo and the residue dissolved in 10 mL MeOH. Formaldehyde (37 w% in water, 2.0 mL, 25 mmol, 27 equiv) and AcOH (34 µL) were added. The mixture was stirred over night, concentrated in vacuo, taken up in Et_2O and basified with aqueous NaOH (cooling). The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 2/1 cyclohexane/EtOAc) to give 84 mg (34% yield) pure product as a white solid (m_p = 36-37 °C).

R_f = 0.53 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^1^H NMR (300 MHz, CDCl_3): δ 7.34 (d, 2H, J = 8.5 Hz), 6.95 (d, 2H, J = 8.4 Hz), 4.96 (d, 2H, J = 5.6 Hz), 4.64 (m, 2H), 2.18 (m, 2H), 2.14 (s, 6H), 2.06 (m, 2H), 1.31 (s, 9H); ^1^C NMR (75 MHz, CDCl_3): δ 148.9, 141.7, 125.3, 125.2,
82.0, 59.8, 47.0, 45.5, 38.9, 34.5, 31.5, 23.0; IR (thin film) ν 2961, 2867, 2814, 2763, 1511, 1462, 11364, 1269, 1114, 986, 828 cm\(^{-1}\); HRMS (EI) calcd for C\(_{18}\)H\(_{29}\)NO [M]+, 275.2249. Found, 275.2247.

[3-(4-tert-Butyl-benzyl)-oxetan-3-yl]-acetic acid ethyl ester: To a suspension of Cul (38 mg, 0.20 mmol, 0.10 equiv) and Oxetan-3-ylidene-acetic acid ethyl ester 89 (309 mg, 2.17 mmol, 1.00 mmol) in 4 mL dry THF was added freshly distilled TMSCl (0.3 mL, 2.4 mmol, 1.1 equiv) at room temperature. After stirring for 5 min, the mixture was cooled to –15 °C in a MeOH/ice bath. A solution of 4-\(^t\)Bu-BnMgBr (4 mL, 1 M in Et\(_2\)O) was dropwise added over 1 h. After stirring for 2 h, saturated aqueous KHSO\(_4\) was added. The aqueous phase was extracted three times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO\(_2\); 8/1 to 2/1 cyclohexane/EtOAc) to give 439 mg (70% yield) pure product as a colorless oil.

\(R_f = 0.53\) (SiO\(_2\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.31 (d, 2H, J = 8.3 Hz), 7.06 (d, 2H, J = 8.3 Hz), 4.65 (d, 1H, J = 6.2 Hz), 4.52 (d, 2H, J = 6.2 Hz), 4.16 (q, 1H, J = 7.1 Hz), 3.10 (s, 2H), 2.65 (s, 2H), 1.31 (s, 9H), 1.29 (t, 3H, J = 7.1 Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 171.2, 149.4, 134.2, 129.3, 125.3 80.9, 60.5, 41.8, 41.3, 40.1, 34.5, 31.5, 14.4; IR (thin film) ν 2967, 2871, 1733, 1509, 1371, 1177, 1028, 981, 668 cm\(^{-1}\); HRMS (EI) calcd for C\(_{18}\)H\(_{26}\)O\(_3\) [M]+ 290.1882. Found: 290.1880.
[2-[3-(4-tert-Butyl-benzyl)-oxetan-3-yl]-ethyl]-dimethyl-amine: To a solution of ester 89 (359 mg, 1.23 mmol, 1.00 equiv) in 10 mL Et<sub>2</sub>O was added a solution of DIBAL-H (20 w% in hexanes, 2.0 mL, 5.2 mmol, 1.7 equiv) at −78 °C over 45 min. After stirring for 1 h at this temperature, the solution was poured into ice cold 4 N HCl. The aqueous phase was extracted three times with Et<sub>2</sub>O. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was dissolved in 50 mL MeOH, before NEt<sub>3</sub> (0.3 mL, 1.8 mmol, 1.5 equiv) and dimethylammonium chloride (1.04 g, 12.8 mmol, 10.4 equiv) were added. AcOH was added until the pH was between 4 and 5. The mixture was stirred for 1.5 h, before NaCNBH<sub>3</sub> (785 mg, 12.3 mmol, 10.0 equiv) was added. The mixture was stirred overnight at room temperature, concentrated in vacuo and taken up with Et<sub>2</sub>O. Water was added, followed by NaOH with cooling. The aqueous phase was extracted three times with Et<sub>2</sub>O. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al<sub>2</sub>O<sub>3</sub>; 20/1 to 4/1 cyclohexane/EtOAc) to give 95 mg (28% yield) pure product as yellowish oil.

\[ \text{R}_f = 0.39 \text{ (Al}_2\text{O}_3, 2/1 \text{ cyclohexane/EtOAc)}; \]  \textsuperscript{1}H NMR (300 MHz, CDCl<sub>3</sub>): \( \delta \) 7.29 (d, 2H, J = 8.2 Hz), 7.06 (d, 2H, J = 8.2 Hz), 4.59 (d, 2H, J = 5.9 Hz), 4.43 (d, 2H, J = 5.9 Hz), 2.94 (s, 2H), 2.37 (m, 2H), 2.24 (s, 6H), 1.80 (m, 2H), 1.30 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl<sub>3</sub>): \( \delta \) 149.1, 134.5, 129.0, 125.2, 81.0, 55.1, 45.8, 42.5, 41.5, 34.4, 33.3, 31.4; IR (thin film) ν 2961, 2866, 1463, 1365, 1267, 981, 835 cm<sup>−1</sup>; Anal. calcd for C<sub>18</sub>H<sub>29</sub>N<sub>2</sub>O: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.38; H, 10.83; N, 4.96; HRMS (El) calcd for C<sub>18</sub>H<sub>29</sub>N<sub>2</sub>O [M]<sup>+</sup>, 275.2249. Found, 275.2241.
3-[2-(4-tert-Butyl-phenyl)-vinyl]-3-nitromethyl-oxetane: To a solution of [Rh(cod)Cl]₂ (10 mg, 20 μmol, 0.030 equiv) in 4 mL dry dioxane was added aqueous KOH (1.5 M, 0.60 mL, 0.90 mmol, 1.3 equiv) at room temperature. After stirring for 2 min, nitromethylene oxetane 96 (0.10 g, 0.90 mmol, 1.0 equiv) was added, followed by a solution of (E)-4-tert-butylstyrylboronic acid (0.20 g, 1.1 mmol, 1.2 equiv) in 3 mL dry dioxane. After stirring for 30 min, additional (E)-4-tert-butylstyrylboronic acid 354 (75 mg, 0.40 mmol, 0.40 equiv) was added. After stirring for further 20 min, Et₂O and brine were added. The aqueous phase was extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 8/1 to 4/1 cyclohexane/EtOAc) to give 137 mg pure product (55% yield) as a white solid (m.p. = 108-110 °C).

Rₚ = 0.40 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 7.34 (q, 4H, J = 8.4 Hz), 6.55 (d, 1H, J = 16.3 Hz), 6.30 (d, 1H, J = 16.3 Hz), 4.89 (s, 2H), 4.85 (d, 2H, J = 6.5 Hz), 4.74 (d, 2H, J = 6.5 Hz), 1.32 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 151.4, 132.9, 131.7, 126.1, 126.0, 125.5, 80.2, 78.7, 44.6, 34.7, 31.3; IR (thin film) ν 2953, 2919, 2868, 1547, 1377, 1270, 1108, 976, 814 cm⁻¹; Anal. calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.50; H, 7.96; N, 5.00; HRMS (EI) calcd for C₁₆H₂₁NO₃ [M]+, 275.1521. Found, 275.1515.

[3-[2-{4-tert-Butyl-phenyl}-ethyl]-oxetan-3-ylmethyl]-dimethyl-amine: Through a mixture of 3-[2-{4-tert-butyl-phenyl}-vinyl]-3-nitromethyl-oxetane (152, 0.16 g, 0.60 mmol, 1.0 equiv) and Pd(OH)$_2$/C (20 w%, 70 mg) was bubbled hydrogen for 50 min. The mixture was then vigorously stirred over night. After filtration through a pad of celite, aqueous formaldehyde (37w%, 1.6 mL, 2.0 mmol, 3.3 equiv) and the solution adjusted to a pH between 4 and 5 with AcOH. After stirring for 30 min, NaCNBH$_3$ (120 mg, 1.90 mmol, 3.20 equiv) was added. The mixture was stirred for 5.5 h, concentrated in vacuo to approximately 1 mL and Et$_2$O and aqueous NaOH were added with cooling. The aqueous phase was saturated with NaCl and extracted three times with Et$_2$O. The combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al$_2$O$_3$; 20/1 cyclohexane/EtOAc) to give 109 mg pure product (67% yield) as a yellowish oil that solidified in the freezer (mp = 40–42 °C).

$R_f = 0.74$ (Al$_2$O$_3$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): δ 7.32 (d, 2H, J = 8.3 Hz), 7.18 (d, 2H, J = 8.2 Hz), 4.46 (d, 2H, J = 5.9 Hz), 4.40 (d, 2H, J = 5.9 Hz), 2.58 (m, 4H), 2.17 (s, 6H), 2.12 (m, 2H), 1.31 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 148.5, 139.1, 127.9, 125.1, 81.0, 64.3, 46.3, 46.3, 42.7, 36.6, 34.4, 31.5, 29.8; IR (thin film) ν 2961, 2859, 2817, 2765, 1517, 1458, 1364, 1266, 1036, 989, 823, 772 cm$^{-1}$; Anal. calcd for C$_{18}$H$_{29}$NO: C, 78.49; H 10.61, N, 5.09. Found: C, 78.41, H, 10.60, N, 5.16; HRMS (EI) calcd for C$_{18}$H$_{29}$NO [M]$^+$, 275.2249. Found, 275.2245.
[3-[3-(4-tert-Butyl-phenyl)-propyl]-oxetan-3-yl]-dimethyl-amine: To a solution of a catalytic amount of DBU in 1.5 mL dry THF was added dimethyl amine (0.5 M in Et₂O, 2.4 mL, 1.2 mmol, 1.0 equiv) followed by a solution of α,β-unsaturated aldehyde 90 (117 mg, 1.20 mmol, 1.00 equiv) in 1 mL dry THF at –15 °C. The solution was stirred for 50 min, before it was added to a solution of p-tBu-phenylmethylene triphenylphosphorane (154) in 20 mL dry THF (This solution was made by adding ´BuLi (1.6 M solution in hexanes, 3.0 mL, 4.8 mmol, 4.0 equiv) at 0 °C to a dispersion of (4-tert-Butyl-benzyl)-triphenyl-phosphonium bromide (2.8 g, 4.8 mmol, 4.0 equiv) in 20 mL dry THF at 0 °C and stirring this mixture for 30 min at 0 °C. ). The reaction mixture was stirred for 30 min at 0 °C, and then warmed for 30 min to 60 °C. After cooling to 0 °C, 1 M aqueous HCl was added and the THF concentrated in vacuo. The residue was washed three times with toluene, and then extracted four times with chloroform. The combined chloroform phases were washed once with brine (acidified with HCl), dried over MgSO₄, filtered, concentrated in vacuo and the residue dissolved in 20 mL MeOH. To this solution Pd/C (10 w%, 100 mg) was added and the atmosphere exchanged with hydrogen. Hydrogen was bubbled through the mixture for 30 min and the mixture was vigorously stirred overnight and filtered through a plug of celite. The filtrate was concentrated in vacuo and the residue mixed with water and Et₂O. Aqueous NaOH (2 M, 2.5 mL) was added with cooling and the aqueous phase extracted four times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Al₂O₃; 8/1 cyclohexane/EtOAc) to give 120 mg pure product (36% yield) as a colorless oil.

R_f = 0.60 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 7.32 (d, 2H, J = 8.3 Hz), 7.15 (d, 2H, J = 8.1 Hz), 4.64 (d, 2H, J = 6.2 Hz), 4.32 (d, 2H, J = 6.3 Hz), 2.66 (t, 2H, J = 7.0 Hz), 2.24 (s, 6H), 1.81 (m, 4H), 1.32 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 148.5,
6.5 Preparation of Oxetanes of the Cyclic Scaffolds

6-{benzo[d][1,3]dioxol-5-ylmethyl}-2-oxa-6-azaspiro[3.3]heptane: Piperonal (1.0 g, 6.9 mmol, 1.3 equiv) was dissolved in 20 mL CH₂Cl₂ and to the solution was added 2-oxa-6-azaspiro[3.3]heptane (130, 0.53 g, 5.3 mmol, 1.0 equiv) and NaBH(OAc)₃ (2.8 g, 13 mmol, 2.5 equiv). The resulting white suspension was stirred overnight at room temperature. Saturated aqueous K₂CO₃ was added until complete dissolution of the borate byproducts. The aqueous phase was extracted with EtOAc three times. The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in 250 mL Et₂O and a solution of anhydrous oxalic acid (0.48 g, 5.3 mmol, 1.0 equiv) in little EtOH was added. The white precipitation formed was filtered, washed with Et₂O and then dissolved in 1 M KOH. The aqueous phase was extracted with EtOAc, the combined organic phases were dried over Na₂SO₄, filtered concentrated in vacuo to give 0.91 g of clear white liquid as pure product (74% yield).

\[ R_f = 0.24 \] (Al₂O₃, 2/1 cyclohexane/EtOAc); \[^1^H \text{NMR (300 MHz, CDCl}_3\] \( \delta 6.76 – 6.71 \) (m, 2H), 6.71 – 6.64 (m, 1H), 5.93 (s, 2H), 4.74 (s, 4H), 3.43 (s, 2H), 3.34 (s, 4H); \[^{13}\text{C NMR (75 MHz, CDCl}_3\] \( \delta 147.6, 146.5, 131.5, 121.4, 108.8, 107.9, 100.8, 81.3, 63.4, 63.1, 38.9 \); IR (thin film) ν 2931, 2863, 2815, 1608, 1503, 1410, 1442, 1377, 1247, 1110, 1039, 973, 927, 869, 811, 774, 746 cm\(^{-1}\); Anal. calcd for C₁₃H₁₅NO₃: C: 70.92, H: 6.45, N: 6.89, O: 15.74.
7-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-7-azaspiro[3.5]nonane 3: To a solution of dimethyl malonate (1.1 mL, 9.6 mmol, 3.2 equiv) in 25 mL dry THF was added Sodium hydride (60 w% suspension in mineral oil, 0.32 g, 8.0 mmol, 2.5 equiv) at room temperature. After stirring for 20 min, tetrabutylammonium bromide (0.32 g, 1.0 mmol, 0.30 equiv) was added, followed by a solution of the α,β-unsaturated ester 89 (0.43 g, 3.0 mmol, 1.0 equiv) in 1 mL dry Et₂O. The mixture was stirred overnight at room temperature and quenched by adding 0.47 mL glacial AcOH. The solvent was concentrated in vacuo and the residue treated with Et₂O. The aqueous phase was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in 30 mL DMSO, water (150 µL) and sodium chloride was added and the mixture stirred at 160 °C for 2 h. Brine and Et₂O (200 mL) were added and the aqueous phase washed twice with brine. The aqueous phase was dried over MgSO₄, filtered, concentrated in vacuo and the residue being product (Rf = 0.31 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 4.54 (m, 4H), 4.12 (q, 2H, J = 7.1 Hz), 3.67 (s, 3H), 2.93 (s, 2H), 2.90 (s, 2H), 1.25 (t, 3H, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 170.8, 81.0, 60.5, 51.6, 40.0, 39.8, 38.8, 14.2; IR (thin film) ν 2934, 1736, 1440, 1375, 1176, 1070, 1028, 978 cm⁻¹) of good purity used without further purification. This crude material was dissolved in 30 mL dry Et₂O, the solution cooled to 0 °C and LiAlH₄ (3 mL, 4.0 M in Et₂O, 12 mmol, 3.8 equiv) added dropwise leading to white precipitation. After stirring for 3 h at 0 °C, Na₂SO₄·10 H₂O was cautiously added. The mixture was filtered after stirring for 20 min. The filter cake was boiled with two portions of 20 mL EtOAc. The combined filtrates were dried over Na₂SO₄, filtered, concentrated in vacuo and the residual diol (¹H NMR (300 MHz, CDCl₃) δ 4.47 (s, 4H), 3.78 (t, 4H, J = 6.4 Hz), 2.06 (t, 4H, J = 6.4 Hz), 1.94 (s, 2H)) dissolved in 30 mL dry CH₂Cl₂. The
solution was cooled to 0 °C, MsCl (0.74 mL, 9.6 mmol, 3.0 equiv) was added, followed by dropwise addition of NEt₃ (1.8 mL, 13 mmol, 4.0 equiv). After stirring for 1 h, a sample in the NMR indicated full conversion. Aqueous saturated NH₄Cl was added and the aqueous phase extracted three times with EtOAc. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residual bismesylate (¹H NMR (300 MHz, CDCl₃) δ 4.49 (s, 4H), 4.35 (t, 4H, J = 6.4 Hz), 3.03 (s, 6H), 2.26 (t, 4H, J = 6.4 Hz)) dissolved in 4.0 mL piperonylamine (32 mmol, 10 equiv). After stirring for 40 min at 90 °C, a sample in the NMR showed full conversion of starting material. Saturated aqueous Sodium bicarbonate was added and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed once with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified on column (Al₂O₃, cyclohexane to 8/1 cyclohexane/EtOAc) to give 0.26 g pure product as a white solid (mp = 78 – 80 °C).

Rᶠ = 0.54 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.82 (d, 1H, J = 0.9 Hz), 6.72 (m, 2H), 5.93 (s, 2H), 4.39 (s, 4H), 3.34 (s, 2H), 2.28 (s, 4H), 1.85 (t, 4H, J = 5.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 147.4, 146.3, 132.1, 121.9, 109.2, 107.7, 100.7, 81.8, 62.9, 50.3, 38.6, 35.0; IR (thin film) ν 2924, 2858, 2361, 1480, 1441, 1370, 1241, 1099, 1039, 977, 929, 810, 688 cm⁻¹; Anal. calcd for C₁₅H₁₉NO₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.00; H, 7.47; N, 5.27.; HRMS (El) calcd for C₁₅H₁₉NO₃ [M]+ = 261.1360. Found: 261.1361.

(3-Nitromethyl-oxetan-3-yl)-acetic acid ethyl ester: To a solution of α,β-unsaturated ester 89 (1.62 g, 11.4 mmol, 1.00 equiv) in 10 mL dry MeCN was added nitro methane (3.08 mL, 56.9 mmol, 5.00 equiv), followed by a catalytic amount of DBU (340 μL, 2.28 mmol, 0.200 equiv) at 0 °C. After stirring for 4 h at room temperature, the mixture
was filtered through a plug of SiO$_2$ with 4/1 cyclohexane/EtOAc to give 2.13 g almost (>98 w% by NMR) pure material as a colorless liquid (92% yield).

$R_f = 0.26$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.95 (s, 2H), 4.63 (d, 2H, $J = 7.0$ Hz), 4.56 (d, 2H, $J = 7.0$ Hz), 4.16 (q, 2H, $J = 7.1$ Hz), 2.95 (s, 2H), 1.27 (t, 1H, $J = 7.1$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.1, 78.6, 78.6, 61.2, 40.3, 38.1, 14.3; IR (thin film) $\nu$ 2918, 2872, 1723, 1549, 1378, 1188, 1075, 1024 977 cm$^{-1}$; Anal. calcd for C$_8$H$_{13}$NO$_5$: C, 47.29; H, 6.45. Found: C, 47.11; H, 6.39; HRMS (El) calcd for C$_8$H$_{13}$NO$_5$: [M]+$^+$ = 203.0794. Found: 203.0747.

6-(benzo[\textit{d}][1,3]dioxol-5-ylmethyl)-2-oxa-6-azaspiro[3.4]octane: To a solution of (3-Nitromethyl-oxetan-3-yl)-acetic acid ethyl ester (103, 0.64 in 15 mL dry toluene was added Dibal-H (1.4 M in toluene, 4.3 mL, 6.3 mmol, 2.0 equiv) at -78 °C over 15 min. After 30 min, TLC indicated full conversion. After further 10 min, 5 mL 1 M aqueous HCl were added and the mixture allowed to warm to room temperature. Et$_2$O and another 15 mL of 1 M HCl were added and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed once with 1 M HCl, brine and saturated aqueous sodium bicarbonate, dried over Na$_2$SO$_4$, filtered, concentrated in vacuo and the residue (0.41 g) found to be ~90% pure by NMR with the residual material being the primary alcohol resulting from overreduction. ($R_f = 0.15$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.74 (s, 1H), 4.92 (s, 2H), 4.63 (d, 2H, $J = 7.1$ Hz), 4.50 (d, 2H, $J = 7.1$ Hz), 3.18 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 198.7, 78.8, 78.6, 47.3, 39.5; IR (thin film) $\nu$ 2934, 2819, 2734, 1715, 1545, 1428, 1382, 1258, 1097, 990, 901 cm$^{-1}$; HRMS (El) calcd for C$_6$H$_9$NO$_4$ [M-CH$_2$NO$_2$]+$^+$ = 99.0442; Found: 99.0446.) This material was used without further purification, dissolved in 25 mL MeOH and 48 mg Pd(OH)$_2$/C (20 w%), were added. After
exchanging the atmosphere with hydrogen, hydrogen was bubbled through the mixture for 45 min and stirred under hydrogen overnight (balloon), when a sample in the NMR indicated clean conversion to product. The mixture was filtered through celite, concentrated in vacuo and the residue (1H NMR (300 MHz, CDCl3) δ 4.64 (d, 2H, J = 5.9 Hz), 4.60 (d, 2H, J = 5.9 Hz), 3.15 (s, 2H), 2.91 (t, 2H, J = 7.0 Hz), 2.05 (t, 2H, J = 7.1 Hz)) dissolved in 30 mL CH₂Cl₂. Piperonal (0.41 g, 2.7 mmol, 1.2 equiv), followed by NaHB(OAc)₃ (1.2 g, 5.7 mmol, 2.5 equiv). The mixture was stirred for 7 h. Aqueous saturated K₂CO₃ (80 mL) was added and the mixture stirred vigorously for 15 min. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, filtered, concentrated in vacuo and the residue (1H NMR (300 MHz, CDCl₃) δ 4.64 (d, 2H, J = 5.9 Hz), 4.60 (d, 2H, J = 5.9 Hz), 3.15 (s, 2H), 2.91 (t, 2H, J = 7.0 Hz), 2.05 (t, 2H, J = 7.1 Hz)) dissolved in 30 mL CH₂Cl₂. Piperonal (0.41 g, 2.7 mmol, 1.2 equiv), followed by NaHB(OAc)₃ (1.2 g, 5.7 mmol, 2.5 equiv). The mixture was stirred for 7 h. Aqueous saturated K₂CO₃ (80 mL) was added and the mixture stirred vigorously for 15 min. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 1/2 cyclohexane/EtOAc to 5% MeOH in EtOAc) to give 0.29 g pure product as a slightly yellowish oil (53% yield).

Rᵣ = 0.2 (SiO₂, EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.82 (d, 1H, J = 0.5 Hz), 6.73 (m, 2H), 5.94 (s, 2H), 4.60 (q, 4H, J = 5.9 Hz), 3.48 (s, 2H), 2.78 (s, 2H), 2.51 (t, 2H, J = 7.0 Hz), 2.11 (t, 2H, J = 7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 147.5, 146.4, 132.6, 121.6, 109.0, 107.8, 100.7, 83.8, 64.6, 59.8, 53.4, 44.9, 36.3; IR (thin film) ν 2921, 2861, 2788, 1489, 1442, 1382, 1345, 1240, 1097, 1039, 976, 928, 809 cm⁻¹; Anal. calcd for C₁₄H₁₇NO₃: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.71; H, 7.06; N, 5.72; HRMS (EI) calcd for C₁₄H₁₇NO₃: [M]⁺=247.1203. Found: 247.1201.

3-(3-Hydroxymethyl-oxetan-3-yl)-propionic acid tert-butyl ester: To a solution of N,N-diisopropylamine (0.48 mL, 3.6 mmol, 6.0 equiv) in 3 mL dry THF was added ⁶⁷BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol, 5.5 equiv) at −78 °C. After stirring for 20 min, 3 mL dry hexane was added and stirring was continued for another 20 min, before tert-butyl acetate (0.40 mL, 3.0 mmol, 5.0 equiv) was added as a solution in dry THF (2 mL). After stirring for
25 min, the mixture was cooled to −95 °C (Et₂O/liquid nitrogen cooling bath) and 2,6-dioxaspiro[3.3]heptane (140, 60 mg, 0.60 mmol, 1.0 equiv) was added, followed by dropwise addition of BF₃·OEt₂ (0.37 mL, 3.0 mmol, 5.0 equiv). The mixture was allowed to warm to −78 °C. After stirring for 2.5 h, another 0.3 mL BF₃·OEt₂ (2.4 mmol, 4.1 equiv) were added. After stirring for further 5 h, the mixture was quenched by adding saturated aqueous NH₄Cl. The aqueous phase was extracted four times with EtOAc. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 2/1 cyclohexane/EtOAc to EtOAc) to give 109 mg (89 w% by NMR, rest EtOAc) product as a colorless liquid (75% yield).

Rᶠ = 0.31(SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 4.39 (q, 4H, J = 6.1 Hz), 3.74 (d, 2H, J = 5.4 Hz), 2.66 (s, 1H), 2.24 (dd, 2H, J = 6.8 Hz, 7.4 Hz), 2.04 (t, 2H, J = 7.0 Hz), 1.44 (d, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 81.1, 78.6, 65.4, 43.8, 30.3, 28.1, 27.9; IR (thin film) ν 3424, 2977, 2873, 1728, 1452, 1368, 1306, 1256, 1157, 1047, 977, 844 cm⁻¹; HRMS (EI) calcd for C₁₁H₂₀O₄: [M-C₄H₈]⁺ = 159.0652. Found: 159.0652.

6-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-6-azaspiro[3.5]nonane: To a solution of 3-(3-Hydroxymethyl-oxetan-3-yl)-propionic acid tert-butyl ester (144) (0.16 g, 0.76 mmol, 1.0 equiv) in 25 mL dry Et₂O was slowly added LiAlH₄ (4.0 m in Et₂O, 0.57 mL, 2.3 mmol, 3.0 equiv) at 0 °C. After stirring for 45 min, Na₂SO₄·10 H₂O was added and the mixture stirred for 15 min. After filtration, the filter cake was boiled with two portions of 20 mL EtOAc. The combined filtrates were dried over Na₂SO₄, filtered, concentrated in vacuo and the residual diol dissolved in 20 mL dry CH₂Cl₂, cooled to 0 °C and MsCl (0.18 mL, 2.3 mmol, 3.0 equiv) was added, followed by slow addition of NEt₃ (0.42 mL, 3.0 mmol, 4.0 equiv). After 1 h, a sample in the NMR indicated full conversion. Saturated aqueous NH₄Cl was added, the aqueous phase extracted three times with EtOAc. The combined

organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and the residue ($R_f = 0.19$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.46 (m, 4H), 4.42 (d, 2H, $J = 1.4$ Hz), 4.28 (t, 2H, $J = 6.0$ Hz), 3.08 (s, 3H), 3.04 (s, 3H), 1.92 (m, 2H), 1.81 (m, 2H)) mixed with piperonylamine (0.95 mL, 7.6 mmol, 10 equiv). The mixture was heated to 90 °C for 1 h, when a sample in the NMR showed full conversion. EtOAc was added and 1 m aqueous KOH. The aqueous phase was extracted three times with EtOAc, the combined organic phases washed once with brine, dried over MgSO$_4$, filtered, concentrated in vacuo and purified by flash chromatography (Al$_2$O$_3$, 20/1 to 8/1 cyclohexane/EtOAc) to give a mixture of product and piperonal. This material was dissolved in 40 mL Et$_2$O, and a solution of oxalic acid (54 mg, 0.76 mmol, 1.0 equiv) in EtOH was added. The white precipitate was collected and dissolved in 1 m aqueous KOH. The mixture was extracted three times with Et$_2$O, the combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo to give 97 mg pure product (49% yield) as slightly yellowish oil.

$R_f = 0.19$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.84 (s, 1H), 6.73 (m, 2H), 5.95 (s, 2H), 4.35 (q, 4H, $J = 5.9$ Hz), 3.40 (s, 2H), 2.51 (s, 2H), 2.30 (s, 2H), 1.68 (s, 2H), 1.51 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.4, 146.3, 132.4, 121.7, 109.0, 107.7, 100.7, 81.0, 62.8, 61.1, 53.3, 39.7, 33.5, 22.6; IR (thin film) $\nu$ 2931, 2860, 2765, 1857, 1732, 1607, 1489, 1441, 1369, 1243, 1100, 1040, 976, 931, 810 cm$^{-1}$; Anal. calcd for C$_{15}$H$_{19}$NO$_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.69; H, 7.40; N, 5.29.; HRMS (EI) calcd for C$_{15}$H$_{19}$NO$_3$: [M]$^+$ = 261.1360. Found: 261.1362.

2-(3-(benzo[d][1,3]dioxol-5-ylmethylamino)oxetan-3-yl)ethanol : To 2-(oxetan-3-ylidene)acetate (89, 305 mg, 2.15 mmol; 1.00 equiv) was added piperonylamine (0.28 mL; 2.4 mmol; 1.1 equiv). This mixture was heated at 60 °C under argon atmosphere for 2 h,
before 30 mL dry Et₂O were added and the reaction mixture was cooled to 0 °C, LiAlH₄ (4.0 M in Et₂O; 2.4 mL, 9.4 mmol, 4.0 equiv) was drop wise added, and the white suspen-
sion stirred for 2 h. Na₂SO₄·10 H₂O was added slowly and the mixture stirred at room
temperature for 25 min, before it was filtered. The filter cake was cooked with 4 portions
of EtOAc and the combined filtrates dried over Na₂SO₄, filtered, concentrated in vacuo
and the residue purified by flash chromatography (SiO₂; CHCl₃ to CHCl₃/MeOH 92:8) to
give 399 mg (95w% by NMR) product (70% yield) as a yellowish oil.

Rf = 0.78 (SiO₂, CHCl₃/MeOH 4:1); ¹H NMR (300 MHz, CDCl₃) δ 6.77 (m, 3H), 5.94 (s, 2H),
4.56 (d, 2H, J = 6.7 Hz), 4.50 (d, 2H, J = 6.8 Hz), 3.82 (t, 2H), 3.72 (s, 2H), 2.14 (m, 2H);
¹³C NMR (75 MHz, CDCl₃) δ 147.6, 146.5, 132.7, 121.5, 108.7, 108.3, 101.0, 81.4, 61.0,
59.5, 47.0, 35.1; IR (thin film) ν 3386, 2873, 1503, 1490, 1443, 1250, 1099, 1039, 975,
928.0, 810 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₇NO₄ [M+CH₂O]⁺ = 221.1052. Found: 221.1052

\[
\begin{align*}
\text{Rf} &= 0.78 \\
¹H\ NMR\ (300\ MHz,\ CDCl₃)\ δ &= 6.77\ (m,\ 3H),\ 5.94\ (s,\ 2H),\ 4.56\ (d,\ 2H,\ J = 6.7\ Hz),\ 4.50\ (d,\ 2H,\ J = 6.8\ Hz),\ 3.82\ (t,\ 2H),\ 3.72\ (s,\ 2H),\ 2.14\ (m,\ 2H);
\end{align*}
\]

1-(benzo[d][1,3]dioxol-5-ylmethyl)-6-oxa-1-azaspiro[3.3]heptanes: Tetrabromocar-
bon (750 mg, 2.26 mmol, 1.50 equiv) is added to a solution of 2-(3-(benzo[d][1,3]dioxol-5-
ylmethylamino)oxetan-3-yl)ethanol (106, 379 mg, 1.51 mmol, 1.00 equiv) and PPh₃
(593 mg, 2.26 mmol, 1.50 equiv) in 25 mL dry MeCN (immediate orange color), followed
by distilled NEt₃ (475 μL, 3.41 mmol, 2.00 equiv). The flask is wrapped in aluminum foil
and stirred for 40 h at room temperature. Brine and Et₂O is added and the aqueous
phase extracted three times with Et₂O. The combined organic phases are dried over
Na₂SO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography
(Al₂O₃, cyclohexane to 8/1 cyclohexane/EtOAc) to give 253 mg pure product (72% yield)
as a yellow oil that solidified upon storage in the fridge (mp = 62.5 °C, measured by DSC).
**Experimental Section**

\[ R_f = 0.15 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } \]  
\[ ^1\text{H NMR (300 MHz, CDCl}_3 \] \( \delta \) 6.85 (s, 1H), 6.76 (m, 2H), 5.93 (s, 2H), 4.97 (d, 2H, \( J = 7.9 \) Hz), 4.63 (d, 2H, \( J = 7.9 \) Hz), 3.72 (s, 2H), 3.03 (t, 2H, \( J = 6.8 \) Hz), 2.36 (t, 2H, \( J = 6.8 \) Hz); \[ ^{13}\text{C NMR (75 MHz, CDCl}_3 \] \( \delta \) 173.5, 146.5, 131.7, 121.4, 109.0, 108.1, 100.9, 81.4, 56.2, 49.8, 29.5; IR (thin film) ν 3403, 2939, 2864, 1608, 1502, 1490, 1442, 1377, 1347, 1247, 1185, 1117, 1094, 1038, 973, 927, 866, 810, 776 cm\(^{-1}\); Anal. calcd for C\(_{13}\)H\(_{15}\)NO\(_3\): C, 66.94; H, 6.48; N, 6.00; O, 20.58; Found: C, 66.65; H, 6.53; N, 6.04; O, 20.78; HRMS (El) calcd for C\(_{13}\)H\(_{15}\)NO\(_3\) \([\text{M}^+]\) 233.1052. Found: 233.1048.

**3-allyl-N-(benzo[d][1,3]dioxol-5-ylmethyl)oxetan-3-amine:** To a solution of piperonylamine (0.82 mL, 6.6 mmol, 1.1 equiv) and DBU (9.0 μL, 60 μmol, 1.0mol%) in 6 mL dry THF was added the \( \alpha,\beta \)-unsaturated aldehyde 90 (0.60 g, 6.0 mmol, 1.0 equiv) at –18 °C (MeOH/ice bath). After stirring for 4 h at this temperature, the solution was transferred to a solution H\(_2\)C=PPh\(_3\) in THF (prepared by addition of \( \text{nBuLi (2.5 m in hexanes, 6.7 mL, } 17 \text{ mmol, 2.8 equiv) to a suspension of Ph}_3\text{PMeBr (6.4 g, 18 mmol, 3.0 equiv) in 50 mL dry THF at } 0 \degree \text{C). The mixture was allowed to warm to room temperature and stirred over night, before water and brine were added. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Na\(_2\)SO\(_4\), filtered, concentrated in vacuo and the residue purified by flash chromatography (Al\(_2\)O\(_3\), 8/1 to 2/ cyclohexane/EtOAc) to give 435 mg pure product as a yellowish oil (29% yield).
ν 3312, 3072, 2398, 1490, 1250, 1099, 1037, 980, 926, 811 cm⁻¹; HRMS (El) calcd for C_{14}H_{17}NO₃: [M-CH₂O]⁺= 217.1103. Found: 217.1100.

5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.4]octane: 3-allyl-N-(benzo[d][1,3]dioxol-5-ylmethyl)oxetan-3-amine (115, 0.20 g, 0.81 mmol, 1.00 equiv) was dissolved in 5 mL dry THF. Hg(O₂CCF₃)₂ (659 mg, 1.42 mmol, 1.76 equiv) was added at room temperature. The mixture was heated to 60 °C (turning dark brown, formation of a grey precipitate), before it was cooled to 0 °C and a solution of sodium borohydride (70 mg, 1.8 mmol, 2.3 equiv; 0.5 M in 2 N aqueous NaOH) was added. The mixture was allowed to warm to room temperature and stirred for 2.5 h. To this mixture Et₂O (30 mL) was added and the aqueous phase decanted off. The aqueous phase was dried over K₂CO₃, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 2/1 to 1/2 cyclohexane/EtOAc). The material isolated with R_f = 0.31 (SiO₂, 2/1 cyclohexane/EtOAc) was repurified (Al₂O₃, cyclohexane to 8/1 cyclohexane/EtOAc) to give 75 mg pure product (38% yield) as a slightly yellowish oil that solidified upon storage in the fridge m_p = 39.2 °C (measured by DSC).

R_f = 0.31 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.87 (dd, 1H, J = 0.5 Hz, 1.5 Hz), 6.77 (m, 2H), 5.94 (s, 2H), 4.89 (d, 2H, J = 6.8 Hz), 4.55 (d, 2H, J = 6.7 Hz), 3.92 (s, 2H), 2.58 (m, 2H), 2.19 (dd, 2H, J = 6.7 Hz, 8.8 Hz), 1.69 (tt, 2H, J = 6.9 Hz, 7.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 147.5, 146.3, 133.7, 121.0, 108.6, 107.9, 100.8, 80.1, 66.4, 53.2, 51.4, 37.2, 20.9; IR (thin film) ν 2940, 2867, 2802, 1857, 1607, 1503, 1489, 1443, 1378, 1363, 1241, 1171, 1115, 1093, 1039, 978, 929, 865, 809, 774 cm⁻¹; Anal. calcd for C_{14}H_{17}NO₃: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.97; H, 7.11; N, 5.75; HRMS (El) calcd for C_{14}H_{17}NO₃: [M⁺]= 247.1203. Found: 247.1204.
Experimental Section

**N,3-diallyl-N-(benzo[d][1,3]dioxol-5-ylmethyl)oxetan-3-amine**: To a solution of N-allyl-N-piperonylamine (0.95 g, 5.0 mmol, 1.0 equiv) and DBU (7.6 μL, 50 μmol, 1.0 mol%) in 4 mL dry THF was added the α,β-unsaturated aldehyde 90 (0.61 g, 5.0 mmol, 1.0 equiv) as a solution in 1 mL dry THF at –18 °C (MeOH/ice bath). The solution was stored for 5 d in the freezer (−18 °C), when a sample in the NMR showed 73% conversion to the 1,4-addition product. The solution was then transferred to a solution of H$_2$C=PPh$_3$ in THF (prepared by addition of nBuLi (2.5 M in hexanes, 5.0 mL, 13 mmol, 2.6 equiv) to a suspension of Ph$_3$PMeBr (4.73 g, 13.0 mmol, 2.60 equiv) in 50 mL dry THF at 0 °C). After 2 h, the reaction was quenched by adding 1 M aqueous HCl. Most of the solvents were concentrated in vacuo and the aqueous phase washed three times with toluene. The aqueous phase was then three times extracted with chloroform. The combined chloroform phases were concentrated in vacuo and the residue treated with aqueous Na$_2$CO$_3$ and extracted four times with Et$_2$O. The combined Et$_2$O phases were dried over MgSO$_3$ and extracted in vacuo and the residue purified by flash chromatography (SiO$_2$, 20/1 to 2/1 cyclohexane/EtOAc) to give 0.77 g (53% yield) pure product as colorless oil.

$R_f = 0.60$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.93 (m, 1H), 6.76 (m, 2H), 6.09 (m, 1H), 5.94 (m, 2H), 5.72 (m, 1H), 5.24 (m, 2H), 5.04 (dddd, 2H, $J = 1.0$ Hz, 2.5 Hz, 3.0 Hz, 10.1 Hz), 4.59 (d, 2H, $J = 6.2$ Hz), 4.26 (d, 2H, $J = 6.3$ Hz), 3.48 (s, 2H), 3.07 (d, 2H, $J = 6.6$ Hz), 2.63 (d, 2H, $J = 7.3$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.6, 146.4, 136, 134.0, 133.9, 121.1, 118.2, 116.7, 108.3, 107.7, 100.8, 79.8, 63.2, 53.0, 53.6, 36.2; IR (thin film) ν 3073, 2943, 2873, 1364, 1488, 1441, 1380, 1238, 1182, 1093, 1039, 981, 918, 867, 808, 779 cm$^{-1}$; HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_3$ [M]$^+$ = 287.1516. Found: 287.1518.
**5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.5]non-7-ene:** To a solution of N,3-diallyl- N-(benzo[d][1,3]dioxol-5-ylmethyl)oxetan-3-amine (165, 760 mg, 2.64 mmol, 1.00 equiv) in 100 mL dry CH₂Cl₂ was added pTosOH·H₂O (503 mg, 6.64 mmol, 1.00 equiv) at room temperature. The mixture was stirred until complete solvation (30 min) was reached and then degassed twice (freezing with liquid nitrogen, then applying high vacuum, melting under Argon atmosphere). Grubbs II catalyst (56 mg, 66 μmol, 2.5 mol%) was added and the mixture stirred for 15 h at room temperature, before 1 M aqueous NaOH was added and the mixture stirred for 15 min. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 2/1 cyclohexane to EtOAc) to give 604 mg pure product (88% yield) as a white solid (m.p. = 76 – 77 °C).

\[ R_f = 0.29 \text{ (SiO}_2, \text{ 2/1 cyclohexane/EtOAc)}; \] ³¹H NMR (300 MHz, CDCl₃) δ 6.95 (m, 1H), 6.77 (m, 2H), 5.93 (s, 2H), 5.77 (m, 1H), 5.55 (m, 1H), 4.66 (d, 2H, J = 6.0 Hz), 4.30 (d, 2H, J = 6.1 Hz), 3.42 (s, 2H), 3.07 (m, 2H), 2.51 (m, 2H); \¹³C NMR (75 MHz, CDCl₃) δ 147.5, 146.4, 133.1, 125.0, 123.3, 121.5, 109.0, 107.7, 100.8, 81.1, 59.1, 52.2, 45.0, 29.8; IR (thin film) ν 3026, 2868, 1608, 1502, 1490, 1441, 1384, 1342, 1251, 1184, 1118, 1093, 1039, 980, 918, 810, 654 cm⁻¹; Anal. calcd for C₁₅H₁₇NO₃; HRMS (EI) calcd for C₁₅H₁₇NO₃: [M]+ = 259.1203. Found: 259.1202.
5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.5]nonane: Through a mixture of 5-(benzo[d][1,3]dioxol-5-ylmethyl)-2-oxa-5-azaspiro[3.5]non-7-ene (166, 552 mg, 2.13 mmol, 1.00 equiv) and 5 w% Rh/C (39 mg) in 100 mL MeOH under hydrogen was bubbled hydrogen for 45 min, when a sample in the NMR indicated full consumption of starting material. The mixture was filtered through a plug of Celite, the filtrate concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 8/1 to 2/1 cyclohexane/EtOAc) to give 438 mg pure product (79% yield) as a white solid (mp = 44-44.5 °C).

Rf = 0.37(SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.92 (d, 1H, J = 1.1 Hz), 6.80 (d, 1H, J = 7.9 Hz), 6.74 (d, 1H, J = 7.9 Hz), 5.94 (s, 2H), 4.75 (d, 2H, J = 6.4 Hz), 4.36 (d, 2H, J = 6.4 Hz), 3.74 (s, 2H), 2.41 (m, 2H), 1.93 (m, 2H), 1.50 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 147.5, 146.2, 133.9, 121.0, 108.5, 107.7, 100.7, 79.0, 61.7, 52.7, 47.5, 33.8, 22.9, 21.3; IR (thin film) ν 2934, 2867, 1608, 1502, 1489, 1441, 1375, 1357, 1249, 1133, 1039, 979, 928, 864, 810, 775 cm⁻¹; Anal. calcd for C₁₅H₁₉NO₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.94; H, 7.37; N, 5.36; HRMS (EI) calcd for C₁₅H₁₉NO₃: [M-CH₃O]⁺ = 230.1176. Found: 230.1175.

3-(benzo[d][1,3]dioxol-5-ylmethyl)-6-oxa-3-azabicyclo[3.1.1]heptane:³⁵⁶ Cis/trans-(4-Benzyloxymethyl-oxetan-2-yl)-methanol³⁵⁷ (216 mg, 1.04 mmol, 1.00 equiv) was hydrogenated at 1.2 bar for 2 h over 73 mg (0.10 equiv) 20% Pd(OH)₂/C in 5 mL MeOH at room temperature.

³⁵⁶ This reaction was performed in the laboratories of F. Hoffmann-La Roche, Basel by Dr. Thierry Godel.
temperature. The suspension was filtered and concentrated to give crude cis/trans-(4-
hydroxymethyl-oxetan-2-yl)-methanol as a yellow liquid. This first intermediate was dis-
solved in 5 mL dry pyridine at 0 °C under argon. MsCl (0.32 mL, 4.2 mmol, 4.0 equiv) was
added drop wise and the mixture was stirred overnight, allowing the ice bath to expire.
The mixture was poured onto cold water, acidified with 4 M aq. HCl and extracted with
CH₂Cl₂. The aqueous phase was washed with brine, dried over MgSO₄, filtered and con-
centrated to give a crude oily mixture containing cis/trans-4-methanesulfonyloxymethyl-
oxetan-2-ylmethyl methanesulfonate. This second intermediate was dissolved in 5 mL dry
dioxane and piperonylamine (0.62 mL, 5.0 mmol, 4.8 equiv) was added dropwise at reflux.
The mixture was further stirred for 16 h at reflux, concentrated in vacuo, the mixture sus-
pended in EtOAc and filtered (Sartorius). After concentration (625 mg) the product was
chromatographed (MPLC, 80 g SiO₂, EtOAc (200 mL), EtOAc/iPrOH 99:1, 49:1, 19:1, 9:1,
4:1, 1:1 (100 mL each)) to give 48 mg 3-benzo[1,3]dioxol-5-ylmethyl-6-oxa-3-aza-
bicyclo[3.1.1]heptane as a yellow liquid. Analysis by HPLC showed a purity of 97.5%. Prior
to the measurements, an additional purification via preparative HPLC on a Chiralpak AD
column was conducted.

\[
R_f = 0.30 \text{ (SiO}_2, \text{ EtOAc)}; \quad ^1H \text{ NMR } (300 \text{ MHz, CDCl}_3) \delta 6.89 \text{ (s, 1H), 6.80 (d, J = 8.0 Hz, 1H),} \\
6.75 \text{ (d, J = 7.9 Hz, 1H), 5.94 (s, 2H), 4.49 (d, J = 6.3 Hz, 2H), 3.66 (s, 2H), 3.04 (d, J =} \\
11.4 \text{ Hz, 2H), 3.05 (q, J = 7.2 Hz, 1H), 2.77 (d, J = 11.4, 2H), 2.41 (d, J = 7.8 Hz, 1H);} \quad ^{13}\text{C NMR} \\
(75 \text{ MHz, CDCl}_3) \delta 160.8, 147.7, 146.5, 132.6, 121.7, 109.1, 108.4, 100.9, 80.2, 60.7, 55.4, \\
30.5; \text{ IR (thin film) } v 2960, 2877, 2808, 1685, 1609, 1502, 1487, 1439, 1389, 1361, 1239, \\
1179, 1148, 1116, 1094, 1034, 958, 926, 877, 836, 806, 772, 714 \text{ cm}^{-1}; \text{ HRMS (ESI) calcd} \\
\text{for C}_{13}\text{H}_{15}\text{NO}_3: [M+H]^+ = 234.1247. \text{ Found: 234.1242.}
\]
6.6 Preparation of Nonpublished Oxetanes

6.6.1 3-Aryloxetan-3-ols

3-Phenylloxetan-3-ol: To a solution of bromobenzene (1.1 mL, 10 mmol, 2.5 equiv) in 25 mL dry THF was added {\textsuperscript{6}}BuLi (1.6 mL in hexanes, 6.3 mL, 10 mmol, 2.5 equiv) at −78 °C. After the addition was finished, the mixture was stirred for 5 h, before 15 mL of this mixture were added to a solution of oxetan-3-one (33, 0.14 g, 2.0 mmol, 1.0 equiv) in 5 mL dry THF at −78 °C. The mixture was stirred over night, allowing it to warm to room temperature. Saturated aqueous ammonium chloride was added and the aqueous phase extracted twice with Et{\textsubscript{2}}O. The combined organic phases were dried over MgSO{\textsubscript{4}}, concentrated in vacuo and the residue purified by flash chromatography (SiO\textsubscript{2}, 1/1 hexane/EtOAc) to give 260 mg pure product (87% yield) as colorless crystals (mp = 48 °C).

R\text{f} = 0.17(SiO\textsubscript{2}, 2/1 cyclohexane/EtOAc); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.60 (m, 2H), 7.42 (m, 2H), 7.34 (m, 1H), 4.93 (m, 4H), 2.65 (s, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 142.4, 128.9, 128.2, 124.6, 85.8, 76.0; IR (thin film) ν 3387, 2953, 2877, 1603, 1495, 1449, 1176, 971, 876, 759 cm\textsuperscript{-1}; Anal. calcd for C\textsubscript{9}H\textsubscript{10}O\textsubscript{2}: C, 71.98; H, 6.71. Found: C, 72.02; H, 6.81.

The spectra collected for this compound are in accordance with the literature.\textsuperscript{358}

3-Pyridin-3-yl-oxetan-3-ol: A dry and argon-flushed 10-mL flask equipped with a magnetic stirrer and a septum was charged with freshly prepared iPrMgCl-LiCl\textsuperscript{177} (2.0 mL, 1.0 M in THF, 2.0 mmol, 2.0 equiv). The reaction mixture was cooled to 0 °C, and 3-

bromopyridine (0.31 g, 2.0 mmol, 2.0 equiv) was added in one portion. The mixture was allowed to warm to room temperature for 10 min. (orange color, turbid), cooled to 0 °C again and stirred for 40 min. A solution of oxetan-3-one (72 mg, 1.0 mmol, 1.0 equiv) in 1 mL dry THF was added and the mixture stirred for 1 h at 0 °C, before it was allowed to warm to room temperature and stirred for further 72 h. Et₂O was added, followed by saturated aqueous ammonium chloride solution. The aqueous phase was extracted three times with Et₂O; the combined organic phases were dried over magnesium sulfate, concentrated in vacuo and the residue purified by flash chromatography (SiO₂; EtOAc) to give 0.14 g pure product (yield 83%) as slightly yellow solid (mp = 93-94 °C).

$$R_f = 0.05 \text{ (SiO₂, 2/1 cyclohexane/EtOAc)}$$

$^{1}H$ NMR (300 MHz, CDCl₃) $\delta$ 8.85 (s, 1H), 8.51 (d, 1H, $J = 4.0$ Hz), 8.03 (m, 1H), 7.37 (dd, 1H, $J = 4.8$ Hz, $J = 7.9$ Hz), 4.97 (d, 2H, $J = 7.4$ Hz), 4.85 (d, 2H, $J = 7.4$ Hz), 4.70 (s, 1H); $^{13}C$ NMR (75 MHz, CDCl₃) $\delta$ 148.3, 145.7, 138.7, 132.8, 123.6, 85.8, 74.0; IR (thin film) ν 3108, 2954, 2876, 2712, 1576, 1479, 1418, 1338, 1227, 1179, 1039, 978, 876, 773, 710, 636 cm⁻¹; HRMS (EI) calcd for C₈H₉NO₂: [M-CH₂O]⁺= 121.0528. Found, 121.0540

![Image](64.png)

3-(4-methoxyphenyl)oxetan-3-ol: To a solution of 4-methoxyphenylmagnesium bromide in THF (2.0 mL, 2.0 mmol, 2.0 equiv) was added a solution of oxetan-3-one (33, 72 mg, 1.0 mmol, 1.0 equiv) in 1 mL THF at 0 °C. The mixture was allowed to slowly warm to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution was added. The aqueous phase was extracted three times with Et₂O, the combined organic phases were dried over MgSO₄, concentrated in vacuo and the residue purified by flash chromatography (SiO₂; hexane/EtOAc= 4/1 to 2/1) to give 0.14 g pure product (77% yield) as white solid (mp = 60-61 °C).

$$R_f = 0.30 \text{ (SiO₂, 2/1 cyclohexane/EtOAc)}$$

$^{1}H$ NMR (300 MHz, CDCl₃) $\delta$ 7.47 (d, 2H, $J = 8.6$ Hz) 6.93 (d, 2H, $J = 8.7$ Hz), 4.88 (m, 4H), 3.82 (s, 3H), 2.99 (s, 1H); $^{13}C$ NMR (75 MHz,
CDCl$_3$ δ 159.03, 134.4, 125.8, 113.9, 85.6, 75.5, 55.4; IR (thin film) ν 3319, 2993, 2954, 2882, 2837, 1611, 1581, 1464, 1441, 1301, 1245, 1179, 1027, 970, 876, 772 cm$^{-1}$; HRMS (El) calcd for C$_{10}$H$_{12}$O$_3$: [M]$^+$ = 180.0781. Found: 180.0776.

The spectra collected for this compound are in accordance with the literature.$^{359}$

![Image](https://example.com/image.png)

3-(4-Bromo-phenyl)-oxetan-3-ol: To a solution of oxetan-3-one (33, 0.20 g, 2.8 mmol, 1.0 equiv) in 5 mL dry Et$_2$O was added a solution of 4-bromophenylmagnesium bromide (≈0.63 M in Et$_2$O, 6.3 mmol, 2.3 equiv) in 10 mL dry Et$_2$O at 0 °C. The mixture was stirred for 5 h, allowing it to warm to room temperature, before water was added. The aqueous phase was extracted three times with EtOAc, the combined organic phases dried over MgSO$_4$, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO$_2$, 4/1 to 2/1 hexane/EtOAc) to give 0.54 g pure product (85% yield) as white crystals (mp = 93-94 °C).

$^3$H NMR (300 MHz, CDCl$_3$) δ 7.55 (d, 2H, J = 8.8 Hz), 7.49 (d, 2H, J = 8.7 Hz), 4.90 (d, 2H, J = 7.2 Hz), 4.85 (d, 2H, J = 7.2 Hz), 2.74 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 141.5, 132.0, 126.4, 122.1, 85.9, 75.6; IR (thin film) ν 3364, 2948, 2878, 1416, 984, 668 cm$^{-1}$; HRMS (El) calcd for C$_{9}$H$_{9}$BrO$_2$: [M-CH$_2$O]$^+$ = 197.9680. Found: 197.9674. Anal. calcd for C$_{9}$H$_{9}$BrO$_2$: C, 47.19; H, 3.96. Found: C, 47.24; H, 3.84.

![Image](https://example.com/image.png)

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3-(2,4-dimethylphenyl)oxetan-3-ol: A few drops of 1-bromo-2,4-dimethylbenzene (0.93 g, 5.0 mmol, 5.0 equiv) were added to magnesium turnings (0.14 g, 6.0 mmol, 6.0 equiv) suspended in 5 mL dry Et₂O, followed by a grain of iodine to activate the magnesium and promote metalation. After adding the residual aryl bromide (turbid solution, slight boiling of Et₂O), the mixture was stirred overnight at room temperature and a solution of oxetan-3-one (33, 72 mg, 1.0 mmol, 1.0 equiv) in 1 mL dry THF was added at 0 °C (white precipitation). After the addition was finished the mixture was allowed to warm to room temperature and stirred for further 6 h. Saturated aqueous ammonium chloride solution was added. The aqueous phase was extracted three times with Et₂O, the combined organic phases were dried over MgSO₄, concentrated in vacuo and the residue purified by flash chromatography (SiO₂; hexane/EtOAc= 4/1 to 2/1) to give 0.15 g pure product as a colorless oil (87% yield) that solidified upon standing (mp = 48-50 °C).

R_f = 0.17 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.03 (m, 2H), 6.88 (s, 1H), 5.07 (d, 1H, J = 7.7 Hz), 4.73 (d, 1H, J = 7.8 Hz), 3.65 (s, 1H) δ 139.4, 135.5, 133.3, 131.7, 129.3, 126.7, 83.8, 77.0, 21.2 18.9; IR (thin film) ν 3368, 2946, 1501, 1217, 1132, 976, 850, 813, 772 cm⁻¹; HRMS (El) calcd for C₁₁H₁₄O₂: [M]+ = 178.0989. Found: 178.0983.

3-(4-tert-Butyl-phenyl)-oxetan-3-ol: To a solution of 4-¹Bu-phenyl bromide (0.21 mL, 1.5 mmol, 1.5 equiv) in 25 mL dry THF was added ⁷BuLi (1.6 M in hexanes, 0.81 mL, 1.2 mmol, 1.2 equiv) at −78 °C. After the addition was finished, the mixture was stirred for 30 min, before a solution of oxetan-3-one (72 mg, 1.0 mmol, 1.0 equiv) in 1 mL dry THF was added at −78 °C. The mixture was allowed to warm to room temperature over night and quenched with water. The aqueous phase was extracted twice with Et₂O, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash
chromatography (SiO$_2$, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.17 g pure product (80% yield) as white crystals (m$_p$ = 126 °C).

$R_f = 0.27$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.52 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.7 Hz), 4.94 (d, 2H, J = 7.0 Hz), 4.90 (d, 2H, J = 7.0 Hz), 2.55 (s, 1H), 1.34 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.2, 139.8, 125.8, 124.5, 85.7, 76.0, 34.8, 31.5; IR (thin film) ν 3373, 2960, 2873, 1514, 1424, 1237, 1193, 971, 872, 834 cm$^{-1}$; HRMS (El) calcd for C$_{13}$H$_{18}$O$_2$: [M−CH$_2$O]$^+$ = 176.1201. Found: 176.1205. Anal. calcd for C$_{13}$H$_{18}$O$_2$: C, 75.69; H, 8.79. Found: C, 75.85; H, 8.87.

3-Biphenyl-4-yl-oxetan-3-ol: To a solution of 4-bromobiphenyl (1.0 g, 4.3 mmol, 1.4 equiv) in 10 mL dry THF was added $^6$BuLi (1.6 M in hexanes, 2.5 mL, 4.0 mmol, 1.3 equiv) at −78 °C. After the addition was finished, the mixture was stirred for 45 min, before a solution of oxetan-3-one (33, 216 mg, 3.0 mmol, 1.0 equiv) in 3 mL dry THF was added at −78 °C. The mixture was allowed to warm to room temperature over night and quenched with water. The aqueous phase was extracted twice with Et$_2$O, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash chromatography (SiO$_2$, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.46 g pure product (68% yield) as white crystals (m$_p$ = 139-142 °C (toluene)).

$R_f = 0.27$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54 (m, 9H), 4.97 (d, 2H, J = 6.8 Hz), 4.94 (d, 2H, J = 6.9 Hz), 2.79 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 141.4, 141.1, 140.6, 129.0, 127.7, 127.6, 127.3, 125.2, 85.9, 75.9; IR (thin film) ν 3686, 1557, 1220, 963, 875, 773, 697 cm$^{-1}$; Anal. calcd for C$_{15}$H$_{14}$O$_2$: C, 79.62; H, 6.24. Found: C, 79.78; H, 6.39.
3-(2,4-Dimethoxy-phenyl)-oxetan-3-ol: To a solution of 1-bromo-2,4-dimethoxybenzene (0.58 mL, 4.0 mmol, 1.3 equiv) in 10 mL dry THF was added n-BuLi (1.6 M in hexanes, 2.5 mL, 4.0 mmol, 1.3 equiv) at −78 °C. After the addition was finished, the mixture was stirred for 2.5 h, before a solution of oxetan-3-one (33, 216 mg, 3.00 mmol, 1.00 equiv) in 3 mL dry THF was added at −78 °C. The mixture was allowed to warm to room temperature overnight and quenched with water. The aqueous phase was extracted twice with Et₂O, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 4/1 to 1/2 cyclohexane/EtOAc) to give 0.50 g pure product (80% yield) as white crystals (mp = 72-75 °C).

R_f = 0.11 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.16 (d, 1H, J = 9.0 Hz), 6.49 (m, 2H), 5.01 (d, 2H, J = 7.0 Hz), 4.84 (d, 2H, J = 6.9 Hz), 3.83 (s, 1H), 3.82 (s, 1H), 3.21 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 160.6, 126.7, 126.5, 122.3, 103.9, 99.1, 83.1, 75.3, 55.6, 55.4; IR (thin film) ν 2946, 1613, 1510, 1462, 1219, 1030, 973, 773 cm⁻¹; Anal. calcd for C₁₁H₁₄O₄: C, 62.85; H, 6.71. Found: C, 62.84; H, 6.82

Preparation and analytical data of compound 70 can be found on page 155.

3-(4-(1-(dimethylamino)-3-methylbutyl)cyclobutyl)phenyl]oxetan-3-ol: To a solution of aryl bromide 223 (see page 215 for its preparation, 0.71 g, 2.4 mmol, 1.2 equiv) in 10 mL dry THF was added n-BuLi (1.6 M in hexanes, 1.4 mL, 2.2 mmol, 1.1 equiv) at −78 °C. After the addition was finished, the mixture was stirred for 10 min, before a solution of oxetan-3-one (33, 144 mg, 2.0 mmol, 1.0 equiv) in 3 mL dry THF was added at −78 °C. The mixture was allowed to warm to 0 °C and quenched with water. The aqueous phase was
extracted three times with EtOAc, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash chromatography (nAl₂O₃, 4/1 to 1/2 cyclohexane/EtOAc) to give 0.46 g pure product (73% yield) as slightly yellowish crystals (m.p. = 64-66 °C).

R_f = 0.40 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 4.94 (d, 2H, J = 6.9 Hz), 4.89 (d, 2H, J = 6.6 Hz), 3.03 (s, 1H), 2.91 (dd, 1H, J = 2.9 Hz, J = 10.5 Hz), 2.39 (m, 3H), 2.16 (s, 6H), 2.10 (m, 1H), 1.94 (m, 1H), 1.76 (m, 1H), 1.54 (m, 1H), 1.22 (m, 1H), 1.09 (m, 1H), 0.96 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 147.4, 139.0, 128.0, 123.2, 85.6, 67.6, 51.8, 44.0, 36.2, 33.4, 33.1, 26.2 (cyclohexane), 24.2, 21.6, 15.8; IR (thin film) ν 3389, 2951, 2866, 2773, 1611, 1514, 1466, 1366, 1278, 1172, 1113, 972, 881, 835 cm⁻¹; HRMS (EI) calcd for C₂₀H₃₁NO₂: [M-H]⁺ = 316.2271. Found: 316.2272.

6.6.2 3-Aryl-3-fluorooxetanes

3-[4-tert-butylphenyl]-3-fluorooxetane: To a solution of alcohol 67 (41 mg, 0.20 mmol, 1.0 equiv) in 1 mL dry CH₂Cl₂ was added DAST (26 μL, 0.20 mmol, 1.0 equiv) at −78 °C. After stirring for 1 min, saturated aqueous NaHCO₃ was added and the mixture allowed to warm to room temperature. The aqueous phase was extracted twice with CH₂Cl₂, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, pentane/Et₂O = 10/1) to give 19 mg pure product (47% yield) as a colorless oil.

R_f = 0.63 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.48 (m, 4H), 5.10 (ddd, 2H, J = 0.9 Hz, J = 7.8 Hz, J = 21.2 Hz), 4.90 (ddd, 2H, J = 1.0 Hz, J = 7.8 Hz, J = 21.6 Hz), 1.35 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 151.9, 135.5 (d, 1H, J = 23.7 Hz), 125.8, 124.0
Experimental Section

(d, 1H, J = 8.4 Hz), 95.4 (d, 1H, J = 206.8 Hz), 83.3 (d, 1H, J = 25.6 Hz), 34.8, 31.5, 24.2, 21.6, 15.8; ¹⁹F NMR(282 MHz, CDCl₃): δ 149.1; IR (thin film) ν 2963, 2872, 1466, 1364, 1300, 1142, 983, 833, 668, 575 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₇FO: [M⁺] = 208.1258. Found: 208.1260.

The analytical data of compound 73 can be found on page 156.

1-(1-(4-(3-fluorooxetan-3-yl)phenyl)cyclobutyl)-N,N,3-trimethylbutan-1-amine: To a solution of alcohol 71 (see page 187, 0.11 g, 0.35 mmol, 1.0 equiv) in 10 mL dry CH₂Cl₂ was added DAST (75 μL, 0.63 mmol, 1.8 equiv) at −78 °C. The mixture was allowed to warm to −10 °C, stirred for 15 min at this temperature and quenched by dropwise addition of 2 M aqueous NaOH. The aqueous phase was extracted three times with EtOAc, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash chromatography (nAl₂O₃, cyclohexane to 2/1 cyclohexane/EtOAc) to give 47 mg pure product (43% yield) as a yellowish oil. R_f = 0.40 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.43 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 5.10 (dd, 2H, J = 7.9 Hz, J = 21.2 Hz), 4.92 (dddd, 2H, J = 1.1 Hz, J = 3.3 Hz, J = 7.5 Hz, J = 21.7 Hz), 2.93 (dd, 1H, J = 2.8 Hz, J = 10.5 Hz), 2.41 (m, 3H), 2.17 (s, 6H), 2.14 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.54 (m, 1H), 1.23 (ddd, 1H, J = 3.4 Hz, J = 10.6 Hz, J = 14.0 Hz), 1.10 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 148.3, 134.9 (d, J = 24.1 Hz), 128.0, 122.8 (d, J = 8.1 Hz), 95.4 (d, J = 205.7 Hz), 83.2 (dd, J = 2.3 Hz, J = 25.6 Hz), 67.6, 52.0, 44.1, 36.3, 33.2 (d, J = 22.2 Hz), 27.0, 24.2, 21.6, 15.9; ¹⁹F NMR(282 MHz, CDCl₃): δ 147.2; IR (thin film) ν 2951, 2866, 1611, 1467, 1366, 1299, 1176, 1113, 1075, 1016, 982, 881, 835 cm⁻¹; HRMS (EI) calcd for C₂₀H₃₀FNO: [M-C₃H₇]⁺ = 262.1607. Found: 262.1601.
6.6.3 3-Aryl-oxetanes

**3-(4-Methoxyphenyl)-oxetane:** To a solution of alcohol 64 (18 mg, 0.10 mmol, 1.0 equiv) and triethylsilane (17 μL, 0.11 mmol, 1.1 equiv) in 2 mL dry CH₂Cl₂ was added trifluoroacetic acid (84 μL, 1.1 mmol, 11 equiv) at 0 °C. After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature and stirred for further 24 h, before the reaction was quenched by addition of saturated aqueous NaHCO₃. The aqueous phase was extracted twice with Et₂O, the combined organic phases were dried, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 8/1 to 2/1 cyclohexane/EtOAc) to give 12 mg pure product (76% yield) as a colorless oil.

Rᵥ = 0.42 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, 2H, J = 8.6 Hz), 6.91 (d, 2H, J = 8.6 Hz), 5.05 (dd, 2H, J = 5.9 Hz, J = 8.3 Hz), 4.75 (t, 2H, J = 6.4 Hz), 4.19 (m, 1H), 3.81 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 158.4, 133.5, 127.7, 114.0, 79.3, 55.3, 39.7; IR (thin film) ν 2957, 2870, 1161, 1582, 1514, 1464, 1292, 1249, 1179, 1036, 980, 912, 828, 743 cm⁻¹; HRMS (EI) calcd for C₁₀H₁₂O₂: [M]⁺ = 164.0832. Found: 163.0830.

**3-Phenyloxetane:** To a solution of 3-phenyloxetan-3-ol (62, 60 mg, 0.40 mmol, 1.0 equiv) in 2 mL dry THF was added sodium hydride (60% dispersion in mineral oil, 19 mg, 0.48 mmol, 1.2 equiv) at 0 °C. After stirring for 30 min, a solution of pTsCl (92 mg, 0.48 mmol, 1.2 equiv) in 0.8 mL dry THF was added dropwise. The mixture was stirred for 2 h at 0 °C, before saturated aqueous KHSO₄ was added. The aqueous phase was extracted twice with Et₂O, the combined organic phases were dried, concentrated in vacuo
and the residue treated with 1 mL cold Et₂O/pentane = 3/1 to give 112 mg 95w% tosylate 78

\( R_f = 0.42 \) (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.37 – 7.19 (m, 7H), 7.11 – 6.99 (m, 2H), 5.30 (d, J = 8.6, 2H), 5.02 (d, J = 8.6, 2H), 2.35 (s, 3H); \(^1^3\)C NMR (75 MHz, CDCl₃) \( \delta \) 144.3, 136.7, 135.3, 129.5, 129.2, 128.6, 127.4, 127.0, 86.0, 81.4, 21.7).

Of this material 38 mg were dissolved in 5 mL dry Et₂O, before LiAlH₄ (0.10 g, 2.6 mmol, 20 equiv) was added at 0 °C. After stirring for 40 min at 0 °C, the mixture was added slowly to a saturated aqueous solution of K₂CO₃. The aqueous phase was extracted three times with Et₂O, the combined organic phases were dried, concentrated in vacuo and the residue filtered through a short plug of silica gel (10/1 pentane/Et₂O) to give 12 mg product (~60% yield calculated from tosylate 78) as a colorless oil.

\( R_f = 0.47 \) (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.35 (m, 5H), 5.08 (dd, 1H, J = 6.0 Hz, J = 8.4 Hz), 4.79 (dd, 2H, J = 6.0 Hz, J = 6.7 Hz), 4.24 (tt, 1H, J = 7.0 Hz, J = 8.2 Hz)

The spectrum is identical with the one reported in the literature.\(^{360}\)

The analytical data of oxetane 81 can be found on page 155.

**6.6.4 3-Phenyl-3-aminooxetanes**

![Structure of 3-Dibenzylamino-oxetane-3-carbonitrile](image)

3-Dibenzylamino-oxetane-3-carbonitrile\(^{361}\) To a mixture of dibenzylamine (1.0 mL, 5.0 mmol, 4.5 equiv) and 6 mL AcOH was added oxetan-3-one (33, 79 mg, 1.1 mmol, 1.0 equiv), followed by TMSCN (0.33 mL, 2.5 mmol, 2.3 equiv). The mixture was stirred overnight at room temperature, before most of the AcOH was evaporated in vacuo and Et₂O and water were added. The aqueous phase was extracted three times with Et₂O. The

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combined organic phases were washed with aqueous Na₂CO₃ until evolution of CO₂ ceased, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 8/1 to 4/1 cyclohexane/EtOAc) to give pure product (88% yield) as slightly yellow crystals (m_p = 64–66 °C).

R_f = 0.46 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.34 (m, 10H), 4.34 (d, 2H, J = 6.8 Hz), 4.29 (d, 2H, J = 6.8 Hz), 3.51 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 136.9, 129.4, 128.8, 128.3, 118.0, 78.6, 60.9, 55.7; IR (thin film) ν 3029, 2923, 2849, 1494, 1454, 1369, 750, 700 cm⁻¹; Anal. calcd for C₁₈H₁₈N₂O: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.61; H, 6.41; N, 10.06.

Dibenzyl-(3-phenyl-oxetan-3-yl)-amine:³⁶¹ To a solution of PhMgBr (c ~3.0 M, 8 mL THF, 2.8 mL bromobenzene, 584 mg magnesium turnings, 15 equiv ) was added a solution of aminonitrile 82 (0.45 g, 1.6 mmol, 1.0 equiv) in 2.3 mL dry THF at 50 °C. After stirring for 2.5 h, a sample in the NMR indicated full conversion and clean reaction. The mixture (green-grey solution) was cooled to 0 °C, Et₂O was added, followed by brine (slowly). Saturated aqueous KHSO₄ and water were added to dissolve salts (pH~10). The aqueous phase was extracted four times with Et₂O, the combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, cyclohexane to 20/1 cyclohexane/EtOAc; 0.1% NEt₃) to give 0.43 g pure product (71% yield) as a colorless solid (m_p = 88-90 °C).

R_f = 0.46 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.40 (m, 15H), 4.85 (d, 2H, J = 6.3 Hz), 4.72 (d, 2H, J = 6.3 Hz), 3.43 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 139.6, 139.0, 128.6, 128.0, 127.5, 126.9, 80.7, 67.7, 54.0; IR (thin film) ν 3251, 3057, 3029, 2923, 2879, 1681, 19616, 1576, 1493, 1455, 1358, 1165, 1116, 1027, 990, 959, 696 cm⁻¹; HRMS (El) calcd for C₂₃H₂₃NO: [M-CH₂O]+ = 299.1674. Found 299.1650.
3-Phenyl-oxetan-3-ylamine. To a solution of \(N,N\)-dibenzylamine 83 (0.42 g, 1.3 mmol, 1.0 equiv) in 40 mL MeOH was added \( \text{Pd(OH)}_2/C \) (20w%). After exchanging the atmosphere with hydrogen, hydrogen was bubbled through the mixture for 45 min. The mixture was then vigorously stirred for 72 h, filtered through a plug of Celite and concentrated in vacuo. The residue was then dissolved in EtOAc, MgSO\(_4\) was added, filtered and concentrated in vacuo to give 183 mg almost pure product. After distillation, 168 mg pure compound (88% yield) were obtained as a colorless oil that solidified in the freezer (mp = 52-54 °C).

\( R_f = 0.03 \) (SiO\(_2\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.39 (m, 5H), 5.01 (d, 2H, \(J=6.3\)Hz), 4.74 (d, 2H, \(J=6.3\)Hz), 2.13 (s, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 128.9, 127.6, 125.1, 86.7, 59.3; IR (thin film) \(\nu\) 3360, 2951, 2870, 2360, 1604, 1495, 1445, 1326, 1220, 1057, 1030, 978, 861, 761, 709 cm\(^{-1}\); Anal. calcd for C\(_9\)H\(_{11}\)NO: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.20; H, 7.64; N, 9.17.

6.6.5 Conjugate-Addition Products

6.6.5.1 Additions to Acrylate 89

\( \text{(3-Cyano-oxetan-3-yl)-acetic acid ethyl ester.} \) To a solution of acrylate 89 (30 mg, 0.21 mmol, 1.0 equiv) in 2 mL dry MeCN was added acetone cyanohydrine (16 \(\mu\)L, 0.42 mmol, 2.0 equiv), KCN (14 mg, 0.42 mmol, 2.0 equiv) and 18-crown-6 (0.11 g, 0.42 mmol, 2.0 equiv) at ambient temperature. After stirring for 20 h, the mixture was concentrated in vacuo and the residue purified by flash chromatography (SiO\(_2\), 4/1 cyclohexane/EtOAc) to give 29 mg pure product as a colorless oil.

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Experimental Section

R_f = 0.10 (SiO_2, 2/1 cyclohexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 5.01 (d, 2H, J = 6.6 Hz), 4.55 (d, 2H, J = 6.6 Hz), 4.22 (q, 2H, J = 7.1 Hz), 3.08 (s, 2H), 1.29 (t, 3H, J = 7.2 Hz); ^13C NMR (75 MHz, CDCl_3) δ 168.6, 120.3, 78.1, 61.9, 40.2, 34.0, 14.3; IR (thin film) ν 2981, 2895, 2242, 1732, 1374, 1347, 1203, 989 cm⁻¹; HRMS (EI) calcd for C_8H_11NO_3: [M]⁺=169.0739. Found: 169.0739.

![Structure](image)

**Ethyl 2-(3-(dimethylamino)oxetan-3-yl)acetate:** To a solution of acrylate 89 (1 M in Et_2O, 0.2 mL, 0.2 mmol, 1 equiv) in EtOH was added N,N-dimethylammonium chloride (0.15 g, 1.9 mmol, 9.3 equiv), followed by NEt_3 (0.4 mL, 2.8 mmol, 14 equiv). After stirring for 9 h at room temperature, the solvent was concentrated in vacuo and the residue partitioned between EtOAc and water. The aqueous phase was extracted three times with EtOAc, the combined organic phases dried over MgSO_4, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO_2, 7% MeOH in CH_2Cl_2, 0.1% NEt_3) to give 53 mg pure product (135% yield) as a colorless oil.\(^{363}\)

R_f = 0.66 (SiO_2, 10% MeOH in CH_2Cl_2, 0.1% NEt_3); ^1H NMR (300 MHz, CDCl_3) δ 4.57 (d, 2H, J = 6.2 Hz), 4.53 (d, 2H, J = 6.3 Hz), 4.13 (q, 2H, J = 7.1 Hz), 2.67 (s, 2H), 2.17 (s, 6H), 1.24 (t, 3H, J = 7.2 Hz); ^13C NMR (75 MHz, CDCl_3) δ 171.9, 78.9, 62.9, 60.9, 38.2, 34.4, 14.3; IR (thin film) ν 3502, 2875, 2787, 1730, 1457, 1369, 1306, 1180, 1102, 1067, 1030, 983, 836 cm⁻¹; HRMS (EI) calcd for C_9H_17NO_3: [M]⁺=187.1208. Found: 187.1196; [M-CH_2O]⁺= 157.1098. Found: 157.1098; Anal. calcd for C_9H_17NO_3: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.46; H, 9.23; N, 7.59

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\(^{363}\) Supraquantitative yield probably results from evaporation of Et_2O from the solution of acrylate 89.
**Experimental Section**

**Ethyl 2-(3-(4-chlorophenyl)oxetan-3-yl)acetate:** To a solution of $[\text{Rh(cod)Cl}_2]$ (45 mg, 90 μmol, 0.04 equiv) in 7 mL dioxane was added 1.5 M aqueous KOH (1.6 mL, 2.4 mmol, 1.0 equiv) and the yellow solution was stirred for 15 min. Then, a mixture of 4-Chlorobenzeneboronic acid (0.59 g, 3.7 mmol, 1.6 equiv) and acrylate 89 (0.33 g, 2.3 mmol, 1.0 equiv) in 7 mL dioxane was slowly added and the color of the solution turned to orange. After stirring 30 min at room temperature additional 4-Chlorobenzeneboronic acid (0.17 g, 1.1 mmol, 0.48 equiv) as well as 1.5 M aqueous KOH (0.50 mL, 0.75 mmol, 0.33 equiv) were added. The reaction was quenched after further 2 h by the addition of Et₂O (60 mL) and brine (40 mL). The aqueous phase was extracted two times with Et₂O (25 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 8/1 to 2/1 cyclohexane/EtOAc) to give 0.33 g of pure product (56% yield) as slightly yellowish oil.

$R_f = 0.31$ (SiO₂, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl₃) δ 7.31 (m, 2H), 7.12 (m, 2H), 4.96 (d, 2H, $J = 6.2$ Hz), 4.84 (d, 2H, $J = 6.2$ Hz), 4.01 (q, 2H, $J = 7.1$ Hz), 3.11 (s, 2H), 1.13 (t, 3H, $J = 7.1$ Hz); $^{13}$C NMR (75 MHz, CDCl₃) δ 170.3 142.0 132.6, 128.6, 127.2, 81.7, 60.6, 45.1, 44.7, 14.2; IR (thin film) ν 2979, 2875, 2360, 1732, 1494, 1402, 1370, 1344, 1253, 1227, 1189, 1094, 1061, 1014, 984, 829, 720 cm⁻¹; HRMS (El) calcd for C₁₃H₁₅ClO₃: [M-CH₂O]⁺ 224.0595. Found: 224.0604.

**2-(3-Naphthalen-2-ylmethyl-oxetan-3-yl)-ethanol:** A suspension of Cul (0.11 g, 0.56 mmol, 0.1 equiv), acrylate 89 (0.80 g, 5.6 mmol, 1.0 equiv) and TMSCl (0.86 mL, 6.7 mmol, 1.2 equiv) in 20 mL dry THF was stirred for 5 min at ambient temperature, be-
fore it was cooled to −18 °C. Then, a solution of (naphthalen-2-ylmethyl)magnesium bromide in 20 mL dry Et₂O (~0.7 M, prepared by addition of 2-(bromomethyl)naphthalene (3.1 g, 14 mmol, 2.5 equiv) to magnesium turnings (0.37 g, 14.5 mmol, 2.6 equiv) in Et₂O) was added dropwise. After the addition was finished, the flask broke, because of which the reaction stopped at low conversion. The crude product isolated from the cooling bath was dissolved in dry THF, the solution cooled to 0 °C, before LiAlH₄ (0.15 g, 4.0 mmol) was cautiously added. After stirring for 3 h, Na₂SO₄·10 H₂O was added and the mixture stirred for 20 min. After filtration, the filtration residue was boiled three times with EtOAc and the combined filtrates then dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 8/1 cyclohexane/EtOAc to EtOAc) to give 0.18 g pure product (13% yield) as a colorless oil that crystallized upon standing (mp = 60-62 °C).

\[ R_f = 0.38 \text{ (SiO}_2, \text{ EtOAc)}; \ H NMR (300 MHz, CDCl}_3) \delta 7.86 - 7.70 (m, 3H), 7.59 (s, 1H), 7.51 - 7.40 (m, 2H), 7.32 - 7.18 (m, 1H), 4.71 (d, J = 6.0, 2H), 4.55 (d, J = 6.0 Hz, 2H), 3.84 (t, J = 6.8 Hz, 2H), 3.19 (s, 2H), 1.93 (t, J = 6.8 Hz, 2H), 1.74 (s, 1H); \ C NMR (75 MHz, CDCl}_3) \delta 135.5, 133.5, 132.2, 128.1, 128.0, 127.8, 127.6, 127.6, 126.2, 125.6, 81.3, 59.4, 42.5, 42.3, 37.8; IR (thin film) ν 3400, 3051, 2932, 2869, 1633, 1600, 1508, 1444, 1051, 1018, 976, 820, 753 cm⁻¹; HRMS (EI) calcd for C₁₆H₁₈O₂: [M⁺] = 242.1301. Found 242.1301.

6.6.5.2 Additions to Nitroolefin 96

3-(4-Chloro-phenyl)-3-nitromethyl-oxetane: To 1-bromo-4-chlorobenzene (13.1 g, 68.3 mmol, 5.00 equiv) in 180 mL dry THF was added \(^7\)BuLi (2.5 M in hexanes, 24 mL, 60 mmol, 4.5 equiv) at −78 °C. The solution was stirred for 35 min, before a solution of 3-nitromethyleneoxetane (96, 1.57 g, 13.7 mmol, 1.00 equiv) in 10 mL dry THF was slowly
added over 80 min. The mixture was then stirred for 40 min before it was poured on 150 mL ice-cold 5% aqueous HCl. After stirring for 15 min at 0 °C, the aqueous phase was extracted with CH₂Cl₂ three times (100 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 8/1 to 2/1 cyclohexane/EtOAc) giving 1.20 g of >90% pure product (35% yield) as a colorless solid (mp = 115-117 °C).

R₂ = 0.39 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, 2H, J = 8.6 Hz), 7.03 (d, 2H, J = 8.6 Hz), 5.03 (d, 2H, J = 6.7 Hz), 5.00 (s, 2H), 4.90 (d, 2H, J = 6.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 138.0, 133.8, 129.1, 127.1, 82.0, 78.9, 46.8; IR (thin film) ν 2936, 2884, 2360, 1553, 1495, 1424, 1379, 1339, 1100, 1015, 989, 903, 834, 820 cm⁻¹; HRMS (EI) calcd for C₁₀H₁₀ClNO₃: [M]+ 227.0349. Found: 227.0343; Anal. calcd for C₁₀H₁₀ClNO₃: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.54; H, 4.55; N, 6.34.

3-(4-tert-butylphenyl)-3-(nitromethyl)oxetane: To a solution of [Rh(cod)Cl]₂ (5 mg, 9 μmol, 0.04 equiv) in 2 mL dry dioxane was added 1.5 M aqueous KOH (0.17 mL, 0.25 mmol, 1.0 equiv) and the yellow solution was stirred for 3 min. Then, 4-tert-butylbenzeneboronic acid (0.10 g, 0.50 mmol, 2.0 equiv) and nitroolefin 96 (29 mg, 0.25 mmol, 1.0 equiv) were consecutively added. After 2 h, the reaction mixture was partitioned between 120 mL Et₂O and brine. The aqueous phase was extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 8/1 cyclohex-
ane/EtOAc) to give 65 mg (105% yield)\(^{364}\) of pure product as a colorless solid (mp = 86-87 °C).

\[ R_f = 0.39 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } \text{^1H NMR (300 MHz, CDCl}_3) \delta 7.39 \text{ (d, } J = 8.6 \text{ Hz, } 2\text{H), } 7.04 \text{ (d, } J = 8.6 \text{ Hz, } 2\text{H), } 5.09 \text{ (d, } J = 6.6 \text{ Hz, } 2\text{H), } 5.01 \text{ (s, } 2\text{H), } 4.92 \text{ (d, } J = 6.7 \text{ Hz, } 2\text{H), } 1.31 \text{ (s, } 9\text{H); } \text{^13C NMR (75 MHz, CDCl}_3) \delta 151.0, 136.7, 126.1, 125.6, 82.4, 79.4, 47.0, 34.7, 31.4; \text{ IR (thin film) } \nu 2960, 2878, 1548, 1380, 1220, 980, 773, 569 \text{ cm}^{-1}; \text{ HRMS (El) calcd for } \text{C}_{14}\text{H}_{19}\text{NO}_3: } [\text{M}]^+ 249.1360. \text{ Found: 249.1360.} \]

![Image of aldehyde 112](attachment:image.png)

**2-(3-(nitromethyl)oxetan-3-yl)acetaldehyde:** To a solution of nitroolefin 96 (0.45 g, 3.9 mmol, 1.0 equiv) and acetaldehyde (2.5 mL, 44 mmol, 11 equiv) in 15 mL dry THF was added pyrrolidine (80 μL, 1.0 mmol, 0.26 equiv) slowly at room temperature. The mixture was stirred at room temperature over night. CH\(_2\)Cl\(_2\) (50 mL) was added, followed by 1 M aqueous HCl. The aqueous phase was extracted three times with CH\(_2\)Cl\(_2\), the combined organic phases dried over MgSO\(_4\), filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO\(_2\), 2/1 to 1/1 cyclohexane/EtOAc) to give 0.29 g pure product (46% yield) as a yellow oil that solidified in the freezer.

The analytical data of aldehyde 112 can be found on page 170.

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\(^{364}\) The deviation from 100% probably results from a weighing error that is within the error margin of 5% (2 significant digits).
6.6.5.3 Additions to Aldehyde 90

2-(3-azidooxetan-3-yl)ethanol: To a solution of sodium azide (0.98 g, 15 mmol, 3.0 equiv) in 10 mL 80v% AcOH was slowly added a solution of acrolein 90 (0.49 g, 5.0 mmol, 1.0 equiv) in 1 mL Et₂O at room temperature. After 20 min, the mixture was cooled to 0 °C and NaBH₄ (0.55 g, 15 mmol, 3.0 equiv) was cautiously added in two portions. After 20 min, the reaction mixture was partitioned between water and Et₂O and the aqueous phase extracted four times with Et₂O. The combined organic phases were washed twice with 2 M aqueous NaOH, dried over MgSO₄, filtered, concentrated in vacuo and the residue analyzed by NMR, showing product (0.44 g) with greater than 90% purity. Due to potential explosion hazards, this material was not further purified, but used crude.

Rᵣ = 0.06 (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) δ 4.74 (d, 2H, J = 7.1 Hz), 4.66 (d, 2H, J = 7.1 Hz), 3.79 (t, 2H, J = 5.8 Hz), 2.11 (t, 2H, J = 6.0 Hz), 1.94 (s, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 80.5, 63.5, 58.7, 38.1; IR (thin film) ν 3402, 2956, 2882, 2106, 1667, 1431, 1261, 1052, 978, 837 cm⁻¹; HRMS (EI): A mass-spectrum could not be obtained for this compound.

6.6.5.4 Additions to Phenylsulfone 93

3-phenyl-3-(phenylsulfonylmethyl)oxetane: To a solution of [Rh(cod)Cl]₂ (2 mg, 4 μmol, 0.05 equiv) in 1.6 mL dry dioxane was added 1.5 M aqueous KOH (0.16 mL, 0.24 mmol, 1.0 equiv) and the yellow solution was stirred for 1 min. Then, phenylboronic
acid (58 mg, 0.48 mmol, 2.0 equiv) and phenylsulfone 93 (50 mg, 0.24 mmol, 1.0 equiv) were consecutively added. After 6h, a sample showed 60% conversion, so more [Rh(cod)Cl]₂ (2 mg, 4 μmol, 0.05 equiv), KOH (0.16 mL, 0.24 mmol, 1.0 equiv) and phenylboronic acid (58 mg, 0.48 mmol, 2.0 equiv) were added to the mixture. After stirring for 1 h, the reaction mixture was partitioned between Et₂O and brine. The aqueous phase was extracted four times with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; 20/1 to 2/1 cyclohexane/EtOAc) to give 60 mg of pure product (87% yield) as a colorless solid (mp = 162 °C).

Rf = 0.21 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.41 (m, 3H), 7.38 – 7.28 (m, 2H), 7.25 – 7.14 (m, 3H), 7.06 (m, 2H), 5.07 (d, J = 6.5 Hz, 2H), 4.95 (d, J = 6.6 Hz, 2H), 4.04 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 140.4, 140.3, 133.1, 128.8, 128.5, 127.3, 127.2, 126.3, 80.9, 65.1, 45.8; IR (thin film) ν 3063, 2959, 2906, 0870, 1583, 1498, 1446, 1319, 1308, 1268, 1132, 1084, 982, 858, 751, 687, 550, 525 cm⁻¹; HRMS (EI) calcd for C₁₆H₁₆O₃S: [M-CH₂O]⁺=258.0709. Found: 258.0710.

3-methyl-3-phenyloxetane: To a solution of sulfone 172 (0.25 g, 0.86 mmol, 1.0 equiv) in 20 mL MeOH was added mg granulate (1.0 g, 42 mmol, 48 equiv) and the mixture stirred for 2 min in an ultrasound bath. Stirring was continued for 12 h, when a sample in the NMR showed full conversion to product. Et₂O (40 mL) was added followed by Na₂SO₄·10 H₂O. After stirring for 15 min, the mixture was filtered, the filtrate dried over MgSO₄, filtered, evaporated and the residue filtered through a plug of silica gel. The combined filtrate was evaporated and the residue distilled bulb-to-bulb at 200 mbar to give 76 mg pure product (59% yield) as a colorless oil.
Experimental Section

\( R_f = 0.21 \) (SiO\(_2\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.39-7.29 (m, 3H), 7.23 – 7.12 (m, 2H), 4.96 (d, \( J = 5.7 \) Hz, 2H), 4.61 (d, \( J = 5.2 \) Hz, 2H), 1.71 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 146.2, 128.4, 126.1, 124.9, 83.7, 43.5, 28.1; IR (thin film) \( \nu \) 2924, 2852, 1220, 772 cm\(^{-1}\); HRMS (EI) calcd for C\(_{10}\)H\(_{12}\)O: \([M-C_6H_5]^+\) = 71.0497. Found: 71.0854.

![Diagram](image)

1-benzyl-4-(3-methyloxetan-3-yl)piperazine: A solution of N-benzypiperazine (0.19 mL, 1.1 mmol, 1.1 equiv) and sulfone 93 (0.21 g, 1.0 mmol, 1.0 equiv) in 5 mL MeOH was stirred for 20 h at 50 °C. Then, magnesium turnings (0.13 g, 5.0 mmol, 5.0 equiv) were added to the solution and the mixture stirred for 30 sec in an ultrasound bath to start the reaction (slight bubbling). After stirring over night, more magnesium (0.13 g, 5.0 mmol, 5.0 equiv) was added and stirring was continued for 16 h. Et\(_2\)O was added, followed by Na\(_2\)SO\(_4\)·10 H\(_2\)O and the mixture was stirred for 20 min, filtered, dried over Na\(_2\)SO\(_4\), filtered, concentrated \textit{in vacuo} and the residue purified by flash chromatography (nAl\(_2\)O\(_3\), 20/1 to 4/1 cyclohexane/EtOAc) to give 141 mg pure product (57% yield) as a yellowish oil.

\( R_f = 0.39 \) (Al\(_2\)O\(_3\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.35 – 7.23 (m, 5H), 4.57 (d, \( J = 5.3 \) Hz, 2H), 4.20 (d \( J = 5.3 \) Hz, 2H), 3.51 (s, 2H), 2.51 (s, 4H), 2.45 – 2.33 (m, 4H), 1.37 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 137.8, 129.0, 128.0, 126.9, 81.4, 63.0, 60.0, 53.1, 45.1, 15.3; IR (thin film) \( \nu \) 2937, 2866, 2814, 1493, 1451, 1384, 1367, 1352, 1317, 1294, 1269, 1239, 1215, 1134, 1016, 972, 906, 836, 743, 701 cm\(^{-1}\); HRMS (EI) calcd for C\(_{35}\)H\(_{29}\)N\(_2\)O: \([M-CH_2O]^+\) = 216.1621. Found: 216.1621.

![Diagram](image)
**N-benzyl-3-methyloxetan-3-amine:** A solution of benzylamine (0.12 mL, 1.1 mmol, 1.1 equiv) and sulfone 93 (0.21 g, 1.0 mmol, 1.0 equiv) in 5 mL MeOH was stirred for 3 h at 50 °C. Then, magnesium turnings (0.13 g, 5.0 mmol, 5.0 equiv) were added to the solution and the mixture stirred for 30 sec in an ultrasound bath to start the reaction (slight bubbling). After stirring over night, more magnesium (0.13 g, 5.0 mmol, 5.0 equiv) was added and stirring was continued for 16 h. Et₂O was added, followed by Na₂SO₄·10 H₂O and the mixture was stirred for 20 min, filtered, dried over Na₂SO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (nAl₂O₃, 20/1 to 4/1 cyclohexane/EtOAc) to give 140 mg pure product (79% yield) as a yellowish oil.

Rₛ = 0.50 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.39 – 7.22 (m, 5H), 4.57 (d, J = 6.6, 2H), 4.41 (d, J = 6.6, 2H), 3.79 (s, 2H), 1.65 (s, 1H), 1.55 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 140.0, 128.4, 127.9, 127.0, 83.1, 57.5, 47.9, 23.6; IR (thin film) ν 3302, 3028, 2935, 2867, 1604, 1495, 1453, 1378, 1227, 1151, 1070, 1029, 978, 914, 740, 701 cm⁻¹; HRMS (EI) calcd for C₁₁H₁₅NO: [M-CH₃O]+ = 146.0965. Found: 146.0966.

**6.6.6 2-Oxa-6-azaspiro[3.3]heptanes**

![Diagram of 2-Oxa-6-azaspiro[3.3]heptane]

**6-tosyl-2-oxa-6-azaspiro[3.3]heptane:** To a solution of KOH (33.23 g, 0.5923 mol, 3.200 equiv) and p-tosylamide (37.96 g, 0.2217 mol, 1.200 equiv) in 600 mL EtOH 3-Bromo-2,2-bis(bromomethyl)propan-1-ol (60.12 g, 0.1851 mol, 1.000 equiv) was added at room temperature and the reaction mixture was heated to reflux for 90 h. The solvent was removed by evaporation, 500 mL 1 M KOH was added and the white suspension was left to stir for another 2 h at room temperature. The mixture was filtered and the white filter cake was rinsed with water until the washing water was neutral. The filter cake was dried under high vacuum to give 30.55 g of product containing 10 mole-% of tosylamide.
Experimental Section

as a white solid. The overall yield of pure N-tosyl-2-oxa-6-azaspiro[3.3]heptane was calculated to be 27.38 g (58% yield).

\[ R_f = 0.14 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 7.71 (d, 2H, } J = 8.3 \text{ Hz), 7.37 (d, 2H, } J = 8.0 \text{ Hz), 4.59 (s, 4H), 3.91 (s, 4H), 2.46 (s, 3H); } ^13C \text{ NMR (75 MHz, CDCl}_3 \delta 144.6, 131.6, 130.0, 128.5, 80.5, 59.7, 37.7, 21.8; IR \text{ (thin film) } \nu 2930, 2865, 1958, 1846, 1595, 1459, 1442, 1335, 1312, 1292, 1209, 1165, 1143, 1039, 973, 943, 890, 829, 683, 542 \text{ cm}^{-1}; \text{ Anal. calcd for C}_{12}H_{15}NO_3S; C, 56.90; H, 5.97; N, 5.53. Found: C, 56.79; H, 5.98; N, 5.48. HRMS (EI) calcd for C}_{12}H_{15}NO_3S: [M]^+ \text{ = 253.0768. Found: 253.0769.}

\[
\text{[} \begin{array}{c}
\text{NH}_2 \\
\text{O}
\end{array} \text{]}_2 \text{C}_2\text{O}_4^{-} \]

2-oxa-6-azoniaspiro[3.3]heptane oxalate salt: N-tosyl-2-oxa-6-azaspiro[3.3]heptane (129, 7.30 g, 28.8 mol, 1.00 equiv) and magnesium granulate (4.90 g, 0.202 mol, 7.00 equiv) were sonicated for 1 h in MeOH (500 ml). Almost all solvent was removed from the grey reaction mixture on a rotary evaporator to give a viscous grey residue. Et\textsubscript{2}O (500 ml) and Na\textsubscript{2}SO\textsubscript{4}·10 H\textsubscript{2}O (15 g) were added and the resulting light grey mixture was stirred vigorously for 30 min before filtration. The filtrate was dried over Na\textsubscript{2}SO\textsubscript{4} and anhydrous oxalic acid (1.30 g, 14.4 mol, 0.500 equiv) dissolved in EtOH (~1 ml) was added to the organic phase. A thick white precipitate formed instantly. It was filtered off and dried under vacuum to give 3.37 g (81% yield) of an amorphous white solid. The obtained product showed the anticipated signals in \textsuperscript{13}C NMR and \textsuperscript{1}H NMR with no impurities but did not pass elemental analysis. This may be due to the presence of a certain fraction of the hydroxalate salt in the product.
Experimental Section

$^1$H NMR (300 MHz, D$_2$O) δ 4.87 (s, 4H), 4.34 (s, 4H), 2.22 (m, 2H); $^{13}$C NMR (75 MHz, D$_2$O) δ 168.6, 79.9, 54.5, 40.0; IR (thin film of 2-Oxa-6-aza-spiro[3,3]heptane) ν 3400, 2953, 2875, 1653, 1556, 1431, 1352, 1250, 963, 829, 774 cm$^{-1}$; HRMS (EI) done with 2-Oxa-6-aza-spiro[3,3]heptane, calcd for C$_5$H$_9$NO [M-H]$^+$ = 98.0601. Found 98.0603.

\[
\begin{align*}
\text{N,4-biphenyl-2-oxa-6-azaspiro[3,3]heptane:} & \text{ In a dry 50 mL two-neck flask 4-bromobiphenyl (0.517 g, 2.22 mmol, 1.00 equiv) was dissolved in 10 mL of dry and degassed toluene. To the clear solution were added palladium(II)acetate (0.026 g, 0.12 mmol, 0.050 equiv), BINAP (0.078 g, 0.18 mmol, 0.050 equiv), dry Cesium carbonate (0.666 g, 11.1 mmol, 5.00 equiv), bis(2-oxa-6-azoniaspiro[3,3]heptane) oxalate (130, 0.384 g, 1.33 mmol, 0.600 equiv) and 4 drops of NEt$_3$. The mixture was heated to reflux over night and then filtered through a plug of celite. The filter cake was washed with CH$_2$Cl$_2$ and the solvent was removed from the filtrate. The orange oily residue was purified by flash chromatography (nAl$_2$O$_3$, cyclohexane to 4/1 cyclohexane/EtOAc) yielding 0.327 g (59% yield) yellow crystals as the pure product.} \\
R_f = 0.5 (Al$_2$O$_3$, cyclohexane/EtOAc 2:1); mp 164-165 °C; $^1$H NMR 7.50 (dd, 4H, J = 7.9 Hz, 16.2 Hz), 7.40 (t, 2H, J = 7.7 Hz), 7.28 (d, 1H, J = 9.0 Hz), 6.53 (d, 2H, J = 8.6 Hz), 4.86 (s, 4H), 4.07 (s, 4H); $^{13}$C NMR 150.3, 141.0, 130.9, 128.6, 127.6, 126.3, 126.2, 111.9, 81.2, 61.7, 39.2; IR (thin film) ν/cm$^{-1}$: 3061, 2940, 2871, 1626, 1572, 1494, 1450, 1420, 1352, 1317, 1219, 1121, 1067, 1028, 973, 935, 866, 788, 758, 711; HRMS (EI) calculated for C$_{17}$H$_{17}$NO [M]$^+$ 251.1305. Found 251.1308; EA calculated for C$_{17}$H$_{17}$NO C: 81.24, H: 6.82, N: 5.57, O: 6.37. Found C: 81.23, H: 7.07, N: 5.50, O: 6.20.
\end{align*}
\]
**Experimental Section**

*N-benzoyl-2-oxa-6-azaspiro[3.3]heptane:* Benzoylchloride (0.7 mL, 6.0 mmol, 1.5 equiv), NEt₃ (3.0 mL, 22 mmol, 5.0 equiv) and bis(2-oxa-6-azoniaspiro[3.3]heptane) oxalate (130, 0.577 g, 2.00 mmol, 0.5 equiv) were suspended in 25 mL DCM. The reaction mixture was stirred vigorously for 30 min and sonicated for another 30 min. Then the yellow reaction mixture was poured into a separation funnel, 30 mL water was added and the aqueous phase was extracted four times with 30 mL CH₂Cl₂. The combined organic phases were dried over MgSO₄ and the solvent was removed. The resulting yellow liquid was purified by flash chromatography (Al₂O₃, cyclohexane/EtOAc 2:1 to pure EtOAc) to give 0.623 g white solid as the pure product (77% yield).

Rᵣ = 0.065 (Al₂O₃, cyclohexane/EtOAc 2:1); mp 95-96 °C; ¹H NMR (300 MHz, CDCl₃) 7.61 (m, 2H), 7.44 (m, 3H), 4.81 (d, 4H, J = 10.7 Hz), 4.44 (s, 2H), 4.36 (s, 2H); ¹³C NMR 170.2, 132.7, 131.1, 128.3, 127.7, 80.7, 62.7, 58.1, 38.2; IR (thin film) ν/cm⁻¹: 3061, 2940, 2872, 1625, 1572, 1494, 1450, 1420, 1352, 1317, 1219, 1121, 1067, 1028, 973, 935, 866, 788, 758, 711; MS (EI) calculated for C₁₂H₁₃NO₂ [M-H]⁺ 202.0863. Found 202.0862; EA calculated for C₁₂H₁₃NO₂: 70.92, H: 6.45, N: 6.89, O: 15.74. Found C: 70.80, H: 6.53, N: 6.88, O: 15.79.
**N-((anthracen-10-yl)methyl)-2-oxa-6-azaspiro[3.3]heptan**: Bis(2-oxa-6-azoniaspiro-[3.3]heptane) oxalate (130, >90% pure, 0.23 g, 0.78 mmol, 0.50 equiv) was stirred together with K₂CO₃ (1.17 g, 8.47 mmol, 6.00 equiv) in 8 mL DMF for 10 min at room temperature. 10-(chloromethyl)anthracene (0.322 g, 1.42 mmol, 1.00 equiv) was added to the mixture and the reaction was left to stir overnight. After 24 h TLC indicated remaining starting material. To complete conversion the reaction was refluxed for 10 min. To the reaction mixture was added Et₂O (200 mL) and the aqueous phase was washed three times with brine in order to remove residual DMF. The aqueous phase was dried over Na₂SO₄ and anhydrous oxalic acid (0.0639 g, 0.710 mmol, 0.500 equiv) dissolved in little EtOH was added. The resulting yellow precipitate was filtered, washed with ether and dissolved in chloroform. In a separation funnel 150 mL NaOH (2 M) were added and the aqueous phase was extracted three times with 100 mL EtOAc. The combined organic phases were dried over Na₂SO₄ and the solvent was concentrated in vacuo to give 0.217 g pure product (52% yield) as yellow crystals (mp = 177-178 °C).

Rᶠ = 0.41 (Al₂O₃, cyclohexane/EtOAc 2:1); mp 177-178 °C; ¹H NMR (300 MHz, CDCl₃) 8.42 (m, 3H), 8.01 (m, 2H), 7.50 (m, 4H), 4.69 (s, 4H), 4.54 (s, 2H), 3.46 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) 131.3, 130.8, 129.0, 127.4, 125.7, 124.6, 81.3, 63.5, 53.4, 39.0, two aromatic signals overlap and cannot be distinguished; IR (golden gate) ν/cm⁻¹: 3053, 2916, 2890, 2858, 2825, 2809, 1733, 1622, 1521, 1490, 1444, 1338, 1308, 1243, 1223, 1184, 1161, 1136, 1113, 1068, 1025, 989, 970, 940, 906, 893, 880, 865, 839, 784, 753, 721, 703, 647, 631; MS (El) calculated for C₂₀H₁₉NO [M]⁺ 289.15. Found 289.15.
(1R,2S)-1-phenyl-2-(2-oxa-6-aza-spiro[3.3]heptan-6-yl)propan-1-ol: To a solution of 3,3-bis(bromomethyl)oxetane (119, 5.0 g, 22 mmol, 1.0 equiv) and (1R,2S)-norephedrine (3.2 g, 22 mmol, 1.0 equiv) in 50 mL toluene was added NaHCO₃ (3.8 g, 45 mmol, 2.1 equiv). The mixture was refluxed for 60 h using a Dean-Stark trap, allowed to cool to room temperature, before water was added. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (nAl₂O₃, 2/1 cyclohexane/EtOAc to EtOAc) to give 0.67 g pure product (13% yield) as a white solid (mp = 144-146 °C) Rₓ = 0.12 (SiO₂: hexane/EtOAc 2:1); ¹H NMR (300 MHz, CDCl₃): δ 7.29 (m, 5H), 4.76 (s, 4H), 4.68 (d, 1H, J = 3.0 Hz), 3.43 (q, 4H, J = 7.0 Hz), 2.96 (s, 1H), 2.35 (dq, 1H, J = 3.0 Hz, J = 6.5 Hz), 0.64 (d, 3H, J = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 128.0, 126.9, 125.7, 81.2, 71.2, 68.2, 62.1, 38.3, 9.2 (aromatic quat. carbon not observed); IR (thin film) ν 3404, 2936, 2866, 1450, 1383, 1333, 1245, 1199, 1170, 1068, 1043, 972 cm⁻¹; Anal. calcd. for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00; Found: C, 71.96; H, 8.21; N, 6.03; MS (EI) calcd. for C₁₄H₁₉NO₂ [M-H]⁺ 232.1333; Found, 232.1330.

6-Benzhydryl-2-oxa-6-aza-spiro[3.3]heptane: A solution of bis(bromomethyl)oxetane (119, 5.0 g, 22 mmol, 1.0 equiv), benzhydrylamine (4.1 g, 22 mmol, 1.0 equiv) and N,N-diisopropylethylamine in 140 mL MeCN was refluxed for 20 h. The mixture was cooled to room temperature and concentrated in vacuo. Et₂O was added and the mixture filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography. The yield was 65%.

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³⁶⁶ Procedure adapted from: F. H. Tsai, C. G. Overberger, R. Zand, Biopolymers 1990, 30, 1039.
tography (nAl₂O₃, 20/1 to 2/1 cyclohexane/EtOAc) to give 0.59 g pure product (10% yield) as colorless crystals (mᵰ = 139-141 °C).

\[ R_f = (\text{SiO}_2: \text{hexane/EtOAc} 2:1); \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3): \delta 7.26 (m, 10H), 4.75 \text{ (s, 4H),} \]
\[ 4.23 \text{ (s, 1H),} 3.29 \text{ (s, 4H);} \]
\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3): \delta 141.7, 128.3, 127.3, 127.0, 81.6, 78.0, 63.0, 38.1; \]
\[ \text{IR (thin film)} \nu 3024, 2934, 2864, 2822, 1597, 1492, 1451, 1342, 1240, 1074, 973, 744, 707 \text{ cm}^{-1}; \]
\[ \text{MS (El) calcd. for } C_{18}H_{19}NO \ [M-H]^+ \text{ 232.1333; Found, 232.1330.} \]

6.6.7 Sibutramine Analogues

![3-(4-Chlorophenyl)-oxetane-3-carbonitrile](image)

3-(4-Chlorophenyl)-oxetane-3-carbonitrile: \(^{367}\) To 3-(4-Chlorophenyl)-3-nitromethyloxetane (110\(^{368}\), 83 mg, 0.40 mmol, 1.0 equiv) in 3.5 mL dry THF was added tetrabutylammonium iodide (6.9 mg, 19 µmol, 0.050 equiv), benzyl bromide (47 µL, 0.40 mmol, 1.1 equiv) and potassium hydroxide (22 mg, 0.39 mmol, 1.1 equiv). The white mixture was stirred for 24 h at room temperature. It was then cooled to −20 °C and NEt₃ (0.45 mL, 3.20 mmol, 9.0 equiv) and thionyl chloride (0.11 mL, 1.6 mmol, 4.5 equiv) was added. The slightly yellow mixture was stored for 8 h at −20 °C before it was quenched with 10 mL water. The aqueous phase was extracted with Et₂O three times (20 mL). The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; cyclohexane/EtOAc 20/1 to 2/1) giving 47 mg of 90% pure product (61% yield) as yellow oil. Upon upscaling (899.6 mg of 3-(4-chlorophenyl)-3-nitromethyloxetane), the yield decreased to 40% but pure product as colorless solid (mᵰ = 42-44 °C) was obtained by distillation (0.27 mbar, bᵰ = 140 °C).


\(^{368}\) For the preparation of this compound, refer to page 195.
Experimental Section

\[
\text{R}_f = 0.51 \quad (\text{SiO}_2: \text{hexane/EtOAc} \ 2:1); \quad ^{1}H \text{ NMR (300 MHz, CDCl}_3): \delta 7.59 (m, 4H), 5.32 (d, 2H, J = 6.3 Hz), 4.82 (d, 2H, J = 6.3 Hz); \quad ^{13}C \text{ NMR (75 MHz, CDCl}_3): \delta 135.0, 134.5, 129.5, 126.7, 119.6, 81.0, 40.6; \text{ IR (thin film)} \ \nu 3046, 2965, 2889, 2360, 2243, 1905, 1597, 1493, 1406, 1329, 1281, 1097, 1013, 985, 942, 861, 824, 714 \text{ cm}^{-1}; \text{ Anal. calcd. for C}_{10}H_8ClNO: C, 62.03; H, 4.16; N, 7.23. \text{ Found: C, 61.79; H, 4.28; N, 7.11; MS (EI) calcd. for C}_{10}H_8ClNO [M]^+ 193.0294. \text{ Found: 193.0286.}
\]

![Chemical structure image](image)

**1-[3-(4-Chlorophenyl)-oxetane-3-yl]-3-methylbutyl]-dimethylamine 3**: To magnesium (137.1 mg, 5.6 mmol, 4.0 equiv) in 3 mL dry Et\(_2\)O was slowly added isobutyl bromide (0.8 mL, 7.0 mmol, 5.0 equiv). The mixture was refluxed for 20 min. 3-(4-Chlorophenyl)-oxetane-3-carbonitrile (158, 274.5 mg, 1.4 mmol, 1.0 equiv) in 4.5 mL dry toluene was then added at the rate the Et\(_2\)O was removed by distillation. Distillation was stopped when the internal temperature reached 90 °C and the mixture was stirred for 2 h at this temperature. A slurry of NaBH\(_4\) (0.22 g, 5.7 mmol, 4.0 equiv) in 10 mL iPrOH was added. The mixture was refluxed for 5 h and then stirred for 19 h at room temperature before the iPrOH was evaporated *in vacuo*. Water (20 mL) was added and the mixture was allowed to stand for 30 min before the aqueous phase was extracted with EtOAc three times (50 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated *in vacuo*. For purification, the residue was dissolved in 30 mL EtOAc and the solution was acidified with 3 M HCl to pH 1. The mixture was extracted with 1 M HCl three times (30 mL) and the combined aqueous phases were extracted with EtOAc three times (40 mL). The aqueous phase was basified with KOH to pH 14 and extracted with EtOAc three times (40 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated *in vacuo* giving 244 mg (69% yield) of 85% pure 1-[3-(4-Chlorophenyl)-oxetane-3-yl]-3-methylbutylamine (159, \text{R}_f = 0.50 \quad (\text{Al}_2\text{O}_3: \text{hexane/EtOAc} \ 2:1); \quad ^{1}H \text{ NMR (300 MHz, CDCl}_3): \delta 7.32 (m, 2H), 6.95 (m, 2H), 4.89 (m, 3H), 4.66 (d, 1H, J = 5.9 Hz), 3.41 (dd, 1H, J = 2.0 Hz, J = 10.8 Hz), 1.70 (m, 1H), 1.63 (m, 2H), 1.15 (m, 1H), 0.90 (m, 6H), 0.76 (m, 1H);
Experimental Section

MS (El) calcd. for C₆H₁₂N [M- C₆H₆ClO]⁺ 86.0969. Found: 86.0972. To 1-[3-(4-Chlorophenyl)-oxetane-3-yl]-3-methylbutylamine (159, 40 mg, 0.20 mmol, 1.0 equiv) in 1 mL MeCN was added 37% formaldehyde (58 μL, 0.80 mmol, 5.0 equiv) and the solution was stirred for 15 min. NaCNBH₃ (22 mg, 0.40 mmol, 2.3 equiv) was added, followed 15 min later by AcOH (50 μL, 0.90 mmol, 5.8 equiv). The mixture was stirred for 2.25 h before 10 mL 2% MeOH-CH₂Cl₂ was added. The aqueous phase was extracted with 1 mL NaOH three times (10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂; cyclohexane/EtOAc 8/1 to 4/1) giving 21.1 mg of a white solid as pure product (50% yield).

Rᵣ = 0.47 (SiO₂: hexane/EtOAc 2:1); ¹H NMR (300 MHz, CDCl₃): δ 7.27 (m, 2H), 6.99 (m, 2H), 4.89 (m, 2H), 4.75 (d, 1H, J = 5.8 Hz), 4.56 (d, 1H, J = 5.8 Hz), 3.42 (dd, 1H, J = 2.9 Hz, J = 10.8 Hz), 2.18 (s, 6H), 1.56 (m, 1H), 1.31 (dd, 1H, J = 3.4 Hz, J = 10.8 Hz, J = 14.2 Hz), 1.01 (d, 3H, J = 6.5 Hz), 0.97 (m, 1H), 0.90 (d, 3H, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 141.5, 132.1, 128.9, 127.7, 82.0, 81.2, 66.6, 52.0, 43.8, 36.4, 26.0, 23.9, 21.4; IR (thin film) ν 2955, 2868, 2826, 2780, 2359, 1897, 1772, 1494, 1466, 1398, 1368, 1276, 1095, 1045, 1014, 985, 822 cm⁻¹; Anal. calcd. for C₇H₁₂O₃: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.22; H, 8.37; N, 4.92; MS (El) calcd. for C₇H₁₆N [M- C₆H₆ClO]⁺ 114.1277. Found: 144.1308.

6-(4-Chloro-phenyl)-2-oxa-spiro[3.3]heptane-6-carbonitrile. A solution of 4-chlorophenylacetonitrile (13.1 g, 86.4 mmol, 1.00 equiv) and bis(bromomethyl)oxetane (119, 21.0 g, 86.4 mmol, 1.00 equiv) in 22 mL Et₂O was added dropwise over 30 min to a vigorously stirred suspension of KOH (11.3 g, 201 mmol, 2.34 equiv) in 60 mL DMSO at room temperature. After the addition was complete, the mixture was stirred for 3 h, be-

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fore the reaction was quenched by addition of ice water (40 mL). Et₂O (40 mL) was added, the mixture filtered through Celite and the filter cake washed with EtOAc. The aqueous layer of the combined filtrate was extracted twice with EtOAc. The combined organic phases were washed three times with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue recrystallized from 25 mL toluene to give 1.97 g pure product (10% yield) as colorless crystals (mp = 148-150 °C (toluene)).

\[ R_f = 0.38 \text{ (SiO}_2: \text{ cyclohexane/EtOAc 2:1)}; \] ¹H NMR (300 MHz, CDCl₃): δ 7.44 – 7.32 (m, 2H), 7.29 – 7.24 (m, 2H), 4.96 (s, 2H), 4.63 (s, 2H), 3.16 – 3.06 (m, 2H), 2.83 – 2.72 (m, 2H);

¹³C NMR (75 MHz, CDCl₃): δ 136.9, 129.2, 126.9, 123.1, 83.4, 81.6, 44.6, 39.1, 35.0; IR (thin film) ν 3498, 2939, 2863, 2614, 2353, 2230, 1961, 1898, 1808, 1601, 1494, 1449, 1425, 1274, 975, 772, 698 cm⁻¹; Anal. calcd. for C₁₃H₁₂ClNO: C, 66.81; H, 5.18; N, 5.99; Cl, 15.17. Found: C, 66.77; H, 5.19; N, 5.96; Cl, 14.98; HRMS (EI) calcd. for C₁₃H₁₂ClNO: [M⁺] = 233.0602. Found: 233.0598.

**2,6-Diphenyl-spiro[3.3]heptane-2,6-dicarbonitrile.**³⁶⁹ A solution of phenylacetonitrile (2.4 g, 21 mmol, 2.0 equiv) in Et₂O was added to a mixture of tetrabromoerithrytol (4.0 g, 10 mmol, 1.0 equiv) and KOH (2.4 g, 43 mmol, 4.1 equiv) in 15 mL DMSO over the course of 30 min at room temperature. The mixture was stirred for 1 h, before the reaction was stopped by the addition of ice water. Et₂O was added and the mixture filtered through a plug of sand. The aqueous phase of the filtrate was extracted three times with Et₂O, the combined organic phases were washed three times with water, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 4/1 cyclohexane/EtOAc) to give 0.45 g pure product (15% yield) as colorless crystals (mp = 114-116 °C).
Experimental Section

Rf = 0.59 (SiO2: cyclohexane/EtOAc 2:1); 1H NMR (300 MHz, CDCl3): δ 7.38 (m, 10H), 3.35 (dd, 2H, J = 4.3 Hz, J = 12.2 Hz), 3.01 (d, 2H, J = 12.3 Hz), 2.88 (dd, 2H, J = 4.3 Hz, J = 12.3 Hz), 2.70 (d, 2H, J = 12.3 Hz); 13C NMR (75 MHz, CDCl3): δ 168.0, 139.0, 129.3, 128.4, 125.8, 124.2, 47.2, 46.2, 35.9, 35.2; IR (thin film) ν 3065, 3028, 2981, 2938, 2230, 1961, 1884, 1812, 1601, 1495, 1448, 1426, 1272, 1081, 755, 699 cm⁻¹; Anal. calcd. for C21H18N2: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.31; H, 6.19; N, 9.32; HRMS (EI) calcd. for C21H18N2: [M]+ = 298.1465. Found: 298.1463.

[2-[1-(4-Chloro-phenyl)-cyclobutyl]-2-oxo-ethyl]-phosphonic acid dimethyl ester: To a solution of dimethyl methylphosphonate (5.62 mL, 64.0 mmol, 4.00 equiv) in 50 mL dry THF was added nBuLi (2.5 M in hexanes, 22.3 mL, 55.9 mmol, 3.5 equiv) at −78 °C. After stirring for 15 min, a solution of 1-(4-chlorophenyl)cyclobutanecarbonitrile (3.05 g, 15.9 mmol, 1.00 equiv) in 10 mL dry THF was added over 30 min. The bright red mixture was then allowed to warm to room temperature and stirred for further 2 h. Saturated aqueous KHSO4 was added (resulting in pH 5) and the aqueous phase extracted three times with EtOAc. The combined organic phases were dried over MgSO4, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO2, 2/1 cyclohexane/EtOAc to EtOAc) to give a mixture of product and probably the corresponding imine. This mixture was dissolved in THF and stirred with saturated aqueous KHSO4 for 30 min. The mixture was extracted three times with EtOAc, dried over MgSO4, filtered, concentrated in vacuo, giving 3.45 g pure product (68% yield) as a colorless oil.

Rf = 0.12 (SiO2: cyclohexane/EtOAc 2:1); 1H NMR (300 MHz, CDCl3): δ 7.35 – 7.29 (m, 2H), 7.19 – 7.09 (m, 2H), 3.70 (dd, J = 0.8, 11.2, 6H), 2.92 – 2.74 (m, 4H), 2.35 (ddd, J = 7.5, 9.4, 12.2, 2H), 2.03 – 1.71 (m, 2H); 13C NMR (75 MHz, CDCl3): δ 201.3 (d, J = 6.9 Hz), 140.4, 133.3, 129.2, 127.3, 59.8 (d, J = 4.3 Hz), 53.1 (d, J = 6.5 Hz), 35.3 (d, J = 137.2 Hz), 30.3, 15.8; 31P NMR (121 MHz, CDCl3): δ 24.2; IR (thin film) ν 3468, 2954, 2854, 1708, 1492,
1399, 1255, 1184, 1034, 998, 872, 816 cm⁻¹; HRMS (ESI) calcd for C₁₄H₁₂ClO₂P: [M+Na]⁺ = 339.0523. Found: 339.0529

The analytical data for α,β-unsaturated ketone 94 can be found on page 151.

1-[1-[4-Chloro-phenyl]-cyclobutyl]-2-oxetan-3-yl-ethanol: To a solution of ketophosphonate 220 (see page 211 for its preparation; 1.22 g, 3.84 mmol, 1.05 equiv) in 10 mL dry THF was added sodium hydride (60% dispersion in mineral oil, 146 mg, 3.65 mmol, 1.00 equiv) at 0 °C. After stirring for 20 min, a solution of oxetan-3-one (33, 263 mg, 3.65 mmol, 1.00 equiv) in 1 mL dry THF was added and the solution stirred at 0 °C for 30 min. The solvent was partially concentrated in vacuo, toluene was added and the mixture put on a column (SiO₂, 20/1 to 4/1 cyclohexane/EtOAc) to give 1-[1-[4-Chloro-phenyl]-cyclobutyl]-2-oxetan-3-ylidene-ethanone (94) as a colorless oil. This material was dissolved in 10 mL MeOH and added over 20 min to a suspension of Rh/C (5 w%, 70 mg) in 60 mL MeOH under hydrogen. Stirring was continued for 20 min, when a sample in the NMR indicated full conversion. The mixture was filtered through a plug of Celite, the filtrate concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.56 g of the pure ketone (58% yield) as a colorless oil (Rf = 0.35 (SiO₂: cyclohexane/EtOAc 2:1); ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, 2H, J = 8.5 Hz), 7.15 (d, 2H, J = 8.5 Hz), 4.76 (dd, 2H, J = 6.2 Hz, J = 7.8 Hz), 4.13 (t, 2H, J = 6.3 Hz), 3.21 (m, 1H), 2.72 (m, 2H), 2.64 (d, 2H, J = 7.6 Hz), 2.38 (ddd, 2H, J = 5.5 Hz, J = 9.7 Hz, J = 9.0 Hz), 1.88 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 208.4, 141.1, 132.7, 129.0, 128.8, 127.6, 127.5, 77.1, 58.2, 40.3, 30.9, 30.6, 16.0; HRMS (EI) calcd. for C₁₃H₁₁₇ClO₂: [M]⁺ = 264.0912. Found: 264.0914). Parts of this material (365 mg, 1.38 mmol, 1.00 equiv) were dissolved in 10 mL ¹PrOH and NaBH₄ (52 mg, 1.4 mmol, 1.0 equiv) was added at 0 °C. After stirring
for 20 min, the mixture was allowed to warm to room temperature and stirred over night. The mixture was partitioned between brine and Et₂O and the aqueous phase extracted three times with Et₂O. The combined organic phases were washed once with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 4/1 to 1/1 cyclohexane/EtOAc) to give 300 mg pure product as a colorless oil (82% yield).

\[ R_f = 0.11 \] (SiO₂: cyclohexane/EtOAc 2:1); \(^1\)H NMR (300 MHz, CDCl₃): δ 7.29 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 8.5 Hz), 4.75 (ddd, 2H, J = 6.0 Hz, J = 7.9 Hz, J = 10.2 Hz), 4.33 (dt, 2H, J = 3.6 Hz, J = 6.2 Hz), 3.66 (dd, 1H, J = 5.3 Hz, J = 10.0 Hz), 3.15 (m, 1H), 2.31 (m, 4H), 1.92 (m, 3H), 1.32 (d, 1H, J = 6.7 Hz), 1.21 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ 143.8, 131.8, 128.3, 127.9, 77.9, 75.7, 50.5, 35.6, 33.1, 30.6, 30.4, 15.6; IR (thin film) ν 3414, 2937, 1492, 1395, 1294, 1092, 1012, 970, 826 cm⁻¹; Anal. calcd. for C₁₁H₁₂ClNO: C, 66.81; H, 5.18; N, 5.99; Cl, 15.17. Found: C, 66.77; H, 5.19; N, 5.96; Cl, 14.98; HRMS (EI) calcd. for C₁₁H₁₀ClO₂: [M]+ = 266.1074. Found: 266.1035.

3-[2-Azido-2-[1-(4-chlorophenyl)-cyclobutyl]-ethyl]oxetane: To a solution of alcohol 160 (490 mg, 1.84 mmol, 1.00 equiv), PPh₃ (600 mg, 2.28 mmol, 1.24 equiv) and DEAD (367 µL, 2.33 mmol, 1.26 equiv) in 30 mL dry THF was added DPPA (500 µL, 2.33 mmol, 1.26 equiv) at 0 °C over 15 min. The mixture was allowed to warm to room temperature and stirred over night, before PPh₃ (600 mg, 2.28 mmol, 1.24 equiv), DEAD (367 µL, 2.33 mmol, 1.26 equiv) and DPPA (500 µL, 2.33 mmol, 1.26 equiv) were added consecutively to drive the reaction to completion. After stirring for further 20 h, the solvent was concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 2/1 cyclohexane/EtOAc) to give 306 mg pure product (57% yield) as a yellowish oil.

R_f = 0.53 (SiO_2: cyclohexane/EtOAc 2:1); ^1^H NMR (300 MHz, CDCl_3): δ 7.30 (d, 2H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 4.78 (m, 2H), 4.33 (dt, 2H, J = 1.1 Hz, J = 6.2 Hz), 3.44 (dd, 1H, J = 2.3 Hz, J = 11.1 Hz), 3.09 (m, 1H), 2.43 (m, 3H), 2.28 (m, 1H), 2.04 (m, 1H), 1.85 (m, 2H), 1.37 (m, 1H); ^1^C NMR (75 MHz, CDCl_3): δ 142.9, 132.1, 128.5, 127.9, 77.2, 76.7, 69.0, 50.5, 33.5, 33.1, 31.7, 31.2, 15.7; IR (thin film) ν 2961, 2867, 2182, 1492, 1255, 1093, 1012, 978, 829 cm^{-1}.

1-(4-Bromo-phenyl)-cyclobutanecarbonitrile

To a mixture of powdered KOH (13.3 g, 237 mmol, 4.31 equiv) and DMSO (42 mL) was added a solution of 4-bromophenylacetetonitrile (10.8 g, 55.0 mmol, 1.00 equiv) and 1,3-dibromopropane (5.78 mL, 57 mmol, 1.04 equiv) in 15 mL Et_2O in a way so that the inner temperature of the flask did not exceed 10 °C (ice-cooling). After the addition was finished, the mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched by addition of ice water (30 mL) to the precooled mixture, followed by Et_2O (35 mL). The mixture was then filtered through Celite and the aqueous phase of the filtrate extracted twice with Et_2O. The combined organic phases were washed three times with water, dried over MgSO_4, filtered, concentrated in vacuo and the residue distilled to give 5.94 g pure product (46% yield) as a slightly yellowish oil.

R_f = 0.61 (SiO_2: cyclohexane/EtOAc 2:1); ^1^H NMR (300 MHz, CDCl_3): δ 7.52 (d, 2H, J = 8.7 Hz), 7.29 (d, 1H, J = 8.6 Hz), 2.82 (m, 1H), 2.59 (m, 1H), 2.43 (m, 1H), 2.07 (m, 1H); ^1^C NMR (75 MHz, CDCl_3): δ 138.7, 131.9, 127.3, 123.8, 121.8, 39.8, 34.7, 17.1; IR (thin film) ν 2951, 2234, 1590, 1488, 1398, 1074, 1009, 820 cm^{-1}; Anal. calcd. for C_{11}H_{10}BrN: C, 55.96; H, 4.27, N, 5.93. Found: C, 56.18; H, 4.25, N, 5.76.; HRMS (El) calcd. for C_{13}H_{10}BrN: [M]^+ = 234.9991. Found: 234.9993.
[1-[1-(4-Bromo-phenyl)-cyclobutyl]-3-methyl-butyl]-dimethyl-amine: \(^{369}\)

To a mixture of dry Et\(_2\)O (7 mL) and Grignard turnings (0.49 g, 20 mmol, 2.0 equiv) was added slowly isobutyl bromide (2.2 mL, 20 mmol, 2.0 equiv) maintaining slight reflux of the solution. The mixture was stirred at 40 °C for 1 h, before a solution of nitrile 227 (2.3 g, 10 mmol, 1.0 equiv) in 7 mL dry toluene was added dropwise. Et\(_2\)O was distilled out of the reaction mixture at the same rate as the solution was added (bath temperature adjusted to 102 °C during the addition). When the temperature of the mixture reached 90 °C, the distillation was stopped and stirring at 90 °C continued for 8 h. Then, a slurry of NaBH\(_4\) (1.5 g, 40 mmol, 4.0 equiv) in 12 mL \(^1\)PrOH was added cautiously. The mixture was refluxed for 20 h, before it was allowed to cool to room temperature. Water was added and after stirring for 30 min, the aqueous phase was extracted three times with EtOAc. The combined organic phases were concentrated in vacuo and dissolved in 60 mL MeCN, before formaldehyde (37\%, aqueous solution, 4.1 mL, 50 mmol, 5.0 equiv) was added. The mixture was stirred for 15 min, NaCNBH\(_3\) (1.3 g, 20 mmol, 2.0 equiv) was added, stirring was continued for another 15 min. AcOH (3.0 mL) was added and the mixture was stirred for 2 h. 200 mL CH\(_2\)Cl\(_2\) were added and the mixture washed twice with 1 M aqueous NaOH. The organic phase was dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue treated with 3 M aqueous HCl. The aqueous phase was washed twice with Et\(_2\)O, basified and extracted three times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue purified by vacuum distillation to give 2.43 g pure product (82\% yield) as a colorless oil that solidified in the freezer (m\(_p\) = 63-64 °C).

\[ R_f = 0.50 \] (SiO\(_2\): cyclohexane/EtOAc 2:1); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.37 (d, 1H, J = 8.6 Hz), 7.10 (d, 1H, J = 8.5 Hz), 2.90 (dd, 1H, J = 2.8 Hz, J = 10.7 Hz), 2.45 (m, 1H), 2.28 (m, 1H), 2.17 (s, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.76 (ttd, 1H, J = 5.6 Hz, J = 9.3 Hz, J = 11.3 Hz), 1.54 (dtdd, 1H, J = 3.3 Hz, J = 6.6 Hz, J = 9.9 Hz, J = 13.1 Hz), 1.21 (ddd, 1H, J = 3.3 Hz, J = 10.7 Hz, J = 14.1 Hz), 1.06 (m, 1H), 0.97 (d, 1H, J = 6.5 Hz), 0.88 (d, 1H, J = 6.6 Hz); \(^{13}\)C
**Experimental Section**

NMR (75 MHz, CDCl₃): δ 146.6, 130.0, 129.5, 119.0, 67.4, 51.7, 44.1, 36.2, 33.2, 33.0, 26.2, 24.2, 21.5, 15.7; IR (thin film) ν 2955, 2866, 2822, 1898, 1589, 1487, 1467, 1392, 1367, 1278, 1110, 1010, 820, 741 cm⁻¹; Anal. calcd. for C₁₇H₂₆BrN: C, 62.96; H, 8.08; N, 4.32. Found: C, 63.17; H, 8.12; N, 4.44; HRMS (EI) calcd. for C₁₇H₂₆BrN: [M]⁺ = 322.1165. Found: 322.3163.

For the analytical data of 3-hydroxyoxetane 71, see page 187.

For the analytical data of 3-fluorooxetane 74, see page 188.

### 6.7 Preparation of Analogues

#### 6.7.1 Methylene Analogues

![Chemical Structure](image)

1-(1-{4-(3-fluorooxetan-3-yl)phenyl)cyclobutyl}-N,N,3-trimethylbutan-1-amine: To a suspension of the hydrobromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide³⁵³ (3.8 g, 7.5 mmol, 1.0 equiv) in 100 mL dry THF was added n-BuLi (1.6 M in hexanes, 9.9 mL, 15 mmol, 2.0 equiv) at 0 °C. After stirring for 40 min at 0 °C, a solution of p'-Bu-benzaldehyde (1.2 g, 7.5 mmol, 1.0 equiv) in 5 mL dry THF was added slowly. The mixture was stirred at 60 °C over night, cooled to 0 °C; water was added, followed by concentrated aqueous HCl. The clear yellowish solution was freed from THF by evaporation and washed twice with 50 mL toluene. The aqueous phase was extracted five times with 40 mL chloroform. The combined chloroform phases were dried over magnesium sulfate, evaporated and the residue dissolved in 100 mL methanol. After addition of 60 mg Pd/C (10w%), hydrogen was bubbled through the solution for 45 min and the mixture vigorously stirred for 24 h. The mixture was filtered through a pad of celite, the filtrate evaporated and the residue taken up in ~25 mL water. Diethyl ether (50 mL) was added, followed by excess sodium hydroxide (cooling) to free the amine. The aqueous phase was extracted 3 times with diethyl ether, the combined organic phases were dried over magnesium sulfate, filtered, the filtrate evaporated and the residue distilled to give 1.044 g (60%) pure product as a colorless oil.
Experimental Section

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.30 (d, 2H, J=8.3 \text{ Hz}), 7.13 (d, 2H, J=8.2 \text{ Hz}), 2.61 (m, 2H), 2.27 (m, 2H), 2.22 (s, 6H), 1.56 (m, 4H), 1.32 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 148.3, 139.3, 127.9, 125.0, 59.7, 45.5, 35.2, 34.2, 31.3, 29.2, 27.5\); IR (thin film) \(\nu = 2939, 2858, 2813, 2762, 1515, 1461, 1392, 1363, 1268, 1042, 828, 570 \text{ cm}^{-1}\); Anal. calcd for C\(_{16}\)H\(_{27}\)N: C, 82.34; H, 11.66; N, 6.00. Found: C, 82.27; H, 11.63; N, 5.95; HRMS (EI) calcd for C\(_{16}\)H\(_{27}\)N: [M]+ = 233.2139. Found 233.2139.

\[ \text{1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidine:} \]

Piperidine (0.99 mL, 10 mmol, 1.0 equiv) and piperonyl chloride (1.7 g, 10 mmol, 1.0 equiv) were dissolved in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et\(_2\)O. The aqueous phase was extracted two times with Et\(_2\)O. The combined organic phases were washed with brine 5 times, dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue distilled (Kugelrohr) to give 1.64 g pure product as a colorless oil (75% yield).

\(R_f = 0.84 (\text{Al}_2\text{O}_3, 2/1 \text{ cyclohexane/EtOAc}); \) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 6.88 – 6.82 (m, 1H), 6.73 (d, J = 1.0 \text{ Hz}, 2H), 5.93 (s, 2H), 3.37 (s, 2H), 2.35 (s, 4H), 1.63 – 1.49 (m, 4H), 1.49 – 1.37 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 147.4, 146.2, 132.5, 122.1, 109.5, 107.7, 100.8, 63.6, 54.4, 26.1, 24.5\); IR (thin film) \(\nu = 2934, 2853, 2800, 2760, 1700, 1609, 1503, 1489, 1442, 1394, 1370, 1240, 1104, 1039, 995, 933, 868, 808, 780 \text{ cm}^{-1}\); Anal. calcd for C\(_{13}\)H\(_{17}\)NO\(_2\): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 7.84; N, 6.47; HRMS (EI) calcd for C\(_{13}\)H\(_{17}\)NO\(_2\): [M]+ = 219.1254. Found: 219.1254.

**1-(benzo[\(d\)][1,3]dioxol-5-ylmethyl)pyrrolidine:** To a solution of pyrrolidine (0.80 mL, 10 mmol, 1.0 equiv) and piperonal (1.5 g, 10 mmol, 1.0 equiv) in 20 mL dry CH\(_2\)Cl\(_2\) was added NaBH(OAc)\(_3\) (5.3 g, 25 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K\(_2\)CO\(_3\) was added until complete solvation of borate byproducts occurred. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue distilled (Kugelrohr) to give 1.50 g pure product (73% yield) as a colorless oil.

R\(_f\) = 0.63 (Al\(_2\)O\(_3\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 6.85\) (dd, \(J = 0.5\) Hz, 1.4 Hz, 1H), 6.80 – 6.69 (m, 2H), 5.93 (s, 2H), 3.51 (s, 2H), 2.55 – 2.38 (m, 4H), 1.78 (dd, \(J = 3.4\) Hz, 7.0, 4H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 147.4, 146.2, 133.3, 121.8, 109.3, 107.8, 100.8, 60.5, 54.1, 23.5\); IR (thin film) \(\nu = 2964, 2784, 1502, 1489, 1441, 1247, 1040, 937, 810\) cm\(^{-1}\); Anal. calcd for C\(_{12}\)H\(_{15}\)NO\(_2\): C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.45; N, 6.82; HRMS (El) calcd for C\(_{12}\)H\(_{15}\)NO\(_2\): [M-H]\(^+\) = 204.1019. Found: 204.1018.

**1-(benzo[\(d\)][1,3]dioxol-5-ylmethyl)azetidine:** To a solution of azetidine (0.52 mL, 7.7 mmol, 1.1 equiv) and piperonal (1.1 g, 7.0 mmol, 1.0 equiv) in 30 mL CH\(_2\)Cl\(_2\) was added NaBH(OAc)\(_3\) (3.7 g, 18 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K\(_2\)CO\(_3\) was added until complete solvation of borate byproducts. The
aqueous phase was extracted three times with EtOAc. The combined organic phases were
dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chro-
matography (SiO₂, EtOAc to 10% MeOH in CH₂Cl₂) to give 1.06 g pure product (79% yield)
as a colorless oil.

1H NMR (300 MHz, CDCl₃) δ = 6.76 (dd, J = 0.4 Hz, 1.0 Hz, 1H), 6.74 – 6.65 (m, 2H),
5.89 (d, J = 0.4 Hz, 2H), 3.44 (s, 2H), 3.16 (t, J = 7.0 Hz, 4H), 2.05 (p, J = 7.0 Hz, 2H);
13C NMR (75 MHz, CDCl₃) δ = 147.4, 146.3, 132.1, 121.4, 108.9, 107.9, 100.7, 63.6, 54.9, 17.7; IR (thin
film) ν 2958, 2820, 1503, 1499, 1375, 1301, 1249, 1176, 1114, 1040, 938, 864, 811, 773
cm⁻¹; Anal. calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.80; H, 6.76; N,

6.7.2 Gem-dimethyl Analogues

6.7.2.1 Open-Chain Scaffold

![Diagram](attachment:image.png)

[4-(4-tert-Butyl-phenyl)-4-methyl-pentyl]-dimethyl-amine: To tert-butylbenzene
(5.8 mL, 38 mmol, 5.0 equiv) was added sulfuric acid (80 μL, 1.5 mmol, 0.2 equiv) followed
by 5-bromo-2-methylpent-2-ene (1.0 mL, 7.5 mmol, 1.0 equiv) at 0 °C. The mixture was
then allowed to warm to room temperature, stirred overnight and poured on ice. The
aqueous phase was extracted three times with Et₂O, the combined organic phases were
washed once with brine, dried over MgSO₄, filtered and concentrated in vacuo. The re-
sulting mixture was dissolved in EtOH, Me₂NH₂Cl (5.0 g, 61 mmol, 8.2 equiv) and K₂CO₃
(8.3 g, 60 mmol, 8.0 equiv) were added and the mixture heated at 50 °C for 2 d. The sol-
vent was concentrated in vacuo and the residue partitioned between 1 M aqueous NaOH
and Et₂O. The aqueous phase was extracted three times with Et₂O. The combined organic
phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 10% MeOH in CH₂Cl₂, 0.1% NEt₃) to give pure product together with SiO₂. This material was then distilled to give 0.29 g pure product (13% yield) as a colorless oil.

Rᵣ = 0.37 (SiO₂, 10% MeOH in CH₂Cl₂, 0.1% NEt₃); ¹H NMR (300 MHz, CDCl₃) δ = 7.27 (m, 4H), 2.21 (m, 8H), 1.60 (m, 2H), 1.27 (m, 17H); ¹³C NMR (75 MHz, CDCl₃) δ = 148.0, 146.4, 125.5, 125.0, 60.5, 45.6, 42.3, 37.2, 34.3, 31.5, 29.0, 23.2; IR (thin film) ν 2963, 2762, 1513, 1464, 1362, 1272, 1122, 1042, 831 cm⁻¹; Anal. calcd for C₁₈H₃₁N: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.64; H, 11.97; N, 5.43.; HRMS (El) calcd for C₁₈H₃₁N: [M]+ = 261.2452. Found: 261.2453.

[4-(4-tert-Butyl-phenyl)-3,3-dimethyl-butyl]-dimethyl-amine: To a suspension of Grignard turnings (0.63 g, 26 mmol, 1.3 equiv) in 30 mL dry Et₂O was added 4-(tert-butyl)benzyl bromide (5.5 mL, 21 mmol, 1.0 equiv) in 24 mL dry Et₂O over 30 min. After stirring for 30 min, a solution of diethyl 2-(propan-2-ylidene)malonate (4.0 mL, 20 mmol, 1.0 equiv) in 20 mL dry Et₂O was added over 2 h. The mixture was poured on ice, the aqueous phase extracted three times with Et₂O, the combined organic phases dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, cyclohexane to 20/1 cyclohexane/EtOAc) to give 5.41 g pure diethyl 2-(1-(4-tert-butylphenyl)-2-methylpropan-2-yl)malonate. Parts of this material (2.95 g, 8.47 mmol, 1.00 equiv) were dissolved in 20 mL DMSO, water (228 μL, 12.7 mmol, 1.50 equiv) and NaBr (958 mg, 9.32 equiv, 1.10 equiv) were added and the mixture heated to 190 °C for 20 h. The mixture was cooled to room temperature and five times extracted with Et₂O. The combined organic phases were washed three times with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 4/1 cyclohexane/EtOAc). The product containing fractions were concentrated in vacuo and the residue distilled to give 0.93 g ethyl 4-(4-tert-butylphenyl)-3,3-
dimethylbutanoate in a 3/1 together with starting material. This mixture was used without further purification and dissolved in 20 mL dry Et₂O. To this mixture was added LiAlH₄ (4.0 M solution in Et₂O, 2.5 mL, 10 mmol, 2.9 equiv) at 0 °C. After the addition was finished, the mixture was allowed to warm to room temperature and stirred for 1.5 h. Na₂SO₄·10 H₂O was slowly added and after stirring for 30 min, the mixture was filtered. The filter cake was boiled three times with EtOAc and the combined filtrates dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 4/1 to 1/1 cyclohexane/EtOAc) to give 0.48 g pure 4-(4-tert-butylphenyl)-3,3-dimethylbutan-1-ol as a colorless oil (20% yield, 3 steps). Parts of this material (0.47 g, 2.0 mmol, 1.0 equiv) were dissolved in 20 mL CH₂Cl₂, NEt₃ (0.36 mL, 2.6 mmol, 1.3 equiv) was added and the solution cooled to 0 °C. MsCl (0.17 mL, 2.2 mmol, 1.1 equiv) was added and the mixture stirred for 1 h, before it was concentrated in vacuo and taken up in Et₂O. The solution was washed once with water and once with brine. The organic phase was dried over MgSO₄, filtered, concentrated in vacuo and the residue dissolved in Me₂NH (2.0 mL in THF, 5.0 mL, 10 mmol, 5.0 equiv). The mixture was stirred for 20 h at 50 °C, before the solvent was concentrated in vacuo. The residue was partitioned between EtOAc and 1 M aqueous NaOH. The aqueous phase was extracted three times with EtOAc, the combined organic phases dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (n-Al₂O₃, cyclohexane to 8/1 cyclohexane/EtOAc) to give 0.18 g pure product (34% yield) as a colorless oil.

\[ R_f = 0.88 (\text{Al}_2\text{O}_3, 2/1 \text{cyclohexane/EtOAc}) \]

\[ ^1\text{H} \text{NMR (300 MHz, CDCl}_3) \delta = 7.27 (d, 2H, J = 8.2 \text{ Hz}), 7.05 (d, 2H, J = 8.2 \text{ Hz}), 2.48 (s, 2H), 2.31 (m, 2H), 2.23 (s, 6H), 1.42 (m, 2H), 1.31 (s, 9H), 0.88 (s, 6H); ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3) \delta = 148.3, 135.7, 130.1, 124.4, 55.4, 48.3, 45.8, 39.6, 34.3, 33.6, 31.4, 26.9; \text{IR (thin film) v 2962, 2867, 2814, 2762, 1512, 1463, 1364, 1269, 1203, 1110, 1023, 837 cm}^{-1}; \text{Anal. calcd for C}_{18}\text{H}_{33}\text{N: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.47; H, 11.99 N, 5.34; HRMS (EI) calcd for C}_{18}\text{H}_{33}\text{N: [M]}^+ = 261.2452. \text{Found: 261.2448.} \]
[4-(4-tert-Butyl-phenyl)-2,2-dimethyl-butylo]-dimethyl-amine: To a suspension of 4-(tert-butylbenzyl)triphenylphosphonium bromide (2.2 g, 3.9 mmol, 1.0 equiv) in 20 mL dry THF was added "BuLi (2.5 M in hexanes, 2.4 mL, 3.9 mmol, 1.0 equiv) at 0 °C over 15 min. The red solution was stirred for 20 min, before a solution of 3-(dimethylamino)-2,2-dimethylpropanal\(^{372}\) (0.5 g, 3.9 mmol, 1.0 equiv) in 5 mL dry THF was added. The mixture was stirred for 10 h at room temperature, before 1 M aqueous HCl was added and the organic solvent concentrated in vacuo. The aqueous residue was washed three times with toluene, basified and then extracted three times with Et\(_2\)O. The combined ethereal phases were dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue dissolved in 20 mL MeOH. Pd/C (10w%, 0.13 g) were added and the atmosphere exchanged with hydrogen. The mixture was stirred for 16 h, filtered through Celite, the filtrate concentrated in vacuo and the residue purified by flash chromatography (nAl\(_2\)O\(_3\), cyclohexane to 20/1 cyclohexane to EtOAc) to give 0.32 g pure product (32% yield) as a yellowish oil.

\[ R_f = 0.88 \ (Al_2O_3, \ 2/1 \ cyclohexane/EtOAc); \ H \ NMR \ (300 \ MHz, \ CDCl_3) \ \delta = 7.31 \ (d, \ 2H, \ J = 8.3 \ Hz), \ 7.14 \ (d, \ 2H, \ J = 8.2 \ Hz), \ 2.54 \ (m, \ 2H), \ 2.32 \ (s, \ 2H), \ 2.14 \ (s, \ 6H), \ 1.55 \ (m, \ 2H), \ 1.32 \ (s, \ 9H), \ 0.95 \ (s, \ 6H); \ ^{13}C \ NMR \ (75 \ MHz, \ CDCl_3) \ \delta = 148.4, \ 140.6, \ 128.1, \ 125.3, \ 71.0, \ 49.1, \ 42.8, \ 35.7, \ 34.5, \ 31.6, \ 30.2, \ 25.7; \ IR \ (thin \ film) \ \nu = 2962, \ 2866, \ 2817, \ 2765, \ 1896, \ 1788, \ 1516, \ 1455, \ 1363, \ 1268, \ 1150, \ 1109, \ 1045, \ 832, \ 814 \ cm^{-1}; \ Anal. \ calcd \ for \ C_{18}H_{31}N: \ C, \ 82.69; \ H, \ 11.95; \ N, \ 5.36. \ Found: \ C, \ 82.43; \ H, \ 11.84 \ N, \ 5.41; \ HRMS \ (EI) \ calcd \ for \ C_{18}H_{31}N: [M]^+ = 261.2452. \ Found: \ 261.2453. \]

\[ 4-(4-tert-butylphenyl)-N,N-dimethylbutanamide: \ To \ a \ suspension \ of \ AlCl_3 \ (29.3 \ g, \ 220 \ mmol, \ 2.20 \ equiv) \ in \ 300 \ mL \ dry \ CH_2Cl_2 \ at \ 0 \ °C \ was \ added \ succinic \ anhydride \ (11.0 \ g, \ 110 \ mmol, \ 1.10 \ equiv) \ and \ the \ mixture \ was \ allowed \ to \ warm \ to \ room \ temperature. \ A \ solution \ of \ tert-butylbenzene \ (15.4 \ mL, \ 100 \ mmol, \ 1.00 \ equiv) \ in \ 50 \ mL \ dry \ CH_2Cl_2 \ was \ added \ dropwise \ and \ the \ mixture \ stirred \ for \ 9 \ h \ at \ room \ temperature. \ The \ mixture \ was \]

slowly poured on a mixture of ice and concentrated aqueous HCl. The aqueous phase was extracted twice with CH₂Cl₂, the combined organic phases washed twice with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue recrystallized from toluene. The crude material was washed with cold toluene, dried under high-vacuum and dissolved in 200 mL AcOH. Pd/C (10 w%, 250 mg) was added and the atmosphere exchanged with hydrogen. The mixture was stirred for 10 h, before it was filtered through a plug of Celite. The filtrate was concentrated in vacuo and water was added to the residue, causing precipitation of pure 4-(4-tert-butylphenyl) butanoic acid (16.4 g, 75% yield over 2 steps). Parts of this material (15 g, 68 mmol, 1.0 equiv) were dissolved in 200 mL Et₂O, before oxalyl chloride (7.1 mL, 81 mmol, 1.2 equiv) was added, followed by three drops of DMF. After stirring for 2 h at room temperature, the mixture was concentrated in vacuo, Et₂O was added and the solution cooled to 0 °C. Aqueous Me₂NH (7.8 mL, 35 mL, 0.27 mol, 4.0 equiv) was added and the mixture stirred at room temperature for 1 h. Et₂O was added and the aqueous phase extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue distilled (bₚ~230 °C at 0.3 mbar) to give 14.964 g pure product (88% yield) as a yellowish oil (R₁₁ = 0.13 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 7.30 (d, 2H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.2 Hz), 2.95 (s, 3H), 2.94 (s, 3H), 2.65 (t, 2H, J = 7.6 Hz), 2.33 (m, 2H), 1.98 (m, 2H), 1.31 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ = 148.4, 138.6, 128.0, 125.1, 37.3, 35.4, 34.9, 34.4, 32.7, 31.5, 26.6; IR (thin film) ν 2953, 1651, 1462, 1397, 1268, 1135, 834 cm⁻¹; HRMS (El) calcd for C₁₆H₂₅NO: [M⁺] = 247.1931. Found: 247.1930

[4-(4-tert-Butyl-phenyl)-1,1-dimethyl-butyl]-dimethyl-amine:³⁷³ To a solution of amide 228 (4.9 g, 20 mmol, 1.0 equiv) in 40 mL dry THF was added ZrCl₄ (4.7 g, 20 mmol, 1.0 equiv) in two portions at −10 °C. After stirring for 30 min, a solution of MeMgBr (3.0 M in Et₂O, 40 mL, 0.12 mol, 6.0 equiv) was added in a way that the inner temperature did

not rise above 0 °C. The mixture was allowed to warm to room temperature over the course of 4 h and was quenched by cautious addition of 30w% aqueous NaOH. The aqueous phase was extracted three times with Et₂O, the combined organic phases concentrated in vacuo and the residue treated with 1 m aqueous HCl. The aqueous phase was washed three times with EtOAc, basified and extracted three times with Et₂O. The combined ethereal phases were dried over MgSO₄, filtered, concentrated in vacuo and the residue distilled to give 1.01 g pure product (19% yield) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ = 7.30 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.2 Hz), 2.57 (t, 2H, J = 7.7 Hz), 2.20 (s, 6H), 1.64 (ddd, 2H, J = 6.1 Hz, J = 10.0 Hz, J = 11.3 Hz), 1.43 (m, 2H), 1.31 (s, 9H), 1.22 (t, 2H, J = 7.1 Hz), 0.99 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ = 148.5, 139.7, 128.1, 125.2, 55.7, 39.4, 38.6, 36.2, 34.5, 31.6, 26.0, 22.6; IR (thin film) ν 2963, 2818, 2777, 1899, 1789, 1721, 1661, 1513, 1462, 1362, 1268, 1046, 974, 831 cm⁻¹; Anal. calcd for C₁₈H₃₁N: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.53; H, 12.01 N, 5.20; HRMS (El) calcd for C₁₈H₃₁N: [M-CH₃]⁺ = 246.2217. Found: 246.2217.

6.7.2.2 Cyclic Scaffolds

![Diagram](image)

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylazetidine: To a solution of 3-chloro-2,2-dimethylpropanal¹⁷⁴ (3.5 g, 29 mmol, 1.0 equiv) in 30 mL dry Et₂O was added MgSO₄·0.5 H₂O (3.0 g), followed by piperonylamine (3.7 mL, 30 mmol, 1.0 equiv). After stirring for 4 h, a sample in the NMR indicated full conversion. The mixture was filtered, the filtrate slowly added to a solution of LiAlH₄ (6.0 mL of 4.0 M solution in Et₂O, 30 mmol, 1.0 equiv) at room temperature. The mixture was then refluxed over night, cooled to room temperature, before Na₂SO₄·10 H₂O was slowly added. After stirring for 20 min, the solvent was decanted off and the residue refluxed with five times 20 mL EtOAc. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and the re-

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sidue filtered through a column (nAl₂O₃, 4/1 cyclohexane/EtOAc) to give 3.8 g pure product (58% yield) as a colorless oil.

R_f = 0.74 (Al₂O₃, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta = 6.80\) (d, \(J = 0.5\) Hz, 1H), 6.77 – 6.67 (m, 2H), 5.92 (s, 2H), 3.50 (s, 2H), 2.95 (s, 4H), 1.21 (s, 6H). \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta = 147.4, 146.2, 132.6, 121.2, 108.7, 107.8, 100.7, 66.5, 63.4, 31.4, 27.4\); IR (thin film) \(\nu = 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1193, 1041, 937, 810, 776\) cm\(^{-1}\); Anal. calcd for C₁₃H₁₇NO₂: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.07; H, 8.00; N, 6.39. HRMS (El) calcd for C₁₃H₁₇NO₂: [M]⁺ = 219.1254. Found: 219.1252.

1-(benzo[d][1,3]dioxol-5-ylmethyl)-4,4-dimethylpiperidine: To a solution of 4,4-dimethylpiperidine-2,6-dione (5.7 g, 40 mmol, 1.0 equiv) in 45 mL DMF was added KOH (2.5 g, 44 mmol, 1.1 equiv) at 0 °C. After stirring for 30 min, piperonyl bromide\(^{377}\) (9.1 g, 42 mmol, 1.1 equiv) was added as a solution in 8 mL DMF. The mixture was then stirred at room temperature for 5 h and then poured on water. The aqueous phase was extracted three times with Et₂O and the combined organic phases were washed with 2 M aqueous NaOH twice, once with water and once with saturated aqueous NH₄Cl. After drying over MgSO₄, filtration and evaporation, the residue was purified by flash chromatography (SiO₂, 8/1 to 2/1 cyclohexane/EtOAc) to 3.9 g pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)-4,4-dimethylpiperidine-2,6-dione (R_f = 0.33 (SiO₂, 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta = 6.88\) (d, \(J = 7.4\) Hz, 2H), 6.71 (d, \(J = 8.6\) Hz, 1H), 5.91 (s, 2H), 4.85 (s, 2H), 2.51 (s, 4H), 1.04 (s, 6H). \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta = 171.7, 147.3, 146.7, 131.0, 122.6, 109.6, 108.0, 100.9, 46.5, 42.5, 29.3, 27.8\); IR (thin film) \(\nu = 2959, 2896, 2779, 1724, 1674, 1609,
Experimental Section

1504, 1491, 1446, 1365, 1344, 1330, 1249, 1137, 1101, 1038, 926, 891 cm\(^{-1}\); HRMS (El) calcd for C\(_{15}\)H\(_{23}\)NO\(_2\) [M]+, 275.1157. Found, 275.1157 as a white solid (mp = 70–72 °C). Of this material, 2.8 g (10 mmol, 1.0 equiv) were dissolved in 100 mL dry Et\(_2\)O and slowly added to a solution of LiAlH\(_4\) (1.2 g, 30 mmol, 3.0 equiv) in 100 mL dry Et\(_2\)O at 0 °C. The mixture was then allowed to warm to room temperature refluxed for 12 h and cooled to 0 °C. Na\(_2\)SO\(_4\)·10 H\(_2\)O was slowly added, the mixture stirred for 20 min at room temperature and filtered. The filter cake was boiled with 2 portions EtOAc for 30 seconds. The combined filtrates were dried over Na\(_2\)SO\(_4\), filtered, concentrated in vacuo and the residue purified by Kugelrohr distillation to give 1.8 g pure product as white crystals (mp = 53–54 °C).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 6.85\) (s, 1H), 6.74 (s, 2H), 5.92 (s, 2H), 3.41 (s, 2H), 2.44 – 2.23 (m, 4H), 1.44 – 1.29 (m, 4H), 0.91 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 147.4, 146.3, 132.6, 122.1, 109.5, 107.7, 100.7, 63.3, 50.0, 38.8, 28.6\); IR (thin film) \(\nu = 2948, 2910, 2838, 2805, 2765, 1609, 1502, 1489, 1442, 1369, 1331, 1295, 1241, 1207, 1182, 1128, 1105, 1042, 989, 940, 865, 810, 799, 776, 715\) cm\(^{-1}\); Anal. calcd for C\(_{15}\)H\(_{21}\)NO\(_2\): C, 72.84; H, 8.56; N, 5.66. Found: C, 72.68; H, 8.46; N, 5.55; HRMS (El) calcd for C\(_{15}\)H\(_{21}\)NO\(_2\) [M]+, 247.1567. Found, 247.1565

![Chemical structure](image)

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpyrrolidine: A solution of 3,3-dimethyldihydrofuran-2,5-dione (1.0 g, 7.8 mmol, 1.0 equiv) and piperonylamine (1.0 mL, 7.8 mmol, 1.0 equiv) in 30 mL dry toluene were refluxed overnight using a Dean-Stark trap. After cooling to room temperature, aqueous HCl (1 M) was added and the aqueous phase extracted three times with EtOAc. The organic phases were washed with brine,
filtered, concentrated in vacuo and the crude 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpyrrolidine-2,5-dione (Rf = 0.33 (SiO2, 2/1 cyclohexane/EtOAc) used without further purification. This material was dissolved in 90 mL dry Et2O and slowly added at 0 °C to a solution of LiAlH4 (0.89 g, 2.3 mmol, 3.0 equiv) in 45 mL dry Et2O. The mixture was then allowed to warm to room temperature refluxed for 12 h and cooled to 0 °C. Na2SO4·10 H2O was slowly added, the mixture stirred for 20 min at room temperature and filtered. The filter cake was boiled with two portions of EtOAc for 30 seconds. The combined filtrates were dried over Na2SO4, filtered, concentrated in vacuo and the residue purified by Kugelrohr distillation to give 1.3 g pure product as waxy solid (mp = 33-35 °C).

1H NMR (300 MHz, CDCl3) δ = 6.87 (s, 1H), 6.80 – 6.67 (m, 2H), 5.93 (s, 2H), 3.49 (s, 2H), 2.59 (t, J = 7.0 Hz, 2H), 2.27 (s, 2H), 1.58 (t, J = 7.0 Hz, 2H), 1.07 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 147.4, 146.1, 133.7, 121.4, 109.1, 107.7, 100.7, 68.2, 60.4, 54.3, 39.9, 37.7, 29.7; IR (thin film) ν 2952, 2868, 2783, 1609, 1503, 1489, 1442, 1378, 1346, 1316, 1245, 1185, 1106, 1041, 940, 864, 810, 776 cm⁻¹; Anal. calcd for C14H19NO2: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.78; H, 8.05; N, 6.11; HRMS (El) calcd for C14H19NO2 [M]+, 233.1411. Found, 233.1408

1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine: To a solution of 3,3-dimethylidihydro-2H-pyran-2,6(3H)-dione (2.8 g, 20 mmol, 1.0 equiv) in 40 mL THF was added piperonylamine (3.3 g, 22 mmol, 1.1 equiv) at room temperature. The mixture was stirred for 30 min, before the solvent was concentrated in vacuo. The residue was dissolved in EtOAc and 1 M aqueous HCl was added and the aqueous phase extracted three times with EtOAc. The aqueous phase was washed once with brine, dried over MgSO₄,
filtered and concentrated in vacuo. The residue was dissolved in 20 mL acetic anhydride and 3.5 mL NEt₃ was added. The mixture was heated to 80 °C and stirred for 1 h. Then the solvent was concentrated in vacuo. The residue was dissolved in EtOAc and 1 M aqueous HCl was added and the aqueous phase extracted three times with EtOAc. The aqueous phase was washed once with 1 M aqueous HCl, brine and saturated aqueous sodium bicarbonate, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified via chromatography (SiO₂, 1/1 cyclohexane/EtOAc) to give 2.7 g 90w% (NMR) pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine-2,6-dione (49% yield) (¹H NMR (300 MHz, CDCl₃) δ = 6.82 (dd, J = 1.7 Hz, 6.0, 2H), 6.69 (d, J = 8.4 Hz, 1H), 5.90 (s, 2H), 4.82 (s, 2H), 2.71 (t, J = 6.8 Hz, 2H), 1.78 (t, J = 6.8 Hz, 2H), 1.25 (s, 6H); IR (thin film) ν 2969, 1805, 1765, 1722, 1674, 1504, 1491, 1446, 1690, 1355, 1282, 1247, 1164, 1038, 1017, 927, 885, 808, 778 cm⁻¹; HRMS (EI) calcld for C₁₅H₁₂NO₄ [M]⁺, 275.1153. Found, 275.1155). To a solution of 0.29 g LiAlH₄ (7.7 mmol, 3.0 equiv) in 15 mL dry Et₂O was added a solution 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine-2,6-dione in 30 mL dry Et₂O slowly at 0 °C. The mixture was then allowed to warm to room temperature and refluxed for 2.5 h. After cooling to room temperature, Na₂SO₄·10 H₂O was slowly added, stirred for 20 min and filtered. The filter cake was refluxed once with EtOAc, the combined filtrates concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 4/1 cyclohexane/EtOAc) to give 0.26 g pure product as a slightly yellowish oil (42% yield).

Rf = 0.50 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.88 (s, 1H), 6.74 (d, J = 0.8 Hz, 2H), 5.94 (s, 2H), 3.33 (s, 2H), 2.29 (s, 2H), 1.98 (s, 2H), 1.58 (dt, J = 5.6 Hz, 11.1 Hz, 2H), 1.26 – 1.14 (m, 2H), 0.92 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 147.4, 146.1, 133.4, 121.4, 108.9, 107.5, 100.6, 65.7, 62.9, 54.4, 37.5, 30.8, 27.2, 22.6; IR (thin film) ν 2974, 2771, 1608, 1488, 1441, 1365, 1240, 1181, 1107, 1042, 991, 936, 865, 804, 774 cm⁻¹; Anal. calcld for C₁₅H₁₁NO₂: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.97; H, 8.46; N, 5.79; HRMS (EI) calcld for C₁₅H₁₁NO₂ [M]⁺, 247.1567. Found, 247.1567
1-{benzo[d][1,3]dioxol-5-ylmethyl}-2,2-dimethyldazetidine: A mixture of ethyl 3-methylbut-2-enoate (4.1 mL, 30 mmol, 1.0 equiv) and piperonylamine was stirred at 120 °C for 6 d in a sealed vessel. The mixture was then separated by flash chromatography (SiO₂, CH₂Cl₂ to 6% MeOH in CH₂Cl₂) to give 1.9 g pure ethyl 3-{benzo[d][1,3]dioxol-5-ylmethylamino}-3-methylbutanoate in 23% yield (R_f = 0.19 (SiO₂, EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.91 – 6.84 (m, 1H), 6.84 – 6.69 (m, 2H), 5.95 – 5.87 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.62 (s, 2H), 2.49 (s, 2H), 1.71 (s, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.22 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ = 171.8, 147.5, 146.2, 134.9, 121.1, 108.9, 108.0, 100.7, 60.0, 52.4, 46.6, 44.1, 27.5, 14.2; IR (thin film) ν 3410, 2972, 2901, 2901, 1726, 1490, 1442, 1368, 1327, 1249, 1098, 1039, 931, 809 cm⁻¹; HRMS (EI) calcd for C₁₅H₂₁NO₄: [M-H]+ = 278.1387. Found: 278.1388.). This material (1.9 g, 6.7 mmol, 1.0 equiv) was added slowly as a solution in 10 mL dry Et₂O to a solution of LiAlH₄ (5.0 mL of a 4.0 m solution in Et₂O, 20 mmol, 3.0 equiv) in 40 mL dry Et₂O at room temperature. After stirring overnight at room temperature, Na₂SO₄·10 H₂O was slowly added. After stirring for 20 min, the mixture was filtered, the filter cake washed with five times 20 mL EtOAc for 30 seconds each. The combined filtrates were dried over Na₂SO₄, filtered, concentrated in vacuo and the residue (2.5 g pure amino alcohol, R_f = 0.27 (Al₂O₃, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.78 (s, 1H), 6.74 (d, J = 0.6 Hz, 2H), 5.95 – 5.88 (m, 2H), 3.92 – 3.81 (m, 2H), 3.66 (s, 2H), 1.68 – 1.57 (m, 2H), 1.24 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ = 147.6, 146.6, 133.7, 121.2, 108.8, 108.1, 100.8, 60.5, 54.2, 46.3, 40.1, 26.8; IR (thin film) ν 3298, 2965, 1609, 1490, 1442, 1367, 1249, 1039, 928, 809 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₉NO₃: [M-CH₃]+ = 222.1125. Found: 222.1124.) dissolved without further purification in 100 mL dry MeCN. PPh₃ (4.1 g, 16 mmol, 2.3 equiv) was added, followed under cooling (ice bath) by carbon tetrabromide (5.2 g, 16 mmol, 2.3 mmol) and NEt₃ (2.9 mL, 21 mmol, 3.1 equiv). After stirring overnight, the NMR showed full conversion. The mixture was
concentrated *in vacuo* and the residue dispersed in Et₂O. Aqueous 1 M NaOH (60 mL) was added and the aqueous layer extracted three times with Et₂O. The combined organic phases were dried over MgSO₄, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO₂, CH₂Cl₂ to 10% MeOH in CH₂Cl₂) to give 656 mg pure product (44% yield) as a slightly yellowish oil.

Rₛ = 0.11 (SiO₂, EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.88 – 6.80 (m, 1H), 6.77 – 6.63 (m, 2H), 5.91 (s, 2H), 3.44 (s, 2H), 3.15 – 3.01 (m, 2H), 1.94 – 1.77 (m, 2H), 1.19 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 147.3, 146.6, 133.1, 121.4, 109.2, 107.8, 100.7, 63.4, 55.0, 49.3, 31.9, 25.0; IR (thin film) ν 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1041, 937, 810, 776 cm⁻¹; Anal. calcd for C₁₃H₁₇NO₂: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.04; H, 7.80; N, 6.58; HRMS (EI) calcd for C₁₃H₁₇NO₂: [M]+ = 219.1254. Found: 219.1253.

**1-(benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethylpyrrolidine:** To a solution of 1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-2-one (210) (2.2 g, 10 mmol, 1.0 equiv) in 20 dry THF was added ZrCl₄ (2.3 g, 10 mmol, 1.0 equiv) in 2 portions at –10 °C. After stirring for 30 min, a solution of MeMgBr (3.0 M in Et₂O, 20 mL, 60 mmol, 6.0 equiv) was added slowly enough not to exceed a temperature of the reaction mixture of 0 °C. The mixture was stirred for 4 h and allowed to warm to room temperature. Aqueous NaOH (30w%) was added slowly and the aqueous phase extracted three times with CH₂Cl₂. The combined organic phases were dried over MgSO₄, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (nAl₂O₃, 20/1 cyclohexane/EtOAc) to give 0.84 g pure product (36% yield) as a yellowish solid (mp = 33-34 °C).
**Experimental Section**

\[ R_f = 0.91 \, (\text{Al}_2\text{O}_3, \, 2/1 \, \text{cyclohexane/EtOAc}); \quad ^1\text{H} \text{NMR} \,(300 \, \text{MHz, CDCl}_3) \delta = 6.86 \, (dd, \, J = 0.5 \, \text{Hz, 1.4, 1H}), \, 6.78 - 6.68 \, (m, \, 2H), \, 5.92 \, (s, \, 2H), \, 3.42 \, (s, \, 2H), \, 2.60 \, (ddd, \, J = 2.7 \, \text{Hz, 5.4, 6.0, 2H}), \, 1.68 \, (d, \, J = 2.9 \, \text{Hz, 4H}), \, 1.07 \, (s, \, 6H); \quad ^{13}\text{C} \text{NMR} \,(75 \, \text{MHz, CDCl}_3) \delta = 135.0, \, 121.2, \, 109.0, \, 107.7, \, 100.7, \, 53.0, \, 50.9, \, 40.0, \, 23.1, \, 20.5; \quad \text{IR (thin film)} \, 2960, \, 2795, \, 1609, \, 1489, \, 1441, \, 1381, \, 1360, \, 1242, \, 1180, \, 1094, \, 940, \, 865, \, 809, \, 776 \, \text{cm}^{-1}; \quad \text{Anal. calcd for C}_{14}\text{H}_{19}\text{NO}_2: \, \text{C}, \, 72.07; \, \text{H}, \, 8.21; \, \text{N}, \, 6.00. \quad \text{Found:} \, \text{C}, \, 72.16; \, \text{H}, \, 8.13; \, \text{N}, \, 5.96; \quad \text{HRMS (El)} \text{calcd for C}_{14}\text{H}_{19}\text{NO}_2 [\text{M}]^+ \, 233.1410. \quad \text{Found,} \, 233.1411 \]

![Image 284x415 to 292x460]

**1-(benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethylpiperidine:** To a solution of 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-2-one (211) (2.3 g, 10 mmol, 1.0 equiv) in 20 dry THF was added ZrCl4 (2.3 g, 10 mmol, 1.0 equiv) in 2 portions at –10 °C. After stirring for 30 min, a solution of MeMgBr (3.0 M in Et2O, 20 mL, 60 mmol, 6.0 equiv) was added slowly enough not to exceed a temperature of the reaction mixture of 0 °C. The mixture was stirred for 4 h and allowed to warm to room temperature. Aqueous NaOH (30 w%) was added slowly and the aqueous phase extracted three times with CH2Cl2. The combined organic phases were dried over MgSO4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (nAl2O3, cyclohexane to 4/1 cyclohexane/EtOAc) to give 0.23 g pure product (10% yield) as a yellowish liquid.

\[ R_f = 0.80 \, (\text{Al}_2\text{O}_3, \, 2/1 \, \text{cyclohexane/EtOAc}); \quad ^1\text{H} \text{NMR} \,(300 \, \text{MHz, CDCl}_3) \delta = 6.92 \, (dd, \, J = 0.5 \, \text{Hz, 1.5 Hz, 1H}), \, 6.75 \, (dd, \, J = 4.3 \, \text{Hz, 5.1 Hz, 1H}), \, 6.72 \, (dd, \, J = 0.5 \, \text{Hz, 7.9 Hz, 1H}), \, 5.92 \, (s, \, 2H), \, 3.39 \, (s, \, 2H), \, 2.38 - 2.22 \, (m, \, 2H), \, 1.47 \, (s, \, 6H), \, 1.10 \, (s, \, 6H); \quad ^{13}\text{C} \text{NMR} \,(75 \, \text{MHz, CDCl}_3) \delta = 147.4, \, 145.9, \, 135.6, \, 121.1, \, 108.8, \, 107.6, \, 100.7, \, 53.8, \, 53.3, \, 47.0, \, 40.7, \, 26.8, \, 21.4; \quad \text{IR (thin
Experimental Section

2966, 2929, 2794, 1609, 1502, 1489, 1440, 1396, 1284, 1244, 1201, 1184, 1144, 1127, 1093, 1041, 940, 861, 810, 774 cm\(^{-1}\); Anal. calcd for C\(_{15}\)H\(_{21}\)NO\(_2\): C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.61; N, 5.76; HRMS (El) calcd for C\(_{15}\)H\(_{21}\)NO\(_2\) [M\(^+\)], 247.1568. Found, 247.1567

6.7.3 Carbonyl Analogues

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-4-one\(^{375}\): 4-hydroxy-piperidine (1.0 g, 10 mmol, 1.0 equiv) and piperonyl chloride (1.7 g, 10 mmol, 1.0 equiv) were dissolved in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et\(_2\)O. The aqueous phase was extracted two times with Et\(_2\)O. The combined organic phases were washed with brine 5 times, dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue (~95% pure by NMR) used without further purification (R\(_f\) = 0.61 (Al\(_2\)O\(_3\), 2/1 cyclohexane/EtOAc)); \(^1\)H NMR (300 MHz, CDCl\(_3\) \(\delta = 6.85\) (s, 1H), \(6.74\) (t, \(J = 3.9\) Hz, 2H), \(6.00 – 5.86\) (m, 2H), \(3.77 – 3.57\) (m, 1H), \(3.40\) (s, 2H), \(2.73\) (d, \(J = 11.7\) Hz, 2H), \(2.11\) (t, \(J = 10.8\) Hz, 2H), \(1.88\) (dd, \(J = 4.0\) Hz, 12.8 Hz), \(1.65 – 1.50\) (m, 2H), \(1.50 – 1.42\) (m, 1H); IR (thin film) \(\nu\) 3341, 2939, 2360, 1490, 1442, 1367, 1245, 1096, 1064, 4040, 933, 810, 778 cm\(^{-1}\); HRMS (El) calcd for C\(_{13}\)H\(_{17}\)NO\(_3\): [M-H]\(^+\) = 234.1125. Found: 234.1125). From this material 0.70 g (3.0 mmol, 1.0 equiv) were dissolved in mixture 7 mL dry benzene and 3.5 mL DMSO, followed by the addition of DCC (1.9 g, 9.0 mmol, 3.0 equiv) and dry pyridine (0.24 mL, 3.0 mmol, 1.0 equiv). After cooling to 0 °C, TFA (0.11 mL, 3.0 mmol, 1.0 equiv) was added dropwise and the mixture then stirred over night, allowing it to warm to room temperature. EtOAc (50 mL) was added and the mixture filtered. The filtrate was washed with

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brine three times, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 2/1 cyclohexane/EtOAc to EtOAc) to give 0.39 g pure product as white crystalline solid (m_p = 65-69 °C).

R_f = 0.14 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.90 (s, 1H), 6.77 (d, J = 0.9 Hz, 2H), 5.96 (s, 2H), 3.53 (s, 2H), 2.73 (t, J = 6.1 Hz, 4H), 2.45 (t, J = 6.2 Hz, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 209.0, 147.6, 132.0, 121.9, 109.1, 107.8, 100.9, 61.7, 52.8, 41.4; IR (thin film) v 3323, 2911, 2808, 1716, 1623, 1502, 1542, 1489, 1368, 1342, 1244, 1195, 1113, 1085, 1038, 933, 866, 799, 776 cm⁻¹; Anal. calcd for C₁₃H₁₅NO₃: C, 66.94; H, 6.84; N, 6.00. Found: C, 66.94; H, 6.48; N, 6.00; HRMS (El) calcd for C₁₃H₁₅NO₃ [M]^+, 233.1047. Found, 233.1046

![Image](image.png)

**1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-one:**³⁷⁶ 3-hydroxy-pyrrolidine (0.30 g, 3.5 mmol, 1.0 equiv), piperonyl chloride (0.59 g, 3.5 mmol, 1.0 equiv) and K₂CO₃ (2.9 g, 21 mmol, 6.0 equiv) were dispersed in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et₂O. The aqueous phase was extracted two times with Et₂O. The combined organic phases were washed with brine 5 times, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (Al₂O₃, 8/1 to 1/1 cyclohexane/EtOAc) to give pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrroloidin-3-one (0.67 g, 88% yield). This material (0.67 g, 3.1 mmol, 1.0 equiv) was added at −78 °C to a solution containing DMSO (0.43 mL, 6.1 mmol, 2.0 equiv) and oxalyl chloride (0.39 mL, 4.6 mmol, 1.5 equiv) in a way that the temperature of the mixture stays below −60 °C.

Then, NEt$_3$ (1.3 mL, 9.2 mmol, 3.0 equiv) was added drop wise and after stirring for 2 h at −78 °C, the mixture was allowed to warm to room temperature. Aqueous 1 M NaOH was added and the aqueous phase extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine, dried over K$_2$CO$_3$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$, 4/1 to 2/1 cyclohexane/EtOAc) to give 0.32 g pure product (48% yield) as a colorless oil that decomposes quickly when stored at room temperature.

$R_f = 0.17$ (SiO$_2$, 2/1 cyclohexane/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ = 6.84 (s, 1H), 6.75 (d, $J = 1.0$ Hz, 2H), 5.94 (s, 2H), 3.61 (s, 2H), 2.96 – 2.84 (m, 5H), 2.40 (t, $J = 6.9$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 206.9, 147.6, 146.7, 131.0, 121.7, 109.0, 107.9, 100.9, 61.5, 60.5, 51.2, 38.1; IR (thin film) ν 2909, 2800, 1756, 1608, 1502, 1490, 1443, 1383, 1330, 1246, 1187, 1132, 1038, 928, 874, 810 cm$^{-1}$; Anal. calcd for C$_{12}$H$_{13}$NO$_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.60; H, 6.13; N, 6.36; HRMS (El) calcd for C$_{12}$H$_{13}$NO$_3$ [M]$^+$, 218.0890. Found, 219.0888

1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-3-one: 3-hydroxy-piperidine (3.0 g, 30 mmol, 1.0 equiv), piperonyl chloride (5.1 g, 30 mmol, 1.0 equiv) and K$_2$CO$_3$ (25 g, 180 mmol, 6.0 equiv) were dispersed in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et$_2$O. The aqueous phase was extracted two times with Et$_2$O. The combined organic phases were washed with brine five times, dried over MgSO$_4$, filtered, concentrated in vacuo and the residue purified by flash chromatography ($n$Al$_2$O$_3$, 8/1 to 1/1 cyclohexane/EtOAc) to give pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-
3-ol (4.4 g, 91 w% by NMR, rest DMF and EtOAc, yield 56%) as a white solid (mp = 57-58 °C; Rf = 0.14 (SiO2, 2/1 cyclohexane/EtOAc); IR (thin film) ν 3362, 2937, 2800, 1666, 1608, 1502, 1489, 1442, 1392, 1369, 1242, 1155, 1097, 1039, 973, 930, 885, 867, 810, 775 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₆NO₃ [M]⁺, 234.1125. Found, 234.1124). Of this material (0.50 g, 2.1 mmol, 1.0 equiv) was added at −78 °C to a solution containing DMSO (0.30 mL, 4.2 mmol, 2.0 equiv) and Oxalyl chloride (0.27 mL, 3.2 mmol, 1.5 equiv) in a way that the temperature of the mixture stays below −60 °C. Then, NEt₃ (0.88 mL, 6.4 mmol, 3.0 equiv) was added drop wise, and after stirring for 2 h at −78 °C, the mixture was allowed to warm to room temperature. Aqueous 1 m NaOH was added and the aqueous phase extracted three times with CH₂Cl₂. The combined organic phases were washed with brine, dried over K₂CO₃, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO2, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.21 g pure product (77% yield) as a colorless crystals (mp = 54-55 °C) that decompose quickly when stored at room temperature.

Rf = 0.23 (SiO2, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.85 – 6.78 (m, 1H), 6.78 – 6.67 (m, 2H), 5.92 (s, 2H), 3.49 (s, 2H), 2.98 (s, 2H), 2.64 (dd, J = 4.1 Hz, 6.9, 2H), 2.36 (t, J = 6.9 Hz, 2H), 1.94 (dt, J = 6.9 Hz, 12.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 206.9, 147.6, 146.7, 130.9, 122.1, 109.2, 107.8, 100.8, 64.3, 62.1, 51.3, 38.6, 23.8; IR (thin film) ν 2928, 2803, 1714, 1605, 1483, 1441, 1245, 1124, 1038, 987, 933, 870, 808 cm⁻¹; Anal. calcd for C₁₃H₁₅NO₃: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.47; N, 5.93; HRMS (EI) calcd for C₁₃H₁₅NO₃ [M]⁺, 233.1047. Found, 233.1048
1-(benzo[d][1,3]dioxol-5-ylmethyl)azetidin-2-one: To a solution of piperonylamine (1.6 mL, 13 mmol, 1.1 equiv) and NEt₃ (2.5 mL, 18 mmol, 1.5 equiv) was added 3-bromopropanoyl chloride (1.2 mL, 12 mmol, 1.0 equiv). The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH₄Cl and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed three times with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 20/1 to 1/2 cyclohexane/EtOAc) to give 2.4 g pure N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-bromopropanamide (Rₓ = 0.31 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.82 – 6.76 (m, 1H), 6.74 (t, J = 1.0 Hz, 2H), 5.94 (s, 2H), 4.39 (dd, J = 5.7 Hz, 13.7 Hz, 2H), 3.66 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ = 169.4, 147.8, 147.0, 131.5, 121.1, 108.3, 108.2, 101.0, 43.5, 39.7, 27.4; IR (thin film) ν 3267, 3075, 2899, 1634, 1556, 1503, 1445, 1420, 1366, 1261, 1223, 1190, 1100, 1037, 926, 872, 812 cm⁻¹; HRMS (El) calcd for C₁₀H₉NO₃Br [M⁺] = 284.9995. Found, 284.9998). Of this material, 1.0 g (3.5 mmol, 1.0 equiv) were dissolved in 45 mL dry CH₂Cl₂. This solution was added over 6 h to a suspension of finely powdered KOH (0.23 g, 4.2 mmol, 1.2 equiv) in 45 mL CH₂Cl₂. After filtration and evaporation of the filtrate, the residue was purified by flash chromatography (SiO₂, 4/1 cyclohexane/EtOAc to EtOAc) to give 0.22 g pure product (31% yield) as a colorless oil.

Rₓ = 0.39 (SiO₂, 2/1 cyclohexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ = 6.80 – 6.62 (m, 3H), 5.94 (s, 2H), 4.26 (s, 2H), 3.12 (t, J = 4.1 Hz, 2H), 2.92 (t, J = 4.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 147.9, 147.0, 129.4, 121.5, 108.5, 108.3, 101.1, 46.0, 38.5, 36.9; IR (thin film) ν 3477, 2962, 2904, 1744, 1608, 1503, 1491, 1446, 1404, 1371, 1296, 1247,
1190, 1124, 1098, 1037, 926, 865, 811, 770, 739, 713 cm\(^{-1}\); Anal. calcd for C\(_{11}\)H\(_{11}\)NO\(_3\): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.09; H, 5.41; N, 6.79; HRMS (EI) calcd for C\(_{11}\)H\(_{11}\)NO\(_3\) [M]\(^+\), 205.0733. Found, 205.0733

1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-2-one: To a solution of \(\gamma\)-butyro lactam (3.5 mL, 45 mmol, 1.0 equiv) in 50 mL dry THF was cautiously added sodium hydride (60% in mineral oil, 2.0 g, 50 mmol, 1.1 equiv) at 0 °C. After stirring for 30 min, a solution of piperonyl bromide\(^{377}\) (9.7 g, 45 mmol, 1.0 equiv) in 10 mL dry THF was slowly added over 10 min, the mixture allowed to warm to room temperature and stirred over night. Brine and water were added and the mixture was extracted three times with EtOAc. The combined organic phases were washed once with brine, dried over MgSO\(_4\), filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO\(_2\), 2/1 cyclohexane/EtOAc to EtOAc) to give 5.67 g pure product (58% yield) as white crystals (m\(_p\) = 63-65 °C).

\(R_f = 0.11\) (SiO\(_2\), 2/1 cyclohexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 6.79 – 6.65\) (m, 3H), 5.93 (s, 2H), 4.34 (s, 2H), 3.30 – 3.17 (m, 2H), 2.42 (t, \(J = 8.1\) Hz, 2H), 1.97 (dq, \(J = 7.5\) Hz, 11.3 Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 174.6, 147.8, 146.9, 130.4, 121.4, 108.5, 108.1, 101.0, 46.5, 46.4, 31.1, 17.8; IR (thin film) \(\nu = 2895, 1682, 1491, 1443, 1245, 1037, 925, 810, 772\) cm\(^{-1}\); Anal. calcd for C\(_{12}\)H\(_{13}\)NO\(_3\): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 5.97; N, 6.27; HRMS (EI) calcd for C\(_{12}\)H\(_{13}\)NO\(_3\): [M]\(^+\) = 219.0890. Found: 219.0891.

**1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-2-one:** To a solution of δ-valero lactam (4.5 g, 45 mmol, 1.0 equiv) in 50 mL dry THF was cautiously added sodium hydride (60w% in mineral oil, 2.0 g, 50 mmol, 1.1 equiv) at 0 °C. After stirring for 30 min, a solution of piperonyl bromide (9.7 g, 45 mmol, 1.0 equiv) in 10 mL dry THF was slowly added over 10 min, the mixture allowed to warm to room temperature and stirred over night. Brine and water were added and the mixture was extracted three times with EtOAc. The combined organic phases were washed once with brine, dried over MgSO₄, filtered, concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 4/1 cyclohexane/EtOAc to EtOAc) to give 7.78 g pure product (58% yield) as white crystals (m.p. = 68-69 °C).

\[ R_f = 0.09 \text{ (SiO}_2, 2/1 \text{ cyclohexane/EtOAc); } \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3 ) \delta = 6.81 – 6.64 \text{ (m, 3H), 5.94 (s, 2H), 4.49 (s, 2H), 3.19 (d, } J = 6.0 \text{ Hz, 2H), 2.44 (d, } J = 6.3 \text{ Hz, 2H), 2.17 (s, 3H), 1.85 – 1.65 \text{ (m, 4H). } } \]
\[ ^13C \text{ NMR (75 MHz, CDCl}_3 ) \delta = 169.6, 147.8, 146.7, 131.1, 121.4, 108.5, 108.0, 100.9, 49.9, 47.1, 32.5, 23.3, 21.5; \]
\[ \text{IR (thin film) } \nu 2945, 1638, 1491, 1443, 1352, 1241, 1177, 1038, 927, 808, 772, 664 \text{ cm}^{-1}; \]
\[ \text{Anal. calcd for } C_{13}H_{15}NO: \text{ C, } 66.94; \text{ H, } 6.48; \text{ N, } 6.00. \text{ Found: C, } 67.03; \text{ H, } 6.49; \text{ N, } 5.95; \text{ HRMS (EI) calcd for } C_{13}H_{15}NO: [M]^+= 233.1046. \text{ Found: } 233.1045. \]
Curriculum Vitae

Born January 05, 1980 in Bad Tölz, Germany as son of Rosa and Josef jun. Wuitschik.

1986-1990 Primary school, Sachsenkam, Germany
1990-1999 Gymnasium, Bad Tölz, Germany
10/1999 – 09/2004 Undergraduate studies, Technical University Munich, Germany
08/2001 – 09/2001 Max-Planck-Institut für Biochemie, Martinsried, Germany; Internship dealing with peptide synthesis
03/2002 – 10/2003 Bayerische Eliteakademie, Munich, Germany
03/2004 – 09/2004 Diploma thesis in the group of Prof. Barry M. Trost, Stanford University, USA

Title: Towards a Synthesis of Bryostatin 7

01/2005 – present Ph.D. studies in the group of Prof. Erick M. Carreira, ETH Zürich

Title: Oxetanes in Drug Discovery

Fellowships:

Foreign exchange scholarship of the Studienstiftung des deutschen Volkes (03 – 09/2004)
Scholarship from e-Fellows.net (since July 2002)
Scholarship from F. Hoffmann-La Roche AG, Basel (since 01/2005)

During my Ph.D. studies, I was three times teaching assistant for organic chemistry exercises and lectures and responsible for the training of a chemistry technician apprentice for 3 years as well as for four undergraduate students in the context of their research projects.

Zürich, July 2008 Georg Wuitschik
Appendix

GW-X04-43-1 main fraction
File: PROTON
Pulse Sequence: s2pul

File: CARBON
Pulse Sequence: s2pul
OXETANES IN DRUG DISCOVERY

Appendix

File: PROTON
Pulse Sequence: t2ad

File: CARBON
Pulse Sequence: t2ad
Appendix
OXETANES IN DRUG DISCOVERY

Appendix
Appendix
Appendix

GWIV-19%1 fractions 2-9 after high vac

File: PROTON
Pulse Sequence: zgdpul

GWIV-19%1 fractions 2-9 after high vac

File: CARBON
Pulse Sequence: zgdpul
Appendix
Appendix

Sample directory:
File: path/to/file.txt
Pulse Sequence: c2puf
OXETANES IN DRUG DISCOVERY

Appendix

\[
\begin{align*}
\text{PROTON} & \quad \text{Peak 1: 2.94 ppm} \\
\text{Peak 2: 2.21 ppm} \\
\text{Peak 3: 1.84 ppm} \\
\text{C Audience} & \quad \text{Peak 1: 2.08 ppm} \\
\text{Peak 2: 2.00 ppm} \\
\text{Peak 3: 2.00 ppm} \\
\text{Peak 4: 10.62 ppm} \\
\text{CARBON} & \quad \text{Peak 1: 123.71 ppm} \\
\text{Peak 2: 105.07 ppm} \\
\text{Peak 3: 103.97 ppm} \\
\text{Peak 4: 74.49 ppm} \\
\text{Peak 5: 34.59 ppm} \\
\end{align*}
\]
OXETANES IN DRUG DISCOVERY

Appendix

GW-VI-48-1 3H-7:25 after reductive methylation

Flu: PROTON
Pulse Sequence: s2pul

GW-VI-48-1 pure

Flu: CARBON
Pulse Sequence: s2pul
OXETANES IN DRUG DISCOVERY

Appendix

File: PROTON
Pulse Sequence: sqpul

File: CARBON
Pulse Sequence: sqpul
Appendix
OXETANES IN DRUG DISCOVERY

Appendix

Sample directory:
File: /export/homeboxmmn-vm/mass/spectra/exp020.text

Pulse Sequence: s2psl
Appendix
These NMR-spectra were recorded by the NMR-service of F. Hoffmann-La Roche, Basel.
Appendix
Appendix

GW-08-30-1 fractions 21-30
File: PROTON
Pulse Sequence: zgupl

HDO-observe

File: CARBON
Pulse Sequence: zgupl
Appendix

Oxetanes in Drug Discovery

286
Appendix

290

OXETANES IN DRUG DISCOVERY

GW-8-26-1 fractions 7-9
File: PROTON
Pulse Sequence: s2p4

GW-8-26-1 fractions 7-9
File: CARBON
Pulse Sequence: s2p4
Appendix
OXETANES IN DRUG DISCOVERY

Appendix

[Chemical structure and spectra image]

File: PROTON
Pulse Sequence: d2psd

File: CARBON
Pulse Sequence: d2psd
OXETANES IN DRUG DISCOVERY

Appendix

File: PROTON
Pulse Sequence: s2psf

File: CARBON
Pulse Sequence: s2psf
Appendix

RM416-6 product nach trocknen an HV
Res: PROTON
Pulse Sequence: 2D pul

RM417-7 produkt nach trocknen an HV
Res: CARBON
Pulse Sequence: 2D pul
OXETANES IN DRUG DISCOVERY

Appendix

[Chemical structure image]

[Graphs and spectral data]

GW-VHS-19-10-14
File: PROTON
Pulse Sequence: h2pul

GW-VHS-19-10-14
File: CARBON
Pulse Sequence: h2pul
Appendix

GW-XI-39-1 crude
File: PROTON
Pulse Sequence: s2pul

N3
OH

GW-XI-39-1 crude
File: CARBON
Pulse Sequence: s2pul
Appendix

Sample directory:
File: /Users/home/sdoslev/oxysys/1st/1st.txt
Pulse Sequence: s2uv1

harmapromorphine oxalate salt
File: CARBON
Pulse Sequence: s2uv1
Appendix

OXETANES IN DRUG DISCOVERY

AB-8-12 new Fraktionen
Sample directory:
File: /work/home/scoren/xenopeak/exp1
Pulse Sequence: 2Dpsyd

8 7 6 5 4 3 2 1
ppm

AB-8-12
File: CARBON
Pulse Sequence: 2Dpsyd

160 150 140 130 120 110 100 90 80 70 60 50 40 30
ppm
Appendix
OXETANES IN DRUG DISCOVERY

Appendix

NMR-2D-1 fraction 31-04
Filer: PROTON
Pulse Sequence: s2pul

NMR-2D-1 fraction 31-09
Filer: CARBON
Pulse Sequence: s2yul
OXETANES IN DRUG DISCOVERY

Appendix

File: PROTON
Pulse Sequence: 52psf

File: CARBON
Pulse Sequence: 52psf
OXETANES IN DRUG DISCOVERY

Appendix

Sample directory:
Files: joporphine/opernv/summey/jpg1/text

Pulse Sequences: s2pol
Appendix

316

OXETANES IN DRUG DISCOVERY

Appendix

[Image of chemical structures and spectra]

File: PROTON
Pulse Sequence: s2p1

File: CARBON
Pulse Sequence: s2p1
OXETANES IN DRUG DISCOVERY

Appendix

[Chemical diagrams and spectra]

M94-45-11-10-22
File: CARBON
Pulse Sequence: s2pol

M94-45-11-10-22
File: PROTON
Pulse Sequence: s2pol
Appendix

GaN-X-44-1 h 22-43 after drying overnight highvac
File: PROTON
Pulse Sequence: c2pul

Cl

OMe

OMe

GaN-X-44-1 h 22-43
File: CARBON
Pulse Sequence: c2pul

200 180 160 140 120 100 80 60 40 20 pp
15.198 33.53 55.93 53.39 50.948 77.406 77.55 128.201 138.058 146.142 153.345 201.293 201.548

8 7 6 5 4 3 2 1 0 ppm
1.98 2.02

1.13 1.23 1.38

3.117 3.717 3.817 3.982 4.831

15.198 33.53 55.93 53.39 50.948 77.406 77.55 128.201 138.058 146.142 153.345 201.293 201.548

200 180 160 140 120 100 80 60 40 20 pp
15.198 33.53 55.93 53.39 50.948 77.406 77.55 128.201 138.058 146.142 153.345 201.293 201.548
Appendix
OXETANES IN DRUG DISCOVERY

Appendix

\[
\begin{align*}
\text{File: PROTON} \\
\text{Pulse Sequence: s2yul}
\end{align*}
\]

\[
\begin{align*}
\text{File: CARBON} \\
\text{Pulse Sequence: s2yul}
\end{align*}
\]
OXETANES IN DRUG DISCOVERY

Appendix

GW-IV-35-2 hydrogenation product after distillation vial 1
Sample directory:
File: isoprene/ioseiv/emmys/exp1/text
Pulse Sequence: s2ps

GW-IV-30-2 hydrogenation product after distillation vial 1
Sample directory:
File: isoprene/ioseiv/emmys/exp1/text
Pulse Sequence: s2ps
OXETANES IN DRUG DISCOVERY

Appendix

Gmp-XIV-7A after distillation

File: PROTON
Pulse Sequence: s2psl

Gmp-XIV-7A after distillation

File: CARBON
Pulse Sequence: s2psl
OXETANES IN DRUG DISCOVERY

Appendix

GK X-21-1 after column and distillation
File: PROTON
Pulse Sequence: 1Dppul

GK X-21-1 after column and distillation
File: CARBON
Pulse Sequence: 1Dppul
OXETANES IN DRUG DISCOVERY

Appendix

File: PROTON
Pulse Sequence: s2pul

File: CARBON
Pulse Sequence: s2pul
Appendix
OXETANES IN DRUG DISCOVERY

Appendix

GW-X-39-1 after distillation
File: PROTON
Pulse Sequence: s2pul

GW-X-39-1 after distillation
File: CARBON
Pulse Sequence: s2pul
Appendix
OXETANES IN DRUG DISCOVERY

Appendix
Appendix