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Oxetanes in Drug Discovery

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This work would not have been possible without the strong and sustained support of a number of people of Roche, who not only measured the compounds, but also were extremely helpful in interpreting and understanding the results. In particular I would like to thank André Alker, Dr. Holger Fischer, Dr. Manfred Kansy, Pia Warga, Isabelle Parrilla, Dr. Stefanie Bendels, Dr. Liudmila Polonchuk, Frank Senner, Björn Wagner, Dr. Franz Schuler, Dr. Thierry Godel and Dr. Josef Schneider. I want to thank my supervisors for enabling me to come to Roche for three months to apply the oxetane chemistry in a real project. I’m grateful to Dr. Mark Rogers-Evans, my host at Roche and his coworker Didier Rombach, as well as Olivier Gavelle and Dr. Rainer Martin.

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Gewidmet meinen Eltern

Publications

1. Trost, B. M.; Yang, H. B.; Wuitschik, G., A Ru-catalyzed tandem alkyne-enone coupling/Michael addition: Synthesis of 4-methylene-2,6-cis-tetrahydropyrans. *Org. Lett.* **2005,** 7, (21), 4761-64.
2. Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M., Oxetanes as Promising Modules in Drug Discovery. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736-39
3. Wuitschik, G., Carreira, E. M., Rogers-Evans M., Müller, K., Oxetan-3-one: chemistry and synthesis in *Process Chemistry in the Pharmaceutical Industry* (Eds.: K. Gadamasetti, T. Braish), CRC Press LLC, Boca Raton, Fla, **2008**, pp. 217-29.
4. Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M., Spirocyclic Oxetanes: Synthesis and Properties. *Angew. Chem., Int. Ed.* **2008,** 47, 4512-15

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Presentation at LSYR Summer School 2006, Molėtai, Lithuania

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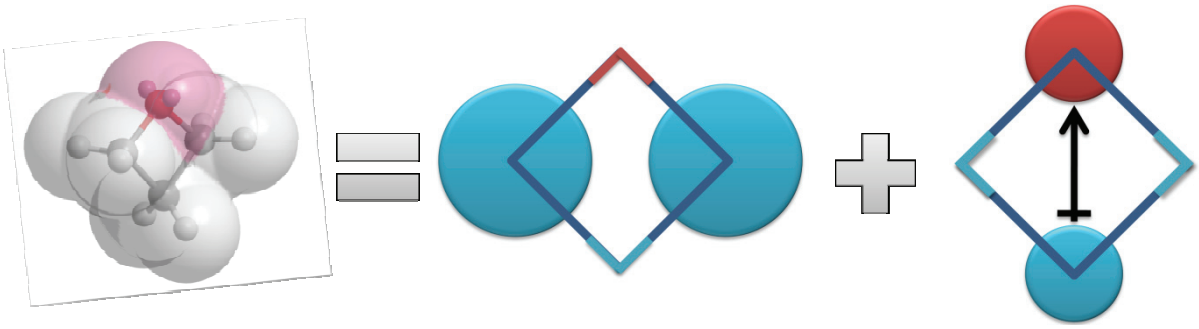
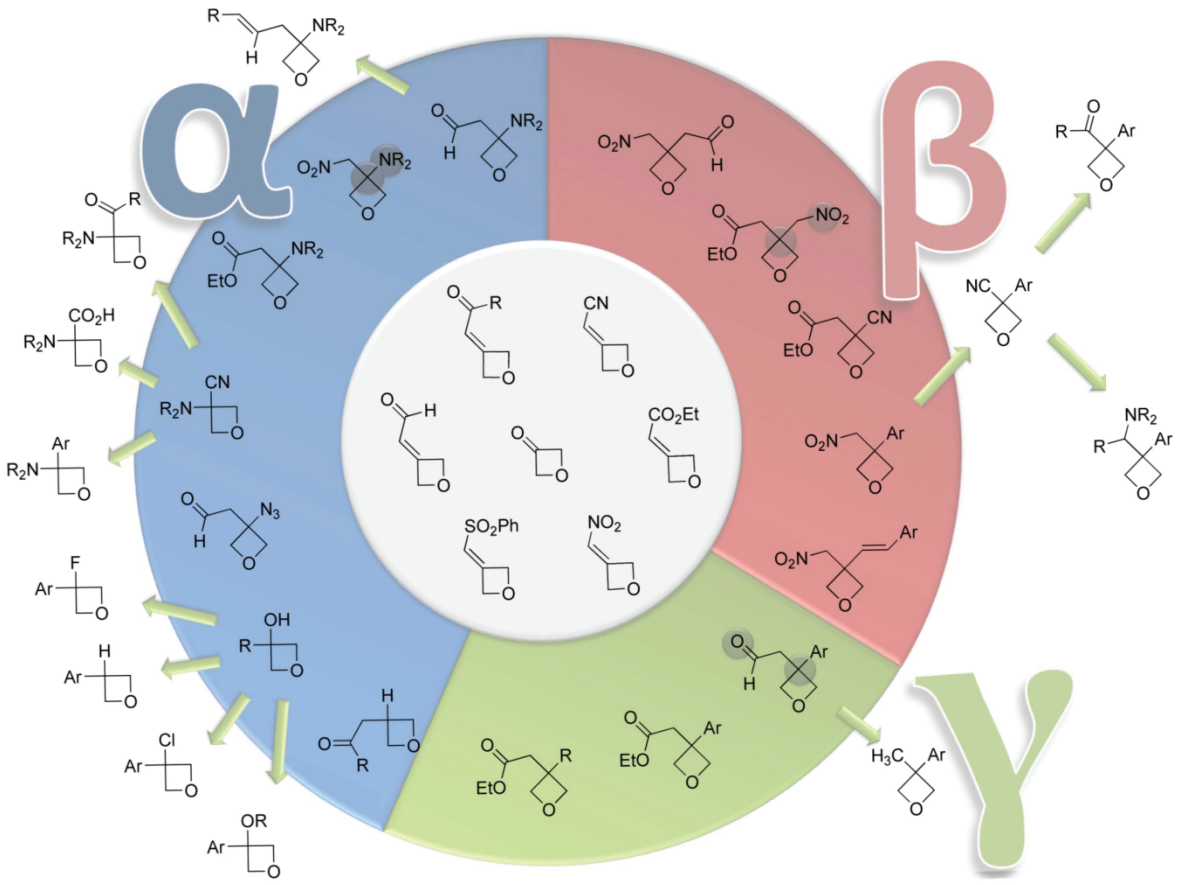
Abstract

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.

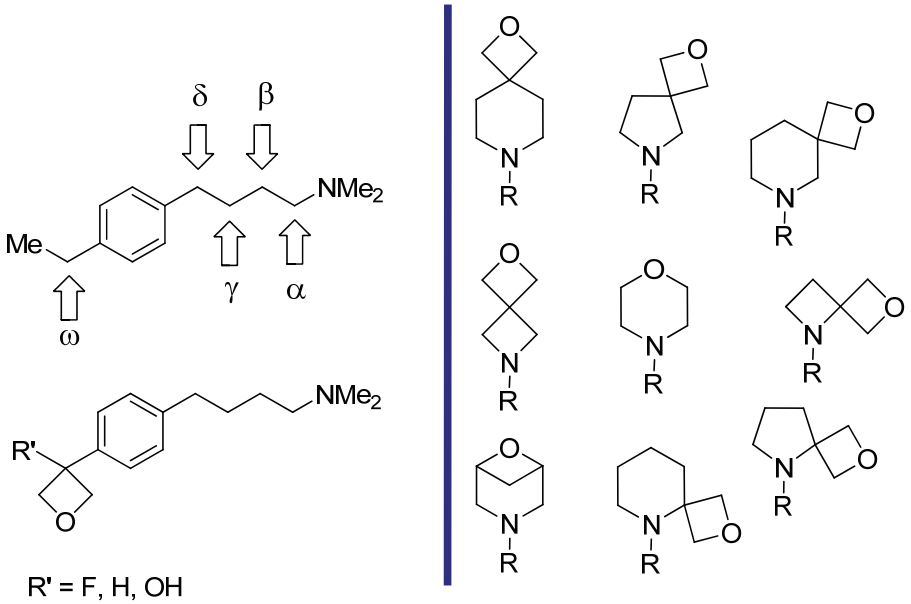


From a structural point of view, 3,3-disubstituted oxetanes can be described as a combination of steric bulk exhibited by its methylene groups and the polarity introduced by the ethereal oxygen. Therefore, an oxetane poses a more hydrophilic alternative to bulky functionalities such as *gem*-dimethyl 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.

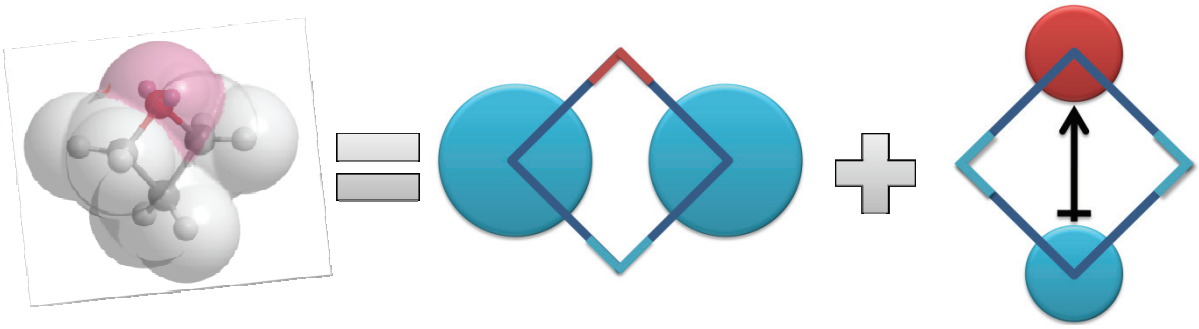
The results clearly show that the integration of an oxetane can have a dramatic influence on the physico- and biochemical properties of the underlying scaffold. When compared with their *gem*-dimethyl counterparts, oxetanes are less lipophilic, more soluble and in most cases also metabolically more stable. 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.

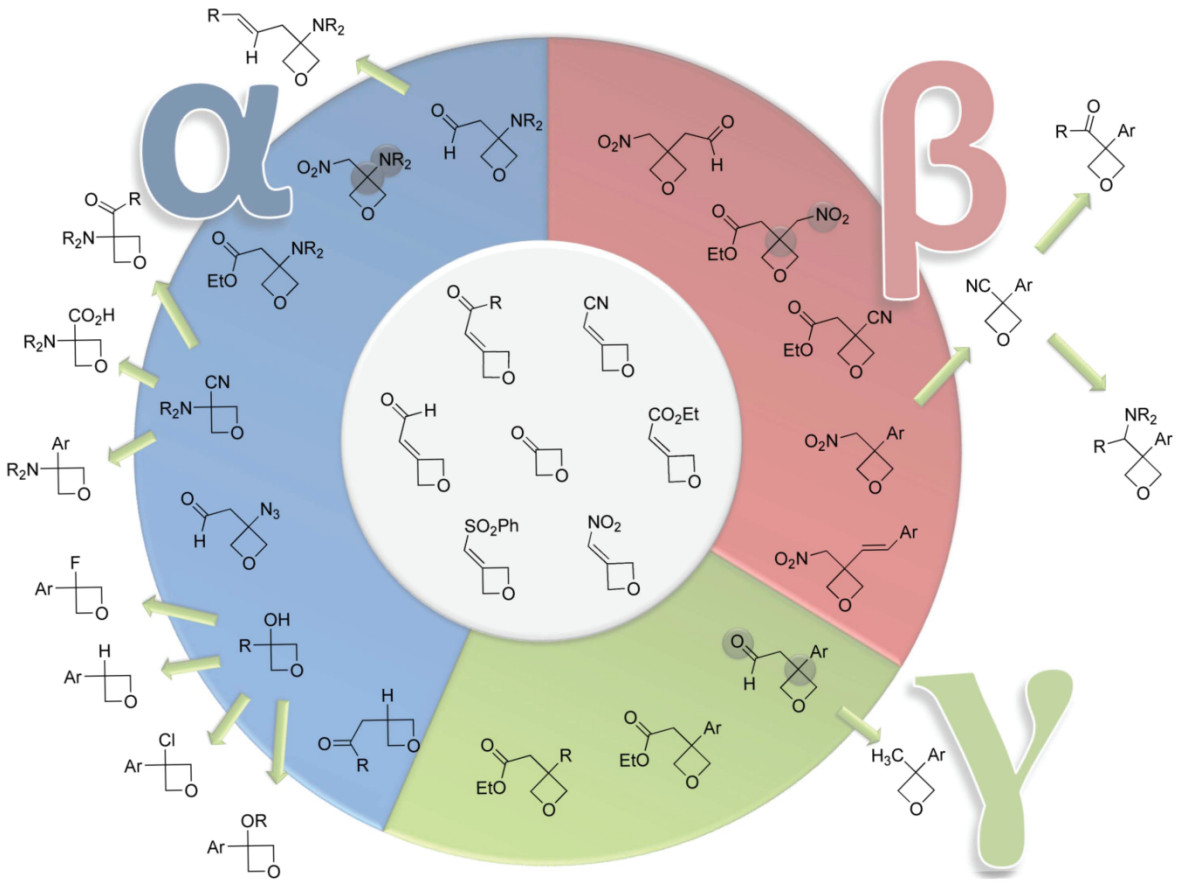
Zusammenfassung

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.

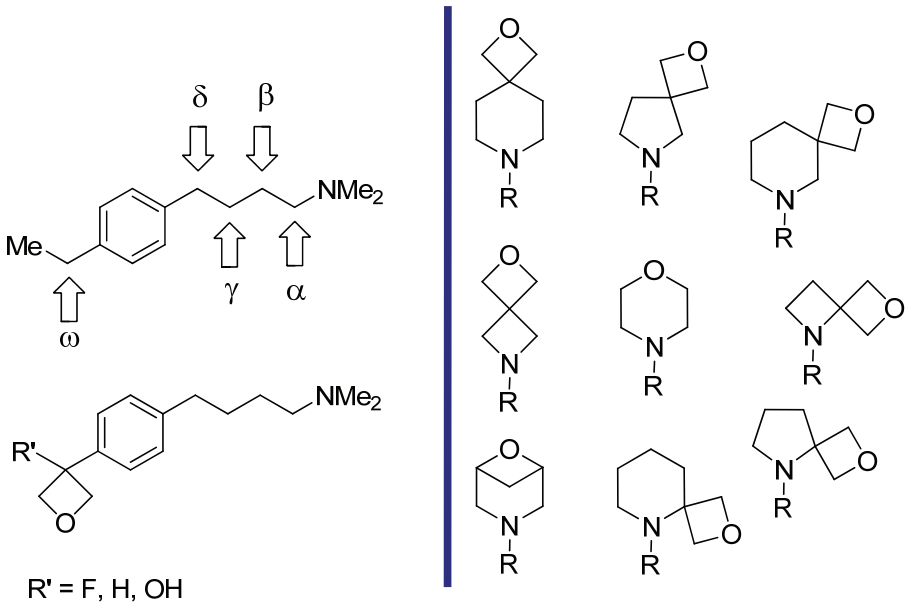


Aus Sicht ihrer Struktur, können 3,3-disubstituierte Oxetane beschrieben werden als eine Kombination des sterischen Anspruchs der beiden Methylengruppen und der Hydrophilie des polaren Ethersauerstoffs. Daher stellen Oxetane eine polare Alternative zu sterisch anspruchsvollen Funktionalitäten wie geminalen Dimethylgruppen dar. Im Gegensatz dazu besitzen Moleküle, die Carbonylgruppen enthalten oft eine unerwünschte chemische Reaktivität an oder um die Carbonylgruppe herum. Ein Oxetan vermeidet dies durch seine reduzierte Elektrophilie und durch das Fehlen jenes elektronenarmen π-Systems, durch welches benachbarte negative Ladungen stabilisiert würden. Darüberhinaus ist eine bestimmte Klasse spirozyklischer Oxetane aufgrund ähnlicher Struktur und Eigenschaften in der Lage, den in der Medizinalchemie oft verwendeten Baustein Morpholin zu ersetzen.

Um aber praktische Relevanz zu erlangen, müssen verschiedenste Oxetane synthetisch einfach zugänglich sein. Wir entschieden uns für eine Herangehensweise, in der Bausteine, welche bereits ein Oxetan enthalten mit einem Molekülgerüst verbunden und danach weiter funktionalisiert würden. Ausgehend von Oxetan-3-on konnte so eine breite Palette von Oxetanen dargestellt werden. Diese Vielfalt resultiert aus der Flexibilität der Chemie von Oxetan-3-on und mehr noch der der davon abgeleiteten Michaelakzeptoren.



Darauf aufbauend konnten wir zwei Klassen von Molekülen herstellen, in welchen der Einfluss von Oxetanen an verschiedenen Stellen des Molekülgerüstes studiert wurde. In der unten links gezeigten Klasse von Molekülen konnten die Eigenschaften des Oxetans mit jenen der geminalen Dimethylgruppe verglichen werden.



Die Spirozyklen rechts wiederum, ermöglichten zusätzlich noch den Vergleich mit den entprechenden Carbonylanaloga und Morpholin. Für all diese Verbindungen wurden dann bei F. Hoffmann-La Roche Schlüsselparameter wie zum Beispiel wässrige Löslichkeit, Lipophilie, metabolische Stabilität bestimmt.

Die Ergebnisse dieser Untersuchungen zeigen deutlich, dass die Integration eines Oxetans dramatische Auswirkungen auf die physiko- wie auch biochemischen Parameter des zugrundeliegenden Molekülgerüsts 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 verringerter 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
b_p	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

d	day, doublet
DAST	diethylaminosulfur trifluoride
DIBAL-H	diisobutylaluminum hydride
DMAP	4-*N*,*N*'-dimethylamino pyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethylsulfoxide
dppa	diphenylphosphoryl azide
ECG	electrocardiogram
EI	electron impact ionization
ent	reversal of stereocenters
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
et al.	and others
FT	Fourier transformation
g	gram
gem	geminal
h	hour, human
hERG	human-Ether-a-go-go Related Gene
HPLC	high-performance liquid chromatography
HR	high resolution

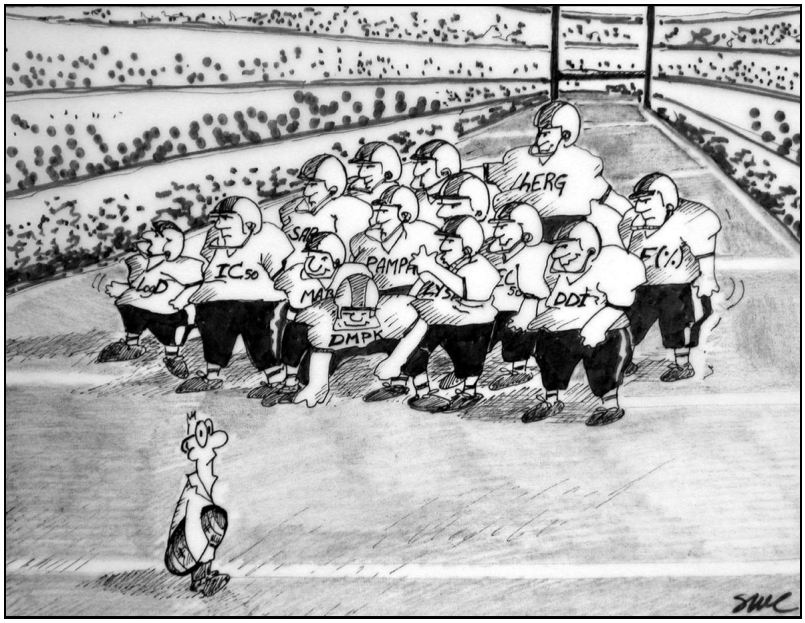
Hz	Hertz
i	*iso*
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant, Joule
kcal	kilocalorie
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
LDA	lithium di*iso*propyl amide
LiDBB	lithium Di-*tert*-butylbiphenyl
logD	intrinsic lipophilicity
logP	lipophilicity
m	multiplet, mouse
m	*meta*
M	molecule ion
M	molar
mbar	millibar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
ml	milliliter

m_p	melting point
µl	microliter
mmol	millimole
µm	micromole
mol%	mole per cent
Ms	methylsulfonyl
MS	molecular sieves, mass spectrometry
$n Al_2O_3$	neutral aluminum oxide
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
ν	vibration frequency in cm^{-1}
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
pH	negative decadic logarithm of hydrogen ion concentration
Ph	phenyl
pKa	negative decadic logarithm of the acid dissociation constant
ppm	parts per million
Pr	propyl
pyr	pyridine
q	quartet

quant.	quantitative
R_f	retention factor
rt	room temperature
s	singlet, second
t	triplet
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]

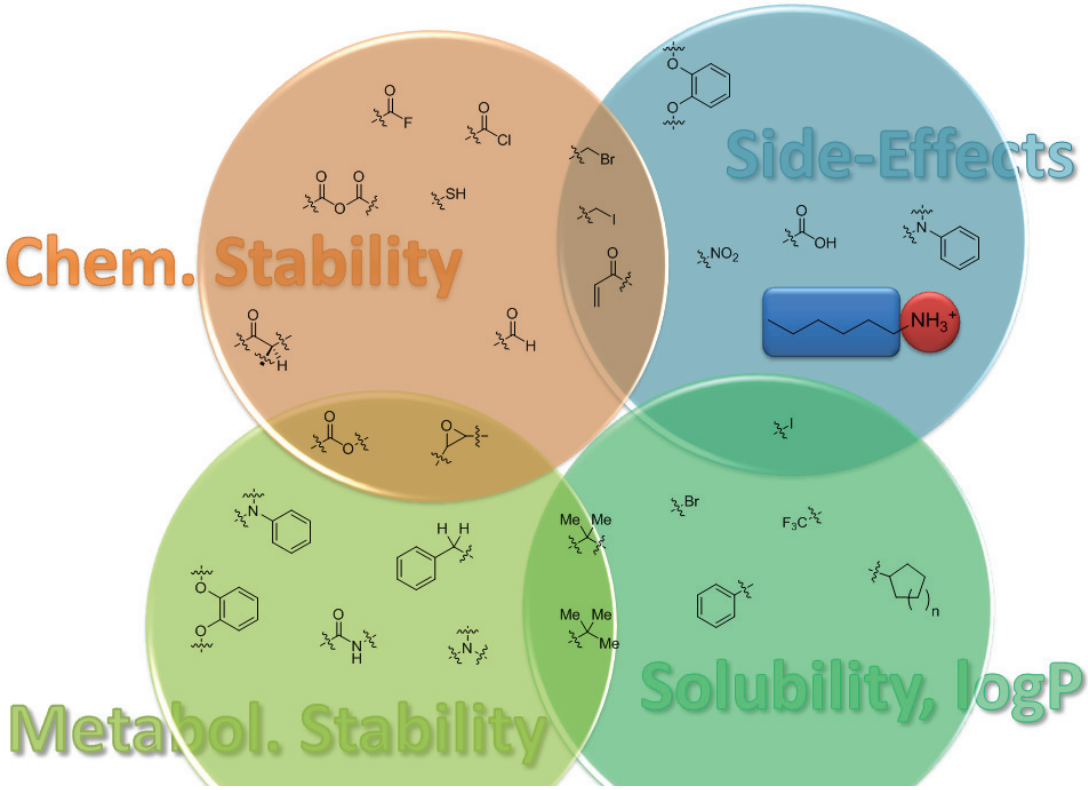
The acceptable ranges for these properties are tight, because of the attrition risk a deviation poses for the clinical development of a drug candidate. As clinical studies and registration absorb the majority of costs in the drug discovery and development process it is critical to anticipate which compounds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

[2] K. H. Bleicher, H. J. Böhm, K. Müller, A. I. Alanine, *Nat. Rev. Drug Discov.* **2003**, *2*, 369. Several empirical sets of rules have been proposed in order to predict the "drug-likeness" of a given compound, "Lipinski's Rule of Five" being the most well known (C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Del. Rev.* **2001**, *46*, 3.).

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.



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-

[3] I. Kola, J. Landis, *Nat. Rev. Drug Discov.* **2004**, *3*, 711.

[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, interconverting 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.[5] 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.[6] This lack of structural diversity among test compounds has already been identified earlier as a potential bottleneck in the drug discovery process.[7]

Oxetanes are clearly one of the neglected frameworks of organic, but also medicinal chemistry.[8] 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 Stuctural 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-

[5] A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt, R. J. Schenck, A. J. Trippe, *J. Org. Chem.* **2008**, *73*, 4443.
[6] G. W. Bemis, M. A. Murcko, *J. Med. Chem.* **1996**, *39*, 2887.
[7] M. D. Burke, E. M. Berger, S. L. Schreiber, *Science* **2003**, *302*, 613.
[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.[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° (90 K data) and 8.7° (140 K data) respectively).[10] Introduction of substituents increases eclipsing interactions and therefore also often leads to puckered structures.[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.[12]

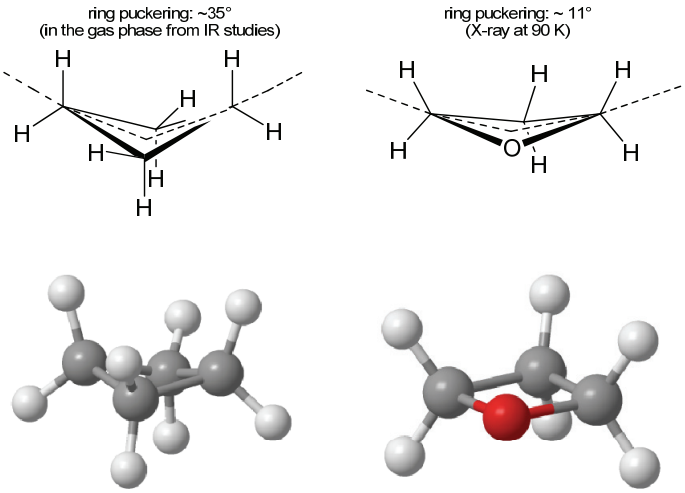


Figure 1: Comparison of the puckering angles between cyclobutane[13] and oxetane.

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.[14]

[9] W. D. Gwinn, *Discuss. Faraday. Soc.* **1955**, 43.; J. Fernandez, R. J. Myers, W. D. Gwinn, *J. Chem. Phys.* **1955**, *23*, 758. The upper boundary for puckering of the oxetane-ring at ambient temperature was determined to be 0°20‘.
[10] P. Luger, J. Buschmann, *J. Am. Chem. Soc.* **1984**, *106*, 7118.
[11] For examples of puckered oxetanes, see: a) J. H. Noordik, J. M. Cillissen, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1981**, *10*, 345. b) G. Holan, C. Kowala, J. Wunderli, *J. Chem. Soc., Chem. Commun.* **1973**, 34.
[12] S. I. Chan, W. D. Gwinn, J. Zinn, *J. Chem. Phys.* **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.
[13] T. Ueda, T. Shimanou, *J. Chem. Phys.* **1968**, *49*, 470.
[14] M. Berthelot, F. Besseau, C. Laurence, *Eur. J. Org. Chem.* **1998**, 925. The equilibrium concentrations were determined by measuring the absorbances of the O-H stretching of 4-fluorophenol for different initial base concentrations.

Introduction

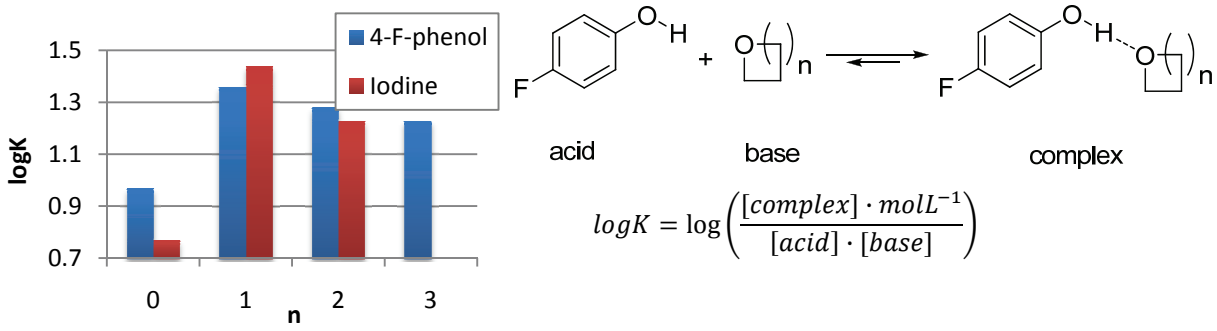


Diagram 1: Strength of association with 4-fluorophenol and iodine in cyclic ethers against ring-size.[14,17]

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.[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.[16]

Oxetane also forms complexes with iodine[17] and with dinitrogen pentoxide[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.[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.

[15] L. Bellon, R. W. Taft, J. L. M. Abboud, *J. Org. Chem.* **1980**, *45*, 1166.
[16] a) R. West, L. S. Whatley, M. K. T. Lee, D. L. Powell, *J. Am. Chem. Soc.* **1964**, *86*, 3227. b) E. Lippert, H. Prigge, *Justus Liebigs Ann. Chem.* **1962**, *659*, 81.
[17] M. Brandon, M. Tamres, S. Searles, *J. Am. Chem. Soc.* **1960**, *82*, 2129. In Diagram 1 the point for iodine with n = 0 refers to propylene oxide.
[18] H. H. Sisler, P. E. Perkins, *J. Am. Chem. Soc.* **1956**, *78*, 1135.
[19] G. M. Bennett, W. G. Philip, *J. Chem. Soc.* **1928**, 1937.

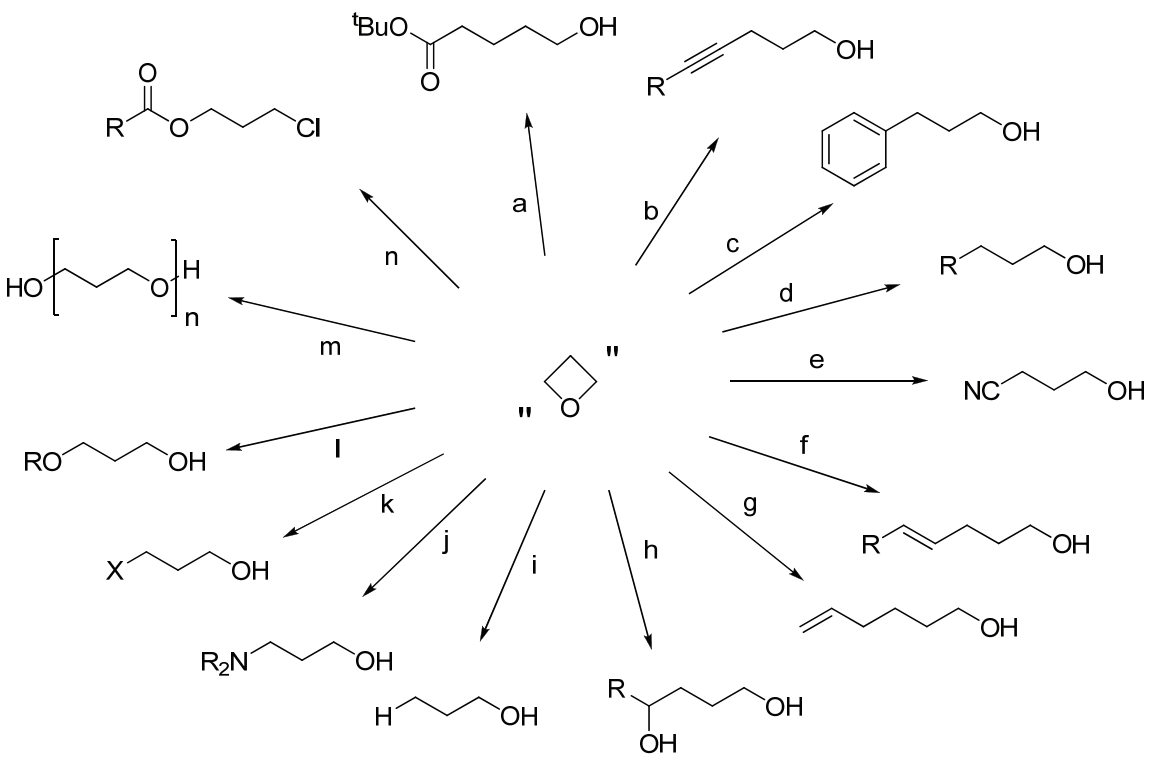
1.2 Ring-Opening Reactions of Oxetanes

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 “Penta-plast” 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]

[20] A. C. Farthing, R. J. W. Reynolds, *J. Polym. Sci.* **1954**, *12*, 503.
[21] J. G. Pritchard, F. A. Long, *J. Am. Chem. Soc.* **1958**, *80*, 4162. For kinetic studies on the mechanism of acid-catalyzed ring opening of oxetane, see: M. Lajunen, J.-M. Koskinen, *Acta Chem. Scand.* **1994**, *48*, 788.
[22] a) J. L. Wolk, M. Sprecher, H. Basch, S. Hoz, *Org. Biomol. Chem.* **2004**, *2*, 1065. b) J. L. Wolk, T. Hoz, H. Basch, S. Hoz, *J. Org. Chem.* **2001**, *66*, 915. c) A. Sella, H. Basch, S. Hoz, *J. Am. Chem. Soc.* **1996**, *118*, 416. Hoz rejects previously made claims (H. D. Banks, *J. Org. Chem.* **2003**, *68*, 2639.) that the reactivity difference can be traced back to different degrees of stabilization of the reacting center’s partial positive charge by the leaving alkoxide.
[23] D. Sawicka, K. N. Houk, *J. Mol. Model.* **2000**, *6*, 158.



Scheme 1: Ring-opening reaction of oxetanes:[24] *a) LiO(tBuO)C=CH2, BF3·OEt2; b) RC≡CLi, BF3·OEt2; c) ArH, AlCl3; d) RLi or RMgX; e) TMSCN, ZnI2; f) RHC=CHAlR3Li, BF3·OEt2 or H2C=CHMgX; g) allylTMS, TiCl4; h) 1. Li, cat DBB, 2. RCHO; i) LiAlH4; j) R2NH or R2NMgX; k) HX; l) ROH, cat. H2SO4; m) BF3·OEt2, BF3, AlCl3 or PCl5; 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 neopentylic centers.

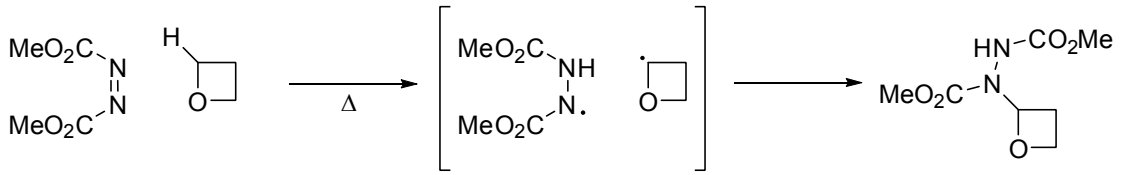
[24] a) M. Yamaguchi, K. Shibato, I. Hirao, *Tetrahedron Lett.* **1984**, *25*, 1159. b) M. Yamaguchi, Y. Nobayashi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 5121. c) S. Searles, *J. Am. Chem. Soc.* **1954**, *76*, 2313. d) S. Searles, *J. Am. Chem. Soc.* **1951**, *73*, 124. e) S. A. Carr, W. P. Weber, *Synth. Commun.* **1985**, *15*, 775. f) A. Alexakis, D. Jachiet, *Tetrahedron* **1989**, *45*, 6197. or S. Julia, C. Gueremy, *Bull. Soc. Chim. Fr.* **1965**, 2994. g) S. A. Carr, W. P. Weber, *J. Org. Chem.* **1985**, *50*, 2782. h) B. Mudryk, T. Cohen, *J. Org. Chem.* **1989**, *54*, 5657. i) S. Searles, K. A. Pollart, E. F. Lutz, *J. Am. Chem. Soc.* **1957**, *79*, 948. Opening of 3,3-disubstituted oxetanes is much slower than in less substituted oxetanes (S. Searles, E. F. Lutz, *J. Am. Chem. Soc.* **1959**, *81*, 3674.) j) S. Searles, V. P. Gregory, *J. Am. Chem. Soc.* **1954**, *76*, 2789. k) S. Searles, Jr., *Chem. Heterocyclic Compds. (Arnold Weissberger, editor. Interscience)* **1964**, *19*, 983. l) S. Searles, C. F. Butler, *J. Am. Chem. Soc.* **1954**, *76*, 56. m) A. R. Katritzky, C. W. Rees, in *Comprehensive Heterocyclic Chemistry*, Pergamon Press plc, Oxford (UK), **1984**, p. 382. n) C. G. Derick, D. W. Bissell, *J. Am. Chem. Soc.* **1916**, *38*, 2478.

Being kinetically more stable than epoxides toward nucleophilic ring opening, oxetanes should also be less prone to react with endogenous nucleophiles like glutathione (GSH)[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[26] and shields the oxetane sterically[24i] from attack.

1.3 Tendency of Oxetane to Form Radicals

Oxidative primary metabolism relies mainly on the cytochrome P450 (CYP) enzyme family.[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· to form a radical, making positions in molecules that give rise to more stable radicals more susceptible towards metabolism.[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.[29] Therefore cyclic ethers should be good substrates for CYPs.[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.[31] Oxetane was found to react under thermal conditions with dimethyl azodicarboxylate via a proposed radical intermediate:[32]

[25] For a review on GSH-adducts, see: I. A. Blair, *Current Drug Metabolism* **2006**, *7*, 853.
[26] B. Ringner, S. Sunner, H. Watanabe, *Acta Chem. Scand.* **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.
[27] For a review about the P450 gene superfamily and their evolution, see: F. J. Gonzalez, D. W. Nebert, *Trends Genet.* **1990**, *6*, 182.
[28] F. P. Guengerich, G. P. Miller, I. H. Hanna, H. Sato, M. V. Martin, *J. Biol. Chem.* **2002**, *277*, 33711.
[29] One prominent consequence is the formation of peroxides in many cyclic as well as acyclic ethers under the influence of oxygen and light.
[30] THF is metabolized in the body to γ-hydroxybutyric acid via the intermediary 2-hydroxytetrahydrofuran. B. Cartigny, N. Azaroual, M. Imbenotte, N. Sadeg, F. Testart, J. Richecoeur, G. Vermeersch, M. Lhermitte, *J. Anal. Toxicol.* **2001**, *25*, 270.
[31] Search done in MDL® Drug Metabolite Database on May 12 2008. Hits where the oxetane ring was cleaved, can mainly be attributed to hydrolysis.
[32] G. Ahlgren, *Tetrahedron Lett.* **1974**, 2779. No yield given. The related reaction of oxetane with dimethyl acetylenedicarboxylate was reported by the same author: G. Ahlgren, *J. Org. Chem.* **1973**, *38*, 1369.



Scheme 2: Hydrazination of oxetane under thermal conditions.[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.

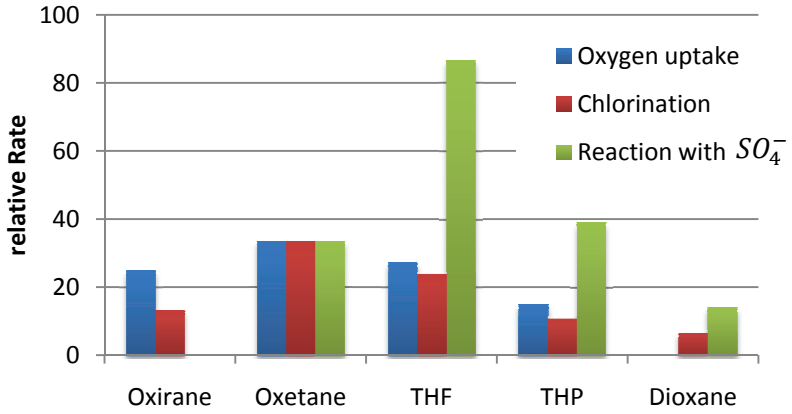


Diagram 2: Relative reaction rates of a variety of substrates standardized for oxetane.[33]

For the reaction with oxygen the rate of oxygen consumption was measured irrespective of the different reaction pathways.[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.[35] Therefore the rate would not be solely determined by the stability of the ether radical.

[33] Oxygen-uptake in case of epoxides refers to propylene oxide.
[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).
[35] V. I. Stenberg, R. D. Olson, C. T. Wang, N. Kulevsky, *J. Org. Chem.* **1967**, *32*, 3227.

In case of the chlorination, the formation of the particular α-chloro ether was measured,[36] whereas for the reaction with 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]

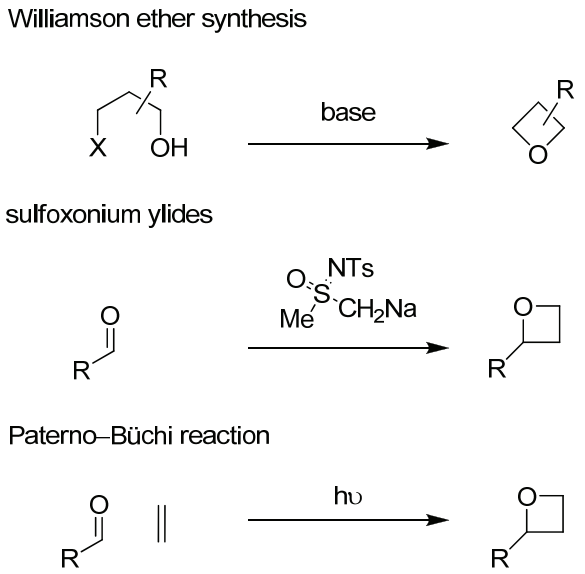
The rate with which cyclic ethers participate in a radical chain reaction depends largely on the reaction chosen, and seemingly does not allow for ranking their propensity to form radicals. From this data it is therefore not clear, how likely the oxetane in a given molecule will be a target of metabolic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

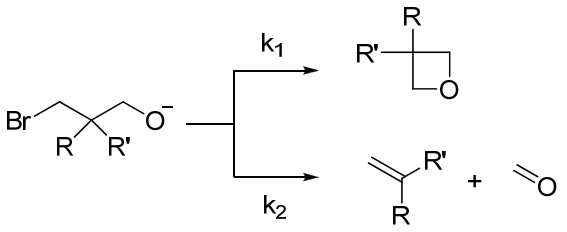
Oxetane, the parent heterocycle has first been reported by Reboul in 1878, who prepared it by reaction of 3-chloropropanol with aqueous base.[39] This class of saturated oxygen heterocycles has been made in a variety of different ways. Those that have found repeated use in the literature include intramolecular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

[36] C. Walling, M. J. Mintz, *J. Am. Chem. Soc.* **1967**, *89*, 1515.
[37] R. E. Huie, C. L. Clifton, S. A. Kafafi, *J. Phys. Chem.* **1991**, *95*, 9336. The radical was prepared by laser-induced photolysis of $S_2O_8^{2-}$.
[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.
[39] M. Reboul, *Ann. Chim. (Paris)* **1878**, *14*, 496.



Scheme 3: Common ways to prepare oxetanes.

Among these, the Williamson ether synthesis is the most general.[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.[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.[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:[43]



Scheme 4: Grob fragmentation as side reaction competing with ring closure. [44]

[40] S. Searles, Jr., *Chem. Heterocyclic Compds. (Arnold Weissberger, editor. Interscience)* **1964**, *19*, 983.
[41] G. Forsberg, *Acta Chem. Scand.* **1954**, *8*, 135.
[42] a) G. Forsberg, *Acta Chem. Scand.* **1954**, *8*, 135. b) L. Ruzicka, *Helv. Chim. Acta* **1926**, *9*, 230.
[43] W. Fischer, C. A. Grob, *Helv. Chim. Acta* **1978**, *61*, 2336.
[44] S. Searles, R. G. Nickerson, W. K. Witsiepe, *J. Org. Chem.* **1959**, *24*, 1839. S. Searles, M. J. Gortatowski, *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: R = Ph > Alkyl > H.

The one-pot conversion of aldehydes or ketones with sulfoxonium ylides to give 2-substituted oxetanes provides an alternate route.[45] This reaction is considered to proceed *via* an epoxide intermediate that subsequently undergoes ring opening by a second equivalent of the ylide. The resulting γ-alkoxy sulfonium ylide then participates in an intramolecular displacement reaction to furnish a 2-substituted oxetane (Scheme 3).[46] The same class of substituted oxetanes can be accessed *via* the Paterno-Büchi reaction.[47] This cycloaddition reaction between an aldehyde or a ketone and an electron-rich alkene affords regioselectively the corresponding oxetanes in good yield.[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.

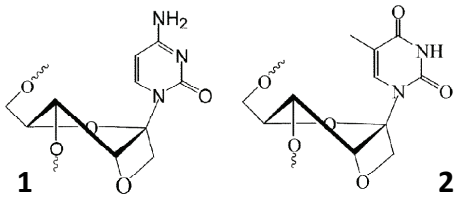
The latter two methods necessarily lead to oxetanes that incorporate substitution at C-2 and are therefore not suitable for the preparation of 3,3-disubstuted oxetanes, the focus of this project. Although the remaining approach involving intramolecular Williamson ether synthesis provides access to 3,3-disubstitued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

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.

[45] S. C. Welch, A. S. C. P. Rao, *J. Am. Chem. Soc.* **1979**, *101*, 6135.
[46] A. O. Fitton, J. Hill, D. E. Jane, R. Millar, *Synthesis-Stuttgart* **1987**, 1140.
[47] G. Büchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc.* **1954**, *76*, 4327.
[48] T. Bach, *Synthesis-Stuttgart* **1998**, 683.

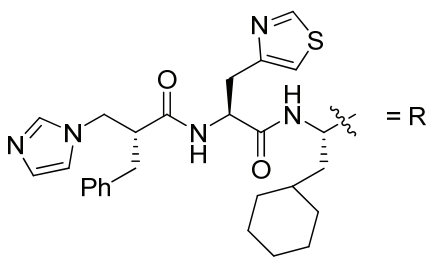
Early studies in rats involving 3,3-diethyloxetane and other simple oxetanes revealed their anesthetic, sedative and anticonvulsant properties.[49] Conformationally restrained oxetane derivatives of cytidine **1** and thymidine **2** have been investigated for their use as part of antisense oligonuclotides (AON).



1 **2**

*Scheme 5: Oxetane analogues (**1**,**2**) of Cytidine and Thymidine used for Antisense oligonuclotides*[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]



= R

	3	**4**	**5**
IC_{50}	22 nM	9.8 nM	1.2 nM

Scheme 6: Oxetanes as transition-state analogues for Renin, an aspartate protease[51]

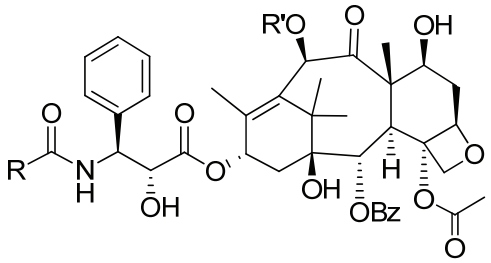
[49] H. T. Gier, S. Searles, *J. Med. Pharmaceut. Ch.* **1959**, *1*, 355. Zarudii *et al.* found a variety of 3,3-disubstituted oxetanes to possess broncholytic activity in cats (F. S. Zarudii, D. N. Lazareva, E. S. Kurmaeva, O. B. Chalova, T. K. Kiladze, E. A. Kantor, D. L. Rakhmankulov, *Pharm. Chem. J. (Engl. Transl.)* **1985**, *19*, 108.). In a recent study, the anesthetic properties of some fluorinated oxetanes were examined and found to have no advantage compared to commonly used anesthetics (E. I. Eger, II, D. Lemal, M. J. Laster, M. Liao, K. Jankowska, A. Raghavanpillai, A. V. Popov, Y. Gan, Y. Lou, *Anesth. Analg.* **2007**, *104*, 1090.).

[50] a) P. I. Pradeepkumar, J. Chattopadhyaya, *J. Chem. Soc., Perkin Trans. 2* **2001**, 2074. b) P. I. Pradeepkumar, N. V. Amirkhanov, J. Chattopadhyaya, *Org. Biomol. Chem.* **2003**, *1*, 81.

[51] S. H. Rosenberg, K. P. Spina, H. Stein, J. Cohen, W. R. Baker, H. D. Kleinert, *Bioorg. Med. Chem.* **1994**, *2*, 927. Despite the high binding affinity the authors state that lack of oral availability and high molecular weight necessitate further development. In case of Carbapenem antibiotics, the replacement of a tetrahydrofuran with an oxetane brought no improvement in activity (S. M. Sakya, T. W. Strohmeyer, P. Bitha, S. A. Lang, Y. I. Lin, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1805.).

In case of the dihydroxy isoster **3** it is believed that the diol interacts with both aspartate residues in the active site.[52] 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.[53] Taxol® (**6**, first commercially developed by Bristol-Myers-Squibb) was isolated[54] 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.



R = Ph, R' = Ac, Paclitaxel (Taxol) **6**
R = OtBu, R' = H, Taxotere (Docetaxel) **7**

Scheme 7: Marketed drugs containing oxetanes[53]

Both compounds act by interfering with normal microtubule breakdown during cell division.[55] 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[56] and acts as a hydrogen-bond acceptor partner for a threonine-OH in the putative binding pocket.[57] Replacement of the oxetane in taxol with azetidine,

[52] S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner, F. S. Han, *J. Med. Chem.* **1987**, *30*, 976. For a review about different transition-state mimics of Renin, see: W. J. Greenlee, *Med. Res. Rev.* **1990**, *10*, 173.
[53] Prous Science Integrity, Search on May 6 2008
[54] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. Mcphail, *J. Am. Chem. Soc.* **1971**, *93*, 2325.
[55] V. Farina, Editor, *The Chemistry and Pharmacology of Taxol and its Derivatives. [In: Pharmacochem. Libr., 1995: 22]*, **1995**.
[56] T. C. Boge, M. Hepperle, D. G. Vander Velde, C. W. Gunn, G. L. Grunewald, G. I. Georg, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3041.
[57] M. Wang, B. Cornett, J. Nettles, D. C. Liotta, J. P. Snyder, *J. Org. Chem.* **2000**, *65*, 1059.

thietane, and selenetane invariably resulted in lower activity.[58] 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[59] 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.[60] Thromboxane A_2 (**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 B_2.[61] Merrilactone A (**10**) was first isolated from *Illicium merrillianum.*[62] 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.[63]

Mitrephorone A (**12**) has been isolated from *Mitrephora glabra* and was found to be cytotoxic for a variety of cancer cell lines.[64] 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. [65]

[58] a) A. A. L. Gunatilaka, F. D. Ramdayal, M. H. Sarragiotto, D. G. I. Kingston, D. L. Sackett, E. Hamel, *J. Org. Chem.* **1999**, *64*, 2694. b) R. Marder-Karsenti, J. Dubois, L. Bricard, D. Guenard, F. Gueritte-Voegelein, *J. Org. Chem.* **1997**, *62*, 6631.

[59] N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, T. Takita, *J. Antibiot.* **1986**, *39*, 1623.

[60] For a review on its biological activity, see: a) H. Hoshino, N. Shimizu, N. Shimada, T. Takita, T. Takeuchi, *J. Antibiot.* **1987**, *40*, 1077. b) J. Seki, N. Shimada, K. Takahashi, T. Takita, T. Takeuchi, H. Hoshino, *Antimicrob. Agents Chemother.* **1989**, *33*, 773. Norbeck published in 1988 the first total synthesis of (-)-Oxetanocin A: D. W. Norbeck, J. B. Kramer, *J. Am. Chem. Soc.* **1988**, *110*, 7217.

[61] S. M. Roberts, F. Scheinmann, Editors, *New Synthetic Routes to Prostaglandins and Thromboxanes*, **1982**.

[62] J. M. Huang, R. Yokoyama, C. S. Yang, Y. Fukuyama, *Tetrahedron Lett.* **2000**, *41*, 6111.

[63] a) V. B. Birman, S. J. Danishefsky, *J. Am. Chem. Soc.* **2002**, *124*, 2080. b) G. Mehta, S. R. Singh, *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 953. c) S. J. Danishefsky, *Asymm. Synth.* **2007**, 251. d) M. Inoue, N. Lee, S. Kasuya, T. Sato, M. Hirama, M. Moriyama, Y. Fukuyama, *J. Org. Chem.* **2007**, *72*, 3065. e) W. He, J. Huang, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2008**, *130*, 300.

[64] C. Li, D. Lee, T. N. Graf, S. S. Phifer, Y. Nakanishi, J. P. Burgess, S. Riswan, F. M. Setyowati, A. M. Saribi, D. D. Soejarto, N. R. Farnsworth, J. O. Falkinham, D. J. Kroll, A. D. Kinghorn, M. C. Wani, N. H. Oberlies, *Org. Lett.* **2005**, *7*, 5709.

[65] S. Omura, M. Murata, N. Imamura, Y. Iwai, H. Tanaka, A. Furusaki, T. Matsumoto, *J. Antibiot.* **1984**, *37*, 1324.

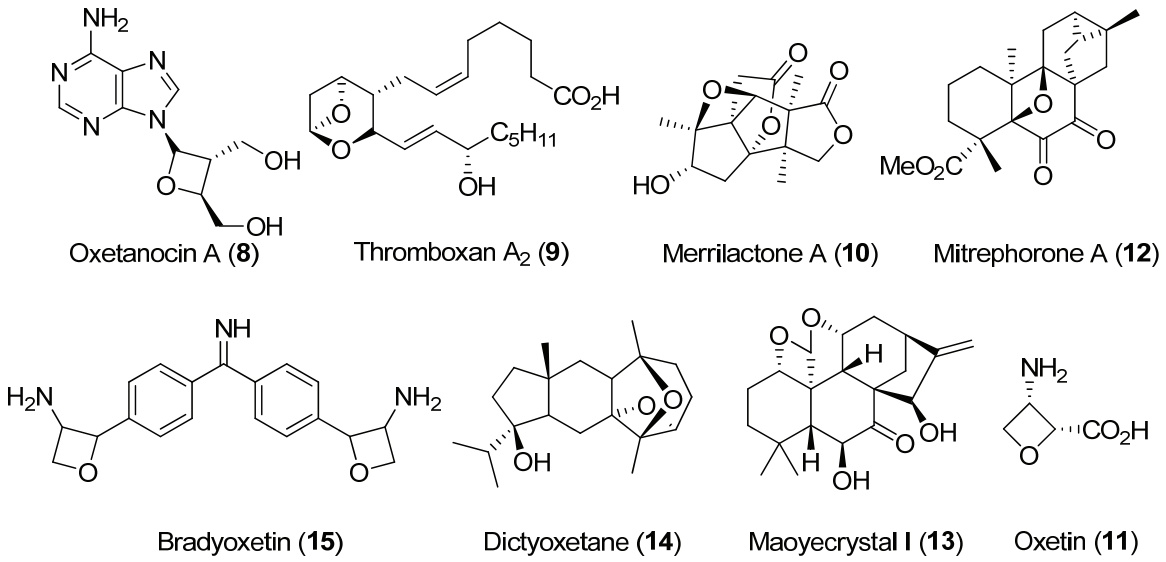


Figure 2: Natural products containing oxetanes

Maoyecrystal I (**13**) was isolated from *Isidon japonicus* and shows cytotoxic properties.[66] Dictyoxetane (**14**) is a diterpenoid first isolated from the brown algae *Dictyoata dichotoma*.[67] Its polycyclic ether core has triggered considerable synthetic interest.[68] Bradyoxetin (**15**) was found to be an important chemical signal for *Bradyrhizobium japonicum* involved in symbiotic gene regulation.[69]

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-**e**thoxyphenyl)-3,3-**d**imethyl**o**xetane) 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.[70]

[66] Q. B. Han, J. X. Zhang, Y. Lu, Y. S. Wu, Q. T. Zheng, H. D. Sun, *Planta Med.* **2004**, *70*, 581. A derivative in which the oxetane ring was cleaved methanolytically showed no cytotoxicity.
[67] K. C. Pullaiah, R. K. Surapaneni, C. B. Rao, K. F. Albizati, B. W. Sullivan, D. J. Faulkner, C. H. He, J. Clardy, *J. Org. Chem.* **1985**, *50*, 3665.
[68] a) J. Reinecke, H. M. R. Hoffmann, *Chem-Eur. J.* **1995**, *1*, 368. b) K. A. Marshall, A. K. Mapp, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 9135. c) J. Wittenberg, W. Beil, H. M. R. Hoffmann, *Tetrahedron Lett.* **1998**, *39*, 8259. d) S. Proemmel, R. Wartchow, H. M. R. Hoffmann, *Tetrahedron* **2002**, *58*, 6199.
[69] J. Loh, R. W. Carlson, W. S. York, G. Stacey, *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 14446.
[70] G. Holan, *Nature (London)* **1971**, *232*, 644.

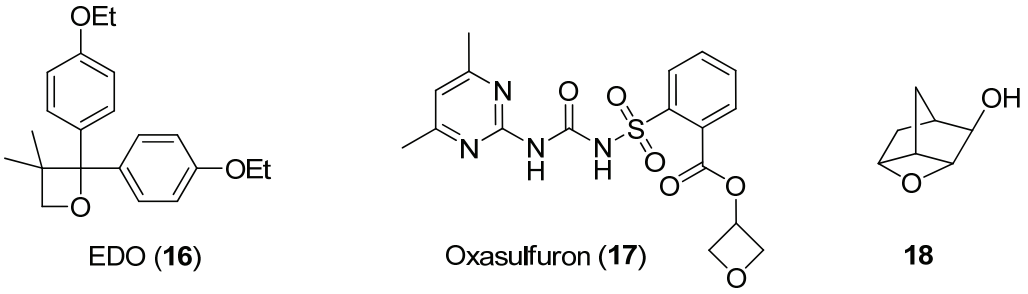


Figure 3: Oxetane-containing pesticides

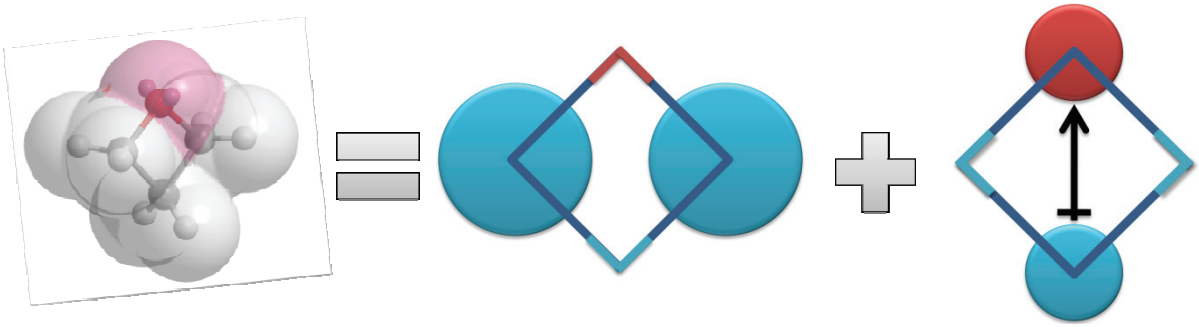
Oxasulfuron (**17**)[71] acts by inhibiting the biosynthesis of valine and isoleucine in cells. It is used, for example, in the cultivation of soybeans to keep weeds under control. This agrochemical is effective because crop rapidly metabolizes.[72] At the end of 2007 its production was stopped due to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

[71] W. Meyer, EP 92-810027, **1992**.
[72] M. K. Koeppe, H. M. Brown, *Agro Food Ind. Hi-Tech* **1995**, *6*, 9.
[73] personal communication, Syngenta AG, 2008
[74] S. B. Soloway, P. Vogel, C. H. Aubin le Drian, J. E. Powell, U.S. Patent 86-916334, **1986**.

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.[75] By that, *gem*-dimethyl groups are slightly more common than carboxylic esters.[76]

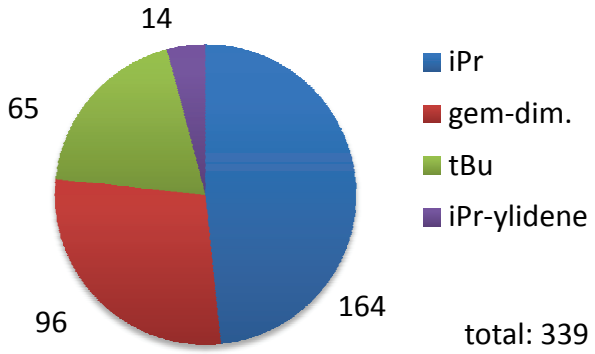


Diagram 3: Launched drugs containing different forms of gem-dimethyl groups.[77]

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.[78] For the formation of three- or four-[79] 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.[80] In larger rings, the contribution of this was found to be small,[81] here the effect predominantly stems from a change in the conformational distribution of the open-chain form:[82]

[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.
[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
[77] Prous Science Integrity®, May 16 2008: Substructure search for all compounds with the given motif which have „launched“ as development status.
[78] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **1915**, *107*, 1080.
[79] J. Jager, T. Graafland, H. Schenk, A. J. Kirby, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1984**, *106*, 139.
[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.).
[81] M. E. Jung, J. Gervay, *J. Am. Chem. Soc.* **1991**, *113*, 224.
[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)

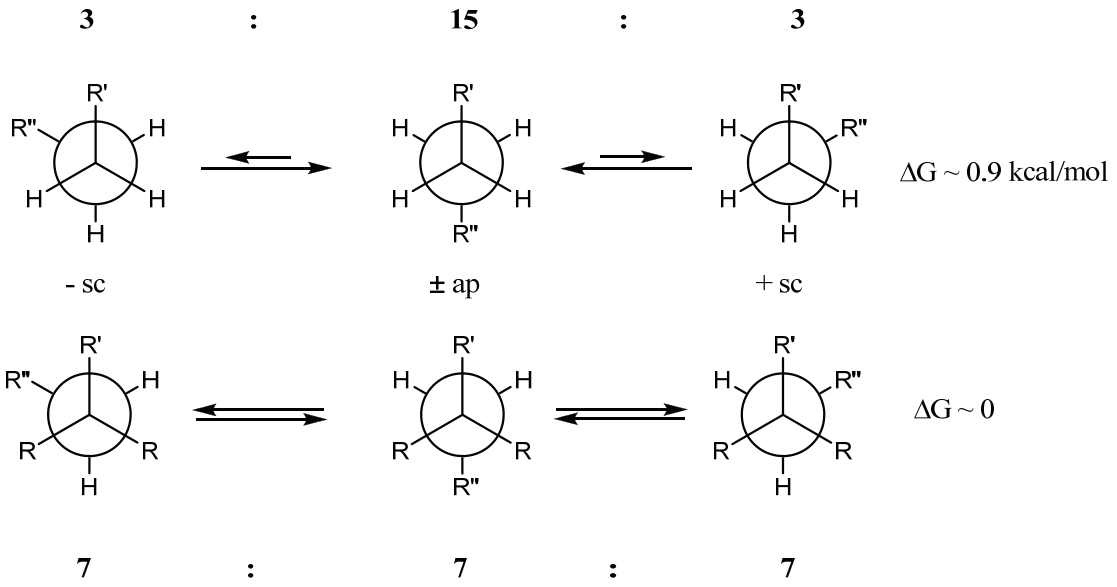


Figure 4: Effect of geminal substitution on the distribution between antiperiplanar (± ap) and synclinal (+sc, -sc) conformations.[83]

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[84] or metabolic[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.[86]

[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).

[84] a) Magnin *et al.* reported the protection of an α-(acylamino)-nitrile from hydrolysis by introduction of sterick bulk in the aminonitrile part. D. R. Magnin, J. A. Robl, R. B. Sulsky, D. J. Augeri, Y. T. Huang, L. M. Simpkins, P. C. Taunk, D. A. Betebenner, J. G. Robertson, B. E. Abboa-Offei, A. Y. Wang, M. Cap, L. Xin, L. Tao, D. F. Sitkoff, M. F. Malley, J. Z. Gougoutas, A. Khanna, Q. Huang, S. P. Han, R. A. Parker, L. G. Hamann, *J. Med. Chem.* **2004**, *47*, 2587. b) For an example, where an imidazoline is protected from hydrolyis by bulky substituents, see: M. von Rauch, M. Schlenk, R. Gust, *J. Med. Chem.* **2004**, *47*, 915.

[85] a) P. M. Manoury, J. L. Binet, J. Rousseau, F. M. Lefevreborg, I. G. Cavero, *J. Med. Chem.* **1987**, *30*, 1003. b) For an example, where steric bulk reduced susceptibility towards imide cleavage, see: A. D. Borthwick, D. E. Davies, P. F. Ertl, A. M. Exall, T. M. Haley, G. J. Hart, D. L. Jackson, N. R. Parry, A. Patikis, N. Trivedi, G. G. Weingarten, J. M. Woolven, *J. Med. Chem.* **2003**, *46*, 4428. c) Addition of steric bulk can help to reduce glucuronidation (phase II metabolism): P. Madsen, A. Ling, M. Plewe, C. K. Sams, L. B. Knudsen, U. G. Sidelmann, L. Ynddal, C. L. Brand, B. Andersen, D. Murphy, M. Teng, L. Truesdale, D. Kiel, J. May, A. Kuki, S. H. Shi, M. D. Johnson, K. A. Teston, J. Feng, J. Lakis, K. Anderes, V. Gregor, J. Lau, *J. Med. Chem.* **2002**, *45*, 5755.

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.[87] Moreover, the *gem*-dimethyl group can become a target of metabolic degradation itself.[88] A search in the MDL® Metabolite Database reveals how prevalent oxidative attack on *gem*-dimethyl groups is:[89]

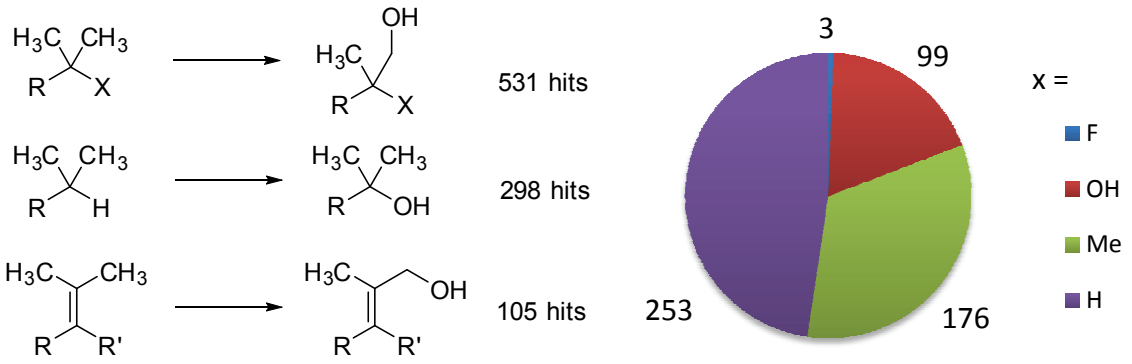


Diagram 4: Hydroxylation of gem-dimethyl containing compounds.[89]

All these applications of steric bulk currently rely on a pool of functionalities that – like the *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.[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 *gem*-dimethyl group. An oxetane might thus introduce steric bulk and at the same time reduce lipophilicity.

---

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

[87] For the proposed evolutionary origin of the preference of P450-class enzymes for lipophilic molecules, see: F. J. Gonzalez, D. W. Nebert, *Trends Genet.* **1990**, *6*, 182. For quantitative correlation of metabolic stability with lipophilicity, refer to: a) B. Testa, P. Crivori, M. Reist, P. A. Carrupt, *Perspect. Drug Discovery Des.* **2000**, *19*, 179. b) K. A. S. Algailany, J. B. Houston, J. W. Bridges, *Biochem. Pharmacol.* **1978**, *27*, 783. c) A. L. Upthagrove, W. L. Nelson, *Drug Metab. Dispos.* **2001**, *29*, 1377.

[88] R. B. Bambal, R. P. Hanzlik, *Arch. Biochem. Biophys.* **1996**, *334*, 59.

[89] MDL® Metabolite Database, July 2006: Substructure search for metabolic oxidation as shown in Diagram 4.

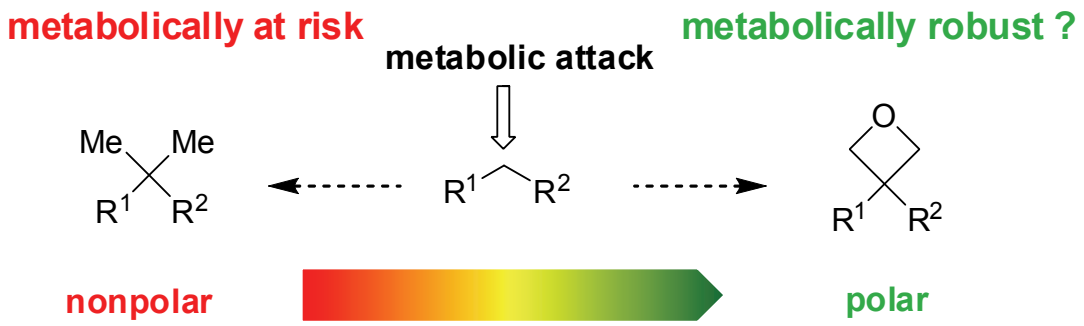
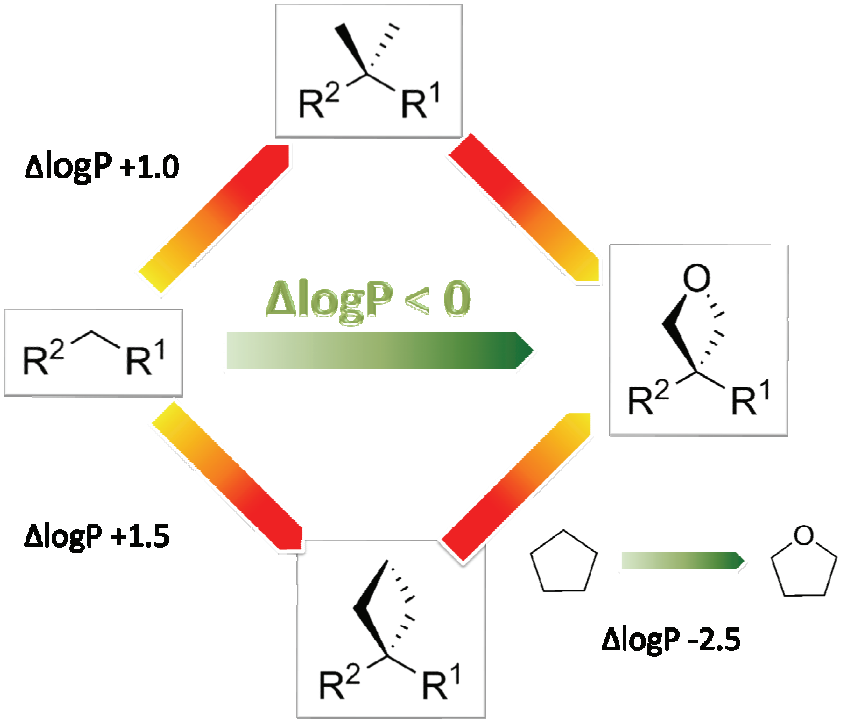


Figure 5: Oxetanes as a replacement for gem-dimethyl groups.

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^3mol^{-1}) in water is even smaller than that of propane (70.7 cm^3mol^{-1}).[90]



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

[90] a) J. C. Moore, R. Battino, T. R. Rettich, Y. P. Handa, E. Wilhelm, *J. Chem. Eng. Data* **1982**, *27*, 22. b) J. T. Edward, P. G. Farrell, F. Shahidi, *J. Chem. Soc. Lond. Faraday Trans. 1* **1977**, *73*, 705.

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.[91] 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[92] as well as their ability to stabilize α-carbanions[93] 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[94] 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.

[91] F. Wöhler, *Ann. Phys.* **1828**, *37*, 330.
[92] V. Grignard, *C. R. Hebd. Seances 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).

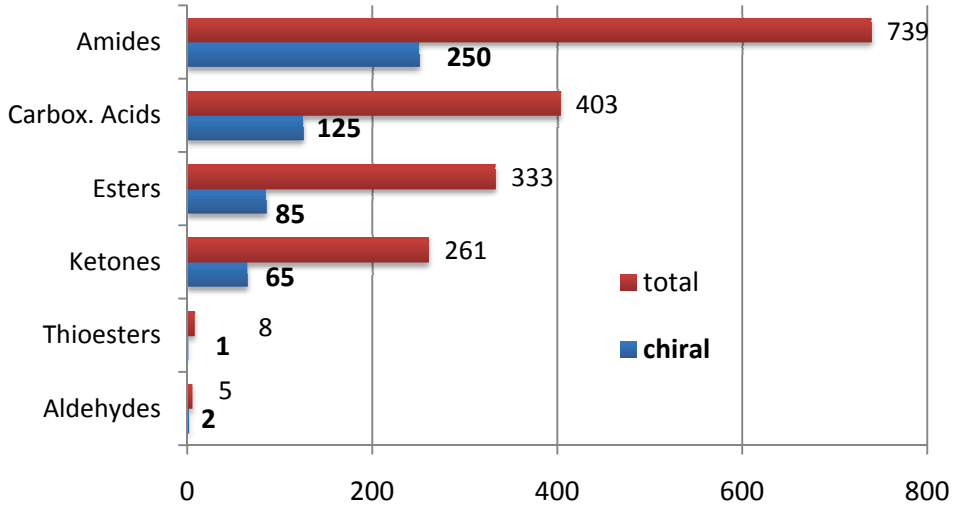
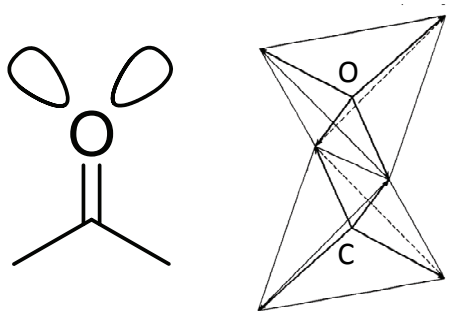


Diagram 5: Prevalence of carbonyl groups in marketed drugs.[95]

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 exposition 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).

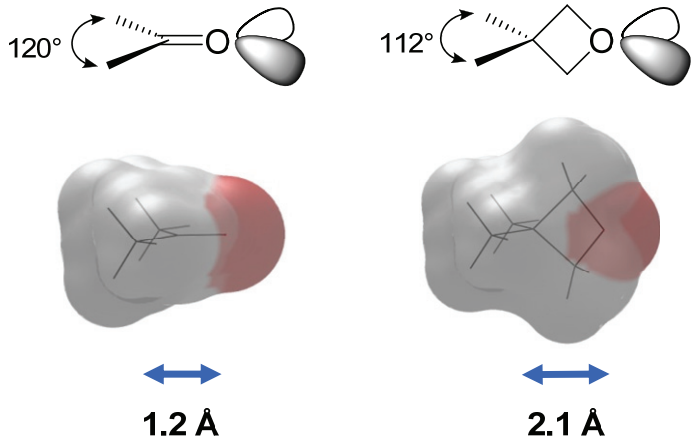
Van't Hoff provided a very influential rational for the stereochemistry of organic compounds by postulating a tetrahedral coordination sphere for carbon in all its compounds, also the ones containing multiple bonds.[96] The atom would be represented by a tetrahedron with its substituents attached to 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



Picture 4: Van't Hoff representation of a carbonyl group.[97]

While nowadays multiple bonds are rationalized differently,[98] better accounting for the spectroscopic characteristics of these molecules, van't Hoff's and Pauling's 'bent bond' model[99] 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.



Picture 5: Structural comparison of a carbonyl group with an oxetane. [100]

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

[97] Picture adapted from ref. 99a.
[98] E. Hückel, *Z. Physik*, **1930**, *60*, 423.
[99] a) L. Pauling, *J. Am. Chem. Soc.* **1931**, *53*, 1367. b) W. E. Palke, *J. Am. Chem. Soc.* **1986**, *108*, 6543. c) K. B. Wiberg, *Acc. Chem. Res.* **1996**, *29*, 229.
[100] 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.[101]

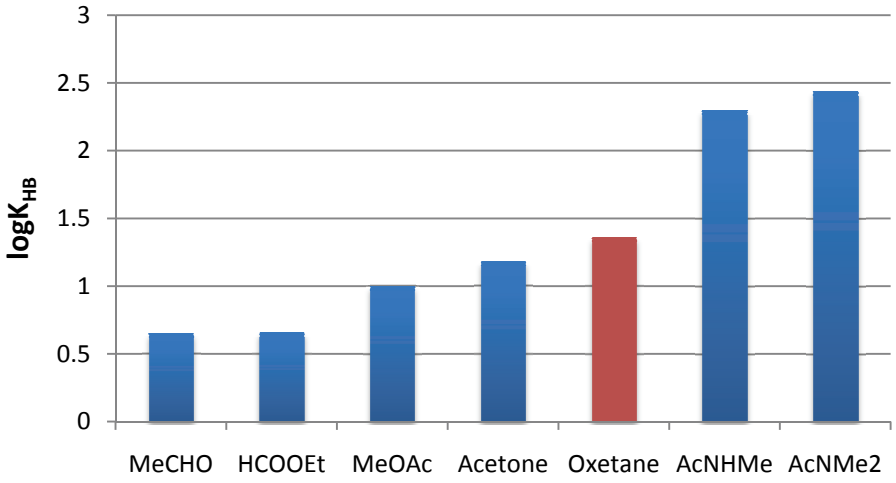


Diagram 6: Affinity to act as an acceptor for hydrogen bonds for oxetane and different carbonyl compounds.[102]

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.[103] The examples shown in Figure 6 highlight the different benefits an oxetane might have when replacing a carbonyl group. Acetyl choline (**19**)[104], cocaine (**20**)[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.

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[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 π-conjugation in the former and may result in substantially non-planar arrangements in the latter.

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

[103] For the H-bonding affinitiy of oxetanes, see: M. Berthelot, F. Besseau, C. Laurence, *Eur. J. Org. Chem.* **1998**, 925. For related studies with a variety of carbonyl compounds, see: a) F. Besseau, M. Lucon, C. Laurence, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1998**, 101. b) F. Besseau, C. Laurence, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1994**, 485. c) J. Y. Lequestel, C. Laurence, A. Lachkar, M. Helbert, M. Berthelot, *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091.

[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.

[105] Cocaine is mainly metabolized by hydrolysis of the methyl ester into benzoylecgonine which is then excreted via the urine.

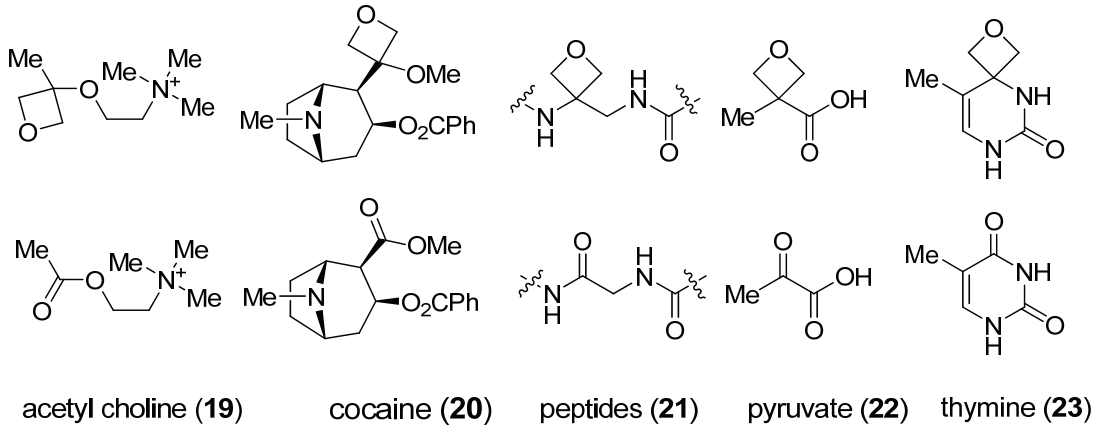


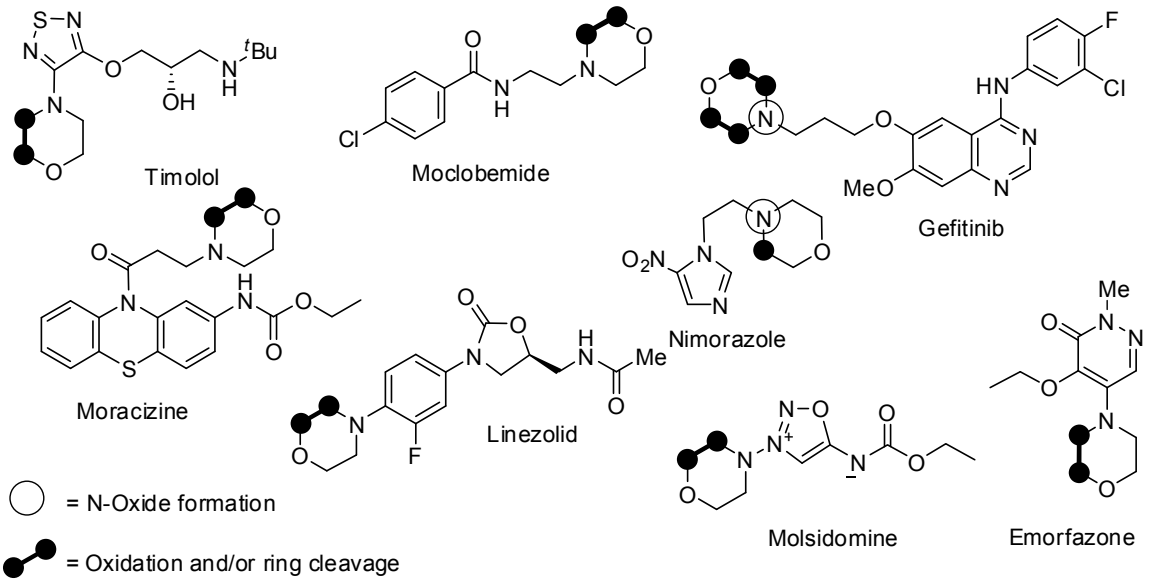
Figure 6: Possible applications for oxetanes as a carbonyl surrogate.

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 Spirocyclic 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]

[106] Prous Science Integrity®, May 21 2008: Substructure search for launched compounds containing a morpholine unit. a) D. McKillop, A. D. McCormick, G. S. Miles, P. J. Phillips, K. J. Pickup, N. Bushby, M. Hutchison, *Xenobiotica* **2004**, *34*, 983 b) S. K. Balani, S. M. Pitzenberger, M. S. Schwartz, H. G. Ramjit, W. J. Thompson, *Drug Metab. Dispos.* **1995**, *23*, 185. c) T. Hayashi, M. Aoyama, M. Fukuda, M. Ohki, T. Kishikawa, *Chem. Pharm. Bull.* **1979**, *27*, 317. d) P. N. Giraldi, G. P. Tosolini, E. Dradi, G. Nannini, R. Longo, G. Meinardi, G. Monti, I. D. Carneri, *Biochem. Pharmacol.* **1971**, *20*, 339. e) A. Betts, F. Atkinson, I. Gardner, D. Fox, R. Webster, K. Beaumont, P. Morgan, *Drug Metab. Dispos.* **2007**, *35*, 1435. f) R. Jauch, E. Griesser, G. Oesterhelt, W. Arnold, W. Meister, W. H. Ziegler, T. W. Guentert, *Acta Psychiatr. Scand, Suppl* **1990**, *360*, 87. g) R. T. Coutts, F. Jamali, F. Malek, A. Peliowski, N. N. Finer, *Xenobiotica* **1991**, *21*, 1407.



Scheme 8: Marketed drugs containing a morpholine liable to metabolic oxidation.[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.

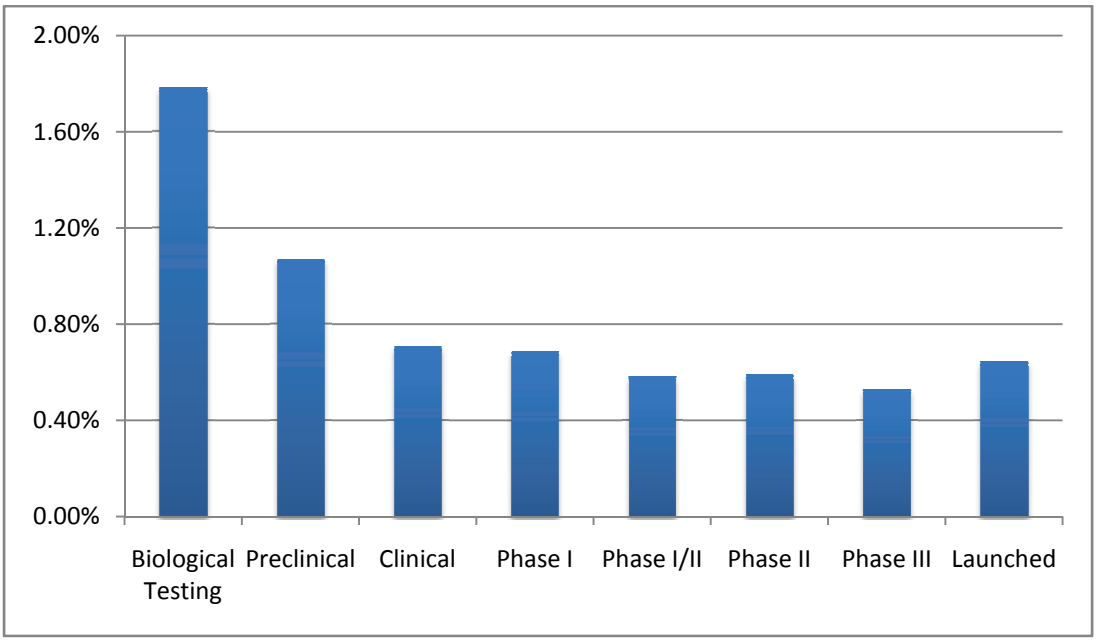
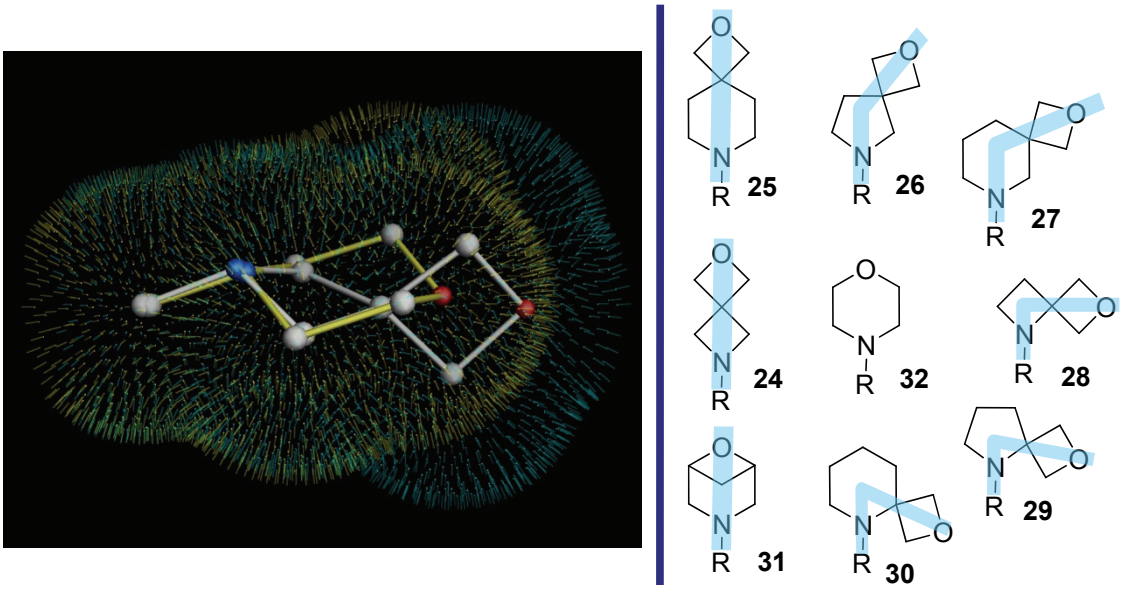


Diagram 7: Ratio of drug candidates containing a morpholine in the substructure and all compounds.[107]

[107] Prous Science Integrity®, 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.[108]

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

[108] Overlay of substituted a 2-oxa-6-azaspiro[3.3]heptane and a morpholine on the left done by Prof. Klaus Müller with Moloc (P. R. Gerber, K. Müller, *J. Comp-Aided. Mol. Design* **1995**, *9*, 251; for further information, see *www.moloc.ch).*

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, *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 engrafted 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

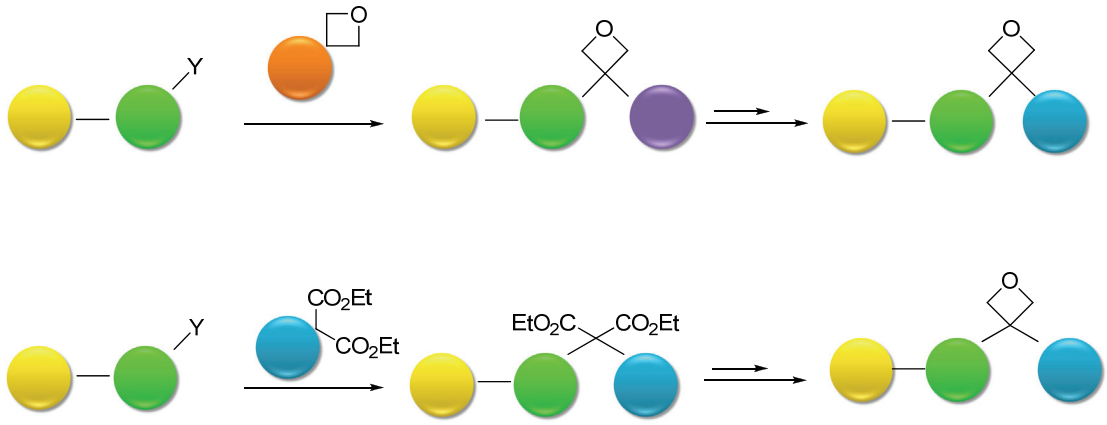
[109] a) J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 157. b) R. K. Khazipov, N. L. Izbitskaya, T. K. Kiladze, O. B. Chalova, E. S. Kurmaeva, E. A. Kantor, *Izv. Vyssh. Uchebn. Zaved., Neft Gaz* **1984**, *27*, 86. c) F. S. Zarudii, D. N. Lazareva, E. S. Kurmaeva, O. B. Chalova, T. K. Kiladze, E. A. Kantor, D. L. Rakhmankulov, *Pharm. Chem. J. (Engl. Transl.)* **1985**, *19*, 108. d) C. G. Krespan, *J. Org. Chem.* **1975**, *40*, 1205.

[110] a) J. L. Castro Pineiro, K. Dinnell, J. M. Elliott, G. J. Hollingworth, D. E. Shaw, C. J. Swain, (Merck Sharp & Dohme Limited, UK). WO2001087838, **2001**, p. 199 pp; b) N. Watanabe, N. Karibe, K. Miyazaki, F. Ozaki, A. Kamada, S. Miyazawa, Y. Naoe, T. Kaneko, I. Tsukada, T. Nagakura, H. Ishihara, K. Kodama, H. Adachi, (Eisai Co., Ltd., Japan). WO 9942452, **1999**, p. 148 pp.

[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.

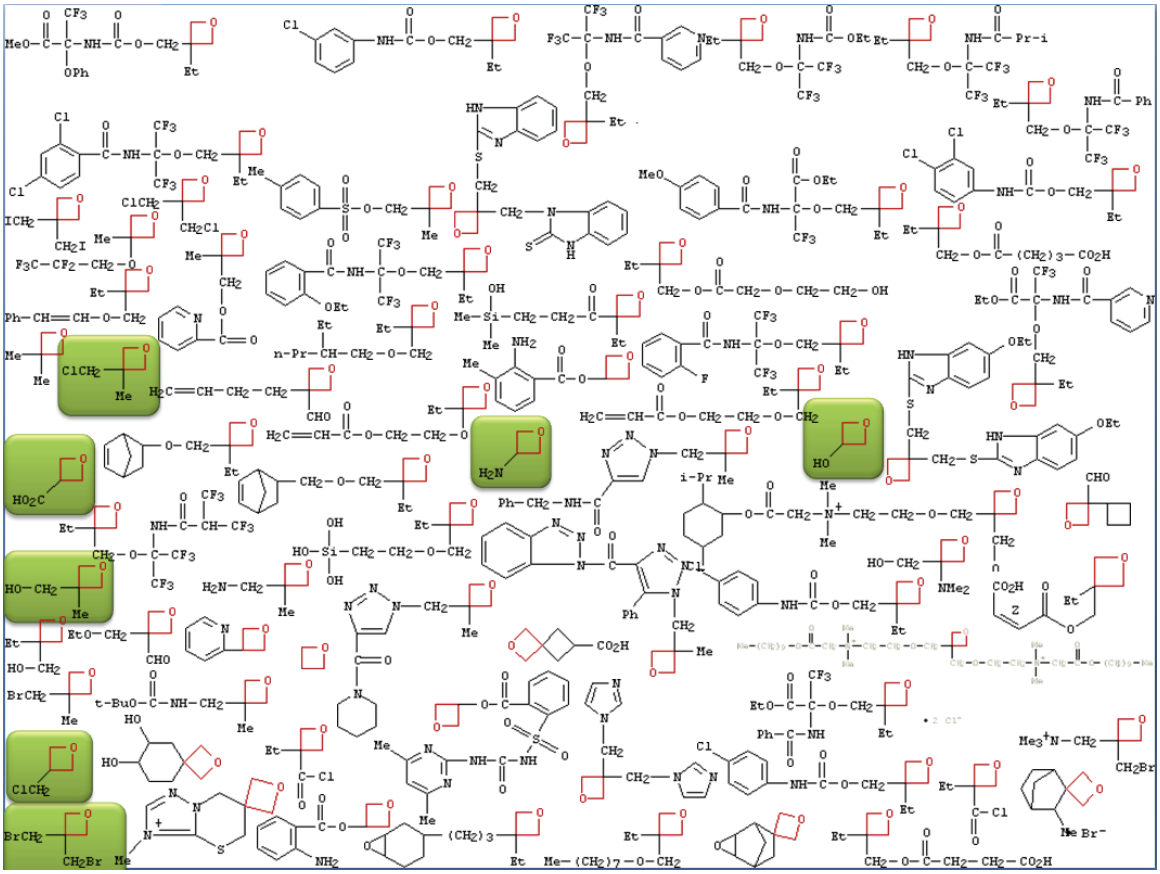
If the precursor already contains an oxetane, the problem of ring closure might be solved for the particular case, or deferrable to a commercial supplier. A small set of oxetanes would then be used as building blocks that, once attached to a scaffold, would be amenable to synthetic modification.



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.

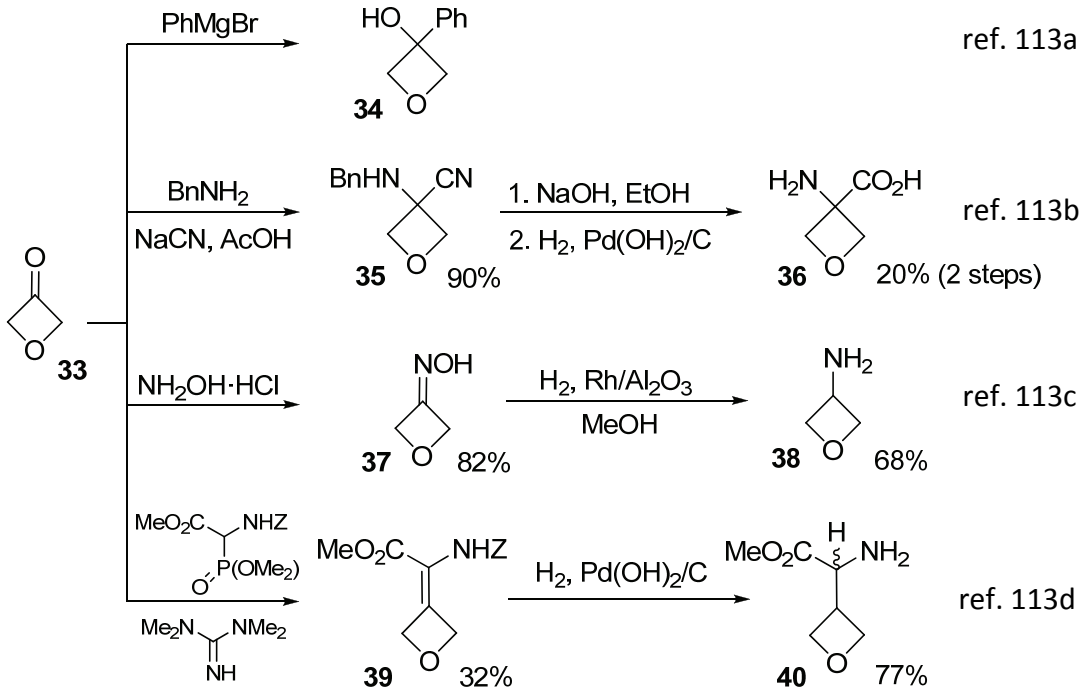
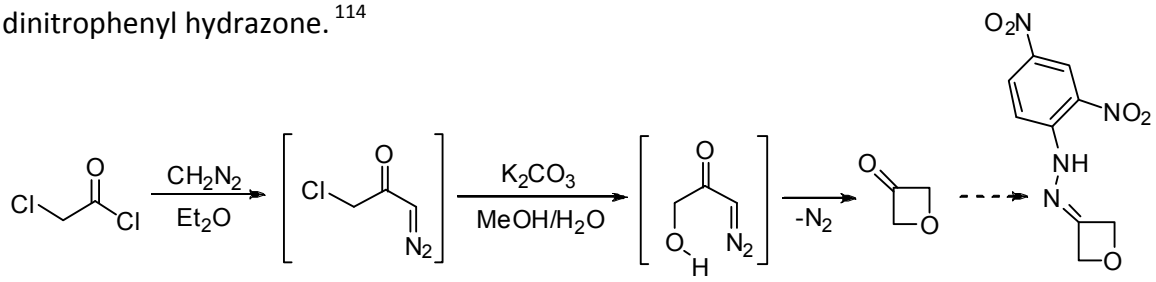


Figure 7: Reactions of oxetane-3-one in the literature.[113]

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.[114]

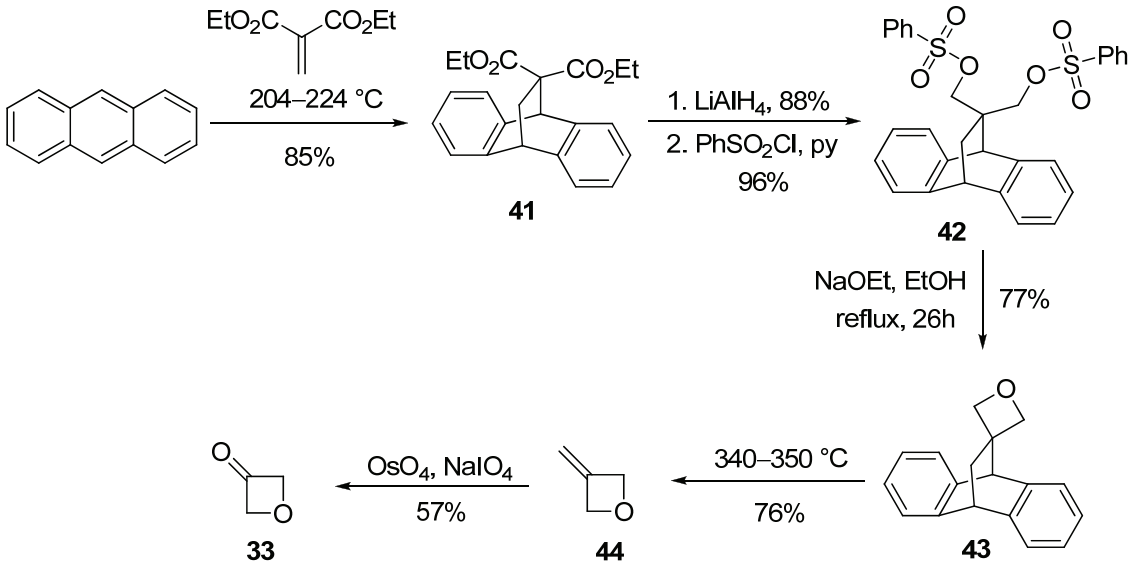


Equation 2: Preparation of oxetan-3-one from chloroacetyl chloride.[114]

[113] a) P. Yates, A. G. Szabo, *Tetrahedron Lett.* **1965**, *6*, 485. b) A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783. c) G. H. Berezin, US 3449369, **1969**. d) M. D. T. Moldes, G. Costantino, M. Marinozzi, R. Pellicciari, *Farmaco* **2001**, *56*, 609. For a review about the preparation of oxetan-3-ones and their chemistry, see: Y. Dejaegher, N. M. Kuz'menok, A. M. Zvonok, N. De Kimpe, *Chem. Rev.* **2002**, *102*, 29.

[114] J. R. Marshall, J. Walker, *J. Chem. Soc.* **1952**, 467.

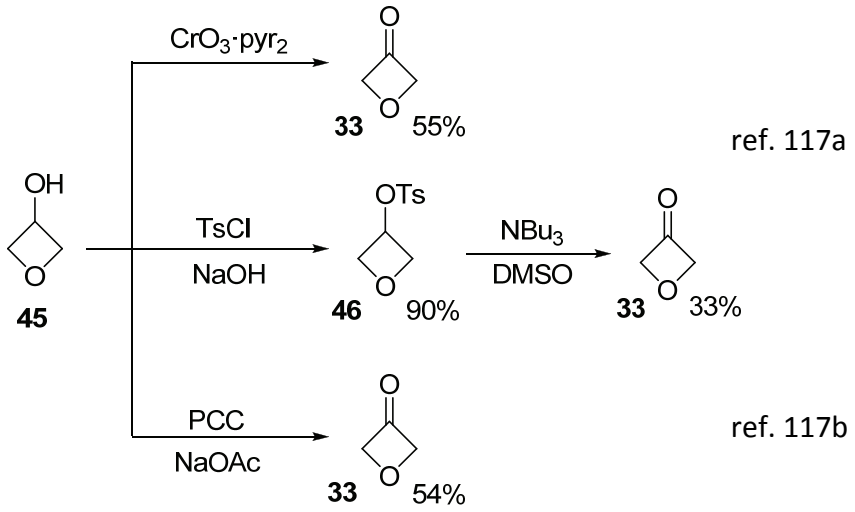
The first synthesis of oxetan-3-one in pure form and significant quantities was reported in a patent from DuPont, wherein oxetan-3-one was investigated as a potential solvent for cyanoethyl cellulose.[115]



Scheme 11: DuPont route to oxetan-3-one.[115]

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.[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:

[115] G. H. Berezin, US 3297719, **1967**.
[116] D. E. Applequist, J. D. Roberts, *J. Am. Chem. Soc.* **1956**, *78*, 4012.

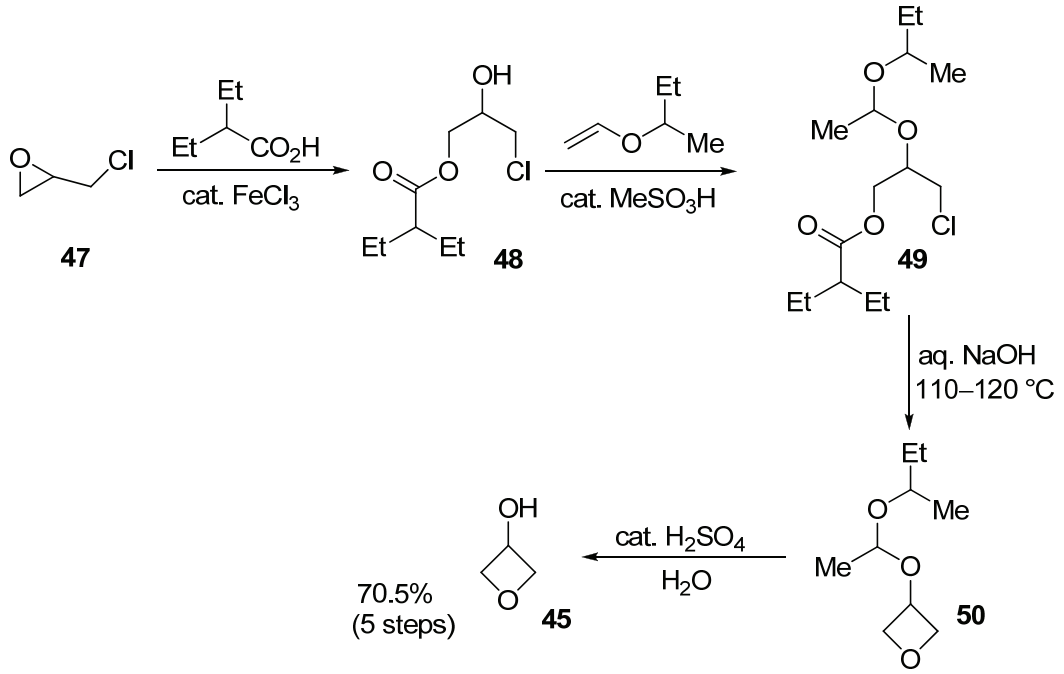


*Scheme 12: Oxidation of oxetan-3-ol (**45**).*[117]

Whereas the oxidation of oxetan-3-ol (**45**) with Collins reagent ($CrO_3 \cdot py_2$) 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.[117a] Oxidation with pyridinium chlorochromate (PCC) also furnishes oxetan-3-one (**33**).[118]

At the outset of the project, oxetan-3-ol was not available commercially in significant quantities.[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.*[120] laid the foundation for the optimized route used by Syngenta[121] to prepare oxetan-3-ol as part of the synthesis of the herbicide Oxasulfuron (see Chapter 1.5).

[117] a) J. A. Wojtowicz, R. J. Polak, *J. Org. Chem.* **1973**, *38*, 2061. b) A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783.
[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.
[119] Indicated through search for commercially available chemicals in Scifinder® Scholar. Oxetan-3-ol is now commercially available from a variety of suppliers.
[120] K. Baum, P. T. Berkowitz, V. Grakauskas, T. G. Archibald, *J. Org. Chem.* **1983**, *48*, 2953.
[121] W. Stutz, R. Waditschatka, K. Winter, M. Von Frieling, R. Gressly, B. Jau, S. Buerki, EP 751136, **1997**.



*Scheme 13: Preparation of oxetan-3-ol (**45**) on industrial scale.*[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):

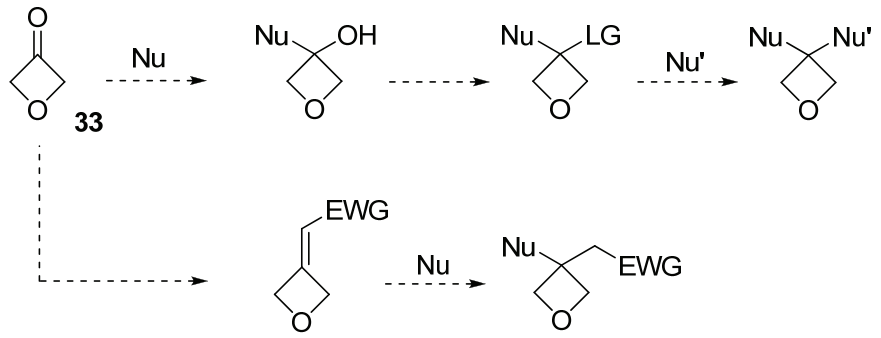


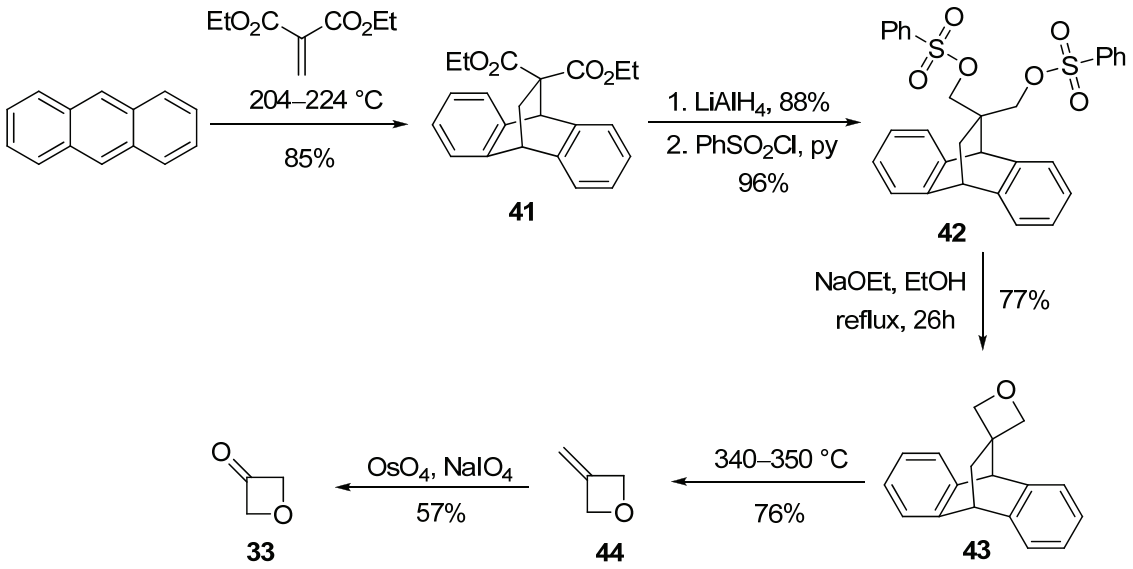
Figure 8: Proposed buildup of oxetanes starting from oxetan-3-one

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.

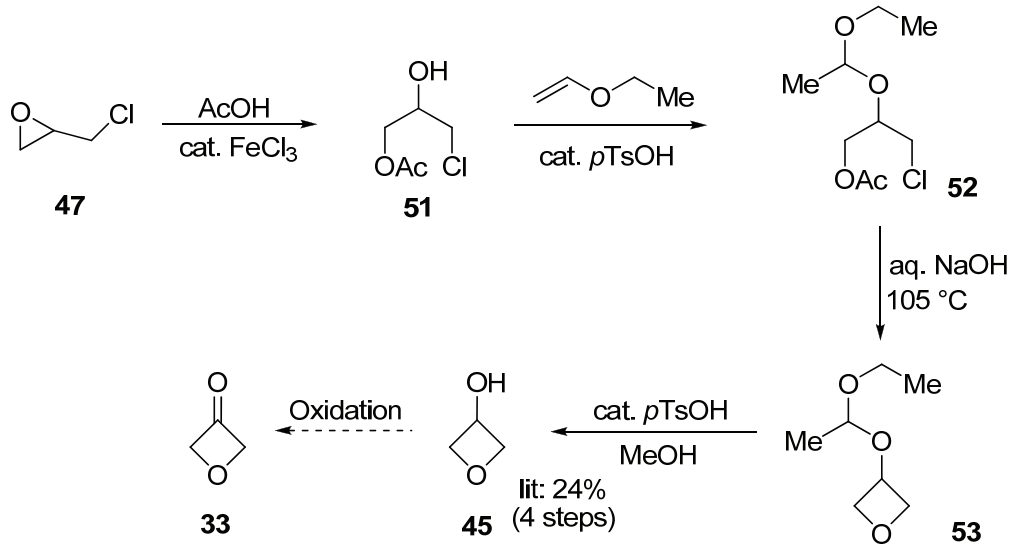
3.1 Preparation of Oxetan-3-one

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[115] involved 6 steps, included 3-methyleneoxetane as an unstable intermediate[116] and a retro-Diels-Alder reaction that seemed difficult to accomplish with standard laboratory equipment.



Scheme 14: Preparation of oxetan-3-one by DuPont.[115]

Further attempts to prepare oxetan-3-ol (**45**) as described by Baum *et al.*[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.



Scheme 15: Preparation of oxetan-3-ol from epichlorohydrine.[120]

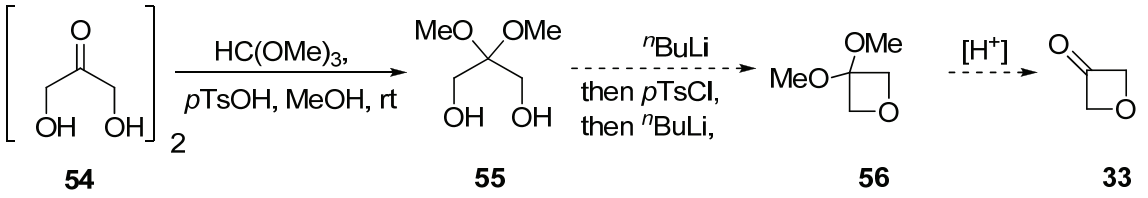
The oxidation of oxetan-3-ol was known to fail with various methods other than Cr(VI)-based reagents, and the procedure with Collins reagent[122] necessitates separation of the

[122] J. C. Collins, W. W. Hess, *Org. Synth.* **1988**, *50-9*, 644.

product from co-distilling pyridine by preparative GC.[123] 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.[124] 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[125] dihydroxyacetone dimethylketal (**55**), a one-pot ring closure,[126] precedent for the preparation of 3,3-disubstituted oxetanes, would lead to 3,3-dimethoxyoxetane (**56**). This would yield oxetan-3-one upon deprotection.



54 **55** **56** **33**

*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%.[127] Literature precedence existed for the cleavage of steroidal ketal **57** to give the corresponding oxetan-3-one **58** with dilute sulfuric acid.[128]

[123] Other methods unsuccessfully tried include: Oppenauer oxidation, permanganate and dichromate (J. A. Wojtowicz, R. J. Polak, *J. Org. Chem.* **1973**, *38*, 2061.).

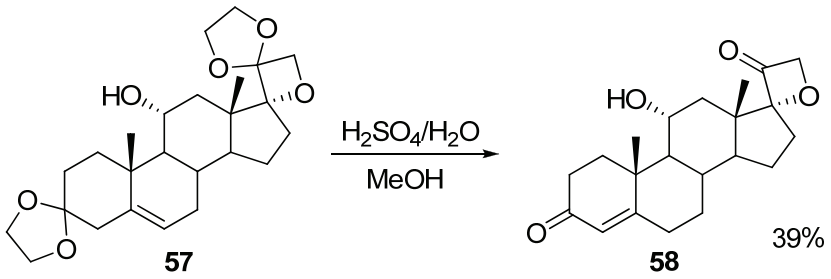
[124] It was expected that due to the hydrophilicity and volatility (b_p 106 °C, ref. 123) of oxetan-3-one, only low-boiling solvents and non-aqueous workup were permissible. Distillation would then be used for purification.

[125] a) E. L. Ferroni, V. DiTella, N. Ghanayem, R. Jeske, C. Jodlowski, M. O'Connell, J. Styrsky, R. Svoboda, A. Venkataraman, B. M. Winkler, *J. Org. Chem.* **1999**, *64*, 4943. b) F. Charmantray, L. El Blidi, T. Gefflaut, L. Hecquet, J. Bolte, M. Lemaire, *J. Org. Chem.* **2004**, *69*, 9310.

[126] P. Picard, D. Leclercq, J. P. Bats, J. Moulines, *Synthesis-Stuttgart* **1981**, 550.

[127] The closest example reported, a 3,3-dialkyl oxetane was prepared in 72% yield (ref. 126).

[128] W. S. Allen, S. Bernstein, M. Heller, R. Littell, *J. Am. Chem. Soc.* **1955**, *77*, 4784.



*Equation 3: Proposed cleavage of dioxolane **57** to give oxetan-3-one **58**.*[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.[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,[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.*[126]

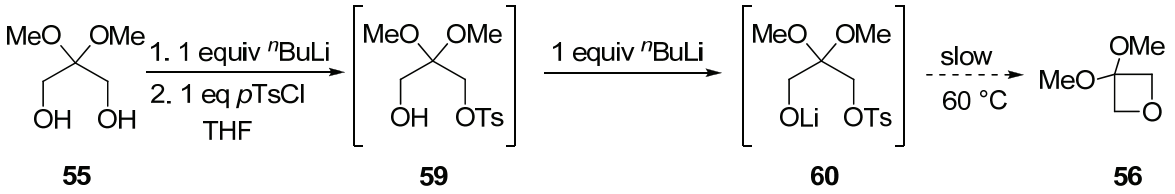


*Figure 9: Slow ring closure of γ-tosylatolithioxide **60**.*

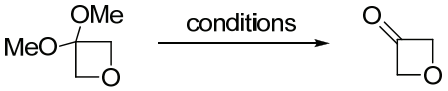
After heating at 60 °C for 4 h, the reaction yielded product **56** and monotosylate **59** in a ratio of 1/1 upon workup. We reasoned that cyclization of the corresponding sodium alkoxide would be faster. If however only the second portion of ^{n}BuLi is replaced with sodium hydride, the reaction does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

[129] a) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, J. M. Chemerda, *J. Am. Chem. Soc.* **1956**, *78*, 4812. b) J. E. Herz, J. Fried, P. Grabowich, E. F. Sabo, *J. Am. Chem. Soc.* **1956**, *78*, 4812.

[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.[131] Therefore ^{n}BuLi 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.[132] 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:[133]

Table 1: Screening of conditions for ketal cleavage.



56 **33**

Entry	Conditions	Result
1[134]	aq. H_2SO_4, CH_2Cl_2, 0 °C	no reaction
2	aq. H_2SO_4, acetone, rt	no reaction
3	aq. H_2SO_4, THF, rt	no reaction
4[128]	aq. H_2SO_4, MeOH, reflux	no reaction
5	aq. H_2SO_4, acetone, reflux	traces of product
6	aq. H_2SO_4, THF, rt	no reaction
7	2.5 equiv *p*TSA·H_2O, 25 equiv glyoxalic acid·H_2O, CH_2Cl_2, rt	7% conversion
7[135]	Amberlyst 15, acetone/H_2O, rt	no reaction
8[136]	15% H_2SO_4 on SiO_2, CH_2Cl_2, rt	no reaction
9[137]	Montmorillon–ite K10, CH_2Cl_2, rt	7% conversion
10	Montmorillonite K10, CH_2Cl_2, reflux, 26 h, 0.08 M	12% conversion
11[137]	Montmorillonite K10, CH_2Cl_2, reflux, 26 h, 0.03 M	44% conversion

[131] If ^{n}BuLi 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 sp^2-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).
[134] R. Breslow, J. Pecoraro, T. Sugimoto, *Org. Synth.* **1988**, *50-9*, 361.
[135] G. M. Coppola, *Synthesis* **1984**, 1021.
[136] F. Huet, A. Lechevallier, M. Pellet, J. M. Conia, *Synthesis-Stuttgart* **1978**, 63.
[137] E. C. L. Gautier, A. E. Graham, A. McKillop, S. P. Standen, R. J. K. Taylor, *Tetrahedron Lett.* **1997**, *38*, 1881.

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 (b_p 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]

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[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.

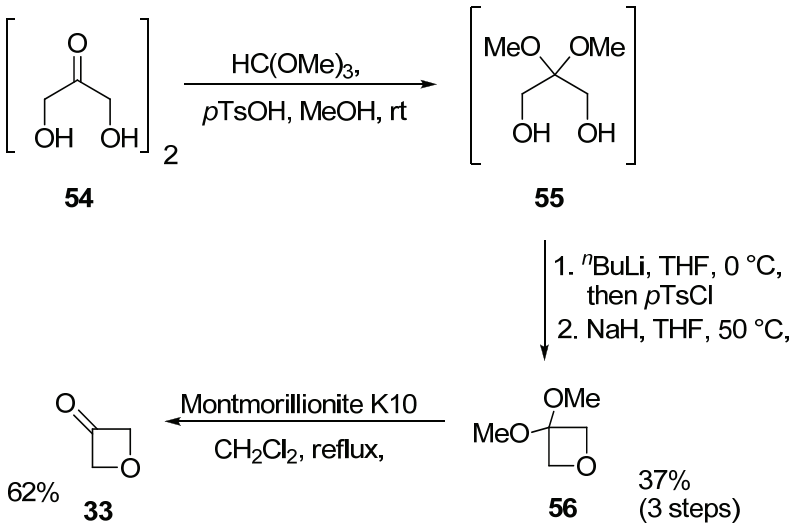
[139] Increasing the amount of Montmorillonite K10 from 0.3 g/mmol to 1.5 g/mmol substrate did not bring significant improvement of conversion (59% instead of 50 – 57%).

[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.

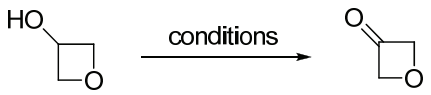
Syngenta chemists unsuccessfully tried Dess–Martin[145] and Swern[146] oxidations beforehand, facing problems in the isolation of oxetan-3-one. Its polar nature and volatility contribute significantly to the criteria a good oxidation procedure leading to oxetan-3-one should fulfill:

[144] G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem., Int. Ed.* **2006**, *45*, 7736.
[145] For a review, see: T. Wirth, U. H. Hirt, *Synthesis-Stuttgart* **1999**, 1271.
[146] For a review, see: T. T. Tidwell, *Synthesis-Stuttgart* **1990**, 857.

- 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[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.



45 **33**

Entry	Conditions	Yield (NMR)	Comment
1[148]	CrO_3/Et_2O, 0 °C to rt[a]	n.d. [b]	no completion, sluggish
2[149]	CrO_3, TBAC, KCl [a]	n.d. [b]	slow, sluggish
3[149]	CrO_3, TBAC, NaOAc [a]	n.d. [b]	no completion, slow
4[150]	PCC, 4 Å-MS, rt [a]	n.d. [b]	fast (15 min), clean, difficult purification
5[150]	PCC, n-Al_2O_3 [a]	n.d. [b]	slow
6[150]	PCC, Celite [a]	n.d. [b]	slow
7[151]	TPAP, NMO (1.5 equiv) [a]	47% [c]	fast (5 min), side reactions
8[152]	TPAP, O_2 [a]	~34% (10 h) [c]	slow, catalyst dies
9[153]	TEMPO, H_5IO_6 [a]	0% [c]	decomposition
10[154]	TEMPO, Oxone, TBAB [a]	0% [c]	no reaction
11[155]	IBX, EtOAc, reflux	89% (3 d) [c]	slow, high-boiling solvent
12[155]	IBX, rt [a]	34% (3 d) [c]	very slow
13[155]	IBX, reflux [a]	85%, (64 h) [c]	very slow
14[155]	IBX, acetone, reflux	83% (3 d) [c]	slow
15[156]	DMSO, P_4O_{10}, NEt_3, –5 °C [a]	63% (45 min) [c]	fast, cheap

[a] CH_2Cl_2 used as solvent. [b] broad signals in the NMR, probably due to the presence of Cr-species. [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.

[147] For an excellent book on oxidations of alcohols to ketones and aldehydes, see: G. Tojo, M. Fernández, *Oxidation of Alcohols to Aldehydes and Ketones*, Springer US, **2006**.
[148] S. J. Flatt, G. W. J. Fleet, B. J. Taylor, *Synthesis-Stuttgart* **1979**, 815.
[149] G. Gelbard, T. Brunelet, C. Jouitteau, *Tetrahedron Lett.* **1980**, *21*, 4653.
[150] J. Herscovici, M. J. Egron, K. Antonakis, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1967.
[151] For a review, see: S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis-Stuttgart* **1994**, 639.
[152] R. Lenz, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291.
[153] S. S. Kim, K. Nehru, *Synlett* **2002**, 616.
[154] C. Bolm, A. S. Magnus, J. P. Hildebrand, *Org. Lett.* **2000**, *2*, 1173.
[155] J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001.
[156] D. F. Taber, J. C. Amedio, K. Y. Jung, *J. Org. Chem.* **1987**, *52*, 5621.

Chromium-based reagents were investigated first as they are closest to the literature precedence (Table 2, entries 1–6).[157] Whereas chromium(VI)oxide in different variations led to slow reactions and the formation of byproducts, pyridinium chlorochromate[158] when combined with 4 Å molecular sieves as a catalyst[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.[159]

In the case of the Ley oxidation,[151] use of *N*-methyl morpholine *N*-oxide (NMO) as a stoichiometric cooxidant resulted in a rapid reaction, but the yield was low as judged from the crude NMR. Furthermore, *N*-methyl morpholine (b_p 115 °C), produced in stoichiometric amounts as a byproduct would probably be difficult to separate from the product (b_p 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.[160] The sensitivity of IBX towards detonation on impact or heat greatly depends on its purity.[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.[162]

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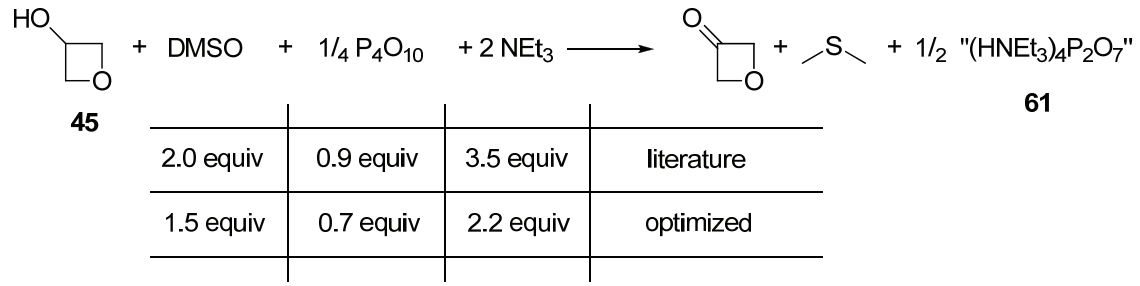
[157] a) Oxidation with PCC: A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783. b) Oxidation with Collins reagent ($CrO_3 \cdot 2\ C_5H_5N$): J. A. Wojtowicz, R. J. Polak, *J. Org. Chem.* **1973**, *38*, 2061.
[158] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, 2647.
[159] For an excellent overview, see: D. Michaels, C. Monforton, P. Lurie, *Environ. Health* **2006**, *5*, 5.
[160] J. B. Plumb, D. J. Harper, *Chem. Eng. News* **1990**, *68*, 3.
[161] a) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277. b) Boeckman Jr., R. K.; Shao, P.; Mullins, J. J.; *Org. Synth.* **2000**, *77*, 141.
[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,[147] a DMSO-based method caught our attention that could potentially fulfill all the conditions previously highlighted. A variety of dehydrating agents[163] can be used to activate DMSO, the most well known probably being dicyclohexylcarbodiimide (DCC)[164] in the Pfitzner–Moffatt oxidation and oxalyl chloride[165] in the Swern modification of the Pfitzner–Moffat oxidation. Much less used in that respect is phosphorous pentoxide, first proposed by Onodera *et al.*[166] (later modification by Taber *et al*.[167]). 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.[168] 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.

[163] For an overview, see: G. Tojo, M. Fernández, in *Oxidation of Alcohols to Aldehydes and Ketones*, Springer US, **2006**, pp. 97.
[164] K. E. Pfitzner, J. G. Moffatt, *J. Am. Chem. Soc.* **1963**, *85*, 3028.
[165] Often also referred to as the Swern oxidation (K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.).
[166] a) K. Onodera, S. Hirano, N. Kashimur, *J. Am. Chem. Soc.* **1965**, *87*, 4651. b) K. Onodera, S. Hirano, N. Kashimur, T. Yajima, *Tetrahedron Lett.* **1965**, 4327.
[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.



2.0 equiv	0.9 equiv	3.5 equiv	literature
1.5 equiv	0.7 equiv	2.2 equiv	optimized

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.[169] 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.[170] 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.[171]

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,[172] which should facilitate its use in drug discovery and spur the exploration of its chemistry.

[169] 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_4O_{10} can support the reaction.

[170] Normal aqueous workup under acidic conditions was reported in ref. 167.

[171] 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.

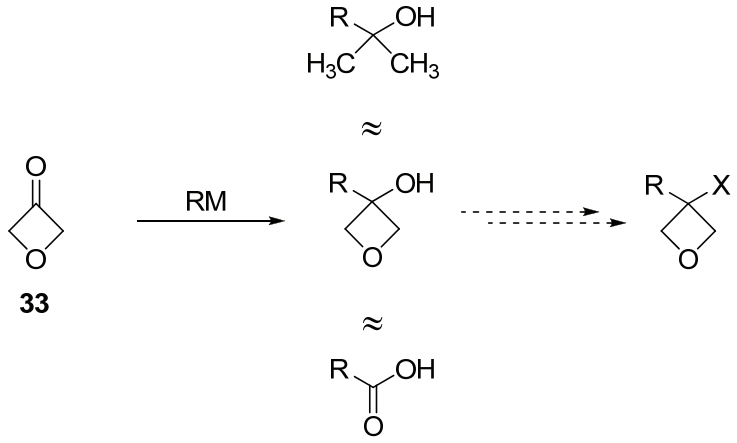
[172] At the start of the project, oxetan-3-one was not commercially available (Scifinder Scholar). It was first introduced to the market by Molbridge in February 2007. Since then Chemgenx, Parkway Scientific and Research Support International also started offering oxetan-3-one commercially.

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.

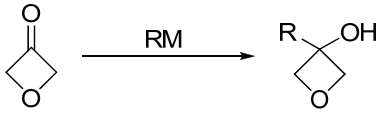


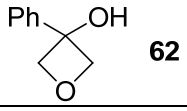
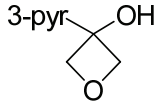
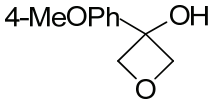
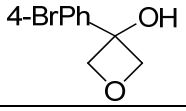
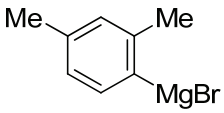
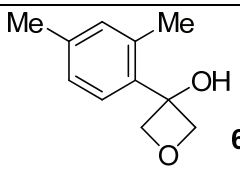
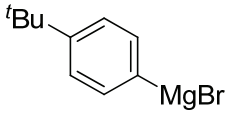
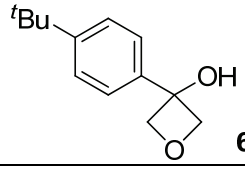
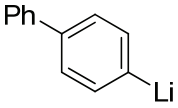
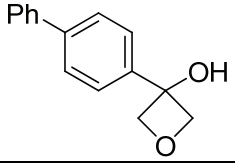
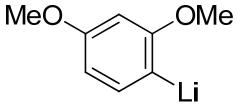
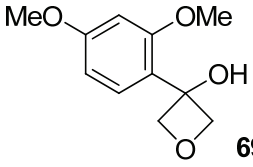
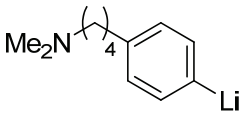
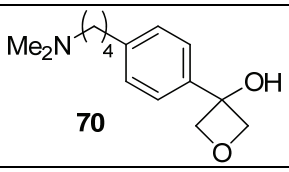
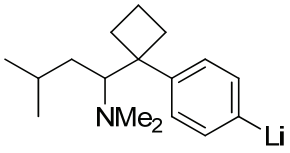
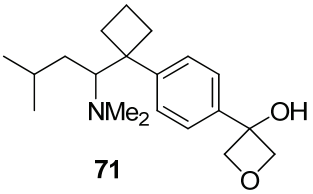
Scheme 18: Oxetan-3-ols, structural analogues and starting points for further derivatization.

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.

[173] G. H. Berezin, US 3449369, **1969**. In this patent the hydrogenation of oxetan-3-one oxime to 3-amino oxetane is reported.
[174] P. Yates, A. G. Szabo, *Tetrahedron Lett.* **1965**, *6*, 485.
[175] K. A. Marshall, A. K. Mapp, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 9135.
[176] A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783.

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



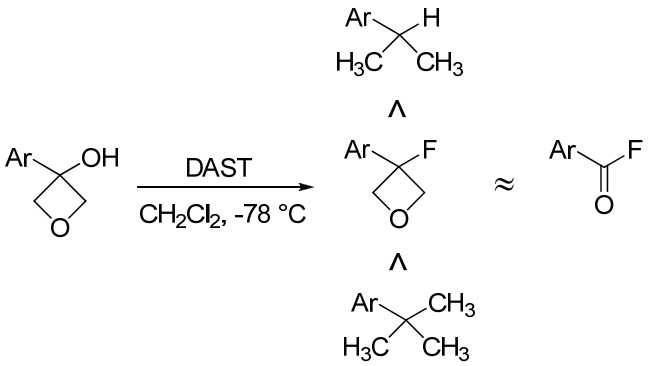
Entry	RM	Product	Yield
1	PhLi	 **62**	87%
2[177]	3-pyrMgCl·LiCl	 **63**	83%
3	4-MeOPhMgBr	 **64**	77%
4	4-BrPhMgBr	 **65**	79%
5		 **66**	quant.
6		 **67**	80%
7		 **68**	68%
8		 **69**	80%
9		 **70**	71%
10		 **71**	73%

[177] Grignard reagent prepared via magnesium–halogen exchange (A. Krasovskiy, P. Knochel, *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.).

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]



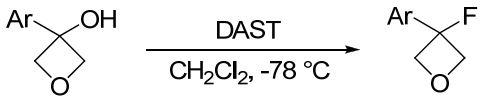
Scheme 19: Significance of 3-fluorooxetanes and their preparation of oxetan-3-ols by treatment with DAST.

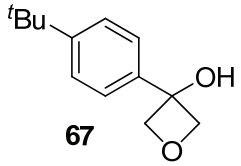
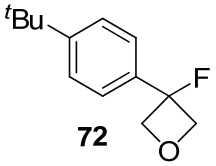
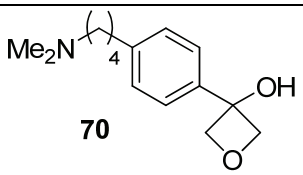
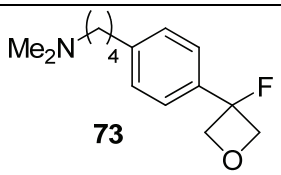
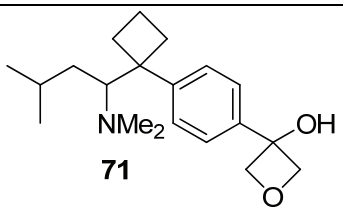
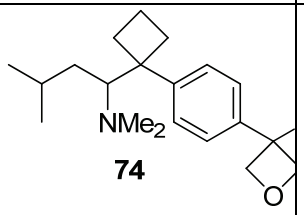
Diethylaminosulfur trifluoride (DAST) and *bis*(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) are standard reagents for the conversion of alcohols, ketones and carboxylic acids into their fluorinated counterparts.[179] Although substitution reactions at the 3-position of the oxetane were expected 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 ΔV 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 ΔV.

[179] For examples of the conversion of tertiary alcohols into the respective fluorides with DAST, see: a) D. Guijarro, P. Martinez, M. Yus, *Tetrahedron* **2003**, *59*, 1237. b) G. C. B. Harriman, J. Shao, J. R. Luly, *Tetrahedron Lett.* **2000**, *41*, 8853. c) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2004**, *6*, 4873. For a review about the usage of Deoxofluor and its advantages to DAST, see: R. P. Singh, J. n. M. Shreeve, *J. Fluorine Chem.* **2002**, *116*, 23.

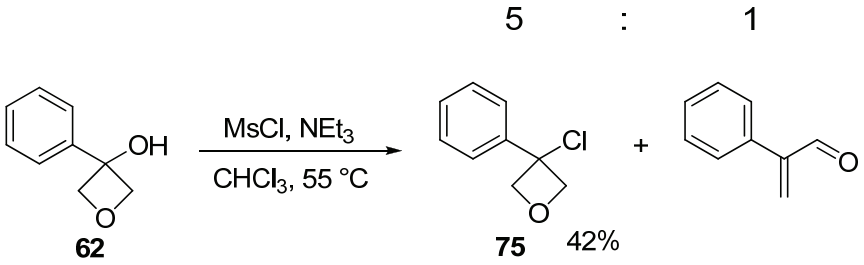
Table 4: Conversion of 3-aryloxetan-3-ols into the corresponding fluorinated compounds.



Entry	Starting Material	Product	Yield
1	 **67**	 **72**	47%
2	 **70**	 **73**	40%
3	 **71**	 **74**	43%

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.

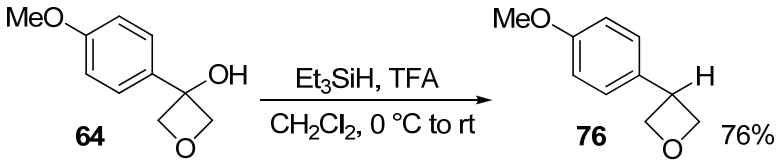


*Equation 5: Preparation of 3-chloro-3-phenyloxetane (**75**) and formation of 2-phenylpropenal[181] as byproduct.*

In a similar reaction[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[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.[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.

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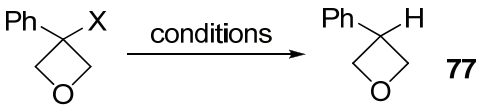
[181] This compound was identified by comparison of its NMR spectrum with literature data (R. H. Newman-Evans, R. J. Simon, B. K. Carpenter, *J. Org. Chem.* **1990**, *55*, 695.)

[182] Adapted from a literature procedure: E. Bacque, J. M. Paris, S. Le Bitoux, *Synth. Commun.* **1995**, *25*, 803.

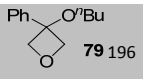
[183] J. Pataki, R. G. Harvey, *J. Org. Chem.* **1987**, *52*, 2226.

[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.

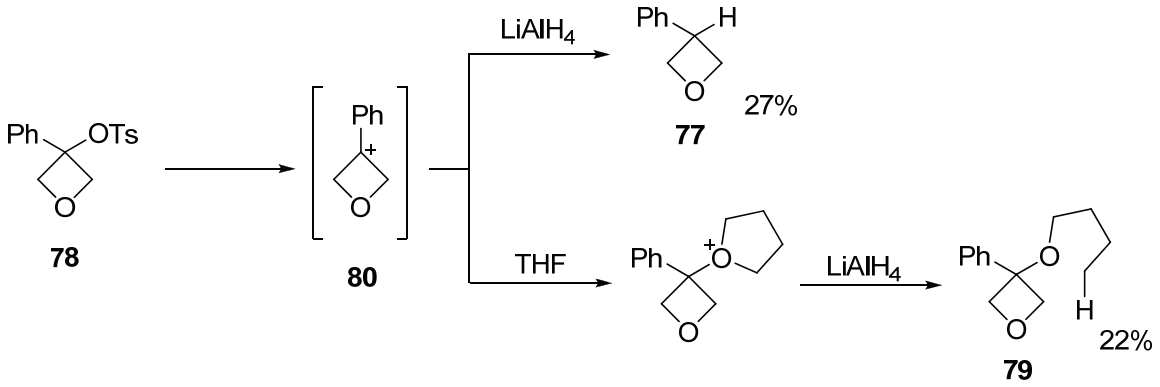


77

Entry	X	Conditions	Comment
1[185]	OH	Pd/C, H_2, EtOH, 4 d	no reaction
2	OH	Pd/C, HCO_2H, EtOH, 4 d	no reaction
3	OH	$Pd(OH)_2$/C, H_2, HCO_2H, EtOH, 2 d	no reaction
4	OH	Pd/C, H_2, AcOH, 70 °C, 15 h	no reaction
5[186]	OC(S)SMe	Lauroyl peroxide, ^{i}PrOH, reflux	decomposition
6[187]	Cl	Bu_3SnH, AIBN, PhMe, reflux	no reaction
7	Cl	$Pd(OH)_2$/C, H_2, MeOH, 12 h	decomposition
8[188]	OH	5% $InCl_3$, Ph_2SiHCl, 80 °C or rt, 1 d	decomposition
9[189]	$OC(O)CO_2Me$	Bu_3SnH, AIBN, PhMe, reflux	alcohol recovered
10[190]	Cl	$LiAlH_4$, rt	decomposition
11[191]	OH	$Pd(OH)_2$/C, H_2, TFAA, THF, 2 d	decomposition
12[192]	OH	1. NaI, TMSCl, 2. AcOH, Zn	$H_2C=C(Ph)CH_2OH$[193] (34%)
13	OH	Et_3SiH, TFA, rt, 4 d	decomposition
14[183]	OH	Et_3SiH, F_3CSO_3H, CH_2Cl_2	decomposition
15[194]	OH	Pd/C, cyclohexene, $AlCl_3$, 75 °C, 60 h	rec. sm, decomposition
16	OTs (**78**)	$Pd(OH)_2$/C, H_2, EtOAc, 4 d	decomposition
17[195]	OH	P_2I_4, PhMe, reflux	decomposition
18	OTs (**78**)	$LiAlH_4$, 0 °C, Et_2O, 45 min	68%
19	OH	1. NaH 2. *p*TsCl, 3. $LiAlH_4$, THF, 0 °C	27%, 22%  **79** 196
20	OH	1. NaH 2. *p*TsCl (3. $LiAlH_4$) Et_2O, 0 °C	no reaction[197]

[185] S. Mitsui, Y. Kudo, M. Kobayashi, *Tetrahedron* **1969**, *25*, 1921.
[186] B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1998**, *39*, 9435.
[187] S. Lesniak, *Pol. J. Chem.* **1995**, *69*, 1484.
[188] M. Yasuda, Y. Onishi, M. Ueba, T. Miyai, A. Baba, *J. Org. Chem.* **2001**, *66*, 7741.
[189] N.-S. Li, J. A. Piccirilli, *J. Org. Chem.* **2003**, *68*, 6799.
[190] S. Miyano, N. Mibu, M. Irie, S. Fujii, F. Fujisaki, N. Abe, K. Sumoto, *J. Chem. Soc., Perkin Trans. 1* **1987**, 313.
[191] a) M. Tanaka, K. Chiba, M. Okita, T. Kaneko, K. Tagami, S. Hibi, Y. Okamoto, H. Shirota, M. Goto, et al., *J. Med. Chem.* **1992**, *35*, 4665. b) D. L. Varie, *Tetrahedron Lett.* **1990**, *31*, 7583.
[192] T. Morita, Y. Okamoto, H. Sakurai, *Synthesis-Stuttgart* **1981**, 32.
[193] identified by comparison of NMR with literature: M. G. Organ, A. P. Murray, *J. Org. Chem.* **1997**, *62*, 1523.
[194] G. A. Olah, G. K. S. Prakash, *Synthesis-Stuttgart* **1978**, 397.
[195] H. Suzuki, H. Tani, H. Kubota, N. Sato, J. Tsuji, A. Osuka, *Chem. Lett.* **1983**, 247.
[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 diethylether.

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 *p*TsCl 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]

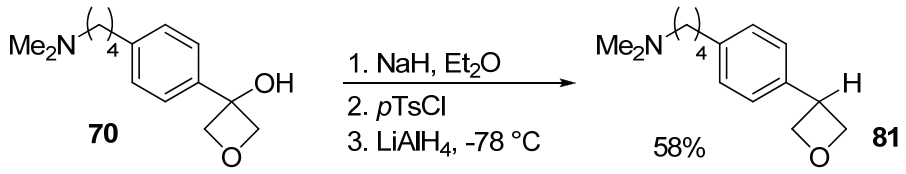


*Equation 7: Formation of n-butyl ether **79** suggests S_N1-pathway for the hydro-detosylation of **78**.*

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 $LiAlH_4$. 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 $LiAlH_4$ might result in formation of product rather than hydride attack on diethylether.

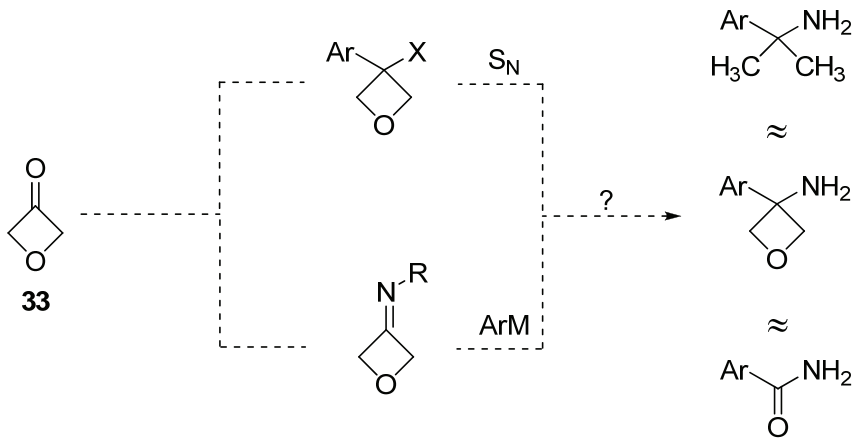


*Equation 8: One-pot preparation of 3-aryloxetane **81** from its corresponding alcohol **70**.*

In this case, tosylate formation in diethylether succeeds[200] and the reduction proceeds smoothly at –78 °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.[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.

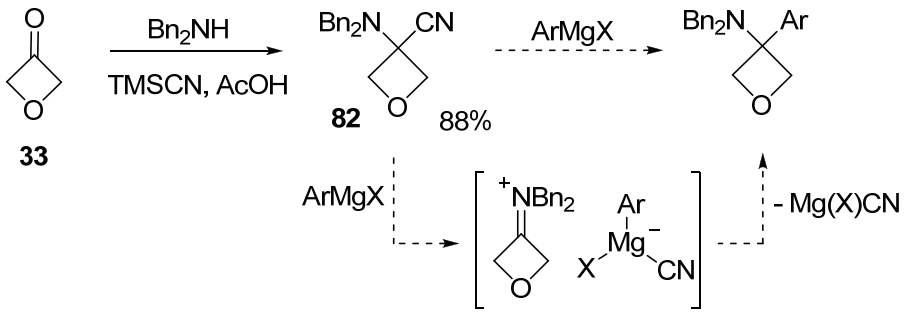
Two approaches to this compound class were selected to be examined first, nucleophilic displacement and addition to a C=N double bond. Several attempts to displace a

[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 20 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 indolamide invariably led to decomposition.[202] Addition reactions of phenyl lithium to oxetan-3-one *N,N*-dimethylhydrazone also yielded no product.[203]

The known preparation of amino acid **36**[204] (see Figure 7) from oxetan-3-one (**33**) inspired us to use α-amino nitriles derived from oxetan-3-one as precursors for 3-aminooxetanes. In the so-called Bruylants' reaction, arylmagnesium halides react with α-amino nitriles to give the corresponding aryl amine.[205]



Equation 9: Preparation of 3-amino-3-aryloxetanes from aminonitriles.

Aminonitrile **82** can be prepared in high yield by treatment of oxetan-3-one with dibenzylamine 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.[206] High concentration of the Grignard reagent as well as a switch from diethylether 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.[207]

[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.

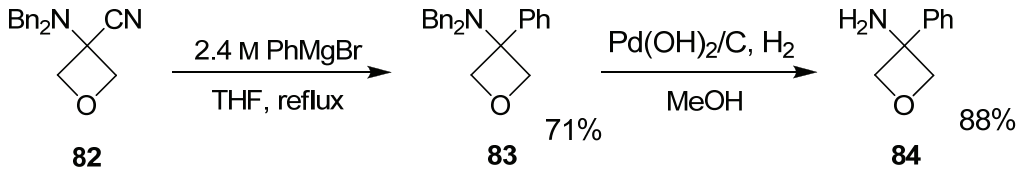
[203] Preparation of the hydrazone adapted from a literature procedure (D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506.). Attempts using published methods for the preparation tosylimines did not work for oxetan-3-one: a) M. Gordon, R. Wright, *Synthesis* **1984**, 1058. b) F. Chemla, V. Hebbe, J. F. Normant, *Synthesis-Stuttgart* **2000**, 75.

[204] A. P. Kozikowski, A. H. Fauq, *Synlett* **1991**, 783.

[205] P. Bruylants, *Bull. Soc. Chim. Belges*, **1924**, *33*, 467.

[206] E. Bacque, J. M. Paris, S. Le Bitoux, *Synth. Commun.* **1995**, *25*, 803.

[207] Attempts to preform the iminium ion by treating the aminonitrile **82** with $AgBF_4$ (C. Agami, F. Couty, G. Evano, *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.[208]

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**.

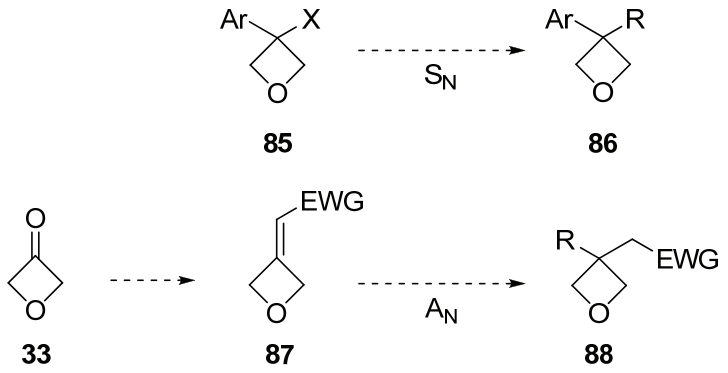


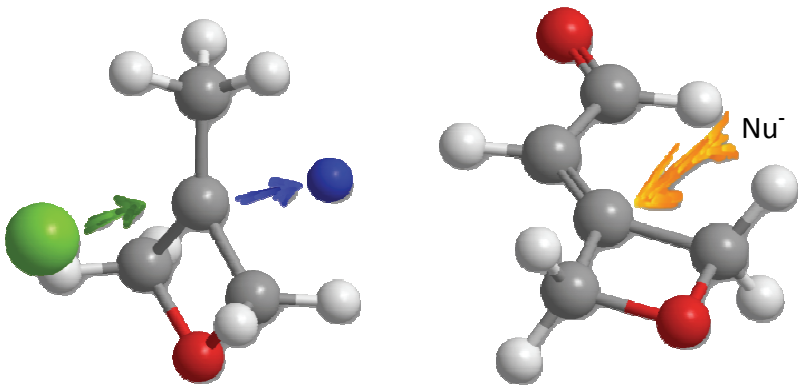
Figure 10: Preparation of quaternary centers by substitution or conjugate addition.

[208] See Table *5* for the stability of 3-phenyloxetan-3-ol under towards hydrogenolysis. Examples for hydrogenolytic cleavage of benzylic 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.[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.

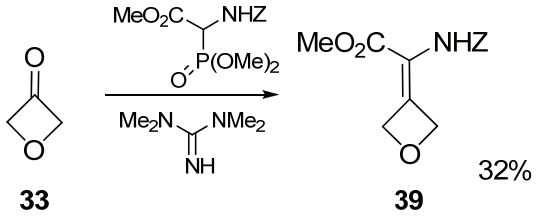
These impediments that render nucleophilic substitutions difficult foster the conjugate addition to compounds of the type shown in Picture 7 on the right. Here, the strained planar geometry which raises the energy of the S_N-transition state is preformed in the reagent. The sp^2-hybridized 3-position 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^3, reducing the deviation from the preferred bond angle to approximately 20°.[210] The inductive effect of the oxetane oxygen which obstructs the buildup of partial positive charge in the S_N-transition state promotes the 1,4-addition to alkylidene oxetanes, making the 3-position in oxetanes more electrophilic.

[209] Neither Ruppert's reagent (TMS-CF_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 $H_2C{=}C(Ph)CH_2OH$[193].

[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.[211]



33 **39**

*Equation 11: Preparation of the α,β-unsaturated ester **39** by HWE-reaction.*[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.[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**.

[211] M. D. T. Moldes, G. Costantino, M. Marinozzi, R. Pellicciari, *Farmaco* **2001**, *56*, 609.
[212] Workup was performed by filtering the reaction mixtures through a plug of silica gel.

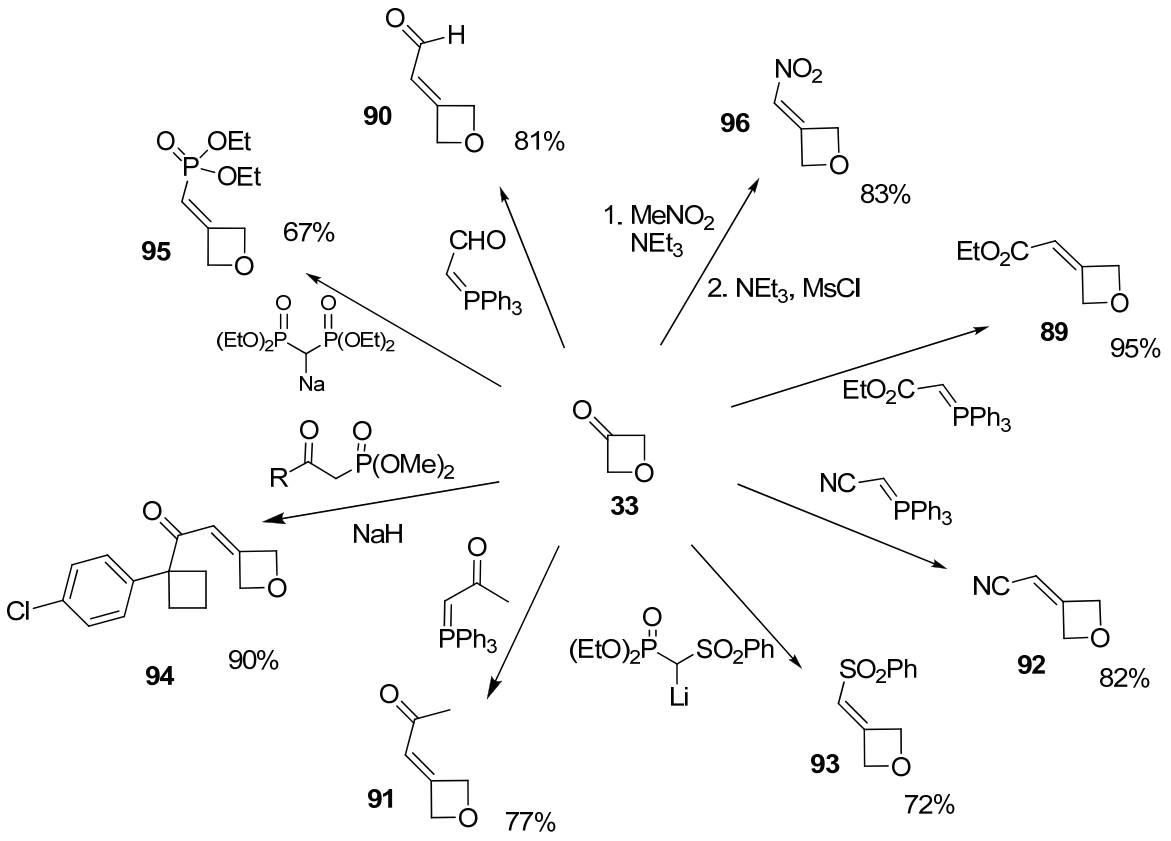


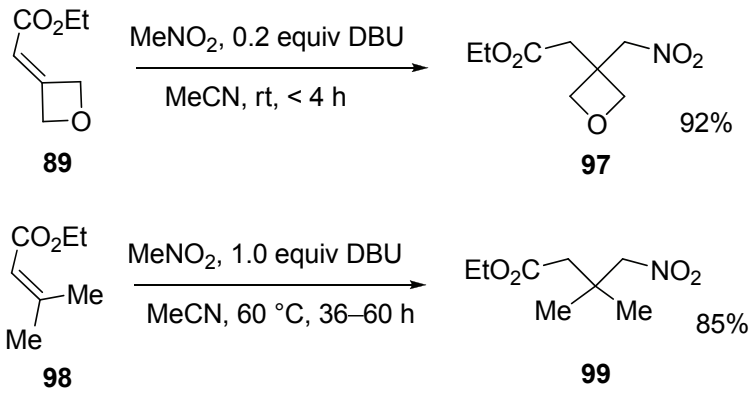
Figure 11: Michael-acceptors prepared from oxetan-3-one.

All compounds show no signs of decomposition when stored in the freezer.[213] Only in one case, vigorous and spontaneous decomposition of an impure sample of aldehyde **90** was observed.[214]

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.

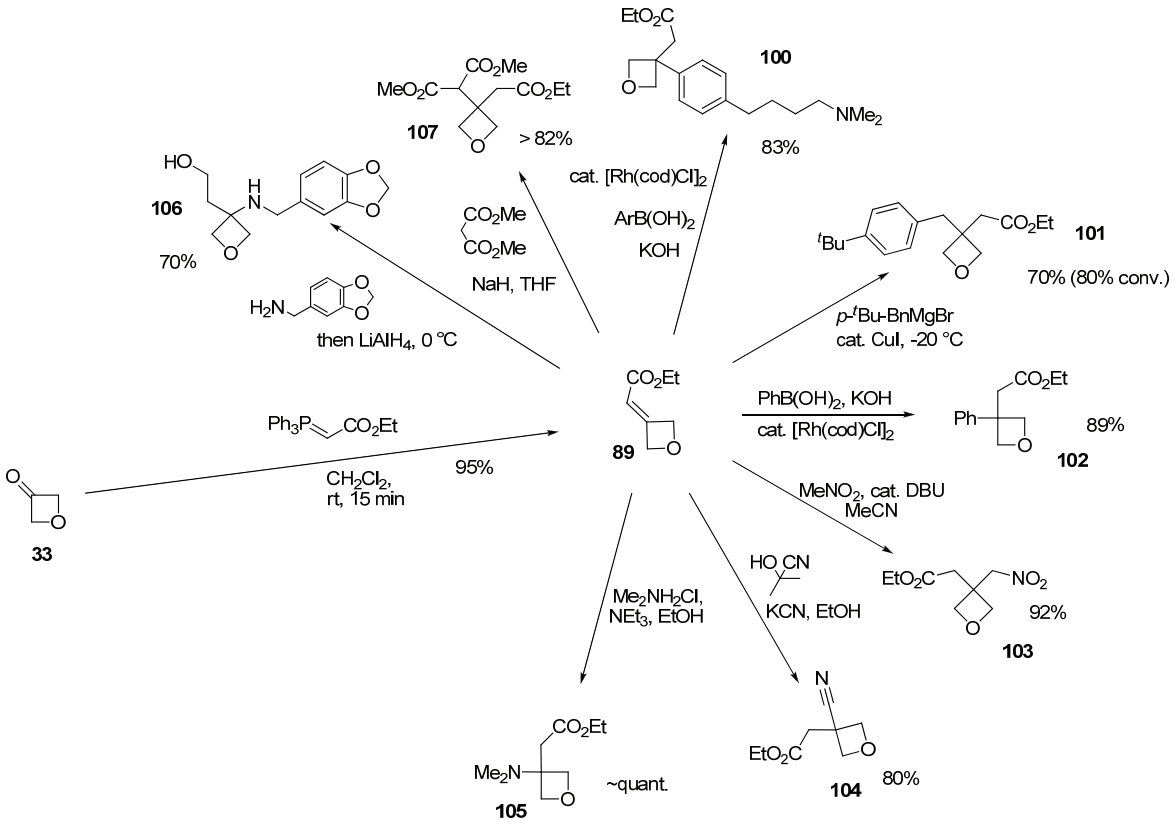
[213] Sulfone **93** is stable also at ambient temperature.
[214] Traces of base present in the material which had been recovered from a reaction mixture might have triggered polymerization.



*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.

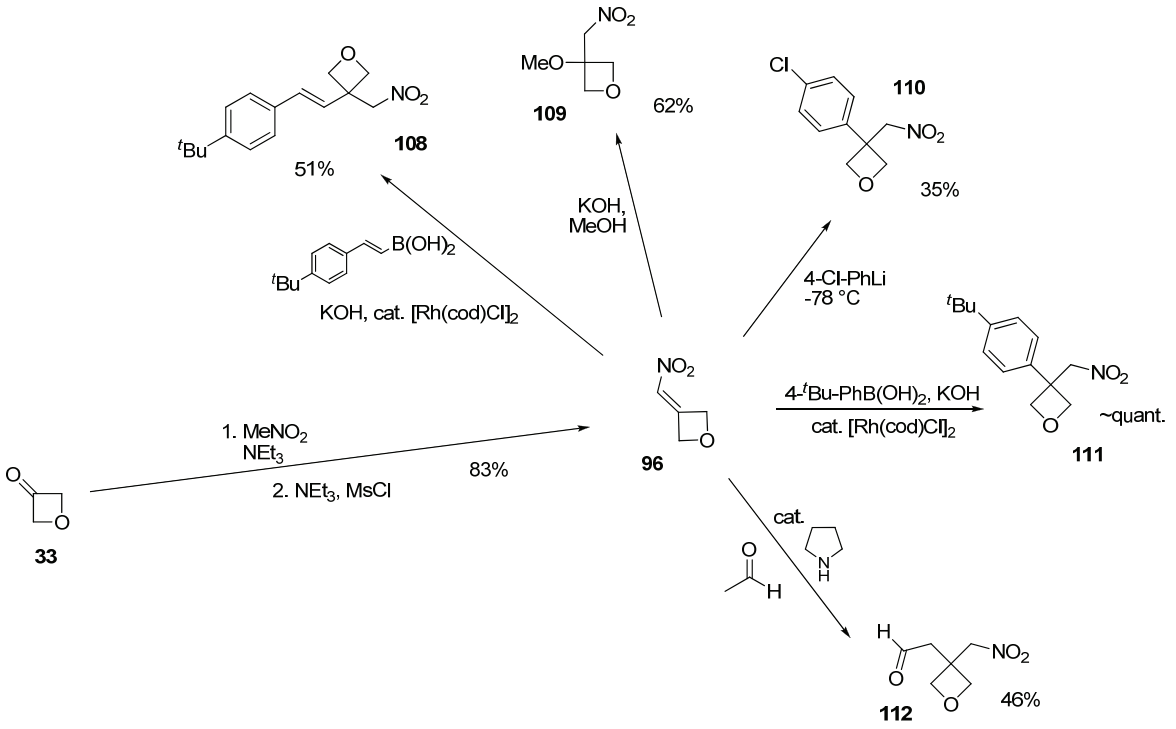
[215] Five equivalents of nitromethane were used in both reactions. Data for the second reaction taken from: R. A. Bunce, R. E. Drumright, *Org. Prep. Proced. Int.* **1987**, *19*, 471.



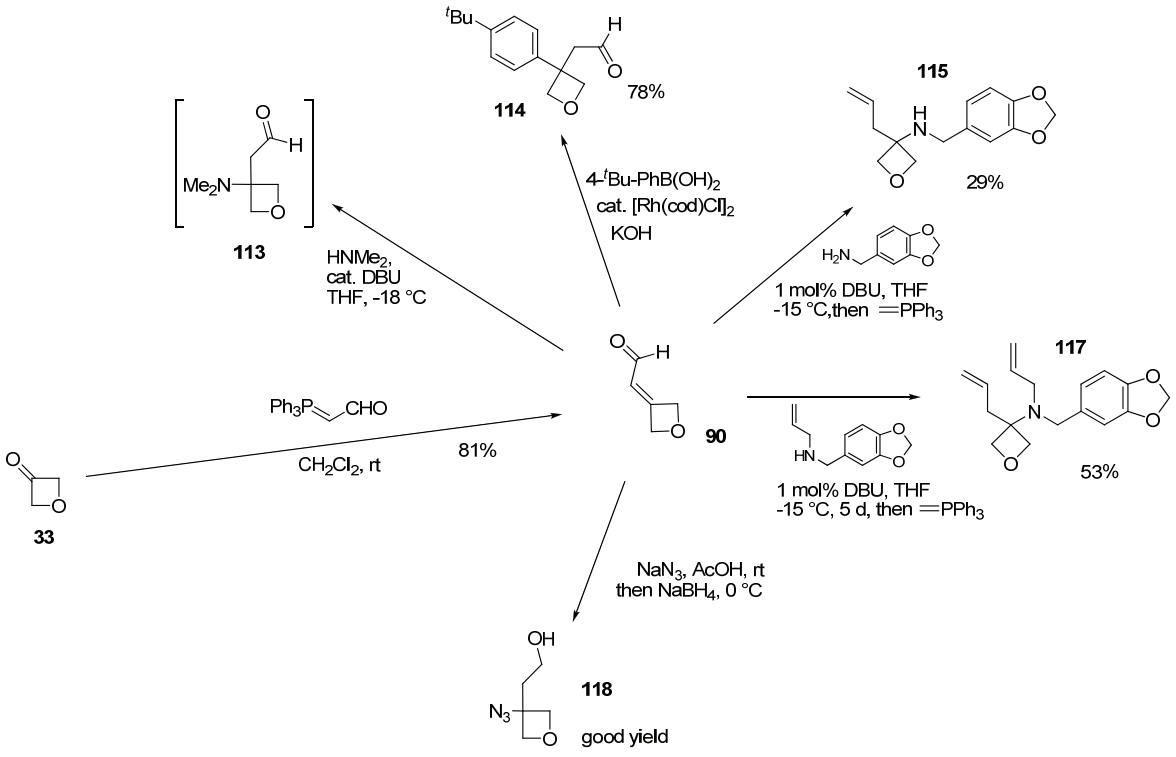
*Scheme 21: Addition products derived from ester **89**.*

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[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.

[216] The rhodium-catalyzed addition of boronic acids to Michael acceptors was pioneered by Hayashi and Miyaura. For key publications, see: a) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229. b) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.



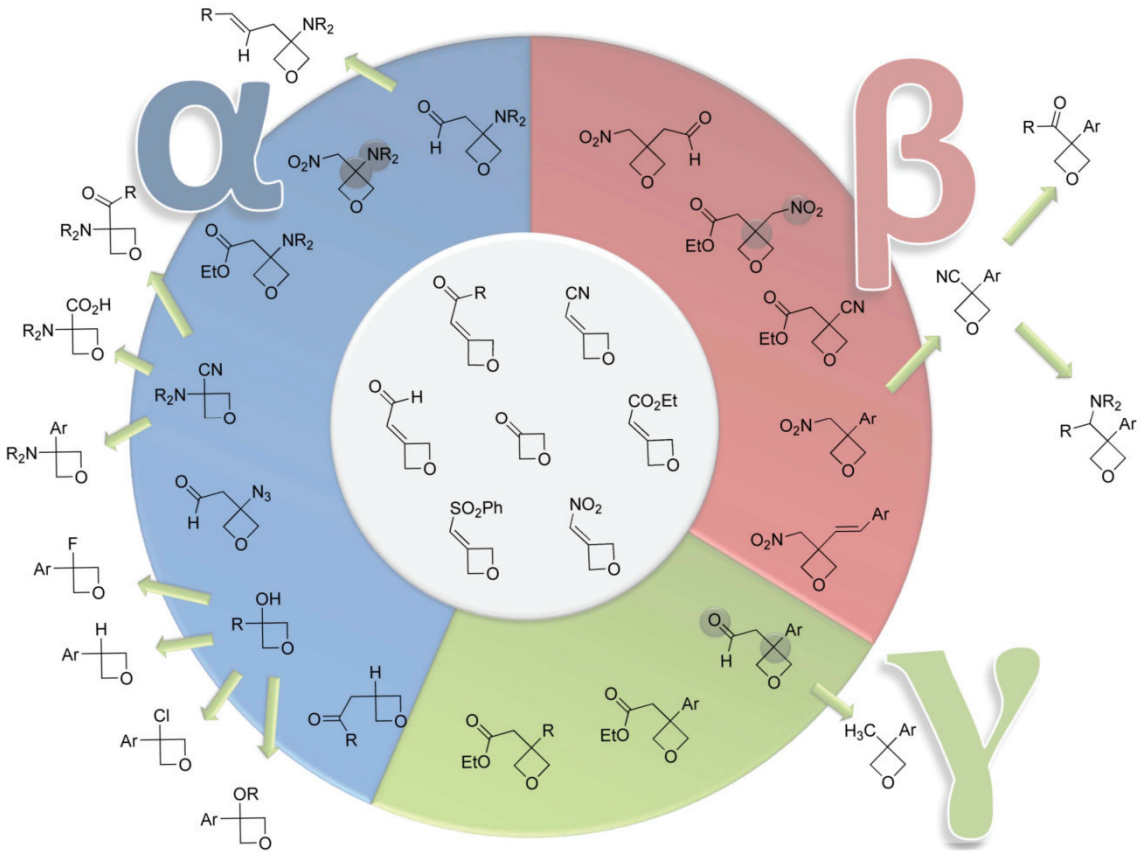
*Scheme 22: Addition products derived from nitro compound **96**.*



*Scheme 23: Addition products derived from aldehyde **90**.*[217]

[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.



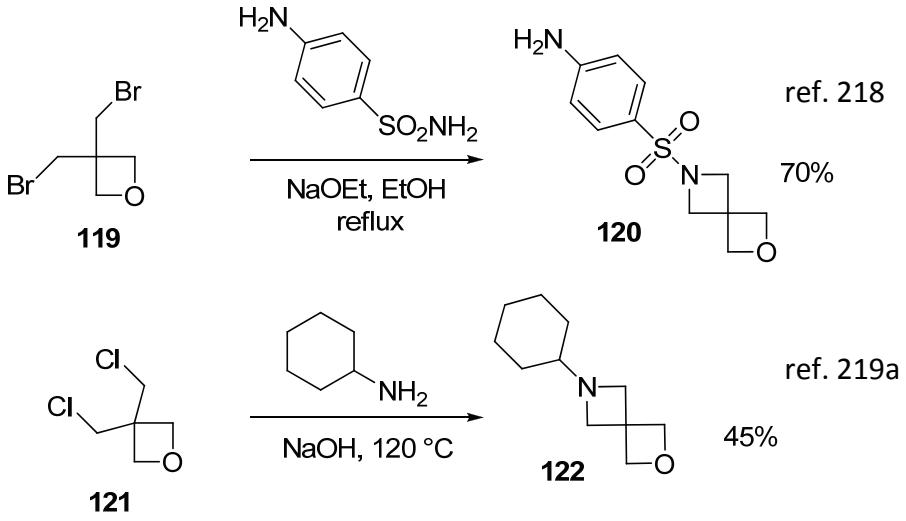
Picture 8: Selection of addition products accessible through oxetan-3-one.

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.

have a high propensity to undergo polymerization (A. Chesney, I. E. Marko, *Synth. Commun.* **1990**, *20*, 3167.).

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**).[218] Other articles followed that also used nucleophilic displacement in 3,3-bis(halomethyl)oxetanes to build up this class of spirocycles.[219]

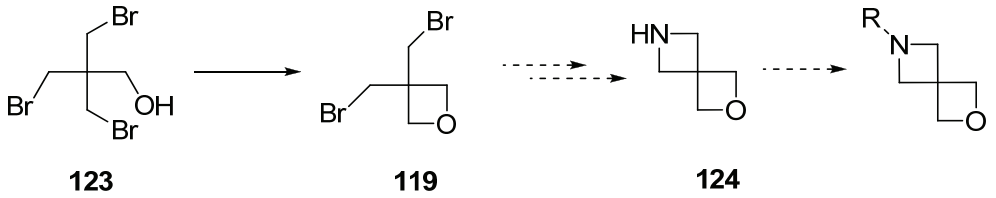


Scheme 24: Preparation of substituted 2-oxa-6-azaspiro[3.3]heptanes from 3,3-bis(halomethyl)oxetanes.

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.

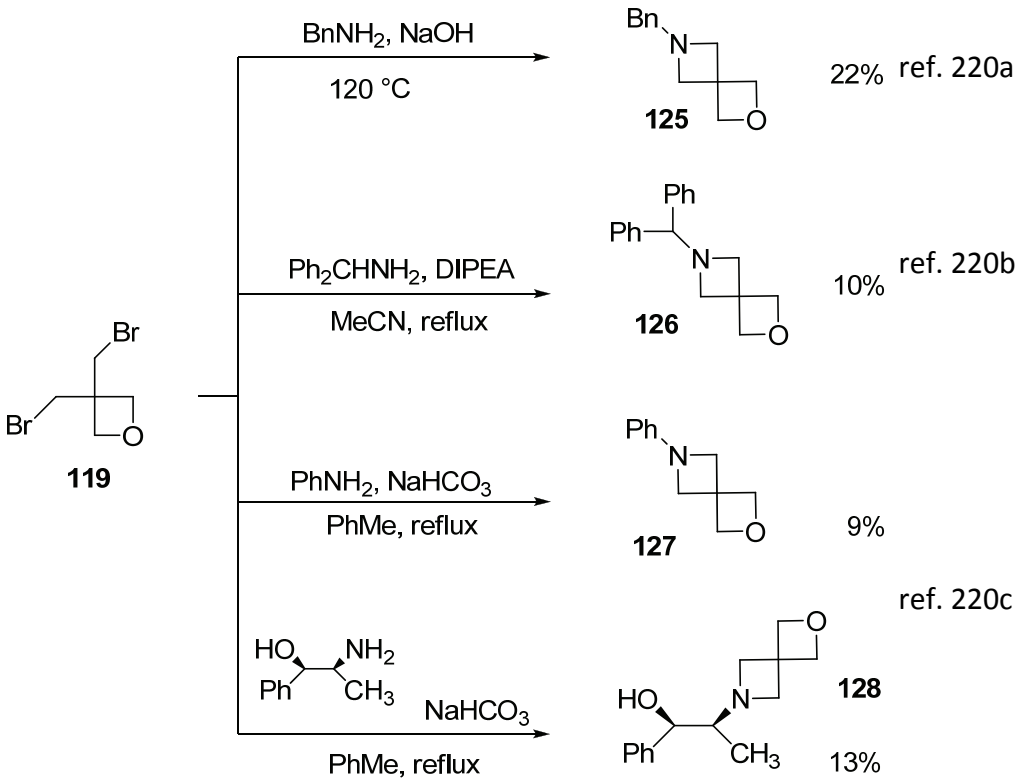
[218] J. Hoste, F. Govaert, *Bull. Soc. Chim. Belg.* **1949**, *58*, 157.

[219] a) F. S. Zarudii, D. N. Lazareva, E. S. Kurmaeva, O. B. Chalova, T. K. Kiladze, E. A. Kantor, D. L. Rakhmankulov, *Pharm. Chem. J. (Engl. Transl.)* **1985**, *19*, 108. b) R. K. Khazipov, N. L. Izbitskaya, T. K. Kiladze, O. B. Chalova, E. S. Kurmaeva, E. A. Kantor, *Izv. Vyssh. Uchebn. Zaved., Neft Gaz* **1984**, *27*, 86. A 2-oxa-6-azaspiro[3.3]heptane was also used as a synthetic intermediate for the preparation of 2,6-diazaspiro[3.3]heptanes (C. G. Overberger, Y. Okamoto, V. Bulacovschi, *Macromolecules* **1975**, *8*, 31.). Krespan reports the isolation of a 2-oxa-6-azaspiro[3.3]heptane derivative as a byproduct (C. G. Krespan, *J. Org. Chem.* **1975**, *40*, 1205.).



*Scheme 25: Envisioned preparation of 2-oxa-6-azaspiro[3.3]heptane (**124**) as a starting point for the synthesis of substituted 2-oxa-6-azaspiro[3.3]heptanes.*

Therefore, conditions[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**)[221]. In all cases, the reactions were found to be slow[222] and the products could be isolated only in small yield.



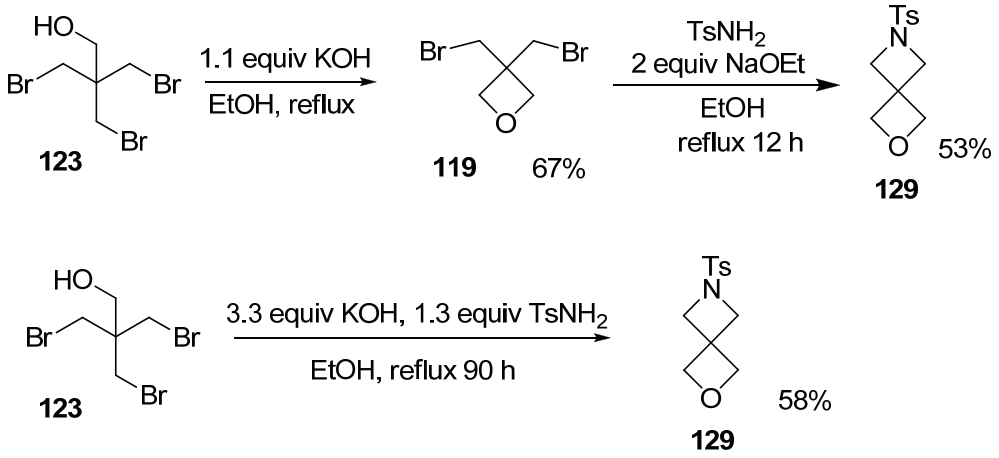
Scheme 26: Screening of conditions for the preparation of 2-oxa-6-azaspiro[3.3]heptanes.[220]

[220] a) F. S. Zarudii, D. N. Lazareva, E. S. Kurmaeva, O. B. Chalova, T. K. Kiladze, E. A. Kantor, D. L. Rakhmankulov, *Pharm. Chem. J. (Engl. Transl.)* **1985**, *19*, 108. b) F. H. Tsai, C. G. Overberger, R. Zand, *Biopolymers* **1990**, *30*, 1039. c) D. Zhao, C.-Y. Chen, F. Xu, L. Tan, R. Tillyer, M. E. Pierce, J. R. Moore, *Org. Synth.* **2000**, *77*, 12.

[221] This material was prepared from commercial tribromopentaerythritol (**123**): C. G. Overberger, Y. Okamoto, V. Bulacovschi, *Macromolecules* **1975**, *8*, 31.

[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[223], it was decided to use the high-yielding preparation of sulfonamide **120** as a starting point and investigate the cleavage of the sulfonamide bond.[224]



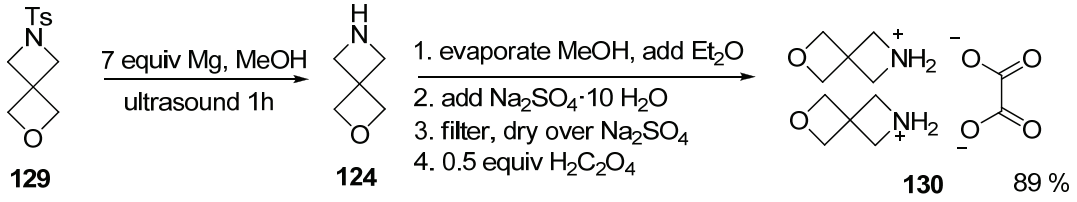
*Scheme 27: Preparation of tosyl amide **129** from commercial tribromopentaerythritol.*[225]

Instead of sulfanil amide, *p*-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*-tosyl amide dissolves.

Common conditions for the deprotection of tosyl amides include boiling in strong mineral acid[226] or the reductive cleavage[227] with an alkali metal. A more recent study found that *N*-tosylaziridines can be deprotected with magnesium in methanol.[228] This method

[223] Increase in time and reaction temperature did not give any improvement.
[224] This work was carried out by Andreas Buckl as part of his Semesterarbeit.
[225] Tribromopentaerythritol is used as a flame retardant for polymers: a) S. Ezra, S. Feinstein, I. Bilkis, E. Adar, J. Ganor, *Environ. Sci. Technol.* **2005**, *39*, 505. b) R. Borms, P. Georlette, *Kunststoffe* **2001**, *91*, 195.
[226] For an example, see: S. Varghese, D. Gupta, T. Baran, A. Jiemjit, S. D. Gore, R. A. Casero, P. M. Woster, *J. Med. Chem.* **2005**, *48*, 6350.
[227] For the sulfonamide cleavage with alkali metals of azetidines, see: a) H. Takikawa, T. Maeda, M. Seki, H. Koshino, K. Mori, *J. Chem. Soc., Perkin Trans. 1* **1997**, 97. b) D. Enders, J. Gries, Z. S. Kim, *Eur. J. Org. Chem.* **2004**, 4471.
[228] D. A. Alonso, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 9455.

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 benzoylation. 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**.*

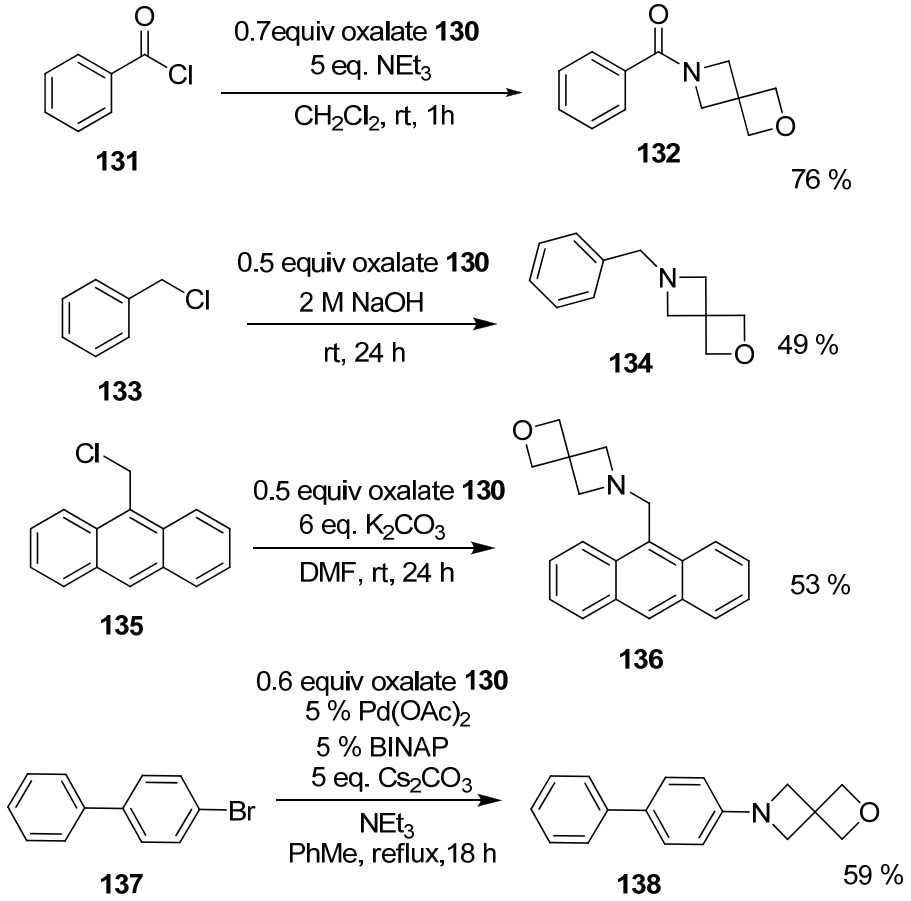
Several additives were screened to precipitate the magnesium salts from the reaction so that the crude mixture can be filtered.[229] Only $Na_2SO_4 \cdot 10\ H_2O$ however was successful in providing filterable precipitates. This simple method involves only filtrations as purification steps and is amenable 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[230] 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**).[231]

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

[230] Procedure adapted from: S. Surprenant, W. D. Lubell, *J. Org. Chem.* **2006**, *71*, 848.

[231] 2-oxa-6-azaspiro[3.3]heptane can be isolated and characterized, but decomposes upon storage at ambient temperature.



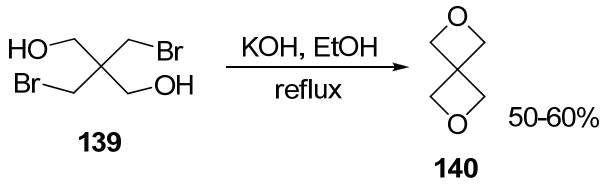
*Scheme 29: Use of oxalate **130** as a reagent in the amination of benzoyl chloride, benzyl halides and an aryl bromide.*

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[232] in 1934 by treatment of dibromopentaerythritol (**139**)[233] with base in hot ethanol.

[232] H. J. Backer, K. J. Keuning, *Recl. Trav. Chim. Pays-Bas* **1934**, *53*, 798. The initially low yield of this transformation was then optimized by Abdun-Nur *et al.* (A.-R. Abdun-Nur, C. S. Issidorides, *J. Org. Chem.* **1962**, *27*, 67.). Following that procedure, the maximum yield obtained in our hands was 23%.

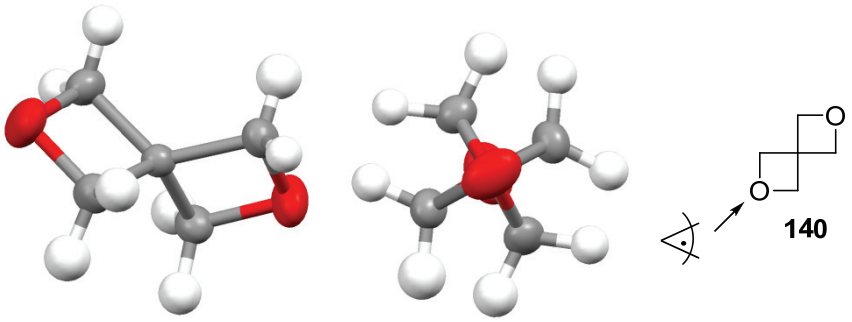
[233] Dibromopentaerythritol (**139**) is commercially available and used as a flame retardant for polymers. A study in mice documented its cancerogenic properties: J. K. Dunnick, J. E. Heath, D. R. Farnell, J. D. Prejean, J. K. Haseman, M. R. Elwell, *Toxicol. Pathol.* **1997**, *25*, 541.



139 **140**

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

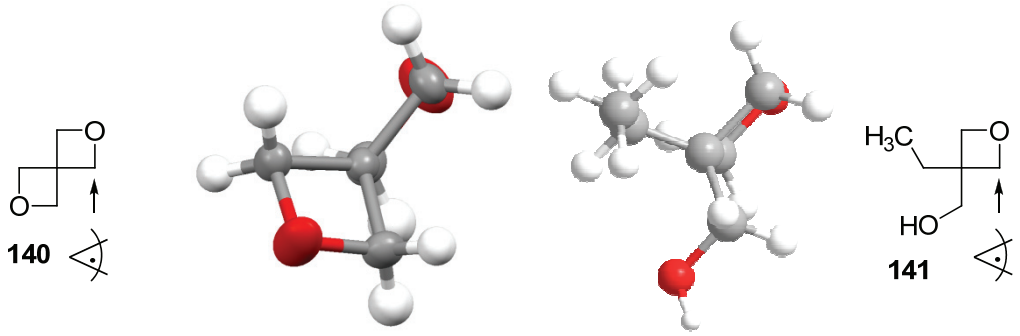
We reasoned that there might be the possibility to attack selectively one of the two rings with a nucleophile and thereby use 2,6-dioxaspiro[3.3]heptane (**140**) as a building block for the preparation of oxetanes. Interestingly, this compound is crystalline and crystals suitable for single-crystal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



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

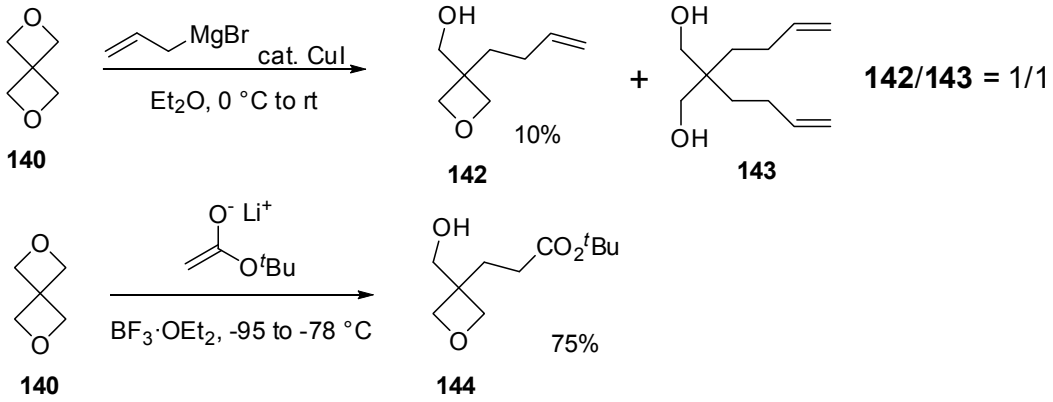
Both oxetane rings are planar and the C–C–C–valence angle is 85° which is similar to what is observed in other oxetanes.[235] In solution, 2,6-dioxaspiro[3.3]heptane (**140**) has a dipole moment of 0.79 D[236] on the basis of which a puckering angle of 22° was predicted for both rings.[237] The only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

[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_p 89–90 °C, ref. 232) rather than a liquid.
[235] Refer to Picture 11 for comparison.
[236] H. Cohen, *Recl. Trav. Chim. Pays-Bas* **1934**, *53*, 1139.
[237] B. A. Arbousow, *Bull. Soc. Chim. Fr.* **1960**, 1311.
[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.



*Picture 10: View along the trajectory of attack of a nucleophile on 2,6-spirocycle **140** (left) and 3-ethyl-3-(hydroxymethyl)oxetane (**141**, right).*[239]

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[239] reflects the situation after opening of one of the two rings. In the conformation which is likely adopted,[240] the methyl group and the newly formed alcohol[241] shield the remaining oxetane from further attack. Therefore, selectivity should increase with increasing bulk of the nucleophile being used.[242]



Scheme 31: Comparison of selectivities observed using an allyl cuprate[243] *versus a ester lithium enolate*[244].

[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. Derguiniboumechal, G. Linstrumelle, *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.

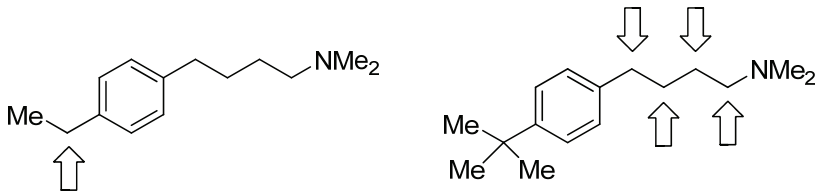
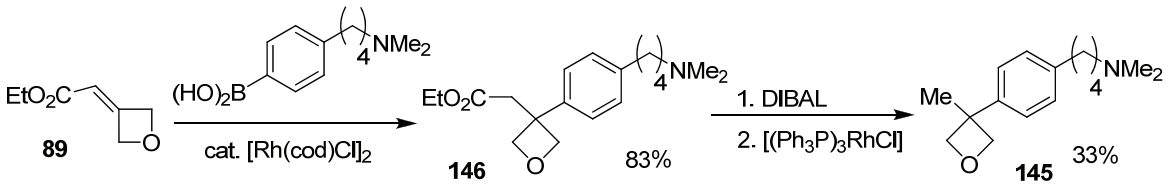


Figure 12: Locations in which the oxetane should be integrated in the initial series.

[244] Adapted from a procedure published for oxetane: M. Yamaguchi, K. Shibato, I. Hirao, *Tetrahedron Lett.* **1984**, *25*, 1159.

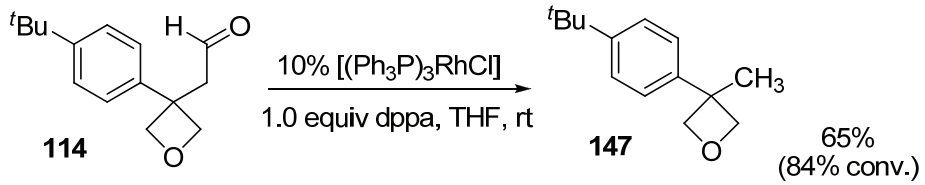
[245] Although the *t*-butyl group seems to be far away from the reaction center, it is plausible that the lithium alkoxide of **144** present in the reaction mixture places the *t*-butyl group close to the incoming nucleophile allowing the carbonyl of the ester to coordinate to the lithium.

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 decarbonylation[246] with Wilkinson's catalyst.



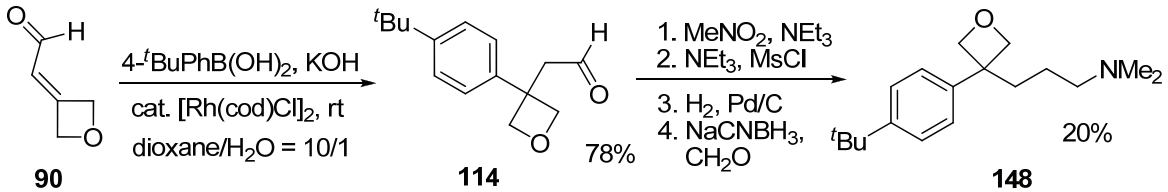
*Scheme 32: Preparation of 3-aryl-3-methyloxetane **145**.*

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 *et al.* in which the rhodium catalyst is regenerated by reaction with dppa was tried for a simpler substrate.[247]



*Scheme 33: Decarbonylation of aldehyde **114** with catalytic amounts of Wilkinson's catalyst.*[247]

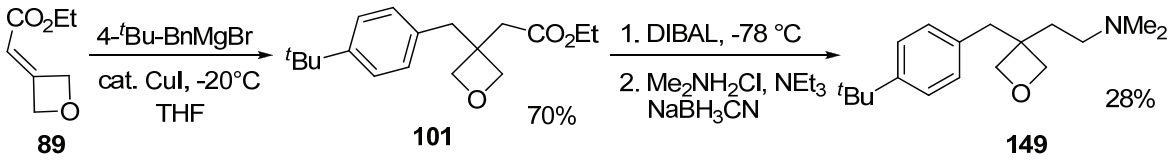
Aldehyde **114** was prepared by conjugate addition to acrolein **90** and was also used in the synthesis of compound **148**. There it was condensed with nitromethane;[248] the resulting nitroolefin was then reduced and reductively alkylated to give compound **148** in 20% yield over 4 steps.



*Scheme 34: Preparation of compound **148**.*

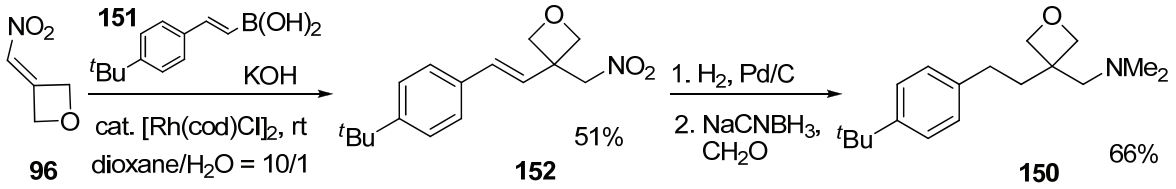
[246] B. Danieli, G. Lesma, D. Passarella, A. Silvani, *J. Org. Chem.* **1998**, *63*, 3492.
[247] J. M. O'Connor, J. Ma, *J. Org. Chem.* **1992**, *57*, 5075.
[248] Adapted from a literature procedure: C. Palomo, J. M. Aizpurua, F. P. Cossio, J. M. Garcia, M. C. Lopez, M. Oiarbide, *J. Org. Chem.* **1990**, *55*, 2070.

Conjugate addition of a cuprate to acrylate **89** provided ester **101**.[249] Reduction to the corresponding aldehyde and reductive amination then gave the final product.[250]



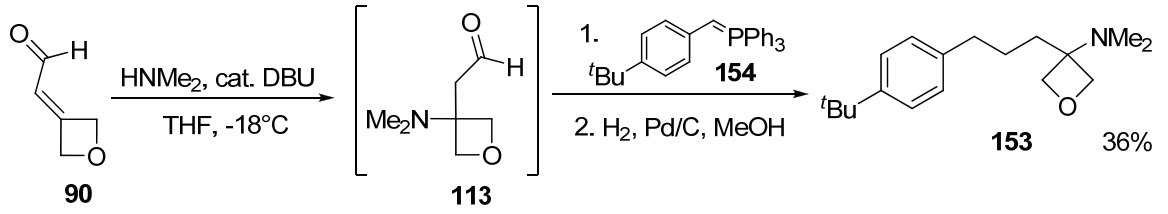
*Scheme 35: Preparation of compound **149**.*

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**.[251] 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

[249] Adapted from a literature procedure: D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097.

[250] Procedure used for the reductive amination: C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik, D. Aharony, *Bioorg. Med. Chem.* **2004**, *12*, 2653. The low yield can in part be attributed to difficulties in purifying this product by chromatography on *n*Al_2O_3.

[251] Procedure adapted from: A. Chesney, I. E. Marko, *Synth. Commun.* **1990**, *20*, 3167.

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.[252] It represents an interesting target for the introduction of an oxetane, because of its reported sites of metabolic oxidation. [253]

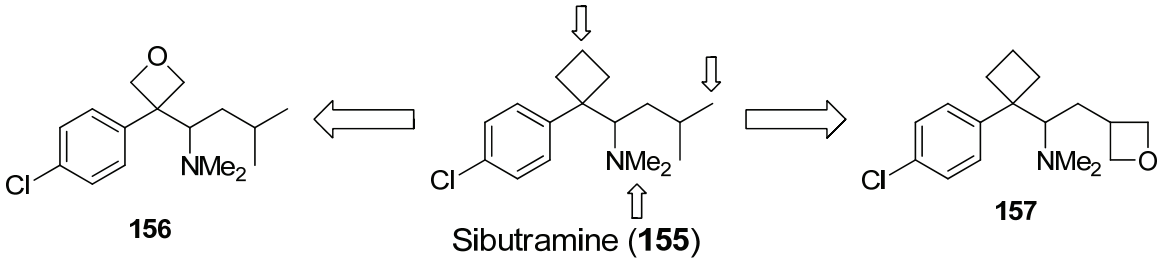
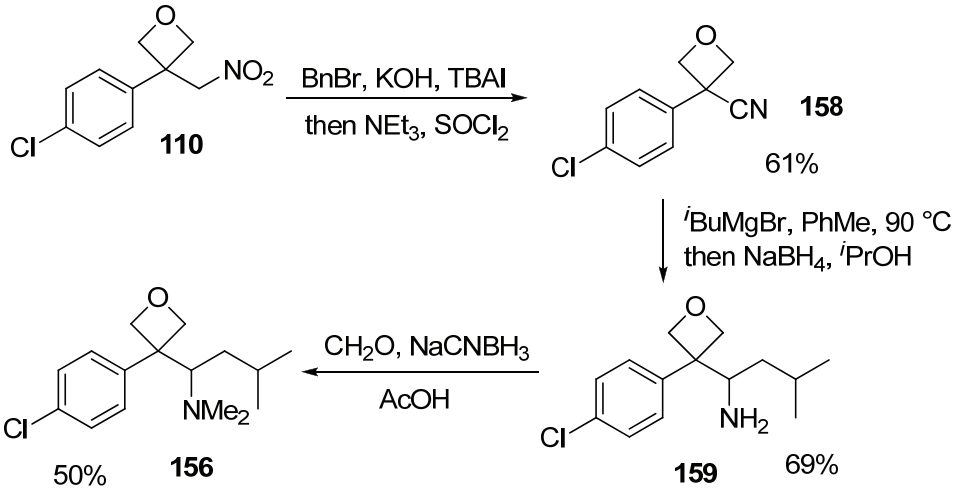


*Figure 13: Sibutramine (sites of metabolic attack are marked with arrows) and proposed oxetane analogues **156** and **157**.*

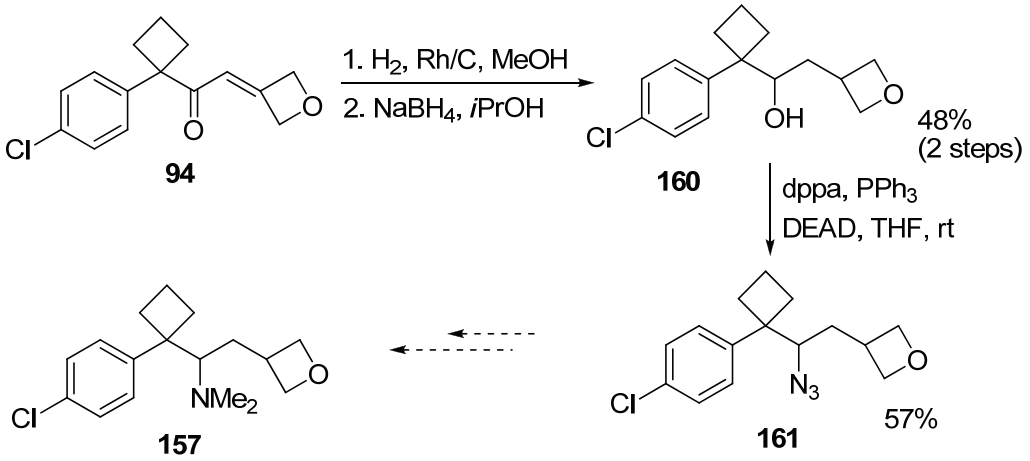
It was envisioned to replace either the cyclobutane or the isopropyl group with an oxetane and test these compounds for their metabolic stability and activity *in vitro*. The synthesis of compound **156** commenced with the addition *p*-chlorophenyl lithium to nitroolefin **96** in 35% yield (see Scheme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



*Scheme 38: Preparation of compound **156**.*[254]

[252] K. Eun-Joo, P. Eun-Kyung, S. Kwee-Hyun, *Human Exp. Toxicol.* **2005**, *24*, 109.
[253] B. Z. Lu, C. Senanayake, N. S. Li, Z. X. Han, R. P. Bakale, S. A. Wald, *Org. Lett.* **2005**, *7*, 2599.
[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.[255] Subsequent treatment of nitrile **158** with isobutylmagnesium bromide at elevated temperature in toluene and reduction of the addition product *in situ* with sodium borohydride provided primary amine **159** in good yield.[256]



*Scheme 39: Attempted preparation of compound **157**.*[257]

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[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 *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.

[255] C. Czekelius, E. M. Carreira, *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 612

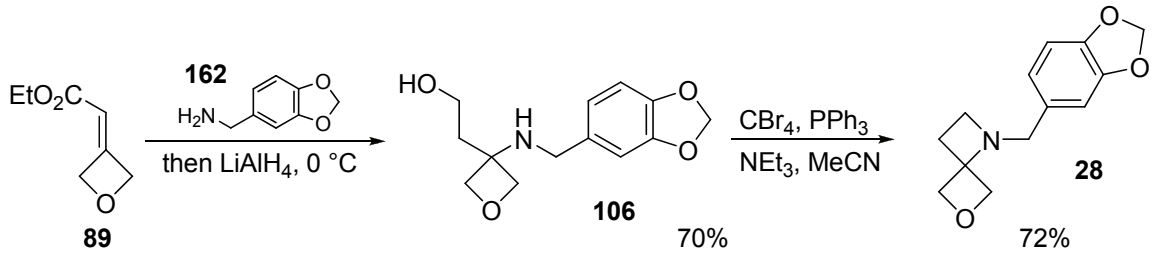
[256] Following a procedure for the synthesis of Sibutramine itself: J. E. Jeffery, F. Kerrigan, T. K. Miller, G. J. Smith, G. B. Tometzki, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2583.

[257] Conditions for the Mitsunobu reaction were adapted from: A. Miyadera, K. Satoh, A. Imura, *Chem. Pharm. Bull.* **2000**, *48*, 563.

[258] For a related example, see: P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450.

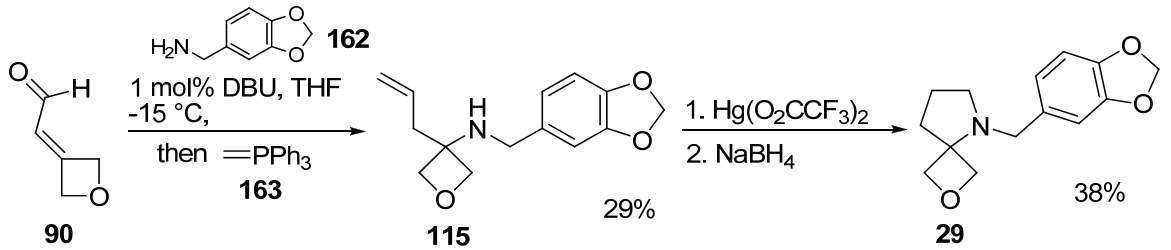
3.7.3 Spirocyclic Oxetanes

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.



*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]



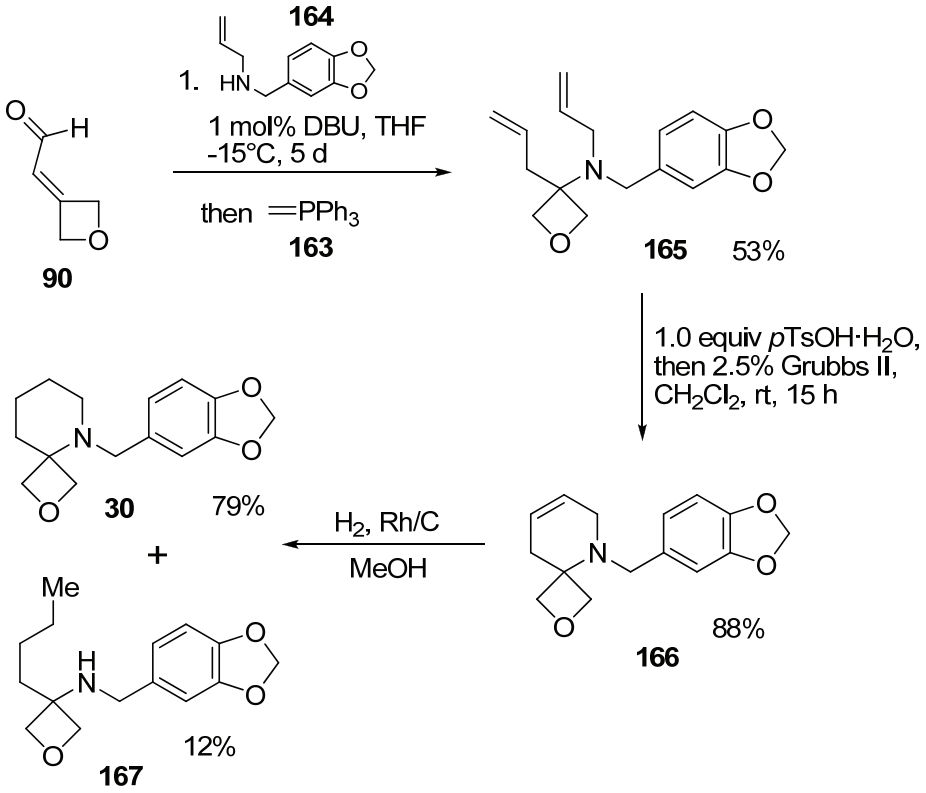
*Scheme 41: Preparation of pyrrolidine **29**.*

[259] This route was developed as part of the Semesterarbeit of Maurizio Bernasconi.

[260] Procedure adapted from: H. Suga, N. Tanimoto, A. J. Sinskey, S. Masamune, *J. Am. Chem. Soc.* **1994**, *116*, 11197.

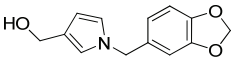
[261] Attempts to build up the 6-oxa-1-azaspiro[3.3]heptane system by conjugate addition of azide to acrolein **90** were not successful.

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 dimethylamine[264], *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**: 

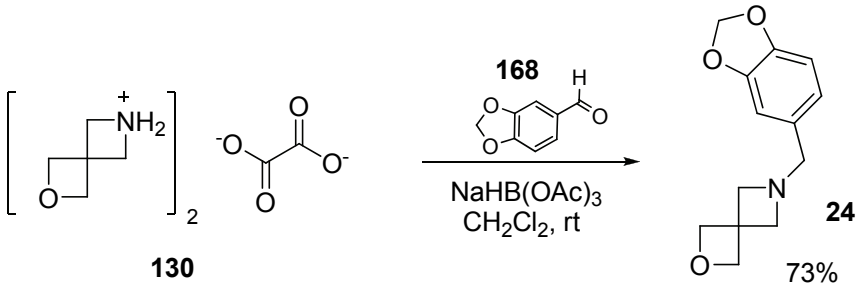
[263] Procedure adapted from: J. Blid, P. Brandt, P. Somfai, *J. Org. Chem.* **2004**, *69*, 3043. The reaction with less reactive $Hg(OAc)_2$ (according to: N. S. Karanjule, S. D. Markad, V. S. Shinde, D. D. Dhavale, *J. Org. Chem.* **2006**, *71*, 4667.) instead of $Hg(O_2CCF_3)_2$ stopped at low conversion.

[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 *in situ* protonated amine **165** then gave 3,4-dehydropiperidine **166**[266] 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.



*Scheme 43: Preparation of compound **24**.*[268]

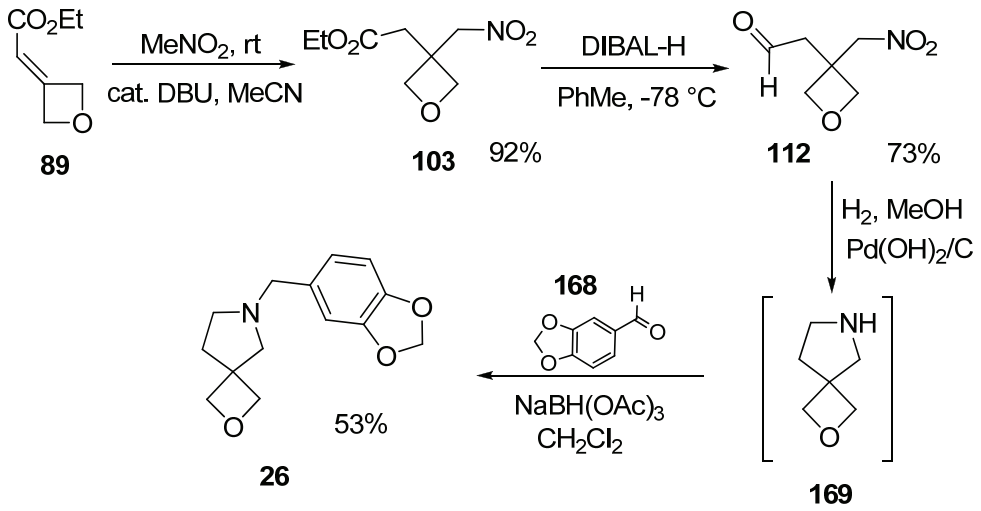
With the availability of oxalate salt **130** in large quantities (see chapter 3.5), azetidine **24** could be prepared by reductive alkylation with piperonal (**168**).[269]

[266] Procedure adapted from: D. L. Wright, J. P. Schulte, M. A. Page, *Org. Lett.* **2000**, *2*, 1847. *In situ* hydrogenation (J. Louie, C. W. Bielawski, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 11312.) of the alkene after the metathesis did not give any product.

[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.

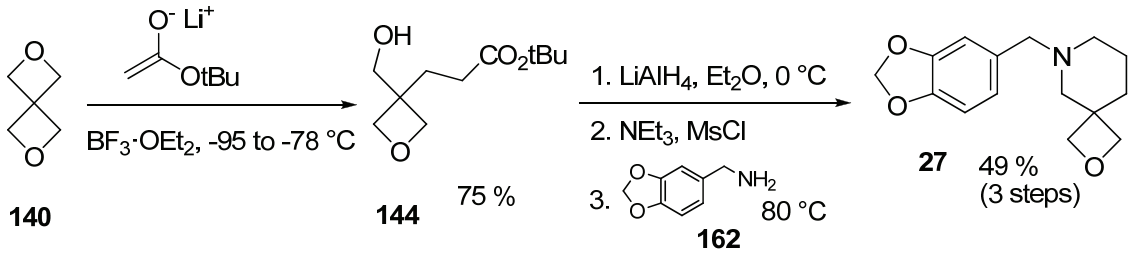
[268] This compound was prepared by Andreas Buckl as part of his Semesterarbeit. Procedure adapted from: B. Poulain, D. Horvath, B. Bonnet, C. Eckhoff, B. Chapelain, M. C. Bodinier, B. Deprez, *J. Med. Chem.* **2001**, *44*, 3378.

[269] Procedure adapted from: S. P. Khanapure, D. S. Garvey, D. V. Young, M. Ezawa, R. A. Earl, R. D. Gaston, X. Q. Fang, M. Murty, A. Martino, M. Shumway, M. Trocha, P. Marek, S. W. Tam, D. R. Janero, L. G. Letts, *J. Med. Chem.* **2003**, *46*, 5484.



*Scheme 44: Preparation of pyrrolidine **26**.*

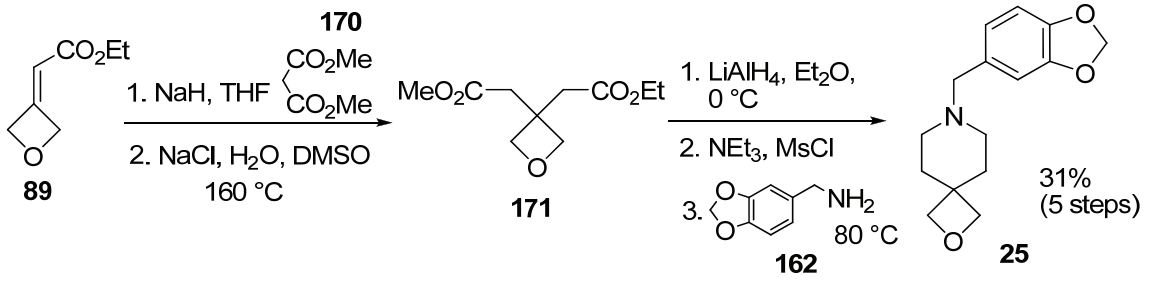
Conjugate addition of nitromethane to acrylate **89** gave nitroester **103** in excellent yield. This compound was then reduced to the corresponding aldehyde[270] which was reductively cyclized to give crude spiropyrrolidine **169**. Reductive alkylation then furnished the final product **26**.



*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.[271] 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.[272] Moreover, it might be used as a handle for the Julia olefination and its variations.[273]

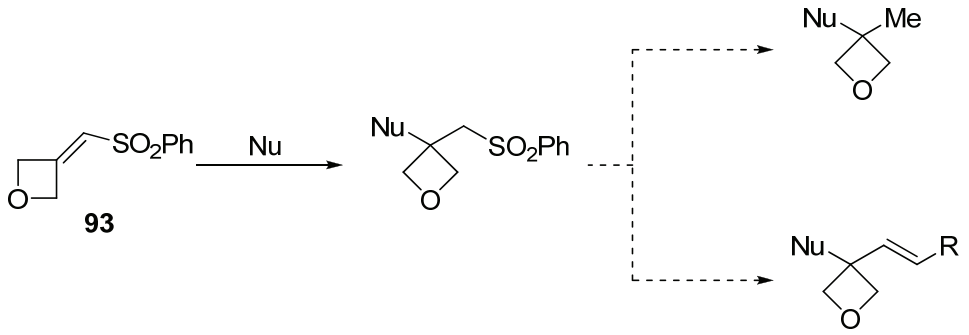


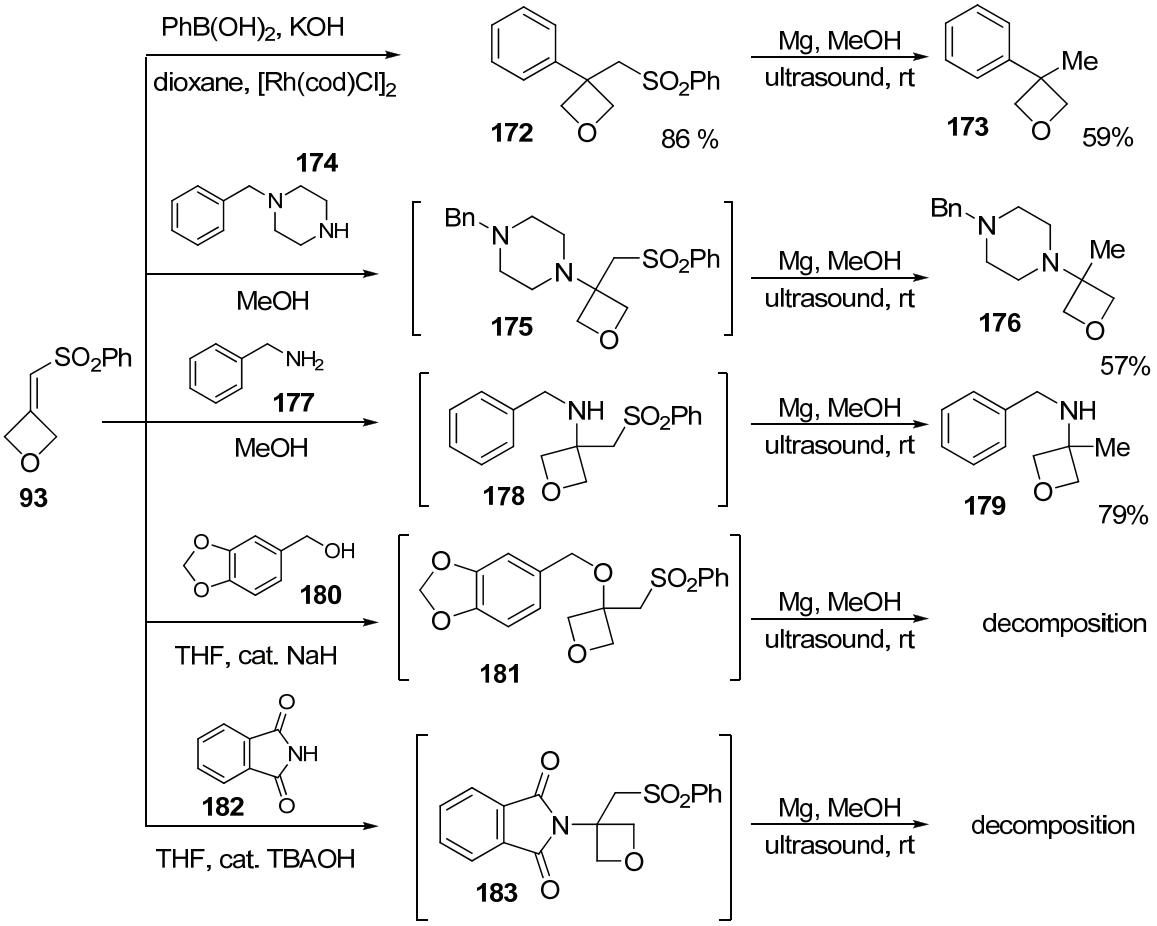
*Figure 14: Nucleophilic additions to α,β-unsaturated sulfone **93** and follow-up reactions.*

[271] Procedure adapted from: F. Matsuda, S. Terashima, *Tetrahedron* **1988**, *44*, 4721.

[272] a) I. Das, T. K. Pal, C. G. Suresh, T. Pathak, *J. Org. Chem.* **2007**, *72*, 5523. b) D. Diez, M. T. Beneitez, I. S. Marcos, N. M. Garrido, P. Basabe, J. G. Urones, *Tetrahedron: Asymmetry* **2002**, *13*, 639. c) T. Kimura, T. Nakata, *Tetrahedron Lett.* **2007**, *48*, 43. d) G. H. Lee, E. B. Choi, E. Lee, C. S. Pak, *Tetrahedron Lett.* **1993**, *34*, 4541.

[273] a) M. Julia, J. M. Paris, *Tetrahedron Lett.* **1973**, 4833. b) P. J. Kocienski, B. Lythgoe, I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045. For a review of sulfone chemistry, see: B. M. Trost, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107.

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.

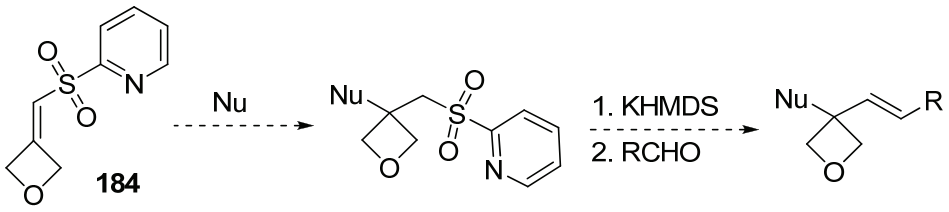


*Scheme 47: Additions to α,β-unsaturated sulfone **93** and consecutive reductive sulfone cleavage.*

For addition products like **181** and **183**, decomposition was observed under these conditions, maybe due to elimination.[274] Further experiments might solve this problem by adding catalytic amounts of mercury(II) salts[272d] to the reaction or by switching to Raney Nickel[272b,c] 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.



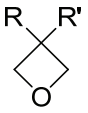
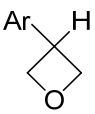
*Scheme 48: Addition products of 2-pyridylsulfone **184** and their proposed ability to undergo Julia–Kocienski olefination.*

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[275] protocol.[276]

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.[277]

			
	Reflux	RMgX, NaOH, RNH_2, AcOH, Krapcho	
	rt	$NaBH_4$, BH_3·THF, aqueous acid	$NaBH_4$, BH_3·THF
	0 °C	$LiAlH_4$, TFA/Et_3SiH, H_3PO_4 (often)	sometimes: TFA/Et_3SiH, H_3PO_4
	Reflux	aqueous HCl	
	rt	intramolecular nucleophiles[a]	HCl in dioxane
	0 °C		often: TFA/Et_3SiH, H_3PO_4
	–78 °C		$LiAlH_4$ (slow opening)

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

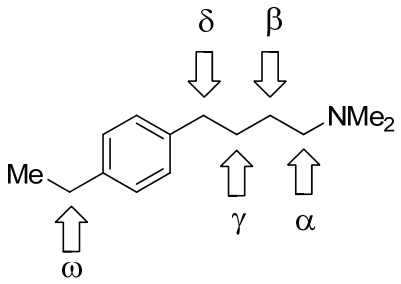
[275] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26. b) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175.
[276] P. Mauleon, J. C. Carretero, *Org. Lett.* **2004**, *6*, 3195.
[277] Only conditions are listed that might cause concern of ring opening because of the acidity or nucleophilicity of the reagents involved.

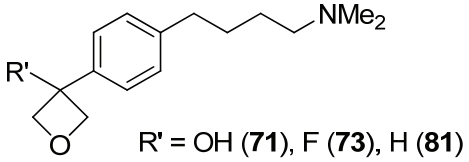
3,3-Disubstituted oxetanes are in general more resistant to decomposition than mono-substituted ones. Strong anhydrous acid is problematic for both groups and can lead to decomposition for example when trying to cleave a Boc group. Other commonly used reagents like strong base or reducing agents are 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.





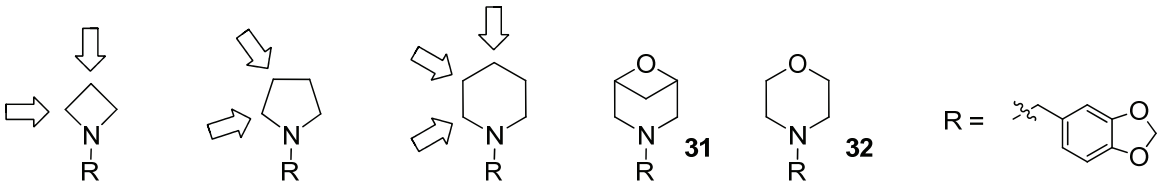
	ω	δ	γ	β	α
gem-Me_2	**185**	**186**	**187**	**188**	**189**
Oxetane	**145**	**148**	**149**	**150**	**153**

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

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.[278] Furthermore, the combination of a terminal basic amine and the lipophilic arylated chain should render the molecule amphiphilic[279] and a substrate of the hERG-receptor.[280] By that, this scaffold represents a group of molecules for which the integration of an oxetane might be considered. The respective oxetane derivatives would

[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.

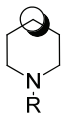
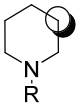
highlight the ability of the oxetane to influence these properties depending on the structural context.



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

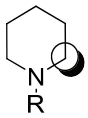
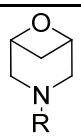
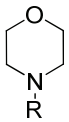
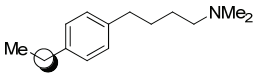
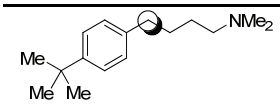
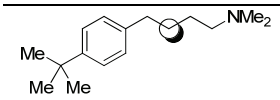
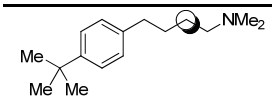
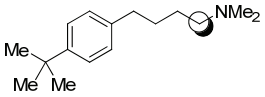
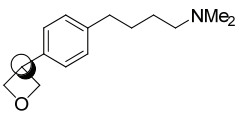
The series of spirocyclic oxetanes shown in Scheme 50 was chosen to serve several purposes. A comparison of the oxetanes with the corresponding carbonyl compounds would give an indication as to whether the analogy on paper translates into similar physicochemical properties. Additionally, these spirocyclic 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]

		No.	LogD[a] (LogP)[b]	Sol. [c]	Cl_{int} [d] (h/m)	pKa [e]
	*gem*-Me_2	**190**	0.8 (3.1)	290	0 / 16	9.6
	oxetane	**24**	0.5 (1.2)	24000	3 / 7	8.0
	carbonyl	**205**	*n.d.*[f]	*n.d.* [f]	*n.d.* [f]	*n.d.* [f]
	*gem*-Me_2	**191**	2.3 (4.4)	220	23 / 31	9.5
	oxetane	**25**	1.0 (2.0)	1400	6 / 22	8.3
	carbonyl	**206**	1.2 (1.6)	4000	120 / 88	7.5
	*gem*-Me_2	**192**	1.4 (3.7)	40	10 / 39	9.7
	oxetane	**26**	0.7 (1.5)	730	2 / 27	8.1
	carbonyl	**207**	-0.1 (-0.1)	4100	100 / 580	6.1
	*gem*-Me_2	**193**	2.3 (4.3)	13	31 / 89	9.4
	oxetane	**27**	1.7 (2.3)	2000	16 / 55	7.9
	carbonyl	**208**	0.1 (0.5)	2100	120 / 120	7.6
	*gem*-Me_2	**194**	0.1 (2.8)	380	7 / 14	10.1
	oxetane	**28**	1.3 (1.3)	1400	21 / 26	6.2
	carbonyl	**209**	1.1 (1.1)	2100	5 / 190	-

[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

		No.	LogD[a] (LogP)[b]	Sol. [c]	Cl_{int} [d] (h/m)	pKa [e]
	*gem*-Me_2	**195**	0.9 (3.5)	41	0 / 13	10.0
	oxetane	**29**	1.9 (1.9)	2100	31 / 74	6.3
	carbonyl	**210**	1.2 (1.2)	1500	5 / 16	-
	*gem*-Me_2	**196**	1.1 (3.9)	30	0 / 18	10.2
	oxetane	**30**	2.2 (2.4)	750	19 / 230	7.0
	carbonyl	**211**	1.6 (1.6)	6200	8 /39	-
		**31**	1.6 (1.8)	>2600	15 / 41	7.1
	x = 3	**197**	0.9 (3.1)	450	8 /18	9.6
	x = 2	**198**	0.2 (2.5)	580	6 / 18	9.7
	x = 1	**199**	-0.1 (2.1)	2500	0 / 11	9.5
		**32**	1.5 (1.6)	8000	9 /8	7.0
	*gem*-Me_2	**185**	1.8 (4.3)	< 1	16 / 417	9.9
	oxetane	**145**	0.8 (3.3)	4400	0 / 43	9.9
	CH_2	**200**	1.8 (4.3)	52	37 / 523	9.9
	*gem*-Me_2	**201**	2.3 (4.4)	220	13 / 502	9.8
	oxetane	**148**	1.7 (3.9)	270	0 / 147	9.6
	*gem*-Me_2	**202**	n.d. (n.d.)[g]		21 / 502	9.5
	oxetane	**149**	1.7 (3.5)	4100	6 / 13	9.2
	*gem*-Me_2	**203**	n.d. (n.d.) [g]	1	∞ / 858	9.4
	oxetane	**150**	3.3 (4.0)	25	42 / 383	8.0
	*gem*-Me_2	**204**	n.d. (n.d.) [g]		20 / 423	10.4
	oxetane	**153**	3.3 (3.6)	57	57 / 13	7.2
	OH	**71**	n.d. (n.d.) [g]	74000	0 / 68	9.6
	F	**73**	-0.5 (2.0)	6100	6 / 50	9.9
	H	**81**	-0.1 (2.4)	4000	2 / 27	9.9

*R = piperonyl; [a] logarithmic n-octanol/water distribution coefficient at pH 7.4; [b] intrinsic lipophilicity of the neutral base, according to log*P = *log*D + $log_{10}(1+10^{(pKa-pH)})$*; [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_2O *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.*

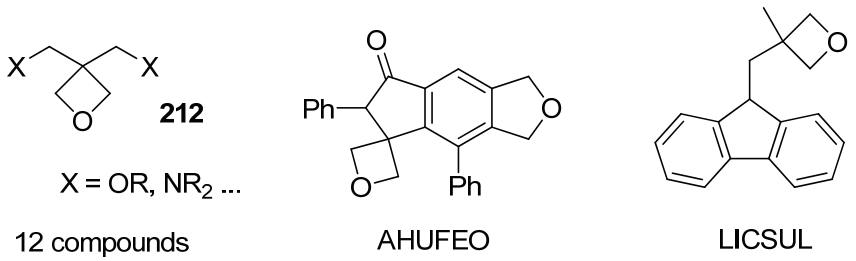
Table 7 combines the properties of all compounds measured. A discussion of absolute numbers, however would not provide insight in whether the substitution of some functional group for an oxetane made sense. Therefore, in the following, pairs of values are compared and their implications for a given substitution 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.

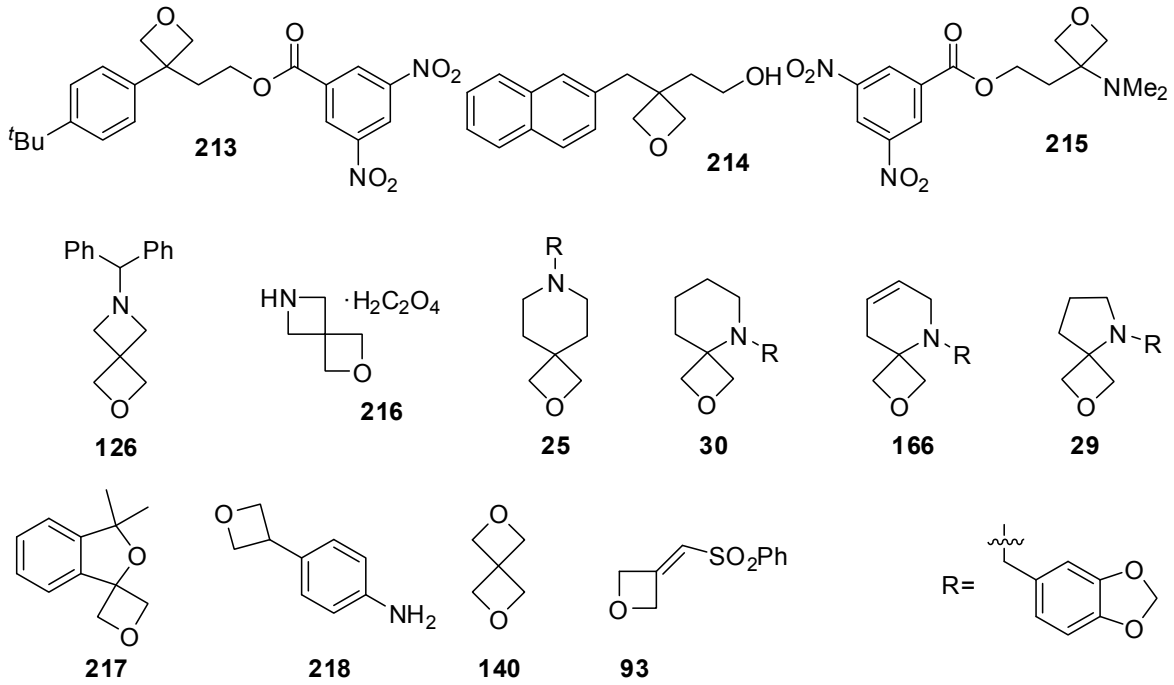


Scheme 51: Oxetanes registered in the Cambridge Structural Database (CSD).[282]

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.

[282] Search done on version 5.29 (November 2007). AHUFEO: G. H. Lee, E. B. Choi, E. Lee, C. S. Pak, *Tetrahedron Lett.* **1993**, *34*, 4541. LICSUL: J. Vogelgesang, G. Huttner, E. Kaifer, P. Kircher, P. Rutsch, S. Cunskis, *Eur. J. Inorg. Chem.* **1999**, 2187.

[283] See page 67 for their preparation.



Scheme 52: Compounds of which x-ray structures were prepared.[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.[285] This helped to define more precisely the structure of the oxetanes that are subject of this study.

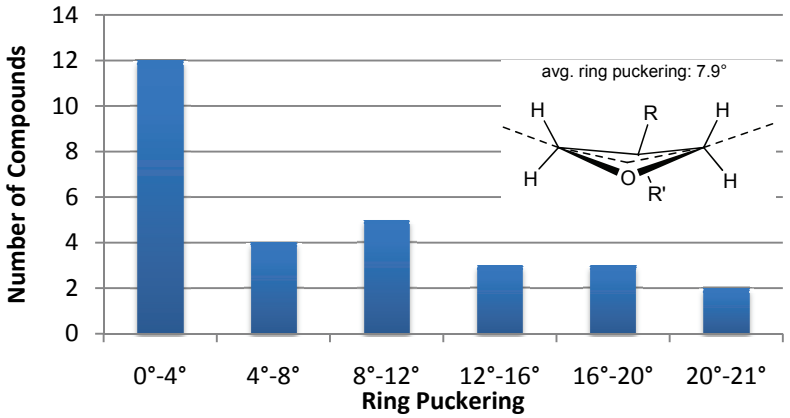
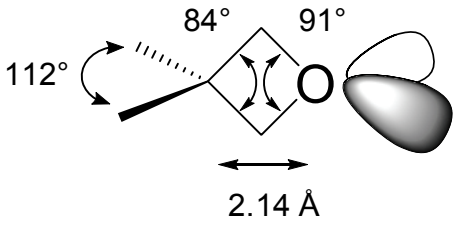


Diagram 8: Histogram showing the distribution of puckering angles.[286]

[284] X-ray structures were prepared by Dr. W. B. Schweizer (ETH Zürich) and André Alker (Roche).
[285] The program *Prequest* was used to combine x-ray structure files into a database that can then be read by the data retrieval program *Conquest* which is used to search the CSD.
[286] The data was retrieved from CSD and the database of oxetanes described in Ref. 285 using the programs *Conquest* and *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.



Picture 11: Averaged structural parameters of 3-substituted oxetanes.[287]

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' ≠ H).

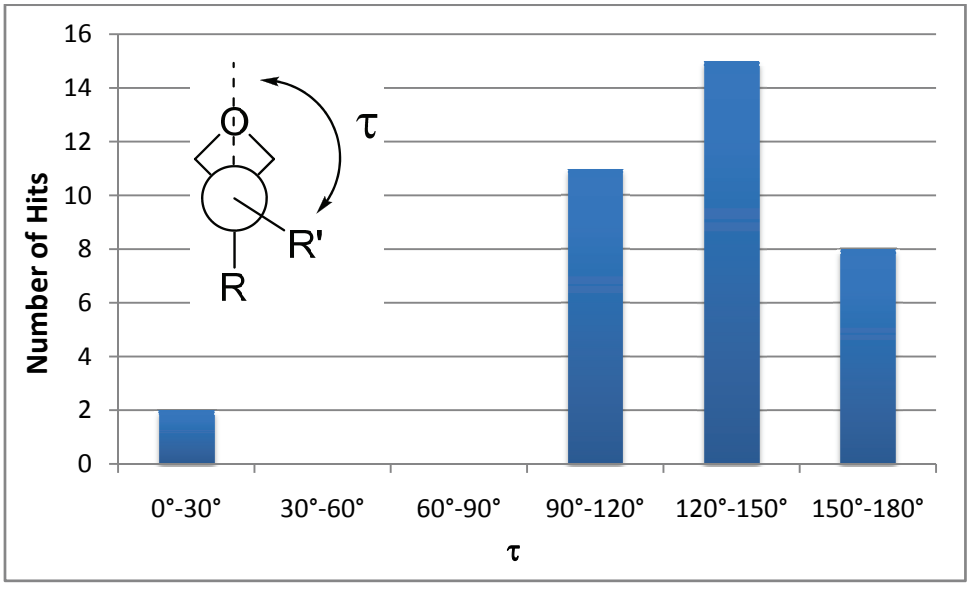
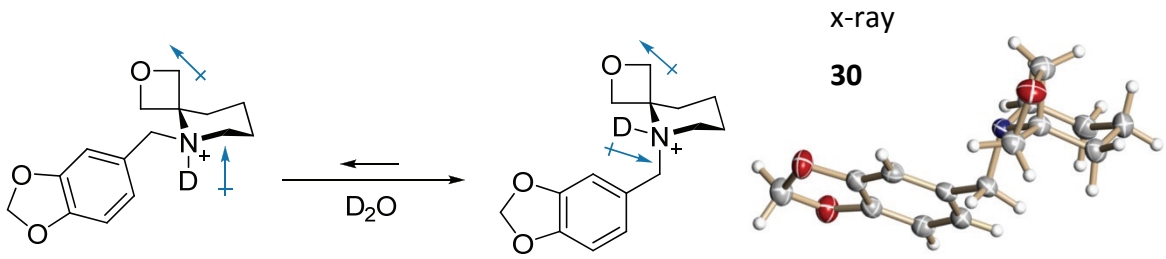


Diagram 9: The introduction of an oxetane leads to a preferred gauche relationship of R and R'.[288]

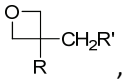
[287] 2-oxa-6-azaspiro[3.3]heptanes **216** and **126** were excluded for the determination of the exocyclic bond angles as the spirocyclic ring system limits this angle to ~87°.

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 ($\tau \approx 120°$) 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.[289] 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.[290] 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.[291] Hence, the antiperiplanar conformation is disfavored.[292] 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.[293] In the proto-

[288] Derived from the combined data base of 3-substituted oxetanes for the substructure  , R, R'≠H.

[289] 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.

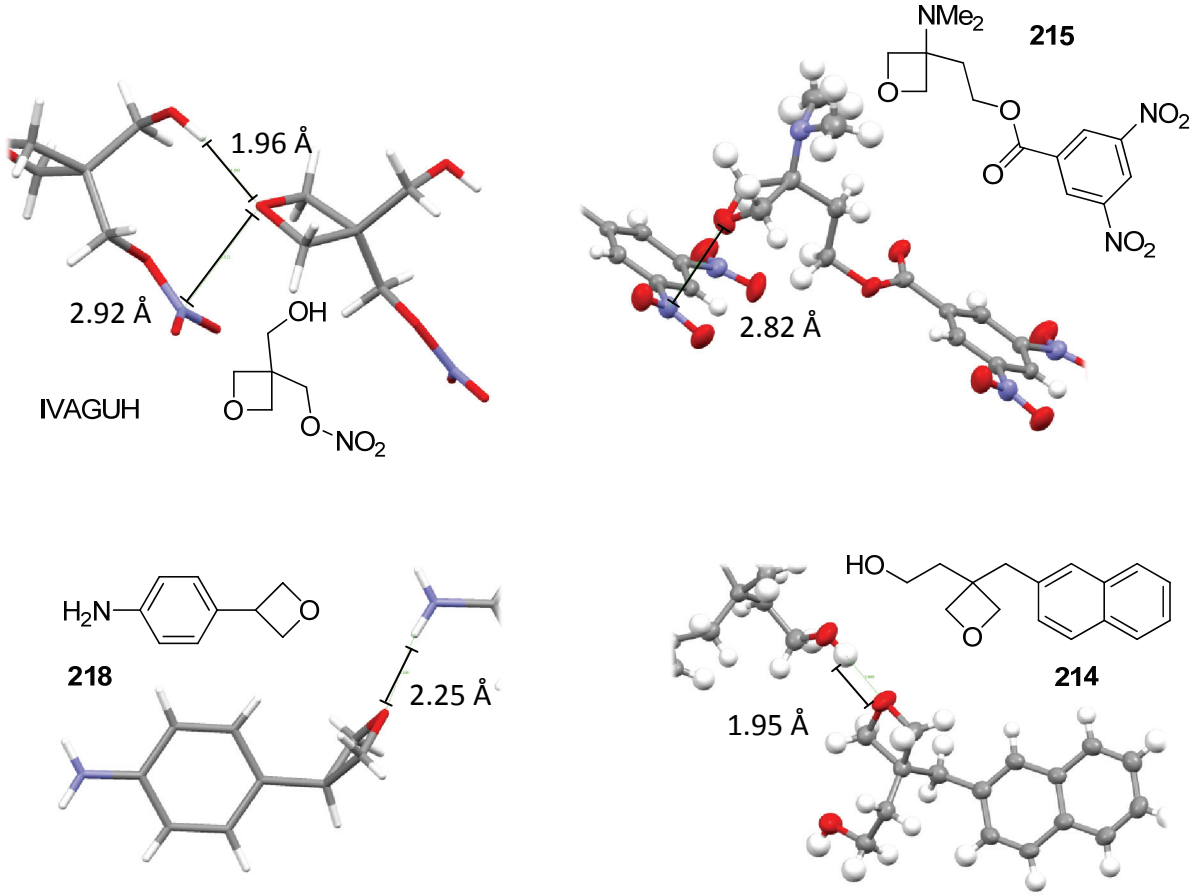
[290] Antiperiplanar conformations are found in 3,3-*bis*(methylnitraminomethyl)oxetane (DUMPAC, C. George, R. Gilardi, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *42*, 1161.) and in aminooxetane **215** (see Picture 12 top right for a pictorial representation). In DUMPAC the almost 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.

[291] See Picture 15 on page 106 for detailed explanation.

[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-NOESY 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 pK_a.



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-

[294] IVAGUH: A. M. Korolev, L. T. Eremenko, L. V. Meshikhina, I. L. Eremenko, G. G. Aleksandrov, N. P. Konovalova, V. P. Lodygina, *Russ. Chem. Bull.* **2003**, *52*, 1859.

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.[295] Electrostatic attraction of ionized functionalities is also an important contributor to target binding.

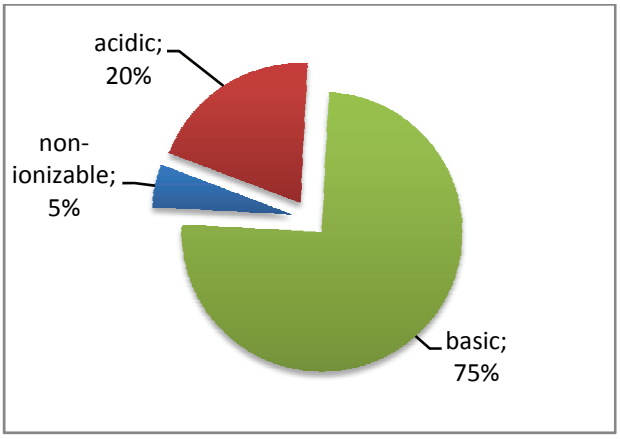


Diagram 10: Most drugs contain ionizable functionalities.[295]

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.

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

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-

[295] E. H. Kerns, L. Di, *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo, **2008**.

able and correlated with ionization, ionized compounds have difficulties permeating through lipid-bilayer membranes.[296] Therefore it is often necessary to fine-tune pK_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_a depends on the topological distance between the two. Diagram 11 shows how the introduction of an oxetane changes the basicity of an amine.

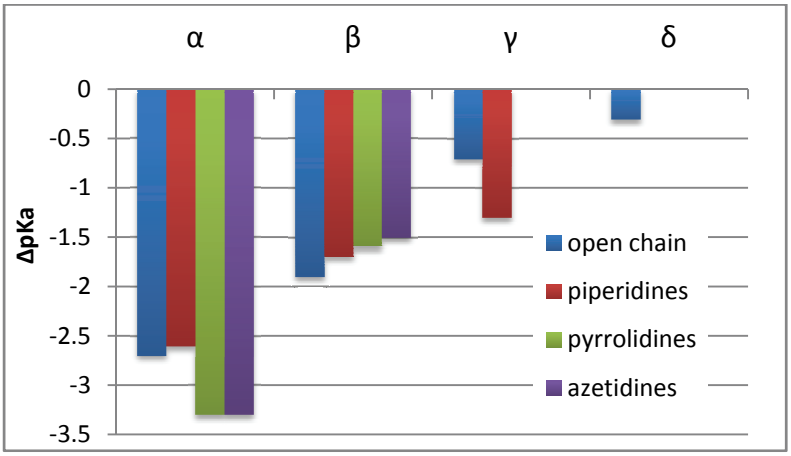


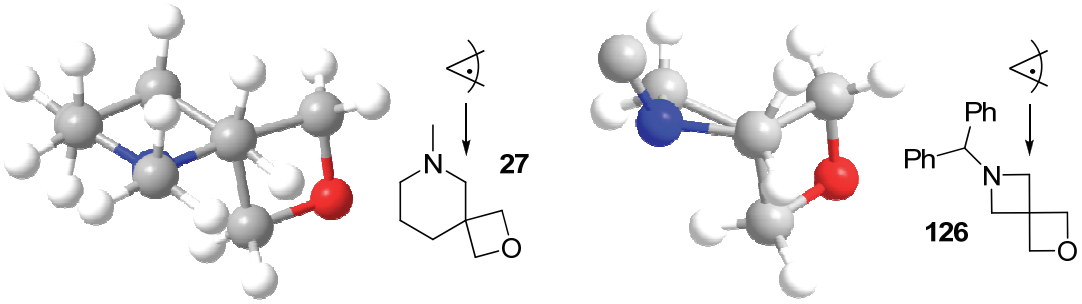
Diagram 11: Change in pK_a depending on the distance to an oxetane.[297]

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_a of the cyclic amines should be stronger than in the open chain case. Moreover, *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_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 azeti-

[296] Low membrane permeability does not only affect permeation through cell membranes, but also hampers intestinal uptake and thus reduces oral bioavailability.
[297] Difference of pK_a between the unsubstituted scaffold and the one that contains an oxetane.

dine.[298] Whereas in the open chain and also in the 6-membered ring staggered conformations dominate, in smaller rings eclipsing interactions become prevalent (Picture 13).



*Picture 13: Staggered conformation of piperidine **27** compared with the partially eclipsed conformation of azetidine **126**.*[299]

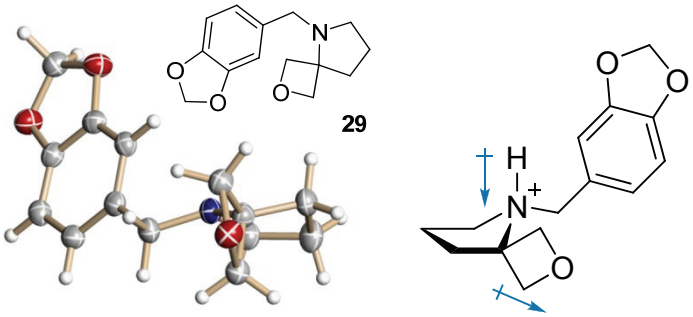
In a related study, it was found that the fluorine-induced pK_a shifts are much smaller in pyrrolidines than in piperidines. This was explained on the basis of the conformational dependence of pK_a-shifts and the different conformational preferences in cyclic systems, The authors state that more experiments are necessary to elucidate the origin of these results.[300] It seems likely that in the oxetane case the same effects are responsible for the decreased pK_a-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 pK_a-shifts in the open chain, the extent as 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 pK_a-shifts of the open chain, e.g. for piperidine **27**: $\Delta pK_a(\beta) + \Delta pK_a(\delta)$.

[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).

[300] M. Morgenthaler, E. Schweizer, A. Hoffmann-Roder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100.

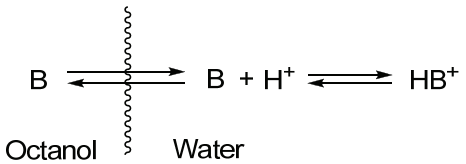


*Picture 14: Equatorial piperonyl substituent in an x-ray structure of pyrrolidine **29** (left). Unfavorable dipole alignment leads to destabilization of the deduced structure of protonated **29**.*

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).[301]

4.1.3 Lipophilicity

The lipophilicity of a compound has a major impact on its aqueous solubility, absorption and metabolic stability.[302] 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.



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

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

Equation 15: Definition of LogD and LogP as logarithmic partition coefficients for a basic compound.[303]

[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.

[302] a) C. Hansch, A. Leo, S. B. Mekapati, A. Kurup, *Bioorg. Med. Chem.* **2004**, *12*, 3391. b) F. Lombardo, R. S. Obach, M. Y. Shalaeva, F. Gao, *J. Med. Chem.* **2002**, *45*, 2867.

[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 pK_a of the compound and the pH of the medium, as the concentration of charged molecules is part of the definition of LogD.

$$LogP = LogD + \lg\left(1 + 10^{(pK_a - pH)}\right)$$

Equation 16: Correlation of LogP and LogD.

The presence of an oxetane influences both, the lipophilicity of a scaffold as well as the pK_a 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.

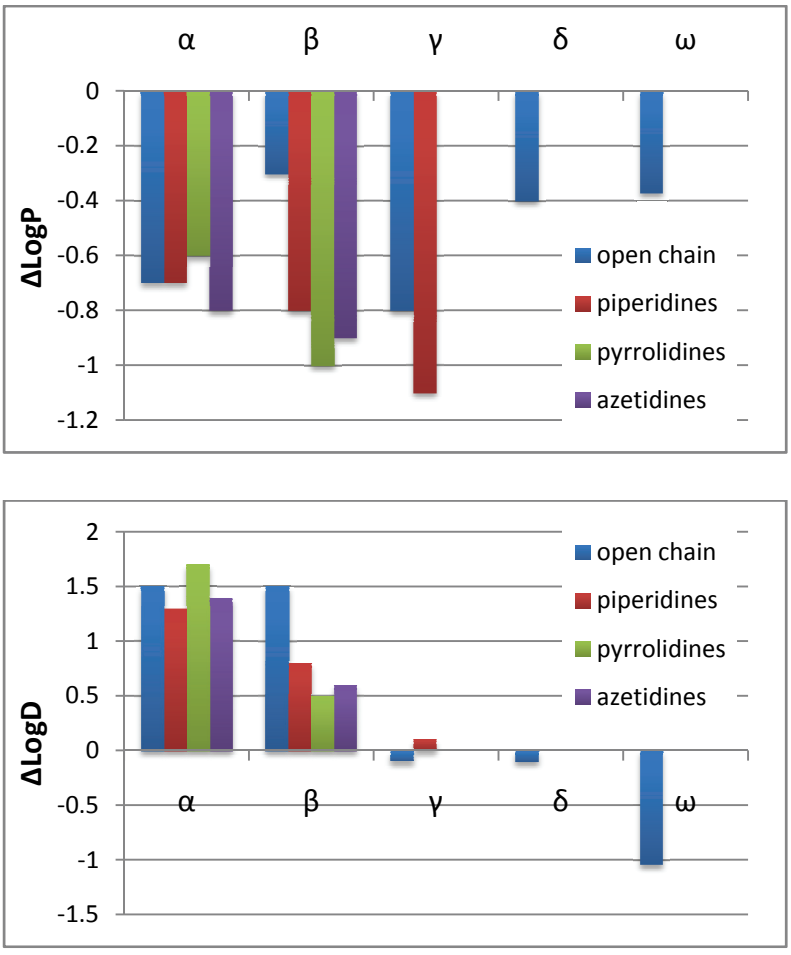


Diagram 12: Change in lipophilicity upon integration of an oxetane.

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 pK_a), 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 pK_a 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 pK_a 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.
[305] E. H. Kerns, L. Di, *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo, **2008**. p. 56.

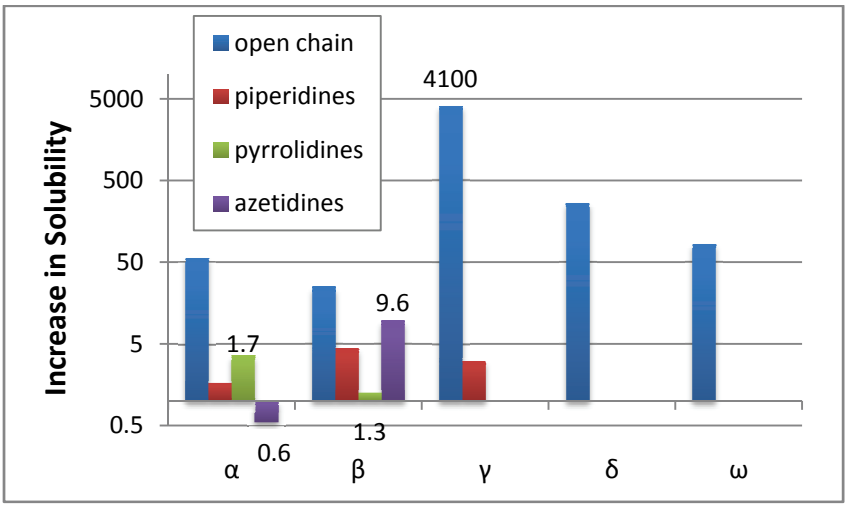


Diagram 13: Factor by which aqueous solubility at pH 9.9 increases upon replacement of a methylene group with an oxetane.

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 oxtetane and *vice versa*. This is evidenced also by the unexpectedly low pK_a 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 pK_a 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]

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

[306] For a broader discussion of biotransformation reactions, see: J. Magdalou, S. Fournel-Gigleux, B. Testa, M. Ouzzine, M. Nencki, in *Practice of Medicinal Chemistry (2nd Edition)*, **2003**, pp. 517.

active site.[307] Main purpose of oxidative metabolism is to make molecules more water soluble for excretion. Therefore, these enzymes have an evolutionary preference for lipophilic molecules.[308] This correlation is also found for the oxetane-containing compounds measured in this study.

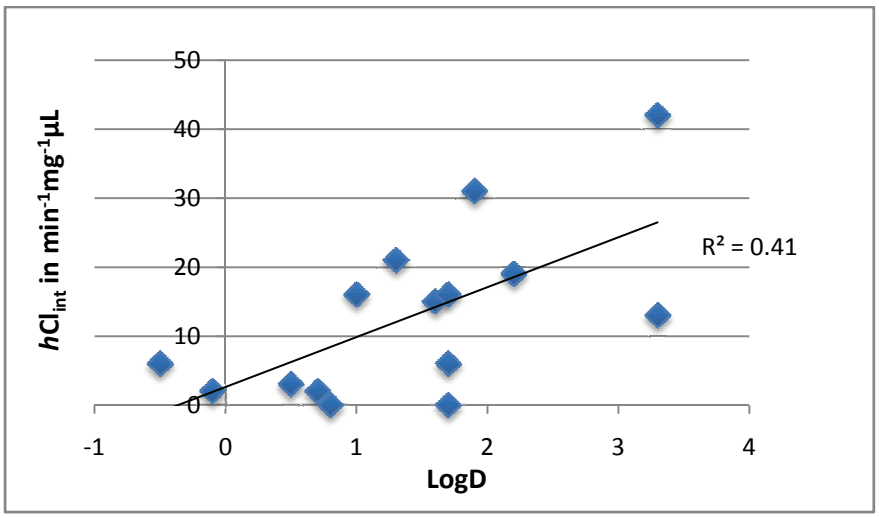


Diagram 14: Correlation of LogD and hCl_{int} for the oxetanes in this study.

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.

[307] E. H. Kerns, L. Di, *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo, **2008**. p. 139.
[308] F. J. Gonzalez, D. W. Nebert, *Trends Genet.* **1990**, *6*, 182.

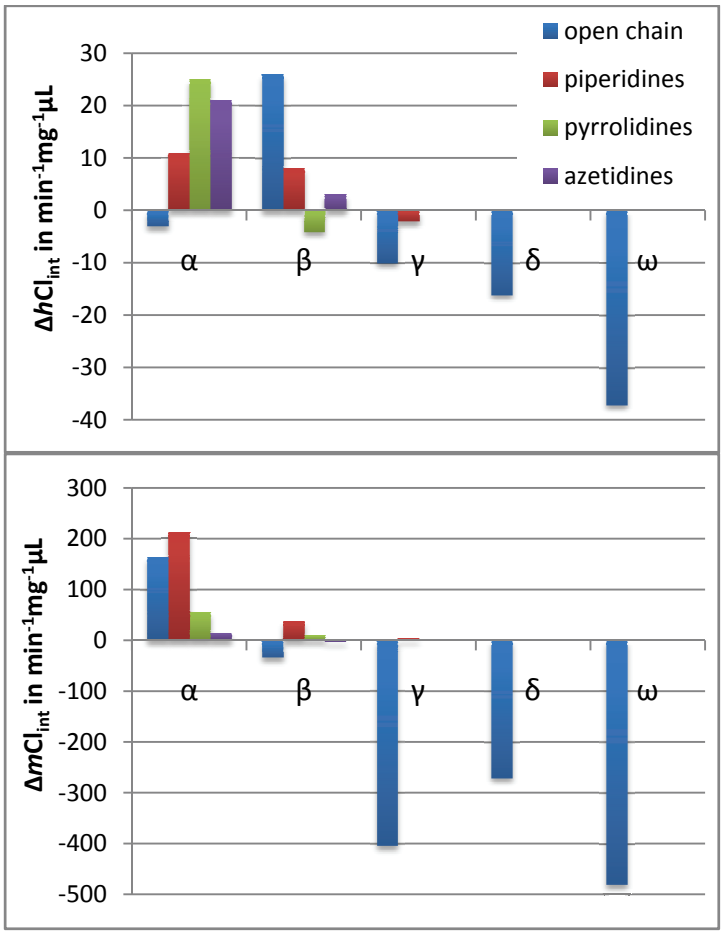


Diagram 15: Change in intrinsic clearance upon exchange of a methylene group with an oxetane.

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.

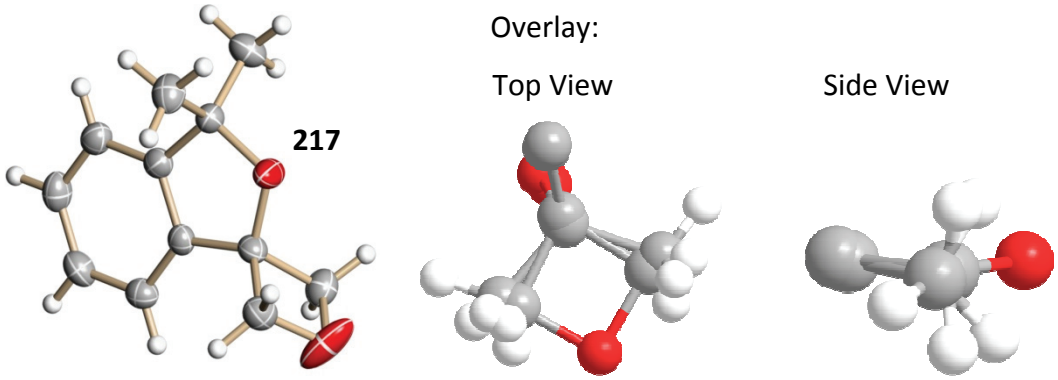
The presence of an oxetane changes the physicochemical properties of the underlying scaffold in many ways. When compared with a methylene group, in most cases, the oxetane effects a decrease in intrinsic lipophilicity and often a dramatic increase in aqueous solubility. Attention should be paid to the structural context. The strong electron-withdrawing nature of the oxetane not only tempers the pK_a 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.[309] The x-ray structure of spirocycle **217** allows a side-by-side comparison of the oxetane and the *gem*-dimethyl moiety.



*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.

[309] Oxetane has a partial molar volume of 61.4 cm^3/mol (J. C. Moore, R. Battino, T. R. Rettich, Y. P. Handa, E. Wilhelm, *J. Chem. Eng. Data* **1982**, *27*, 22.). Propane has a partial molar volume of 70.7 cm^3/mol (J. T. Edward, P. G. Farrell, F. Shahidi, *J. Chem. Soc. Lond. Faraday Trans. 1* **1977**, *73*, 705.).

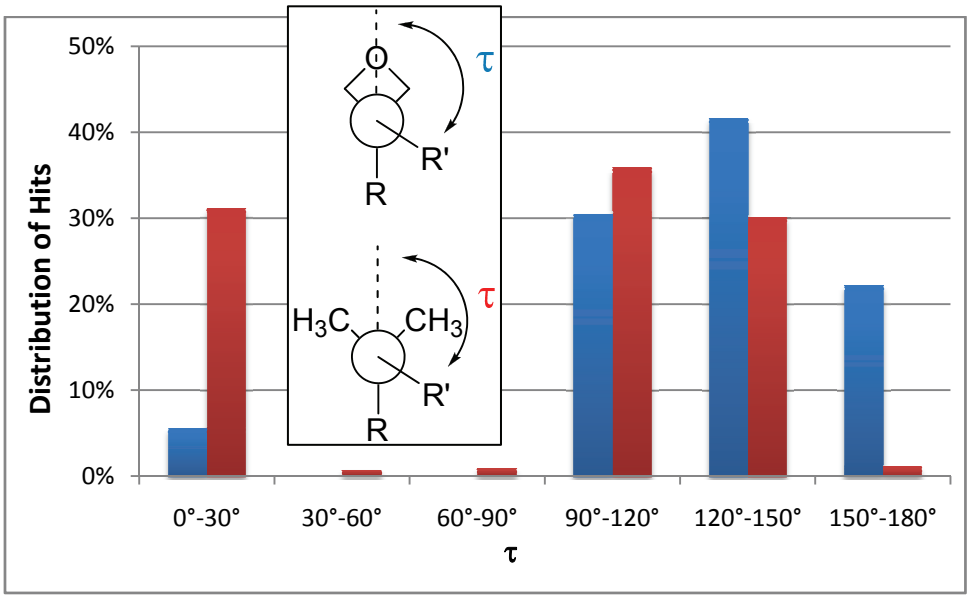
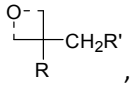


Diagram 16: Arrangements of CH_2–R' relative to an oxetane or a gem-dimethyl.[310]

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 

, R, R' ≠ H.

[311] The respective substituents on the 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.

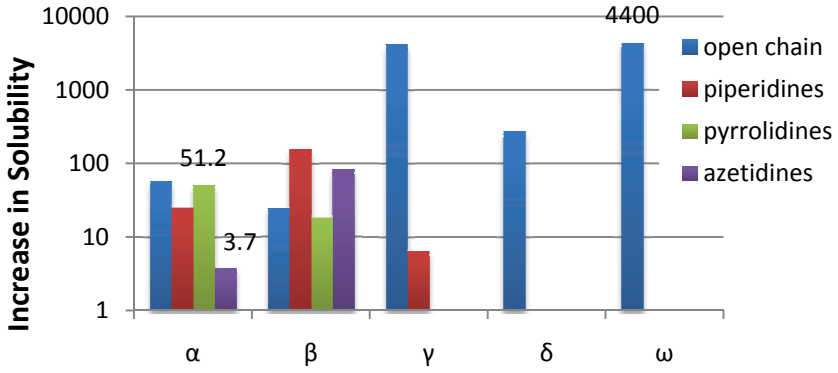


Diagram 17: Increase in solubility when replacing a gem-dimethyl group with an oxetane.

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.

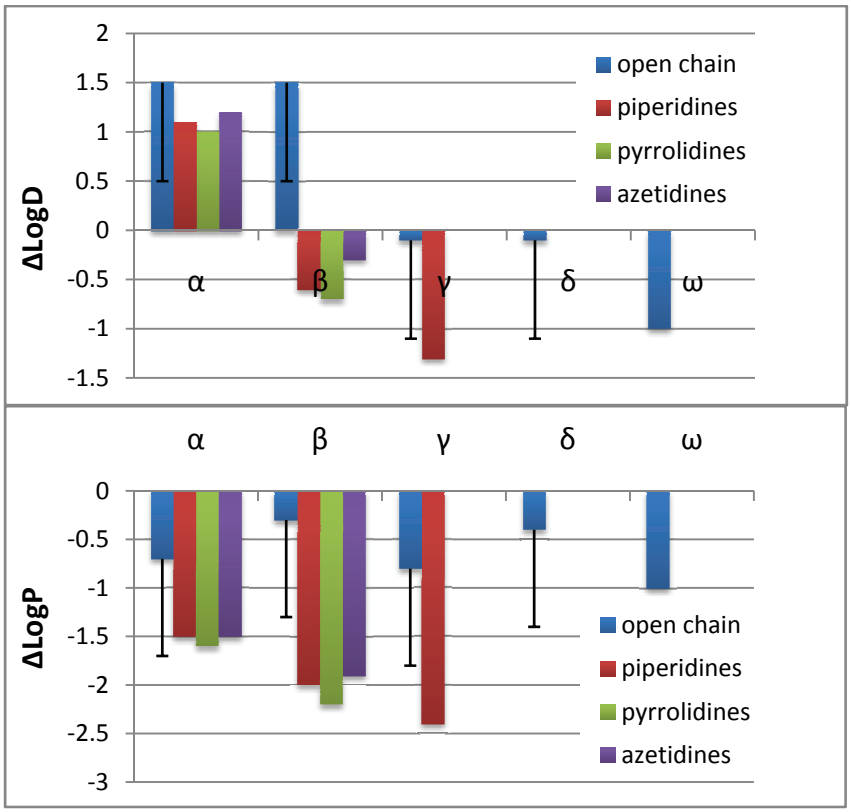


Diagram 18: Change in lipophilicity LogP upon replacement of a gem-dimethyl group with an oxetane.[312]

[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.[304] 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.

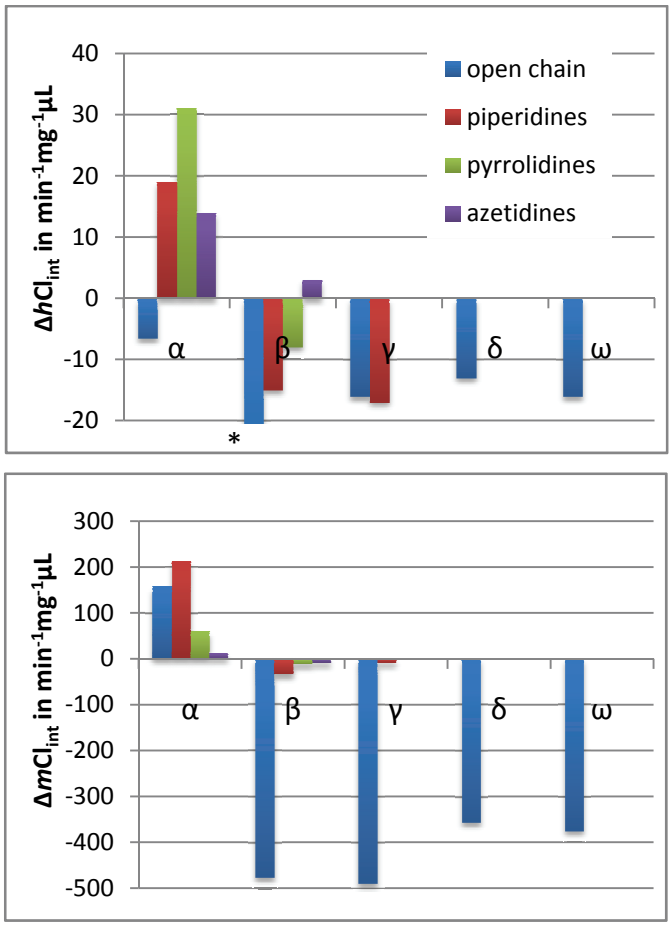


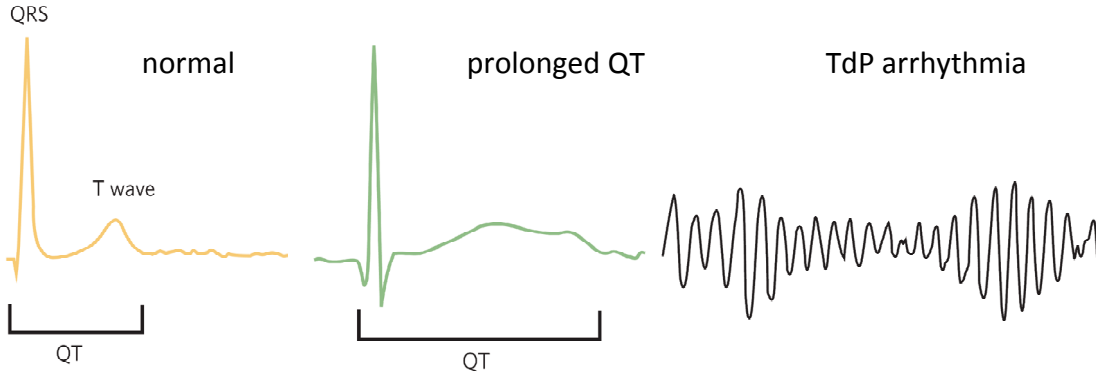
*Diagram 19: Change in the rate of metabolic degradation upon replacement of a gem-dimethyl group with an oxetane. *(gem-dimethyl compound was completely degraded in assay)*

diagram. 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.[313]

4.2.4 hERG-Channel

The **h**uman **E**ther-a-go-go **R**elated **G**ene (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).[314] This can together with other risk factors cause life-threatening torsades de pointes (TdP) arrhythmia:[315]



Picture 16: Normal ECG (left), an ECG showing a prolonged QT-interval (middle) and an ECG of torsades de pointes arrhythmia (right).[316]

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

[313] 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 $min^{-1}mg^{-1}\mu L$.
[314] M. C. Sanguinetti, M. Tristani-Firouzi, *Nature* **2006**, *440*, 463.
[315] M. C. Sanguinetti, J. S. Mitcheson, *Trends Pharmacol. Sci.* **2005**, *26*, 119.
[316] Taken from Ref. 314 with permission.

arrhythmia, hERG blocking has become one of the leading causes for market withdrawal or use restrictions imposed by the FDA.[317]

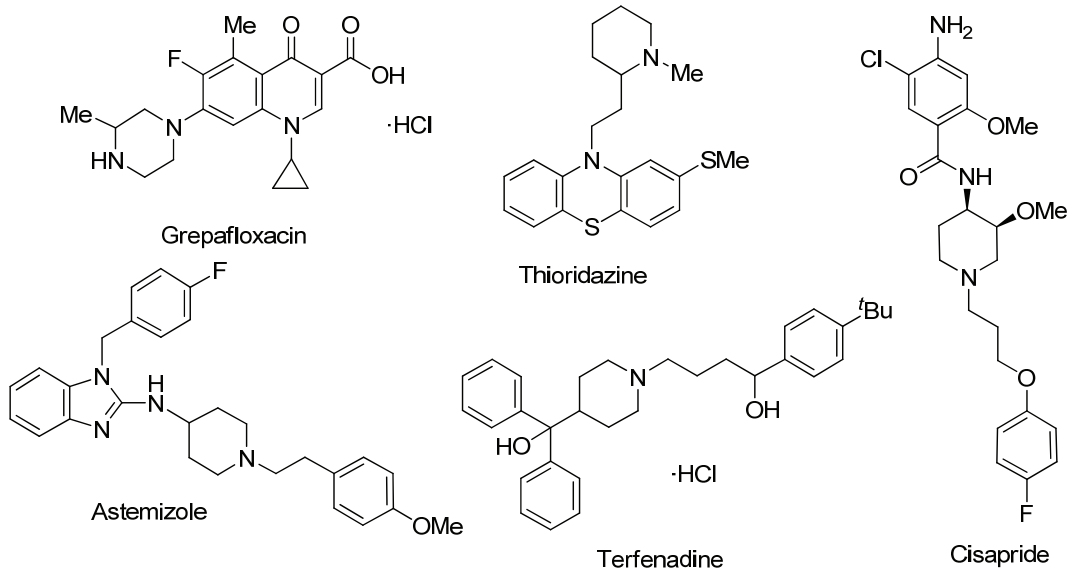
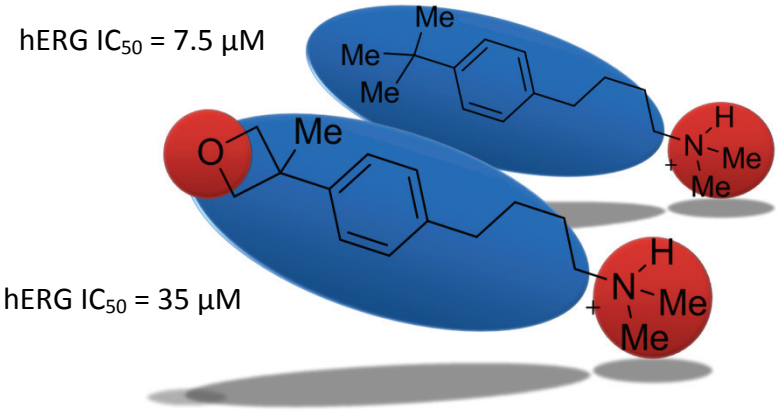


Figure 15: Drugs that were withdrawn or experienced major labeling restrictions due to hERG blocking.

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

[317] E. H. Kerns, L. Di, *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo, **2008**. p. 209.
[318] P. K. Honig, D. C. Wortham, K. Zamani, D. P. Conner, J. C. Mullin, L. R. Cantilena, *JAMA, J. Am. Med. Assoc.* **1993**, *269*, 1513.
[319] see Ref. 317 and Ref. 315



Picture 17: Change in hERG binding upon replacement of a gem-dimethyl group with an oxetane.[320]

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.[321]

4.2.5 Amphiphilicity and Phospholipidosis

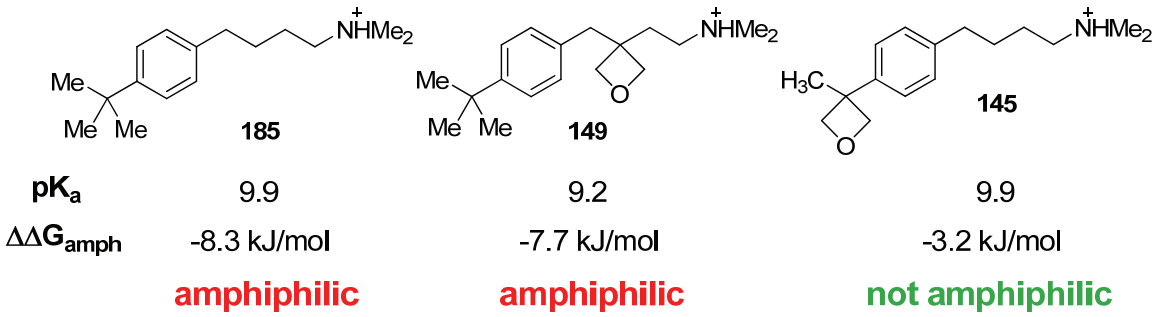
Molecules that combine a large nonpolar residue with a highly hydrophilic, often charged tail are termed amphiphilic. Cationic amphiphilic drugs can induce the accumulation of phospholipids in lysosomes; an event that has been connected to cell toxicity.[322] Different mechanisms have been proposed to 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.[323] 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.[324]

[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.
[322] For reviews, see: a) N. Anderson, J. Borlak, *FEBS Lett.* **2006**, *580*, 5533. b) M. J. Reasor, *Toxicol. Appl. Pharmacol.* **1989**, *97*, 47. c) W. H. Halliwell, *Toxicol. Pathol.* **1997**, *25*, 53.
[323] P. Vitovic, J. M. Alakoskela, P. K. J. Kinnunen, *J. Med. Chem.* **2008**, *51*, 1842.
[324] For a detailed description, refer to: H. Fischer, M. Kansy, D. Bur, *Chimia* **2000**, *54*, 640.

$$\Delta\Delta G_{amph} = \Delta G_{awi-w} - \Delta G_{mc-w}$$

Equation 18: $\Delta\Delta G_{amph}$ 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 $\Delta\Delta G_{amph}$ 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.



Picture 18: Introduction of an oxetane in the lipophilic part of the molecule reduces $\Delta\Delta G_{amph}$ below the critical threshold.[325]

Whereas amine **185** is highly amphiphilic, $\Delta\Delta G_{amph}$ 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 $\Delta\Delta G_{amph}$ 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.

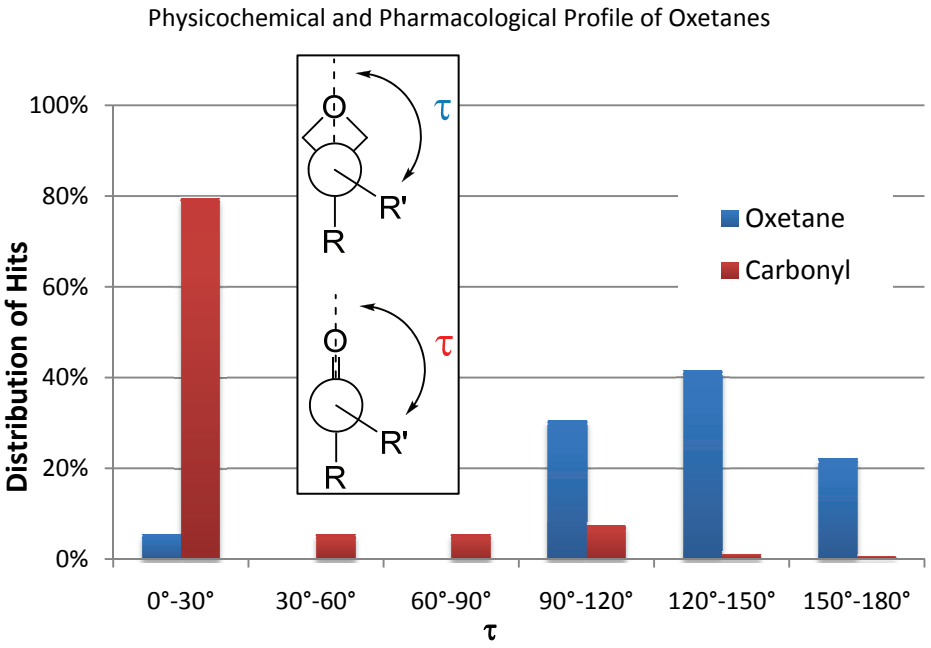


Diagram 20: Arrangements of CH_2–R' relative to an oxetane or a carbonyl.[326]

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.

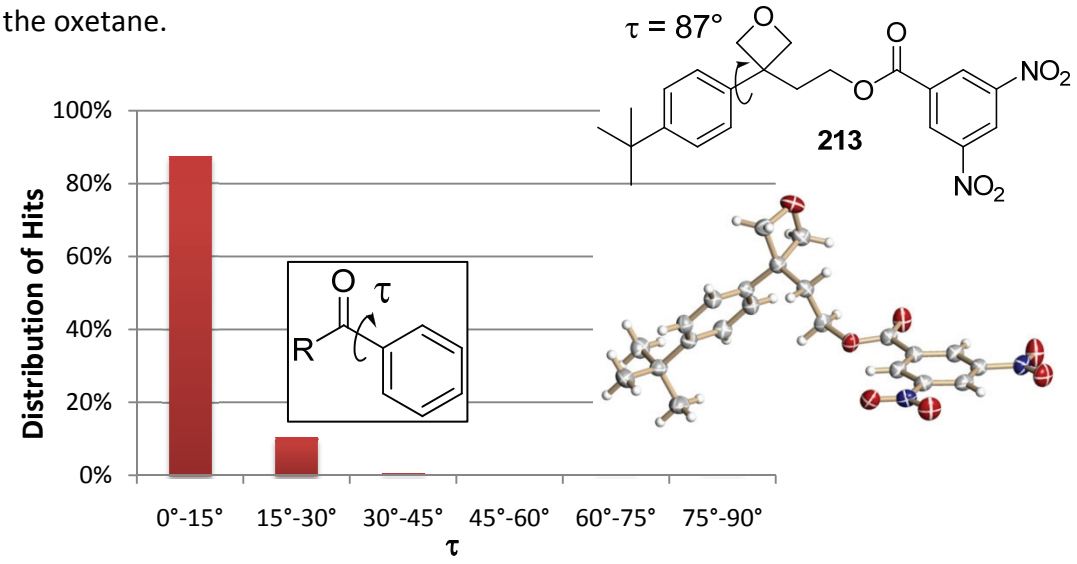
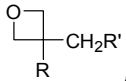


Diagram 21: Rotative arrangement of a phenyl ring with respect to a carbonyl and oxetane ***213****.*[327]

[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.[328]

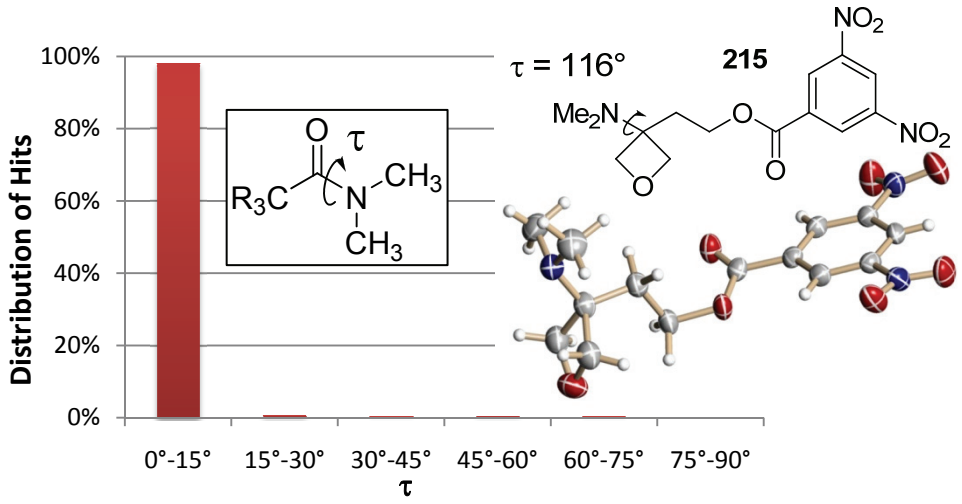


*Diagram 22: Conformational preference for rotation around an amide bond and what is found in oxetane analogue **215**.*[329]

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.

4.3.2 Influence on pK_a

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

[328] Nonplanar amides have been made and shown to be very unstable when not protonated (K. Tani, B. M. Stoltz, *Nature* **2006**, *441*, 731.).
[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°.

Physicochemical and Pharmacological Profile of Oxetanes

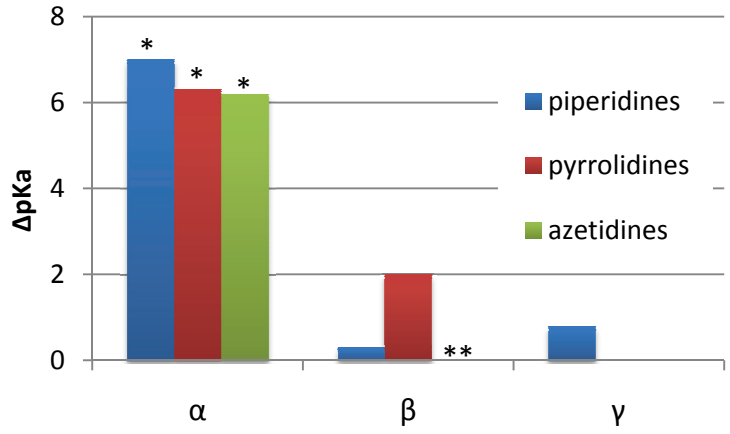


*Diagram 23: Change in pK_a upon replacement of a carbonyl group with an oxetane. *shown is the pK_a of the oxetane;*[330] **Azetidin-3-one **205** was not sufficiently stable to be purified and measured.*

Diagram 23 shows that the reduction of pK_a 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 pK_a 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 pK_a.

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 pK_a 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 pK_a-change to be expected when replacing an amide with an aminooxetane.

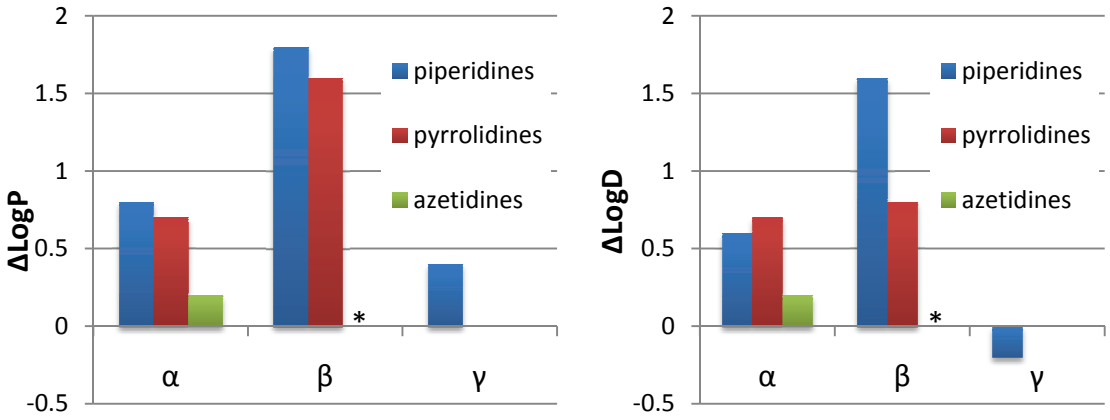


*Diagram 24: Change in LogP and LogD upon replacement of a carbonyl group with an oxetane. *Azetidin-3-one **205** was not sufficiently stable to be purified and measured.*

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]

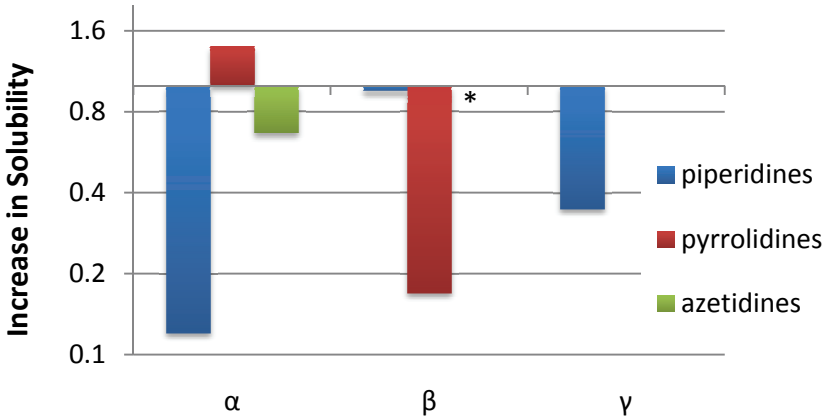


*Diagram 25: Change in solubility upon replacement of a carbonyl group with an oxetane. * Azetidin-3-one **205** was not sufficiently stable to be purified and measured.*

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.[332] 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.

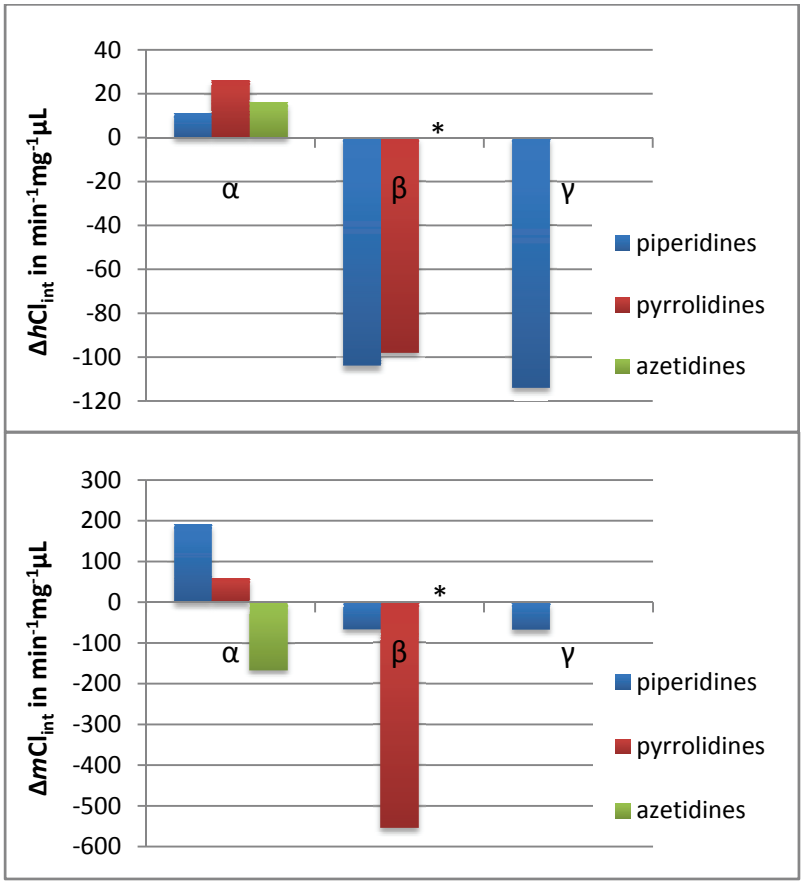


*Diagram 26: Change in rate of metabolic degradation upon replacement of a carbonyl group with an oxetane. * Azetidin-3-one **205** was not sufficiently stable to be purified and measured.*

[332] 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: $\log(S) = 0.8 - \text{LogP} - 0.01(m_p - 25)$ 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.[333]

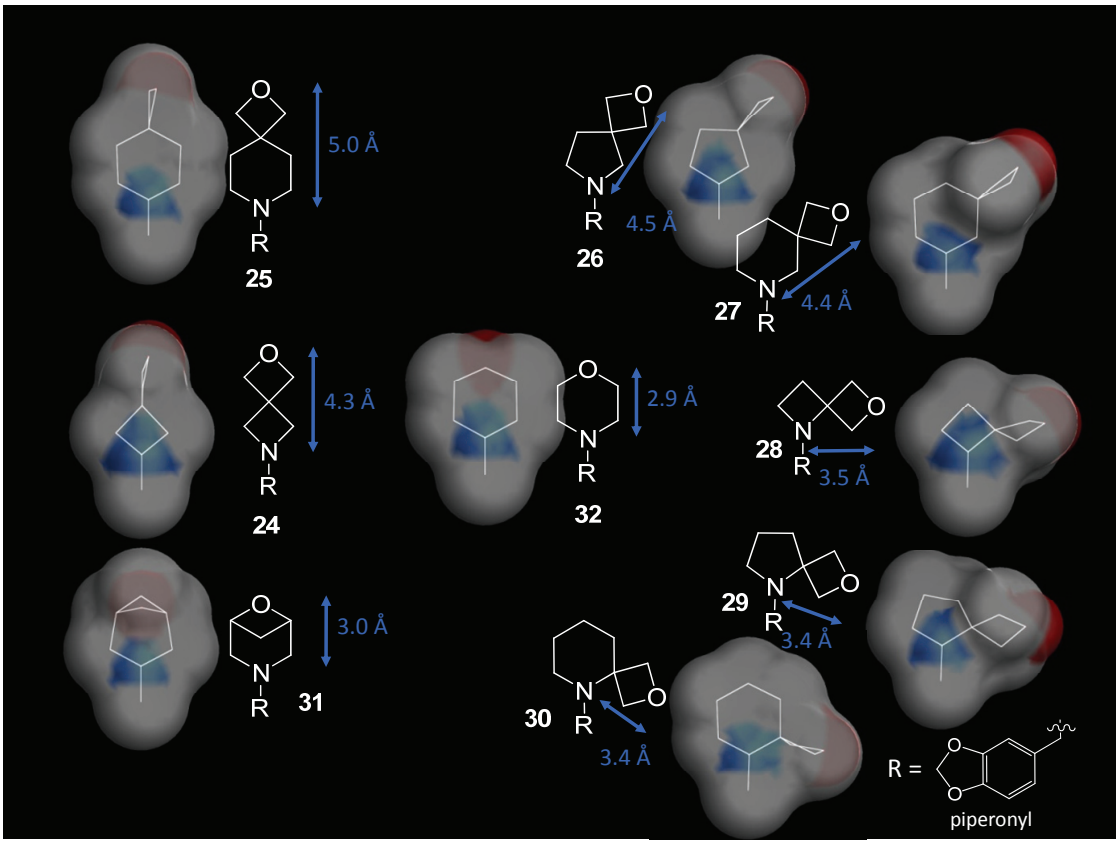
The replacement of a carbonyl group with an oxetane can lead to significant changes in the conformational preference, basicity, lipophilicity and metabolic stability of the underlying scaffold. The introduction of an oxetane in place of a carbonyl group seems to be attractive in situations where the 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.

[333] At ambient temperature, decomposition occurs in less than one day.



*Picture 19: Spatial distribution of polar and apolar groups in morpholine **32** and its spirocyclic oxetane analogues **24** to **31**.*[334]

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.

[334] Calculation of van-der-Waals surfaces done by Prof. Klaus Müller with Moloc (P. R. Gerber, K. Mueller, *J. Comp-Aided. Mol. Design* **1995**, *9*, 251; for further information, see *www.moloc.ch).*

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.

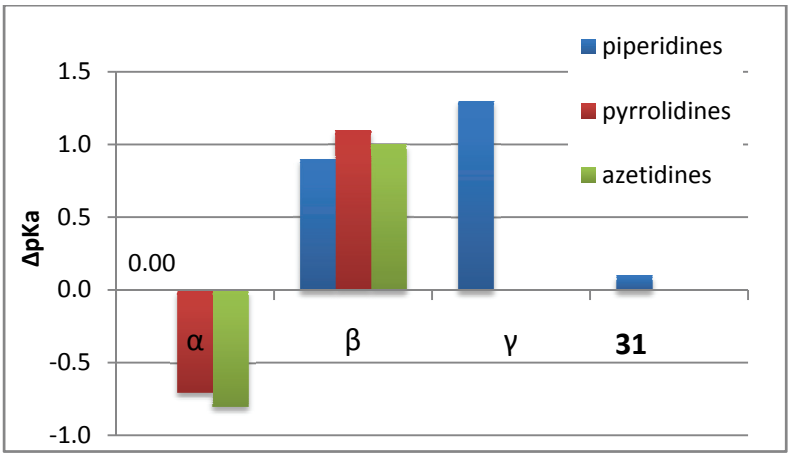


*Diagram 27: Change in pK_a upon replacement of morpholine **32** with an oxetane.*

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]

[335] See chapter 4.1.2 for detailed treatment.
[336] See chapter 4.1.3 and footnote 304 for detailed treatment.

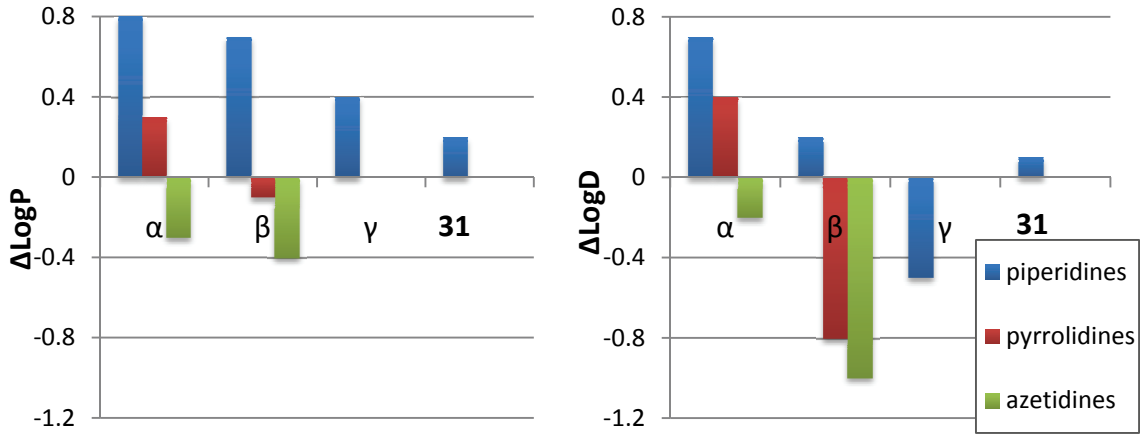


*Diagram 28: Change in lipophilicity upon replacement of morpholine **32** with an oxetane.*

For LogD, pK_a 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.

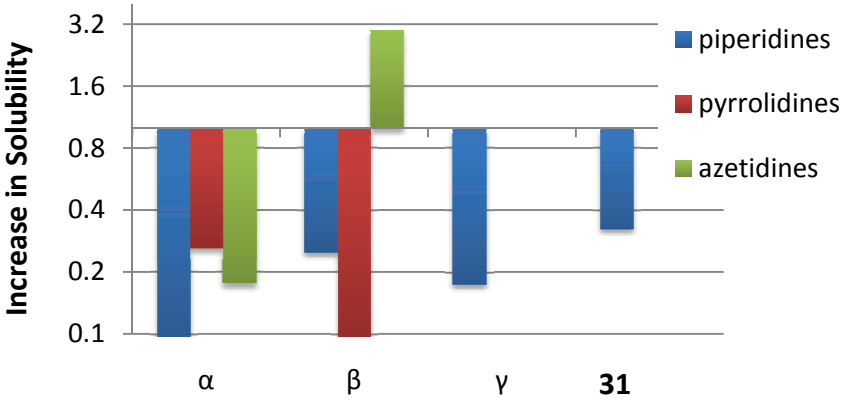


*Diagram 29: Change in aqueous solubility at pH 9.9 upon replacement of morpholine **32** with an oxetane.*

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.

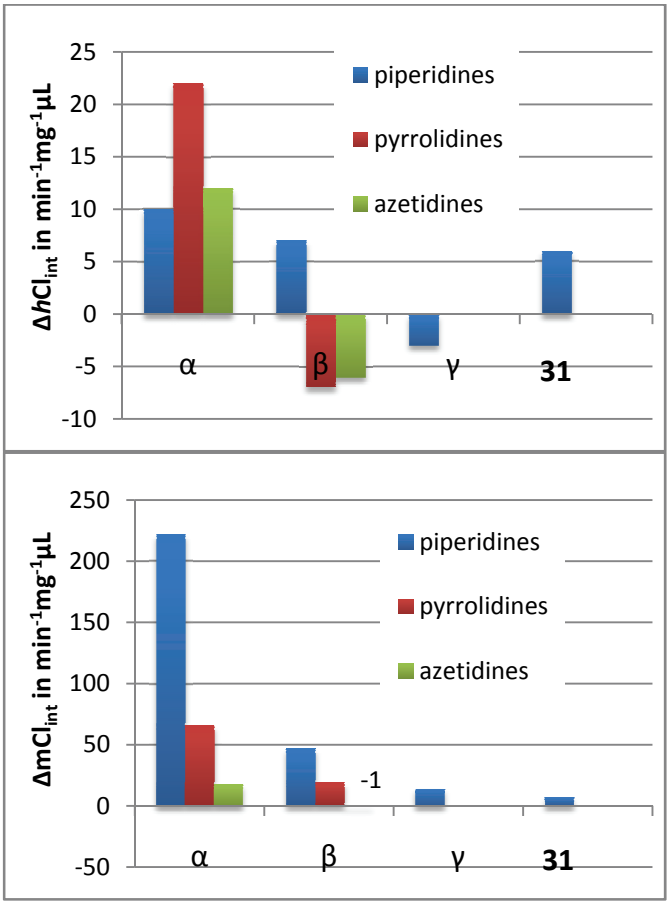


Diagram 30: Change in internal clearance upon replacement of morpholine with a spirocyclic oxetane.

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]

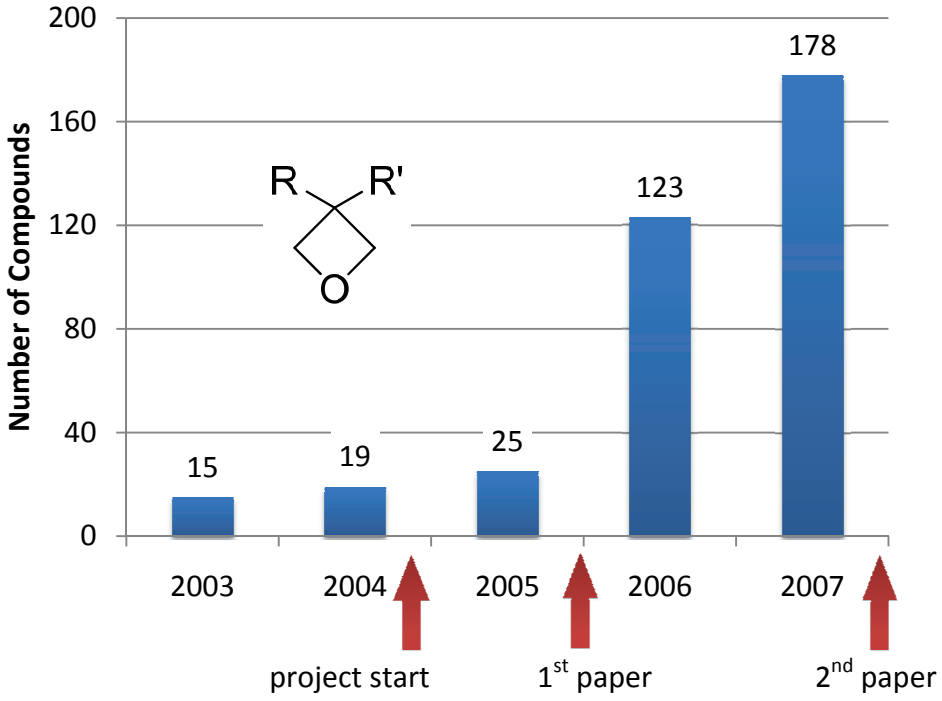


Diagram 31: Number of compounds that contain a 3-substituted oxetane within the global Roche database.[339]

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 paper[340] together with presentations in front of Roche chemists led to a surge of requests by mail concerning oxetane chemistry and registration

[338] A few patents have appeared that cover oxetane-containing structures and use chemistry starting from oxetan-3-one. These however do not present significant information on how successful the integration of an oxetane was compared with other measures taken. Patents of Roche: a) S. Jolidon, R. Narquizian, R. D. Norcross, E. Pinard, 2006-EP761, **2006**. b) G. Galley, A. Goergler, K. Groebke Zbinden, R. Norcross, H. Stalder, 2007-EP60666, **2008**. c) J. Ackermann, K. Amrein, D. Hunziker, B. Kuhn, A. V. Mayweg, W. Neidhart, T. Takahashi, 2007-EP60667, **2008**. Patent outside Roche: a) H. Meier, E. Bender, U. Brueggemeier, I. Flamme, D. Karthaus, P. Kolkhof, D. Meibom, D. Schneider, V. Voehringer, C. Fuerstner, J. Keldenich, D. Lang, E. Pook, C. Schmeck, 2007-EP4615, **2007**.

[339] Private communication from Dr. Mark Rogers-Evans.

[340] G. Wuitschik, M. Rogers-Evans, K. Müller, H. Fischer, B. Wagner, F. Schuler, L. Polonchuk, E. M. Carreira, *Angew. Chem., Int. Ed.* **2006**, *45*, 7736.

of the resulting compounds in the database. The second paper[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.[342]

Picture 20: Companies that have shown interest in and/or applied the oxetane chemistry in projects.[343]

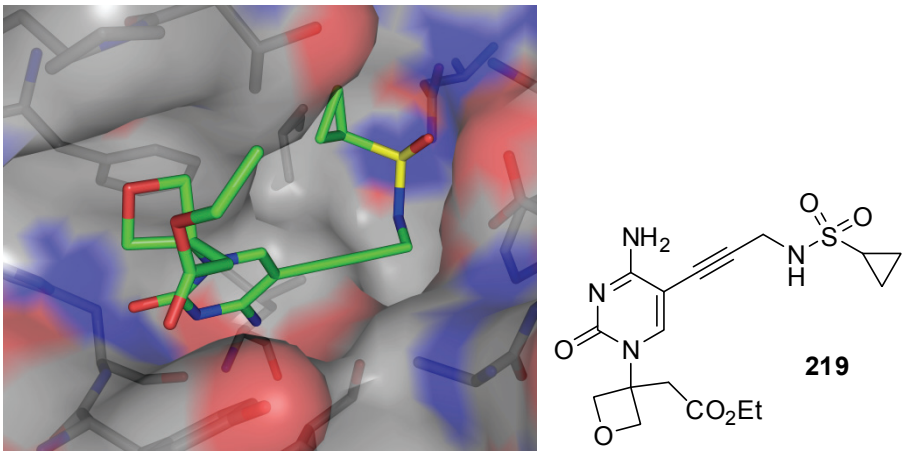
Oxetanes have also been applied by Anna Hirsch from the group of Prof. Diederich in the design of inhibitors of 4-diphosphocytidyl-2*C*-methyl-D-erythritol kinase (IspE), an enzyme of central importance to the isoprenoid biosynthesis via the non-mevalonate pathway in human pathogens such as *Plasmodium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

[341] G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Märki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller, E. M. Carreira, *Angew. Chem., Int. Ed.* **2008**, *47*, 4512.

[342] Oxetan-3-one is now commercially available through MolBridge, Research Support International Ltd. and Parkway Scientific.

[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. Duncton, M. A. Estiarte, D. Tan, C. Kaub, D. J. R. O'Mahony, R. J. Johnson, M. Cox, W. T. Edwards, M. Wan, J. Kincaid, M. G. Kelly, *Org. Lett.* **2008**, *10*, 3259).

[344] A. K. H. Hirsch, M. S. Alphey, S. Lauw, M. Seet, L. Barandun, W. Eisenreich, F. Rohdich, W. N. Hunter, A. Bacher, F. Diederich, Org. Biomol. Chem. **2008**, *in print*, DOI: 10.1039/b804375b.



*Picture 21: Oxetane **219** cocrystallized with Aquifex aeolicus IspE*[344]

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.[345] Picture 21 shows a crystal structure of oxetane **219** bound to IspE.

[345] 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.

Conclusion and Outlook

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 (H_2O content < 30 ppm as determined by Karl-Fischer titration).[346] Et_2O was distilled from a mixture of $FeSO_4 \cdot 7\ H_2O$ and Na_2SO_4 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. NEt_3, 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 $BF_3 \cdot OEt_2$ 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 F_{254} 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.[347] 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-

[346] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
[347] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

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 (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 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 (log$D^{pH=7.4}$): 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_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_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 (SIRIUS 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 CO_2. 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), $MgCl_2$ (10 mM), EDTA (1 mM), $NADP^+$ (2 mM), glucose-6-phosphate·2 H_2O (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 XTerra® MS C18 column (1 mm·50 mm) and a Sciex API 2000 mass spectrometer. A two-component mobile phase, pumped at 0.15 mL/min, contained the following solvents: solvent A (1% aqueous formic acid and

MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. The intrinsic clearance (Cl_{int}) was determined in semi-logarithmic plots of compound concentrations *versus* time.

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.

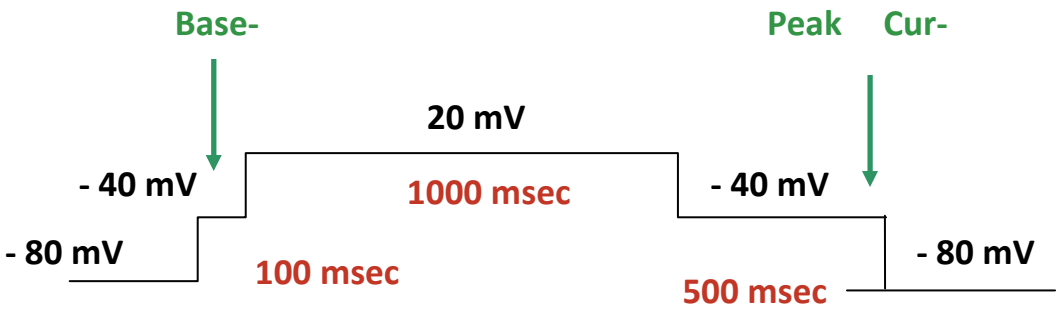
Measurement of amphiphilicity *via* the measurement of surface tension: An aqueous solution of the compound of known concentration at the limit of its solubility is diluted 1:1 (v/v) with aqueous MOPSO buffer 11 times in sequence. Samples of 5 µL of compound solution are taken at each dilution step and transferred to a 96-well plate containing 45 µL pure aqueous MOPSO 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.[348]

Automated patch clamp procedure for the hERG current measurement at Patch-Xpress 7000A: Electrophysiologcal recordings of K^+ currents (IK_{hERG}) were conducted at room temperature (22-25 °C) using Aviva Bioscience *Seal*Chip$_{16}$™ (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 mV and they were stimulated by a voltage pattern to activate hERG channels and conduct outward IK_{hERG} current (Figure 1) at a stimulation frequency of 0.1 Hz (6 bpm). Cell health and membrane parameters (access resistance (Ra), membrane resistance (Rm) and membrane capacitance (Cm)) were monitored online. After the cells stabilized and the currents were steady, the amplitude and kinetics of IK_{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 IK_{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.

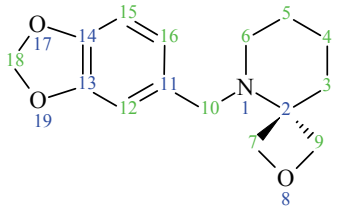
[348] H. Fischer, M. Kansy, D. Bur, *Chimia* **2000**, *54*, 640.



NMR spectroscopic analysis of *N*-piperonyl-piperidine 30[349]

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)

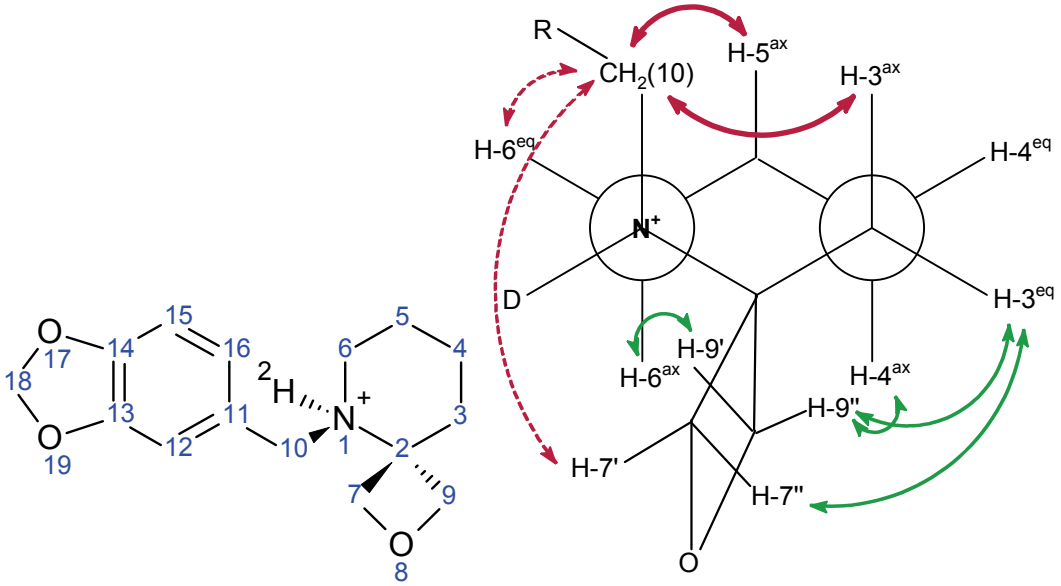
2) DCl salt of Oxetane **30**

The DCl salt form of **30** was produced by dissolving **30** in a mixture of D_2O and DCl (0.4 mL D_2O 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

[349] 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).



*Structure of deuterated oxetane **30** and stereochemical assignments of protons based on observed NOE's (green: NOE's identifying the oxetane protons; red: NOE'sdetermining 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).*

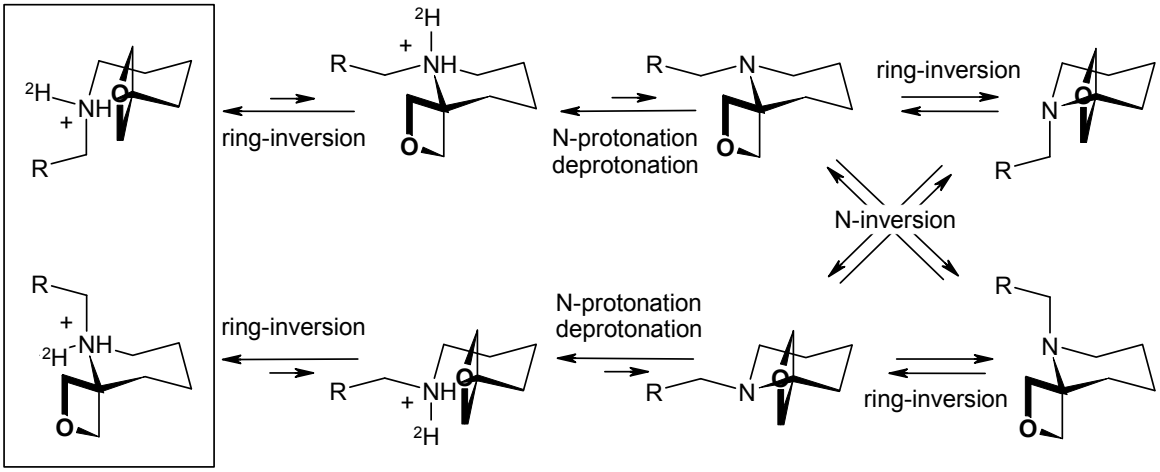
^{1}H NMR (400 MHz, D_2O/DCl*; d_4-TSP = 0 ppm*) δ ppm 1.62 (m, 1 h, H-4ax) 1.68 (m, 1 h, H-5equiv) 1.84 (m, 1 h, H-4equiv) 2.00 (m, 1 h, H-5ax) 2.29 (dt, *J* = 15.0, 4.3 Hz, 1 h, H-3equiv) 2.36 (td, *J* = 15.0, 1.3 Hz, 1 h, H-3ax) 3.09 (ddd, *J* = 13.7, 11.6, 3.5 Hz, 1 h, H-6ax) 3.14 (dt, *J* = 13.7, 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 CH_2-10 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 CH_2-10 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.

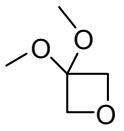


The observation of only one set of ^{1}H-signals in the NMR-spectrum of deuterated oxetane **30** with well separated and sharp signals for the equatorial and axial protons is clear evidence for the predominance of the chair conformation with an axial N-piperonyl substituent. Furthermore, the clear differentiation 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 ºC 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 *p*TSA (377 mg, 1.98 mmol, 0.00375 equiv) at room temperature.

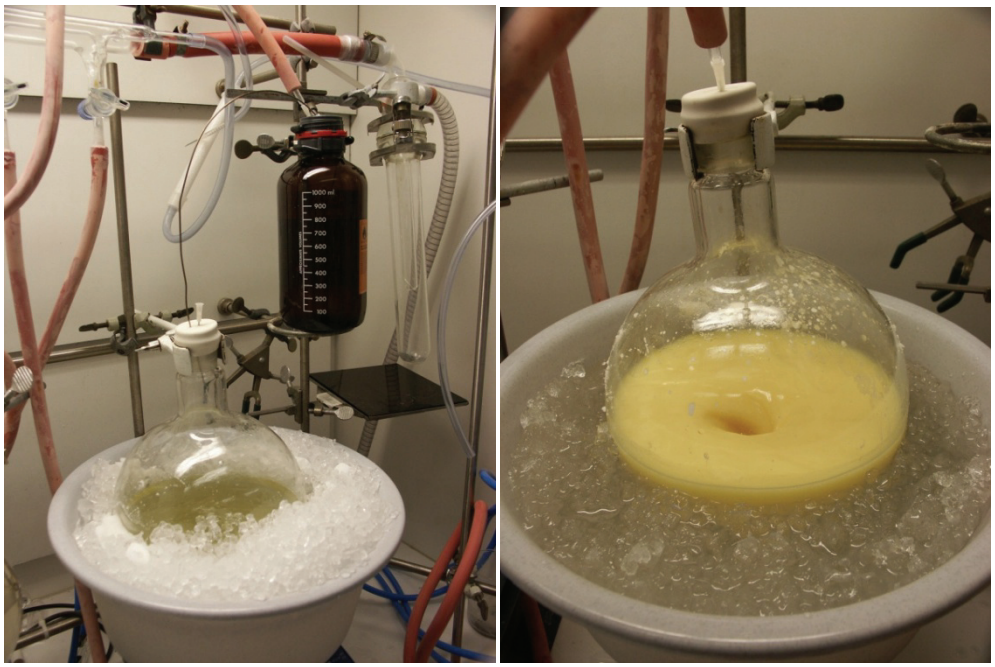
Picture 22: Clarification of mixture upon addition of pTSA. It is important that the solution becomes clear. Undissolved material or turbidity indicates that the qualityof the di-hydroxyacetone dimer used is not good and problems might result in the following step.

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.[350]

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.

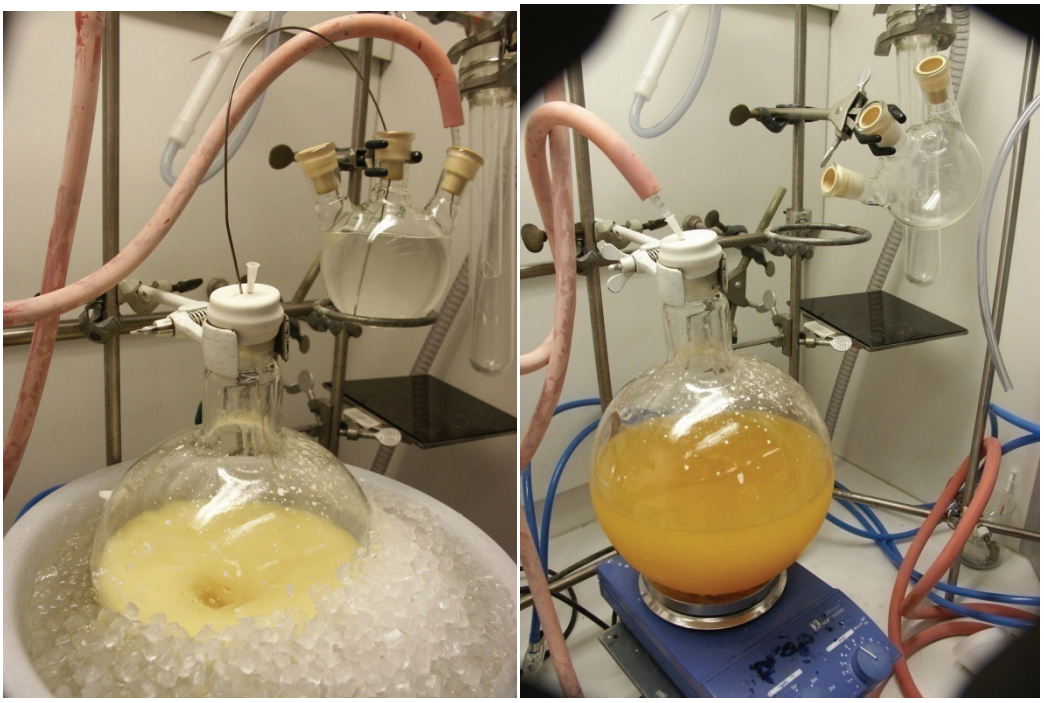
This material was dissolved in 1.5 L of a 2/1 mixture of THF (Acros, p.a.) and Et_2O (Fluka, puriss.) and cooled to 0 °C. A 2.5 M solution of ^{n}BuLi in hexanes (400 mL, 1.00 mol, 1.91 equiv, Acros) was added slowly over 45 min using a transfer cannula.

[350] Following a known procedure: a) F. Charmantray, L. El Blidi, T. Gefflaut, L. Hecquet, J. Bolte, M. Lemaire, *J. Org. Chem.* **2004**, *69*, 9310. b) E. L. Ferroni, V. DiTella, N. Ghanayem, R. Jeske, C. Jodlowski, M. O'Connell, J. Styrsky, R. Svoboda, A. Venkataraman, B. M. Winkler, *J. Org. Chem.* **1999**, *64*, 4943.



Picture 24: The solution of the dihydroxyacetone dimethyl ketal in THF should be clear. Upon addition of ^{n}BuLi, 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.



Picture 25: 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 Et_2O.

Brine was added and the aqueous phase extracted with Et_2O (400 mL) twice. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* until all Et_2O 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 H_2-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.)

Picture 27: 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_2O and poured on ice. The aqueous phase was saturated with NaCl and extracted with Et_2O (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

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 Et_2O over night.

R_f = 0.41 (hexane/EtOAc 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (s, 4H), 3.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 100.6, 79.8, 49.4; IR (thin film) ν 2954, 2878, 2835, 1473, 1716, 1453, 1352, 1204, 1134, 1044, 980 cm^{-1}; Anal. calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 51.07; H, 8.45;

Oxetan-3-one: 3,3-dimethoxyoxetane (15.8 g, 0.134 mol) was dissolved in 7 L CH_2Cl_2 (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.

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_2Cl_2. The CH_2Cl_2 was removed from the filtrate by distillation employing a 30 cm Vigreux column to prevent product from distilling over.

Picture 29: Distillation of ~ 9 L CH_2Cl_2 should take ~7 h. If an unstirred oil bath is employed, a temperature of 100 °C had to be used to get to these distillation rates. When using an oil bath the level of the oil should be adjusted to the one inside the flask. Also, towards the end of the distillation, the oil bath temperature should be reduced as well as the power output of the heating mantle.

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_2Cl_2. The material should be stored in the freezer, where the neat compound solidifies (m_p = ~–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, $CDCl_3$): δ 5.40 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ.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_2Cl_2 is removed at ambient pressure with vigorous stirring and boiling chips added in an oil-bath of 62 °C. Once no more CH_2Cl_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

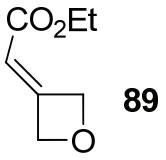
Phosphorous pentoxide (184.5 g, 1.300 moles, 1.300 equiv) was suspended in 600 mL CH_2Cl_2. Glassware need not be previously dried, the reaction is not air-sensitive. This suspension was cooled in an ice/salt-bath to a temperature below 0 °C, before DMSO (106 mL, 1.50 moles, 1.50 equiv) was added followed 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_2O 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 Et_2O. 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% CH_2Cl_2. 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.

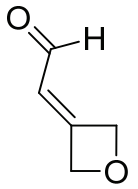
6.3 Preparation of Michael Acceptors



89

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 CH_2Cl_2 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.

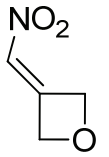
R_f = 0. 0.33 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.47 (m, 2H), 5.27 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 159.3, 111.3, 81.2, 78.6, 60.5, 14.4; IR (thin film) ν 2983, 2927, 2858, 1722, 1698, 1446, 1372, 1346, 1298, 1266, 1206, 1100, 1038, 961, 870, 833 cm^{-1}; Anal. calcd for $C_7H_{10}O_3$: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98.



90

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 over night 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); ^{1}H 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); ^{13}C 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 (EI) calcd for $C_5H_6O_2$ $[M]^+$ 98.0368. Found: 98.0359

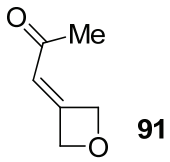


96

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 CH_2Cl_2. The mixture was cooled to –78 °C, NEt_3 (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 Et_2O /pentane = 1/1 to give 243 mg (81% yield) of product as a white solid (m_p = 41-43 °C).

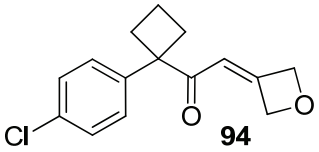
R_f = 0.28 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (m, 1H), 5.66 (m, 2H), 5.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 130.0, 79.6, 75.5; IR (thin film) ν 3092, 2925, 2848, 1698, 1525, 1421, 1350, 1319, 1186, 1125, 960, 947, 904, 828, 777, 725 cm^{-1}; HRMS (EI) calcd for $C_4H_5NO_3$ $[M-H]^+$ 114.0186. Found: 114.0184.



91

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 CH_2Cl_2 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/Et_2O) to give 75 mg pure product as a colorless oil in 77% yield.

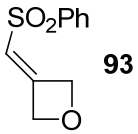
R_f = 0.16 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (m, 1H), 5.49 (m, 2H), 5.27 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 158.3, 118.0, 82.0, 78.9, 30.4; IR (thin film) ν 2923, 2855, 1724, 1709, 1694, 1672, 1651, 1431, 1366, 1198, 954 cm^{-1}; HRMS (EI) calcd for $C_6H_8O_2$ $[M]^+$ 112.0524. Found: 112.0519



94

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 (SiO_2, 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 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{15}ClO_2$ $[M]^+$ 262.0756. Found: 262.0752



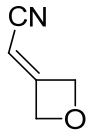
93

3-Benzenesulfonylmethylene-oxetane:[351] To a solution methylphenylsulfone (5.0 g, 32 mmol, 1.0 equiv) in 150 mL dry THF was added ^{n}BuLi (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.

45.1 mmol, 1.41 equiv) was added as a solution in 5 mL dry Et_2O. 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 (m_p = 51-53 °C).

R_f = 0.25 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, 2H, J = 7.8 Hz), 7.66 (m, 1H), 7.57 (t, 2H, J = 7.3 Hz), 6.12 (m, 1H), 5.64 (m, 2H), 5.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 140.6, 133.7, 129.3, 127.2, 119.9, 79.6, 77.9; IR (thin film) v 3057, 2923, 2856, 1692, 1445, 1324, 1303, 1147, 1085, 960, 872, 821, 755 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}O_3S$ $[M]^+$ 210.0351. Found: 210.0345

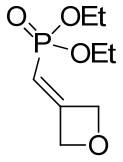


92

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 CH_2Cl_2 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/Et_2O) to give 235 mg pure product (82% yield) as slightly yellow crystals (m_p = 56-58 °C).

R_f = 0.30 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.39 (m, 2H), 5.30 (m, 2H), 5.25 (td, 1H, J = 2.5 Hz, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 114.0, 90.8, 78.6, 78.4; IR (thin film) v 3065, 3015, 3940, 2220, 1696, 1445, 1328, 1219, 943 cm^{-1}; HRMS (EI) calcd for C_5H_5NO $[M]^+$ 95.0371. Found: 95.0365

Experimental Section



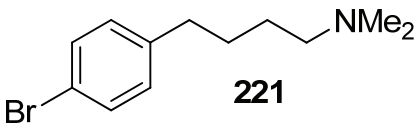
95

Diethyl oxetan-3-ylidenemethylphosphonate:[352] 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*, Et_2O and water were added and the aqueous phase extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 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 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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, $CDCl_3$): 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, $CDCl_3$): δ 15.8; IR (thin film) ν 3466, 2985, 1699, 1480, 1444, 1393, 1317, 1221, 1164, 1026, 871, 770 cm^{-1}; HRMS (EI) calcd for $C_8H_{15}O_4P$ $[M-H]^+$ = 205.0625. Found: 205.0624

[352] Procedure adapted from: R. D. Allan, J. R. Hanrahan, T. W. Hambley, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, *J. Med. Chem.* **1990**, *33*, 2905.

6.4 Preparation of Oxetanes of the Open-Chain Scaffold

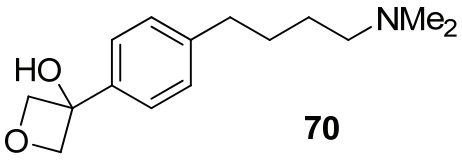


221

[4-(4-Bromo-phenyl)-butyl]-dimethyl-amine: To a suspension of the hydro bromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide[353] (12.2 g, 24.0 mmol, 1.00 equiv) in 150 mL dry THF was added ^{n}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_2O (50 mL) was added, followed by excess sodium hydroxide (with cooling) to free the amine. The aqueous phase was extracted three times with Et_2O, 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, $CDCl_3$): δ 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, $CDCl_3$): δ 141.3, 131.2, 130.1, 119.3, 59.6, 45.6, 35.3, 29.2, 27.4; IR (thin film) ν 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.

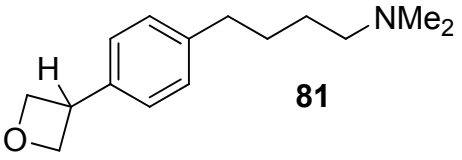
[353] Prepared according to: E. J. Corey, M. C. Desai, *Tetrahedron Lett.* **1985**, *26*, 5747.



70

3-[4-(4-Dimethylamino-butyl)-phenyl]-oxetan-3-ol: To a solution of [4-(4-Bromo-phenyl)-butyl]-dimethyl-amine (**221**, 0.89 g, 3.5 mmol, 1.3 equiv.) in 10 mL dry THF was added a solution of ^{n}BuLi (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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2; 10% to 40% MeOH in CH2Cl2, 0.1% NEt_3) to give 480 mg pure product (71% yield) as a viscous colorless oil which solidified upon cooling (m_p=57-58 °C).

R_f = 0.17 (SiO_2, 40% MeOH in CH_2Cl_2, 0.1% NEt_3); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) v 3373, 2940, 2859, 2780, 1467, 1175, 981 cm^{-1}; Anal. calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.13; H, 9.30; N, 5.54; HRMS (EI) calcd for $C_{15}H_{23}NO_2$ $[M]^{+}$, 249.1729. Found, 249.1723

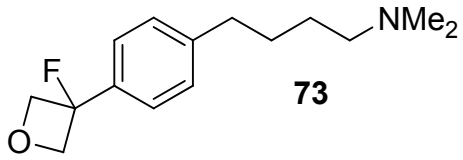


81

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 Et_2O 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, *p*TosCl (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 Et_2O) 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 Et_2O. The combined organic phases were washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 1/1 cyclohexane/EtOAc) to give 73 mg (58% yield) pure product as a colorless oil.

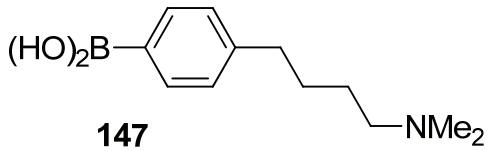
R_f = 0.44 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, J = 8.1 Hz), 7.18 (d, 2H, J = 8.0 Hz), 5.05 (dd, 2H, J = 5.9 Hz, J = 8.4 Hz), 4.77 (dd, 2H, J = 6.1 Hz, J = 6.7 Hz), 4.20 (m, 1H), 2.63 (m, 2H), 2.26 (m, 2H), 2.20 (s, 6H), 1.63 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 138.7, 128.7, 126.6, 79.1, 59.8, 45.7, 40.1, 35.5, 29.4, 27.6; IR (thin film) ν 2937, 2868, 2813, 2763, 1515, 1463, 983 cm^{-1}; Anal. calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98; HRMS (EI) calcd for $C_{15}H_{23}NO$ $[M]^+$, 233.1775. Found, 233.1776.



73

[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 CH_2Cl_2 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 Et_2O. The combined organic phases were washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 1/1 cyclohexane/EtOAc) to give 54 mg (40% yield) pure product as a colorless oil.

R_f = 0.43 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 5.08 (ddd, 2H, J = 1.1 Hz, J = 7.8 Hz, J = 21.2 Hz), 4.88 (ddd, 2H, J = 1.1 Hz, J = 7.8 Hz, J = 21.5 Hz), 2.65 (t, 2H, J = 7.5 Hz), 2.26 (m, 2H), 2.20 (s, 6H), 1.64 (m, 2H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 135.6 (d, J = 23.8 Hz), 128.6, 124.0 (d, J = 8.2 Hz), 83.2 (d, J = 25.5 Hz), 95.2 (d, J = 206.3 Hz), 59.72, 45.64, 35.6, 29.30, 27.5; ^{19}F NMR(282 MHz, $CDCl_3$): δ 147.8; IR (thin film) ν 1940, 2858, 2814, 2764, 1518, 1460, 1299, 1174, 982, 820 cm^{-1}; Anal. calcd for $C_{15}H_{22}FNO$: C, 71.68; H, 8.82; N, 5.57. Found: C, 71.44; H, 8.93; N, 5.77; HRMS (EI) calcd for $C_{15}H_{22}FNO$ $[M]^+$, 251.1680. Found, 251.1682

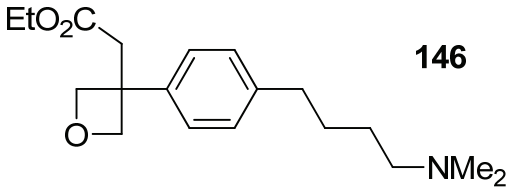


147

2-(4-(4-(dimethylamino)butyl)phenyl) 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_2O and THF was slowly added ^{n}BuLi (1.6 M in hexanes, 3.0 mL, 4.8 mmol, 1.3 equiv) at –78 °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_2O. The pH was adjusted to 9-10 with aqueous HCl. The aqueous phase was saturated with sodium chloride and extracted 5 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue (white foam) used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, 2H, J = 7.7 Hz), 7.22 (d, 2H, J = 7.9 Hz), 2.68 (t, 2H, J = 6.7 Hz), 2.43 (m, 2H), 2.28 (s, 6H), 1.62 (m, 4H).

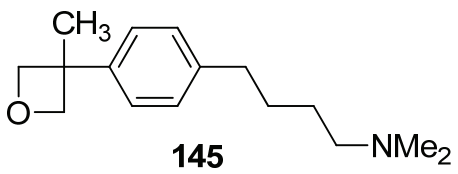
Experimental Section



146

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, Et_2O and brine were added. The aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Al_2O_3; 8/1 to 2/1 cyclohexane/EtOAc) to give 256 mg (83% yield) pure product as a colorless oil.

R_f = 0.29 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{19}H_{29}NO_3$ $[M]^+$ 319.2142. Found: 319.2142.

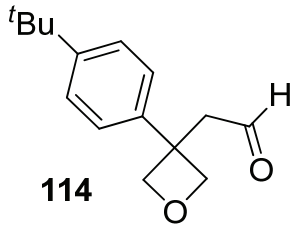


145

***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 Et_2O 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 Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in 30 mL toluene. $[(Ph_3P)_3RhCl]$ (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 Et_2O and 2 M aqueous NaOH. The aqueous phase was extracted three times with EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (Al_2O_3; 20/1 to 4/1 cyclohexane/EtOAc) to give 66 mg (33% yield) pure product as colorless oil.

R_f = 0.45 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) v 2935, 2865, 2814, 2763, 1517, 1461, 1041, 985, 821 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{25}NO$ $[M]^+$ 247.1931. Found: 247.1933.

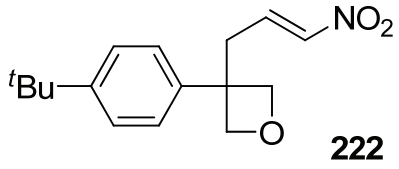


114

[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*-^{t}Bu-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*-*t*Bu-phenylboronic acid (0.96 mmol, 1.9 equiv) were added to drive the reaction to completion. After further stirring for 1 h, Et_2O (20 mL) and water was added. The aqueous phase was extracted three times with Et_2O. 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 90 mg (78% yield) pure product as a white solid (m_p = 66-67 °C).

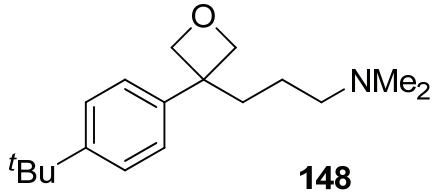
R_f = 0.35 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (t, 1H, J = 1.7 Hz), 7.38 (d, 2H, J = 8.6 Hz), 7.10 (d, 2H, J = 8.5 Hz), 5.06 (d, 2H, J = 6.2 Hz), 4.77 (m, 2H), 3.25 (d, 2H, J = 1.7 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 149.7, 140.2, 125.5, 125.4, 82.0, 53.3, 44.6, 34.6, 31.4; IR (thin film) ν 3092, 2925, 2848, 1698, 1525, 1421, 1350, 1319, 1186, 1125, 960, 947, 904, 828, 777, 725 cm^{-1}; Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.72.



222

3-(4-*tert*-Butyl-phenyl)-3-(3-nitro-allyl)-oxetane: To a solution of [3-(4-*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 *in vacuo*, the residue dissolved in 10 mL dry CH_2Cl_2 and cooled to –78 °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 °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_2O. 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 4/1 cyclohexane/EtOAc) to give 62 mg almost pure product (58% yield) as a yellowish oil that solidified in the freezer (m_p = 69-72 °C).

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); ^{13}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.

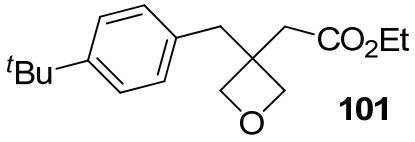


148

[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 (20w%, 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 141.7, 125.3, 125.2,

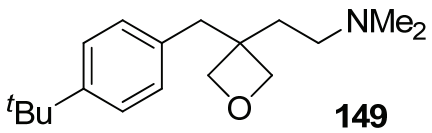
82.0, 59.8, 47.0, 45.5, 38.9, 34.5, 31.5, 23.0; IR (thin film) ν 2961, 2867, 2814, 2763, 1511, 1462, 11364, 1269, 1114, 986, 828 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$, 275.2249. Found, 275.2247.



101

[3-(4-*tert*-Butyl-benzyl)-oxetan-3-yl]-acetic acid ethyl ester: To a suspension of CuI (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_2O) 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_2O. 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.

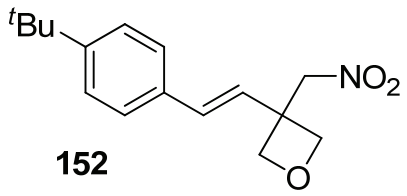


149

[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_2O 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_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in 50 mL MeOH, before NEt_3 (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 $NaCNBH_3$ (785 mg, 12.3 mmol, 10.0 equiv) was added. The mixture was stirred over night at room temperature, concentrated *in vacuo* and taken up with Et_2O. Water was added, followed by NaOH with cooling. The aqueous phase was extracted three times with Et_2O. 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 4/1 cyclohexane/EtOAc) to give 95 mg (28% yield) pure product as yellowish oil.

R_f = 0.39 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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^{-1}; Anal. calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.38; H, 10.83; N, 4.96; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$, 275.2249. Found, 275.2241.

Experimental Section



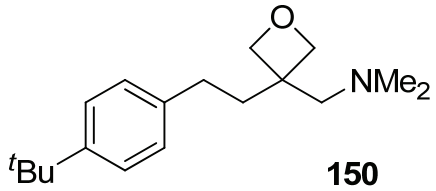
152

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, Et_2O and brine were added. The aqueous phase was extracted three times with Et_2O. 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 4/1 cyclohexane/EtOAc) to give 137 mg pure product (55% yield) as a white solid (m_p = 108-110 °C).

R_f = 0.40 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) v 2953, 2919, 2868, 1547, 1377, 1270, 1108, 976, 814 cm^{-1}; Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.50; H, 7.96; N, 5.00; HRMS (EI) calcd for $C_{16}H_{21}NO_3$ $[M]^+$, 275.1521. Found, 275.1515.

[354] Prepared according to: A. Torrado, S. Lopez, R. Alvarez, A. R. Delera, *Synthesis-Stuttgart* **1995**, 285.

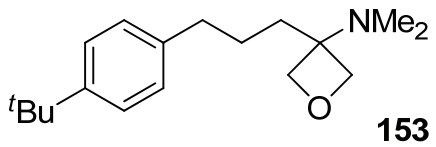
Experimental Section



150

[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_2O and aqueous NaOH were added with cooling. The aqueous phase was saturated with NaCl and extracted three times with Et_2O. 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 cyclohexane/EtOAc) to give 109 mg pure product (67% yield) as a yellowish oil that solidified in the freezer (m_p = 40-42 °C).

R_f = 0.74 (Al_2O_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) v 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.



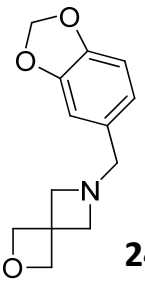
153

[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 Et_2O, 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*-*t*Bu-phenylmethylene triphenylphosphorane (**154**) in 20 mL dry THF (This solution was made by adding ^{n}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 $MgSO_4$, 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 over night and filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the residue mixed with water and Et_2O. Aqueous NaOH (2 M, 2.5 mL) was added with cooling and the aqueous phase extracted four times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Al_2O_3; 8/1 cyclohexane/EtOAc) to give 120 mg pure product (36% yield) as a colorless oil.

R_f = 0.60 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5,

138.9, 127.9, 125.1, 77.9, 63.4, 38.2, 35.8, 34.3, 31.3, 30.7, 25.8; IR (thin film) ν 2952, 2870, 2782, 1902, 1511, 1476, 1462, 1364, 1269, 1109, 1046, 1019, 984, 830, 573 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M\text{-}CH_3]^+$, 260.2009. Found, 260.2007.

6.5 Preparation of Oxetanes of the Cyclic Scaffolds

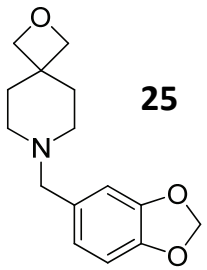


24

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 CH_2Cl_2 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 K_2CO_3 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 Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in 250 mL Et_2O 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 Et_2O and then dissolved in 1 M KOH. The aqueous phase was extracted with EtOAc, the combined organic phases were dried over Na_2SO_4, filtered concentrated *in vacuo* to give 0.91 g of clear white liquid as pure product (74% yield).

R_f = 0.24 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{13}H_{15}NO_3$: C: 70.92, H: 6.45, N: 6.89, O: 15.74.

Found C: 70.80, H: 6.53, N: 6.88, O: 15.79; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$ 233.1047. Found 233.1052.

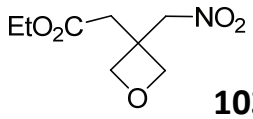


25

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 Et_2O. 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 Et_2O. The aqueous phase was washed with brine, dried over $MgSO_4$ 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 Et_2O (200 mL) were added and the aqueous phase washed twice with brine. The aqueous phase was dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue being product (R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 Et_2O, the solution cooled to 0 °C and $LiAlH_4$ (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, $Na_2SO_4 \cdot 10\ H_2O$ 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 Na_2SO_4, filtered, concentrated *in vacuo* and the residual diol (^{1}H NMR (300 MHz, $CDCl_3$) 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 CH_2Cl_2. The

solution was cooled to 0 °C, MsCl (0.74 mL, 9.6 mmol, 3.0 equiv) was added, followed by dropwise addition of NEt_3 (1.8 mL, 13 mmol, 4.0 equiv). After stirring for 1 h, a sample in the NMR indicated full conversion. Aqueous saturated NH_4Cl was added and the aqueous phase extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residual bismesylate (^{1}H NMR (300 MHz, $CDCl_3$) 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 $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified on column (Al_2O_3, cyclohexane to 8/1 cyclohexane/EtOAc) to give 0.26 g pure product as a white solid (mp = 78 – 80 °C).

R_f = 0.54 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.00; H, 7.47; N, 5.27.; HRMS (EI) calcd for $C_{15}H_{19}NO_3$ $[M]^+$= 261.1360. Found: 261.1361.

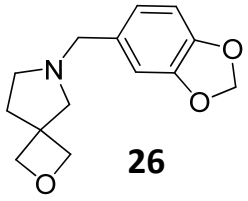


103

(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, $CDCl_3$) δ 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, $CDCl_3$) δ 170.1, 78.6, 78.6, 61.2, 40.3, 38.1, 14.3; IR (thin film) ν 2918, 2872, 1723, 1549, 1378, 1188, 1075, 1024 977 cm^{-1}; Anal. calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45. Found: C, 47.11; H, 6.39; HRMS (EI) calcd for $C_8H_{13}NO_5$: $[M]^+$= 203.0794. Found: 203.0747.

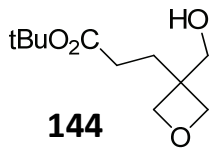


26

6-(benzo[*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_2O 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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 198.7, 78.8, 78.6, 47.3, 39.5; IR (thin film) ν 2934, 2819, 2734, 1715, 1545, 1428, 1382, 1258, 1097, 990, 901 cm^{-1}; HRMS (EI) calcd for $C_6H_9NO_4$ $[M\text{-}CH_2NO_2]^+$ = 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 (^{1}H NMR (300 MHz, $CDCl_3$) 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 CH_2Cl_2. 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 K_2CO_3 (80 mL) was added and the mixture stirred vigorously for 15 min. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 1/2 cyclohexane/EtOAc to 5% MeOH in EtOAc) to give 0.29 g pure product as a slightly yellowish oil (53% yield).

R_f = 0.2 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.71; H, 7.06; N, 5.72; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M]^+$=247.1203. Found: 247.1201.

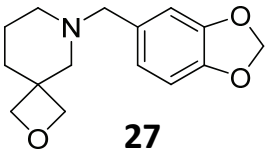


144

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 ^{n}BuLi (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 (Et_2O/liquid nitrogen cooling bath) and 2,6-dioxaspiro[3.3]heptane (**140**, 60 mg, 0.60 mmol, 1.0 equiv)[355] was added, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (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 $BF_3{\cdot}OEt_2$ (2.4 mmol, 4.1 equiv) were added. After stirring for further 5 h, the mixture was quenched by adding saturated aqueous NH_4Cl. The aqueous phase was extracted four times with EtOAc. The combined organic phases were 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 109 mg (89 w% by NMR, rest EtOAc) product as a colorless liquid (75% yield).

R_f = 0.31(SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{11}H_{20}O_4$: $[M\text{-}C_4H_8]^+$= 159.0652. Found: 159.0652.



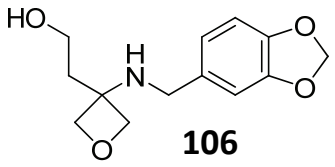
27

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 Et_2O was slowly added $LiAlH_4$ (4.0 M in Et2O, 0.57 mL, 2.3 mmol, 3.0 equiv) at 0 °C. After stirring for 45 min, $Na_2SO_4{\cdot}10\ H_2O$ 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 Na_2SO_4, filtered, concentrated *in vacuo* and the residual diol dissolved in 20 mL dry CH_2Cl_2, cooled to 0 °C and MsCl (0.18 mL, 2.3 mmol, 3.0 equiv) was added, followed by slow addition of NEt_3 (0.42 mL, 3.0 mmol, 4.0 equiv). After 1 h, a sample in the NMR indicated full conversion. Saturated aqueous NH_4Cl was added, the aqueous phase extracted three times with EtOAc. The combined

[355] Prepared according to: A.-R. Abdun-Nur, C. S. Issidorides, *J. Org. Chem.* **1962**, *27*, 67.

organic phases were washed with brine, dried over Na_2SO_4, filtered and the residue (R_f = 0.19 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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_2O_3, 20/1 to 8/1 cyclohexane/EtOAc) to give a mixture of product and piperonal. This material was dissolved in 40 mL Et_2O, 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_2O, 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) ν 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.

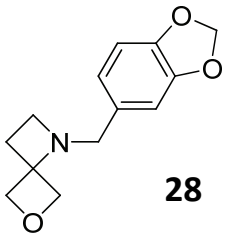


106

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 Et_2O were added and the reaction mixture was cooled to 0 °C, $LiAlH_4$ (4.0 M in Et_2O; 2.4 mL, 9.4 mmol, 4.0 equiv) was drop wise added, and the white suspension stirred for 2 h. $Na_2SO_4 \cdot 10\ H_2O$ 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 Na_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2; $CHCl_3$ to $CHCl_3$/MeOH 92:8) to give 399 mg (95w% by NMR) product (70% yield) as a yellowish oil.

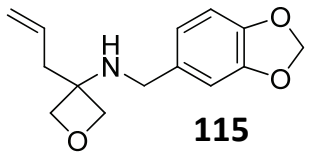
R_f = 0.78 (SiO_2, $CHCl_3$/MeOH 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (m, 3H), 5.94 (s, 2H), 4.56 (d, 2H, J = 6.7 Hz), 4.50 (d, 2H, J = 6.8 Hz), 3.82 (t, 2H), 3.72 (s, 2H), 2.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.5, 132.7, 121.5, 108.7, 108.3, 101.0, 81.4, 61.0, 59.5, 47.0, 35.1; IR (thin film) ν 3386, 2873, 1503, 1490, 1443, 1250, 1099, 1039, 975, 928.0, 810 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}NO_4$ $[M\text{-}CH_2O]^+$ = 221.1052. Found: 221.1052



28

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6-oxa-1-azaspiro[3.3]heptanes: Tetrabromocarbon (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 PPh_3 (593 mg, 2.26 mmol, 1.50 equiv) in 25 mL dry MeCN (immediate orange color), followed by distilled NEt_3 (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 Et_2O. The combined organic phases are dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (Al_2O_3, 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).

R_f = 0.15 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ; 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}C NMR (75 MHz, $CDCl_3$) δ 173.5, 146.5, 131.7, 121.4, 109.0, 108.1, 100.9, 81.4, 69.1, 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 (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$ 233.1052. Found: 233.1048.

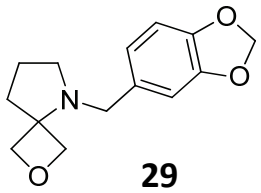


115

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 α,β-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 $H_2C{=}PPh_3$ in THF (prepared by addition of ^{n}BuLi (2.5 M in hexanes, 6.7 mL, 17 mmol, 2.8 equiv) to a suspension of Ph_3PMeBr (6.4 g, 18 mmol, 3.0 equiv) in 50 mL dry THF at 0 °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_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (Al_2O_3, 8/1 to 2/ cyclohexane/EtOAc) to give 435 mg pure product as a yellowish oil (29% yield).

R_f = 0.68 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 1H), 6.76 (m, 2H), 5.94 (s, 2H), 5.85 (m, 1H), 5.20 (m, 2H), 4.57 (d, 2H, J = 6.6 Hz), 4.43 (d, 2H, J = 6.7 Hz), 3.71 (s, 2H), 2.65 (d, 2H, J = 7.1 Hz), 1.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.5, 134.0, 132.6, 120.9, 118.6, 108.5, 108.0, 100.8, 80.7, 59.3, 46.9, 40.3; IR (thin film)

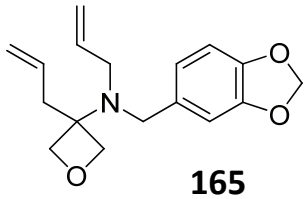
ν 3312, 3072, 2398, 2870, 1640, 1607, 1503, 1490, 1442, 1250, 1099, 1037, 980, 926, 811 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M\text{-}CH_2O]^+$= 217.1103. Found: 217.1100.



29

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. $Hg(O_2CCF_3)_2$ (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 Et_2O (30 mL) was added and the aqueous phase decanted off. The aqueous phase was dried over K_2CO_3, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 2/1 to 1/2 cyclohexane/EtOAc). The material isolated with R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc) was repurified (Al_2O_3, 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).

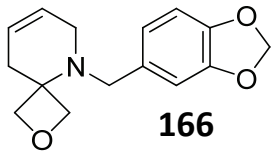
R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, 1H, J = 0.5 Hz, 1.5 Hz), 6.77 (m, 2H), 5.94 (s, 2H), 4.89 (d, 2H, J = 6.8 Hz), 4.55 (d, 2H, J = 6.7 Hz), 3.92 (s, 2H), 2.58 (m, 2H), 2.19 (dd, 2H, J = 6.7 Hz, 8.8 Hz), 1.69 (tt, 2H, J = 6.9 Hz, 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.97; H, 7.11; N, 5.75; HRMS (EI) calcd for $C_{14}H_{17}NO_3$: $[M]^+$= 247.1203. Found: 247.1204;.



165

***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, 1.0mol%) 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 $H_2C{=}PPh_3$ in THF (prepared by addition of ^{n}BuLi (2.5 M in hexanes, 5.0 mL, 13 mmol, 2.6 equiv) to a suspension of Ph_3PMeBr (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_2CO_3 and extracted four times with Et_2O. The combined Et_2O phases were dried over $MgSO_4$, filtered, concentrated *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.

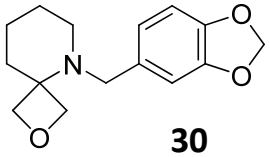
R_f = 0.60 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (m, 1H), 6.76 (m, 2H), 6.09 (m, 1H), 5.94 (m, 2H), 5.72 (m, 1H), 5.24 (m, 2H), 5.04 (dddd, 2H, J = 1.0 Hz, 2.5 Hz, 3.0 Hz, 10.1 Hz), 4.59 (d, 2H, J = 6.2 Hz), 4.26 (d, 2H, J = 6.3 Hz), 3.48 (s, 2H), 3.07 (d, 2H, J = 6.6 Hz), 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, 108.7, 107.7, 100.8, 79.8, 63.2, 53.0, 53.6, 36.2; IR (thin film) v 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.



166

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 CH_2Cl_2 was added *p*TosOH·H_2O (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 CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 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).

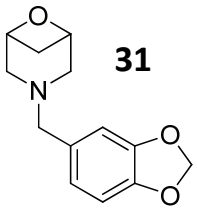
R_f = 0.29 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.77 (m, 2H), 5.93 (s, 2H), 5.77 (m, 1H), 5.55 (m, 1H), 4.66 (d, 2H, J = 6.0 Hz), 4.30 (d, 2H, J = 6.1 Hz), 3.42 (s, 2H), 3.07 (m, 2H), 2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.4, 133.1, 125.0, 123.3, 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 $C_{15}H_{17}NO_3$; HRMS (EI) calcd for $C_{15}H_{17}NO_3$: $[M]^+$= 259.1203. Found: 259.1202.



30

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 (SiO_2, 8/1 to 2/1 cyclohexane/EtOAc) to give 438 mg pure product (79% yield) as a white solid (m_p = 44-44.5 °C).

R_f = 0.37(SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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) v2934, 2867, 1608, 1502, 1489, 1441, 1375, 1357, 1249, 1133, 1103, 1039, 979, 928, 864, 810, 775 cm^{-1}; Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.94; H, 7.37; N, 5.36; HRMS (EI) calcd for $C_{15}H_{19}NO_3$: $[M-CH_3O]^+$= 230.1176. Found: 230.1175.



31

3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6-oxa-3-azabicyclo[3.1.1]heptane:[356] Cis/trans-(4-Benzyloxymethyl-oxetan-2-yl)-methanol[357] (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

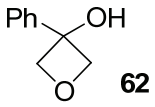
[356] This reaction was performed in the laboratories of F. Hoffmann-La Roche, Basel by Dr. Thierry Godel.
[357] Prepared according to: S.-K. Chung, S. H. Ban, S. H. Kim, S. H. Woo, *Korean Journal of Medicinal Chemistry* **1996**, *6*, 294.

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 dissolved 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 CH_2Cl_2. The aqueous phase was washed with brine, dried over $MgSO_4$, filtered and concentrated 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 suspended in EtOAc and filtered (Sartorius). After concentration (625 mg) the product was chromatographed (MPLC, 80 g SiO_2, 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 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.75 (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 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 147.7, 146.5, 132.6, 121.7109.1, 108.4, 100.9, 80.2, 60.7, 55.4, 30.5; IR (thin film) ν 2960, 2877, 2808, 1685, 1609, 1502, 1487, 1439, 1389, 1361, 1239, 1179, 1148, 1116, 1094, 1034, 958, 926, 877, 836, 806, 772, 714 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_3$: $[M+H]^+$ = 234.1247. Found: 234.1242.

6.6 Preparation of Nonpublished Oxetanes

6.6.1 3-Aryloxetan-3-ols

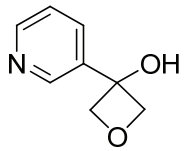


62

3-Phenyloxetan-3-ol: To a solution of bromobenzene (1.1 mL, 10 mmol, 2.5 equiv) in 25 mL dry THF was added ^{n}BuLi (1.6 M 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_2O. The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 1/1 hexane/EtOAc) to give 260 mg pure product (87% yield) as colorless crystals (m_p = 48 °C).

R_f = 0.17(SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.42 (m, 2H), 7.34 (m, 1H), 4.93 (m, 4H), 2.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 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^{-1}; Anal. calcd for $C_9H_{10}O_2$: 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.[358]



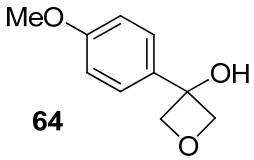
63

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[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-

[358] L. E. Friedrich, P. Y. S. Lam, *J. Org. Chem.* **1981**, *46*, 306.

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. Et_2O was added, followed by saturated aqueous ammonium chloride solution. The aqueous phase was extracted three times with Et_2O; the combined organic phases were dried over magnesium sulfate, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2; EtOAc) to give 0.14 g pure product (yield 83%) as slightly yellow solid (m_p = 93-94 °C).

R_f = 0.05 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_8H_9NO_2$: $[M\text{-}CH_2O]^+$ = 121.0528. Found, 121.0540



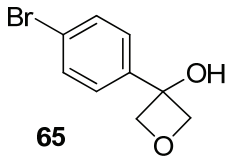
64

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 over night. Saturated aqueous ammonium chloride solution was added. The aqueous phase was extracted three times with Et_2O, the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2; hexane/EtOAc= 4/1 to 2/1) to give 0.14 g pure product (77% yield) as white solid (m_p = 60-61 °C).

R_f = 0.30 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, 1514, 1464, 1441, 1301, 1245, 1179, 1027, 970, 876, 772 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}O_3$: $[M]^+$= 180.0781. Found: 180.0776.

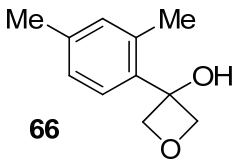
The spectra collected for this compound are in accordance with the literature.[359]



65

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_2O was added a solution of 4-bromophenylmagnesium bromide (~0.63 M in Et_2O, 6.3 mmol, 2.3 equiv) in 10 mL dry Et_2O 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 (m_p = 93-94 °C).

R_f = 0.25 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}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 (EI) calcd for $C_9H_9BrO_2$: $[M\text{-}CH_2O]^+$ = 197.9680. Found: 197.9674. Anal. calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.24; H, 3.84.

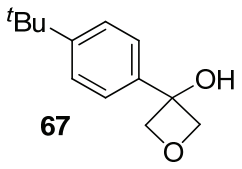


66

[359] F. D. Lewis, N. J. Turro, *J. Am. Chem. Soc.* **1970**, *92*, 311.

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 Et_2O, followed by a grain of iodine to activate the magnesium and promote metalation. After adding the residual aryl bromide (turbid solution, slight boiling of Et_2O), 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 Et_2O, the combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2; hexane/EtOAc= 4/1 to 2/1) to give 0.15 g pure product as a colorless oil (87% yield) that solidified upon standing (m_p = 48-50 °C).

R_f = 0.17 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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 (EI) calcd for $C_{11}H_{14}O_2$: $[M]^+$= 178.0989. Found: 178.0983.

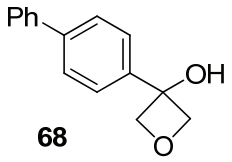


67

3-(4-*tert*-Butyl-phenyl)-oxetan-3-ol: To a solution of 4-^{t}Bu-phenyl bromide (0.21 mL, 1.5 mmol, 1.5 equiv) in 25 mL dry THF was added ^{n}BuLi (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 Et_2O, 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, 1178, 971, 872, 834 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}O_2$: $[M\text{-}CH_2O]^+$ = 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.

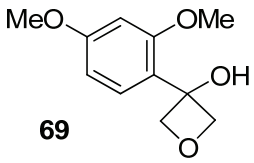


68

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 ^{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 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_2O, 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

Experimental Section

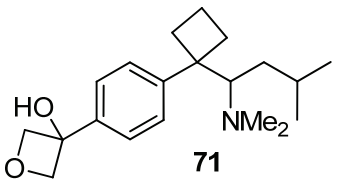


69

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 over night and quenched with water. The aqueous phase was extracted twice with Et_2O, the combined organic phases were dried, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 4/1 to 1/2 cyclohexane/EtOAc) to give 0.50 g pure product (80% yield) as white crystals (m_p = 72-75 °C).

R_f = 0.11 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{11}H_{14}O_4$: 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.



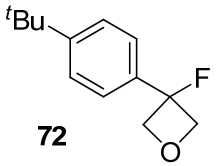
71

3-(4-(1-(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 (*n*Al_2O_3, 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 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 14667, 1366, 1278, 1172, 1113, 972, 881, 835 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{31}NO_2$: $[M-H]^+$ = 316.2271. Found: 316.2272.

6.6.2 3-Aryl-3-fluorooxetanes



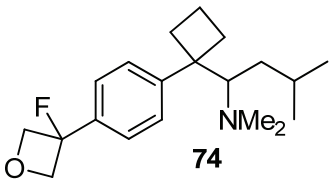
72

3-(4-tert-butylphenyl)-3-fluorooxetane: To a solution of alcohol **67** (41 mg, 0.20 mmol, 1.0 equiv) in 1 mL dry CH_2Cl_2 was added DAST (26 µL, 0.20 mmol, 1.0 equiv) at –78 °C. After stirring for 1 min, saturated aqueous $NaHCO_3$ was added and the mixture allowed to warm to room temperature. The aqueous phase was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, pentane/Et_2O = 10/1) to give 19 mg pure product (47% yield) as a colorless oil.

R_f = 0.63 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 135.5 (d, 1H, J = 23.7 Hz), 125.8, 124.0

(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; ^{19}F NMR(282 MHz, $CDCl_3$): δ 149.1; IR (thin film) ν 2963, 2872, 1466, 1364, 1300, 1142, 983, 833, 668, 575 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}FO$: $[M]^+$ = 208.1258. Found: 208.1260.

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

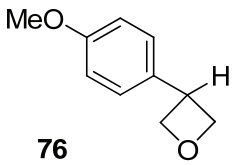


74

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 CH_2Cl_2 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 (*n*Al_2O_3, cyclohexane to 2/1 cyclohexane/EtOAc) to give 47 mg pure product (43% yield) as a yellowish oil.

R_f = 0.40 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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; ^{19}F NMR(282 MHz, $CDCl_3$): δ 147.2; IR (thin film) ν 2951, 2866, 2773, 1611, 1467, 1366, 1299, 1176, 1113, 1075, 1016, 982, 881, 835 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{30}FNO$: $[M\text{-}C_3H_7]^+$ = 262.1607. Found: 262.1601.

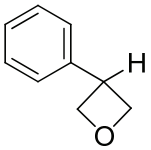
6.6.3 3-Aryl-oxetanes



76

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 CH_2Cl_2 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 $NaHCO_3$. The aqueous phase was extracted twice with Et_2O, 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 12 mg pure product (76% yield) as a colorless oil.

R_f = 0.42 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_{12}O_2$: $[M]^+$ = 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 *p*TsCl (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 $KHSO_4$ was added. The aqueous phase was extracted twice with Et_2O, the combined organic phases were dried, concentrated *in vacuo*

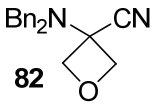
and the residue treated with 1 mL cold Et_2O/pentane = 3/1 to give 112 mg 95w% tosylate **78** (R_f = 0.42 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 7H), 7.11 – 6.99 (m, 2H), 5.30 (d, J = 8.6, 2H), 5.02 (d, J = 8.6, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 Et_2O, before $LiAlH_4$ (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 K_2CO_3. The aqueous phase was extracted three times with Et_2O, the combined organic phases were dried, concentrated *in vacuo* and the residue filtered through a short plug of silica gel (10/1 pentane/Et_2O) to give 12 mg product (~60% yieldcalculated from tosylate **78**) as a colorless oil.

R_f = 0.47 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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



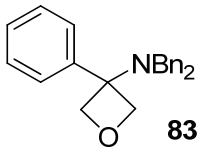
82

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 Et_2O and water were added. The aqueous phase was extracted three times with Et_2O. The

[360] a) P. Picard, D. Leclercq, J. P. Bats, J. Moulines, *Synthesis-Stuttgart* **1981**, 550. b) B. Delmond, J. C. Pommier, J. Valade, *J. Organomet. Chem.* **1973**, *47*, 337.
[361] Procedure dapted from: E. Bacque, J. M. Paris, S. Le Bitoux, *Synth. Commun.* **1995**, *25*, 803.

combined organic phases were washed with aqueous Na_2CO_3 until evolution of CO_2 ceased, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 8/1 to 4/1 cyclohexane/EtOAc) to give pure product (88% yield) as slightly yellow crystals (m_p = 64–66 °C).

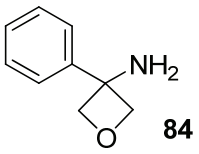
R_f = 0.46 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 10H), 4.34 (d, 2H, J = 6.8 Hz), 4.29 (d, 2H, J = 6.8 Hz), 3.51 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 129.4, 128.8, 128.3, 118.0, 78.6, 60.9, 55.7; IR (thin film) ν 3029, 2923, 2849, 1494, 1454, 1369, 750, 700 cm^{-1}; Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.61; H, 6.41; N, 10.06.



83

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, Et_2O was added, followed by brine (slowly). Saturated aqueous $KHSO_4$ and water were added to dissolve salts (pH~10). The aqueous phase was extracted four times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, cyclohexane to 20/1 cyclohexane/EtOAc; 0.1% NEt_3) to give 0.43 g pure product (71% yield) as a colorless solid (m_p = 88-90 °C).

R_f = 0.46 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 3025, 2936, 2879, 1681, 19616, 1576, 1493, 1455, 1358, 1165, 1116, 1027, 990, 959, 696 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{23}NO$: $[M\text{-}CH_2O]^+$= 299.1674. Found 299.1650.



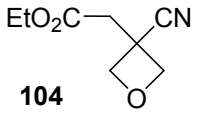
84

3-Phenyl-oxetan-3-ylamine:[361] To a solution of *N,N*-dibenzylamine **83** (0.42 g, 1.3 mmol, 1.0 equiv) in 40 mL MeOH was added $Pd(OH)_2/C$ (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 (m_p = 52-54 °C).

R_f = 0.03 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.01 (d, 2H, J=6.3Hz), 4.74 (d, 2H, J=6.3Hz), 2.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.9, 127.6, 125.1, 86.7, 59.3; IR (thin film) ν 3360, 2951, 2870, 2360, 1604, 1495, 1445, 1326, 1220, 1057, 1030, 978, 861, 761, 709 cm^{-1}; Anal. calcd for $C_9H_{11}NO$: 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

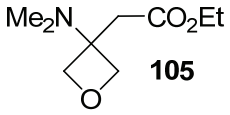


104

(3-Cyano-oxetan-3-yl)-acetic acid ethyl ester:[362] To a solution of acrylate **89** (30 mg, 0.21 mmol, 1.0 equiv) in 2 mL dry MeCN was added acetone cyanohydrine (16 µL, 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.

[362] Procedure adapted from: S. Proemmel, R. Wartchow, H. M. R. Hoffmann, *Tetrahedron* **2002**, *58*, 6199.

R_f = 0.10 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H 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); ^{13}C 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 $C_8H_{11}NO_3$: $[M]^+$=169.0739. Found: 169.0739.

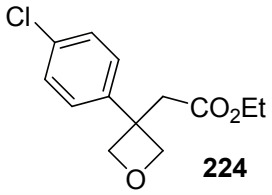


105

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*-dimethylammmonium 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); ^{1}H 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); ^{13}C 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 $C_9H_{17}NO_3$: $[M]^+$= 187.1208. Found: 187.1196; $[M\text{-}CH_2O]^+$= 157.1098. Found: 157.1098; Anal. calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.46; H, 9.23; N, 7.59

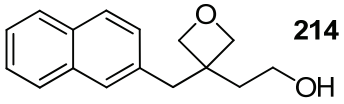
[363] Supraquantitative yield probably results from evaporation of Et_2O from the solution of acrylate **89**.



224

Ethyl 2-(3-(4-chlorophenyl)oxetan-3-yl)acetate: To a solution of $[Rh(cod)Cl]_2$ (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 Et_2O (60 mL) and brine (40 mL). The aqueous phase was extracted two times with Et_2O (25 mL). 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 0.33 g of pure product (56% yield) as slightly yellowish oil.

R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 (EI) calcd for $C_{13}H_{15}ClO_3$: $[M\text{-}CH_2O]^+$ 224.0595. Found: 224.0604.



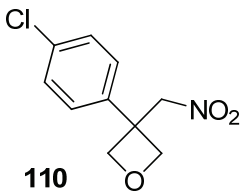
214

2-(3-Naphthalen-2-ylmethyl-oxetan-3-yl)-ethanol: A suspension of CuI (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 Et_2O (~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 Et_2O) 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 $LiAlH_4$ (0.15 g, 4.0 mmol) was cautiously added. After stirring for 3 h, $Na_2SO_4 \cdot 10\ H_2O$ 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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 8/1 cyclohexane/EtOAc to EtOAc) to give 0.18 g pure product (13% yield) as a colorless oil that crystallized upon standing (m_p = 60-62 °C).

R_f = 0.38 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{16}H_{18}O_2$: $[M]^+$ = 242.1301. Found 242.1301.

6.6.5.2 Additions to Nitroolefin 96

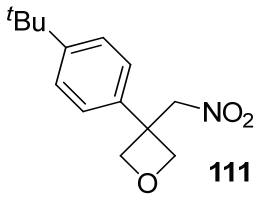


110

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 ^{n}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 CH_2Cl_2 three times (100 mL). 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) giving 1.20 g of >90% pure product (35% yield) as a colorless solid (m_p = 115-117 °C).

R_f = 0.39 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_{10}ClNO_3$: $[M]^+$ 227.0349. Found: 227.0343; Anal. calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.54; H, 4.55; N, 6.34.

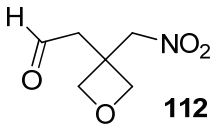


111

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 Et_2O and brine. The aqueous phase was extracted three times with Et_2O. 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 cyclohex-

ane/EtOAc) to give 65 mg (105% yield)[364] of pure product as a colorless solid (m_p = 86-87 °C).

R_f = 0.39 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 5.09 (d, J = 6.6 Hz, 2H), 5.01 (s, 2H), 4.92 (d, J = 6.7 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 136.7, 126.1, 125.6, 82.4, 79.4, 47.0, 34.7, 31.4; IR (thin film) ν 2960, 2878, 1548, 1380, 1220, 980, 773, 569 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{19}NO_3$: $[M]^+$ 249.1360. Found: 249.1360.



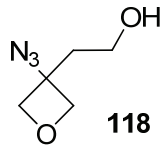
112

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_2Cl_2 (50 mL) was added, followed by 1 M aqueous HCl. The aqueous phase was extracted three times with CH_2Cl_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.

[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

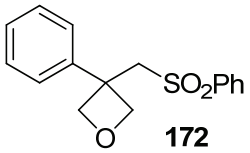


118

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 Et_2O at room temperature. After 20 min, the mixture was cooled to 0 °C and $NaBH_4$ (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 Et_2O and the aqueous phase extracted four times with Et_2O. The combined organic phases were washed twice with 2 M aqueous NaOH, dried over $MgSO_4$, 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.

R_f = 0.06 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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

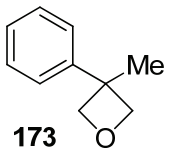


172

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 Et_2O and brine. The aqueous phase was extracted four times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 20/1 to 2/1 cyclohexane/EtOAc) to give 60 mg of pure product (87% yield) as a colorless solid (m_p = 162 °C).

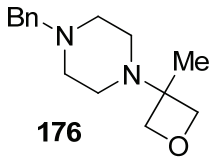
R_f = 0.21 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 3H), 7.38 – 7.28 (m, 2H), 7.25 – 7.14 (m, 3H), 7.06 (m, , 2H), 5.07 (d, J = 6.5 Hz, 2H), 4.95 (d, J = 6.6 Hz, 2H), 4.04 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 140.3, 133.1, 128.8, 128.5, 127.3, 127.2, 126.3, 80.9, 65.1, 45.8; IR (thin film) v 3063, 2959, 2906, 0870, 1583, 1498, 1446, 1319, 1308, 1268, 1132, 1084, 982, 858, 751, 687, 550, 525 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}O_3S$: $[M\text{-}CH_2O]^+$=258.0709. Found: 258.0710.



173

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. Et_2O (40 mL) was added followed by $Na_2SO_4 \cdot 10\ H_2O$. After stirring for 15 min, the mixture was filtered, the filtrate dried over $MgSO_4$, 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.

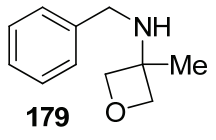
R_f = 0. 0.21 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 3H), 7.23 – 7.12 (m, 2H), 4.96 (d, J = 5.7 Hz, 2H), 4.61 (d, J = 5.2 Hz, 2H), 1.71 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 128.4, 126.1, 124.9, 83.7, 43.5, 28.1; IR (thin film) ν 2924, 2852, 1220, 772 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}O$: $[M\text{-}C_6H_5]^+$=71.0497. Found: 71.0854.



176

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_2O was added, followed by Na_2SO_4·10 H_2O and the mixture was stirred for 20 min, filtered, dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_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_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 137.8, 129.0, 128.0, 126.9, 81.4, 63.0, 60.0, 53.1, 45.1, 15.3; IR (thin film) ν 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 $C_{15}H_{22}N_2O$: $[M\text{-}CH_2O]^+$= 216.1621. Found: 216.1621.

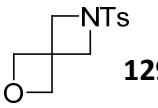


179

***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. Et_2O was added, followed by $Na_2SO_4 \cdot 10\ H_2O$ and the mixture was stirred for 20 min, filtered, dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_3, 20/1 to 4/1 cyclohexane/EtOAc) to give 140 mg pure product (79% yield) as a yellowish oil.

R_f = 0.50 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{11}H_{15}NO$: $[M\text{-}CH_3O]^+$= 146.0965. Found: 146.0966.

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

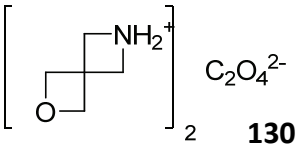


129

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

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).

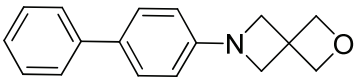
R_f = 0.14 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.3 Hz), 7.37 (d, 2H, J = 8.0 Hz), 4.59 (s, 4H), 3.91 (s, 4H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 131.6, 130.0, 128.5, 80.5, 59.7, 37.7, 21.8; IR (thin film) ν 2930, 2865, 1958, 1846, 1687, 1595, 1459, 1442, 1335, 1312, 1292, 1209, 1165, 1143, 1039, 973, 943, 890, 829, 683, 542 cm^{-1}; 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 $C_{12}H_{15}NO_3S$: $[M]^+$ = 253.0768. Found: 253.0769.



130

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_2O (500 mL) and $Na_2SO_4 \cdot 10\ H_2O$ (15 g) were added and the resulting light grey mixture was stirred vigorously for 30 min before filtration. The filtrate was dried over Na_2SO_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 ^{13}C NMR and ^{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 hydrooxalate salt in the product.

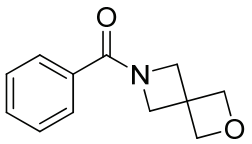
^{1}H NMR (300 MHz, D_2O) δ 4.87 (s, 4H), 4.34 (s, 4H), 2.22 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 168.6, 79.9, 54.5, 40.0; IR (thin film of 2-Oxa-6-aza-spiro[3.3]heptane) ν 3400, 2953, 2875, 1653, 1556, 1431, 1352, 1315, 1250, 963, 829, 774 cm^{-1}; HRMS (EI) done with 2-Oxa-6-aza-spiro[3.3]heptane, calcd for C_5H_9NO $[M-H]^+$ = 98.0601. Found 98.0603.



138

***N*,4-biphenyl-2-oxa-6-azaspiro[3.3]heptane[5]:** 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 de-gassed 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 (0.666g, 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_2Cl_2 and the solvent was removed from the filtrate. The orange oily residue was purified by flash chromatography (*n*Al_2O_3, cyclohexane to 4/1 cyclohexane/EtOAc) yielding 0.327 g (59% yield) yellow crystals as the pure product.

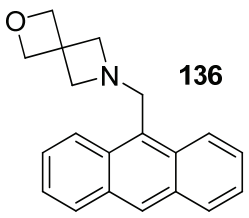
R_f = 0.5 (Al_2O_3, cyclohexane/EtOAc 2:1); mp 164-165 °C; ^{1}H NMR 7.50 (dd, 4H, J = 7.9 Hz, 16.2 Hz), 7.40 (t, 2H, J = 7.7 Hz), 7.28 (d, 1H, J = 9.0 Hz), 6.53 (d, 2H, J = 8.6 Hz), 4.86 (s, 4H), 4.07 (s, 4H); ^{13}C NMR 150.3, 141.0, 130.9, 128.6, 127.6, 126.3, 126.2, 111.9, 81.2, 61.7, 39.2; IR (thin 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.



132

***N*-benzoyl-2-oxa-6-azaspiro[3.3]heptane:** Benzoylchloride (0.7 mL, 6.0 mmol, 1.5 equiv), NEt_3 (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 CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed. The resulting yellow liquid was purified by flash chromatography (Al_2O_3, cyclohexane/EtOAc 2:1 to pure EtOAc) to give 0.623 g white solid as the pure product (77% yield).

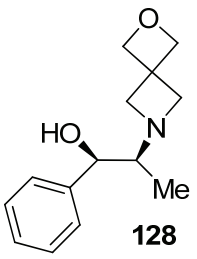
R_f = 0.065 (Al_2O_3, cyclohexane/EtOAc 2:1); mp 95-96 °C; ^{1}H NMR (300 MHz, CDCl3) 7.61 (m, 2H), 7.44 (m, 3H), 4.81 (d, 4H, J = 10.7 Hz), 4.44 (s, 2H), 4.36 (s, 2H); ^{13}C NMR 170.2, 132.7, 131.1, 128.3 , 127.7, 80.7, 62.7, 58.1, 38.2; IR (thin film) v/cm^{-1}: 3061, 2940, 2872, 1625, 1572, 1494, 1450, 1420, 1352, 1317, 1219, 1121, 1067, 1028, 973, 935, 866, 788, 758, 711; MS (EI) calculated for $C_{12}H_{13}NO_2$ $[M-H]^+$ 202.0863. Found 202.0862; EA calculated for $C_{12}H_{13}NO_2$: 70.92, H: 6.45, N: 6.89, O: 15.74. Found C: 70.80, H: 6.53, N: 6.88, O: 15.79.



136

***N*-((anthracen-10-yl)methyl)-2-oxa-6-azaspiro[3.3]heptan[4]:** 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 K_2CO_3 (1.17 g, 8.47 mmol, 6.00 equiv) in 8 mL DMF for 10 min at room temperature. 10-(chloromethyl)anthracene (0.322g, 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 Et_2O (200 mL) and the aqueous phase was washed three times with brine in order to remove residual DMF. The aqueous phase was dried over Na_2SO_4 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 Na_2SO_4 and the solvent was concentrated *in vacuo* to give 0.217 g pure product (52% yield) as yellow crystals (m_p = 177-178 °C).

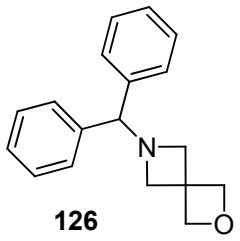
R_f = 0.41 (Al_2O_3, cyclohexane/EtOAc 2:1); mp 177-178 °C; ^{1}H NMR (300 MHz,CDCl3) 8.42 (m, 3H), 8.01 (m, 2H), 7.50 (m, 4H), 4.69 (s, 4H), 4.54 (s, 2H), 3.46 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 131.3, 130.8, 129.0, 127.4, 125.7, 124.6, 81.3, 63.5, 53.4, 39.0, two aromatic signals overlap and cannot be distinguished; IR (golden gate) v/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 (EI) calculated for $C_{20}H_{19}NO$ $[M]^+$ 289.15 . Found 289.15.



128

(1R,2S)-1-phenyl-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propan-1-ol:[365] 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 $NaHCO_3$ (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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_3, 2/1 cyclohexane/EtOAc to EtOAc) to give 0.67 g pure product (13% yield) as a white solid (m_p = 144-146 °C)

R_f = 0.12 (SiO_2: hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{14}H_{19}NO_2$: C, 72.07 ; H, 8.21 ; N, 6.00; Found: C, 71.96; H, 8.21; N, 6.03; MS (EI) calcd. for $C_{14}H_{19}NO_2$ $[M-H]^+$ 232.1333; Found, 232.1330.



126

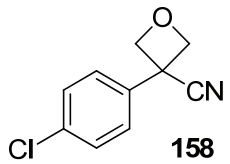
6-Benzhydryl-2-oxa-6-aza-spiro[3.3]heptane:[366] A solution of bis(bromomethyl)-oxetane (**119**, 5.0 g, 22 mmol, 1.0 equiv), benzhydrylamine (4.1 g, 22 mmol, 1.0 equiv) and *N,N*-diisoproylethylamine in 140 mL MeCN was refluxed for 20 h. The mixture was cooled to room temperature and concentrated *in vacuo*. Et_2O was added and the mixture filtered. The filtrate was concentrated *in vacuo* and the residue purified by flash chroma-

[365] Procedure adapted from: D. Zhao, C.-Y. Chen, F. Xu, L. Tan, R. Tillyer, M. E. Pierce, J. R. Moore, *Org. Synth.* **2000**, *77*, 12.
[366] Procedure adapted from: F. H. Tsai, C. G. Overberger, R. Zand, *Biopolymers* **1990**, *30*, 1039.

tography ($n$$Al_2O_3$, 20/1 to 2/1 cyclohexane/EtOAc) to give 0.59 g pure product (10% yield) as colorless crystals (m_p = 139-141 °C).

R_f = (SiO_2: hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 10H), 4.75 (s, 4H), 4.23 (s, 1H), 3.29 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 128.3, 127.3, 127.0, 81.6, 78.0, 63.0, 38.1; IR (thin film) ν 3024, 2934, 2864, 2822, 1597, 1492, 1451, 1342, 1240, 1074, 973, 744, 707 cm^{-1}; MS (EI) calcd. for $C_{18}H_{19}NO$ $[M-H]^+$ 232.1333; Found, 232.1330.

6.6.7 Sibutramine Analogues

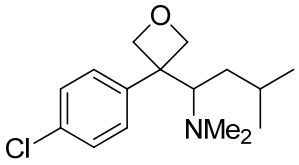


158

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), benzylbromide (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 NEt_3 (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 Et_2O three times (20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 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 (m_p = 42-44 °C) was obtained by distillation (0.27 mbar, b_p = 140 °C).

[367] Adapted from: C. Czekelius, E. M. Carreira, *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 612
[368] For the preparation of this compound, refer to page 195.

R_f = 0.51 (SiO_2: hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 4H), 5.32 (d, 2H, J = 6.3 Hz), 4.82 (d, 2H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.0, 134.5, 129.5, 126.7, 119.6, 81.0, 40.6; IR (thin film) ν 3046, 2965, 2889, 2360, 2243, 1905, 1597, 1493, 1406, 1329, 1281, 1097, 1013, 985, 942, 861, 824, 714 cm^{-1}; Anal. calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23. Found: C, 61.79; H, 4.28; N, 7.11; MS (EI) calcd. for $C_{10}H_8ClNO$ $[M]^+$ 193.0294. Found: 193.0286.

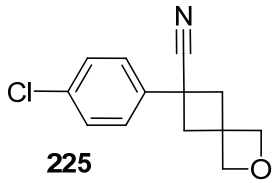


156

[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_2O 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_2O 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 ^{i}PrOH was added. The mixture was refluxed for 5 h and then stirred for 19 h at room temperature before the ^{i}PrOH 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**, R_f = 0.50 (Al_2O_3: hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 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);

MS (EI) calcd. for $C_5H_{12}N$ [M- $C_9H_8ClO]^+$ 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 37w% formaldehyde (58 µL, 0.80 mmol, 5.0 equiv) and the solution was stirred for 15 min. $NaCNBH_3$ (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-CH_2Cl_2 was added. The aqueous phase was extracted with 1 M NaOH three times (10 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash chromatography (SiO_2; cyclohexane/EtOAc 8/1 to 4/1) giving 21.1 mg of a white solid as pure product (50% yield).

R_f = 0.47 (SiO_2: hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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 (ddd, 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_7H_{10}O_3$: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.22; H, 8.37; N, 4.92; MS (EI) calcd. for $C_7H_{16}N$ [M- $C_9H_8ClO]^+$ 114.1277. Found: 144.1308.



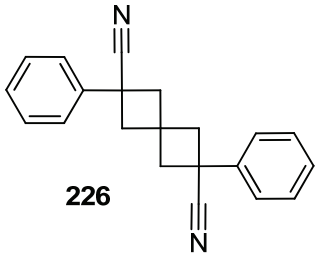
225

6-(4-Chloro-phenyl)-2-oxa-spiro[3.3]heptane-6-carbonitrile:[369] 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 Et_2O 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-

[369] Procedure adapted from: J. E. Jeffery, F. Kerrigan, T. K. Miller, G. J. Smith, G. B. Tometzki, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2583.

fore the reaction was quenched by addition of ice water (40 mL). Et_2O (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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue recrystallized from 25 mL toluene to give 1.97 g pure product (10% yield) as colorless crystals (m_p = 148-150 °C (toluene)).

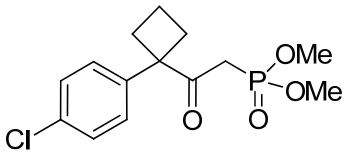
R_f = 0.38 (SiO_2: cyclohexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.32 (m, 2H), 7.29 – 7.24 (m, 2H), 4.96 (s, 2H), 4.63 (s, 2H), 3.16 – 3.06 (m, 2H), 2.83 – 2.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9, 129.2, 126.9, 123.1, 83.4, 81.6, 44.6, 39.1, 35.0; IR (thin film) ν 3498, 2939, 2863, 2614, 2353, 2230, 1961, 1898, 1808, 1601, 1494, 1449, 1425, 1274, 975, 772, 698 cm^{-1}; Anal. calcd. for $C_{13}H_{12}ClNO$: 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 $C_{13}H_{12}ClNO$: $[M]^+$ = 233.0602. Found: 233.0598.



226

2,6-Diphenyl-spiro[3.3]heptane-2,6-dicarbonitrile:[369] A solution of phenylacetonitrile (2.4 g, 21 mmol, 2.0 equiv) in Et_2O 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. Et_2O was added and the mixture filtered through a plug of sand. The aqueous phase of the filtrate was extracted three times with Et_2O, the combined organic phases were washed three times with water, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 20/1 to 4/1 cyclohexane/EtOAc) to give 0.45 g pure product (15% yield) as colorless crystals (m_p = 114-116 °C).

R_f = 0.59 (SiO_2: cyclohexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.31; H, 6.19; N, 9.32; HRMS (EI) calcd. for $C_{21}H_{18}N_2$: $[M]^+$ = 298.1465. Found: 298.1463.



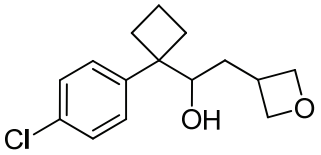
220

[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 ^{n}BuLi (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 $KHSO_4$ was added (resulting in pH 5) and the aqueous phase extracted three times with EtOAc. The combined organic phases were 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 a mixture of product and probably the corresponding imine. This mixture was dissolved in THF and stirred with saturated aqueous $KHSO_4$ for 30 min. The mixture was extracted three times with EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo*, giving 3.45 g pure product (68% yield) as a colorless oil.

R_f = 0.12 (SiO_2: cyclohexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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; ^{31}P NMR (121 MHz, $CDCl_3$): 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 $C_{14}H_{18}ClO_4P$: $[M+Na]^+$ = 339.0523. Found: 339.0529

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

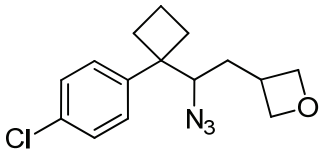


160

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 (SiO_2, 20/1 to 4/1 cyclohexane/EtOAc) to give 1-[1-(4-Chlorophenyl)-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 (5w%, 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 (SiO_2, 8/1 to 2/1 cyclohexane/EtOAc) to give 0.56 g of the pure ketone (58% yield) as a colorless oil (R_f = 0.35 (SiO_2: cyclohexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{13}H_{117}ClO_2$: $[M]^+$ = 264.0912. Found: 264.0914.). Parts of this material (365 mg, 1.38 mmol, 1.00 equiv) were dissolved in 10 mL ^{i}PrOH and $NaBH_4$ (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 Et_2O and the aqueous phase extracted three times with Et_2O. 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, 4/1 to 1/1 cyclohexane/EtOAc) to give 300 mg pure product as a colorless oil (82% yield).

R_f = 0.11 (SiO_2: cyclohexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): 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, $CDCl_3$): 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, 2058, 1492, 1395, 1294, 1092, 1012, 970, 826 cm^{-1}; Anal. calcd. for $C_{13}H_{12}ClNO$: 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 $C_{15}H_{19}ClO_2$: $[M]^+$ = 266.1074. Found: 266.1035.

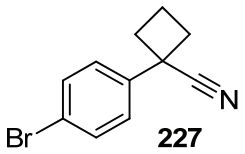


161

3-[2-Azido-2-[1-(4-chlorophenyl)-cyclobutyl]-ethyl]oxetane:[370] To a solution of alcohol **160** (490 mg, 1.84 mmol, 1.00 equiv), PPh_3 (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 PPh_3 (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 (SiO_2, 20/1 to 2/1 cyclohexane/EtOAc) to give 306 mg pure product (57% yield) as a yellowish oil.

[370] Procedure adapted from: A. Miyadera, K. Satoh, A. Imura, *Chem. Pharm. Bull.* **2000**, *48*, 563.

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); ^{13}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}.

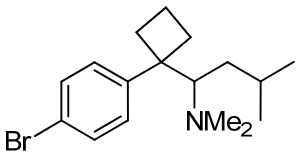


227

1-(4-Bromo-phenyl)-cyclobutanecarbonitrile:[369] To a mixture of powdered KOH (13.3 g, 237 mmol, 4.31 equiv) and DMSO (42 mL) was added a solution of 4-bromophenylacetonitrile (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); ^{13}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 (EI) calcd. for $C_{11}H_{10}BrN$: $[M]^+$ = 234.9991. Found: 234.9993.

Experimental Section



223

[1-[1-(4-Bromo-phenyl)-cyclobutyl]-3-methyl-butyl]-dimethyl-amine:[369] To a mixture of dry Et_2O (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_2O 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 ^{i}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 (37w%, 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_2Cl_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_2O, basified and extracted three times with Et_2O. 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, $CDCl_3$): δ 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

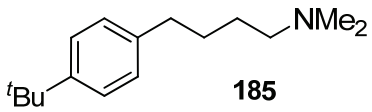
NMR (75 MHz, $CDCl_3$): δ 146.6, 130.0, 129.5, 119.0, 67.4, 51.7, 44.1, 36.2, 33.2, 33.0, 26.2, 24.2, 21.5, 15.7; IR (thin film) ν 2955, 2866, 2822, 1898, 1589, 1487, 14671392, 1367, 1278, 1110, 1074, 1010, 820, 741 cm^{-1}; Anal. calcd. for $C_{17}H_{26}BrN$: C, 62.96 ; H, 8.08; N, 4.32. Found: C, 63.17 ; H, 8.12; N, 4.44; HRMS (EI) calcd. for $C_{17}H_{26}BrN$: $[M]^+$ = 322.1165. Found: 3223.1163.

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

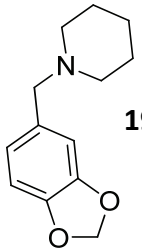
6.7.1 Methylene Analogues



185

1-(1-(4-(3-fluorooxetan-3-yl)phenyl)cyclobutyl)-*N,N*,3-trimethylbutan-1-amine: To a suspension of the hydro bromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide[353] (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-^{t}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.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 (d, 2H, J=8.3 Hz), 7.13 (d, 2H, J=8.2 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, $CDCl_3$) δ = 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) ν 2939, 2858, 2813, 2762, 1515, 1461, 1392, 1363, 1268, 1042, 828, 570 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.



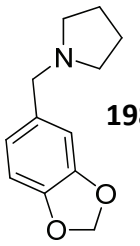
197

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidine:[371] 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_2O. The aqueous phase was extracted two times with Et_2O. 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 (Al_2O_3 , 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.88 – 6.82 (m, 1H), 6.73 (d, *J* = 1.0 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, $CDCl_3$) δ = 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) ν 2934, 2853, 2800, 2760, 1700, 1609, 1503, 1489, 1442, 1394, 1370, 1240, 1104, 1039, 995, 933, 868, 808, 780 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.

[371] K. Hejno, Z. Arnold, *Chem. Listy* **1953**, *47*, 601.

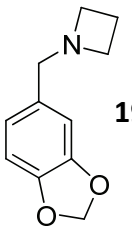
Experimental Section



198

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_2Cl_2 was added $NaBH(OAc)_3$ (5.3 g, 25 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K_2CO_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_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.4, 146.2, 133.3, 121.8, 109.3, 107.8, 100.8, 60.5, 54.1, 23.5; IR (thin film) ν 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 (EI) calcd for $C_{12}H_{15}NO_2$: $[M-H]^+$= 204.1019. Found: 204.1018.



199

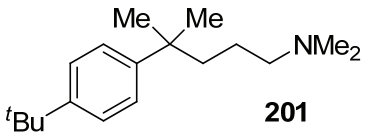
1-(benzo[*d*][1,3]dioxol-5-ylmethyl)azetidine: To a solution of azetidine (0.52 mL, 7.7 mmol, 1.1 equiv) and piperonal (1.1 g, 7.0 mmol, 1.0 equiv) in 30 mL CH_2Cl_2 was added $NaBH(OAc)_3$ (3.7 g, 18 mmol, 2.5 equiv) at room temperature and stirred overnight. Saturated aqueous K_2CO_3 was added until complete solvation of borate byproducts. The

aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, EtOAc to 10% MeOH in CH_2Cl_2) to give 1.06 g pure product (79% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C 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 $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.80; H, 6.76; N, 7.25; HRMS (EI) calcd for $C_{11}H_{13}NO_2$: $[M]^+$= 191.0946. Found: 191.0941.

6.7.2 *Gem*-dimethyl Analogues

6.7.2.1 Open-Chain Scaffold

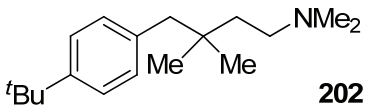


201

[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 Et_2O, the combined organic phases were washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting mixture was dissolved in EtOH, Me_2NH_2Cl (5.0 g, 61 mmol, 8.2 equiv) and K_2CO_3 (8.3 g, 60 mmol, 8.0 equiv) were added and the mixture heated at 50 °C for 2 d. The solvent was concentrated *in vacuo* and the residue partitioned between 1 M aqueous NaOH and Et_2O. The aqueous phase was extracted three times with Et_2O. The combined organic

phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 10% MeOH in CH_2Cl_2, 0.1% NEt_3) to give pure product together with SiO_2. This material was then distilled to give 0.29 g pure product (13% yield) as a colorless oil.

R_f = 0.37 (SiO_2, 10% MeOH in CH_2Cl_2, 0.1% NEt_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27 (m, 4H), 2.21 (m, 8H), 1.60 (m, 2H), 1.27 (m, 17H); ^{13}C 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 $C_{18}H_{31}N$: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.64; H, 11.97; N, 5.43.; HRMS (EI) calcd for $C_{18}H_{31}N$: $[M]^+$= 261.2452. Found: 261.2453.

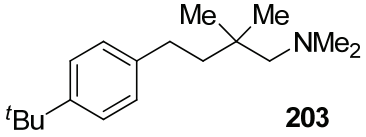


202

[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 Et_2O was added 4-(*tert*-butyl)benzyl bromide (5.5 mL, 21 mmol, 1.0 equiv) in 24 mL dry Et_2O 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 Et_2O was added over 2 h. The mixture was poured on ice, the aqueous phase extracted three times with Et_2O, the combined organic phases dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 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 Et_2O. The combined organic phases were washed three times with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 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 Et_2O. To this mixture was added $LiAlH_4$ (4.0 M solution in Et_2O, 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. $Na_2SO_4 \cdot 10\ H_2O$ 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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 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 CH_2Cl_2, NEt_3 (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 Et_2O. The solution was washed once with water and once with brine. The organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue dissolved in Me_2NH (2.0 M 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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_3, cyclohexane to 8/1 cyclohexane/EtOAc) to give 0.18 g pure product (34% yield) as a colorless oil.

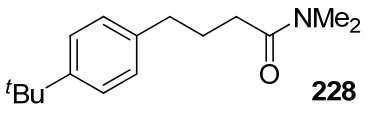
R_f = 0.88 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27 (d, 2H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.2 Hz), 2.48 (s, 2H), 2.31 (m, 2H), 2.23 (s, 6H), 1.42 (m, 2H), 1.31 (s, 9H), 0.88 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.3, 135.7, 130.1, 124.4, 55.4, 48.3, 45.8, 39.6, 34.3, 33.6, 31.4, 26.9; IR (thin film) ν 2962, 2867, 2814, 2762, 1512, 1463, 1364, 1269, 1203, 1110, 1023, 837 cm^{-1}; Anal. calcd for $C_{18}H_{31}N$: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.47; H, 11.99 N, 5.34; HRMS (EI) calcd for $C_{18}H_{31}N$: $[M]^+$ = 261.2452. Found: 261.2448.



203

[4-(4-*tert*-Butyl-phenyl)-2,2-dimethyl-butyl]-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 ^{n}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_2O. 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 (*n*Al_2O_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); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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) ν 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.

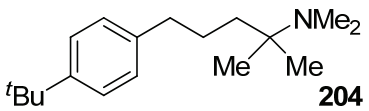


228

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

[372] Prepared according to: M. S. Newman, A. Tye, W. J. J. Broger, J. B. Lapidus, *J. Med. Chem.* **1972**, *15*, 1003.

slowly poured on a mixture of ice and concentrated aqueous HCl. The aqueous phase was extracted twice with CH_2Cl_2, the combined organic phases washed twice with brine, dried over $MgSO_4$, 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 (10w%, 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 Et_2O, 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*, Et_2O was added and the solution cooled to 0 °C. Aqueous Me_2NH (7.8 M, 35 mL, 0.27 mol, 4.0 equiv) was added and the mixture stirred at room temperature for 1 h. Et_2O was added and the aqueous phase extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue distilled (b_p~230 °C at 0.3 mbar) to give 14.964 g pure product (88% yield) as a yellowish oil (R_f = 0.13 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (EI) calcd for $C_{16}H_{25}NO$: $[M]^+$ = 247.1931. Found: 247.1930)



204

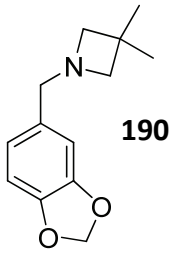
[4-(4-*tert*-Butyl-phenyl)-1,1-dimethyl-butyl]-dimethyl-amine:[373] To a solution of amide **228** (4.9 g, 20 mmol, 1.0 equiv) in 40 mL dry THF was added $ZrCl_4$ (4.7 g, 20 mmol, 1.0 equiv) in two portions at –10 °C. After stirring for 30 min, a solution of MeMgBr (3.0 M in Et_2O, 40 mL, 0.12 mol, 6.0 equiv) was added in a way that the inner temperature did

[373] Prepared adopting a procedure: S. M. Denton, A. Wood, *Synlett* **1999**, 55.

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 Et_2O, 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 Et_2O. The combined ethereal phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue distilled to give 1.01 g pure product (19% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{31}N$: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.53; H, 12.01 N, 5.20; HRMS (EI) calcd for $C_{18}H_{31}N$: $[M\text{-}CH_3]^+$ = 246.2217. Found: 246.2217.

6.7.2.2 Cyclic Scaffolds



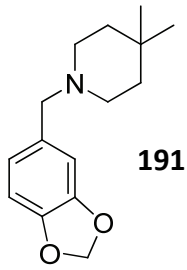
190

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3,3-dimethylazetidine*:* To a solution of 3-chloro-2,2-dimethylpropanal[374] (3.5 g, 29 mmol, 1.0 equiv) in 30 mL dry Et_2O was added $MgSO_4 \cdot 0.5\ H_2O$ (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 $LiAlH_4$ (6.0 mL of 4.0 M solution in Et_2O, 30 mmol, 1.0 equiv) at room temperature. The mixture was then refluxed over night, cooled to room temperature, before $Na_2SO_4 \cdot 10\ H_2O$ 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 $MgSO_4$, filtered, concentrated *in vacuo* and the re-

[374] Prepared according to: F. Effenberger, J. Eichhorn, J. Roos, *Tetrahedron: Asymmetry* **1995**, *6*, 271.

sidue filtered through a column (*n*Al_2O_3, 4/1 cyclohexane/EtOAc) to give 3.8 g pure product (58% yield) as a colorless oil.

R_f = 0.74 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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) ν 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1041, 937, 810, 776 cm^{-1}; Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.07; H, 8.00; N, 6.392951, 2902, 2814, 1609, 1503, 1489, 1442, 1374, 1337, 1247, 1187,1159, 1115, 1094, 1041, 939, 886, 863, 811, 759; HRMS (EI) calcd for $C_{13}H_{17}NO_2$: $[M]^+$= 219.1254. Found: 219.1252.

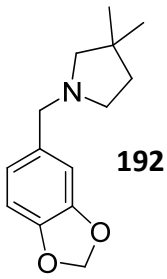


191

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 Et_2O and the combined organic phases were washed with 2 M aqueous NaOH twice, once with water and once with saturated aqueous NH_4Cl. After drying over $MgSO_4$, filtration and evaporation, the residue was purified by flash chromatography (SiO_2, 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 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 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, $CDCl_3$) δ 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) ν 2959, 2896, 2779, 1724, 1674, 1609,

1504, 1491, 1446, 1365, 1344, 1330, 1249, 1137, 1101, 1038, 926, 891 cm^{-1}; HRMS (EI) 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_2O and slowly added to a solution of $LiAlH_4$ (1.2 g, 30 mmol, 3.0 equiv) in 100 mL dry Et_2O at 0 °C. The mixture was then allowed to warm to room temperature refluxed for 12 h and cooled to 0 °C. $Na_2SO_4 \cdot 10\ H_2O$ 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_2SO_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, $CDCl_3$) δ = 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, $CDCl_3$) δ 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) ν 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 (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1567. Found, 247.1565

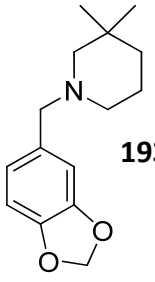


192

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 (R_f = 0.33 (SiO_2, 2/1 cyclohexane/EtOAc) used without further purification. This material was dissolved in 90 mL dry Et_2O and slowly added at 0 °C to a solution of $LiAlH_4$ (0.89 g, 2.3 mmol, 3.0 equiv) in 45 mL dry Et_2O. The mixture was then allowed to warm to room temperature refluxed for 12 h and cooled to 0 °C. Na_2SO_4·10 H_2O 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 Na_2SO_4, 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).

^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.78; H, 8.05; N, 6.11; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ $[M]^+$, 233.1411. Found, 233.1408



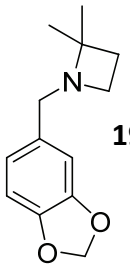
193

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine: To a solution of 3,3-dimethyldihydro-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 $MgSO_4$,

filtered and concentrated *in vacuo*. The residue was dissolved in 20 mL acetic anhydride and 3.5 mL NEt_3 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 $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified via chromatography (SiO_2, 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) (^{1}H NMR (300 MHz, $CDCl_3$) 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, 1325, 1282, 1247, 1164, 1038, 1017, 927, 885, 808, 778 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_4$ $[M]^+$, 275.1153. Found, 275.1155). To a solution of 0.29 g $LiAlH_4$ (7.7 mmol, 3.0 equiv) in 15 mL dry Et_2O was added a solution 1-(benzo[d][1,3]dioxol-5-ylmethyl)-3,3-dimethylpiperidine-2,6-dione in 30 mL dry Et_2O 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, $Na_2SO_4 \cdot 10\ H_2O$ 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 (SiO_2, 20/1 to 4/1 cyclohexane/EtOAc) to give 0.26 g pure product as a slightly yellowish oil (42% yield).

R_f = 0.50 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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. calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.97; H, 8.46; N, 5.79; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1567. Found, 247.1567

Experimental Section

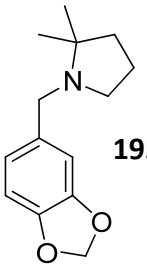


194

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2,2-dimethylazetidine: 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 (SiO_2, CH_2Cl_2 to 6% MeOH in CH_2Cl_2) to give 1.9 g pure ethyl 3-(benzo[d][1,3]dioxol-5-ylmethylamino)-3-methylbutanoate in 23% yield (R_f = 0.19 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 1726, 1490, 1442, 1368, 1327, 1249, 1098, 1039, 931, 809 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{21}NO_4$: $[M\text{-}H]^+$= 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 Et_2O to a solution of $LiAlH_4$ (5.0 mL of a 4.0 M solution in Et_2O, 20 mmol, 3.0 equiv) in 40 mL dry Et_2O at room temperature. After stirring overnight at room temperature, $Na_2SO_4 \cdot 10\ H_2O$ was slowly added. After stirring for 20 min, the mixture was filtered, the filter cake cooked with five times 20 mL EtOAc for 30 seconds each. The combined filtrates were dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue (2.5 g pure amino alcohol, R_f = 0.27 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{19}NO_3$: $[M\text{-}CH_3]^+$= 222.1125. Found: 222.1124.) dissolved without further purification in 100 mL dry MeCN. PPh_3 (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 NEt_3 (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 Et_2O. Aqueous 1 M NaOH (60 mL) was added and the aqueous layer extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, CH2Cl2 to 10% MeOH in CH_2Cl_2) to give 656 mg pure product (44% yield) as a slightly yellowish oil.

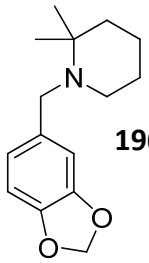
R_f = 0.11 (SiO_2, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.88 – 6.80 (m, 1H), 6.77 – 6.63 (m, 2H), 5.91 (s, 2H), 3.44 (s, 2H), 3.15 – 3.01 (m, 2H), 1.94 – 1.77 (m, 2H), 1.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.3, 146.6, 133.1, 121.4, 109.2, 107.8, 100.7, 63.4, 55.0, 49.3, 31.9, 25.0; IR (thin film) ν 2958, 2820, 1608, 1503, 1489, 1442, 1376, 1252, 1193, 1041, 937, 810, 776 cm^{-1}; Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.24; H, 7.81; N, 6.39. Found: C, 71.04; H, 7.80; N, 6.58; HRMS (EI) calcd for $C_{13}H_{17}NO_2$: $[M]^+$= 219.1254. Found: 219.1253.



195

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 $ZrCl_4$ (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 Et_2O, 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 CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_3, 20/1 cyclohexane/EtOAc) to give 0.84 g pure product (36% yield) as a yellowish solid (mp = 33-34 °C).

R_f = 0.91 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.86 (dd, *J* = 0.5 Hz, 1.4, 1H), 6.78 – 6.68 (m, 2H), 5.92 (s, 2H), 3.42 (s, 2H), 2.60 (ddd, *J* = 2.7 Hz, 5.4, 6.0, 2H), 1.68 (d, *J* = 2.9 Hz, 4H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 121.2, 109.0, 107.7, 100.7, 60.0, 53.0, 50.9, 40.0, 23.1, 20.5; IR (thin film) 2960, 2795, 1609, 1489, 1441, 1381, 1360, 1242, 1180, 1094, 1041, 940, 865, 809, 776 cm^{-1}; Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.13; N, 5.96; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ $[M]^+$, 233.1410. Found, 233.1411



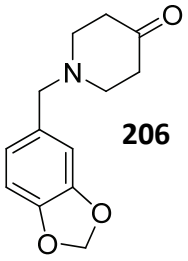
196

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 $ZrCl_4$ (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 Et_2O, 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 CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (*n*Al_2O_3, cyclohexane to 4/1 cyclohexane/EtOAc) to give 0.23 g pure product (10% yield) as a yellowish liquid.

R_f = 0.80 (Al_2O_3, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.92 (dd, *J* = 0.5 Hz, 1.5 Hz, 1H), 6.75 (dd, *J* = 4.3 Hz, 5.1 Hz, 1H), 6.72 (dd, *J* = 0.5 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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; IR (thin

film) ν 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 (EI) calcd for $C_{15}H_{21}NO_2$ $[M]^+$, 247.1568. Found, 247.1567

6.7.3 Carbonyl Analogues



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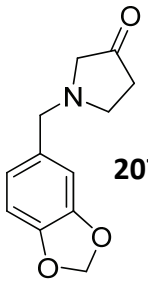
1-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-4-one:[375] 4-hydroxy-piperidine (1.0 g, 10 mmol, 1.0 equiv) and piperonyl chloride (1.7 g, 10 mmol, 1.0 equiv) were dissolved in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et_2O. The aqueous phase was extracted two times with Et_2O. 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_2O_3, 2/1 cyclohexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ = 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, 2H), 2.11 (t, *J* = 10.8, 2H), 1.88 (dd, *J* = 4.0 Hz, 12.8, 2H), 1.65 – 1.50 (m, 2H), 1.50 – 1.42 (m, 1H); IR (thin film) ν 3341, 2939, 2360, 1490, 1442, 1367, 1245, 1096, 1064, 4040, 933, 810, 778 cm^{-1}; HRMS (EI) 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

[375] J. K. Lynch, C. A. Collins, J. C. Freeman, J. Gao, R. R. Iyengar, A. S. Judd, P. R. Kym, M. M. Mulhern, H. L. Sham, A. J. Souers, G. Zhao, **2005**.

brine three times, 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 0.39 g pure product as white crystalline solid (m_p = 65-69 °C).

R_f = 0.14 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 147.6, 132.0, 121.9, 109.1, 107.8, 100.9, 61.7, 52.8, 41.4; IR (thin film) ν 3323, 2911, 2808, 1716, 1623, 1502, 1489, 1442, 1368, 1342, 1244, 1195, 1113, 1085, 1038, 933, 866, 799, 776 cm^{-1}; Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.84; N, 6.00. Found: C, 66.94; H, 6.48; N, 6.00; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$, 233.1047. Found, 233.1046



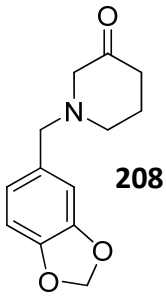
207

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 K_2CO_3 (2.9 g, 21 mmol, 6.0 equiv) were disperged in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et_2O. The aqueous phase was extracted two times with Et_2O. The combined organic phases were washed with brine 5 times, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (Al_2O_3, 8/1 to 1/1 cyclohexane/EtOAc) to give pure 1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ol (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.

[376] D. J. McCaustland, W. H. Burton, C. C. Cheng, *J. Heterocycl. Chem.* **1971**, *8*, 89.

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_2Cl_2. The combined organic phases were washed with brine, dried over K_2CO_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, 1106, 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 (EI) calcd for $C_{12}H_{13}NO_3$ $[M]^+$, 218.0890. Found, 219.0888



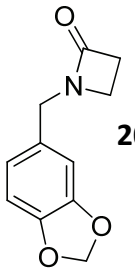
208

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_2CO_3 (25 g, 180 mmol, 6.0 equiv) were disperged in 20 mL DMF and stirred overnight at room temperature. Brine was added and Et_2O. The aqueous phase was extracted two times with Et_2O. 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 (nAl_2O_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, 91w% by NMR, rest DMF and EtOAc, yield 56%) as a white solid (mp = 57-58 °C; R_f = 0.14 (SiO_2, 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 $C_{13}H_{16}NO_3$ $[M]^+$, 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, NEt_3 (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 CH_2Cl_2. The combined organic phases were washed with brine, dried over K_2CO_3, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 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.

R_f = 0.23 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.47; N, 5.93; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ $[M]^+$, 233.1047. Found, 233.1048

Experimental Section

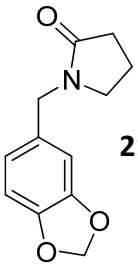


209

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 NEt_3 (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 NH_4Cl and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed three times with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* and the residue purified by flash chromatography (SiO_2, 20/1 to 1/2 cyclohexane/EtOAc) to give 2.4 g pure N-(benzo[d][1,3]dioxol-5-ylmethyl)-3-bromopropanamide (R_f = 0.31 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (EI) calcd for $C_{10}H_9NO_3Br$ $[M]^+$= 284.9995. Found, 284.9998). Of this material, 1.0 g (3.5 mmol, 1.0 equiv) were dissolved in 45 mL dry CH_2Cl_2. 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 CH_2Cl_2. After filtration and evaporation of the filtrate, the residue was purified by flash chromatography (SiO_2, 4/1 cyclohexane/EtOAc to EtOAc) to give 0.22 g pure product (31% yield) as a colorless oil.

R_f = 0.39 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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

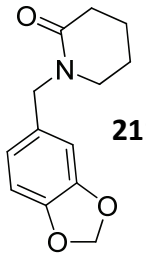


210

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyrrolidin-2-one: To a solution of γ-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, $CDCl_3$) δ = 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, $CDCl_3$) δ = 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) ν 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.

[377] A. R. Beard, S. J. Hazell, J. Mann, C. Palmer, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1235.



211

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[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, 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 (SiO_2, 2/1 cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.81 – 6.64 (m, 3H), 5.94 (s, 2H), 4.49 (s, 2H), 3.19 (d, *J* = 6.0 Hz, 2H), 2.44 (d, *J* = 6.3 Hz, 2H), 2.17 (s, 3H), 1.85 – 1.65 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 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; IR (thin film) ν 2945, 1638, 1491, 1443, 1352, 1241, 1177, 1038, 927, 808, 772, 664 cm^{-1}; Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.03; H, 6.49; N, 5.95; HRMS (EI) calcd for $C_{13}H_{15}NO$: $[M]^+$= 233.1046. 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
07/2003 – 11/2003	Wacker Siltronic, Singapore; Internship; planning, programming and implementation of a database mining tool in MS Excel.
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:

Scholarship of the Fritz-ter-Meer-Foundation (01/2002 – 09/2004)

Scholarship of the Studienstiftung des deutschen Volkes (03/2002 – 04/2004)

Foreign exchange scholarship of the Studienstiftung des deutschen Volkes (03 – 09/2004)

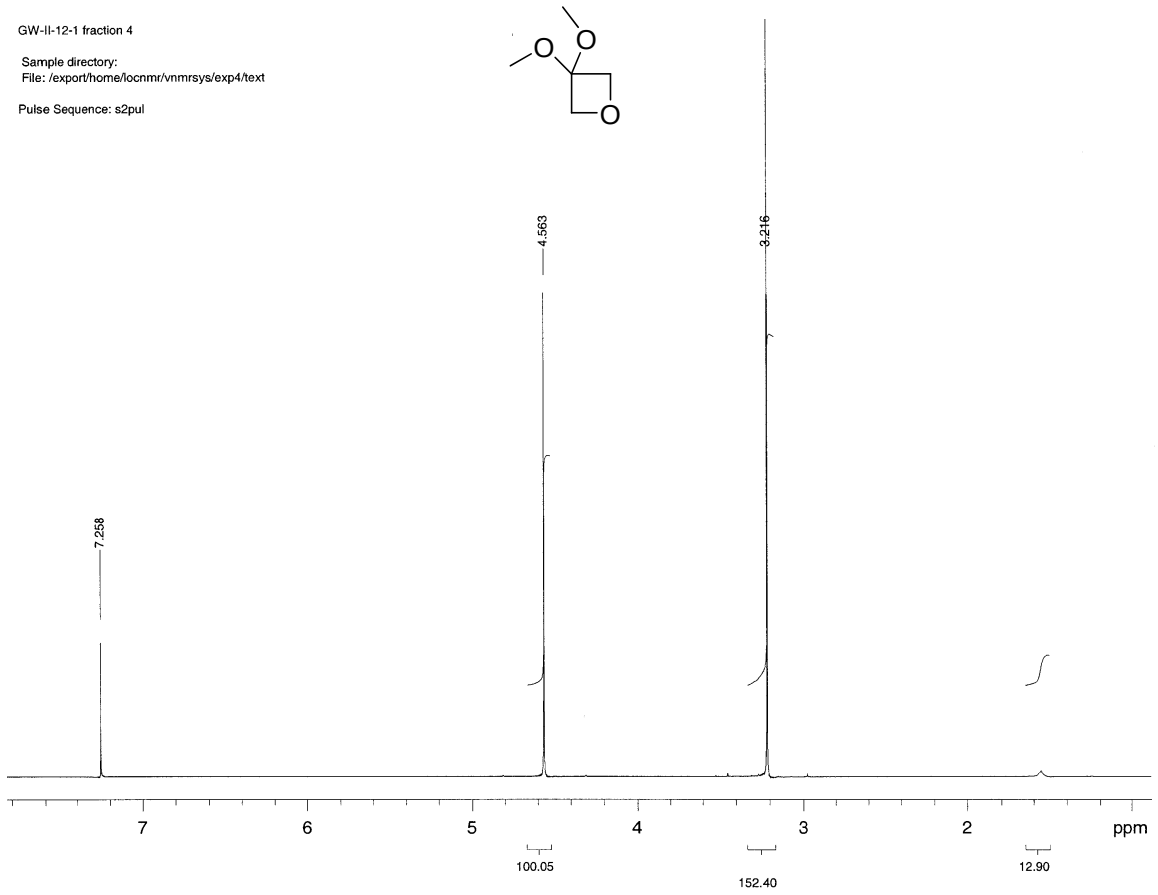
Scholarship from e-Fellows.net (since July 2002)

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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5
4
3
2
ppm
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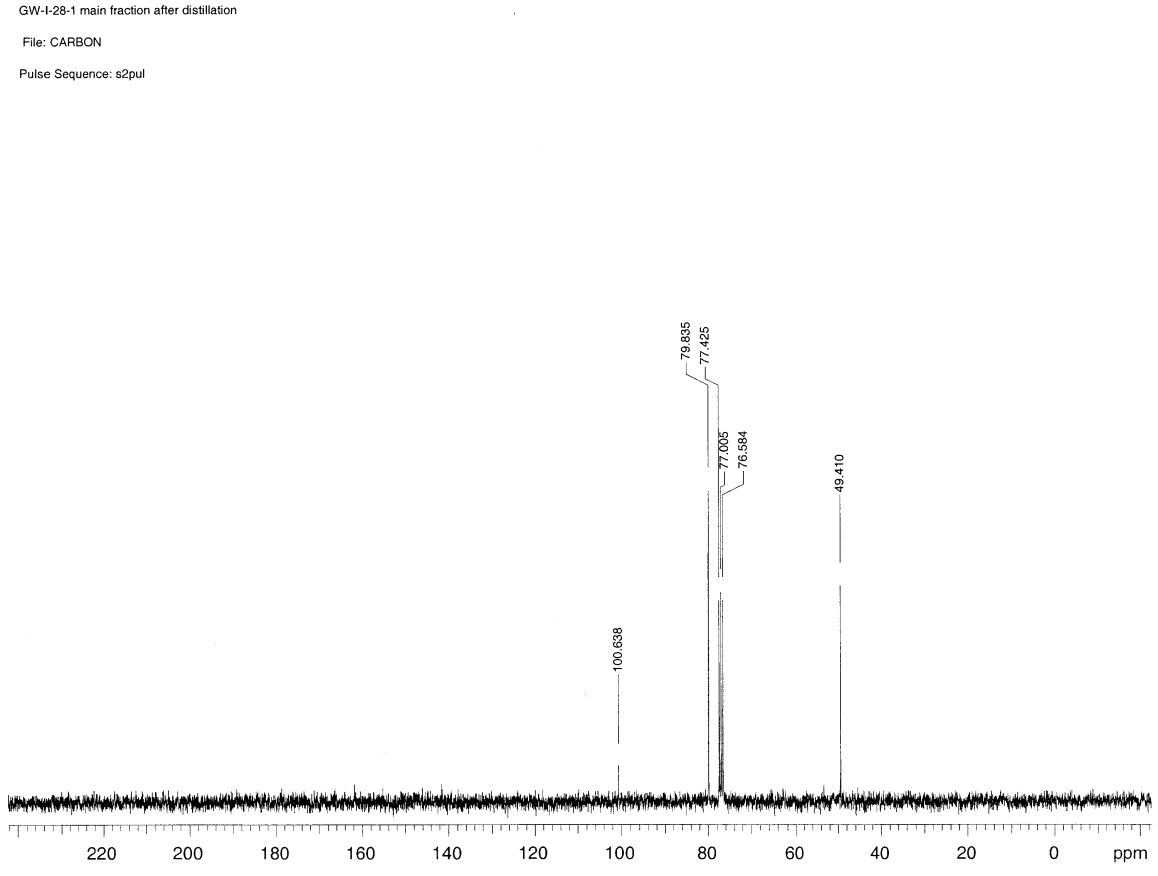
12.90


GW-I-28-1 main fraction after distillation
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40
20
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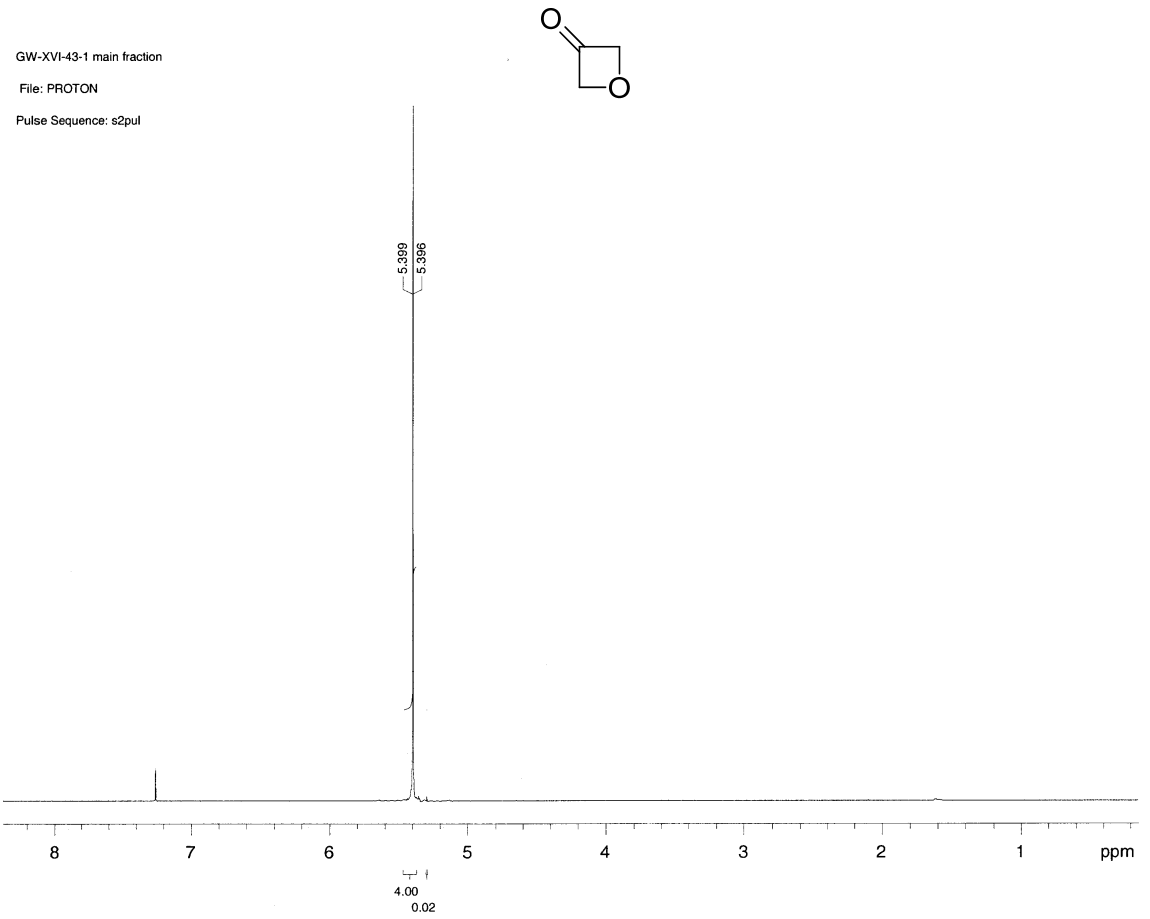
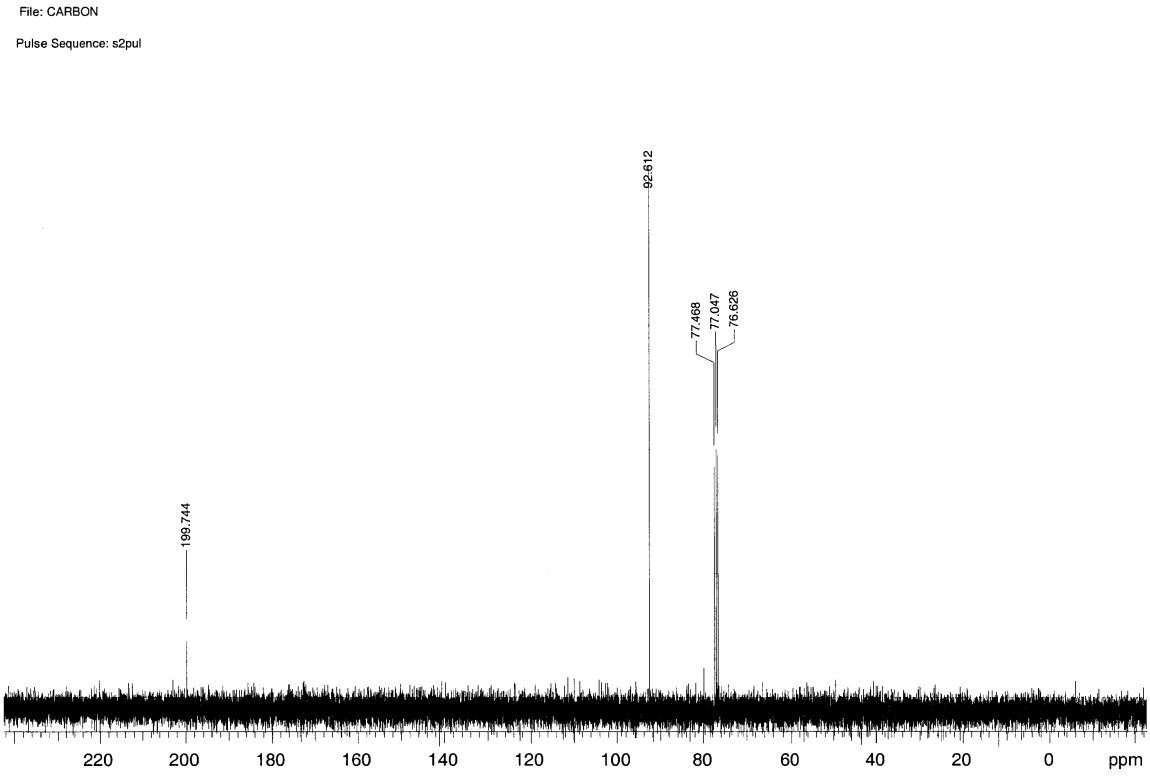
ppm

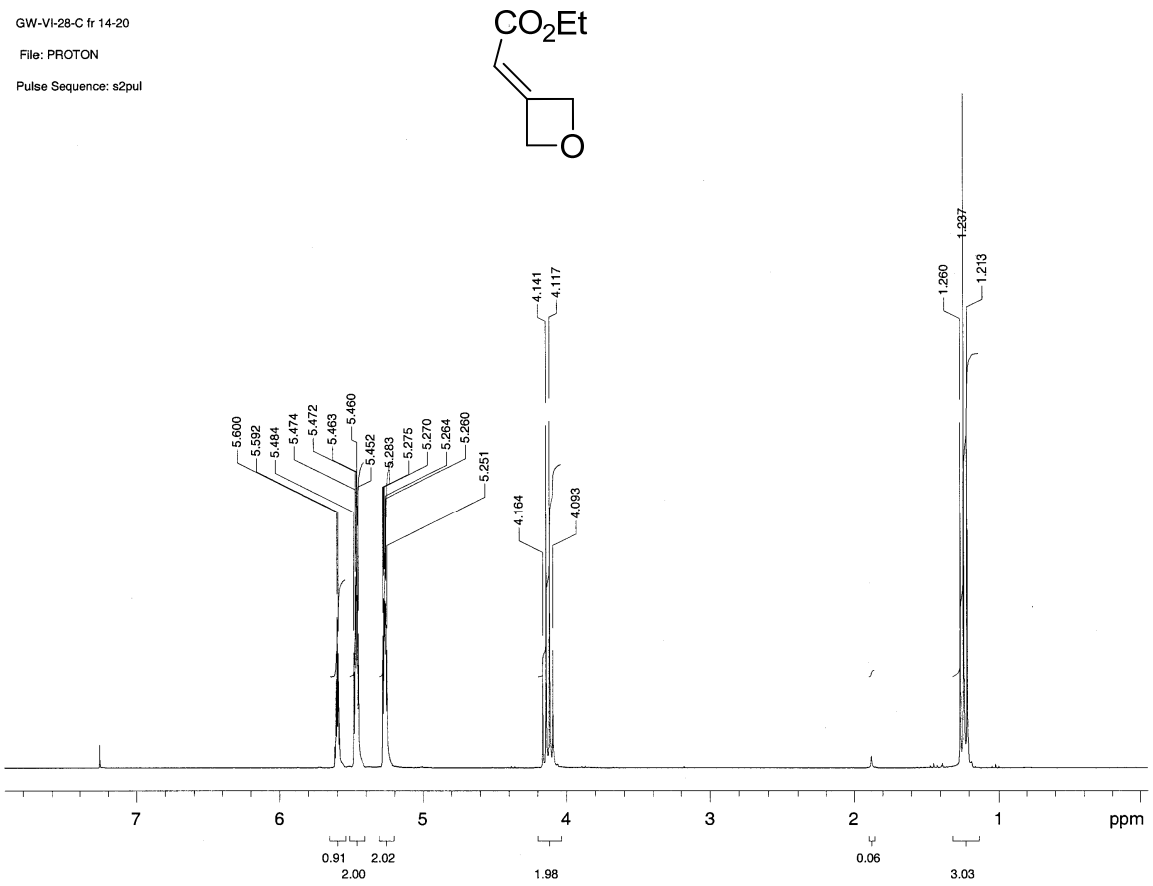
Appendix



~~13C OBSERVE~~ GW-



Appendix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5.264
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4.164
4.141
4.117
4.093
1.260
1.237
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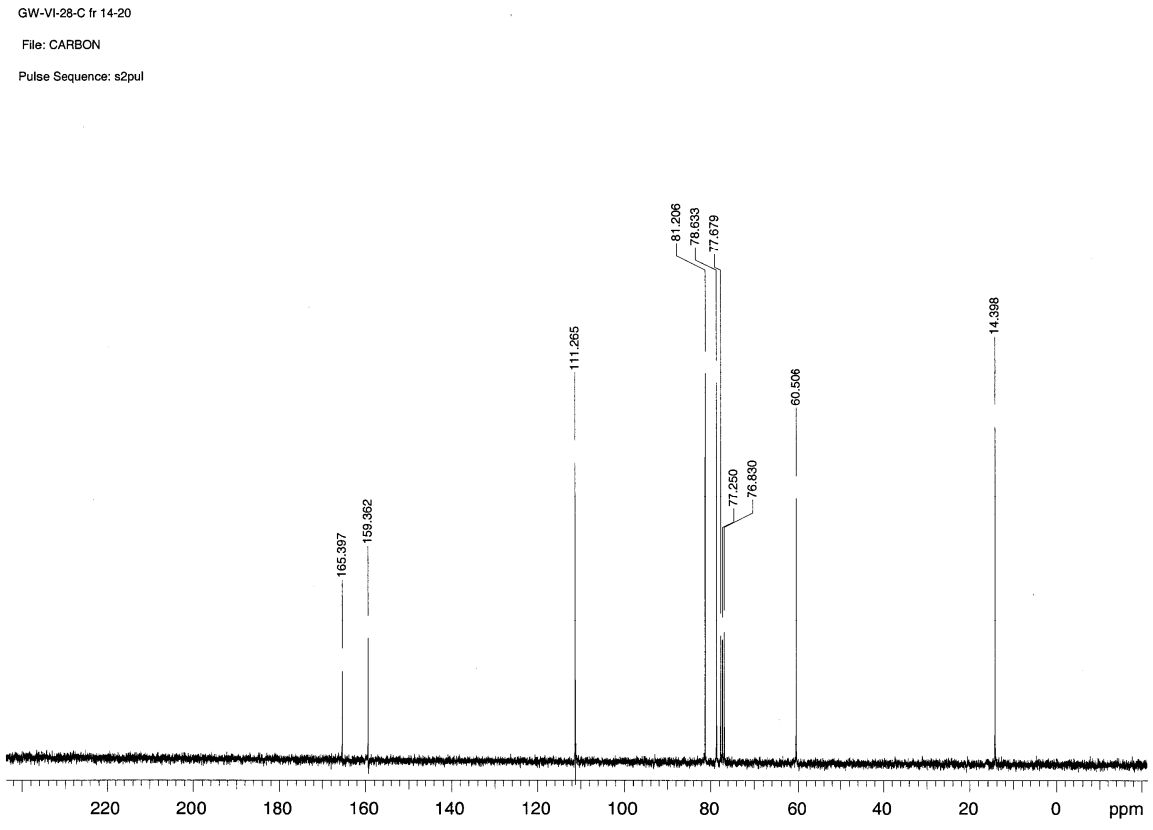
3.03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100
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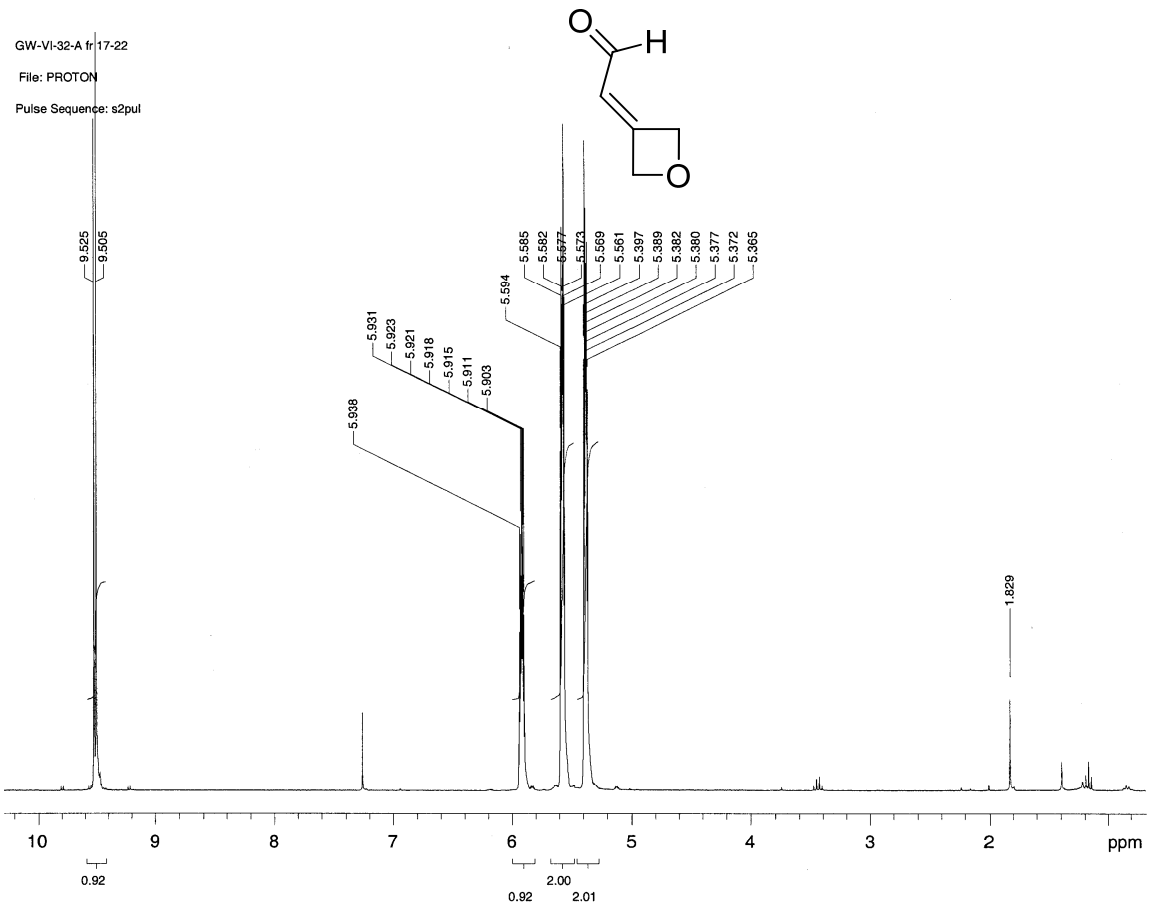
60
40
20
0
ppm

Appendix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5.380
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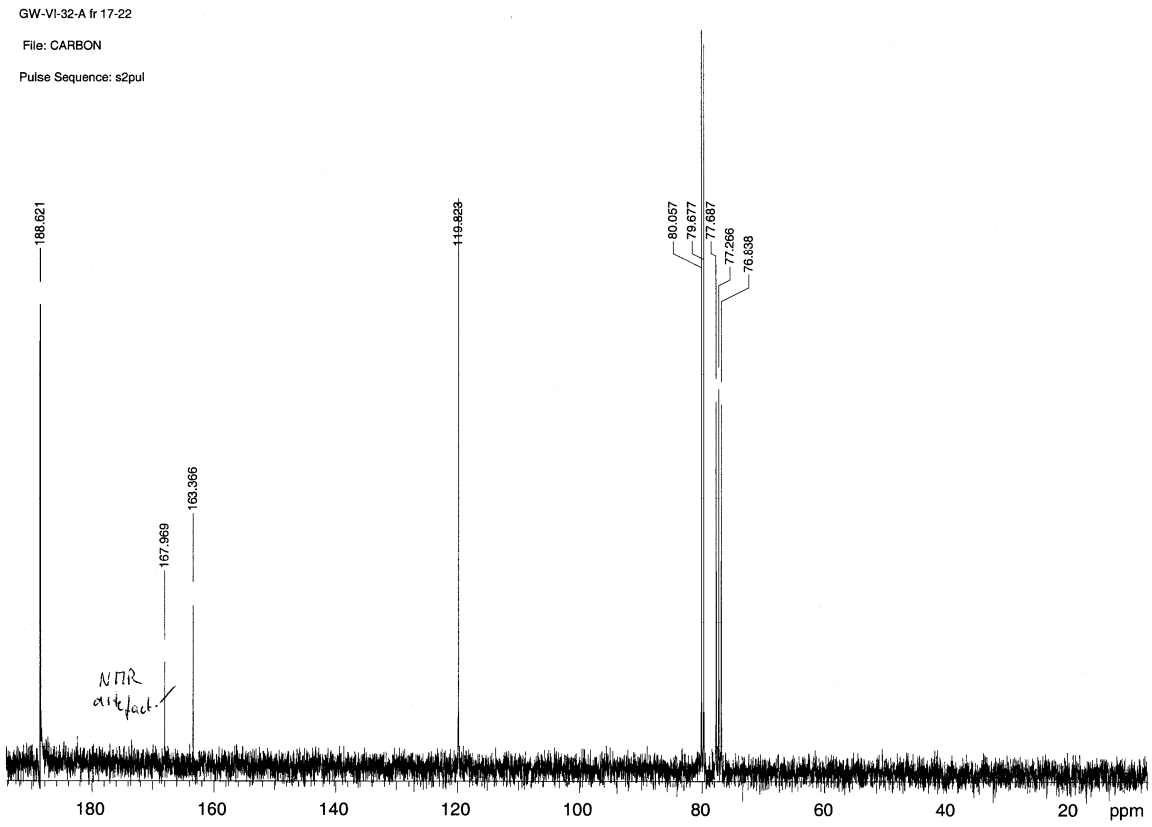
2.01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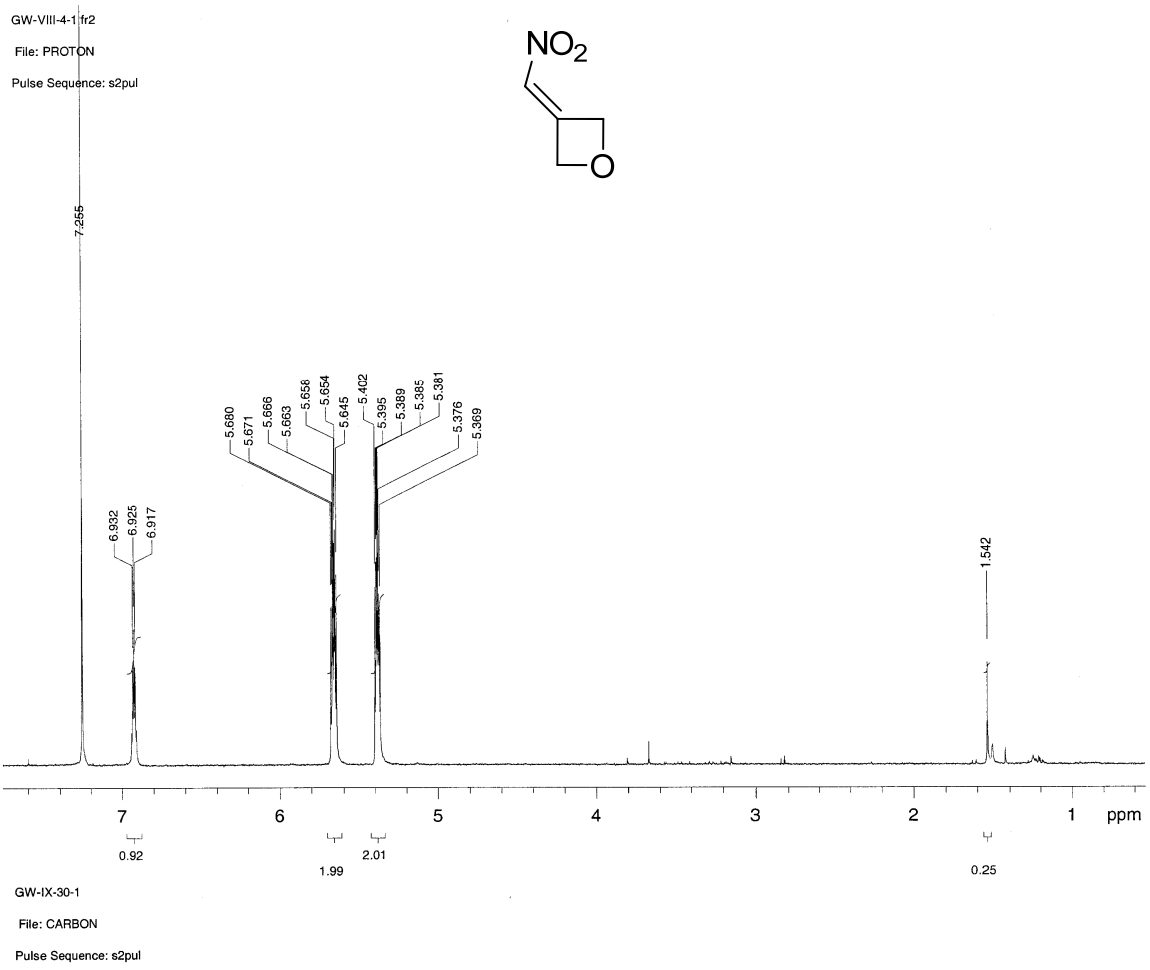
120
100
80
60
40
20
ppm

Appendix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5.395
5.389
5.385
5.381
5.376
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ppm
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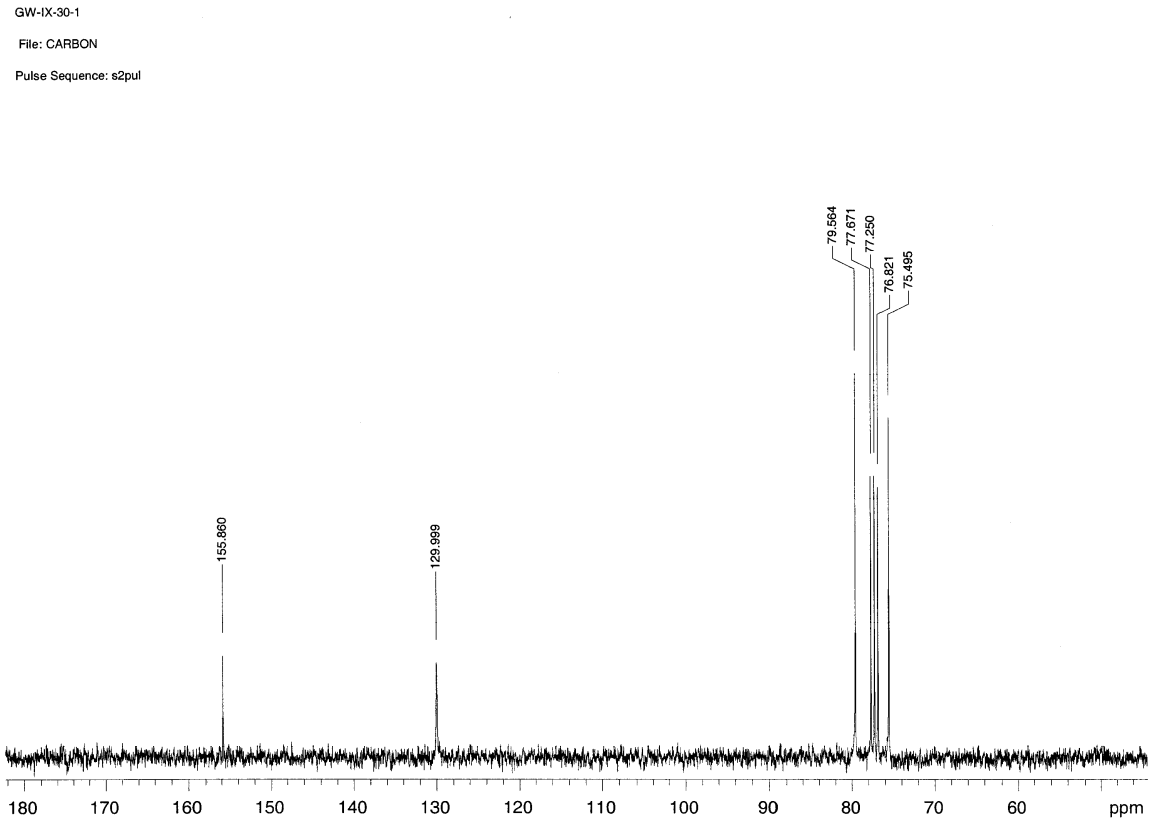
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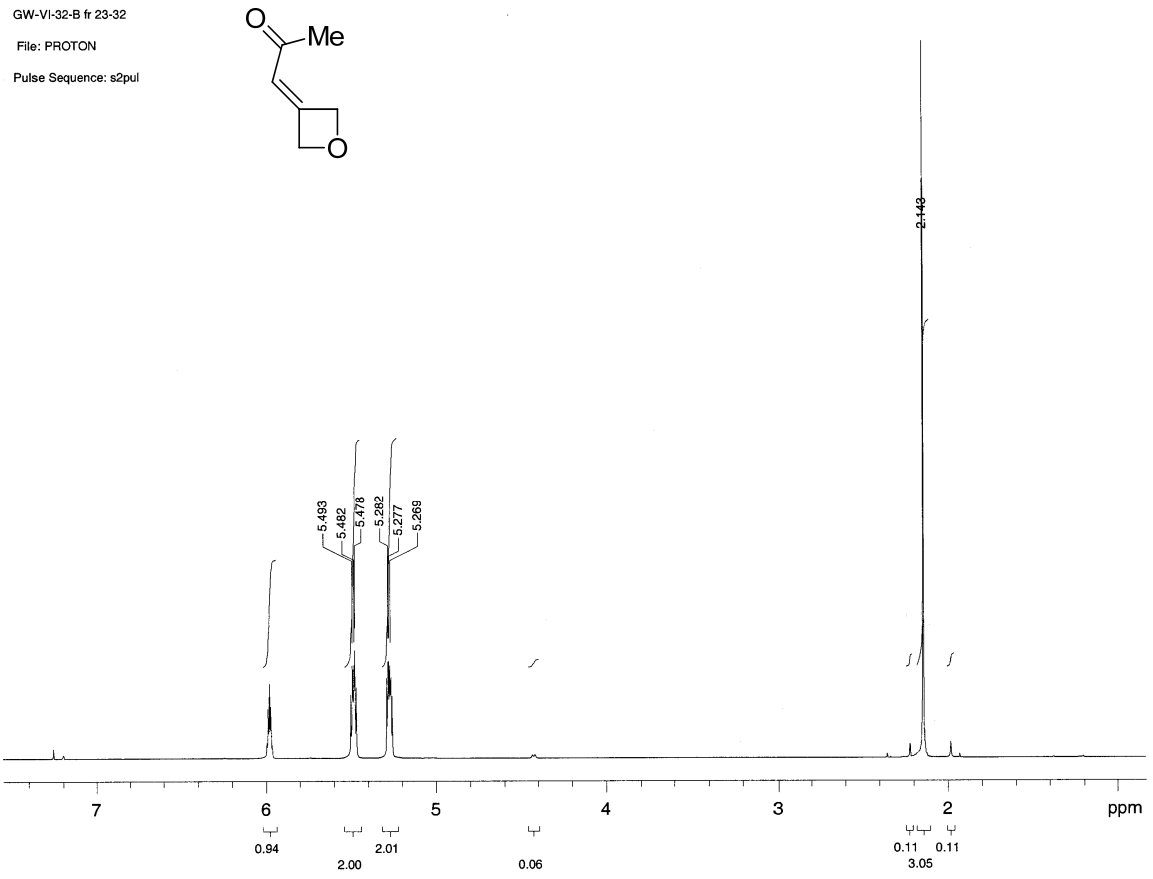
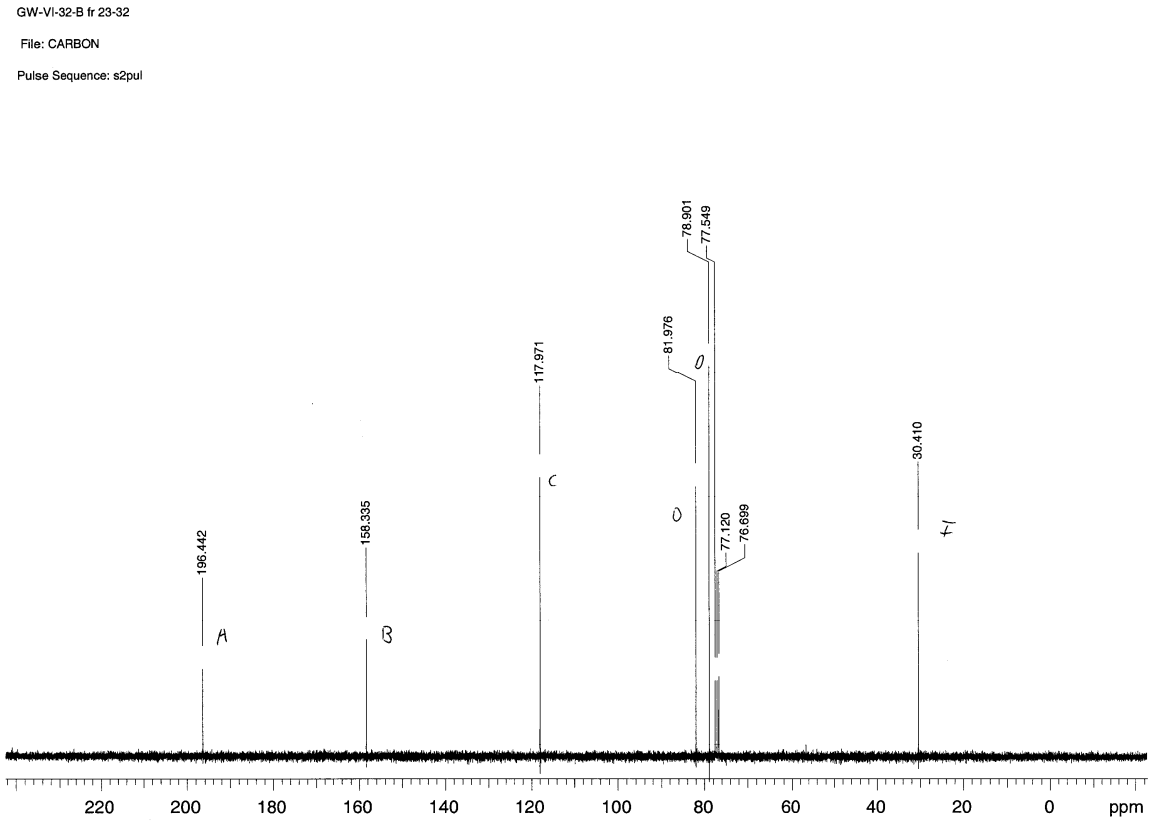
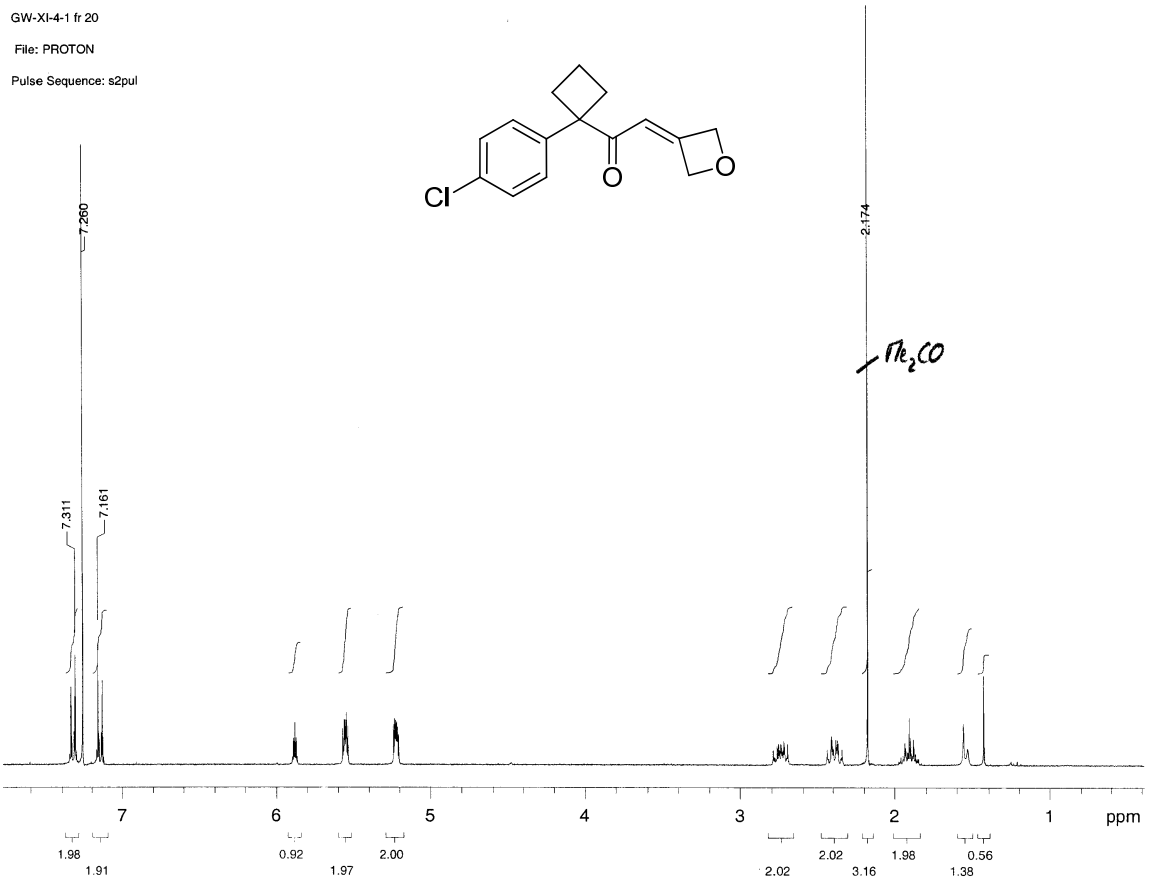
110
100
90
80
70
60
ppm

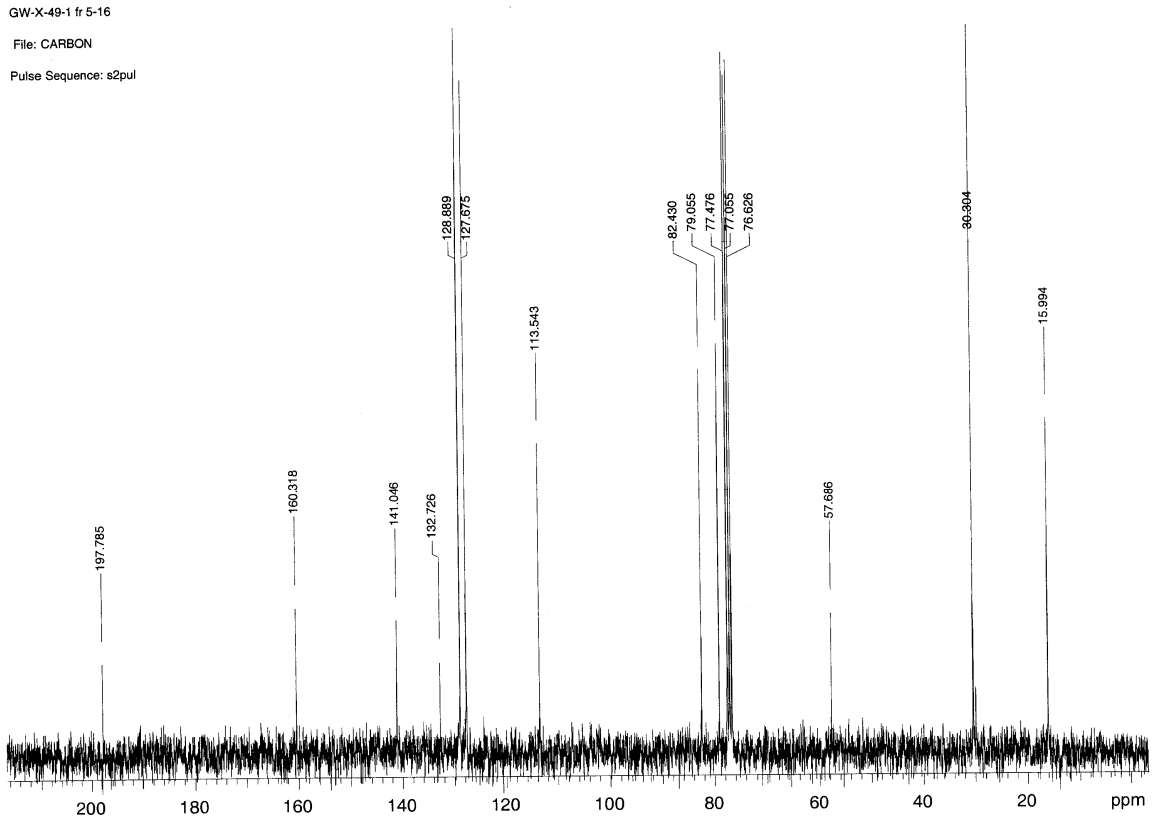
Appendix


GW-VI-32-B fr 23-32
File: PROTON
Pulse Sequence: s2pul
O
Me
O
2.148
5.493
5.482
5.478
5.282
5.277
5.269
7
6
5
4
3
2
ppm
0.94
2.00
2.01
0.06
0.11
0.11
3.05

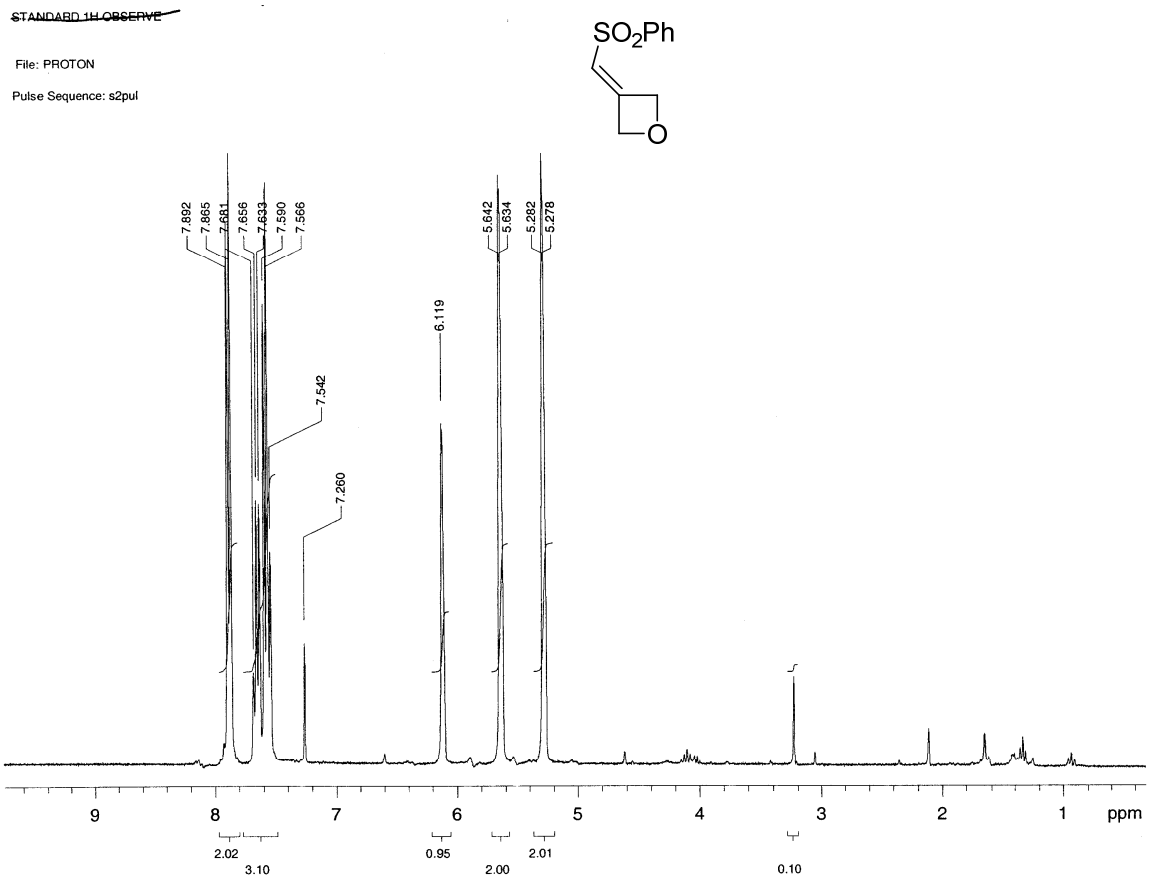

GW-VI-32-B fr 23-32
File: CARBON
Pulse Sequence: s2pul
78.901
77.549
81.976
117.971
30.410
158.335
196.442
77.120
76.699
A
B
C
D
E
F
220
200
180
160
140
120
100
80
60
40
20
0
ppm

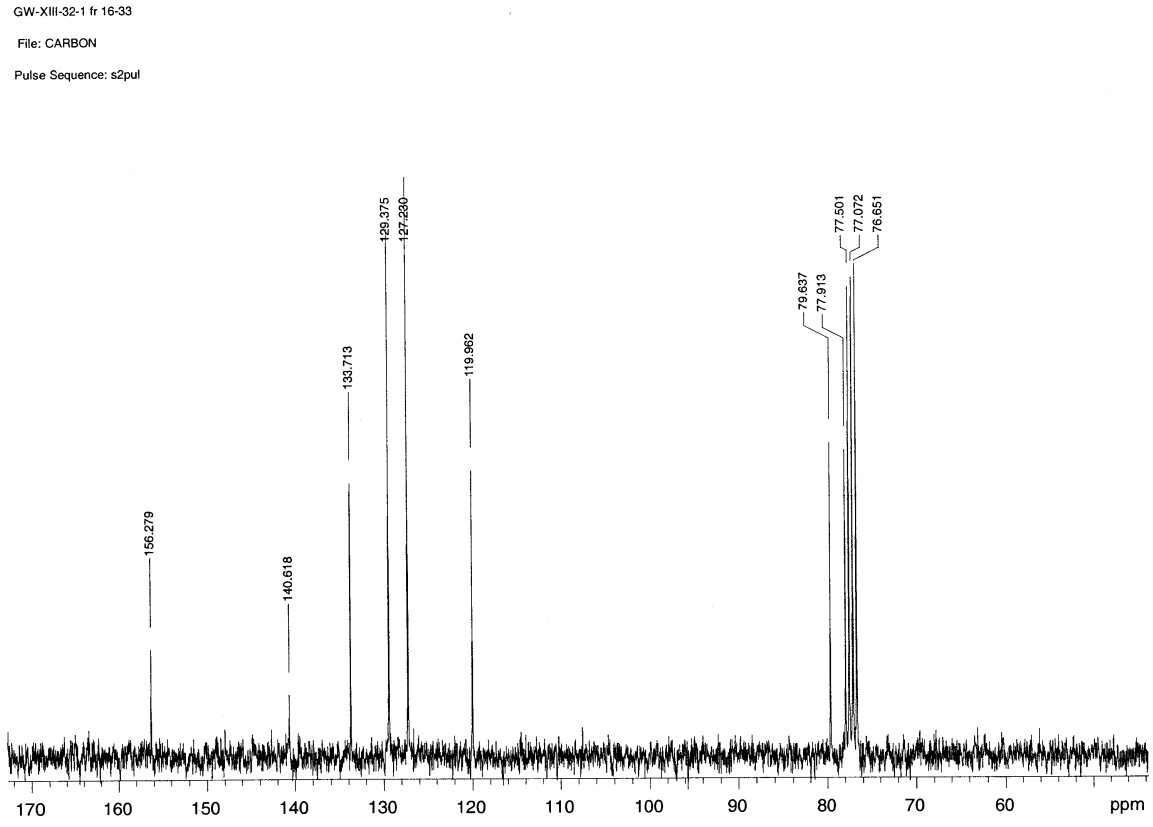
Appendix


GW-XI-4-1 fr 20
File: PROTON
Pulse Sequence: s2pul
Cl
O
O
7.260
2.174
Me2CO
7.311
7.161
7
6
5
4
3
2
1
ppm
1.98
1.91
0.92
1.97
2.00
2.02
3.16
2.02
1.98
1.38
0.56

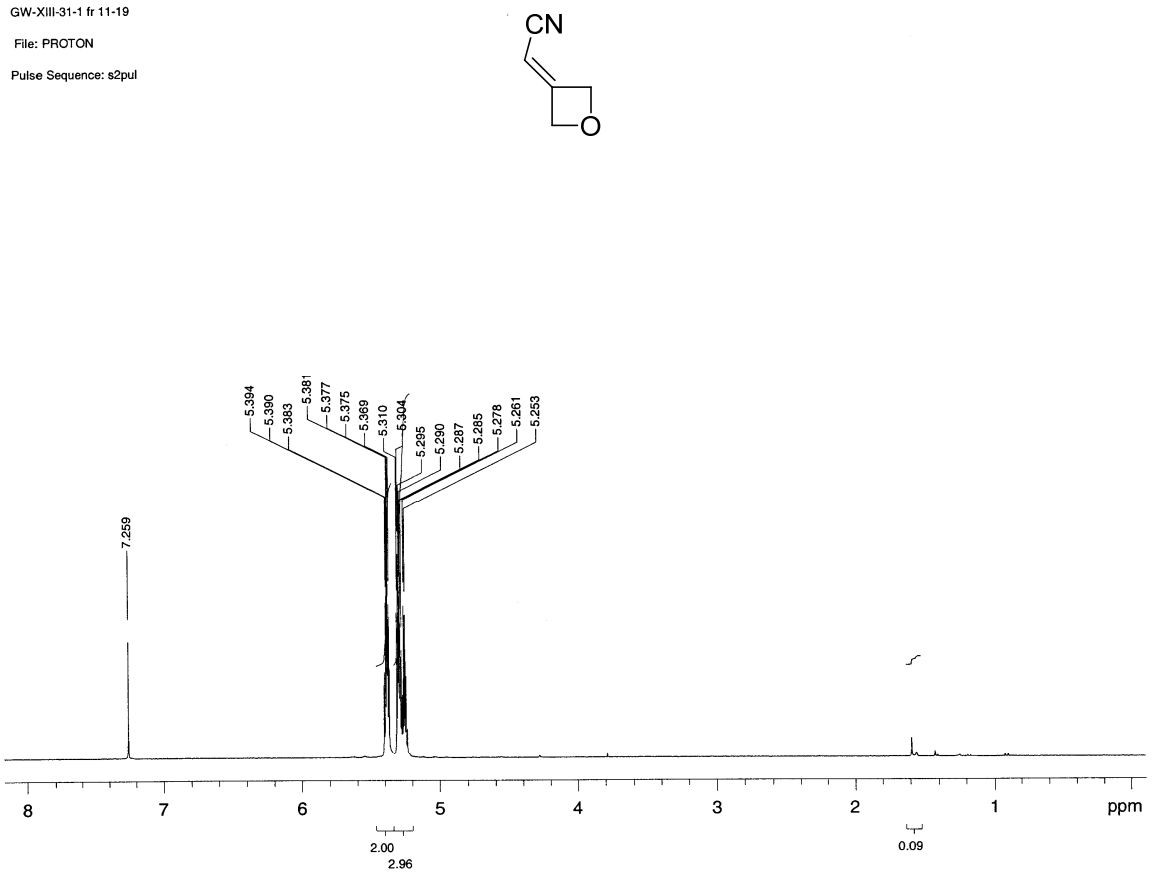

GW-X-49-1 fr 5-16
File: CARBON
Pulse Sequence: s2pul
197.785
160.318
141.046
132.726
128.889
127.675
113.543
82.430
79.055
77.476
77.055
76.626
57.686
30.304
15.994
200
180
160
140
120
100
80
60
40
20
ppm

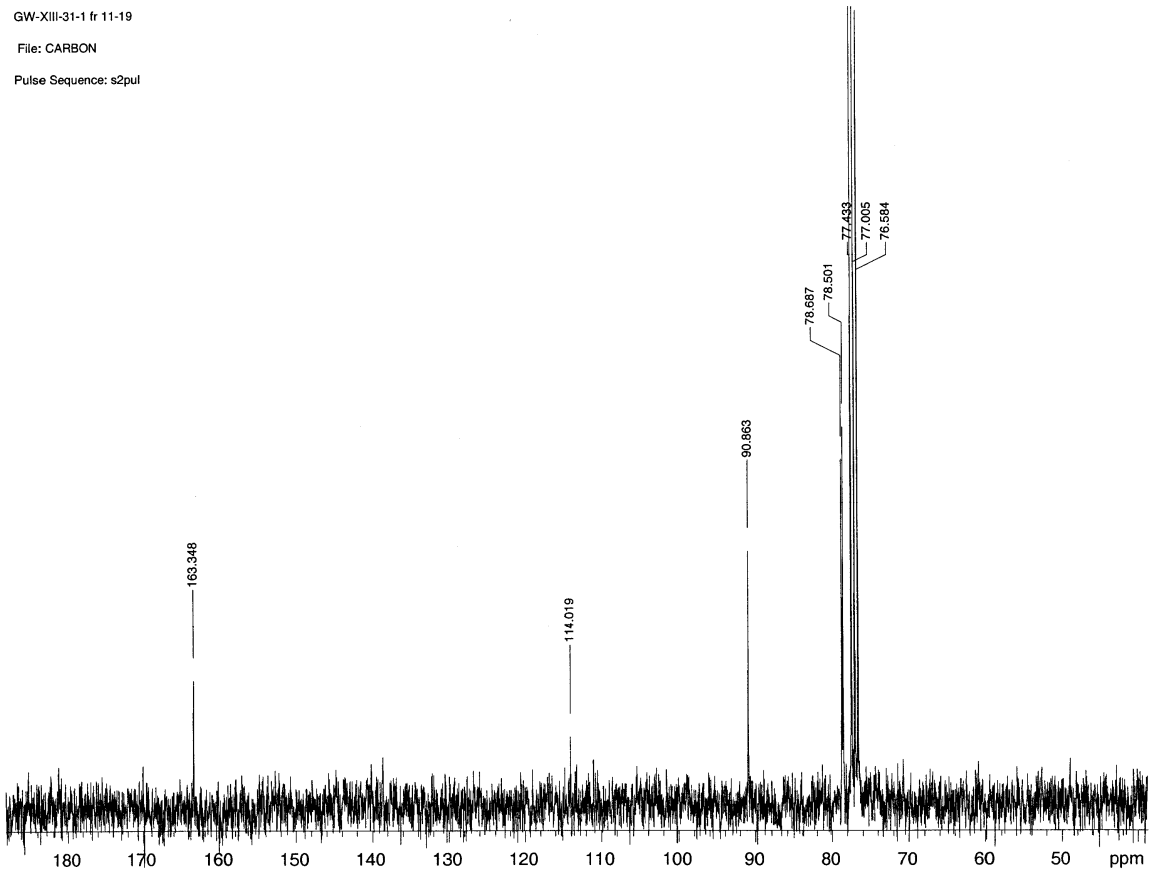
Appendix


STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
SO2Ph
O
7.892
7.865
7.681
7.656
7.633
7.590
7.566
7.542
7.260
6.119
5.642
5.634
5.282
5.278
9
8
7
6
5
4
3
2
1
ppm
2.02
3.10
0.95
2.00
2.01
0.10

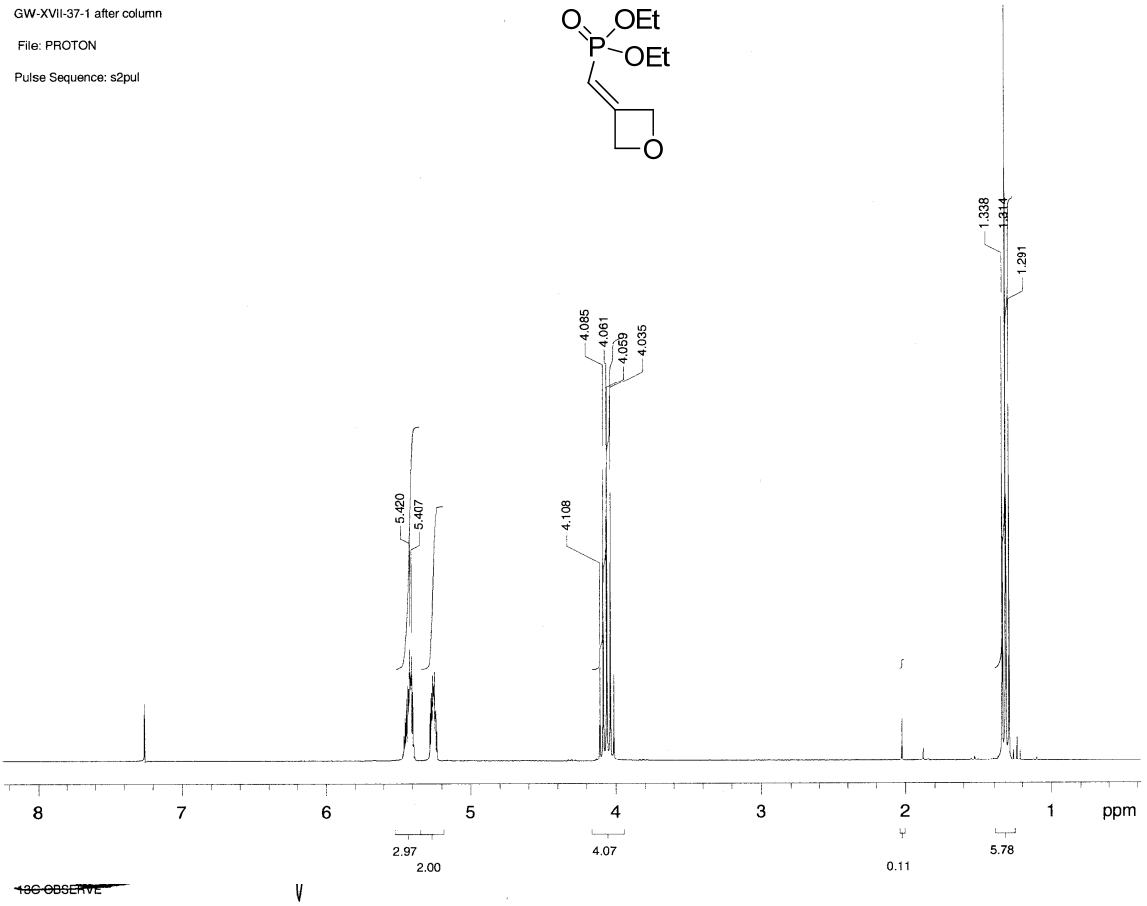

GW-XIII-32-1 fr 16-33
File: CARBON
Pulse Sequence: s2pul
156.279
140.618
133.713
129.375
127.280
119.962
79.637
77.913
77.501
77.072
76.651
170
160
150
140
130
120
110
100
90
80
70
60
ppm

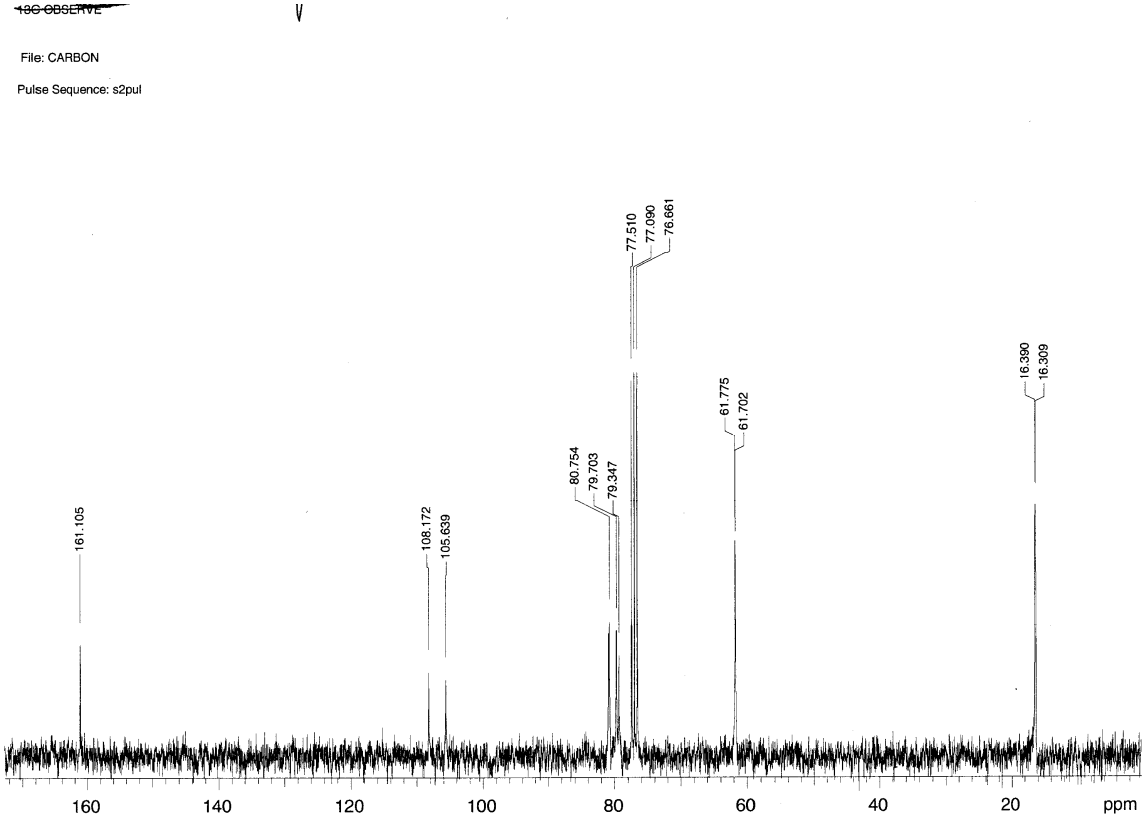
Appendix


GW-XIII-31-1 fr 11-19
File: PROTON
Pulse Sequence: s2pul
CN
O
5.394
5.390
5.383
5.381
5.377
5.375
5.369
5.310
5.304
5.295
5.290
5.287
5.285
5.278
5.261
5.253
7.259
8
7
6
5
4
3
2
1
ppm
2.00
2.96
0.09

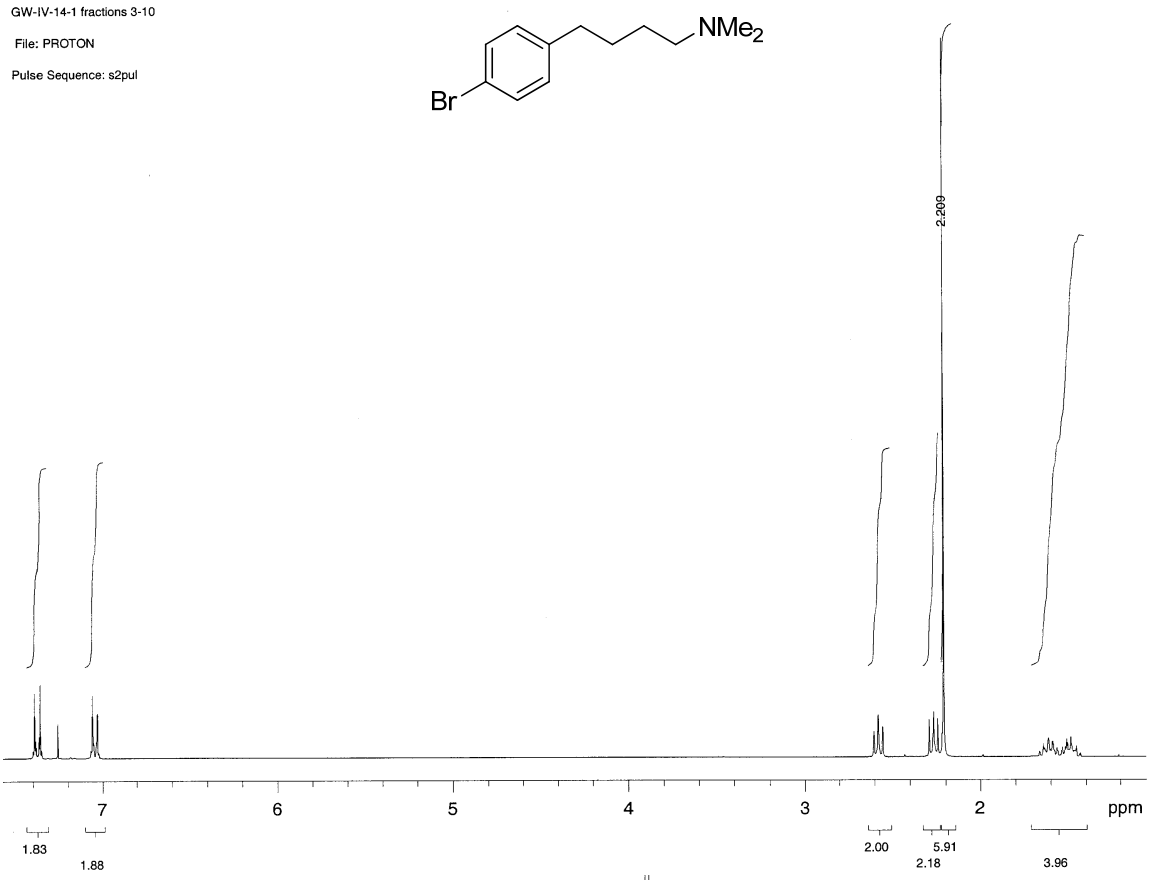

GW-XIII-31-1 fr 11-19
File: CARBON
Pulse Sequence: s2pul
163.348
114.019
90.863
78.687
78.501
77.433
77.005
76.584
180
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

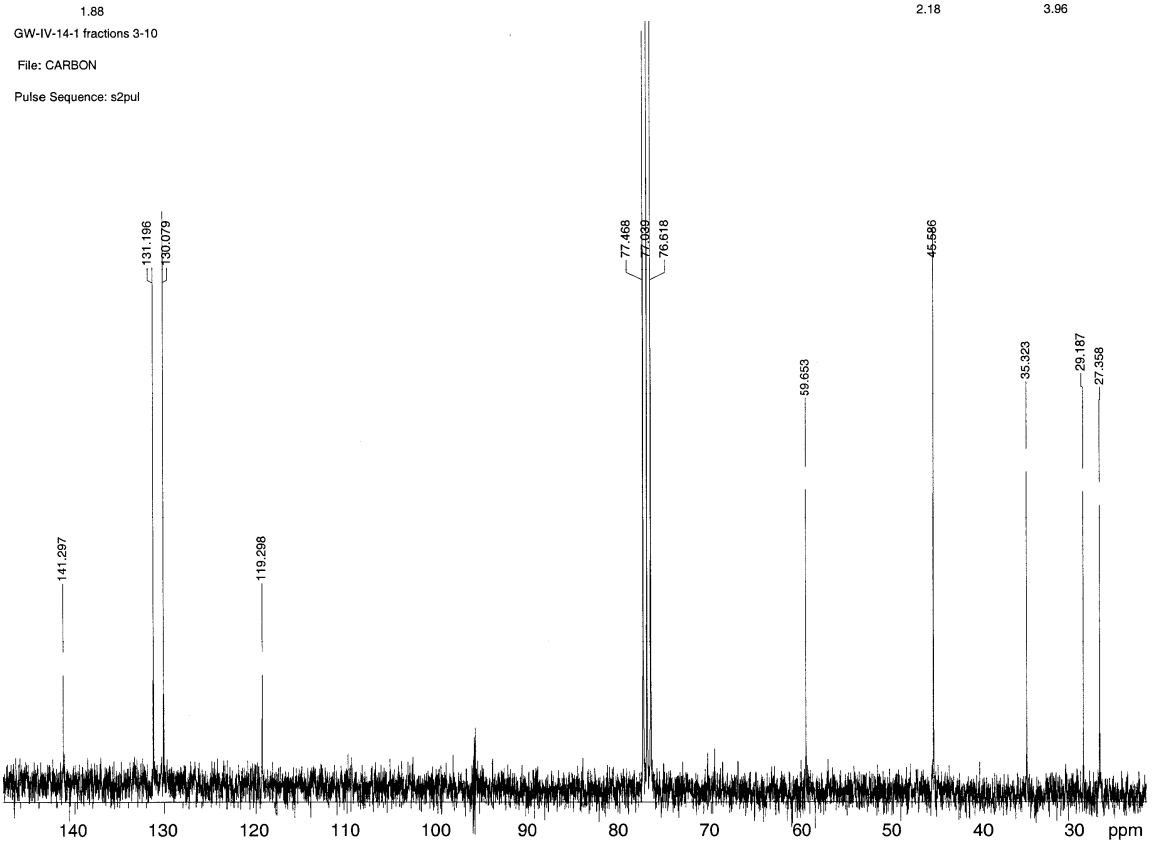
Appendix


GW-XVII-37-1 after column
File: PROTON
Pulse Sequence: s2pul
O
OEt
P
OEt
O
1.338
1.314
1.291
4.085
4.061
4.059
4.035
5.420
5.407
4.108
8
7
6
5
4
3
2
1
ppm
2.97
2.00
4.07
0.11
5.78

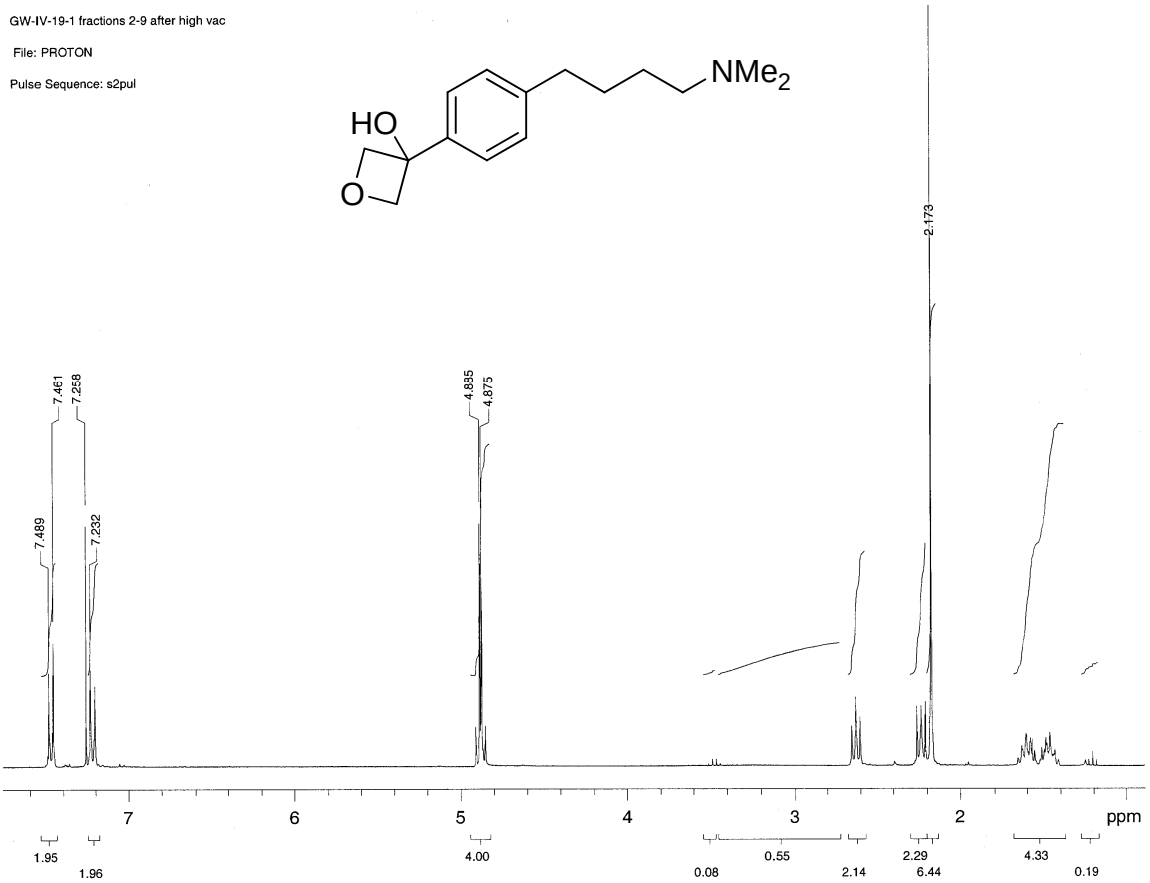

13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
77.510
77.090
76.661
16.390
16.309
61.775
61.702
80.754
79.703
79.347
161.105
108.172
105.639
160
140
120
100
80
60
40
20
ppm

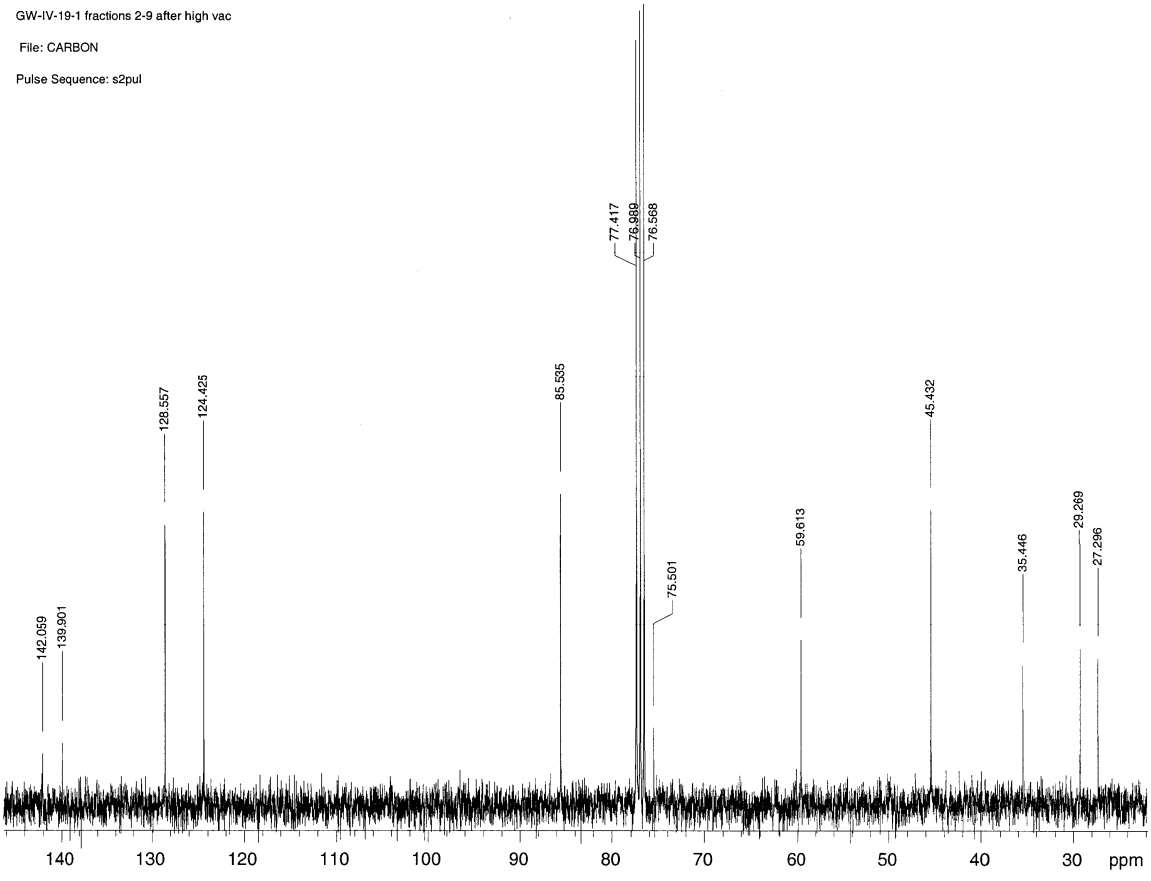
Appendix


GW-IV-14-1 fractions 3-10
File: PROTON
Pulse Sequence: s2pul
Br
NMe2
2.209
7
6
5
4
3
2
ppm
1.83
1.88
2.00
5.91
2.18
3.96

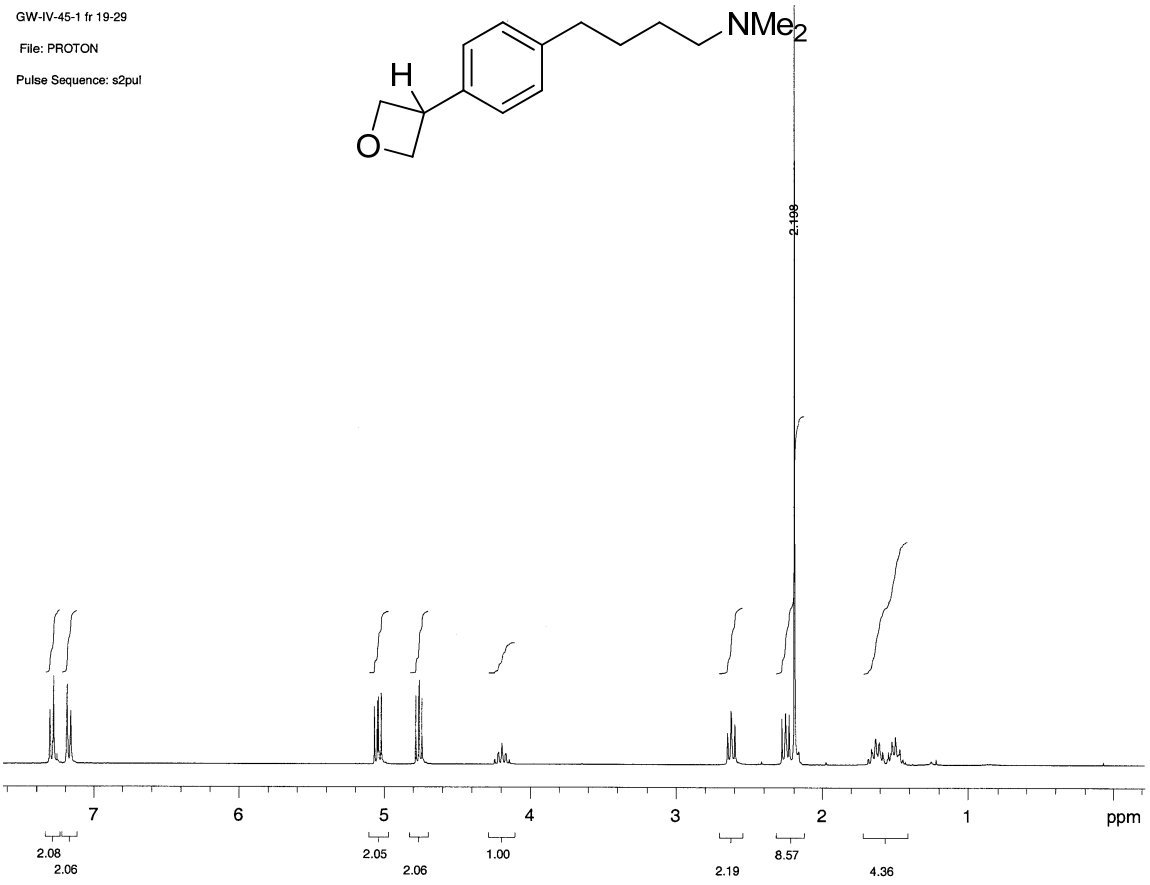

GW-IV-14-1 fractions 3-10
File: CARBON
Pulse Sequence: s2pul
131.196
130.079
77.468
77.039
76.618
45.586
59.653
35.323
29.187
27.358
141.297
119.298
140
130
120
110
100
90
80
70
60
50
40
30
ppm

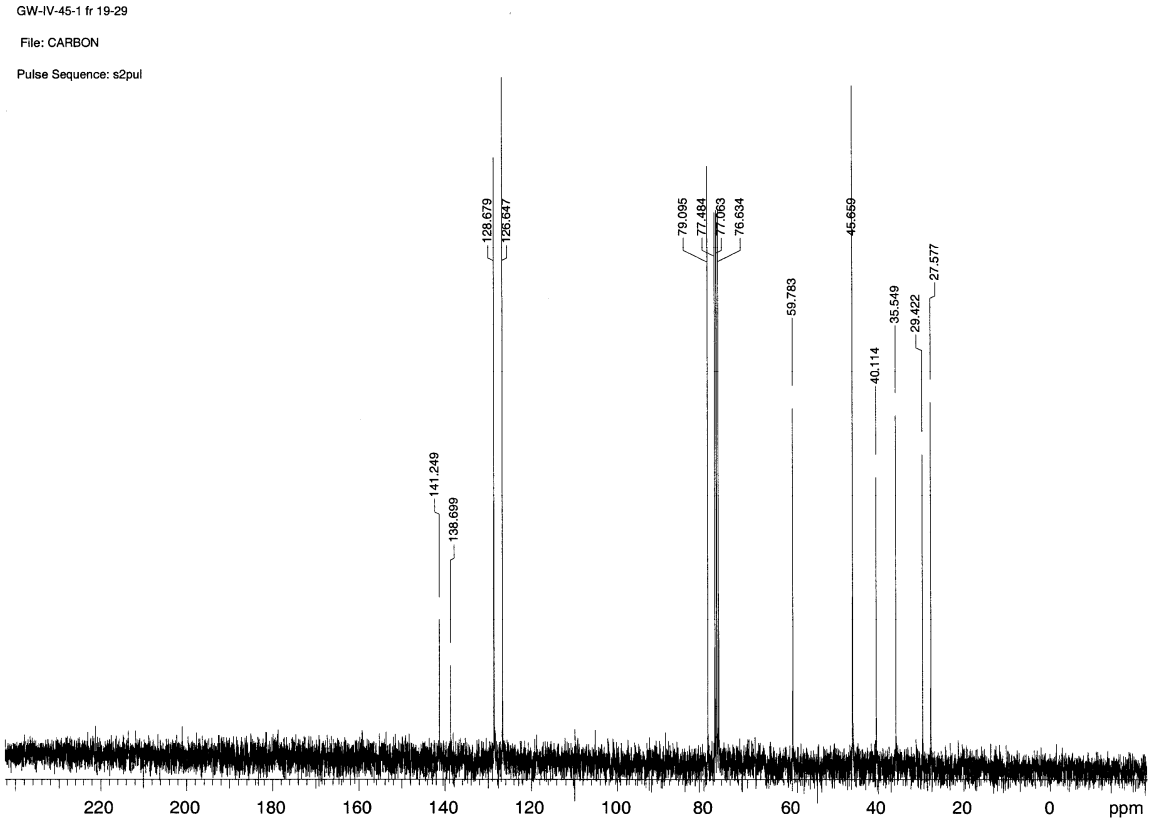
Appendix


GW-IV-19-1 fractions 2-9 after high vac
File: PROTON
Pulse Sequence: s2pul
HO
O
NMe2
7.461
7.258
7.489
7.232
4.835
4.875
2.173
7
6
5
4
3
2
ppm
1.95
1.96
4.00
0.08
0.55
2.14
2.29
6.44
4.33
0.19

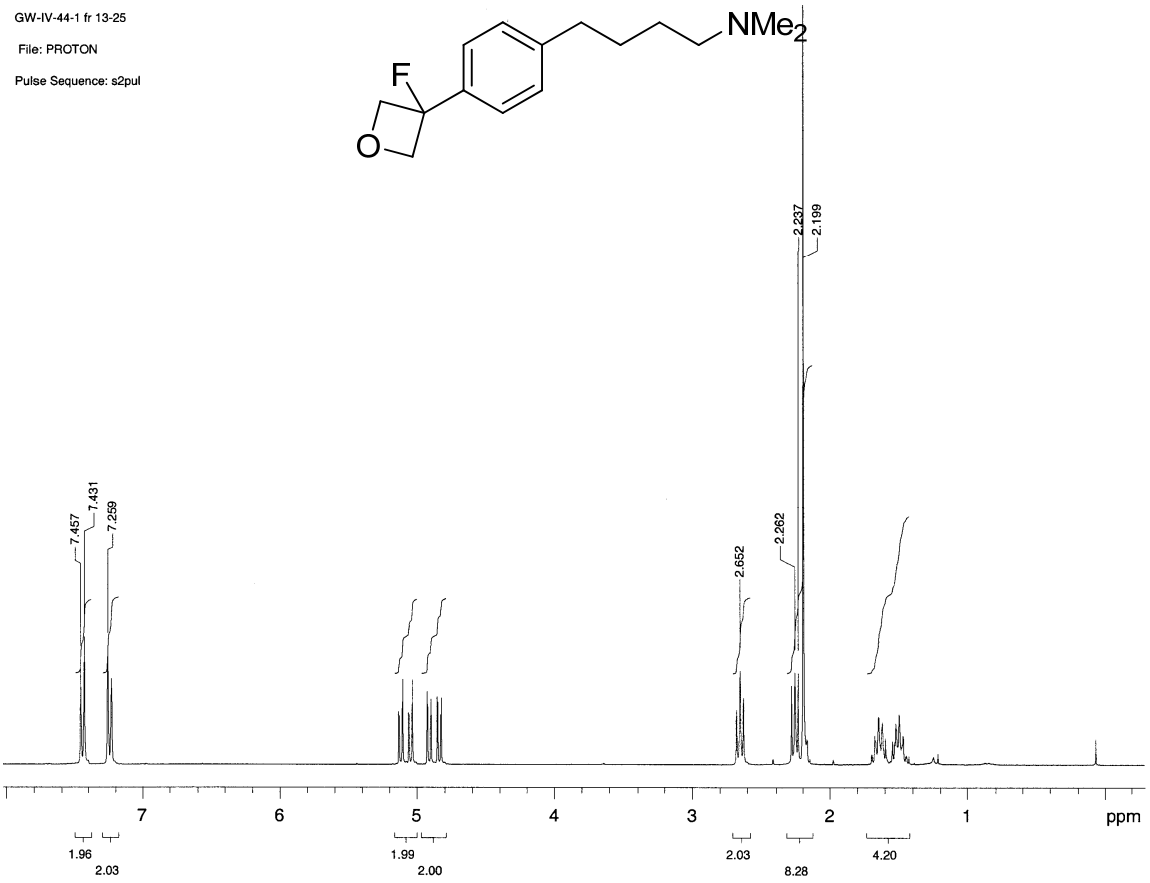

GW-IV-19-1 fractions 2-9 after high vac
File: CARBON
Pulse Sequence: s2pul
142.059
139.901
128.557
124.425
85.535
77.417
76.989
76.568
75.501
59.613
45.432
35.446
29.269
27.296
140
130
120
110
100
90
80
70
60
50
40
30
ppm

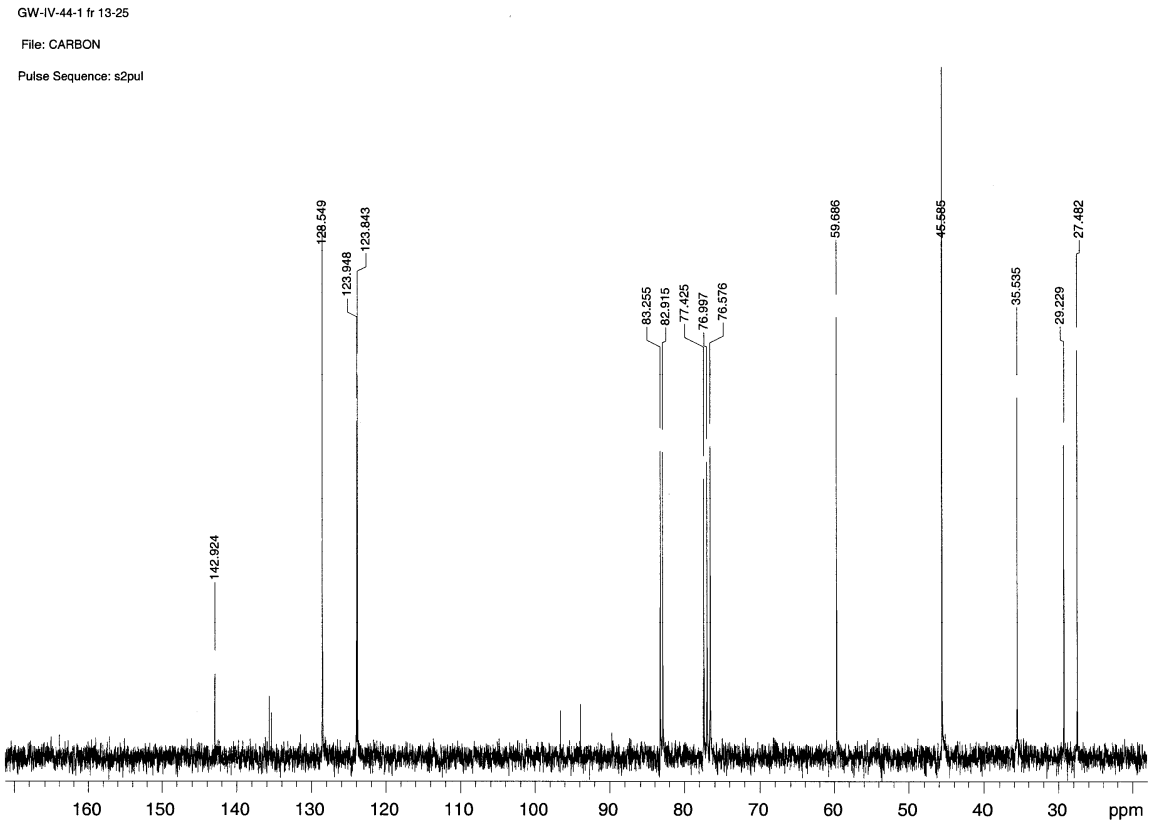
Appendix


GW-IV-45-1 fr 19-29
File: PROTON
Pulse Sequence: s2pul
NMe2
H
O
2.108
7
6
5
4
3
2
1
ppm
2.08
2.06
2.05
2.06
1.00
2.19
8.57
4.36

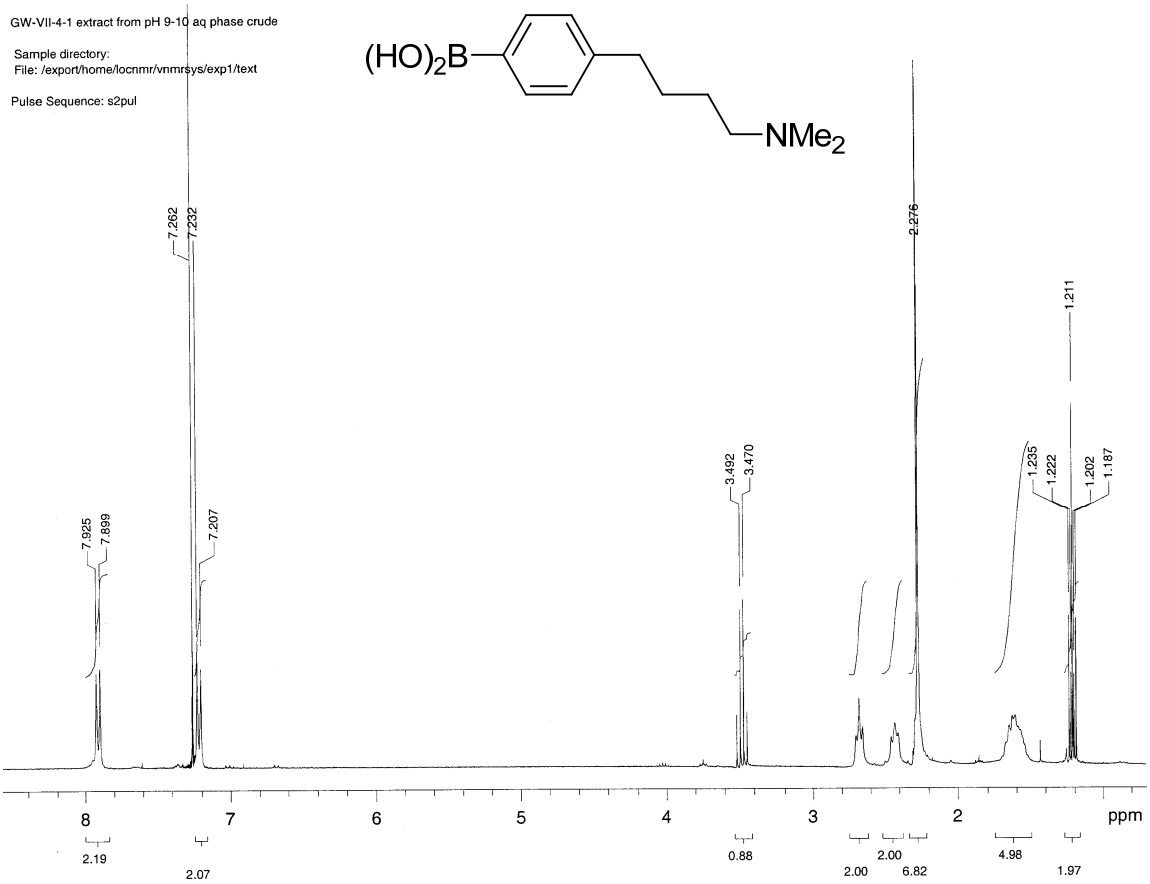

GW-IV-45-1 fr 19-29
File: CARBON
Pulse Sequence: s2pul
141.249
138.699
128.679
126.647
79.095
77.484
77.063
76.634
59.783
45.669
40.114
35.549
29.422
27.577
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix

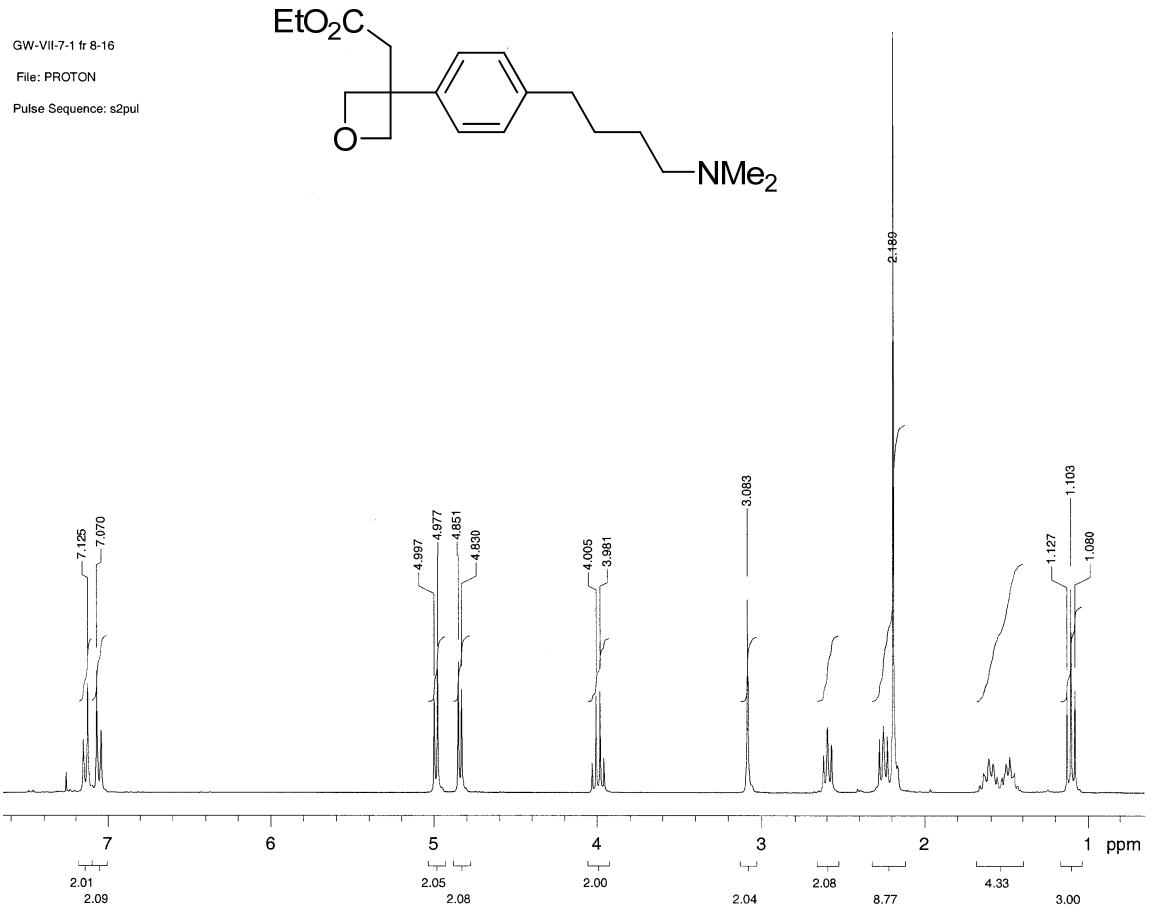

GW-IV-44-1 fr 13-25
File: PROTON
Pulse Sequence: s2pul
NMe2
F
O
2.237
2.199
7.457
7.431
7.259
2.652
2.262
7
6
5
4
3
2
1
ppm
1.96
2.03
1.99
2.00
2.03
8.28
4.20

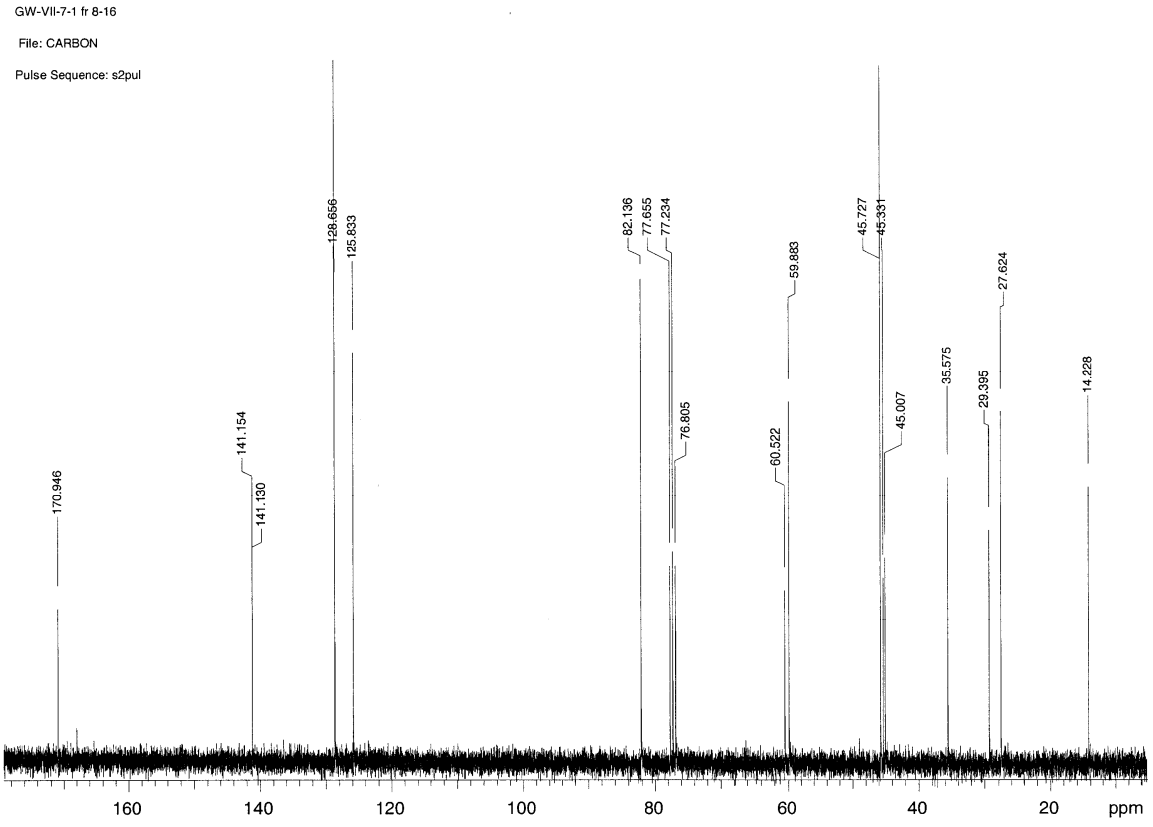

GW-IV-44-1 fr 13-25
File: CARBON
Pulse Sequence: s2pul
128.549
123.948
123.843
142.924
83.255
82.915
77.425
76.997
76.576
59.686
45.585
35.535
29.229
27.482
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Appendix

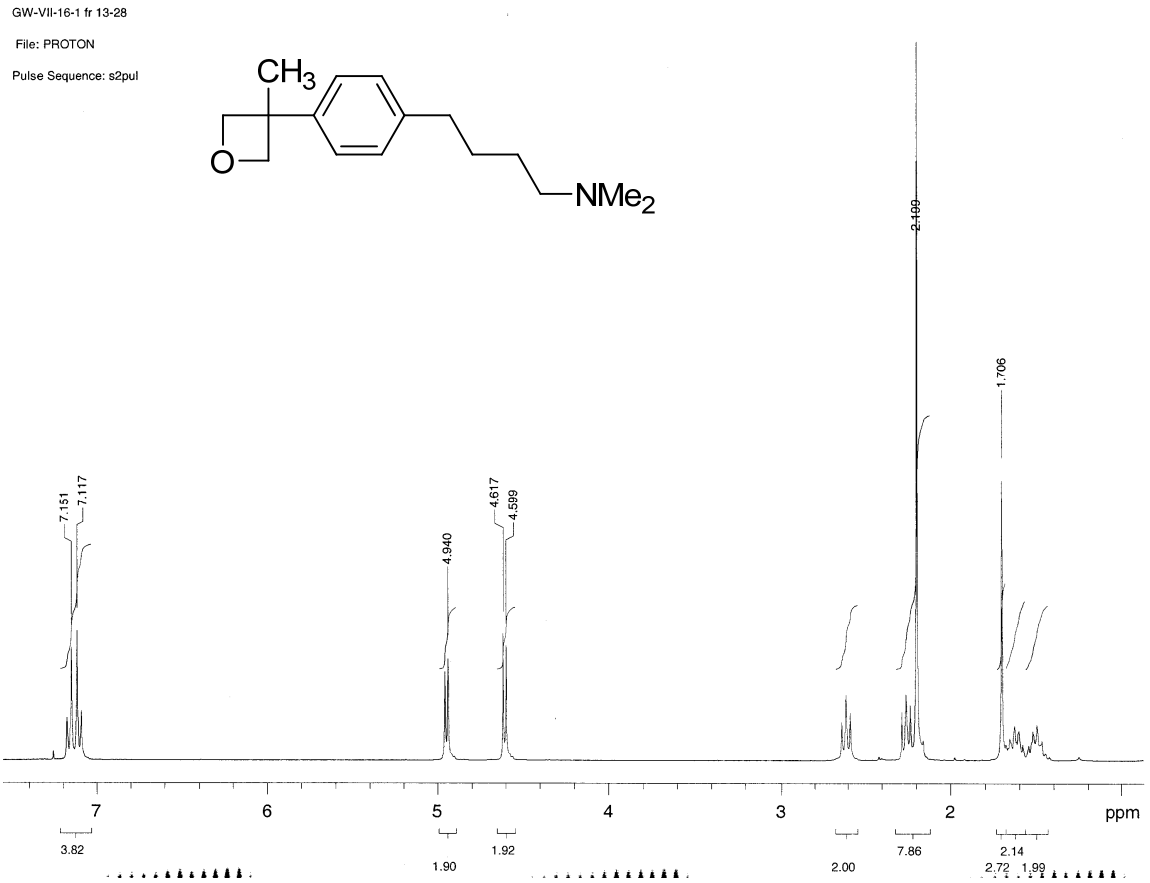

GW-VII-4-1 extract from pH 9-10 aq phase crude
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
(HO)2B
NMe2
7.925
7.899
7.262
7.232
7.207
3.492
3.470
2.276
1.235
1.222
1.211
1.202
1.187
8
7
6
5
4
3
2
ppm
2.19
2.07
0.88
2.00
2.00
6.82
4.98
1.97

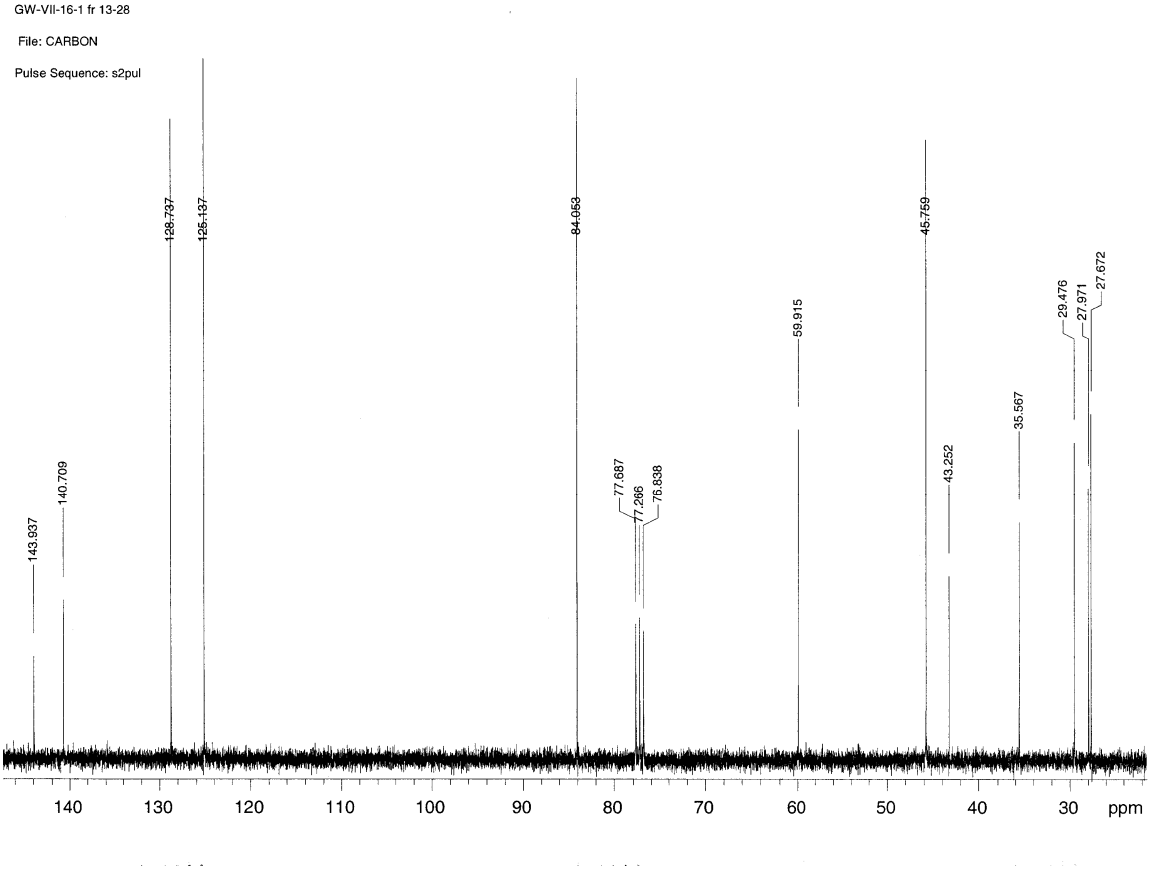
Appendix


GW-VII-7-1 fr 8-16
File: PROTON
Pulse Sequence: s2pul
EtO2C
O
NMe2
7.125
7.070
4.997
4.977
4.851
4.830
4.005
3.981
3.083
2.180
1.127
1.103
1.080
7
6
5
4
3
2
1 ppm
2.01
2.09
2.05
2.08
2.00
2.04
2.08
8.77
4.33
3.00

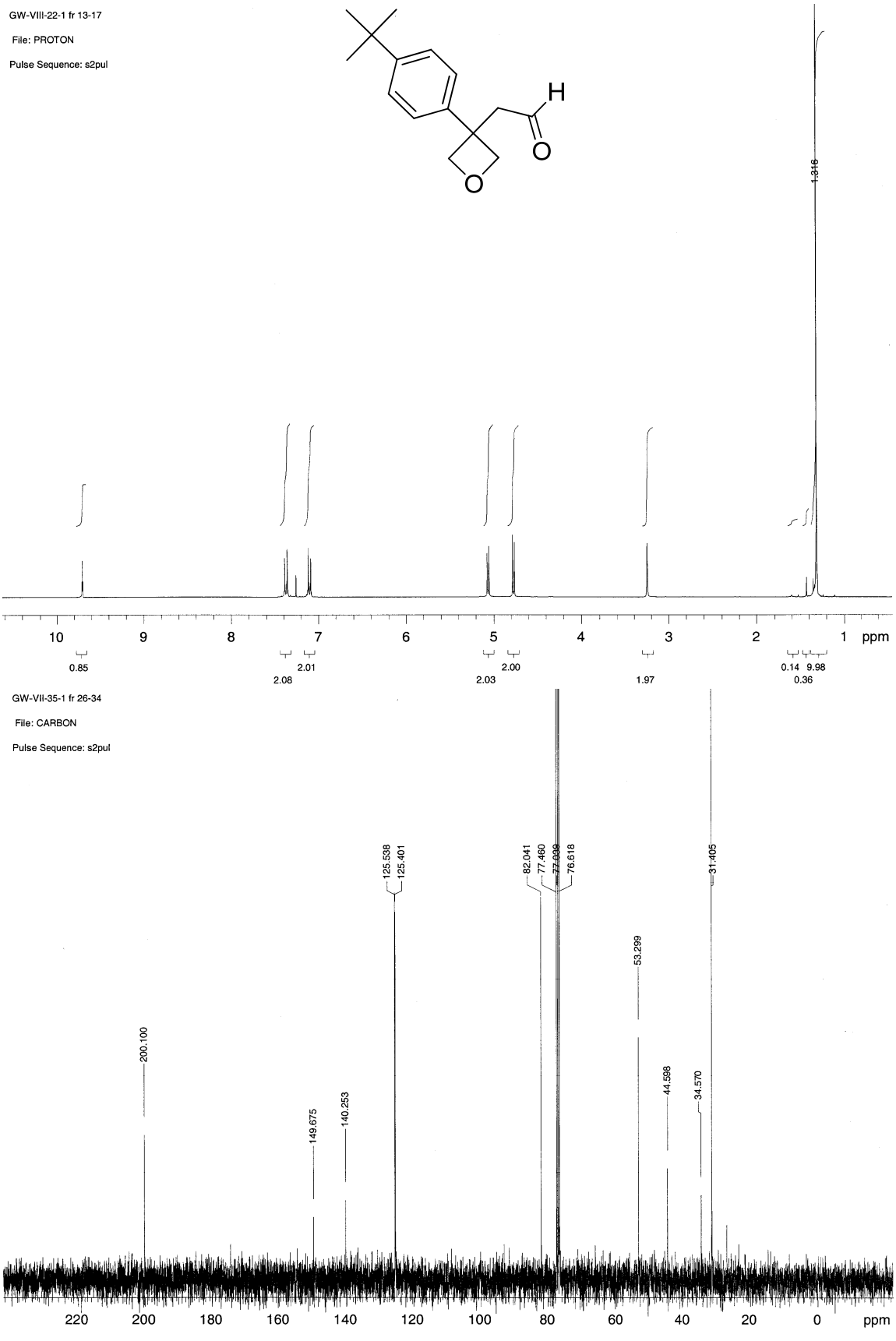

GW-VII-7-1 fr 8-16
File: CARBON
Pulse Sequence: s2pul
170.946
141.154
141.130
128.656
125.833
82.136
77.655
77.234
76.805
60.522
59.883
45.727
45.331
45.007
35.575
29.395
27.624
14.228
160
140
120
100
80
60
40
20
ppm

Appendix

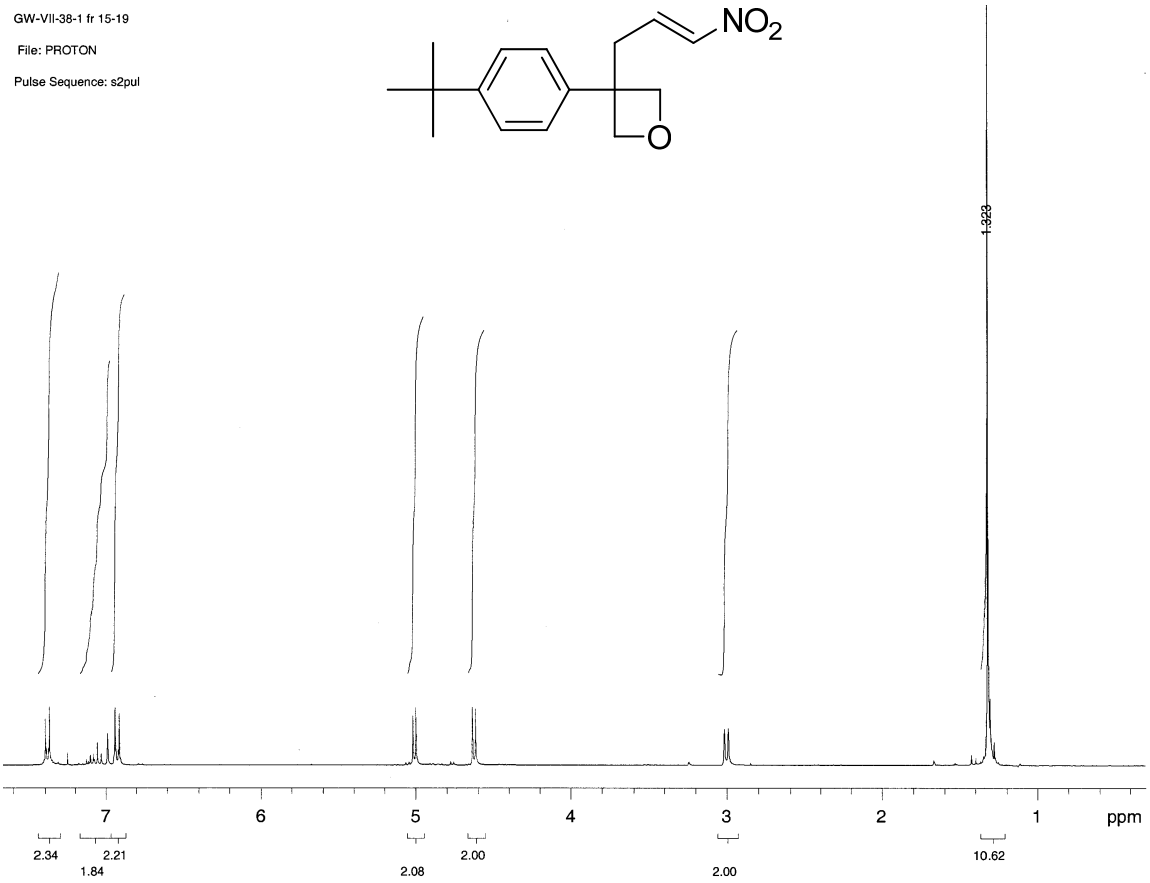

GW-VII-16-1 fr 13-28
File: PROTON
Pulse Sequence: s2pul
CH3
O
NMe2
2.109
1.706
7.151
7.117
4.940
4.617
4.599
7
6
5
4
3
2
ppm
3.82
1.90
1.92
2.00
7.86
2.14
2.72
1.99

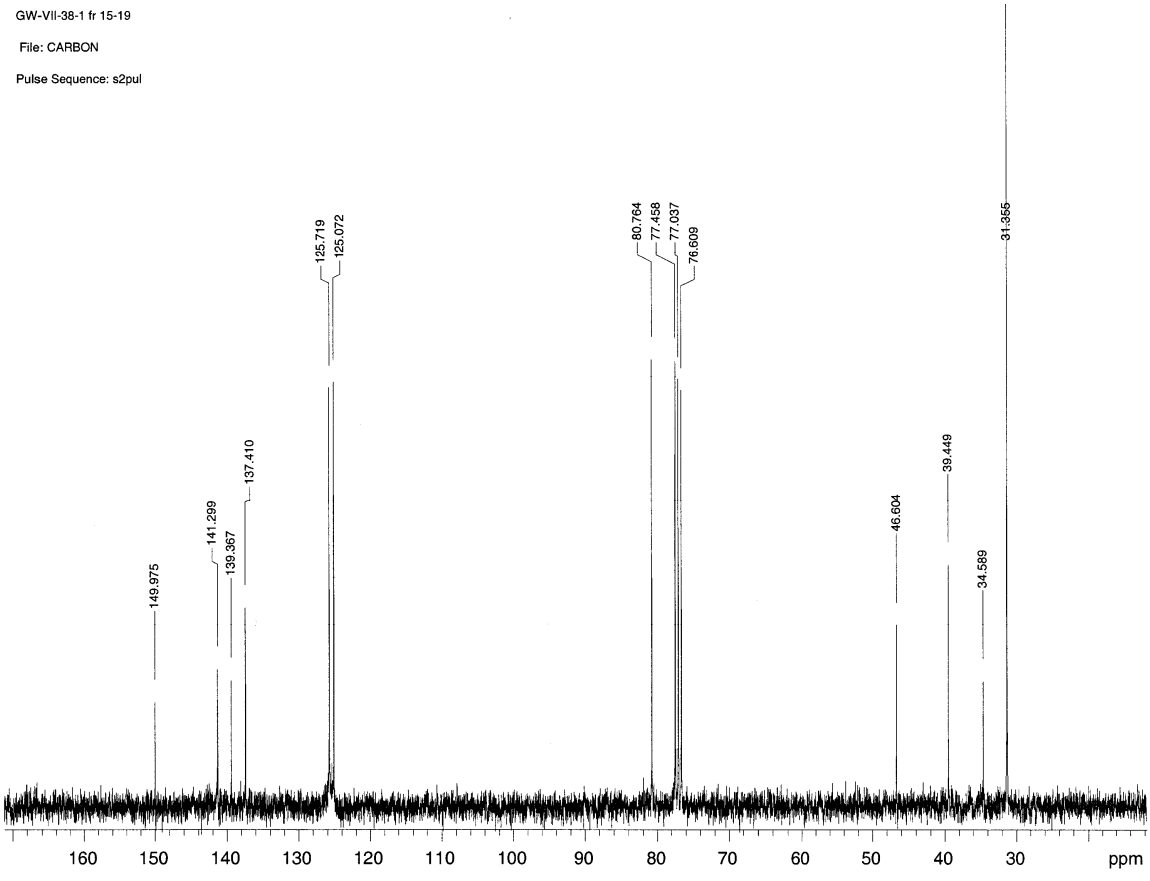

GW-VII-16-1 fr 13-28
File: CARBON
Pulse Sequence: s2pul
143.937
140.709
128.737
126.137
84.053
77.687
77.266
76.838
59.915
45.759
43.252
35.567
29.476
27.971
27.672
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Appendix

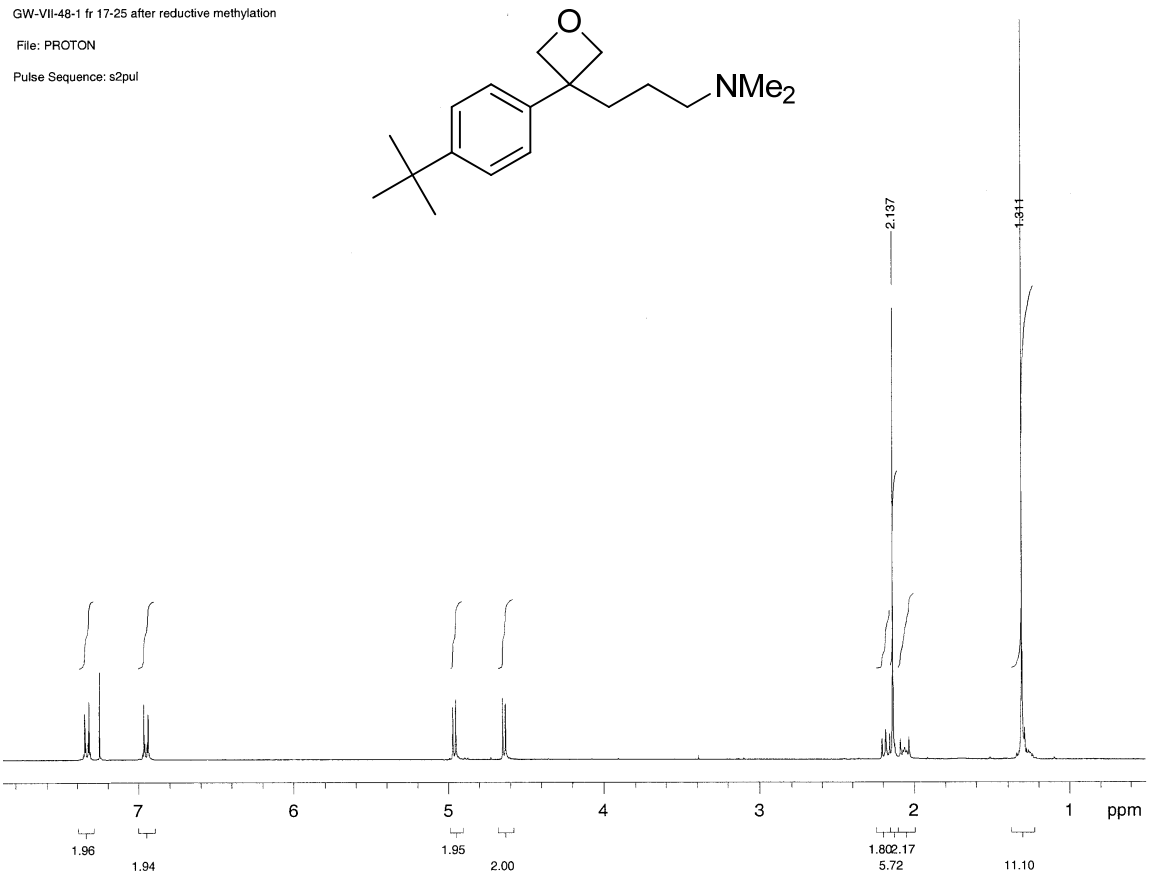

GW-VIII-22-1 fr 13-17
File: PROTON
Pulse Sequence: s2pul
H
O
O
1.816
10
9
8
7
6
5
4
3
2
1
ppm
0.85
2.01
2.08
2.00
2.03
1.97
0.14
9.98
0.36
GW-VII-35-1 fr 26-34
File: CARBON
Pulse Sequence: s2pul
200.100
149.675
140.253
125.538
125.401
82.041
77.460
77.038
76.618
53.299
44.598
34.570
31.405
220
200
180
160
140
120
100
80
60
40
20
0
ppm

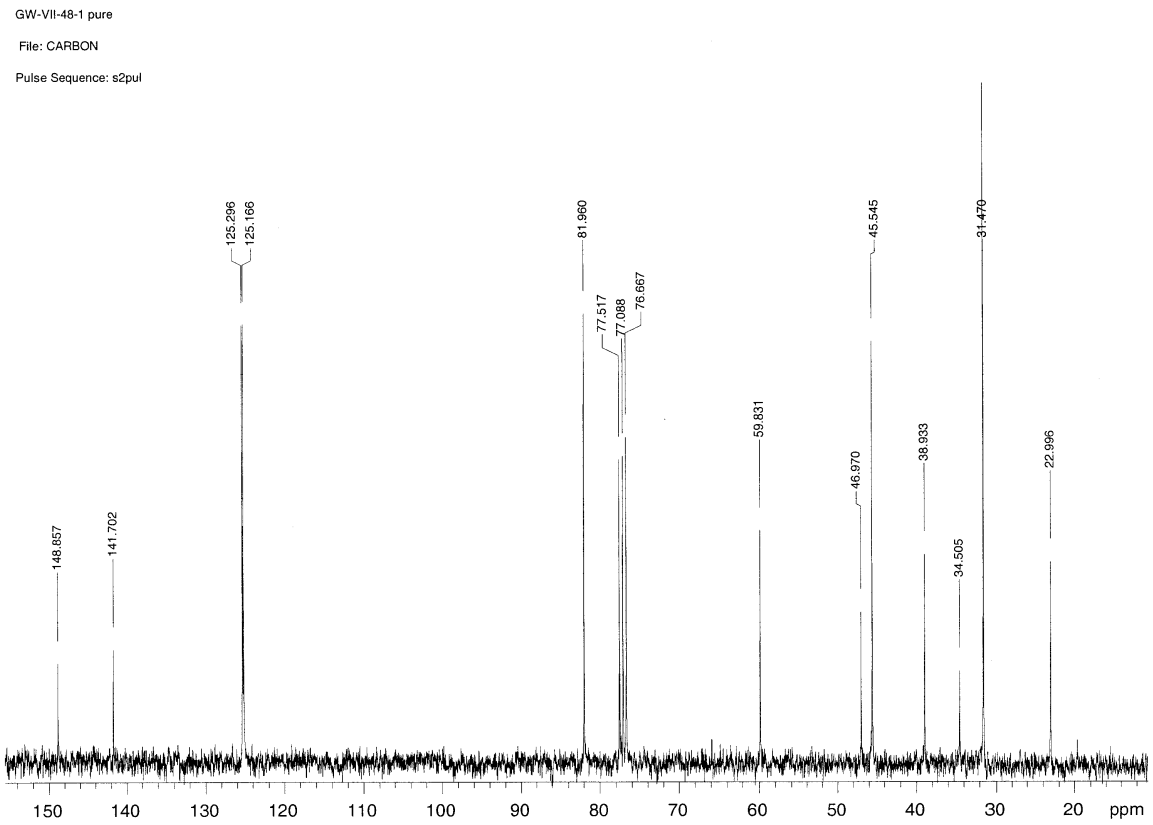
Appendix


GW-VII-38-1 fr 15-19
File: PROTON
Pulse Sequence: s2pul
NO2
O
1.323
7
6
5
4
3
2
1
ppm
2.34
2.21
1.84
2.08
2.00
2.00
10.62

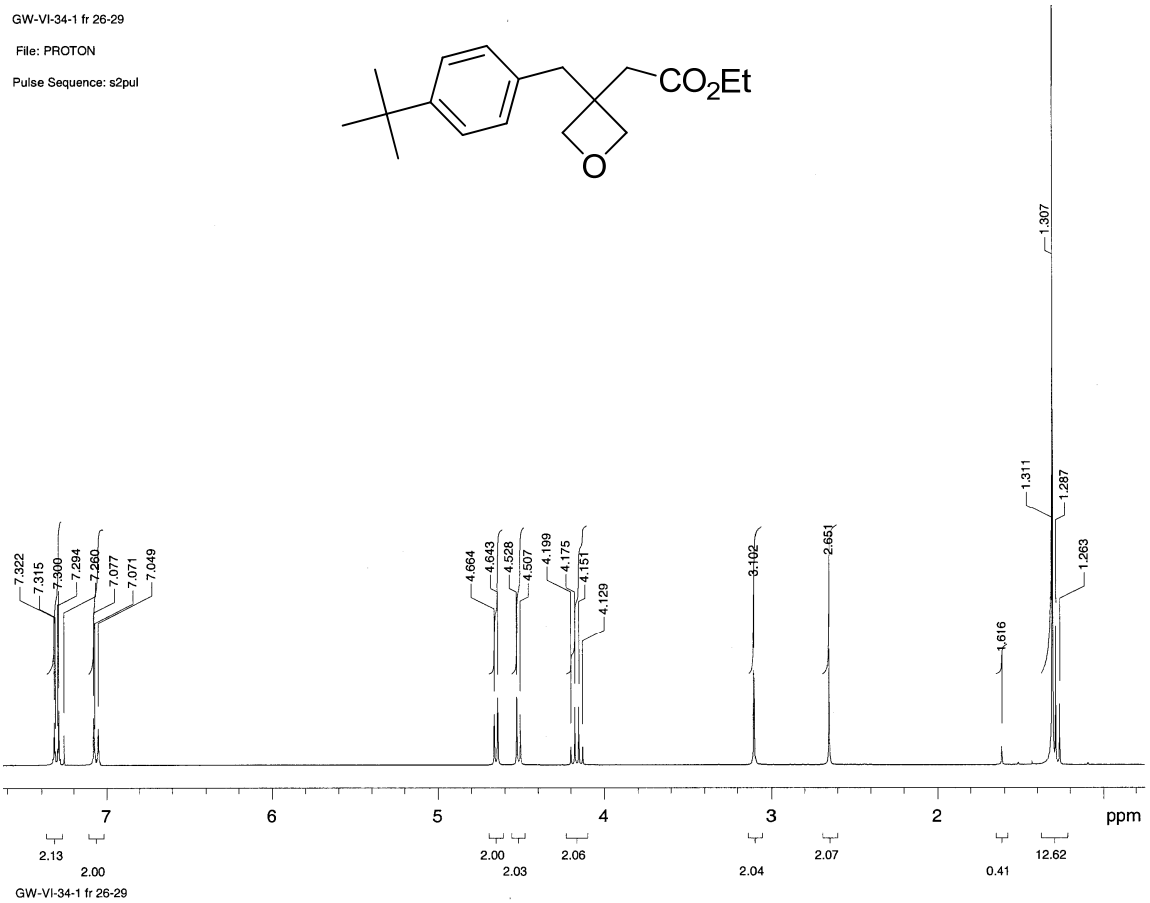

GW-VII-38-1 fr 15-19
File: CARBON
Pulse Sequence: s2pul
149.975
141.299
139.367
137.410
125.719
125.072
80.764
77.458
77.037
76.609
46.604
39.449
34.589
31.366
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

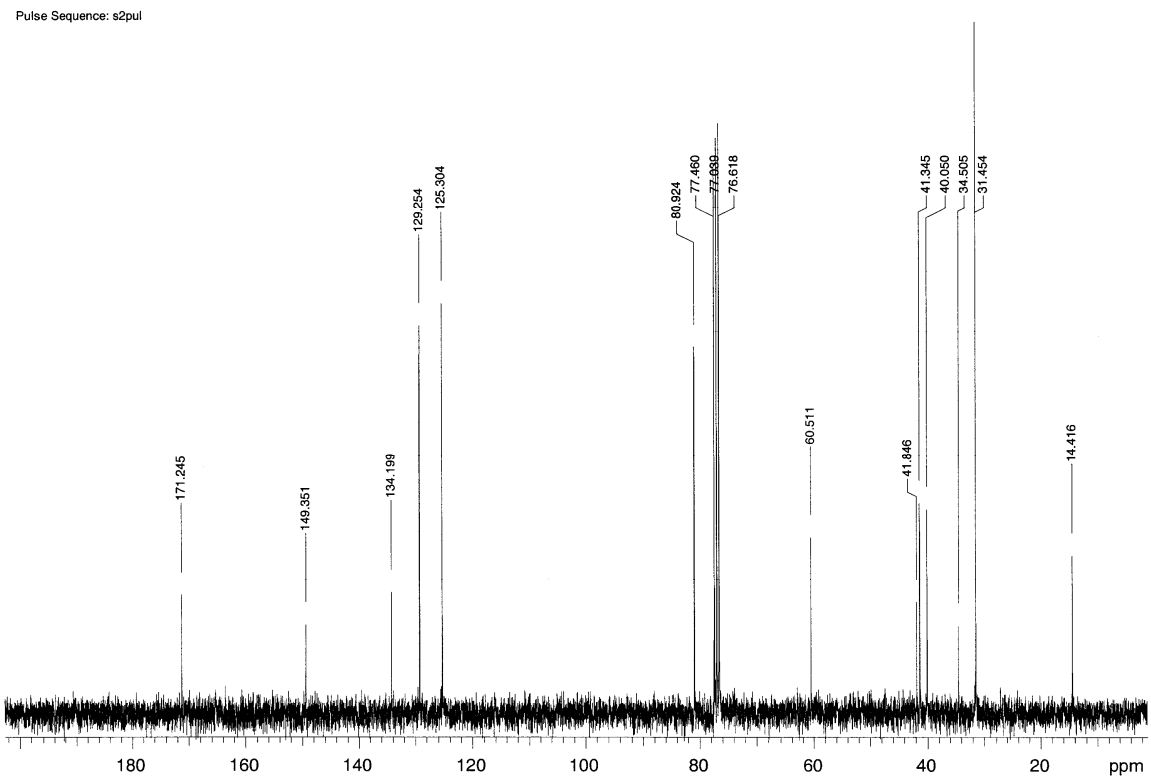
Appendix


GW-VII-48-1 fr 17-25 after reductive methylation
File: PROTON
Pulse Sequence: s2pul
O
NMe2
2.137
1.311
7
6
5
4
3
2
1
ppm
1.96
1.94
1.95
2.00
1.80
2.17
5.72
11.10

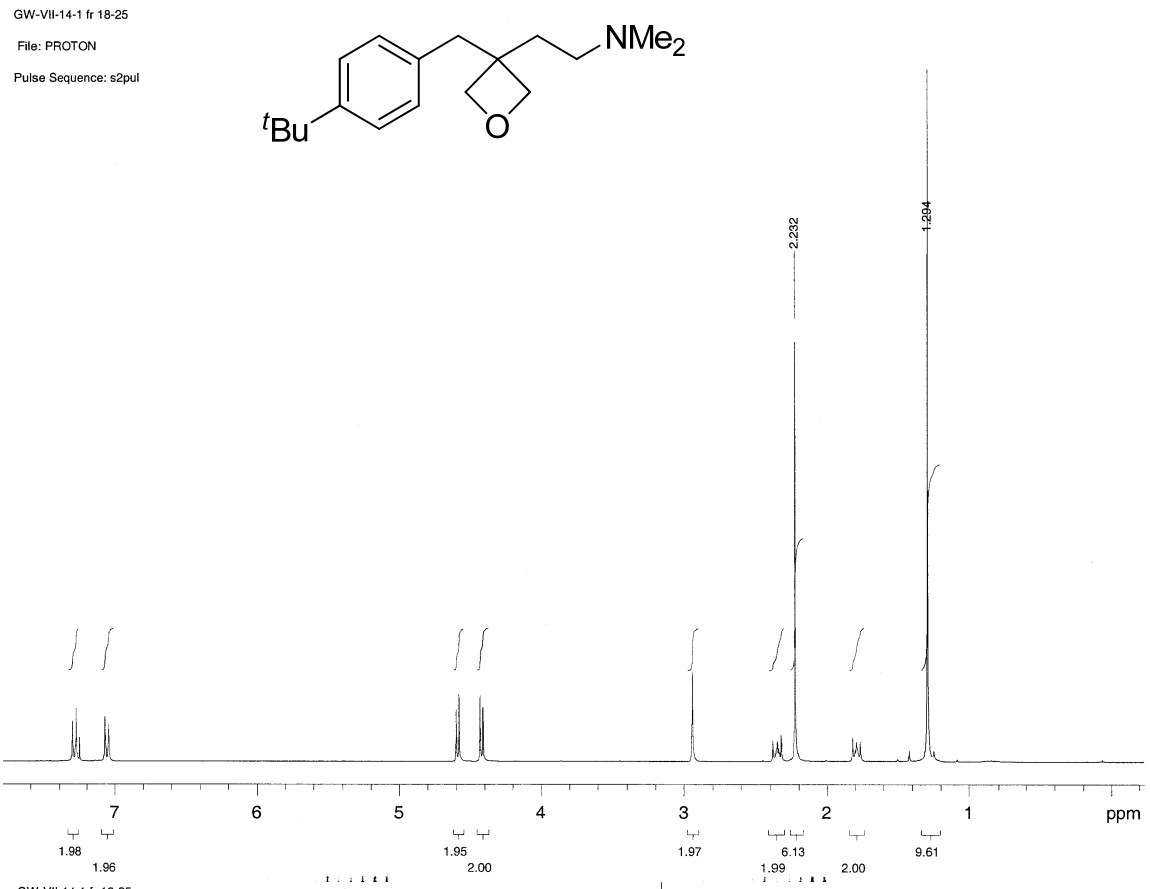

GW-VII-48-1 pure
File: CARBON
Pulse Sequence: s2pul
125.296
125.166
81.960
77.517
77.088
76.667
59.831
46.970
45.545
38.933
34.505
31.470
22.996
148.857
141.702
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

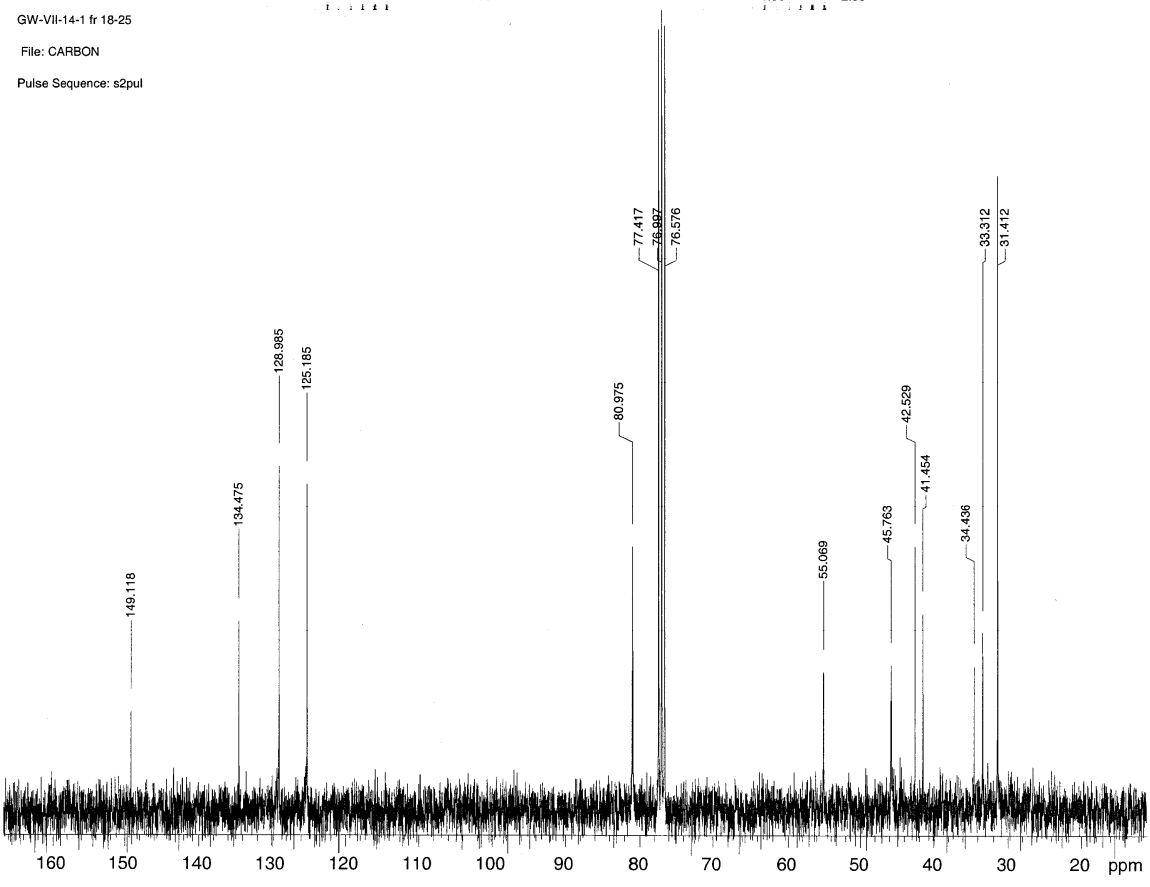
Appendix


GW-VI-34-1 fr 26-29
File: PROTON
Pulse Sequence: s2pul
CO2Et
O
1.307
1.311
1.287
1.263
1.616
7.322
7.315
7.300
7.294
7.260
7.077
7.071
7.049
4.664
4.643
4.528
4.507
4.199
4.175
4.151
4.129
3.102
2.651
7
6
5
4
3
2
ppm
2.13
2.00
2.00
2.03
2.06
2.04
2.07
0.41
12.62

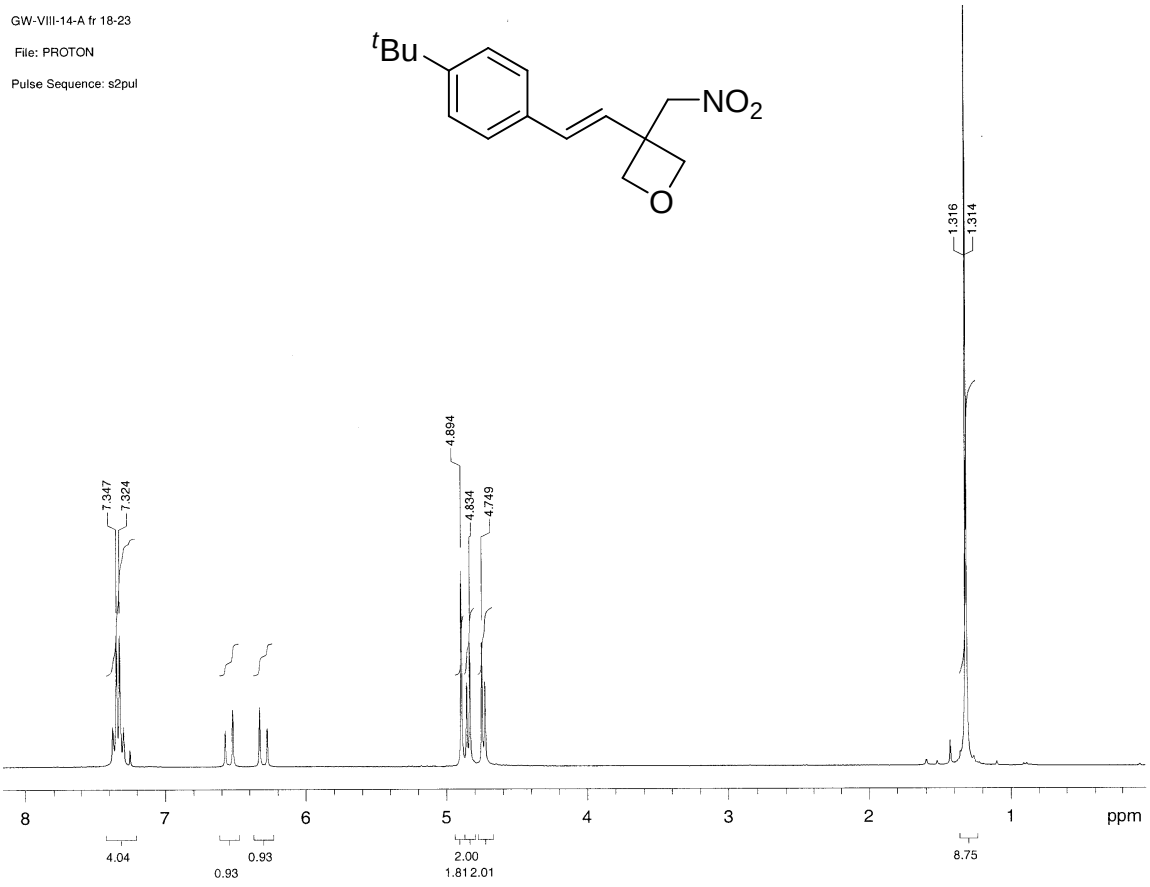

GW-VI-34-1 fr 26-29
Pulse Sequence: s2pul
171.245
149.351
134.199
129.254
125.304
80.924
77.460
77.039
76.618
60.511
41.846
41.345
40.050
34.505
31.454
14.416
180
160
140
120
100
80
60
40
20
ppm

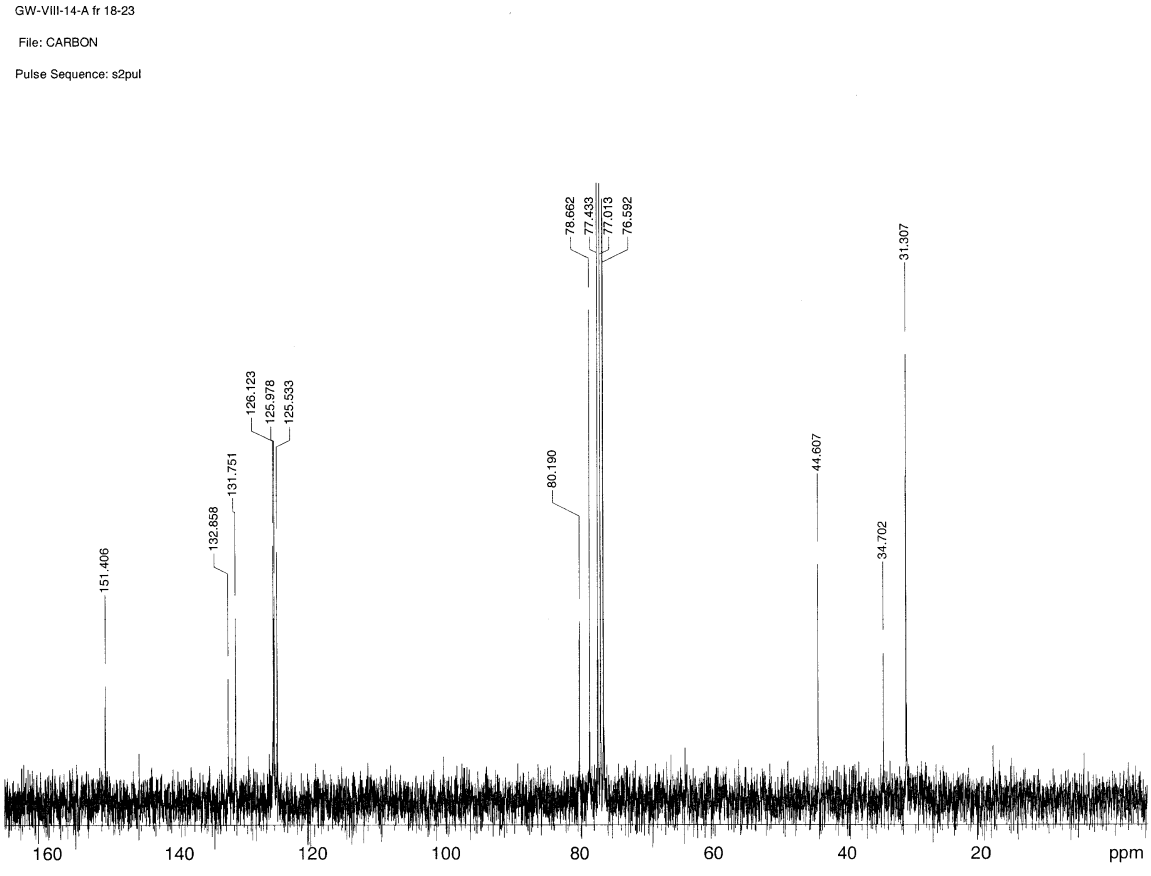
Appendix


GW-VII-14-1 fr 18-25
File: PROTON
Pulse Sequence: s2pul
NMe2
tBu
O
2.232
1.294
7
6
5
4
3
2
1
ppm
1.98
1.96
1.95
2.00
1.97
6.13
1.99
2.00
9.61

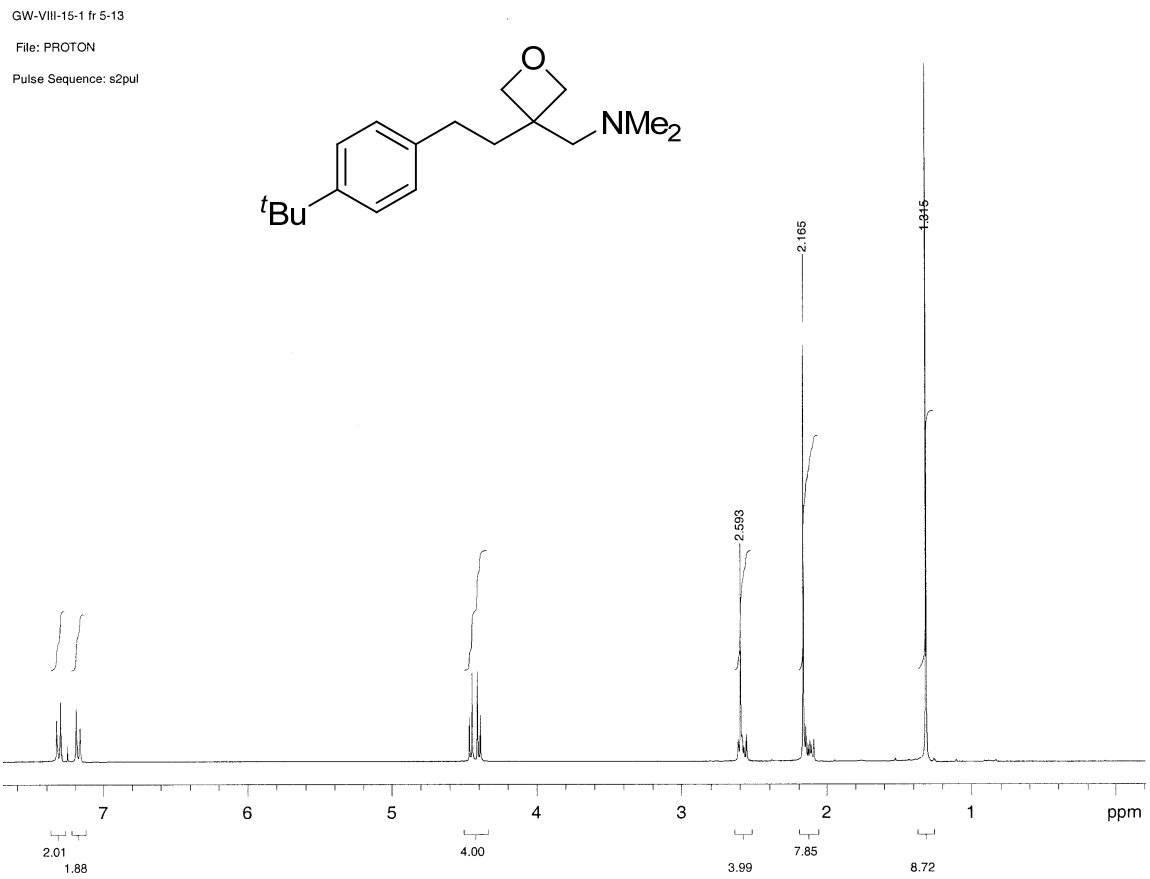

GW-VII-14-1 fr 18-25
File: CARBON
Pulse Sequence: s2pul
149.118
134.475
128.985
125.185
80.975
77.417
76.997
76.576
55.069
45.763
42.529
41.454
34.436
33.312
31.412
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

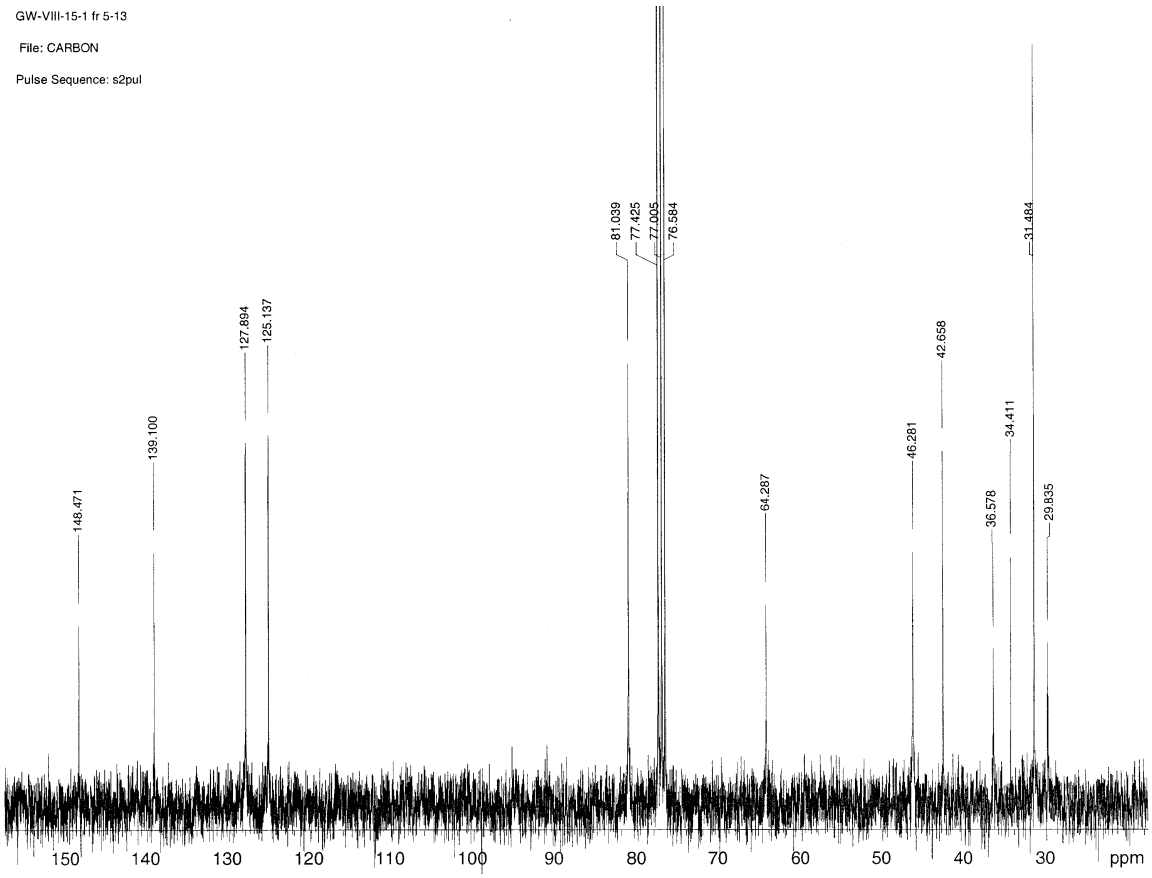
Appendix


GW-VIII-14-A fr 18-23
File: PROTON
Pulse Sequence: s2pul
tBu
NO2
O
1.316
1.314
4.894
4.834
4.749
7.347
7.324
8
7
6
5
4
3
2
1
ppm
4.04
0.93
0.93
2.00
1.81
2.01
8.75

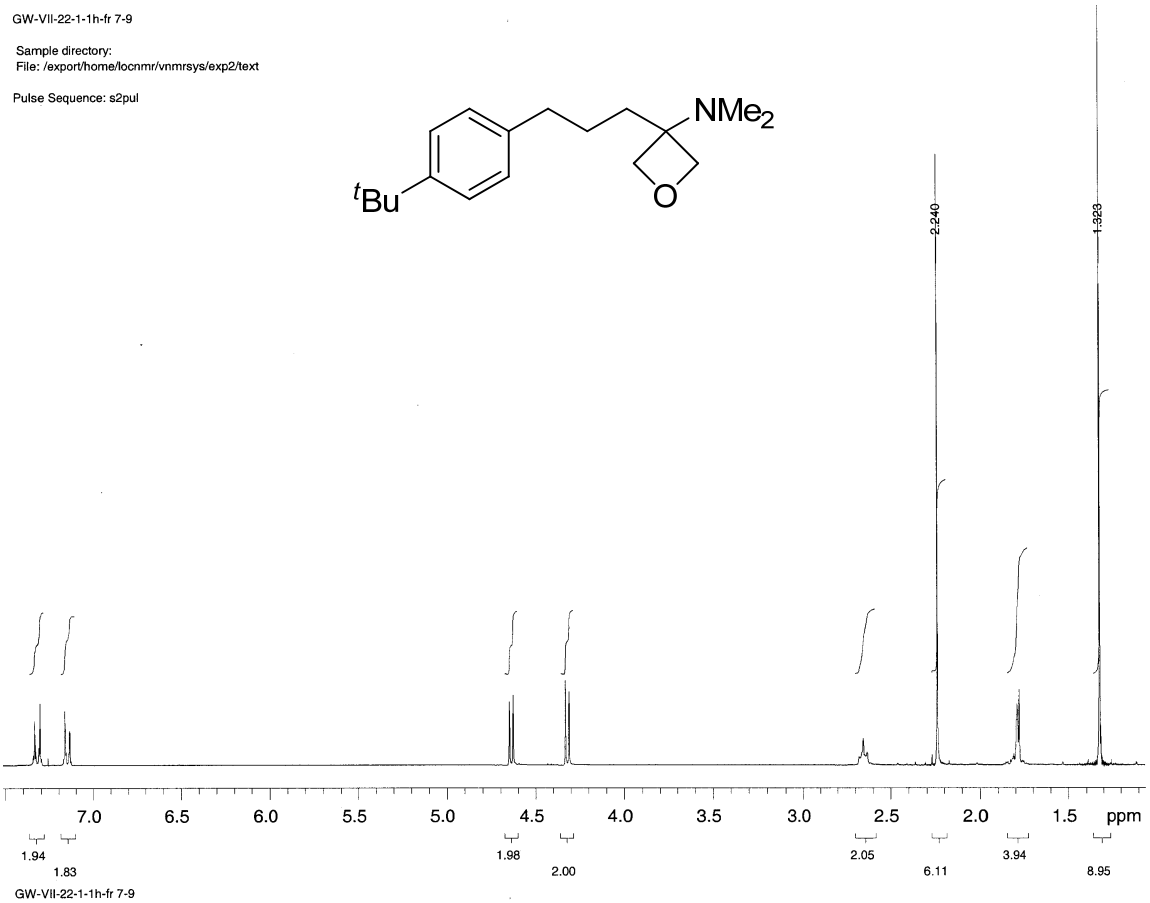

GW-VIII-14-A fr 18-23
File: CARBON
Pulse Sequence: s2pul
78.662
77.433
77.013
76.592
31.307
126.123
125.978
125.533
131.751
132.858
151.406
80.190
44.607
34.702
160
140
120
100
80
60
40
20
ppm

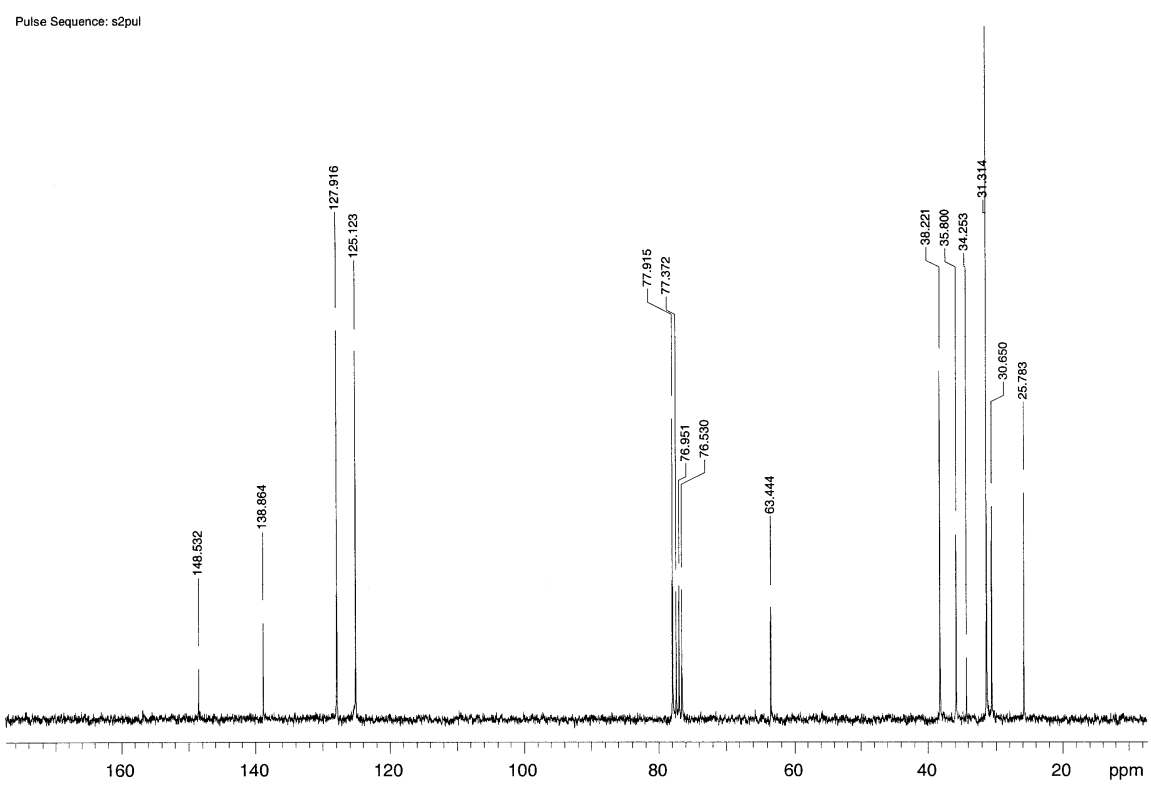
Appendix


GW-VIII-15-1 fr 5-13
File: PROTON
Pulse Sequence: s2pul
O
NMe2
tBu
2.165
1.315
2.593
7
6
5
4
3
2
1
ppm
2.01
1.88
4.00
3.99
7.85
8.72

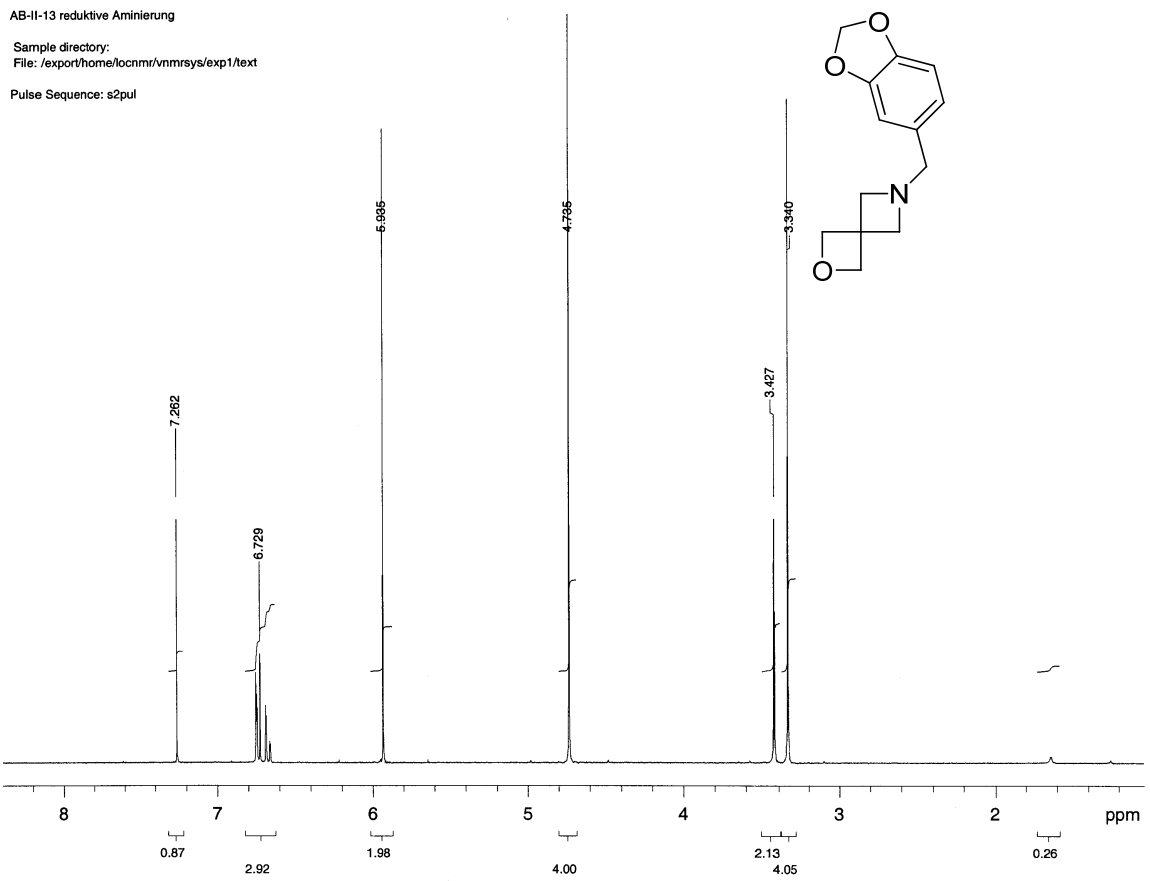

GW-VIII-15-1 fr 5-13
File: CARBON
Pulse Sequence: s2pul
81.039
77.425
77.005
76.584
31.484
127.894
125.137
42.658
139.100
46.281
34.411
64.287
36.578
29.835
148.471
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

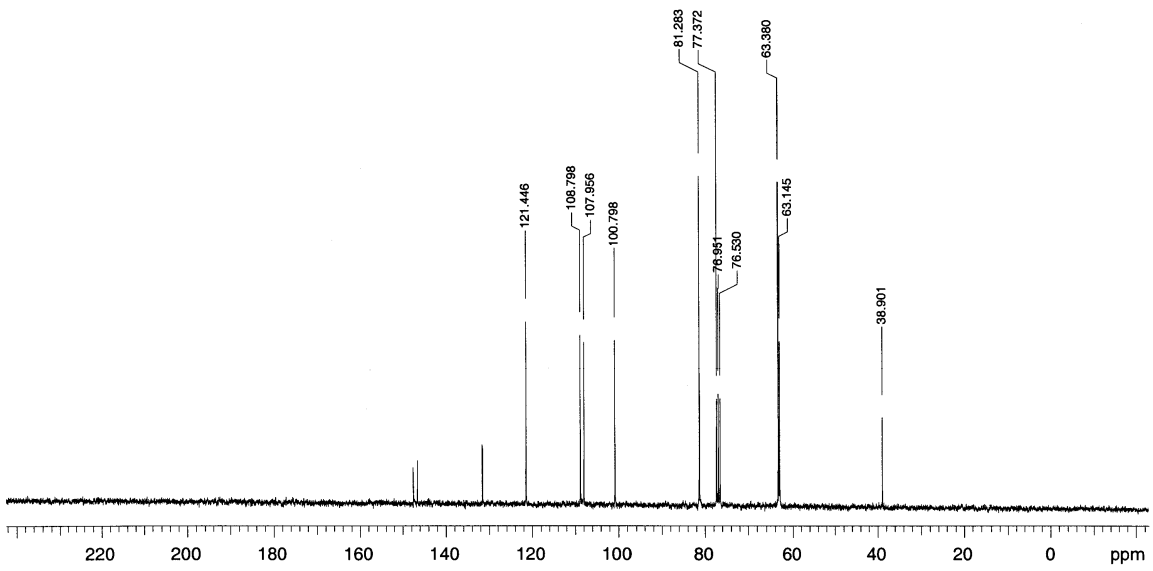
Appendix


GW-VII-22-1-1h-fr 7-9
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
NMe2
tBu
O
2.240
1.323
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.94
1.83
1.98
2.00
2.05
6.11
3.94
8.95

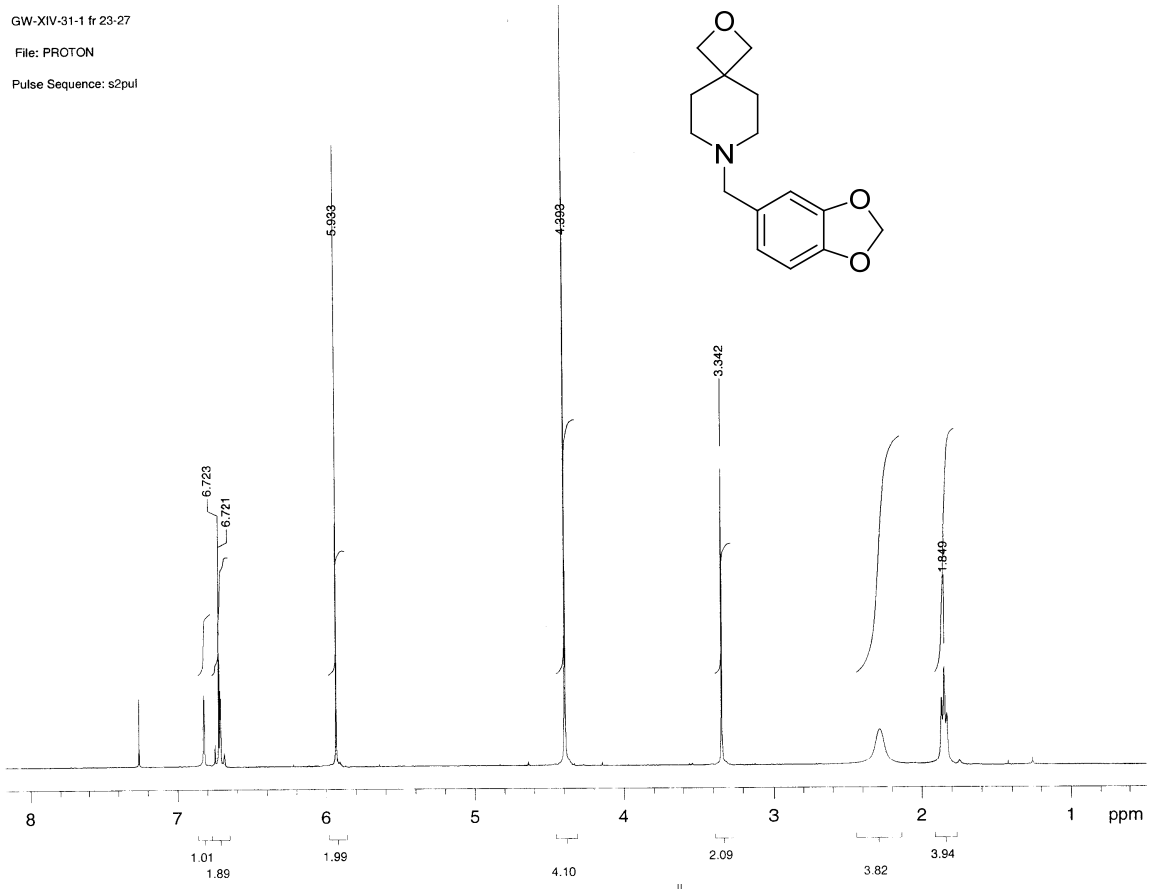

GW-VII-22-1-1h-fr 7-9
Pulse Sequence: s2pul
148.532
138.864
127.916
125.123
77.915
77.372
76.951
76.530
63.444
38.221
35.800
34.253
31.314
30.650
25.783
160
140
120
100
80
60
40
20
ppm

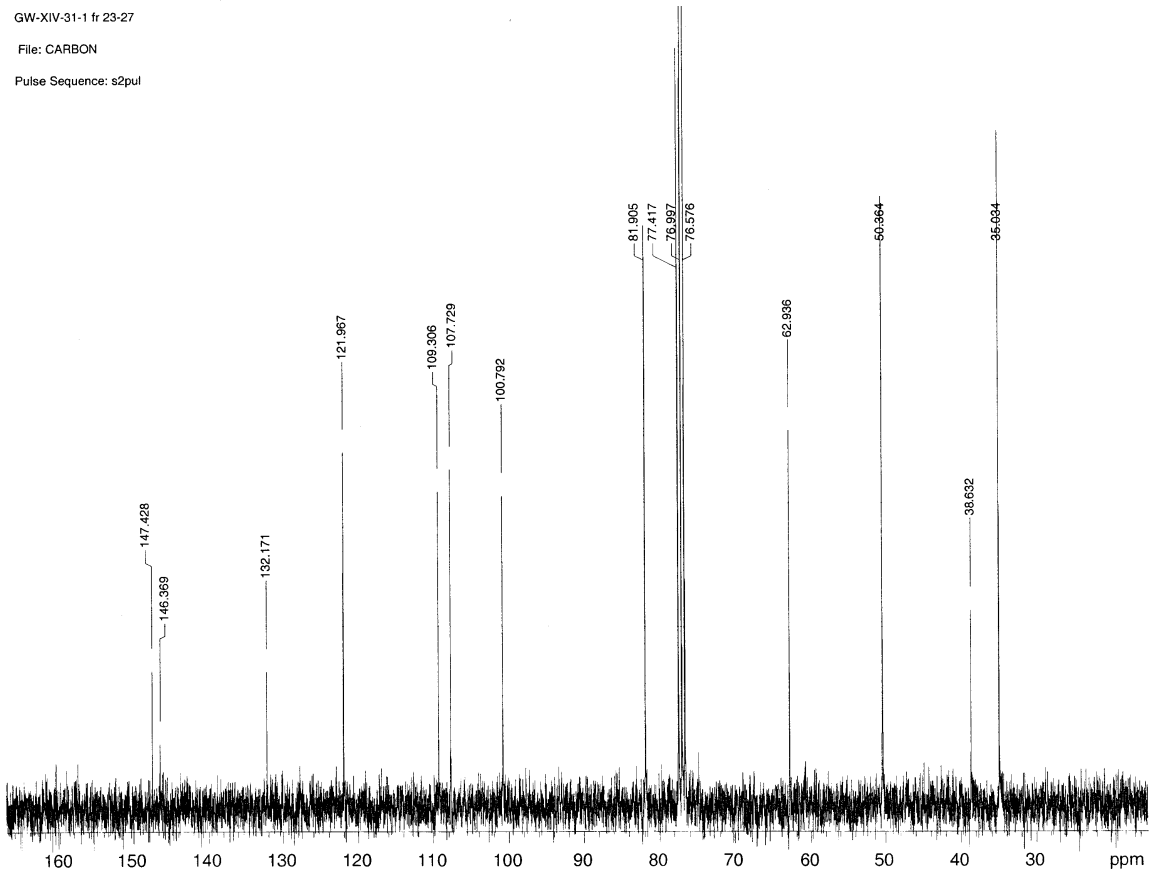
Appendix


AB-II-13 reduktive Aminierung
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
7.262
6.729
5.935
4.735
3.427
3.340
O
O
N
O
8
7
6
5
4
3
2
ppm
0.87
2.92
1.98
4.00
2.13
4.05
0.26

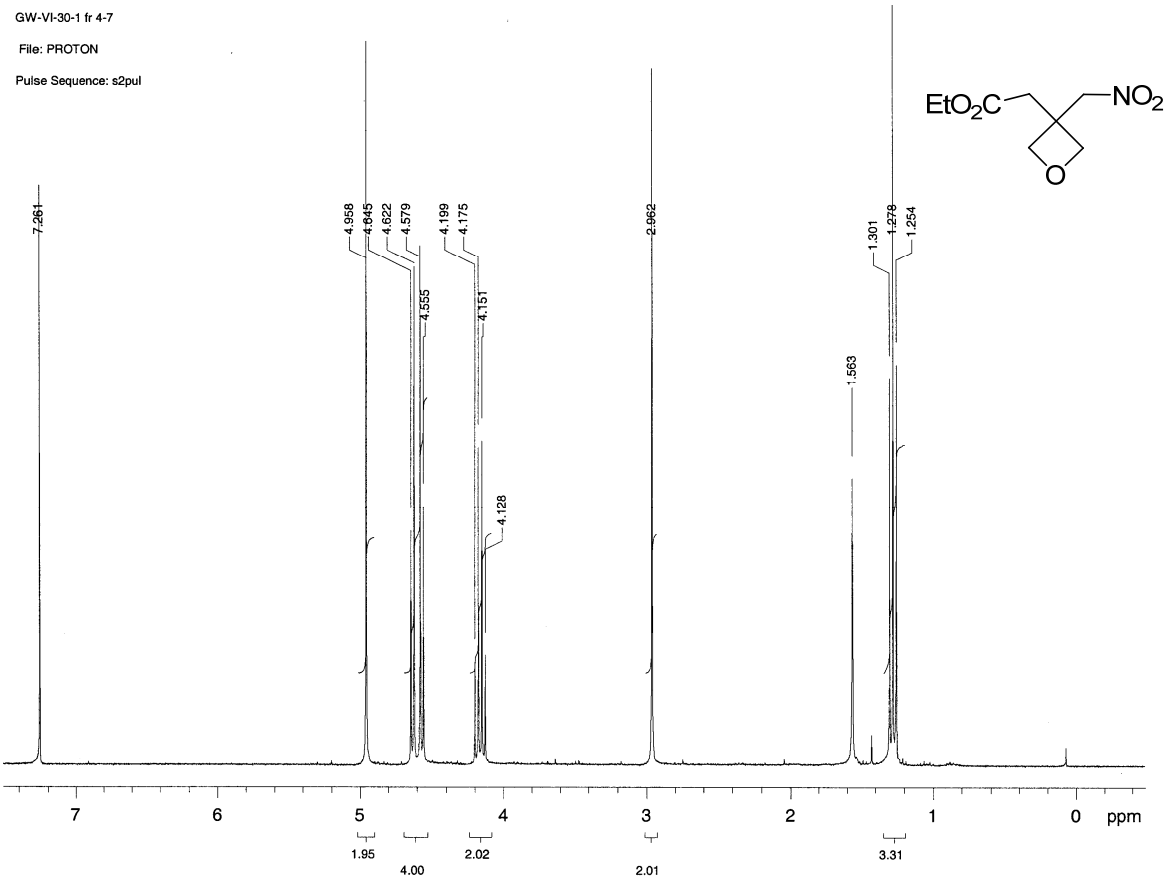

AB-II-13 CharakterisierungsC13
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
81.283
77.372
63.380
121.446
108.798
107.956
100.798
76.951
76.530
63.145
38.901
220
200
180
160
140
120
100
80
60
40
20
0
ppm

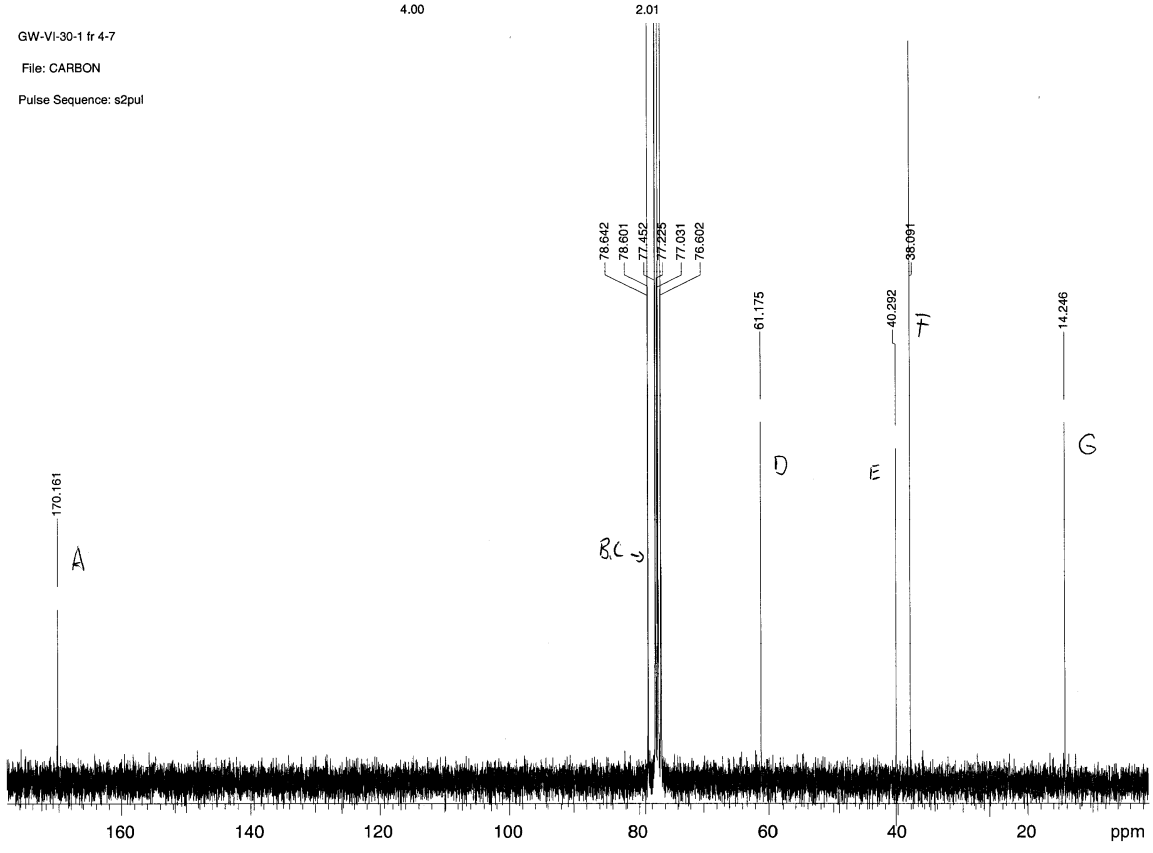
Appendix


GW-XIV-31-1 fr 23-27
File: PROTON
Pulse Sequence: s2pul
O
N
O
O
6.723
6.721
5.933
4.393
3.342
1.849
8
7
6
5
4
3
2
1
ppm
1.01
1.89
1.99
4.10
2.09
3.82
3.94

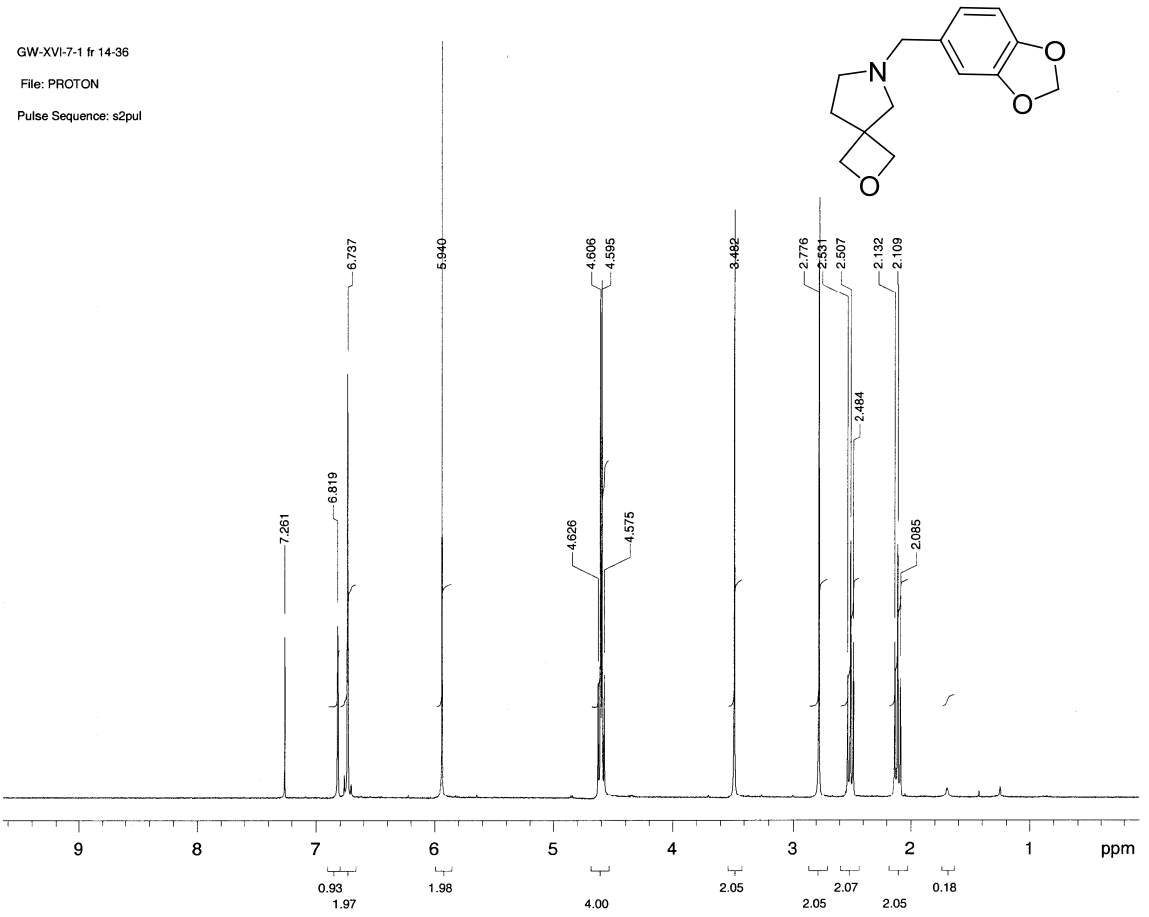

GW-XIV-31-1 fr 23-27
File: CARBON
Pulse Sequence: s2pul
147.428
146.369
132.171
121.967
109.306
107.729
100.792
81.905
77.417
76.997
76.576
62.936
60.364
38.632
35.034
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

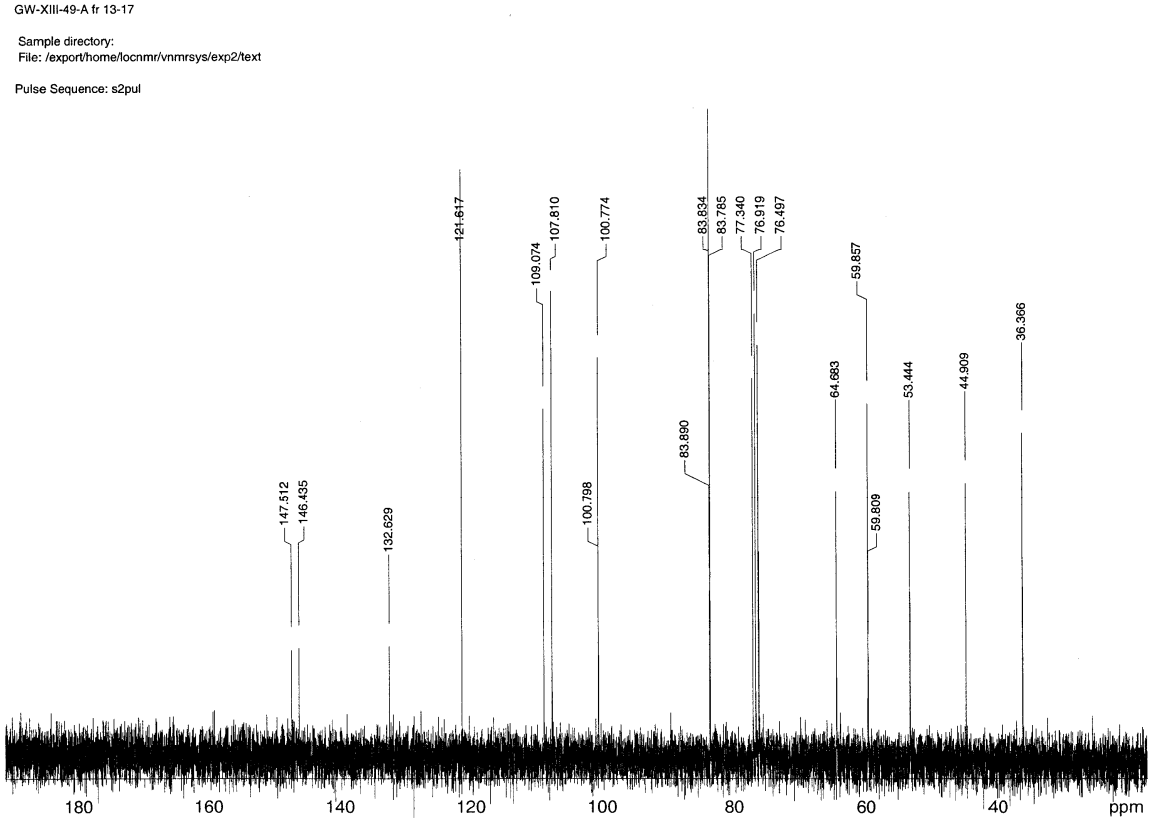
Appendix


GW-VI-30-1 fr 4-7
File: PROTON
Pulse Sequence: s2pul
EtO2C
NO2
O
7.261
4.958
4.845
4.622
4.579
4.555
4.199
4.175
4.151
4.128
2.962
1.563
1.301
1.278
1.254
7
6
5
4
3
2
1
0
ppm
1.95
4.00
2.02
2.01
3.31

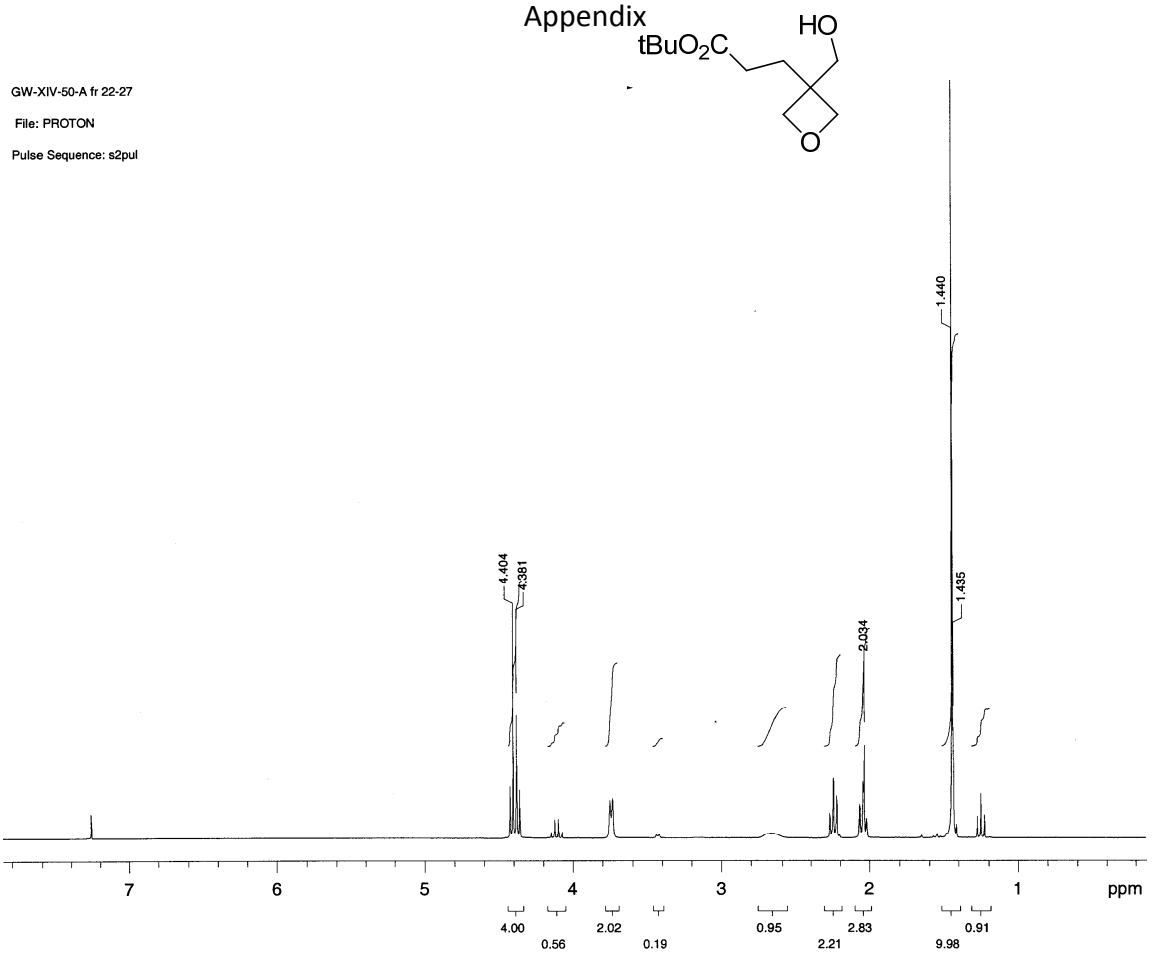

GW-VI-30-1 fr 4-7
File: CARBON
Pulse Sequence: s2pul
78.642
78.601
77.452
77.225
77.031
76.602
61.175
40.292
38.091
14.246
170.161
A
BC
D
E
F
G
160
140
120
100
80
60
40
20
ppm

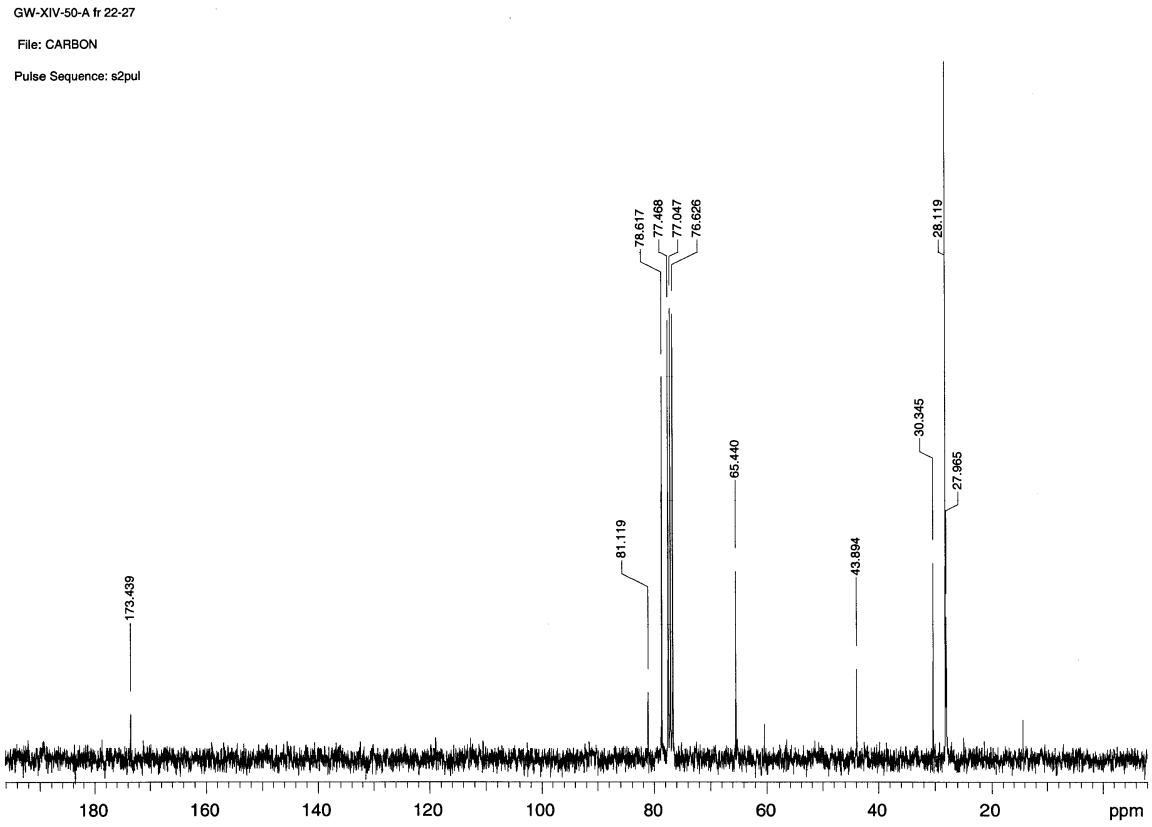
Appendix


GW-XVI-7-1 fr 14-36
File: PROTON
Pulse Sequence: s2pul
N
O
O
O
7.261
6.819
6.737
5.940
4.626
4.606
4.595
4.575
3.482
2.776
2.531
2.507
2.484
2.132
2.109
2.085
9
8
7
6
5
4
3
2
1
ppm
0.93
1.97
1.98
4.00
2.05
2.05
2.07
2.05
0.18

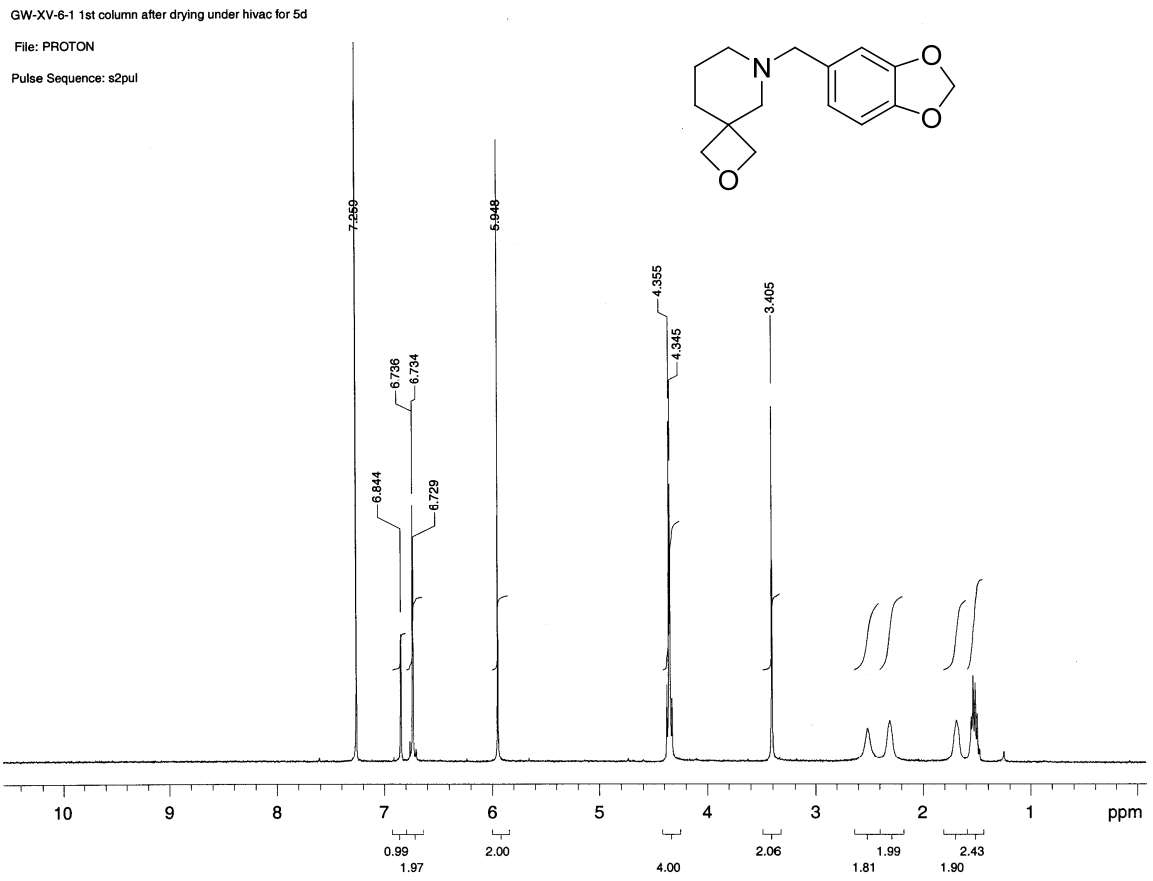

GW-XIII-49-A fr 13-17
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
147.512
146.435
132.629
121.617
109.074
107.810
100.798
100.774
83.890
83.834
83.785
77.340
76.919
76.497
64.883
59.857
59.809
53.444
44.909
36.366
180
160
140
120
100
80
60
40
ppm

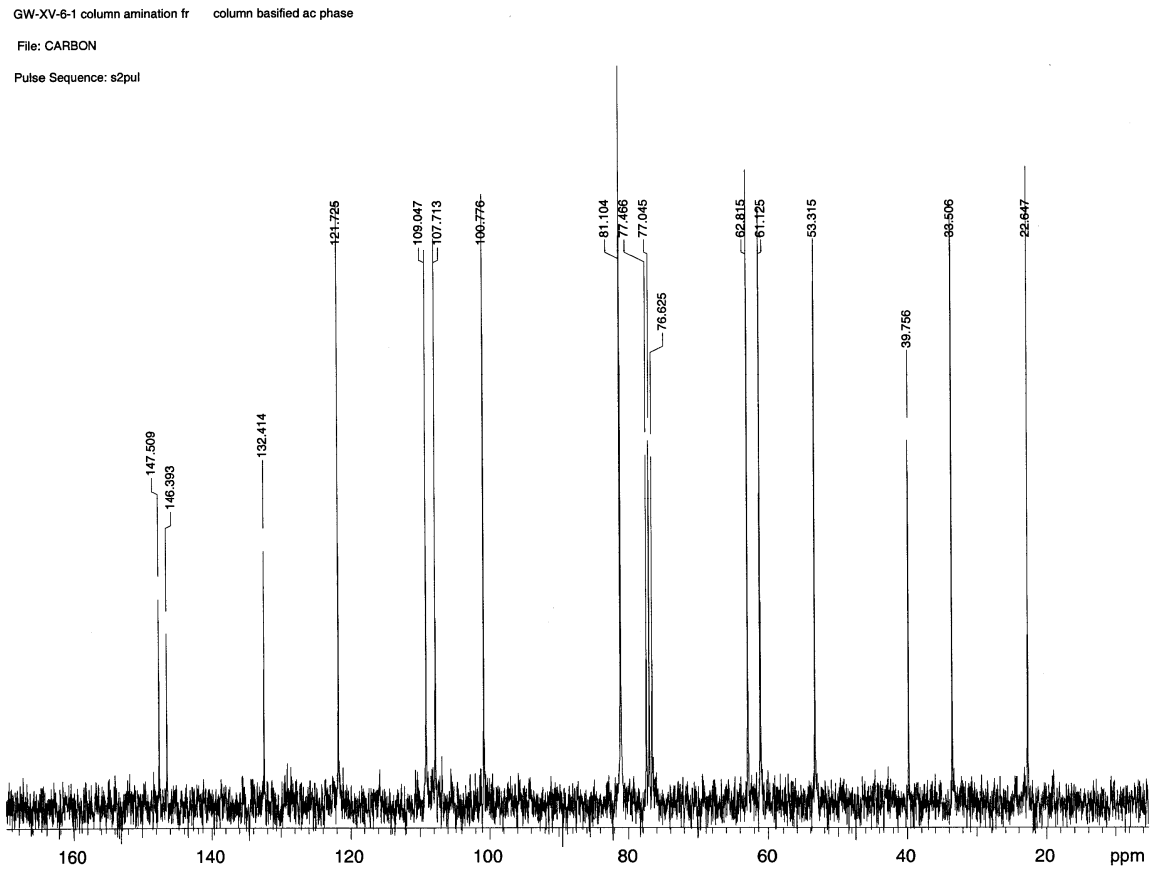
Appendix


tBuO2C
HO
O
GW-XIV-50-A fr 22-27
File: PROTON
Pulse Sequence: s2pul
1.440
4.404
4.381
1.435
2.034
7
6
5
4
3
2
1
ppm
4.00
0.56
2.02
0.19
0.95
2.21
2.83
9.98
0.91

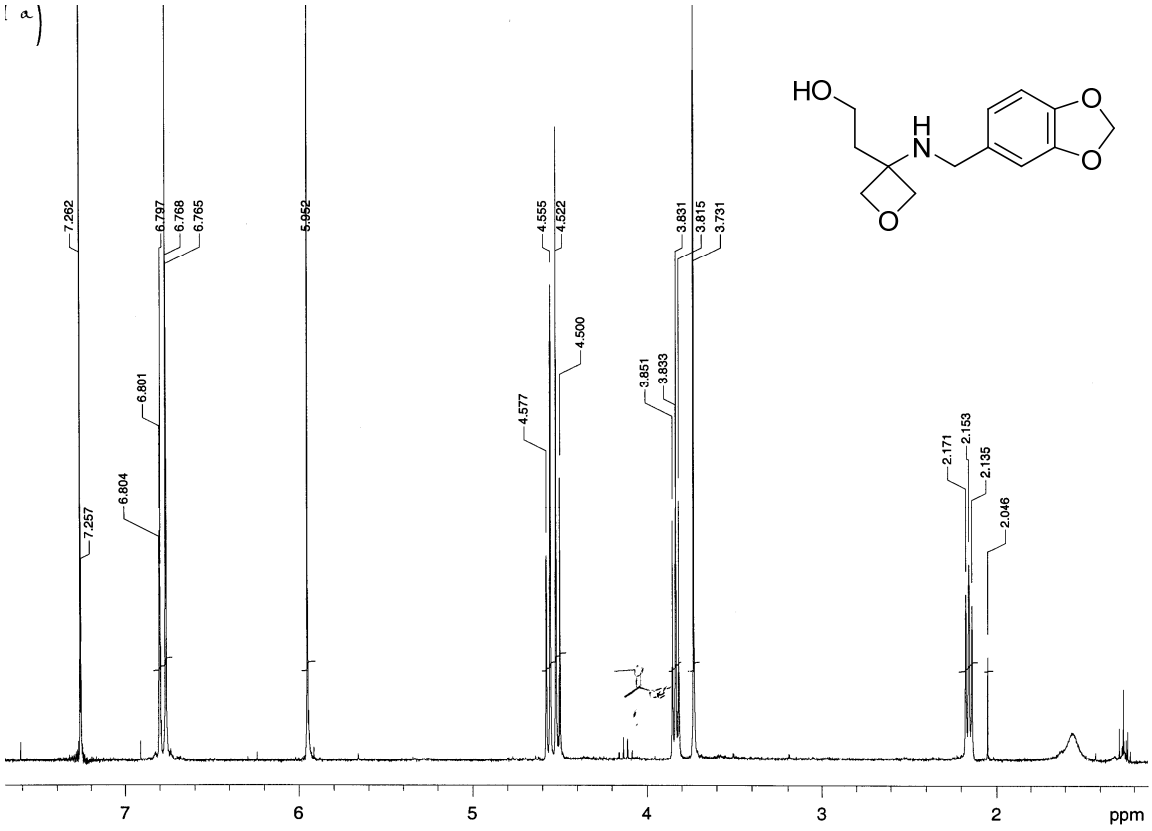

GW-XIV-50-A fr 22-27
File: CARBON
Pulse Sequence: s2pul
78.617
77.468
77.047
76.626
28.119
30.345
27.965
65.440
81.119
43.894
173.439
180
160
140
120
100
80
60
40
20
ppm

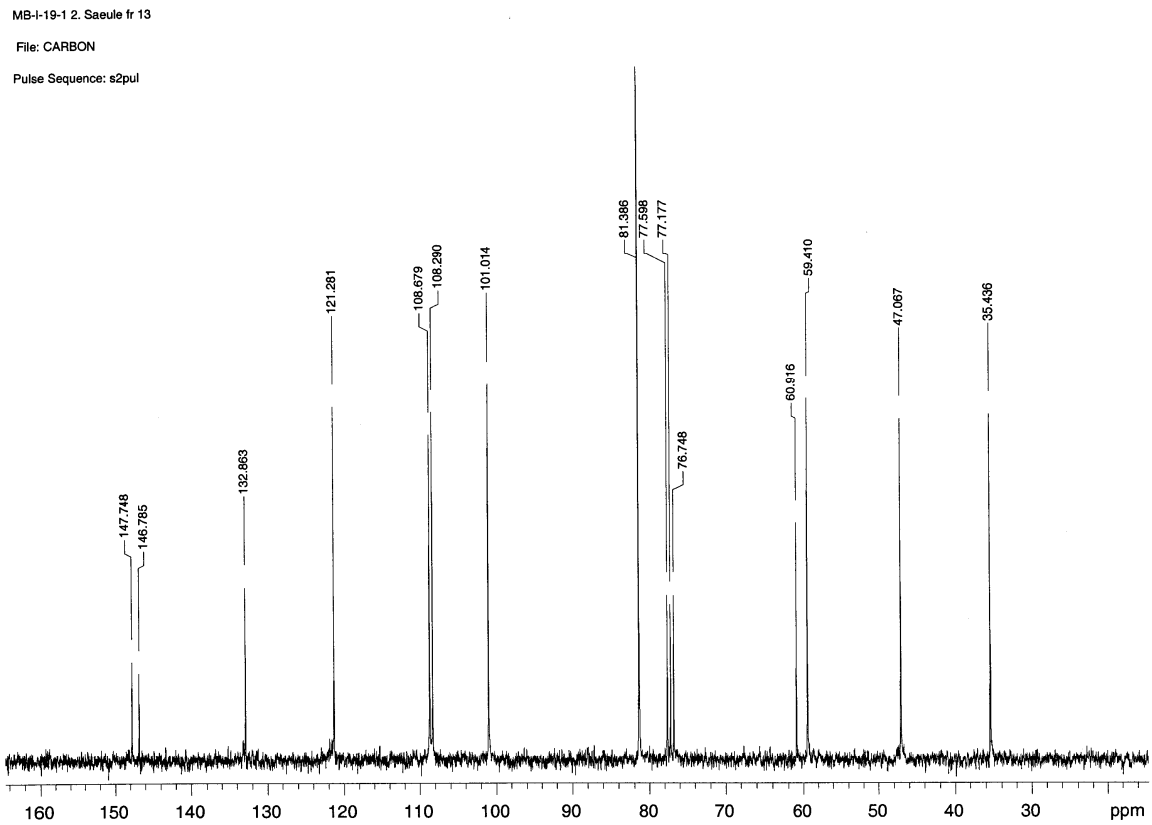
Appendix


GW-XV-6-1 1st column after drying under hivac for 5d
File: PROTON
Pulse Sequence: s2pul
N
O
O
O
7.259
6.844
6.736
6.734
6.729
5.948
4.355
4.345
3.405
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.97
2.00
4.00
2.06
1.99
1.81
2.43
1.90

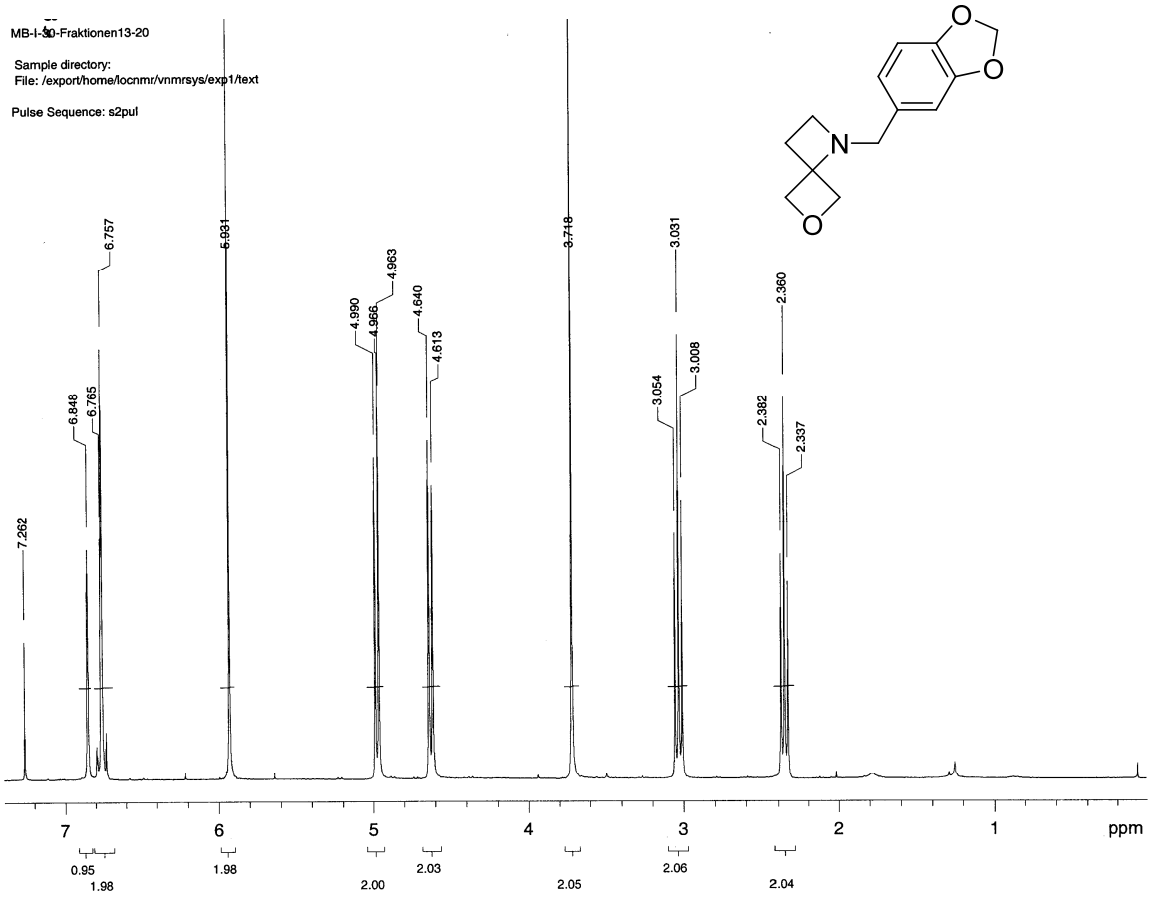

GW-XV-6-1 column amination fr column basified ac phase
File: CARBON
Pulse Sequence: s2pul
147.509
146.393
132.414
121.725
109.047
107.713
100.776
81.104
77.466
77.045
76.625
62.815
61.125
53.315
39.756
38.506
22.647
160
140
120
100
80
60
40
20
ppm

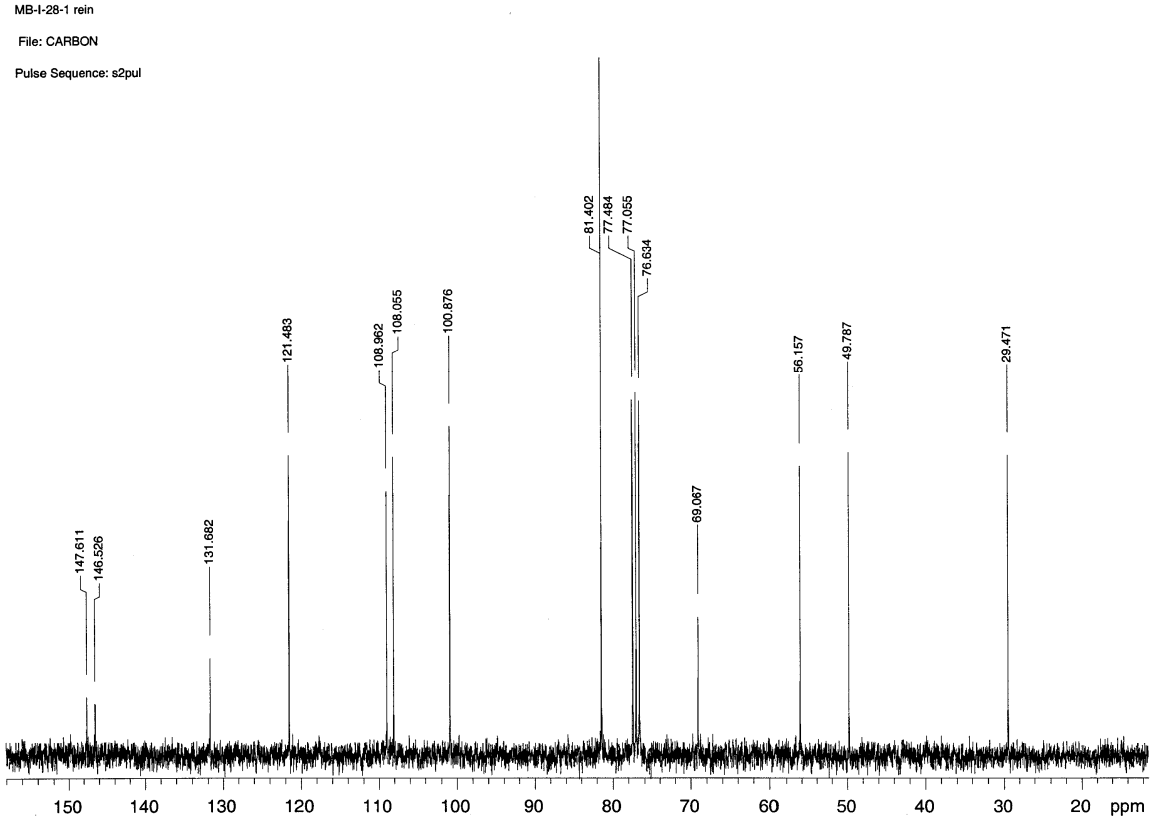
Appendix


HO
H
N
O
O
O
7.262
7.257
6.804
6.801
6.797
6.788
6.765
5.962
4.577
4.555
4.522
4.500
3.851
3.833
3.831
3.815
3.731
2.171
2.153
2.135
2.046
7
6
5
4
3
2
ppm

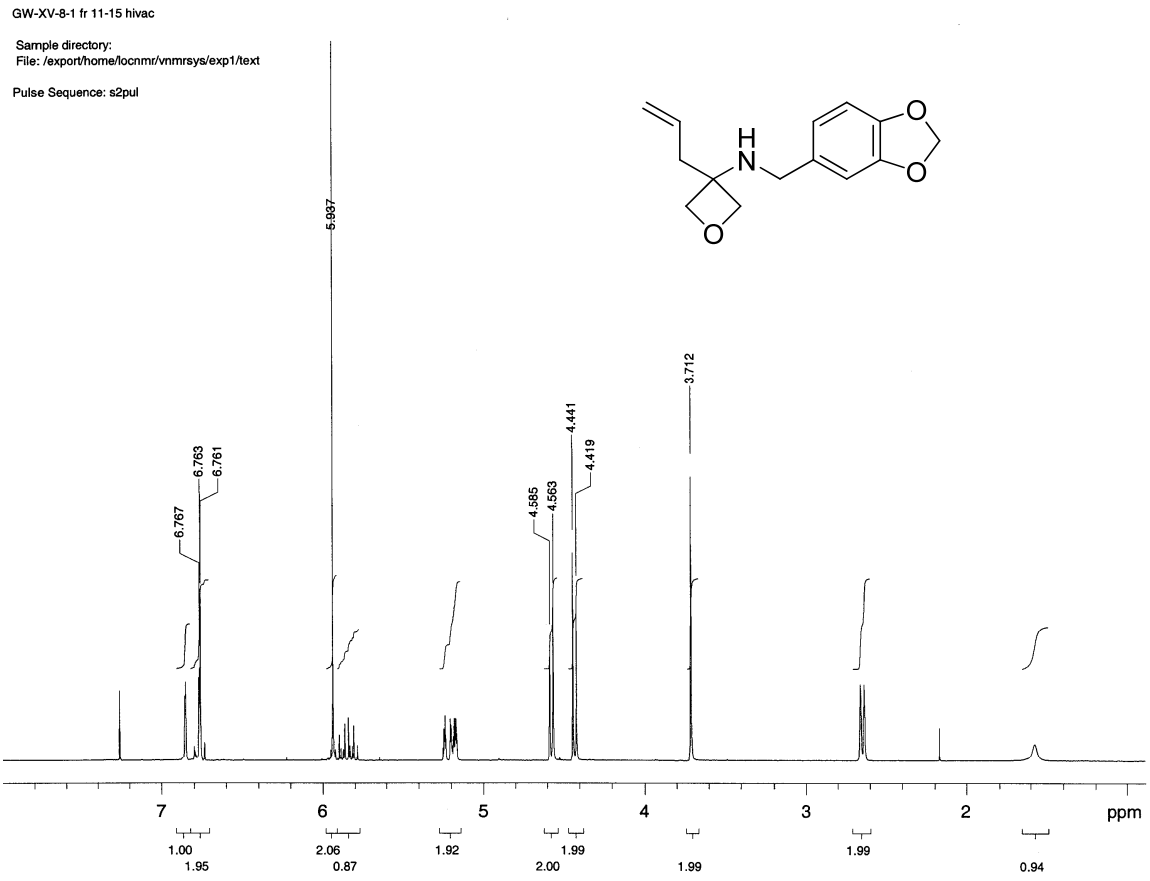

MB-I-19-1 2. Saeule fr 13
File: CARBON
Pulse Sequence: s2pul
147.748
146.785
132.863
121.281
108.679
108.290
101.014
81.386
77.598
77.177
76.748
60.916
59.410
47.067
35.436
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

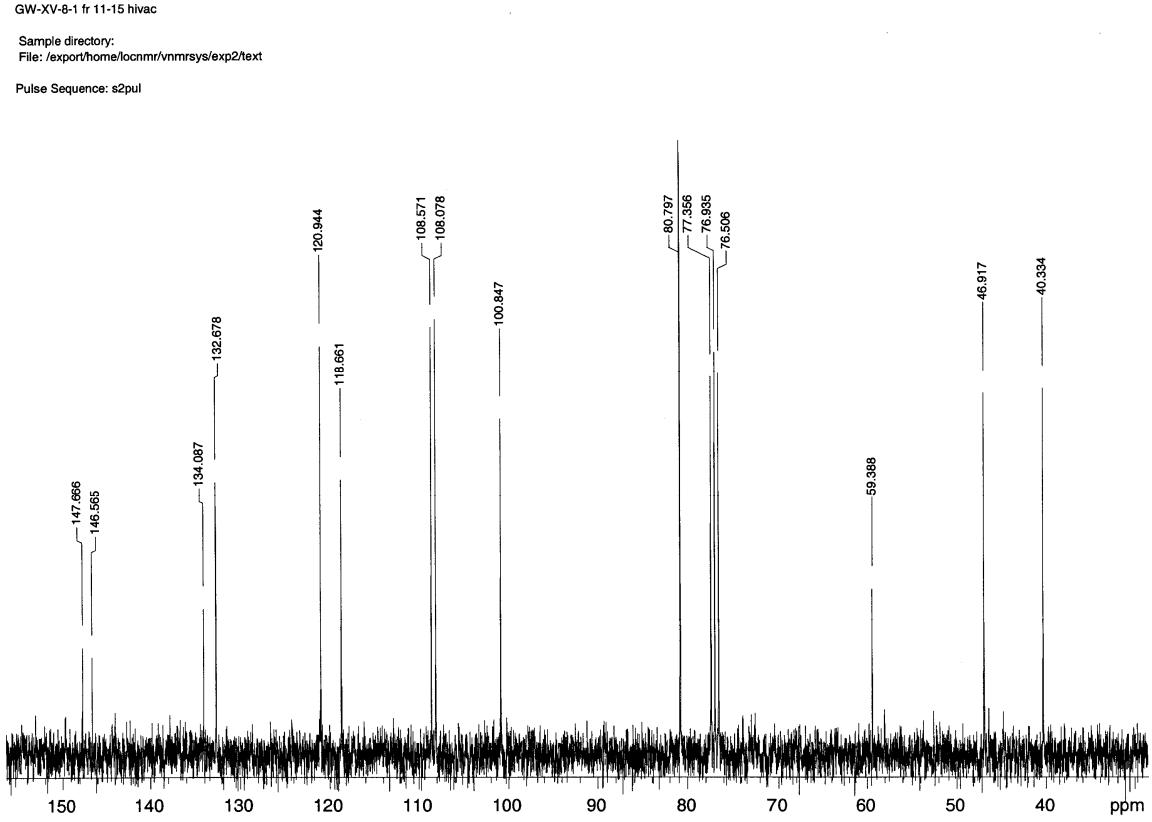
Appendix


MB-I-30-Fraktionen13-20
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
7.262
6.848
6.765
6.757
5.931
4.990
4.966
4.963
4.640
4.613
3.718
3.054
3.031
3.008
2.382
2.360
2.337
O
O
N
O
7
6
5
4
3
2
1
ppm
0.95
1.98
1.98
2.00
2.03
2.05
2.06
2.04

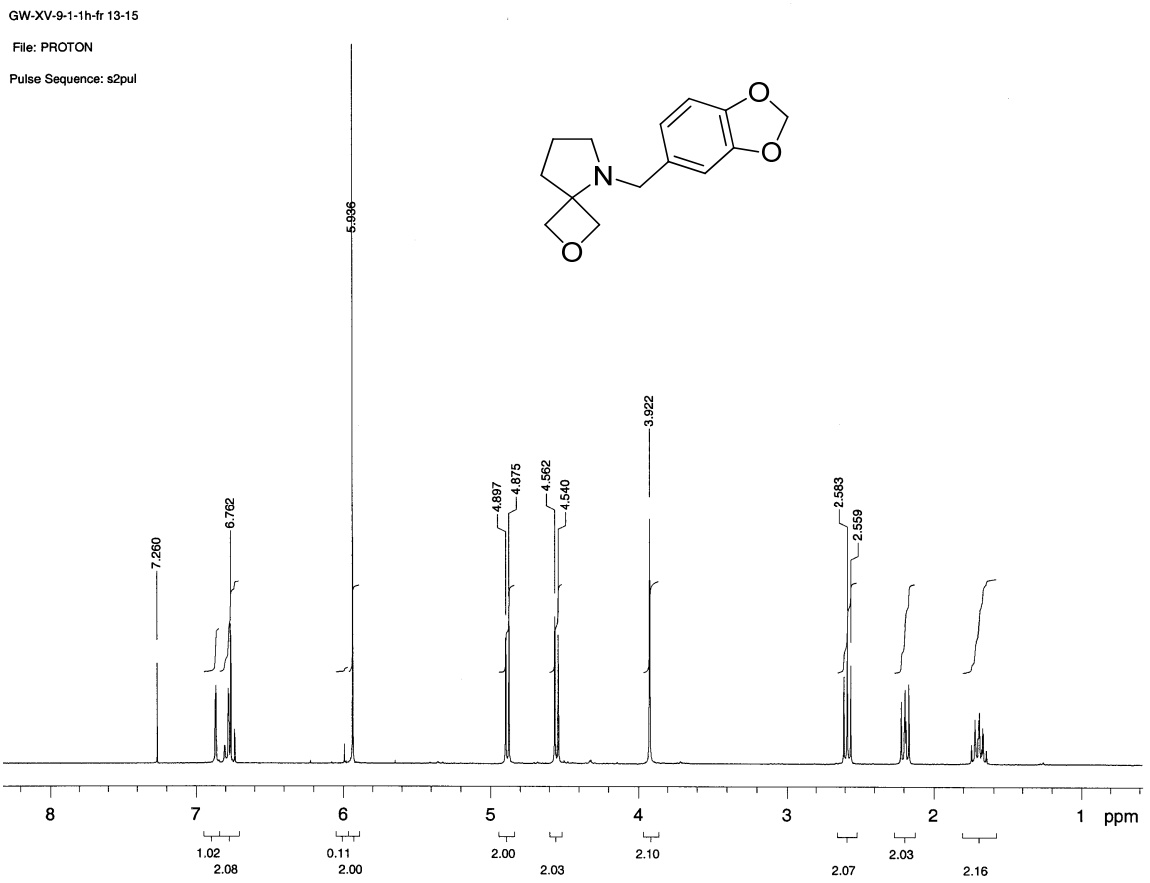

MB-I-28-1 rein
File: CARBON
Pulse Sequence: s2pul
147.611
146.526
131.682
121.483
108.962
108.055
100.876
81.402
77.484
77.055
76.634
69.067
56.157
49.787
29.471
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

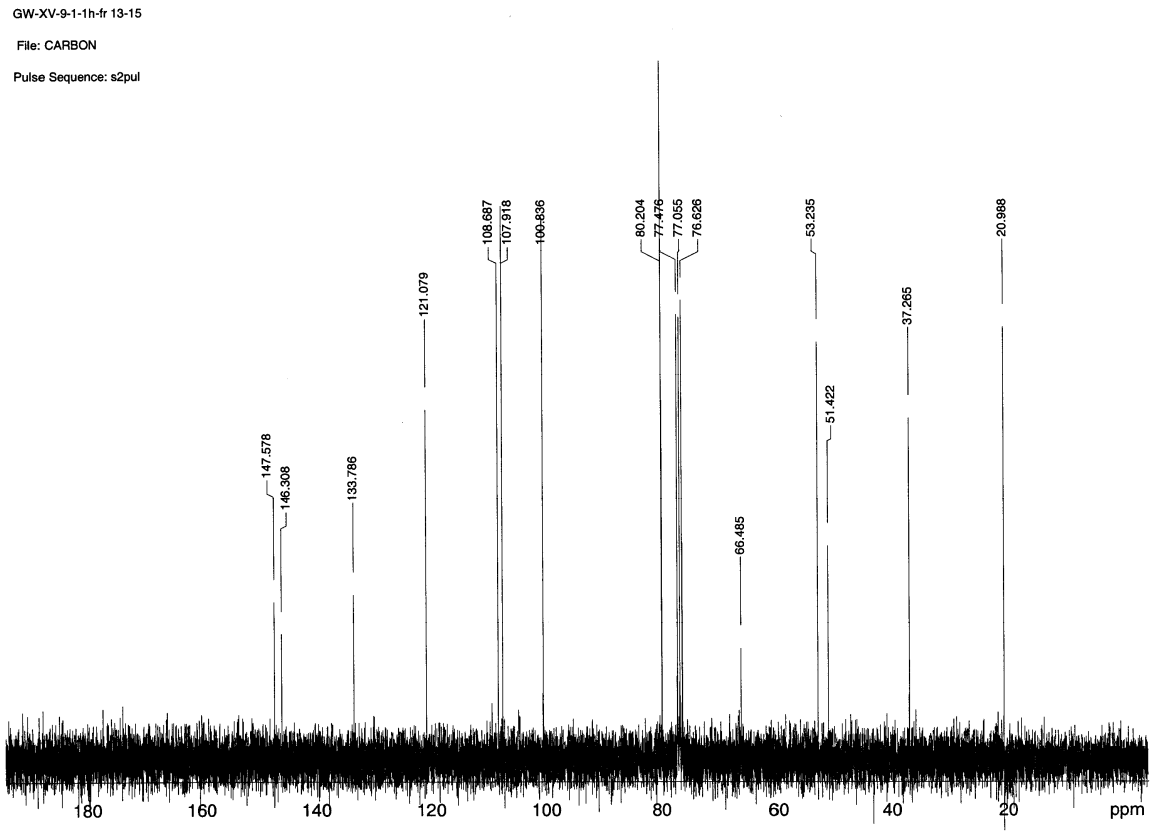
Appendix


GW-XV-8-1 fr 11-15 hivac
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
H
N
O
O
O
5.937
6.767
6.763
6.761
4.585
4.563
4.441
4.419
3.712
7
6
5
4
3
2
ppm
1.00
1.95
2.06
0.87
1.92
1.99
2.00
1.99
1.99
0.94

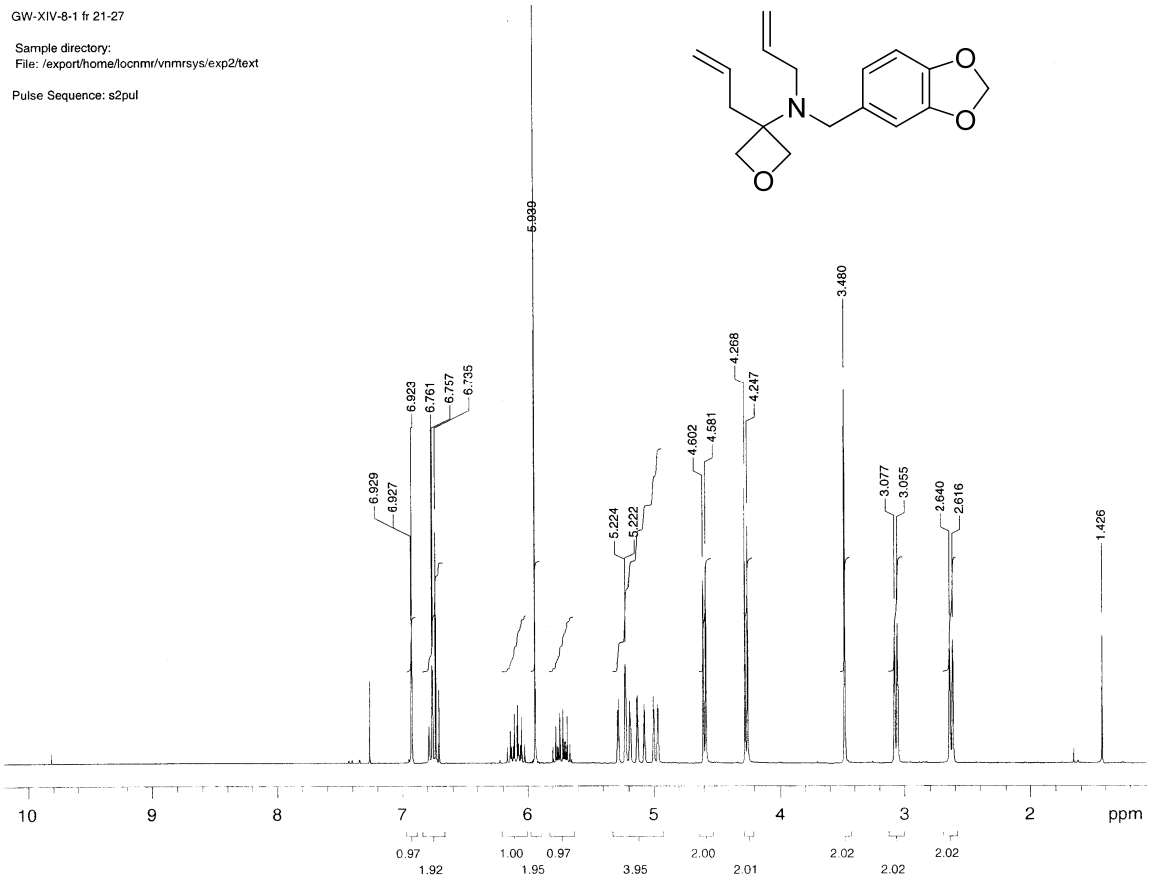

GW-XV-8-1 fr 11-15 hivac
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
147.666
146.565
134.087
132.678
120.944
118.661
108.571
108.078
100.847
80.797
77.356
76.935
76.506
59.388
46.917
40.334
150
140
130
120
110
100
90
80
70
60
50
40
ppm

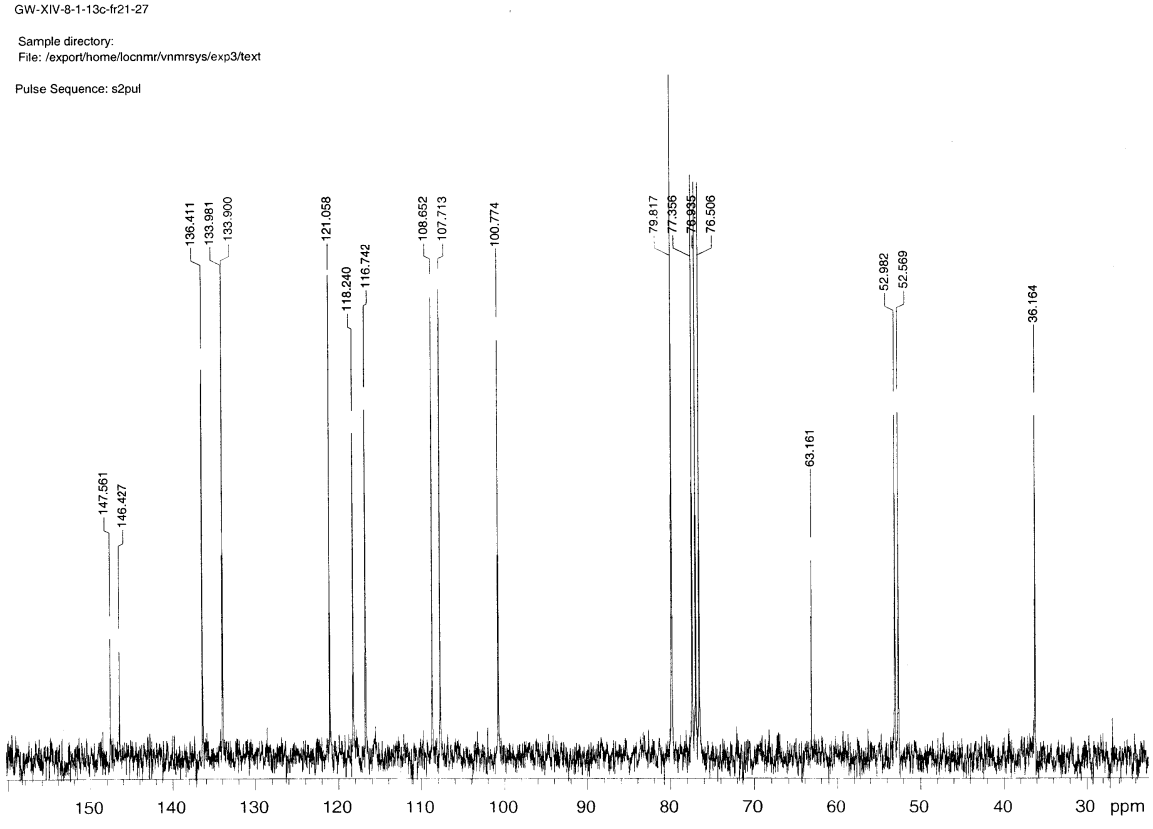
Appendix


GW-XV-9-1-1h-fr 13-15
File: PROTON
Pulse Sequence: s2pul
O
O
N
O
7.260
6.762
5.936
4.897
4.875
4.562
4.540
3.922
2.583
2.559
8
7
6
5
4
3
2
1 ppm
1.02
2.08
0.11
2.00
2.00
2.03
2.10
2.07
2.03
2.16

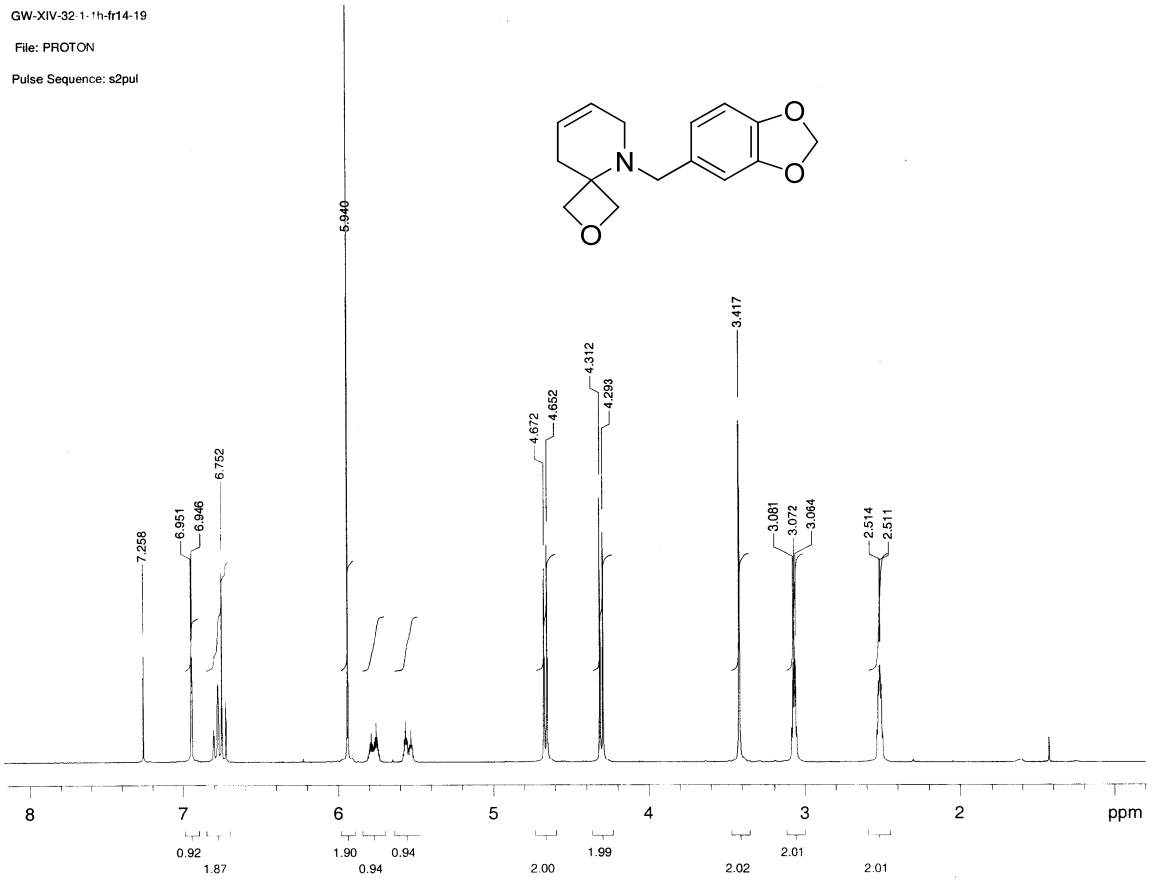

GW-XV-9-1-1h-fr 13-15
File: CARBON
Pulse Sequence: s2pul
147.578
146.308
133.786
121.079
108.687
107.918
100.836
80.204
77.476
77.055
76.626
66.485
53.235
51.422
37.265
20.988
180
160
140
120
100
80
60
40
20
ppm

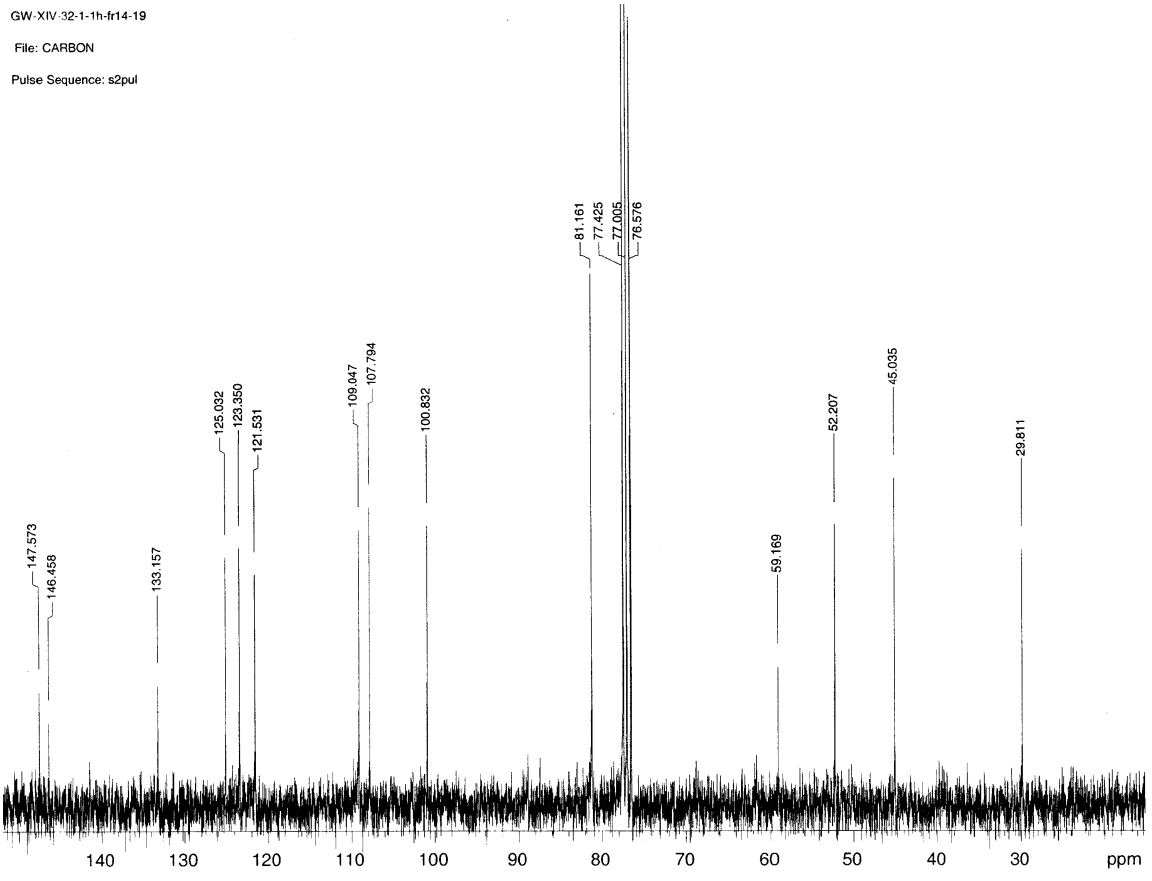
Appendix


GW-XIV-8-1 fr 21-27
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
N
O
O
O
6.929
6.927
6.923
6.761
6.757
6.735
5.939
5.224
5.222
4.602
4.581
4.268
4.247
3.480
3.077
3.055
2.640
2.616
1.426
10
9
8
7
6
5
4
3
2
ppm
0.97
1.92
1.00
1.95
0.97
3.95
2.00
2.01
2.02
2.02
2.02

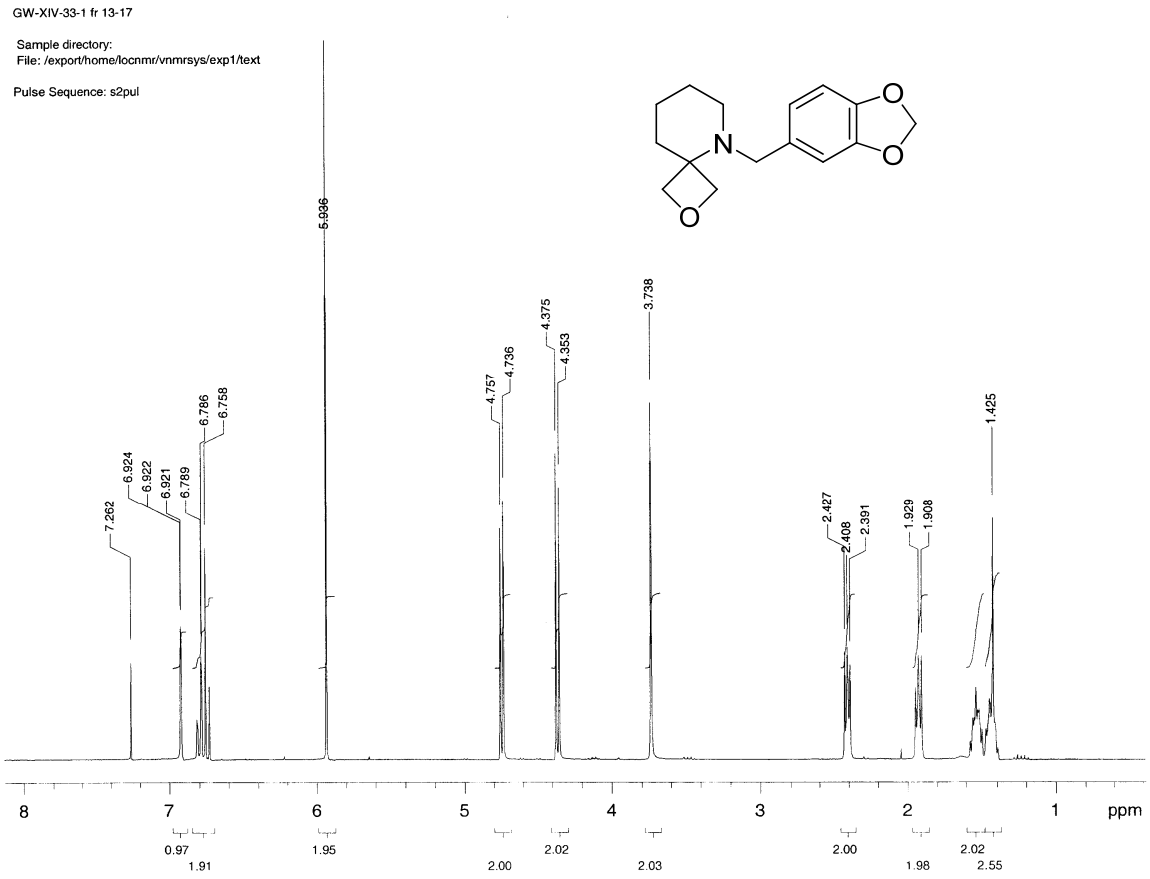

GW-XIV-8-1-13c-fr21-27
Sample directory:
File: /export/home/locnmr/vnmrsys/exp3/text
Pulse Sequence: s2pul
147.561
146.427
136.411
133.981
133.900
121.058
118.240
116.742
108.652
107.713
100.774
79.817
77.356
76.935
76.506
63.161
52.982
52.569
36.164
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

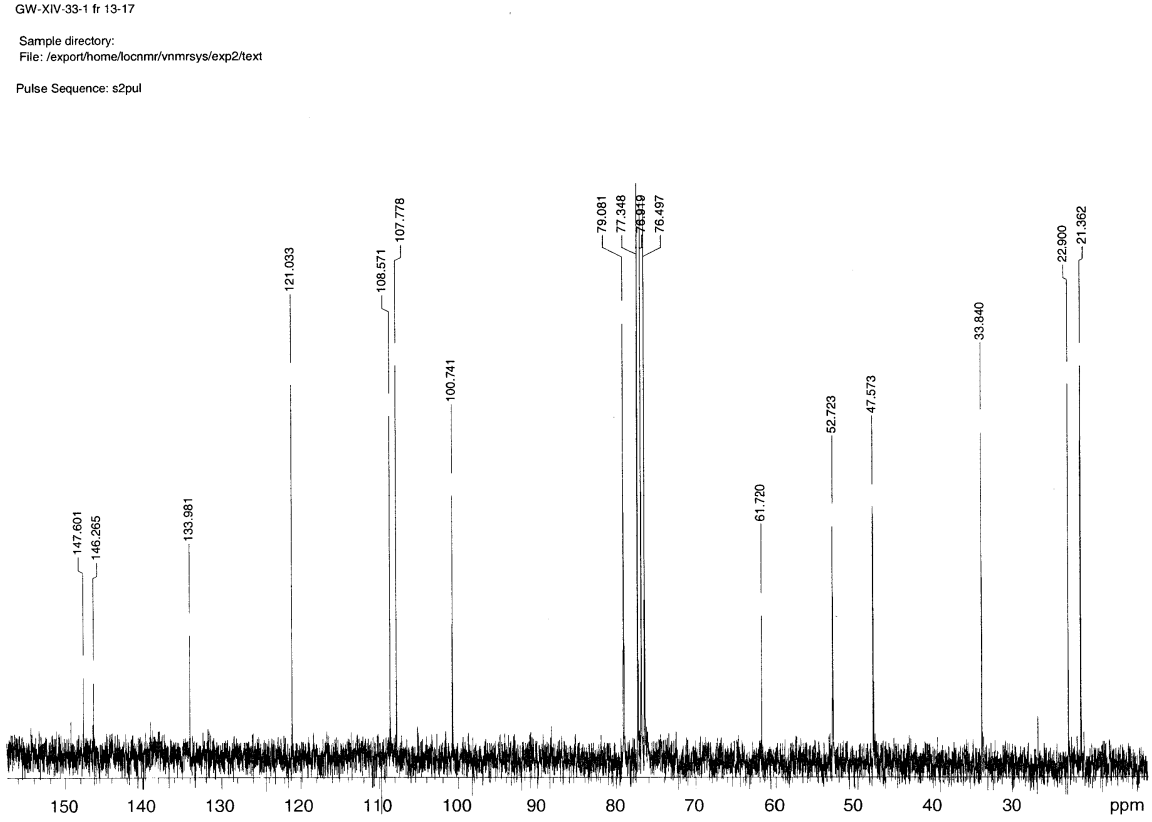
Appendix


GW-XIV-32-1-1h-fr14-19
File: PROTON
Pulse Sequence: s2pul
7.258
6.951
6.946
6.752
5.940
4.672
4.652
4.312
4.293
3.417
3.081
3.072
3.064
2.514
2.511
8
7
6
5
4
3
2
ppm
0.92
1.87
1.90
0.94
0.94
2.00
1.99
2.02
2.01
2.01


GW-XIV-32-1-1h-fr14-19
File: CARBON
Pulse Sequence: s2pul
147.573
146.458
133.157
125.032
123.350
121.531
109.047
107.794
100.832
81.161
77.425
77.005
76.576
59.169
52.207
45.035
29.811
140
130
120
110
100
90
80
70
60
50
40
30
ppm

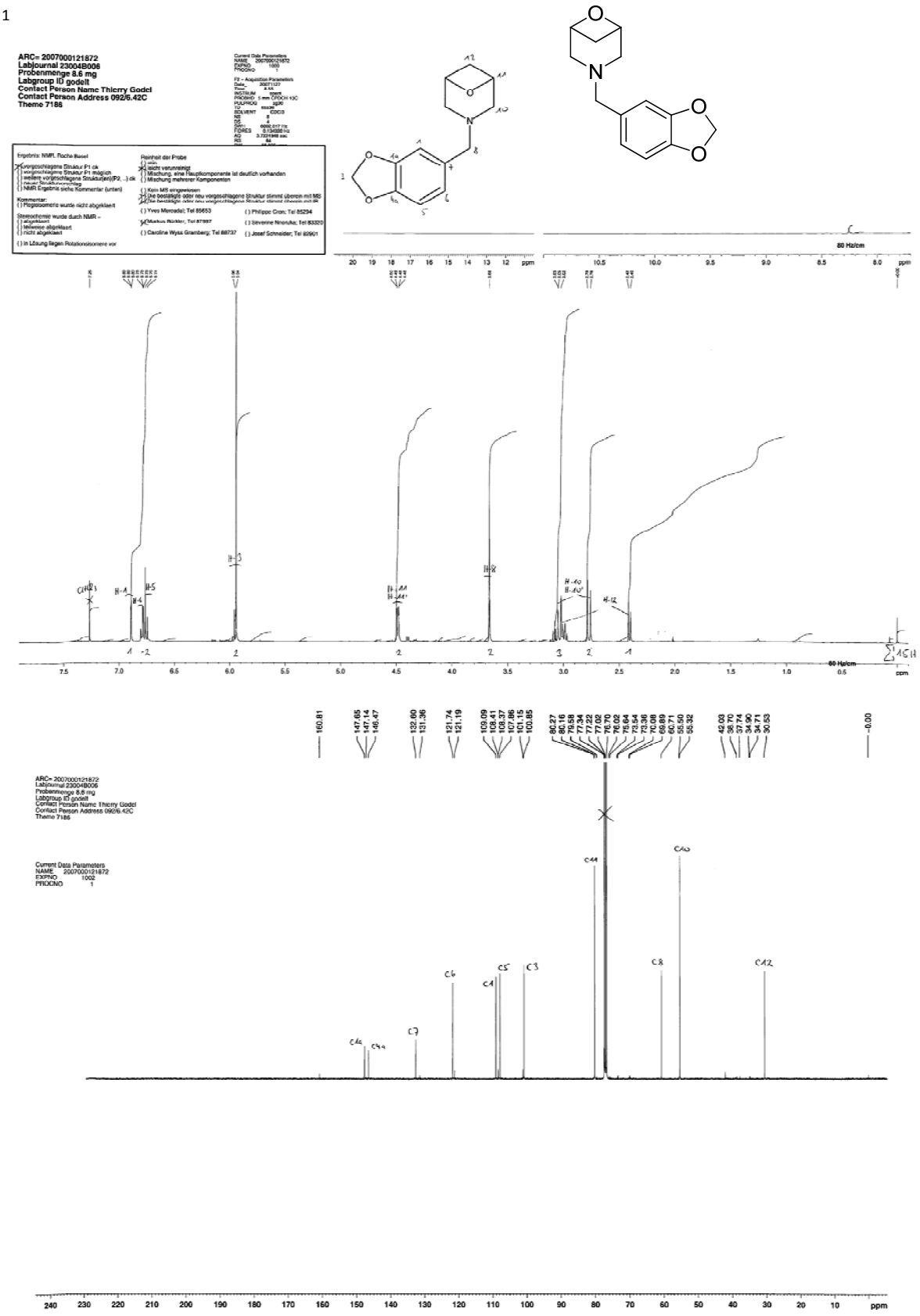
Appendix


GW-XIV-33-1 fr 13-17
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
5.936
4.757
4.736
4.375
4.353
3.738
7.262
6.924
6.922
6.921
6.789
6.786
6.758
2.427
2.408
2.391
1.929
1.908
1.425
8
7
6
5
4
3
2
1
ppm
0.97
1.91
1.95
2.00
2.02
2.03
2.00
1.98
2.02
2.55


GW-XIV-33-1 fr 13-17
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
147.601
146.265
133.981
121.033
108.571
107.778
100.741
79.081
77.348
76.919
76.497
61.720
52.723
47.573
33.840
22.900
21.362
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Appendix

1



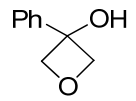
[1] These NMR-spectra were recorded by the NMR-service of F. Hoffmann-La Roche, Basel.

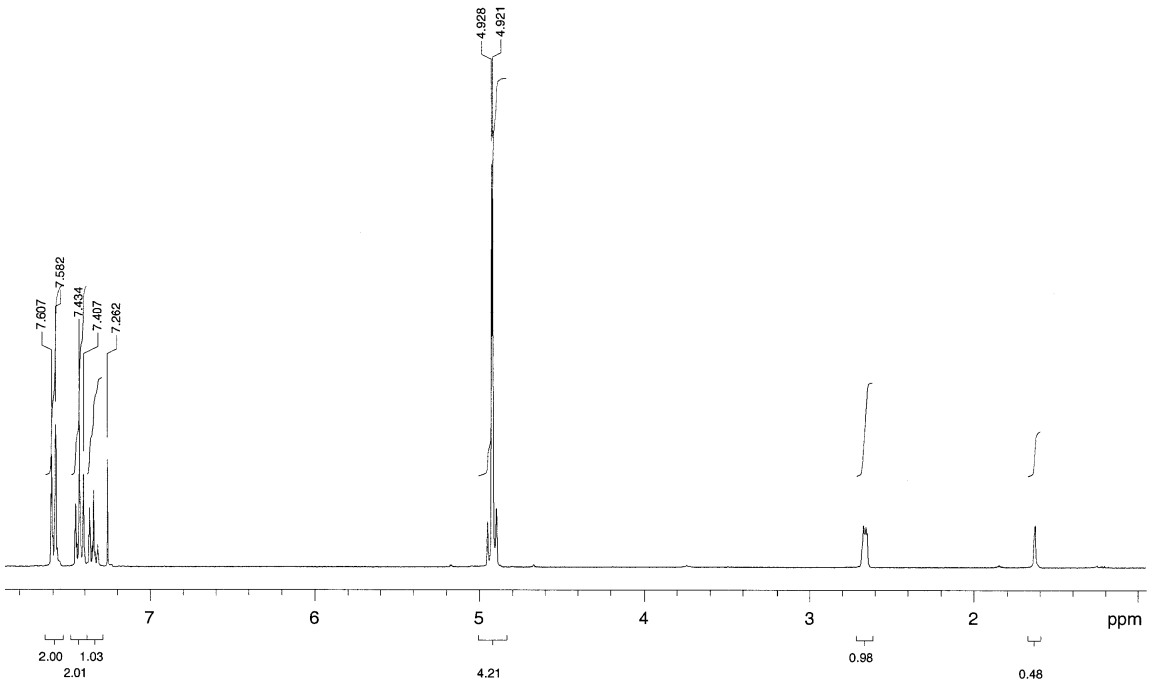
Appendix

GW-II-36-1 fractions 16-27

File: PROTON

Pulse Sequence: s2pul

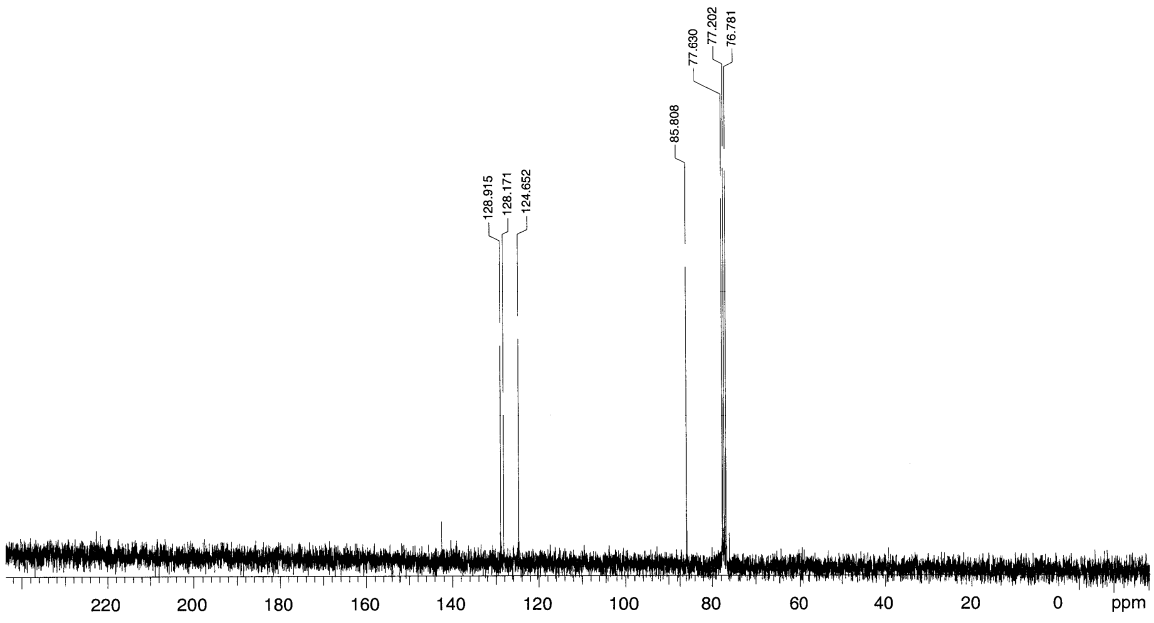




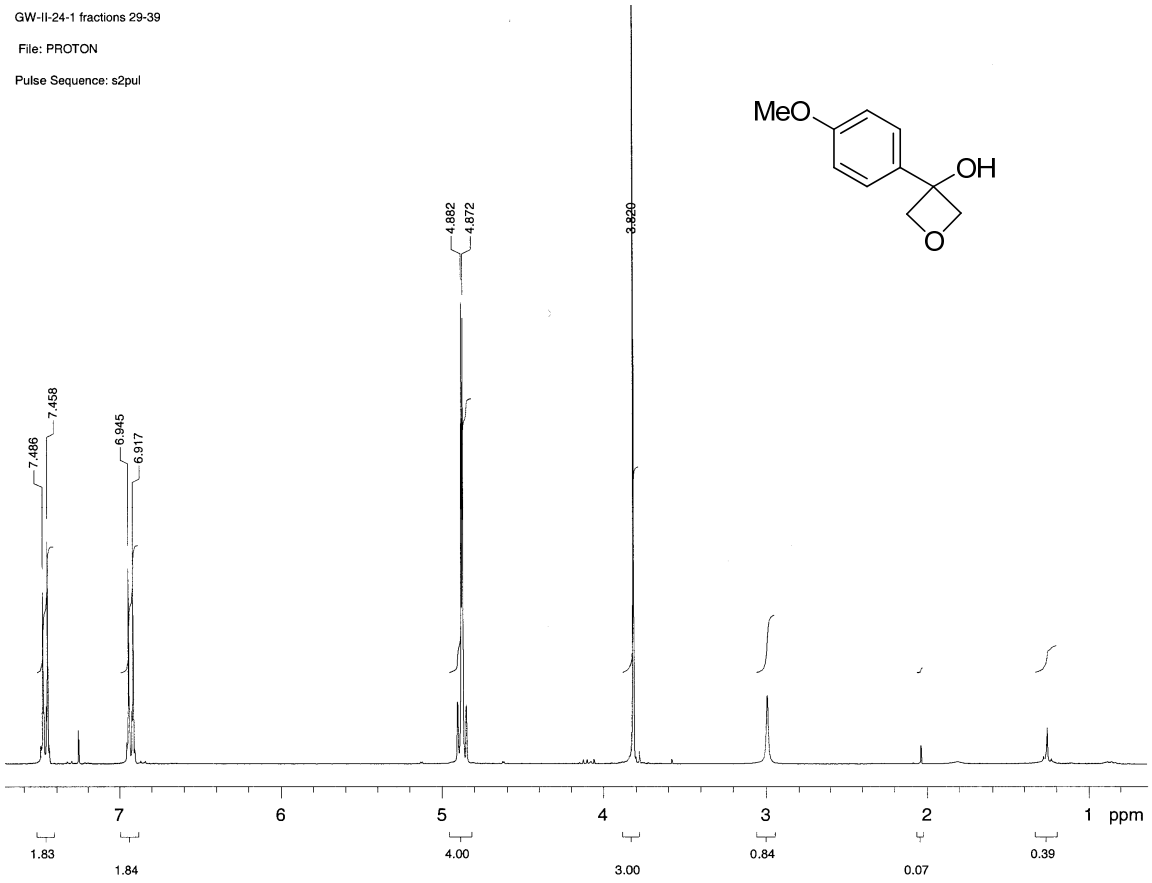
GW-II-36-1 fractions 16-27

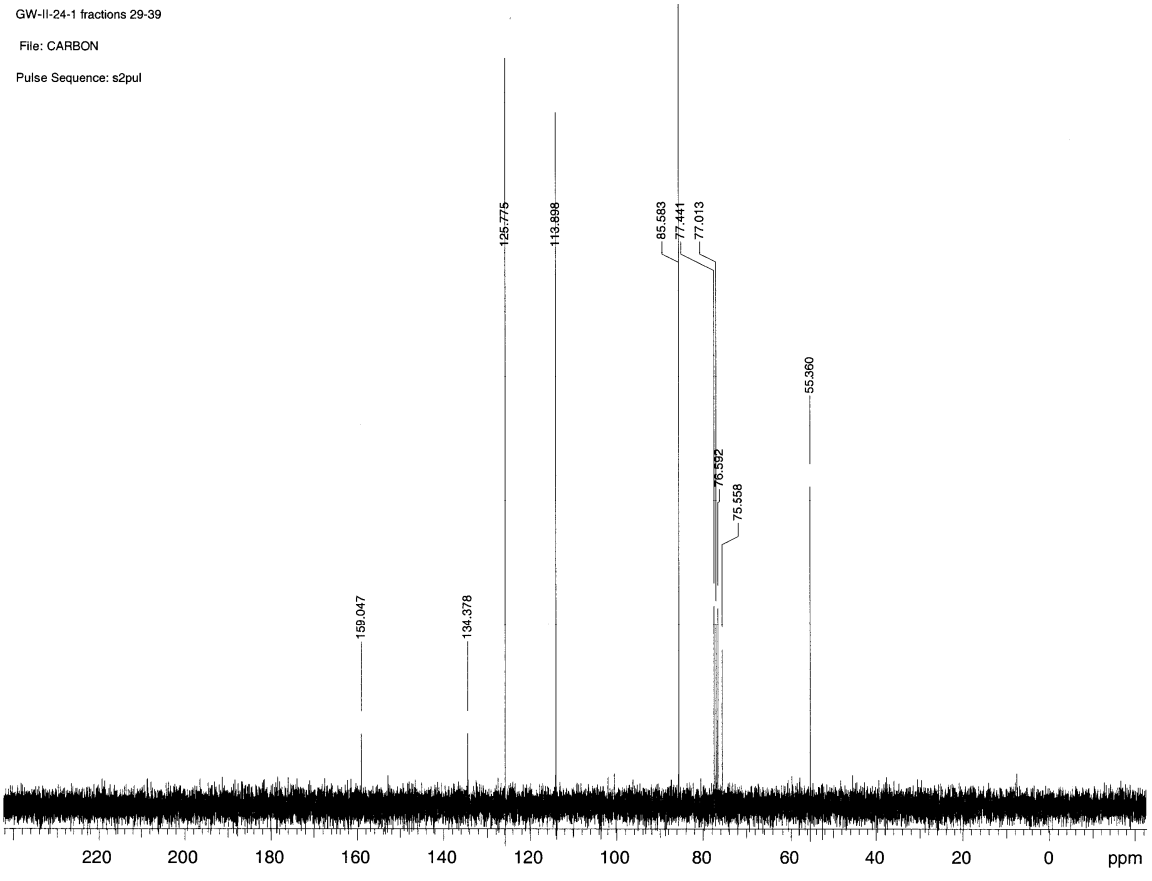
File: CARBON

Pulse Sequence: s2pul

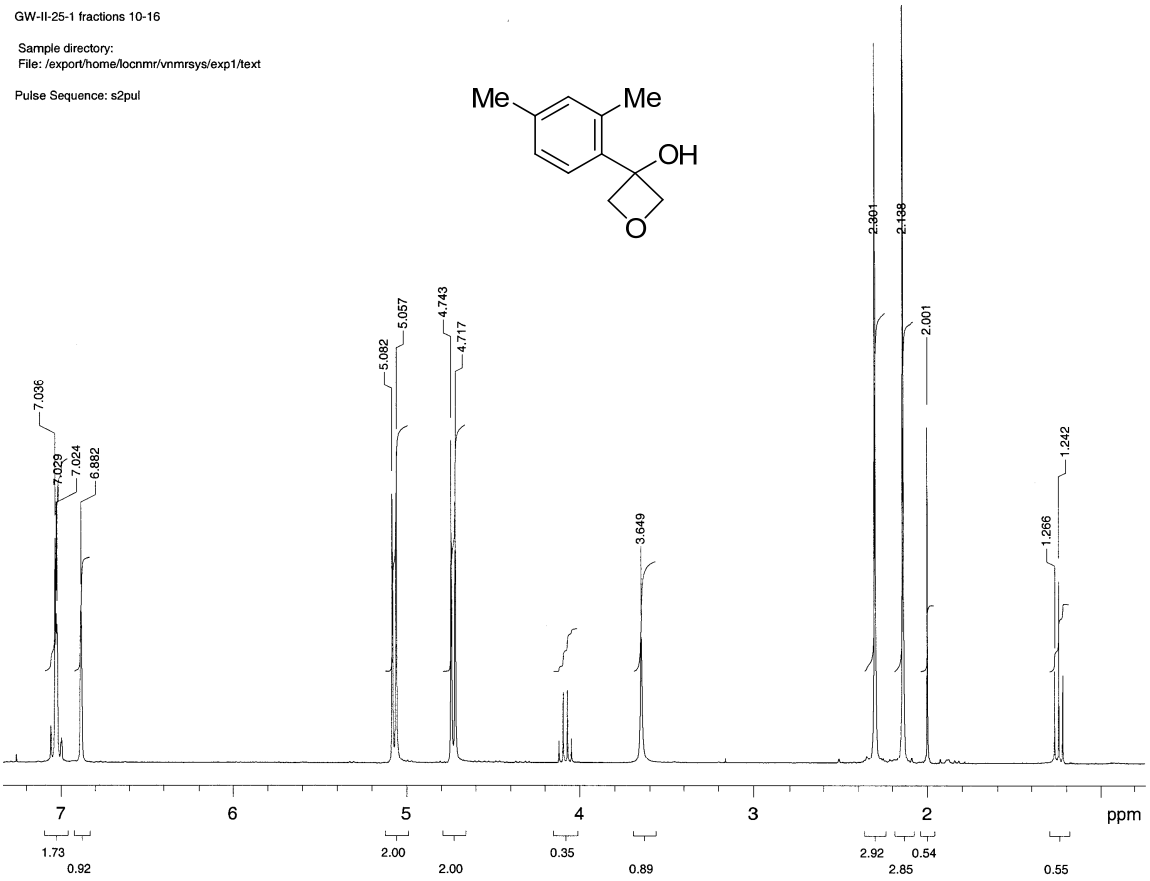


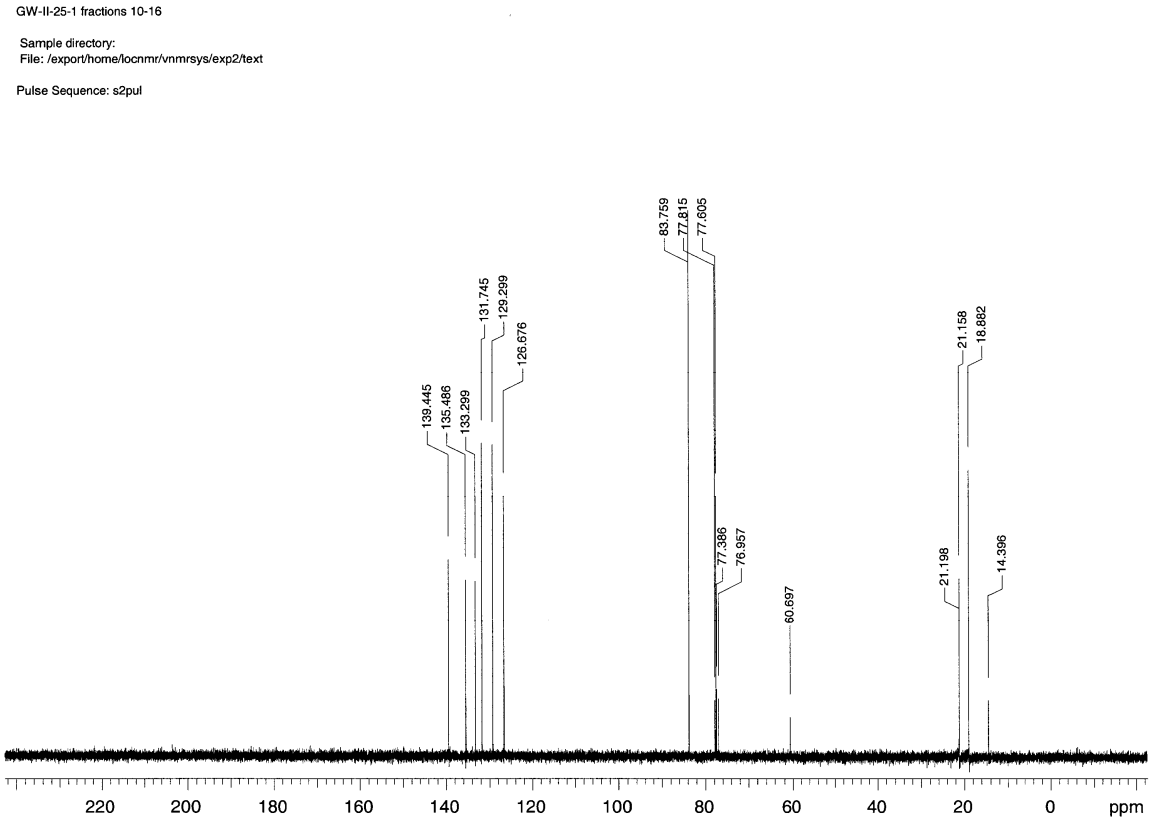
Appendix


GW-II-24-1 fractions 29-39
File: PROTON
Pulse Sequence: s2pul
MeO
OH
O
4.882
4.872
3.820
7.486
7.458
6.945
6.917
7
6
5
4
3
2
1 ppm
1.83
1.84
4.00
3.00
0.84
0.07
0.39

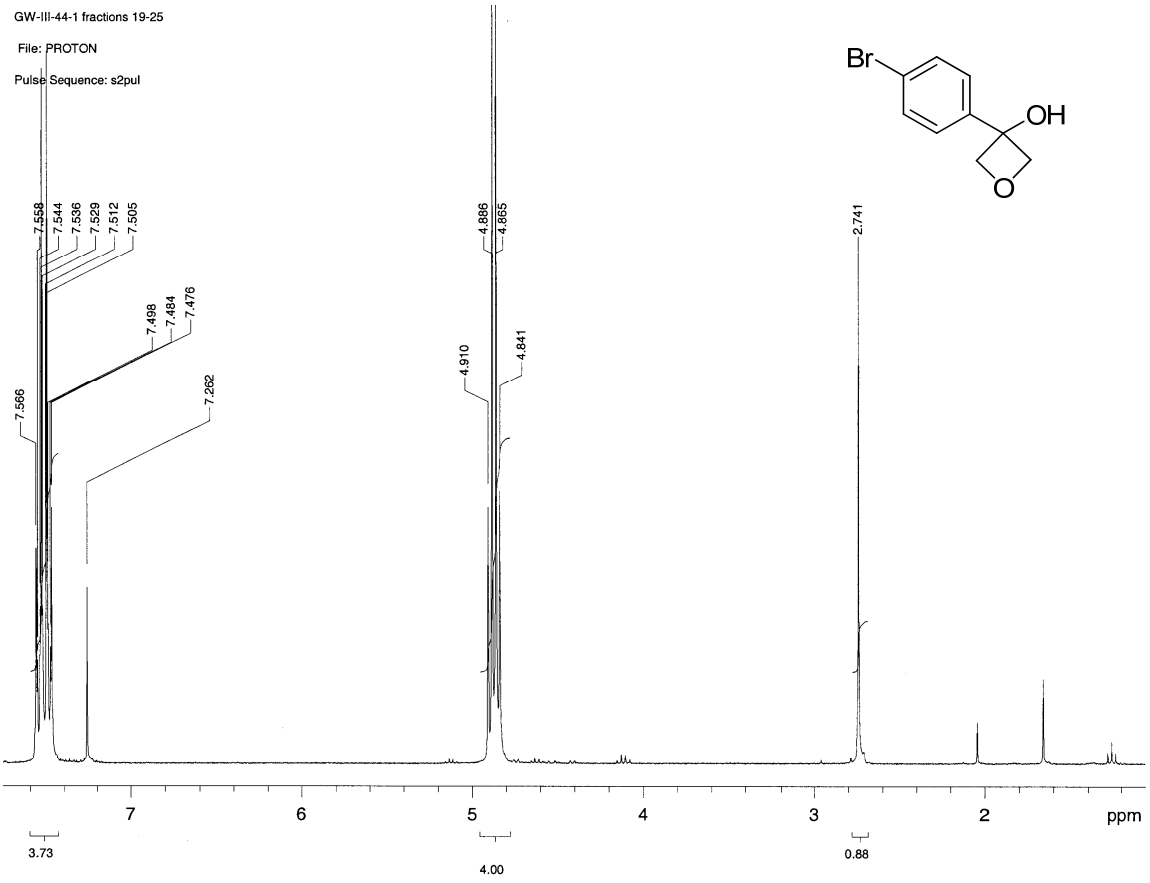

GW-II-24-1 fractions 29-39
File: CARBON
Pulse Sequence: s2pul
159.047
134.378
125.775
113.898
85.583
77.441
77.013
76.592
75.558
55.360
220
200
180
160
140
120
100
80
60
40
20
0
ppm

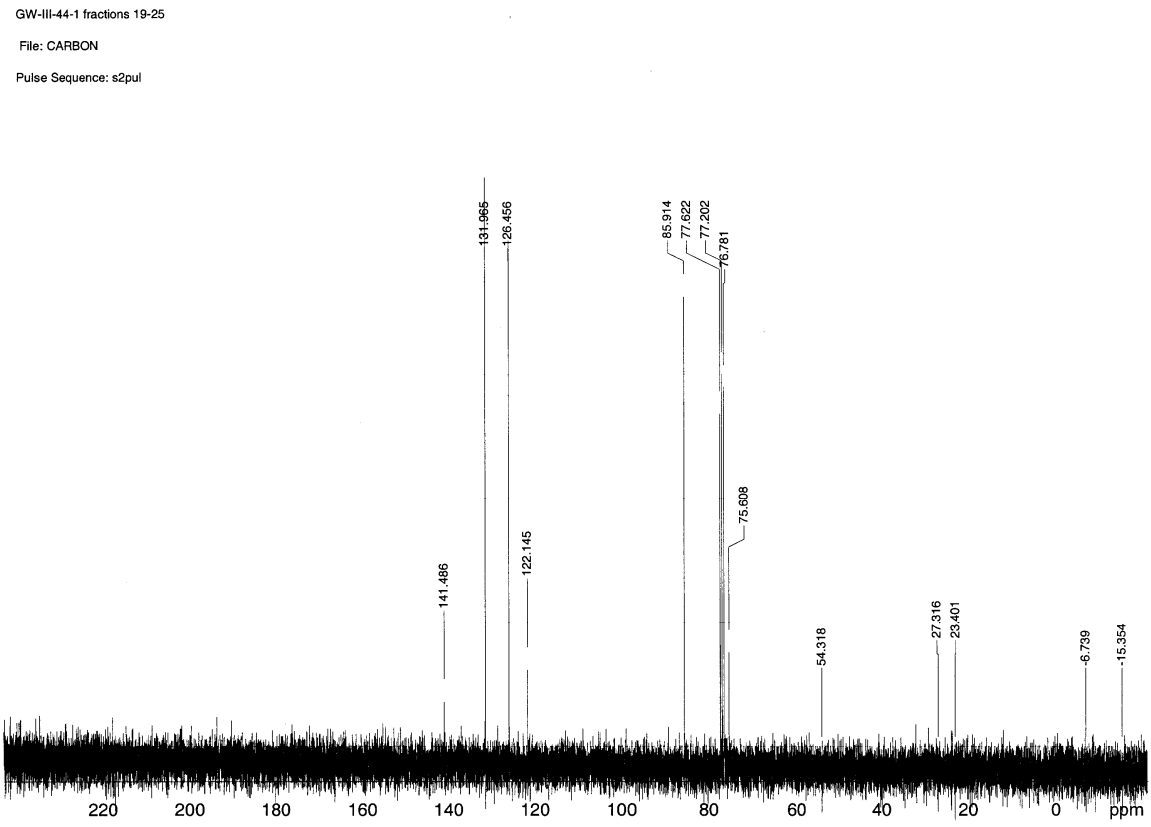
Appendix


GW-II-25-1 fractions 10-16
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
Me
Me
OH
O
7.036
7.029
7.024
6.882
5.082
5.057
4.743
4.717
3.649
2.901
2.138
2.001
1.266
1.242
7
6
5
4
3
2
ppm
1.73
0.92
2.00
2.00
0.35
0.89
2.92
0.54
2.85
0.55

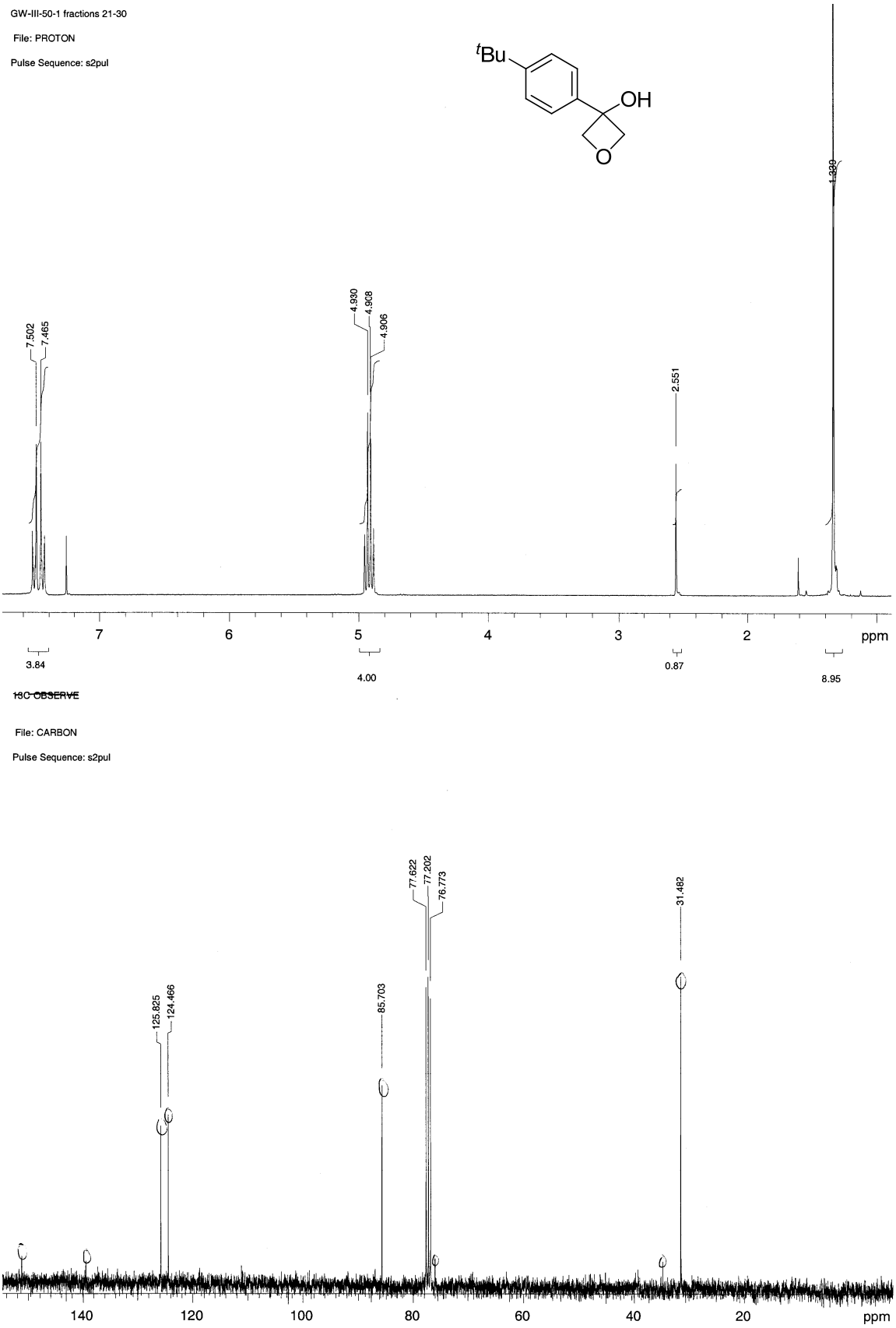

GW-II-25-1 fractions 10-16
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
139.445
135.486
133.299
131.745
129.299
126.676
83.759
77.815
77.605
77.386
76.957
60.697
21.198
21.158
18.882
14.396
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix

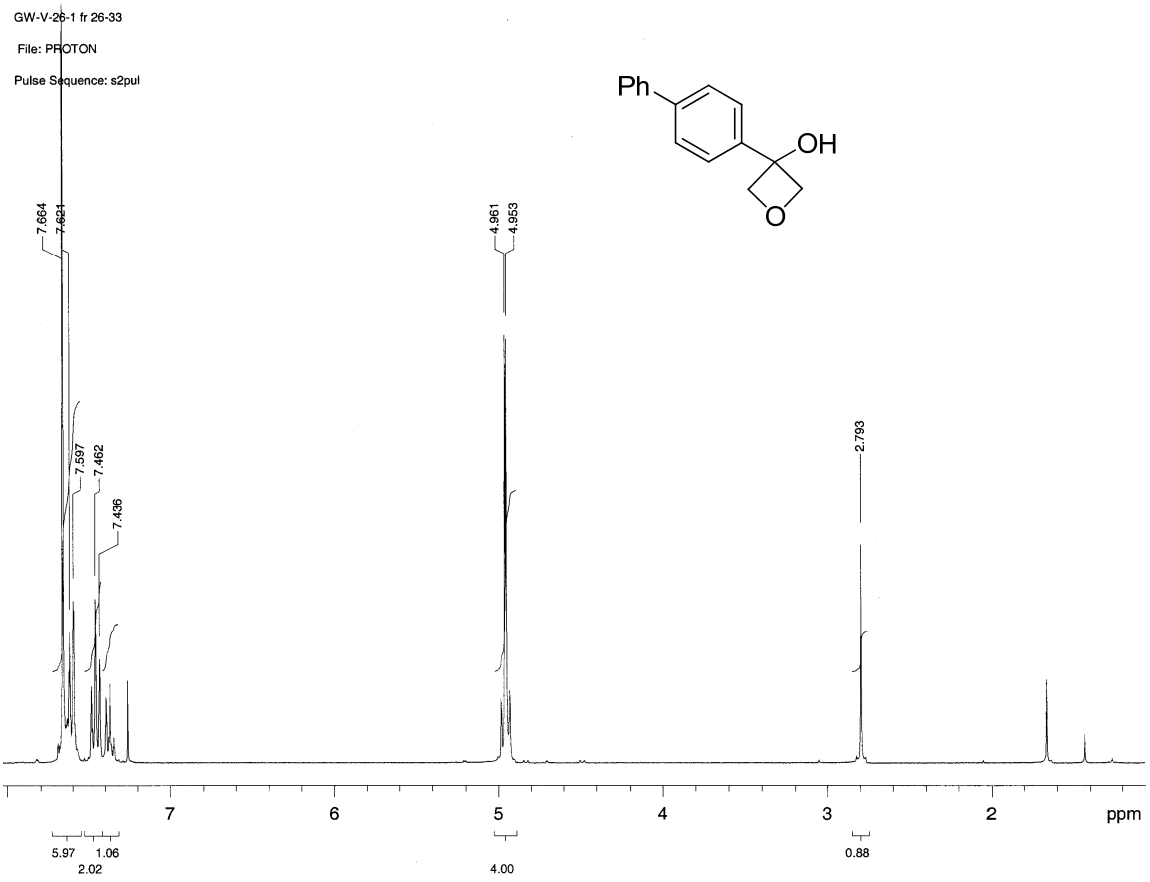

GW-III-44-1 fractions 19-25
File: PROTON
Pulse Sequence: s2pul
Br
OH
O
7.566
7.558
7.544
7.536
7.529
7.512
7.505
7.498
7.484
7.476
7.262
4.910
4.886
4.865
4.841
2.741
7
6
5
4
3
2
ppm
3.73
4.00
0.88

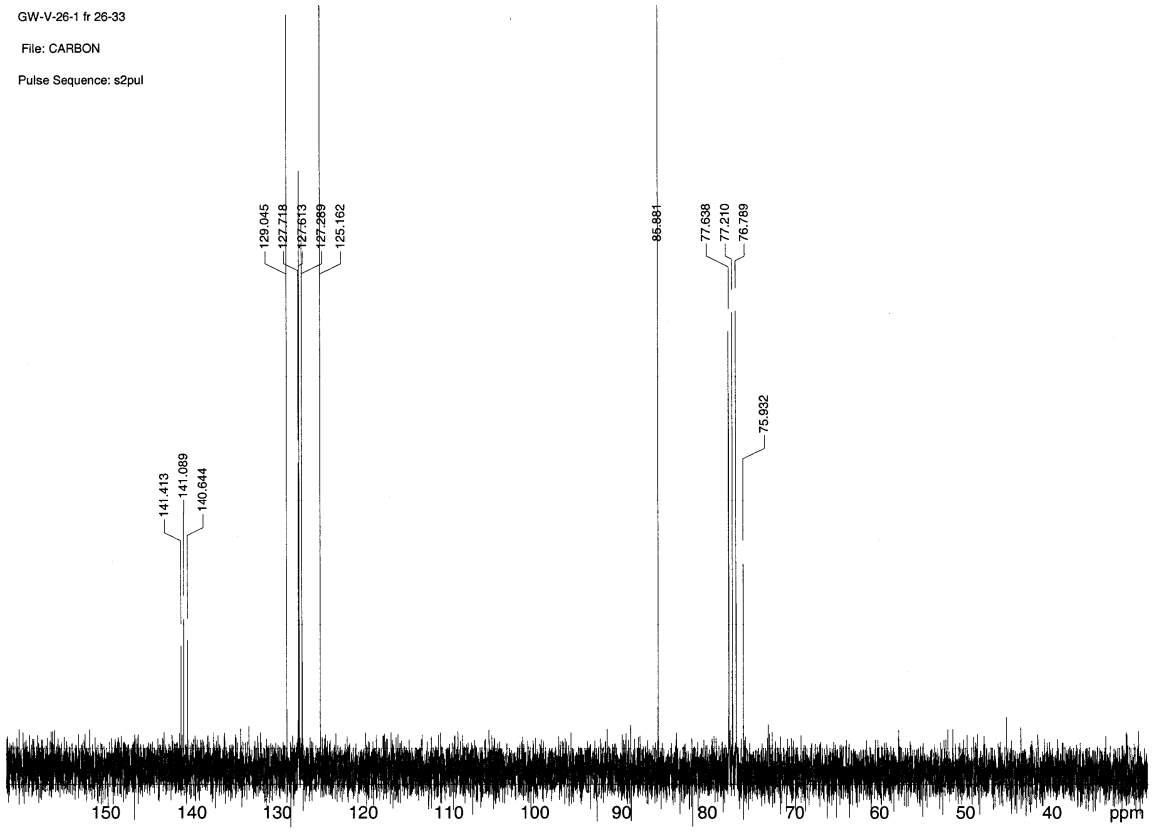

GW-III-44-1 fractions 19-25
File: CARBON
Pulse Sequence: s2pul
141.486
131.965
126.456
122.145
85.914
77.622
77.202
76.781
75.608
54.318
27.316
23.401
-6.739
-15.354
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix

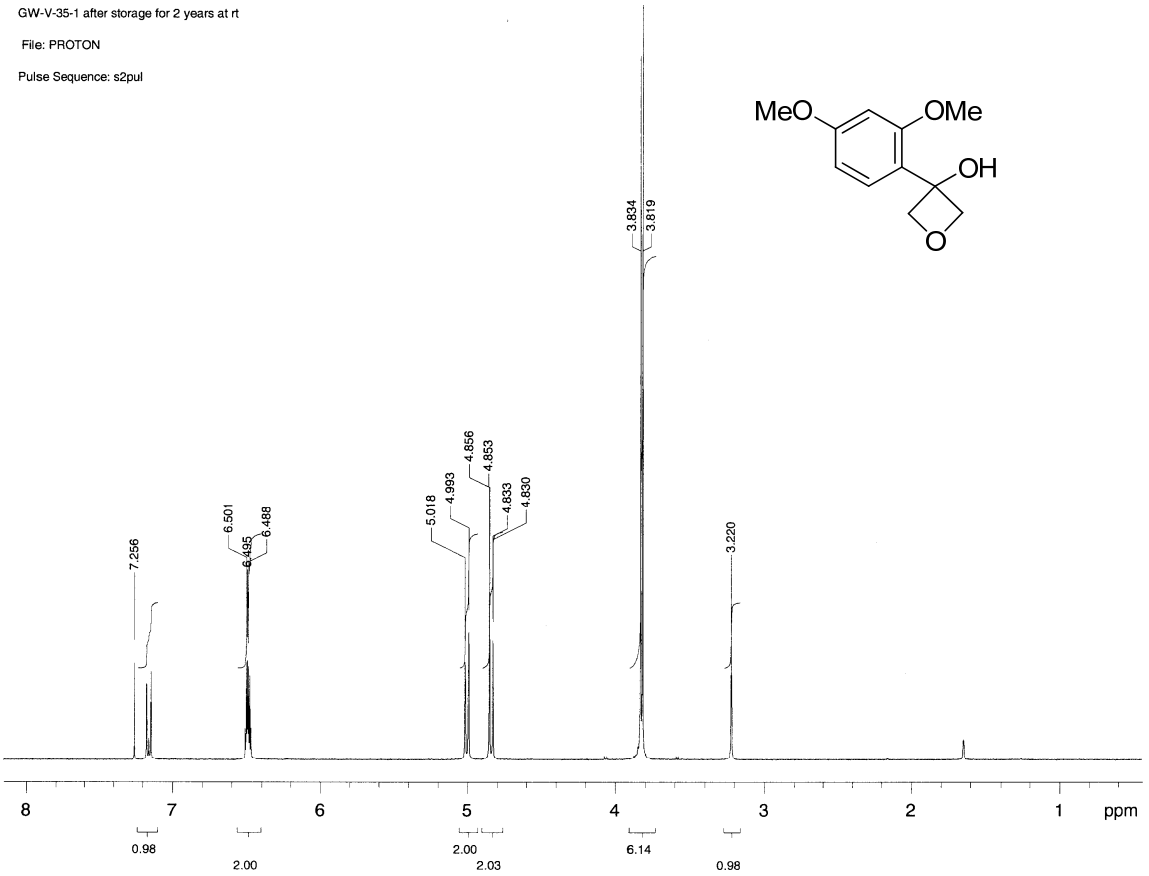

GW-III-50-1 fractions 21-30
File: PROTON
Pulse Sequence: s2pul
tBu
OH
O
7.502
7.465
4.930
4.908
4.906
2.551
1.339
7
6
5
4
3
2
ppm
3.84
4.00
0.87
8.95
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
77.622
77.202
76.773
31.482
125.825
124.466
85.703
140
120
100
80
60
40
20
ppm

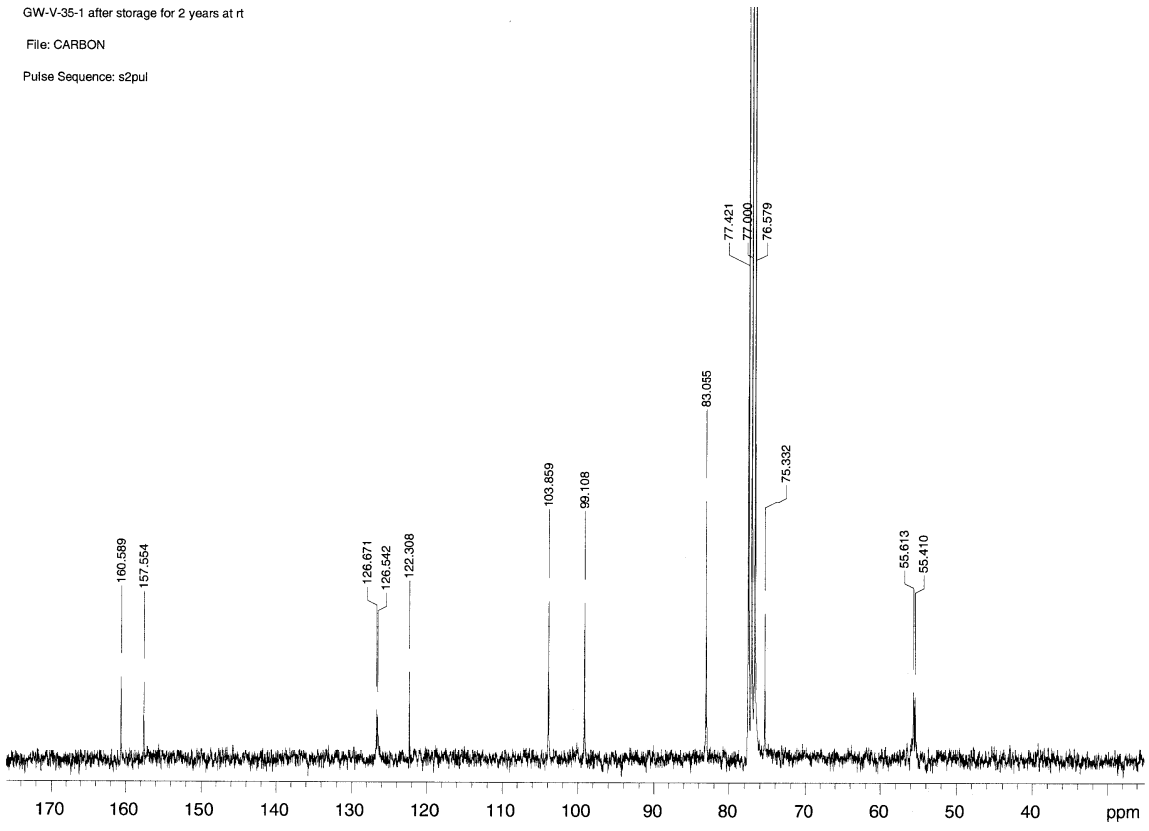
Appendix


GW-V-26-1 fr 26-33
File: PROTON
Pulse Sequence: s2pul
Ph
OH
O
7.664
7.621
7.597
7.462
7.436
4.961
4.953
2.793
7
6
5
4
3
2
ppm
5.97
1.06
2.02
4.00
0.88

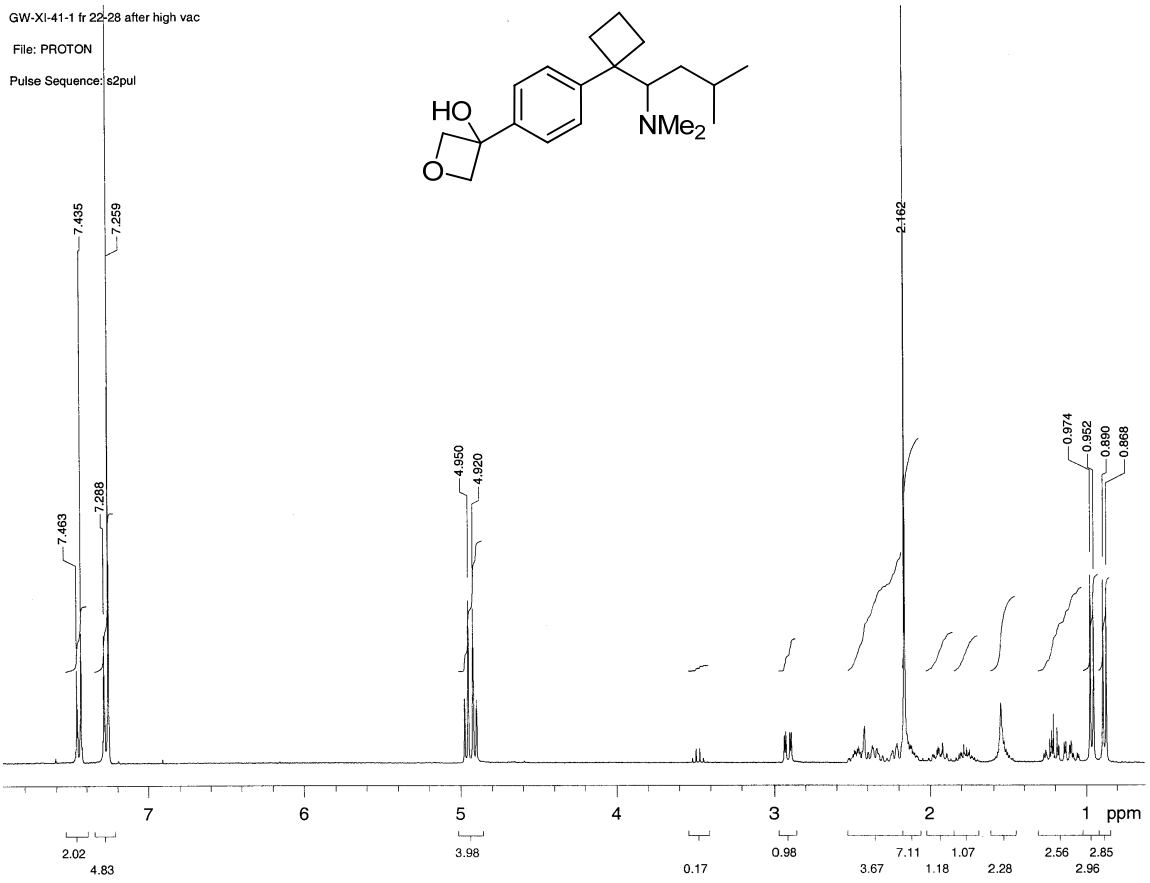

GW-V-26-1 fr 26-33
File: CARBON
Pulse Sequence: s2pul
129.045
127.718
127.613
127.289
125.162
86.881
77.638
77.210
76.789
75.932
141.413
141.089
140.644
150
140
130
120
110
100
90
80
70
60
50
40
ppm

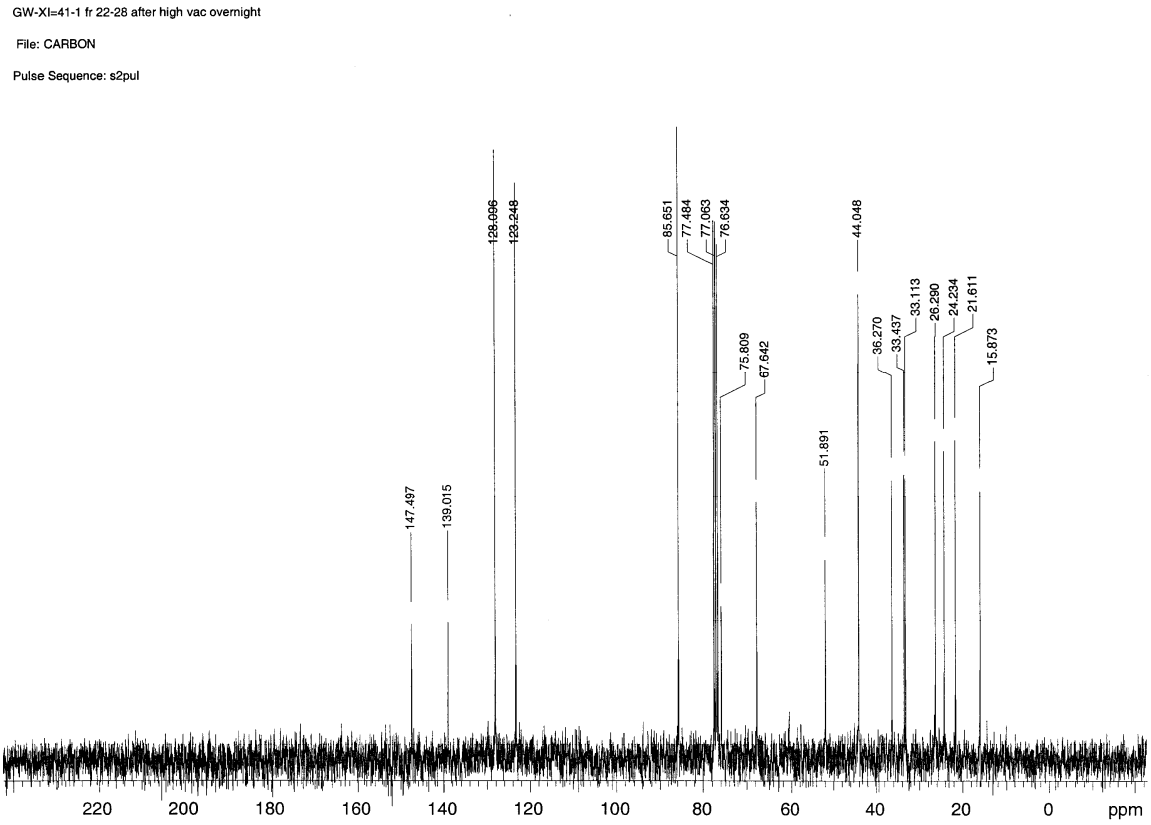
Appendix


GW-V-35-1 after storage for 2 years at rt
File: PROTON
Pulse Sequence: s2pul
MeO
OMe
OH
O
7.256
6.501
6.495
6.488
5.018
4.993
4.856
4.853
4.833
4.830
3.834
3.819
3.220
8
7
6
5
4
3
2
1
ppm
0.98
2.00
2.00
2.03
6.14
0.98

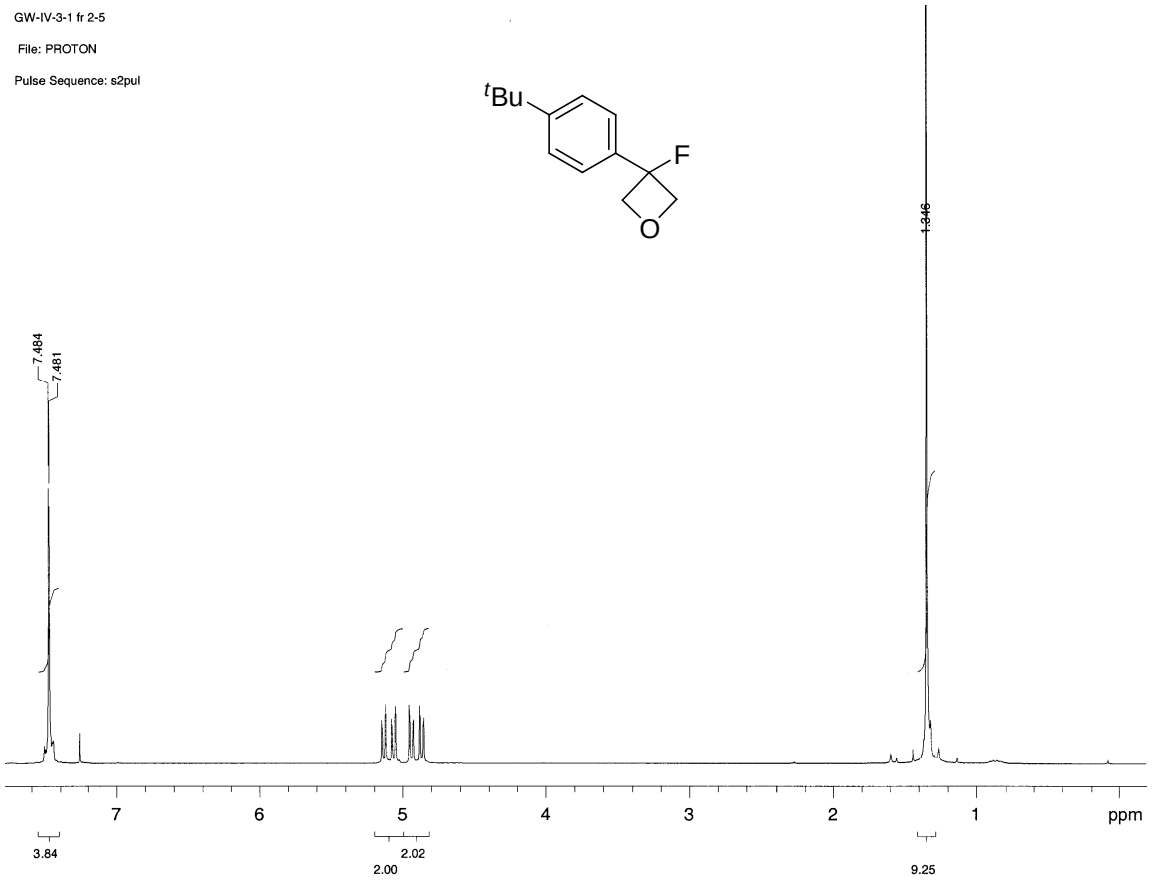

GW-V-35-1 after storage for 2 years at rt
File: CARBON
Pulse Sequence: s2pul
160.589
157.554
126.671
126.542
122.308
103.859
99.108
83.055
77.421
77.000
76.579
75.332
55.613
55.410
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

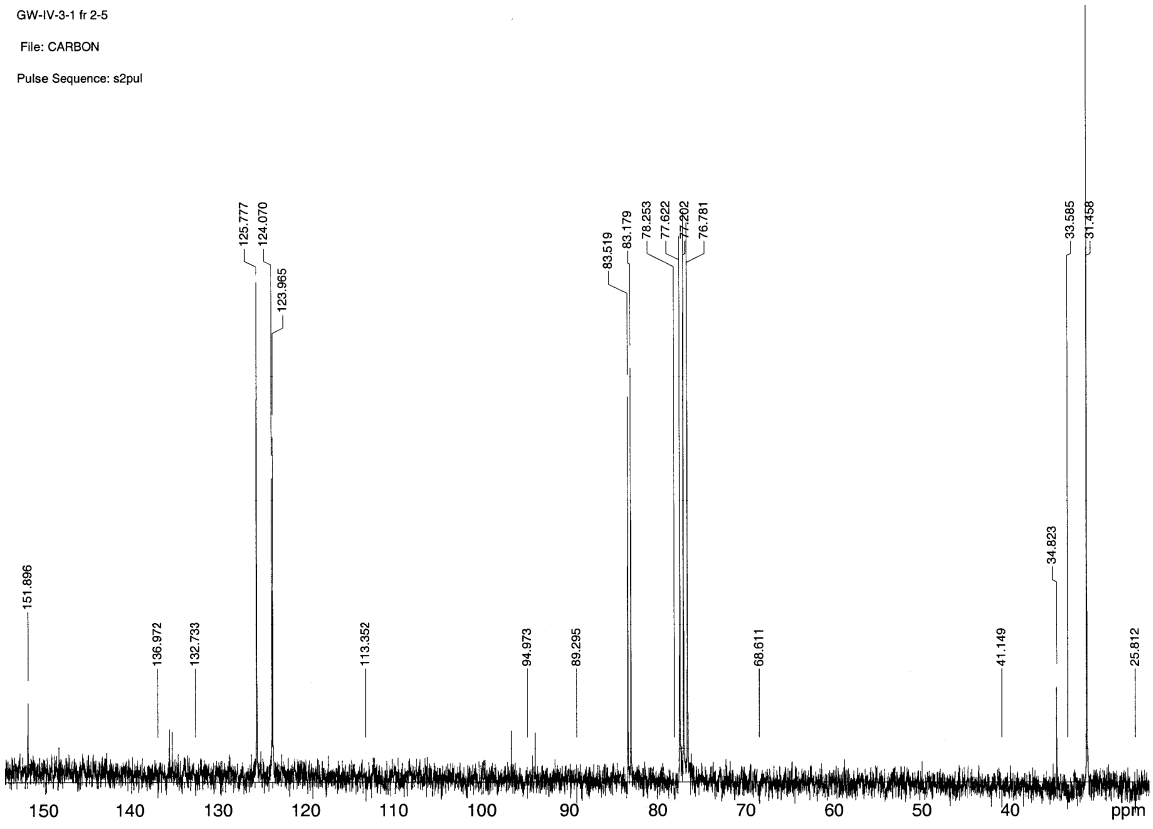
Appendix


GW-XI-41-1 fr 22-28 after high vac
File: PROTON
Pulse Sequence: s2pul
HO
O
NMe2
7.435
7.259
7.463
7.288
4.950
4.920
2.162
0.974
0.952
0.890
0.868
7
6
5
4
3
2
1 ppm
2.02
4.83
3.98
0.17
0.98
3.67
7.11
1.18
1.07
2.28
2.56
2.85
2.96

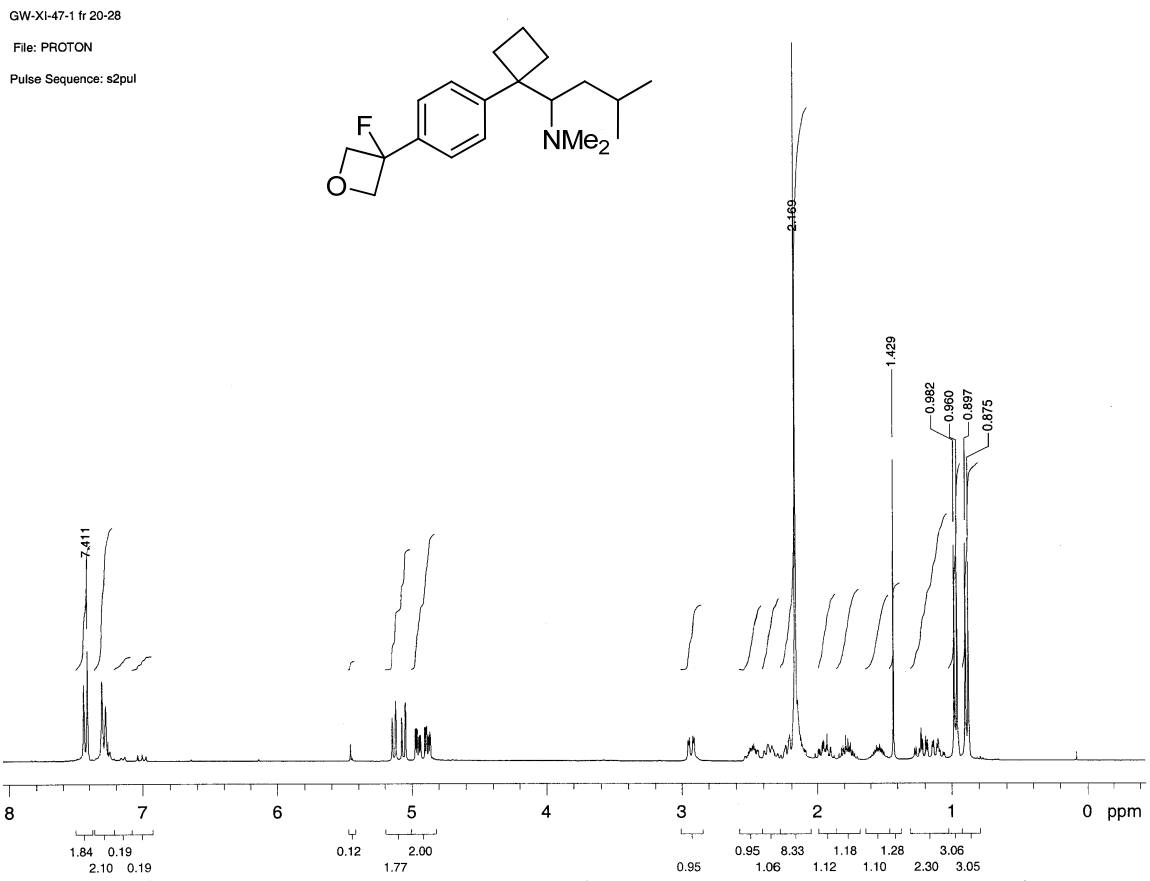

GW-XI=41-1 fr 22-28 after high vac overnight
File: CARBON
Pulse Sequence: s2pul
147.497
139.015
128.096
128.248
85.651
77.484
77.063
76.634
75.809
67.642
51.891
44.048
36.270
33.437
33.113
26.290
24.234
21.611
15.873
220
200
180
160
140
120
100
80
60
40
20
0
ppm

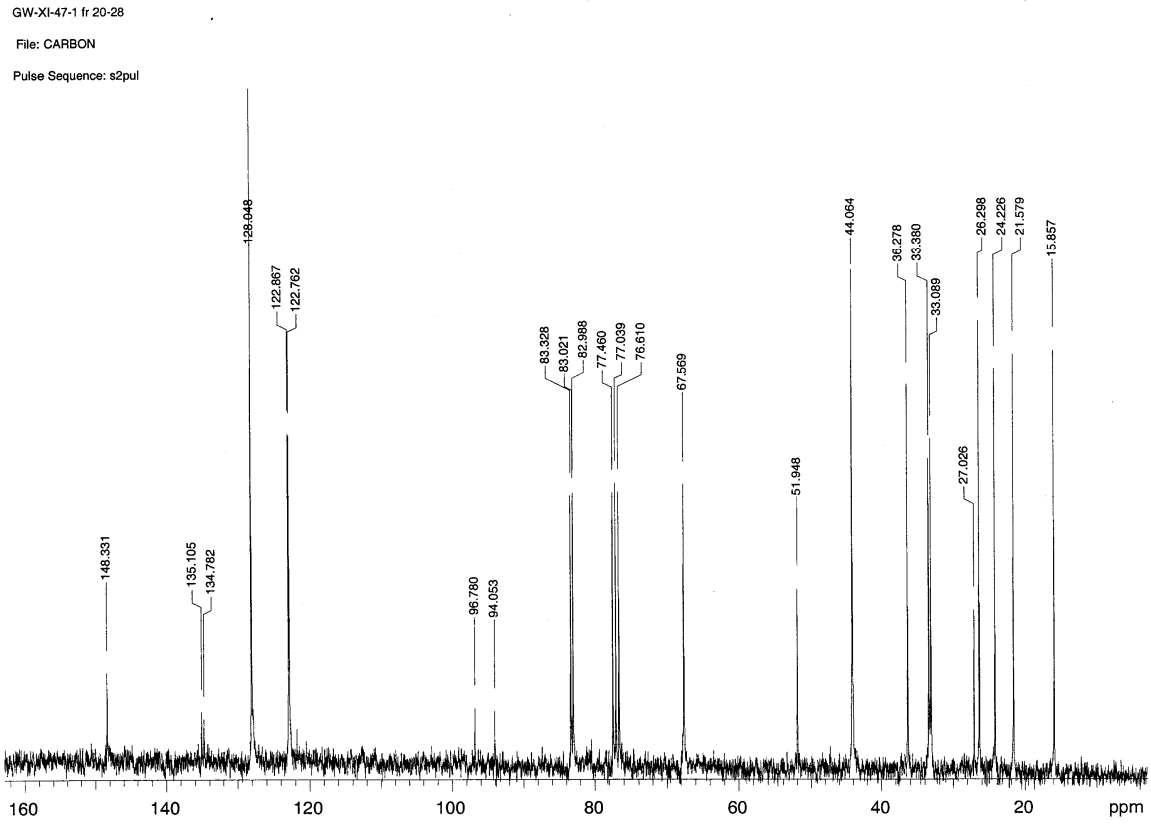
Appendix


GW-IV-3-1 fr 2-5
File: PROTON
Pulse Sequence: s2pul
tBu
F
O
7.484
7.481
1.346
7
6
5
4
3
2
1
ppm
3.84
2.00
2.02
9.25

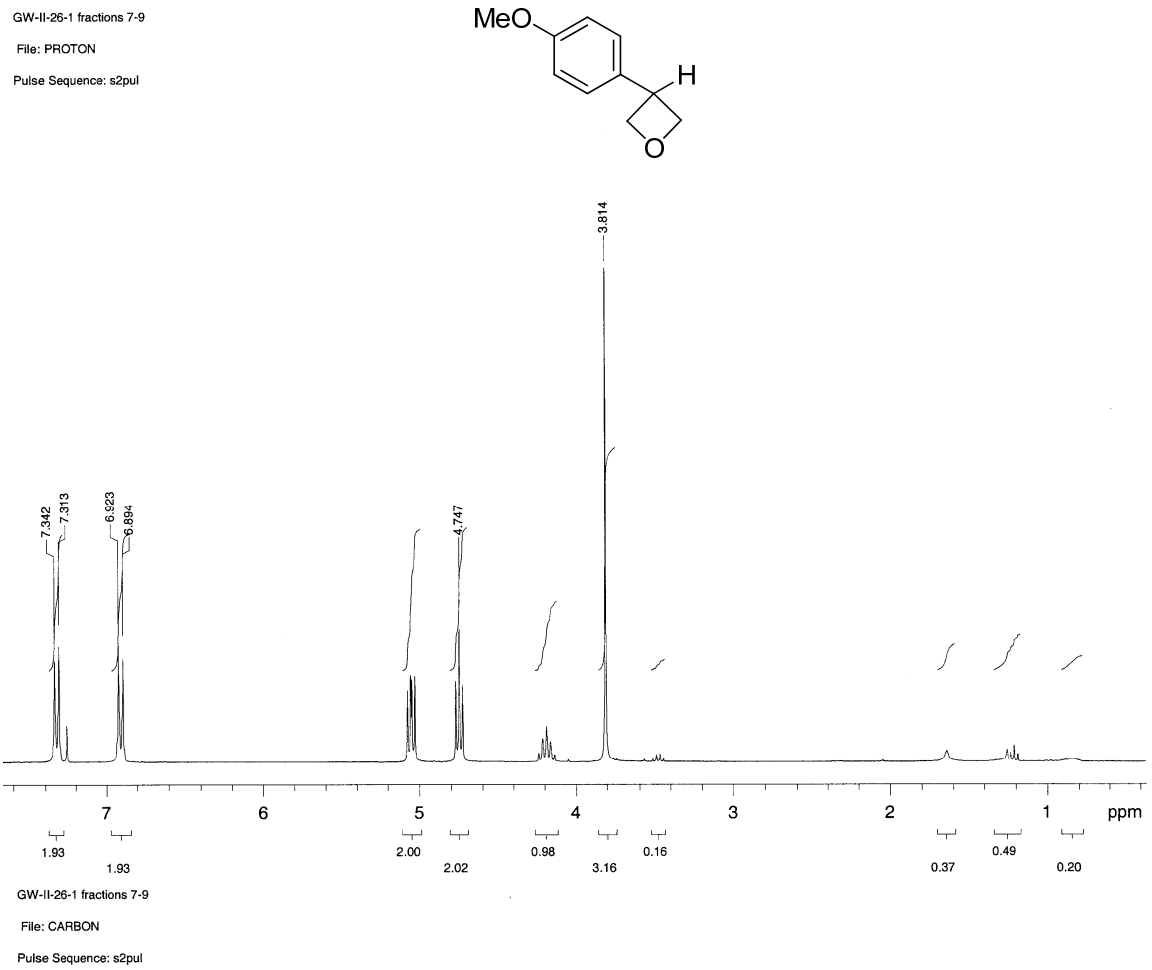

GW-IV-3-1 fr 2-5
File: CARBON
Pulse Sequence: s2pul
151.896
136.972
132.733
125.777
124.070
123.965
113.352
94.973
89.295
83.519
83.179
78.253
77.622
77.202
76.781
68.611
41.149
34.823
33.585
31.458
25.812
150
140
130
120
110
100
90
80
70
60
50
40
ppm

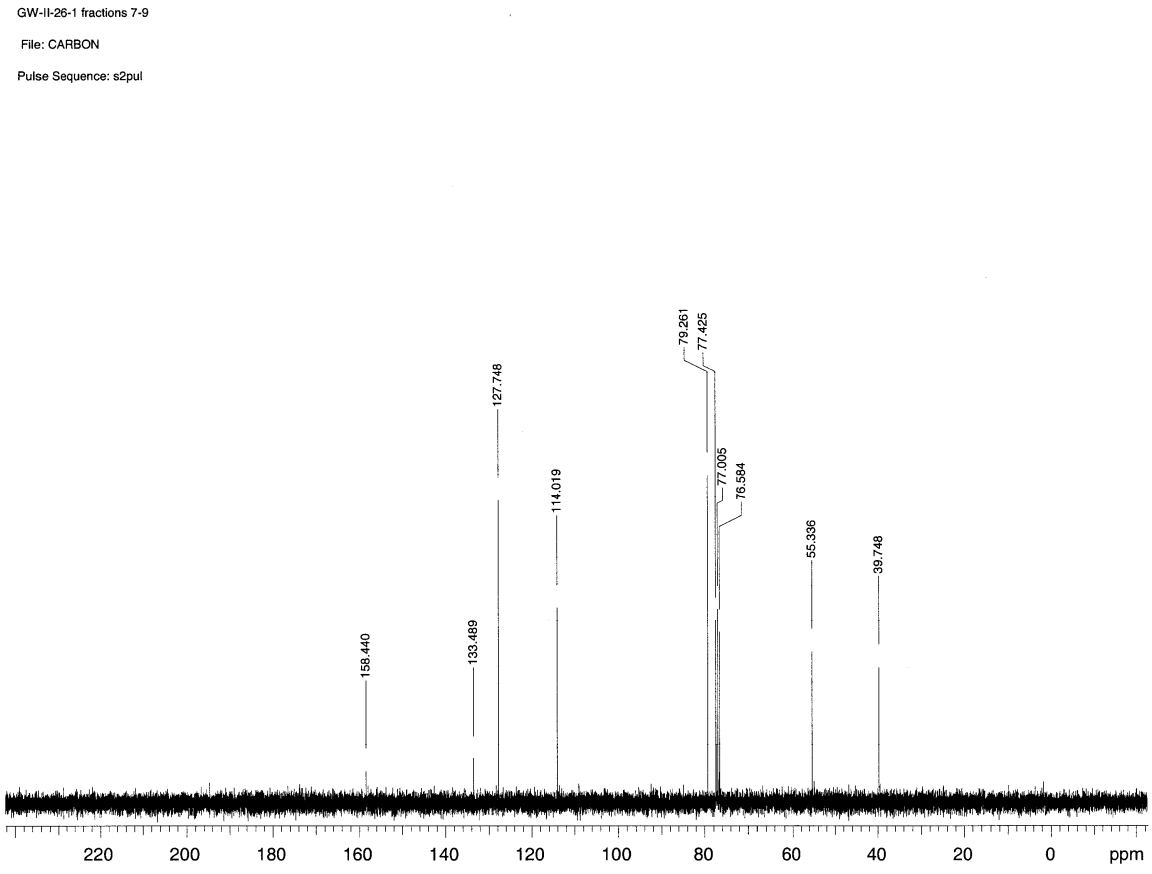
Appendix


GW-XI-47-1 fr 20-28
File: PROTON
Pulse Sequence: s2pul
F
O
NMe2
2.169
1.429
0.982
0.960
0.897
0.875
7.411
8
7
6
5
4
3
2
1
0 ppm
1.84 0.19
2.10 0.19
0.12
2.00
1.77
0.95
0.95 8.33
1.06
1.18
1.12
1.28
1.10
3.06
2.30 3.05

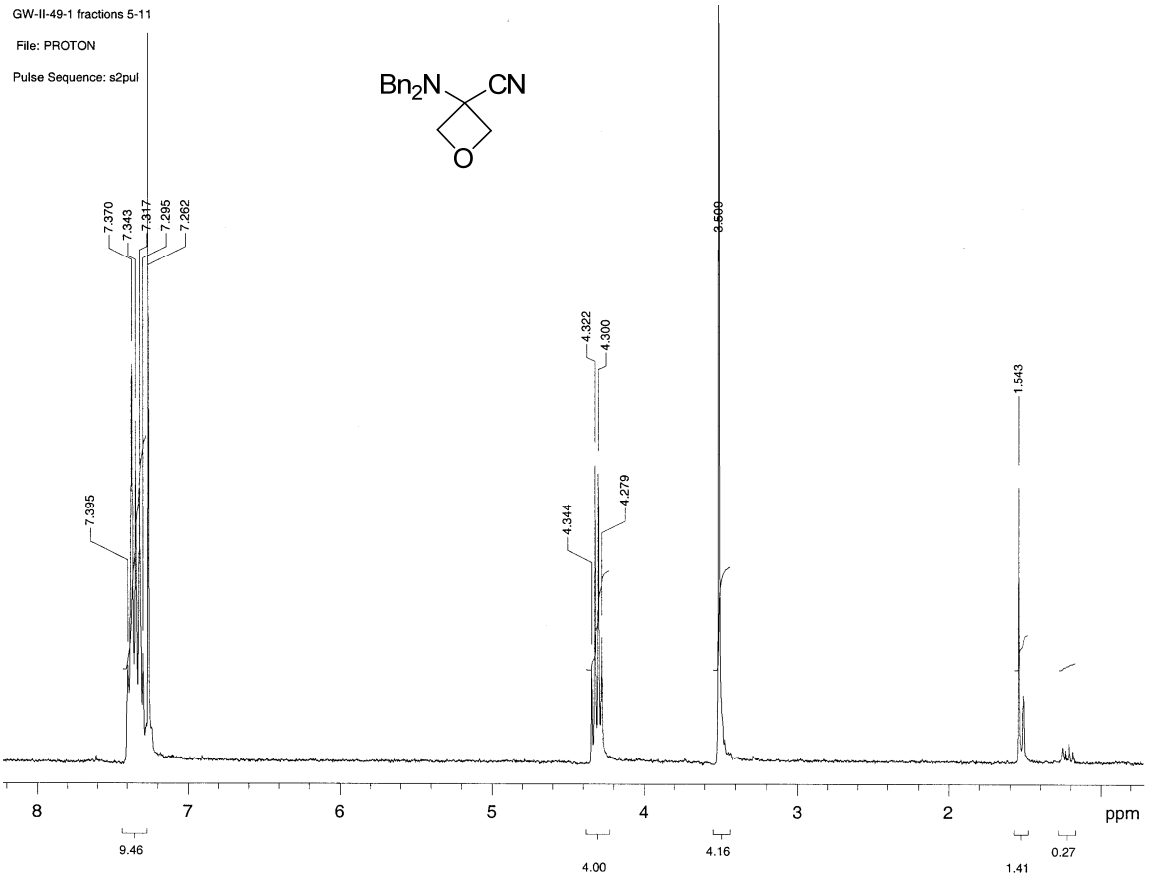

GW-XI-47-1 fr 20-28
File: CARBON
Pulse Sequence: s2pul
148.331
135.105
134.782
128.648
122.867
122.762
96.780
94.053
83.328
83.021
82.988
77.460
77.039
76.610
67.569
51.948
44.064
36.278
35.380
33.089
27.026
26.298
24.226
21.579
15.857
160
140
120
100
80
60
40
20
ppm

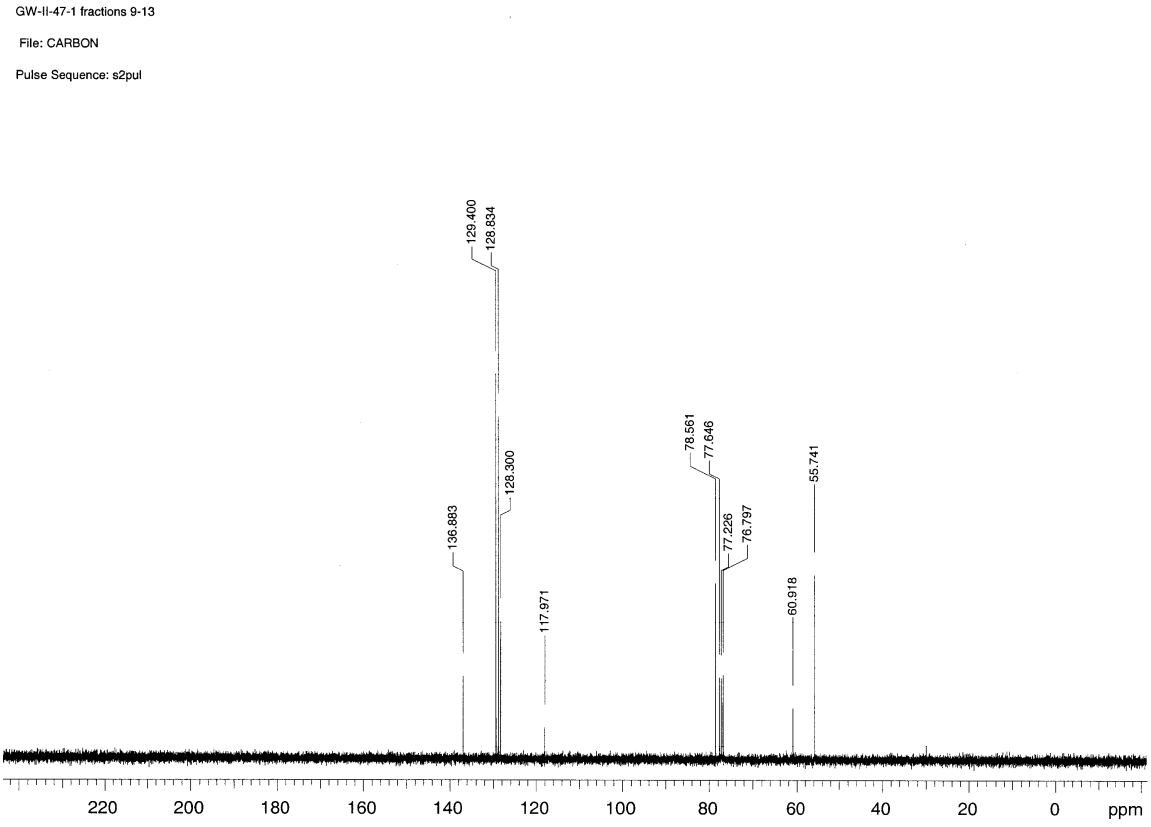
Appendix


GW-II-26-1 fractions 7-9
File: PROTON
Pulse Sequence: s2pul
MeO
H
O
3.814
7.342
7.313
6.923
6.894
4.747
7
6
5
4
3
2
1
ppm
1.93
1.93
2.00
2.02
0.98
3.16
0.16
0.37
0.49
0.20

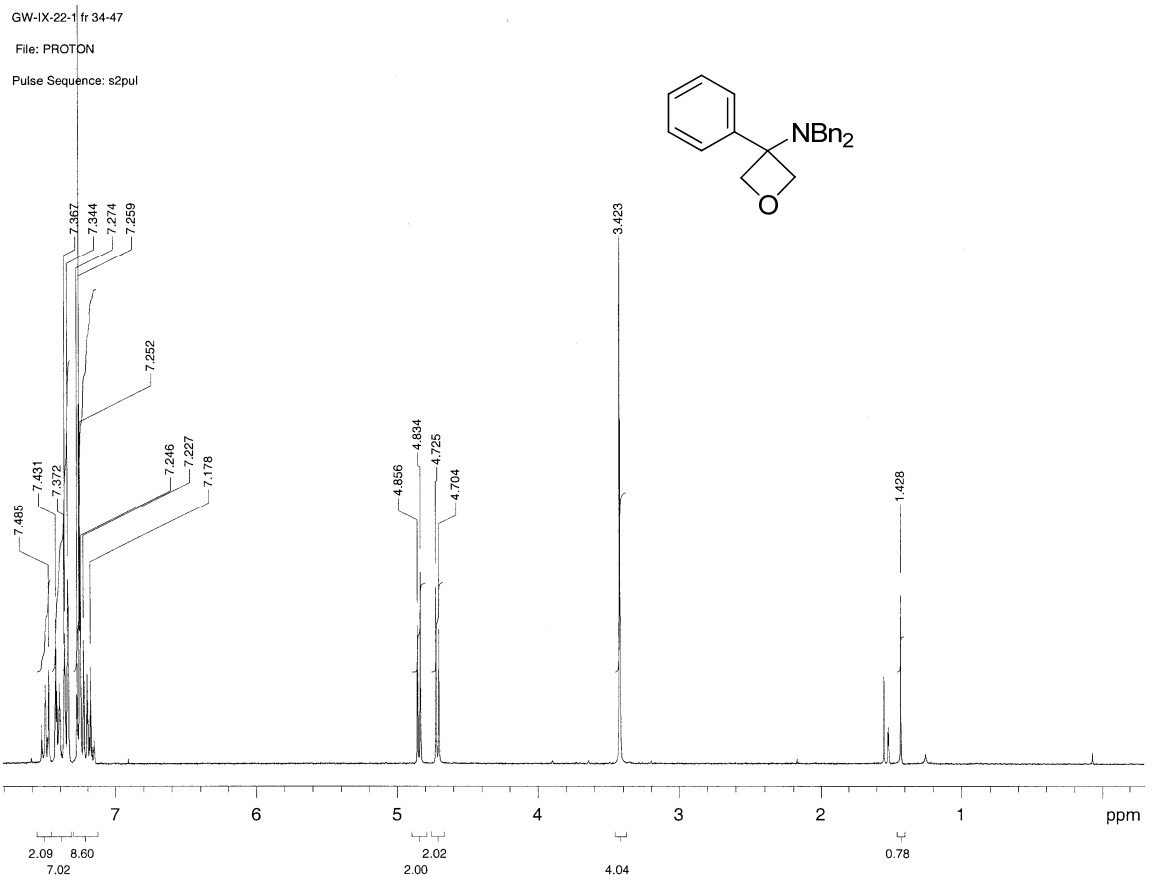

GW-II-26-1 fractions 7-9
File: CARBON
Pulse Sequence: s2pul
79.261
77.425
127.748
114.019
77.005
76.584
55.336
39.748
158.440
133.489
220
200
180
160
140
120
100
80
60
40
20
0
ppm

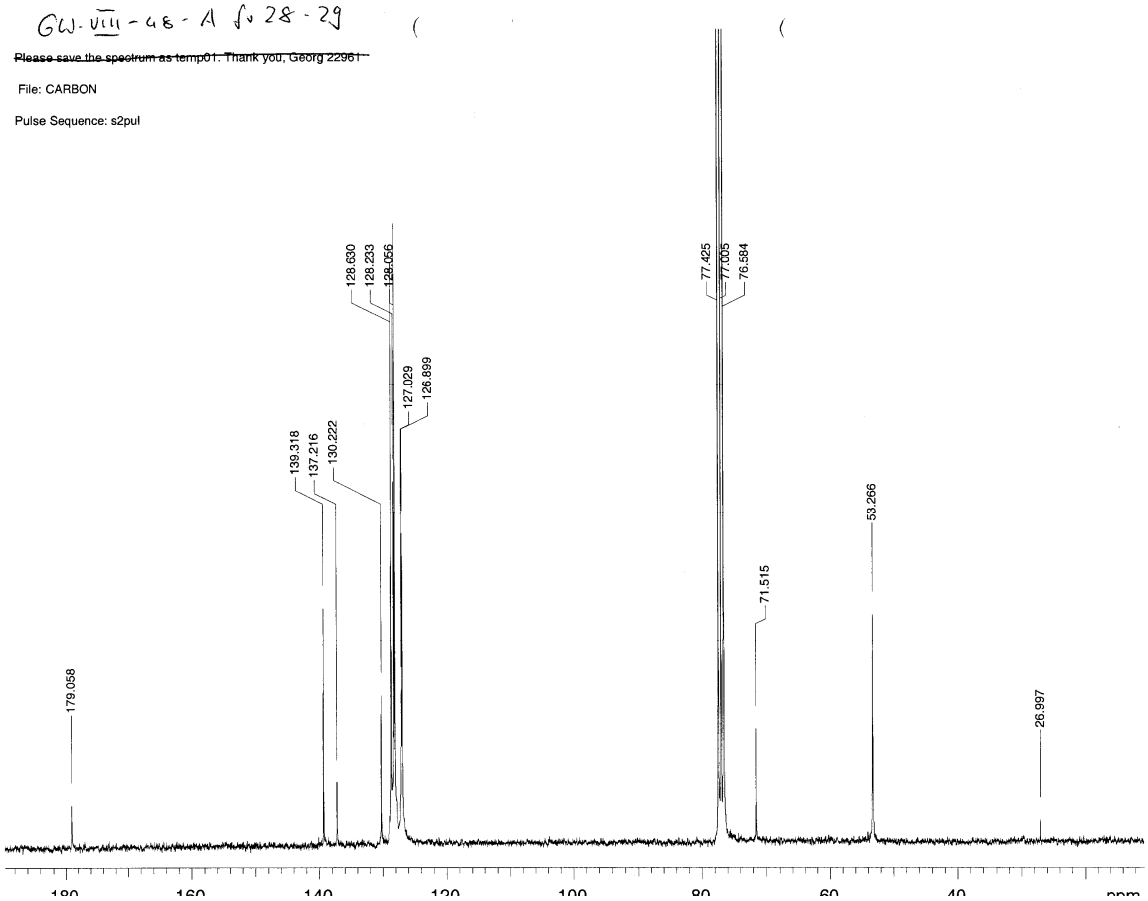
Appendix


GW-II-49-1 fractions 5-11
File: PROTON
Pulse Sequence: s2pul
Bn2N
CN
O
7.370
7.343
7.317
7.295
7.262
7.395
4.322
4.300
4.344
4.279
3.500
1.543
8
7
6
5
4
3
2
ppm
9.46
4.00
4.16
1.41
0.27

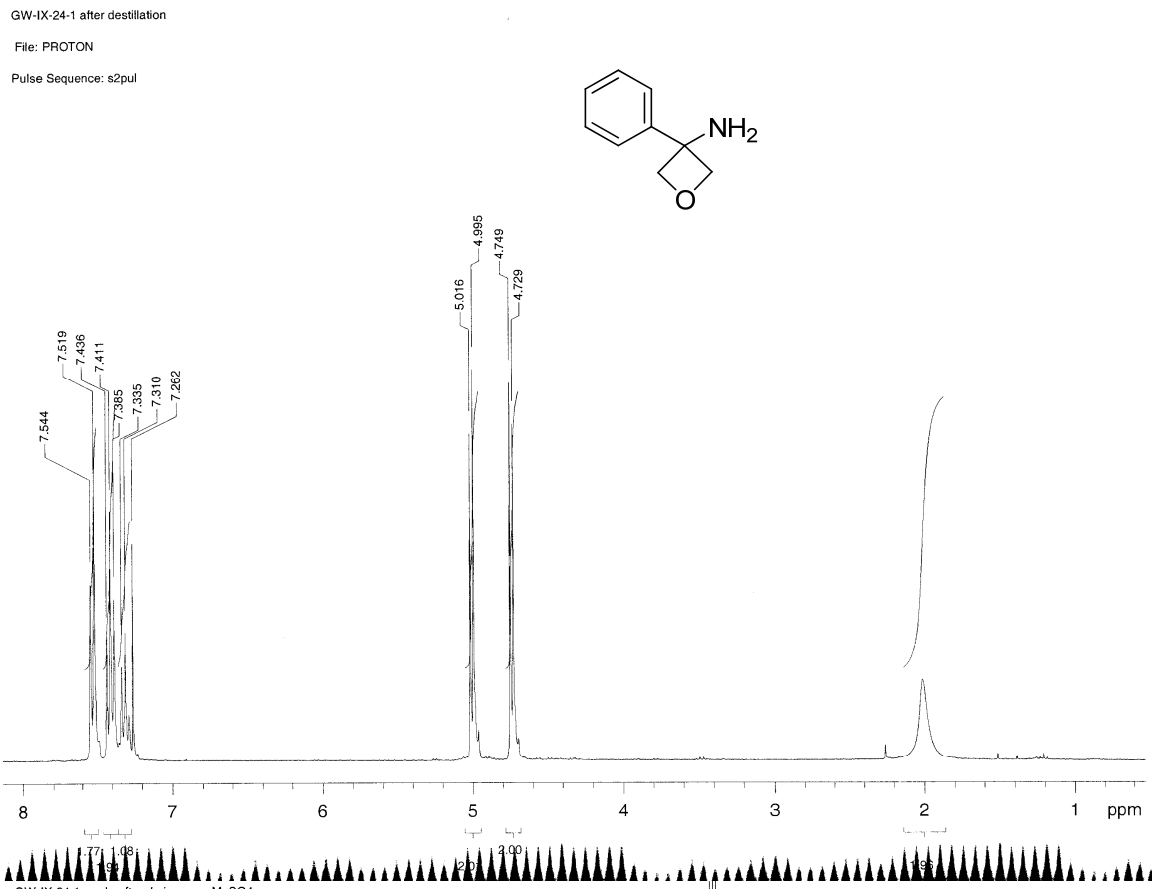

GW-II-47-1 fractions 9-13
File: CARBON
Pulse Sequence: s2pul
129.400
128.834
128.300
136.883
117.971
78.561
77.646
77.226
76.797
60.918
55.741
220
200
180
160
140
120
100
80
60
40
20
0
ppm

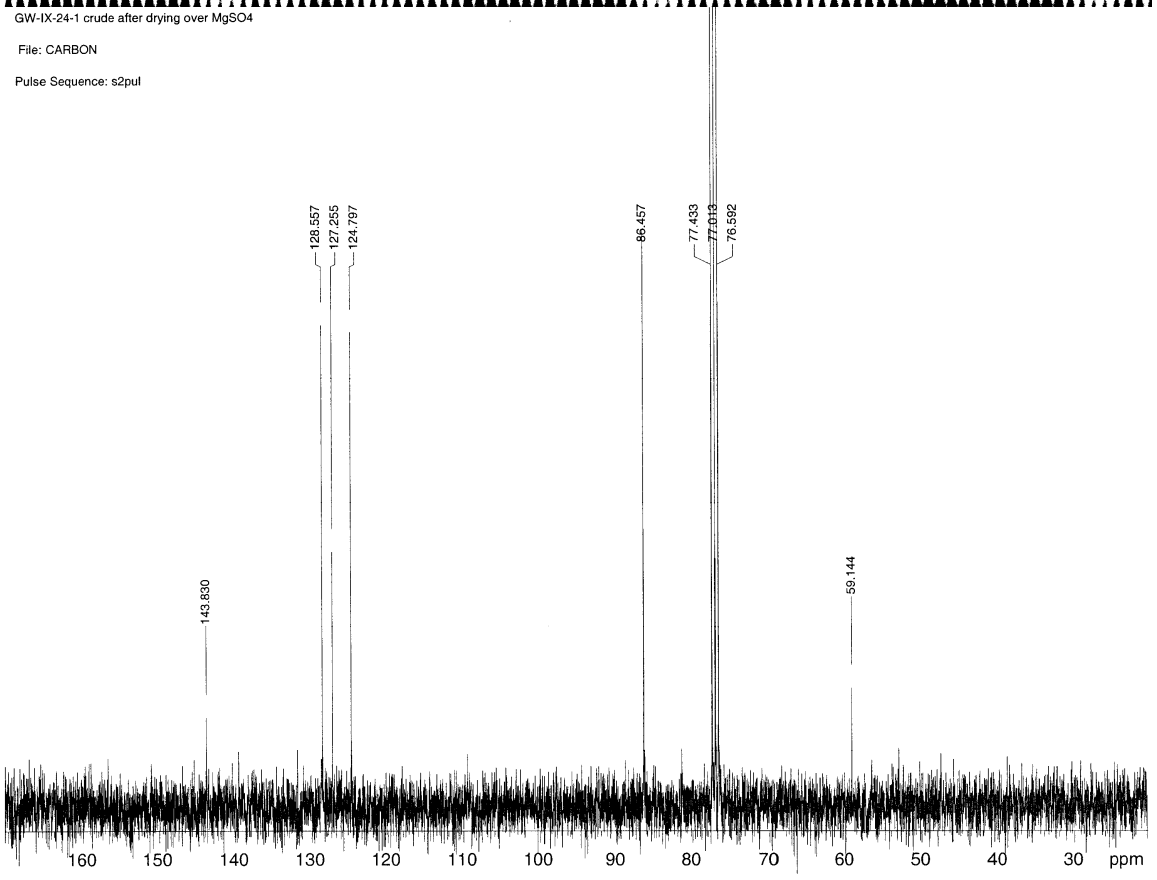
Appendix


GW-IX-22-1 fr 34-47
File: PROTON
Pulse Sequence: s2pul
NBn2
O
7.485
7.431
7.372
7.367
7.344
7.274
7.259
7.252
7.246
7.227
7.178
4.856
4.834
4.725
4.704
3.423
1.428
7
6
5
4
3
2
1
ppm
2.09
8.60
7.02
2.02
2.00
4.04
0.78

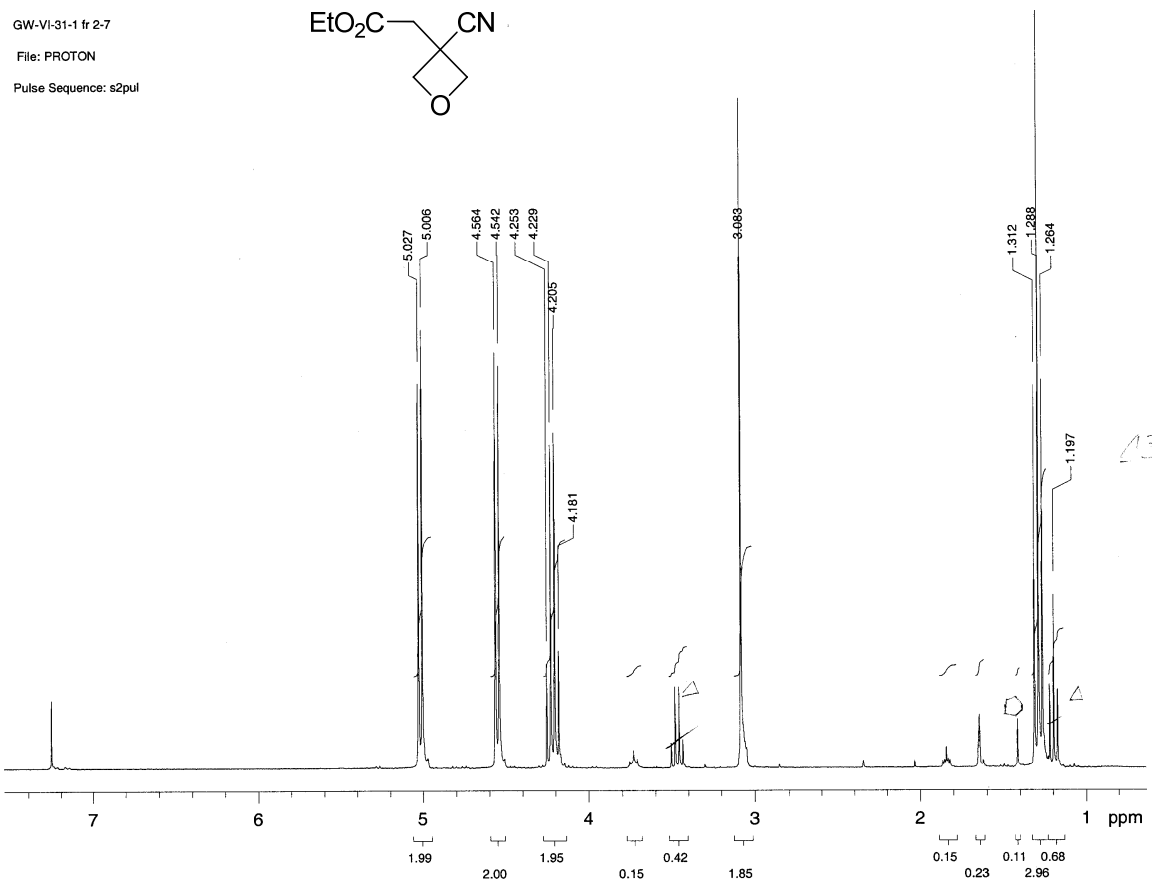

GW-VIII-48-A fr 28-29
Please save the spectrum as temp01. Thank you, Georg 22961
File: CARBON
Pulse Sequence: s2pul
179.058
139.318
137.216
130.222
128.630
128.233
128.056
127.029
126.899
77.425
77.005
76.584
71.515
53.266
26.997
180
160
140
120
100
80
60
40
ppm

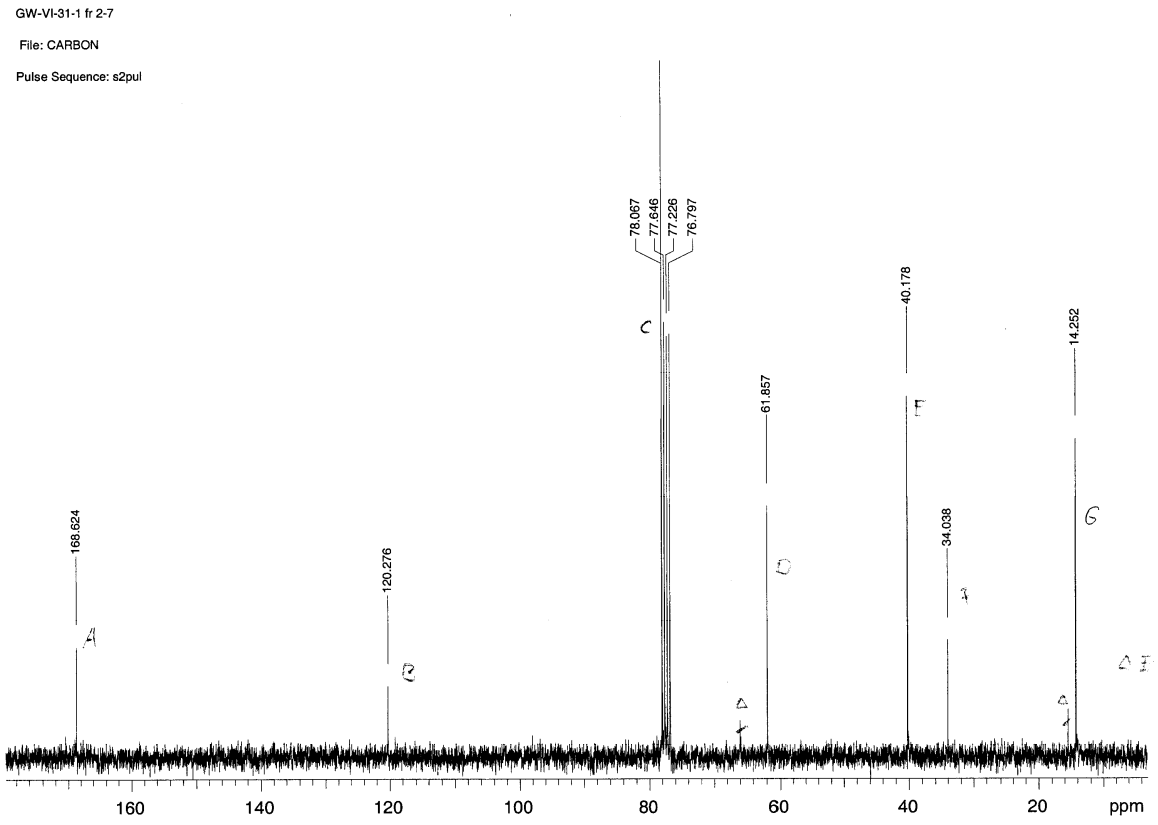
Appendix


GW-IX-24-1 after destillation
File: PROTON
Pulse Sequence: s2pul
NH2
O
7.544
7.519
7.436
7.411
7.385
7.335
7.310
7.262
5.016
4.995
4.749
4.729
8
7
6
5
4
3
2
1
ppm
1.77
1.08
2.00

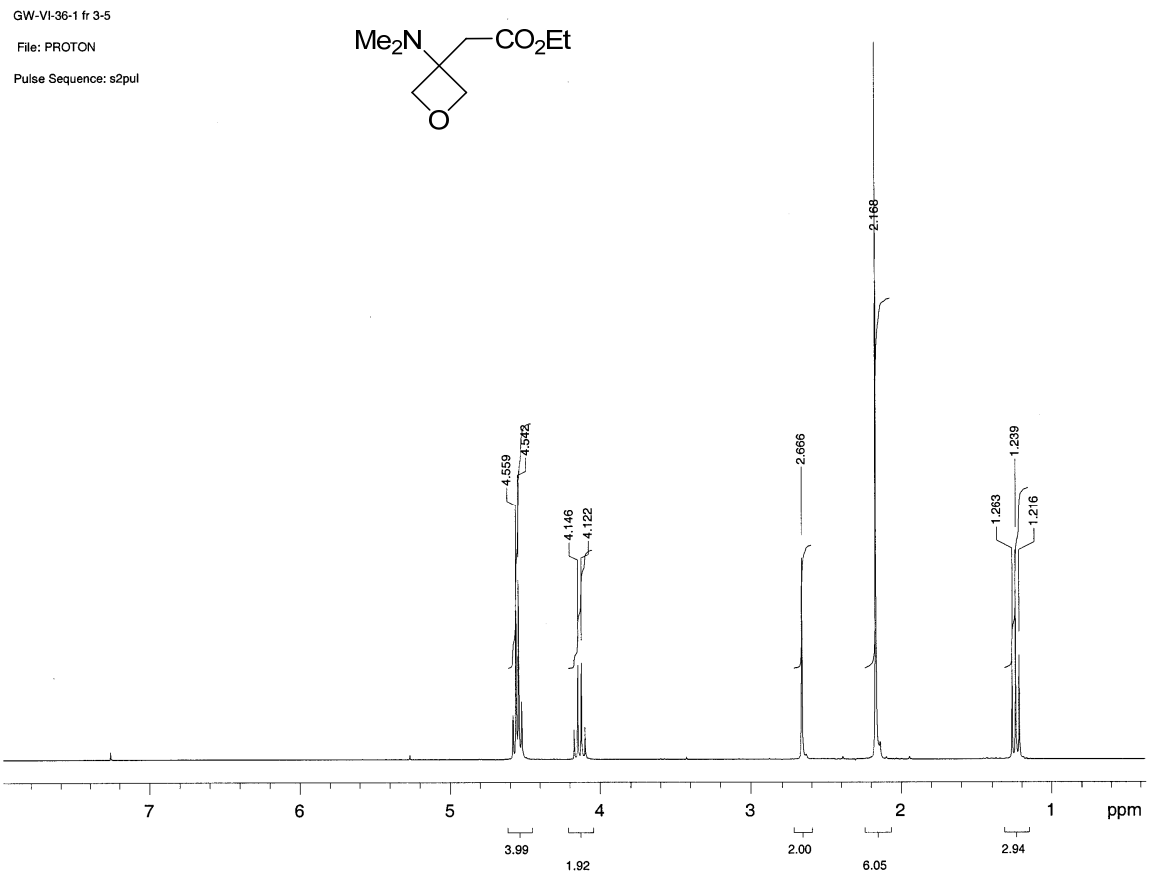

GW-IX-24-1 crude after drying over MgSO4
File: CARBON
Pulse Sequence: s2pul
143.830
128.557
127.255
124.797
86.457
77.433
77.013
76.592
59.144
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

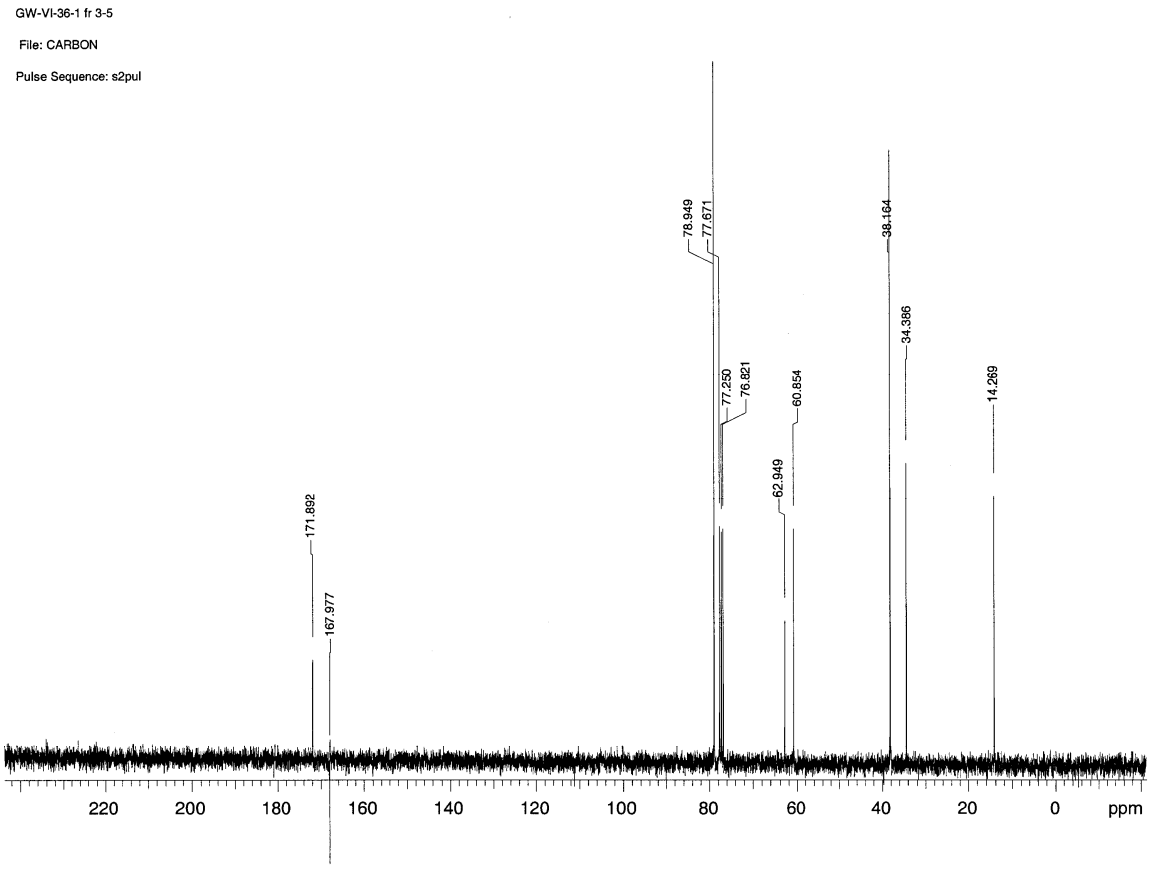
Appendix


GW-VI-31-1 fr 2-7
File: PROTON
Pulse Sequence: s2pul
EtO2C
CN
O
5.027
5.006
4.564
4.542
4.253
4.229
4.205
4.181
3.083
1.312
1.288
1.264
1.197
7
6
5
4
3
2
1 ppm
1.99
2.00
1.95
0.15
0.42
1.85
0.15
0.23
0.11
2.96
0.68

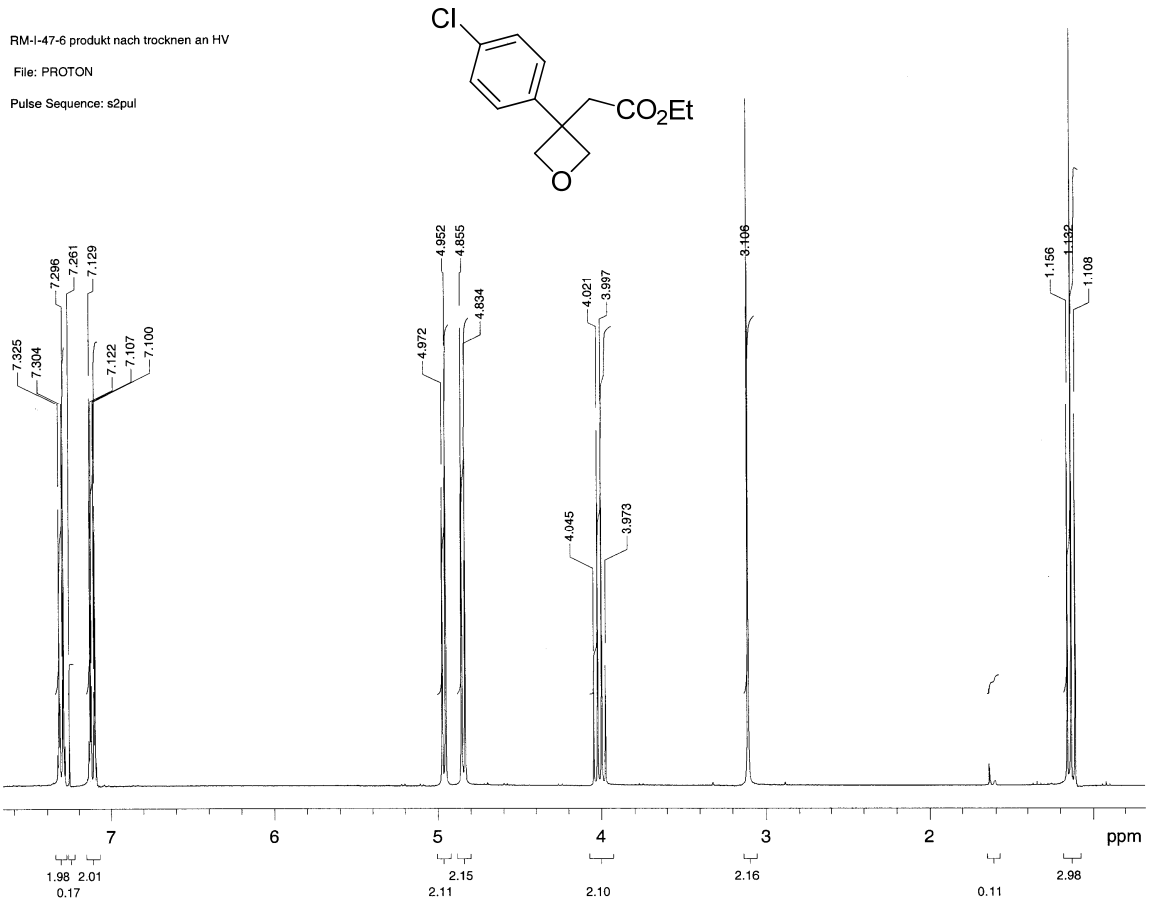

GW-VI-31-1 fr 2-7
File: CARBON
Pulse Sequence: s2pul
168.624
120.276
78.067
77.646
77.226
76.797
61.857
40.178
34.038
14.252
160
140
120
100
80
60
40
20
ppm

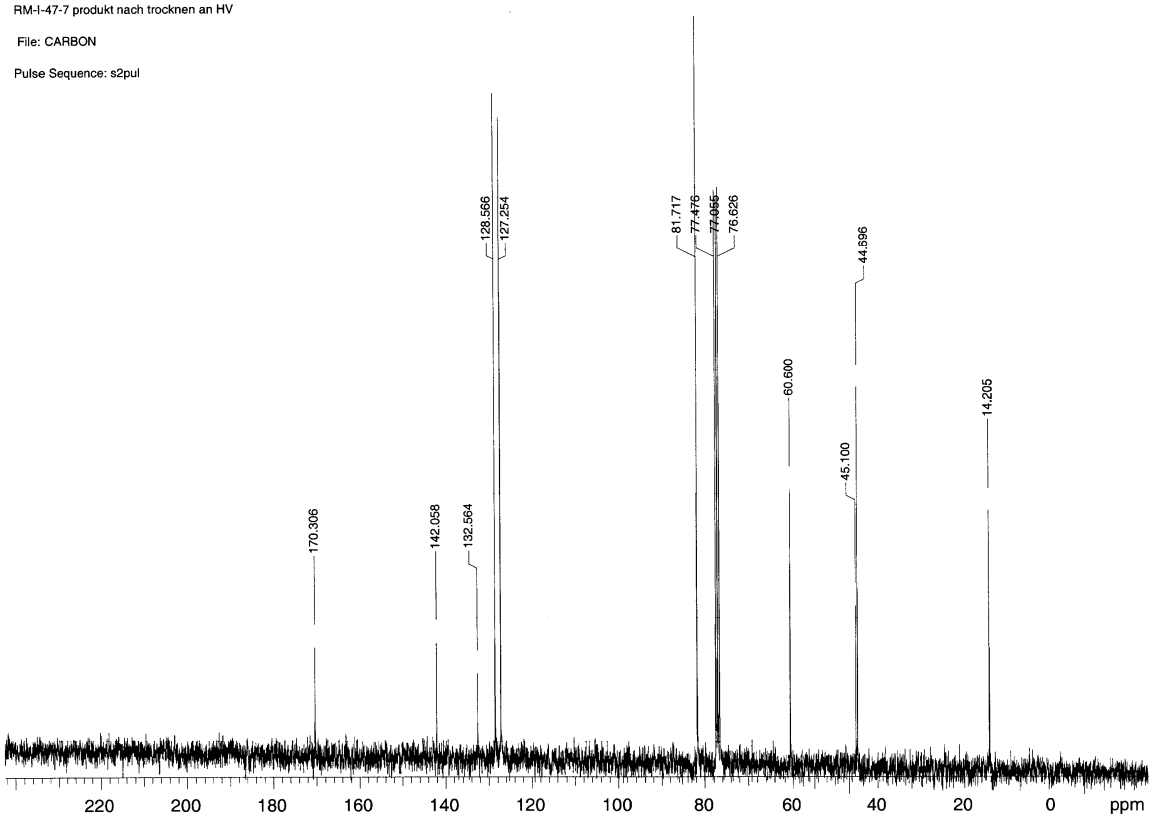
Appendix


GW-VI-36-1 fr 3-5
File: PROTON
Pulse Sequence: s2pul
Me2N
CO2Et
O
4.559
4.542
4.146
4.122
2.666
2.168
1.263
1.239
1.216
7
6
5
4
3
2
1
ppm
3.99
1.92
2.00
6.05
2.94

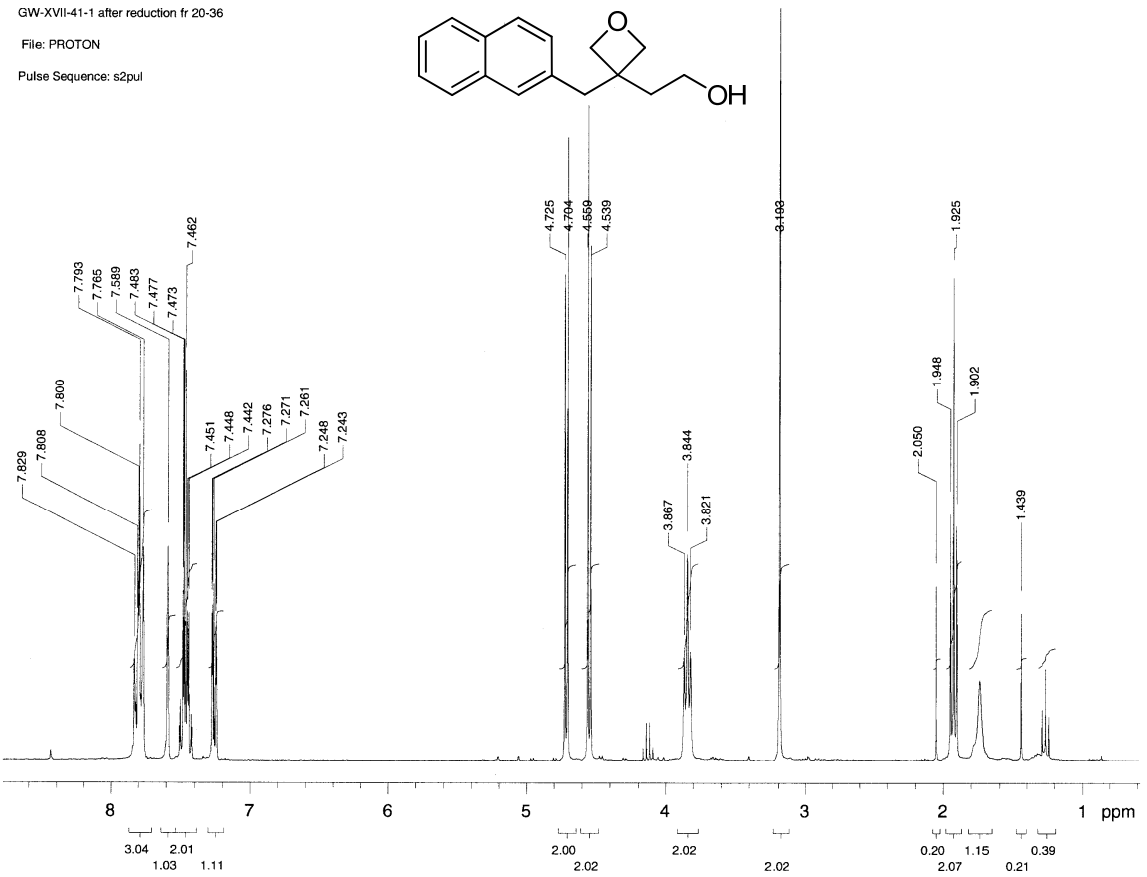

GW-VI-36-1 fr 3-5
File: CARBON
Pulse Sequence: s2pul
78.949
77.671
77.250
76.821
62.949
60.854
38.164
34.386
14.269
171.892
167.977
220
200
180
160
140
120
100
80
60
40
20
0
ppm

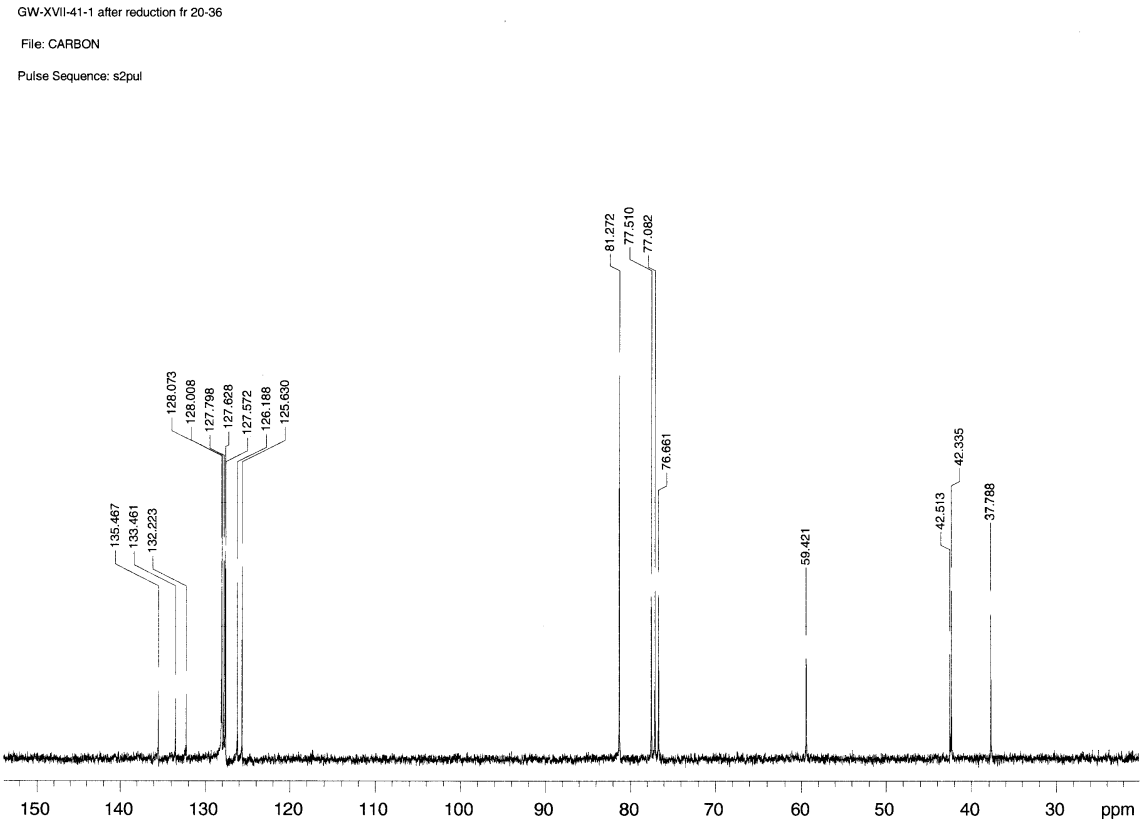
Appendix


RM-I-47-6 produkt nach trocknen an HV
File: PROTON
Pulse Sequence: s2pul
Cl
CO2Et
O
7.325
7.304
7.296
7.261
7.129
7.122
7.107
7.100
4.972
4.952
4.855
4.834
4.045
4.021
3.997
3.973
3.106
1.156
1.132
1.108
7
6
5
4
3
2
ppm
1.98
2.01
0.17
2.11
2.15
2.10
2.16
0.11
2.98

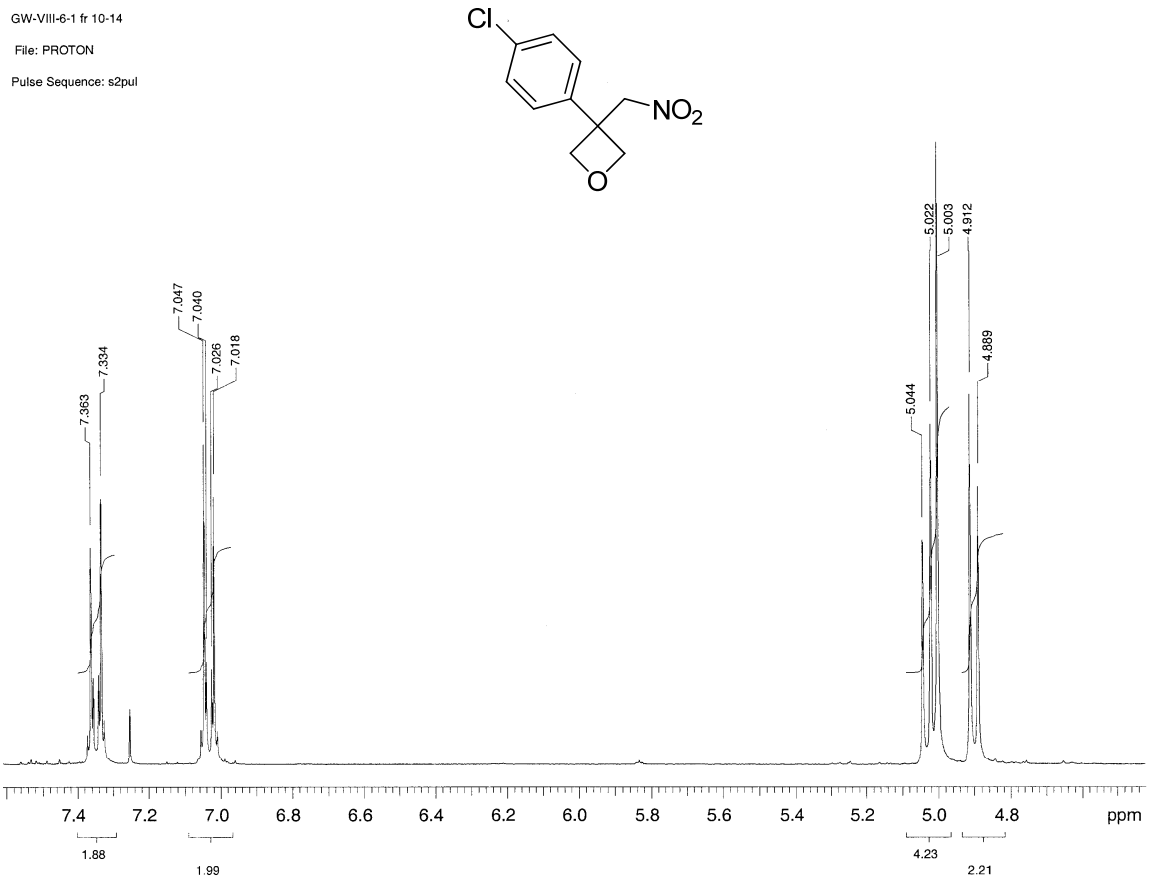

RM-I-47-7 produkt nach trocknen an HV
File: CARBON
Pulse Sequence: s2pul
170.306
142.058
132.564
128.566
127.254
81.717
77.476
77.055
76.626
60.600
45.100
44.596
14.205
220
200
180
160
140
120
100
80
60
40
20
0
ppm

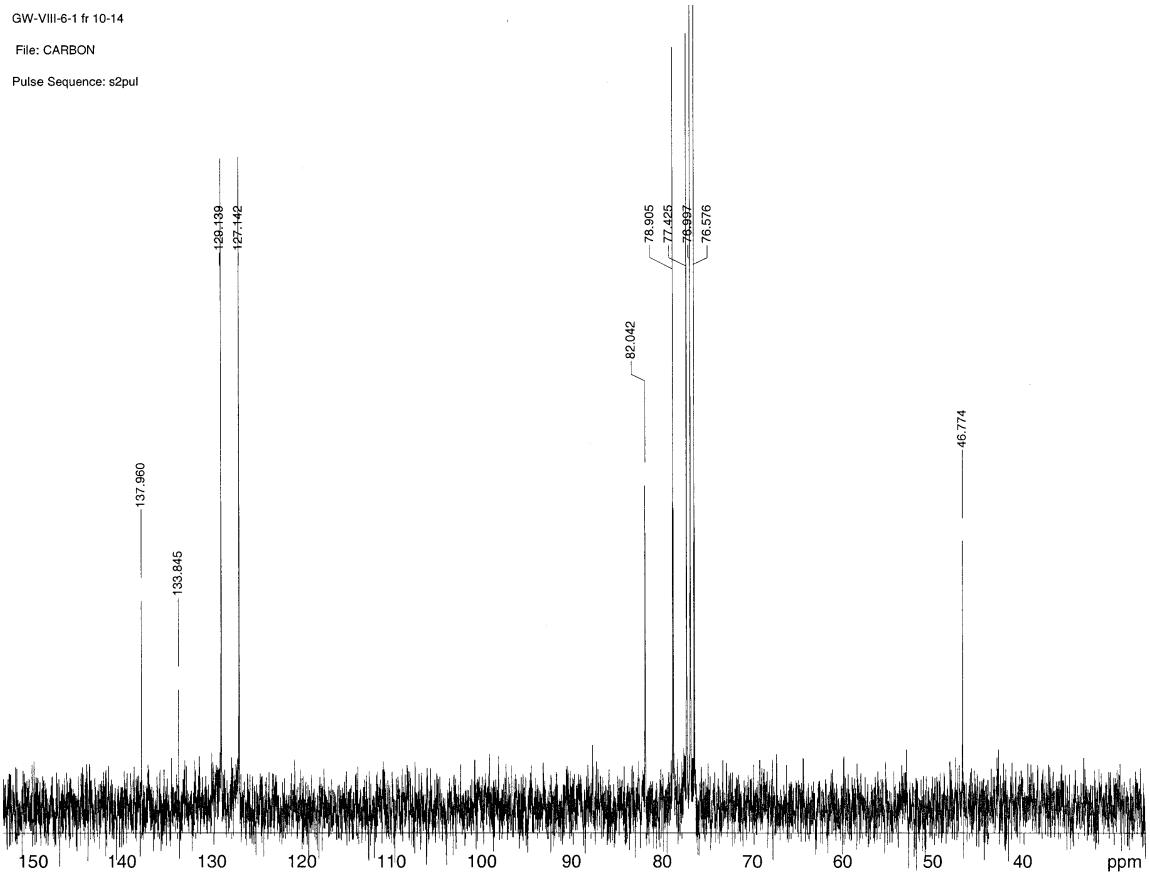
Appendix


GW-XVII-41-1 after reduction fr 20-36
File: PROTON
Pulse Sequence: s2pul
O
OH
7.829
7.808
7.800
7.793
7.765
7.589
7.483
7.477
7.473
7.462
7.451
7.448
7.442
7.276
7.271
7.261
7.248
7.243
4.725
4.704
4.559
4.539
3.867
3.844
3.821
3.488
2.050
1.948
1.925
1.902
1.439
8
7
6
5
4
3
2
1 ppm
3.04
2.01
1.03
1.11
2.00
2.02
2.02
2.02
0.20
1.15
2.07
0.39
0.21

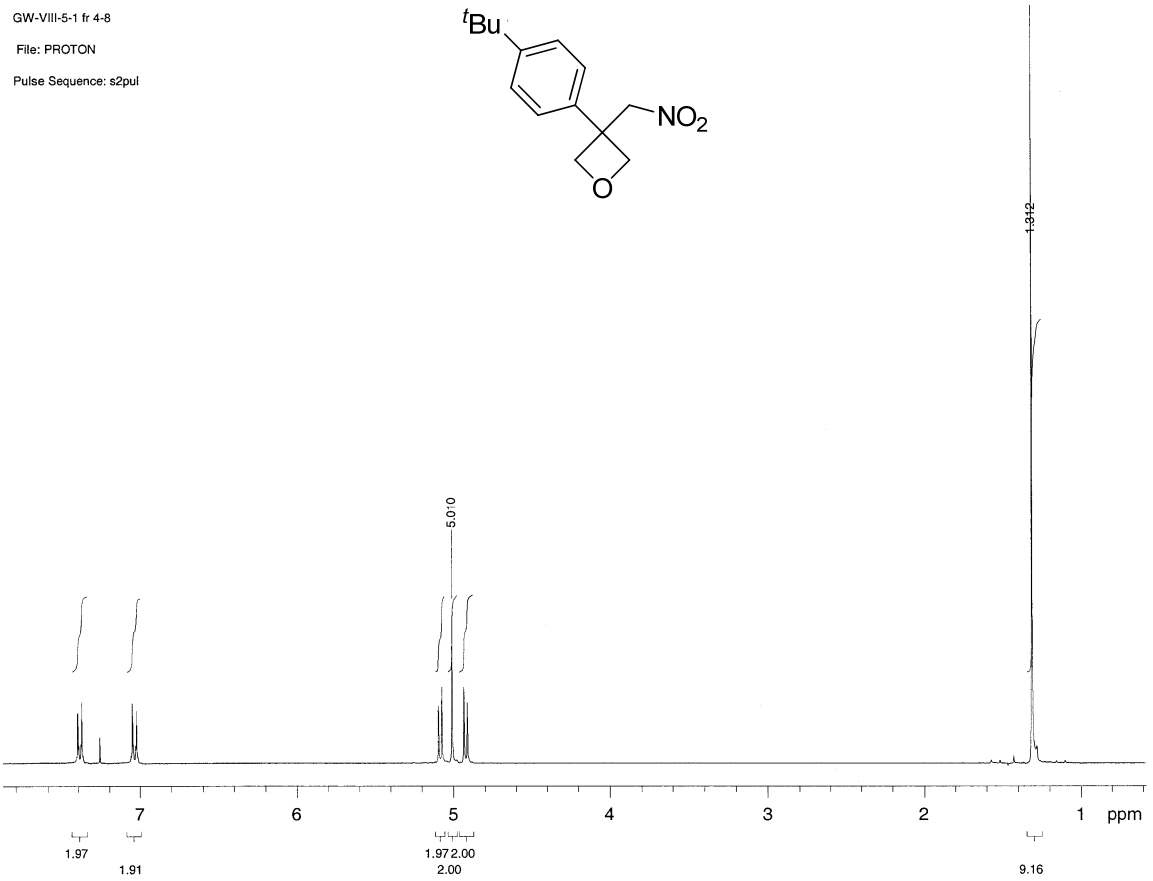

GW-XVII-41-1 after reduction fr 20-36
File: CARBON
Pulse Sequence: s2pul
135.467
133.461
132.223
128.073
128.008
127.798
127.628
127.572
126.188
125.630
81.272
77.510
77.082
76.661
59.421
42.513
42.335
37.788
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

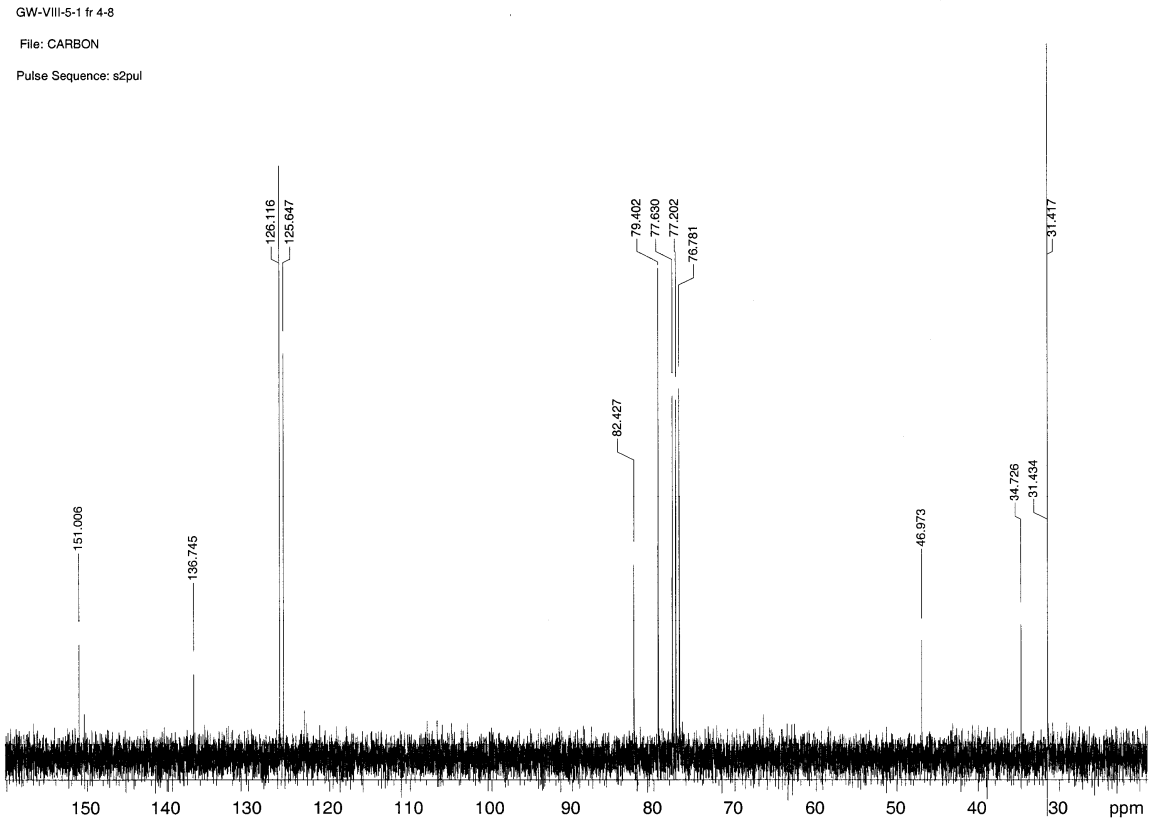
Appendix


GW-VIII-6-1 fr 10-14
File: PROTON
Pulse Sequence: s2pul
Cl
NO2
O
7.363
7.334
7.047
7.040
7.026
7.018
5.044
5.022
5.003
4.912
4.889
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
ppm
1.88
1.99
4.23
2.21

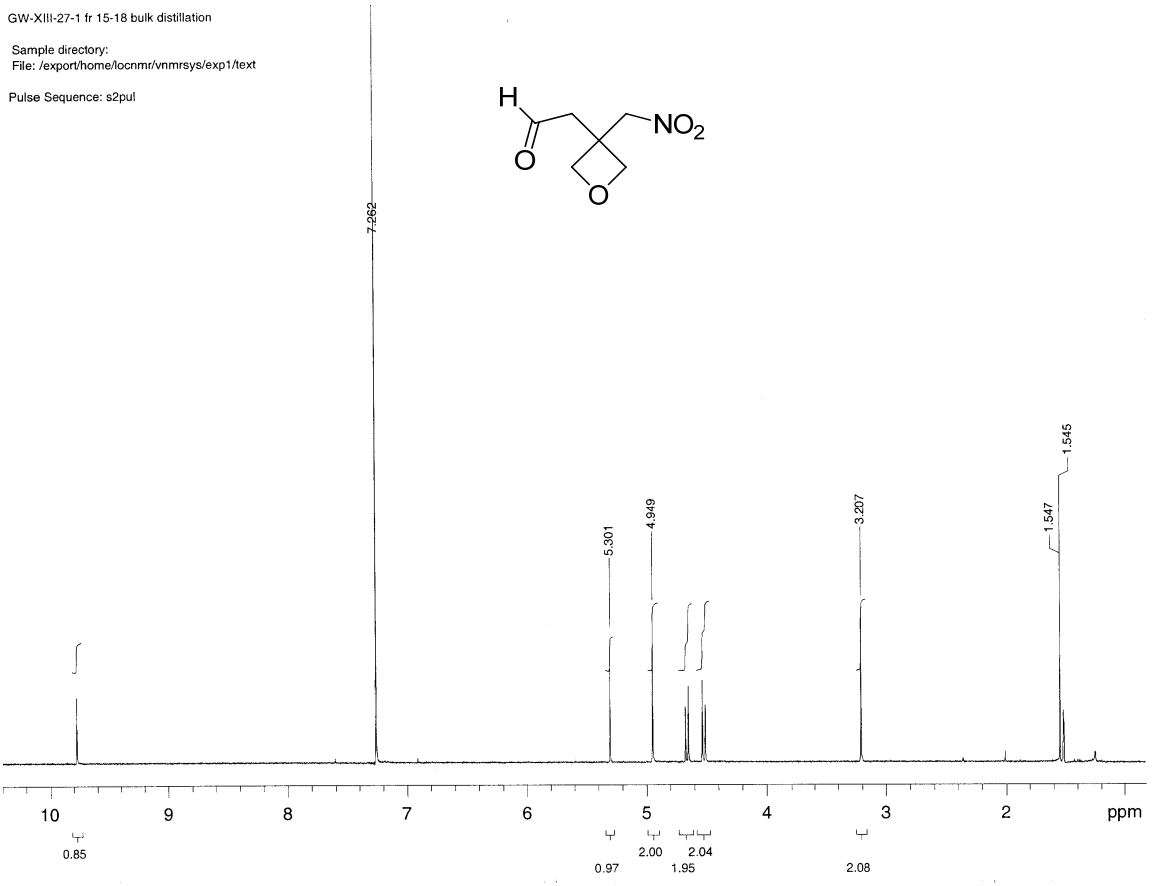

GW-VIII-6-1 fr 10-14
File: CARBON
Pulse Sequence: s2pul
137.960
133.845
128.139
127.142
82.042
78.905
77.425
76.997
76.576
46.774
150
140
130
120
110
100
90
80
70
60
50
40
ppm

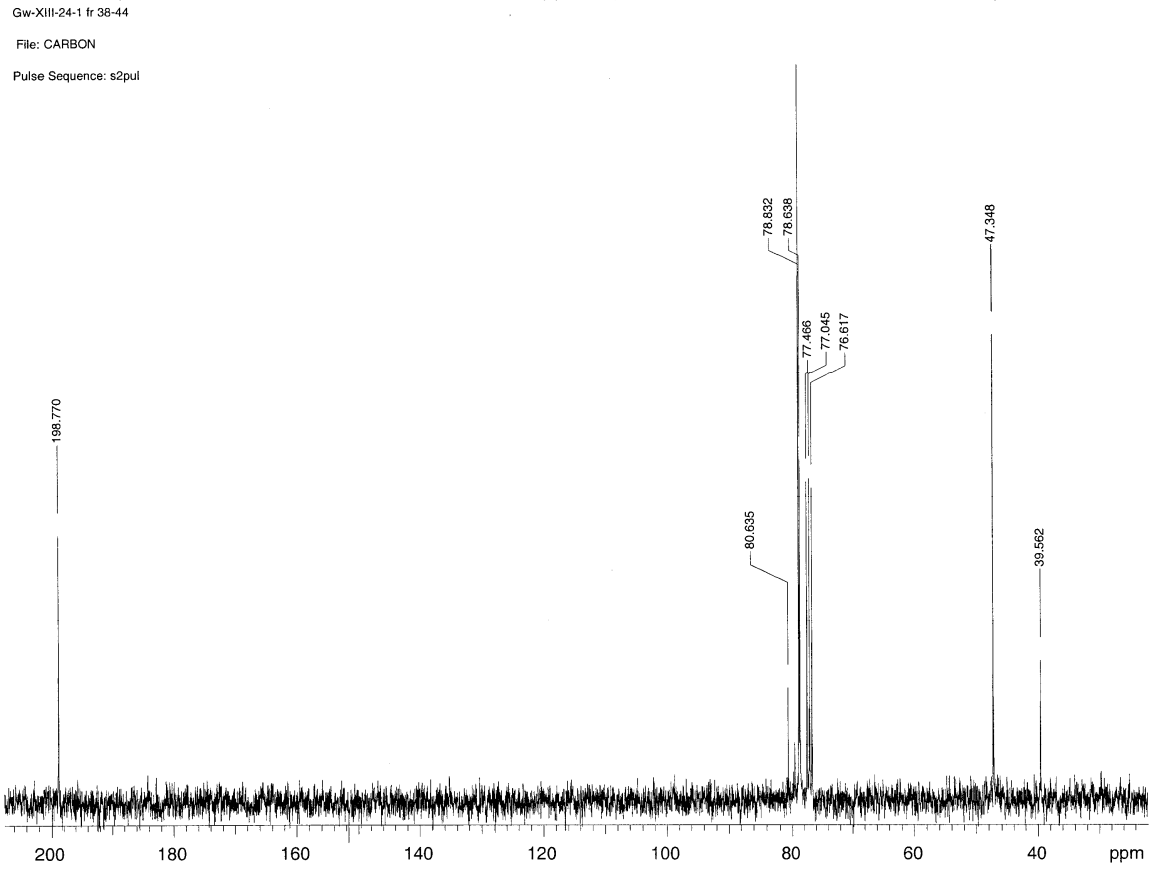
Appendix


GW-VIII-5-1 fr 4-8
File: PROTON
Pulse Sequence: s2pul
tBu
NO2
O
1.912
5.010
7
6
5
4
3
2
1
ppm
1.97
1.91
1.97
2.00
2.00
9.16

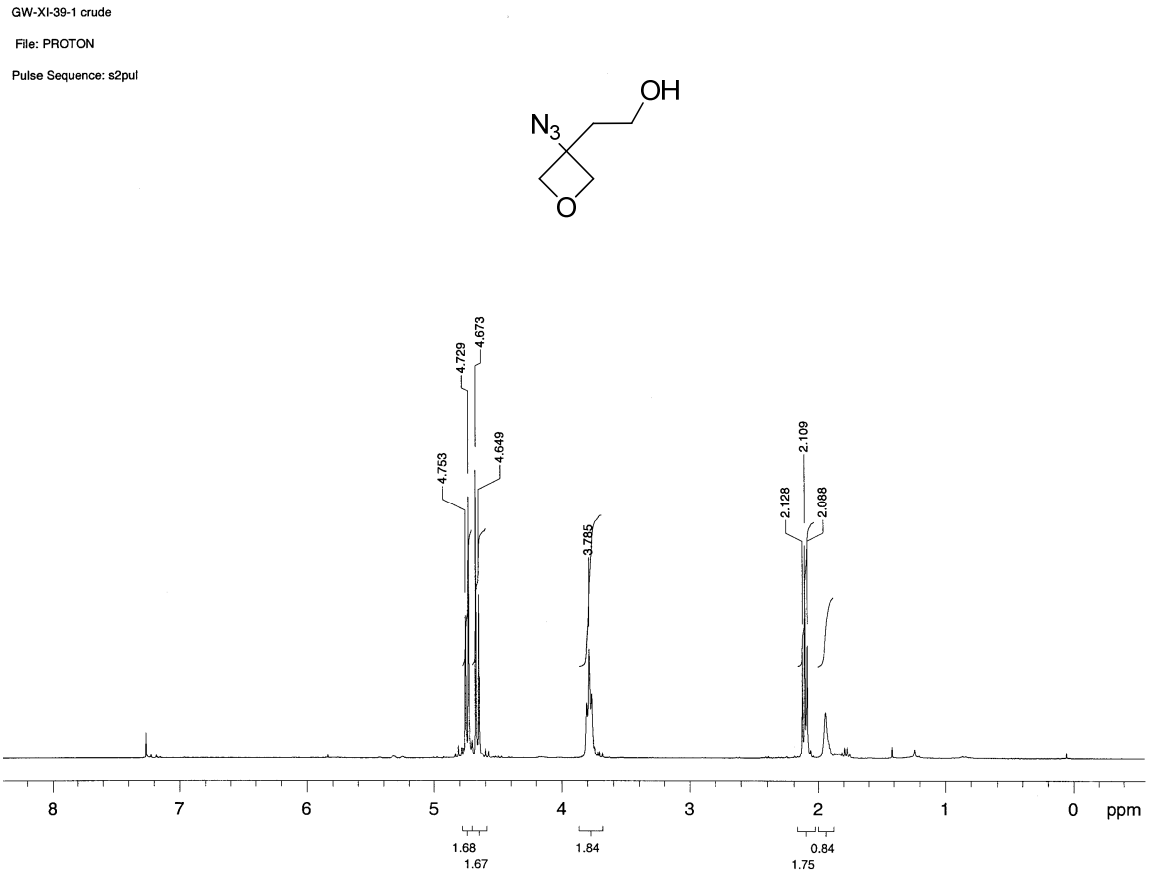

GW-VIII-5-1 fr 4-8
File: CARBON
Pulse Sequence: s2pul
126.116
125.647
79.402
77.630
77.202
76.781
31.417
82.427
34.726
31.434
151.006
136.745
46.973
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

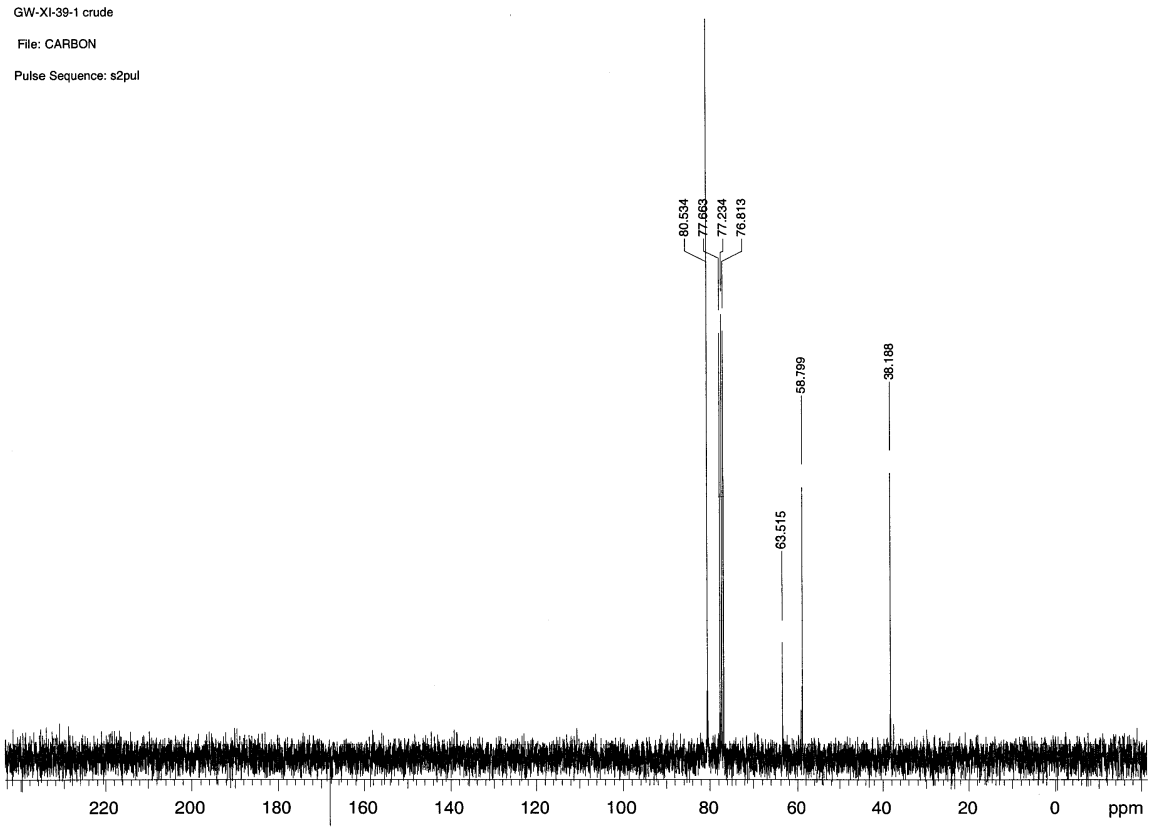
Appendix


GW-XIII-27-1 fr 15-18 bulk distillation
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
H
O
NO2
O
7.262
5.301
4.949
3.207
1.547
1.545
10
9
8
7
6
5
4
3
2
ppm
0.85
0.97
2.00
2.04
1.95
2.08

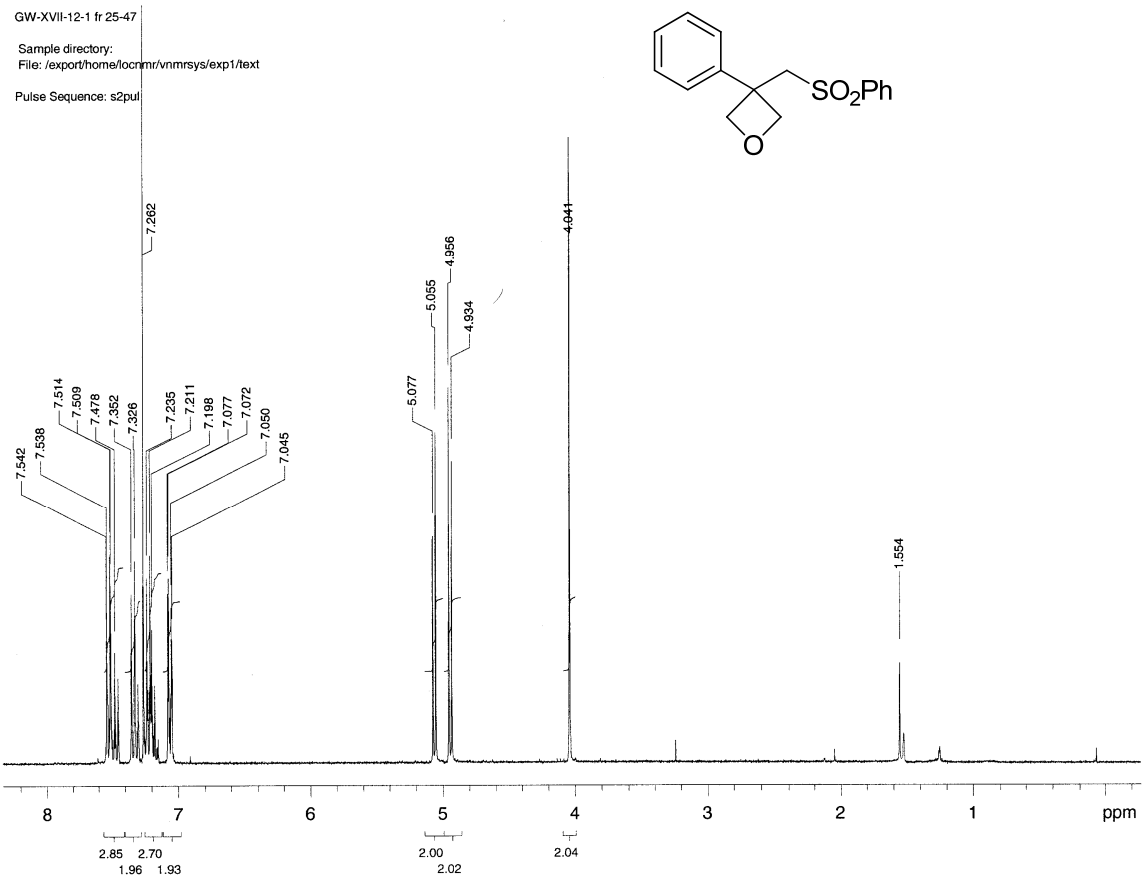

Gw-XIII-24-1 fr 38-44
File: CARBON
Pulse Sequence: s2pul
198.770
80.635
78.832
78.638
77.466
77.045
76.617
47.348
39.562
200
180
160
140
120
100
80
60
40
ppm

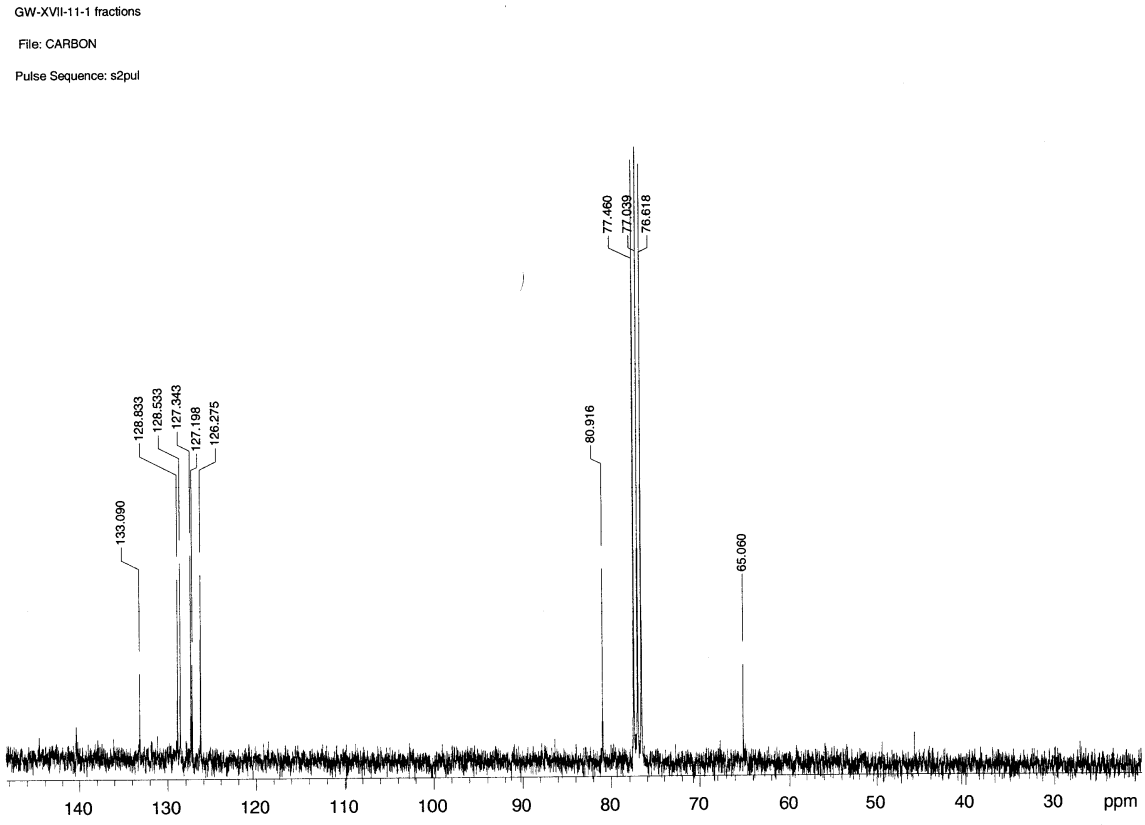
Appendix


GW-XI-39-1 crude
File: PROTON
Pulse Sequence: s2pul
OH
N3
O
4.729
4.673
4.753
4.649
3.785
2.109
2.128
2.088
8
7
6
5
4
3
2
1
0
ppm
1.68
1.67
1.84
0.84
1.75

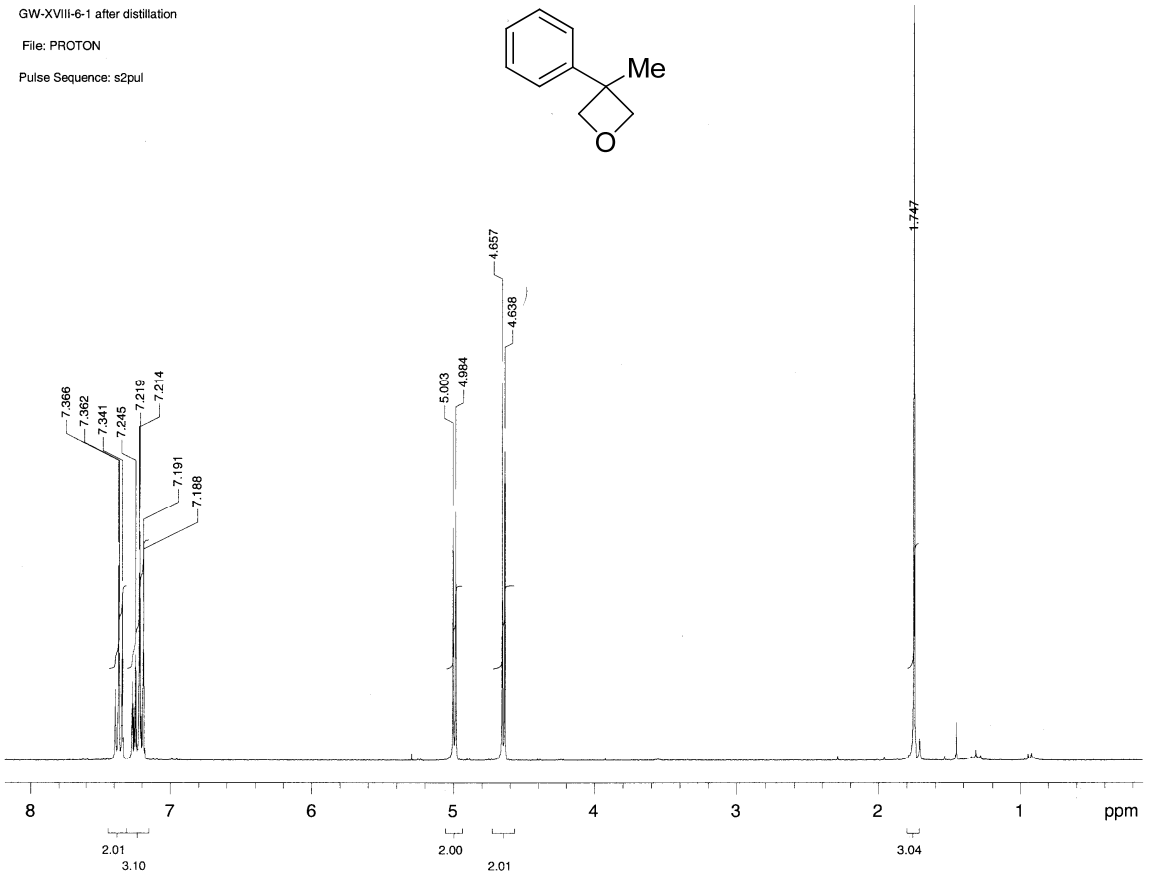

GW-XI-39-1 crude
File: CARBON
Pulse Sequence: s2pul
80.534
77.663
77.234
76.813
58.799
38.188
63.515
220
200
180
160
140
120
100
80
60
40
20
0
ppm

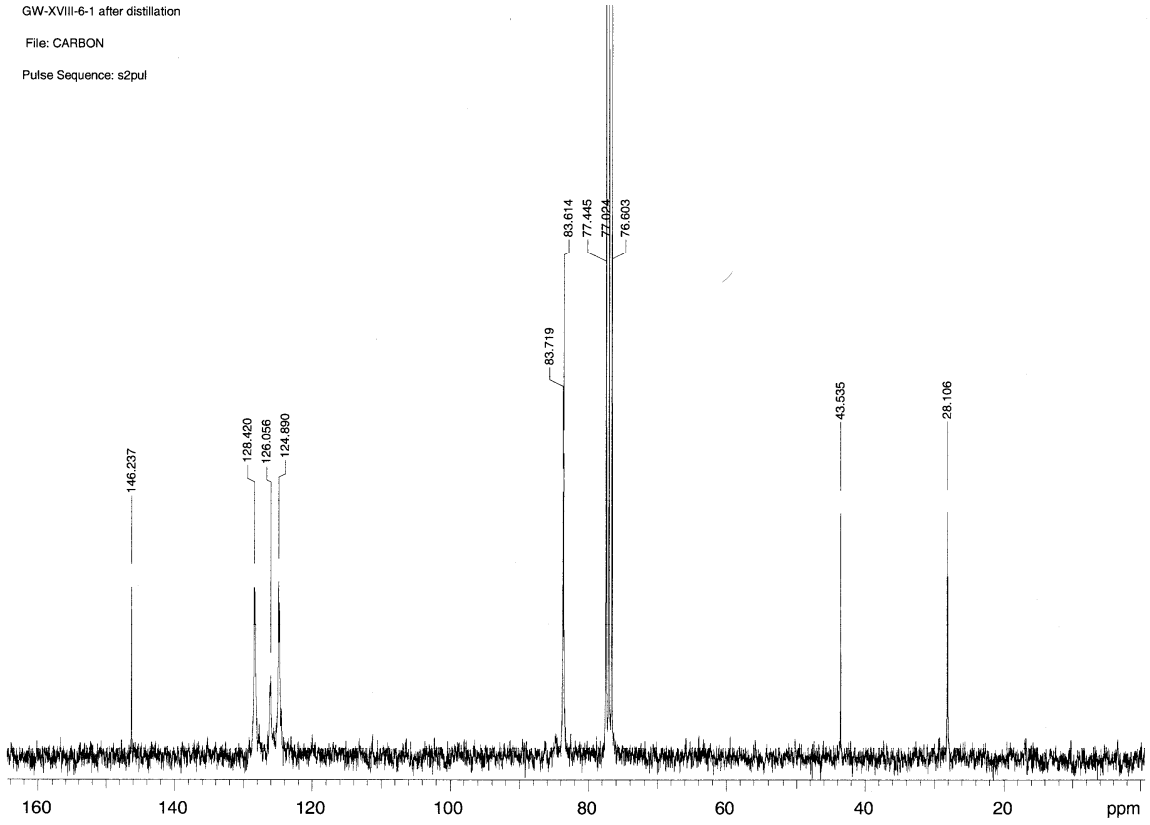
Appendix


GW-XVII-12-1 fr 25-47
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
SO2Ph
O
7.262
4.956
5.055
4.934
4.041
5.077
7.514
7.509
7.478
7.352
7.326
7.235
7.211
7.198
7.077
7.072
7.050
7.045
7.542
7.538
1.554
8
7
6
5
4
3
2
1
ppm
2.85
2.70
1.96
1.93
2.00
2.02
2.04

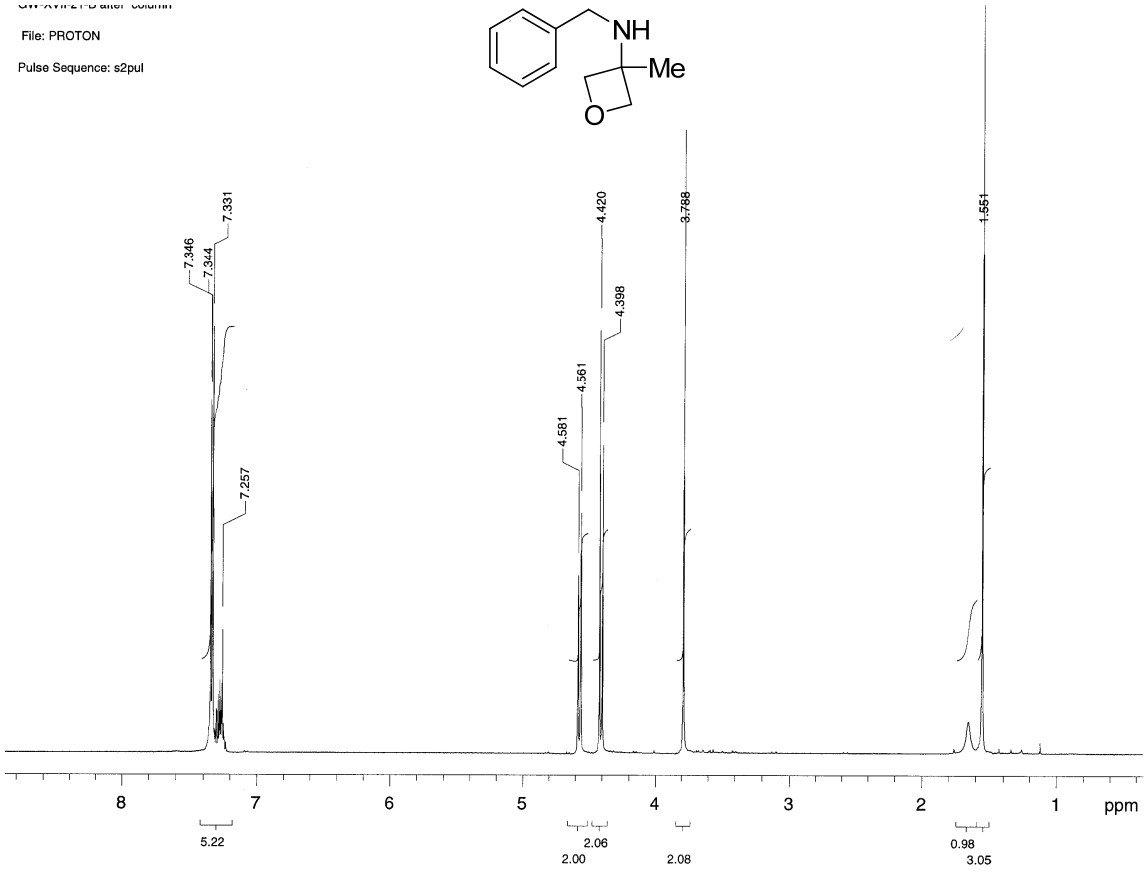

GW-XVII-11-1 fractions
File: CARBON
Pulse Sequence: s2pul
77.460
77.039
76.618
128.833
128.533
127.343
127.198
126.275
80.916
133.090
65.060
140
130
120
110
100
90
80
70
60
50
40
30
ppm

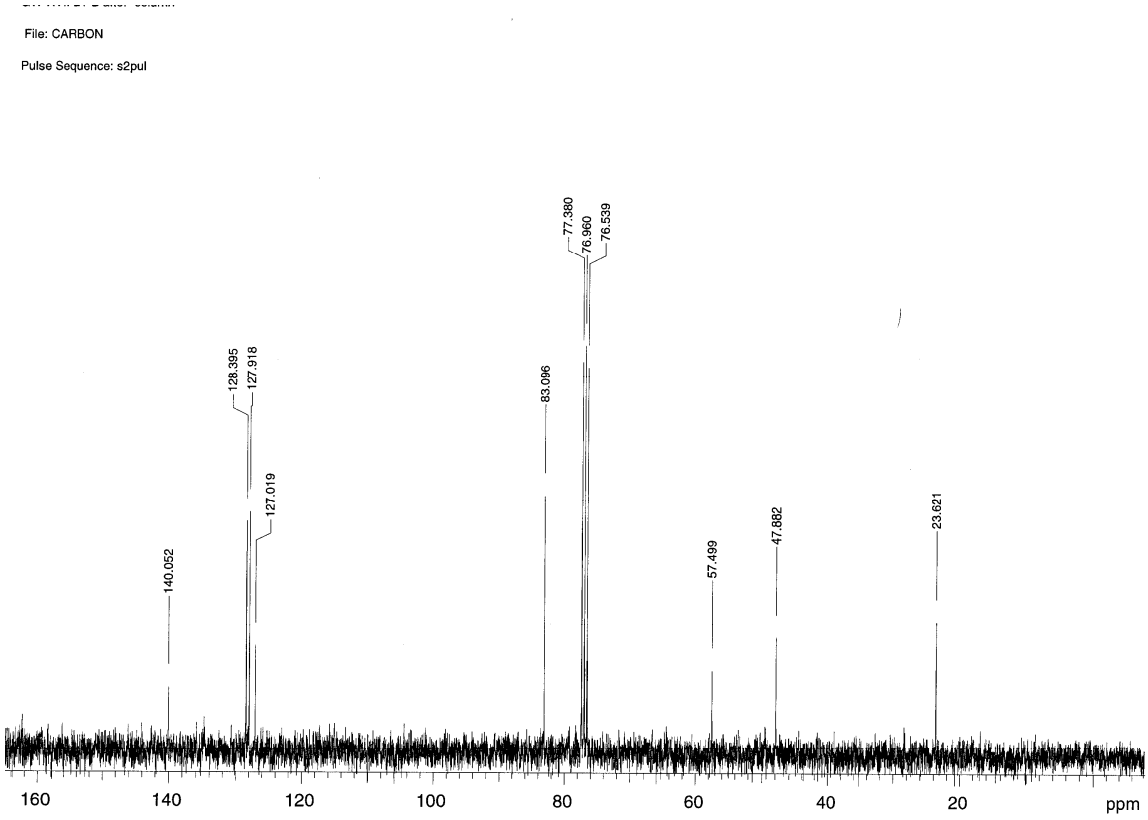
Appendix


GW-XVIII-6-1 after distillation
File: PROTON
Pulse Sequence: s2pul
Me
O
7.366
7.362
7.341
7.245
7.219
7.214
7.191
7.188
5.003
4.984
4.657
4.638
1.747
8
7
6
5
4
3
2
1
ppm
2.01
3.10
2.00
2.01
3.04

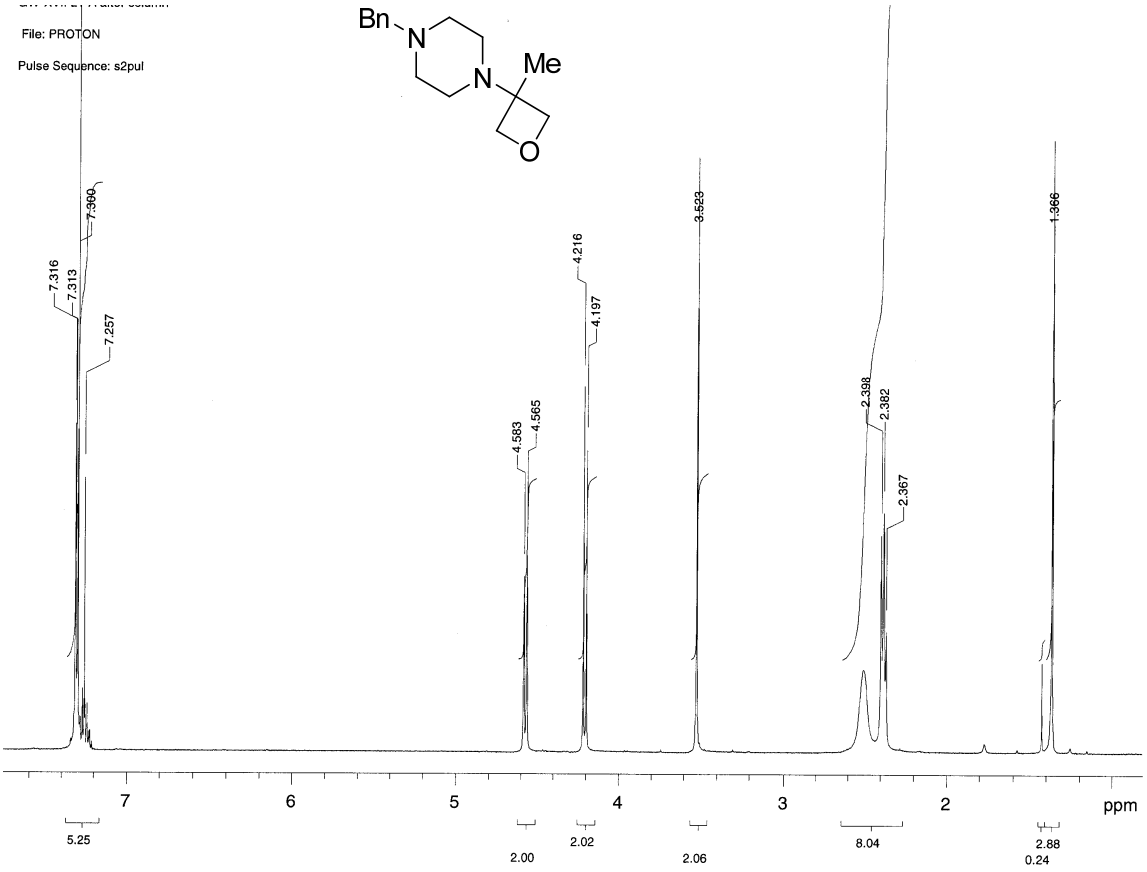

GW-XVIII-6-1 after distillation
File: CARBON
Pulse Sequence: s2pul
146.237
128.420
126.056
124.890
83.719
83.614
77.445
77.024
76.603
43.535
28.106
160
140
120
100
80
60
40
20
ppm

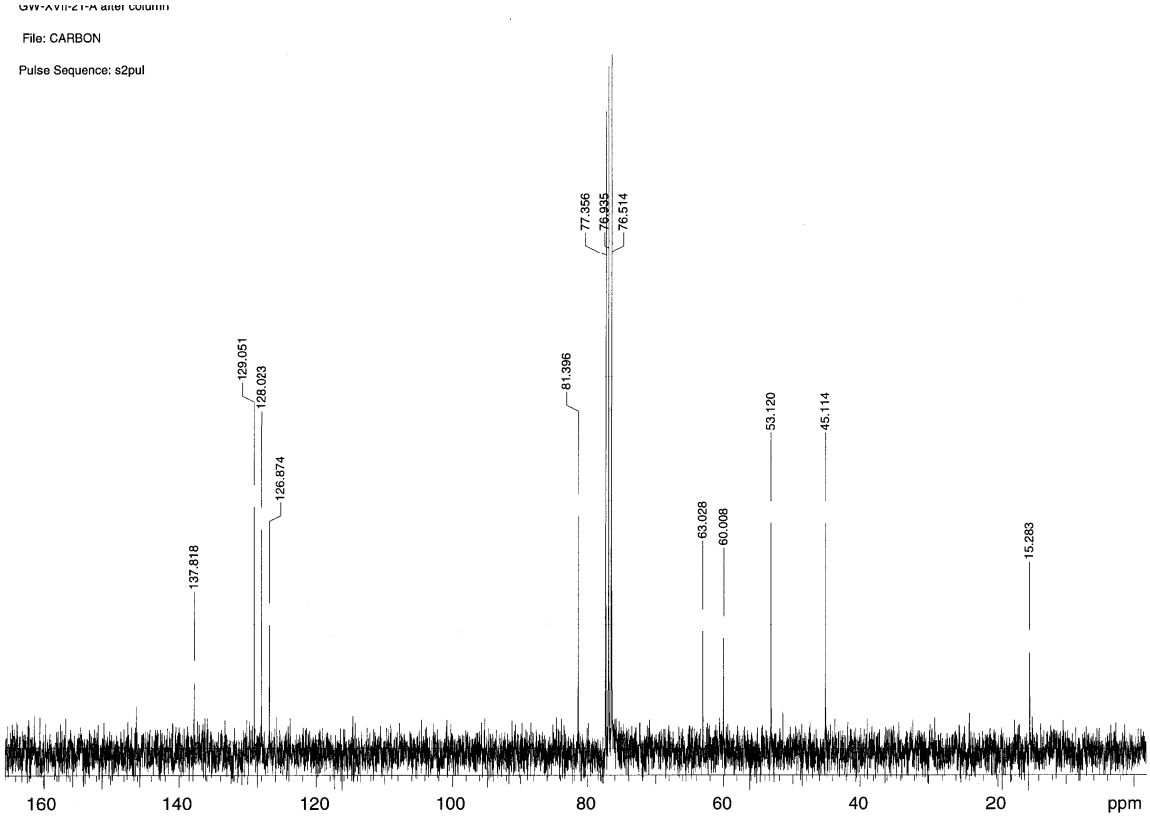
Appendix


File: PROTON
Pulse Sequence: s2pul
NH
Me
O
7.346
7.344
7.331
7.257
4.581
4.561
4.420
4.398
3.788
1.551
8
7
6
5
4
3
2
1
ppm
5.22
2.06
2.00
2.08
0.98
3.05

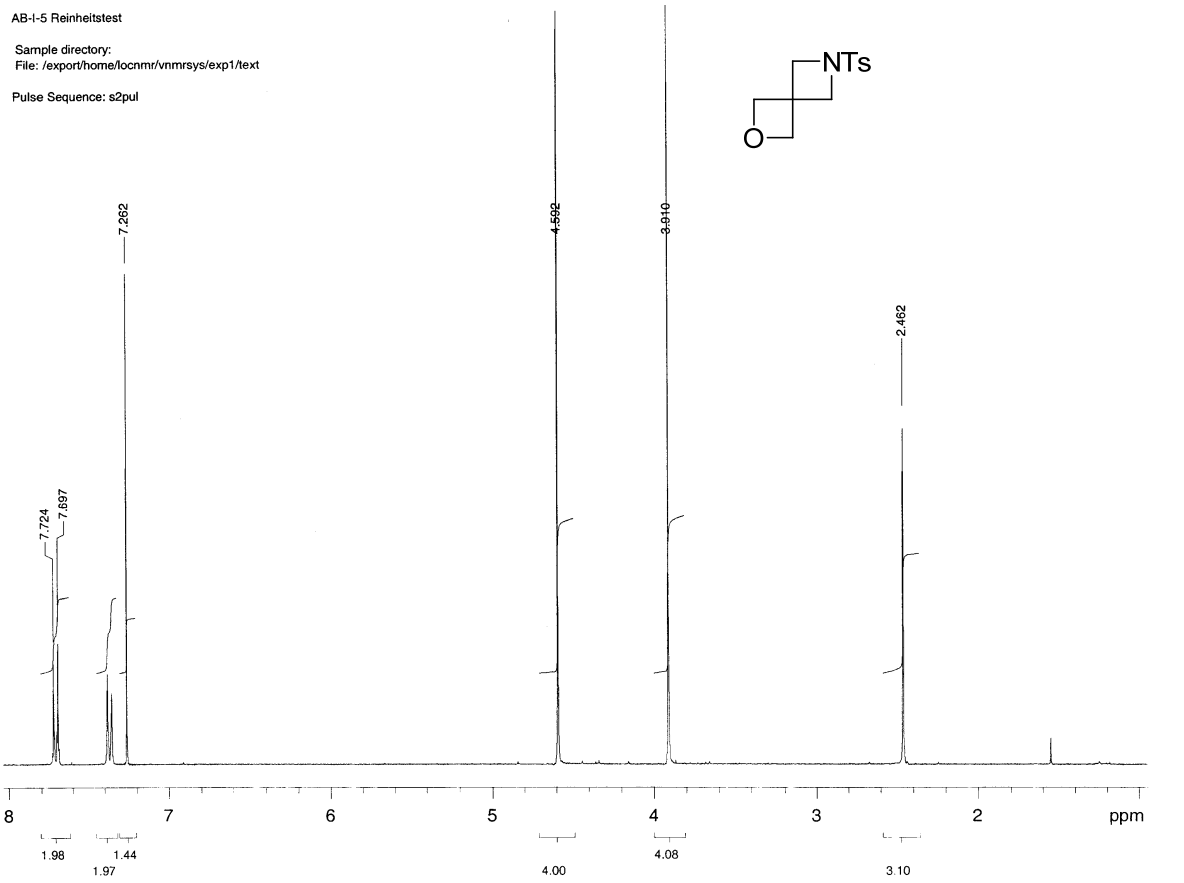

File: CARBON
Pulse Sequence: s2pul
140.052
128.395
127.918
127.019
83.096
77.380
76.960
76.539
57.499
47.882
23.621
160
140
120
100
80
60
40
20
ppm

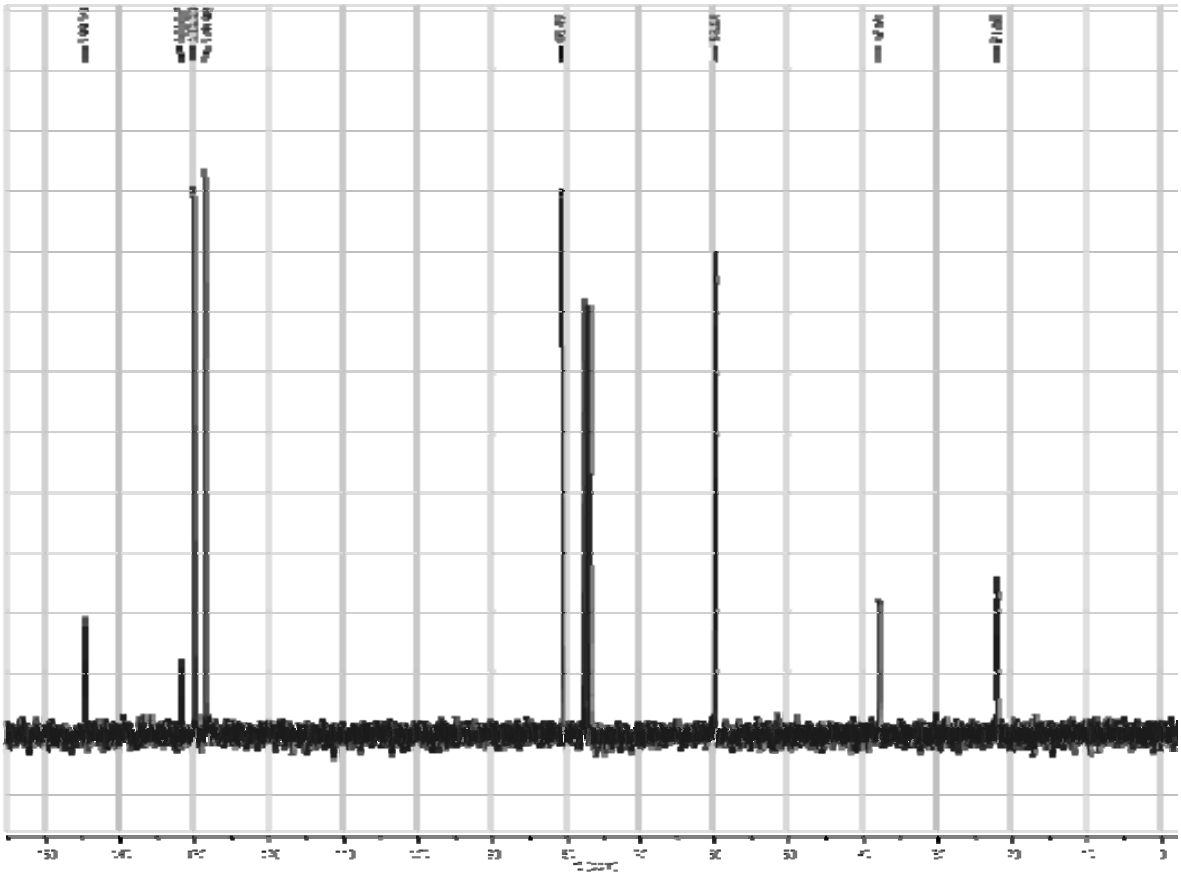
Appendix


File: PROTON
Pulse Sequence: s2pul
Bn
N
N
Me
O
7.316
7.313
7.300
7.257
4.583
4.565
4.216
4.197
3.523
2.398
2.382
2.367
1.366
7
6
5
4
3
2
ppm
5.25
2.00
2.02
2.06
8.04
2.88
0.24

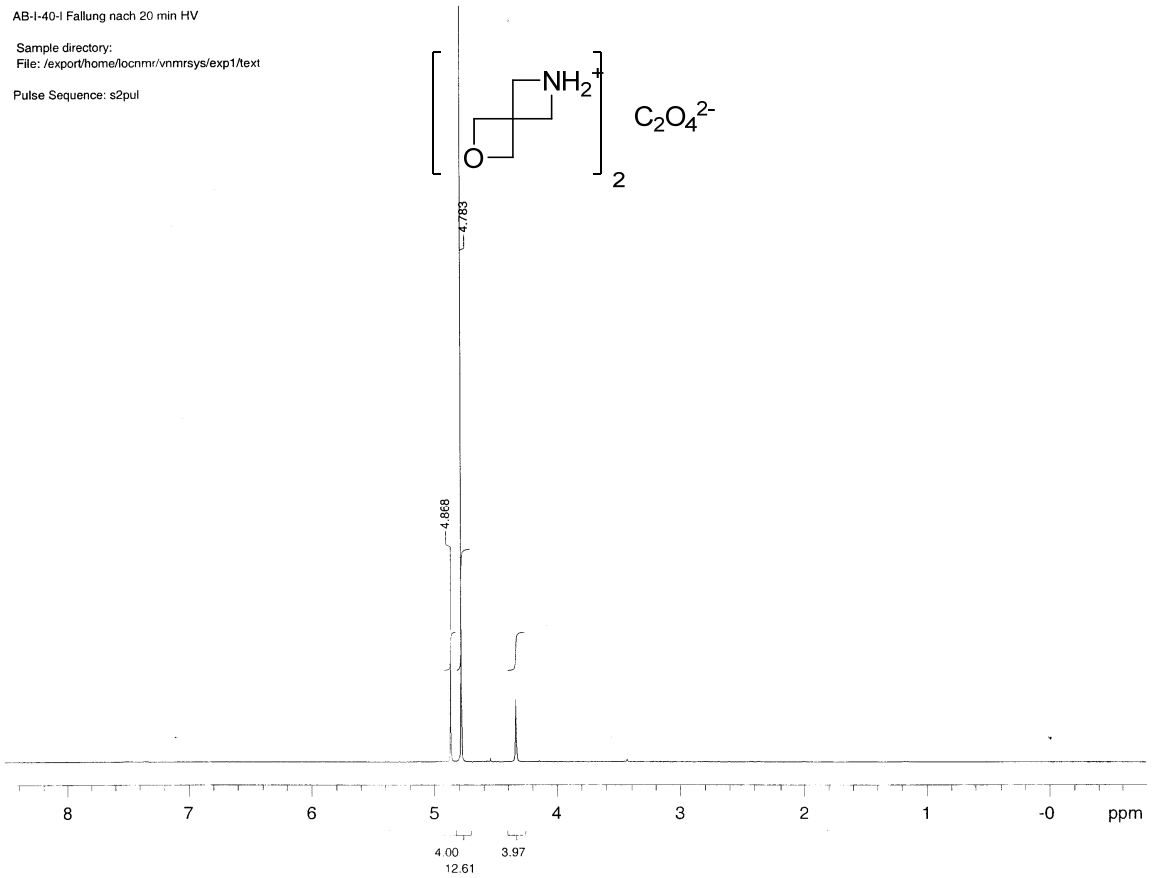

File: CARBON
Pulse Sequence: s2pul
77.356
76.935
76.514
81.396
129.051
128.023
126.874
137.818
63.028
60.008
53.120
45.114
15.283
160
140
120
100
80
60
40
20
ppm

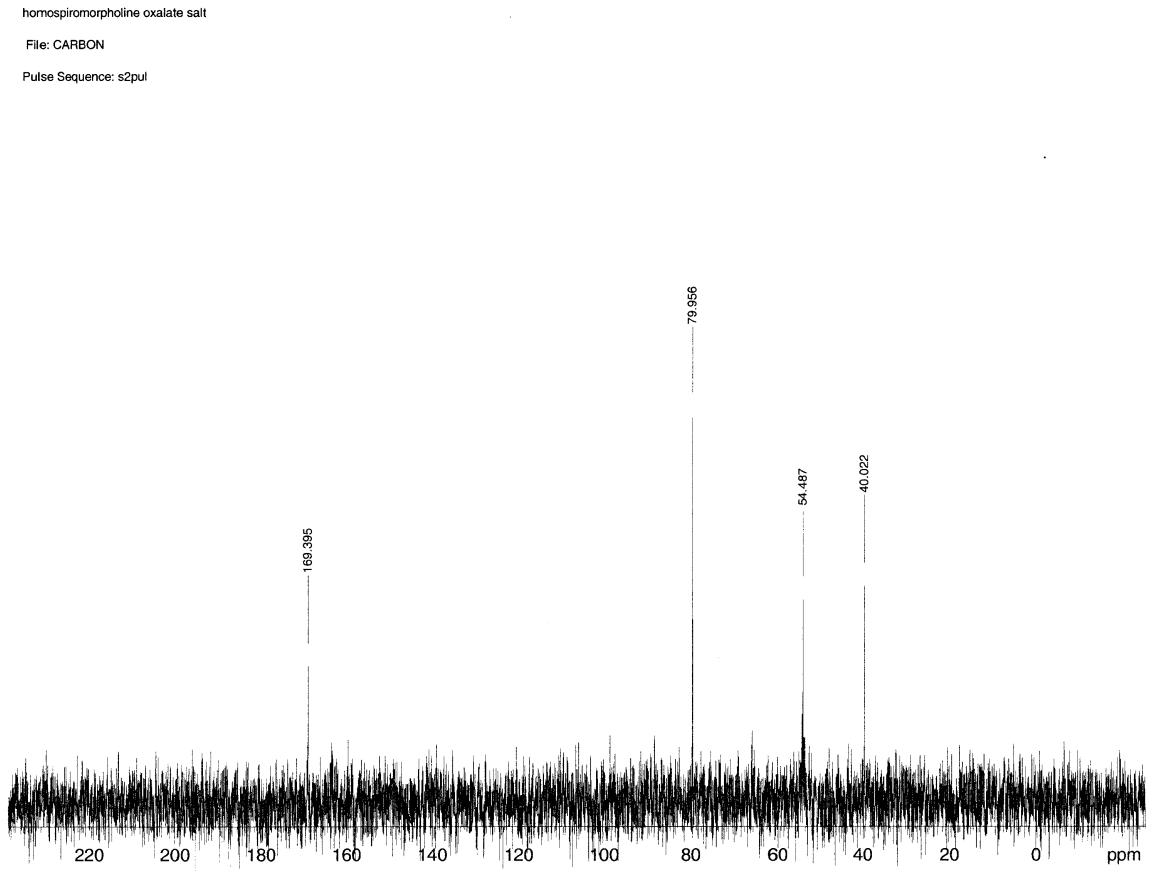
Appendix


AB-I-5 Reinheitstest
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
NTs
O
7.724
7.697
7.262
4.592
3.910
2.462
8
7
6
5
4
3
2
ppm
1.98
1.44
1.97
4.00
4.08
3.10

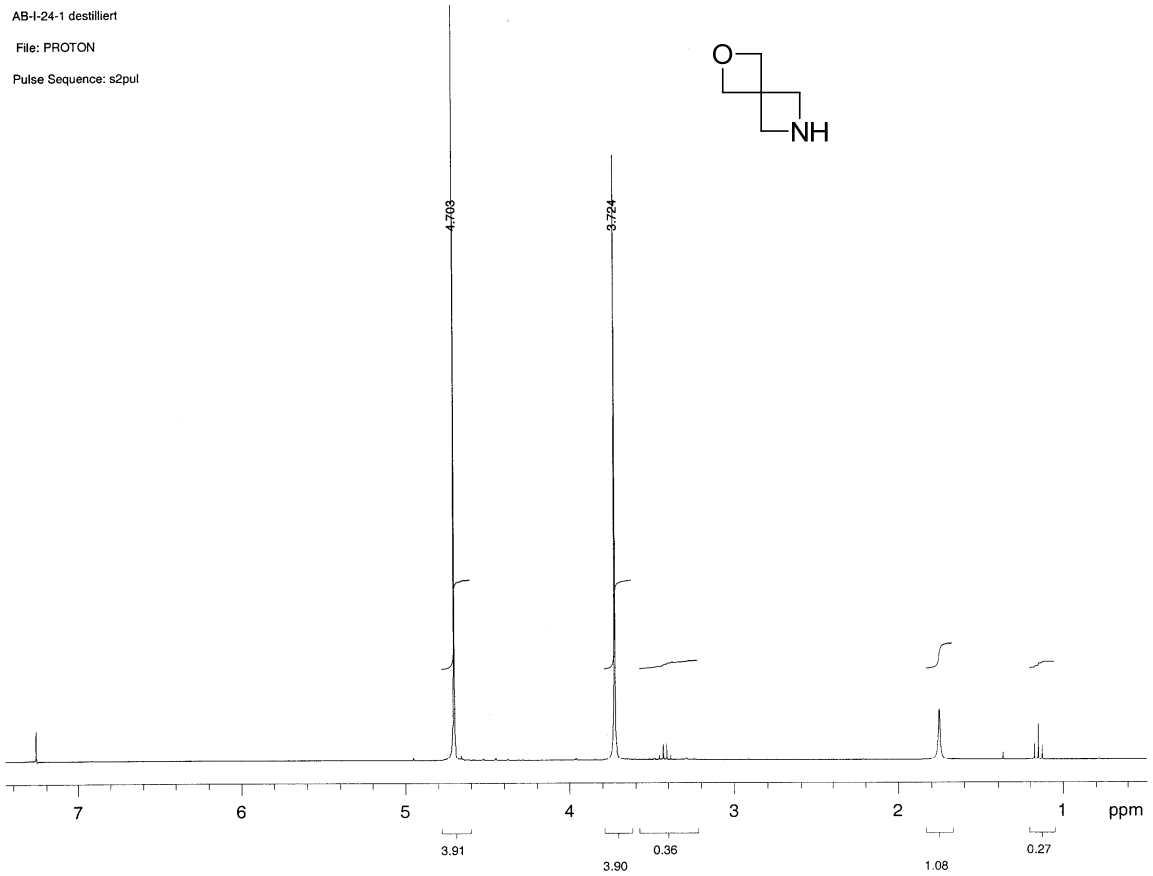


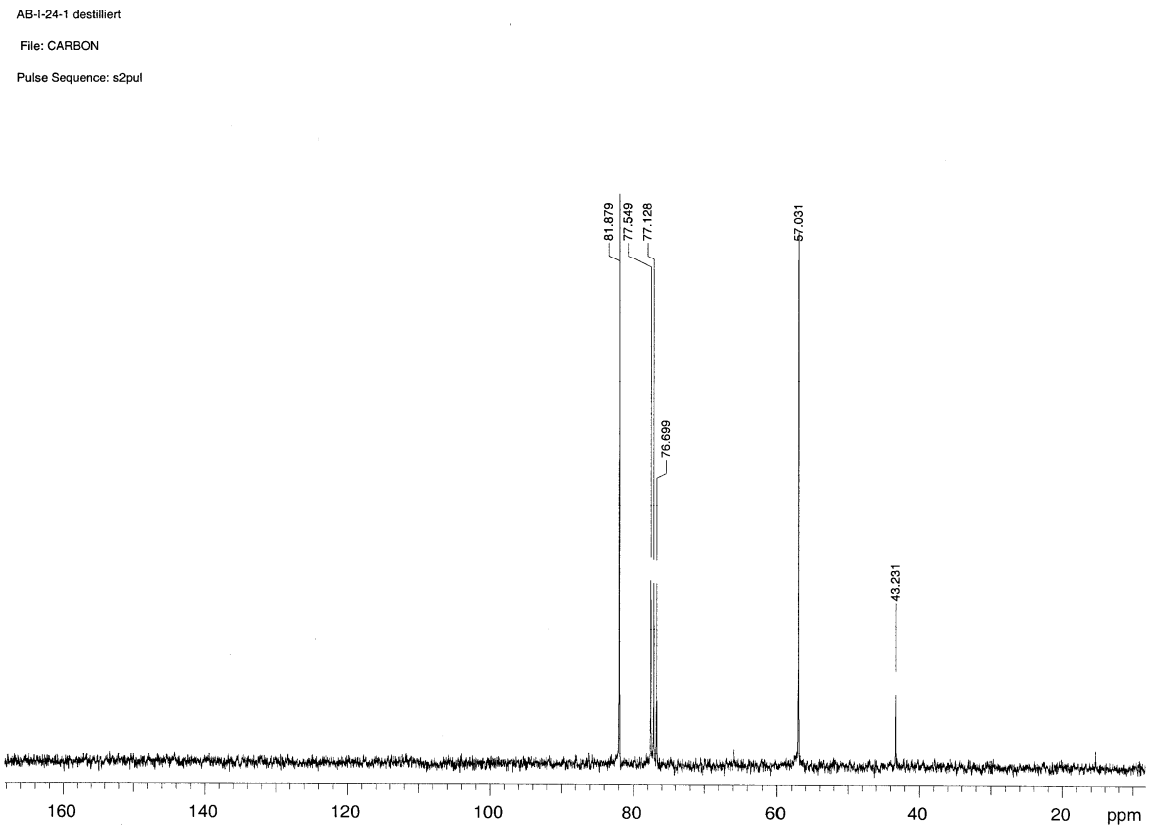
Appendix


AB-I-40-I Fallung nach 20 min HV
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
NH2+
O
2
C2O4 2-
4.783
4.868
8
7
6
5
4
3
2
1
-0
ppm
4.00
12.61
3.97

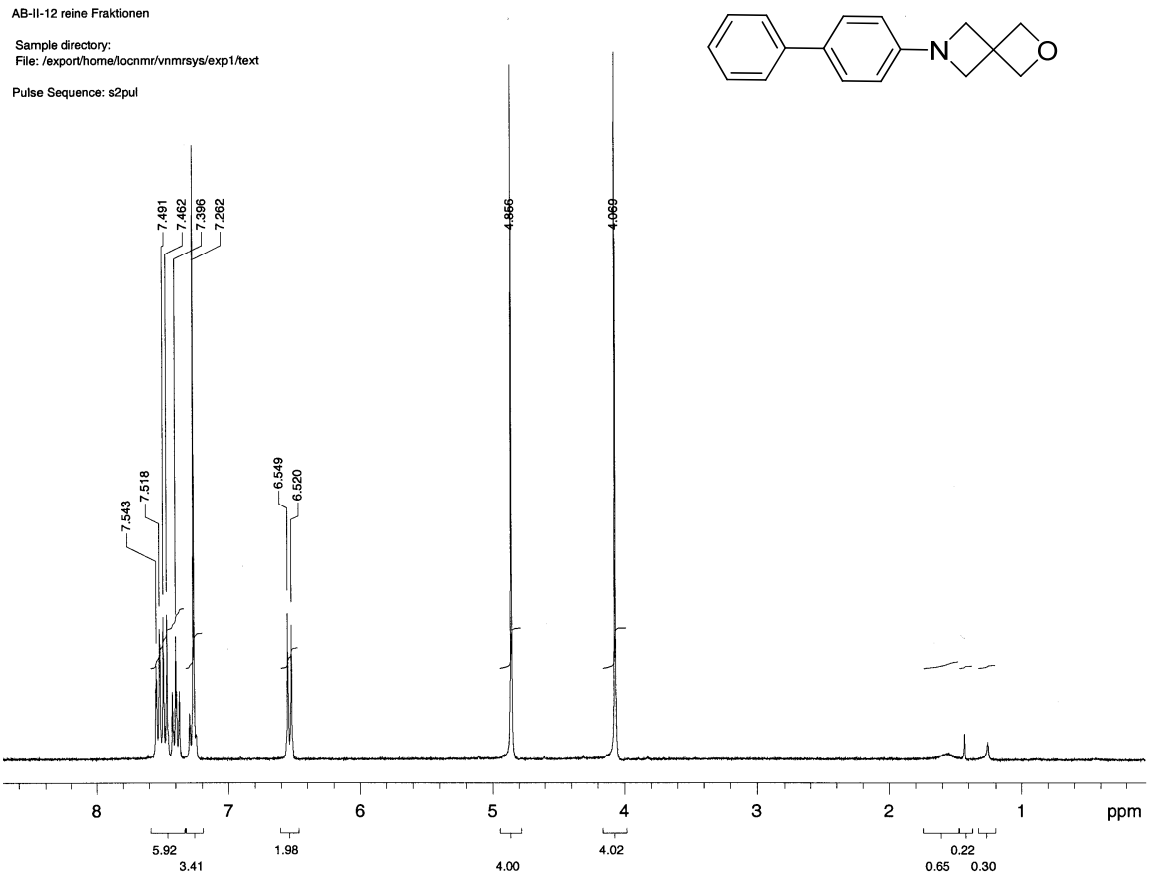

homospiromorpholine oxalate salt
File: CARBON
Pulse Sequence: s2pul
79.956
54.487
40.022
169.395
220
200
180
160
140
120
100
80
60
40
20
0
ppm

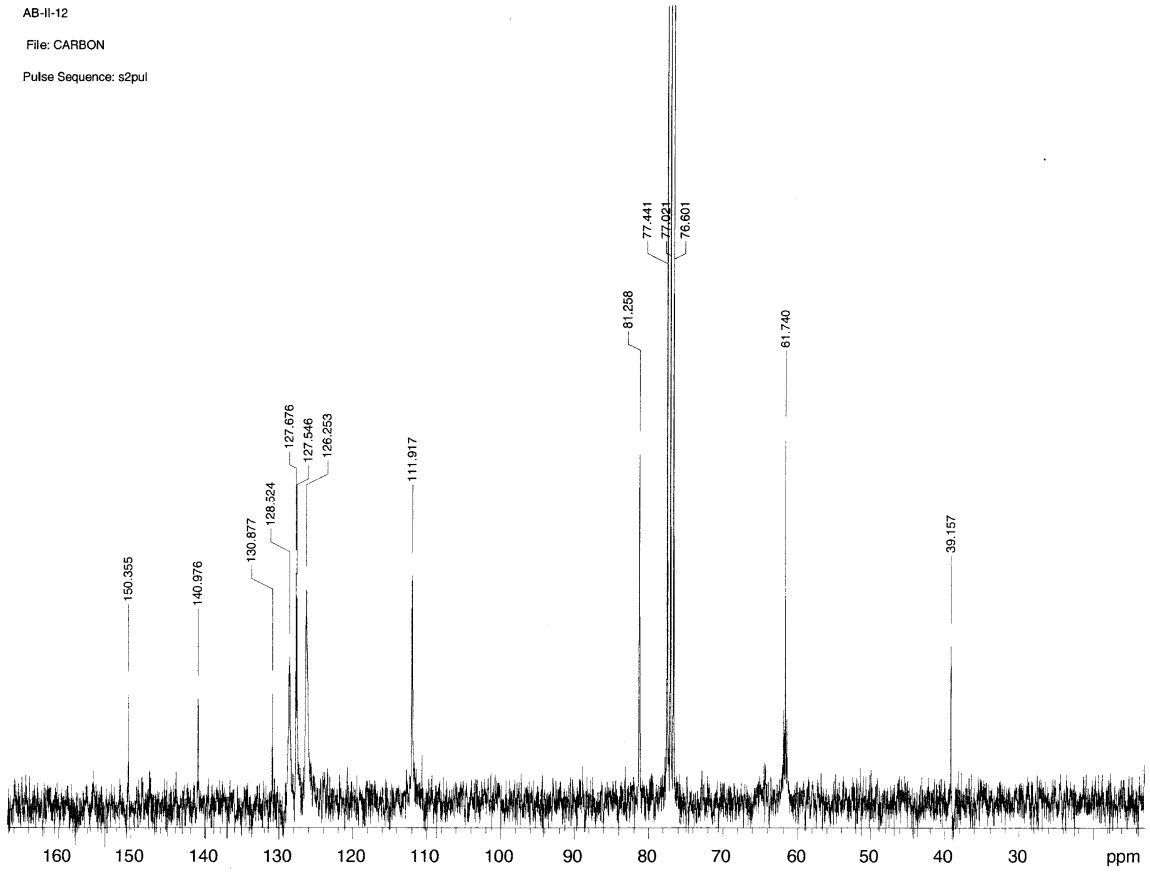
Appendix


AB-I-24-1 destilliert
File: PROTON
Pulse Sequence: s2pul
O
NH
4.703
3.724
7
6
5
4
3
2
1
ppm
3.91
3.90
0.36
1.08
0.27

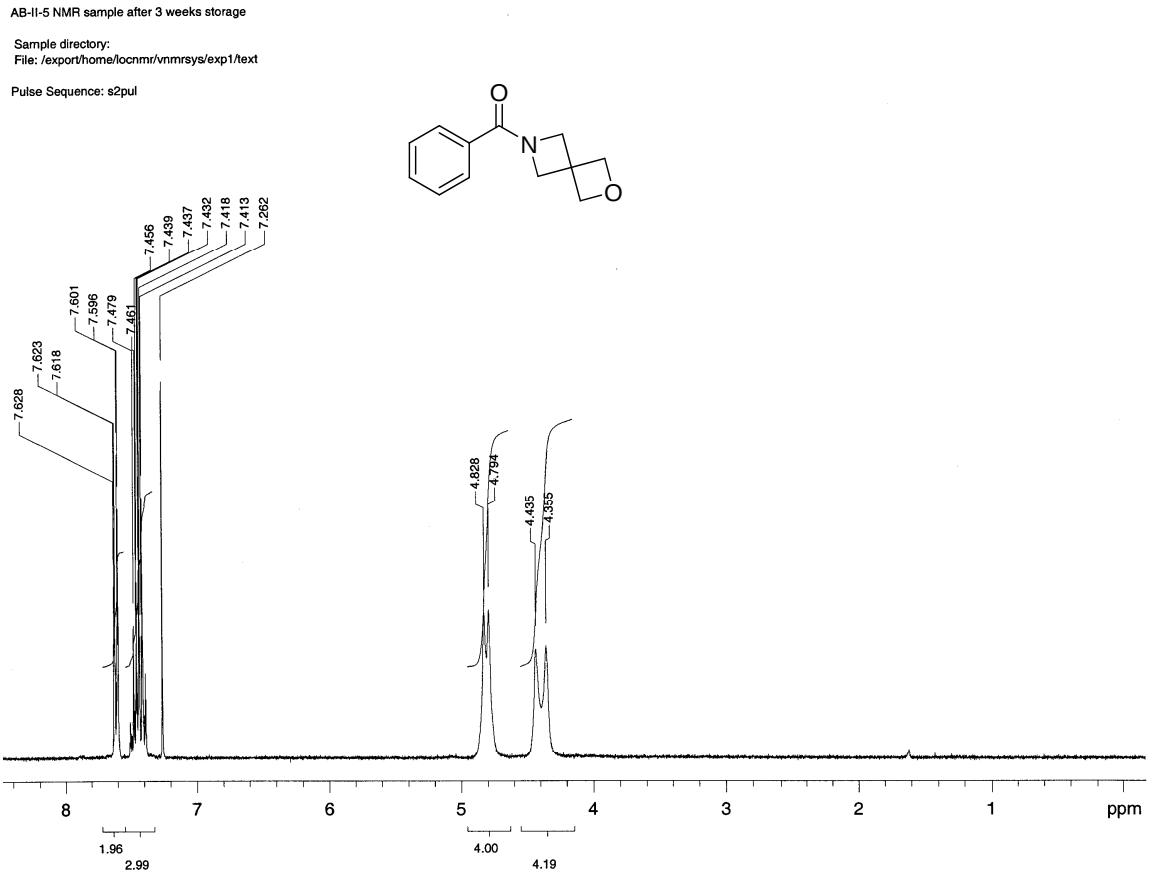

AB-I-24-1 destilliert
File: CARBON
Pulse Sequence: s2pul
81.879
77.549
77.128
76.699
67.031
43.231
160
140
120
100
80
60
40
20
ppm

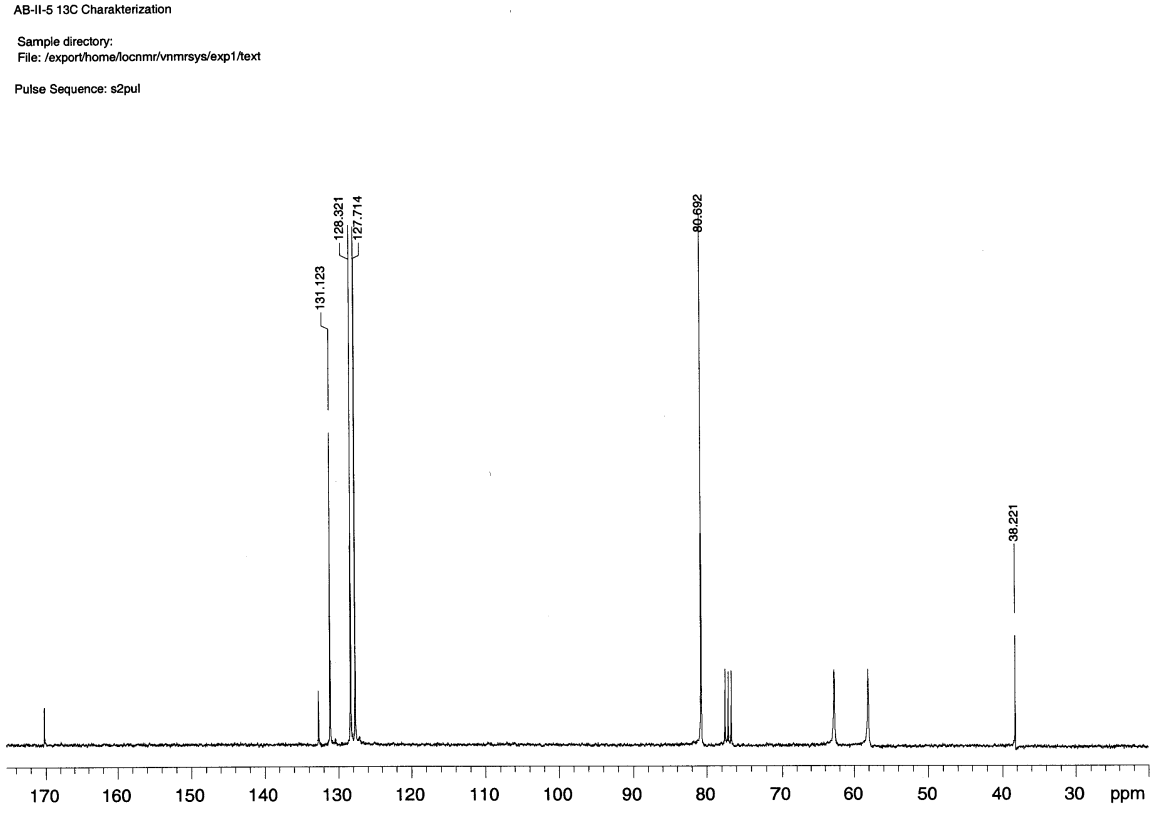
Appendix


AB-II-12 reine Fraktionen
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
7.543
7.518
7.491
7.462
7.396
7.262
6.549
6.520
4.856
4.069
8
7
6
5
4
3
2
1
ppm
5.92
3.41
1.98
4.00
4.02
0.22
0.65
0.30

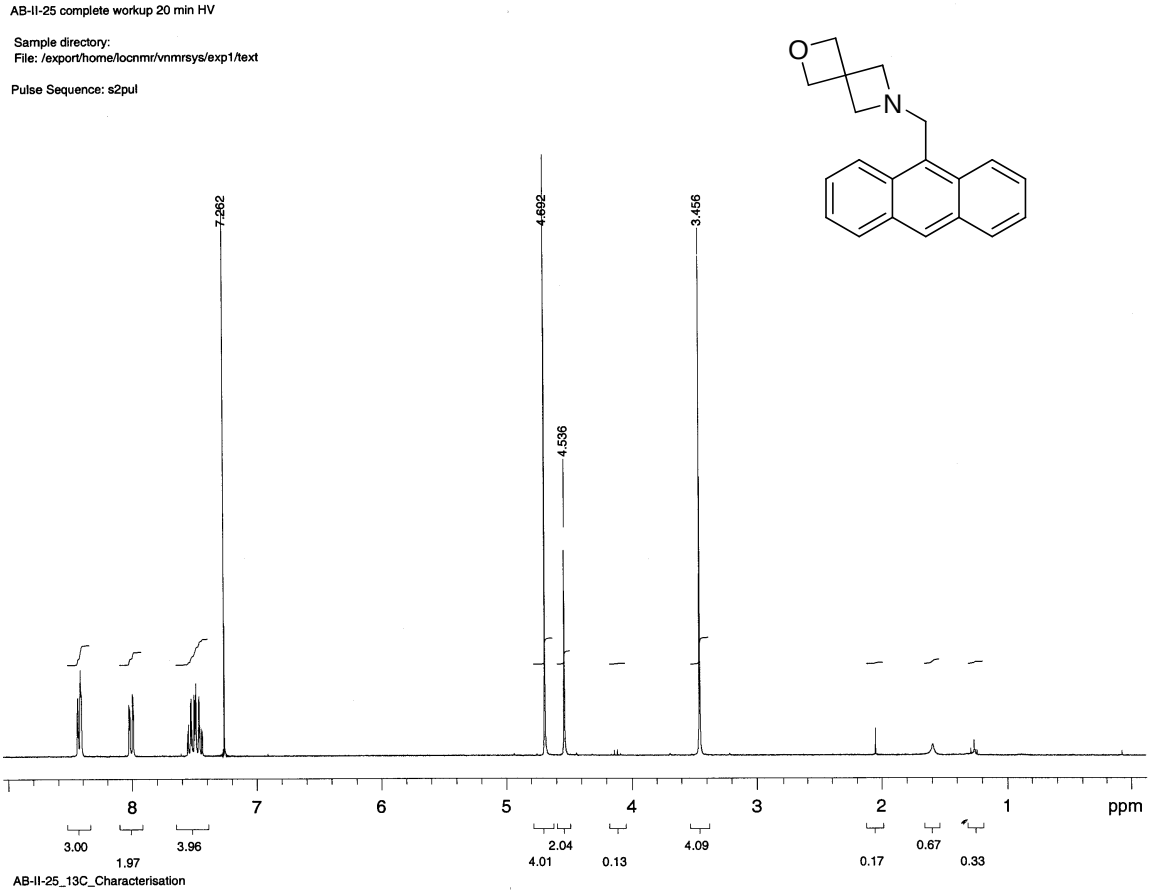

AB-II-12
File: CARBON
Pulse Sequence: s2pul
150.355
140.976
130.877
128.524
127.676
127.546
126.253
111.917
81.258
77.441
77.021
76.601
61.740
39.157
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

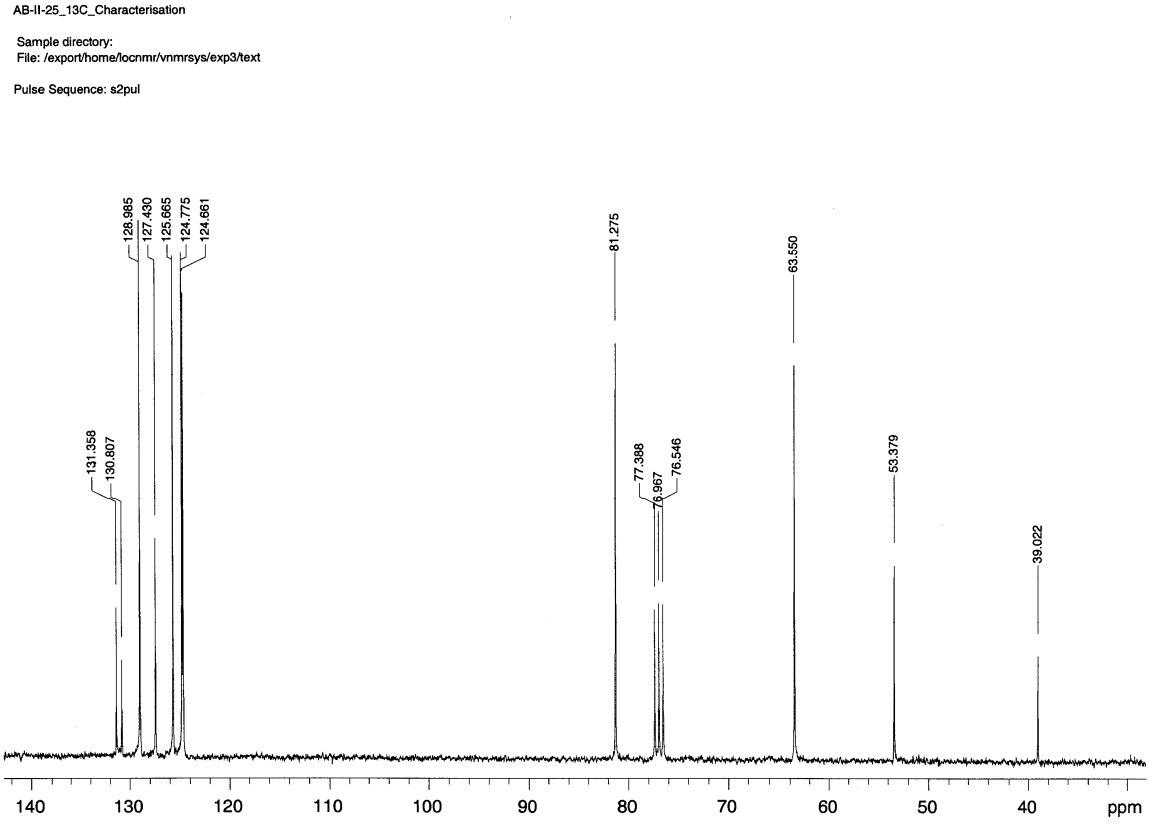
Appendix


AB-II-5 NMR sample after 3 weeks storage
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
O
N
O
7.628
7.623
7.618
7.601
7.596
7.479
7.461
7.456
7.439
7.437
7.432
7.418
7.413
7.262
4.828
4.794
4.435
4.355
8
7
6
5
4
3
2
1
ppm
1.96
2.99
4.00
4.19

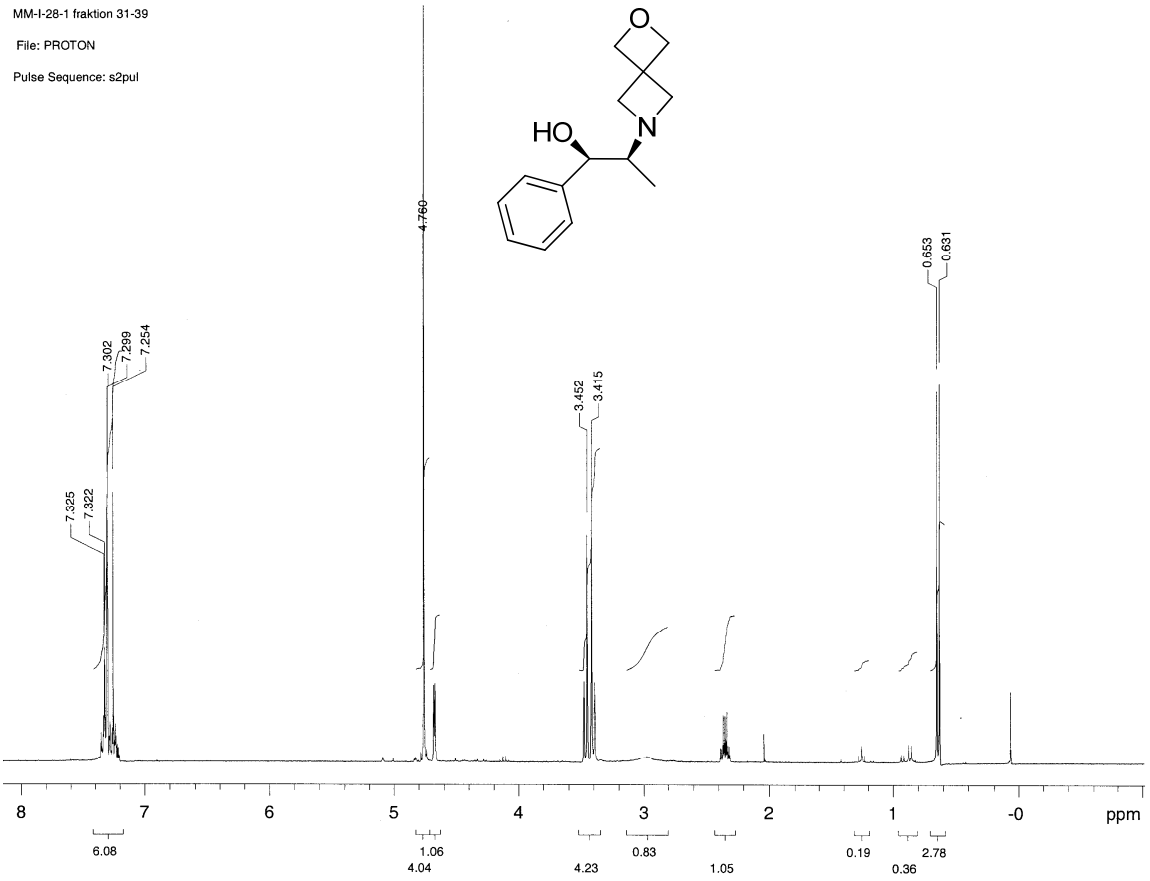

AB-II-5 13C Charakterization
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
131.123
128.321
127.714
80.692
38.221
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

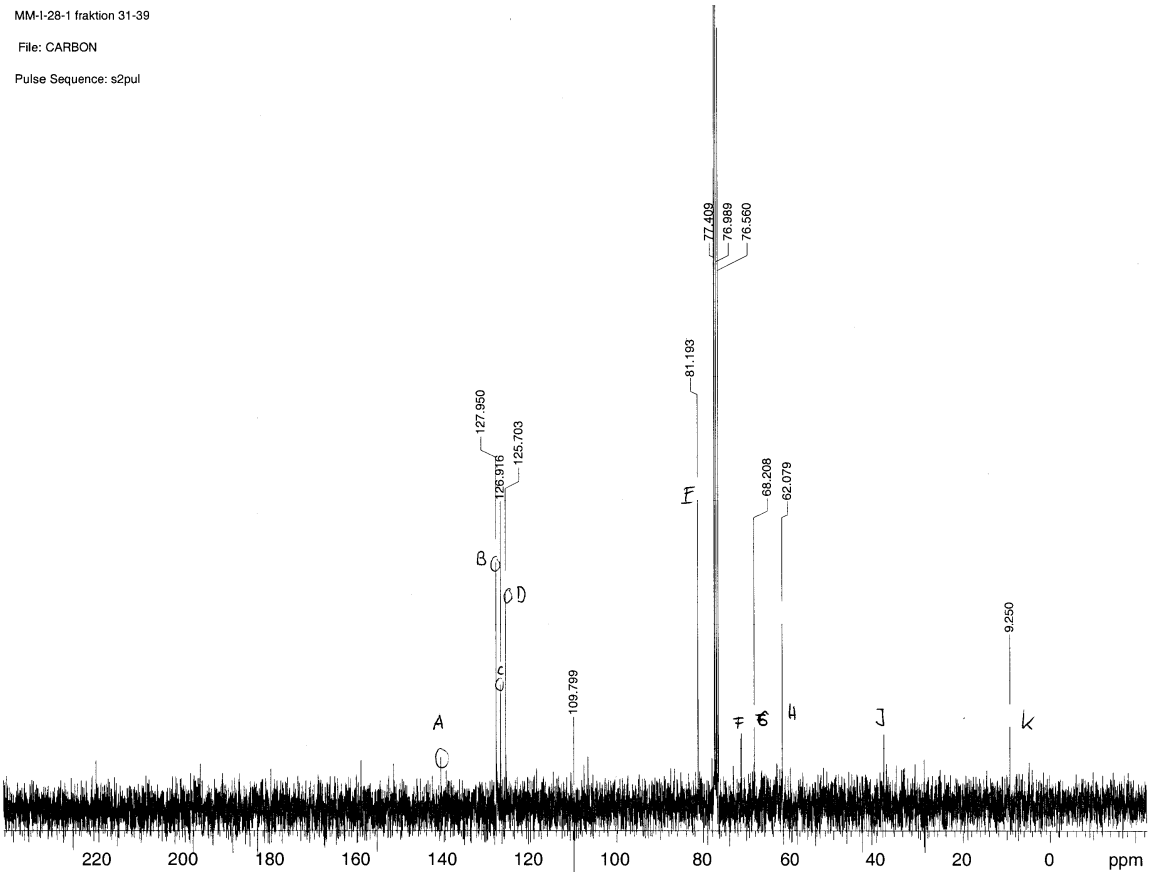
Appendix


AB-II-25 complete workup 20 min HV
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
O
N
7.262
4.692
4.536
3.456
8
7
6
5
4
3
2
1
ppm
3.00
1.97
3.96
2.04
4.01
0.13
4.09
0.17
0.67
0.33

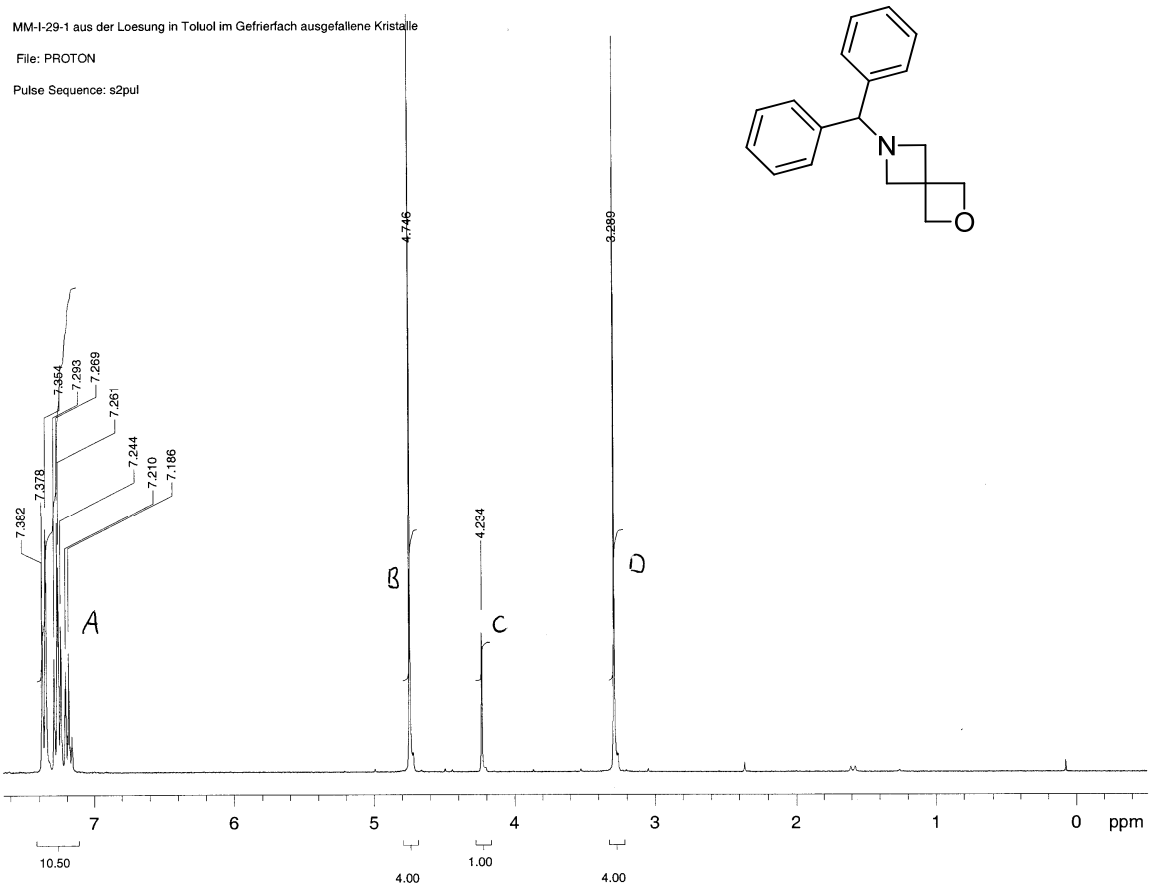

AB-II-25_13C_Characterisation
Sample directory:
File: /export/home/locnmr/vnmrsys/exp3/text
Pulse Sequence: s2pul
128.985
127.430
125.665
124.775
124.661
131.358
130.807
81.275
77.388
76.967
76.546
63.550
53.379
39.022
140
130
120
110
100
90
80
70
60
50
40
ppm

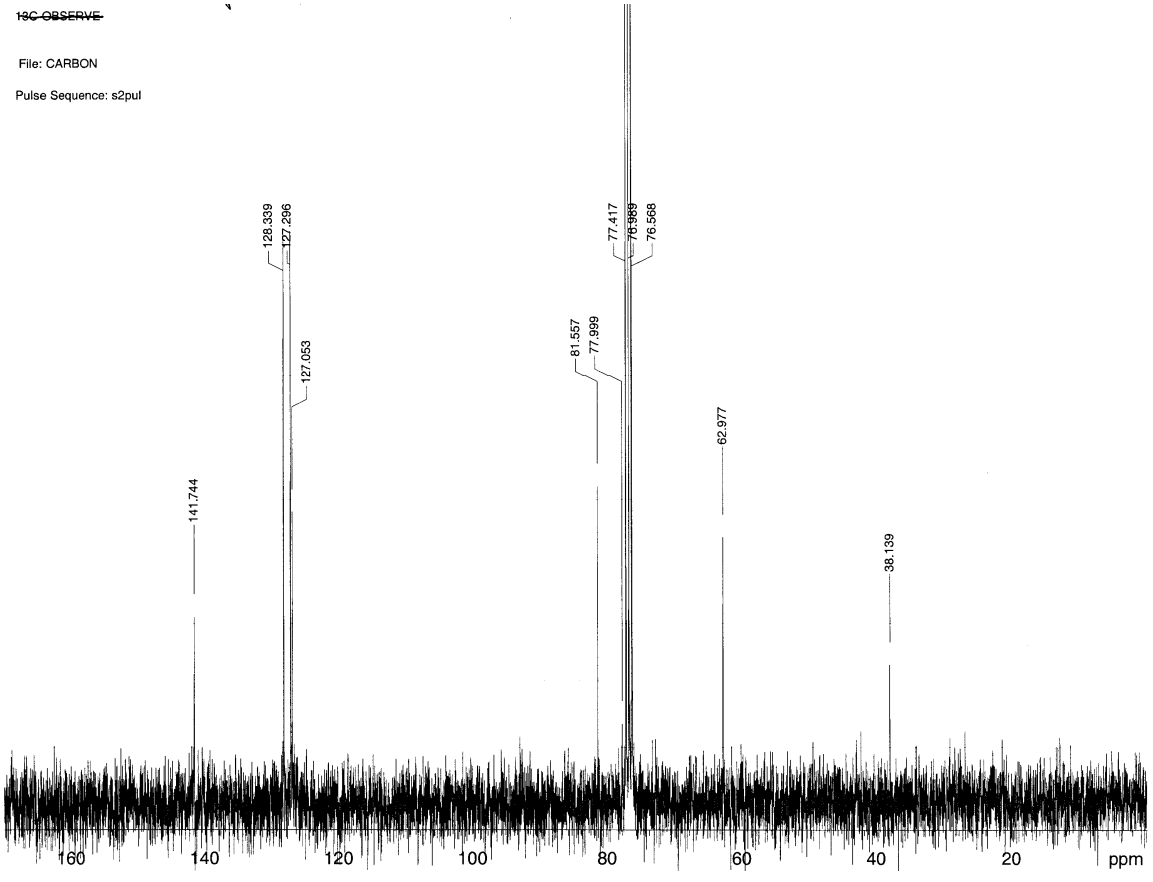
Appendix


MM-I-28-1 fraktion 31-39
File: PROTON
Pulse Sequence: s2pul
O
HO
N
4.760
0.653
0.631
7.302
7.299
7.254
7.325
7.322
3.452
3.415
8
7
6
5
4
3
2
1
-0
ppm
6.08
1.06
4.04
4.23
0.83
1.05
0.19
0.36
2.78

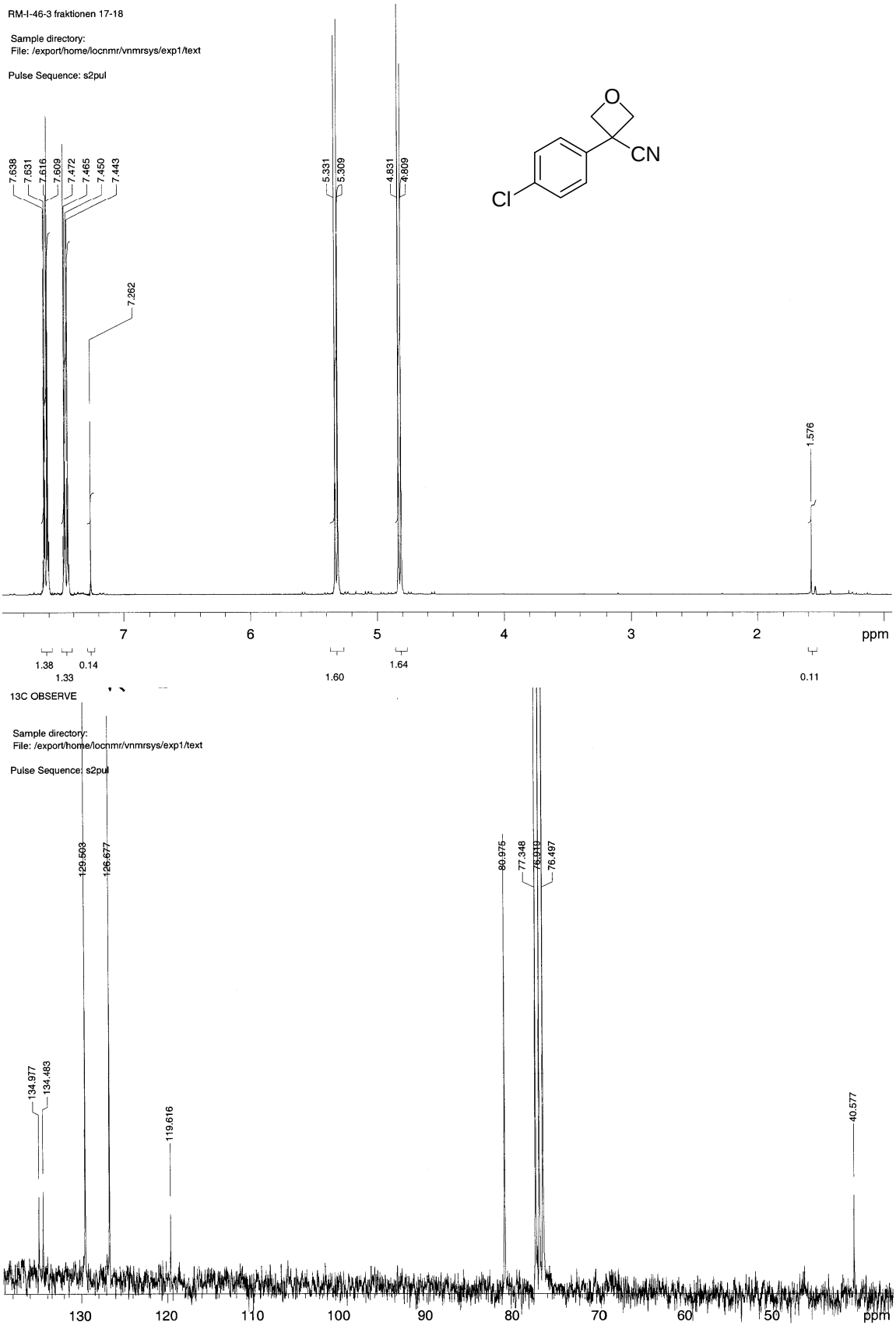

MM-I-28-1 fraktion 31-39
File: CARBON
Pulse Sequence: s2pul
77.409
76.989
76.560
81.193
127.950
126.916
125.703
68.208
62.079
109.799
9.250
A
B
C
D
E
F
G
H
J
K
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix

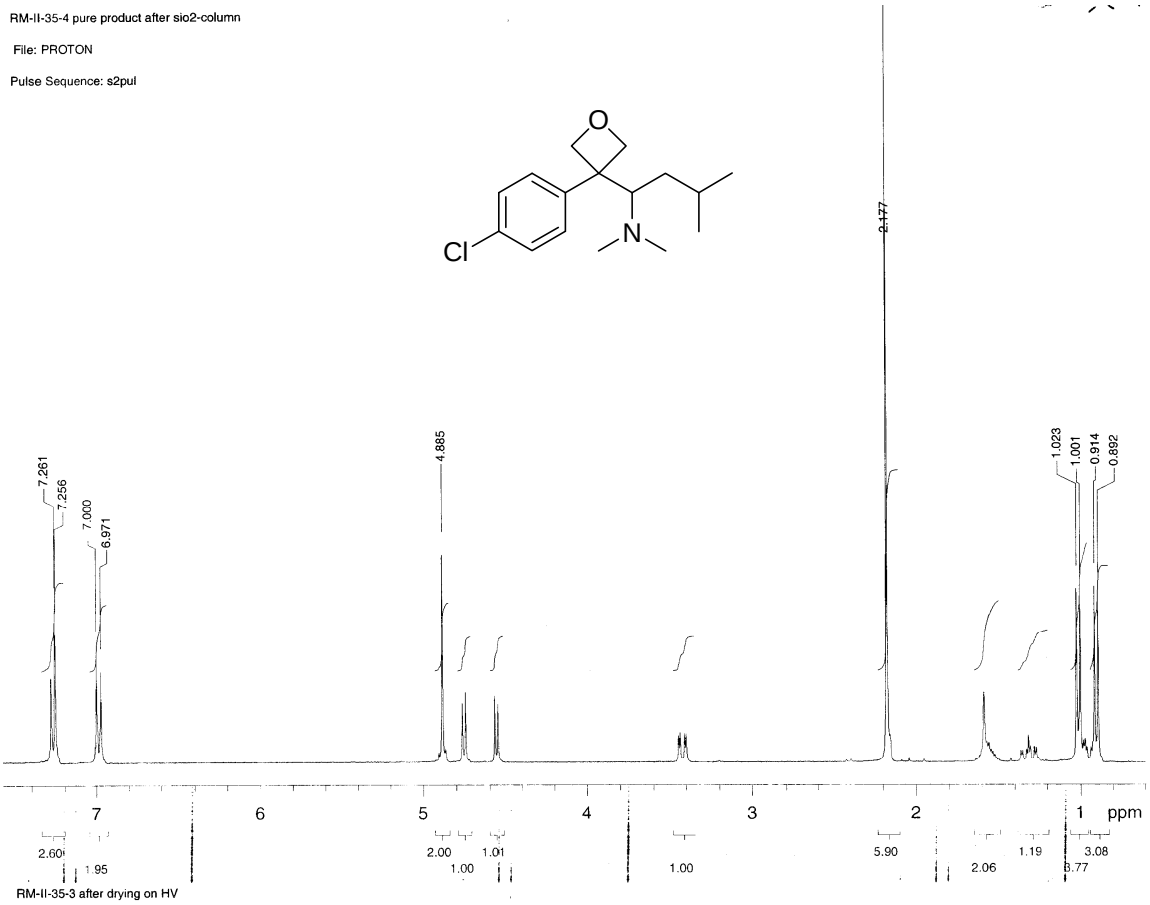

MM-I-29-1 aus der Loesung in Toluol im Gefrierfach ausgefallene Kristalle
File: PROTON
Pulse Sequence: s2pul
N
O
7.364
7.293
7.269
7.261
7.244
7.210
7.186
7.378
7.362
4.746
4.224
3.289
A
B
C
D
7
6
5
4
3
2
1
0
ppm
10.50
4.00
1.00
4.00

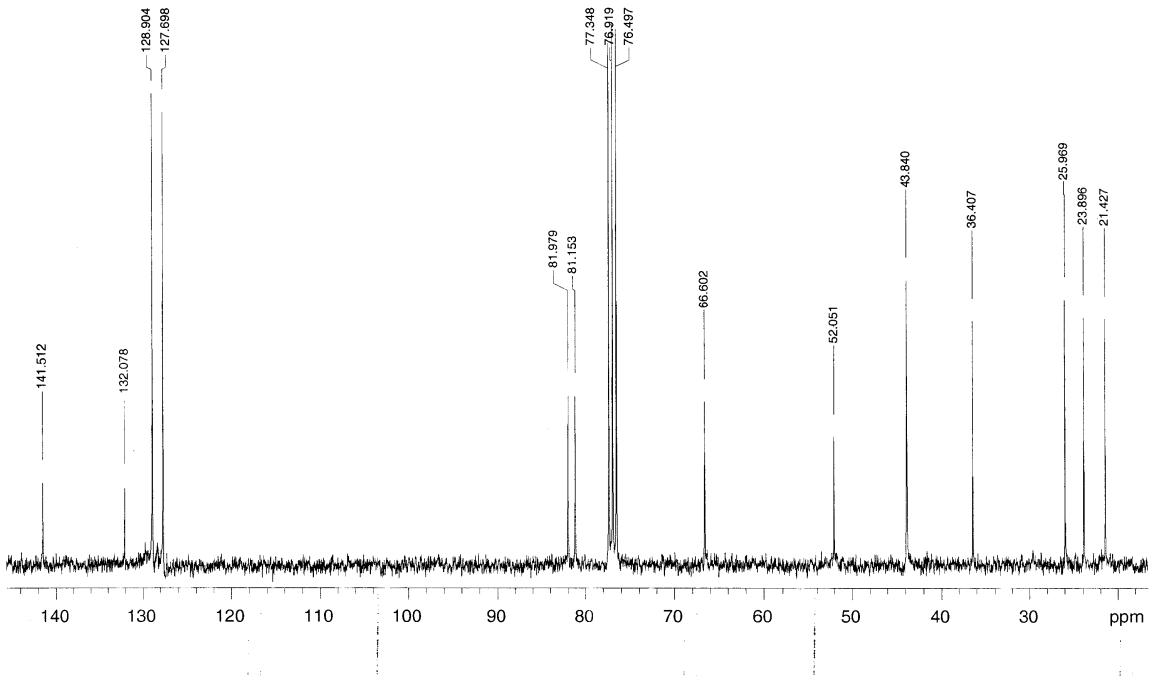

13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
128.339
127.296
127.053
141.744
81.557
77.999
77.417
76.989
76.568
62.977
38.139
160
140
120
100
80
60
40
20
ppm

Appendix

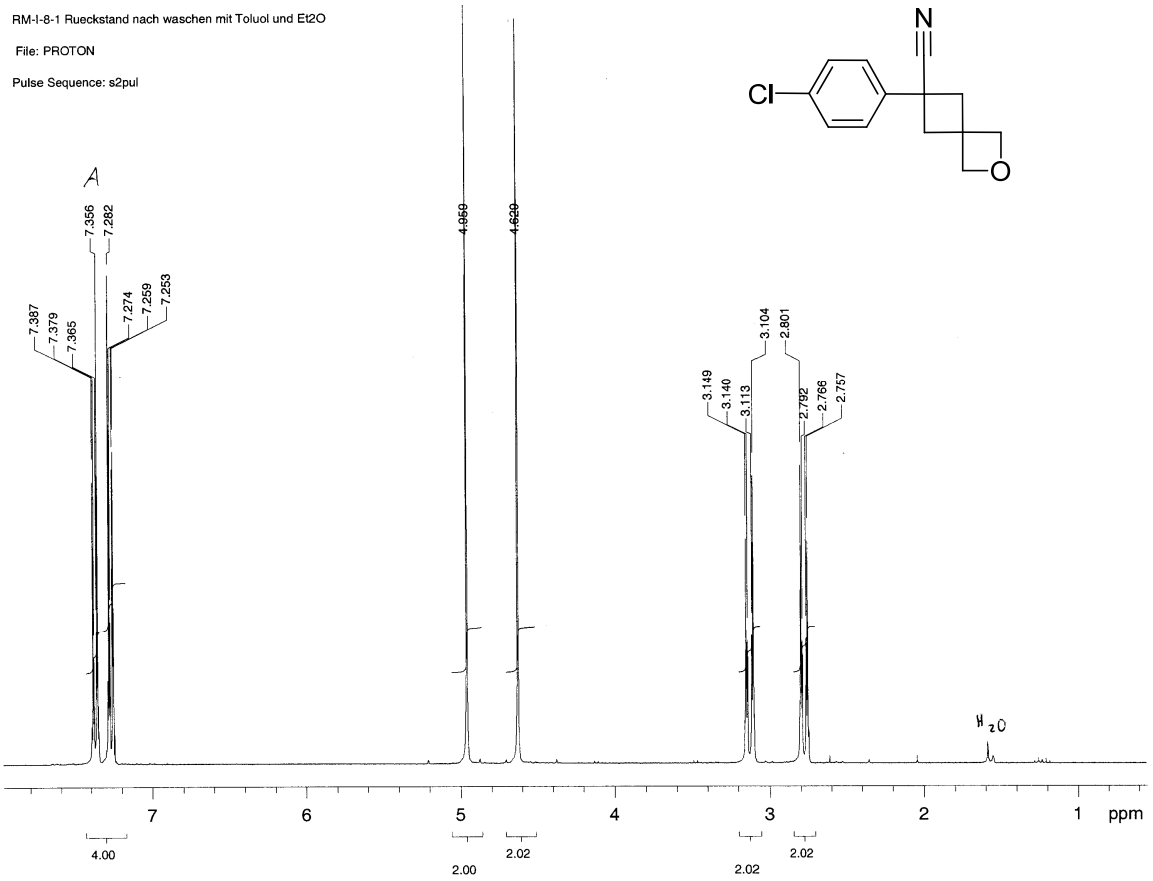

RM-I-46-3 fraktionen 17-18
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
7.638
7.631
7.616
7.609
7.472
7.465
7.450
7.443
7.262
5.331
5.309
4.831
4.809
1.576
O
CN
Cl
7
6
5
4
3
2
ppm
1.38
0.14
1.33
1.60
1.64
0.11
13C OBSERVE
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
129.568
126.677
80.975
77.348
76.010
76.497
134.977
134.483
119.616
40.577
130
120
110
100
90
80
70
60
50
ppm

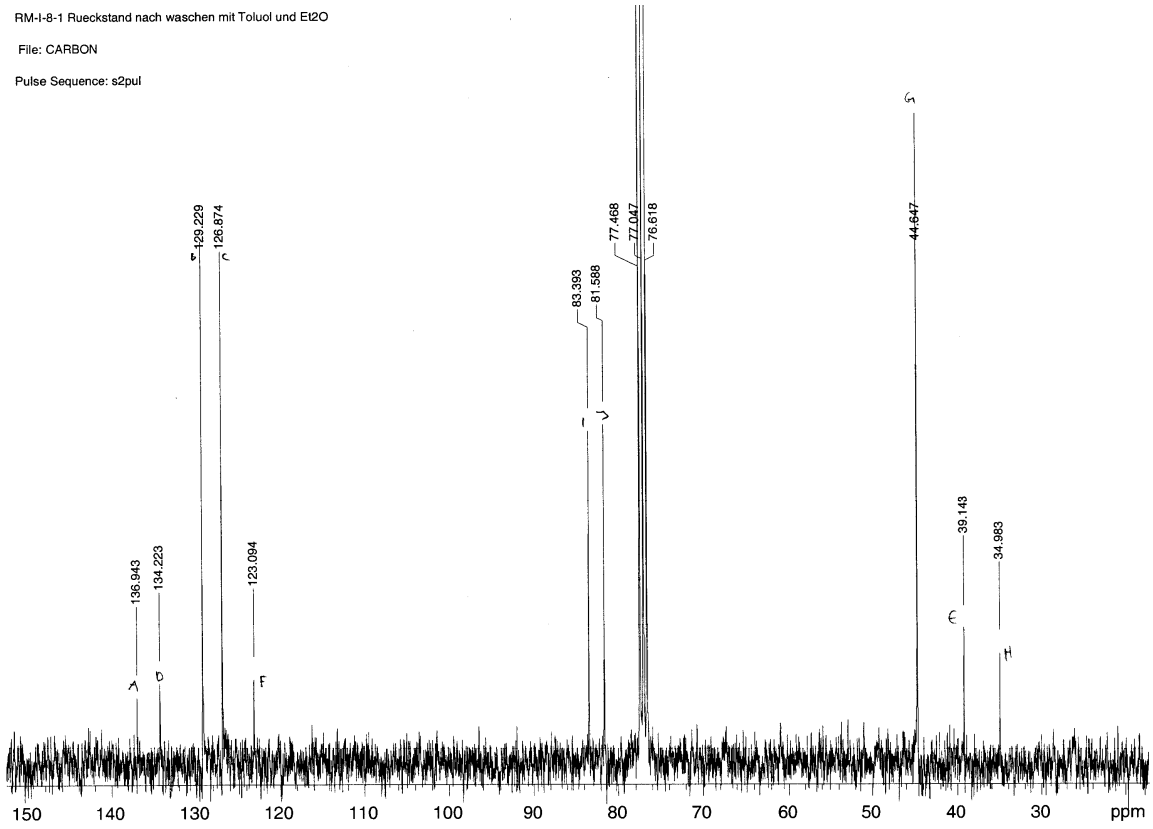
Appendix


RM-II-35-4 pure product after sio2-column
File: PROTON
Pulse Sequence: s2pul
O
Cl
N
7.261
7.256
7.000
6.971
4.885
2.177
1.023
1.001
0.914
0.892
7
6
5
4
3
2
1
ppm
2.60
1.95
2.00
1.01
1.00
1.00
5.90
2.06
1.19
3.08
6.77
RM-II-35-3 after drying on HV
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul

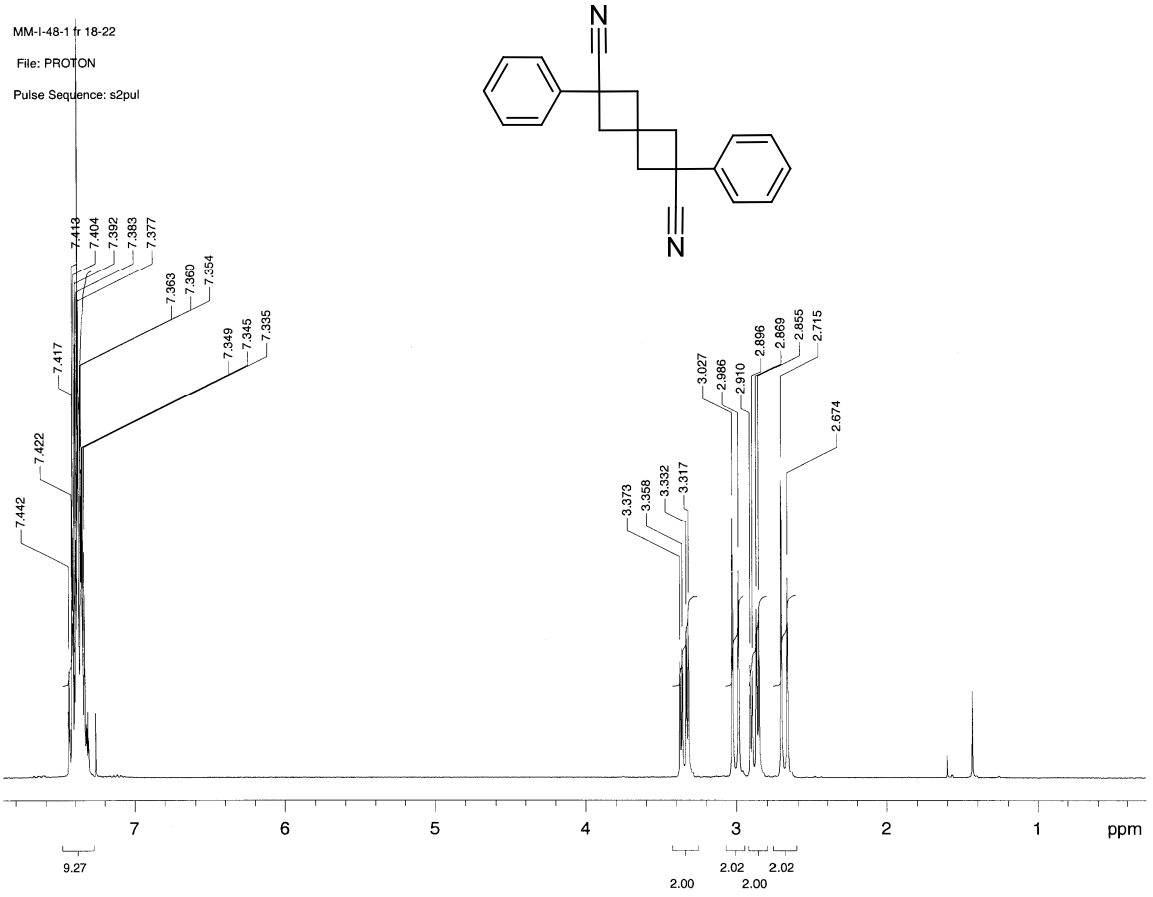

141.512
132.078
128.904
127.698
81.979
81.153
77.348
76.919
76.497
66.602
52.051
43.840
36.407
25.969
23.896
21.427
140
130
120
110
100
90
80
70
60
50
40
30
ppm

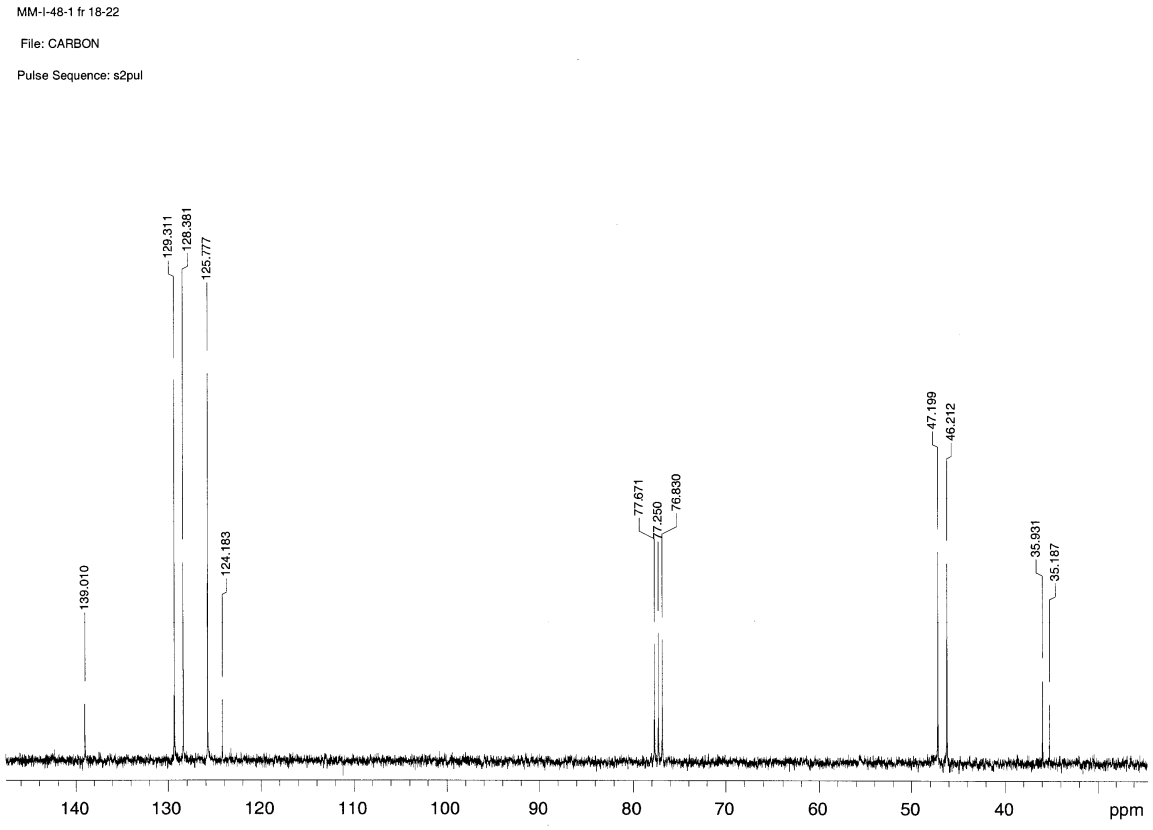
Appendix


RM-I-8-1 Rueckstand nach waschen mit Toluol und Et2O
File: PROTON
Pulse Sequence: s2pul
Cl
N
O
A
7.356
7.282
7.387
7.379
7.365
7.274
7.259
7.253
4.959
4.629
3.104
2.801
3.149
3.140
3.113
2.792
2.766
2.757
H2O
7
6
5
4
3
2
1
ppm
4.00
2.00
2.02
2.02
2.02

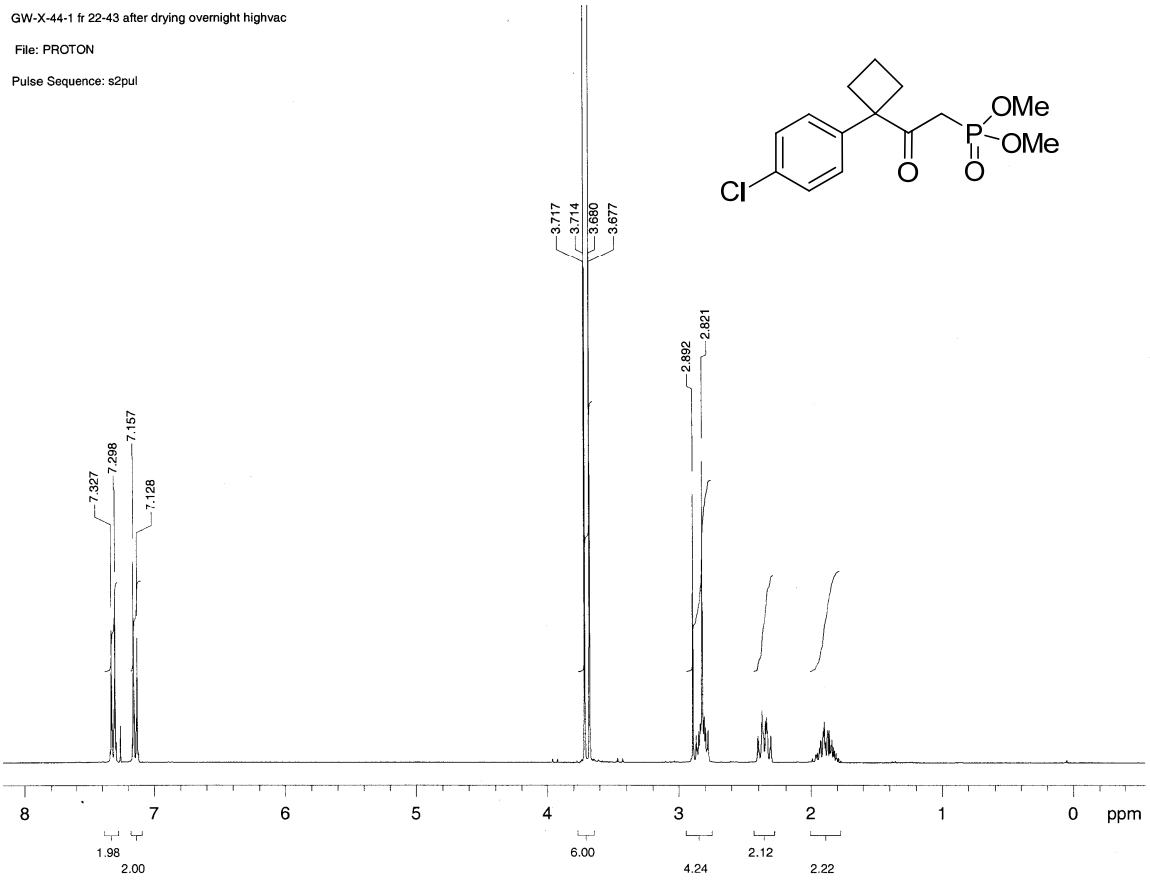

RM-I-8-1 Rueckstand nach waschen mit Toluol und Et2O
File: CARBON
Pulse Sequence: s2pul
129.229
126.874
123.094
136.943
134.223
83.393
81.588
77.468
77.047
76.618
44.647
39.143
34.983
A
B
C
D
E
F
G
H
I
J
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

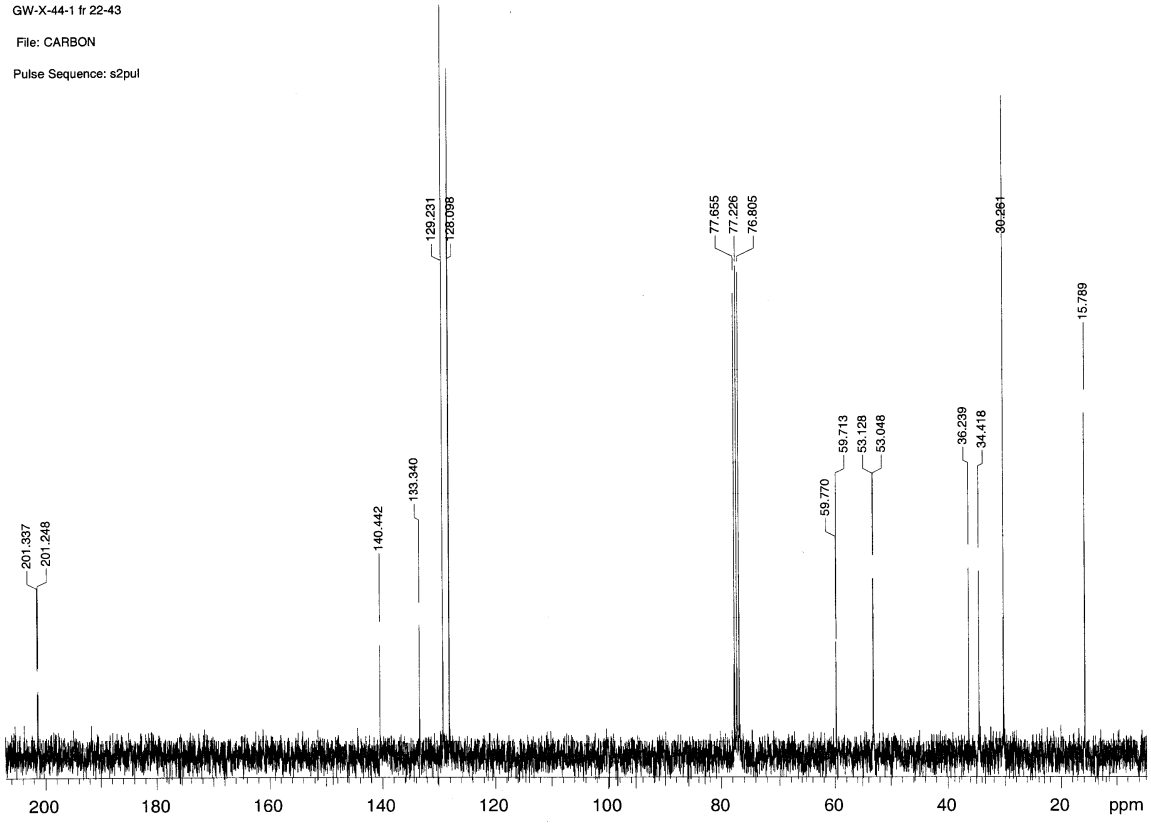
Appendix


MM-I-48-1 fr 18-22
File: PROTON
Pulse Sequence: s2pul
N
N
7.442
7.422
7.417
7.413
7.404
7.392
7.383
7.377
7.363
7.360
7.354
7.349
7.345
7.335
3.373
3.358
3.332
3.317
3.027
2.986
2.910
2.896
2.869
2.855
2.715
2.674
7
6
5
4
3
2
1
ppm
9.27
2.00
2.02
2.00
2.02

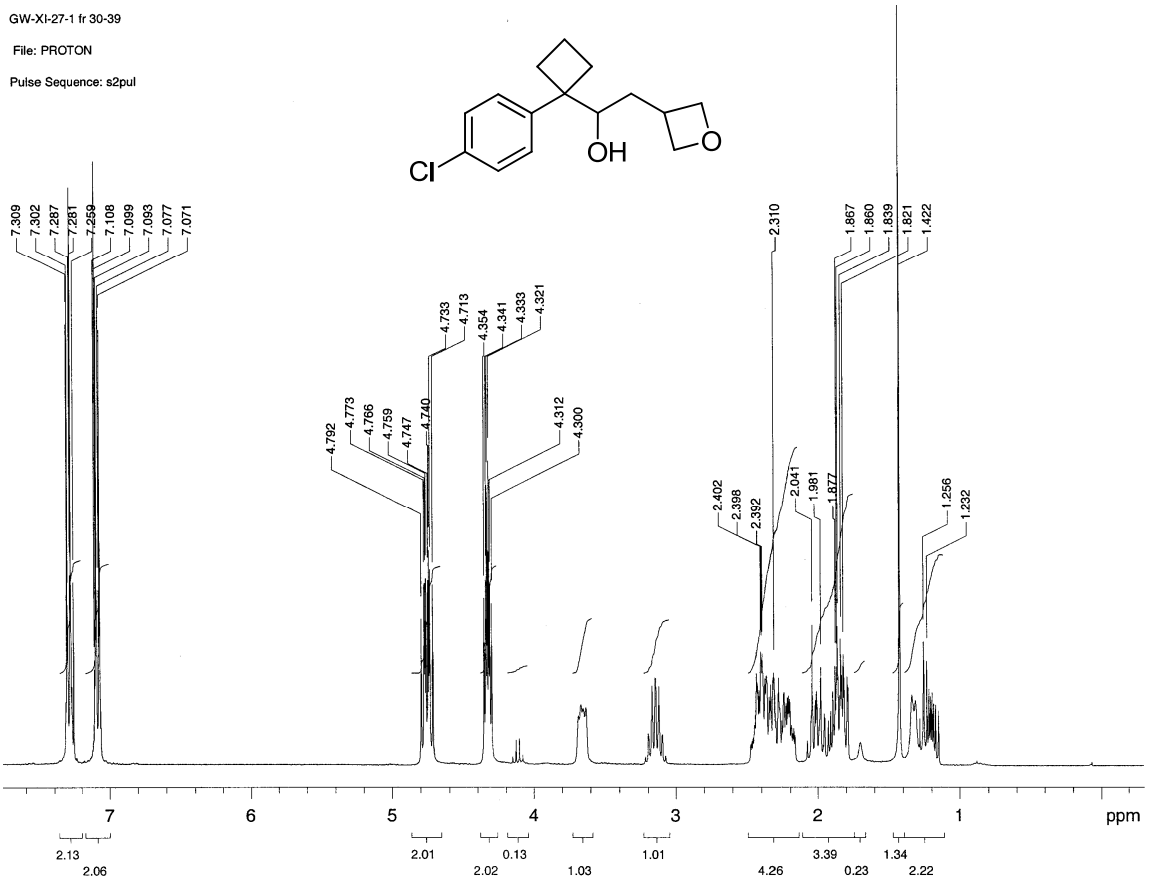

MM-I-48-1 fr 18-22
File: CARBON
Pulse Sequence: s2pul
139.010
129.311
128.381
125.777
124.183
77.671
77.250
76.830
47.199
46.212
35.931
35.187
140
130
120
110
100
90
80
70
60
50
40
ppm

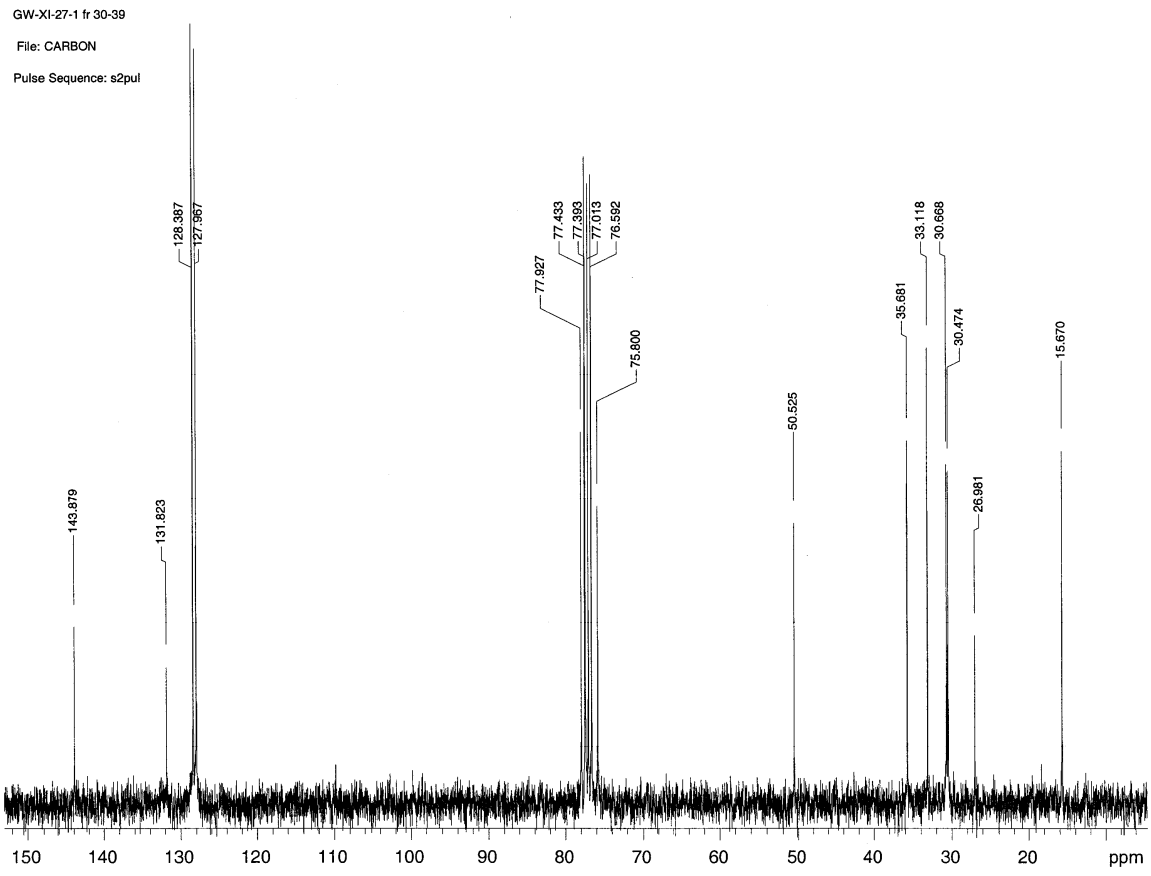
Appendix


GW-X-44-1 fr 22-43 after drying overnight highvac
File: PROTON
Pulse Sequence: s2pul
OMe
OMe
P
O
O
Cl
3.717
3.714
3.680
3.677
2.892
2.821
7.327
7.298
7.157
7.128
8
7
6
5
4
3
2
1
0
ppm
1.98
2.00
6.00
4.24
2.12
2.22

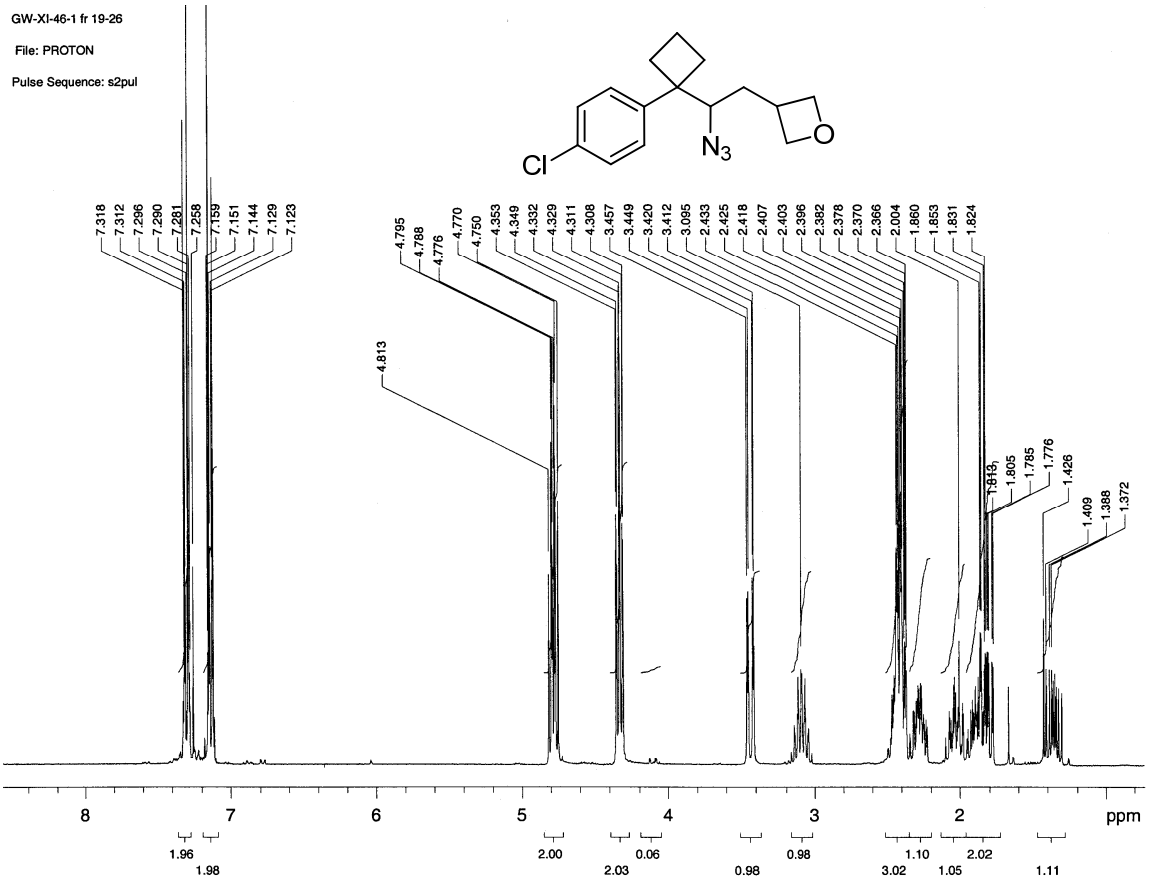

GW-X-44-1 fr 22-43
File: CARBON
Pulse Sequence: s2pul
201.337
201.248
140.442
133.340
129.231
128.098
77.655
77.226
76.805
59.770
59.713
53.128
53.048
36.239
34.418
30.261
15.789
200
180
160
140
120
100
80
60
40
20
ppm

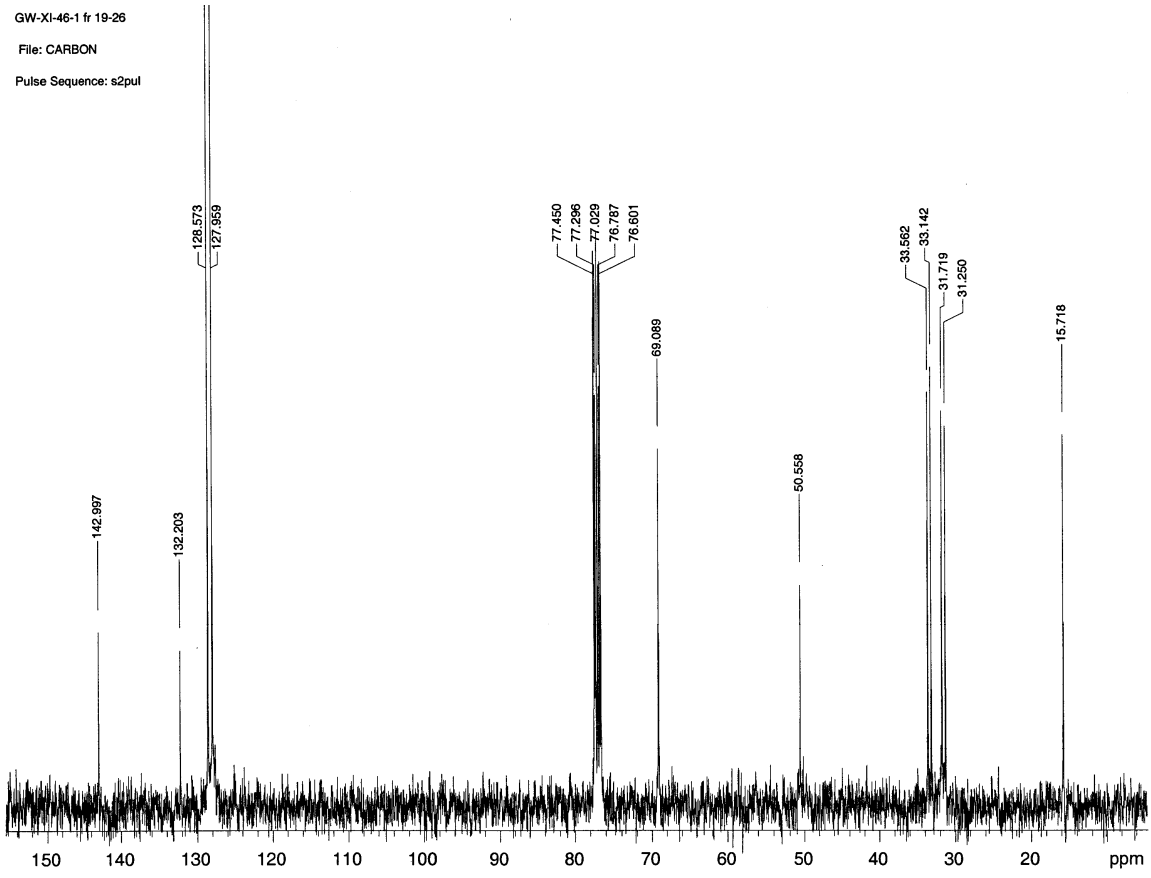
Appendix


GW-XI-27-1 fr 30-39
File: PROTON
Pulse Sequence: s2pul
Cl
OH
O
7.309
7.302
7.287
7.281
7.259
7.108
7.099
7.093
7.077
7.071
4.792
4.773
4.766
4.759
4.747
4.740
4.733
4.713
4.354
4.341
4.333
4.321
4.312
4.300
2.402
2.398
2.392
2.310
2.041
1.981
1.877
1.867
1.860
1.839
1.821
1.422
1.256
1.232
7
6
5
4
3
2
1
ppm
2.13
2.06
2.01
0.13
2.02
1.03
1.01
4.26
3.39
0.23
1.34
2.22

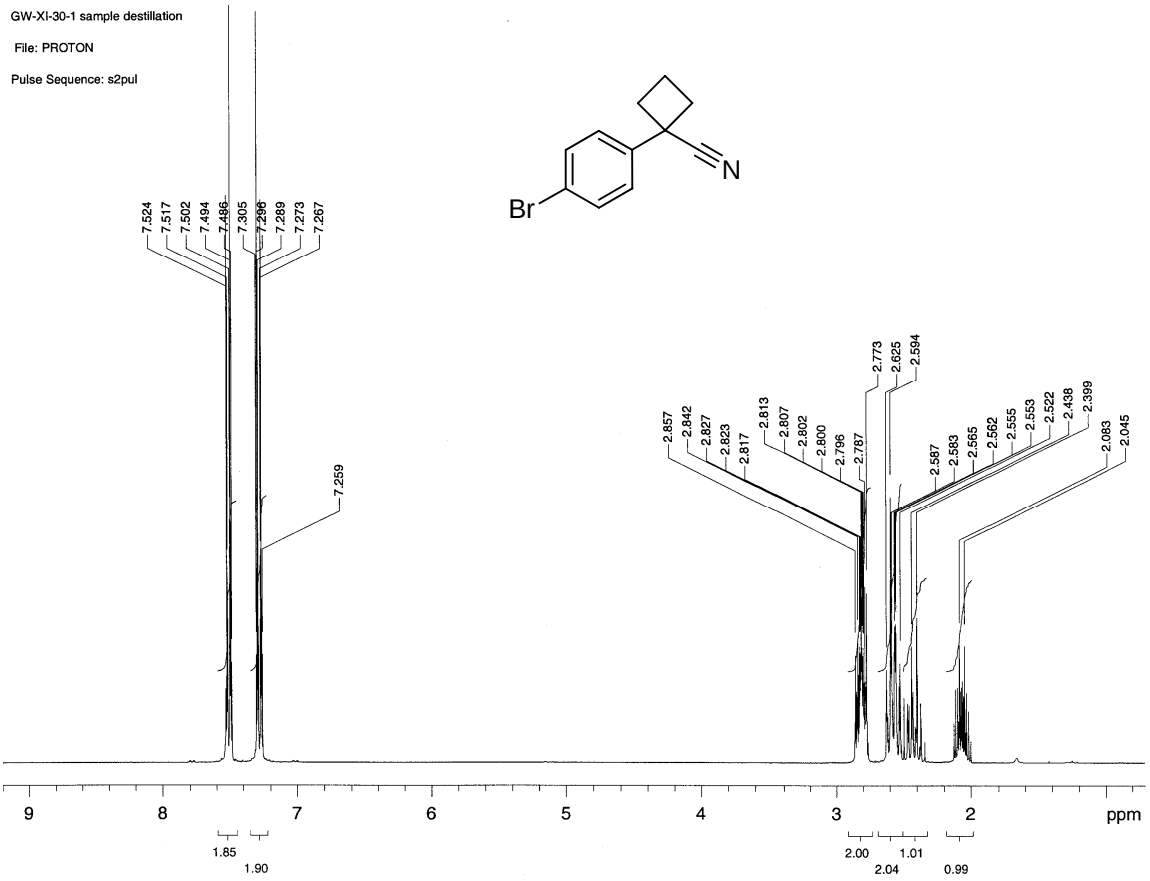

GW-XI-27-1 fr 30-39
File: CARBON
Pulse Sequence: s2pul
143.879
131.823
128.387
127.967
77.927
77.433
77.393
77.013
76.592
75.800
50.525
35.681
33.118
30.668
30.474
26.981
15.670
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

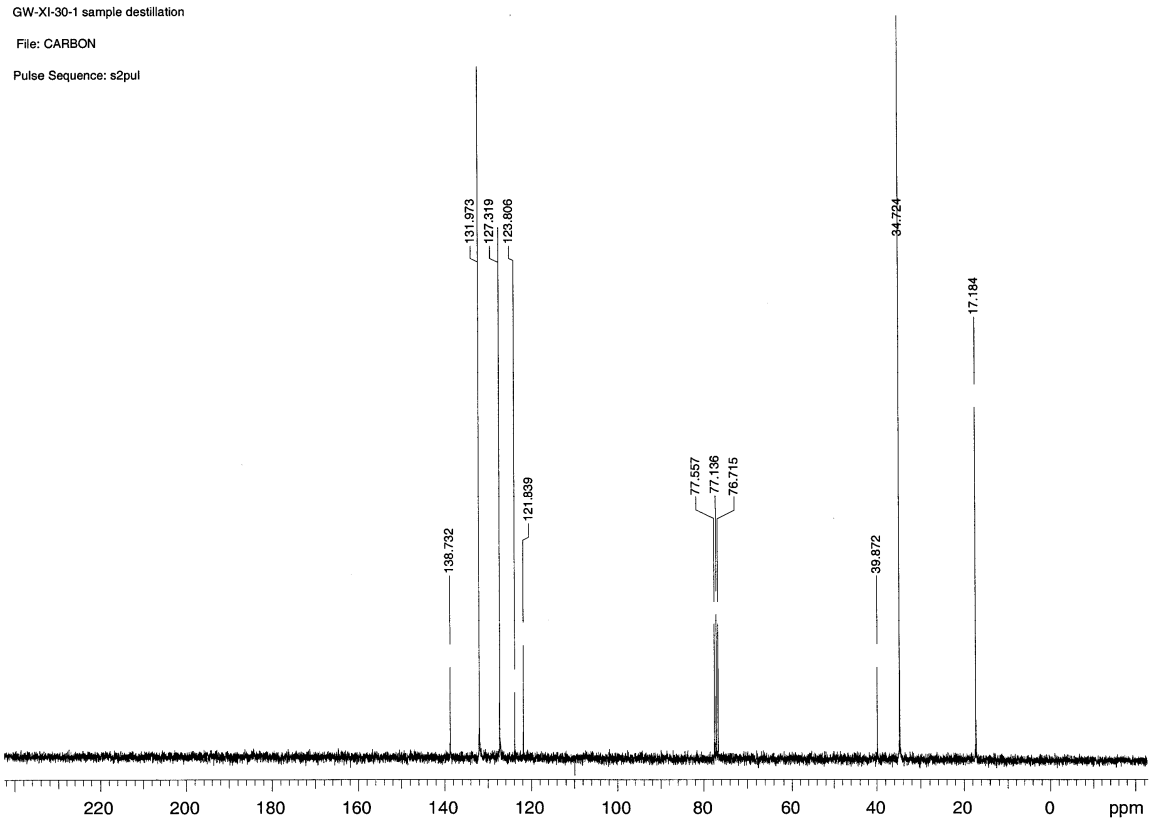
Appendix


GW-XI-46-1 fr 19-26
File: PROTON
Pulse Sequence: s2pul
Cl
N3
O
7.318
7.312
7.296
7.290
7.281
7.258
7.159
7.151
7.144
7.129
7.123
4.795
4.788
4.776
4.770
4.750
4.353
4.349
4.332
4.329
4.311
4.308
3.457
3.449
3.420
3.412
3.095
2.433
2.425
2.418
2.407
2.403
2.396
2.382
2.378
2.370
2.366
2.004
1.860
1.853
1.831
1.824
4.813
1.805
1.785
1.776
1.426
1.409
1.388
1.372
8
7
6
5
4
3
2
ppm
1.96
1.98
2.00
2.03
0.06
0.98
0.98
1.10
3.02
2.02
1.05
1.11

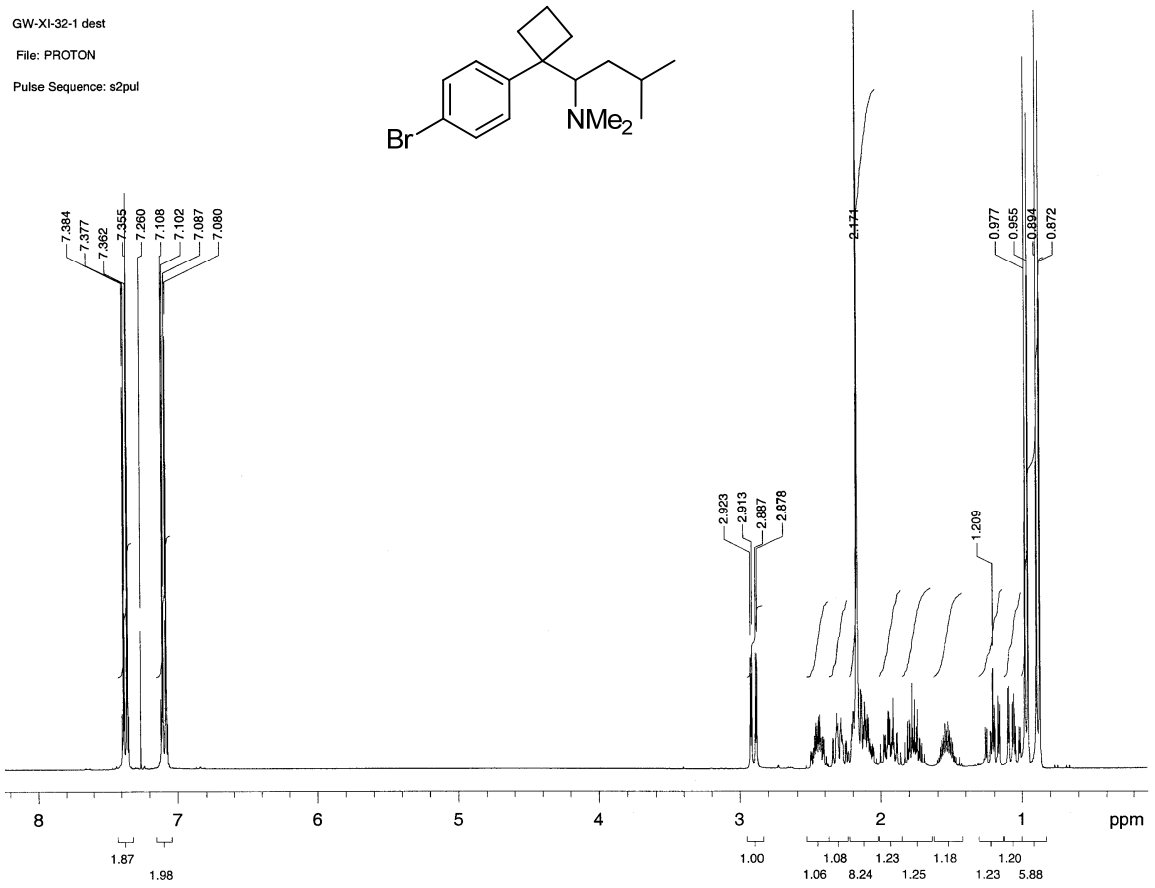

GW-XI-46-1 fr 19-26
File: CARBON
Pulse Sequence: s2pul
128.573
127.959
77.450
77.296
77.029
76.787
76.601
69.089
33.562
33.142
31.719
31.250
15.718
50.558
142.997
132.203
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

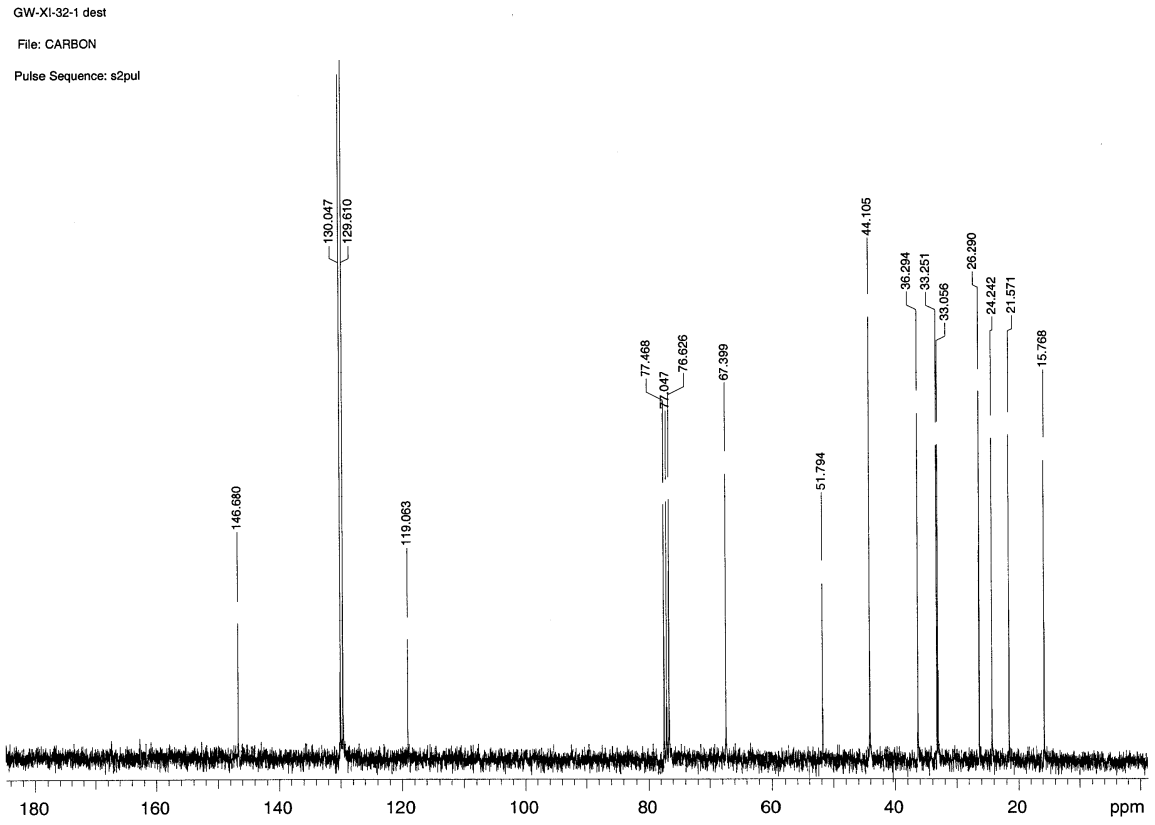
Appendix


GW-XI-30-1 sample destillation
File: PROTON
Pulse Sequence: s2pul
Br
N
7.524
7.517
7.502
7.494
7.486
7.305
7.296
7.289
7.273
7.267
7.259
2.857
2.842
2.827
2.823
2.817
2.813
2.807
2.802
2.800
2.796
2.787
2.773
2.625
2.594
2.587
2.583
2.565
2.562
2.555
2.553
2.522
2.438
2.399
2.083
2.045
9
8
7
6
5
4
3
2
ppm
1.85
1.90
2.00
2.04
1.01
0.99

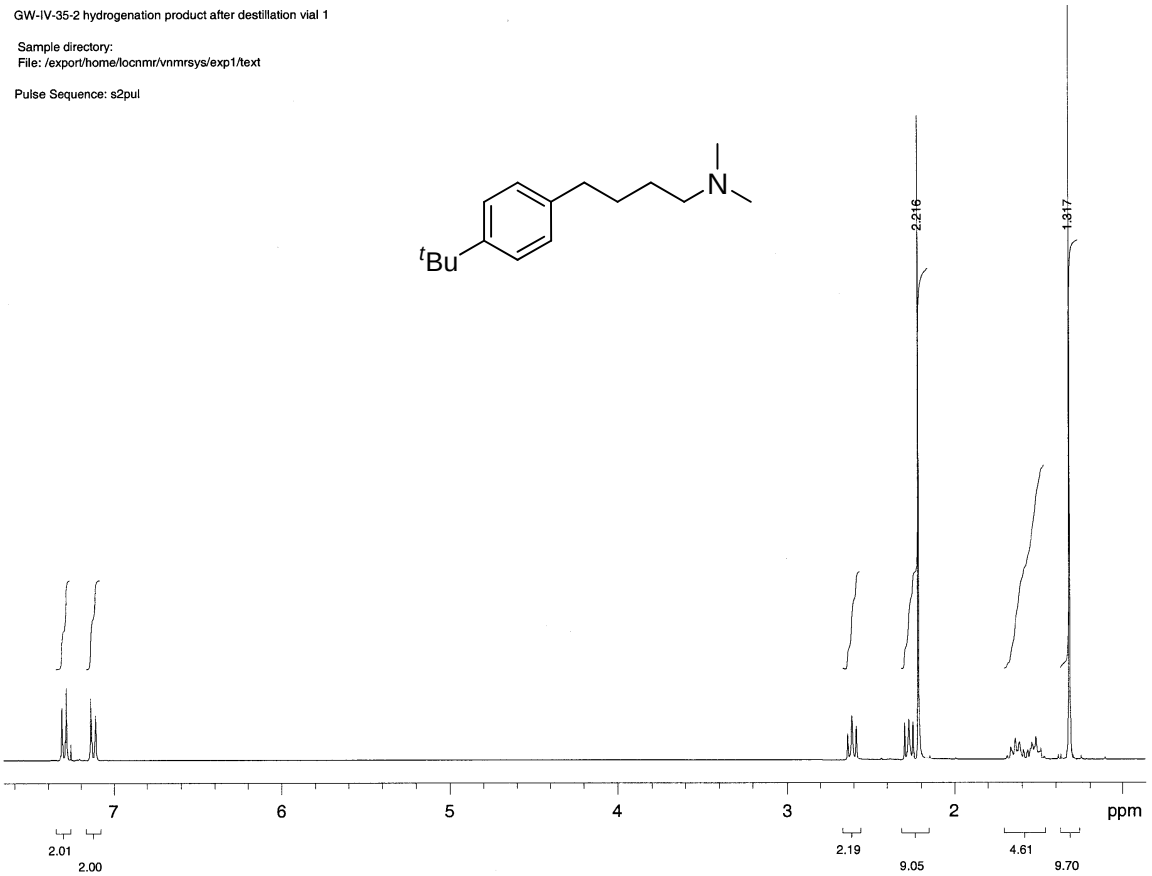

GW-XI-30-1 sample destillation
File: CARBON
Pulse Sequence: s2pul
131.973
127.319
123.806
121.839
138.732
77.557
77.136
76.715
84.724
39.872
17.184
220
200
180
160
140
120
100
80
60
40
20
0
ppm

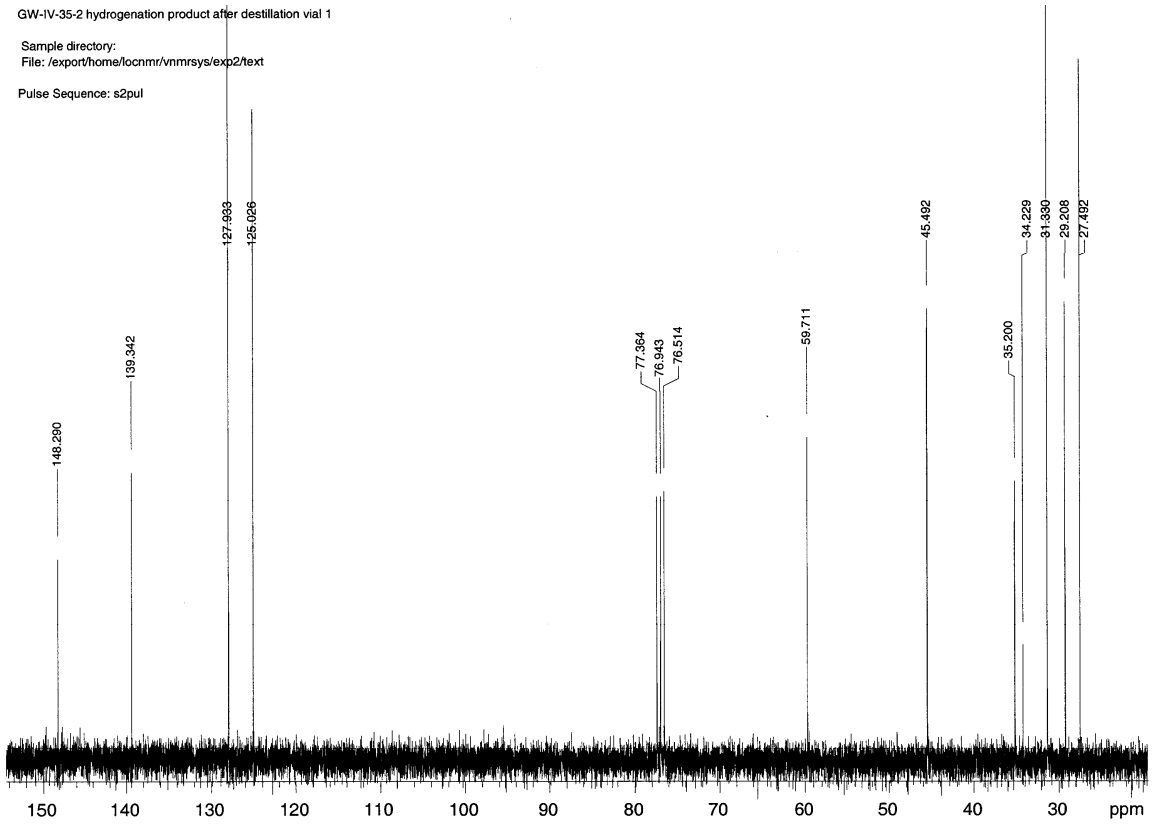
Appendix


GW-XI-32-1 dest
File: PROTON
Pulse Sequence: s2pul
Br
NMe2
7.384
7.377
7.362
7.355
7.260
7.108
7.102
7.087
7.080
2.923
2.913
2.887
2.878
2.471
1.209
0.977
0.955
0.894
0.872
8
7
6
5
4
3
2
1
ppm
1.87
1.98
1.00
1.08
1.23
1.18
1.06
8.24
1.25
1.20
1.23
5.88

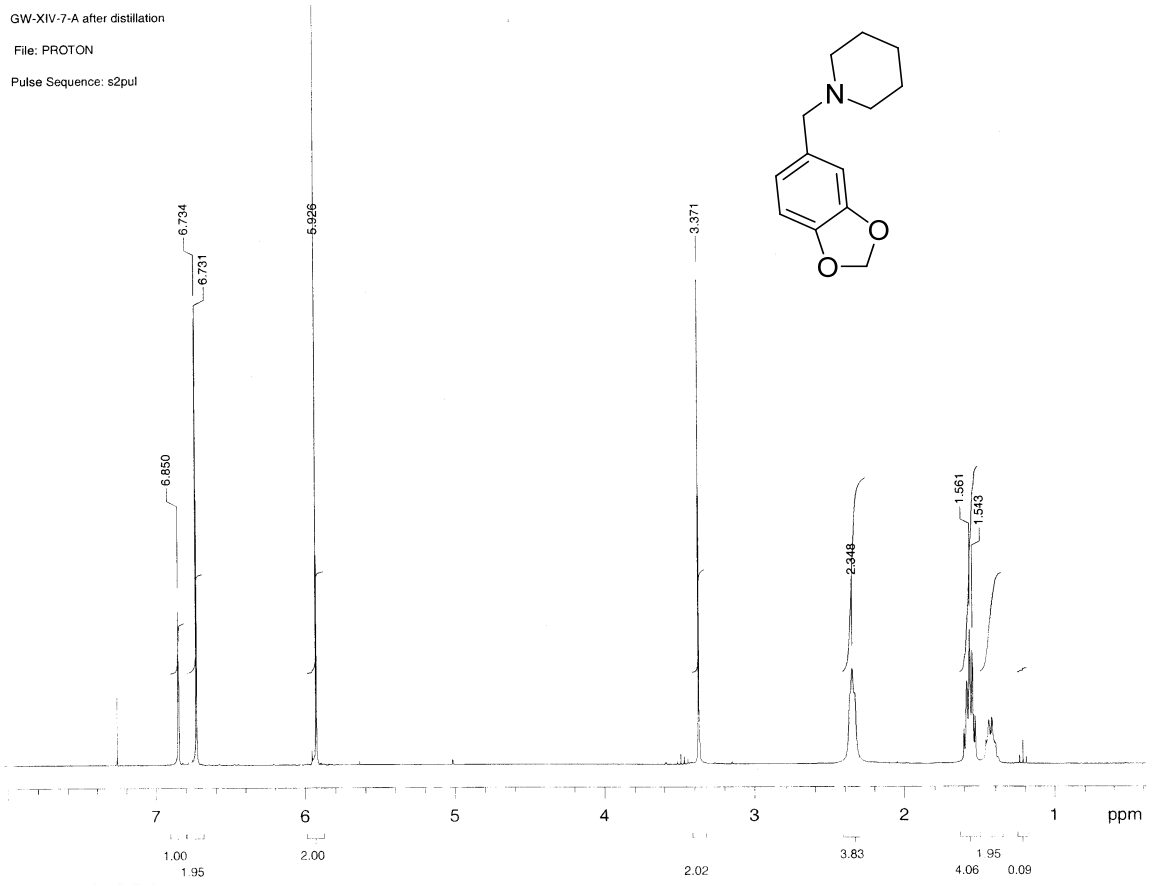

GW-XI-32-1 dest
File: CARBON
Pulse Sequence: s2pul
146.680
130.047
129.610
119.063
77.468
77.047
76.626
67.399
51.794
44.105
36.294
33.251
33.056
26.290
24.242
21.571
15.768
180
160
140
120
100
80
60
40
20
ppm

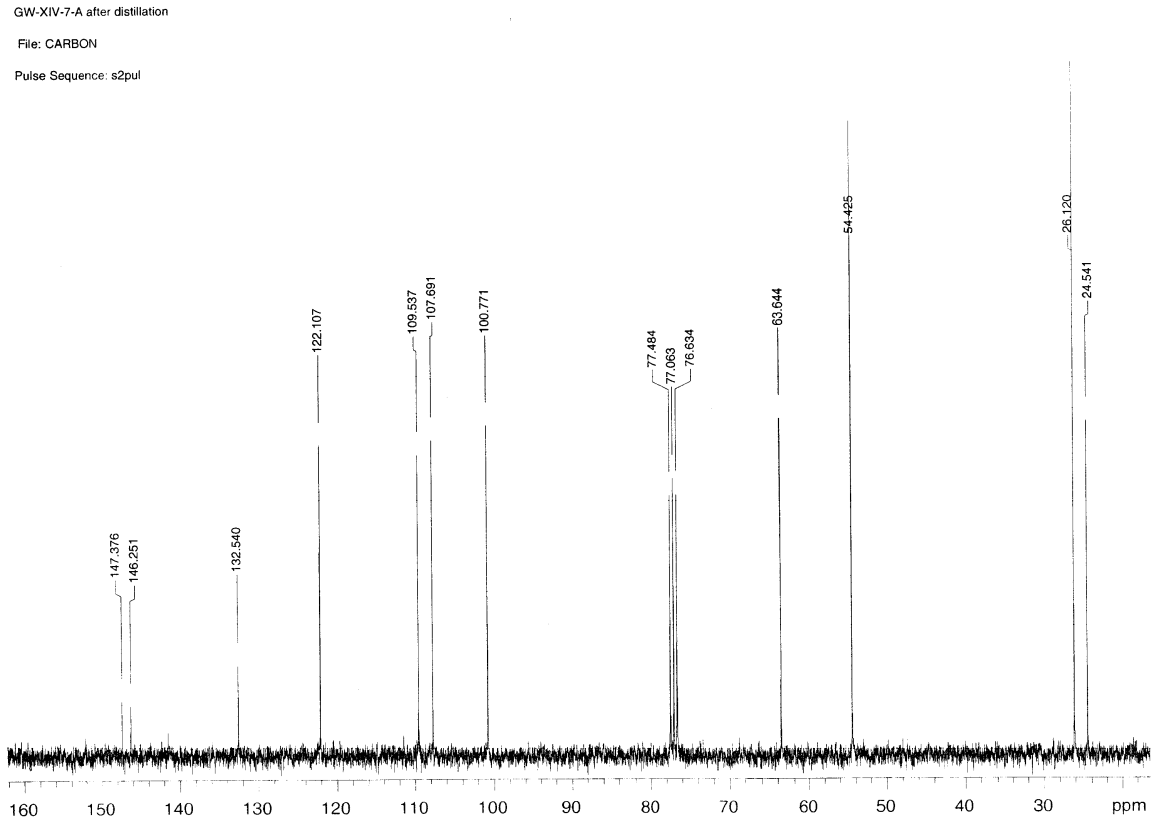
Appendix


GW-IV-35-2 hydrogenation product after destillation vial 1
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
tBu
N
2.216
1.317
7
6
5
4
3
2
ppm
2.01
2.00
2.19
9.05
4.61
9.70

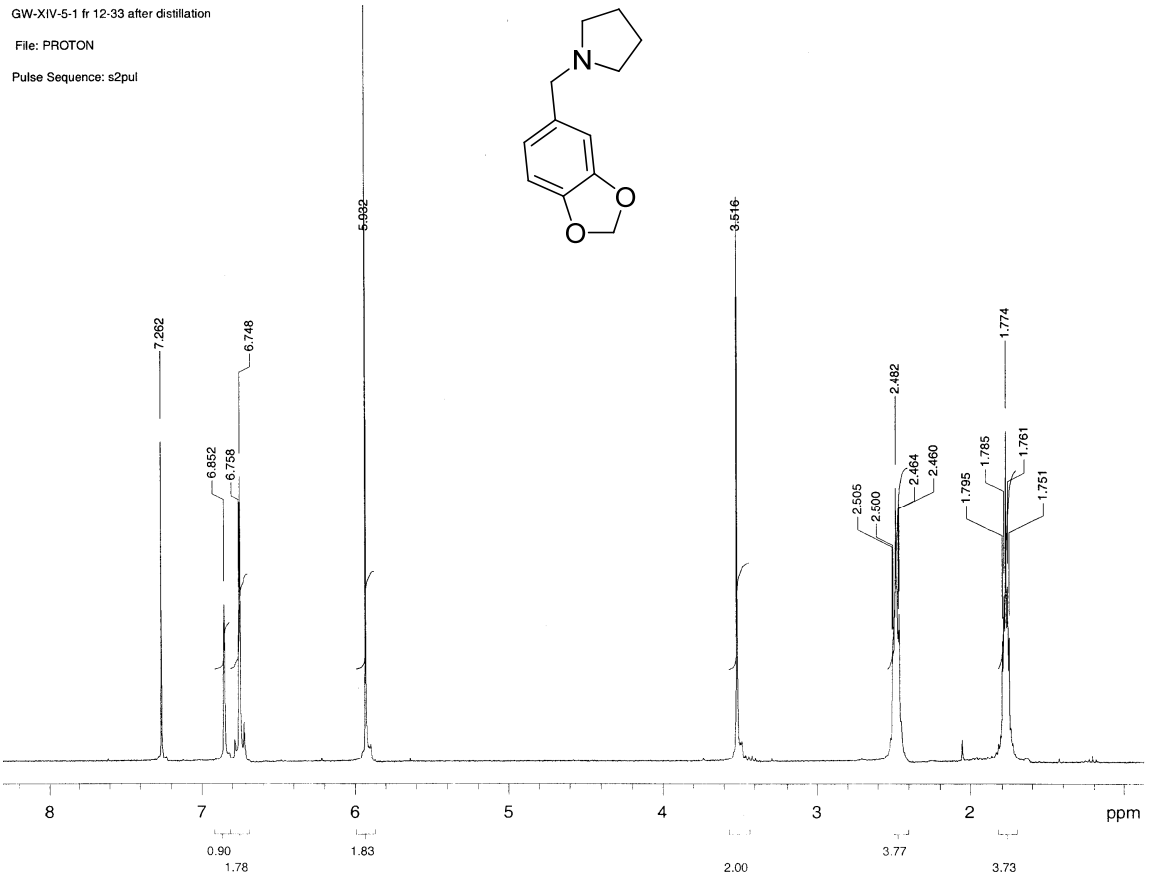

GW-IV-35-2 hydrogenation product after destillation vial 1
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
148.290
139.342
127.933
125.026
77.364
76.943
76.514
59.711
45.492
35.200
34.229
31.330
29.208
27.492
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

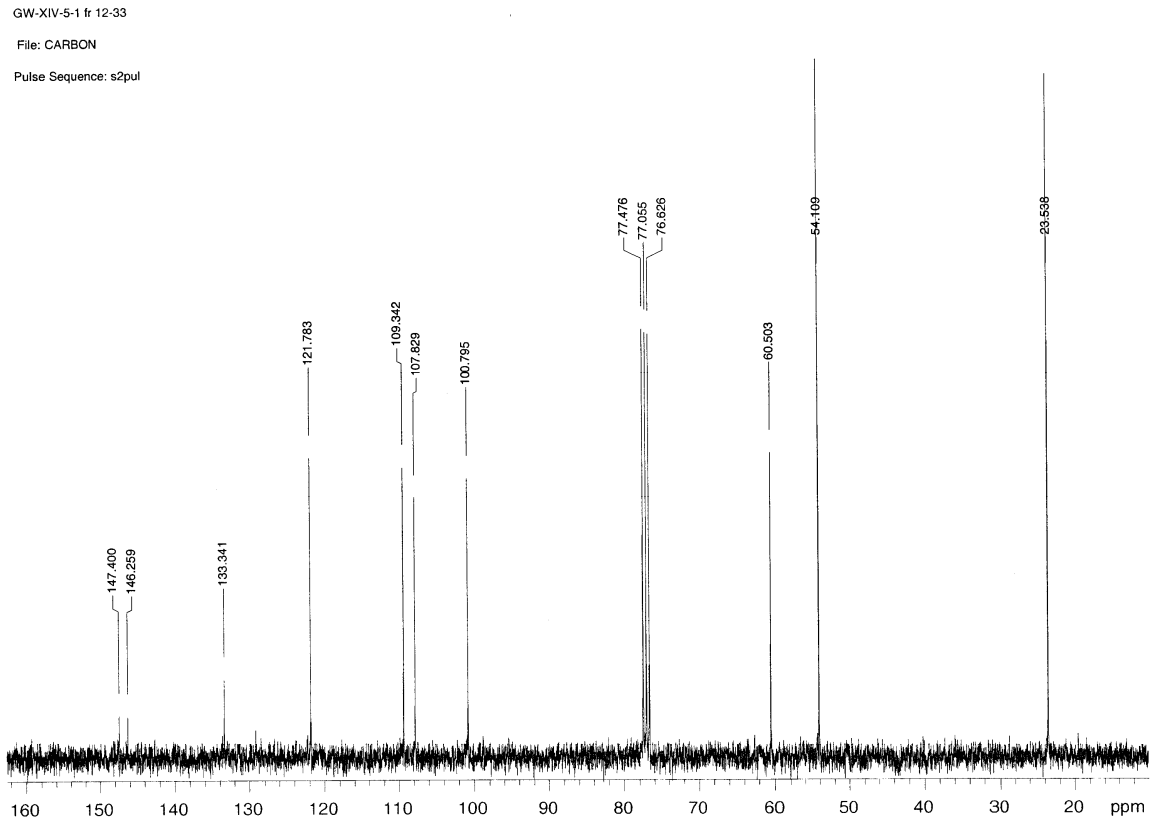
Appendix


GW-XIV-7-A after distillation
File: PROTON
Pulse Sequence: s2pul
6.734
6.731
6.926
3.371
6.850
2.348
1.561
1.543
7
6
5
4
3
2
1
ppm
1.00
1.95
2.00
2.02
3.83
1.95
4.06
0.09

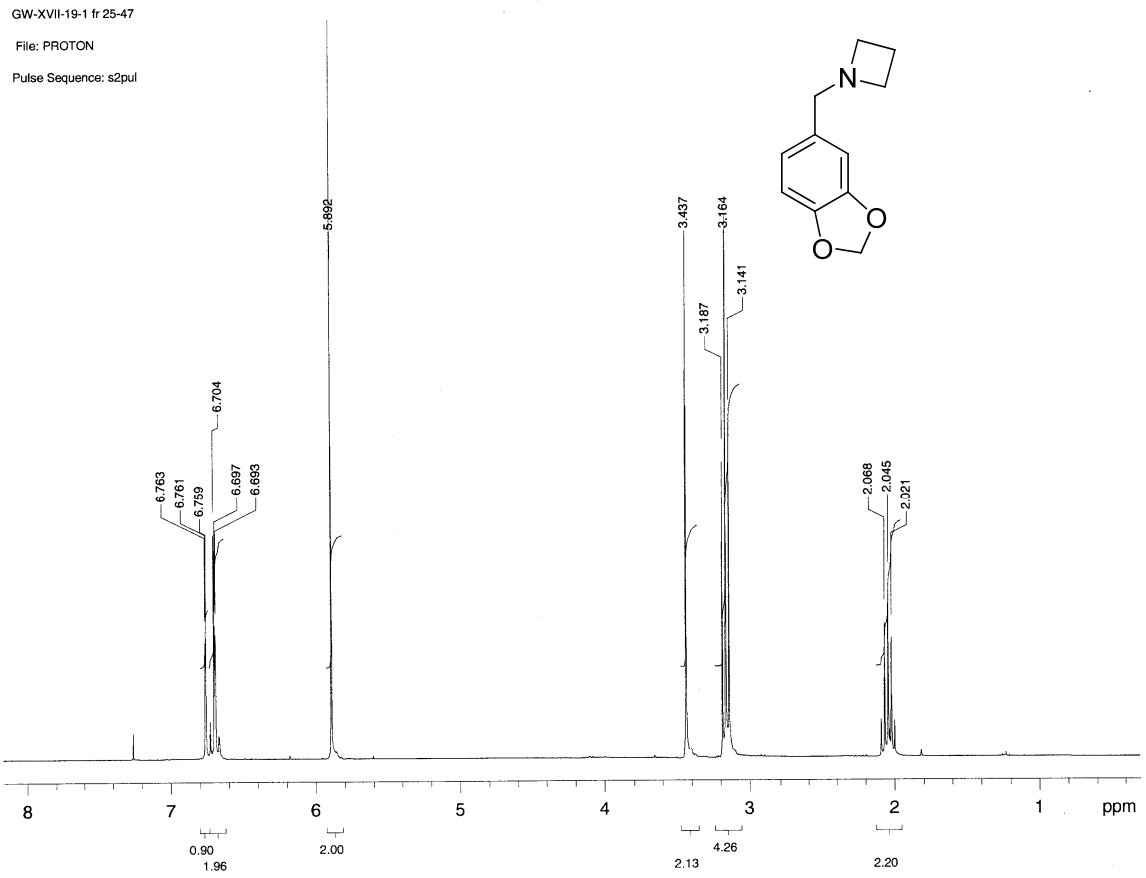

GW-XIV-7-A after distillation
File: CARBON
Pulse Sequence: s2pul
147.376
146.251
132.540
122.107
109.537
107.691
100.771
77.484
77.063
76.634
63.644
54.425
26.120
24.541
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

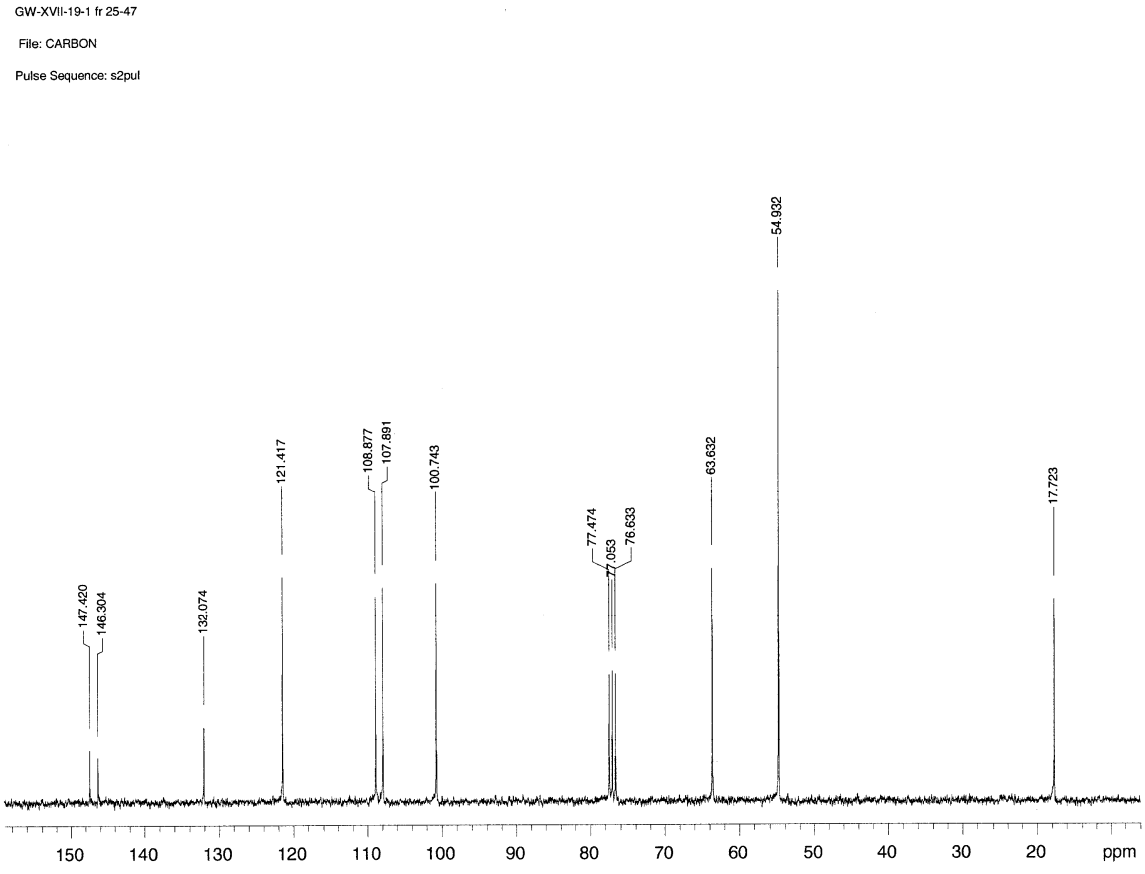
Appendix


GW-XIV-5-1 fr 12-33 after distillation
File: PROTON
Pulse Sequence: s2pul
N
O
O
7.262
6.852
6.758
6.748
5.932
3.516
2.505
2.500
2.482
2.464
2.460
1.795
1.785
1.774
1.761
1.751
8
7
6
5
4
3
2
ppm
0.90
1.78
1.83
2.00
3.77
3.73

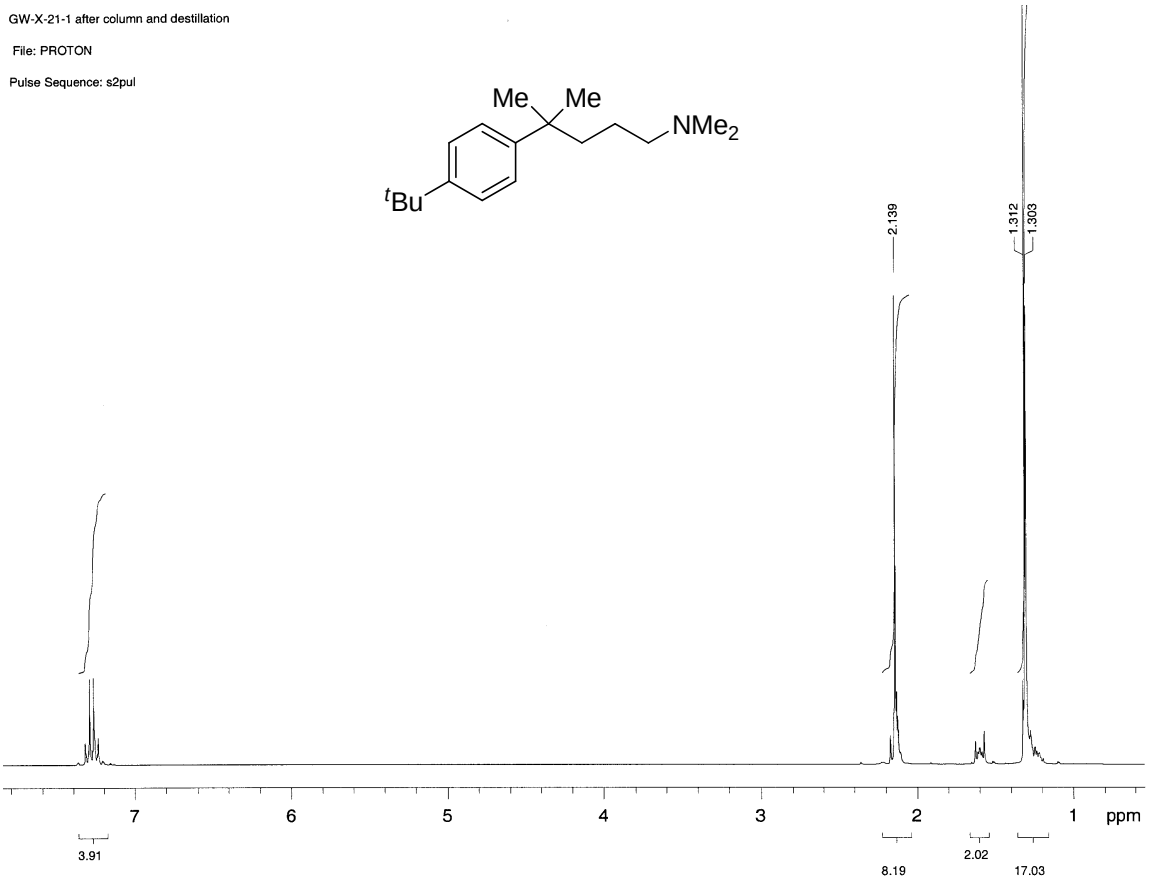

GW-XIV-5-1 fr 12-33
File: CARBON
Pulse Sequence: s2pul
147.400
146.259
133.341
121.783
109.342
107.829
100.795
77.476
77.055
76.626
60.503
54.109
28.538
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

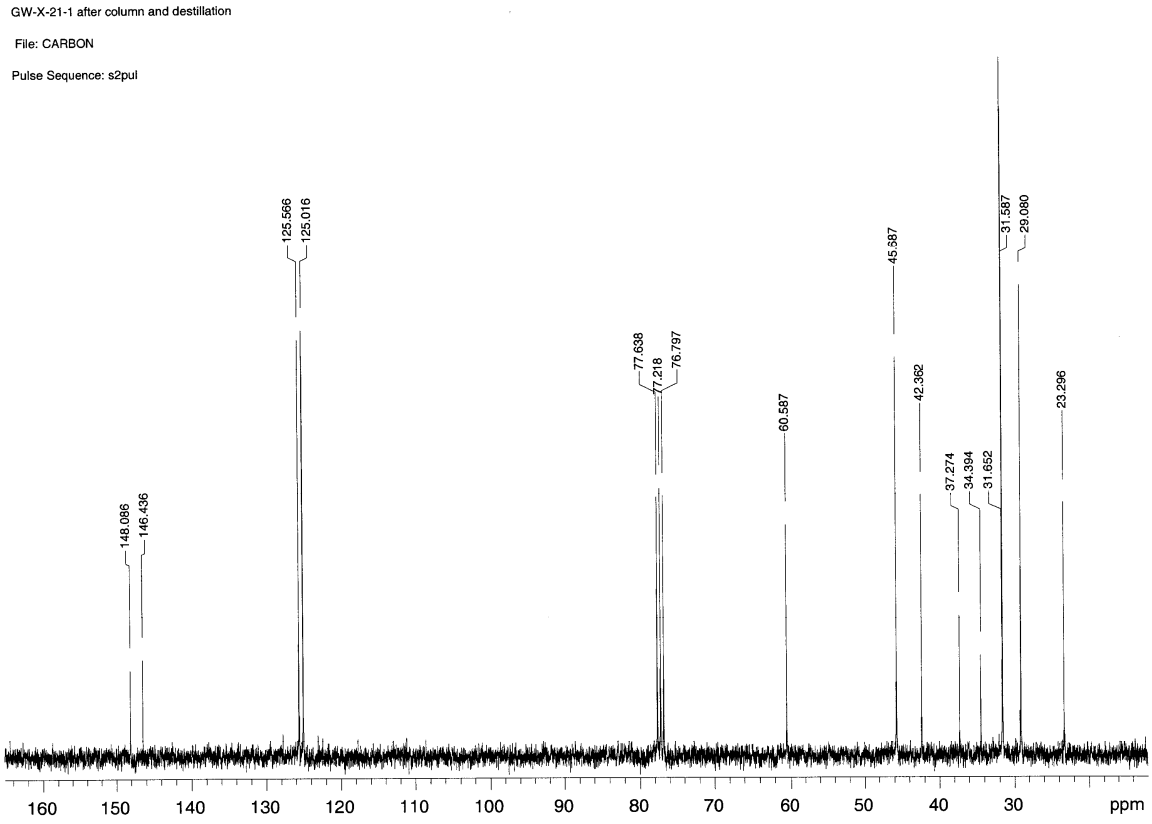
Appendix


GW-XVII-19-1 fr 25-47
File: PROTON
Pulse Sequence: s2pul
N
O
O
6.763
6.761
6.759
6.704
6.697
6.693
5.892
3.437
3.187
3.164
3.141
2.068
2.045
2.021
8
7
6
5
4
3
2
1
ppm
0.90
1.96
2.00
2.13
4.26
2.20

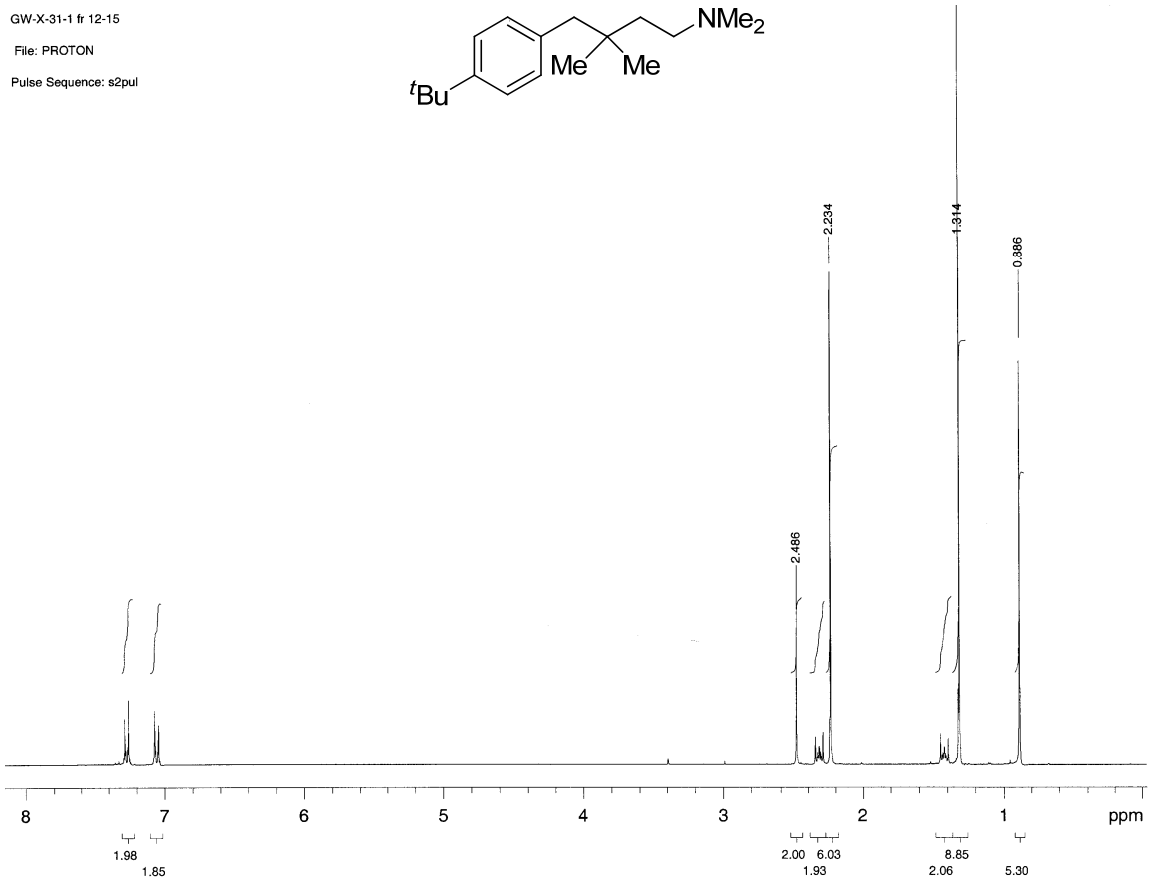

GW-XVII-19-1 fr 25-47
File: CARBON
Pulse Sequence: s2pul
147.420
146.304
132.074
121.417
108.877
107.891
100.743
77.474
77.053
76.633
63.632
54.932
17.723
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

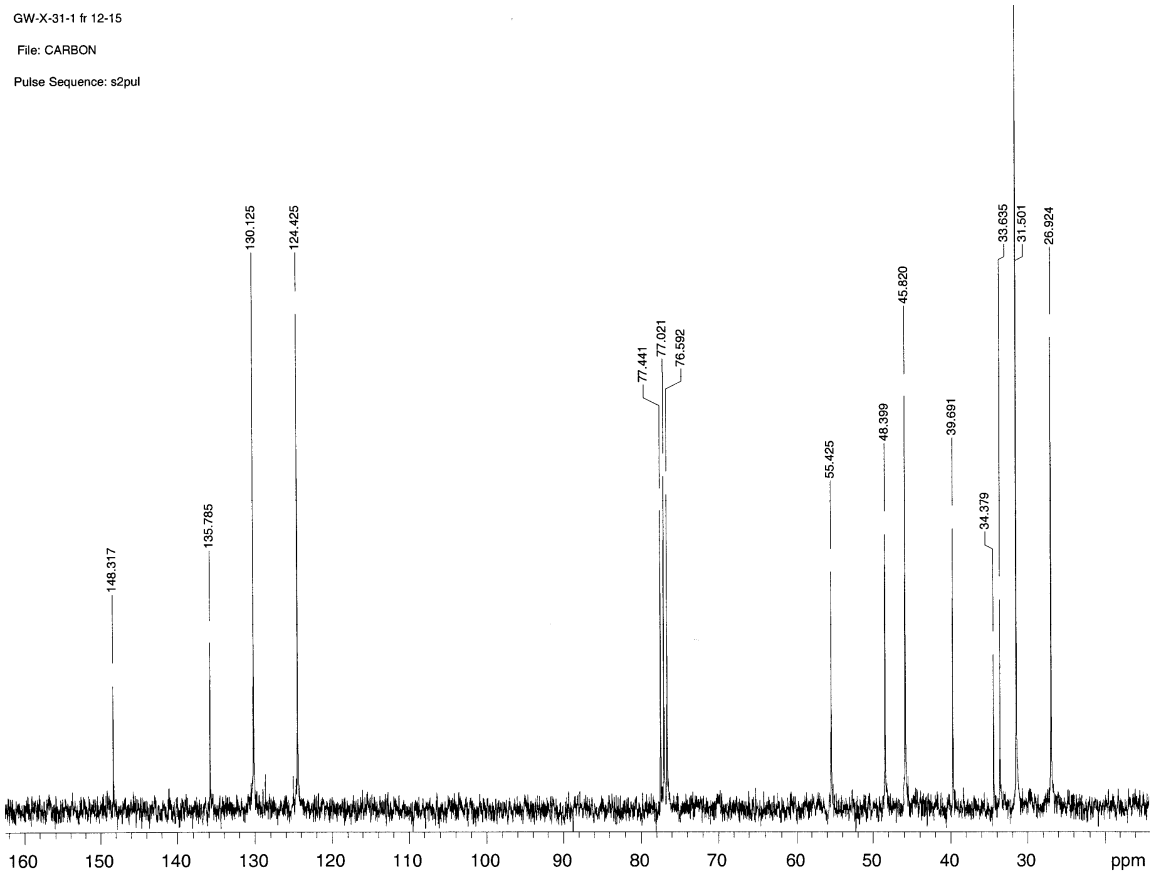
Appendix


GW-X-21-1 after column and destillation
File: PROTON
Pulse Sequence: s2pul
Me
Me
NMe2
tBu
2.139
1.312
1.303
7
6
5
4
3
2
1
ppm
3.91
8.19
2.02
17.03


GW-X-21-1 after column and destillation
File: CARBON
Pulse Sequence: s2pul
125.566
125.016
77.638
77.218
76.797
60.587
45.587
42.362
37.274
34.394
31.652
31.587
29.080
23.296
148.086
146.436
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Appendix


GW-X-31-1 fr 12-15
File: PROTON
Pulse Sequence: s2pul
NMe2
Me
Me
tBu
2.234
1.314
0.386
2.486
8
7
6
5
4
3
2
1
ppm
1.98
1.85
2.00
6.03
1.93
8.85
2.06
5.30


GW-X-31-1 fr 12-15
File: CARBON
Pulse Sequence: s2pul
130.125
124.425
77.441
77.021
76.592
45.820
33.635
31.501
26.924
48.399
39.691
55.425
34.379
148.317
135.785
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

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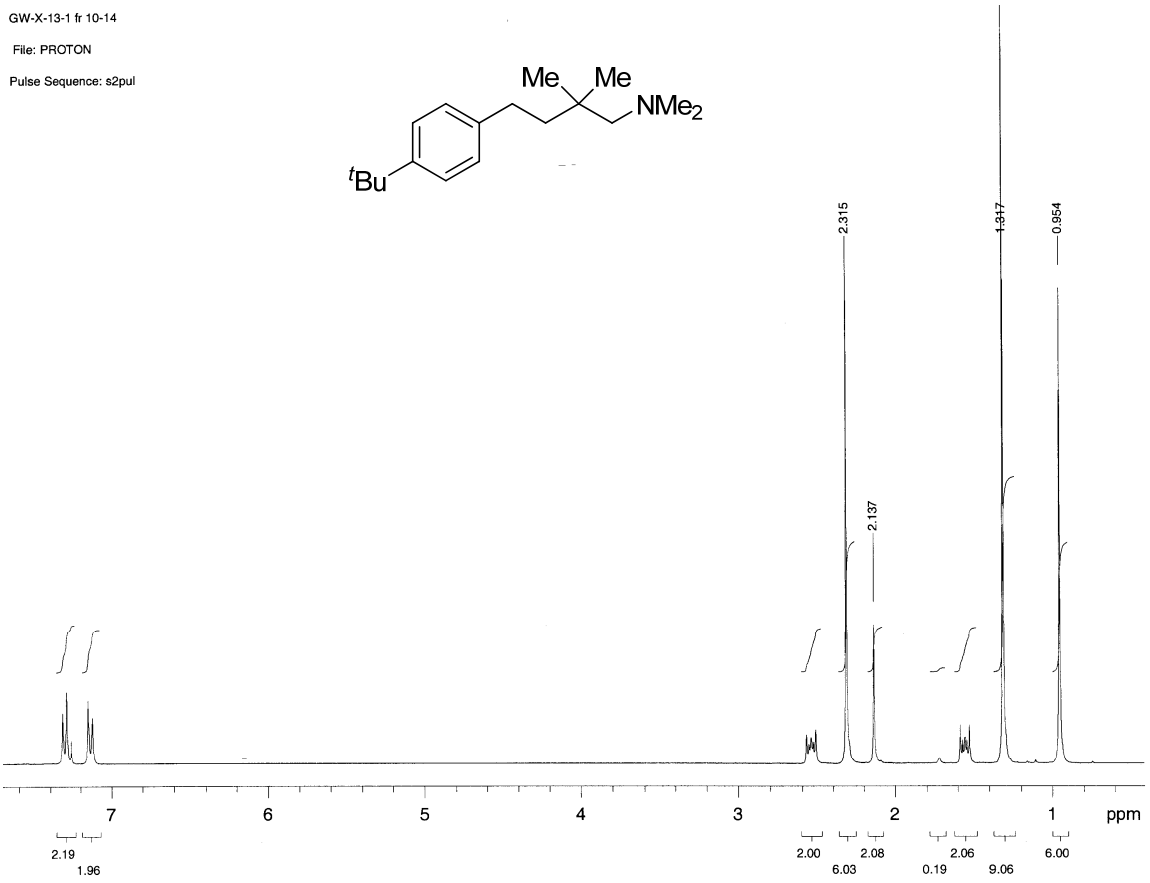
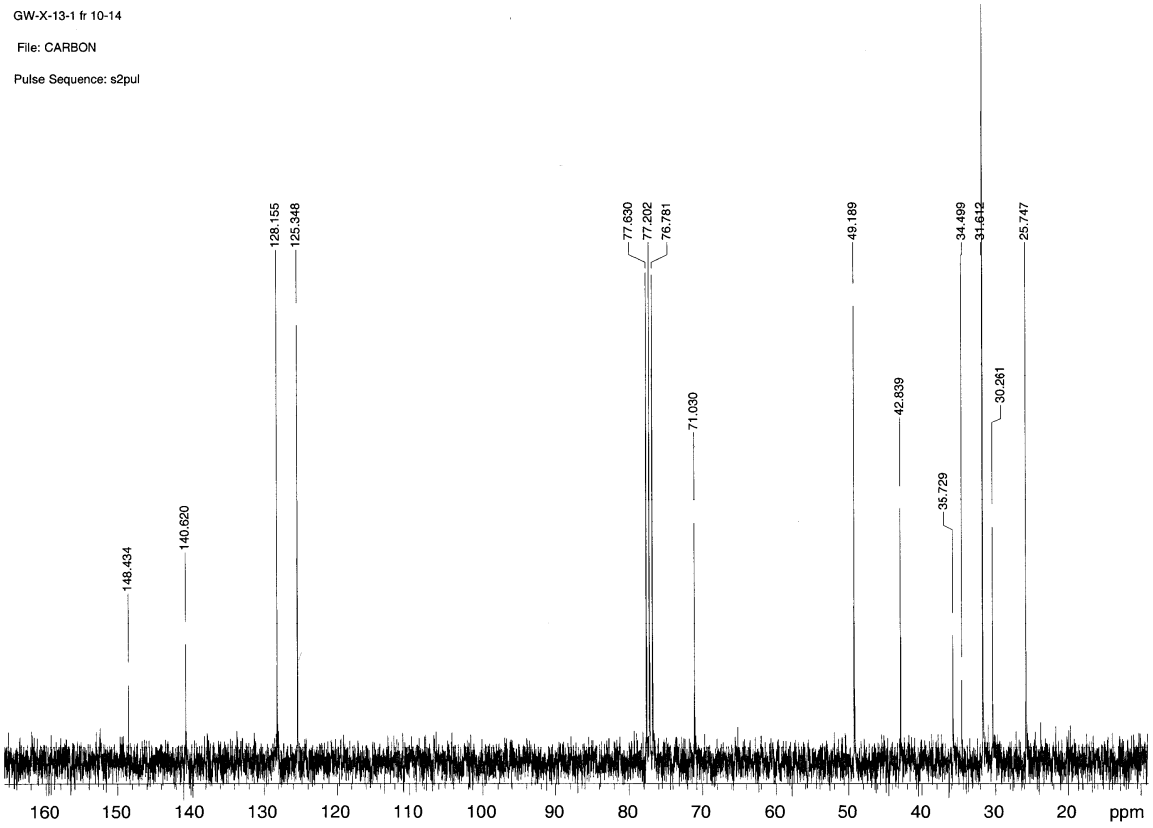
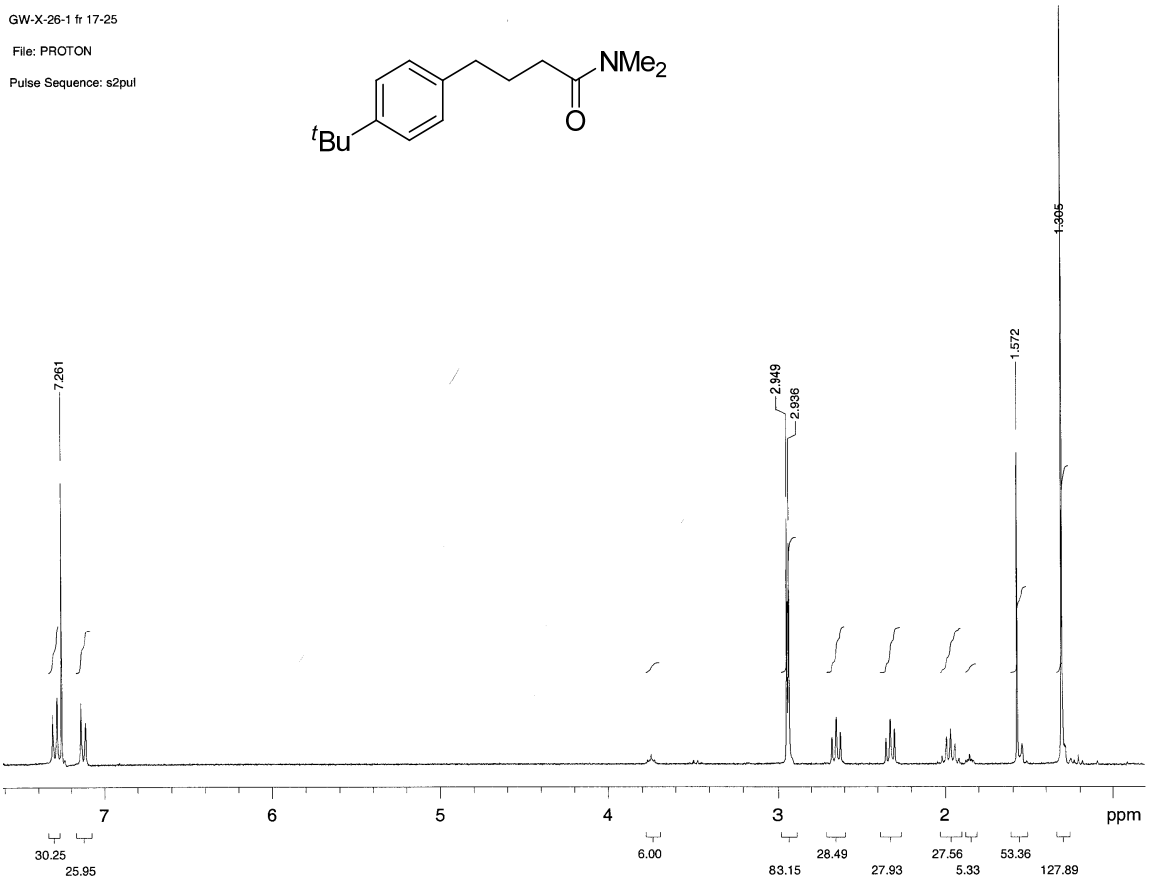
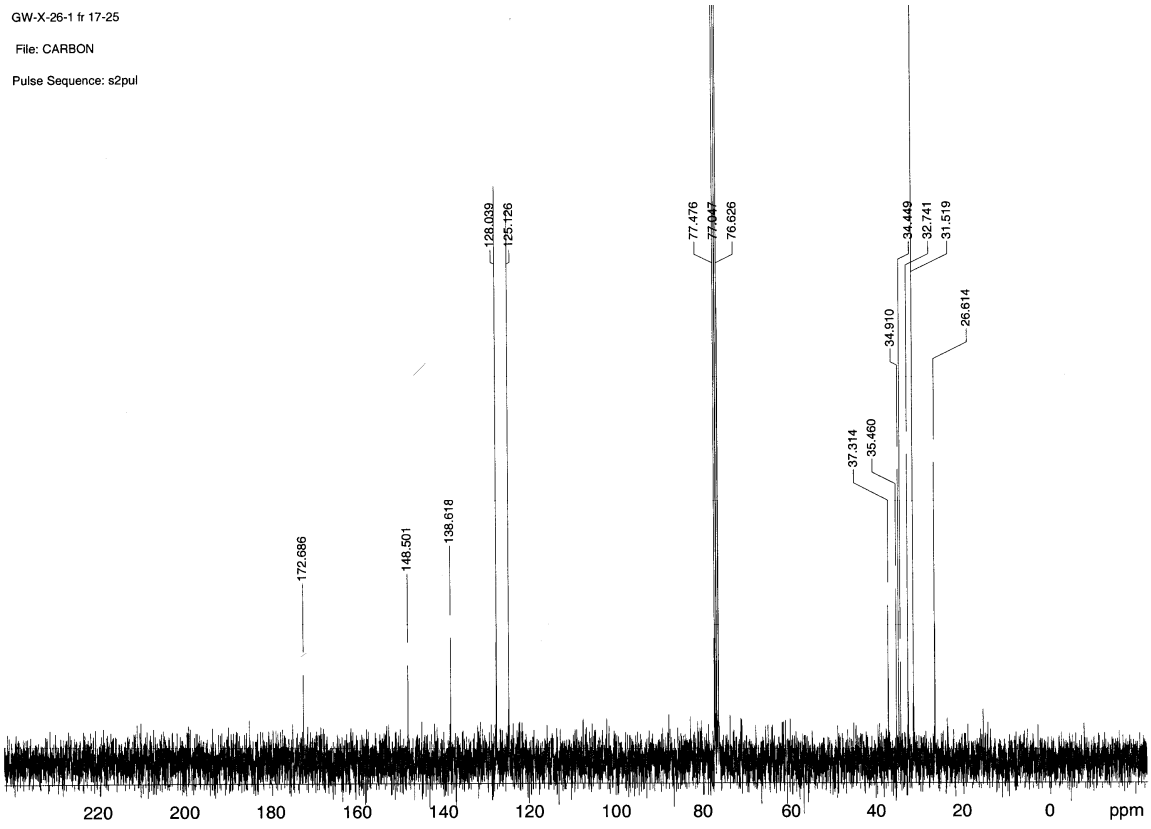

GW-X-13-1 fr 10-14
File: PROTON
Pulse Sequence: s2pul
Me
Me
NMe2
tBu
2.315
2.137
1.317
0.954
7
6
5
4
3
2
1
ppm
2.19
1.96
2.00
6.03
2.08
2.06
0.19
9.06
6.00


GW-X-13-1 fr 10-14
File: CARBON
Pulse Sequence: s2pul
148.434
140.620
128.155
125.348
77.630
77.202
76.781
71.030
49.189
42.839
35.729
34.499
31.612
30.261
25.747
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Appendix


GW-X-26-1 fr 17-25
File: PROTON
Pulse Sequence: s2pul
NMe2
O
tBu
7.261
2.949
2.936
1.572
1.305
7
6
5
4
3
2
ppm
30.25
25.95
6.00
83.15
28.49
27.93
27.56
5.33
53.36
127.89


GW-X-26-1 fr 17-25
File: CARBON
Pulse Sequence: s2pul
128.039
125.126
77.476
77.047
76.626
34.449
32.741
31.519
34.910
26.614
37.314
35.460
172.686
148.501
138.618
220
200
180
160
140
120
100
80
60
40
20
0
ppm

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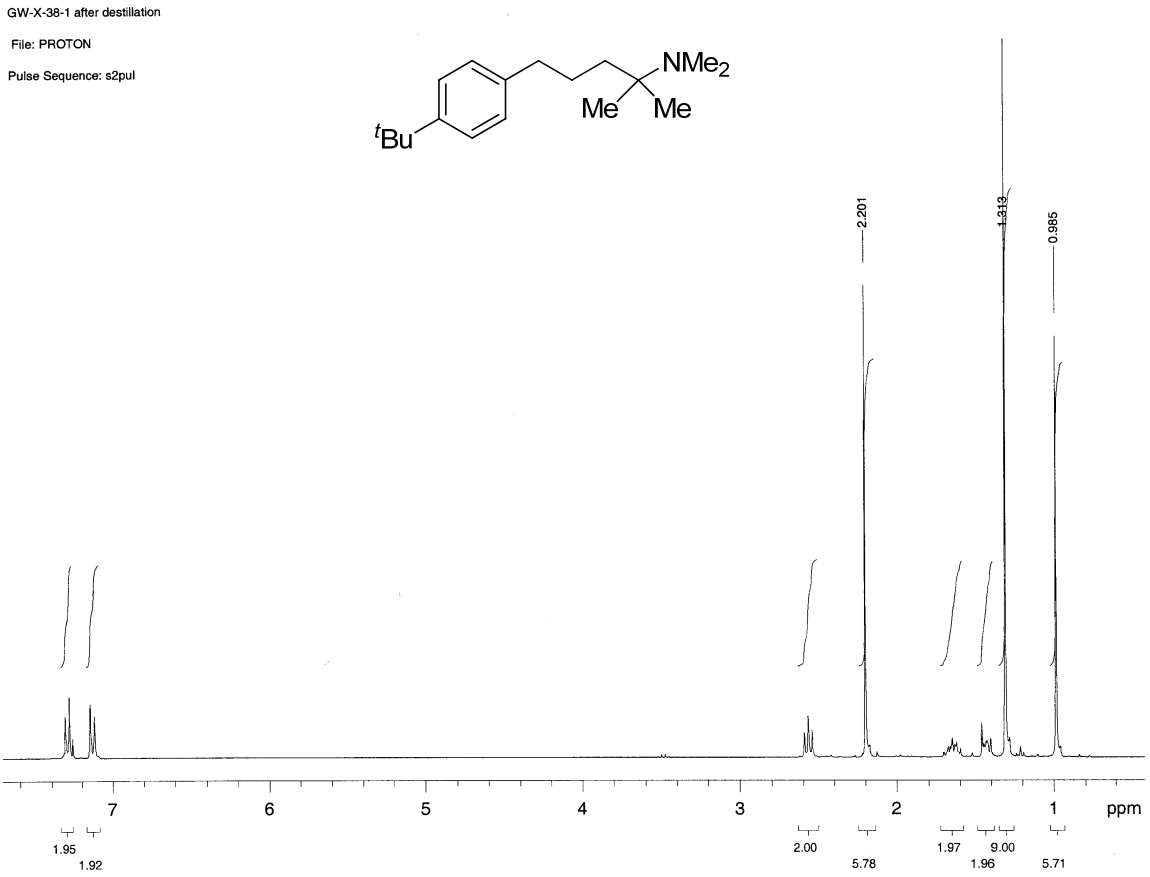
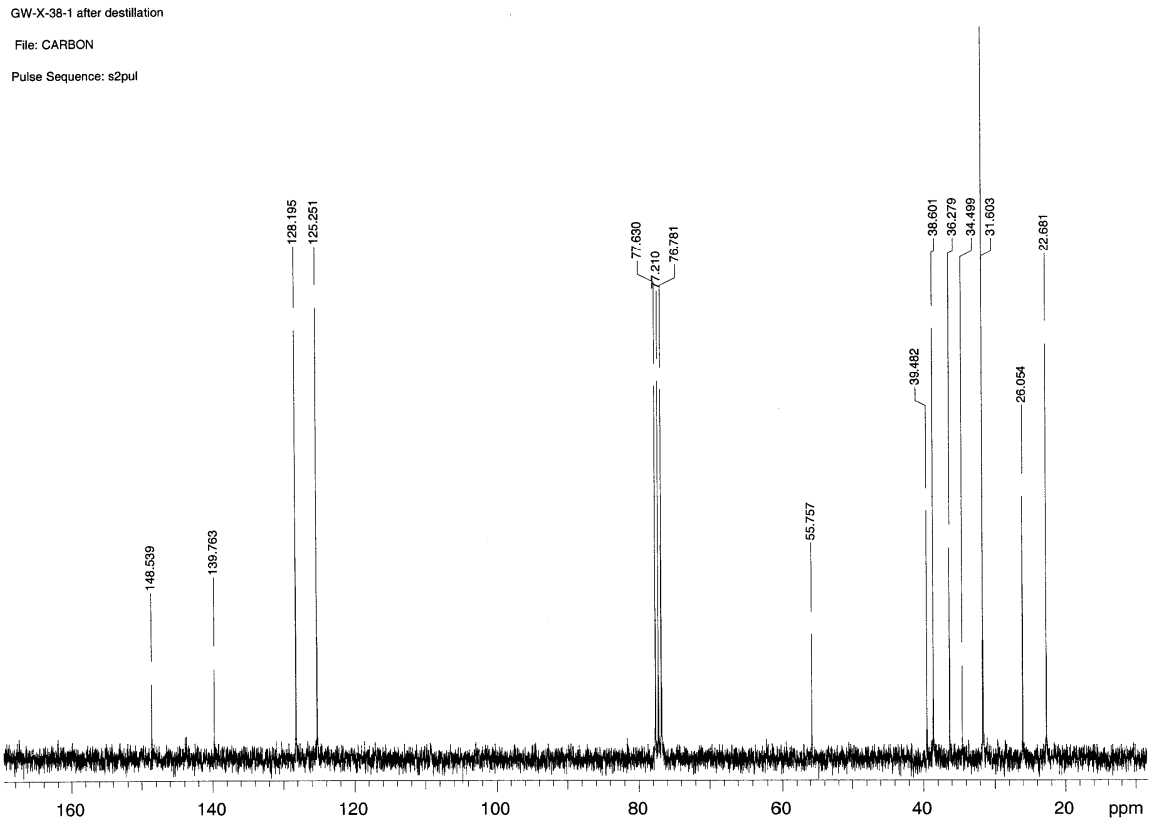
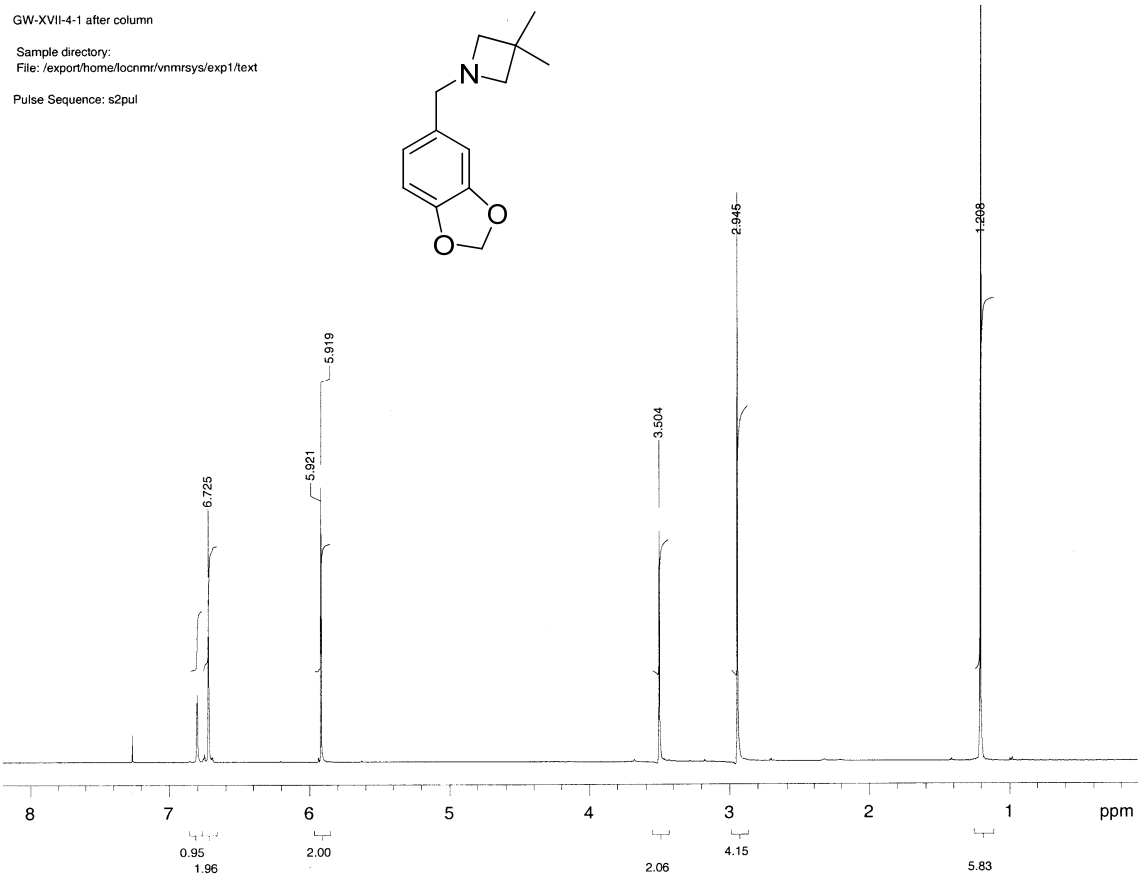
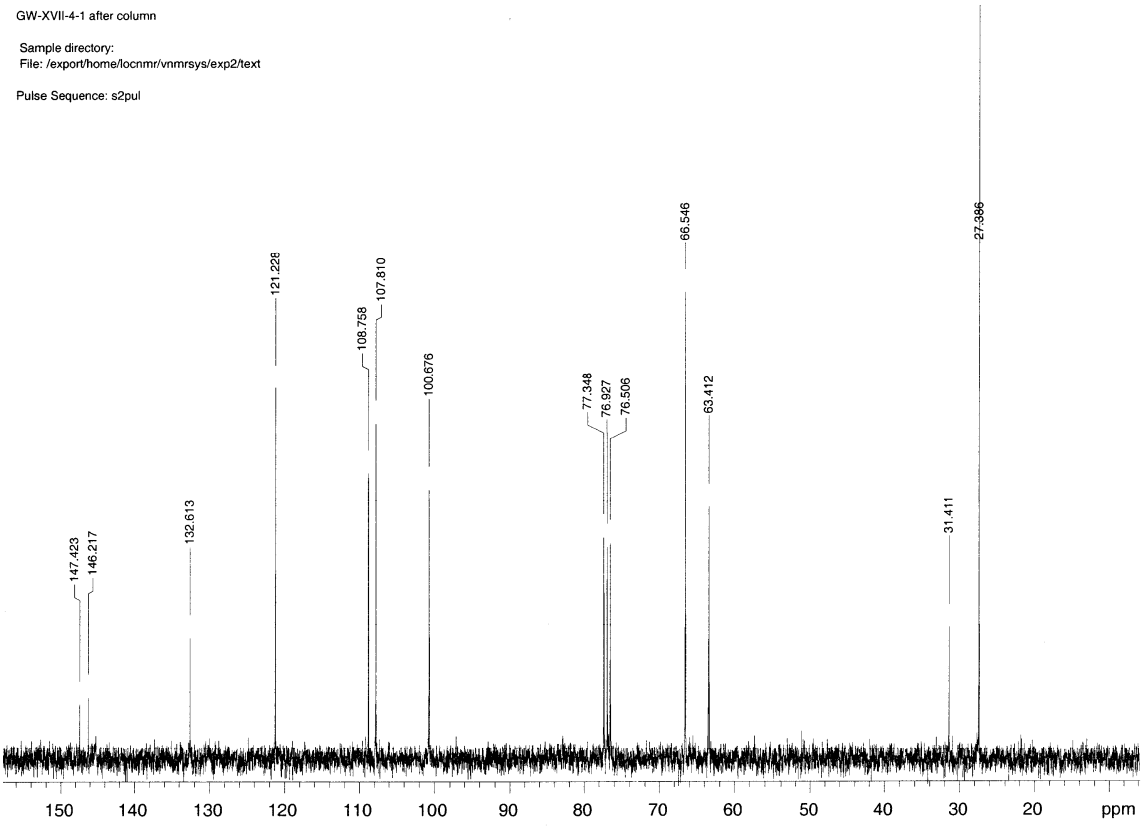

GW-X-38-1 after destillation
File: PROTON
Pulse Sequence: s2pul
NMe2
Me
Me
tBu
2.201
1.313
0.985
7
6
5
4
3
2
1
ppm
1.95
1.92
2.00
5.78
1.97
9.00
1.96
5.71

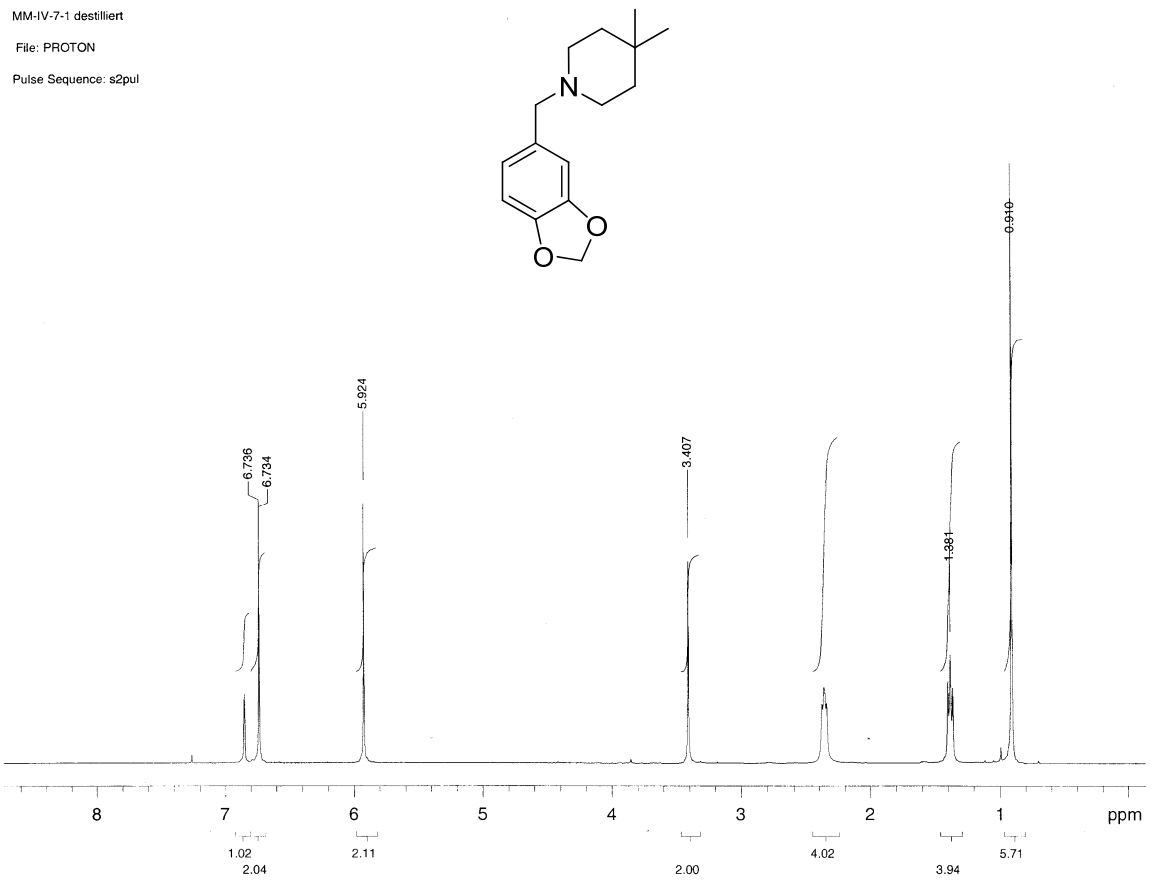

GW-X-38-1 after destillation
File: CARBON
Pulse Sequence: s2pul
148.539
139.763
128.195
125.251
77.630
77.210
76.781
55.757
39.482
38.601
36.279
34.499
31.603
26.054
22.681
160
140
120
100
80
60
40
20
ppm

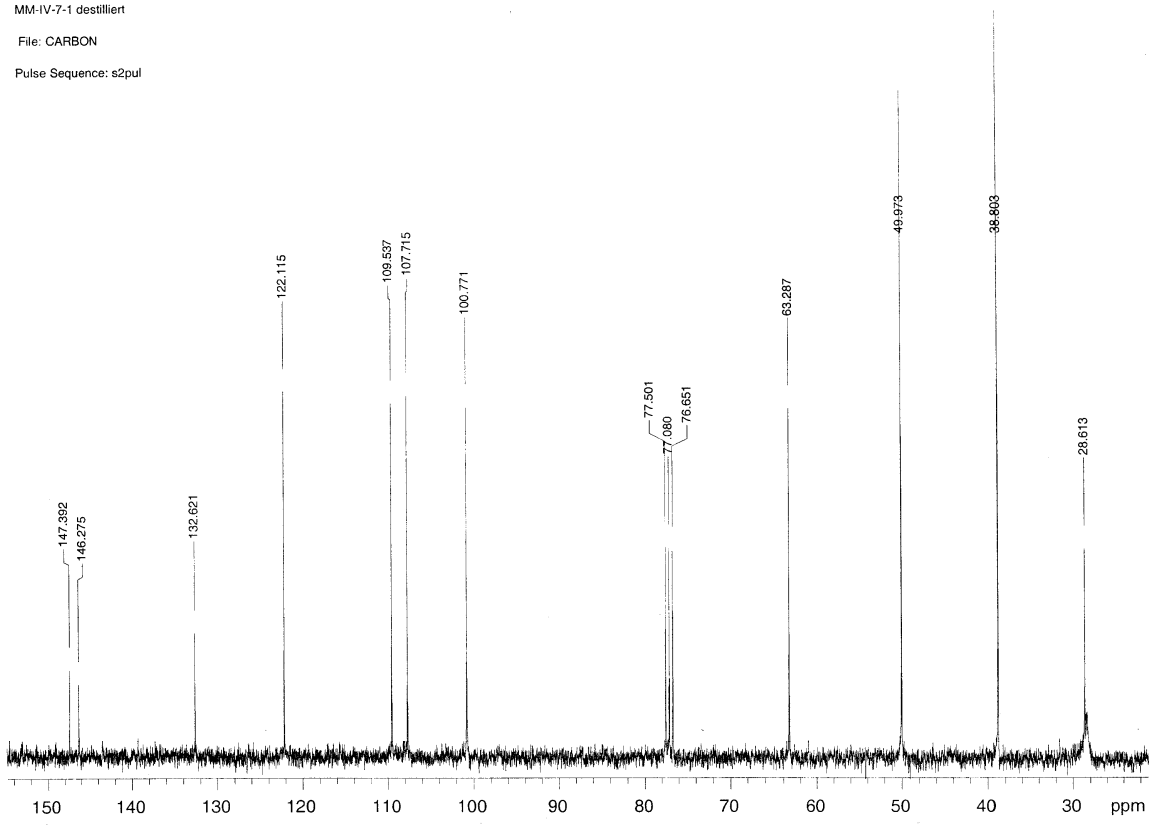
Appendix


GW-XVII-4-1 after column
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
N
O
O
6.725
5.921
5.919
3.504
2.945
1.208
8
7
6
5
4
3
2
1
ppm
0.95
1.96
2.00
2.06
4.15
5.83


GW-XVII-4-1 after column
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
147.423
146.217
132.613
121.228
108.758
107.810
100.676
77.348
76.927
76.506
66.546
63.412
31.411
27.386
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Appendix


MM-IV-7-1 destilliert
File: PROTON
Pulse Sequence: s2pul
N
O
O
6.736
6.734
5.924
3.407
1.381
0.910
8
7
6
5
4
3
2
1
ppm
1.02
2.04
2.11
2.00
4.02
3.94
5.71


MM-IV-7-1 destilliert
File: CARBON
Pulse Sequence: s2pul
147.392
146.275
132.621
122.115
109.537
107.715
100.771
77.501
77.080
76.651
63.287
49.973
38.803
28.613
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

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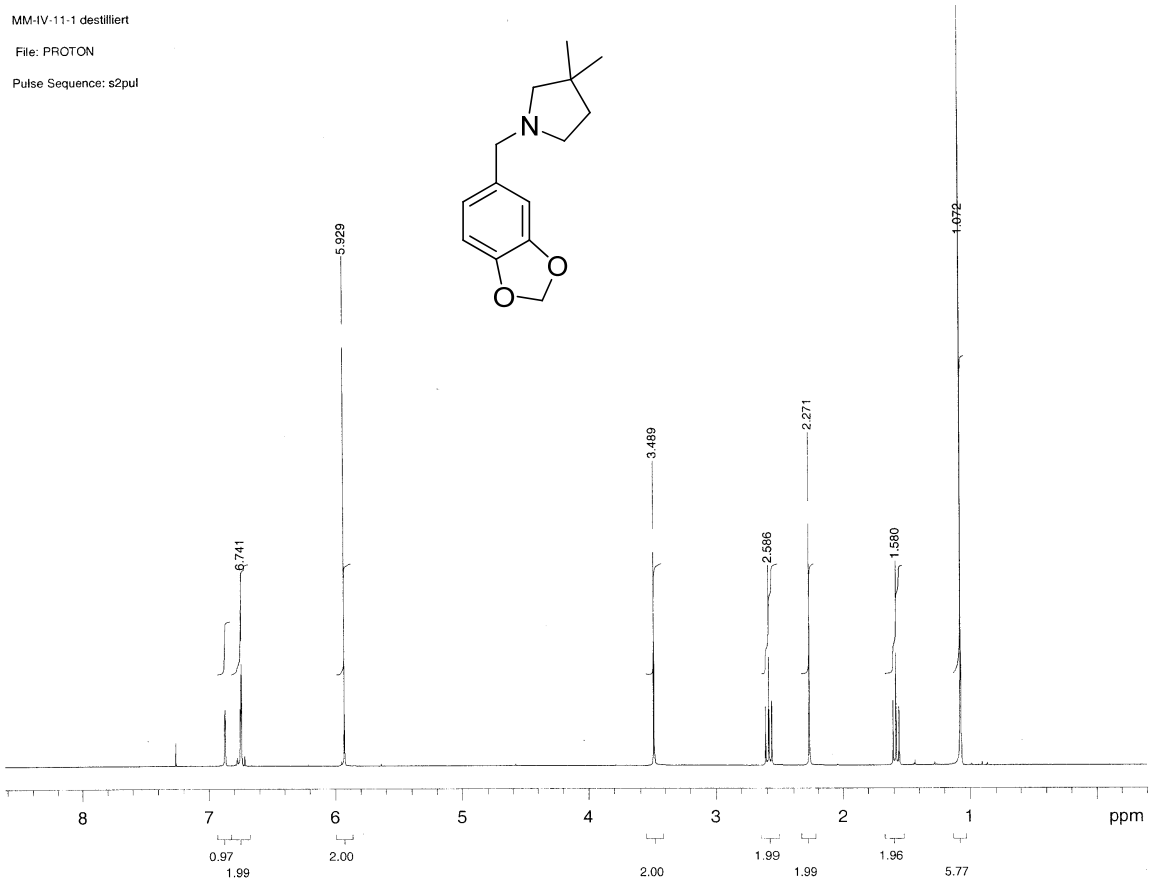
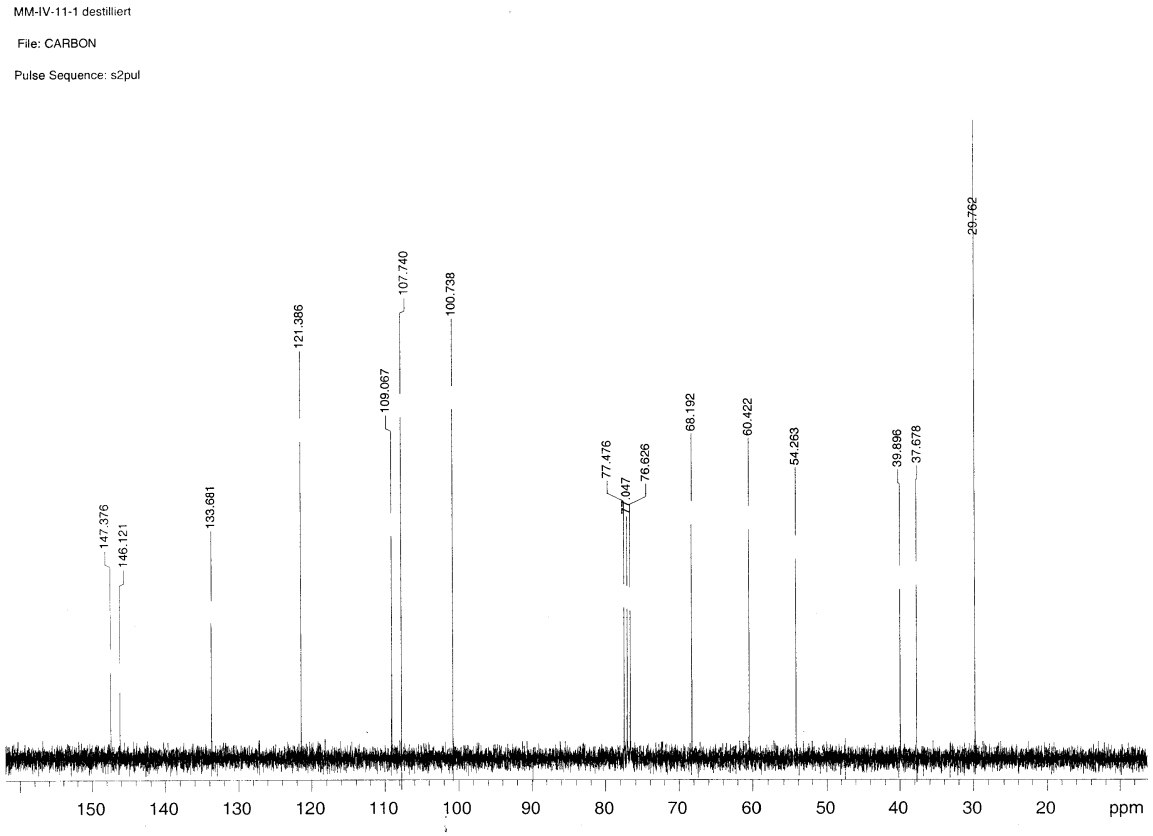

MM-IV-11-1 destilliert
File: PROTON
Pulse Sequence: s2pul
N
O
O
6.741
5.929
3.489
2.586
2.271
1.580
1.072
8
7
6
5
4
3
2
1
ppm
0.97
1.99
2.00
2.00
1.99
1.99
1.96
5.77


MM-IV-11-1 destilliert
File: CARBON
Pulse Sequence: s2pul
147.376
146.121
133.681
121.386
109.067
107.740
100.738
77.476
77.047
76.626
68.192
60.422
54.263
39.896
37.678
29.762
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

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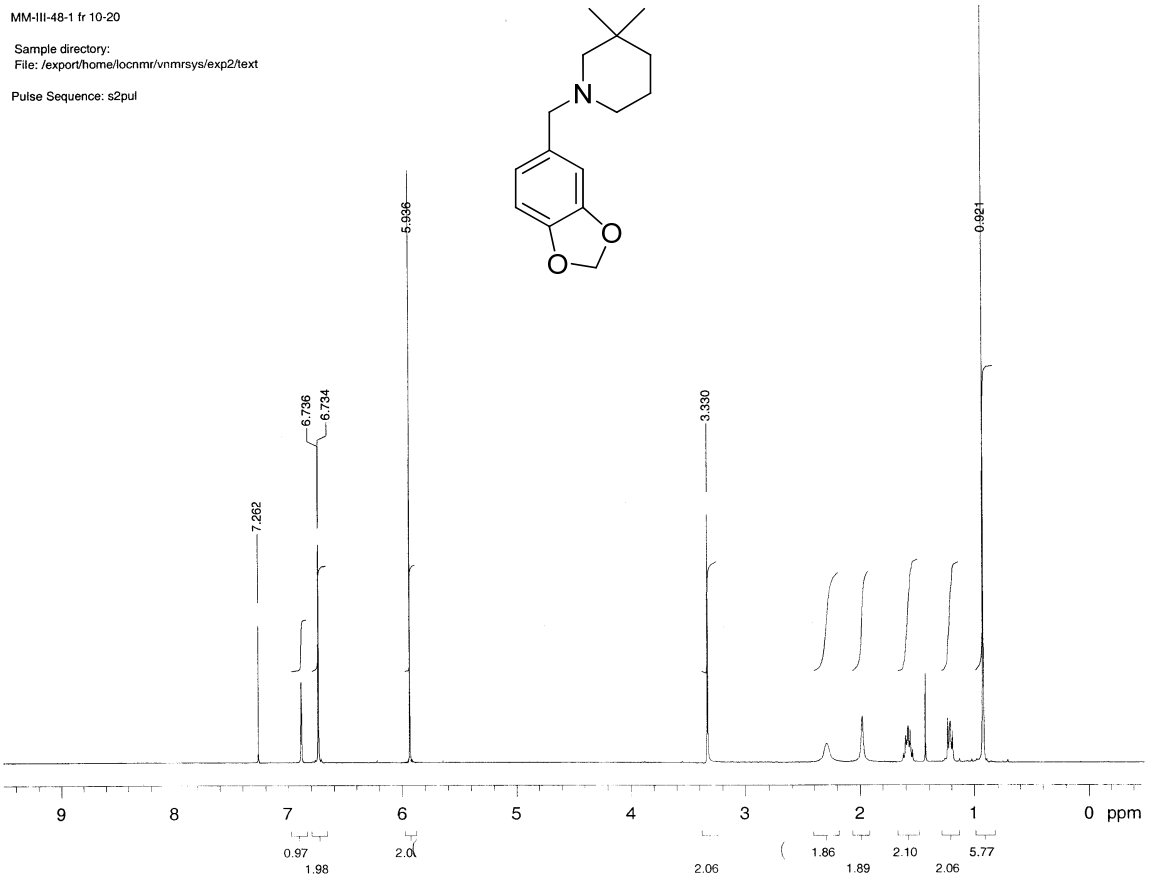
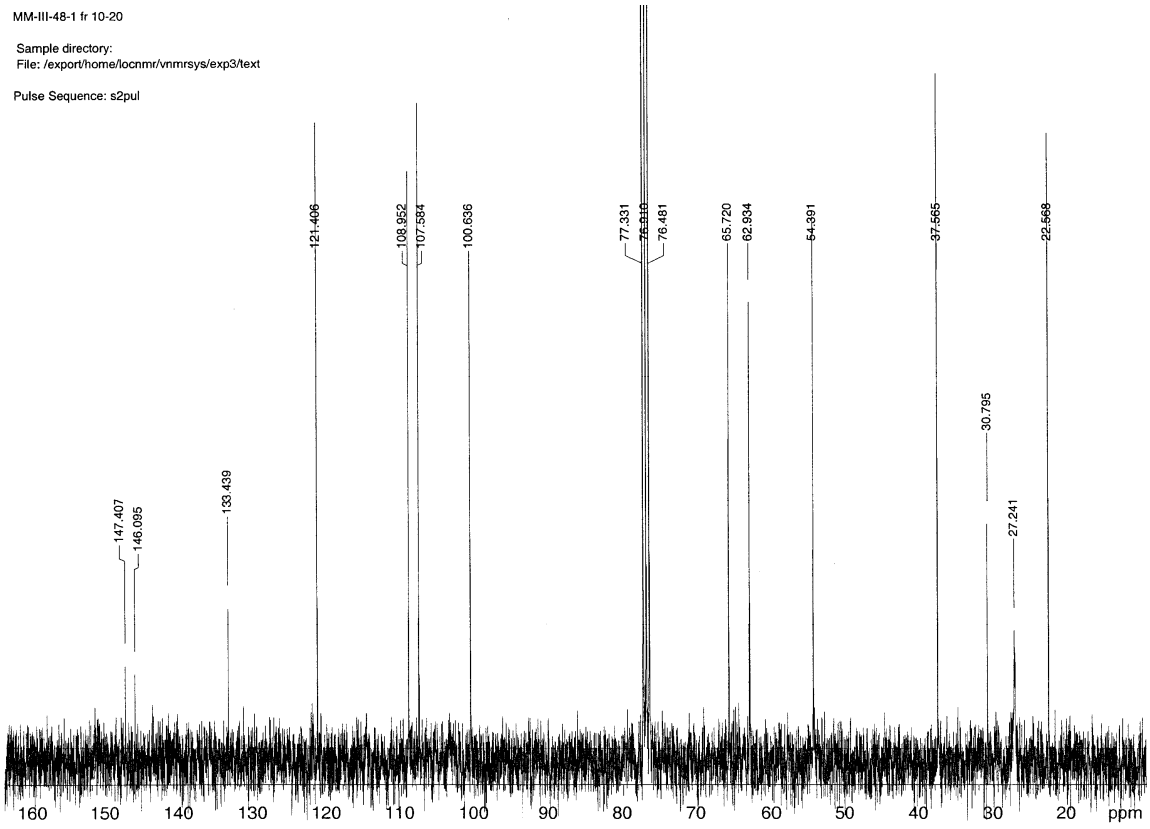

MM-III-48-1 fr 10-20
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
N
O
O
7.262
6.736
6.734
5.936
3.330
0.921
9
8
7
6
5
4
3
2
1
0 ppm
0.97
1.98
2.0
2.06
1.86
1.89
2.10
2.06
5.77


MM-III-48-1 fr 10-20
Sample directory:
File: /export/home/locnmr/vnmrsys/exp3/text
Pulse Sequence: s2pul
147.407
146.095
133.439
121.406
108.952
107.584
100.636
77.331
76.810
76.481
65.720
62.934
54.391
37.565
30.795
27.241
22.568
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

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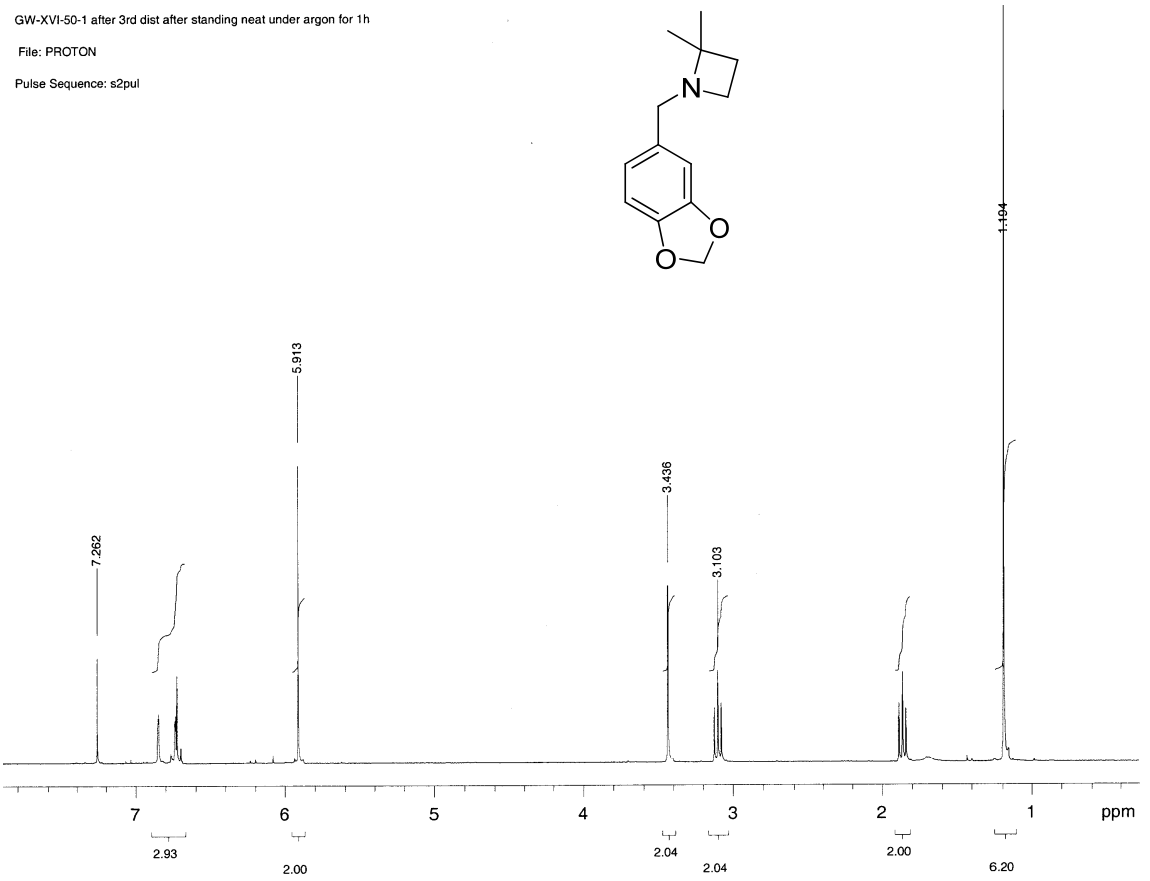
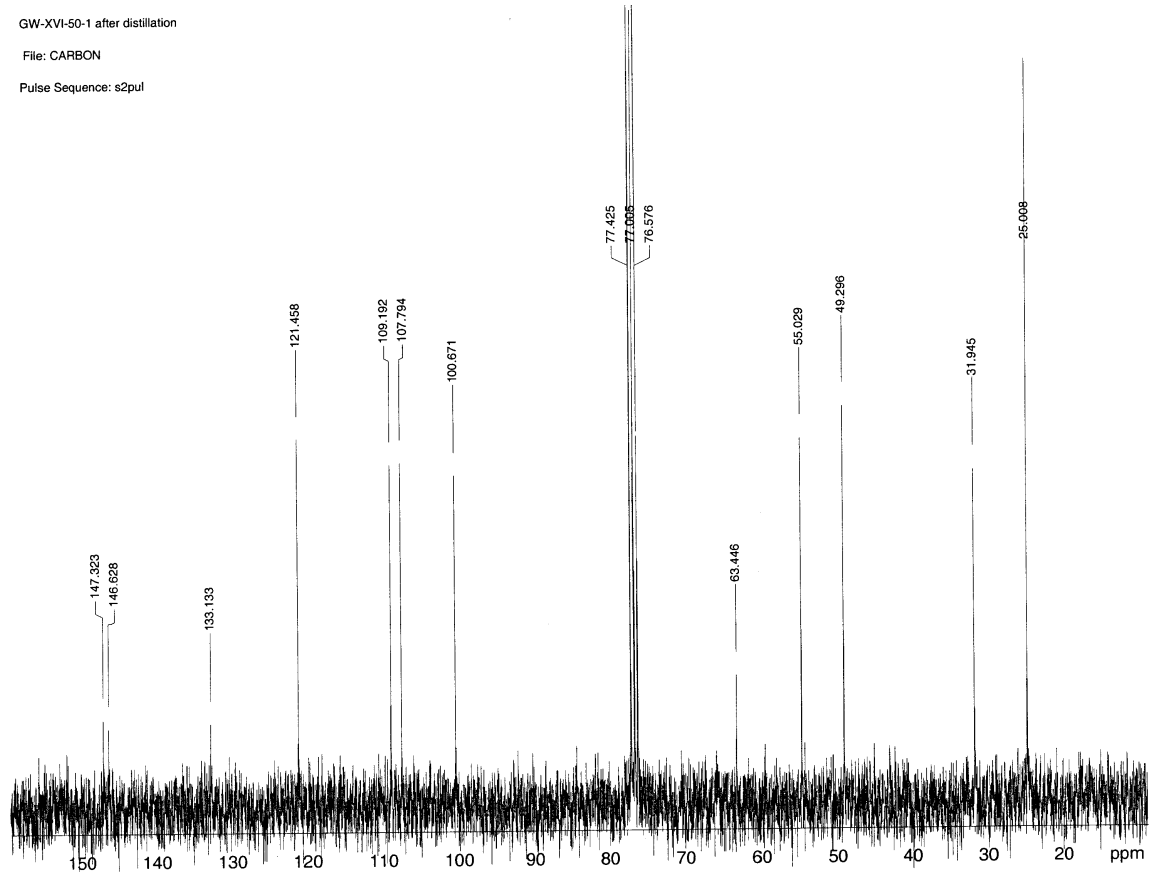

GW-XVI-50-1 after 3rd dist after standing neat under argon for 1h
File: PROTON
Pulse Sequence: s2pul
N
O
O
7.262
5.913
3.436
3.103
1.194
7
6
5
4
3
2
1
ppm
2.93
2.00
2.04
2.04
2.00
6.20


GW-XVI-50-1 after distillation
File: CARBON
Pulse Sequence: s2pul
147.323
146.628
133.133
121.458
109.192
107.794
100.671
77.425
77.005
76.576
63.446
55.029
49.296
31.945
25.008
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

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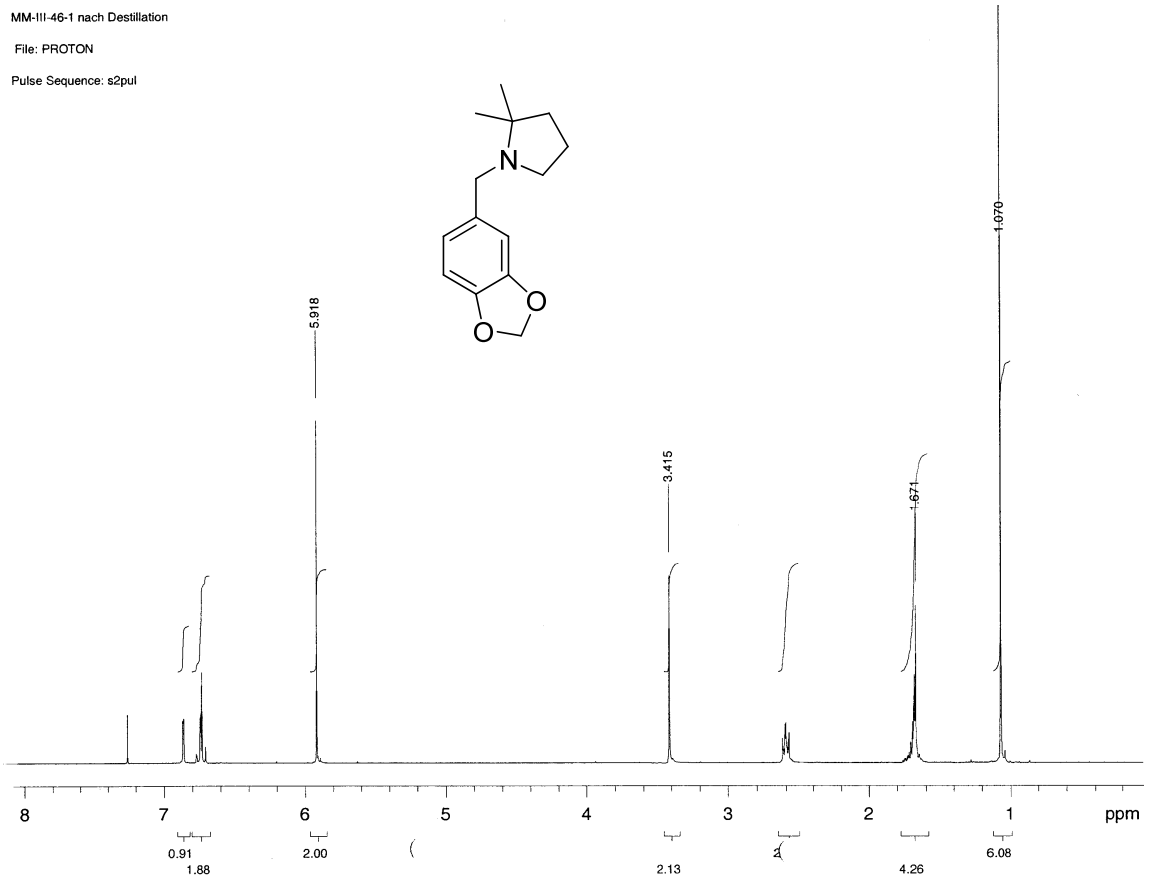
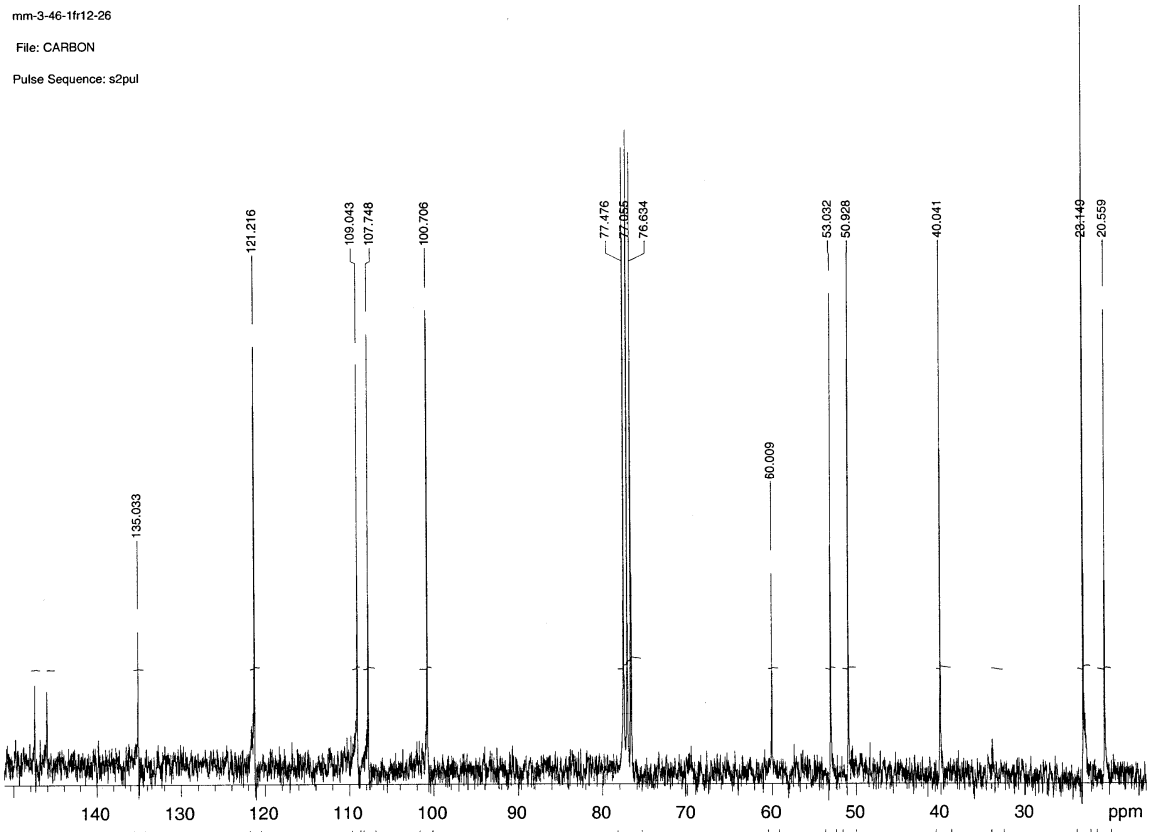

MM-III-46-1 nach Destillation
File: PROTON
Pulse Sequence: s2pul
N
O
O
5.918
3.415
1.671
1.670
8
7
6
5
4
3
2
1
ppm
0.91
1.88
2.00
2.13
4.26
6.08


mm-3-46-1fr12-26
File: CARBON
Pulse Sequence: s2pul
135.033
121.216
109.043
107.748
100.706
77.476
77.055
76.634
60.009
53.032
50.928
40.041
28.149
20.559
140
130
120
110
100
90
80
70
60
50
40
30
ppm

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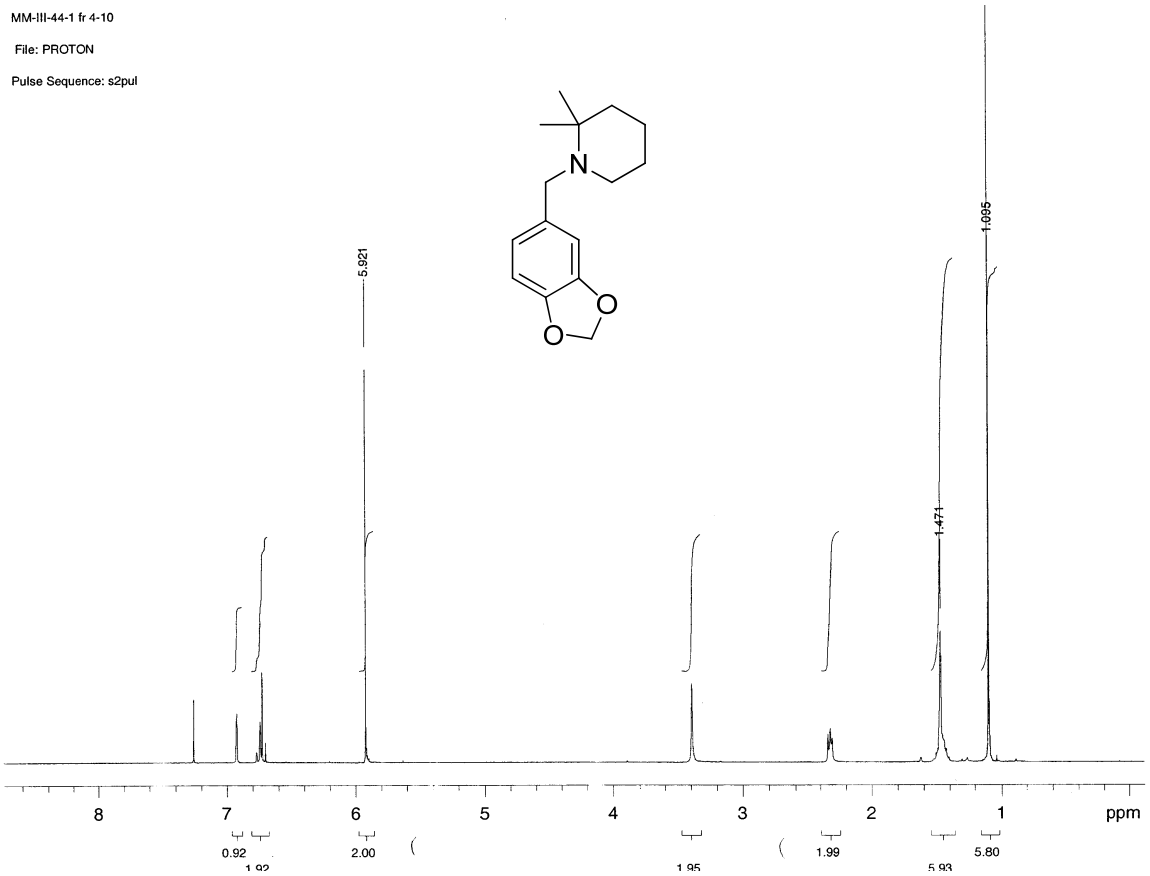
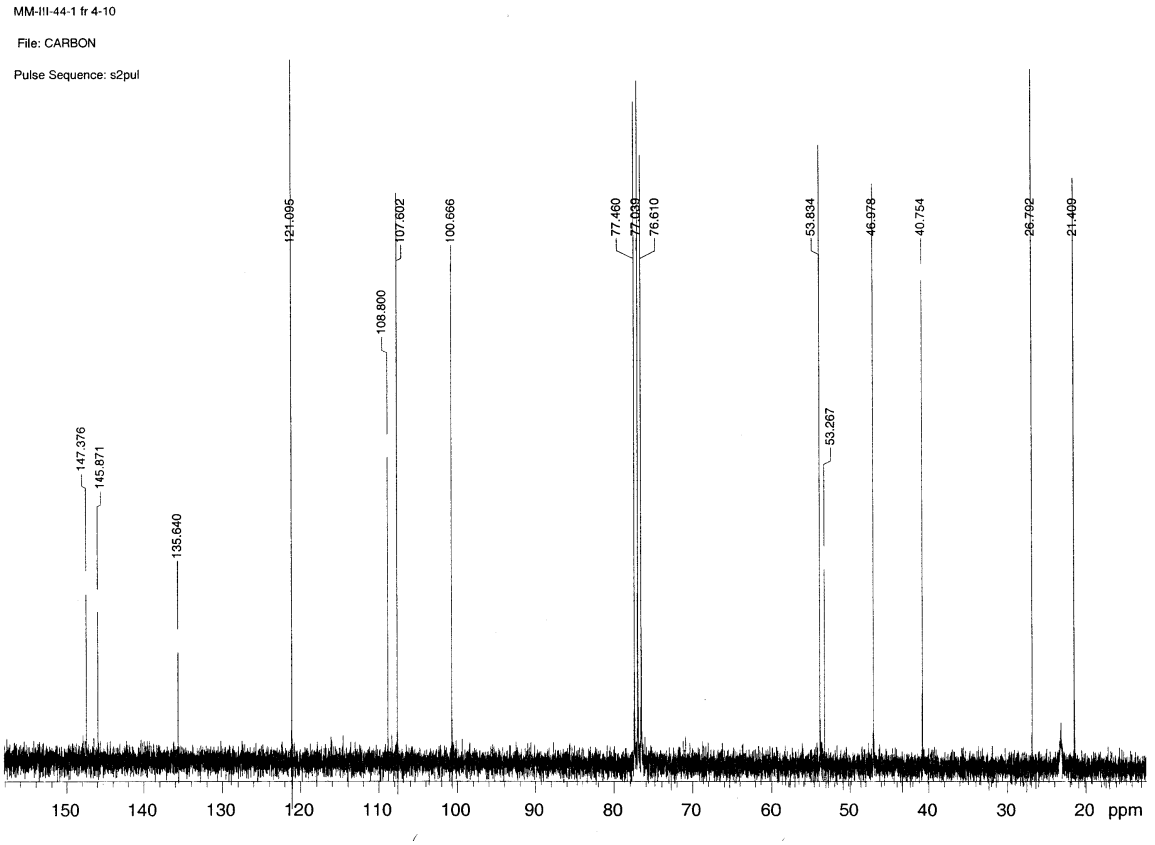

MM-III-44-1 fr 4-10
File: PROTON
Pulse Sequence: s2pul
5.921
1.695
1.471
8
7
6
5
4
3
2
1
ppm
0.92
2.00
1.95
1.99
5.80


MM-III-44-1 fr 4-10
File: CARBON
Pulse Sequence: s2pul
147.376
145.871
135.640
121.095
108.800
107.602
100.666
77.460
77.039
76.610
53.834
53.267
46.978
40.754
28.792
21.409
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

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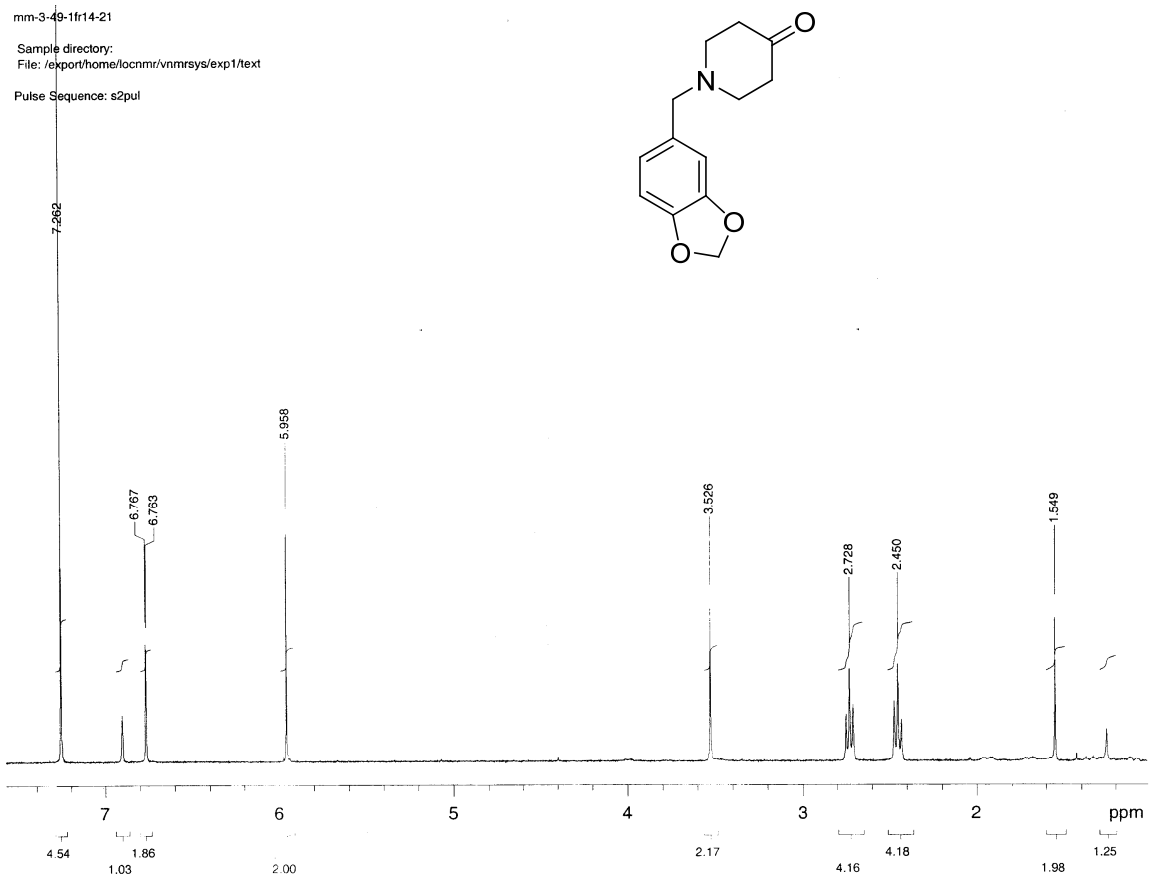
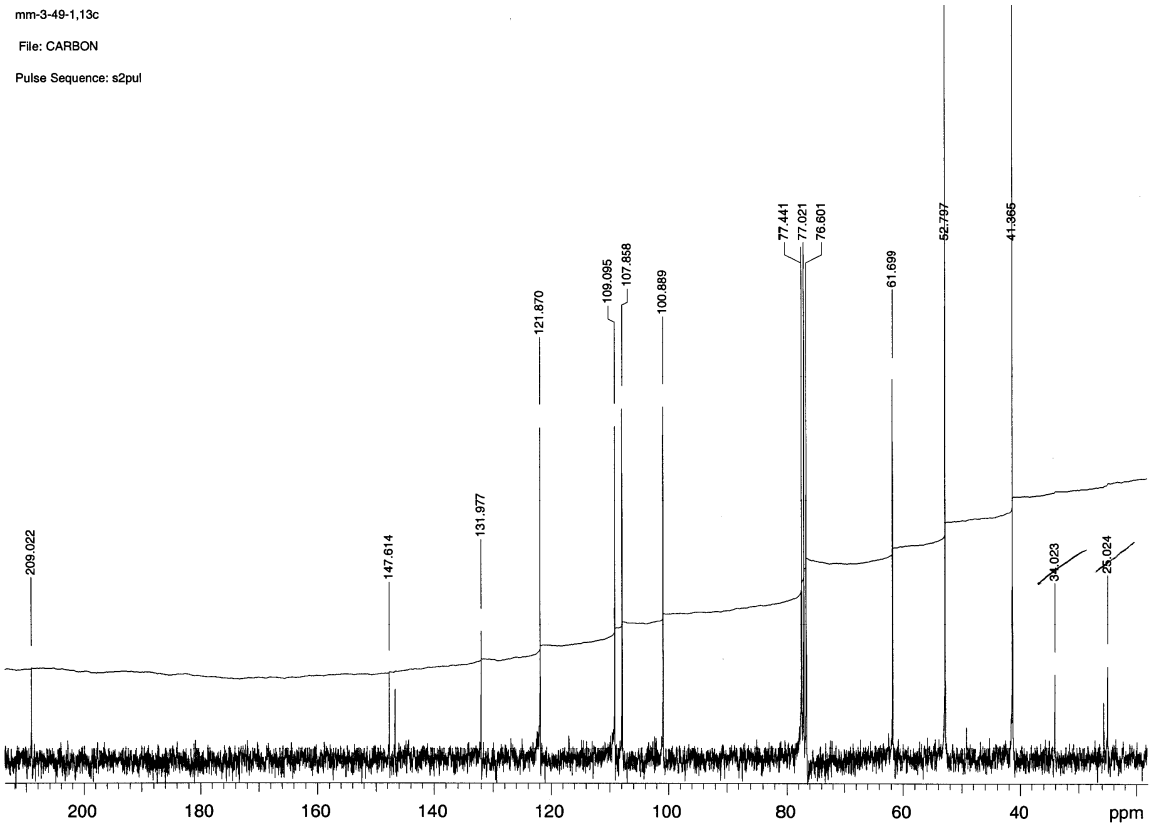
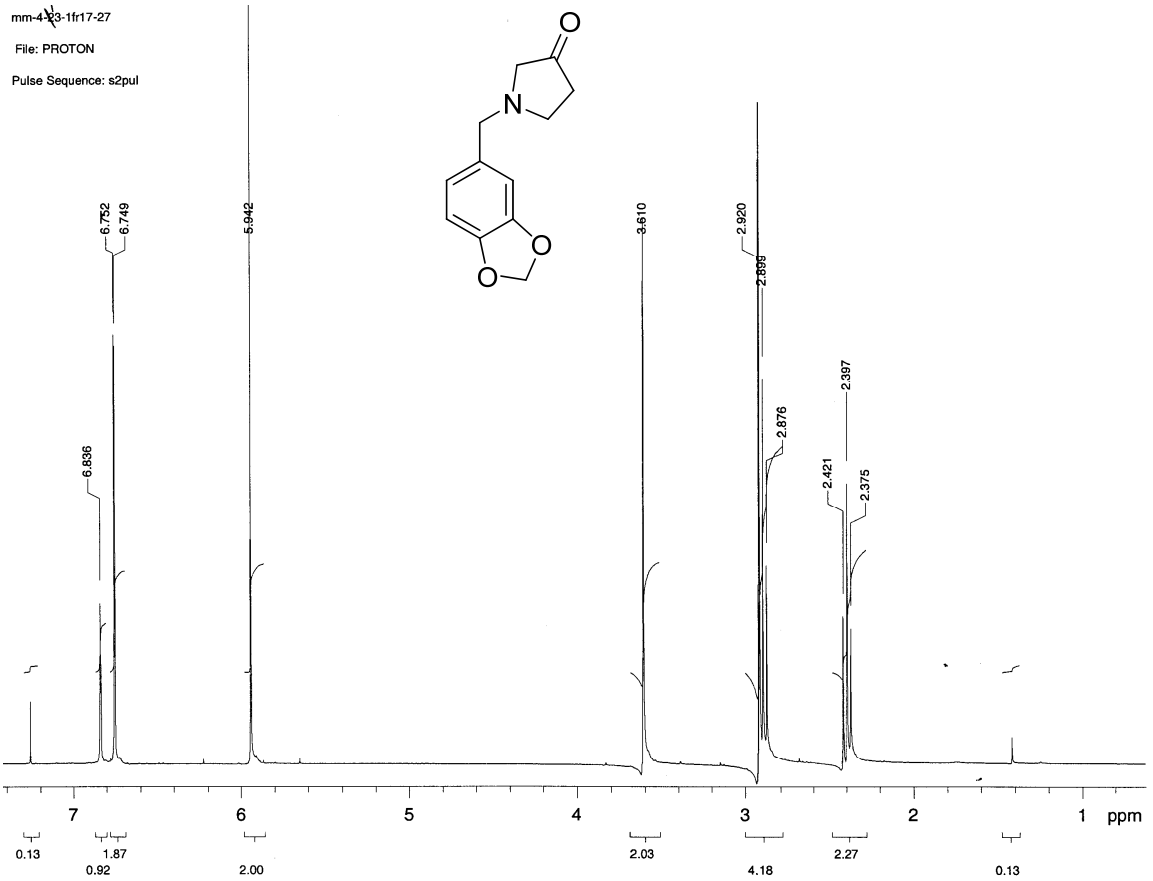
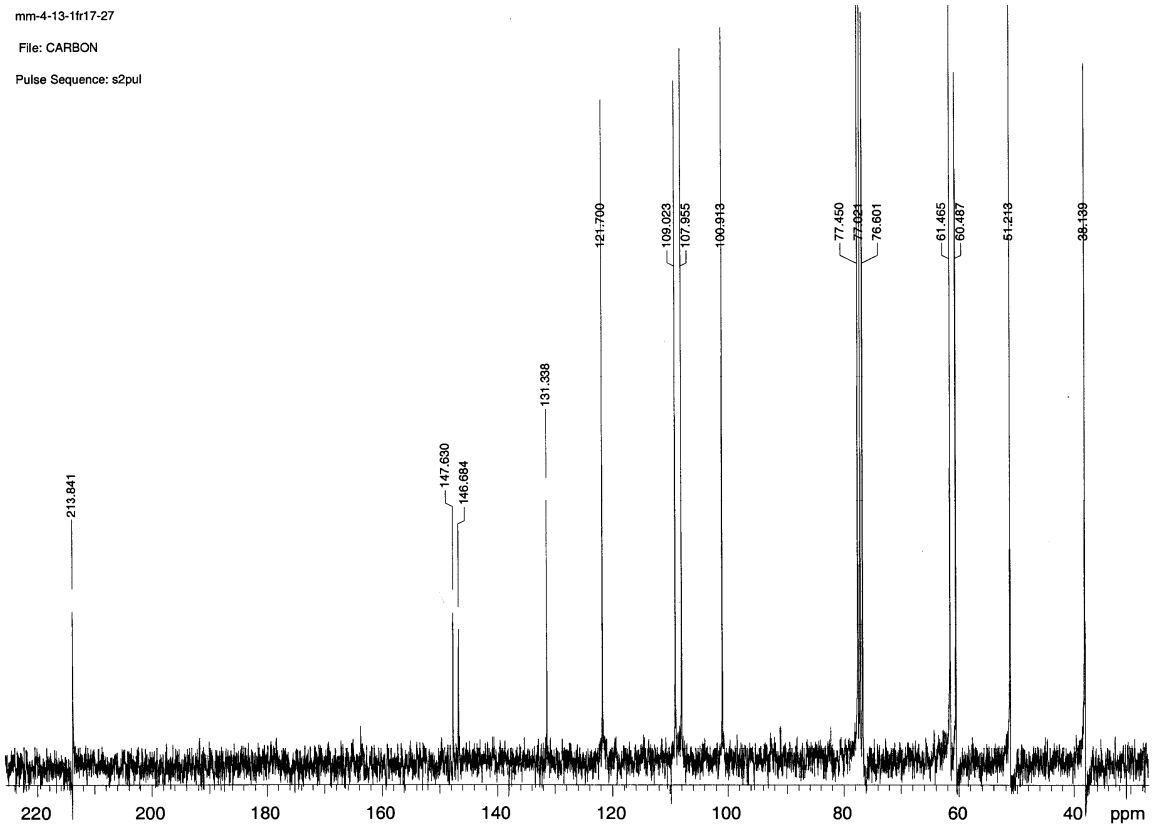

mm-3-49-1fr14-21
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
7.262
6.767
6.753
5.958
3.526
2.728
2.450
1.549
ppm
4.54
1.86
1.03
2.00
2.17
4.16
4.18
1.98
1.25

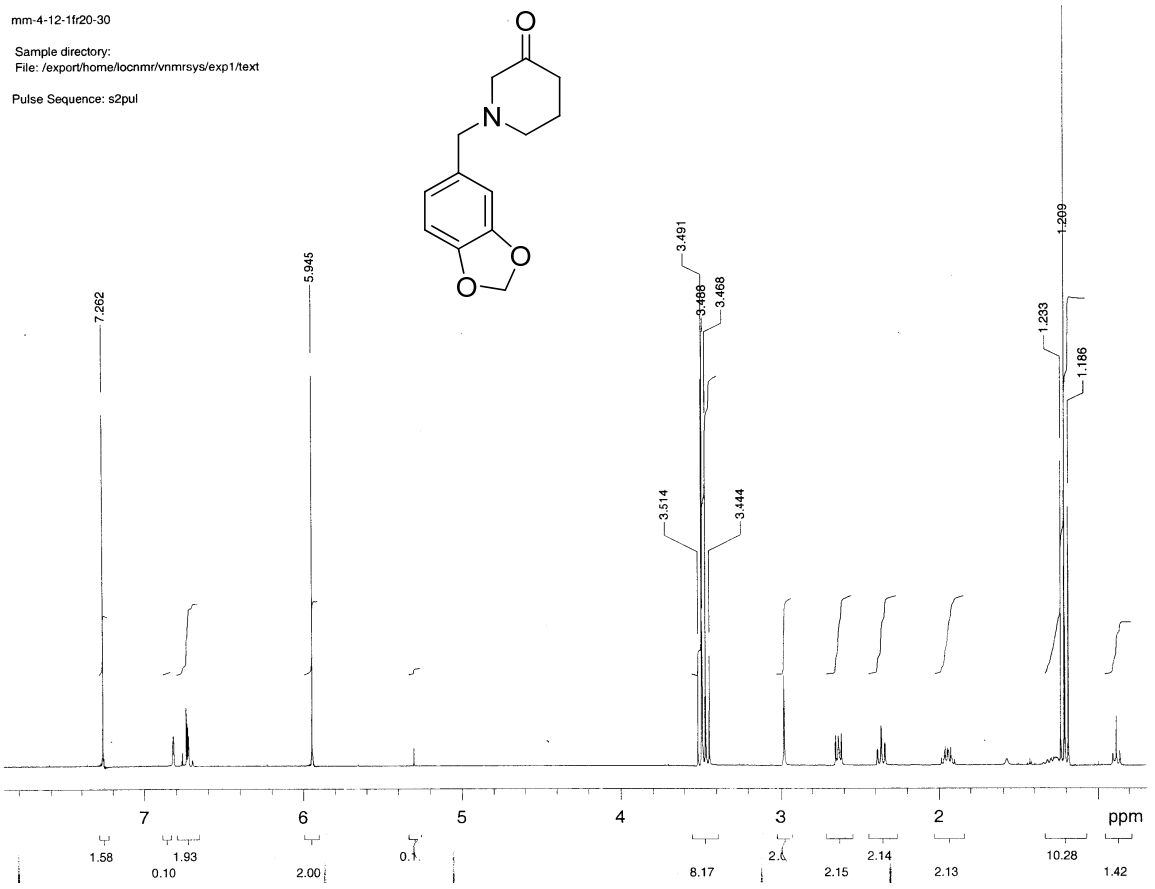

mm-3-49-1,13c
File: CARBON
Pulse Sequence: s2pul
209.022
147.614
131.977
121.870
109.095
107.858
100.889
77.441
77.021
76.601
61.699
52.797
41.365
34.023
25.024
ppm

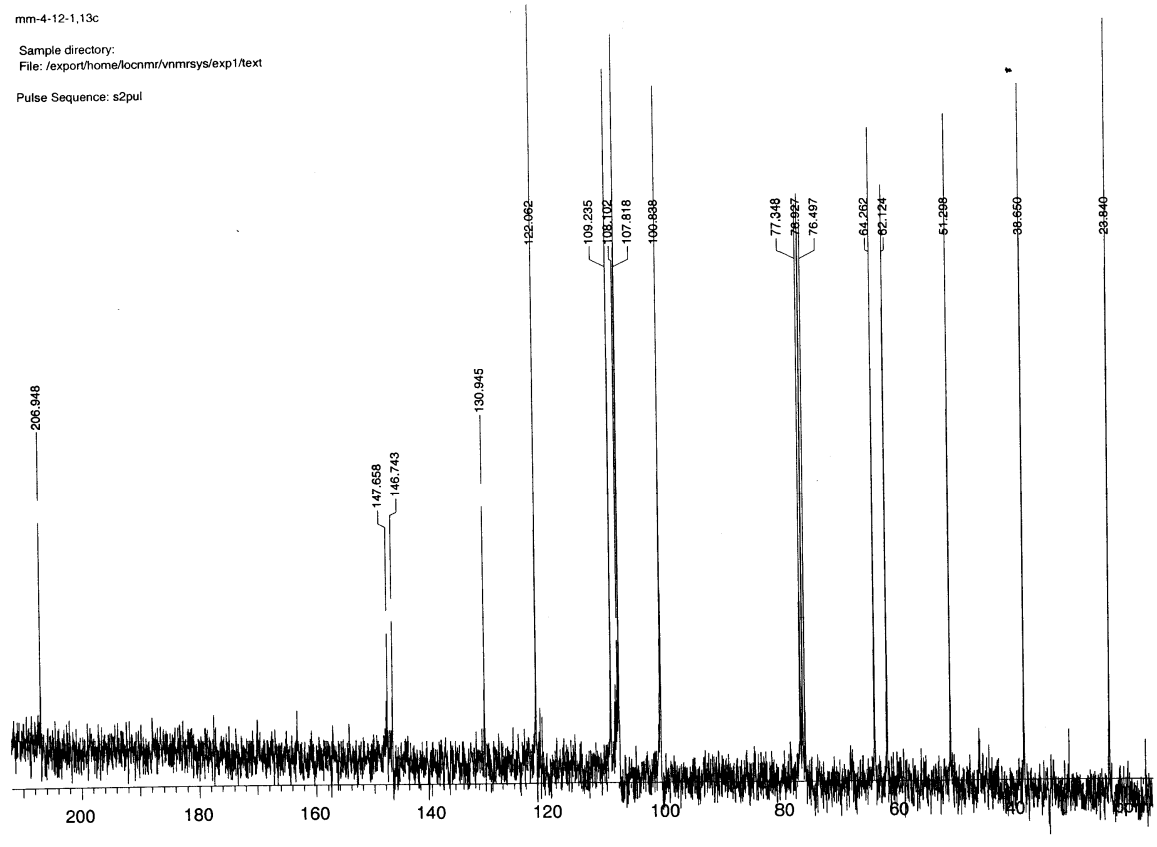
Appendix


mm-4-13-1fr17-27
File: PROTON
Pulse Sequence: s2pul
O
N
O
O
6.752
6.749
6.842
6.836
3.610
2.920
2.898
2.876
2.397
2.421
2.375
7
6
5
4
3
2
1
ppm
0.13
1.87
0.92
2.00
2.03
4.18
2.27
0.13

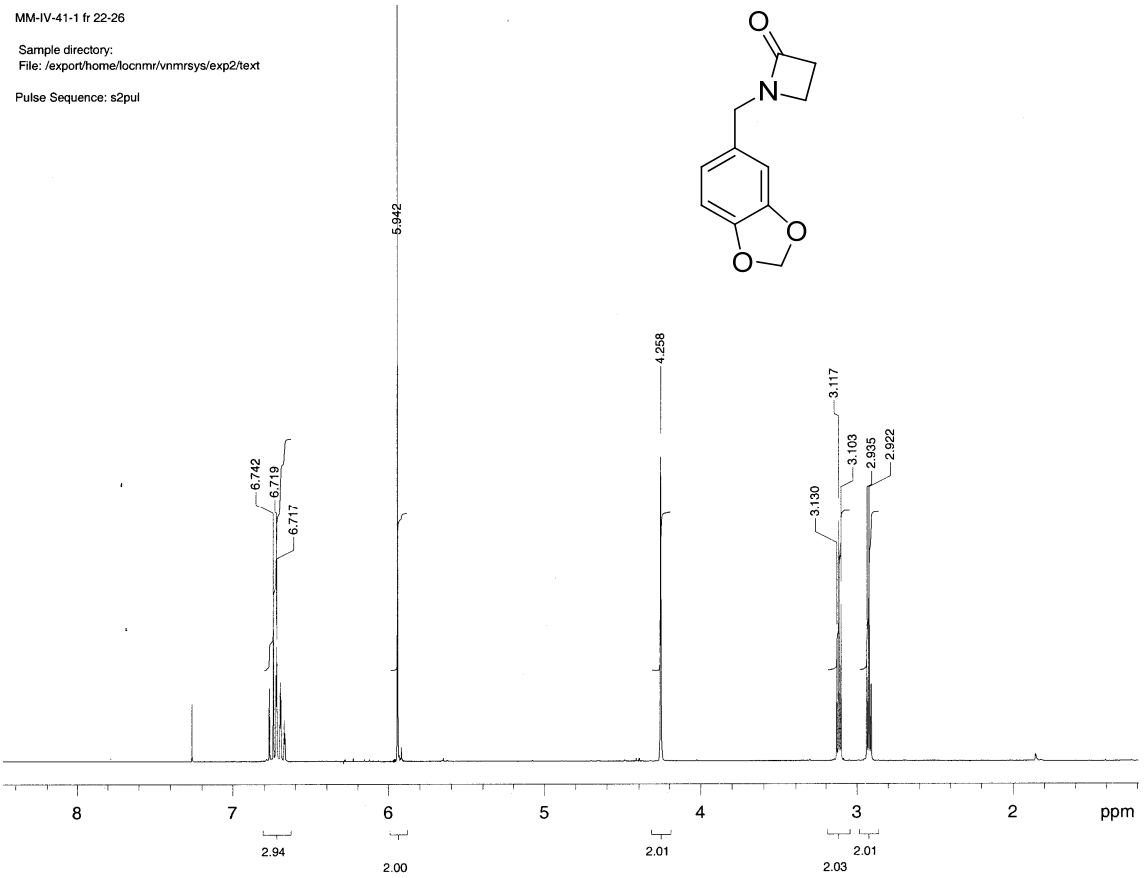

mm-4-13-1fr17-27
File: CARBON
Pulse Sequence: s2pul
213.841
147.630
146.684
131.338
121.700
109.023
107.955
100.913
77.450
77.021
76.601
61.465
60.487
51.213
38.139
220
200
180
160
140
120
100
80
60
40
ppm

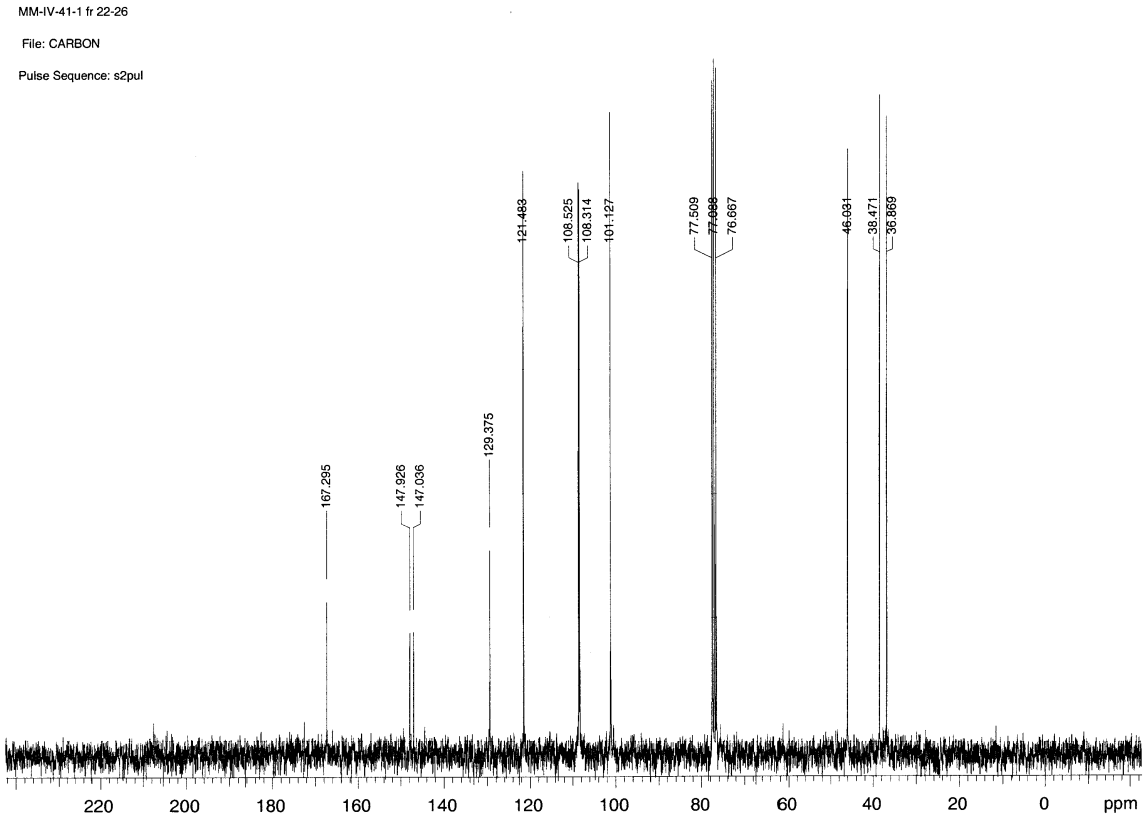
Appendix


mm-4-12-1fr20-30
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
O
N
O
O
7.262
5.945
3.491
3.488
3.468
3.514
3.444
1.269
1.233
1.186
7
6
5
4
3
2
ppm
1.58
1.93
0.10
2.00
0.1
8.17
2.0
2.15
2.14
2.13
10.28
1.42

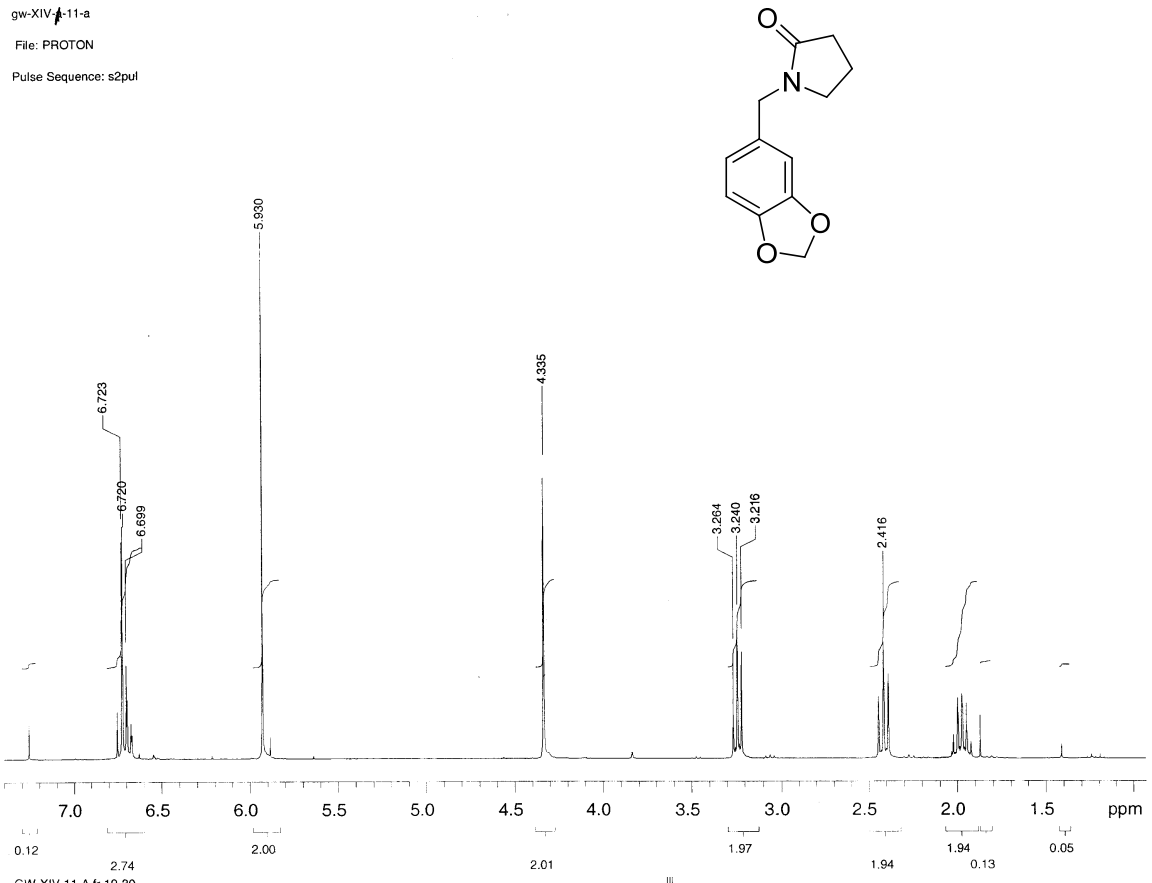

mm-4-12-1,13c
Sample directory:
File: /export/home/locnmr/vnmrsys/exp1/text
Pulse Sequence: s2pul
206.948
147.658
146.743
130.945
122.062
109.235
108.102
107.818
100.838
77.348
76.927
76.497
64.262
62.124
51.298
38.660
28.840
200
180
160
140
120
100
80
60
40

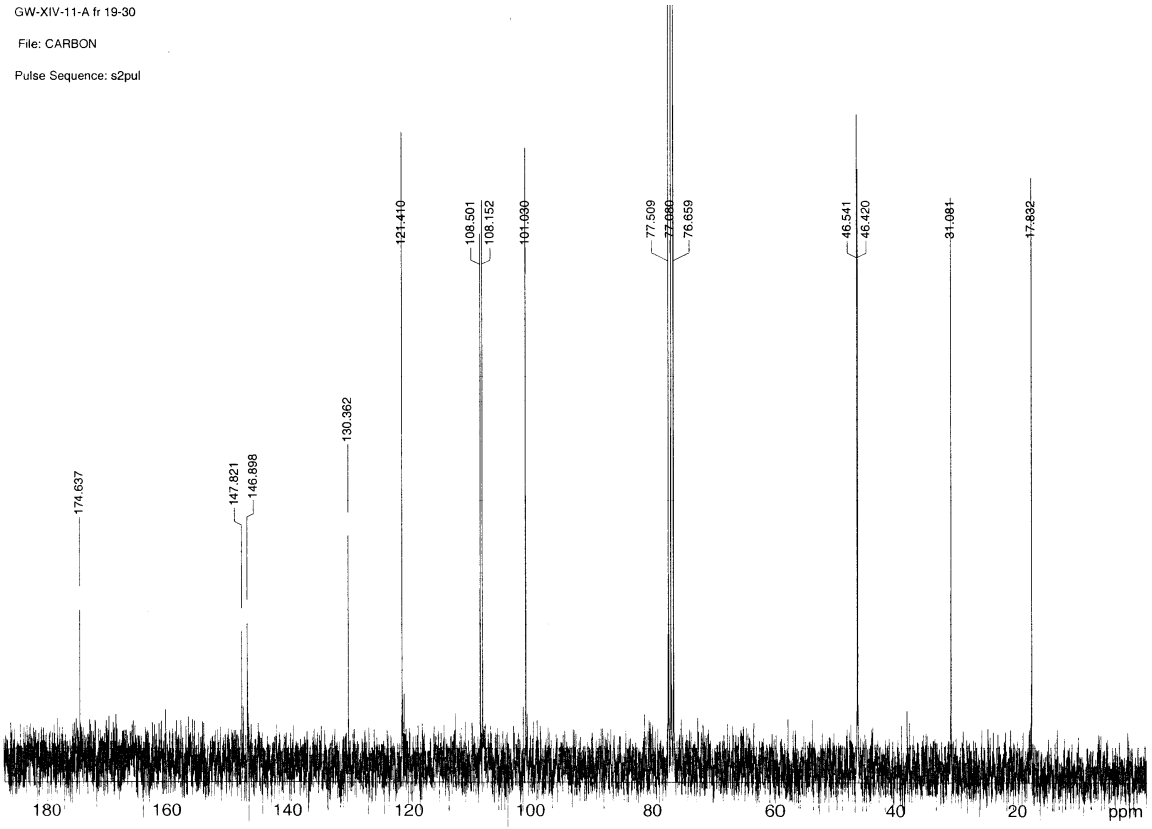
Appendix


MM-IV-41-1 fr 22-26
Sample directory:
File: /export/home/locnmr/vnmrsys/exp2/text
Pulse Sequence: s2pul
O
N
O
O
5.942
4.258
3.117
3.103
2.935
2.922
3.130
6.742
6.719
6.717
8
7
6
5
4
3
2
ppm
2.94
2.00
2.01
2.03
2.01

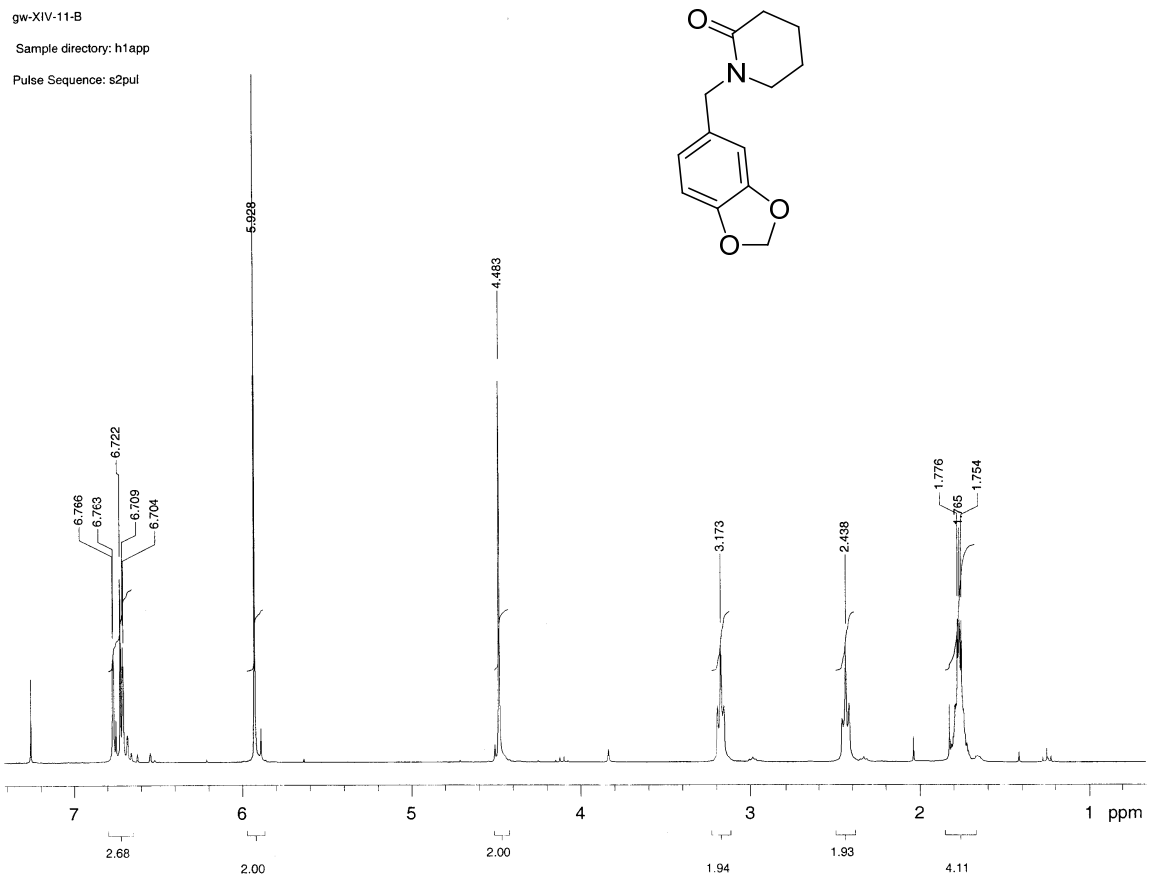

MM-IV-41-1 fr 22-26
File: CARBON
Pulse Sequence: s2pul
167.295
147.926
147.036
129.375
121.483
108.525
108.314
101.127
77.509
77.088
76.667
46.031
38.471
36.869
220
200
180
160
140
120
100
80
60
40
20
0
ppm

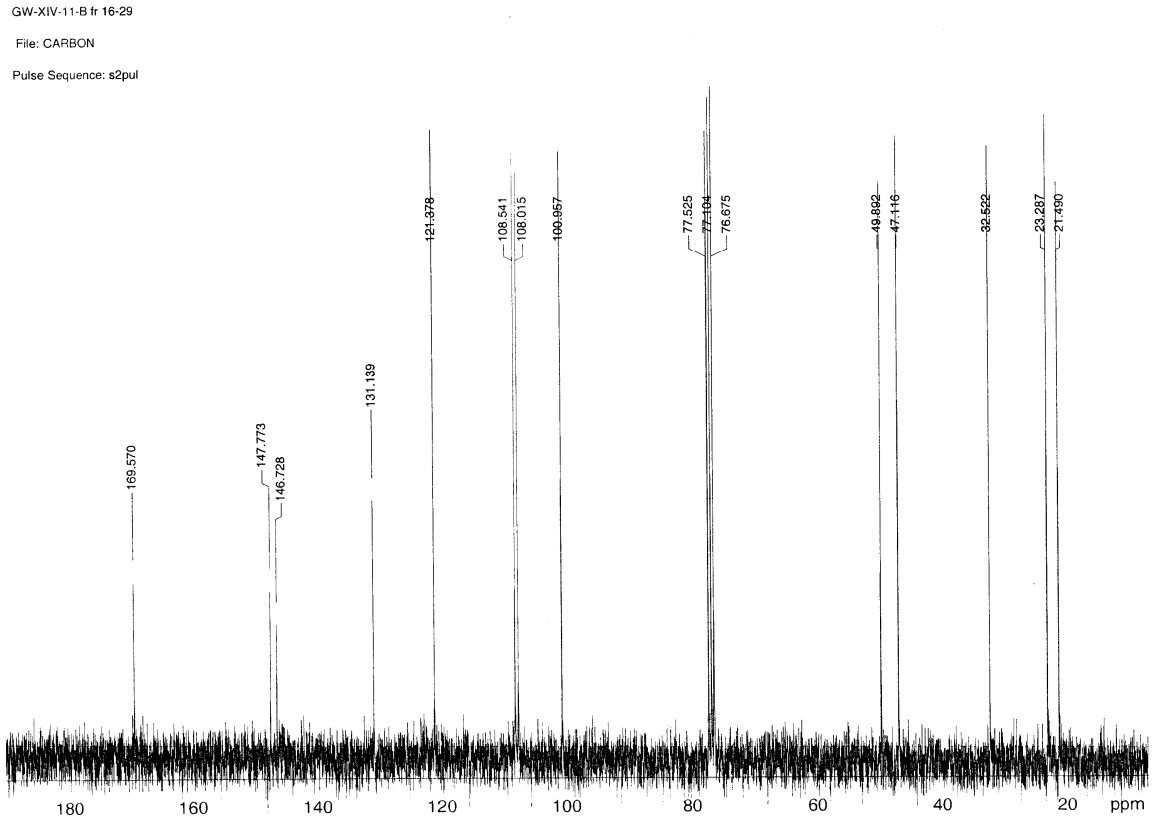
Appendix


gw-XIV-A-11-a
File: PROTON
Pulse Sequence: s2pul
O
N
O
O
5.930
6.723
6.720
6.699
4.335
3.264
3.240
3.216
2.416
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.12
2.74
2.00
2.01
1.97
1.94
0.13
0.05


GW-XIV-11-A fr 19-30
File: CARBON
Pulse Sequence: s2pul
174.637
147.821
146.898
130.362
121.410
108.501
108.152
101.030
77.509
77.080
76.659
46.541
46.420
31.081
17.832
180
160
140
120
100
80
60
40
20
ppm

Appendix


gw-XIV-11-B
Sample directory: h1app
Pulse Sequence: s2pul
O
N
O
O
5.928
4.483
6.722
6.766
6.763
6.709
6.704
3.173
2.438
1.776
1.765
1.754
7
6
5
4
3
2
1 ppm
2.68
2.00
2.00
1.94
1.93
4.11


GW-XIV-11-B fr 16-29
File: CARBON
Pulse Sequence: s2pul
169.570
147.773
146.728
131.139
121.378
108.541
108.015
100.957
77.525
77.104
76.675
49.892
47.116
32.522
23.287
21.490
180
160
140
120
100
80
60
40
20
ppm