NEW DIOXA AND OXAZA-TRICYCLONONANES AND STUDY OF THEIR BIOLOGICAL ACTIVITY

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von

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Hiermit versichere ich and Eides Statt, die vorliegende Dissertation selbständing durchgeführt und keine unerlaubte Hilfe in Anspruch genommen zu haben. Die aus fremden Quellen übernommenen Gedanken sind als solche kenntlich gemacht.

Hannover, im Juni 2003

Referent: Prof. H. M. R. Hoffmann, PhD, DSc
Korreferent: Prof. Dr. H. Meyer
Tag der Prüfung: 31.07.2003

KURZFASSUNG

María Vidal Pascual

New Dioxa and Oxaza-tricyclononanes and Study of their Biological Activity

Mehrere Naturstoffe, die einen Oxetanring in ihrer Struktur besitzen, zeigen interessante pharmakologische Eigenschaften. In dieser Doktorarbeit wurden eine Reihe neuer oxygenierter 2,7-Dioxatricyclo[4.2.1.0]nonan ausgehend von funktionalisiertem 8-Oxabicyclo[3.2.1]oct-6-en-3-on synthetisiert.

Als Vorläufersubstanzen für die Dioxatricyclen dienten tricyclische Epoxyalkohole mit verschiedenen Etherfunktionalitäten (Methyl, Ethyl und Propyl) an der C3-Position. Hierbei erwies sich der Methylether als beste Schutzgruppe zur Herstellung des dioxatricyclischen Systems. Dieser Dioxatricyclus kann zur Herstellung pharmakologisch aktiver C-Glycoside und Glycosidmimetica benutzt werden.

Die PCC-Oxidation der Hydroxygruppe der tricyclischen Struktur 4α-Methoxy-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonan-6-on generiert das tricyclische Lacton 9α-Methoxy-2,4,7-trioxa-tricyclo[4.2.2.$0^{3,8}$]decan-5-on über eine Art Baeyer-Villiger-Oxidation.

Die [4+3] Cycloaddition zwischen dem chiralen Silyloxyallylkationen und Furan bildet eine Schlüsselreaktion zur Herstellung des enantiomerenreinen, oxygenierten 2,7-Dioxatricyclo[4.2.1.$0^{3,8}$]nonan.

Eine elektrophile Substitution konkurrierte sehr stark mit der [4+3] Cycloadditionsreaktion zwischen N-Alkylpyrrolen und Silyloxyallylkationen und führte ausschließlich zu der Formierung sogennanter Klasse C Produkte (Hoffmann-Terminologie).

Tropan-Alkaloide bilden eine Naturstoffklasse mit wertvollen pharmakologischen Eigenschaften sowie verblüffender phytochemischer Diversität. Mehrere Derivate des Tropan-Alkaloids Scopolin wurden in der folgenden Doktorarbeit synthetisiert. Eine reduktive Aminierung von 8-Oxabicyclo[3.2.1]oct-6-en-3-on gefolgt von einer N-BOC-Schützung generierte verschiedene 2-Oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonanscopolinderivate. Eines dieser hergestellten Scopolinderivate zeigte Cytotoxizität (< 0.5 μg/mL) gegenüber Tumorzelllinien (Zell-Linien: HM02, Hep G2 und MCE 7).

Schlagworte:

Oxetan - C-Glycosid – Scopolin - Pharmakologische Aktivität

ABSTRACT

María Vidal Pascual

New Dioxa and Oxaza-tricyclononanes and Study of their Biological Activity

Several natural products containing an oxetane ring in their structure show important pharmacological properties. In the present thesis, a series of new oxygenated 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes are synthesized starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one.

The precursors of the dioxatricyclic structures are tricyclic epoxy alcohols with different ether functions (methyl, ethyl, and propyl) located at the C3-position. The methyl ether as protecting group is the best choice to prepare the dioxatricyclic system. The generated dioxatricycles can be employed to develop pharmacologically active C-glycoside and glycoside mimetics.

The PCC oxidation of the free alcohol function in the tricycle 4a-Methoxy-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane-6-one generates the tricyclic lactone 9a-Methoxy-2,4,7-trioxa-tricyclo[4.2.2.$0^{3,8}$]decane-5-one which is similar to that of a Baeyer-Villiger oxidation product.

The [4+3] cycloaddition between chiral silyloxyallyl cation and furan is the key reaction to provide enantiopure oxygenated 2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes.

In the [4+3] cycloaddition between N-alkylpyrroles and silyloxyallyl cations electrophilic substitution competed strongly with cycloaddition reaction leading to the exclusive formation of substitution products of Class C process, using the terminology by Hoffmann.

Tropane alkaloids are a group with valuable pharmacological characteristics and perplexing phytochemical diversity. In the present doctoral thesis, several derivatives of the tropane alkaloid Scopoline are synthesized.

A reductive amination of 8-oxabicyclo[3.2.1]oct-6-en-3-one followed by *N*-BOC protection generates Scopoline derivatives, 2-oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonanes. One of the synthesized Scopoline derivative shows cytotoxicity (< 0.5 µg/mL) towards tumor cells (cell-lines: HM02, Hep G2 and MCE 7).

Keywords:

Oxetane - C-Glycoside – Scopoline - Pharmacological activity

DANKSAGUNG

Die vorliegende Arbeit wurde in der Zeit vom Januar 2000 bis Juli 2003 am Institut für Organische Chemie der Universität hannover unter der Leitung von Herrn Professor H. M. R. Hoffmann, PhD, DSc, angefertigt.

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A mis padres,

José y Margarita

"Venturoso es el futuro,

como aquellos horizontes

de pórfido y mármol puro

donde respiran los montes"

(Miguel Hernández)

“A Dios rogando

y con el mazo dando”

CONTENTS

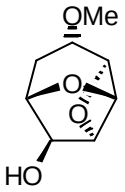
THEORETICAL PART

ABBREVIATIONS

$BF_3 \cdot OEt_2$	Boron Trifluoride Etherate	m	multiplet / medium intensity
Bn	Benzyl group	M	Molarity
BnBr	Benzyl bromide	Me	Methyl group
BOC	*tert*-butoxycarbonyl	min	minute
br	broad signal	mL	mililiter
BuLi	Butyllithium	m.p.	melting point
Bu^tMgCl	*tert*-butylmagnesiumchloride	MS	Mass Spectroscopy
Calcd.	Calculated	MTBE	*tert*-butylmethyl ether
CH	Cyclohexane	NMO	N-Methylmorpholine N-oxide
CH-COSY	Carbon-Hydrogen Correlation Spectroscopy	NMR	Nuclear Magnetic Resonance
$(COCl)_2$	Oxalyl Chloride	NOE	Nuclear Overhauser Enhancement
m-CPBA	*m*-Chloroperoxybenzoic acid	$NaBH(OAc)_3$	Sodium triacetoxyborohydride
d	Doublet	$NaBH_3CN$	Sodium cyanoborohydride
DCM	Dichloromethane	*o, p*	*ortho*- and *para*-position in phenyl group
DIBAH	Diisobutylaluminium hydride	PCC	Pyridinium Chlorochromate
DMAP	4-Dimethylaminopyridine	Ph	Phenyl group
DMF	*N*,*N*-Dimethylformamide	PivCl	Pivaloyl chloride
DMSO	Dimethyl Sulfoxide	PrBr	Propyl bromide
EA	Ethyl acetate	PrMgCl	Propylmagnesiumchloride
EtBr	Ethylbromide	rt	room temperature
Et_3N	Triethylamine	s	strong intesity / singlet
e.e.	Enantioselectivity	TBDS	*tert*-butyldimethylsilyl
eq	equatorial / equivalent	TES	Triethylsilane
Et_2O	Diethyl ether	THF	Tetrahydrofuran
h	Hour	TLC	Thin Lied Chromatography
HR-MS	High resolution mass spectroscopy	TMS	Trimethylsilane
IR	Infrared spectroscopy	TMSOTf	Trimethylsilyl Trifluoromethanesulfonate
$KOBu^t$	Potassium *tert*-butoxide	TPAP	tetra-*n*-propylammonium perruthenate
LDA	Lithium Diisopropylamine	TsCl	Tosyl chloride
M	*meta*-position in phenyl group	w	weak intesity

PRELIMINARY REMARKS

The stereochemical notation at the figures and scheme follows the convention given by Maehr.[1] Enantiopure substances are drawn using solid and broken wedge to represent its absolute configuration. The relative configuration of racemic substances is drawn employing bold and broken lines.



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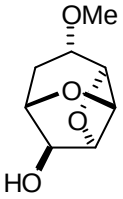
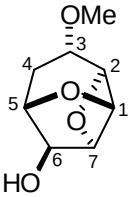


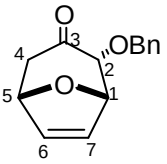
***rac*-108**

The nomenclature for the dioxatricycle ***rac*-108** and for the oxazatricycle ***rac*-141** is according to the IUPAC system.[2] The atom numbering follows generally the IUPAC rules. For reasons of clarity, the numbering of the atomic positions in the tricyclic systems was changed to follow the numeration of the bicycle ***rac*-94**.



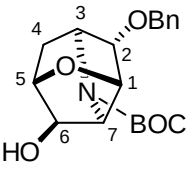
***rac*-108**

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



***rac*-94**

8-Oxabicyclo[3.2.1] octane



***rac*-141**

2-Oxa-6-azatricyclo [3.3.1.0^{3,7}]nonane

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[1] Maehr, H. J. Chem. Ed. 1985, 26, 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.

1. INTRODUCTION

Most of the natural products with important pharmacological activity are isolated from the nature only in small quantities. The search for new synthetic compounds with a pharmacological activity similar to these natural products has been the objective of the modern synthetic organic chemistry in the last years. Under the medical point of view these substances showing potential anti-cancerous properties have special importance in terms of cytotoxic and cytostatic activity. In fact, the search for microtubules stabilizing agents is a major activity for pharmaceutical companies and scientist.

1.1 Structure and properties of natural products containing an oxetane ring

The oxetane ring is present in several natural products which show important pharmacological properties. General interest in naturally occurring oxetanes continues to be high because of their variable activity with a wide spectrum of indications.[3] The structures and properties of some important biologically active compounds are described in this chapter into three different groups.

Dictyoxetane **1** has been isolated from the algae *Dictyota dichotoma*[4] and is structurally related to the class of dolabellanes which shown a variety of pharmacological properties. Oxetanocin A **2** is anti HIV active and has an antiviral effect.[5] The oxatricyclic norbornane **3** is a potent herbicide and plant growth regulator.[6] Taxol **4** was isolated as the first high potent anti-cancerous agent extracted from the bark of the Pacific yew (*Taxus brevifolia Nutt*). Thromboxane A_2 **5** is a powerful vasoconstrictor and a promoter of blood platelet aggregation[7] (Figure **1**).

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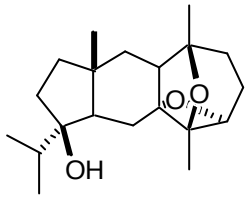
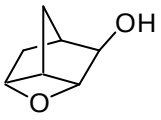
[5] syntheis of L-oxetanocin: Gumina, G.; Chu, C. C. *Org. Lett*. **2002**, *4*, 1147.

[6] 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.

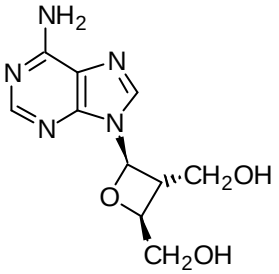
[7] a) New synthetic routes of Prostaglandins and Thromboxanes, Roberts, S. M. Scheinmann, F., Eds.; Academic: New York, 1982; b) total synthesis of TXA2: Bhawat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*,6372; c) Corey, E. *J. Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 455.



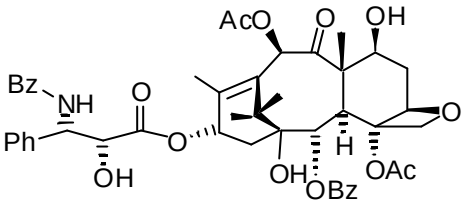
1 Dictyoxetane



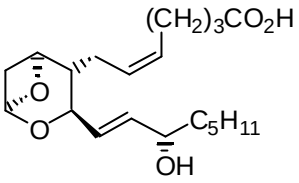
3 Norbornane



2 Oxetanocin A



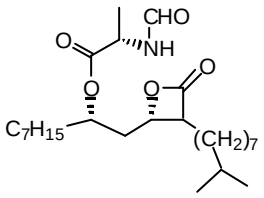
4 Taxol



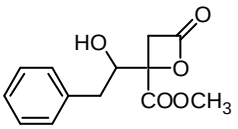
5 Thromboxane A_2 (TXA_2)

Figure 1: Pharmacologically active natural products containing an oxetane ring in their structure

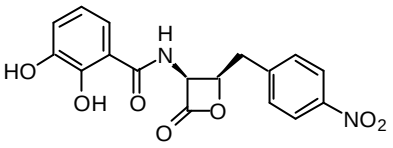
There are some natural compounds with a four-ring *ß*-lactone present in their structure: Ebelactone **6** is an enzyme-inhibitor, lipstatine **7** and panclicine **8** are inhibitors of the pancreas-lipase, obafluorine **9** is an antibiotic and papulinone **10** which shows a phytotoxic effect (Figure **2**).



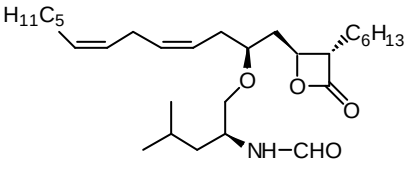
8 Panclicine



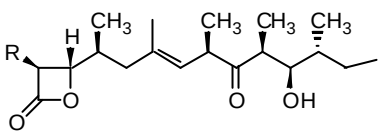
10 Papulinone



9 Obafluorine



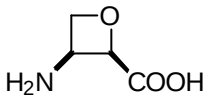
7 Lipstatine



6 Ebelactone

Figure 2: Pharmacologically active natural products with *ß*-lactone structure containing an oxetane ring

The antibiotic oxetin[8] **11** (Figure **3**) is a naturally occurring ß-amino acid containing an oxetane ring. In order to study the potential of oxetane amino acids as a new family of foldamers, an efficient route to suitable oxetane scaffolds is reported by Barker[9] using an oxetane ring.



11 Oxetin

Figure 3: The naturally occurring ß-amino acid antibiotic oxetin

1.2 Alkaloids

Studies on alkaloids and their biosynthesis were originally initiated because of their pharmacological characteristics and perplexing phytochemical diversity.

The term *Alkaloid* is designed to the members of a class of natural products of a basic nature, and it is derived from the name "vegetable alkali" first applied to these substances. In a broad sense, alkaloids are nitrogenous bases, which occur naturally in plants. Alkaloids usually show specific pharmacological activity on the animal organism. Alkaloids are very interesting compounds for the organic chemists in terms of the complex structural and synthetic puzzles that they pose.

There is not any structural classification of alkaloids but an attempt has been made to arrange them in different groups on the basis of their basic ring system: Pyrrolidine group, Pyridine group, Isoquinoline group, Morphine group, Quinoline group, Indole group, Erythrina alkaloids and Colchicine **13**.

Recently, has been demonstrated that the [4+3] cycloaddition reaction of an oxyallyl cation to a suitable functionalized furan, followed by a double elimination of the resulting oxabridge, provides ready access to the tropoisoquinoline alkaloids, imerubine, grandirubine and isoimerubrine, as well as colchicine.[10] Some of these alkaloids showed cytotoxic properties and colchicine **13** is well-known because its antimiotic properties (Figure **4**).

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[8] a) Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M.; Omura, S. *Chem. Pharm. Bull*. **1986**, *34*, 3102-3110; b) Schröder, J.; Bach, T. *Liebigs Ann./Recl*. **1997**, *11*, 2265-2267.

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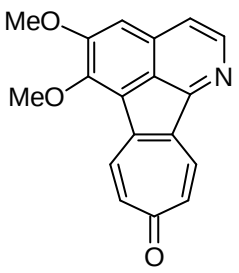
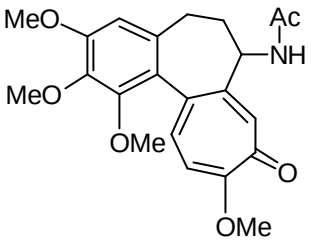
[10] Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc*. **2001**, *123*, 3243-3246.



12

a) Pareitropone



13

b) Colchicine

Figure 4: Tropoisoquinoline alkaloids with: a) cytotoxic effect; b) antimiotic properties

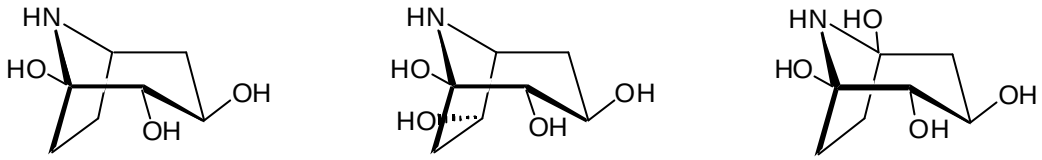
The realization that alkaloidal sugar mimics might have enormous therapeutic potential in many diseases such as viral infection, cancer and diabetes has led to increasing interest and demand for these compounds. Most of these effects can be shown to result from the direct or indirect inhibition of glycosidases. Naturally occurring sugar mimics with a nitrogen in the ring are classified into five structural classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes. An entirely new class has now been added to this group with the discovery of the calystegines.

1.2.1 Tropane Alkaloids

Tropane alkaloids are a well-established group with valuable pharmacological properties which have been frequently and comprehensively review.[11] Scopolamine and related alkaloids occur in the plant family Solanaceae (*Physalis alkekengi*) and bear a methyl substituent on the nitrogen atom. In contrast, nortropane alkaloids have rarely been isolated although they occasionally occur as minor constituents in plants containing tropane alkaloids. The genera *Datura*, *Atropa*, *Hyoscyamus*, *Scopolia* and *Duboisia* of the Solanaceae are especially rich sources of hyoscyamine and/or scopolamine. Calystegines have now been found in all of these genera, and *Atropa belladonna* contained higher amounts of calystegines A_3, B_1 and B_2 in the aerial parts than in the roots[12] (Figure **5**).

[11] a) Lounasmaa, M. In *The Alkaloids*: *Chemistry and Pharmacology*; Brossi, A., Ed., Academic Press: New York, 1988; Vol. 33, pp. 1-81; b) Lounasmaa, M.; Tamminen, T. In *The Alkaloids*: *Chemistry and Pharmacology*; Cordell, G. A., Ed., Academic Press: New York, 1993; Vol. 44, pp. 1-115.

[12] Dräger, B. *Phytochem. Anal*. **1995**, *6*, 31.

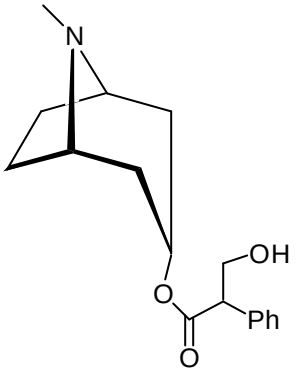


14 A_3 **15** B_1 **16** B_2

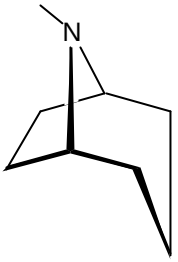
Figure 5: Calystegines contained in *Atropa belladonna*

Most of the medicinally important tropane alkaloids are obtained from plants. However, tremendous efforts have been made to develop economically feasible methods to produce hyoscyamine, scopolamine, anisodamine and isodine.[13] The important major aromatic tropanes, hyoscyamine **17** (named also atropine) and hyoscine **18** (also scopolamine)[14] act as acetylcholine antagonist[15] and have stimulated considerable interest in determining their biosynthetic pathways.[16] Hyoscyamine **17** is the most common tropane alkaloid and was first isolated from henbane by Geiger[17] in 1883, and it was subsequently isolated from *Datura* species. Scopolamine **18** presents an analgesic action and showed similarly properties as atropine **17** which is a muscle relaxant of high potency and it is used in the medicine as sedative against the travel sickness, as respiratory stimulant and as strong anesthesia. Scopoline **19** is isolated from *Datura* species and from *Scopolia tanguticus* and it is possible to obtain from the hydrolysis of the scopolamine **18**. A pharmacological effect can not be assigned to the scopoline **19** since it always occurs in the nature in connection with the scopolamine **18** or their derivates (Figure **6**).

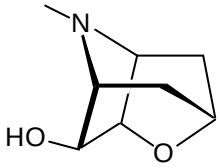
[13] Review of the biosynthesis of tropane alkaloids published by: Lounasmaa, M.; Tamminen, T. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Academic Press: New York 1993; Vol. 44, p. 1.
[14] a) Fodor, G. *Nature* **1952**, *170*, 218; b) Fodor, G.; Kovacs, O. *J. Org. Chem.* **1953**, 2341.
[15] Evans, W. C. In *Trease and Evans´ Pharmacognosy* 13th edn., Ed., Baillière Tindall, London 1989, p. 832.
[16] a) Leete, E. *Planta Med*. **1990**, *56*, 339; b) Leete, E. *Planta Med*. **1979**, *36*, 97.
[17] Geiger, L. *Liebigs Ann. Chem.* **1833**, *7*, 269.



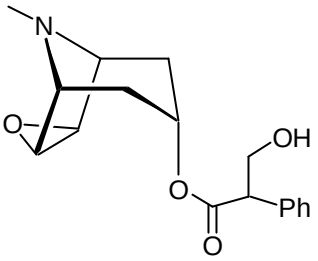
17 Hyoscyamine (Atropine)



20 Tropane



19 Scopoline



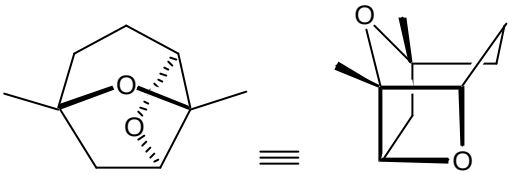
18 Hyoscine (Scopolamine)

Figure 6: Structures of the Scopoline **19** and Tropane **20** and the major aromatic tropane alkaloids Scopolamine **18** and Atropine **17**

2. REVIEW OF THE PAST RESULTS

2.1 Dioxatricyclononanes

For the synthesis of the 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane system **21** (Figure **7**), three different strategies have been published in the last ten years. The first publication appeared in 1995 by J. Reinecke and H. M. R. Hoffmann.[35] In 1996 Heathcock *et al.*[36] presented a second strategy and two years later, J. Wittenberg and H. M. R. Hoffmann published an improved synthesis of dioxatricyclic systems some of which showed cytostatic and cytotoxic activity toward HMO2 and HEP G2 cells (see chapter 2.1.5).[37] In 2002, S. Proemmel and H. M. R. Hoffmann published several new dioxatricyclic structures which showed cytostatic activity towards tumor cells HEP G7 and MCF7 (see chapter 2.1.5).[38]



21

Figure 7: Structure of 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane

2.1.1 [4+3] Cycloaddition reactions

The [4C(4p) + 3C(2p)] cycloaddition reaction of oxyallyl cations to furans is a general and efficient method to synthesize seven-membered carbocycles.[39]

Figure **8** shows a general view of the generation of a-alkoxylated oxabicyclo[3.2.1] ketones. Starting from 1,1-dimethoxyaceton **22** and under standard acetylation conditions is synthesized the corresponding ketone and by addition of a catalytic amount of a Lewis acid an allyl cation is obtained which with the 4p-partner (e. g. furan) attempt the bicyclic

[35] a) Reinecke, J. *Doctoral thesis*, University of Hannover **1994**; b) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *1*, 368.
[36] Marshall, K. A.; Mapp, A. K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9135.
[37] Wittenberg, J.; Beil, W.; Hoffmann, H. M. R. *Tet. Lett.* **1998**, 39, 8259-8262.
[38] Proemmel, S.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2002**, *58*, 6199-6206.
[39] For [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 Vol. 5*, Trost, B. M.; Fleming, I.; Eds., Pergamon: Oxford **1991**, 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.

adduct. To obtain the oxabicyclic system two types of coupling are possible through both faces of the oxyallyl cation and the in case of non chiral furans the resulting cycloadducts are enantiomers.

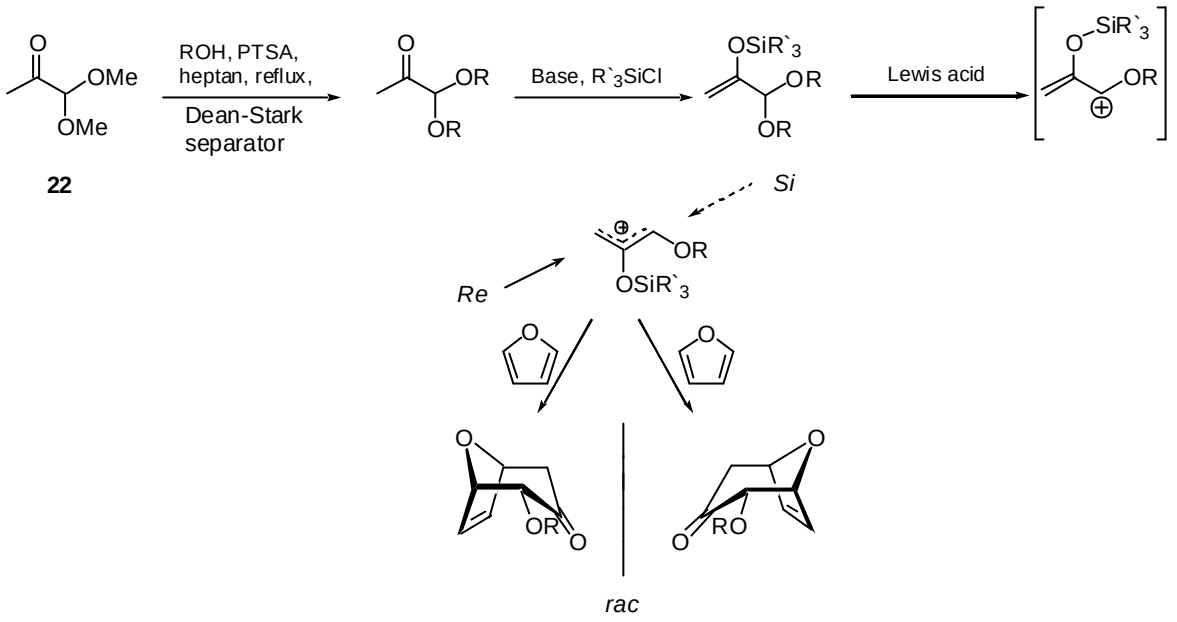


Figure 8: Synthetic route to oxabicycles by [4+3] cycloaddition

Some examples of different [4+3] cycloadditions were reported previously[40] by using furan as 1,3-diene partner with various oxyallyl cations (Figure **9**).

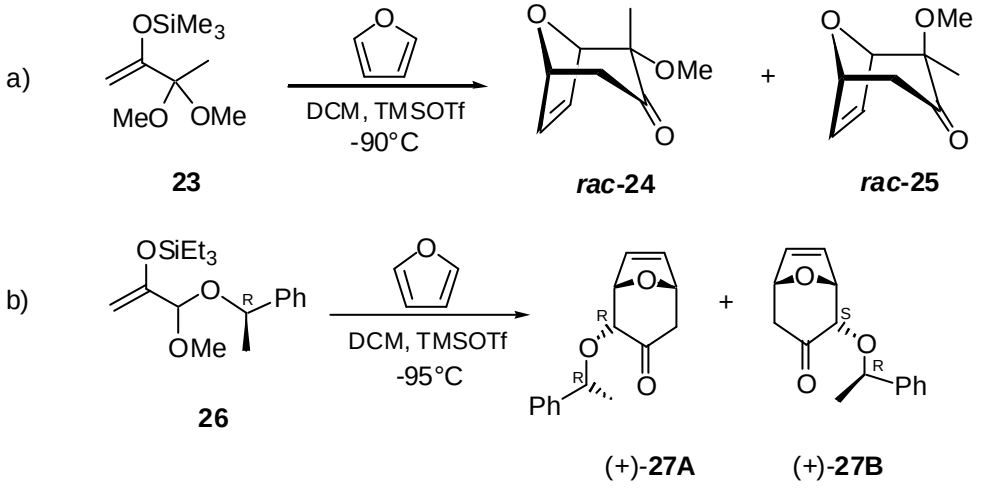


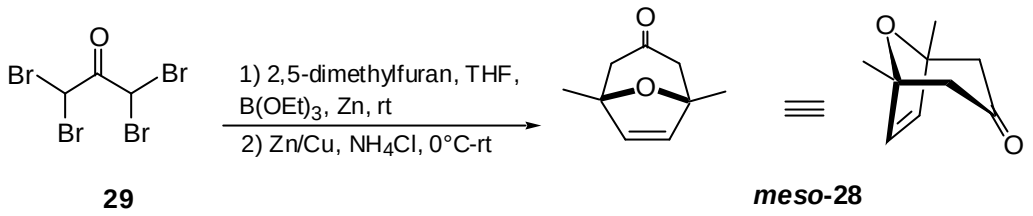
Figure 9: Some examples of [4+3] cycloaddition by: a) A. M. Misske; b) C. B. W. Stark

2.1.2 J. Reinecke strategy

[40] See: a) Pierau, S. *Doctoral thesis*, University of Hannover **1997**; b) Gaertzen, O. *Doctoral thesis*, University of Hannover **1999**; c) Misske, A. M. *Doctoral thesis*, University of Hannover **1999**; d) Stark, C. B. W. *Doctoral thesis*, University of Hannover **2000**.

To obtain the desired oxatricyclic system **21**, the oxabicycle[3.2.1]ketone ***meso*-28** was employed as starting material. This type of bicycle structure has a special importance in the synthesis of natural products as a precursor of subunits of biologically active natural compounds.[41]

Bicyclic system ***meso*-28** was synthesized by a [4+3] cycloaddition between 2,5-dimethylfuran and an oxyallyl cation which was prepared by reducing the polyhaloketone **29** with Zn and $B(OEt)_3$ (Figure **10**).



29 ***meso*-28**

Figure 10: Synthesis of the bicycle system ***meso*-28** by J. Reinecke

The bicycle ketone ***meso*-28** was transformed into the mesylate ketone **30** in four steps and further treatment with DBU in acetonitrile yielded the unsaturated ketone **31** which was separated from its diastereomer **32** by column chromatography. The bicycle structure **34** was obtained after six steps and afterwards it was employed as precursor to generate the tricycle system **21** by an anionic intramolecular cyclization (Figure **11**).

[41] a) Montaña, A. M.; García, F.; Grima, P. M. *Tet. Lett*. **1999**, *40*, 1375-1378; b) Montaña, A. M.; García, F.; Grima, P. M. *Tet. Lett*. **1999**, *55*, 5483-5504; c) Rama Rao, A.V.; Yadav, J.S.; Vidyasagar, V. *Chem. Comm*. **1985**, 55-56.

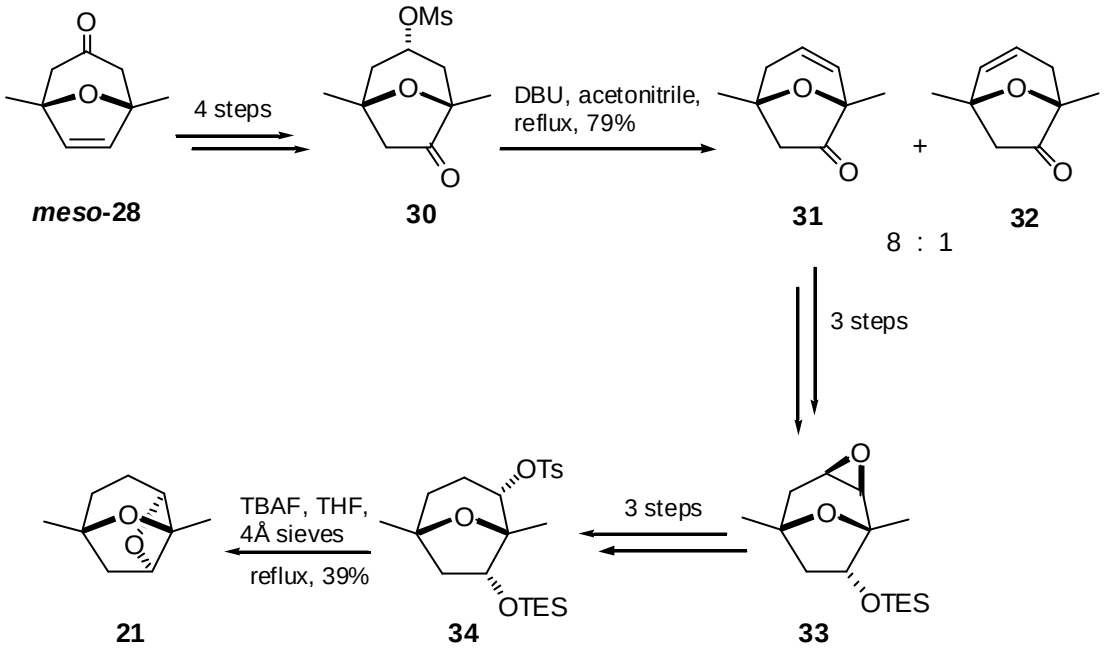


Figure 11: Synthesis of dioxatricycle **21** by an anionic intramolecular cyclization by J. Reinecke

Dioxatricycles **36** and **37** were prepared from the epoxy alcohol **35** by a non-selective intramolecular epoxy opening with $BF_3.OEt_2$. On the other hand, the treatment of **35** under basic conditions yielded selectively the dioxatricycle **36** (Figure **12**).

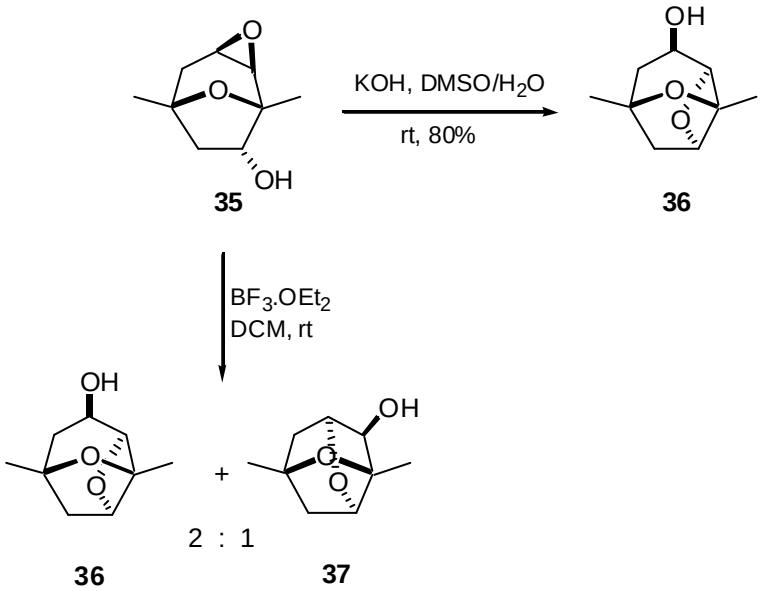


Figure 12: Synthesis of dioxatricycles **36** and **37** by intramolecular epoxy opening, by J. Reinecke

2.1.3 Heathcock et al. strategy

In this second strategy the bicycle ketone **38** was employed as starting material to obtain the desired dioxatricycles system **21** and **42**. The bicycle structure **38** was prepared in three steps from the 5-methylfurfural **39**. After further eight steps, the hydroxyl bicycle **40** was obtained and utilized as precursor for the cyclization to obtain the tricycle structure **21**. Moreover, another precursor **41** was synthesized from bicycle **38** to obtain the highly functionalized dioxatricyclic structure **42**. Both dioxatricyclic systems **21** and **42** were obtained using the same reaction conditions. The precursors **40** and **41** were treated with NaH in THF in reflux (Figure **13**).

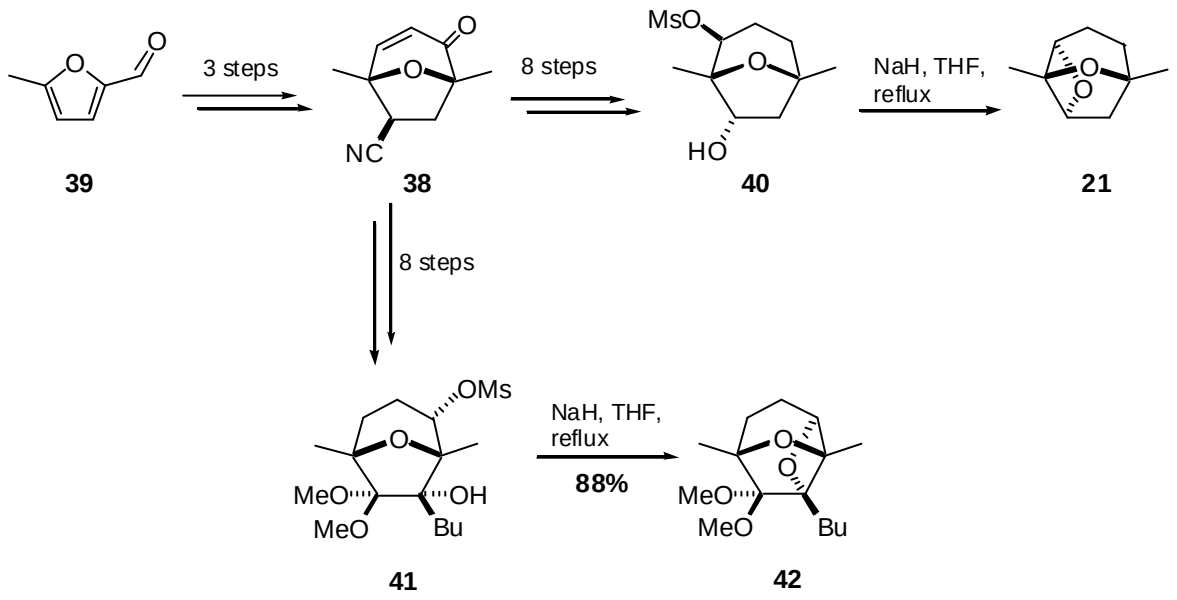


Figure 13: Synthesis of dioxatricycle core **21** and **42** by Heathcock *et al.*

2.1.4 The improved strategy of J. Wittenberg

Starting from 1,1-bisbenzyloxy propanone **43** four biologically active Dictyoxetane structures were synthesized in only eight steps. The a-keto acetal **43** was converted into silyl enol ether **44** and reacted by a [4+3] cycloaddition with 2,5-dimethylfuran.[42] A diastereoselective reduction of ***rac*-45** generated selectively the *endo*-alcohol **46**, which was utilized as precursor for the four dioxatricyclic systems. Deoxygenation of bicycle **46** followed by epoxidation and debenzylation provided the hydroxy oxetane **49**.

[42] a) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J*. **1995**, *1*, 368; b) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew, Chem.* **1998**, *110*, 1137; *Angew. Chem. Int. Ed*. **1998**, *37*, 1266.

Alternatively, the hydroxy group of **38** was methylated and afterwards the oxabicyclic system was epoxidized and deprotected of the benzyl group to provide the epoxy alcohol **50** as the precursor for the other three oxetane systems (Figure **14**). The synthesized dictyoxetane structures **49**, **51**, **52** and **53** showed cytotoxic and cytostatic activity (see chapter 2.1.6).

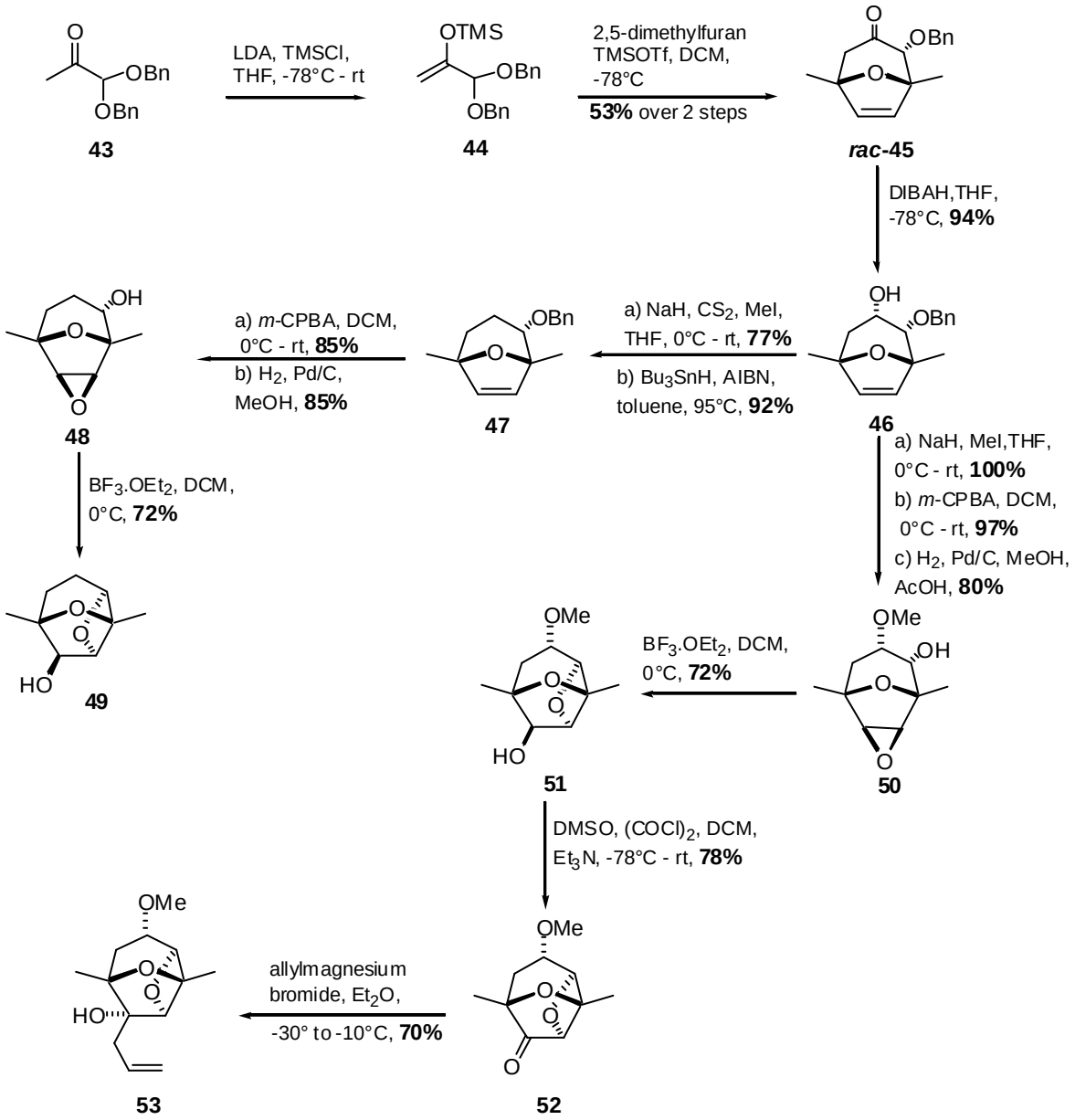


Figure 14: Synthesis strategy employed by J. Wittenberg to obtain the dioxatricyclic skeleton

2.1.5 New dioxatricyclic systems by S. Proemmel

Starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-45** series of tricyclic oxetanes were prepared in short synthetic order following the strategy of J. Wittenberg. Ketone ***rac*-45** was reduced and the resulting hydroxy group was protected with benzoyl and pivaloyl groups. Oxidation of the double bond and debenzylation at C2-position generated a bicyclic epoxy alcohol structure. The four-membered ring was synthesized by intramolecular epoxy opening carried out with equimolar $BF_3.OEt_2$. After cyclization the ester was cleaved reductively to diol **56** which was oxidized to the diketone **57**. The oxidation of the hydroxy ester **55b** generated the keto ester **58** which was further reduced to the alcohol **59** (Figure **15**).

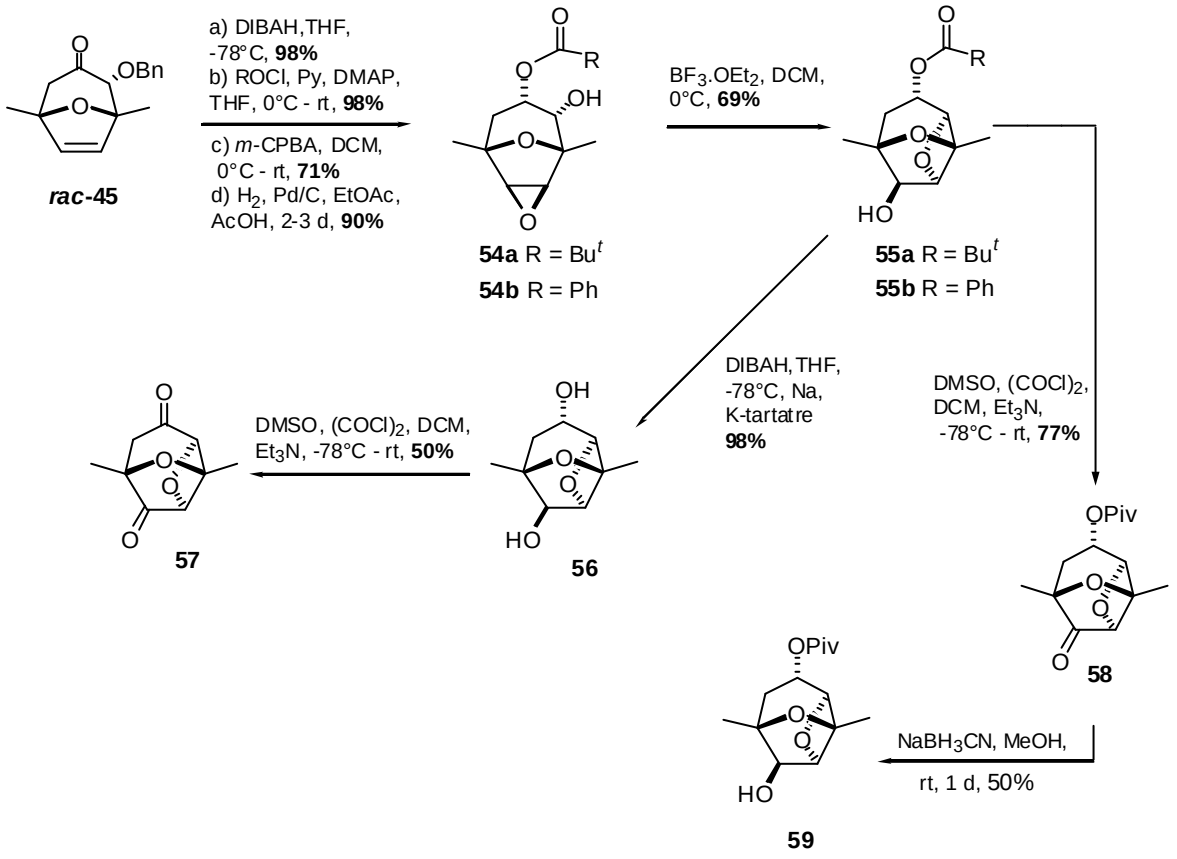


Figure 15: Route employed by S. Proemmel to generate oxatricycles and dioxatricycles

Wittig-olefination of the keto ester **58** gave olefins **60a** and **60b**. Further derivations of the olefin **60a** conduced to the protected keto alcohol **61**. Afterwards, silyl protected keto

alcohol **62** was converted into alkynyl substituted alcohol **63**. Structure **64** was generated by a nitrile oxide cycloaddition[43] using as dipolarophile the exocyclic olefin double bond contained in tricyclic silylether **61** (Figure **16**).

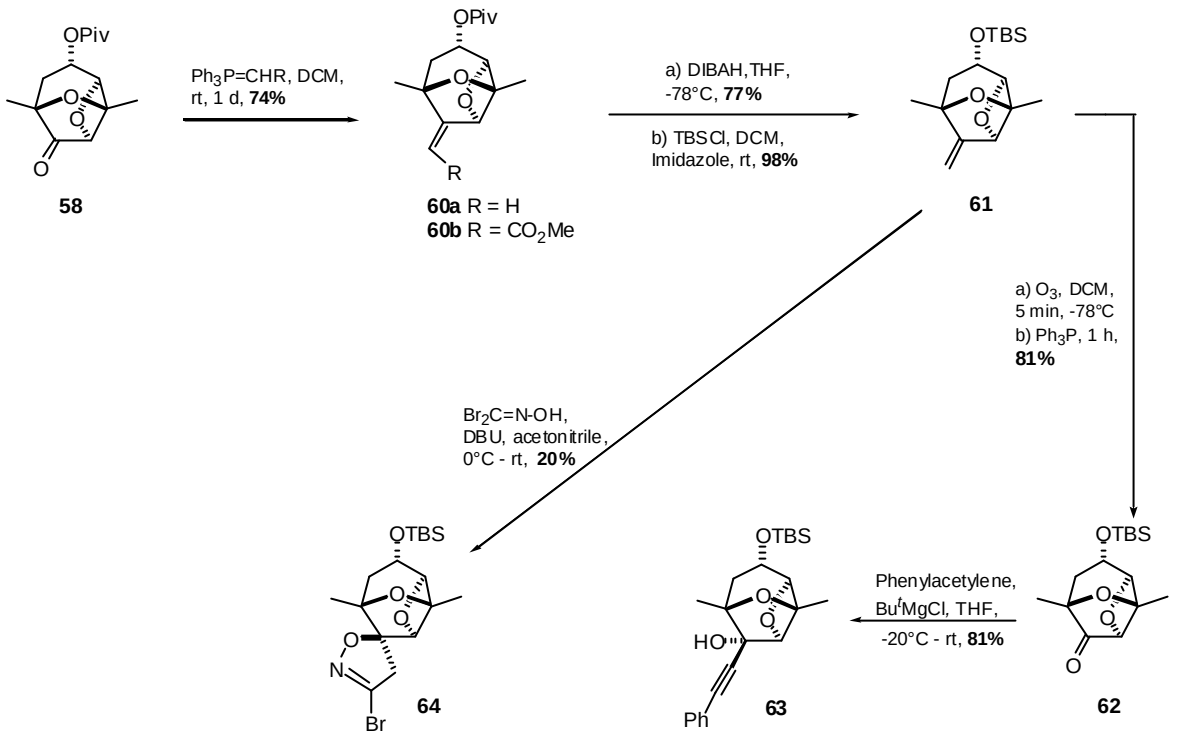


Figure 16: Derivations of some dioxatricycles synthesized by S. Proemmel

After the evaluation of biological activities of several tricyclic systems, only the dioxatricyclic ester ***rac*-60b** showed weak cytostatic activity, but no cytotoxic activity towards tumor cells (see chapter 2.1.6).

Aminated oxetanes were generated by reductive amination[44] of oxabicyclic ketone ***rac*-45** and posterior protection of the amino function aminated bicyclic olefin **65**. Epoxidation and debenzylation at the C2-position provided a proper precursor for the synthesis of desired tricycle **66** (Figure **17**).

[43] a) De Amici, M.; De Micheli, C.; Misani, V. *Tetrahedron* **1990**, *46*, 1975; b) Halling, K.; Thomsen, I.; Torssell, K. B. G.; Lach, D. L. *Liebigs Ann. Chem.* **1989**, 985; c) De Amici, M.; De Micheli, C.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646.

[44] a) Lane, C. F.; *Synthesis* **1975**, 135; b) Borch, R. F.; Berstein, M. D.; Durst; H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; c) Mori, K.; Sugai, T.; Maeda, Y.; Okazaki, T.; Naito, H. *Tetrahedron*, **1985**, *41*, 5307; d) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

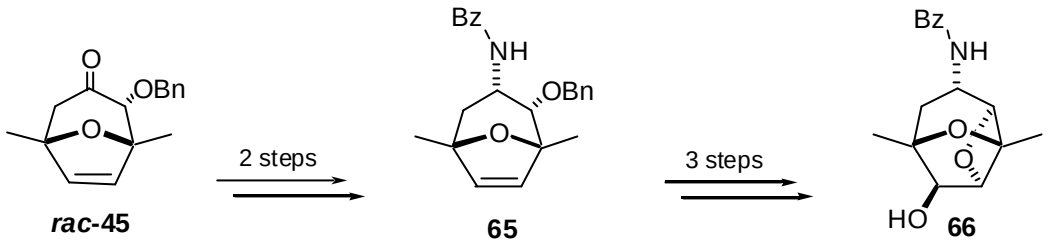


Figure 17: Aminated oxetane synthesized by S. Proemmel

Analogue oxatricycles containing an acetate ester at the C3-position were obtained employing a similar route as in previous synthesis (Figure **18**).

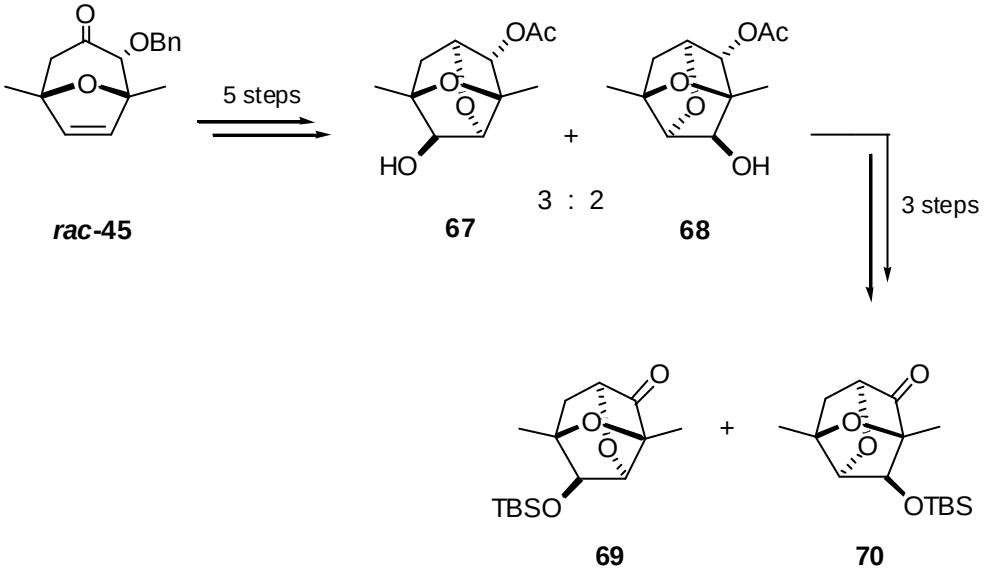
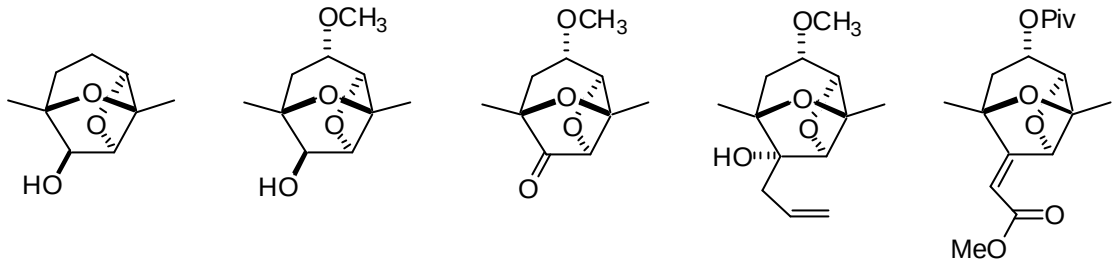


Figure 18: Oxatricyclic systems with acetate ester at the C3-position (S. Proemmel)

Several tricyclic structures were evaluated in terms of biological activity. Substances **66** and **67** did not show any cytostatic or cytotoxic activity up to concentrations of 50 µMol.

2.1.6 In-vitro test for the characterization of dioxatricyclic structures

Some of the dioxatricycles synthesized by J. Wittenberg and S. Proemmel showed biological activity (cytotoxic and cytostatic) towards tumor cells (Figure **19**).



49 **51** **52** **53** ***rac*-60b**

Figure 19: Biological active oxatricycles synthesized by J. Wittenberg and S. Proemmel

The four substrates **49**-**53** show cytostatic activity, in the range of 5-fluorouracil, a well known antimetabolite, capable of entering the synthesis and function of nucleic acids, similar to AZT, an anti-AIDS drug. Substance ***rac*-60b** showed cytostatic but no cytotoxic activity towards tumor cells (cell lines: HEP G7 and MCF7). The results of the investigation are summarized in the Table **1**.

Table 1. Antitumor activity (µmol/l) measured toward HMO2, HEP G2 and MCF7 cells

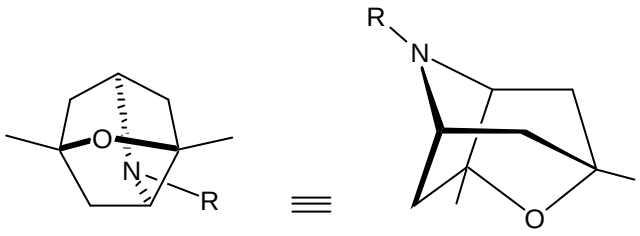
Substance	Carcinoma type	GI_{50}[a]	TGI[b]	LC_{50}[c]
49	HMO2	4.0	50	>100
	HEP G2	0.1	30	>50
51	HMO2	3.0	57	>100
	HEP G2	<0.1	45	>50
52	HMO2	<1.0	72	>100
	HEP G2	<0.1	35	>50
53	HMO2	<1.0	54	>100
	HEP G2	<0.1	30	>50
***rac*-60b**	HMO2	>50	>50	>50
	HEP G2	13	>50	>50
	MCF7	10	>50	>50
5-fluorouracil	HMO2	1.2	35	>50
	HEP G2	0.15	50	>50
cis-platinum	HMO2	0.1	2.5	40
	HEP G2	0.5	30	>50

[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.

Due to these results, the synthesis of new dioxatricyclic derivatives with an increased cytostatic and/or cytotoxic effect was an interesting goal of the present work.

2.2 Oxazatricyclononane structures

Recently, a short synthetic route to generate structures similar to the system 1,3-dimethyl-2-oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonane **71** with the same skeleton as the Scopolamine **18** was introduced by S. Proemmel[45] (Figure **20**).



71

Figure 20: Structure of 1,3-dimethyl-2-oxa-6-azatricyclo[3.3.1.$0^{3,7}$]nonane

Starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-45** two new oxazatricyclic systems were prepared following similar strategy as in previously described routes. The amino bicyclic olefin **72** was generated by reductive amination of ketone ***rac*-45**. Oxidation of the double bond and debenzylation at C2-position generated a bicyclic epoxy alcohol structure **73**. An intramolecular cyclization using a Grignard agent provided the tricyclic noradamantanes **74** and **75** (Figure **21**).

[45] Proemmel, S. *Doctoral thesis*, University of Hannover **2001**.

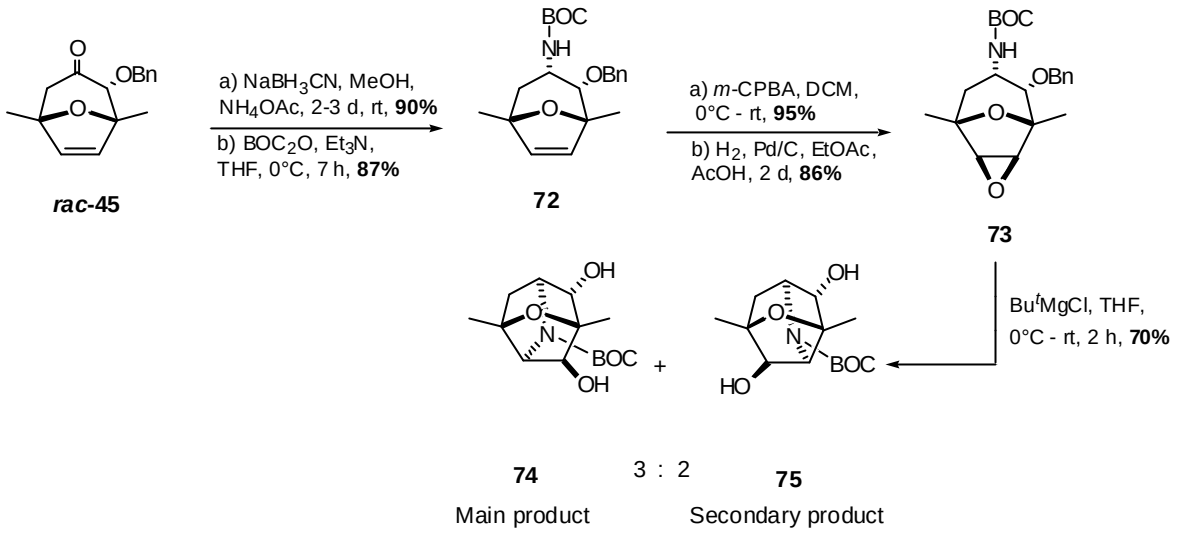


Figure 21: Oxazatricycles synthesized by S. Proemmel

Structures **74** and **75** were separated by column chromatography. Further derivations of the main product **74** gave biologically active oxazatricycle **77** (Figure **22**).

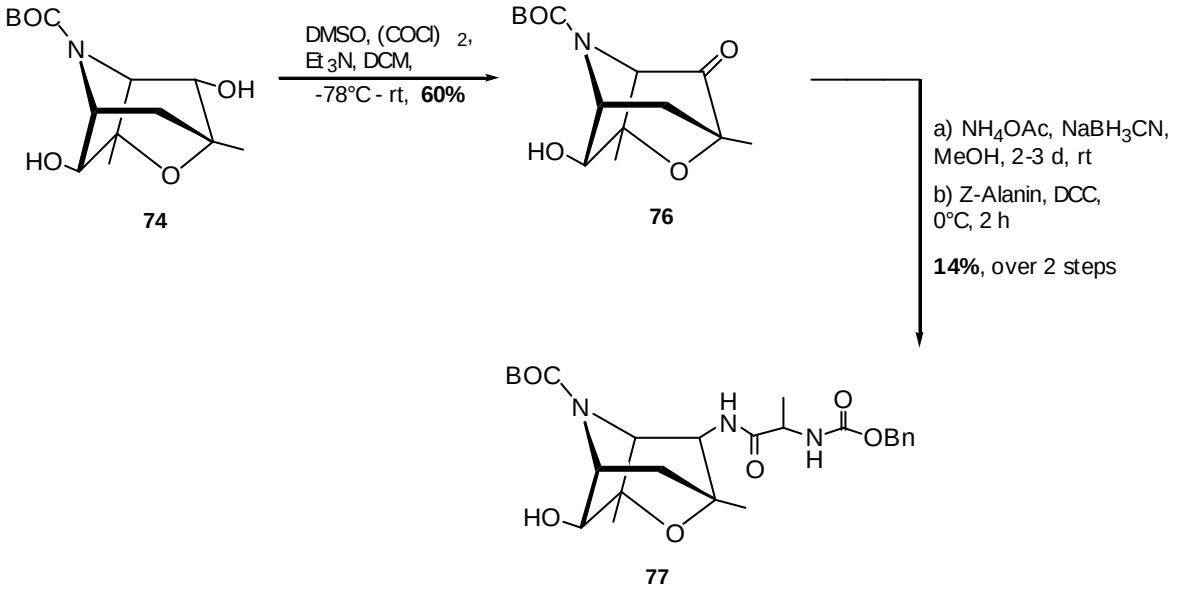
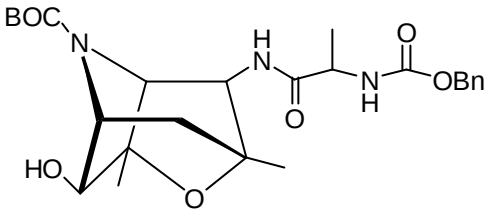


Figure 22: Derived oxazatricyclic systems synthesized by S. Proemmel

2.2.1 in-vitro Test for the characterization of oxazatricyclic structure

Scopolamine derivates **74** and **77** were evaluated in terms of biological activity. Tricyclic system **74** does not show any cytostatic or cytotoxic effect up to concentrations of 10 µMol. Oxazatricyclic compound **77** present a cytostatic effect tumor cells (cell lines: HEP G2, HMO2 and MCF7) (Figure **23**). The results of the investigation are summarized in the Table **2**.



77

Figure 23: Oxazatricycle with cytostatic effect towards tumor cells (S. Proemmel)

Table 2. Antitumor activity (µg/mL) measured toward HMO2, HEP G2 and MCF7 cells

Oxazatricyclic	Carcinoma type	GI_{50}[a]	TGI[b]	LC_{50}[c]
77	HMO2	18	>50	>50
	HEP G2	18	>50	>50
	MCF7	18	>50	>50

[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 Scopolin derivate **77** showed cytotoxic activity in the three cell lines. Due to this result the synthesis of new Scopolamine derivates with an enhanced cytostatic and/or cytotoxic activity was an important aim for the present work.

2.3 Azabicyclic structures

For the synthesis of the system 8-azabicyclo[3.2.1]octane **78**, a [4+3] cycloaddition between substituted pyrroles and an oxyallyl cation was employed in 1993 by C. Dannenberg.[46] Cycloadduct **78** had obvious structural similarities to the tropane alkaloids as Tropane **20**, Cocaine **79** and Tropinone **80** (Figure **24**).

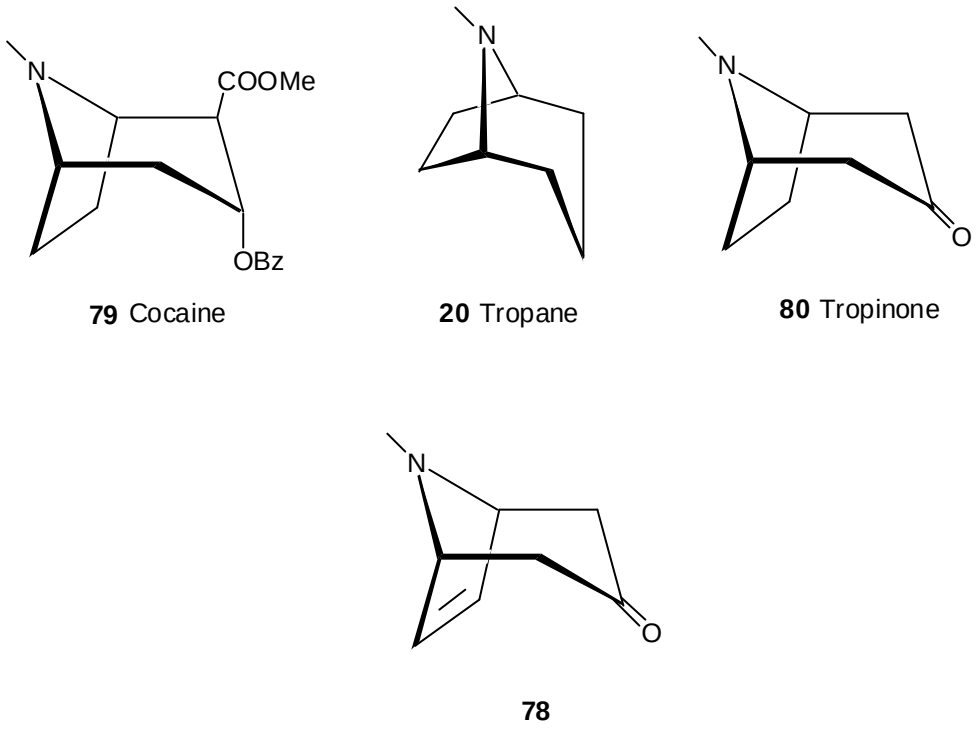


Figure 24: Azabicycle **78**, synthesized by C. Dannenberg, similar to the structures of Tropane **20**, Cocaine **79** and Tropinone **80**

2.3.1 Synthesized substituted pyrrole by C. Dannenberg

The first step to get the cycloadduct **78** was to protect the amino group of the pyrrole **81**. Several protecting groups were employed: different ester groups, arylsulfonyl and alkyl silyl groups (Figure **25**).

[46] Dannenberg, C. *Doctoral thesis*, University of Hannover **1993**.

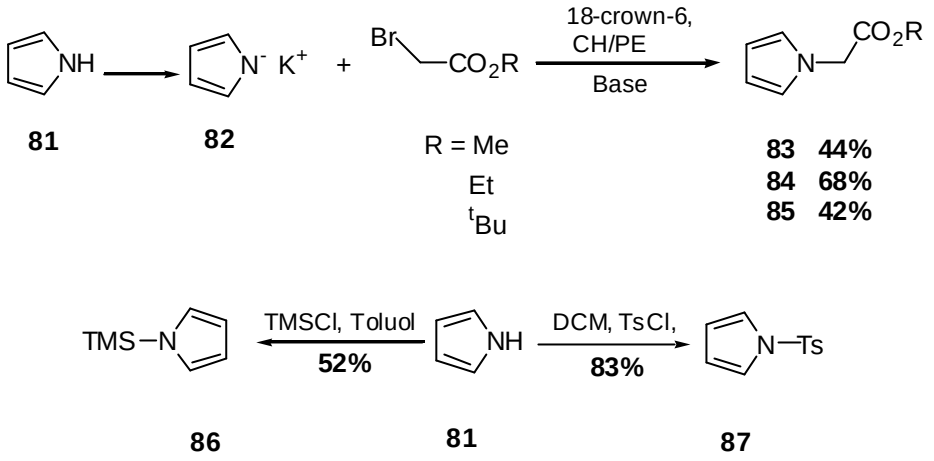


Figure 25: Some examples of synthesized substituted pyrroles by C. Dannenberg

To obtain the substituted pyrrole **83-85** different a-bromo acetic acid alkyl ester were used to react with the potassium salt **82** and a catalytic amount of 18-crown-6. To form the potassium salt **82** in quantitative yield, bases like KH or KOBu^t are efficient reagents. The TMS-protected pyrrole **86** was synthesized following the method of Fessenden[47] with acceptable yield. Compound **87** was generated using tosyl chloride in dichloromethane employing the method proposed by Illi.[48]

2.3.2 [4+3] Cycloaddition of substituted pyrrole by C. Dannenberg

Several [4+3] cycloadditions were carried out with substituted pyrroles toward the synthesis of similar structures to Tropane **20** and Tropinone **80** (Figure **26**).

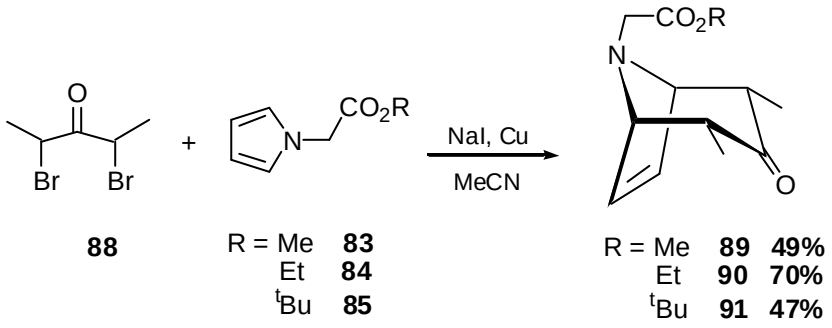


Figure 26: Examples of [4+3] cycloadditions by using NaI/Cu method by C. Dannenberg

[47] Fessenden, R.; Crowe, D. F. *J. Org. Chem.* **1960**, *25*, 598.
[48] Illi, V. O. *Synthesis* **1979**, 136

These cycloaddition reactions were carried out using the NaI/Cu method developed by Hoffmann and Mann.[49] In this reaction, the oxyallyl cation reaction partner was generated from the dibromo ketone **88** in the presence of NaI and Copper by a consecutive nucleophilic substitution S_N2 reaction to the diiodo ketone **92**. Reducing the ketone **92** the enolate **93** was obtained which through a S_N1 reaction lost an iodide anion (Figure **27**).

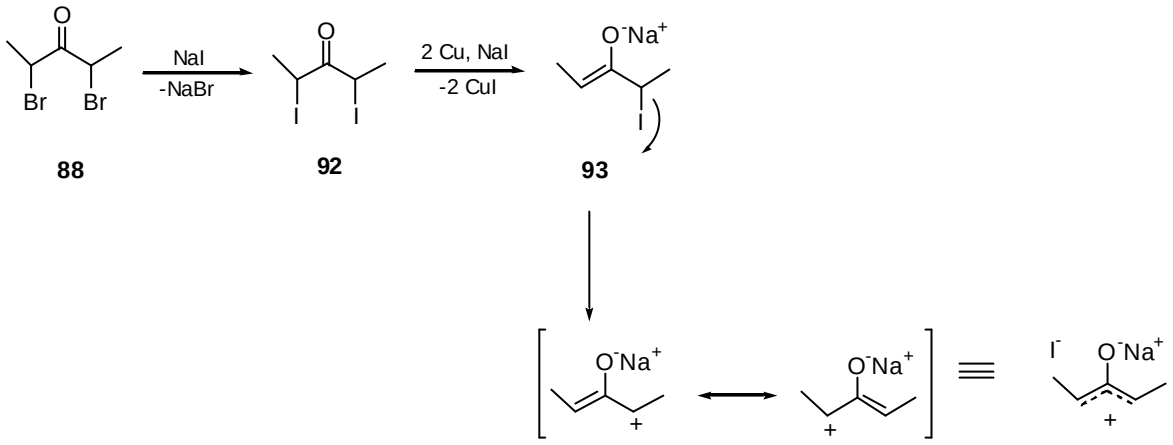


Figure 27: Generation of the oxyallyl cation employed in the NaI/Cu method

To obtain a cycloadduct with a similar skeleton such as the tropane alkaloids several [4+3] cycloadditions with substituted pyrroles and different oxyallyl cations as reaction partner were carried out and reported. Various methods were developed to obtain an adequate oxyallyl cation. For example, Mann[50] elaborated a method to generate the oxyallyl cation using Et_2Zn and Noyori[51] employed an iron reagent with N-Methyloxycarbonylpyrrole to generate the corresponding cycloadduct.

One of the objectives in the present work is the synthesis of azabicycles by a [4+3] cycloaddition between substituted pyrroles and silyl oxyallyl cations instead of the oxyallyl cation generated in the NaI/Cu method.

[49] a) Hoffmann H. M. R., Fierz, G.; Chidgey, R. *Angew. Chem.* **1974**, *86*, 444; b) Mann, J; Cowling, A. P. *J. Chem. Soc. Perkin Trans. I* **1978**, 1564.

[50] Mann, J; de Almeida Barbosa, L. C. *J. Chem. Soc. Perkin Trans. I* **1992**, 787.

[51] Noyori, R.; Hayakawa, Y.; Baba, Y.; Makino, S. *J. Am. Chem. Soc*. **1978**, *100*, 1786.

3. CONCEPTUAL FORMULATION

The main aim of this project was to synthesize new oxatricyclic and oxazatricyclic structures to evaluate their biological activities following one of the investigation lines in our research group. In previous published works of the group of Prof. H. M. R. Hoffmann some synthesized dioxatricyclic compounds showed cytotoxic and cytostatic effects in human carcinoma.

Following this objective new tricyclic structures were prepared introducing several ether and amino functions at the C3-position in the functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one structure.

A second objective of this work was to synthesize new bicyclic molecules with tropane skeleton using the [4+3] cycloaddition methodology developed in our group.

As a third objective was projected to synthesize a bicyclic system containing an alkynyl chain side at the C1-position.

Finally, several X-ray structures were analyzed to determinate the absolute configuration of the stereocenters contained in the different molecules.

4. RESULTS AND DISCUSSION

4.1 Synthesis of Oxatricyclic substances

Cycloaddition in its many manifestations represents one of the most powerful methods in organic chemistry to obtain cyclic structures. A [4+3] cycloaddition reaction between a 1,3-diene and an allyl, or more frequently an oxyallyl cation, offers rapid access to functionalized seven-membered carbocyclic rings with many of the attendant advantages of other cycloaddition processes. Starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-45** and ***rac*-94**, a series of dioxatricyclic structures were synthesized to evaluate their biological activity. Several dioxatricyclic structures obtained in previous works presented cytostatic activities (see chapter 2.1.6).

R = H ***rac*-94**
R = Me ***rac*-45**

Figure 28: Starting oxabicycles for oxetane series

4.1.1 [4 + 3] Cycloaddition reaction using silyl enol ethers

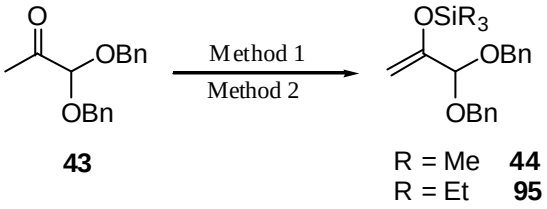
The [4+3] cycloaddition reaction of oxyallyl cations to furans is a general and efficient method to synthesize functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one like the bicyclic systems ***rac*-45** and ***rac*-94**.

In the present work, two different methods to obtain the silyl enol ether were used, kinetic method and thermodynamic method. In the kinetic method LDA in THF at -78°C is used to obtain silyl enol ethers and the thermodynamic method was carried out by using triethylamine in DMF at 75°C.

Silyl enol ethers **44** and **95** were prepared from **43** by the two methods, kinetic method (named in this work method 1) and thermodynamic method (named method 2). Method 1 is recommended for relatively small scale reactions, (up to 30 mmol of dibenzyl acetal **43**), while method 2 is employed for large scale reactions (up to 130 mmol of dibenzyl acetal **43**).

Due to its acid sensitivity, [1-(benzyloxy-methoxy-methyl)-vinyloxy]-trimethyl-silane **44** cannot easily be purified by column chromatography, unlike the TES-enol-ether. Using Et_3SiCl as precursor to obtain the silyl enol ether, only Method 1 gave a good yield, Table **3**.

Table 3

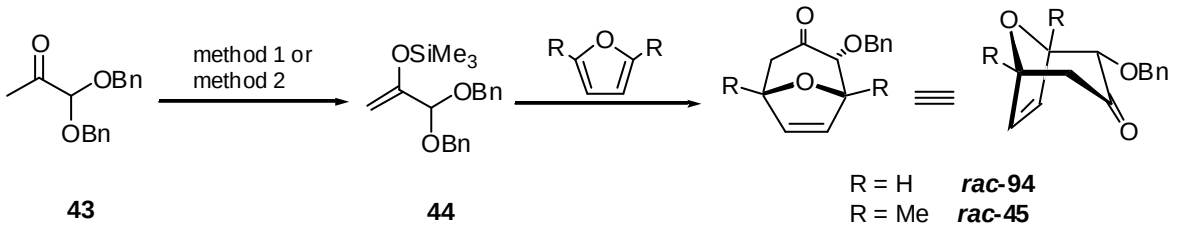


Entry	Method	Conditions	Yield [%]
1	1	LDA, TMSCl, THF, -78°C	no isolated
2	1	LDA, TESCl, Et_3N, THF, -78°C	82
3	2	TMSCl, DMF, Et_3N, 75°C, 16 h	no isolated
4	2	TESCl, DMF, Et_3N, 75°C, 16 h	no reaction

Method 1: kinetic method; Method 2: thermodynamic method

To get the desired cycloadducts silyl enol ether **44,** synthesized by using method 1 and method 2, was reacted with furan and 2,5-dimethylfuran as 1,3-diene partners. The best yield (over two steps) was obtained with the substituted furan, Table **4**.

Table 4



Entry	Silyl enol ether **44**	1,3-diene	Conditions	Yield [%] (over 2 steps)
1	by method 1	Furan	TMSOTf cat., DCM, -78°C	41
2	by method 2	Furan	TMSOTf cat., DCM, -78°C	61
3	by method 1	2,5-Dimethylfuran	TMSOTf cat., DCM, -78°C	53
4	by method 2	2,5-Dimethylfuran	TMSOTf cat., DCM, -78°C	67

4.1.2 Synthesis of Dioxatricyclic oxetanes as rigid C-Glycosides

According to the results from the dioxatricycle α-methoxy-substituted at C3-position and its higher biological activity (see chapter 2.1.6), it was decided to continue synthesizing new dioxatricyclic derivatives to seek out their biological activities. The introduction of different ether functionalities to the oxabicycles ***rac*-45** and ***rac*-94** was the first kind of derivations investigated in the present work. Alkyl ethers are stable to a wide range of aqueous acidic and basic conditions, and are not readily attacked by most metal hydride reducing agents or mild oxidizing agents like Swern, PCC, etc. Methyl, ethyl, propyl and benzyl ether were utilized to observe possible variations in the biological activity for the corresponding oxetane structures (Figure **29**).

The dioxatricyclic systems were also synthesized by using a similar strategy from J. Wittenberg where an epoxy alcohol was employed as precursor in an intramolecular epoxy opening (see chapter 4.1.6).

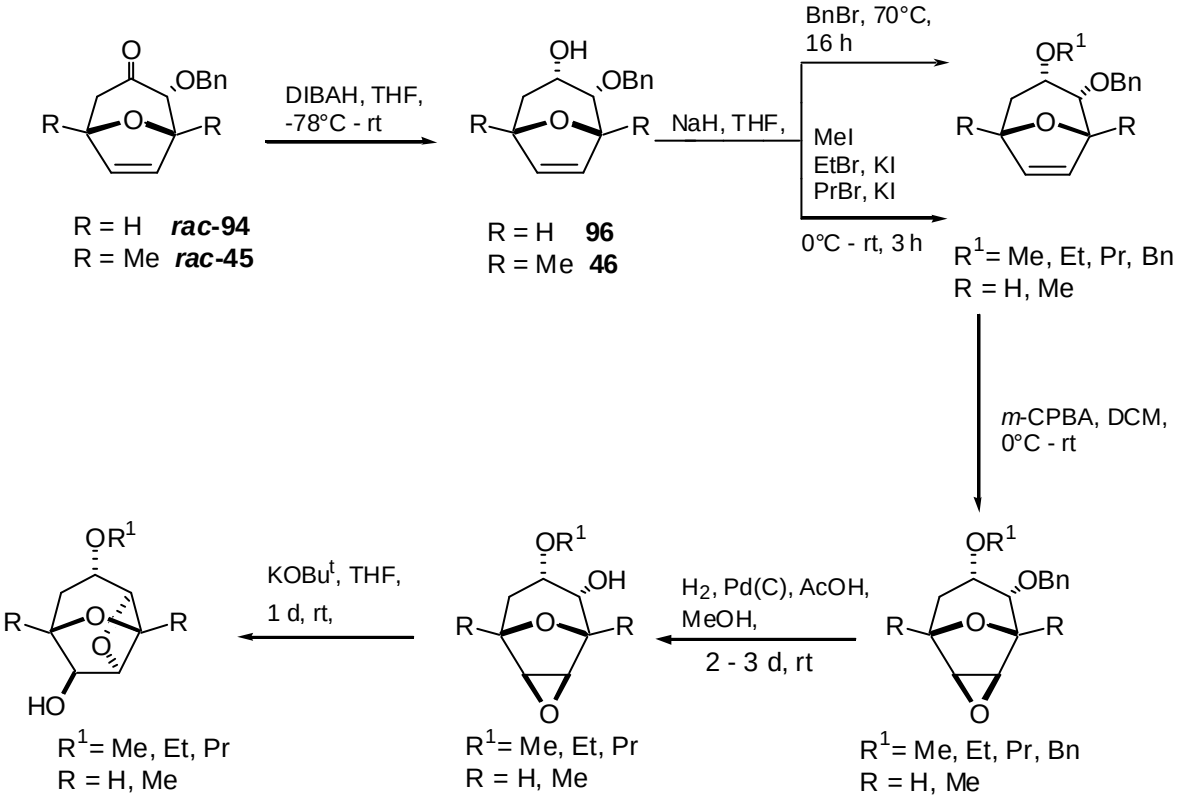


Figure 29: Route to oxetanes with an alkyl ether function at the C3-position

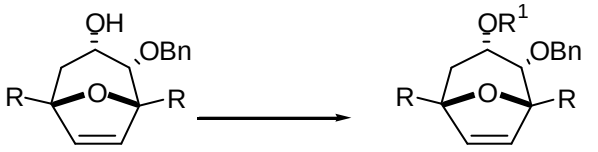
4.1.2.1 Bicyclic skeleton with alkyl ether in the C3-position

The oxabicycles ***rac*-45** and ***rac*-94** obtained were treated with a DIBAH solution in THF at -78°C to reduce the corresponding ketone function and to generate the alcohols **96** and **46**.

The introduction of a methoxy group at the C3-carbon atom in alcohols **96** and **46** gave excellent product yields obtained by following the Williamson[69] ether synthesis method (Table **5**, entries 1-2). In the case of other ether functions a catalytic amount of KI was needed to obtain the desired bicyclic ether. Alkyl bromide gave better results than alkyl chloride, due to the better leaving-group qualities of bromine.

In accordance with the on growing sterical demands from methyl to propyl ether groups the yields in ether formation are decreasing. Interestingly, in comparison to the unsubstituted furan system the yields for the 2,5-dimethylfuran adducts are remarkably higher. This may be due to the stabilizing effects of the methyl groups at C1- and C5-position for the whole molecule. These observations are summarized in Table **5**.

Table 5



R = H **96**
R = Me **46**

R_1 = Me, Et, Pr
R = H, Me

Entry	R	R^1	Conditions	Yield [%]
1	Me	Me	NaH, MeI, THF, 0°C – rt, 3h	98
2	H	Me	NaH, MeI, THF, 0°C – rt, 3h	86
3	Me	Et	NaH, EtBr, KI, THF, 0°C – rt, 3h	83
4	H	Et	NaH, EtBr, KI, THF, 0°C – rt, 3h	60
5	Me	Pr	NaH, PrBr, KI, THF, 0°C – rt, 3h	60
6	H	Pr	NaH, PrBr, KI, THF, 0°C – rt, 3h	54
7	H	Pr	NaH, PrCl, KI, THF, 0°C – rt, 3h	20
8	Me	Pr	NaH, PrI, THF, 0°C – rt, 3h	no reaction
9	H	Pr	NaH, PrI, THF, 0°C – rt, 3h	no reaction

[69] W. Williamson *Justus Liebigs Ann. Chem.* **1851**, *77*, 37-49.

4.1.2.2 Bicyclic skeleton with benzyl ether at the C3-position

Due to the stability of the bicyclic skeleton with benzyl ether at C3-position, was decided to synthesize such oxabicyclic compounds to observe possible variations in biological activity on corresponding oxetane structures. The Williamson ether synthesis is employed as the most common method for preparing benzyl ethers. As in the case of alkyl ethers (see Table **5,** entries 3-7), a catalytic amount of KI (TBAI could be also used) was added to accelerate the alkylation because iodide displaces bromide or chloride to give benzyl iodide *in situ* which is a much better alkylating agent.[70] The iodide ion is then regenerated during the alkylation with benzyl iodide. Under these conditions also tertiary alcohols can be benzylated.[71]

Several different conditions to generate in good yield the desired bicyclic structures **177** and **178** were used, Table **6**.

Table 6

R = H **96**
R = Me **46**

R = H **178**
R = Me **177**

Entry	R	Conditions	Yield [%]
1	Me	NaH, BnCl, KI, THF, RT, 1 h	26
2	Me	NaH, BnBr, KI, THF, RT, 1 h	51
3	Me	NaH, BnBr, THF, 70°C , 16 h	89
4	H	NaH, BnBr, THF, 70°C , 16 h	80

Above results showed higher yields for higher temperature and longer reaction time (the reaction time could be reduced, possibly, with the addition of a catalytic amount of KI). The same reaction was carried out at room temperature using KI and as previously mentioned (see Table **5**, entries 6 and 7) the maximum yield was obtained by employing BnBr as alkyl halogenated agent. In comparison to the unsubstituted furan system the yield for the 2,5-dimethyl oxabicyclic structure **177** was better. This may be due to the stabilizing effects of the methyl groups at C1- and C5-position on the whole molecule.

[70] Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. *Tetrahedron* **1990**, *46*, 1767.

[71] a) Nicolau, K. C.; Liu, J. J.; Wwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun*. **1992**, 1118; b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc*. **1998**, *110*, 2506.

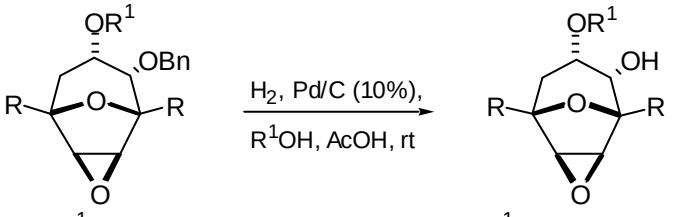
4.1.2.3 Cleavage of benzyl ether group

After the protection of the free alcohol function the double bond of the corresponding oxabicyclic structures was oxidized using *m*-CPBA in DCM at 0°C. Resulting epoxy bicyclic structures were afterwards, debenzylated at the C2-position.

Numerous methods were available for benzyl ether removal.[72] At elevated temperature, and in the presence of Lewis acids, benzyl ethers may cleave with metal hydrides by removing a benzylic proton from benzyl ether. In the presence of multiple functionalities several problems can occur, slow debenzylation rate, acyl group migration and reagent incompatibility. Takeda developed a different cleavage way by using anhydrous ferric chloride, which was highly efficient for the removal of benzyl and phenylbenzyl ethers at room temperature.[73] With this method, methyl ether, benzoate and acetate groups were not affected by the removal conditions.

Catalytic hydrogenolysis offers the mildest reaction conditions for the deprotection of benzyl ethers. The catalyst of choice was Pd(C) 10%. In this method, a solution of benzyl ether in ethanol was treated with Pd(C) in the presence of AcOH for 3 days. This method was used for deprotecting water-soluble alcohols and the yields were usually high in most bicyclic systems with alkyl ether function at the C3-position, Table **7**.

Table 7



R = Me	R^1 = Me	**163**	R^1 = Me	**50**
	Et	**164**	Et	**101**
	Pr	**173**	Pr	**102**
R = H	R^1 = Me	**174**	R^1 = Me	**105**
	Et	**175**	Et	**106**
	Pr	**176**	Pr	**107**

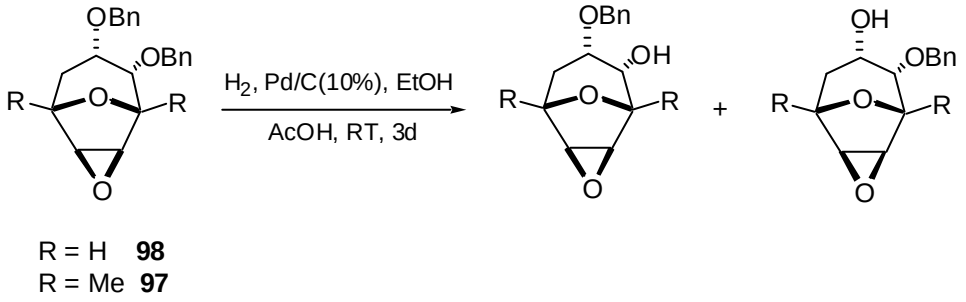
[72] a) Fuji, K.; Kawataba, T.; Fujita, E. *Chem Pharm. Bull*. **1980**, *28*, 3662; b) Kon, K; Ito, K.; Isoe S. *Tet. Lett*. **1984**, 3739.

[73] Park, M. H.; Takeda, R.; Nakanishi, K. *Tet. Lett*. **1987**, *28*, 3823-3824.

Entry	R	R^1	R^2	Yield [%]
1	H	Me	Me	52
2	H	Et	Et	50
3	H	Pr	Et	47
4	Me	Me	Me	81
5	Me	Et	Et	64
6	Me	Pr	Et	54

Obtained epoxy alcohols by entries 1 and 2 showed low yields, most probably due to their polarity and consequently their hydrophilic character which is unfavorable during aqueous work-up.

In the case of structures **97** and **98**, with benzyl groups in the C2 and C3-positions, the selective reduction of benzyl group at the C2-position was not obtained. The same conditions (Pd/C in MeOH in the presence of acetic acid for 3 days) were used for the selective reduction of one benzyl group. Several 1D and 2D-NMR measurements indicated that the cleavage was performed only to one benzyl group but most likely, to give a mixture of compounds with similar polarity and for this reason difficult to separate by column chromatography (Figure **30**).



R = H **98**
R = Me **97**

Figure 30: Unselective cleavage of benzyl ether group at the C2-position

4.1.2.4 Formation of new tricyclic oxetane structures with an ether function in the C3-position

The cyclization towards the oxetane ring using $BF_3 \cdot OEt_2$ was presented recently by J. Wittenberg (see chapter 2). In that case of epoxy alcohol **50** the $BF_3 \cdot OEt_2$-mediated cyclizations caused cleavage of the methyl ether to the *endo*-alcohol, which entered into

facile 5-*exo*-tet cyclizations leading to a second tetrahydrofuran unit (two structural isomers, **100a** and **100b**) (Figure **31**). However, base treatment, using $KOBu^t$ in THF, afforded the desired tricyclic skeleton in good yield.

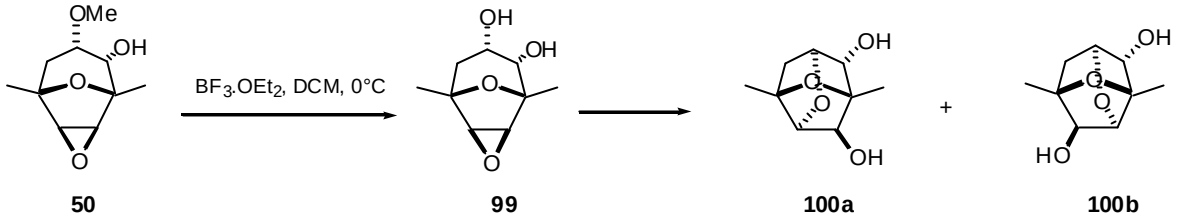
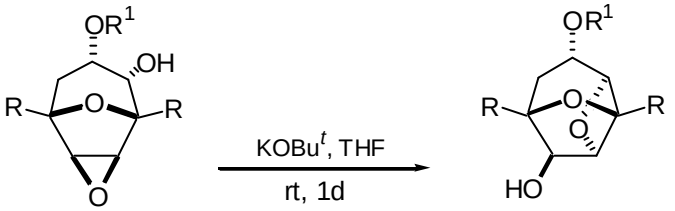


Figure 31: Cleavage of methyl ether by using $BF_3 \cdot OEt_2$

Because of these results, the synthesis to the oxetane ring was carried out using an intramolecular epoxy opening by base treatment by using $KOBu^t$ in THF at room temperature for 24 h, employing corresponding epoxy alcohol; yields are summarized in the Table **8**.

Table 8



R = Me	R^1 = Me	**50**	R^1 = Me **51**
	Et	**101**	Et **103**
	Pr	**102**	Pr **104**
R = H	R^1 = Me	**105**	R^1 = Me **108**
	Et	**106**	Et **109**
	Pr	**107**	Pr **110**

Entry	R	R^1	Yield [%]
1	H	Me	62
2	H	Et	52
3	H	Pr	49
4	Me	Me	83
5	Me	Et	58
6	Me	Pr	56

The epoxy ring opening reaction afforded better yields for those epoxy alcohol which had smaller ether group at the C3-position. Comparing bicyclic epoxy alcohol skeletons (R = H, Me) we observed that the more substituted structure was easier opened. The reason is because the higher thermodynamic stability of the second type of structure. Crystal structure of compounds **108** and **109** confirmed the spectroscopic results (Figure **32**).

Figure 32: Crystal structure of oxetanes **108** and **109**

The transformation of the epoxy alcohol to the corresponding oxatricyclic structure must proceed *via* prior conformational change of the six membered oxacyclic ring into a minor boat, which brings the hydroxyl group close enough to the epoxy ring system for a stereo-electronically controlled formation of the new oxetane C-O bond (Figure **33**).

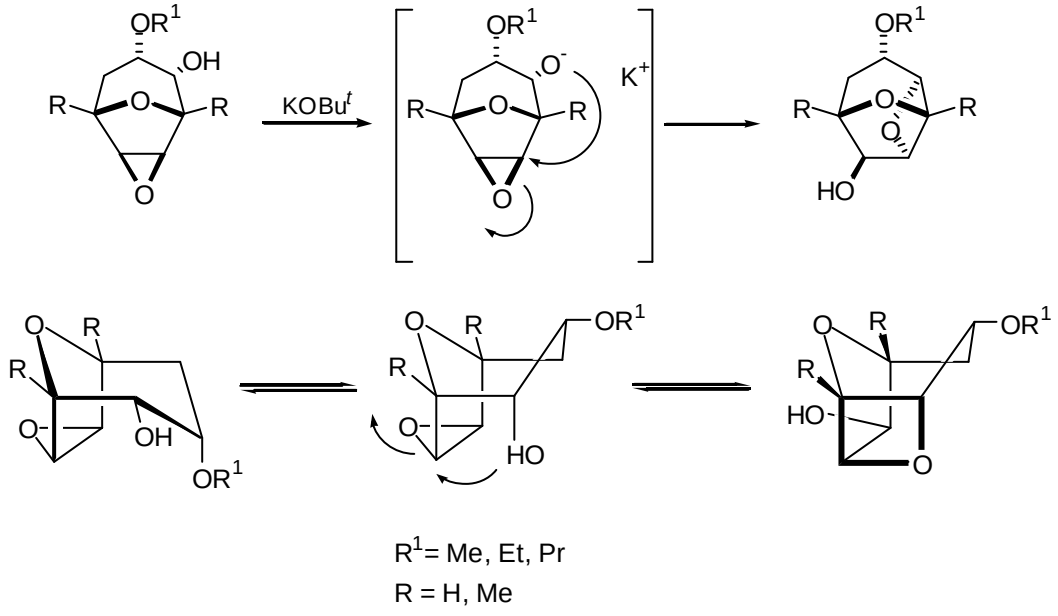


Figure 33: Mechanism for intramolecular cyclization to oxetane using KOBu^t

The epoxy alcohol mixture obtained in chapter 4.1.2.3 (see Figure **30**) was treated with KOBu^t to afford the corresponding oxetane structures by intramolecular epoxy opening (Figure **34**). The resulting mixture could not be separated by column chromatography. A posterior oxidation of oxetane tricyclic compounds was carried out with the idea to find a polarity difference to reach a column chromatography separation but again this method was not useful.

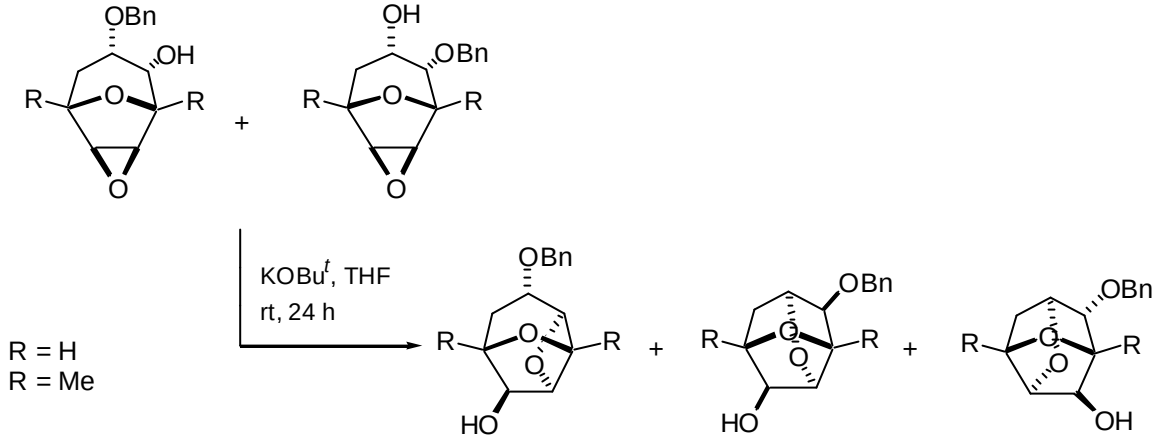
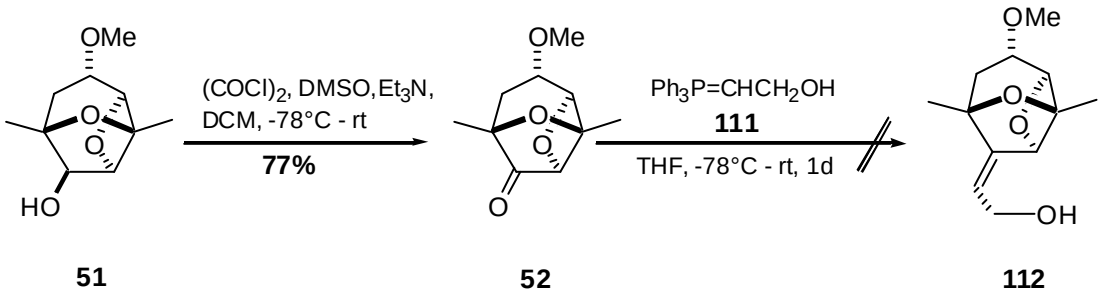


Figure 34: Resulting mixture of dioxatricycles by intramolecular epoxy opening

4.1.3 Synthesis of new tricyclic oxetanes

The free alcohol function in the oxetane **51** structure was oxidized using the Swern oxidation[74] method to generate corresponding ketone **52**. Afterwards a Wittig reaction[75] using the ylid[76] **111** did not give the desired tricyclic product (Figure **35**).



51 **52** **112**

Figure 35: Swern oxidation to oxetane **52** and attempted Wittig reaction

[74] Shishido, K.; Takahashi, K.; Fukumoto, K. *J. Org. Chem*. **1987**, *52*, 5704.
[75] Wittig, G.; Geissler, G. *Justus Liebigs Am. Chem.* **1953**, *580*, 44-57.
[76] provided by S. Malik, see: a) Malik, S. *Doctoral thesis*, University of Hannover **2002**; b) see also: Johnson, A. W. *Ylid Chemistry*, Academic Press, New York, **1979**.

Although the tricyclic system **112** was not generated, Hands[77] reported that the structure **113** can reacted as a phosphonium ylid with aldehydes and ketones to give ?,d-unsaturated alcohols (Figure **36**).

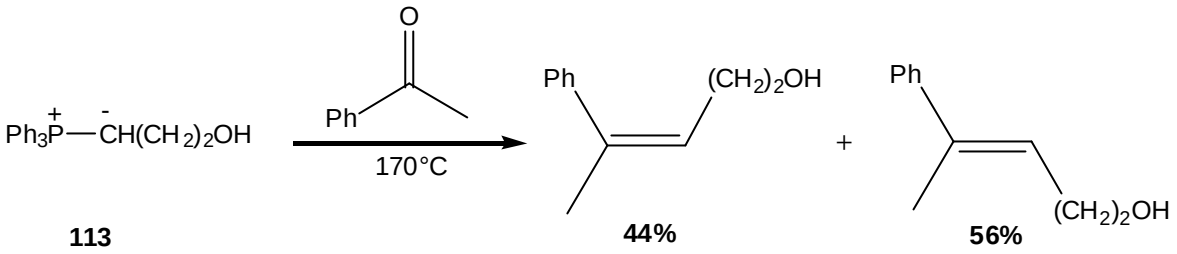


Figure 36: Wittig olefination with the ylid **113** by Hands

The same Swern oxidation procedure in the case of tricyclic **109** afforded ketone **114** with an acceptable yield (Figure **37**).

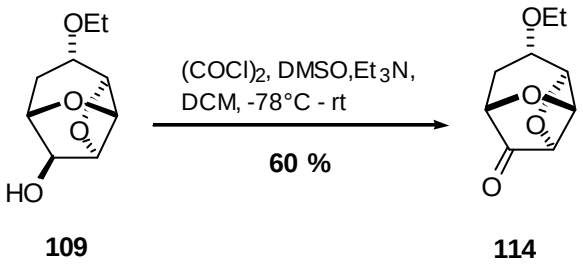


Figure 37: Swern oxidation to tricyclic ketone **114**

As an alternative oxidative agent PCC was employed despite the above result. The tricyclic alcohol **108** was oxidized to the lactone **115** by PCC oxidation.[78] This oxidation was carried out using Pyridinium Chlorochromate in DCM at room temperature. The resulting unexpected lactone product **115** could be isolated in small yield (Figure **38**).

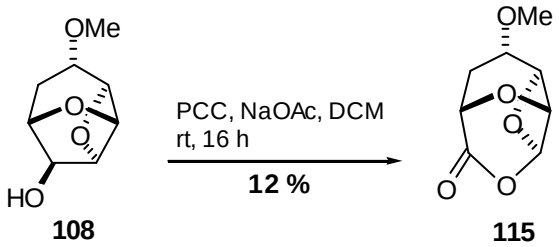


Figure 38: Oxatricyclic lactone by PCC oxidation from oxetane **115**

[77] Hands, A. R.; Mercer, A. J. H. *J. Chem. Soc.* (C) **1968**, 2448-2452.
[78] Kassou, M.; Castillón, S. *J. Org. Chen.* **1997**, *62*, 3696-3701.

The product obtained was similar to that of a Baeyer-Villiger oxidation[79] where a cyclic ketone is transformed into a lactone by peracid. Overoxidations reactions by using PCC are rare, but acids can be directly prepared from aldehydes with stoichiometric sodium cyanide and PCC in THF.[80] Pyridinium chlorochromate shows a slightly acidic character and in presence of compounds bearing acid-sensitive groups, the reaction can be buffered with powdered sodium acetate. Lactone **115** was obtained from alcohol **108** the most probable reason was an overoxidation effect of PCC generating at first ketone **116** which was oxidized immediately to lactone (Figure **39**).

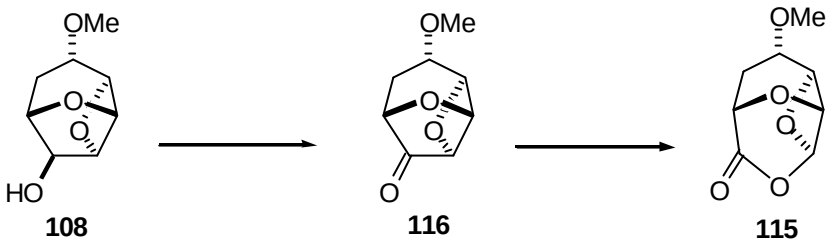


Figure 39: Reaction steps of the PCC oxidation to lactone **115**

Lactone **115** represents a new interesting oxetane tricycle structure, which can be employed as precursor to further synthesis of new dioxatricyclic structures and as a source of biological activities and in total synthesis of natural products. The crystal structure of compound **115** confirmed the spectroscopic results (Figure **40**).

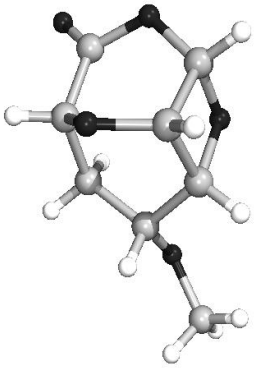


Figure 40: Crystal structure of lactone **115**

[79] a) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625-3633; b) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges*. **1900**, *33*, 858-864; c) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737-750.
[80] Reddy, P. S.; Yadagiri, P.; Lumin, S.; Shin, D.-S.; Falck, J. R. *Synthetic Comm*. **1988**, *18*, 545.

4.1.4 Synthesis of enantiomerically pure oxatricyclic structures

The racemic dioxatricyclic structure synthesized by J. Wittenberg a-methoxy-substituted at the C3-position showed anti-tumor activity (see chapter 2.1.6). Because of this interesting result an enantiomerically pure oxetane was synthesized to observe its biological activity. Diastereoselective generation of an a-alkoxy-substituted 8-oxabicyclico[3.2.1]ketone was accomplished by an asymmetric [4+3] cycloaddition[81] at low temperature. In previous works a method for the asymmetrical [4+3] cycloaddition was developed by using a chiral oxy allyl cation in which a mixture of bicyclic diastereomers (7:1) was obtained (see chapter 2). The diastereoselective [4+3] cycloaddition between furan and oxy allyl cation **(*R*)-117**, optimized by C. B. W. Stark, generated diastereomers **(2*R*)-27A** and **(4*S*)-27B** which were separated by column chromatography. The 1-phenylethoxy group at carbon C2 of the cycloadduct adopted the equatorial position exclusively[82] (Figure **41**).

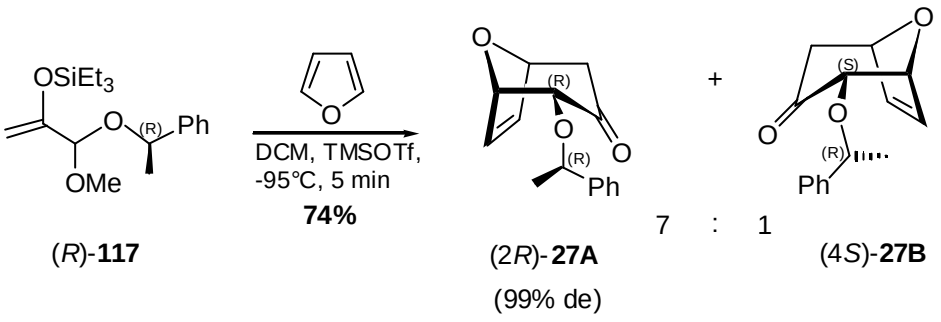


Figure 41: Asymmetric [4+3] cycloaddition to oxabicyclic (+)-(2*R*)-**27A**

After the derivation of the alcohol function at the C3-position to obtain the methoxy ether further derivations were carried out following the strategy previously mentioned. The bicyclic[83] (+)-**27A** was reduced selectively by using DIBAH into the a-alcohol (+)-**118** which was protected with a methyl ether group affording methoxy bicyclic (+)-**119**. Alkene methyl ether was treated with a peracid, *m*-CPBA, to obtain the epoxy (+)-**120** and the epoxy alcohol (+)-**121** was generated by debenzylation. Base treatment with KOBu^t made possible an intramolecular epoxy opening to the desired oxetane structure (+)-**122** in

[81] 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. M. R. *Chem. Eur. J.* **2000**, *6*, 684; d) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883.
[82] Pierau, S.; Hoffmann, H. M. R. *Synlett* **1999**, 213.
[83] provided by M. Schumann, unpublished work.

acceptable yield. The following Figure **42** illustrates the reaction sequence to synthesize the enantiomerically pure oxetane.

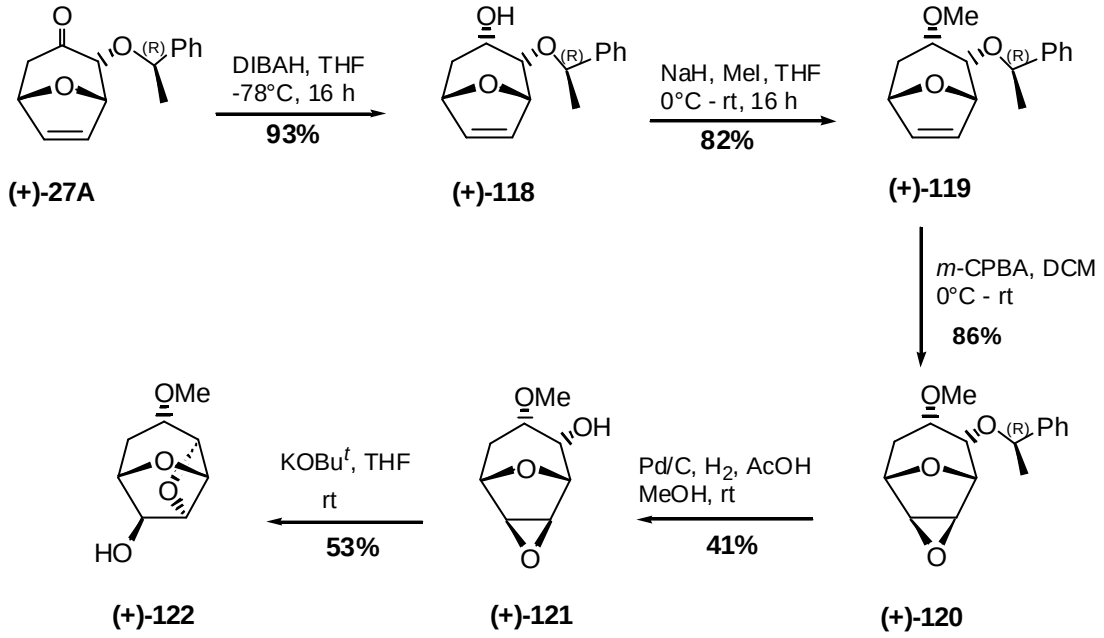


Figure 42: Strategy employed to synthesize enantiomer oxetane (+)-**122**

4.1.5 Synthesis of new dioxatricyclic structures

Epoxy alcohol **50** was oxidized to ketone **123** by per-ruthenate oxidation[84] in acceptable yield. The same structure was obtained in previous work[85] by Swern oxidation[86] (Figure **43**).

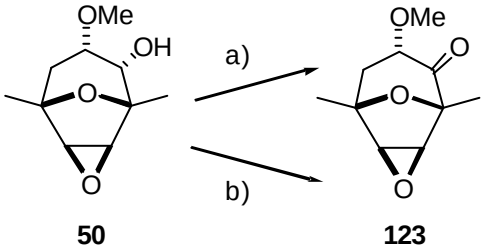


Figure 43: Oxidations of epoxy alcohol **50**, a) Per-ruthenate oxidation: TPAP, NMO, DCM, RT, 50%; b) Swern oxidation, $(COCl)_2$, DMSO, Et_3N, DCM, -78°C-rt, 70%

[84] a) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*,13; b) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc. , Chem. Comm*. **1987**,1625.
[85] See chapter 2 by: Proemmel, S. *Doctoral thesis*, University of Hannover **2001**
[86] Shishido, K.; Takahashi, K.; Fukumoto, K. *J. Org. Chem*. **1987**, *52*, 5704.

Ketone **123** was exposed to ylid **111** under Wittig conditions but the desired product was not obtained (Figure **44**) although similar Ylids were employed in several Wittig reactions (see chapter 4.1.3).

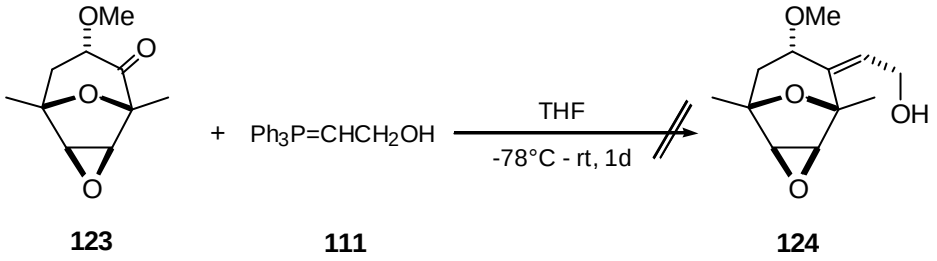


Figure 44: Attempted Wittig olefination of the epoxy ketone **123**

In structure **124** a protection of the free alcohol function would be possible followed by the selective deprotection of the methoxy function to an alcohol. A subsequent intramolecular epoxy opening would generate a new dioxatricycle, which is highly functionalized and would offer several sites for further derivations (Figure **45**).

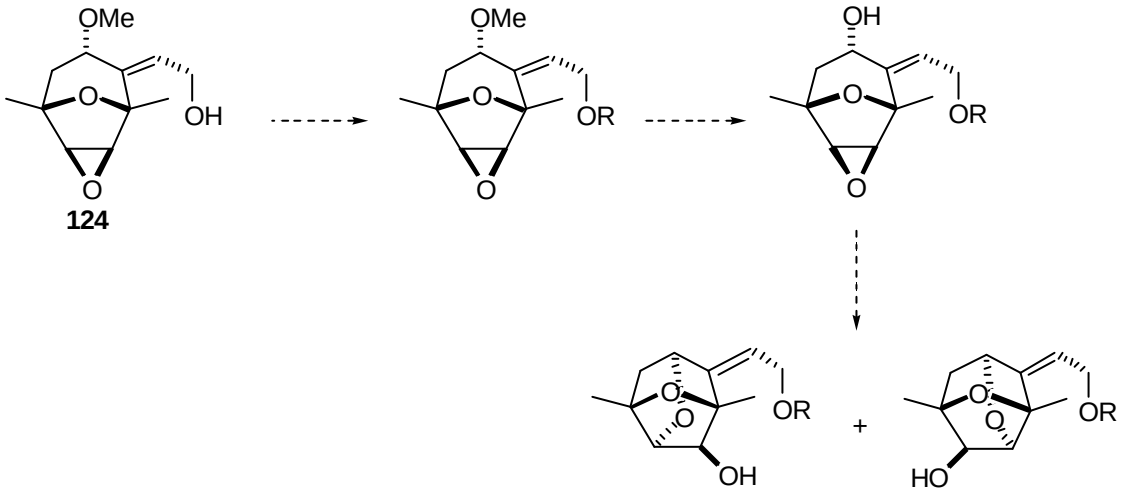
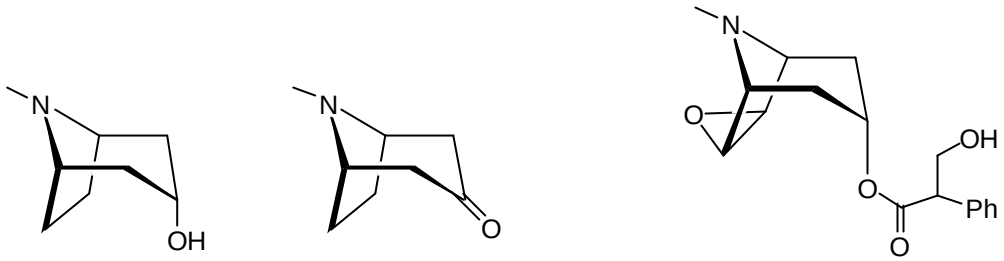


Figure 45: A route to obtain new dioxatricyclic structures

4.2 Studies to synthesize tropane alkaloids *via* [4+3] cycloaddition by using oxyallyl cations

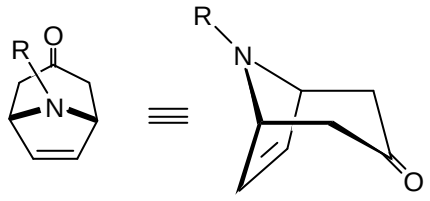
The [4+3] cycloaddition of pyrrole and their derivatives should offer a favorable synthetic pathway to building blocks, which in further synthetic steps could be transformed to the tropane alkaloids Tropine **125**, Tropinone **80** and Scopolamine **18**, are compounds of pharmacological and toxicological interest (Figure **46**).



125 Tropine **80** Tropinone **18** Scopolamine

Figure 46: Structure of some tropane alkaloids

The cycloaddition reaction was executed between an oxyallyl cation and several substituted pyrrole structures. The desired bicyclic compound **126** should present a skeleton similar to the highly biological active Scopolamine **18**, Tropine **125** and Tropinone **80** alkaloids (Figure **47**).



126

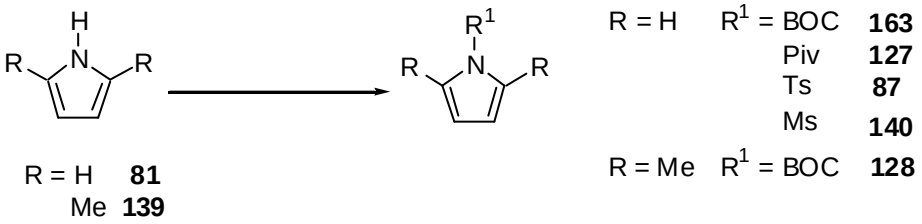
Figure 47: Structure of the desired cycloadduct **126** similar to tropane skeleton

4.2.1 Protecting groups for the pyrrole

It was necessary to protect the amino group at the pyrrole whose nucleophilicity and basicity could present a problem by the use of oxyallyl cations in the [4+3] cycloaddition to generate the corresponding cycloadduct.

Several protecting groups such as BOC, Ts, Piv and Ms were employed to protect the amino group in the pyrrole structure. *N*-acyl protecting groups (e. g. *tert*-butoxycarnonyl, Boc) are easy to introduce and offer a wide range of deprotection conditions. Arylsulfonyl groups (e. g. p-toluenesulfonyl, Ts) are effective protecting groups for secondary amines. Pivaloyl group (Piv), is a typical hydroxyl protecting group but was also employed to protect the amino group of pyrrole structures and the corresponding products were generated with acceptable yields, Table **9**.

Table 9



Entry	R	R^1	Conditions	Yield [%]
1	H	BOC	$(BOC)_2O$, THF, Et_3N, DMAP, rt, 16 h	78
2	H	Piv	PivCl, THF, Et_3N, DMAP, 0°C - rt, 20 h	70
3	H	Ts	TsCl, THF, Et_3N, DMAP, 0°C - rt, 16 h	n. r.
4	H	Ts	TsCl, $KOBu^t$, DMF, 0°C - rt, 16 h	81
5	H	Ms	MsCl, THF, Et_3N, DMAP, 0°C - rt, 24 h	42
6	Me	BOC	$(BOC)_2O$, THF, Et_3N, DMAP, rt, 16 h	82

The results above showed that the p-toluenesulfonyl group was the most appropriate protecting group in case of pyrrole. The *tert*-butoxycarbonyl group was also adequate for pyrrole and 2,5-dimethylpyrrole being obtained acceptable yields.

4.2.2 [4+3] Cycloaddition between substituted pyrrole and oxy allyl cation

The protected pyrrole was used afterwards in the [4+3] cycloaddition under the reaction conditions used for furan and 2,5-dimethylfuran as (4p)-component.
In the present work was it interesting to try the [4+3] cycloaddition reaction employing silyl enol ether **44** as oxyallyl cation which had given excellent results in the same cycloaddition reactions with furan and 2,5-dimethylfuran. Several cycloaddition conditions with silyl enol ether **44** were tried to obtain the desired bicyclic structure, Table **10**.

Table 10

R = H R^1 = BOC **163**
Piv **127**
R = Me R^1 = BOC **128**

44

Entry	R	R^1	Temperature	t
1	H	Piv	-78°C	10 min
2	H	Piv	-78°C	7 min
3	H	BOC	0°C - rt	3 h
4	H	BOC	-30°C	3 h
5	H	BOC	-40°C	1.5 h
6	H	BOC	-90°C	1 h
7	H	BOC	-90°C	2 h
8	H	BOC	-78°C	2 h
9	H	BOC	-90°C	2 h
10	Me	BOC	0°C - rt	3 h
11	Me	BOC	-20°C - rt	3 h

A short time reaction (entry 1) showed the existence of the desired cycloadduct. It was not possible to isolate the bicycle *via* aqueous work-up.
Afterwards, it was tried to obtain the cycloaddition product by using a smaller protecting group like methyl. Further, another type of silyl enol ether was employed in the reaction to observe the influence of different oxyallyl cations. The cycloaddition reaction between

N-methylpyrrole **129** and silyl enol ethers **44** and **130**[87] were also unsuccessful (Figure **48**).

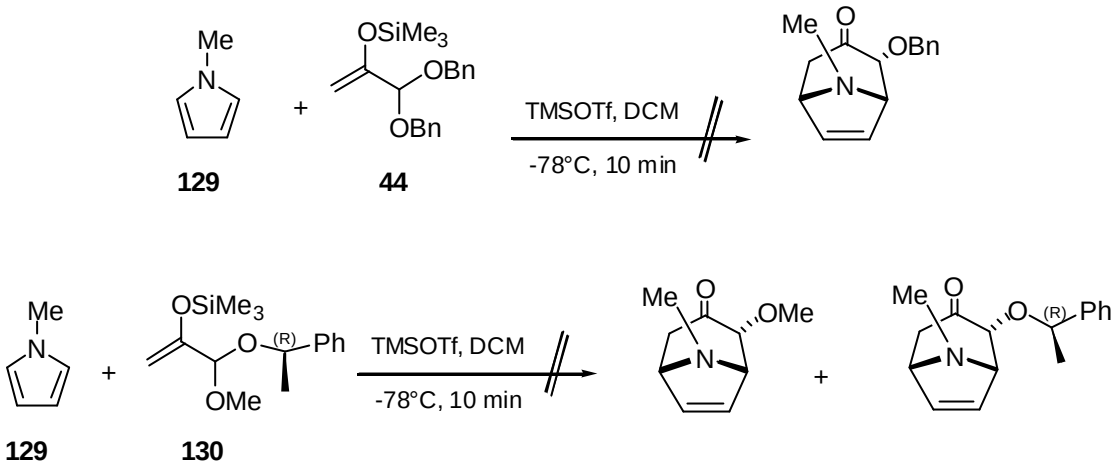


Figure 48: Failed [4+3] Cycloaddition between methylpyrrole and oxy allyl cations **44** and **130**

To obtain the desired cycloaddition products six different substituted pyrrole structures were used, two different silyloxyallyl cation and a range of temperatures between -90° and 0°C was employed. In all the cases, the same solvent and catalyst were employed. In no case an appropriate way was found to generate the expected cycloadduct. These results suggest to the necessity to choose a different type of oxyallyl cations with a proper blend of electrophilicity and nucleophilicity.

Using pyrrole as diene partner in the [4+3] cycloaddition, electrophilic substitution competed strongly with cycloaddition reaction which can be accomplished by using an oxyallyl moiety[88] (Figure **49**).

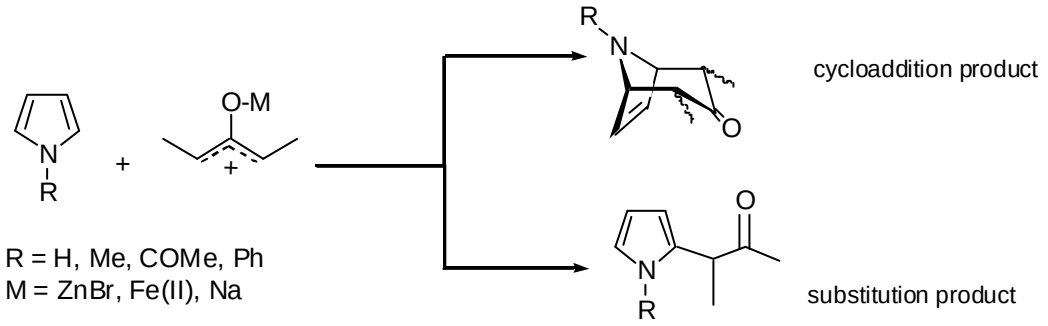


Figure 49: Possible products by [4+3] cycloaddition with substituted pyrrole

[87] provided by M. Schumann, unpublished work.
[88] Sarhan, Abd El-Wareth A. O. *Curr. Org. Chem.* **2001**, *5*, 827-844.

It is suggested that in this case, the formation of the seven-membered ring proceeds in distinct stages, i.e., the stepwise pull-push mechanism involving formation of the first sigma bond in an electrophilic step and a second sigma bond in a nucleophilic step,[89] Class B process using the terminology of Hoffmann[90] (Figure **50**).

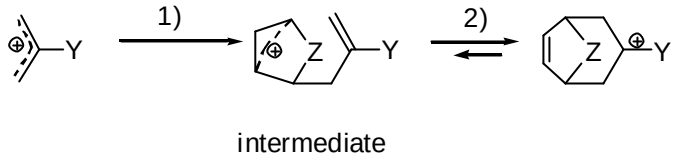


Figure 50: Class B, Stepwise bond-formation

It is reported that the use of the more electrophilic oxyallyl cations in conjunction with N-alkylpyrroles leads to the exclusive formation of substitution products.[91] These are formally products of a Class C process, using the terminology by Hoffmann in which an electrophilic addition is followed by loss of a proton with overall electrophilic substitution (Figure **51**).

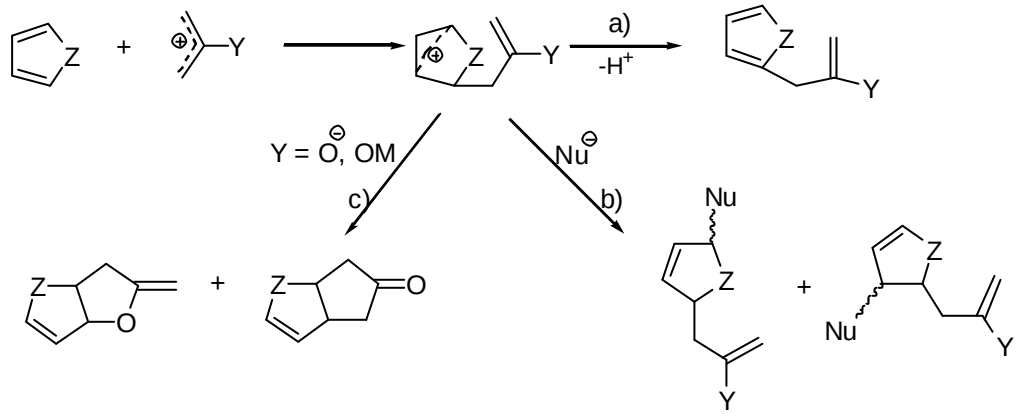
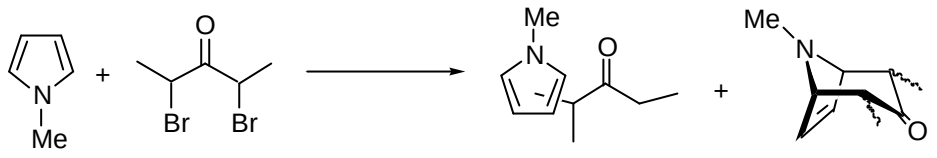


Figure 51: Class C, Electrophilic addition followed by a) loss of a proton with overall electrophilic substitution or b) intermolecular or c) intramolecular-nucleophilic capture of the carbocation

[89] Rawson, D. I.; Carpenter, B. K.; Hoffmann, H. M. R. *J. Am. Chem. Soc*. **1979**, *101*, 1786.
[90] a) Hoffmann, H. M. R.; *Angew. Chem. Int. Ed. Engl*. **1984**, *23*, 1-19; b) Hoffmann, H. M. R.; *Angew. Chem*. **1984**, *96*, 29-48.
[91] For cycloaddition with pyrrole see: a) Mann, *J. Tetrahedron* **1986**, *42*, 4611-4659; b) Sarhan Abd El-Wareth A. O. *Current Org. Chem*. **2011**, *5*, 827-844.

An example of the influence of cation electrophilicity on the course of this reaction can be seen with *N*-methylpyrrole serving as the diene partner (Figure **52**) where only the less electrophilic 2p(3C) partner (from NaI/Cu) generates [4+3] cycloadducts. Even a slightly more electrophilic species (from Zn/Cu) gives rise to regioisomeric mixtures of electrophilic substitution (Class C) products, and the strongly electrophilic oxyallyliron species gives only Class C products.



129 **131** **132** **133**

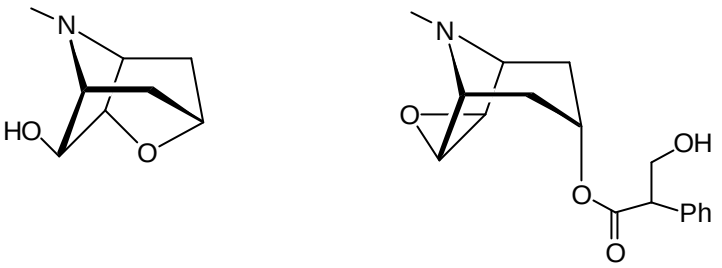
Conditions		
Zn/Cu	60%	-----
$Fe_2(CO)_9$	81%	-----
Cu, NaI	-----	89%

Figure 52: Influence of cation electrophilicity in [4+3] cycloaddition

Presumably, silyl enol ethers as oxyallyl cation precursors in cycloaddition reaction conditions with pyrroles generate only substitution products.

4.3 Synthesis of new biologically active Scopoline derivates from 8-oxabicyclo[3.2.1]oct-6-en-3-one

A synthetic way to generate the scopoline skeleton started from the bicyclic ***rac*-45** and ***rac*-94** which in further synthetical steps could be transformed to the tropane alkaloids Scopoline **19** and Scopolamine **18**, compounds of pharmacological and toxicological interest (Figure **53**).



19 Scopoline **18** Scopolamine

Figure 53: Structure of some tropane alkaloids

The synthetic strategy started from oxabicyclic systems ***rac*-45** and ***rac*-94** and further derivations yielded epoxides **134** and **135** which through an epoxy opening generated the desired Scopoline skeletons (Figure **54**).

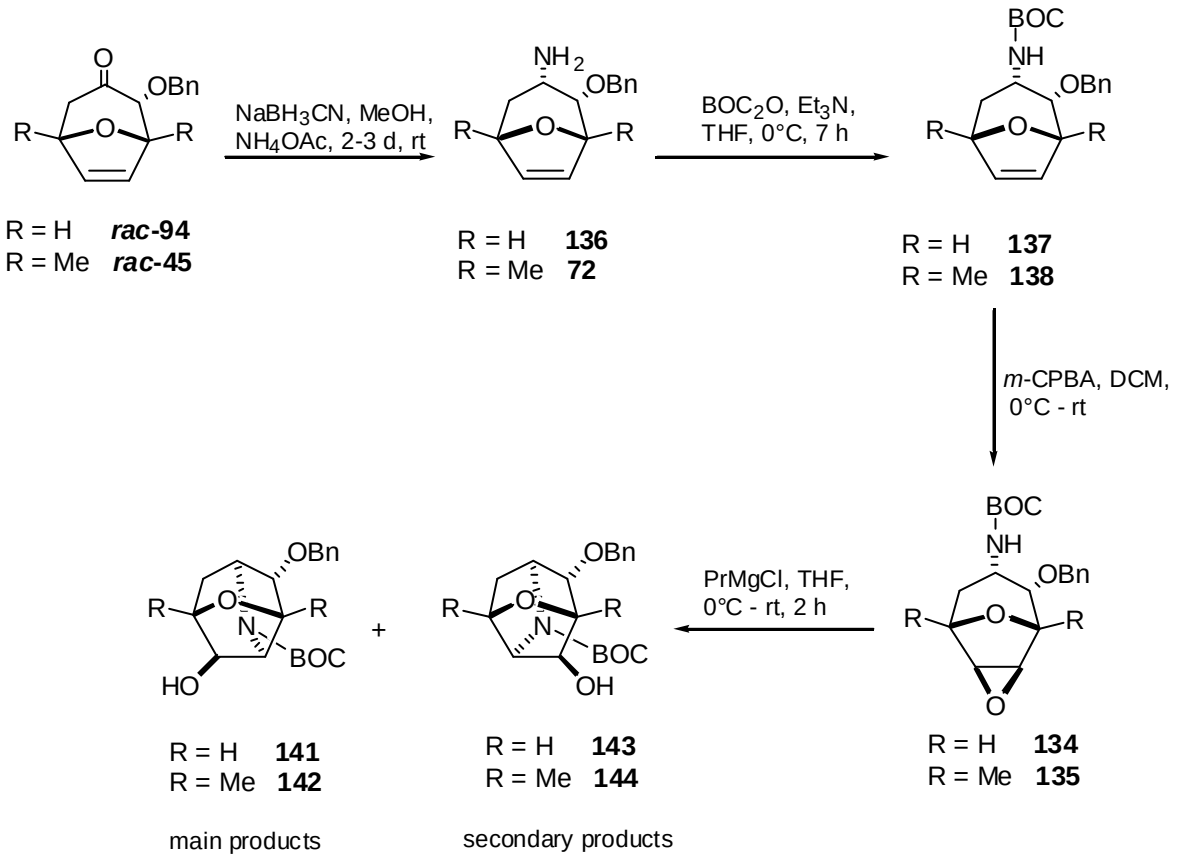
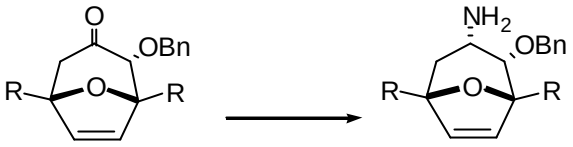


Figure 54: Synthesis strategy to Scopoline analogues

4.3.1 Amine function at the C3-Position in bicyclic skeleton

The introduction of an amino group at the C3-position was realized by a reductive amination under different reaction conditions, the results are shown in Table **11**.

Table 11



R = H ***rac*-94**
R = Me ***rac*-45**

R = H **136**
R = Me **72**

Entry	R	Conditions	Yield [%]
1	Me	NH_4OAc, $NaBH_3CN$, MeOH, RT, 2-3 d	63
2	H	NH_4OAc, $NaBH_3CN$, MeOH, RT, 2-3 d	55
3	Me	NH_4OAc, $NaBH(OAc)_3$, MeOH, 7 d	no reaction

Reductive amination with sodium triacetoxyborohydride (entry 3) was not successful because of the side reaction of the ketone to the corresponding alcohol, although procedures using this mild and selective reagent have been developed for a wide variety of substrates.[92] Limitations of the reaction include aromatic and unsaturated ketones and some sterically hindered ketones and amines. Amines **72** and **136** were generated using sodium cyanoborohydride in methanol, by the method introduced by Borch and coworkers.[93] The electron-withdrawing cyano ligand of $NaBH_3CN$ decreases the hydridic reactivity compared to sodium borohydride and allows the selective reduction of carbon-nitrogen double bonds in the presence of aldehydes or ketones at slightly acidic pH in the range of 5-7 and is typically performed in alcoholic solvents.

[92] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.
[93] Borch, R. F.; Bernstein, M. D.; Durst, H. P. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

4.3.2 Protection of the free amino function

The amino function has nucleophilic and basic character which represents a problem in the synthesis of a diverse array of biological molecules such as amino acids and alkaloids. The *tert*-butoxycarbonyl group (Boc), is one of the most frequently used amino protecting groups in organic synthesis being inert towards catalytic hydrogenolysis and extremely resistant towards basic and nucleophilic reagents. For this reason, the *tert*-butoxycarbonyl group was used to protect the amino function in both oxabicyclic systems **137** and **138**. The amino compound was dissolved in THF/Et_3N mixture and treated with $(BOC)_2O$ in the presence of a catalytic amount of DMAP at 0°C (Figure **55**).

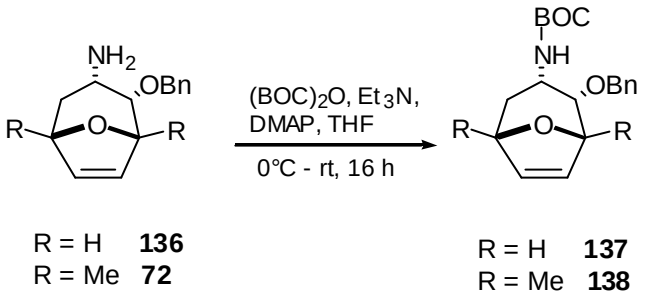


Figure 55: Protection of free amino function at the bicyclic structure **72** and **136**

After this protection, the bicyclic compounds could be used in the next steps of the synthetic pathway to the desired tropane skeleton.

4.3.3 Formation of a tricyclic structure analogue to Scopoline skeleton

In a previous chapter (see chapter 4.1.2.4) the interest of an intramolecular epoxy opening as a route to an oxetane structure was outlined. In a similar way, we made use of this strategy to come to analogous tricyclic structures of Scopoline by intramolecular epoxy opening.

The cyclization of ß-amino acids was first reported in 1975 by using a Grignard-mediated cyclization of an N-silylated aspartate diester.[94] This method was used in the synthesis of Thienamycin, synthesized by Merck.[95] In this synthetic method, the cyclization to the desired β-lactam **145** was carried out from *N*-trimethylsilyl-dibenzylaspartate **146** by using

[94] Birkofer, L.; Schramm, *J. Justus Liebigs Ann. Chem.* **1975**, 2195.
[95] Salzman, T. N.; Ratclife, R. W.; Christensen, B. G.; Bouffard, F. A.; *J. Am. Chem. Soc*. **1980**, *102*, 6161.

tert-butylmagnesium chloride through an intramolecular cyclization (Figure **56**).

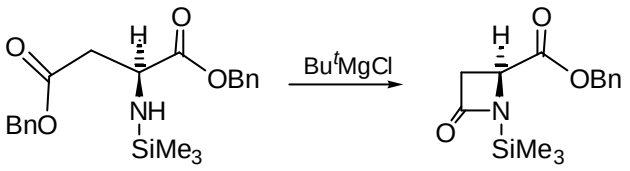


Figure 56: Intra-molecular lactonization using Bu^{t}MgCl

A possible mechanism was described by Testa[96] who carried out a cyclization with a Grignard reagent as strong and electrophilic base in an amount of 2 mol per mol of the amino ester **147**. The pathway for the synthesis of the amide firstly involves a substitution step followed by a cyclization to generate the corresponding intermediate which after substitution and cleavage yields the desired amide (Figure **57**).

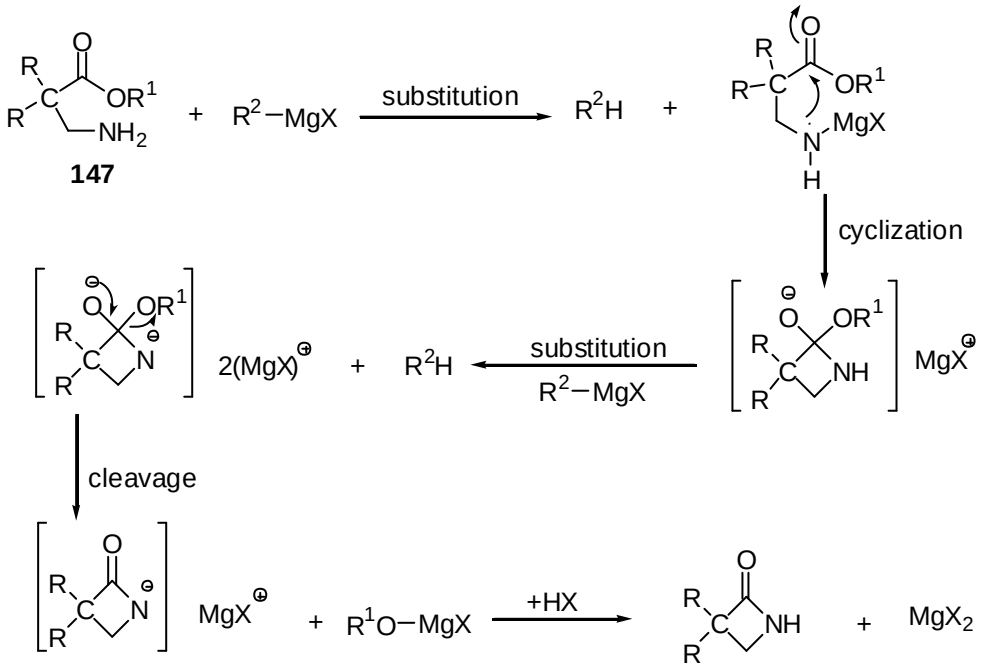
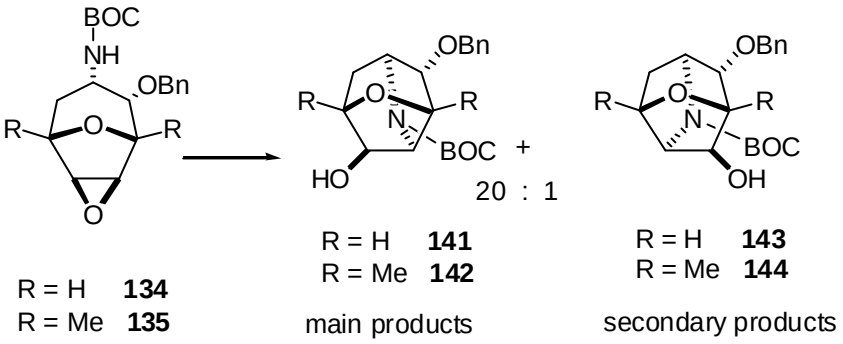


Figure 57: Mechanism suggested by Testa for the cyclization using Grignard reagent

To afford the Tropane structure by intramolecular epoxy opening several Grignard compounds were used, Table **12**.

[96] Testa, E.; Fontanella, L.; Cristiani, G. F.; Fava, F. *Liebigs Ann. Chem.* **1958**, *614*, 158.

Table 12



Entry	R	Conditions	Yield [%]
1	Me	Bu^{t}MgCl, THF, 0°C - rt, 2 h	77
2	Me	PrMgCl, THF, 0°C - rt, 4 h	75
3	Me	PrMgCl, THF, 0°C - rt, 65 h	68
5	H	Bu^{t}MgCl, THF, 0°C - rt, 2 h	60
6	H	PrMgCl, THF, 0°C - rt, 4 h	61

Above results showed good yields when *tert*-butylmagnesium chloride or propylmagnesium chloride were used. The Grignard compounds were ideal reagents for the formation of the stable *NH*-BOC-protected tricycle. The generated Tropane skeletons were highly functionalized and offered well defined stereocenters and functionality for further derivations (Figure **58**).

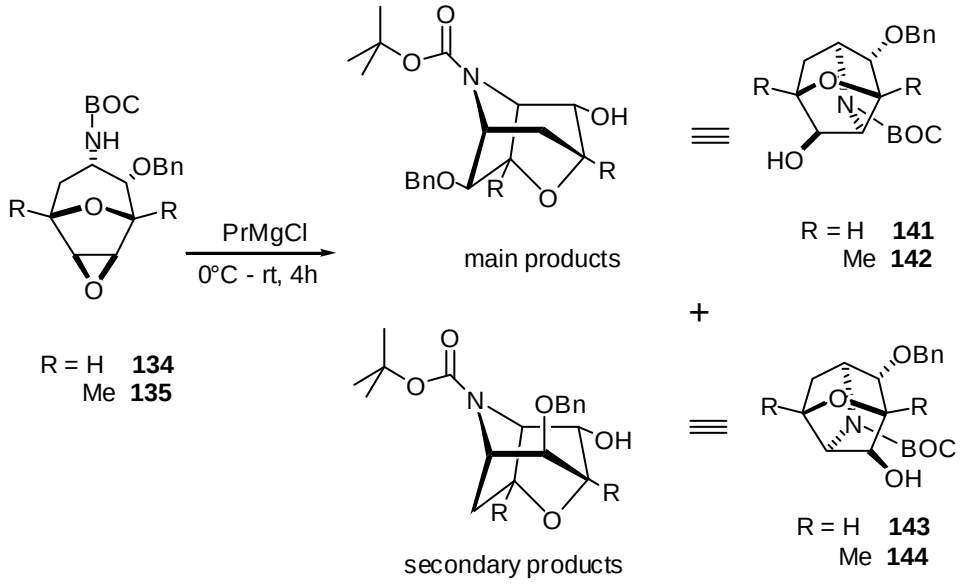


Figure 58: Synthesized tricyclic products by intramolecular epoxy opening with Grignard-reagent

The intra-molecular cyclization of the epoxides **134** and **135** to the Scopolin derivates gave two different diastereomers **141**-**143** and **142**-**144** (see figure **58**). It was unexpected that the main products were generated by the cyclization to the C7-position giving a free alcohol function at the C6-position. It is possible that due the free electron pairs of the oxygene atom from the benzyl group a stable five membered ring chelat complex is generated attempting a selective ring opening (Figure **59**).

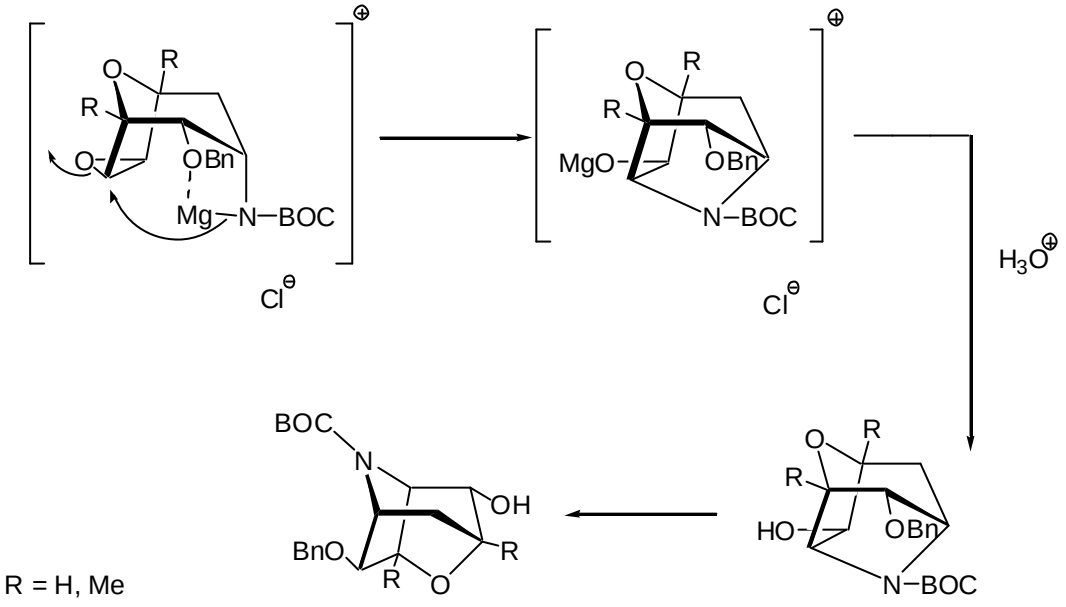


Figure 59: Chelat complexes formed at the epoxy opening toward the main products **141** and **142**

In the oxazatricycle structures **141** and **142** the hydroxyl and the benzyl groups are in the equatorial position at the C2 and C6-carbon atom respectively, unlike in the secondary product **143** and **144** where the hydroxyl groups were in the equatorial position at C2 and the benzyl groups were in the axial position at the C4-carbon atom. The diastereomers represented are different in two of the six containing stereocenters. Both diastereomers were available for separation by column chromatography and the crystal structure of compound **142** confirmed the spectroscopic results (Figure **60**).

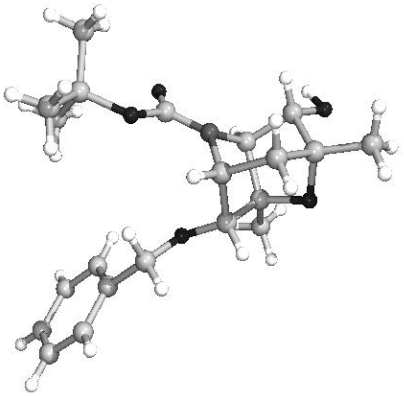
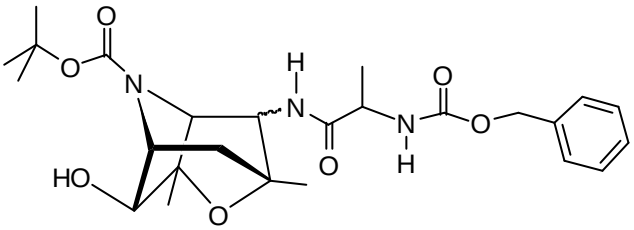


Figure 60: Crystal structure of the main tricyclic alcohol **142**

4.3.4 Derivation at the Tropane skeleton

The free alcohol function offers possibilities for further transformations of the tropane structures **141**-**144**. Oxidation of the major alcohols **141** and **142** under Swern conditions generates two new compounds, which nearly have a similar skeleton as **77**, synthesized by S. Proemmel (see chapter 2), and later investigated for its cytostatic activity.



77

Figure 61: Tropane derivate with cytostatic activity

Due to its potential biological importance, ketones **148** and **149** were synthesized to gain further information about for SAR studies.

Swern oxidation reaction was carried out under similar conditions as used previously (chapter 4.1.3). Oxidation of tricyclic compound **141** gave low yields due to its structural instability, but the oxidation of oxazatricyclic **142** gave excellent yields (Figure **62**).

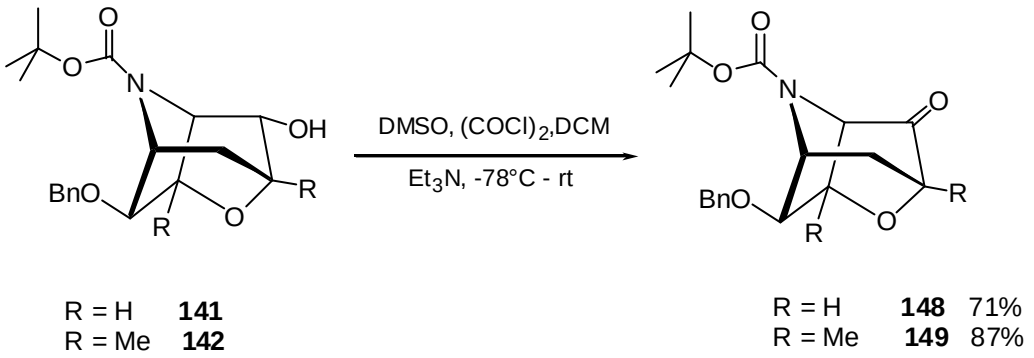


Figure 62: Swern oxidation of main alcohols **141** and **142** to obtain similar tropane skeleton **148** and **149**

The X-ray crystal structure of compound **148** confirmed the spectroscopic results (Figure **63**).

Figure 63: Crystal structure of two conformations of the oxazatricyclic ketone **148**

Tricyclic ketone **148** was examined for its pharmacological activity and showed strong cytotoxic activity (see chapter 4.5).

4.4 Studies toward substituted furans for [4+3] cycloadditions

Substituted furans are an attractive target for biological active bicyclic compounds and a [4+3] cycloaddition seems to offer a simple access to these highly functionalized oxabicyclic systems.

4.4.1 Furan substituted with alkyne function at the C2-position

The alkyne function offers possibilities for further derivations at the bicyclic ring that could lead, after ring opening, to different cycloheptanones, which are valuable in carbohydrate and natural product chemistry.
A 2-alkynyl substituted furan system should lead after [4+3] cycloaddition with the silyl enol ether **44** to a bicyclic system with the desired alkynyl side chain (Figure **64**).

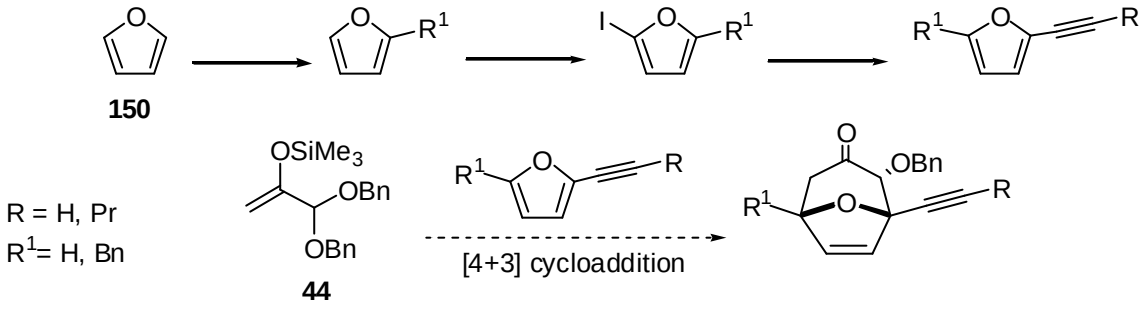


Figure 64: Strategy to synthesize desired oxabicycle by [4 + 3] cycloaddition between silyl enol ether **44** and substituted furan

A prior introduction of a benzyl group firstly leads to a much more stable furan system. After introducing the benzyl group at the C2-position iodine should be incorporated in the C5-position by deprotonation with *n*-BuLi and iodination with I_2 in THF at -40°C (Figure **65**).[97]

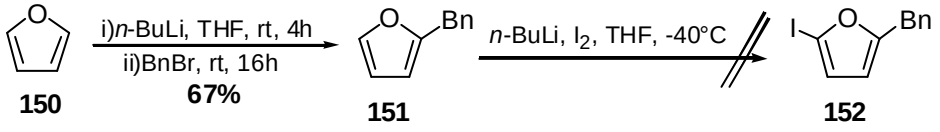


Figure 65: Failed introduction of I_2 atom in structure **151**

[97] Kauffmann, T.; Lexy, H. *Chem. Ber.* **1981**, *114*, 3667-3673.

The desired product was not obtained. Different spectroscopy measurements showed the existence of an I atom in the structure. Two different possibilities were considered for the position of this iodine atom: at the *ortho*-position of the phenyl ring or at the $-CH_2$ group of the benzyl moiety (Figure **66**).

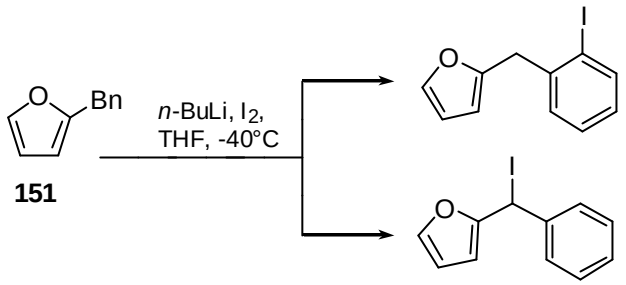


Figure 66: Possible products of substitution reaction

As next step a Sonogashira coupling[98] was planned between heterocyclic halide **152** and acetylene in the presence of a catalytic amount of bis(triphenylphosphine)palladium dichloride and cuprous iodide in diethylamine under mild condition (Figure **67**).

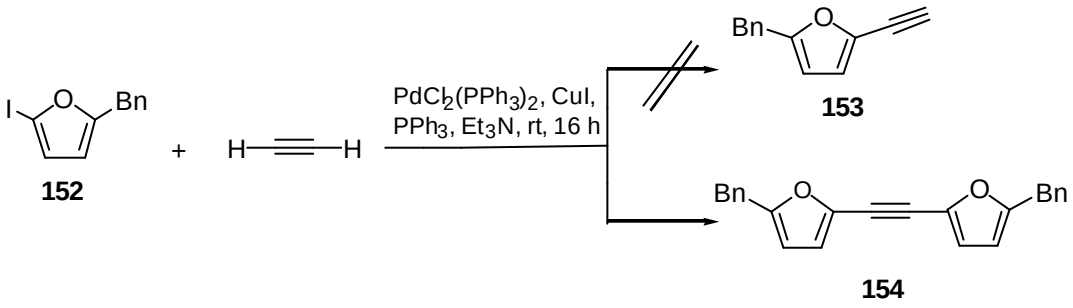


Figure 67: Failed Sonogashira coupling with substituted furan and symmetrically acetylene

The desired substituted furan was not generated because the use of the symmetrically acetylene generate the diyne **154** which was not possible to isolate. Doye et al[99] synthesized alkyl(aryl)alkyne **157** *via* 2-iodofuran and 1-pentyne by Sonogashira coupling under the following conditions (Figure **68**).

[98] a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tet. Lett*. **1975**, *16*, 4467-4470.; b) Sonogashira, K. in *Comprehensive Organic Synthesis Vol. 3*, Trost, B. M.; Fleming, I.; Eds., Pergamon: Oxford **1991**, 521.
[99] Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem*., **2002**, 1213-1220.

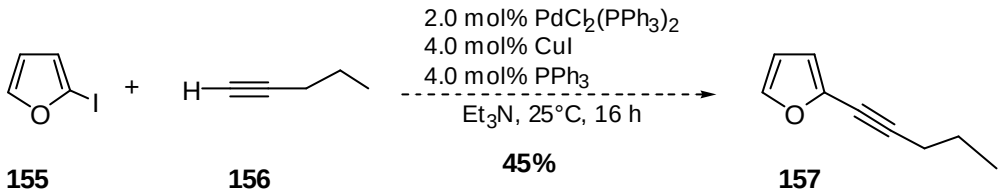


Figure 68: Sonogashira coupling with substituted furan and asymmetrically acetylene by Doye

The [4+3] cycloaddition between substituted furan[100] **157** and the silyl enol ether **44** did not yield the desired adduct **158** (Figure **69**). It is possible that the existence of a terminal alkyne leads to a [2+3] cycloaddition reaction unlike the expected [4+3] cycloaddition.

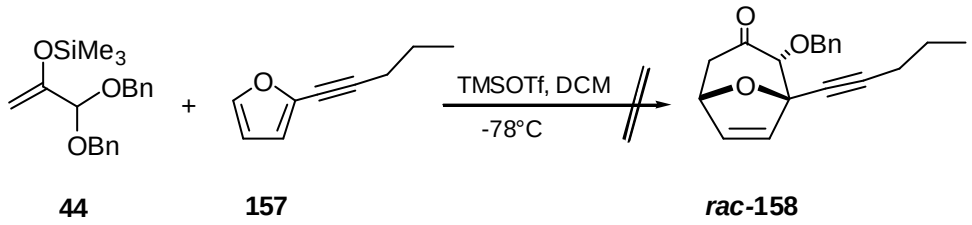


Figure 69: Failed [4+3] Cycloaddition between substituted furan **157** and silyl enol ether **44**

Another route to a substituted furan with an ethynyl rest at C2-position was attempted (Figure **70**). Intermediate dibromo olefin function was generated from furfural **159** by a synthetic method from by Corey and Fuchs[101] in good yield. The dibromo olefin **160** was taken for the next reaction to get the terminal alkyne **161** following the reaction conditions used by Rossi[102] who realized this transformation into the corresponding terminal alkyne according to the Corey-Fuchs method but using methyllithium instead of n-butyllithium in the reaction with the dibromo olefin **160** in tetrahydrofuran at -78°C for 1 h. Unfortunately, alkyne **161** was not obtained in adequate yield so, the corresponding [4+3] cycloaddition was not attempted.

[100] provided by H. Siebeneicher
[101] Corey, E. J.; Fuchs, P. L. *Tet. Lett.* **1972**, *36*, 3769-3772.
[102] Carpita, A.; Rossi, R.; Veracini, C. A. *Tetrahedron*, **1985**, *41*, 1919-1929.

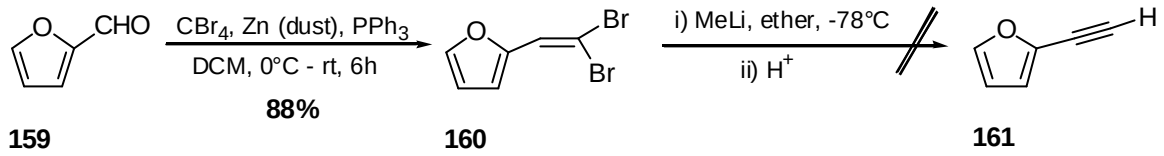


Figure 70: Failed substituted alkyne by Corey-Fuchs method

Furfural was also treated with the anion of dimethyldiazomethylphosphonate[103] **162** from Bestmann[104] to afford compound **161**. In this method, the reaction can be performed by adding the phosphonate **162** to a solution of K_2CO_3 and the aldehyde in methanol at room temperature. This method avoids the use of strong bases, low temperature and inert gas techniques unlike previous methods.[105] The desired product was not isolated (Figure **71**).

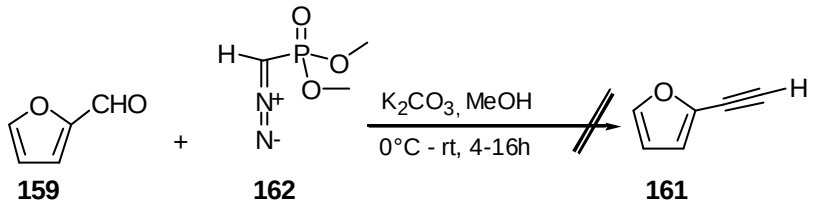


Figure 71: Failed substituted furan with terminal alkyne using Bestmann method

4.5 In-vitro-tests for the characterization of the cytostatic or cytotoxic effect of functionality in Dioxa and Oxaza-tricyclononane structures

The most commonly employed *in vitro* system is a cell line from a human epidermoid carcinoma of the nasopharynx, named KB. The KB procedure is used routinely for evaluating extracts from natural products. When the antineoplastic agent has been isolated, it is evaluated further in the cell line and studies begin in different systems like colon, mammary, etc. Biosynthetic products selected for preclinical development must show a high level of activity in several of these representative experimental tumor systems.

A cytostatic activity means a preventive action on grow and proliferation of tumor cells and a cytotoxic effect means an attack and destroying action in the tumor cells.

In the context of the thesis some of the synthesized compounds were examined for their pharmacological activity. Dioxatricyclic C-glycosides **108** and its cyclization precursor,

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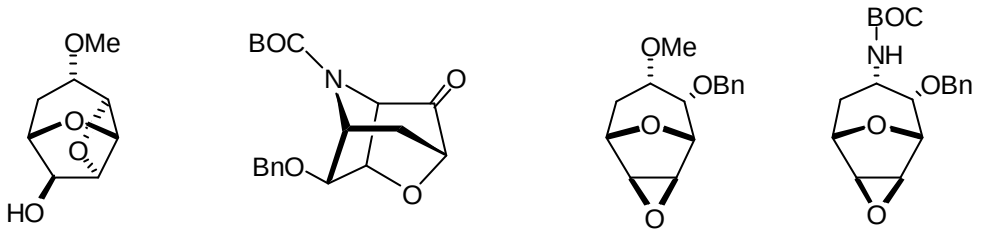
[103] provided by L. O. Haustedt, see: Haustedt, L. O. *Doctoral thesis*, University of Hannover, **2002**.

[104] Müller, S; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.

[105] see: a) Köbrich, G.; Trapp, H.; Flory, K.; Drischel, W. *Chem. Ber*. **1966**, *99*, 689; b) Matsumoto, M.; Kuroda, K. *Tet. Lett*. **1980**, *21*, 4021; c) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc*. **1969**, *91*, 4318; d) Bestmann, H. J.; Rippel, H.; Dostalek, R. *Tet. Lett*. **1989**, *30*, 5261.

the epoxy alcohol **105**; the Scopoline derivate **148** and its cyclization precursor **134** were tested (Figure **72**). The examination, *in vitro*, about cytostatic and cytotoxic effects of the 4 substances was attempted on growing tumor cell of three different cell-lines: HMO2 (Gastric carcinoma), HEP G2, (Hepatic carcinoma), MCF7 (Mamma carcinoma). Only the Scopoline derivate **148** show a significant biological activity. The exact results are presented and discussed in following chapter 4.5.1.



108 **148** **105** **134**

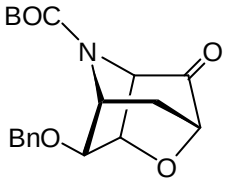
Figure 72: Structures tested for biological activity

4.5.1 Results of the cytostatic and cytotoxic in vitro test

A relative strong cytotoxic effect could be determined in the Scopolin derivative **148**. The other tested compounds did not show any effect until concentration of 10 µg/ml at the three cell-lines HMO2, HEP G2, MCF7 previously mentioned. The results of the investigation[106] are summarized in the Table **13**.

[106] Characterization of the pharmacological effects was realized by: Prof. W. Beil, Institut für Allgemeine Pharmakologie, Medizinische Hochschule Hannover.

Table 13



148

	Cell-line		
Carcinoma type	GI_{50}	TGI	LC_{50}
HMO2 (Gastric carcinoma)	0,17	0,26	0,42
HEP G2 (Hepatic carcinoma)	0,16	0,25	1,80
MCF7 (Mamma carcinoma)	0,42	0,38	4,40

Above values of cell line show the cytostatic effect (GI50 and TGI) and the cytotoxic effect (LC50) by concentration level of tested compound (all specification in µg/mL):

GI_{50} = Drug concentration causing 50% growth inhibition

TGI = Drug concentration causing 100% growth inhibition

LC_{50} = Drug concentration causing 50% reduction of the cells present at time zero, i.e at 24 h

Internal limiting values for the evaluation of cytotoxic effect are related to standard cytostatic (5-fluorouracil and *cis*-platinum, see chapter 2.1.6) are shown in Table **14**.

Table 14

Estimation of cytotoxic activity	Cytostatic limits
good	GI_{50} < 1 µmol/L + TGI < 5 µmol/L
satisfactory	GI_{50} < 5 µmol/L + TGI < 10 µmol/L
weak efficient	GI_{50} < 10 µmol/L oder TGI < 50 µmol/L
inefficient	GI_{50} > 10 µmol/L

The comparison of the values in both tables (Table **13** and Table **14**) indicated that the measured GI_{50} values were in the interval of GI_{50} < 1 µmol/L as well, values of TGI were in the interval TGI < 1 µmol/L too. In conclusion, the estimation of the cytotoxic effect of the Scopolin derivate **148** was relative strong.

5. SUMMARY AND CONCLUSIONS

A series of tricyclic structures containing different ether functions at the C3-position were prepared from 8-oxabicyclo[3.2.1]oct-6-en-3-one as starting material. Three differing alkyl groups, methoxy, ethoxy and propoxy were employed to protect the free alcohol function at the C3-atom position in the bicyclic structures ***rac*-45** and ***rac*-94** (see chapter 4.1.2.1). Further derivations at the dioxatricyclic structures synthesized afforded two new compounds, ketone **114** and lactone **115** (Figure **73**).

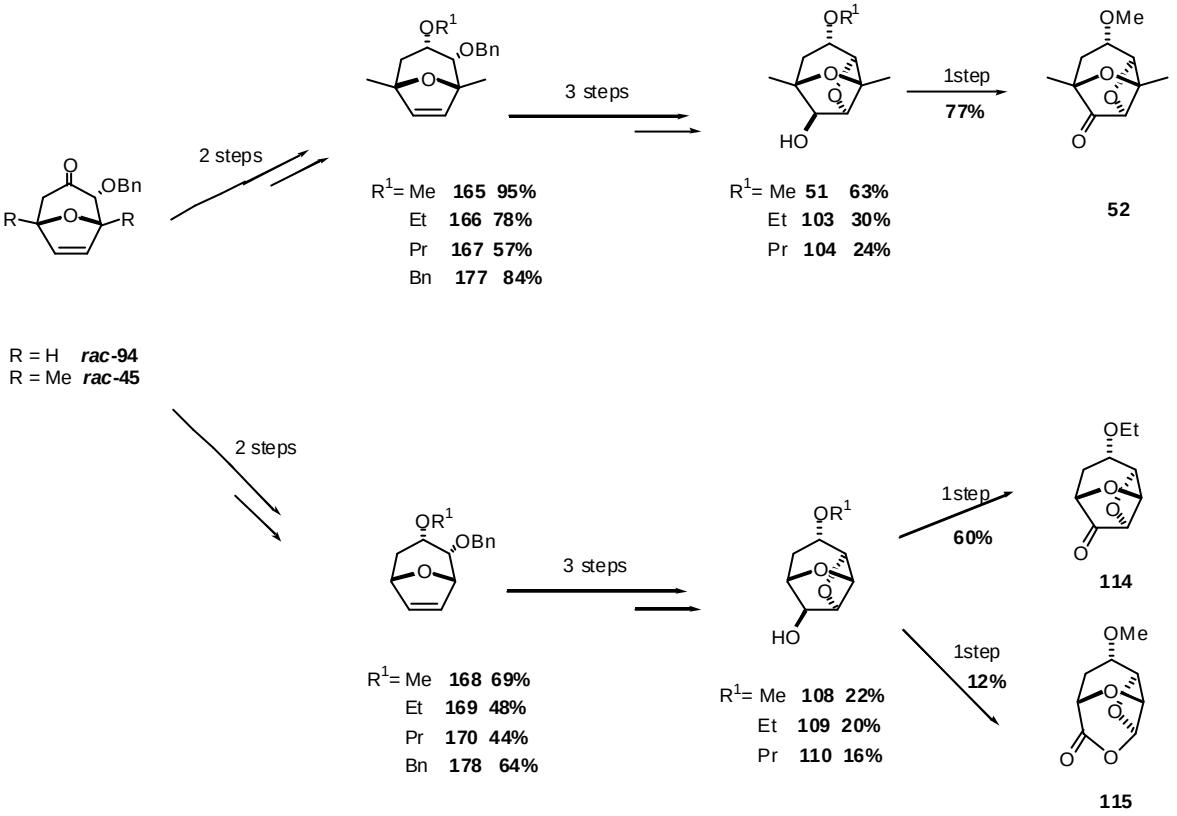


Figure 73: View of substituted oxatricyclic structures with an ether function at the C3-position

In previous works the oxetane system **51** was synthesized and it showed cytostatic and cytotoxic effects using a human gastric carcinoma and a human heptocellular cell line (see chapter 2). The biological activity of the tricyclic structure **108** was measured by *in vitro* test. No cytostatic or cytotoxic activity up to a concentration of 10 µg/mL was observed (see chapter 4.5). The difference of the biological activity in both substances related to their structure. Dioxatricyclic systems **51** and **108** have a similar but they contain a different ether function at the C3-atom position. Moreover oxetane **51** include two methyl

groups at C1 and C5. It is not clear which group causes the distinction in biological activity. For this reason, it would be of pharmacological interest to synthesize and test some derivated oxetanes (Figure **74**).

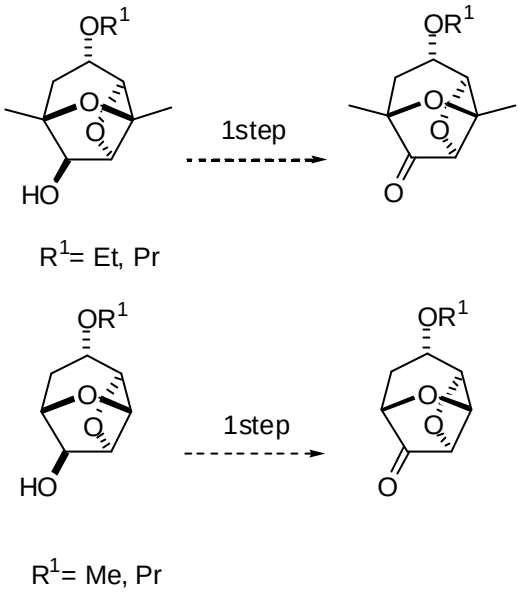


Figure 74: Oxatricycles structures as pharmacological targets

Lactone **115** represents an unexpected overoxidation with PCC from tricyclic alcohol **108** (see chapter 4.1.3). The biological activity of this lactone has, as yet, not been tested, but if in-vitro-test gives a positive result, similar lactones with different alkyl ether functions at the C3-position will be of interest.

The diastereoselective asymmetrical [4+3] cycloaddition with chiral oxyallyl cations was employed for the synthesis of enantiomerically pure tricyclic oxetane (Figure **75**). A short and efficient synthesis provides access to enantiopure dioxatricycle (+)-**122** (see chapter 4.1.4).

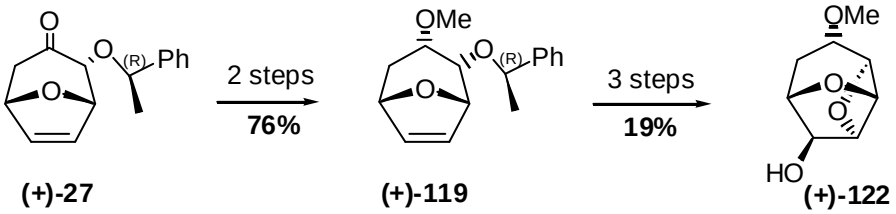


Figure 75: Synthesized enantiopure dioxatricycle (+)-**122**

The reductive amination of the bicyclic ketones ***rac*-45** and ***rac*-94** with NH_4OAc in the presence of $NaBH_3CN$ is a good method for the introduction of a primary α-amino function at the C3-position. After protecting the amino group with the BOC group, the oxazatricyclo-nonanes **141** and **142** were obtained in acceptable yields. Ketones **148** and **149** were generated from the corresponding alcohols (Figure **76**).

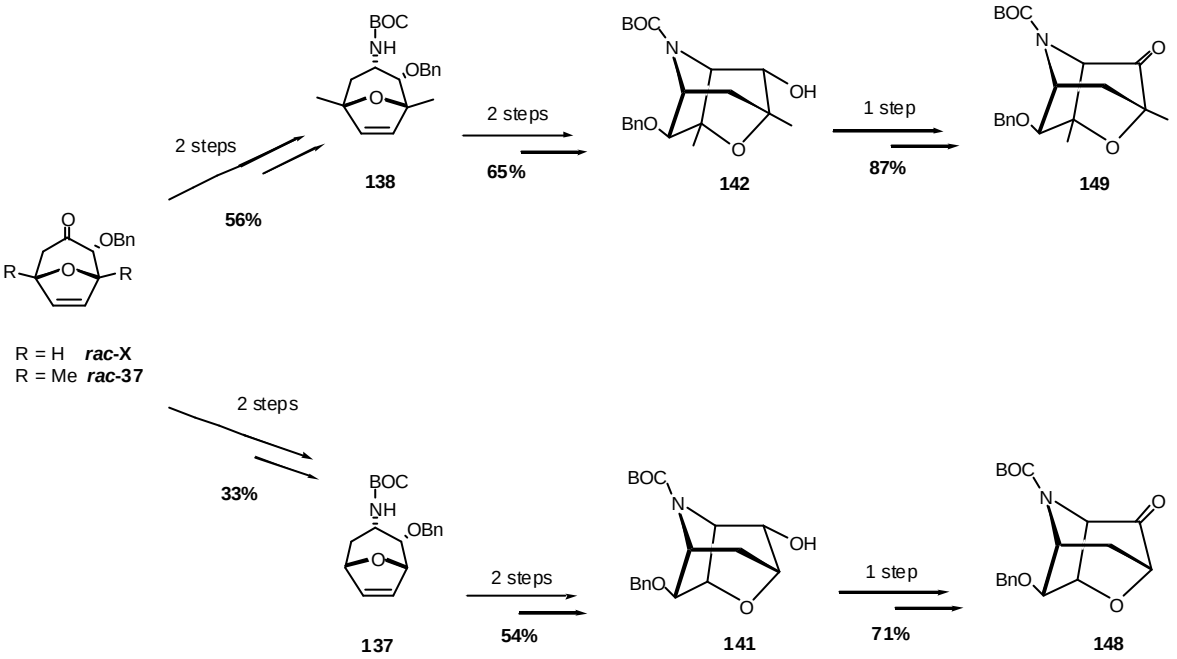


Figure 76: Oxatricycles substituted at the C3-position with an amine function

Scopoline skeleton **148** showed cytotoxic activity at the human gastric, human hepatic and human mamma carcinoma cell lines (see chapter 4.5.1). In only 5 steps the cytotoxic oxazatricyclic **148** was synthesized with a yield of 13% over all.

Ketone **149** and tricyclic alcohols **141** and **142** have not yet been tested. It is expected that they show biological activity similar to ketone **148**. Besides, different derivatives of the mentioned tricyclic alcohols **141** and **142** would be of interest to evaluate possible cytotoxic or cytostatic activity. The Scopoline derivative **77** showed cytostatic activity (see chapter 2.2.1). For this reason, new oxazatricyclic-nonane structures derived from ketones **148** and **149** require further study (Figure **77**).

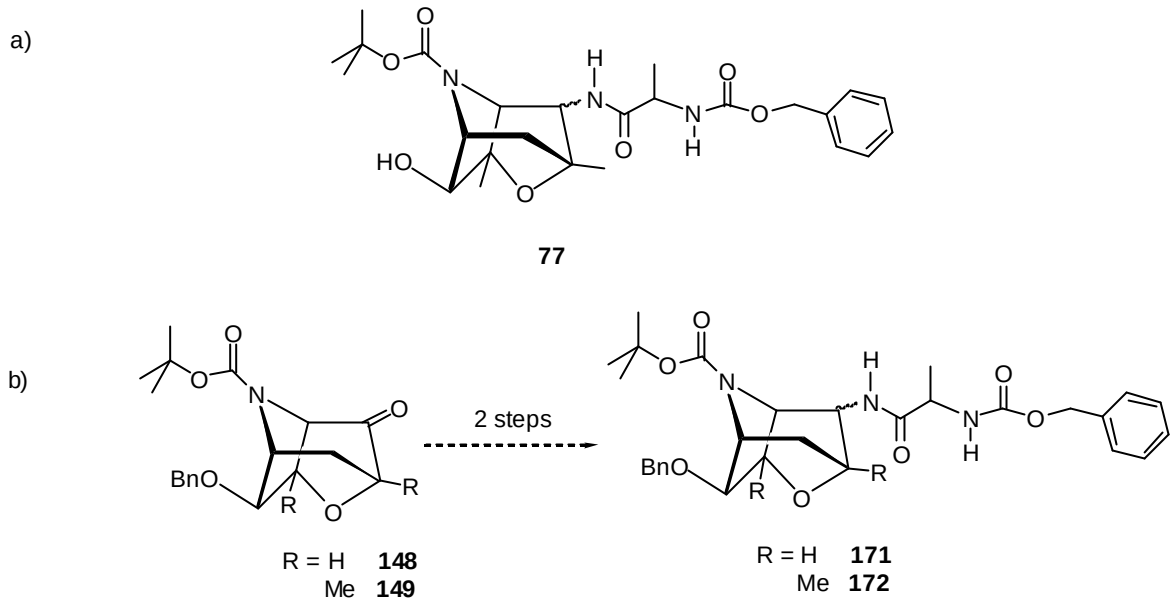


Figure 77: a) Scopoline derivative with cytostatic effect; b) Scopoline derivatives with potential biological activity

A new synthetic strategy was employed to obtain structures with Tropane skeleton by [4+3] cycloaddition between pyrrole or substituted pyrrole and different oxyallyl cations (see chapter 4.2). In previous works, similar structures were prepared using other oxyallyl cations with acceptable yields (see chapter 2). Pyrrole **81** and 2,5-dimethylpyrrole **139** were protected with several groups before attempting the mentioned cycloaddition (Figure **78**).

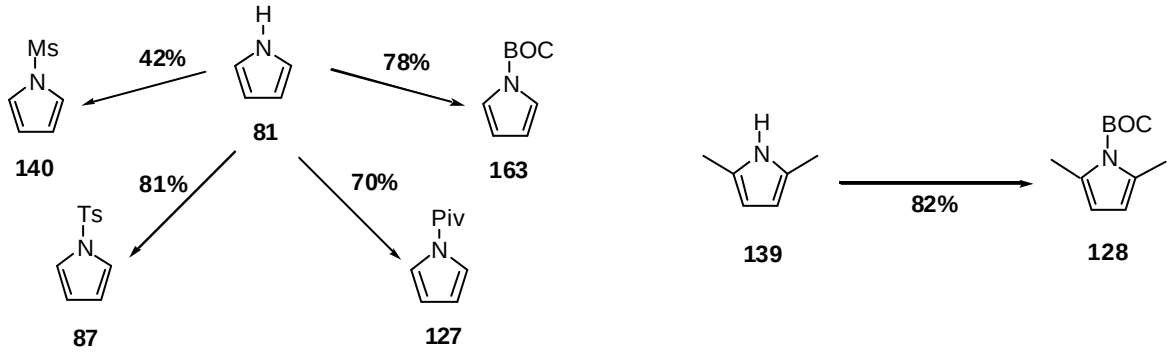


Figure 78: Substituted pyrrole and 2,5-dimethylpyrrole

After several attempts, no cycloadduct product was synthesized. Although no compound could be isolated, it was supposed that, in the [4+3] cycloaddition reaction between the pyrrole structure and the silyloxyallyl cation probably only substitution products were generated (chapter 4.2.2).

With the aim of preparing bicyclic systems with an alkynyl side chain several reactions were carried out to obtain the substituted furans **152** and **161** (Figure **79**). Unfortunately, the desired alkyne furans were not obtained and consequently [4+3] cycloadditions could not be carried out (chapter 4.4).

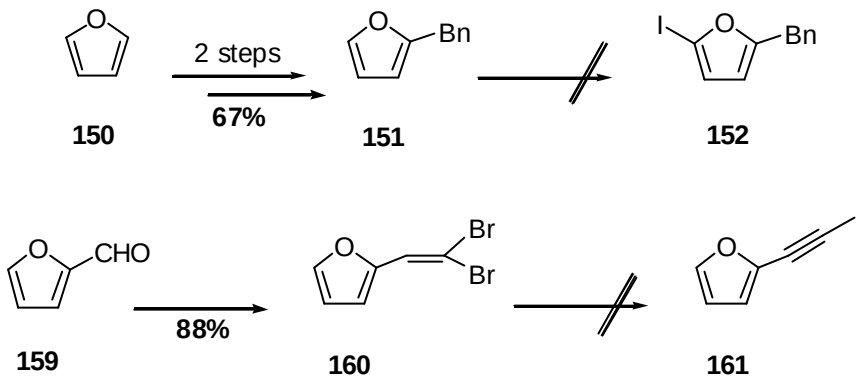


Figure 79: Synthesized substituted furans as precursors of the corresponding alkyne furans

Some X-ray structures were obtained to determine the relative configuration of the stereocenters in different molecules (chapter 7): the bicyclic ketone ***rac*-45** and ***rac*-94**, the tricyclic structures with methyl and ethyl function at the C3-atom position **105**, **108**, **109**, the bicyclic amino compound **134**, the Scopoline derivative **142** and two conformational structures from tricyclic Scopoline derivative **148** (Figure **80**).

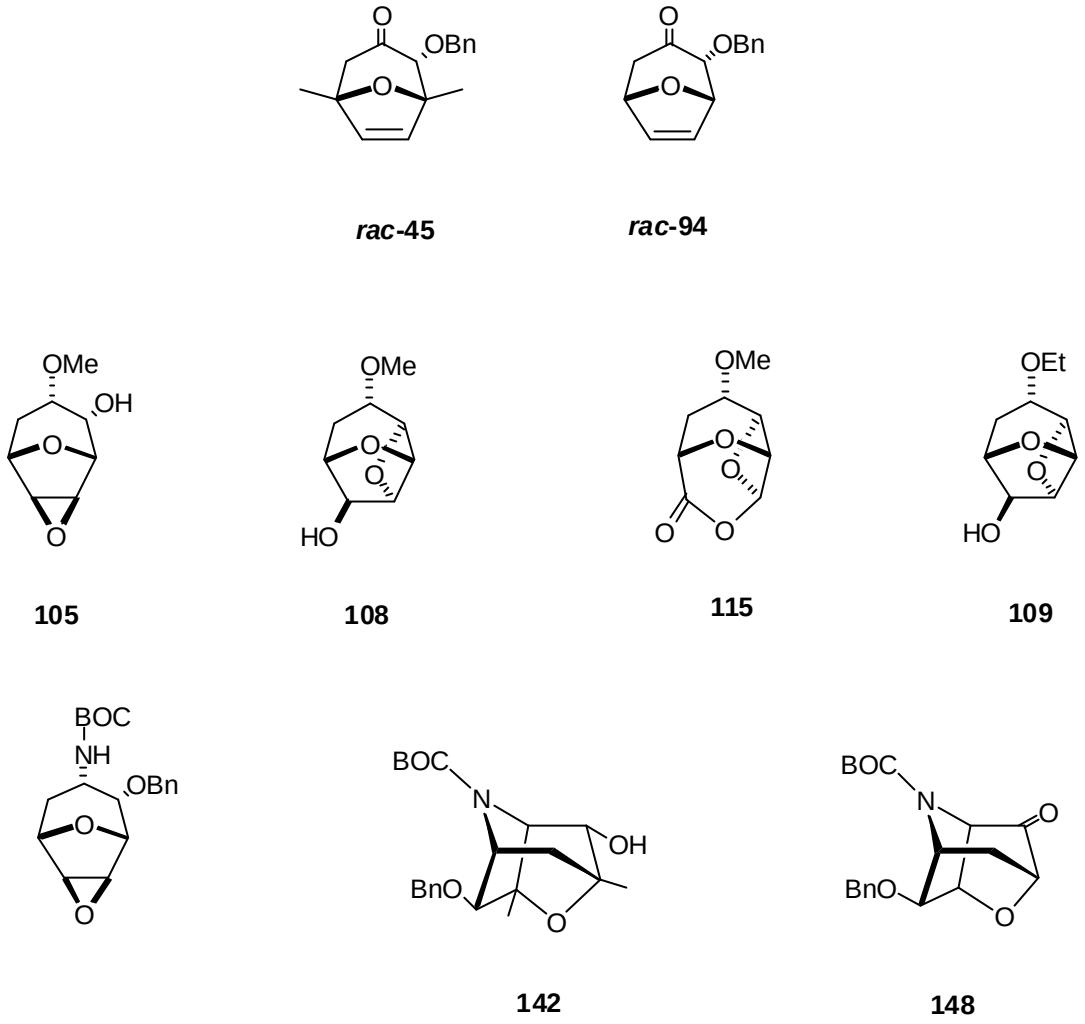


Figure 80: Structures corroborated by X-ray crystal diffraction analysis

6.1 Analytical Methods

^{1}H NMR spectra were measured using the instrument Bruker WP 200 (200.1 MHz), 400 (400 MHz) and AVS 400 (400.1 MHz). All NMR- measurements were curried out at room temperature in 5 mm NMR tubes, and in deuterated solvents, $CDCl_3$ or CD_3OD. Tetramethylsilane (TMS, d = 0.00) was used as internal standard. The chemical shifts d are represented in (ppm) and the coupling constant over n bond (^nJ) is represented in Hertz (Hz). The multiplicity of the peaks were abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublets, ddd = doublet of double doublets, dt = doublet of triplets, dq = doublet of quartets.
^{13}C-NMR-Spectra were measured under ^{1}H broad-band decoupling using the instrument Bruker AVS 200 (50.3 MHz) and AVS 400 (100.6 MHz). $CDCl_3$ was used as solvent and as internal standard. The multiplicities of the signals were determined with DEPT90 (pulse angle $q = 90^0$ gave a CH-subspectrum with positive signal amplitudes) and the DEPT135 (pulse angle $q = 135^0$ gave a CH/CH_3-subspectrum with positive as well as the CH_2-subspectrum in negative signal amplitudes).
H,H-COSY-, C,H-COSY, HBMC-, HMQC and NOE spectra was measured with the devices AVD-500, AM-400 and AVS 400 of the company Bruker in $CDCl_3$ with 400 or 500 MHz.
Infrared spectra (IR) were obtained using a PERKIN-ELMER FT 1710 spectrometer. The following abbreviations were used to indicate the intensity of the absorption bands: s = strong, m = middle, w = weak. The characteristic IR absorptions are presented in cm^{-1}.
Mass spectra (EI MS) were carried out using a FINNIGAN AM 400 mass spectrometer (Ionization potential 70 ev). The characteristic EI MS peaks are given m/z (mass to charge ratio) and relative percentage intensity of base peak (100 %).
HR-MS was carried out using a VG-Autospec spectrometer with the peak-matching method (PKF), and the NBA-Matrix was used.
Melting points (m.p.) were measured by using a Büchi equipment according to Dr.Tottoli and are not corrected.
Elementary analyses (EA) were executed for CHN with a Häraeus instrument.
Thin layer chromatography (TLC) was carried out using aluminium TLC plates coated with the silica gel $60F_{254}$ from Merck. The detection of substance over the TLC was done with the help of the UV-lamp (? = 254 nm) and developed in Ce(IV) sulfate/Molybdatophosphoric acid-solvent.
Column chromatography was carried out using silica gel 60 ? (40-60 µm) and 60 ? (20-45 µm) from the J.T. Baker.
Absolute solvents were prepared according to the well-known regulations[145] and stored over molecular sieves, CaH_2 or under an argon atmosphere. THF was distilled over Na/benzophenone in an argon atmosphere. Ethanol and methanol were dried over calcium hydride. Dichloromethane was dried over calcium chloride. Pyridine was dried over KOH.
Reactions were executed under nitrogen atmosphere.
General Remark: The naming of the molecules is according to the IUPAC system. The atom numbering follows generally the IUPAC rules. For reasons of clarity in some cases the numbering of the atomic positions was changed, this is indicated in the respective scheme.

[145] Perring, D.D.; Armarego, W.L.F.; Purification of Laboratory Chemicals, 3rd Ed., Pergamon Press Oxford, **1998**.

6.2 General Procedures (GP)

GP1. General Procedure for the preparation of silyl enol ether from dibenzyl acetal (kinetic conditions)

LDA solution was prepared adding diisopropylamine (1.4 eq) in a solution mixture of THF and *n*BuLi (1.6 M/hexane, 1.4 eq) at -78°C. The resulting mixture was stirred for a further 15 min at room temperature. In another round-bottomed flask dibenzyl acetal (1.0 eq) and trialkylsilyl chloride (1.6 eq) were dissolved in THF and stirred at -78°C. To this mixture LDA and triethylamine (4.5 eq) was added. The resulting reaction mixture was stirred for one hour at -78°C then warm till room temperature. The reaction mixture was washed with distilled water. The aqueous phase was then extracted twice with cyclohexane. The organic layer was dried over Na_2SO_4 and concentrated under vacuum.

GP2. General Procedure for the preparation of silyl enol ether from dibenzyl acetal (thermodynamic conditions)

Dibenzyl acetal (1.0 eq) was dissolved in dry DMF (3M). To this mixture was added trialkylsilyl chloride (2.3 eq) and heated at 75°C. Triethylamine (2.8 eq) was then added *via* perfusion (30 ml/h). The reaction mixture was refluxed for 16 h at 75°C, and then cooled till 0°C, washed with saturated solution of ammonium chloride and with distilled water. The aqueous phase was re-extracted with cyclohexane for two times. The organic phase dried over Na_2SO_4 and the solvent removed with a rotatory evaporator.

GP3. General Procedure for the [4+3] Cycloaddition at low temperature

Silyl enol ether (1.0 eq) was dissolved in dichloromethane at -78°C. Under nitrogen atmosphere furan (1.0 eq) was added to the reaction mixture. After 15 min TMSOTf (0.1 eq) was added. The mixture was stirred for 30 min at –78°C and then poured into a separating funnel containing a saturated solution of sodium bicarbonate. The solution was shaken thoroughly, it is important, until reach at room temperature. The aqueous layer was extracted with dichloromethane for three times and the combined organic phase was dried over Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography on silica gel.

GP4. General Procedure for the diastereoselective DIBAH reduction of ketone

Bicycled ketone (1.0 eq) was dissolved in THF at -78°C and then was added, slowly, a DIBAH solution (1.2 M/toluene, 2.2 eq).The solution was left at this temperature over

night and quenched at room temperature with 6N aqueous HCl. The aqueous phase was extracted four times with MTBE. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel.

GP5. General Procedure of epoxidation using *m*-CPBA

Bicycled alkene (1.0 eq) was dissolved in DCM and cooled at 0°C, then *m*-CPBA (70 - 75%, 2.0-2.4 eq) was added. The solution was stirred for 1.5 h at 0°C and then, the reaction mixture was washed for three times with a 5% Na_2CO_3 solution. The aqueous phase was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel.

GP6. General Procedure for debenzylation

A catalytic amount of Pd/C (10%) was dissolved in alcohol. To this suspension was added a solution of benzyl ether (1.0 eq) in methanol and AcOH. The mixture was stirred at room temperature under hydrogen atmosphere for three days, and then was filtered through a short silica gel column (EtOH/MTBE 1:1), concentrated under vacuum and washed for three times with a 5% Na_2CO_3 solution. The aqueous phase was extracted several times with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel to afford the alcohol.

GP7. General Procedure for oxetane formation with base treatment

Epoxy alcohol (1.0 eq) was dissolved in THF and to this solution was added ^{t}BuOK (1.2 – 2.5 eq). The mixture was stirred for 1 day at room temperature, and then was washed with distilled water. The aqueous phase was extracted several times with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel.

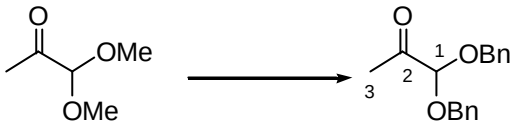
GP8. Formation of keto oxetane through Swern oxidation

Oxalyl chloride (4.0 eq) was dissolved in DCM. To this mixture was added, at -78°C, DMSO (4.2 eq) and tricyclic alcohol (1.0 eq) in DCM. The solution was stirred for 1h at -78°C and then NEt_3 (9.0 eq) was added. Stirring was continued for 1h at -78°C and 1.5 h more at room temperature. The solvent was removed; the residue dissolved in MTBE and treated with water. The aqueous layer was extracted several times with MTBE. The combined organic phase was dried over Na_2SO_4, evaporated under vacuum and purified by column chromatography on silica gel.

6.3 Attempts to chapter 4

6.3.1 Attempts to chapter 4.1.1

1,1-Bis-benzyloxy-propan-2-one **43**



22 **43**

Pyruvic aldehyde dimethyl acetal 24.2 mL (200 mmol, 1.0 eq) was dissolved in 50 mL of cyclohexane. To this mixture were added benzyl alcohol 45.5 mL (440 mmol, 2.2 eq) and 1.9 g *p*-toluenesulfonic acid (1.9 g, 10 mmol, 0.05 eq). The resulting mixture was heated for 6 h at 100°C to reflux using a Dean–Stark separator for the removal of MeOH. Upon the completion of reaction after 5.0 h, 16 mL (400 mmol) of MeOH was obtained. The reaction mixture was cooled down to room temperature and washed with 25 mL of saturated potassium carbonate solution and 20 mL of dist. water. The aqueous layer was extracted twice with cyclohexane (50 mL each). The combined organic phase was dried over Na_2SO_4, evaporated and purified by column chromatography on silica gel (MTBE/CH 1:10) solvent system to afforded a-Keto acetal **43**.

Yield: 44.5 g (164.8 mmol), yellowish oil, 82 %

$C_{17}H_{18}O_3$ (270.32)

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

7.43-7.26 (m, 10 H, Ar-H), 4.74 (s, 1 H, H-1), 4.69 (dd, ^2J = 12.0 Hz, 2H, -OC$\underline{H}_2$Ph), 4.58 (dd, ^2J = 12.0 Hz, 2H, -OC$\underline{H}_2$Ph), 2.56 (s, 3 H, H-3)

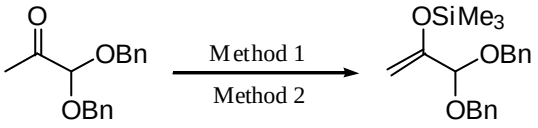
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

203.87(C, C-2), 136.92 (C, Ar-C), 128.17 (CH, Ar-C), 128.04 (CH, Ar-C), 100.94 (CH, C-1), 69.41 (2XCH_2, -O$\underline{C}H_2$Ph), 25.11 (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 (9.8), 227 (28.5, M^+-CH_3CO),182 (27.8), 181(43.4), 164 (13.6); 135 (9.7); 108 (18.9); 93 (12.1); 92 (46.7); 91 (100)

[1-(benzyloxy-methoxy-methyl)-vinyloxy]-trimethyl-silane **44**

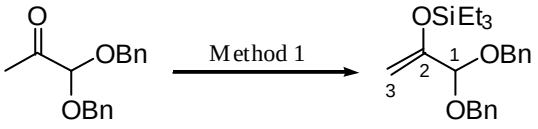


43 **44**

Method 1: GP1; LDA solution was prepared with diisopropylamine (4.8 mL, 35 mmol, 1.4 eq) in 34.8 mL of THF and *n*BuLi (1.6 M/hexane, 21.8 mL, 35 mmol, 1.4 eq). Dibenzyl acetal **43** (6.75 g, 25 mmol, 1.0 eq) and chlorotrimethylsilane (5.0 mL, 40 mmol, 1.6 eq) were dissolved in 25 mL of THF. To this mixture the LDA solution and triethylamine (15.6 mL, 112.5 mmol, 4.5 eq) was added. After completion the reaction was washed with 20 mL distilled water. The obtained yellowish oil was used directly in the next steps.

Method 2: GP2; Dibenzyl acetal **43** (27 g, 100 mmol, 1 eq) was dissolved in anhydrous DMF (36 mL, 3M solution) and then, chlorotrimethylsilane (28.8 mL, 230 mmol, 2.3 eq) was added. The reaction mixture was heated at 75°C. Triethylamine (38.9 mL, 280 mmol, 2.8 eq) was added *via* perfusion (30 mL/h). When the reaction was completed, was washed with 24 mL saturated solution of ammonium chloride and 20 mL distilled water. The resulting brown viscous oil was used directly in the next step.

[1-(benzyloxy-methoxy-methyl)-vinyloxy]-triethyl-silane **95**



43 **95**

Method 1: GP1; LDA solution was prepared with diisopropylamine (3.6 mL, 25.9 mmol, 1.4 eq) in 26 mL of THF and *n*-BuLi (1.6M/hexane, 18 mL, 25.9 mmol, 1.4 eq). Dibenzyl acetal **35** (5 g, 18.5 mmol, 1.0 eq) and triethylsilane chloride (4.9 mL, 29.6 mmol, 1.6 eq) were dissolved in 26 mL of THF. To this mixture the LDA solution and triethylamine (15.6 mL, 112.5 mmol, 4.5 eq) was added. After completion the reaction was washed with

20 mL distilled water. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:10) to afford compound **95**.

Yield: 5.84 g (15.2 mmol), 82 %

$C_{23}H_{32}O_3Si$ (384.58)

^{1}H-NMR (400MHz, $CDCl_3$ + 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, ^2J = 12.0 Hz, 2H, -OC$\underline{H}_2$Ph), 4.60 (d, ^2J = 12.0 Hz, 2H, -OC$\underline{H}_2$Ph), 4.43 (d, ^2J= 1 Hz, 1H, H-3*cis*), 1.00 (t, ^3J= 8.0 Hz, 9H, -Si($CH_2C\underline{H}_3)_3$), 0.74 (q, ^3J= 8.0 Hz, 6H, -Si($C\underline{H}_2CH_3)_3$)

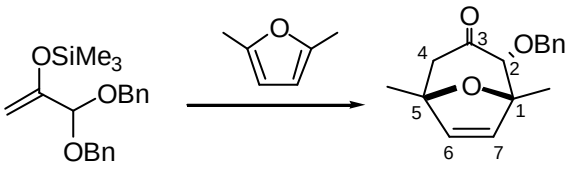
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

153.73 (C, C-2), 138.12 (C, Ar-C), 128.27 (CH, *m*-Ar-C), 127.76 (CH, *o*-Ar-C), 127.46 (CH, *p*-Ar-C), 99.09 (CH_2, C-3), 92.23 (CH, C-1), 67.89 (CH_2, -O$\underline{C}H_2$Ph), 6.62 (CH_3, -Si($CH_2\underline{C}H_3)_3$), 4.82 (CH_2, -Si($\underline{C}H_2CH_3)_3$)

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

EI MS (RT): no M^+; 279 (9.2), 249 (4.2), 248 (2.7), 193 (3.7), 187 (6.4), 181 (6.5), 159 (14.3), 157 (12.7), 115 (16.7), 91 (100)

2a-Benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-45**



44 ***rac*-45**

GP3; Silyl enol ether **36** (32.0 g, 93.5 mmol, 1.0 eq) was dissolved in 98 mL of dichloromethane and to the mixture 2,5-dimethylfuran (10 mL, 93.5 mmol, 1.0 eq) was added. After 15 min TMSOTf (1.7 mL, 9.35 mmol, 0.1 eq) was added. When the reaction was completed was poured into a separating funnel containing 84 mL of a saturated solution of sodium bicarbonate. The crude product was purified by column chromatography on silica gel (MTBE/CH, 1:2) to afford cycloadduct ***rac*-37** as light yellow oil which crystallizes into a white solid.

Yield: 1.48 g (5.73 mmol), white solid, 67% (after two steps)

$C_{16}H_{18}O_3$ (258.31)

m.p.: 79-80°C

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

7.41-7.29 (m, 5 H, *o*, *m*, *p*-Ar-H), 6.06 (d, ^3J = 6.0 Hz, 1 H, H-7), 6.00 (d, ^3J = 6.0 Hz, 1H, H-6), 5.03 (d, ^2J = 12.0 Hz, 1 H, -OC$\underline{H}_2$Ph), 4.58 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.81 (s, 1H, H-2), 2.63 (d, ^2J = 15.0 Hz, 1 H, H-4ax), 2.44 (dd, ^3J= 0.5 Hz, ^2J= 15.0 Hz, 1 H, H-4eq), 1.48 (s, 6 H, 2x -CH_3)

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

206.22 (C, C-3), 137.62 (C, Ar-C), 137.12 (CH, C-6), 134.79 (CH, C-7), 128.33-127.89 (CH, *o*, *m*, *p*-Ar-C), 87.43 (CH, C-2), 86.74 (C, C-5), 84.79 (C, C-1), 74.35 (CH_2, -O$\underline{C}H_2$Ph), 51.71 (CH_2, C-4), 23.05 (CH_3), 20.50 (CH_3)

IR (neat): 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

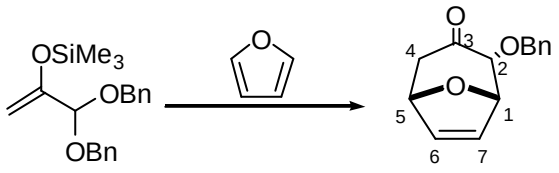
EI MS (RT): no M^+: 167 (34, M^+-Bn); 152 (30); 139 (14); 109 (19); 97 (20); 95 (15); 92 (12); 91 (100)

EA: C = 74.26 %, Calcd. C = 74.39 %

H = 6.91 %, Calcd. H = 7.02 %

X-rays: Its X-rays crystal structure data can be seen in chapter 7, pp. 127

2a-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-94**



44 ***rac*-94**

GP3; Silyl enol ether **36** (32.0 g, 93.5 mmol, 1.0 eq) was dissolved in 98 mL of dichloromethane and to the mixture furan (6.8 mL, 93.5 mmol, 1.0 eq) was added. After 15 min TMSOTf (1.7 mL, 9.35 mmol, 0.1 eq) was added. When the reaction was completed was poured into a separating funnel containing 84 mL of a saturated solution of sodium bicarbonate. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:2) to afford cycloadduct ***rac*-94** as light yellow oil which crystallizes into a light yellowish solid.

Yield: 13.98 g (60.79 mmol), light yellowish solid, 61% (after two steps)

$C_{14}H_{14}O_3$ (230.26)

m.p.: 64-65°C

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

7.39-7.30 (m, 5H, *o*, *m*, *p*-Ar-H), 6.33 (dd, ^3J = 1.5 Hz, ^2J = 6.2 Hz, 1H, H-7), 6.29 (dd, ^3J = 1.5 Hz, ^2J = 6.2 Hz, 1H, H-6), 4.99 (d, ^2J = 12.0 Hz, 1 H, -OC$\underline{H}_2$Ph), 4.97 (dt, ^3J = 1.2 Hz, ^2J = 4.9 Hz, 1H, H-5), 4.90 (dd, ^2J = 5.0 Hz, ^2J = 1.5 Hz, 1 H, H-1), 4.62 (d, ^2J = 12.0 Hz, 1 H, -OC$\underline{H}_2$Ph), 4.12 (d, ^3J = 5.0 Hz, 1H, H-2), 2.74 (dd, ^3J = 4.9 Hz, ^2J =15.3 Hz, 1 H, H-4ax); 2.35 (d, ^2J = 15.3 Hz, 1H, H-4eq)

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

204.9 (C, C-3), 140.9 (C, Ar-C), 137.6 (CH, C-6), 134.6 (CH, C-7), 128.5- 126.9 (CH, *o*, *m*, *p*-Ar-C), 84.1 (CH, C-2), 79.8 (C, C-5), 78.3 (C, C-1), 73.5 (CH_2, -O$\underline{C}H_2$Ph), 45.9 (CH_2, C-4)

IR (neat): 3063 w, 2977 m, 2862 m, 1719 s, 1497 m, 1453 m, 1411 w, 1385 m, 1329 m, 1149 s, 1117 s, 1017 s, 730 s, 697 s

EI MS (RT): 230 (M^+, 28), 139 (48, M^+-Bn), 158 (51), 121 (31), 107 (28), 91 (100), 81 (60), 69 (55)

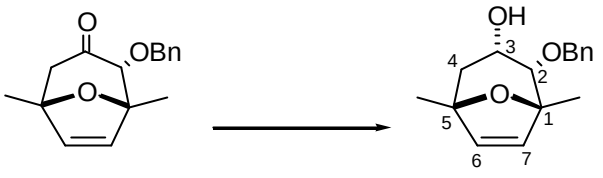
EA: C = 72.89 %, Calcd. C = 73.03 %

H = 6.05 %, Calcd. H = 6.13 %

X-rays: Its X-rays crystal structure data can be seen in chapter 7, pp. 129

6.3.2 Attempts to chapter 4.1.2 – 4.1.3

2a-Benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3a-ol **46**



***rac*-45** **46**

GP4; Bicycled ketone ***rac*-45** (3.0 g, 11.8 mmol, 1.0 eq) was dissolved in 8.5 mL THF at -78°C. A DIBAH solution (1.2 M/toluene, 21.6 mL, 25.9 mmol, 2.2 eq) was added, slowly. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **46** as white solid.

Yield: 2.9 g (11.1 mmol), white solid, 94 %

$C_{16}H_{20}O_3$ (260.33)

m.p.: 65-66°C

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

7.40-7.24 (m, 5H, Ar-H), 6.06 (d, ^3J = 6.0 Hz, 1H, H-7), 6.00 (d, ^3J = 6.0 Hz, 1H, H-6), 4.68 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.49 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.20 (m, 1H, H-3), 3.45 (dt, ^3J = 5.5 Hz, 1H, H-2), 2.58 (d, ^3J = 3.5 Hz, 1H, -OH), 1.93-1.91 (m, 2H, H-4), 1.39 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3)

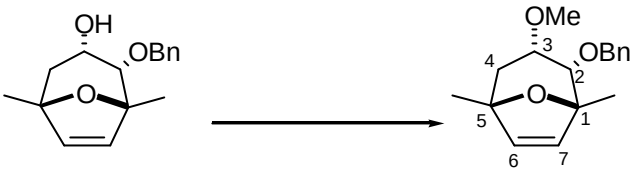
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

139.5 (CH, C-6), 134.7 (CH, C-7), 137.4 (C, *ipso*-Ar-C), 128.4-128.0 (CH, *o,m,p*-Ar-C), 85.0 (C, C-1), 84.1 (C, C-5), 79.3 (CH, C-2), 71.8 (CH_2, -O$\underline{C}H_2$Ph), 64.6 (CH, C-3), 39.9 (CH_2, C-4), 23.9 (CH_3, -CH_3), 21.2 (CH_3, -CH_3)

IR (neat)**:** 3532 m, 3073 w, 2983 m, 2916 m, 2850 m, 1454 w, 1389 m, 1354 w, 1186 m, 1114 s, 1051 m

EI MS (RT)**:** 260 (2, M^+), 203 (2), 169 (4, M^+-Bn), 167 (6), 154 (26), 109 (93), 91 (100)

2a-Benzyloxy-3a-methoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **165**



46 **165**

NaH (60 % suspension in oil, 0.1 g, 2.2 mmol, 2.0 eq) was dissolved in 5 mL THF and stirred at 0°C. In another R.B. bicycled alcohol **46** (0.3 g, 1.1 mmol, 1.0 eq) was dissolved in 3 mL THF, this mixture was added to the NaH solution and stirred for 1 h more at the same temperature. Then, CH_3I (0.1 mL, 1.9 mmol, 1.7 eq) was added at 0°C and the resulting solution was stirred for 2 h more at 0°C then warm till the room temperature. The reaction mixture was washed with 10 mL of saturated solution of sodium thiosulfate and with 30 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **165**.

Yield: 0.29 g (1.04 mmol), yellowish oil, 95 %

$C_{17}H_{22}O_3$ (274.16)

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

7.38-7.26 (m, 5H, Ar-H), 6.07 (d, ^3J = 5.8 Hz, 1H, H-7), 6.00 (d, ^3J = 5.8 Hz, 1H, H-6), 4.68 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.46 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 3.65 (dt, ^3J = 5.4 Hz, ^3J = 1Hz, 1H, H-3), 3.47 (dd, ^3J = 5.4 Hz, 1H, H-2), 3.33 (s, 3H, -OCH_3), 1.93 (dd, ^2J = 14.5 Hz, ^3J = 1.1 Hz, 1H, H-4ax), 1.78 (dd, ^2J = 14.5 Hz, ^3J = 5.2 Hz, 1H, H-4eq), 1.39 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3)

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

138.2 (C, *ipso*-Ar-C), 137.6 (CH, C-6), 135.2 (CH, C-7), 128.2 (CH, *o*-Ar-C), 128.0 (CH, *m*-Ar-C), 127.6 (CH, *p*-Ar-C), 85.5 (C, C-1), 83.8 (C, C-5), 79.8 (CH, C-2), 75.1 (CH_2, -O$\underline{C}H_2$Ph), 71.3 (CH, C-3), 57.8 (CH_3, -OCH_3), 36.5 (CH_2, C-4), 24.0 (CH_3, -CH_3), 21.0 (CH_3, -CH_3)

IR (neat)**:** 3030 w, 2928 m, 2869 m, 1453 m, 1373 w, 1351 m, 1240 m, 1167 m, 1086 s

EI MS (RT)**:** 275 (3, M^+), 215 (2), 183 (4), 168 (11), 151 (6), 137 (32), 109 (76), 91 (100)

HR MS: $C_{17}H_{22}O_3$, Exact: 274.1575, Calcd.: 274.1569

6a-Benzyloxy-7a-methoxy-1,5-dimethyl-3,9-dioxa-tricyclo[3.3.1.0^{2,4}]nonane **163**

165 **163**

GP5; Bicycled alkene **165** (1.5 g, 5.3 mmol, 1.0 eq) was dissolved in 10 mL DCM and cooled at 0°C. To this mixture *m*-CPBA (70-75%, 2.6 g, 10.6 mmol, 2.0 eq) dissolved in 5 mL DCM was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **163**.

Yield: 1.5 g (5.0 mmol), white solid, 94 %

$C_{17}H_{22}O_4$ (290.15)

m.p.: 63-64°C

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

7.36-7.26 (m, 5H, Ar-H), 4.68 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.49 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 3.61 (d, ^3J = 3.3 Hz, 1H, H-7), 3.58 (dt, ^3J = 4.5 Hz, ^3J = 1.7 Hz, 1H, H-3), 3.38 (d, ^3J = 4.6 Hz, 1H, H-2), 3.36 (s, 3H, -OCH_3), 3.33 (d, ^3J = 3.3 Hz, 1H, H-6), 3.38 (d, ^3J = 4.6 Hz, 1H, H-2), 2.01 (dd, ^2J = 14.9 Hz, ^3J = 1.6 Hz, 1H, H-4ax), 1.74 (dd, ^2J = 14.9 Hz, ^3J = 4.4 Hz, 1H, H-4eq), 1.38 (s, 3H, -CH_3), 1.29 (s, 3H, -CH_3)

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

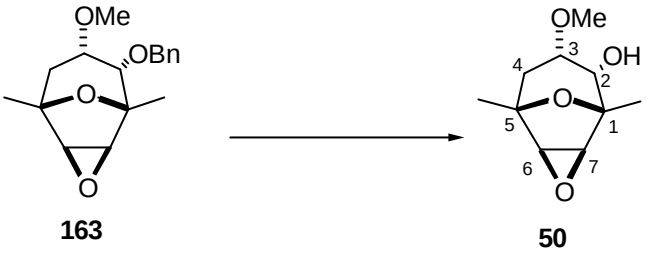
137.8 (C, *ipso*-Ar-C), 128.3 (CH, *o*-Ar-C), 128.0 (CH, *m*-Ar-C), 127.8 (CH, *p*-Ar-C), 79.7 (C, C-1), 79.4 (CH, C-2), 77.2 (C, C-5), 74.2 (CH, C-3), 71.4 (CH_2, -O$\underline{C}H_2$Ph), 58.1 (CH, C-7), 57.8 (CH, C-6), 57.2 (CH_3, -OCH_3), 37.0 (CH_2, C-4), 19.9 (CH_3, -CH_3), 17.3 (CH_3, -CH_3)

IR (neat)**:**3031 w, 2937 m, 2886 m, 1452 m, 1368 w, 1224 w, 1120 m, 1092 s, 764 s, 699 s

EI MS (RT)**:** 290 (4, M^+), 258 (19), 207 (10), 143 (76), 164 (13), 125 (20), 91 (100)

HR MS: $C_{17}H_{22}O_4$, Exact: 290.1520, Calcd.: 290.1518

7a-Methoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol **50**



GP6; A catalytic amount of Pd/C (10%) was dissolved in 20 mL methanol. To this suspension a solution of benzyl ether (0.9 g, 3.1 mmol, 1.0 eq) in 40 mL methanol and 0.4 mL AcOH was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford epoxy alcohol **50**.

Yield: 0.5 g (2.5 mmol), white solid, 81 %

$C_{10}H_{16}O_4$ (200. 10)

m.p.: 119-120°C

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

3.58 (dt, ^3J = 4.0 Hz, ^3J = 1.5 Hz, 1H, H-3), 3.53 (dd, ^3J = 9.5 Hz, ^3J = 5.0 Hz 1H, H-2), 3.45 (d, ^3J = 3.2 Hz, 1H, H-7), 3.40 (s, 3H, -OCH_3), 3.28 (d, ^3J = 3.2 Hz, 1H, H-6), 3.02 (d, ^3J = 9.5 Hz, 1H, -OH), 2.07 (dd, ^2J = 15.0 Hz, ^3J = 1.5 Hz, 1H, H-4ax), 1.82 (dd, ^2J = 15.0 Hz, ^3J = 4.0 Hz, 1H, H-4eq), 1.41 (s, 3H, -CH_3), 1.31 (s, 3H, -CH_3)

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

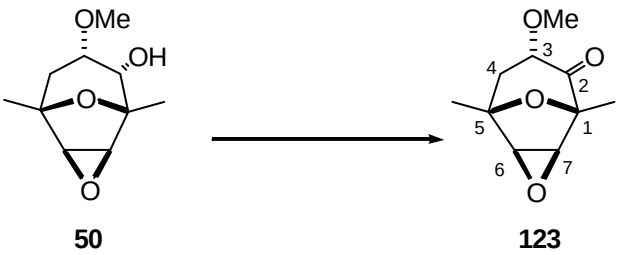
79.7 (C, C-1), 76.7 (C, C-5), 76.2 (CH, C-2), 72.0 (CH, C-3), 57.9 (CH, C-7), 57.6 (CH_3, -OCH_3), 56.5 (CH, C-6), 36.0 (CH_2, C-4), 19.9 (CH_3, -CH_3), 17.0 (CH_3, -CH_3)

IR (neat)**:** 3463 s, 2969 m, 2930 s, 1455 w, 1390 m, 1121 m, 1093 s, 1075 s, 878 m

EI MS (RT)**:** 200 (12, M^+), 168 (28), 143 (85), 101 (48), 85 (34), 74 (100), 69 (28)

HR MS: $C_{10}H_{16}O_4$, Exact: 200.1042, Calcd.: 200.1049

7a-Methoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6-one **123**



Epoxy alcohol **50** (0.23 g, 1.20 mmol, 1.0 eq) was dissolved in 5 mL THF and stirred at room temperature. To this mixture TPAP (0.008 g, 0.02 mmol, 0.02 eq) and NMO (0.21 g, 1.80 mmol, 1.5 eq) were added and the solution was stirred for 8 h at room temperature. The resulting reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography on silica gel using MTBE as eluent to afford **123**.

Yield: 0.12 g (0.60 mmol), white solid, 50 %

$C_{10}H_{14}O_4$ (198. 22)

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

3.52 (dd, ^3J = 8.5 Hz, ^3J = 5.6 Hz, 1H, H-3), 3.50 (d, ^3J = 3.2 Hz, 1H, H-7), 3.46 (d, ^3J = 3.2 Hz, 1H, H-6), 2.52 (dd, ^2J = 13.9 Hz, ^3J = 8.5 Hz, 1H, H-4ax), 1.90 (dd, ^2J = 13.9 Hz, ^3J = 5.6 Hz, 1H, H-4eq), 3.38 (s, 3H, -OCH_3), 1.50 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3)

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

205.8 (CH, C-2), 84.0 (C, C-1), 78.0 (CH, C-3), 77.1 (C, C-5), 58.7 (CH_3, -OCH_3), 58.0 (CH, C-7), 55.9 (CH, C-6), 38.9 (CH_2, C-4), 20.8 (CH_3, -CH_3), 15.0 (CH_3, -CH_3)

IR (neat)**:** 2978 m, 2930 m, 2829 w, 1730 s, 1452 m, 1373 m, 1212 w, 1307 s, 1070 m, 859 w

EI MS (RT)**:** 198 (14, M^+), 170 (9), 141 (22), 127 (100), 112 (25), 109 (25), 98 (49), 85 (38)

4a-Methoxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **51**

50 **51**

GP7; Epoxy alcohol **50** (0.2 g, 1.2 mmol, 1.0 eq) was dissolved in 12 mL THF and to this mixture a solution of $KOBu^t$ (0.2 g, 1.4 mmol, 1.2 eq) in 11 mL THF was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford **51**.

Yield: 0.2 g (1.0 mmol), white solid, 83 %

$C_{10}H_{16}O_4$ (200. 10)

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

4.69 (d, ^3J = 1.7 Hz, 1H, H-2), 4.56 (s, 1H, H-7), 3.91 (s1H, H-6), 3.48 (dt, ^3J = 8.8 Hz, ^3J = 1.9 Hz, 1H, H-3), 3.32 (s, 3H, -OCH_3), 2.40 (br.s, 1H, -OH), 2.30 (dd, ^2J = 13.4 Hz, ^3J = 8.0 Hz, 1H, H-4ax), 1.83 (dd, ^2J = 13.4 Hz, ^3J = 8.9 Hz, 1H, H-4eq), 1.60 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3)

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

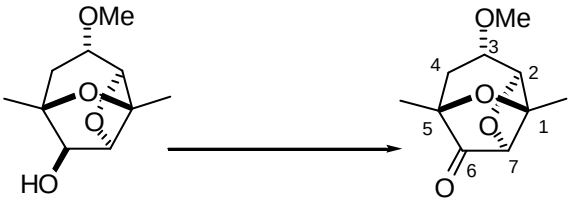
94.1 (CH, C-2), 85.0 (CH, C-7), 83.5 (C, C-1), 81.1 (C, C-5), 80.5 (CH, C-6), 75.3 (CH, C-3), 56.0 (CH_3, -OCH_3), 34.8 (CH_2, C-4), 21.6 (CH_3, -CH_3), 19.1 (CH_3, -CH_3)

IR (neat)**:** 3420 s, 2933 m, 1446 m, 1390 w, 1374 m, 1096 s, 1066 m, 986 m, 914 w

EI MS (RT)**:** 200 (6, M^+), 169 (17), 155 (15), 141 (85), 127 (41), 112 (100), 101 (87), 85 (76), 71 (66)

HR MS: $C_{10}H_{16}O_4$, Exact: 200. 1046, Calcd.: 200. 1049

4a-Methoxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9-one **52**



51 **52**

GP8; Oxalyl chloride (0.3 mL, 3.6 mmol, 4.0 eq) was dissolved in 5 mL DCM. To this mixture was added, at -78°C, DMSO (0.3 mL, 3.8 mmol, 4.2 eq) and tricyclic alcohol (0.2 g, 0.9 mmol, 1.0 eq) in 3 mL DCM. The solution was stirred for 1h at -78°C and then NEt_3 (1.1 mL, 8.1 mmol, 9.0 eq) was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford **52**.

Yield: 0.13 g (0.67 mmol), yellowish solid, 74 %

$C_{10}H_{14}O_4$ (198.09)

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

5.12 (d, ^3J = 1.8 Hz, 1H, H-2), 4.40 (s, 1H, H-7), 3.68 (dt, ^3J =8.8 Hz, ^3J =1.8 Hz, 1H, H-3), 3.35 (s, 3H, -OCH_3), 2.34 (dd, ^2J = 14.0 Hz, ^3J = 8.8 Hz, 1H, H-4ax), 1.90 (dd, ^2J = 14.0 Hz, ^3J = 8.2 Hz, 1H, H-4eq), 1.63 (s, 3H, -CH_3), 1.41 (s, 3H, -CH_3)

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

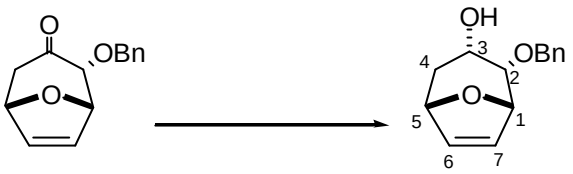
207.9 (C, C-6), 86.6 (CH, C-2), 83.9 (CH, C-3), 80.1 (C, C-1), 78.4(C, C-5), 74.1 (CH, C-7), 56.2 (CH_3, -OCH_3), 33.9 (CH_2, C-4), 20.8 (CH_3, -CH_3), 18.8 (CH_3, -CH_3)

IR (neat)**:** 3410 s, 2980 w, 2933 m, 2825 w, 1767 s, 1375 m, 1207 m, 1140 m, 1092 s, 956

EI MS (RT)**:** no M^+, 169 (4), 141 (100), 138 (10), 127 (15), 111 (22), 95 (70), 85 (59)

HR MS: $C_{10}H_{14}O_4$, Exact: 198.0883, Calcd.: 198.0892

2a-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene-3a-ol **96**



***rac*-94** **96**

GP4; Bicycled ketone ***rac*-94** (1.9 g, 8.5 mmol, 1.0 eq) was dissolved in 8.5 mL THF at -78°C. A DIBAH solution (1.2 M/toluene, 15.6 mL, 18.7 mmol, 2.2 eq) was added, slowly. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **96** as white solid.

Yield: 1.58 g (6.8 mmol), yellowish solid, 80%

$C_{14}H_{16}O_3$ (232.11)

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

7.39-7.30 (m, 5H, Ar-H), 6.37 (dd, ^3J = 2.0 Hz, ^3J = 5.8 Hz, 1H, H-7), 6.32 (dd, ^3J = 2.0 Hz, ^3J = 5.8 Hz, 1H, H-6), 4.70 (br.m, 1H, H-5), 4.69/4.57 (d, ^2J = 12.0 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.64 (br.d, 1H, H-1), 4.22 (dt, ^3J = 1.0 Hz, ^3J = 5.0 Hz, 1H, H-3), 3.77 (dd, ^3J = 5.0 Hz, 1H, H-2), 2.60 (br.s, 1H, O<u>H</u>), 2.08 (m, 1H, H-4ax), 1.81 (dd, ^2J = 15.0 Hz, ^3J = 4.5 Hz, 1H, H-4eq)

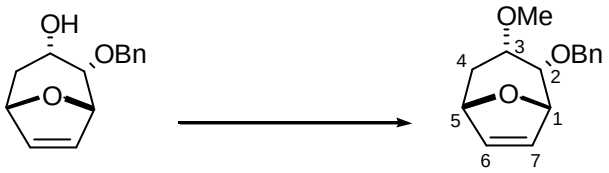
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

137.6 (C, *ipso*-Ar-C), 136.6 (CH, C-6), 131.7 (CH, C-7), 78.3 (CH, C-5), 128.5-127.8 (CH, *o,m,p*-Ar-C), 78.2 (CH, C-1), 74.3 (CH, C-2), 71.2 (CH, C-3), 65.4 (CH_2, -O<u>C</u>H_2Ph), 32.9 (CH_2, C-4)

IR (neat)**:** 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)

2a-Benzyloxy-3a-methoxy-8-oxabicyclo[3.2.1]oct-6-ene **168**



96 **168**

NaH (60 % suspension in oil, 7.9 g, 19.7 mmol, 2.0 eq) was dissolved in 25 mL THF and stirred at 0°C. In another R.B. bicycled alcohol **96** (2.3 g, 9.9 mmol, 1.0 eq) was dissolved in 15 mL THF, this mixture was added to the NaH solution and stirred for 1 h more at the same temperature. Then, CH_3I (1.2 mL, 19.8 mmol, 2.0 eq) was added at 0°C and the resulting solution was stirred for 2 h more at 0°C then warm till the room temperature. The reaction mixture was washed with 15 mL of saturated solution of sodium thiosulfate and with 30 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **168**.

Yield: 2.1 g (8.5 mmol), yellowish oil, 86%

$C_{15}H_{18}O_3$ (246.13)

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

7.38-7.28 (m, 5H, Ar-H), 6.37 (dd, ^3J = 2.0 Hz, ^3J = 5.7 Hz, 1H, H-7), 6.26 (dd, ^3J = 1.9 Hz, ^3J = 5.7 Hz, 1H, H-6), 4.65 (m, 1H, H-5), 4.61 (m, 1H, H-1), 4.55/4.66 (d, ^2J = 11.9 Hz, 1H, -OC<u>H</u>$_2$Ph), 3.78 (dd, ^3J = 5.4 Hz, 1H, H-2), 3.68 (dt, ^3J = 5.4 Hz, ^3J = 1Hz, 1H, H-3), 3.33 (s, 3H, -OCH_3), 1.96 (m, 1H, H-4ax), 1.82 (dm, 1H, H-4eq)

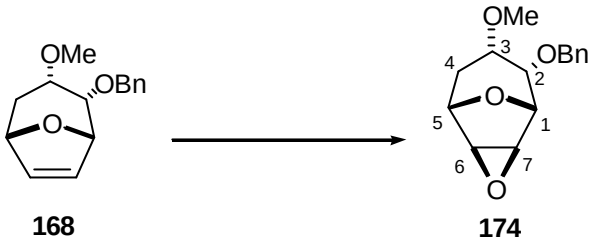
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.3 (C, *ipso*-Ar-C), 134.9 (CH, C-6), 132.1 (CH, C-7), 128.3-127.7 (CH, *o,m,p*-Ar-C), 78.6 (CH, C-5), 78.1 (CH, C-1), 75.9 (CH, C-2), 75.5 (CH, C-3), 70.9 (CH_2, -O<u>C</u>H_2Ph), 58.4 (CH_3, -OCH_3), 30.2 (CH_2, C-4)

IR (neat)**:** 3030 w, 2942 s, 2873 m, 1454 m, 1376 w, 1349 m, 1211 m, 1103 s, 1089 s, 1028 s, 925 m

EI MS (RT)**:** 246 (9, M^+), 214 (5), 155 (46), 140 (39), 123 (49), 108 (10), 91 (79), 81 (100)

6a-Benzyloxy-7a-methoxy-3,9-dioxa-tricyclo[3.3.1.0^{2,4}]nonane **174**



168 **174**

GP5; Bicycled alkene **168** (2.0 g, 8.3 mmol, 1.0 eq) was dissolved in 17 mL DCM and cooled at 0°C. To this mixture *m*-CPBA (70-75%, 3.8 g, 16.6 mmol, 2.0 eq) dissolved in 10 mL DCM was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **174**.

Yield: 1.5 g (5.6 mmol), light yellowish solid, 68%

$C_{15}H_{18}O_4$ (262.30)

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

7.42-7.38 (m, 5H, Ar-H), 4.59/4.68 (d, ^2J = 12.0 Hz, 2H, -OC$\underline{H}_2$Ph), 4.20 (br.d, ^3J = 4.5 Hz, 1H, H-2), 4.18 (m, 1H, H-3), 3.84 (d, ^3J = 3.2 Hz, 1H, H-7), 3.69 (br.d, ^3J = 4.5 Hz, 1H, H-1), 3.62 (m, 1H, H-5), 3.55 (d, ^3J = 3.2 Hz, 1H, H-6), 3.40 (s, 3H, -OCH_3), 1.95 (m, 2H, H-4ax/eq)

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

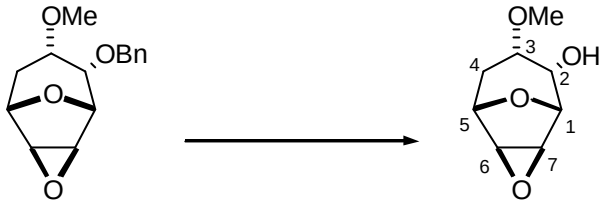
137.8 (C, *ipso*-Ar-C), 128.4-127.7 (CH, *o,m,p*-Ar-C), 75.2 (CH, C-1), 74.4 (CH, C-5), 72.6 (CH, C-2), 71.5 (CH, C-3), 71.1 (CH_2, -O$\underline{C}H_2$Ph), 58.2 (CH_3, -OCH_3), 53.9 (CH, C-7), 53.3 (CH, C-6), 30.5 (CH_2, C-4)

IR (neat)**:** 2949 m, 2923 m, 1453 m, 1371 w, 1205 s, 1107 s, 1087 s, 1026 s, 964 m

EI MS (RT)**:** 262 (14, M^+), 172 (9), 156 (9), 154 (8), 139 (14), 123 (13), 107 (14), 91 (100)

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectres

7a-Methoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol **105**



174 **105**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 20 mL methanol. To this suspension a solution of benzyl ether (3.5 g, 13.2 mmol, 1.0 eq) in 40 mL methanol and 1.7 mL AcOH was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford epoxy alcohol **105**.

Yield: 1.2 g (6.9 mmol), colourless solid, 52 %

$C_8H_{12}O_4$ (172. 18)

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

4.19 (m, 1H, H-3), 4.16 (br.d, ^3J = 5.0 Hz, 1H, H-2), 3.87 (m, 1H, H-1), 3.68 (d, ^3J = 3.0 Hz, 1H, H-7), 3.59 (m, 1H, H-5), 3.48 (d, ^3J = 3.0 Hz, 1H, H-6), 3.40 (s, 3H, -OCH_3), 2.01/1.98 (m, 2H, H-4ax/eq)

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

75.2 (CH, C-5), 74.0 (CH, C-1), 70.8 (CH, C-2), 67.2 (CH, C-3), 57.5 (CH_3, -OCH_3), 53.6 (CH, C-7), 52.5 (CH, C-6), 29.0 (CH_2, C-4)

IR (neat)**:** 3465 m, 2924 m, 2853 w, 1717 m, 1456 w, 1396 w, 1249 w, 1126 m, 1083 s

EI MS (RT)**:** 172 (30, M^+), 140 (11), 116 (4), 115 (24), 97 (36), 83 (35), 73 (23), 71 (100)

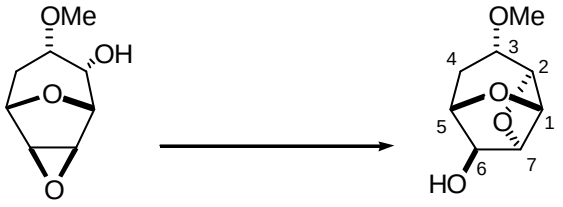
Structure confirmation: H,H-COSY, HMBC, HMQC-Spectres

EA: C = 55.73 %, Calcd. C = 55.81 %

H = 6.86 %, Calcd. H = 7.02 %

X-rays: Its x-rays crystal structure data can be seen in chapter 7, pp. 131

4a-Methoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **108**



105 **108**

GP7; Epoxy alcohol **105** (0.5 g, 2.9 mmol, 1.0 eq) was dissolved in 25 mL THF and to this mixture a solution of KOBu^t (0.4 g, 3.5 mmol, 1.2 eq) in 25 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as eluent to afford **108**.

Yield: 0.3 g (1.8 mmol), white solid, 62 %

$C_8H_{12}O_4$ (172. 18)

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

5.18 (dd, ^3J = 5.0 Hz, 1H, H-7), 5.01 (dd, ^3J = 6.0 Hz, 1H, H-2), 4.94 (dd, ^3J = 5.0 Hz, 1H, H-6), 4.53 (m, 1H, H-5), 4.20 (br.s, 1H, H-1), 3.50 (dt, ^3J = 10.0 Hz, ^3J = 2.0 Hz, 1H, H-3), 3.31 (s, 3H, -OCH_3), 2.61 (m, 1H, H-4ax), 1.70 (dd, ^3J = 10.0 Hz, 1H, H-4eq)

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

89.7 (CH, C-2), 81.5 (CH, C-7), 80.4 (CH, C-1), 78.6 (CH, C-6), 74.6 (CH, C-5), 74.0 (CH, C-3), 56.0 (CH_3, -OCH_3), 28.0 (CH_2, C-4)

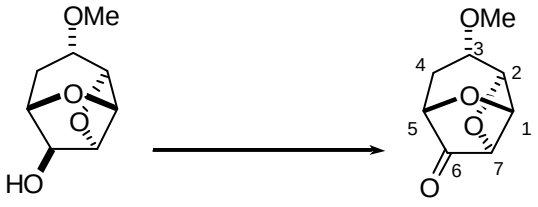
IR (neat)**:** 3338 m, 2975 w, 2915 w, 1695 s, 1491 s, 1049 s, 962 m

EI MS (RT)**:** 171 (2, M^+ -1), 155 (2), 141 (2), 122 (6), 111 (95), 97 (10), 84 (100), 71 (23)

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectres

X-rays: Its x-rays crystal structure data can be seen in chapter 7, pp. 133

9a-Methoxy-2,4,7-trioxa-tricyclo[4.2.2.0^{3,8}]decane-5-one **115**



108 **115**

PCC (1.5 g, 6.8 mmol, 4.0 eq) and anhydrous sodium acetate (0.6 g, 6.8 mmol, 4.0 eq) were dissolved in 14 mL DCM and placed in a light-protected flask which containing 4? molecular sieves (previously activated) (1.7 g). The mixture was stirred under argon atmosphere for 30 min. Tricyclic oxetan **108** (0.3 g, 1.7 mmol, 1.0 eq) was dissolved in 5 mL DCM and added to the obtained suspension, and stirring was maintained for 16 h at room temperature. The remaining solution was then diluted with 25 mL MTBE and then filtered through a short silica gel column (EA/MTBE 1:1) and concentrated under vacuum to afford **115**.

Yield: 0.04 g (0.2 mmol), yellowish solid, 12 %

$C_8H_{10}O_5$ (186. 16)

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

6.15 (d, ^3J = 4.5 Hz, 1H, H-7), 5.14 (dd, ^3J = 2.0 Hz, 1H, H-2), 4.92 (ddt, ^3J = 1.0 Hz, 1H, H-1), 4.88 (dd, ^3J = 2.8 Hz, 1H, H-5), 3.63 (ddt, ^3J =2.0 Hz, ^3J =1.8 Hz, 1H, H-3), 3.38 (s, 3H, -OCH_3), 2.80 (ddd, ^2J = 9.0 Hz, ^3J = 2.8 Hz, 1H, H-4ax), 2.09 (ddd, ^2J = 9.0 Hz, ^3J = 1.8 Hz, ^3J = 1.0 Hz, 1H, H-4eq)

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

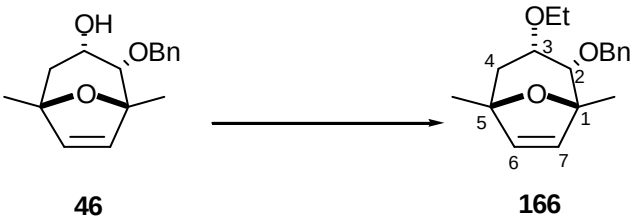
168.4 (C, C-6), 100.7 (CH, C-7), 77.6 (CH, C-2), 68.0 (CH, C-3), 72.7 (CH, C-1), 69.2 (CH, C-5), 56.2 (CH_3, -OCH_3), 25.7 (CH_2, C-4)

IR (neat)**:** 2922 s, 1764 s, 1389 m, 1218 m, 1132 s, 1059 s, 960 s, 896 s, 859 m

EI MS (RT)**:** no M^+, 155 (7), 140 (13), 129 (10), 126 (9), 111 (100), 81 (52)

X-rays: Ist x-rays crystal structure data can be seen in chapter 7, pp. 135

2a-Benzyloxy-3a-ethoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **166**



46 **166**

NaH (60 % suspension in oil, 9.1 g, 227.5 mmol, 5.0 eq) was dissolved in 75 mL THF and stirred at 0°C. In another R.B. bicyclic alcohol **46** (11.8 g, 45.5 mmol, 1.0 eq) was dissolved in 25 mL THF, this reaction mixture was added to the NaH solution and stirred

further for 1 h at the same temperature. Then, EtBr (17.0 mL, 227.5 mmol, 5.0 eq) and a catalytic amount of KI was added and the resulting solution was stirred for 2 h at 0°C then warm till the room temperature. The reaction mixture was washed with 160 mL of saturated solution of sodium thiosulfate and with 400 mL of distilled water. The aqueous phase was extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:5) to afford cycloadduct **166**.

Yield: 10.8 g (37.7 mmol), yellowish oil, 83 %

$C_{18}H_{24}O_3$ (288.38)

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

7.35-7.33 (m, 5H, Ar-H), 6.10 (d, ^3J = 5.8 Hz, 1H, H-7), 5.90 (d, ^3J = 5.8 Hz, 1H, H-6), 4.70 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.40 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.78 (td, ^3J = 1.2 Hz, ^3J = 5.5 Hz, 1H, H-3), 3.46 (d, ^3J = 5.5 Hz, 1H, H-2), 3.40 (m, 2H, -OC$\underline{H}_2$CH$_3$), 1.90 (dd, ^2J = 14.4 Hz, ^3J = 1.2 Hz, 1H, H-4ax), 1.78 (dd, ^2J = 14.4 Hz, ^3J = 5.0 Hz, 1H, H-4eq), 1.38 (s, 3H, -CH$_3$), 1.31 (s, 3H, -CH$_3$), 1.17 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

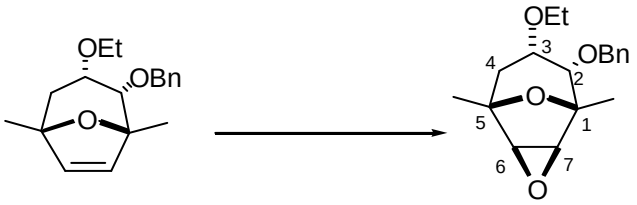
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.3 (C, *ipso*-Ar-C), 137.6 (CH, C-6), 135.2 (CH, C-7), 128.2-127.6 (CH, *o,m,p*-Ar-C), 85.5 (C, C-1), 83.8 (C, C-5), 79.9 (CH, C-2), 72.8 (CH, C-3), 71.2 (CH_2, -O$\underline{C}$H$_2$Ph), 65.2 (CH_2, -O$\underline{C}$H$_2$CH$_3$), 37.5 (CH_2, C-4), 24.0 (CH_3, -CH$_3$), 21.3 (CH_3, -CH$_3$), 15.6 (CH_3, -OCH$_2$$\underline{C}H_3$)

IR (neat)**:** 2971 m, 2928 m, 2866 m, 1453 w, 1372 m, 1351 m, 1171 m, 1085 s, 1028 s, 761 m, 736 m, 697 s

EI MS (RT)**:** 288 (6, M^+), 242 (3), 215 (4), 182 (35), 137 (96), 124 (39), 109 (100), 91 (99)

6a-Benzyloxy-7a-ethoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **164**



166 **164**

GP5; Bicyclic alkene **166** (9.6 g, 33.3 mmol, 1.0 eq) was dissolved in 200 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 19.7 g, 79.9 mmol, 2.4 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **164**.

Yield: 8.1 g (26.6 mmol), colourless oil, 80 %

$C_{18}H_{24}O_4$ (304.38)

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

7.36-7.35 (m, 5H, Ar-H), 4.65 (d, ^2J = 11.8 Hz, 1H, -OC$\underline{H}_2$Ph), 4.46 (d, ^2J = 11.8 Hz, 1H, -OC$\underline{H}_2$Ph), 3.72 (m, 1H, H-3), 3.65 (d, ^3J = 3.3 Hz, 1H, H-6), 3.51 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.38 (d, ^3J = 4.5 Hz, 1H, H-2), 3.35 (d, ^3J = 3.3 Hz, 1H, H-7), 1.95 (dd, ^2J = 14.8 Hz, ^3J = 1.8 Hz, 1H, H-4ax), 1.89 (dd, ^2J = 14.8 Hz, ^3J = 4.3 Hz, 1H, H-4eq), 1.39 (s, 3H, -CH$_3$), 1.37 (s, 3H, -CH$_3$), 1.19 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

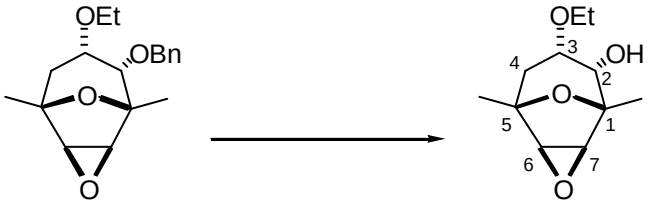
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.0 (C, *ipso*-Ar-C), 128.6-127.8 (CH, *o,m,p*-Ar-C), 79.7 (C, C-1), 79.5 (C, C-5), 77.5 (C, C-2), 72.0 (CH_2, -O$\underline{C}$H$_2$Ph), 71.2 (CH, C-3), 65.5 (CH_2, -O$\underline{C}$H$_2$CH$_3$), 58.4 (CH, C-6), 57.4 (CH, C-7), 38.1 (CH_2, C-4), 20.0 (CH_3, -CH$_3$), 17.3 (CH_3, -CH$_3$), 15.7 (CH_3, -OCH$_2$$\underline{C}H_3$)

IR (neat)**:** 2973 m, 2931 m, 2871 m, 1724 m, 1451 w, 1373 w, 1119 s, 1074 s, 737 s, 698 s

EI MS (RT)**:** no M^+, 276 (29), 185 (31), 157 (43), 149 (43), 115 (37), 109 (33), 91 (100)

7a-Ethoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol **101**



164 **101**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 100 mL ethanol. To this suspension a solution of benzyl ether (6.6 g, 21.8 mmol, 1.0 eq) in 80 mL ethanol and 3.6 mL AcOH was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford epoxy alcohol **101**.

Yield: 3.0 g (14.0 mmol), white solid, 64 %

$C_{11}H_{18}O_4$ (214.26)

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

4.20 (m, 1H, H-3), 4.09 (dd, ^3J = 11.8 Hz, 1H, H-2), 3.79 (d, ^3J = 3.3 Hz, 1H, H-7), 3.47 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.22 (d, ^3J = 3.3 Hz, 1H, H-6), 2.05 (d, ^3J = 11.8 Hz, 1H, -OH), 1.88 (dt, ^2J = 13.8 Hz, ^3J = 4.5 Hz, 1H, H-4ax), 1.79 (dd, ^2J = 13.8 Hz, ^3J = 1.1 Hz, 1H, H-4eq), 1.37 (s, 3H, -CH$_3$), 1.30 (s, 3H, -CH$_3$), 1.20 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

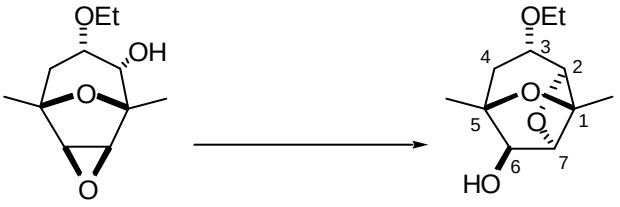
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

80.1 (C, C-1), 78.7 (C, C-5), 76.1 (CH, C-2), 73.5 (CH, C-3), 63.9 (CH$_2$, -O$\underline{C}$H$_2$CH$_3$), 58.1 (CH, C-6), 57.2 (CH, C-7), 39.8 (CH$_2$, C-4), 21.3 (CH$_3$, -CH$_3$), 17.6 (CH$_3$, -CH$_3$), 15.2 (CH$_3$, -OCH$_2$$\underline{C}H_3$)

IR (neat)**:** 3385 s, 2925 s, 2854 m, 1377 m, 1217 m, 1067 s, 1027 m, 798 w

EI MS (RT)**:** no M^+, 169 (61), 157 (12), 109 (68), 99 (30), 95 (100), 71 (40)

4a-Ethoxy-6,8-dimethyl -2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **103**



101 **103**

GP7; Epoxy alcohol **101** (0.5 g, 2.4 mmol, 1.0 eq) was dissolved in 20 mL THF and to this reaction mixture, a solution of KOBu^t (0.7 g, 6.0 mmol, 2.5 eq) in 20 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as eluent to afford **103**.

Yield: 0.3 g (1.4 mmol), colourless oil, 58 %

$C_{11}H_{18}O_4$ (214.26)

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

4.52 (s, 1H, H-7), 4.47 (d, ^3J = 1.8 Hz, 1H, H-2), 4.28 (d, ^3J = 6.0 Hz, 1H, H-6), 4.05 (m, 1H, H-3), 3.53 (m, 2H, -OC$\underline{H}_2$CH$_3$), 1.94 (m, 1H, H-4ax), 1.86 (dd, ^2J = 12.0 Hz, ^3J = 0.9 Hz, 1H, H-4eq), 1.35 (s, 3H, -CH$_3$), 1.29 (s, 3H, -CH$_3$), 1.18 (t, ^3J = 7.1 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

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

94.3 (CH, C-2), 90.2 (CH, C-7), 79.4 (C, C-1), 76.8 (C, C-5), 74.7 (CH, C-6), 72.6 (CH, C-3), 65.4 (CH_2, -O<u>C</u>H_2CH_3), 36.5 (CH_2, C-4), 21.5 (CH_3, -CH_3), 19.2 (CH_3, -CH_3), 16.3 (CH_3, -OCH_2<u>C</u>H_3)

IR (neat)**:** 3369 m, 2925 s, 2855 m, 1455 w, 1376 m, 1237 s, 1073 s, 701 m

EI MS (RT)**:** no M^+, 185 (64), 167 (79), 149 (78), 132 (79), 114 (79), 91 (100), 71 (71)

2a-Benzyloxy-3a-ethoxy-8-oxabicyclo[3.2.1]oct-6-ene **169**

96 **169**

NaH (60 % suspension in oil, 11.8 g, 294.5 mmol, 5.0 eq) was dissolved in 75 mL THF and stirred at 0°C. In another R.B. bicyclic alcohol **96** (13.7 g, 58.9 mmol, 1.0 eq) was dissolved in 25 mL THF, this reaction mixture was added to the NaH solution and stirred further for 1 h at the same temperature. Then, EtBr (22.0 mL, 294.7 mmol, 5.0 eq) and a catalytic amount of KI was added and the resulting solution was stirred for 2 h more at 0°C then warm till the room temperature. The reaction mixture was washed with 160 mL of saturated solution of sodium thiosulfate and with 400 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **169**.

Yield: 9.2 g (35.3 mmol), yellowish oil, 60 %

$C_{16}H_{20}O_3$ (260.33)

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

7.36-7.35 (m, 5H, Ar-H), 6.40 (dd, ^3J = 6.0 Hz, ^3J = 1.5 Hz, 1H, H-7), 6.20 (dd, ^3J = 6.0 Hz, ^3J = 1.5 Hz, 1H, H-6), 4.66 (br.t, ^3J = 1.9 Hz, 1H, H-1), 4.65 (d, ^2J = 12.0 Hz, 1H, -O<u>C</u>H_2Ph), 4.61 (br.t, ^3J = 1.9 Hz, 1H, H-5), 4.54 (d, ^2J = 12.0 Hz, 1H, -O<u>C</u>H_2Ph), 3.81 (m, 1H, H-3), 3.77 (m, 1H, H-2), 3.47 (m, 2H, -O<u>C</u>H_2CH_3), 1.97 (ddd, ^2J = 14.5 Hz, ^3J = 8.9 Hz, 1H, H-4eq), 1.78 (br.d, ^2J = 14.5 Hz, 1H, H-4ax), 1.17 (t, ^3J = 7.0 Hz, 3H, -OCH_2<u>C</u>H_3)

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

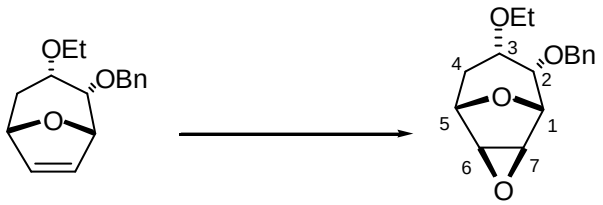
138.4 (C, *ipso*-Ar-C), 134.9 (CH, C-6), 132.2 (CH, C-7), 128.3-127.6 (CH, *o,m,p*-Ar-C), 78.7 (CH, C-1), 78.2 (CH, C-5), 75.6 (CH, C-2), 73.4 (CH, C-3), 65.8 (CH_2, -O<u>C</u>H_2CH_3), 70.7 (CH_2, -O<u>C</u>H_2Ph), 31.3 (CH_2, C-4), 15.6 (CH_3, -OCH$_2$<u>C</u>H_3)

IR (neat)**:** 2941 m, 2864 m, 1454 w, 1346 m, 1207 m, 1084 s, 1028 s, 855 s

EI MS (RT)**:** 260 (2, M^+), 215 (4), 169 (29), 123 (21), 105 (22), 91 (100), 81 (100)

HR MS: $C_{18}H_{23}NO_3Na$ M^+ + CH_3CN + Na, Exact: 324.1576, Calcd.: 324.1573

6a-Benzyloxy-7a-ethoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **175**



169 **175**

GP5; Bicycled alkene **169** (5.0 g, 19.2 mmol, 1.0 eq) was dissolved in 100 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 11.4 g, 46.1 mmol, 2.4 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **175**.

Yield: 4.2 g (14.4 mmol), colourless oil, 75 %

$C_{16}H_{20}O_4$ (276.33)

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

7.36-7.35 (m, 5H, Ar-H), 4.70 (d, ^2J = 11.9 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.60 (d, ^2J = 11.9 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.20 (br.d, ^3J = 4.0 Hz, 1H, H-1), 4.17 (m, 1H, H-5), 3.85 (d, ^3J = 3.8 Hz, 1H, H-6), 3.75 (m, 1H, H-3), 3.67 (d, ^3J = 4.0 Hz, 1H, H-7), 3.56 (m, 1H, H-2), 3.54 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 1.95 (dt, ^2J = 14.9 Hz, ^3J = 8.0 Hz, ^3J = 4.0 Hz, 1H, H-4ax), 1.89 (dt, ^2J = 14.9 Hz, ^3J = 3.3 Hz, ^3J = 1.6 Hz, 1H, H-4eq), 1.19 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C<u>H</u>$_3$)

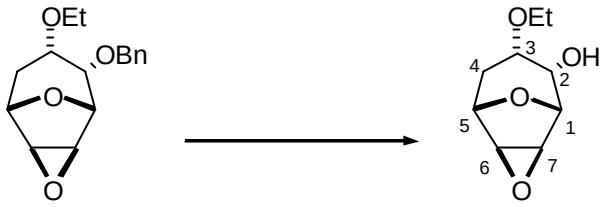
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.1 (C, *ipso*-Ar-C), 128.4-127.6 (CH, *o,m,p*-Ar-C), 75.4 (CH, C-1), 72.8 (CH, C-5), 72.1 (CH, C-2), 71.6 (CH, C-3), 70.8 (CH_2, -O<u>C</u>H_2Ph), 65.9 (CH_2, -O<u>C</u>H_2CH_3), 54.3 (CH, C-6), 53.5 (CH, C-7), 31.7 (CH_2, C-4), 15.6 (CH_3, -OCH$_2$<u>C</u>H_3)

IR (neat)**:** 3016 w, 2970 m, 2947 w, 1739 s, 1441 w, 1367 s, 1229 s, 1217 s, 1091 m, 1028 w, 854 w

EI MS (RT)**:** 276 (10, M^+), 204 (12), 178 (15), 139 (20), 111 (36), 97 (29), 91 (100), 72 (30)

7a-Ethoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol **106**



175 **106**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 20 mL ethanol. To this suspension a solution of benzyl ether (3.6 g, 13.0 mmol, 1.0 eq) in 40 mL ethanol and 1.8 mL AcOH was added. The crude product was purified by column chromatography on silica gel using MTBE as an eluent to afford epoxy alcohol **106**.

Yield: 1.2 g (6.5 mmol), white solid, 50 %

$C_9H_{14}O_4$ (186.21)

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

4.20 (br.d, ^3J = 1.0 Hz, 1H, H-5), 4.17 (br.d, ^3J = 4.5 Hz, 1H, H-1), 3.87 (m, 1H, H-2), 3.69 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.48 (d, ^3J = 3.3 Hz, 1H, H-6), 3.37 (m, 1H, H-3), 3.33 (d, ^3J = 9.9 Hz, 1H, H-7), 2.0 (m, 2H, H-4ax/eq), 1.23 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

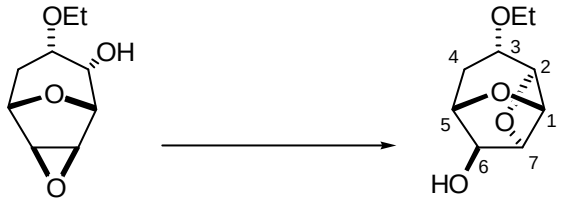
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

74.1 (CH, C-1), 73.2 (CH, C-5), 70.9 (CH, C-3), 67.0 (CH, C-2), 65.4 (CH_2, -O$\underline{C}$H$_2$CH$_3$), 53.9 (CH, C-6), 52.7 (CH, C-7), 30.0 (CH_2, C-4), 15.3 (CH_3, -OCH$_2\underline{C}$H$_3$)

IR (neat)**:** 3471 s, 2970 m, 2879 w, 1378 m, 1242 m, 1132 w, 1052 s, 1030 s, 793 m, 710 s

EI MS (RT)**:** 186 (17, M^+), 141 (17), 129 (20), 114 (27), 101 (29), 91 (20), 88 (48), 71 (100)

4a-Ethoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **109**



106 **109**

GP7; Epoxy alcohol **106** (1.0 g, 5.4 mmol, 1.0 eq) was dissolved in 45 mL THF and to this mixture a solution of KOBu^t (1.5 g, 13.5 mmol, 2.5 eq) in 45 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as an eluent to afford **109**.

Yield: 0.5 g (2.8 mmol), white solid, 52 %

$C_9H_{14}O_4$ (186.21)

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

5.17 (dd, ^3J = 10.0 Hz, ^3J = 4.2 Hz, 1H, H-7), 4.96 (dd, ^3J = 6.0 Hz, ^3J = 1.6 Hz, 1H, H-2), 4.93 (dd, ^3J = 4.2 Hz, ^3J = 1.6 Hz, 1H, H-1), 4.53 (d, ^3J = 10.0 Hz, 1H, H-6), 4.20 (m, 1H, H-5), 3.60 (dt, ^3J = 8.5 Hz, ^3J = 2.0 Hz, 1H, H-3), 3.47 (m, 2H, -OC$\underline{H}_2$CH$_3$), 2.63 (m, 1H, H-4eq), 2.10 (br.s, 1H, -OH), 1.75 (dq, ^3J = 8.5 Hz, ^3J = 0.8 Hz, 1H, H-4ax), 1.18 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C$\underline{H}_3$)

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

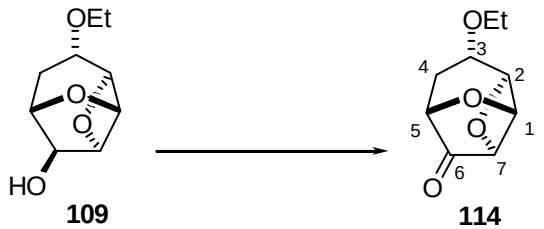
89.7 (CH, C-7), 82.1 (CH, C-2), 80.5 (CH, C-6), 78.6 (CH, C-1), 74.6 (CH, C-5), 72.4 (CH, C-3), 63.8 (CH_2, -O$\underline{C}$H$_2$CH$_3$), 28.5 (CH_2, C-4), 15.3 (CH_3, -OCH$_2\underline{C}$H$_3$)

IR (neat)**:** 3406 s, 2969 m, 2871 w, 1347 w, 1103 m, 1072 s, 1040 m, 984 s, 946 m, 921 w, 764 m

EI MS (RT)**:** no M^+, 157 (4), 140 (6), 127 (7), 111 (34), 99 (17), 86 (100), 71 (27)

X-rays: Ist x-rays crystal structure data can be seen in chapter 7, pp. 137

4a-Ethoxy -2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9-one **114**



109 **114**

GP8; Oxalyl chloride (0.9 mL, 10.8 mmol, 4.0 eq) was dissolved in 40 mL DCM. To this reaction mixture DMSO (0.8 mL, 11.3 mmol, 4.2 eq) and tricyclic alcohol (0.5 g, 2.7 mmol, 1.0 eq) in 15 mL DCM was added, at -78°C. The solution was stirred for 1h at same temperature and then NEt_3 (3.4 mL, 24.3 mmol, 9.0 eq) was added. The crude product was purified by column chromatography on silica gel using EA as an eluent to afford **114**.

Yield: 0.3 g (1.6 mmol), yellowish oil, 60 %

$C_9H_{12}O_4$ (184.19)

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

5.34 (dd, ^3J = 6.1 Hz, ^3J = 2.2 Hz, 1H, H-7), 5.27 (dd, ^3J = 4.4 Hz, 1H, H-2), 4.67 (m, 1H, H-5), 4.64 (m, 1H, H-1), 3.68 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 3.52 (m, 1H, H-3), 2.18 (m, 1H, H-4eq), 1.93 (dq, ^3J = 8.0 Hz, ^3J = 1.0 Hz, 1H, H-4ax), 1.20 (t, ^3J = 7.0 Hz, 3H, -OCH$_2$C<u>H</u>$_3$)

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

206.6 (C, C-6), 83.5 (CH, C-7), 80.1 (CH, C-2), 74.3 (CH, C-5), 73.9 (CH, C-3), 71.1 (CH, C-1), 64.1 (CH_2, -O<u>C</u>H$_2$CH$_3$), 28.3 (CH_2, C-4), 15.2 (CH_3, -OCH$_2$<u>C</u>H$_3$)

IR (neat)**:** 3367 s, 2973 m, 2872 m, 1765 s, 1659 m, 1069 s, 1034 m, 986 m, 946 m, 898 m

EI MS (RT)**:** 185 (3, M^+ +1), 184 (6, M^+), 127 (50), 113 (14), 109 (26), 99 (40), 82 (100)

2a-Benzyloxy-3a-propoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **167**

46 **167**

NaH (60 % suspension in oil, 3.0 g, 76.0 mmol, 5.0 eq) was dissolved in 50 mL THF and stirred at 0°C. In another R.B. bicyclic alcohol **46** (3.9 g, 15.2 mmol, 1.0 eq) was dissolved in 25 mL THF, this reaction mixture was added to the NaH solution and stirred further for 1 h at the same temperature. Then, PrBr (7.4 mL, 76.0 mmol, 5.0 eq) and a catalytic amount of KI were added and the resulting solution was stirred for 2 h more at 0°C then warm till the room temperature. The reaction mixture was washed with 53 mL of saturated solution of sodium thiosulfate and with 150 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and

concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:2) to afford cycloadduct **167**.

Yield: 2.8 g (9.2 mmol), yellowish oil, 60%

$C_{19}H_{26}O_3$ (302.41)

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

7.35-7.34 (m, 5H, Ar-H), 6.10 (d, ^3J = 5.8 Hz, 1H, H-7), 5.90 (d, ^3J = 5.8 Hz, 1H, H-6), 4.70 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.40 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.76 (td, ^3J = 1.2 Hz, ^3J = 5.5 Hz, 1H, H-3), 3.46 (d, ^3J = 5.5 Hz, 1H, H-2), 3.30 (m, 2H, - OC$\underline{H}_2$CH$_2$CH$_3$), 1.91 (dd, ^2J = 14.4 Hz, ^3J = 1.1 Hz, 1H, H-4ax), 1.77 (dd, ^2J = 14.4 Hz, ^3J = 5.2 Hz, 1H, H-4eq), 1.58 (m, 2H, -OCH$_2$C$\underline{H}_2$CH$_3$), 1.38 (s, 3H, -CH$_3$), 1.32 (s, 3H, -CH$_3$), 0.89 (t, ^3J = 7.3 Hz, 3H, -OCH$_2$ CH$_2$C$\underline{H}_3$)

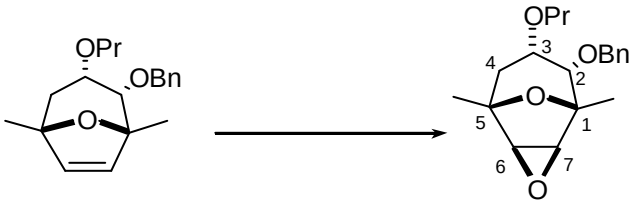
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.4 (C, *ipso*-Ar-C), 137.5 (CH, C-6), 135.3 (CH, C-7), 128.2-127.6 (CH, *o,m,p*-Ar-C), 85.5 (C, C-1), 83.8 (C, C-5), 80.0 (CH, C-2), 73.1 (CH, C-3), 71.8 (CH$_2$, -O$\underline{C}$H$_2$Ph), 71.1 (CH$_2$, -O$\underline{C}$H$_2$CH$_2$CH$_3$), 37.4 (CH$_2$, C-4), 24.0 (CH$_3$, -CH$_3$), 23.3 (CH$_2$, -OCH$_2\underline{C}$H$_2$CH$_3$), 21.3 (CH$_3$, -CH$_3$), 10.8 (CH$_3$, -OCH$_2$CH$_2\underline{C}$H$_3$)

IR (neat)**:** 2914 m, 2849 m, 1353 m, 1161 m, 1109 s, 1049 s, 949 m, 862 m, 748 s, 699 m

EI MS (RT)**:** no M^+, 326 (1, M^+ +1 +Na), 260 (7), 154 (40), 136 (12), 109 (100), 93 (29)

6a-Benzyloxy-7a-propoxy -1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **173**



167 **173**

GP5; Bicyclic alkene **167** (1.6 g, 5.3 mmol, 1.0 eq) was dissolved in 200 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 3.1 g, 12.7 mmol, 2.4 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:2) to afford epoxy **173**.

Yield: 1.3 g (4.1 mmol), white solid, 78 %

$C_{19}H_{26}O_4$ (318.41)

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

7.35-7.34 (m, 5H, Ar-H), 4.70 (d, ^2J = 11.8 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.40 (d, ^2J = 11.8 Hz, 1H, -OC<u>H</u>$_2$Ph), 3.72 (td, ^3J = 1.7 Hz, ^3J = 4.5 Hz, 1H, H-3), 3.63 (d, ^3J = 3.3 Hz, 1H, H-6), 3.45 (m, 2H, - OC<u>H</u>$_2$CH$_2$CH$_3$), 3.37 (d, ^3J = 4.5 Hz, 1H, H-2), 3.34 (d, ^3J = 3.3 Hz, 1H, H-7), 1.98 (dd, ^2J = 14.9 Hz, ^3J = 1.7 Hz, 1H, H-4ax), 1.76 (dd, ^2J = 14.9 Hz, ^3J = 4.1 Hz, 1H, H-4eq), 1.58 (q, ^3J = 7.4 Hz 2H, -OCH$_2$C<u>H</u>$_2$CH$_3$), 1.38 (s, 3H, -CH$_3$), 1.30 (s, 3H, -CH$_3$), 0.92 (t, ^3J = 7.4 Hz, 3H, -OCH$_2$ CH$_2$C<u>H</u>$_3$)

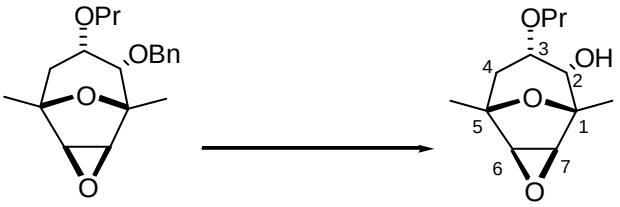
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.1 (C, *ipso*-Ar-C), 128.4-127.7 (CH, *o,m,p*-Ar-C), 79.8 (C, C-1), 79.5 (CH, C-2), 77.2 (C, C-5), 72.3 (CH, C-3), 72.1 (CH$_2$, -O<u>C</u>H$_2$Ph), 71.1 (CH$_2$, -O<u>C</u>H$_2$CH$_2$CH$_3$), 58.4 (CH, C-6), 57.5 (CH, C-7), 38.0 (CH$_2$, C-4), 23.5 (CH$_2$, -OCH$_2$<u>C</u>H$_2$CH$_3$), 20.0 (CH$_3$, -CH$_3$), 17.3 (CH$_3$, -CH$_3$), 10.9 (CH$_3$, -OCH$_2$CH$_2$<u>C</u>H$_3$)

IR (neat)**:** 3330 m, 2971 m, 2932 m, 2874 m, 1453 m, 1374 w, 1088 s, 986 s, 953 m, 699 s

EI MS (RT)**:** no M$^+$, 259 (1), 213 (2), 192 (11), 171 (100), 129 (23), 91 (53), 71 (11)

7a-Propoxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol **102**



173 **102**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 10 mL ethanol. To this suspension a solution of benzyl ether (1.2 g, 3.7 mmol, 1.0 eq) in 15 mL ethanol and 0.6 mL AcOH was added. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **102**.

Yield: 0.5 g (2.0 mmol), yellowish oil, 54 %

$C_{12}H_{20}O_4$ (228.28)

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

3.68 (m, 1H, H-3), 3.58 (m, 1H, H-2), 3.52 (m, 1H, H-7), 3.46 (d, ^3J = 3.1 Hz, 1H, H-6), 3.28 (m, 2H, - $OC\underline{H}_2CH_2CH_3$), 3.02 (d, ^3J = 9.8 Hz, 1H, -OH), 2.03 (dd, ^2J = 15.2 Hz, ^3J = 1.4 Hz, 1H, H-4ax), 1.82 (dd, ^2J = 15.2 Hz, ^3J = 4.4 Hz, 1H, H-4eq), 1.62 (q, ^3J = 7.0 Hz 2H, $-OCH_2C\underline{H}_2CH_3$), 1.41 (s, 3H, $-CH_3$), 1.32 (s, 3H, $-CH_3$), 0.94 (t, ^3J = 7.0 Hz, 3H, $-OCH_2CH_2C\underline{H}_3$)

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

79.7 (C, C-1), 76.7 (C, C-5), 74.5 (CH, C-2), 72.0 (CH, C-3), 71.7 (CH_2, $-O\underline{C}H_2CH_2CH_3$), 58.0 (CH, C-6), 56.6 (CH, C-7), 36.8 (CH_2, C-4), 23.1 (CH_2, $-OCH_2\underline{C}H_2CH_3$), 19.9 ($CH_3$, $-CH_3$), 17.0 (CH_3, $-CH_3$), 10.8 (CH_3, $-OCH_2CH_2\underline{C}H_3$)

IR (neat)**:** 3499 s, 2970 m, 2932 m, 1371 w, 1118 w, 1074 s, 1038 m, 952 m, 876 m

EI MS (RT)**:** 229 (20, M^+ +1), 212 (23), 185 (18), 171 (88), 129 (92), 113 (70), 95 (100), 85 (92), 71 (81)

HR MS: $C_{14}H_{23}NO_4Na$ M^+ + CH_3CN + Na, Exact: 292.1525, Calcd.: 292.1512

7a-Propoxy-6,8-dimethyl -2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **104**

102 **104**

GP7; Epoxy alcohol **102** (0.2 g, 0.9 mmol, 1.0 eq) was dissolved in 10 mL THF and to this reaction mixture a solution of $KOBu^t$ (0.7 g, 6.0 mmol, 2.0 eq) in 10 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as eluent to afford **104**.

Yield: 0.1 g (0.5 mmol), dark yellow oil, 56 %

$C_{12}H_{20}O_4$ (228.28)

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

4.67 (d, ^3J = 1.8 Hz, 1H, H-2), 4.57 (s, 1H, H-7), 3.93 (s, 1H, H-6), 3.57 (dt, ^3J = 8.5 Hz, ^3J = 1.8 Hz, 1H, H-3), 3.37 (m, 2H, - $OC\underline{H}_2CH_2CH_3$), 2.29 (dq, ^2J = 13.5 Hz, ^3J = 8.5 Hz, ^3J = 0.7 Hz, 1H, H-4ax), 1.87 (dd, ^2J = 13.6 Hz, ^3J = 9.0 Hz, 1H, H-4eq), 1.61 (s, 3H, $-CH_3$),

1.57 (q, ^3J = 6.9 Hz 2H, -OCH$_2$C<u>H$_2$</u>CH$_3$), 1.45 (s, 3H, -CH$_3$), 1.25 (br.s, 1H, -OH), 0.96 (t, ^3J = 7.4 Hz, 3H, -OCH$_2$ CH$_2$C<u>H$_3$</u>)

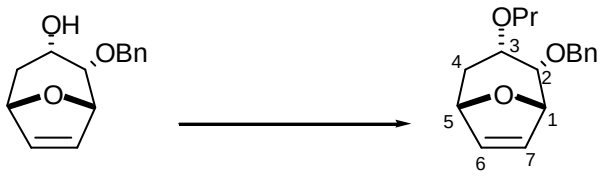
^{13}C-NMR (100 MHz, CDCl$_3$ + TMS)

94.0 (CH, C-2), 85.6 (CH, C-7), 83.6 (C, C-1), 81.2 (C, C-5), 80.6 (CH, C-6), 73.8 (CH, C-3), 70.4 (CH$_2$, -O<u>C</u>H$_2$CH$_2$CH$_3$), 35.2 (CH$_2$, C-4), 23.0 (CH$_2$, -OCH$_2$<u>C</u>H$_2$CH$_3$), 21.7 (CH$_3$, -CH$_3$), 19.2 (CH$_3$, -CH$_3$), 10.4 (CH$_3$, -OCH$_2$CH$_2$<u>C</u>H$_3$)

IR (neat)**:** 3427 s, 2973 m, 2932 s, 2873 m, 1374 m, 1201 m, 1094 s, 1070 s, 922 s, 959 m, 894 m, 824 m

EI MS (RT)**:** no M$^+$, 169 (19), 140 (15), 127 (25), 112 (100), 99 (26), 85 (29)

2a-Benzyloxy-3a-propoxy-8-oxabicyclo[3.2.1]oct-6-ene **170**



***rac*-96** **170**

NaH (60 % suspension in oil, 2.4 g, 61.0 mmol, 5.0 eq) was dissolved in 50 mL THF and stirred at 0°C. In another R.B. bicyclic alcohol ***rac*-96** (2.8 g, 12.2 mmol, 1.0 eq) was dissolved in 25 mL THF, this reaction mixture was added to the NaH solution and stirred further for 1 h at the same temperature. Then, PrBr (5.9 mL, 61.0 mmol, 5.0 eq) and a catalytic amount of KI was added and the resulting solution was stirred for further 2 h at 0°C then warm till the room temperature. The reaction mixture was washed with 43 mL of saturated solution of sodium thiosulfate and with 127 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH x) to afford cycloadduct **170**.

Yield: 1.8 g (6.6 mmol), yellowish oil, 54%

$C_{17}H_{22}O_3$ (274.35)

^{1}H-NMR (400MHz, CDCl$_3$ + TMS)

7.36-7.34 (m, 5H, Ar-H), 6.38 (dd, ^3J = 7.2 Hz, ^3J = 1.1 Hz, 1H, H-7), 6.23 (dd, ^3J = 7.2 Hz, ^3J = 1.7 Hz, 1H, H-6), 4.65 (m, 1H, H-1), 4.64 (d, ^2J = 11.5 Hz, 1H, -OC<u>H$_2$</u>Ph), 4.62 (td, ^3J = 1.6 Hz, ^3J = 3.3 Hz, 1H, H-5), 4.52 (d, ^2J = 11.5 Hz, 1H, -OC<u>H$_2$</u>Ph), 3.79 (m, 2H,

H-2, H-3), 3.34 (t, ^3J = 6.6 Hz, 2H, - OC<u>H</u>$_2$CH$_2$CH$_3$), 1.96 (dd, ^2J = 14.4 Hz, ^3J = 4.2 Hz, 1H, H-4ax), 1.78 (br,d, ^2J = 14.4 Hz, 1H, H-4eq), 1.56 (m, 2H, -OCH$_2$C<u>H</u>$_2$CH$_3$), 0.89 (t, ^3J = 7.4 Hz, 3H, -OCH$_2$ CH$_2$C<u>H</u>$_3$)

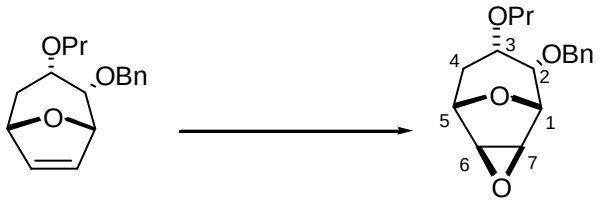
^{13}C-NMR (100 MHz, CDCl$_3$ + TMS)

138.5 (C, *ipso*-Ar-C), 134.8 (CH, C-6), 132.2 (CH, C-7), 128.3-127.7 (CH, *o,m,p*-Ar-C), 78.8 (CH, C-2), 78.2 (CH, C-1), 75.9 (CH, C-5), 73.7 (CH, C-3), 72.4 (CH$_2$, -O<u>C</u>H$_2$Ph), 70.7 (CH$_2$, -O<u>C</u>H$_2$CH$_2$CH$_3$), 31.1 (CH$_2$, C-4), 23.3 (CH$_2$, -OCH$_2$<u>C</u>H$_2$CH$_3$), 10.8 (CH$_3$, -OCH$_2$CH$_2$<u>C</u>H$_3$)

IR (neat)**:**2922 m, 2853 m, 1454 w, 1348 m, 1206 w, 1087 s, 1051 m, 1030 m, 732 s, 698 s

EI MS (RT)**:** 274 (1, M$^+$), 232 (2), 214 (2), 185 (6), 141 (17), 126 (31), 91 (57), 81 (100)

6a-Benzyloxy-7a-propoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **176**



170 **176**

GP5; Bicyclic alkene **170** (1.6 g, 6.0 mmol, 1.0 eq) was dissolved in 230 mL DCM and cooled at 0°C. To this mixture *m*-CPBA (70-75%, 3.5 g, 14.4 mmol, 2.4 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:2) to afford epoxy **176**.

Yield: 1.2 g (4.1 mmol), yellowish oil, 69 %

C$_{17}$H$_{22}$O$_4$ (290.15)

^{1}H-NMR (400MHz, CDCl$_3$ + TMS)

7.38-7.35 (m, 5H, Ar-H), 4.67 (d, ^2J = 11.4 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.59 (d, ^2J = 11.4 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.15 (br.d, ^3J = 4.2 Hz, 1H, H-1), 3.92 (t, ^3J = 4.0 Hz, 1H, H-5), 3.83 (d, ^3J = 7.0 Hz, 1H, H-6), 3.51 (d, ^3J = 7.0 Hz, 1H, H-7), 3.37 (t, ^3J = 6.3 Hz, 2H, - OC<u>H</u>$_2$CH$_2$CH$_3$), 3.05 (m, 1H, H-3), 3.01 (dd, ^3J = 4.2 Hz, ^3J = 1.1 Hz, H-2), 1.98 (dd, ^2J = 14.2 Hz, ^3J = 4.0 Hz, 1H, H-4ax), 1.83 (br,d, ^2J = 14.2 Hz, 1H, H-4eq), 1.51 (m, 2H, -OCH$_2$C<u>H</u>$_2$CH$_3$), 0.91 (t, ^3J = 7.2 Hz, 3H, -OCH$_2$ CH$_2$C<u>H</u>$_3$)

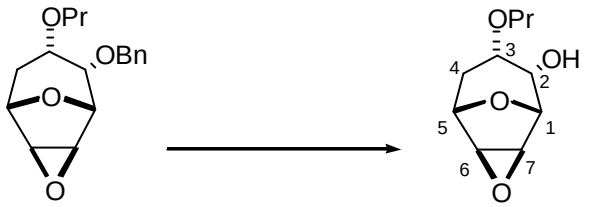
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

138.3 (C, *ipso*-Ar-C), 128.5-127.3 (CH, *o,m,p*-Ar-C), 73.1 (CH_2, -O<u>C</u>H_2Ph), 72.9 (CH, C-1), 72.4 (CH, C-2), 70.2 (CH, C-5), 69.8 (CH, C-3), 69.5 (CH_2, -O<u>C</u>$H_2CH_2CH_3$), 60.1 (CH, C-6), 55.2 (CH, C-7), 28.8 (CH_2, C-4), 22.7 (CH_2, -OCH_2<u>C</u>H_2CH_3), 10.5 (CH_3, -OCH_2CH_2<u>C</u>H_3)

IR (neat)**:** 3328 w, 2969 m, 2929 m, 2864 w, 1447 m, 1369 w, 1078 s, 975 s, 946 m, 689 s

EI MS (RT)**:** no M^+, 231 (3), 185 (1), 164 (10), 143 (100), 101 (12), 91 (65), 71 (6)

7a-Propoxy-3,9-dioxa-tricyclo[3.3.1.0^{2,4}]nonane-6a-ol **107**



176 **107**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 15 mL ethanol. To this suspension a solution of benzyl ether (1.7 g, 5.7 mmol, 1.0 eq) in 25 mL ethanol and 0.9 mL AcOH was added. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **107**.

Yield: 0.54 g (2.7 mmol), yellow oil, 47 %

$C_{10}H_{16}O_4$ (200.23)

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

4.28 (d, ^3J = 4.1 Hz, 1H, H-1), 4.15 (t, ^3J = 4.3 Hz, 1H, H-5), 3.75 (dd, ^3J = 4.1 Hz, ^3J = 1.1 Hz, H-2), 3.52 (t, ^3J = 6.0 Hz, 2H, - O<u>C</u>$H_2CH_2CH_3$), 3.16 (dt, ^3J = 5.2 Hz, ^3J = 1.1 Hz, 1H, H-3), 2.73 (d, ^3J = 7.2 Hz, 1H, H-6), 2.61 (d, ^3J = 7.2 Hz, 1H, H-7), 1.97 (m, 2H, H-4ax,eq), 1.53 (m, 2H, -OCH_2<u>C</u>H_2CH_3), 0.88 (t, ^3J = 7.3 Hz, 3H, -OCH_2 CH_2<u>C</u>H_3)

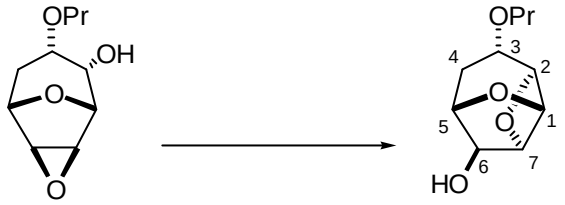
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

76.1 (CH, C-1), 72.8 (CH, C-3), 71.6 (CH, C-5), 69.8 (CH_2, -O<u>C</u>$H_2CH_2CH_3$), 69.5 (CH, C-2), 62.8 (CH, C-6), 58.3 (CH, C-7), 28.5 (CH_2, C-4), 22.8 (CH_2, -OCH_2<u>C</u>H_2CH_3), 10.4 (CH_3, -OCH_2CH_2<u>C</u>H_3)

IR (neat)**:** 3499 s, 2968 m, 2882 m, 1364 w, 1109 m, 1072 s, 1035 m, 948 m, 896 m

EI MS (RT)**:** 201 (7, M^+ +1), 184 (15), 157 (8), 143 (38), 101 (74), 85 (53), 67 (100), 57 (19)

4a-Propoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol **110**



107 **110**

GP7; Epoxy alcohol **107** (0.4 g, 1.8 mmol, 1.0 eq) was dissolved in 20 mL THF and to this reaction mixture a solution of KOBu^t (0.4 g, 3.6 mmol, 2.0 eq) in 20 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as eluent to afford **110**.

Yield: 0.18 g (0.88 mmol), yellowish oil, 49 %

$C_{10}H_{16}O_4$ (200.23)

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

5.19 (dd, ^3J = 9.7 Hz, ^3J = 5.2 Hz, 1H, H-7), 5.05 (dd, ^3J = 5.9 Hz, ^3J = 1.3 Hz, H-2), 4.86 (d, ^3J = 9.6 Hz, 1H, H-6), 4.75 (m, 1H, H-5), 4.07 (dd, ^3J = 5.1 Hz, ^3J = 1.3 Hz, 1H, H-1), 3.49 (t, ^3J = 6.3 Hz, 2H, - OC$\underline{H}_2$CH$_2$CH$_3$), 3.31 (dt, ^3J = 5.7 Hz, ^3J = 1.2 Hz, 1H, H-3), 2.07 (m, 1H, H-4ax), 1.70 (dd, ^2J = 14.7 Hz, ^3J = 1.1 Hz, 1H, H-4eq), 1.52 (m, 2H, -OCH$_2$C$\underline{H}_2$CH$_3$), 0.90 (t, ^3J = 7.1 Hz, 3H, -OCH$_2$ CH$_2$C$\underline{H}_3$)

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

90.4 (CH, C-7), 88.6 (CH, C-2), 76.1 (CH, C-6), 73.7 (CH, C-1), 71.7 (CH, C-5), 70.2 (CH$_2$, -O$\underline{C}$H$_2$CH$_2$CH$_3$), 69.9 (CH, C-3), 27.8 (CH$_2$, C-4), 22.9 (CH$_2$, -OCH$_2\underline{C}$H$_2$CH$_3$), 10.6 (CH$_3$, -OCH$_2$CH$_2\underline{C}$H$_3$)

IR (neat)**:** 3427 s, 2972 w, 2928 m, 2869 m, 1370 w, 1201 m, 1082 s, 908 s, 963 m, 889 m

EI MS (RT)**:** no M$^+$, 141 (10), 112 (9), 99 (20), 84 (100), 71 (32), 57 (26)

2a,3a-Dibenzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **177**

***rac*-46** **177**

Bicyclic alcohol ***rac*-46** (3.9 g, 15.4 mmol, 1.0 eq) was dissolved in 30 mL THF. To this reaction mixture NaH (60 % suspension in oil, 1.2 g, 30.8 mmol, 2.0 eq) was added and the resulting solution was heated to reflux at 70°C for 0.5 h. Then, BnBr (2.7 mL, 23.1 mmol, 1.5 eq) was added and the reaction mixture was further heated for 15 h at the same temperature and cooled till room temperature. The remaining solution was dissolved in 20 mL distilled water and 20 mL MTBE. The organic layer was washed with dist. water for three times. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1: 5) to afford cycloadduct **177**.

Yield: 4.8 g (13.7 mmol), yellowish oil, 89 %

$C_{23}H_{26}O_3$ (350.45)

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

7.29-7.31 (m, 10H, Ar-H), 6.11 (d, ^3J = 5.9 Hz, 1H, H-7), 5.97 (d, ^3J = 5.9 Hz, 1H, H-6), 4.57/4.36 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.53/4.43 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.90 (dt, ^3J = 1.4 Hz, ^3J = 5.5 Hz, 1H, H-3), 3.47 (d, ^3J = 5.5 Hz, 1H, H-2), 1.96 (dd, ^2J = 14.5 Hz, ^3J = 1.3 Hz, 1H, H-4eq), 1.80 (dd, ^2J = 14.5 Hz, ^3J = 5.5 Hz, 1H, H-4ax), 1.39 (s, 3H, CH_3), 1.32 (s, 3H, CH_3),

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

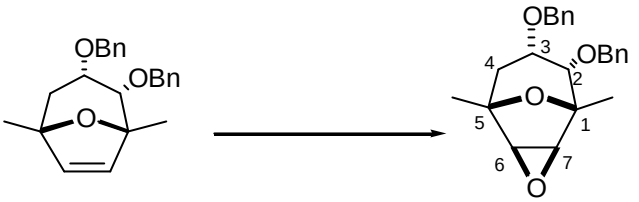
138.8 (C, *ipso*- Ar-C), 138.2 (C, *ipso*-Ar-C), 137.6 (CH, C-6), 135.4 (CH, C-7), 128.3-127.4 (CH, *o,m,p*-Ar-C), 85.6 (C, C-1), 83.8 (C, C-5), 80.3 (CH, C-2), 72.3 (CH, C-3), 71.7 (CH_2, -O$\underline{C}H_2$Ph), 71.4 (CH_2, -O$\underline{C}H_2$Ph), 37.5 (CH_2, C-4), 24.0 (CH_3), 21.3 (CH_3)

IR (neat)**:** 3001 w, 2867 w, 1496 m, 1453 m, 1350 m, 1168 s, 1097 s, 1028 m, 945 m

EI MS (RT)**:** 350 (4, M^+), 259 (17), 242 (5), 199 (14), 153 (27), 137 (53), 109 (25), 96 (27), 91 (100)

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectra

6a,7a-Dibenzyloxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **97**



177 **97**

GP5; Bicyclic alkene **177** (5.3 g, 15.2 mmol, 1.0 eq) was dissolved in 50 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 6.9 g, 30.4 mmol, 2.0 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **97**.

Yield: 4.2 g (11.4 mmol), colourless oil, 75%

$C_{23}H_{26}O_4$ (366.45)

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

7.32-7.31 (m, 10H, Ar-H), 4.62/4.59 (d, ^2J = 11.8 Hz, 1H, -OC$\underline{H}_2$Ph), 4.54/4.40 (d, ^2J = 11.8 Hz, 1H, -OC$\underline{H}_2$Ph), 3.87 (dt, ^3J = 1.8 Hz, ^3J = 4.4 Hz, 1H, H-3), 3.70 (d, ^3J = 3.2 Hz, 1H, H-7), 3.38 (d, ^3J = 3.2 Hz, 1H, H-6), 3.41 (d, ^3J = 4.4 Hz, 1H, H-2), 2.05 (dd, ^2J = 14.9 Hz, ^3J = 1.6 Hz, 1H, H-4eq), 1.81 (dd, ^2J = 14.9 Hz, ^3J = 4.2 Hz, 1H, H-4ax), 1.39 (s, 3H, CH_3), 1.30 (s, 3H, CH_3),

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

138.6 (C, *ipso*- Ar-C), 137.9 (C, *ipso*-Ar-C), 128.4-127.3 (CH, *o,m,p*-Ar-C), 80.1 (CH, C-2), 79.5 (C, C-1), 77.3 (C, C-5), 72.2 (CH_2, -O$\underline{C}H_2$Ph), 71.9 (CH, C-3), 71.5 (CH_2, -O$\underline{C}H_2$Ph), 58.4 (CH, C-6), 57.4 (CH, C-7), 38.1 (CH_2, C-4), 20.0 (CH_3), 17.4 (CH_3)

IR (neat)**:** 3030 w, 2931 w, 2871 w, 1496 m, 1453 s, 1200 m, 1179 m, 1158 s, 952 s, 923 s, 734 s, 696 s

EI MS (RT)**:** no M^+, 276 (13), 219 (10), 193 (5), 169 (6), 147 (6), 105 (7), 91 (100)

2a,3a-Dibenzyloxy-8-oxabicyclo[3.2.1]oct-6-ene **178**

***rac*-94** **178**

Bicyclic alcohol ***rac*-94** (5.4 g, 23.2 mmol, 1.0 eq) was dissolved in 40 mL THF. To this reaction mixture NaH (60 % suspension in oil, 1.9 g, 46.4 mmol, 2.0 eq) was added and the resulting solution was heated to reflux at 70°C for 0.5 h. BnBr (4.2 mL, 34.8 mmol, 1.5 eq) was added and the reaction mixture further heated for 15 h at the same temperature and cooled till room temperature. The remaining solution was dissolved in 25 mL distilled water and 25 mL MTBE. The organic layer was washed with dist. water for three times. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:2) to afford cycloadduct **178**.

Yield: 6.0 g (18.6 mmol), colourless oil, 80%

$C_{21}H_{22}O_3$ (322.40)

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

7.32-7.30 (m, 10H, Ar-H), 6.40 (dd, ^3J = 6.1 Hz, ^3J = 1.8 Hz, 1H, H-7), 6.30 (dd, ^3J = 6.0 Hz, ^3J = 1.5 Hz, 1H, H-6), 4.66 (m, 1H, H-1), 4.65 (m, 1H, H-5), 4.60/4.57 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.54/4.51 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.92 (m, 1H, H-3), 3.80 (dd, ^3J = 5.3 Hz, ^3J = 3.8 Hz, 1H, H-2), 1.98 (qd, ^2J = 14.6 Hz, ^3J = 4.0 Hz, 1H, H-4eq), 1.82 (td, ^2J = 14.6 Hz, ^3J = 1.3 Hz, 1H, H-4ax),

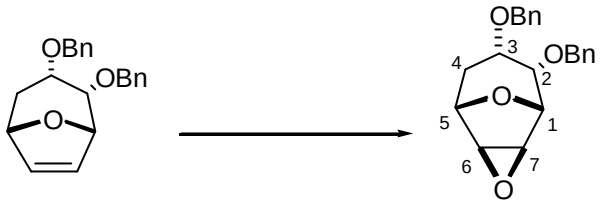
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

139.0 (C, *ipso*- Ar-C), 138.4 (C, *ipso*-Ar-C), 134.9 (CH, C-6), 132.3 (CH, C-7), 128.3-127.2 (CH, *o,m,p*-Ar-C), 78.6 (C, C-1), 78.1 (C, C-5), 76.1 (CH, C-2), 73.1 (CH, C-3), 72.4 (CH_2, -O$\underline{C}H_2$Ph), 70.9 (CH_2, -O$\underline{C}H_2$Ph), 31.3 (CH_2, C-4)

IR (neat)**:** 2948 m, 1453 m, 1272 m, 1176 w, 1096 s, 1070 s, 1026 s, 712 m, 698 m

EI MS (RT)**:** no M^+, 248 (14), 141 (14), 124 (25), 111 (15), 105 (32), 91 (100), 69 (28)

6a,7a-Dibenzyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **98**



178 **98**

GP5; Bicyclic alkene **178** (5.5 g, 17.1 mmol, 1.0 eq) was dissolved in 50 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 10.1 g, 41.0 mmol, 2.4 eq) was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **98**.

Yield: 4.1 g (12.0 mmol), colourless oil, 70 %

$C_{21}H_{22}O_4$ (338.40)

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

7.34-7.33 (m, 10H, Ar-H), 4.68/4.62 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.60/4.55 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.26 (d, ^3J = 3.90 Hz, 1H, H-1), 4.20 (m, 1H, H-3), 3.93 (d, ^3J = 3.2 Hz, 1H, H-6), 3.90 (m, 1H, H-2), 3.73 (t, ^3J = 4.1 Hz, 1H, H-5), 3.61 (d ^3J = 3.2 Hz, 1H, H-7), 2.00 (td, ^2J = 15.0 Hz, ^3J = 3.9 Hz, 1H, H-4eq), 1.95 (td, ^2J = 15.0 Hz, ^3J = 1.8 Hz, 1H, H-4ax),

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

138.6 (C, *ipso*-Ar-C), 137.9 (C, *ipso*- Ar-C), 128.4-127.3 (CH, *o,m,p*-Ar-C), 75.8 (CH, C-1), 72.8 (CH_2, -O$\underline{C}H_2$Ph), 72.7 (CH, C-5), 72.1 (CH, C-2), 71.6 (CH, C-3), 71.1 (CH_2, -O$\underline{C}H_2$Ph), 54.3 (CH, C-6), 53.5 (CH, C-7), 31.9 (CH_2, C-4)

IR (neat)**:** 2948 w, 2866 w, 1496 w, 1453 m, 1359 w, 1200 m, 1092 s, 1065 s, 1038 s, 1027 s, 858 s, 733 s, 696 s

EI MS (RT)**:** 338 (3, M^+), 247 (65), 141 (24), 111 (11), 107 (32), 91 (100), 69 (19)

6.3.3 Attempts to chapter 4.1.4

*2a-(1-Phenyl-ethoxy)-8-oxabicyclo[3.2.1]oct-6-ene-3a-ol (+)-***118**

(+)-27A **(+)-118**

GP4; Bicyclic ketone **(+)-27A** (1.1 g, 4.5 mmol, 1.0 eq) was dissolved in 5.0 mL THF at -78°C. A DIBAH solution (1.2 M/toluene, 7.5 mL, 9.0 mmol, 2.0 eq) was added, slowly. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **(+)-118** as white solid.

Yield: 1.03 g (4.2 mmol), viscous oil, 93%

$C_{15}H_{18}O_3$ (246.13)

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

7.36-7.33 (m, 5H, Ar-H), 6.35 (dd, ^3J = 6.1 Hz, ^3J = 1.6 Hz, 1H, H-7), 6.29 (dd, ^3J = 6.1 Hz, ^3J = 1.8 Hz, 1H, H-6), 4.65 (br.m, 1H, H-5), 4.60 (q, ^3J = 6.4 Hz, 1H, -OC<u>H</u>(CH_3)Ph), 4.35 (m, 1H, H-1), 4.22 (dt, ^3J = 5.4 Hz, ^3J = 1.2 Hz, 1H, H-3), 3.61 (dd, ^3J = 5.4 Hz, ^3J = 4.4 Hz, 1H, H-2), 2.48 (br.s, 1H, -OH), 2.01 (ddd, ^2J = 14.7 Hz, ^3J = 5.2 Hz, ^3J = 4.2 Hz, 1H, H-4eq), 1.81 (d, ^2J = 14.7 Hz, 1H, H-4ax), 1.46 (d, ^3J = 6.4 Hz, 3H, -OCH(C<u>H</u>$_3$)Ph)

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

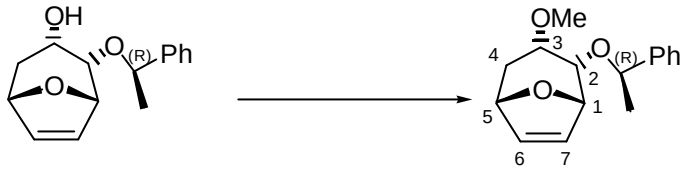
143.1 (C, *ipso*-Ar-C), 136.5 (CH, C-6), 131.7 (CH, C-7), 128.6 (CH, *o*-Ar-C), 127.9 (CH, *m*-Ar-C), 126.2 (CH, *p*-Ar-C), 78.8 (CH, C-1), 78.3 (CH, C-5), 76.4 (CH, C-2), 72.4 (CH, -O<u>C</u>H(CH_3)Ph), 65.0 (CH, C-3), 32.8 (CH_2, C-4), 24.3 (CH_3, -OCH(<u>C</u>H_3)Ph)

IR (neat)**:**3514 s, 2942 w, 2916 m, 1455 w, 1348 w, 1272 m, 1055 s, 1024 s, 872 m, 689 m

EI MS (RT)**:** 246 (1, M^+), 141 (47), 105 (55), 91 (3), 81 (100), 77 (9), 69 (4)

HR MS: $C_{15}H_{18}O_3$, Exact: 246.1257, Calcd.: 246.1256

2a-(1-phenyl-ethoxy)-3a-methoxy-8-oxabicyclo[3.2.1]oct-6-ene (+)-**119**



(+)-118 **(+)-119**

NaH (60 % suspension in oil, 0.3 g, 8.0 mmol, 2.0 eq) was dissolved in 5 mL THF and stirred at 0°C. In another R.B. bicycled alcohol **(+)-118** (1.0 g, 4.0 mmol, 1.0 eq) was dissolved in 5 mL THF, this reaction mixture was added to the NaH solution and stirred for further 1 h at the same temperature. Then, CH_3I (0.4 mL, 6.8 mmol, 1.7 eq) was added at 0°C and the resulting solution was stirred for further 2 h at 0°C then warm till the room temperature. The reaction mixture was washed with 10 mL of saturated solution of sodium thiosulfate and with 30 mL of distilled water. The aqueous phase was then extracted four times with MTBE. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford cycloadduct **(+)-119**.

Yield: 0.8 g (3.3 mmol), yellow oil, 82%

$C_{16}H_{20}O_3$ (260.33)

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

7.37-7.34 (m, 5H, Ar-H), 6.36 (dd, ^3J = 6.0 Hz, ^3J = 1.6 Hz, 1H, H-7), 6.24 (dd, ^3J = 6.0 Hz, ^3J = 1.7 Hz, 1H, H-6), 4.59 (br.m, 1H, H-1), 4.50 (q, ^3J = 6.5 Hz, 1H, -OC<u>H</u>(CH_3)Ph), 4.33 (br.m, 1H, H-5), 3.68 (dt, ^3J = 5.4 Hz, ^3J = 1.0 Hz, 1H, H-3), 3.62 (dd, ^3J = 5.4 Hz, ^3J = 4.0 Hz, 1H, H-2), 3.38 (s, 1H, -OCH_3), 1.46 (d, ^3J = 6.5 Hz, 3H, -OCH(C<u>H</u>$_3$)Ph), 1.91 (qd, ^2J = 14.8 Hz, ^3J = 5.0 Hz, ^3J = 4.0 Hz, 1H, H-4eq), 1.80 (br.d, ^2J = 14.7 Hz, 1H, H-4ax)

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

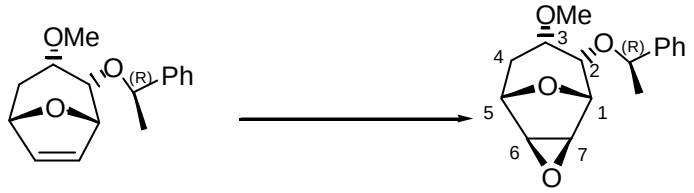
143.7 (C, *ipso*-Ar-C), 134.8 (CH, C-6), 132.3 (CH, C-7), 128.5 (CH, *o*-Ar-C), 127.6 (CH, *m*-Ar-C), 126.2 (CH, *p*-Ar-C), 79.3 (CH, C-1), 78.0 (CH, C-5), 76.0 (CH, C-2), 75.6 (CH, -O<u>C</u>H(CH_3)Ph), 73.8 (CH, C-3), 58.5 (CH_3, -OCH_3), 30.3 (CH_2, C-4), 24.4 (CH_3, -OCH(<u>C</u>H_3)Ph)

IR (neat)**:** 2972 w, 2939 m, 2824 w, 1452 w, 1347 w, 1209 m, 1099 s, 1084 s, 1089 s, 1021 m, 879 m, 700 s, 685 m

EI MS (RT)**:** no M^+, 251 (10), 161 (34), 116 (6), 105 (100), 101 (18), 87 (49), 78 (17)

6a-(1-phenyl-ethoxy)-7a-methoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane

(+)-**120**



(+)-119 **(+)-120**

GP5; Bicycled alkene **(+)-119** (0.8 g, 3.0 mmol, 1.0 eq) was dissolved in 5 mL DCM and cooled at 0°C. To this reaction mixture *m*-CPBA (70-75%, 1.4 g, 6.0 mmol, 2.0 eq) dissolved in 5 mL DCM was added and the resulting reaction mixture was stirred for 1.5 h at the same temperature. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **(+)-120**.

Yield: 0.7 g (2.6 mmol), light yellowish oil, 86 %

$C_{16}H_{20}O_4$ (276.33)

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

7.36-7.34 (m, 5H, Ar-H), 4.52 (q, ^3J = 6.5 Hz, 1H, -OC<u>H</u>(CH_3)Ph), 4.10 (dd, ^3J = 3.4 Hz, ^3J = 1.8 Hz, 1H, H-5), 3.90 (dd, ^3J = 4.0 Hz, 1H, H-1), 3.82 (d, ^3J = 3.3 Hz, 1H, H-6), 3.63 (m, 1H, H-3), 3.53 (m, 1H, H-2), 3.51 (d, ^3J = 3.3 Hz, 1H, H-7), 3.44 (s, 1H, -OCH_3), 1.94 (m, 2H, H-4ax,eq), 1.48 (d, ^3J = 6.5 Hz, 3H, -OCH(C<u>H</u>$_3$)Ph)

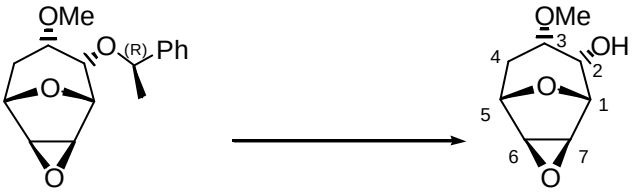
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

143.3 (C, *ipso*-Ar-C), 128.6 (CH, *o*-Ar-C), 127.8 (CH, *m*-Ar-C), 126.2 (CH, *p*-Ar-C), 76.4 (CH, C-1), 74.2 (CH, C-5), 73.8 (CH, C-2), 73.4 (CH, - O<u>C</u>H(CH_3)Ph), 71.5 (CH, C-3), 58.5 (CH_3, -OCH_3), 54.0 (CH, C-6), 53.4 (CH, C-7), 30.9 (CH_2, C-4), 24.3 (CH_3, -OCH(<u>C</u>H_3)Ph)

IR (neat)**:**2972 w, 2927 m, 2883 w, 1452 w, 1205 m, 1104 s, 1087 s, 1030 s, 879 m, 853 m

EI MS (RT)**:** 276 (5, M^+), 171 (15), 156 (17), 139 (21), 111 (17), 105 (100), 97 (11), 77 (10)

7a-Methoxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane-6a-ol (+)-**121**



(+)-120 **(+)-121**

GP6; A catalytic amount of Pd/C (10%) was dissolved in 20 mL methanol. To this suspension a solution of benzyl ether (0.7 g, 2.4 mmol, 1.0 eq) in 40 mL methanol and 0.4 mL AcOH was added. The crude product was purified by column chromatography on silica gel using MTBE as eluent to afford epoxy alcohol **(+)-121**.

Yield: 0.17 g (0.99 mmol), yellowish solid, 41 %

$C_8H_{12}O_4$ (172. 18)

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

4.19 (m, 1H, H-3), 4.16 (br.d, ^3J = 5.0 Hz, 1H, H-2), 3.87 (m, 1H, H-1), 3.68 (d, ^3J = 3.0 Hz, 1H, H-7), 3.59 (m, 1H, H-5), 3.48 (d, ^3J = 3.0 Hz, 1H, H-6), 3.40 (s, 3H, -OCH_3), 2.01/1.98 (m, 2H, H-4ax/eq)

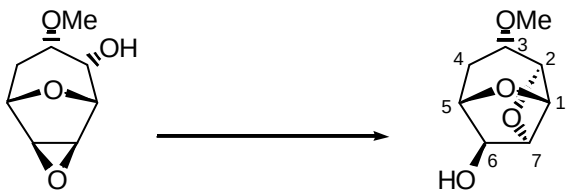
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

75.2 (CH, C-5), 74.0 (CH, C-1), 70.8 (CH, C-2), 67.2 (CH, C-3), 57.5 (CH_3, -OCH_3), 53.6 (CH, C-7), 52.5 (CH, C-6), 29.0 (CH_2, C-4)

IR (neat)**:** 3465 m, 2924 m, 2853 w, 1717 m, 1456 w, 1396 w, 1249 w, 1126 m, 1083 s

EI MS (RT)**:** 172 (30, M^+), 140 (11), 116 (4), 115 (24), 97 (36), 83 (35), 73 (23), 71 (100)

4a-Methoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane-9ß-ol (+)-**122**



(+)-121 **(+)-122**

GP7; Epoxy alcohol **(+)-121** (0.2 g, 1.2 mmol, 1.0 eq) was dissolved in 10 mL THF and to this mixture a solution of $KOBu^t$ (0.2 g, 1.4 mmol, 1.2 eq) in 10 mL THF was added. The crude product was purified by column chromatography on silica gel using EA as eluent to afford **(+)-122**.

Yield: 0.11 g (0.64 mmol), yellowish oil, 53 %

$C_8H_{12}O_4$ (172. 18)

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

5.18 (dd, ^3J = 5.0 Hz, 1H, H-7), 5.01 (dd, ^3J = 6.0 Hz, 1H, H-2), 4.94 (dd, ^3J = 5.0 Hz, 1H, H-6), 4.53 (m, 1H, H-5), 4.20 (br.s, 1H, H-1), 3.50 (dt, ^3J = 10.0 Hz, ^3J = 2.0 Hz, 1H, H-3), 3.31 (s, 3H, -OCH_3), 2.61 (m, 1H, H-4eq), 1.70 (dd, ^3J = 10.0 Hz, 1H, H-4ax)

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

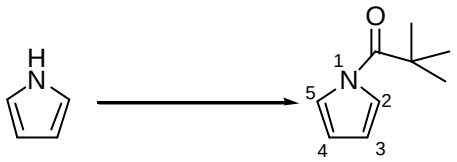
89.7 (CH, C-2), 81.5 (CH, C-7), 80.4 (CH, C-1), 78.6 (CH, C-6), 74.6 (CH, C-5), 74.0 (CH, C-3), 56.0 (CH_3, -OCH_3), 28.0 (CH_2, C-4)

IR (neat)**:** 3338 m, 2975 w, 2915 w, 1695 s, 1491 s, 1049 s, 962 m

EI MS (RT)**:** 171 (2, M^+ -1), 155 (2), 141 (2), 122 (6), 111 (95), 97 (10), 84 (100), 71 (23)

6.3.4 Attempts to chapter 4.2

Pyrrole-1-en- tert-butyl **127**



81 **127**

Pyrrole (4.2 mL, 60.0 mmol, 1.0 eq) was dissolved in 120mL THF and stirred at 0°C. To this solution Triethylamine (8.3 mL, 60.0 mmol, 1.0 eq), PivCl (8.1 mL, 66.0 mmol, 1.1 eq) and a catalytic amount of DMAP were added. The resulting mixture was stirred for 20 h at room temperature and then, the solvent was removed. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:5) to afford **127**.

Yield: 6.3 g (42 mmol), yellowish oil, 70 %

$C_9H_{13}NO$ (151.21)

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

6.83 (d, ^3J = 2.4 Hz, 1H, H-2), 6.81 (d, ^3J = 2.2 Hz, 1H, H-5), 6.26 (d, ^3J = 2.4 Hz, 1H, H-3), 6.23 (d, ^3J = 2.2 Hz, 1H, H-4), 1.27 (s, 9H, $C(C\underline{H}_3)_3$)

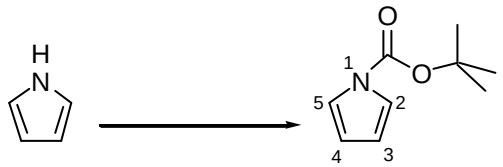
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

174.0 (C, C=O), 120.5 (CH, C-2), 117.7 (CH, C-5), 111.8 (CH, C-3), 108.0 (CH, C-4), 40.1 (C, $\underline{C}(CH_3)_3$), 26.4 (CH_3, $C(\underline{C}H_3)_3$)

IR (neat)**:**2975 m, 2935 w, 2876 w, 1811 w, 1698 s, 1483 m, 1302 m, 1198 s, 994 s, 730 w

EI MS (RT)**:** 151 (6, M^+), 124 (1), 108 (2), 91 (2), 85 (100)

Pyrrole-1-carboxylic acid tert-butyl ester **163**



81 **163**

Pyrrole (0.7 mL, 10.0 mmol, 1.0 eq) was dissolved in 20mL THF and stirred at 0°C. To this solution Triethylamine (1.4 mL, 10.0 mmol, 1.0 eq), BoC_2O (2.4 g, 11.0 mmol, 1.1 eq) and a catalytic amount of DMAP were added. The resulting mixture was stirred for 16 h at

room temperature and then, the solvent was removed. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:10) to afford **163**.

Yield: 1.3 g (7.8 mmol), colourless oil, 78 %

$C_9H_{13}NO_2$ (167.21)

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

7.18 (t, ^3J = 2.4 Hz, 2H, H-2/H-5), 6.22 (t, ^3J = 2.2 Hz, 2H, H-3/H-4), 1.59 (s, 9H, $C(C\underline{H}_3)_3$)

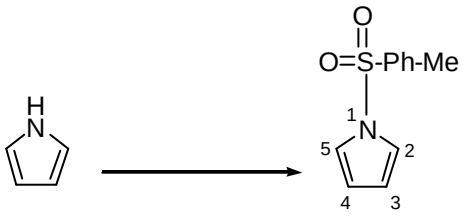
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

148.9 (C, C=O), 120.0 (CH, C-1), 119.9 (CH, C-5), 111.8 (CH, C-2), 111.0 (CH, C-3), 83.4 (C, $\underline{C}(CH_3)_3$), 27.9 (CH_3, $C(\underline{C}H_3)_3$)

IR (neat)**:** 2980 w, 2935 w, 1743 s, 1472 m, 1400 m, 1371 w, 1342 s, 1317 s, 1152 m, 1075 m, 951 m, 737 m

EI MS (RT)**:** 168 (3, M^+ +1), 167 (37, M^+), 111 (69), 94 (60), 67 (86), 57 (100)

Pyrrole-1-(Toluene-4-sulfonyl) **87**



81 **87**

Pyrrole (0.7 mL, 10.0 mmol, 1.0 eq) was added at 0°C to a solution of ^{t}BuOK (1.3 g, 11.6 mmol, 1.2 eq) in 6.5 mL DMF. After 1 h stirring, at room temperature, the reaction mixture was cooled at 0°C and tosylchloride (2.7 g, 14.0 mmol, 1.4 eq) in 9.5 mL DMF was added. After one night at room temperature under stirring, the solution was poured into distilled water, extracted three times with EA and dried over Na_2SO_4. Crystallisation in heptane afforded product **87**.

Yield: 1.8 g (8.1 mmol), colourless solid, 81 %

$C_{11}H_{11}NO_2S$ (221.28)

m.p.: 91-92°C

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

7.75 (d, ^{3}J = 8.3 Hz, *o*-Ar-C), 7.66 (d, ^{3}J = 8.3 Hz, 1H, *o*-Ar-C), 7.29 (d, ^{3}J = 8.0 Hz, 1H, *p*-Ar-C), 7.34 (d, ^{3}J = 8.0 Hz, 1H, *p*-Ar-C), 7.15 (d, ^{3}J = 2.2 Hz, 1H, H-2), 6.82 (d, ^{3}J = 2.1 Hz, 1H, H-5), 6.29 (d, ^{3}J = 2.2 Hz, 1H, H-3), 6.24 (d, ^{3}J = 2.1 Hz, 1H, H-4), 2.06 (s, 3H, -CH_3)

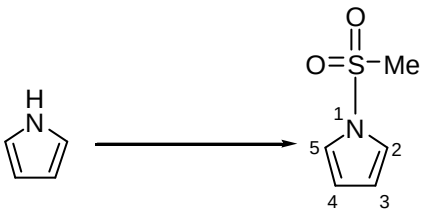
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

143.4 (C, *p*-Ar-C), 134.0 (C, *ipso*-Ar-C), 129.9-126.7 (CH, *o,m*-Ar-C), 120.6 (CH, C-2), 117.6 (CH, C-5), 113.4 (CH, C-3), 107.8 (CH, C-4), 20.7 (CH_3, -CH_3)

IR (neat)**:** 3306 w, 2929 w, 1660 s, 1386 s, 1161 m, 1091 m, 1055 w, 931 m, 813 m, 740 s

EI MS (RT)**:** 221 (46, M^+), 199 (38), 155 (45), 91 (100), 65 (16)

Pyrrole-1-Methanesulfonyl **140**



81 **140**

Pyrrole (4.2 mL, 60.0 mmol, 1.0 eq) in 60 mL THF was stirred at 0°C. To this solution triethylamine (8.3 mL, 60.0 mmol, 1.0 eq), $MeSO_2Cl$ (5.1 mL, 66.0 mmol, 1.1 eq) and a catalytic amount of DMAP were added. The resulting mixture was stirred for 1 h at room temperature and the remaining solution was washed with saturated sodium bicarbonate solution. The aqueous phase was then extracted four times with (MTBE/CH 1:1). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford **140**.

Yield: 3.6 g (25.5 mmol), white solid, 42 %

$C_5H_7NO_2S$ (145.18)

m.p.: 55-56°C

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

7.12 (m, 2H, H-2/H-5), 6.37 (m, 2H, H-3/H-4), 3.14 (s, 3H, -C<u>H</u>$_3$)

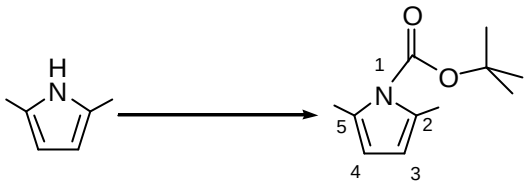
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

123.5 (CH, C-2/C-5), 112.8 (CH, C-3/C-4), 39.7 (CH_3, -CH_3)

IR (neat)**:** 3158 w, 2927 w, 1359 s, 1190 s, 1169 s, 1064 m, 1034 m, 930 m

EI MS (RT)**:** 146 (4, M^++1), 145 (52, M^+), 66 (100)

2,5-Dimethyl-pyrrole-1-carboxylic acid tert-butyl ester **128**



139 **128**

2,5-Dimethyl-pyrrole (0.5 mL, 5.0 mmol, 1.0 eq) was dissolved in 25 mL THF and stirred at 0°C. To this solution Triethylamine (0.7 mL, 5.0 mmol, 1.0 eq), BoC_2O (1.2 g, 5.5 mmol, 1.1 eq) and a catalytic amount of DMAP were added. The resulting mixture was stirred for 16 h at room temperature and then, the solvent was removed. The crude product was purified by column chromatography on silica gel (MTBE/CH 1:5) to afford **128**.

Yield: 0.8 g (4.1 mmol), colourless oil, 82 %

$C_{11}H_{17}NO_2$ (195.26)

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

5.77 (s, 2H, H-3/H-4), 2.38 (s, 6H, -C$\underline{H}_3$), 1.59 (s, 9H, -C(C$\underline{H}_3$)$_3$)

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

150.5 (C, C=O), 131.2 (CH, C-2/C-5), 110.1 (CH, C-3/C-4), 83.2 (C, -$\underline{C}$(CH_3)$_3$), 28.1 (CH_3, C($\underline{C}H_3$)$_3$), 16.5 (CH_3, -CH_3)

IR (neat)**:** 3090 w, 2977 w, 2931 w, 1737 s, 1389 m, 1369 s, 1333 s, 1311 s, 1249 m, 1122 s, 782 m

EI MS (RT)**:** 195 (31, M^+), 122 (16), 139 (68), 95 (66), 94 (100), 80 (7)

6.3.5 Attempts to chapter 4.3

3a-amino-2a-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **72**

***rac*-45** **72**

NH_4OAc (8.0 g, 103.8 mmol, 10.7 eq) was dissolved in a vigorously stirred mixture of bicyclic ketone ***rac*-45** (2.5 g, 9.7 mmol, 1.0 eq) and molecular sieves 3 ? in 30 mL abs. MeOH. Then $NaBH_3CN$ (0.6 g, 9.7 mmol, 1.0 eq) was added portion wise within 30 min. The resulting reaction mixture was stirred for 3 days at room temperature and then acidified with concentrated HCl until pH 2-3. The MeOH was removed and the residue was dissolved in 63 mL MTBE and 6 mL water. The aqueous layer was washed with saturated KOH solution and then extracted three times with (EA/MTBE 1:1). The combined organic layer was washed once with saturated NaCl solution and dried over Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography on silica gel (EA/MeOH 1:5).

Yield: 1.6 g, (6.2 mmol), viscous oil, 64%

$C_{16}H_{21}NO_2$ (259.34)

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

7.40-7.24 (m, 5H, Ar-H), 6.38 (d, ^3J = 5.8 Hz, 1H, H-7), 6.18 (d, ^3J = 5.8 Hz, 1H, H-6), 5.23 (d, ^3J = 9.3 Hz, 1H, N<u>H</u>), 4.86 (d, ^2J = 11.7 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.50 (d, ^2J = 11.7 Hz, 1H, -OC<u>H</u>$_2$Ph), 3.87 (t, ^3J = 6.2 Hz, 1H, H-3), 3.53 (d, ^3J = 6.3 Hz, 1H, H-2), 2.33 (dd, ^2J = 15.0 Hz, ^3J = 6.0 Hz, 1H, H-4eq), 1.98 (d, ^2J = 15.0 Hz, 1H, H-4ax), 1.35 (s, 3H, -CH_3), 1.33 (s, 3H, -CH_3)

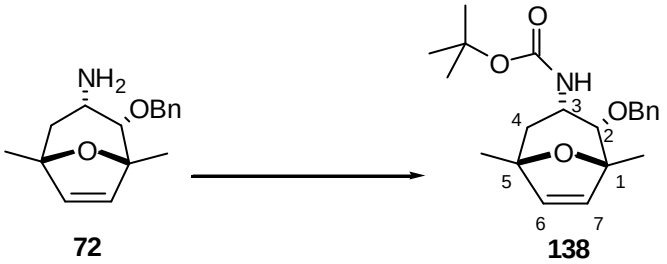
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

139.8 (CH, C-6), 137.7 (C, *ipso*-Ar-C), 135.3 (CH, C-7), 128.5 (CH, *o*-Ar-C), 128.3 (CH, *m*-Ar-C), 128.0 (CH, *p*-Ar-C), 85.4 (CH, C-1), 84.0 (CH, C-5), 73.0 (CH_2, -OC<u>H</u>$_2$Ph), 70.4 (CH, C-2), 46.2 (CH, C-3), 35.4 (CH_2, C-4), 23.2 (CH_3, -CH_3), 20.9 (CH_3, -CH_3)

IR (neat)**:** 3251 m, 3034 w, 2974 m, 2835 m, 1586 s, 1513 s, 1454 s, 1375 m, 1206 s, 1181 m, 1049 m, 895 m

EI MS (RT)**:** 259 (5, M^+), 232 (2), 200 (1), 182 (3), 167 (19), 152 (20), 136 (9), 109 (20), 91 (100), 77 (11)

3a-amino-(NH-tert-butyloxycarbonyl)-2a-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene **138**



Amine **72** (1.6 g, 6.0 mmol, 1.0 eq) was dissolved in 20 mL THF and Et_3N (0.8 mL, 6.0 mmol, 1.0 eq). To this solution, a catalytic amount of DMAP was added and at 0°C cooled. At this temperature BOC_2O (1.4 g, 6.6 mmol, 1.1 eq) was added and the resulting mixture was stirred for 16 h. Then, the solvent was removed and the remaining solution was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford **138**.

Yield: 1.9 g, (5.3 mmol), colourless oil, 88%

$C_{21}H_{29}NO_4$ (359.46)

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

7.29-7.37 (m, 5H, Ar-H), 6.15 (s, 2H, H-6/H-7), 5.23 (d, ^3J = 9.3 Hz, 1H, NH), 4.58/4.34 (d, ^2J = 12.3 Hz, 1H, -OCH_2Ph), 4.38 (dt, ^3J = 6.6 Hz, ^3J = 6.7 Hz, 1H, H-3), 3.59 (d, ^3J = 6.7 Hz, 1H, H-2), 2.07 (dd, ^2J = 14.4 Hz, ^3J = 6.6 Hz, 1H, H-4ax), 1.83 (d, ^2J = 14.4 Hz, 1H, H-4eq), 1.35 (s, 9H, C(CH_3)$_3$), 1.4 (s, 3H, -CH_3), 1.3 (s, 3H, -CH_3)

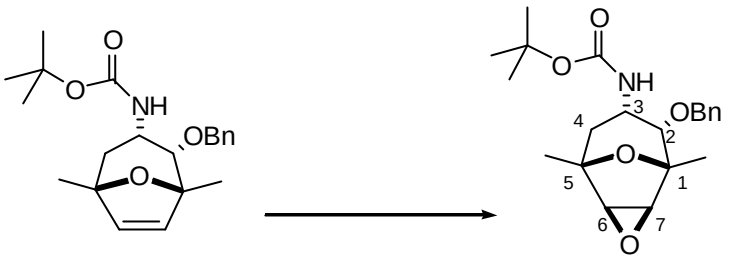
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

155.6 (C, -O-C=O), 139.6 (CH, C-6), 137.9 (C, *ipso*-Ar-C), 135.8 (CH, C-7), 128.3 (CH, *o*-Ar-C), 128.1 (CH, *m*-Ar-C), 127.8 (CH, *p*-Ar-C), 85.7 (CH, C-1), 84.4 (CH, C-5), 79.1 (C, C(CH_3)$_3$), 78.7 (CH, C-2), 71.5 (CH_2, -OCH_2Ph), 44.9 (CH, C-3), 40.2 (CH_2, C-4), 28.4 (CH_3, C(CH_3)$_3$), 23.6 (CH_3, -CH_3), 21.1 (CH_3, -CH_3)

IR (neat)**:** 3469 m, 2976 m, 2931 m, 2871 w, 1809 m, 1756 m, 1712 s, 1493 s, 1455 m, 1369 m, 1167 s, 1118 s, 1071 m, 950 m

EI MS (70°C)**:** 359 (1, M^+), 303 (4), 268 (2), 251 (2), 227 (6), 195 (10), 167 (12), 152 (31), 136 (33), 109 (30), 91 (100), 79 (8)

7a-amino-(NH-tert-butyloxycarbonyl)-6a-benzyloxy-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane **135**



138 **135**

Bicyclic alkene (9.1 g, 25.3 mmol, 1.0 eq) was dissolved in 90 mL DCM and cooled at 0°C, then *m*-CPBA (70 - 75%, 14.6 g, 63.3 mmol, 2.5 eq) was added. The solution was stirred for 1.5 h at 0°C and then, in 450 mL MTBE dissolved. The remaining solution was washed for three times with a 5% Na_2CO_3 solution. The aqueous phase was extracted three times with MTBE. The combined organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **135**.

Yield: 8.2 g, (21.8 mmol), white solid, 86 %

$C_{21}H_{29}NO_5$ (375.46)

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

7.30 (m, 5H, Ar-H), 5.03 (dt, ^3J = 4.9 Hz, ^3J = 2.3 Hz, 1H, H-3), 4.57/4.37 (d, ^2J = 11.0 Hz, 1H, -OC$\underline{H}_2$Ph), 3.55 (d, ^3J = 2.8 Hz, 1H, H-7), 3.52 (d, ^3J = 5.0 Hz, 1H, H-2), 3.41 (d, ^3J = 2.8 Hz, 1H, H-6), 2.15 (d, ^2J = 15.2 Hz, 1H, H-4eq), 2.07 (dd, ^2J = 15.1 Hz, ^3J = 5.6 Hz, 1H, H-4ax), 1.47 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.4 (s, 3H, -CH_3), 1.3 (s, 3H, -CH_3)

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

155.9 (C, -O-$\underline{C}$=O), 137.0 (C, *ipso*-Ar-C), 128.5 (CH, *o*-Ar-C), 128.3 (CH, *m*-Ar-C), 127.8 (CH, *p*-Ar-C), 78.8 (CH, C-1), 77.4 (CH, C-5), 77.4 (CH, C-2), 76.7 (C, $\underline{C}$(CH$_3$)$_3$), 71.7 (CH_2, -O$\underline{C}H_2$Ph), 57.6 (CH, C-6), 55.9 (CH, C-7), 44.8 (CH, C-3), 38.7 (CH_2, C-4), 28.4 (CH_3, C($\underline{C}H_3$)$_3$), 19.9 (CH_3, -CH_3), 17.6 (CH_3, -CH_3)

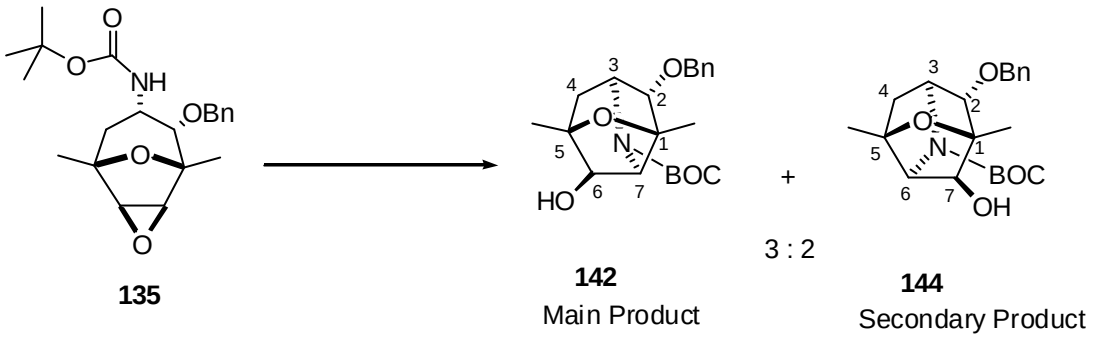
IR (neat)**:** 3430 w, 2976 m, 2932 m, 2871 w, 1709 s, 1486 s, 1454 m, 1366 m, 1242 m, 1161 s, 1090 s, 1060 m, 957 m

EI MS (RT)**:** 376 (1, M^++1), 320 (10), 276 (7), 229 (3), 190 (10), 183 (12), 178 (10), 147 (21), 128 (8), 114 (11), 108 (22), 91 (100), 84 (638)

HR MS: $C_{23}H_{32}N_2O_5Na$ M^+ + CH_3CN + Na, Exact: 439.2209, Calcd.: 439.2217

1,3-dimethyl-4a-Benzyloxy-8ß-hydroxy-2-oxa-6-aza-(N-tert-butyloxycarbonyl)-tricyclo[3.3.1.0^{3,7}]nonane **142**

and *1,3-dimethyl-4a-Benzyloxy-7ß-hydroxy-2-oxa-6-aza-(N-tert-butyloxycarbonyl)--tricyclo[3.3.1.0^{3,7}]nonane* **144**



Epoxy alcohol (1.1 g, 2.8 mmol, 1.0 eq) was dissolved in 30mL THF. To this solution, PrMgCl (2M/Et_2O, 1.9 mL, 3.7 mmol, 1.3 eq) was added at 0°C. The mixture was stirred for 4 h at room temperature, and then was washed with 5 mL NH_4Cl, 2 mL NaK-tartrat solution and 50 mL MTBE and further stirred for 1 h. The aqueous phase was extracted several times with (MTBE/EE 1:1). The combined organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel (EA/CH 1:2).

Dates of Main Product **142**:

Yield: 0.8 g, (2.1 mmol), colourless oil, 75 %

$C_{21}H_{29}NO_5$ (375.46)

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

7.29 (m, 5H, Ar-H), 4.64 (dd, ^2J = 11.8 Hz, ^3J = 4.3 Hz, 1H, H-3), 4.44 (m, 1H, H-7), 4.40/3.72 (d, ^2J = 26.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.12 (br.s, 1H, H-6), 3.60 (d, ^3J = 3.6 Hz, 1H, H-2), 1.85 (dd, ^2J = 13.7 Hz, ^3J = 4.3 Hz, 1H, H-4eq), 1.71 (dt, ^2J = 13.7 Hz, ^3J = 1.6 Hz, ^3J = 1.0 Hz, 1H, H-4ax), 1.41 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.5 (s, 3H, -CH_3), 1.3 (s, 3H, -CH_3)

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

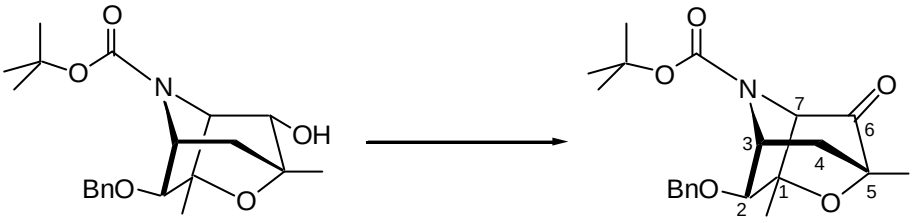
153.9 (C, -O-$\underline{C}$=O), 137.9 (C, *ipso*-Ar-C), 128.3-127.1 (CH, *o,m,p*-Ar-C), 88.8 (CH, C-1), 84.3 (CH, C-2), 83.6 (CH, C-5), 80.0 (C, $\underline{C}$(CH$_3$)$_3$), 79.6 (CH, C-6), 70.4 (CH_2, -O$\underline{C}H_2$Ph), 68.5 (CH, C-7), 55.5 (CH, C-3), 38.9 (CH_2, C-4), 28.3 (CH_3, C($\underline{C}$H$_3$)$_3$), 18.5 (CH_3, -CH_3), 17.8 (CH_3, -CH_3)

IR (neat)**:** 3432 m, 2974 m, 2931 m, 2870 w, 1677 s, 1392 s, 1367 s, 1241 w, 1166 s, 1096 s, 1076 s, 914 m, 730 s

EI MS (RT)**:** 376 (1, M^++1), 320 (18), 274 (6), 212 (4), 191 (6), 186 (10), 170 (4), 149 (8), 129 (6), 121 (13), 107 (28), 109 (36), 91 (24), 84 (100)

X-rays: Its x-rays crystal structure data can be seen in chapter 7, pp. 139

1,3-dimethyl-4a-Benzyloxy-8-oxo-2-oxa-6-aza-(N-tert-butyloxycarbonyl)tricyclo[3.3.1.0^{3,7}]nonane **149**



142 **149**

GP8; Oxalyl chloride (0.7 mL, 7.7 mmol, 4.0 eq) was dissolved in 18 mL DCM. To this mixture, DMSO (0.6 mL, 8.1 mmol, 4.2 eq) and tricycle alcohol (0.7 g, 1.9 mmol, 1.0 eq) in 18 mL DCM was added at -78°C. The solution was stirred for 1h at -78°C and then NEt_3 (2.4 mL, 17.3 mmol, 9.0 eq) was added. Stirring was continued for 1h at -78°C and 1.5 h more at room temperature. The crude product was purified by column chromatography on silica gel (EA/CH 1:2).

Yield: 0.6 g, (1.7 mmol), colourless oil, 87 %

$C_{21}H_{27}NO_5$ (373.44)

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

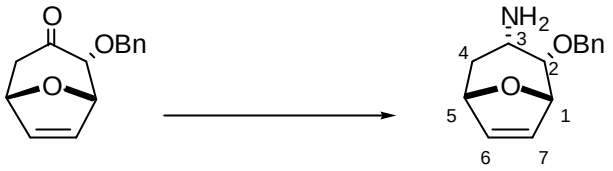
7.32 (m, 5H, Ar-H), 4.66 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.50 (m, 1H, H-3), 4.42 (d, ^2J = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 4.07 (s, 1H, H-7), 3.64 (d, ^3J = 9.2 Hz, 1H, H-2), 2.16 (dd, ^2J = 14.1 Hz, ^3J = 4.6 Hz, 1H, H-4eq), 1.90 (dd, ^2J = 14.2 Hz, ^3J = 1.2 Hz, 1H, H-4ax), 1.45 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.55 (s, 3H, -CH_3), 1.38 (s, 3H, -CH_3)

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

198.5 (C, C-6), 153.4 (C, -O-$\underline{C}$=O), 137.6 (C, *ipso*-Ar-C), 128.4-127.8 (CH, *o,m,p*-Ar-C), 85.8 (CH, C-1), 84.6 (CH, C-2), 81.0 (CH, C-5), 80.8 (C, $\underline{C}$(CH$_3$)$_3$), 70.4 (CH_2, -O$\underline{C}H_2$Ph), 65.2 (CH, C-7), 56.0 (CH, C-3), 43.5 (CH_2, C-4), 28.2 (CH_3, C($\underline{C}H_3$)$_3$), 17.2 (CH_3, -CH_3), 16.6 (CH_3, -CH_3)

IR (neat)**:** 2975 m, 2932 m, 1772 m, 1694 s, 1391 s, 1367 s, 1241 w, 1165 s, 1096 s, 1027 w, 933 w, 738 m

3a-amino-2a-benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene **136**



***rac*-94** **136**

NH_4OAc (41.9 g, 544.6 mmol, 10.7 eq) was dissolved in a vigorously stirred mixture of bicyclic ketone ***rac*-94** (11.71 g, 50.9 mmol, 1.0 eq) and molecular sieves 3 ? in 150 mL abs. MeOH. Then $NaBH_3CN$ (3.2 g, 50.9 mmol, 1.0 eq) was added portion wise within 30 min. The resulting reaction mixture was stirred for 3 days at room temperature and then acidified with concentrated HCl till pH 2-3. The MeOH was removed and the residue was dissolved in 330 mL MTBE and 33 mL water. The aqueous layer was washed with saturated KOH solution and then extracted three times with (EA/MTBE 1:1). The combined organic layer was washed once with saturated NaCl solution and dried over Na_2SO_4. After removal of the solvent the crude product was purified by column chromatography on silica gel (EA/MeOH 1:5).

Yield: 6.5 g, (28.0 mmol), viscous yellowish oil, 55%

$C_{14}H_{17}NO_2$ (231.29)

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

7.39-7.31 (m, 5H, Ar-H), 6.41 (dd, ^3J = 6.0 Hz, ^3J = 1.8 Hz, 1H, H-7), 6.30 (dd, ^3J = 6.0 Hz, ^3J = 1.6 Hz, 1H, H-6), 4.87 (dd, ^2J = 5.8 Hz, ^3J = 1.5 Hz, 1H, H-1), 4.81 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 4.62 (m, 1H, H-5), 4.55 (d, ^2J = 11.9 Hz, 1H, -OC$\underline{H}_2$Ph), 3.81 (dt, ^3J = 5.6 Hz, 1H, H-3), 3.49 (d, ^3J = 5.8 Hz, 1H, H-2), 2.25 (dd, ^2J = 14.7 Hz, ^3J = 5.8 Hz, 1H, H-4eq), 2.02 (br.d, ^2J = 14.7 Hz, 1H, H-4ax)

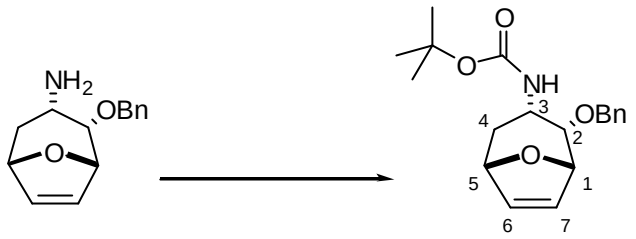
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

142.8 (CH, C-6), 138.5 (C, *ipso*-Ar-C), 131.7 (CH, C-7), 128.5 (CH, *o*-Ar-C), 128.3 (CH, *m*-Ar-C), 127.8 (CH, *p*-Ar-C), 82.9 (CH, C-1), 79.1 (CH, C-5), 72.5 (CH_2, -O$\underline{C}H_2$Ph), 71.9 (CH, C-2), 49.0 (CH, C-3), 29.0 (CH_2, C-4)

IR (neat)**:** 3112 m, 2963 m, 2801 m, 1587 m, 1455 m, 1392 s, 1113 m, 737 m, 698 m

EI MS (RT)**:** 232 (22, M^+ + 1), 201 (19), 158 (46), 141 (69), 126 (41), 111 (21), 91 (100), 81 (25), 69 (56)

3a-amino-(NH-tert-butyloxycarbonyl)-2a-benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene **137**



136 **137**

Amine 136 (6.0 g, 26.0 mmol, 1.0 eq) was dissolved in 50 mL THF and Et_3N (3.6 mL, 26.0 mmol, 1.0 eq). To this solution, a catalytic amount of DMAP was added and cooled till 0°C. At this temperature BOC_2O (6.2 g, 28.6 mmol, 1.1 eq) was added and the resulting mixture was stirred for 16 h. Solvent was removed and the remaining solution was purified by column chromatography on silica gel (MTBE/CH 1:1) to afford **137**.

Yield: 5.2 g, (15.7 mmol), white solid, 60 %

$C_{19}H_{25}NO_4$ (331.18)

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

7.32-7.29 (m, 5H, Ar-H), 6.24 (dd, ^3J = 6.1 Hz, ^3J = 1.8 Hz, 1H, H-7), 6.18 (dd, ^3J = 6.1 Hz, ^3J = 1.7 Hz, 1H, H-6), 4.77 (m, 1H, H-1), 4.71 (br.d, 1H, H-5), 4.58/4.70 (d, ^2J = 12.3 Hz, 1H, -OC$\underline{H}_2$Ph), 4.33 (m, 1H, H-3), 3.82 (br.s, 1H, N$\underline{H}$), 3.27 (dd, ^3J = 8.8 Hz, 1H, H-2), 1.89 (dd, ^2J = 15.0 Hz, ^3J = 3.2 Hz, 1H, H-4eq), 1.53 (m, 1H, H-4ax), 1.49 (s, 9H, C(C$\underline{H}_3$)$_3$)

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

138.3 (C, *ipso*-Ar-C), 155.4 (C, -O-$\underline{C}$=O), 132.0 (CH, C-6), 129.6 (CH, C-7), 128.3-127.7 (CH, *o,m,p*-Ar-C), 79.0 (C, $\underline{C}(CH_3)_3$), 78.5 (CH, C-5), 78.2 (2xCH, C-1/C-2), 72.1 (CH_2, -O$\underline{C}H_2$Ph), 66.0 (CH, C-3), 32.3 (CH_2, C-4), 28.4 (CH_3, C($\underline{C}H_3$)$_3$)

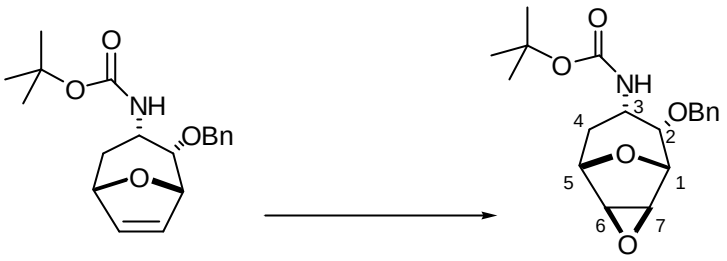
IR (neat)**:** 3466 w, 2924 m, 2853 m, 1809 w, 1711 s, 1493 m, 1455 m, 1366 m, 1163 s, 1099 s, 966 m

EI MS (RT)**:** no M^+, 311 (1), 275 (2), 258 (2), 240 (2), 181 (22), 149 (30), 108 (40), 91 (100)

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectra

7a-amino-(NH-tert-butyloxycarbonyl)-6a-benzyloxy-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonane

134



137 **134**

Bicyclic alkene (7.0 g, 21.1 mmol, 1.0 eq) was dissolved in 73 mL DCM and cooled at 0°C, then *m*-CPBA (70 - 75%, 13.0 g, 52.8 mmol, 2.5 eq) was added. The solution was stirred for 1.5 h at 0°C and then dissolved in 300 mL MTBE. The remaining solution was washed for three times with 5% Na_2CO_3 solution. The aqueous phase was extracted three times with MTBE. The combined organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel (MTBE/CH 1:1) to afford epoxy **134**.

Yield: 6.4 g, (18.5 mmol), white solid, 88%

$C_{19}H_{25}NO_5$ (347.41)

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

7.33-7.35 (m, 5H, Ar-H), 4.44/4.57 (d, ^2J = 11.5 Hz, 1H, -OC$\underline{H}_2$Ph), 4.19 (m, 1H, H-5), 4.18 (m, 1H, H-1), 4.09 (br.s, 1H, H-3), 3.84 (m, 1H, H-2), 3.74 (d, ^3J = 2.9 Hz, 1H, H-7), 3.58 (d, ^3J = 2.9 Hz, 1H, H-6), 2.14-2.04 (m, 2H, H-4ax/eq), 1.45 (s, 9H, C(C$\underline{H}_3$)$_3$)

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

155.8 (C, -O-$\underline{C}$=O), 137.0 (C, *ipso*-Ar-C), 128.5-127.9 (CH, *o,m,p*-Ar-C), 79.8 (C, $\underline{C}$(CH$_3$)$_3$), 72.3 (2xCH, C-1/C-5), 71.6 (CH, C-2), 71.4 (CH_2, -O$\underline{C}H_2$Ph), 53.1 (CH, C-6), 51.9 (CH, C-7), 44.5 (CH, C-3), 31.6 (CH_2, C-4), 28.4 (CH_3, C($\underline{C}$H$_3$)$_3$)

IR (neat)**:** 3338 m, 2975 w, 2928 w, 2870 w, 1694 s, 1490 s, 1364 w, 1246 m, 1163 s, 1128 s, 1049 m, 1029 w, 962 w, 861 m

EI MS (RT)**:** no M^+, 291 (17), 246 (29), 200 (50), 182 (6), 156 (21), 128 (25), 111 (14), 91 (100), 73 (31)

HR MS: $C_{19}H_{25}O_5$, Exact: 347.1875, Calcd.: 347.1733

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectra

EA: N = 3.89 %, Calcd. N = 4.03 %

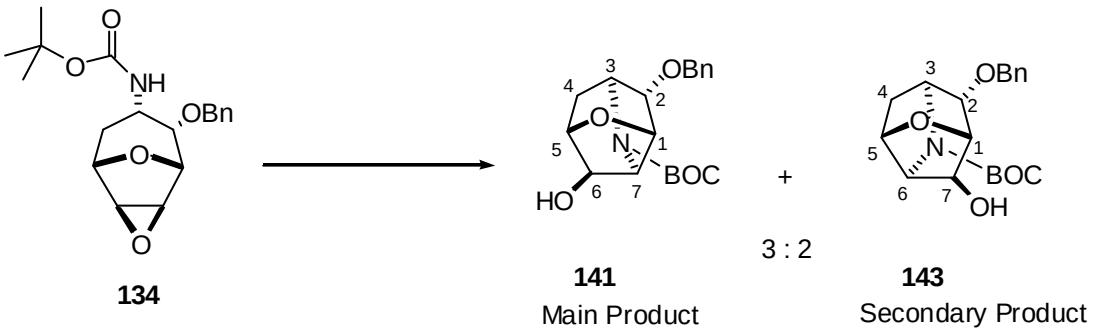
C = 65.41 %, Calcd. C = 65.69 %

H = 7.13 %, Calcd. H = 7.25 %

X-rays: Its x-rays crystal structure data can be seen in chapter 7, pp. 141

4a-Benzyloxy-8ß-hydroxy-2-oxa-6-aza-(N-tert-butyloxycarbonyl)-tricyclo[3.3.1.0^{3,7}]nonane **141**

and *4a-Benzyloxy-7ß-hydroxy-2-oxa-6-aza-(N-tert-butyloxycarbonyl)--tricyclo[3.3.1.0^{3,7}]nonane* **143**



Epoxy alcohol (5.4 g, 15.5 mmol, 1.0 eq) was dissolved in 150mL THF. To this solution, PrMgCl (2M/Et_2O, 10.1 mL, 20.1 mmol, 1.3 eq) was added at 0°C. The mixture was stirred for 3 h at room temperature, then washed with 19 mL NH_4Cl, 4 mL NaK-tartrat solution and 9 mL MTBE. After washing the mixture was stirred for further 1 h. The aqueous phase was extracted ten times with (MTBE/EA 1:1). The combined organic layer was dried over Na_2SO_4, filtered, concentrated under vacuum and purified by column chromatography on silica gel (EA/CH 1:2).

Dates of Main Product **141**:

Yield: 3.3 g, (9.5 mmol), colourless oil, 61 %

$C_{19}H_{25}NO_5$ (347.41)

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

7.30-7.32 (m, 5H, Ar-H), 4.72 (m, 1H, H-7), 4.38/4.62 (d, ^2J = 11.7 Hz, 1H, -OC$\underline{H}_2$Ph), 4.59 (m, 1H, H-6), 4.50 (m, 1H, H-1), 4.15 (br.m, 1H, H-5), 4.00 (d, ^3J = 21.3 Hz, 1H, H-

3), 3.80 (d, ^3J = 11.5 Hz, 1H, H-2), 1.80 (m, 1H, H-4ax), 1.75 (m, 1H, H-4eq), 1.46 (s, 9H, C(C<u>H</u>$_3$)$_3$)

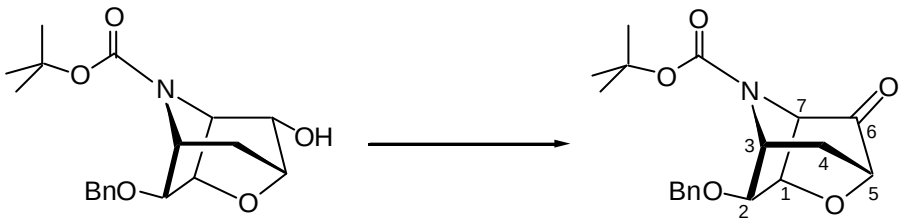
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

153.7 (C, -O-<u>C</u>=O), 137.6 (C, *ipso*-Ar-C), 128.4-127.3 (CH, *o,m,p*-Ar-C), 81.4 (CH, C-2), 80.6 (CH, C-6), 80.2 (C, <u>C</u>(CH$_3$)$_3$), 79.4 (CH, C-7), 76.8 (CH, C-3), 70.1 (CH_2, -O<u>C</u>H$_2$Ph), 63.3 (CH, C-5), 54.3 (CH, C-1), 32.2 (CH_2, C-4), 28.4 (CH_3, C(<u>C</u>H$_3$)$_3$)

IR (neat)**:** 3401 m, 3064 w, 2973 w, 2926 m, 2856 w, 1693 s, 1392 s, 1339 m, 1163 s, 1100 s, 960 w, 878 m, 698 m

EI MS (RT)**:** 347 (10, M^+), 291 (57), 246 (44), 205 (3), 185 (17), 156 (56), 139 (30), 111 (18), 91 (100), 68 (26)

4a-Benzyloxy-8-oxo-2-oxa-6-aza-(N-tert-butyloxycarbonyl)tricyclo[3.3.1.0^{3,7}]nonane **148**



141 **148**

GP8; Oxalyl chloride (5.0 mL, 58.8 mmol, 4.0 eq) was dissolved in 140 mL DCM. To this mixture, DMSO (4.4 mL, 61.7 mmol, 4.2 eq) and tricycle alcohol (5.1 g, 14.7 mmol, 1.0 eq) in 140 mL DCM were added at -78°C. The solution was stirred for 1h at -78°C and then NEt_3 (18.3 mL, 132.3 mmol, 9.0 eq) was added. Stirring was continued for 1h at -78°C and 1.5 h more at room temperature. The crude product was purified by column chromatography on silica gel (EA/CH 1:2).

Yield: 3.6 g, (10.4 mmol), white solid, 71 %

$C_{19}H_{23}NO_5$ (345.16)

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

7.30-7.32 (m, 5H, Ar-H), 4.80 (m, 1H, H-7), 4.61 (m, 1H, H-1), 4.44/4.63 (d, ^2J = 11.7 Hz, 1H, -OC<u>H</u>$_2$Ph), 4.48 (m, 1H, H-5), 4.02 (m, 1H, H-3), 3.90 (br.d, ^3J = 13.7 Hz, 1H, H-2), 2.23 (ddd, ^2J = 14.0 Hz, ^3J = 3.8 Hz, ^3J = 1.5 Hz, 1H, H-4eq), 2.02 (m, 1H, H-4ax), 1.43 (s, 9H, C(C<u>H</u>$_3$)$_3$)

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

197.3 (C=O, C-6), 153.2 (C, -O-C=O), 137.2 (C, *ipso*-Ar-C), 128.4-127.3 (CH, *o,m,p*-Ar-C), 81.2 (C, $C(CH_3)_3$), 79.9 (CH, C-2), 79.6 (CH, C-7), 74.1 (CH, C-3), 70.3 (CH_2, -OCH_2Ph), 60.5 (CH, C-5), 55.7 (CH, C-1), 37.5 (CH_2, C-4), 28.2 (CH_3, $C(CH_3)_3$),

IR (neat)**:** 3405 (w), 2974 (w), 1777 (s), 1690 (s), 1367 (s), 1319 (m), 1242 (m), 1156 (s), 1094 (s)

EI MS (RT)**:** 346 (7, M^++1), 290 (7), 273 (24), 245 (36), 217 (82), 173 (12), 140 (34), 110 (73), 91 (100)

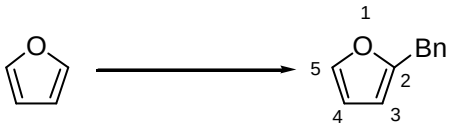
HR MS: $C_{19}H_{26}N_2O_5Na$ M^+ + CH_3CN + Na, Exact: 409.1739, Calcd.: 409.1750

Structure confirmation: H,H-COSY, HMBC, HMQC-Spectra

X-rays: Its x-rays crystal structure data can be seen in chapter 7, pp. 143-146

6.3.6 Attempts to chapter 4.4

2-Benzyl-furan **151**



150 **151**

Furan (1.5 mL, 20.0 mmol, 1.0 eq) was dissolved in 33 mL of THF and stirred at -10°C. Then, *n*-BuLi (1.6 M/hexane, 12.5 mL, 20.0 mmol, 1.0 eq) was added, slowly, at the same temperature and the resulting solution was stirred further 4 h more at room temperature. To this mixture BnBr (1.9 mL, 16.0 mmol, 0.8 eq) was added at -10°C and the resulting reaction mixture was stirred for 16 h at room temperature. The remaining solution was then washed with 20 mL of saturated solution of ammonium chloride. The aqueous phase was extracted three times with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using CH as eluent to afford **151**.

Yield: 2.1 g (13.3 mmol), yellow oil, 67 %

$C_{11}H_{10}O$ (158.20)

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

7.32 (m, 1H, H-5), 7.29 (m, 2H, *m*-Ar-H), 7.21 (m, 3H, *o*,*p*-Ar-H), 6.28 (dd, ^3J = 1.9 Hz, ^3J = 0.5 Hz, 1H, H-4), 5.99 (qd, ^3J = 3.1 Hz, ^3J = 1.9 Hz, 1H, H-3), 4.02 (s, 2H, -C$\underline{H}_2$Ph)

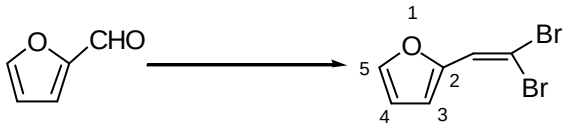
^{13}C-NMR (100 MHz, $CDCl_3$ + TMS)

154.5 (C, C-2), 141.5 (CH, C-3), 138.1 (C, *ipso*-Ar-C), 128.7 (CH, *o*-Ar-C), 127.5 (CH, *m*-Ar-C), 126.5 (CH, *p*-Ar-C), 110.3 (CH, C-4), 106.2 (CH, C-3), 34.5 (CH_2, -$\underline{C}H_2$Ph)

IR (neat)**:** 2906 w, 1595 m, 1505 m, 1494 s, 1454 m, 1147 m, 1075 m, 1009 s, 727 s, 702 s

EI MS (RT)**:** 158 (100, M^+), 129 (50), 115 (16), 91 (5), 82 (12)

2-(2,2-Dibromo-vinyl)-furan **160**



159 **160**

Carbontetrabromide-triphenylphosphine reagent was prepared by adding PPh_3 (2.9 g, 11.0 mmol, 2.2 eq), zinc dust (1.0 mL, 150.0 mmol, 3.0 eq) and CBr_4 (4.2 mL, 12.5 mmol, 2.5 eq) in 31.0 mL DCM. The resulting mixture was stirred for 38 h at room temperature. Then, furfural (0.4 mL, 5.0 mmol, 1.0 eq) was added, slowly, at 0°C and the resulting solution was stirred for further 6 h until get room temperature. The remaining solution was then washed with sodium bicarbonate. The aqueous phase was extracted three times with CH. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using CH as eluent to afford **160**.

Yield: 1.0 g (4.4 mmol), orange solid, 88 %

$C_6H_4Br_2O$ (251.90)

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

7.58 (s, 1H, C<u>H</u>=CBr_2), 7.43 (d, ^3J = 0.5 Hz, 1H, H-5), 6.95 (t, ^3J = 0.5 Hz, 1H, H-4), 6.46 (d, ^3J = 0.5 Hz, 1H, H-3)

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

150.0 (C, C-2), 142.5 (CH, C-5), 132.5 (CH, <u>C</u>H=CBr_2), 111.6 (CH, C-3), 112.5 (CH, C-4), 87.1 (C, CH=<u>C</u>Br_2)

IR (neat)**:** 3416 m, 1482 m, 1437 m, 1159 m, 1119 s, 1020 m, 947 w, 750 s, 721 s, 693 s

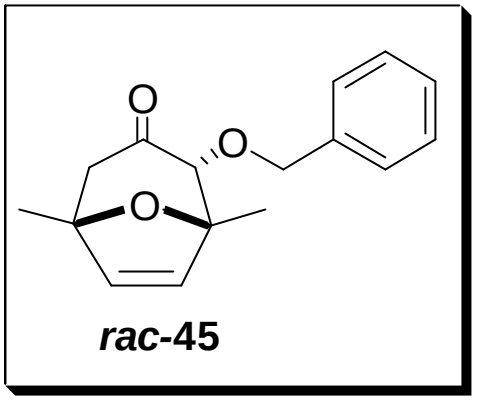
EI MS (RT)**:** 252 (100, M^+), 201 (15), 183 (8), 152 (4), 164 (2), 76 (6)

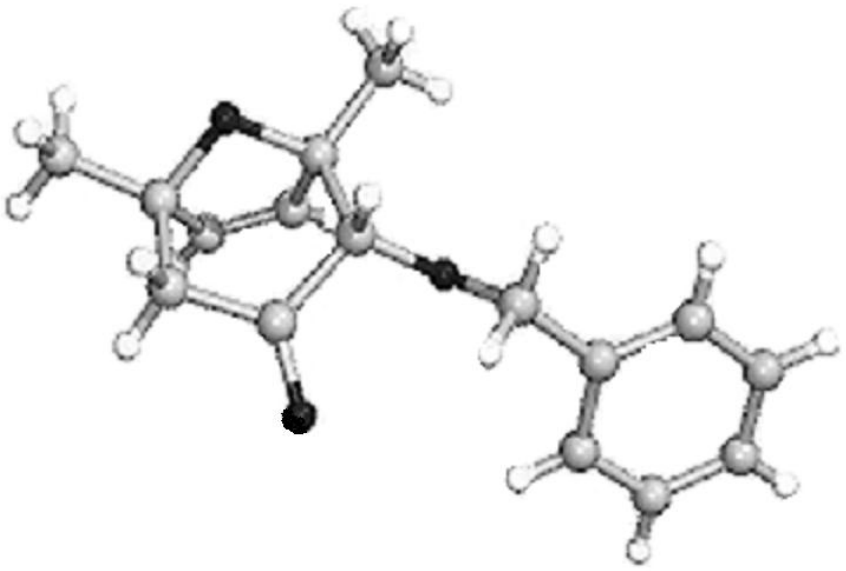
7. X – RAY CRYSTAL STRUCTURES

In the present work crystal structures for 10 compounds were obtained. Complete information about every structure was explained offering data collection about these parameters:

- Details of structure determination
- Coordinate and equivalents isotropic terminal parameters of C, N, O atoms
- Atoms positions
- Isotropic parameters of H atom
- Wavelength
- Unit cell dimensions (Bond length and bond angle)
- Calculated density
- Absorption coefficient
- Crystal size and Volume
- Minimal and maximal residual electron density

2a-Benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-45**

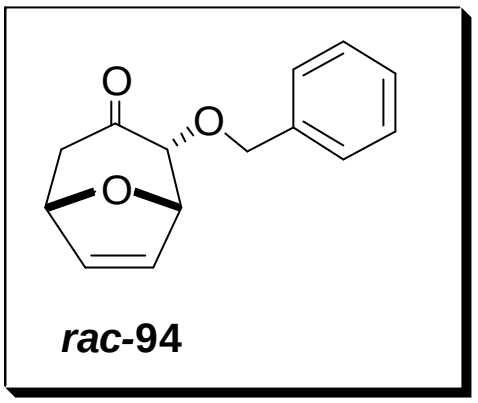


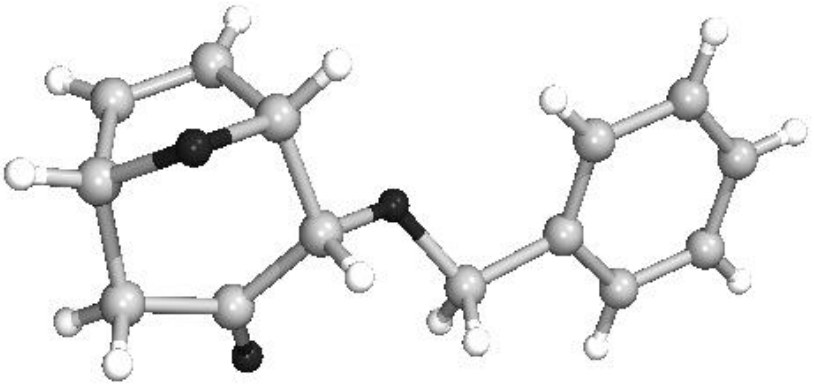


Data collection and handling:

Empirical formula	$C_{16}H_{18}O_3$
Molecular weight ($gmol^{-1}$)	258.30
Crystal system	monoclinic
Space group	P 21/c (No.14)
Crystal	colourless distorted octahedron
Size (mm)	0.89 x 0.41 x 0.37
a, b, c (?)	7.680(2) 16.206(4) 11.371(2)
a, ß, ? (degree)	90.00 92.81(2) 90.00
Volume, *V* (? ^{3})	1413.6(6)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.214
F(000) (e)	552
Absorption coefficient µ (cm^{-1})	0.083
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.19, θ_{max} = 26.02
Index ranges	-9 = h = 9, -19 = k = 19, -13 = l = 13
Reflections collected / unique	20125 / 2704 [$R(I)_{int}$ = 0.0472]
Completeness to θ = 26.02	98 %
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2704 / 0 / 172
Goodness-of-fit on F^2	0.959
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0341 , wR2 = 0.0633
R indices (all data)	R1 = 0.0628 , wR2 = 0.0657
Largest diff. peak and hole (eA^{-3})	0.714 and -0.104

2a-Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one ***rac*-94**

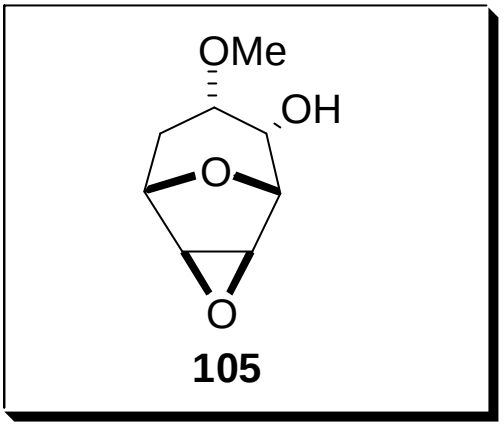




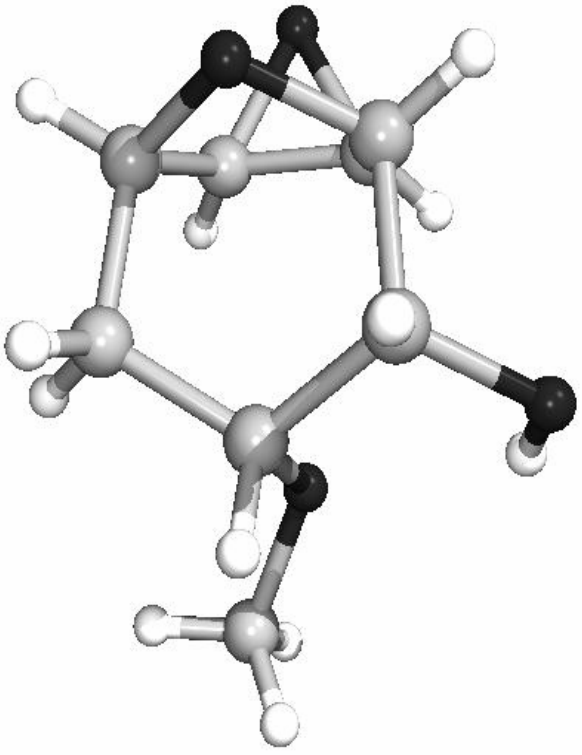
Data collection and handling:

Empirical formula	$C_{14}H_{14}O_3$
Molecular weight ($gmol^{-1}$)	230.25
Crystal system	monoclinic
Space group	I a (No.9)
Crystal	colourless plate || (010)
Size (mm)	0.2 x 0.1 x 0.03
a, b, c (?)	8.795(2) 61.364(8) 8.842(2)
a, ß, ? (degree)	90.00 90.18(2) 90.00
Volume, *V* (? ^{3})	4772 (2)
Z	16
$d_{calcd.}$ (gcm^{-3})	1.282
F(000) (e)	1952
Absorption coefficient µ (cm^{-1})	0.090
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 1.99, θ_{max} = 24.10
Index ranges	-9 = h = 10, -69 = k = 70, -10 = l = 9
Reflections collected / unique	16690 / 7085 [$R(I)_{int}$ = 0.0702]
Completeness to θ = 24.10	98 %
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7085 / 2 / 333
Goodness-of-fit on F^2	0.940
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0569 , wR2 = 0.0796
Absolute structure parameter	0.4(12)
Largest diff. peak and hole (eA^{-3})	0.262 and -0.220

3a-Methoxy-6,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-2a-ol **105**



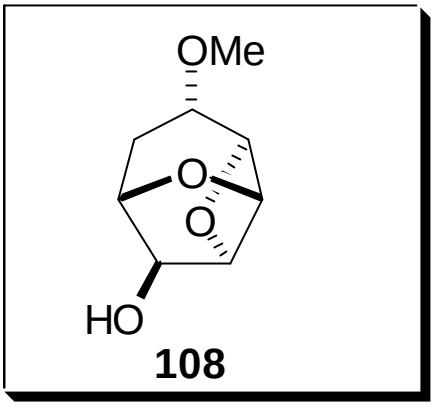
105

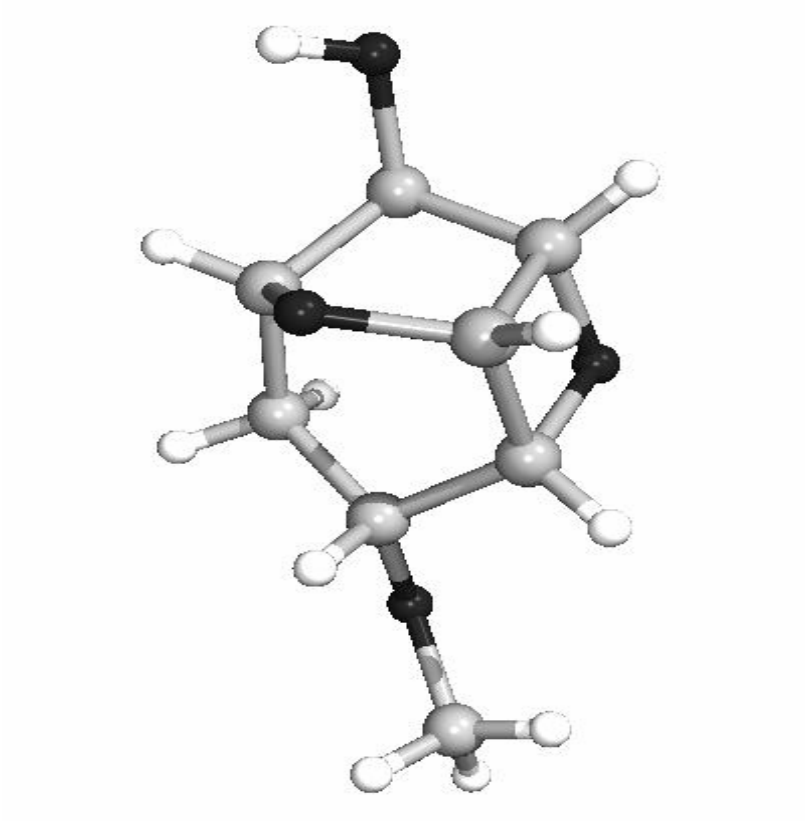


Data collection and handling:

Empirical formula	$C_8H_{12}O_4$
Molecular weight ($gmol^{-1}$)	172.18
Crystal system	Orthorhombic
Space group	P b c a (No.61)
Crystal	colourless plate || (010)
Size (mm)	0.70 x 0.25 x 0.07
a, b, c (?)	10.402(2) 11.121(2) 13.855(4)
a, ß, ? (degree)	90.00 90.00 90.00
Volume, *V* (? ^{3})	1602.8(6)
Z	8
$d_{calcd.}$ (gcm^{-3})	1.427
F(000) (e)	736
Absorption coefficient µ (cm^{-1})	0.115
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.94, θ_{max} = 26.07
Index ranges	-12 = h = 12, -13 = k = 13, -17 = l = 17
Reflections collected / unique	21120 / 1570 [$R(I)_{int}$ = 0.0685]
Completeness to θ = 26.07	100 %
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1570 / 0 / 114
Goodness-of-fit on F^2	1.043
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0320 , wR2 = 0.0707
R indices (all data)	R1 = 0.0628 , wR2 = 0.0657
Extinction coefficient	0.0037(8)
Largest diff. peak and hole (eA^{-3})	0.130 and -0.142

3a-Methoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-6ß-ol **108**

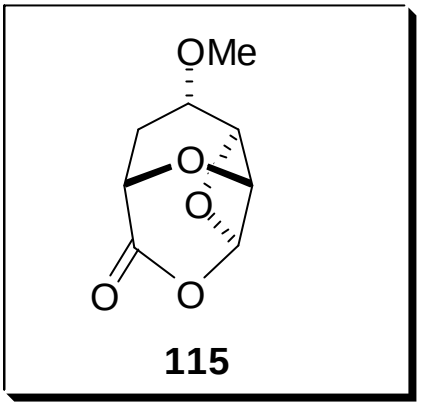




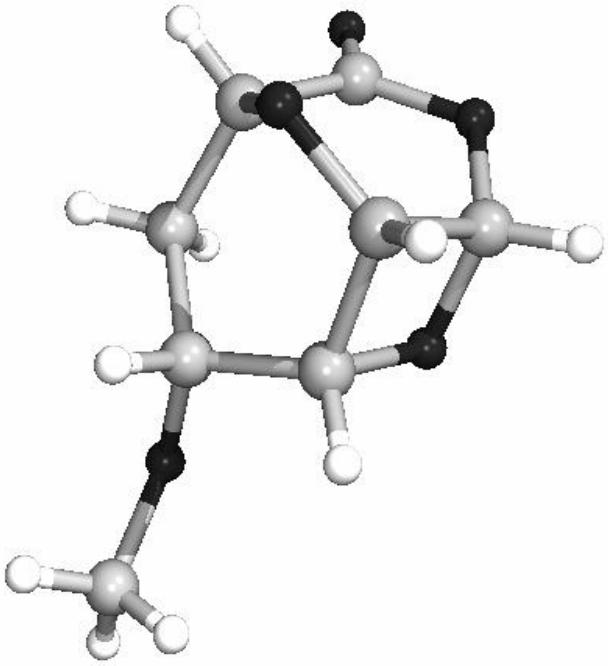
Data collection and handling:

Empirical formula	$C_8H_{12}O_4$
Molecular weight ($gmol^{-1}$)	172.18
Crystal system	Orthorhombic
Space group	P c a 21 (No.29)
Crystal	colourless prism || [010]
Size (mm)	0.38 x 0.89 x 0.48
a, b, c (?)	15.746(3) 5.902(1) 8.439(2)
a, ß, ? (degree)	90.00 90.00 90.00
Volume, *V* (? ^{3})	784.3(3)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.458
F(000) (e)	368
Absorption coefficient µ (cm^{-1})	0.117
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.59, θ_{max} = 25.96
Index ranges	-19 = h = 19, -7 = k =7, -10 = l = 10
Reflections collected / unique	10261 / 1494 [$R(I)_{int}$ = 0.0326]
Completeness to θ = 25.96	97.3 %
Absorption correction, Extinction correction	none, none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1491 / 1 / 114
Goodness-of-fit on F^2	1.166
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0265 , wR2 = 0.0717
R indices (all data)	R1 = 0.0278 , wR2 = 0.0721
Extinction coefficient	0.012(9)
Absolute structure parameter	0.0(9)
Largest diff. peak and hole (eA^{-3})	0.146 and -0.140

3a-Methoxy-2,4,7-trioxa-tricyclo[4.2.2.0^{3,8}]octan-6-one **115**



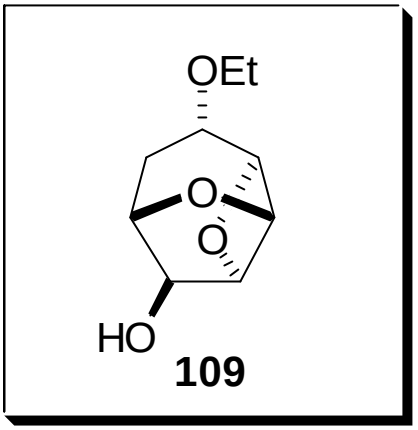
115



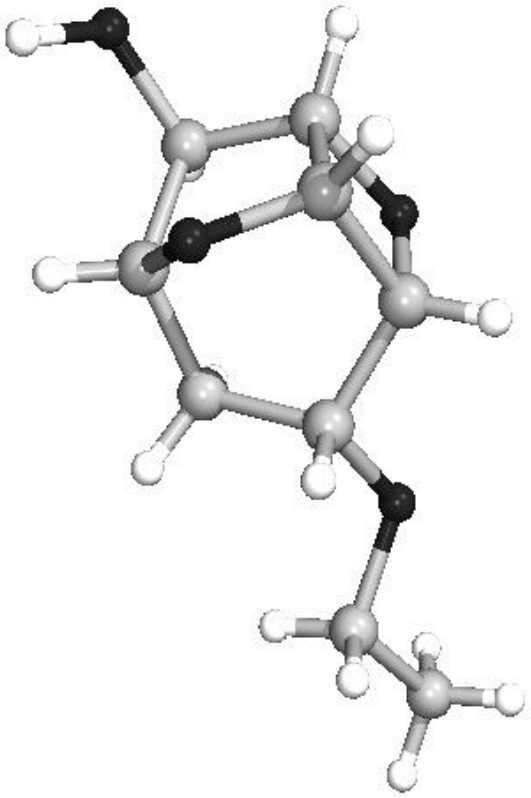
Data collection and handling:

Empirical formula	$C_8 H_{10} O_5$
Molecular weight ($gmol^{-1}$)	186.16
Crystal system	Monoclinic
Space group	P 21/n
Size (mm)	0.37 x 0.30 x 0.18
a, b, c (?)	6.511(1) 8.283(2) 15.196(3)
a, ß, ? (degree)	90.00 100.00 90.00
Volume, *V* (? ^{3})	807.1(3)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.532
F(000) (e)	392
Absorption coefficient µ (cm^{-1})	0.129
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.72, θ_{max} = 26.05
Index ranges	-7 = h = 8, -10 = k = 10, -18 = l = 18
Reflections collected / unique	11034 / 1569 [R(I)$_{int}$ = 0.0408]
Completeness to θ = 26.05	99.9 %
Absorption correction	none, none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1569 / 0 / 119
Goodness-of-fit on F^2	1.199
Final R indices [I_t > 2.0 s(I)]	R1 = 0.0313 , wR2 = 0.0670
R indices (all data)	R1 = 0.0477 , wR2 = 0.0690
Minimal and maximal residual electron density (eA^{-3})	0.006(3)

3a-Ethoxy-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-6ß-ol **109**



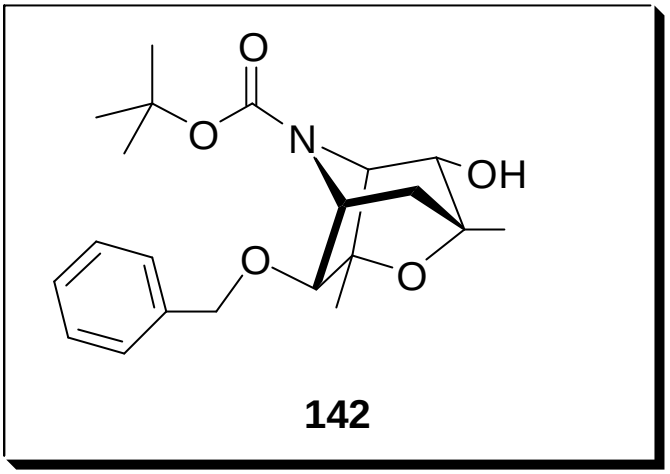
109

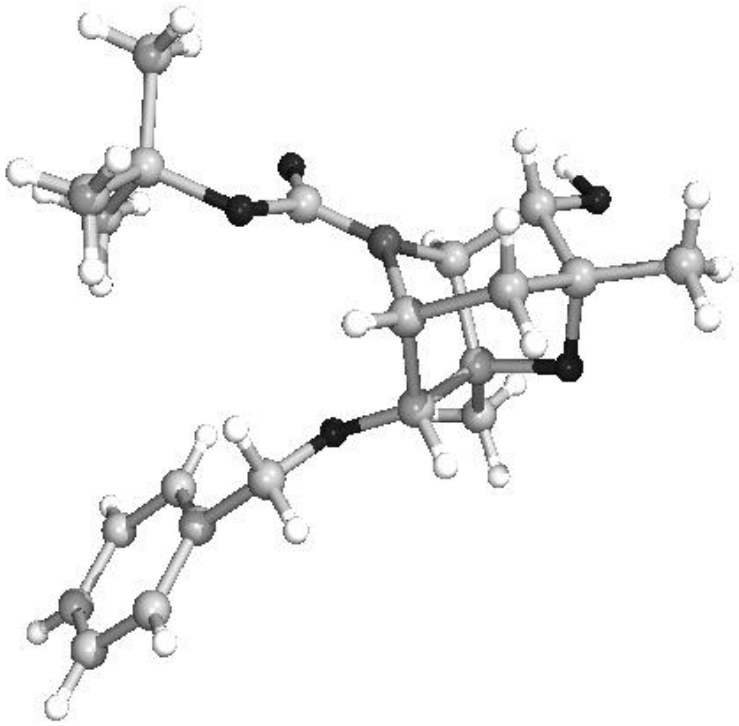


Data collection and handling:

Empirical formula	$C_9H_{14}O_4$
Molecular weight ($gmol^{-1}$)	186.20
Crystal system	Orthorhombic
Space group	P 21
Size (mm)	0.52 x 0.09 x 0.01
a, b, c (?)	5.988 (2) 9.327 (4) 15.752 (2)
a, ß, ? (degree)	90.00 90.00 90.00
Volume, *V* ($?^3$)	879.8(6)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.406
F(000) (e)	400
Absorption coefficient µ (cm^{-1})	0.110
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.54, θ_{max} = 26.06
Index ranges	-7 = h = 7, -11 = k = 11, -19 = l = 19
Reflections collected / unique	12581 / 1736 [$R(I)_{int}$ = 0. 1256]
Completeness to θ = 26.06	100%
Absorption correction	none
Decay correction	yes (32%)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1736 / 2 / 77
Goodness-of-fit on F^2	1.017
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0501 , wR2 = 0.0619
R indices (all data)	R1 = 0.1195 , wR2 = 0.0691
Minimal and maximal residual electron density (eA^{-3})	0.277 and -0.243

1,5-dimethyl-2a-Benzyloxy-6ß-hydroxy-2-oxa-3-aza-(N-tert-butyloxycarbonyl)-tricyclo[3.3.1.0^{3,7}]nonane **142**



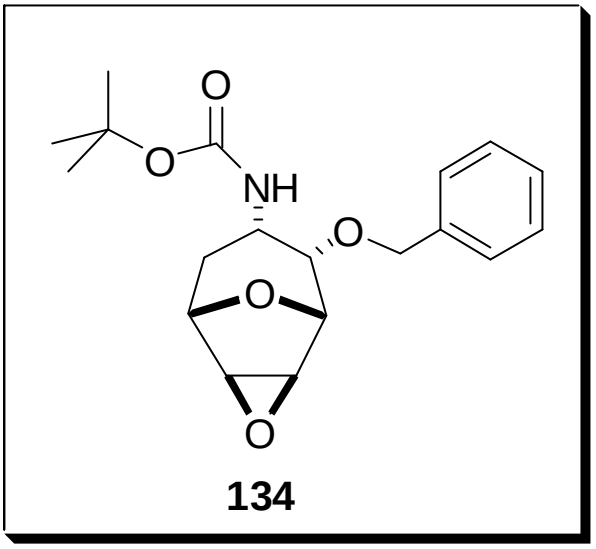


Data collection and handling:

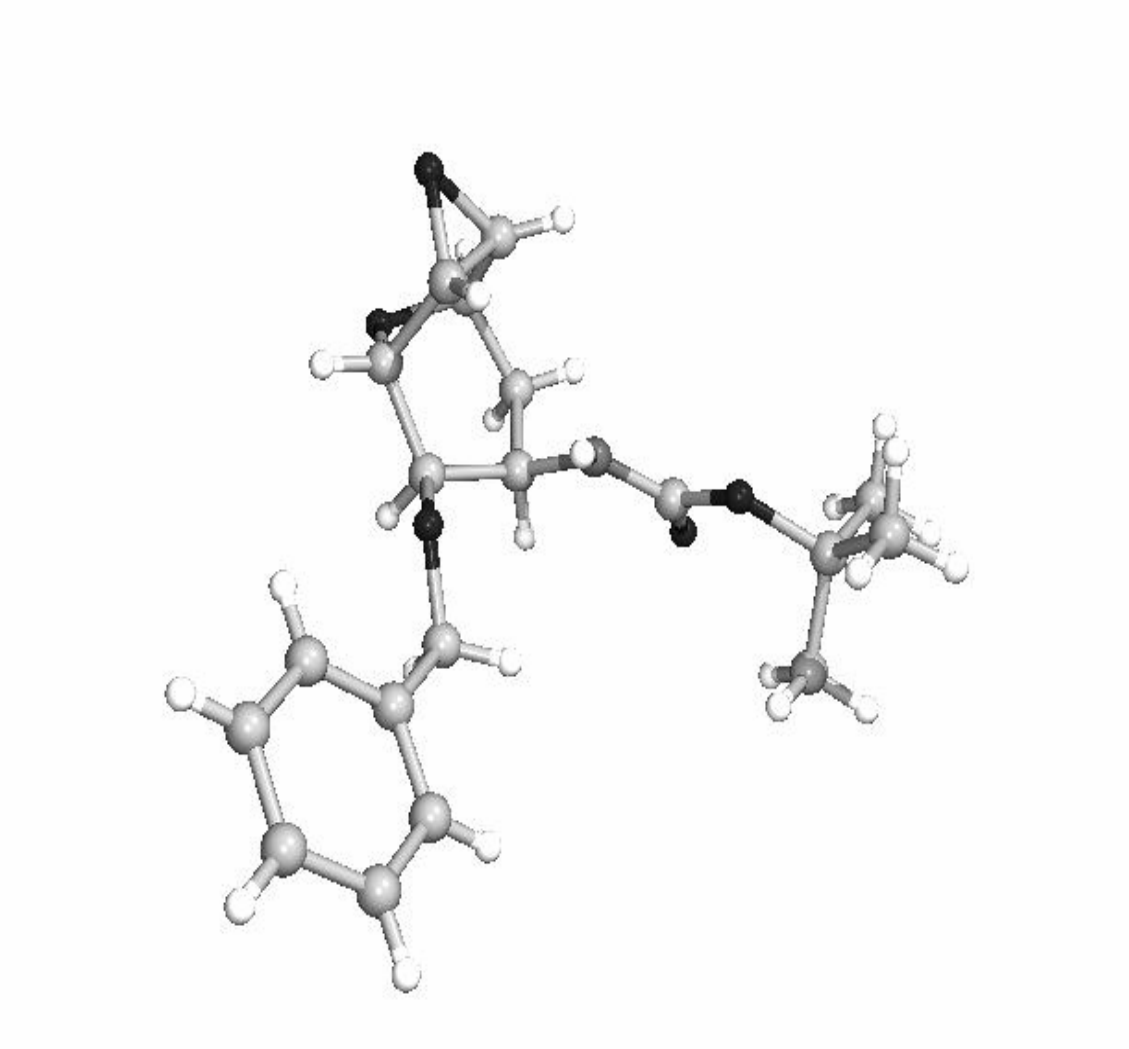
Empirical formula	$C_{21}H_{29}NO_5$
Molecular weight ($gmol^{-1}$)	375.45
Crystal system	monoclinic
Space group	P 21/c
Size (mm)	0.56 x 0.41 x 0.26
a, b, c (?)	12.579 (4) 8.094 (2) 20.794 (5)
a, ß, ? (degree)	90.00 96.10(3) 90.00
Volume, *V* ($?^3$)	2105.1(10)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.185
F(000) (e)	808
Absorption coefficient µ (cm^{-1})	0.084
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 1.97, θ_{max} = 24.15
Index ranges	-14 = h = 14, -9 = k = 9, -23 = l = 23
Reflections collected / unique	23765 / 3313 [$R(I)_{int}$ = 0. 0908]
Completeness to θ = 24.3	98.3%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3313 / 2 / 248
Goodness-of-fit on F^2	1.118
Final R indices [$I_t > 2.0$ s(I)]	R1 = 0.0574, wR2 = 0.0669
R indices (all data)	R1 = 0.1147 , wR2 = 0.0703
Minimal and maximal residual electron density (eA^{-3})	0.279 and -0.191

3a-amino-(NH-tert-butyloxycarbonyl)-2a-benzyloxy-6,9-dioxatricyclo[3.3.1.0^{2,4}]nonan

134



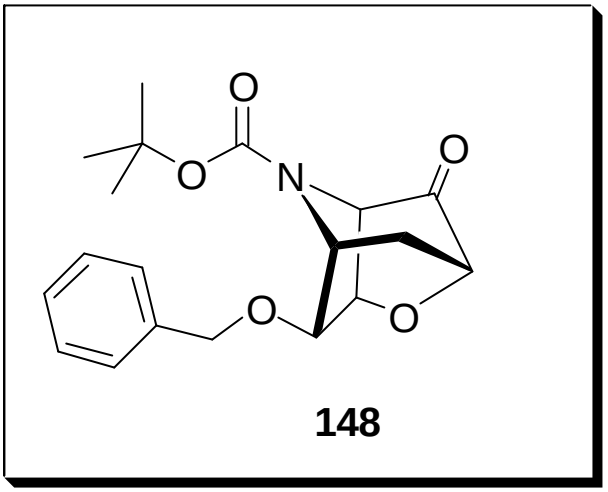
134



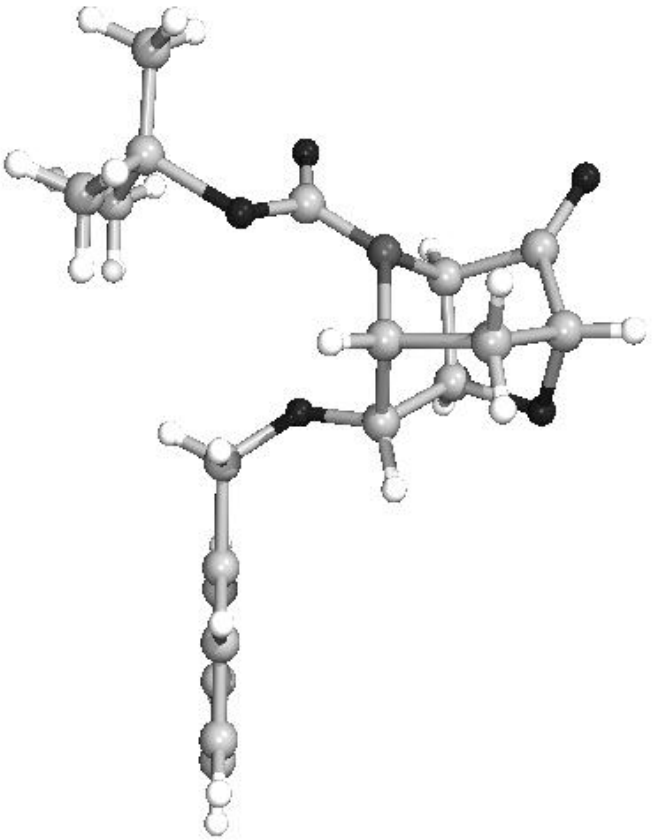
Data collection and handling:

Empirical formula	$C_{19}H_{25}NO_5$
Molecular weight ($gmol^{-1}$)	347.40
Crystal system	Monoclinic
Space group	P 21/n
Size (mm)	0.33 x 0.33 x 0.06
a, b, c (?)	11.739(3) 10.598(2) 14.867(4)
a, ß, ? (degree)	90.00 96.38(3) 90.00
Volume, *V* (? ^{3})	1838.1(8)
Z	4
$d_{calcd.}$ (gcm^{-3})	1.255
F(000) (e)	744
Absorption coefficient µ (cm^{-1})	0.091
Diffractometer	Stoe IPDS area detector
T (K)	300 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.10, θ_{max} = 25.98
Index ranges	-14 = h = 14, -13 = k = 13, -18 = l = 18
Reflections collected / unique	25528 / 3439 [$R(I)_{int}$ = 0. 0990]
Completeness to θ = 26	96%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3439/ 0 / 230
Goodness-of-fit on F^2	1.046
Final R indices [I_t > 2.0 s(I)]	R1 = 0. 0403, wR2 = 0. 0475
R indices (all data)	R1 = 0. 1144, wR2 = 0. 0511
Minimal and maximal residual electron density (eA^{-3})	0. 167 and -0.162

2a-Benzyloxy-6-oxo-2-oxa-3-aza-(N-tert-butyloxycarbonyl)tricyclo[3.3.1.0^{3,7}]nonane **148**



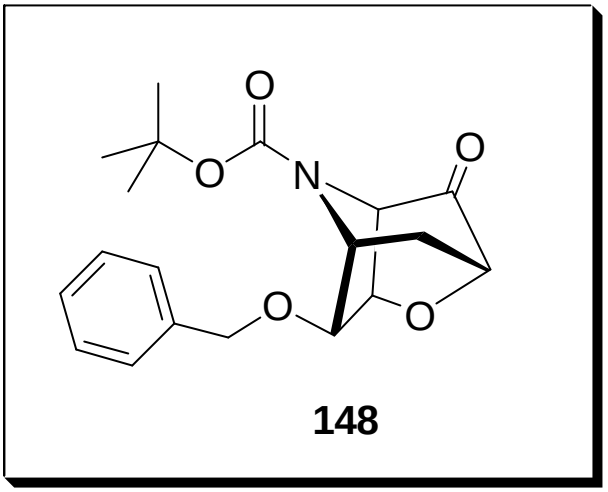
148



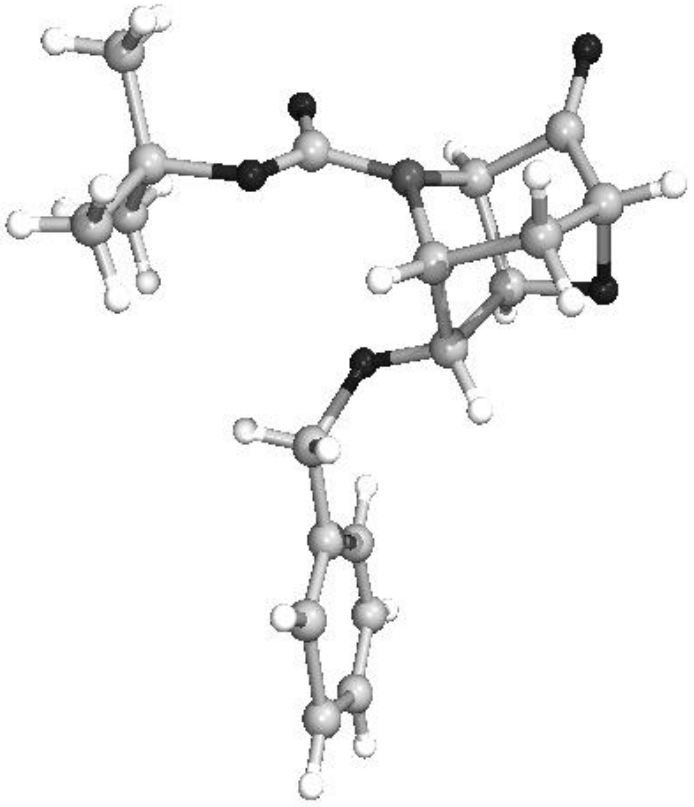
Data collection and handling:

Empirical formula	$C_{19}H_{23}NO_5$
Molecular weight ($gmol^{-1}$)	345.38
Crystal system	Orthorhombic
Space group	I a (No.9)
Size (mm)	0.2 x 0.1 x 0.03
a, b, c (?)	29.615(8) 6.615(2) 18.645(6)
a, ß, ? (degree)	90.00 90.00 90.00
Volume, *V* (? ^{3})	3653 (2)
Z	8
$d_{calcd.}$ (gcm^{-3})	1.256
F(000) (e)	1472
Absorption coefficient µ (cm^{-1})	0.091
Diffractometer	Stoe IPDS area detector
T (K)	250 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.18, θ_{max} = 26.26
Index ranges	-36 = h = 36, -7 = k = 7, -23 = l = 23
Reflections collected / unique	48090 / 7083 [R(I)$_{int}$ = 0. 2740]
Completeness to θ = 26.3	97.9%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7083 / 9 / 261
Goodness-of-fit on F^2	0.784
Final R indices [I_t > 2.0 s(I)]	R1 = 0.0751 , wR2 = 0.0985
R indices (all data)	R1 = 0.2731, wR2 = 0. 1272
Absolute structure parameter	0.00
Minimal and maximal residual electron density (eA^{-3})	0.376 and -0.336

2a-Benzyloxy-6-oxo-2-oxa-3-aza-(N-tert-butyloxycarbonyl)tricyclo[3.3.1.0^{3,7}]nonane **148**



148



Data collection and handling:

Empirical formula	$C_{19}H_{23}NO_5$
Molecular weight ($gmol^{-1}$)	345.38
Crystal system	Orthorhombic
Space group	I a (No.9)
Size (mm)	0.2 x 0.1 x 0.03
a, b, c (?)	29.615(8) 6.615(2) 18.645(6)
a, ß, ? (degree)	90.00 90.00 90.00
Volume, *V* (? ^{3})	3653 (2)
Z	8
$d_{calcd.}$ (gcm^{-3})	1.256
F(000) (e)	1472
Absorption coefficient µ (cm^{-1})	0.091
Diffractometer	Stoe IPDS area detector
T (K)	250 (2)
Wavelength, Mo K_a radiation (?)	0.71073
Theta range for data collection	θ_{min} = 2.18, θ_{max} = 26.26
Index ranges	-36 = h = 36, -7 = k = 7, -23 = l = 23
Reflections collected / unique	48090 / 7083 [R(I)$_{int}$ = 0. 2740]
Completeness to θ = 26.3	97.9%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7083 / 9 / 261
Goodness-of-fit on F^2	0.784
Final R indices [I_t > 2.0 s(I)]	R1 = 0.0751 , wR2 = 0.0985
R indices (all data)	R1 = 0.2731, wR2 = 0. 1272
Absolute structure parameter	0.00
Minimal and maximal residual electron density (eA^{-3})	0. 376 and -0.336

CURRICULUM VITAE

Dr. María Vidal Pascual

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Education

Ph.D. (Organic Chemistry), 2003

(University of Hannover, Germany)

Thesis Title: New Dioxa and Oxaza-tricyclononanes and Study of their Biological Activity

Graduated in Chemistry

(University Complutense in Madrid)

Research Scholarship

June 1998 - December 1998 ***Leonardo da Vinci program***

WATERMAN Wasser- und Umwelttechnik GmbH in collaboration with the University of Bremen.

October 1995 - December 1997 ***State Investigation Program***

Canary Island Project in collaboration with the University of Las Palmas de Gran Canaria.

March 1995 - September 1995 ***EU Investigation Program***

European Union Project in collaboration with the University of Las Palmas de Gran Canaria.

Research Experiences

Department of Chemistry at the University of Bremen.
Position: Co-Investigator, 1998.
Type of work: Development of a small mobile water purification system.

Bionat. Nuevas Tecnologías Bioquímicas S.A.
Position: Technical Chemist in R&D, 1998.
Type of work: GC, HPLC.

Department of Process Engineering at the University Las Palmas of Gran Canaria.
Position: Co-Investigator, 1995-1997.
Type of work: Determination of excess thermodynamics properties in binary mixtures of esters-alkanes.

Department of development and investigation in Repsol Química S.A.
Position: Technical Chemist in R&D, 1993.

Type of work: Development of new analytical methods.

Department of analytical Chemistry at the University Complutense of Madrid.
Position: Co-Investigator, 1992-1993.
Type of work: Atomic Absorption and UV Spectroscopy.

Instrumental Experiences

Good knowledge: Mechanical Oscillation Densimeter, GC, IR, TLC and Column Chromatography.

Hand on experience: NMR, HPLC, UV.

Good Knowledge: IBM-PC and Macintosh Computer with use of different software packages e.g., WIN-NMR, MS word, Chemdraw, Corel DRAW, Power point, Excel etc.

Courses attended

2001 One- and Two- Dimensional NMR Methods for Structure Elucidation of Organic Compounds and Natural Products. Universtität Hannover.
1998 - 99 Master in Environment. Institute of Ecological Investigations. Málaga.
1997 Waste Treatment. Complutense University of Madrid.
1997 Pedagogical Course. Complutense University of Madrid.
1997 Thermodynamics of phases equilibrium. Las Palmas University of Gran Canaria.
1997 Numerical Solutions of equations. Las Palmas University of Gran Canaria.
1997 Thermodynamic of Chemistry Solutions. Las Palmas University of Gran Canaria.
1996 Thermodynamic properties of mixtures. Las Palmas University of Gran Canaria.
1996 Methods of Investigation. Las Palmas University of Gran Canaria.
1995 Models of liquids mixtures. Las Palmas University of Gran Canaria.
1994 Quality of Nourishment. Minister of Health. Madrid.
1993 Environment Engineering. Alcalá de Henares University. Madrid.
1992 Analytical determination of drugs with GC and HPLC. Complutense University. Madrid.

Personal Data

Languages: Spanish, English, German.
Nationality: Spaniard

Publications

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