Synthesis of Branched Amino Acids: Isonorstatine, Phenylisothreonine, Lactacystin Analogues, and Amino Polyols

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Preliminary remarks and abbreviations

Figures, equations, literature citations, Schemes, and Tables are numbered consecutively.

All the compounds prepared during this work and cited in the Experimental Part are consecutively numbered with **1**, **2**, **3** etc. and are assembled in the **Table of Structure Formulas** at the end of this work. Some preparations yield diastereomeric mixtures; the diastereomers are assigned as **a** and **b**.

Starting from Chapter 1, all the other formulas and structures are consecutively labelled in bold capitals, i. e. **A**, **B**,....., **Z**, **AA**, **AB** etc.

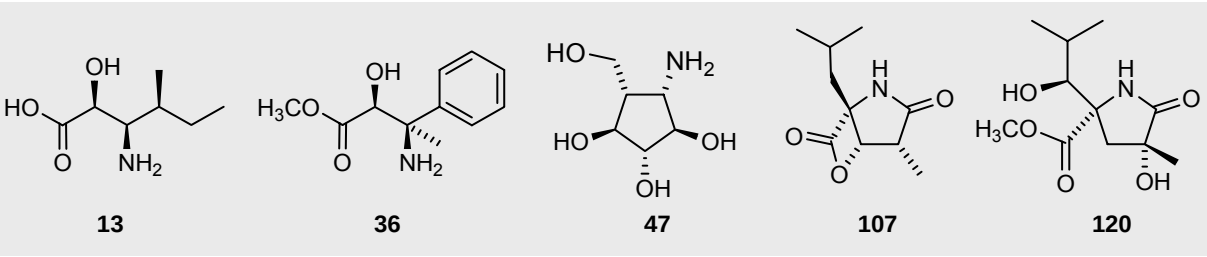
List of abbreviations:

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	α,α'-azodiisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]-nonane
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
BOPCl	bis(2-oxo-3-oxazolidinyl) phosphinic chloride
CSA	camphorsulfonic acid
CAN	ceric ammonium nitrate
cat.	catalyst
Z	benzyloxycarbonyl
Chx	cyclohexyl
DABCO	1,4-diazabicyclo[2,2,2]-octane
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQ	dihydroquinine
$(DHQ)_2AQN$	hydroquinine (anthra-quinone-1,4-diyl) diether
DHQD	dihydroquinidine
$(DHQD)_2PHAL$	dihydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxy ethane
DMF	*N,N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
DQCB	dihydroquinidine 4-chloro-benzoate
dr	diastereomeric ratio
ee	enantiomeric excess
Eq.	equation
Et	ethyl
HBCat	catecholborane
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosohoramide
imid	imidazole
Ipc	isopinocampheyl
KHMDS	potassium bis(trimethyl-silyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl) amide
M	molarity
m-CPBA	*m*-chloroperbenzoic acid
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	mass spectrometry
p-NBSP	*p*-nitrobenzenesulfonyl peroxide
NaHMDS	sodium bis(trimethylsilyl) amide
NIS	*N*-iodosuccinimide
NMMO	*N*-methylmorpholine *N*-oxide
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

Ph	phenyl
PHAL	phthalazine
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluene sulphonate
p-TsOH	*p*-toluenesulphonic acid
py	pyridine
r. t.	room temperature
t	tertiary
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy (free radical)
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'N'*-tetramethylethylene-diamine
TMS	trimethylsilyl tetramethylsilane
Ts	tosyl *p*-toluenesulfonyl

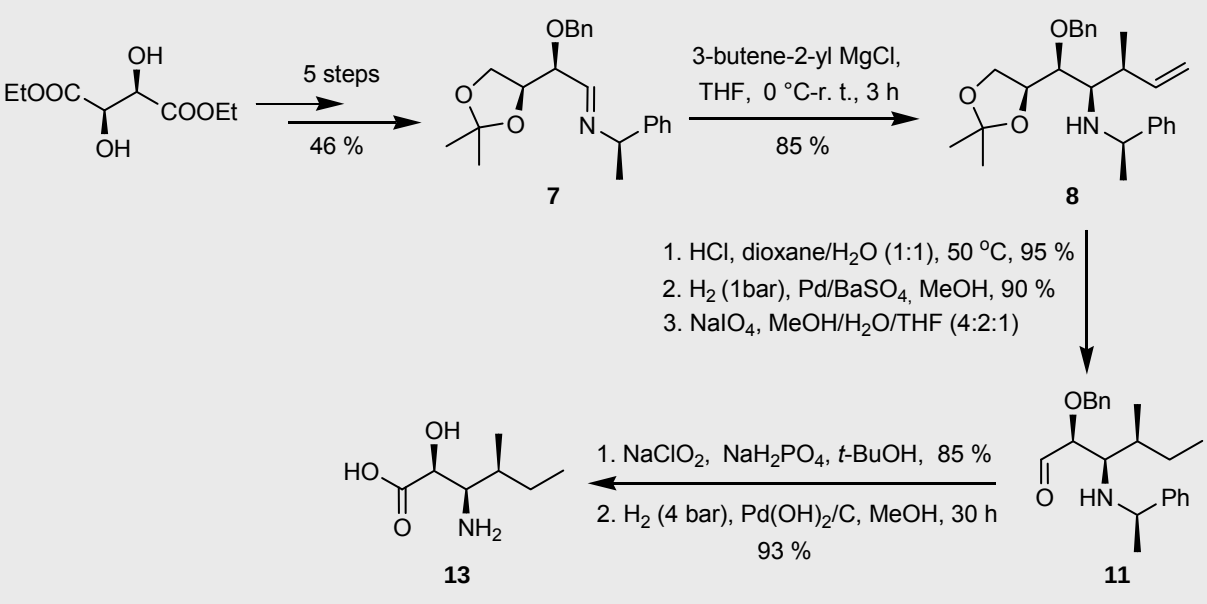
Zusammenfassung

Das 1,2-Aminoalkoholfragment wird in vielen Naturstoffen und Arzneimitteln gefunden. Zum Beispiel als zentraler Teil einiger nicht-proteinogener Aminosäuren. Es besteht deshalb ein besonderes Interesse an der Synthese von verzweigten Aminohydroxysäuren, wie beispielsweise Isonorstatin **13**, Phenylisothreonin **36**, Aminopolyol **47** und Lactacystin-Derivaten **107** und **120**.



Synthese von Isonorstatin (**13**)

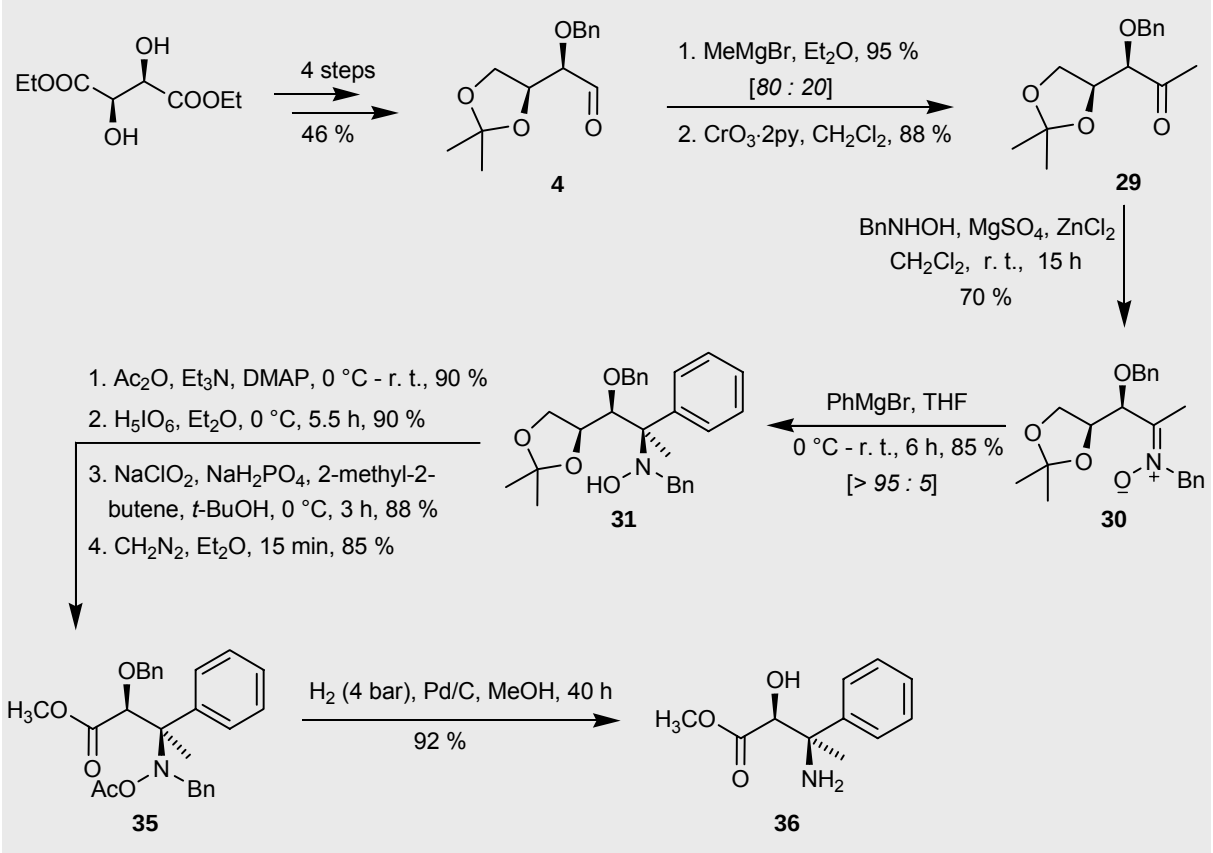
Ausgehend von dem *L*-Diethylweinsäureester erhielt man nach 5 Stufen das *L*-Threoseimin, das nach regio- und stereoselektiver Addition von 3-Butenyl-2-magnesiumchlorid das Schlüsselzwischenprodukt **8** ergab. Diolspaltung und weitere Ausarbeitung führte zur Bildung des angestrebten Aminoalkohols Isonorstatin **13** (11 Stufen, Σ 25 % ausgehend von dem *L*-Diethylweinsäureester).



Synthese von Phenylisothreoninester (36)

Ebenso ausgehend von *L*-Diethylweinsäureester, wurde der *L*-threose aldehyd **4** in das Methylketon **29** umgewandelt und mit Benzylhydroxylamin in das Ketonitron **30** überführt.

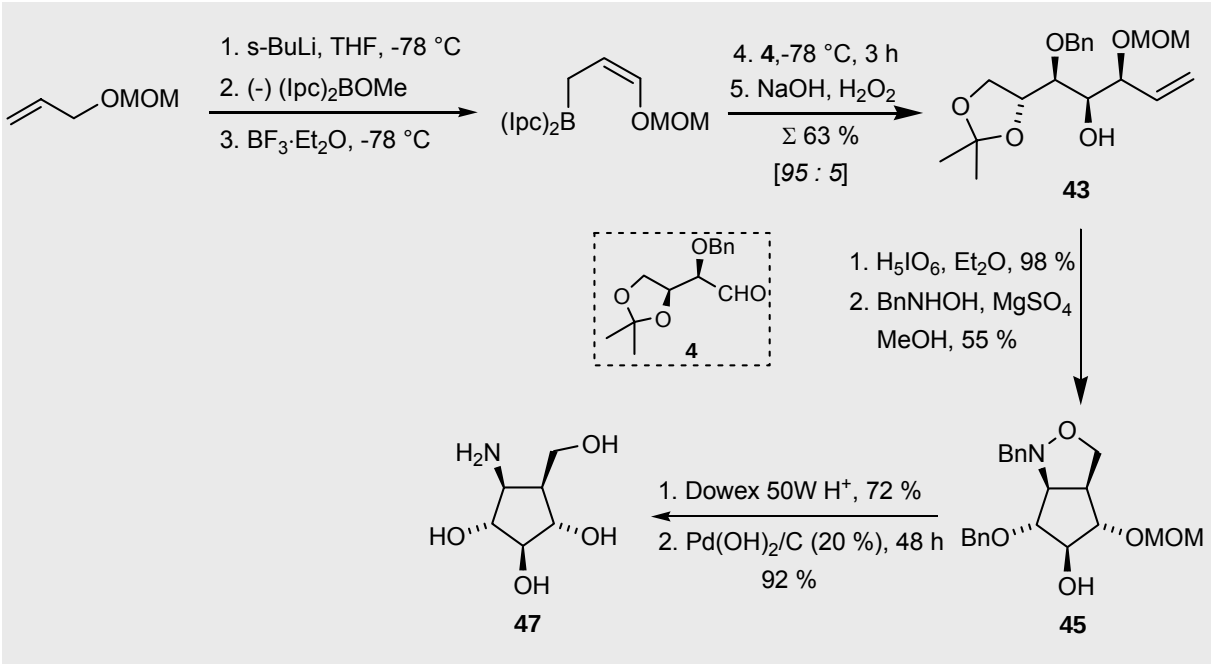
Die diastereoselektive Addition von Phenylmagnesiumbromid ermöglichte die Darstellung des Schlüsselprodukts **31**. Alle Versuche der Diolspaltung mit einer freien Hydroxylgruppe scheiterten. Sie führten zur Zersetzung des Produktes. Es gelang jedoch das 3-*O*-acetylierte Derivat mit Periodsäure oxidativ zu spalten. Man erhielt den Aldehyd, der dann unter Standardbedingungen zur Carbonsäure oxidiert wurde. Nach Veresterung mit Diazomethan wurde der Ester **35** katalytisch zum Zielprodukt, Phenylisothreoninester **36** (13 Stufen, Σ 12 % ausgehend von *L*-Diethylweinsäureester) reduziert.



Synthese von Amino(hydroxymethyl)cyclopentantriol (47)

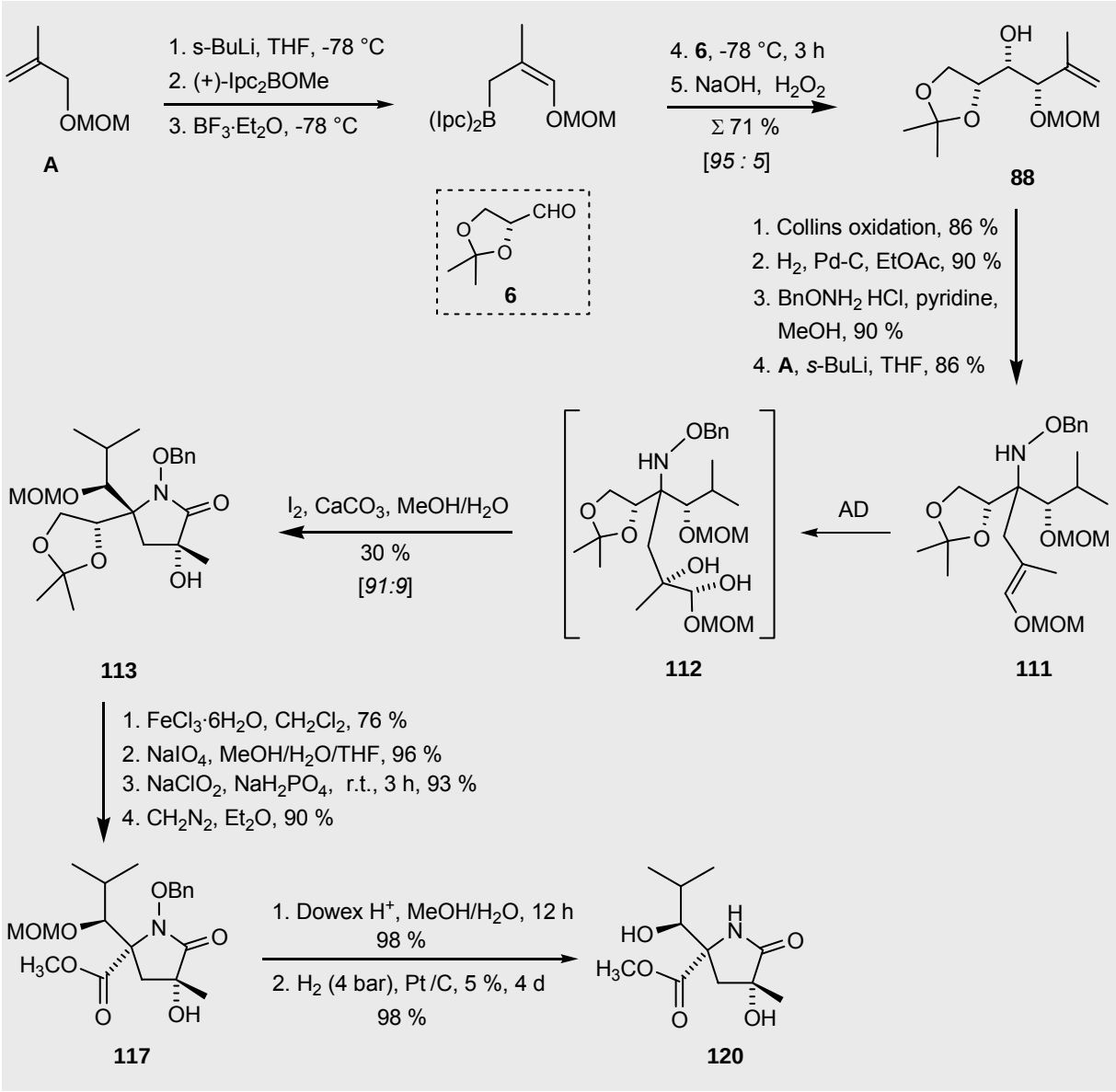
In Anlehnung an unsere Erfahrungen mit der enantioselektiven Addition von Boran reagenzien an verschiedene Aldehyde ermöglichte der *L*-threose aldehyd **4** (der auf einfache Weise in 4 Stufen aus *L*-Diethylweinsäureester dargestellt werden konnte) in Anlehnung an Browns Alkoxyallylreagenz die Darstellung des Alkohols **43**. Die Ausbeute, mit einer sehr hohen enantioselektiven Reinheit (>95 *syn*; >95 *dr*) betrug 68 %. Das Isopropylidenacetal wurde, wie oben dargestellt, mit Periodsäure gespalten, um zu dem zugehörigen Aldehyd zu gelangen. Kondensation mit Benzylhydroxylamin führte zum betreffenden Nitron, das eine anschließende [3 + 2]-Cycloaddition zum Isoxazolidin **45** durchlief. Zum Schluss wurde noch die Methoxymethylether-Schutzgruppe unter sauren Bedingungen mit Dowex (H^+ Form)

entfernt und begleitende Reduktion des Benzylethers sowie *N*-*O*-Bindungsbruch bildete das Amino(hydroxymethyl)cyclopentantriol **47**, [5 Stufen, Σ 22 % ausgehend von 3-(Methoxymethoxy)prop-1-en] als ein neues Beispiel dieser Serie potentieller Glycosidase-Inhibitoren.



Versuche zur Synthese von Lactacystin-Derivaten (120)

Die Annäherung an die Synthese des Lactacystin-Kerns beruhte darauf, die erforderlichen Kohlenstoffstereozentren mit enantioselektiven Additionen der geeigneten Bor-Reagenzien, ausgehend vom *D*-Glyceraldehyd **6**, aufzubauen. Die Sequenz begann mit 3-(Methoxymethoxy)-2-methylprop-1-en, das mit *sec*-Buthyllithium in THF bei -78 °C zum Lithiumsalz metalliert wurde. Die lithiierte Spezies wurde mit (+)-B-Methoxydiisopino-campheylboran [(+)-Ipc$_2$BOMe], anschließend mit Bortrifluoridetherat zum entsprechenden Dialkylallylboran, gefolgt von der direkten *in situ*-Addition des Aldehyds **6**, umgesetzt. Nach oxidativer Aufarbeitung erhielt man das Diol **88** mit einer exzellenten Diastereoselektivität (95 : 5). Mit dem daraus abgeleiteten *O*-Benzyloxim war nur der γ-Angriff des lithiierten MOM-Ethers erfolgreich, der zu der Seitenkette des Amins **111** führte. Die C=C-Doppelbindung wurde nach Sharpless-Methode zum *syn*-Diol hydroxyliert und man erhielt so das Halbacetal **112**. Durch eine interessante Transformation wurde die sekundäre Hydroxygruppe in Anwesenheit eines Überschusses Iod offensichtlich zum Ester oxidiert, der dann, ungeachtet der bescheidenen Ausbeute von 30 %, zum Lactam **113** cyclisierte. Die Entfernung der Isopropyliden-Gruppe und Periodatspaltung führte zum Aldehyd, der unter ähnlichen Bedingungen wie bei der Synthese des Phenylisothreonin **36** dargestellt, zum Ester **117** überführt wurde.



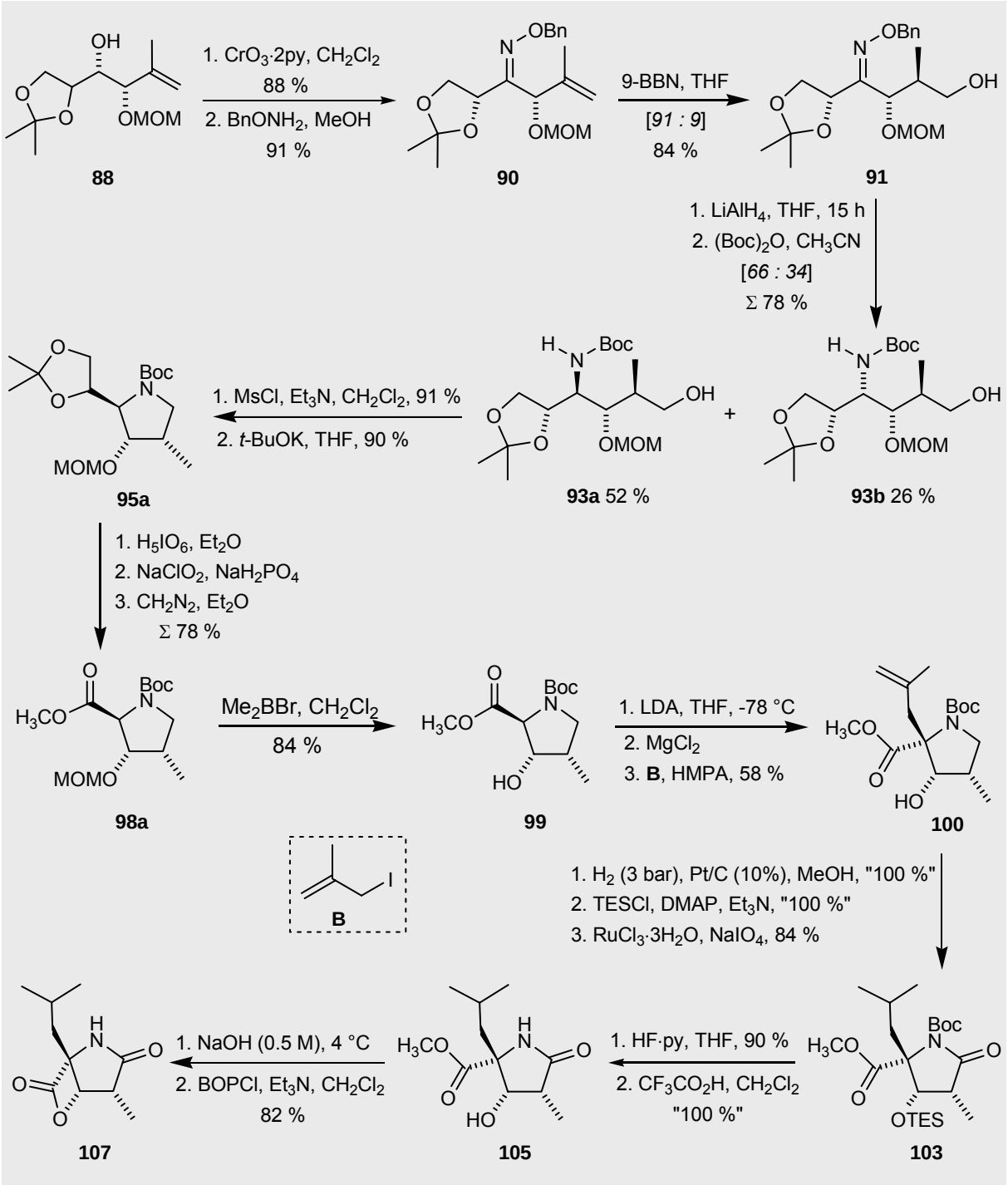
Zum Schluss wurde noch die Methoxymethylether-Schutzgruppe unter sauren Bedingungen mit Dowex (H^+ Form) entfernt und begleitende Reduktion des Benzylethers sowie *N*-*O* Bindungsbruch bildete eine neue Lactacystin-Analoge **120**, (13 Stufen, Σ 7.4 % ausgehend von **A**).

Die Enantiomeren des Lactacystin-Kerns **120**, **81** wurden unter der gleichen Strategie synthetisiert.

Synthese eines analogen Lactacystin-β-Lacton (107)

Die Synthese des Lactacystin-β-Lacton-Analogons **120**, ausgehend von Diol **88**, das leicht zum Keton oxidiert und dann mit *O*-Benzylhydroxylamin zum *O*-Benzyloxim **90** kondensiert, wurde dargestellt. Nach asymmetrischer Hydroborierung von **90** mit 9-Borabicyclo[3.3.1]-

nonan (9-BBN) erhielt man den Alkohol **91**. Durch Reduktion des *O*-Benzyloxims mit Lithiumaluminiumhydrid ($LiAlH_4$) und Schützen des entstehenden Amins mit *tert*-Butyldicarbonat entstanden die beiden Carbamate **93a** und **93b**, die leicht durch flash-Chromatographie getrennt werden konnten.



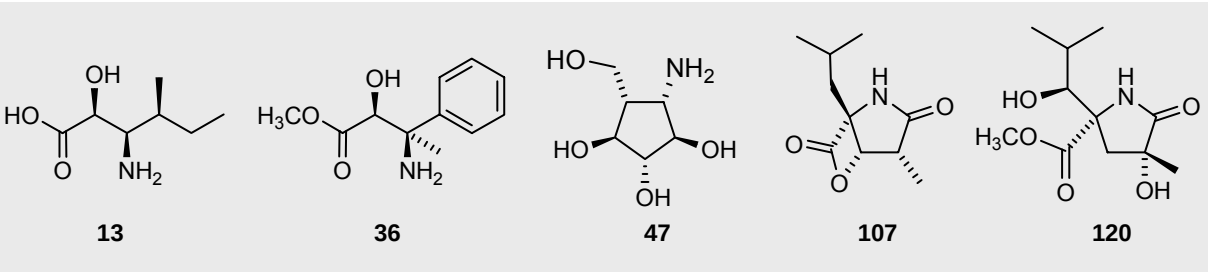
Das Hauptprodukt **93a**, das mit einer Ausbeute von 52 % isoliert wurde, wurde in fünf weiteren Stufen zum substituierten Pyrrolidin **98a** umgewandelt; das letztere führte zum

Schlüsselintermediat **99**, nachdem bei niedriger Temperatur die Methoxymethylgruppe mit Dimethylborylbromid (Me_2BBr) selektiv entschützt wurde.
(Hinweis: Das Nebenprodukt **93b** wurde auch zum zugehörigen Pyrrolidin umgewandelt; Entschützen der Methoxymethylgruppe blieb jedoch erfolglos.)

Nach Hydrierung der C=C-Doppelbindung und Schützen der Hydroxylgruppe wurde das substituierte Pyrrolidin mit Rutheniumtrichlorid und Natriumperiodat ($RuCl_3/NaIO_4$) mit guter Ausbeute zum Lactam **103** oxidiert. Mit all den notwendigen strukturellen Merkmalen an der richtigen Stelle, konnte das Entfernen der Schutzgruppen vollendet werden. Die Trimethylsilylgruppe wurde unter milden Bedingungen durch Aussetzen des Lactams **103** mit Fluorwasserstoff-Pyridin-Komplex in THF mit hoher Ausbeute entfernt, gefolgt von der Entfernung der *tert*-Butoxycarbonylgruppe (Boc) unter Standardbedingungen mit Trifluoressigsäure in Dichlormethan (CF_3COOH, CH_2Cl_2), um das γ-Lactam **105** zu erhalten, den Vorläufer des Deoxy-Lactacystin-β-Lactons. Die letzten Schritte, um das β-Lacton **107** (gesamt 20 Stufen, Σ 5.1 % ebenso ausgehend von **A**) zu erhalten, waren in Anlehnung an Donohoes Prozess die Lactonisierung, die gleiche Strategie wurde für die Synthese des β-Lactons **68** angewandt (das Enantiomer von **107**).

Abstract

The 1,2-aminoalcohol fragment is found in many natural products and drugs, for example as a central moiety of non-proteinogenic amino acids. It is also an integral part of doxorubicin and daunomycin, which have been used for the treatment of human malignancies. There is, therefore, a particular interest in the synthesis of branched amino hydroxy acids such as isonorstatine **13**, phenylisothreonine **36**, amino polyols **47** and lactacystin derivatives **107**, **120**.



13 **36** **47** **107** **120**

Norstatine [(2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid] is part of amastatin, an inhibitor of leucine amino-peptidase, and a fragment of a new human renin inhibitor, KRI-1230. Due to the importance of this kind of compounds, new routes have been explored to synthesize various branched amino acids, such as isonorstatine [(2*S*,3*R*,4*R*)-3-amino-2-hydroxy-4-methylhexanoic acid] **13** and its derivatives. The key step is a highly stereoselective addition of 1-butene-3-yl Grignard reagent to an L-threose-derived imine.

(2*R*,3*S*)-Phenylisoserine constitutes the side-chain of taxol, a drug which has been approved for treatment of ovarian cancer by U.S. FDA. A novel methyl-branched analogue of phenylisoserine, the phenylisothreonine methyl ester **36**, was obtained by addition of methylmagnesium bromide to a protected-L-threose derivative followed by addition of phenyl to the derived nitrone.

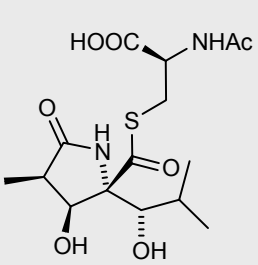
Amino-hydroxymethyl-cyclopentane polyols of type **47** are known to be potent inhibitors of hydrolytic enzymes (glycosidases). The derivative **47** was obtained via intramolecular [3 + 2] cyclization of nitrone and olefin.

Lactacystin, a microbial natural product, is an inhibitor of mammalian 20S proteasome which is a large and highly conserved multi-catalytic proteinase complex that constitutes the catalytic core of the 26S proteasome, present in all eukaryotic organisms. An analogue of lactacystin core, **120**, was obtained in 13 steps starting from 3-(methoxymethoxy) -2-methylprop-1-ene **A**.

The related β-lactone (omuralide) is currently in preclinical development for treatment of ischemia-reperfusion injury in stroke and myocardial infarction. The new route afforded a deoxy analogue of omuralide **107** in 20 steps, also starting from 3-(methoxymethoxy) -2-methylprop-1-ene (**A**). During the synthesis of **107**, the stereoselective alkylation of the substituted proline ester with 3-iodo-2-methylprop-1-ene (**B**) served as the key step.

1. Introduction

The stereoselective synthesis of β-amino acids and their derivatives has been an active area of research, due to the importance of β-amino acids in various fields,[1] for example, inhibitors of proteasome, lactacystin **C**,[2] salinosporamide A **D**[3] and an inhibitor of lymphocyte proliferation, myriocin **E**[4]



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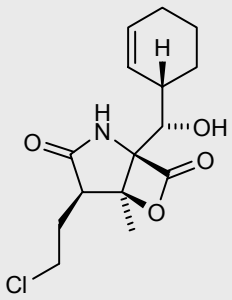

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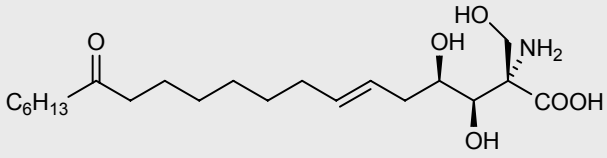
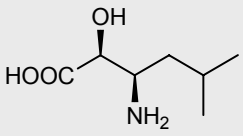
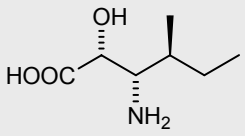


E

In particular, non-proteinogenic β-amino-α-hydroxy acids are found in many natural products and drugs, for instance as a central moiety of oligopeptide-related structures such as pepstatin.[5] Thus, (2*S*,3*R*)-norstatine **F** is part of amastatin, an inhibitor of leucine aminopeptidase.[6] On the other hand, the enantiomer of **F** has been found in human rennin inhibitors KRI-1230[14,15] and KRI-1314.[18,19] (2*R*,3*S*,4*S*)-Isonorstatine **G** and other analogues of cyclohexylstatine **H** have been used as the terminal amino acid part of such inhibitors.



F



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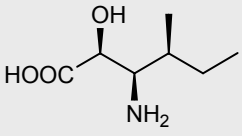

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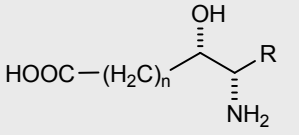


n = 0, 1, 2

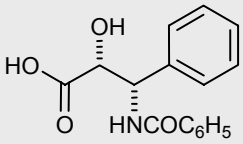
R = Ph, *i*-Bu, Bn, $CH_2C_6H_{11}$

H, Statine Family

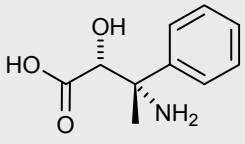
In our group,[27] several approaches to various substituted 1,2-amino alcohols have been developed. Addition of organometallic reagents to aldimines led to α-secondary carbon amines. Using this strategy, the (2*S*,3*R*,4*S*)-isonorstatine **13** was synthesized starting from L-diethyl tartrate, based on a highly stereoselective addition of 3-butenyl Grignard to L-threose-derived imine.

N-Benzoyl-(2*R*,3*S*)-phenylisoserine **I** constitutes the side-chain of taxol, a drug approved for treatment of ovarian and breast cancer by U.S. FDA in 1992.[44d] Due to the importance of these structures, in the last 20 years efficient syntheses of phenylisoserine and its analogues

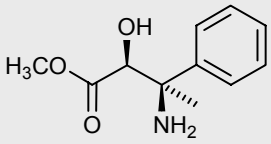
J have attracted much attention from the academic community as well as from industry.[7] A novel methyl-branched analogue of phenylisoserine, the ester **36**, was obtained by sequential addition of methyl and phenyl to threose and the derived nitrone, respectively.



I

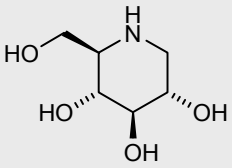


J

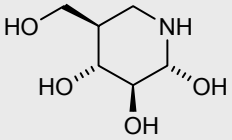


36

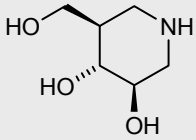
Amino(hydroxymethyl)cyclopentanetriols constitute an emerging class of potent glycosidase inhibitors.[8,10b,10c] Glycosidase inhibitors can be used for treating diabetes, cancer, viral (HIV, influenza) and bacterial infections. Most of these inhibitors are monosaccharide analogues displaying a basic nitrogen function near the anomeric center such as found in deoxynojirimycin **K**[9a], noeuromycin **L**[9d] and isofagomine **M**.[9]



K

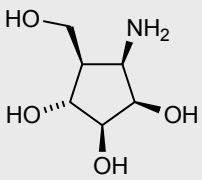


L

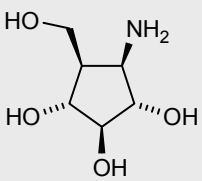


M

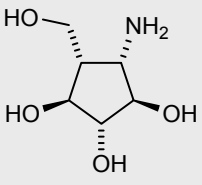
Numerous analogues of such cyclopentanetriols were synthesized in the last years such as **N**, **O**.[8,10,67,70]



N



O

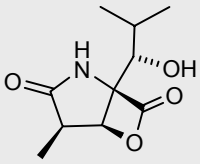


47

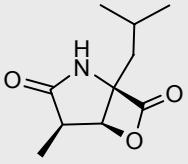
In our group, many types of [3 + 2] cycloadditions were explored.[8,67,70] Now (1*S*,2*R*,3*R*,4*S*,5*S*)- 1-amino-5-(hydroxymethyl)-cyclopentane-2,3,4-triol **47** was synthesized based on a highly stereoselective, intramolecular [3 + 2] nitrone cycloaddition as a key step.

Lactacystin **C**, a microbial natural product, is an inhibitor of mammalian 20S proteasome which is a large and highly conserved multi-catalytic proteinase complex that constitutes the

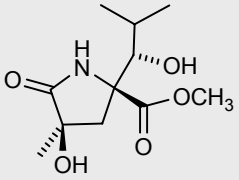
catalytic core of the 26S proteasome, present in all eukaryotic organisms. The proteasome is responsible for the normal turnover of cellular proteins and degradation of damaged and mutated proteins, and **C** has played a vital role in the study of its function. The remarkable biological activity and intriguing structure of **C** has sparked continued interest over the last 14 years and a great number of syntheses have been published to date.[11] In our group, a new route to lactacystin core analogue **120** was developed starting from 3-(methoxymethoxy)-2-methylprop-1-ene **A**.



P



107



120

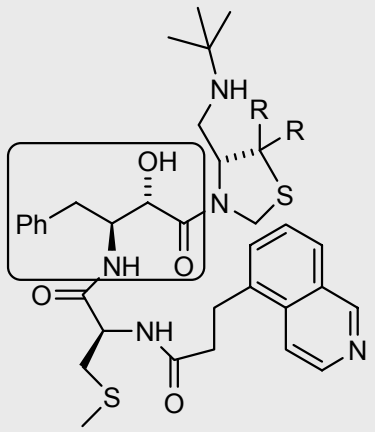
The related β-lactone (omuralide) **P**[12] is currently in preclinical development for treatment of ischemia-reperfusion injury in stroke and myocardial infarction. In view of the bioactivities and intriguing structure of omuralide, an analogue of omuralide **107** was synthesized, also starting from 3-(methoxymethoxy)-2-methylprop-1-ene **A**.

2. Syntheses of Isonorstatine and its Derivatives

2.1 Background

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid **H**, a naturally occurring amino acid of nonproteinogenic origin, is a key component in the pepstatin family of aspartic protease inhibitors.[13] Similarly, norstatine **F**, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid, constituting one of the amino acids of KRI-1230, a human renin inhibitor peptide, has also attracted a great deal of attention, with many efforts to prepare modified peptides with improved properties as drugs.[14,15]. For example, norstatine is part of amastatin, an inhibitor of leucine aminopeptidase.[16] A modified norstatine such as (2*S*,3*R*)-phenylnorstatine [(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid] is contained in two tripeptides, the kynostatins (KNI)-227 and (KNI)-272 which are highly potent HIV-1 protease inhibitors (Figure 1).[17]

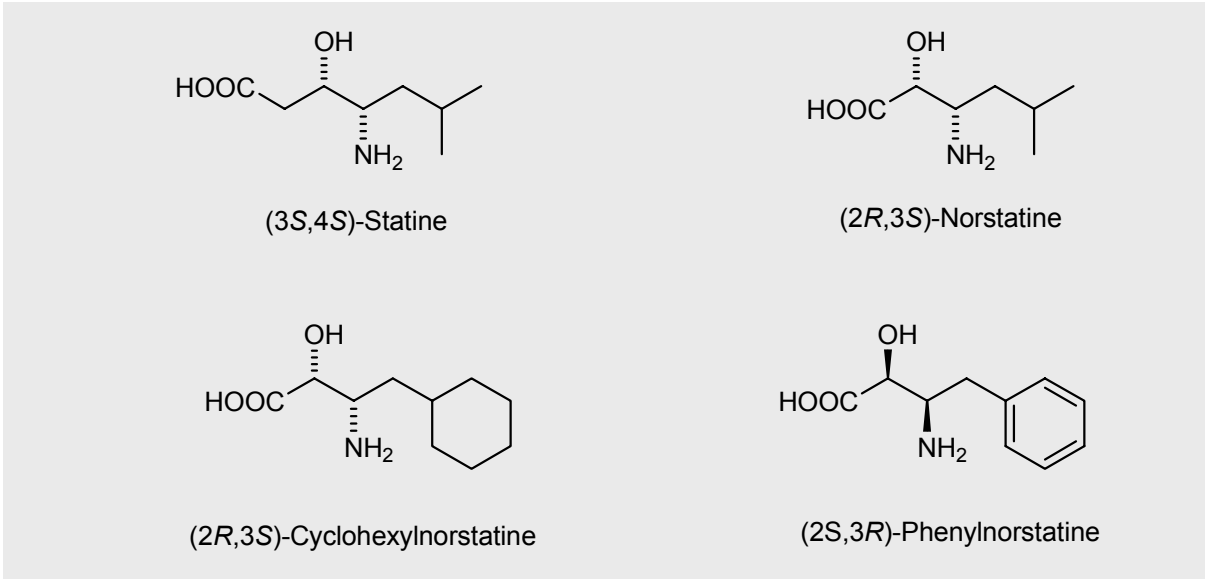
Figure 1. Structures of (KNI)-227 and (KNI)-272



(KNI)-227, R = Me
(KNI)-272, R = H

Isonorstatine **G** [(2*R*,3*S*,4*S*)-3-amino-2-hydroxy-4-methylhexanoic acid] and other analogues of cyclohexylnorstatine have been used as the terminal amino acid part of such a renin inhibitor, KRI-1314 (Figure 2).[18,19]

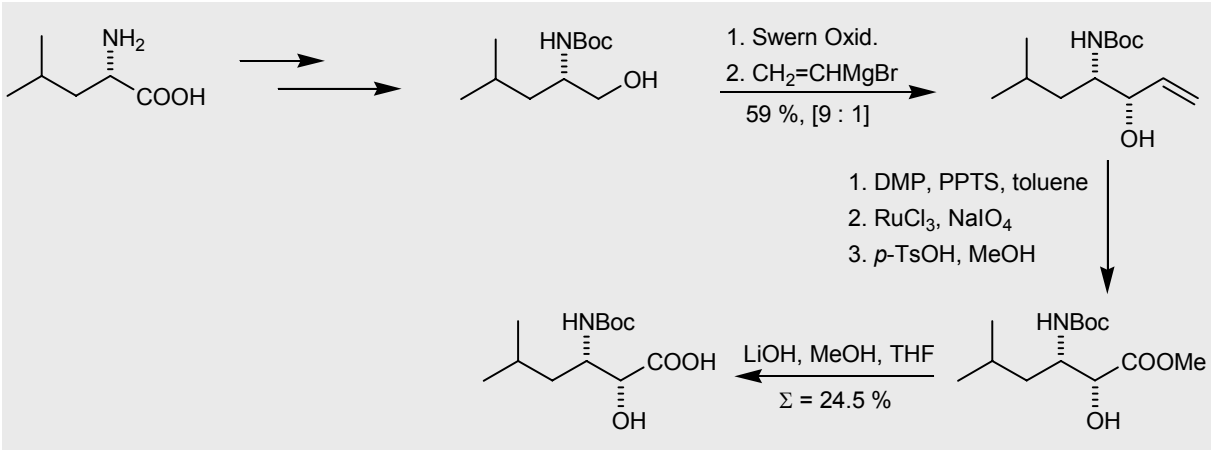
Figure 2. Members of the statine family



Due to the importance of this type of amino acids, a great number of methods has already been developed for the synthesis of norstatine,[14, 20, 21, 22] cyclohexylnorstatine,[23, 24] and phenylnorstatine.[17,25]

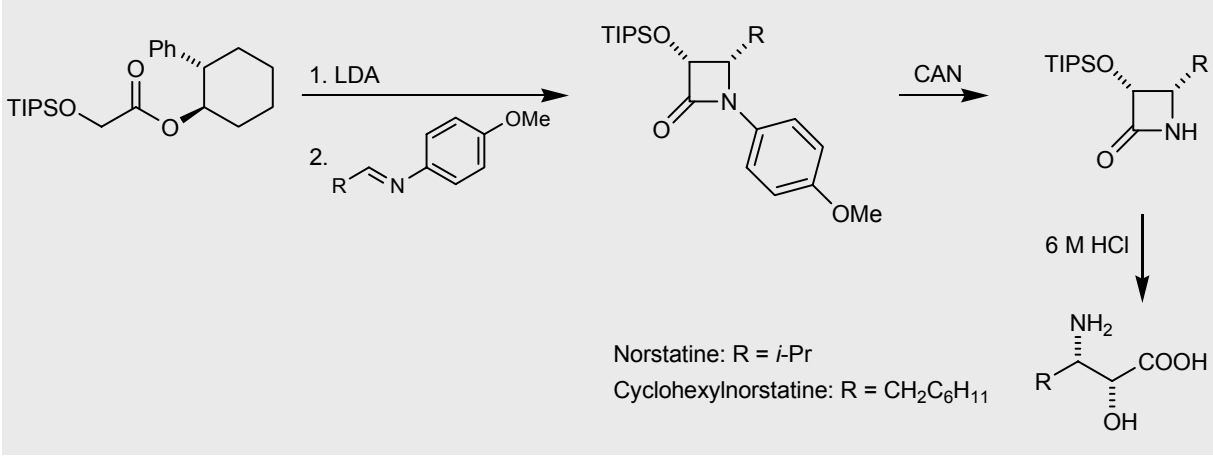
Datta and Veeresha[14] stereoselectively synthesized (2*R*,3*S*)-*N*-Boc-norstatine starting from L-leucine. The synthesis was based on the chelation-controlled reaction of *N*-Boc-valinal with vinylmagnesium bromide inducing a high level of *syn* selectivity (Scheme 1).

Scheme 1. Synthesis of (2*R*,3*S*)-*N*-Boc-norstatine[14]



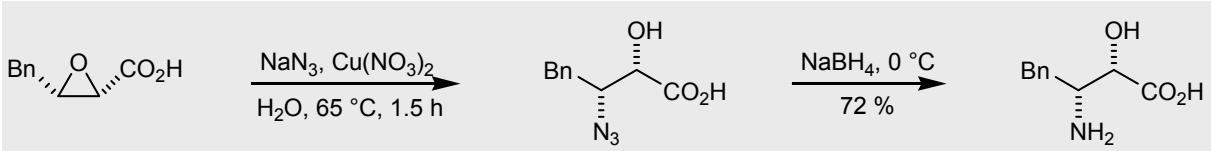
The Ojima[20] group has been applying the "*β-Lactam Synthon Method*" to the asymmetric synthesis of various non-protein amino acids. This method was employed for the asymmetric synthesis of norstatine and its analogues. The synthesis is detailed in Scheme 2.

Scheme 2. Synthesis of (2*R*,3*S*)-norstatine and cyclohexylnorstatine[20a]



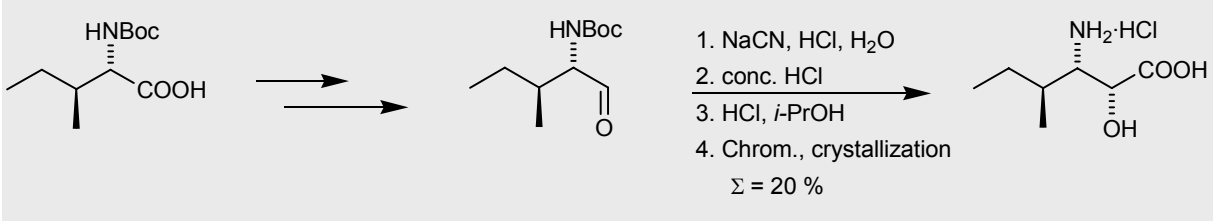
(2*S*,3*R*)-Phenylnorstatine[17b] was synthesized using a one-pot copper-catalyzed nucleophilic ring opening of an appropriate epoxide. Metal salts such as $Cu(NO_3)_2$ or $InCl_3$, once believed to be not usable in water, were shown to be efficient catalysts for highly β-regio- and *anti*-stereoselective azidolysis of α,β-epoxycarboxylic acids in aqueous medium (Scheme 3).[26]

Scheme 3. Synthesis of (2*S*,3*R*)-phenylnorstatine[17b]



The synthesis of (2*R*,3*S*,4*S*)-isonorstatine isopropyl ester by Kiso *et al.*[18] was based on (2*S*,3*S*)-isoleucine, using a less selective cyanide addition to leucinal. (2*R*,3*S*,4*S*)-Isonorstatine was finally obtained by separation of a diastereomeric mixture with no details given on intermediates nor yields (Scheme 4).

Scheme 4. Synthesis (2*R*,3*S*,4*S*)-isonorstatine isopropyl ester[18]



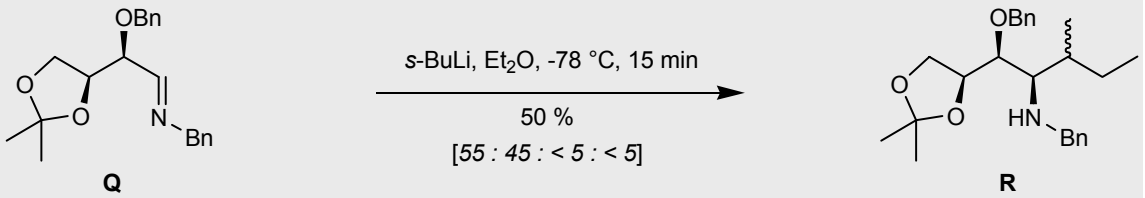
2.2 Results and discussion

2.2.1 Addition to *L*-threose-derivated imine

In our group, several approaches to variously substituted 1,2-amino alcohols have been developed, such as diastereoselective nitroaldol additions of a series of chiral aldehydes and nitro compounds. [27] In a complementary way, highly stereoselective additions to α-alkoxyimines [28] have provided efficient and versatile access to aminopolyols, [29] 1,4-iminopolyol derivatives such as anisomycin,[30] and to the statine family.[31]

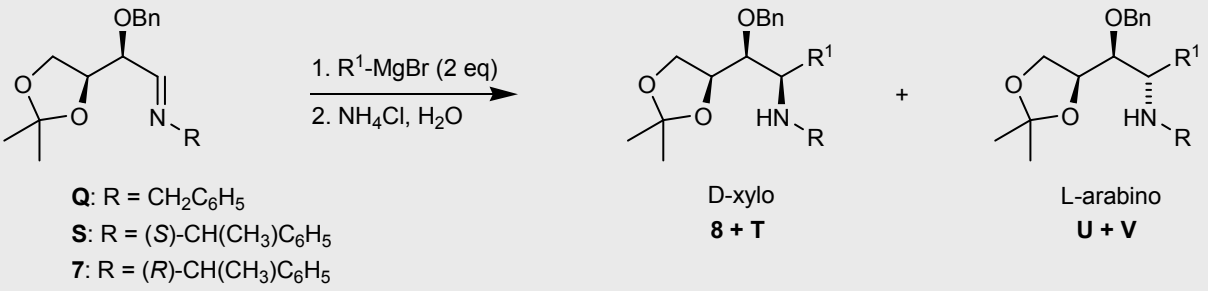
The additions of Grignard and lithium reagents to the C=N bond of the *N*,*O*-dibenzylthreose derivative **Q**[27a,30,32,33,34,35] have been found to proceed with high 3,4-*threo* selectivity.[30,32,33,35] We were then attracted by the question if an α-branched alkyl-chain introducing a new vicinal stereocentre could be connected likewise. Indeed, the addition of *sec*-butyllithium proved highly *threo*-selective concerning C-3/C-4, however, both C-5 diastereomers **R** were formed non-selectively (Eq. 1).[33a]

(1)



In order to overcome this non-selectivity, we then examined allyl additions[28,36] to the imine **Q** in different solvent and to the auxiliary-adorned *N*-(1-phenylethyl)imines **S** [*N*-(*S*)] and **7** [*N*-(*R*)].[29b,31,33,35,36] with the results gathered in Table 1.

Table 1. Addition of Grignard reagents to imine



Q: R = $CH_2C_6H_5$
S: R = (*S*)-$CH(CH_3)C_6H_5$
7: R = (*R*)-$CH(CH_3)C_6H_5$

D-xylo
8 + T

L-arabino
U + V

Entry	Imine	R^1	Solvent	Product	dr[a] [(D-*xylo*):(L-*arabino*)]	Yield[b] [%]
1	**Q**	3-Butenyl/Crotyl[c]	Et_2O	**8a,Ta/Ua**	(42:51) : (7:<5)	79
2	**S**	3-Butenyl/Crotyl[c]	Et_2O	**8b,Tb**/-	(42:58) : (<5:<5)	77
3	**7**	3-Butenyl/Crotyl[c]	Et_2O	**8c,Tc/Uc**	(57:18) : (25: 5)	82
4	**Q**	3-Butenyl/Crotyl[c]	THF	**8a,Ta/Ua**	(67:28) : (5:<5)	71
5	**S**	3-Butenyl/Crotyl[c]	THF	**8b,Tb**/ -	(92:8) : (<5:<5)	81
6	**7**	3-Butenyl/Crotyl[c]	THF	**8c**	(>95:<5) : (<5:<5)	85[33b]

a Diastereomeric ratio (dr) from ^{13}C NMR analyses of crude addition products.
b Yield based on imine, after chromatography on basic alumina.
c Reagent prepared from crotyl bromide.

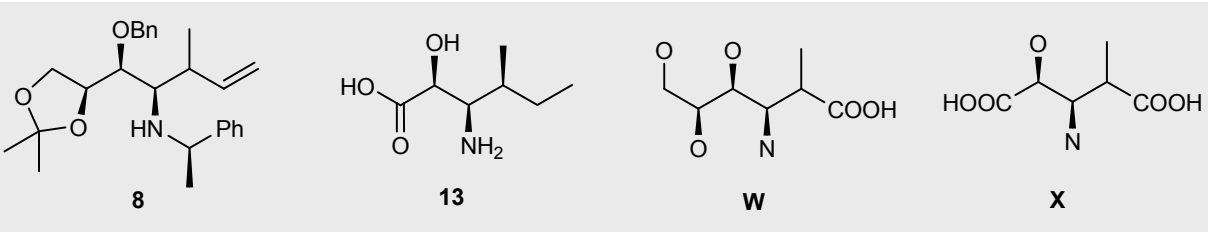
In view of the intended 2-butyl group to be added, the results with the crotyl/3-butenyl Grignard derivative were of particular relevance. The first tests run in ether paralleled those with *sec*-butyl (*vide supra*) though (entries 1-3 in Table 1); the best result obtained with the (*S*)-imine **S** consisted of a mixture of 5-epimers of the *xylo* compounds **8b**/**Tb** only. With the (*R*)-imine **7** a third diastereomer **Uc** was formed. The latter was assigned the L-*arabino* configuration, based on $J_{3,4}$ = 5.2 Hz. The coupling constant $J_{3,4}$ had proved diagnostic with all simpler addition products from **Q** earlier, with the D-*xylo*-aminotriol derivatives consistently showing a small value $J_{3,4}$ = 1.4 to 1.8 Hz. Similar values of ca. 1.2 Hz were found with all the diastereomers designated as D-*xylo* (3,4-*threo*) which are described here.[30,33]

A dramatic, unexpected improvement was found when the solvent ether was substituted by tetrahydrofuran[33b]. With the "parent" imine **Q** one of the D-*xylo* **8a**/**Ta** isomers was favoured by 67 : 28; this rose to 92 : 8 with the (*S*)-imine **S** and, gratefully, to >95 : 5 for **8c** with the (*R*)-imine **7**, where none of the other three diastereomers could be detected by NMR analyses of the crude reaction product!

Consequently, the initial objective of finding access to methyl-branched amino hydroxy acids

of the isonorstatine – which had failed with direct *sec*-butyl addition – could now be reconsidered, and extended: The amino-heptenetriol **8** constitutes an advanced intermediate with orthogonally structured termini in view of further transformations to carboxy groups.[37] Either end would be amenable to regioselective oxidative degradation, eventually leading to β-amino-α-hydroxy-γ-methyl acids (isonorstatine) **13**, to β-amino-γ-hydroxy-α-methyl acids **W**, or to β-amino-α-hydroxy-γ-methyl diacids **X** (Figure 3).

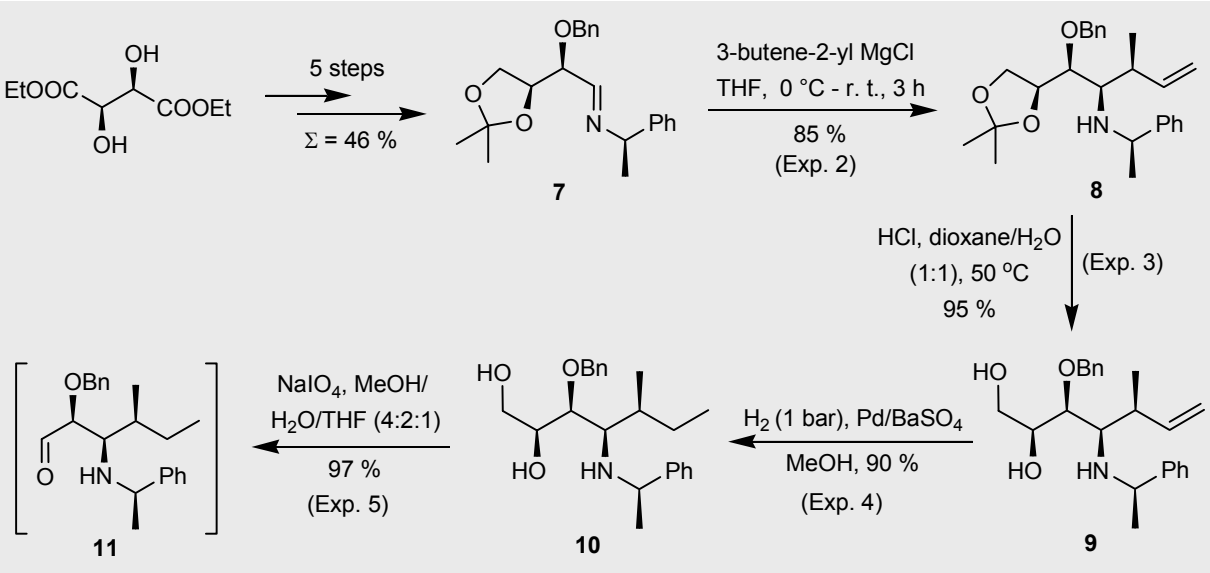
Figure 3



2.2.2 Synthesis of (2*S*,3*R*,4*S*)-isonorstatine (13)

With the key intermediate **8c** in hand, the synthesis of isonorstatine **13** was accomplished in a straightforward manner. The aminotriol **9** was obtained pure and in high yield by hydrolysis of the acetal group under acidic conditions. The olefinic double bond was then saturated by catalytic hydrogenation (H_2, 1 bar, 5 % $Pd/BaSO_4$) at room temperature in good yield without loss of the benzyl-protecting group. Next, the free diol **10** was cleaved by means of sodium periodate to give the aldehyde **11** which was oxidized to the carboxylic acid **12** with sodium chlorite.[38, 39] Finally, the *N*,*O*-protected amino acid **12** on catalytic hydrogenation was converted into free, analytically pure isonorstatine **13** in 93 % yield (Scheme 5).

Scheme 5. Synthesis of (2*S*,3*R*,4*S*)-isonorstatine **13**[*]



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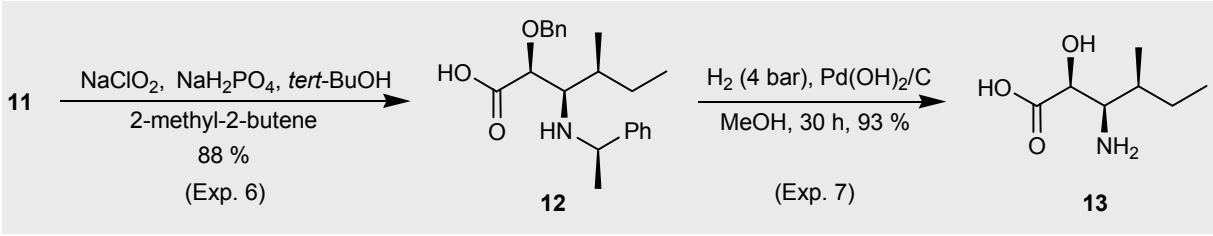
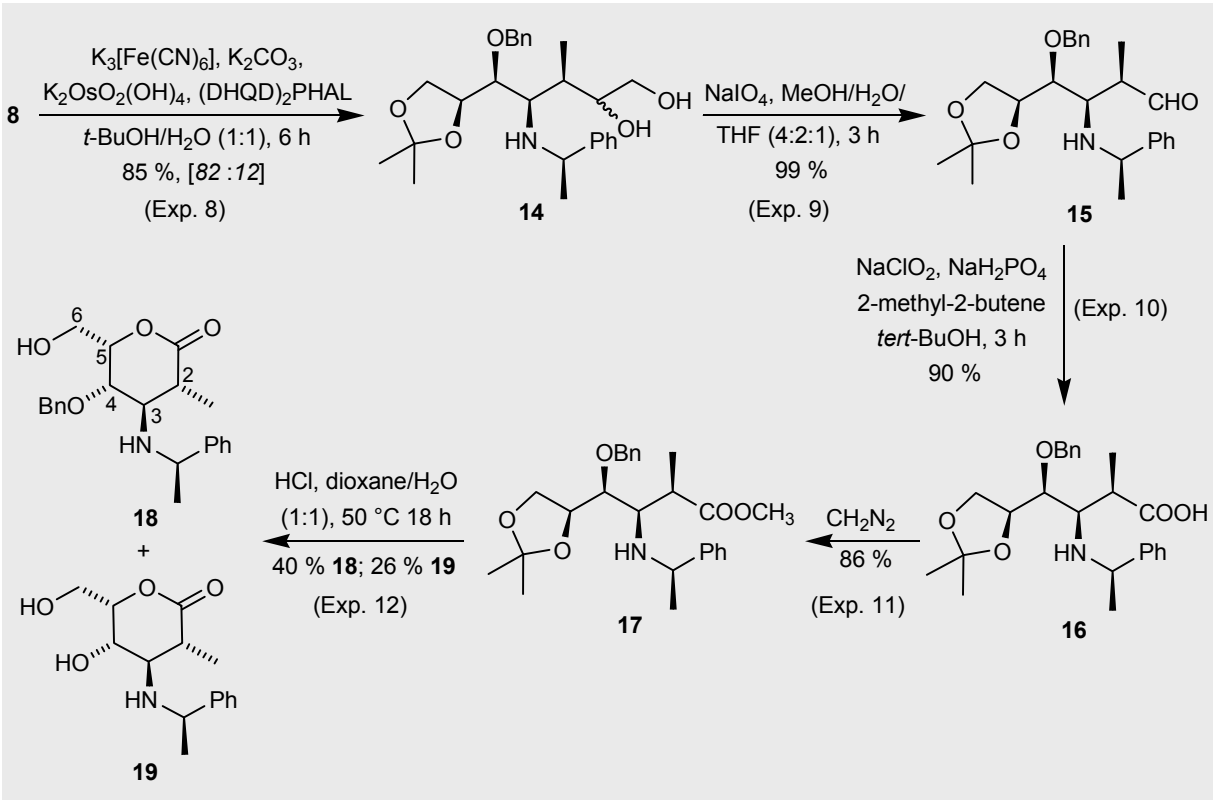


** For assignment of configuration at C-5 in **8** (C-4 in **13**) vide infra.*

2.2.3 Assignment of configuration at C-5 in 8

A remaining problem, however, concerned the configuration at the methyl-bearing stereocentre which had to be elucidated. We then turned to the elaboration of the olefinic terminus, with both objectives in mind – assignment of the configuration at C-5 in **8** (C-4 in **13**), combined with finding access to the second type of C-methyl-branched β-amino acids **W** –. Dihydroxylation of the key intermediate **8** according to Sharpless' procedure[40] provided the 6,7-diol **14**. The diol **14** was cleaved by means of sodium periodate to furnish the aldehyde **15** which was directly oxidized to the acid **16**. On treatment of the latter with excess diazomethane the corresponding ester **17** was isolated.

Scheme 6. Assignment of configuration at C-5 in **8**



Hydrolysis of the acetonide ester **17** was now expected to lead to a δ-lactone, with the methyl group positioned within the ring which should permit to establish its orientation. Indeed, on acid-mediated hydrolysis the ester and the acetal group were cleaved, but this was accompanied by partial loss of the *O*-benzyl group. Anyway, the lactones **18** and **19** were readily separable by flash column chromatography leading to the analytically pure γ-benzyloxy-δ-lactone **18** and to the γ-hydroxy-δ-lactone **19** (Scheme 6). The lactone **18** now permitted to determine the configuration at C-2, since the proton signals appeared well separated in the ^{1}H NMR spectrum. From this, coupling constants $J_{2,3}$ = 0.7, $J_{3,4}$ = "0", and $J_{4,5}$ = 1.1 Hz were derived. This information was complemented by NOE (nuclear Overhauser effect) measurements which showed enhancement concerning 2-CH_3/3-H and 2-H/5-H (Figure 5). Aside from this evidence, the 3D model of **18** was simulated by means of ChemDraw software. The torsional angles between 2-H and 3-H, 3-H/4-H, 4-H/5-H were computed by this program as 82° (ca. 90°), 71° and 57.5° respectively. These coupling constants observed are in accordance with the torsional angles according to the Karplus curve (see Table 2, a slight deviation for 4-H/5-H probably attributes to the model whose protecting groups are removed). The corresponding diastereoisomer **18a** was simulated as well; the torsional angles between 2-H and 3-H, 3-H/4-H, 4-H/5-H were 50°, 66° and 58° respectively.

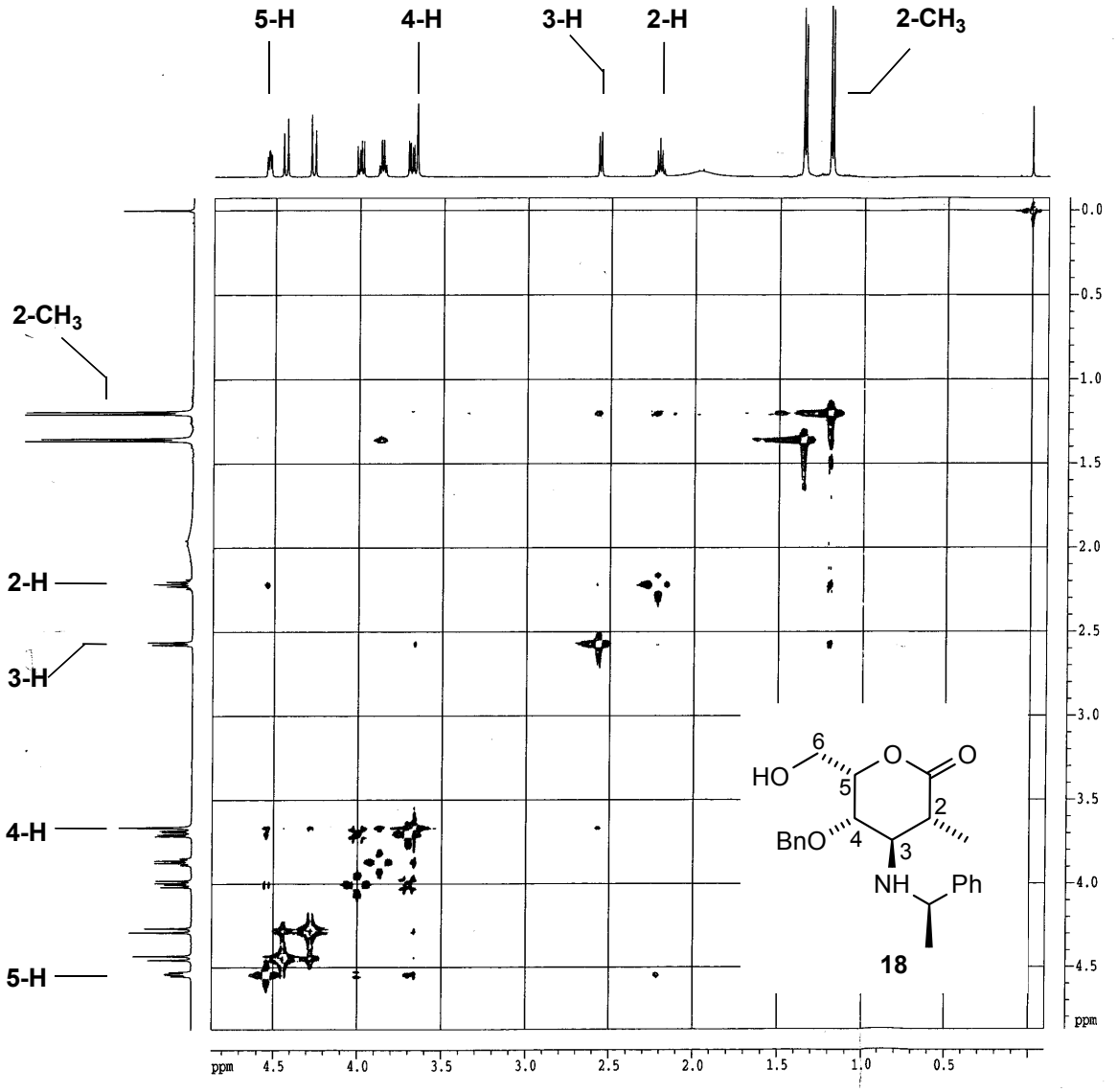
Figure 4. 3D-model of **18** (protecting groups removed)

18 **18a**

Table 2

Experimental value			Modelling value		
Coupling constants [Hz]		Torsional angel by Karplus curve [°]	Torsonal angle [°]		Coupling constants [Hz] by Karplus curve
$J_{2,3}$	0.7	75	2H/3H	82	0.5
$J_{3,4}$	0	90	3H/4H	71	1.1
$J_{4,5}$	1.1	71	4H/5H	57.5	2.4

Figure 5. The NOESY of the δ-lactone **18**



In NOE spectroscopy, the cross peaks signals arise from protons which are close in space. In the NOESY of the γ-lactone **18**, 3-H/2-CH_3 and 2-H/5-H show the strong correlations. It follows that 3-H and 2-CH_3 is close to each other in space; so is 2-H and 5-H.

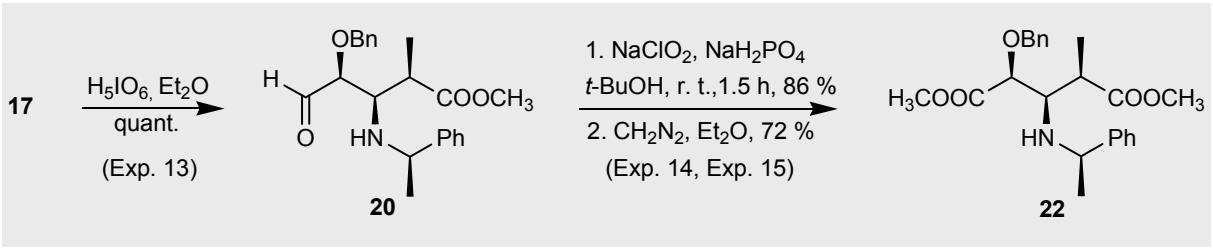
In summary, the 2-methyl and the 3-amino group are situated *trans*, as are 3-amino/5-CH_2OH; for 4-BnO/5-CH_2OH the *cis*-arrangement as present in the starting material L-threose was confirmed.

2.2.4 Synthesis of *N*,*O*-protected β-amino-γ-methyl-α-hydroxy-glutarate (22)

Access to an amino-hydroxy-methyl diacid (type **X** in Figure 3) remained to be demonstrated, by twofold oxidative conversion of the diol-acetonide and the olefinic double bond into carboxyl groups, as had been effected individually with the approaches to **13** and **W**,

respectively. To this purpose, the ester **17** with the acetal-protected 5,6-diol was treated with orthoperiodic acid which caused both diol deprotection and cleavage. The resulting aldehyde **20** without purification was oxidized with sodium chlorite as above to afford the glutaric acid monoester which with diazomethane was transformed into the dimethyl ester of the **22** (Scheme 7). The synthesis of such β-amino-α-hydroxy-diacids may be useful as an oligopeptide constituent, as present in the pseudomycins, a class of antifungal cyclic depsinonapeptides.[41]

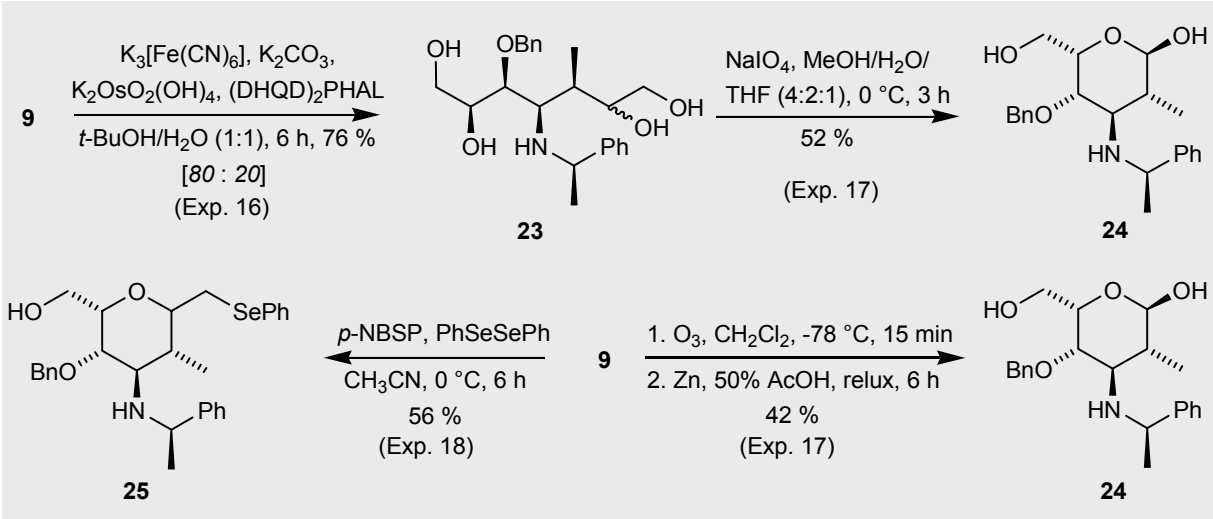
Scheme 7. Synthesis of the diester **22**[39e]



2.2.5 Synthesis of cyclic derivatives from the diol 9

The free diol **9** is a very flexible intermediate which could be transformed to relevant cyclic compounds by means of elaboration of the double bond. Ring-closure initiated by peroxydisulfate oxidation of diphenyl diselenide allowed access to the substituted 2*H*-pyran **25** (Scheme 8). Thus, the diol **9** was treated with *p*-nitrobenzenesulfonyl peroxide (*p*-NBSP) and diphenyl diselenide in CH_3CN to give the 2*H*-pyran **25** as a single diastereoimer in moderate yield (56 %).[42]

Scheme 8. Synthesis of cyclic derivatives of the diol **9**



On the other hand, the cyclic hemiacetal **24** was obtained on treatment of the terminal olefin **9** with ozone, followed by work-up with zinc in acetic acid (Scheme 8).[43] Moreover, the tetraol **23** derived from **9** by dihydroxylation was oxidized with various equivalents (4.0 eq or 6.0 eq) sodium periodate to provide the hemiacetal **24** (α : β = 90 : 10); the dialdehydes expected were not observed. The reason explain to this result may be that formation of the hemiacetal is much faster than further oxidation of second diol unit. Interestingly, the two different pathways produced the same product **24** whose structure and configuration was secured by spectroscopic data.

The hemiacetal **24** resembles a six-membered ring sugar. Thus, the property of the anomeric hydrogen atom is similar to the one in sugar. In six-membered ring sugar, the coupling constants of the anomeric hydrogen in α-form is small, *ca.* 3 Hz; the coupling constants in β-form is larger, *ca.* 8 Hz. Finally, the configuration of C-1 in the hemiacetal **24** was assigned as α-anomer form relying on the coupling constant (”0” Hz) of its anomeric proton.

2.3 Conclusion

In conclusion, a new route to methyl-branched β-amino-hydroxy acids of types **W**, **X** has been outlined, based on the highly stereoselective reaction of 3-butenyl Grignard with the threose-derived imine **7**. In particular, (2*S*,3*R*,4*S*)-isonorstatine **13** was obtained via the threose-derived imine **7** from diethyl L-tartrate in 11 steps with 25 % overall yield. Furthermore, the configuration at C-4 in the isonorstatine **13** was ascertained through NOE measurements of the cyclic derivative **18**, a δ-lactone.

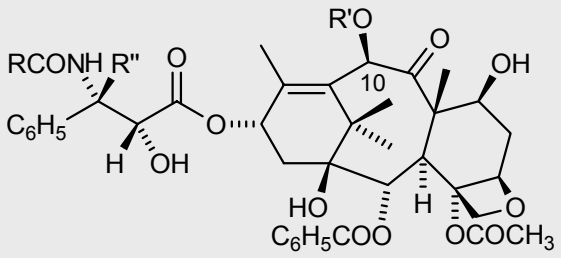
3. Synthesis of Phenylisothreonine

3.1 Background

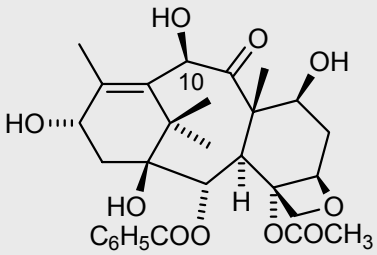
Taxol **Y**,[44] (Figure 6) isolated from the bark of the pacific yew *Taxus brevifolia*, is considered one of the most promising anticancer drug and has been approved for treatment of metastatic ovarian and breast cancer.[45] Structure-activity relationship studies have revealed that the *N*-benzoyl-3-phenylisoserine side chain of the taxol is essential for the antitumor activity of taxol.[46] Fortunately, the naturally derived 10-deacetylbaccatin III **AA** is readily available in relatively high yield from the needles of the European yew *T. Baccata* (1 g/1 kg).[44,45]

With the availability of 10-deacetylbaccatin III **AA**, many efforts have focused on semi-synthesis of taxol by condensation of **AA** with a side-chain such as *N*-benzoyl-(2*R*,3*S*)-phenylisoserine **I**. Therefore, over the last 20 years, the efficient syntheses of enantiopure side-chain **I** and its analogues have attracted much attention from the academic community as well as from industry.[29b,47,48,49,50,51,52]

Figure 6. Structures of taxol and anologues



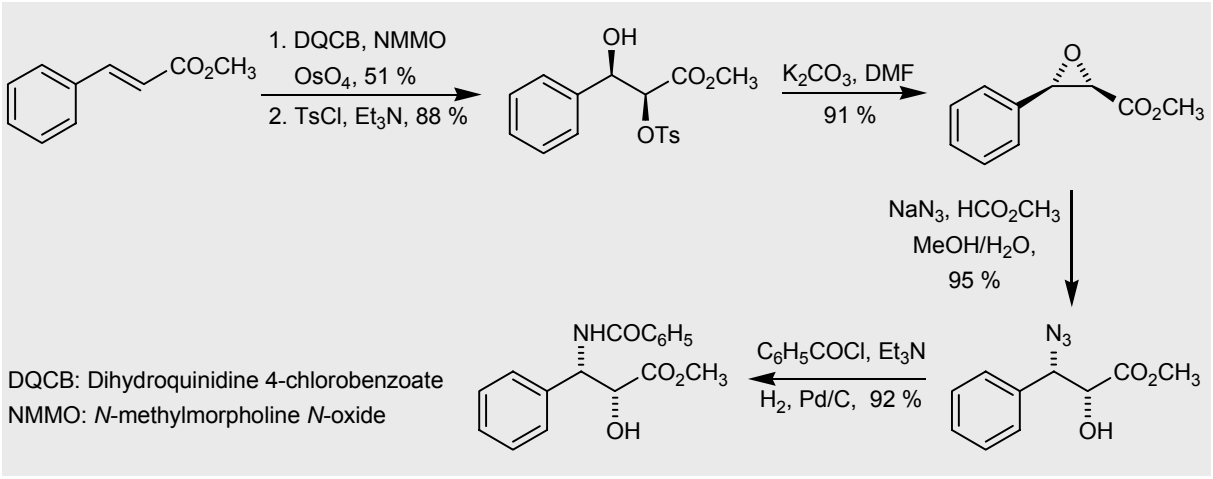
Y: R = C_6H_5; R' = CH_3CO; R'' = H (Taxol)
Z: R = $(CH_3)_3CO$; R' = H; R'' = CH_3 (Methyl taxotere)



AA:10-Deacetylbaccatin III

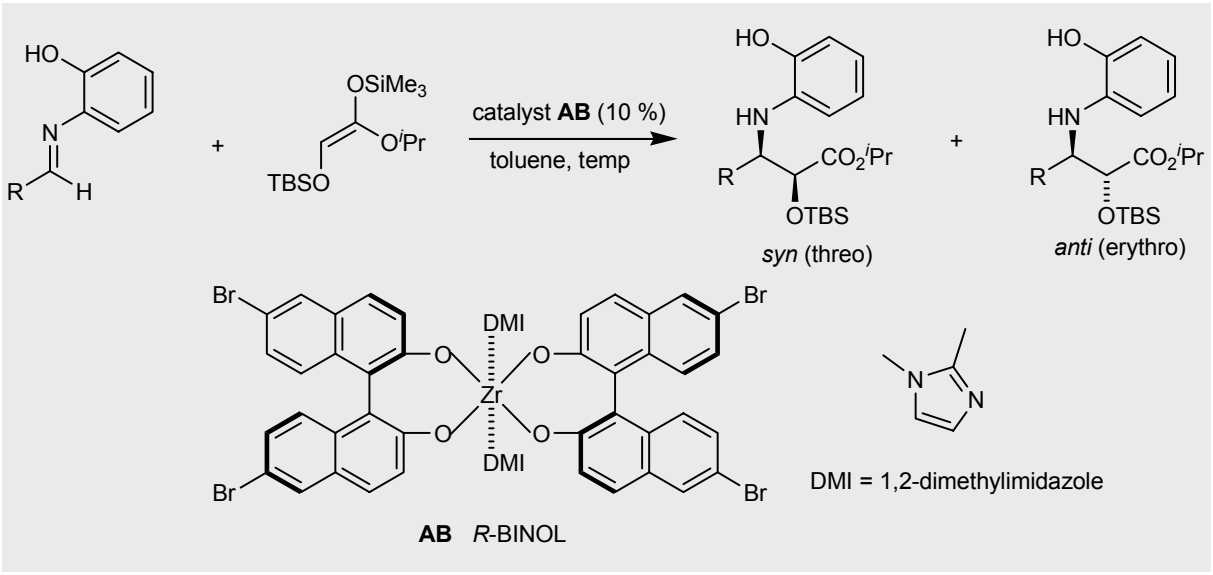
Greene and coworker[52f] synthesized phenylisoserine using the Sharpless asymmetric dihydroxylation of inexpensive methyl cinnamate, followed by monotosylation in the presence of triethylamine. Treatment of the hydroxy tosylate with potassium carbonate afforded the corresponding epoxide which underwent selective ring-opening with sodium azide to give a hydroxy azide. One-pot catalytic hydrogenation and then benzoylation directly provided the methyl ester of phenylisoserine. The synthesis is illustrated in Scheme 9.

Scheme 9. Synthesis of (2*R*,3*S*)-phenylisoserine methyl ester[52f]



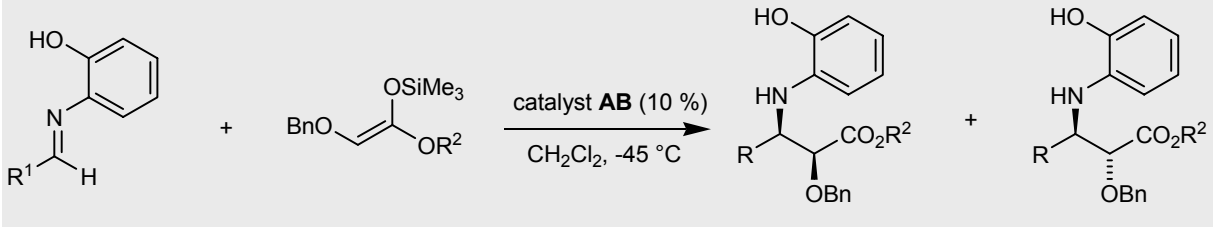
Kobayashi and his group[48h] described a flexible approach for the synthesis of chiral β-amino alcohols depending on catalytic diastero- and enantioselective Mannich-type reactions of α-alkoxy enolates with aldimines. The advantage of this method is that both *syn*- and *anti*-β-amino acids could be obtained in high selectivity by simply choosing the protective groups of the alkoxy and of the ester part of the enolates (Table 3 and Table 4).

Table 3. Synthesis of the *syn*-amino hydroxy ester unit[48h]



R	Temp [°C]	Yield [%]	*syn*/*anti*	ee [%] (*syn*)
Ph	-78	quant	96/4	95
1-naphthyl	-78	65	>99/1	91
2-furyl	-45	68	82/18	92
4-ClPh	-78	73	92/8	98

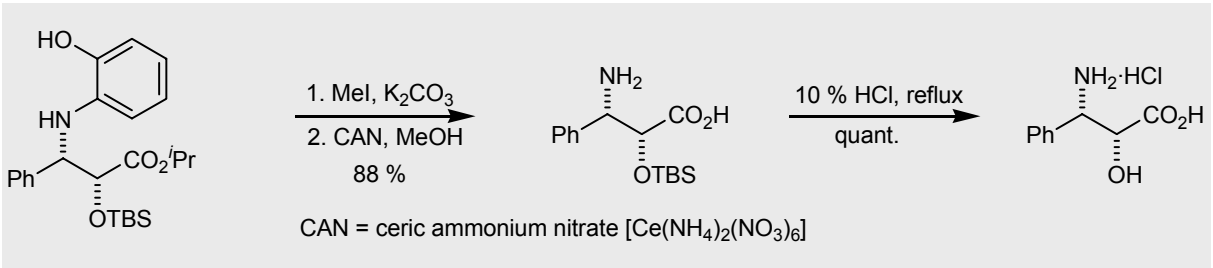
Table 4. Synthesis of the *anti*-amino alcohol unit



R^1	R^2	yield [%]	*syn*/*anti*	ee [%] (*anti*)
Ph	PMB	91	6/94	80
1-naphthyl	*c*-C_6H_{11}	80	8/92	96
4-ClPh	PMB	72	8/92	76

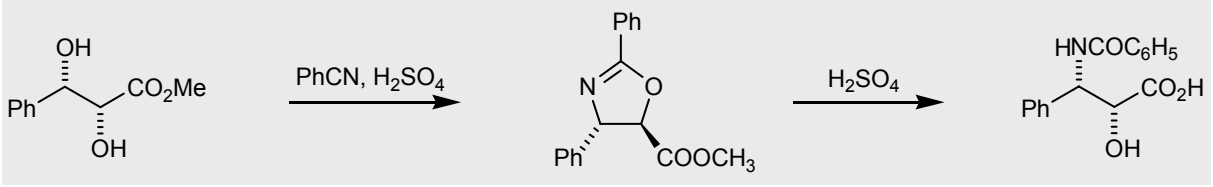
The synthesis of (2*R*,3*S*)-phenylisoserine was achieved using this method with the *S*-BINOL zirconium complex serving as the catalyst. The synthetic sequence is outlined in Scheme 10. Methylation of the phenolic hydroxyl group of the adduct and oxidative *N*-dearylation using cerium ammonium nitrate (CAN) gave α-amino ester. Hydrolysis of the ester and deprotection of the *tert*-butyldimethylsilyl (TBS) group were performed using 10 % HCl to afford (2*R*,3*S*)-phenylisoserine quantitatively.

Scheme 10. Synthesis of (2*R*,3*S*)-phenylisoserine hydrochloride



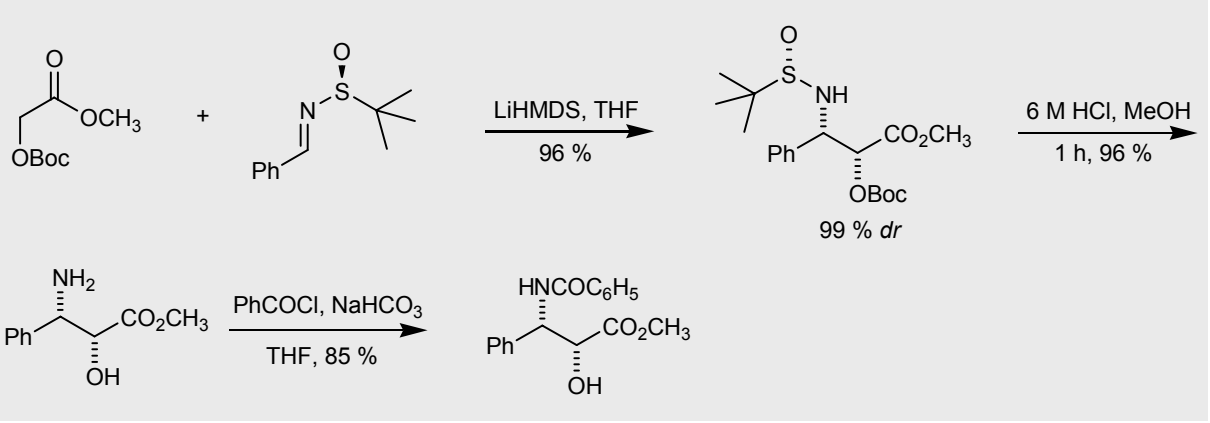
Voronkov *et al.*[47a] reported a simple one-step protocol for preparation of phenylisoserine from 2,3-dihydroxycinnamic acids or esters based on the Ritter reaction (Scheme 11).[53] Vicinal diols reacted with nitriles in the presence of an acid through oxazoline intermediates, which were treated by dilute acid at room temperature to effect opening of the oxazoline and hydrolysis while keeping the amide bond intact.

Scheme 11. One-pot synthesis of the side-chain of taxol[47a]



The latest synthesis of phenylisoserine was described by Qin's group,[7] using a lithium enolate addition of methyl *O*-Boc-α-hydroxyacetate to a chiral *N*-sulfinylimine (Scheme 12).

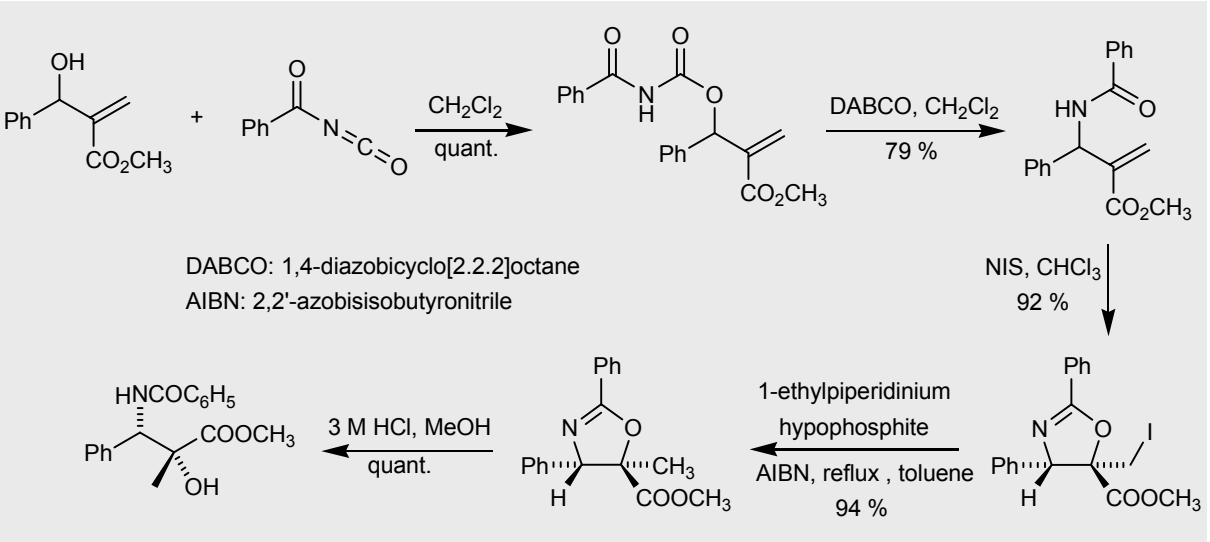
Scheme 12. Synthesis of (2*R*,3*S*)-*N*-benzoxy-phenylisoserine methyl ester[7]



In view of the large number of diverse syntheses of phenylisoserine and derivatives published to date, it is surprising that there were only two examples of branched phenylisoserines reported.[54]

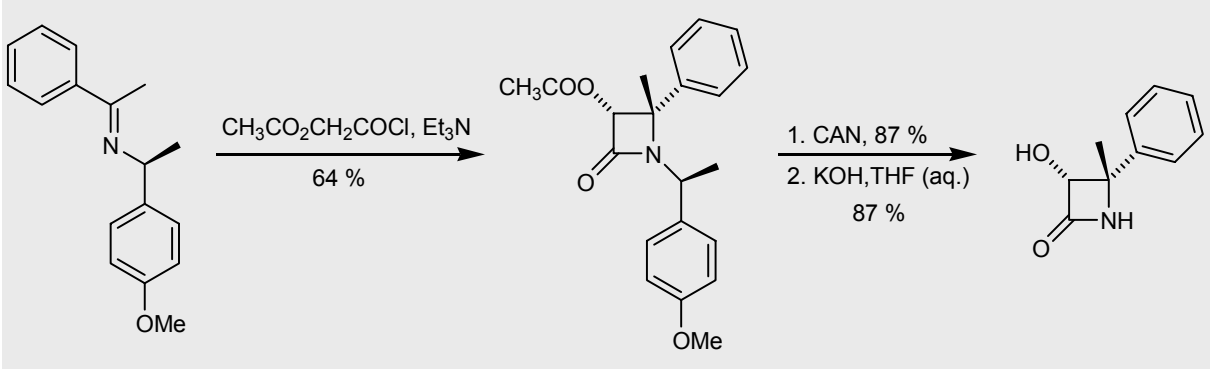
Galeazzi's group developed a convenient approach to branched phenylisoserines via stereoselective iodocyclization of amides obtained from Baylis-Hillman adducts. Finally, the phenylisoserine with a α-methyl was obtained (Scheme 13).

Scheme 13. Synthesis of branched phenylioserine[54b]



Greene and coworkers[54a] reported the first synthesis of methyl-branched phenylisoserine as a side-chain of taxol at C-3 via a β-lactam (Scheme 14).

Scheme 14. Synthesis of the methyl-branched phenylisoserine precursor[54a]

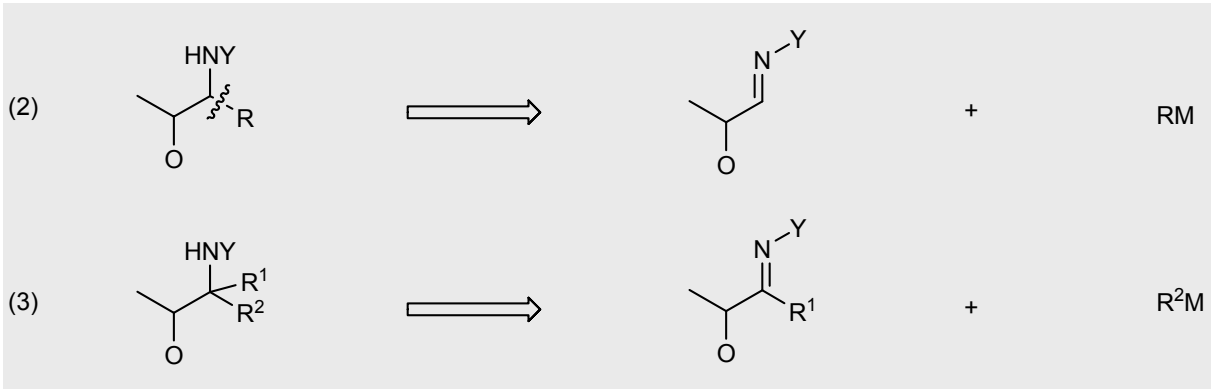


Due to the importance of this class of β-amino acids, a new approach was exploited by us for asymmetrical synthesis of branched phenylisoserine (phenylisothreonine **36**) which will be discussed later on.

3.2 Results and discussion

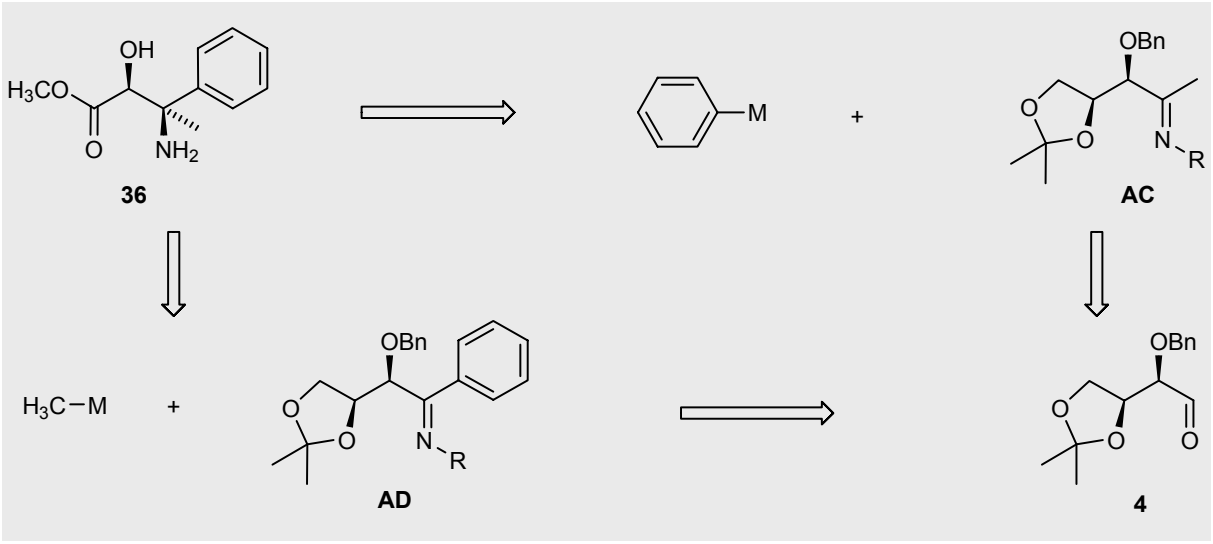
3.2.1 Attempts at C=N formation and Grignard additions

In our group, variously substituted 1,2-aminoalcohols had been prepared by several methods.[27a-d] Highly stereoselective additions to α-alkoxyimines or derivatives had provided efficient and versatile access to 1,2-aminoalcohols.[28] Addition of organometallic reagents to aldimines leads to amines which are attached to secondary carbon (see Eq. 2). In principle, amines attached to tertiary carbon could be obtained from ketimines or its derivatives by selective addition of organometallic reagents (Eq. 3).



The addition of Grignard and lithium reagents to the C=N double bond of the *N*,*O*-dibenzylthreose derivative **Q**[27a,30,32-35] had been found to proceed with high *threo* selectivity. Consequently, we wondered if (2*S*,3*R*)-phenylisothreonine **36** could be dealt with in this manner. The initial plan is outlined in Scheme 15.

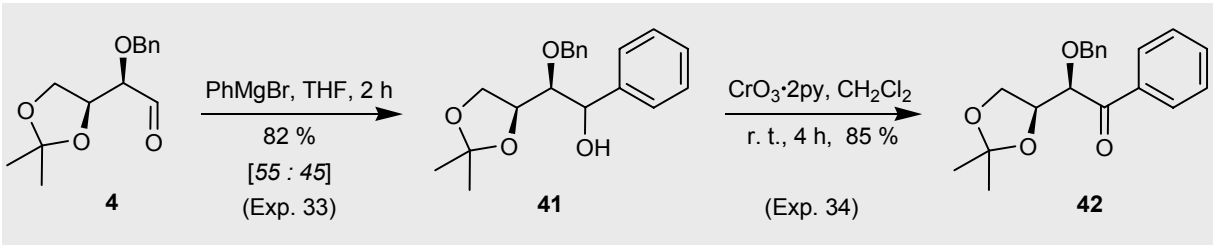
Scheme 15. Initial plan for the synthesis of (2*S*,3*R*)-phenylisothreonine **36**



Based on the analysis presented above, the C=N double bond formation is required for the synthesis of phenylisothreonine. Imine formation might be achieved by the following strategies: a) Condensation of a ketone with various sources of amine nitrogen such as benzylamine or *O*-benzyl hydroxylamine; b) oxidation of secondary amine or hydroxylamine.

For the former, the first task was the synthesis of the ketone **42** as a precursor of the **AD** type C=N species. The aldehyde **4** reacted with phenylmagnesium bromide in THF to give the alcohol **41** (*dr* = 55 : 45) which was oxidized by Collins reagent[32b] to provide the ketone **42** in 69 % overall yield (Scheme 16).

Scheme 16. Synthesis of **AD** type ketone **42**



With the ketone **42** at hand, the **AD** type ketimine formation[55] was tested under several conditions but all proved unsuccessful. Some of these results are listed in Table 5.

Table 5. Attempts at the synthesis of **AD** type imine

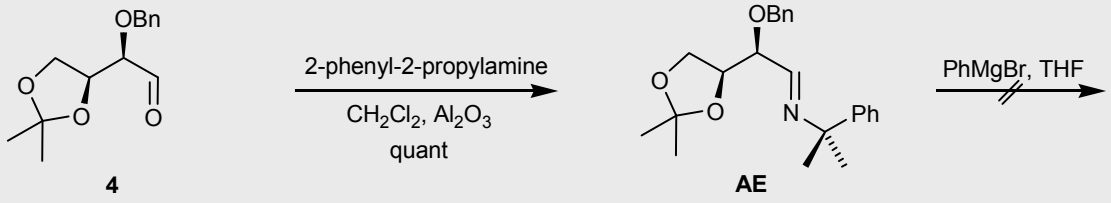
Entry	R	Conditions	Temp [°C]	Yield [%]
1	Bn	Al_2O_3, CH_2Cl_2	r. t.	0
2	Bn	Al_2O_3, CH_2Cl_2	40 °C	0
3[a]	Bn	$TiCl_4$, Et_3N, CH_2Cl_2	0 - r. t.	-
4[a]	(*R*)-$C_6H_5(CH_3)CH$	$TiCl_4$, Et_3N, CH_2Cl_2	0 - r. t.	-

a Starting material was not be detected in the ^{13}C NMR spectrum.

The crude product obtained according to entries 3 and 4 were directly used for the addition of methylmagnesium bromide, but no reaction occurred. Therefore, we shifted our attention to prepare the nitrone derivative. Treatment of the ketone **42** with benzylhydroxylamine in dichloromethane in the presence of magnesium sulfate, however, did not afford the expected product (even with Lewis acid zinc chloride as an additive, only a trace of amount of the nitrone was observed). This failure might result from the structure of the ketone, because the phenyl group could reduce its reactivity.

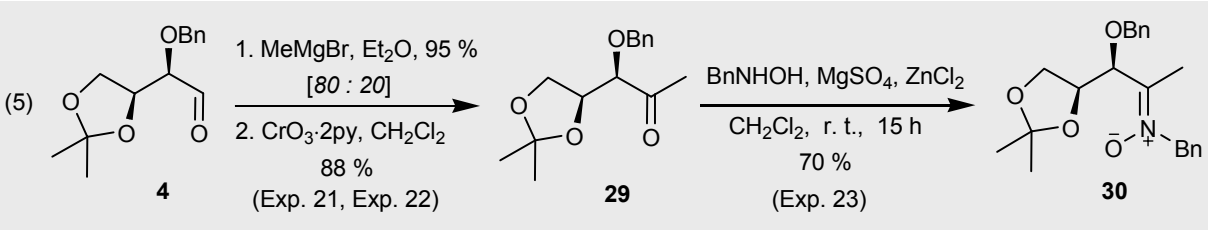
Our attention was then turned towards the oxidation of a respective intermediate secondary amine.[56] Secondary amines usually can be obtained by addition of organometallic reagents to aldimines as depicted in equation (4). The aldimine **AE** was prepared through condensation of the aldehyde **4** with 2-phenyl-2-propylamine in the presence of aluminium oxide[33] in quantitive yield. Unfortunately, the subsequent addition of this imine **AE** to phenylmagnesium bromide did not take place. In addition, the corresponding imine derived from tritylamine did not form. Thus, access to an intermediate with C=N double bond by oxidation of a secondary amine was not successful.

(4)

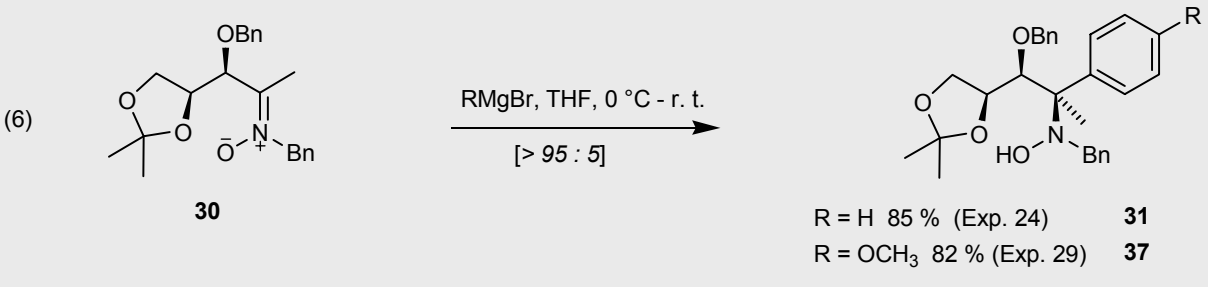


4 **AE**

Accordingly, formation of a **AC** type imine was considered. The ketone **29** was prepared in the same way described in Scheme 16. The aldehyde **4** reacted with methylmagnesium bromide to provide the corresponding alcohol (*dr* = 80 : 20); this was followed by oxidation leading to the ketone **29**. Treatment of the ketone **29** with benzylhydroxylamine in the presence of magnesium sulfate provided the expected nitrone **30** in 38 % yield after 2 days.[57] However, this yield could be improved dramatically to 70 % by addition of zinc chloride with shorter reaction time (Eq. 5); 20 % of the ketone **29** was recovered.



With the nitrone **30** at hand, the addition of Grignard reagents[58] was investigated. In order to synthesize phenylisothreonine, phenylmagnesium bromide and *p*-anisylmagnesium bromide were employed for test additions. Gratifyingly, the reactions proceeded smoothly in high yield with excellent diastereoselectivities (> 95 : 5) in both cases (Eq. 6), which allowed the synthesis of phenylisothreonine ester **36** in a straightforward manner.

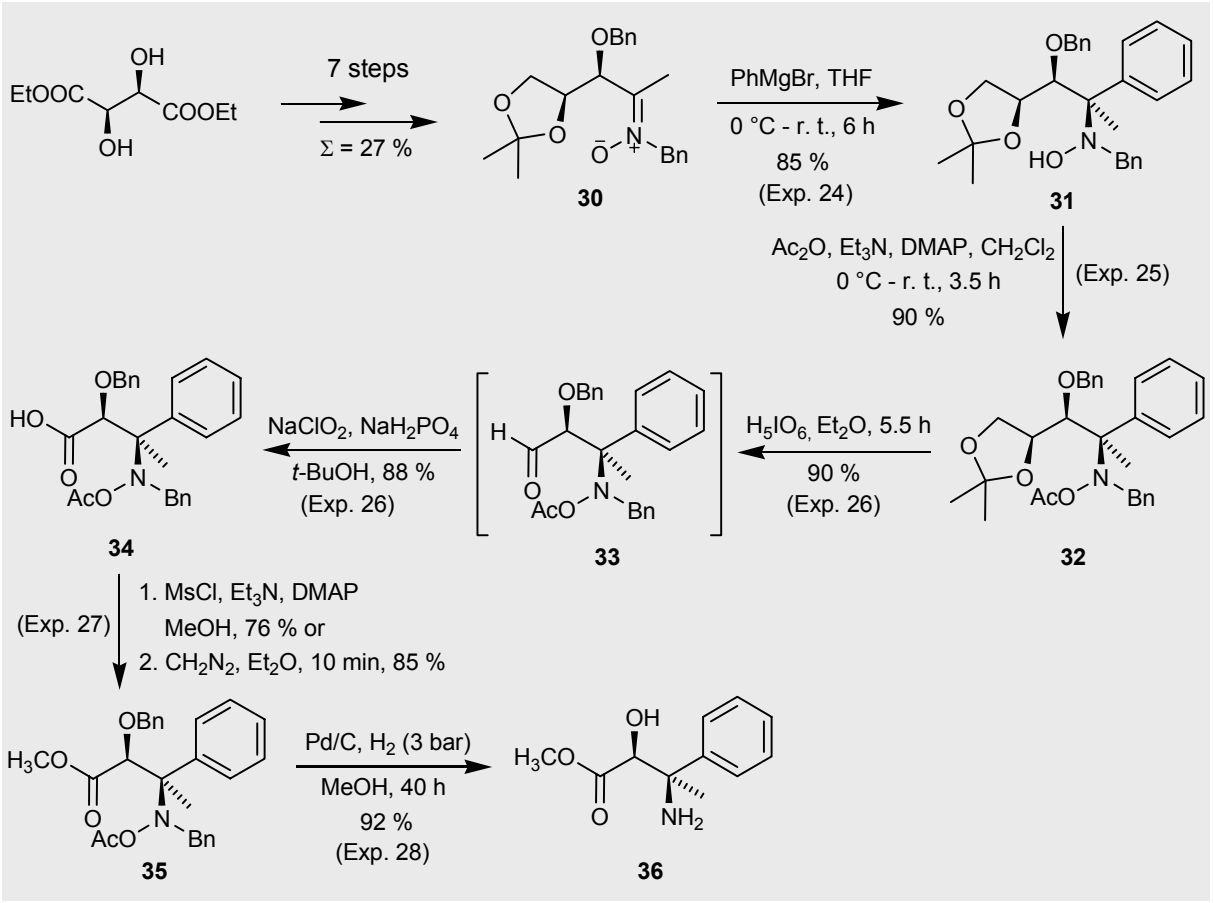


3.2.2 Synthesis of (2*S*,3*R*)-phenylisothreonine 36

The synthesis of (2S,3*R*)-phenyliosthreonine **36** commenced with the aldehyde **4** which was readily available from the L-diethyl tartrate in 4 steps [32b,33b]. The nitrone **30** was obtained from corresponding ketone **29** according to the method presented in equation (5). The stereoselective addition of phenylmagnesium bromide to the nitrone **30** furnished the key intermediate **31** as a single diastereoisomer. The substituted hydroxylamine **31**, with all elements of phenylisothreonine **36** needed, was elaborated to this target structure.

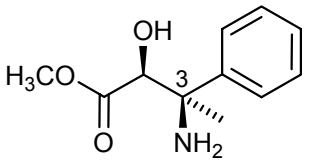
Attempts to carry out diol cleavage of **31** with the free *N*-hydroxy group proved unsuccessful leading to decomposition. The acetylated derivative **32**,[59] however, underwent oxidative cleavage in diethyl ether with periodic acid cleanly to give the intermediate aldehyde **33**[26b] which was then oxidised to the carboxylic acid **34** under standard conditions ($NaClO_2$). After esterification with diazomethane, the *N*,*O*-protected ester **35** was catalytically reduced to afford (2*R*,3*S*)-phenylisothreonine **36** as colourless crystals in high yield (Scheme 17).

Scheme 17. Synthesis of (2*S*,3*R*)-phenylisothreonine methyl ester **36**

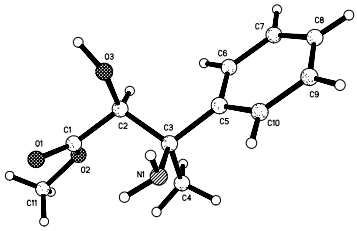


Unexpectedly, an attempted one-pot conversion of the aldehyde **33** into its methyl ester by bromine oxidation of the hemiacetal intermediate using Lichtenthaler's method failed.[60] The esterfication of acid **34** to **35** was accomplished by either treatment with diazomethane or mesylation followed by methanolysis.[61] Finally, the configuration at C-3 was established by X-ray diffraction analysis (Figure 7).

Figure 7. X-ray diffraction analysis of **36**



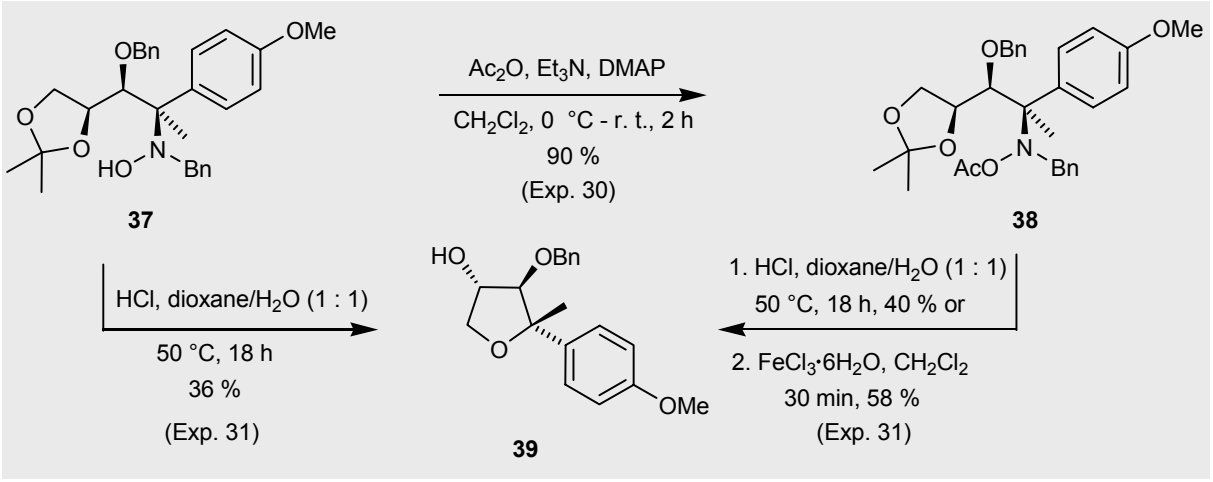
36



3.2.3 Synthesis of the substituted tetrahydrofuran 39

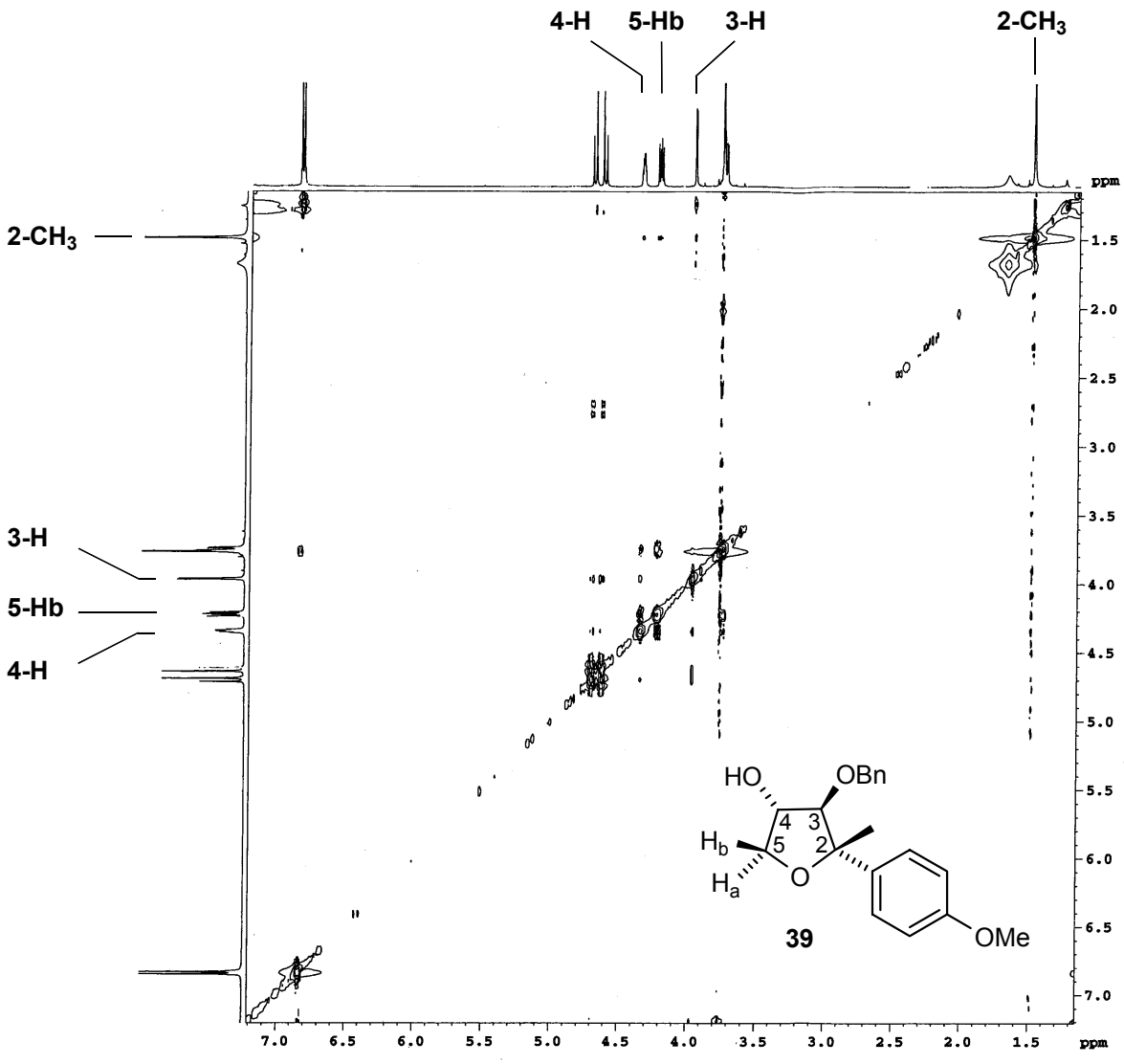
The hydroxylamine **37**, obtained by addition of *p*-anisylmagnesium bromide to the nitrone **30** was treated with acetic anhydride in the presence of triethylamine and DMAP to give the acetylated hydroxylamine **38**. To our disappointment, the hydroxylamine **38** when treated with periodic acid in diethyl ether gave rise to decomposition only. Efforts to get the free diol from the hydroxylamine **37** or from **38** by acidic hydrolysis or action of ferric chloride hexahydrate to deprotect the acetal, surprisingly provided the substituted tetrahydrofuran **39** in low yield. A plausible explanation is that the benzylhydroxylamine moiety under the acidic conditions formed an ammonium salt serving as a good leaving group, with the hydroxy group attacking the C-4 as a nucleophile, leading to cyclization to furnish the tetrahydrofuran **39** (Scheme 18).

Scheme 18. Synthesis of the substituted tetrahydrofuran **39**



The configuration at C-2 in the substituted tetrahydrofuran **39** was established by NOE measurements which indicated enhancement concerning 2-CH_3/4-H, 2-CH_3/5-H_b and 4-H/5-H_b (Figure 8). The cross peak arising from 4-H and 2-CH_3 reveals that 4-H and 2-CH_3 are close in space. Therefore, the 2-methyl and the 3-OBn are situated *cis*, as are 3-BnO/4-OH (the 1,2-*syn*-arrangement present in the starting material L-threose).

Figure 8. NOESY of the substituted tetrahydrofuran **39**



3.3 Conclusion

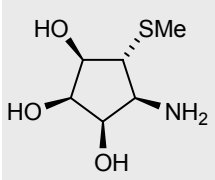
In summary, a new approach to the branched aminohydroxy acid **36**, has been elaborated, based on the highly stereoselective reaction of phenyl Grignard with the threose-derived nitrone **30**. (2*R*,3*S*)-Phenylisothreonine methyl ester **36** was obtained in 13 steps from diethyl L-tartrate in 12 % overall yield. In addition, the highly substituted tetrahydrofuran **39** was obtained and its configuration was secured by the 2D NMR spectroscopy (nuclear Overhauser effect, NOE).

4. Synthesis of Amino-hydroxymethyl-cyclopentanetriols

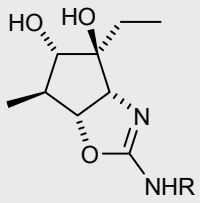
4.1 Background

Glycosidase inhibitors[8,9,10,62,63] can be used or have been proposed for treating diabetes, cancer, viral (HIV, influenza) and bacterial infections, and as insecticide. [64] Aminocyclopentane polyols analogues glycosidase inhibitors resemble intermediates and the transition state of glycosidic bond hydrolysis.[10b,10c] Aminocyclopentane polyols derivatives substructures are found in a number of natural products such as mannostatin A **AF** and trehezolin **AG**.[65] The neuraminidase inhibitor BCX-1812 **AH**, in clinical development to treat influenza, is also an aminocyclopentane polyols analogue (Figure 9).[66] This series of compounds such as **N**, **O** and **47** have already been mentioned in the introduction.

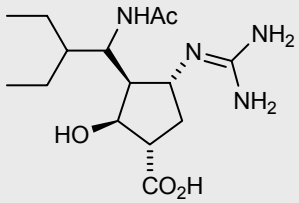
Figure 9. Stuctures of glycosidases inhibitors[66]



AF



AG (R = α-1-Glc)

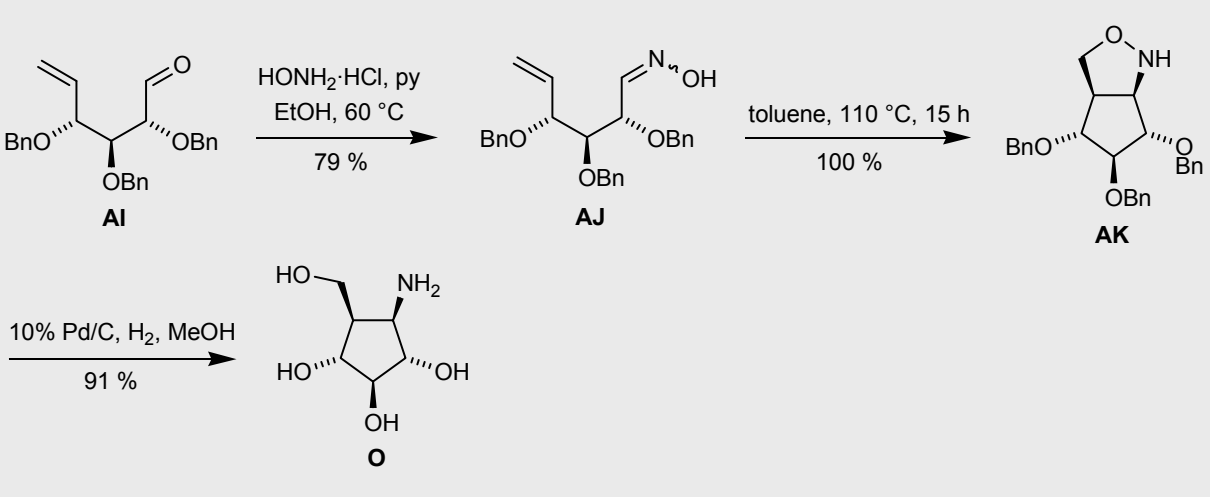


AH

The biological activities of these and related structures have stimulated considerable interest in the synthesis of aminocyclopentane derivatives, and a number of elegant strategies have been devised.[65]

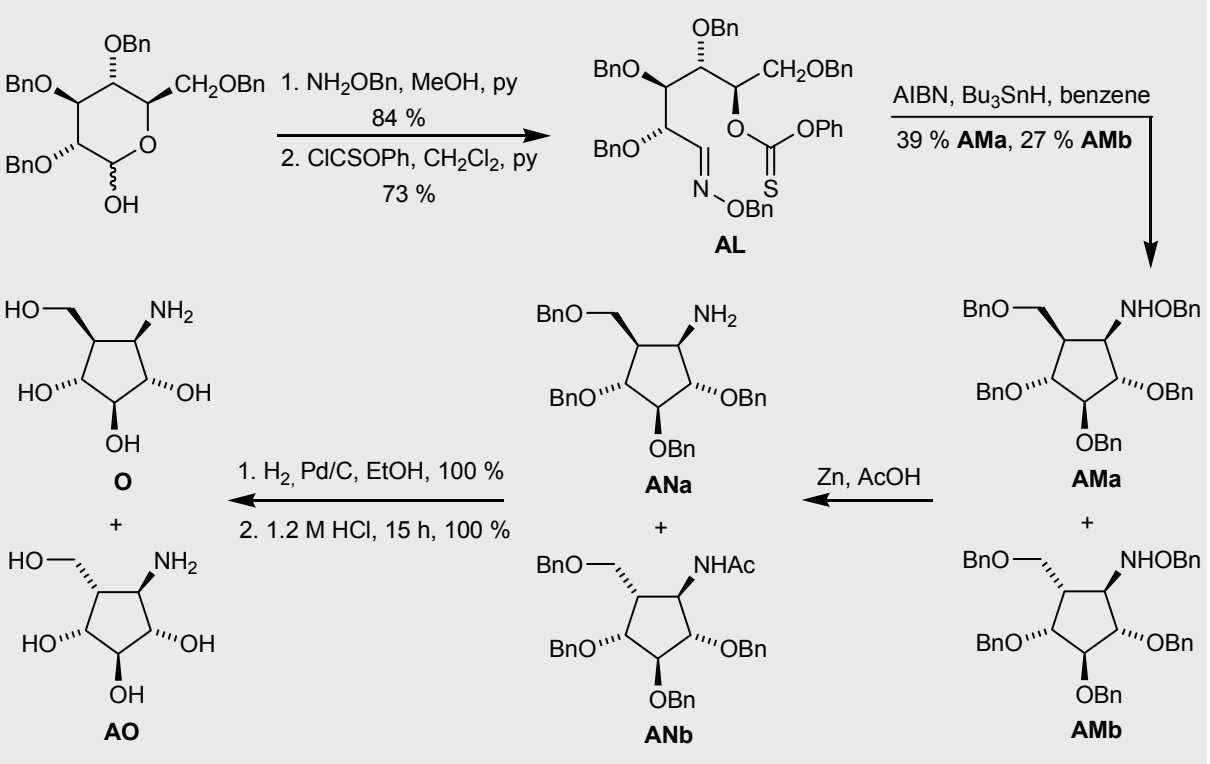
Our group[8, 67 ,70] and Shipman's group[63a] have investigated the synthesis of amino-cyclopentitols starting from the aldehyde **AI** in which the three hydroxy groups along the backbone were protected as benzyl ethers. This compound was readily prepared from methyl α-glucopyranoside in 5 steps.[8, 68] Treatment of the aldehyde **AI** with hydroxylamine hydrochloride in warm ethanol in the presence of pyridine furnished the oxime **AJ**. Thermolysis of this oxime in toluene at 110 °C for 15 h yielded the isoxazolidine **AK** in quantitative yield essentially as a single stereoisomer. The isoxazolidine **AK** can further be converted into the aminocyclopentitol **O** after cleavage of the *N*–*O* bond by catalytic hydrogenation (Scheme 19).

Scheme 19. Synthesis of amino-hydroxymethyl-cyclopentanetriol **L**[63a]



The strategy of closing the cyclopentane ring by radical cyclization[10,69] was employed in the synthesis of aminocyclopentitol **O** and related structures. The synthesis started from *tetra*-*O*-benzyl D-glucose which reacted with *O*-benzylhydroxylamine to form the corresponding oxime. The hydroxy group was acylated to provide the phenyl thionocarbonate **AL**. The radical induced cyclization of the oxime formed the benzylated cyclopentane hydroxylamines **AMa** and **AMb**. The process is demonstrated in Scheme 20.

Scheme 20. Synthesis of amino-hydroxymethyl-cyclopentanetriol **O** and related structures[10b]

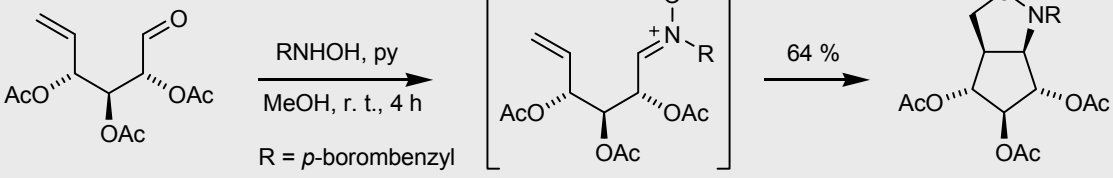


The *N*-*O* bond cleavage with zinc in acetic acid give the free amine and acyl amide which were catalytically hydrogenated to provide the corresponding free hydroxyl amine **ANa** and amide **ANb**. Finally, acidic hydrolysis with 1.2 M HCl afforded aminocyclopentitol **O** and **AO**.

4.2 Results and discussion

A series of amino-hydroxymethyl-cyclopentanetriols were synthesized using sugars as starting materials.[8,65,67,70] In our group, nitrones **AQ** (and other, related dipoles) undergoing [3 + 2] cycloadditions to form the precursors of cyclopentanetriols have been studied (Eq. 7).[8,67,70]

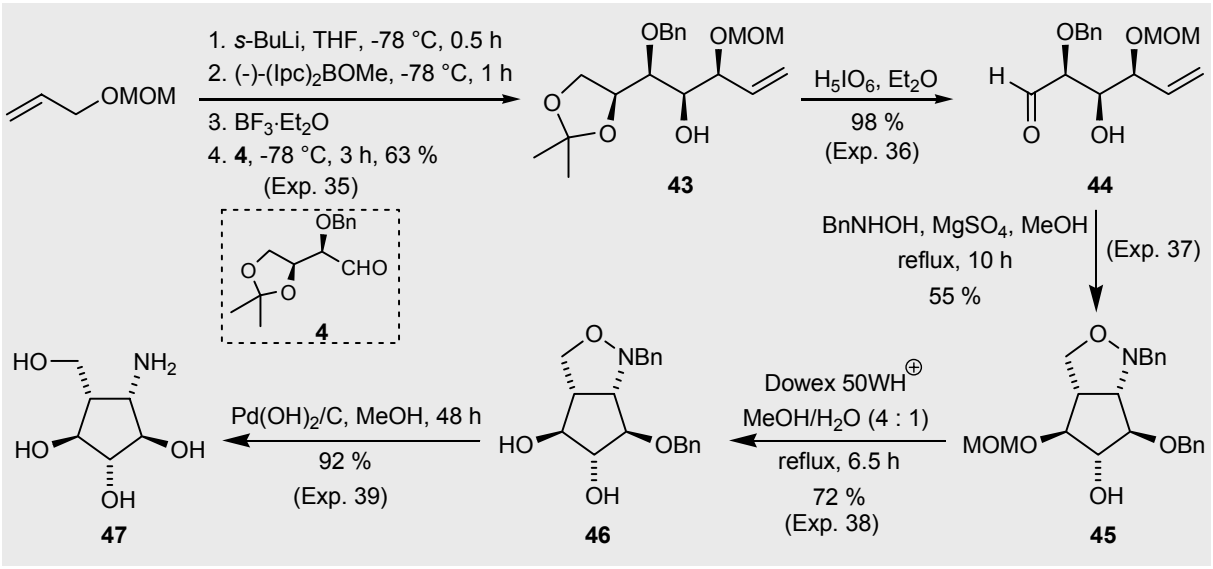
(7)



Synthesis of 1,5-*trans* amino (hydroxylmethyl)cyclopentanetriols were also investigated in our group using the polar [4 + 2]$^{\oplus}$ cycloadditions of *N*-acyliminium ions with olefins.[70a]

According to our experience with enantioselective additions of boron reagents to different aldehydes, 2-*O*-benzyl-3,4-*O*-isopropylidine-L-threose **4** (which was easily prepared in four steps from diethyl L-tartrate[32b,33b]) was subjected to Brown's alkoxylallylboration reagent to furnish the alcohol **43** in 68 % yield with a high level stereoselectivity (> 95 *syn*; > 95 *dr*).[71] The isopropylidene acetal in the olefin **43** was cleaved with periodic acid in diethyl ether, as shown in the synthesis of phenylisothreonine above, leading to the corresponding aldehyde **44**.[26b,39e] Condensation of the aldehyde **44** with *N*-*O*-benzylhydroxylamine resulted in the intermediate nitrone undergoing a one-pot [3 + 2] cycloaddition to generate the isoxazolidine **45**.[8,65,67,70] Finally, removal of the methoxymethylether using acidic ion exchande resin (Dowex, H^+ form),[72] and concomitant reduction of the benzyl ether as well as *N*-*O* bond cleavage furnished (1*S*,2*R*,3*R*,4*S*,5*S*)-1-amino-5-(hydroxymethyl)-cyclopentane -2,3,4-triol **47** (Σ 22 %, from the aldehyde **4**). The synthetic sequence to obtain **47** is detailed in Scheme 21.

Scheme 21. Synthesis of the aminocyclopentanetriol **47**



Intramolecular oxime-olefin cycloaddition by thermolysis in toluene has been reported.[73] Condensation of the aldehyde **44** with hydroxylamine afforded the oxime-olefin, which was heated to reflux in toluene. Unfortunately, the reaction proved unsuccessful: the substrate bearing a free hydroxyl group behaved different from those cases reported in the literature.[73] To our delight, the [3 + 2] cycloaddition between nitrone and olefin worked well. The aldehyde **44** was treated with benzylhydroxylamine in the presence of magnesium sulphate to form the intermediate nitrone undergoing the intramolecular cycloaddition to furnish the isoxazolidine **45** as a single isomer in 55 % yield.

4.3 Results of biological test*

The results of biological test of the aminocyclopentanetriol **47** was summarized in Table 6.

Table 6. Inhibitory activities of the aminocyclopentanetriol **47**

Enzymes	Source	% I (1mM)	IC_{50} (μM)	K_i (μM)
α-L-fucosidase	bovine kidney	63	611	-
β-D-glucosidase	bovine liver	53	889	-
α-D-glucosidase (maltase)	yeast	66	629	-
	Saccharomyces cerevisiae	78	81	5.3
α-D-mannosidase	jack beans	85	111	43.2
	almonds	87	82	43.1
β-D-xylosidase	Aspergillus niger	57	496	1085

**The experiment was carried out by Mrs. Saring.*

As results shown in Table 6, the aminocyclopentanetriol **47** is a weak inhibitor for many kinds of enzyme. Good results of the inhibitor **47** were observed for α-D-glucosidase (maltase) (IC_{50} = 81 μM, K_i = 5.3 μM for saccharomyces cerevisiae α-D-glucosidase) and for α-D-mannosidase (IC_{50} = 82 μM, K_i = 43.1 μM for amond α-D- mannosidase). For the rest of the enzymes, the IC_{50} values are above 100 μM.

4.4 Conclusion

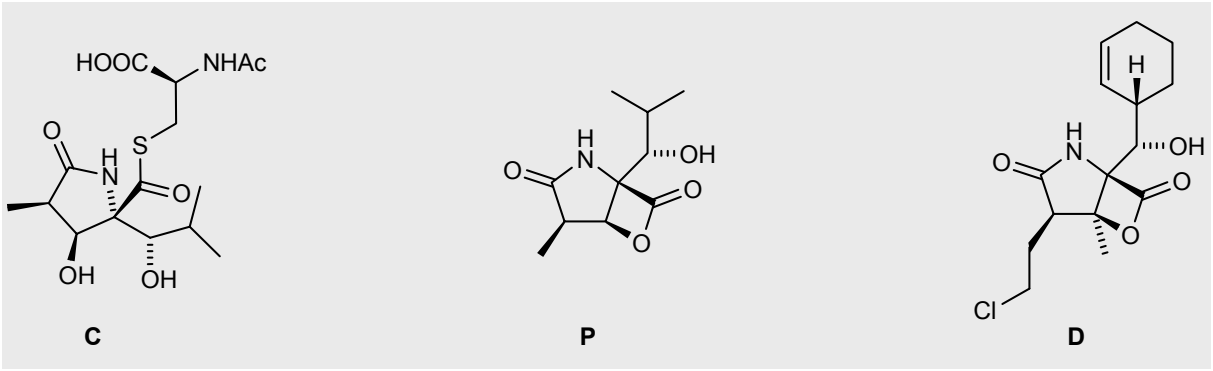
In conclusion, (1*S*,2*R*,3*R*,4*S*,5*S*)-1-amino-5-hydroxymethyl-cyclopentane-2,3,4-triol **47** was synthesized for the first time in 5 steps and 22 % yield starting from 3-(methoxymethoxy)prop-1-ene.

5. Syntheses of Lactacystin Derivatives

5.1 Biological activity of lactacystin

Lactacystin **C** is a Streptomyces metabolite that inhibits cell cycle progression and induces neurite outgrowth in a murine neuroblastoma cell line.[74] Tritium-labeled lactacystin was used to identify the 20S proteasome as its specific cellular target. Three distinct peptidase activities of this enzyme complex (trypsin-like, chymotrypsin-like, and peptidylglutamyl-peptide hydrolyzing activities) were inhibited by lactacystin, the first two irreversibly and all at different rates. None of five other proteases were inhibited, and the ability of lactacystin analogs to inhibit cell cycle progression and induce neurite outgrowth correlated with their ability to inhibit the proteasome.[75] Key work by Corey, Schreiber, and co-workers,[75a,75b] Huber and co-workers,[75c] and Dick *et al.*[75d] clearly defined the mechanism of inhibition displayed by lactacystin **C**. These investigations showed that lactacystin is, in fact, a prodrug for lactacystin β-lactone **P**, formed by the loss of *N*-acetylcysteine. Once inside a cell, the lactacystin β-lactone **P** then acylates the proteasome, causing inhibition. Salinosporamide A **D** exhibits potent cancer cell cytotoxicity and appears to exert its cytotoxic effects through inhibition of the 20S proteasome (Figure 10).[76]

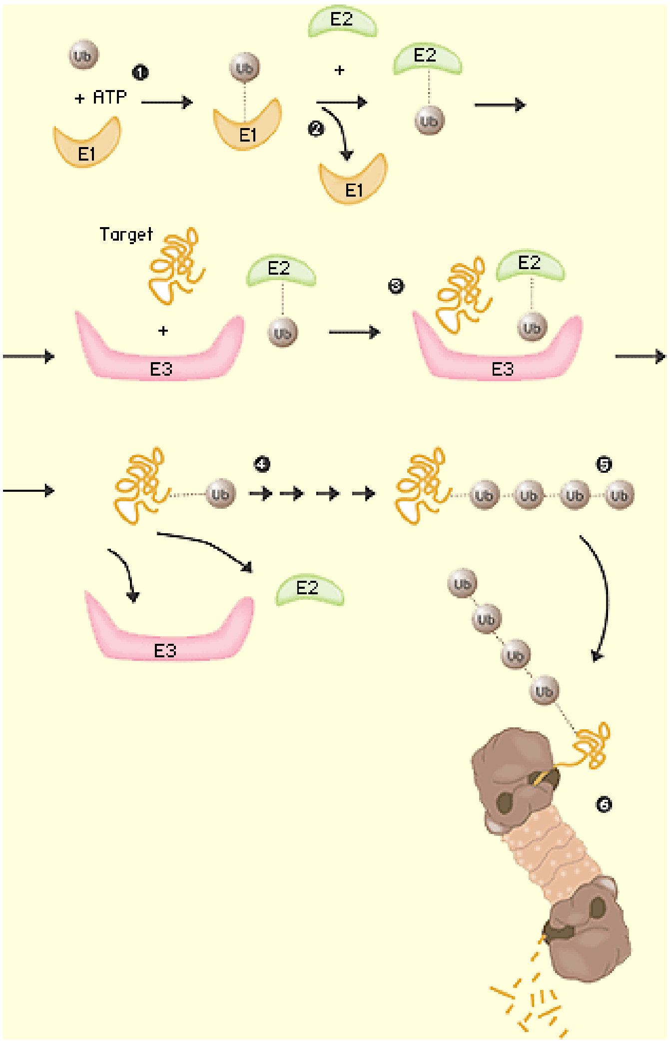
Figure 10. Proteasome inhibitors



Proteasomes are complex structures inside cells that break down proteins. Ubiquitin proteasome system or ubiquitin-26S proteasome system is a barrel-shaped multi-protein complex that can specifically digest other proteins into short polypeptides and amino acids in an ATP-driven reaction. The ubiquitin proteasome system is essential for many cellular processes including cell cycle, signal transduction, and regulation of gene expression.[77]

The ubiquitin-proteasome system is the primary mechanism in eukaryotic cells for degrading unwanted and misfolded proteins.[78] Through the cascade of E1 ubiquitin activating, E2 ubiquitin conjugating, and E3 ubiquitin ligase enzymes, ubiquitin monomers are attached sequentially to target proteins. The poly-ubiquitinated proteins are then recognized by the 26S proteasome, a large ATP-dependent multicatalytic protease, which removes the ubiquitin chain and degrades the proteins to short peptides. The selection and specific timing of poly-ubiquitination of the target proteins are conferred by different E3 ubiquitin ligases (Figure 11).

Figure 11. Ubiquitin-proteasome system[77a]



1. The E1 enzyme activates the ubiquitin molecule. This reaction requires energy in the form of ATP.

2. The ubiquitin molecule is transferred to a different enzyme, E2.

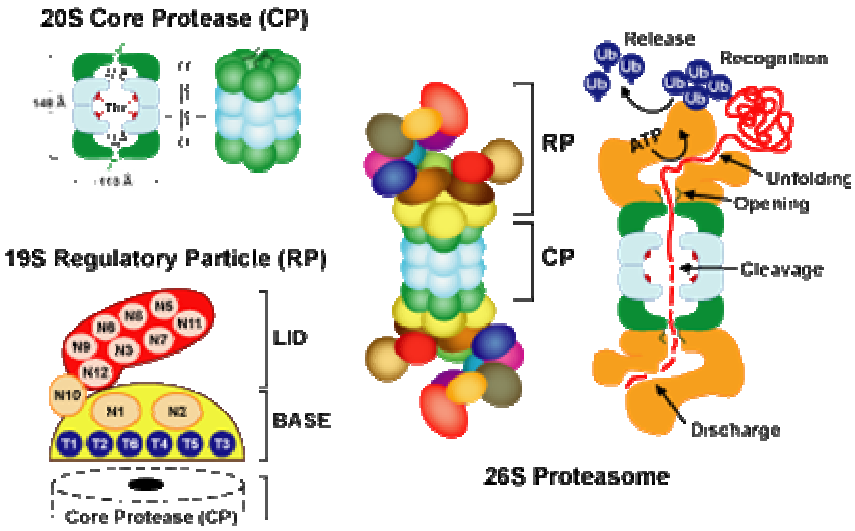
3. The E3 enzyme can recognise the protein target which is to be destroyed. The E2-ubiquitin complex binds so close to the protein target that the actual ubiquitin label can be transferred from E2 to the target. 4. The E3 enzyme now releases the ubiquitin-labelled protein.

5. This last step is repeated until the protein has a short chain of ubiquitin molecules attached to itself.

6. This ubiquitin chain is recognised in the opening of the proteasome. The ubiquitin label is disconnected and the protein is admitted and chopped into small pieces.

The 26S proteasome[79] (Figure 12) is used for the digestion of ubiquitin-marked proteins. The proteasome is hollow, providing an enclosed space for protein digestion, and has openings at the two ends to allow entry of the targeted protein. It is located on both sides of a cell's nuclear membrane and consists of a 20S core protease particle and two 19S regulatory particles. The 20S unit consists of two rings of α subunits and two rings of β subunits, stacked in the order αββα as a series of heptameric rings. It is about 15 nm long and 11.5 nm wide. The alpha subunits are structural, while three of the beta subunits are catalytic and exert the proteolytic activity: β1, β2, and β5. In mammals, different catalytic subunits can be induced or repressed in response to cytokines such as interferon; the different beta subunits alter the cleavage and length preferences of the proteasome.

Figure 12. 26S proteasome[79b]



Each 19S unit consists of a lid and a base with a 19S regulatory particle attached to each end of the 20S core particle via its base.

The core 20S proteasome associates with different caps, including the PA28 complex; these different caps modify the activity of the proteasome. The 20S core particle is also known as the Catalytic Particle (or CP) and can exert its proteolytic activity without ubiquitin/ATP. In many mammalian cells the 20S proteasome is the most represented species and has been shown to degrade target proteins that have been oxidized or unfolded.[77a]

5.2 Studies on the total syntheses of lactacystin and salinosporamide A

Lactacystin is a nonprotein γ-lactam thioester consisting of (*R*)-*N*-acetylcysteine and a pyroglutamic acid residue. The pyroglutamate residue is an α,α-disubstituted α-amino acid,

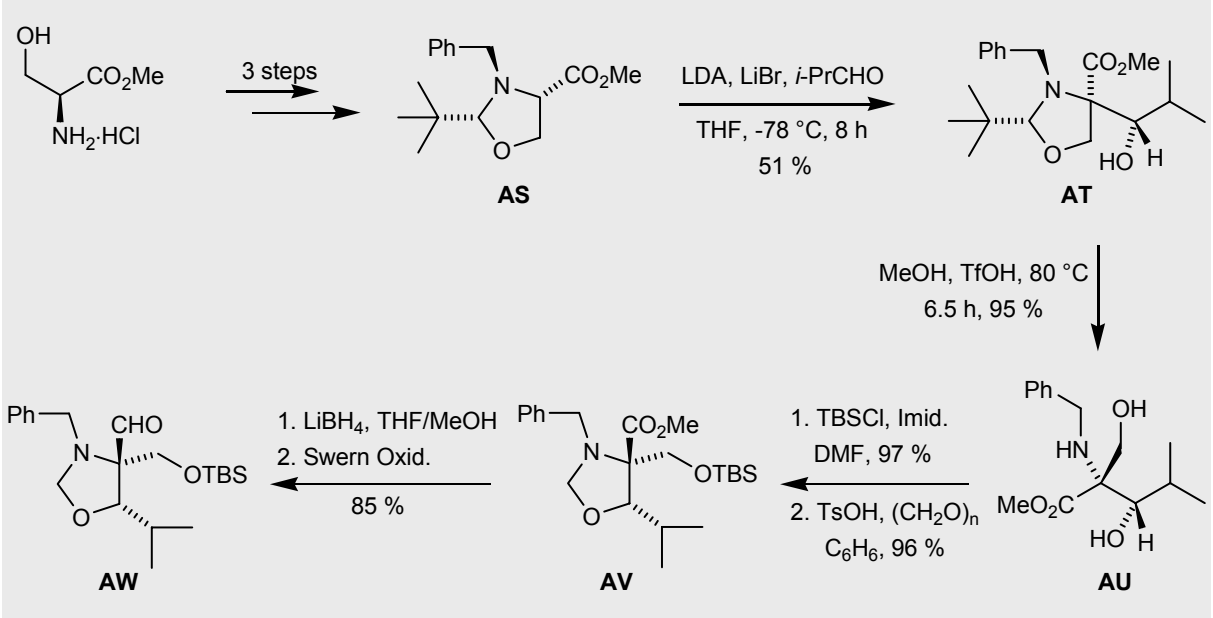
and there are four contiguous asymmetric centers arrayed in its compact frame which intrigued numerous chemists. Since three reviews[80] on lactacystin have been reported to date, only a brief description of lactacystin will be given here.

Corey synthesis of lactacystin (1992)

The first total synthesis of (+)-lactacystin was achieved by Corey and Reichard in 1992;[2] subsequent refinements to this approach have since been reported by the Corey group.[83] The original synthetic approach (Scheme 22) utilized the *cis*-oxazolidine derivative **AS** which is derived from the (*S*)-serine methyl ester in a three-step sequence.

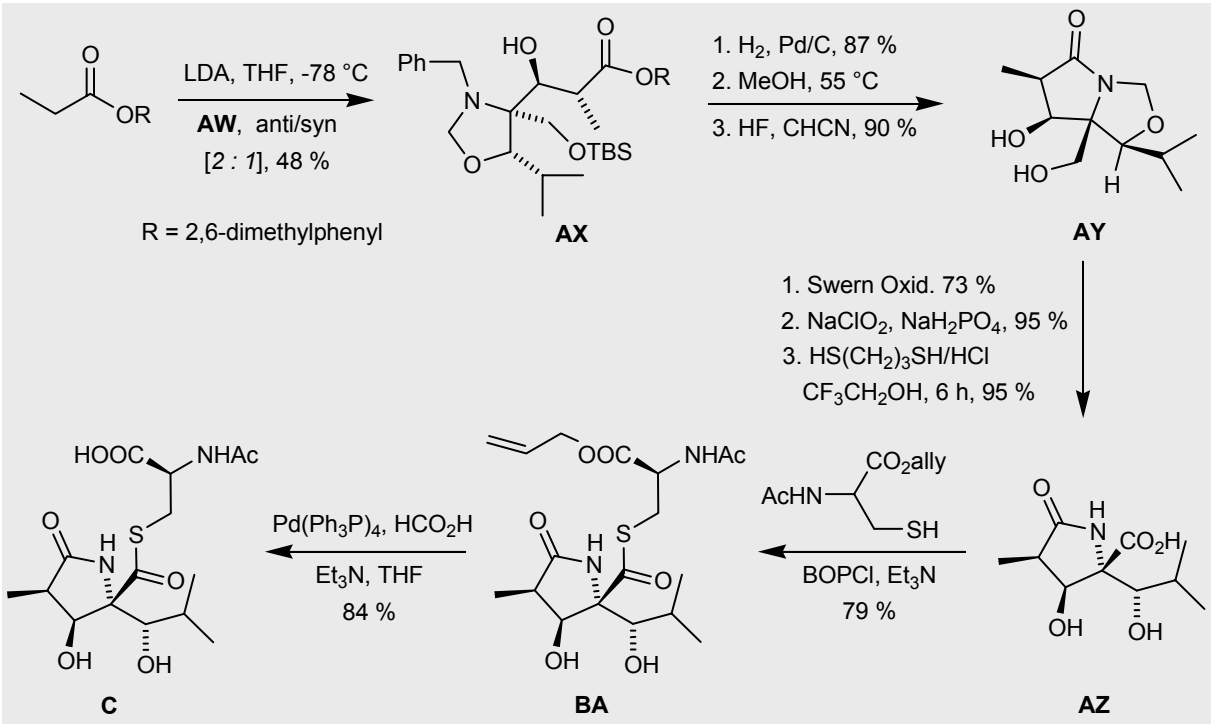
The oxazolidine **AS** undergoes a highly stereoselective aldol reaction via the lithium enolate-lithium bromide complex with isobutyraldehyde to afford, after recrystallization, the diastereomerically pure β-hydroxy ester **AT**. Methanolysis of the *N*,*O*-acetal in **AT**, protection of the resulting primary hydroxy group as its TBS ether, formation of a topologically different methylene *N*,*O*-acetal by an acid-catalyzed condensation with formaldehyde, and conversion of the methyl ester to an aldehyde (i. $LiBH_4$; ii. Swern Oxid.) afforded oxazolidine aldehyde **AW** (Scheme 22a).

Scheme 22a. Synthesis of lactacystin by the Corey group[2]



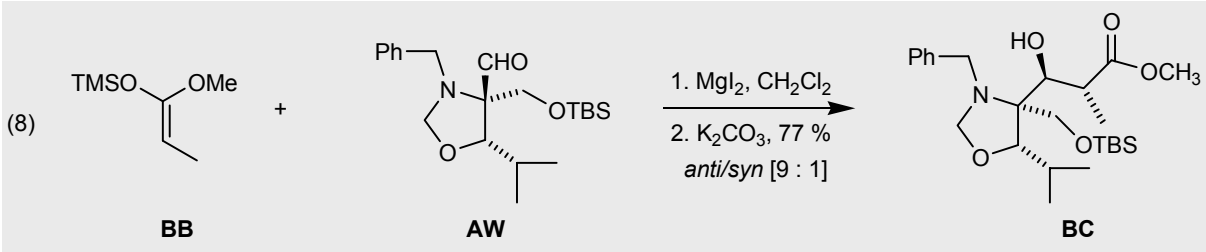
The *anti*-aldol reaction with aldehyde **AW** to establish the stereogenic centers in the γ-lactam ring of **C** was originally accomplished using the Pirrung-Heathcock *anti*-aldol forming conditions (lithium enolate of 2,6-dimethylphenylpropionate).

Scheme 22b.



This transformation provided the *anti*-aldol product **AX** in moderate yields and with low levels of induction (*dr* = 2 : 1). Catalytic hydrogenolysis of the alcohol **AX** to remove the *N*-benzyl group, conversion of the resulting amino ester to the γ-lactam by heating in methanol, and desilylation of primary TBS ether affords the dihydroxy γ-lactam **AY**. Selective oxidation of primary hydroxy group in the lactam **AY** afforded the acid, from which the *N*,*O*-methylene bridge was removed by acid-catalyzed transfer of methylene to 1,3-propanedithiol to form the dihydroxy acid lactam **AZ**. The carboxylic acid function of **AZ** was esterified selectively without hydroxyl protection by treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), triethylamine, and *N*-acetyl-L-cysteine allyl ester to form the allyl ester of the lactacystin **BA**. Deallylation of the allylester **BA** under transfer hydrogenation conditions afforded lactacystin **C**.

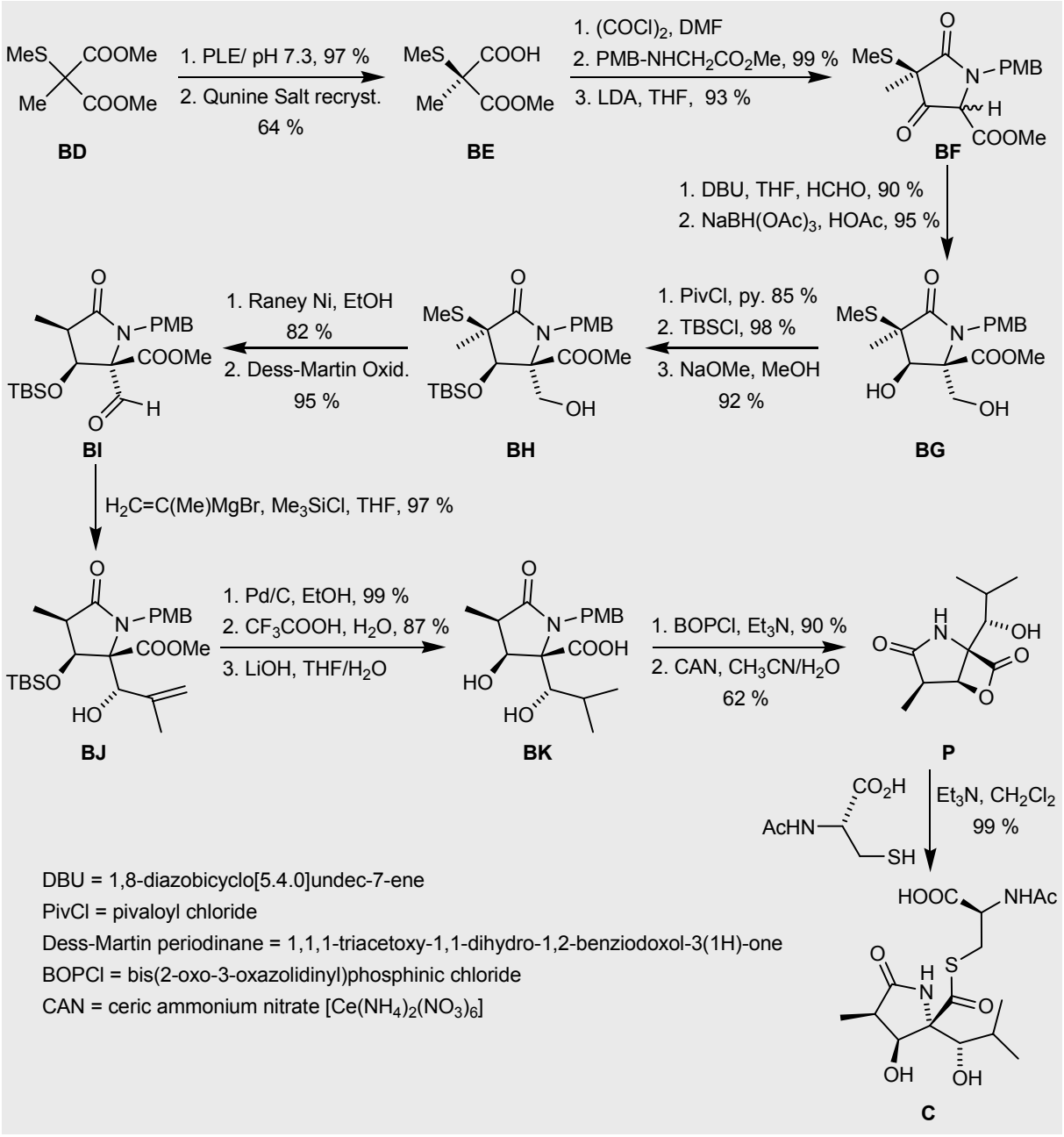
In the first modification of the Corey approach (1998)[81a], the challenging *anti*-aldol step was revised using a modification of the Mukaiyama aldol coupling of the oxazolidine **AW** and the silyl-ketene acetal **BB** with magnesium iodide (MgI_2) as a catalyst.



This aldol reaction proceeded with a useful degree levels of stereoselectivity (*dr* = 9 : 1 *anti/syn*) and in good yield to afford the aldol product **BC** (Eq. 8).[81]

The most recent synthesis by Corey's group (1998) utilized racemic starting materials whose enantiopurity was generated using enzymatic resolution techniques.[82] More specifically, the synthesis was initiated with the dimethymethylmalonate derivative **BD**, prepared from dimethymethylmalonate in one step (sodium hydride, methanesuphenyl chloride in THF). Enantioselective pig-liver esterase (PLE) catalyzed hydrolysis of **BD** gave the enantioenriched acid **BE**. The acid was purified by one recrystallization of its corresponding quinine salt from aqueous ethanol to give an acid in 95 % enantiomeric excess (ee).

Scheme 23. Synthesis of lactacystin by Corey group.[82a]



Coupling of the acid **BE** as its acid chloride to a glycine ester component and subsequent Dieckmann cyclization gave the β-keto lactam **BF** as a 1 : 1 mixture of diasteromers (with respect to the α-carbon of the β-keto ester moiesty). Stereoselective α-hydroxymethylation of the keto lactam **BF** (*dr* = 9 : 1) and substrate-controlled reduction of the ester with sodium triacetoxyborohydride [$NaBH(OAc)_3$] afforded the γ-lactam **BG** whose absolute configuration was confirmed by an X-ray crystallographic analysis. The lactam **BG** was converted into the primary alcohol **BH** in a three-step sequence: i) Selective protection of the primary hydroxy group of the lactam **BG** as its pivolyl ester; ii) protection of the secondary hydroxyl group as its *tert*-butyldimethylsilyl ether, and iii) deprotection of pivolyl ester. The desulfurization of the alcohol **BH** with Raney nickel was surprisingly stereoselective (*dr* = 10 : 1) to afford the aldehyde **BI** after column chromatography and Dess-Martin oxidation. The reaction of the aldehyde **BI** with the 2-propenyl Grignard reagent in the presence of trimethylchlorosilane (essential to prevent retro-aldol cleavage) provided the desired alcohol **BJ** stereoselectively. The trimethylchlorosilane (Me_3SiCl) was found to be essential to the reaction as it traps the resulting alkoxide ion at a rate that is faster than retro-aldol cleavage, which **BI** was found to be prone to in the absence of Me_3SiCl. The stereoslectivity of the Grignard addition is consistent with a steric screening model by means of a bidentate chelation of the Mg^{II} complex with carbonyl groups of the formyl and ester moieties. The alcohol **BJ** was converted into the dihydroxy acid **BK** by catalytic hydrogenation, desilylation of the TBS ether, and saponification of the methyl ester. Selective β-lactonization of the hydroxy acid **BK** with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and removal the *p*-methoxylbenzyl group with ceric ammonium nitrate (CAN) afforded the β-lactone **P**. This reacted with *N*-acetyl-L-cysteine to produce the lactacystin **C** in high yield without the need to use a protected cysteine derivative and subsequent protecting group removal. The synthetic sequence is portrayed in Scheme 23.

The Corey processes outlined in Scheme 21 and 22 have been utilized to prepare a variety of analogues of lactacystin **C**.[83]

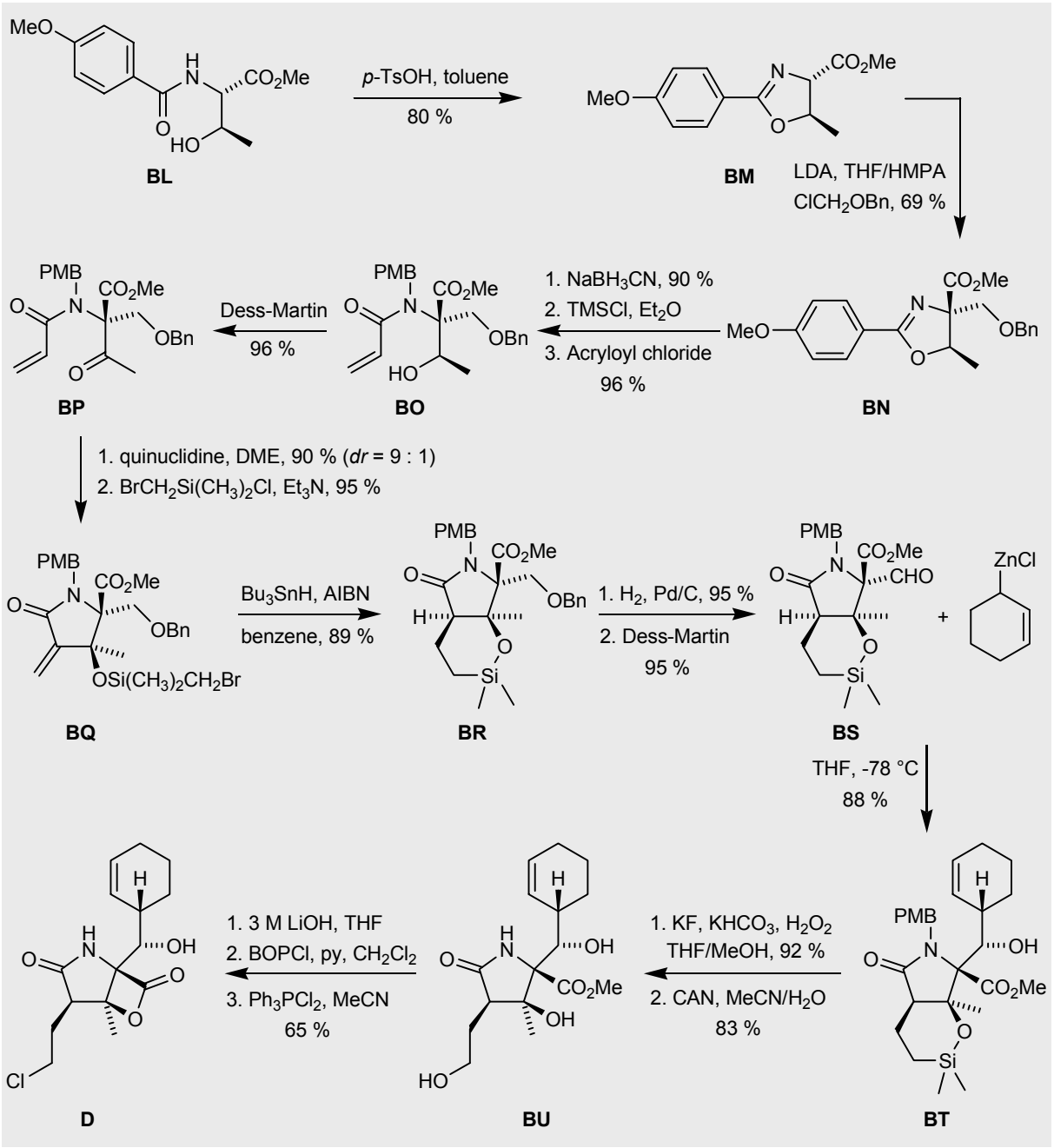
Corey synthesis of Salinosporamide A (2004)

Salinosporamide A[84] **D** is an even more effective proteasome inhibitor than omuralide **P**, and in addition it displayed surprisingly high in vitro cytotoxic activity against tumor cell lines. The first total synthesis of **D** was also reported by Corey group.[84a]

The synthesis of salinosporamide A **D** is outlined in Scheme 24. (*S*)-Threonine methyl ester was *N*-acylated with 4-methoxybenzoyl chloride to form the amide **BL** which was then

cyclized to the oxazoline **BM** by heating at reflux in toluene with *p*-toluenesulfonic acid. Deprotonation of the oxazoline **BM** with lithium diisopropylamide (LDA) in THF and alkylation of the resulting enolate with chloromethyl benzyl ether afforded the required tertiary stereocenter of **BN** selectively. Reduction of the oxazoline **BN** with sodium cyanoborohydride ($NaCNBH_3$-HOAc) gave *N*-4-methoxy-benzylamine which was transformed to the *N*-acryloyl-PMB derivative **BO** by a one-pot sequence: i) Reaction with trimethylsilyl chloride (Me_3SiCl) to form trimethylsilyl ether, ii) acylation with acryloyl chloride, and iii) acidic work up with aqueous HCl.

Scheme 24. Corey synthesis of salinosporamide A in 2004[84a]



Dess-Martin periodinane oxidation of the secondary alcohol in **BO** produced the keto amide ester **BP**. Cyclization of the keto amide **BP** to the lactam was accomplished by means of an internal Baylis-Hillman reaction. Silylation of the γ-lactam with bromomethyldimethylsilyl chloride afforded the protected γ-lactam **BQ** which was easily separated from its diastereomer by silica gel chromatography. The required stereochemical relationship of the γ-lactam core was established by tri-*n*-butyltin hydride-mediated radical cyclization which transformed **BQ** cleanly into the *cis*-fused γ-lactam **BR**. Cleavage of the benzyl ether of **BR** (H_2, Pd/C) and Dess-Martin periodinane oxidation provided the aldehyde **BS**. The attachment of the 2-cyclohexenyl group to the the formyl carbon and the establishment of the remaining two stereocenters were accomplished by reaction of 2-cyclohexenylzink chloride with the aldehyde **BS** with high selectivity (20 : 1). Tamao-Fleming oxidation of the lactam **BT** gives the triol, followed by Ce(IV)-induced oxidative cleavage of the PMB group to afford the triol ester **BU**. The ester **BU** was hydrolyzed to the corresponding γ-lactam-carboxylic acid using 3 M lithium hydroxide. This acid was converted to salinosporamide A **D** by successive reaction with bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and then triphenylphosphine dichloride.

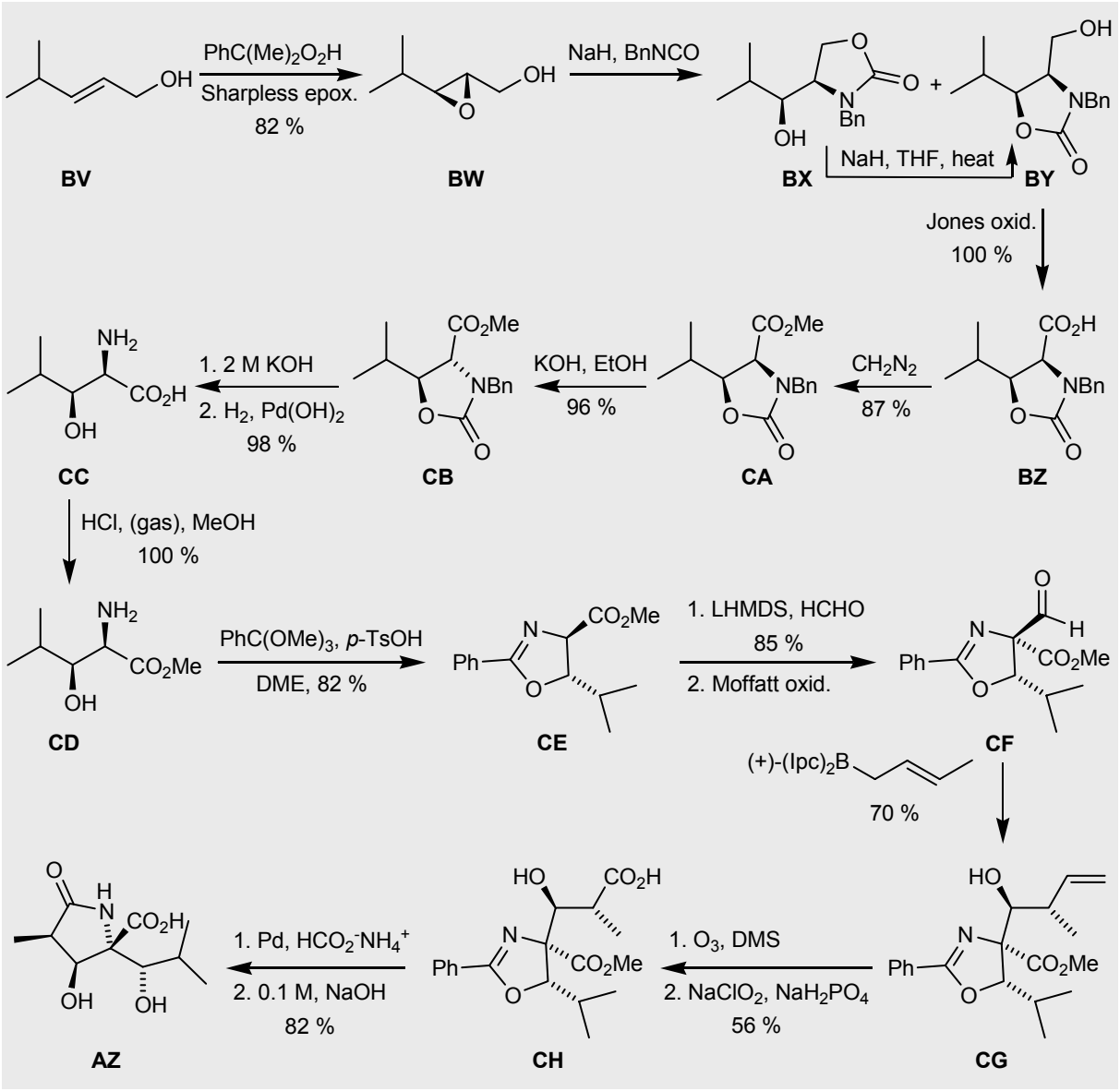
The second total synthesis of salinosporamide A was reported by Danishefsky *et al*.[84b] and studies towards the synthesis of salinosporamide A were investigated in Langlois' group.[84c]

The methods described in Scheme 24 have been utilized to prepare a variety of analogues of salinosporamide A **D** and lactacystin **C**.[85]

Omura-Smith synthesis of lactacystin (1996)

The critical (2*R*,3*S*)-hydroxyleucine building block has been utilized by Omura and Smith in the total synthesis of lactacystin **C**, as illustrated in Scheme 25.[86] In this work, the hydroxyleucine derivative **CD** was prepared by Sharpless asymmetric epoxidation of (*E*)-4-methyl-2-penten-1-ol **BV** to give the chiral epoxide **BW** which was elaborated in a eight-step sequence to furnish the amino ester **CD**. Treatment of the epoxy alcohol **BX** with benzyl isocyanate and sodium hydride in THF furnished a 5 : 1 ratio of regioisomeric oxazolidinones **BX** and **BY**; re-exposure of the mixture to sodium hydride (NaH) in THF then produced the rearranged heterocycle **BY**. Jones oxidation gave the corresponding carboxylic acid **BZ** quantitatively. After esterification, the ester **CA** was exposed to ethanolic KOH to afford the epimer **CB**. Urethane cleavage and hydrogenolysis gave the (2*R*,3*S*)-hydroxyleucine **CC** which was transformed to the corresponding methyl ester **CD** with acidic methanol. Treatment of the amino ester **CD** with trimethyl orthobenzoate in the presence of *p*-toluenesulfonic acid as a catalyst yielded the oxazoline **CE**. A key step in the Omura-Smith synthesis now involved diastereoselective hydroxymethylation of the oxazoline **CE**, where the observed stereoselectivity is controlled by the topology of the substrate. Oxidation of the primary alcohol under Moffatt conditions afforded the labile heterocyclic aldehyde **CF**. The aldehyde was subjected to Brown asymmetric allylboration with (*E*)-crotyl(diisopinocampheyl)borane. This sequence afforded a 4 : 1 mixture of the required homoallylic alcohol **CG** which was converted into the labile acid **CH** in a two-step sequence, involving oxidative cleavage of the double bond by ozone and subsequent oxidation of resultant aldehyde. Catalytic transfer hydrogenation (Pd/C, ammonium formate) then afforded the γ-lactam ester which was hydrolysed to yield the acid **AZ**. To complete the synthesis of **P** with the β-lactone structure, the two-step sequence devised by Corey[2] was employed (Scheme 22).

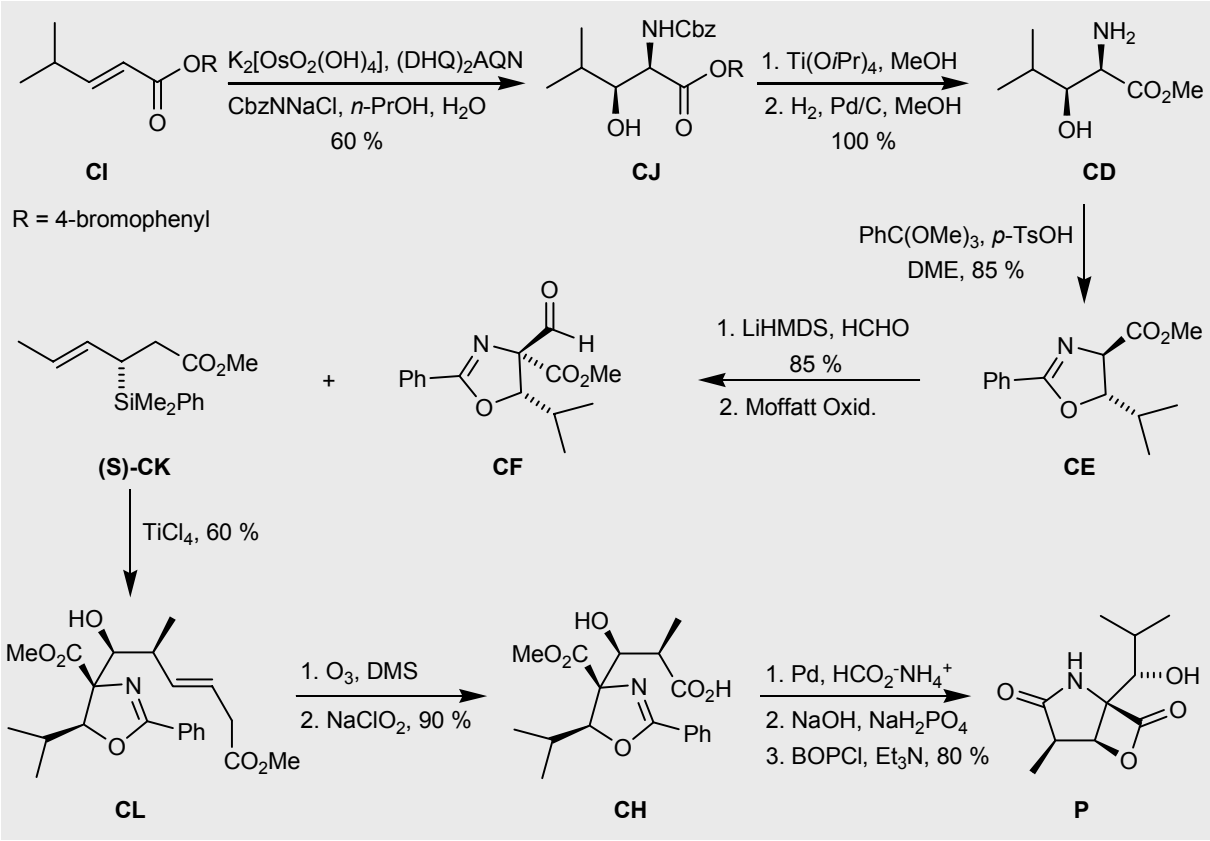
Scheme 25. Omura-Smith synthesis of lactacystin[86]



Panek synthesis of lactacystin (1999)[87]

The synthesis of lactacystin by the Panek group is displayed in Scheme 26. In this work, efficient synthesis of the 3-hydroxyleucine was investigated based on the Sharpless asymmetric aminohydroxylation of olefins. The aminohydroxylation of **CI** with hydroquinine (anthra-quinone-1,4-diyl)diether [$(DHQ)_2AQN$] and the benzylcarbamate-based Sharpless asymmetric aminohydroxylation gave the amino acid **CJ** with good levels of regioselection (7 : 1) favoring the α-amino ester, and high levels of enantioselectivity (87 %). Subsequent transesterification of the amino acid **CJ** to the methyl ester in the presence of $Ti(O\textit{i}Pr)_4$ and removal of the benzyloxycarbonyl group by hydrogenolysis afforded the hydroxyamino ester **CD**.

Scheme 26. Panek synthesis of lactacystin[87]



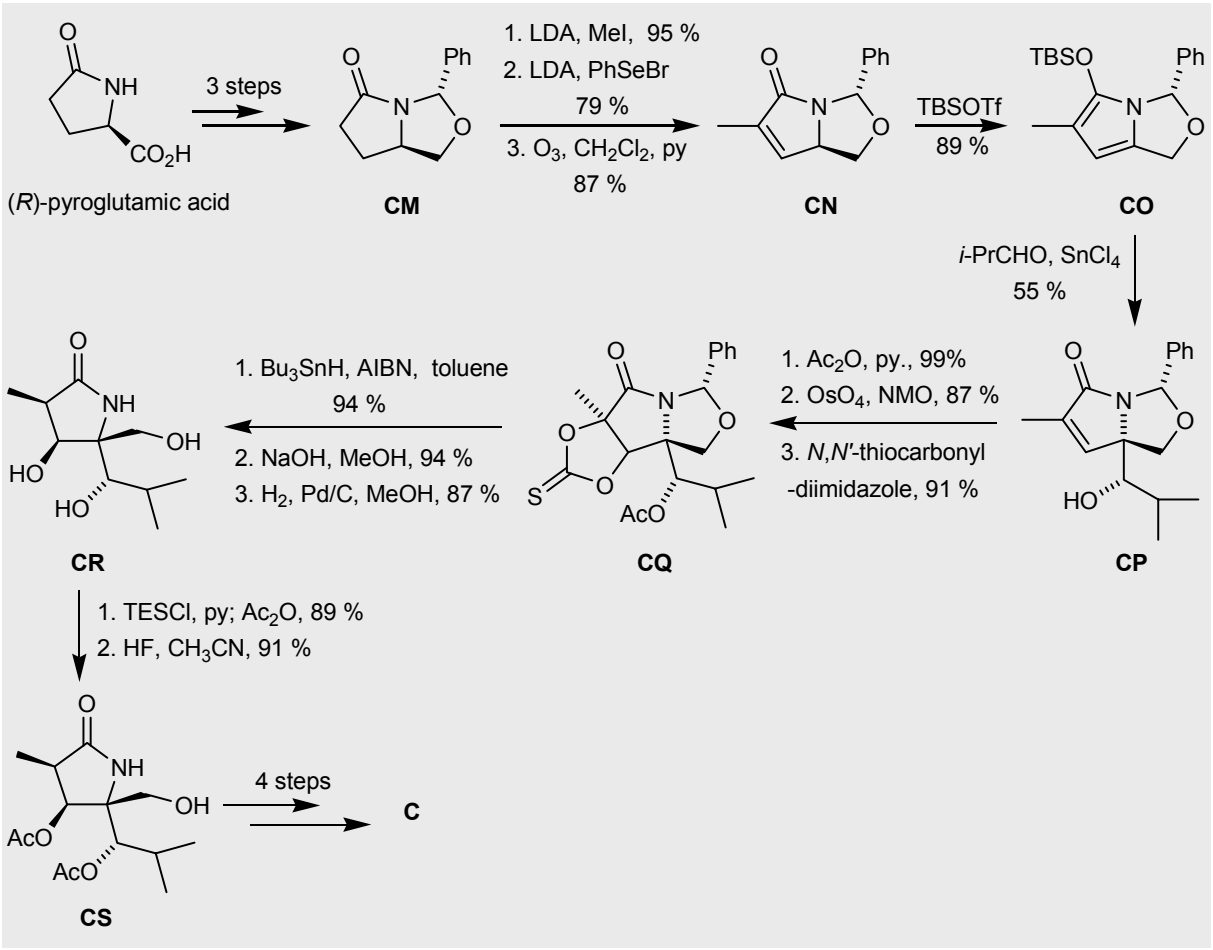
Treatment of the amino ester **CD** with trimethyl orthobenzoate in the presence of *p*-toluenesulfonic acid provided the *trans*-oxazoline **CE**. The preparation of the heterocyclic aldehyde **CF** was accomplished according to the method established by Smith[86] (Scheme 25). With the required aldehyde **CF** at hand, the critical *anti*-selective crotylation reaction with the silane reagent (*S*)-**CK** was carried out to establish the stereochemical relationship in the ring of lactacystin **C**. This double stereodifferentiating reaction was readily accomplished using titanium tetrachlordie ($TiCl_4$) to afford the homoallylic alcohol **CL**.[88] Oxidative cleavage of the (*E*)-olefin part of **CL** under standard ozonolysis conditions and subsequent oxidation with sodium chlorite furnished the carboxylic acid **CH**. Catalytic transfer hydrogenation of the oxazoline moiety of **CL** using Pd/C gave the γ-lactam methyl ester after cyclization. Saponification of the methyl ester under Smith's conditions[86] afforded the dihydroxyacid which was directly converted into β-lactone **P** by treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). To attach the *N*-acetyl-L-cysteine side chain, the lactone-opening strategy developed by Corey[82a] was adopted (Scheme 23).

Baldwin-Uno synthesis of lactacystin (1994)[89]

Lactacystin has been synthesized by Baldwin and coworkers strating from (*R*)-pyroglutamic acid (Scheme 27). The bicyclic oxazolidine **CM** was prepared from (*R*)-pyroglutamic acid in

three steps[90] and was elaborated to the unsaturated derivative **CN** by sequential methylation and selenenylation/ozonolysis. Generation of the silyoxy pyrrole was accomplished by treatment of the lactam **CN** with *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) to give the intermediate **CO**, which underwent a vinylogous Mukaiyama aldol reaction with isobutyraldehyde to give the aldol product **CP** (*dr* = 9 : 1).

Scheme 27. Synthesis of lactacystin by Baldwin[89]

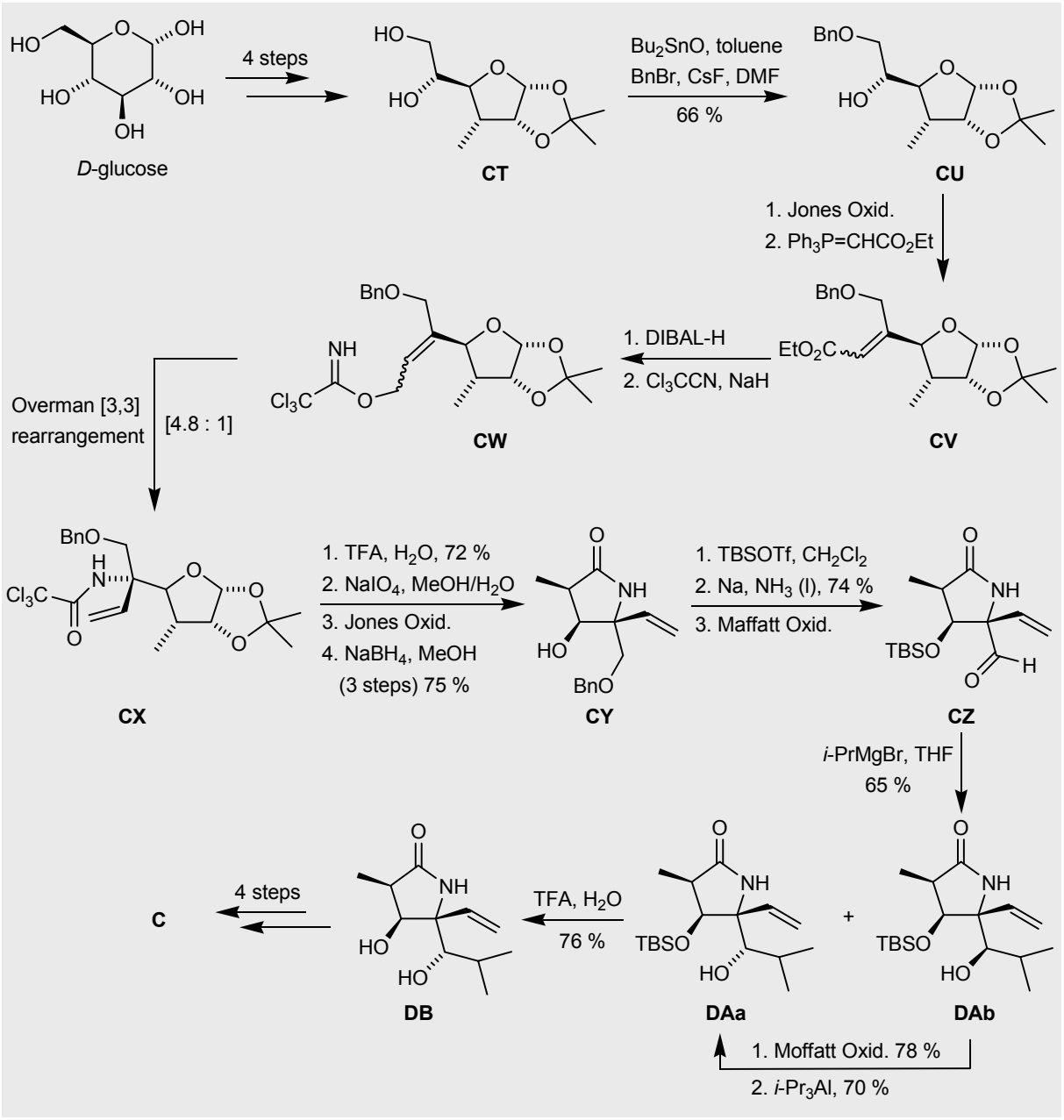


Installation of the stereogenic centers required a number of steps involving: i) dihydroxylation of the lactam **CP**; ii) selective deoxygenation of the quaternary hydroxy group via the cyclic thiocarbamate **CQ**; iii) base-catalyzed epimerization of the methyl group; iv) hydrogenolysis of the benzylidene *N*,*O*-acetal to give the hydroxy lactam **CR**; and v) protecting group manipulations to afford the hydroxylactam **CS**. The lactam **CS** was converted into lactacystin **C** by a sequence analogous to that of Scheme 22.

Chida synthesis of lactacystin (1995)[91]

Using a fundamentally different appraoch to the synthesis of lactacystin, Chida and coworkers utilized D-glucose as a scaffold to construct the γ-lactam core of **C** (Scheme 28).

Scheme 28. Chida synthesis of lactacystin[91a]



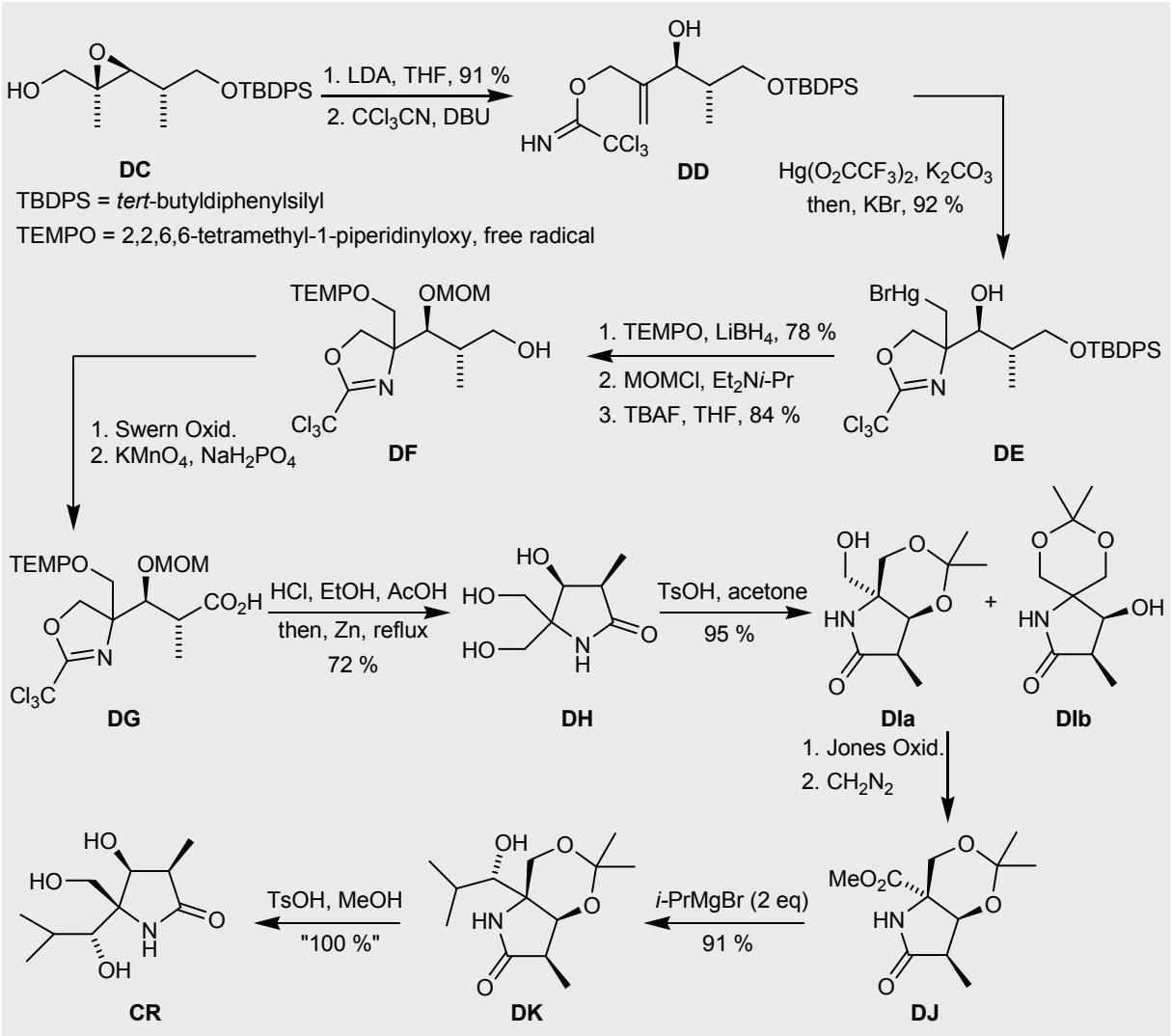
The synthesis started with furanose **CT** which was prepared from D-glucose. Reaction of **CT** with dibutyltin oxide followed by treatment with benzyl bromide afforded the mono-protected alcohol **CU** in 66 %. Oxidation of secondary alcohol in **CU** furnished the corresponding ketone and homologated under Wittig conditions to the α,β-unsaturated ester **CV** (1 : 1 mixture of E/Z isomers). Reduction of the ester to the allylic alcohol was followed by in situ formation of the trichloroacetimidate **CW** which underwent a thermal Overman rearrangement ([3,3] sigmatropic rearrangement) to afford the aminofuranose **CX** with 4.8 : 1 diastereoselectivity in favor of the correct quaternary stereocenter. Diol cleavage of **CX** with sodium periodate afforded an *O*-formyl hemiaminal which was oxidized under Jones conditions to furnish the *O*-formyl-γ-lactam. Removal of the *O*-formyl group with

sodium borohydride ($NaBH_4$) gave the γ-lactam **CY**. Construction of the stereocenter of the side-chain involved Grignard addition of isopropylmagnesium bromide to the heterocyclic aldehyde **CZ**. This addition suffered from a lack of stereoselectivity and a low yield of 65 % due to unwanted formyl reduction by isopropylmagnesium bromide to give the primary alcohol side product. Completion of the synthesis of lactacystin **C** involved oxidative cleavage of terminal olefin of **DB** and thioesterification with *N*-acetyl-L-cysteine using the methods similar to those in Scheme 22.

Kang partial synthesis of lactacystin (1998)[92]

The synthesis of Kang *et al.* was initiated by ring-opening of the know epoxide **DC**[93] (containing the chiral stereocenters of the targeted 5-membered ring) to the allylic alcohol, followed by conversion of the primary alcohol to the trichloroacetimidate **DD** (Scheme 29).

Scheme 29. Synthesis of lactacystin by Kang[92a]

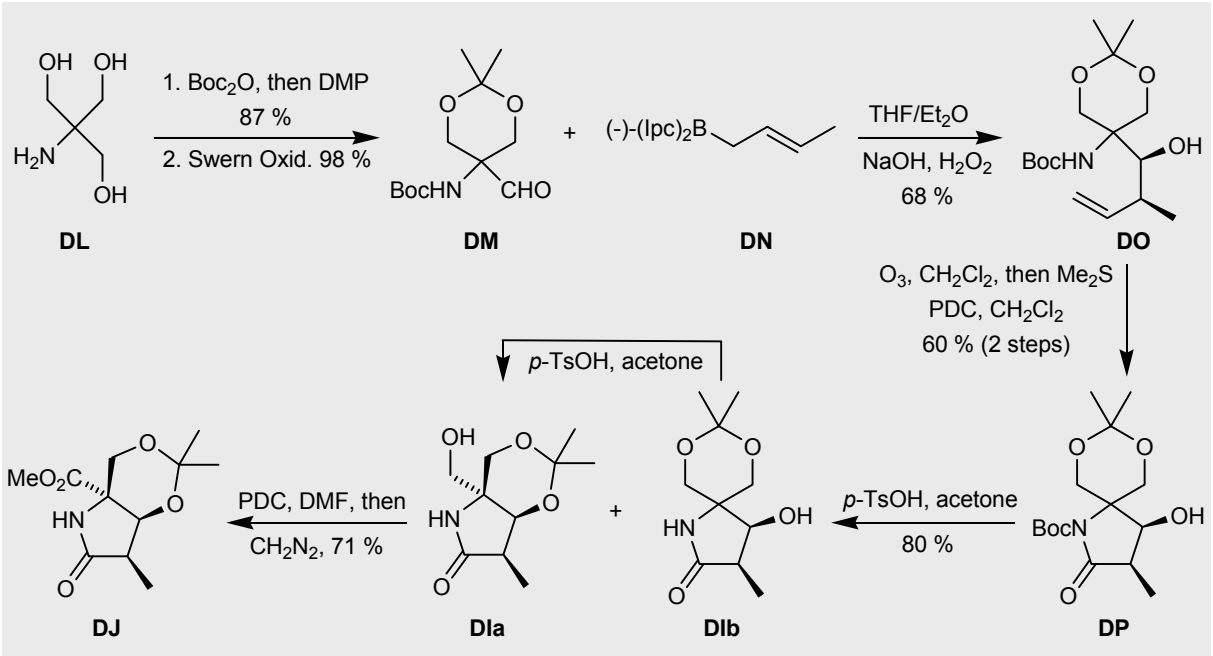


Mercuriocyclization of the thrichloroacetimidate **DD** yielded a 1 : 1 diastereomeric mixture of oxazoline **DE**. The oxazoline **DE** was exposed to TEMPO in the presence of lithium borohydride ($LiBH_4$) to provide the oxidized product **DF**, after protection of the secondary alcohol with bromomethyl methyl ether (MOMBr) and removal of silyl group. The primary alcohol in **DF** was efficiently oxidized to the carboxylic acid **DG** by Swern's method, followed by potassium permanganate ($KMnO_4$) oxidation. Complete hydrolysis and ensuing cyclization were effected by heating the acid **DG** at reflux with ethanolic HCl in acetic acid. 2,2,6,6-Tetramethyl-1-piperidinyl group (TEMP) of pyrolidinone was reductively cleaved in situ by adding zinc to the hot reaction mixture to produce the trihydroxypyrrolidinone **DH**. For the elaboration of the hyroxymethyl groups in the substituted pyrrolidinone **DH**, this chemoselectively reacted with acetone under acidic condition to give a 7 : 1 mixture of the acetonide **DIa** and **DIb**. The acetonide **DIa** was converted into the corresponding ester **DJ** after Jones oxidation and esterification with diazomethane. Treatment of the lactam **DJ** with excess *i*-PrMgBr achieved not only Grignard addition but also perfectly stereoselective reduction of the formed carbonyl group to furnish the trihydroxypyrrolidinone **CR**, Baldwin's intermediate.[89]

Hatakeyama partial synthesis of lactacystin (2004)[94]

Hatakeyama and co-workers made use of Brown's asymmetric crotylboration for installation of the stereocenter in the target (Scheme 30). The aldehyde **DM** was secured from the aminotriol **DL** which was successively subjected to *tert*-butoxycarbonylation and acetalization in one pot, followed by Swern oxidation.

Scheme 30. Synthesis of lactacystin by Hatakeyama[94]

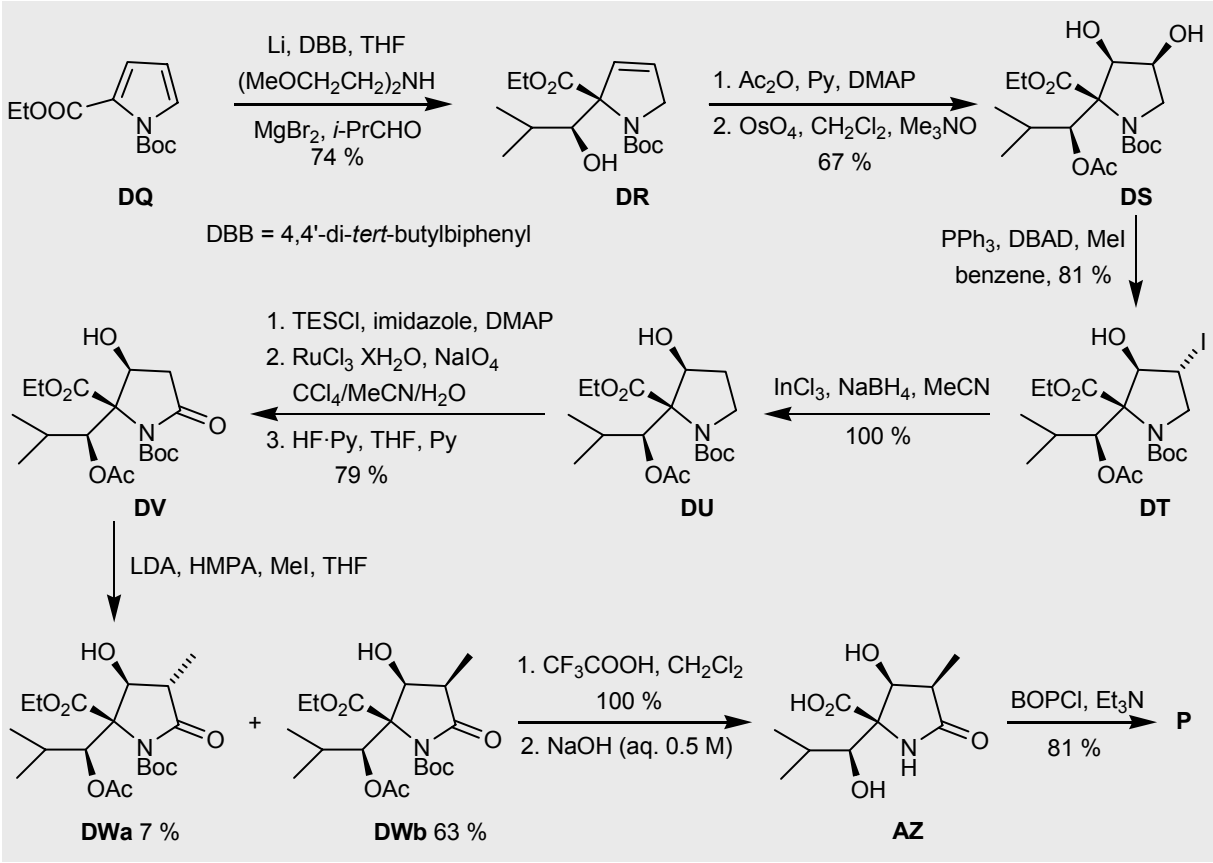


The aldehyde **DM** reacted with Brown's boron reagent **DN** to give the olefinic carbamate **DO**, which was transformed to the pyrrolidinone **DP** through olefin ozonolysis and lactam formation. Treatment of the substituted pyrrolidinone **DP** with *p*-toluenesulfonic acid in acetone led to cleavage of the *tert*-butoxycarbonyl group and concomitant migration of the acetonide group to produce a 5 : 1 mixture of γ-lactam **DIa** and **DIb**. Oxidation of the primary alcohol in the lactam **DIa** followed by esterification of the resulting carboxylic acid with diazomethane gave the ester **DJ**, Kang' intermidate.[92]

Donohoe synthesis of lactacystin (2004)[12,95]

Donohoe and colleagues commenced on the synthesis of lactacystin β-lactone **P** (Omuralide), the true inhibitor, using reductive aldol condensation as a key step (Scheme 31).[96] The (*Z*)-enolate generated from the pyrrole carboxylate **DQ** with lithium di-*tert*-butylbiphenylide was condensed with isobutyraldehyde in the presence of magnesium bromide ($MgBr_2$) to produce the adduct **DR** with *anti* selectivity greater than 20 : 1.

Scheme 31. Synthesis of lactacystin by Donohoe[12]



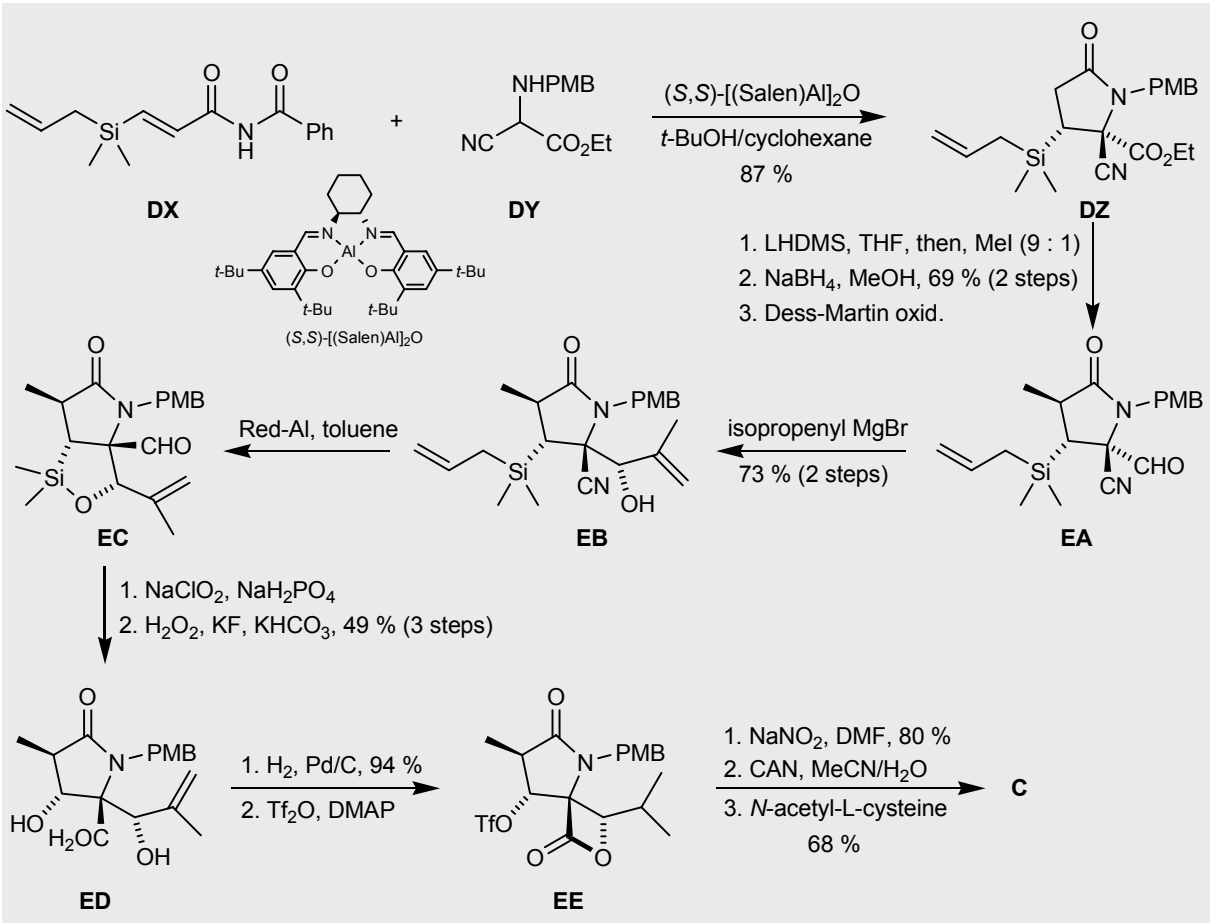
Subsequent protection of the alcohol **DR** as an acetate, followed by diastereoselective dihydroxylation, proceeded to yield the diol **DS**. A selective conversion of the 4-hydroxy group

of **DS** into 4-iodo compound **DT** was effected by Mitsunobu reaction (Scheme 31). The resulting iodide **DT** was deiodinated to the 3-hydroxy pyrrolidine **DU** through a method producing (catalytic) indium hydride in situ.[97] The hydroxy group was protected with a triethylsilyl group (TES), the product was oxidized with catalytic ruthenium tetroxide (RuO_4) to form a lactam, and the triethylsilyl group was then removed to furnish the pyrrolidinone **DV**. Methylation of the lactam **DV** afforded a 9 : 1 mixture of the **DWb** with the right configuration and its isomer **DWa**. Cleaveage of the *tert*-butoxycarbonyl group of **DWb** with trifloroacetic acid, followed by basic hydrolysis of the ethyl ester gave the acid **AZ** and subsequent lactonization supplied the lactacystin β-lactone **P** (omuralide).

Jacobsen synthesis of lactacystin (2006)[11]

The total syntesis of lactacytin commenced with a β-silyl α,β-unsaturated imide substrate for catalytic, enantioselective conjugate addition. Aluminum salen complexes have proven effective for a variety of asymmetric catalytic conjugate additions including Michael additions of “electron-deficient” nitrile nucleophiles to α,β-unsaturated imides.[98]

Scheme 32. Synthesis of lactacystin by Jacobsen[11]



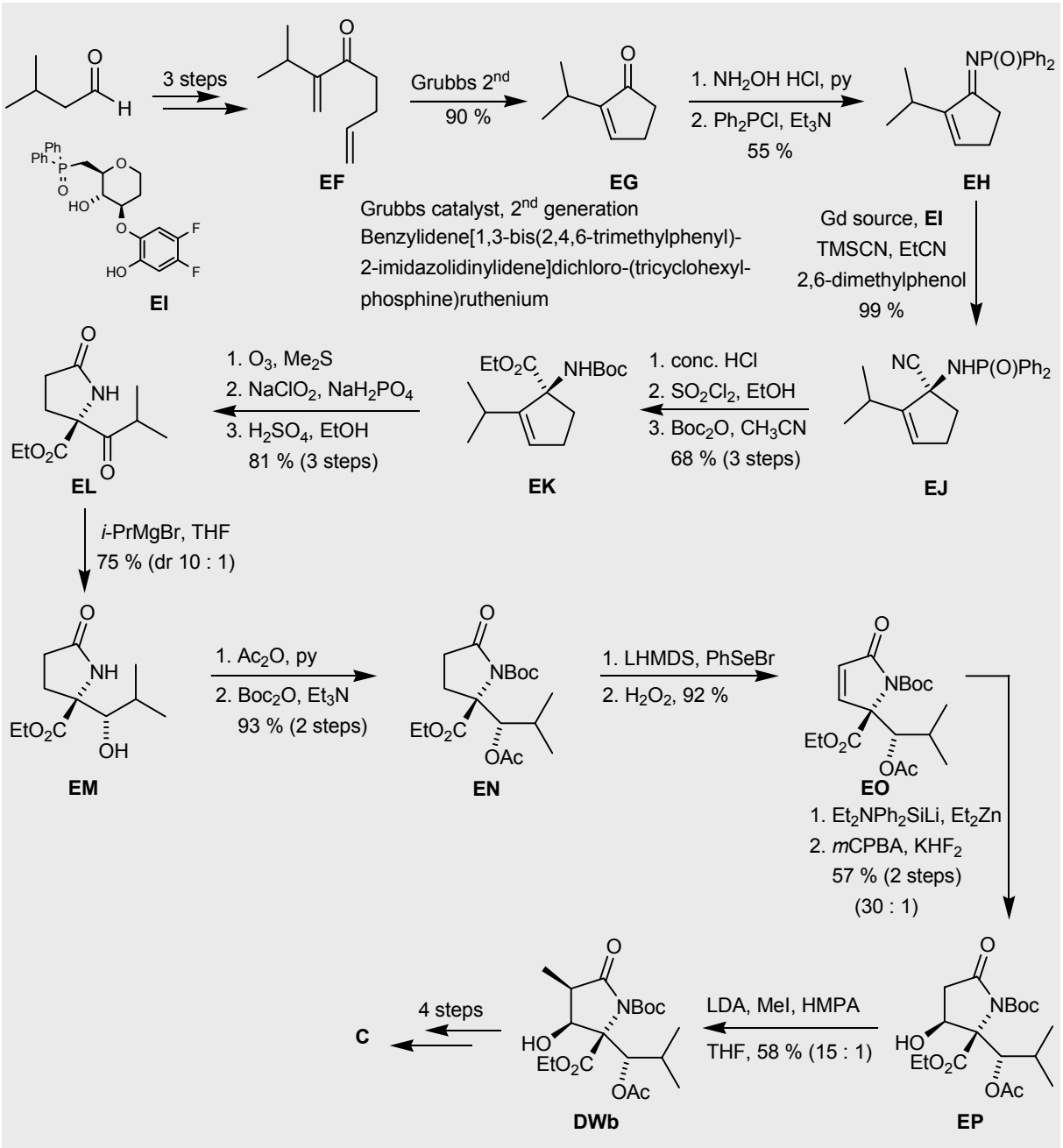
Addition of aminocyanoacetate derivatives can result in direct formation of γ-lactam derivatives with high enantio- and diastereoselectivity. The lactam **DZ** was obtained by conjugate addition of the β-silyl imide **DX** and the aminocyanoacetate derivative **DY** with high enantioselectivity (98 : 2) and diastereoselectivity (9 : 1). Methylation in the α-position proceeded with complete diastereoselectivity, followed by a two-step transformation of the ethyl ester to the corresponding aldehyde **EA**. Treatment of the aldehyde **EA** with isopropenylmagesium bromide provided the alcohol **EB** with excellent diastereoselectivity (> 95 : 5). Formal hydrolysis of the nitrile **EB** was envisaged using a mild two-step reduction/oxidation sequence. Unexpectedly, reduction of the intermediate **EB** with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) was accompanied by intramolecular Si-allyl displacement by alkoxide with formation of the cyclic silyl ether **EC**. This aldehyde **EC** was subjected to oxidation to the corresponding acid, and Si-C bond cleavage was accomplished under standard Tamao oxidative conditions to provide the diol **ED** as a single diastereomer. After hydrogenation of the olefin **ED** to the corresponding isopropyl derivative, sulfonylation with an excess of triflic anhydride (Tf_2O) resulted in construction of the β-lactone and triflate formation **EE** in one pot. Triflate displacement was accomplished cleanly in the presence of the β-lactone by treating it with sodium nitrite ($NaNO_2$) in DMF. After removal of the *N*-*p*-methoxybenyl (*N*-PMB) group, the corresponding lactam reacted with *N*-acetyl-L-cysteine in the presence of dimethylethylamine to provide lactacystin **C** in 68 % yield.

Shibasaki synthesis of lactacystin (2006)[99]

Shibasaki and co-workers employed the catalytic enantioselective Strecker reaction as a key step in the synthesis of lactacystin (Scheme 33). The known ketone **EF**[100] was synthesized from 3-methylbutanal in 3 steps. From this, the ketimine **EH**, the substrate for the catalytic asymmetric Strecker reraction, was synthesized by ring-closing metathesis, oxime formation, and diphenylphosphinoylimine formation.[101] Shibasaki *et al.*[101b-d] developed a practical enantioseletive Strecker reaction of ketimines using gadolinium (Gd) complex ligand **EI** as a catalyst. In the Strecker reaction of the ketimine **EH** the amidonitrile **EJ** was obtained with 98 % ee using $Gd(HMDS)_3$ (HMDS = hexamethyldisilazane) as a metal source and **EI** as a chiral ligand. The aminonitrile **EJ** obtained was converted to the corresponding α,α-disubstituted amino acid derivative **EK** in high yield. Ozonolysis, oxidation of resulting aldehyde to the carboxylic acid, and γ-lactam formation under acidic condations afforded the ketolactam **EL**. The stereoselective reduction of the keto-latam **EL** to give the hydroxyl lactam **EM** was achieved using isopropylmagnesium bromide as a reducing reagent through a probable chelated transition state with high selectivity (10 : 1). The next key step was the introduction of

the hydroxy group at C-4 of the lactam by stereoselective conjugate addition of a silyl group and the following Tamao oxidation. The α,β-unsaturated lactam precursor **EO** was synthesized from the saturated lactam **EM** by following sequence: i) Chemoselective protection of the hydroxyl group; ii) lactam nitrogen atom with an acetyl and *tert*-butyl carbonyl group, respectively, to give the intermediate **EN**. After selenenylation and elimination of the intermediate **EN** the unsaturated lactam **EO** was obatined.

Scheme 33. Synthesis of lactacystin by Shibasaki *et al.* in 2006[99]



Conjugate addition of silyl, followed by Tamao oxidation[102] is a reliable method for the construction of β-hydroxyl carbonyl compounds. This sequence is advantageous for the stereoselctive introduction of an oxygen functionality into a sterically hindered position.[103] The Tamao oxidation sometimes requires highly acidic conditions, depending on the substituted silyl groups. Therefore, proper selection of silyl reagent is important for the required stability of conjugate addition products which are susceptible to the Tamao oxidation under mild conditions. In this synthesis, the diphenyldiethylaminosilyl (Et_2NPh_2Si) group met these requirements. The conjugate addition of the corresponding silyl zincate proceeded with complete stereoselectivity from the α-face. This excellent stereoselectivity was attributed to the shielding of the β-face by the sterically bulkier acetoxyisobutyl group. The hydroxy imide **EP** was obtained after the oxidative cleavage of silyl group in 57 % yield. The methylation of the lactam **EP** to give the lactam **DWb** was then conducted under the conditions reported by Donohoe.[95] The total synthesis of lactacystin was completed from the protected lactam **DWb** following the reported procedure.[81a,95]

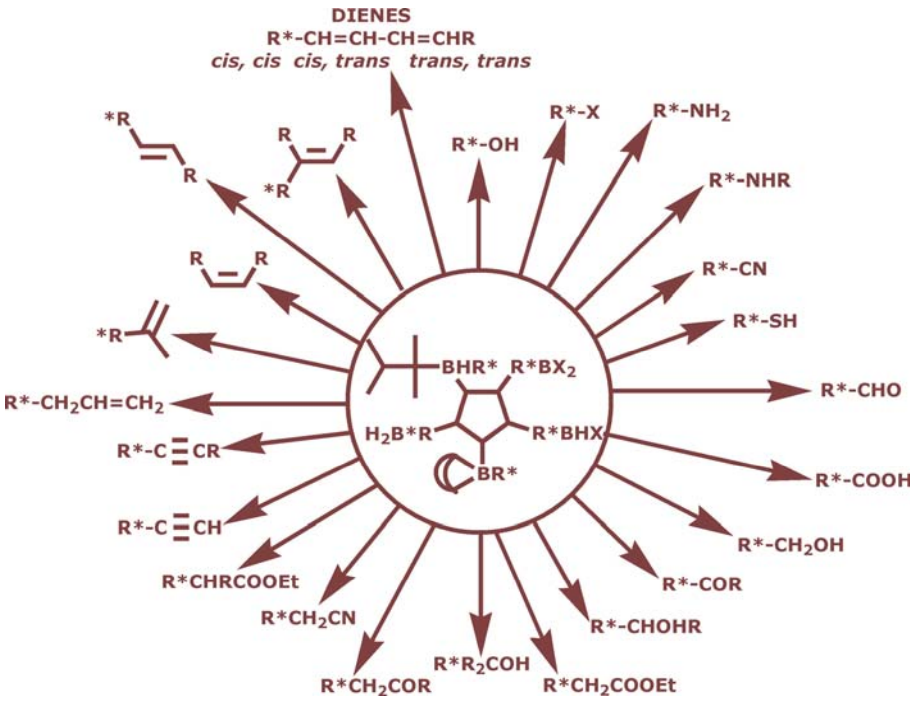
Due to the importance of lacytacystin, many efforts have been made to the total synthesis of lactacystin. Highly active analogue of lactacystin β-lactone was reported by Adams.[104] Hayes and Wardrop's groups synthesized the lactacystin using a highly stereoselective alkylidene carbene 1,5-CH insertion reaction as a method to construct the key quaternary stereocentre.[105] Radical cyclization of an α-ethynyl substituted serine was employed to synthesize the lactacystin by Pattenden.[106] Attempts to synthesis of lactacystin have been made by some groups.[107]

In summary, the synthetic approaches devised by the research groups working on this target have demonstrated considerable creativity and mechanistic insight en route to the total synthesis. The successful approaches presented represent an inventive application of several important strategies in the area of acyclic stereocontrol. These include the use of chiral metal enolate and chiral allylmetal-based bond construction methods.

5.3 Introduction on the use of organoboron reagents

A systematic study of the reactions of organoboranes revealed their exceptional versatility.[108] The typical transformations are indicated in Figure 13.[110b,110c] These studies showed that the substitutions reactions of organoboranes proceed with essentially complete retention of configuration of the substituents attached to the boron. Only a few exceptions are known.[109]

Figure 13. General asymmetric transformations *via* organoboranes[110c]



*Following synthesis of R*B<, where R* is chiral, essentially any type of chiral organic compounds can be synthesized by transfer of the R* group from boron without loss of chirality.*

For these reasons, organoboron reagents are widely used as important and effective tools in the asymmetric organic syntheses.[110] The unique chemistry of organoboranes applied in the asymmetric synthesis was described from the following aspects: i) asymmetric hydroboration,[110f] ii) asymmetric allyl- and crotylboration,[110d] iii) asymmetric reduction,[110e] and iv) asymmetric aldol reaction via boron enolates.[110g-q] It is evident that boron chemistry is providing major new routes for asymmetric synthesis. Herein, I would like to place emphasis on the asymmetric hydroboration and asymmetric allylboration employed in the chemistry of the present work to be described later.

5.3.1 Asymmetric hydroboration

Hydroboration is the term given to the addition of a boron-hydrogen bond to either the carbon-carbon double bond of an alkene or the triple bond of alkyne. The first hydroboration was reported by H. C. Brown *et al.* which led to practical applications in asymmetric synthesis.[111]

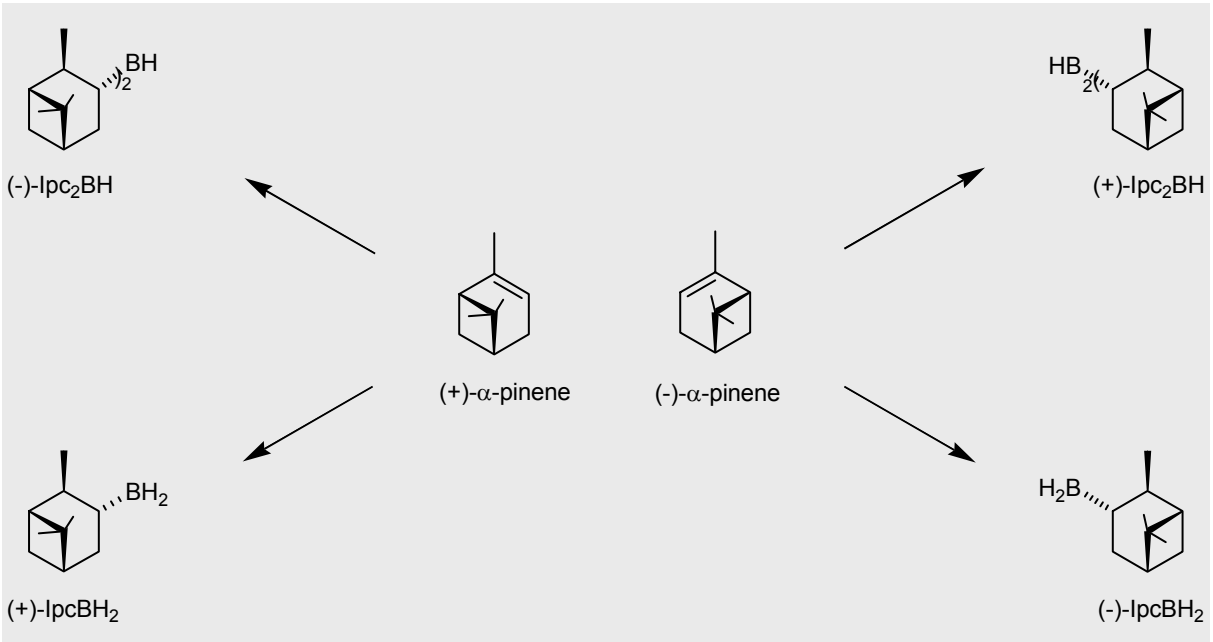
It has been observed that hydroboration exhibits the following characteristics:[108c]

a) The boron atom preferentially adds to the least hindered end of an unsymmetrically substituted double bond.
b) Controlled *syn*-addition of the boron-hydrogen bond to the alkene occurs.
c) Addition of boron-hydrogen to the carbon-carbon double bond takes place from the least hindered face.

5.3.1.1 Diisopinocampheylborane and momoisopinocampheylborane

Brown and Zweifel found that the reaction of *cis*-alkenes with (-)-diisopinocampheylborane, [(-)-Ipc_2BH], readily obtained from (+)-α-pinene, leads to optically active secondary alcohols after oxidation with alkaline hydrogen peroxide. Since both enantiomers of α-pinene are readily available, both enantiomers of Ipc_2BH and $IpcBH_2$ are also easily accessible (Figure 14).

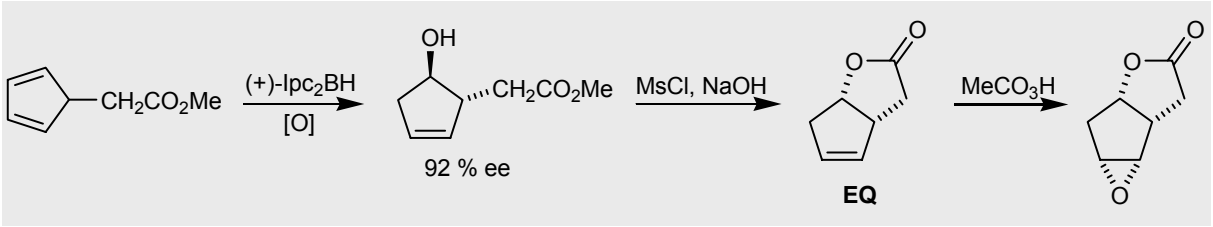
Figure 14. Preparation of enantiomers of Ipc_2BH and $IpcBH_2$



The hydroboration of *cis*-alkenes with high optical induction was realized by utilizing diisopinocampheylborane (Ipc_2BH) of "100 ee" which could be obtained by recrystallization. These results could be extended to heterocyclic alkenes as well. The hydroboration of heterocyclic alkenes likewise is both regio- and stereoselective.[112]

The exceptional ability of diisopinocampheylborane (Ipc_2BH) to hydroborate *cis* alkenes has been used in many organic synthesis, for example for Corey's lactone intermediate **EQ** for prostaglandin synthesis (Scheme 34).[113]

Scheme 34. Corey's lactone intermediate for the synthesis of prostaglandin[113]

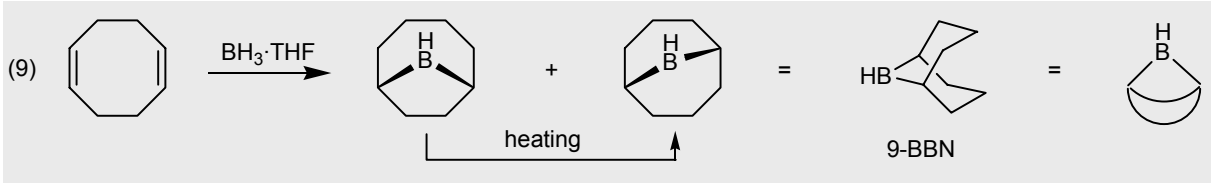


When Ipc_2BH was used for asymmetric hydroboration of other classes of alkenes such as *trans*-alkenes, 2-methyl-1-alkene, and trisubstituted alkenes, the optical inductions were poor.[110b,110c]

Considering the steric requirements of different classes of alkenes, it was envisaged that momoisopinocampheylborane ($IpcBH_2$) would handle classes of alkenes that were more hindered than the *cis* derivatives. $IpcBH_2$ has been found to be useful for the asymmetric hydroboration of *trans* alkenes and trisubstitued alkenes.[114] Thus, Ipc_2BH and $IpcBH_2$ are complementary to each other and together handle three of the four classes of alkenes with good to excellent asymmetric induction.[110b,110c]

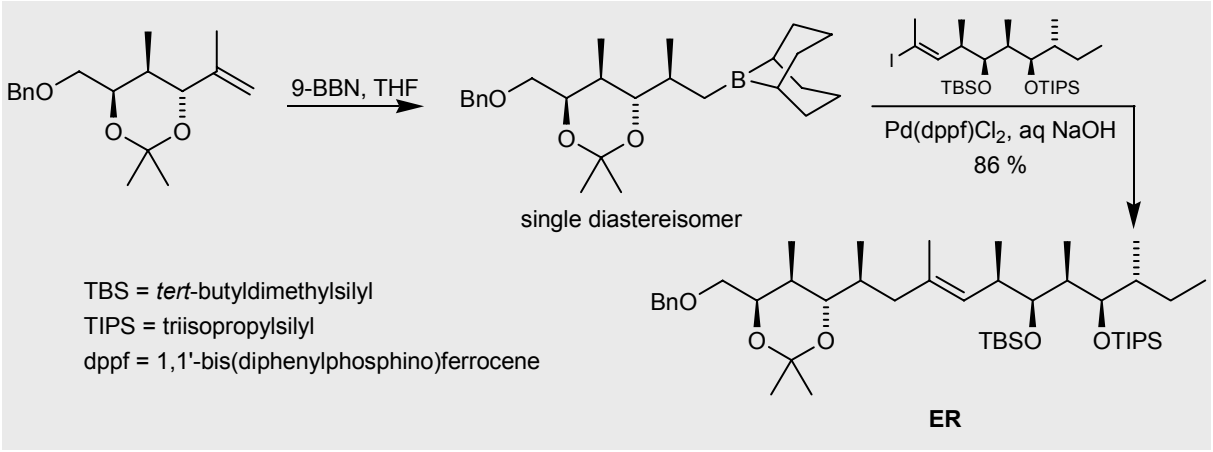
5.3.1.2 9-Borabicyclo[3.3.1]nonane (9-BBN)

Addition of borane tetrahydrofuran (BH_3·THF) to *cis*,*cis*-1,5-cyclooctadiene gives a mixture of 9-borabicyclo[4.2.1]nonane and 9-borabicyclo[3.3.1]nonane. On heating, the [4.2.1] system isomerizes to the thermodynamically more stable [3.3.1] compound which is known as 9-BBN (Eq. 9).[108c]



9-BBN is mainly used for hydroboration but also is valuable in selected functional group reductions. Hydroboration of alkenes by 9-BBN gives excellent regioselectivity for boron at the less hindered carbon, an advantage over other hydroboration reagents.[115a,115b] The rate of hydroboration increases with electron-donating substitutes on the alkenes but decreases as the steric demands of the alkenes increase. Studies showed that 9-BBN was an excellent hydroboration reagent for disubstituted terminal olefins. [115] The diastereoslective hydroboration of this class of substrates has been documented by Still and Barrish,[115c] who found that reactions of allylic alcohol derivatives generally afford the *anti* isomer, with 9-BBN furnishing the highest selectivities. For example, ebelactone was prepared by a convergent approach, coupling a functionalized 9-alkyl-9-BBN with a vinyl iodide using palladium complex as a catalyst (Scheme 35).[116]

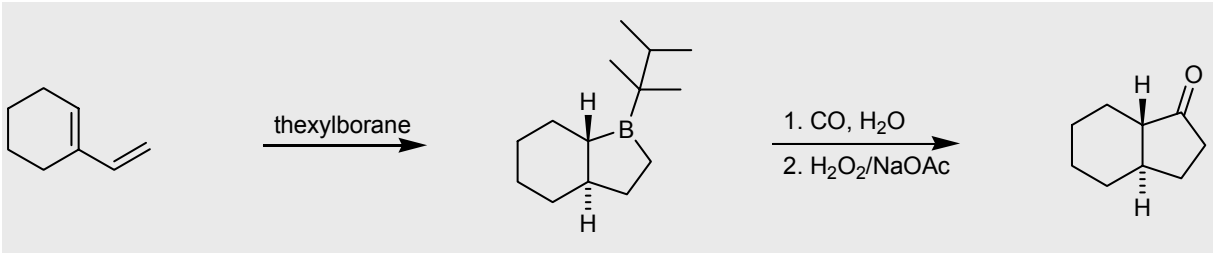
Scheme 35. Diastereoselective hydroboration of a 1,1-disubstituted terminal olefin with 9-BBN in the course of a synthesis of ebelactone via the coupling product **ER**.



5.3.1.3 Thexylborane

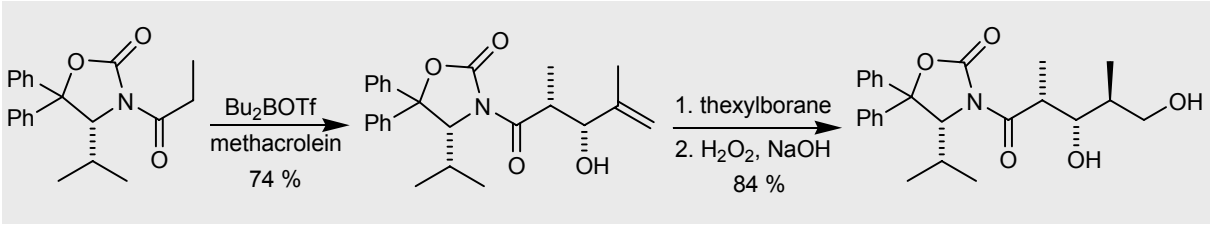
1,1,2-Trimethylpropylborane (thexylborane) is a monoalkylborane prepared by hydroboration of 2,3-dimethylbut-2-ene with borane tetrahydrofuran (BH_3·THF). The presence of two boron-hydrogen bonds in thexylborane makes it ideal for hydroboration of dienes. Hydroboration of dienes is often coupled with subsequent carbonylation or oxidation to give cyclic ketones (Scheme 36).

Scheme 36. Synthesis of cyclic ketone via hydroboration with thexylborane



Loiseleur and co-workers[117] found that thexylborane was the preferred hydroborating agent to convert 1,1-disubstituted alkenes to the corresponding alcohol in the synthesis of discodermolide, because this not only gave similar diasteroselectivities as 9-BBN, but it also facilitated the isolation of the diol product due to the higher volatility of the 2,3-dimethyl-2-butanol byproduct after oxidative workup (Scheme 37).

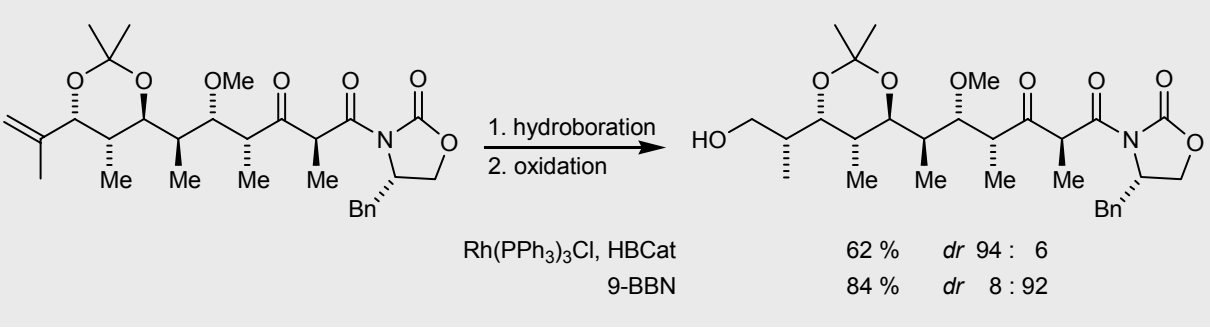
Scheme 37. Asymmetric hydroboration with thexylborane[117]



Some other dialkylboranes, such as dicyclohexylborane,[118] disiamylborane[118b] were also employed in asymmetric synthesis. Selective hydroborations of terminal alkenes in the presence of aldehyde and ketone have been realized using dicyclohexylborane or disiamylborane.[118d]

In addition, transition metal-catalysis of asymmetric hydroborations provides access to functionalized organoboron derivatives that can't easily be prepared using traditional reagents.[119] Catecholborane (HBCat) plays a significant role in this type of hydroboration. Rhodium-catalyzed hydroboration[119c] of 1,1-disubstitued olefins provides a stereochemical outcome complementary to that observed with 9-BBN. The reaction has some importance for the preparation of highly substituted propionate units as demonstrated by Evans and Sheppard in a synthesis of Ionomycin (Scheme 38).[119e]

Scheme 38. Diastereoselective rhodium-catalyzed hydroboration[119c]



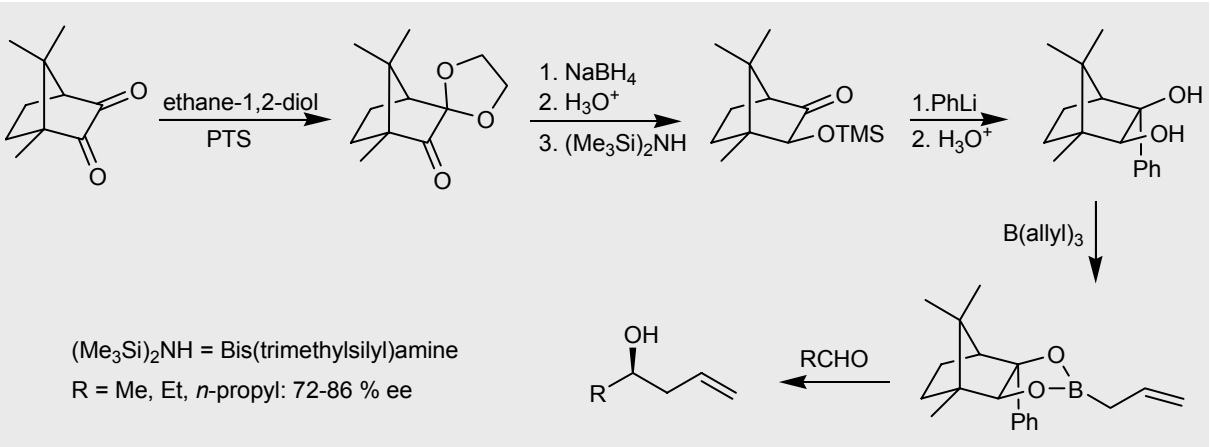
5.3.2 Asymmetric allyl- and crotylboration[36a,d,e,i,110d,120,121,122]

Allylboration was introduced by Mikhailov *et al.* who pointed out that triallylborane, in marked contrast to the saturated trialkylboranes, undergoes fast addition to carbonyl groups.[123]

5.3.2.1 Allyl- and crotylboration of aldehydes

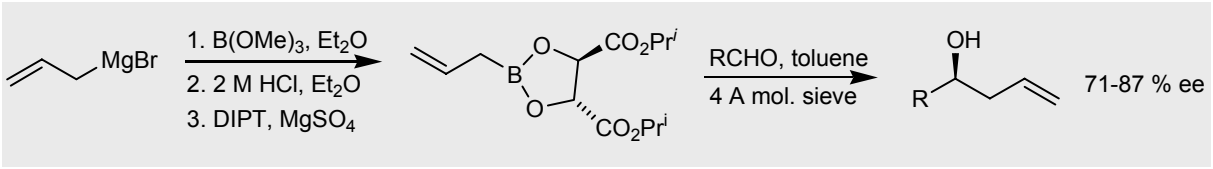
Allylboranes that react with aldehydes to produce homoallylic alcohols have attained considerable importance in stereoselective synthesis. The first “chiral” version of this reaction was carried out by Hoffmann *et al.* with moderate success using a chiral auxiliary derived from camphor (Scheme 39).[124] Hoffmann and colleagues studied various allyl- and crotylborations utilizing this auxiliary for asymmetric synthesis.[124b-e]

Scheme 39. The first asymmetric allylboration



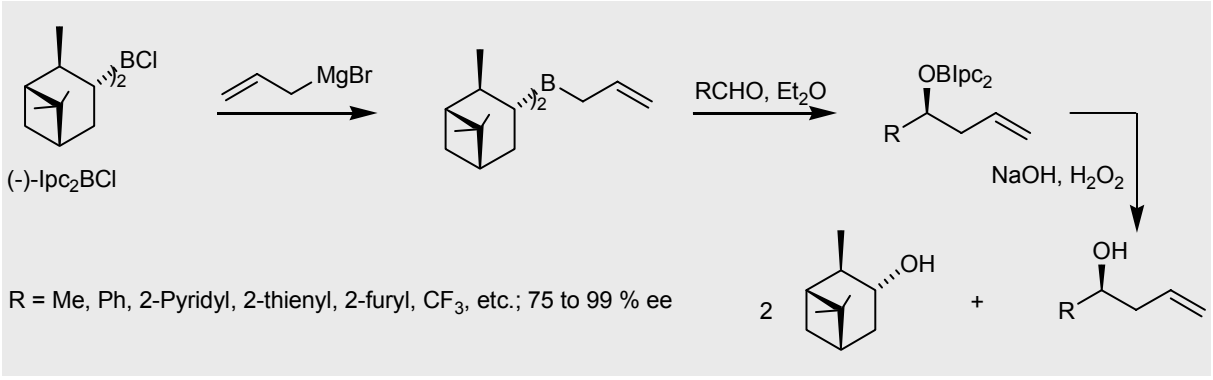
Diisopropyl tartrate was used as a chiral auxiliary for allylboration and crotylboration of aldehydes by Roush and coworkers (Scheme 40).[120d-g] Tetramidoallylboronates provide better selectivity in allylboration than tartrate esters.[125]

Scheme 40. Tartrate ester for crotylboration[120d-f]



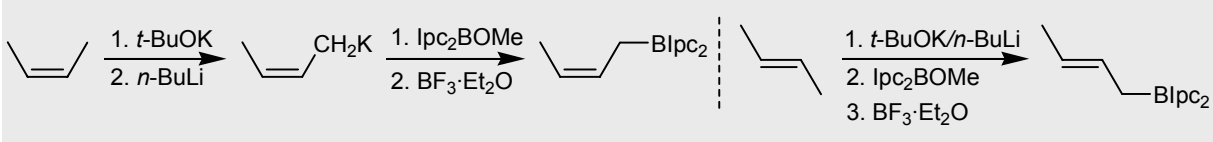
Brown and Jadhav[120h] put α-pinene to test for allylboration and achieved an economical reaction with predictable stereochemistry and high enantioselectivity. *B*-Allyldiisopino campheylborane, prepared from either *B*-chlorodiisopinocampheylborane (DIP-Chloride™) or *B*-methoxydiisopinocampheylborane and allyl Grignard reagent, provided high ee's for most of the aldehydes tested, including heterocyclic and fluorinated aldehydes (Scheme 41).[126] With chiral aldehydes, the reagent controlled the diastereoselectivity leading to high de and ee values. High selectivities were also achieved in the allylboration of a series of dialdehydes.[126b]

Scheme 41. Preparation and reaction of *B*-allyldiisopinocamphenylborane[120h-m]



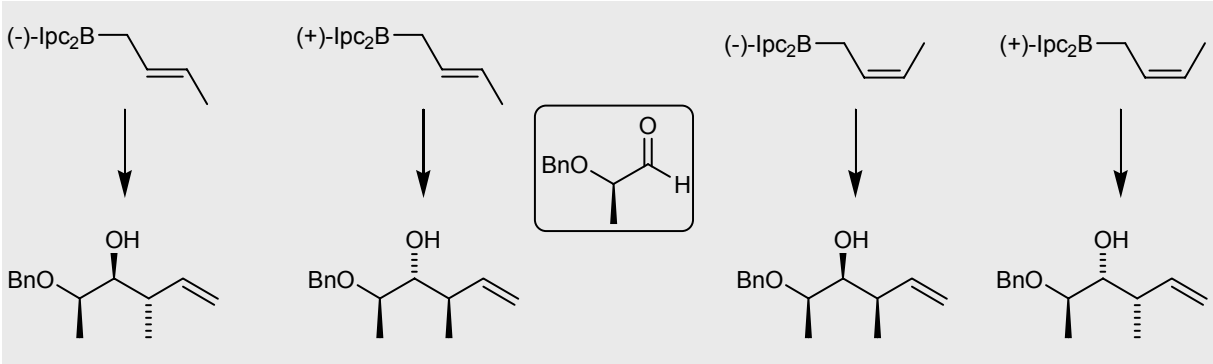
Hoffmann and coworkers synthesized (*E*)-and (*Z*)-crotylboronates and reported that the configuration is transferred during the crotylboration of aldehydes.[120b] The preparation of isomerically pure (*E*)- and (*Z*)- crotylboronates from isomerically pure crotylpotassium was reported by Schlosser *et al.*.[127] Brown and Bhat[120j] utilized a similar procedure for the synthesis of isomerically pure *B*-(*E*)- and *B*-(*Z*)-crotyldiisopinocampheylboranes (Scheme 42).

Scheme 42. Preparation of crotyldiisopinocampheylborane[120j]



With the reaction of these derivatives with aldehydes the synthesis of the four possible isomers of β-methylhomoallyic alcohols was achieved with remarkable enantiomeric and diastereomeric efficiency. It proved important, however, to maintain the temperature below -45 °C to avoid scrambling of the crotylboranes. Since the reagent controls the diastereoselectivity in reactions with chiral aldehydes, it is possible to prepare all eight diastereomeric homoallylic alcohols at will by the appropriate choice of reagent and chiral aldehyde (Scheme 43).[127b]

Scheme 43. Crotylboration of chiral aldehydes by Brown *et al.*[127b]

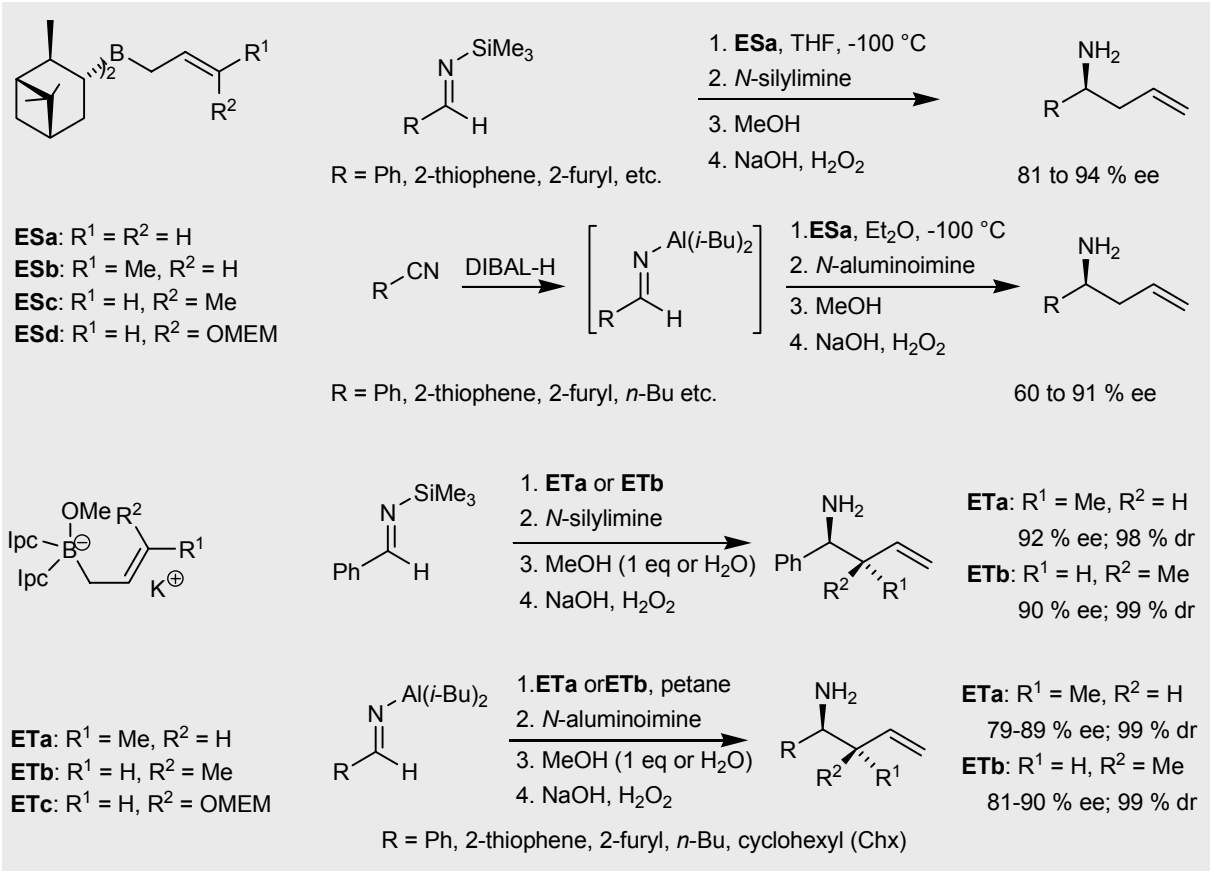


Regarding the allylboration of ketones, up to now, only moderate success was obtained.[127c]

5.3.2.2 Allyl- and cryotylboration of *N*-masked imines[121]

Asymmetric allyl- and crotylboration of *N*-masked imines with boron-based chiral reagents to form homoallylic amines remains a significantly undeveloped area. Itsuno and co-workers had reported the preparation of many kinds of homoallylic amine with moderate to good enantioselectivities from various *N*-protected imines.[121d,e] Recently, Ramachandran and coworkers systematically studied the allyl-, crotyl- and alkoxyallyl-boration of *N*-silyl or *N*-aluminoimines for the preparation of densely functionalized homoallylic amines (Scheme 44).[121h]

Scheme 44. Allyl- and crotylboration of *N*-silyl or *N*-aluminoimines[121h]

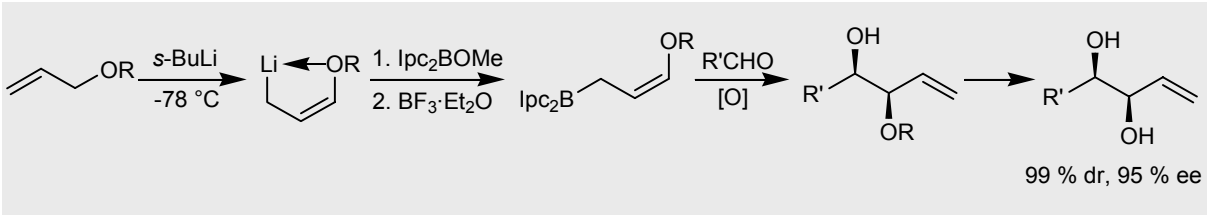


Methanol (one equivalent, or water) is a critical additive for the "allyl"-boration of both *N*-silyl- and *N*-aluminoimines. It was observed that crotylborations proceed well with the boron "ate" complexes **ETa** or **ETb** rather than with "allyl"-dialkylborane reagents **ESa**-**ESc**. Due to the ready availability or the ease of preparation of nitriles, the simplicity of the reactions and high reliability in obtaining both enantiomers of the homoallylic amines in excellent diastereo- and enantioselectivities, this methodology will find wide application in organic synthesis.

5.3.2.3 Asymmetric synthesis of vicinal diols or vicinal amino alcohols[122]

The α-hydroxyallylation of aldehydes with (γ-alkoxyallyl)metal reagents is a particularly attractive strategy, since these α-hydroxyallylations generate *syn*- or *anti*-1,2-diols in concert with the formation of a carbon-carbon bond.[36j, 128] Brown *et al.* developed highly enantioselective procedures for the synthesis of *syn* diols by the reaction of aldehydes with [(*Z*)-γ-alkoxyallyl]diisopinocampheylborane. The reaction of this reagent with aldehydes at low temperatures exhibits high *syn* selectivity, and allows the preparation of *syn*-1,2-diols with high ee value after removal of the *O*-alkyl protection groups (Scheme 45).[71]

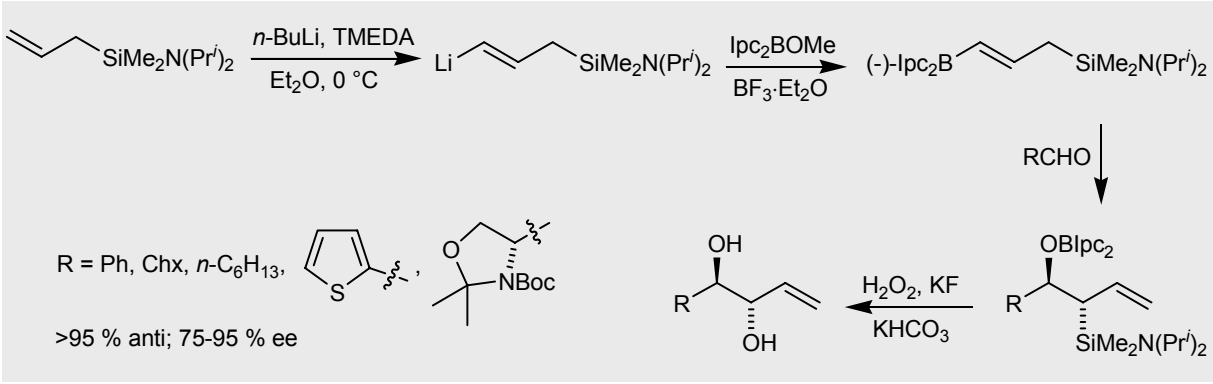
Scheme 45. Asymmetric synthesis of vicinal *syn* diols with alkoxyallylation of aldehydes[71]



Efforts to synthesize substituted *anti*-diols from (*E*)-(γ-alkoxyallyl)metal reagents, however, have not met with as much success. (*E*)-(γ-Alkoxyallyl)boron reagents have proved difficult to prepare because of the configurational instability of the (*E*)-γ-alkoxyallyl anion precursors.[128c]

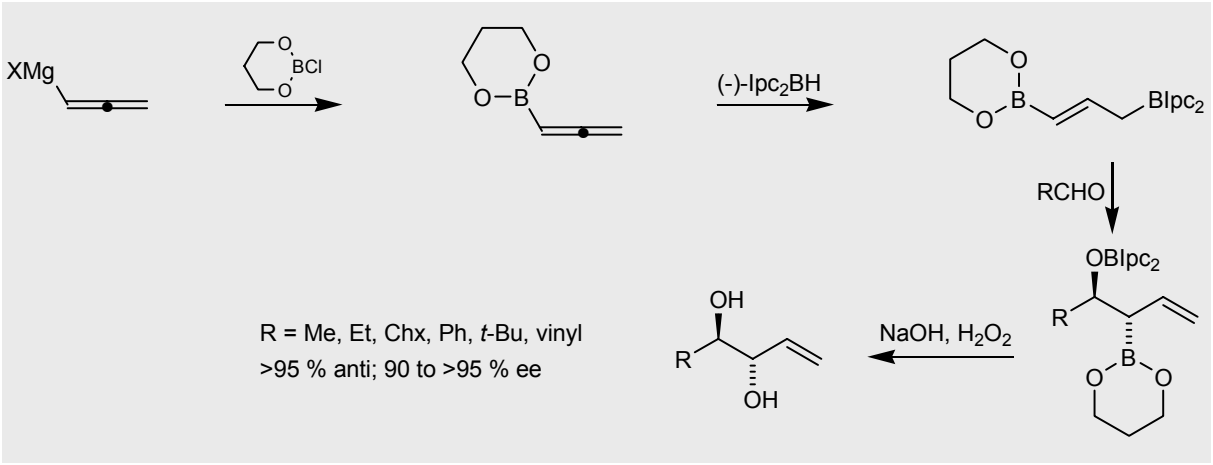
Barrett and Malecha[122d] synthesized γ-(dialkylaminosilyl)allyldiisopinocampheylborane as a surrogate for the preparation of *anti* diols with excellent absolute and relative stereocontrol (Scheme 46).

Scheme 46. Asymmetric synthesis of of vicinal *anti* diols[122d]



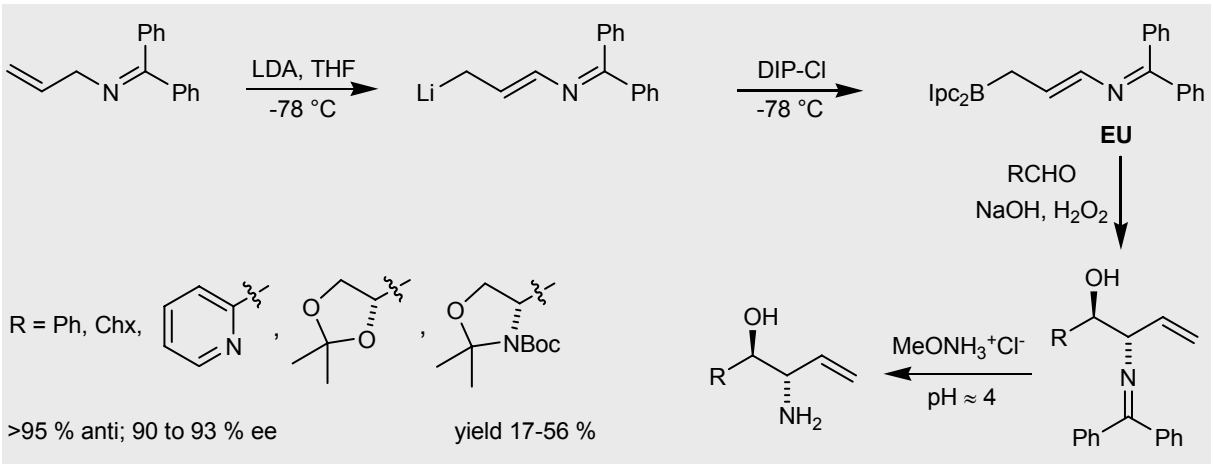
Brown and Narla achieved the synthesis of a [(*E*)-γ-(1,3,2-dioxaborinanyl)allyl]diisopinocampheylborane reagent by hydroboration of *B*-allenyl-(1,3,2-dioxaborinane), which was prepared by treatment of allenylmagnesium bromide with a *B*-chloro(1,3,2-dioxaborinane). This reagent permitted the synthesis of *anti*-diols in excellent isomeric and enantiomeric purity (Scheme 47).[122a]

Scheme 47. Asymmetric synthesis of vicinal *anti* diols[122a]



Vicinal amino alcohol units are abundently found in many natural products with pharmacological properties and are of utmost importance in medicinal and biological research.[1c] Barrett and coworkers reported a convenient synthesis of *anti* vicinal amino alcohols with high diastereoselectivity and enantoselectivity using an "imino" allylborane reagent **EU** (Scheme 48).[122i]

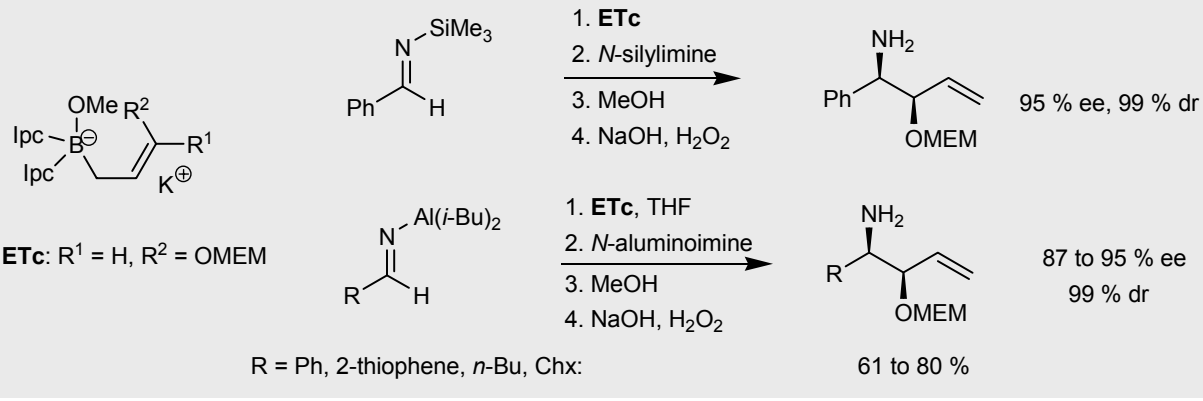
Scheme 48. Asymmetric synthesis of vicinal *anti* amino alcohols



Alkoxyallylboration of aldehydes with the chiral boron reagent **ESd** has found many applications in the synthesis of vicinal *syn*-diols as discussed in Scheme 45. However, there are no literature reports regarding alkoxyallylboration of imines for the prepartion of vicinal amino alcohols. Ramachandran and Burghardt[121h] gave the first report about alkoxyallylboration of *N*-silyl and *N*-aluminoimines using the corresponding boron "ate" complex **ETc**, which was obtained by reaction of allylic anion with *B*-methoxydiisopinocampheylborane.

Alkoxyallylboration with the “ate” complex **EQc** proceeded smoothly, and after alkaline oxidative workup, the *syn* alkoxy amines were obtained with high ee value and excellent diastereoselectivity (Scheme 49). In this type of reaction, the addition of methanol (one equivalent) is as critical for alkoxyallylboration as in the “allyl”-boration of both *N*-silyl- and *N*-aluminoimines. The homoallylic amines could readily be converted into β-amino acids or γ-lactams by elaboration of the terminal double bond.[121h]

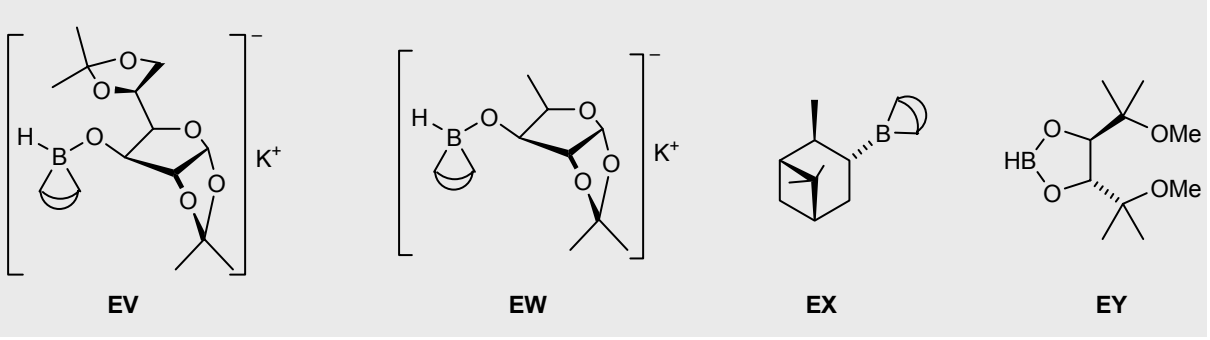
Scheme 49. Asymmetric alkoxyallylboration of *N*-silyl or *N*-aluminoimines[121h]



5.3.3 Asymmetric reduction of ketones and ketimines with boron-based reagents[110e,f,129]

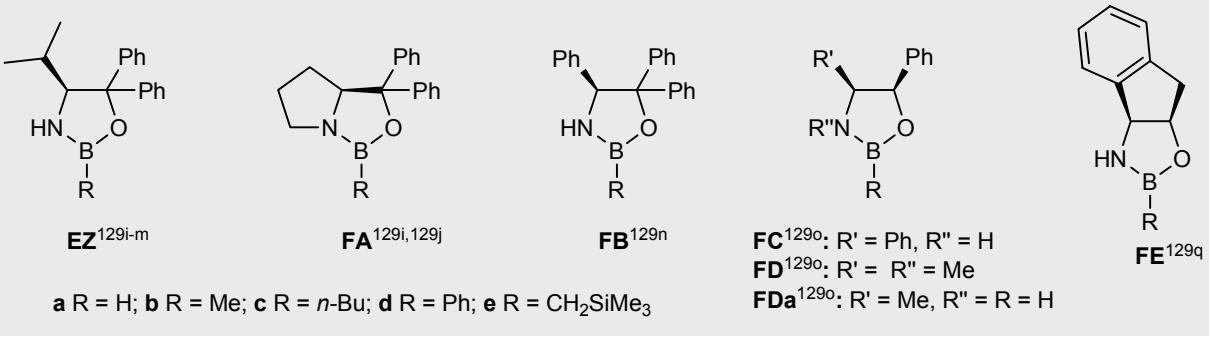
Potentially useful asymmetric reductions using boron-based agents involve both stoichiometric and catalytic processes. Of the stoichiometric reagents reported, those that are most promising for the highly enantioselective reduction of various functionalized ketone are borohydrides modified by monosaccharides – K-glucoride [potassium 9-*O*-(1,2:5,6)-di-*O*-isopropylidene-α-D-glucofuranosyl]-9-boratabicyclo[3.3.1]-nonane] **EV**,[129e] and K-xylide [potassium 9-*O*-(1,2-*O*-isopropylidene-5-deoxy-α-D-xylofuranosyl)-9-boratabicyclo[3.3.1]-nonane] **EW**[129f] – and α-pinene-based organoboranes including Ipc_2BH,[112a] Ipc_2BCl,[129g] and *B*-Ipc-9-BBN **EX**[129a]. These reagents show extraordinary consistency and predictable as induction stereochemistry in the reduction of ketones. A chiral dialkoxyborane, **EY**,[129h] was effectively used for the reduction of imines (Figure 15). Despite much remarkable success using these stoichiometric reagents, limitations to their widespread use remain such as availability, cost, the need for product purification and recovery of the chiral auxiliary. Thus, it appeared desirable to develop catalytic processes for these types of reduction as shown in Figure 16.[110e]

Figure 15. Stoichiometric boron-based chiral reducing agents



Since Itsuno[129l,129m] and Corey[129i-k] reported the oxazaborolidine-catalyzed asymmetric borane reduction, a number of such reductions of prochiral ketones have extensively been studied.[129b-d] These reductions furnish high enantioselectivities and predictable configuration even in the presence of 2 mol % of oxazaborolidines.[129j] The oxazaborolidines **EZ**–**FE**[129i-q] have successfully been applied to the reduction of functionalized ketones and imines (Figure 16). Borane-THF, borane methyl sulfide (BMS), and catecholborane (HBCat) have so far been the most commonly used borane carriers for such catalytic reductions.[110e]

Figure 16. Catalytic boron-based reagents

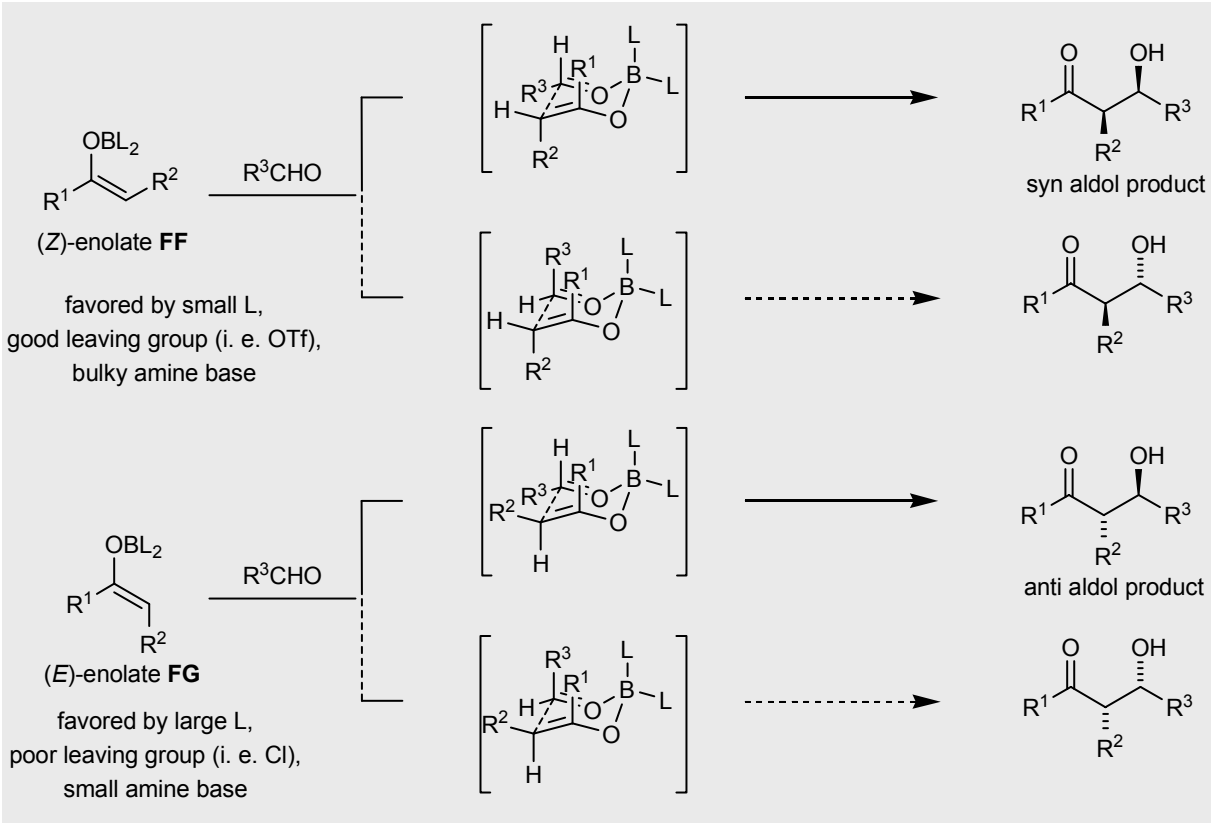


5.3.4 Boron-mediated asymmetric aldol reaction[110g-q]

Among all the possible enolates that one could form from a ketone, boron enolates would appear to provide the greatest potential for accomplishing high levels of “aldol asymmetry” on the basis of their physical properties. Not only are these intermediates homogenous and uncomplicated in terms of aggregation state, but they provide access to tight and organized transition states because *B*-*O* bonds are relative short and far less nucleophilic than their metallated counterparts. As such, “chiral” information that has been encoded into the reactants should, in principle, be faithfully expressed in the aldol products. In practice, in order

to accomplish any level of aldol stereoselectivity, one must first be able to convert a given ketone into its corresponding (*E*)- or (*Z*)- enolate at will and with complete stereoselectivity.

Scheme 50. Models for stereoselectivity in aldol additions with boron enolate*[110g]



The oxygen-boron substitutent always has a higher priority than R^1 in structures **FF and **FG** in assigning (E)-and (Z)-enolate configurations.*

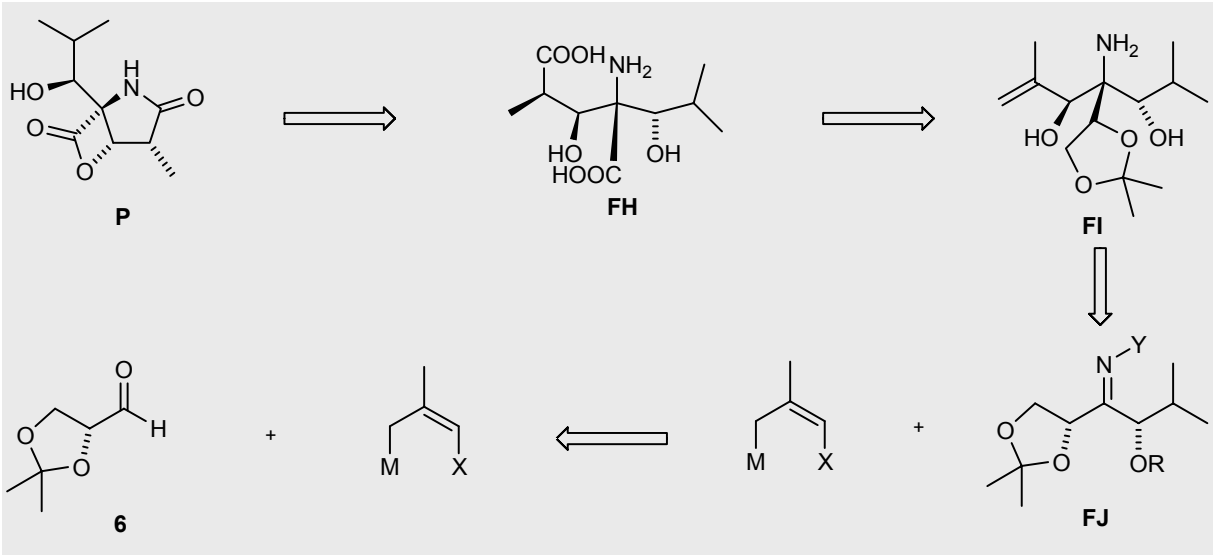
Which enolates regio- and stereochemistry ultimately results, however, are governed by several factors, including the steric requirements of the substrate and the boron ligands, the leaving group on the boron reagent (only triflate or chloride will be considered here), and the size of the amine base. The outcomes then are quite predictable. The general rule is simply that the use of dialkylboron chloride reactants with large ligands (such as a cyclohexyl ring) in combination with small bases (such as Et_3N) affords (*E*)-enolate **FG**, while the joint power of dialkylboron triflates bearing small alkyl ligands (such as *n*-butyl) and sterically demanding amine bases (such as *i*-Pr_2NEt) provides (*Z*)-enolates **FF** (Scheme 50). This boron-mediated asymmetric aldol reaction was applied to many total syntheses of natural products, for example, to that of the total synthesis of swinholide A by Paterson *et al.*.[110q]

5.4 Synthesis of lactacystin analogues

5.4.1 Retrosynthetic analysis and original synthetic plan of lactacystin C

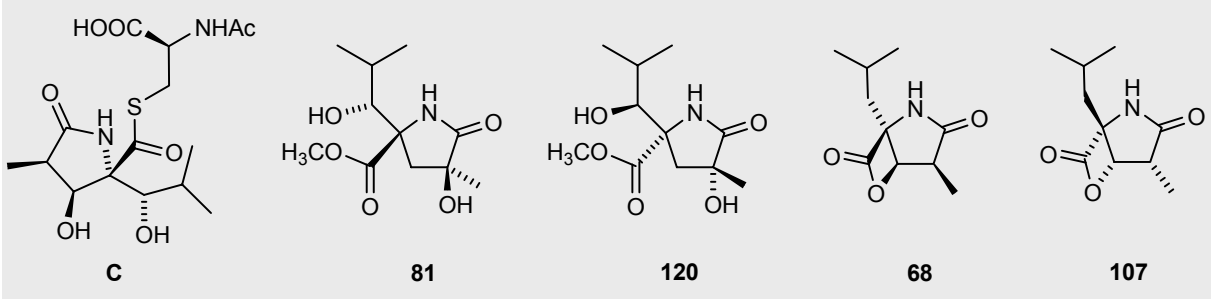
Lactacystin **C** is a highly complex γ-lactam, and, in itself a complicated α-amino acid as well. The lactacystin could be readily synthesized by treatment of the true inhibitor omuralide **P** with *N*-acetyl *L*-cysteine according the reported procedure.[12,95] Omuralide, in principle, could be constructed from the α,γ-amino acid **FH** by lactamization and lactonization respectively. Elaboration of the diol-acetonide and the terminal double bond in the intermediate **FI** could furnish the precursor **FH**. The tertiary carbon amine **FI** could be obtained from ketimine **FJ** or its derivatives by selective addition of organometallic reagents. The alkoxyallylation of glyceraldehydes **6**, followed by oxidation and imine formation, could afford the ketimine **FJ**. The synthetic plan of the omuralide **P**, easily transformed to lactacystin **C**, is displayed in Scheme 51.

Scheme 51. Retrosynthesis plan of omuralide **P**



We herein describe a synthesis of lactacystin core analogue **120** and **81** (enantiomer of **120**) and the synthesis of the lactacystin β-lactone analogue **107** and **68** (enantiomer of **107**).

Figure 17. Analogues of the lactacystin core and its β-lactone

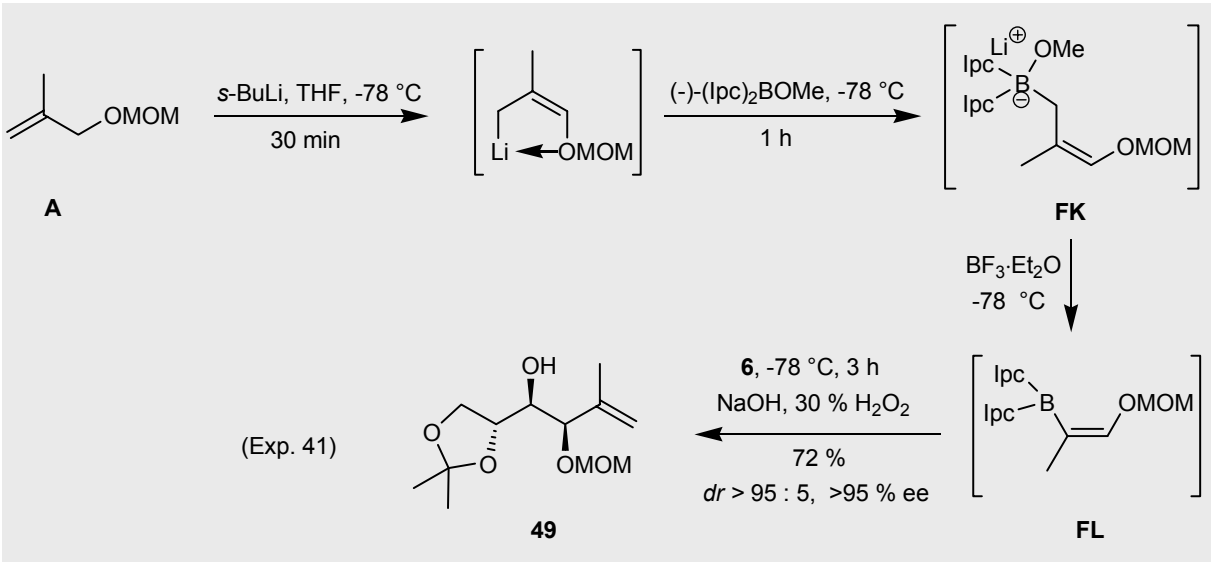


5.4.2 Efforts towards the synthesis of the lactacystin core analogue 120 and its enantiomer 81

5.4.2.1 Results and discussion*

Initial focus was directed towards investigating an approach to the total synthesis of the lactacystin β-lactone **P** according to the original plan (Scheme 51). The alkoxyallylation of D-glyceraldehyde **6** was accomplished successfully as shown in Scheme 52. 3-(Methoxymethoxy)-2-methylprop-1-ene **A** was prepared from 2-methylprop-2-en-1-ol by reacting with methoxymethyl bromide (MOMBr) [130] and then was metalated with *sec*-butyllithium in THF at – 78 °C according to Brown's method.[71] The resulting organolithium compound was treated with (-)-*B*-methoxydiisopinocampheylborane [derived from (+)-α-pinene] to form the "ate" complex **FK**. This intermediate ate complex reacted with boron trifluoride etherate to generate the corresponding [(*Z*)-γ-methoxyallyl] borane **FL** which was immediately treated with D-glyceraldehyde acetonide **6**[131] at – 78 °C. The reaction mixture upon oxidative work-up with hydrogen peroxide under alkaline conditions furnished the *threo* diol **49** with >95 % *syn* and >95 % diastereoselectivity.

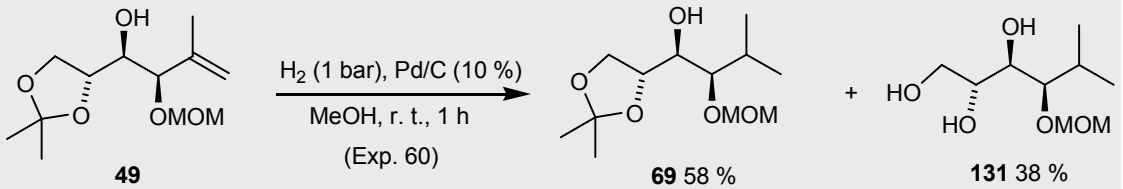
Scheme 52. Alkoxyallylation of glyceraldehyde **6**



The catalytic hydrogenation of the double bond in the olefin **49** proved to depend on the solvent: when the reaction was carried out in methanol, the required alcohol **69** was accompanied by the triol **131** (Eq. 10). However, the hydrogenation could smoothly be effected in ethyl acetate without loss of the protecting group, see equation (10).

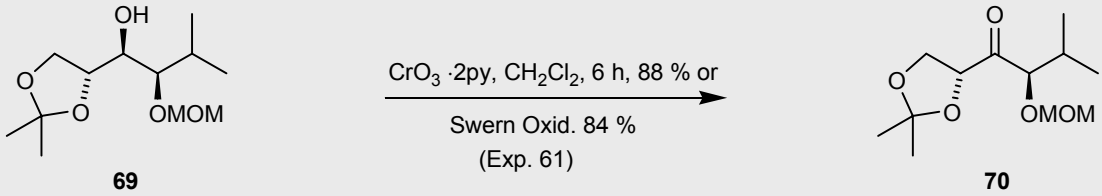
The discussion about this part concentrates on the synthesis of **81 (an enantiomer of **120**).*

(10)



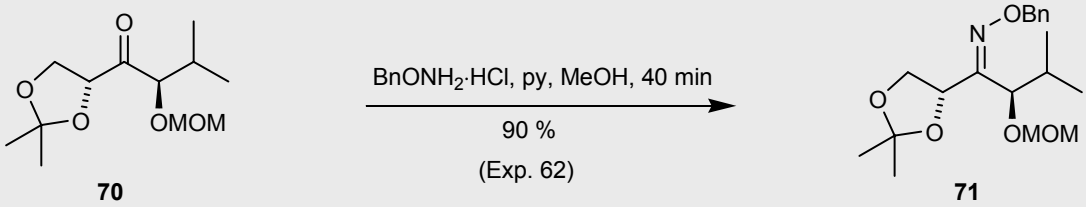
After oxidation of the alcohol **69** under Swern conditions[132] or with Collins reagent,[32b] the corresponding ketone **70** was obtained with good yield (Eq. 11).

(11)



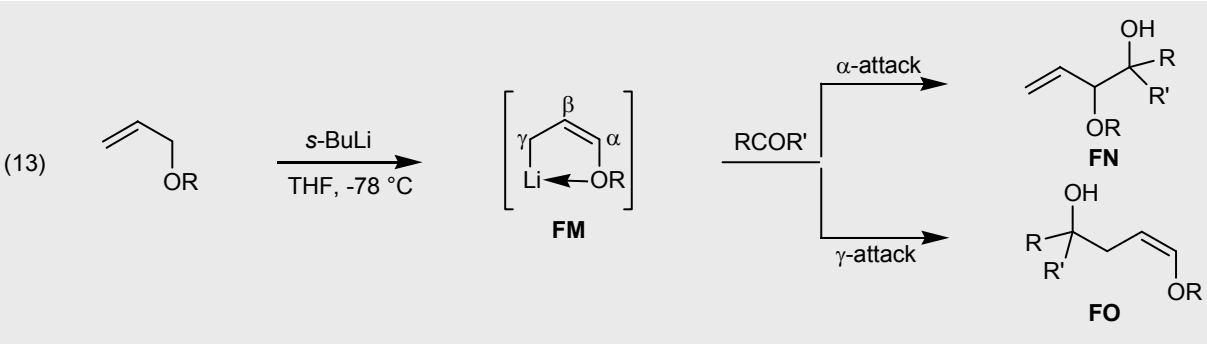
Next, we turned our attention to C=N double bond formation (**FJ** type) for the installation of left wing of the key intermediate **FI**. Unfortunately, it proved difficult to form an imine or nitrone under a variety of different conditions.[55,57] Nevertheless, to our delight, the *O*-benzyloxime ether **71** was readily obtained by condensation of the ketone **70** with *O*-benzylhydroxylamine in methanol as a single isomer in 90 % (Eq. 12).

(12)



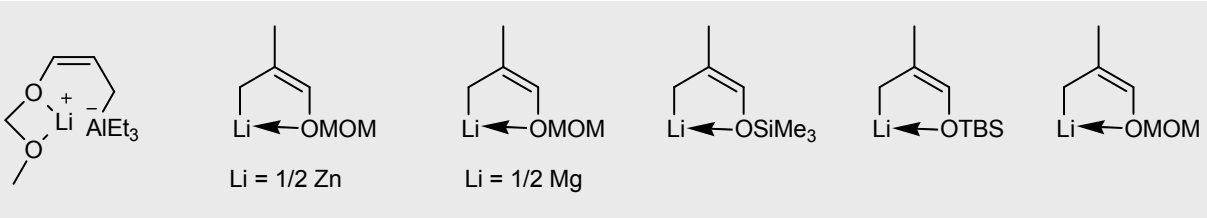
With the oxime ether **71** in hand, we investigated the stereoselective alkoxylallylation to form an intermediate of the **FI** type (Scheme 51). According to our “first-generation” synthetic plan, attempts at alkoxylallylboration of the oxime ether **71** had only returned starting material under different conditions. For example, the reaction carried out at both high pressure (280 bar) and at higher temperature (room temperature) failed. Therefore, we attempted to utilize the alternative of allyloxy carbanions via an allylic metal “ate” complex. Still[133] reported that alloxy carbanions **FM** was prepared by metalation of allyl ethers with *sec*-butylithium at low temperature. The reaction of this highly nucleophilic compound with electrophiles (carbonyl compounds) can lead to allylic ethers **FN** via α-substitution or to enol ethers **FO** via

γ-substituttion (Eq. 13). On the other hand, the lithium salt of trimethylallyloxysilane in THF-HMPA is known to undergo α-attack on a variety of aldehydes and ketones with 98-100 % regioselectivity.

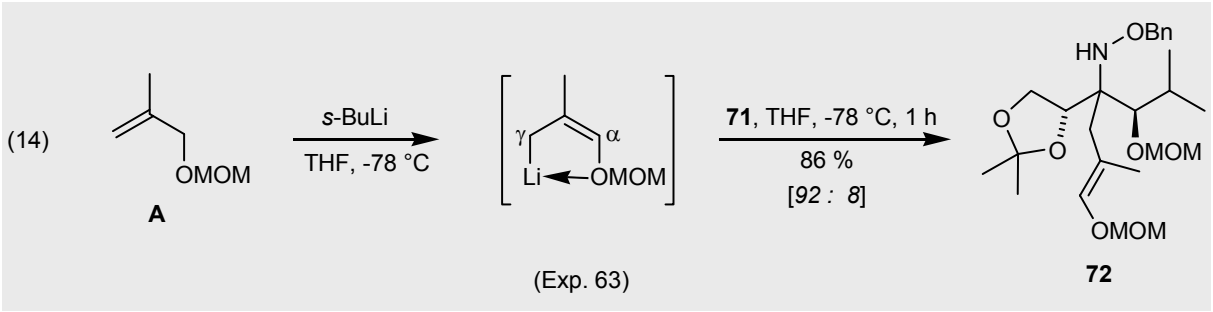


Later, Yamamoto *et al.*[134] discovered that the addition of the α-position was regioselectivity realized by using triethylaluminium and boron ate complexes of allyloxy carbanions **FM**. The aluminium ate complex reacted more smoothly with carbonyl compounds than the corresponding boron ate complex, and generally the regioselectivity was extremely high. The corresponding allylzinc reagent (**FM**, Li = *1/2* Zn) was demonstrated to effect regioselective α-attack by Evans.[135] Only one report of allyloxy carbanions (**FM**, R = TBS) reacting with a nitrone at the α-position was available in the literature.[136] With our care, however, the addition of allyloxy carbanions metal ate complexes mentioned above to the oxime ether **71** all failed to give expected products (Figure 18).

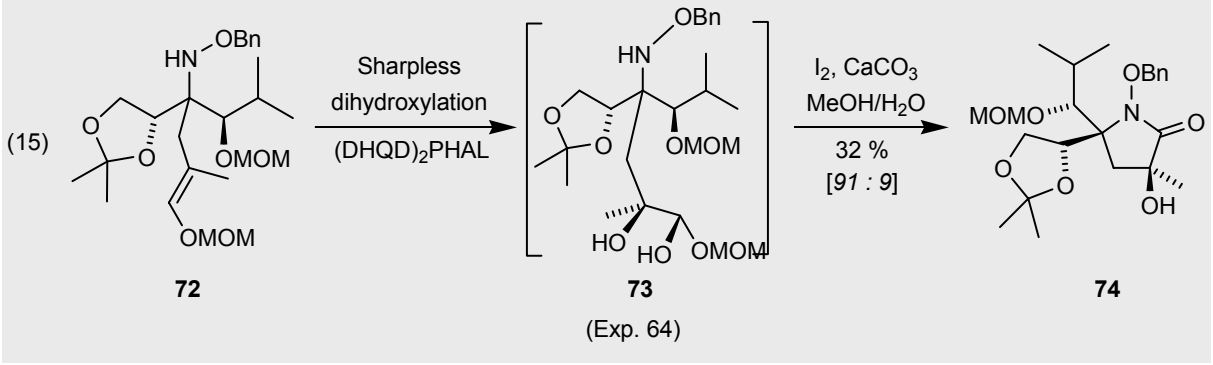
Figure 18. Allyloxy carbanions metal ate complexes, used in this work



The aluminium ,zinc, and magnesium “ate“ complexes did not react with the *O*-benzyloxime ether **71**. Only the lithiated allylic silyl ether indeed gave an addition product, but this proved to be problematic. The lithiated **A** reacted with the oxime ether **71** by γ-attack to afford the enol ethers **72** with high diastereoselectivity (92 : 8) (Eq. 14).



We then tried to correct this, but all efforts to allylic oxidation of the enol ether **72** with selenium dioxdie[137] for installing the required hydroxyl group were fruitless. At this point, it became clear that our initial idea of second addition to C=N was not viable partly because of the lack of reactivity of these imine derivatives and also of the oxime ether **71**. We realized that it should be possible to transform the enol ether **72** into the lactacytin core analogue by careful elaboration of the double bond. Gratifyingly, dihydroxylation of the enol ether double bond with Sharpless' method[40,138] [$(DHQ)_2PHAL$)] as a chiral ligand in this case, followed by oxidation of the hemiacetal with excess iodine in the presence of calcium carbonate,[139]directly afforded the lactam **74** in moderate yield (32 % from **72**), see equation (15).



The diastereoselectivity of dihydroxylation was determined by ^1H NMR of **74** (91 : 9). Removal of acetal protected group with ferric chloride hexahydrate[140] provided the vicinal diol **75**. This on periodate cleavage led to the corresponding aldehyde which was transformed to the ester **78** by oxidation with sodium chlorite and esterification with diazomethane (Scheme 53). Deprotection of the methoxymethyl group using acidic resin Dowex[72] and subsequent reduction of the benzyl ether as well as of the *N-O* bond afforded the lactacystin core analogue **81**.

Scheme 53

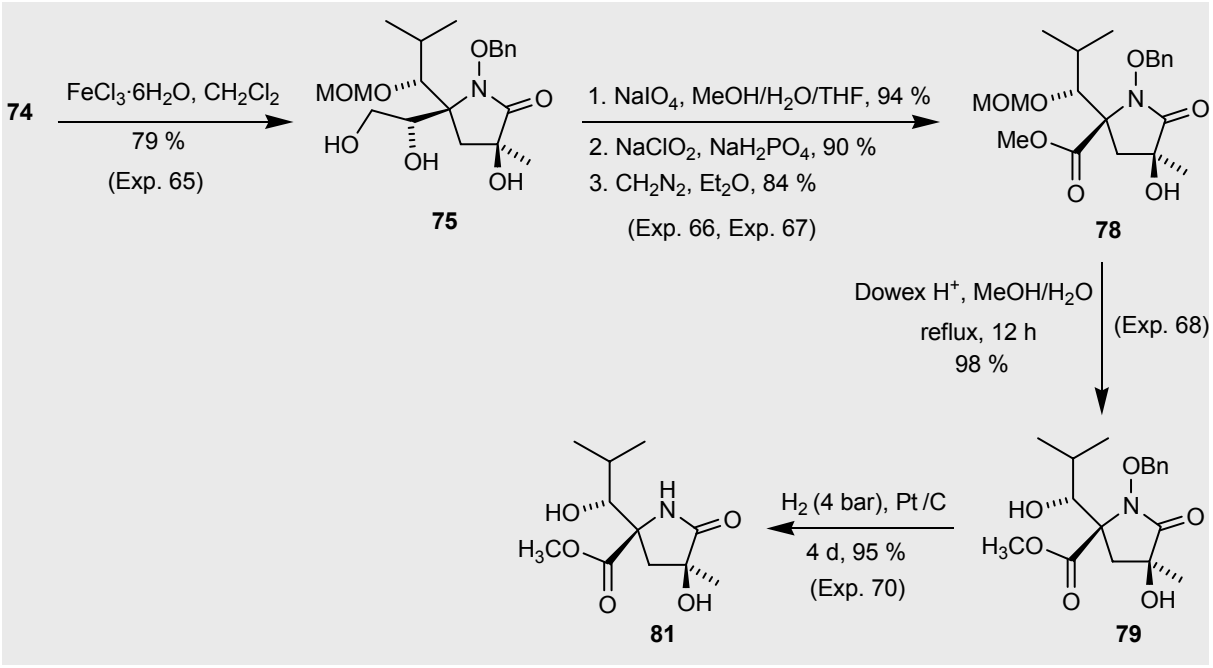
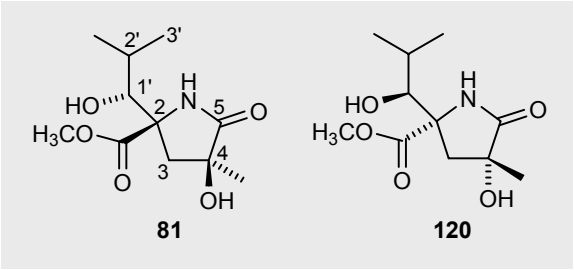


Figure 19. The optical rotation data of the lactacystin core analogues **81** and **120**

81: $[\alpha]_D^{20}$ = - 21.5 (*c* = 0.61, MeOH)

120: $[\alpha]_D^{20}$ = + 22.0 (*c* = 0.80, MeOH)



The lactam **81** was confirmed to constitute the enantiomer of the lactam **120**, for example, by comparison of the values of optical rotation and the NMR spectroscopic characteristics. The NMR data of the proline esters **81** and **120** are identical (Table 7 and Table 8) and the optical rotation values of **81** and **120** are almost same, but with the opposite sign (Figure 19).

Table 7. ^{1}H NMR data (δ in ppm) of the proline esters **81** and **120**

lactacystin core analogues	2'-CH_3	3'-H	4-CH_3	2'-H	3-H_a	3-H_b	1'-H	OCH_3
81	0.90	0.97	1.38	1.70	2.35	2.50	3.45	3.73
120	0.90	0.97	1.38	1.70	2.35	2.50	3..45	3.73
$\Delta\delta$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 8. Selected ^{13}C NMR data (δ in ppm) of the proline esters **81** and **120**

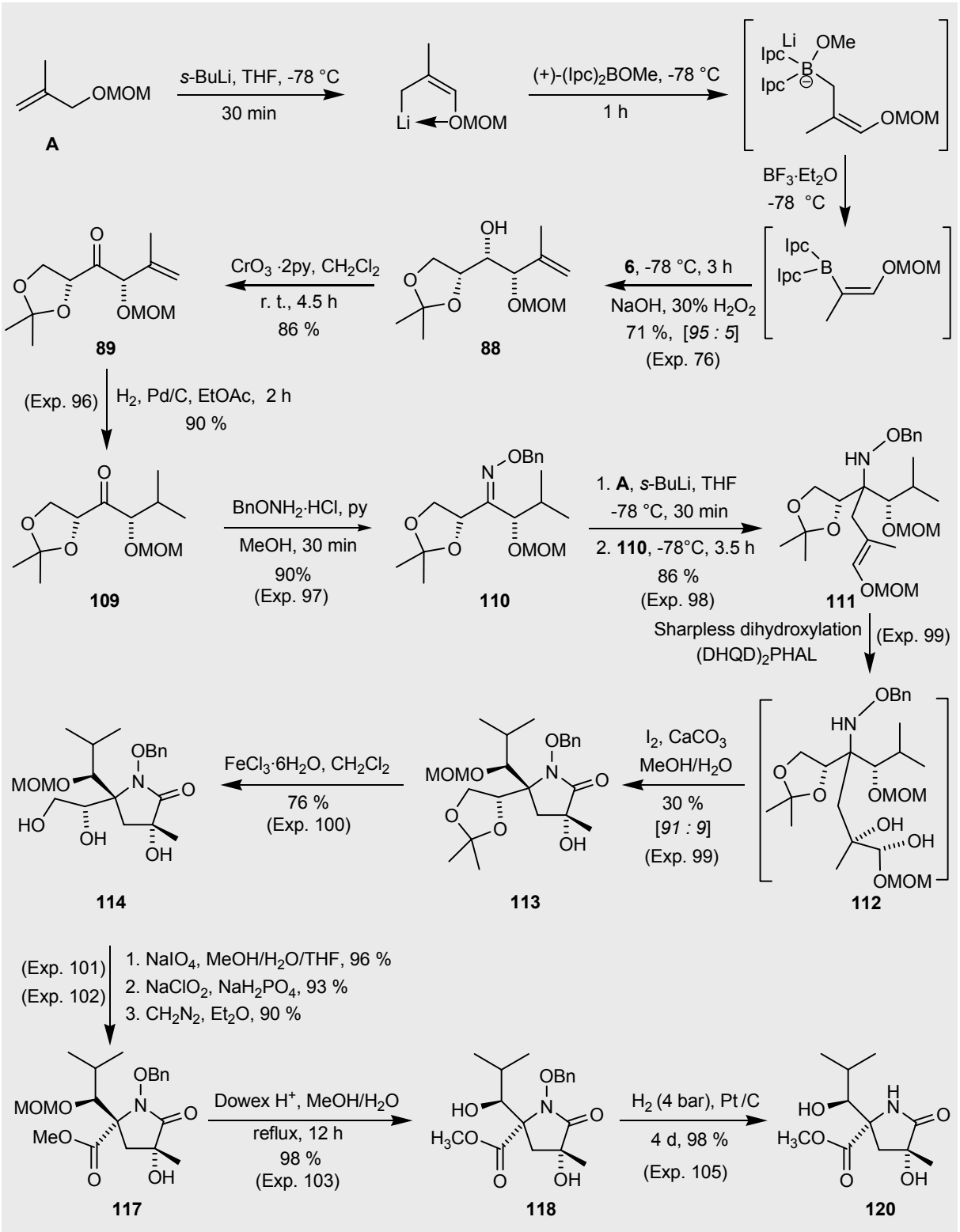
lactacystin core analogues	C-2	C-3	C-4	4-CH_3	C-5	$\underline{C}OOCH_3$
81	68.0	46.2	74.5	19.3	175.5	180.4
120	68.0	46.2	74.5	19.3	175.5	180.4
$\Delta\delta$	0.0	0.0	0.0	0.0	0.0	0.0

5.4.2.2 Synthesis of the lactacystin core analogue 120

The approach to the synthesis of the lactacystin core analogue **120** commenced on asymmetric alkoxyallylboration of aldehyde **6**[131] which provided the alcohol **88** (*dr* > 95 %, 95 % ee) in 71 % yield using the similar procedure as shown in Scheme 52.[71] During the synthesis of the alcohol **88**, the only difference from that of the alcohol **49** is that after metalation of 3-methoxymethoxy-2- methylprop-1-ene **A**, the resulting organolithium compound was treated with (+)-*B*-methoxydiisopinocampheylborane instead of (-)-*B*-methoxydiisopino- campheylborane.

With the diol **88** at hand, the ketone **109** could be readily obtained by a two-step sequence: i) oxidation with Collins reagent[32b] (86 %); ii) saturation of the C=C double bond by catalytic hydrogenation in ethyl acetate at normal pressure (H_2, Pd/C; yield 90 %). The ketone **109** was condensed with *O*-benzylhydroxylamine in methanol to provide the corresponding oxime ether **110** as a colourless oil (90 %). Only γ-attack was successful with lithiated **A**, leading to the *O*-benzylhydroxylamine **111** as a colourless oil in high diastereoselectivity (91 : 9) and good yield (86 %). The C=C double bond was *syn*-dihydroxylated according to Sharpless dihydroxylation[40,138] which gave the hemiacetal **112**. In an interesting transformation sequel, the hemiacetal **112** apparently underwent oxidation in the presence of an excess of iodine[139] to give the ester that cyclized to the lactam **113** with a high degree of diastereoselectivity (91 : 9), albeit in moderate yield (30 %). Removal of the isopropylidene group with ferric chloride hexahydrate[140] gave the free vicinal diol **114** in 76 % yield. This, on periodate cleavage led to the respective aldehyde which was transformed to the ester **117** in excellent yield (three steps, 80 %) by oxidation with sodium chlorite and esterification with diazomethane (Scheme 54).

Scheme 54. Synthesis of 3-deoxy lactacystin analogue **120**



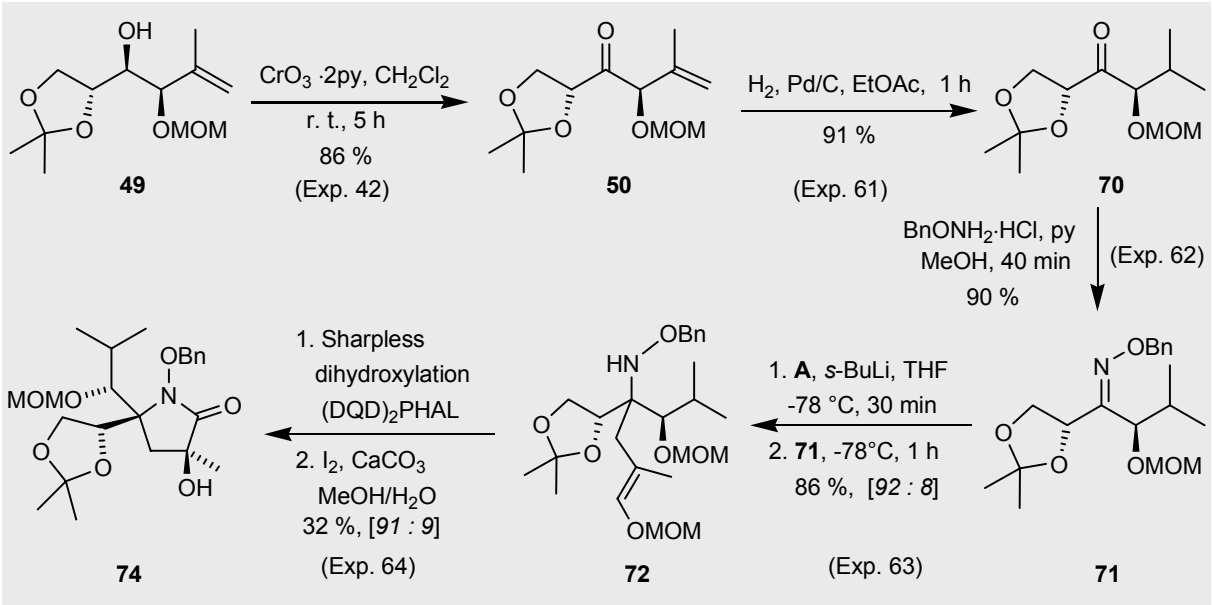
Finally, removal of the methoxymethyl group under acidic conditions using Dowex (H^+ form) in methanol/water (5 : 1)[72] gave the hydroxyl lactam **118** in excellent yield (98 %) and subsequent reduction of the benzyl ether as well as of the *N-O* bond furnished a novel lactacystin core analogue **120** (98 %) as a colourless, analytically pure powder.

5.4.2.3 Synthesis of the lactacystin core analogue 81

Utilizing the same strategy, the lactam **81** (the enantiomer of **120)** was synthesized also, by changing the chiral regents and ligands such as boron reagents for alkoxyallylation and Sharpless ligands for dihydroxylation.

The synthesis of the lactacystin core analogue **81** also started from the alkoxyallylation of the glyceraldehyde **6**. The alkoxyallylation provided the alcohol **49** with a high diastereoselectivity (> 95 : 5) and enantioselectivity (> 95 %) (see Scheme 52). The alcohol **49** was oxidized to the ketone **50** (88 %) which after hydrogenation was condensed with the *O*-benzylhydroxylamine in methol to furnish the corresponding oxime ether **71** as a single isomer (Eq. 11 and Scheme 55). The lithiated **A** reacted with the oxime ether **71** by γ-attack, leading to the enol ether **72** with a good diastereoselectivity (92 : 8) in high yield (86 %) (Eq. 14).

Scheme 55. Synthesis of the lactacystin core analogue **81**

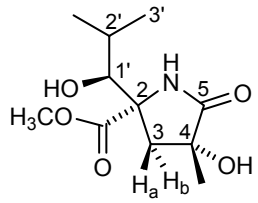


The Sharpless dihydroxylation of the enol ether **72**, followed by oxidation with iodine afforded the lactam **74** (*dr* = 91 : 9) in moderate yield (32 %). The lactam **74** was converted into the lactacystin core analogue **81** in five steps as detailed in Scheme 53. Finally, the lactam **81** was obtained as a colourless, analytically pure powder.

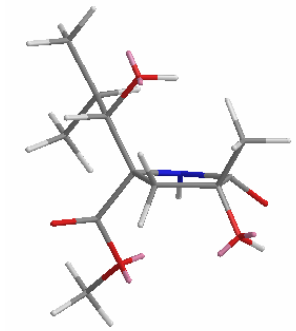
5.4.2.4 Determination of the configuration of 81 and 120

The configuration of the lactacystin core analogues **81** and **120** was established by 2D NMR spectroscopy (nuclear Overhauser effect spectroscopy, NOESY) The configuration of the γ-lactam **120** was assigned based on the following sequence: The configuration of the lactam **120** at C-1' was known from the alcohol **88** which was generated by stereoselective alkoxylallylation (Scheme 54). The stereoselective alkoxylation was performed by an addition of [(*Z*)-γ-methoxyallyl]borane **FK** which was generated from (+)-*B*-methoxydiiospinocamopheylborane with the aldehyde **6**. According to the literature,[71] the configuration at C-1' in the lactam **120** (at C-4 in the diol **88**) was confirmed. The configuration of the γ-lactam **120** at C-4 was assigned as predicted by Sharpless' empirical mnemonic rules[138a]. During the synthesis of the lactam **120**, the dihydroxylation of the olefin **111** was performed using $(DHQD)_2PHAL$ as a chiral ligand. In this case, the olefin **111** should be attacked from the top face (i. e. β face) which would lead to the orientation of the 4-methyl group as shown in the γ-lactam **120**.

Figure 20. 3D-model of **120**

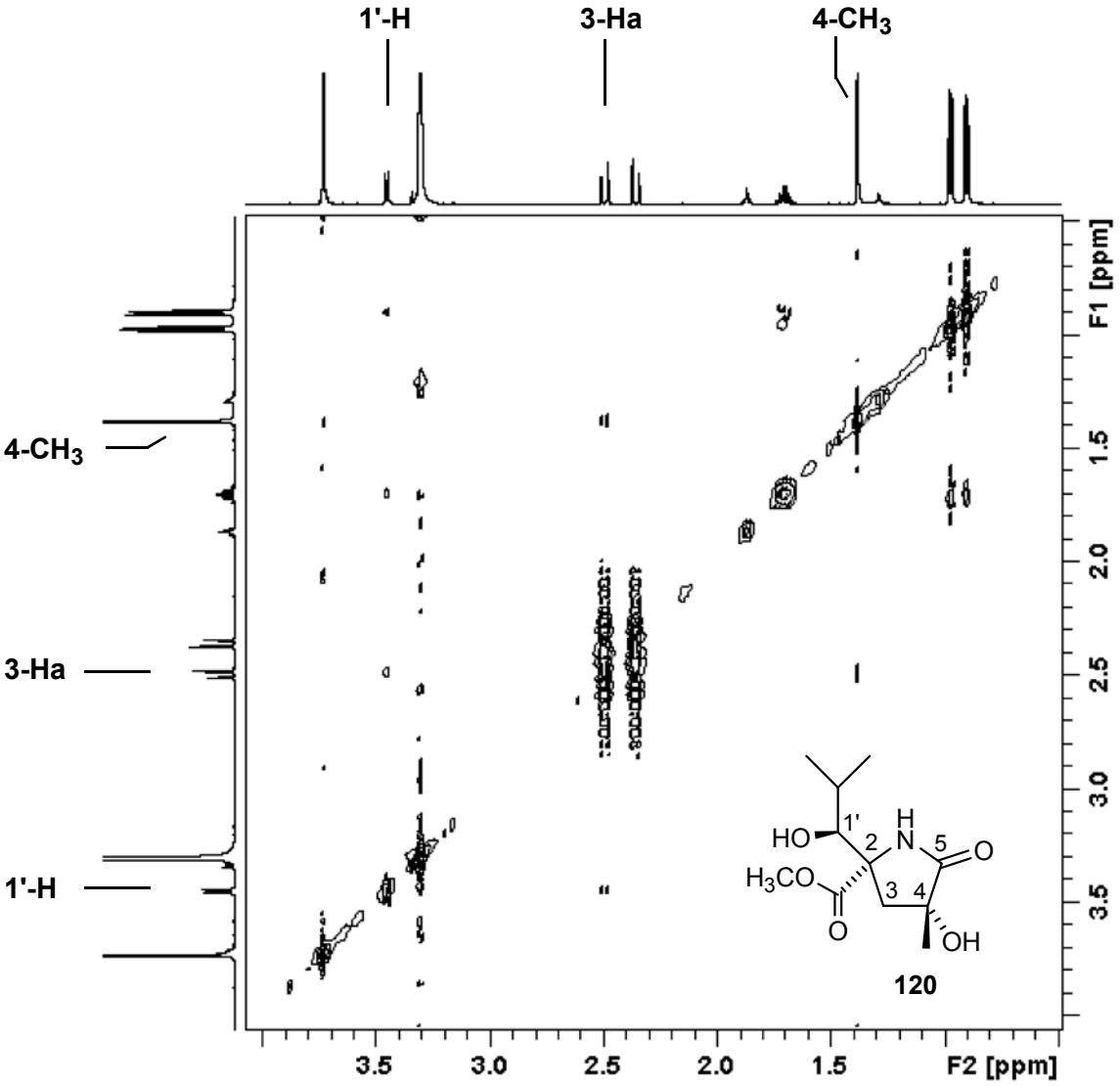


120



The remaining problem was the configuration at C-2 which was solved by NOE measurement (Figure 21). The NOE measurement displayed enhancement between 4-CH_3/3-H_a, 3-H_a/1'-H. Based on these observatives, 4-CH_3 and 3-H_a are located in the *cis* and 3-H_a and 1'-H are close in space. The 3D-model of the lactacystin core analogue **120** was simulated by means of ChemDraw software. According to this model, only the hydroxyisobutyl side-chain and 3-H_a are in *cis*, the correlation between 3-H_a and the side-chain could be observed (Figure 20). Thus, the hydroxyisobutyl side-chain and 4-CH_3 are situated *cis.*

Figure 21. NOESY of the γ-lactam **120**



5.4.2.5 Conclusion

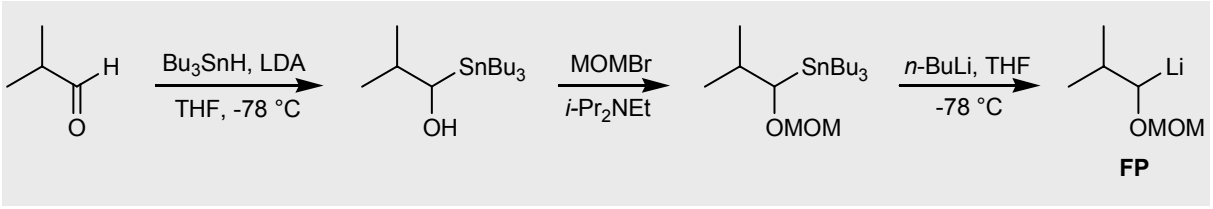
In summary, we have achieved the synthesis of the lactacystin core analogue **120** (13 steps, 7.4 %) and its enantiomer **81** (13 steps, 7.2 %) utilizing 3-(methoxymethoxy)-2-methylprop-1-ene as the starting material. The syntheses involve asymmetric alkoxylallylation, Sharpless dihydroxylation of an enol ether and subsequent oxidation by means of iodine to a γ-lactam via the ester as key steps. The configuration of the γ-lactam **120** was confirmed by NOE spectroscopy.

5.4.3 Synthesis of lactacystin β-lactone analogue 107 and its enantiomer 68

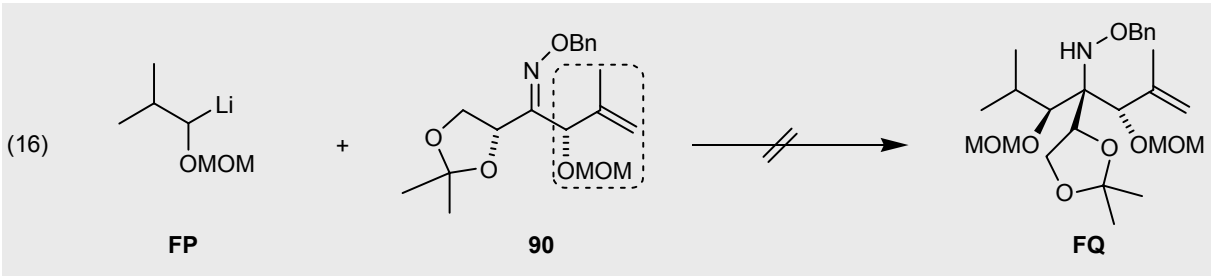
5.4.3.1 Results and discussion*

Albeit the expected addition of organoboron reagent to the oxime ether **71** could not be accomplished as laid out in the initial plan (Scheme 51), the addition of the organolithium reagents to oxime ethers had been reported.[141] The premise of our second synthetic approach towards lactacystin β-lactone **P** was based on the installation of the side-chain by addition of the α-alkoxylorganolithium reagent **FP** which could be prepared from isobutyraldehyde[142] to the oxime ether **90** (Scheme 56).

Scheme 56. Synthesis of the α-alkoxyllithium reagent **FP**[142]



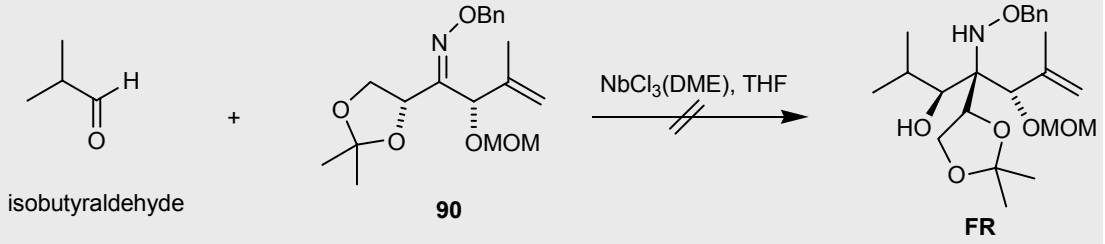
Unfortunately, the α-alkoxyl alkyllithium reagent **FP** reacted with the oxime ether **90** to give complex mixtures and the anticipated adduct **FQ** was not observed even in the presence of $BF_3{\cdot}EtO_2$ which was thought to activate the oxime ether. It was postulated that this failure to achieve the expected addition had to be attributed to the alkoxylalkyllithium **FP** as a strong base reacting with the right part of the oxime ether **90** to form the metalated complex, like **FM** in equation (13) (Eq. 16).



Pedersen[143] reported that coupling of imines with aldehydes or ketones could be achieved by using niobium trichloride dimethoxyethane complex [$NbCl_3$(DME)]. Based on this idea, the coupling of the oxime ether **90** with isobutyraldehyde might introduce the side-chain. To our dismay, the starting material was recovered instead of any coupling product (Eq. 17).

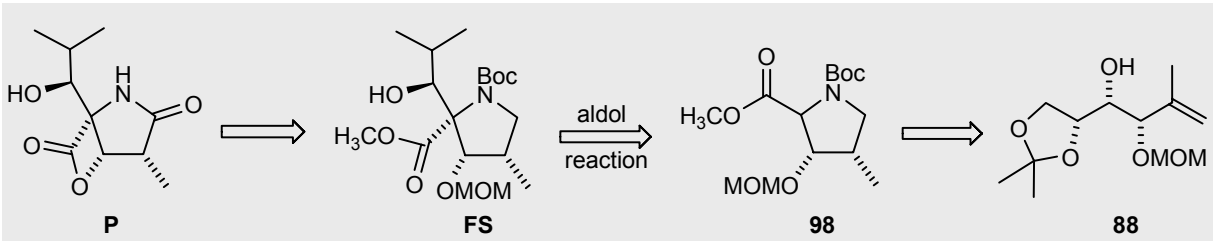
The discussion focuses on the synthesis of the β-actone **107*

(17)



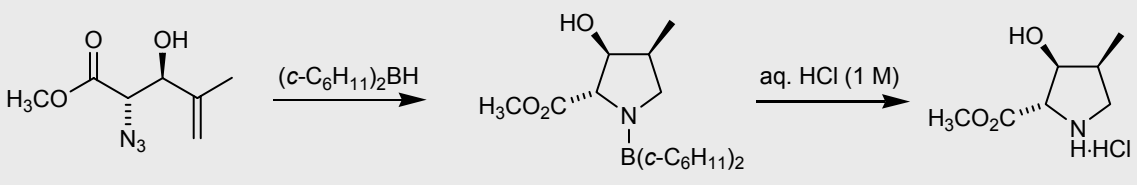
The attempts at elaboration of the C=N double bond remained unsuccessful with a varity of reagents. Therefore, this route was deemed not viable and another synthetic strategy had to be taken into account. The omuralide **P** could be derived from the intermediate **FS** in several steps according to the similar sequence in the literature.[12,95] Oxidation of the pyrrolidine **FS** could afford the corresponding lactam, which should readily be transformed into the lactacystin β-lactone **P**. In theory, the pyrrolidine **FS** could be obtained by aldol reaction of the proline ester **98** (Scheme 57).

Scheme 57. The third synthetic plan of the lactacystin β-lactone **P**



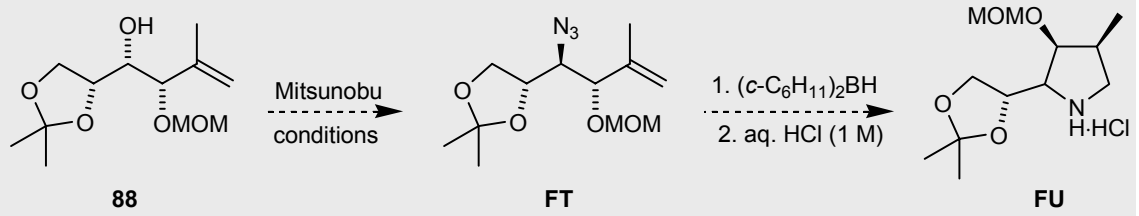
With this design in mind, the synthesis of the substituted pyrrolidine **98** was considered. Evans and co-workers described that this kind of pyrrolidine could be obtained from an azido olefin in one pot as outlined in equation (16).[118a]

(18)



In our case, it was possible to transform the alcohol **88** into the pyrrolidine **FU** using a two-step sequence: i) conversion of the alcohol **88** into the azide **FT**; ii) hydroboration of the azido olefin with dicyclohexylborane hydride to the pyrrolidine **FU** as illustrated in equation (19). The pyrrolidine **FU** could be transformed to the proline ester **98** by elaboration the isopropylidene-protected diol according to the literature.[39]

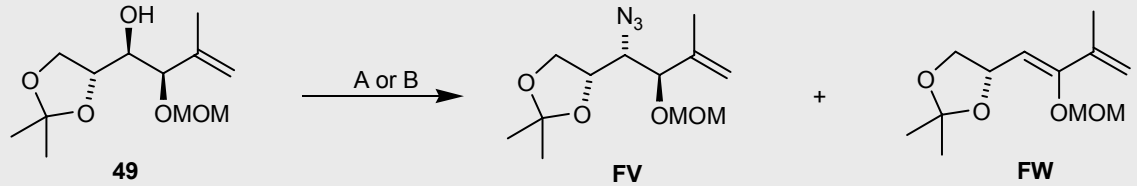
(19)



88 **FT** **FU**

The model study was carried out utilizing the alcohol **49**, the diastereoisomer of **88**. In order to transform the hydroxy group to an azide group, the Mitsunobu reaction[144] seemed to preferable. Conversion of alcohols to azides using Mitsunobu conditions has been utilized very often, for example, in the synthesis of phorboxazole B[145a] and modified condition had been reported as well.[145b] Both of these reaction conditions now were attempted to convert the alcohol **49** to the azide **FV**. Unfortunately, the azide **FV** was not observed under the former conditions (A); with the modified conditions (B), only an elimination product, the diene **FW**, was formed in high yield (Eq. 20).

(20)

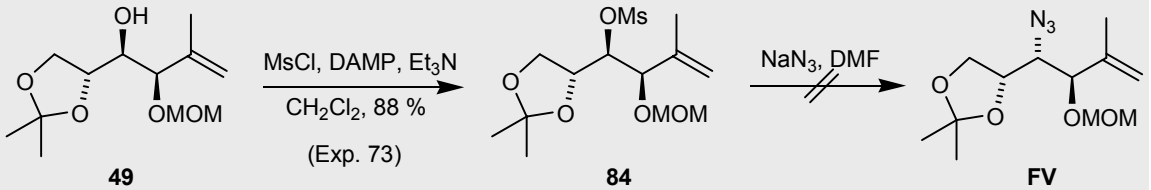


49 **FV** **FW**

A. Ph_3P, DEAD, DPPA, THF, r. t., 30 min	< 5 %	0
B. DEAD, DPPA, DBU, toluene, r. t. 22 h	0	100 %

Thus, endeavor to synthesize the azide **FV** by one-step Mitsunobu reaction was unsuccessful. Consequently, a two-step sequence was employed: i) sulfonation of the alcohol **49**, ii) substitution with azide ion under S_N2 conditions.[146] The mesylation of the alcohol **49** proceeded smoothly to give the mesylate **84**. However, subsequent replacement of mesylate group failed to provide the azide **FV** under a variety of reaction conditions (Eq. 21) such as elevated temperature, other sources of azide ion (LiN_3, *n*-Bu_4NN_3).

(21)



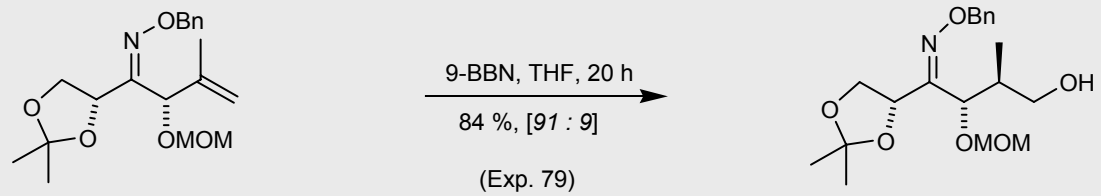
49 **84** **FV**

The triflate was tested, based on literature precedent whereby the trifluoromethanesulfonate group could be replaced by azide under mild conditions.[146f-h,147] Following this, the alcohol **49**

was treated with triflic anhydride in the presence of pyridine, followed by reaction with azide anion to furnish a mixture of the azide **FV** and the diene **FW** (84 : 16 from ^{13}C NMR). It proved difficult to separate the mixture at this stage, so it was subjected to treatment with dicyclohexylborane,[148] but this did not afford the expected pyrrolidine either.

Despite all the efforts above concerning the substituted pyrrolidine being unsuccessful, the substituted pyrrolidines **59** and **98** were eventually obtained in this manner as portrayed in Eq. (22) – Eq. (28). The ketone **89** (Scheme 54), which after condensation with *O*-benzylhydroxylamine gave the *O*-benzyloxime ether **90** in a high yield (91 %) as a single isomer. After asymmetric hydroboration of the olefin **90** with 9-BBN,[116] the alcohol **91** was obtained in 84 % yield (*dr* = 91 : 9), see equation 22.

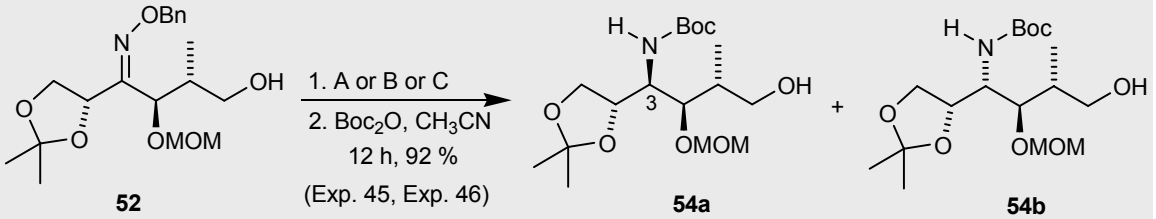
(22)



90 **91**

In course of the syntheses of the substituted pyrrolidines **59** and **98**, the reduction of the oxime ethers **52** and **91** was examined under several conditions (Eq. 23 and Eq. 24). First (Eq. 23), palladium-catalyzed reduction of the oxime ether **52** only afforded the *O*-debenzylated oxime. However, the γ-amino alcohols **54a** and **54b** were obtained when ruthenium on γ-Al_2O_3 was employed as a catalyst after protection with *tert*-butyl dicarbonate[149] (ratio of **54a**/**54b** = 40 : 60).

(23)

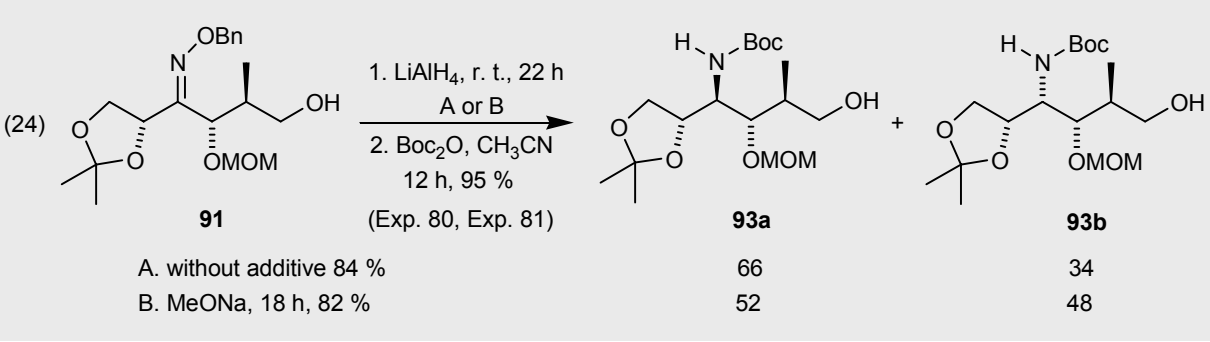


52 **54a** **54b**

A. $LiAlH_4$, r. t., 14 h, MeONa, 83 %	33	67
B. $LiAlH_4$, r. t., 18 h, 80 %	49	51
C. H_2 (4 bar),Ru/γ-Al_2O_3 (5 %), 6 d, 78 %	40	60

Narasaka and coworkers[158] had reported on the stereoselective reduction of the β-hydroxy *O*-benzyloxime ether with lithium aluminium hydride at low temperature. In our case, the *O*-benzyloximes **52** and **91** could readily be reduced to the corresponding amines in shorter time at room temperature using this condition. Narasaka pointed out that the stereoselectivity

could be improved by addition of sodium methoxide to the reaction system. Our results obtained under different conditions are listed in equations (23) and (24).

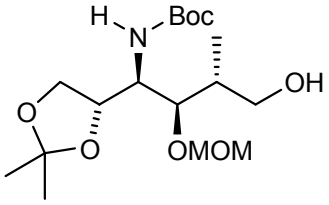


91 **93a** **93b**

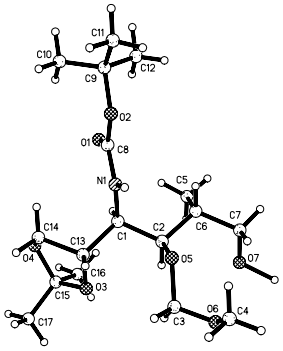
A. without additive 84 %	66	34
B. MeONa, 18 h, 82 %	52	48

As shown in the equation 23 and 24, the selectivity was slightly improved to 33 : 67 for **54a**/**54b** for the oxime **52**; on the other hand, addition of sodium methoxide decreased the stereoselectivity of the reduction of the oxime ether **91**. In short, both amines **54** and **93** were obtainable by reduction of the respective *O*-benzyloximes. The configuration of the amino alcohol **54a** was elucidated by means of a single crystal X-ray diffraction (Figure 22). This permitted also to assign all configurations of the preceding intermediates without ambiguity.

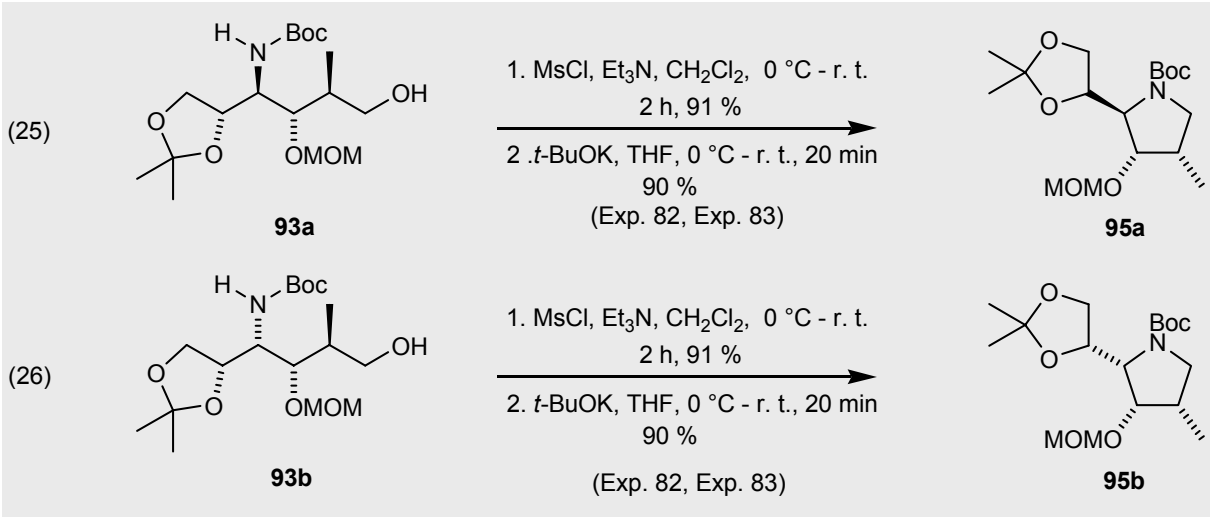
Figure 22. X-ray diffraction analysis of the γ-amino alcohol **54a**



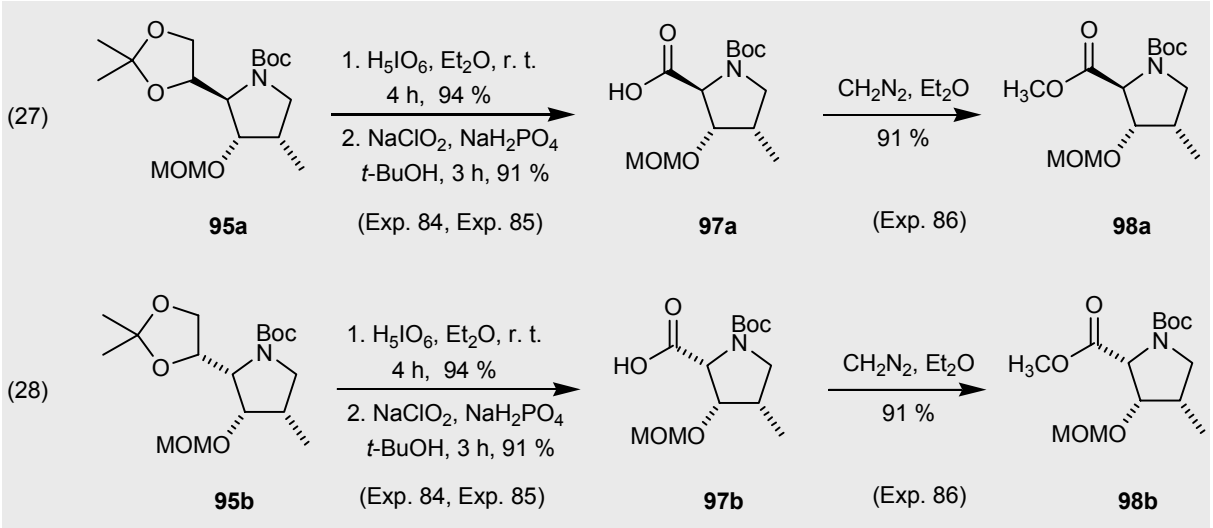
54a



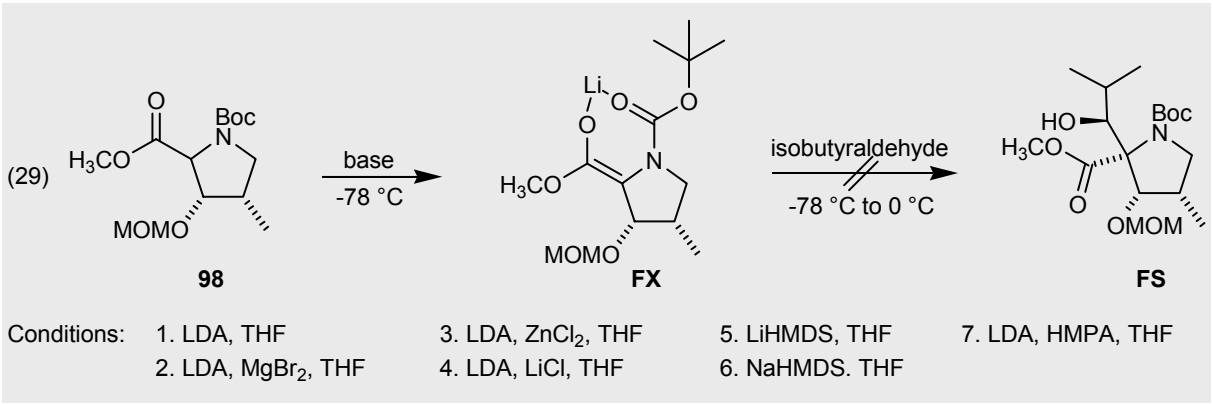
After mesylation of the carbamates **93a** and **93b** with methanesulfonyl chloride respectively, the resulted mesylates were treated with potassium tertiary butylate (*tert*-BuOK) in THF to form the corresponding pyrrolidines **95a** (Eq. 25) and **95b** (Eq. 26) in high yield.[159]



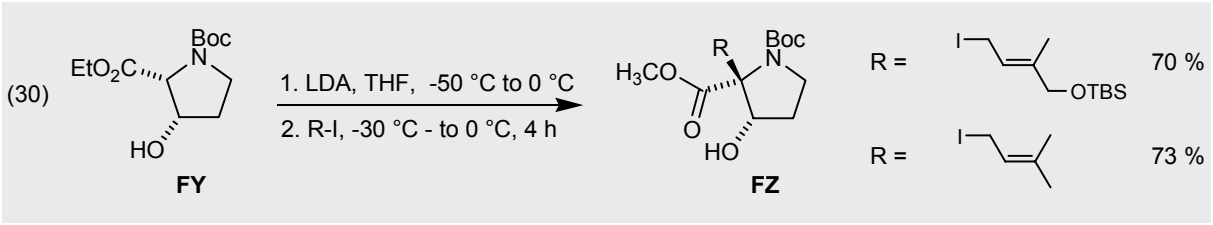
The diol-acetonides **95a** and **95b** were converted into the substituted proline methyl ester **98a** and **98b** by a three-step sequence: i) acetonide cleavage with periodic acid in diethyl ether[39e] to give the corresponding aldehyde; ii) oxidation of the aldehyde to the acid **97a** with sodium chlorite; iii) ester formation upon exposure to excess diazomethane (a yellow solution) in high yiled (Eq. 27 and Eq. 28).[39e]



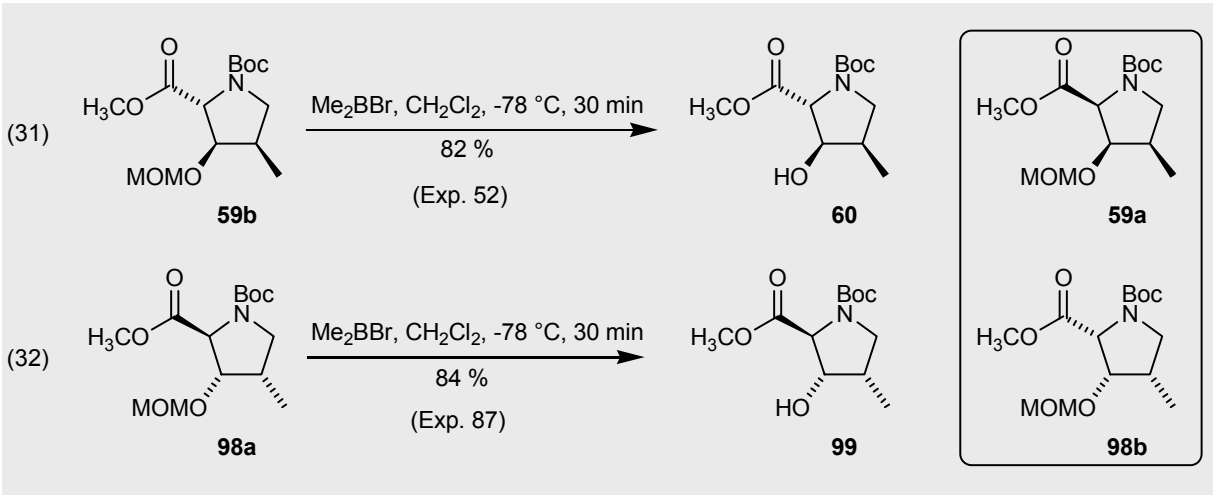
In terms of our plan described in Scheme 57, the aldol reaction[150] may produce the key intermediate **FS** with good selectivity because in our opinion the reaction could proceed via the chelated enolate **FX** (Eq. 29). Unfortunately, this idea could not be realized under a variety of conditions (various bases and additives). To our disappointment, the alkylation[151] of the substituted pyrrolidine **98** was unsuccessful either. The reaction conditions used are shown in equation 29.



To our relief, Williams *et al.*[152] described that (2*R*,3*S*)-*N*-Boc-3-hydroxyproline ethyl ester when treaded with lithium diisopropylamide (LDA) in THF formed the corresponding alkoxy enolate dianion, and the subsequent alkylation occured by addition of a mixture of alkyl halide and HMPA (hexamethylphosphoramide), see equation (30).



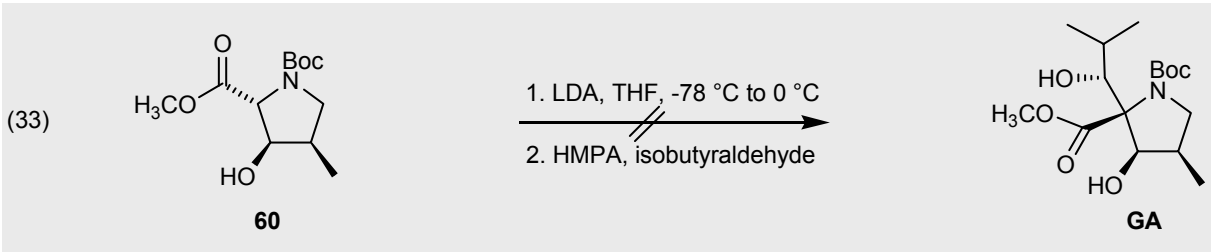
We were intrigued by this report and considered to adopt this variant to our strategy. In fact, selective removal of the methoxymethyl group of the substituted proline derivatives **59** and **98** could furnish the *N*-Boc-3-hydroxy-4-methylprolines **60**, **99** which are structurally similar to the Williams substrate **FY**. Accordingly, our efforts focused on the selective deprotection of methoxymethyl group (MOM) of the the proline derivatives **59** and **98** while keeping the *tert*-butyl carbonyl group (Boc) intact, with several reagents such as trimethylchlorosilane/ tetrabutylammonium bromide ($Me_3SiCl/n\text{-}Bu_4NBr$), [153] trimethylbromosilane (Me_3SiBr), [154] boron tribromide (BBr_3)[155] along with dimethylboron bromide (Me_2BBr).[160] Of the reagents screened, dimethylboron bromide (Me_2BBr) was outstanding in terms of chemical yield (Eq. 23, 24: yield 80-88 %). Trimethylchlorosilane/tetrabutylammonium bromide ($TMSCl/n\text{-}Bu_4NBr$) seemed too mild to effect efficient cleavage of the methoxymethyl group in our case. Trimethylbromosilane (TMSBr) caused the cleavage of methoxymethyl group slowly, albeit with concomitant decomposition. The use of boron tribromide, however, resulted in complete decomposition of the starting material.



Me_2BBr is only effective for transformation of **59b and **98a**, not of the **59a** and **98b**.*

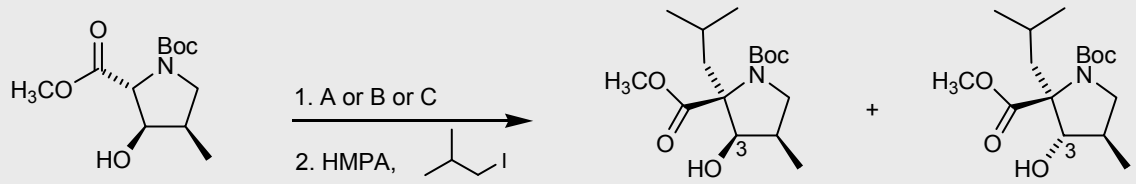
To our surprise, dimethylboron bromide (Me_2BBr) proved ineffective for the conversion of the substituted pyrrolidines **59a** and **98b** (Eq. 31, 32). Both an increase of the temperature and prolonged reaction time led to decomposition. Fortunately, the substituted pyrrolidines **59b** and **98a** could be obtained cleanly from the major products **54b** and **93a**, which came from the reduction of the oxime ethers **52** and **91** (Eq. 22, 23).

With the substrates **60** and **99** now at hand, we anticipated that the side-chain of the lactacystin β-lactone could be constructed by alkoxide enolate dianion reaction with isobutyraldehyde. Thus, the ester **69** was treated with lithium diisopropylamide, followed by addition of isobutyraldehyde in HMPA (hexamethylphosphoramide). This reaction led to the decomposition of the ester **69** instead of the formation of the β-hydroxy ester **GA**. This proved not to be viable (Eq. 33).



Our attention was turned to the investigation of alkylation of the free hydroxy proline derivatives **60** and **99** which would allow access to the lactacystin β-lactone analogues. The alkylation of the proline ester **60** with 1-iodo-2-methylpropane which could furnish a key intermediate for the synthesis of the deoxy lactacystin β-lactone, was studied using the Willams conditions and several others (Eq. 34).

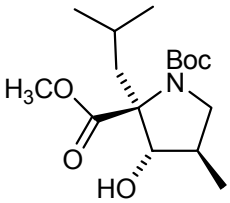
(34)



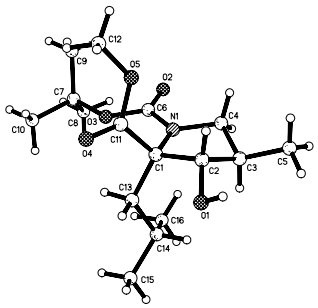
	62	123
A. LDA, THF, 48 %	50	50
B. LDA, THF, $MgBr_2$, 51 %	55	45
C. LDA, THF, LiCl, 46 % (Exp. 107)	10	90

In spite of this alkylation proceeding with excellent stereoselectivity, this was accompanied by partial epimerization at the C-3 postion. As shown in Eq 25 (conditions C), lithium chloride accelerated this epimerization, but magnesium bromide made little difference. The configuration of the isobutylpyrrolidine **123** was again secured by single crystal X-ray analysis (Figure 23), that of the substituted pyrrolidine **62** was assigned at a later stage.

Figure 23. X-ray diffraction analysis of crystal structure of the isobutylpyrrolidine **123**

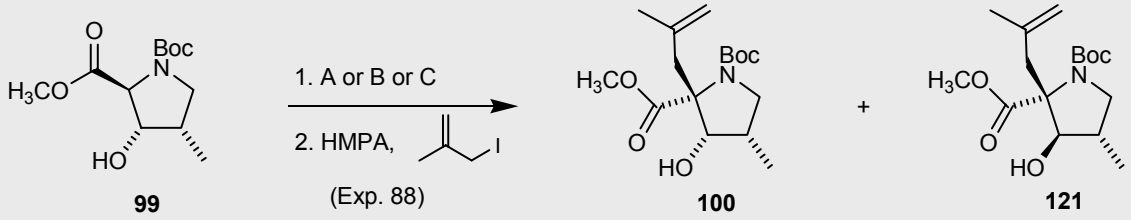


123



In the literature[152] (Eq. 30), the above epimerization was not observed with allyl iodide serving as alkylation reagents. Consequently, 3-iodo-2-methylprop-1-ene,[161] prepared from 3-chloro-2 -methylprop-1-ene and sodium iodide, was examined under a variety of conditions (Eq. 35). The lithium enolate led to a the similar result as shown in equation (34). The lithium enolate was further transmetallated in situ into the corresponding zinc enolate, but the use of this did not avoid the epimerization either. Gratifyingly, when the reaction was carried out in the presence of magnesium chloride, the required alkylation product **100** was obtained as a single isomer without epimerization in moderate yield (58 %).

(35)

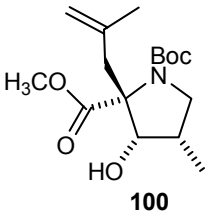


99 (Exp. 88) **100** **121**

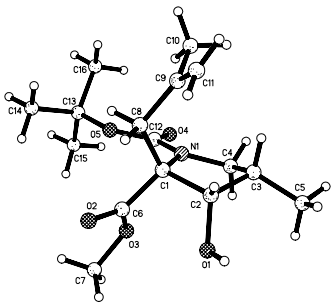
	100	**121**
A. LDA, THF, 52 %	52	48
B. LDA, THF, $ZnCl_2$, 55 %	60	40
C. LDA, THF, $MgCl_2$, 58 %	100	0

The X-ray crystal structure analysis of the substituted pyrrolidene **100** proved the configuration of the newly formed stereocenter at the C-2 (Figure 24).

Figure 24. X-ray analysis of crystal structure of the pyrrolidene **100**

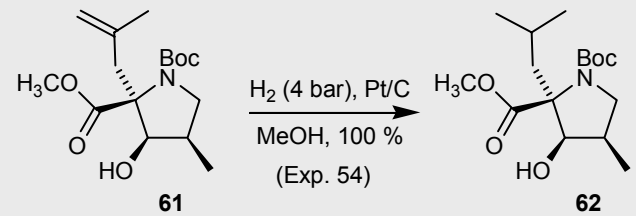


100

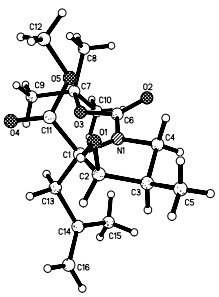


The substituted pyrrolidine **61**, the enantiomer of **100**, was synthesized in like manner; its configuration was established likewise by X-ray analysis. Here the double bond was unaffected by palladium on charcoal, but catalytic hydrogenation of the olefin **61** (Eq. 36) with platinum on charcoal furnished a saturated product, whose optical rotation and spectroscopic characteristics were identical to those of the isobutylpyrrolidine **62** obtained from equation (34). Thus, the confinguration of the isobutylpyrrolidine **62** was confirmed by comparison of the optical rotation and spectroscopic characteristics with the product obtained from the the equation (36) as mentioned before.

(36)



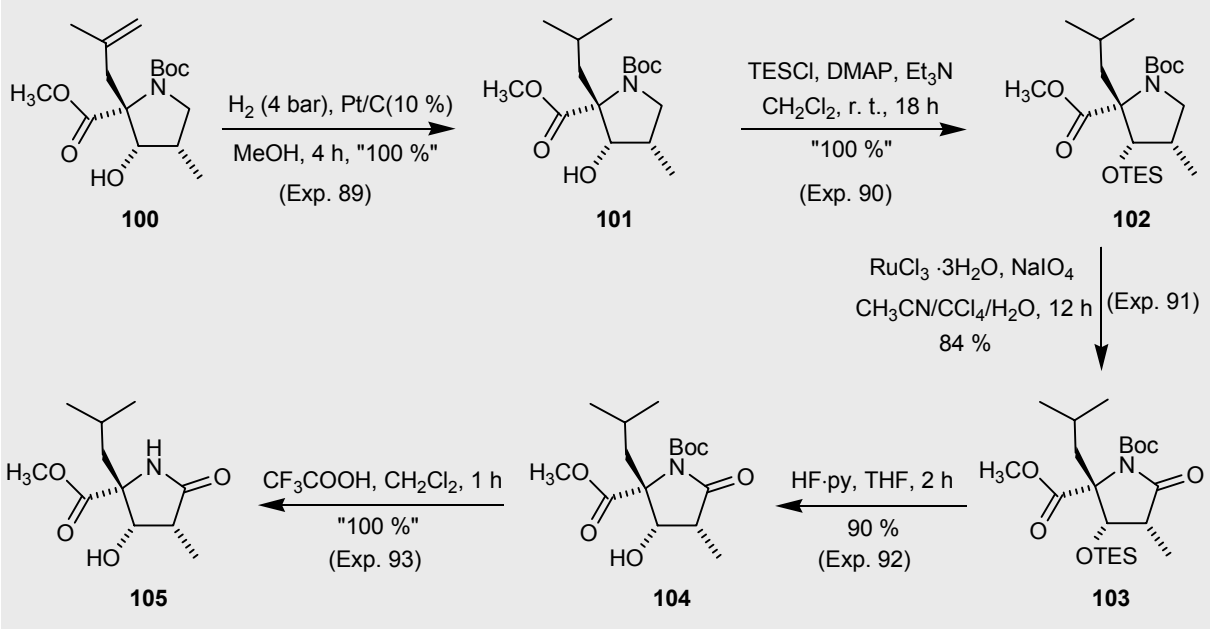
61 **62**



Crystal structure of **61**

The key intermediate **100** was transformed into the lactam **105** in 5 steps as shown in Scheme 58. After hydrogenation of the double bond (H_2, Pt/C, quantitative yield of the isobutyl-pyrrolidine **101**) and protection of the hydroxy group with triethylsilyl chloride (TESCl, quantitative yield),[95,156] the substituted pyrrolidine **102** was oxidized to the lactam **103** using ruthenium trichloride ($RuCl_3/NaIO_4$).[95,157] The lactam **103** was obtained as an analytically pure, colourless oil in good yield (84 %).

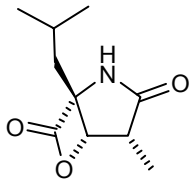
Scheme 58



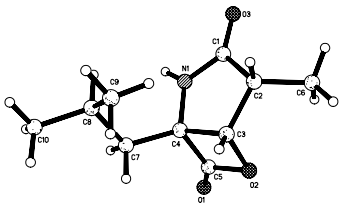
With all the requisite structural features in place, the removal of protecting groups remained to be accomplished. The triethylsilyl group was smoothly removed by exposure of the lactam **103** to hydrogen fluoride-pyridine complex in THF, followed by removal of the *tert*-butoxycarbonyl group by a standard method (CF_3COOH, CH_2Cl_2, quantitative yield) to provide the free hydroxy lactam **105**, the precursor of deoxy lactacystin β-lactone.

In the end, the β-lactone **107** (an analogue of lactacystin β-lactone **P**) was secured from the lactam **105** in a two-step sequence: i) Hydrolysis of the methyl ester to the corresponding acid in 94 % yield; ii) lactone formation with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) to provide the β-lactone **107** as colourless, analytically pure crystals in 82 % yield (two steps). The The X-Ray crystal structure of the β-lactone **107** provided verification of the final product (Figure 25).

Figure 25. X-ray crystal structure analysis of the β-lactone **107**

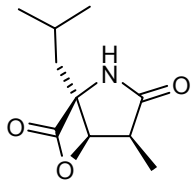


107

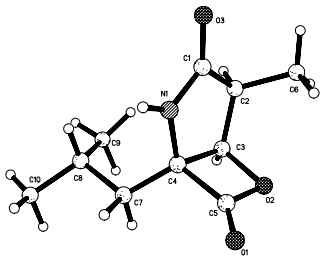


The synthesis of the β-lactone-γ-lactam **68** (the enantiomer of **107**) was achieved in the same manner. The configuration was secured by X-ray diffraction of the deoxy-lactacystin β-lactone **68** (Figure 26).

Figure 26. X-ray diffraction analysis of crystal structure of the 1'-deoxy-omuralide **68**



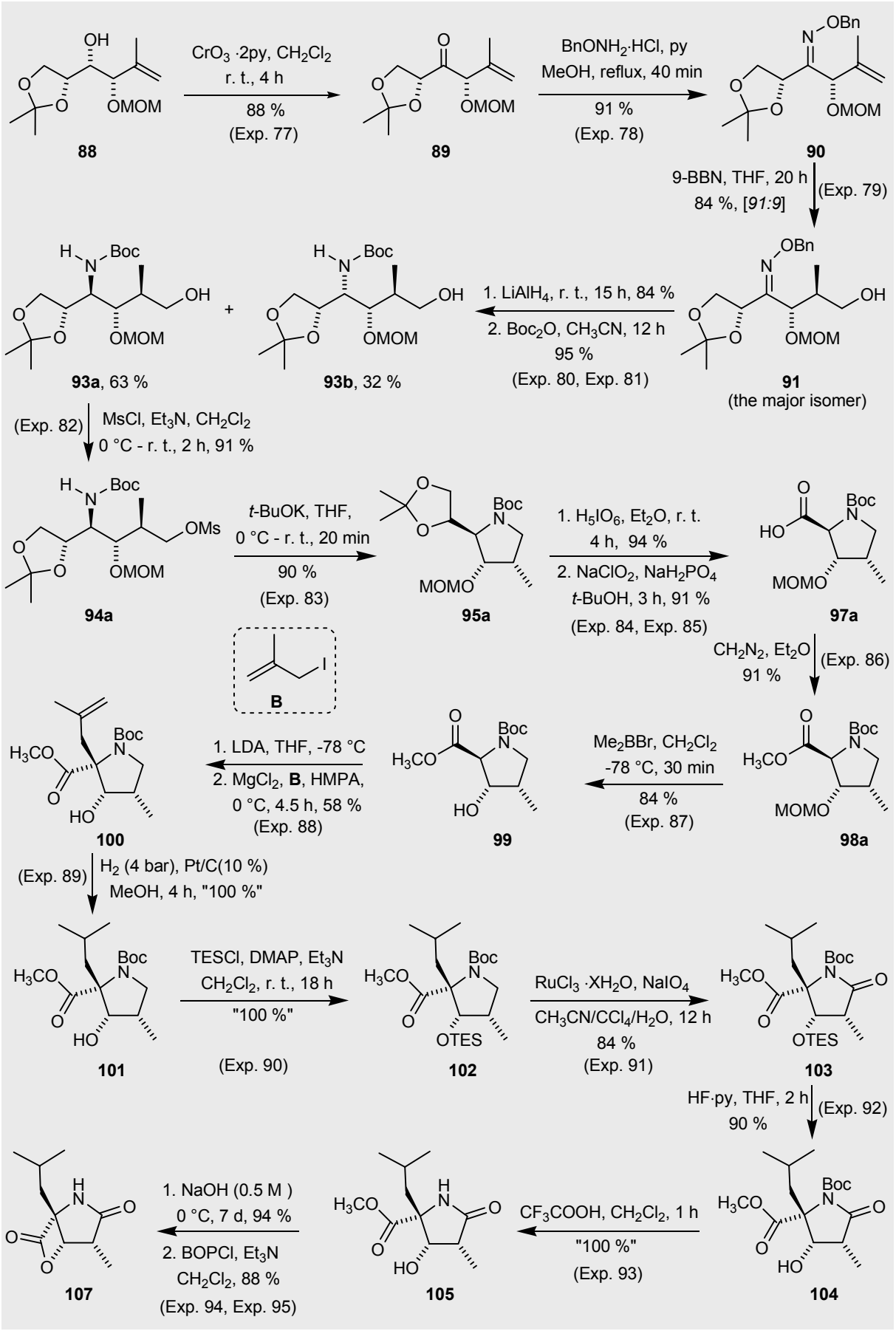
68



5.4.3.2 Synthesis of the lactacystin β-lactone analogue 107

The synthesis of the lactacystin β-lactone analogue (1'-deoxy omuralide) **107** started from the alcohol **88**, which was prepared by asymmetric alkoxyallylboration of the glyceraldehyde **6** as well (see Scheme 54). The alcohol **88** could easily be oxidized to the ketone **89**, which after condensation with *O*-benzylhydroxylamine gave the *O*-benzyloxime ether **90** in a high yield (91 %) as a single isomer (Scheme 59). After asymmetric hydroboration of the olefin **90** with 9-BBN, the alcohol **91** was obtained as a colourless oil in 84 % yield (*dr* = 91 : 9) (Eq. 22).

Scheme 59. Synthesis of the lactacystin β-lactone analogue **107**



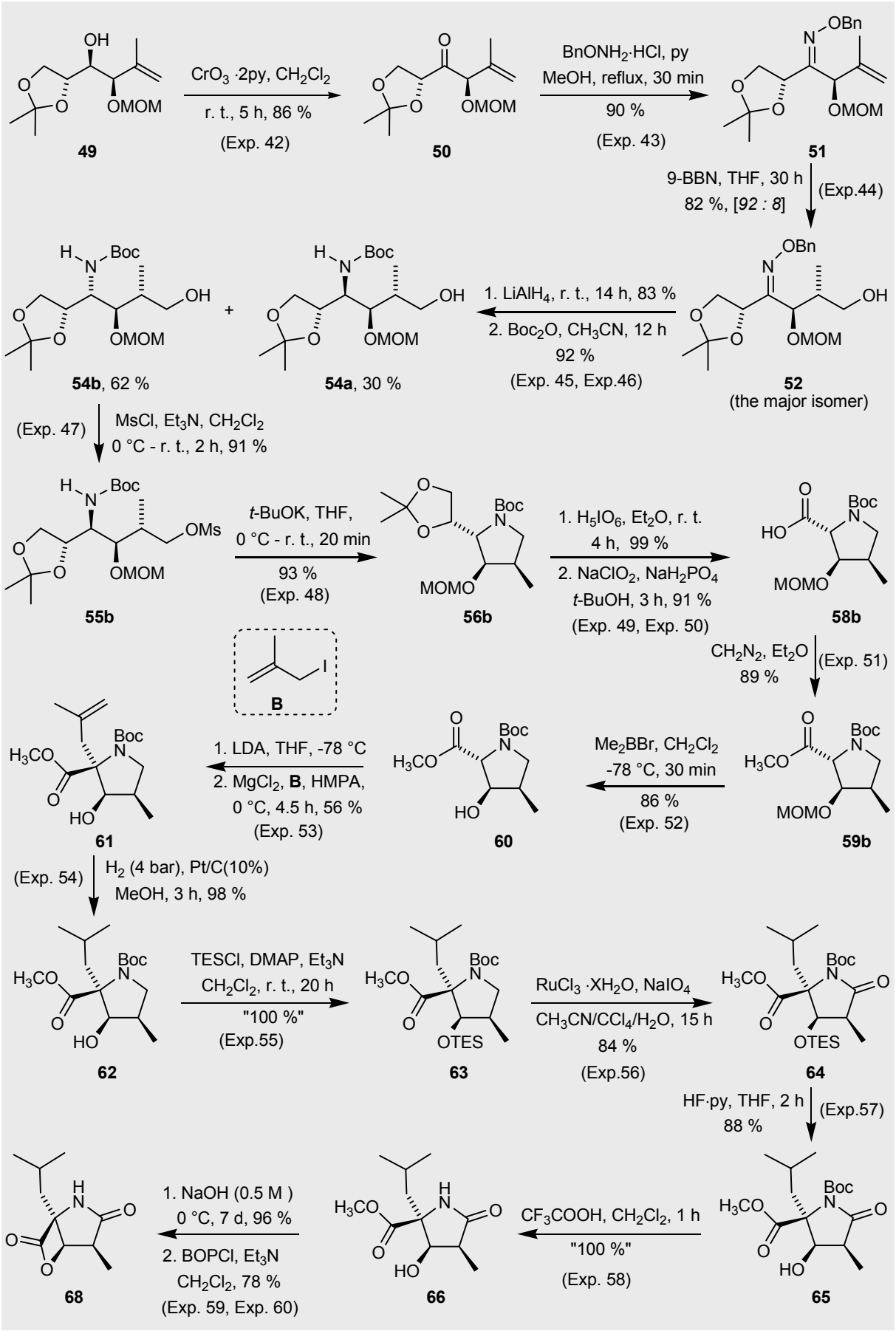
The C=N reduction of the major product of the alcohol **91** with lithium aluminium hydride ($LiAlH_4$)[158] to form the primary amine and protection of the amine with *tert*-butyl dicarbonate [$(Boc)_2O$] led to the carbamates **93a** and **93b** (*dr* = 66 : 34, the ratio was determined according to the yield of isolated products), which could readily be separated by flash chromatography. The major diastereomer **93a** was subjected successively to mesylation (**94a**) and cyclization,[159] leading to the substituted pyrrolidine **95a**. The diol-acetonide **95a** was converted into the substituted proline methyl ester **98a** by a three-step sequence as shown in equation (27).[39e] Deprotection of methoxymethyl group of the proline derivative **98a** with dimethylboron bromide (Me_2BBr)[160] at low temperature yielded the key intermediate **99** in 84 % yield. (Note: the γ-amino alcohol **93b** was also transformed to the corresponding pyrrolidine **98b** in the same manner; methoxymethyl group deprotection of the intermediate **98b**, however, was not successful, see Eq. 32).

The next key step, the stereoselective alkylation of the proline ester **99**, was realized after testing a variety of different Lewis acids such as lithium chloride (LiCl), magnesium bromide ($MgBr_2$), zinc chloride ($ZnCl_2$) and magnesium chloride ($MgCl_2$) (Eq. 35). Treatment of the ester **99** with lithium diisopropylamide (LDA), followed by addition of anhydrous magnesium chloride and methallyl iodide **B**[161] in HMPA gave the anticipated β-hydroxyl ester **100**. The key intermediate **100** was converted into the hydroxylactam **105** in 5 steps as illustrated in Scheme 58. Finally, the ester **105** was hydrolyzed to the corresponding acid which was lactonized with bis(2-oxo-3-oxazolidyl)phosphinic chloride (BOPCl) to give the β-lactone **107** as analytically pure, colourless crystals according to Donohoe's procedure[12,95].

5.4.3.3 Synthesis of the lactacystin β-lactone analogue 68

The like strategy for synthesis of the β-lactone **107** was applied to the synthesis of the deoxy omuralide **68** (an enantiomer of β-lactone **107**) from the alcohol **49** (see Scheme 60). Only the reduction of oxime ether **52** is different from that of the oxime ether **91**. Sodium methoxide was employed as an additive to improve the stereoselectivity in the reduction of oxime ether **52**. More information about the reduction can be found in the discussion part (Eq. 23). Finally, the deoxy omuralide **68** was obtained as colourless, analytically pure crystals.

Scheme 60. Synthesis of the lactacystin β-lactone analogue **68**



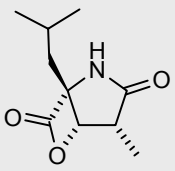
5.4.3.4 Conclusion

To sum up, the analogue **107** of lactacystin β-lactone (5.1 % overall yield) and its enantiomer **68** (4.6 % overall yield) were obtained from 3-(methoxymethoxy)-2-methylprop-1-ene in 20 steps using similar sequences. This pair of enantiomers **107** and **68** was synthesized respectively relying on elaborately choosing chiral boron reagents and asymmetric hydroboration. The stereoselective alkylation is the crucial step for the synthesis of **107** and **68**. This strategy permits access to various analogues by means of altering alkylation reagents. Moreover, it is worth mentioning that the deoxy omuralide **68** was prepared for the first time.

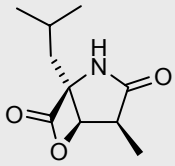
5.5 Results of biological test*

The activities on 20S proteasome of the lactacystin core analogues, **120** and **81** and the lactacystin β-lactone analogues, **107** and **68** were tested. The results were listed in the Table 9.

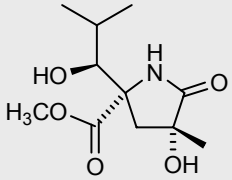
Table 9. Results of biological test of lactacystin analogues



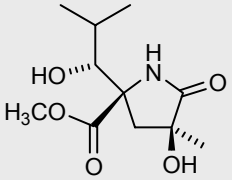
107



68



120



81

20S proteasome fluorimetric substrate *Suc*-LLVY-AMC: *N*-succinyl-leu-leu-val-tyr-AMC
Reference: lactacystin β-lactone (omuralide)
Chymotrypsin-like activity of 20S proteasome:

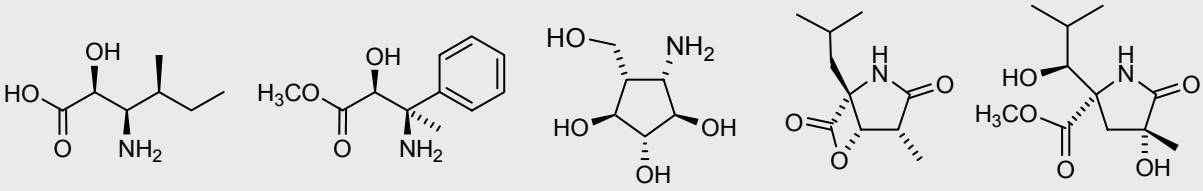
Sample	Conc. [μM]	%	Conc. [μM]	%
Omuralide	1	4.4	10	2.6
107	10	1.2	100	1.0
68	10	79.8	100	72.9
120	10	67.2	100	61.1
81	10	71.1	100	64.5

According to results summarized in Table 9, the 1'-deoxy omuralide **107** at 10 μM and 100 μM completely inhibits the 20S proteasome. The analogues **68**, **120**, **81** only exhibit partial inhibition of the 20S proteasome.

* *The experiment was carried out by Dr. Heinemeyer (Institut für Biochemie)*

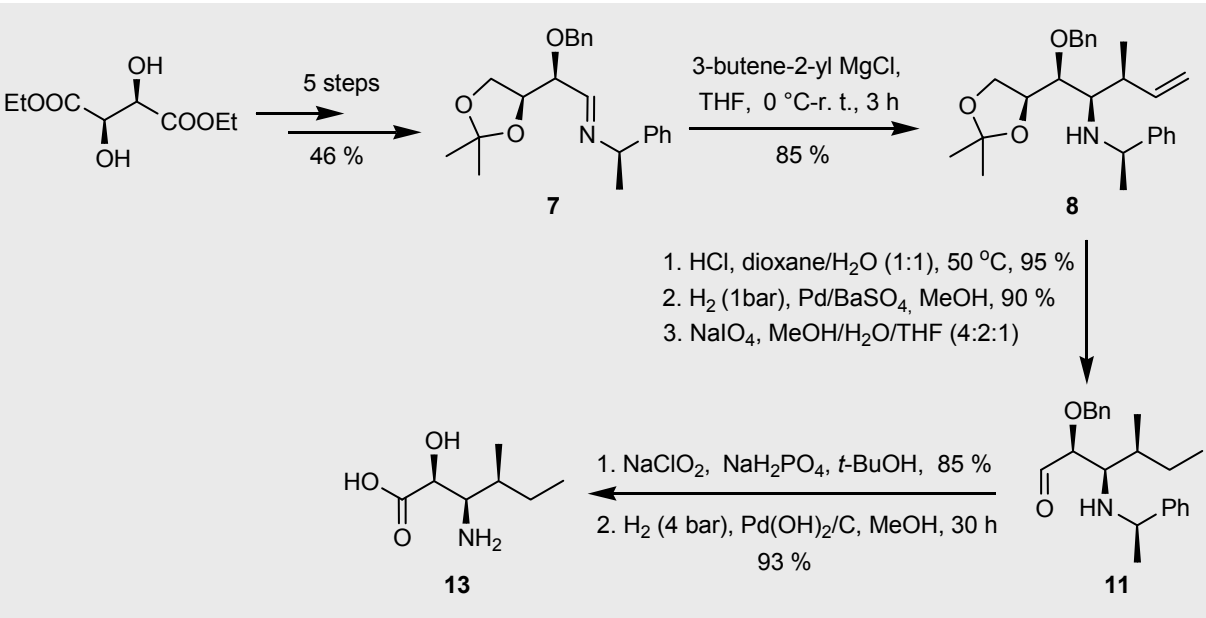
6. Summary

The 1,2-aminoalcohol fragment is abundantly found in many natural products and drugs, for instance as a central moiety of non-proteinogenic amino acids. There is, therefore, a particular interest in the synthesis of branched amino hydroxy acids such as isonorstatine **13**, phenylisothreonine **36**, amino polyols **47**, and lactacystin derivatives **107** and **120**.



6.1 Synthesis of isonorstatine (13)

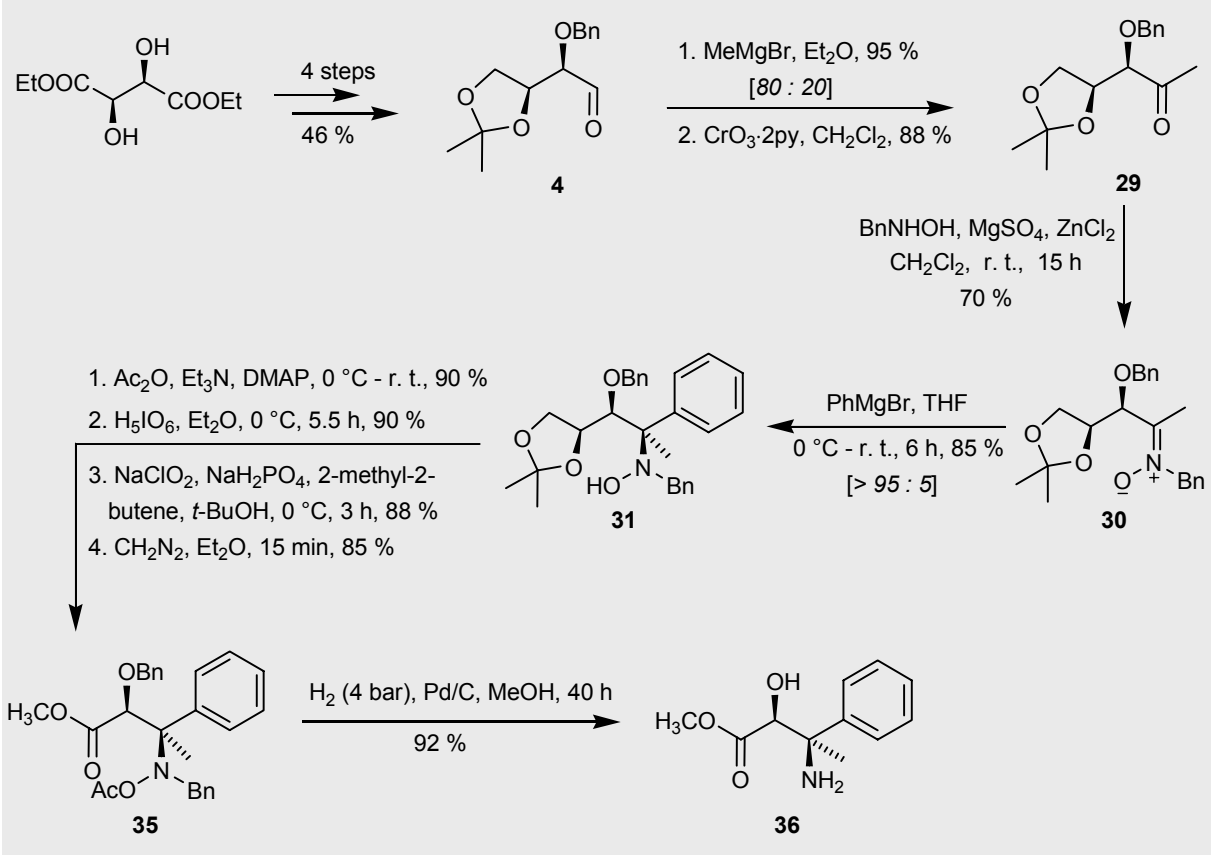
Starting from L-diethyl tartrate, the *L*-threose-derived imine was obtained in 5 steps, which after stereo- and regio- selective addition of 3-butenyl-2-ylmagnesium chloride gave the key intermediate **8**. Diol cleavage and further elaborations led to the formation of the target amino alcohol, isonorstatine **13** (11 steps, Σ 25 % from L-diethyl tartrate).



6.2 Synthesis of phenylisothreonine ester (36)

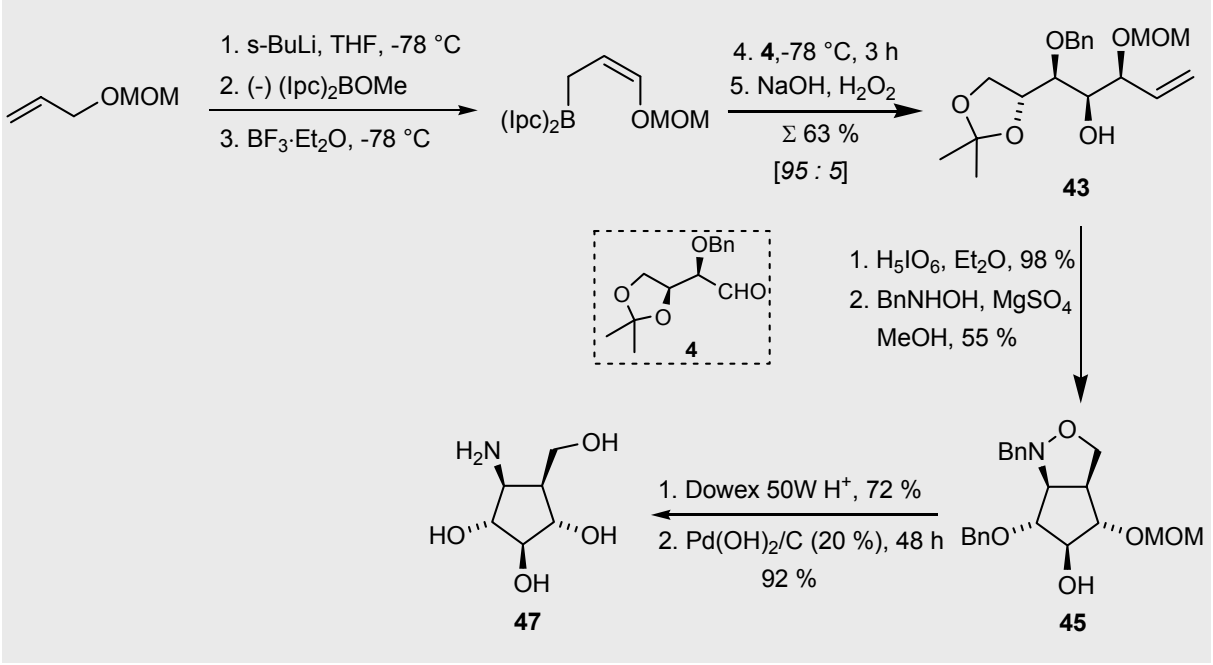
Also starting from *L*-diethyl tartrate, the *L*-threose-derived aldehyde **4** was converted into the methyl ketone **29** then condensed with benzylhydroxylamine to obtain the keto-nitrone **30**. Addition of phenylmagnesiumbromide afforded the key intermediate **31** as a single

diastereoisomer. Attempts to carry out diol cleavage with the free hydroxyl group proved unsuccessful, leading to decomposition. The 3-*O*-acetylated derivative, however, underwent oxidative cleavage with periodic acid cleanly to give the intermediate aldehyde which was then oxidised to the carboxylic acid under standard conditions. After esterification with diazomethane, the ester **35** was reduced catalytically to afford the target amino alcohol, phenylisothreonine ester **36** (13 steps, Σ 12 % from *L*-diethyl tartrate).



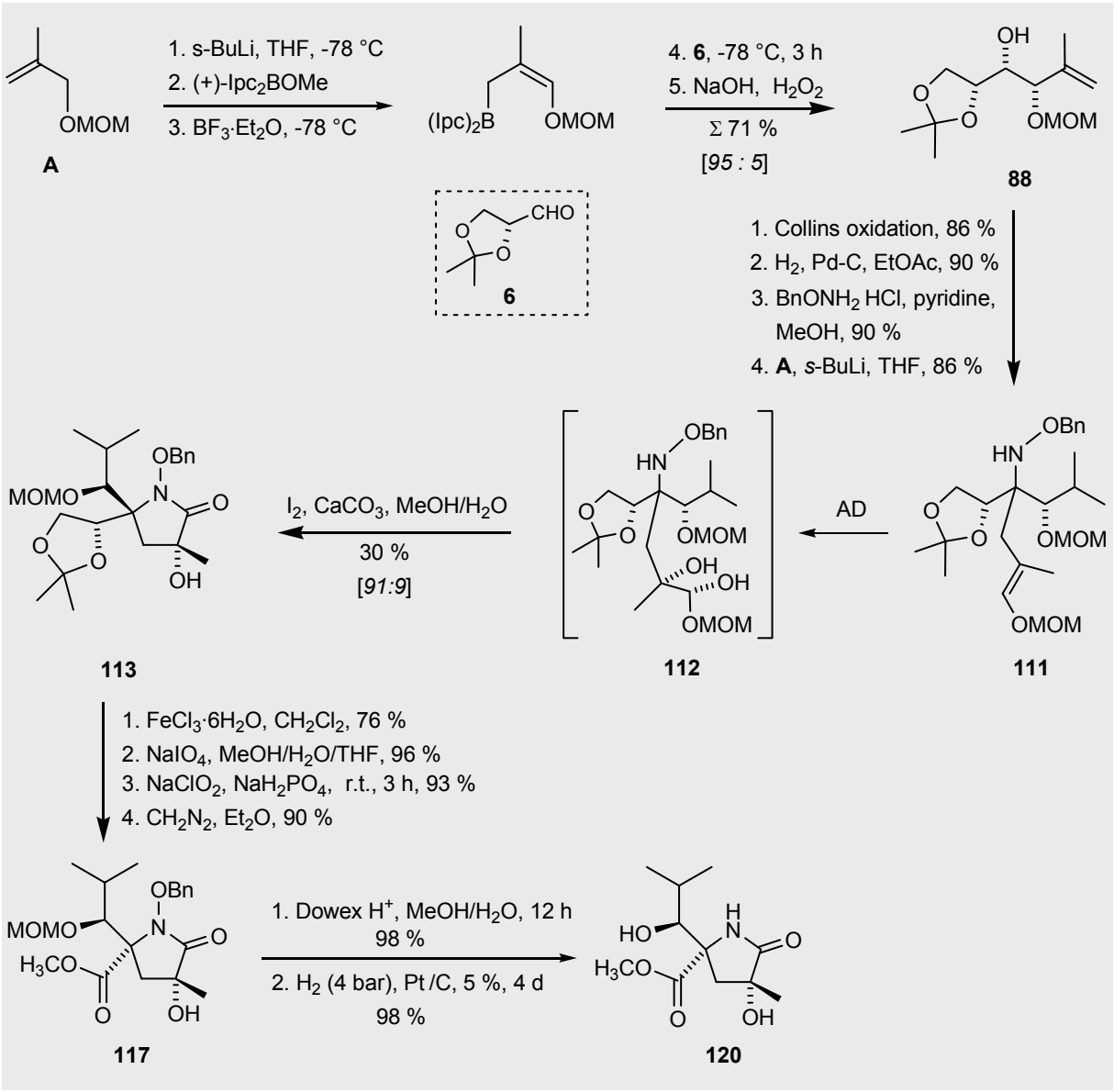
6.3 Synthesis of amino(hydroxymethyl)cyclopentanetriols (47)

According to our experience with enantioselective additions of boron reagents to different aldehydes, *L*-threose **4** (which was prepared easily in four steps from diethyl *L*-tartrate) was subjected to Brown's alkoxyallylation reagents to furnish the alcohol **43** in 68 % yield with a high level stereoselectivity (>95 *syn*; > 95 *dr*). The isopropylidene acetal was cleaved, as shown above, with periodic acid leading to the corresponding aldehyde. Condensation with benzyl hydroxylamine resulted in the respective nitrone, undergoing a [3 + 2] cycloaddition to generate the isoxazolidine **45**. Finally, removal of the methoxymethylether under acidic conditions using Dowex (H^+ form), and concomitant reduction of the benzyl ether as well as *N*-*O* bond cleavage furnished the amino-hydroxymethyl-cyclopentanetriol **47** (5 steps, Σ 22 % from 3-(methoxymethoxy)prop-1-ene) as a new example for this series of potent glycosidase inhibitors.



6.4 Efforts towards the synthesis of lactacystin core analogue (120)

The approach to the synthesis of the lactacystin core relied upon installing the necessary carbon stereocentres by enantioselective addition of a suitable boron reagent to the protected D-glyceraldehyde derivative **6**. The sequence starts with a known protocol using 3-(methoxymethoxy)-2-methylprop-1-ene, metalated with *sec*-butyllithium in THF at -78 °C to give the lithium salt. The resulting lithiated species was treated with (+)-*B*-methoxydiisopinocampheylborane [(+)-Ipc$_2$BOMe] and then boron trifluoride ethereate to furnish the corresponding dialkylallylborane, followed immediately by *in situ* addition of the aldehyde **6**. After oxidative work-up, the diol **88** was obtained in excellent diastereoselectivity (95 : 5). With the derived *O*-benzyloxime, only γ-attack was successful with lithiated MOM ether, leading to the assembly of the side-chain in the amine **111**. The C=C double bond was *syn*-dihydroxylated according to Sharpless which gave the hemiacetal **112**. In an interesting transformation, the secondary hydroxyl group apparently underwent oxidation in the presence of an excess of iodine giving the ester that cyclized to the lactam **113**, albeit in moderate 30 % yield. Removal of the isopropylidene group and periodate cleavage led to the aldehyde which was converted to the ester **117** under similar conditions to those seen above for the synthesis of phenylisothreonine **36**.



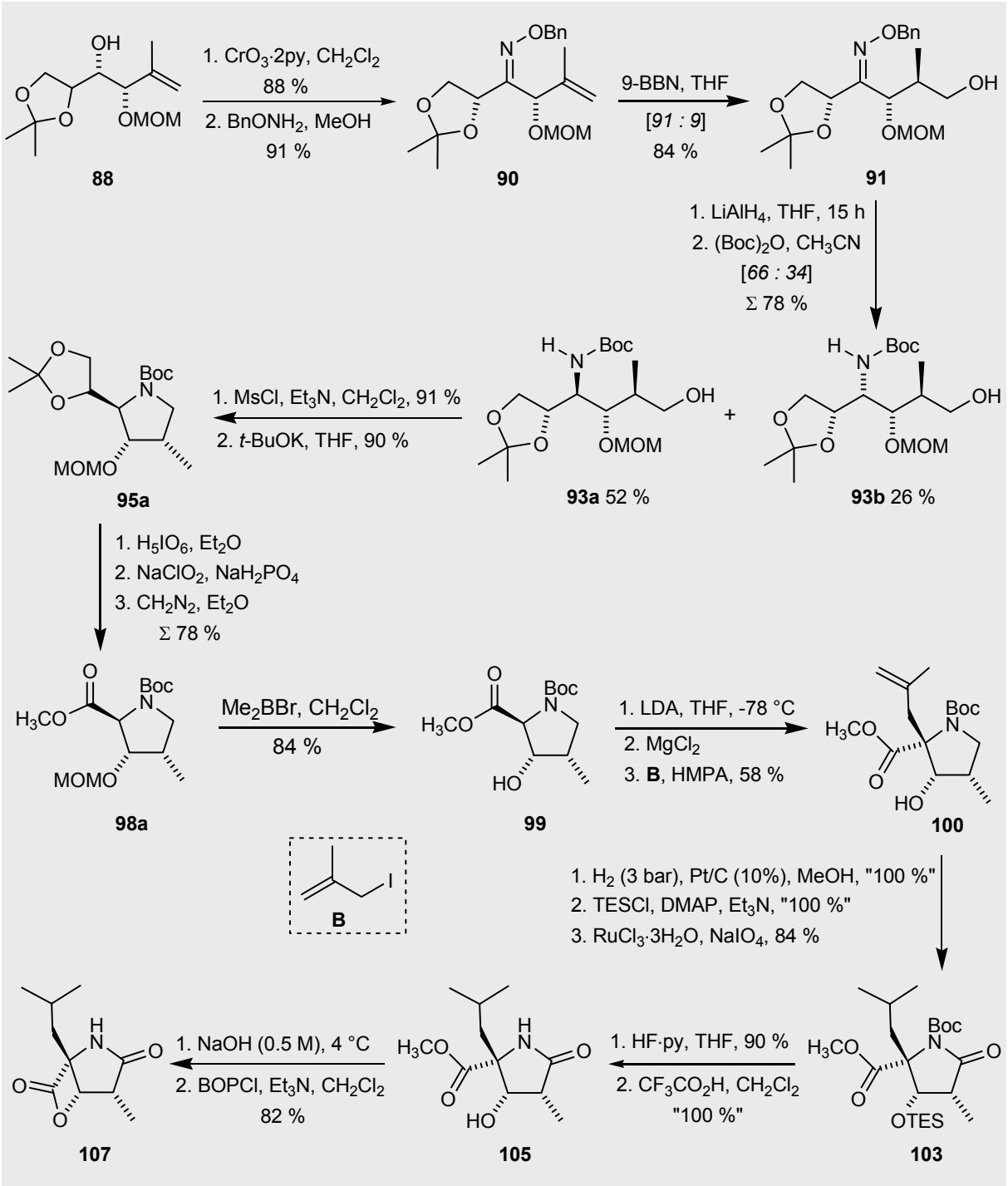
Finally, removal of the methoxymethyl group under acidic conditions using Dowex (H^+ form), and concomitant reduction of the benzyl ether as well as *N*-*O* bond cleavage furnished the novel lactacystin analogue **120** (13 steps, Σ 7.4 % starting from **A**).

The enantiomer **81** of the lactacystin core analogue **120**, was synthesized using the same strategy and steps.

6.5 Synthesis of an analogue of lactacystin β-lactone (107)

The synthesis of lactacystin β-lactone analogue **107** started from the diol **88** which was easily oxidized to the ketone and after condensation with *O*-benzylhydroxylamine gave the *O*-benzyloxime **90**. After asymmetric hydroboration of **90** with 9-borabicyclo[3.3.1]nonane

(9-BBN), the alcohol **91** was obtained. Reduction of the C=N double bond with lithium aluminium hydride ($LiAlH_4$) and protection of the resulting amine with *tert*-butyl dicarbonate gave the carbamates **93a** and **93b**, which could readily be separated by flash chromatography.



The major product **93a**, isolated in 52 % yield, was then converted to the substituted pyrrolidine **98a** in five steps; the later after selective deprotection of methoxymethyl group with dimethylboron bromide (Me_2BBr) at low temperature yielded key intermediate **99**.

(Note: the minor product **93b** was also transformed to the corresponding pyrrolidine; methoxymethyl group deprotection was, however, unsuccessful).

After hydrogenation of the C=C double bond and protection of the hydroxy group, the substituted pyrrolidine was oxidized to the lactam **103** using ruthenium trichloride/sodium periodate ($RuCl_3/NaIO_4$) in good yield. With all the requisite structural features in place, the removal of the protecting groups remained to be accomplished. The triethylsilyl group was smoothly removed by exposure of the lactam **103** to hydrogen fluoride pyridine complex in THF in high yield, followed by removal of *tert*-butoxycarbonyl group (Boc) by a standard method (CF_3COOH, CH_2Cl_2) to provide the γ-lactam**105**, the precursor of deoxy-lactacystin β-lactone. The final steps to obtain the β-lactone **107** (overall 20 steps, Σ 5.1 % from **A** as well) were those according to Donohoe's procedure for lactonisation; The same strategy was applied to the synthesis of the β-lactone **68** (the enantiomer of **107**).

7. Experimental Part

7. 1. General

Nuclear magnetic resonance spectroscopy

^{1}H NMR spectra	Bruker AC 250 (250.1 MHz)
	Brucker ARX 300 (300.1 MHZ)
	Brucker ARX 500 (500.1 MHz)
^{13}C NMR spectra	Bruker AC 250 (62.90 MHz)
	Brucker ARX 300 (75.50 MHZ)
	Brucker ARX 500 (125.8 MHz)

Chemical shifts are given in ppm. The TMS signal is taken as the reference (δ = 0.00 ppm). Coupling constants (*J*) are given in Hertz (Hz). All chemical shift values and multiplicities of NMR signals are shown with standard notations as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal).
The determinations of diastereomeric ratios (*dr*) are based on the intensities of separated signal pairs in the ^{13}C NMR spectra or on the integral of separated signal pairs of ^{1}H NMR spectra.

Elemental Analyses

Elemental analyses were performed at the Institut für Organische Chemie, Universität Stuttgart.

Melting Points

Melting points were measured with a Fisher-Johns heating apparatus and are not corrected.

Infrared Spectroscopy

FT-IR spectra were recorded on a Bruker (IFS 28) spectrophotometer. Measurements of samples were done directly without matrix. The positions of the absorption bands ν are given in cm^{-1}, the intensities are given as follows: vs (very strong), s (strong), m (medium), w (weak), b (broad).

Optical Rotations

Angles of rotation were measured with the polarimeter 241 MC of Perkin-Elmer. The optical rotations were calculated either from the Na_D absorption or by extrapolation of the two Hg lines (546 and 578 nm) by means of the Drude equation:[162]

$$[\alpha]_D^T = \frac{[\alpha]_{578}^T \cdot 3.199}{4.199 - \frac{[\alpha]_{578}^T}{[\alpha]_{546}^T}} \quad \text{with} \quad [\alpha]_\lambda^T = \frac{\alpha \cdot 100}{c \cdot d}$$

α	=	measured optical rotation. The sample is dissolved in absolute solvent and filled into the cuvette.
c	=	concentration in g/100 mL
d	=	layer thickness in dm
T	=	temperature in °C
λ	=	wavelength in nm

Crystal Structure Analyses (Dr. Wolfgang Frey)

For the X-ray structure analyses a Nicolet P3 refractometer with graphite monochromator was used. The measurements were done with Mo-K_α wavelength. The calculation of the structures was done with SHELXS-86 or SHELXL-93,[163] XRAY 76,[164] ORTEP II,[165] and FRIEDA[166] programmes.

Thin Layer Chromatography

Thin layer chromatography was performed on precoated aluminium sheets (silical gel 60 F_{254}) purchased from E. Merck (layer thickness 0.2 mm). The TLC plate was treated by staining with a solution prepared from 2 g $KMnO_4$, 20 g K_2CO_3, 5 mL of NaOH solution (5 %) in 300 mL water and developed by heating with a heat gun. For the amino acids, the TLC plate was stained with a solution prepared from 1.5 g ninhydrin, 5 mL acetic acid and 500 mL 95 % ethanol and developed by heating.[167]

Medium Pressure Liquid Chromatography (MPLC)

A dosage pump FL1 with pulsation attenuator MPD 3 (both from Lewa company) was used. The detection was done using a UV/VIS spectrometer 97.00 (Knauer company) and a differential refractometer connected to a plotter 41.21 (Knauer company). Type B columns filled with silica gel (column dimensions: 28 cm length x 3 cm width, pressure 15-20 bar, flow

30-50 mL/min) were prepared according to G. Helmchen and B. Glatz.[168]

Solvents and Reagents

All the solvents and reagents used were purified and dried according to standard methods.

Filtration and Flash Column Chromatography

Silica gel 60 with mesh size 40-62 μm (E. Merck) was used. The column dimensions and the eluent used are mentioned in each experiment respectively.

Starting Materials and Suppliers

Pd/C (10 %), Pd/$BaSO_4$: Degussa Company.
All the other reagents employed in this work were purchased from Aldrich Company, Fluka Company and Lancaster Company.

Diethyl (-)-2,3-*O*-benzylidene-*L*-tartrate (**1**): prepared according to lit.,[32a] yield 70 %, m. p. 46 °C, $[\alpha]_D^{20}$ = - 30.4 (*c* = 2.10, $CHCl_3$); [lit.:[32a] yield 71 %, m. p. = 47 °C $[\alpha]_D^{20}$ = - 30.7 (*c* = 2.20, $CHCl_3$)].

(+)-2-*O*-Benzyl-*L*-threitol (**2**): prepared according to lit.,[32a] yield 81 %, m. p. 74-75 °C, $[\alpha]_D^{20}$ = + 17.2 (*c* = 1.10, EtOH); [lit.:[32a] yield 80 %, m. p. = 75-76 °C, $[\alpha]_D^{20}$ = + 17.5 (*c* = 1.14, EtOH)].

2-*O*-Benzyl-3,4-*O*-isopropylidene-*L*-threitol (**3**): prepared according to lit.,[32b] yield 98 %, $[\alpha]_D^{20}$ = + 16.6 (*c* = 1.60, $CHCl_3$); [lit.:[32b] yield 98 %, $[\alpha]_D^{20}$ = + 16.8 (*c* = 1.63, $CHCl_3$)].

2-*O*-Benzyl-3,4-*O*-isopropylidene-*L*-threose (**4**): prepared according to lit.,[32b,33b] yield 85 %, $[\alpha]_D^{20}$ = + 34.2 (*c* = 1.50, $CHCl_3$); [lit.:[32b] yield 87 %, $[\alpha]_D^{20}$ = + 34.6, (*c* = 1.51, $CHCl_3$)[lit.33b]].

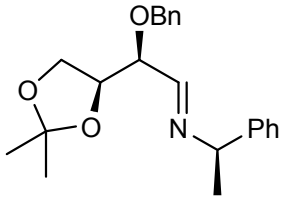
1,2:5,6-*O*-Diisopropylidene-*D*-mannitol (**5**): prepared according to lit.,[131c] yield 58 %, m.p. 120-121 °C, $[\alpha]_D^{20}$ = + 2.20 (*c* = 1.72, MeOH); [lit.:[131c] yield 54 %, m. p. 121-123 °C, $[\alpha]_D^{20}$ = + 1.90 (*c* = 1.74, MeOH)].

2,3-*O*-Isopropylidene-*D*-glyceraldehyde (**6**): prepared according to lit.,[131c] yield 62 %, $[\alpha]_D^{20}$ = + 78.9 (*c* = 1.50, benzene); [lit.:[131c] yield 67 %, $[\alpha]_D^{20}$ = + 80.1 (*c* = 1.53, benzene)].

7.2 Experimental Procedures

Experiment 1 (FLi 11)

(2*R*,3*S*,1'*R*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-*N*-(1'-phenylethyl)-threose-imine (**7**)

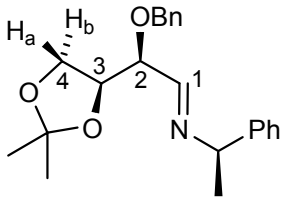


7

According to lit.,[33b] 2-*O*-benzyl-3,4-*O*-isopropyliden-*L*-threose **4** (1.25 g, 5.0 mmol) was mixed with neutral Al_2O_3 (1.28 g, 12.5 mmol), (*R*)-1-phenylethylamine (605 mg, 5.0 mmol), and CH_2Cl_2 (3 mL). After 1 h at r. t. CH_2Cl_2 (8 mL) was added and stirring was continued for 10 min. The mixture was filtered, the filter cake washed with CH_2Cl_2 (2 × 4 mL), the filtrate was dried ($MgSO_4$) and concentrated in vacuo (40 °C/660 mbar). The imine **7** (1.76 g, 98 %, lit.[33b] 98 %) was obtained as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = + 72.4 (*c* = 0.85, $CHCl_3$) lit.: $[\alpha]_D^{20}$ = + 73.5 (*c* = 1.48, $CHCl_3$)[33b]

IR (neat): υ = 2981 (w), 2866 (w), 1667 (C=N), 1494 (w), 1453 (m), 1370 (m), 1257 (m), 1210 (m), 1154 (w), 1066 (s), 846 (m), 737 (m), 696 (vs) cm^{-1}.



7

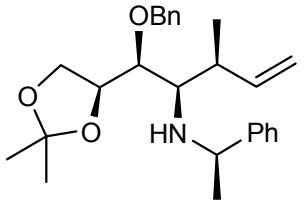
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.33, 1.38 [2 s, 6 H, C(C<u>H</u>$_3$)$_2$], 1.47 (d, ^3J = 6.6 Hz, 3 H, NCHC<u>H</u>$_3$), 3.85 (dd, $^2J_{4a,4b}$ = 8.5 Hz, $^3J_{3,4a}$ = 6.7 Hz, 1 H, 4-H_a), 3.86 (dd, $^2J_{4a,4b}$ = 8.5 Hz, $^3J_{3,4b}$ = 6.4 Hz, 1 H, 4-H_b), 4.02 (dd, $^3J_{2,3}$ = 6.2 Hz, $^3J_{1,2}$ = 5.6 Hz, 1 H, 2-H), 4.27 (m, 1 H, 3-H), 4.32 (q, ^3J = 6.6 Hz, NC<u>H</u>CH$_3$), 4.65, 4.71 (A, B of AB, ^2J = 12.2 Hz, 2 H, OC<u>H</u>$_2$Ph), 7.20–7.38 (m, 10 H, 2 C_6H_5), 7.65 (d, $^3J_{1,2}$ = 5.6 Hz, 1 H, 1-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.5 (q, NCH<u>C</u>H$_3$), 25.2, 26.2 [2 q, C(<u>C</u>H$_3$)$_2$], 65.4 (t, C-4), 69.7 (d, N<u>C</u>HCH$_3$), 71.9 (t, OCH$_2$Ph), 76.4 (d, C-3), 80.9 (d, C-2), 109.4 [s, <u>C</u>(CH$_3$)$_2$], 126.3, 126.9, 127.7, 127.9, 128.3, 128.4 (6 d, 2 C_6H_5), 137.9 (s, *i*-C of OCH$_2$<u>C</u>$_6$H$_5$), 144.1 [(s, *i*-C of NCH(CH$_3$)<u>C</u>$_6$H$_5$], 160.9 (d, C-1).

The spectroscopic data were in accordance with those given in literature.[33b]

Experiment 2 (FLi 13)

(2*S*,3*S*,4*R*,5S,1'*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-(*N*-1'-phenylethylamino)-5-methyl-6-heptene-1,2,3-triol (**8**)



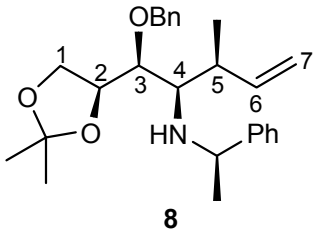
8

According to lit.[33b], two-necked 50-mL flask was charged with Mg (314 mg, 13.1 mmol) and THF (6.0 mL). A small amount of 3-chloro-1-butene was added to initiate the reaction. Then the rest of 3-chloro-1-butene total (1.13 g, 12.5 mmol) in THF (10 mL) was added dropwise within 15 min. The reaction mixture was heated to reflux for 30 min and then cooled to 0 °C. The imine **7** (2.10 g, 5.95 mmol) in THF (8.0 mL) was added over a period of 15 min. The mixture was allowed to warm to r. t. and stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl (4 mL) and extracted with Et_2O (4 × 40 mL). The organic layers were combined, washed with sat. $NaHCO_3$ (50 mL), and dried ($MgSO_4$). After removal of the solvents, the crude product as a light-yellow oil was purified by flash chromatography on silica gel (25 g, column 8 cm × 3 cm, petroleum ether/EtOAc 10 : 1 with 1 % Et_3N) to afford the aminotriol **8** (2.08 g, 85 %) as an analytically pure, colourless oil; *dr* = > 95 : < 5 : < 5 : < 5 from ^{1}H NMR.

$[\alpha]_D^{20}$ = + 15.6 (*c* = 1.15, $CHCl_3$) $[\alpha]_D^{20}$ = + 13.6 (*c* = 1.02, $CHCl_3$)[33b]

$C_{26}H_{35}NO_5$	calcd.	C	76.25	H	8.61	N	3.43
(409.6)	found	C	76.26	H	8.65	N	3.45

IR (neat): υ = 3348 (w, b, NH), 3028 (m), 2981 (m), 2868 (m), 1638 (w; C=C), 1494 (m), 1453 (m), 1369 (m), 1252 (m), 1211 (m), 1156 (m), 1069 (s), 1028 (m), 997 (m), 910 (m), 856 (m), 760 (m), 734 (m), 697 (vs) cm^{-1}.



8

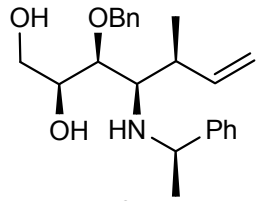
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.94 (d, $^3J_{5,CH_3}$ = 6.8 Hz, 3 H, 5-CH_3), 1.26 (d, ^3J = 6.4 Hz, 3 H, NCHCH_3), 1.44, 1.45 [2 s, 6 H, $C(CH_3)_2$], 1.88 (s, 1 H, NH), 2.22 (dd, $^3J_{4,5}$ = 6.1 Hz,

$^3J_{3,4}$ = 1.6 Hz, 1 H, 4-H), 2.37 (m, 1 H, 5-H), 3.52-3.59 (m, 2 H, 3-H, 1-H_a), 3.90 (q, ^3J = 6.4 Hz, 1 H, NCHCH$_3$), 3.97 (dd, $^3J_{1a,1b}$ = 8.1 Hz, $^3J_{1b,2}$ = 6.4 Hz, 1 H,1-H_b), 4.55 (m, 1 H, 2-H), 4.57, 4.96 (A, B of AB, ^2J = 11.5 Hz, 2 H, OCH$_2$Ph), 4.83-5.03 (m, 2 H, 7-H), 5.69 (ddd, $^3J_{6,7Z}$ = 17.8 Hz, $^3J_{6,7E}$ = 10.1 Hz, $^3J_{5,6}$ = 8.2 Hz, 1 H, 6-H), 7.19-7.36 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.3 (q, 5-CH_3), 24.2 (q, NCH$\underline{C}$H$_3$), 25.7, 26.8 [2 q, C($\underline{C}$H$_3$)$_2$], 40.8 (d, C-5), 55.8 (d, N$\underline{C}$HCH$_3$), 59.4 (d, C-4), 66.4 (t, C-1), 73.3 (t, OCH$_2$Ph), 79.4 (d, C-2), 80.5 (d, C-3), 109.2 [s, $\underline{C}$(CH$_3$)$_2$], 114.2 (t, C-7), 126.9, 127.1, 127.3, 127.7, 128.1, 128.2 (6 d, 2 C_6H_5), 139.0 (s, *i*-C of OCH$_2\underline{C}_6$H$_5$), 142.0 (d, C-6), 146.2 [s, *i*-C of NCH(CH$_3$)$\underline{C}_6$H$_5$].

Experiment 3 (FLi 16)

(2*S*,3*S*,4*R*,5*S*,1'*R*)-3-*O*-Benzyl-5-methyl-4-(*N*-1'-phenylethylamino)-6-heptene-1,2,3-triol (**9**)



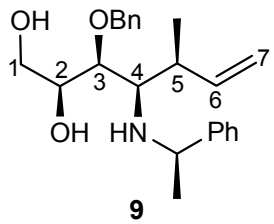
9

In analogy to lit.[33b], the amino heptenetriol **8** (1.8 g, 4.4 mmol) was dissolved in dioxane/water (16 mL, 1 : 1) to which concentrated HCl (0.4 mL) was added. The reaction mixture was kept at 50 °C for 18 h. The resulting solution was evaporated (40 °C/60 mbar) and dissolved in sat. $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc (4 × 40 mL) and dried ($MgSO_4$). The filtrate was concentrated (40 °C/220 mbar) and the crude product was purified by flash chromatography on silica gel (50 g, column 12 cm × 4 cm, petroleum ether/EtOAc 1 : 1, with 1 % Et_3N) to yield the free diol **9** (1.54 g, 95 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 34.9 (*c* = 1.03, $CHCl_3$) lit.[33b] $[\alpha]_D^{20}$ = - 32.3 (*c* = 1.10, $CHCl_3$)

$C_{23}H_{31}NO_3$	calcd.	C	74.76	H	8.46	N	3.79
(369.5)	found	C	74.59	H	8.32	N	3.71

IR (neat): υ = 3306 (b, w), 3066 (w), 3028 (w), 2965 (w), 2870 (w), 1637 (w), 1494 (m), 1452 (m), 1375 (m), 1209 (w), 1056 (vs), 912 (m), 861 (m), 758 (m), 734 (m), 697 (vs) cm^{-1}.



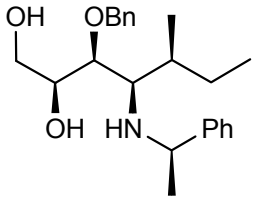
9

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.13 (d, $^3J_{5,CH_3}$ = 6.9 Hz, 3 H, 5-CH_3), 1.36 (d, ^3J = 6.5 Hz, 3 H, NCHCH_3), 1.98 (s, 1 H, NH), 2.86 (m, 1 H, 5-H), 3.11 (dd, $^3J_{4,5}$ = 4.2 Hz, $^3J_{3,4}$ = 0.8 Hz, 1 H, 4-H), 3.57 (dd, $^2J_{1a,1b}$ = 12.7 Hz, $^3J_{1a,2}$ = 5.7 Hz, 1 H, 1-H_a), 3.79 (dd, $^3J_{2,3}$ = 4.2 Hz, $^3J_{3,4}$ = 0.8 Hz, 1 H, 3-H), 3.88 (m, 1 H, 2-H), 3.90 (dd, $^2J_{1a,1b}$ = 12.8 Hz, $^3J_{1b,2}$ = 2.7 Hz, 1 H, 1-H_b), 4.07 (q, ^3J = 6.5 Hz, 1 H, NCHCH_3), 4.48, 4.52 (A, B of AB, ^2J = 12.2 Hz, 2 H, OCH_2Ph), 5.00-5.13 (m, 2 H, 7-H), 5.87 (ddd, $^3J_{6,7Z}$ = 17.4 Hz, $^3J_{6,7E}$ = 10.3 Hz, $^3J_{5,6}$ = 7.6 Hz, 1 H, 6-H), 7.24-7.31 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.8 (q, 5-CH_3), 20.9 (q, NCH<u>C</u>H_3), 37.0 (d, C-5), 53.4 (d, N<u>C</u>HCH_3), 57.3 (d, C-4), 61.5 (t, C-1), 71.4 (d, C-2), 73.2 (t, OCH_2Ph), 78.1 (d, C-3), 115.3 (t, C-7), 127.1, 128, 128.2, 128.8, 129.2 (5 d, 2 C_6H_5), 138.2 (s, *i*-C of OCH_2<u>C</u>$_6H_5$), 140.4 (d, C-6), 145.2 [s, *i*-C of NCH(CH_3)<u>C</u>$_6H_5$].

<u>Experiment 4 (FLi 19)</u>

(2*S*,3*S*,4*R*,5*S*,1'*R*)-3-*O*-Benzyl-4-(*N*-1'-phenylethyl-amino)-5-methylheptane-1,2,3-triol (**10**)



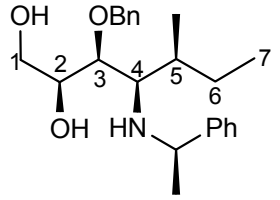
10

Following a lit. procedure[33b], a 25-mL flask was charged with Pd/$BaSO_4$ (35 mg, 5%); MeOH (2 mL) and the diol **9** (350 mg, 0.95 mmol) was added. The reaction mixture was hydrogenated for 4 h at normal pressure. After centrifugation of the solids the filtrate was concentrated (40 °C/300 mbar). The residue, a colourless oil, was purified by flash chromatography on silica gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 1 : 2.5 with 1 % Et_3N) to afford the heptanetriol **10** (318 mg, 90 %, lit.[33b]: 95 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 19.9 (*c* = 1.30, $CHCl_3$) lit.[33b] $[\alpha]_D^{20}$ = - 13.1 (*c* = 1.08, $CHCl_3$)

$C_{23}H_{33}NO_3$	calcd.	C	74.36	H	8.95	N	3.77
(371.5)	found	C	74.25	H	8.67	N	3.85

IR (neat): υ = 3329 (b, w, OH), 3031 (w), 2961 (m), 2930 (m), 2873 (m), 1576 (w), 1495 (w), 1454 (m), 1384 (w), 1210 (w), 1064 (s), 916 (w), 761 (s), 734 (s), 698 (vs) cm^{-1}.



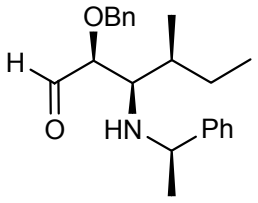
10

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.87 (t, $^{3}J_{6,7}$ = 7.3 Hz, 3 H, 7-H), 0.99 (d, $^{3}J_{5,CH_3}$ = 6.9 Hz, 3 H, 5-CH_3), 1.08 (m, 1 H, 6-H_a), 1.35 (d, ^{3}J = 6.5 Hz, 3 H, NCHCH_3), 1.54 (m, 1 H, 6-H_b), 1.88 (m, 1 H, 5-H), 3.03 (dd, $^{3}J_{4,5}$ = 4.0 Hz, $^{3}J_{3,4}$ = 1.3 Hz, 1 H, 4-H), 3.57 (dd, $^{2}J_{1a,1b}$ = 11.5 Hz, $^{3}J_{1a,2}$ = 4.4 Hz, 1-H_a), 3.76 (dd, $^{3}J_{2,3}$ = 4.8 Hz, $^{3}J_{3,4}$ = 1.3 Hz, 1 H, 3-H), 3.85-3.96 (m, 3 H, 2-H, 1-H_b and NCHCH_3), 4.50, 4.54 (A, B of AB, ^{2}J = 11.2 Hz, 2 H, OCH_2Ph), 7.23-7.28 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (q, C-7), 16.8 (q, 5-CH_3), 20.9 (q, NCH<u>C</u>H_3), 24.5 (t, C-6), 34.3 (d, C-5), 53.6 (d, N<u>C</u>HCH_3), 56.5 (d, C-4), 61.3 (t, C-1), 70.8 (d, C-2), 72.9 (t, OCH_2Ph), 78.6 (d, C-3), 126.7, 127.5, 127.8, 128.4, 128.8 (5 d, 2 C_6H_5), 137.8 (s, *i*-C of OCH_2<u>C</u>$_6H_5$), 145.0 [s, *i*-C of NCH(CH_3)<u>C</u>$_6H_5$].

<u>Experiment 5 (FLi 22)</u>

(2S,3*R*,4*S*,1'*R*)-2-Benzyloxy-3-(*N*-1'-phenylethyl-amino)-4-methylhexanal (**11**)

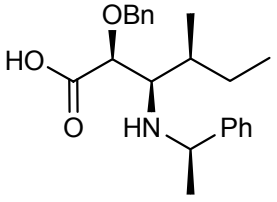


11

According to lit.[33b], to the solution of the diol **10** (220 mg, 0.59 mmol) in MeOH/H_2O/THF (7 mL, 4 : 2 : 1) was added $NaIO_4$ (218 mg, 1.01 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature, then quenched with sat. aq. $NaHCO_3$ (4.5 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated (40 °C/600 mbar) to give the aldehyde **11** (192 mg, 97 %; lit[33b]: 95 %) as a colourless oil which was used directly in the next step.

<u>Experiment 6 (FLi 23)</u>

(2*S*,3*R*,4*S*,1'*R*)-2-Benzyloxy-3-(*N*-1'-phenylethyl-amino)-4-methylhexanoic acid (**12**)



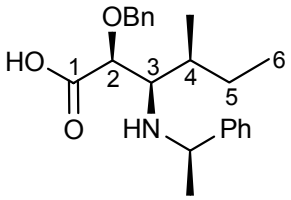
12

Following a lit.[33b], the aldehyde **11** (192 mg) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (2.5 mL) and treated with a solution of $NaClO_2$ (93 mg, 1.01 mmol) and NaH_2PO_4 (122 mg, 1.01 mmol) in water (1.2 mL). After stirring for 90 min, the same amount of $NaClO_2$ and NaH_2PO_4 was added again. After stirring for 1 h, NaOH (8 M, 0.5 mL) was added. The solvent was removed under reduced pressure (40 °C/60 mbar), the resulting residue was dissolved in water (8.0 mL), and extracted with ether (2 × 10 mL). The pH of the aqueous phase was adjusted to 3–4 by adding 6 M HCl and then it was extracted with EtOAc (5 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated (40 °C/220 mbar); the remaining solid was recrystallized (EtOAc/heptane) to afford the hexanoic acid **12** (178 mg, 88 %; lit.[33b]: 90 %) as a colourless, analytically pure powder; m. p. = 112-113 °C.

$[\alpha]_D^{20}$ = - 29.1 (*c* = 0.95, $CHCl_3$) lit.[33b]: $[\alpha]_D^{20}$ = - 29.9 (*c* = 1.03, $CHCl_3$)

$C_{22}H_{29}NO_3$	calcd.	C	74.33	H	8.22	N	3.94
(355.5)	found	C	74.37	H	8.26	N	3.89

IR (solid): υ = 3307 (b, m), 2943 (m), 2830 (m), 1611 (m), 1455 (m), 1387 (m), 1210 (w), 1108 (m), 1021 (vs), 701 (s), 628 (s) cm^{-1}.



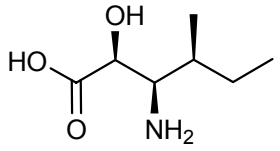
12

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.62 (t, $^3J_{5,6}$ = 7.4 Hz, 3 H, 6-H), 0.88 (d, $^3J_{4,CH_3}$ = 7.0 Hz, 3 H, 4-CH_3), 1.05–1.15 (m, 2 H, 5-H), 1.48 (d, ^3J = 6.7 Hz, 3 H, NCHCH_3), 1.89 (m, 1 H, 4-H), 2.81 (t, $^3J_{2,3}$ = 4.1, $^3J_{3,4}$ = 4.1 Hz, 1 H, 3-H), 3.79 (q, ^3J = 6.7 Hz, NCHCH_3), 3.98 (d, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.59, 4.89 (A, B of AB, ^2J = 12.3 Hz, 2 H, OCH_2Ph), 7.26-7.38 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.6 (q, C-6), 14.4 (q, 4-CH_3), 21.1 (q, NCH$\underline{C}H_3$), 26.2 (t, C-5), 33.7 (d, C-4), 56.6 (d, N$\underline{C}HCH_3$), 59.5 (d, C-3), 72.4 (t, OCH_2Ph), 73.3 (d, C-2), 127.2, 128.0, 128.2, 128.5, 128.8, 129.2 (6 d, 2 C_6H_5), 137.5 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 139.7 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$], 174.1 (s, C-1).

Experiment 7 (FLi 43)

(2*S*,3*R*,4S)-3-Amino-2-hydroxy-4-methylhexanoic acid (**13**)



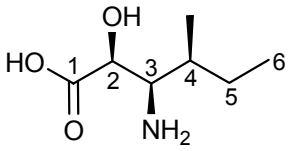
13

The protected isonorstatine **12** (50 mg, 0.14 mmol) was dissolved in MeOH (3 mL) and hydrogenated (H_2, 4 bar) in the presence of Pearlman's catalyst $Pd(OH)_2/C$ (20 mg, 20 %). After 18 h, the reaction mixture was filtered and the filtrate was concentrated (40 °C/300 mbar) to give the free hexanoic acid **13** (21 mg, 93 %) as a light-yellow, analytically pure powder; m. p. = 204-205 °C.

$[\alpha]_D^{20}$ = - 20.8 (*c* = 0.36, MeOH)

$C_7H_{15}NO_3$ HCl	calcd.	C	42.53	H	8.16	N	7.09
(161.2)	found	C	42.21	H	7.82	N	6.75

IR (solid): υ = 3500-2500 (b, m), 1733 (m), 1599 (vs), 1511 (s), 1461 (s), 1377 (s), 1281 (m), 1228 (m), 1143 (m), 1073 (s), 1024 (s), 908 (w), 823 (m), 694 (s) cm^{-1}.



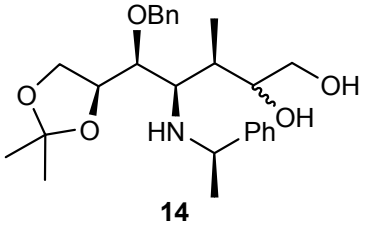
13

^{1}H NMR (D_2O, 300.1 MHz): δ = 0.78 (t, $^3J_{5,6}$ = 7.4 Hz, 3 H, 6-H), 0.89 (d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4'-H), 1.38 (m, 2 H, 5-H), 1.71 (m, 1 H, 4-H), 3.53 (dd, $^3J_{3,4}$ = 5.6 Hz, $^3J_{2,3}$ = 4.6 Hz, 1 H, 3-H), 4.41 (d, $^3J_{2,3}$ = 4.3 Hz, 1 H, 2-H).

^{13}C NMR (D_2O, 75.5 MHz): δ = 10.7 (q, C-6), 14.1 (q, 4-CH_3), 25.7 (t, C-5), 34.4 (d, C-4), 58.0 (d, C-3), 70.1 (d, C-2), 177.2 (s, C-1).

Experiment 8 (FLi 91)

(2*R*,3*S*,4*R*,5*R*,6*RS*,1'*R*)-2-*O*-Benzyl-1,2-*O*-isopropylidene-4-(*N*-1'-phenylethylamino)-5-methylheptane-1,2,3,6,7-pentaol (**14**)



14

According to a procedure given by Sharpless *et al.*,[40] a 50-mL round-bottom flask, equipped with a magnetic stirrer, was charged with *t*-BuOH/H_2O (8.0 mL, 1 : 1). To the mixture were added $K_3[Fe(CN)_6]$ (724 mg, 2.20 mmol), K_2CO_3 (306 mg, 2.20 mmol), $K_2OsO_2(OH)_4$ (5.4 mg, 0.015 mmol), and hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$, 28 mg, 0.036 mmol] at r. t.. The mixture was stirred for 15 min at the same temperature, then the heptene **8** (300 mg, 0.73 mmol) was added at 0 °C. The temperature was allowed to rise to r. t.. After 8 h, the reaction was treated with $Na_2S_2O_5$ (1.67 g, 8.80 mmol) at 0 °C and stirred for 1 h. Water (5 mL) was then added and the mixture was extracted with EtOAc (4 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, CH_2Cl_2/MeOH 7 : 1) to yield the diol **14** (276 mg, 85 %) as a colourless, analytically pure oil; (*dr* = 82 : 18, by ^{13}C NMR).

$C_{26}H_{37}NO_5$	calcd.	C	70.40	H	8.41	N	3.16
(443.6)	found.	C	70.10	H	8.53	N	3.10

Major isomer

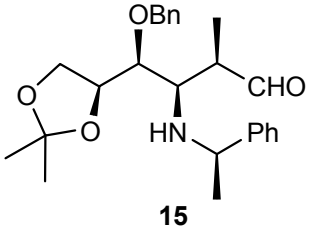
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (q, 5-CH_3), 24.5 (q, NCH<u>C</u>H_3), 26.0, 27.1 [2 q, C(<u>C</u>$H_3)_2$], 37.9 (d, C-5), 57.6 (d, N<u>C</u>HCH_3), 57.7 (d, C-4), 65.2 (t, C-7), 66.5 (t, C-1), 74.3 (d, C-6), 76.0 (t, OCH_2Ph), 80.2 (d, C-2), 80.9 (d, C-3), 110.2 [s, <u>C</u>$(CH_3)_2$], 127.7, 127. 9, 128.0, 128.1, 128.2, 128.8 (6 d, 2 C_6H_5), 138.8 (s, *i*-C of OCH_2<u>C</u>$_6H_5$), 144.3 [s, *i*-C of NCH(CH_3)<u>C</u>$_6H_5$].

Minor isomer

^{13}C NMR ($CDCl_3$, 75.5 MHz), δ = 14.6 (q, 3-CH_3), 25.8 (q, NCH<u>C</u>H_3), 26.1, 27.1 [2 q, C(<u>C</u>$H_3)_2$], 39.9 (d, C-3), 57.1 (d, N<u>C</u>HCH_3), 59.6 (d, C-4), 64.9 (t, C-1), 66.3 (t, C-7), 74.1 (d, C-2), 75.6 (t, OCH_2Ph), 80.7 (d, C-6), 82.8 (d, C-5), 139.1 (s, *i*-C of OCH_2<u>C</u>$_6H_5$), 143.0 [s, *i*-C of NCH(CH_3)<u>C</u>$_6H_5$]. Some peaks could not be identified due to overlap with those of the major isomer.

<u>Experiment 9 (FLi 93)</u>

(2*R*,3*R*,4*S*,1'*R*)-4-Benzyloxy-5,6-isopropylidenedioxy-3-(*N*-1'-phenylethylamino)-2-methylhexanal (**15**)



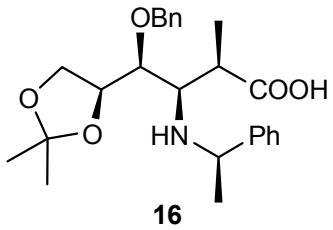
15

To a solution of the diol **14** (253 mg, 0.57 mmol) in MeOH/THF/H_2O (10 mL, 4 : 2 : 1) was added $NaIO_4$ (428 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred for 3 h at the same

temperature, then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give the aldehyde **15** (234 mg, 99 %) as a colourless oil which was used directly for the next step.

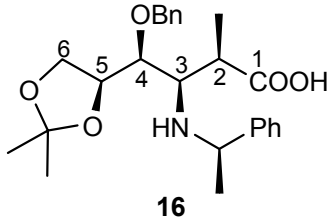
Experiment 10 (FLi 94)

(2*R*,3*R*,4*S*,1'*R*)-4-Benzyloxy-5,6-isopropylidenedioxy-3-(*N*-1'-phenylethylamino)-2-methylhexanoic acid (**16**)



16

The aldehyde **15** was dissolved in *t*-BuOH (5.0 mL) and 2-methyl-2-butene (2.5 mL). To the mixture was added a solution of $NaClO_2$ (78 mg, 0.86 mmol) and NaH_2PO_4 (104 mg, 0.86 mmol) in water (1.0 mL). After stirring for 90 min the same amounts of $NaClO_2$ and NaH_2PO_4 were added again. After further stirring for 1 h, NaOH solution (8 M, 0.5 mL) was added. The solvent was removed under reduced pressure and the resulting residue was dissolved in water (6.0 mL). The pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 40 mL) and the organic extracts were dried ($MgSO_4$). After removal of the solvents, the carboxylic acid **16** (219 mg, 90 %) was obtained as a colourless, spectroscopically pure oil, which was directly converted into the corresponding ester.



16

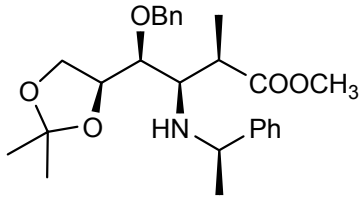
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.99 (d, $^3J_{2,CH_3}$ = 7.2 Hz, 3 H, 2-CH_3), 1.40, 1.42 [2 s, 6 H $C(CH_3)_2$], 1.47 (d, ^3J = 6.6 Hz, 3 H, NCHCH_3), 1.94 (m, 1 H, 2-H), 2.84 (dd, $^3J_{2,3}$ = 5.7 Hz, $^3J_{3,4}$ = 1.3 Hz, 1 H, 3-H), 3.59 (dd, $^3J_{4,5}$ = 4.0 Hz, $^3J_{3,4}$ = 1.2 Hz, 1 H, 4-H), 3.74 (dd, $^2J_{6a,6b}$ = 8.2 Hz, $^3J_{5,6a}$ = 7.6 Hz, 1 H, 6-H_a), 3.91 (q, ^3J = 6.6 Hz, 1 H, NCHCH_3), 4.01 (dd, $^2J_{6a,6b}$ = 8.3 Hz, $^3J_{5,6b}$ = 6.5 Hz, 1 H, 6-H_b), 4.21 (m, 1 H, 5-H), 4.51, 4.66 (A, B of AB, ^2J = 10.4 Hz, 2 H, OCH_2Ph), 7.29-7.41 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 12.5 (q, 2-CH_3), 23.1 (q, NCH<u>C</u>H_3), 25.7, 26.3 [2 q, C(<u>C</u>H_3)$_2$], 39.0 (d, C-2), 59.0 (d, N<u>C</u>HCH_3), 61.6 (d, C-3), 66.0 (t, C-6), 74.7 (t, OCH_2Ph), 75.1 (d, C-5),

79.1 (d, C-4), 110.0 [s, $\underline{C}(CH_3)_2$], 125. 9, 127.1, 128.0, 128.3, 128.4, 128.7, 129.0 (7 d, 2 C_6H_5), 137.1 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 141.9 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$], 176.0 (s, C-1).

Experiment 11 (FLi 95)

Methyl (2*R*,3*R*,4*S*,1'*R*)-4-benzyloxy-5,6-isopropylidenedioxy-3-(*N*-1'-phenylethyl-amino)-2-methylhexanoate (**17**)



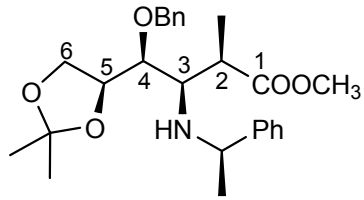
17

The acid **16** (219 mg, 0.51 mmol) was treated with a solution of ethereal CH_2N_2 (excess, a yellow solution prepared accoding to lit.[169]). After 20 min the solvent was evaporated and the residue was purified by flash chromatography on silica gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 6 : 1) to afford the methyl ester **17** (195 mg, 86 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 4.08 (*c* = 1.45, $CHCl_3$)

$C_{26}H_{35}NO_5$	calcd.	C	70.72	H	7.99	N	3.17
(441.6)	found	C	70.57	H	7.99	N	3.10

IR (neat): υ = 3029 (w), 2981 (w), 1730 (s), 1062 (w), 1494 (m), 1453 (m), 1369 (m), 1252 (m), 1199 (s), 1071 (s), 899 (m), 855 (m), 799 (w), 738 (m), 698 (vs) cm^{-1}.



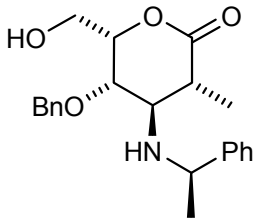
17

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.11 (d, $^3J_{2,CH_3}$ = 6.6 Hz, 3 H, 2-CH_3), 1.25 (d, ^3J = 6.4 Hz, 3 H, $NCHCH_3$), 1.41, 1.44 [2 s, 6 H, $C(CH_3)_2$], 2.66 (m, 2 H, 2-H, $NCHCH_3$), 3.34 (s, 3 H, OCH_3), 3.49 (dd, $^3J_{3,4}$ = 7.7 Hz, $^3J_{4,5}$ = 0.9 Hz, 1 H, 4-H), 3.69 ("t", $^3J_{5,6a}$ = $^2J_{6a,6b}$ = 8.1 Hz, 1 H, 6-H_a), 3.90 (q, ^3J = 6.5 Hz, 1 H, $NCHCH_3$), 4.09 (dd, $^2J_{6a,6b}$ = 8.1 Hz, $^3J_{5,6b}$ = 6.3 Hz, 1 H, 6-H_b), 4.47, 4.94 (A, B of AB, ^2J = 11.2 Hz, 2 H, OCH_2Ph), 4.59 (m, 1 H, 5-H), 7.22-7.27 (m, 10 H, 2 C_6H_5).

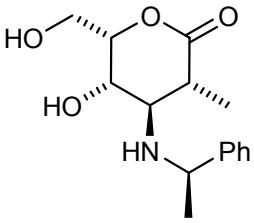
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.7 (q, 2-CH_3), 23.6 (q, NCH$\underline{C}H_3$), 26.2, 27.2 [2 q, C($\underline{C}H_3)_2$], 40.3 (d, C-2), 51.7 (q, OCH_3), 55.7 (d, N$\underline{C}HCH_3$), 59.0 (d, C-3), 66.8 (t, C-6), 74.0 (t, OCH_2Ph), 79.5 (d, C-5), 81.3 (d, C-4) 109.7 [s, $\underline{C}(CH_3)_2$], 127.5, 127.8, 128.5, 128.7 (4 d, 2 C_6H_5), 139.1 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 146.4 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$], 175.9 (s, C-1).

Experiment 12 (FLi 99)

(1'*R*)-4-*O*-Benzyl-2-methyl-3-(*N*-1'phenylethyl-amino-2,3-dideoxy-*L*-idono-1,5-lactone (**18**) and (1'*R*)-2-Methyl-3-(*N*-1'-phenylethylamino)-2,3-didexoy-*L*-idono-1,5-lactone (**19**)



18



19

The methyl ester **17** (240 mg, 0.54 mmol) was dissolved in dioxane/water (4.0 mL, 1 : 1) to which 6 drops of concentrated HCl was added. The reaction mixture was stirred at 50 °C for 16 h. The solvent was evaporated under reduced pressure (40 °C/60 mbar). The residue was dissolved in saturated $NaHCO_3$ (5.0 mL) and extracted with EtOAc (4 × 20 mL). The organic extracts after drying ($MgSO_4$) were concentrated in vacuo (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 2 : 1) to yield the lactone **18** (80 mg, 40 %) as an analytically pure, colourless oil and the free γ-hydroxy-δ-lactone **19** (40 mg, 26 %) as a colourless, spectroscopically pure powder, with slightly deviating analysis for the δ-lactone **19**.

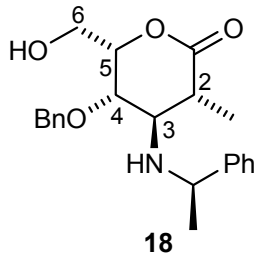
γ-Benzyloxy-δ-lactone **18**:

$[\alpha]_D^{20}$ = + 90.2 (*c* = 1.10, $CHCl_3$)

MS (EI, 70 eV): *m/z* (%) = 369 (1.2) $[M]^+$, 206 (38), 105 (77), 91 (100), 57 (13).

$C_{22}H_{27}NO_4$	calcd.	C	71.52	H	7.37	N	3.79
(369.5)	found	C	70.91	H	7.47	N	3.69

IR (neat): υ = 3320 (b, OH), 3022 (w), 2974 (w), 2873 (w), 1729 (s, C=O), 1494 (w), 1453 (m), 1369 (m), 1247 (m), 1193 (s), 1113 (s), 1054 (s), 1027 (s), 942 (m), 808 (w), 762 (m), 734 (s), 698 (vs) cm^{-1}.



18

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.20 (d, $^3J_{2,CH_3}$ = 6.8 Hz, 3 H, 2-CH_3), 1.36 (d, ^3J = 6.6 Hz, 3 H, NCHCH_3), 2.02 (b, 2 H, OH, NH), 2.22 (m, 1 H, 2-H), 2.57 (dd, $^3J_{3,4}$ = 7.3 Hz, $^3J_{2,3}$ = 0.7 Hz, 1 H, 3-H), 3.66 (“d”, $^3J_{4,5}$ = 1.1 Hz, 1 H, 4-H), 3.70 (dd, $^2J_{6a,6b}$ = 11.8 Hz, $^3J_{5,6a}$ = 4.8, 1 H, 6-H_a), 3.87 (q, ^3J = 6.6 Hz, 1 H, NCHCH_3), 4.00 (dd, $^2J_{6a,6b}$ = 11.8 Hz, $^3J_{5,6b}$ = 7.2 Hz, 1 H, 6-H_b), 4.28, 4.44 (A, B of AB, ^2J = 12.0 Hz, 2 H, OCH_2Ph), 4.54 (ddd, $^3J_{5,6b}$ = 7.1 Hz, $^3J_{5,6a}$ = 4.8 Hz, $^3J_{4,5}$ = 1.0 Hz, 1 H, 5-H), 7.19–7.35 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.0 (q, 2-CH_3), 25.4 (q, NCH$\underline{C}H_3$), 41.0 (d, C-2), 55.6 (d, N$\underline{C}HCH_3$), 59.3 (d, C-3), 62.4 (t, C-6), 71.1 (t, OCH_2Ph), 75.0 (d, C-5), 77.9 (d, C-4), 126.9, 128.0, 128.4, 128.9, 129.2 (5 d, 2 C_6H_5), 137.9 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 144.9 [s, *i*-C of NCH(CH_3)$\underline{C}_6H_5$], 174.0 (s, C-1).

γ-Hydroxy-δ-lactone **19**:

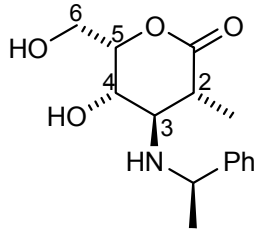
M. p. = 103-105 °C; $[\alpha]_D^{20}$ = + 103.2 (*c* = 0.46, $CHCl_3$)

$C_{15}H_{21}NO_4$	calcd.	C	64.50	H	7.58	N	5.01
(279.3)	found	C	62.58	H	7.56	N	4.69

MS (EI, 70 eV): *m/z* (%) = 279 (9) $[M]^+$, 161 (13), 105 (100), 57 (18).

HRMS (EI): *m/z* calcd. for $C_{15}H_{21}NO_4$: 279.1471; found 279.1470.

IR (solid): υ = 3464 (m), 3307 (m), 2968 (w), 2935 (w), 2886 (w), 1736 (s), 1492 (w), 1454 (w), 1371 (m), 1348. (m), 1326 (w), 1275 (w), 1244 (w), 1188 (s), 1162 (m), 1127 (s), 1091 (m), 1027 (s), 975 (s), 909 (w), 841 (w), 761 (s), 689 (s) cm^{-1}.



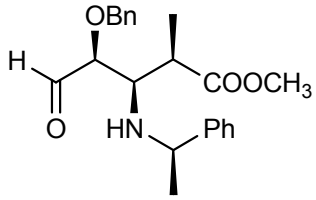
19

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.12 (d, J_{2,CH_3} = 7.1 Hz, 3 H, 2-CH_3), 1.38 (d, ^3J = 6.6 Hz, 3 H, NCHCH_3), 2.69 (m, 3 H, 3-H, OH and NH) , 3.17 (dd, $^2J_{6a,6b}$ = 10.5 Hz, $^3J_{5,6a}$ = 7.6 Hz, 1 H, 6-H_a), 3.73–3.86 (m, 3 H, 2-H, 6-H_b, NCHCH_3), 4.15 (m, 1 H, 5-H), 4.44 (dd, $^3J_{3,4}$ = 7.6 Hz, $^3J_{4,5}$ = 1.4 Hz, 1 H, 4-H), 7.26–7.38 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.9 (q, 2-CH_3), 24.7 (q, NCH$\underline{C}H_3$), 40.4 (d, C-2), 56.9 (d, N$\underline{C}$HCH_3), 60.5 (d, C-3), 63.4 (t, C-6), 70.9 (d, C-5), 84.8 (d, C-4), 126.4, 127.6, 128.8 (3 d, C_6H_5), 144.3 [s, *i*-C of NCH(CH_3)$\underline{C}_6H_5$], 178.5 (s, C-1).

Experiment 13 (FLi 101)

Methyl (2*R*,3*R*,4*S*,1'*R*)-4-benzyloxy-4-formyl-3-(*N*-1'-phenylethylamino)-2-methylbutanoate (**20**)

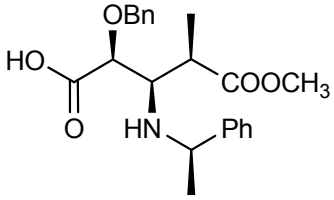


20

Similar to lit.[39e], H_5IO_6 (159.6 mg, 0.70 mmol) was added to a solution of the acetonide ester **17** (123 mg, 0.28 mmol) in Et_2O (6.0 mL) and the reaction mixture was stirred under N_2 for 6 h. A solution of $Na_2S_2O_3$ (2 M, 1.5 mL) was added; the mixture was extracted with Et_2O (3 × 15 mL) and dried ($MgSO_4$). The organic solution was concentrated in vacuo (40 °C/650 mbar) to afford the aldehyde **20** as a colourless oil used directly for next step.

Experiment 14 (FLi 102)

(2*S*,3*R*,4*R*,1'*R*)-2-Benzyloxy-3-(*N*-1'-phenylethylamino)-4-methylpentane-1,5-dioic acid 5-methyl ester (**21**)

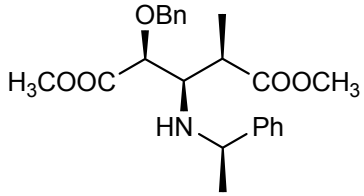


21

The aldehyde **20** was dissolved in *t*-BuOH (4.0 mL) and 2-methyl-2-butene (1.5 mL), then $NaClO_2$ (38 mg, 0.42 mmol) and NaH_2PO_4 (50.4 mg, 0.42 mmol) were added. After stirring for 90 min, NaOH solution (2.0 mL, 4 M) was added and the solvent was removed under reduced pressure (40 °C/60 mbar). The residue, a colourless powder, was dissolved in water (4.0 mL), then 6 M HCl was added dropwise until a pH of 3–4 was reached. The mixture was extracted with EtOAc (5 × 30 mL) and dried ($MgSO_4$). After removal of the solvent, the diacid monoester **21** (93 mg, 86 %) was obtained as a colourless oil. The acid was directly converted into the corresponding ester for analysis.

Experiment 15 (FLi 103)

Dimethyl (2*S*,3*R*,4*R*,1'*R*)-2-benzyloxy-4-methyl-3-(*N*-1'-phenylethylamino)-pentanedioate (**22**)



22

Without purification, the acid **21** was treated with an excess of an ethereal CH_2N_2 (a yellow solution). After stirring for 10 min, the solvent was evaporated and the light-yellow oil was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 4 : 1). Thus, the diester **22** (80 mg, 72 %) was obtained as a spectroscopically pure (analytically almost pure), colourless oil;.

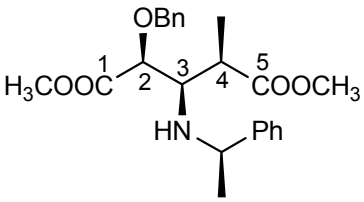
$[\alpha]_D^{20}$ = - 8.70 (*c* = 1.02, $CHCl_3$).

$C_{23}H_{29}NO_5$	calcd.	C	69.15	H	7.32	N	3.51
(399.5)	found	C	68.31	H	7.43	N	3.59

MS (CI, pos.): *m/z* (%) = 400 (100) $[M+H]^+$, 220 (35).

HRMS (CI, pos.): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{30}NO_5$: 400.2124; found 400.2111.

IR (neat): υ = 3028 (w), 2950 (w), 1731 (vs, 2 C=O), 1495 (w), 1453 (m), 1434 (m), 1345 (m), 1256 (m), 1198 (s), 1162 (m), 1105 (s), 1027 (m), 953 (w), 913 (w), 842 (w), 749 (s), 698 (vs) cm^{-1}.



22

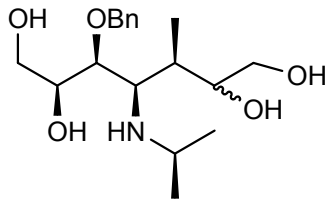
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.09 (d, $^3J_{4,CH_3}$ = 7.1 Hz, 3 H, 4-CH_3), 1.23 [d, ^3J = 6.4 Hz, 3 H, NCHCH_3], 2.66 (m, 1 H, 4-H), 3.21 (dd, $^3J_{3,4}$ = 6.3 Hz, $^3J_{2,3}$ = 2.4 Hz, 1 H, 3-H), 3.39 (s, 3 H, OCH_3), 3.79 (m, 4 H, NCHCH_3, OCH_3), 4.01 (d, $^2J_{2,3}$ = 2.3 Hz, 1 H, 2-H), 4.34, 4.76 (A, B of AB, ^2J = 11.0 Hz, 2 H, OCH_2Ph), 7.19-7.28 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.1 (q, 4-CH_3), 24.1 (q, NCH<u>C</u>H_3), 41.5 (d, C-4), 51.4, 51.8 (2 q, 2 OCH_3), 55.6 (d, N<u>C</u>HCH_3), 59.5 (d, C-3), 72.9 (t, OCH_2Ph), 77.4 (d, C-2), 127.0, 127.1,

127.9, 128.2, 128.3, 128.4 (6 d, 2 C_6H_5), 137.23 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 145.63 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$], 172.57, 175.40 (2 s, C-1, C-5).

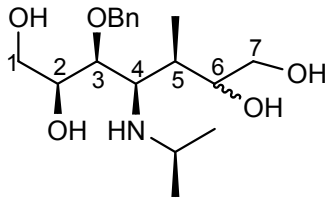
Experiment 16 (FLi 31)

(2*S*,3*S*,4*R*,5*S*,6*RS*,1'*R*)-3-*O*-Benzyl-5-methyl-4-(*N*-1'-phenylethylamino)-heptane-1,2,3,6,7-pentaol (**23**)



23

Following a lit. procedure[40], a 50-mL round-bottom flask, equipped with a magnetic stirrer, was charged with *t*-BuOH/H_2O (6.0 mL, 1:1). To the mixture were added $K_3[Fe(CN)_6]$ (325 mg, 0.976 mmol), K_2CO_3 (134 mg, 0.976 mmol), $K_2OsO_2(OH)_4$ (3.6 mg, 0.009 mmol), and hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$, 12 mg, 0.015 mmol] at r. t. The mixture was stirred for 15 min at the same temperature, then the heptene **9** (120 mg, 0.325 mmol) was added at 0 °C. The temperature was allowed to rise to r. t.. After stirring for 6 h, the reaction was treated with $Na_2S_2O_5$ (696 mg, 3.66 mmol) at 0 °C and stirred for 1 h. Water (3 mL) was then added and the mixture was extracted with EtOAc (5 × 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated (40 °C/200 mbar). The crude product was purified by flash column chromatography on silica gel (5 g, column 2.5 cm × 2 cm, CH_2Cl_2/MeOH 2 : 1) to yield the tetraol **23** (84 mg, 76 %) as a colourless, analytically almost pure oil; *dr* = 80 : 20 from ^{13}C NMR.



23

$C_{23}H_{33}NO_5$	calcd.	C	68.46	H	8.24	N	3.47
(403.5)	found	C	67.72	H	8.28	N	3.31

Major isomer from the diastereoisomer mixture

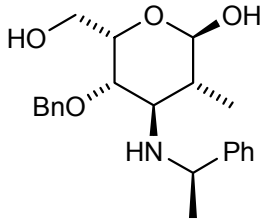
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.77 (q, 5-CH_3), 22.43 (q, NCH$\underline{C}H_3$), 36.14 (d, C-5), 57.75, 58.19 (2 d, N$\underline{C}HCH_3$, C-4), 64.33, 65.77 (2 t, C-7, C-1), 74.70 (d, C-6), 76.17 (t, OCH_2Ph), 77.83 (d, C-2), 80.75 (d, C-3), 129.15, 129.55, 129.80, 129.91, 130.13, 130.28 (6 d, 2 C_6H_5), 140.15 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 144.61 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$].

Minor isomer for the diastereoisomer mixture

^{13}C NMR ($CDCl_3$, 75.5 MHz), δ = 24.4 (q, NCH<u>C</u>H$_3$), 36.4 (d, C-5), 58.4, 60.9 (2 d, N<u>C</u>HCH$_3$, C-4), 64.6, 65.2 (2 t, C-7, C-1), 74.5 (d, C-6), 75.8 (t, OCH_2Ph), 76.6 (d, C-2), 76.8 (d, C-3), 140.6 [s, *i*-C of NCH(CH_3)<u>C</u>$_6$H$_5$]. Some signals could not be assigned as they overlapped with those of the major isomer.

<u>Experiment 17</u>

(1'*R*)-4-*O*-Benzyl-2-methyl-3-(*N*-1'-phenylethyl-amino-2,3-dideoxy-α-*L*-idopyranose (**24**)



24

Method A (FLi 33)

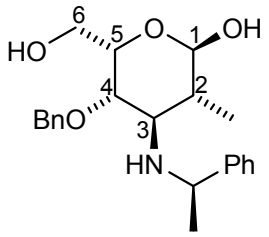
In analogy to lit.[43], the free diol **9** (152 mg, 0.41 mmol) was dissolved in dry CH_2Cl_2 (4 mL) at -78 °C. Ozone passed through the solution for 10 min, and then the reaction mixture was flushed with oxygen to remove the excess ozone. The solution was added to a stirred mixture of zinc dust (54 mg, 0.82 mmol) and 50 % aqueous AcOH (6 mL). The mixture was refluxed for 6 h and extracted with EtOAc (4 × 20 mL). The organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (6 g, column 4 cm × 1.5 cm, petroleum ether/EtOAc 2 : 1) to yield the hemiacetal **24** (69 mg, 42 %) as an analytically almost pure, colourless oil.

Method B (FLi 34)

The free diol **9** (215 mg, 0.48 mmol) was dissolved in MeOH/THF/H_2O (7 mL, 4 : 2 : 1). $NaIO_4$ (308 mg, 1.45 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue, a colourless oil, was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 2 : 1) to give the hemiacetal **24** (92 mg, 52 %) as a colourless, analytically almost pure oil; α : β = 90 : 10 from ^{1}H NMR signal of anomeric hydrogen (coupling constants $J_{1,2}$ = "0" Hz).

$C_{22}H_{29}NO_4$	calcd.	C	71.13	H	7.87	N	3.77
(371.5)	found	C	70.52	H	8.06	N	3.63

IR (neat): υ = 3299 (b, w), 3028 (w), 2878 (w), 1494 (w), 1453 (m), 1207 (w), 1026 (s), 972 (s), 910 (m), 733 (s), 699 (s), 643 (s), 609 (s) cm^{-1}.



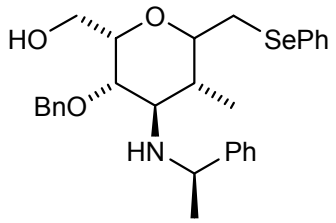
24

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ =1.11 (d, $^{3}J_{2,CH_3}$ = 7.5 Hz, 3 H, 2-CH_3), 1.38 [d, ^{3}J = 6.6 Hz, 3 H, NCHCH_3], 1.76 (m, 1 H, 2-H), 2.99 ("d", ^{3}J = 1.6 Hz, 1 H, 3-H), 3.48 ("s" 1 H, 4-H), 3.40 (b, 3 H; NH; 2 OH), 3.70 (dd, $^{2}J_{6a,6b}$ = 11.4 Hz, $^{3}J_{5,6a}$ = 4.6 Hz, 1 H, 6-H_a), 3.87 (q, ^{3}J = 6.5 Hz, 1 H, NCHCH_3), 3.91 (dd, $^{2}J_{6a,6b}$ = 11.4 Hz, $^{3}J_{5,6b}$ = 6.5 Hz, 1 H, 6-H_b), 4.11 (A, B of AB, ^{2}J = 11.8 Hz, 1 H, OCH_2Ph), 4.27 (m, 1 H, 5-H), 4.32 (A, B of AB, ^{2}J = 11.8 Hz, 1 H, OCH_2Ph), 4.97 ("s", 1 H, 1-H), 7.17-7.41 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.9 (q, 2-CH_3), 24.4 (q, NCH$\underline{C}H_3$), 37.9 (d, C-2), 53.9 (d, N$\underline{C}HCH_3$), 55.7 (d, C-3), 63.7 (t, C-6), 66.7 (d, C-5), 71.9 (t, OCH_2Ph), 74.6 (d, C-4), 97.33 (d, C-1), 126.4, 127.6, 127.8, 128.4, 128.9 (5 d, 2 C_6H_5), 138.15(s, *i*-C of $OCH_2\underline{C}_6H_5$), 143.71 [s, *i*-C of NCH(CH_3)$\underline{C}_6H_5$].

Experiment 18 (FLi 36)

(2*S*,3*S*,4*R*,5*R*,6*RS*,1''*R*)-3-Benzyloxy-5-methyl-4-(1''-phenylethylamino)-6-phenylselanylmethyl-tetrahydro-2*H*-pyran (**25**)



25

a) Preparation of *p*-nitrobenzenesulfonyl peroxide (*p*-NBSP)[42a]

According to lit.[42a], in a 250-mL flask with a magnetic stirrer, *p*-nitrobenzenesulfonyl chloride (5.6 g, 25 mmol) was dissolved in $CHCl_3$ (10 mL) and added with stirring to a cold (-20 °C) solution of K_2CO_3 (4.25 g, 32.2 mmol) in water (70 mL), EtOH (35 mL), and 30 % H_2O_2 (10 g). Agitation was slowly increased to full power and held there for 1 min. EtOH (50 mL) was added and the mixture was stirred slowly for a few minutes. The resulting precipitate was collected by filtration. The solid was washed thoroughly with water (3 × 20 mL) and dried under vacuum (15 mbar). The crude product as slight yellow powder was dissolved in acetone at r. t. and the solution was filtered. Then the filtrate was concentrated under reduced pressure (30 °C/400 mbar) to yield pure peroxide (2.1 g, 41%) which decomposed at 127 °C (lit.[42a]: 128 °C).

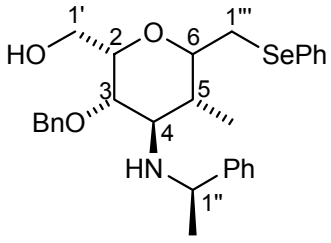
b) Reaction of the olefin **9** with diphenyl diselenide/*p*-NBSP

Diphenyl diselenide (PhSeSePh) (44 mg, 0.14 mmol) was dissolved in freshly distilled CH_3CN (2 mL), and *p*-NBSP (56 mg, 0.14 mmol) was added to the solution in small portions at 0 °C. The color of the solution turned reddish-brown at once, and the resulting solution was further allowed to stir for 10 min at 0 °C. To the freshly prepared solution was added the olefin **9** (100 mg, 0.27 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature and then 2 h at r. t.. After addition of Et_2O (5 mL), the solution was washed with H_2O (5 mL), $NaHCO_3$ (5 mL, 5 %), and then again with H_2O (5 mL). The separated organic layer was dried over $MgSO_4$. After removal of the solvent, the crude product (88 mg), a colourless oil, was obtained, which was purified by MPLC (EtOAc/petroleum ether 3 : 1) to give the tetrahydro-2H-pyran **25** (79 mg, 56 %) as a colourless, spectroscopically pure oil; *dr* = 90 : 10.

$[\alpha]_D^{20}$ = + 14.3 (*c* = 1.10, $CHCl_3$)

$C_{29}H_{35}NO_3Se$	calcd.	C	66.40	H	6.73	N	2.67
(524.5)	found	C	65.66	H	6.92	N	2.61

IR (neat): υ = 3438 (b, w), 2926 (w), 2878 (w), 1578 (w), 1536 (w), 1494 (m), 1477 (m), 1454 (m), 1367 (m), 1351 (m), 1205 (m), 1158 (m), 1071 (s), 1023 (s), 910 (w), 831 (w), 762 (m), 734 (vs), 697 (vs), 669 (m) cm^{-1}.



25

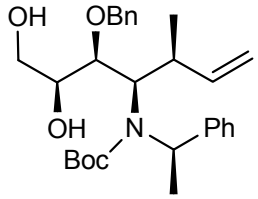
^1H NMR ($CDCl_3$, 300.1 MHz): δ =1.01 (d, $^3J_{5,CH_3}$ = 7.3 Hz, 3 H, 5-CH_3), 1.28 (d, ^3J = 6.6 Hz, 3 H, NCHCH_3), 1.67 (m, 1 H, 5-H), 2.79 (dd, $^2J_{1'''a,1'''b}$ = 12.3 Hz, $^3J_{1'''a,6}$ = 6.2 Hz, 1 H, 1'''-H_a), 2.86 ("t", $^3J_{4,5}$ = $^3J_{3,4}$ = 1.8 Hz,1 H, 4-H), 3.18 (dd, $^2J_{1'''a,1'''b}$ = 12.3 Hz, $^3J_{1'''b,6}$ = 8.0 Hz, 1 H, 1'''-H_b), 3.24 ("s" 1 H, 1'-H_a), 3.54 (dd, $^3J_{2,3}$ = 8.4 Hz, $^3J_{3,4}$ = 1.8 Hz, 1 H, 3-H), 3.74 (q, ^3J = 6.6 Hz, 1 H, NCHCH_3), 3.84-3.97 (m, 2 H, 6-H, 1'-H_b), 3.99 (m, 1 H, 2-H), 4.18, 4.45 (A, B of AB, ^2J = 11.9 Hz, 2 H, OCH_2Ph), 7.21-7.54 (m, 15 H, 3 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 12.4 (q, 5-CH_3), 24.8 (q, NCH<u>C</u>H_3), 30.2 (t, C-1'''), 37.4 (d, C-5), 55.3 (d, C-4), 56.0 (d, N<u>C</u>HCH_3), 63.7 (t, C-1'), 71.3 (t, OCH_2Ph), 74.7 (d, C-6),

75.4 (d, C-2), 76.7 (d, C-3), 126.3, 127.1, 127.7, 127.8, 128.4, 128.6, 129.1, 132.7 (8 d, 3 C_6H_5), 130.3 (s, *i*-C of Se$\underline{C}_6H_5$), 138.0 (s, *i*-C of $OCH_2\underline{C}_6H_5$), 145.5 [s, *i*-C of $NCH(CH_3)\underline{C}_6H_5$].

Experiment 19 (FLi 29)

(2*S*,3*S*,4*R*,5*S*,1'*R*)-3-*O*-Benzyl-4-*N*-*tert*-butoxy-carbonyl-5-methyl-4-(*N*-1'-phenylethylamino)-6-heptene-1,2,3-triol (**26**)



26

Method A:

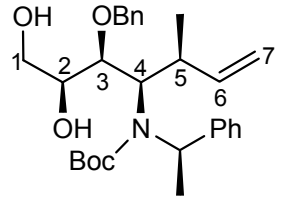
The diol **9** (93 mg, 0.25 mmol) was dissolved in THF (5 mL), followed by addition of $(Boc)_2O$ (109 mg, 0.50 mmol). The reaction mixture was stirred for 16 h at r. t.. After removal of the solvents, EtOAc (10 mL) was added, and the organic phase was washed with brine (2 × 4.0 mL), and dried ($MgSO_4$). After concentration (40 °C/220 mbar), the residue, a colourless oil, was purified by flash chromatography on silica gel (4.5 g, column 3 cm × 1.5 cm, petroleum ether/EtOAc 1 : 1) to afford the carbamate **26** (18 mg,15 %) as a colourless oil (79 mg, 85 % starting material **9** was recovered).

Method B:

To a solution of the diol **9** (80 mg, 0.22 mmol) in CH_3CN (2.0 mL) were added Et_3N (67 mg, 0.66 mmol), a catalytic amount DMAP (5 mg) and $(Boc)_2O$ (52 mg, 0.24 mmol). The reaction mixture was stirred for 24 h at r. t.. After solvent removal in vacuum (40 °C/30 mbar), CH_2Cl_2 (10 mL) was added and the organic phase was washed with brine (2 × 5 mL) and dried ($MgSO_4$). After concentration, the crude product was purified by flash chromatography on silica gel (8 g, column 2 cm × 4 cm, petroleum ether/EtOAc 1 : 1) to afford the carbamate **26** (20 mg, 25 %) as a courless, analytically pure oil (56 mg, 70 % starting material **9** was recovered).

$[\alpha]_D^{20}$ = + 22.6 (*c* = 1.15, $CHCl_3$)

$C_{28}H_{39}NO_5$	calcd.	C	71.61	H	8.73	N	2.98
(469.6)	found	C	71.95	H	8.35	N	3.04



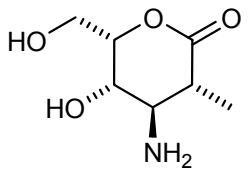
26

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ= 1.13 (d, $^{3}J_{5,CH_3}$ = 7.0 Hz, 3 H, 5-CH_3), 1.37 (d, ^{3}J = 6.5 Hz, 3 H, NCHCH_3), 1.50 [s, 9 H, OC(CH_3)$_3$], 2.70 (m, 1 H, 5-H), 3.00 (dd, $^{3}J_{4,5}$ = 5.0 Hz, $^{3}J_{3,4}$ = 1.2 Hz, 1 H, 4-H), 3.72 ("s" 1 H, 3-H), 3.99 (q, ^{3}J = 6.5 Hz, 1 H, NCHCH$_3$), 4.13 (m, 1 H, 2-H), 4.19-4.22 (m, 2 H, 1-H), 4.58 ("s", 2 H, OCH_2Ph), 4.98 (dd, $^{3}J_{6,7E}$ = 10.3 Hz, $^{2}J_{7E,7Z}$ = 1.4 Hz, 1 H, 7-H_E), 5.02 (dd, $^{3}J_{6,7Z}$ = 17.2 Hz, $^{2}J_{7E,7Z}$ = 1.4 Hz, 1 H, 7-H_Z), 5.80 (ddd, $^{3}J_{6,7Z}$ = 17.2 Hz, $^{3}J_{6,7E}$ = 10.3 Hz, $^{3}J_{5,6}$ = 7.6 Hz, 1 H, 6-H), 7.25-7.29 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 17.5 (q, 5-CH_3), 22.0 (q, NCH<u>C</u>H$_3$), 28.2 [q, C(<u>C</u>H$_3$)$_3$], 38.9 (d, C-5), 54.7 (d, N<u>C</u>HCH$_3$), 62.8 (d, C-4), 68.2 (t, C-1), 74.5 (d, C-2), 76.2 (t, OCH_2Ph), 77.1 (d, C-3), 82.7 [s, O<u>C</u>(CH$_3$)$_3$], 115.7 (t, C-7), 127.1, 128.0, 128.2, 128.7, 129.1 (5 d, 2 C_6H_5), 138.3 (s, *i*-C of OCH_2<u>C</u>$_6$H$_5$), 140.9 (d, C-6), 145.6 [s, *i*-C of NCH(CH$_3$)<u>C</u>$_6$H$_5$], 153.8 (s, C=O).

<u>Experiment 20 (FLi 172)</u>

3-Amino-2-methyl-2,3-dideoxy-*L*-idono-1,5-lactone (**27**)

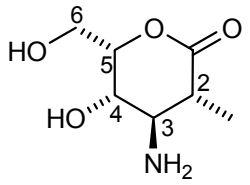


27

The γ-benzyloxy-lactone **18** (15 mg, 0.041 mmol) and the hydroxyl γ-lactone **19** (15 mg, 0.054 mmol) were dissolved in MeOH (2.0 mL) and hydrogenated (H_2, 4 bar) in the presence of Pearlman's catalyst Pd(OH)$_2$/C (16 mg, 20 %). After 3 d, the catalyst was filtered and the filtrate was concentrated under reduced pressure (40 °C/300 mbar) to give the lactone **27** (14.6 mg, 88 %) as a colourless, spectroscopically pure wax.

$[\alpha]_D^{20}$ = + 68.5 (*c* = 0.40, MeOH)

IR (neat): υ = 3285 (b, m, OH), 2936 (w), 1754 (s, C=O), 1598 (w), 1456 (m), 1351 (m), 1174 (s), 1119 (m), 1034 (vs), 972 (s), 872 (m), 798 (m), 687 (m), 628 (s), 605 (s) cm^{-1}.



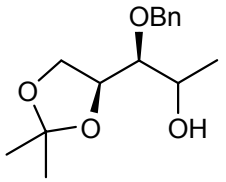
27

^{1}H NMR (D_2O, 300.1 MHz): δ = 1.15 (d, $^{3}J_{2,CH_3}$ = 7.3 Hz, 3 H, 2-CH_3), 2.65 (m, 1 H, 2-H), 3.49-3.57 (m, 3 H, 3-H, 6-H), 3.98 (m, 1 H, 5-H), 4.56 (dd, $^{3}J_{4,5}$ = 7.9 Hz, $^{3}J_{3,4}$ = 2.0 Hz, 1 H, 4-H).

^{13}C NMR (D_2O, 75.5 MHz): δ = 12.6 (q, 2-CH_3), 42.1 (d, C-2), 55.8 (d, C-3), 62.1 (t, C-6), 69.2 (d, C-5), 80.1 (d, C-4), 182.0 (s, C-2).

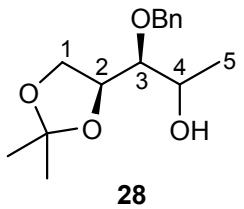
Experiment 21 (FLi 48)

(2*S*,3*R*,4*RS*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-pentane-1,2,3,4-tetraol (**28**)



28

To a solution of the aldehyde **4** (750 mg, 3.0 mmol) in dry Et_2O (20 mL) was added CH_3MgBr (2.5 mL, 7.5 mmol, 3 M in Et_2O) at 0 °C. The mixture was stirred at 0 °C for 2 h, and then quenched with sat. NH_4Cl (4 mL) solution. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$). After concentration, the crude product was purified by flash chromatography over silica gel (20 g, column 7 cm × 3 cm, petroleum ether/EtOAc 5 : 1) to afford alcohol **28** (758 mg, 95 %) as a colorless oil; *dr* = 80 : 20 from ^{13}C NMR directly used for next step.



28

Major isomer:

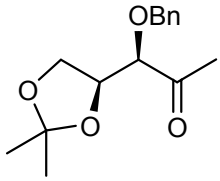
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.3 (q, C-5), 25.5, 26.6 [2 q, C($\underline{C}H_3)_2$], 66.0 (t, C-1), 67.7 (d, C-4), 74.5 (t, OCH_2Ph), 77.3 (d, C-2), 82.8 (d, C-3), 109.2 [s, $\underline{C}(CH_3)_2$], 127.8, 127.2, 128.4 (3 d, C_6H_5), 138.3 (s, *i*-C of $\underline{C}_6H_5$).

Minor Isomer:

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.2 (q, C-5), 25.5, 26.4 [2 q, C($\underline{C}H_3)_2$], 65.9 (t, C-1), 67.4 (d, C-4), 73.7 (t, OCH_2Ph), 76.9 (d, C-2), 82.2 (d, C-3), 109.2 [s, $\underline{C}(CH_3)_2$], 138.3 (s, *i*-C of $\underline{C}_6H_5$); some signals could not be assigned due to overlap with those of the major isomer.

Experiment 22 (FLi 51)

(2*S*,3*R*)-3-Benzyloxy-1,2-isopropylidenedioxy-4-pentanone (**29**)



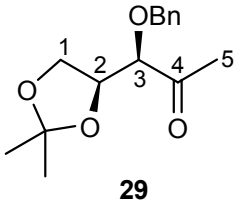
29

In analogy to lit.[32b], to a solution of pyridine (2.53 g, 32.0 mmol) in dry CH_2Cl_2 (50 mL) was added CrO_3 (1.6 g, 16 mmol) within 10 min. The reaction mixture was stirred for 1 h, and then the alcohol **28** (532 mg, 2.00 mmol) was added in CH_2Cl_2 (2 mL). The resulting mixture was stirred at r. t. for 3 h. The organic phase was washed with saturated $NaHCO_3$ (2 × 20 mL), H_2O (2 × 20 mL), and HCl (4 M, 2 × 20 mL). After drying over $MgSO_4$, the organic phase was concentrated (40 °C/700 mbar) to give a brown oil, which was purified by flash chromatography on silica gel (16 g, column 5 cm × 3 cm, petroleum ether/EtOAc 6 : 1) to yield the ketone **29** (464 mg, 88 %) as an analytically pure, colourless oil.

$[\alpha]_D^{20}$ = + 67.9 (*c* = 1.60, $CHCl_3$)

$C_{15}H_{20}O_4$	calcd.	C	68.16	H	7.63
(264.3)	found	C	68.03	H	7.61

IR (neat): υ = 2986 (w), 2882 (w), 1713 (s, C=O), 1497 (w), 1455 (m), 1371 (m), 1354 (m), 1255 (m), 1211 (s), 1072 (vs), 1027 (s), 844 (s), 737 (s), 697 (vs) cm^{-1}.



29

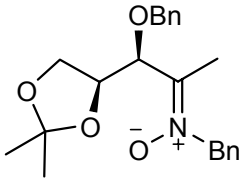
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.34, 1.43 [2 s, 6 H, $C(CH_3)_2$], 2.22 (s, 3 H, 5-H), 3.78 (d, $^3J_{2,3}$ = 5.1 Hz, 1 H, 3-H), 3.87 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1a,2}$ = 6.6 Hz, 1 H, 1-H_a), 4.01 (dd, $^2J_{1a,1b}$

= 8.5 Hz, $^3J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.31 (m, 1 H, 2-H), 4.57, 4.72 (A, B of AB, ^2J = 11.1 Hz, 2 H, OCH_2Ph), 7.31-7.37 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 25.4, 26.2 [2 q, $C(\underline{C}H_3)_2$], 27.6 (q, C-5), 65.7 (t, C-1), 73.4 (t, OCH_2Ph), 76.2 (d, C-2), 84.6 (d, C-3), 109.8 [s, $\underline{C}(CH_3)_2$], 128.0, 128.1, 128.5 (3 d, C_6H_5), 137.1 (s, *i*-C of $\underline{C}_6H_5$), 209.7 (s, C-4).

Experiment 23 (FLi 63)

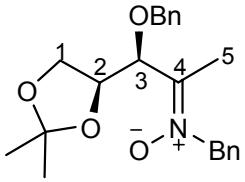
(2*S*,3*R*)-3-Benzyloxy-1,2-isopropylidenedioxy-4-pentanone-*N*-benzylnitrone (**30**)



30

In analogy to lit.[57b], to a well stirred solution of the ketone **29** (792 mg, 3.00 mmol) in CH_2Cl_2 (25 mL) were added anhydrous $ZnCl_2$ (408 mg, 3.00 mmol), *N*-benzylhydroxylamine (443 mg, 3.60 mmol) and $MgSO_4$ (432 mg, 3.60 mmol) sequentially. The resulting mixture was stirred at r. t. for 15 h. The solid was filtered and the filtrate was evaporated. The residue, a light-yellow oil, was purified by flash chromatography on silica gel (25 g, column 10 cm × 2.5 cm, petroleum ether/EtOAc 3 : 1 to pure EtOAc) to give the ketonitrone **30** (775 mg, 70 %) as a colourless, spectroscopically pure oil. The nitrone **30** is not stable, thus, after analysis by NMR, it was directly used for next step.

IR (neat): υ = 3030 (w), 2984 (w), 2872 (w), 1580 (w), 1496 (w), 1454 (m), 1369 (m), 1254 (m), 1210 (s), 1152 (s), 1056 (vs), 1027 (s), 921 (m), 888 (w), 841 (m), 735 (s), 696 (vs), 623 (w) cm^{-1}.



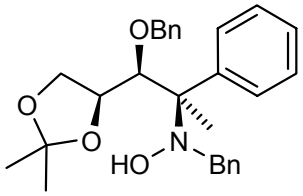
30

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.32, 1.43 [2 s, 6 H, $C(CH_3)_2$], 2.03 (s, 3 H, 5-H), 3.97 (m, 2 H, 1-H), 4.47-4.54 (m, 3 H, 2-H, NCH_2Ph), 5.01, 5.02 (A, B of AB, ^2J = 14.2 Hz, 2 H, OCH_2Ph), 5.08 (d, $^3J_{2,3}$ = 3.6 Hz, 1 H, 3-H), 7.27-7.36 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.8 (q, C-5), 25.6, 26.1 [2 q, $C(\underline{C}H_3)_2$], 65.0 (t, NCH_2Ph), 65.3 (t, C-1), 73.1 (t, OCH_2Ph), 75.0 (d, C-2), 75.7 (d, C-3), 109.7 [s, $\underline{C}(CH_3)_2$], 127.7, 127.8, 127.9, 128.3, 128.4, 128.9 (6 d, 2 C_6H_5), 133.2, 137.4 (2 s, *i*-C of 2 $\underline{C}_6H_5$), 147.7 (s, C-4).

Experiment 24 (FLi 66)

(2*S*,3*S*,4*R*)-3-*O*-Benzyl-4-(*N*-benzylhydroxylamino)-1,2-*O*-isopropylidene-4-phenylpentane-1,2,3-triol (**31**)



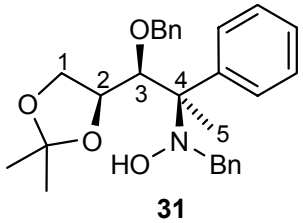
31

According to the procedure given in lit.[39e], a 100-mL two-necked round-bottomed flask with a refluxing condenser was charged with Mg (224 mg, 9.3 mmol) in absolute THF (10 mL). At the beginning, a small amount of bromobenzene was added to initiate the reaction; the rest (1.37 g, 7.50 mmol) in THF (10 mL) was added dropwise over a period of 15 min. The mixture was refluxed for 20 min, cooled to 0 °C, then the nitrone **30** (369 mg, 0.54 mmol) in THF (8 mL) was added. After stirring for 6 h at r. t., the reaction was quenched with sat. aq. NH_4Cl (2 mL) and the mixture was poured into brine (10 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (15 g, column 6 cm × 2.5 cm, petroleum ether/EtOAc 8 : 1) to afford the hydroxylamine **31** (570 mg, 85 %) as a colourless, analytically pure oil; *dr* > 95 : 5. (for assignment of the configuration, see Figure 7)

$[\alpha]_D^{20}$ = + 28.3 (*c* = 1.25, $CHCl_3$)

$C_{28}H_{33}NO_4$	calcd.	C	75.14	H	7.43	N	3.13
(447.6)	found	C	75.36	H	7.43	N	2.93

IR (neat): υ = 3410 (b, w, OH), 3028 (w), 2983 (w), 1602 (w), 1495 (m), 1453 (m), 1369 (m), 1212 (m), 1158 (m), 1071 (s), 1047 (s), 1028 (s), 941 (m), 912 (m), 853 (m), 735 (s), 692 (vs) cm^{-1}.



31

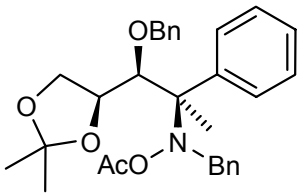
^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.25, 1.37 [2 s, 6 H, $C(CH_3)_2$], 1.71 (s, 3 H, 5-H), 3.57-3.73 (m, 3 H, 1-H_a, NCH_2Ph), 3.83 ("t", $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1b,2}$ = 7.8 Hz, 1 H, 1-H_b), 3.92 (m, 1 H, 2-H), 4.10 (d, $^3J_{2,3}$ = 7.1 Hz, 1 H, 3-H), 4.66, 5.03 (A, B of AB, ^2J = 11.6 Hz, 2 H, OCH_2Ph), 4.70

(s, 1 H, OH), 7.21-7.55 (m, 15 H, 3 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.3 (q, C-5), 26.0, 26.7 [2 q, C($\underline{C}H_3)_2$], 57.5 (t, NCH_2Ph), 67.2 (t, C-1), 70.2 (s, C-4), 75.6 (t, OCH_2Ph), 78.5 (d, C-2), 84.5 (d, C-3), 107.7 [s, $\underline{C}(CH_3)_2$], 127.3, 127.4, 127.6, 127.9, 128.0, 128.2, 128.4, 128.7, 129.6 (9 d, 3 C_6H_5), 139.0, 139.1, 140.8 (3 s, *i*-C of 3 $\underline{C}_6H_5$).

Experiment 25 (FLi 72)

(2*S*,3*S*,4*R*)-4-(*N*-Acetoxybenzylamino)-3-*O*-benzyl-1,2-*O*-isopropylidene-4-phenylpentane-1,2,3-triol (**32**)



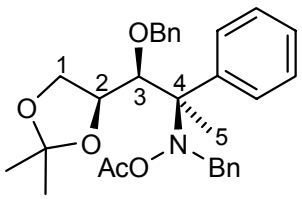
32

To a solution of the hydroxylamine **31** (320 mg, 0.716 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added dropwise DMAP (10 mg, 0.081 mmol), Et_3N (145 mg, 1.43 mmol), and acetic anhydride (139 mg, 1.36 mmol) dropwise. The reaction mixture was stirred for 3.5 h at r. t. and quenched by slow addition of aqueous HCl (5 %) at 0 °C until a pH of 7 was reached. The reaction mixture was diluted with Et_2O (20 mL), and washed with water (10 mL), sat. aq. $NaHCO_3$ (2 × 10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuum (40 °C/ 700 mabr). The crude product was purified by flash chromatography on silca gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to yield the protected hydroxylamine **32** (315 mg, 90 %) as an analytically pure, colourless oil.

$[\alpha]_D^{20}$ = + 10.6 (*c* = 1.20, $CHCl_3$)

$C_{30}H_{35}NO_5$	calcd.	C	73.59	H	7.21	N	2.86
(489.6)	found	C	73.04	H	7.35	N	2.70

IR (neat): υ = 2984 (b, w), 1761 (m, C=O), 1496 (w), 1454 (w), 1368 (m), 1240 (s), 1195 (s), 1049 (s), 1029 (s), 994 (m), 913 (w), 863 (m), 771 (w), 735 (vs), 697 (vs) cm^{-1}.



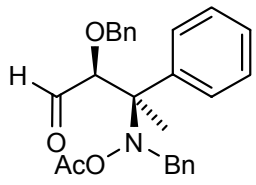
32

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.19, 1.31 [2 s, 6 H, $C(CH_3)_2$], 1.32 (s, 3 H, 5-H), 1.84 (s, 3 H, $OCOCH_3$), 2.66 ("t", $^2J_{1a,1b}$ = 6.9 Hz, $^3J_{1a,2}$ = 6.9 Hz, 1 H, 1-H_a), 3.21 ("t", $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 8.3 Hz, 1 H, 1-H_b), 3.70, 3.72 (A, B of AB, ^2J = 13.7 Hz, 2 H, NCH_2Ph), 3.90 (m, 1 H, 2-H), 4.15 (d, $^3J_{2,3}$ = 6.9 Hz, 1 H, 3-H), 4.48, 5.11 (A, B of AB, ^2J = 11.5 Hz, 2 H, OCH_2Ph), 7.18-7.70 (m, 15 H, 3 C_6H_5).

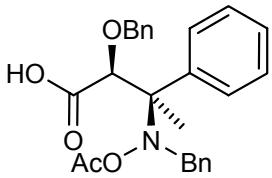
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.2 (q, C-5), 19.5 (q, $OCO\underline{C}H_3$), 26.0, 26.9, [2 q, $C(\underline{C}H_3)_2$], 58.0 (t, NCH_2Ph), 68.3 (t, C-1), 71.6 (s, C-4), 74.5 (t, OCH_2Ph), 77.9 (d, C-2), 85.9 (d, C-3), 108.5 [s, $\underline{C}(CH_3)_2$], 127.4, 127.5, 128.4, 128.5, 128.6, 128.9, 129.9 (7 d, 3 C_6H_5), 137.6, 139.6, 141.5 (3 s, *i*-C of 3 $\underline{C}_6H_5$), 171.4 (s, $O\underline{C}OCH_3$).

Experiment 26 (FLi 80, FLi 81)

(2*S*,3*R*)-3-(*N*-Acetoxybenzylamino)-2-benzyloxy-3-phenylbutanal (**33**) and (2*S*,3*R*)-3-(*N*-Acetoxybenzylamino)-2-benzyloxy-3-phenylbutanoic acid (**34**)



33



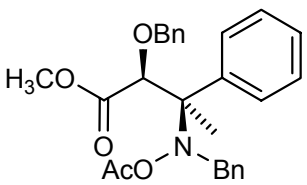
34

H_5IO_6 (378 mg, 1.65 mmol) was added to a solution of the acetonide **32** (324 mg, 0.66 mmol) in Et_2O (10 mL) and the resulting mixture was stirred under N_2 for 5.5 h. The solid was filtered off and aq. $Na_2S_2O_3$ (2 M, 3.0 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL) and the organic phases were dried ($MgSO_4$) and concentrated (40 °C/660 mabr) to afford the aldehyde **33** (248 mg, 90 %) as a colourless oil.

The aldehyde **33** (248 mg, 0.59 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (2.5 mL), then $NaClO_2$ (90 mg, 0.99 mmol) and NaH_2PO_4 (119 mg, 0.99 mmol) were added. After stirring for 90 min, the same amount of $NaClO_2$ and NaH_2PO_4 was added again. After 1 h, NaOH solution (4 M, 2.5 mL) was added and the solvent was removed under reduced pressure (40 °C/50 mbar). The residue, a colourless powder, was dissolved in water (6.0 mL), then 6 M HCl was added dropwise until a pH of 3–4 was obtained. The mixture was extracted with EtOAc (4 × 30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo (40 °C/220 mbar) to give the acid **34** (225 mg, 88 %) as a colourless oil, used directly for the next step.

Experiment 27 (FLi 82, FLi 83)

Methyl (2*S*,3*R*)-3-(*N*-acetoxybenzylamino)-2-benzyloxy-3-phenylbutanoate (**35**)



35

Method A: (FLi 82)

Without purification, the acid **34** was treated with a solution of ethereal CH_2N_2 (excess, a yellow solution). After stirring for 10 min, the solvent was evaporated and the light-yellow oil was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 4 : 1). Thus, the ester **35** (196 mg, 85 %) was obtained as a colourless, analytically pure oil.

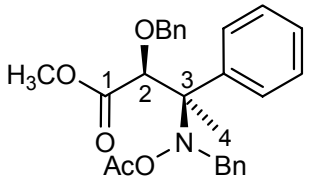
Method B: (FLi 83)

A solution of the carboxylic acid **34** (80 mg, 0.185 mmol) in dry CH_2Cl_2 (8 mL) under nitrogen was stirred with cooling and kept between -30 °C and -20 °C, then treated successively with Et_3N (38 mg, 0.37 mmol) and methanesulphonyl chloride (21 mg, 0.185 mmol). After 1 h, methanol (18 mg, 0.56 mmol) and DMAP (5 mg, 0.04 mmol) were added. The reaction mixture was allowed to warm up to r. t.. After 3 h, a solution of $NaHCO_3$ (3 mL, 5 %) was added, then the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was washed with sat. brine (2 × 6 mL), and dried ($MgSO_4$). After concentration in vacuum (40 °C/660 mbar), the crude product was purified by flash chromatography on silica gel (3.5 g, column 3 cm × 1 cm) to give the ester **35** (63 mg, 76 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 74.6 (*c* = 1.50, $CHCl_3$)

$C_{27}H_{29}NO_5$	calcd.	C	72.46	H	6.53	N	3.13
(447.5)	found	C	72.08	H	6.63	N	2.94

IR (neat): υ = 3030 (w), 2949 (w), 1759 (s, C=O), 1740 (vs, C=O), 1495 (m), 1454 (m), 1399 (m), 1362 (m), 1306 (m), 1241 (m), 1199 (vs), 1109 (s), 1073 (s), 1027 (m), 997 (s), 916 (m), 833 (m), 736 (vs), 694 (vs) cm^{-1}.



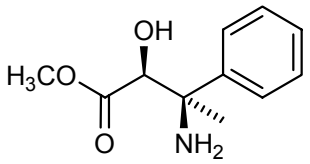
35

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.43 (s, 3 H, 4-H), 1.92 (s, 3 H, $OCOCH_3$), 3.14 (s, 3 H, OCH_3), 3.72 (s, 2 H, NCH_2Ph), 4.24, 4.33 (A, B of AB, ^2J = 11.0 Hz, 2 H, OCH_2Ph), 4.80 (s, 1 H, 2-H), 7.18-7.36 (m, 15 H, 3 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.0, (q, C-4), 19.7 (q, OCO<u>C</u>H_3), 51.7 (q, OCH_3), 56.9 (q, NCH_2Ph), 71.0 (t, OCH_2Ph), 72.4 (s, C-3), 86.7 (d, C-2), 127.7, 128.0, 128.1, 128.3, 128.6, 128.7, 128.8, 129.3 (8 d, 3 <u>C</u>$_6H_5$), 137.9, 138.1, 140.8 (3 s, *i*-C of 3 C_6H_5), 171.2 (s, C-1, O<u>C</u>OCH_3).

<u>Experiment 28 (FLi 87)</u>

(2*S*,3*R*)-Phenylisothreonine methyl ester (**36**)



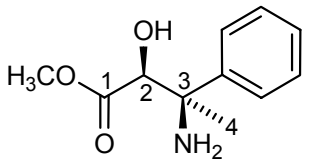
36

The ester **35** (70 mg, 0.16 mmol) was dissolved in MeOH (6 mL), followed by addition of Pd/C (33 mg, 10 %). The mixture was hydrogenated (3 bar) at r. t. for 40 h. The catalyst was then filtered and the filtrate was concentrated in vacuo (40 °C /300 mbar). The crude product was crystallized from a mixture of Et_2O and CH_2Cl_2 (6 mL, 10 : 1) to provide the amino hydroxy ester **36** (31 mg, 92 %) as analytically pure, colourless crystals; m. p. = 125 °C.

$[\alpha]_D^{20}$ = + 15.4 (*c* = 1.00, $CHCl_3$)

$C_{11}H_{15}NO_3$	calcd.	C	63.14	H	7.23	N	6.69
(209.2)	found	C	62.89	H	7.19	N	6.41

IR (neat): υ = 3303-2760 (b, w), 1736 (vs, C=O), 1595 (m), 1496 (w), 1436 (m), 1378 (m), 1358 (m), 1216 (s), 1173 (m), 1124 (s) 1106 (s), 1078 (m), 1026 (m), 971 (s), 929 (s), 906 (m), 866 (m), 764 (s), 734 (m), 694 (vs), 615 (s) cm^{-1}.



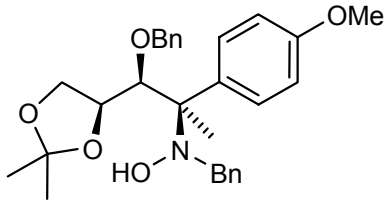
36

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.56 (s, 3 H, 4-H), 2.58 (b, 3 H, OH and NH_2), 3.69 (s, 3 H, OCH_3), 4.31 (s, 1 H, 2-H), 7.26-7.49 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 26.7, (q, C-4), 52.2 (q, OCH_3), 58.0 (s, C-3), 78.2 (d, C-2), 125.5, 127.2, 128.3 (3 d, C_6H_5), 144.6 (s, *i*-C of <u>C</u>$_6H_5$), 173.4 (s, C-1).

Experiment 29 (FLi 69)

(2*S*,3*S*,4*R*)-3-*O*-Benzyl-4-(*N*-benzylhydroxyl-amino)-1,2-isopropylidene-4-(4-methoxyphenyl)-pentane-1,2,3-triol (**37**)



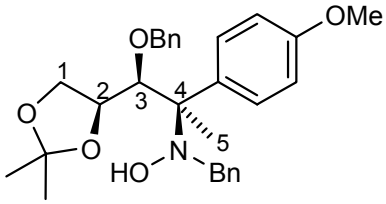
37

A 50-mL two-necked round-bottomed flask with a refluxing condenser was charged with Mg (81 mg, 3.4 mmol) in absolute THF (6 mL). At first, a small amount 4-bromoanisole was added to initiate the reaction, followed by addition of the rest of bromoanisole (506 mg, 2.71 mmol) in THF (15 mL) within 15 min. The mixture was refluxed for 20 min, then cooled to 0 °C and the nitrone **30** (200 mg, 0.540 mmol) in THF (5 mL) was added. After stirring at r. t. for 6 h, the reaction was quenched with sat. aq. NH_4Cl (2 mL). The mixture was poured into brine (6 mL) and extracted with EtOAc (3 × 20 mL). The organic solutes were dried ($MgSO_4$) and concentrated in vacuo (40 °C/220 mbar). The residue, a light-yellowish oil, was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to afford the hydroxylamine **37** (211 mg, 82 %) as a colourless, analytically pure oil; *dr* > 95 : 5.

$[\alpha]_D^{20}$ = + 29.2 (*c* = 1.20, $CHCl_3$)

$C_{29}H_{35}NO_5$	calcd.	C	72.93	H	7.39	N	2.93
(477.6)	found	C	72.83	H	7.57	N	2.79

IR (neat): υ = 3434 (b, w), 2984 (b, w), 1608 (m), 1509 (s), 1454 (m), 1368 (m), 1298 (m), 1246 (s), 1179 (m), 1158 (m), 1099 (s), 1071 (s), 1028 (vs), 938 (m), 912 (m) 839 (m), 795 (s), 735 (vs), 695 (vs) cm^{-1}.



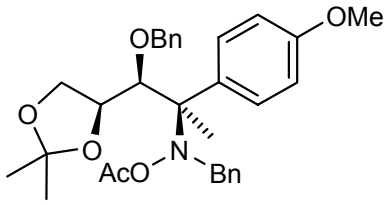
37

^1H NMR ($CDCl_3$, 500.1 MHz): δ = 1.28, 1.38 [2 s, 6 H, $C(CH_3)_2$], 1.69 (s, 3 H, 5-H), 3.52 (b, 1 H, 1-H_a), 3. 63, 3.66 (A, B of AB, ^2J = 13.9 Hz, 2 H, NCH_2Ph), 3.78-3.81 (m, 4 H, OCH_3, 1- H_b), 3.96 (m, 1 H, 2-H), 4.08 (d, $^3J_{2,3}$ = 7.8 Hz, 1 H, 3-H), 4.59 (b, 1 H, OH), 4.67, 5.03 (A, B of AB, ^2J = 11.6 Hz, 2 H, OCH_2Ph), 6.86-7.40 (m, 14 H, 2 C_6H_5, C_6H_4).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.3 (q, C-5), 26.0, 26.8 [2 q, C($\underline{C}H_3)_2$], 55.2 (q, OCH_3), 57.4 (t, NCH_2Ph), 67.3 (t, C-1), 69.7 (s, C-4), 75.9 (t, OCH_2Ph), 78.5 (d, C-2), 84.7 (d, C-3), 107.7 [s, $\underline{C}(CH_3)_2$)], 113.3, 127.0, 127.3, 127.6, 128.2, 128.4, 128.5, 128.7, 128.9 (9 d, 2 C_6H_5 and C_6H_4), 132.7, 139.0, 139.1, 158.8 (4 s, *i*-C of 2 $\underline{C}_6H_5$, $\underline{C}_6H_4$).

Experiment 30 (FLi 89)

(2*S*,3*S*,4*R*)-4-(*N*-Acetoxybenzylamino)-3-*O*-benzyl-1,2-*O*-isopropylidene-4-(4-methoxy-phenyl)pentane-1,2,3-triol (**38**)



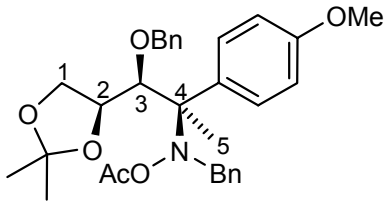
38

To a solution of the hydroxylamine **37** (224 mg, 0.500 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added 4-DMAP (7.0 mg, 0.057 mmol), Et_3N (102 mg, 1.01 mmol), and acetic anhydride (98 mg, 0.96 mmol) respectively. The reaction mixture was stirred for 2 h at room temperature and quenched by slow addition of aqueous HCl (5 %) at 0 °C until a pH of 7 was obtained. The reaction mixture was diluted with Et_2O (25 mL), washed with water (10 mL), saturated $NaHCO_3$ (2 × 10 mL), and brine (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo (40 °C/600 mbar). The product was purified by flash chromatography on silica gel (8 g, column 4.5 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to yield the *N*-acetoxy amine **38** (234 mg, 90 %) as an analytically pure, colourless oil.

$[\alpha]_D^{20}$ = + 22.1 (*c* = 1.05, $CHCl_3$)

$C_{31}H_{37}NO_6$	calcd.	C	71.65	H	7.18	N	2.70
(519.6)	found	C	71.41	H	7.22	N	2.70

IR (neat): υ = 2983 (w), 2934 (w), 1759 (m, C=O), 1607 (w), 1579 (w), 1510 (m), 1454 (m), 1368 (m), 1297 (w), 1249 (s), 1181 (s), 1056 (s), 1029 (s), 994 (m), 913 (m), 864 (m), 840 (m), 732 (vs), 691 (vs) cm^{-1}.



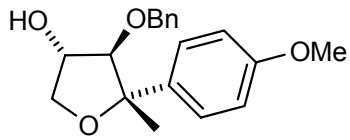
38

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.21 (s, 3 H, 5-H), 1.32, 1.33 [2 s, 6 H, $C(CH_3)_2$], 1.82 (s, 3 H, $OCOCH_3$), 2.72 (b, 1 H, 1-H_a), 3.18 ("t", $^3J_{1a,1b}$ = 8.4 Hz , $^3J_{1b,2}$ = 8.4 Hz, 1 H, 1-H_b), 3.69, 3.85 (A, B of AB, ^2J = 13.7 Hz, 2 H, NCH_2Ph), 3.82 (s, 3 H, OCH_3), 3.90 (m, 1 H, 2-H), 4.45, 5.12 (A, B of AB, ^2J = 11.5 Hz, 2 H, OCH_2Ph), 6.89-7.30 (m, 14 H, 2 C_6H_5 and C_6H_4).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.5 (q, C-5), 19.2 (q, $OCO\underline{C}H_3$), 25.6, 26.4 [2 q, $C(\underline{C}H_3)_2$], 55.2 (q, OCH_3), 57.3 (t, NCH_2Ph), 68.0 (t, C-1), 70.6 (s, C-4), 74.0 (t, OCH_2Ph), 77.6 (d, C-2), 85.7 (d, C-3), 108.0 [s, $\underline{C}(CH_3)_2$], 113.7, 126.9, 127.0, 127.3, 128.0, 128.1, 129.1, 129.5 (8 d, 2 C_6H_5 and C_6H_4), 133.0, 137.3, 139.3, 159.3 (4 s, *i*-C of 2 $\underline{C}_6H_5$, $\underline{C}_6H_4$), 170.3 (s, $O\underline{C}OCH_3$).

Experiment 31

(2*R*,4*R*,5*S*)-3-Benzyloxy-4-hydroxy-2-(4-methoxy-phenyl)-2-methyltetrahydrofuran (**39**)



39

Method A: (FLi 107)

The acetonide **38** (150 mg, 0.314 mmol) was dissolved in dioxane/H_2O (6 mL, 1 : 1), then concentrated HCl (3 drops) was added. The reaction mixture was stirred at 50 °C for 18 h. The solvent was evaporated under reduced pressure (40 °C/60 mbar). The residue was dissolved in saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (4 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography on silica gel (5 g, column 5 cm × 1 cm, petroleum ether/EtOAc 4 : 1) to afford the substituted tetrahydrofuran **39** (55 mg, 40 %) as a colourless, analytically pure oil.

The hydroxylamine **37** (95 mg, 0.20 mmol) was likewise treated according to method A to provide the tetrahydrofuran **39** (23 mg, 36 %) as a colourless, analytically pure oil.

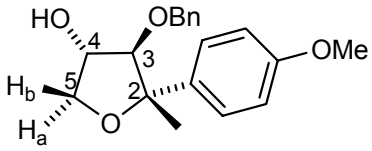
Method B: (FLi 109)

Following a lit. procedure[140], the acetonide **38** (120 mg, 0.231 mmol) was dissolved in CH_2Cl_2 (5 mL), then $FeCl_3 \cdot 6H_2O$ (219 mg, 0.81 mmol) was added. The yellow mixture was stirred at r. t. for 30 min. The solid was filtered and the filtrate was diluted with CH_2Cl_2 (10 mL) which was washed with sat. $NaHCO_3$ (2 × 8 mL) and brine (2 × 8 mL) respectively. The organic phase was dried ($MgSO_4$) and concentrated (40 °C/680 mbar) to give a yellowish oil which was purified by flash chromatography on silica gel (4 g, column 3.5 cm × 1 cm, petroleum ether/EtOAc 4 : 1) to furnish the tetrahydrofuran **39** (42 mg, 58 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 74.8 (*c* = 1.00, $CHCl_3$)

$C_{19}H_{22}O_4$	calcd.	C	72.59	H	7.05
(314.4)	found	C	72.15	H	7.06

IR (neat): υ = 3421 (b, w), 2933 (w), 1610 (m), 1582 (w), 1510 (s), 1454 (m), 1397 (w), 1369 (w), 1299 (m), 1245 (s), 1176 (s), 1119 (s), 1069 (s), 1028 (vs), 830 (s), 735 (s), 697 (s) cm^{-1}.



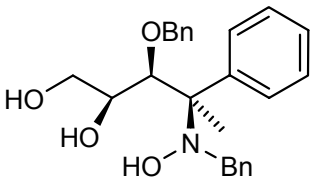
39

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.50 (s, 3 H, 2-CH_3), 3.78 (dd, $^2J_{5a,5b}$ = 9.8 Hz, $^3J_{4,5a}$ = 3.5 Hz, 1 H, 5-H_a), 3.79 (s, 3 H, OCH_3), 3.99 (d, $^3J_{3,4}$ = 2.7 Hz, 1 H, 3-H), 4.30 (dd, $^2J_{5a,5b}$ = 9.9 Hz, $^3J_{4,5b}$ = 5.7 Hz, 1 H, 5-H_b), 4.37 (m, 1 H, 4-H), 4.65, 4.73 (A, B of AB, ^2J = 12.0 Hz, 2 H, OCH_2Ph), 6.84-7.31 (m, 9 H, C_6H_5, C_6H_4).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 24.4 (q, 2-CH_3), 55.7 (q, OCH_3), 72.7 (t, C-5), 72.8 (t, OCH_2Ph), 77.6 (d, C-4), 85.9 (s, C-2), 91.8 (d, C-3), 114.2, 126.3, 128.0, 128.3, 128.9 (5 d, C_6H_5, C_6H_4), 138.5, 138.7, 158.9 (3 s, *i*-C of 2 $\underline{C}_6H_5$, $\underline{C}_6H_4$).

Experiment 32

(2*S*,3*S*,4*R*)-3-*O*-Benzyl-4-(*N*-benzylhydroxylamino)-4-phenylpentane-1,2,3-triol (**40**)



40

Method A: (FLi 75)

The hydroxylamine **31** (66 mg, 0.15 mmol) was dissolved in dioxane/H_2O (3.5 mL, 1 : 1), then concentrated HCl (4 drops) was added. The reaction mixture was stirred at 50 °C for 18 h. The solvent was evaporated under reduced pressure (40 °C/60 mbar). The residue was dissolved in saturated $NaHCO_3$ (3 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure (40 °C, 220 mbar) to furnish a colorless oil which was purified by flash chromatography on silica gel (4 g, column

4 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to afford the free diol **40** (50 mg, 82 %) as an analytically pure, colourless powder; m. p. = 137-138 °C.

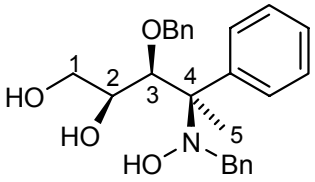
Method B: (FLi 76)

To a solution of the hydroxylamine **31** (50 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added $FeCl_3 \cdot 6\ H_2O$ (116 mg, 0.39 mmol). The yellow mixture was stirred at r. t. for 30 min. The solid was filtered and the filtrate was diluted with CH_2Cl_2 (10 mL) which was washed with sat. $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuum (40 °C/660 mbar). The crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to give the diol **40** (36 mg, 78 %) as an analytically pure, colourless powder; m. p. = 138-139 °C.

$[\alpha]_D^{20}$ = + 48.5 (*c* = 1.20, $CHCl_3$)

$C_{25}H_{29}NO_4$	calcd.	C	73.68	H	7.17	N	3.44
(407.5)	found	C	73.65	H	7.12	N	3.36

IR (solid): υ = 3370 (b, w, OH), 3028 (w), 2938 (w), 1602 (w), 1495 (m), 1454 (m), 1372 (m), 1242 (m), 1157 (w), 1067 (s), 1045 (s), 1027 (s), 913 (w), 866 (w), 731 (s), 696 (vs) cm^{-1}.



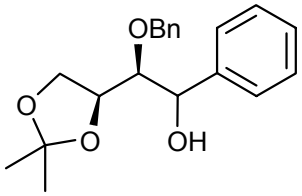
40

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.75 (s, 3 H, 5-H), 3.53 (dd, $^2J_{1a,1b}$= 10.8 Hz, $^3J_{1a,2}$ = 5.2 Hz, 1 H, 1-H_a), 3.72 (s, 2 H, NCH_2Ph), 3.83 (dd, $^2J_{1a,1b}$ = 10.8 Hz, $^3J_{1b,2}$ = 5.4 Hz, 1 H, 1-H_b), 3.98 (m, 1 H, 2-H), 4.08 (d, $^3J_{2,3}$ = 3.6 Hz, 1 H, 3-H), 4.68, 4.77 (A, B of AB, ^2J = 11.4 Hz, 2 H, OCH_2Ph), 7.23-7.62 (m, 15 H, 3 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.8 (q, C-5), 56.8 (t, NCH_2Ph), 66.1 (t, C-1), 69.2 (d, C-2), 70.2 (s, C-4), 76.1 (t, OCH_2Ph), 82.2 (d, C-3), 127.3, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.5, 128.7 (9 d, 3 C_6H_5), 137.8, 139.2, 140.7 (3 s, *i*-C of 3 $\underline{C}_6H_5$).

Experiment 33 (FLi 37)

(2*S*,3*S*,4*RS*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-phenylbutane-1,2,3,4-tetraol (**41**)



41

A 50-mL two-necked round-bottomed flask with a refluxing condenser was charged with Mg (38 mg, 1.56 mmol) in absolute THF (5 mL). A small amount of bromobenzene was added to initiate the reaction. The rest of bromobenzene (236 mg, 1.5 mmol) in THF (4 mL) was added dropwise within 5 min. The mixture was refluxed for 20 min and cooled to 0 °C. The aldehyde **4** (150 mg, 0.6 mmol) in THF (4 mL) was added dropwise and the reaction mixture was stirred at r. t. for 2 h. The reaction was quenched with sat. aq. NH_4Cl (2.5 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to provide a yellowish oil which was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to afford the alcohol **41** (162 mg, 82 %) as a colourless, analytically pure oil; *dr* = 55 : 45 from ^{13}C NMR spectrum.

$C_{20}H_{24}O_4$	calcd.	C	73.15	H	7.36
(328.4)	found	C	72.98	H	7.37

Major isomer:

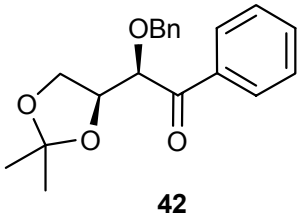
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.49, 26.24 [2 q, C($\underline{C}H_3)_2$], 66.06 (t, C-1), 73.54 (d, C-4), 74.87 (d, C-2), 76.95 (t, OCH_2Ph), 83.44 (d, C-3), 109.27 [s, $\underline{C}(CH_3)_2$], 126.42, 126.65, 127.96, 128.06, 128.19, 128.37 (6 d, 2 C_6H_5), 137.82, 141.12 (2 s, *i*-C of $\underline{C}_6H_5$).

Minor isomer:

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.44, 26.51 [2 s, C($\underline{C}H_3)_2$], 65.95 (t, C-1), 73.09 (d, C-4), 73.96 (d, C-2), 75.88 (t, OCH_2Ph), 81.33 (d, C-3), 109.33 [s, $\underline{C}(CH_3)_2$], 137.82, 141.05 (2 s, *i*-C of $\underline{C}_6H_5$); some signals not assigned as they overlapped with those of the major isomer.

Experiment 34 (FLi 39)

(2*S*,3*R*)-3-Benzyloxy-1,2-isopropylidenedioxy-4-phenylbutanone (**42**)



42

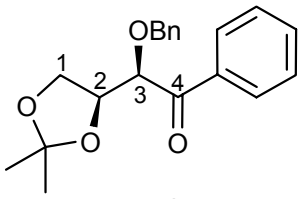
To a solution of pyridine (790 mg, 10.0 mmol) in dry CH_2Cl_2 (15 mL) was added CrO_3

(500 mg, 5.00 mmol) with stirring within 5 min. The mixture was stirred for an additional hour, then the alcohol **41** (162 mg, 0.493 mmol) was added in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 4 h at r. t.. For work-up, the organic phase was washed with sat. $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL), and 4 M HCl (2 × 10 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo (40 °C/660 mbar). The residue, a brown oil, was purified by flash chromatography on silica gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to afford the ketone **42** (137 mg, 85 %) as a colourless, analytically pure powder; m. p. = 105-106 °C.

$[\alpha]_D^{20}$ = + 46.5 (*c* = 1.18, $CHCl_3$)

$C_{20}H_{22}O_4$	calcd.	C	73.60	H	6.79
(326.4)	found	C	73.26	H	6.89

IR (neat): υ = 2986 (b, w), 1694 (s, C=O), 1371 (m), 1262 (m), 1227 (m), 1207 (s), 1147 (vs), 1059 (vs), 1030 (vs), 998 (m), 967 (s), 924 (m), 897 (m), 829 (s), 777 (s), 753 (m), 727 (s), 691 (vs), 674 (s), 646 (m) cm^{-1}.



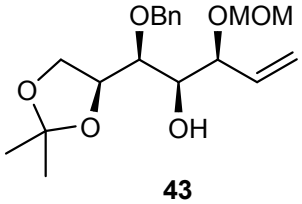
42

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.31, 1.33 [2 s, 6 H, $C(CH_3)_2$], 3.87 (dd, $^2J_{1a,1b}$ = 8.7 Hz, $^3J_{1a,2}$ = 6.3 Hz, 1 H, 1-H_a), 4.02 (dd, $^2J_{1a,1b}$ = 8.7 Hz, 1 H, $^3J_{1b,2}$ = 6.6 Hz, 1-H_b), 4.52 (A of AB, ^2J = 11.7 Hz, 1 H, OC*H*$_a$H$_b$Ph), 4.57 (m, 1 H, 2-H), 4.66 (d, $^3J_{2,3}$ = 6.0 Hz, 3-H), 4.72 (B of AB, ^2J = 11.7 Hz, 1 H, OCH$_a$*H*$_b$Ph), 7.25-8.05 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 25.2, 26.2 [2 q, C(<u>C</u>H$_3$)$_2$], 65.7 (t, C-1), 72.5 (t, OCH_2Ph), 76.4 (d, C-2), 82.4 (d, C-3), 109.9 [s, <u>C</u>$(CH_3)_2$], 128.0, 128.2, 128.4, 128.5, 129.3, 133.6 (6 d, 2 C_6H_5), 135.9, 137.1 (2 s, *i*-C of 2 <u>C</u>$_6$H$_5$), 199.02 (s, C-4).

<u>Experiment 35 (FLi 111)</u>

(2*S*,3*S*,4S,5S)-3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methoxymethyl-6-heptene-1,2,3,4,5-pentaol (**43**)



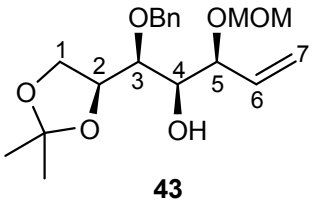
43

According to a procedure given by Brown *et al.*[71] to a stirred solution of 3-(methoxymethoxy)prop-1-ene (510 mg, 5.0 mmol) in THF (16 mL) was added *sec*-BuLi (3.69 mL, 2.84 g, 4.80 mmol, 1.3 M in cyclohexane) at -78 °C over a period of 10 min. After stirring for additional 30 min at the same temperature, (-)-*B*-methoxydiisopinocampheylborane (1.52 g, 4.80 mmol) in THF (3.43 mL, 1.40 M) was added dropwise. After the reaction mixture was stirred at -78°C for 1 h, $BF_3 \cdot Et_2O$ (0.78 mL, 6.0 mmol) was added dropwise. Immediately afterwards, the aldehyde **4** (1.20 g, 4.80 mmol) was added dropwise and the mixture was stirred at -78 °C for 3 h and then slowly warm to the room temperature. The oxidation was carried out by adding NaOH (3.6 mL, 4.0 M) and 30 % H_2O_2 (2.2 mL) at 0 °C. The resulting mixture was stirred at r. t. for 3 h and then a solution of $Na_2S_2O_3$ (4.6 mL, 9 M) was added. The mixture was extracted with EtOAc (3 × 45 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (60 g, column 15 cm × 4 cm, petroleum ether/EtOAc 6 : 1) to furnish the alcohol **43** (1.07 g, 63 %) as a colourless, analytically pure oil; > 95 % *syn*; *dr* > 95 : 5.

$[\alpha]_D^{20}$ = - 71.3 (*c* = 1.20, $CHCl_3$)

$C_{19}H_{28}O_6$	calcd.	C	64.75	H	8.01
(352.4)	found	C	64.58	H	8.08

IR (neat): υ = 3464 (b, w), 2984 (w), 2890 (w), 1454 (w), 1369 (m), 1255 (m), 1210 (m), 1151 (s), 1025 (vs), 919 (s), 856 (s), 736 (s), 697 (s), 604 (w) cm^{-1}.



43

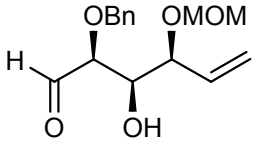
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.39, 1.45 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OCH_3), 3.58-3.64 (m, 2 H, 4-H, 5-H), 3.84 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1a,2}$ = 7.8 Hz, 1 H, 1-H_a), 4.10 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1b,2}$ = 6.4 Hz, 1 H, 1-H_b), 4.34-4.40 (m, 2 H, 2-H, 3-H), 4.59, 4.72 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 4.67, 4.87 (A, B of AB, ^2J = 11.1 Hz, 2 H, OCH_2Ph), 5.32 (m, 2 H, 7-H), 5.85 (m, 1 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.8, 26.9 [2 q, $C(\underline{C}H_3)_2$], 56.3 (q, OCH_3), 65.7 (t, C-1), 74.0 (t, OCH_2Ph), 74.4 (d, C-4), 77.2 (d, C-2), 78.2 (d, C-3), 79.5 (d, C-5), 94.6 (t, OCH_2O), 108.9

[s, C(CH$_3$)$_2$], 119.3 (t, C-7), 127.9, 128.2, 128.6 (3 d, C$_6$H$_5$), 135.3 (s, *i*-C of C$_6$H$_5$), 138.6 (d, C-6).

Experiment 36 (FLi 113)

(2*S*,3*R*,4*S*)-2-Benzyloxy-3-hydroxy-4-methoxymethoxy-hex-5-enal (**44**)

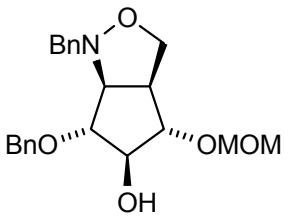


44

H_5IO_6 (262 mg, 1.15 mmol) was added to a solution of the acetonide **43** (160 mg, 0.46 mmol) in Et_2O (10 mL) and the resulting mixture was stirred under N_2 for 3.5 h at r. t.. After filtration, a solution of $Na_2S_2O_3$ (3 M, 3.0 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL) and died ($MgSO_4$). The organic solution was concentrated to afford the aldehyde **44** (127 mg, 98 %) as a colourless oil, which was directly used for the next step.

Experiment 37 (FLi 114)

(3*aS*,4*S*,5*R*,6*R*,*6aS*)-1-*N*-Benzyl-6-benzyloxy-hexahydro-5-hydroxy-4-methoxymethoxy-1H-cyclopenta[c]isoxazole (**45**)



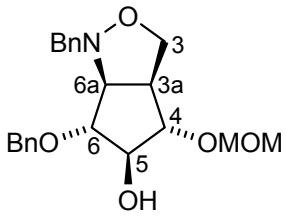
45

To a solution of the aldehyde **44** (127 mg, 0.455 mmol) in absolute MeOH (6 mL) were added benzyl hydroxylamine (73 mg, 0.59 mmol) and $MgSO_4$ (110 mg, 0.910 mmol). The resulting mixture was refluxed overnight. The solid was filtered off and the filtrate was concentrated under reduced pressure (40 °C/300 mabr to 30 mbar). After addition of CH_2Cl_2 (30 mL), the organic phase was washed with sat. aq. $NaHCO_3$ (3 × 10 mL) and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel (7 g, column 3.5 cm × 2 cm, petroleum ether/EtOAc 1.5 : 1) to give the isoxazole **45** (95 mg, 56 %) as a colourless, analytically pure oil. The isoxazolidine **45** was obtained as a single stereoisomer.

$[\alpha]_D^{20}$ = - 45.4 (*c* = 1.00, $CHCl_3$)

$C_{22}H_{27}NO_5$	calcd.	C	68.55	H	7.06	N	3.63
(385.5)	found	C	68.96	H	6.85	N	4.07

IR (neat): υ = 3422 (b, w), 3029 (w), 2885 (w), 1584 (w), 1496 (w), 1454 (m), 1349 (w), 1212 (w), 1113 (s), 1067 (s), 1038 (vs), 914 (m), 850 (w), 817 (w), 729 (s), 695 (vs), 623 (w), 598 (m) cm^{-1}.



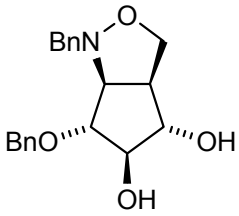
45

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 2.86 (b, OH), 3.37 (m, 1 H, 3a-H), 3.38 (s, 3 H, OCH_3), 3.46 (dd, $^3J_{3a,6a}$ = 8.4 Hz, $^3J_{6,6a}$ = 1.3 Hz, 1 H, 6a-H), 3.68 (m, 1 H, 5-H), 3.72, 4.06 (A, B of AB, ^2J = 12.5 Hz, 2 H, NCH_2Ph), 3.68 (dd, $^2J_{3a',3b'}$ = 9.0 Hz, $^3J_{3a,3a'}$ = 8.1 Hz, 1 H, 3-H_a), 4.01-4.11 (m, 2 H, 4-H, 6-H), 4.15 (dd, $^2J_{3a',3b'}$ = 9.0 Hz, $^3J_{3a,3b'}$ = 3.7 Hz, 1 H, 3-H_b), 4.67 (s, 2 H, OCH_2Ph), 4.71, 4.75 (A, B of AB, ^2J = 6.8 Hz, 2 H, OCH_2O), 7.14-7.33 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 46.5 (d, C-3a), 55.7 (q, OCH_3), 60.4 (t, NCH_2Ph), 65.7 (t, C-3), 69.9 (d, C-6a), 71.9 (t, OCH_2Ph), 74.9 (d, C-5), 81.8 (d, C-6), 82.3 (d, C-4), 96.9 (t, OCH_2O), 127.7, 127.8, 127.9, 128.4, 128.6, 129.2 (6 d, 2 C_6H_5), 136.7, 137.6 (2 s, *i*-C of 2 $\underline{C}_6H_5$).

Experiment 38 (FLi 116)

(3*aS*,4*S*,5*R*,6*R*,6*aS*)-1-*N*-Benzyl-6-benzyloxy-hexahydro-1H-cyclopenta[c]isoxazole-4,5-diol (**46**)



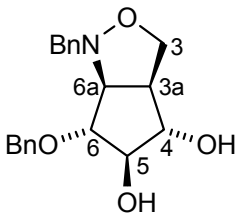
46

According to lit.[72], acidic resin (Dowex 50W, H^+ form, 60 mg) was added to a solution of the protected alcohol **45** (60 mg, 0.16 mmol) in a mixture MeOH (5.0 mL) and water (1.0 mL). The heterogeneous mixture was refluxed with stirring for 6.5 h. The resin was filtered and washed with MeOH (2 × 5 mL). After concentration under reduced pressure (40 °C/300 mbar), the crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 1 : 1.5) to give the diol **46** (38 mg, 72 %) as a colourless, spectroscopically oil.

$[\alpha]_D^{20}$ = - 49 (*c* = 0.90, $CHCl_3$)

$C_{20}H_{23}NO_4$	calcd.	C	70.36	H	6.79	N	4.10
(341.4)	found	C	69.53	H	6.86	N	3.90

IR (neat): υ = 3418 (b, w), 3027 (w), 2926 (w), 2863 (w), 1494 (w), 1452 (m), 1358 (w), 1315 (w), 1258 (w), 1212 (w), 1174 (w), 1112 (vs), 1059 (s), 1019 (m), 968 (m), 907 (w), 879 (w), 845 (w), 816 (w), 726 (vs), 694 (vs), 624 (m), 593 (m) cm^{-1}.



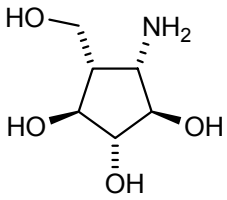
46

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 2.77 (b, 2 H, OH), 3.31 (m, 1 H, 3a-H), 3.53 ("d", $^3J_{3a,6a}$ = 8.2 Hz, 1 H, 6a-H), 3.73 (A of AB, ^2J = 12.4 Hz, 2 H, NCH_aH$_b$Ph), 3.74 (m, 1 H, 5-H), 3.92-4.02 (m, 2 H, 3-H$_{a'}$, 4-H), 4.07 (B of AB, ^2J = 12.4 Hz, 2 H, NCH$_a$$H_b$Ph), 4.12 (m, 1 H, 6-H), 4.23 (dd, $^2J_{3a',3b'}$ = 8.9 Hz, $^3J_{3a,3b'}$ = 3.3 Hz, 1 H, 3-H$_{b'}$), 4.24, 4.29 (A, B of AB, ^2J = 11.8 Hz, 2 H, OCH$_2$Ph), 7.14-7.38 (m, 10 H, 2 C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 47.5 (d, C-3a), 60.3 (t, NCH$_2$Ph), 65.1 (t, C-3), 70.4 (d, C-6a), 71.8 (t, OCH$_2$Ph), 75.9 (d, C-5), 76.7 (d, C-4), 82.6 (d, C-6), 127.9, 128.0, 128.5, 128.6, 129.4 (5 d, 2 C_6H_5), 136.4, 137.4 (2 s, *i*-C of 2 $\underline{C}_6H_5$).

Experiment 39 (FLi 118)

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-Amino-5-hydroxymethyl-cyclopentane-2,3,4-triol (**47**)



47

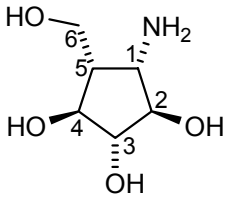
The diol **46** (36 mg, 0.094 mmol) was dissolved in MeOH (2 mL), followed by addition of Pd(OH)$_2$/C (12 mg, 20 %). The resulting mixture was hydrogenated (H_2, 4 bar) for 3 d at r. t.. The mixture was then filtered and concentrated in vacuo (40 °C/300 mabr). The crude product was treated with the concentrated HCl. After removal of the solvent, MeOH (3 mL) was added and the insoluble black precipitate was filtered. The filtrate was concentrated under reduced pressure (40 °C/300 to 30 mbar) to provide the aminohydroxy cyclopentane **47** (17 mg, 92 %) as a light-yellow, spectroscopically pure wax.

$[\alpha]_D^{20}$ = + 86 (*c* = 0.30, MeOH)

MS (CI, pos.): *m/z* (%) = 164 (100) $[M+H]^+$, 146 (24), 73 (22), 60 (20).

HRMS (CI, pos.): *m/z* calcd. for $C_6H_{13}NO_4$: 164.0923; found 164.0924.

IR (neat): υ = 3256-3000 (b, OH, NH_2), 2923 (b, m), 1608 (m), 1402 (m), 1217 (m), 1042 (s) cm^{-1}.



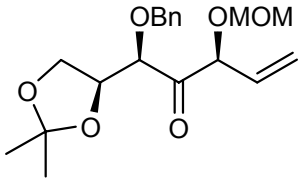
47

^1H NMR (D_2O, 300.1 MHz): δ = 2.61 (m, 1 H, 5-H), 3.5 (dd, $^3J_{4,5}$ = 9.1 Hz, $^3J_{3,4}$ = 6.2 Hz, 1 H, 1-H), 3.68 (dd, $^2J_{6a,6b}$ = 11.6 Hz, $^3J_{5,6a}$ = 7.7 Hz, 1 H, 6-H_a), 3.75 (dd, $^2J_{6a,6b}$ = 11.6 Hz, $^3J_{5,6b}$ = 6.0 Hz, 1 H, 6-H_b), 3.90 (dd, $^3J_{4,5}$ = 5.5 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, 4-H), 4.03 (dd, $^2J_{2,3}$ = 5.3 Hz, $^2J_{3,4}$ = 3.0 Hz, 3-H), 4.23 (dd, $^2J_{1,2}$ = 6.0 Hz, $^2J_{2,3}$ = 5.4 Hz, 2-H).

^{13}C NMR (D_2O, 75.5 MHz): δ = 43.0 (d, C-5), 56.8 (d, C-1), 57.2 (t, C-6), 76.0 (d, C-3), 76.2 (d, C-2), 77.1 (d, C-4).

Experiment 40 (FLi 119)

(2*S*,3*R*,5*S*)-3-Benzyloxy-1,2-isopyrolidenedioxy-5-methoxymethoxy-hept-6-en-4-one (**48**)



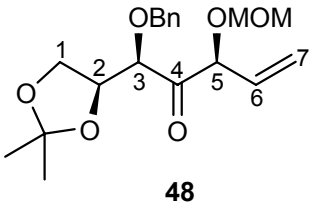
48

To a solution of pyridine (1.6 g, 20 mmol) in CH_2Cl_2 (45 mL) was added CrO_3 (1.0 g, 10 mmol) in portions over a period of 10 min. The resulting mixture was stirred for 1 h at r. t.. The solution of the alcohol **43** (352 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 6 h at r. t.. The solution was washed with sat. aq. $NaHCO_3$ (2 × 20 mL), H_2O (2 × 20 mL), and then 4 M HCl (2 × 10 mL). The combined organic phase was dried ($MgSO_4$). After removal of the solvent, the residue, a brown oil, was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to give the ketone **48** (308 mg, 88 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = -60.8 (*c* = 1.40, $CHCl_3$)

$C_{19}H_{26}O_6$	calcd.	C	65.13	H	7.48
(350.4)	found	C	65.03	H	7.59

IR (neat): υ = 2985 (w), 2889 (w), 1729 (m, C=O), 1454 (w), 1371 (m), 1255 (w), 1212 (m), 1151 (s), 1027 (vs), 919 (s), 846 (m), 739 (m), 699 (s), 635 (w), 618 (w) cm^{-1}.



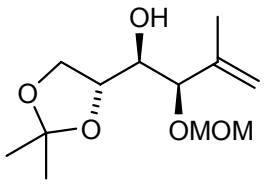
48

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.34, 1.42 [2 s, 6 H, $C(CH_3)_2$], 3.32 (s, 3 H, OCH_3), 3.85 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1a,2}$ = 6.9 Hz, 1 H, 1-H_a), 3.99 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 6.5 Hz, 1 H, 1-H_b), 4.25 (d, $^3J_{2,3}$ = 6.1 Hz, 1 H, 3-H), 4.40 (d, $^3J_{5,6}$ = 6.5 Hz, 1 H, 5-H), 4.59, 4.74 (A, B of AB, ^2J = 11.8 Hz, 2 H, OCH_2Ph), 4.60, 4.67 (A, B of AB, ^2J = 6.8 Hz, 2 H, OCH_2O), 4.95 (m, 1 H, 2-H), 5.44 (m, 2 H, 7-H), 5.79 (m, 1 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.4, 26.4 [2 q, $C(\underline{C}H_3)_2$], 56.0(q, OCH_3), 65.7 (t, C-1), 73.4 (t, OCH_2Ph), 76.2 (d, C-2), 80.8 (d, C-3), 81.8 (d, C-5), 95.1 (t, OCH_2O), 109.8 [s, $\underline{C}(CH_3)_2$], 121.0 (t, C-7), 128.2, 128.3, 128.6 (3 d, C_6H_5), 131.8 (s, *i*-C of $\underline{C}_6H_5$), 137.4 (d, C-6), 205.5 (s, C-4).

Experiment 41 (FLi 127)

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidene-4-*O*-methoxy-methyl-5-methyl-5-hexene-1,2,3,4-tetraol (**49**)



49

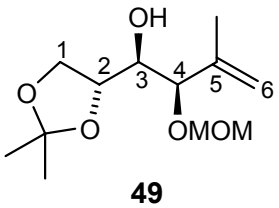
According to a procedure given by Brown *et al.*,[71] to a solution of 3-methoxy -methoxy-2-methylprop-1-ene[130] (1.74 g, 15.0 mmol, prepared from 2-methylprop- 2-en-1-ol) in THF (15 mL) was added *sec*-BuLi (8.3 g, 14 mmol, 10.8 mL, 1.3 M in cyclohexane) at -78 °C over a period of 15 min. The mixture was stirred at -78 °C for an additional 30 min, and (-)-*B*-methoxydiisopinocampheylborane (4.43 g, 14.0 mmol) in THF was added dropwise. After the reaction mixture was stirred at -78°C for 1 h, $BF_3 \cdot Et_2O$ (2.05 mL, 16.0 mmol) was

added dropwise. Immediately afterwards, the aldehyde **6** (1.82 g, 14.0 mmol) was added dropwise and the mixture was stirred at -78 °C for 3 h and then slowly warmed to r. t.. The oxidation was carried out by addition of NaOH (7.0 mL, 4 M) and 30 % H_2O_2 (6.4 mL) at 0 °C. The resulting mixture was stirred for 3 h at r. t. and then a solution of $Na_2S_2O_3$ (6 mL, 9 M) was added. The mixture was extracted with Et_2O (3 × 80 mL) and the combined organic phases were dried ($MgSO_4$). After removal of the solvent (40 °C/680 mbar), the crude product was purified by flash chromatography on silica gel (100 g, column 20 cm × 5 cm, petroleum ether/EtOAc 5 : 1) to give the alcohol **49** (2.48 g, 72 %) as a colourless, analytically pure oil; >95 % *syn*; *dr* = > 95 : 5.

$[\alpha]_D^{20}$ = - 84.5 (*c* = 1.20, $CHCl_3$)

$C_{12}H_{22}O_5$	calcd.	C	58.52	H	9.00
(246.3)	found	C	58.47	H	8.98

IR (neat): υ = 3470 (b, w), 2985 (w), 2932 (w), 2892 (w), 1649 (w), 1454 (w), 1371 (m), 1250 (m), 1213 (m), 1150 (s), 1096 (m), 1067 (s), 1024 (vs), 983 (m), 917 (m), 848 (m) cm^{-1}.



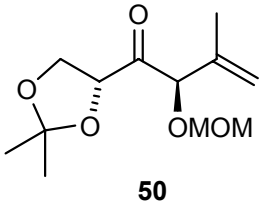
49

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ= 1.35, 1.42 [2 s, 6 H, $C(CH_3)_2$], 1.76 (s, 3 H, 5-CH_3), 2.39 (b, 1 H, OH), 3.42 (s, 3 H, OCH_3), 3.66 (m, 3-H), 4.00-4.13 (m, 3 H, 1-H, 2-H), 4.16 (d, $^3J_{3,4}$ = 3.7 Hz, 1 H, 4-H), 4.61, 4.68 (A, B of AB, ^2J = 6.6 Hz, OCH_2O), 5.05 (d, ^2J = 4.6 Hz, 2 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 19.2 (q, 5-CH_3), 25.8, 27.1 [2 q, $C(\underline{C}H_3)_2$], 56.3 (q, OCH_3), 66.7 (t, C-1), 72.9 (d, C-3), 75.8 (d, C-2), 78.6 (d, C-4), 94.5 (t, OCH_2O), 109.4 [s, $\underline{C}(CH_3)_2$], 115.1 (t, C-6), 142.0 (s, C-5).

Experiment 42 (FLi 129)

(2*R*,4*R*)-1,2-Isopyropylidenedioxy-4-*O*-methoxy-methoxy-5-methyl-5-hexen-3-one (**50**)



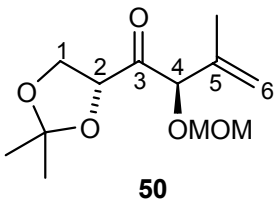
50

To a solution of pyridine (3.16 g, 40.0 mmol) in CH_2Cl_2 (60 mL) was added CrO_3 (2.0 g, 20 mmol) in portions over a period of 10 min. The resulting mixture was stirred for 1 h at r. t.. The solution of the alcohol **49** (492 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 5 h at room temperature. The solution was washed with sat. aq. $NaHCO_3$ (2 × 30 mL), H_2O (2 × 30 mL) and 4 M HCl (2 × 20 mL) sequentially. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue, a brown oil, was purified by flash chromatography on silica gel (12 g, column 4 cm × 3 cm, petroleum ether/EtOAc 6 : 1) to give the ketone **50** (420 mg, 86 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 110 (*c* = 1.10, $CHCl_3$)

$C_{12}H_{20}O_5$	calcd.	C	59.00	H	8.25
(244.3)	found	C	58.86	H	8.23

IR (neat): υ = 2986 (w), 2939 (w), 1732 (m, C=O), 1649 (w), 1454 (w), 1372 (m), 1259 (w), 1213 (m), 1149 (s), 1102 (m), 1024 (vs), 985 (s), 916 (s), 843 (s), 793 (w), 601 (w) cm^{-1}



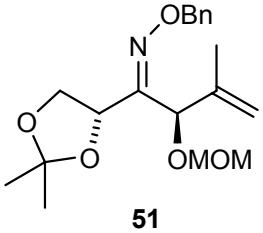
50

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.41, 1.47 [2 s, 6 H, $C(CH_3)_2$], 1.72 (s, 3 H, 5-CH_3), 3.39 (s, 3 H, OCH_3), 3.96 (dd, 1 H, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1a,2}$ = 6.4 Hz, 1-H_a), 4.27 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 7.7 Hz, 1-H_b), 4.63, 4.69 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O), 4.74 (s, 1 H, 4-H), 4.88 (dd, $^3J_{1b,2}$ = 7.7 Hz, $^3J_{1a,2}$ = 6.4 Hz, 2-H), 5.16 (m, 2 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.7 (q, C-7), 25.8, 25.2 [2 q, $C(\underline{C}H_3)_2$], 56.5 (q, OCH_3), 66.7 (t, C-1), 78.7 (d, C-2), 83.2 (d, C-4), 95.1 (t, OCH_2O), 111.3 [s, $\underline{C}(CH_3)_2$], 118.0 (t, C-6), 139.4 (s, C-5), 205.1 (s, C-3).

Experiment 43 (FLi 146)

(*E*)- or (*Z*)-(2*R*,4*R*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-methoxymethyl-5-methyl-5-hexene-1,2,3-triol (**51**)



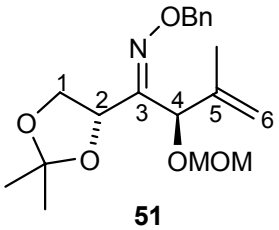
51

To a solution of the ketone **50** (488 mg, 2.00 mmol) in MeOH (12 mL) were added *O*-benzylhydroxylamine hydrochloride (383 mg, 2.40 mmol) and pyridine (190 mg, 2.40 mmol). The reaction mixture was refluxed for 30 min. After most of the methanol had been removed in vacuo, water (5.0 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were dried ($MgSO_4$) and concentrated in vacuum (40 °C/600 mbar). The crude product was purified by flash chromatography on silica gel (12 g, column 5 cm × 2.5 cm, petroleum ether/EtOAc 10 : 1) to yield the oxime ether **51** (628 mg, 90 %) as a colourless, analytically pure oil (a single diastereoisomer).

$[\alpha]_D^{20}$ = + 24.5 (*c* = 1.50, $CHCl_3$)

$C_{19}H_{27}NO_5$	calcd.	C	65.31	H	7.79	N	4.01
(349.4)	found	C	65.13	H	7.80	N	4.01

IR (neat): υ = 2985 (w), 2935 (w), 2886 (w), 1653 (w), 1497 (w), 1454 (m), 1370 (m), 1211 (m), 1150 (s), 1099 (m), 1032 (vs), 918 (s), 859 (s), 797 (w), 735 (m), 697 (s) cm^{-1}.



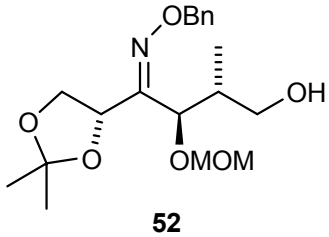
51

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.32, 1.41 [2 s, 6 H, $C(CH_3)_2$], 1.72 (s, 3 H, 5-CH_3), 3.37 (s, 3 H, OCH_3), 3.57 (dd, 1 H, $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1a,2}$ = 7.9 Hz, 1-H_a), 4.29 (dd, $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1b,2}$ = 7.4 Hz, 1-H_b), 4.63, 4.66 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 5.00 (s, 1 H, 4-H), 5.03-5.16 (m, 3 H, 6-H and 2-H), 5.14, 5.18 (A, B of AB, ^2J = 11.9 Hz, 2 H, OCH_2Ph), 7.28-7.34 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.8 (q, 5-CH_3), 25.9, 25.2 [2 q, C($\underline{C}H_3)_2$], 56.2 (q, OCH_3), 68.3 (t, C-1), 72.3 (d, C-2), 76.2 (d, C-4), 77.1 (t, OCH_2Ph), 98.8 (t, OCH_2O), 109.8 [s, $\underline{C}(CH_3)_2$], 115.5 (t, C-6), 128.4, 128.6, 128.8 (3 d, C_6H_5), 137.8 (s, *i*-C of $\underline{C}_6H_5$), 141.8 (s, C-5), 158.0 (s, C-3).

Experiment 44 (FLi 175)

(*E*)- or (*Z*)-(2*R*,4*R*,5*R*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**52**)



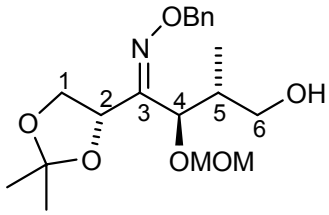
52

To a solution of the oxime ether **51** (698 mg, 2.00 mmol) in THF (22 mL) at 0 °C under N_2 was added 9-BBN-H (10 mL, 5 mmol, 0.5 M in THF), and the resulting mixture was stirred for 30 h at r. t.. A solution of NaOH (2 mL, 4 M) and then 30 % H_2O_2 (3.0 mL) were added slowly at 0 °C. And stirring was continued for a further 2 h at r. t.. The reaction mixture was extracted with Et_2O (4 × 40 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product which was purified by flash chromatography on silca gel (15 g, column 6 cm × 2.5 cm, petroleum ether/EtOAc 1.5 : 1) to afford the alcohol **52** (601 mg, 82 %) as a colourless, analytically pure oil; *dr* = 92 : 8.

$[\alpha]_D^{20}$ = + 138 (*c* = 1.25, $CHCl_3$)

$C_{19}H_{29}NO_6$	calcd.	C	62.11	H	7.95	N	3.81
(367.4)	found	C	62.17	H	8.05	N	3.74

IR (neat): υ = 3472 (b, w), 2935 (w), 2882 (w), 1455 (w), 1371 (m), 1242 (m), 1210 (s), 1153 (s), 1096 (s), 1025 (vs), 919 (s), 858 (s), 804 (w), 733 (m), 698 (s), 617 (w) cm^{-1}



52

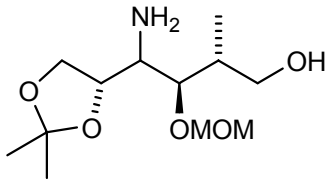
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.91 (d, $^3J_{5,CH_3}$ = 7.0 Hz, 3 H, 5-CH_3), 1.33, 1.45 [2 s, 6 H, 'C(CH_3)$_2$], 2.34 (m, 1 H, 5-H), 3.38 (s, 3 H, OCH_3), 3.62 (dd, $^2J_{6a,6b}$ = 11.4 Hz, $^3J_{5,6a}$ = 5.7 Hz, 1 H, 6-H_a), 3.65 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1a,2}$ = 7.0 Hz, 1 H, 1-H_a), 3.74 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6b}$ = 3.6 Hz, 1 H, 6-H_b), 4.34 (d, $^3J_{4,5}$ = 7.6 Hz, 1 H, 4-H), 4.35 (dd, $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1b,2}$ = 7.7 Hz,

1 H, 1-H_b), 4.56, 4.64 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O), 5.08, 5.13 (A, B of AB, ^2J = 12.3 Hz, 2 H, OCH_2Ph), 5.14 (d, $^3J_{1b,2}$ = 7.8 Hz, $^3J_{1a,2}$ = 7.0 Hz, 1 H, 2-H), 7.29-7.36 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.2 (q, 5-CH_3), 24.6, 24.8 [2 q, C($\underline{C}H_3)_2$], 37.4 (d, C-5), 56.1 (q, OCH_3), 65.6 (t, C-6), 68.0 (t, C-1), 72.1 (t, OCH_2Ph), 76.7 (d, C-2), 79.4 (d, C-4), 95.4 (t, OCH_2O), 109.6 [s, $\underline{C}(CH_3)_2$], 128.1, 128.2, 128.4 (3 d, C_6H_5), 137.3 (s, *i*-C of $\underline{C}_6H_5$), 159.2 (s, C-3).

Experiment 45

(2*R*,3*RS*,4*R*,5*R*)-3-Amino-1,2-*O*-isopyropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**53**)



53

Method A: (FLi 200)

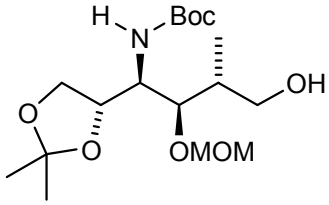
In analoy to lit.[158a], to a suspension of $LiAlH_4$ (1.03 g, 27.0 mmol) in THF (85 mL) was added MeONa (972 mg, 18 mmol) under N_2 and the mixture was stirred for 20 min at 0 °C. To the solution was added the *O*-benzyl oxime ether **52** (660 mg, 1.80 mmol) in THF (25 mL) dropwise and the reaction mixture was stirred for 14 h at r. t.. The reaction was quenched carefully with sat. aq. Na_2SO_4 (10 mL) and the resulting precipitate was filtered through a pad of Celite. After concentration, the crude product **53** (393 mg, 83 %) was obtained as a colourless oil which was directly used in the next step without further purification. The *dr* was determined after protection of the amine with *tert*-butyl dicarbonate (see the next step).

Method B: (FLi 202)

The oxime ether **52** (184 mg, 0.50 mmol) was dissolved in EtOAc (2 mL) and hydrogenated (H_2, 4 bar) in the presence of Ru/γ-Al_2O_3 (15 mg, 5 %). After 6 d, the catalyst was filtered off and the filtrate was concentrated under reduced pressure (40 °C/300 mbar) to give the amine **53** (103 mg, 78 %) as a colourless oil; (*dr* = 40 : 60; similar to those obtained by method A, the *dr* was also determined after conversion of amine into the corresponding carbamate).

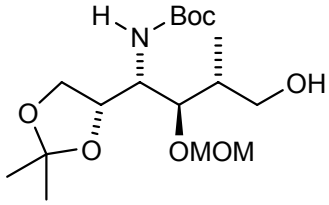
Experiment 46 (FLi 201)

(2*R*,3*S*,4*R*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopyropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**54a**) and



54a

(2*R*,3*R*,4*R*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopyropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**54b**)



54b

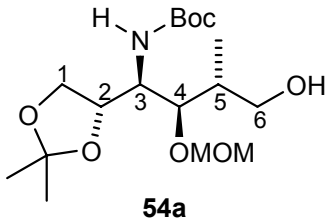
The amine **53** (393 mg, 1.49 mmol) was dissolved in CH_3CN (15 mL) to which $(Boc)_2O$ (432 mg, 1.98 mmol) was added. The reaction mixture was stirred overnight and the solvent was removed under reduced pressure (40 °C/40 mbar). The residue was purified by flash chromatography over silica gel (20 g, column 6 cm × 3 cm, petroleum/EtOAc 1 : 1) to give the protected amine **54a** (165 mg, 30 %) as a colourlesss, analytically pure crystalline and **54b** (331 mg, 62 %) as a colourless, analytically pure oil; ratio of **54a/55b** is 33 : 67 according to yield of isolated products.

Data of **54a**

M. p. = 69-70 °C; $[\alpha]_D^{20}$ = + 98.6 (*c* = 1.25, $CHCl_3$)

$C_{17}H_{33}NO_7$	calcd.	C	56.18	H	9.15	N	3.85
(363.5)	found	C	56.09	H	9.06	N	3.81

IR (solid): υ = 3445 (b, w, OH), 2979 (w), 2935 (w), 1703 (m, C=O), 1497 (m), 1455 (w), 1368 (m), 1325 (w), 1302 (w), 1215 (m), 1162 (s), 1023 (vs), 918 (m), 881 (w), 851 (m), 777 (w), 733 (m), 700 (w), 646 (w) cm^{-1}.



54a

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.01 (d, $^3J_{5,CH_3}$ = 6.9 Hz, 1 H, 5-CH_3), 1.34, 1.41 [2 s, 6 H, $C(CH_3)_2$], 1.43 [s, 9 H, $OC(CH_3)_3$], 1.67 (b, 1 H, OH), 1.79 (m, 1 H, 5-H), 2.85 (b, 1 H, NH), 3.50 (m, 4 H, 3-H, OCH_3), 3.78-3.96 (m, 4 H, 1-H_a, 4-H and 6-H), 4.01 (dd, $^3J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 5.7 Hz, 1 H, 1-H_b), 4.68, 4.86 (A, B of AB, ^2J = 6.3 Hz, 2 H, OCH_2O), 4.84 (m, 1 H, 2-H).

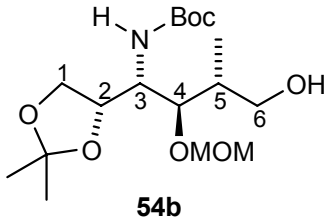
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0 (q, 5-CH_3), 25.7, 26.9 [2 q, C($\underline{C}H_3$)$_2$], 28.3 [q, OC($\underline{C}H_3$)$_3$], 37.0, (d, C-5), 53.7 (q, OCH_3), 56.6 (d, C-3), 64.8 (t, C-6), 67.8 (t, C-1), 75.4 (d, C-2), 79.7 [s, O$\underline{C}$(CH_3)$_3$], 80.4 (d, C-4), 98.8 (t, OCH_2O), 109.7 [s, $\underline{C}$(CH_3)$_2$], 155.7 (s, C=O).

Data of **54b**:

$[\alpha]_D^{20}$ = + 54.3 (*c* =1.40, $CHCl_3$)

$C_{17}H_{33}NO_7$	calcd.	C	56.18	H	9.15	N	3.85
(363.5)	found	C	56.53	H	9.14	N	3.75

IR (neat): υ = 3449 (b, OH), 2978 (w), 2934 (w), 1708 (m), 1504 (m), 1455 (w), 1366 (m), 1311 (w), 1249 (m), 1213 (m), 1160 (s), 1026 (vs), 919 (m), 864 (m), 775 (w) cm^{-1}.



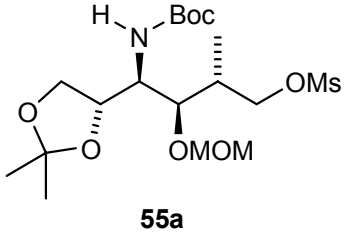
54b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.05 (d, $^3J_{5,CH_3}$ = 7.1 Hz, 1 H, 5-CH_3), 1., 1.41 [2 s, 6 H, C(CH_3)$_2$], 1.45 [s, 9 H, OC(CH_3)$_3$], 1.96 (m, 1 H, 5-H), 2.83 (b, 1 H, NH), 3.43-3.49 (m, 4 H, 6-H_a, OCH_3), 3.63 (dd, $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1a,2}$ = 7.8 Hz, 1 H, 1-H_a), 3.67 (m, 1 H, 3-H), 3.96 ("t", $^2J_{6a,6b}$ = 9.3 Hz, $^3J_{5,6b}$ = 8.6 Hz, 1 H, 6-H_b), 4.04 (dd, $^2J_{1a,1b}$ = 8.1 Hz, $^3J_{1b,2}$ = 6.8 Hz, 1 H, 1-H_b), 4.45 ("t", $^3J_{4,5}$ = 7.6 Hz, $^3J_{3,4}$ =6.7 Hz, 1 H, 4-H), 4.68, 4.78 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O), 4.84 (m, 1 H, 2-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.6 (q, 5-CH_3), 25.0, 26.2 [2 q, C(CH_3)$_2$], 28.3 [q, C(CH_3)$_3$], 36.3 (d, C-5), 51.6 (q, OCH_3), 56.4 (d, C-3), 64.8 (t, C-6), 66.4 (t, C-1), 73.3 (d, C-2), 80.0 [s, OC(CH_3)$_3$], 83.1 (d, C-4), 98.3 (t, OCH_2O), 109.2 [s, C(CH_3)$_2$], 156.5 [s, C=O].

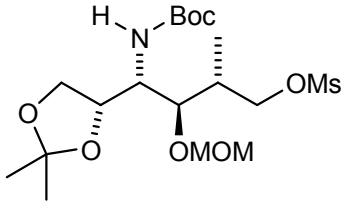
Experiment 47 (FLi 209, FLi 210)

(2*R*,3*S*,4*R*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-6-*O*-mesyl-4-*O*-methoxymethyl-5-methyl-hexane-1,2,4,6-tetraol (**55a**) and



55a

(2*R*,3*R*,4*R*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-6-*O*-mesyl-4-*O*-methoxymethyl-5-methyl-hexane-1,2,4,6-tetrol (**55b**)



55b

FLi 209

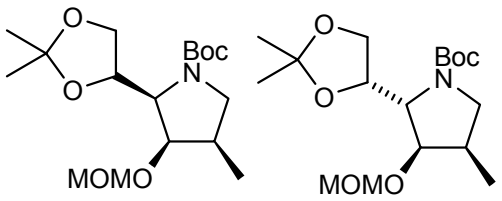
To a solution of the alcohol **54a** (363 mg, 1.00 mmol) in CH_2Cl_2 (8 mL) and Et_3N (303 mg, 3.00 mmol) at 0 °C was added $MeSO_2Cl$ (344 mg, 3.00 mmol). The mixture was stirred at 0 °C for 10 min and then warmed to ambient temperature. After stirring for 1 h, the solvent was evaporated in vacuo (40 °C/600 mbar). The crude product was purified by flash chromatography on silica gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 1 : 1) to afford the protected alcohol **55a** (386 mg, 88 %) as a colourless oil. Due to the instability of the methanesulfonate **55a**, it was directly used for next step.

FLi 210

To a solution of the alcohol **54b** (552 mg, 1.52 mmol) in CH_2Cl_2 (12 mL) and Et_3N (461 mg, 4.56 mmol) at 0 °C was added $MeSO_2Cl$ (523 mg, 4.56 mmol). The mixture was stirred at 0 °C for 10 min and then warmed to ambient temperature. After stirring for 1 h, the solvent was evaporated in vacuo (40 °C/600 mbar). The crude product was purified by flash chromatography on silica gel (14 g, column 4 cm × 3.5 cm, petroleum ether/EtOAc 1 : 1) to afford the protected alcohol **55b** (607 mg, 91 %) as a colourless oil.

Experiment 48 (FLi 213, FLi 214)

(2*S*,3*R*,4*R*,1'*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methyl-2-(1',2'-isopropylidenedioxy-ethyl)-pyrrolidine (**56a**) and (2*R*,3*R*,4*R*,1'*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methyl-2-(1',2'-isopropylidenedioxy-ethyl)-pyrrolidine (**56b**)



56a **56b**

FLi 213

To a suspension of *t*-BuOK (148 mg, 1.32 mmol) in THF (10 mL) was added the methanesulfonate **55a** (386 mg, 0.88 mmol) in THF (2.0 mL) dropwise at 0 °C. The reaction mixture was stirred for 20 min and quenched with water (0.5 mL). The mixture was extracted

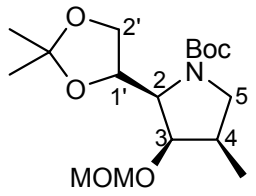
with Et_2O (3 × 20 mL) and the organic extracts were dried ($MgSO_4$). After solvent removal, the product was purified by flash chromatography on silica gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 4 : 1) to yield the substituted pyrrolidine **56a** (276 mg, 91 %) as a colourless, analytically pure powder; m. p. = 46-47 °C.

Data of **56a**:

$[\alpha]_D^{20}$ = + 19.5 (*c* = 1.35, $CHCl_3$)

$C_{17}H_{31}NO_6$	calcd.	C	59.11	H	9.05	N	4.05
(345.4)	found	C	59.45	H	9.09	N	3.99

IR (neat): υ = 2980 (w), 2891 (w), 1696 (s, C=O), 1455 (w), 1366 (s), 1313 (w), 1245 (m), 1211 (m), 1154 (s), 1091 (m), 1058 (s), 1027 (vs), 974 (w), 921 (m), 859 (m), 773 (m), 664 (w) cm^{-1}.



56a

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.07 (d, $^3J_{4,CH_3}$ = 6.8 Hz, 3 H, 4-CH_3), 1.34, 1.37 [2 s, 6 H, $C(CH_3)_2$], 1.45 [s, 9 H, $OC(CH_3)_3$], 2.05 (m, 1 H, 4-H), 2.97 ("t", $^2J_{5a,5b}$ = 11.1 Hz, $^3J_{4,5a}$ = 11.0 Hz, 1 H, 5-H_a), 3.43 (s, 3 H, OCH_3), 3.73 ("t", $^2J_{5a,5b}$ = 9.1 Hz, $^3J_{4,5b}$ = 7.8 Hz, 1 H, 5-H_b), 3.88 (dd, $^3J_{2,3}$ = 8.1 Hz, $^3J_{1',2}$ = 4.9 Hz, 1 H, 2-H), 3.98-4.15 (m, 4 H, 3-H, 1'-H and 2'-H), 4.62, 4.88 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.5 (q, CH_3-4), 26.1, 26.7 [2 q, $C(\underline{C}H_3)_2$], 28.4 [q, $OC(\underline{C}H_3)_3$], 37.7 (d, C-4), 53.1 (t, C-5), 56.5 (q, OCH_3), 64.3 (d, C-2), 69.4 (t, C-2'), 75.5 (d, C-1'), 77.2 [s, $O\underline{C}(CH_3)_3$], 82.3 (d, C-3), 98.7 (t, OCH_2O), 109.6 [s, $\underline{C}(CH_3)_2$], 155.8 (s, C=O).

FLi 214

To a suspension of *t*-BuOK (202 mg, 1.80 mmol) in THF (12 mL) was added the methanesulfonate **55b** (526 mg, 1.20 mmol) in THF (3.0 mL) dropwise at 0 °C. The reaction mixture was stirred for 20 min and quenched with water (0.6 mL). The mixture was extracted with Et_2O (3 × 25 mL) and the organic layer was dried ($MgSO_4$). After removal of the solvent,

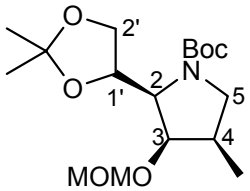
the product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 4 : 1) to yield the substituted pyrrolidine **56b** (384 mg, 93 %) as a colourless, analytically pure powder; m. p. = 64-65 °C.

Data of **56b**:

$[\alpha]_D^{20}$ = + 86.3 (*c* = 1.20, $CHCl_3$)

$C_{17}H_{31}NO_6$	calcd.	C	59.11	H	9.05	N	4.05
(345.4)	found	C	59.16	H	8.98	N	4.02

IR (solid): υ = 2975 (w), 1671 (s, C=O), 1475 (w), 1401 (s), 1362 (m), 1253 (m), 1151 (s), 1096 (s), 1063 (s), 1027 (vs), 915 (m), 871 (s), 828 (w), 765 (m) cm^{-1}.



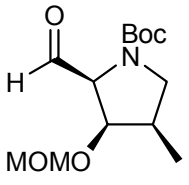
56b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.06 (d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.34, 1.35 [2 s, 6 H, $C(CH_3)_2$], 1.46 [s, 9 H, $OC(CH_3)_3$], 2.67 (m, 1 H, 4-H), 3.13 (b, 1 H, 5-H_a), 3.37 (s, 3 H, OCH_3), 3.45(dd, $^2J_{5a,5b}$ = 13.6 Hz, $^3J_{4,5b}$ = 9.8 Hz, 1 H, 5-H_b), 3.87 (b, 1 H, 2-H), 3.97-4.05 (m, 3 H, 1'-H, 3-H and 2'-H_a), 4.21 (b, 1 H, 2'-H_b), 4.62, 4.72 (A, B of AB, ^2J = 7.8 Hz, 2 H, OCH_2O).

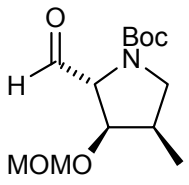
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.7 (q, 4-CH_3), 25.9, 26.1 [2 q, $C(\underline{C}H_3)_2$], 28.4 [q, $OC(\underline{C}H_3)_3$], 36.0 (d, C-4), 52.9 (q, OCH_3), 55.5 (t, C-5), 63.9 (d, C-2), 66.5 (t, C-2'), 77.1 (d, C-1'), 79.5 (s, $O\underline{C}(CH_3)_3$), 80.7 (d, C-3), 95.4 (t, OCH_2O), 108.8 [s, $\underline{C}(CH_3)_2$], 156.1 (s, C=O).

<u>Experiment 49 (FLi 227, FLi 230)</u>

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-formyl-3-methoxy-methoxy-4-methylpyrrolidine (**57a**) and (2*R*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-formyl-3-methoxy-methoxy-4-methylpyrrolidine (**57b**)



57a



57b

FLi 227

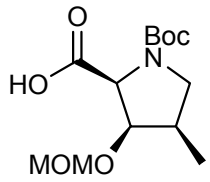
According to a lit. procedure[39e], H_5IO_6 (570 mg, 2.50 mmol) was added to a solution of **56a** (345 mg, 1.00 mmol) in Et_2O (10 mL) and the resulting mixture was stirred under N_2 at r. t. for 3 h. A solution of $Na_2S_2O_3$ (4 mL, 4 M) was added; the mixtute was extracted with Et_2O (3 × 20 mL) and dried ($MgSO_4$). The organic extracts were evaporated to afford the aldehyde **57a** (268 mg, 98 %) as a colourless oil.

FLi 230

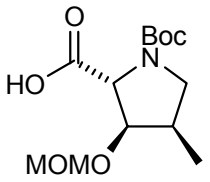
H_5IO_6 (1.03 g, 4.50 mmol) was added to a solution of **56b** (621 mg, 1.80 mmol) in Et_2O (20 mL) and the resulting mixture was stirred under N_2 at r. t. for 6 h. A solution of $Na_2S_2O_3$ (6 mL, 4 M) was added; the mixtute was extracted with Et_2O (3 × 30 mL) and dried ($MgSO_4$). The organic extracts were evaporated to afford the aldehyde **57b** (486 mg, 99 %) as a colourless oil.

Experiment 50 (FLi 228, FLi 231)

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline (**58a**) and (2*R*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline (**58b**)



58a



58b

FLi 228

The aldehyde **57a** (268 mg, 0.980 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (3.0 mL). Then the solution of $NaClO_2$ (136 mg, 1.50 mmol) and NaH_2PO_4 (180 mg, 1.50 mmol) in water (1.0 mL) were added within 10 min. After stirring for 90 min, the same amount $NaClO_2$ and NaH_2PO_4 was added again. The mixture was stirred for further 1 h and NaOH (1.0 mL, 4 M) was added. After removal of solvent under reduced pressure (40 °C/60 mbar), the residue, a white powder, was dissolved in water (4.0 mL) and 6 M HCl was added till a pH value of 3–4 was obtained. The mixture was extracted with EtOAc (5 × 30 mL) and dried ($MgSO_4$). After evaporation of the solvent, the acid **58a** (257 mg, 89 %) was obtained as a colourless oil.

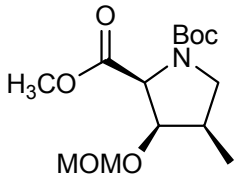
FLi 231

The aldehyde **57b** (486 mg, 1.78 mmol) was dissolved in *t*-BuOH (10 mL) and 2-methyl-2-butene (5.0 mL). Then the solution of $NaClO_2$ (242 mg, 2.67 mmol) and NaH_2PO_4 (320 mg, 2.67 mmol) in water (1.5 mL) were added within 10 min. After stirring for 90 min, the same amount $NaClO_2$ and NaH_2PO_4 was added again. The mixture was stirred for further 1 h and NaOH (2.0 mL, 4 M) was added. After removal of solvent under reduced pressure

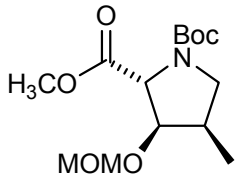
(40 °C/60 mbar), the residue, a white powder, was dissolved in water (6.0 mL) and 6 M HCl was added till a pH value of 3–4 was obtained. The mixture was extracted with EtOAc (5 × 35 mL) and dried ($MgSO_4$). After evaporation of the solvent, the acid **58b** (468 mg, 91 %) was obtained as a colourless oil.

Experiment 51 (FLi 229, FLi 232)

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline methyl ester (**59a**) and (2*R*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline methyl ester (**59b**)



59a



59b

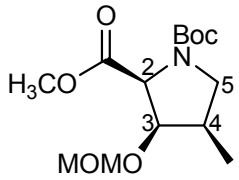
Without purification, the acid **58a** (257 mg, 0.89 mmol) was treated with an ethereal solution of CH_2N_2 (excess). After stirring for 10 min, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 3 : 1) to give the ester **59a** (248 mg, 92 %) as a colourless, analytically pure oil.

Data of **59a**

$[\alpha]_D^{20}$ = - 18.2 (*c* = 1.02, $CHCl_3$)

$C_{14}H_{25}NO_6$	calcd.	C	55.43	H	8.31	N	4.62
(303.4)	found	C	55.54	H	8.39	N	4.78

IR (neat): υ = 2974 (w), 1763 (m, C=O), 1696 (s, C=O), 1454 (w), 1436 (w), 1398 (s) 1365 (m), 1287 (w), 1255 (m), 1151 (s), 1117 (m), 1095 (m), 1071 (m), 1029 (vs), 920 (m), 899 (m), 868 (w), 767 (w) cm^{-1}.



59a

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.10/1.09 (2 d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.40/1.46 [2 s, 9 H, $C(CH_3)_3$], 2.26 (m, 1 H, 4-H), 3.21 (dd, $^2J_{5a,5b}$ = 10.3 Hz , $^3J_{4,5a}$ = 10.3 Hz, 1 H, 5-H_a), 3.36 (s, 3 H, OCH_3), 3.64/3.70 (2 dd, $^2J_{5a,5b}$ = 10.2 Hz, $^3J_{4,5b}$ = 2.7 Hz, 1 H, 5-H_b), 3.75/3.76 (2 s, 3 H, $COOCH_3$), 4.39 (dd, $^3J_{2,3}$ = 4.8 Hz, $^3J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 4.46/5.52 (2 d, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 4.57/4.58, 4.62/4.63 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 11.5 (q, 4-CH_3), 28.20/28.4 [2 q, OC($\underline{C}H_3)_3$], 37.5/38.2 (2 d, C-4), 51.0/51.6 (2 t, C-5), 51.8/51.9 (2 q, COO$\underline{C}H_3$), 56.3 (2 q, OCH_3), 64.7/65.0 (2 d, C-2), 79.6 [s, O$\underline{C}(CH_3)_3$], 80.0/80.4 (2 d, C-3), 97.0/97.1 (2 t, OCH_2O), 153.6/154.3 [2 s, $COOC(CH_3)_3$], 169.2/169.9 (2 s, $\underline{C}OOCH_3$).

FLi 232

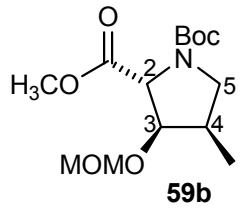
Without purification, the acid **58b** (468 mg, 1.62 mmol) was treated with an ethereal solution of CH_2N_2 (excess, a yellow solution). After stirring for 10 min, the solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (12 g, column 5 cm × 2.5 cm, petroleum ether/EtOAc 3 : 1) to give the ester **59b** (437 mg, 89 %) as a colourless, analytically pure oil.

Data of **59b**:

$[\alpha]_D^{20}$ = + 49.8 (*c* = 1.25, $CHCl_3$)

$C_{14}H_{25}NO_6$	calcd.	C	55.43	H	8.31	N	4.62
(303.4)	found	C	55.59	H	8.43	N	4.55

IR (neat): υ = 2974 (w), 1750 (m, C=O), 1697 (s, C=O), 1455 (w), 1396 (s), 1365 (m), 1305 (w), 1254 (w), 1199 (m), 1174 (m), 1149 (s), 1126 (m), 1099 (m), 1031 (vs), 919 (m), 891 (m), 860 (w), 771 (w) cm^{-1}.



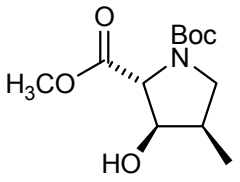
59b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.07 (d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.41/1.46 [2 s, 9 H, $OC(CH_3)_3$], 2.40 (m, 1 H, 4-H), 3.13 (dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{4,5a}$ = 10.7 Hz, 1 H, 5-H_a), 3.40 (s, 3 H, OCH_3), 3.67/3.72 (2 dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{4,5b}$ = 8.6 Hz, 1 H, 5-H_b), 3.73/3.74 (2 s, 3 H, $COOCH_3$), 4.10 (m, 1 H, 3-H), 4.27/4.40 (d, $^3J_{2,3}$ = 1.2 Hz, 1 H, 2-H), 4.64/4.66, 4.77/4.79 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 11.0/11.1 (2 q, 4-CH_3), 28.2/28.4 [2 q, OC($\underline{C}H_3)_3$], 35.6/36.4 (2 d, C-4), 50.8/51.3 (2 t, C-5), 52.2/52.3 (2 q, COO$\underline{C}H_3$), 55.7 (q, OCH_3), 65.3/65.6 (2 d, C-2), 79.9 [s, O$\underline{C}(CH_3)_3$], 79.9/81.1 (2 d, C-3), 95.1/95.4 (2 t, OCH_2O), 153.6/154.5 [2 s, $NCOOC(CH_3)_3$], 171.1/171.4 (2 s, $\underline{C}OOCH_3$).

Experiment 52 (FLi 307)

(2*R*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-methylproline methyl ester (**60**)



60

a) Preparation of dimethylboron bromide (Me_2BBr)[160a]

According to lit.[160a], a dry 25-mL two-necked flask was equipped with a septum, and a short-path distillation apparatus utilizing as the receiver a flask with a septum. After flushing with N_2, the reaction vessel was cooled to -50 °C and charged with BBr_3 (5.0 g, 20 mmol). Tetramethyltin (3.6 g, 20 mmol) was then added dropwise by means of a syringe within 20 min. After complete addition, the septum was replaced by a glass stopper and the mixture was stirred for an additional 30 min at -50 °C and for 30 min at r. t..

The Me_2BBr (b.p. = 31-32 °C) was separated from the by-product Me_2SnBr_2 by simple distillation (75 °C maximum bath temperature, receiver cooled to 0 °C). Me_2BBr (1.6 g, 66 %; lit:[160a] 84 %) was obtained as a colourless liquid. CH_2Cl_2 (6.0 mL) was then added to the receiver to afford a solution of dimethylboron bromide (ca. 2.1 M in CH_2Cl_2).

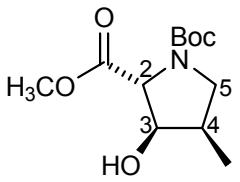
b) Acetal cleavage of **59b**

A solution of Me_2BBr (0.48 mL, 2.1 M in CH_2Cl_2) was added dropwise to a cold (-78 °C) stirred solution of the proline ester **59b** (100 mg, 0.33 mmol) in dry CH_2Cl_2 (5 mL). After 30 min at -78 °C, the reaction mixture was poured into a solution of THF (7.0 mL) and saturated $NaHCO_3$ (3.5 mL) with vigorous stirring. After 5 min the mixture was diluted with ether (25 mL) and the organic layer was separated and washed sequentially with water, 10 % $NaHSO_4$ (6 mL), and saturated brine (6 mL). The ethereal layer was dried ($MgSO_4$), filtered, and concentrated in vacuo (40 °C/600 mbar to 300 mbar). The residue, a light-yellow oil, was purified by flash chromatography on silica gel (5 g, column 4 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to give the hydroxy proline ester **60** (74 mg, 86 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 28.5 (*c* = 1.20, $CHCl_3$)

$C_{12}H_{21}NO_5$	calcd.	C	55.59	H	8.16	N	5.40
(259.3)	found	C	55.44	H	8.41	N	5.22

IR (neat): υ = 3423 (b, w, OH), 2975 (w), 2882 (w), 1748 (m, C=O), 1673 (s, C=O), 1478 (w), 1399 (s), 1366 (m), 1305 (w), 1249 (m), 1172 (s), 1148 (vs), 1111 (m), 1081 (m), 991 (m), 924 (w), 889 (m), 857 (w), 771 (m), 752 (w) cm^{-1}.



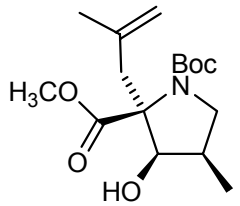
60

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.06/1.07 (2 d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1,40/1.46 [2 s, 9 H, OC(CH_3)$_3$], 2.34 (m, 1 H, 4-H), 2.61 (b, 1 H, OH), 3.15 (m, 1 H, 5-H_a), 3.64/3.74 (2 dd, $^2J_{5a,5b}$ = 9.9 Hz, $^3J_{4,5}$ = 8.1 Hz, 5-H_b), 3.75/3.76 (2 s, OCH_3), 4.19 (m, 1 H 3-H), 4.22/4.33 (2 "s", 1 H, 2-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 10.8 (q, 4-CH_3), 28.3/28.4 [2 q, OC($\underline{C}H_3$)$_3$], 36.2/36.9 (2 d, C-4), 50.3/50.8 (2 q, OCH_3), 52.2/52.3 (2 t, C-5), 68.1/68.3 (2 d, C-2), 76.0 (d, C-3), 80.1 [s, O$\underline{C}$(CH_3)$_3$], 153.9/154.6 [2 s, $\underline{C}$OOC(CH_3)$_3$], 171.3/171.7 (2 s, $\underline{C}$OOCH_3).

Experiment 53 (FLi 323)

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-(2'-methylallyl)-4-methylproline methyl ester (**61**)



61

a) Preparation of 3-iodo-2-methylpropene[161]

Following a procedure given in lit.[161], to a stirred solution of 3-chloro-2-methylpropene (5.0 g, 55 mmol) in DMF (100 mL) was added NaI (20.5 g, 132 mmol). The reaction mixture was stirred at 50 °C overnight and quenched with water (70 mL). The aqueous phase was extracted with pentane (2 × 100 mL). The combined extracts were washed with water (40 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated in vacuo (5 °C/100 mbar). The residue, a colourless liquid was distilled in vacuo (40 °C/40 mbar) to give 3-iodo-2-methylpropene as light-yellow liquid (4.4 g, 45 %; lit.[161] 50 %).

b) Allylation of the proline ester **60**

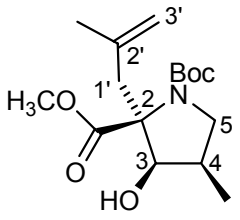
According to a lit.[152], diisopropylamine (116 mg, 1.15 mmol) was dissolved in dry THF (2.5 mL) and cooled down to 0 °C. A solution of *n*-BuLi (495 mg, 1.04 mmol, 1.58 M in hexane) was added dropwise. The solution was stirred for 40 min at 0 °C and then cooled to -50 °C. The ester **60** (85 mg, 0.33 mmol) in THF (1.5 mL) was added dropwise by means of syringe. The resulting mixture was stirred for 50 min at 0 °C, then $MgCl_2$ (46 mg, 0.492 mmol) was added. The reaction mixture was stirred at 0 °C for an additional 30 min, and then cooled again to -50 °C. A solution of the methallyl iodide (149 mg, 0.820 mmol) in HMPA (147 mg, 0.820 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for 4.5 h before quenching with sat. aq. NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were washed with brine (2 × 5 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (40 °C/220 mbar). The crude product, a colourless oil, was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to afford the substituted pyrrolidene **61** (57 mg, 56 %) as colourless, spectroscopically pure crystals, *dr* = > 95 : 5; m. p. = 125-126 °C.

$[\alpha]_D^{20}$ = + 24.3 (*c* = 1.05, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 314 (100) $[M+H]^+$, 258 (90), 214 (36), 200 (35), 158 (44).

HRMS (CI, pos.): *m/z* calcd for $C_{16}H_{28}NO_5$: 314.1967; found 314.1954.

IR (solid): υ = 3382 (b), 2940 (w), 1738 (s, C=O), 1659 (s, C=O), 1405 (s), 1366(s), 1314 (w), 1249 (s), 1202 (m), 1160 (s), 1137 (s), 1090 (m), 1068 (s), 1031 (m), 1001 (s), 922 (m), 864 (s), 781 (m) cm^{-1}.



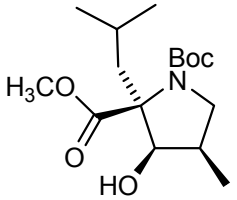
61

^1H NMR ($CDCl_3$, 500.1 MHz): δ = 1.00/1.01 (2 d, $^3J_{4,CH_3}$ = 7.1 Hz, 3 H, 4-CH_3), 1.43/1.45 [2 s, 9 H, $C(CH_3)_3$], 1.73 (s, 3 H, 2'-CH_3), 2.24 (m, 1 H, 4-H), 2.35 (b, 1 H, OH), 2.78/2.82, 2.99/3.24 (A, B of AB, ^2J = 13.8 Hz, 2 H, 1'-H), 3.18 (m, 1 H, 5-H_a), 3.59/3.65 (2 dd, $^2J_{5a,5b}$ = 10.5 Hz, $^3J_{4,5b}$ = 7.9 Hz, 1 H, 5-H_b), 3.74 (s, 3 H, OCH_3), 4.09/4.13 (2 dd, $^3J_{3,4}$ = 7.2 Hz, $^3J_{3,OH}$ = 5.5 Hz, 1 H, 3-H), 4.80/4.90 (2 d, ^2J = 11.4 Hz, 2 H, 3'-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.7 (q, 4-CH_3), 23.4/23.6 (2 q, 2'-CH_3), 28.4/28.5 [2 q, OC(<u>C</u>H_3)$_3$], 35.0/35.8 (2 t, C-5), 40.3/41.6 (2 d, C-4), 52.22 (q, OCH_3), 52.3 (t, C-1'), 74.7/75.0 (2 s, C-2), 79.5/79.6 [2 s, O<u>C</u>(CH_3)$_3$], 80.3/80.9 (2 d, C-3), 116.0/116.3 (2 t, C-3'), 141.8/142.1 (2 s, C-2'), 153.7/153.8 [2 s, <u>C</u>OOC(CH_3)$_3$], 172.1/172.5 (s, <u>C</u>OOCH_3).

<u>Experiment 54 (FLi 339)</u>

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methylproline methyl ester (**62**)



62

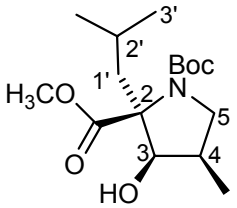
The olefin **61** (44 mg, 0.14 mmol) was dissolved in MeOH (2.0 mL) and hydrogenated (H_2, 4 bar) in the presence of Pt/C (20 mg, 10 %). After 3 h at r. t., the catalyst was filtered off and the filtrate was concentrated under reduced pressure (40 °C/300 mbar). The product, a colourless powder, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to give the isobutyl-proline ester **62** (43 mg, 98 %) as a colourless, analytically pure powder; m. p. = 103-104 °C.

$[\alpha]_D^{20}$ = - 26.4 (*c* = 1.05, $CHCl_3$)

$C_{16}H_{29}NO_5$	calcd.	C	60.92	H	9.27	N	4.44
(315.4)	found	C	60.53	H	9.19	N	4.45

IR (neat): υ = 3459 (b, OH), 2956 (w), 1739 (s, C=O), 1671 (s, C=O), 1391 (s), 1364 (s), 1246 (s), 1164 (vs), 1230 (s), 1084 (m), 1036 (m), 995 (m), 928 (w), 866(w), 821 (w) cm^{-1}

.



62

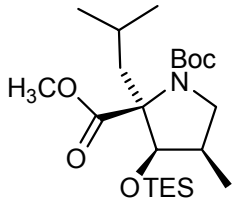
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.90/0.91 (2 d, $^3J_{2',CH_3}$ = 6.5 Hz, 3 H, 2'-CH_3), 0.95/0.97 (2 d, $^3J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 1.05/1.07 (d, $^3J_{4,CH_3}$ = 6.8 Hz, 3 H, 4-CH_3), 1.41/1.44 [2 s, 9 H, OC(CH_3)$_3$], 1.69 (m, 1 H, 7-H), 2.03 (dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'a,2'}$ = 3.5 Hz, 1 H, 1'-H_a),

2.21 (dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'b,2'}$ = 8.3 Hz, 1 H, 1'-H_b), 2.34 (m, 1 H, 4-H), 3.21/3.27 (2 "t", $^2J_{5a,5b}$ = 10.9 Hz, $^3J_{4,5a}$ = 10.9 Hz, 1 H, 5-H_a), 3.62-3.75 (m, 1 H, 5-H_b), 3.72 (s, OCH_3), 4.04/4.12 (2 d, $^3J_{3,4}$ = 5.3 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.0 (q, 4-CH_3), 22.9/23.3 (2 q. 2'-CH_3), 24.1/24.3 (2 q, C-3'), 25.5/25.6 (2 d, C-2'), 28.3 [q, OC($\underline{C}H_3)_3$], 35.6/36.3 (2 t, C-1'), 41.5/42.4 (2 d, C-4), 52.0/52.2 (2 q, OCH_3), 52.5 (t, C-5), 75.2/75.3 (2 s, C-2), 79.5/79.8 [2 s, O$\underline{C}(CH_3)_3$], 80.1/81.2 (d, C-3), 153.9 [s, $\underline{C}OOC(CH_3)_3$], 173.0 (s, $\underline{C}OOCH_3$).

Experiment 55 (FLi 340)

(2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-isobutyl-3-triethylsilyloxy-4-methylproline methyl ester (**63**)



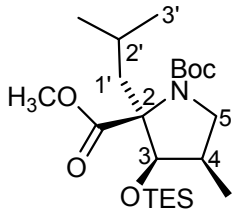
63

Acoording to a procedure given by Donohoe *et al.*[12,95] DMAP (10 mg, 0.064 mmol), imidazole (42 mg, 0.64 mmol) and TESCl (59 mg, 97 %, 0.38 mmol) were added to a stirred solution of the alcohol **62** (40 mg, 0.127 mmol) in distilled CH_2Cl_2 (4.0 mL). The reaction mixture was stirred for 20 h, then poured into water (3.0 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (3.0 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo (40 °C/660 mbar). The crude product was purified by flash chromatography on silica gel (4 g, column 4 cm × 1 cm, petroleum ether/EtOAc 12 : 1) to afford the protected alcohol **63** (55 mg, 100 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 3.5 (*c* = 1.1, $CHCl_3$)

$C_{22}H_{43}NO_5Si$	calcd.	C	61.50	H	10.09	N	3.26
(429.7)	found	C	61.60	H	10.07	N	3.27

IR (neat): υ = 2954 (m), 2876 (m), 1743 (C=O, m), 1703 (C=O, vs), 1456 (w), 1391 (s), 1365 (s), 1241 (m), 1167 (s), 1138 (m), 1076 (s), 1004 (s), 867 (w), 811 (w), 729 (vs), 689 (m) cm^{-1}.



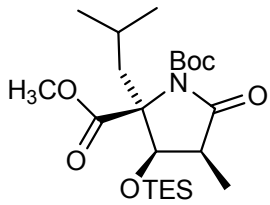
63

^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 0.59/0.60 [2 t, ^3J = 8.0 Hz, 6 H, $OSi(CH_2CH_3)_3$], 0.90-0.98 [m, 15 H, 2'-CH_3, 3'-H and $OSi(CH_2CH_3)_3$], 1.01/1.03 (2 d, $^3J_{4,CH_3}$ = 7.1 Hz, 3 H, 4-CH_3), 1.40/1.43 [2 s, 9 H, $OCOC(CH_3)_3$], 1.62 (m, 1 H, 8-H), 1.98/2.00 (2 dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'a,1'b}$ = 3.4 Hz, 1 H, 1'-H_a), 2.14/2.31 (2 dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'b,2'}$ = 8.5 Hz, 1 H, 1'-H_b), 2.25 (m, 1 H, 4-H), 3.30/3.46 (2 dd, $^2J_{5a,5b}$ = 10.3 Hz, $^3J_{4,5a}$ = 9.1 Hz, 1 H, 5-H_a), 3.54/3.56 (2 dd, $^2J_{5a,5b}$ = 10.7 Hz, $^3J_{4,5b}$ = 7.0 Hz, 1 H, 5-H_b), 3.65 (s, 3 H, OCH_3), 4.25/4.33 (2 d, $^3J_{3,4}$ = 6.5 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 4.8/4.9 [2 t, $Si(\underline{C}H_2CH_3)_3$], 6.5/6.8 [2 q, $Si(CH_2\underline{C}H_3)_3$], 12.2/12.6 (2 q, 4-$CH_3$), 22.9/23.6, 24.1/24.2 (4 q, 2'-CH_3, C-9), 25.8/25.8 (2 d, C-2'), 28.4/28.45 [2 q, $OC(\underline{C}H_3)_3$], 36.1/36.9 (2 t, C-1'), 41.2/42.4 (2 d, C-4), 51.4/51.5 (2 q, OCH_3), 53.2/53.4 (2 t, C-5), 74.2/75.2 (2 s, C-2), 79.3/79.9 [2 s, $O\underline{C}(CH_3)_3$], 80.6/81.5 (2 d, C-3), 153.9/154.0 [2 s, $\underline{C}OOC(CH_3)_3$], 172.3/172.5 (2 s, $\underline{C}OOCH_3$).

Experiment 56 (FLi 341)

(2*S*,3*R*,4*S*)-1-*tert*-Butoxycarbony-2-isobutyl-3-triethylsilyloxy-4-methyl-5-oxo-proline methyl ester (**64**)



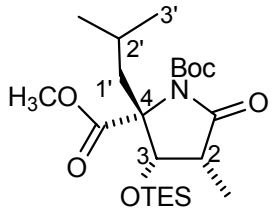
64

According to a lit. procedure[12], to a solution of MeCN (2 mL), CCl_4 (2 mL), and water (3 mL) was added the protected proline ester **63** (55.0 mg, 0.127 mmol), followed by addition of $NaIO_4$ (54 mg, 0.25 mmol) and $RuCl_3 \cdot 3H_2O$ (12.8 mg, 0.051 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then warmed to r. t. and stirred for 15 h. The reaction mixture was filtered through a pad of Celite and evaporated under reduced pressure (40 °C/40 mbar). The crude product was purified by flash chromatography on silica gel (4 g, column 4 cm × 1 cm, petroleum ether/EtOAc 8 : 1) to furnish the lactam **64** (47 mg, 84 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 20.8 (*c* = 1.36, $CHCl_3$)

$C_{22}H_{41}NO_6Si$	calcd.	C	59.56	H	9.31	N	3.16
(443.7)	found	C	59.57	H	9.23	N	3.13

IR (neat): υ = 2954 (b), 2876 (m), 1790 (C=O, s), 1748 (C=O, vs), 1720 (C=O, s), 1456 (w), 1368 (m), 1297 (vs), 1240 (vs), 1144 (vs), 1114 (s), 1089 (s), 1006 (m), 972 (m), 841 (m), 806 (w), 781 (s), 728 (vs) cm^{-1}.



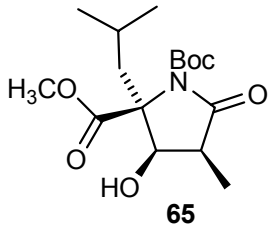
64

^1H NMR ($CDCl_3$, 500.1 MHz): δ = 0.62 [q, ^3J = 8.0 Hz, 6 H, $OSi(CH_2CH_3)_3$], 0.90-1.00 [m, 15 H, 2'-CH_3, 3'-H and $OSi(CH_2CH_3)_3$], 1.25 (d, $^3J_{2,CH_3}$ = 7.6 Hz, 3 H, 2-CH_3), 1.48 [s, 9 H, $OC(CH_3)_3$], 1.54 (m, 1 H, 1'-H), 2.00 (dd, $^2J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'a,7}$ = 4.6 Hz, 1 H, 1'-H_a), 2.31 (dd, $^2J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'b,2'}$ = 7.5 Hz, 1 H, 1'-H_b), 2.71 (m, 1 H, 2-H), 3.68 (s, 3 H, OCH_3), 4.41 (d, $^3J_{2,3}$ = 9.1 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 4.7 [t, $Si(\underline{C}H_2CH_3)_3$], 6.6 [q, $Si(CH_2\underline{C}H_3)_3$], 11.1 (q, 2-$CH_3$), 23.7, 24.1 (2 q, 2'-$CH_3$, C-3'), 25.1 (d, C-2'), 27.8 [q, $OC(\underline{C}H_3)_3$], 41.2 (t, C-1'), 42.2 (d, C-2), 51.8 (q, OCH_3), 71.6 (s, C-4), 73.7 (d, C-3), 83.5 [s, $O\underline{C}(CH_3)_3$], 149.2 [s, $\underline{C}OOC(CH_3)_3$], 171.0 (s, C-1), 176.3 (s, $\underline{C}OOCH_3$).

Experiment 57 (FLi 342)

(2*S*,3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-isobutyl-4-methyl-5-oxo-proline methyl ester (**65**)



65

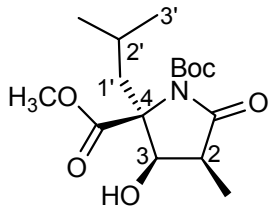
Pyridine (1.8 mL) and HF·pyridine complex (1.8 mL) were added to a solution of the lactam **64** (64.0 mg, 0.145 mmol) in THF (7 mL) and the mixture was stirred for 15 min at 0 °C before warming to r. t.. After stirring for 2 h, $NaHCO_3$ was added to the reaction mixture until a pH 7

was obtained. The reaction mixture was poured into water (2 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure (40 °C /220 mbar). The crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to give the lactam **65** (42 mg, 88 %) as a colourless, analytically pure powder; m. p. = 113 °C.

$[\alpha]_D^{20}$ = + 6.6 (*c* = 1.4, $CHCl_3$)

$C_{16}H_{27}NO_6$	calcd.	C	58.34	H	8.26	N	4.25
(329.4)	found	C	58.24	H	8.33	N	4.03

IR (solid): υ = 3496 (s), 2952 (b), 1758 (vs, C=O,), 1690 (m, C=O), 1371 (m), 1348 (m),1297 (vs), 1249 (s), 1230 (s), 1208 (m), 1138 (vs), 1120 (s), 1083 (m), 1042 (m), 975 (m), 890 (m), 841 (m), 807 (m), 784 (m), 755 (w), 730 (m), 715 (m) cm^{-1}.



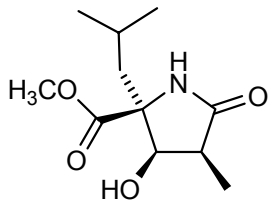
65

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.89, (d, $^3J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 0.99 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.26 (d, $^3J_{2,CH_3}$ = 7.4 Hz, 3 H, 2-CH_3), 1.49 [s, 9 H, $C(CH_3)_3$], 1.64 (m, 1 H, 2'-H), 2.16 (dd, $^3J_{1'a,1'b}$ = 15.0 Hz, $^3J_{1'a,2'}$ = 4.3 Hz, 1 H, 1'-H_a), 2.22 (dd, $^3J_{1'a,1'b}$ = 15.0 Hz, $^3J_{1'b,2'}$ = 7.6 Hz, 1 H, 1'-H_b), 2.80 (m. 1 H, 2-H), 3.74 (s, 3 H, OCH_3), 4.32 (d, $^3J_{2,3}$ = 7.4 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 9.2 (q, 2-CH_3), 23.5 (2 q, C-3', 2'-CH_3), 25.4 (d, C-2'), 27.9 [q, $C(CH_3)_3$], 41.9 (t, C-1'), 42.1 (d, C-2), 52.4 (q, OCH_3), 71.8 (d, C-3), 74.3 (s, C-4), 83.6 [s, $OC(CH_3)_3$], 149.5 [s, $\underline{C}OOC(CH_3)_3$], 171.4 (s, C-1), 175.8 (s, $\underline{C}OOCH_3$).

Experiment 58 (FLi 343)

(2*S*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-4-methyl-5-oxo-proline methyl ester (**66**)



66

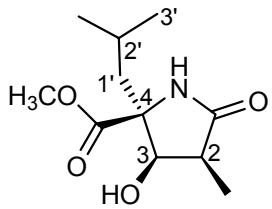
CF_3COOH (0.5 mL) was added dropwise to the carbamate **65** (48 mg, 0.146 mmol) in distilled CH_2Cl_2 (2 mL) at 0 °C; the mixture was stirred for 10 min and then warmed to r. t.. After stirring for 1 h, K_2CO_3 (897 mg) was added to the reaction mixture. The solid was filtered and the filtrate was concentrated in vacuo to yield the lactam **66** (34 mg, 100 %) as a colourless, spectroscopically pure powder; m. p. = 124-125 °C.

$[\alpha]_D^{20}$ = - 12.0 (*c* = 1.10, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 230 $[M + H]^+$ (100), 170 (48).

HRMS (CI, pos.): *m/z* calcd. for $C_{11}H_{20}NO_4$: 230.1390; found 230.1390.

IR (solid): υ = 3496 (s), 2952 (b), 1758 (2 C=O, vs), 1690 (m), 1371 (m), 1348 (m),1297 (vs), 1249 (s), 1230 (s), 1208 (m), 1138 (vs), 1120 (s), 1083 (m), 1042 (m), 975 (m), 940 (w), 890 (m), 841 (m), 807 (m), 784 (m), 755 (w), 730 (m), 715 (m) cm^{-1}.



66

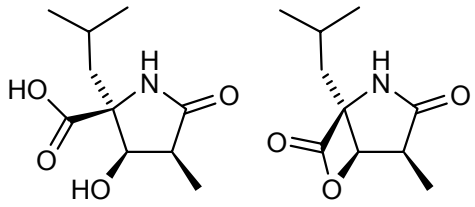
^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.88 (d, $^3J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H), 0.97 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.20 (d, $^3J_{2,CH_3}$ = 7.3 Hz, 3 H, 2-CH_3), 1.52 (dd, $^2J_{1'a,1'b}$ = 13.8 Hz, $^3J_{1'a,2'}$ = 5.0 Hz, 1 H, 1'-H_a), 1.75 (m, 1 H, 2'-H), 2.02 (dd, $^2J_{1'a,1'b}$ = 13.7 Hz, $^3J_{1'b,2'}$ = 8.7 Hz, 1 H, 1'-H_b), 2.70 (m, 1 H, 2-H), 3.84 (s, 3 H, OCH_3), 4.06 (d, $^3J_{3,OH}$ = 11.8 Hz, $^3J_{2,3}$ = 5.1 Hz, 1 H, 3-H), 5.35 (d, $^3J_{3,OH}$ = 12.2 Hz, 1 H, OH), 7.27 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 7.6 (q, 2-CH_3), 21.7 (q, C-3'), 23.9 (q, 2'-CH_3), 24.9 (d, C-2'), 40.0 (d, C-2), 43.3 (t, C-1'), 52.7 (q, OCH_3), 72.1 (s, C-4), 78.9 (d, C-3), 174.3 (s, C-1), 178.1 (s, $\underline{C}OOCH_3$).

Experiment 59 (FLi 344, FLi 345)

(2*S*,3*R*,4*S*)-3-Hydroxy-2-isobutyl-4-methyl -5-oxo-proline (**67**) and

(2*S*,3*R*,4*S*)-1'-Deoxy-omuralide (**68**)



67 **68**

a) Hydrolysis of the ester lactam **67**

Following a lit. procedure[95], cold (0 °C) aqueous NaOH (2.0 mL, 0.5 M) was added to the lactam **66** (30 mg, 0.13 mmol) and left in the refrigerator for one week at 4 °C. Aqueous HCl (1.0 M) was then added dropwise to the reaction mixture till a pH of 1 was obtained, and the mixture was concentrated in vacuo (30 °C/20 mbar). Hot THF (12 mL) was added to the residue, a colourless oil, and the insoluble inorganic salt was filtered off. The filtrate was concentrated in vacuo (40 °C/280 mbar) to afford the carboxylic acid **67** (26.8 mg, 96 %) as a colourless oil that was directly used for next lactonisation without further purification.

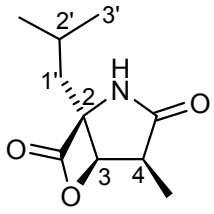
b) Lactonisation of 3-hydroxyproline derivative **67**

A suspension of the acid **67** (26.8 mg, 0.124 mmol) in CH_2Cl_2 (2.5 mL) was treated with Et_3N (37.6 mg, 0.372 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 48.0 mg, 0.186 mmol) at ambient temperature. After stirring for 3 h at r. t., water (2.5 mL) was added to the reaction mixture, which was then extracted with EtOAc (4 × 8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo (40 °C/200 mbar). The crude product was purified by flash chromatography on silica gel (4.5 g, column 3 cm × 1.5 cm, petroleum ether/EtOAc 1 : 1) to give the deoxy lactacystin β-lactone **68** (21 mg, 86 %) as a colourless, analytically pure crystals which were recrystallized from CH_2Cl_2 (5 mL); after recrystallization, the lactam **67** (18 mg, 78 %) was obatined; m. p. = 140-141°C.

$[\alpha]_D^{20}$ = + 55.6 (*c* = 0.52, $CHCl_3$)

$C_{10}H_{15}NO_3$	calcd.	C	60.90	H	7.67	N	7.10
(197.2)	found	C	60.72	H	7.65	N	6.97

IR (solid): υ = 3087 (w), 2958 (w), 1831 (vs, C=O of β-lactone), 1706 (s, C=O of γ-lactam), 1463 (m), 1423 (w), 1385 (m), 1370 (w), 1355 (m), 1324 (m), 1254 (w), 1160 (w), 1144 (m), 1125 (w), 1102 (m), 1070 (m), 1026 (m), 986 (m), 945 (m), 898 (m), 850 (s), 769 (m).687 (w), 655 (m) cm^{-1}.



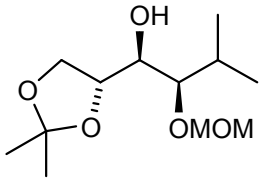
68

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.93 (d, $^{3}J_{2',CH_3}$ = 6.3 Hz, 3 H, 2'-CH_3), 1.03 (d, $^{3}J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 1.33 (d, $^{3}J_{4,CH_3}$ = 7.5 Hz, 3 H, 4-CH_3), 1.80 (dd, $^{2}J_{1'a,1'b}$ = 13.5 Hz, $^{3}J_{1'a,2'}$ = 7.9 Hz, 1 H, 1'-H_a), 1.84 (m, 1 H, 2'-H), 1.99 (dd, $^{2}J_{1'a,1'b}$ = 13.5 Hz, $^{3}J_{1'b,2'}$ = 4.6 Hz, 1 H, 1'-H_b), 2.76 (m, 1 H, 4-H), 4.95 (d, $^{3}J_{3,4}$ = 6.1 Hz, 1 H, 3-H), 6.92 (b, 1 H, NH).

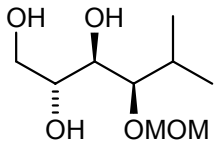
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 8.1 (q, 4-CH_3), 22.8, 23.5 (2 q, 2'-CH_3, C-3'), 24.2 (d, C-2'), 37.6 (t, C-1'), 38.7 (d, C-4), 75.1 (s, C-2), 78.6 (d, C-3), 169.7 (s, C-5), 176.7 (COO, β-lactone).

Experiment 60

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidene-4-methoxymethyl-5-methylhexane-1,2,3,4-tetraol (**69**) and (2*R*,3*S*,4*R*)-4-Methoxymethyl-5-methylhexane-1,2,3,4-tetraol (**131**)



69



131

Method A: (FLi 131)

The olefin **49** (369 mg, 1.50 mmol) was dissolved in MeOH (10 mL) and hydrogenated (H_2, 1 bar) under normal pressure in the presence of Pd/C (32 mg, 10 %). After 1 h, the reaction mixture was filtered through a pad of celite. After evaporation of solvent, the product was purified by flash chromatography on silica gel (10 g, column 4 cm × 2.5 cm, petroleum ether/EtOAc 5 : 1 to 1 : 2) to give the alcohol **69** (215 mg, 58 %) as a colourless, analytically pure oil and the triol **131** (106 mg, 38 %) as a colourless, analytically pure powder.

Method B: (FLi 132)

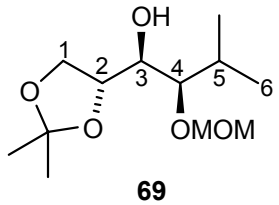
The olefin **49** (246 mg, 1.00 mmol) was dissolved in EtOAc (6 mL) and hydrogenated (H_2, 1 bar) under normal pressure in the presence of Pd/C (22 mg, 10 %). After 1 h, the reaction mixture was filtered through a pad of Celite. After solvent removal, the product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to yield the alcohol **69** (222 mg, 89 %) as a colourless, analytically pure oil.

Data of **69** from FLi 131:

$[\alpha]_D^{20}$ = - 10.2 (*c* = 1.00, $CHCl_3$).

$C_{12}H_{24}O_5$	calcd.	C	58.04	H	9.74
(248.3)	found	C	58.16	H	9.71

IR (neat): υ = 3449 (b, w), 2935 (b, w), 1470 (w), 1370 (m), 1252 (m), 1215 (m), 1149 (s), 1095 (m), 1065 (s), 1024 (s), 919 (m), 846 (s) cm^{-1}.



69

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.98 (d, ^3J = 6.8 Hz, 6 H, 5-CH_3, 6-H), 1.34, 1.40 [s, 6 H, $C(CH_3)_2$], 2.00 (m, 1 H, 5-H), 3.44 (s, 3 H, OCH_3), 3.41-3.49 (m, 2 H, 3-H, 4-H), 3.96 (m, 1 H, 2-H), 4.02 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1a,2}$ = 5.2 Hz, 1 H, 1-H_a), 4.12 (dd, $^2J_{1a,1b}$ = 8.2 Hz, $^3J_{1b,2}$ = 6.1 Hz, 1 H, 1-H_b), 4.71, 4.78 (A, B of AB, ^2J = 6.5 Hz, 2 H, OCH_2O).

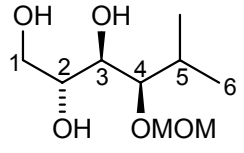
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.8, 19.3 (2 q, 5-CH_3, C-6), 25.8, 27.2 [2 q, C($\underline{C}H_3)_2$], 30.4 (d, C-5), 56.6 (q, OCH_3), 67.8 (t, C-1), 72.1 (d, C-2), 76.3 (d, C-3), 83.5 (d, C-4), 98.2 (t, OCH_2O), 109.6 [s, $\underline{C}(CH_3)_2$].

Data of **131**:

M. p. = 54-55 °C; $[\alpha]_D^{20}$ = - 8.9 (*c* = 1.2, $CHCl_3$)

$C_9H_{20}O_5$	calcd.	C	51.91	H	9.68
(208.3)	found	C	52.04	H	9.64

IR (solid): υ = 3289 (b, OH), 2957 (b, w), 1467 (w), 1362 (w), 1305 (w), 1180 (w), 1133 (m), 1072 (s), 1040 (s), 1019 (s), 976 (m), 957 (m), 896 (s), 843 (w), 728 (m), 682 (m) cm^{-1}.



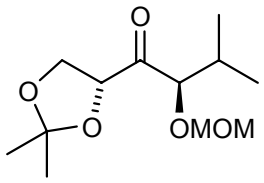
131

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.96 (d, $^3J_{5,CH_3}$ = 7.1 Hz, 3 H, 5-CH_3), 0.98 (d, $^3J_{5,6}$ = 7.2 Hz, 3 H, 6-H), 1.99 (m, 1 H, 5-H), 3.38-3-47 (m, 4 H, 1-H_a, OCH_3), 3.60-3.87 (m, 4 H, 1-H_b, 2-H, 3-H and 4-H), 4.72, 4.76 (A, B of AB, ^2J = 6.5 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 19.0, 19.8 (2 q, 5-CH_3, C-6), 30.4 (d, C-5), 56.6 (q, OCH_3), 64.5 (t, C-1), 72.0 (d, C-2), 72.4 (d, C-3), 84.6 (d, C-4), 99.0 (t, OCH_2O).

Experiment 61

(2*R*,4*R*)-1,2-*O*-Isopyropylidenedioxy-4-methoxy-methoxy-5-methylhexan-3-one (**70**)



70

Method A: (FLi 134)

To a solution of pyridine (5.06 g, 64 mmol) in CH_2Cl_2 (100 mL) was added CrO_3 (3.2 g, 32 mmol) in portions over 15 min. The reaction mixture was stirred for 1 h at r. t.. The alcohol **69** (794 mg, 3.20 mmol) in CH_2Cl_2 (6 mL) was added, and the mixture was stirred for 6 h at r. t.. The solution was washed with sat. aq. $NaHCO_3$ (2 × 40 mL), H_2O (2 × 30 mL) and 4 M HCl (2 × 20 mL) sequentially. The organic phases were dried over $MgSO_4$. After solvent removal, the crude product was purified by flash chromatography on silica gel (15 g, column 5 cm × 3 cm, petroleum ether/EtOAc 6 : 1) to give the ketone **70** (694 mg, 88 %) as a colourless, analytically pure oil.

Method B: (FLi 136)

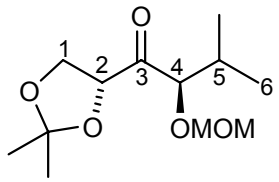
The alcohol **50** (293 mg, 1.20 mmol) was dissolved in EtOAc (6 mL) and hydrogenated under normal pressure in the presence of Pd/C (24 mg, 10 %). After 1 h, the reaction mixture was filtered through a pad of Celite. After solvent removal, the product was purified by flash chromatography on silica gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to yield the ketone **70** (268 mg, 91 %) as a colorless, analytically pure oil.

Data of **70** from FLi 134

$[\alpha]_D^{20}$ = + 5.98 (*c* = 1.20, $CHCl_3$)

$C_{12}H_{22}O_5$	calcd.	C	58.52	H	9.00
(246.3)	found	C	58.52	H	8.99

IR (neat): υ =2965 (w), 2891 (w), 1726 (m, C=O), 1469 (w), 1372 (m), 1261 (m), 1215 (m), 1150 (s), 1039 (vs), 983 (m), 919 (s), 847 (s), 797 (w), 693 (w) cm^{-1}.



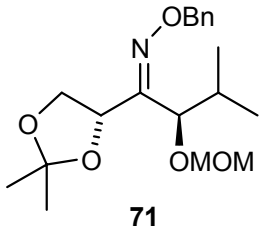
70

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.92 (d, $^3J_{5,CH_3}$ = 6.8 Hz, 3 H, 5-CH_3), 1.03 (d, $^3J_{5,6}$ = 6.9 Hz, 3 H, 6-H), 1.39, 1.50 [s, 6 H, $C(CH_3)_2$], 2.17 (m, 1 H, 5-H), 3.35 (s, 3 H, OCH_3), 3.98 (dd, $^2J_{1a,1b}$ = 8.7 Hz, $^3J_{1a,2}$ = 6.2 Hz, 1 H, 1-H_a), 4.18 (d, $^3J_{4,5}$ = 4.5 Hz, 1 H, 4-H), 4.25 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1b,2}$ = 8.1 Hz, 1 H, 1-H_b), 4.62, 4.65 (A, B of AB, ^2J = 6.8 Hz, 2 H, OCH_2O), 4.72 (dd, $^3J_{1b,2}$ = 8.0 Hz, $^3J_{1a,2}$ = 6.2 Hz, 1 H, 2-H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.3, 19.8 (2 q, 5-CH_3, C-6), 25.2, 26.2 [2 q, C($\underline{C}H_3)_2$], 30.3 (d, C-5), 56.5 (q, OCH_3), 66.6 (t, C-1), 79.2 (d, C-2), 84.6 (d, C-4), 97.6 (t, OCH_2O), 111.2 [s, $\underline{C}(CH_3)_2$], 209.1 (s, C-3).

Experiment 62 (FLi 145)

(*E*) or (*Z*)-(2*R*,4*R*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4-triol (**71**)



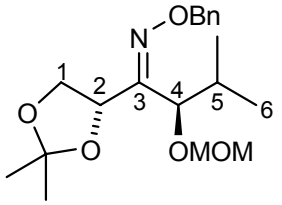
71

To a solution of the ketone **70** (295 mg, 1.20 mmol) in MeOH (8.0 mL) were added *O*-benzylhydroxylamine hydrochloride (229 mg, 1.44 mmol) and pyridine (114 mg, 1.44 mmol). The resulting mixture was refluxed for 40 min. After most of methanol was removed in vacuo, water (4.0 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 10 : 1) to give the oxime ether **71** (383 mg, 90 %) as a colourless, analytically pure oil (a single diastereoisomer).

$[\alpha]_D^{20}$ = + 126 (*c* = 1.40, $CHCl_3$)

$C_{19}H_{29}NO_5$	calcd.	C	64.94	H	8.32	N	3.98
(351.4)	found	C	64.85	H	8.43	N	3.88

IR (neat): υ =2962 (w), 2885 (w), 1455 (w), 1371 (m), 1261 (w), 1210 (m), 1154 (s), 1136 (m), 1092 (m), 1031 (vs), 975 (m), 950 (m), 919 (s), 859 (s), 804 (w), 731 (m), 697 (s) cm^{-1}.



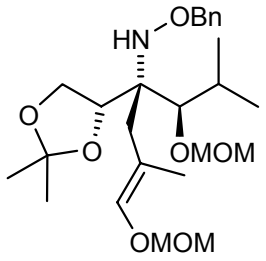
71

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.93 (d, $^3J_{5,CH_3}$ = 6.8 Hz, 3 H, 5-CH_3), 1.03 (d, $^3J_{5,6}$ = 6.8 Hz, 3H, 6-H), 1.31, 1.35 [2 s, 6 H, $C(CH_3)_2$], 2.16 (m, 1 H, 5-H), 3.33 (s, 3 H, OCH_3), 3.63 (dd, $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1a,2}$ = 7.1 Hz, 1 H, 1-H_a), 4.19 (d, $^3J_{4,5}$ = 6.3 Hz, 1 H, 4-H), 4.33 (dd, $^2J_{1a,1b}$ = 8.2 Hz, $^3J_{1b,2}$ = 7.9 Hz, 1 H, 1-H_b), 4.54, 4.62 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 5.07-5.14 (m, 3 H, OCH_2Ph, 2-H), 7.28-7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.0, 19.9 (2 q, 5-CH_3, C-6), 24.8, 26.3 [2 q, $C(\underline{C}H_3)_2$], 31.0 (d, C-5), 56.2 (q, OCH_3), 68.7 (t, C-1), 72.5 (t, OCH_2Ph), 77.0 (d, C-2), 80.1 (d, C-4), 95.7 (t, OCH_2O), 109.7 [s, $\underline{C}(CH_3)_2$], 128.3, 128.5, 128.8 (3 d, C_6H_5), 137.9, (s, *i*-C of $\underline{C}_6H_5$), 160.1 (s, C-3).

Experiment 63 (FLi 163)

(*E*)-(2*S*,3*S*,1'*R*)-3-Benzyloxylamino-1,2,-*O*-isopropylidene-3-(1'-methoxymethoxy-2'-methylpropyl)--6-methoxymethoxy-5-methylhex-5-ene-1,2-diol (**72**)



72

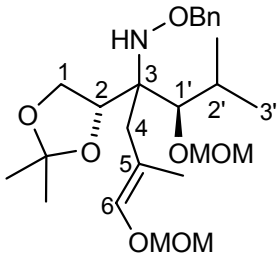
To a stirred solution of 3-(methoxymethoxy)-2-methylprop-1-ene (371 mg, 3.20 mmol) in THF (8 mL) was added *sec*-BuLi (1.78 g, 2.3 mL, 3.0 mmol, 1.3 M in cyclohexane) at -78 °C. The resulting mixture was stirred for an additional 30 min. The oxime ether **71** (702 mg, 2.00 mmol) was dissolved in THF (3.0 mL) and HMPA (1.5 mL) and added dropwise. The resulting mixture was stirred for 1 h at -78 °C. The reaction was quenched with sat. aq. NH_4Cl (2.0 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo (40 °C/600 mbar). The residue, a light-yellowish oil, was

purified by flash chromatography on silica gel (18 g, column 6 cm × 3 cm, petroleum ether/EtOAc 10 : 1) to give the enol ether **72** (802 mg, 86 %) as a colourless, analytically pure oil; *dr* = 92 : 8 by ^{1}H NMR spectrum).

$[\alpha]_D^{20}$ = + 56.6 (*c* = 1.10, $CHCl_3$)

$C_{25}H_{41}NO_7$	calcd.	C	64.22	H	8.84	N	3.00
(467.6)	found	C	64.32	H	8.92	N	2.92

IR (neat): υ = 2933 (b, w), 1679 (w), 1454 (w), 1367 (m), 1209 (m), 1152 (s), 1030 (vs), 977 (s), 919 (s), 865 (m), 736 (m), 698 (m), 628 (w) cm^{-1}.



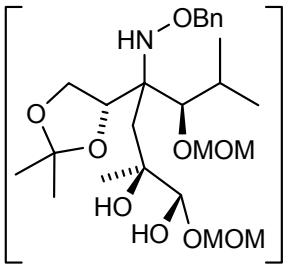
72

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.98 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 1.05 (d, $^3J_{2',3'}$ = 6.9 Hz, 3 H, 3'-H), 1.32, 1.36 [2 s, 6 H, $C(CH_3)_2$], 1.68 (d, $^4J_{6,5CH_3}$ = 1.2 Hz, 3 H, 5-CH_3), 2.09 (m, 1 H, 2'-H), 2.63, 2.68 (A, B of AB, ^2J = 14.2 Hz, 2 H, 4-H), 3.37, 3.40 (2 s, 6 H, 2 OCH_3), 3.65 (d, $^3J_{1',2'}$ = 0.8 Hz, 1 H, 1'-H), 3.95 (dd, $^2J_{1a,1b}$ = 7.4 Hz, $^3J_{1a,2}$ = 6.5 Hz, 1 H, 1-H_a), 4.20 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 7.7 Hz, 1 H, 1-H_b), 4.29 (dd, $^3J_{1a,2}$ = 6.4 Hz, $^3J_{1b,2}$ = 8.3 Hz, 1 H, 2-H), 4.59, 4.79 (A, B of AB, ^2J = 6.3 Hz, 1 H, OCH_2O), 4.66, 4.71 (A, B of AB, ^2J = 11.7 Hz, 2 H, OCH_2Ph), 4.72, 4.74 (A, B of AB, ^2J = 6.5 Hz, 2 H, OCH_2O), 6.01 (s, 1 H, 6-H), 6.17 (s, 1 H, NH), 7.26-7.33 (m, 5 H, C_6H_5).

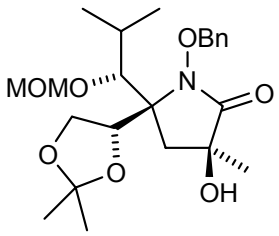
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.1 (q, 2'-CH_3), 20.5 (q, 5-CH_3), 24.1 (q, C-3'), 25.2, 26.6 [2 q, $C(\underline{C}H_3)_2$], 27.9 (d, C-2'), 29.4 (t, C-4), 56.2, 56.5 (2 q, 2 OCH_3), 66.4 (t, C-1), 67.8 (s, C-3), 76.1 (t, OCH_2Ph), 77.9 (d, C-2), 86.0 (d, C-1'), 96.5, 99.5 (2 t, 2 OCH_2O), 108.0 [s, $\underline{C}(CH_3)_2$], 112.6 (s, C-5), 128.0, 128.6, 128.7, (3 d, C_6H_5), 138.5 (s, *i*-$\underline{C}$ of C_6H_5), 140.6 (d, C-6).

Experiment 64 (FLi 206, FLi 207)

(1*S*,2*S*,4,*R*,5*S*,1'*R*)-4-Benzyloxyamino-5,6-*O*-isopropylidene-1-methoxymethoxy-4-(1'-methoxymethoxy-2'-methylpropyl)-2-methyl-hexane-1,2,5,6-tetraol (**73**) and (3*S*,5*R*,1'*R*,1''*S*)-1-Benzyloxy-3-hydroxy-5-(1'',2''-isopropylidenedioxyethyl)-5-(1'-methoxy-methoxy-2'-methylpropyl)-3-methylpyrrolidin-2-one (**74**)



73



74

a) Dihyroxylation of the enol ether **72**

According to a lit. procedure[40], a 50-mL round-bottom flask, equipped with a magnetic stirrer, was charged with *t*-BuOH/H_2O (10 mL, 1 : 1). To the mixture were added $K_3[Fe(CN)_6]$ (928 mg, 2.83 mmol), K_2CO_3 (390 mg, 2.83 mmol), $K_2OsO_2(OH)_4$ (7.0 mg, 0.019 mmol), and $(DHQ)_2PHAL$ (36 mg, 0.047 mmol) at r. t.. The mixture was stirred for 10 min at the same temperature, followed by addition of $CH_3SO_2NH_2$ (90 mg, 0.94 mmol), then the olefin **72** (300 mg, 0.730 mmol) was added at 0 °C. The temperature was allowed to rise to r. t.. After stirring for 10 h, the mixture was treated with $Na_2S_2O_5$ (1.94 g, 12.3 mmol) at 0 °C and stirred for 1 h. Water (6 mL) was added and then the mixture was extracted with EtOAc (4 x 40 mL). The organic phases were combined and dried ($MgSO_4$). The solvent was evaporated under reduced pressure (40 °C/220 mbar). The crude product **73** (385 mg, 82 %) was obtained as a light-yellow oil which was used directly in the next step without further purification.

b) Oxidation of the hemiacetal **73**

Following a procedure given by Curran *et al.*[139b], to a solution of the diol **73** (385 mg) in MeOH/H_2O (25 mL, 10 : 1) were added I_2 (2.08 g, 8.50 mmol) and $CaCO_3$ (188 mg, 1.88 mmol). The reaction mixture was stirred for 24 h at r. t.. Water (8 mL) and solid $Na_2S_2O_3$ were added to remove excess iodine (until a colourless solution was obtained). The reaction mixture was extracted with EtOAc (3 × 35 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (12 g, column 6 cm × 2 cm, petroleum ether/EtOAc 1.5 : 1) to afford the lactam **74** (144 mg, 39 %) as a colourless, analytically somewhat impure, spectroscopically pure oil; *dr* = 91 : 9 by ^1H NMR spetrum.

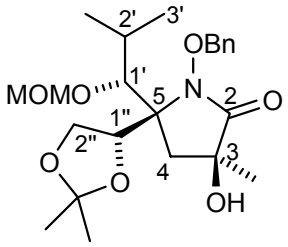
$[\alpha]_D^{20}$ = - 39.4 (*c* = 1.55, $CHCl_3$)

$C_{23}H_{35}NO_7$	calcd.	C	63.14	H	8.06	N	3.20
(437.5)	found	C	61.95	H	8.25	N	3.39

MS (CI, pos.): *m/z* (%) = 438 $[M + H]^+$ (100), 336 (26), 320 (37), 234 (20), 91 (34).

HRMS (CI, pos.): *m/z* calcd for $C_{23}H_{36}NO_7$: 438.2492; found 438.2480.

IR (neat): υ = 3408 (b), 2971 (w), 2934 (w), 1708 (m, C=O), 1453 (m), 1371 (m), 1266 (m), 1210 (m), 1152 (s), 1064 (s), 1027 (vs), 921 (m), 859 (s), 805 (s), 744 (s), 697 (w), 616 (w) cm^{-1}.



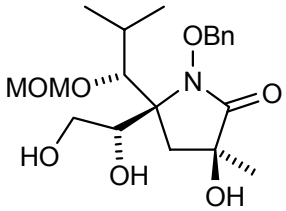
74

^1H NMR ($CDCl_3$, 500.1 MHz): δ = 0.94 (d, $^3J_{2',CH_3}$ = 7.0 Hz, 3 H, 2'-CH_3), 1.00 (d, $^3J_{2',3'}$ = 7.1 Hz, 3 H, 3'-H), 1.40 (s, 3 H, 3-CH_3), 1.46, 1.49 [2 s, 6 H, $C(CH_3)_2$], 1.82 (m, 1 H, 2'-H), 2.00, 2.30 (A, B of AB, ^2J = 15.1 Hz, 2 H, 4-H), 3.40 (s, 3 H, OCH_3), 3.62 (b, OH), 3.68 (d, $^3J_{1',2'}$ = 2.0 Hz, 1 H, 1'-H), 3.85 (dd, $^2J_{2''a,2''b}$ = 8.8 Hz, $^3J_{1'',2''a}$ = 8.7 Hz, 1 H, 2''-H_a), 4.14 (dd, $^2J_{2''a,2''b}$ = 9.2 Hz, $^3J_{1'',2''b}$ = 6.6 Hz, 1 H, 2''-H_b), 4.56 (dd, $^3J_{1'',2''a}$ = 8.1 Hz, $^3J_{1'',2''b}$ = 6.8 Hz, 1 H, 1''-H), 4.60, 4.62 (A, B of AB, ^2J = 5.9 Hz, 2 H, OCH_2O), 4.95, 5.51 (A, B of AB, ^2J = 9.9 Hz, 2 H, OCH_2Ph), 7.28-7.43 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.9 (q, 3-CH_3), 23.2, 23.8 (2 q, 2'-CH_3, C-3'), 25.0, 26.1 [2 q, $C(\underline{C}H_3)_2$], 27.8 (d, C-2'), 35.3 (t, C-4), 56.7 (q, OCH_3), 66.2 (t, C-2''), 67.8, (s, C-5), 70.1 (s, C-3), 77.0 (d, C-1''), 77.3 (t, OCH_2Ph), 83.7, (d, C-1'), 99.0 (t, OCH_2O), 108.5 [s, $\underline{C}(CH_3)_2$], 128.5, 128.7, 128.8 (3 d, C_6H_5), 135.0 (s, *i*-C of $\underline{C}_6H_5$), 169.7 (s, C-2).

Experiment 65 (FLi 216)

(3*S*,5S,1'*R*,1''*S*)-1-Benzyloxy-3-hydroxy-5-(1'',2''-dihydroxyethyl)-5-(1'-methoxymethoxy-2'-methylpropyl)-3-methylpyrrolidine-2-one (**75**)



75

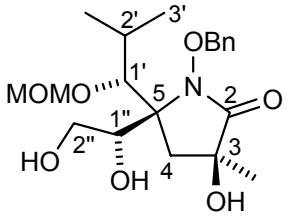
Following a lit. procedure[140], to a solution of the diol-acetonide **74** (80 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added $FeCl_3 \cdot 6H_2O$ (206 mg, 0.760 mmol). The resulting yellow- to amber-colored suspension was stirred for 20 min and the reaction was quenched by addition of sat. aq. $NaHCO_3$ (6 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracs were washed with brine (2 × 10 mL), dried ($MgSO_4$). After concentration, the crude product was purified by flash chromatography on silica gel (5 g, column 3.3 cm × 1.5 cm, CH_2Cl_2/MeOH 12 : 1) to afford the diol **75** (58 mg, 79 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = - 35.4 (*c* = 1.40, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 398 $[M + H]^+$ (100), 366 (52), 320 (37), 234 (20), 91 (34).

HRMS (CI, pos.): *m/z* calcd for $C_{20}H_{32}NO_7$: 398.2179; found 398.2164.

IR (neat): υ = 3372 (b, OH), 2966 (w), 1687 (s, C=O), 1453 (m), 1371 (m), 1216 (w), 1148 (m), 1086 (m), 1027 (vs), 955 (m), 910 (m), 871 (m), 835 (w), 749 (vs), 698 (s), 666 (m) cm^{-1}.



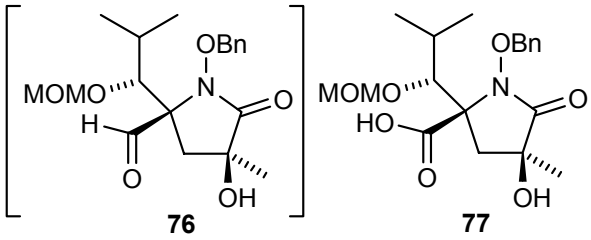
75

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.94 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 0.99 (d, $^3J_{2',3'}$ = 7.0 Hz, 3 H, 3'-H), 1.44 (s, 3 H, 3-CH_3), 1.80 (m, 1 H, 2'-H), 2.10, 2.24 (A, B of AB, ^2J = 15.3 Hz, 2 H, 3-H), 3.42 (s, 3 H, OCH_3), 3.70 (dd, $^2J_{2''a,2''b}$ = 11.5 Hz, $^3J_{1'',2''a}$ = 7.2 Hz, 2 H, 2''-H_a, OH), 3.88 (d, $^3J_{1',2'}$ = 2.1 Hz, 1 H, 1'-H), 3.97-4.06 (m, 3 H, 1''-H, 2''-H_b and OH), 4.53 (b, 1 H, OH), 4.68, 4.71 (A, B of AB, ^2J = 6.4 Hz, 2 H, OCH_2O), 5.17 (s, 2 H, OCH_2Ph), 7.27-7.44 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.3 (q, 3-CH_3), 24.1, 24.6 (2 q, 2'-CH_3, C-3'), 28.0 (d, C-2'), 36.0 (t, C-4), 56.7 (q, OCH_3), 63.1 (t, C-2''), 68.9, (s, C-5), 70.3 (s, C-3), 73.3 (d, C-1''), 76.8 (t, OCH_2Ph), 83.1, (d, C-1'), 99.1 (t, OCH_2O), 128.4, 128.6, 129.2 (3 d, C_6H_5), 134.8 (s, *i*-C of $\underline{C}_6H_5$), 172.2 (s, C-2).

Experiment 66 (FLi 218, FLi 219)

(2*R*,4*S*,1'*R*)-1-Benzyloxy-2-formyl-4-hydroxy-2-(1'-methoxymethoxy-2-methylpropyl)-4-methyl-5-oxo-pyrrolidine (**76**) and (2*R*,4*S*,1'*R*)-1-Benzyloxy-4-hydroxy-2-(1'-methoxymethoxy-2'-methylpropyl)-4-methyl-5-oxo-proline (**77**)



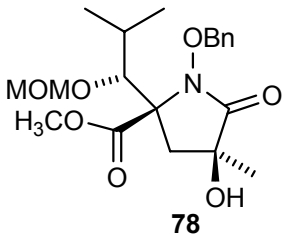
76 **77**

To a solution of the diol **75** (58 mg, 0.146 mmol) in MeOH/H_2O/THF (4 mL, 4 : 2 : 1) was added $NaIO_4$ (48 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (1.5 mL), extracted with CH_2Cl_2 (4 × 10 mL) and dried ($MgSO_4$). After removal of the solvent, the aldehyde **76** (50 mg, 94 %) was obtained as a colourless oil which was used directly in the next step.

The aldehyde **76** (50 mg) was dissolved in *t*-BuOH (2.0 mL) and 2-methyl-2-butene (1.0 mL). To the mixture was added a solution of $NaClO_2$ (21 mg, 0.22 mmol) and NaH_2PO_4 (27 mg, 0.22 mmol) in water (0.5 mL). After stirring for 90 min the same amounts of $NaClO_2$ and NaH_2PO_4 were added again. After stirring for 1 h, NaOH solution (0.3 mL, 4 M) was added. After evaporation under reduced pressure (40 °C/60 mbar), water (3.0 mL) was added. The pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 15 mL) and the solutes were dried ($MgSO_4$). After removal of solvent, the carboxylic acid **77** (47 mg, 90 %) was obtained as a colourless oil, which was directly converted into its ester.

Experiement 67 (FLi 220)

(2*R*,4*S*,1'*R*)-1-Benzyloxy-4-hydroxy-2-(1'-methoxy-methoxy-2'-methylpropyl)-4-methyl-5-oxo-proline methy ester (**78**)



78

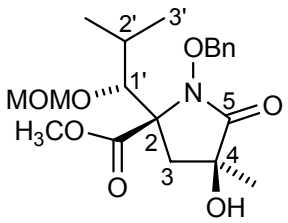
Without purification, the acid **77** (47 mg, 0.123 mmol) was treated with an excess of an ethereal CH_2N_2 (a yellow solution). After stirring for 10 min, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 1.5 : 1) to yield the corresponding ester **78** (41 mg, 84 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = - 51.7 (*c* = 1.10, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 396 (100) $[M + H]^+$, 364 (58), 334 (66), 91 (64).

HRMS (CI, pos.): $[M + H]^+$ calcd for $C_{20}H_{30}NO_7$: 396.2022; found 396.2030.

IR (neat): υ = 3399 (b, OH), 2958 (w), 1701 (s, C=O), 1453 (w), 1371 (w), 1271 (m), 1215 (m), 1141 (s), 1082 (m), 1027 (vs), 955 (s), 910 (m), 874 (w), 732 (s), 698 (s) 647 (s) cm^{-1}.



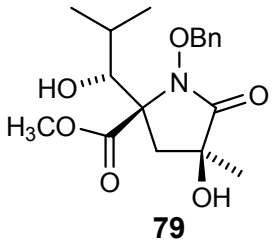
78

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.93 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 0.98 (d, $^3J_{2',3'}$ = 6.9 Hz, 3 H, 3'-H), 1.49 (s, 3 H, 4-CH_3), 1.95 (m, 1 H, 2'-H), 2.42, 2.55 (A, B of AB, ^2J = 14.7 Hz, 2 H, 3-H), 3.36 (s, 3 H, OCH_3), 3.81 (s, 3 H, COOC$\underline{H}_3$), 4.08 (d, $^3J_{1',2'}$ = 3.9 Hz, 1 H, 1'-H), 4.65, 4.69 (A, B of AB, ^2J = 6.5 Hz, 2 H, OCH_2O), 4.99, 5.32 (A, B of AB, ^2J = 9.4 Hz, 2 H, OCH_2Ph), 7.33-7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.3 (q, 4-CH_3), 22.7, 24.2 (2 q, 2'-CH_3, C-3'), 29.1 (d, C-2'), 39.0 (t, C-3), 53.2 (q, OCH_3), 56.5 (q, COO$\underline{C}H_3$), 69.5 (s, C-2), 70.3 (s, C-4), 77.0 (t, OCH_2Ph), 83.8, (d, C-1'), 99.3 (t, OCH_2O), 128.4, 128.7, 129.2 (3 d, C_6H_5), 134.7 (s, *i*-C of $\underline{C}_6H_5$), 170.9 (s, C-5), 173.0 (s, $\underline{C}OOCH_3$).

Experiment 68 (FLi 233)

(2*R*,4*S*,1'*R*)-1-Benzyloxy-4-hydroxy-2-(1'-hydroxy-2-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**79**)



79

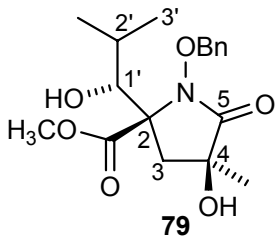
Acidic resin (Dowex 50W, H^+ form, 40 mg) was added to a solution of the ester **78** (40 mg) in MeOH (5.0 mL) and water (1.0 mL). The heterogeneous mixture was refluxed with stirring for 12 h. The resin was filtered off and washed with MeOH (2 × 5 mL). After concentration under reduced pressure (40 °C/300 mbar), the crude product, a colourless oil, was purified by flash chromatography on silica gel (3 g, column 2 cm × 1.5 cm, petroleum ether/EtOAc 1 : 1) to afford the lactam **79** (35 mg, 98 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = - 40.2 (*c* = 1.15, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 352 $[M + H]^+$ (100), 91 (24).

HRMS (CI, pos.) $[M + H]^+$: calcd for $C_{18}H_{26}NO_6$: 352.1760; found 352.1759.

IR (neat): υ = 3385 (b), 2957 (w), 1746 (s, C=O), 1696 (vs, C=O), 1453 (m), 1375 (m), 1274 (m), 1209 (m), 1119 (m), 1069 (m), 1017 (m), 987 (m), 955 (m), 909 (w) 866 (w), 835 (w), 750 (s), 696 (s), 650 (m), 607 (m) cm^{-1}.



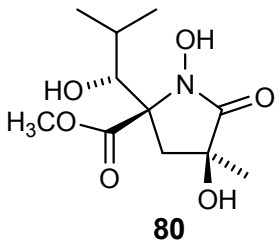
79

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.93 (d, $^3J_{2',CH_3}$ = 6.9 Hz, 3 H, 2'-CH_3), 0.95 (d, $^3J_{2',3'}$ = 6.9 Hz, 3 H, 3'-H), 1.50 (s, 3 H, 4-CH_3), 1.99 (m, 1 H, 2'-H), 2.38, 2.45 (A, B of AB, ^2J = 14.2 Hz, 2 H, 3-H), 3,74 (d, $^3J_{1',2'}$ = 6.7 Hz, 1 H, 1'-H), 3.81 (s, 3 H, OCH_3), 5.28, 5.42 (A, B of AB, ^2J = 9.3 Hz, 2 H, OCH_2Ph), 7.33-7.43 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.3 (q, 4-CH_3), 20.9, 24.6 (2 q, 2'-CH_3, C-3'), 31.3 (d, C-2'), 41.8 (t, C-3), 52.8 (q, OCH_3), 69.9 (s, C-2), 70.7 (s, C-4), 77.8 (t, OCH_2Ph), 79.0, (d, C-1'), 128.5, 128.9, 129.6 (3 d, C_6H_5), 134.7 (s, *i*-C of C_6H_5), 171.7 (s, C-5), 172.7 (s, $\underline{C}OOCH_3$).

Experiment 69 (FLi 235)

(2*R*,4*S*,1'*R*)-1,4-Dihydroxy-2-(1'-hydroxy-2'-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**80**)



80

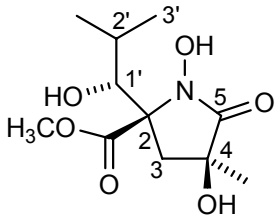
A 250-mL flask was charged with the lactam **79** (34 mg, 0.097 mmol) and $Pd(OH)_2/C$ (8.0 mg, 20 %) in MeOH (2 mL). The resulting mixture was hydrogenated (H_2, 3 bar) for 5 h at r. t.. The catalyst was filtered off and the filtrate was concentrated in vacuo (40 °C/300 mbar). The residue, a colourless oil, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, CH_2Cl_2/MeOH 7 : 1) to afford the *N*-hydroxylactam **80** (25 mg, 99 %) as a colourless, spectroscopically pure powder; m. p. = 135-136 °C.

$[\alpha]_D^{20}$ = - 66.7 (*c* = 0.420, MeOH)

MS: (CI, pos.): *m/z* (%) = 262 $[M + H]^+$ (100), 172 (18), 128 (12).

HRMS (CI, pos.) $[M + H]^+$: $C_{11}H_{20}NO_6$ calcd for 262.1291; found. 262.1273.

IR (solid): υ = 3349 (b, w, OH), 2960 (w), 1733 (m, C=O), 1688 (vs, C=O), 1437 (m), 1374 (m), 1277 (m), 1215 (m), 1137 (m), 1119 (m), 1075 (m), 1034 (s), 987 (m), 956 (m), 861 (w), 835 (w), 755 (m), 690 (m) cm^{-1}.



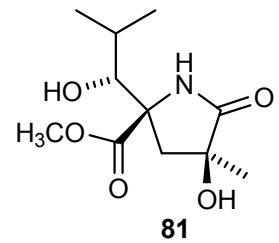
80

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.95 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.05 (d, $^3J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H), 1.44 (s, 3 H, 4-CH_3), 2.14 (m, 1 H, 2'-H), 2.32, 2.55 (A, B of AB, ^2J = 14.1 Hz, 2 H, 3-H), 3.71 (d, $^3J_{1',2'}$ = 7.4 Hz, 1 H, 1'-H), 3.80 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.1 (q, 4-CH_3), 20.4, 24.5 (2 q, 2'-CH_3, C-3'), 31.8 (d, C-2'), 41.8 (t, C-3), 52.9 (q, OCH_3), 70.5 (s, C-2), 71.1 (s, C-4), 78.6 (d, C-1'), 172.3 (s, C-5), 172.7 (s, $\underline{C}OOCH_3$).

Experiment 70 (FLi 237)

(2*R*,4*S*,1'*R*)-4-Hydroxy-2-(1'-hydroxy-2'-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**81**)



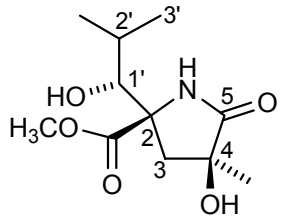
81

A 250-mL flask was charged with the ester **79** (27 mg, 0.076 mmol) and Pt/C (15 mg, 5 %) in MeOH (3 mL). The resulting mixture was hydrogenated (H_2, 4 bar) for 5 d at r. t.. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue, a colourless powder, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, CH_2Cl_2/MeOH 10 : 1) to afford the lactam **81** (17.8 mg, 95 %) as a colourless, analytically pure powder; m. p. = 166 °C.

$[\alpha]_D^{20}$ = - 21.5 (*c* = 0.610, MeOH)

$C_{11}H_{19}NO_5$	calcd.	C	53.87	H	7.81	N	5.71
(245.3)	found	C	54.40	H	7.85	N	5.49

IR (solid): υ = 3349 (b, w, OH), 2960 (w), 1733 (m, C=O), 1688 (vs, C=O), 1437 (m), 1374 (m), 1277 (m), 1215 (m), 1137 (m), 1119 (m), 1075 (m), 1034 (s), 987 (m), 956 (m), 861 (w), 835 (w), 755 (m), 690 (m) cm^{-1}.



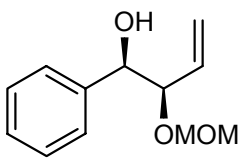
81

^{1}H NMR (CD_3OD, 300.1 MHz): δ = 0.90 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 0.97 (d, $^3J_{2',3'}$ = 6.7 Hz, 3 H, 3'-H), 1.38 (s, 3 H, 4-CH_3), 1.70 (m, 1 H, 2'-H), 2.35, 2.50 (A, B of AB, ^2J = 14.1 Hz, 2 H, 3-H), 3.45 (d, $^3J_{1',2'}$ = 6.5 Hz, 1 H, 1'-H), 3.73 (s, 3 H, OCH_3).

^{13}C NMR (CD_3OD, 75.5 MHz): δ = 19.3 (q, 4-CH_3), 21.0, 24.4 (2 q, 2'-CH_3, C-3'), 32.3 (d, C-2'), 46.2 (t, C-3), 52.9 (q, OCH_3), 68.0 (s, C-2), 74.5 (s, C-4), 79.9 (d, C-1'), 175.5 (s, C-5), 180.4 (s, $\underline{C}OOCH_3$).

Experiment 71 (FLi 110)

(1*R*,2*R*)-2-Methoxymethoxy-1-phenyl-but-3-ene-1-ol (**82**)



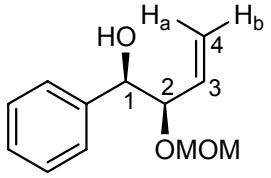
82

In analogy to lit.[71], to a stirred solution of 3-(methoxymethoxy)prop-1-ene (510 mg, 5.0 mmol) in THF (15 mL) was added *sec*-BuLi (2.84 g, 4.8 mmol, 3.7 mL, 1.3 M in cyclohexane) at -78 °C over the course of 10 min. The mixture was stirred at -78 °C for an additional 30 min, and (-)-*B*-methoxydiisopinocampheylborane (1.52 g, 4.8 mmol) in THF (3.43 mL, 1.4 M) was added dropwise. The reaction mixture was stirred at -78°C for 1 h, then $BF_3 \cdot Et_2O$ (0.77 mL, 16.0 mmol) was added dropwise. Immediately afterwards, benzylaldehyde (509 mg, 4.80 mmol) was added dropwise and the mixture was stirred at -78 °C for 3 h and then slowly warmed to r. t.. The oxidative work-up was carried out by adding NaOH solution (4.8 mL, 2.0 M) and 30 % H_2O_2 (2.2 mL) at 0 °C. The resulting mixture was stirred at r. t. for 2 h and then a solution of $Na_2S_2O_3$ (2.5 mL, 9.0 M)) was added. The mixture was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$). After concentration in vacuum (40 °C/660 mbar), the crude product was purified by flash chromatography on silical gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 6 : 1) to give the diol **82** (639 mg, 64 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 129.3 (*c* = 1.60, $CHCl_3$)

$C_{12}H_{16}O_3$	calcd.	C	69.21	H	7.74
(208.3)	found	C	69.03	H	7.77

IR (neat): υ = 3427 (w, OH), 2889 (w), 1494 (w), 1453 (w), 1404 (w), 1332 (w), 1196 (m), 1149 (m), 1095 (m), 1019 (vs), 918 (s), 832 (w), 762 (m), 719 (m), 699 (s) cm^{-1}.



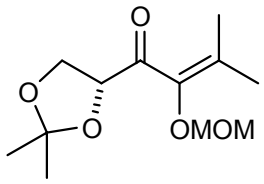
82

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 3.29 (s, 3 H, OCH_3), 4.14 (dd, $^3J_{2,3}$ = 7.0 Hz, $^3J_{1,2}$ = 7.0 Hz, 2-H), 4.59, 4.73 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 4.60 (d, $^3J_{1,2}$ = 6.8 Hz, 1-H), 5.14 (d, $^3J_{3,4a}$ = 17.3 Hz, 4-H_a), 5.18 (dd, $^3J_{3,4b}$ = 10.6 Hz, $^4J_{2,4b}$ = 0.08 Hz, 4-H_b), 5.62 (ddd, $^3J_{3,4a,}$ = 17.3 Hz, $^3J_{3,4b}$ = 10.6 Hz, $^3J_{2,3}$ = 7.2 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 56.1 (q, OCH_3), 77.0 (d, C-1), 82.5 (d, C-2), 94.7 (t, OCH_2O), 119.9 (t, C-4), 127.5, 128.2, 128.5 (3 d, C_6H_5), 134.6 (s, *i*-C of $\underline{C}_6H_5$), 140.4 (d, C-4).

Experiment 72

(2*R*)-1,2-Isopropylidenedioxy-4-methoxymethoxy-5-methyl-4-hexene-3-one (**83**)



83

Method A: (FLi 149)

The ketone **50** (244 mg, 1.00 mmol), Al_2O_3 (neutral, 255 mg, 2.50 mmol), benzylamine (105 mg, 1.00 mmol), and CH_2Cl_2 (1.5 mL) were mixed and refluxed for 1.0 h. To the mixture was added CH_2Cl_2 (5 mL) and stirring was continued for 10 min. The suspension was filtered, the residue was washed with CH_2Cl_2 (2 × 5 mL), and the filtrate was dried ($MgSO_4$). Removal of the solvent in vacuo (40 °C/600 mbar) gave the crude product, a colourless oil, which was purified by flash chromatography on silica gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to afford the conjugated ketone **83** (239 mg, 98 %) as a colourless, analytically pure oil (no expected imine had formed).

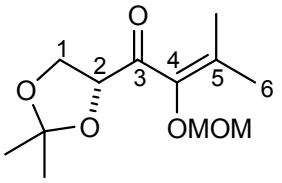
Method B: (FLi 150)

To a solution of the ketone **50** (244 mg, 1.00 mmol) in CH_2Cl_2 (4.0 mL) were added benzylamine (105 mg, 1.10 mmol) and Et_3N (122 mg, 1.20 mmol). The reaction mixture was cooled to 0 °C and $TiCl_4$ (132 mg, 0.72 mmol) was added dropwise. Upon completion of the addition, the reaction mixture was stirred for 4 h at r. t.. The reaction was quenched by slow addition of water (1.0 mL). After stirring for 10 min, the mixture was filtered and the solid was washed with CH_2Cl_2 (3 × 10 mL). The solvent was removed to leave a yellowish oil, (after analysis by NMR, the major product was the conjugated ketone). The crude product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAcl 5 : 1) to afford the conjugated ketone **83** (170 mg, 72 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 4.6 (*c* = 1.0, $CHCl_3$)

$C_{12}H_{20}O_5$	calcd.	C	59.00	H	8.25
(244.3)	found	C	58.86	H	8.27

IR (neat): υ = 2986 (w), 2937 (w), 1703 (m, C=O), 1615 (w), 1454 (w), 1371 (m), 1260 (m), 1214 (m), 1186 (m), 1147 (s), 1101 (m), 1064 (vs), 1001 (m), 969 (s), 926 (m), 843 (s), 700 (w), 634 (w) cm^{-1}.



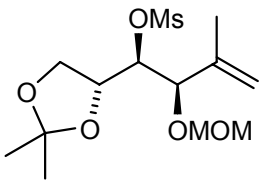
83

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.43, 1.46 [2 s, 6 H, $C(CH_3)_2$], 1.88, 2.05 (2 s, 6 H, 5-CH_3, 6-H), 3.50 (s, 3 H, OCH_3), 4.04 (dd, $^2J_{1a,1b}$ = 8.7 Hz, $^3J_{1a,2}$ = 5.7 Hz, 1 H, 1-H_a), 4.29 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 7.7 Hz, 1 H, 1-H_b), 4.76, 4.79 (A, B of AB, ^2J = 5.7 Hz, OCH_2O), 5.03 (dd, $^3J_{1b,2}$ = 7.5 Hz, $^3J_{1a,2}$ = 5.7 Hz, 1 H, 2-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 19.7, 20.3 (2 q, 5-CH_3, C-6), 25.6, 26.0 [2 q, $C(\underline{C}H_3)_2$], 57.6 (q, OCH_3), 66.4 (t, C-1), 78.6 (d, C-2), 99.5 (t, OCH_2O), 110.6 [s, $\underline{C}(CH_3)_2$], 137.5 (s, C-5), 145.6 (s, C-4), 196.8 (s, C-3).

Experiment 73 (FLi 190)

(2*R*,3*R*,4*R*)-1,2-*O*-Isopropylidene-3-mesyl-4-methoxy-methyl-5-methyl-5-hexene-1,2,3,4-tetraol (**84**)



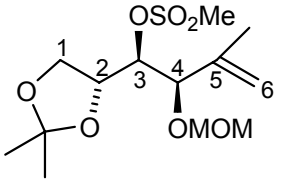
84

To a solution of the alcohol **49** (369 mg 1.50 mmol) in CH_2Cl_2 (5.0 mL) and Et_3N (455 mg, 4.50 mmol) at 0 °C was added $MeSO_2Cl$ (516 mg, 4.5 mmol). The mixture was stirred at 0 °C for 10 min and then warmed to r. t.. Stirring was continued for a further hour, then the solvent was evaporated under reduced pressure (40 °C/600 mbar to 60 mbar). The crude product, a colourless oil, was purified by flash chromatography on silica gel (7 g SiO_2, column 3.5 cm × 2 cm, petroleum ether/EtOAc 3 : 1) to afford the methanesulfonate **84** (386 mg, 88 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 23.8 (*c* = 1.40, $CHCl_3$)

$C_{13}H_{24}SO_7$	calcd.	C	48.13	H	7.46	S	9.88
(324.4)	found	C	48.21	H	7.41	S	9.73

IR (neat): υ = 2985(w), 2939 (w), 2894 (w), 1453 (w), 1347 (s), 1213 (m), 1174 (vs), 1152 (s), 1101 (m), 1063 (s), 1021 (vs), 980 (m), 945 (vs), 911 (vs), 857 (s), 816 (m), 791 (m), 644 (w) cm^{-1}.



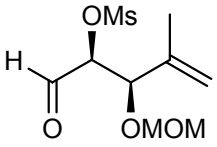
84

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ= 1.36, 1.45 [2 s, 6 H, $C(CH_3)_2$], 1.78 (s, 3 H, 5-CH_3), 3.09 (s, 3 H, OSO_2CH_3), 3.41 (s, 3 H, OCH_3), 3.98 (dd, $^{2}J_{1a,1b}$ = 8.2 Hz, $^{3}J_{1a,2}$ = 7.5 Hz, 1 H, 1-H_a), 4.05 (dd, $^{2}J_{1a,1b}$ = 8.3 Hz, $^{3}J_{1b,2}$ = 6.4 Hz, 1 H, 1-H_b), 4.12 (d, 1 H, $^{3}J_{3,4}$ = 6.4 Hz, 1 H, 4-H), 4.21 (m, 1 H, 2-H), 4.59, 5.66 (A, B of AB, ^{2}J = 6.7 Hz, 2 H, OCH_2O), 4.98 (dd, $^{3}J_{3,4}$ = 6.4 Hz, $^{3}J_{2,3}$ = 4.2 Hz, 1 H, 3-H), 5.11-5.44 (m, 2 H, 6-H).

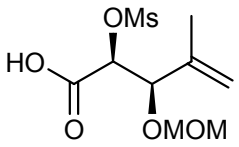
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.5 (q, 5-CH_3), 25.6, 26.6 [2 q, $C(\underline{C}H_3)_2$], 39.4 (q, SO_2CH_3), 56.5 (q, OCH_3), 64.9 (t, C-1), 74.2 (d, C-2), 78.1 (d, C-3), 81.0 (d, C-4), 94.3 (t, OCH_2O), 109.7 [s, $\underline{C}(CH_3)_2$], 117.3 (t, C-6), 140.4 (s, C-5).

Experiment 74 (FLi 196, FLi 197)

(2*S*,3*R*)-2-Mesyloxy-3-methoxymethoxy-4-methyl-4-pentenal (**85**) and (2*S*,3*R*)-2-Mesyloxy-3-methoxymethoxy-4-methyl-4-pentenoic acid (**86**)



85



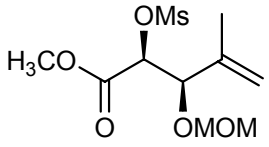
86

To a solution of the diol-acetonide **84** (248 mg, 0.765 mmol) in Et_2O (10 mL) was added H_5IO_6 (438 mg, 1.92 mmol). The reaction mixture was stirred under N_2 for 3 h at r. t.. The solution of $Na_2S_2O_3$ (2.0 mL, 2 M) was added. The reaction mixture was extracted with Et_2O (3 × 20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford the aldehyde **85** (188 mg, 98 %) as a colourless oil.

The aldehyde **85** (188 mg, 0.75 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (3.0 mL). Then $NaClO_2$ (104 mg, 1.15 mmol) and NaH_2PO_4 (138 mg, 1.15 mmol) were added over 5 min. After stirring for 90 min, NaOH (1.5 mL, 4 M) was added and the solvent was removed under reduced pressure (40 °C/60 mbar). The residue, a colourless powder, was dissolved in water (6.0 mL) and 6 M HCl was added utill a pH value of 3–4 was reached. The reaction mixture was extracted with EtOAc (5 × 30 mL) and dried ($MgSO_4$). After solvent removal, the acid **86** (190 mg, 95 %) was obtained as a colourless oil, which was directly transformed into the corresponding ester.

Experiment 75 (FLi 198)

Methyl (2*S*,3*R*)-2-mesyloxy-3-methoxymethoxy-4-methyl-4-pentenoate (**87**)



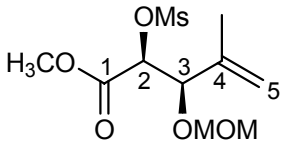
87

Without purification, the acid **86** (190 mg, 0.72 mmol) was treated with an ethereal yellow solution of CH_2N_2 (excess, a yellow solution). After stirring for 10 min, the solvent was evaporated and the residue, a light-yellow oil, was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 3 : 1) to yield the corresponding ester **87** (174 mg, 87 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 104 (*c* = 1.25, $CHCl_3$)

$C_{10}H_{18}SO_7$	calcd.	C	42.54	H	6.43
(282.3)	found	C	42.52	H	6.28

IR (neat): υ = 2955 (w), 1757 (m, C=O), 1439 (w), 1351 (s), 1284 (m), 1219 (m), 1174 (s), 1152 (s), 1108 (m), 1020 (vs), 960 (s), 918 (s), 869 (m), 822 (m), 791 (m), 745 (m), 682 (w) cm^{-1}.



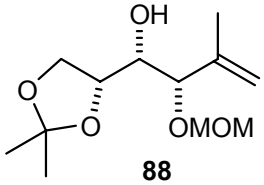
87

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ= 1.78 (s, 3 H, 4-CH_3), 3.16 (s, 3 H, SO_2CH_3), 3.34 (s, 3 H, OCH_3), 3.83 (s, 3 H, $COOCH_3$), 4.56 (d, 1 H, $^3J_{2,3}$ = 3.9 Hz, 1 H, 3-H), 4.57, 4.63 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 5.13 (d, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 5.5 (m, 2 H, 5-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.8 (q, 4-CH_3), 39.4 (q, SO_2CH_3), 53.2 (q, OCH_3), 56.4 (q, OCH_3), 78.6 (d, C-3), 79.1 (d, C-2), 94.8 (t, OCH_2O), 117.2 (t, C-5), 139.2 (s, C-4), 167.9 (s, C-1).

Experiment 76 (FLi 248)

(2*R*,3*R*,4*S*)-1,2-*O*-Isopropylidene-4-*O*-methoxymethxy-5-methyl-5-hexene-1,2,3,4-tetraol (**88**)



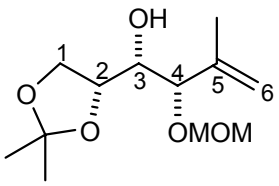
88

According to a lit. procedure[71], to a stirred solution of 3-(methoxymethoxy)-2-methylprop-1-ene (1.24 g, 11.0 mmol) in THF (15 mL) was added *sec*-BuLi (5.91 g, 10.0 mmol, 7.7 mL, 1.3 M in cyclohexane) at -78 °C. The mixture was stirred at -78 °C for an additional 30 min, and (+)-*B*-methoxydiisopinocampheylborane in THF (3.12 g, 10.0 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 1 h, then $BF_3{\cdot}Et_2O$ (12.0 mmol) was added dropwise. Immediately afterwards, the aldehyde **6** (1.3 g, 10 mmol) was added; the reaction mixture was stirred at -78 °C for 3 h and allowed to slowly warm up to r. t.. The oxidation was carried out by adding NaOH (2.5 mL, 4.0 M, 10.0 mmol) and 30 % H_2O_2 (2.5 mL) at 0 °C. The resulting mixture was stirred at r. t. for 3 h and then a solution of $Na_2S_2O_3$ (5 mL, 4 M) was added. The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (50 g, column 12 cm × 4 cm, petroleum ether/EtOAc 5 : 1) to afford the diol **88** (1.75 g, 71 %) as a colourless, analytically pure oil; > 95 % *syn*; *dr* = > 95 : 5.

$[\alpha]_D^{20}$ = + 85.2 (*c* = 1.40, $CHCl_3$)

$C_{12}H_{22}O_5$	calcd.	C	58.20	H	9.00
(246.3)	found	C	58.65	H	9.06

IR (neat): υ = 3495 (b, w), 2984 (w), 2891 (w), 1648 (w), 1454 (w), 1370 (m), 1249 (m), 1211 (m), 1151 (s), 1098 (s), 1064 (s), 1028 (vs), 987 (m), 941 (w), 913 (s), 881 (m), 860 (m), 795 (w), 708 (w) cm^{-1}.



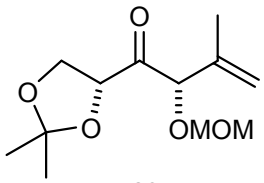
88

^1H NMR ($CDCl_3$, 300.1 MHz): δ= 1.36, 1.45 [2 s, 6 H, $C(CH_3)_2$], 1.75 (s, 3 H, 5-CH_3), 2.52 (b, 1 H, OH), 3.41 (s, 3 H, OCH_3), 3.62 (dd, $^3J_{2,3}$ = 6.2 Hz, $^3J_{3,4}$ = 4.3 Hz, 1 H, 3-H), 3.86 (dd, $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1a,2}$ = 7.4 Hz, 1 H, 1-H_a), 4.00-4.04 (m, 2 H, 1-H_b and 4-H), 4.14 (m, 1 H, 2-H), 4.59, 4.65 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 5.07 (s, 2 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.5 (q, 5-CH_3), 25.5, 26.5 [2 q, $C(\underline{C}H_3)_2$], 55.9 (q, OCH_3), 66.1 (t, C-1), 72.1 (d, C-3), 75.8 (d, C-2), 80.9 (d, C-4), 94.3 (t, OCH_2O), 109.4 [s, $\underline{C}(CH_3)_2$], 116.0 (t, C-6), 141.4 (s, C-5).

Experiment 77

(2*R*,4*S*)-1,2-Isopyropylidenedioxy-4-methoxy-methoxy-5-methyl-5-hexen-3-one (**89**)



89

Method A: (FLi 251)

To a solution of distilled pyridine (6.3 g, 80 mmol) in CH_2Cl_2 (120 mL) was added (4.0 g, 40 mmol) CrO_3 in portions over 15 min. The resulting mixture was stirred for 1 h at r. t.. The alcohol **88** (984 mg, 4.0 mmol) in CH_2Cl_2 (5.0 mL) was added, and the mixture was stirred for 4 h at r. t.. The solution was washed with sat. aq. $NaHCO_3$ (2 × 30 mL), H_2O (2 × 30 mL), and then with 4 M HCl (2 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated to give a brown oil. The crude product was purified by flash chromatography on silica gel (15 g, column 5 cm × 3 cm, petroleum ether/EtOAc 6 : 1) to furnish the ketone **89** (983 mg, 88 %) as a colourless, analytically pure oil.

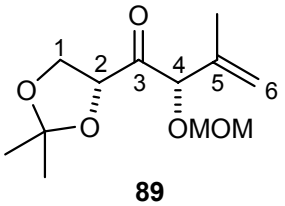
Method B: (FLi 252)

According to a lit. procedure[132a], a 100-mL, three necked, round-bottomed flask was equipped with a low temperature thermometer and two equalizing dropping funnels. One of these was connected to nitrogen and was charged with a solution of the alcohol **88** (492 mg, 2.0 mmol) in CH_2Cl_2 (4 mL), the other was charged with a solution of DMSO (468 mg, 6.0 mmol) in CH_2Cl_2 (2 mL). The flask was charged with ClCOCOCl (381 mg, 3.0 mmol) in CH_2Cl_2 (5 mL), then cooled to -78 °C. DMSO was added dropwise over a period of 4 min. At the end of the addition, the solution was warmed to -60 °C, then the alcohol **88** was added within 5 min. Et_3N (1.22 g, 12 mmol) in CH_2Cl_2 (1 mL) was added over a period of 5 min. After stirring for 20 min at -78 °C, the reaction mixture was allowed to warm to r. t.. After addition of water (5 mL), the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were washed successively with HCl (12 mL, 1 %), $NaHCO_3$ (5 mL, 5 %) and H_2O (2 × 6 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purifed by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 6 : 1) to provide the ketone **89** (405 mg, 83 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 205 (*c* = 1.05, $CHCl_3$)

$C_{12}H_{20}O_5$	calcd.	C	59.00	H	8.25
(244.3)	found	C	58.70	H	8.22

IR (neat): υ = 2988 (w), 2940 (w), 2892 (w), 1731 (m), 1454 (w), 1373 (m), 1257 (m), 1213 (m), 1150 (s), 1103 (m), 1036 (vs), 984 (m), 916 (s), 842 (s), 793 (w) cm^{-1}.



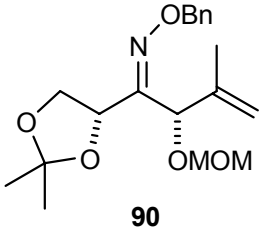
89

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.41, 1.48 [2 s, 6 H, $C(CH_3)_2$], 1.73 (s, 3 H, 5-CH_3), 3.36 (s, 3 H, OCH_3), 4.09 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1a,2}$ = 5.7 Hz, 1 H, 1-H_a), 4.25 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1b,2}$ = 7.6 Hz, 1 H, 1-H_b), 4.60, 4.68 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O), 4.75 (dd, $^3J_{1b,2}$ = 7.6 Hz, $^3J_{1a,2}$ = 5.7 Hz, 1 H, 2-H), 4.96 (s, 1 H, 4-H), 5.18-5.23 (m, 2 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 18.2 (q, 5-CH_3), 25.4, 25.8 [2 q, $C(\underline{C}H_3)_2$], 56.0 (q, OCH_3), 66.4 (t, C-1), 77.8 (d, C-2), 82.3 (d, C-4), 94.4 (t, OCH_2O), 110.9 [s, $\underline{C}(CH_3)_2$], 117.7 (t, C-6), 138.9 (s, C-5), 205.4 (s, C-3).

Experiment 78 (FLi 254)

(*E*)- or (*Z*)-(2*R*,4*S*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methyl-5-hexene-1,2,4-triol (**90**)



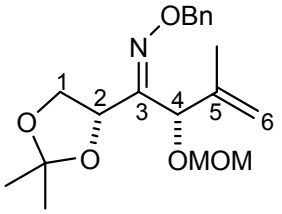
90

To a solution of the ketone **89** (732 mg, 3.00 mmol) and pyridine (249 mg, 3.15 mmol) in MeOH (20 mL) was added *O*-benzylhydroxylamine hydrochloride (502 mg, 3.15 mmol). The reaction mixture was refluxed for 40 min. After solvent removal in vacuo (40 °C/300 mbar), water (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (18 g, column 6 cm × 3 cm, petroleum ether/EtOAc 10 : 1) to afford the oxime ether **90** (952 mg, 91 %) as a colourless, analytically pure oil (a single diastereoisomer).

$[\alpha]_D^{20}$ = + 116 (*c* = 1.46, $CHCl_3$)

$C_{19}H_{27}NO_5$	calcd.	C	65.31	H	7.79	N	4.01
(349.4)	found	C	65.33	H	7.80	N	4.12

IR (neat): υ = 2984 (w), 2934 (w), 2886 (w), 1652 (w), 1454 (w), 1371 (m), 1211 (m), 1150 (s), 1099 (m), 1033 (vs), 917 (s), 857 (s), 796 (w), 736 (m), 697 (s) cm^{-1}.



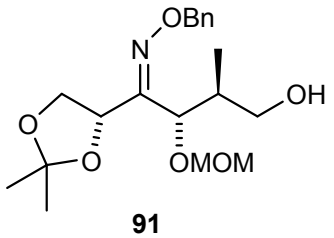
90

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.34, 1.45 [2 s, 6 H, $C(CH_3)_2$], 1.75 (s, 3 H, 5-CH_3), 3.35 (s, 3 H, OCH_3), 3.76 (dd, 1 H, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1a,2}$ = 7.6 Hz, 1-H_a), 4.36 (dd, $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1b,2}$ = 7.3 Hz, 1-H_b), 4.64 (s, 2 H, OCH_2O), 4.96 (s, 1 H, 4-H), 5.02-5.13 (m, 3 H, 6-H, 2-H), 5.13, 5.18 (A, B of AB, ^2J = 12.1 Hz, 2 H, OCH_2Ph), 7.26-7.34 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.6 (q, 5-CH_3), 25.0, 25.7 [2 q, $C(\underline{C}H_3)_2$], 55.7 (q, OCH_3), 68.3 (t, C-1), 72.0 (d, C-2), 76.0 (d, C-4), 76.7 (t, OCH_2Ph), 94.7 (t, OCH_2O), 109.6 [s, $\underline{C}(CH_3)_2$], 114.7 (t, C-6), 128.0, 128.2, 128.4 (d, 5 C, CH of C_6H_5), 137.4 (s, *i*-C of $\underline{C}_6H_5$) 141.6 (s, C-5), 158.5 (s, C-3).

Experiment 79 (FLi 256)

(*E*)- or (*Z*)-(2*R*,4*S*,5*S*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**91**)



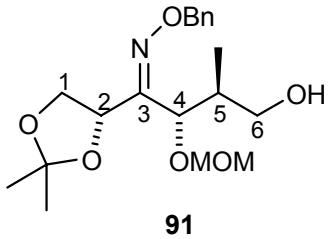
91

To a solution of the oximer ether **90** (1.05 g, 3.00 mmol) in THF (30 mL) at 0 °C under N_2 was added 9-BBN (12 mL, 6 mmol, 0.5 M in THF), and the reaction mixture was stirred for 20 h at r. t.. A solution of NaOH (2.0 mL, 4 M) and 30 % H_2O_2 (2.5 mL) was added slowly at 0 °C. After stirring for 2 h at r. t., the reaction mixture was extracted with Et_2O (4 × 40 mL). The organic phases were dried ($MgSO_4$) and concentrated to give a crude product which was purified by flash chromatography on silica gel (18 g, column 6 cm × 3 cm, petroleum ether/EtOAc 1.5 : 1) to afford the alcohol **91** (923 mg, 84 %) as a colourless, analytically pure oil, *dr* = > 91 : 9.

$[\alpha]_D^{20}$ = + 32.4 (*c* =1.10, $CHCl_3$)

$C_{19}H_{29}NO_6$	calcd.	C	62.11	H	7.95	N	3.81
(367.4)	found	C	61.92	H	8.05	N	3.67

IR (neat): υ = 3460 (b, w), 2933 (w), 2882 (w), 1455 (w), 1372 (m), 1210 (m), 1152 (m), 1099 (m), 1027 (vs), 918 (s), 858 (m), 797 (w), 734 (m), 698 (s) cm^{-1}.



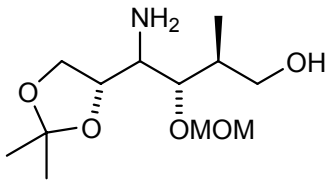
91

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.94 (d, $^3J_{5,CH_3}$ = 7.1 Hz, 3 H, 5-CH_3), 1.35, 1.47 [2 s, 6 H, $C(CH_3)_2$], 2.29 (m, 1 H, 5-H), 3.36 (s, 3 H, OCH_3), 3.58 (dd, $^2J_{6a,6b}$ = 11.4 Hz, $^3J_{5,6a}$ = 6.0 Hz, 1 H, 6-H_a), 3.71 (dd, $^2J_{6a,6b}$ = 11.4 Hz, $^3J_{5,6b}$ = 3.8 Hz, 1 H, 6-H_b), 3.72 (dd, $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1a,2}$ = 4.6 Hz, 1 H, 1-H_a), 4.40 (dd, $^2J_{1a,1b}$ = 8.5 Hz, $^3J_{1b,2}$ = 7.5 Hz, 1 H, 1-H_b), 4.42 (d, $^3J_{4,5}$ = 6.8 Hz, 1 H, 4-H), 4.57, 4.60 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 5.04 ("t", $^3J_{1a,2}$ = 7.4 Hz, $^3J_{1b,2}$ = 7.4 Hz, 1 H, 2-H), 5.12, (s, 2 H, OCH_2Ph), 7.29-7.37 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.7 (q, 5-CH_3), 24.8, 25.8 [2 q, C($\underline{C}H_3)_2$], 38.5 (d, C-5), 55.9 (q, OCH_3), 65.2 (t, C-6), 68.3 (t, C-1), 72.5 (d, C-2), 76.7 (t, OCH_2Ph), 77.9 (d, C-4), 95.5 (t, OCH_2O), 109.6 [s, $\underline{C}(CH_3)_2$], 128.0, 128.2, 128.4 (3 d, C_6H_5), 137.3 (s, *i*-C of $\underline{C}_6H_5$), 159.1 (s, C-3).

Experiment 80 (FLi 257)

(2*R*,3*RS*,4*S*,5S)-3-Amino-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**92**)

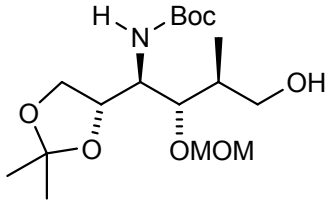


92

Following a lit. procedure[158], to a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in THF (90 mL) was added the *O*-benzyl oxime ether **91** (734 mg, 2.0 mmol) in THF (30 mL) dropwise and the reaction mixture was stirred for 15 h at r. t.. The reaction was quenched carefully with saturated Na_2SO_4 (10 mL) and the resulting precipitate was filtered off. The filtrate was concentrated in vacuo (40 °C/320 mbar) to the amine **92** (441 mg, 84 %) as a colourless oil which was used in the next step without further purification.

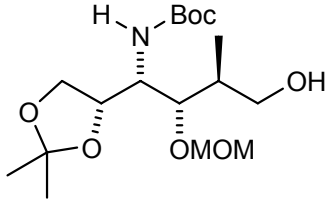
Experiment 81 (FLi 258)

(2*R*,3*S*,4*S*,5S)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**93a**) and



93a

(2*R*,3*R*,4*S*,5S)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,4,6-tetraol (**93b**)



93b

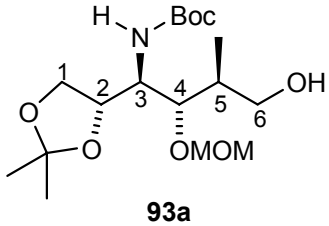
To a solution of the amine **92** (441 mg, 1.64 mmol) in CH_3CN (15 mL) was added $(Boc)_2O$ (376 mg, 1.72 mmol). The reaction mixture was stirred overnight. After solvent removal under reduced pressure (40 °C/40 mbar), the crude product was purified by flash chromatography on silica gel (12 g, column 6 cm × 2 cm, petroleum ether/EtOAc 1 : 1) to give the protected amine **93a** (374 mg, 63 %) as a colorlesss, analytically pure oil and **93b** (181 mg, 32 %) as a colourless, analytically pure oil; the ratio of **93a**/**93b** is 66 : 34 according to yield of the products isolated.

Data of **93a**

$[\alpha]_D^{20}$ = + 25.1 (*c* = 1.25, $CHCl_3$)

$C_{17}H_{33}NO_7$	calcd.	C	56.18	H	9.15	N	3.85
(363.5)	found	C	56.49	H	9.13	N	3.76

IR (neat): υ = 3351 (b, w), 2979 (w), 1691 (m, C=O), 1517 (m), 1455 (w), 1367 (m), 1306 (w), 1242 (m), 1164 (s), 1026 (vs), 954 (w), 917 (m), 850 (m), 784 (w), 731 (s), 646 (w) cm^{-1}.



93a

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 1.04 (d, $^3J_{5,CH_3}$ = 7.0 Hz, 1 H, 5-CH_3), 1.34, 1.41 [2 s, 6 H, $C(CH_3)_2$], 1.44 [s, 9 H, $OC(CH_3)_3$], 2.04 (m, 1 H, 5-H), 2.64 (b, 1 H, OH), 3.43 (s, 3 H, OCH_3),

3.61-3.64 (m, 3 H, 3-H, 6-H), 3.91 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1a,2}$ = 6.9 Hz, 1 H, 1-H_a), 4.02 (m. 1 H, 2-H), 4.03 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 6.3 Hz, 1 H, 1-H_b), 4.20 (dd, $^2J_{3,4}$ = 13.5 Hz, $^2J_{4,5}$ = 6.8 Hz 1 H, 4-H), 4.64, 4.76 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 5.82 (d, $^3J_{3,NH}$ = 9.3 Hz, 1 H, NH).

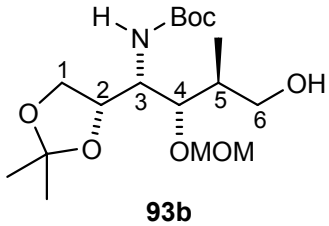
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.8 (q, 5-CH_3), 25.6, 26.4 [2 q, C(<u>C</u>H_3)$_2$], 28.3 [q, C(<u>C</u>H_3)$_3$], 37.1 (d, C-5), 52.9 (q, OCH_3), 56.1 (d, C-3), 64.5 (t, C-6), 67.2 (t, C-1), 74.8 (d, C-2), 79.2 [s, O<u>C</u>$(CH_3)_3$], 80.7 (d, C-4), 98.5 (t, OCH_2O), 109.2 [s, <u>C</u>$(CH_3)_2$], 156.0 [s, C=O].

Data of **93b**:

$[\alpha]_D^{20}$ = - 32.8 (*c* = 1.25, $CHCl_3$)

$C_{17}H_{33}NO_7$	calcd.	C	56.18	H	9.15	N	3.85
(363.5)	found	C	56.14	H	9.08	N	3.77

IR (neat): υ = 3459 (b, w), 2979 (w), 2935 (w), 1711 (m, C=O), 1499 (m), 1456 (w), 1367 (m) 1299 (w), 1244 (m), 1216 (m), 1157 (s), 1093 (m), 1028 (vs), 918 (m), 861 (m), 776 (w) cm^{-1}.



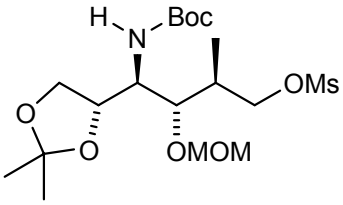
93b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.03 (d, $^3J_{5,CH_3}$ = 7.0 Hz, 1 H, 5-CH_3), 1.34, 1.41 [2 s, 6 H, C$(CH_3)_2$],1.44 [s, 9 H, OC$(CH_3)_3$], 1.88 (m, 1 H, 5-H), 2.79 (b, 1 H, OH), 3.44 (s, 3 H, OCH_3), 3.51-3.56 (m, 2 H, 3-H, 6-H_a), 3.68 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 7.4 Hz, 1 H, 1-H_b), 3.78-3.89 (m, 2 H, 4-H, 6-H_b), 4.05 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 6.5 Hz, 1 H, 1-H_b), 4.20 (m, 1 H, 2-H), 4.64, 4.76 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 5.06 (d, $^3J_{3,NH}$ = 9.3 Hz, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4 (q, 5-CH_3), 25.5, 26.3 [2 q, C(<u>C</u>H_3)$_2$], 28.4 [q, C(<u>C</u>H_3)$_3$], 37.6 (d, C-5), 51.0 (q, OCH_3), 56.5 (d, C-3), 64.6 (t, C-6), 66.9 (t, C-1), 77.1 (d, C-2), 79.5 [s, O<u>C</u>$(CH_3)_3$], 83.0 (d, C-4), 98.7 (t, OCH_2O), 109.5 [s, <u>C</u>$(CH_3)_2$], 156.2 [s, C=O].

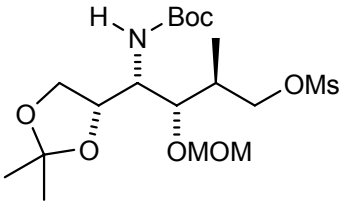
Experiment 82 (FLi 261, FLi 262)

(2*R*,3*S*,4*S*,5S)-3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-6-*O*-mesyl-5-methyl-hexane-1,2,4,6-tetraol (**94a**) and



94a

(2*R*,3*R*,4*S*,5S) -3-(*N*-*tert*-Butoxycarbonylamino)-1,2-*O*-isopropylidene-4-*O*-methoxymethyl-6-*O*-mesyl-5-methyl-hexane-1,2,4,6-tetraol (**94b**)



94b

FLi 261

To a solution of the alcohol **93a** (545 mg, 1.50 mmol) in CH_2Cl_2 (12 mL) and Et_3N (455 mg, 4.5 mmol) at 0 °C was added $MeSO_2Cl$ (516 mg, 4.50 mmol). The reaction mixture was stirred at 0 °C for 10 min and then was warmed to ambient temperature. Stirring was continued for a further 1 h and the solvent was evaporated under reduced pressure (40 °C/600 mbar). The crude product was purified by flash chromatography on silical gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 1 : 1) to give the methanesulfonate **94a** (602 mg, 91 %) as a colourless oil used directly for next step.

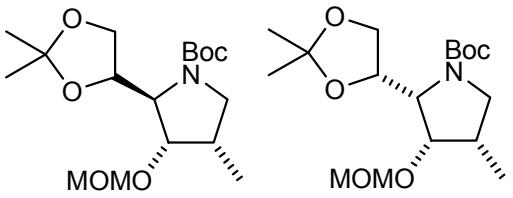
FLi 262

To a solution of the alcohol **93b** (509 mg, 1.40 mmol) in CH_2Cl_2 (10 mL) and Et_3N (425 mg, 4.20 mmol) at 0 °C was added $MeSO_2Cl$ (479 mg, 4.2.0 mmol). The reaction mixture was stirred at 0 °C for 10 min and then was warmed to ambient temperature. Stirring was continued for a further 1 h and the solvent was evaporated under reduced pressure (40 °C/600 mbar). The crude product was purified by flash chromatography on silical gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 1 : 1) to give the methansulfonate **94b** (543 mg, 88 %) as a colourless oil used directly for next step.

Experiment 83 (FLi 263, FLi 264)

(2*S*,3*S*,4*S*,1'*S*)-1-*tert*-Butoxycarbonyl-2-(1',2'-isopropylidenedioxyethyl)-3-methoxymethoxy-4-methylpyrrolidine (**95a**) and

(2*R*,3*S*,4*S*,1'*S*)-1-*tert*-Butoxycarbonyl-2-(1',2'-isopropylidenedioxyethyl)-3-methoxymethoxy-4-methylpyrrolidine (**95b**)



95a **95b**

FLi 263

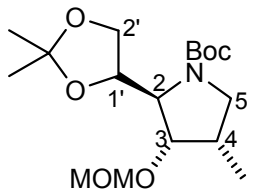
To a suspension of *t*-BuOK (168 mg, 1.50 mmol) in THF (12 mL) was dropwise added the methanesulfonate **94a** (441 mg, 1.00 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then quenched with water (1.0 mL). The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$). After solvent removal, the residue was purified by flash chromatography on silica gel (10 g, column 4 cm × 2.5 cm, petroleum ether/EtOAc 4 : 1) to afford the pyrrolidine **95a** (311 mg, 90 %) as a colourless, analytically pure oil.

Data of **95a**

$[\alpha]_D^{20}$ = - 63.6 (*c* = 1.25, $CHCl_3$)

$C_{17}H_{31}NO_6$	calcd.	C	59.11	H	9.05	N	4.05
(345.4)	found	C	59.32	H	9.09	N	4.05

IR (neat): υ = 2978 (w), 2899 (w), 1689 (vs, C=O), 1454 (w), 1367 (s), 1236 (m), 1149 (s), 1108 (m), 1067 (s), 1028 (vs), 947 (w), 919 (s), 850 (s), 776 (m) cm^{-1}.



95a

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.08 (d, $^3J_{4,CH_3}$ = 6.8 Hz, 3 H, 4-CH_3), 1.33, 1.42 [2 s, 6 H, $C(CH_3)_2$], 1.46 [s, 9 H, $OC(CH_3)_3$], 2.50 (m, 1 H, 4-H), 3.11 ("t", $^2J_{5a,5b}$ = 10.7 Hz, $^3J_{4,5a}$ = 10.5 Hz, 1 H, 5-H_a), 3.38 (s, 3 H, OCH_3), 3.47 ("t", $^2J_{5a,5b}$ = 9.3 Hz, $^3J_{4,5b}$ = 8.8 Hz, 1 H, 5-H_b), 3.88 ("d", $^3J_{1',2}$ = 5.0 Hz, 1 H, 2-H), 3.96-4.19 (m, 4 H, 3-H, 1'-H and 2'-H), 4.64, 4.71 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.4 (q, 4-CH_3), 25.1, 26.4 [2 s, C($\underline{C}H_3)_2$], 28.5 [q, OC($\underline{C}H_3)_3$], 35.9 (d, C-4), 52.1 (q, OCH_3), 55.5 (t, C-5), 66.2 (d, C-2), 67.6 (t, C-2'), 75.8 (d, C-1'), 79.0 (s, O$\underline{C}(CH_3)_3$), 79.6 (d, C-3), 95.5 (t, OCH_2O), 109.3 [s, $\underline{C}(CH_3)_2$], 155.4 [s, $\underline{C}OOC(CH_3)_3$].

FLi 264

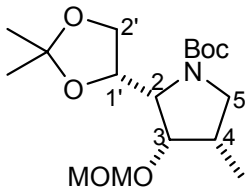
To a suspension of *t*-BuOK (202 mg, 1.80 mmol) in THF (14 mL) was dropwise added the methanesulfonate **94b** (529 mg, 1.20 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then quenched with water (1.5 mL). The mixture was extracted with Et_2O (3 × 22 mL) and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography on silica gel (10 g, column 4 cm × 2.5 cm, petroleum ether/EtOAc 4 : 1) to afford the pyrrolidine **95b** (376 mg, 91 %) as a colourless, analytically pure oil.

Data of **95b**

$[\alpha]_D^{20}$ = + 38.3 (*c* = 1.10, $CHCl_3$)

$C_{17}H_{31}NO_6$	calcd.	C	59.11	H	9.05	N	4.05
(345.4)	found	C	58.89	H	9.09	N	4.01

IR (neat): υ = 2977 (w), 2933 (w), 1689 (vs, C=O), 1477 (w), 1455 (w), 1399 (s), 1367 (s) 1212 (m), 1154 (s), 1099 (s), 1040 (vs), 919 (m), 862 (m), 767 (m) cm^{-1}.



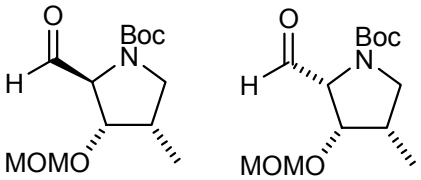
95b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.08 (d, $^3J_{4,CH_3}$ = 7.2 Hz, 3 H, 4-CH_3), 1.36, 1.40 [2 s, 6 H, $C(CH_3)_2$], 1.46 [s, 9 H, $OC(CH_3)_3$], 2.45 (m, 1 H, 4-H), 3.01 (dd, $^3J_{5a,5b}$ = 11.2 Hz, $^3J_{4,5a}$ = 7.2 Hz, 1 H, 5-H_a), 3.40 (s, 3 H, OCH_3), 3.83 ("t", $^2J_{5a,5b}$ = 11.2 Hz, $^3J_{4,5b}$ = 9.6 Hz, 1 H, 5-H_b), 3.98 (b, 1 H, 2-H), 4.03 (dd, $^2J_{2'a,2'b}$ = 8.1 Hz, $^3J_{1',2'a}$ = 6.7 Hz, 1 H, 2'-H_a), 4.14 (dd, $^3J_{2,3}$ = 7.3 Hz, $^3J_{3,4}$ = 4.6 Hz, 1 H, 3-H), 4.27 (dd, $^2J_{2'a,2'b}$ = 8.1 Hz, $^3J_{1',2'b}$ = 7.8 Hz, 1 H, 2'-H_b), 4.40 (m. 1 H, 1'-H), 4.64, 4.68 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.5 (q, 4-CH_3), 25.5, 26.2 [2 s, C($\underline{C}H_3$)$_2$], 28.4 [q, OC($\underline{C}H_3$)$_3$], 34.4 (d, C-4), 52.0 (q, OCH_3), 56.0 (t, C-5), 59.8 (d, C-2), 67.4 (t, C-2'), 74.2 (d, C-1'), 78.2 (d, C-3), 79.6 [s, O$\underline{C}$(CH_3)$_3$], 97.1 (t, OCH_2O), 108.7 [s, $\underline{C}$(CH_3)$_2$], 154.9 [s, $\underline{C}$OC(CH_3)$_3$].

Experiment 84 (FLi 270, FLi 273)

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-2-formyl-3-methoxy-methoxy-4-methylpyrrolidine (**96a**) and (2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-2-formyl-3-methoxy-methoxy-4-methylpyrrolidine (**96b**)



96a **96b**

FLi 270

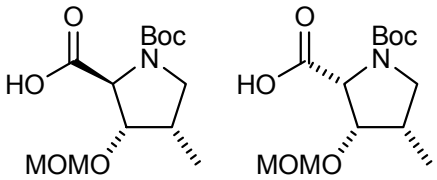
To a solution of the acetonide **95a** (414 mg, 1.20 mmol) in Et_2O (20 mL) was added H_5IO_6 (684 mg, 3.0 mmol). The resulting mixture was stirred under N_2 at r. t. for 6 h and saturated $Na_2S_2O_3$ (5 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$). After concentration in vacuo (40 °C/680 mbar), the aldehyde **96a** (307 mg, 94 %) was obtained as a colourless oil, which was directly used for the next step.

FLi 273

To a solution of the acetonide **95b** (435 mg, 1.26 mmol) in Et_2O (20 mL) was added H_5IO_6 (718 mg, 3.15 mmol). The resulting mixture was stirred under N_2 for 6 h at r. t. and sat. $Na_2S_2O_3$ (5 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were dried ($MgSO_4$). After concentration in vacuo (40 °C/680 mbar), the aldehyde **96b** (329 mg, 96 %) was obtained as a colourless oil, which was directly used for the next step.

Experiment 85 (FLi 271, FLi 274)

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline (**97a**) and (2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline (**97b**)



97a **97b**

FLi 271

The aldehyde **96a** (307 mg, 1.13 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (3.0 mL). Then a solution of $NaClO_2$ (163 mg, 1.80 mmol) and NaH_2PO_4 (216 mg, 1.80 mmol) in water (1.5 mL) was added within 8 min. After stirring for 90 min, the same amount of $NaClO_2$ and NaH_2PO_4 was added. The mixture was stirred for further another hour, then NaOH (1.8 mL, 4 M) was added. After removal of the solvent in vacuo (40 °C,/60 mbar), the residue, a white powder, was dissolved in water (8.0 mL), 6 M HCl was added until

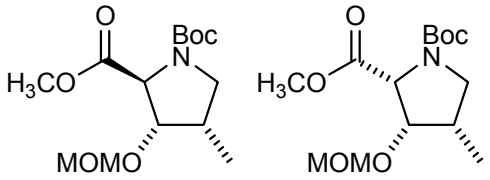
a pH value of 3–4 was obtained. The mixture was extracted with EtOAc (5 × 35 mL) and dried ($MgSO_4$). After concentration, the acid **97a** (296 mg, 91 %) was obtained as a colourless oil, which was directly converted into the corresponding ester.

FLi 274

The aldehyde **96b** (328 mg, 1.21 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (3.0 mL). Then a solution of $NaClO_2$ (173 mg, 1.82 mmol) and NaH_2PO_4 (218 mg, 1.82 mmol) in water (1.5 mL) was added within 8 min. After stirring for 90 min, the same amount of $NaClO_2$ and NaH_2PO_4 was added. The mixture was stirred for further another hour, then NaOH (2.0 mL, 4 M) was added. After removal of the solvent in vacuo (40 °C/60 mbar), the residue, a white powder, was dissolved in water (8.5 mL), 6 M HCl was added until a pH value of 3–4 was obtained. The mixture was extracted with EtOAc (5 × 35 mL) and dried ($MgSO_4$). After concentration, the acid **97b** (321 mg, 92 %) was obtained as a colourless oil, which was directly converted into the corresponding ester.

Experiment 86 (FLi 272, FLi 275)

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline methyl ester (**98a**) and (2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-methoxy-methoxy-4-methylproline methyl ester (**98b**)



98a **98b**

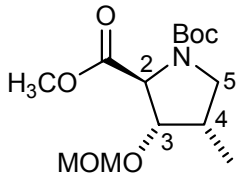
FLi 272

The acid **97a** (296 mg) was treated with a solution of ethereal CH_2N_2 (excess). After 10 min the solvent was evaporated and the residue was purified by flash chromatography on silica gel (8 g, column 4 cm x 2 cm, petroleum ether/EtOAc 3 : 1) to afford the ester **98a** (283 mg, 91 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 48.5 (*c* = 1.05, $CHCl_3$)

$C_{14}H_{25}NO_6$	calcd.	C	55.43	H	8.31	N	4.62
(303.4)	found	C	55.14	H	8.26	N	4.62

IR (neat): υ = 2974 (w), 1750 (m, C=O), 1697 (s, C=O), 1447 (w), 1455 (w), 1396 (s), 1365 (s), 1343 (w), 1255 (s), 1199 (s), 1173 (s), 1148 (s), 1066 (w), 1030 (vs), 953 (w), 936 (w), 919 (m), 890 (m), 860 (w) cm^{-1}.



98a

^{1}H NMR (C_5D_5N, 500.1 MHz): δ = 0.98/1.03 (2 d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.50/1.53 [2 s, 9 H, OC(CH_3)$_3$], 2.16 (m, 1 H, 4-H), 3.30-3.36 (m, 4 H, 5-H_a, OCH_3), 3.69/3.79 (2 s, 3 H, $COOCH_3$), 3.71/3.83 (2 dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{4,5b}$ = 7.3 Hz, 1 H, 5-H_b), 4.45 (dd, $^3J_{3,4}$ = 7.3 Hz, $^3J_{2,3}$ = 5.4 Hz, 1 H, 3-H), 4.62/4.63, 4.68/4.69 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 4.71/4.82 (2 d, $^3J_{2,3}$ = 5.9 Hz, 1 H, 2-H).

^{13}C NMR (C_5D_5N, 125.8 MHz): δ = 11.6/11.7 (2 q, 4-CH_3), 28.3/28.4 [2 q, OC($\underline{C}H_3$)$_3$], 37.6/38.4 (2 d, C-4), 51.6/51.7 (2 t, C-5), 51.7/52.2 (2 q, COO$\underline{C}H_3$), 56.1 (q, OCH_3), 65.1/65.2 (2 d, C-2), 79.5/79.6 [2 s, O$\underline{C}$(CH_3)$_3$], 79.9/80.8 (d, C-3), 97.4/97.5 (2 t, OCH_2O), 153.8/154.5 [2 s, $\underline{C}$OOC(CH_3)$_3$], 169.7/170.3 (2 s, $\underline{C}$OOCH_3).

^{1}H NMR (C_5D_5N, 343 K, 500.1 MHz): δ = 1.02 (d, $^3J_{4,CH_3}$ = 6.3 Hz, 3 H, 4-CH_3), 1.51 [s, 9 H, OC(CH_3)$_3$], 2.18 (b, 1 H, 4-H), 3.29-3.34 (m, 4 H, 5-H_a, OCH_3), 3.67-3.73 (b, 4 H, 5-H_b, $COOCH_3$), 4.43 (“t”, $^3J_{2,3}$ = 5.7 Hz, $^3J_{3,4}$ = 5.8 Hz, 1 H, 3-H), 4.60, 4.67 (A, B of AB, ^2J = 6.5 Hz, 2 H, OCH_2O), 4.72 (d, $^3J_{2,3}$ = 5.9 Hz, 1 H, 2-H).

FLi 275

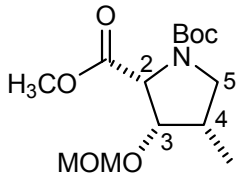
The acid **97b** (321 mg) was treated with a solution of ethereal CH_2N_2 (excess, a yellow solution). After 10 min the solvent was evaporated and the residue was purified by flash chromatography on silica gel (8 g, column 4 cm x 2 cm, petroleum ether/EtOAc 3 : 1) to afford the ester **98b** (312 mg, 93 %) as a colourless, analytically pure oil.

Data of **98b**

$[\alpha]_D^{20}$ = + 19.3 (*c* = 1.10, $CHCl_3$)

$C_{14}H_{25}NO_6$	calcd.	C	55.43	H	8.31	N	4.62
(303.4)	found	C	55.37	H	8.24	N	4.55

IR (neat): υ = 2974 (w), 1763 (m, C=O), 1696 (vs, C=O), 1436 (w), 1398 (vs), 1365 (s), 1287 (w), 1255 (m), 1151 (vs), 1117 (s), 1095 (m), 1071 (m), 1029 (vs), 920 (m), 899 (m), 867 (w) cm^{-1}.



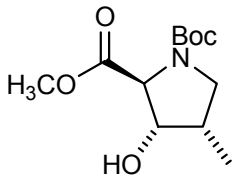
98b

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.09/1.11 (2 d, $^{3}J_{4,CH_3}$ = 6.8 Hz, 3 H, 4-CH_3), 1.40/1.46 [2 s, 9 H, $OC(CH_3)_3$], 2.26 (m, 1 H, 4-H), 3.21 (“t”, $^{2}J_{5a,5b}$ = 10.3, $J_{4,5a}$ = 10.3 Hz, 1 H, 5-H_a), 3.36 (s, 3 H, OCH_3), 3.64/3.69 (2 dd, $^{2}J_{5a,5b}$ = 10.2 Hz, $^{3}J_{4,5b}$ = 2.9 Hz, 1 H, 5-H_b), 3.75/3.76 (2 s, 3 H, $COOCH_3$), 4.38 (dd, $^{3}J_{3,4}$ = 9.7 Hz, $^{3}J_{2,3}$ = 4.6 Hz, 1 H, 3-H), 4.46/4.52 (d, $^{3}J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 4.52 4.59/4.60 (A, B of AB, ^{2}J =7.0 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.5 (q, 4-CH_3), 28.2/28.4 [2 q, $OC(\underline{C}H_3)_3$], 37.5/38.2 (2 d, C-4), 51.0/51.6 (2 t, C-5), 51.8/51.9 (2 q, $COO\underline{C}H_3$), 56.3 (q, OCH_3), 64.7/65.0 (2 d, C-2), 79.6/80.0 [2 s, $O\underline{C}(CH_3)_3$], 80.4 (d, C-3), 97.0/97.1 (2 t, OCH_2O), 153.6/154.3 [2 s, $\underline{C}OOC(CH_3)_3$], 169.2/169.9 (2 s, $\underline{C}OOCH_3$).

Experiment 87 (FLi 301)

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-methylproline methyl ester (**99**)



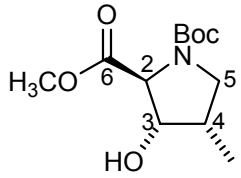
99

To a cold (-78 °C) stirred solution of the pyrrolidine **98a** (152 mg, 0.500 mmol) in dry CH_2Cl_2 (8 mL) was added dropwise a solution of Me_2BBr (2.1 M, 0.72 mL) in CH_2Cl_2. After 30 min at -78 °C, the reaction mixture was poured into a solution of THF (10 mL) and saturated aqueous $NaHCO_3$ (5 mL) with vigorous stirring. After stirring for 5 min the mixture was diluted with Et_2O (40 mL) and the organic layer was separated and washed sequentially with water (10 mL), $NaHSO_4$ (10 mL, 10 %), and brine (10 mL). The organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (5 g, column 3 cm × 1.5 cm, petroleum ether/EtOAc 2 : 1) to give the alcohol **99** (109 mg, 84 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 31.6 (*c* = 1.10, $CHCl_3$) $[\alpha]_D^{15}$ = - 23.4 (*c* = 0.80, $CHCl_3$)[170]

$C_{12}H_{21}NO_5$	calcd.	C	55.59	H	8.16	N	5.40
(259.3)	found	C	55.38	H	8.14	N	5.23

IR (neat): υ = 3427 (w), 2975 (w), 1746 (m, C=O), 1674 (s, C=O), 1398 (s), 1366 (s), 1248 (m), 1174 (s), 1148 (vs), 1081 (m), 991 (m), 889 (m), 858 (w), 770 (m) cm^{-1}.



99

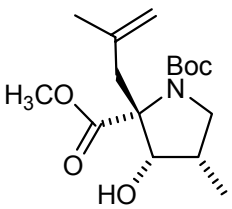
^{1}H NMR (C_6D_6, 500.1 MHz): δ = 0.95/1.02 (2 d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.52/1.54 [2 s, 9 H, OC(CH_3)$_3$], 2.27/2.34 (2 m, 1 H, 4-H), 3.33/3.40 (2 "t", $^2J_{5a,5b}$ = 10.2 Hz, $^3J_{4,5a}$ = 10.1 Hz, 1 H, 5-H_a), 3.51/3.54 (2 s, 3 H, OCH_3), 3.75/3.96 (dd, $^2J_{5a,5b}$ = 9.7 Hz, $^3J_{4,5a}$ = 8.0 Hz, 1 H, 5-H_b), 4.14/4.16 (2 d, $^3J_{2,3}$ = 4.2 Hz, 1 H, 2-H), 4.52/4.74 (2 s, 1 H, 3-H).

^{13}C NMR (C_6D_6, 125.8 MHz): δ = 10.8/10.9 (2 q, 4-CH_3), 28.4/28.5 [2 q, OC(<u>C</u>H_3)$_3$], 36.6/37.2 (2 d, C-4), 51.0/51.4 (2 q, OCH_3), 51.7/51.9 (2 d, C-5), 68.9/69.0 (2 d, C-2), 76.0/77.2 (2 d, C-3), 79.7/79.8 [2 s, O<u>C</u>(CH_3)$_3$], 154.2/155.0 [2 s, <u>C</u>OOC(CH_3)$_3$], 171.4/172.9 (s, C-6).

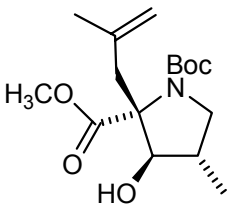
^{1}H NMR (C_6D_6, 343 K, 500.1 MHz): 0.93 (d, $^3J_{4,CH_3}$ = 6.4 Hz, 3 H, 4-CH_3), 1.56 [s, 9 H, OC(CH_3)$_3$], 2.04 (b, 1 H, 4-H), 2.28 (b, 1 H, OH), 3.27 ("t", $^3J_{5a,5b}$ = 9.5 Hz, $^3J_{4,5a}$ = 9.4 Hz, 1 H, 5-H), 3.56 (s, 3 H, OCH_3), 3.79 (b, 1 H, 5-H_b), 4.06 (d, $^3J_{2,3}$ = 4.1 Hz, 1 H, 2-H), 4.46 (b, 1 H, 3-H).

<u>Experiment 88 (FLi 318, FLi 320)</u>

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-2-(2'-methylallyl)-3-hydroxy-4-methylproline methyl ester (**100**) and (2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-2-(2'-methylallyl)-3-hydroxy-4-methylpyrrolidine methyl ester (**121**)



100



121

FLi 318

Similar to lit.[152], diisopropylamine (134 mg, 1.33 mmol) was dissolved in dry THF (3.5 mL) and cooled down to 0 °C. A solution of *n*-BuLi (525 mg, 1.22 mmol, 1.58 M in hexane) was added

dropwise. The solution was stirred for 40 min at 0 °C and then cooled to -50 °C. The ester **99** (98 mg, 0.38 mmol) in THF (1.5 mL) was added dropwise by means of syringe. The resulting mixture was stirred for 40 min at 0 °C and then cooled again to -50 °C. A solution of methallyl iodide (162 mg, 0.89 mmol) in HMPA (147 mg, 0.82 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for further 4.5 h before quenching with sat. aq. NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 × 18 mL), and the combined organic extracts were washed with brine (2 × 6 mL), dried ($MgSO_4$). The solvent was removed under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to afford the substituted pyrrolidine **100** (61 mg, 52 %) as colourless, analytically pure crystals and its epimer **121** as a colourless powder; the ratio of **100** and **121** was 52 : 48 according to the yield of products isolated).

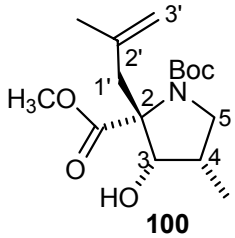
FLi 320

Diisopropylamine (126 mg, 1.25 mmol) was dissolved in dry THF (3.0 mL) and cooled down to 0 °C. A solution of *n*-BuLi (491 mg, 1.14 mmol, 1.58 M in hexane) was added dropwise. The solution was stirred for 40 min at 0 °C and then cooled to -50 °C. The ester **99** (93 mg, 0.36 mmol) in THF (1.5 mL) was added dropwise by means of syringe. The resulting mixture was stirred for 40 min at 0 °C and $MgCl_2$ (50 mg, 0.534 mmol) was added. The reaction mixture was stirred at 0 °C for additional 30 min, and then cooled again to -50 °C. A solution of methallyl iodide (162 mg, 0.89 mmol) in HMPA (147 mg, 0.82 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for further 4.5 h before being quenched with sat. aq. NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 × 16 mL), and the combined organic extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$). The solvent was removed under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to afford the substituted pyrrolidine **100** (64.5 mg, 58 %) as colourless, analytically pure crystals (*dr* = > 95 % from ^1H NMR); m. p. = 124-125 °C.

$[\alpha]_D^{20}$ = - 25.6 (*c* = 1.20, $CHCl_3$)

$C_{16}H_{27}NO_5$	calcd.	C	61.32	H	8.68	N	4.47
(313.4)	found	C	61.12	H	8.71	N	4.36

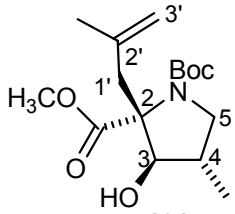
IR (solid): υ = 3386 (b, w, OH), 2976 (w), 1739 (s, C=O), 1660 (vs, C=O), 1403 (vs), 1365 (s), 1249 (s), 1159 (s), 1136 (s), 1068 (s), 1031 (m), 1001 (m), 922 (m), 863 (m), 780 (s) cm^{-1}.



100

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.00/1.01 (2 d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.43/1.45 [2 s, 9 H, C(CH_3)$_3$], 1.73 (s, 3 H, 2'-CH_3), 2.24 (m, 1 H, 4-H), 2.78/2.82, 3.00/3.24 (A, B of AB, ^2J = 13.8 Hz, 2 H, 1'-H), 3.15/3.19 (2 dd, $^2J_{5a,5b}$ = 11.2 Hz, $^3J_{4,5a}$ = 10.9 Hz, 1 H, 5-H_a), 3.61/3.67 (2 dd, $^2J_{5a,5b}$ = 10.5 Hz, $^3J_{4,5b}$ = 7.8 Hz, 1 H, 5-H_b), 3.72/3.75 (2 s, 3 H, OCH_3), 4.11 (d, $^3J_{3,4}$ = 9.5 Hz, 1 H, 3-H), 4.80/4.91 (2 b, 2 H, 3'-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 10.7 (q, 4-CH_3), 23.4/23.6 (2 q. 2'-CH_3), 28.4/28.5 [2 q, OCOC($\underline{C}H_3$)$_3$], 35.0/35.8 (2 d, C-4), 40.3/41.6 (2 t, C-1'), 52.2 (t, C-5), 52.3 (q, OCH_3), 74.6/74.9 (s, C-2), 79.7/80.3 [2 s, O$\underline{C}$(CH_3)$_3$], 79.6/81.0 (2 d, C-3), 116.0/116.4 (2 t, C-3'), 141.8/141.9 (2 s, C-2'), 153.6 [s, $\underline{C}$OOC(CH_3)$_3$], 172.3/172.5 (2 s, $\underline{C}$OOCH_3).



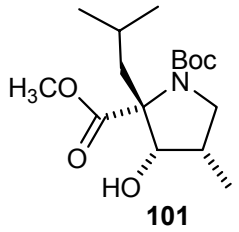
121

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.08/1.10 (2 d, $^3J_{4,CH_3}$ = 6.3 Hz, 3 H, 4-CH_3), 1.42/1.45 [2 s, 9 H, C(CH_3)$_3$], 1.78 (s, 3 H, 2'-CH_3), 2.12 (m, 1 H, 4-H), 2.81-3.06 (m, 3 H, 1'-H and 5-H_a), 3.56/3.62 (2 dd, $^2J_{5a,5b}$ = 10.7 Hz, $^3J_{4,5b}$ = 8.1 Hz, 1 H, 5-H_b), 3.72 (s, 3 H, OCH_3), 3.81 (b, 1 H, 3-H), 4.92/4.94 (2 b, 2 H, 3'-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.5 (q, 4-CH_3), 23.5/23.8 (2 q. 2'-CH_3), 28.4 [q, OCOC($\underline{C}H_3$)$_3$], 36.3/37.1 (2 t, C-1'), 37.6/38.5 (2 d, C-4), 50.3/50.9 (2 t, C-5), 52.3/52.4 (2 q, OCH_3),69.9/67.0 (2 s, C-2), 79.9/80.5 [2 s, O$\underline{C}$(CH_3)$_3$], 83.8/84.4 (2 d, C-3), 116.0/116.4 (2 t, C-3'), 144.0/144.5 (2 s, C-2'), 153.4 [s, $\underline{C}$OOC(CH_3)$_3$], 174.5 (2 s, $\underline{C}$OOCH_3).

Experiment 89 (FLi 326)

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methylproline methyl ester (**101**)



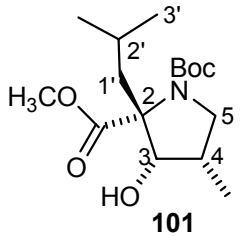
101

The olefin **100** (53 mg, 0.17 mmol) was dissolved in MeOH (2 mL) and hydrogenated (H_2, 4 bar) in the presence of Pt/C (12 mg, 10 %). After 3 h, the catalyst was filtered off and the filtrate was concentrated in vacuo (40 °C/300 mbar). The crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 3.5 : 1) to yield the isobutyl pyrrolidene **101** (53 mg, 100 %) as a colourless, analytically pure powder; m. p. = 104-105 °C.

$[\alpha]_D^{20}$ = + 28.8 (*c* = 1.20, $CHCl_3$)

$C_{16}H_{29}NO_5$	calcd.	C	60.92	H	9.27	N	4.44
(315.4)	found	C	60.73	H	9.18	N	4.45

IR (neat): υ = 3449 (b, w, OH), 2955 (w), 1739 (m, C=O), 1671 (s, C=O), 1391 (vs), 1364 (s), 1248 (s), 1164 (vs), 1115 (m), 1084 (m), 1034 (m), 995 (m), 928 (w), 866(w) cm^{-1}.



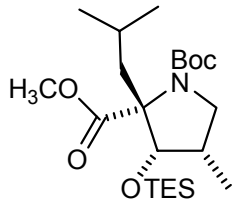
101

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.90/0.91 (2 d, $^3J_{2',CH_3}$ = 6.5 Hz, 3 H, 2'-CH_3), 0.95/0.96 (2 d, $^3J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 1.05/1.07 (2 d, $^3J_{4,CH_3}$ = 6.8 Hz, 3 H, 4-CH_3), 1.41/1.44 [2 s, 9 H, $C(CH_3)_3$], 1.69 (m, 1 H, 2'-H), 1.97-2.08 (m, 1 H, 1'-H_a), 2.29 (dd, $^2J_{1'a,1'b}$ = 14.7 Hz, $^3J_{1'b,2'}$ = 7.6 Hz, 1 H, 1'-H_b), 2.34 (m, 1 H, 4-H), 2.46 (b, 1 H, OH), 3.21/3.27 (2 "t", $^2J_{5a,5b}$ = 10.9 Hz, $^3J_{4,5a}$ = 10.9 Hz, 1 H, 5-H_a), 3.60-3.76 (m, 4 H, 5-H_b, OCH_3), 4.05/4.12 (2 d, $^3J_{3,4}$ = 5.3 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.0 (q, 4-CH_3), 22.9/23.3 (2 q. 2'-CH_3), 24.1/24.3 (2 q, C-3'), 25.6/25.6 (2 d, C-2'), 28.3/28.4 [2 q, OC($\underline{C}H_3)_3$], 35.6/36.3 (2 d, C-4), 41.5/42.4 (2 t, C-1'), 52.0/52.2 (2 q, OCH_3), 52.5 (t, C-5), 75.2/75.3 (2 s, C-2), 79.5/79.8 [2 s, O$\underline{C}(CH_3)_3$], 80.1/80.3 (2 d, C-3), 153.8/153.9 [2 s, $\underline{C}OOC(CH_3)_3$], 172.6/173.0 (2 s, $\underline{C}OOCH_3$).

Experiment 90 (FLi 328)

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-2-isobutyl-3-triethylsilyloxy-4-methylproline methyl ester (**102**)



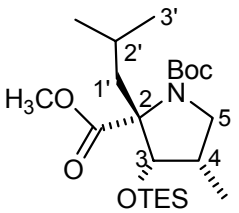
102

According to lit.[12,95], DMAP (12.5 mg, 0.08 mmol), imidazole (53 mg, 0.80 mmol) and TESCl (74 mg, 97 %, 0.48 mmol) were added to a stirred solution of alcohol **101** (50 mg, 0.159 mmol) in distilled CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 22 h and then poured into water (3.5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 3.0 mL), dried ($MgSO_4$). After concentration in vacuo (30 °C/500 mbar), the crude product was purified by flash chromatography on silica gel (4 g, column 4 cm × 1 cm, petroleum ether/EtOAc 12 : 1) to afford the TES protected alcohol **102** (68 mg, 100 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 3.8 (*c* = 1.0, $CHCl_3$)

$C_{22}H_{43}NO_5Si$	calcd.	C	61.50	H	10.09	N	3.26
(429.7)	found	C	61.46	H	10.12	N	3.25

IR (neat): υ = 2954 (m), 2876 (m), 1743 (C=O, m), 1701 (vs, C=O), 1456 (w), 1391 (s), 1365 (s), 1244 (m), 1165 (s), 1138 (m), 1110 (m), 1087 (s), 1044 (m), 1004 (s), 865 (w), 811 (w), 729 (vs), 691 (m) cm^{-1}.



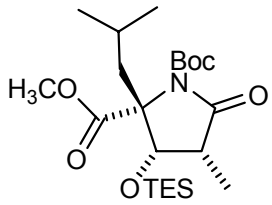
102

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.49/0.58 [2 q, ^3J = 8.0 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.88-0.99 [m, 15 H, $Si(CH_2CH_3)_3$, 2'-CH_3, 3'-H], 1.01/1.04 (2 d, $^3J_{4,CH_3}$ = 7.0 Hz, 3 H, 4-CH_3), 1.40/1.43 [2 s, 9 H, $OCOC(CH_3)_3$], 1.60 (m, 1 H, 2'-H), 1.97/1.99 (2 dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'a,2'}$ = 3.5 Hz, 1 H, 1'-H_a), 2.14/2.24 (2 dd, $^2J_{1'a,1'b}$ = 14.8 Hz, $^3J_{1'b,2'}$ = 8.1 Hz, 1 H, 1'-H_b), 2.25 (m, 1 H, 4-H), 3.29/3.55 (2 dd, $^2J_{5a,5b}$ = 10.3 Hz, $^3J_{4,5a}$ = 9.0 Hz, 1 H, 5-H_a), 3.44/3.56 (2 dd, $^2J_{5a,5b}$ = 10.7 Hz, $^3J_{4,5b}$ = 7.2 Hz, 1 H, 5-H_b), 3.65 (s, 3 H, OCH_3), 4.24/4.32 (2 d, $^3J_{3,4}$ = 6.5 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 4.8/4.9 [2 t, Si(<u>C</u>$H_2CH_3)_3$], 6.7/6.8 [2 q, Si(CH_2<u>C</u>$H_3)_3$], 12.2/12.5 (2 q, 4-CH_3), 22.9/23.5, 24.0/24.1 (4 q, 8-CH_3, C-3'), 25.7 (d, C-2'), 28.3/28.4 [2 q, OCOC(<u>C</u>$H_3)_3$], 36.0/36.8 (2 d, C-4), 41.2/42.3 (2 t, C-1'), 51.4/51.5 (2 q, OCH_3), 53.1/53.3 (2 t, C-5), 74.1/75.2 (2 s, C-2), 79.3/79.9 [2 s, O<u>C</u>$(CH_3)_3$], 80.4/81.5 (2 d, C-3), 153.8/154.0 [2 s, <u>C</u>OOC$(CH_3)_3$], 172.5 (s, <u>C</u>OOCH_3).

<u>Experiment 91 (FLi 329)</u>

(2*R*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-isobutyl-3-triethylsilyloxy-4-methyl-5-oxo-proline methyl ester (**103**)



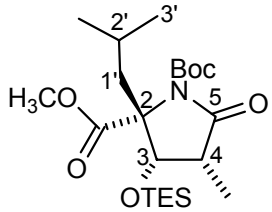
103

Following a procedure given by Donohoe *et al.*[12,95], the alcohol **102** (66 mg, 0.15 mmol) was added to a soultion of MeCN (3 mL), CCl_4 (3 mL), and water (4.5 mL), followed by addition of $NaIO_4$ (65 mg, 0.30 mmol) and $RuCl_3 \cdot 3H_2O$ (15.6 mg, 0.061 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to r. t.. After stirring for 12 h, the reaction mixture was filtered through a pad of celite and evaporated under reduced pressure (40 °C/40 mbar). The crude product was purified by flash chromatography on silical gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 8 : 1) to give the lactam **103** (56 mg, 84 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = - 22.4 (*c* = 1.20, $CHCl_3$)

$C_{22}H_{41}NO_6Si$	calcd.	C	59.56	H	9.31	N	3.16
(443.7)	found	C	59.60	H	9.21	N	3.20

IR (neat): υ = 2954 (m), 2877 (m), 1791 (s, C=O), 1751 (s, C=O), 1720 (s, C=O), 1457 (w), 1369 (w), 1300 (s), 1244 (s), 1147 (m), 1115 (m), 1089 (w), 1017 (w), 843 (w), 781 (w), 731 (w) cm^{-1}.



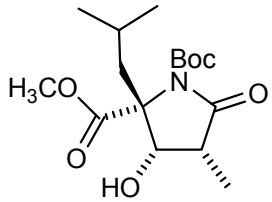
103

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.63 [q, ^3J = 7.7 Hz, 6 H, $OSi(CH_2CH_3)_3$], 0.91, (d, $^3J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 0.96 [t, ^3J = 7.7 Hz, 9 H, $OSi(CH_2CH_3)_3$], 0.99 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.25 (d, $^3J_{4,CH_3}$ = 7.6 Hz, 3 H, 4-CH_3), 1.48 [s, 9 H, $C(CH_3)_3$], 1.52 (m, 1 H, 2'-H), 1.99 (dd, $^3J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'a,2'}$ = 4.6 Hz, 1 H, 1'-H_a), 2.31 (dd, $^3J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'b,2'}$ = 7.3 Hz, 1 H, 1'-H_b), 2.71 (m, 1 H, 4-H), 3.67 (s, 3 H, OCH_3), 4.41 (d, $^3J_{3,4}$ = 9.1 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 4.7 [t, $Si(\underline{C}H_2CH_3)_3$], 6.7 [q, $Si(CH_2\underline{C}H_3)_3$], 11.2 (q, 4-$CH_3$), 23.8, 24.1 (2 q, 2'-$CH_3$, C-3'), 25.1 (d, C-2'), 27.9 [t, $OC(\underline{C}H_3)_3$], 41.2 (t, C-1'), 42.2 (d, C-4), 51.9 (q, OCH_3), 71.6 (s, C-2), 73.8 (d, C-3), 83.6 [s, $O\underline{C}(CH_3)_3$], 149.2 [s, $\underline{C}OOC(CH_3)_3$], 171.0 (s, C-5), 176.4 (s, $\underline{C}OOCH_3$).

Experiment 92 (FLi 332)

(2*R*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methyl-5-oxo-proline methyl ester (**104**)



104

Distilled pyridine (1.4 mL) and HF·pyridine solution (1.4 mL) were added to the lactam **103** (48 mg, 0.108 mmol) dissolved in distilled THF (5.5 mL), and the mixture was stirred for 15 min at 0°C before warming to r. t.. After 2 h, solid $NaHCO_3$ was added to the reaction mixture until pH 7 was reached. The reaction mixture was poured into water (1.5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to afford the hydroxy lactam **104** (32 mg, 90 %) as a colourless, analytically pure powder; m. p. = 113-114 °C.

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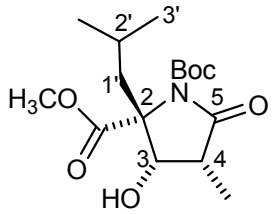
$[\alpha]_D^{20}$ = - 6.2 (*c* = 1.1, $CHCl_3$)

$C_{16}H_{27}NO_6$	calcd.	C	58.34	H	8.26	N	4.25
(329.4)	found	C	58.16	H	8.26	N	4.08

IR (neat): υ = 3409 (b, w, OH), 2951 (w), 1753 (m, C=O), 1726 (vs, C=O), 1456 (w), 1368 (m), 1295 (s), 1240 (vs), 1151 (vs), 1116 (m), 1085 (m), 1033 (m), 997 (m), 969 (m), 889 (w), 806 (w), 774 (m), 733 (w) cm^{-1}.



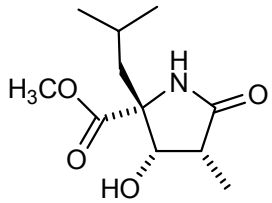
104

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.90, (d, $^3J_{2',3'}$ = 6.5 Hz, 3 H, 3'-H), 0.99 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.26 (d, $^3J_{4,CH_3}$ = 7.4 Hz, 3 H, 4-CH_3), 1.50 [s, 9 H, $C(CH_3)_3$], 1.61-1.71 (m, 2 H, 2'-H, OH), 2.15 (dd, $^3J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'a,7}$ = 4.3 Hz, 1 H, 1'-H_a), 2.24 (dd, $^3J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'b,2'}$ = 7.6 Hz, 1 H, 1'-H_b), 2.45 (d, $^3J_{3,OH}$ = 7.6 Hz, 1 H, OH), 2.81 (m, 1 H, 2-H), 3.75 (s, 3 H, OCH_3), 4.32 ("t", $^3J_{3,OH}$ = 7.3 Hz, $^3J_{3,4}$ = 7.2 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 9.2 (q, 4-CH_3), 23.5 (q, C-3'), 24.2 (q, 2'-CH_3), 25.4 (d, C-2'), 27.9 [q, OC($\underline{C}H_3)_3$], 41.9 (t, C-1'), 42.0 (d, C-4), 52.4 (q, OCH_3), 72.0 (d, C-3), 74.1 (s, C-2), 83.7 [s, O$\underline{C}(CH_3)_3$], 149.5 [s, $\underline{C}OOC(CH_3)_3$], 171.2 (s, C-5), 175.3 (s, $\underline{C}OOCH_3$).

Experiment 93 (FLi 334)

(2*R*,3*S*,4*R*)-3-Hydroxy-2-isobutyl-4-methyl-5-oxo-proline methyl ester (**105**)



105

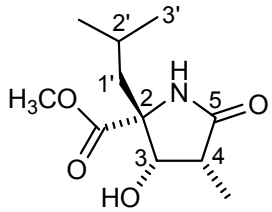
At 0 °C, CF_3COOH (0.4 mL) was added dropwise to the lactam **104** (38 mg, 0.117 mmol), dissolved in distilled CH_2Cl_2 (2 mL). The reaction mixture was stirred for 10 min and then warmed to r. t.. After stirring for 1 h, solid K_2CO_3 (890 mg) was added to the reaction mixture. After filtration and removal of the solvent, the lactam **105** (27 mg, 100 %) was obtained as a colourless, spectroscopically pure powder; m. p. = 124-125 °C.

$[\alpha]_D^{20}$ = + 13.2 (*c* = 1.10, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 230 (100) $[M + H]^+$, 170 (56).

HRMS (CI, pos.) $[M + H]^+$: calcd. for $C_{11}H_{20}NO_4$ 230.1390; found 230.1392.

IR (solid): υ = 3308 (b, m, OH), 2956 (m), 1723 (vs, C=O)), 1682 (vs, C=O), 1449 (m), 1385 (m), 1350 (m), 1307 (m), 1238 (s), 1173 (s), 1137 (s), 1115 (m), 1056 (m), 1034 (w), 1000 (m), 963 (m), 945 (m), 911 (w), 813 (m), 788 (m), 754 (w), 736 (m) cm^{-1}.

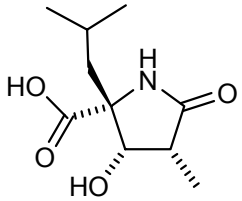


105

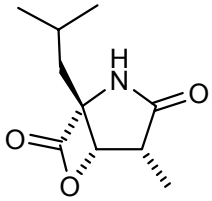
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.88 (d, $^{3}J_{2',CH_3}$ = 6.6 Hz, 3 H, 2'-CH_3), 0.97 (d, $^{3}J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H), 1.20 (d, $^{3}J_{4,CH_3}$ = 6.7 Hz, 3 H, 4-CH_3), 1.52 (dd, $^{2}J_{1'a,1'b}$ = 13.7 Hz, $^{3}J_{1'a,2'}$ = 5.0 Hz, 1 H, 1'-H_a), 1.75 (m, 1 H, 2'-H), 2.02 (dd, $^{2}J_{1'a,1'b}$ = 13.7 Hz, $^{3}J_{1'b,2'}$ = 8.7 Hz, 1 H, 1'-H_b), 2.69 (m, 1 H, 4-H), 3.81 (s, 3 H, OCH_3), 4.06 (d, $^{3}J_{3,4}$ = 5.0 Hz, 1 H, 3-H), 5.30 (b, 1 H, OH), 7.27 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 7.5 (q, 4-CH_3), 21.7, 23.9 (2 q, 2'-CH_3, C-3'), 24.9 (d, C-2'), 40.0 (d, C-4), 43.3 (t, C-1'), 52.7 (q, OCH_3), 72.1 (s, C-2), 78.8 (d, C-3), 174.3 (s, C-5), 178.1 (s, $\underline{C}OOCH_3$).

Experiment 94 (FLi 335, FLi 336)
(2*R*,3*S*,4*R*)-3-Hydroxy-2-isobutyl-4-methyl-5-oxo-proline (**106**) and
(2*R*,3*S*,5*R*)-1'-Deoxy-omuralide (**107**)



106



107

a) Hydrolysis of the ester lactam **105**

Cold (0 °C) aqueous NaOH (1.6 mL, 0.5 M) was added to the lactam **105** (24 mg, 0.11 mmol) and left in the fridge for one week at 4 °C. Aqueous HCl (1.0 M) was then added dropwise to the reaction mixture till a pH of 1 was obtained, and the mixture was concentrated in vacuo (40 °C/40 mbar). Hot THF (10 mL) was added to the residue and the insoluble inorganic salt was filtered. The filtrate was concentrated in vacuo (40 °C/300 mbar) to afford the carboxylic acid **106** (21 mg, 94 %) as a colourless oil which was directly used for the next lactonisation without purification.

b) Lactonisation of the 3-hydroxy acid **106**

A suspension of the acid **106** (21 mg, 0.098 mmol) in CH_2Cl_2 (2.0 mL) was treated with Et_3N (30 mg, 0.294 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (38 mg, 0.147 mmol) at ambient temperature. After stirring for 3 h at r. t., water (2 mL) was added to the reaction

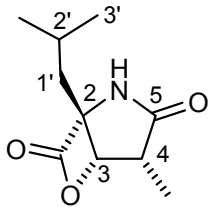
mixture and extracted with EtOAc (4 × 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo (40 °C/200 mbar). The residue, a colouress oil, was purified by flash chromatography on silical gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 1 : 1) to give the deoxy lactacystin β-lactone **107** (14.6 mg, 88 %) as colourless, analytically pure crystals; m. p. = 141-142 °C. Part of these was recrystallized to obtain a sample suitable for crystal structure determination, m. p. = 142 °C.

The data was collected before recrystallization

$[\alpha]_D^{20}$ = - 56.2 (*c* = 0.60, $CHCl_3$)

$C_{10}H_{15}NO_3$	calcd.	C	60.90	H	7.67	N	7.10
(197.2)	found	C	60.64	H	7.66	N	6.86

IR (solid): υ = 3081 (w), 2958 (w), 1830 (vs, C=O of β-lactone), 1706 (s, C=O of γ-lactam), 1463 (m), 1423 (w), 1384 (m), 1370 (m), 1356 (m), 1324 (m), 1293 (w), 1254 (w), 1196 (w), 1144 (w), 1125 (m), 1103 (w), 1070 (m), 1026 (m), 987 (w), 945 (m), 899 (m), 851 (s), 769 (m), 687 (w), 655 (m) cm^{-1}.



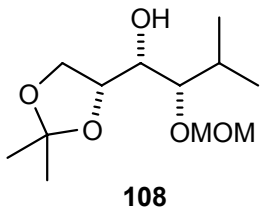
107

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.94 (d, $^3J_{2',CH_3}$ = 6.3 Hz, 3 H, 2'-CH_3), 1.03 (d, $^3J_{2',3'}$ = 6.4 Hz, 3 H, 3'-H), 1.33 (d, $^3J_{4,CH_3}$ = 7.5 Hz, 3 H, 4-CH_3), 1.80 (dd, $^2J_{1'a,1'b}$ = 13.4 Hz, $^3J_{1'a,2'}$ = 7.9 Hz, 1 H, 1'-H_a), 1.84 (m, 1 H, 2'-H), 1.99 (dd, $^2J_{1'a,1'b}$ = 13.5 Hz, $^3J_{1'b,2'}$ = 4.5 Hz, 1 H, 1'-H_b), 2.76 (m, 1 H, 4-H), 4.95 (d, $^3J_{3,4}$ = 6.1 Hz, 1 H, 3-H), 6.72 (b, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 8.1 (q, 4-CH_3), 22.8, 23.5 (2 q, 2'-CH_3, C-3'), 24.2 (d, C-2'), 37.6 (t, C-1'), 38.7 (d, C-4), 75.0 (s, C-2), 78.6 (d, C-3), 169.7 (s, C-5), 176.6 (<u>C</u>$OOCH_3$).

<u>Experiment 95 (FLi 276)</u>

(2*R*,3*R*,4*S*)-1,2-*O*-Isopropylidene-4-*O*-methoxymethyl-5-methylhexane-1,2,3,4-tetraol (**108**)



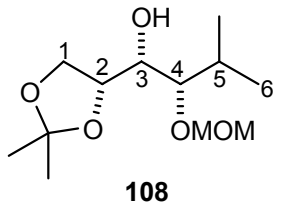
108

The olefin **88** (492 mg, 2.0 mmol) was dissolved in EtOAc (12 mL) and hydrogenated under normal pressure in the presence of Pd/C (40 mg, 10 %). After stirring for 1 h, the reaction mixture was filtered through celite. After evaporation of solvent, the crude product was purified by flash chromatography on silca gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to afford the saturated alcohol **108** (446 mg, 90 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 31.8 (*c* = 1.25, $CHCl_3$)

$C_{12}H_{24}O_5$	calcd.	C	58.04	H	9.74
(248.3)	found	C	58.12	H	9.67

IR (neat): υ = 3489 (b, OH), 2961 (w), 1468 (w), 1369 (w), 1251 (w), 1212 (m), 1148 (m), 1093 (m), 1060 (s), 1027 (vs), 979 (w), 918 (m), 856 (m), 796 (w), 713 (w) cm^{-1}.



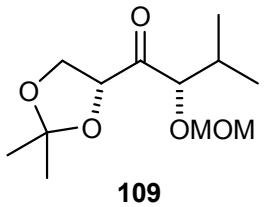
108

^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.94 (s, $^3J_{5,CH_3}$ = 6.9 Hz, 3 H, 5-CH_3), 1.00 (d, $^3J_{5,6}$ = 6.8 Hz, 3 H, 6-H), 1.37, 1.44 [2 s, 6 H, $C(CH_3)_2$], 2.03 (m, 1 H, 5-H), 3.00 (b, 1 H, OH), 3.24 ("t", $^3J_{2,3}$ = 4.6 Hz, $^3J_{3,4}$ = 4.0 Hz, 1 H, 3-H), 3.43 (s, 3 H, OCH_3), 3.58 ("t", $^3J_{3,4}$ = 4.0 Hz, $^3J_{4,5}$ = 4.0 Hz, 1 H, 4-H), 3.87 (dd, $^2J_{1a,1b}$ = 7.6 Hz, $^3J_{1a,2}$ = 7.4 Hz, 1 H, 1-H_a), 4.05 (dd, $^2J_{1a,1b}$ = 7.9 Hz, $^3J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.18 (m, 1 H, 2-H), 4.66, 4.75 (A, B of AB, ^2J = 6.8 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ= 17.5, 19.5 (2 q, 5-CH_3, C-6), 25.5, 26.5 [2 q, $C(\underline{C}H_3)_2$], 29.9 (d, C-5), 56.1 (q, OCH_3), 66.0 (t, C-1), 71.0 (d, C-2), 76.7 (d, C-3), 85.2 (d, C-4), 98.3 (t, OCH_2O), 109.4 [s, $\underline{C}(CH_3)_2$].

Experiment 96 (FLi 279)

(2*R*,4*S*)-1,2-*O*-Isopropylidenedioxy-4-methoxy-methoxy-5-methylhexan-3-one (**109**)



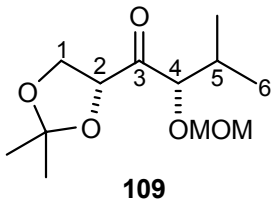
109

To a solution of pyridine (3.16 g, 40.0 mmol) in CH_2Cl_2 (100 mL) was added CrO_3 (2.0 g, 20 mmol) in portions over the course of 10 min. The resulting mixture was stirred for 1 h at room temperature. The solution of the alcohol **108** (496 mg, 2.00 mmol) in CH_2Cl_2 (4 mL) was added, and the mixture was stirred at r. t. for 6 h. The solution was washed with saturated $NaHCO_3$ (2 × 20 mL), followed washed with H_2O (2 × 20 mL), 4 M HCl (2 × 10 mL). The combined organic extract was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 6 : 1) to give the ketone **109** (423 mg, 86 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 79.2 (*c* = 1.50, $CHCl_3$)

$C_{12}H_{22}O_5$	calcd.	C	58.52	H	9.00
(246.3)	found	C	58.59	H	8.95

IR (neat): υ = 2965 (w), 2892 (w), 1726 (m, C=O), 1461 (w), 1373 (m), 1259 (w), 1215 (m), 1150 (m), 1082 (s), 1039 (vs), 983 (m), 920 (m), 842 (m), 792 (w), 741 (w), 679 (w) cm^{-1}.



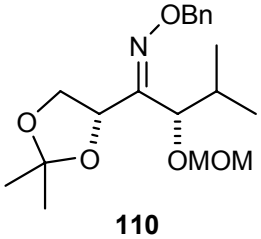
109

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.91 (d, $^3J_{5,CH_3}$ = 6.9 Hz, 3 H, 5-CH_3), 1.06 (d, $^3J_{5,6}$ = 6.9 Hz, 3 H, 6-H), 1.41, 1.47 [2 s, 6 H, $C(CH_3)_2$], 2.25 (m, 1 H, 5-H), 3.36 (s, 3 H, OCH_3), 4.07 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1a,2}$ = 6.0 Hz, 1 H, 1-H_a), 4.23 (dd, $^2J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 7.6 Hz, 1 H, 1-H_b), 4.56 (dd, $^3J_{1b,2}$ = 7.6 Hz, $^3J_{1a,2}$ = 6.0 Hz, 1 H, 2-H), 4.57, 4.62 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.6, 19.5 (2 q, 5-CH_3, C-6), 25.3, 25.8 [2 q, C($\underline{C}H_3$)$_2$], 30.1 (d, C-5), 57.0 (q, OCH_3), 66.6 (t, C-1), 79.0 (d, C-2), 83.9 (d, C-4), 96.9 (t, OCH_2O), 111.0 [s, $\underline{C}(CH_3)_2$], 209.6 (s, C-3).

Experiment 97 (FLi 281)

(*E*) or (*Z*)-(2*R*,4*S*)-3-Benzyloxyimino-1,2-*O*-isopropylidene-4-methoxymethyl-5-methylhexane-1,2,4-triol (**110**)



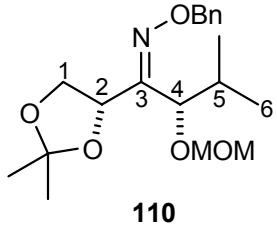
110

To a solution of the ketone **109** (492 mg, 2.0 mmol) and *O*-benzylhydroxylamine hydrochloride (335 mg, 2.1 mmol) in MeOH (15 mL) was added pyridine (166 mg, 2.1 mmol). The resulting mixture was refluxed for 40 min. After removal of methanol under reduced pressure (40 °C/300 mbar), water (5.0 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (15 g, column 5 cm × 3 cm, petroleum ether/EtOAc 10 : 1) to afford the oxime ether **110** (631 mg, 90 %) as a colourless, analytically pure oil (a single diastereoisomer).

$[\alpha]_D^{20}$ = + 28.1 (*c* = 1.70, $CHCl_3$)

$C_{19}H_{29}NO_5$	calcd.	C	64.94	H	8.32	N	3.98
(351.4)	found	C	64.88	H	8.41	N	3.78

IR (neat): υ =2963 (w), 2933 (w), 2883 (w), 1496 (w), 1455 (w), 1371 (m), 1257 (w), 1211 (m), 1153 (m), 1134 (w), 1092 (m), 1037 (s), 977 (m), 919 (m), 859 (m), 732 (m), 697 (m) cm^{-1}.



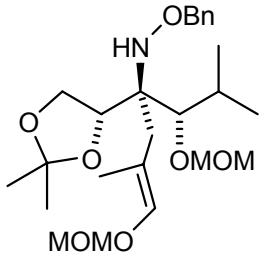
110

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.93 (d, $^3J_{5,CH_3}$ = 6.8 Hz, 3 H, 5-CH_3), 1.00 (d, $^3J_{5,6}$ = 6.7 Hz, 3 H, 6-H), 1.34, 1.45 [2 s, 6 H, $C(CH_3)_2$], 2.19 (m, 1 H, 5-H), 3.31 (s, 3 H, OCH_3), 3.73 (dd, $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1a,2}$ = 7.7 Hz, 1 H, 1-H_a), 4.12 (d, $^3J_{4,5}$ = 6.7 Hz, 1 H, 4-H), 4.40 (dd, $^2J_{1a,1b}$ = 8.4 Hz, $^3J_{1b,2}$ = 7.4 Hz, 1 H, 1-H_b), 4.57, 4.60 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 4.99 ("t", $^3J_{1a,2}$ = 7.5 Hz, $^3J_{1b,2}$ = 7.4 Hz, 1 H, 2-H), 5.12 (s, 2 H, OCH_2Ph), 7.26-7.31 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.9, 19.4 (2 q, 5-CH_3, C-6), 24.9, 25.8 [2 q, $C(\underline{C}H_3)_2$], 31.6 (d, C-5), 55.7 (q, OCH_3), 68.3 (t, C-1), 72.6 (t, OCH_2Ph), 76.6 (d, C-2), 79.8 (d, C-4), 95.6 (t, OCH_2O), 109.4 [s, $\underline{C}(CH_3)_2$], 127.9, 128.2, 128.3 (3 d, C_6H_5), 137.5 (s, *i*-C of $\underline{C}_6H_5$), 156.0 (s, C-3).

Experiment 98 (FLi 282)

(*E*)-(2*S*,3*R*,1'*S*)-3-Benzyloxylamino-1,2,-*O*-isopropylidene--3-(1'-methoxymethoxy-2'-methylpropyl)-6-methoxy-methoxy-5-methylhex-5-ene-1,2-diol (**111**)



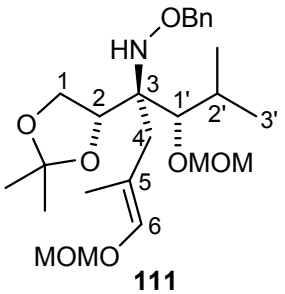
111
(major isomer)

To a stirred solution of 3-(methoxymethoxy)-2-methylprop-1-ene (269 mg, 2.40 mmol) in THF (6 mL) was added *sec*-BuLi (1.18 g, 1.74 mL, 2.25 mmol, 1.3 M in cyclohexane) at -78 °C. The resulting mixture was stirred for an additional 30 min. The oxime ether **110** (567 mg, 1.50 mmol) was added in THF (2.5 mL). The resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched with sat. aq. NH_4Cl (2.0 mL) and extracted with Et_2O (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue, a light-yellowish oil, was purified by flash chromatography on silica gel (12 g, column 5 cm × 2.5 cm, petroleum ether/EtOAc 10 : 1) to give the enol ether **111** (589 mg, 86 %) as a colourless, analytically pure oil; *dr* = 91 : 9.

$[\alpha]_D^{20}$ = + 52.9 (*c* = 1.32, $CHCl_3$)

$C_{25}H_{41}NO_7$	calcd.	C	64.22	H	8.84	N	3.00
(467.6)	found	C	64.43	H	8.80	N	2.90

IR (neat): υ = 2931 (b, w), 1678 (w), 1454 (w), 1367 (w), 1211 (w), 1152 (m), 1136 (m), 1042 (s), 1028 (vs), 978 (m), 920 (m), 864 (m), 749 (w), 698 (m) cm^{-1}.



111

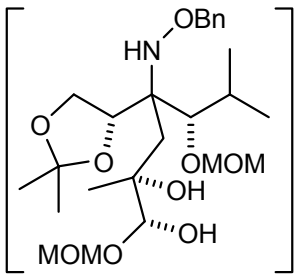
^1H NMR ($CDCl_3$, 300.1 MHz): δ = 0.96 (d, $^3J_{2',CH_3}$ = 6.7 Hz, 3 H, 2'-CH_3), 1.02 (d, $^3J_{2',3'}$ = 7.1 Hz, 3 H, 3'-H), 1.32, 1.38 [2 s, 6 H, $C(CH_3)_2$], 1.70 (d, $^4J_{6,5CH_3}$ = 0.5 Hz, 3 H, 6-CH_3), 2.32 (m, 1 H,

2'-H), 2.51, 2.67 (A, B of AB, ^2J = 14.3 Hz, 2 H, 4-H), 3.34, 3.37 (2 s, 6 H, 2 OCH_3), 3.56 ("s", 1 H, 1'-H), 3.98 (dd, $^2J_{1a,1b}$ = 6.3 Hz, $^3J_{1a,2}$ = 8.2 Hz, 1 H, 1-H_a), 4.08 (dd, $^3J_{1a,2}$ = 8.4 Hz, $^3J_{1b,2}$ = 8.5 Hz, 1 H, 2-H), 4.18 (dd, $^2J_{1a,1b}$ = 6.3 Hz, $^3J_{1b,2}$ = 8.5 Hz, 1 H, 1-H_b), 4.59-4.71 (m, 6 H, 2 OCH_2O, OCH_2Ph), 5.96 (b, 1 H, NH), 6.17 (s, 1 H, 6-H), 7.26-7.32 (m, 5 H, C_6H_5).

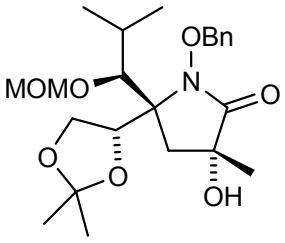
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 17.8 (q, 2'-CH_3), 20.1 (q, 5-CH_3), 24.1 (q, C-3'), 25.6, 26.4 [2 q, C($\underline{C}H_3)_2$], 27.5 (d, C-2'), 28.3 (t, C-4), 55.6, 56.1 (2 q, 2 OCH_3), 66.6 (t, C-1), 67.1 (s, C-3), 75.7 (t, OCH_2Ph), 78.0 (d, C-2), 86.5 (d, C-1'), 96.1, 99.2 (2 t, 2 OCH_2O), 107.6 [s, $\underline{C}(CH_3)_2$], 112.8 (s, C-5), 127.6, 128.2, 128.3 (3 d, C_6H_5), 137.9 (s, *i*-C of $\underline{C}_6H_5$), 139.9 (d, C-6).

Experiment 99 (FLi 284, FLi 285)

(1*R*,2*R*,4*S*,5*S*,1'*S*)-4-Benzyloxyamino-5,6-*O*-isopropylidene-1-methoxymethoxy-4-(1'-methoxymethoxy-2'-methylpropyl)-2-methylhexane-1,2,5,6-tetraol (**112**) and (3*R*,5*S*,1'*S*,1''*S*)-1-Benzyloxy-3-hydroxy-5-(1'',2''-isopropylidenedioxyethyl)-5-(1'-methoxymethoxy-2'-methylpropyl)-3-methylpyrrolidine-2-one (**113**)



112



113

a) Dihydroxylation of the enol ether **111** (FLi 284)

Following a procedure given by Sharpless *et al.*[40], a 50-mL round-bottom flask, equipped with a magnetic stirrer, was charged with *t*-BuOH/H_2O (12 mL, 1 : 1). To the mixture were added $K_3[Fe(CN)_6]$ (1.16 mg, 3.53 mmol), K_2CO_3 (487 mg, 3.53 mmol), $K_2OsO_2(OH)_4$ (11 mg, 0.029 mmol), and $(DHQD)_2PHAL$ (54 mg, 0.07 mmol) at r. t. The mixture was stirred for 10 min at the same temperature, followed by addition of $CH_3SO_2NH_2$ (112 mg, 1.17 mmol), then the olefin **111** (550 mg, 1.17 mmol) was added at 0 °C. The temperature was allowed to rise to r. t.. After stirring for 9 h, the reaction was treated with Na_2SO_3 (1.54 g, 14.0 mmol) at 0 °C and stirred for 1 h. Water (7 mL) was then added and the mixture was extracted with EtOAc (4 × 45 mL). The organic phases were combined and dried ($MgSO_4$). After evaporation under reduced pressure (40 °C/220 mbar), the hemiacetal **112** (469 mg, 80 %) was obtained as a light-yellow oil which was used directly in the next step without further purification.

b) Oxidation of the hemiacetal **112** (FLi285)

According to a lit. procedure[139b], to a solution of the hemiacetal **112** in MeOH/H_2O (30 mL, 10 : 1) were added I_2 (2.60 g, 10.6 mmol) and $CaCO_3$ (235 mg, 2.35 mmol). The reaction mixture was stirred for 22 h at r. t.. Water (10 mL) and solid $Na_2S_2O_3$ were added until a colourless solution was obtained. The reaction mixture was extracted with EtOAc (3 × 50 mL). The organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 1.5 : 1) to afford the lactam **113** (156 mg, 38 %) as a colourless, spectroscopically pure oil; *dr* = 90 : 10 from ^{1}H NMR.

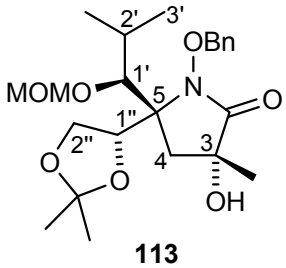
$[\alpha]_D^{20}$ = + 48.7 (*c* = 1.50, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 438 $[M + H]^+$ (100), 320 (40), 234 (24), 91 (40).

HRMS (CI, pos.): $[M + H]^+$ calcd for $C_{23}H_{36}NO_7$: 438.2492; found 438.2464.

$C_{23}H_{35}NO_7$	calcd.	C	63.14	H	8.06	N	3.20
(437.5)	found	C	61.53	H	7.96	N	3.35

IR (neat): υ = 3456 (w, b, OH), 2976 (w), 1712 (m), 1454 (w), 1372 (m), 1264 (w), 1209 (m), 1153 (m), 1027 (vs), 917 (m), 855 (m), 732 (s), 699 (m), 677 (w), 646 (w) cm^{-1}.



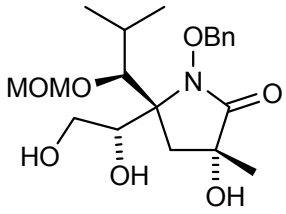
113

^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 0.95 (d, $^3J_{2',CH_3}$ = 6.9 Hz, 3 H, 2'-CH_3), 1.01 (d, $^3J_{2',3'}$ = 7.0 Hz, 3 H, 3'-H), 1.40, 1.43 [2 s, 6 H, $C(CH_3)_2$], 1.55 (s, 3 H, 3-CH_3), 1.94 (m, 1 H, 2'-H), 2.08, 2.40 (A, B of AB, ^2J = 15.0 Hz, 2 H, 4-H), 3.39 (s, 3 H, OCH_3), 3.59 (d, $^3J_{1',2'}$ = 2.2 Hz, 1 H, 1'-H), 4.12 (dd, $^2J_{2''a,2''b}$ = 8.6 Hz, $^3J_{1'',2''a}$ = 7.8 Hz, 1 H, 2''-H_a), 4.19 (b, 1 H, OH), 4.40 (dd, $^2J_{2''a,2''b}$ = 8.8 Hz, $^3J_{1',2''b}$ = 6.9 Hz, 1 H, 2''-H_b), 4.54 (dd, $^3J_{1'',2''a}$ = 7.3 Hz, $^3J_{1',2''b}$ = 7.2 Hz, 1 H, 1''-H), 4.61 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 5.21, 5.41 (A, B of AB, ^2J = 9.2 Hz, 2 H, OCH_2Ph), 7.34-7.44 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.1 (q, 3-CH_3), 23.6, 24.0 (2 q, 2'-CH_3, C-3'), 24.5, 25.9 [2 q, $C(CH_3)_2$], 28.4 (d, C-2'), 40.2 (t, C-4), 56.4 (q, OCH_3), 64.7 (t, C-2''), 67.0 (s, C-5), 69.4 (s, C-3), 76.3 (t, OCH_2Ph), 78.2 (d, C-1''), 83.7 (d, C-1'), 98.8 (t, OCH_2O), 109.7 [s, $C(CH_3)_2$], 128.5, 128.6, 128.9 (3 d, C_6H_5), 134.9 (s, *i*-C of C_6H_5), 172.3 (s, C-2).

Experiment 100 (FLi 286)

(3*R*,5*S*,1'*S*,1''*S*)-1-Benzyloxy-5-(1'',2''-dihydroxyethyl)-3-hydroxy-5-(1'-methoxymethoxy-2'-methylpropyl)-3-methyl-pyrrolidin-2-one (**114**)



114

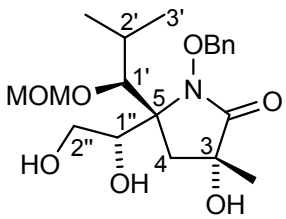
Following a lit. procedure[140], to a solution of the acetonide **113** (100 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) at r. t. was added $FeCl_3 \cdot 6\ H_2O$ (249 mg, 0.92 mmol). The resulting yellow to amber coloured suspension was stirred for 30 min and the reaction was quenched by addition of sat. aq. $NaHCO_3$ (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organics were washed with brine (2 × 12 mL), dried ($MgSO_4$). After concentration, the resulting oil was purified by flash chromatography on silical gel (4.5 g, column 3 cm × 1.5 cm, CH_2Cl_2/MeOH 10 : 1) to afford the diol **114** (69 mg, 76 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = + 59.2 (*c* = 1.20, $CHCl_3$)

MS (CI, pos.): *m/z* (%) = 398 $[M + H]^+$ (100), 366 (44), 336 (46), 91 (72).

HRMS (CI, pos.) $[M + H]^+$: calcd for $C_{20}H_{32}NO_7$: 398.2179; found 398.2160.

IR (neat): υ = 3375 (w, b, OH), 2964 (w), 1689 (s, C=O), 1453 (w), 1370 (w), 1214 (m), 1147 (m), 1082 (m), 1025 (vs), 909 (m), 868 (w), 835 (w), 735 (s), 697 (s), 607 (m) cm^{-1}.



114

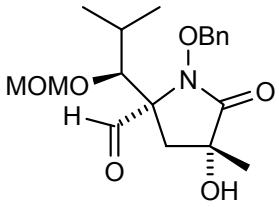
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.00 (d, $^3J_{2',CH_3}$ = 6.9 Hz, 3 H, 2'-CH_3), 1.06 (d, $^3J_{2',3'}$ = 7.1 Hz, 3 H, 3'-H), 1.43 (s, 3 H, 3-CH_3), 1.91 (m, 1 H, 2'-H), 2.16, 2.32 (A, B of AB, ^2J = 15.1 Hz, 2 H,

4-H), 3.39 (s, 3 H, OCH_3), 3.78 (d, $^3J_{1',2'}$ = 2.0 Hz, 1 H, 1'-H), 3.86 (dd, $^2J_{2''a,2''b}$ = 11.8 Hz, $^3J_{1'',2'''}$ = 7.6 Hz, 1 H, 2''-H_a), 3.95 (dd, $^2J_{2''a,2''b}$ = 11.9 Hz, $^3J_{1'',2''b}$ = 3.0 Hz, 1 H, 2''-H_b), 4.08 (dd, $J_{1'',2''a}$ = 7.3 Hz, $^3J_{1'',2''b}$ = 3.0 Hz, 1 H, 1''-H), 4.64, 4.68 (A, B of AB, ^2J = 6.6 Hz, 2 H, OCH_2O), 5.18, 5.27 (A, B of AB, ^2J = 9.6 Hz, 2 H, OCH_2Ph), 7.27-7.33 (m, 5 H, C_6H_5).

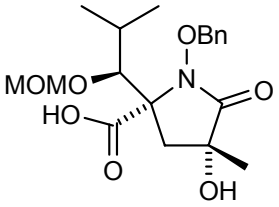
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.4 (q, 3-CH_3), 24.4, 24.5 (2 q, 2'-CH_3, C-3'), 28.1 (d, C-2'), 39.1 (t, C-4), 56.7 (q, OCH_3), 62.1 (t, C-2''), 69.2, (s, C-5), 69.7 (s, C-3), 74.8 (d, C-1''), 76.2 (t, OCH_2Ph), 82.6 (d, C-1'), 98.4 (t, OCH_2O), 128.5, 128.6, 128.7 (3 d, C_6H_5), 134.5 (s, *i*-C of $\underline{C}_6H_5$), 173.4 (s, C-2).

Experiment 101 (FLi 288, FLi 289)

(2*S*,4*R*,1'*S*)-1-Benzyloxy-2-formyl-4-hydroxy-2-(1'-methoxymethoxy-2'-methylpropyl)-4-methyl-5-oxo-pyrrolidine (**115**) and (2*S*,4*R*,1'*S*)-1-Benzyloxy-4-hydroxy-2-(1'-methoxymethoxy-2'-methylpropyl)-4-methyl-5-oxo-proline (**116**)



115



116

a) Cleavage of the diol **114** (FLi 288)

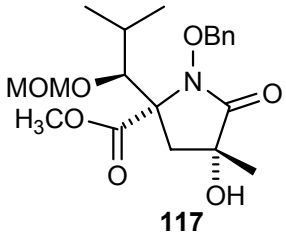
To a solution of the diol **114** (69 mg, 0.174 mmol) in MeOH/H_2O/THF (6 mL, 4 : 2 : 1) was added $NaIO_4$ (56 mg, 0.26 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (4 × 15 mL), and dried ($MgSO_4$). After removal of the solvent, the aldehyde **115** (61 mg, 96 %) was obtained as a colourless oil which was used directly in the next step.

b) Oxidation of the aldehyde **115** to the acid **116** (FLi 289)

The aldehyde **115** (61 mg) was dissolved in *t*-BuOH (3.0 mL) and 2-methyl-2-butene (1.5 mL). To the mixture was added a solution of $NaClO_2$ (24 mg, 0.26 mmol) and NaH_2PO_4 (32 mg, 0.26 mmol) in water (0.5 mL). After stirring for 90 min, a solution of NaOH (0.5 mL, 4 M) was added. After concentration under reduced pressure (40 °C/60 mbar), water (3.5 mL) was added. The pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 25 mL) and the solutes were dried ($MgSO_4$). After removal of the solvent, the carboxylic acid **116** (56 mg, 93 %) was obtained as a colourless oil, which was directly converted into the corresponding ester.

Experiment 102 (FLi 290)

(2*S*,4*R*,1'*S*)-1-Benzyloxy-4-hydroxy-2-(1'-methoxymethoxy-2'-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**117**)



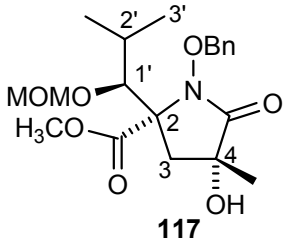
117

Without purification, the acid **116** (56 mg) was exposed to an excess of an ethereal CH_2N_2 (a yellow solution). After stirring for 10 min, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (3 g, column 3 cm × 1 cm, petroleum ether/EtOAc 1.5 : 1) to yield the ester **117** (55 mg, 90 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 50.4 (*c* = 1.10, $CHCl_3$)

$C_{20}H_{29}NO_7$	calcd.	C	60.75	H	7.39	N	3.54
(395.5)	found	C	60.52	H	7.46	N	3.42

IR (neat): υ = 3403 (w, b, OH), 2957 (w), 1730 (m, C=O of the ester), 1701 (s, C=O of the lactam), 1453 (w), 1371 (w), 1271 (m), 1215 (m), 1141 (s), 1082 (m), 1026 (vs), 981 (m), 955 (m), 921 (m), 875 (w), 835 (w), 749 (s), 698 (s) cm^{-1}.



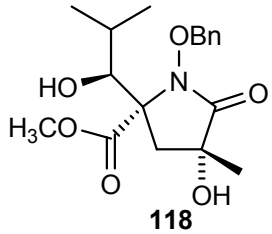
117

^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 0.93 (d, $^3J_{2',CH_3}$ = 6.9 Hz, 3 H, 2'-CH_3), 0.98 (d, $^3J_{2',3'}$ = 7.0 Hz, 3 H, 3'-H), 1.49 (s, 3 H, 4-CH_3), 1.95 (m, 1 H, 2'-H), 2.42, 2.55 (A, B of AB, ^2J = 14.7 Hz, 2 H, 3-H), 3.36 (s, 3 H, OCH_3), 3.80 (s, 3 H, $COOCH_3$), 4.06 (d, $^3J_{1',2'}$ = 3.8 Hz, 1 H, 1'-H), 4.65, 4.69 (A, B of AB, ^2J = 6.4 Hz, 2 H, OCH_2O), 5.01, 5.32 (A, B, of AB, ^2J = 9.4 Hz, 2 H, OCH_2Ph), 7.35-7.46 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 18.3 (q, 4-CH_3), 22.7, 24.2 (2 q, 2'-CH_3, C-3'), 29.1 (d, C-2'), 39.1 (t, C-3), 53.1 (q, OCH_3), 56.5 (q, $COO\underline{C}H_3$), 69.6 (s, C-2), 70.3 (s, C-4), 77.0 (t, OCH_2Ph), 83.9, (d, C-1'), 99.3 (t, OCH_2O), 128.4, 128.7, 129.2 (3 d, C_6H_5), 134.7 (s, *i*-C of $\underline{C}_6H_5$), 170.9 (s, C-5), 172.9 (s, $\underline{C}OOCH_3$).

Experiment 103 (FLi 294)

(2*S*,4*R*,1'*S*)-1-Benzyloxy-4-hydroxy-2-(1'-hydroxy-2'-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**118**)



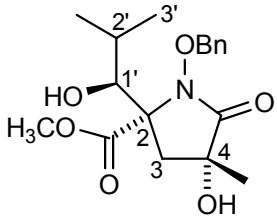
118

Acidic ion exchange resin (Dowex 50W, H^+ form, 60 mg) was added to a solution of the lactam **117** (60 mg, 0.152 mmol) in a mixture of MeOH (5.0 mL) and water (1.0 mL). The heterogeneous mixture was refluxed with stirring for 12 h. The resin was filtered off and washed with MeOH (2 × 6 mL). After concentration under reduced pressure (40 °C/300 mbar), the crude product obtained was purified by flash chromatography on silica gel (3 g, column 2 cm × 1.5 cm, petroleum ether/EtOAc 1 : 1) to afford the alcohol **118** (52 mg, 98 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 43.1 (*c* = 1.20, $CHCl_3$)

$C_{18}H_{25}NO_6$	calcd.	C	61.53	H	7.17	N	3.99
(351.4)	found	C	61.05	H	7.26	N	3.92

IR (neat): υ = 3398 (w, b, OH), 2957 (w), 1747 (m, C=O), 1697 (vs, C=O), 1454 (w), 1375 (m), 1274 (m), 1209 (m), 1136 (m), 1118 (m), 1069 (m), 1017 (s), 987 (m), 955 (m), 909 (w), 835 (w), 750 (s), 696 (s), 652 (w), 606 (m) cm^{-1}.



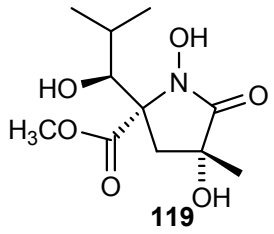
118

^1H NMR ($CDCl_3$. 300.1 MHz): δ = 0.92 (d, $^3J_{2',CH_3}$ = 7.3 Hz, 3 H, 2'-CH_3), 0.95 (d, $^3J_{2',3'}$ = 6.9 Hz, 3 H, 3'-H), 1.50 (s, 3 H, 4-CH_3), 1.99 (m, 1 H, 2'-H), 2.38, 2.44 (A, B of AB, ^2J = 14.2 Hz, 2 H, 3-H), 3.74 (d, $^3J_{6,7}$ = 6.6 Hz, 1 H, 1'-H), 3.80 (s, 3 H, OCH_3), 5.28, 5.42 (A, B of AB, ^2J = 9.3 Hz, 2 H, OCH_2Ph), 7.33-7.45 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.3 (q, 4-CH_3), 20.9, 24.6 (2 q, 2'-CH_3, C-3'), 31.3 (d, C-2'), 41.8 (t, C-3), 52.8 (q, OCH_3), 70.0 (s, C-2), 70.7 (s, C-4), 77.8 (t, OCH_2Ph), 78.9, (d, C-1'), 128.5, 128.8, 129.6 (3 d, C_6H_5), 134.7 (s, *i*-C of $\underline{C}_6H_5$), 171.7 (s, C-5), 172.6 (s, $\underline{C}OOCH_3$).

Experiment 104 (FLi 295)

(2*S*,4*R*,1'*S*)-1,4-Dihydroxy-2-(1'-hydroxy-2'-methylpropyl)-4-methyl-5-oxo-proline methyl ester (**119**)



119

A 250-mL flask was charged with the *N*-benzyloxy lactam **118** (48 mg, 0.14 mmol) and $Pd(OH)_2$/C (12 mg, 20 %) in MeOH (3 mL). The resulting mixture was hydrogenated (H_2, 3 bar) for 6 h at r. t.. The catalyst was filtered off and the filtrate was concentrated in vacuo (40 °C/300 mbar). The residue, a colourless oil, was purified by flash chromatography on silica gel (2 g SiO_2, column 2 cm × 1 cm, CH_2Cl_2/MeOH 7 : 1) to afford the *N*-hydroxy lactam **119** (34 mg, 96 %) as a colourless, analytically almost pure powder; m. p. = 132-134 °C.

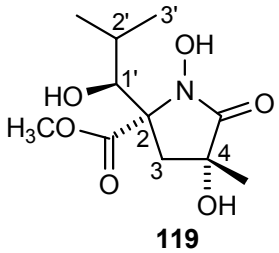
$[\alpha]_D^{20}$ = + 66.4 (*c* = 0.85, MeOH)

MS (CI, pos.): *m/z* (%) = 262 (100) $[M + H]^+$, 172 (36), 128 (20).

HRMS (CI, pos.): $[M + H]^+$ calcd for $C_{11}H_{20}NO_6$: 262.1291; found 262.1272.

$C_{11}H_{19}NO_6$	calcd.	C	50.56	H	7.32	N	5.36
(261.3)	found	C	49.92	H	7.45	N	4.98

IR (solid): υ = 3389 (b, OH), 3152 (b), 2960 (m), 1723 (s, C=O), 1679 (s, C=O), 1433 (m), 1384 (m), 1274 (m), 1222 (s), 1142 (m), 1121 (m), 1074 (s), 1054 (s), 1038 (m), 995 (m), 862 (w), 756 (m), 692 (s), 648 (m) cm^{-1}.



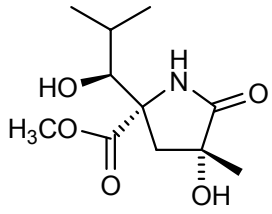
119

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.98 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 1.06 (d, $^3J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H), 1.44 (s, 3 H, 4-CH_3), 2.13 (m, 1 H, 2'-H), 2.33, 2.52 (A, B of AB, ^2J = 14.2 Hz, 2 H, 3-H), 3.76 (d, $^3J_{1',2'}$ = 7.0 Hz, 1 H, 1'-H), 3.82 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 19.8 (q, 4-CH_3), 20.8, 24.6 (2 q, 2'-CH_3, C-3'), 31.7 (d, C-2'), 41.3 (t, C-3), 53.0 (q, OCH_3), 70.6 (s, C-2), 71.2 (s, C-4), 78.3 (d, C-1'), 172.2 (s, C-5), 172.7 (s, $\underline{C}OOCH_3$).

Experiment 105 (FLi 296)

(2*S*,4*R*,1'*S*)-4-Hydroxy-2-(1'-hydroxy-2'-methylpropyl)
-4-methyl-5-oxo-proline methyl ester (**120**)



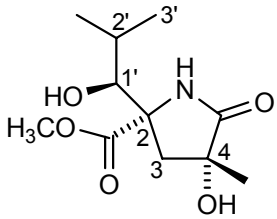
120

A 250-mL flask was charged with the *N*-benzyloxy lactam **118** (24 mg, 0.069 mmol) and Pt/C (12 mg, 10 %) in MeOH (2.0 mL). The resulting mixture was hydrogenated (H_2, 4 bar) at r. t. for 5.5 days. The catalyst was filtered through Celite. The filtrate was concentrated in vacuum (40 °C/300 mbar). The residue, a white powder, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, CH_2Cl_2/MeOH 10 : 1) to afford the lactam **120** (16.6 mg, 98 %) as a colourless, analytically pure powder; m. p. = 165 °C.

$[\alpha]_D^{20}$ = + 22.0 (*c* = 0.80, MeOH)

$C_{11}H_{19}NO_5$	calcd.	C	53.87	H	7.81	N	5.71
(245.3)	found	C	53.69	H	7.80	N	5.38

IR (solid): υ = 3338 (b, w, OH), 2967 (w), 1724 (m, C=O), 1690 (vs, C=O), 1433 (m), 1415 (m), 1374 (m), 1324 (m), 1262 (m), 1240 (s), 1131 (m), 1057 (m), 1017 (m), 963 (w), 920 (w), 758 (m), 738 (s), 701 (m) cm^{-1}.



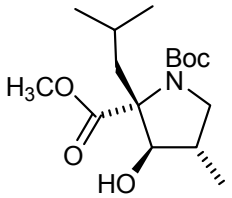
120

^{1}H NMR (CD_3OD, 300.1 MHz): δ = 0.90 (d, $^3J_{2',CH_3}$ = 6.8 Hz, 3 H, 2'-CH_3), 0.97 (d, $^3J_{2',3'}$ = 6.7 Hz, 3 H, 3'-H), 1.38 (s, 3 H, 4-CH_3), 1.70 (m, 1 H, 2'-H), 2.35, 2.50 (A, B of AB, ^2J = 14.1 Hz, 2 H, 3-H), 3.45 (d, $^3J_{6,7}$ = 6.5 Hz, 1 H, 1'-H), 3.73 (s, 3 H, OCH_3).

^{13}C NMR (CD_3OD, 75.5 MHz): δ = 19.3 (q, 4-CH_3), 21.0, 24.4 (2 q, 2'-CH_3, C-3'), 32.3 (d, C-2'), 46.2 (t, C-3), 52.9 (q, OCH_3), 68.0 (s, C-2), 74.5 (s, C-4), 79.9 (d, C-1'), 175.5 (s, C-5), 180.4 (s, $\underline{C}OOCH_3$).

Experiment 106 (FLi 310)

(2*S*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methylproline methyl ester (**122**)



122

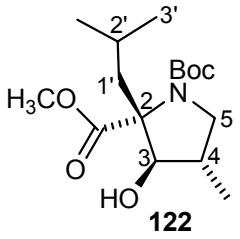
Following a procedure in lit.[152], diisopropylamine (85 mg, 0.84 mmol) was dissolved in dry THF (2.0 mL) and cooled down to 0 °C. A solution of *n*-BuLi (361 mg, 0.759 mmol, 1.58 M in hexane) was added dropwise. The solution was stirred for 30 min at 0 °C and then cooled to -50 °C. The ester **99** (62 mg, 0.24 mmol) in THF (1.0 mL) was added dropwise via syringe. The resulting mixture was stirred for 50 min at 0 °C and LiCl (16 mg, 0.376 mmol) was added. The reaction mixture was stirred at 0 °C for additional 30 min, and then cooled to -50 °C. A solution of 1-iodo-2-methylpropane (109 mg, 0.60 mmol) in HMPA (108 mg, 0.60 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for further 6 h before being quenched with sat. aq. NH_4Cl (1.5 mL). The mixture was extracted with EtOAc (3 × 12 mL), and the combined organic extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$). The solvent was removed under reduced pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (2.5 g, column 2.5 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to afford the isobutyl pyrrolidine **122** (42 mg, 57 %) as colourless, spectroscopically pure crystals (*dr* = 90 : 10 from ^{1}H NMR); m. p. = 102-103 °C.

$[\alpha]_D^{20}$ = + 12.1 (*c* = 1.20, $CHCl_3$)

MS (FAB, pos.): *m/z* (%) = 316 (52) $[M + H]^+$, 260 (56), 216 (100), 156 (28), 57 (56).

HRMS (FAB, pos.): $[M + H]^+$ calcd for $C_{16}H_{30}NO_5$: 316.2124; found 316.2110.

IR (solid): υ = 3393 (s, OH), 2951 (w), 2873 (w), 1741 (s, C=O), 1662 (vs, C=O), 1477 (w), 1459 (w), 1432 (m), 1408 (s), 1369 (s), 1337 (m), 1236 (m), 1160 (s), 1123 (m), 1102 (s), 1074 (m), 1017 (m), 971 (m), 910 (m), 879 (w), 825 (w), 775 (m), 687 (w) cm^{-1}.



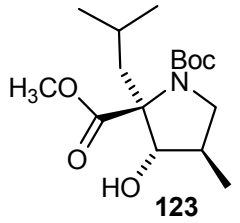
122

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.89 (d, $^{3}J_{2',CH_3}$ = 6.3 Hz, 3 H, 2'-CH_3), 0.95 (d, $^{3}J_{2',3'}$ = 6.4 Hz, 3 H, 3'-H), 1.11/1.14 (2 d, $^{3}J_{4,CH_3}$ = 6.3 Hz, 3 H, 4-CH_3), 1.41/1.43 [2 s, 9 H, $C(CH_3)_3$], 1.77-1.93 (m, 2.5 H, 1'-H_a, 2'-H and 1'-H_b), 2.09 (dd, $^{2}J_{1'a,1'b}$ = 14.4 Hz, $^{3}J_{1'b,2'}$ = 7.9 Hz, 0.5 H, 1'-H_b), 2.21 (m, 1 H, 4-H), 2.86/2.90 (b, 1 H, OH), 2.98/2.99 (2 "t", $^{2}J_{5a,5b}$ = 11.0 Hz, $^{3}J_{4,5a}$ = 11.0 Hz, 1 H, 5-H_a), 3.61/3.67 (2 dd, $^{2}J_{5a,5b}$ = 10.6 Hz, $^{3}J_{4,5b}$ = 8.2 Hz, 1 H, 5-H_b), 3.69/3.70 (2 s, 3 H, OCH_3), 3.81 (d, $^{3}J_{3,4}$ = 10.5 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.3/15.4 (2 q, 4-CH_3), 22.9/23.1 (2 q. 2'-CH_3), 24.5 (q, C-3'), 25.4/25.5 (2 d, C-2'), 28.3 [q, $OC(\underline{C}H_3)_3$], 37.6/38.1 (2 t, C-1'), 37.7/38.4 (d, C-4), 50.4/50.9 (2 t, C-5), 52.2/53.4 (2 q, OCH_3), 70.5 (s, C-2), 79.6/80.3 [2 s, $COO\underline{C}(CH_3)_3$], 82.9/83.5 (2 d, C-3), 153.8 [s, $\underline{C}OOC(CH_3)_3$], 175.3/175.5 (2 s, $\underline{C}OOCH_3$).

Experiment 107 (FLi 313)

(2*S*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methylproline methyl ester (**123**)



123

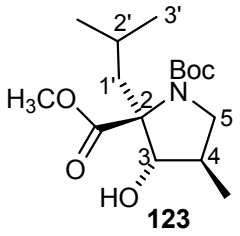
In analogy to lit.[152] diisopropylamine (71 mg, 0.70 mmol) was dissolved in dry THF (2.0 mL) and cooled down to 0 °C. A solution of *n*-BuLi (300 mg, 0.62 mmol, 1.58 M in hexane) was added dropwise. The solution was stirred for 30 min at 0 °C and then cooled to -50 °C. The ester **60** (52 mg, 0.20 mmol) in THF (1.0 mL) was added dropwise via syringe. The resulting mixture was stirred for 50 min at 0 °C and LiCl (14 mg, 0.31 mmol) was added. The reaction mixture was stirred at 0 °C for additional 30 min, and then cooled to -50 °C. A solution of 1-iodo-2-methylpropane (91 mg, 0.50 mmol) in HMPA (90 mg, 0.50 mmol) was introduced in one portion. The reaction was allowed to proceed at 0 °C for further 5 h before being quenched with sat. NH_4Cl (1.5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (2 × 5 mL), dried ($MgSO_4$). The solvent was removed under reduced

pressure (40 °C/220 mbar). The crude product was purified by flash chromatography on silica gel (2.0 g, column 2 cm × 1 cm, petroleum ether/EtOAc 3 : 1) to afford the isobutyl pyrrolidine**123** (28.5 mg, 46 %) as colourless, analytically pure crystals (*dr* = 90 : 10 from ^{1}H NMR); m. p. = 101-102 °C.

$[\alpha]_D^{20}$ = -11.6 (*c* = 1.50, $CHCl_3$)

$C_{16}H_{29}NO_5$	calcd.	C	60.92	H	9.27	N	4.44
(315.4)	found	C	60.64	H	9.23	N	4.46

IR (solid): υ = 3392 (w), 2952 (w), 2873 (w), 1741 (s, C=O), 1663 (vs, C=O), 1461 (w), 1408 (s), 1369 (s), 1337 (m), 1237 (m), 1218 (m), 1160 (s), 1103 (s), 1074 (m), 1017 (m), 972 (m), 910 (m), 879 (w), 861 (m) cm^{-1}.



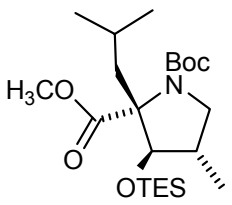
123

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.89 (d, $^3J_{2',CH_3}$ = 6.2 Hz, 3 H, 2'-CH_3), 0.95 (d, $^3J_{2',3'}$ = 6.4 Hz, 3 H, 3'-H), 1.12/1.14 (2 d, $^3J_{4,CH_3}$ = 6.4 Hz, 3 H, 4-CH_3), 1.41/1.43 [2 s, 9 H, $C(CH_3)_3$], 1.77-1.93 (m, 2.5 H, 1 H, 2'-H and 1'-H_a), 2.09 (dd, $^2J_{1'a,1'b}$ = 14.5 Hz, $^3J_{1'b,2'}$ = 8.0 Hz, 0.5 H, 1'-H_b), 2.21 (m, 1 H, 4-H), 2.85/2.90 (2 d, $^3J_{3,OH}$ = 5.9 Hz, 1 H, OH), 2.98/2.99 (2 "t", $^2J_{5a,5b}$ = 11.0 Hz, $^3J_{4,5a}$ = 11.0 Hz, 1 H, 5-H_a), 3.61/3.66 (2 dd, $^2J_{5a,5b}$ = 10.6 Hz, $^3J_{4,5b}$ = 8.2 Hz, 1 H, 5-H_b), 3.69/3.70 (2 s, 3 H, OCH_3), 3.81 (dd, $^3J_{3,4}$ = 10.3 Hz, $^3J_{3,OH}$ = 5.7 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.3/15.4 (2 q, 4-CH_3), 22.9/23.1 (2 q. 2'-CH_3), 24.5 (q, C-3'), 25.4/25.5 (2 d, C-2'), 28.3 [q, OC($\underline{C}H_3)_3$], 37.6/38.1 (2 t, C-1'), 37.7/38.4 (d, C-4), 50.4/50.9 (2 t, C-5), 52.2/53.4 (2 q, OCH_3), 70.5 (s, C-2), 79.6/80.3 [2 s, O$\underline{C}(CH_3)_3$], 82.9/83.5 (2 d, C-3), 153.8 [s, $\underline{C}OOC(CH_3)_3$], 175.3/175.5 (2 s, $\underline{C}OOCH_3$).

Experiment 108 (FLi 314)

(2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-2-isobutyl-3-triethylsilyloxy-4-methylproline methyl ester (**124**)



124

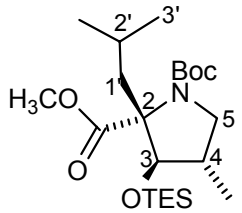
DMAP (6.7 mg, 0.043 mmol), imidazole (28 mg, 0.43 mmol) and Me_3SiCl (40 mg, 97%, 0.25 mmol) were added to a stirred solution of the alcohol **123** (27 mg, 0.085 mmol) in distilled CH_2Cl_2 (3 mL). The reaction mixture was stirred for 22 h, then poured into water (2 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product, a colourless oil, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, petroleum ether/EtOAc 12 : 1) to afford the protected lactam **124** (37 mg, 100 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = + 21.2 (*c* = 1.10, $CHCl_3$)

MS (FAB, pos.): *m/z* (%) = 430.3 (28) $[M + H]^+$, 344.2 (78), 330.2 (100), 314 (48).

HRMS (FAB, pos.): *m/z* $[M + H]^+$ calcd for $C_{22}H_{44}NO_5Si$: 430.2989; found 430.2975.

IR (neat): υ = 2955 (w), 2876 (w), 1743 (m, C=O), 1700 (s, C=O), 1456 (w), 1433 (w), 1392 (s), 1365 (s), 1228 (m), 1149 (s), 1107 (s), 1071 (w), 1017 (m), 975 (m), 916 (w), 884 (w), 830 (s), 802 (w), 778 (w), 726 (m) cm^{-1}.



124

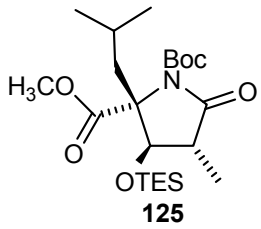
^1H NMR ($CDCl_3$, 300.1 MHz) δ = 0.57/0.58 [2 q, ^3J = 8.0 Hz, 6 H, $OSi(CH_2CH_3)_3$], 0.85-0.98 [m, 15 H, 2'-CH_3, 3'-H and $OSi(CH_2CH_3)_3$], 1.06/1.08 (2 d, $^3J_{4,CH_3}$ = 6.4 Hz, 3 H, 4-CH_3), 1.40/1.42 [2 s, 9 H, $C(CH_3)_3$], 1.80 (dd, $^2J_{1'a,1'b}$ = 14.2 Hz, $^3J_{1'a,2'}$ = 3.4 Hz, 1 H, 1'-H_a), 1.88 (m, 1 H, 2'-H), 2.04 (dd, $^2J_{1'a,1'b}$ = 14.2 Hz, $^3J_{1'b,2'}$ = 7.8 Hz, 1 H, 1'-H_b), 2.19 (m, 1 H, 4-H), 2.95/2.96 (2 "t", $^2J_{5a,5b}$ = 11.1 Hz, $^3J_{4,5a}$ = 11.0 Hz, 1 H, 5-H_a), 3.56/3.64 (2 dd, $^2J_{5a,5b}$ = 10.8 Hz, $^3J_{4,5b}$ = 8.3 Hz, 1 H, 5-H_b), 3.68/3.69 (2 s, 3 H, OCH_3), 3.87 (d, $^3J_{3,4}$ = 9.9 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 4.9/5.0 [2 t, $Si(\underline{C}H_2CH_3)_3$], 6.8 [q, $Si(CH_2\underline{C}H_3)_3$], 15.4/15.5 (2 q, 4-$CH_3$), 22.9/23.1, 24.3 (3 q, 2'-CH_3, C-3'), 25.3/25.5 (2 d, C-2'), 28.3/28.4 [2 t, $OC(\underline{C}H_3)_3$], 37.7/38.3 (2 t, C-1'), 38.5/39.1 (2 d, C-4), 50.2/50.7 (2 t, C-5), 51.9 (q, OCH_3), 70.7 (s, C-2),

79.5/80.2 [2 s, O<u>C</u>$(CH_3)_3$], 83.8/84.4 (2 d, C-3), 153.6/153.7 [2 s, O<u>C</u>OC$(CH_3)_3$], 175.0/175.2 (2 s, <u>C</u>OOCH$_3$).

<u>Experiment 109 (FLi 316)</u>

(2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-2-isobutyl-4-methyl-3-triethylsilyloxy-5-oxo-proline methyl ester (**125**)



125

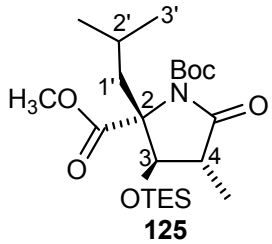
To a solution of MeCN (2 mL), CCl_4 (2 mL), and water (3 mL) were added the pyrrolidine **124** (42 mg, 0.098 mmol), followed by addition of $NaIO_4$ (42 mg, 0.19 mmol) and $RuCl_3 \cdot 3H_2O$ (9.8 mg, 0.039 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to r. t. for 14 h. The reaction mixture was filtered through a pad of Celite and evaporated under reduced pressure (40 °C/40 mbar). The crude product, a colourless oil, was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, petroleum ether/EtOAc 8 : 1) to give the lactam **125** (39 mg, 89 %) as a colourless, spectroscopically pure oil.

$[\alpha]_D^{20}$ = - 16.3 (*c* = 0.65, $CHCl_3$)

MS (FAB, pos.): *m/z* (%) = 444 (4) $[M + H]^+$, 366 (30), 344 (100), 314 (28).

HRMS (FAB, pos.): *m/z* $[M + H]^+$ calcd for $C_{22}H_{42}NO_6Si$: 444.2781; found 444.2794.

IR (neat): υ = 2958 (w), 2876 (w), 1749 (vs, C=O), 1714 (s, C=O), 1456 (w), 1367 (m), 1300 (vs), 1241 (m), 1143 (s), 1125 (s), 1107 (s), 1078 (m), 1018 (m), 977 (m), 834 (m), 807 (m), 787 (w), 746 (m), 726 (m) cm^{-1}.

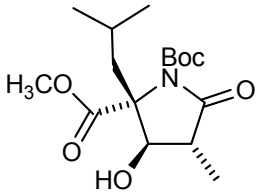


125

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.61 [q, ^3J = 8.0 Hz, 6 H, OSi$(CH_2CH_3)_3$], 0.86-0.99 [m, 15 H, 2'-CH_3, 3'-H and OSi$(CH_2CH_3)_3$], 1.28 (d, $^3J_{4,CH_3}$ = 7.0 Hz, 3 H, 4-CH_3), 1.48 [s, 9 H, OC$(CH_3)_3$], 1.84 (m, 1 H, 2'-H), 2.01 (dd, $^2J_{1'a,1'b}$ = 15.0 Hz, $^3J_{1'a,2'}$ = 8.4 Hz, 1 H, 1'-H_a), 2.15 (dd, $^2J_{1'a,1'b}$ = 15.1 Hz, $^3J_{1'b,2'}$ = 3.1 Hz, 1 H, 1'-H_b), 2.63 (m, 1 H, 4-H), 3.71 (s, 3 H, OCH_3), 4.06 (d, $^3J_{3,4}$ = 9.6 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 4.9 [t, Si(<u>C</u>$H_2$$CH_3$)$_3$], 6.7 [q, Si($CH_2$<u>C</u>$H_3$)$_3$], 14.1 (q, 4-$CH_3$), 23.4, 24.2 (2 q, 2'-$CH_3$, C-3'), 25.4 (d, C-2'), 27.9 [q, OC(<u>C</u>H_3)$_3$], 37.5 (t, C-1'), 45.6 (d, C-4), 52.4 (q, OCH_3), 70.9 (s, C-2), 78.5 (d, C-3), 83.7 [s, O<u>C</u>(CH_3)$_3$], 149.3 [s, <u>C</u>OOC(CH_3)$_3$], 173.0 (s, C-5), 173.3 (s, <u>C</u>OOCH_3).

Experiment 110 (FLi 317)
(2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-isobutyl-4-methyl-5-oxo-proline methyl ester (**126**)



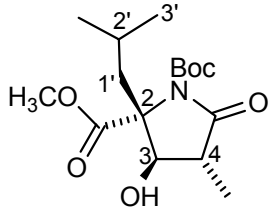
126

Distilled pyridine (1.0 mL) and HF·pyridine complex (1.0 mL) were added to the lactam **125** (36 mg, 0.81 mmol) dissolved in distilled THF (5 mL) and the mixture was stirred for 15 min at 0 °C before warming to r. t.. After stirring for another 2 h, $NaHCO_3$ was added to the reaction mixture till pH 7 was reached. The reaction mixture was poured into water (1.2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo (40 °C/300 mbar). The crude product was purified by flash chromatography on silica gel (2 g, column 2 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to afford the lactam **126** (24 mg, 88 %) as a colourless, analytically pure powder; m. p. = 127-128 °C.

$[\alpha]_D^{20}$ = -16.2 (*c* = 0.65, $CHCl_3$)

$C_{16}H_{27}NO_6$	calcd.	C	58.34	H	8.26	N	4.25
(329.4)	found	C	58.08	H	8.41	N	3.99

IR (solid): υ = 3456 (w, OH), 2951 (w), 1776 (s, C=O of ester), 1749 (s, C=O of lactam), 1698 (w, C=O of carbamate), 1455 (w), 1432 (w), 1371 (m), 1337 (m), 1287 (m), 1254 (s), 1234 (s), 1143 (vs), 1099 (s), 1070 (m), 1016 (m), 979 (m), 951 (m), 918 (w), 846 (m), 785 (m), 769 (m), 680 (m) cm^{-1}.



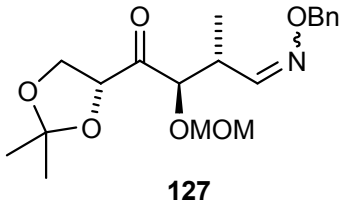
126

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 0.90 (d, $^3J_{2',3'}$ = 6.6 Hz, 3 H, 3'-H), 0.99 (d, $^3J_{2',CH_3}$ = 6.6 Hz, 3 H, 2'-CH_3), 1.31 (d, $^3J_{4,CH_3}$ = 6.9 Hz, 3 H, 4-CH_3), 1.49 [s, 9 H, $C(CH_3)_3$], 1.64 (b, 1 H, OH), 1.85 (m, 1 H, 2'-H), 2.08 (dd, $^3J_{1'a,1'b}$ = 15.2 Hz, $^3J_{1'a,2'}$ = 8.3 Hz, 1 H, 1'-H_a), 2.18 (dd, $^3J_{1'a,1'b}$ = 15.2 Hz, $^3J_{1'b,2'}$ = 3.4 Hz, 1 H, 1'-H_b), 2.54 (d, $^3J_{3,OH}$ = 5.5 Hz, 1 H, OH), 2.70 (m, 1 H, 4-H), 3.74 (s, 3 H, OCH_3), 4.04 (dd, $^3J_{3,4}$ = 10.0 Hz, $^3J_{3,OH}$ = 4.0 Hz, 1 H, 3-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.9 (q, 4-CH_3), 23.4 (q, C-3'), 24.3 (q, 2'-CH_3), 25.5 (d, C-2'), 27.9 [q, $OC(\underline{C}H_3)_3$], 37.3 (t, C-1'), 44.6 (d, C-4), 52.6 (q, OCH_3), 70.6 (s, C-2), 77.6 (d, C-3), 83.8 [s, $O\underline{C}(CH_3)_3$], 149.3 [s, $\underline{C}OOC(CH_3)_3$], 173.0 (s, C-5), 173.2 (s, $\underline{C}OOCH_3$).

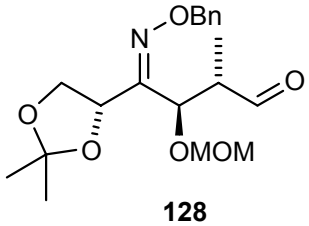
Experiment 111 (FLi 179)

(2*R*,4*R*,5*R*)-6-Benzyloxyimino-1,2-isopropylidenedioxy-4-methoxymethoxy-5-methylhexan-3-one (**127**) and



127

(2*S*,3*R*,5*R*)-4-Benzyloxyimino-5,6-isopropylidinedioxy-3-methoxymethoxy-2-methylhexanal (**128**)



128

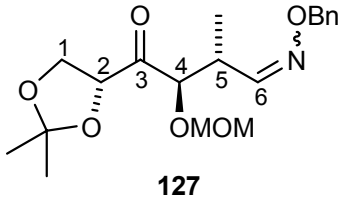
To a solution of pyridine (2.58 g, 32.0 mmol) in CH_2Cl_2 (50 mL) was added (1.6 g, 16 mmol) CrO_3 in portion within 15 min. The reaction mixture was stirred for 1 h at r. t., then the alcohol **52** (587 mg, 1.60 mmol) in CH_2Cl_2 (4 mL) was added, and the mixture was stirred for 30 min. The solution was washed sequentially with sat. aq. $NaHCO_3$ (2 × 15 mL), H_2O (2 × 15 mL) and 4 M HCl (2 × 10 mL). The organic phases were dried ($MgSO_4$) and concentrated. The crude product, a brown oil, was purified by flash chromatography on silica gel (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 6 : 1) to give the ketone oxime ether **127** (200 mg, 38 %) as a colourless, analytically pure oil (*Z*/*E* = 78 : 22 by ^{13}C NMR spectra) and the aldehyde **128** (237 mg, 45 %) as a colourless oil, which was directly used for the next step.

Data of **127**

$[\alpha]_D^{20}$ = + 25.1 (*c* = 1.40, $CHCl_3$)

$C_{16}H_{27}NO_6$	calcd.	C	58.34	H	8.26	N	4.25
(329.4)	found	C	58.08	H	8.41	N	3.99

IR (neat): υ = 2985 (w), 2935 (w), 1728 (m, C=O), 1455 (w), 1372 (m), 1260 (w), 1212 (m), 1148 (s), 1032 (vs), 979 (m), 920 (s), 846 (s), 735 (m), 698 (s) cm^{-1}.



127

Data of *Z* isomer from the diastereoisomer mixture

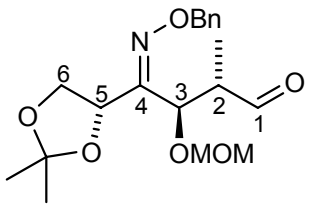
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.20 (d, $^3J_{5,CH_3}$ = 7.0 Hz, 3 H, 5-CH_3), 1.36, 1.47 [2 s, 6 H, $C(CH_3)_2$], 2.97 (m, 1 H, 5-H), 3.33 (s, 3 H, OCH_3), 3.92 (dd, $^3J_{1a,1b}$ = 8.8 Hz, $^3J_{1a,2}$ = 6.2 Hz, 1 H, 1-H_a), 4.08 (dd, $^3J_{1a,1b}$ = 8.6 Hz, $^3J_{1b,2}$ = 8.1 Hz, 1 H, 1-H_b), 4.45 (d, $^3J_{4,5}$ = 4.3 Hz, 1 H, 4-H), 4.59-4.67 (m, 3 H, 2-H, OCH_2O), 5.03 (s, 2 H, OCH_2Ph), 7.26-7.36 (m, 5 H, C_6H_5), 7.41 (d, $^3J_{5,6}$ = 7.4 Hz, 1 H, 6-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 15.6 (q, 2-CH_3), 25.1, 26.3 [2 q, C($\underline{C}H_3)_2$], 36.5 (d, C-2), 66.3 (t, C-6), 76.0 (t, OCH_2Ph), 79.3 (d, C-3), 82.3 (d, C-5), 97.5 (t, OCH_2O), 116.2 [q, $\underline{C}(CH_3)_2$], 128.1, 128.5, 128.7 (3 d, C_6H_5), 138.1 (s, *i*-C of $\underline{C}_6H_5$), 151.7 (d, C-1), 207.5 (s, C-4).

Data of E isomer from the diastereoisomer mixture

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.15 (d, $^3J_{2,CH_3}$ = 7.1 Hz, 3 H, 2-CH_3), 1.36, 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.34 (s, 3 H, OCH_3), 3.91 (dd, $^3J_{6a,6b}$ = 8.6 Hz, $^3J_{5,6a}$ = 6.0 Hz, 1 H, 6-H_a), 4.21 (dd, $^3J_{6a,6b}$ = 8.6 Hz, $^3J_{5,6b}$ = 8.1 Hz, 1 H, 6-H_b), 5.07 (s, 2 H, OCH_2Ph), 6.78 (d, $^3J_{1,2}$ = 7.2 Hz, 1 H, 1-H); some signals were not assigned due to overlap with those of Z isomer.

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.6 (q, 2-CH_3), 25.4, 26.2 [2 q, C($\underline{C}H_3)_2$], 32.6 (d, C-2), 66.4 (t, C-6), 76.3 (t, OCH_2Ph), 79.3 (d, C-3), 81.3 (d, C-5), 97.3 (t, OCH_2O), 111.2 [s, $\underline{C}(CH_3)_2$], 128.2, 128.5, 128.7 (3 d, C_6H_5), 138.1 (s, *i*-C of $\underline{C}_6H_5$), 151.7 (d, C-1), 207.1 (s, C-4); some signals were not assigned due to overlap with those of Z isomer.



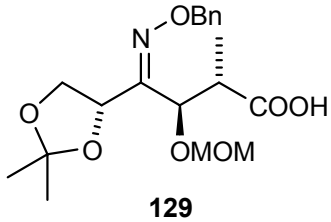
128

^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.03 (d, $^3J_{2,CH_3}$ = 7.2 Hz, 3 H, 2-CH_3), 1.33, 1.45 [2 s, 6 H, $C(CH_3)_2$], 3.07 (m, 1 H, 2-H), 3.31 (s, 3 H, OCH_3), 3.67 (dd, $^3J_{6a,6b}$ = 8.5 Hz, $^3J_{5,6a}$ = 6.9 Hz, 1 H, 6-H_a), 4.36 (dd, $^3J_{6a,6b}$ = 8.6 Hz, $^3J_{5,6b}$ = 8.4 Hz, 1 H, 6-H_b), 4.55, 4.62 (A, B of AB, ^2J = 6.9 Hz, 2 H, OCH_2O), 4.57 (d, $^3J_{2,3}$ = 7.8 Hz, 1 H, 3-H), 5.10-5.17 (m, 3 H, 5-H, OCH_2Ph), 7.29-7.37 (m, 5 H, C_6H_5), 9.76 (d, $^3J_{1,2}$ = 2.4 Hz, 1 H, 1-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.6 (q, 2-CH_3), 25.0, 26.2 [2 q, C($\underline{C}H_3)_2$], 48.8 (d, C-2), 56.4 (q, OCH_3), 68.8 (t, C-6), 72.5 (d, C-3), 76.7 (d, C-5), 77.3 (t, OCH_2Ph), 95.7 (t, OCH_2O), 110.1 [s, $\underline{C}(CH_3)_2$], 128.5, 128.6, 128.8 (3 d, C_6H_5), 137.6 (s, *i*-C of $\underline{C}_6H_5$), 158.4 (d, C-4), 203.9 (s, C-1).

Experiment 112 (FLi 181)

(2*S*,3*R*,5*S*)-4-Benzyloxyimino-5,6-isopropylidenedioxy-3-methoxymethoxy-2-methylhexanoic acid (**129**)

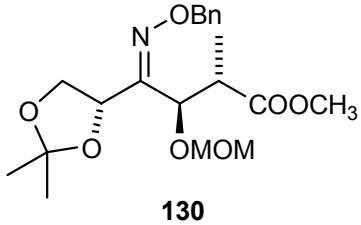


129

The aldehyde **128** (237 mg, 0.72 mmol) was dissolved in *t*-BuOH (5.0 mL) and 2-methyl-2-butene (2.5 mL). To the mixture was added a solution of $NaClO_2$ (97 mg, 1.08 mmol) and NaH_2PO_4 (130 mg, 1.08 mmol) in water (1 mL). After stirring for 90 min, NaOH solution (4 M, 1.0 mL) was added. The solvent was removed under reduced pressure (40 °C/60 mbar) and the resulting residue was dissolved in water (5.0 mL). The pH was adjusted to 3–4 by dropwise addition of 6 M HCl. The mixture was extracted with EtOAc (5 × 35 mL) and the solutes were dried ($MgSO_4$). After removal of the solvent, the carboxylic acid **129** (246 mg, 90 %) was obtained as a colourless oil, which was directly converted into the corresponding ester.

Experiment 113 (FLi 182)

Methyl (2*S*,3*R*,5*S*)-4-benzyloxyimino-5,6-*O*-isopropylidenedioxy-3-methoxymethoxy-2-methylhexanoate (**130**)



130

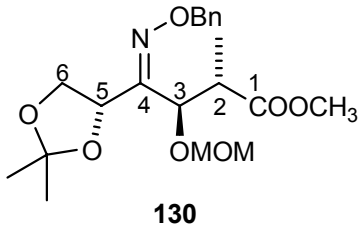
The hexanoic acid **129** (246 mg) was treated with an ethereal solution of CH_2N_2 (excess, a yellow solution). After 10 min, the solvent was removed and the crude product was purified by

flash chromatography on silica gel (10 g, column 4 cm × 2.5 cm, petroleum ether/EtOAc 5 : 1) to afford the ester **130** (205 mg, 80 %) as a colourless, analytically pure oil.

$[\alpha]_D^{20}$ = + 108 (*c* = 1.30, $CHCl_3$)

$C_{20}H_{29}NO_7$	calcd.	C	60.74	H	7.39	N	3.54
(395.5)	found	C	60.54	H	7.33	N	3.42

IR (neat): υ = 2986 (w), 2937 (w), 2886 (w), 1738 (s, C=O), 1455 (w), 1436 (w), 1371 (m), 1260 (w), 1212 (m), 1155 (s), 1140 (s), 1099 (m), 1058 (s), 1026 (vs), 920 (s), 853 (s), 736 (m), 698 (s) cm^{-1}.



130

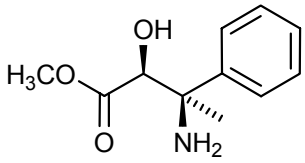
^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.04 (d, $^3J_{2,CH_3}$ = 7.1 Hz, 3 H, 2-CH_3), 1.34, 1.48 [2 s, 6 H, $C(CH_3)_2$], 2.69 (m, 1 H, 2-H), 3.27 (dd, $^3J_{6a,6b}$ = 8.5 Hz, $^3J_{5,6a}$ = 7.2 Hz, 1 H, 6-H_a), 3.28 (s, 3 H, OCH_3), 3.68 (s, 3 H, $COOCH_3$), 3.70 (dd, $^3J_{6a,6b}$ = 8.5 Hz, $^3J_{5,6b}$ = 6.9 Hz, 1 H, 6-H_b), 4.34 (dd, $^3J_{5,6a}$ = 8.4 Hz, $^3J_{5,6b}$ = 7.4 HZ, 1 H, 5-H), 4.54-4.60 (m, 3 H, 3-H, OCH_2O), 5.09, 5.14 (A, B of AB, ^2J = 10.6 Hz, 2 H, OCH_2Ph), 7.27-7.31 (m, 5 H, C_6H_5).

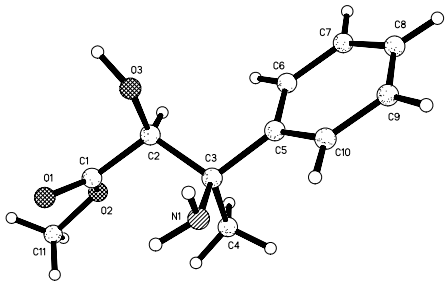
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.5 (q, 2-CH_3), 25.2, 26.2 [2 q, $C(\underline{C}H_3)_2$], 43.4 (d, C-2), 52.0 (q, OCH_3), 56.3 (q, $COO\underline{C}H_3$), 68.6 (t, C-6), 72.6 (d, C-3), 77.1 (t, OCH_2Ph), 78.1 (d, C-5), 95.8 (t, OCH_2O), 110.1 [q, $\underline{C}(CH_3)_2$], 128.4, 128.6, 128.8 (3 d, C_6H_5), 137.69 (s, *i*-C of $\underline{C}_6H_5$), 158.5 (d, C-4), 175.6 (s, C-1).

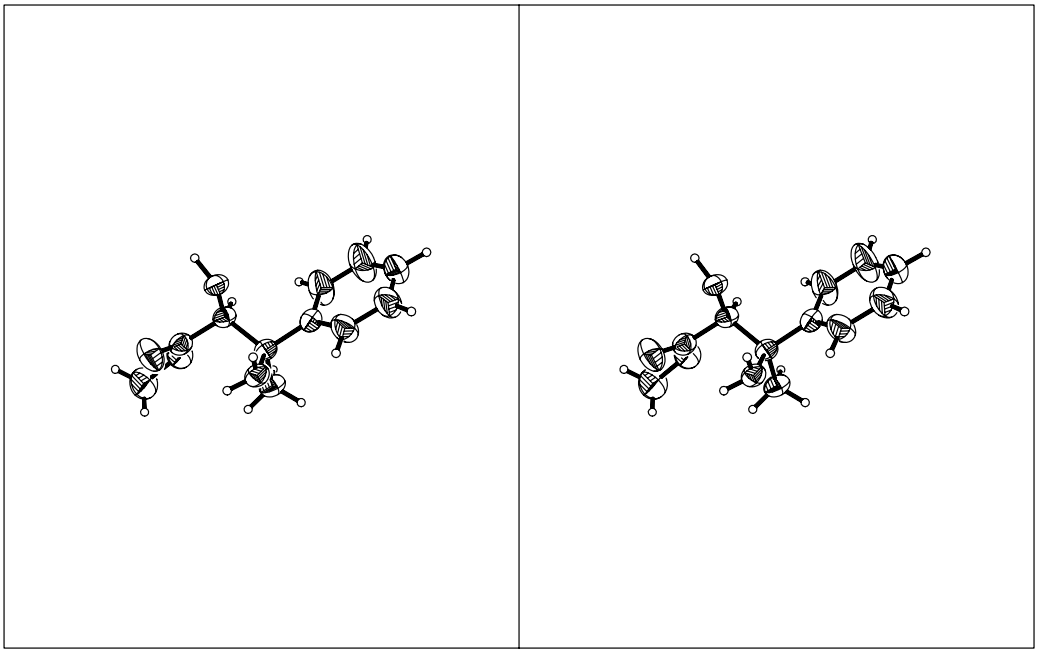
8. Crystal Structure Data

8.1 (2*S*,3*R*)-Phenylisothreonine methyl ester (36)

$C_{11}H_{15}NO_3$
Orthorhombic $P2_12_12_1$
a = 5.5816 (3) Å
b = 8.0072 (6) Å
c = 24.7417 (19) Å
V = 1105.78 (13) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0529
Rw*(F^2)* = 0.1457
Crystal size: 1.0 × 0.4 × 0.15 mm^3
Calculated density: 1.257 g/cm^3
2Θ-range for data collection: 3.57-67.97°
Independent reflections: 2020
Observed reflections: 1670
Contributed reflections to refinement: 1670
Refined parameters: 185







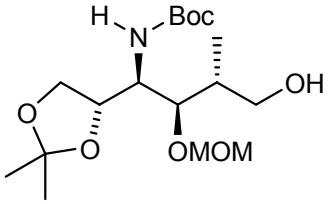
Bond lengths [A] and angles [deg]

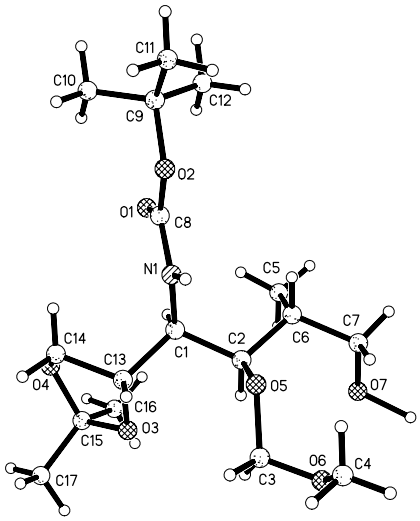
N(1)-C(3)	1.471(3)	C(3)-C(2)-H(2)	109.1(17)
N(1)-H(1A)	0.93(4)	C(2)-O(3)-H(3)	108.5(17)
N(1)-H(1B)	0.84(5)	N(1)-C(3)-C(4)	108.1(2)
C(1)-O(1)	1.202(3)	N(1)-C(3)-C(5)	109.3(2)
C(1)-O(2)	1.323(3)	C(4)-C(3)-C(5)	108.8(2)
C(1)-C(2)	1.520(4)	N(1)-C(3)-C(2)	111.3(2)
O(2)-C(11)	1.450(4)	C(4)-C(3)-C(2)	110.4(2)
C(2)-O(3)	1.404(3)	C(5)-C(3)-C(2)	108.9(2)
C(2)-C(3)	1.550(3)	C(3)-C(4)-H(4A)	112.2(18)
C(2)-H(2)	1.00(3)	C(3)-C(4)-H(4B)	111(2)
O(3)-H(3)	1.05(3)	H(4A)-C(4)-H(4B)	105(3)
C(3)-C(4)	1.529(4)	C(3)-C(4)-H(4C)	111(2)
C(3)-C(5)	1.540(4)	H(4A)-C(4)-H(4C)	110(3)
C(4)-H(4A)	0.98(4)	H(4B)-C(4)-H(4C)	108(3)
C(4)-H(4B)	0.98(4)	C(6)-C(5)-C(10)	117.2(3)
C(4)-H(4C)	1.05(4)	C(6)-C(5)-C(3)	121.4(3)
C(5)-C(6)	1.369(4)	C(10)-C(5)-C(3)	121.3(2)
C(5)-C(10)	1.371(4)	C(5)-C(6)-C(7)	121.2(4)
C(6)-C(7)	1.385(6)	C(5)-C(6)-H(6)	120(3)
C(6)-H(6)	0.98(5)	C(7)-C(6)-H(6)	119(3)
C(7)-C(8)	1.362(6)	C(8)-C(7)-C(6)	121.6(4)
C(7)-H(7)	0.98(6)	C(8)-C(7)-H(7)	120(3)
C(8)-C(9)	1.356(6)	C(6)-C(7)-H(7)	119(4)
C(8)-H(8)	0.98(5)	C(9)-C(8)-C(7)	117.7(3)
C(9)-C(10)	1.397(5)	C(9)-C(8)-H(8)	124(3)
C(9)-H(9)	0.98(7)	C(7)-C(8)-H(8)	118(3)
C(10)-H(10)	0.99(5)	C(8)-C(9)-C(10)	121.2(4)
C(11)-H(11A)	0.9600	C(8)-C(9)-H(9)	125(3)
C(11)-H(11B)	0.9600	C(10)-C(9)-H(9)	114(3)
C(11)-H(11C)	0.9600	C(5)-C(10)-C(9)	121.1(3)
		C(5)-C(10)-H(10)	115(3)
C(3)-N(1)-H(1A)	110(2)	C(9)-C(10)-H(10)	124(3)
C(3)-N(1)-H(1B)	114(3)	O(2)-C(11)-H(11A)	109.5
H(1A)-N(1)-H(1B)	100(3)	O(2)-C(11)-H(11B)	109.5
O(1)-C(1)-O(2)	123.6(3)	H(11A)-C(11)-H(11B)	109.5
O(1)-C(1)-C(2)	124.6(3)	O(2)-C(11)-H(11C)	109.5
O(2)-C(1)-C(2)	111.8(2)	H(11A)-C(11)-H(11C)	109.5
C(1)-O(2)-C(11)	117.5(3)	H(11B)-C(11)-H(11C)	109.5
O(3)-C(2)-C(1)	110.6(2)		
O(3)-C(2)-C(3)	108.9(2)	Torsion angles [deg]	
C(1)-C(2)-C(3)	111.7(2)	O(1)-C(1)-O(2)-C(11)	-5.1(5)
O(3)-C(2)-H(2)	112.9(17)	C(2)-C(1)-O(2)-C(11)	174.1(3)
C(1)-C(2)-H(2)	103.5(17)	O(1)-C(1)-C(2)-O(3)	-31.2(4)

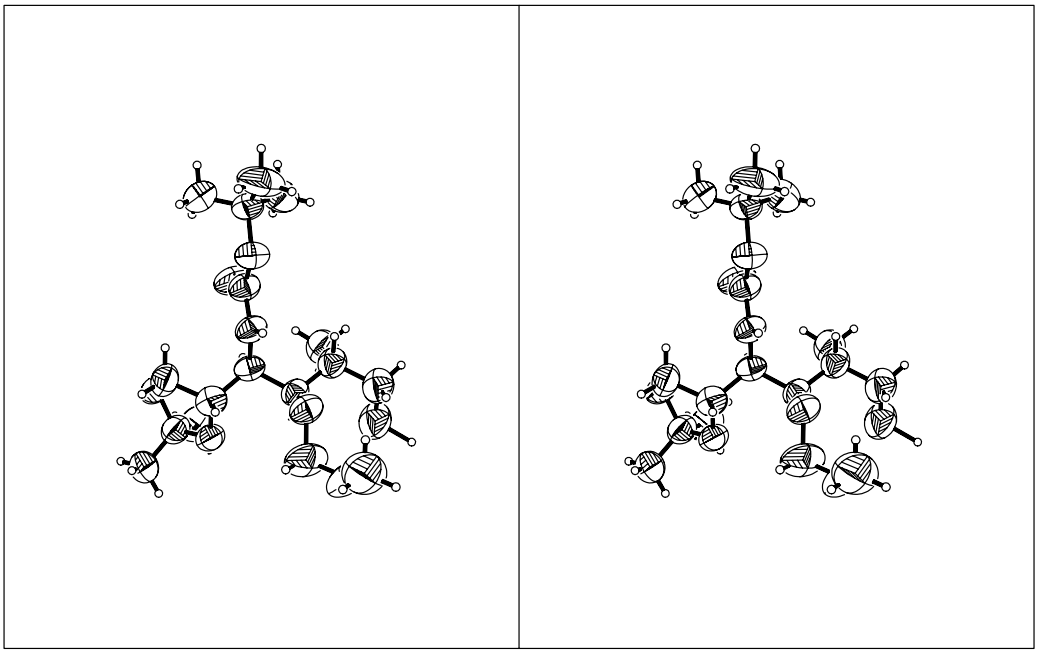
O(2)-C(1)-C(2)-O(3)	149.6(2)	N(1)-C(3)-C(5)-C(10)	16.9(4)
O(1)-C(1)-C(2)-C(3)	90.3(4)	C(4)-C(3)-C(5)-C(10)	-101.0(3)
O(2)-C(1)-C(2)-C(3)	-88.9(3)	C(2)-C(3)-C(5)-C(10)	138.7(3)
O(3)-C(2)-C(3)-N(1)	56.0(3)	C(10)-C(5)-C(6)-C(7)	-1.1(6)
C(1)-C(2)-C(3)-N(1)	-66.5(3)	C(3)-C(5)-C(6)-C(7)	-177.6(4)
O(3)-C(2)-C(3)-C(4)	176.1(2)	C(5)-C(6)-C(7)-C(8)	0.7(8)
C(1)-C(2)-C(3)-C(4)	53.6(3)	C(6)-C(7)-C(8)-C(9)	0.4(8)
O(3)-C(2)-C(3)-C(5)	-64.5(2)	C(7)-C(8)-C(9)-C(10)	-1.1(7)
C(1)-C(2)-C(3)-C(5)	173.0(2)	C(6)-C(5)-C(10)-C(9)	0.3(6)
N(1)-C(3)-C(5)-C(6)	-166.7(3)	C(3)-C(5)-C(10)-C(9)	176.9(3)
C(4)-C(3)-C(5)-C(6)	75.5(4)	C(8)-C(9)-C(10)-C(5)	0.8(6)
C(2)-C(3)-C(5)-C(6)	-44.9(4)		

8.2 (2*S*,3*S*,4*R*,5*R*)-3-*N*-*tert*-Butoxycarbonylamino-1,2-*O*-isopropylidene-4-*O*-methoxy-methyl-5-methylhexane-1,2,4,6-tetraol (54a)

$C_{17}H_{33}NO_7$
Orthorhombic $P2_12_12_1$
a = 9.5027 (13) Å
b = 10.2463 (12) Å
c = 21.100 (2) Å
V = 2054.4 (4) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0764
Rw*(F^2)* = 0.1810
Crystal size: 0.5 × 0.35 × 0.04 mm^3
Calculated density: 1.175 g/cm^3
2Θ-range for data collection: 4.19-67.98°
Independent reflections: 3827
Observed reflections: 3335
Contributed reflections to refinement: 3335
Refined parameters: 236







Bond lengths [A] and	angles [deg]		
O(1)-C(8)	1.191(7)	C(4)-O(6)	1.384(13)
C(1)-N(1)	1.460(6)	C(4)-O(6A)	1.522(18)
C(1)-C(2)	1.536(7)	C(4)-H(4A)	0.9600
C(1)-C(13)	1.548(8)	C(4)-H(4B)	0.9600
C(1)-H(1)	0.9800	C(4)-H(4C)	0.9600
N(1)-C(8)	1.364(7)	C(5)-C(6)	1.522(9)
N(1)-H(1A)	0.9796	C(5)-H(5A)	0.9600
O(2)-C(8)	1.348(7)	C(5)-H(5B)	0.9600
O(2)-C(9)	1.481(7)	C(5)-H(5C)	0.9600
C(2)-O(5)	1.432(6)	C(6)-C(7)	1.533(8)
C(2)-C(6)	1.517(8)	C(6)-H(6)	0.9800
C(2)-H(2)	0.9800	O(7)-C(7)	1.415(7)
O(3)-C(15)	1.437(7)	O(7)-H(7)	1.3215
O(3)-C(13)	1.440(6)	C(7)-H(7A)	0.9700
C(3)-O(6A)	1.208(18)	C(7)-H(7B)	0.9700
C(3)-O(6)	1.336(12)	C(9)-C(12)	1.466(10)
C(3)-O(5)	1.474(9)	C(9)-C(10)	1.475(9)
C(3)-H(3A)	0.9700	C(9)-C(11)	1.523(10)
C(3)-H(3B)	0.9700	C(10)-H(10A)	0.9600
O(4)-C(14)	1.402(8)	C(10)-H(10B)	0.9600
O(4)-C(15)	1.410(7)	C(10)-H(10C)	0.9600

C(11)-H(11A)	0.9600	O(5)-C(3)-H(3B)	109.0
C(11)-H(11B)	0.9600	H(3A)-C(3)-H(3B)	107.8
C(11)-H(11C)	0.9600	C(14)-O(4)-C(15)	107.9(5)
C(12)-H(12A)	0.9600	O(6)-C(4)-O(6A)	56.9(8)
C(12)-H(12B)	0.9600	O(6)-C(4)-H(4A)	109.5
C(12)-H(12C)	0.9600	O(6A)-C(4)-H(4A)	151.7
C(13)-C(14)	1.530(8)	O(6)-C(4)-H(4B)	109.5
C(13)-H(13)	0.9800	O(6A)-C(4)-H(4B)	60.9
C(14)-H(14A)	0.9700	H(4A)-C(4)-H(4B)	109.5
C(14)-H(14B)	0.9700	O(6)-C(4)-H(4C)	109.5
C(15)-C(17)	1.496(10)	O(6A)-C(4)-H(4C)	98.8
C(15)-C(16)	1.505(9)	H(4A)-C(4)-H(4C)	109.5
C(16)-H(16A)	0.9600	H(4B)-C(4)-H(4C)	109.5
C(16)-H(16B)	0.9600	C(2)-O(5)-C(3)	115.0(5)
C(16)-H(16C)	0.9600	C(6)-C(5)-H(5A)	109.5
C(17)-H(17A)	0.9600	C(6)-C(5)-H(5B)	109.5
C(17)-H(17B)	0.9600	H(5A)-C(5)-H(5B)	109.5
C(17)-H(17C)	0.9600	C(6)-C(5)-H(5C)	109.5
		H(5A)-C(5)-H(5C)	109.5
N(1)-C(1)-C(2)	110.7(5)	H(5B)-C(5)-H(5C)	109.5
N(1)-C(1)-C(13)	110.0(4)	C(2)-C(6)-C(5)	111.9(6)
C(2)-C(1)-C(13)	111.0(5)	C(2)-C(6)-C(7)	112.8(6)
N(1)-C(1)-H(1)	108.3	C(5)-C(6)-C(7)	109.5(6)
C(2)-C(1)-H(1)	108.3	C(2)-C(6)-H(6)	107.5
C(13)-C(1)-H(1)	108.3	C(5)-C(6)-H(6)	107.5
C(8)-N(1)-C(1)	119.6(5)	C(7)-C(6)-H(6)	107.5
C(8)-N(1)-H(1A)	120.1	C(3)-O(6)-C(4)	111.6(9)
C(1)-N(1)-H(1A)	119.4	C(3)-O(6A)-C(4)	110.5(16)
C(8)-O(2)-C(9)	119.2(5)	C(7)-O(7)-H(7)	118.0
O(5)-C(2)-C(6)	110.0(5)	O(7)-C(7)-C(6)	107.0(5)
O(5)-C(2)-C(1)	108.2(5)	O(7)-C(7)-H(7A)	110.3
C(6)-C(2)-C(1)	113.1(5)	C(6)-C(7)-H(7A)	110.3
O(5)-C(2)-H(2)	108.5	O(7)-C(7)-H(7B)	110.3
C(6)-C(2)-H(2)	108.5	C(6)-C(7)-H(7B)	110.3
C(1)-C(2)-H(2)	108.5	H(7A)-C(7)-H(7B)	108.6
C(15)-O(3)-C(13)	108.7(4)	O(1)-C(8)-O(2)	126.7(6)
O(6A)-C(3)-O(6)	66.0(9)	O(1)-C(8)-N(1)	125.0(6)
O(6A)-C(3)-O(5)	115.5(13)	O(2)-C(8)-N(1)	108.3(5)
O(6)-C(3)-O(5)	112.8(9)	C(12)-C(9)-C(10)	113.8(7)
O(6A)-C(3)-H(3A)	44.7	C(12)-C(9)-O(2)	110.5(6)
O(6)-C(3)-H(3A)	109.0	C(10)-C(9)-O(2)	110.1(6)
O(5)-C(3)-H(3A)	109.0	C(12)-C(9)-C(11)	110.0(7)
O(6A)-C(3)-H(3B)	133.3	C(10)-C(9)-C(11)	110.2(7)
O(6)-C(3)-H(3B)	109.0	O(2)-C(9)-C(11)	101.5(5)

C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(9)-C(11)-H(11A)	109.5
C(9)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(9)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(9)-C(12)-H(12A)	109.5
C(9)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(9)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(3)-C(13)-C(14)	102.2(5)
O(3)-C(13)-C(1)	109.7(4)
C(14)-C(13)-C(1)	112.3(5)
O(3)-C(13)-H(13)	110.8
C(14)-C(13)-H(13)	110.8
C(1)-C(13)-H(13)	110.8
O(4)-C(14)-C(13)	103.2(5)
O(4)-C(14)-H(14A)	111.1
C(13)-C(14)-H(14A)	111.1
O(4)-C(14)-H(14B)	111.1
C(13)-C(14)-H(14B)	111.1
H(14A)-C(14)-H(14B)	109.1
O(4)-C(15)-O(3)	106.5(5)
O(4)-C(15)-C(17)	113.0(6)
O(3)-C(15)-C(17)	108.6(6)
O(4)-C(15)-C(16)	107.0(6)
O(3)-C(15)-C(16)	108.0(5)
C(17)-C(15)-C(16)	113.4(7)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

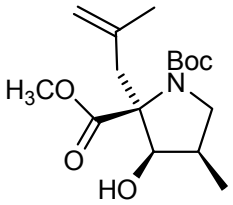
Torsion angles [deg]

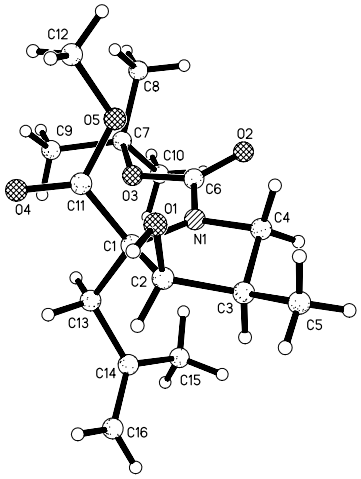
C(2)-C(1)-N(1)-C(8)	117.5(6)
C(13)-C(1)-N(1)-C(8)	-119.4(6)
N(1)-C(1)-C(2)-O(5)	61.1(6)
C(13)-C(1)-C(2)-O(5)	-61.4(6)
N(1)-C(1)-C(2)-C(6)	-61.1(6)
C(13)-C(1)-C(2)-C(6)	176.4(5)
C(6)-C(2)-O(5)-C(3)	-123.9(6)
C(1)-C(2)-O(5)-C(3)	112.1(7)
O(6A)-C(3)-O(5)-C(2)	-174.2(13)
O(6)-C(3)-O(5)-C(2)	112.6(8)
O(5)-C(2)-C(6)-C(5)	178.4(5)
C(1)-C(2)-C(6)-C(5)	-60.4(6)
O(5)-C(2)-C(6)-C(7)	54.5(6)
C(1)-C(2)-C(6)-C(7)	175.6(5)
O(6A)-C(3)-O(6)-C(4)	-32.7(13)
O(5)-C(3)-O(6)-C(4)	76.2(12)
O(6A)-C(4)-O(6)-C(3)	27.9(11)
O(6)-C(3)-O(6A)-C(4)	29.2(12)
O(5)-C(3)-O(6A)-C(4)	-75.8(18)
O(6)-C(4)-O(6A)-C(3)	-30.9(13)
C(2)-C(6)-C(7)-O(7)	65.9(7)
C(5)-C(6)-C(7)-O(7)	-59.3(8)
C(9)-O(2)-C(8)-O(1)	-2.4(10)
C(9)-O(2)-C(8)-N(1)	179.3(5)
C(1)-N(1)-C(8)-O(1)	7.8(10)
C(1)-N(1)-C(8)-O(2)	-173.9(5)
C(8)-O(2)-C(9)-C(12)	-61.4(8)
C(8)-O(2)-C(9)-C(10)	65.2(8)
C(8)-O(2)-C(9)-C(11)	-178.0(6)
C(15)-O(3)-C(13)-C(14	18.3(6)
C(15)-O(3)-C(13)-C(1)	-101.0(6)
N(1)-C(1)-C(13)-O(3)	179.4(4)
C(2)-C(1)-C(13)-O(3)	-57.7(6)
N(1)-C(1)-C(13)-C(14)	66.5(6)
C(2)-C(1)-C(13)-C(14)	-170.6(5)
C(15)-O(4)-C(14)-C(13)	33.7(7)
O(3)-C(13)-C(14)-O(4)	-31.4(6)
C(1)-C(13)-C(14)-O(4)	86.1(6)

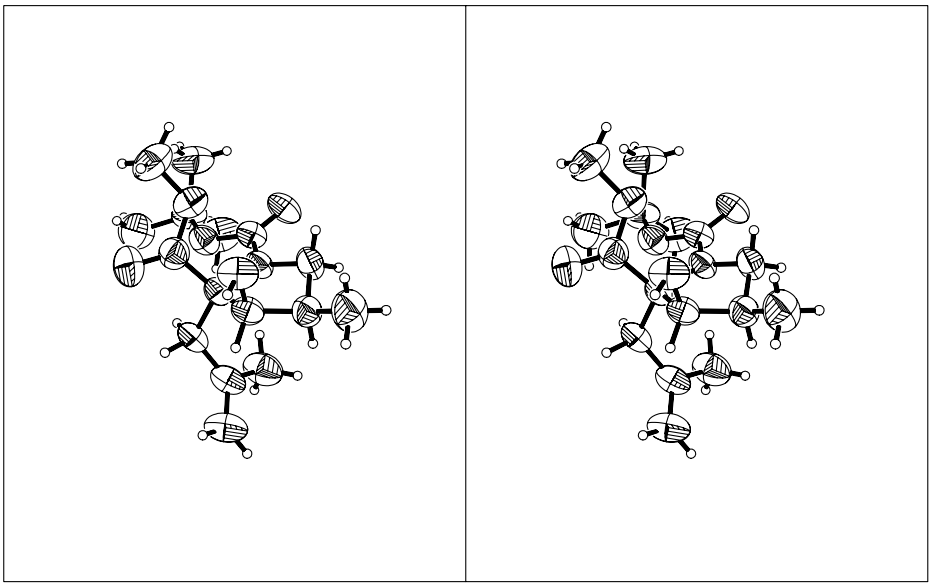
C(14)-O(4)-C(15)-O(3)	-22.7(7)	C(13)-O(3)-C(15)-O(4)	1.3(7)
C(14)-O(4)-C(15)-C(17)	96.4(7)	C(13)-O(3)-C(15)-C(17)	-120.8(6)
C(14)-O(4)-C(15)-C(16)	-138.1(6)	C(13)-O(3)-C(15)-C(16)	115.9(6)

8.3 (2*S*,3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-hydroxy-2-(2'-methylallyl)-4-methylproline methyl ester (61)

$C_{16}H_{27}NO_5$
Monoclinic $P2_1$
a = 9.0983 (7) Å
b = 10.8380 (9) Å
c = 9.3763 (6) Å
V = 899.70 (12) Å^3
α = 90°, β= 90°, γ = 90°
Z = 2, R*(F)* = 0.0562
Rw*(F^2)* = 0.1402
Crystal size: 1.7 × 0.15 × 0.10 mm^3
Calculated density: 1.157 g/cm^3
2Θ-range for data collection: 4.85-67.99°
Independent reflections: 3334
Observed reflections: 2974
Contributed reflections to refinement: 2974
Refined parameters: 200







Bond lengths [A] and angles [deg]

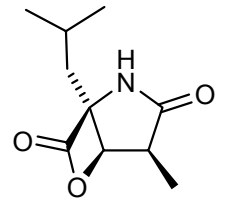
N(1)-C(6)	1.343(4)	C(14)-C(15)	1.483(6)
N(1)-C(4)	1.458(4)	C(15)-H(15A)	0.9600
N(1)-C(1)	1.469(4)	C(15)-H(15B)	0.9600
O(1)-C(2)	1.420(4)	C(15)-H(15C)	0.9600
O(1)-H(1)	1.0425	C(16)-H(16A)	0.9300
C(1)-C(11)	1.512(5)	C(16)-H(16B)	0.9300
C(1)-C(13)	1.550(5)		
C(1)-C(2)	1.561(5)	C(6)-N(1)-C(4)	120.0(3)
O(2)-C(6)	1.223(4)	C(6)-N(1)-C(1)	125.4(3)
C(2)-C(3)	1.521(5)	C(4)-N(1)-C(1)	112.9(3)
C(2)-H(2)	0.9800	C(2)-O(1)-H(1)	111.2
O(3)-C(6)	1.344(4)	N(1)-C(1)-C(11)	111.4(3)
O(3)-C(7)	1.483(4)	N(1)-C(1)-C(13)	114.2(3)
C(3)-C(4)	1.523(5)	C(11)-C(1)-C(13)	108.7(3)
C(3)-C(5)	1.523(5)	N(1)-C(1)-C(2)	102.6(3)
C(3)-H(3)	0.9800	C(11)-C(1)-C(2)	107.8(3)
O(4)-C(11)	1.205(5)	C(13)-C(1)-C(2)	112.0(3)
C(4)-H(4A)	0.9700	O(1)-C(2)-C(3)	111.5(3)
C(4)-H(4B)	0.9700	O(1)-C(2)-C(1)	110.0(3)
O(5)-C(11)	1.345(5)	C(3)-C(2)-C(1)	104.4(3)
O(5)-C(12)	1.439(5)	O(1)-C(2)-H(2)	110.2
C(5)-H(5A)	0.9600	C(3)-C(2)-H(2)	110.2
C(5)-H(5B)	0.9600	C(1)-C(2)-H(2)	110.2
C(5)-H(5C)	0.9600	C(6)-O(3)-C(7)	121.7(3)
C(7)-C(8)	1.494(6)	C(2)-C(3)-C(4)	103.1(3)
C(7)-C(10)	1.512(6)	C(2)-C(3)-C(5)	114.8(4)
C(7)-C(9)	1.514(7)	C(4)-C(3)-C(5)	113.7(3)
C(8)-H(8A)	0.9600	C(2)-C(3)-H(3)	108.3
C(8)-H(8B)	0.9600	C(4)-C(3)-H(3)	108.3
C(8)-H(8C)	0.9600	C(5)-C(3)-H(3)	108.3
C(9)-H(9A)	0.9600	N(1)-C(4)-C(3)	102.5(3)
C(9)-H(9B)	0.9600	N(1)-C(4)-H(4A)	111.3
C(9)-H(9C)	0.9600	C(3)-C(4)-H(4A)	111.3
C(10)-H(10A)	0.9600	N(1)-C(4)-H(4B)	111.3
C(10)-H(10B)	0.9600	C(3)-C(4)-H(4B)	111.3
C(10)-H(10C)	0.9600	H(4A)-C(4)-H(4B)	109.2
C(12)-H(12A)	0.9600	C(11)-O(5)-C(12)	117.3(4)
C(12)-H(12B)	0.9600	C(3)-C(5)-H(5A)	109.5
C(12)-H(12C)	0.9600	C(3)-C(5)-H(5B)	109.5
C(13)-C(14)	1.495(6)	H(5A)-C(5)-H(5B)	109.5
C(13)-H(13A)	0.9700	C(3)-C(5)-H(5C)	109.5
C(13)-H(13B)	0.9700	H(5A)-C(5)-H(5C)	109.5
C(14)-C(16)	1.339(6)	H(5B)-C(5)-H(5C)	109.5

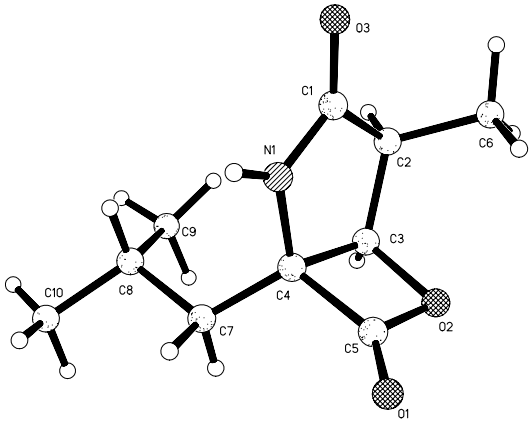
O(2)-C(6)-N(1)	123.7(3)	C(15)-C(14)-C(13)	118.4(4)
O(2)-C(6)-O(3)	125.0(3)	C(14)-C(15)-H(15A)	109.5
N(1)-C(6)-O(3)	111.3(3)	C(14)-C(15)-H(15B)	109.5
O(3)-C(7)-C(8)	110.9(3)	H(15A)-C(15)-H(15B)	109.5
O(3)-C(7)-C(10)	108.4(3)	C(14)-C(15)-H(15C)	109.5
C(8)-C(7)-C(10)	112.7(4)	H(15A)-C(15)-H(15C)	109.5
O(3)-C(7)-C(9)	102.3(3)	H(15B)-C(15)-H(15C)	109.5
C(8)-C(7)-C(9)	111.1(4)	C(14)-C(16)-H(16A)	120.0
C(10)-C(7)-C(9)	111.0(4)	C(14)-C(16)-H(16B)	120.0
C(7)-C(8)-H(8A)	109.5	H(16A)-C(16)-H(16B)	120.0
C(7)-C(8)-H(8B)	109.5		
H(8A)-C(8)-H(8B)	109.5	Torsion angles [deg]	
C(7)-C(8)-H(8C)	109.5	C(6)-N(1)-C(1)-C(11)	-51.7(4)
H(8A)-C(8)-H(8C)	109.5	C(4)-N(1)-C(1)-C(11)	113.5(3)
H(8B)-C(8)-H(8C)	109.5	C(6)-N(1)-C(1)-C(13)	71.9(4)
C(7)-C(9)-H(9A)	109.5	C(4)-N(1)-C(1)-C(13)	-122.9(3)
C(7)-C(9)-H(9B)	109.5	C(6)-N(1)-C(1)-C(2)	-166.8(3)
H(9A)-C(9)-H(9B)	109.5	C(4)-N(1)-C(1)-C(2)	-1.6(4)
C(7)-C(9)-H(9C)	109.5	N(1)-C(1)-C(2)-O(1)	98.1(3)
H(9A)-C(9)-H(9C)	109.5	C(11)-C(1)-C(2)-O(1)	-19.6(4)
H(9B)-C(9)-H(9C)	109.5	C(13)-C(1)-C(2)-O(1)	-139.1(3)
C(7)-C(10)-H(10A)	109.5	N(1)-C(1)-C(2)-C(3)	-21.8(3)
C(7)-C(10)-H(10B)	109.5	C(11)-C(1)-C(2)-C(3)	-139.4(3)
H(10A)-C(10)-H(10B)	109.5	C(13)-C(1)-C(2)-C(3)	101.1(3)
C(7)-C(10)-H(10C)	109.5	O(1)-C(2)-C(3)-C(4)	-82.4(4)
H(10A)-C(10)-H(10C)	109.5	C(1)-C(2)-C(3)-C(4)	36.3(4)
H(10B)-C(10)-H(10C)	109.5	O(1)-C(2)-C(3)-C(5)	41.7(5)
O(4)-C(11)-O(5)	122.6(4)	C(1)-C(2)-C(3)-C(5)	160.5(4)
O(4)-C(11)-C(1)	124.5(4)	C(6)-N(1)-C(4)-C(3)	-169.9(3)
O(5)-C(11)-C(1)	112.9(3)	C(1)-N(1)-C(4)-C(3)	24.0(4)
O(5)-C(12)-H(12A)	109.5	C(2)-C(3)-C(4)-N(1)	-36.5(4)
O(5)-C(12)-H(12B)	109.5	C(5)-C(3)-C(4)-N(1)	-161.4(4)
H(12A)-C(12)-H(12B)	109.5	C(4)-N(1)-C(6)-O(2)	4.2(5)
O(5)-C(12)-H(12C)	109.5	C(1)-N(1)-C(6)-O(2)	168.5(3)
H(12A)-C(12)-H(12C)	109.5	C(4)-N(1)-C(6)-O(3)	-177.7(3)
H(12B)-C(12)-H(12C)	109.5	C(1)-N(1)-C(6)-O(3)	-13.5(5)
C(14)-C(13)-C(1)	117.1(3)	C(7)-O(3)-C(6)-O(2)	1.9(5)
C(14)-C(13)-H(13A)	108.0	C(7)-O(3)-C(6)-N(1)	-176.1(3)
C(1)-C(13)-H(13A)	108.0	C(6)-O(3)-C(7)-C(8)	-60.8(5)
C(14)-C(13)-H(13B)	108.0	C(6)-O(3)-C(7)-C(10)	63.4(5)
C(1)-C(13)-H(13B)	108.0	C(6)-O(3)-C(7)-C(9)	-179.3(4)
H(13A)-C(13)-H(13B)	107.3	C(12)-O(5)-C(11)-O(4)	3.6(6)
C(16)-C(14)-C(15)	120.4(5)	C(12)-O(5)-C(11)-C(1)	-175.1(3)
C(16)-C(14)-C(13)	121.1(4)	N(1)-C(1)-C(11)-O(4)	159.2(4)

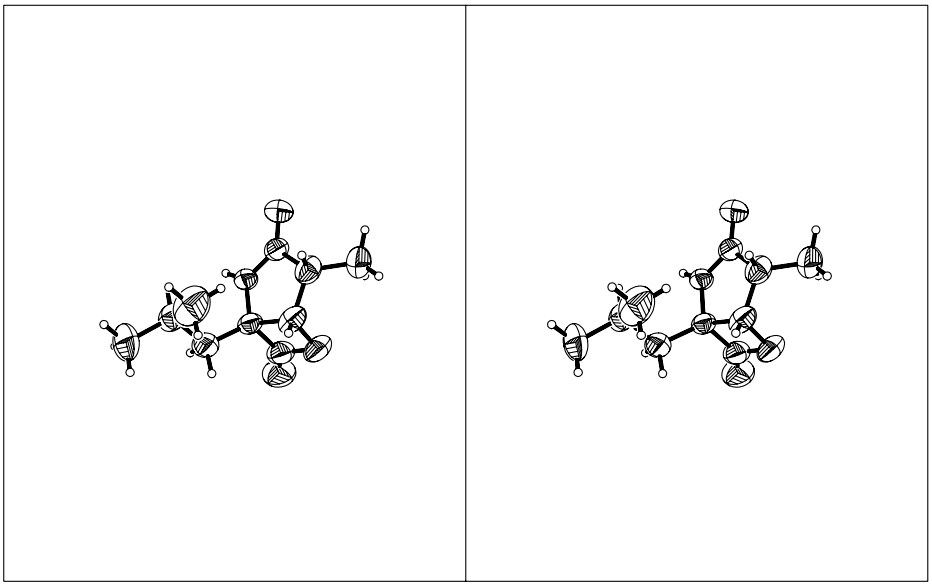
C(13)-C(1)-C(11)-O(4)	32.6(5)	N(1)-C(1)-C(13)-C(14)	59.2(4)
C(2)-C(1)-C(11)-O(4)	-88.9(5)	C(11)-C(1)-C(13)-C(14)	-175.7(3)
N(1)-C(1)-C(11)-O(5)	-22.1(4)	C(2)-C(1)-C(13)-C(14)	-56.8(4)
C(13)-C(1)-C(11)-O(5)	-148.7(3)	C(1)-C(13)-C(14)-C(16)	108.5(5)
C(2)-C(1)-C(11)-O(5)	89.7(4)	C(1)-C(13)-C(14)-C(15)	-73.9(5)

8.4 (2*S*,3*R*,4*R*)-1'-Deoxy-omuralide (68)

$C_{10}H_{15}NO_3$
Orthorhombic $P2_12_12_1$
a = 7.5297 (18) Å
b = 7.7321 (17) Å
c = 18.921 (19) Å
V = 1105.78 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0573
Rw*(F^2)* = 0.1329
Crystal size: 2.5 × 0.8 × 0.5 mm^3
Calculated density: 1.189 g/cm^3
2Θ-range for data collection: 2.15-30.00°
Independent reflections: 3635
Observed reflections: 3212
Contributing reflections to refinement: 3212
Refined parameters: 188







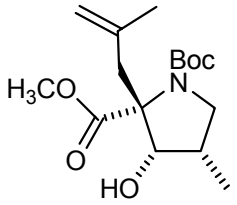
Bond lengths [A] and angles [deg]

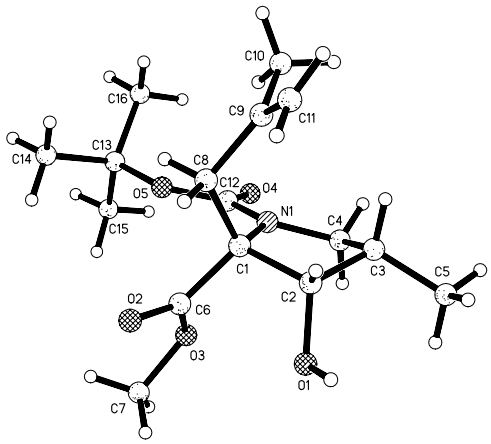
N(1)-C(1)	1.336(2)	C(6)-C(2)-H(2)	99.2(16)
N(1)-C(4)	1.452(2)	O(2)-C(3)-C(2)	113.11(19)
N(1)-H(1)	0.841(19)	O(2)-C(3)-C(4)	89.49(16)
C(1)-O(3)	1.231(2)	C(2)-C(3)-C(4)	108.15(15)
C(1)-C(2)	1.528(3)	O(2)-C(3)-H(3)	109.5(18)
O(1)-C(5)	1.185(3)	C(2)-C(3)-H(3)	116.4(17)
O(2)-C(5)	1.357(3)	C(4)-C(3)-H(3)	117.3(17)
O(2)-C(3)	1.483(3)	N(1)-C(4)-C(7)	114.86(16)
C(2)-C(3)	1.521(3)	N(1)-C(4)-C(5)	111.65(14)
C(2)-C(6)	1.531(4)	C(7)-C(4)-C(5)	115.03(17)
C(2)-H(2)	1.04(3)	N(1)-C(4)-C(3)	103.03(15)
C(3)-C(4)	1.546(3)	C(7)-C(4)-C(3)	124.71(18)
C(3)-H(3)	0.92(3)	C(5)-C(4)-C(3)	83.41(15)
C(4)-C(7)	1.515(3)	O(1)-C(5)-O(2)	127.0(2)
C(4)-C(5)	1.538(3)	O(1)-C(5)-C(4)	138.3(2)
C(6)-H(6A)	1.01(4)	O(2)-C(5)-C(4)	94.69(18)
C(6)-H(6B)	1.05(5)	C(2)-C(6)-H(6A)	110(2)
C(6)-H(6C)	1.10(4)	C(2)-C(6)-H(6B)	105(2)
C(7)-C(8)	1.524(3)	H(6A)-C(6)-H(6B)	103(3)
C(7)-H(7A)	1.04(3)	C(2)-C(6)-H(6C)	103.9(18)
C(7)-H(7B)	0.92(3)	H(6A)-C(6)-H(6C)	115(3)
C(8)-C(9)	1.521(5)	H(6B)-C(6)-H(6C)	119(3)
C(8)-C(10)	1.02(6)	C(4)-C(7)-C(8)	116.28(19)
C(8)-H(8)	1.02(3)	C(4)-C(7)-H(7A)	107.0(16)
C(9)-H(9A)	1.00(4)	C(8)-C(7)-H(7A)	107.8(17)
C(9)-H(9B)	1.04(5)	C(4)-C(7)-H(7B)	109.5(18)
C(9)-H(9C)	0.98(5)	C(8)-C(7)-H(7B)	111(2)
C(10)-H(10A)	1.05(5)	H(7A)-C(7)-H(7B)	105(2)
C(10)-H(10B)	1.00(5)	C(9)-C(8)-C(7)	112.5(2)
C(10)-H(10C)	1.535(4)	C(9)-C(8)-C(10)	111.4(3)
		C(7)-C(8)-C(10)	108.9(3)
C(1)-N(1)-C(4)	115.26(15)	C(9)-C(8)-H(8)	107.3(16)
C(1)-N(1)-H(1)	125.5(12)	C(7)-C(8)-H(8)	109.7(18)
C(4)-N(1)-H(1)	119.2(12)	C(10)-C(8)-H(8)	106.9(16)
O(3)-C(1)-N(1)	124.43(17)	C(8)-C(9)-H(9A)	105(2)
O(3)-C(1)-C(2)	125.53(18)	C(8)-C(9)-H(9B)	110(2)
N(1)-C(1)-C(2)	110.04(16)	H(9A)-C(9)-H(9B)	112(3)
C(5)-O(2)-C(3)	92.41(15)	C(8)-C(9)-H(9C)	105(2)
C(3)-C(2)-C(1)	103.21(17)	H(9A)-C(9)-H(9C)	117(4)
C(3)-C(2)-C(6)	116.8(2)	H(9B)-C(9)-H(9C)	126(4)
C(1)-C(2)-C(6)	112.1(2)	H(10B)-C(10)-H(10C)	106(2)
C(3)-C(2)-H(2)	112.1(17)	C(8)-C(10)-H(10B)	109(3)
C(1)-C(2)-H(2)	113.9(15)	H(10A)-C(10)-H(10B)	108(4)

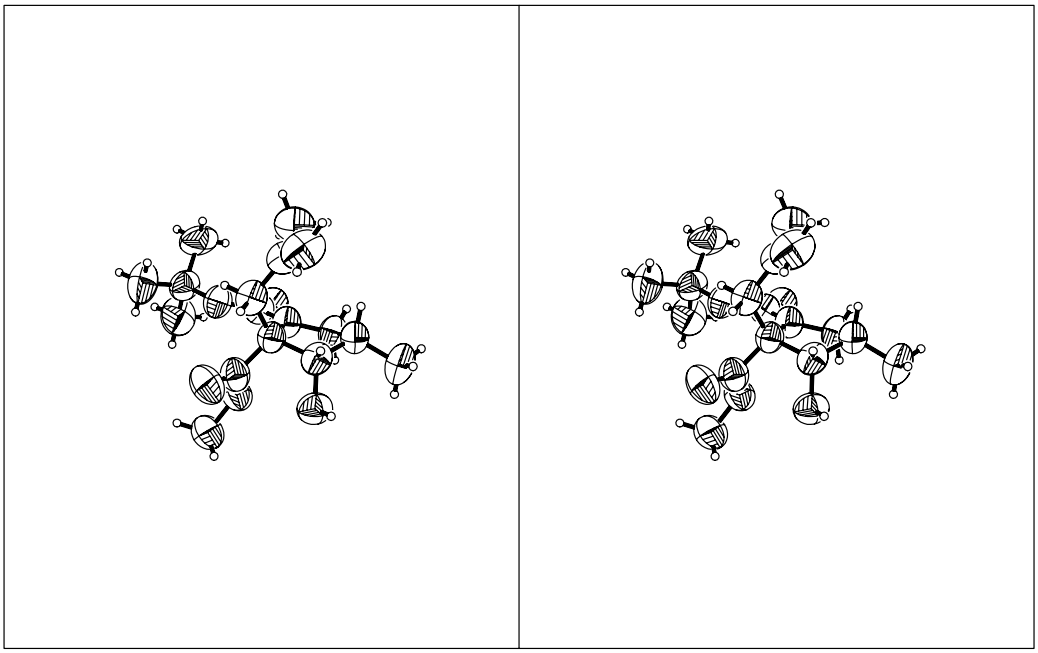
C(8)-C(10)-H(10C)	101(3)
H(10A)-C(10)-H(10C)	104(4)
C(8)-C(10)-H(10A)	109(3)
Torsion angles [deg]	
C(4)-N(1)-C(1)-O(3)	-177.62(17)
C(4)-N(1)-C(1)-C(2)	2.8(2)
O(3)-C(1)-C(2)-C(3)	175.31(19)
N(1)-C(1)-C(2)-C(3)	-5.1(2)
O(3)-C(1)-C(2)-C(6)	48.8(3)
N(1)-C(1)-C(2)-C(6)	-131.7(2)
C(5)-O(2)-C(3)-C(2)	110.26(19)
C(5)-O(2)-C(3)-C(4)	0.69(16)
C(1)-C(2)-C(3)-O(2)	-92.0(2)
C(6)-C(2)-C(3)-O(2)	31.5(3)
C(1)-C(2)-C(3)-C(4)	5.5(2)
C(6)-C(2)-C(3)-C(4)	128.9(2)
C(1)-N(1)-C(4)-C(7)	-137.91(19)
C(1)-N(1)-C(4)-C(5)	88.8(2)
C(1)-N(1)-C(4)-C(3)	0.79(19)
O(2)-C(3)-C(4)-N(1)	110.15(15)
C(2)-C(3)-C(4)-N(1)	-4.1(2)
C(4)-C(7)-C(8)-C(10)	-116.60(19)
C(2)-C(3)-C(4)-C(7)	-172.8(3)
O(2)-C(3)-C(4)-C(5)	-0.62(14)
C(2)-C(3)-C(4)-C(5)	-114.83(17)
C(3)-O(2)-C(5)-O(1)	179.0(3)
C(3)-O(2)-C(5)-C(4)	-0.70(16)
N(1)-C(4)-C(5)-O(1)	79.6(3)
C(7)-C(4)-C(5)-O(1)	-53.6(4)
C(3)-C(4)-C(5)-O(1)	-179.0(3)
N(1)-C(4)-C(5)-O(2)	-100.76(19)
C(7)-C(4)-C(5)-O(2)	126.03(19)
C(3)-C(4)-C(5)-O(2)	0.67(16)
N(1)-C(4)-C(7)-C(8)	50.4(3)
C(5)-C(4)-C(7)-C(8)	-177.9(2)
C(3)-C(4)-C(7)-C(8)	-78.1(3)
C(4)-C(7)-C(8)-C(9)	63.2(3)
O(2)-C(3)-C(4)-C(7)	129.2(2)

8.5 (2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonylamino-3-hydroxy-2-(2'-methyl-allyl)-4- methylproline methyl ester (100)

$C_{16}H_{27}NO_5$
Monoclinic $P2_1$
a = 9.098 (2) Å
b = 10.8457 (18) Å
c = 9.382 (2) Å
V = 901.0 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 2, R*(F)* = 0.0833
Rw*(F^2)* = 0.2101
Crystal size: 0.35 × 0.10 × 0.10 mm
Calculated density: 1.155
2Θ-range for data collection: 4.84-64.91°
Independent reflections: 2077
Observed reflections: 1744
Contributing reflections to refinement: 1744
Refined parameters: 204







Bond lengths [A] and angles [deg]

N(1)-C(12)	1.351(10)	C(5)-H(5B)	0.9600
N(1)-C(4)	1.434(10)	C(5)-H(5C)	0.9600
N(1)-C(1)	1.464(10)	C(7)-H(7A)	0.9600
O(1)-C(2)	1.455(9)	C(7)-H(7B)	0.9600
O(1)-H(1)	1.08(15)	C(7)-H(7C)	0.9600
C(1)-C(6)	1.519(12)	C(8)-C(9)	1.519(12)
C(1)-C(8)	1.553(11)	C(8)-H(8A)	0.9700
C(1)-C(2)	1.561(11)	C(8)-H(8B)	0.9700
C(2)-C(3)	1.510(11)	C(9)-C(11)	1.358(14)
C(2)-H(2)	0.9800	C(9)-C(10)	1.482(13)
O(2)-C(6)	1.203(12)	C(10)-H(10A)	0.9600
O(3)-C(6)	1.353(12)	C(10)-H(10B)	0.9600
O(3)-C(7)	1.442(10)	C(10)-H(10C)	0.9600
C(3)-C(5)	1.526(11)	C(11)-H(11A)	0.9300
C(3)-C(4)	1.529(12)	C(11)-H(11B)	0.9300
C(3)-H(3)	0.9800	C(13)-C(15)	1.479(14)
O(4)-C(12)	1.238(11)	C(6)-C(1)-C(2)	1.524(14)
C(4)-H(4A)	0.9700	C(13)-C(16)	1.532(13)
C(4)-H(4B)	0.9700	C(14)-H(14A)	0.9600
O(5)-C(12)	1.336(10)	C(14)-H(14B)	0.9600
O(5)-C(13)	1.468(9)	C(14)-H(14C)	0.9600
C(5)-H(5A)	0.9600	C(15)-H(15A)	0.9600

C(15)-H(15B)	109.0(6)	O(3)-C(6)-C(1)	112.0(8)
C(15)-H(15C)	0.9600	O(3)-C(7)-H(7A)	109.5
C(16)-H(16A)	0.9600	O(3)-C(7)-H(7B)	109.5
C(16)-H(16B)	0.9600	H(7A)-C(7)-H(7B)	109.5
C(16)-H(16C)	0.9600	O(3)-C(7)-H(7C)	109.5
		H(7A)-C(7)-H(7C)	109.5
C(12)-N(1)-C(4)	120.3(7)	H(7B)-C(7)-H(7C)	109.5
C(12)-N(1)-C(1)	124.6(6)	C(9)-C(8)-C(1)	116.4(7)
C(4)-N(1)-C(1)	113.6(7)	C(9)-C(8)-H(8A)	108.2
C(2)-O(1)-H(1)	92(7)	C(1)-C(8)-H(8A)	108.2
N(1)-C(1)-C(6)	112.0(7)	C(9)-C(8)-H(8B)	108.2
N(1)-C(1)-C(8)	114.1(6)	C(1)-C(8)-H(8B)	108.2
C(6)-C(1)-C(8)	107.4(7)	H(11A)-C(11)-H(11B)	107.3
N(1)-C(1)-C(2)	102.7(6)	C(11)-C(9)-C(10)	120.2(11)
C(13)-C(14)	0.9600	C(11)-C(9)-C(8)	121.4(10)
C(8)-C(1)-C(2)	111.5(7)	C(10)-C(9)-C(8)	118.3(9)
O(1)-C(2)-C(3)	111.1(7)	C(9)-C(10)-H(10A)	109.5
O(1)-C(2)-C(1)	108.0(6)	C(9)-C(10)-H(10B)	109.5
C(3)-C(2)-C(1)	111.1(9)	H(10A)-C(10)-H(10B)	109.5
O(1)-C(2)-H(2)	111.1	C(9)-C(10)-H(10C)	109.5
C(3)-C(2)-H(2)	111.1	H(10A)-C(10)-H(10C)	109.5
C(1)-C(2)-H(2)	111.1	H(10B)-C(10)-H(10C)	109.5
C(6)-O(3)-C(7)	116.8(9)	C(9)-C(11)-H(11A)	120.0
C(2)-C(3)-C(5)	114.4(7)	C(9)-C(11)-H(11B)	120.0
C(2)-C(3)-C(4)	103.9(6)	H(8A)-C(8)-H(8B)	120.0
C(5)-C(3)-C(4)	114.2(8)	O(4)-C(12)-O(5)	124.6(8)
C(2)-C(3)-H(3)	108.0	O(4)-C(12)-N(1)	123.0(8)
C(12)-O(5)-C(13)	108.0	C(14)-C(13)-C(16)	112.4(8)
C(4)-C(3)-H(3)	108.0	O(5)-C(13)-C(15)	111.5(8)
N(1)-C(4)-C(3)	102.4(7)	O(5)-C(13)-C(14)	102.3(8)
N(1)-C(4)-H(4A)	111.3	C(15)-C(13)-C(14)	110.0(8)
C(3)-C(4)-H(4A)	111.3	O(5)-C(13)-C(16)	108.0(7)
N(1)-C(4)-H(4B)	111.3	C(15)-C(13)-C(16)	113.4(10)
C(3)-C(4)-H(4B)	111.3	O(5)-C(12)-N(1)	104.2(6)
H(4A)-C(4)-H(4B)	109.2	C(13)-C(14)-H(14A)	109.5
C(5)-C(3)-H(3)	121.6(7)	C(13)-C(14)-H(14B)	109.5
C(3)-C(5)-H(5A)	109.5	H(14A)-C(14)-H(14B)	109.5
C(3)-C(5)-H(5B)	109.5	C(13)-C(14)-H(14C)	109.5
H(5A)-C(5)-H(5B)	109.5	H(14A)-C(14)-H(14C)	109.5
C(3)-C(5)-H(5C)	109.5	H(14B)-C(14)-H(14C)	109.5
H(5A)-C(5)-H(5C)	109.5	C(13)-C(15)-H(15A)	109.5
H(5B)-C(5)-H(5C)	109.5	C(13)-C(15)-H(15B)	109.5
O(2)-C(6)-O(3)	122.7(8)	H(15A)-C(15)-H(15B)	109.5
O(2)-C(6)-C(1)	125.3(10)	C(13)-C(15)-H(15C)	109.5

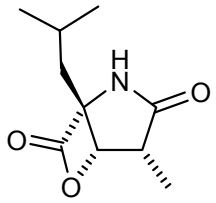
H(16B)-C(16)-H(16C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(13)-C(16)-H(16A)	109.5
C(13)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(13)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(15A)-C(15)-H(15C)	109.5

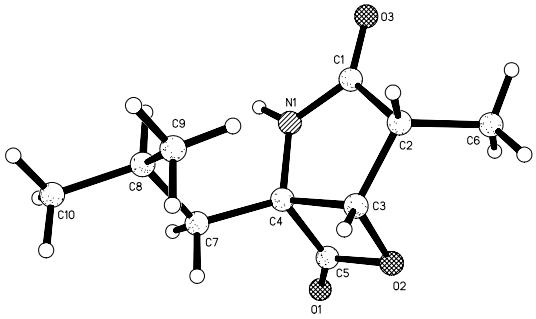
Torsion angles [deg]

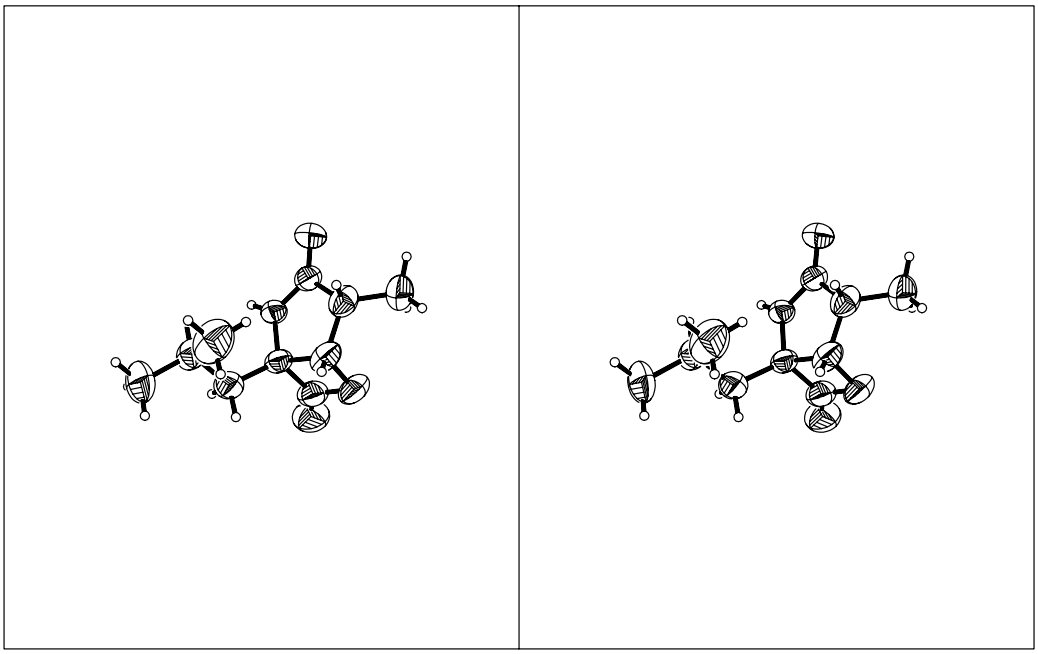
C(12)-N(1)-C(1)-C(6)	51.5(10)
C(4)-N(1)-C(1)-C(6)	-114.4(7)
C(12)-O(5)-C(13)-C(16)	-70.8(9)
C(4)-N(1)-C(1)-C(8)	123.3(8)
C(12)-N(1)-C(1)-C(2)	168.4(7)
C(4)-N(1)-C(1)-C(2)	2.5(8)
N(1)-C(1)-C(2)-O(1)	-98.2(7)
C(6)-C(1)-C(2)-O(1)	20.8(9)
C(8)-C(1)-C(2)-O(1)	139.3(7)
N(1)-C(1)-C(2)-C(3)	20.0(8)
C(6)-C(1)-C(2)-C(3)	139.0(7)
C(8)-C(1)-C(2)-C(3)	-102.6(8)
O(1)-C(2)-C(3)-C(5)	-43.3(10)
C(1)-C(2)-C(3)-C(5)	-159.4(8)
O(1)-C(2)-C(3)-C(4)	81.9(8)
C(1)-C(2)-C(3)-C(4)	-34.1(8)
C(2)-C(3)-C(4)-N(1)	170.0(7)
C(12)-N(1)-C(4)-C(3)	-23.5(9)
C(1)-N(1)-C(4)-C(3)	35.1(8)
C(5)-C(3)-C(4)-N(1)	160.4(7)
C(7)-O(3)-C(6)-O(2)	-5.4(14)
C(7)-O(3)-C(6)-C(1)	174.7(7)
N(1)-C(1)-C(6)-O(2)	-158.0(9)
C(8)-C(1)-C(6)-O(2)	-32.0(12)
C(2)-C(1)-C(6)-O(2)	89.0(11)
N(1)-C(1)-C(6)-O(3)	-63.8(11)
C(8)-C(1)-C(6)-O(3)	147.9(7)
C(2)-C(1)-C(6)-O(3)	-91.2(9)
N(1)-C(1)-C(8)-C(9)	-60.2(9)
C(6)-C(1)-C(8)-C(9)	175.0(8)
C(2)-C(1)-C(8)-C(9)	55.6(9)
C(1)-C(8)-C(9)-C(11)	-109.0(10)
C(1)-C(8)-C(9)-C(10)	75.7(11)
C(13)-O(5)-C(12)-O(4)	-0.9(12)
C(13)-O(5)-C(12)-N(1)	176.6(6)
C(4)-N(1)-C(12)-O(4)	-3.8(13)
C(1)-N(1)-C(12)-O(4)	-168.8(8)
C(4)-N(1)-C(12)-O(5)	178.6(7)
C(1)-N(1)-C(12)-O(5)	13.6(10)
C(12)-O(5)-C(13)-C(15)	61.4(10)
C(12)-O(5)-C(13)-C(14)	179.0(8)
C(12)-N(1)-C(1)-C(8)	21.8(10)

8.6 (2*R*,3*S*,4*S*)-1'-Deoxy-omuralide (107)

$C_{10}H_{15}NO_3$
Orthorhombic $P2_12_12_1$
a = 7.5269 (6) Å
b = 7.6821 (7) Å
c = 18.8867 (12) Å
V = 1105.78 (3) $Å^3$
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0678
Rw(F^2) = 0.1594
Crystal size: 0.25 × 0.10 × 0.05 mm^3
Calculated density: 1.200 g/cm^3
2Θ-range for data collection: 2.15-30.00°
Independent reflections: 2079
Observed reflections: 1745
Contributing reflections to refinement: 1745
Refined parameters: 128







Bond lengths [A] and angles [deg]

N(1)-C(1)	1.342(5)	C(3)-C(2)-H(2)	108.0
N(1)-C(4)	1.447(4)	C(6)-C(2)-H(2)	108.0
N(1)-H(1)	0.8600	O(2)-C(3)-C(2)	112.9(4)
O(1)-C(5)	1.200(6)	O(2)-C(3)-C(4)	89.7(3)
C(1)-O(3)	1.230(5)	C(2)-C(3)-C(4)	103.5(3)
C(1)-C(2)	1.517(6)	O(2)-C(3)-C(5)	41.9(2)
O(2)-C(5)	1.356(6)	C(2)-C(3)-C(5)	120.3(4)
O(2)-C(3)	1.478(5)	C(4)-C(3)-C(5)	47.8(2)
C(2)-C(3)	1.521(6)	O(2)-C(3)-H(3)	114.6
C(2)-C(6)	1.521(7)	C(2)-C(3)-H(3)	114.6
C(2)-H(2)	0.9800	C(4)-C(3)-H(3)	114.6
C(3)-C(4)	1.535(6)	C(5)-C(3)-H(3)	125.1
C(3)-C(5)	2.031(8)	N(1)-C(4)-C(7)	114.4(3)
C(3)-H(3)	0.9800	N(1)-C(4)-C(5)	111.8(3)
C(4)-C(7)	0.9600	C(7)-C(4)-C(5)	115.3(4)
C(4)-C(5)	1.515(6)	C(1)-C(2)-C(6)	108.0(3)
C(6)-H(6A)	0.9600	C(7)-C(4)-C(3)	124.3(4)
C(6)-H(6B)	0.9600	C(5)-C(4)-C(3)	83.5(3)
C(6)-H(6C)	0.9600	O(1)-C(5)-O(2)	125.6(5)
C(7)-C(8)	1.516(6)	O(1)-C(5)-C(4)	139.1(5)
C(7)-H(7A)	0.9700	O(2)-C(5)-C(4)	95.3(4)
C(7)-H(7B)	0.9700	O(1)-C(5)-C(3)	172.2(5)
C(8)-C(10)	1.518(7)	O(2)-C(5)-C(3)	46.7(3)
C(8)-C(9)	1.529(8)	C(4)-C(5)-C(3)	48.7(3)
C(8)-H(8)	0.9800	C(2)-C(6)-H(6A)	109.5
C(9)-H(9A)	0.9600	C(2)-C(6)-H(6B)	109.5
C(9)-H(9B)	0.9600	H(6A)-C(6)-H(6B)	109.5
C(9)-H(9C)	0.9600	C(2)-C(6)-H(6C)	109.5
C(10)-H(10A)	0.9600	H(6A)-C(6)-H(6C)	109.5
C(10)-H(10B)	0.9600	H(6B)-C(6)-H(6C)	109.5
C(10)-H(10C)	1.512(6)	C(4)-C(7)-C(8)	107.9
		C(4)-C(7)-H(7A)	117.5(4)
C(1)-N(1)-C(4)	114.7(3)	C(8)-C(7)-H(7A)	107.9
C(1)-N(1)-H(1)	122.6	C(4)-C(7)-H(7B)	107.9
C(4)-N(1)-H(1)	122.6	C(8)-C(7)-H(7B)	107.9
O(3)-C(1)-N(1)	123.8(4)	H(10B)-C(10)-H(10C)	107.2
O(3)-C(1)-C(2)	126.0(4)	C(7)-C(8)-C(10)	109.6(5)
N(1)-C(1)-C(2)	110.2(3)	C(7)-C(8)-C(9)	111.6(5)
C(5)-O(2)-C(3)	91.5(3)	C(10)-C(8)-C(9)	111.5(5)
C(1)-C(2)-C(3)	103.3(4)	C(7)-C(8)-H(8)	108.0
N(1)-C(4)-C(3)	112.7(4)	C(10)-C(8)-H(8)	108.0
C(3)-C(2)-C(6)	116.3(4)	C(9)-C(8)-H(8)	108.0
C(1)-C(2)-H(2)	108.0	C(8)-C(9)-H(9A)	109.5

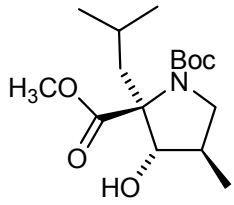
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(7A)-C(7)-H(7B)	109.5

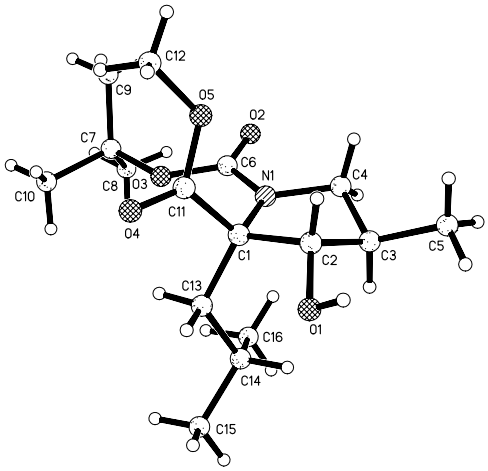
Torsion angles [deg]

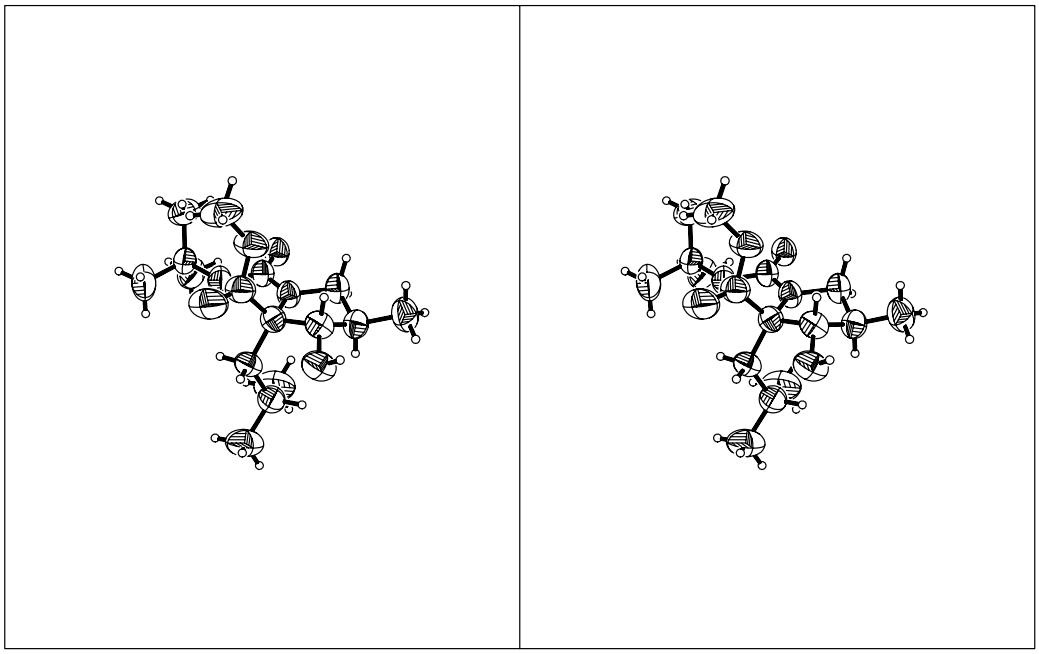
C(4)-N(1)-C(1)-O(3)	177.6(4)
C(4)-N(1)-C(1)-C(2)	-2.2(5)
O(3)-C(1)-C(2)-C(3	-175.2(4)
N(1)-C(1)-C(2)-C(3)	4.6(5)
O(3)-C(1)-C(2)-C(6)	-48.8(6)
N(1)-C(1)-C(2)-C(6)	131.0(4)
C(5)-O(2)-C(3)-C(2)	-110.5(4)
C(5)-O(2)-C(3)-C(4)	-1.0(3)
C(1)-C(2)-C(3)-O(2)	92.4(4)
C(7)-C(4)-C(5)-O(1)	-31.7(6)
C(1)-C(2)-C(3)-C(4)	-5.2(5)
C(6)-C(2)-C(3)-C(4)	-129.2(4)
C(1)-C(2)-C(3)-C(5	45.9(5)
C(6)-C(2)-C(3)-C(5)	-78.1(5)
C(1)-N(1)-C(4)-C(7)	114.9(4)
C(1)-N(1)-C(4)-C(5)	-89.5(5)
C(1)-N(1)-C(4)-C(3	-1.2(4)
O(2)-C(3)-C(4)-N(1)	-110.0(3)
C(2)-C(3)-C(4)-N(1)	4.0(4)
C(5)-C(3)-C(4)-N(1)	-110.9(3)
O(2)-C(3)-C(4)-C(7)	117.3(4)
C(2)-C(3)-C(4)-C(7)	-128.7(4)
C(5)-C(3)-C(4)-C(7)	116.4(5)
O(2)-C(3)-C(4)-C(5)	0.9(3)
C(2)-C(3)-C(4)-C(5)	-179.0(5)
C(3)-O(2)-C(5)-O(1)	137.1(4)
C(3)-O(2)-C(5)-C(4)	1.0(4)
N(1)-C(4)-C(5)-O(1)	-78.9(7)
C(6)-C(2)-C(3)-O(2)	54.0(8)
C(3)-C(4)-C(5)-O(1)	179.1(7)
N(1)-C(4)-C(5)-O(2)	101.0(4)
C(7)-C(4)-C(5)-O(2)	-126.0(4)
C(3)-C(4)-C(5)-O(2)	-1.0(3)
N(1)-C(4)-C(5)-C(3)	125.0(4)
C(7)-C(4)-C(5)-C(3)	102.0(4)
C(4)-C(7)-C(8)-C(9)	78.4(6)
C(2)-C(3)-C(5)-O(1)	97(3)
C(4)-C(3)-C(5)-O(1)	-176(3)
C(2)-C(3)-C(5)-O(2)	91.3(5)
C(4)-C(3)-C(5)-O(2)	178.6(5)
O(2)-C(3)-C(5)-C(4)	-178.6(5)
C(2)-C(3)-C(5)-C(4)	-87.3(4)
N(1)-C(4)-C(7)-C(8)	-50.0(6)
C(5)-C(4)-C(7)-C(8)	178.3(4)
C(3)-C(4)-C(7)-C(8)	6(3)
C(4)-C(7)-C(8)-C(10)	-63.3(6)
O(2)-C(3)-C(5)-O(1)	172.7(5)

8.7 (2S,3S,4R)-1-*tert*-Butoxycarbonylamino-3-hydroxy-2-isobutyl-4-methylproline methyl ester (123)

$C_{16}H_{29}NO_5$
Orthorhombic $P2_12_12_1$
a = 9.1627 (7) Å
b = 11.9106 (12) Å
c = 16.6391 (13) Å
V = 1815.9 (3) Å^3
α = 90°, β= 90°, γ = 90°
Z = 4, R*(F)* = 0.0613
Rw*(F^2)* = 0.1564
Crystal size: 0.5 × 0.35 × 0.07 mm^3
Calculated density: 1.154 g/cm^3
2Θ-range for data collection: 4.57-67.91°
Independent reflections: 3284
Observed reflections: 2838
Contributing reflections to refinement: 2838
Refined parameters: 200







Bond lengths [A] and angles [deg]

N(1)-C(6)	1.341(5)	C(14)-C(15)	1.500(6)
N(1)-C(4)	1.457(5)	C(14)-H(14)	0.9800
N(1)-C(1)	1.473(5)	C(15)-H(15A)	0.9600
C(1)-C(11)	1.533(6)	C(15)-H(15B)	0.9600
C(1)-C(13)	1.539(5)	C(15)-H(15C)	0.9600
C(1)-C(2)	1.559(6)	C(16)-H(16A)	0.9600
O(1)-C(2)	1.412(4)	C(16)-H(16B)	0.9600
O(1)-H(1)	0.8540	C(16)-H(16C)	0.9600
O(2)-C(6)	1.229(4)		
C(2)-C(3)	1.527(6)	C(6)-N(1)-C(4)	120.0(3)
C(2)-H(2)	0.9800	C(6)-N(1)-C(1)	125.8(3)
O(3)-C(6)	1.338(5)	C(4)-N(1)-C(1)	113.6(3)
O(3)-C(7)	1.474(5)	N(1)-C(1)-C(11)	111.1(3)
C(3)-C(5)	1.521(6)	N(1)-C(1)-C(13)	115.2(3)
C(3)-C(4)	1.524(6)	C(11)-C(1)-C(13)	107.6(3)
C(3)-H(3)	0.9800	C(12)-H(12C)	101.2(3)
C(4)-H(4A)	0.9700	C(11)-C(1)-C(2)	107.1(3)
C(4)-H(4B)	0.9700	C(13)-C(1)-C(2)	114.3(3)
O(4)-C(11)	1.197(5)	C(2)-O(1)-H(1)	102.2
O(5)-C(11)	1.339(5)	O(1)-C(2)-C(3)	115.2(3)
O(5)-C(12)	1.440(6)	O(1)-C(2)-C(1)	110.9(3)
C(5)-H(5A)	0.9600	C(3)-C(2)-C(1)	104.4(3)
C(5)-H(5B)	0.9600	O(1)-C(2)-H(2)	108.7
C(5)-H(5C)	0.9600	C(3)-C(2)-H(2)	108.7
C(7)-C(9)	1.529(7)	C(1)-C(2)-H(2)	108.7
C(7)-C(10)	1.510(7)	C(6)-O(3)-C(7)	123.0(3)
C(7)-C(8)	1.515(6)	C(4)-C(3)-C(5)	113.7(4)
C(8)-H(8A)	0.9600	C(4)-C(3)-C(2)	102.2(3)
C(8)-H(8B)	0.9600	C(5)-C(3)-C(2)	113.8(4)
C(8)-H(8C)	0.9600	C(4)-C(3)-H(3)	109.0
C(9)-H(9A)	0.9600	C(5)-C(3)-H(3)	109.0
C(9)-H(9B)	0.9600	C(9)-C(7)-C(10)	109.0
C(9)-H(9C)	0.9600	N(1)-C(4)-C(3)	103.1(3)
C(10)-H(10A)	0.9600	N(1)-C(4)-H(4A)	111.1
C(10)-H(10B	0.9600	C(3)-C(4)-H(4A)	111.1
C(10)-H(10C)	0.9600	N(1)-C(4)-H(4B)	111.1
C(12)-H(12A)	0.9600	C(3)-C(4)-H(4B)	111.1
C(12)-H(12B)	0.9600	H(4A)-C(4)-H(4B)	109.1
N(1)-C(1)-C(2)	0.9600	C(11)-O(5)-C(12)	116.0(4)
C(13)-C(14)	1.520(6)	C(3)-C(5)-H(5A)	109.5
C(13)-H(13A)	0.9700	C(3)-C(5)-H(5B)	109.5
C(13)-H(13B)	0.9700	H(5A)-C(5)-H(5B)	109.5
C(14)-C(16)	1.506(7)	C(3)-C(5)-H(5C)	109.5

H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
O(2)-C(6)-O(3)	124.9(4)
O(2)-C(6)-N(1)	123.8(4)
O(3)-C(6)-N(1)	111.3(3)
O(3)-C(7)-C(9)	109.5(3)
O(3)-C(7)-C(10)	102.0(4)
C(2)-C(3)-H(3)	112.4(4)
O(3)-C(7)-C(8)	111.3(4)
C(9)-C(7)-C(8)	111.6(4)
C(10)-C(7)-C(8)	109.5
C(7)-C(8)-H(8A)	109.8(5)
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
O(5)-C(12)-H(12C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(10)-H(10A)	109.5
C(7)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(7)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(4)-C(11)-O(5)	122.0(4)
O(4)-C(11)-C(1)	125.2(4
O(5)-C(11)-C(1)	112.7(4)
O(5)-C(12)-H(12A)	109.5
O(5)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(7)-C(8)-H(8C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-C(1)	120.2(4)
C(14)-C(13)-H(13A)	107.3
C(1)-C(13)-H(13A)	107.3
C(14)-C(13)-H(13B)	107.3
C(1)-C(13)-H(13B)	107.3
H(13A)-C(13)-H(13B)	106.9
C(16)-C(14)-C(13	114.7(4)
C(16)-C(14)-C(15)	108.7(4)
C(13)-C(14)-C(15)	107.6(4)
C(16)-C(14)-H(14)	108.6
C(13)-C(14)-H(14)	108.6
H(16B)-C(16)-H(16C)	108.6
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(14)-C(16)-H(16A)	109.5
C(14)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(14)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
C(15)-C(14)-H(14)	109.5
Torsion angles [deg]	
C(6)-N(1)-C(1)-C(11)	-51.7(5)
C(4)-N(1)-C(1)-C(11)	118.9(4)
C(6)-N(1)-C(1)-C(13)	71.0(5)
C(4)-N(1)-C(1)-C(13)	-118.4(4)
C(6)-N(1)-C(1)-C(2)	-165.2(4)
C(4)-N(1)-C(1)-C(2)	5.5(4)
N(1)-C(1)-C(2)-O(1)	-152.2(3)
C(11)-C(1)-C(2)-O(1)	91.4(4)
C(13)-C(1)-C(2)-O(1)	-27.8(5)
N(1)-C(1)-C(2)-C(3)	-27.6(4)
C(11)-C(1)-C(2)-C(3)	-144.0(3)
C(13)-C(1)-C(2)-C(3)	96.9(4)
O(1)-C(2)-C(3)-C(4)	161.1(3)
C(1)-C(2)-C(3)-C(4)	39.2(4)
O(1)-C(2)-C(3)-C(5)	-76.0(5)
C(1)-C(2)-C(3)-C(5)	162.2(4)
C(6)-N(1)-C(4)-C(3)	-170.0(3)
C(1)-N(1)-C(4)-C(3)	18.7(4)
C(5)-C(3)-C(4)-N(1)	-158.0(4)
C(2)-C(3)-C(4)-N(1)	-35.0(4)
C(7)-O(3)-C(6)-O(2)	-1.1(6)
C(7)-O(3)-C(6)-N(1)	178.8(3)
C(4)-N(1)-C(6)-O(2)	4.5(6)
C(1)-N(1)-C(6)-O(2)	174.6(4)

C(4)-N(1)-C(6)-O(3)	-175.4(3)	C(2)-C(1)-C(11)-O(4)	-100.7(6)
C(1)-N(1)-C(6)-O(3)	-5.3(5)	N(1)-C(1)-C(11)-O(5)	-32.5(5)
C(6)-O(3)-C(7)-C(9)	-67.9(5)	C(13)-C(1)-C(11)-O(5)	166.5(4)
C(1)-C(13)-C(14)-C(15)	172.9(4)	C(2)-C(1)-C(11)-O(5)	77.2(4)
C(6)-O(3)-C(7)-C(8)	55.9(5)	N(1)-C(1)-C(13)-C(14)	54.9(5)
C(12)-O(5)-C(11)-O(4)	-1.6(7)	C(11)-C(1)-C(13)-C(14)	179.5(4)
C(12)-O(5)-C(11)-C(1)	-179.6(4)	C(2)-C(1)-C(13)-C(14)	-61.7(5)
N(1)-C(1)-C(11)-O(4)	149.6(5)	C(1)-C(13)-C(14)-C(16)	-72.4(6)
C(13)-C(1)-C(11)-O(4)	22.6(6)	C(6)-O(3)-C(7)-C(10)	-159.5(4)

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11. Curriculum Vitae

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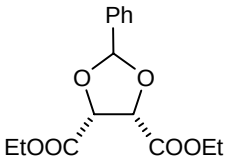
12. Formula table of structures



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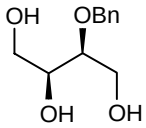

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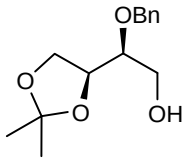

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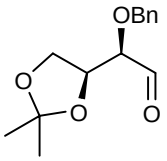

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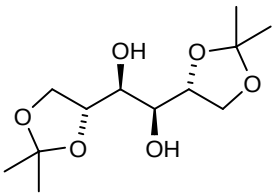

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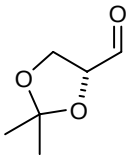

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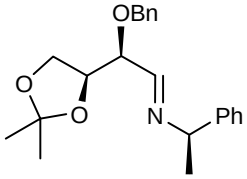

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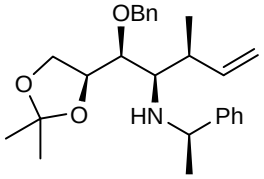

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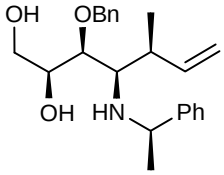

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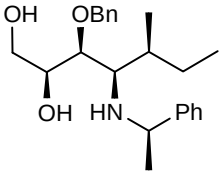

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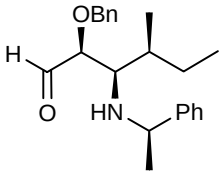

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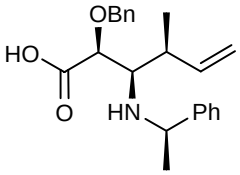

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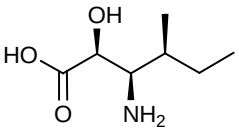

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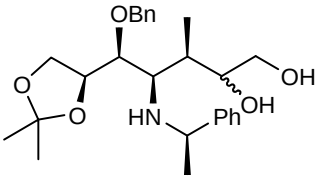

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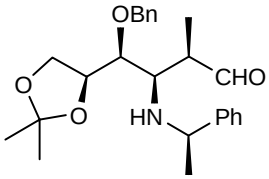

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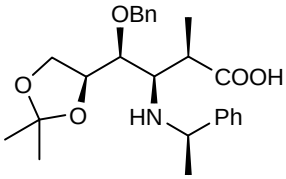

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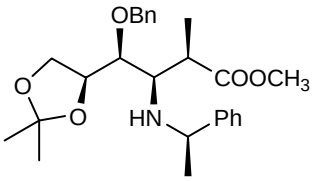

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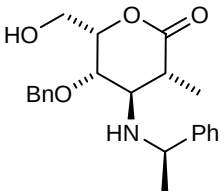

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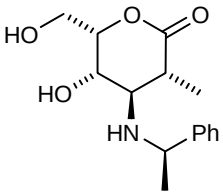

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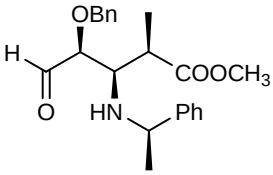

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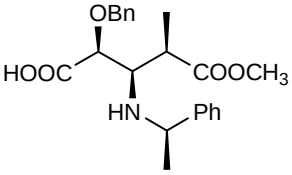

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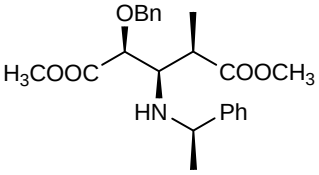

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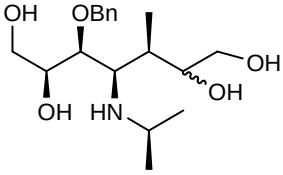

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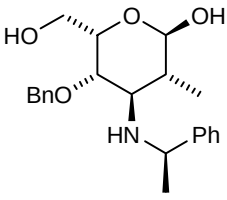

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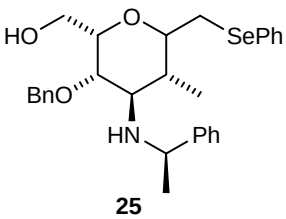

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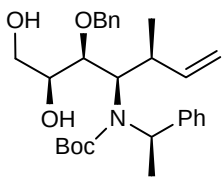

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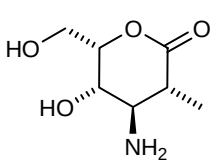

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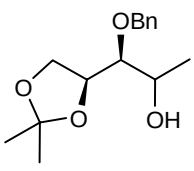

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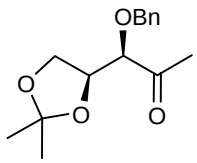

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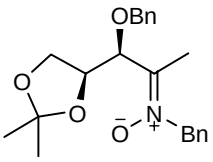

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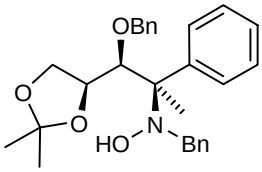

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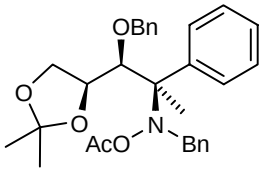

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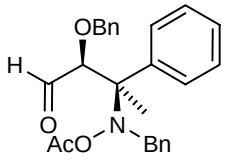

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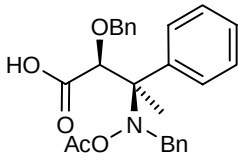

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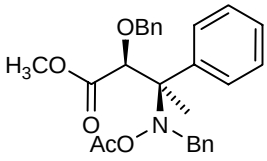

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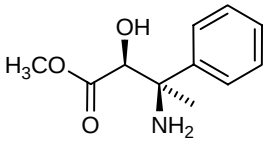

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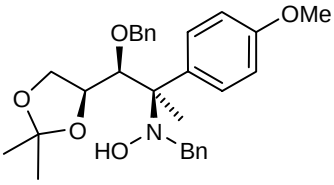

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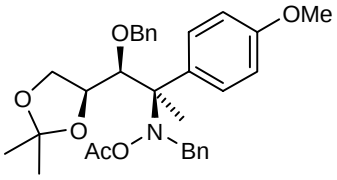

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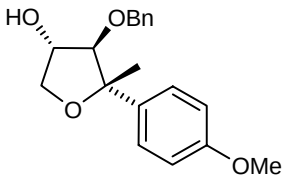

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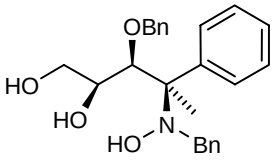

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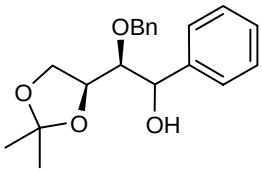

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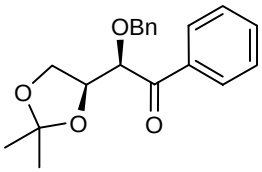

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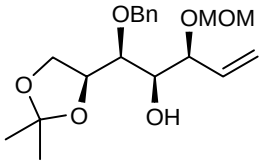

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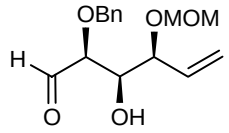

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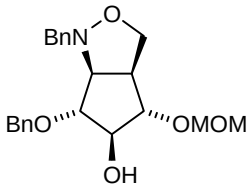

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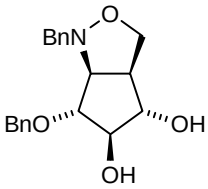

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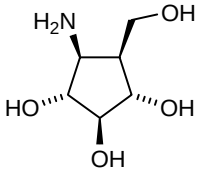

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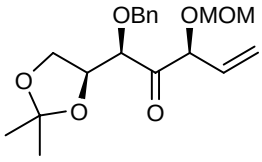

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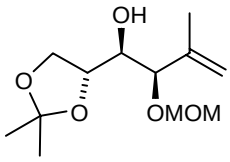

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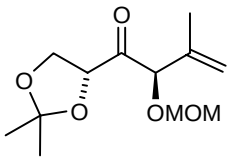

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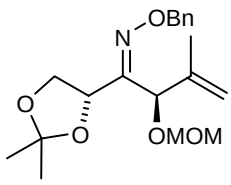

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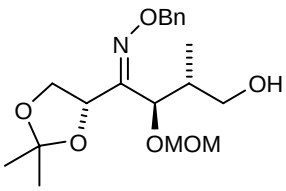

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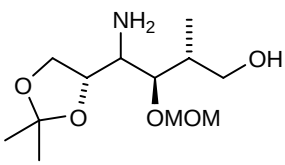

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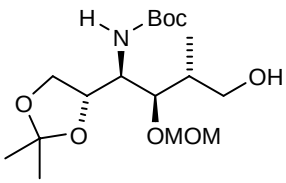

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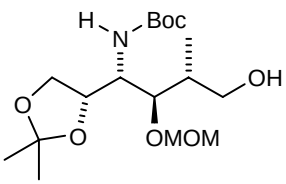

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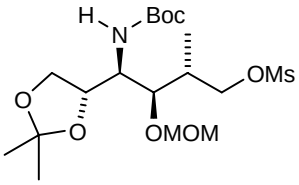

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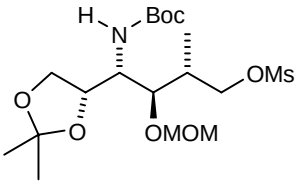

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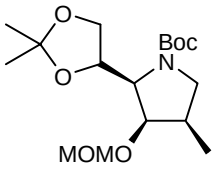

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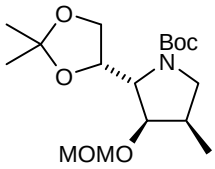

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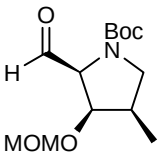

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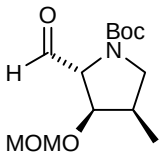

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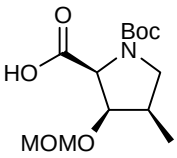

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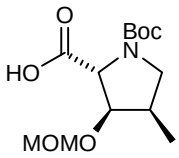

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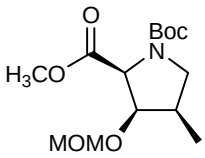

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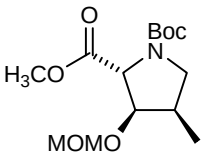

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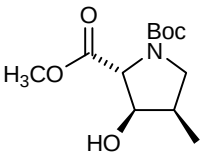

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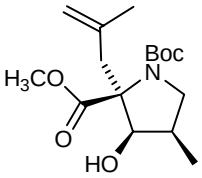

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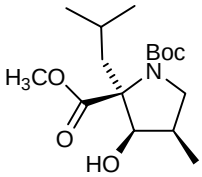

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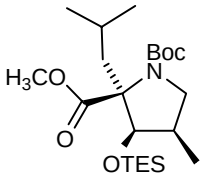

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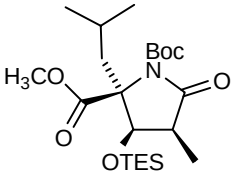

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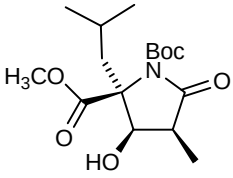

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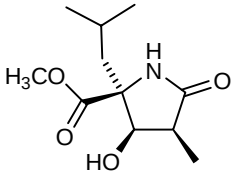

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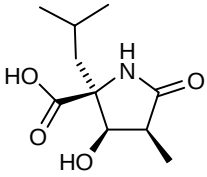

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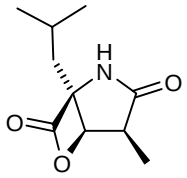

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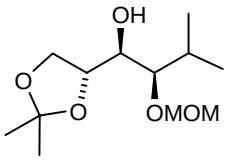

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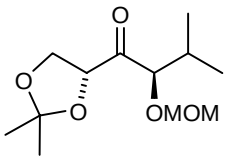

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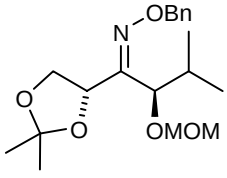

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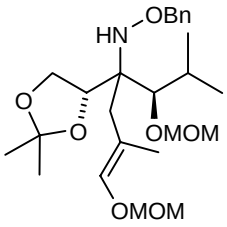

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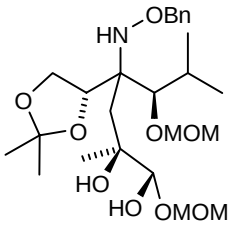

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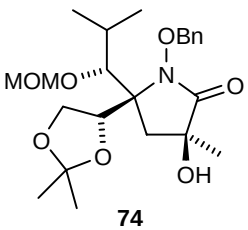

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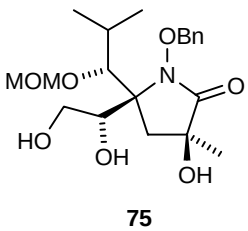

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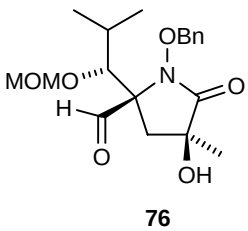

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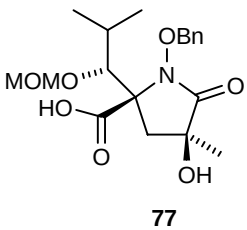

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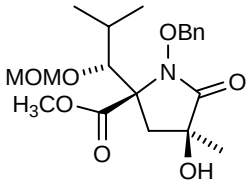

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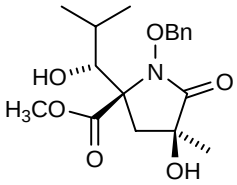

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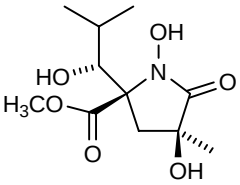

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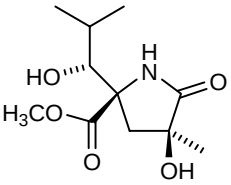

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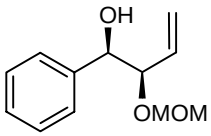

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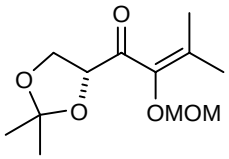

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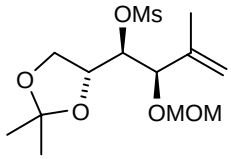

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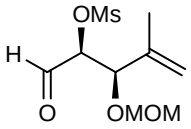

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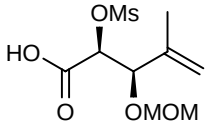

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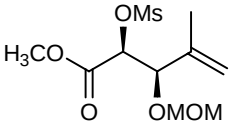

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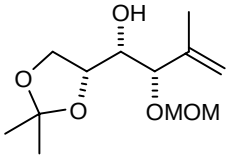

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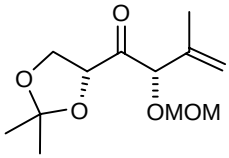

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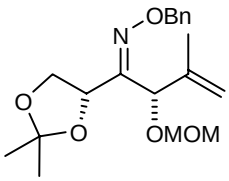

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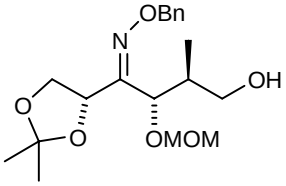

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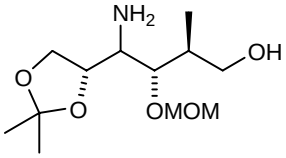

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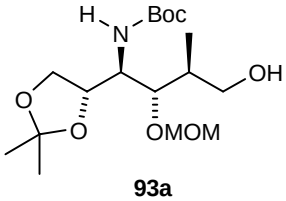

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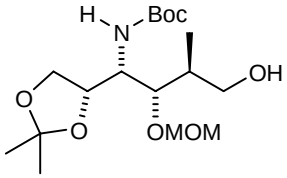

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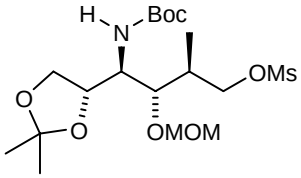

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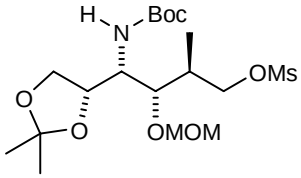

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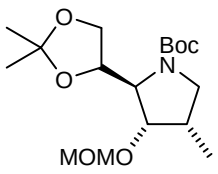

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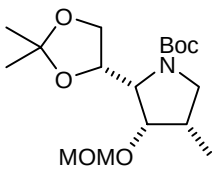

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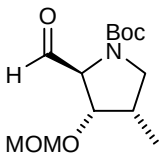

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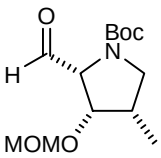

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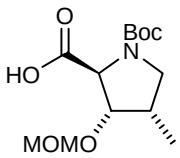

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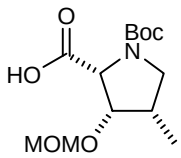

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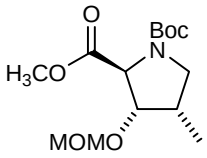

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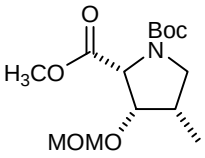

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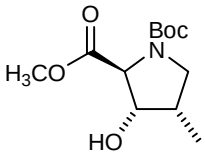

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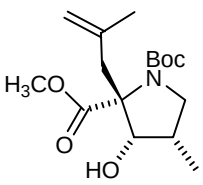

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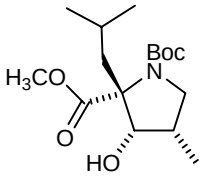

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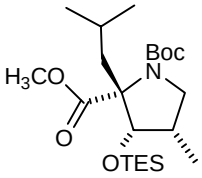

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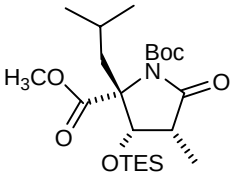

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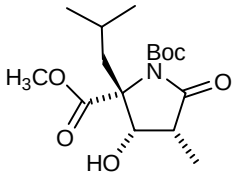

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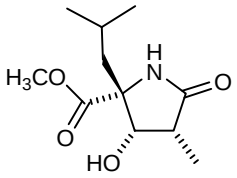

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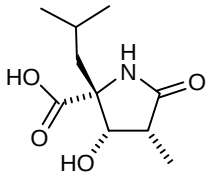

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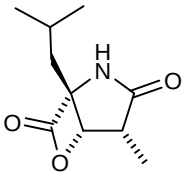

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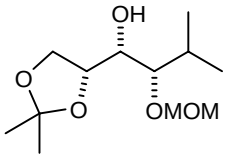

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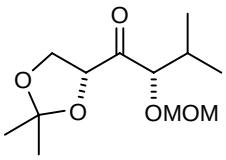

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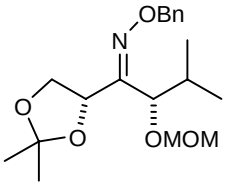

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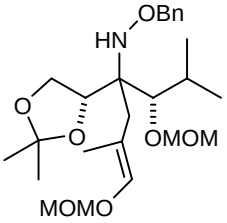

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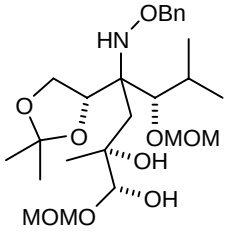

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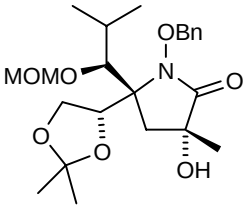

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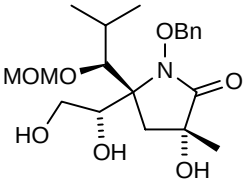

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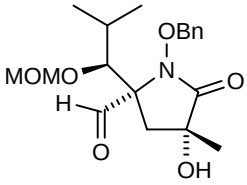

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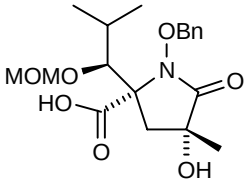

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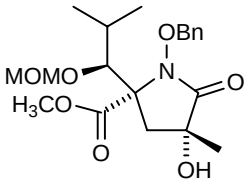

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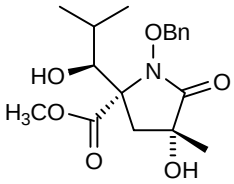

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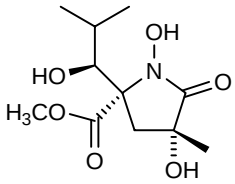

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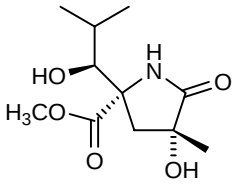

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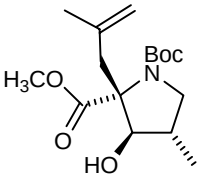

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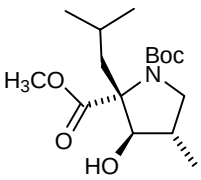

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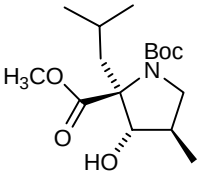

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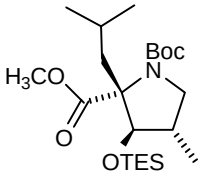

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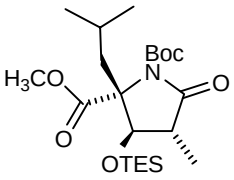

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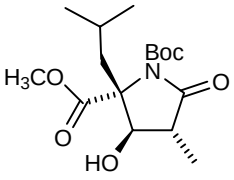

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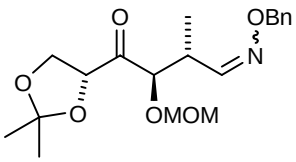

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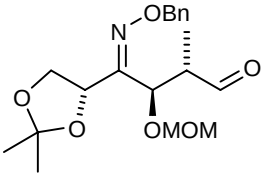

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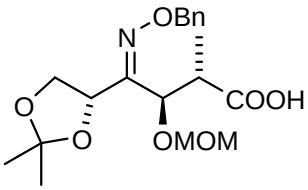

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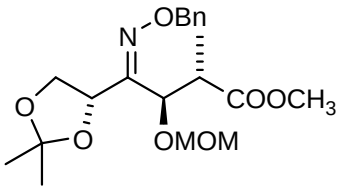

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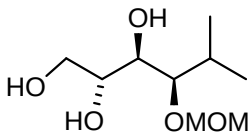

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