Synthesis of New Dioxatricyclic Oxetanes and Aza-analogues of the Marine Natural Product Dictyoxetane

Dem Fachbereich Chemie
der Universität Hannover

zur Erlangung des Grades

Doktor der Naturwissenschaften
-Dr. rer. nat.-

genehmigte Dissertation

von

Diplom Chemikerin Carolina Martínez Lamenca
geboren am 25. September 1976
in Barcelona

2004

Hiermit versichere ich an Eides Statt, dass ich die vorliegende Arbeit selbständig verfasst und alle benutzten Hilfsmittel angegeben habe.

Hannover, den 30 Juni 2004

Referent:	Prof. H. M. R. Hoffmann, PhD, DSc
Korreferent:	Prof. Dr. H. H. Meyer
Tag der Promotion:	24. August 2004

A mis padres, José Luis y María Jesús.

Kurzfassung

Carolina Martínez Lamenca

„Synthese von neuen dioxatricyclische Oxetanen and Aza-Analoga von dem marinen Naturstoff Dictyoxetan“

Das dioxatricyclische Grundgerüst des Dictyoxetans und verwandte Strukturen besitzen ein hohes pharmakologisches Potential. In der vorliegenden Arbeit wurden dioxatricyclische Oxetane und Aza-Analoga der Dictyoxetan synthetisiert.

Oxygenierte 2,7-Dioxatricyclo[4.2.1.$0^{3,8}$]nonane wurden ausgehend von 8-Oxabicyclo[3.2.1]oct-6-en-3-on mit verschiedenen Estergruppen am C3-Kohlenstoffatom dargestellt. Das Pivaloat erwies sich als die beste Schutzgruppe. Die Verwendung eines deoxygenierten Dioxatricyclus führte zu Oxetan und tricyclischen Fünfring-Ethern.

Die Verkürzung der Synthese von Dioxatricyclen wurde mittels einer Lewissäure-induzierten Tandem Entschützungs-Cyclisierungs-Reaktion versucht, was zum Oxetan (4-*exo*-tet) und zu tricyclischen Ethern (5-*exo*-tet) führte. Im Gegensatz dazu ermöglichte die Umsetzung mit BCl_3 die Synthese von 2,6-Dioxatricyclo[3.3.1.$0^{3,7}$]nonanen mit dem Grundgerüst der TXA_2-Analoga.

Die Einführung eines Bromoisoxazolins am C3-Kohlenstoffatom wurde mittels einer 1,3-dipolaren Cycloaddition vor dem Ringschluss zum Oxetan versucht. Die Addition von Nitriloxid mit oxabicyclischen Dialkenen lief chemoselektiv an der endocyclischen Doppelbindung ab, während die Epoxidierung ein Gemisch von Epoxid und Bisepoxid ergab.

Durch quantitative PCC Oxidation von tricyclischen Epoxyalkoholen und einer Grignard-Reagenz-induzierten Tandem-Additions-Cyclisierungs-Reaktion wurden C2-alkylierte tricyclische Oxetane generiert.

Nach einer sechs-stufigen Synthese wurden Aza-Analoga von Dictyoxetan ausgehend von funktionalisierten 8-Oxabicyclo[3.2.1]oct-6-en-3-on dargestellt. Die Sequenz aus reduktive Aminierung mit nachfolgender Cyclisierung ergab ausgehen von den Epoxyketonen tricyclischen Azetidine, die Vorläufer von Aminoglykoside sind.

Abstract

Carolina Martínez Lamenca

"Synthesis of New Dioxatricyclic Oxetanes and Aza-analogues of the Marine Natural Product Dictyoxetane"

The dioxatricyclic core of dictyoxetane and structurally related segments are potential pharmacologically active compounds. In this PhD thesis, highly functionalized dioxatricyclic oxetanes and aza-analogues of dictyoxetane were synthesized.

New oxygenated 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes were prepared starting from 8-oxabicyclo[3.2.1]oct-6-en-3-one. After some tuning of the oxygen protecting group at carbon C3, pivaloyl protection proved to be more advantageous in terms of yield and stability. Synthesis of deoxygenated dioxatricycle led to oxetane and more stable bistetrahydrofuran.

Shortening of the synthetic route towards dioxatricyclic compounds by tandem Lewis acid-catalyzed debenzylation-cyclization reaction afforded oxetanes (4-*exo*-tet) and tricyclic ethers (5-*exo*-tet). In contrast, the tandem strategy using BCl_3 provided 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonanes as TXA_2-analogues.

The introduction of a highly versatile isoxazoline ring at carbon C3 was attempted by 1,3-dipolar cycloaddition before the oxetane ring closure. Addition of bromonitrile oxide to oxabicyclic dialkenes occurred selectively on the endocyclic double bond while epoxidation proceeded non-selectively on both double bonds.

After quantitative PCC oxidation of tricyclic epoxy alcohols and tandem Grignard reagent-mediated addition-cyclization reaction, C2-arylated and alkylated oxatricyclic oxetanes were synthesized.

Aza-analogues of dictyoxetane were prepared following a short and efficient route starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-ones. Tandem reductive amination-cyclization reaction of epoxy ketones afforded highly functionalized tricyclic azetidines which are potential bioactive compounds and precursors of a wide variety of derivatives including azaglycosides.

Schlagworte

dioxatricyclische Grundgerüst - Oxetane – Azetidine – Tandem Reaktion - Aminoglykoside

Keywords

dioxatricyclic segments - oxetane – azetidine – tandem reactions - azaglycosides

Die vorliegende Arbeit wurde in der Zeit vom Februar 2001 bis Juli 2004 am Institut für Organische Chemie der Universität Hannover unter der Leitung von Herrn Professor H. M. R. Hoffmann, PhD, DSc angefertigt.

Für die Themenstellung und die freundliche Unterstützung während dieser Arbeit sowie für den gewährten kreativen Freiraum möchte ich mich bei Professor H. M. R. Hoffmann, PhD, DSc, herzlich bedanken.

Professor Dr. H. H. Meyer danke ich für die Übernahme des Korreferats.

Ich danke Herrn Professor Dr. W. Beil vom Institut für Allgemeine Pharmakologie der Medizinischen Hochschule Hannover für die Durchführung der pharmakologischen Tests.

Für die organisatorischen Belange möchte ich mich bei Frau Mettig, Frau Haß, Frau Kandil, Frau Eckert-Hupe und Frau Griese bedanken.

Für die sorgfältige Korrektur der vorliegenden Arbeit und die immer freundliche Diskussionsbereitschaft danke ich María Vidal Pascual, Steffen Proemmel, Núria Merayo und Aitor Cortabarria.

Meinen Laborkollegen Peter Schäfer, Jens Holzgrefe, Lars Haustedt, Martin Seidel, Wilhelm Adam, René Smits, Ulrike Eggert, Barbara Nieß und ganz besonders meiner Freundin María Vidal Pascual möchte ich für die angenehme Arbeitsatmosphäre danken.

Marco Retzlaff, Michael Reck, Julia-Maria Martynczuk, Elisabet Lafitte, Roman Gupta und Christian Endres danke ich für Ihre engagierte Mitarbeit im Rahmen ihrer F-Praktika danken.

Den Spektroskopie-Abteilung, insbesondere Dagmar Körtje, Monika Rettstatt, Dr. D. Albert und Dr. E. Hofer, danke ich für ihr Engagement und ihre Mühen beim Anfertigen der Spektren und ihre stete Hilfsbereitschaft bei der Spektrendiskussion.

Steffen Proemmel danke ich für die konstruktive Diskussionen und seine Hilfsbereitschaft.

Für ihre Freundschaft und die vielen schönen Freuden des Lebens außerhalb de Promotion danke ich meine Freunde insbesonders Michael Greiff, Albane Douillet und Eleonora Schulz sowie die Freunden in der Ferne.

Mi agradecimiento más sincero a Núria Merayo por su apoyo y sus valiosos consejos.

Meine Mitbewohner in „WG 43“, insbesondere Stefanie Greiff und Nino Schäfer, mit denen ich nicht nur ein warmes „zu Hause“ geteilt habe, danke ich ganz herzlich.

A mi hermana Irene por su confianza y apoyo en la distancia.

A María por cada palabra de aliento, por su sincera amistad y su confianza incondicional.

A Aitor le dedico mi más sincero agradecimiento por haber compartido todo este largo camino que me ha llevado hasta aquí. Gracias a su amor, su apoyo y su comprensión no me ha faltado energía para seguir adelante sin rendirme.

A mis padres, José Luis y María Jesús, quiero agradecerles todo su cariño, entusiasmo y confianza en mí que me ha ayudado a alcanzar todas mis metas.

Table of Contents

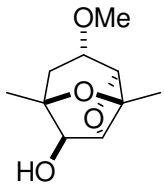
Table of Abbreviations

abs.	absolute
Ac	acetyl
AIBN	azobis(isobutyronitrile)
Ar	aryl
ax	axial
$BF_3 \cdot OEt_2$	boron trifluoride etherate
$BH_3 \cdot py$	borane pyridine complex
Bn	benzyl
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
Bz	benzoyl
C,H-COSY	Two dimensional ^{13}C-^{1}H-NMR-spectrum
cat.	catalytic
Cbz	benzoyloxycarbonyl
CH	cyclohexane
CH_3CN	acetonitrile
d	day(s)
DBF	dibromoformaldoxime
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichlorometane
DEPT	Distortionless Enhancement by Polyrization Transfer
dest.	distilled
DIBAH	diisobutylaluminium hydride
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl Sulfoxide
EA	ethylacetate
e.e.	enantiomeric excess
eq	equatorial/equivalent
Et_2O	diethylether
Et_3N	triethylamine
EtOH	ethanol
GC	gas chromatography
h	hour(s)
H,H-COSY	Two dimensional ^{1}H-^{1}H-NMR-spectrum
HOMO	High Occupied Molecular Orbital
HR-MS	High Resolution Mass Spectroscopy

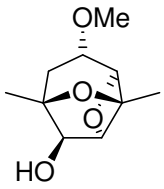
Hz	Hertz
IR	Infrared Spectroscopy
t-BuOK	potassium *tert*-butoxide
LDA	lithiumdiisopropyl amide
LUMO	Low Unoccupied Molecular Orbital
M	molar
m.p.	melting point
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
min	minute(s)
MS	Mass Spectroscopy/molecular sieves
MTBE	*tert*-butylmethyl ether
n-BuLi	*n*-butyllithium
NMR	Nuclear Molecular Resonance Spectroscopy
NOE	Nuclear Overhauser Effect
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PivCl	pivaloyl chloride
Py	pyridine
Rt	room temperature
sat.	saturated
SET	Single Electron Transfer
SO_3·Py	sulfur trioxide pyridine complex
sol.	solution
t	time
T	temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMSOTf	*tert*-butyldimethylsilyl triflate
TES	triethylsilane
THF	tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMS	Trimethylsilane

Preliminary Remarks

The stereochemical notation in the present work follows the convention proposed by H. Maehr.[1] Bold and hashed wedges indicate absolute configuration. Bold and hashed lines represent relative configuration of racemic compounds.



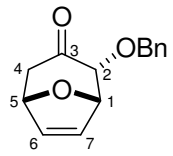
***rac*-58**



(+)-**113**

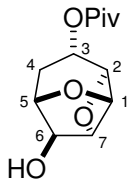
Oxabicycles, dioxatricycles and oxaazatricycles are named according to the IUPAC rules.[2]

The numeration of oxabicycles follow the IUPAC regulations. For the sake of clarity the oxabicyclic atom numbering is maintained in dioxatricycles and oxaazatricycles.



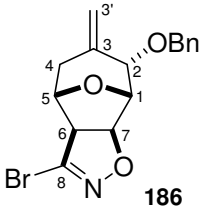
***rac*-90**

8-Oxabicyclo [3.2.1]octane



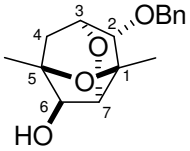
132

2,7-dioxatricyclo [4.2.1.0^{3,8}]nonane



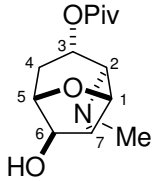
186

3,11-dioxa-4-azatricyclo [5.3.1.0^{2,6}]undecane



161

2,6-dioxa-tricyclo [3.3.1.0^{3,7}]nonane



268

7-oxa-2-azatricyclo [4.2.1.0^{3,8}]nonane

[1] Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114.

[2] a) Bowers, K. G.; Mann, J.; Walsh, E. B.; Howarth, O. W. *J. Chem. Soc. Perkin. Trans 1* **1987**, 1657; b) Khuoung-Huu, F. C. R. *Hebd. Seances Acad. Sci. Ser. C.,* Fr, **1975**, *275*, 499.

Background and Overview

1. Introduction

Plant-based medicines have been used since prehistoric times and are still being used by a large part of the world population either in traditional (e.g. Chinese) or alternative medicine (in developed countries). Natural products have also been the basis for many pharmaceutical drugs in the past and their future importance is out of question, being one of the reasons why biological diversity has attracted such international attention in the last few decades. Even though Brazil and India are usually quoted as being hotspots of biodiversity,[3] the oceans could easily rival them in terms of both biological and chemical diversity. Marine animals, algae, fungi and bacteria exhibit not only unusual and beautiful chemical structures, but these often show exceptional levels of biological activity combined with unique modes of action. Obviously, marine natural products have a great potential of yielding lead compounds for the development of new generation pharmaceuticals whose novel activity could lessen such problems as the antibiotic resistance in bacteria and fungi or the multi-drug resistance (MDR) in cancer chemotherapy.

In order to fully develop the potential of a natural product, enough quantities of the compound must be available for the initial evaluation. This is where total synthesis offers two major advantages: produces useful quantities of the target compound and allows synthetic analogues that might be even more interesting than the natural product itself.

1.1 Naturally Occurring Oxetanes

Several important naturally occurring compounds enclose the oxetane ring, which is difficult to build by standard chemical reactions. Examples include taxol® (a potent anti-cancer drug), oxetanocin (anti- AIDS activity) and thromboxane A (the counterpart of the prostaglandins) (see Scheme 1).

[3] "Biodiversity." Wikipedia. 2004. 17 June 2004 <http://en.wikipedia.org/wiki/Biodiversity>.

The marine natural product dictyoxetane **1** has been isolated from the brown algae *Dictyota dichotoma* and is structurally related to the class of diterpenoid dolabellanes,[4] which show a wide spectrum of biological activities. The compact molecule of dictyoxetane **1** encloses a small ring ether (*n*=4), three normal ring ethers (*n*=5-7) and even a medium ring diether (*n*=8), a 1,4-dioxacyclooctane. Such an intricate dioxatricyclic framework has not been encountered in any other natural product. A biogenetic pathway has been suggested for dictyoxetane **1** from a known dolabellane metabolite supported by the experimental introduction of the oxetane moiety *in vitro*.[2]

A potent anti-cancer drug and naturally occurring oxetane is paclitaxel (taxol®)[5] **3**, a tricyclic diterpene (C_{20}) isolated from the bark of the western yew (*Taxus brevifolia*),[6] a slow-growing tree found in the Pacific Northwest forests. Paclitaxel **3,** considered a prototype for new chemotherapeutic agents,[7] shows high activity against different tumor types like mama or ovarian cancer. In contrast to other microtubule antagonists, paclitaxel promotes microtubule assembly, rather than disassembly. The increase of tubulin's polymerization and the consequent stabilization of microtubules cause disruption of mitosis. The oxetane ring seems to be essential for its biological activity.[8] One of the major problems with the development of paclitaxel **3** as a chemotherapeutic agent has been the supply. It is only isolated from the Pacific yew tree, despite its low content (100 mg/kg of dry bark). Therefore, other sources has been investigated, like for instance, the synthesis from natural precursor. An example is baccatin III, whose precursor can be isolated from the needles of several types of yews, including some ornamental yews.

The counter part of the prostaglandins, thromboxane A_2 (TXA_2) **3,** has a bicyclic oxane-oxetane structure. It is synthesized predominantly by platelets to promote vasoconstriction and platelet aggregation. With a half-life of thirty seconds, TXA_2 is an unstable intermediate between prostaglandin endoperoxides and inactive thromboxane B_2 (TXB_2).[9]

---

[4] a) Pullaiah, K. C.; Suprapaneni, R. K.; Rao, C. B.; Albizati, K. F.; Faulkner, D. J.; Cunheng, H.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3666; b) Pullaiah, K. C.; Suprapaneni, R. K.; Rao, C. B.; Albizati, K. F.; Faulkner, D. J.; Cunheng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 2736.

[5] Paclitaxel is the generic name for Taxol®, which is now a registered trademark.

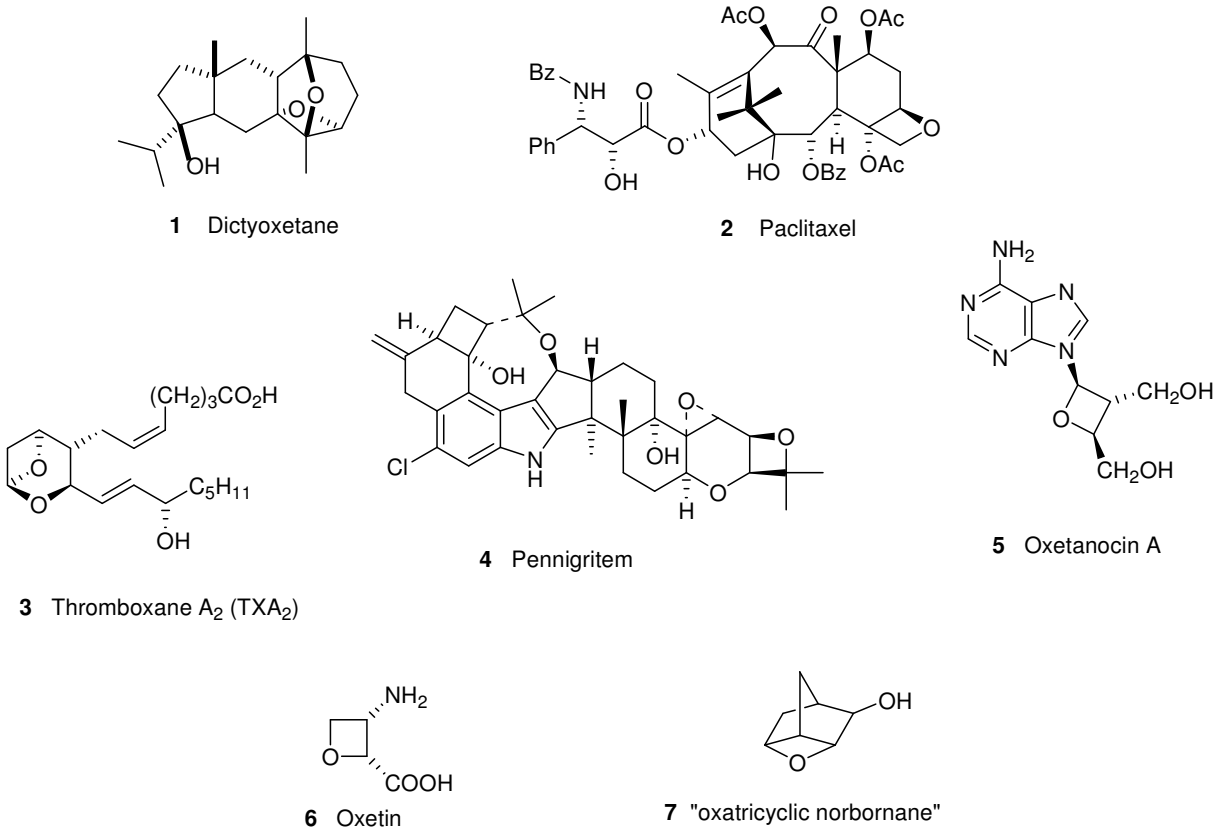
[6] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

[7] a) *Taxol Science and Applications;* Suffnes, M., Ed.; CRC Press: Boca Raton, 1995; b) *The Chemistry and Pharmacology of Taxol and Its Derivatives;* Farina, V., Ed.; Elsevier: Amsterdam, 1995; c) *Paclitaxel in Cancer Treatment;* McGuire, W. P., Rowinski, E. K., Eds.; Marcel Dekker: New York, 1995.

[8] Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder J. P. *J. Org. Chem.* **2000**, *65*, 1059.

[9] a) *New Synthetic Routes of Prostaglandins and Thromboxane;* Roberts, S. M., Scheimann, F., Eds.; Academic Press: London, 1982; b) Hamman, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372; c) Corey, E. J. *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 455.

Another example of natural product containing an oxetane ring is pennigritem **4**, a toxin isolated from *Penicillium nigricans* and related to the family of penitrems. The penitrems belong to the tremorgenic mycotoxins and have been isolated from the ergot fungus *Penicillium crustosum.* Penitrems intercede in amino-acid neurotransmitter-release mechanisms. These toxins induce an excessive release of neurotransmitters into the synaptic cleft and over stimulate the receptors on the postsynaptic membrane.



Scheme 1: Natural products containing an oxetane ring.

Oxetanocin A **5** is a potent antiviral antibiotic, formally a nucleoside with an oxetanosyl-*N*-glycoside, which has been isolated from a culture filtrate from *Bacillus megaterium.*[10] Natural occurring oxetanocin A **5** and its synthetic derivatives are reverse transcriptases of retrovirus and therefore potential drugs for the treatment of AIDS,[11] cytomegalovirus (CMV),[12] hepatitis B-virus and herpes simplex-virus (HSV-1 and HSV-2).

[10] Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiotics* **1986**, *39*, 1623.

[11] a) Jacobo-Molina, A.; Ding, J.; Nanni, R. G.; Clark, A. D.; Lu, X.; Tantillo, C.; Williams, R. L.; Kamer, G.; Ferris, A. L.; Clark, P.; Hizi, A.; Hughes, S. H.; Arnold, E. *Proc. Natl. Acad. Sci.* **1993**, *90*, 6320; b) Arnold, E.; Ding, J.; Hughes, S. H.; Hostomsky Z. *Curr. Opin. Struct. Biol.* **1995**, *5*, 27.

Another naturally occurring oxetane is oxetin **6,** an amino acid-antimetabolite produced by a fermentation broth of a *Streptomyces sp*. It can inhibit the growth of *Bacillus subtilis* and *Piricularia oryzae*.[13] Oxetin also exhibits herbicidal activity and is a non-competitive inhibitor of glutamine synthetase.

Finally, oxatricyclic "norbornane" **7** is a potent herbicide and plant growth regulator.[14]

1.2 Naturally Occurring Azetidines

The azetidine ring is a rare structure that has been identified in few natural products comprising significant biological activity like (*S*)-azetidine-2-carboxylic acid (proline antagonist) or penaresidines (azetidine alkaloids).[15]

A first example of naturally occurring azetidine is (*S*)-azetidine-2-carboxylic acid (AZC) **9** which found in roots and leaves of some species of the *Liliaceae*, like lily-of-the-valley (*Convallaria majalis*), and also in seeds of some legumes like *Clavaria miyabeana*.[16] This L-proline analogue is a competitive inhibitor of the proline transport system. In other words, AZC is integrated into proteins competitively with L-proline and induces the synthesis of abnormal misfolded proteins, thus inhibiting cell growth in both bacterial and animal cells.

Azetidine alkaloids are rare substances mostly found in nature as sphingosine-like compounds containing an azetidin-3-ol nucleus.[17] Penaresidin A **10** and B **11** and penazetidin A **12** are original azetidine alkaloids isolated from the marine sponges *Penares sp*.[18] and *Penares sollasi*,[19] respectively. Penaresidin A **10** and B **11** have shown potent actomyosin ATPase-

---

[12] a) Nishiyama, Y.; Yamamoto, Y.; Yamada, Y.; Daikoku, T.; Ichikawa, T.; Takahashi, K. *J. Antibiotics* **1989**, *52*, 1854; b) Braitman, A.; Swerdel, M. R.; Olsen, S. J.; Tuomari, A. V.; Lynch, J. S.; Blue, B.; Michalik, T.; Field, A. K.; Bonner, D. P.; Clark, J. M. *Antimicrob. Agents Chemother*. **1991**, *35*, 1464.

[13] a) Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A; Matsumoto, T. *J. Antibiot.* **1984**, *37*, 1324; b) Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M.; Omura, S. *Chem. Pharm. Bull.* **1984**, *34*, 3102; c) Shimada, N. *J. Antibiot.* **1988**, 41, 1868; d) Greco, F. A. *J. Nat. Prod.* **1991**, *54*, 207; e) Betina, S. chap. 16, *Chem: Express:* **1992**, *8*, 177; f) *rac*-oxetin: Bach, T.; Schroeder, J. *Liebigs Ann./Recueil* **1997**, *11*, 2265; g) Bach, T.; Bergmann, H.; Brummerhop, H.; Lewis, W.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 4512 and references therein; h) Griesbeck, A. G.; Bondock, S.; Gudipati, M. S. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 4684 and preceding work.

[14] Soloway, S. B.; Vogel, P.; Le Drian, C. H. A.; Powell, J. E. U.S. Patent 916 334, 1986; Eur. Pat. Appl. 87201907.87201900, 1987.

[15] de Kimpe, N. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science Ltd.: Oxford, 1996; p. 507.

[16] Burkhard Fugmann, B.; Lang-Fugmann, S.; Steglich, W. *Römpp-Lexikon Naturstoffe*; Georg Thieme Verlag: Stuttgart, 1997.

[17] Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc. Heterocycles* **1996**, *42*, 943.

[18] Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135.

[19] Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Biomed. Chem. Lett.* **1994**, *4*, 2447.

activating activity,[18] while penazetidin A **12** exhibits protein kinase C inhibitory activity.[19] In view of their unusual structure and pharmacological properties, several reports on the synthesis of these azetidine alkaloids and structural analogues have emerged in the literature.[20]

An azetidine ring system is also present in polyoxin A **13**. It belongs to a class of peptidyl nucleoside antibiotics and has been isolated from cultures of *Streptomyces cacaoi var. asoensis*.[21] Structurally, polyoxins include two distinct structural components: the right hand side is a nucleoside fragment and the left hand side is the peptidyl region. These natural products inhibit the synthesis of chitin, an essential component of the cell wall. As a result, these antibiotics are active against various fungi like the phytopathogenic fungus *Pellicularia filamentosa f. sasakii*, which causes sheath blight disease of rice plants, or the human pathogenic fungus *Candida albicans*.[22] Polyoxins have been widely used as efficient agricultural fungicides in Japan since 1966.

Mugineic acid **14** and nicotinamine (NA) **15** are naturally occurring azetidines ubiquitously present in graminaceous plants. Nicotianamine **15**, a chelator of various transition metals, is the direct precursor of phytosiderophores like mugineic acid **14**, an amino acid secreted from the roots to solubilize ferric iron from the root environment under conditions of iron deficiency.

An example of azetidine antibiotic is antibiotic FR-29038 **16**, one of a number of structurally similar antibiotics isolated from cultures of *Nocardia uniformis* subsp. *tsuyamanensis*. It has been found to be effective against *Bacillus, Escherichia, Klebsiella, Pseudomonas, Salmonella* and *Shiguella* species.[23]

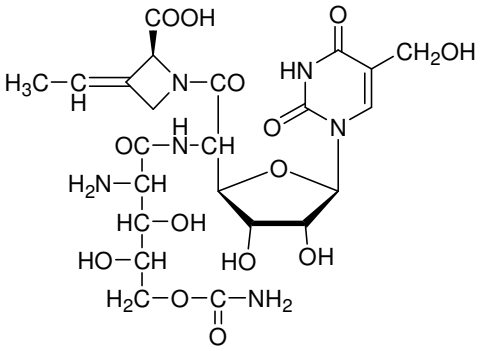
---

[20] For reported synthesis of azetidine alkaloids and analogues: a) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett*. **1995**, *36*, 4841; b) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett*. **1995**, *36*, 7689; c) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2113; d) Yashima, A.; Takikawa, H.; Mori, K. *Liebigs Ann.* **1996**, *7*, 1083; e) Mori, K. *J. Heterocyclic Chem*. **1996**, *33*, 1497; f) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283; g) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813; h) Takikawa, H.; Maeda, T.; Seki, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *2*, 97; i) Lin, G. Q.; Liu, D. G. *Heterocycles* **1998**, *47*, 337; j) Lin, G. Q.; Liu, D. G. *Tetrahedron Lett.* **1999**, *40*, 337; k) Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763; l) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977; m) Salgado, A.; Boeykens, M.; Gauthier, C.; Dejaegher, Y.; Verniest, G.; Lopin, C.; Tehrani, K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231.

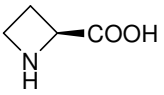
[21] Suzuki, S.; Isono, K.; Nagatsu, J.; Mizutani, T.; Kawashima, Y.; Mizuno, T. *J. Antibiot.* **1965**, 131.

[22] For reviews, see: a) Isono, K. *J. Antibiot.* **1988**, *41*, 1711; b) Garner, P. Synthetic approaches to complex nucleoside antibiotics. In *Studies in Natural Products Chemistry*. Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Stereoselective synthesis (Part A), Vol. 1, 397; c) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269; d) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859; e) Zhang, D.; Miller, M. J. *Curr. Pharm. Design*, **1999**, *5*, 73.

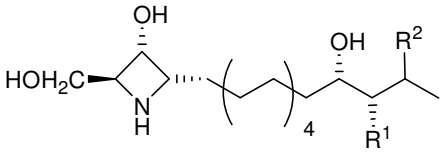
[23] Glasby, J. S. *Encyclopedia of Antibiotics*; Wiley: Chichester, 1979.



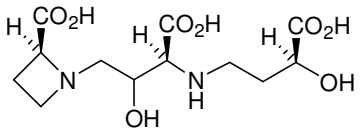
13 Polyoxine A



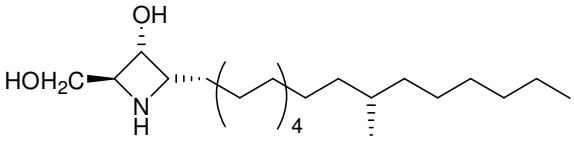
9 (S)-(-)-Azetidine-2-carboxylic acid



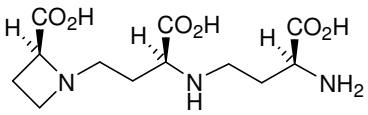
10 Penaresidin A: R^1 = Me, R^2 = H
11 Penaresidin B: R^1 = H, R^2 = Me



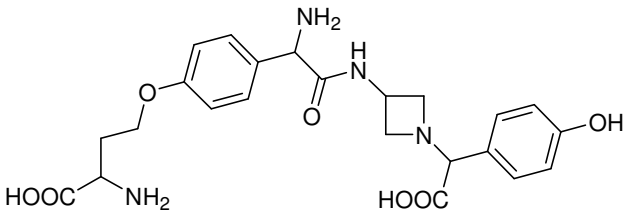
14 Mugineic acid



12 Penazetidin A



15 Nicotianamine



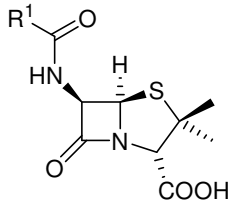
16 Antibiotic FR-29038

Scheme 2: Natural products containing an azetidine ring.

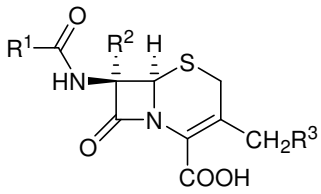
In a greater extent, ß-lactam antibiotics also contain an azetidine ring system.[24] Antibiotics are specific chemical substances derived from living organisms capable of destroying bacteria through the inhibition of the synthesis of the bacterial cell wall. In addition to their bactericidal action, many antibiotics are also capable of inhibiting tumor cell growth by DNA intercalation. These antibiotics possess very low toxicity and new semisynthetic or total synthetic derivatives with an enhanced spectrum of biological activites have been developed

[24] For reviews on ß-lactams, see: a) *The Chemistry of ß-Lactams;* Page, M. I., Ed.; Blackie Academic & Professional: New York, 1992; b) *Chemistry and Biology of ß-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1; c) *The Organic Chemistry of ß-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; d) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 1B, Chapters 1.18-1.20; e) *Synthesis of ß-Lactam Antibiotics*; Bruggink, A., Ed.; Kluwer: Dordrecht, Netherlands, 2001; f) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377; g) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.

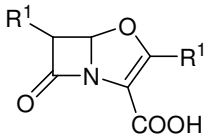
continuously. Over 3,000 antibiotics have been identified but only a few dozen are used in medicine.[25]



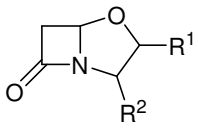
17 Penicillins



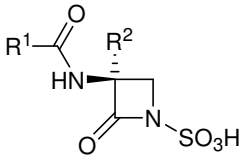
18 Cefalosporins



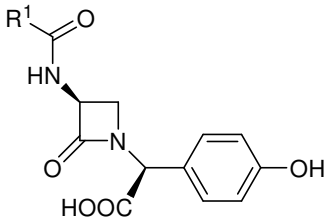
19 Carbapenems



20 Clavame



21 Monobactams



22 Nocardicine

Scheme 3: ß-Lactam antibiotics.

These ß-lactam antibiotics share beta-lactam ring which is essential for the bactericidal activity. According to their structure ß-lactam antibiotics can be classified into penicillins **17**, cephalosporins **18**, carbapenems **19**, clavams **20** and monolactams – monobactams **21** and norcardicines **22** (see Scheme 3).[26]

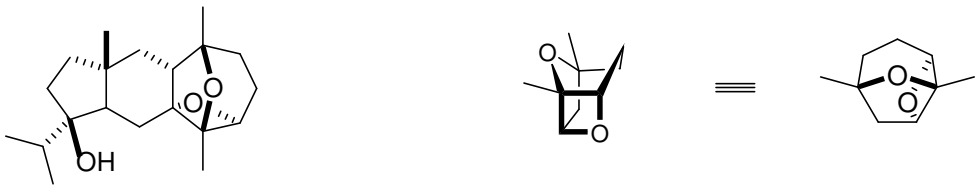
[25] Kuhn, D.; Coates, C.; Daniel, K.; Chen, D.; Bhuiyan, M.; Kazi, A.; Turos, E.; Dou, Q. P. *Frontiers in Bioscience*, **2004**, *9*, 2605.

[26] Gunda, T. E. "On the ß-Lactam Antibiotics." 1 June 2004 <http://www.cic.klte.hu/~gundat/betalaca.htm>.

2. Literature Review

2.1 Dioxatricyclic Subunits of Dictyoxetane

Research on the total synthesis of dictyoxetane **1** has focused on the synthesis of the oxatricyclic substructure **23**, the 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane (see Scheme 4). Three strategies have been published for the synthesis of this oxatricyclic skeletal structure. In 1995, J. Reinecke and H. M. R. Hoffmann reported the first synthesis of a 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane[27] (see Section 2.1.1). A second strategy appeared one year later by Heathcock *et al.*[28] (see Section 2.1.2). In 1998, J. Wittenberg and H. M. R. Hoffmann presented an improved *de novo* synthesis of deoxygenated and oxygenated dioxatricyclic segments with cytostatic activity towards tumor cells (see Section 2.1.3).[29] Following the same strategy, S. Proemmel and H. M. R. Hoffmann published the synthesis of new dioxatricyclic compounds in 2002 (see Section 2.1.4).[30] Amongst the reported oxetanes, one showed cytostatic activity towards tumor cells. More recently, M. Vidal Pascual synthesized a series of new ether substituted dioxatricyclononanes (see Section 2.1.5).[31]



1 Dictyoxetane
(relative stereochemistry)

23 dioxatricyclic core
[4.2.1.$0^{3,8}$]

Scheme 4: Dioxatricyclic core **23** from of dictyoxetane **1**.

2.1.1 Synthetic Strategy by J. Reinecke

The first strategy towards the synthesis of the dioxatricyclic framework **23** was designed starting from 2,5-dimethyl-8-oxabicyclo[3.2.1]ketone **25**, a valuable synthetic building block

[27] a) Reinecke, J. *PhD Thesis*, Universität Hannover, **1994**; b) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J*. **1995**, *1*, 3682.

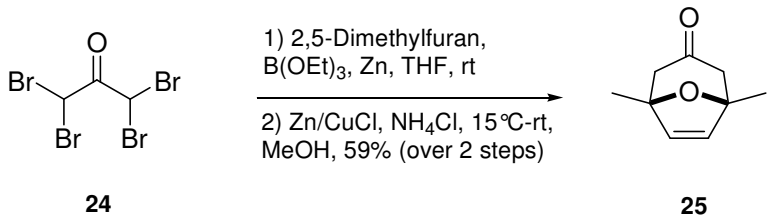
[28] Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9135.

[29] a) Wittenberg, J. *PhD Thesis*, Universität Hannover, **1998**; b) Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett*. **1998**, 39, 8259.

[30] Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199.

[31] Vidal Pascual, M. *PhD Thesis*, Universität Hannover, **2003**.

for the synthesis of several natural products.[32] [4+3] Cycloaddition between a furan ring and an oxyallyl cation offers rapid access to functionalized seven-membered carbocycles with and oxygen bridgehead, which already contain two of the three rings of the skeletal structure 2,7-dioxatricyclo[4.2.1.$0^{3.8}$]nonane **23**.[33]



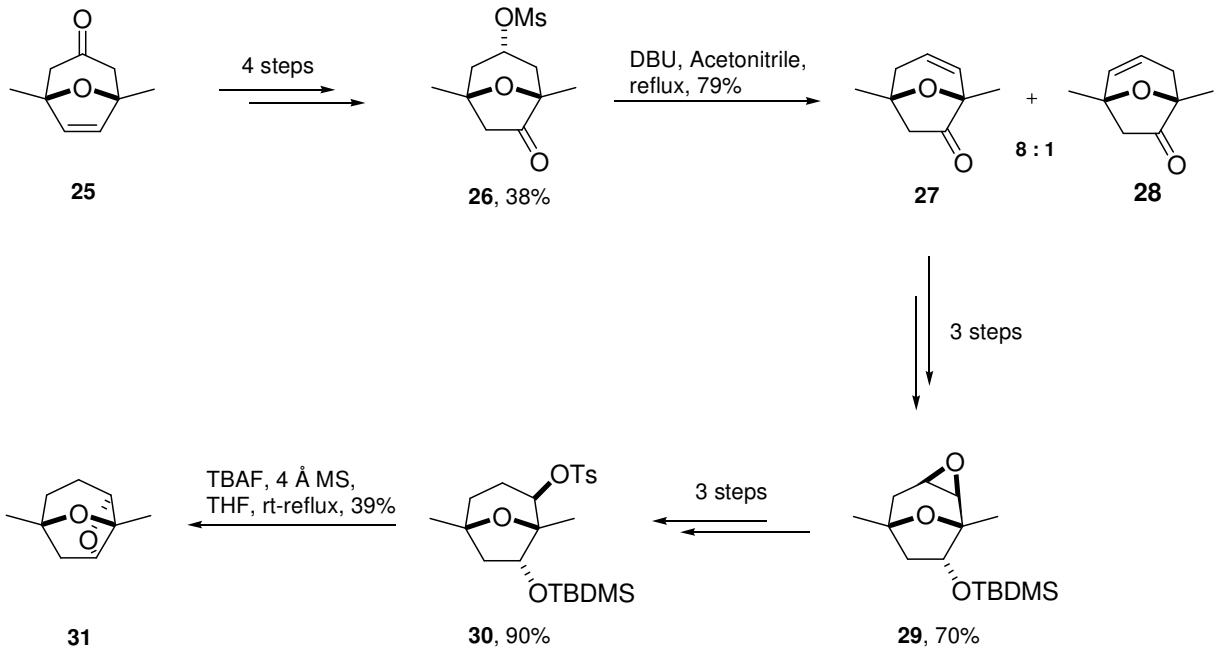
24 **25**

Scheme 5: Synthesis of 1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **25** by J. Reinecke.

1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **25** was prepared by the ethyl borate method introduced by Hoffmann and Iqbal from 2,5-dimethylfuran and 1,1,3,3-tetrabromo-2-propanone in 59% overall yield (see Scheme 5). Stereoselective reduction of oxabicyclic ketone **25** with diisobutylaluminium hydride (DIBAH) afforded the *endo*-alcohol, which was converted into the mesylate and then subjected to a combined hydroboration/oxidation to give ketomesylate **26** (see Scheme 6). A base mediated elimination of ketomesylate **26** afforded the desired ketoolefin **27** as the major product (**27**:**28** = 8:1). Moreover, the isomers **27** and **28** were separable by column chromatography. Isolated olefin **27** was then converted into precursor **30** over six steps in 63% overall yield. Deprotection and cyclization of tosylate **30** in a one-pot reaction proceeded well using tetrabutylammonium fluoride (TBAF) in the presence of molecular sieves. Dioxatricyclononane **31** was obtained as a volatile liquid in 39% yield. The low yield may be due to the low boiling point of oxetane **31**.

[32] [3.2.1]Oxabicycles as precursors in the synthesis of natural products, see: a) Weiss, J. M.; Hoffmann, H. M. R. *Tetrahedron Asymmetry* **1997**, *8*, 3913; b) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001; c) Beck, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **1999**, 2991; d) Dunkel, R.; Treu, J.; Hoffmann, H. M. R. *Tetrahedron Asymmetry* **1999**, *10*, 1539; e) Dunkel, R.; Hoffmann, H. M. R. *Tetrahedron Asymmetry* **1999**, *10*, 8385; f) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905; g) Misske, A. M.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 3313; h) Montaña, A. M.; García, F.; Grima, P. M. *Tetrahedron. Lett*. **1999**, *40*, 1375; i) Montaña, A. M.; García, F.; Grima, P. M. *Tetrahedron. Lett*. **1999**, *55*, 5483; j) Rama Rao, A.V.; Yadav, J.S.; Vidyasagar, V. *Chem. Comm*. **1985**, 55.

[33] For reviews in [4+3]-cycloaddition, see: a) Hoffmann, H. M. R. *Angew. Chem*. **1973**, *85*, 877; b) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163; c) Hoffmann, H. M .R. *Angew. Chem*. **1984**, *96*, 29; d) Mann, J. *Tetrahedron* **1986**, *42*, 4611; e) Hosomi, A.; Tominga, Y. *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p. 593; f) Lautens, M. *Top. Curr. Chem.* Metz, P.; Ed.; Springer: Berlin, **1997**, *190*, 1; g) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351.



25 **26**, 38% **27** **28**

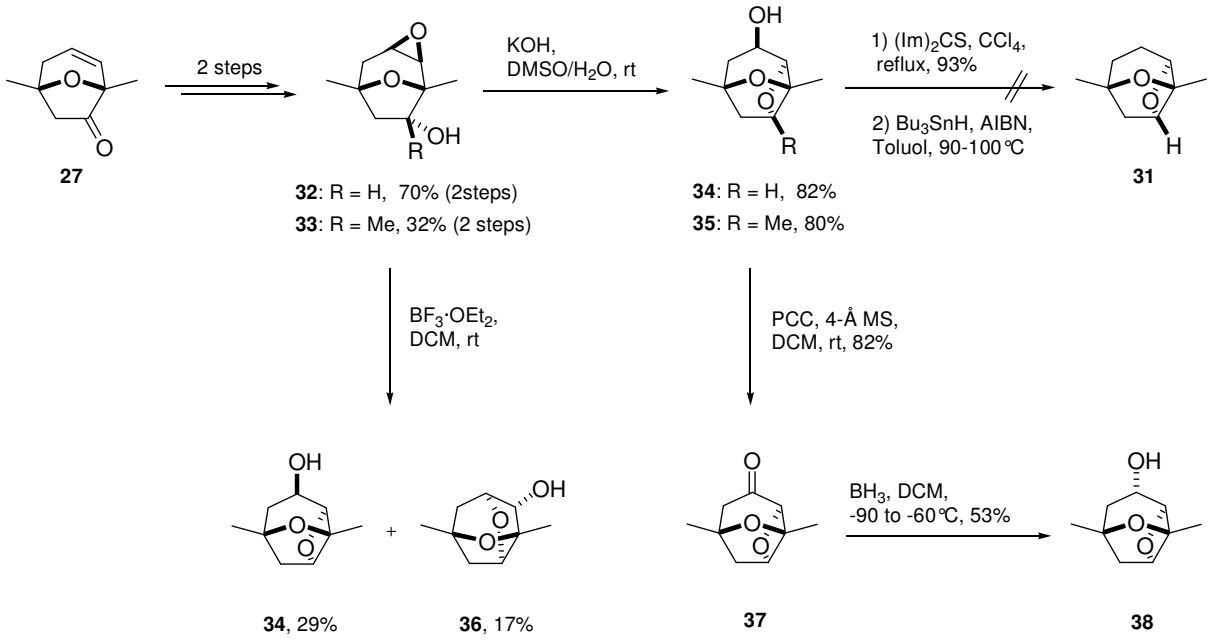
31 **30**, 90% **29**, 70%

Scheme 6: Synthesis of 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane **31** by J. Reinecke.

An alternative route to parent dioxatricycles **34** and **35** was also developed starting from ketoolefin **27** (see Scheme 7). Stereoselective reduction of the carbonyl group in oxabicycle **27** with DIBAH followed by epoxidation furnished tricyclic epoxide **32** in 70% yield over two steps. On the other hand, alkylation of **27** with methylmagnesium bromide followed by epoxidation led to epoxide **33** in 32% yield over two steps. Both epoxides **32** and **33** underwent a base-catalyzed intramolecular epoxide opening to give tricyclic oxetanes **34** and **35** in 82 and 80% yield, respectively. Deoxygenation of hydroxyoxetane **34** was attempted by means of radical methodology but oxetane **31** was not isolated. On the contrary, the labile oxetane system did not resist the Barton-Mc. Combie reaction conditions.

Tricyclic oxetane **34** was prepared not only under basic conditions but also under Lewis acid catalysis. Intramolecular epoxide opening of epoxy alcohol **32** with $BF_3{\cdot}OEt_2$ proceeded unselectively affording tricyclic oxetane **34** and isomeric tetrahydrofuran **36** in 2:1 ratio (see Scheme 7).

Finally, tricyclic oxetane **38** was afforded by inversion of the hydroxyl group at carbon C3 in hydroxyketone **34**. PCC oxidation of alcohol **34** afforded ketooxetane **37**, which was treated with BH_3 at low temperature giving epimeric alcohol **38** as the major product (**38:34** = 3.7:1) (see Scheme 7).

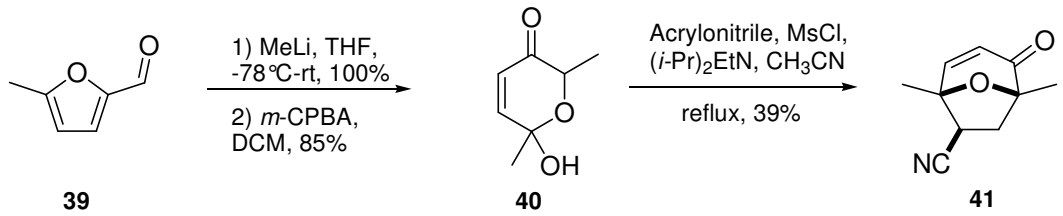


Scheme 7: Synthesis of substituted 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonanes **34, 35** and **38** by J. Reinecke.

2.1.2 Synthetic Strategy by Heathcock *et al.*

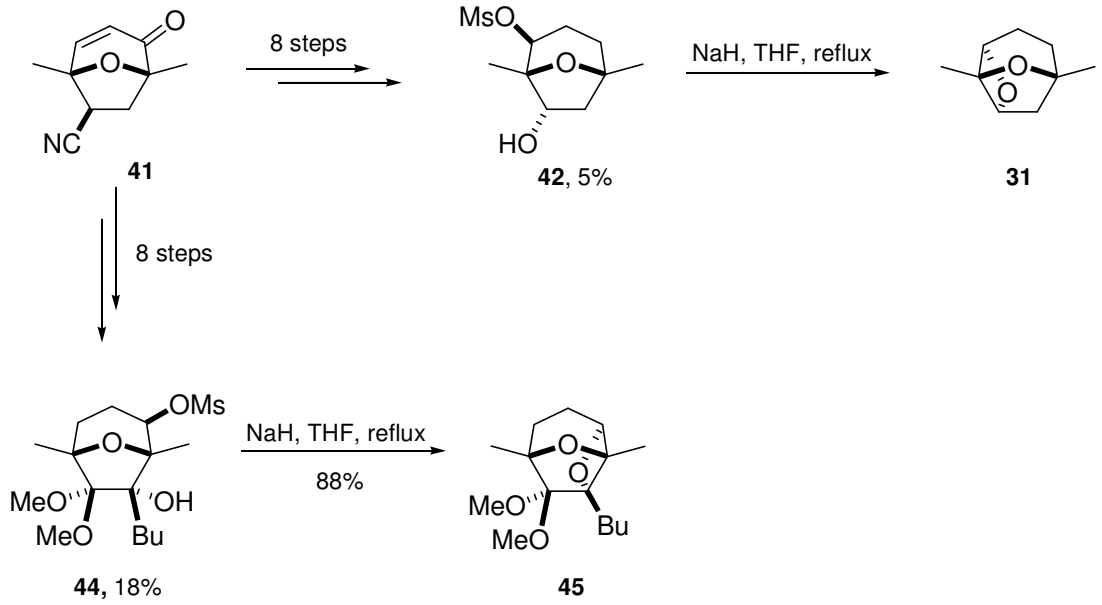
The second strategy for the synthesis of the tricyclic substructure of dictyoxetane was reported by Heathcock *et al.* in 1996.[28] The method chosen to construct the basic carbon skeleton of the target compounds **31** and **45** was a dipolar cycloaddition of a 3-oxidopyrylium salt with acrylonitrile.

The synthesis of intermediate bicyclic ketone **41** started from commercially available 5-methylfurfural **39**, which was treated with methyllithium followed by oxidative rearrangement using *m*-CPBA to give enone **40** in 85% yield. Reaction of acrylonitrile and hemiketal **40** in refluxing acetonitrile afforded desired cycloadduct **41** (see Scheme 8).



Scheme 8: Synthesis of basic carbon skeleton by dipolar cycloaddition of an oxidopyrylium salt and acrylonitrile by Heathcock *et al.*

Starting from oxabicyclic ketonitrile **41** oxetane precursors **42** and **44** were prepared following two synthetic paths and the key intermediates are highlighted in Scheme 9. On the one hand, oxabicyclic alcohol **42** was obtained in 5% yield over eight steps. Treatment of the oxetane precursor **42** with NaH in refluxing THF furnished volatile oxatricyclic oxetane **31**. Although the synthesized compound could not be isolated completely free of residual solvents, the ^{1}H NMR spectrum of the product indicated the formation of tricyclic diether **31**. Because of the high volatility of this compound, the model system was adjusted adding more molecular weight. Therefore, oxetane precursor **44** was prepared in 18% yield over eight steps. Mesylate **44** was cyclized under the same basic conditions affording oxatricyclic oxetane **45** in 88% yield. The synthesis of substituted dioxatricyclic oxetane **45** proceeded in better yields than that of the volatile oxetane **31.** For this reason, the substituted tricyclic oxetanes are preferred for the total synthesis of dictyoxetane.



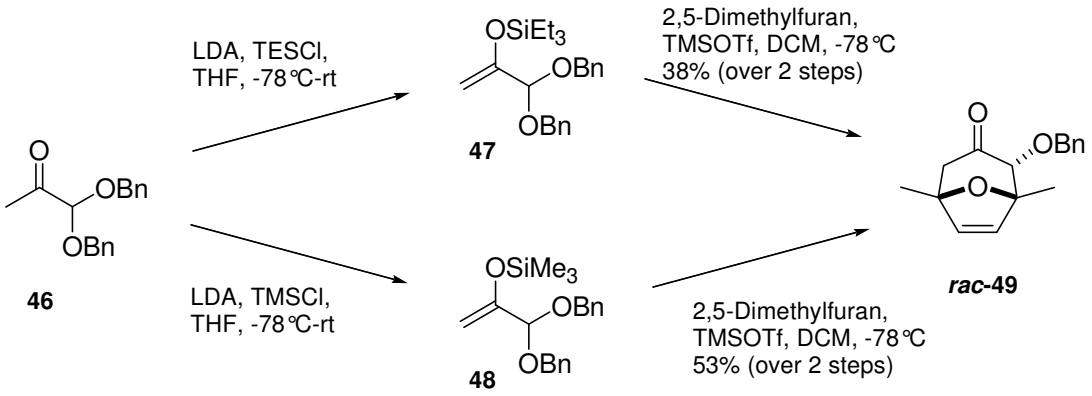
41 **42**, 5% **31**

44, 18% **45**

Scheme 9: Synthesis of substituted 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonanes **31** and **45** by Heathcock *et al.*

2.1.3 Synthetic Strategy by J. Wittenberg

The third strategy for the synthesis of the dioxatricyclic framework of dictyoxetane was reported by J. Wittenberg and H. M. R. Hoffmann.[29] Deoxygenated and oxygenated dioxatricyclononanes were obtained following a shorter synthetic pathway starting from α-*O*-benzylated oxabicyclo[3.2.1]ketone ***rac*-49** (Scheme 10).



Scheme 10: Synthesis of 2α-benzyloxy-2,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **49** by J. Wittenberg.

Much of the research work associated with [4+3] cycloaddition has been focused on approaches to generate appropriate oxyallyl cations and a number of useful synthetic methods have emerged.[33] The classic method developed by H. M. R. Hoffmann[34] with a polyhalogenated ketone as precursor of the oxyallylcation was used by J. Reinecke to construct the starting material of the synthesis of tricyclic oxetanes **31**, **34**, **37** and **38** as mentioned in Section 2.1.1. In the strategy of J. Wittenberg, oxyallyl cations were generated from non-halogenated precursors (bis-benzyloxy silyl enol ether) as reported by Albizati *et al.*.[35] The advantage of this method is the introduction of a α-benzyl ether in the oxabicyclic skeletal structure offering a wide range of applications in the synthesis of natural products, particularly in the construction of tetrahydropyran units.[36]

As outlined in Scheme 10, silyl enol ethers **47** and **48** were prepared from 1,1-bis-benzyloxy-propan-2-one **46** using LDA and the corresponding trialkyl silyl chloride (kinetic method). Treatment of silyl enol ethers **47** and **48** with a catalytic amount of TMSOTf afforded oxyallyl cations, which reacted with the 4π-component. The oxyallyl cation approaches both sides of the furan so that the 2α-benzyloxy-8-oxabicyclo[3.2.1]ketone ***rac*-49** is obtained as a racemate.[37]

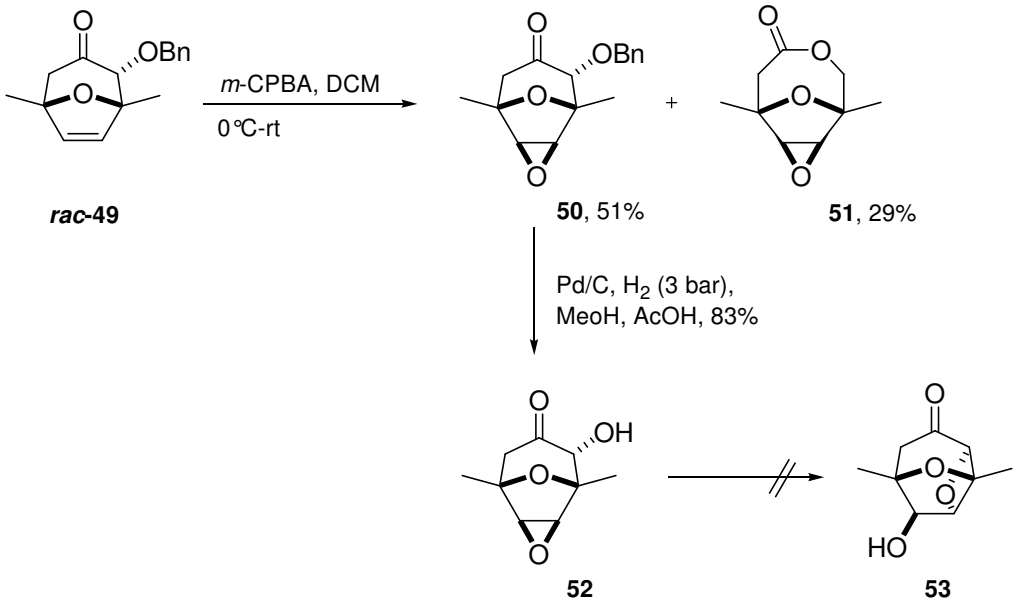
[34] Hoffmann, H. M. R. *Angew. Chem.* **1973**, *85*, 877.

[35] Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *29*, 4109.

[36] a) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem.* **1998**, *110*, 1337; b) Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 684; c) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315; d) Beck, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **1999**, 2991; e) Gaertzen, O.; Misske, A. M.; Wolbers, P.; Hoffmann, H. M. R. *Synlett* **1999**, 1041; f) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4317.

[37] Hoffmann, H. M. R. *Angew. Chemie* **1984**, *96*, 29; *Angew. Chemie, Int. Ed. Engl.* **1984**, *23*, 1.

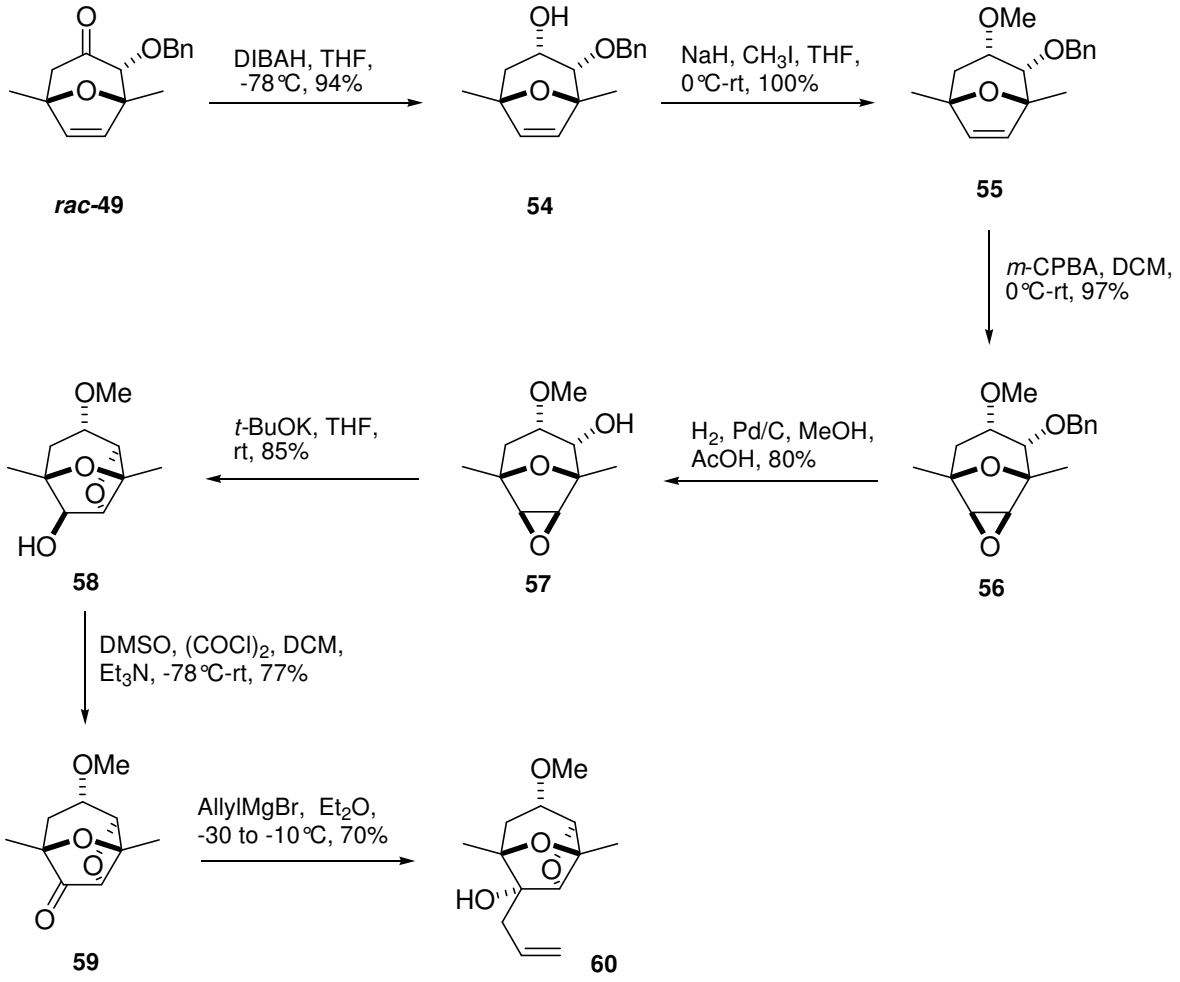
In a first strategy, the synthesis of oxatricyclic oxetanes was attempted without modifying the carbonyl function at C3 position (see Scheme 11). Epoxidation of oxabicyclic ketone ***rac*-49** yielded a mixture of desired ketoepoxide **50** and lactone **51**. Catalytic hydrogenolysis of isolated ketoepoxide **50** led to ketohydroxy alcohol **52**. Afterwards the attempted intramolecular cyclization of oxetane precursor **52** to oxetane **53** under either basic or acid catalysis was not successful. Presumably the presence of the carbonyl group (sp^2 carbon atom) in the oxabicycle increases the rigidity of the skeletal structure and the ring strain in the target molecule **53**.



Scheme 11: First attempted strategy for the synthesis of oxygenated dioxatricycles by J. Wittenberg.

Since the synthesis of tricyclic oxetane **53** was not feasible, a more efficient route was designed involving the stereoselective reduction of the carbonyl group in oxabicyclic ketone ***rac*-49** with DIBAH (see Scheme 12). Oxygenated and deoxygenated oxatricyclic oxetanes were then obtained starting from *endo*-alcohol **54** (see Scheme 12 and Scheme 13).

For the synthesis of oxygenated tricyclic oxetanes **58, 59** and **60**, methyl ether was chosen as protecting group for the hydroxy group at carbon C3. *Endo*-alcohol **54** was converted into methyl ether **55** and then epoxidized. Resulting epoxide **56** underwent debenzylation and yielded the oxetane precursor **57**. Following intramolecular cyclization of epoxy alcohol **57** proceeded under basic conditions using potassium *tert*-butoxide in THF. Oxatricyclic **58** was afforded in 62% overall yield starting from oxabicyclic ketone ***rac*-49** and in 33% overall yield starting from 1,1-bis-benzyloxy-propan-2-one **46**.

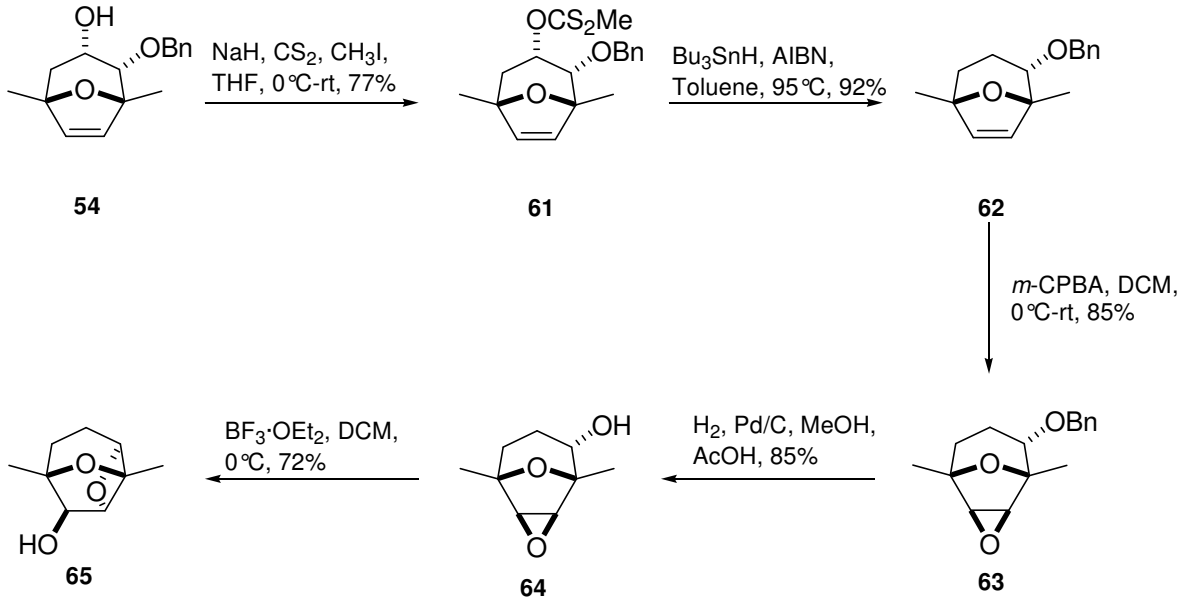


Scheme 12: Synthesis of oxygenated oxatricyclic oxetanes **58**, **59** and **60** by J. Wittenberg.

Swern oxidation of dioxatricyclic oxetane **58** led to tricyclic oxetane **59.** The oxetane ring in the tricyclic system showed stability upon treatment with Grignard reagents when ketone **59** was converted stereoselectively into *endo*-configurated tertiary homo allylic alcohol **60**.

The synthesis of deoxygenated oxatricyclic oxetane **65** was successful following the Barton-McCombie deoxygenation method, which was already used by J. Reinecke in a similar system.[27a] Deoxygenation was achieved prior to the formation of the oxetane ring by conversion of *endo*-alcohol **54** into S-methylthiocarbonate **61** followed by hydrogenation. Deoxygenated benzyl ether **62** was oxidized with *m*-CPBA and debenzylated to give oxetane precursor **64**. Under Lewis acid catalysis, epoxy alcohol **64** underwent intramolecular cyclization affording oxetane **65** in 72% yield. Starting from 1,1-bis-benzyloxy-propan-2-one **46**, oxatricyclic oxetane **65** was obtained in 18% overall yield, lower than in the case of oxygenated oxetane **58**. The higher hydrophilicity of deoxygenated oxatricycles as well as the

lower molecular weight explain the lower yields in the synthesis of the dioxatricyclic segment **65**.[29a]



Scheme 13: Synthesis of deoxygenated oxatricyclic oxetane **65** by J. Wittenberg

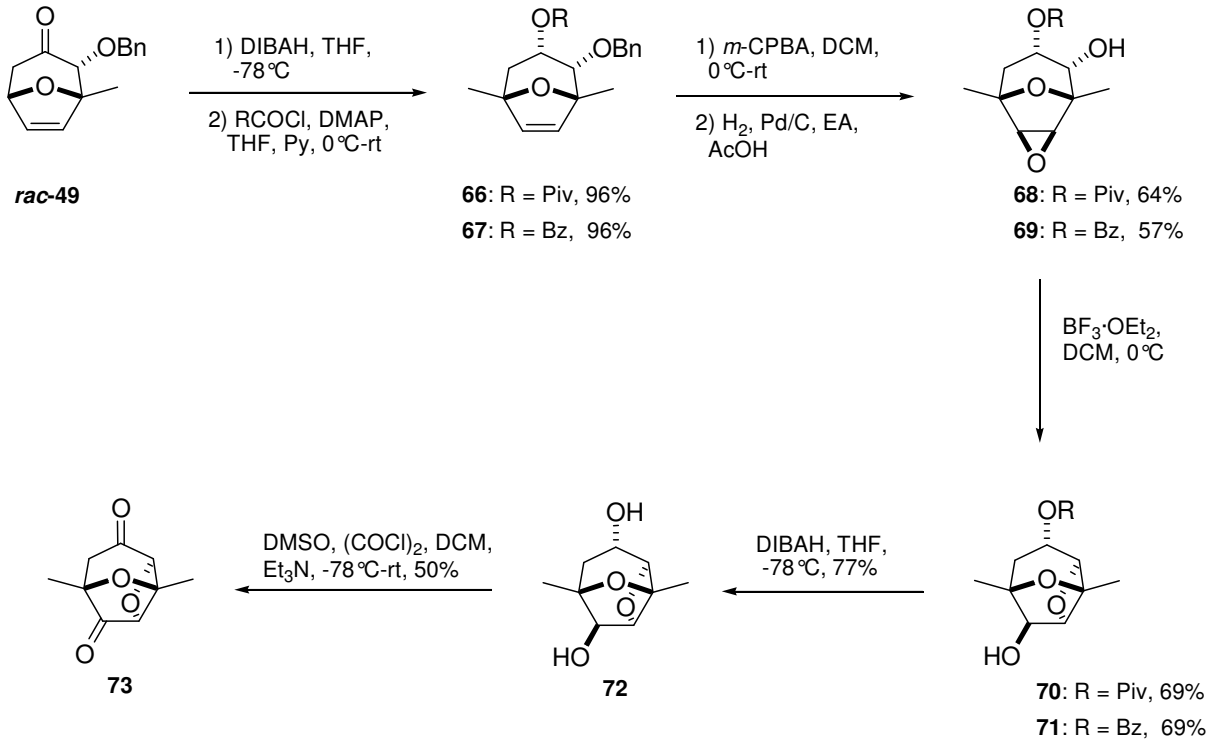
The four dictyoxetane segments **58, 59, 60** and **65** showed cytostatic activity towards HMO 2 and HEP G2 cell lines (see Section 2.1.6).

2.1.4 New Dioxatricycles by S. Proemmel

In 2002, S. Proemmel and H. M. R. Hoffmann reported progress on the synthesis of the dioxatricyclic substructure of dictyoxetane and its functionalization.[30] The oxatricyclic framework was prepared starting from oxabicyclic ketone ***rac*-49** as in the synthetic approach by J. Wittenberg. Pivaloate and benzoate were chosen to protect the hydroxy group at carbon C3 as an alternative to the more stable methyl ether, which need harsh conditions to be deprotected after the oxetane ring closure and leads to descomposition.[29a]

Starting from cycloadduct ***rac*-49**, the ketone was reduced stereoselectively with DIBAH and the resulting hydroxy group was protected quantitative to afford pivaloate **66** and benzoate **67** (see Scheme 14). Epoxidation of the homo allylic double bond followed by debenzylation led to oxetane precursors **68** and **69**. The key intramolecular ring closure of epoxy alcohols **68** and **69** was carried out under Lewis acid conditions using $BF_3 \cdot OEt_2$ in good yield. Starting from oxabicyclic ketone ***rac*-49**, benzoate substituted oxatricyclic oxetane **71** and pivaloate **70**

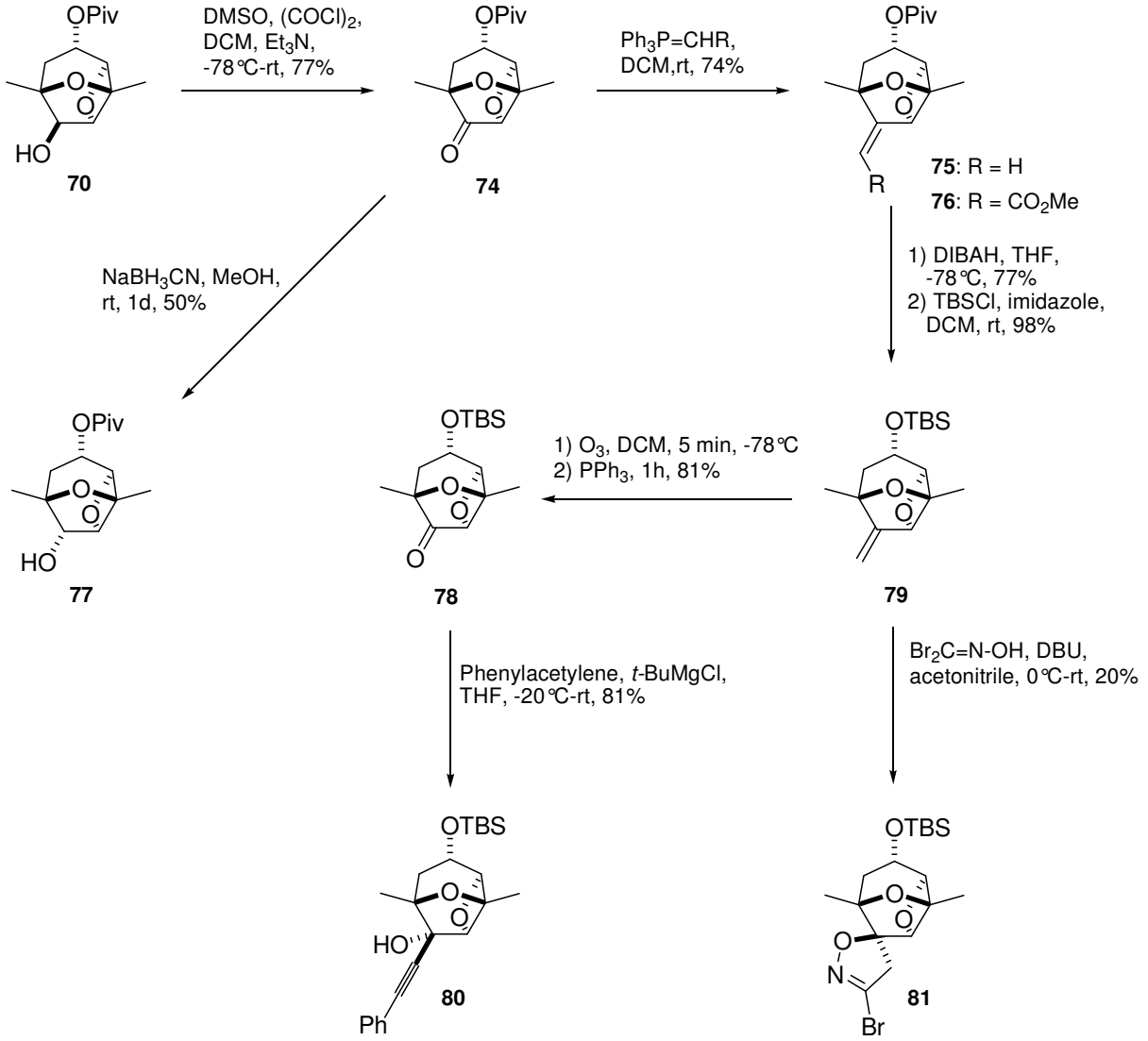
were obtained in 38 and 42 % overall yield respectively. The *tert*-butyl ester as protecting group proved to be the best choice for preparing tricyclic oxetanes.



Scheme 14: Synthesis of ester substituted oxetanes **70** and **71**, dioxatricyclic diol **72** and diketone **73** by S. Proemmel.

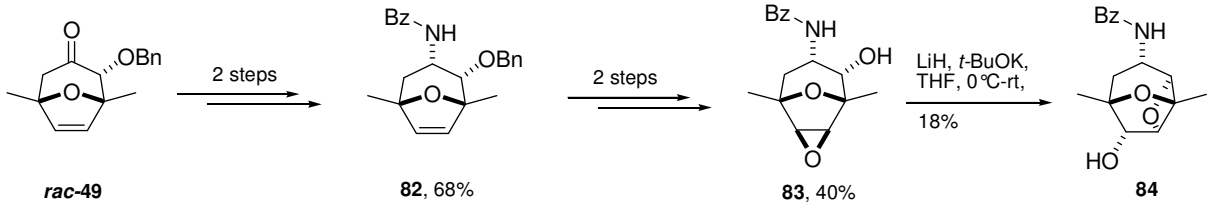
After cyclization, the ester was cleaved reductively to tricyclic diol **72**. In one-step, double oxidation of diol **72** yielded diketone **73.**

Further functionalization of the dioxatricyclic framework was carried out starting from pivaloate substituted oxetane **70** (see Scheme 15). Swern oxidation of the hydroxy group at carbon C6 afforded keto ester **74**, which was reduced to epimeric alcohol **77**. Wittig-olefination of keto ester **74** led to exocyclic olefins **75** and **76**. Olefin **75** was subjected to reductive cleavage of the pivaloate group and reprotection with TBSCl to give olefin **79**, which is the starting material for further transformations, like for example, nitrile oxide cycloaddition (**79→81**) or oxidative cleavage to silyl protected keto alcohol **78** followed by conversion into alkynyl substituted alcohol **80**. Remarkably, the pericyclic reaction as well as all the nucleophilic additions to the carbonyl group proceeded selectively from the *exo* face (*trans* to the oxetane oxygen), which appears to be more accessible.



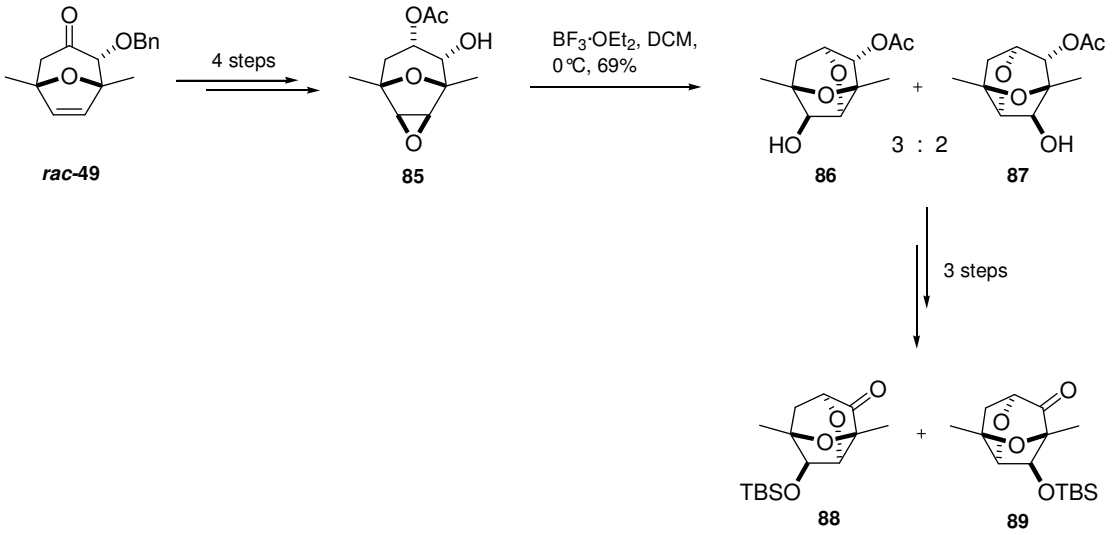
Scheme 15: Functionalization of the dioxatricyclic framework by S. Proemmel.

Following a similar route, the synthesis of aminated oxetane **84** was carried out starting from oxabicyclic ketone ***rac*-49** (see Scheme 16). Reductive amination of the carbonyl group in ketone ***rac*-49** was chosen as method to introduce an axial amino group at C3. The resulting amine was protected as *N*-benzamide **82** and then epoxidized and debenzylated to afford *N*-benzoyl protected tricyclic precursor **83**. Intramolecular cyclization of epoxy alcohol **83** proceeded under mild conditions in 18% yield. Aminated oxetane **84** was prepared in 5% overall yield over five steps, much lower than in the case of oxygenated dioxatricyclic oxetanes **70** and **71** because of the lability of the *N*-benzamide group.



Scheme 16: Synthesis of aminated oxetane **84** by S. Proemmel.

Attempted synthesis of dioxatricyclic oxetanes with acyl protection of the 3-hydroxy group yielded a mixture of bistetrahydrofurans **86** and **87** in 3:2 ratio (see Scheme 17). Under the cyclization conditions, the acyl group migrated to the thermodynamically favored equatorial position at carbon C2 and the free hydroxy group at carbon C3 underwent a facile 5-*exo*-tet cyclization leading to compounds **86** and **87**, which contains a noradamantane skeleton.



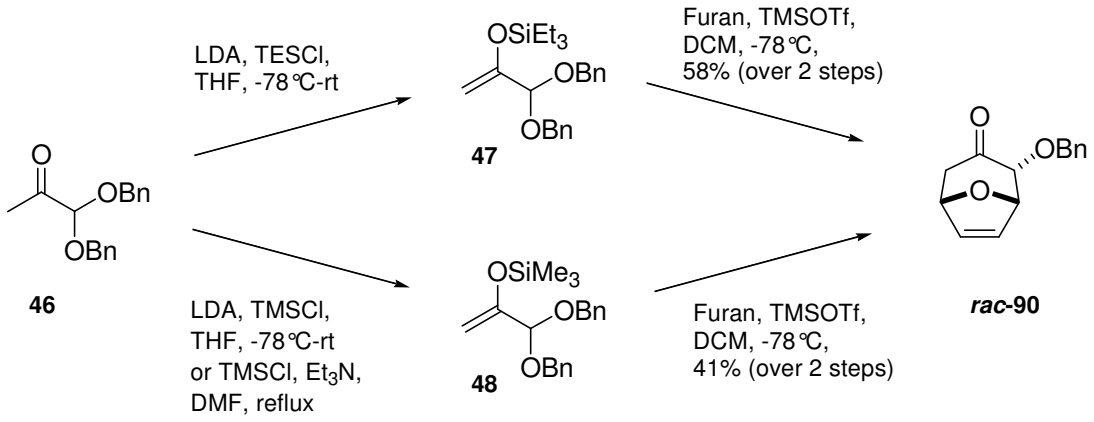
Scheme 17: Synthesis of tricyclic acetates **86** and **87** after migration of the acyl group and further functionalization by S. Proemmel.

Amongst dictyoxetane segments **70**, **71**, **72**, **73**, **74**, **75** and **76**, only dioxatricyclic ester **76** showed cytostatic but not cytotoxic activity towards tumor cells (see Section 2.1.6).

2.1.5 New Ether Protected Dioxatricycles by M. Vidal Pascual

Within the research work of M. Vidal Pascual, a series of ether protected oxatricyclic segments were prepared.[31] Following the synthetic approach by J. Wittenberg, the oxatricyclic framework was also constructed by [4+3] cycloaddition using trialkylsilyloxyallyl cations but furan was chosen instead of 2,5-dimethylfuran. The resulting oxabicyclo[3.2.1]oct-6-en-3-one

***rac*-90** was the starting material for the synthesis of the dioxatricyclic oxetanes (see Scheme 18).

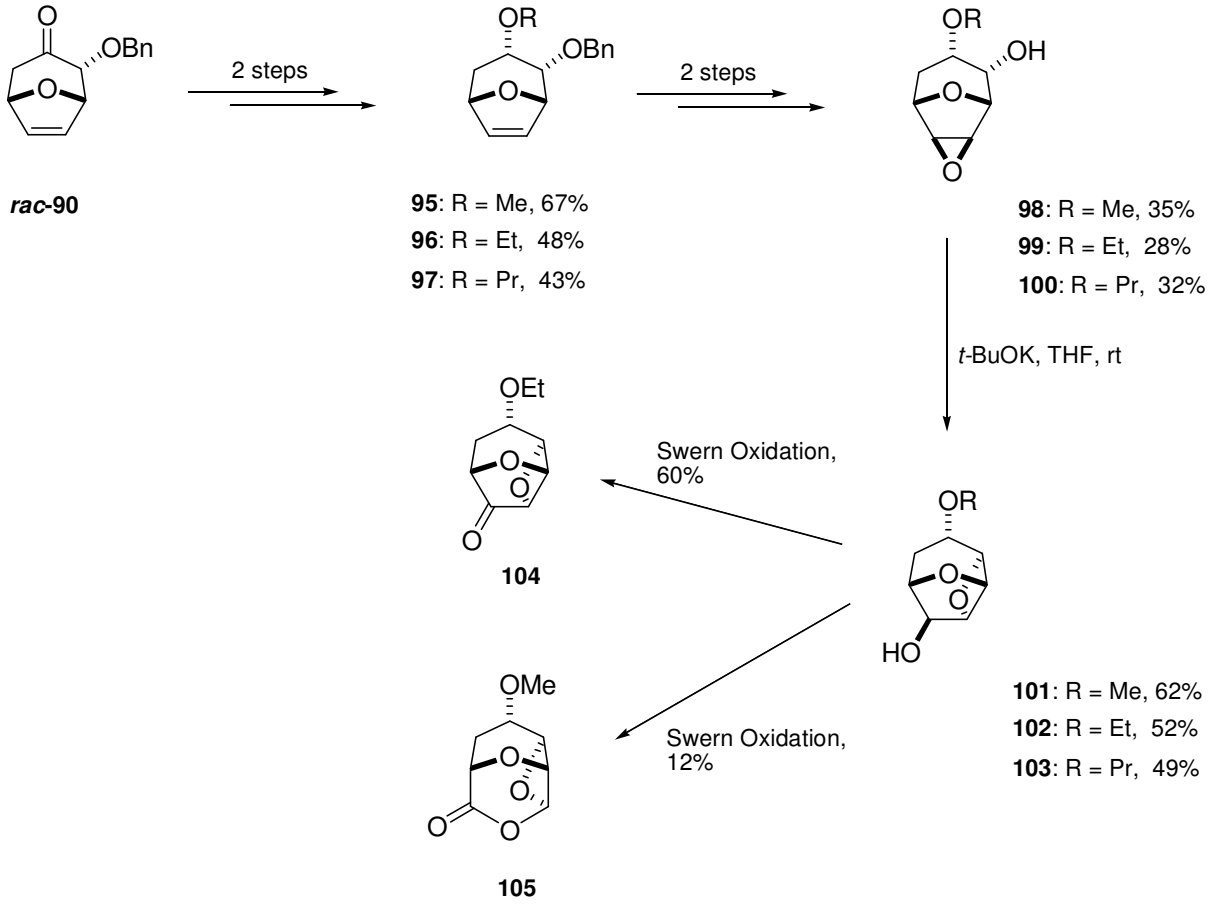


Scheme 18: Synthesis of oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-90** by [4+3] cycloaddition.

For the synthesis of oxabicyclic ketone ***rac*-90** two different silyl enol ethers **47** and **48** were prepared from 1,1-bis-benzyloxy-propan-2-one **46**.[38] Triethylsilyl enol ether **47** was prepared from 1,1-bis-benzyloxy-propan-2-one **46** by the kinetic method using LDA in THF at –78°C. Trimethylsilyl enol ether **48** was prepared either by the kinetic method or by the thermodynamic method (triethylamine in DMF at 75°C). In this case, the resulting trimethyl silyl enol ether cannot be purified by column chromatography because of its acid sensitivity and the crude product was used directly in the [4+3] cycloaddition reaction. The trialkylsilyl oxyallyl cation with a π-donating benzyloxy substituent was generated via treatment of triethylsilyl enolether with a catalytic amount of TMSOTf and following [4+3] cycloaddition , of the 4π-component (furan) proceeded smoothly giving 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-90**.

A series of ether protected dioxatricyclic segments were obtained following a similar route as in the case of J. Wittenberg (see Scheme 19). Starting from oxabicyclic ketone ***rac*-90** tricyclic oxetanes **101, 102** and **103** were synthesized in 5 steps in 15, 7 and 6% overall yield respectively. The absence of methyl groups at the bridgehead carbon atoms and the higher hydrophilicity of these compounds may explain the lower yields comparing to their parent dioxatricycles prepared from oxabicycle ***rac*-49**. Further funtionalization of oxatricyclic skeletal structures **102** and **101** afforded ketone **104** and lactone **105.**

[38] Vidal, M.; Martínez, C.; Hoffmann, H. M. R. *Org. Synth.* **2003** (submitted) and references therein.

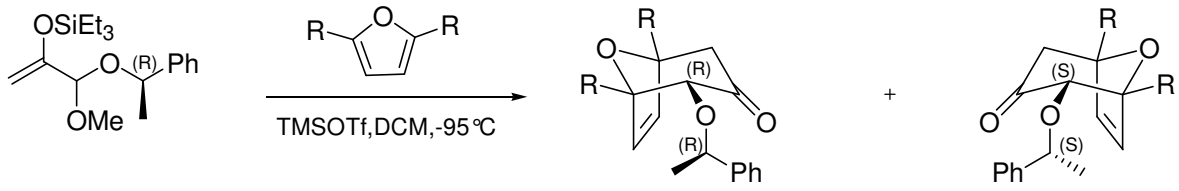


Scheme 19: Synthesis of ether substituted oxatricyclic oxetanes **101**, **102**, **103** and **104** and lactone **105** by M. Vidal Pascual.

Epoxy alcohol **98** and oxetane **101** were tested towards tumor cells and did not show cytostatic or cytotoxic activity.

2.1.6 Enantioselective Synthesis of Dioxatricyclic Subunits of Dictyoxetane

The synthesis of enantiopure dioxatricyclic subunits of dictyoxetane was reported by S. Proemmel and M. Vidal Pascual.[39] The asymmetric [4+3] cycloaddition with chiral oxyallyl cations developed by Hoffmann *et al.*[40] offered an efficient method for the enantioselective synthesis of oxabicycles.



R = H: (+)-(2*R*)-**107**, 74% (99% de) 7 : 1 (-)-(4*S*)-**108**

R = Me: (+)-(2*R*)-**109**, 40% (>97% de) 3 : 1 (-)-(4*S*)-**110**

Scheme 20: Diastereoselective asymmetric [4+3]cycloaddition to oxabicycles (+)-**107** and (+)-**109**.

Enantiomerically pure oxabicycles (+)-**107** and (+)-**109** were prepared by asymmetric [4+3] cycloaddition of furans to chiral silyloxyallyl cation generated from mixed acetal (*R*)-**106** following a low temperature protocol optimized by C. B. W. Stark (see Scheme 20).[40] The resulting [4+3] cycloadducts were isolated in high enantiomeric purity. Asymmetric [4+3] cycloaddition using furan afforded oxabicyclic diastereomers (2*R*)-**107** and (4*S*)-**108** in a 7:1 diastereomeric ratio and enantiopure oxabicycle (2*R*)-**107** was isolated in 74% yield and in 99% enantiomeric purity. In the case of 2,5-dimethylfuran, diastereoselectivity and chemical yield were lower owing to the presence of the methyl groups.[30,41] Enantiopure oxabicycle (2*R*)-**109** was isolated in 40% yield and in >97% enantiomeric purity.

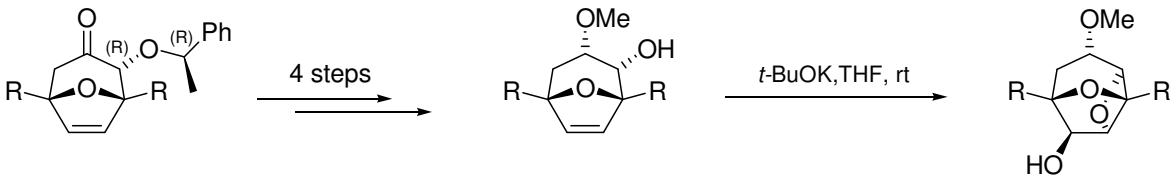
Enantiomerically pure oxabicyclic ketones (2*R*)-**107** and (2*R*)-**109** were the starting material of the enantioselective synthesis of dioxatricyclic segments oxetane (+)-**113** and (+)-**114**. Following the same strategy as for the synthesis of methoxy substituted oxetanes **58** and **101**, dioxatricyclic oxetane (+)-**113** and (+)-**114** were prepared in 14 and 63% overall yield (see

[39] Proemmel, S. *PhD Thesis*, Universität Hannover, **2001**; Vidal Pascual, M. *PhD Thesis*, Universität Hannover, **2003**.

[40] a) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem.* **1998**, *110*, 1337; b) Pierau, S.; Hoffmann, H. M. R. *Synlett* **1999**, 213; c) Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. R. M. *Chem. Eur. J.* **2000**, *6*, 684; d) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883.

[41] First diastereoselective asymmetric [4+3] cycloadditions with 2,5-dimethylfuran were carried out by S. Pierau, H. Beck und C. B. W. Stark. See: Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883.

Scheme 21). Higher yields were obtained for more sterically hindered (+)-**114**, presumably because of the stability conferred by the additional methyl groups and lower hydrophilicity of the compound.



(+)-**107**: R = H
(+)-**109**: R = Me

(+)-**111**: R = H, 27%
(+)-**112**: R = Me, 74%

(+)-**113**: R = H, 53%
(+)-**114**: R = Me, 85%

Scheme 21: Synthesis of enantiopure oxatricyclic oxetanes (+)-**113** and (+)-**114** by M. Vidal Pascual and S. Proemmel.

The anti-tumor activity of enantiopure oxetane (+)-**114** was tested but it showed neither cytostatic nor cytotoxic activity towards tumor cells.

2.1.7 Characterization of the Cytostatic and Cytotoxic Activity of Dioxatricyclic Segments

The anti-tumor activity of several dioxatricyclic segments of dictyoxetane was investigated considering the pharmacological potential attributed to the strained oxetane ring.[42] Five dioxatricycles have showed cytostatic activity towards tumor cells (see Scheme 22).

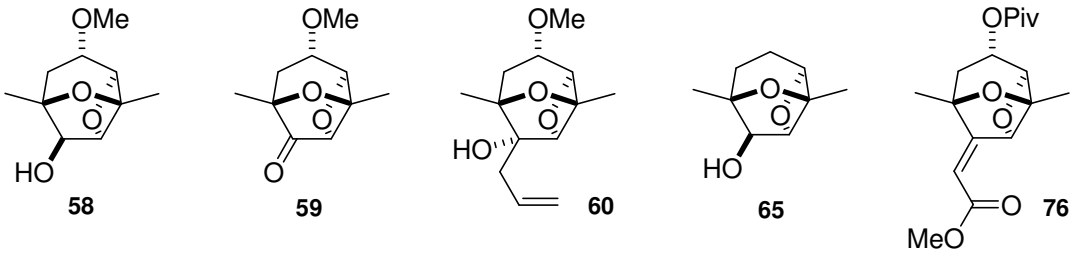
The cytostatic and cytotoxic activity of these dioxatricyclic segments was tested *in vitro*, via the HMO 2 (human gastric carcinoma), the HEP G2 (human heptocellular carcinoma) and the MCF 7 (mamma carcinoma) cell lines.[43,44] The antitumor activity was determined according to the NCI guidelines.[45]

[42] For the pharmacological potential of oxetane ring, see: a) Goez, C. E.; Wright, A. D.; König, G. M.; Sticher. O. *Phytochem. Anal*. 1994, *5*, 68; b) Rao, C. B.; Trimurtulu, G.; Sreedhara, C.; Rao, D. V.; Bobzin, S. C.; Faulkner, D. *J. Phytochemistry* 1994, *37*, 509; c) König, G. M.; Wright, A. D. *Tetrahedron* 1994, *50*, 8011; d) König, G. M.; Wright, A. D.; Fronczek, F. R. *J. Nat. Prod*. 1994, *57*, 1529; e) Knops, L.; Nieger, M.; Steffan, B.; Steglich, W. *Liebigs Ann.* 1995, 77; f) Rodrigues, A. D. *Tetrahedron* 1995, *51*, 4571, 4581; g) Corey, E. .; Kania, R. S. *Tetrahedron Lett*. 1998, *39*, 741.

[43] Pharmacological tests were carried out by Prof. W. Beil, Institut für Allgemeine Pharmakologie, Medizinische Hochschule Hannover.

[44] Cytostatic activity means a preventive action on growth and proliferation of tumor cells. Cytotoxic effect means an attack and destroying action in the tumor cells.

[45] Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622.



Scheme 22: Dioxatricyclic compounds with cytostatic activity towards tumor cells.

The data obtained from the concentration-extinction curves of the pharmacological assays of dioxatricycles **58, 59, 60** and **65** are listed in Table 1.

Compound	Carcinoma type	GI_{50}[a]	TGI_{50}[b]	LC_{50}[c]
58	HMO 2	3.0	57	>100
	HEP G2	<0.1	45	>50
59	HMO 2	<1.0	72	>100
	HEP G2	<0.1	35	>50
60	HMO 2	<1.0	54	>100
	HEP G2	<0.1	30	>50
65	HMO 2	4.0	50	>100
	HEP G2	0.1	30	>50
76	HMO 2	>50	>50	>50
	HEP G2	13	>50	>50
	MCF 7	10	>50	>50
5-fluorouracil	HMO 2	1.2	35	>50
	HEP G2	0.15	50	>50
***cis*-platinum**	HMO 2	0.1	2.5	40
	HEP G2	0.5	30	>50

Table 1: Antitumor activity (µmol/l) measured towards HMO 2, HEP G2 and MCF 7 cells. a) Drug concentration causing 50% growth inhibition; b) drug concentration causing 100% growth inhibition; c) drug concentration causing 50% reduction of the cells present at time point zero, i.e. at 24 h.

The internal limiting values for the evaluation of cytotoxicity based on standard cytostatic agents (5-fluorouracil or *cis*-platinum) are outlined in Table 2. Comparison between Table 1 and Table 2 indicates that all five substances **58, 59, 60**, **65** and **76** showed anti-tumor activity. Four of these dictyoxetane segments, **58, 59, 60** and **65**, showed cytostatic activity

towards HMO 2 and HEP G2 cell lines comparable to 5-fluorouracil, which is a well known metabolite capable of entering the synthesis and function of nucleic acids, similar to AZT, an anti-AIDS drug. The most potent substance towards the HMO 2 cell lines, dioxatricyclic **59**, inhibited cell growth by 68% at 1µmol/l. On the other hand, dioxatricyclic ester **76** showed cytostatic activity towards HEP G2 and MCF 7.

Evaluation of cytotoxicity	
good	GI_{50} < 1 µmol/L + TGI < 5 µmol/L
satisfactory	GI_{50} < 5 µmol/L + TGI < 10 µmol/L
weakly efficient	GI_{50} < 10 µmol/L or TGI < 50 µmol/L
inefficient	GI_{50} > 10 µmol/L

Table 2: Internal limiting values for the evaluation of cytotoxicity based on standard cytostatic agents (5-fluorouracil or *cis*-platinum).

Although the activity of these dioxatricyclic segments is lower than of the structurally related taxol®, both compounds contain a functionalized oxetane ring and their biogenesis are related.[46]

The anti-tumor activity shown by the above mentioned oxetanes demonstrates the pharmacological potential of the dioxatricyclic substructure of dictyoxetane, which is, moreover, easily available following an efficient synthetic route.

Variation of substituents in the dioxatricyclic framework is essential to provide more information to understand the pharmacological activity of this class of substances. Therefore, the synthesis and functionalization of new dioxatricyclic oxetanes and aza-analogues of the natural product dictyoxetane was one of the goals of the present work.

[46] a) Kobayashi, J.; Shigemori, H. *Heterocycles* **1998**, *47*, 1111, 1126; b) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *1*, 3682.

2.2 Aza-analogues of Dictyoxetane

2.2.1 Azetidines

Although the chemistry of azetidines has been developed almost simultaneously with the rapid growth of heterocyclic chemistry in the past decades, azetidines are still a rare class of compounds.[47] Medicinal and pharmacological properties of azetidines have been covered properly.[48] Most notable advances have been reported in the synthesis of azetidin-2-ones (ß-lactams) than in azetidine chemistry.

Azetidines are not especially labile even relatively stable towards basic conditions and nucleophiles. An evidence for their stability is that many routes leading to azetidines employ such conditions.

The most important method for the synthesis of azetidines is the cyclization of open-chain compounds, most generally by formation of the C-N bond. Few azetidines have been obtained by cycloaddition methods, by rearrangement of larger rings or by expansion of aziridines. The important developments of the ß-lactam chemistry in recent decades have provided several routes for the synthesis of azetidin-2-ones. As a consequence, many methods for the reduction of the carbonyl group of the ß-lactam to azetidine have also emerged.[47]

The chemistry of azetidines and its derivatives have been comprehensively reviewed.[47]

2.2.2 Azetidine Ring in the Dioxatricyclic Framework of Dictyoxetane

The synthesis of aza-analogues of the dioxatricyclic subunit of Dictyoxetane with an azetidine ring substituting the oxetane ring has not been accomplished until now. Such an intricate oxazatricyclic skeletal type has not been encountered in natural or unnatural compounds.[49] Therefore, the introduction of an azetidine ring in the tricyclic skeletal structure constitutes an important synthetic challenge and also, an access to potential pharmacological activity.

---

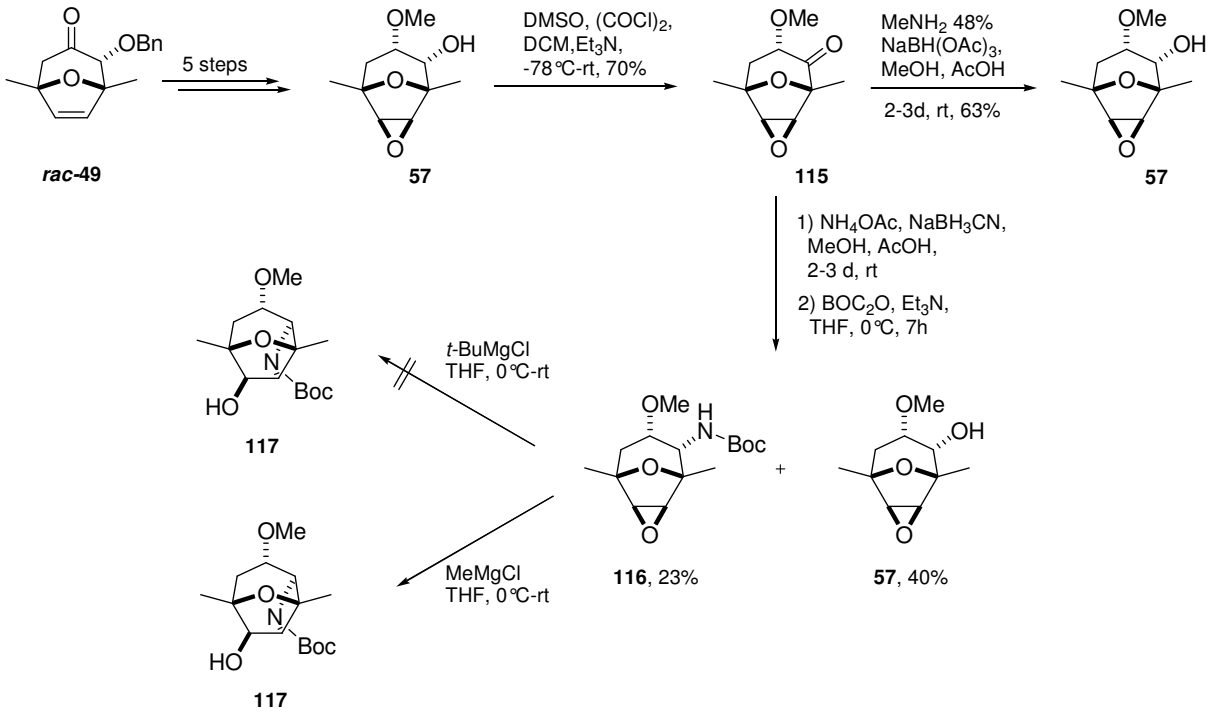
[47] a) Davies, D. E.; Storr, R. C. *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R.; Rees, C. W. Eds.; Pergamon Press: Oxford, 1984; Vol. 7, p. 237-362.; b) Moore, J. A. *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley:Chichester, 1983; Vol. 42.

[48] Testa, E.; Wittgens, A.; Maffii, G.; Bianchi, G. *Research Progress in Organic-Biological and Medicinal Chemistry*; Gallo, U.; Santamaria, L., Eds.; Società Editoriale Farmaceutica:Milan, 1994; Vol. 1.

[49] Beilstein on-line search.

2.2.2.1 Attempted Synthesis by S. Proemmel

The synthesis of tricyclic azetidines was attempted by S. Proemmel following a similar route to that of oxetanes (Scheme 23).[39] Starting from cycloadduct ***rac*-49**, epoxy alcohol **57** was synthesized as reported by J. Wittenberg.[29] Swern oxidation led to epoxy ketone **115** in 70% yield. Attempted reductive amination of epoxy ketone **115** with methylamine and sodium cyanoborohydride led exclusively to epoxy alcohol **57**, by-product from the competing reduction**.** On the other hand, attempted Borch reduction followed by protection with Boc group led to a mixture of epoxy alcohol **57** in higher ratio than desired amine **116**. Attempted cyclization using *tert*-butylmagnesium chloride did not afford tricyclic azetidine **117** whereas the reaction was less disappointing using methylmagnesium chloride; the azetidine was not characterized, though.



Scheme 23: Attempted synthesis of tricyclic azetidines by S. Proemmel.

The difficulties of the synthesis of primary epoxy amines using common reductive amination methods exemplify the hindered environment of the carbonyl group in the oxatricyclic epoxy ketones. The steric hindrance and electrophilicity of the epoxy ketone **115** possibly makes the imine intermediate formation difficult and, consequently, the competing reduction of the ketone is faster. In order to improve the results of the reductive amination, additives or step-

wise protocols should be employed instead of the common methods, which are less appropriate for sluggish reactions such as those involving tricyclic epoxy ketone **115**.

3. Conceptual Formulation

As part of one of the research projects in the work group of Prof. H. M. R. Hoffmann, the present work deals with the synthesis of new dioxatricyclic subunits of dictyoxetane and their analogous oxazatricyclononanes.

The first aim of the present work was the synthesis of new dioxatricyclic oxetanes starting from 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one. The introduction of different ester functions in the oxabicyclic skeletal structure was chosen as a promising alternative to improve the overall yield and allow an easier deprotection. As a broader goal, emphasis was put on the shortening of the synthetic route towards dioxatricyclic compounds.

The present work was also concerned with the development of an efficient strategy for the synthesis of higher functionalized dioxatricyclic structures. For this purpose, three possibilities were considered: functionalization of ester substituted oxetanes, introduction of an isoxazoline ring in the oxatricyclic skeletal structure and attachment of aryl and alkyl groups directly to the oxetane ring system.

Finally, the main aim was the development of a valuable synthetic route towards aza-analogues of the dioxatricyclic subunit of dictyoxetane. The synthesis of the oxazatricyclic compounds and their functionalization provide access not only to potential pharmacologically active compounds but also to versatile precursors of a wide variety of derivatives including azasugars.

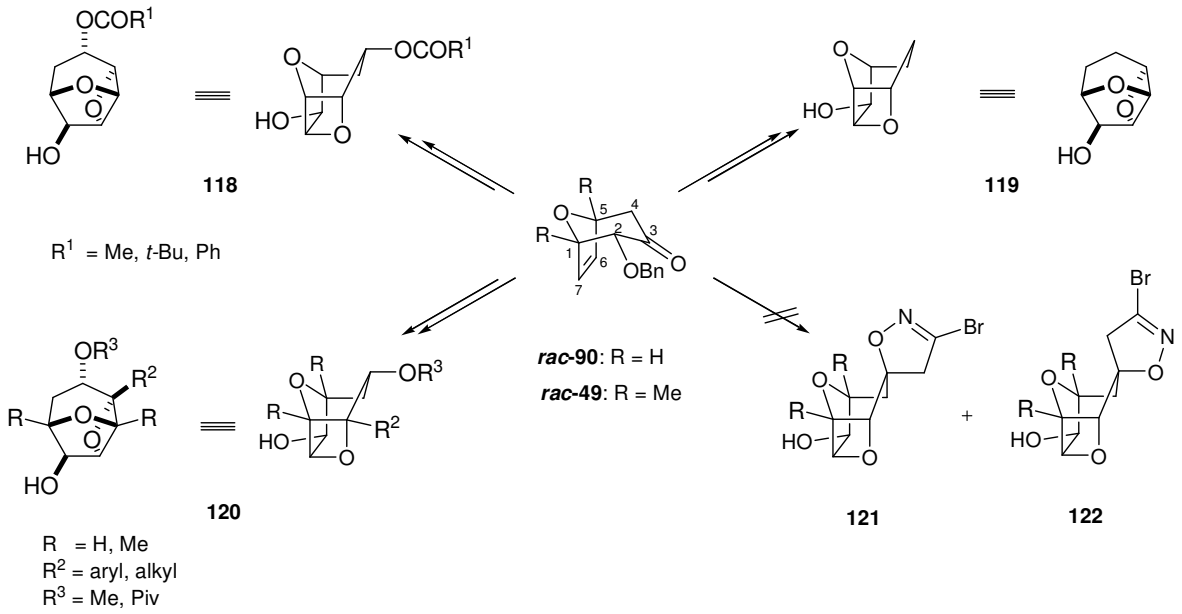
Because of the pharmacological potential of the dioxatricyclic subunits of dictyoxetane and its aza-analogues, the biological activity of new dioxatricyclononanes and oxazatricyclononanes was tested providing information to understand the structure-activity relationship of the oxatricyclic segments.

Results and Discussion

4. Synthesis of New Dioxatricyclic Subunits of Dictyoxetane

As described in Chapter 2, the biological activity shown by some dioxatricyclic subunits of dictyoxetane[50] stressed the importance of the synthesis of new dioxatricycles containing the skeletal structure 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane (see Scheme 24).

The first aim of the present work was the synthesis of new dioxatricyclic oxetanes from *meso*-oxabicycle ***rac*-90**. The introduction of different ester groups at carbon C3 offered the possibility of milder deprotection after ring closure and better overall yields (see Section 4.1). On the other hand, considering the dioxatricyclic framework of dictyoxetane with no functionality at carbon C3, the synthesis of deoxygenated dioxatricyclic oxetane **119** was carried out starting from *meso*-oxabicycle ***rac*-90** (see Section 4.2). The shortening of the synthetic route towards dioxatricyclic oxetanes was also investigated by means of Lewis acids (see Section 4.4).



Scheme 24: General synthetic strategy to obtain new dioxatricyclic oxetanes starting from *meso*-oxabicycles ***rac*-49** *and* ***rac*-90**.

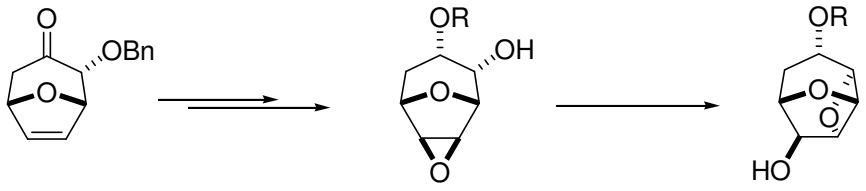
[50] See Chapter 2.

A second aim of the present work was the synthesis of higher functionalized dioxatricyclic structures starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**. For this purpose, a further functionalization of ester substituted oxetane **118** was studied starting by oxidation of the hydroxyl group at C6 (see Section 4.3). The introduction of an isoxazoline ring at carbon C3 in the oxatricyclic skeletal structure **121** and **122** was also investigated since a wide variety of open chain compounds are accessible by cleavage of the N-O bond (see Section 4.5). Finally, attachment of aryl and alkyl groups directly to the oxetane ring led to the synthesis of valuable C2-arylated and alkylated dioxatricyclic oxetanes **120** (see Section 4.6).

4.1 Synthesis of Tricyclic Oxetanes with an Ester Function at Carbon C3

As mentioned in Chapter 2, oxygenated tricyclic oxetanes are synthesized following a short route, which involves protection of the hydroxyl group at C3 position from unwanted reactions (see Scheme 25).

The low overall yield of the synthesis of ether substituted dioxatricyclic oxetanes starting from *meso*-oxabicycle ***rac*-90**[51] as well as the reported difficulties to cleave the ether function after ring closure[52] stressed the importance of an alternative synthesis of dioxatricyclic substructure **10** without methyl groups at the bridgehead carbon atoms. Consequently, the use of alternative protecting groups to the more stable ethers was considered in the present work.



***rac*-90** **123** **124**

Scheme 25: Synthetic strategy to oxygenated dioxatricyclic structures.

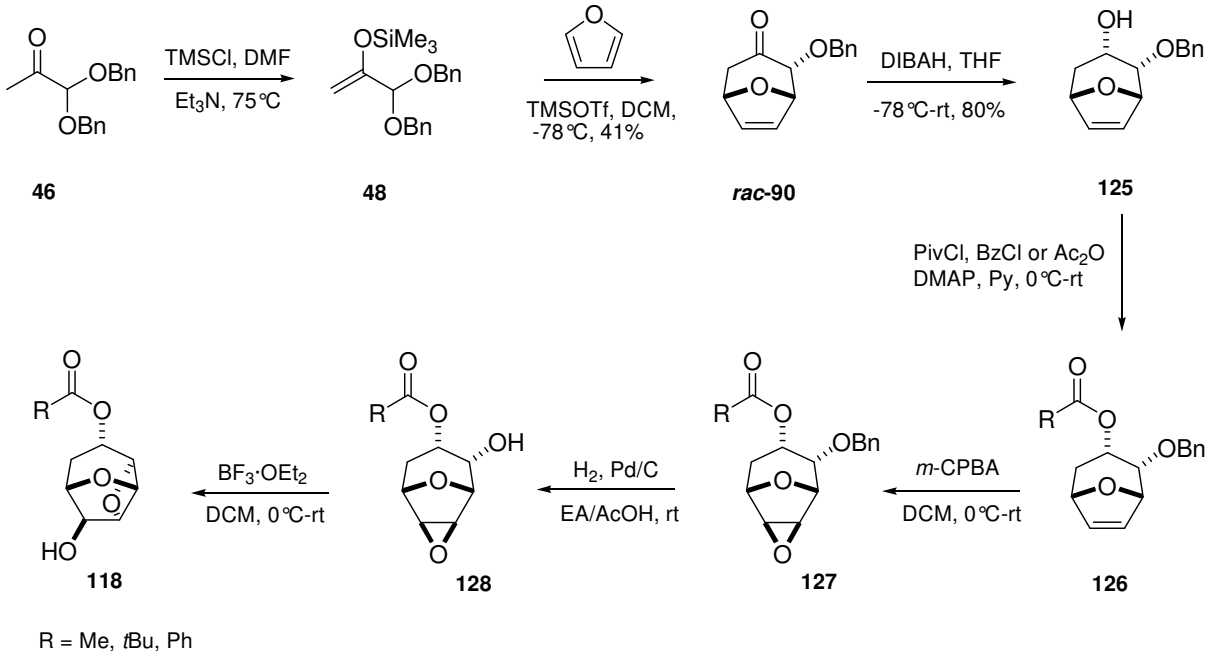
Protection of the 3-hydroxyl group with silyl ethers proved to be inappropriate in the synthesis of tricyclic oxetanes by J. Wittenberg. Even a bulky TBDMS-group shows a 1,2-migration tendency as long as an alkoxy anion is generated in the bicyclic vicinal diol under

[51] Vidal Pascual, M. *PhD Thesis*, University of Hannover, **2003**.

[52] a) Wittenberg, J. *PhD Thesis*, Universität Hannover, **1998**; b) Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Le*tt. **1998**, 39, 8259.

the reaction conditions.[52] In contrast to silyl ethers, the use of an ester as protecting group for the hydroxyl group offers the alternative to a more efficient synthetic pathway.

The synthesis of oxygenated dioxatricyclic oxetanes **124** with an ester function at carbon C3 was accomplished following the efficient synthetic pathway outlined in Scheme 26, which has been explained in detail in Section 2.1.[50] Silyl enolether **48** of 1,1-*Bis*-benzyloxy propanone **46** underwent a trimethylsilyltriflate-catalyzed [4+3]-cycloaddition with furan affording *meso*-oxabicycle ***rac*-90.**[53] Diastereoselective reduction with DIBAH of cycloadduct ***rac*-90** provided exclusively endo-alcohol **125**, which was protected afterwards using different ester functions. Epoxidation of the homoallylic double bond proceeded stereoselectively to afford epoxide **127**. Mild catalytic hydrogenolysis of epoxy ester **127** led to ester **128**, which are substituted precursors of the dioxatricyclic dictyoxetane segments. Finally, the key four-membered ring closure to oxetane **118** was carried out with $BF_3{\cdot}OEt_2$ in DCM.



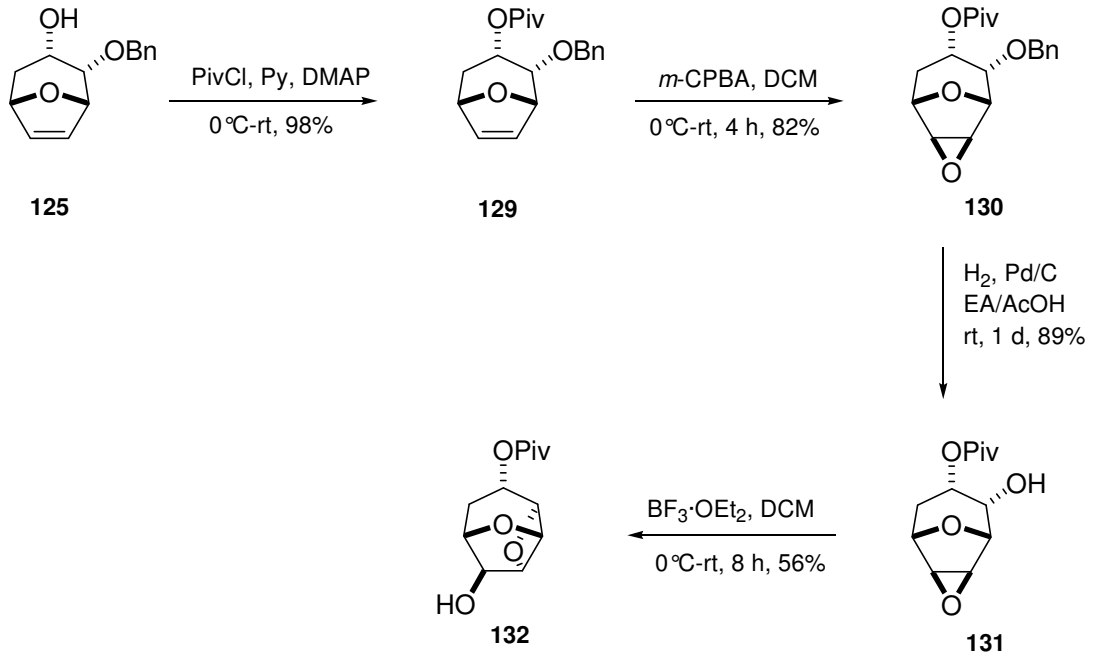
Scheme 26: Proposed synthetic route to prepare dioxatricyclic oxetanes with an ester function at C3.

4.1.1 Pivaloate as Protecting Group

The synthesis of oxygenated dioxatricyclic oxetanes with an ester was first accomplished using pivaloate as protecting group for the hydroxyl function at carbon C3. Compared to other commonly used ester protecting groups, pivaloates do not show any tendency for migration

[53] Vidal, M.; Martínez, C.; Hoffmann, H. M. R. *Org. Synth.* **2003** (submitted).

and are more stable. Thus, pivaloates are slow to deprotect in contrast to acetates and their cleavage may require strongly basic reagents. Nevertheless, deprotection of the pivaloate group in similar dioxatricycles proceeded in good to high yield by using DIBAH in THF.[54]



Scheme 27: Synthesis of oxetane **132** with pivaloate as protecting group at carbon C3.

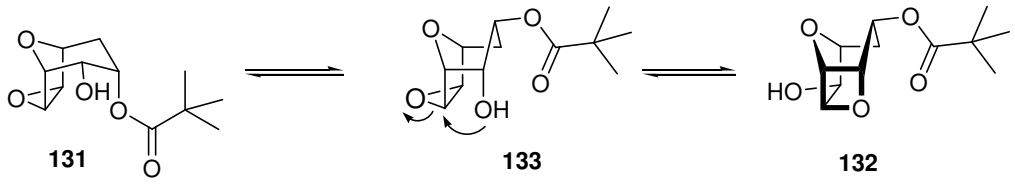
Following the above mentioned route for the synthesis of dioxatricycles, racemic axial alcohol **125** was quantitavely protected as its pivaloate **129** under standard conditions adding a catalytic amount of 4-dimethylaminopyridine (DMAP),[55] which increases the rate of acylation by a factor of 10^4. The homoallylic double bond was then oxidized to *exo*-epoxide **130** with *m*-CPBA in DCM at 0 °C. Afterwards, the benzyl ether group was cleaved by catalytic hydrogenolysis using 10% Pd/C as catalyst. The debenzylation reaction time was faster in ethyl acetate than in methanol. The following key ring closure of epoxy alcohol **131** was carried out with $BF_3 \cdot OEt_2$ in DCM in good yield (see Scheme 27).

The conformational aspects of the key cyclization to oxetane **132** are illustrated in Scheme 28. The conversion of epoxy alcohol **131** into oxetane **132** is a cycloisomerization, in which a four-membered ring is formed at the expense of a three-membered ring. A conformational change in epoxy alcohol **131** must precede the reaction. The six-membered oxacyclic ring has to populate a minor boat **133**, which brings the hydroxyl group sufficiently close for a

[54] Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199.

[55] Kociénski, P. J. *Protecting Groups;* G. Thieme: Stuttgart, 1994.

stereoelectronically favoured formation of the new oxetane C-O bond. After formation of the tricyclic oxetane, the bulky substituent adopts a less hindered equatorial position in an oxacyclohexane boat **132**. Therefore, pivaloyl protection is advantageous to force formation of oxetane **132** from epoxy alcohol **131**.



Scheme 28: Conformational aspects of the key cyclization to oxetane **132**.

Summarizing, the synthesis of pivaloate substituted dioxatricyclic oxetane **132** proceeded smoothly over four steps in a 40% overall yield without unwanted by-products. Furthermore, the absence of acyl migration as well as a forcing effect in the formation of the oxetane ring showed the advantages of the pivaloyl protection.

4.1.2 Benzoate as Protecting Group

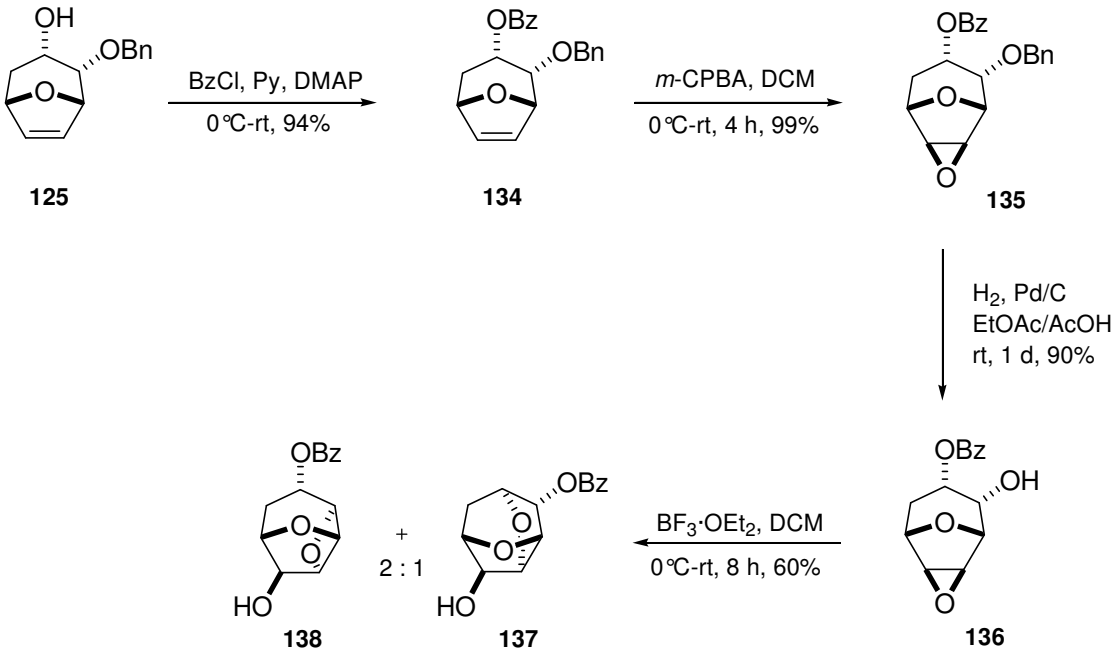
The synthesis of ester substituted dioxatricyclic oxetanes was further studied using benzoate as protecting group for the hydroxyl group. Benzoates esters are less readily hydrolyzed than acetates and not as slow as pivaloates to be cleaved. Moreover, the tendency for benzoate migration to adjacent hydroxyls, in contrast to that of acetates, is not nearly as strong,[56,57] although they can be forced to migrate under a strong driving force, e. g. to a thermodynamically more stable position.[58,59] In view of these advantages, the synthesis of a dioxatricyclic oxetane with a benzoate protecting group was promising.

[56] Fromageot, H. P. M.; Reese, C. B.; Sulston, J. E. *Tetrahedron* **1968**, *24*, 3533.

[57] Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11.

[58] Danishefsky, S. J.; DeNinno, M. P.; Chen, S-hui *J. Am. Chem. Soc.* **1988**, *110*, 3929.

[59] a) Nicolau, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674-8680; b) LeBel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624.



Scheme 29: Synthesis of oxetane **138** with a benzoate group at C3 position.

The synthesis towards desired oxetane **138** started with quantitative conversion of racemic alcohol **125** to benzoate **134** using BzCl and DMAP. Alkene **134** was oxidized with *m*-CPBA in excellent yield and the resulting epoxy bicycle **135** was afterwards debenzylated under H_2 atm with Pd/C as catalyst. The hydrogenolysis was completed after 1 day and changing the solvent (EA, MeOH or EtOH) did not alter the reaction time. Upon treatment of epoxy alcohol **136** with $BF_3{\cdot}OEt_2$, a mixture of desired oxetane **138** and dioxatricycle **137** was obtained in a 2:1 ratio in 60% yield (see Scheme 29). Dioxatricycle **137** resulted from the migration of the benzoate group to the more stable equatorial position at carbon C2 followed by a 5-*exo*-tet cyclization. Compounds **137** and **138** were not separable by column chromatography.

The synthesis of benzoate protected dioxatricyclic oxetane **138** was less efficient than in the case of pivaloyl protection since the benzoate group showed a tendency to migrate and the overall yield (34%) was lower than that of pivaloate (40%).

4.1.3 Acetate as Protecting Group

The next step was the synthesis of an oxygenated dioxatricyclic oxetane with a methyl ester group at carbon C3 which would also favor a later enzymatic resolution. Acetate is probably the most employed of all the ester protecting groups and a common substrate in enzymatic

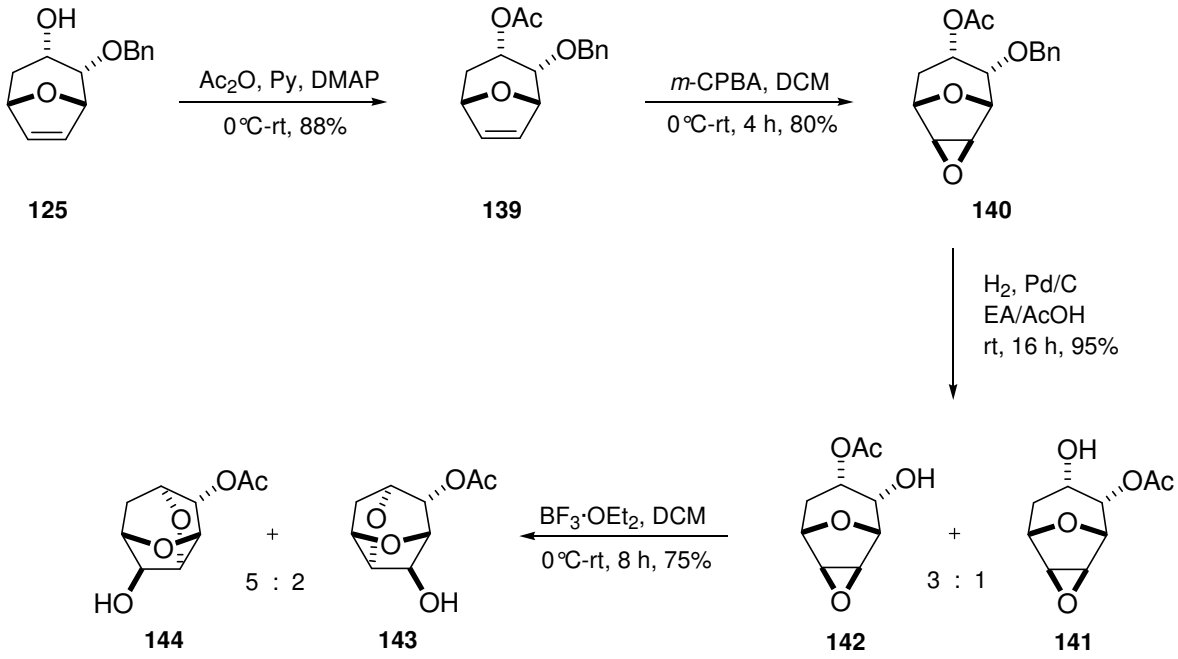
reactions. Deprotection of acetates proceed under mildly basic conditions, by acid catalyzed solvolysis (transesterification) or by enzymatic hydrolysis using high stereoselective and substrate selective esterases (lipases) with the added benefit that racemic or *meso*-substrate can often be resolved with excellent enantioselectivity.[60] The synthesis of a dioxatricyclic oxetane with an acetate group at C3 would offer not only the possibility of a milder deprotection of the hydroxyl group at carbon C3 but also a valuable later enzymatic hydrolysis of the *meso*-compounds in order to determine their absolute configuration.

Following the same synthetic route as for the preceding ester substituted oxetanes, racemic alcohol **125** was converted to acetate **139** and then treated with *m*-CPBA to obtain epoxide **140** in good yield. Hydrogenolytic debenzylation with a catalytic amount of 10% Pd/C yielded a mixture of desired product **142** and epoxy alcohol **141**, resulting from the 1,2-migration of the acyl group to the equatorial position, in a 3:1 ratio. Changing the solvent (EA, MeOH or EtOH) did not alter the ratio of products **142** and **141**. Compounds **142** and **141** were not separable by column chromatography and, therefore, the mixture of both epoxy alcohols was treated with $BF_3{\cdot}OEt_2$ leading to dioxatricycles **143** and **144** in a 5:2 ratio without traces of desired oxetane (see Scheme 30). Dioxatricycles **143** and **144** were not separable by column chromatography either.

Similarly to the reported migration of the benzoate group (see Section 4.1.2), the axial acetate in epoxy alcohol **142** migrated to the adjacent equatorial position. Moreover, in the case of acetate protection, the acyl migration occurred not only under Lewis acid conditions ($BF_3{\cdot}OEt_2$) but also under the acidic conditions of the hydrogenolytic debenzylation. After cis-migration of the acyl group to the thermodynamically favoured equatorial position at carbon C2, the free hydroxyl group at carbon C3 underwent a facile 5-*exo*-tet cyclization leading to compounds **143** and **144**, which contain the skeletal structure of thromboxan A_2 analogues (TXA_2).[61]

[60] a) Wang, Y.-F; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *Enzymes in Organic Synthesis* **1985**, (*Ciba Foundation Symposium*, Vol. 111), 128; b) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189; c) Csuk, R.; Glaenzer, B. I. *Z. Naturforsch. B, Chem. Sci.* **1988**, *43*, 1355; d) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073; e) Naemura, K.; Takahashi, N.; Chikamatsu, H. *Chem. Lett.* **1988**, 1717; f) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735; g) Deardoff, D. R.; Matthews, A. J.; McMeekin, D.S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255; h) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061.

[61] See Section 1.1.

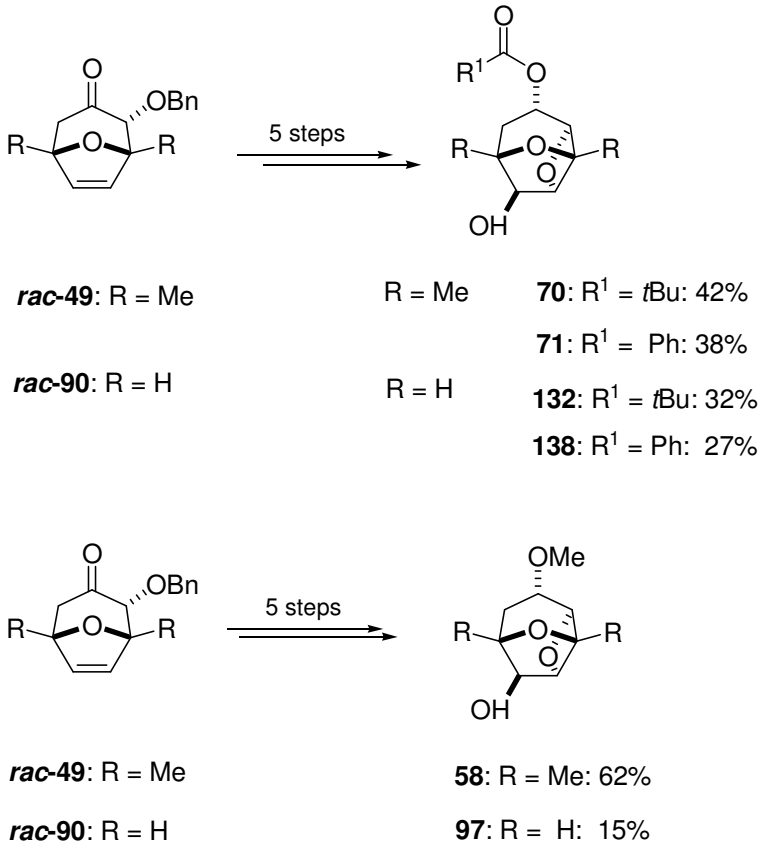


Scheme 30: Synthetic route towards dioxatricycles **144** and **143** using acetate as protecting group.

In view of the foregoing results, the synthesis of acetate substituted dioxatricyclic oxetanes as substrates for enzymatic resolution failed because of the acyl migration tendency. In Chapter 5, other alternatives for determination of the absolute configuration of dioxatricyclic compounds are outlined.

4.1.4 Summary of the Synthesized Ester Substituted Dioxatricyclic Oxetanes and Comparison with Similar Dioxatricyclic Substructures

Starting from *meso*-oxabicycle ***rac*-90**, the synthesis of oxygenated dioxatricyclic oxetanes **132** and **138** with pivaloate and benzoate as protecting groups was accomplished offering a milder deprotection after ring closure. *Tert*-butylester proved to be the best choice for preparing tricyclic oxetane compared to benzoate and acetate since pivaloate did not show any tendency for migration of the acyl function. Furthermore, pivaloate substituted dioxatricyclic oxetane **132** was obtained starting from *meso*-oxabicycle ***rac*-90** over five steps in 32% overall yield, better than that of benzoate **138** (27%) (see Scheme 31).



Scheme 31: Comparison of different dioxatricyclic oxetanes from *meso*-oxabicycles ***rac*-49** and ***rac*-90.**

Comparing the synthesis of ester-substituted dioxatricyclic oxetanes **132** and **138** from *meso*-oxabicycle ***rac*-90** to that of ester-substituted dioxatricyclic oxetanes **70** and **71** from *meso*-oxabicycle ***rac*-49**, dioxatricycles **132** and **138** without methyl groups at the bridgehead carbon atoms are obtained in lower overall yield than oxetanes **70** and **71**.[54] The methyl groups confer more stability to the skeletal structure and also increase the lipophilicity and molecular weight of the compounds, thus increasing the yield.

Moreover, the benzoate group showed a migration tendency under Lewis acid-catalyzed cyclization conditions in the synthesis of dioxatricyclic **138**, while benzoate **71** was obtained in good yield without by-products resulting from intramolecular transesterification. For both cases, the use of pivaloate is more advantageous in terms of yield and stability.

In the case of methoxy substituted oxetanes, dioxatricyclic **58** is prepared from *meso*-oxabicycle ***rac*-49** in 62% overall yield over five steps[63] while the corresponding pivaloate substituted oxetane **70** is synthesized in 42% overall yield from the same *meso*-oxabicycle ***rac*-49**. Consequently, the use of methyl ether as protecting group is more efficient for the

synthesis of oxatricyclic oxetanes starting from *meso*-oxabicycle ***rac*-49**. On the contrary, methoxy substituted oxetane **97** is prepared in 15% overall yield while pivaloate substituted oxetane **131** is synthesized in 32% overall yield from *meso*-oxabicycle ***rac*-90**. Therefore, the synthesis of dioxatricyclic oxetanes starting from *meso*-oxabicycle ***rac*-90** is clearly more successful using pivaloate than methyl ether[62] as protecting group, as outlined in Scheme 31.

Summarizing, protection of the hydroxyl group at carbon C3 with pivaloate proved to be the best choice for the synthesis of oxygenated dioxatricyclic oxetanes starting from *meso*-oxabicycle ***rac*-90**. In addition, pivaloyl protection is not only advantageous to force formation of the oxetane ring but it also opens the possibility of milder deprotection of the 3-hydroxyl group after cyclization.

4.2 Synthesis of C3-Deoxygenated Tricyclic Oxetanes

Looking carefully at the dioxatricyclic framework of dictyoxetane, there is a non functionalized carbon atom at C3 position. On the other hand, most of the previously reported dioxatricyclic oxetanes have a protected hydroxyl group at carbon C3. Therefore, the synthesis of deoxygenated dioxatricyclic analogues is very interesting.

A deoxygenated 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonan-9ß-ol was synthesized by J. Wittenberg[63] from 2α-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one following the deoxygenation method already used by J. Reinecke in a similar dioxatricyclic system.[64]

In the present work, the synthesis of a deoxygenated 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonan-9ß-ol from 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-90** was attempted to complete the series of deoxygenated dioxatricyclic analogues.

As reported by J. Reinecke in similar tricyclic systems,[64] deoxygenation in the presence of a labile oxetane ring is not feasible because of radical fragmentation or decomposition of the substrate under the reaction conditions. Therefore, deoxygenation at C3 position must be

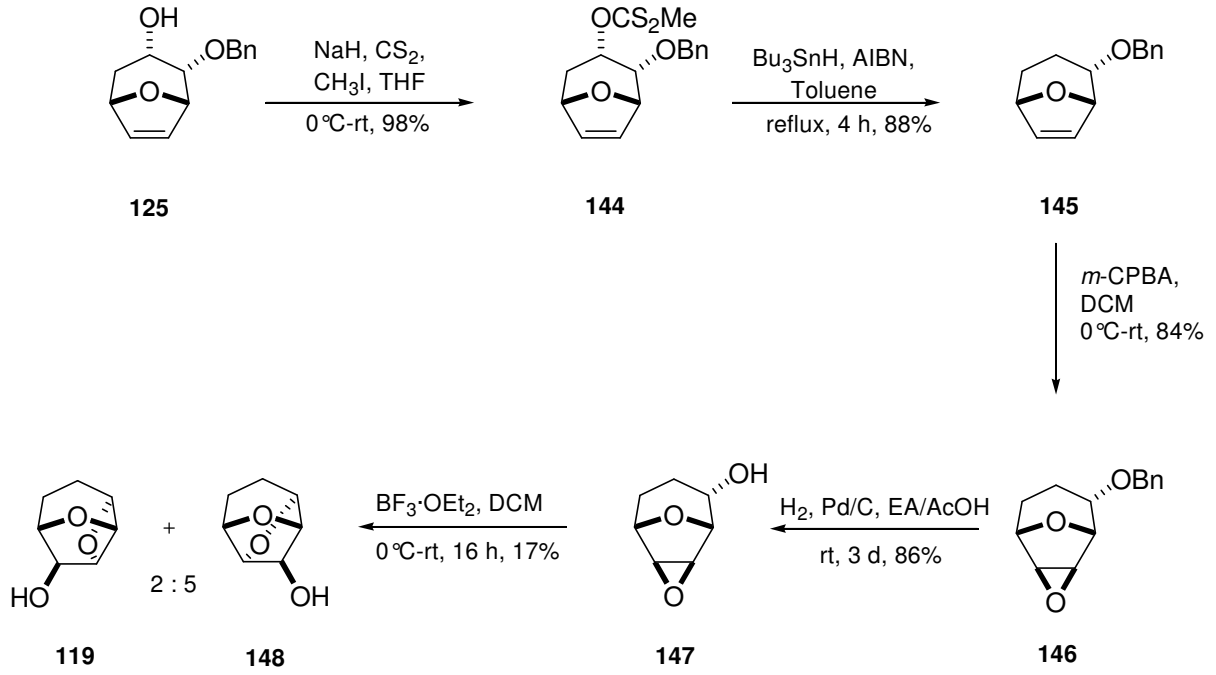
[62] Vidal Pascual, M. *PhD Thesis*, University of Hannover, **2003**.

[63] Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1998**, *39*, 8259.

[64] Reinecke, J. *PhD Thesis*, University of Hannover, **1994**.

achieved prior to the formation of the oxetane ring by conversion of the hydroxyl group into S-methylthiocarbonate followed by Barton-McCombie hydrogenation.[65]

Following the synthetic path outlined in Scheme 32, racemic alcohol **125** was converted quantitatively to S-methylthiocarbonate **144**, which underwent a Barton-McCombie deoxygenation affording simplified oxabicycle **145**. In two steps the deoxygenated compound **145** was obtained in an excellent overall yield (86%), unexpected better than the similar 2α-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene, in which methyl groups provide stability to the compound and lower its hydrophilicity. Afterwards, alkene **145** was epoxidized with *m*-CPBA and debenzylated to epoxy alcohol **147** in good yield. Stereoselective cyclization with $BF_3{\cdot}OEt_2$ in DCM afforded tricyclic hydroxyl oxetane **119** and dioxatricycle **148** in a 2:5 ratio in very poor yield. Compounds **119** and **148** were not separable by column chromatography.



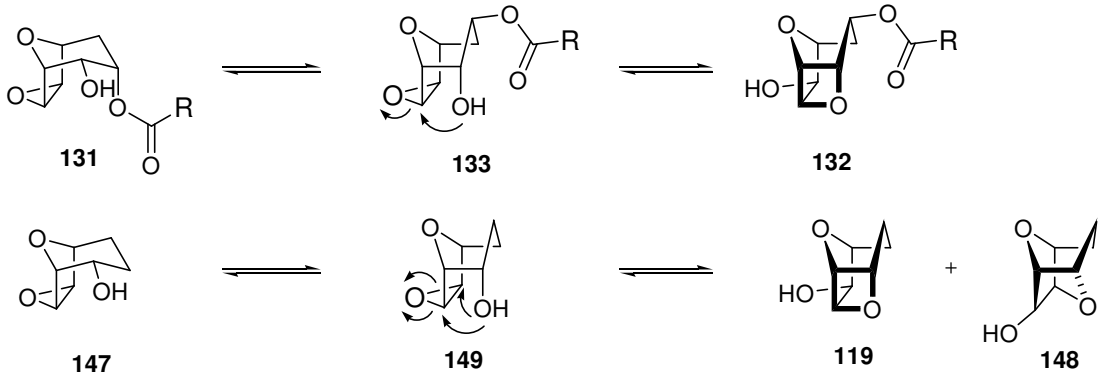
Scheme 32: Synthesis of C3-deoxygenated dioxatricyclic oxetane **119**.

The increasing hydrophilicity of these deoxygenated dioxatricycles along the synthetic route raises the risk of losses during the work-up and lowers consequently the yield of oxetane **119**. In addition, the conformational aspects of the cyclization reaction explain a weaker driving

[65] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans I* **1975**, 1574.

force for the formation of the oxetane ring compared to the corresponding oxygenated dioxatricyclic oxetanes.

As outlined in Scheme 33, the six-membered ring of both epoxy alcohols **131** and **147** changes to a minor boat, in which the hydroxyl function occupies the ideal axial position to attack the epoxide and form the new oxetane C-O bond. Simultaneously, in epoxy **133** the ester group at C3 moves from the axial position to the most favorable equatorial position lowering the energy difference between chair conformation **131** and boat transition state **133**, while in deoxygenated dioxatricycle this effect does not occur. Deoxygenated epoxy alcohol **147** changes to minor boat dioxatricycle **149** where the hydroxyl group is in axial position but there is no lowering of energy due to an additional substituent at carbon C3, so that the energy difference between chair and boat conformers is proportionally bigger for the deoxygenated oxatricycle. In contrast to similar deoxygenated oxetanes, the absence of additional methyl groups at the bridgehead carbon atoms in deoxygenated oxetane **119** reduces its stability and, consequently, the formation energy difference between oxetane **119** and furan **148** appears to be lowered. Attack at the farther side of the epoxide leading to a more stable furan ring also takes place.



Scheme 33: Key cyclization to dioxatricyclic oxetanes **132** and **119** and dioxatricycle **148**.

The synthesis of a deoxygenated oxatricyclic oxetane **119** from *meso*-oxabicycle ***rac*-90** completes the series of deoxygenated dioxatricyclic analogues. Deoxygenated oxetane **119** is rather hydrophilic which raises the risk of losses during the work-up. Compared to oxygenated oxatricycles, a weaker driving force was observed for the formation of the oxetane ring in the case of deoxygenated dioxatricycle. In addition the more stable dioxatricycle **148** was obtained together with the oxetane. All these factors are responsible for the low yield of oxetane **119**.

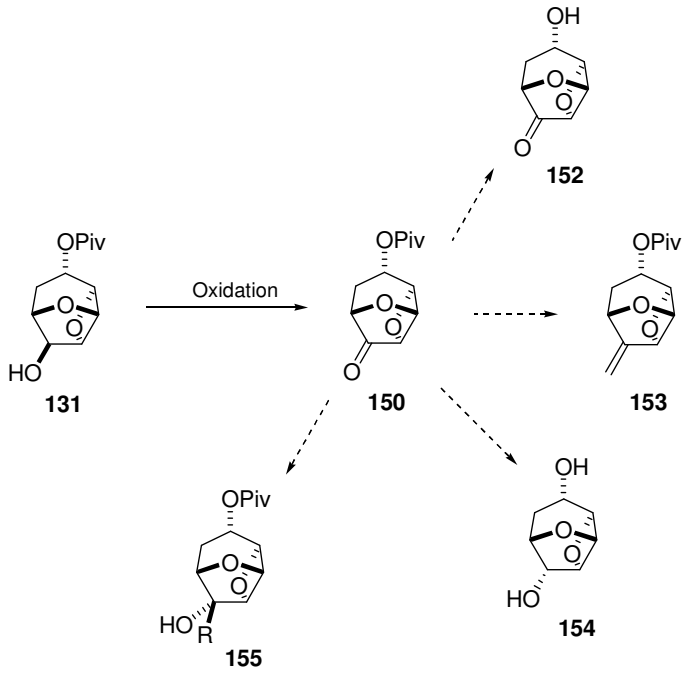
The intramolecular cyclization of epoxy alcohol **147** may proceed in higher selectivity by base-catalyzed cyclization using potassium *tert*-butoxide, which however does not activate the epoxide ring in contrast to Lewis acids. Such an increase of selectivity was obtained by J. Reinecke in an intramolecular epoxide opening by using potassium *tert*-butoxide instead of $BF_3 \cdot OEt_2$.[66]

4.3 Functionalization of the Oxetane Skeletal Structure

In view of the high biological activity of some dioxatricycles,[50] the functionalization of dioxatricyclic skeletal structure without "non natural" methyl groups at carbons C1 and C5 constitutes a valuable access to potential pharmacological active derivatives. For this purpose, the oxidation of free hydroxy group at carbon C6 of the oxatricyclic oxetane **131** was chosen as starting point for further functionalization.

Following an efficient strategy, similar to the reported by S. Proemmel,[54] functionalization of oxatricyclic ketone **150** would provide a series of tricyclic oxetanes (see Scheme 34).

[66] See Section 2.1.1.



Scheme 34: Synthetic strategy for functionalization of the dioxatricyclic skeletal structure of ketone **150**.

4.3.1 Studies towards Oxidation of the β-Hydroxyl Group at Carbon C6

The first step towards new derivatives of the oxetane skeletal structure was the oxidation of the hydroxyl group of oxatricyclic oxetane **131**. Pivaloate **132** was chosen as starting material because pivaloyl protection proved to be the best choice for the synthesis of dioxatricyclic oxetanes without methyl groups at the bridgehead carbon atoms.[67]

The oxidation of the hydroxyl group of oxatricyclic oxetane **131** was attempted using different methods. As summarized in Table 3, PCC[68] did not generate the desired ketone while Swern[69] and Parikh-Doering[70] oxidations afforded the desired tricyclic ketone **150** in good yield.

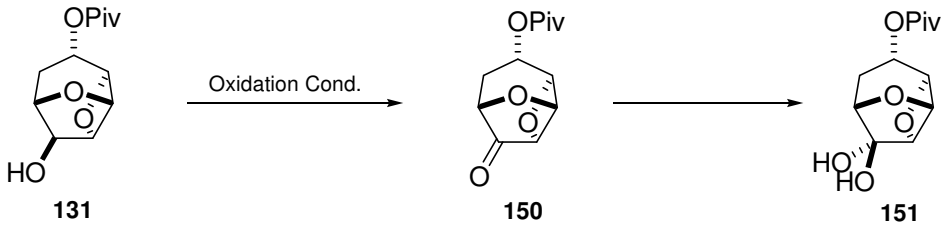
Tricyclic ketone **150** is moisture sensitive and acetal **151** is progressively formed, so that both compounds coexist and are not separable by column chromatography.

[67] See Section 4.1.4.

[68] Kassou, M.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 3696.

[69] Reviews on Swern Oxidation: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

[70] Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.



Entry	Conditions	Yield [%]
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 16 h	66
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	83
3	PCC, NaOAc, 4 Å MS, DCM, rt, 72 h	-

Table 3: Oxidation conditions to afford ketone **150**.

After oxidation of the 6β-hydroxyl group, the resulting caged ketone **150** contains a high ring strain (sp^2 carbon atom). Nucleophilic attack on the carbonyl group releases this strain by forming acetal **151** (sp^3 carbon atom), which explains the moisture sensitivity of ketone **150**. Therefore the oxidation of the 6-hydroxyl group is not recommendable as starting point for the functionalization of oxetane **131**. A better alternative would be the protection of the 6-hydroxyl group in oxetane **131** before further functionalization of the dioxatricyclic skeletal structure.

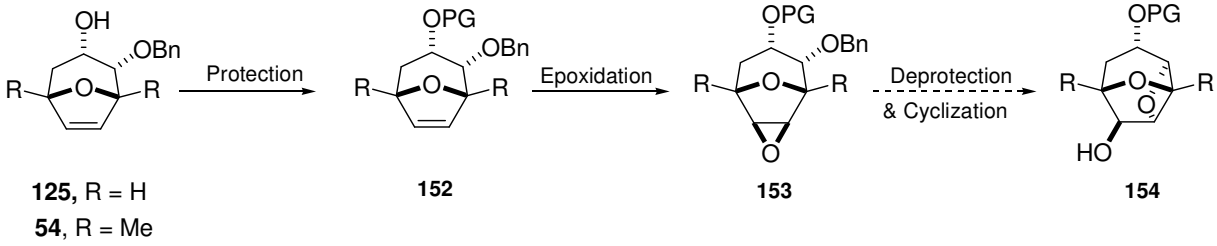
Further functionalization of dioxatricyclic oxetane **131** was not studied in the framework of the present work.

4.4 Attempts to a Short and Efficient Synthetic Route towards Dioxatricyclic Oxetanes

As summarized in Section 4.1.4, the synthetic strategy towards dioxatricyclic subunits of dictyoxetane starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** offers a straightforward route to a series of versatile compounds containing the skeletal structure 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane. Examining this route carefully, the idea of shortening the number of synthetic steps was offered by the possibility that epoxide **153** could be debenzylated and undergo an intramolecular cyclization in a one-step reaction by using an appropriate Lewis acid (see Scheme 35).

The reactant of choice was boron trichloride, a Lewis acid capable of selective cleavage of ether and acetal protecting groups. Like many other Lewis acids, BCl_3, has been extensively used as a reagent for the cleavage of a wide variety of ethers, different acetals, and certain types of esters.[71] The reagent is less reactive than boron tribromide for ether cleavage; however the chloride ion is also nucleophilic and capable of attacking the primary benzyl carbon. The type and extent of deetherification can be controlled by the ratio of the substrate to BCl_3 as well as by variation of the reaction temperature. The transition state is predominantly S_N1 in character, as evidenced by partial racemization of chiral ethers[71] and the rearrangement of allyl phenyl ethers to allylphenols.[72] When methoxy groups are *ortho* to a carbonyl group, the reaction is accelerated by the formation of a chelate between boron and the carbonyl oxygen atom.[73]

The synthesis of oxygenated tricyclic oxetanes involves protection of the hydroxyl group at carbon C3 from side reactions (see Scheme 35). Esters were chosen as protecting groups in epoxide **153** for a selective Lewis acid catalyzed cleavage of the benzyl ether group at C2-position.



Scheme 35: Attempted shortening of the synthetic route towards dioxatricyclic oxetanes **154**.

4.4.1 Benzoate Protection at Carbon C3

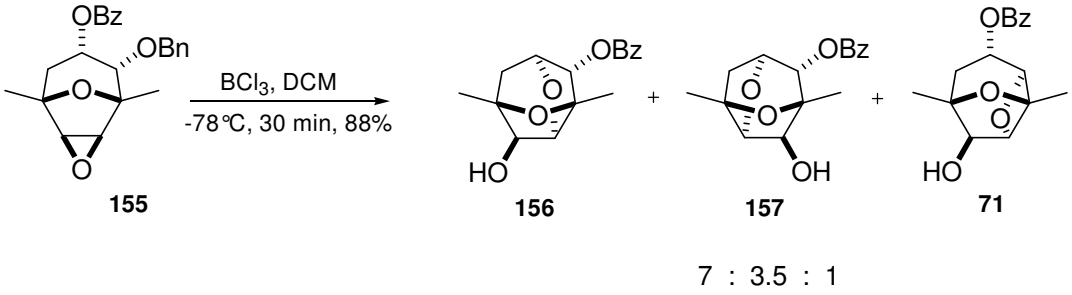
Synthesis of oxygenated dioxatricyclic oxetane **154** from epoxide **153** using BCl_3 was first attempted using benzoate as protecting group (see Scheme 36). Epoxide **155** was synthesized starting from racemic axial alcohol **54** over two steps in 62% overall yield as reported by S. Proemmel.[54] Treatment of epoxide **155** with BCl_3 in DCM at –78°C afforded desired oxetane **71** together with dioxatricycles **156** and **157** in a 1:7:3.5 ratio. The three compounds were

[71] a) Bhatt, M.; Kulkarni, S. U. *Synthesis* **1983**, 249; b) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.

[72] a) Gerrard, W.; Lappert, M. F.; Silver, H. B. *Proc. Chem. Soc.* **1957**, 19; b) Borgulya, J.; Madeja, R.; Fahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14.

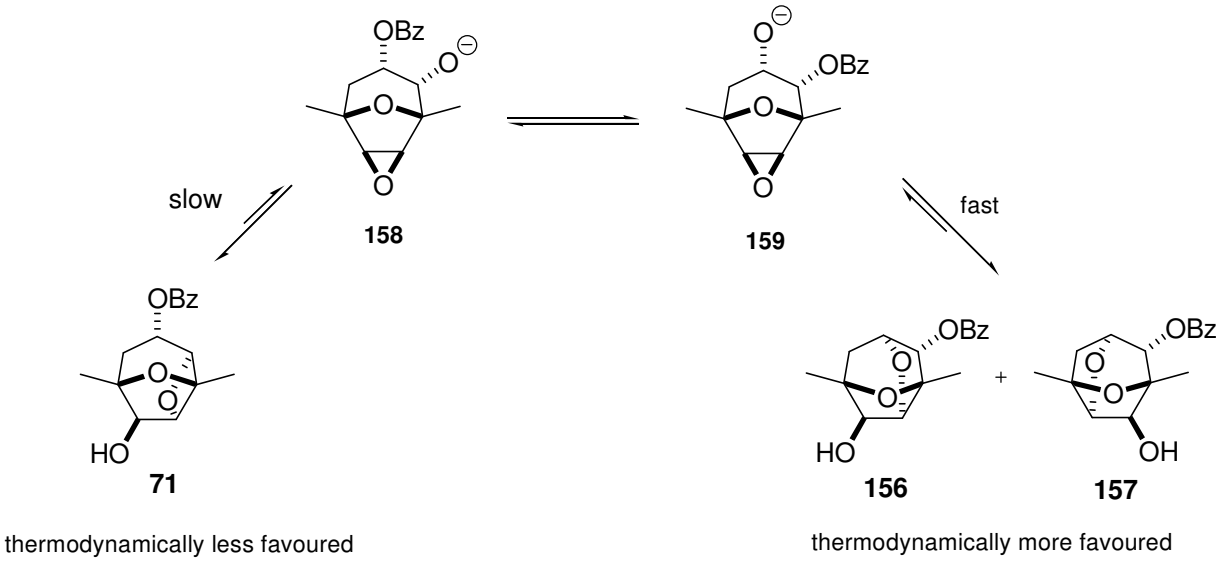
[73] a) Dean, R. B.; Goodchild, J.; Houghton, L. E.; Martin, J. A. *Tetrahedron Lett.* **1966**, 4153.; b) Arkley, V.; Attenburrow, J.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1962**, 1260; c) Barton, D. H. R.; Bould, L. ; Clive, D. L. J.; Magnus, P.D.; Hase, T. *J. Chem. Soc.* **1971**, 2204.

separable by column chromatography. The yield of the deprotection/cyclization reaction was high (88%) but the migration of the benzoate group to the adjacent equatorial position lead to oxetane **71** as minor product of the reaction.



Scheme 36: Treatment of epoxide **155** with BCl_3 to afford dioxatricycles **156**, **157** and **71**.

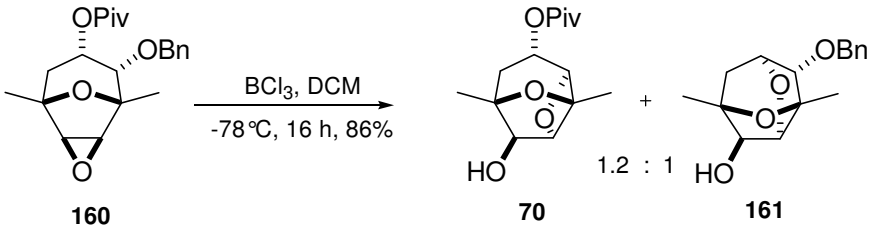
The tendency for benzoate migration to adjacent hydroxyls is not strong but it can be forced into a thermodynamically more stable position as illustrated by the benzoate migration *en route* to *N*-acetyl neuraminic acid.[58] In this case the migration was thermodynamically driven by the greater stability of the equatorial benzoate in the product. A similar driving force appeared in the case of epoxide **155**: after debenzylation at C2 position, the axial benzoate migrated to the adjacent equatorial hydroxyl group and the resulting epoxy alcohol entered into facile 5-*exo*-tet cyclization to dioxatricycles **156** and **157** in a 2:1 ratio. The formation of desired oxetane **71** is thermodynamically and kinetically disfavoured, as illustrated in Scheme 37.



Scheme 37: Formation of dioxatricycles **155** and **156** is thermodynamically and kinetically favoured in contrast to the synthesis of dioxatricyclic oxetane **71**.

4.4.2 Pivaloyl Protection at Carbon C3

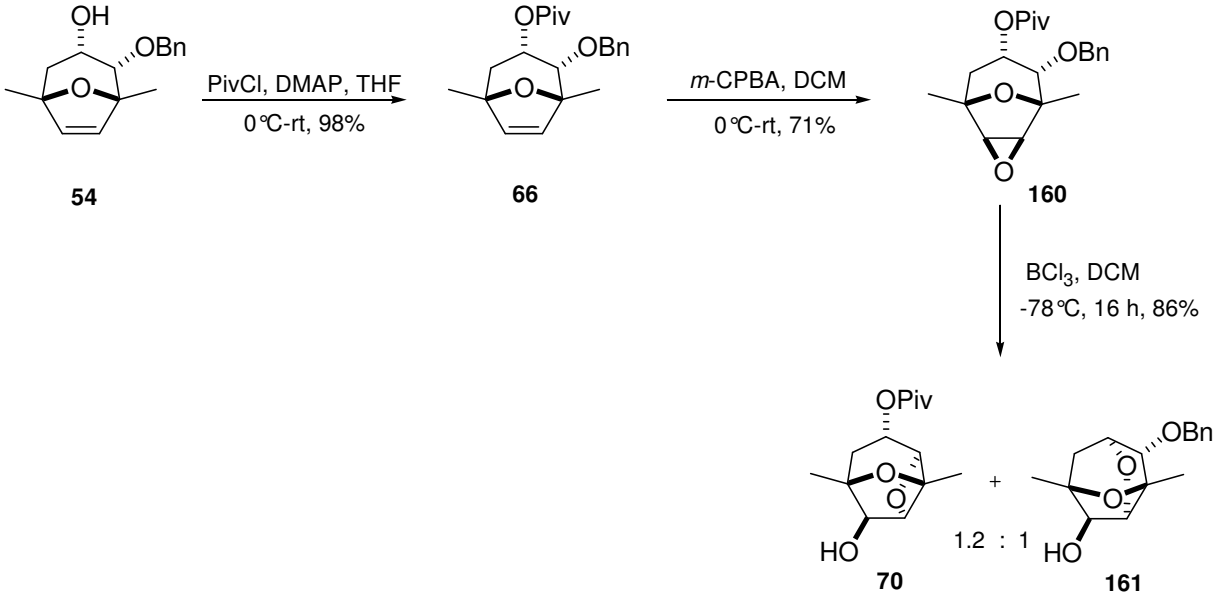
In view of the migration tendency of the benzoate group, synthesis of oxygenated dioxatricyclic oxetanes using BCl_3 was attempted with more stable pivaloate protecting group. Starting from racemic axial alcohol **54**, epoxide **160** was obtained over two steps in 70% overall yield as reported by S. Proemmel.[54] Treatment of epoxide **160** with one equivalent of BCl_3 at –78°C afforded desired oxetane **70** in poor yield and in the presence of unreacted substrate. Changing the ratio of substrate to BCl_3 as well as the reaction temperature in order to optimize the reaction was attempted without success (see Table 4). However, by addition of two equivalents of Lewis acid the reaction proceeded in good yield (86%) giving a mixture of desired oxetane **70** and dioxatricycle **161** in a 1.2:1 ratio. Dioxatricycle **161** results from cleavage of the pivaloate group and 5-*exo*-tet cyclization of the resulting hydroxy epoxide.



Entry	BCl_3 [eq]	Conditions	Total Yield [%]	Ratio of **70**:**161**
1	1	-78°C → rt, 16 h	33[a]	1:0
2	2.2	-78°C, 16 h	86	1.2:1

Table 4: Attempted reaction conditions to obtain selectively desired dioxatricyclic oxetane **70**. a) Epoxide **160** recovered unreacted.

Nevertheless, starting from racemic alcohol **54**, dioxatricyclic oxetane **70** was obtained in three steps with an overall yield of 33%, lower than the four-steps synthesis of pivaloate **70** by catalytic hydrogenolysis and Lewis acid-catalyzed cyclization using $BF_3{\cdot}OEt_2$ (41% overall yield).

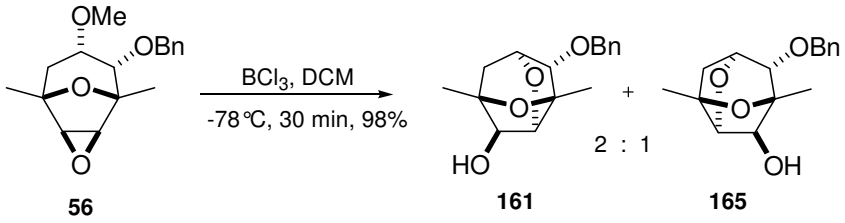


Scheme 38: Shorter synthetic route towards oxetane **70**.

4.4.3 Synthesis of Dioxatricycles as TXA_2-Analogues by 5-*exo*-tet Cyclization

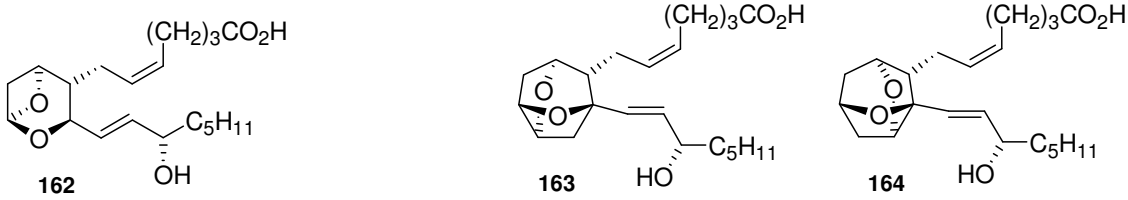
In view of the reactivity of BCl_3, the synthesis of 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonanes was attempted by a tandem deetherification-cyclization reaction of methoxy substituted epoxide **56**.

Starting from *meso*-oxabicycle **54**, methoxy substituted epoxide **56** was synthesized over three steps as reported by J. Wittenberg.[63] Resulting epoxide **56** was treated with the Lewis acid and, as expected, benzyl ether remained unaffected while methyl ether was cleaved and the free hydroxyl group attacked the epoxide affording dioxatricycles **161** and **165** in a 2:1 ratio in excellent yield (see Scheme 39).



Scheme 39: Synthesis of dioxatricycles **161** and **165** containing a noradamantane structure by one-step reaction using BCl_3.

2,6-Dioxatricyclo[3.3.1.$0^{3,7}$]nonanes such as **156** and **157** contain a similar skeletal structure as thromboxane A_2-analogues (TXA_2) **163** and **164** synthesized by K. G. Bowers and J. Mann (see Scheme 40).[74]

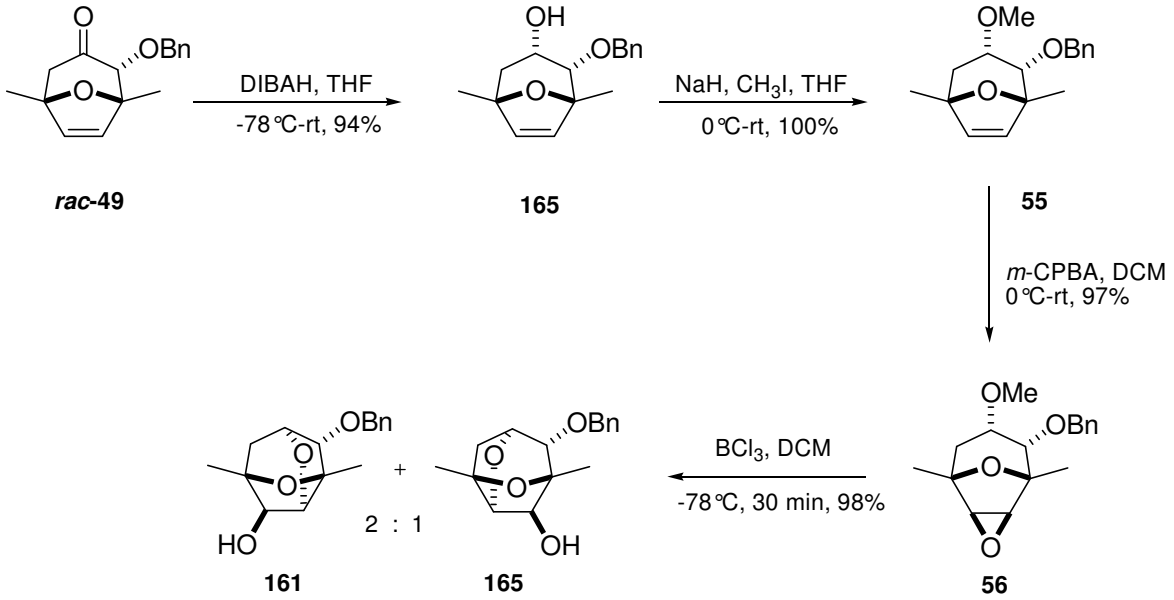


Scheme 40: Thromboxane A_2-analogues **163** and **164** synthesized by K. G. Bowers and J. Mann.

As outlined in Scheme 41, this new approach, similar to the synthetic route towards dioxatricyclic oxetanes,[75] provides a facile access to 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonanes as TXA_2-analogues starting from 2α-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one in four steps in an overall yield of 89%.

[74] a) Bowers, K. G.; Mann, J. *Tetrahedron Lett.* **1985**, *26*, 4411; b) Bowers, K. G.; Mann, J.; Walsch, E. B.; Howarth, O. W. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1657.

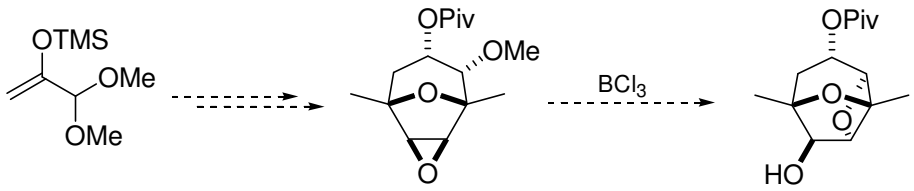
[75] See Chapter 2 and Section 4.1.



Scheme 41: Synthetic route to dioxatricycles **161** and **165** as TXA_2-analogues.

4.4.4 Outlook for a Short Synthetic Route towards Dioxatricyclic Oxetanes

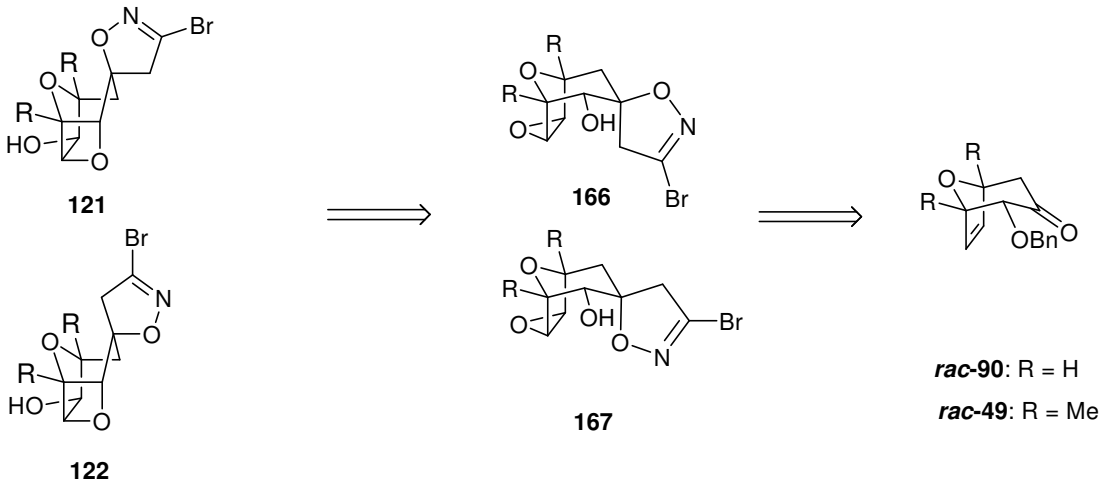
The above reported capability of BCl_3 for a selective cleavage of methyl ether in the presence of a benzyl ether group may be used for a more efficient route towards dioxatricyclic oxetanes. A promising alternative would be the treatment with BCl_3 of a C3-pivaloate substituted epoxide with a methyl ether group at C2, instead of a benzyl ether, as outlined in Scheme 42. In this case, the selectivity of the Lewis acid towards both protecting groups: pivaloate and methyl ether would be studied. The synthesis of this C2-methoxy substituted epoxide should start from a methylated silyl enol ether.



Scheme 42: Promising alternative for a shorter synthetic route to dioxatricyclic oxetanes.

4.5 Studies towards Dioxatricyclic Oxetanes with an Isoxazoline Ring at C3 Position

Another aim of the present work was the introduction of a new functionality into the dioxatricyclic structures starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** (see Scheme 43).



Scheme 43: Synthetic strategy to dioxatricyclic oxetanes **121** and **122** including a 3-bromo-2-isoxazoline ring.

Among the known 1,3-dipolar cycloaddition reactions, the formation of an isoxazoline ring from an olefin and a nitrile oxide has been shown to be particularly useful in organic synthesis. This heterocycle is stable toward several reagents, so transformations can be carried out on pendant groups. Furthermore, 3-bromo-2-isoxazoline derivatives have been used in many natural product syntheses and have also proved to be efficient precursors for a wide variety of open chain scaffolds, including γ-amino alcohols,[76] ß-hydroxy ketones,[77] β-hydroxy esters,[78] β-hydroxy ketones,[79] 1,3-butadienes and β-hydroxy nitriles,[80] as outlined in Scheme 44. Moreover, the moderate rigidity of the five-membered ring and the heteroatom lone pairs have made isoxazolines been attractive candidates for stereocontrolled transformations. Incorporation of a bromoisoxazoline ring at C3 position by 1,3-dipolar cycloaddition[81] results in a tetracyclic system and offers a wide range of possibilities for further functionalization.

[76] a) Burri, K. F; Cardone, R. A.; Chen, W. Y.; Rosen, R. *J. Am. Chem. Soc.* **1978***, 100*, 7069; b) Müller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, 2*3*, 4777; c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410; d) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Scröter, B. *Lect. Heterocycl. Chem.* **1985**, *8*, 79; e) Wade, P.A.; Rao, J. A.: Bereznak, J. F.; Yuan, C.-k. *Tetrahedron Lett.* **1989**, *30*, 5969; f) Wade, P. A.; Price, D. T. *Tetrahedron Lett.* **1989**, *30*, 1185.

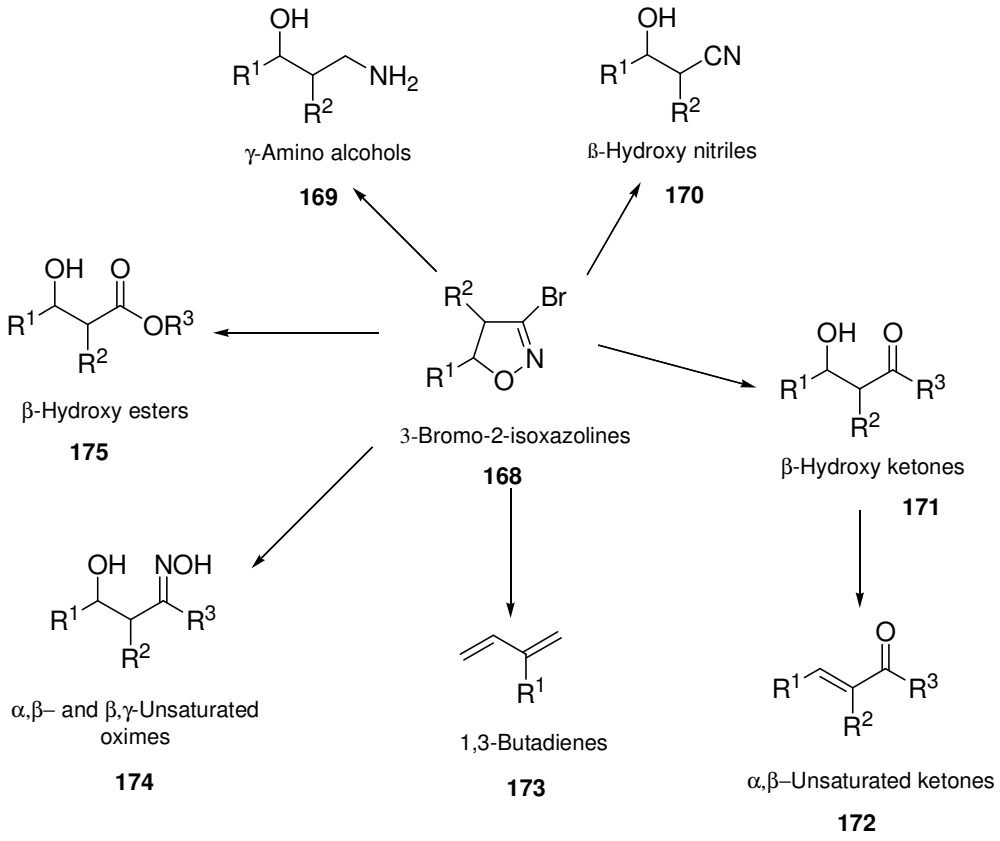
[77] Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719.

[78] Curran, D. P.; Scanga, S.; Fenk, C. J. *J. Org. Chem.*. **1984***, 49*, 3474.

[79] a) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982***, 104*, 4023; b) Curran, D. P. *J. Am. Chem. Soc.* **1982***, 104*, 4024; c) Curran, D. P. *J. Am. Chem. Soc.* **1983***, 105*, 5826.

[80]a) Wade, P.A.; Hinney, H. R. *J. Am. Chem. Soc.* **1979***, 101*, 1319; b) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983***, 48*, 366; c) Wade, P.A; Bereznak, J. F. *J. Org. Chem.* **1987***, 52*, 2973.

[81] For recent reviews of [3+2]-cycloadditions, see: a) Tufariello, J. *1,3-Dipolar Cycloaddition Chemistry;* Padwa, A., Ed.; John Wiley & Sons: Chichester, 1984; Vol. 2, p. 83; b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988; c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

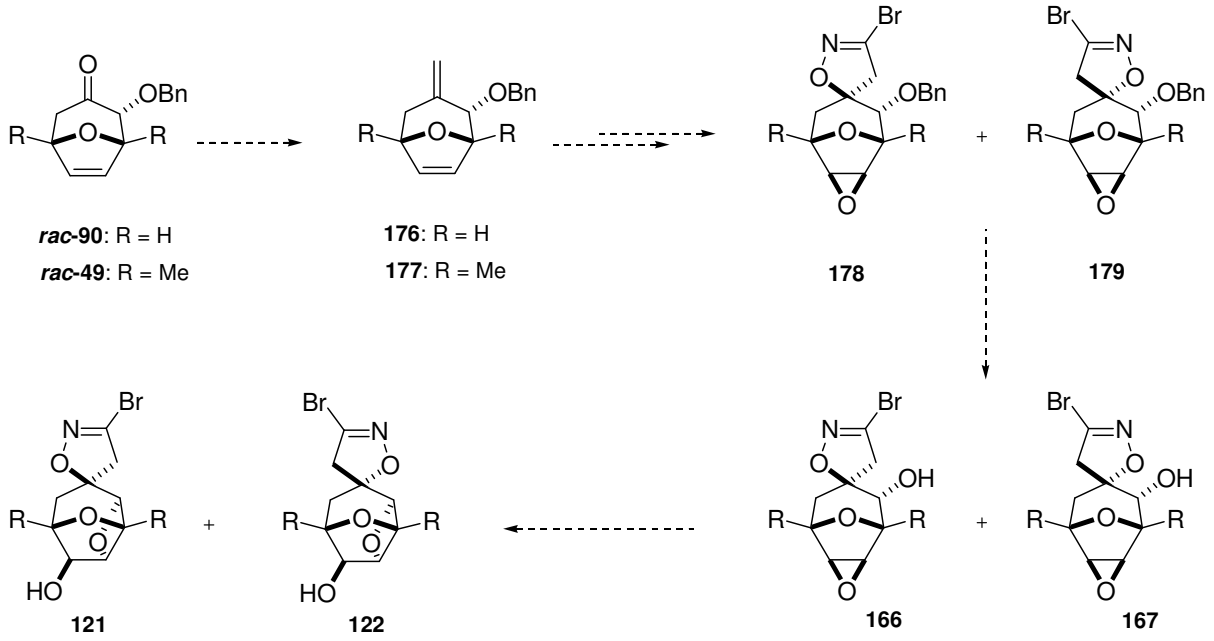


Scheme 44: 3-Bromo-2-isoxazolines are precursors of a wide variety of open-chain scaffolds through cleavage of the N-O bond.

A similar route compared to that of the oxygenated dioxatricyclic oxetanes was chosen for the synthesis of dioxatricyclic oxetanes with an isoxazoline ring attached at C3 position (see Scheme 45). The introduction of the bromoisoxazoline ring at carbon C3 should proceed by facile 1,3-dipolar cycloaddition of bromonitrile oxide to an alkene. Therefore, starting oxabicyclic ketones ***rac*-49** and ***rac*-90** should be converted by Wittig reaction into dialkenes **176** and **177**. The methylenation of ketones ***rac*-49** and ***rac*-90** should be achieved prior to epoxidation of the endocyclic double bond in order to avoid the competing oxidation of the ketone to lactone.[82] In addition, 1,3-dipolar cycloaddition should precede the formation of the labile oxetane ring.

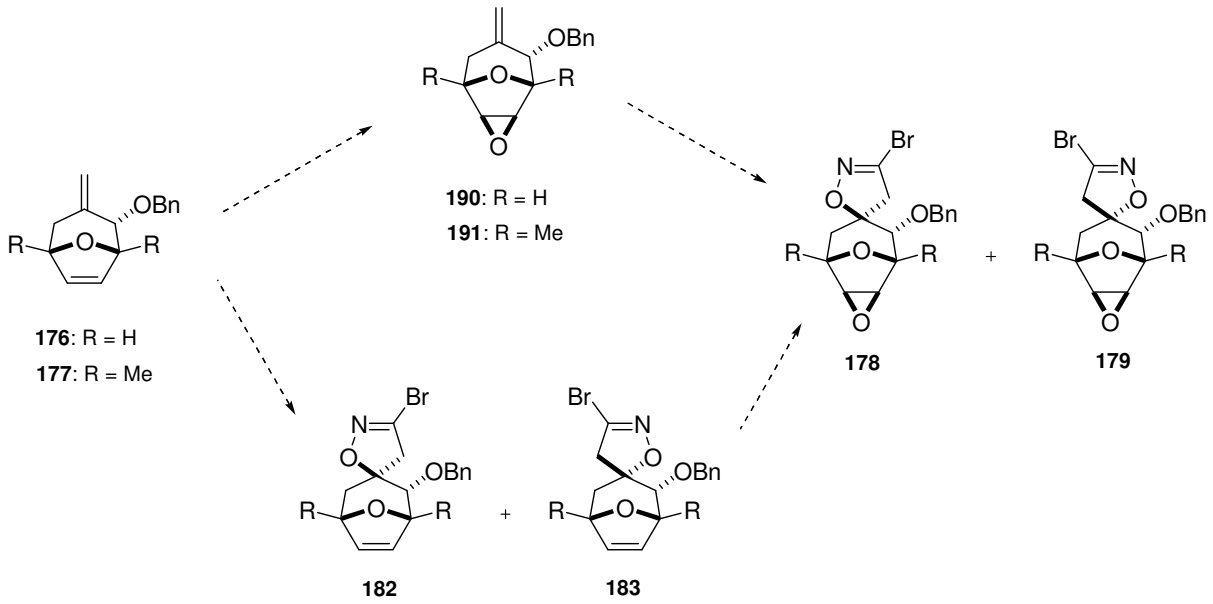
With this background in mind, the synthetic route towards oxatricyclic oxetanes **121** and **122** should start by methylenation of oxabicyclic ketones ***rac*-49** and ***rac*-90**. Dialkenes **176** and **177** should be converted into epoxides **178** and **179** in two steps. Afterwards, debenzylation of epoxides **178** and **179** would led to oxetane precursors **166** and **167**, which should undergo an intramolecular cyclization to highly functionalized oxetanes **121** and **122**.

[82] See Section 2.1.3.



Scheme 45: Synthetic path to dioxatricyclic oxetanes **121** and **122** containing an isoxazoline ring.

The question which remained open was the pathway between dialkenes **176** and **177** and epoxides **178** and **179** (see Scheme 46). For this purpose, two strategies were studied. The first possibility should start with a site selective 1,3-dipolar cycloaddition of bromonitrile oxide with the exocyclic double bond in dialkenes **176** and **177** followed by epoxidation of endocyclic double bond to obtain epoxides **178** and **179**. The second strategy would involve a site selective epoxidation of the 1,2-disubstituted double bond of oxabicyclic **176** and **177** preceding the 1,3-dipolar cycloaddition of bromonitrile oxide to the exocyclic double bond at carbon C3. Further considerations about the reactivity of both double bonds as well as the feasibility of the mentioned two strategies are presented in later chapters.

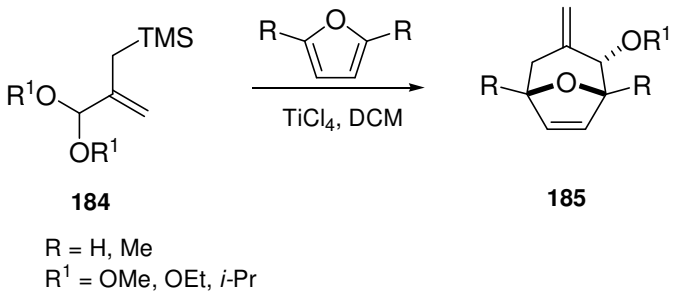


Scheme 46: Two strategies for the synthesis of epoxides **178** and **179** with an isoxazoline ring at C3.

4.5.1 Conversion of Oxabicyclic Ketones to Dialkenes by Wittig Reaction

The starting point of the synthetic route towards oxatricyclic oxetanes **121** and **122** with a bromoisoxazoline ring at C3 position is the synthesis of an oxabicyclic dialkene with an exocyclic double bond at carbon C3 (see Scheme 45).

Harmata *et al.*[83] reported the synthesis of similar methylenated oxabicycles by [4+3] cycloaddition (see Scheme 47).

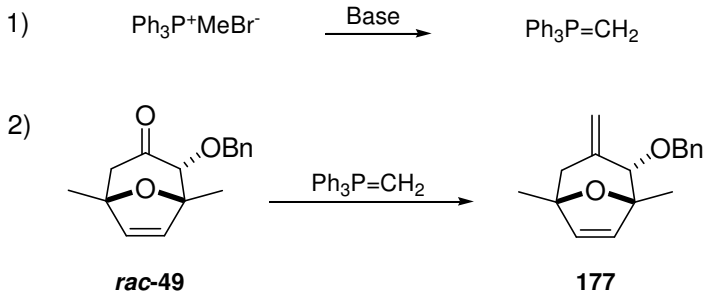


Scheme 47: [4+3]-Cycloaddition of allylic acetals by Harmata *et al.*

The yields of these [4+3] cycloaddition reactions are good except from the reaction of diisopropoxy acetal with 2,5-dimethylfuran, which do not proceed because of apparent steric

[83] Harmata, M.; Jones, D. E. *J. Org. Chem.* **1997**, *62*, 1578.

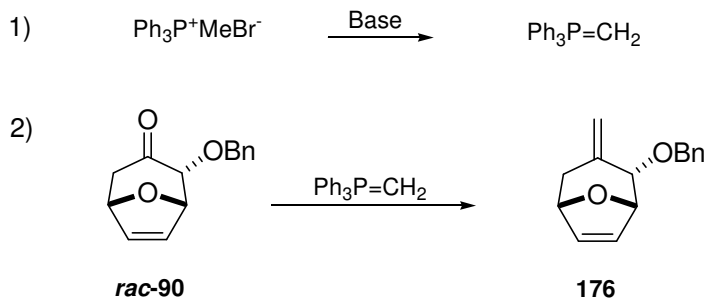
effect. The presence of methyl, ethyl or isopropyl ether in the cycloadduct would cause difficulties by ether cleavage to obtain the convenient precursor for an intramolecular cyclization to desired oxetane. Such alkyl ethers need drastic conditions for cleavage compared to benzyl ether, which is easily removed under mild conditions. Therefore, Harmata *et al.*'s methylenated oxabicycles **185** were not considered as an efficient starting material for the synthesis of new dioxatricyclic oxetanes. Moreover, the synthesis of a similar benzyl substituted allylic acetal would involve a longer synthetic path than that of *meso*-oxabicycles ***rac*-49** and ***rac*-90.** Instead, introduction of a methylene group into oxabicycles ***rac*-49** and ***rac*-90** proceeded by Wittig reaction in high yield affording desired olefins **176** and **177** as reported below.



***rac*-49** **177**

Entry	$Ph_3P^+Me\ Br^-$ [eq]	Deprot. Cond.[a]	Ketone [eq]	Wittig Cond.[a]	Yield [%]
1	1.2	2.2 eq *n*-BuLi, 0°C, 30 min	1	16 h, -78°C → rt	12[b]
2	1.3	1.3 eq *n*-BuLi, rt, 3 h	1	2 d, rt	18[b]
3	1.3	1.3 eq *t*-BuOK, rt, 15 h	1	15 h, rt	26[b]
4	2.7	2.5 eq *t*-BuOK, reflux, 30 min	1	16 h, reflux	99

Table 5: Reaction conditions for the generation of ethylenetriphenylphosphorane and following Wittig reaction with oxabicycle ***rac*-49.** a) THF was the solvent used; b) unreacted ketone was recovered.



***rac*-90** **176**

Entry	$Ph_3P^+Me\ Br^-$ [eq]	Deprot. Cond.[a]	Ketone [eq]	Wittig Cond.[a]	Yield [%]
1	1.2	2.2 eq *n*-BuLi, 0°C, 30 min	1	16 h, -78°C→ rt	5[b]
2	1.3	1.3 eq *n*-BuLi, rt, 3 h	1	2 d, rt	12[b]
3	1.3	1.3 eq *t*-BuOK, rt, 15 h	1	15 h, rt	17[b]
4	2.7	2.5 eq *t*-BuOK, reflux, 30 min	1	16 h, reflux	80

Table 6: Reaction conditions for the generation of ethylenetriphenylphosphorane and following Wittig reaction with oxabicycle ***rac*-90**. a) THF was the solvent used; b) unreacted ketone was recovered.

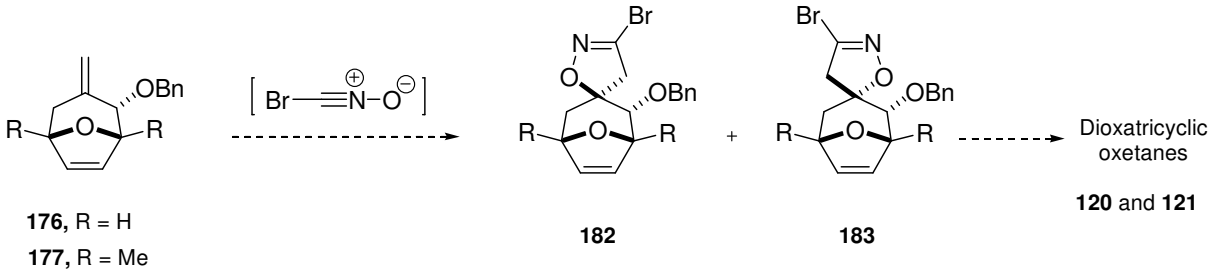
Methyltriphenylphosphonium bromide was used to prepare the corresponding ylide upon treatment with *n*-butyllithium or potassium *tert*-butoxide. The use of *n*-butyllithium to generate the ylide gave olefin **177** in 12 to 18% yield and olefin **176** in 5 to 12% yield, which was increased to 26% for **177** and 17% for **176** when the ylide was generated with potassium *tert*-butoxide at room temperature, as suggested by Schlosser and Christmann[84] (see Table 5 and Table 6). Best results were obtained by treatment of methyltriphenylphosphonium bromide with potassium *tert*-butoxide under reflux conditions to afford **177** in 99% yield and **176** in 80% yield.

Summarizing, the Wittig reaction proceeded well to generate an exocyclic double bond at C3 position in good to high yield. In the case of oxabicyclic **176**, without the bridgehead methyl groups, the olefination reaction proceeded in 80% yield. With additional stabilizing methyl groups, dialkene **177** was obtained in quantitative yield. In view of these results, oxabicyclic ketones ***rac*-49** and ***rac*-90** proved to be efficient starting materials for the synthetic route to dioxatricyclic oxetanes with a bromoisoxazoline ring at C3.

[84] a) Schlosser, M.; Christmann, K. F. *Angew. Chem.* **1964**, *76*, 683.

4.5.2 Site Selective 1,3-Dipolar Cycloaddition of Bromonitrile Oxide to Oxabicyclic Dialkenes

The next step towards the synthesis of dioxatricyclic oxetanes with an isoxazoline ring at C3 position was investigating the feasibility of a site selective 1,3-dipolar cycloaddition of the bromonitrile oxide to the exocyclic double bond in oxabicycles **176** and **177**; particularly, the chemoselective attack of the dipole to the endocyclic or exocyclic double bond. Addition of bromonitrile oxide may occur on the terminal double bond or on the 1,2-disubstituted alkene depending on the dipolarophilic activity of both double bonds. The convenient regioselectivity of the 1,3-dipolar cycloaddition for the synthesis of dioxatricyclic oxetanes **120** and **121** is outlined in Scheme 48.



Scheme 48: Illustrated site selective 1,3-dipolar cycloaddition to oxabicyclic dialkenes **176** and **177**.

In following sections 4.5.2.1 and 4.5.2.2, different aspects related to the dipolarophilic activity of double bonds and different selectivities of 1,3-dipolar cycloaddition are explained to anticipate the regioselectivity and stereoselectivity of the 1,3-dipolar cycloadditions of bromonitrile oxide to oxabicyclic dialkenes **176** and **177**.

4.5.2.1 Reactivity of Nitrile Oxides in 1,3-Dipolar Cyclodditions

Relative rates of cycloadditions of nitrile oxides to various dipolarophiles[85] have revealed characteristic features of reactivity in 1,3-dipolar cycloadditions. Both *n*- and π-conjugation have a strong promoting effect on the reactivity and a general retardation is observed in disubstituted alkenes, principally owing to steric factors compared to unsubstituted dipolarophiles. Moreover, 1,2-disubstitution in alkenes decreases the addition rates more than 1,1-disubstitution in dipolarophiles.

[85] Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition Reactions*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984, 291.

Electronic, steric and ion-pairing effects influence mainly the reactivity of dipolarophiles. Beyond these contributions, there are also some additional factors, which affect the ground-state energy of molecules and thus their reactivity, like strain, aromaticity, hydrogen-bonding or solvent effects.

The frontier molecular orbital (FMO) theory offers a satisfactory interpretation of the electronic contribution in the dipolarophilic activity and its dependence on the frontier orbital (FO) energies of the π-components. The reactivity of the 1,3-dipole with the double bond is mainly determined by the interaction between Highest Occupied Molecular Orbital (HOMO) and low Lowest Unoccupied Molecular Orbital (LUMO). The stabilization energy is associated with this interaction and is inversely proportional to the energy difference between the interacting orbitals.

The FMO theory can predict the effect of substituents on reactivity: electron-donating substituents raise the FO energies, while conjugating substituents raise the HOMOs and lower the LUMOs. Both donor and acceptor substituents increase the reactivity by a LUMO(dipole)- or a HOMO(dipole)-controlled cycloaddition, respectively. Besides, alkyl substitution decrease the reactivity mainly because of steric effects and the dipolarophilic activity decreases more in 1,2-disubstituted than in 1,1-disubstituted dipolarophiles.[86]

Steric effects derive from increases of repulsion or from secondary orbital interactions, which reduce the overlap between the interacting orbitals. These secondary interactions are not considered in the FO predictions, nor are the changes in the flexibility of the dipolarophiles, which affect the energy of activation through the deformation energy, and their importance is apparently pre-eminent in the reduced dipolarophilic activity of 1,2-*cis*-disubstituted alkenes.

Special attention must be paid to cyclic dipolarophiles like norbornene, cyclopentene, bicyclo[2.2.2]octene or cyclohexene,[87] in which ring strain can only account partially for their high reactivity. A satisfactory rationalization in terms of deformation energies and staggering of forming bonds with respect to allylic bonds has been provided.[88] Calculations show that C=C bonds of cyclic dipolarophiles with diastereotopic faces are considerably deformed away from planarity.[88a] For example, in norbornene, the olefinic C-H bonds are bent in the *endo*

[86] Boyd, E. C.; Paton, R. M. *Tetrahedron Lett.* **1993**, *34*, 3169.

[87] Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951.

[88] a) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houkd, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436; b) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

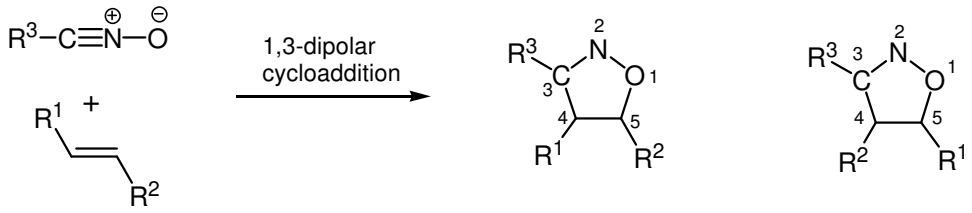
direction by 3.4°, and only a small expenditure of energy is required to effect the 10° *cis* bending to achieve the cycloaddition transition state geometry. Similar deformations have been found in molecules such as norbornadiene, bicyclopentene, and Dewar benzene.[89] In these molecules, the deformations always take place in direction of staggering of the olefinic carbon substituents with the allylic bond which is most nearly eclipsed with the π orbital. Thus, the capability of the reactant for deformation toward the *cis*-bent geometry correlates the reactivity of cyclic dipolarophiles. Furthermore, in addition reactions to π systems, the staggering of the forming bonds with the allylic bond is highly favoured[88b] and this tendency for staggering directs the geometry of the dipolarophile in the transition state. For instance, the high reactivity of norbornene can then also be partly attributed, aside from their easy deformation, to the fact that the forming bonds in the *exo* addition are almost perfectly staggered with the bonds to the bridgehead carbons.

Additional increased reactivity can be adequately explained in part by the reduction in strain caused by the conversion of the olefin into a saturated product.

The rates of 1,3-dipolar cycloadditions are barely influenced by the nature of solvents but selectivities (regioselectivity, stereoselectivity, site selectivity and periselectivity) may be significantly altered, even reversed upon a change of solvent.

4.5.2.2 Regioselectivity and Stereoselectivity of 1,3-Dipolar Cyclodditions with Nitrile Oxides

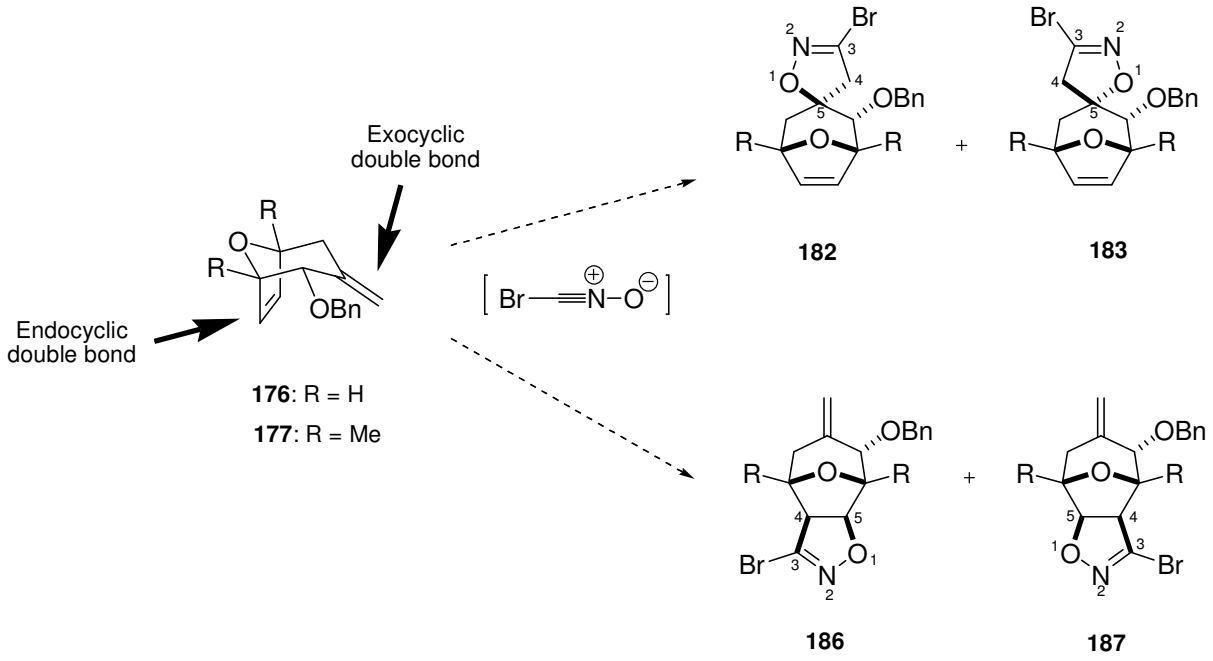
1,3-Dipolar cycloadditions of nitrile oxides to alkenes can afford two regioisomers of the 2-isoxazoline, in which the relative configuration between the 4- and 5-substituents is determined by the geometry of the alkene (see Scheme 49).



Scheme 49: 1,3-Dipolar cycloaddition of nitrile oxides can afford two regioisomers.

[89] Fusco, F.; Garanti, L.; Zecchi, G. *Tetrahedron Lett.* **1974**, 269.

Generally, nitrile oxides react with terminal alkenes to give the 5-isomer of the isoxazoline, i.e. the nitrile oxide carbon atom attacks the terminal carbon atom of the alkene. The sensitivity of the cationic carbon of the bromonitrile oxide to steric effects is greater than that of the oxygen, which favors the sterically less hindered 5-substituted isomer in the 1,3-dipolar cycloaddition with a terminal double bond. Mixtures of regioisomers are usually obtained with 1,2-disubstituted alkenes. Consequently, addition of bromonitrile oxide to 1,1-disubstituted alkene in oxabicycles **176** and **177** would mostly afford 5-substituted regioisomers **182** and **183**, while in the case of addition to the symmetrically 1,2-substituted double bond, a mixture of regioisomers **186** and **187** would be obtained (see Scheme 50).



Scheme 50: Illustrated 1,3-dipolar cycloaddition reaction of bromonitrile oxide to oxabicyclic **176** and **177.**

When the two faces of the double bond are nonequivalent, the attack of the 1,3-dipole may occur on the same side as the perturbing substituent or on the opposite one. In such cases, the 1,3-dipolar cycloaddition proceeds under facial stereoselectivity. Several examples of facial selectivity have been reported in 1,3-dipolar cycloadditions of nitrile oxides to bicyclic systems.[90] These stereoselectivities seem to be a consequence of the geometry of the dipolarophiles.

[90] a) Flige, W.; Huisgen, R. *Liebigs. Ann. Chem.* **1973**, 2038; b) Sasaki, T.; Hayakawa, K.; Manabe, T.; Nishida, S. *J. Am. Chem. Soc.* **1981**, *103*, 565; c) Anderson, P. S.; Christy, M. E.; Engelhardt, E. L.; Lundell, G. F.; Ponticello, G. S. *J. Heterocycl. Chem.* **1977**, *14*, 213; d) De Micheli, C.; Gandolfi, R.; Oberti, R. *J. Org. Chem.* **1980**, *45*, 1209.

Addition of bromonitrile oxide to the 1,2-disubstituted alkene in oxabicycles **176** and **177** would occur exclusively on the *exo* face, as observed in 1,3-dipolar cycloadditions to [3.2.1]oxabicyclic alkenes.[91] In the 1,1-disubstituted double bond in oxabicycles **176** and **177**, the two faces of the π system are not equivalent either, so addition of the 1,3-dipole may occur under facial stereoselectivity affording bromoisoxazolines **182** and **183** in different ratio (see Scheme 50).

4.5.2.3 Attempted Site Selective 1,3-Dipolar Cycloddition of Bromonitrile Oxide to Oxabicyclic Dialkenes

1,3-Dipolar cycloadditions of bromonitrile oxide to oxabicyclic olefins **176** and **177** were attempted following two optimized procedures successfully used in [3.2.1]oxabicycles.[91] The first one involves the use of DBU as base and acetonitrile as solvent while the second method proceeds using KOH as base in THF with aliquat®336.

The nitrile oxide of choice for the 1,3-dipolar cycloaddition to oxabicyclic dialkenes **176** and **177** was bromonitrile oxide. The most widely used method to generate nitrile oxides is the dehydrohalogenation of the halogenated aldoxime,[92] which can be effected by action of bases[93] or silver salts, or by thermal dissociation of the halides (see Scheme 51). Dibromoformaldoxime (DBF) was chosen as the precursor for the nitrile oxide since the synthesis of dichloro derivatives is complicated and affords lower yields.[94, 95] Generation of bromonitrile oxide was carried out *in situ* adding slowly a base to an ice cold solution of dibromoformaldoxime[96b] and dipolarophile in order to keep a low stationary concentration of nitrile oxide, thus preventing its dimerization.[92, 96]

[91] Martínez Lamenca, C. *Master Thesis*, University of Hannover, **2000**.

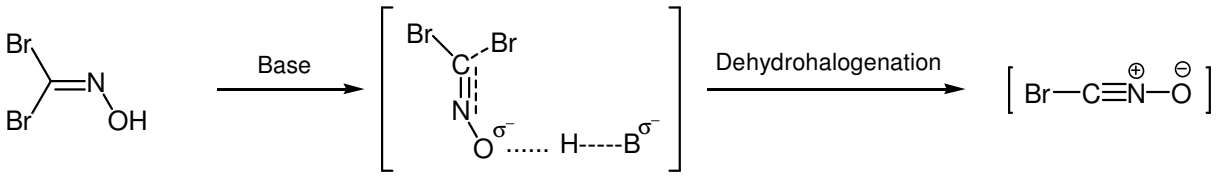
[92] Grundmann, C.; Grünanger, P., *The nitrile oxides*; Springer-Verlag: Berlin, 1978.

[93] Beltrame, P.; Veglio, C.; Simonetta, M. *J. Chem. Soc.* **1967**, 867.

[94] Halling, K.; Thomsen, I.; Torssell, K. B. G. *Liebigs Ann. Chem.* **1989**, 985.

[95] a) Stevens, V.; Polniaszek, R. P. *Tetrahedron* **1983**, *39*, 743.; b) De Amici, M.;. De Michaeli, C.; V. Misani, V. *Tetrahedron.* **1990**, *46*, 1975.

[96]a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565.; b) N. Sewald, K. Burger, *Liebigs Ann. Chem.* **1992**, 947.



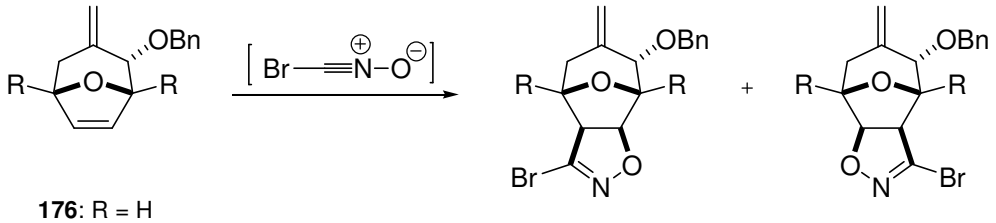
Scheme 51: Dehydrohalogenation of dibromoformaldoxime by action of bases.

Attempted 1,3-dipolar cycloaddition of bromonitrile oxide to oxabicyclic dialkenes did not give the desired oxabicycles **182** and **183**. Instead, bromonitrile oxide attacked oxabicyclic olefins **176** and **177** stereospecifically from the *exo* face[97] of the 1,2-disubstituted double bond to give both regiosisomers **186** and **187** in almost equivalent ratio. No traces of 1,3-dipolar cycloaddition to the terminal alkene at C3 were detected, even when a significant excess of dipole was added to the reaction.

As summarized in Table 7, 1,3-dipolar cycloaddition of bromonitrile oxide to dialkene **176** led to regioisomers **188** and **189** in 66 to 77% yield without either by-products or recovered dipolarophile. Regioisomers **188** and **189** were separable by column chromatography. In the case of dialkene **177**, addition of bromonitrile oxide provided azatricycles **190** and **191** in 32 to 58% yield with recovered unreacted dipolarophile and longer reaction times were needed. Regioisomers **190** and **191** were not separable by column chromatography.

Best results were obtained using KOH as ionic base in THF. When phase transfer catalyst methyltrioctylammonium chloride (aliquat®336) was added, the reaction was finished in shorter time (no increase of product was observed when the reaction mixture was stirred for longer time), though yields were smaller. In dialkene **177**, the steric hindrance of the two methyl substituents at the bridgehead carbon atoms decreases its dipolarophilic activity, which explains the lower yield compared to the 1,3-dipolar cycloaddition to less hindered double bond of dialkene **176**.

[97] Different nomenclature is used to describe the diastereotopic attacks: *syn-anti/endo-exo.* In [3.2.1]oxabicycles, the diastereotopic faces are described as *endo* and *exo*, where *endo* refers to the side cis to the larger bridge of the oxabicycle and *exo* to the trans one.



176: R = H
177: R = Me

188: R = H
190: R = Me

189:R = H
191: R = Me

Entry	R	DBF [eq]	Base	Conditions	Total Yield [%]	Ratio of **188:189** **(190:191)**
1	H	2+2[a]	2.2 eq KOH	Aliquat®336, THF, 0°C → rt, 5 h	66	4:5
2	H	2+2[b]	2.2 eq KOH	THF, 0°C → rt, 2 d	77	4:5
3	H	2.5+2[b]	3 eq DBU	CH_3CN, 0°C → rt, 3 d	73	4:5
4	Me	2+2[a]	2.2 eq KOH	Aliquat®336, THF, 0°C → rt, 16 h	35	3:4
5	Me	2+2[b]	2.2 eq KOH	THF, 0°C → rt, 4 d	58[c]	1:1
6	Me	2.5+2[b]	3 eq DBU	CH_3CN, 0°C → rt, 4 d	32[c]	3:4

Table 7: Attempted 1,3- dipolar cycloaddition reactions of bromonitrile oxide to **176** and **177**. a) Addition of 2 eq of DBF after 2 h reaction time; b) addition of 2 eq of DBF after 16 h reaction time; c) additionally 20% dipolarophile was recovered.

As a result of the symmetry of the 1,2-disubstituted double bond in both oxabicycles **176** and **177**, a mixture of two regioisomers is obtained. ß-Substituents in dialkenes **176** and **177** (benzyl ether at C2 position) are too far from the double bond to exert an outstanding electronic or steric effect on the regioselectivity of the cycloaddition. Additionally, in oxabicycle **177** the methyl groups at α-position decrease the dipolarophilic activity but do not influence the regioselectivity of the 1,3-dipolar cycloaddition.

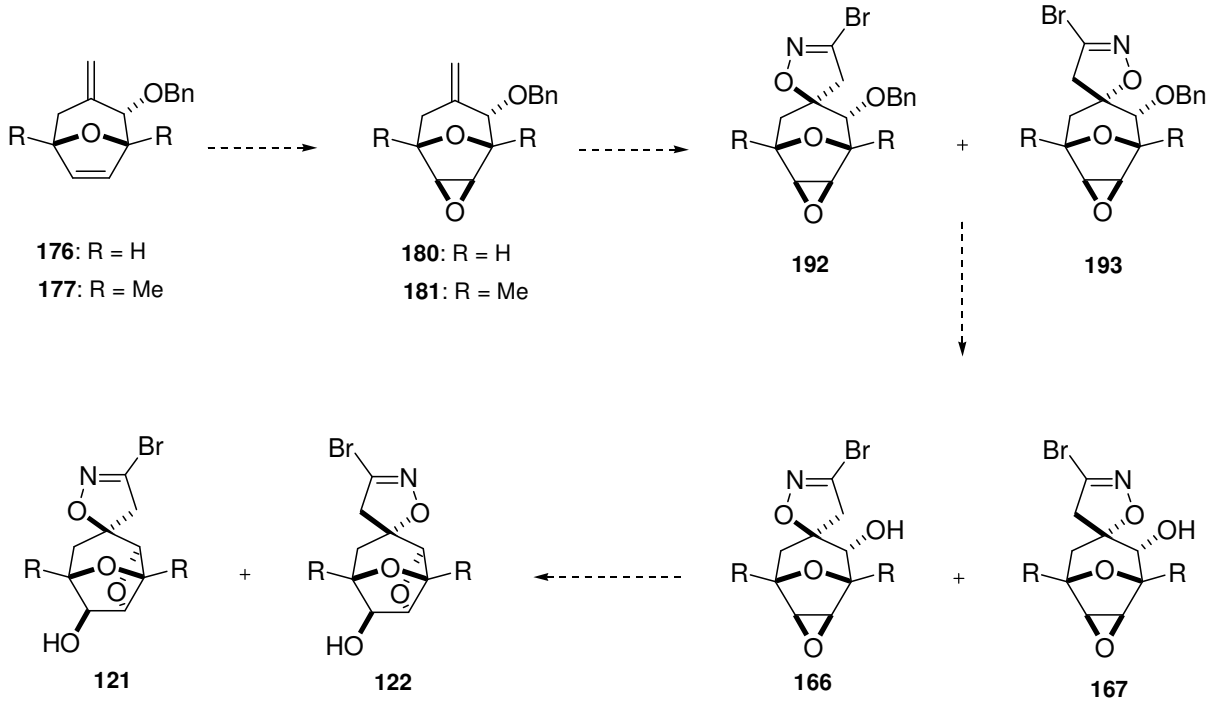
As observed in 1,3-dipolar cycloadditions to [3.2.1]oxabicyclic alkenes,[91] addition of bromonitrile oxide to the 1,2-disubstituted alkenes proceed under facial selectivity.

Summarizing the above described results, the 1,2-disubstituted double bond in oxabicyclic dialkenes shows higher dipolarophilic activity than the 1,1-disubstituted π system towards bromonitrile oxide under the attempted conditions. The strain of the 1,2-disubstituted double bond in oxabicyclic **176** and **177** increases its reactivity but it is not the only effect for a

satisfactory rationalization of the observed reactivity. As in other cyclic dipolarophiles,[98] deformation energies and staggering of forming bonds with respect to allylic bonds may also have an important influence on its dipolarophilic activity. Thus, these contributions in terms of deformation energies and tendency for staggering should be further studied with *ab initio* calculations.

4.5.3 Alternative Approach for the Synthesis of Dioxatricyclic Oxetanes with an Isoxazoline Ring

In view of the results of the attempted 1,3-dipolar cycloadditions (see Section 4.5.2.3), the synthetic route towards higher functionalized oxetanes **121** and **122** was reexamined. In a second strategic route, site selective epoxidation of oxabicyclic dialkenes **176** and **177** should provide dipolarophiles **181** and **182** for a later 1,3-dipolar cycloaddition with bromonitrile oxide. Debenzylation and following cyclization should lead to desired oxetanes **121** and **122**, as outlined in Scheme 53.



Scheme 52: Alternative synthetic strategy to generate isoxazolines rings attached to dioxatricyclic oxetanes.

[98] See Section 1.5.2.1.

4.5.4 Attempted Site Selective Epoxidation of Oxabicyclic Dialkenes

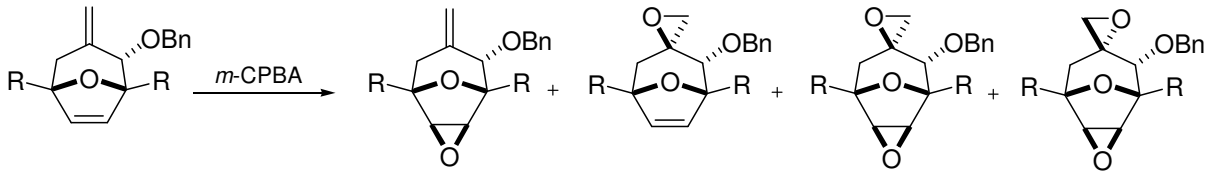
The second synthetic approach starts with a site selective epoxidation of dialkenes **176** and **177** on the endocyclic bond to form dioxatricyclic **180** and **181**, as precursors of 1,3-dipolar cycloaddition. The reactivity of alkenes towards epoxidation increases with substitution of the double bond because of the electron-releasing effect of alkyl groups.[99] In the presence of two double bonds in one molecule, epoxidation takes place selectively at the more electron-rich double bond and a high chemoselectivity is observed. A widely used reagent in selective epoxidations is *m*-CPBA, thus it was chosen for the attempted chemoselective oxidations of dialkenes **176** and **177**.

As outlined in Scheme 53, epoxidation took place non-selectively on both double bonds of oxabicyclic dialkenes **176** and **177** forming a mixture of epoxides and diepoxides in high yield. Changing the ratio of the substrate to *m*-CPBA as well as the solvent (DCM or H_2O/THF)[100] did not improve either yield or ratio of desired epoxides **180** and **181** (see Table 8). All diepoxides **196**, **197**, **198** and **199** and epoxides **180**, **181**, **194** and **195** were separable with difficulty by column chromatography.

Comparing the ratios of the obtained epoxides, certain selectivities may be observed in the case of dialkene **176**: *m*-CPBA reacts preferably with the exocyclic double bond. In the case of dialkene **177**, the attack of *m*-CPBA is nearly the same on both double bonds. Possibly, the methyl groups at the bridgehead carbon atoms limit free movement of the benzyl group at carbon C2 to the "north" part of the molecule, thus increasing the steric hindrance of the exocyclic bond. As a result, both exocyclic and endocyclic double bonds of dialkene **177** react similarly with *m*-CPBA. This steric effect does not occur in dialkene **176**, in which the benzyl group moves more freely due to the absence of the methyl groups and the exocyclic bond is less sterically hindered compared to that in dialkene **177**.

[99] McDonald, R. N.; Steppel, R. N.; Dorsey, J. E. *Org. Synth.* **1970**, *50*, 15.

[100] Different epoxidation conditions using *m*-CPBA in DCM or in THF/$H_2$0 (1:1) and with different ratios of substrate/ *m*-CPBA were carried out on micro scale and have not been included in Table 8. *m*-CPBA was too reactive and unwanted mixtures of epoxides and diepoxides were always obtained.



176: R = H
177: R = Me

180: R = H
181: R = Me

194: R = H
195: R = Me

196: R = H
197: R = Me

198: R = H
199: R = Me

Scheme 53: Epoxidation of dialkenes **176** and **177** with *m*-CPBA afforded a mixture of epoxides and diepoxides.

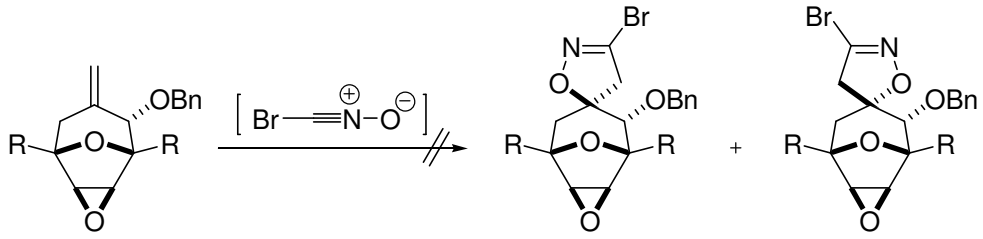
Entry	R	*m*-CPBA [eq]	Conditions	Total Yield [%]	Ratio of **180:194:196:198** (**181:195:197:199**)
1	H	1	DCM, 0°C → rt, 16 h	75	2:7:14:15
2	H	1.25	DCM, 0°C → rt, 16 h	93	2:7:9:9
3	Me	1	DCM, 0°C → rt, 16 h	94	3:2:3:2
4	Me	1.25	DCM, 0°C → rt, 16 h	96	2:1:5:3

Table 8: Some attempted regioselective epoxidation conditions of dialkenes **176** and **177** with *m*-CPBA.

Although attempted site selective epoxidation to dialkenes **176** and **177** was inefficient, desired epoxides **180** and **181** were isolated and used as dipolarophiles in a 1,3-dipolar cycloaddition with bromonitrile oxide (see Section 4.5.5). Therefore, the synthesis of dioxatricyclic oxetanes with an isoxazoline ring at C3 was further investigated.

4.5.5 Attempted 1,3-Dipolar Cycloaddition of Bromonitrile Oxide to Oxabicyclic Epoxy Alkenes

Epoxides **180** and **181** were utilized for the next step of the second synthetic route towards highly functionalized oxetanes with an isoxazoline ring at C3. For this purpose, the optimized protocol for 1,3-dipolar cycloaddition, described in Section 4.5.2.3, was followed without success. Only unreacted oxabicyclic olefines **180** and **181** were isolated, even if the reaction mixture was heated to reflux or excess of 1,3-dipole or phase transfer catalyst were added (see Table 9).



180: R = H
181: R = Me

200: R = H
202: R = Me

201: R = H
203: R = Me

Entry	R	DBF [eq]	Base	Conditions	Total Yield [%][b]
1	H	2+2[a]	2.2 eq KOH	Aliquat-336, THF, 0°C → rt	n.r.
2	H	2+2[a]	2.2 eq KOH	THF, 0°C → rt	n.r.
3	H	2.5+2[a]	3 eq DBU	CH_3CN, 0°C → rt	n.r.
3	Me	2+2[a]	2.2 eq KOH	Aliquat-336, THF, 0°C → rt	n.r.
4	Me	2+2[a]	2.2 eq KOH	THF, 0°C → rt	n.r.
5	Me	2.5+2[a]	3 eq DBU	CH_3CN, 0°C → rt	n.r.

Table 9: Attempted 1,3-dipolar cycloaddition reactions of bromonitrile oxide to epoxy alkene **180** and **181**. a) Addition of 2 eq after 16 h reaction time; b) unreacted epoxides **180** and **181** were recovered.

Further 1,3-dipolar cycloaddition conditions could be attempted such as change of solvent or use of different nitrile oxides. However, the low observed dipolarophilic activity of the exocyclic double bond of epoxides **180** and **181** indicates an sterically hindered environment, which impedes the addition of bromonitrile oxide.

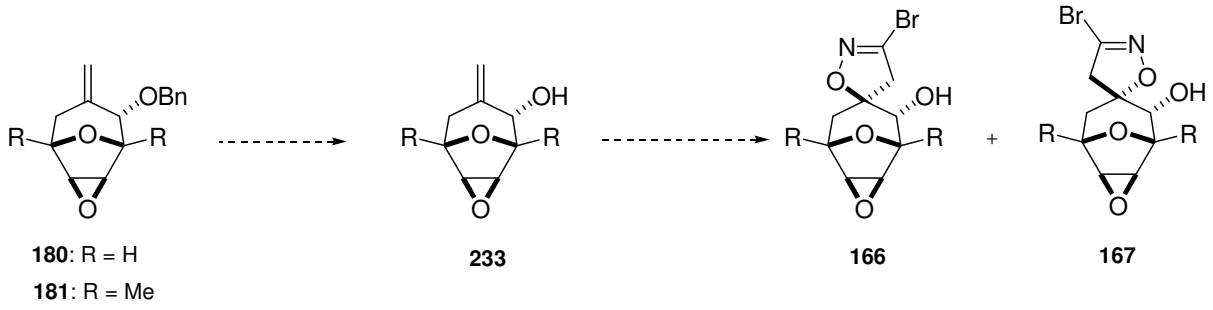
4.5.6 Summary and Conclusions of Attempted Synthesis of Oxatricyclic Oxetanes with an Isoxazoline Ring at C3 Position

For the synthesis of dioxatricyclic oxetanes with an isoxazoline ring at C3 position, two strategic routes were studied starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** In first place, conversion of the ketone function into a double bond proceeded by Wittig reaction in excellent yield affording the dipolarophile for a later 1,3-dipolar cycloaddition. In the following steps, the reactivity of both double bonds played an important role. On the one hand, a site selective 1,3-dipolar cycloaddition to the exocyclic double bond failed since the endocyclic alkene showed higher dipolarophilic activity towards bromonitrile oxide than the exocyclic double bond, which coincides with the high reactivity shown by other cyclic

dipolarophiles.[101] On the other hand, attempted site selective epoxidation of oxabicyclic dialkenes on the endocyclic double bond provided a mixture of epoxides and diepoxides. Furthermore, attempted 1,3-dipolar cycloaddition of bromonitrile oxide with desired epoxides **180** and **181** was not successful under the studied conditions.

The study of other nitrile oxides as well as different reaction conditions for 1,3-dipolar cycloaddition to the 1,1-disubstituted double bond or the optimization of a selective epoxidation of the endocyclic double bond of oxabicyclic dialkenes leave the door open for the future synthesis of oxetanes with an isoxazoline ring at C3.

A more promising alternative strategy would be the debenzylation of epoxides **180** and **181** without reduction of the exocyclic double bond before attempting the 1,3-dipolar cycloaddition (see Scheme 54). In the absence of the benzyl group at carbon C2, the steric hindrance of the 1,1-disubstituted alkene would diminish, thus facilitating the addition of the bromonitrile oxide to the exocyclic double bond and releasing the ring strain (sp^2 carbon atom).



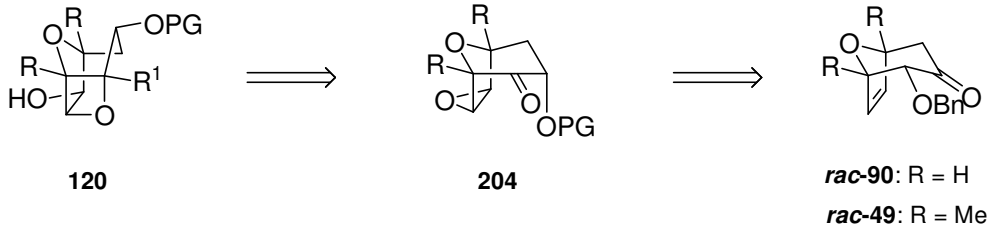
Scheme 54: Alternative for the introduction of an isoxazoline ring in the oxatricyclic skeletal structure.

4.6 Synthesis of C2-Arylated and Alkylated Oxatricyclic Oxetanes using Grignard Reagents

The synthesis of dioxatricyclic oxetanes with an additional aryl or alkyl group at carbon C2 was the next goal of the present work completing a series of higher functionalized dioxatricyclic structures (see Scheme 55). The attachment of an alkyl or aryl group should be achieved prior to the intramolecular cyclization to oxetane ring. The method of choice for the

[101] See Section 1.5.2.1.

introduction of an aryl or alkyl group at C2 position was the addition of an organometallic compound to the carbonyl group.



120 **204** ***rac*-90**: R = H
***rac*-49**: R = Me

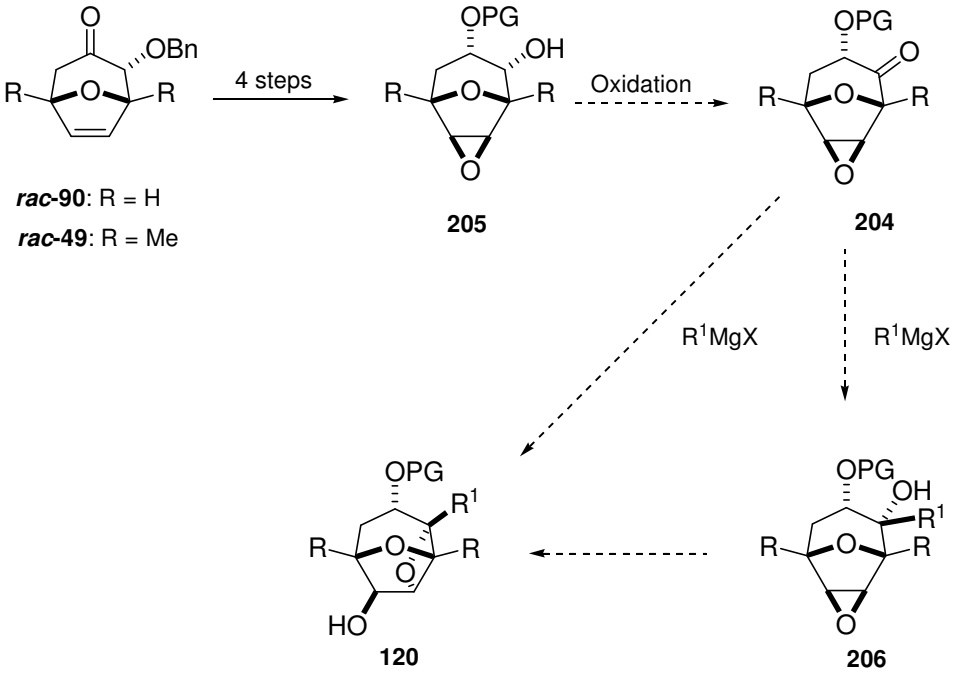
Scheme 55: Retrosynthesis of dioxatricyclic oxetanes with alkyl or aryl groups at C2 starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

Starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**, epoxy alcohol **205** is easily accessible following the route towards precursors of dioxatricyclic oxetanes.[102] Then, epoxy alcohol **205** should be first oxidized to epoxy ketone **204** and treated with an organometallic reagent affording a tertiary alcohol **206**, which is the precursor of alkylated dioxatricyclic oxetane **120** (see Scheme 56).

Organomagnesium compounds can function as a strong base and a Lewis acid.[103] Therefore, after nucleophilic attack to the carbonyl group, these organometallic reagents can catalyze the intramolecular cyclization of tertiary alcohol **206** to desired oxetane ring. In addition, competing reactions would be minimize because of their lower reactivity compared to the corresponding organolithium compounds.

[102] See Section 2.1 and Section 4.1.

[103] a) Wakefield, B. L. In *Comprehensive Organometalic Chemistry* ; Wilkinson, G.; Stone, F. G. A.; Abel. E. W., Eds.; Pergamon: Oxford, 1982, Chapter 44; b) Nützel, K. *J. Organomet. Chem.* **1973**, *13/2a*, 47; c) Raston, C. L.; Salem, G. *The Chemistry of the Metal-Carbon Bond* Hartley, F. R.; Ed.; Wiley: Chichester, 1987; Vol. 4, Chapter 2; d) Kharasch, M.; Reinmuth, O. *Grignard Reactions of Non-metallic Substances;* Prentice-Hall: New York, 1954; e) Ioffe, S. T.; Nesmeyanov, A. N. *The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium and Barium*; North-Holland: Amsterdam, 1967.



Scheme 56: Synthetic route to dioxatricyclic oxetanes with alkyl or aryl groups at C2 starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90.**

As outlined in Scheme 56, epoxy alcohol **205** was synthesized starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** in four steps following the developed route towards precursors of dioxatricyclic oxetanes. The synthesis of pivaloate and benzoate substituted epoxy alcohols from *meso*-oxabicycle ***rac*-90** was already described in Section 4.1, while the synthesis of pivaloate and benzoate substituted epoxy alcohols from *meso*-oxabicycle ***rac*-49** was carried out as reported by S. Proemmel.[104] Methoxy substituted epoxy alcohols from *meso*-oxabicycles ***rac*-49** and ***rac*-90** were prepared as described by J. Wittenberg[105] and M. Vidal Pascual.[106]

4.6.1 Oxidation of Epoxy Alcohols

The first step towards the synthesis of arylated or alkylated dioxatricyclic oxetanes was the oxidation of the 2-*endo*-hydroxyl group to afford the required ketone **204** for a later reaction with Grignard reagents. Starting from epoxy alcohol **205**, different oxidation methods and protecting groups at carbon C3 were chosen to obtain desired epoxy ketone **204** (see Scheme 56).

[104] Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199.

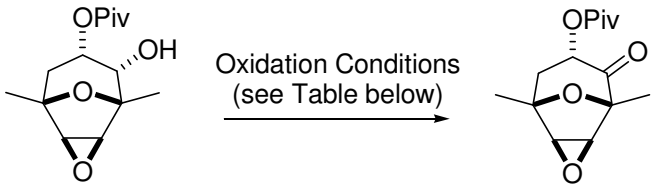
[105] Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1998**, 39, 8259.

[106] Vidal Pascual, M. *PhD Thesis*, University of Hannover, **2003**.

PCC oxidation proved to be the best choice because of excellent yields, absence of by-products and several practical advantages: inexpensive reagent, straightforward reaction, mild conditions, easy work-up procedure and no need of chromatographic purification (compounds are obtained in high purity).

*4.6.1.1 Oxidation of Pivaloate **160***

In the case of pivaloate protected epoxy alcohol **160**, ketone **207** was obtained in excellent yield under the attempted oxidation conditions except for Parikh-Doering oxidation (see Table 10).



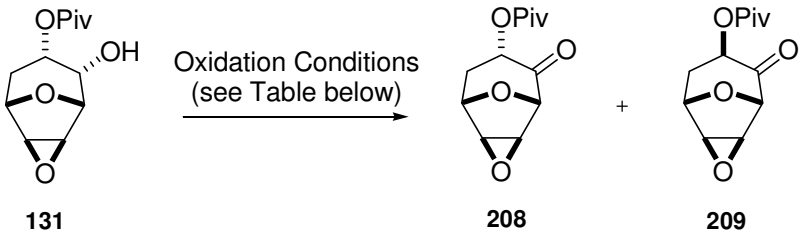
160 **207**

Entry	Conditions	Yield [%]
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt - rt, 2.5 h	91
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	47
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	99
4	Dess-Martin Periodinane, DCM, rt, 2 h	92

Table 10: Attempted oxidations of epoxy alcohol **160**.

*4.6.1.2 Oxidation of Pivaloate **131***

The oxidation of epoxy alcohol **131** using DMP or PCC led exclusively to ketone **208** in excellent yield. Swern and Parikh-Doering oxidations afforded desired ketone **208** together with ketone **209**, in which the pivaloate function is in equatorial position (see Table 11).

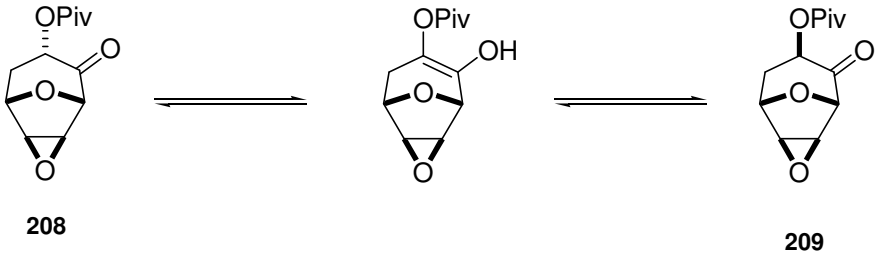


131 208 209

Entry	Conditions	Total Yield [%]	Ratio of products **208:209**
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 2 h	90	1:2
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	60	1:1
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	95	100% **208**
4	Dess-Martin Periodinane, DCM, rt, 4 h	89	100% **208**

Table 11: Attempted oxidations of epoxy alcohol **131**.

Under Swern and Parikh-Doering oxidation conditions the pivaloate function at C3 adopts the thermodynamically favoured equatorial position. This inversion of the carbon center at carbon C3 proceeds by keto-enol-tautomerism under the basic conditions (triethylamine) (see Scheme 57).

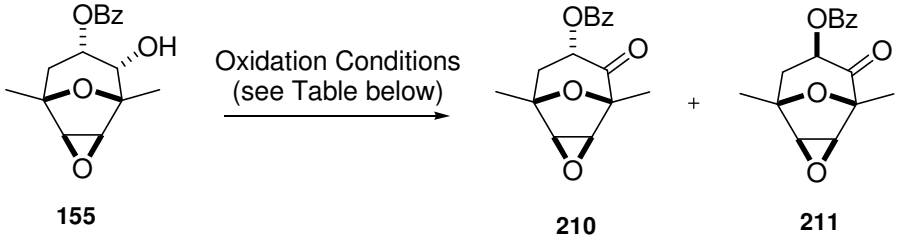


208 209

Scheme 57: Keto-enol-tautomerism of epoxy ketone **208**.

*4.6.1.3 Oxidation of Benzoate **155***

Benzoate protected epoxy alcohol **155** was oxidized exclusively to ketone **210** using either PCC or DMP in quantitative yield, while Swern and Parikh-Doering oxidations afforded again a mixture of ketones **210** and **211** (see Table 12). Moreover, under Swern oxidation conditions 16% of deprotected epoxy ketone was obtained because of the basicity of the reaction medium.

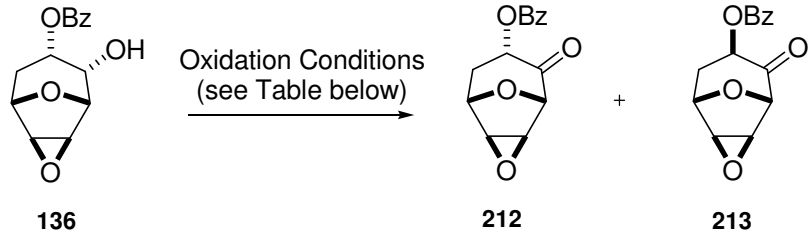


Entry	Conditions	Total Yield [%]	Ratio of products **210:211**
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 2.5 h	53[a]	4:1
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	95	1:5
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	99	100% **210**
4	Dess-Martin Periodinane, DCM, rt, 4 h	95	100% **210**

Table 12: Attempted oxidations of epoxy alcohol **155**. a) Obtention of additional 16% of deprotected ketone.

*4.6.1.4 Oxidation of Benzoate **136***

PCC oxidation of benzoate protected epoxy alcohol **136** led to desired epoxy ketone **212** in excellent yield while the other three oxidation methods afforded a mixture of epoxy ketones **212** and **213** in lower yield (see Table 13). In constrast to the methylated analogue **155**, DMP oxidation of epoxy alcohol **136** gave a mixture of both diastereomers after epimerisation.

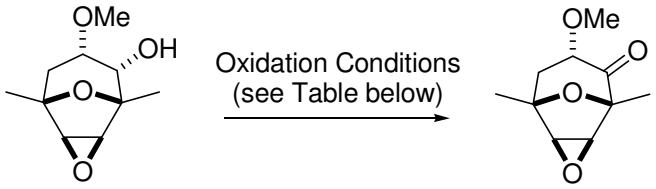


Entry	Conditions	Total Yield [%]	Ratio of products **212:213**
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 16 h	24	1:3
2	SO_3·Py, DMSO, Et_3N, 0°C, 16 h	72	1:1
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	95	100% **212**
4	Dess-Martin Periodinane, DCM, rt, 16 h	54	3:1

Table 13: Attempted oxidations of epoxy alcohol **136**.

*4.6.1.5 Oxidation of Methyl Ether **56***

Epoxy methyl ether **56** was oxidized to ketone **214** under different oxidation conditions. The best results were obtained using PCC or DMP as summarized in Table 14. No inversion tendency to the equatorial position was observed using the less electron attracting ether function.



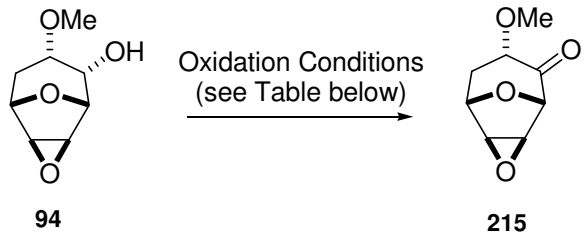
56 **214**

Entry	Conditions	Yield [%]
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 2.5 h	50
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	30
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	95
4	Dess-Martin Periodinane, DCM, rt, 2 h	99

Table 14: Attempted oxidations for epoxy alcohol **56**.

*4.6.1.6 Oxidation of methyl ether **94***

O-Methyl protected epoxy alcohol **94** was not stable under Swern and Parikh-Doering oxidation conditions and the desired epoxy ketone **215** was only obtained using PCC or DMP in good yield.



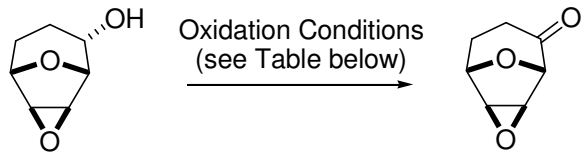
94 **215**

Entry	Conditions	Yield [%]
1	$(COCl)_2$, DMSO, Et_3N, -78°C → rt, 2.5 h	-
2	SO_3·Py, DMSO, Et_3N, 0°C, 24 h	-
3	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	56
4	Dess-Martin Periodinane, DCM, rt, 2 h	57

Table 15: Attempted oxidations for epoxy alcohol **94**.

*4.6.1.7 Oxidation of Deoxygenated Epoxy Alcohol **147***

Finally, the oxidation of deoxygenated epoxy alcohol **147** using DMP occurred in higher yield compared to PCC oxidation.



147 **216**

Entry	Conditions	Yield [%]
1	PCC, NaOAc, 4 Å MS, DCM, rt, 1 h	58
2	Dess-Martin Periodinane, DCM, rt, 16 h	77

Table 16: Attempted oxidation for deoxygenated alcohol **147**.

4.6.2 Synthesis of C2-Arylated and Alkylated Oxatricyclic Oxetanes using Grignard Reagents

The next step of the synthetic route towards new arylated and alkylated dioxatricyclic oxetanes was the introduction of an aryl or alkyl group at carbon C2 by chemoselective and exo-selective addition of a Grignard reagent to the carbonyl function of different epoxy ketones. It was anticipated that, after addition of Grignard reagents, the resulting tertiary

alcohols could undergo immediately intramolecular cyclization to oxetane ring, because of the Lewis acidic character of the organomagnesium compounds.[103] In other words, C2-arylated and alkylated would be synthesized by a tandem Grignard reagent-mediated addition-cyclization reaction.

The relative reactivity of a series of carbon nucleophiles may be assessed to a first approximation by comparing the pKa values of their conjugate acids. The weakest acids produce the strongest conjugate bases, i.e. the most reactive nucleophiles. Table 17 presents a list of representative systems ranked in order of increasing acidity.

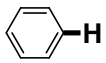
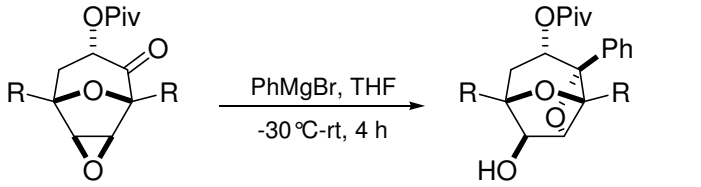
Compound	Structure	pK_a
Methane	CH_3-**H**	60
Ethene	CH_2=CH-**H**	45
Benzene		43
Ethyne	HC≡C-**H**	25
Water	HO-**H**	15.7

Table 17: Values of pK_a's of a selection of representative systems.

Hydrocarbons are very weak acids, implying that the corresponding carbanions will be strong bases. Considering the Grignard reagents used in the above studied synthesis of alkylated dioxatricyclic oxetanes, vinyl magnesium bromide is the most reactive followed closely by phenylmagnesium bromide while ethynylmagnesium halides are weaker.

4.6.2.1 Synthesis of Oxatricyclic Oxetanes with a Phenyl Group at Carbon C2

The attachment of an aryl group at carbon C2 of the oxatricyclic skeletal structure was first attempted by treatment of pivaloate substituted epoxy ketones **207** and **208** with phenylmagnesium bromide (see Scheme 58). In general, pivaloate ester could be attacked by the nucleophilic Grignard reagent but the steric hindrance of the phenyl carbanion as well as the shielding effect of the methyl groups of the pivaloate ester diminished this competing reaction. Epoxy ketones **207** and **208** reacted indeed with phenylmagnesium bromide to afford exclusively desired dioxatricyclic oxetanes **217** and **218** without affecting the pivaloate group at carbon C3.



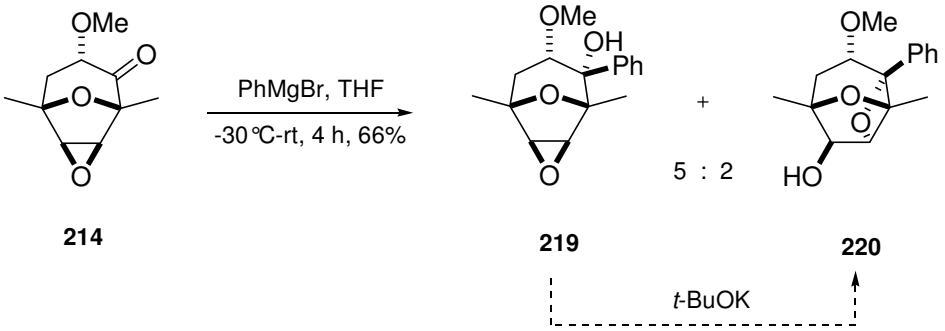
208: R = H
207: R = Me

217: R = H (65%)
218: R = Me (61%)

Scheme 58: Synthesis of dioxatricyclic oxetanes **217** and **218** using phenylmagnesium bromide.

The same tandem strategy was applied for methoxy substituted epoxy ketone **214**, which provided a mixture of arylated *endo*-hydroxy epoxide **219** and dioxatricyclic oxetane **220** in a 5:2 ratio in 66% yield (see Scheme 59).

The obtained alkylated α-configured hydroxy epoxide **219** could undergo a base-catalyzed intramolecular cyclization to desired oxetane **220** using potassium *tert*-butoxide in THF, as in the synthesis of similar methoxy-substituted dioxatricyclic oxetanes.[52,63]



214

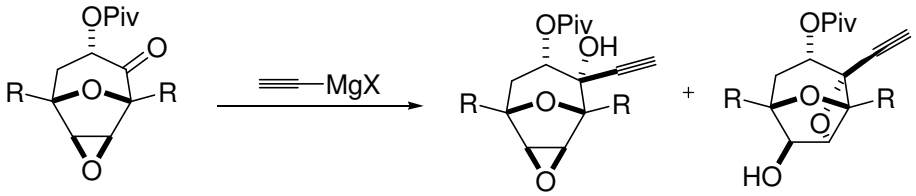
219

220

Scheme 59: Synthesis of dioxatricyclic oxetane **220** using phenylmagnesium bromide.

4.6.2.2 Synthesis of Oxatricyclic Oxetanes with an Ethynyl Group at Carbon C2

In view of the satisfactory results using phenylmagnesium bromide in the synthesis of arylated dioxatricyclic oxetanes, the use of other Grignard reagents was further investigated. Epoxy ketones **207** and **208** were also treated with ethynyl magnesium halides to afford a mixture of desired oxetane and *endo*-hydroxy epoxide. Yields and ratio of products are summarized in Table 18. Treatment of epoxy ketones with ethynyl magnesium bromide yielded desired oxetane in higher ratio than using ethynyl magnesium chloride, the former being more reactive than the later.



208: R = H
207: R = Me

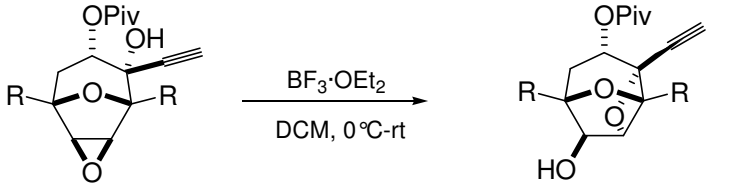
221: R = H
223: R = Me

222: R = H
224: R = Me

Entry	R	Conditions	Total Yield [%]	Ratio of **221:222** **(223:224)**
1	H	EthynylMgBr, THF, -30°C → rt, 16 h	25	0:1
2	H	EthynylMgCl, THF, -30°C → rt, 16 h	65	5:1
3	Me	EthynylMgBr, THF, -30°C → rt, 16 h	55	1:4
4	Me	EthynylMgCl, THF, -30°C → rt, 16 h	34	2:7

Table 18: Attempted reaction conditions using ethynylmagnesium halides for the synthesis of dioxatricyclic oxetanes **222** and **224**.

The obtained alkylated α-configured hydroxy epoxides **221** and **223** underwent Lewis acid-catalyzed intramolecular cyclization to desired oxetanes **222** and **224** in 56 and 61% yield, respectively, as outlined in Scheme 60.



221: R = H
223: R = Me

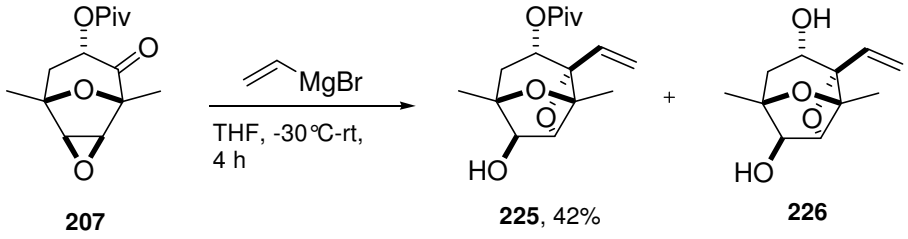
222: R = H (56%)
224: R = Me (61%)

Scheme 60: Lewis acid-catalyzed intramolecular cyclization using $BF_3{\cdot}OEt_2$ in THF to dioxatricyclic oxetanes **222** and **224**.

4.6.2.3 Synthesis of Oxatricyclic Oxetanes with a Vinyl Group at Carbon C2

Treatment of epoxy ketone **207** with the more reactive vinyl magnesium bromide led to oxetane **225** in low yield and unwanted by-product **226**, which results from the cleavage of the pivaloate at carbon C3 (see Scheme 61). To explain these results, the reactivity and the

conformational aspects of the addition of Grignard reagents to epoxy ketones are carefully examined in the next section.



207 **225**, 42% **226**

Scheme 61: Tandem addition-cyclization reaction by using vinylmagnesium bromide afforded dioxatricyclic oxetane **225** and by-product **226**.

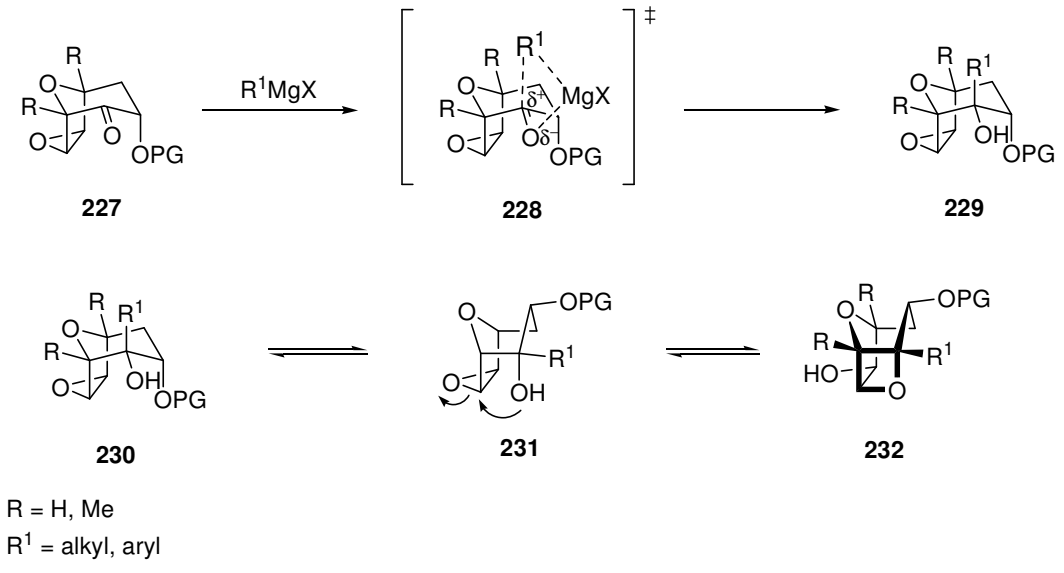
4.6.2.4 Reactivity Considerations in the Synthesis of Alkylated Dioxatricyclic Oxetanes

The above reported results of the addition of different Grignard reagents to dioxatricyclic epoxy ketones agree with the relative reactivity of organomagnesium compounds. Weaker ethynylmagnesium halides reacted with epoxy ketones leading to a mixture of *endo*-hydroxy epoxide and desired oxetane. As mentioned in Section 4.6.2.2, addition of ethynylmagnesium chloride provided the oxetane in lower yield than that of ethynyl magnesium bromide because of the lower reactivity of the chloride compared to the bromide. Pivaloate ester was unaffected by these Grignard reaction conditions because of the lower basic character of these halides and the high stability of the pivaloate protecting group.

In the case of more reactive phenylmagnesium bromide, C2-arylated dioxatricyclic oxetane was obtained exclusively without cleavage of the pivaloate ester. In contrast, addition of slightly more reactive vinylmagnesium bromide proceeded in lower yield because desired oxetane was obtained together with by-products resulting from the pivaloate cleavage. The fact that this competing side reaction did not occur using similarly reactive phenylmagnesium bromide can be explained by the steric hindrance of the phenyl group in comparison to the vinyl group. Sterically hindered phenyl carbanion adds only to the accessible and more reactive ketone rather than to the stable pivaloate ester whose carbonyl group is shielded from nucleophilic attack by methyl groups. In contrast, less sterically hindered vinyl group is able to add partially to the electrophilic carbonyl group of pivaloate.

4.6.2.5 Mechanistic Considerations in the Synthesis of C2-Alkylated Dioxatricyclic Oxetanes

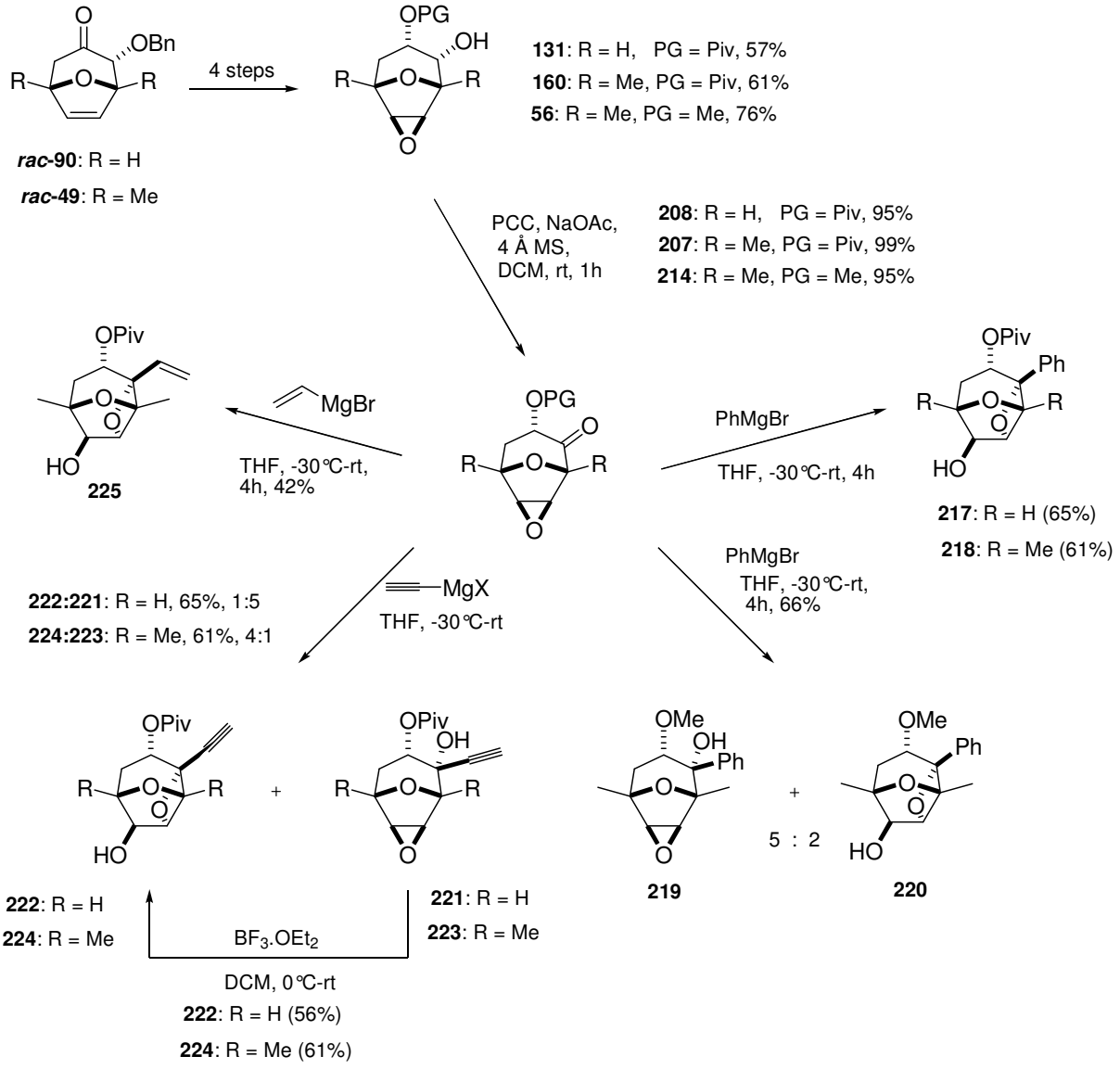
Mechanistic and conformational aspects of the Grignard reaction to epoxy ketones and later intramolecular cyclization towards dioxatricyclic oxetanes are outlined in Scheme 62. The addition of the organomagnesium compound to the ketone proceeds with facial selectivity on the less hindered side of the carbonyl group through a complex formation between both substrates. Afterwards, a conformational change in resulting tertiary *endo*-hydroxy epoxide **230** must precede the cyclization. The six-membered oxacyclic ring changes to a minor boat **231**, in which the hydroxyl function moves to axial position for a stereoelectronically favoured formation of the new oxetane C-O bond. Simultaneously, the protecting group at C3 (methyl ether or pivaloate ester) and the aryl or alkyl group at C2 move from axial positions to thermodynamically favoured equatorial positions, lowering the energy difference between chair conformation **230** and boat transition state **231**. After formation of the tricyclic oxetane **232**, the bulky substituents at carbons C3 and C2 occupy less hindered equatorial positions in an oxacyclohexane boat. Thus, conformational analysis shows a driving force for the formation of arylated or alkylated oxetanes despite the steric hindrance of the substituents. Besides, additional methyl groups at the bridgehead carbons increase the stability of dioxatricyclic oxetane structure.



Scheme 62: Addition of Grignard reagents to epoxy ketones and intramolecular cyclization to alkylated oxetanes.

4.6.3 Summary and Conclusions of the Synthesis of C2-Alkylated and Arylated Dioxatricyclic Oxetanes

Following a short and valuable route a series of arylated and alkylated dioxatricyclic oxetanes was synthesized. Starting from versatile *meso*-oxabicycles ***rac*-49** and ***rac*-90**, epoxides **56**, **131** and **160** were obtained over four steps in good yield. The conversion of the *endo*-hydroxyl group into ketone was attempted with different oxidants (PCC, Swern, Parikh-Doering and DMP). PCC oxidation proved to be the best method to prepare epoxy ketones **207**, **208** and **214**. Afterwards, the introduction of aryl and alkyl groups at carbon C2 was accomplished by a Grignard reagent-mediated addition/cyclization tandem reaction of epoxy ketones **207**, **208** and **214**. Moreover, dioxatricyclic oxetanes **222** and **224** could be obtained by Lewis acid-catalyzed cyclization of isolated tertiary alcohols.



Scheme 63: Synthesis of alkylated and arylated dioxatricyclic oxetanes.

4.7 Summary of new Synthesized Dioxatricyclic Oxetanes

The biological activity shown by some dioxatricyclic subunits of dictyoxetane[107] stressed the importance of the synthesis of new dioxatricycles starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

Starting from 2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one, dioxatricyclic oxetanes with different ester functions at C3 position were synthesized as an alternative to the more stable ether protecting group. *Tert*-butylester was the best choice for preparing tricyclic oxetanes

[107] See Section 2.1.

compared to benzoate and acetate groups since pivaloate did not show any tendency for migration. Furthermore, the synthesis of dioxatricyclic oxetanes proved to be clearly more successful using a pivaloate ester than an ether function[108] at C3 position in absence of stabilizing methyl groups at the bridgehead carbons.

The possibility of reducing the number of steps in the synthetic route towards dioxatricyclic oxetanes by tandem Lewis acid-catalyzed debenzylation-cyclization reaction was investigated. Treatment of different oxatricyclic epoxides with BCl_3 afforded a mixture of oxetanes and unwanted dioxatricycles as a result of pivaloate cleavage or migration of the benzoate group. Nevertheless, the reactivity of BCl_3 opened a new synthetic access to 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonanes as TXA_2-analogues starting from *meso*-oxabicycle ***rac*-49**.

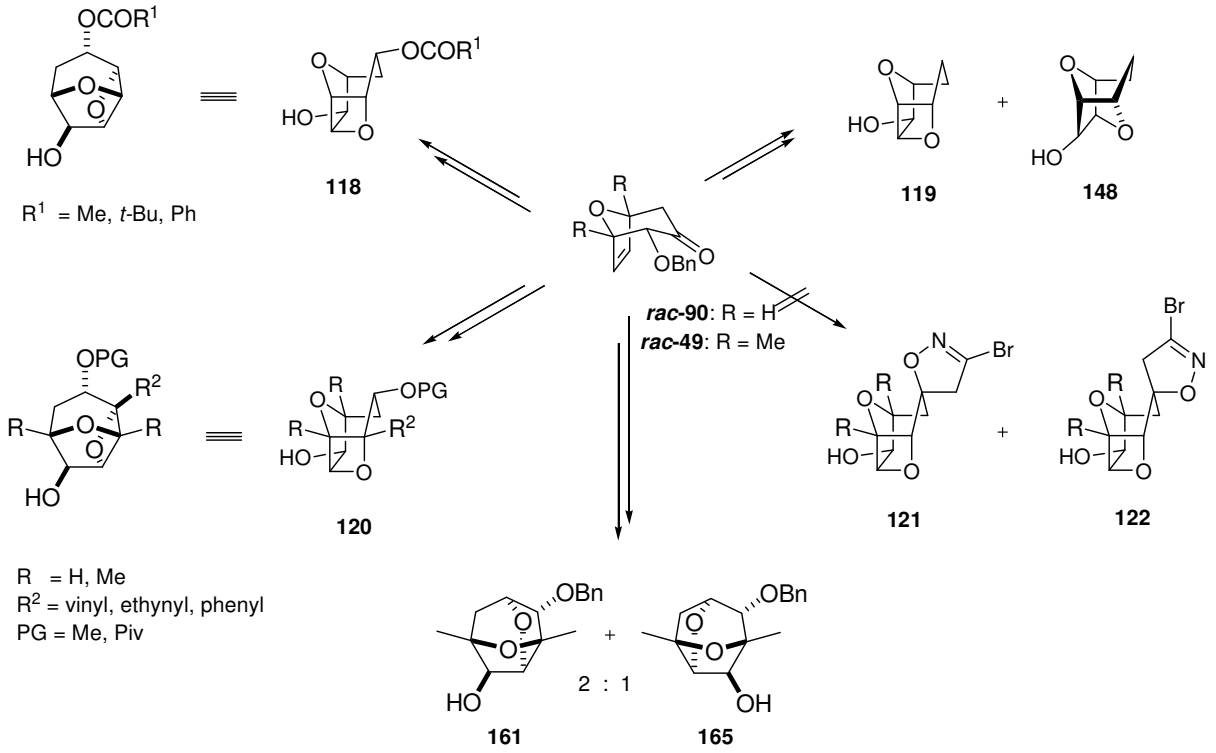
Attempted synthesis of a new deoxygenated oxatricyclic oxetane starting from *meso*-oxabicycle ***rac*-90** led only to a mixture of desired oxetane **119** and dioxatricycle **148** in poor yield.

Starting from oxabicyclic dialkenes, the synthesis of higher functionalized oxetanes with a bromoisoxazoline ring at C3 was studied. Whereas a site selective 1,3-dipolar cycloaddition to the 1,1-disubstituted double bond of the oxabicyclic dialkene was unsuccessful, attempted site selective epoxidation of the 1,2-disubstituted alkene provided a mixture of epoxides. Nevertheless, other nitrile oxides as well as different reaction conditions for the 1,3-dipolar cycloaddition to the 1,1-disubstituted double bond as well as the optimization of a regioselective epoxidation should be further investigated.

An efficient route to higher functionalized dioxatricyclic oxetanes with alkyl and phenyl groups at C2 position was accomplished starting from versatile *meso*-oxabicycles ***rac*-49** and ***rac*-90**. The introduction of alkyl and phenyl groups proceeded by stereoselective tandem addition-cyclization reaction upon treatment of epoxy ketones with different Grignard reagents.

In summary, the synthetic strategy towards dioxatricyclic subunits of dictyoxetane starting from oxabicycles ***rac*-49** and ***rac*-90** offers a valuable and straightforward route to a series of versatile compounds containing the skeletal structure 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane with potential biological activity.

[108] Vidal Pascual, M. *PhD Thesis*, University of Hannover, **2003**.



Scheme 64: Overview of the new dioxatricycles starting from oxabicycles ***rac*-49** and ***rac*-90**.

5. Attempted Enzymatic Resolution of Tricyclic Subunits of Dictyoxetane

Until now only the relative configuration of dictyoxetane has been established.[109] The determination of the absolute configuration of this natural product is essential not only for the understanding of its biological activity but also for a more comprehensive approach of its biogenesis in *Dictyota dichotoma*. Furthermore, the anti-tumor activity shown by some reported dioxatricycles[110] stresses the interest for the stereochemistry of dioxatricyclic subunits of dictyoxetane.

As reported in Section 4.1.3, the direct synthesis of acetate protected dioxatricyclic oxetanes for enzymatic resolution failed because of the acyl migration tendency. In the present chapter, determination of the absolute configuration of new oxabicyclic and dioxatricyclic segments was attempted after enzymatic resolution of acetate protected *meso*-compounds.

In recent years, esterases and lipases with high stereoselectivity and substrate selectivity have been exploited for transformations which would otherwise be difficult to achieve using "standard" synthetic methodology. For instance, the enzymatic desymmetrization of *meso* substrates has recently become a powerful tool in the *de novo* synthesis of enantiomerically pure compounds.[111]

One of the most promising enzymes in terms of substrate specificity and stereoselectivity is the lipase PS from *Pseudomonas cepacia* (Amano).[112] One example of lipase PS catalyzed hydrolysis is the enzymatic desymmetrization of *meso*-diacetates ***meso*-233** and ***meso*-235** by T. Lampe.[113] Benzyl ether ***meso*-233** and ***meso*-235** were desymmetrized with >98% e.e. upon the action of lipase PS in a 4:1 mixture of 0.5 molar phosphate buffer and toluene at pH 7. The corresponding 2,4,6-trifunctionalized C-glycosides **(-)-234** and **(-)-236** were obtained in high chemical yield and excellent optical purity (see Scheme 65).

---

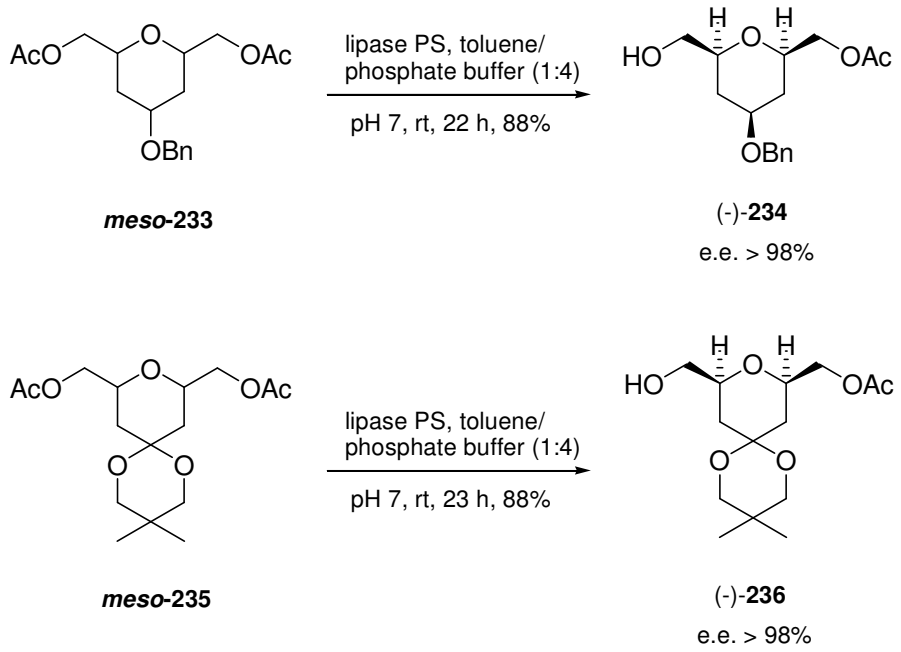
[109] See Chapter 1.

[110] a) Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1998**, *39*, 8259; b) Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199.

[111] a) Hoye, T. R.; Witowsky, N. E. *J. Am. Chem. Soc.* **1992**, *114*, 7291; b) Gais, H.-J.; Hemmerle, H.; Kossek, S. *Synthesis* **1992**, 169.

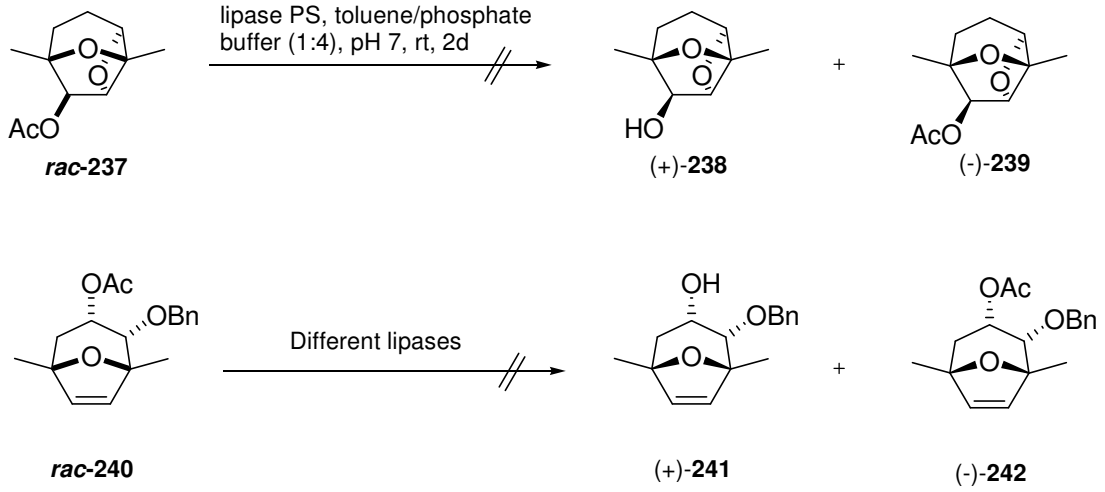
[112] a) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531; b) Zhuo-Feng, X. *Tetrahedron Asymmetry* **1991**, *2*, 733; c) Bosetti, A.; Bianchi, D.; Cesti, P.; Golini, P.; Spezia, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2395.

[113] a) Lampe, T. F. J.; Hoffmann, H. M. R.; Bornscheuer, U. T. *Tetrahedron Asymmetry* **1996**, *7*, 2889; b) Lampe, T. F. J.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1996**, *37*, 7695.



Scheme 65: Desymmetrization of *meso*-diacetates ***meso*-233** and ***meso*-235** with Lipase PS by T. Lampe.

Lipase PS catalyzed hydrolysis of deoxygenated dioxatricycle ***rac*-237** was attempted by S. Proemmel[114] under standard conditions without success (see Scheme 66). Presumably the acetate group may not reach the reactive center of the lipase PS because of the steric hindrance of dioxatricycle ***rac*-237**. Enzymatic hydrolysis of *meso*-acetate ***rac*-240** using different lipases (PS, PV, PPL) also failed owing to the proximity of the acetate group to the sterically hindered carbon skeleton.



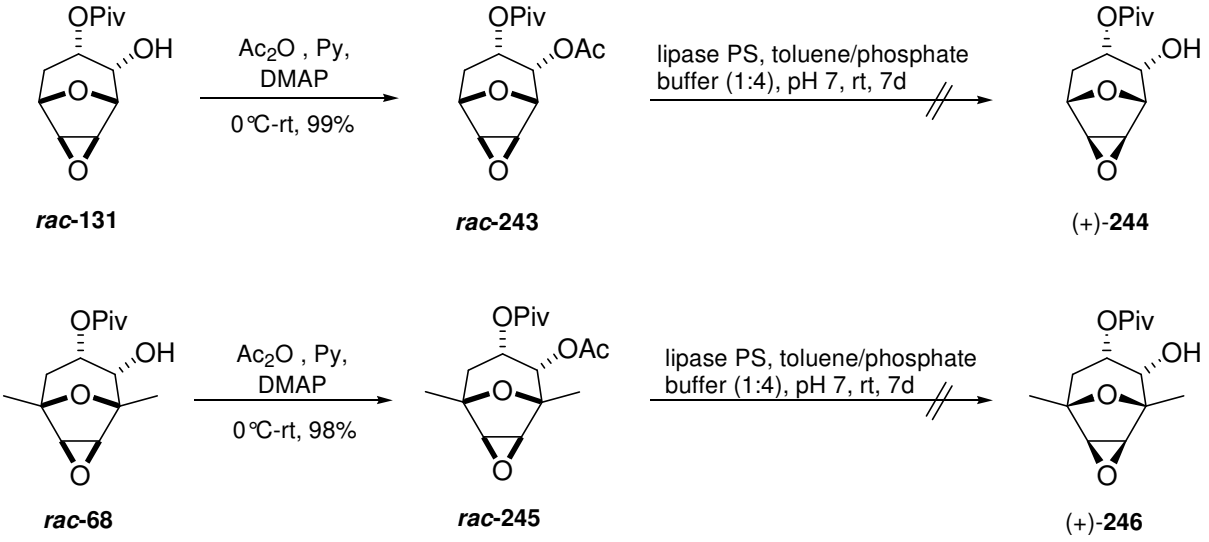
Scheme 66: Attempted enzymatic hydrolysis of acetates ***rac*-237** and ***rac*-240** by S. Proemmel.

[114] Proemmel, S. *PhD Thesis* Universität Hannover, **2001**.

Despite the disappointing results of the attempted enzymatic hydrolysis of dioxatricycle ***rac*-237** and oxabicycle ***rac*-240** by S. Proemmel, the enzymatic resolution of dioxatricyclic *meso*-compounds was investigated in the present work.

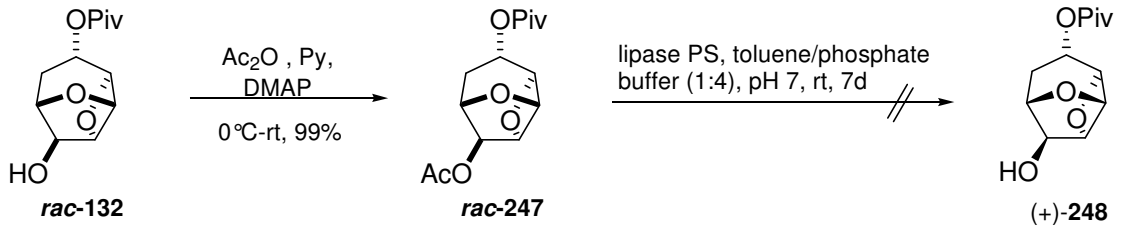
Meso-alcohols ***rac*-131** and ***rac*-68** were first converted quantitatively into *meso*-acetates ***rac*-243** and ***rac*-246**. Racemic acetates ***rac*-243** and ***rac*-246** were then subjected to the conditions for lipase PS catalyzed enzymatic hydrolysis optimized by T. Lampe. After one week no products of hydrolysis were observed and both reactions were quenched (see Scheme 67).

The acetate group in both pivaloates ***rac*-243** and ***rac*-245** may not reach the reactive center of the lipase PS owing to steric hindrance of the dioxatricyclic structure. The absence of the methyl groups at the bridgehead carbon atoms in pivaloate ***rac*-243** does not improve the results of the attempted enzymatic hydrolysis comparing to more sterically hindered pivaloate ***rac*-245**. The access of the acetate group to the reactive center of the lipase PS is hindered in both cases.



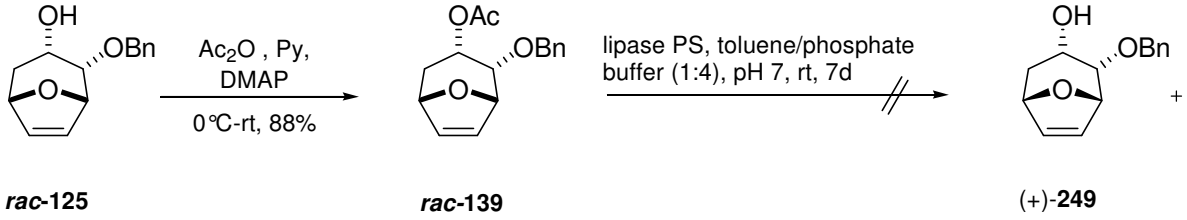
Scheme 67: Attempted enzymatic hydrolysis of racemic acetates ***rac*-131** and ***rac*-68**.

Enzymatic resolution was also attempted with a dioxatricyclic oxetane system. For this purpose, *meso*-pivaloate ***rac*-131** was acetylated quantitatively and *meso*-acetate ***rac*-247** was subjected to lipase PS catalyzed enzymatic hydrolysis. After one week the reaction was quenched without products of hydrolysis (see Scheme 68).



Scheme 68: Attempted enzymatic hydrolysis of *meso*-acetate ***rac*-247**.

In view of the failed enzymatic resolution of the caged dioxatricyclic ***rac*-243**, ***rac*-245** and ***rac*-247**, the *meso*-oxabicycle ***rac*-139** was used as a model compound for further investigation. After acetylation of *meso*-oxabicycle ***rac*-90**, resulting *meso*-acetate ***rac*-139** was treated with lipase PS under hydrolysis conditions without success (see Scheme 69). The proximity of the acetate group to the shielding benzyl ether group in the oxabicyclic structure possibly makes the approach to the reactive center of the lipase difficult.

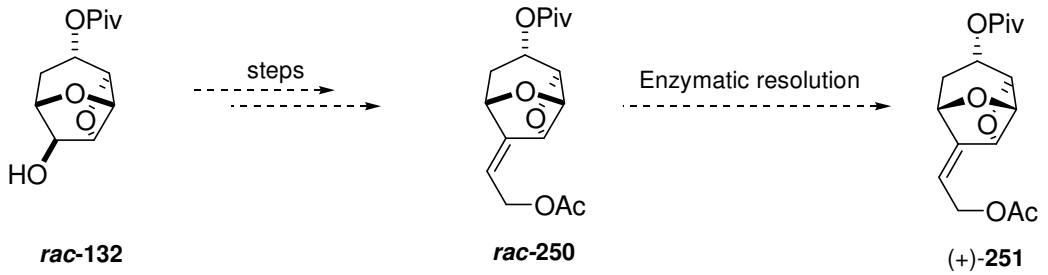


Scheme 69: Attempted enzymatic hydrolysis of *meso*-acetate ***rac*-139**.

Further attempts on the synthesis of enantiopure dioxatricycles were not carried out in the framework of the present work.

5.1 Outlook

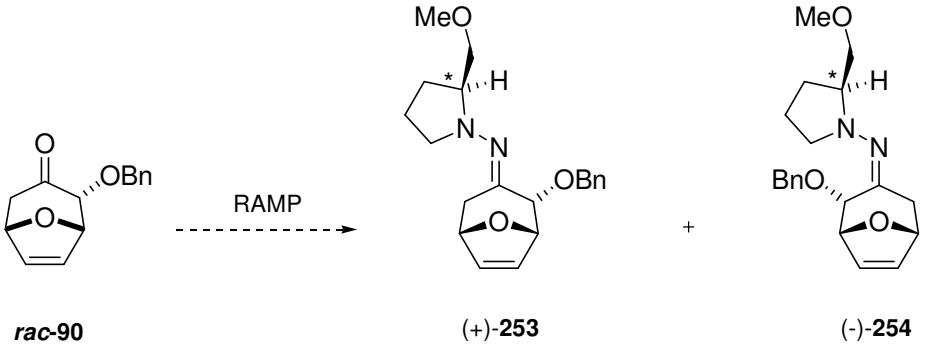
Regarding the reported results, oxabicyclic and oxatricyclic compounds are sluggish substrates for enzymatic resolution because of the proximity of the acetate group to the sterically hindered skeletal structure. An alternative to these sterically congested *meso*-acetates would be the synthesis of the *meso*-allyl ester ***rac*-250**, where the acetate group is in farther distance from the skeletal structure.



Scheme 70: Proposed synthesis of less sterically hindered *meso*-allyl ester ***rac*-250** for enzymatic resolution.

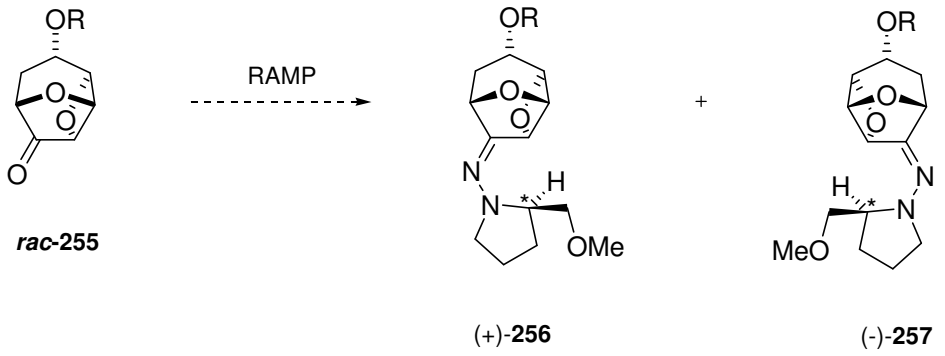
Another valuable alternative reported by S. Proemmel and M. Vidal Pascual is the synthesis of enantiomerically pure oxatricyclic structures using asymmetric [4+3]-cycloaddition of enantiopure silylenolether, as mentioned in Section 2.1.

Other methods for enantioselective synthesis include the use of chiral reagents. The synthetic route towards tricyclic compounds offers several possibilities for the use of chiral reagents. For instance, *meso*-oxabicycle ***rac*-90** could be converted into a diastereomeric mixture using (R)-(+)-*N*-amino-(methoxymethyl)-pyrrolidine (RAMP) (see Scheme 71).



Scheme 71: Proposed obtention of a diastereomeric mixture using (R)-(+)-*N*-amino-(methoxymethyl)-pyrrolidine (RAMP).

The conversion of *meso*-tricyclic ketone ***rac*-255** into a diastereomeric mixture in a later step of the synthetic route should be even more advantageous (see Scheme 72).



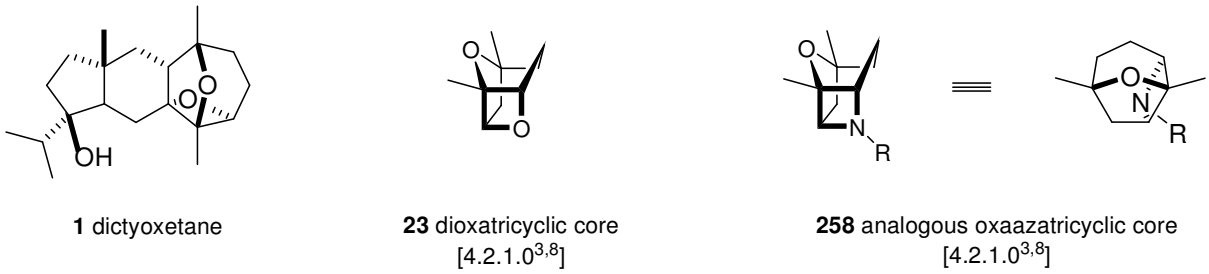
***rac*-255** (+)-**256** (-)-**257**

Scheme 72: Proposed obtention of a diastereomeric mixture using (R)-(+)-*N*-amino-(methoxymethyl)-pyrrolidine (RAMP).

As outlined in Scheme 71 and Scheme 72, several alternatives for the synthesis of enantiopure dioxatricyclic subunits of dictyoxetane remain open for further investigation.

6. Synthesis of Aza-analogous Tricyclic Systems

The second major aim of the present work was the synthesis of aza-analogues of the dioxatricyclic subunit of dictyoxetane with an azetidine ring substituting the oxetane ring (see Scheme 73). As described in Chapter 1, the azetidine ring system represents an unusual substructure of several relevant classes of drugs and has also been identified as a structural feature in some natural products with significant biological activity. Therefore, the introduction of an azetidine ring in the tricyclic skeletal structure constituted not only an important synthetic challenge but also offered an access to potential pharmacologically active compounds.



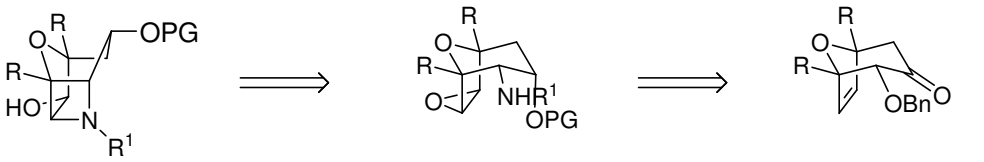
1 dictyoxetane

23 dioxatricyclic core [4.2.1.0^{3,8}]

258 analogous oxaazatricyclic core [4.2.1.0^{3,8}]

Scheme 73: Oxazatricyclic system **258** is analogous to the dioxatricyclic subunit of dictyoxetane.

The synthetic route towards oxatricyclic azetidines was designed starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** , which already contain two of the three rings of the skeletal structure 7-oxa-2-aza-tricyclo[4.2.1.0$^{3.8}$]nonane (see Scheme 74). The key reaction of the synthetic strategy is the introduction of an *endo*-amine function at C2 position to afford the appropriate precursors **260** for the key intramolecular cyclization to tricyclic azetidine **259**.



259

260

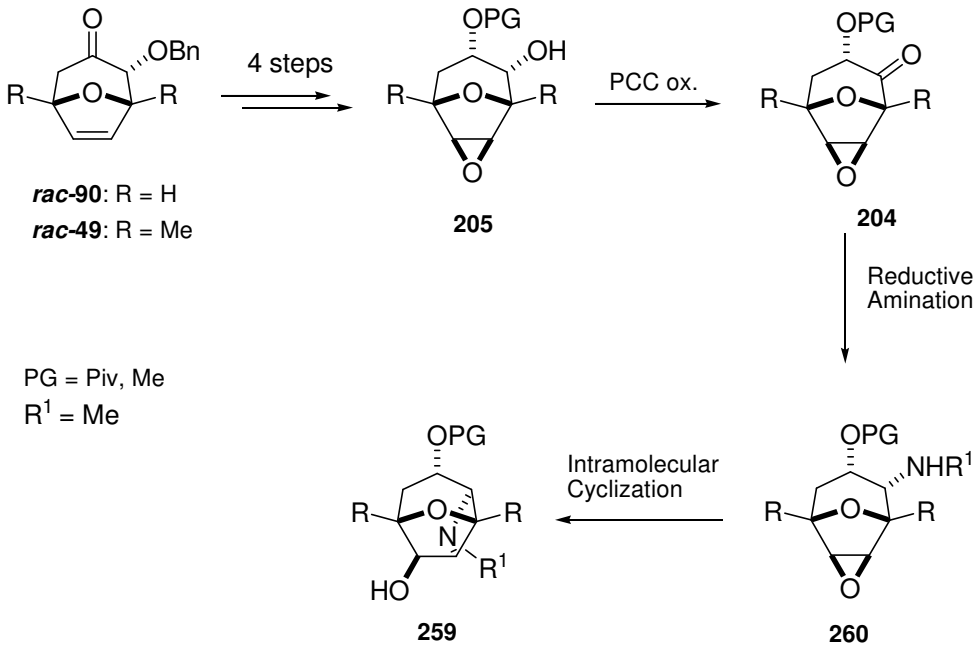
***rac*-90**: R = H

***rac*-49**: R = Me

Scheme 74: Synthetic strategy towards oxatricyclic azetidines.

6.1 Synthetic Strategy towards Tricyclic Azetidines by Reductive Amination

The synthesis of oxatricyclic azetidines containing the skeletal structure 7-oxa-2-aza-tricyclo[4.2.1.$0^{3.8}$]nonane was approached following the synthetic pathway outlined in Scheme 75. In this strategy, the method of choice for the introduction of an *endo*-amino group was the reductive amination[115] of a ketone function, one of the most useful routes to synthesize amines.



Scheme 75: Synthetic strategy for the synthesis of tricyclic azetidines starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

Starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**, epoxy alcohols **205** were obtained over four steps in good yield.[116] The α-configurated hydroxyl group of these oxatricyclic structures was protected with either pivaloate ester or methyl ether because both protecting groups showed already high stability towards Grignard reagents in the synthesis of C2-alkylated

[115] For reviews on reductive amination see: a) Emerson,W. S. *Org. Reactions*, Wiley; **1948**, *4*, 174; b) Lane, C. F. *Synthesis*, **1975**, 135; c) Hutchins, R.O.;Hutchins, M. K. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, *Vol. 8*, 25; d) Baxter, E.W.; Reitz, A. B. *Org. Reactions*,Wiley, **2002**, *59*, 1.

[116] The synthesis of pivaloate substituted epoxy alcohol **131** was already described in Section 4.1 and pivaloate **160** and methyl ether **56** were synthesized following reported methods by J. Wittenberg and S. Proemmel, as mentioned in Section 4.6.

dioxatricyclic oxetanes.[117] Synthesized versatile epoxy alcohols **205** were then oxidized with PCC to afford the epoxy ketones **204**.[118]

Epoxy ketones **204** were then converted to tricyclic azetidines in two steps: reductive amination and intramolecular cyclization. For the reductive amination of epoxy ketones two possibilities were investigated: the introduction of a primary *endo*-amine and the introduction of a secondary *endo-N*-alkylamine.

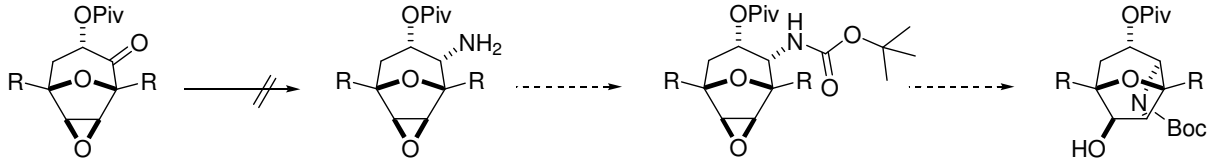
The synthesis of primary epoxy amines was not successful using common reductive amination methods, as it is reported in Section 6.2. The synthesis of secondary epoxy *endo-N*-alkylamines showed difficulties that took many attempts and a great deal of effort to overcome. The examined reductive amination procedures are thoroughly discussed in Section 6.3. Under the optimized reaction conditions reductive amination of epoxy ketones afforded desired secondary epoxy amines in good yield without affecting the epoxide ring. Once synthesized, secondary epoxy amines underwent an intramolecular cyclization leading to the desired oxatricyclic azetidines **259** (see Section 6.4).

6.2 Attempted Synthesis of Primary Epoxy Amines

Following the route towards tricyclic azetidines, the synthesis of primary epoxy amines was first studied using pivaloate substituted epoxy ketones **208** and **207** as starting material. Reductive amination of these epoxy ketones was attempted following common methods in order to afford primary amines **261** and **262**. Once synthesized, primary epoxy amines should be protected using Boc. Intramolecular cyclization of resulting N-Boc-protected epoxy amines **263** and **264** would lead to desired oxatricyclic azetidines **265** and **266** (see Scheme 76).

[117] See Section 4.6.2.

[118] As reported in Section 4.6.1, PCC oxidation proved to be the best choice.



208: R = H
207: R = Me

261: R = H
262: R = Me

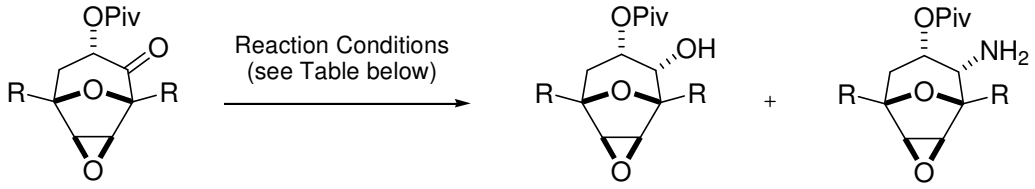
263: R = H
264: R = Me

265: R = H
266: R = Me

Scheme 76: Attempted synthesis of Boc-protected primary amines **263** and **264**, precursors of azetidines **265** and **266**.

As outlined in Table 19, the synthesis of primary amines by reductive alkylation of ammonia was unsuccessful using standard methods. The most popular reductive amination in recent years, the Borch reduction,[119] uses sodium cyanoborohydride as reductant and a large excess of ammonium acetate. Treatment of epoxy ketones **208** and **207** under these Borch conditions afforded exclusively epoxy alcohols **131** and **160**, resulting from the competing reduction of the carbonyl function (see entries 1 and 3, Table 19). Addition of 3Å molecular sieves to promote imine formation by absorbing water did not alter the results. Use of titanium (IV) isopropoxide prior to addition of $NaBH_3CN$ was also unsuccessful and only the epoxy alcohol was obtained (see entries 2 and 4, Table 19). Presumably, the formation of the iminium intermediate upon exposure of the epoxy ketone to ammonium acetate is so slow that the ketone function is reduced faster by $NaBH_3CN$ to the corresponding epoxy alcohol.

[119] a) Borch, R. F.; Bernstein, M. D.; Durst, H. P. *J. Am. Chem. Soc.* **1971**, *93*, 2897; b) Borch, R. F. *Org. Synth.* **1972**, *52*, 124; c) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.



208: R = H
207: R = Me

131: R = H
160: R = Me

261: R = H
262: R = Me

Entry	R	Conditions	Yield [%]
1	H	NH_4OAc, $NaBH_3CN$, MeOH, rt[a]	25% Epoxy alcohol
2	H	NH_4OAc, $NaBH_3CN$, $Ti(Oi\text{-}Pr)_4$, MeOH, rt,	29% Epoxy alcohol
3	Me	NH_4OAc, $NaBH_3CN$, MeOH, rt[a]	40% Epoxy alcohol
4	Me	NH_4OAc, $NaBH_3CN$, $Ti(Oi\text{-}Pr)_4$, MeOH, rt	50% Epoxy alcohol

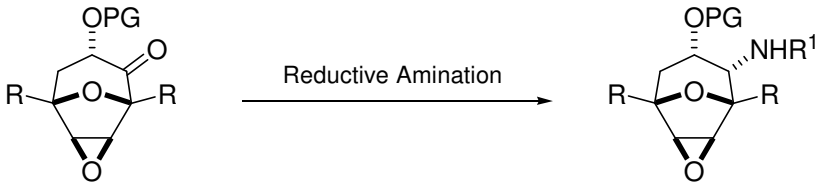
Table 19: Attempted reductive amination conditions for the synthesis of primary *endo*-amines **261** and **262**. a) Addition of 3 Å molecular sieves.

Attempted reductive amination reactions using ammonium acetate and $NaBH_3CN$ with different additives, e. g. 3 Å molecular sieves and titanium (IV) isopropoxide, were not successful. Nevertheless, the synthesis of primary epoxy amines remains open for further investigation. Recent literature examples report alternative methods for the conversion of ketones to primary amines. For instance, the synthesis of 3-*endo*-tropanamine by a modified palladium catalyzed reduction of tropanone in an aqueous/alcoholic medium with ammonium formate salt as nitrogen and hydrogen source.[120]

6.3 Synthesis of Secondary Epoxy Amines

In view of the disappointing results of the synthesis of primary epoxy amines, the introduction of a secondary *endo*-amino group in different epoxy ketones was next attempted.

[120] a) Allegretti, M.; Berdini, V.; Cesta, M. C.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257; b) Berdini, V.; Cesta, M. C.; Curti, R.; D'Anniballe, G.; Di Bello, N.; Nano, G.; Nicolini, L.; Topai, A.; Allegretti, M. *Tetrahedron* **2002**, *58*, 5669.



204 **260**

R = H, Me

PG = Piv, Me

R^1 = Me, Et

Scheme 77: Reductive amination of epoxy ketones by reductive amination affording epoxy *N*-methylamines, precursors of tricyclic azetidines.

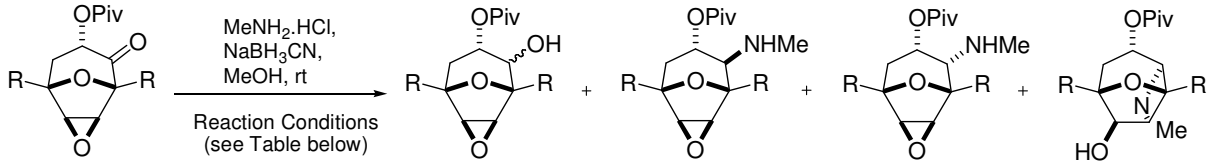
Reductive amination is dependent not only on the reactivity of the carbonyl function but also on the basicity of the amine. A ketone generally reacts with a more basic amine in the absence of factors such as steric hindrance. Thus sterically hindered epoxy ketones will preferentially react with a more basic and small amine than with a less basic or more sterically hindered one. Therefore, the amine of choice for the first attempted synthesis of secondary amines was methylamine.

The synthesis of secondary epoxy ***N***-methylamines was first attempted by reductive amination of pivaloate substituted epoxy ketones **208** and **207** using several procedures. Once optimized, the reductive amination conditions were also applied for the conversion methoxy substituted epoxy ketone **214**.

6.3.1 Synthesis of C3-Pivaloate Substituted Epoxy *N*-Methylamines

6.3.1.1 Synthesis of C3-Pivaloate Substituted Epoxy N-Methylamines using $NaBH_3CN$

The first reductive amination method for the one-pot conversion of epoxy ketones **207** and **208** to primary amines was the Borch reduction.[119] This protocol involves sodium cyanoborohydride as the reductant and a fivefold excess amount of methylamine to prevent the product amine from undergoing further reaction with the carbonyl compound. Besides, methylamine HCl salt is used as the starting material in order to achieve the optimal pH for reduction of the intermediate iminium species (pH 5-7).



208: R = H
207: R = Me

131: R = H
160: R = Me

263: R = H
264: R = Me

265: R = H
266: R = Me

267: R = H
268: R = Me

Entry	R	Conditions	Total Yield[f] of **263+265+267 (264+266+268)** [%]	Ratio of **263:265:267 (264:266:268)**	Yield of Alcohol **131/160** [%]
1	H	Direct reaction, 3 d[a, c]	30	0:3:1:	28
2	H	Stepwise reac., 3 Å MS, 3 d[b, c]	48	2:5:4	0
3	H	$TiCl_4$[d]	complex mixture of products		
4	H	Ti(O*i*-Pr)$_4$[e]	complex mixture of products		
5	Me	Direct reaction, 3 d[a, c]	18	0:3:2	53
6	Me	Stepwise reac., 3 Å MS, 3 d[b, c]	22	0:2:1	7
7	Me	$TiCl_4$[d]	complex mixture of products		
8	Me	Ti(O*i*-Pr)$_4$[e]	complex mixture of products		

Table 20: Reductive amination conditions using $NaBH_3CN$. a) Direct reaction: reductant was added at the same time as the epoxy ketone and amine; b) stepwise reaction: reductant was added after 16 h; c) addition of 3Å molecular sieves; d) amine and ketone are stirred in $TiCl_4$/MeOH for 16 h followed by addition of $NaBH_3CN$; e) amine and ketone are stirred in Ti(O*i*-Pr)$_4$/EtOH for 16 h followed by addition of $NaBH_3CN$; f) products were separated by column chromatography.

As indicated by entries 1 and 5 in Table 20, direct reductive amination of epoxy ketones **208** and **207** using $NaBH_3CN$ and 3Å molecular sieves afforded a mixture of *endo*-*N*-methylamine, azetidine and undesirable epoxy alcohol. The compounds could be separated by column chromatography. Better yields and lower competing reduction of the ketone function were obtained when the reaction was carried out stepwise[121,122] (see entries 2 and 6 in Table 20). In this case, the epoxy ketones were stirred with an excess amount of methylamine in the presence of the dehydrating agent (3Å molecular sieves) to allow the preformation of the intermediate imine prior to addition of the reductant. Under these conditions, less hindered epoxy ketone **208** was partially converted to *exo*-amine **263** in contrast to the more sterically

[121] Mićović, I. V.; Roglic, G. M.; Dosen-Mićović, L.; Kirićojević, V. D.; Popović, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2041.

[122] The reductive amination is termed as direct when a mixture of the carbonyl compound and the amine is treated with proper reducing agent in a single operation. A stepwise or indirect reaction involves the preformation of the intermediate imine followed by reduction in a separate step.

hindered epoxy ketone **207**, in which the introduction of the amino group at the axial position did not occur.

Competing reduction of the ketone function to alcohol is more significant for sterically hindered epoxy ketone **207**. Moreover, reductive amination of epoxy ketone **207** proceeded in lower yields and higher stereoselectivity than less sterically hindered epoxy ketone **208**. These facts show the remarkable steric effect of the methyl groups at the bridgehead carbon atoms. Presumably, the formation of the imine intermediate upon exposure of epoxy ketone **207** to the amine is slower owing to this steric effect, thus lowering the yield of the reductive amination but increasing its stereoselectivity.

In order to improve yields and ratio of the reductive amination of epoxy ketones **207** and **208**, the use of titanium (IV) additives was next investigated. These Lewis acids facilitate the imine formation in reductive amination reactions with sodium cyanoborohydride because they form a complex with the carbonyl oxygen, thereby increasing the electrophilicity of the carbonyl carbon. Moreover Lewis acids can act as water scavengers and may also coordinate with the intermediate imine increasing its electrophilicity.[123] Their use has been reported for particularly sluggish reactions, such as those involving weakly electrophilic carbonyl groups, poorly nucleophilic amines or sterically congested reactive centers.

Reductive amination of epoxy ketones **208** and **207** was then carried out by treatment of the ketone with stoichiometric amounts of methylamine and titanium (IV) chloride[124] during 16 h followed by addition of $NaBH_3CN$. A complex mixture of products was obtained (see entries 3 and 7 in Table 20). The high reactivity of $TiCl_4$ as well as the use of an equimolar ratio of ketone and amine would explain the obtained results. Use of titanium (IV) isopropoxide[125] with stoichiometric amounts of methylamine and epoxy ketone followed by treatment with $NaBH_3CN$ led also to a complicated mixture of products (see entries 4 and 8 in Table 20). Although titanium (IV) isopropoxide is less reactive than titanium (IV) chloride and more compatible with acid-sensitive functional groups,[125,126] side reactions as the bisalkylation of primary amines are promoted when ketone and amine are added in equimolar ratio.

[123] For mechanistic aspects of reductive amination reactions in the presence of $Ti(OiPr)_4$, see Section 6.6.

[124] Barney, C. L.; Huber, E. W.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5547.

[125] Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.

[126] Seebach, D.; Hungerbuhler, E.; Naef, R.; Scnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138.

In some of the attempted reductive amination reactions, azetidines **267** and **268** were already isolated (see entries 1, 2, 5 and 6 in Table 20). Presumably the intramolecular cyclization of the *endo*-amino group takes place catalyzed by the reaction conditions and the long reaction times.

Summarizing the results in Table 20, the introduction of an *endo*-amino group at epoxy ketones **207** and **208** was accomplished using one of the most common hydride reagents for this conversion: $NaBH_3CN$. Nevertheless, the low yields as well as the formation of by-products stressed the importance of a further optimization of this conversion.

6.3.1.2 Synthesis of C3-Pivaloate Substituted Epoxy N-Methylamines using $NaBH(OAc)_3$

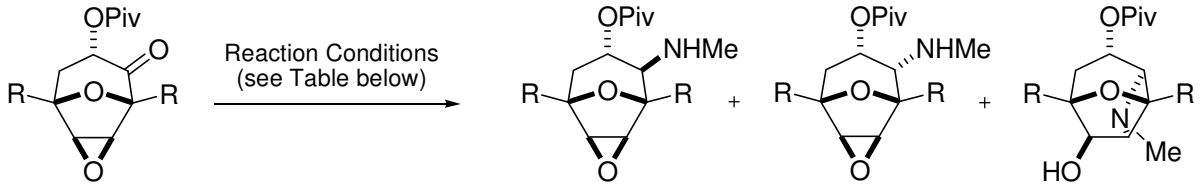
Another commonly used reductant is sodium triacetoxyborohydride,[127] a mild and selective hydride reagent[128] with a high degree of tolerance for a variety of functional groups. $NaBH(OAc)_3$ has also the advantage of reducing aldehydes but not ketones if the reaction is conducted in an aprotic solvent such as DCM, 1,2-dichlorethane (DCE), THF or acetonitrile.[129]

Attempted reductive amination using $NaBH(OAc)_3$ involved 1,2-dichlorethane as solvent and a fivefold excess of methylamine as an acid salt to promote reductive amination. Under these reaction conditions conversion of epoxy ketone **208** afforded epoxy *N*-methylamines **263** and **265** in 34% yield in a 3:4 ratio (see entry 1 in Table 21). In the case of epoxy ketone **207**, a 2:5 mixture of *endo*-amine **266** and azetidine **268** was obtained in 21% yield (see entry 2 in Table 21).

[127] a) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595; b) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537.; c) Abdel-Magid, A. F.; Maryanoff, C. A. In *ACS Symp. Ser.*; Abdel-Magid, A. F., Ed. American Chemical Society: Washington, DC, **1996**; Vol. 641, pp. 201-216; d) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

[128] The mildness of the reagent has been attributed to both steric and the electron withdrawing effects of the acetoxy groups which stabilize the boron-hydrogen bond. Gribble, G. W. *Eastman Organic Chemical Bulletin* **1979**, *51*, 1.

[129] Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535.



208: R = H
207: R = Me

263: R = H
264: R = Me

265: R = H
266: R = Me

267: R = H
268: R = Me

Entry	R	Conditions	Azaprod. Yield [%][a]	Ratio of **263:265:267 (264:266:268)**
1	H	5 eq $MeNH_2$.HCl, $NaBH(OAc)_3$, DCE, rt, 7 d	34	3:4:0
2	Me	5 eq $MeNH_2$.HCl, $NaBH(OAc)_3$, DCE, rt, 7 d	21	0:2:5

Table 21: Reductive amination conditions using $NaBH(OAc)_3$. a) Products were separated by column chromatography.

The low solubility of the methylamine hydrochloride in the reaction solvent (DCE) explains the low yields and the long reaction times for the reported reductive amination using $NaBH(OAc)_3$.

6.3.1.3 Synthesis of C3-Pivaloate Substituted Epoxy N-Methylamines using $NaBH_4$

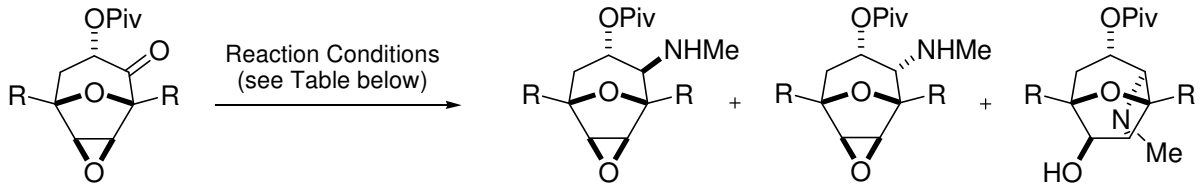
Other commonly used reductive amination methods include the use of sodium borohydride in combination with different additives. Amongst these procedures, stepwise reductive amination using $NaBH_4$ and titanium (IV) isopropoxide has been developed as an efficient and mild alternative to the other current methods.[130,127d]. However, since sodium borohydride also reduces aldehydes and ketones, it is important to ensure that imine formation is completed prior to addition of the reducing agent.

Following this efficient protocol, epoxy ketones **208** and **207** were treated with titanium (IV) isopropoxide prior to addition of $NaBH_4$. The solvent of choice was methanol, in which imine formation is faster relative to THF or 1,2-dichloroethane, as demonstrated by Abdel-Magid *et al.*[127d] Besides, a mixture of methylamine hydrochloride and triethylamine was employed as

[130] a) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079; b) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928; c) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928.

the convenient source of nucleophilic methylamine; this requires no special handling techniques and obviates the use of excess gaseous amine.[130b]

Reductive amination of epoxy ketone **208** afforded a mixture of *endo*-amine **265**, *exo*-amine **263** and azetidine **267** in 44% yield (see entry 1, Table 22). In the case of epoxy ketone **207** equatorial amine **266** was exclusively isolated in 70% yield when the reaction was quenched two hours after addition of the reductant, as indicated by entry 2 in Table 22. In contrast, when the reaction mixture was stirred for a longer time, though reduction was completed, a mixture of *endo*-amine **266** and azetidine **268** was obtained in a 1:12 ratio in 78% yield (see entry 3 in Table 22). This fact confirms the suggestion that intramolecular cyclization of the *endo*-epoxy amine to azetidine already occurs catalyzed by the reaction conditions.



208: R = H
207: R = Me

263: R = H
264: R = Me

265: R = H
266: R = Me

267: R = H
268: R = Me

Entry	R	Conditions	Total Yield [%][c]	Ratio of **263:265:267** **(264:266:268)**
1	H	$MeNH_2$.HCl, $NaBH_4$, Ti(O*i*-Pr)$_4$, MeOH, rt, 18 h[a]	44	2:3:2
2	Me	$MeNH_2$.HCl, $NaBH_4$, Ti(O*i*-Pr)$_4$, MeOH, rt, 18 h[a]	70	100% **266**[b]
3	Me	$MeNH_2$.HCl, $NaBH_4$, Ti(O*i*-Pr)$_4$, MeOH, rt, 2 d[a]	78	0:1:12[b]

Table 22: Reductive amination conditions using $NaBH_4$. a) Amine and ketone were stirred in Ti(O*i*Pr)$_4$/MeOH for 16 h followed by addition of reductant; b) epoxy *exo*-amine **264** was isolated in traces and therefore it has not been included in the total yield; c) products were separated by column chromatography.

In order to study the influence of the reaction time, several experiments were carried out. On the one hand, changing the work-up procedure did not alter the results, which indicates that the formation of the azetidine ring takes place before the reaction is quenched. On the other hand, increasing considerably the amount of titanium (IV) isopropoxide led to lower yields and complementary addition of 3Å molecular sieves did not improve results either. Most significant was the influence of the reaction times, as indicated by entries 2 and 3 in Table 22.

The reductive amination of epoxy ketone **207** using sodium borohydride and titanium (IV) isopropoxide proceeded in good yield. In contrast, moderate yields were obtained for the conversion of epoxy ketone **208**, presumably because of its lower stability towards $NaBH_4$.

6.3.1.4 Synthesis of C3-Pivaloate Substituted Epoxy N-Methylamines using BH_3·py

The next alternative for the synthesis of epoxy *endo-N*-methylamines **265** and **266** was the use of borane-pyridine complex,[131] developed for reductive aminations because it typically reduces imines and iminium salts preferentially relative to carbonyl groups.[132, 133] As reactions with borane-pyridine complex run significantly faster in methanol than in other solvents,[131] attempted reductive aminations were carried out in this solvent.

In a first *in situ* reaction, equimolar amounts of epoxy ketone **208** and methylamine were treated with borane-pyridine complex in the presence of 4Å molecular sieves affording a mixture of *endo*-amine **265**, *exo*-amine **263** and azetidine **267** in 20% yield (see entry 1, Table 23). Increasing the amount of methylamine to two equivalents led to slightly higher yields (see entry 2, Table 23). Better yields were obtained with a fivefold excess of methylamine and allowing the preformation of the imine intermediate prior to addition of the reducing agent (see entry 3, Table 23).

Direct reductive amination of epoxy ketone **207** with borane-pyridine complex and 4 Å molecular sieves afforded azetidine **268** in 12% yield (see entry 5 in Table 23). Comparing entries 3 and 5 in Table 23, reductive amination of epoxy ketone **208** proceeded in higher yield under the same conditions than the conversion of epoxy ketone **207** owing to the steric effect of the methyl groups.

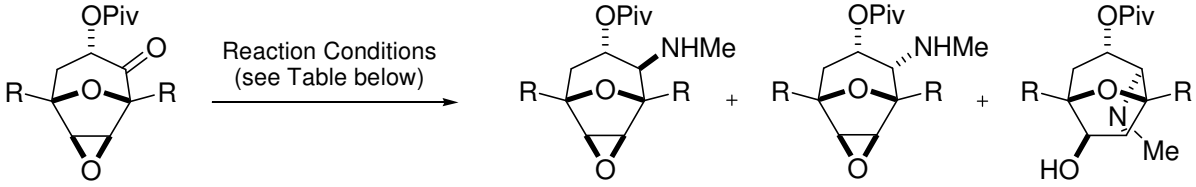
A new protocol was developed combining titanium (IV) isopropoxide, as an efficient catalyst for the imination of epoxy ketones **207** and **208**, with borane-pyridine complex as a mild selective reductant. Following reductive amination of epoxy ketone **208** yielded a mixture of *exo*-amine **263**, *endo*-amine **265** and azetidine **267** (see entry 4 in Table 23). In this case, the reaction mixture was stirred for a longer time, although reduction was already completed some hours after addition of the reductant. In contrast, epoxy ketone **207** was converted

[131] Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.

[132] Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, *37*, 1309.

[133] Hutchins, R. O.; Learn, K.; Mazer, B.; Pytlewski, D.; Pelter, A. *Org. Prep. Proced. Int.* **1984**, *16*, 335.

exclusively into equatorial amine **266** in 69% yield when the reaction was quenched 4 hours after addition of the reductant (see entry 6 in Table 23).



208: R = H
207: R = Me

263: R = H
264: R = Me

265: R = H
266: R = Me

267: R = H
268: R = Me

Entry	R	Conditions	Total Yield [%][c]	Ratio of **263:265:267** **(264:266:268)**
1	H	1 eq $MeNH_2$.HCl, BH_3·py, MeOH, rt, 2 d[a, c]	20	1:9:1
2	H	2 eq $MeNH_2$.HCl, BH_3·py, MeOH, rt, 2 d[a, c]	33	1:5:1
3	H	5 eq $MeNH_2$.HCl, BH_3·py, MeOH, rt, 2 d[b, c]	73	1:1:1
4	H	5 eq $MeNH_2$.HCl, BH_3·py, Ti(O*i*Pr)$_4$, MeOH, rt, 2 d[d]	74	2:1:3
5	Me	2 eq $MeNH_2$.HCl, BH_3·py, MeOH, rt, 3 d[a, c]	12	100% **268**
6	Me	5 eq $MeNH_2$.HCl, BH_3·py, Ti(O*i*Pr)$_4$, MeOH, rt, 20 h[d]	69	100% **266**

Table 23: Reductive amination conditions using BH_3·py. a) Direct reaction; b) stepwise reaction: reductant was added after 16 h; c) addition of 4Å molecular sieves; d) amine and ketone were stirred in Ti(O*i*Pr)$_4$/MeOH for 16 h followed by addition of reductant; e) products were separated by column chromatography.

As indicated by entries 4 and 6 in Table 23, the reductive amination procedure combining borane-pyridine complex and titanium (IV) isopropoxide proceeded in good yields. This protocol proved to be the best choice to synthesize desired epoxy *endo-N*-methylamines compared to the preceding attempted procedures.

6.3.1.5 Summary of the Synthesis of C3-Pivaloate Substituted Epoxy N-Methylamines

Following the route towards tricyclic azetidines, the synthesis of secondary epoxy *N*-methylamines was first attempted by reductive amination of pivaloate substituted epoxy ketones with methylamine. For this purpose, several procedures were carried out in search of an optimized protocol which promoted the formation of the imine intermediate, in order to diminish competing reactions.

The first attempted method was the Borch reduction of epoxy ketones **207** and **208** with a fivefold excess amount of methylamine as an acid salt. Under this reaction conditions the synthesis of epoxy *N*-methylamines was accomplished in low yields and with the obtention of the epoxy alcohols resulting from the competing reduction of the ketone function.

Another attempted procedure was the direct reductive amination of epoxy ketones **207** and **208** using $NaBH(OAc)_3$ in DCE. In this case, the low solubility of the methylamine hydrochloride in the reaction solvent led to the desired *N*-methylamines in low yields and after long reaction times.

Reductive amination of the epoxy ketones was also carried out using sodium borohydride and titanium (IV) isopropoxide. The conversion of sterically hindered epoxy ketone **207** led stereoselectively to the epoxy *endo*-amine in 70% yield or to a 1:12 mixture of epoxy *endo*-amine **266** and azetidine **268** in 78% yield depending on the reaction time. In contrast, moderate yields were obtained for the conversion of epoxy ketone **208**, presumably because of its lower stability towards $NaBH_4$.

Direct reductive amination of the epoxy ketones using milder borane-pyridine complex and 4Å molecular sieves proceeded in low yields. Better results were obtained when the reaction was carried out stepwise and with a fivefold excess of methylamine. Under these conditions, conversion of less sterically hindered epoxy ketone **208** afforded a 1:1:1 mixture of *endo*-amine **265**, *exo*-amine **263** and azetidine **267** in 73% yield.

An efficient protocol was developed combining titanium (IV) isopropoxide as catalyst and borane-pyridine complex as a mild selective reductant. Following this procedure, epoxy ketone **207** was converted exclusively into equatorial amine **266** in 69% yield. In the case of epoxy ketone **208**, a mixture of *exo*-amine **263**, *endo*-amine **265** and azetidine **267** was obtained in 74% yield in a 2:1:3. Comparing all the attempted procedures, combination of borane-pyridine complex and titanium (IV) isopropoxide proved to be the best choice for the synthesis of pivaloate substituted epoxy *endo-N*-methylamines.

Pivaloate ester showed stability not only towards all the attempted reductive amination conditions but also to the work-up procedures and methylamines were accessible without cleavage of the protecting group. The steric hindrance of the pivaloate ester, whose methyl groups shield the carbonyl group from nucleophilic attack, explains this great stability.

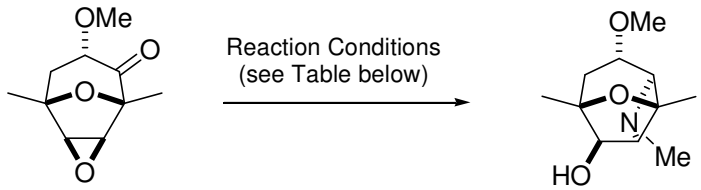
The steric effect of the methyl groups at the bridgehead carbon atoms has an influence on the formation of the imine intermediate and on the stereoselectivity of the reductive amination. This steric effect impedes the formation of the intermediate imine, thus lowering the yield of the reaction in the absence of an efficient catalyst. The competing reduction to alcohol proceeds faster and undesired epoxy alcohols are obtained in higher ratio than in the reductive amination of less sterically hindered epoxy ketone **208**. The different steric hindrance of both epoxy ketones **207** and **208** also have an influence on the stereoselectivity of the reductive amination. In the case of epoxy ketone **207**, reductive amination led selectively to epoxy 2α-configurated amine **266**, resulting from an axial attack of hydride reagent on the intermediate imine. In contrast, epoxy ketone **208** underwent reductive amination affording both epoxy *exo-N*-methylamine and epoxy *endo-N*-methylamine with moderated selectivity.

Under the reductive amination conditions, tricyclic azetidines **267** and **268** were already isolated. Tricyclic azetidine **268** was afforded almost exclusively when the reaction mixture was stirred for a longer time, though reduction of the imine intermediate was completed. Presumably, the intramolecular cyclization of the *endo*-amino group takes place catalyzed by the reaction conditions and the long reaction times.

6.3.2 Synthesis of C3-Methoxy Substituted Epoxy *N*-Methylamines

After the synthesis of pivaloate substituted epoxy *endo-N*-methylamines, reductive amination of methoxy substituted epoxy ketone **214** was attempted. For this purpose, three of the most efficient procedures for the reductive amination of epoxy ketone **214** were carried out as summarized in Table 24.

Stepwise reductive amination of epoxy ketone **214** using sodium borohydride and titanium (IV) isopropoxide afforded azetidine **270** in 27 % yield (see entry 1 in Table 24). Better yields were obtained by treatment of the epoxy ketone and a fivefold excess of methylamine with borane-pyridine complex and 4Å molecular sieves (see entry 2 in Table 24). As for the synthesis of pivaloate substituted aza-products, the most efficient method proved to be the combination of borane-pyridine complex and titanium (IV) isopropoxide affording tricyclic azetidine **270** in 51% yield (see entry 3 in Table 24).



214 **270**

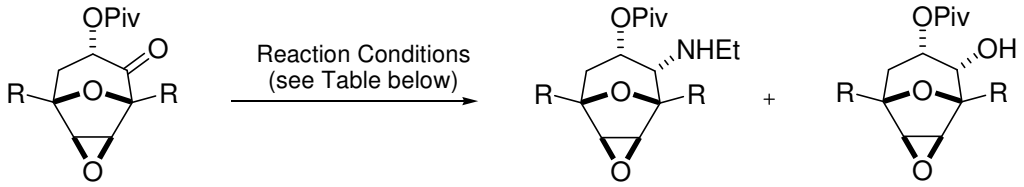
Entry	Conditions	Yield [%]
1	2 eq $MeNH_2$.HCl, $NaBH_4$, Ti(O*i*-Pr)$_4$, MeOH, rt, 20 h[c]	27
2	5 eq $MeNH_2$.HCl, BH_3·py, MeOH, rt, 1 d[a, b]	46
3	2 eq $MeNH_2$.HCl, BH_3·py, Ti(O*i*-Pr)$_4$, MeOH, rt, 20 h[c]	51

Table 24: Reductive amination conditions using $NaBH_4$ and BH_3·py. a) Stepwise reaction; b) addition of 4Å molecular sieves; c) amine and ketone were stirred in Ti(O*i*-Pr)$_4$/MeOH for 16 h followed by addition of reductant.

As can be seen in Table 24, all attempted reductive amination reactions afforded exclusively tricyclic azetidine **270** and the corresponding epoxy amine could not be isolated even if the reaction was quenched directly after addition of the hydride reagent. This fact shows that the intramolecular cyclization of the methoxy substituted epoxy α-configurated amine is highly favoured and proceeds catalyzed by the reaction conditions. Consequently, the synthesis of methoxy substituted azetidine **270** proceeded through a stereoselective one-pot reductive amination/cyclization tandem reaction starting from epoxy ketone **214** in 51% yield.

6.3.3 Synthesis of Pivaloate Substituted Epoxy *N*-Ethylamines

Since the synthesis of epoxy *endo*-*N*-methylamines was accomplished successfully, the introduction of a different secondary amino group in the oxatricyclic structure was next attempted. Considering the steric hindrance and electrophilicity of the epoxy ketones, the amine of choice was ethylamine, which is slightly more sterically hindered than methylamine.



208: R = H
207: R = Me

271: R = H
272: R = Me

131: R = H
160: R = Me

Entry	R	Conditions	Amine Yield [%][e]	Alcohol Yield [%][e]
1	H	$EtNH_2$.HCl, $NaBH_3CN$, MeOH, rt, 4 d[a, b]	21	40
2	H	$EtNH_2$.HCl, BH_3·py, MeOH, rt, 2 d[a, c]	24	0
3	Me	$EtNH_2$.HCl, $NaBH_3CN$, MeOH, rt, 4 d[a, b]	0	50
4	Me	$EtNH_2$.HCl, $NaBH_4$, Ti(O*i*-Pr)$_4$, MeOH, rt, 2 d[d]	12	0

Table 25: Reductive amination conditions. a) Direct reaction; b) addition of 3Å molecular sieves; c) addition of 4Å molecular sieves; d) amine and ketone were stirred in Ti(O*i*-Pr)$_4$/MeOH for 16 h followed by addition of $NaBH_4$; e) products were separated by column chromatography.

The first attempted method was the Borch reduction using $NaBH_3CN$, a fivefold excess amount of ethylamine as an acid salt and 3Å molecular sieves. Under these conditions epoxy ketone **208** was converted into desired ethylamine **271** in low yield (21%) together with undesired epoxy alcohol **131** (see entry 1 in Table 25). In the case of more sterically hindered epoxy ketone **207**, epoxy alcohol **160** was exclusively obtained without traces of the aminated tricycle **272** (see entry 3 in Table 25).

In order to improve yields and lower competing reactions, the use of pyridine-borane complex and 4 Å molecular sieves was attempted. Following this direct protocol, epoxy ketone **208** was converted selectively into epoxy ethylamine **271** in 24% yield and no by-products were isolated (see entry 2 in Table 25).

In the case of more sterically hindered epoxy ketone **207**, titanium (IV) isopropoxide was used to promote the imine formation prior to addition of the hydride reagent. This reductive amination procedure afforded desired ethylamine **272** in 12% yield and without by-products (see entry 4 in Table 25).

The formation of the imine intermediate upon exposure of sterically hindered epoxy ketones to the amine is a reversible and slow reaction. The steric hindrance and electrophilicity of the

carbonyl group as well as the chain length and basicity of the amine influence the imine formation. The lower yields of the reductive amination of epoxy ketones **207** and **208** with ethylamine compared to methylamine exemplify the influence of the basicity and chain length of the amine.

Since the synthesis of epoxy *endo*-*N*-ethylamines was not extensively studied in the framework of the present work, optimization of this conversion remains open. For instance, better yields could be obtained combining pyridine-borane complex and titanium (IV) isopropoxide with a larger excess of ethylamine.

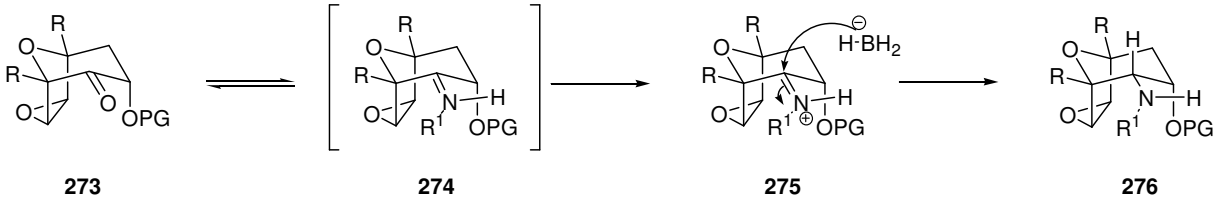
6.3.4 Mechanistic Aspects of the Synthesis of Epoxy *N*-Alkylamines

The mechanism of reductive aminations depends on the reducing agent and additives employed. A reasonable mechanism for the reductive amination of epoxy ketone **273** would involve condensation of the carbonyl group and amine to give a carbinol amine, followed by dehydration to form an imine **274** (see Scheme 78). Under weakly acidic or neutral reaction conditions the imine would be protonated to form an iminium ion.[134] Subsequent reduction of the imine intermediate or of the iminium ion would led to epoxy *N*-alkylamine **276**.[119] However, some reports provide evidence suggesting a direct reduction of the intermediate carbinol amine in some reactions to provide the target amine directly.[135]

The attack of the hydride may occur on both diastereotopic faces of the epoxy ketones with different selectivity owing to steric effects. As reported in the preceding chapters, reductive amination of epoxy ketone **208** led to both epoxy *exo*-amine and epoxy *endo*-amine with moderated selectivity. In the case of sterically hindered epoxy ketones **207** and **214**, reductive amination proceeded with higher selectivity affording almost exclusively epoxy α-configurated amine, resulting from an axial attack of hydride reagent on the intermediate imine.

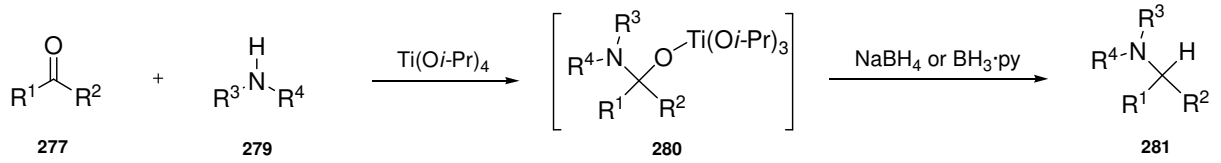
[134] The formation of imines or iminium ions has been reported as possible intermediates in reductive amination reactions in catalytic hydrogenation methods, see: a) Emerson, W. S. *Org. React.* **1984**, *4*, 174 and references therein. It has also been proposed in hydride methods, see: b) Schellenberg, K. A. *J. Org. Chem.* **1963**, *28*, 3259.

[135] Tadanier, J.; Hallas, R.; Martin, J. R.; Stanastek, R. S. *Tetrahedron* **1981**, *37*, 1309.



Scheme 78: Proposed mechanism for the reductive amination of epoxy ketone **273** leading to epoxy *N*-alkylamine **276**.

In the presence of the titanium (IV) isopropoxide, reductive amination of epoxy ketones is possibly proceeding through coordination of the Lewis acid with the carbonyl compound and the amine. In one possible mechanism, the formation of an intermediate aminocarbinolatotitanium (IV) complex **280** has been proposed,[125,136] which is then reduced either directly or via transient iminium species[137] to afford alkylated amine **276** (see Scheme 79).



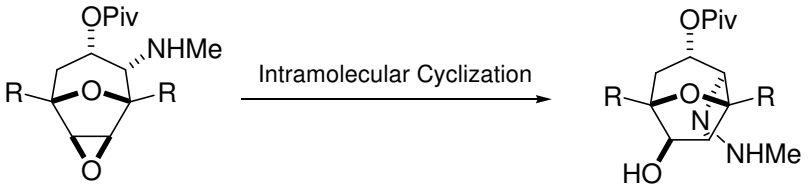
Scheme 79: Possible mechanism of reductive aminations in the presence of titanium (IV) isopropoxide through formation of an intermediate aminocarbinolatotitanium (IV) complex **280**.

6.4 Intramolecular Cyclization of Epoxy *N*-Methylamines to Tricyclic Azetidines

The last step of the synthetic strategy towards tricyclic azetidines was the intramolecular cyclization of the intermediate epoxy *endo*-amines **265** and **266** to afford desired azetidines **267** and **268**. Since reductive amination of methoxy substituted epoxy ketones afforded directly the tricyclic azetidine, intramolecular cyclization towards tricyclic azetidine was only studied for isolated pivaloate substituted epoxy *endo*-amines **265** and **266** (see Scheme 80).

[136] a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis;* Springer-Verlag: Berlin, 1986; 107; b) Takahashi, H.; Tasubuki, T.; Higashiyama, K. *Synthesis* **1988**, 238; c) Imwinkelried, R.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1496.

[137] Hine, J.; Yeh, C. Y. *J. Am. Chem. Soc.* **1967**, *89*, 2669.

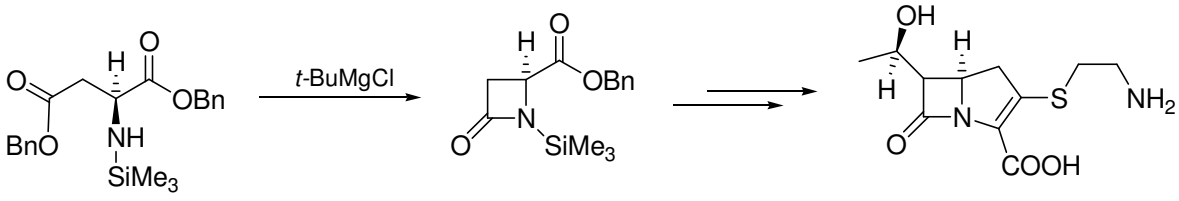


265: R = H
266: R = Me

267: R = H
268: R = Me

Scheme 80: Intramolecular cyclization of epoxy *endo-N*-methylamines **265** and **266** to afford tricyclic azetidines **267** and **268**.

The dual character of Grignard reagents, which can act as a strong base and a Lewis acid, has been used to promote intramolecular cyclization reactions. In the synthesis of Thienamycin **284** by Merck,[138] a Grignard-mediated cyclization of *N*-methylsilyl-dibenzylaspartate **282** using *tert*-butylmagnesium chloride afforded ß-lactam intermediate **283** (see Scheme 81).



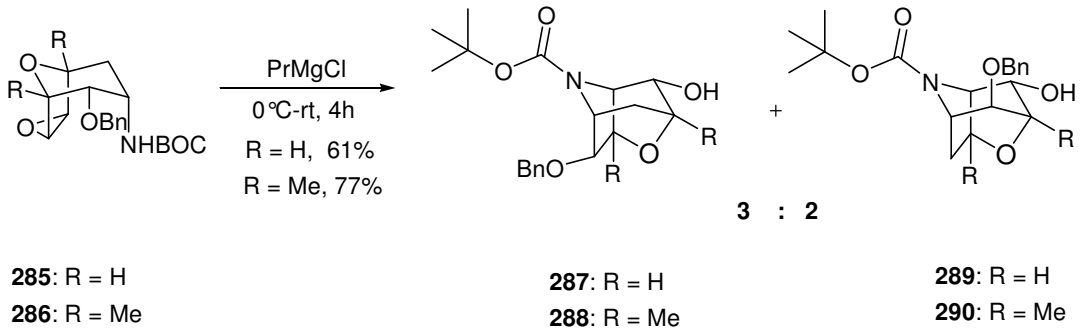
282 **283** **284**

Scheme 81: Grignard-mediated cyclization to ß-lactam **283** in the synthesis of Thienamycin by Merck.

A recent example of Grignard reagent-mediated intramolecular cyclization is the synthesis of oxazatricycles **287**, **288**, **289** and **290** containing the tropanone skeletal structure (see Scheme 82).[139]

[138] Salzman, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A.; *J. Am. Chem. Soc*. **1980**, *102*, 6161.

[139] a) Proemmel, S. *PhD Thesis*, Universität Hannover, **2001**; b) Vidal Pascual, M. *PhD Thesis*, Universität Hannover, **2003**.



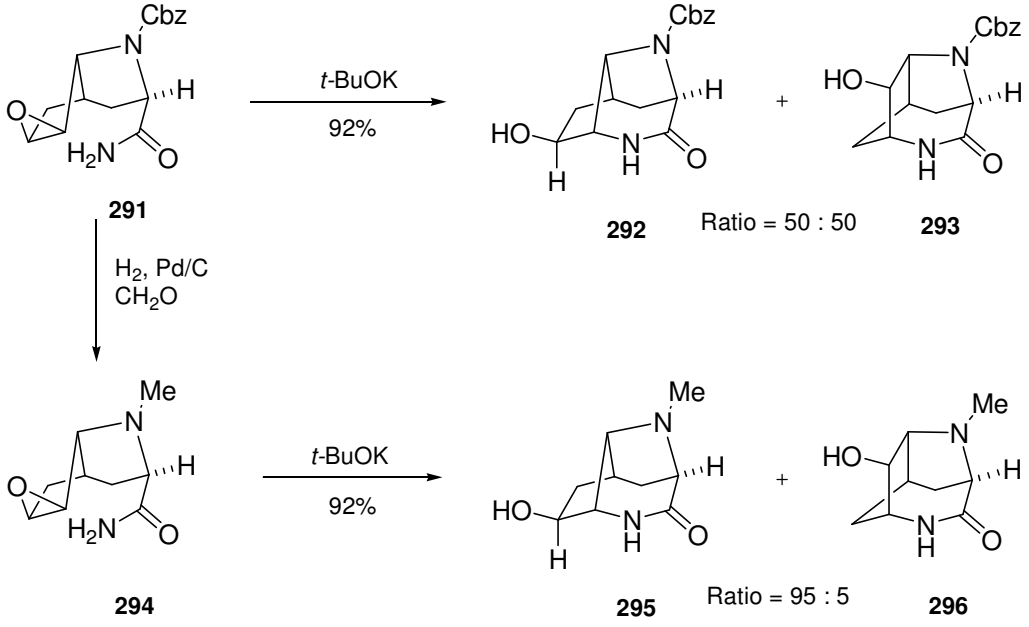
285: R = H
286: R = Me

287: R = H
288: R = Me

289: R = H
290: R = Me

Scheme 82: Grignard-mediated cyclization in the synthesis of scopoline by M. Vidal Pascual.

Base-catalyzed intramolecular cyclization reactions have also been reported in the synthesis of ß-lactams. In the total synthesis of the quinone antibiotic (±)-Naphthyridinomycin,[140] key tricyclic intermediates **292** and **296** were prepared by base-catalyzed intramolecular (see Scheme 83). Treatment of epoxy amide **291** with potassium *tert*-butoxide led to a mixture of desired lactam **292** and isomeric lactam **293** in a 1:1 ratio in 92% yield. Better regioselectivity was obtained when *N*-methyl epoxide **294** was subjected to the same cyclization conditions affording desired lactam **295** in 82% yield. In this cyclization, less than 5% undesired tricyclic lactam **296** was detected. The greater electron withdrawing capability of the Cbz-*N* function apparently disfavours epoxide cleavage at the desired, nearest carbon.[140]

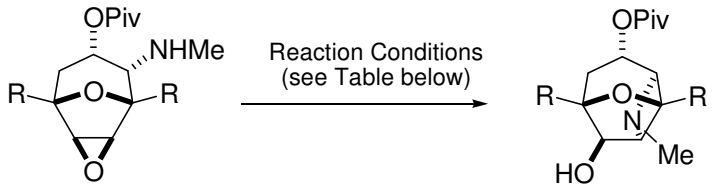


Scheme 83: Synthesis of ß-lactams **292** and **296**, key intermediates in the total synthesis of (±)-Naphthyridinomycin.

[140] Evans, D. A.; Biller, S. A. *Tetrahedron Lett.* **1985**, *26*, 1907.

6.4.1 Intramolecular Cyclization of C3-Substituted Epoxy *N*-Methylamines

In order to accomplish the synthesis of tricyclic azetidines, different conditions for the intramolecular cyclization of epoxy α-configurated amines **265** and **266** were tried out, as indicated in Table 26.



265: R = H
266: R = Me

267: R = H
268: R = Me

Entry	R	Conditions	Total Yield [%]
1	H	*t*-BuOK, THF, rt, 2 d[a, c]	n.r.
2	H	VinylMgBr, THF, 0°C → rt, 4 h	71
3	Me	$BF_3 \cdot OEt_2$, DCM, 0°C → rt	n.r.
4	Me	*t*-BuOK, THF, rt, 2 d[a, c]	n.r.
5	Me	VinylMgBr, THF,0°C → rt, 4 h	83
6	Me	PhMgBr, THF, 0°C → rt, 4 h	82
7	Me	EthynylMgBr, THF, 0°C → rt, 2 d	34[a]
8	Me	EthynylMgCl, THF, 0°C → rt	n.r.

Table 26: Attempted reaction conditions for intramolecular cyclization of 2-*endo*-amino epoxides. a) 20% Amine was additionally recovered unreacted.

As indicated by entries 1 and 4 in Table 26, attempted base-catalyzed cyclization of epoxy *endo*-*N*-methylamines **265** and **266** using potassium *tert*-butoxide did not afford the desired azetidines **267** and **268**. Attempted cyclization of epoxy *endo*-amine **266** using Lewis acid $BF_3 \cdot OEt_2$ was also unsuccessful (see entry 3 in Table 26). In contrast, epoxy *endo*-amines **265** and **266** underwent Grignard-mediated intramolecular cyclization in better yield without cleavage of the pivaloate group. Using vinylmagnesium bromide tricyclic azetidines **267** and **268** were obtained in 71 and 83% yield, respectively (see entries 2 and 5 in Table 26). Upon treatment with more sterically hindered phenylmagnesium bromide, intramolecular cyclization of epoxy *endo*-amine **266** afforded azetidine **268** in 82% yield (see entry 6 in

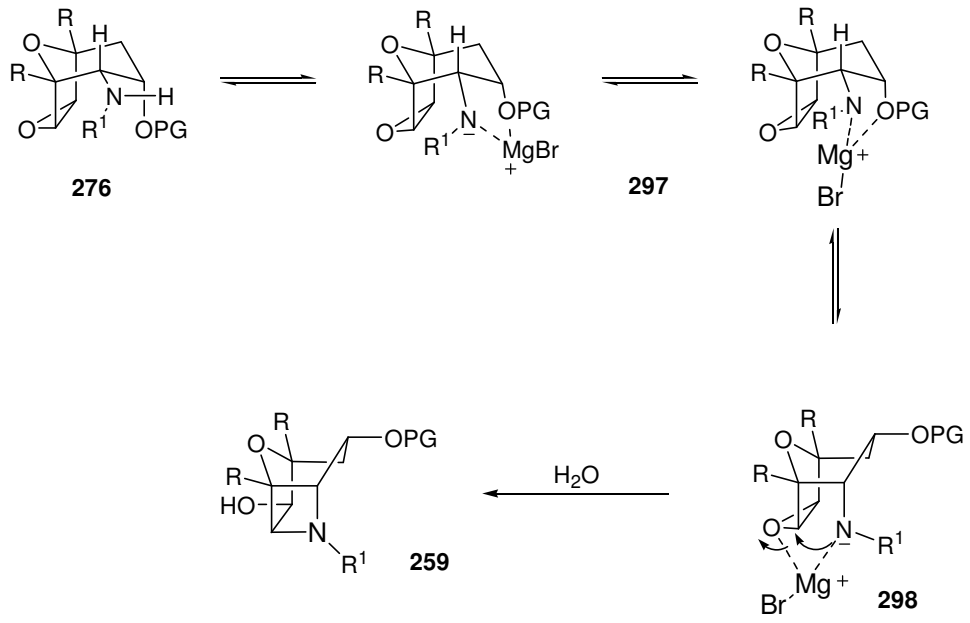
Table 26). Cyclization of epoxy *endo*-amine **266** catalyzed by less reactive ethynylmagnesium bromide led to azetidine **268** in 34% yield and additional 20% of epoxy *endo*-amine **266** was recovered unreacted (see entry 7 in Table 26). On the other hand, epoxy *endo*-amine **266** was recovered unreacted using ethynylmagnesium chloride (see entry 8 in Table 26).

The synthesis of oxatricyclic azetidines was accomplished by Grignard-mediated intramolecular cyclization of pivaloate substituted epoxy *endo*-amines **265** and **266** in good yield. Moreover, the pivaloate group showed high stability towards the reaction conditions and azetidines **267** and **268** were obtained without cleavage of the protecting group.

6.4.2 Mechanistic and Conformational Aspects of the Intramolecular Cyclization

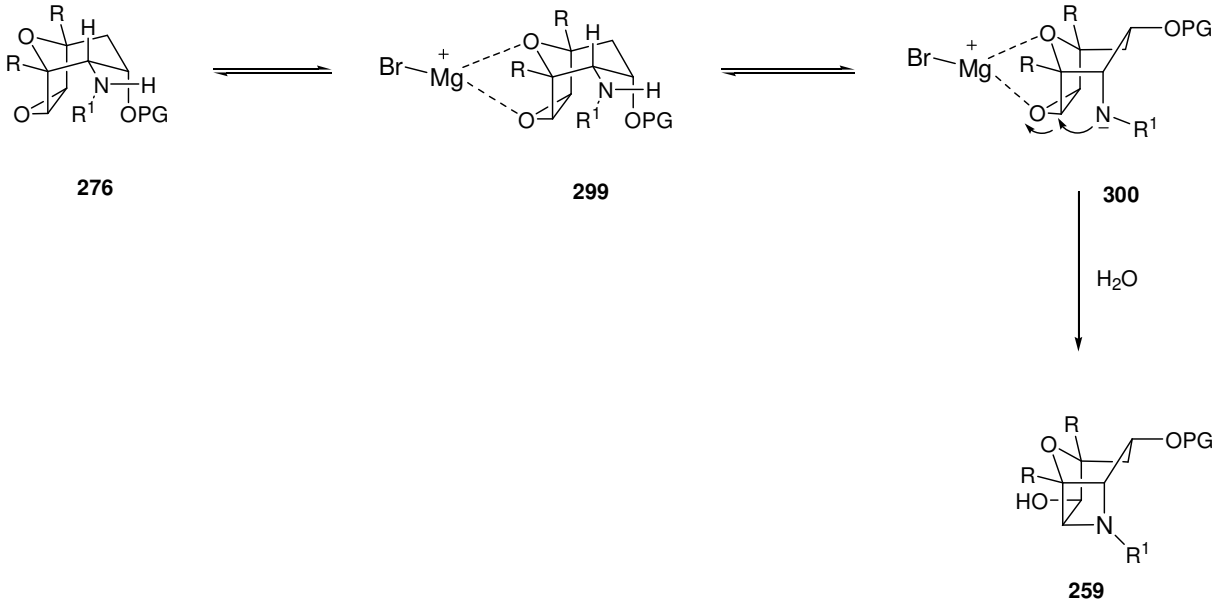
Two proposed mechanisms for the Grignard-mediated intramolecular cyclization of epoxy *N*-methylamines **265** and **266** are outlined in Scheme 84 and in Scheme 85. The organomagnesium compound can act as a strong base and a Lewis acid. Therefore, after deprotonation of the *endo*-amino group, the magnesium atom possibly coordinates with the oxygen atoms in the epoxy *N*-methylamine.

In a first proposed mechanism, the magnesium carbon atom may coordinate with the oxygen atom at carbon C3, with the nitrogen atom of the amino group and with the oxygen atom of the vicinal protected hydroxy group. The five-membered ring resulting from this coordination may populate two conformations. Afterwards, the six-membered oxacyclic ring changes to a boat, in which the amino function moves to axial position for a favoured formation of the new azetidine C-N bond. Simultaneously, the protecting group at C3 (methyl ether or pivaloate ester) moves from axial position to thermodynamically favoured equatorial position, which lowers the energy difference between chair conformation and boat transition state. In this boat transition state, the magnesium atom possibly coordinates with the nitrogen atom of the amino group and the oxygen atom of the epoxide ring. This coordination favours the intramolecular cyclization affording the tricyclic azetidine. After formation of the tricyclic azetidine, the bulky substituents at C3 occupy less hindered equatorial positions in an oxacyclohexane boat. Additional methyl groups at the bridgehead carbons increase the stability of oxazatricyclic structure.



Scheme 84: First proposed mechanism for the synthesis of tricyclic azetidines by Grignard-mediated intramolecular cyclization.

In a second proposed mechanism, the magnesium atom may coordinate with both bridgehead oxygen atom and epoxide oxygen atom simultaneously activating the epoxide towards the attack from the deprotonated amine. Afterwards, the six-membered oxacyclic ring **299** changes to a boat, in which the amino group moves to axial position for a favoured formation of the new azetidine C-N bond. As in the preceding mechanism, a decrease in the energy difference between chair conformation **299** and boat transition state **300** occurs when the protecting group at C3 (methyl ether or pivaloate ester) moves from axial position to thermodynamically favoured equatorial position. Afterwards, the coordination of the magnesium atom with the epoxide oxygen favours the intramolecular cyclization to desired tricyclic azetidine **259**.



Scheme 85: Second proposed mechanism for the synthesis of tricyclic azetidines by Grignard-mediated intramolecular cyclization.

6.5 Summary of the Synthesis of Epoxy Amines and Tricyclic Azetidines

The major aim of the present work was the synthesis of aza-analogues of the dioxatricyclic subunit of dictyoxetane. The introduction of an azetidine ring in the tricyclic skeletal structure constituted an important synthetic challenge which was accomplished following an efficient and valuable route.

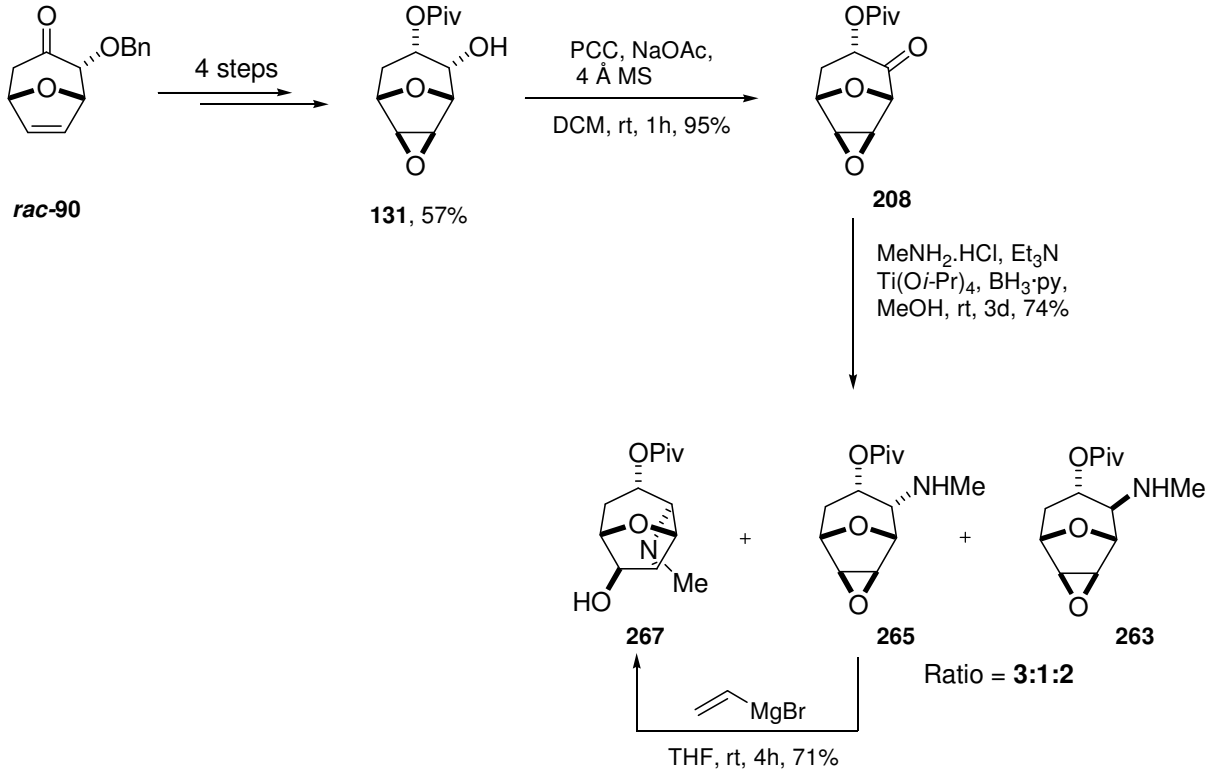
The synthetic route towards oxatricyclic azetidines was designed starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**, which already contain two of the three ring of the oxazatricyclic skeletal structure. In four steps *meso*-oxabicycles ***rac*-49** and ***rac*-90** were converted into versatile epoxy alcohols with pivaloate and methyl ether as protecting groups. Afterwards, epoxy ketones were converted into the azetidine precursors by reductive amination. For this purpose, two possibilities were studied: the synthesis of primary epoxy amines and secondary epoxy *N*-alkylamines.

The synthesis of primary epoxy amines was not successful using common reductive amination methods. The synthesis of secondary epoxy *N*-methylamines was first attempted by reductive amination of pivaloate substituted epoxy ketones **207** and **208** and methylamine. This conversion showed difficulties because of the steric hindrance and electrophilicity of the epoxy ketones. Several procedures were examined to promote the formation of the imine

intermediate. Under the optimized reaction conditions reductive amination of epoxy ketones afforded desired epoxy *endo-N*-methylamines in good yield and without cleavage of the pivaloate group. Synthesized epoxy *endo-N*-methylamines underwent Grignard-mediated intramolecular cyclization leading to the desired oxatricyclic azetidines in good yields. The same efficient reductive amination conditions were also applied for the conversion of methoxy substituted epoxy ketone **214**. In this case, epoxy ketone afforded directly azetidine **270**. The introduction of different amino group was also attempted by reductive amination of pivaloate substituted epoxy ketones **207** and **208** with ethylamine but the reaction proceeded in low yields. Therefore, methylamine proved to be the best choice for synthesis of tricyclic azetidines. In the following chapters the synthesis of the three synthesized tricyclic azetidines is described starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

*6.5.1.1 Synthesis of Pivaloate Substituted Azetidine **267***

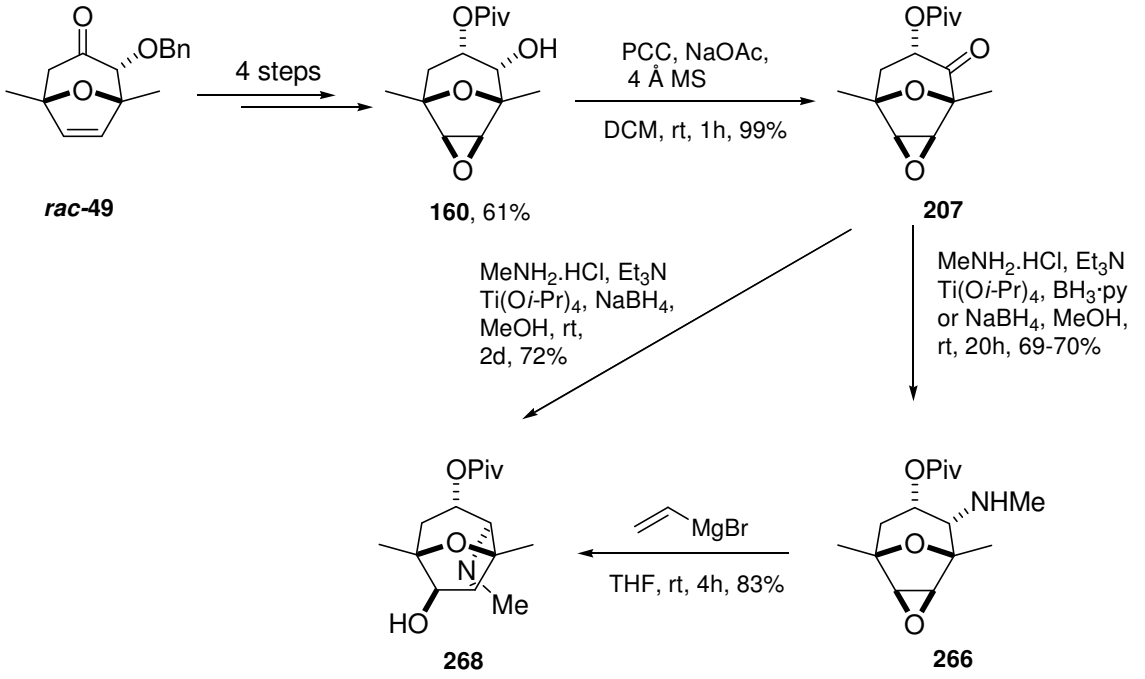
Starting from *meso*-oxabicycle ***rac*-90**, pivaloate substituted epoxy alcohol **131** was synthesized in 57% yield over four steps. Oxidation of epoxy alcohol **131** with PCC afforded epoxy ketone **208** in 95% yield under mild conditions and easy work-up procedures. Reductive amination of epoxy ketone **208** and methylamine under optimized conditions led to a mixture of epoxy *exo-N*-methyllamine **265**, epoxy *endo-N*-methylamine **263** and azetidine **267** in a 2:1:3 ratio in 74% yield. The three compounds were separated by column chromatography. Isolated epoxy *endo*-amine **265** was subjected to intramolecular cyclization using vinylmagnesium bromide and desired azetidine **267** was obtained in 71% (see Scheme 86). Summarizing, pivaloate substituted azetidine **267** was synthesized over seven steps in 25% overall yield starting from *meso*-oxabicycle ***rac*-90**.



Scheme 86: Synthesis of pivaloate substituted epoxy *endo*-*N*-methylamine **266** and oxatricyclic azetidine **267**.

*6.5.1.2 Synthesis of Pivaloate Substituted Azetidine **268***

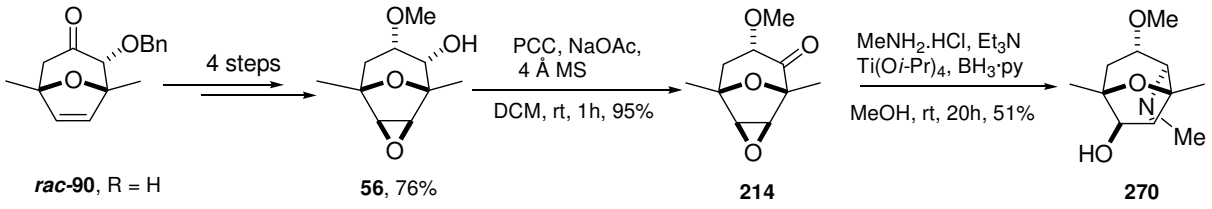
As outlined in Scheme 87, pivaloate substituted epoxy alcohol **160** was prepared 61% yield over four steps starting from *meso*-oxabicycle ***rac*-49**. Oxidation of epoxy alcohol **160** proceeded with PCC affording epoxy ketone **207** in 99% yield. Reductive amination of epoxy ketone **207** using pyridine-borane complex or sodium borohydride and titanium (IV) isopropoxide afforded stereoselectively epoxy *endo*-amine **266** in 69 or 70 % yield when the reaction was quenched four hours after addition of the reductant. Reductive amination using sodium borohydride led also to epoxy *endo*-amine in similar yield and similar reaction time (the reaction was quenched two hours after addition of the hydride reagent). Under the same reductive amination conditions, epoxy ketone **207** was converted almost exclusively into azetidine **268** in 72% yield together with 6% of epoxy *endo*-amine **266** when the reaction mixture was allowed to stir for a long time. Isolated epoxy *endo*-*N*-methylamine **266** was subjected to intramolecular cyclization using vinylmagnesium bromide and desired azetidine **268** was obtained in 83% yield. Starting from *meso*-oxabicycle ***rac*-49** pivaloate substituted azetidine **268** was obtained over six steps in 43% overall yield or over seven steps in 35% overall yield.



Scheme 87: Synthesis of pivaloate substituted epoxy *endo-N*-methylamine **266** and oxatricyclic azetidine **268**.

*6.5.1.3 Synthesis of Methoxy Substituted Azetidine **270***

As outlined in Scheme 88, methoxy substituted epoxy alcohol **160** was prepared in 61% yield over four steps starting from *meso*-oxabicycle ***rac*-49**. Epoxy alcohol **56** was converted quantitatively to epoxy ketone **214** using PCC. Starting from epoxy ketone **214**, methoxy substituted azetidine **270** was prepared by a stereoselective one-pot reductive amination/cyclization tandem reaction in 51% yield. The intermediate epoxy *endo*-amine could not be isolated. Starting from *meso*-oxabicycle ***rac*-49**, methoxy substituted azetidine **270** was synthesized over six steps in 37% yield.



Scheme 88: Synthesis of methoxy substituted oxatricyclic azetidine **270.**

6.5.1.4 Conclusion of the Synthesis of Azetidines

Comparing the synthesis of azetidines **268** and **270** starting from *meso*-oxabicycle ***rac*-49**, the synthesis of methoxy substituted azetidine **270** proceed in lower overall yield than that of the corresponding pivaloate **268**. The higher hydrophilicity of methoxy substituted azetidine **270** compared to that of pivaloate **268** raises the risk of losses during the work-up and lowers consequently the yield of azetidine **270**. An advantage of pivaloate substituted azetidines **267** and **268** is the possibility of a later deprotection of the *endo*-hydroxy group at carbon C3 under milder conditions than the cleavage of the more stable methyl ether. In terms of yield and stability, the synthetic route towards pivaloate substituted azetidine **268** is the best choice for the synthesis of aza-analogues of subunits of dictyoxetane.

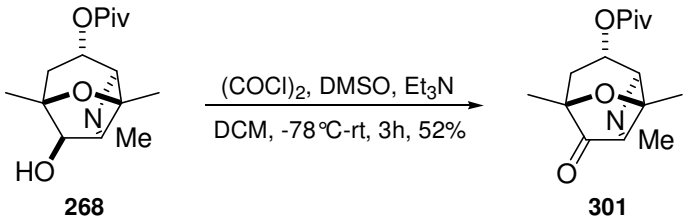
6.6 Functionalization of the Oxatricyclic Azetidine

Since the azetidine ring system as substructure has shown a wide range of biological activities,[141] the synthesis and functionalization of the azatricyclic skeletal structure constitutes an access to potential pharmacological active compounds. The free hydroxy group at carbon C6 of the azetidine **268** offers the possibility of further transformation of the oxazatricyclic skeletal structure.

As reported in Section 6.5, pivaloate substituted azetidine **268** is the best choice for the synthesis of aza-analogues of subunits of dictyoxetane. Therefore, azetidine **268** was chosen as starting material for the functionalization of the oxazatricyclic skeletal structure.

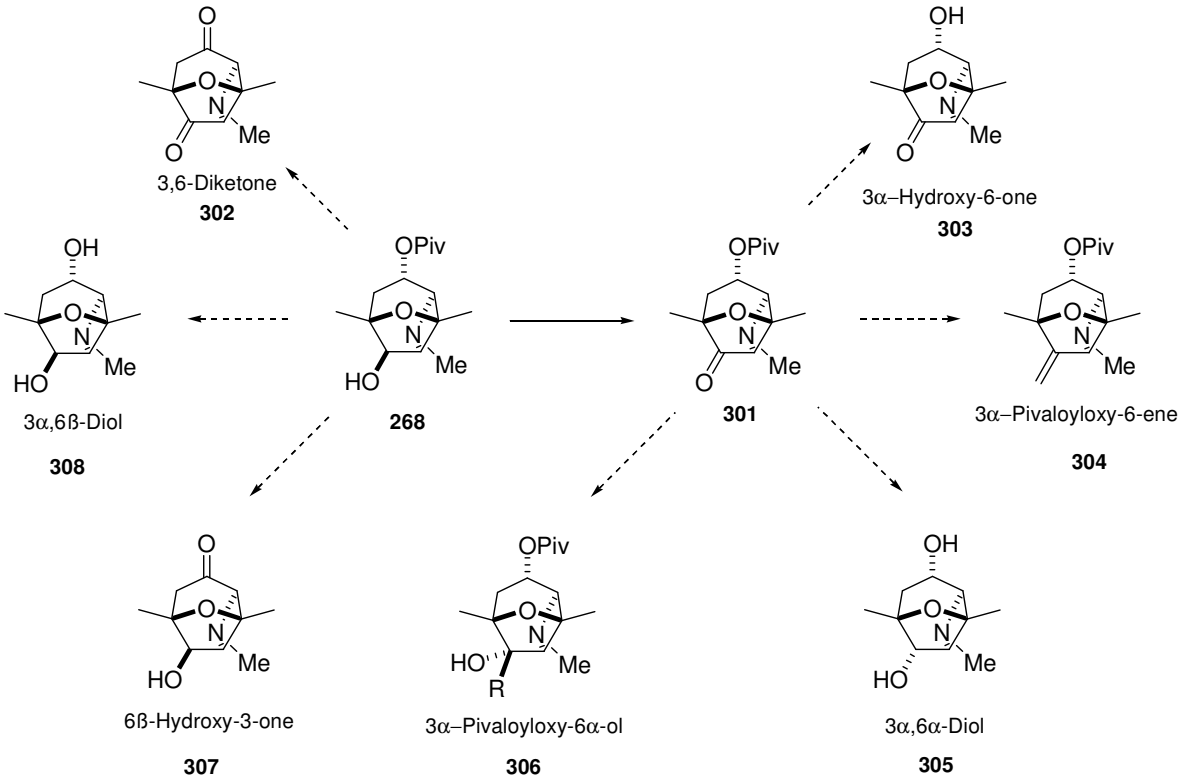
The first step towards derivatives of the oxazatricyclic skeletal structure was the oxidation of the hydroxyl group at carbon C6. Swern oxidation of tricyclic azetidine **268** afforded ketone **301** in 52% yield (see Scheme 89).

[141] See Chapter 1.



Scheme 89: Swern oxidation of tricyclic azetidine **268** to afford ketone **301**.

Further functionalization of the oxazatricyclic skeletal structure was not studied in the framework of the present work. As outlined in Scheme 90, tricyclic azetidines **268** and **301** are valuable precursors of a wide variety of new derivatives including aza-glycosides, whose synthesis remains open for the future.



Scheme 90: Synthetic strategy for further functionalization of the oxazatricyclic skeletal structure.

7. Characterization of the Cytostatic and Cytotoxic Activity of Dioxa and Oxaza-tricyclononanes

Natural products containing a strained oxetane ring show a wide spectrum of biological activities.[142] In dictyoxetane the presence of an oxetane ring in its intricate framework confers pharmacological potential to all structurally related segments. Moreover, since the azetidine ring system represents an important pharmacophore in several bioactive compounds,[143] aza-analogues of the dioxatricyclic substructure are also interesting substances with potential pharmacological activity.

The pharmacological potential of the dioxatricyclic substructure of dictyoxetane was already verified by the anti-tumor activity exhibited by some dioxatricyclic oxetanes. Four dioxatricycles, synthesized by J. Wittenberg,[144] showed cytostatic activity towards HMO 2 and HEP G2 cell lines comparable to 5-fluorouracil and a fifth dioxatricyclic oxetane, reported by S. Proemmel,[145] showed cytostatic activity towards HEP G2 and MCF 7 cell lines.

The anti-tumor activity showed by the above mentioned oxetanes increased the interest in the synthesis and functionalization of new dioxatricyclic oxetanes and aza-analogues of the natural product dictyoxetane. Amongst the dioxatricyclic and oxazatricyclic compounds reported in the present work, the *in vitro* anti-tumor activity of seven substances was tested against different tumor cells (see Section 7.1).

7.1 Results of the *in vitro* Tests in Three Tumor Cell Lines

The anti-tumor activities of dioxazatricycles **186** and **187**, tricyclic amines **265** and **266** and tricyclic azetidines **267**, **268** and **270** were tested against three tumor cell types (see Scheme 91). The cytostatic and cytotoxic assays were carried out *in vitro*, via the HMO 2 (human

[142] See Section 1.1.

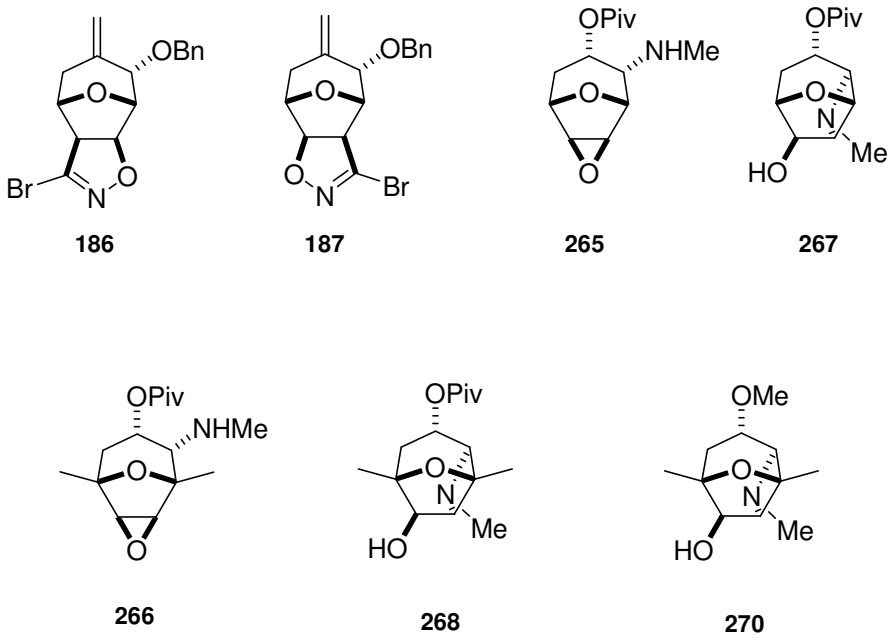
[143] See Section 1.2.

[144] Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tetrahedron Lett*. **1998**, *39*, 8259.

[145] Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199.

gastric carcinoma), the HEP G2 (human heptocellular carcinoma) and the MCF 7 (mamma carcinoma) cell lines,[146] according to the NCI guidelines.[147]

All tested substances did not show any effect until a concentration of 10 µg/ml towards the HMO 2, the HEP G2 and the MCF 7 cell lines. In other words, none of the tricyclic compounds exhibited cytotoxic or cytostatic activity against these three tumor cells.



Scheme 91: Tested oxazatricyclic and oxatricyclic substances.

7.2 Summary and Outlook

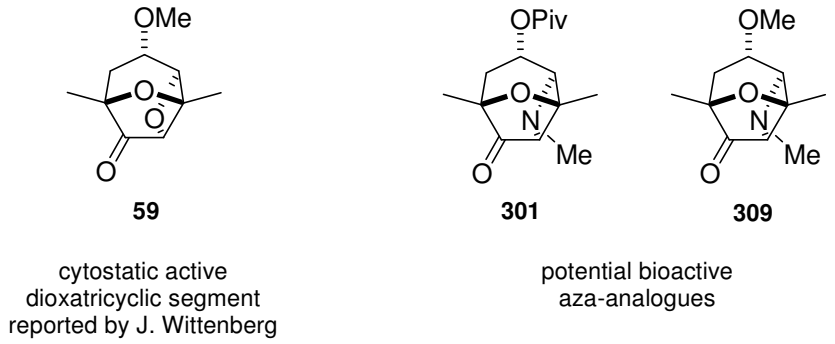
The above mentioned tricyclic compounds exhibited no anti-tumor activity in µmolar range towards three studied tumor cell lines. Further anti-tumor assays on other (tumor) cell types should be carried out to fully determine the cytostatic and cytotoxic potential of the aza-analogues of dictyoxetane. On the other hand, the antiviral activity of these aza-analogues could also be investigated, e.g. against herpes-simplex virus, hepatitis B virus or cytomegalovirus.

The functionalization of the oxazatricyclic skeletal structure allows the preparation of new derivatives with potential biological activity. A promising aza-analogue is azatricyclic ketone

[146] Pharmacological tests were carried out by Prof. W. Beil, Institut für Allgemeine Pharmakologie, Medizinische Hochschule Hannover.

[147] Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622.

301, which contains a carbonyl group instead of the hydroxyl group at carbon C6 as the most potent dioxatricyclic oxetane **59** (see Scheme 92). Therefore, azetidine **301** should be tested. Another interesting derivative is methoxy substituted azatricyclic ketone **309**, which has not been prepared in the framework of the present work.



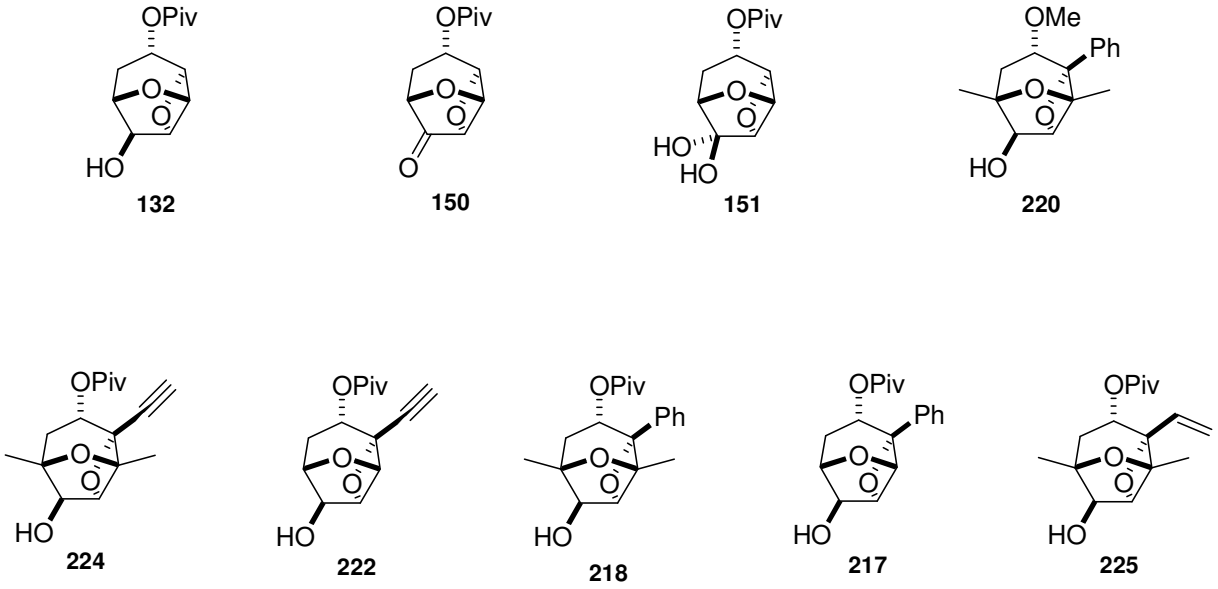
Scheme 92: Dioxatricyclic segment **59** reported by J. Wittenberg and aza-analogues **301** and **309**.

Regarding the dioxatricyclic oxetanes, a variation of substituents in the dioxatricyclic framework is essential to provide more information to understand the pharmacological activity of this class of substances. As summarized in Section 2.1.7, the cytostatic active dioxatricyclic oxetanes differ in the protecting group at carbon atom C3 and in the functional group at carbon atom C6. Amongst these compounds, the most active **59** has a ketone group at carbon atom C6 (see Scheme 92). On the other hand, reported methoxy substituted dioxatricyclic oxetane **101** without methyl groups at the carbons C1 and C5 did not show anti-tumor activity.[148] Nevertheless, similar oxatricyclic oxetanes should be investigated to establish the influence of the methyl groups in the anti-tumor activity. For example, the cytostatic and cytotoxic activity of pivaloate substituted oxetane **132** and of its derivatives ketone **150** and diol **151** should still be tested (see Scheme 93).

Another interesting possibility to deeply study the relation between substituents and pharmacological activity of the dioxatricyclic compounds is offered by the series of highly functionalized dioxatricyclic segments **217**, **218**, **220**, **222**, **224** and **225** (see Scheme 93). These dioxatricyclic oxetanes contain an alkyl or aryl group at carbon atom C2 and a

[148] Vidal Pascual, M. *PhD Thesis*, Universität Hannover, **2003**.

protected 3-*endo*-hydroxy group, which appears to be essential to maintain the anti-tumor activity.[149]



Scheme 93: Dioxatricyclic oxetanes to be tested.

A wide spectrum of dioxatricyclic segments and aza-analogues of dictyoxetane with biological potential are prepared following an efficient and short route. The advantageous availability of this class of substances should be exploited for further SAR (structure-activity relationship) studies relating the dioxatricyclic substructure to its biological activity.

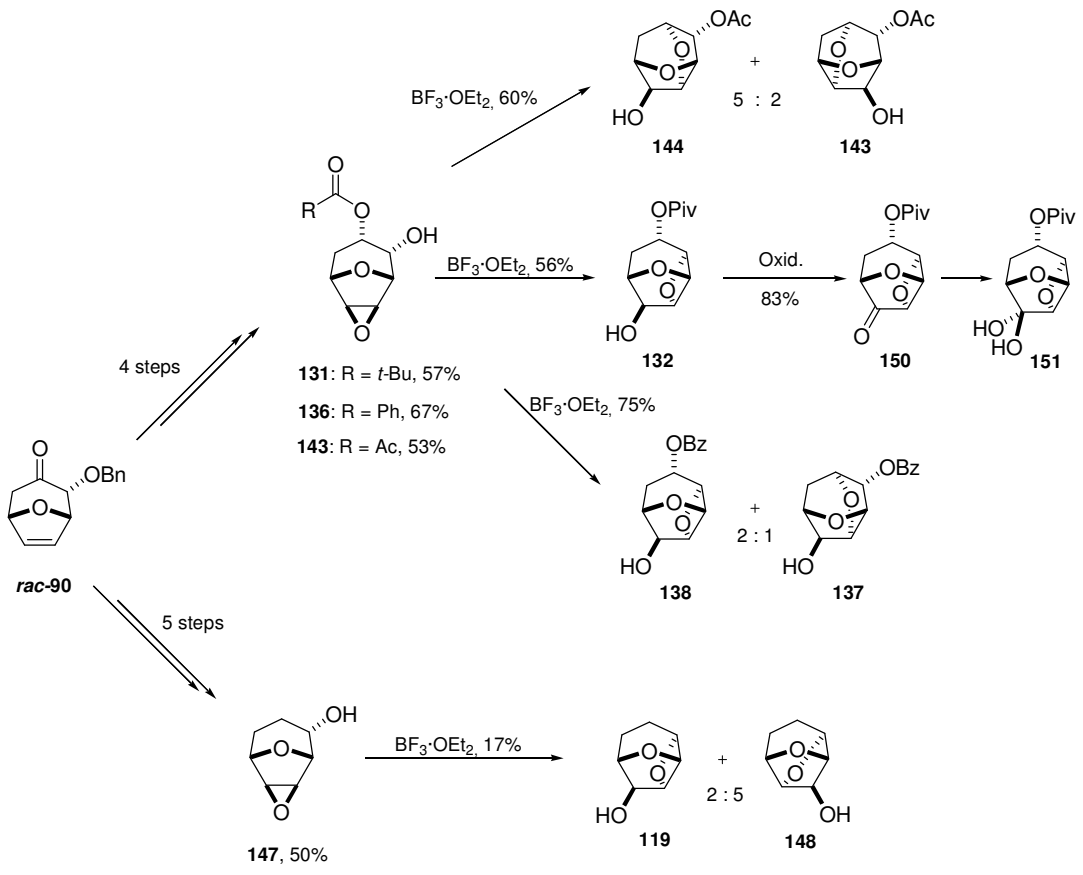
[149] Prof. W. Beil, Institut für Allgemeine Pharmakologie, Medizinische Hochschule Hannover.

8. Summary and Outlook

8.1 Summary

The comprehensive goal of the present work was the synthesis of new dioxatricyclic oxetanes and aza-analogues of dictyoxetane, potential bioactive compounds and also for high-quality libraries.

The first aim was an optimized synthesis of dioxatricyclic oxetanes starting from *meso*-oxabicycle ***rac*-90**. For this purpose, different esters (pivaloate, benzoate, acetate) were chosen as oxygen protecting group at carbon C3 in order to improve the overall yield and allow an easier deprotection after oxetane ring closure.

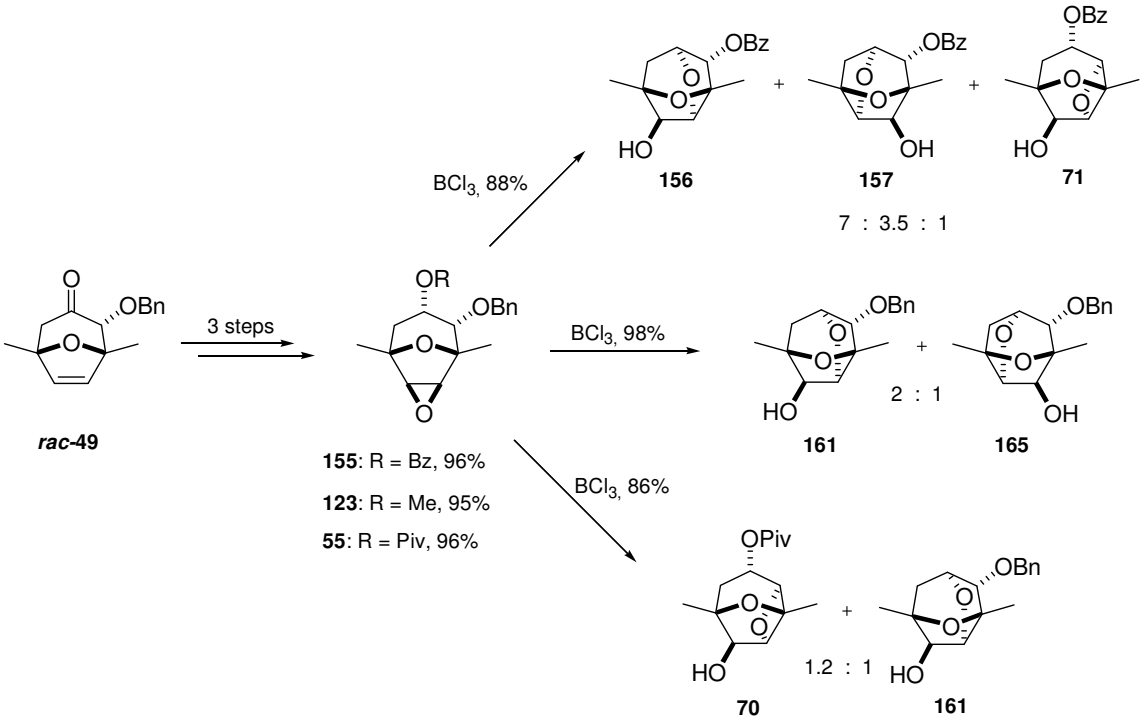


Scheme 94: Synthesis of dioxatricyclic segments starting from *meso*-oxabicycle ***rac*-90**.

Benzoate and acetate showed migration of the acyl group giving mixtures of oxetane **138** and tricyclic **137** or TXA_2 analogues **144** and **143**, respectively (see Scheme 94). In contrast, *tert*-

butylester proved to be the best choice for preparing tricyclic oxetanes. In the absence of stabilizing methyl groups at the bridgehead carbons, the synthesis of pivaloate substituted dioxatricyclic oxetane **131** proved to be clearly more successful than that of the ether substituted analogues.[150] The first step towards new derivatives of the oxetane skeletal structure was then carried out by oxidation of the hydroxyl group at carbon C6 of pivaloate **131** affording ketone **150**, which is moisture sensitive and forms acetal **151** (see Scheme 94). On the other hand, attempted synthesis of parent deoxygenated dioxatricyclic oxetane **65** led to a mixture of desired oxetane **119** and more stable dioxatricycle **148** (see Scheme 94).

A broader goal was the shortening of the synthetic route towards dioxatricyclic compounds by using Lewis acids to debenzylate and catalyze cyclization to the oxetane ring in one-step reaction. Treatment of different oxatricyclic epoxides with BCl_3 afforded mixtures of oxetanes and unwanted dioxatricycles, resulting of the cleavage of the pivaloate or migration of the benzoate group. Nevertheless, the tandem strategy using BCl_3 opened a new synthetic access to 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonanes as TXA_2-analogues starting from *meso*-oxabicycle ***rac*-49** (see Scheme 95).

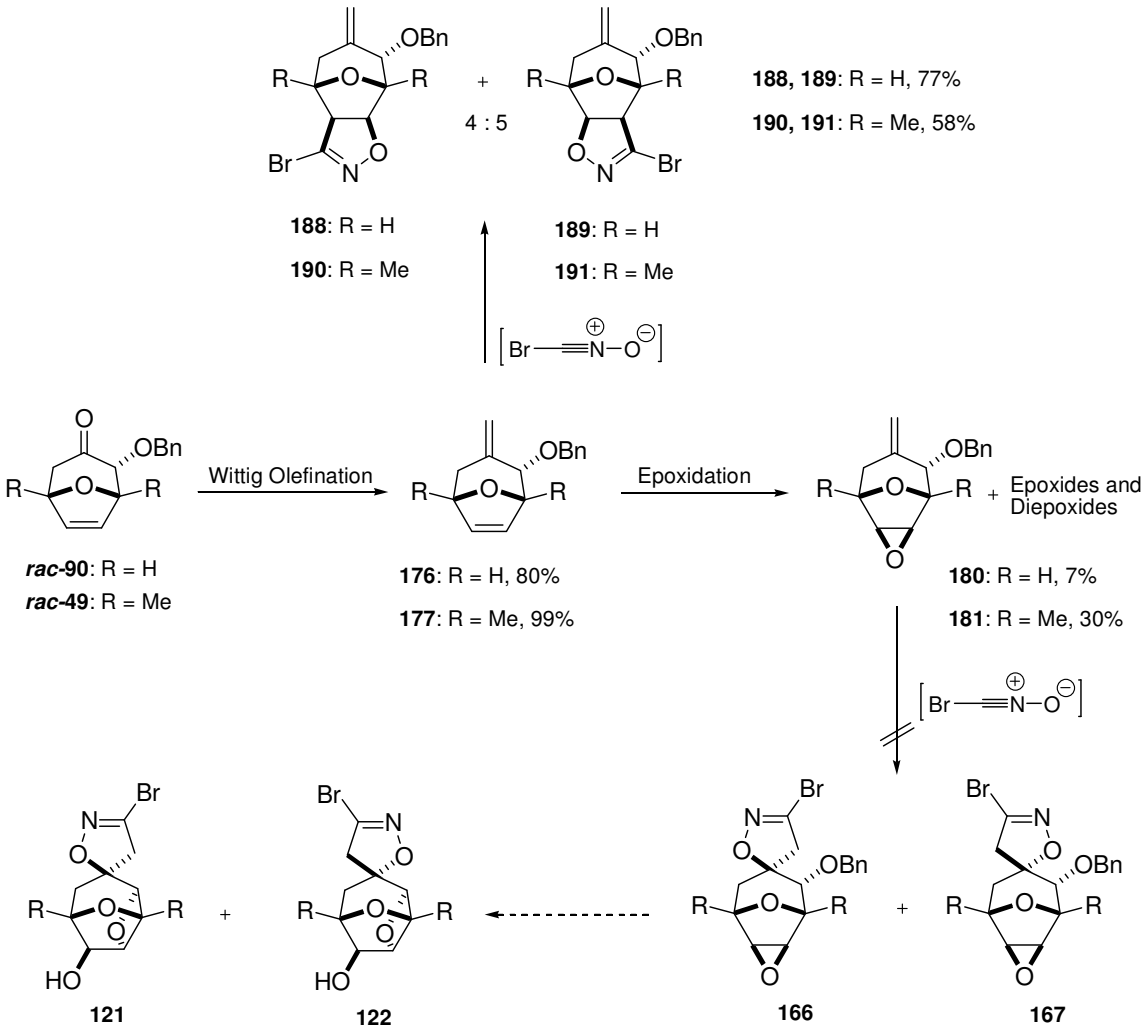


Scheme 95: Attempts to a shorter and efficient synthetic route towards dioxatricyclic oxetanes.

[150] Vidal Pascual, M. *PhD Thesis*, University of Hannover, **2003**.

The present work was also concerned with the synthesis of higher functionalized dioxatricyclic structures. In the first instance, emphasis was put on the introduction of a highly versatile isoxazoline ring in the oxatricyclic skeletal structure. For this purpose, two strategic routes were designed starting from oxabicyclic dialkenes **176** and **177** (see Scheme 96).

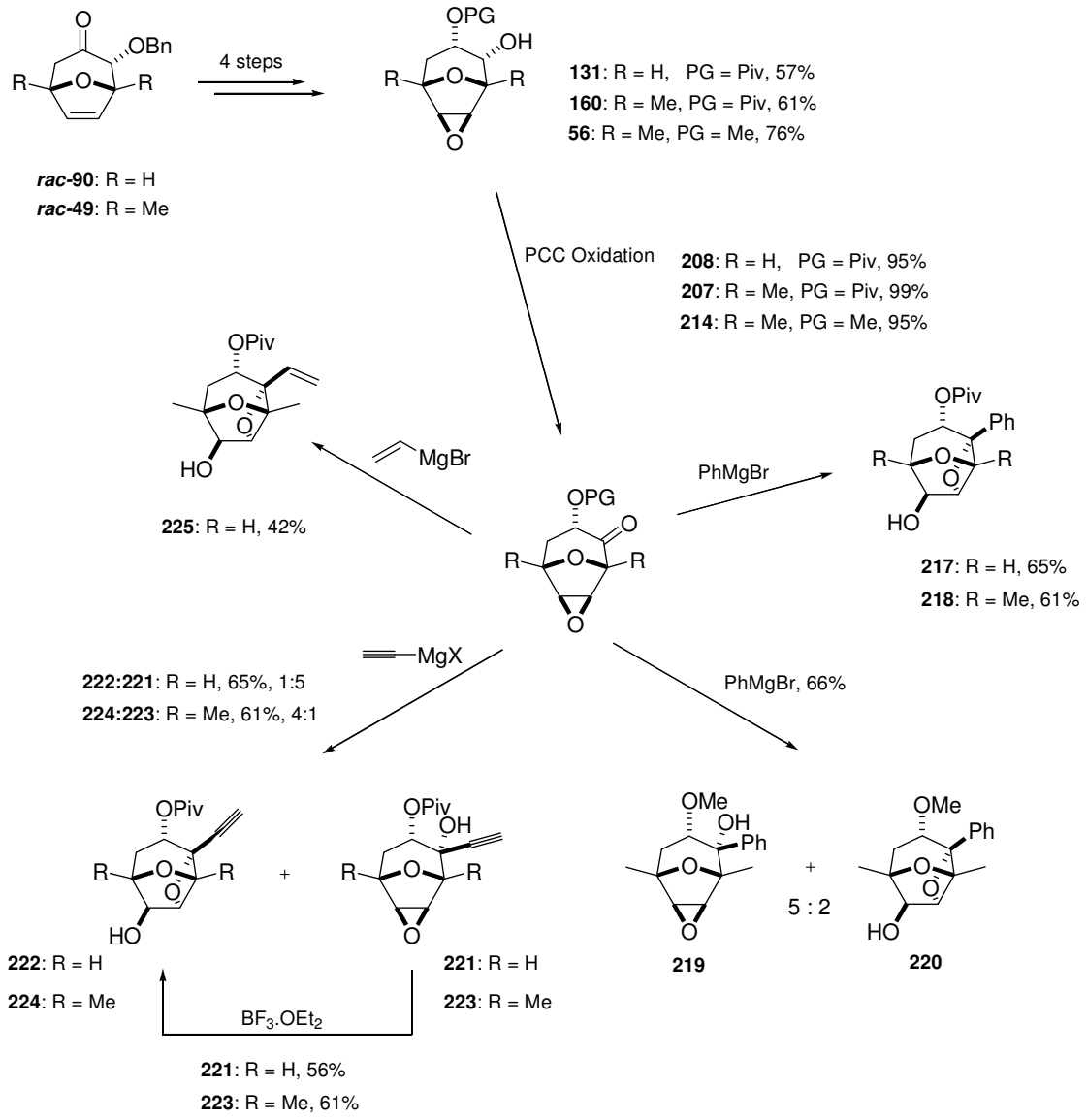
A site selective 1,3-dipolar cycloaddition of bromonitrile oxide to oxabicyclic dialkenes **176** and **177** occurred on the 1,2-disubstituted double bond affording dioxazatricycles **188**, **189**, **190** and **191**, which are valuable precursors of a wide variety of open chain compounds. On the other hand, attempted site selective epoxidation of the 1,2-disubstituted double bond of oxabicyclic dialkenes **176** and **177** provided a mixture of epoxides and diepoxides. The 1,3-dipolar cycloaddition of bromonitrile oxide to isolated epoxy alkenes **180** and **181** showed difficulties under the studied conditions, remaining open for further investigation.



Scheme 96: Attempted synthesis of dioxatricyclic oxetanes with an isoxazoline ring at carbon C3.

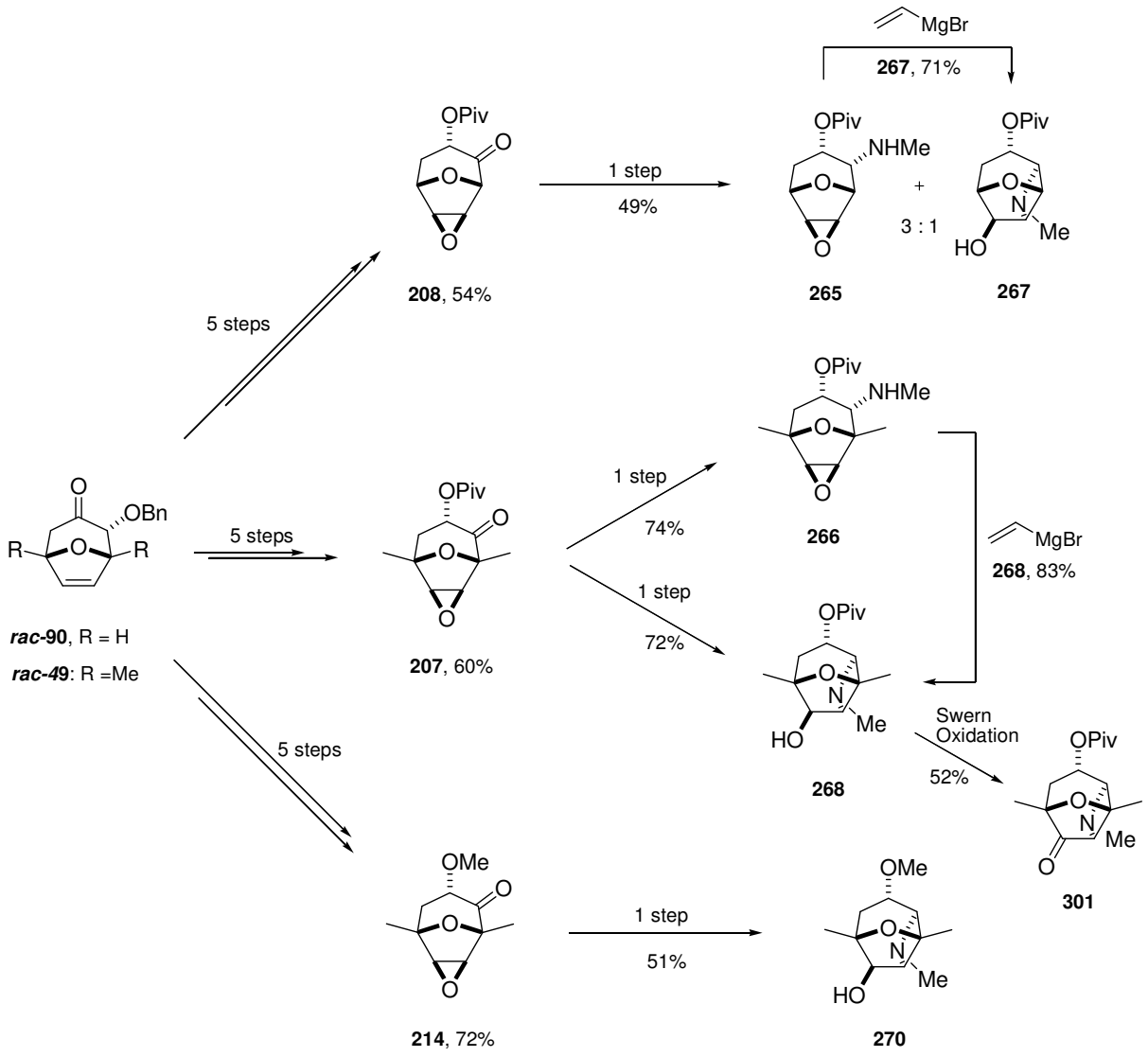
The synthesis of dioxatricyclic oxetanes with an aryl or alkyl group at the oxetane ring system was the next goal providing a series of higher functionalized dioxatricyclic structures.

Following a short and valuable route, arylated and alkylated dioxatricyclic oxetanes were prepared starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** (Scheme 97). The conversion of versatile epoxy alcohols into the corresponding epoxy ketones proceeded quantitatively by using PCC oxidation. The introduction of alkyl and aryl groups at carbon C2 proceeded by a tandem Grignard reagent-mediated addition-cyclization reaction of epoxy ketones affording C2-alkylated and arylated dioxatricyclic oxetanes. Lewis acid-catalyzed cyclization of the isolated tertiary epoxy alcohols led also to alkylated dioxatricyclic oxetanes.



Scheme 97: Synthesis of arylated and alkylated dioxatricyclic oxetanes starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

Finally, the main aim of the present work was the development of an efficient synthetic route towards aza-analogues of the dioxatricyclic subunit of dictyoxetane, which was successfully accomplished after many attempts.



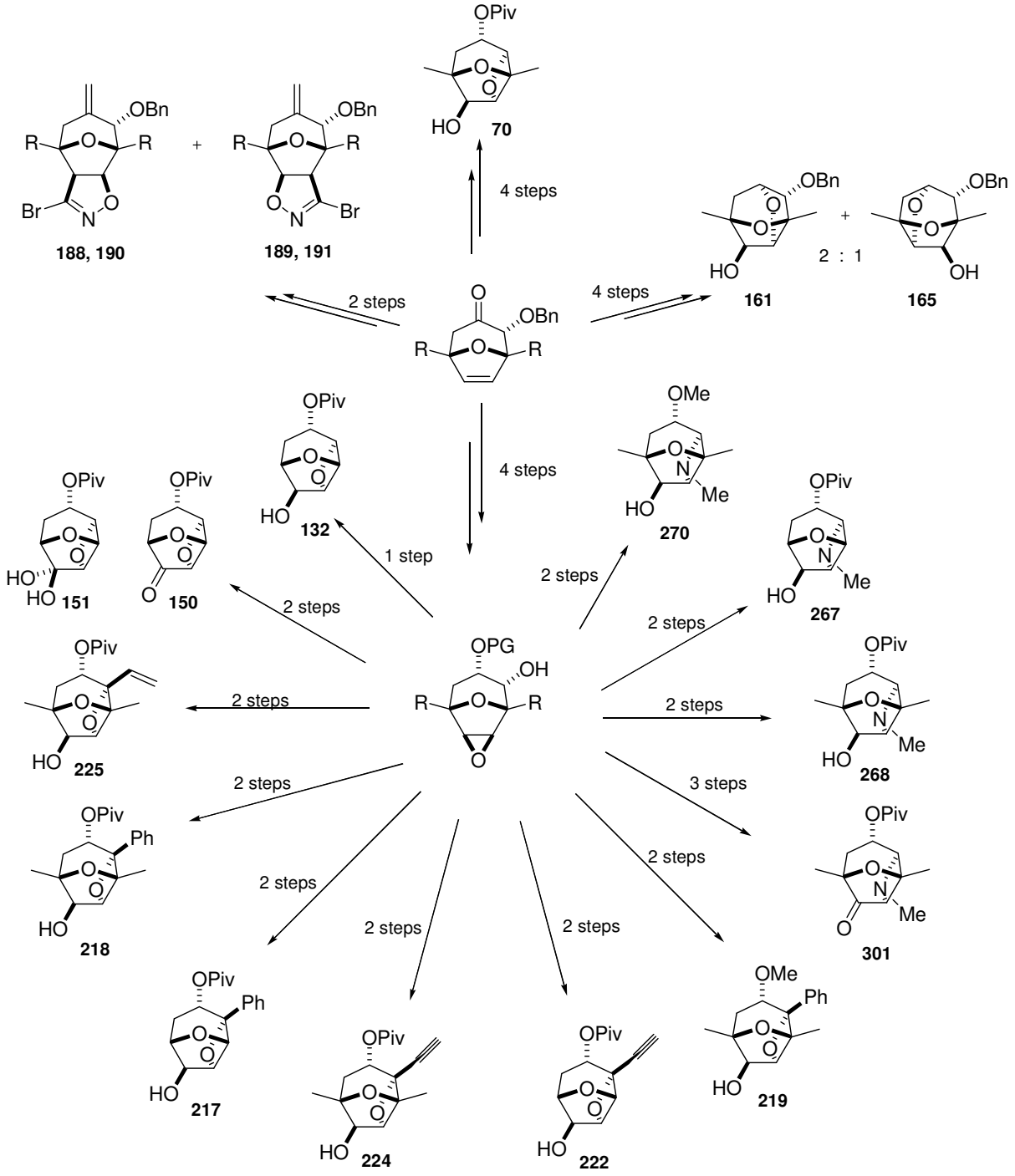
Scheme 98: Synthesis of tricyclic azetidines starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

The synthesis of secondary epoxy amines showed difficulties because of the steric hindrance and electrophilicity of the epoxy ketones and the use of additives was essential to succeed. Pivaloate substituted azetidines **267** and **268** and methoxy substituted azetidine **270** were already obtained in six steps starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90** (Scheme 98)**.** Conversion of epoxy ketones **207**, **208** and **214** under reductive amination conditions proceeded through one-pot reductive amination/cyclization tandem reaction affording directly tricyclic azetidines **267**, **268** and **270**. Moreover, isolated pivaloate epoxy *endo-N*-methylamines **265** and **266** underwent smoothly Grignard-mediated intramolecular

cyclization to afford tricyclic azetidines **267** and **268**. In terms of yield and stability, pivaloate substituted azetidine **268** was the best choice for the synthesis of aza-analogues of dictyoxetane. A first step towards functionalization of the oxazatricyclic skeletal structure was the oxidation of tricyclic azetidine **267** yielding ketone azetidine **301**.

A remarkably short and efficient route to aza-analogues of dictyoxetane has been achieved starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**. This approach provides highly functionalized oxazatricyclic azetidines, which are potential pharmacologically active compounds but also versatile precursors of a wide variety of derivatives including azasugars.

The most important dioxatricyclic oxetanes, oxazatricycles and oxazatricyclononanes prepared from *meso*-oxabicycles ***rac*-49** and ***rac*-90** are outlined in Scheme 99. As can be seen, the epoxy alcohols represent highly versatile precursors of a wide spectrum of highly functionalized dioxatricyclic segments and aza-analogues of dictyoxetane. All compounds have pharmacological potential and are easily accessible through an efficient and short route.

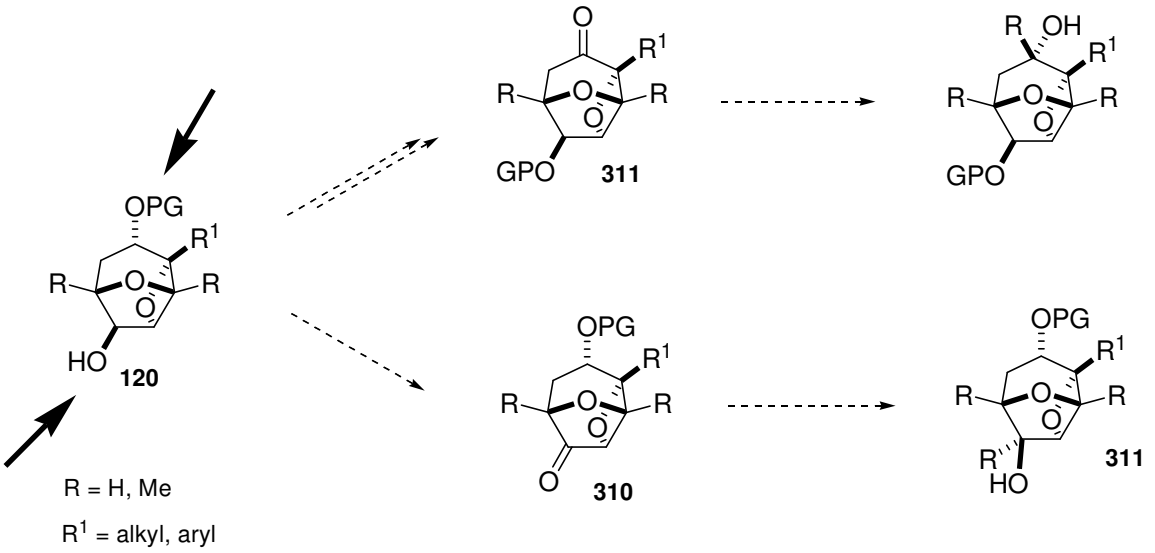


Scheme 99: Summary of dioxatricyclic oxetanes, oxazatricycles and oxazatricyclononanes starting from *meso*-oxabicycles ***rac*-49** and ***rac*-90**.

8.2 Outlook

Further synthesis of new dioxatricyclic subunits of dictyoxetane and aza-analogues is of interest not only because of the pharmacological potential related to these class of compounds but also for understanding the structure-activity relationship of the oxatricyclic segments.

In the present work, highly functionalized dioxatricycles were prepared by introduction of an aryl or an alkyl group at carbon C2. Further functionalization of these compounds may be possible through transformations at carbon C3 and at carbon C6 following an orthogonal protection strategy (see Scheme 100). The release of ring strain in ketones **311** and **310** by addition of nucleophiles similar functionalization could also be applied for tricyclic azetidines.



Scheme 100: Strategy for the synthesis of derivatives of C2-arylated and alkylated oxatricyclic oxetanes.

Regarding the aza-analogues of dictyoxetane, an interesting approach is the synthesis of enantiopure tricyclic azetidines. For this purpose, several possibilities remain open such as an asymmetric reductive amination reaction to afford chiral epoxy amines of defined stereochemistry.

In last years, the synthetic utility of nitrogen substituted oxyallyl cations as attractive reactive intermediates for [4+3] cycloadditions with furan has been already reported.[151] Therefore, an alternative strategy towards tricyclic azetidines could also be explored starting from 8-oxabicyclo[3.2.1]oct-6-en-3-ones with a nitrogen substituent at carbon C2.

[151] Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23.

Experimental Part

9. General remarks

^{1}H-NMR Spectra were recorded at room temperature on a Bruker AVS 400 or AVS 500 spectrometer at 400.13 MHz and 500 MHz respectively. All spectra were run in deuterated chloroform with tetramethylsilane as internal standard (TMS 0.00 ppm), unless otherwise stated. Data are reported in the following order: chemical shift in ppm on the δ-scale, spin multiplicities (s = singlet, d = doblet, t = triplet, q = quartet, qu = quintet, m = multiplet, b = broad signal), coupling constants J (Hz) and integration rates.

^{13}C-NMR Spectra were recorded on the above mentioned spectrometers at 100.6 MHz and 125 MHz under proton broadband decoupling. $CDCl_3$ was used as solvent and as internal standard (77.0 ppm). Chemical shifts are given in ppm on the δ-scale. ^{13}C multiplicities were determined with DEPT 90 and DEPT 135 experiments and indicated by CH_3 (primary), CH_2 (secondary), CH (tertiary) and C_q (quaternary).

H,H-COSY, HBMC, HMQC and NOE spectra were recorded on the above mentioned spectrometers.

Infrared Spectra (IR) were recorded on a Perkin-Elmer 1710 infrared spectrometer using a "Golden Gate" single-reflection ATR system. Characteristic IR bands are specified in cm^{-1} and band intensities are given as follows: vs = very strong, s = strong, m = medium, w = weak, b = broad.

Mass Spectra (EI-MS) were carried out on a Finnigan MAT 312 mass spectrometer (ionization potential 70 eV) at room temperature, unless otherwise stated. Characteristic EI-MS peaks are given in m/z (mass to charge ratio) and percent relative intensity to the base peak.

High Resolution Mass Spectra (HR-MR) were recorded on a VG Autospec spectrometer with the peak matching method (PKF) and the NBA-Matrix was used.

Elemental Analysis was performed on a Heräus CHN-Rapid elemental analyzer.

Melting Points (m.p.) were measured on a Büchi apparatus according to Dr. Tottoli and are uncorrected.

Kugelrohr Distillation was carried out using a Büchi GKR 50 apparatus at reduced.

Gas Chromatography (GC) was performed out on a HP 6890 capillary gas chromatograph with a SE-54 capillary column combined with a flame ionization detector and nitrogen as carrier gas. The integration of the signals was performed on a HP 3896 integrator.

Column Chromatography was performed on 230-400 mesh silica gel from Macherey Nagel.

Thin Layer Chromatography (TLC) was carried out on aluminium backed TLC plates coated with 0.2 mm silica gel 60 F_{254} from Merck. TLC plates were visualized under ultraviolet (λ = 254 nm) and using cerium sulphate or bromocresol green as stains.

Reactions were monitored by TLC or GC. Air and moisture sensitive reactions were performed in oven-dried glassware under nitrogen or argon using standard syringe techniques and magnetic stirring unless otherwise noted.

Solvents were distilled and dried using standard methods. THF was dried, distilled from KOH pellets and then distilled from sodium and benzophenone under argon immediately prior to use. DCM was freshly distilled from CaH_2 before used. Diisopropylamine, triethylamine and pyridine were dried, distilled and stored over KOH. DMF was dried over powdered BaO for 2 weeks, followed by decanting and then distilling under reduced pressure. Ethanol and methanol were dried and distilled from CaH_2.

Reagents were commercially obtained at highest commercial quality and used without further purification except where noted.

Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

10. General Experimental Procedures

GP1 Low Temperature [4+3] Cycloaddition

Silyl enol ether (1.0 eq) was dissolved in dichloromethane (1M) and stirred at −78°C. Furan (1 eq) was added and the mixture was allowed to cool down. After 15 min TMSOTf (0.1 eq) was added carefully. The mixture was stirred for 30 min at −78°C and then poured into a separating funnel containing saturated solution of sodium bicarbonate. The solution was shaken thoroughly until it reached room temperature. The aqueous layer was extracted three times with dichloromethane and the combined organic phase was dried (Na_2SO_4). After removal of the solvent the crude product was purified by silica gel column chromatography.

GP2 Diastereoselective Reduction of Ketones with DIBAH

DIBAH (1.2 M in toluene, 2.2 eq) was added dropwise to a solution of bicyclic ketone (1 eq) in THF (1 M) at −78°C. The solution was stirred at this temperature until completion of the reaction (TLC control) and then allowed to reach room temperature. The reaction mixture was quenched at 0°C with 2 N aqueous HCl and extracted with MTBE. The combined organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography on silica gel.

GP3 Epoxidation of Double Bonds with *m*-CPBA

Bicyclic alkene (1 eq) was dissolved in DCM (0.2-0.4 M) and *m*-CPBA (70-75%, 2.0-2.4 eq) was added portionwise at 0°C. The reaction mixture was stirred at 0°C until the epoxidation was completed (TLC control) and then washed three times with 5% aqueous Na_2CO_3 and extracted with DCM. The combined organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

GP4 Debenzylation with H_2/Pd-C

To a solution of bicyclic benzyl ether (1 eq) in EA (0.15 M) and AcOH (EA/AcOH 49:1) was added a catalytic amount of Pd/C (10% Pd) and the mixture was rapidly stirred at room temperature under hydrogen atmosphere (1 atm) until the reaction was shown to be completed by TLC. Filtration through silica gel (EA/MTBE 1:1) and removal of solvents gave a residue which was diluted in MTBE and then washed three times with saturated aqueous $NaHCO_3$

and once with saturated aqueous NaCl. The aqueous layer was extracted several times with DCM and the combined organic phase was dried (Na_2SO_4), concentrated and purified by column chromatography on silica gel.

GP5 Intramolecular Lewis Acid-Catalyzed Cyclization to Oxetane

To a solution of epoxy alcohol (1 eq) in DCM (0.15 M) was added $BF_3 \cdot OEt_2$ (2.1 eq) dropwise at 0°C. The reaction mixture was stirred at room temperature until completion of the reaction (TLC control) and then quenched with saturated $NaHCO_3$ solution and DCM. The aqueous phase was extracted several times with DCM and the combined organic layer was dried (Na_2SO_4), concentrated and purified by silica gel column chromatography.

GP6 1,3-Dipolar Cycloaddition of Bromonitrile Oxide with [3.2.1] Oxabicycles using DBU

A solution of alkene (1 eq) in acetonitrile (0.5 M) was added to a stirred solution of dibromoformaldoxime (2.5 eq) in acetonitrile (1 M). At 0°C DBU (3.0 eq) was injected dropwise. The mixture was stirred at rt until the reaction was completed and then quenched by careful addition of water. The aqueous layer was extracted with EA and the combined organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography on silica gel.

GP7 1,3-Dipolar Cycloaddition of Bromonitrile Oxide with [3.2.1] Oxabicycles using KOH

A solution of alkene (1 eq) in THF (0.5 M) was added to a stirred solution of dibromoformaldoxime (2.0 eq) in THF (1 M). At 0°C potassium hydroxide (2.2 eq) was added. The mixture was stirred at rt until the reaction was completed and then quenched by careful addition of water. The aqueous layer was extracted with EA and the combined organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography on silica gel.

GP8 Oxidation of Alcohols to Ketones with PCC

PCC (4 eq), anhydrous sodium acetate (4 eq), 4 Å molecular sieves (previously activated) (1g/1 mmol alcohol) and anhydrous DCM (4/5 of the calculated amount) were placed in a light-protected flask and stirred under argon atmosphere for 10 min. A solution of the alcohol (1 eq) in anhydrous DCM (1/5 of the calculated amount) was added to the suspension, so that

a 0.1 M reaction mixture was obtained. The stirring was maintained at room temperature until the reaction was completed (TLC control). The remaining solution was then diluted with MTBE, filtered through silica gel, and evaporated to dryness obtaining the product.

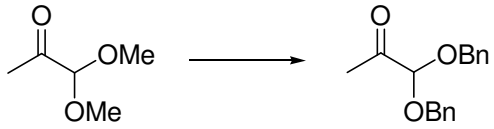
GP9 Acetylation of Alcohols

To a solution of alcohol (1 eq) in pyridine (3.5 M) were added DMAP (0.06 eq) and acetic anhydride (5.2 eq) at 0°C. The mixture was stirred at room temperature until completion of the reaction (TLC control) and quenched with water and MTBE. The aqueous phase was extracted with MTBE and the combined organic layers washed with 2N HCl and sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvents the crude product was purified by column chromatography on silica gel.

11. Attempts to Chapter 4

11.1 Attempts to Section 4.1

1,1-Bis-benzyloxy-propan-2-one ***46***



46

Pyruvic aldehyde dimethyl acetal (12.1 ml, 100 mmol, 1 eq) was dissolved in cyclohexane (50 ml). Benzyl alcohol (22.8 ml, 220 mmol, 2.2 eq) and *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol, 0.05 eq) were added and the resulting mixture was heated at reflux for 2 h using a Dean–Stark separator for the removal of MeOH. When the reaction was completed (approx. 2 h), 8.1 ml (200 mmol) of MeOH were obtained. The reaction mixture was cooled to room temperature and washed with 25 ml of saturated potassium carbonate solution and 20 ml of water. The aqueous layer was extracted twice with cyclohexane (2 x 50 ml). The combined organic phase was dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (MTBE/CH 1:20) to afford keto acetal **46**.

Yield: 22.0 g (81.4 mmol), 80 % yellowish oil

$C_{17}H_{18}O_3$ [270.32 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.40-7.26 (m, 10 H, Ar-H), 4.72 (s, 1 H, H-1), 4.67 (d, *J* = 11.8 Hz, 2 H, OC*H*$_2$Ph), 4.58 (d, *J* = 11.8 Hz, 2 H, OC*H*$_2$Ph), 2.23 (s, 3 H, H-3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

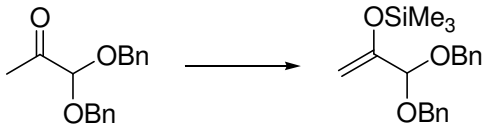
203.7 (C_q, C-2), 136.9 (C_q, Ar-C), 128.5/128.0 (CH, Ar-C), 101.0 (CH, C-1), 69.3 (2 x CH_2, O*C*H$_2$Ph), 24.9 (CH_3, C-3).

IR (neat): 3008 s, 2928 s, 1728 s, 1496 m, 1452 m, 1356 m, 1232 m, 1108 s, 1052 s, 1024 s, 908 w, 828 w.

EI-MS (rt): no M^+, 228 (10), 227 (29, M^+-CH_3CO), 182 (28), 181 (43), 164 (14), 135 (10), 108 (19), 93 (12), 92 (47), 91 (100).

HR-MS: calcd for $C_{15}H_{15}O_2$ (M^+- C_2H_3O) 227.107205, observed 227.107208.

*[1,1-(Bis-benzyloxy-methyl)-vinyloxy]-trimethylsilane **48***



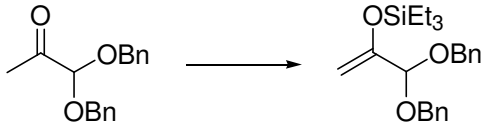
46 **48**

***Method 1**:* A LDA solution was prepared with diisopropylamine (5.1 ml, 36 mmol, 1.2 eq) in THF (36 ml) and *n*-BuLi (1.6 M solution in hexane, 22.5 ml, 36 mmol, 1.2 eq) at −78°C. The resulting mixture was stirred for a further 15 min at room temperature. Separately dibenzyl acetal **46** (8.1 g, 30 mmol, 1 eq) and chlorotrimethylsilane (5.7 ml, 45 mmol, 1.5 eq) were dissolved in THF (30 ml) and stirred at -78°C. To this mixture was added the LDA solution and triethylamine (18.8 ml, 135 mmol, 4.5 eq). The resulting reaction mixture was stirred for one more hour at −78°C and then washed with 25 ml of water and stirred until room temperature was reached. The aqueous phase was extracted twice with cyclohexane. After being dried (Na_2SO_4), the organic solution was concentrated under vacuum giving a light yellowish liquid, which was used directly in the [4+3] cycloaddition reaction.

Method 2: Dibenzyl acetal **46** (27 g, 100 mmol, 1 eq) was dissolved in anhydrous DMF (36 ml, 3M solution) and chlorotrimethylsilane (28.8 ml, 230 mmol, 2.25 eq) and heated at 75°C. Triethylamine (38.9 ml, 280 mmol, 2.8 eq) was added *via* perfusion (30 ml/h). The reaction mixture was refluxed for 16 h at 75°C turning thicker and dark brown. The reaction mixture was cooled to 0°C, washed with 30 ml of a cold saturated solution of ammonium chloride and with ca. 20 ml of water. The aqueous phase was re-extracted with cyclohexane (4 x 50 ml). The organic phase was dried (Na_2SO_4) and the solvent removed with a rotatory evaporator. The resulting brown viscous oil was used directly in the [4+3] cycloaddition reaction.[152]

[152] Method 1 is convenient for up to 30 mmols of dibenzyl acetal **46** and method 2 is recommended up to 130 mmols.

[1,1-(Bis-benzyloxy-methyl)-vinyloxy]-triethylsilane ***47***



46 **47**

A LDA solution was prepared by syringing *n*-BuLi (1.6 M solution in hexane, 22.5 ml, 36 mmol, 1.2 eq) into a solution containing diisopropylamine (5.1 ml, 36 mmol, 1.2 eq) in THF (36 ml) at −78°C. The resulting mixture was stirred for a further 15 min at room temperature. Separately dibenzyl acetal **46** (8.1 g, 30 mmol, 1 eq) and chlorotriethylsilane (7.5 ml, 45 mmol, 1.5 eq) were dissolved in THF (30 ml) and stirred at -78°C. To this mixture was added carefully the LDA solution and then triethylamine (18.8 ml, 135 mmol, 4.5 eq). The resulting reaction mixture was stirred for 16 h at −78°C and then 25 ml of water were poured in and the mixture was stirred until room temperature is reached. The aqueous phase was extracted twice with cyclohexane. After being dried (Na_2SO_4) the organic solution was concentrated under vacuum and purified by column chromatography on silica gel (MTBE/CH 1:100/Et_3N) to afford the silyl enol ether **47**.

Yield: 9.2 g (23.9 mmol), 80 % yellowish oil

$C_{23}H_{32}O_3Si$ [384.58 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.40-7.23 (m, 10 H, Ar-H), 4.94 (s, 1 H, H-1), 4.75 (br s, 1 H, H-3*trans*), 4.68 (d, *J* = 12.0 Hz, 2 H, OC*H*$_2$Ph), 4.60 (d, *J* = 12.0 Hz, 2 H, OC*H*$_2$Ph), 4.43 (d, *J* = 1.0 Hz, 1 H, H-3*cis*), 1.00 (tr, *J* = 8.0 Hz, 9 H, Si($CH_2C\mathit{H}_3$)$_3$), 0.74 (q, *J* = 8.0 Hz, 6H, Si($C\mathit{H}_2CH_3$)$_3$).

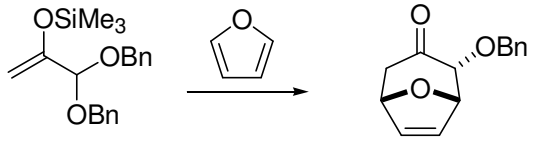
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

153.7 (C_q, C-2), 138.1 (C_q, Ar-C), 128.3 (CH, *m*-Ar-C), 127.8 (CH, *o*-Ar-C), 127.5 (CH, *p*-Ar-C), 99.1 (CH_2, C-3), 92.2 (CH, C-1), 67.9 (CH_2, 2 x O*C*H$_2$Ph), 6.6 (CH_3, Si($CH_2\mathit{C}H_3$)$_3$), 4.8 (CH_2, Si($\mathit{C}H_2CH_3$)$_3$).

MS (rt): no M^+, 279 (9), 249 (4), 248 (3), 193 (4), 187 (6), 181 (7), 159 (14), 157 (13), 115 (17), 91 (100).

IR (neat): 2956 s, 2912 m, 2857 s, 1640 m, 1456 m, 1256 s, 1112 s, 1056 s, 1024 s.

2α-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac-90***



48 ***rac*-90**

According to GP1, silyl enol ether **48** (max. 30 mmol, 1 eq) was dissolved in DCM (30 ml) and furan (2.2 ml, 30 mmol, 1 eq) was added. TMSOTf (0.5 ml, 3.0 mmol, 0.1 eq) was added carefully at –78°C. After completion of the reaction, the mixture was poured into a separating funnel containing 30 ml of a saturated $NaHCO_3$ solution. The crude product was purified by column chromatography on silica gel (MTBE/cyclohexane, 1:2) to afford cycloadduct **4** as a light yellow oil which solidifies to a yellowish solid. The oil was essentially pure cycloadduct ***rac*-90** which can be separated from remaining BnOH by Kugelrohr distillation at 100°C during 2 h. On being kept in the icebox of a refrigerator it crystallized from *tert*-butyl methyl ether or pentane, giving white crystals.

Yield: 2.83 g (12.3 mmol), 41 % (over two steps) white crystals (**m. p**. 64-65°C)
$C_{14}H_{14}O_3$ [230.26 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
7.40-7.27 (m, 5 H, Ar-H), 6.34 (dd, *J* = 6.1, 1.6 Hz, 1 H, H-7), 6.30 (dd, *J* = 6.1, 1.6 Hz, 1 H, H-6), 4.99 (ddd, *J* = 4.9, 1.6, 0.75 Hz, 1 H, H-5), 4.98 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 4.91 (dd, *J* = 5.0, 1.6 Hz, 1 H, H-1), 4.64 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 4.13 (d, *J* = 5.0 Hz, 1H, H-2), 2.76 (dd, *J* = 15.4, 4.9 Hz, 1 H, H_{ax}, H-4), 2.38 (d, *J* = 15.4 Hz, 1H, H_{eq}, H-4).

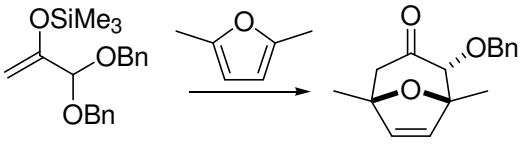
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
204.8 (C_q, C-3), 137.6 (C_q, Ar-C), 134.6 (CH, C-6), 131.7 (CH, C-7), 128.5-127.9 (CH, Ar-C), 84.1 (CH, C-2), 79.8 (CH, C-5), 78.3 (CH, C-1), 73.5 (CH_2, O*C*H$_2$Ph), 45.9 (CH_2, C-4).

IR ($CHCl_3$): 3063 w, 2977 m, 2862 m, 1724 vs, 1112 vs, 731 s, 697 s.

EI-MS (rt): 230 (6, M^+), 201 (4), 158 (38), 139 (31, M^+-Bn), 121 (10), 108 (25), 91 (100), 81 (30), 77 (14), 69 (23).

EA: Anal. Calcd for $C_{14}H_{14}O_3$: C, 72.89; H, 6.05. Found: C, 73.03; H, 6.13.

2α-Benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac-49***



48 ***rac*-49**

According to GP1, silyl enol ether **48** (max. 30 mmol, 1 eq) was dissolved in DCM (30 ml) and 2,5-dimethylfuran (2.2 ml, 30 mmol, 1 eq) was added. TMSOTf (0.5 ml, 3.0 mmol, 0.1 eq) was added carefully at –78°C. When the reaction was completed, it was poured into a separating funnel containing 30 ml of a saturated solution of sodium bicarbonate. The residue was purified by column chromatography on silica gel (MTBE/cyclohexane, 1:4) to afford cycloadduct ***rac*-49** as white crystals.

Yield: 4.11 g (15.9 mmol), 53 % (over two steps) white crystals (m.p**.** 79-80° C)
$C_{16}H_{18}O_3$ [258.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
7.40-7.27 (m, 5 H, Ar-H), 6.05 (d, *J* = 5.8 Hz, 1 H, H-7), 6.00 (d, *J* = 5.8 Hz, 1 H, H-6), 5.03 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 4.59 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 3.80 (s, 1H, H-2), 2.62 (d, *J* = 15.2 Hz, 1 H, H_{ax}, H-4), 2.43 (d, *J* = 15.2 Hz, 1H, H_{eq}, H-4), 1.47 (s, 6 H, 2 × C*H*$_3$).

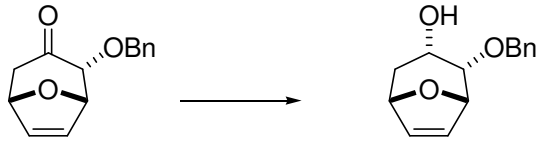
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
206.3 (C_q, C-3), 137.6 (C_q, Ar-C), 137.1 (CH, C-6), 134.8 (CH, C-7), 128.4-127.9 (CH, Ar-C), 87.4 (CH, C-2), 86.8 (CH, C-5), 84.8 (CH, C-1), 74.4 (CH_2, O*C*H$_2$Ph), 51.7 (CH_2, C-4), 23.1/20.5 (CH_3, 2× *C*H$_3$).

IR ($CHCl_3$): 3034 w, 2976 m, 2929 m, 2874 m, 1718 vs, 1498 w, 1454 m, 1401 m, 1378 m, 1340 m, 1319 m, 1269 w, 1243 w, 1220 w, 1177 m, 1109 vs, 758 s, 705 s.

EI-MS (rt): 258 (3, M^+), 191 (5), 167 (84, M^+-Bn), 152 (86), 139 (17), 109 (56), 97 (41), 91 (100), 79 (21), 65 (33).

EA: Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.26; H, 6.91. Found: C, 74.39; H, 7.02.

2α-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-ol ***125***



***rac*-90** **125**

Following GP2, DIBAH (1.2 M in toluene, 27.5 ml, 33 mmol, 2.2 eq) was added at –78°C to a solution of 8-oxabicyclo[3.2.1]oct-6-en-3-one **2** (1.86 g, 15.0 mmol, 1 eq) in THF (15 ml). The solution was stirred at -78°C until completion of the reaction (TLC control). Column chromatography (MTBE/CH 1:2) afforded alcohol **125**.

Yield: 2.79 g (12.0 mmol), 80 % yellowish oil

$C_{14}H_{16}O_3$ [232.28 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.39-7.30 (m, 5 H, Ar-H), 6.37 (dd, *J* = 6.1, 1.6 Hz, 1 H, H-7), 6.30 (ddd, *J* = 6.1, 1.6, 0.4 Hz, 1 H, H-6), 4.70 (m, 1 H, H-5), 4.69 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.64 (m, 1 H, H-1), 4.58 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.22 (dt, *J* = 5.0, 1.0 Hz, 1H, H-3), 3.77 (dd, *J* = 5.3, 4.1 Hz, 1 H, H-2), 2.56 (bd, 1 H, OH), 2.08 (ddd, *J* = 14.7, 5.3, 4.1 Hz, 1H, H_{ax}, H-4), 2.38 (d, *J* = 14.7 Hz, 1H, H_{eq}, H-4).

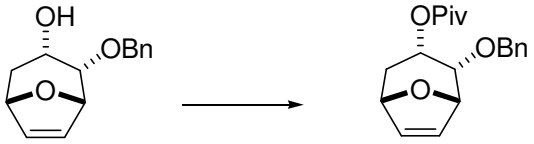
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

137.6 (C_q, Ar-C), 136.6 (CH, C-6), 131.7 (CH, C-7), 128.5/128.1/127.8 (CH, Ar-C), 78.35 (CH, C-2), 78.27 (CH, C-1), 74.3 (CH, C-5), 71.2 (CH_2, O*C*H$_2$Ph), 65.3 (CH, C-3), 32.9 (CH_2, C-4).

IR ($CHCl_3$): 2942 m, 2920 m, 1454 m, 1350 m, 1190 m, 1092 s, 1028 s, 944 m.

EI-MS (rt): 232 (2, M+), 214 (2), 141 (47), 126 (45), 108 (14), 91 (79), 81 (100).

2α-Benzyloxy-3α-pivaloyloxy-8-oxabicyclo[3.2.1]oct-6-ene ***129***



125 **129**

To a solution of the alcohol **125** (5.6 g, 24 mmol, 1 eq) in pyridine (20 ml) were added DMAP (60 mg, 0.48 mmol, 0.02 eq) and pivaloyl chloride (5.9 ml, 48 mmol, 2 eq) at 0°C. The mixture was stirred for 1 h at 0°C and overnight at rt, then water and MTBE were added. The aqueous layer was extracted with MTBE (3x) and the combined organic phase washed with 2N HCl, with sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvent the crude product was purified by column chromatography (CH/MTBE 3:1) to afford pivaloate **129** as a clear liquid.

Yield: 7.44 g (23.5 mmol), 98 % colourless oil

$C_{19}H_{24}O_4$ [316.39 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.34-7.27 (m, 5 H, Ar-H), 6.36 (ddd, *J* = 6.1, 1.8, 0.5 Hz, 1 H, H-7), 6.27 (dd, *J* = 6.1, 1.7 Hz, 1 H, H-6), 5.50 (trm, *J* = 5.2, 1.2 Hz, 1 H, H-3), 4.70 (m, 1 H, H-1), 4.64 (m. 1 H, H-5), 4.56 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.40 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 3.82 (dd, *J* = 5.3, 3.9 Hz, 1 H, H-2), 2.22 (ddd, *J* = 15.1, 5.3, 4.0 Hz, 1 H, H_{ax}, H-4), 1.61 (dtr, *J* = 15.1, 1.3 Hz, 1H, H_{eq}, H-4), 1.15 (s, 9 H, OCOC(C*H*$_3$)$_3$).

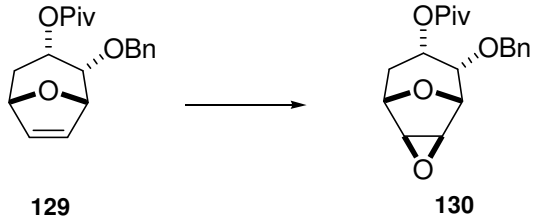
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.8 (C_q, O*C*OC(CH$_3$)$_3$), 138.0 (C_q, Ar-C), 134.5 (CH, C-6), 132.2 (CH, C-7), 128.3/127.6/127.6 (CH, Ar-C), 79.0 (CH, C-5), 77.9 (CH, C-1), 74.1 (CH, C-2), 71.3 (CH_2, O*C*H$_2$Ph), 65.8 (CH, C-3), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 32.1 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$).

IR (neat): 2977 m, 2954 w, 2870 w, 1720 vs, 1479 m, 1286 m, 1159 vs, 1096 s, 1031 s, 1005 m, 879 m, 732 s, 698 s, 683 s.

EI MS (rt): 316 (5, M^+), 272 (3), 225 (20), 191 (12), 185 (6), 167 (4), 141 (5), 123 (97), 108 (85), 95 (23), 91 (100), 85 (82), 81 (27).

6α-Benzyloxy-7α-pivaloyloxy-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonane ***130***



129 **130**

Following GP3, *m*-CPBA (70-75%, 15.6 g, 68 mmol, 2 eq) was added slowly to a solution of the pivaloate **129** (10.8 g, 34 mmol, 1 eq) in DCM (85 ml) at 0°C. The mixture was stirred for 4 h at 0°C and then quenched. The crude product was purified by column chromatography (CH/MTBE 1:1) obtaining epoxide **130**.

Yield: 9.27 g (27.9 mmol), 82 % yellowish oil

$C_{19}H_{24}O_5$ [332.39 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.38-7.24 (m, 5 H, Ar-H), 5.51 (trm, *J* = 4.6, 0.8 Hz, 1 H, H-3), 4.58 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 4.43 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 4.23/4.21 (bs, 2 H, H-1/H-5), 3.87 (d, *J* = 3.1 Hz, 1 H, H-7), 3.75 (tr, *J* = 4.5 Hz, 1 H, H-2), 3.60 (d, *J* = 3.1 Hz, 1 H, H-6), 2.22 (dtr, *J* = 15.6, 4.6 Hz, 1 H, H_{ax}, H-4), 1.76 (d, *J* = 15.8 Hz, 1H, H_{eq}, H-4), 1.18 (s, 9 H, OCOC(C*H*$_3$)$_3$).

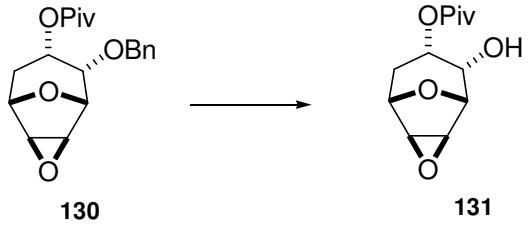
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.3 (C_q, O*C*OC(CH$_3$)$_3$), 137.5 (C_q, Ar-C), 128.4/127.9/127.7 (CH, Ar-C), 73.3 (CH, C-2), 72.7 (CH, C-1), 71.5 (CH, O*C*H$_2$Ph), 71.0 (CH, C-3), 53.8 (CH, C-6), 52.9 (CH, C-7), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 32.2 (CH$_2$, C-4), 27.1 (CH$_3$, OCOC(*C*H$_3$)$_3$).

IR (neat): 2948 w, 2869 w, 1719 vs, 1455 m, 1397 m, 1367 m, 1284 m, 1163 ws, 1109 m, 1044 s, 1030 w, 865 s, 741 s, 694 s.

EI MS (rt): 332 (26, M^+), 241 72), 177 (2), 157 (15), 139 (63), 132 (13), 111 (14), 95 (15), 91 (100), 85 (62), 81 (12), 69 (27).

7α-Pivaloyloxy-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonan-6α-ol ***131***



130 **131**

According to GP4, a solution of epoxide **130** (2.33 g, 7 mmol, 1 eq), AcOH (1 ml) and a catalytic amount of Pd/C (10% Pd) in EA (49 ml) were hydrogenated for 16 h at rt. Column chromatography (CH/MTBE 1:1) afforded epoxy alcohol **131**.

Yield: 1.51 g (6.23 mmol), 89 % white crystals

$C_{12}H_{18}O_5$ [242.27 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.26 (dm, *J* = 4.8, 0.75 Hz, 1 H, H-3), 4.24 (bd, *J* = 4.3 Hz, 1 H, H-5), 4.22 (bd, *J* = 3.7 Hz, 1 H, H-1), 4.10 (tr, *J* = 4.6 Hz, 1 H, H-2), 3.83 (d, *J* = 3.0 Hz, 1 H, H-7), 3.60 (d, *J* = 3.0 Hz, 1 H, H-6), 2.28 (dtr, *J* = 15.7, 4.8 Hz, 1 H, H_{ax}, H-4), 1.81 (d, *J* = 15.7 Hz, 1H, H_{eq}, H-4), 1.23 (s, 9 H, OCOC(C*H*$_3$)$_3$).

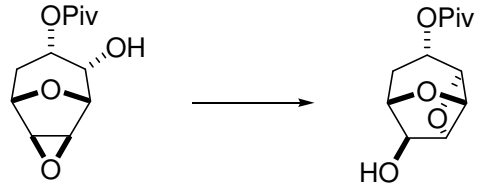
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

179.0 (C_q, O*C*OC(CH$_3$)$_3$), 73.3 (CH, C-1), 70.7 (CH, C-5), 68.0 (CH, C-3), 67.7 (CH, C-2), 53.6 (CH, C-6), 52.5 (CH, C-7), 38.8 (C_q, OCO*C*(CH$_3$)$_3$), 31.6 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$).

IR (neat): 3448 w, 2953 w, 2870 w, 1717 vs, 1477 m, 1393 m, 1279 ws, 1164 ws, 1034 vs, 856 vs, 719 s.

EI MS (rt): 242 (4, M^+), 228 (4), 171 (4), 157 (14), 140 (35), 122 (12), 111 (16), 103 (13), 99 (27), 91 (4), 87 (4), 85 (92), 81 (38), 71 (21), 68 (100).

4α-Pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***132***



131 **132**

Following GP5, $BF_3 \cdot OEt_2$ (1.3 ml, 10.5 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **131** (1.21 g, 5.0 mmol, 1 eq) in DCM (34 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 8 h. Purification of the crude product by column chromatography (CH/MTBE 1:1) yielded oxetane **132** as a white solid.

Yield: 681 mg (2.81 mmol), 56% white solid

$C_{12}H_{18}O_5$ [242.27 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.32 (dd, *J* = 5.9, 4.3 Hz, 1 H, H-1), 4.95 (m, 1 H, H-2), 4.93 (m, 1H, H-3), 4.89 (dm, *J* = 5.2 Hz, 1 H, H-5), 4.56(bd, *J* = 9.7 Hz, H-7), 4.24 (d, *J* = 7.4 Hz, 1 H, H-6), 2.70 (dddd, *J* = 13.5, 9.7, 8.8, 0.9 Hz, 1 H, H_{eq}, H-4), 2.00 (d, *J* = 7.4 Hz, 1 H, OH), 1.78 (ddd, *J* = 13.9, 8.5, 1 Hz, 1H, H_{ax}, H-4), 1.18 (s, 9 H, $OCOC(CH_3)_3$).

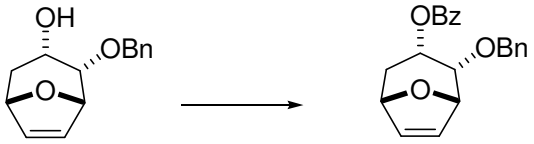
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.8 (C_q, $OCOC(CH_3)_3$), 89.8 (CH, C-2), 82.1 (CH, C-5), 80.3 (CH, C-7), 78.5 (CH, C-6), 74.7 (CH, C-1), 68.0 (CH, C-3), 38.7 (C_q, $OCOC(CH_3)_3$), 27.4 (CH_2, C-4), 27.0 (CH_3, $OCOC(CH_3)_3$).

IR (neat): 3233 w, 2958 wm, 1726 vs, 1479 m, 1282 m, 1159 vs, 1075 s, 1042 vs, 988 vs, 938 m, 852 m.

EI MS (rt): 243 (3, M^+), 197 (2), 181 (9), 157 (22), 140 (77), 122 (53), 113(41), 97 (67), 84 (100), 68 (48).

2α-Benzyloxy-3α-benzoyloxy-8-oxabicyclo[3.2.1]oct-6-ene ***134***



125 **134**

To a solution of the alcohol **125** (2.32 g, 10.0 mmol, 1 eq) in pyridine (2.6 ml) and THF (3.5 ml) were added DMAP (37 mg, 0.3 mmol, 0.03 eq) and benzoyl chloride (2.6 ml, 22.5 mmol, 2.25 eq) at 0°C. The mixture was stirred for 1 h at that temperature and then overnight at rt. The reaction was quenched with water and MTBE and the aqueous layer was extracted with MTBE (3x). The combined organic phase was washed with 2N HCl, with sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvents the crude product was purified by column chromatography (MTBE/CH 1:6) to afford benzoate **134**.

Yield: 3.16 g (9.4 mmol), 94 % yellowish solid

$C_{21}H_{20}O_4$ [336.38 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

8.08 (m, 2 H, *o*-Ar'-H), 7.60 (m, 1 H, *p*-Ar'-H 7), 7.48 (m, 2 H, *m*-Ar'-H), 7.41-7.31 (m, 5 H, Ar-H), 6.56 (ddd, *J* = 6.1, 1.8, 0.6 Hz, 1 H, H-7), 6.39 (dd, *J* = 6.1, 1.7 Hz, 1 H, H-6), 5.75 (trm, *J* = 5.3, 1.2 Hz, 1 H, H-3), 4.75 (m, 1 H, H-1), 4.68 (m. 1 H, H-5), 4.60 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.45 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 3.92 (dd, *J* = 5.2, 3.9 Hz, 1 H, H-2), 2.32 (ddd, *J* = 15.1, 5.3, 4.0 Hz, 1 H, H_{ax}, H-4), 1.8 (dtr, *J* = 15.2, 1.3 Hz, 1H, H_{eq}, H-4)

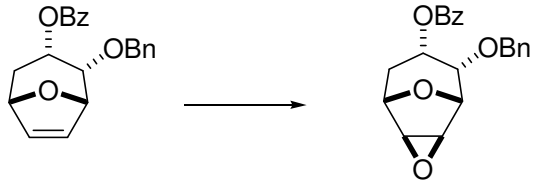
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.8 (C_q, O*C*OPh), 137.9 (C_q, Ar-C), 134.8 (CH, *p*-Ar'-C), 134.5 (CH, C-6), 132.2 (CH, C-7), 130.6 (C_q, Ar'-C), 129.7/128.9 (CH, Ar'-C), 128.3/127.7/127.6 (CH, Ar-C), 79.0 (CH, C-5), 77.9 (CH, C-1), 73.9 (CH, C-2), 71.4 (CH_2, O*C*H$_2$Ph), 66.9 (CH, C-3), 32.1 (CH_2, C-4).

IR (neat): 2947 w, 2873 m; 1705 vs, 1453 m, 1280 wvs, 1096 m, 1028 m, 1006 m, 941 m, 885 m, 751 s, 713 s, 700 vs.

EI MS (rt): no M^+, 244 (29), 214 (37), 161 (34), 123 (55), 105 (100), 91 (65), 77 (36).

6α-Benzyloxy-7α-benzoyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]-nonane ***135***



134 **135**

Following GP3, *m*-CPBA (70-75%, 4.53 g, 19.7 mmol, 2.1 eq) was added portionwise to a solution of the benzoate **134** (3.16 g, 9.4 mmol, 1 eq) in DCM (50 ml) at 0°C. The mixture was stirred for 1.5 h at 0°C and then overnight at rt. Extractive workup followed by column chromatography (MTBE/CH 1:4) afforded the epoxide **135** as a pale syrup which foams turning into a white solid.

Yield: 9.27 g (27.9 mmol), 99% white solid

$C_{21}H_{20}O_5$ [352.38 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

8.02 (m, 2 H, *o*-Ar'-H), 7.57 (m, 1 H, *p*-Ar'-H 7), 7.45 (m, 2 H, *m*-Ar'-H), 7.32-7.21 (m, 5 H, Ar-H), 5.74 (btr, *J* = 4.4 Hz, 1 H, H-3), 4.64 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.47 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.28/4.27 (bs, *J* = 4.5 Hz, 2 H, H-1/H-5), 4.04 (d, *J* = 3.1 Hz, 1 H, H-7), 3.84 (tr, *J* = 4.5 Hz, 1 H, H-2), 3.74 (d, *J* = 3.1 Hz, 1 H, H-6), 2.31 (dtr, *J* = 15.7, 4.6 Hz, 1 H, H_{ax}, H-4), 1.96 (d, *J* = 15.8 Hz, 1H, H_{eq}, H-4).

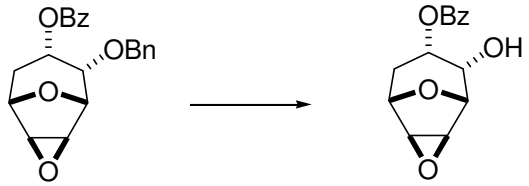
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

165.6 (C_q, O*C*OPh), 137.4 (C_q, Ar-C), 133.2 (CH, *p*-Ar'-C), 130.0 (C_q, Ar'-C), 129.5/128.5 (CH, Ar'-C), 128.3/127.7/127.6 (CH, Ar-C), 73.2 (CH, C-2), 72.7 (CH, C-1), 71.5 (CH_2, O*C*H_2Ph), 71.1 (CH, C-5), 65.8 (CH, C-3), 53.9 (CH, C-6), 52.9 (CH; C-7), 32.2 (CH_2, C-4).

IR (neat): 3031 m, 2955 w, 1714 s, 1452 m, 1367 m, 1313 m, 1269 vs, 1113 s, 1096 s, 1025 m, 967 m, 856 vs, 708 vs.

EI MS (rt): 352 (2, M^+), 261 (17), 191 (3), 139 (19), 111 (4), 105 (100), 91 (56), 77 (12).

7α-Benzoyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6α-ol ***136***



135 **136**

Following GP4, a solution of epoxide **135** (1.16 g, 3.3 mmol, 1 eq), AcOH (0.4 ml) and a catalytic amount of Pd/C (10% Pd) in MeOH (25 ml) was hydrogenated overnight at rt. Column chromatography (CH/MTBE 1:2) afforded epoxy alcohol **136**.

Yield: 779 mg (2.97 mmol), 90 % white crystals

$C_{14}H_{14}O_5$ [262.26 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.99 (m, 2 H, *o*-Ar'-H), 7.60 (m, 1 H, *p*-Ar'-H 7), 7.46 (m, 2 H, *m*-Ar'-H), 5.54 (btr, *J* = 4.8, 0.8 Hz, 1 H, H-3), 4.29 (d, *J* = 4.3 Hz, 1 H, H-5), 4.26 (d, *J* = 4.3 Hz, 1 H, H-1), 4.18 (dd, *J* = 9.3, 4.8 Hz, 1 H, H-2), 3.96 (d, *J* = 3.0 Hz, 1 H, H-7), 3.74 (tr, *J* = 3.0 Hz, 1 H, H-6), 2.53 (bs, 1 H, OH), 2.35 (dtr, *J* = 15.7, 4.7 Hz, 1 H, H_{ax}, H-4), 1.97 (d, *J* = 15.7 Hz, 1H, H_{eq}, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

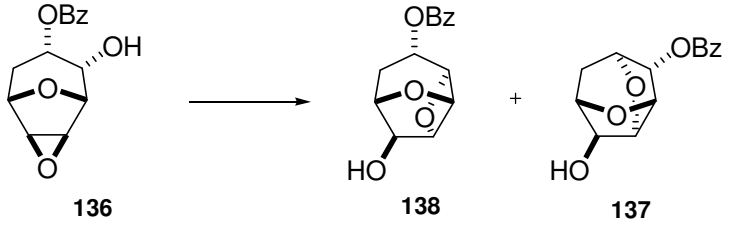
166.8 (C_q, O*C*OPh), 133.5 (CH, *p*-Ar'-C), 129.6 (C_q, Ar'-C), 129.5-128.6 (CH, Ar'-C), 73.5 (CH, C-5), 70.8 (CH, C-1), 68.9 (CH, C-3), 67.7 (CH, C-2), 53.7 (CH, C-6), 52.6 (CH, C-7), 31.8 (CH_2, C-4).

IR (neat): 3461 m, 3401 w, 2970 m, 2930 m, 1711 s, 1365 m, 1271 s, 1118 m, 1024 s, 973 m, 858 s, 710 s.

EI MS (rt): no M^+, 190 (1), 148 (2), 122 (5), 111 (6), 105 (100), 97 (5), 94 (7), 84 (15), 81 (10), 77 (49), 68 (23).

EA: Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.06; H, 5.29.

4α-Benzoyloxy--2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***138*** *and 8α-Benzoyloxy-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol* ***137***



Following GP5, $BF_3 \cdot OEt_2$ (1.3 ml, 10.5 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **136** (1.21 g, 5.0 mmol, 1 eq) in DCM (34 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 8 h. Purification of the crude product by column chromatography (CH/MTBE 1:2) yielded a mixture of oxetane **138** and dioxatricycle **137** in a 2:1 ratio as a white solid. Compounds **137** and **138** were not separable by column chromatography.

Yield: 729 mg (3.01 mmol), 60% white solid

$C_{12}H_{18}O_5$ [242.27 g/mol]

Data for the main product **138**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

8.03 (m, 2 H, *o*-Ar'-H), 7.55 (m, 1 H, *p*-Ar'-H 7), 7.43 (m, 2 H, *m*-Ar'-H), 5.26 (dd, *J* = 6.2, 4.2 Hz, 1 H, H-1), 5.21 (dd, *J* = 8.8, 1.9 Hz, 1 H, H-3), 5.05 (dd, *J* = 6.0, 2.0 Hz, 1H, H-5), 5.01 (dd, *J* = 4.2, 1.5 Hz, 1 H, H-2), 4.62 (bd, *J* = 9.7 Hz, H-7), 4.29 (s, 1 H, H-6), 2.84 (dddd, *J* = 13.5, 9.3, 9.1, 0.6 Hz, 1 H, H_{eq}, H-4), 1.96 (ddd, *J* = 13.6, 8.6, 0.8 Hz, 1H, H_{ax}, H-4).

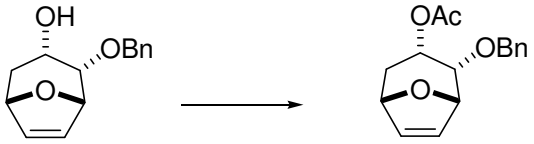
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

165.7 (C_q, Ar-C), 133.3 (CH, *p*-Ar'-C), 129.8 (C_q, Ar'-C), 129.5-128.3 (CH, Ar'-C), 89.9 (CH, C-2), 82.8 (CH, C-5), 80.4 (CH, C-7), 78.6 (CH, C-6), 74.8 (CH, C-1), 68.8 (CH, C-3), 27.6 (CH_2, C-4).

IR (neat): 3434 wm, 2970 wm, 1710 s, 1452 m, 1317 m, 1270 ws, 1068 s, 999 m, 923 m, 815 m, 771 m, 705 s.

EI MS (rt): 262 (4, M^+), 233 (2), 201 (2), 140 (10), 122 (13), 111 (10), 105 (100), 97 (8), 91 (3), 84 (33), 81 (19), 77 (33), 67 (5).

3α-Acetyloxy-2α-benzyloxy-8-oxabicyclo[3.2.1]oct-6-en ***139***



125 **139**

According to GP9, to a solution of the alcohol **125** (6.97 g, 30 mmol, 1 eq) in pyridine (8 ml) were added DMAP (0.22 g, 1.8 mmol, 0.06 eq) and acetic anhydride (14.7 ml, 156 mmol, 5.2 eq) at 0°C. The mixture was stirred for 1 h at 0°C and overnight at rt, then water and MTBE were added. Purification by column chromatography (CH/MTBE 5:1) afforded the acetate **139**.

Yield: 7.24 g (26.4 mmol), 88 % pale yellowish oil

$C_{16}H_{18}O_4$ [274.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.38-7.27 (m, 5 H, Ar-H), 6.34 (ddd, *J* = 6.1, 1.8, 0.5 Hz, 1 H, H-7), 6.26 (dd, *J* = 6.2, 1.7 Hz, 1 H, H-6), 5.49 (trm, *J* = 5.4, 1.1 Hz, 1 H, H-3), 4.68 (m, 1 H, H-1), 4.60 (m. 1 H, H-5), 4.58 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.45 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 3.80 (dd, *J* = 5.4, 3.9 Hz, 1 H, H-2), 2.21 (ddd, *J* = 15.2, 5.5, 4.0 Hz, 1 H, H_{ax}, H-4), 2.02 (s, 3 H, OCOC*H*$_3$), 1.66 (dtr, *J* = 15.2, 1.3 Hz, 1H, H_{eq}, H-4).

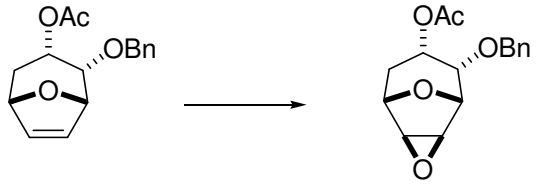
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

170.5 (C_q, O*C*OCH$_3$), 138.0 (C_q, Ar-C), 134.6 (CH, C-6), 132.1 (CH, C-7), 128.4/127.7/127.6 (CH, Ar-C), 79.0 (CH, C-5), 77.8 (CH, C-1), 73.8 (CH, C-2), 71.5 (CH_2, O*C*H$_2$Ph), 66.4 (CH, C-3), 32.0 (CH_2, C-4), 21.3 (CH_3, OCO*C*H$_3$).

IR (neat): 2950 mw, 1729 vs 1375 m, 1241 vs, 1204 s, 1098 s, 1029 vs, 883 s, 733 s, 698 s.

EI-MS (rt): no M^+, 231 (2), 214 (3), 183 (14), 168 (4), 141 (3), 123 (70), 108 (55), 95 (18), 91 (100), 81 (35), 67 (29).

7α-Acetyloxy-6α-benzyloxy-3,9-oxatricyclo-[3.3.1.0^{2,4}]-nonane ***140***



139 **140**

Following GP3, *m*-CPBA (70-75%, 10.95 g, 47.6 mmol, 2 eq) was added to a solution of the acetate **139** (6.53 g, 23.8 mmol, 1 eq) in DCM (60 ml) at 0°C. The mixture was stirred for 2 h at 0°C and then quenched. The crude product was purified by column chromatography (CH/MTBE 2:1) obtaining the epoxide **140**.

Yield: 5.54 g (19.1 mmol), 80 % pale yellow oil

$C_{16}H_{18}O_5$ [290.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.39-7.27 (m, 5 H, Ar-H), 5.48 (trm, *J* = 4.7, 0.8 Hz, 1 H, H-3), 4.61 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.45 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.21 (m, 1 H, H-1), 4.19 (m. 1 H, H-5), 3.84 (d, *J* = 3.1 Hz, 1 H, H-7), 3.72 (tr, *J* = 4.5 Hz, 1 H, H-2), 3.59 (d, *J* = 3.1 Hz, 1 H, H-6), 2.20 (dtr, *J* = 15.6, 4.7 Hz, 1 H, H_{ax}, H-4), 2.07 (s, 3 H, OCOC*H*$_3$), 1.80 (dtr, *J* = 15.6, 0.8 Hz, 1H, H_{eq}, H-4).

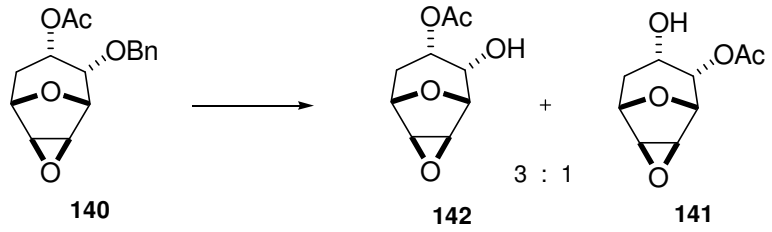
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

169.9 (C_q, O*C*OCH$_3$), 137.5 (C_q, Ar-C), 128.5/127.9/127.6 (CH, Ar-C), 73.2 (CH, C-2), 72.7 (CH, C-1), 71.6 (CH_2, O*C*H$_2$Ph), 71.1 (CH, C-5), 65.2 (CH, C-3), 53.7 (CH, C-6), 52.7 (CH, C-7), 32.1 (CH_2, C-4), 21.2 (CH_3, OCO*C*H$_3$).

IR (neat): 2954 mw, 1731 vs, 1374 m, 1240 vs, 1197 s, 1099 m, 1040 s, 1028 s, 883 m, 856 vs, 739 m, 699 s.

EI-MS (rt): 291 (2, M^+), 248 (1), 218 (1), 199 (37), 183 (3), 157 (12), 150 (7), 139 (23), 123 (8), 111 (24), 105 (8), 97 810), 91 (100), 83 (22), 69 (26).

7α-Acetyloxy-3,9-oxatricyclo-[3.3.1.0^{2,4}]-nonan-6α-ol ***142*** *and 6α-acetyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-7α-ol* ***141***



Following GP4, a solution of epoxide **140** (1.68 g, 5.8 mmol, 1 eq), AcOH (0.6 ml) and a catalytic amount of Pd/C (10% Pd) in MeOH (28 ml) was hydrogenated overnight at rt. Column chromatography (CH/MTBE 1:3) afforded a mixture of epoxy alcohol **136** and epoxy alcohol **141**, which were not separable by column chromatography.

Yield: 1.103 g (5.51 mmol), 95 % white solid

$C_9H_{12}O_5$ [200.18 g/mol]

Data for epoxy alcohol **142**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.26 (btr, *J* = 4.8 Hz, 1 H, H-3), 4.23 (m, 1 H, H-1), 4.22 (m. 1 H, H-5), 4.08 (tr, *J* = 4.6 Hz, 1 H, H-2), 3.81 (d, *J* = 3.1 Hz, 1 H, H-7), 3.59 (d, *J* = 3.1 Hz, 1 H, H-6), 2.28 (dtr, *J* = 15.7, 4.7 Hz, 1 H, H_{ax}, H-4), 2.12 (s, 3 H, OCOC*H$_3$*), 1.85 (d, *J* = 15.6 Hz, 1H, H_{eq}, H-4).

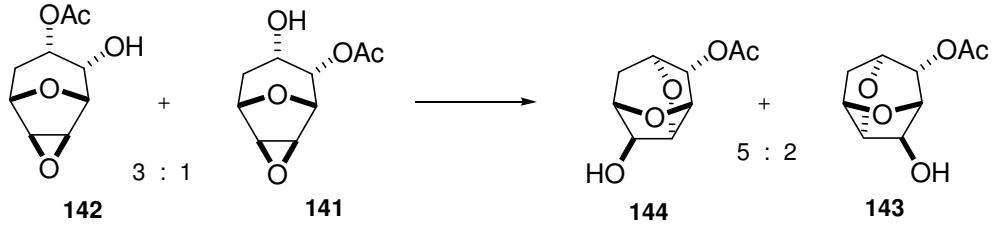
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

171.3 (C_q, O*C*OCH$_3$), 73.4 (CH, C-1), 70.8 (CH, C-5), 68.4 (CH, C-3), 67.6 (CH, C-2), 53.5 (CH, C-6), 52.4 (CH, C-7), 33.5 (CH_2, C-4), 21.2 (CH_3, OCO*C*H$_3$).

IR (neat): 3435 w, 2956 w, 1731 s, 1375 m, 1236 vs, 1196 m, 1052 s, 1029 vs, 977 m, 880 m, 856 s.

EI-MS (rt): 200 (4, M^+), 171 (2), 157 (14), 140 (21), 122 (14), 111 (44), 99 (48), 97 (54), 83 (78), 73 (76), 69 (100).

8α-Acetyloxy-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4ß-ol ***144*** *and 9α-acetyloxy-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4ß-ol* ***143***



Following GP5, $BF_3{\cdot}OEt_2$ (0.26 ml, 2.1 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **136** (200 mg, 1.0 mmol, 1 eq) in DCM (7 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 8 h. Purification of the crude product by column chromatography (CH/MTBE 1:3) yielded a mixture of dioxatricycle **144** and dioxatricycle **143** in a 5:2 ratio as a white solid. Compounds **144** and **143** were not separable by column chromatography.

Yield: 150 mg (0.75 mmol), 75% white solid

$C_9H_{12}O_5$ [200.18 g/mol]

Data for product **144**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.02 (s, 1 H, H-2), 4.69 (m, 1 H, H-5), 4.64 (m, 1 H, H-1), 4.36 (dtr, *J* = 4.8, 1.5 Hz, 1 H, H-3), 4.36 (dtr, *J* = 4.6, 1.4 Hz, 1 H, H-7), 4.09 (d, *J* = 9.99 Hz, 1 H, H-6), 2.08 (s, 1 H, OCOC*H*$_3$), 2.04 (d, 1 H, OH), 1.93 (ddd, *J* = 13.9, 10.2, 1.1 Hz, 1 H, H_{ax}, H-4), 1.84 (d, *J* = 13.9, 4.8, 1.1Hz, 1H, H_{eq}, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

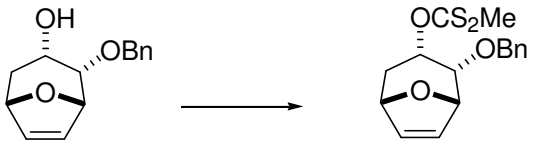
170.1 (C_q, O*C*OCH$_3$), 82.7 (CH, C-1), 80.4 (CH, C-5), 78.0 (CH, C-7), 77.7 (CH, C-2), 76.2 (CH, C-3), 75.9 (CH, C-6), 33.4 (CH_2, C-4), 20.9 (CH_3, OCO*C*H$_3$).

IR (neat): 3408 mw, 2971 m, 2940 m, 1734 vs, 1376 s, 1237 vs, 1218 vs, 1203 s, 1102 s, 1038 s, 994 s, 978 s, 886 vs, 754 m, 701 s.

EI-MS (rt): 200 (10, M^+), 171 (4), 158 (25), 140 (28), 122 (61), 111 (100), 97 (73), 94 (29), 84 (78), 81 (90), 69 (42).

11.2 Attempts to Section 4.2

Dithiocarbonic acid O-(2α–Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3 α-yl)-S-methylester ***144***



125 **144**

A solution of alcohol **125** (950 mg, 4.09 mmol, 1 eq) in THF (8 ml) was dropped slowly into a suspension of sodium hydride (60% dispersion in mineral oil, 262 mg, 6.54 mmol, 1.6 eq) in THF (8 ml) at 0°C. The reaction mixture was stirred for 1 h at rt and then carbon disulfide (0.74 ml, 12.27 mmol, 3 eq) was added. After 4 h, iodomethane (0.46 ml, 7.36 mmol, 1.8 eq) was added and the mixture was stirred overnight. The reaction was quenched with water and MTBE. The aqueous phase was extracted with MTBE (x5) and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (MTBE/CH 1:10).

Yield: 1.293 g (4.01 mmol), 98 % yellow solid

$C_{16}H_{18}O_3S_2$ [322.44 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.38-7.26 (m, 5 H, Ar-H), 6.41 (ddd, *J* = 6.1, 1.8, 0.5 Hz, 1 H, H-7), 6.29 (dd, *J* = 6.1, 1.6 Hz, 1 H, H-6), 6.24 (trm, *J* = 5.2, 1.1 Hz, 1 H, H-3), 4.72 (m, 1 H, H-5), 4.69 (m. 1 H, H-1), 4.55 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 4.40 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 3.93 (dd, *J* = 5.3, 3.9 Hz, 1 H, H-2), 2.52 (s, 1 H, OCS_2C*H*$_3$), 2.52 (ddd, *J* = 15.6, 5.3, 4.0 Hz, 1 H, H_{ax}, H-4), 1.91 (dd, *J* = 15.6, 1.1 Hz, 1H, H_{eq}, H-4).

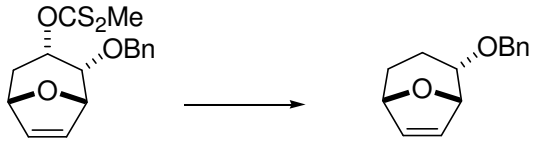
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

214.9 (C_q, O*C*S_2CH_3), 137.6 (C_q, Ar-C), 134.2 (CH, C-6), 132.4 (CH, C-7), 128.4/127.9/127.8 (CH, Ar-C), 78.8 (CH, C-5), 77.7 (CH, C-1), 76.1 (CH, C-2), 73.8 (CH, C-3), 71.3 (CH_2, O*C*H_2Ph), 31.5 (CH_2, C-4), 18.4 (CH_3, OCS_2*C*H_3).

IR (neat): 2951 m, 2860 m, 1739 wm, 1350 m, 1316 m, 1227 s, 1210 s, 1189 s, 1063 s, 1053 s, 1042 s, 1018 s, 898 s, 883 s, 769 vs, 704 vs.

EI MS (rt): 322 (2, M^+), 275 (3), 246 (2), 215 (8), 159 (2), 147 (21), 123 (6), 91 (100), 77 (4), 67 (8).

2α–Benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene ***145***



144 **145**

To a solution of dithiocarbonate **144** (6.23 g, 19.3 mmol, 1 eq) in anhydrous toluene (190 ml) under argon were added tributylstannanne (10.9 ml, 40.5 mmol, 2.1 eq) and AIBN (38 mg, 0.23 mmol, 0.012 eq). The mixture was refluxed 4 h under argon and the solvent was evaporated. The pure product **145** was obtained by column chromatography (MTBE/CH 1:20).

Yield: 3.67 g (16.9 mmol), 88 % clear oil

$C_{14}H_{16}O_2$ [216.28 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.40-7.26 (m, 5 H, Ar-H), 6.22 (dd, *J* = 6.1, 1.8 Hz, 1 H, H-7), 6.16 (dd, *J* = 6.1, 1.8 Hz, 1 H, H-6), 4.74 (m, 1 H, H-5), 4.68 (m. 1 H, H-1), 4.58 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 4.53 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 3.58 (ddd, *J* = 9.6, 5.6, 3.9 Hz, 1 H, H-2), 1.88 (m, 1 H, H-3), 1.76-1.56 (m, 3 H, H-3/H-4).

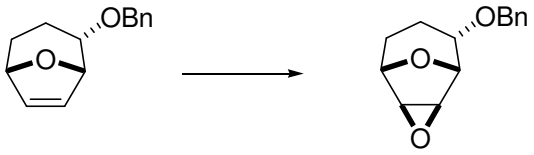
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

138.6 (C_q, Ar-C), 131.6 (CH, C-6), 129.3 (CH, C-7), 128.4/127.6/127.5 (CH, Ar-C), 79.4 (CH, C-5), 79.0 (CH, C-1), 72.0 (CH, C-2), 70.7 (CH_2, O*C*H$_2$Ph), 23.3 (CH_2, C-3/C-4).

IR (neat): 3436 w, 3030 w, 2948 wm, 2868 w, 1738 m, 1721 m, 1453 m, 1347 m, 1204 m, 1090 s, 1074 s, 1049 vs, 888 vs, 738 m, 714 vs, 697 vs.

ESI MS: Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.0650.

6α–Benzyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane ***146***



145 **146**

Following GP3, *m*-CPBA (70-75%, 6.35 g, 27.6 mmol, 2 eq) was added to a solution of alkene **145** (2.98 g, 13.8 mmol, 1 eq) in DCM (46 ml) at 0°C. The mixture was stirred for 4 h at 0 °C and then overnight at rt. The crude product was purified by column chromatography (MTBE/CH 1:4) obtaining the epoxide **146**.

Yield: 2.69 g (11.6 mmol), 84 % orange oil

$C_{14}H_{16}O_3$ [232.28 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

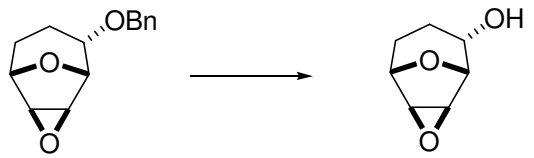
7.39-7.27 (m, 5 H, Ar-H), 4.60 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.56 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.23 (bd, *J* = 4.1 Hz, 1 H, H-5), 4.14 (bd, *J* = 3.6 Hz, 1 H, H-1), 3.79 (d, *J* = 3.1 Hz, 1 H, H-7), 3.70 (ddd, *J* = 10.2, 6.0, 4.2 Hz, 1 H, H-2), 3.52 (d, *J* = 3.1 Hz, 1 H, H-6), 1.94/1.62 (m, 2 H, H-3), 1.85/1.71 (m, 1 H, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

138.1 (C_q, Ar-C), 128.4/127.8/127.5 (CH, Ar-C), 73.1 (CH, C-2), 72.3 (CH, C-5), 71.6 (CH, C-1), 71.0 (CH_2, O*C*H$_2$Ph), 52.6 (CH, C-6), 51.4 (CH, C-7), 25.4 (CH_2, C-4), 24.4 (CH_2, C-3).

ESI MS: Calcd for $C_{14}H_{16}O_3$: 232.1099. Found: 232.0506.

3,9-Dioxatricyclo[3.3.1.0^{2,4}]nonan-6α-ol ***147***



146 **147**

According to GP4, a solution of epoxide **146** (100 mg, 0.43 mmol, 1 eq), AcOH (60 µL) and a catalytic amount of Pd/C (10% Pd) in EA (3 ml) was hydrogenated for 3 d at rt. The high

hydrophilicity of the compound demanded an intensive extractive workup followed by column chromatography (MTBE/CH 6:1) to obtain alcohol **147**.

Yield: 53 mg (0.37 mmol), 86 % white solid

$C_7H_{10}O_3$ [142.25 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

4.15 (bd, *J* = 4.4 Hz, 1 H, H-5), 4.11 (bd, *J* = 4.3 Hz, 1 H, H-1), 3.96 (b, 1 H, H-2), 3.81 (d, *J* = 3.1 Hz, 1 H, H-7), 3.54 (d, *J* = 3.1 Hz, 1 H, H-6), 2.28 (br, 1 H, OH), 1.96-1.85 (m, 2 H, H-3/H-4), 1.72 (m, 1 H, H-3), 1.61 (m, 1 H, H-4).

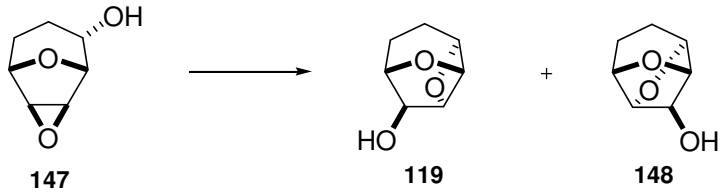
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

74.2 (CH, C-1), 71.4 (CH, C-5), 66.4 (CH, C-2), 52.5 (CH, C-6), 51.1 (CH, C-7), 26.4 (CH_2, C-4), 25.4 (CH_2, C-3).

IR (neat): 3371 s, 2958 m, 2931 m, 2869 m, 1738 wm, 1197 m, 1069 s, 1052 s, 1016 s, 959 s, 901 s, 838 vs, 788 s, 750 s.

ESI MS: Calcd for $C_7H_{10}O_3$: 142.0630. Found: 142.0190.

2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9ß-ol ***119*** *and hexahydro-1,4-dioxa-2,5-cycloinden-3ß-ol* ***148***



Following GP5, $BF_3{\cdot}OEt_2$ (0.49 ml, 3.93 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **147** (266 mg, 1.87 mmol, 1 eq) in DCM (12 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 16 h. Purification of the crude product by column chromatography (MTBE/CH 4:1) yielded a mixture of oxetane **119** and dioxacycle **148** as a white solid. Oxetane **119** and dioxacycle **148** were not separable by column chromatography.

Yield: 45 mg (0.32 mmol), 17% white solid

$C_7H_{10}O_3$ [142.15 g/mol]

Data for the main product **138**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
5.07 (dd, *J* = 5.9, 4.3 Hz, 1 H, H-1), 4.92 (dd, *J* = 4.3, 1.7 Hz, 1 H, H-5), 4.88 (trm, *J* = 4.71 Hz, 1H, H-2), 4.46 (dd, *J* = 9.53, 1.6 Hz, 1 H, H-7), 4.16 (s, 1 H, H-6), 1.93-1.63 (m, 4 H, H-3/H-4).

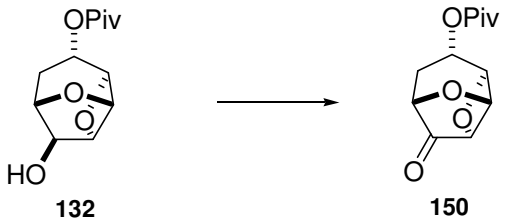
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
89.5 (CH, C-2), 82.9 (CH, C-5), 81.2 (CH, C-7), 79.1 (CH, C-6), 74.8 (CH, C-1), 22.2 (CH_2, C-4), 20.9 (CH_2, C-3).

IR (neat): 3390 w, 2969 wm, 2854 m, 1738 wm, 1203 m, 1085 s, 1041 s, 988 vs, 976 vs, 898 s, 843 s, 829 s, 751 s.

EI MS (rt): 142 (26, M^+), 124 (35), 97 (29), 83 (100), 70 (61), 67 (40), 57 (55), 55 (76).

11.3 Attempts to Section 4.3

*4α-Pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9-one **150***



132 **150**

To a solution of Py.SO_3 complex (526 mgr, 3.30 mmol, 4 eq) in DCM (2.3 ml) was added triethylamine (0.6 ml, 4.13 mmol, 5 eq) and DMSO (0.6 ml) at 0°C. A solution of oxetane **132** (200 mg, 0.83 mmol, 1 eq) in DCM (0.8 ml) was dropped into and the resulting reaction mixture was stirred at 0°C for 24 h. Then saturated NH_4Cl solution was added and the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_sSO_4), evaporated and purified by column chromatography (MTBE/CH 2:1) to afford the ketone **150**.

Yield: 165 mg (0.69 mmol), 83 % white solid
$C_{12}H_{16}O_5$ [240.25 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
5.32 (ddd, *J* = 6.1, 4.3, 0.7 Hz, 1 H, H-1), 5.26 dd, *J* = 5.2, 2.3 Hz, 1 H, H-5), 5.14 (ddd, *J* = 10.1, 9.1, 2.3 Hz, 1H, H-3), 4.68 (ddd, *J* = 4.3, 1.4, 0.5 Hz, 1 H, H-2), 4.37 (dm, *J* = 9.7 Hz, 1 H, H-7), 2.87 (ddd, *J* = 14.1, 9.5, 0.5 Hz, 1 H,

H_{eq}, H-4), 1.93 (ddd, *J* = 14.1, 8.0, 1 Hz, 1H, H_{ax}, H-4), 1.19 (s, 9 H, OCOC(CH_3)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

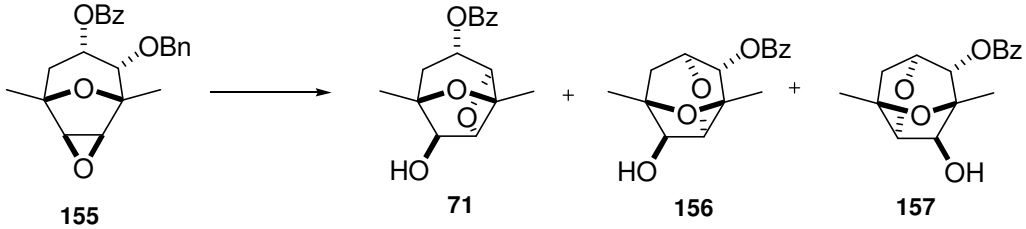
206.2 (C_q, C-6), 177.6 (C_q, O*C*OC(CH_3)$_3$), 83.5 (CH, C-2), 80.2 (CH, C-5), 74.3 (CH, C-1), 73.6 (CH, C-7), 66.4 (CH, C-3), 38.8 (C_q, OCO*C*(CH_3)$_3$), 27.4 (CH_2, C-4), 27.0 (CH_3, OCOC(*C*H_3)$_3$).

IR (neat): 3411 w, 3306 w, 2970 wm, 2873 m, 1730 s, 1281 m, 1142 vs, 1070 vs, 1040 vs, 984 s, 940 s, 905 s, 866 s.

EI MS (rt): 240 (28, M^+), 223 (2), 212 (21), 199 (5), 183 (3), 168 (65), 156 (64), 139 (47), 127 (78), 111 (63), 99 (31), 85 (100), 69 (65).

11.4 Attempts to Section 4.4

4α-Benzoyloxy-6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***71****, 8α-Benzyloxy-5,7-dimethyl-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol* ***156*** *and 9α-benzyloxy-5,7-dimethyl-2,6-dioxatricyclo[3.3.1. 0^{3,7}]nonan-4β-ol* ***157***



1 : 7 : 3.5

BCl_3 (1M solution in hexanes, 1.5 ml, 1.50 mmol, 2.2 eq) was dropped into a solution of epoxide **155** (259 mg, 0.68 mmol, 1 eq) in DCM (3.4 ml) at –78°C. After 2 h, water was added and the mixture was allowed to warm slowly to rt. The aqueous layer was extracted with DCM and the combined organic phase was dried and evaporated. The crude product was purified by column chromatography (MTBE/CH 1:1) and oxetane **71**, dioxatricycle **156** and dioxatricycle **157** were separated in high purity.

Yield: 174 mg (0.60 mmol), 88 % total yield

$C_{16}H_{18}O_5$ [290.31 g/mol]

Data for product **71**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
8.03 (m, 2 H, *o*-Ar-H), 7.54 (m, 1 H, *p*-Ar-H 7), 7.43 (m, 2 H, *m*-Ar'-H), 5.21 (dtr, *J* = 8.8, 1.9 Hz, 1 H, H-3), 4.78 (d, *J* = 1.6 Hz, 1 H, H-2), 4.66 (s, 1 H, H-7), 4.0.2 (s, 1 H, H-6), 2.49 (dd, *J* = 13.4, 8.8 Hz, 1 H, H_{eq}, H-4), 2.17 (bs, 1 H, OH), 2.05 (dd, *J* = 13.5, 9.2 Hz, 1H, H_{ax}, H-4), 1.67 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
165.9 (C_q, Ar-C), 133.2 (CH, *p*-Ar-C), 129.8 (C_q, Ar-C), 129.7/128.4 (CH, *o*- and *m*-Ar-C), 94.4 (CH, C-2), 86.1 (CH, C-7), 83.8/81.6 (C_q, C-1/C-5), 80.6 (CH, C-6), 70.1 (CH, C-3), 34.3 (CH_2, C-4), 21.6/19.2 (CH_3, 2 x CH_3).

IR ($CHCl_3$): 3403 m, 2981 w, 2939 m, 1715 vs, 1450 m, 1377 m, 1263 s, 1199 m, 1110 s, 1070 s, 981 m, 920 m, 826 m.

EI MS (rt): 290 (4, M^+), 229 (5), 185 (5), 168 (6), 150 (4), 125 (6), 112 (38), 105 (100), 95 (8), 77 (16).

Data for dioxatricycle **157**:

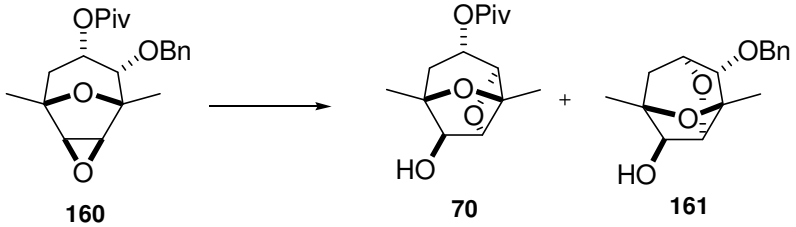
^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
8.06 (m, 2 H, *o*-Ar-H), 7.59 (m, 1 H, *p*-Ar-H 7), 7.46 (m, 2 H, *m*-Ar'-H), 4.97 (s, 1 H, H-2), 4.46 (d, *J* = 5.4 Hz, 1 H, H-3), 4.24 (bs, 1 H, H-7), 4.19 (s, 1 H, H-6), 2.19 (d, *J* = 11.8 Hz, 1 H, H_{ax}, H-4), 1.88 (dd, *J* = 11.8, 5.5 Hz, 1H, H_{eq}, H-4), 1.61 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
165.6 (C_q, Ar-C), 133.4 (CH, *p*-Ar-C), 129.6 (C_q, Ar-C), 129.7/128.5 (CH, *o*- and *m*-Ar-C), 87.0 (CH, C-6), 86.7 (C_q, C-5), 85.4 (C_q, C-1), 77.7 (CH, C-3), 77.0 (CH, C-7), 74.9 (CH, C-2), 43.8 (CH_2, C-4), 21.3/15.3 (CH_3, 2 x CH_3).

IR (neat): 3436 w, 2973 mw, 2936 m, 1718 s, 1451 m, 1378 m, 1319 m, 1260 s, 1094 s, 1070 s, 1038 m, 1026 s, 958 m, 937 m, 802 m, 709 vs.

EI MS (rt): 290 (14, M^+), 168 (16), 150 (7), 139 (12), 125 (11), 111 (9), 105 (100), 84 (41), 77 (34), 51 (10), 43 (37), 29 (6).

6,8-Dimethyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***70*** *and 9α-benzyloxy-5,7-dimethyl-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol* ***161***



BCl_3 (1M solution in hexanes, 1.8 ml, 1.76 mmol, 2.2 eq) was dropped into a solution of epoxide **160** (289 mg, 0.80 mmol, 1 eq) in DCM (15 ml) at –78°C. After 16 h water was added and the mixture was allowed to warm slowly to rt. The aqueous layer was extracted with DCM and the combined organic phase was dried and evaporated. The crude product was purified by column chromatography (MTBE/CH 1:2) and oxetane **70** and dioxatricycle **161** were separated in a 1.2:1 ratio.

Total yield: 86 %

Yield of product 70: 102 mg (0.38 mmol), 47 % white solid
$C_{14}H_{22}O_5$ [270.32 g/mol]

Yield of product 161: 86 mg (0.31 mmol), 39 % white solid
$C_{16}H_{20}O_4$ [276.32 g/mol]

Data for oxetane **70**:

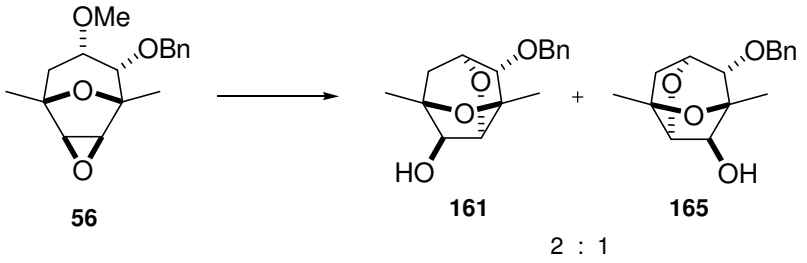
^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
4.92 (dtr, *J* = 8.8, 1.8 Hz, 1 H, H-3), 4.61 (d, *J* = 1.75 Hz, 1 H, H-2), 4.59 (s, 1 H, H-7), 3.95 (s, 1 H, H-6), 2.34 (ddd, *J* = 13.3, 8.7, 0.75 Hz, 1 H, H_{eq}, H-4), 1.87 (dd, *J* = 13.3, 9.2 Hz, 1H, H_{ax}, H-4), 1.61 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.18 (s, 9 H, OCOC(CH_3)$_3$)).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
177.9 (C_q, O*C*OC(CH_3)$_3$)), 94.3 (CH, C-2), 86.1 (CH, C-7), 83.8/81.6 (C_q, C-1/C-5), 80.6 (CH, C-6), 69.2 (CH, C-3), 38.8 (C_q, OCO*C*(CH_3)$_3$)), 34.1 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H_3)$_3$)), 21.6/19.1 (CH_3, 2 x CH_3).

IR ($CHCl_3$): 3403 m, 2981 w, 2939 m, 1715 vs, 1450 m, 1377 m, 1263 s, 1199 m, 1110 s, 1070 s, 981 m, 920 m, 826 m.

EI MS (rt): 270 (11, M^+), 209 (7), 186 (17), 168 (19), 139 (28), 125 (27), 112 (100), 95 (50), 85 (46).

8α-Benzyloxy-5,7-dimethyl-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol ***161*** *and 9α-benzyloxy-5,7-dimethyl-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol* ***165***



BCl_3 (1M solution in hexanes, 1.5 ml, 1.52 mmol, 2.2 eq) was dropped into a solution of epoxide **56** (200 mg, 0.69 mmol, 1 eq) in DCM (3.5 ml) at –78°C. After 5 min, water was added and the mixture was allowed to warm slowly to rt. The aqueous layer was extracted with DCM and the combined organic phase was dried and evaporated. The crude product was purified by column chromatography (MTBE/CH 1:2) and dioxatricycle **161** and dioxatricycle **165** were separated.

Yield: 187 mg (0.68 mmol), 98 % white solid

$C_{16}H_{20}O_4$ [276.32 g/mol]

Data for product **161**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.38-7.28 (m, 5 H, Ar-H), 4.65 (d, *J* = 12.3 Hz, 1 H, OC*H*$_2$Ph), 4.55 (d, *J* = 12.3 Hz, 1 H, OC*H*$_2$Ph), 4.32 (d, *J* = 4.1 Hz, 1 H, H-3), 4.16 (d, *J* = 0.5 Hz, 1 H, H-7), 3.79 (bs, 1 H, H-6), 3.65 (s, 1 H, H-2), 1.87 (dd, *J* = 13.8, 4.6 Hz, 1 H, H_{ax}, H-4), 1.69 (d, *J* = 13.7 Hz, 1H, H_{eq}, H-4), 1.56 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

137.9 (C_q, Ar-C), 128.4/127.8/127.7 (CH, Ar-C), 89.0 (C_q, C-1), 86.9 (CH, C-7), 85.2 (CH, C-2), 83.3 (C_q, C-5), 78.9 (CH, C-6), 77.1 (CH, C-3), 71.3 (CH, O*C*H$_2$Ph), 40.0 (CH_2, C-4), 17.7 (CH_3, 2 x CH_3).

IR (neat): 3393 mw, 2961 m, 2934 m, 1738 mw, 1453 m, 1378 s, 1355 m, 1233 m, 1217 m, 1205 m, 1076 vs, 1026 s, 885 s, 802 s, 735 s.

ESI MS: Calcd for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1295.

Data for product **165**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
7.40-7.27 (m, 5 H, Ar-H), 4.69 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.48 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.39 (d, *J* = 5.5 Hz, 1 H, H-3), 4.10 (s, 1 H, H-7), 4.09 (s, 1 H, H-6), 3.29 (d, *J* = 1.1 Hz, 1 H, H-2), 1.95 (d, *J* = 11.7 Hz, 1 H, H_{ax}, H-4), 1.81 (d, *J* = 11.6 Hz, 1H, H_{eq}, H-4), 1.52 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3).

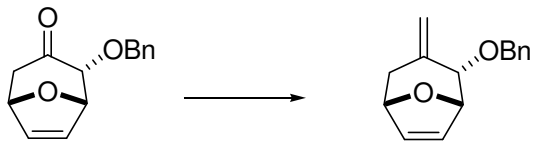
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
137.8 (C_q, Ar-C), 128.3/127.8/127.7 (CH, Ar-C), 87.0.0 (CH, C-6), 86.4 (C_q, C-1), 86.3 (C_q, C-5), 80.0 (CH, C-2), 76.7 (CH, C-7), 76.0 (CH, C-3), 71.5 (CH, O*C*H$_2$Ph), 43.5 (CH_2, C-4), 21.3/15.5 (CH_3, 2 x CH_3).

IR (neat): 3435 w, 2972 m, 2937 m, 2884 m, 1722 mw, 1453 m, 1374 m, 1242 s, 1200 s, 1079 vs, 1030 vs, 937 s, 806 s, 737 s, 697 s.

ESI MS: Calcd for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1846.

11.5 Attempts to Section 4.5

2α-Benzyloxy-3-methylene-8-oxabicyclo[3.2.1]oct-6-ene ***176***



***rac*-90** **176**

A suspension of methyltriphenylphosphonium bromide (3.829 g, 10.72 mmol, 2.7 eq) and potassium *tert*-butoxide (1.114 g, 9.93 mmol, 2.5 eq) in anhydrous THF (38 ml) was heated at reflux for 30 min. The dark yellow mixture was allowed to cool to room temperature before a solution of ketone ***rac*-90** (914 mg, 3.97 mmol, 1 eq) in dry THF (20 ml) was injected. The reaction mixture was heated for 4 h, then cooled to room temperature and quenched with water and MTBE. The organic layer was separated and the aqueous was extracted with MTBE. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by silica-gel column chromatography (MTBE/CH 1:10) furnished alkene **176**.

Yield: 726 mg (3.18 mmol), 80% pale yellowish oil

$C_{15}H_{16}O_2$ [228.29 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.41-7.26 (m, 5 H, Ar-H), 6.20 (dd, *J* = 6.1, 1.8 Hz, 1 H, H-7), 6.16 (dd, *J* = 6.1, 1.6 Hz, 1 H, H-6), 5.28 (m, 1 H, H-3'), 4.89 (m, 1 H, H-3'), 4.75/4.74 (bd, 2 x 1 H, H-1/H-5), 4.73 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 4.69 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 4.01 (bd, 1H, H-2), 2.55 (dm, *J* = 14.4 Hz, 1 H, H_{ax}, H-4), 2.10 (d, *J* = 14.4 Hz, 1H, H_{eq}, H-4).

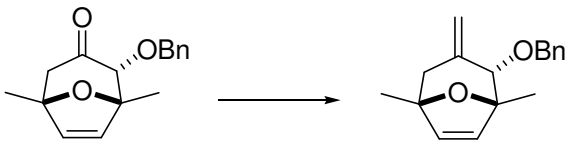
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

142 (C_q, C-3), 138.4 (C_q, Ar-C), 132.9 (CH, C-6), 130.0 (CH, C-7), 128.4/127.7/127.5 (CH, Ar-C), 112.3 (CH_2, C-3'), 79.2/79.0 (CH, C-1/C-5), 78.7 (CH, C-2), 72.4 (CH_2, O*C*H$_2$Ph), 35.8 (CH_2, C-4).

IR (neat): 3435 w, 3030 m, 2952 mw, 2861 m, 1721 vsw, 1454 m, 1343 m, 1268 m, 1229 m, 1216 m, 1096 vsw, 1048 s, 1027 s, 903 m, 881 m, 735 s, 713 s, 698 vs.

ESI MS: Calcd for $C_{15}H_{16}O_2$: 228.1150. Found: 228.1150.

2α-Benzyloxy-1,5-dimethyl-3-methylene-8-oxabicyclo[3.2.1]oct-6-ene ***177***



***rac*-49** **177**

A suspension of methyltriphenylphosphonium bromide (3.733 g, 10.45 mmol, 2.7 eq) and potassium *tert*-butoxide (1.085 g, 9.68 mmol, 2.5 eq) in anhydrous THF (37 ml) was heated at reflux for 30 min. The orange mixture was allowed to cool to room temperature and a solution of ketone ***rac*-49** (1.00 g, 3.87 mmol,1 eq) in anhydrous THF (19 ml) was added dropwise. The reaction mixture was heated for 3h, cooled to rt and quenched with water and MTBE. The organic phase was separated and the aqueous layer was extracted with MTBE. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (MTBE/CH 1:15).

Yield: 982 mg (3.83 mmol), 99% pale yellowish oil

$C_{17}H_{20}O_2$ [256.34 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.43-7.28 (m, 5 H, Ar-H), 5.94 (d, *J* = 5.8 Hz, 1 H, H-7), 5.88 (d, *J* = 5.8 Hz, 1 H, H-6), 5.15 (m, 1 H, H-3'), 4.83 (m, 1 H, H-3'), 4.76 (d, *J* = 11.4 Hz, 1 H, OC*H*$_2$Ph), 4.64 (d, *J* = 11.4 Hz, 1 H, OC*H*$_2$Ph), 3.86 (b, 1H, H-2), 2.43 (bd, *J* = 14.1 Hz, 1 H, H_{ax}, H-4), 2.20 (d, *J* = 14.1 Hz, 1H, H_{eq}, H-4), 1.43 (s, 1 H, CH_3), 1.40 (s, 1 H, CH_3).

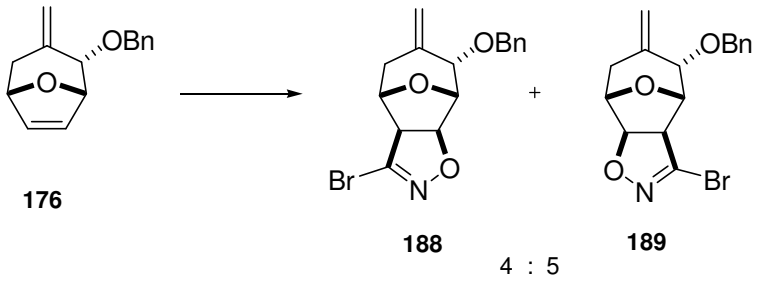
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

144.0 (C_q, C-3), 138.1 (C_q, Ar-C), 135.8 (CH, C-6), 133.3 (CH, C-7), 128.3/128.1/127.7 (CH, Ar-C), 110.5 (CH_2, C-3'), 86.9 (C_q, C-1), 85.3 (C_q, C-5), 84.0 (CH, C-2), 74.8 (CH_2, O*C*H$_2$Ph), 42.9 (CH_2, C-4), 23.1/20.5 (CH_3, 2 x CH_3).

IR (neat): 3435 w, 3030 m, 2971 m, 2930 mw, 2870 m, 1722 s, 1452 m, 1375 m, 1270 m, 1217 m, 1205 m, 1175 m, 1094 vsw, 929 m, 748 m, 699 s.

ESI MS: Calcd for $C_{17}H_{20}O_2$: 256.1463. Found: 256.1430.

10α-Benzyloxy-5-bromo-9-methylene-3,11-dioxa-4-aza-tricyclo[5.3.1.02,6]undec-4-ene ***188*** *and 8α-benzyloxy-5-bromo-9-methylene-3,11-dioxa-4-aza-tricyclo[5.3.1.02,6]undec-4-ene* ***189***



According to GP7, a solution of alkene **176** (92 mg, 0.403 mmol, 1 eq) in THF (0.8 ml) was added to a stirred solution of dibromoformaldoxime (163 mg, 0.806 mmol, 2 eq) in THF (0.8 ml). At 0°C KOH (50 mg, 0.887 mmol, 2.2 eq) was added. After standard extractive workup azatricyclo **188** and azatricyclo **189** were separated by column chromatography on silica gel (MTBE/CH 1:10) in a 4:5 ratio.

Yield: 54 mg (0.385 mmol), 77% white solid

$C_{16}H_{16}BrNO_3$ [350.21 g/mol]

Data for product **188**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.43-7.29 (m, 5 H, Ar-H), 5.32 (dd, *J* = 3.9, 1.9 Hz,1 H, H-3'), 5.00 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-3'), 4.85 (d, *J* = 8.7 Hz, 1 H, H-7), 4.72 (d, *J* = 12.9 Hz, 1 H, OC*H*$_2$Ph), 4.69 (d, *J* = 12.9 Hz, 1 H, OC*H*$_2$Ph), 4.59 (bdd, *J* = 4.3, 1.7 Hz, 1 H, H-5), 4.53 (bd, *J* = 4.3 Hz, 1 H, H-1), 4.03 (dm, *J* = 5.26 Hz, 1 H, H-2), 3.83 (d, *J* = 8.7 Hz, 1 H, H-6), 2.57 (dm, *J* = 14.4 Hz, 1 H, H_{ax}, H-4), 2.29 (dd, *J* = 14.4, 1.6 Hz, 1H, H_{eq}, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

140.0 (C_q, C-3), 137.4 (C_q, *C*Br=N), 137.7 (C_q, Ar-C), 128.5/128.0/127.7 (CH, Ar-C), 111.9 (CH_2, C-3'), 88.1 (CH, C-7), 83.3 (CH, C-5), 80.1 (CH, C-1), 76.6 (CH, C-2), 72.2 (CH_2, O*C*H$_2$Ph), 59.0 (CH, C-6), 37.0 (CH_2, C-4).

IR (neat): 2968 m, 2927 mw, 2874 m, 1738 m, 1373 m, 1281 m, 1268 m, 1215 s, 1109 s, 1077 vs, 1047 s, 1007 m, 946 m, 882 vs, 854 s, 756 s, 705 s, 682 vs.

EI-MS (rt): 351 (3, M^++1), 350 (1, M^+), 349 (3, M^+-1), 91 (100), 65 (7).

Data for product **189**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.41-7.28 (m, 5 H, Ar-H), 5.34 (dd, *J* = 3.8, 1.9 Hz,1 H, H-3'), 5.10 (d, *J* = 8.8 Hz, 1 H, H-6), 4.97 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-3'), 4.71 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 4.68 (d, *J* = 12.1 Hz, 1 H, OC*H*$_2$Ph), 4.60 (bdd, *J* = 3.9, 1.25 Hz, 1 H, H-5), 4.58 (bd, *J* = 4.5 Hz, 1 H, H-1), 3.96 (dm, *J* = 4.41 Hz, 1 H, H-2), 3.55 (d, *J* = 8.8 Hz, 1 H, H-7), 2.57 (dm, *J* = 14.1 Hz, 1 H, H_{ax}, H-4), 2.24 (dd, *J* = 14.2, 0.9 Hz, 1H, H_{eq}, H-4).

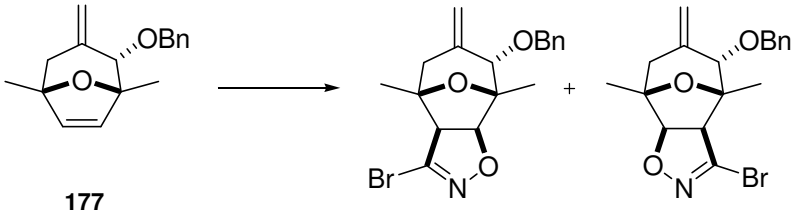
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

140.0 (C_q, C-3), 137.8 (C_q, *C*Br=N), 137.7 (C_q, Ar-C), 128.5/127.9/127.5 (CH, Ar-C), 111.6 (CH_2, C-3'), 85.4 (CH, C-6), 84.2 (CH, C-5), 79.1 (CH, C-1), 76.4 (CH, C-2), 72.2 (CH_2, O*C*H$_2$Ph), 62.4 (CH, C-7), 39.1 (CH_2, C-4).

IR (neat): 3030 m, 2958 mw, 2863 m, 1726 m, 1356 mw, 1208 s, 1100 vs, 1052 vs, 889 vs, 864 s, 739 s, 696 vs, 683 vs.

EI-MS (rt): 351 (9, M^++1), 350 (9, M^+), 349 (7, M^+-1), 91 (100), 77 (5), 65 (15).

10α-Benzyloxy-5-bromo-1,7-dimethyl-9-methylene-3,11-dioxa-4-aza-tricyclo[5.3.1.02,6]undec-4-ene ***190*** *and 8α-benzyloxy-5-bromo-1,7-dimethyl-9-methylene-3,11-dioxa-4-aza-tricyclo[5.3.1.02,6]undec-4-ene* ***191***



Following GP7, a solution of alkene (102 mg, 0.398 mmol, 1 eq) in THF (0.8 ml) was added to a stirred solution of dibromoformaldoxime (161 mg, 0.796 mmol, 2eq) in THF (0.8 ml). At 0°C KOH (49 mg, 0.876 mmol, 2.2 eq) was added. Standard extractive workup followed by column chromatography on silica gel (MTBE/CH 1:9) provided a mixture of azatricycle **190** and azatricycle **191** in a 1:1 ratio.

Yield: 87 mg (0.231 mmol), 58% white solid

$C_{18}H_{20}BrNO_3$ [378.26 g/mol]

Data for azatricycle **191**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.41-7.27 (m, 5 H, Ar-H), 5.24 (dd, *J* = 3.6, 1.9 Hz,1 H, H-3'), 4.95 (dd, *J* = 3.6, 1.7 Hz, 1 H, H-3'), 4.91 (d, *J* = 9.2 Hz, 1 H, H-6), 4.75 (d, *J* = 11.4 Hz, 1 H, OC*H*$_2$Ph), 4.59 (d, *J* = 11.4 Hz, 1 H, OC*H*$_2$Ph), 3.68 (bs, 1 H, H-2), 3.43 (d, *J* = 9.2 Hz, 1 H, H-7), 2.38 (dm, *J* = 13.6 Hz, 1 H, H_{ax}, H-4), 2.30 (dm, *J* = 13.6 Hz, 1H, H_{eq}, H-4), 1.50 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3).

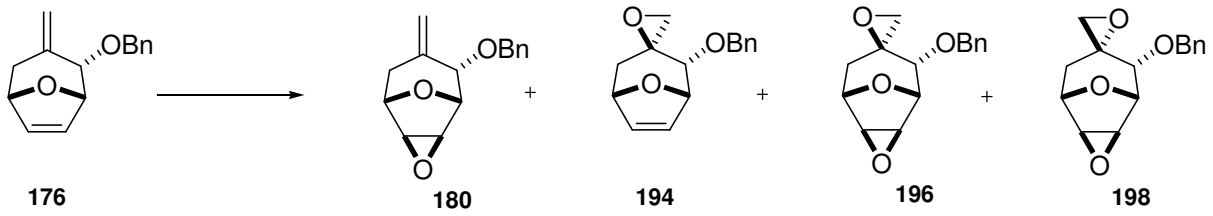
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

140.9 (C_q, C-3), 137.5 (C_q, *C*Br=N), 137.3 (C_q, Ar-C), 128.4-127.9 (CH, Ar-C), 110.8 (CH_2, C-3'), 89.0 (CH, C-6), 87.3/84.8 (C_q, C-1/C-5), 82.0 (CH, C-2), 74.1 (CH_2, O*C*H$_2$Ph), 64.3 (CH, C-7), 47.3 (CH_2, C-4), 22.5/17.2 (CH_3, 2 x CH_3).

IR (neat): 2971 m, 2935 mw, 2859 m, 1738 m, 1454 m, 1377 m, 1237 m, 1210 m, 1094 vs, 961 s, 894 vs, 858 s, 736 s, 698 vs.

EI-MS (rt): 379 (5, M^++1), 378 (2, M^+), 377 (5, M^+-1), 350 (2), 244 (8), 125 (8), 91 (100), 65 (6).

*6α-Benzyloxy-7-methylene-3,9-dioxa-tricyclo[3.3.1.02,4]nonane **180***



Following GP3, *m*-CPBA (70-75%, 410 mg, 1.70 mmol, 1.25 eq) was added to a solution of the alkene **176** (310 g, 1.36 mmol, 1 eq) in DCM (7 ml) at 0°C. The mixture was stirred for 16 h at 0°C and then quenched. The crude product was purified by column chromatography (CH/MTBE 4:1→2:1) and epoxide **180**, epoxide **194**, diepoxide **196** and diepoxide **198** were separated.

Total yield: 93 %

Yield of epoxides 180: 23 mg (0.095 mmol), 7 % oily solid

$C_{14}H_{16}O_3$ [244.11 g/mol]

Yield of epoxides 194: 80 mg (0.33 mmol), 24 % white solid

$C_{14}H_{16}O_3$ [244.11 g/mol]

Yield of diepoxide 196: 110 mg (0.42 mmol), 31 % oily white solid

$C_{15}H_{16}O_4$ [260.29 g/mol]

Yield of diepoxide 198: 110 mg (0.42 mmol), 31 % white solid

$C_{15}H_{16}O_4$ [260.29 g/mol]

Data for product **196**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.39-7.28 (m, 5 H, Ar-H), 4.65 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.52 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.34 (dd, *J* = 4.1, 1.3 Hz, 1H, H-5), 4.30 (d, *J* = 4.4 Hz, 1H, H-1), 3.83 (d, *J* = 4.3 Hz, 1H, H-2), 3.76 (d, *J* = 3.0 Hz, 1H, H-7), 3.52 (d, *J* = 3.0 Hz, 1H, H-6), 3.24 (dd, *J* = 5.9, 1,5 Hz, 1H, H-3'), 2.53 (d, *J* = 5.6 Hz, 1H, H-3'), 2.39 (ddd, *J* = 14.2, 4.3, 1.6 Hz, 1 H, H_{ax}, H-4), 1.53 (dd, *J* = 14.2, 1.0 Hz, 1H, H_{eq}, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

137.7 (C_q, Ar-C), 128.5/127.9/127.6 (CH, Ar-C), 74.6 (CH, C-1), 74.0 (CH_2, O*C*H_2Ph), 73.3 (CH, C-2), 72.4 (CH, C-5), 57.6 (C_q, C-3), 53.0 (CH, C-6), 52.0 (CH_2, C-3'), 51.9 (CH, C-7), 35.3 (CH_2, C-4).

EI-MS (rt): no M^+, 158 (38), 156 (100), 139 (96), 123 (17), 111 (55), 107 (20), 91 (92), 81 (29), 75 (24), 65 (18), 50 (17), 30 (15).

Data for product **198**:

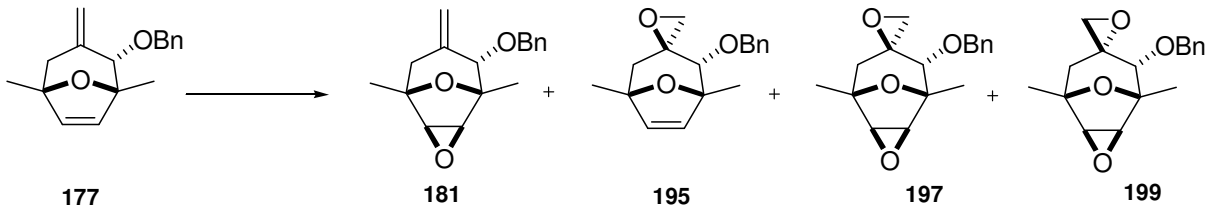
^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
7.41-7.28 (m, 5 H, Ar-H), 4.65 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 4.59 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 4.29 (d, *J* = 3.9 Hz, 1H, H-5), 4.25 (d, *J* = 3.9 Hz, 1H, H-1), 3.94 (d, *J* = 3.1 Hz, 1H, H-7), 3.87 (d, *J* = 4.0 Hz, 1H, H-2), 3.75 (d, *J* = 3.1 Hz, 1H, H-6), 2.87 (d, *J* = 4.9 Hz, 1H, H-3'), 2.45 (dd, *J* = 14.8, 4.4 Hz, 1 H, H_{ax}, H-4), 2.44 (d, *J* = 4.9 Hz, 1H, H-3'), 1.39 (d, *J* = 14.9 Hz, 1H, H_{eq}, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
137.2 (C_q, Ar-C), 128.7/128.3/128.2 (CH, Ar-C), 72.9 (CH_2, O*C*H_2Ph), 72.7 (CH, C-1), 72.4 (CH, C-2), 72.1 (CH; C5), 55.2 (C_q, C-3), 53.6 (CH, C-6), 52.6 (CH, C-7), 47.0 (CH_2, C-3'), 35.8 (CH_2, C-4).

IR (neat): 3285 m, 3031 m, 2954 mw, 1723 mw, 1454 m, 1342 m, 1217 m, 1096 s, 1049 s, 902 m, 856 m, 802 s, 734 s, 698 vs.

EI-MS (rt): no M^+, 199 (7), 169 (8), 158 (14), 156 (42), 139 (43), 111 (22), 105 (10), 91 (100), 77 (11), 69 (14), 55 (10), 41 (14).

*6α-Benzyloxy-1,5-dimethyl-7-methylene-3,9-dioxa-tricyclo[3.3.1.02,4]nonane **181***



Following GP3, *m*-CPBA (70-75%, 600 mg, 2.44 mmol, 1.25 eq) was added to a solution of the alkene **177** (500 g, 1.95 mmol, 1 eq) in DCM (10 ml) at 0°C. The mixture was stirred for 16 h at 0°C and then quenched. The crude product was purified by column chromatography (CH/MTBE 8:1→4:1) and diepoxide **197**, diepoxide **199** and a mixture of epoxide **181** and epoxide **195** were separated.

Total yield: 96 %

Yield of epoxides 181 and 195: 143 mg (0.53 mmol), 27 % clear oil

$C_{17}H_{20}O_3$ [272.34 g/mol]

Yield of diepoxide 197: 234 mg (0.86 mmol), 44 % oily white solid

$C_{16}H_{17}O_4$ [273.30 g/mol]

Yield of diepoxide 199: 133 mg (0.49 mmol), 25 % white solid

$C_{16}H_{17}O_4$ [273.30 g/mol]

Data for product **181**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.43-7.28 (m, 5 H, Ar-H), 5.09 (dd, *J* = 4.3, 2.1 Hz, 1 H, H-3'), 4.88 (dd, *J* = 4.3, 2.1 Hz, 1 H, H-3'), 4.71 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$Ph), 4.61 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$Ph), 3.80 (s, 1H, H-2), 3.39 (d, *J* = 3.1 Hz, 1 H, H-7), 3.38 (d, *J* = 3.1 Hz, 1 H, H-6), 2.49 (bd, *J* = 14.4 Hz, 1 H, H_{ax}, H-4), 2.35 (bd, *J* = 14.4 Hz, 1H, H_{eq}, H-4), 1.24 (s, 1 H, CH_3), 1.19 (s, 1 H, CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

142.6 (C_q, C-3), 138.2 (C_q, Ar-C), 128.3-127.5 (CH, Ar-C), 109.6 (CH_2, C-3'), 82.1 (CH, C-2), 79.1/77.3 (C_q, C-1/C-5), 74.1 (CH_2, O*C*H$_2$Ph), 56.9 (CH, C-6), 55.5 (CH, C-7), 42.6 (CH_2, C-4), 19.4/17.2 (CH_3, 2 x CH_3).

IR (neat): 3307 w, 2971 m, 2932 m, 1725 sw, 1453 m, 1375 s, 1228 m, 1217 m, 1095 vs, 986 m, 955 m, 890 m, 864 m, 699 s.

EI-MS (rt): 272 (2, M^+), 229 (6), 181 (9), 158 (33), 156 (92), 141 (31), 139 (87), 111 (49), 91 (100), 77 (14), 75 (23), 65 (14), 43 (39).

ESI MS: Calcd for $C_{17}H_{20}O_3$: 272.1414. Found: 272.0439.

Data for product **197**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.39-7.26 (m, 5 H, Ar-H), 4.65 (d, *J* = 11.2 Hz, 1 H, OC*H*$_2$Ph), 4.48 (d, *J* = 11.2 Hz, 1 H, OC*H*$_2$Ph), 3.56 (s, 1H, H-2), 3.54 (d, *J* = 3.0 Hz, 1H, H-7), 3.35 (d, *J* = 3.0 Hz, 1H, H-6), 3.23 (dd, *J* = 5.7, 1,5 Hz, 1H, H-3'), 2.54 (d, *J* = 5.7 Hz, 1H, H-3'), 2.28 (dd, *J* = 13.8, 1.5 Hz, 1 H, H_{ax}, H-4), 1.56 (dd, *J* = 13.8 Hz, 1H, H_{eq}, H-4), 1.40 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

137.7 (C_q, Ar-C), 128.4/128.1/127.9 (CH, Ar-C), 80.1/78.1 (C_q, C-1/C-5), 79.4 (CH, C-2), 75.6 (CH_2, O*C*H$_2$Ph), 58.5 (C_q, C-3), 57.3 (CH, C-6), 56.0 (CH, C-7), 52.2 (CH_2, C-3'), 42.0 (CH_2, C-4), 19.6/17.1 (CH_3, 2 x CH_3).

IR (neat): 3030m, 2972 m, 2933 m, 2875 m, 1726 mw, 1454 m, 1374 m, 1218 m, 1099 vs, 1077 s, 990 s, 959 m, 889 m, 868 m, 840 m, 807 m, 769 s, 695 s.

EI-MS (rt): no M^+, 219 (6), 160 (7), 158 (22), 156 (66), 141 (23), 139 (64), 111 (32), 91 (100), 75 (14), 65 (9), 50 (9), 43 (28).

Data for product **199**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
7.40-7.29 (m, 5 H, Ar-H), 4.71 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$Ph), 4.53 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$Ph), 3.73 (d, *J* = 3.0 Hz, 1H, H-7), 3.67 (s, 1H, H-2), 3.55 (d, *J* = 3.0 Hz, 1H, H-6), 2.70 (d, *J* = 4.6 Hz, 1H, H-3'), 2.40 (d, *J* = 4.6 Hz, 1H, H-3'), 2.31 (d, *J* = 14.6 Hz, 1 H, H_{ax}, H-4), 1.45 (dd, *J* = 14.6 Hz, 1H, H_{eq}, H-4), 1.43 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3).

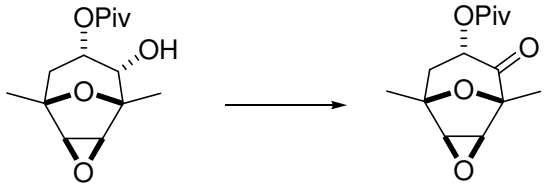
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
137.0 (C_q, Ar-C), 128.6/128.3/128.2 (CH, Ar-C), 80.5/78.2 (C_q, C-1/C-5), 78.4 (CH, C-2), 75.9 (CH_2, O*C*H_2Ph), 57.8 (CH, C-6), 56.6 (CH, C-7), 55.8 (C_q, C-3), 47.0 (CH_2, C-3'), 42.7 (CH_2, C-4), 19.6/17.3 (CH_3, 2 x CH_3).

IR (neat): 3467 w, 2971 m, 2932 mw, 1723 vs, 1454 m, 1375 m, 1253 s, 1217 s, 1095 vs, 1075 vs, 989 m, 953 m, 893 s, 747 s, 698 s.

EI-MS (rt): no M^+, 219 (7), 160 (14), 158 (27), 156 (77), 141 (25), 139 (72), 111 (39), 91 (100), 77 (14), 75 (18), 65 (14), 50 (13), 43 (41).

11.6 Attempts to Section 4.6

1,5-dimethyl-7α-Pivaloyloxy-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonan-6-one ***207***



160 **207**

According to GP8, PCC (23.28 g, 108.0 mmol, 4 eq), anhydrous sodium acetate (8.86 g, 108.0 mmol, 4 eq), 4 Å molecular sieves (previously activated) (27 g) and DCM (140 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol

160 (7.30 g, 27.0 mmol, 1 eq) in DCM (35 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **207**.

Yield: 7.17 g (26.7 mmol), 99 % white crystals

$C_{14}H_{20}O_5$ [268.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.46 (dd, *J* = 10.35, 8.6 Hz, 1 H, H-3), 3.49 (d, *J* = 2.8 Hz, 1 H, H-7), 3.41 (d, *J* = 2.9 Hz, 1 H, H-6), 2.59 (dd, *J* = 13.7, 10.4 Hz, 1 H, H_{ax}, H-4), 1.91 (dd, *J* = 13.7, 8.5 Hz, 1H, H_{eq}, H-4), 1.53/1.47 (s, 3 H, 2 x CH_3), 1.24 (s, 9 H, $OCOC(CH_3)_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

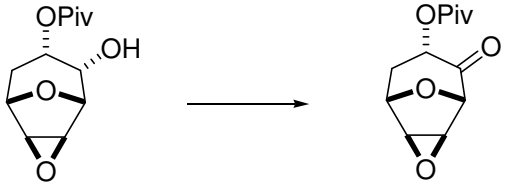
205.4 (C_q, C-2), 177.2 (C_q, $OCOC(CH_3)_3$), 85.1 (C_q, C-1), 76.5 (C_q, C-5), 70.0 (CH, C-3), 58.1 (CH, C-6), 56.2 (CH, C-7), 38.7 (C_q, $OCOC(CH_3)_3$), 36.0 (CH_2, C-4), 27.1 (CH_3, $OCOC(CH_3)_3$), 21.1/13.9 (CH_3, 2 x CH_3)

IR (neat): 2971 mw, 2939 mw, 1740 vs, 1719 vs, 1370 m, 1230 m, 1217 m, 1158 s, 995 m, 955 m, 843 m.

EI-MS (rt): 268 (6, M^+), 253 (2), 240 (4), 182 (57), 156 (59), 138 (69), 125 (33), 112 (66), 109 (36), 95 (59), 85 (100), 69 (51).

EA: Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.70; H, 7.29.

7α-Pivaloyloxy-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonan-6-one ***208***



131 **208**

According to GP8, PCC (11.3 g, 52.4 mmol, 4 eq), anhydrous sodium acetate (4.3 g, 52.4 mmol, 4 eq), 4 Å molecular sieves (previously activated) (13 g) and DCM (68 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol **131** (3.18 g, 13.1 mmol, 1 eq) in DCM (17 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **208**.

Yield: 2.99 g (12.4 mmol), 95% white crystals

$C_{12}H_{16}O_5$ [240.25 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.40 (dd, *J* = 10.5, 8.7 Hz, 1 H, H-3), 4.59 (dd, *J* = 8.6, 1.6 Hz, 1 H, H-5), 4.49 (s, 1 H, H-1), 3.74 (d, *J* = 2.9 Hz, 1 H, H-7), 3.59 (d, *J* = 2.9 Hz, 1 H, H-6), 2.88 (ddd, *J* = 13.6, 10.4, 8.7 Hz, 1 H, H_{ax}, H-4), 1.66 (ddd, *J* = 13.6, 8.7, 1.5 Hz, 1H, H_{eq}, H-4), 1.24 (s, 9 H, $OCOC(CH_3)_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

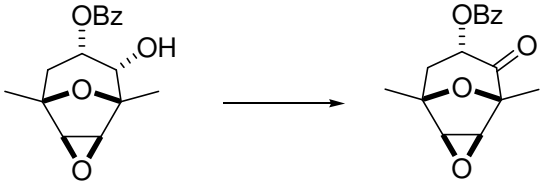
202 (C_q, C-2), 177.1 (C_q, $OCOC(CH_3)_3$), 79.0 (CH, C-1), 70.1 (CH, C-5), 69.8 (CH, C-3), 53.9 (CH, C-6), 52.1 (CH, C-7), 38.7 (C_q, $OCOC(CH_3)_3$), 28.3 (CH_2, C-4), 27.0 (CH_3, $OCOC(CH_3)_3$).

IR (neat): 2970 w, 2932 m, 1745 vs, 1726 vs, 1280 m, 1158 vs, 1145 vs, 1060 s, 1044 m, 857 s, 850 s, 798 s.

EI-MS (rt): 240 (6, M^+), 212 (3), 197 (7), 183 (6), 168 (18), 156 (7), 138 (19), 127 (48), 110 (24), 99 (33), 91 (100), 85 (100), 69 (28).

EA: Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.01; H, 6.47.

7α-Benzoyloxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6-one ***210***



155 **210**

Following GP8, PCC (1207 mg, 5.6 mmol, 4 eq), anhydrous sodium acetate (460 mg, 5.6 mmol, 4 eq), 4 Å molecular sieves (previously activated) (1.4 g) and DCM (7.6 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol **155** (406 mg, 1.4 mmol, 1 eq) in DCM (1.8 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **210**.

Yield: 494 mg (1.9 mmol), 96 % white solid

$C_{16}H_{16}O_5$ [288.30 g/mol]

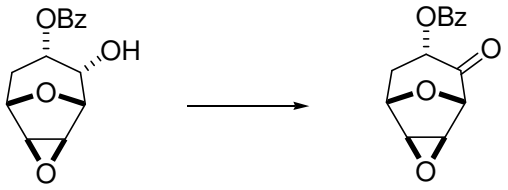
^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
8.04 (m, 2 H, *o*-Ar'-H), 7.58 (m, 1 H, *p*-Ar'-H 7), 7.45 (m, 2 H, *m*-Ar'-H), 5.75 (dd, *J* = 10.4, 8.5 Hz, 1 H, H-3), 3.54 (d, *J* = 2.8 Hz, 1 H, H-7), 3.45 (d, *J* = 2.8 Hz, 1 H, H-6), 2.73 (dd, *J* = 13.6, 10.4 Hz, 1 H, H_{ax}, H-4), 2.05 (dd, *J* = 13.8, 8.5 Hz, 1H, H_{eq}, H-4), 1.55/1.51 (s, 3 H, 2 x CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
205.2 (C_q, C-2), 165.2 (C_q, O*C*OPh), 133.4 (CH, *p*-Ar-C), 129.8 (CH, Ar-C), 129.2 (C_q, Ar-C), 128.4 (CH, Ar-C), 85.2 (C_q, C-1), 70.8 (C_q, C-5), 70.8 (CH, C-3), 58.1 (CH, C-6), 56.2 (CH, C-7), 36.3 (CH_2, C-4), 21.1/14.0 (CH_3, 2 x CH_3).

IR (neat): 2923 mw, 1740 s, 1721 vs, 1450 m, 1376 m, 1291 m, 1271 s, 1228 m, 1119 s, 1062 m, 865 m, 842 m, 823 m, 699 s.

EI MS (rt) : 290 (4, M^+ + 1), 229 (5), 185 (5), 168 (6), 150 (4), 125 (6), 112 (38), 105 (100), 95 (8), 77 (16).

7α-Benzoyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6-one ***212***



136 **212**

Following GP8, PCC (1724 mg, 8.0 mmol, 4 eq), anhydrous sodium acetate (656 mg, 8.0 mmol, 4 eq), 4 Å molecular sieves (previously activated) (2 g) and DCM (10 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol **136** (525 mg, 2.0 mmol, 1 eq) in DCM (2.6 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **212**.

Yield: 489 mg (1.88 mmol), 94 % white solid
$C_{14}H_{12}O_5$ [260.24 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)
8.06 (m, 2 H, *o*-Ar'-H), 7.59 (m, 1 H, *p*-Ar'-H 7), 7.46 (m, 2 H, *m*-Ar'-H), 5.71 (ddd, *J* = 10.5, 8.7, 0.5 Hz, 1 H, H-3), 4.65 (dd, *J* = 8.7, 1.6 Hz, 1 H, H-5), 4.56

(s, 1 H, H-1), 3.79 (d, *J* = 2.9 Hz, 1 H, H-7), 3.64 (tr, *J* = 2.9 Hz, 1 H, H-6), 3.03 (dd, *J* = 13.6, 8.7 Hz, 1 H, H_{ax}, H-4), 1.81 (dd, *J* = 13.6, 8.7, 1.5 Hz, 1H, H_{eq}, H-4).

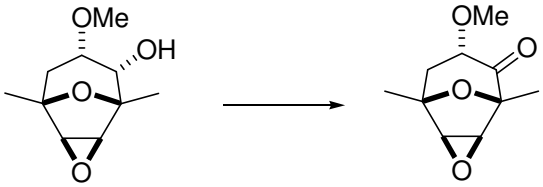
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

202.7 (C_q, C-2), 165.1 (C_q, O*C*OPh), 133.5 (CH, *p*-Ar'-C), 129.8 (CH, *o*-Ar'-C), 129.0 (C_q, Ar'-C), 128.4 (CH, *m*-Ar'-C), 79.1 (CH, C-1), 70.6 (CH, C-3), 70.1 (CH, C-5), 53.9 (CH, C-6), 52.7 (CH, C-7), 28.5 (CH_2, C-4).

IR (neat): 2970 m, 2919 mw, 1742 vs, 1720 vs, 1366 m, 1353 m, 1264 s, 1116 s, 1058 s, 842 s, 799 m, 705 s.

EI-MS (rt): no M^+, 204 (1), 188 (5), 176 (3), 162 (2), 127 (5), 105 (100), 77 (23), 69 (3).

7α-Methoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6-one ***214***



56 **214**

Following GP8, PCC (6661 mg, 30.4 mmol, 4 eq), anhydrous sodium acetate (2536 mg, 30.4 mmol, 4 eq), 4 Å molecular sieves (previously activated) (7.7 g) and DCM (40 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol **56** (1520 mg, 7.6 mmol, 1 eq) in DCM (10 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **214**.

Yield: 1491 mg (7.52 mmol), 99 % white solid

$C_{10}H_{14}O_4$ [198.23 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

3.58 (dd, *J* = 8.5, 5.8 Hz, 1 H, H-3), 3.47 (d, *J* = 3.0 Hz, 1 H, H-7), 3.42 (d, *J* = 3.0 Hz, 1 H, H-6), 3.40 (s, 3 H, OC*H*$_3$), 2.48 (dd, *J* = 14.3, 8.5 Hz, 1 H, H_{ax}, H-4), 1.88 (dd, *J* = 14.3, 5.9 Hz, 1H, H_{eq}, H-4), 1.46 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3).

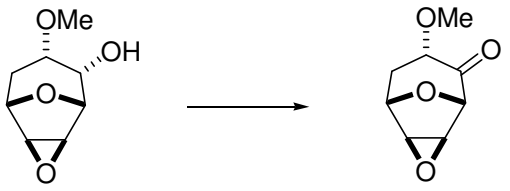
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

205.8 (C_q, C-2), 84.4 (C_q, C-1), 78.0 (CH, C-3), 77.0 (C_q, C-5), 58.5 (CH, OCH_3), 58.2 (CH, C-6), 56.4 (CH, C-7), 39.1 (CH_2, C-4), 20.6/20.5 (CH_3, 2 x CH_3)

IR (neat): 3467 w, 2971 mw, 2938 mw, 1736 vs, 1230 m, 1208 m, 1117 m, 1096 m, 1077 m, 863 m.

EI MS (rt): 198 (14, M^+), 170 (9), 141 (22), 127 (100), 112 (25), 109 (25), 98 (48), 95 (93), 85 (38), 71 (15)

7α-Methoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6-one ***215***



94 **215**

According to GP8, PCC (2138 mg, 9.9 mmol, 4 eq), anhydrous sodium acetate (812 mg, 9.9 mmol, 4 eq), 4 Å molecular sieves (previously activated) (2.5 g) and DCM (13 ml) were placed in a light-protected flask and stirred for 10 min at rt. A solution of the alcohol **94** (427 mg, 2.5 mmol, 1 eq) in DCM (3 ml) was added to the suspension and stirred for further 30 min. Filtration of the reaction mixture through silica gel and evaporation of the solvents provided ketone **215**.

Yield: 236 mg (1.39 mmol), 56 % yellowish oil

$C_8H_{10}O_4$ [170.16 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

4.50 (dd, *J* = 7.5, 1.5 Hz, 1 H, H-5), 4.40 (s, 1 H, H-1), 3.94 (ddd, *J* = 8.8, 6.5, 0.7 Hz, 1 H, H-3), 3.71 (d, *J* = 3.0 Hz, 1 H, H-7), 3.59 (d, *J* = 3.0 Hz, 1 H, H-6), 3.43 (s, 3 H, OC*H*$_3$), 2.80 (ddd, *J* = 14.0, 8.9, 7.6 Hz, 1 H, H_{ax}, H-4), 1.67 (ddd, *J* = 14.0, 6.5, 1.5 Hz, 1H, H_{eq}, H-4).

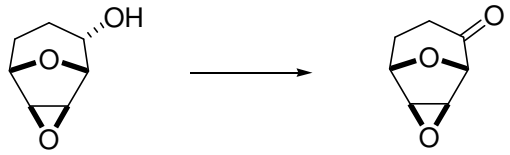
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

204.3 (C_q, C-2), 79.1 (CH, C-1), 77.6 (CH, C-3), 70.6 (CH, C-5), 58.65 (CH_3, O*C*H$_3$), 53.9 (CH, C-6), 52.1 (CH, C-7), 31.0 (CH_2, C-4).

IR (neat): 3435 w, 2970 w, 2835 m, 1732 vs, 1268 m, 1216 m, 1198 m, 1115 s, 1057 s, 1043 s, 980 s, 851 s, 794 m.

ESI MS: Calcd for $C_8H_{10}O_4$: 170.0579. Found: 170.0281.

3,9-Dioxatricyclo[3.3.1.0^{2,4}]nonan-6-one ***216***



147 **216**

A solution of the alcohol **147** (71 mg, 0.5 mmol,1 eq) in DCM (2.5 ml) was added to a stirred solution of Dess-Martin reagent (381 mg, 0.9 mmol, 1.8 eq) in DCM (5 ml). The mixture was stirred overnight at rt and then quenched with DCM (6 ml), $NaHCO_3$ (5 ml) and $Na_2S_2O_3$ (1 ml). After 5 min, the aqueous phase was separated and extracted with DCM (8x) and the combined organic layer was dried (Na_2SO_4) and concentrated. Purification by column chromatography (MTBE/CH 6:1) afforded ketone **216**.

Yield: 54 mg (0.385 mmol), 77% white solid

$C_7H_8O_3$ [140.14 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

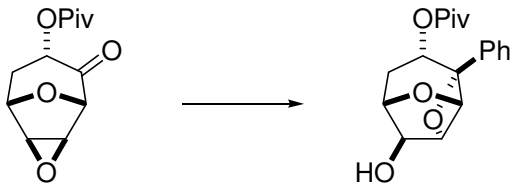
4.46 (d, *J* = 6.0 Hz, 1 H, H-5), 4.27 (s, 1 H, H-1), 3.72 (d, *J* = 2.9 Hz, 1 H, H-7), 3.66 (d, *J* = 2.9 Hz, 1 H, H-6), 2.54-2.45 (m, 1 H, H-3), 2.45-2.32 (2 H, H-3/H-4), 1.97-1.88 (m, 1 H, H-4).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

205.1 (C_q, C-2), 79.6 (CH, C-1), 70.9 (CH, C-5), 52.9 (CH, C-6), 52.4 (CH, C-7), 33.1 (CH_2, C-3), 24.4 (CH_2, C-4).

ESI MS: Calcd for $C_7H_8O_3$: 140.0473. Found: 140.8300.

3β-Phenyl–4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***217***



208 **217**

To a solution of ketone **208** (96 mg, 0.4 mmol, 1 eq) in THF (2 ml) was added dropwise phenylmagnesiumbromide solution (3 M in Et_2O, 0.27 ml, 0.8 mmol, 2 eq) at –30°C. The mixture was allowed to warm slowly to rt and stirring was continued for 4 h. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and extracted with MTBE. The combined organic phase was dried (Na_2SO_4), evaporated and the resulting crude product was purified by column chromatography (MTBE/CH 1:1).

Yield: 83 mg (0.26 mmol), 65 % white solid

$C_{18}H_{22}O_5$ [318.36 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

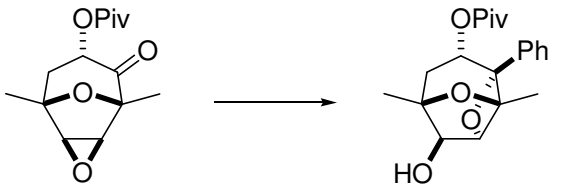
7.58-7.31 (m, 5 H, Ar-H), 5.31 (tr, *J* = 8.5 Hz, 1 H, H-3), 5.03 (d, *J* = 4.3 Hz , 1 H, H-5), 4.96 (ddd, *J* = 4.3, 1.7, 0.7 Hz, 1 H, H-1), 4.68 (d, *J* = 9.9 Hz, 1 H, H-7), 4.35 (s, 1H, H-6), 2.82 (ddd, *J* = 13.4, 9.7, 8.7 Hz, 1 H, H_{eq}, H-4), 1.77 (dd, *J* = 13.4, 8.5, 0.9 Hz, 1H, H_{ax}, H-4), 0.86 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.3 (C_q, O*C*OC(CH$_3$)$_3$), 139.9 (C_q, Ar-C), 128.2-124.4 (CH, Ar-C), 90.3 (C_q, C-2), 86.2 (CH, C-1), 81.3 (CH, C-5), 80.8 (CH, C-7), 78.3 (CH, C-6), 70.3 (CH, C-3), 38.5 (C_q, OCO*C*(CH$_3$)$_3$), 28.4 (CH_2, C-4), 26.9-27.7 (CH_3, OCOC(*C*H$_3$)$_3$).

IR (neat): 3436 w, 2971 m, 2956 m, 2873 m, 1723 vs, 1479 m, 1449 m, 1366 m, 1283 m, 1150 vs, 1096 s, 1054 vs, 990 s, 970 vs, 897 m, 754 s, 698 vs.

6,8-Dimethyl-3β-phenyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***218***



207 **218**

Ketone **207** (107 mg, 0.40 mmol, 1 eq) was dissolved in THF (2 ml) and cooled to –30°C. Phenylmagnesiumbromide solution (3 M in Et_2O, 0.27 ml, 0.8 mmol, 2 eq) was slowly added and the mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:2).

Yield: 98 mg (0.27 mmol), 68 % white solid

$C_{20}H_{26}O_5$ [346.42 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

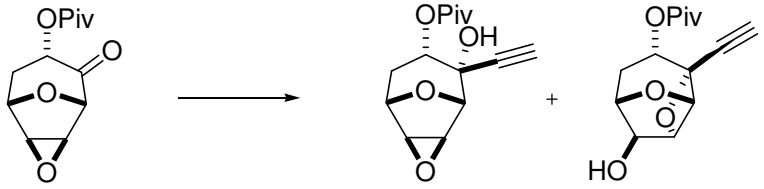
7.65 (m, 1 H, *o*-Ar'-H), 7.39 (m, 1 H, *p*-Ar'-H), 7.27 (m, 2 H, *m*-Ar'-H), 6.98 (m, 1 H, *o*-Ar'-H), 5.52 (tr, *J* = 8.8 Hz, 1 H, H-3), 4.63 (s, 1 H, H-7), 4.10 (s, 1H, H-6), 2.53 (dd, *J* = 13.4, 8.5 Hz, 1 H, H_{eq}, H-4), 1.99 (dd, *J* = 13.3, 9.0 Hz, 1H, H_{ax}, H-4), 1.53/1.16 (CH_3, 2 x CH_3), 0.78 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.5 (C_q, O*C*OC(CH$_3$)$_3$), 138.1 (C_q, Ar-C), 128.4-123.8 (CH, Ar-C), 92.5 (C_q, C-2), 91.6 (CH, C-7), 85.7 (C_q, C-1), 83.7 (C_q, C-5), 80.5 (CH, C-6), 70.5 (CH, C-3), 38.5 (C_q, OCO*C*(CH$_3$)$_3$), 35.6 (CH_2, C-4), 27.0 (CH_3, OCOC(*C*H$_3$)$_3$), 21.6 (CH_3, C5-*C*H$_3$), 18.1 (CH_3, C1-*C*H$_3$).

IR (neat): 3487 w, 2971 m, 2950 m, 2870 m, 1727 vs, 1480 m, 1448 m, 1369 m, 1284 m, 1147 vs, 1078 s, 1034 vs, 981 s, 958 vs, 826 m, 758 s, 698 vs.

6ß-Ethynyl-7α-pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6ß-ol ***221*** *and 3β–ethynyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol* ***222***



208 **221** **222**

3 : 1

To a solution of ketone **208** (96 mg, 0.4 mmol, 1 eq) in THF (2 ml) was added slowly ethynylmagnesiumchloride solution (0.5 M in THF, 1.6 ml, 0.8 mmol, 2 eq) at –30°C. The mixture was allowed to warm slowly to rt and stirred overnight. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and the resulting crude product was purified by column chromatography (MTBE/CH 1:4→1:2). Epoxy alcohol **221** and oxetane **222** were separated in a 5:1 ratio.

Yield: 69 mg (0.26 mmol), 65 % total yield

$C_{14}H_{18}O_5$ [266.29 g/mol]

Data for alcohol **221**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.24 (d, *J* = 5.0 Hz, 1 H, H-3), 4.31 (bd, *J* = 4.4 Hz , 1 H, H-1), 4.19 (bs, 1 H, H-5), 3.82 (d, *J* = 3.0 Hz, 1 H, H-7), 3.62 (d, *J* = 3.1 Hz, 1 H, H-6), 2.78 (s, 1 H, C≡C*H*), 2.65 (s, 1 H,), 2.50 (dtr, *J* = 15.6, 4.7 Hz, 1 H, H_{ax}, H-4), 1.76 (dtr, *J* = 15.6, 1.8 Hz, 1H, H_{eq}, H-4), 1.22 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

179.0 (C_q, O*C*OC(CH$_3$)$_3$), 83.7 (C_q, C-2), 76.0 (CH, C5/C≡*C*H), 74.6 (CH, *C*≡CH), 71.1 (CH, C-1/C-3), 53.3 (CH, C-6), 51.9 (CH, C-7), 38.8 (C_q, OCO*C*(CH$_3$)$_3$), 30.5 (CH$_2$, C-4), 27.1 (CH$_3$, OCOC(*C*H$_3$)$_3$).

Data for oxetane **222**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

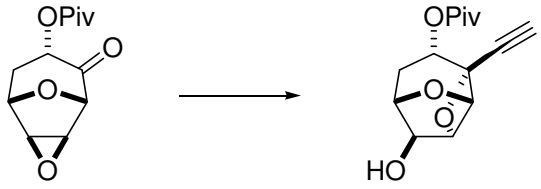
5.16 (d, *J* = 4.3 Hz, 1 H, H-5), 5.07 (dr, *J* = 8.7 Hz, 1 H, H-3), 4.97 (ddd, *J* = 4.3, 1.7, 0.6 Hz, 1 H, H-1), 4.60 (d, *J* = 9.9 Hz, 1 H, H-7), 4.23 (s, 1H, H-6),

2.84 (s, 1 H, C≡C*H*), 2.74 (ddd, *J* = 13.6, 9.7, 9.8, 8.8 Hz, 1 H, H_{eq}, H-4), 1.65 (ddd, *J* = 13.6, 8.6, 0.9 Hz, 1H, H_{ax}, H-4), 1.21 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.4 (C_q, O*C*OC(CH$_3$)$_3$), 87.3 (CH, C-1), 81.9 (C_q, C-2), 80.6 (CH, C-7), 79.9 (CH, C-5), 79.8 (C_q, *C*≡CH), 79.0 (CH, C≡*C*H), 77.9 (CH, C-6), 69.5 (CH, C-3), 38.8 (C_q, OCO*C*(CH$_3$)$_3$), 37.7 (CH_2, C-4), 27.8/27.1/26.9 (CH_3, OCOC(*C*H$_3$)$_3$).

3β–ethynyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***222***



208 **222**

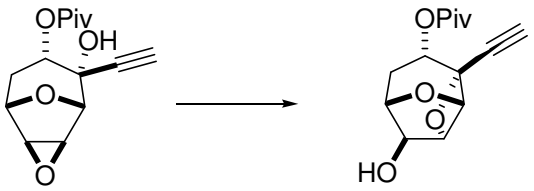
To a solution of ketone **208** (96 mg, 0.4 mmol, 1 eq) in THF (2 ml) was added slowly ethynylmagnesiumbromide solution (0.5 M in THF, 1.6 ml, 0.8 mmol, 2 eq) at –30°C. The mixture was allowed to warm slowly to rt and stirred overnight. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and the resulting crude product was purified by column chromatography (MTBE/CH 1:2) affording oxetane **222**.

Yield: 27 mg (0.10 mmol), 25% oily white solid

$C_{14}H_{18}O_5$ [266.29 g/mol]

Data for product **222**: See preceding reaction.

3β–Ethynyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***222***



221 **222**

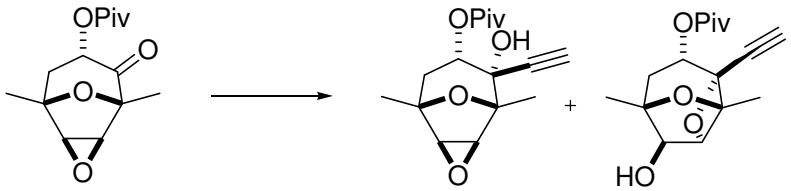
Following GP5, $BF_3 \cdot OEt_2$ (37 µl, 0.29 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **221** (38 mg, 0.14 mmol, 1 eq) in DCM (1.4 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 8 h. Purification of the crude product by column chromatography (CH/MTBE 1:2) yielded oxetane **222**.

Yield: 21 mg (0.08 mmol), 56% oily white solid

$C_{14}H_{18}O_5$ [266.29 g/mol]

Data for product **222**: See preceding reaction-

6β-Ethynyl-6,8-dimethyl-7α-pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6β-ol ***223*** *and 3β-ethynyl-6,8-dimethyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol* ***224***



207 **223** **224**

1 : 4

Ketone (107 mg, 0.40 mmol, 1 eq) was dissolved in THF (2 ml) and cooled to –30°C. Ethynylmagnesiumbromide solution (0.5 M in THF, 1.6 ml, 0.8 mmol, 2 eq) was slowly added and the mixture was stirred at rt overnight. After addition of aq. NH_4Cl solution and sat. aq. Na,K tartrate solution, the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:2). Alcohol **223** and oxetane **224** were separated in a 1.4 ratio.

Yield: 43 mg (0.148 mmol), 55 % total yield

$C_{16}H_{22}O_5$ [294.34 g/mol]

Data for oxetane **224**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

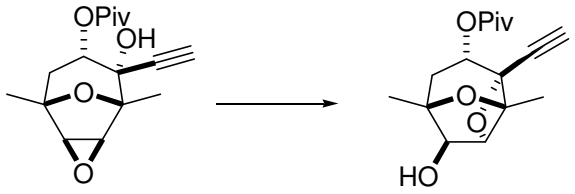
5.08 (tr, *J* = 8.8 Hz, 1 H, H-3), 4.61 (s, 1 H, H-7), 3.97 (s, 1H, H-6), 2.83 (s, 1 H, C≡C*H*), 2.43 (dd, *J* = 13.4, 8.5 Hz, 1 H, H_{eq}, H-4), 1.84 (dd, *J* = 13.3, 9.2 Hz, 1H, H_{ax}, H-4), 1.68/1.46 (CH_3, 2 x CH_3), 1.21 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.5 (C_q, O*C*OC(CH$_3$)$_3$), 93.0 (CH, C-7), 85.0 (C_q, C-2), 84.5 (C_q, C-1), 83.8 (C_q, C-5), 80.1 (CH, C-6), 80.0 (C_q, *C*≡CH), 78.5 (CH, C≡*C*H), 70.5 (CH, C-3), 38.8 (C_q, OCO*C*(CH$_3$)$_3$), 34.9 (CH_2, C-4), 27.1/27.0/26.9 (CH_3, OCOC(*C*H$_3$)$_3$), 21.4/17.8 (CH_3, 2 x CH_3).

IR (neat): 3463 w, 3289 mw, 2960 mw, 2932 m, 1726 s, 1713 vs, 1479 m, 1394 m, 1366 m, 1283 s, 1160 vs, 1064 m, 1037 vs, 1022 s, 987 s, 858 vs, 757 m.

3β-Ethynyl-6,8-dimethyl-4α-pivaloyloxy-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol ***224***



223 **224**

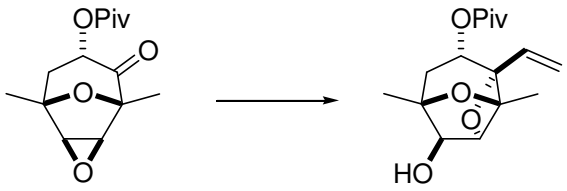
Following GP5, $BF_3{\cdot}OEt_2$ (72 µl, 0.50 mmol, 2.1 eq) was added dropwise to a solution of epoxy alcohol **223** (71 mg, 0.24 mmol, 1 eq) in DCM (2.5 ml) at 0°C. The mixture was allowed to warm slowly to rt and stirring was continued for 8 h. Purification of the crude product by column chromatography (CH/MTBE 1:2) yielded oxetane **224**.

Yield: 43 mg (0.15 mmol), 61% yellowish oil

$C_{16}H_{22}O_5$ [294.34 g/mol]

Data for oxetane **224**: See preceding reaction.

6,8-Dimethyl-4α-pivaloyloxy-3-vinyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9ß-ol ***225***



207 **225**

Ketone **207** (80 mg, 0.30 mmol, 1 eq) was dissolved in THF (1.5 ml) and cooled to –30°C. Vinylmagnesiumbromide solution (1 M in THF, 0.3 ml, 0.30 mmol, 2 eq) was slowly added and the mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 2:1).

Yield: 37 mg (0.13 mmol), 42 % white solid

$C_{16}H_{24}O_5$ [296.36 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

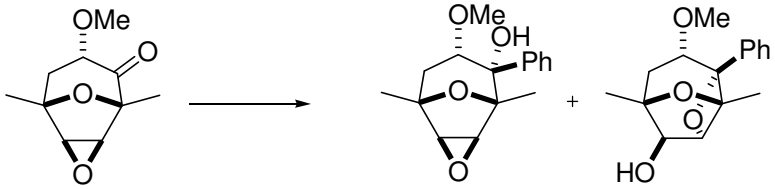
5.72 (dd, J_{trans} = 17.2 Hz, J_{cis} = 10.9 Hz, C*H*=CH_2), 5.47 (dd, J_{trans} = 17.2 Hz, J_{gem} = 1.8 Hz, CH=C*H*$_2$), 5.33 (3d, J_{cis} = 10.9 Hz, J_{gem} = 1.8 Hz, CH=C*H*$_2$), 5.12 (tr, *J* = 8.9 Hz, 1 H, H-3), 4.50 (s, 1 H, H-7), 4.00 (s, 1H, H-6), 2.38 (dd, *J* = 13.4, 8.6 Hz, 1 H, H_{eq}, H-4), 1.90 (dd, *J* = 13.4, 9.0 Hz, 1H, H_{ax}, H-4), 1.42/1.20 (CH_3, 2 x CH_3), 1.12 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.7 (C_q, O*C*OC(CH_3)$_3$), 134.4 (CH, C*H*=CH_2), 117.1 (CH_2, CH=C*H*$_2$), 91.5 (CH, C-7), 85.3 (C_q, C-2), 83.8 (C_q, C-1), 83.4 (C_q, C-5), 80.6 (CH, C-6), 69.4 (CH, C-3), 38.7 (C_q, OCO*C*(CH_3)$_3$), 35.2 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$), 21.5/17.2 (CH_3, 2 x *C*H$_3$).

IR (neat): 3463 w, 3289 mw, 2960 mw, 2932 m, 1726 s, 1713 vs, 1479 m, 1394 m, 1366 m, 1283 s, 1160 vs, 1064 m, 1037 vs, 1022 s, 987 s, 858 vs, 757 m.

7α-Methoxy-6,8-dimethyl-6β-phenyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6β-ol ***219*** *4α-methoxy-6,8-dimethyl-3β-phenyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]-nonan-9β-ol* ***220***



214 **219** **220**

5 : 2

To a solution of ketone **214** (99 mg, 0.50 mmol, 1 eq) in THF (2.5 ml) was added dropwise phenylmagnesiumbromide solution (3 M in Et_2O, 0.3 ml, 1.0 mmol, 2 eq) at -30°C. The mixture was allowed to warm slowly to rt and stirring was continued overnight. The reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution and extracted with MTBE. The combined organic phase was dried (Na_2SO_4), evaporated and the resulting crude product was purified by column chromatography (MTBE/CH 1:8→1:2). Alcohol **219** and oxetane **220** were separated in a 5:2 ratio.

Yield: 91 mg (0.33 mmol), 66% total yield

$C_{16}H_{20}O_4$ [276.33 g/mol]

Data for alcohol **219**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.68 (m, 2 H, *o*-Ar-H), 7.35 (m, 2 H, *m*-Ar-H), 7.29 (m, 1 H, *p*-Ar-H), 3.97 (d, *J* = 3.1 Hz, 1 H, H-7), 3.52 (d, *J* = 3.1 Hz, 1H, H-6), 3.24 (dd, *J* = 4.4, 1.4 Hz, 1 H, H-3), 2.92 (s, 3 H, OC*H$_3$*), 2.16 (dd, *J* = 15.1, 4.4 Hz, 1 H, H_{ax}, H-4), 1.89 (dd, *J* = 15.1, 1.4 Hz, 1H, H_{eq}, H-4), 1.39/1.13 (CH_3, 2 x CH_3).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

139.8 (C_q, Ar-C), 127.8/127.3/127.2 (CH, Ar-C), 83.9 (C_q, C-1), 83.7 (CH, C-3), 78.1 (C_q, C5), 74.9 (C_q, C2), 58.6 (CH, O*C*H$_3$), 58.4 (CH: C-6), 57.2 (CH, C-7), 35.5 (CH_2, C-4), 20.2/14.7 (CH_3, 2 x CH_3).

IR (neat): 3530 m, 2990 m, 2927 mw, 1715 mw, 1490 m, 1446 s, 1373 m, 1357 m, 1247 s, 1138 m, 1086 vs, 997 s, 931 vs, 856 s, 847 s, 763 s, 698 vs.

Data for oxetane **220**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

7.68 (b, 1 H, Ar-H), 7.39 (b, 2 H, Ar-H), 7.28 (m, 1 H, Ar-H), 7.20 (b, 1 H, Ar-H), 4.56 (s, 1 H, H-7), 4.07 (s, 1H, H-6), 3.95 (tr, *J* = 8.5 Hz, 1 H, H-3), 3.05

(s, 3 H, OC*H*$_3$), 2.52 (dd, *J* = 13.5, 8.5 Hz, 1 H, H_{eq}, H-4), 2.01 (dd, *J* = 13.5, 8.7 Hz, 1H, H_{ax}, H-4), 1.52/1.10 (CH_3, 2 x CH_3).

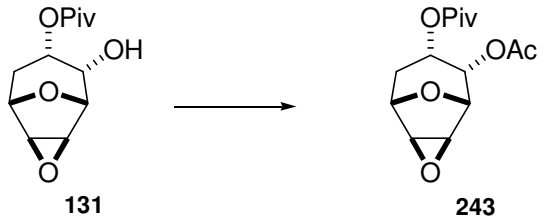
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

139.4 (C_q, Ar-C), 127.1 (CH, Ar-C), 92.8 (C_q, C-2), 91.5 (CH, C-7), 85.4 (C_q, C1), 83.6 (C_q, C5), 80.7 (CH, C-6), 77.6 (CH, C-3), 57.4 (CH_3, O*C*H_3), 35.9 (CH_2, C-4), 21.8/18.3 (CH_3, 2 x CH_3).

IR (neat): 3434 w, 2971 m, 2933 mw, 2826 m, 1738 mw, 1446 m, 1375 m, 1201 s, 1096 vs, 993 vs, 962 vs, 945 s, 828 m, 764 m, 700 s.

12. Attempts to Chapter 5

6α-Acetyloxy-7α-pivaloyloxy-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonane ***243***



Following GP9, DMAP (7 mg, 0.06 mmol, 0.06 eq) and acetic anhydride (0.49 ml, 5.2 mmol, 5.2 eq) were added to a solution of the alcohol **131** (243 mg, 1.0 mmol, 1 eq) in pyridine (270 µL) at 0°C. The mixture was stirred for 1.5 h at 0°C and then water and MTBE were added. Purification by column chromatography (MTBE/CH 1:1) afforded the acetate **243**.

Yield: 282 mg (0.99 mmol), 99 % yellowish oil

$C_{14}H_{20}O_6$ [284.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.41 (tr, *J* = 4.6 Hz, 1 H, H-3), 5.13 (tr, *J* = 4.6 Hz, 1 H, H-2), 4.28 (bd, *J* = 4.4 Hz, 1 H, H-5), 4.22 (bd, *J* = 4.3 Hz, 1 H, H-1), 3.84 (d, *J* = 3.1 Hz, 1 H, H-7), 3.65 (d, *J* = 3.0 Hz, 1 H, H-6), 2.33 (dtr, *J* = 15.7, 4.7 Hz, 1 H, H_{ax}, H-4), 2.03 (s, 3 H, OCOC*H*$_3$), 1.80 (d, *J* = 15.7 Hz, 1H, H_{eq}, H-4), 1.23 (s, 9 H, OCOC(C*H*$_3$)$_3$).

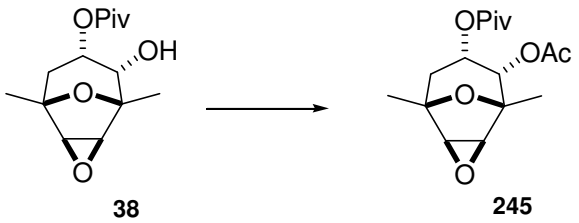
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

176.9 (C_q, O*C*OC(CH$_3$)$_3$), 169.1 (C_q, O*C*OCH$_3$), 71.7 (CH, C-1), 71.0 (CH, C-5), 67.4 (CH, C-3), 65.1 (CH, C-2), 53.6 (CH, C-6), 52.5 (CH, C-7), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 32.1 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$), 20.5 (CH_3, OC*C*H$_3$).

IR (neat): 2969 w, 2877 m, 1742 s, 1718 s, 1372 m, 1285 m, 1231 s, 1154 vs, 1061 s, 1039 s, 876 s, 860 s, 845 m, 724 m.

EI MS (rt): no M^+, 241 (11), 199 (9), 140 (17), 122 (8), 111 (20), 97 (8), 85 (72), 81 (27), 68 (45), 57 (100), 43 (76), 29 (27).

6α-Acetyloxy-7α-pivaloyloxy-1,5-dimethyl-3,9-dioxatricyclo-[3.3.1.0^{2,4}]-nonane ***245***



According to GP9, to a solution of the alcohol **38** (270 mg, 1.0 mmol, 1 eq) in pyridine (270 µL) were added DMAP (7 mg, 0.06 mmol, 0.06 eq) and acetic anhydride (0.49 ml, 5.2 mmol, 5.2 eq) at 0°C. The mixture was stirred for 1.5 h at 0°C and then water and MTBE were added. Purification by column chromatography (MTBE/CH 1:4) afforded the acetate **245**.

Yield: 307 mg (0.98 mmol), 98 % transparent oil

$C_{16}H_{24}O_6$ [312.36 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.39 (tr, *J* = 4.9, 1.5 Hz, 1 H, H-3), 4.91 (d, *J* = 4.6 Hz, 1 H, H-2), 3.63 (d, *J* = 3.0 Hz, 1 H, H-7), 3.44 (d, *J* = 3.0 Hz, 1 H, H-6), 2.13 (dd, *J* = 15.5, 5.0 Hz, 1 H, H_{ax}, H-4), 2.03 (s, 3 H, OCOC*H*$_3$), 1.83 (dd, *J* = 15.5, 1.5 Hz, 1H, H_{eq}, H-4), 1.35 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.21 (s, 9 H, OCOC(C*H*$_3$)$_3$).

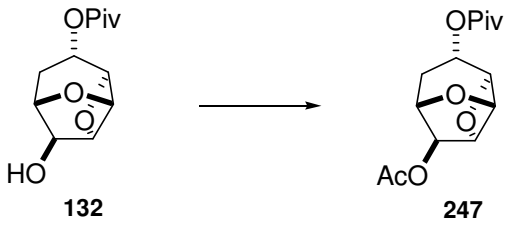
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.0 (C_q, O*C*OC(CH$_3$)$_3$), 169.4 (C_q, O*C*OCH$_3$), 78.1/77.1 (C_q, C-1/C-5), 71.82 (CH, C-3), 66.0 (CH, C-2), 57.8 (CH, C-6), 56.5 (CH, C-7), 38.8 (C_q, OCO*C*(CH$_3$)$_3$), 38.8 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$), 20.6 (CH_3, OC*C*H$_3$), 19.7/16.8 (CH_3, 2 x CH_3).

IR (neat): 2971 w, 2934 m, 2874 m, 1727 vs, 1368 m, 1274 m, 1234 vs, 1220 s, 1144 vs, 1044 s, 911 m, 879 m, 859 m, 803 m, 760 m.

EI MS (rt): no M^+, 213 (22), 168 (17), 150 (17), 129 (37), 125 (37), 108 (11), 95 (70), 85 (72), 82 (22), 69 (8), 57 (100), 43 (90), 29 (22).

9β-Acetyloxy-4α-pivaloyloxy-2,7-oxatricyclo-[4.2.1.0^{3,8}]-nonane ***rac-247***



Following GP9, DMAP (4 mg, 0.03 mmol, 0.06 eq) and acetic anhydride (246 µL, 2.6 mmol, 5.2 eq) were added to a solution of the alcohol **132**(121 mg, 0.5 mmol, 1 eq) in pyridine (134 µL) at 0°C. The mixture was stirred for 1.5 h at 0°C and then water and MTBE were added. Purification by column chromatography (MTBE/CH 1:4) afforded the acetate **247**.

Yield: 141 mg (0.495 mmol), 99 % white solid

$C_{14}H_{20}O_6$ [284.31 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.23 (btr, *J* = 4.9 Hz, 1 H, H-3), 5.15 (s, 1 H, H-6), 5.06 (bd, *J* = 3.0 Hz, 1H, H-1), 4.94 (s, 1 H, H-2), 4.92 (b, 1 H, H-5), 4.66 (d, *J* = 9.7 Hz, 1 H, H-7), 2.75 (bdd, *J* = 13.8, 9.8 Hz, 1 H, H_{eq}, H-4), 2.96 (s, 1 H, OCOC*H*$_3$), 1.85 (dd, *J* = 13.8, 8.6 Hz, 1 H, H_{ax}, H-4), 1.18 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.7 (C_q, O*C*OC(CH$_3$)$_3$), 169.9 (C_q, O*C*OCH$_3$), 88.3 (CH, C-2), 83.0 (CH, C-5), 79.8 (CH, C-7), 78.1 (CH, C-6), 75.0 (CH, C-1), 67.7 (CH, C-3), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 27.6 (CH_2, C-4), 27.0 (CH_3, OCOC(*C*H$_3$)$_3$), 20.8 (177.7 (CH_3, OCO*CH*$_3$).

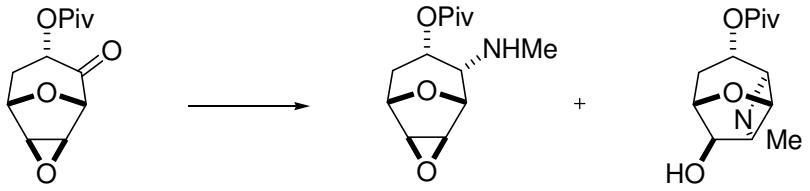
IR (neat): 2969 w, 2873 m, 1724 vs, 1377 m, 1236 s, 1160 s, 1047 s, 988 s, 900 s, 771 m.

EI MS (rt): no M^+, 225 (6), 183 (6), 157 (8), 140 (45), 122 (55), 111 (32), 97 (12), 85 (53), 81 (56), 69 (12), 57 (100), 43 (79), 41 (33), 29 (30).

13. Attempts to Chapter 6

13.1 Attempts to Section 6.3

(7α-Pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]non-6-yl)-methyl-amine ***265*** *and 2-Methyl-4α-pivaloyloxy-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9β-ol* ***267***



208 **265** **267**

1 : 3

A mixture of oxabicyclic ketone **208** (961 mg, 4.0 mmol, 1 eq), methylamine hydrochloride (1.35 g, 20.0 mmol, 5 eq) triethylamine (1.2 ml, 8.8 mmol, 2.2 eq) and titanium (IV) isopropoxide (2.4 ml, 8.0 mmol, 2 eq) in abs MeOH (16 ml) was stirred at rt for 16 h. BH_3·py (0.6 ml, 6.0 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred for 4 h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 10:1).

Yield: 756 mg (2.96 mmol), 74 % total yield

$C_{13}H_{21}NO_4$ [255.31 g/mol]

Data for product **265**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.29 (btr, *J* = 4.5 Hz, 1 H, H-3), 4.26 (bd, *J* = 3.9 Hz, 1H, H-1), 4.24 (bd, *J* = 4.4 Hz, 1H, H-5), 3.72 (d, *J* = 3.1 Hz, 1H, H-7), 3.53 (d, *J* = 3.0 Hz, 1H, H-6), 3.00 (tr, *J* = 4.3 Hz, 1H, H-2), 2.41 (s, 3 H, NHC*H*$_3$), 2.18 (dtr, *J* = 15.7, 4.6 Hz, 1 H, H_{ax}, H-4), 1.76 (d, *J* = 15.7 Hz, 1H, H_{eq}, H-4), 1.23 (s, 9 H, OCOC(C*H*$_3$)$_3$).

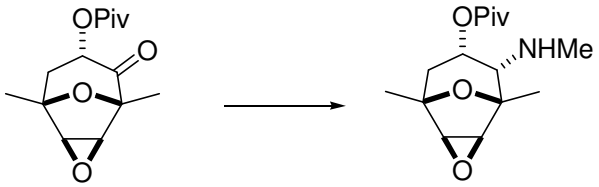
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)
177.3 (C_q, O*C*OC$(CH_3)_3$), 73.0 (CH, C-1), 70.8 (CH, C-5), 65.9 (CH, C-3), 58.6 (CH, C-2), 53.8 (CH, C-6), 52.4 (CH, C-7), 38.8 (C_q, OCO*C*$(CH_3)_3$), 34.0 (CH_3, NHC*H*$_3$), 31.9 (CH_2, C-4), 27.0 (CH_3, OCOC(*C*$H_3)_3$).

IR (neat): 3345 w, 2957 mw, 2798 m, 1721 vs, 1480 m, 1366 m, 1282 s, 1151 vs, 1054 s, 1034 m, 876 m, 855 s.

EI MS (rt): 255 (6, M^+), 170 (15), 157 (80), 98 (12), 85 (31), 81 (26), 73 (94), 70 (47), 57 (100), 44 (25), 41 (39), 29 (29).

Data for product **266**: See Section 13.2.

(1,5-Dimethyl-7α-pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]non-6-yl)-methyl-amine ***266***



207 **266**

Method 1: A mixture of oxabicyclic ketone **207** (1.07 g, 4.0 mmol, 1 eq), methylamine hydrochloride (1.35 g, 20.0 mmol, 5 eq) triethylamine (1.2 ml, 8.8 mmol, 2.2 eq) and titanium (IV) isopropoxide (2.4 ml, 8.0 mmol, 2 eq) in abs MeOH (16 ml) was stirred at rt for 16 h. BH_3·py (0.6 ml, 6.0 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred for 4 h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (CH/MTBE 1:1) affording methylamine **266**.

Yield: 140 mg (0.495 mmol), 69 % white solid
$C_{15}H_{25}NO_4$ [283.36 g/mol]

Method 2: A mixture of oxabicyclic ketone **207** (107 mg, 0.4 mmol, 1 eq), methylamine hydrochloride (54 mg, 0.8 mmol, 2 eq) triethylamine (111 µl, 0.8 mmol, 2.0 eq) and titanium (IV) isopropoxide (240 µl, 0.8 mmol, 2 eq) in abs MeOH (1.6 ml) was stirred at rt for 16 h. $NaBH_4$ (23 mg, 0.6 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred

for 4 h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:1) affording methylamine **266**.

Yield: 79 mg (0.28 mmol), 70 % white solid

$C_{15}H_{25}NO_4$ [283.36 g/mol]

Data for product **266**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.30 (dtr, *J* = 4.8, 1.5 Hz, 1 H, H-3), 3.49 (d, *J* = 3.0 Hz, 1H, H-7), 3.31 (d, *J* = 3.0 Hz, 1H, H-6), 2.63 (d, *J* = 4.6 Hz, 1H, H-2), 2.36 (s, 3 H, NHC*H*$_3$), 2.02 (dd, *J* = 15.6, 4.8 Hz, 1 H, H_{ax}, H-4), 1.84 (dd, *J* = 15.6, 1.4 Hz, 1H, H_{eq}, H-4), 1.43 (CH_3, C1-C*H*$_3$), 1.31 (CH_3, C5-C*H*$_3$), 1.22 (s, 9 H, OCOC(C*H*$_3$)$_3$).

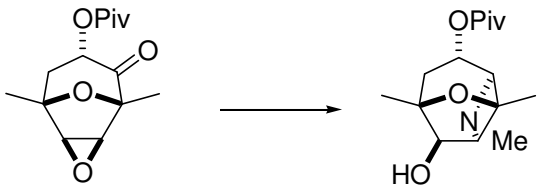
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.3 (C_q, O*C*OC(CH$_3$)$_3$), 80.1 (C_q, C-1), 76.4 (C_q, C-5), 66.1 (CH, C-3), 63.6 (CH, C-2), 58.1 (CH, C-6), 56.6 (CH, C-7), 39.0 (C_q, OCO*C*(CH$_3$)$_3$), 38.9 (CH_2, C-4), 34.9 (CH_3, NHC*H*$_3$), 27.1-26.9 (CH_3, OCOC(*C*H$_3$)$_3$), 19.9 (CH_3, C5-*C*H$_3$), 17.8 (CH_3, C1-*C*H$_3$).

IR (neat): 3352 w, 2972 m, 2933 m, 1723 s, 1480 m, 1455 m, 1370 m, 1283 m, 1144 vs, 991 m, 954 m, 909 m, 866 m, 806 m.

EI MS (rt): 240 (4, M^+), 182 (7), 170 (10), 157 (100), 138 (14), 127 (7), 112 (39), 96 (23), 85 (45), 73 (96), 57 (87), 43 (33), 29 (20).

2,6,8-Trimethyl-4α-pivaloyloxy-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9β-ol ***268***



207 **268**

A mixture of oxabicyclic ketone **207** (537 mg, 2.0 mmol, 1 eq), methylamine hydrochloride (270 mg, 4.0 mmol, 2 eq) triethylamine (0.5 ml, 4.0 mmol, 2.0 eq) and titanium (IV) isopropoxide (1.2 ml, 4.0 mmol, 2 eq) in abs MeOH (8 ml) was stirred at rt for 16 h. $NaBH_4$

(113 mg, 3 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred for 36-48 h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:1) affording azetidine **268**.

Yield: 408 mg (1.44 mmol), 72 % white solid

$C_{15}H_{25}NO_4$ [283.36 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

4.89 (dd, *J* = 8.9, 2.9 Hz, 1 H, H-3), 3.91 (s, 1 H, H-6), 3.27 (b, 1H, H-7), 3.25 (bd, 1 H, H-2), 2.56 (s, 3 H, NHC*H*$_3$), 2.28 (ddd, *J* = 13.3, 8.6, 0.8 Hz, 1 H, H_{eq}, H-4), 1.92 (dd, *J* = 13.3, 9.2 Hz, 1H, H_{ax}, H-4), 1.60 (CH_3, C1-C*H*$_3$), 1.42 (CH_3, C5-C*H*$_3$), 1.18 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

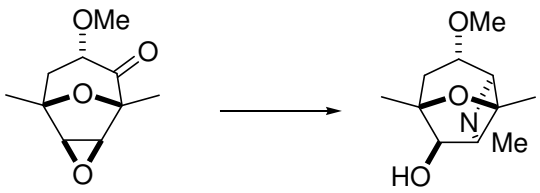
177.9 (C_q, O*C*OC(CH$_3$)$_3$), 83.9 (C_q, C-5), 80.6 (CH, C-6), 80.0 (CH, C-7), 79.8 (C_q, C-1), 69.9 (CH, C-2), 69.5 (CH, C-3), 42.5 (CH_3, NHC*H*$_3$), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 35.1 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$), 22.5 (CH_3, C1-*C*H$_3$), 22.0 (CH_3, C5-*C*H$_3$).

IR (neat): 3435 w, 2970 m, 2930 mw, 2784 m, 1726 vs, 1454 m, 1372 m, 1281 m, 1157 vs, 1140 vs, 1057 m, 989 m.

EI MS (rt): 284 (15, M^+), 268 (6), 240 (10), 198 (9), 182 (34), 164 (17), 152 (14), 138 (36), 127 (33), 112 (69), 109 (86), 96 (59), 85 (30), 84 (34), 73 (48), 70 (100), 57 (90), 42 (70), 29 (46).

EA: Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 62.90; H, 8.61; N, 5.41.

4α-Methoxy-2,6,8-trimethyl-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9β-ol ***270***



214 **270**

A mixture of oxabicyclic ketone **214** (793 mg, 4 mmol, 1 eq), methylamine hydrochloride (540 mg, 8 mmol, 2 eq) triethylamine (1.2 ml, 8.8 mmol, 2.2 eq) and titanium (IV) isopropoxide (2.4 ml, 8.0 mmol, 2 eq) in abs MeOH (16 ml) was stirred at rt for 16 h. BH_3·py (0.6 ml, 6 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred for an additional 4 h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with EtOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/MeOH 10:1) obtaining azetidine **270.**

Yield: 141 mg (0.495 mmol), 51 % white solid

$C_{11}H_{19}NO_3$ [213.27 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

3.90 (s, 1 H, H-6), 3.44 (dtr, *J* = 8.7, 3.1 Hz, 1 H, H-3), 3.32 (s, 3 H, OC*H*$_3$), 3.27 (bd, 1H, H-2), 3.22 (b, H-7), 2.60 (s, 3 H, NHC*H*$_3$), 2.25 (ddd, *J* = 13.5, 8.5, 1.0 Hz, 1 H, H_{eq}, H-4), 1.84 (dd, *J* = 13.5, 9.0 Hz, 1H, H_{ax}, H-4), 1.60 (CH_3, C1-C*H*$_3$), 1.41 (CH_3, C5-C*H*$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

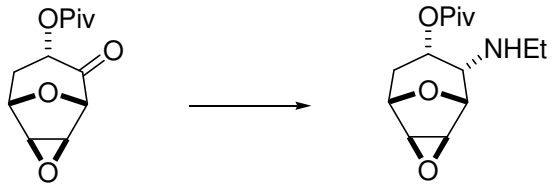
83.8 (C_q, C-5), 81.0 (CH, C-6), 80.2 (CH, C-7), 79.6 (C_q, C-1), 75.3 (CH, C-3), 69.4 (CH, C-2), 56.0 (CH_3, OC*H*$_3$), 43.6 (CH_3, NHC*H*$_3$), 35.8 (CH_2, C-4), 22.9 (CH_3, C1-*C*H$_3$), 22.1 (CH_3, C5-*C*H$_3$).

IR (neat): 3412 w, 2970 m, 2930 mw, 1738 m, 1454 m, 1371 s, 1206 s, 1093 vs, 1060 s, 952 s.

EI MS (rt): 213 (11, M^+), 141 (45), 109 (71), 101 (42), 96 (51), 87 (77), 70 (100), 56 (16), 43 (71), 29 (16).

EA: Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 58.89; H, 9.08; N, 6.39.

(7α-Pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]non-6-yl)-ethyl-amine ***271***



208 **271**

To a suspension of powdered and activated 4 Å molecular sieves (150 mg) in abs. MeOH (2.4 ml) were added sequentially oxabicyclic ketone (144 mg, 0.60 mmol, 1 eq), ethylamine hydrochloride (98 mg, 1.20 mmol, 2 eq), triethylamine (183 µl, 1.32 mmol, 2.2 eq) and pyridine-borane (85 µl, 0.84 mmol, 1.4 eq). After 16 h, the resulting mixture was treated with aq. 2 N HCl until pH<2 and left stirring for 30 min. Methanol was removed *in vacuo* and the aqueous layer was extracted with $CHCl_3$ (3x). Then the aqueous layer was brought to pH>10 by addition of 2 N NaOH and after several extractions with $CHCl_3$, the combined extracts were dried (Na_2SO_4) and evaporated. Purification of the crude extract by column chromatography (MTBE/CH 3:1) afforded ethylamine **271**.

Yield: 141 mg (0.495 mmol), 24 % white solid

$C_{14}H_{23}NO_4$ [269.34 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.27 (trm, *J* = 4.6 Hz, 1 H, H-3), 4.24 (bs, 1H, H-1), 4.23 (bs, 1H, H-5), 3.73 (d, *J* = 3.0 Hz, 1H, H-7), 3.53 (d, *J* = 3.1 Hz, 1H, H-6), 3.11 (btr, *J* = 4.3 Hz, 1H, H-2), 2.62 (m, 2 H, NHC*H*$_2$CH$_3$), 2.22 (dtr, *J* = 15.7, 4.6 Hz, 1 H, H_{ax}, H-4), 1.76 (bd, *J* = 15.7 Hz, 1H, H_{eq}, H-4), 1.23 (s, 9 H, OCOC(C*H*$_3$)$_3$), 1.7 (tr, 3 H, *J* = 7.15 Hz, NHCH$_2$C*H*$_3$).

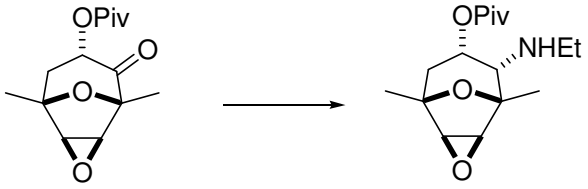
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.3 (C_q, O*C*OC(CH$_3$)$_3$), 73.7 (CH, C-1), 70.9 (CH, C-5), 66.3 (CH, C-3), 56.6 (CH, C-2), 53.9 (CH, C-6), 52.7 (CH, C-7), 41.5 (CH_2, NH*C*H$_2$CH$_3$), 38.9 (C_q, OCO*C*(CH$_3$)$_3$), 32.0 (CH_2, C-4), 27.2 (CH_3, OCOC(*C*H$_3$)$_3$), 15.5 (CH_3, NHCH$_2$C*H*$_3$)

IR (neat): 2976 m, 2928 m, 1749 s, 1717 vs, 1446 m, 1368 m, 1279 s, 1237 s, 1141 vs, 1088 s, 953 s, 851 s.

EI MS (rt): 297 (2, M^+), 281 (2), 259 (3), 212 (2), 196 (6), 184 (8), 171 (79), 126 (19), 87 (100), 84 (53), 57 (77), 43 (23), 29 (16).

(1,5-Dimethyl-7α-pivaloyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]non-6-yl)-ethyl-amine ***272***



207 **272**

A mixture of oxabicyclic ketone **207** (268 mg, 1.0 mmol, 1 eq), ethylamine hydrochloride (163 mg, 2.0 mmol, 2 eq) triethylamine (0.3 ml, 2.2 mmol, 2.2 eq) and titanium (IV) isopropoxide (0.6 ml, 2.2 mmol, 2 eq) in abs MeOH (4 ml) was stirred at rt for 16 h. $NaBH_4$ (57 mg, 1.5 mmol, 1.5 eq) was carefully added and the resulting mixture was stirred for an additional h. The reaction was quenched with 1 N NaOH and the resulting inorganic precipitate was filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and dissolved in $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ and the combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:4) and ethylamine **272** was isolated.

Yield: 36 mg (0.12 mmol), 12 % white solid

$C_{16}H_{27}NO_4$ [297.39 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.26 (dtr, *J* = 4.8, 1.4 Hz, 1 H, H-3), 3.50 (d, *J* = 3.0 Hz, 1H, H-7), 3.31 (d, *J* = 3.0 Hz, 1H, H-6), 2.71 (d, *J* = 4.8 Hz, 1H, H-2), 2.65 (dq, *J* = 11.2, 7.1 Hz, 1 H, NHC*H*$_2$CH$_3$), 2.48 (dq, *J* = 11.2, 7.1 Hz, 1 H, NHC*H*$_2$CH$_3$), 2.02 (dd, *J* = 15.6, 4.8 Hz, 1 H, H_{ax}, H-4), 1.84 (dd, *J* = 15.6, 1.4 Hz, 1H, H_{eq}, H-4), 1.43 (CH_3, C1-C*H*$_3$),1.31 (CH_3, C5-C*H*$_3$), 1.22 (s, 9 H, OCOC(C*H*$_3$)$_3$), 1.7 (tr, 3 H, *J* = 7.1 Hz, NHCH$_2$C*H*$_3$).

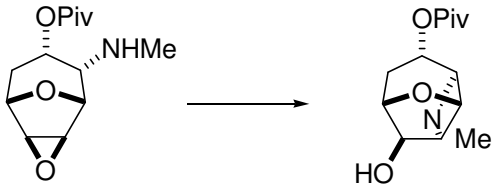
^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.3 (C_q, O*C*OC(CH$_3$)$_3$), 80.2 (C_q, C-1), 76.4 (C_q, C-5), 66.8 (CH, C-3), 61.4 (CH, C-2), 58.2 (CH, C-6), 56.7 (CH, C-7), 41.4 (CH_2, NH*C*H$_2$CH$_3$), 39.0 (CH_2, C-4), 38.9 (C_q, OCO*C*(CH$_3$)$_3$), 27.2 (CH_3, OCOC(*C*H$_3$)$_3$), 19.9 (CH_3, C5-*C*H$_3$), 17.7 (CH_3, C5-*C*H$_3$), 15.6 (CH_3, NHCH$_2$C*H*$_3$).

IR (neat): 3401 w, 2970 mw, 2937 m, 2874 m, 1724 s, 1282 m, 1146 vs, 1069 m, 1027 m, 930 m.

13.2 Attempts to Section 6.4

2-Methyl-4α-pivaloyloxy-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9β-ol ***267***



265 **267**

Methylamine **265** (120 mg, 0.47 mmol, 1 eq) was dissolved in THF (4.7 ml) and cooled to 0°C. Vinylmagnesiumbromide solution (1 M in THF, 0.61 ml, 0.61 mmol, 1.3 eq) was added dropwise and the mixture was stirred at rt until completion of the reaction. After addition of aq. NH_4Cl solution and sat. aq. Na,K tartrate solution, the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/MeOH 10:1) to afford azetidine **267**.

Yield: 141 mg (0.495 mmol), 71 % white solid

$C_{13}H_{21}NO_4$ [255.31 g/mol]

Data for azetidine **267**:

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.15 (dd, *J* = 7.1, 5.1 Hz, 1 H, H-1), 4.88 (dd, *J* = 8.8, 3.0 Hz, 1H, H-3), 4.47 (dd, *J* = 8.9, 0.9 Hz, 1H, H-5), 4.20 (s, 1 H, H-6), 3.61 (dd, *J* = 5.2, 1.5 Hz, 1H, H-7), 3.52 (dd, *J* = 7.2, 1.5 Hz, 1H, H-2), 2.61 (ddd, *J* = 13.6, 9.2, 1.0, 1 H, H_{ax}, H-4), 2.53 (s, 3 H, NHC*H*$_3$), 2.00 (ddd, *J* = 13.5, 8.8, 0.9 Hz, 1H, H_{eq}, H-4), 1.28 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

177.7 (C_q, O*C*OC(CH$_3$)$_3$), 81.1 (CH, C-5), 78.4 (CH, C-6), 75.4 (CH, C-7), 73.1 (CH, C-1), 68.3 (CH, C-3), 66.3 (CH, C-2), 42.5 (CH_3, NHC*H*$_3$), 38.7 (C_q, OCO*C*(CH$_3$)$_3$), 28.4 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$).

IR (neat): 3401 w, 2970 mw, 2937 m, 2874 m, 1724 s, 1282 m, 1146 vs, 1069 m, 1027 m, 930 m.

EA: Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 59.19; H, 8.07; N, 5.25.

2,6,8-Trimethyl-4α-pivaloyloxy-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9β-ol ***268***

266 **268**

Methylamine **266** (57 mg, 0.20 mmol, 1 eq) was dissolved in THF (2 ml) and cooled to 0°C. Vinylmagnesiumbromide solution (1 M in THF, 260 µl, 0.26 mmol, 1.3 eq) was added dropwise and the mixture was stirred at rt until completion of the reaction. After addition of aq. NH_4Cl solution and sat. aq. Na,K tartrate solution, the aqueous phase was extracted with MTBE. The combined organic layer was dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH 1:1) to afford azetidine **268**.

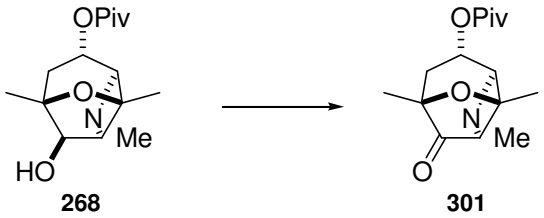
Yield: 47 mg (0.166 mmol), 83 % white solid

$C_{15}H_{25}NO_4$ [283.36 g/mol]

Data for product **268**: See Section 13.1.

13.3 Attempts to Section 6.6

2,6,8-Trimethyl-4α-pivaloyloxy-7-oxa-2-azatricyclo[4.2.1.0^{3,8}]nonan-9-one ***301***



268 **301**

To a solution of oxalyl chloride (94 µL, 1.12 mmol, 4 eq) in DCM (5.7 ml) was added DMSO (84 µL, 1.18 mmol, 4.2 eq) at –78°C. A solution of azetidine **268** (79 mg, 0.28 mmol, 1 eq) in DCM (2.8 ml) was syringed and the mixture was stirred at –78°C for 1 h. Triethylamine (0.35 ml, 2.52 mmol, 9 eq) was added in the solution and the mixture was stirred at –78°C for 1 h and at rt for 1 h. DCM was evaporated *in vacuo* and the residue was dissolved in MTBE and water. The aqueous phase was extracted with MTBE and the combined organic extracts were

dried (N_2SO_4) and evaporated. Purification by column chromatography (MTBE/CH 2:1) afforded ketone **301**.

Yield: 44 mg (0.155 mmol), 55 % yellowish solid

$C_{15}H_{23}NO_4$ [281.35 g/mol]

^{1}H-NMR: (400 MHz, $CDCl_3$ with TMS)

5.13 (ddd, *J* = 9.5, 8.5, 3.4 Hz, 1 H, H-3), 3.85 (d, *J* = 3.4 Hz 1H, H-2), 3.51 (s, 1 H, H-7), 2.43 (dd, *J* = 14.4, 9.5 Hz, 1 H, H_{eq}, H-4), 2.37 (s, 3 H, NHC*H*$_3$), 1.60 (CH_3, C1-C*H*$_3$), 1.42 (dd, *J* = 14.4, 8.5 Hz, 1H, H_{ax}, H-4), 1.38 (CH_3, C5-C*H*$_3$), 1.19 (s, 9 H, OCOC(C*H*$_3$)$_3$).

^{13}C-NMR: (100 MHz, $CDCl_3$ with TMS)

208.4 (C_q, C-6), 177.4 (C_q, O*C*OC(CH_3)$_3$), 81.1 (C_q, C-5), 76.9 (C_q, C-1), 71.3 (CH, C-7), 69.1 (CH, C-2), 67.7 (CH, C-3),38.6 (C_q, OCO*C*(CH_3)$_3$), 35.7 (CH_3, NHC*H*$_3$), 33.6 (CH_2, C-4), 27.1 (CH_3, OCOC(*C*H$_3$)$_3$), 20.9 (CH_3, C5-*C*H$_3$), 20.1 (CH_3, C1-*C*H$_3$).

IR (neat): 2976 m, 2928 m, 1749 s, 1717 vs, 1446 m, 1368 m, 1279 s, 1237 s, 1141 vs, 1088 s, 953 s, 851 s.

ESI MS: Calcd for $C_{15}H_{23}NO_4$: 281.1627. Found: 281.0425.

PERSONAL INFORMATION

Name:	Carolina Martínez Lamenca
Date of birth:	25th September 1976
Place of birth	Barcelona, Spain
Marital status:	Single
Nationality:	Spanish

HIGH SCHOOL

1980 – 1990	Secondary School, Barcelona, Spain.
1990 – 1994	Col·legi Sant Josep, Sant Sadurní d'Anoia, Spain. High school and diploma examination.

GRADUATE

1994 – 1999	**Universitat de Barcelona**, Barcelona, Spain. MSc in Chemistry. Major: Organic Chemistry.
October 1999 – November 2000	Institut für Organische Chemie, **Universität Hannover**, Germany. Master thesis under supervision of Prof. H. M. R. Hoffmann: "Synthetic Strategy for Stereospecific Vicinal Functionalization of Double Bonds in [3.2.1] oxabicycles by 1,3-Dipolar Cycloaddition."

DOCTORATE

2000 – 2004	Institut für Organische Chemie, **Universität Hannover**, Germany. Research work incl. training of graduate and undergraduate students and preparation of the present PhD thesis under supervision of Prof. H. M. R. Hoffmann.
July 2001 – September 2001	Unilever Cambridge Centre for Molecular Informatics, **Cambridge University Chemical Laboratory**, United Kingdom. Research work in Molecular Modeling under supervision of Dr. J. M. Goodman.

PUBLICATIONS

Vidal, M.; Martínez, C.; Hoffmann, H. M. R. Synthesis of 2α-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one by [4+3] Cycloaddition. *Org. Synth.* **2003** (submitted).