Synthesis of Branched Amino Polyols and Amino Hydroxy Acids: Stereoselective Addition of *C*-Nucleophiles to Isoxazolines and Isoxazolinium Salts and Assignment of Configurations

Von der Fakultät Chemie der Universität Stuttgart
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Doktors der Naturwissenschaften
(Dr. rer. nat.)
genehmigte Abhandlung

vorgelegt von
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aus Aleppo/Syrien

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Mitberichter:	Prof. Dr. S. Hashmi
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Institut für Organische Chemie
der Universität Stuttgart
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Dedication

First, to those closest to me: my parents, my sisters and brothers, and second to my Doktorvater Prof. V. Jäger. Without the help and encouragement from all of you, this dissertation could never have been accomplished.

Part of this work has been presented in:

Publications:

Frey, W.; Imerhasan, M.; **Bathich, Y.**; Jäger, V. *Crystal structure of (5S,8S)-8-hydroxymethyl-1-methyl-2,7-dioxa-1-aza-spiro[4,4]nonan-6-one*, $C_8H_{13}NO_4$. Z. Krist. NCS **220**, 2005, 151-152.

Posters:

1. **Yaser Bathich**, Mukhtar Imerhasan, Marco Henneböhle, Pierre-Yves LeRoy, Volker Jäger*, *N-Methylisoxazolinium Salts: New Building Blocks in the Stereoselective Synthesis of Amino Polyols and Amino Acids;* poster presented at the 6th IMINIUMSALZ-TAGUNG (ImSaT-6), September 15-18, 2003, Stimpfach-Rechenberg, Germany; Book of abstracts, pp. 99-107.

2. **Yaser Bathich**, Marco Henneböhle, Pierre-Yves LeRoy, Mukhtar Imerhasan, Volker Jäger, *N-Methylisoxazolinium Salts: New Building Blocks in the Stereoselective Synthesis of Amino Polyols and Amino Acids*; poster presented at ORCHEM 2004, September 9-11, 2004, Bad Nauheim, Germany; Book of abstracts, p 220.

Lectures:

1. Shiva Sunitha, **Yaser Bathich**, Marco Henneböhle, Pierre-Yves LeRoy, Volker Jäger, *N-Methylisoxazolinium Salts: New Building Blocks for the Stereoselective Synthesis of Branched Amino Polyols and Amino Acids*, lecture presented by Ms. Shiva at 1. BBS-SYMPOSIUM ON ORGANIC CHEMISTRY: N,O-HETEROCYCLES AND MORE, April 7-10, 2005, Bratislava, Slovak Republic; Book of abstracts, p 28.

2. **Y. Bathich** and V. Jäger, *Synthesis of Branched Amino Hydroxy Acids and Amino Polyols by Stereoselective Addition of C-Nucleophiles to Isoxazolines and Isoxazolinium Salts,* 10. Tag der Organischen Chemie der Universität Stuttgart (TOCUS 10), 14.10.2005.

Table of Contents

Preliminary remarks and abbreviations

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

All compounds prepared during this work and cited in the Experimental Part are consecutively numbered **1**, **2**, **3** etc. and are assembled in the **Formula Tables of Structures Prepared** at the end. Some preparations yielded diastereomeric mixtures; the diastereomers are assigned as **a** (major diastereomer) and **b** (minor diastereomer).

Starting in chapter 1, all other formulas and structures are consecutively labeled in bold-printed capital letters, i.e. **A**, **B**, ... , **Z**, **AA**, **AB** etc.

List of abbreviations used:

abs.	absolute	FT	Fourier Transformation
Boc	*tert*-butyloxy carbonyl	h	hour(s)
Bn	benzyl	HPLC	High Pressure Liquid
Bu	butyl		Chromatography
c	concentration	Hz	Hertz
calc.	calculated	*i*	ipso
cat.	catalytic	IR	Infrared spectroscopy
Chap.	Chapter	*J*	coupling constant
conc.	concentrated	lit.	literature
corr.	corrected	*m*	meta
COSY	correlated spectroscopy	M	molarity
d	day(s)	m.p.	melting point
d.r.	diastereomeric ratio	Me	methyl
DEPT	distortionless enhancement	min	minute(s)
	by polarization transfer	MPLC	Medium Pressure Liquid
dist.	distilled		Chromatography
DMF	*N*,*N*-dimethylformamide	N	normality
DMSO	dimethyl sulfoxide	NCS	*N*-chlorosuccinimide
eq	equivalent (s)	NMR	Nuclear Magnetic
Eq.	equation		Resonance
Et	ethyl	*o*	ortho
Exp.	experiment No. in	*p*	para
	Experimental Part	PG	protecting group

Ph	phenyl
Py	pyridine
r.t.	room temperature
s	secondary
sat.	saturated
t	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatogarphy
TMS	trimethylsilyl tetramethylsilane
TP	Typical Procedure
UV	Ultraviolett
Z	benzyloxycarbonyl

Zusammenfassung

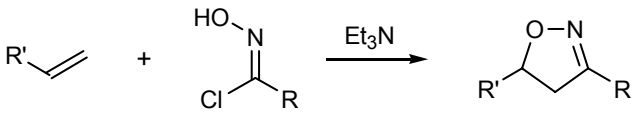
β-Aminosäuren sind aufgrund ihres Vorkommens in einer großen Anzahl von Naturprodukten, pharmazeutischen Wirkstoffen und von Proteinmimetika lohnenswerte Syntheseziele. Aufgrund dieser Wichtigkeit der β–Aminosäuren bestand die diese Arbeit darin, effizienten Zugang zu Aminoalkoholen und -polyolen, sowie zu verzweigten β-Aminosäuren als Zielverbindungen zu entwickeln.

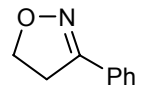
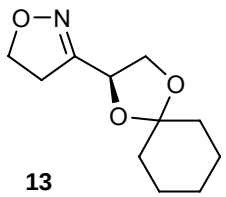
Dabei wird die Umwandlung von Isoxazolinen als Schlüsselzwischenstufen, die entweder durch Lewis-Säuren oder durch Überführen in das entsprechende *N*-Methylisoxazolinium-Salz aktiviert werden, verwendet. Dazu wurde die hoch-stereoselektive Addition von *C*-Nucleophilen an diese „aktivierten'' Isoxazoline untersucht, gefolgt von der Umwandlung zu den Zielstrukturen. Die absolute Konfiguration der verschiedenen enantiomerenreinen Verbindungen wurde bestimmt. Die leicht zugänglichen und unterschiedlich substituierten Verbindungen sollten zukünftige Studien bezüglich Struktur und Funktion dieser wichtigen Verbundungsklasse erleichtern.

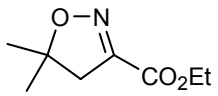
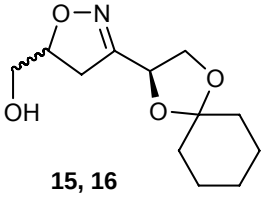
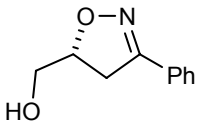
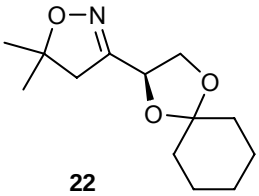
A) Darstellung der Isoxazoline und *N*-Methylisoxazolinium-Salze

Die Isoxazoline wurden durch 1,3-dipolare Cycloaddition der entsprechenden Olefine und Nitriloxide, die in situ aus Oximen über die Hydroxamsäurechloride erhalten wurden, dargestellt (siehe Tabelle I).

Tabelle I. Darstellung der Isoxazoline

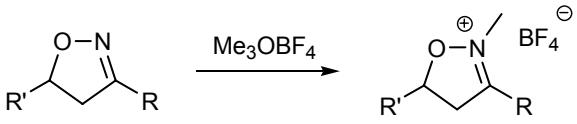


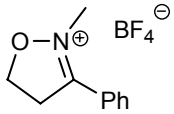
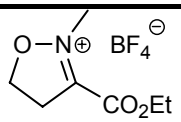
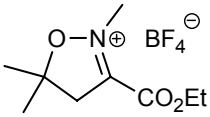
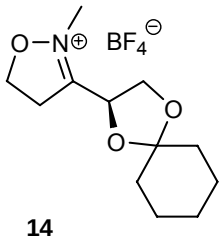
Cycloaddukt	Ausbeute	Cycloaddukt	Ausbeute
 **2**	87 %	 **13**	84 %

 **5**	70 %	 **15, 16**	91 %
 **9**	93 %	 **22**	82 %

Eine Möglichkeit der Aktivierung, die in dieser Arbeit verfolgt wurde, ist die *N*-Alkylierung der Isoxazoline mit Meerwein-Salz (Trimethyloxoniumtetrafluoroborat), um in hoher Ausbeute das entsprechende Isoxazolinium-Salz zu erhalten (Tabelle II).

Tabelle II Darstellung der Isoxazolinium-Salze



Isoxazolinium-Salz	Ausbeute	Isoxazolinium-Salz	Ausbeute
 **3**	95 %	 **8**	(79 %)[a]
 **6**	88 %	 **14**	88 %

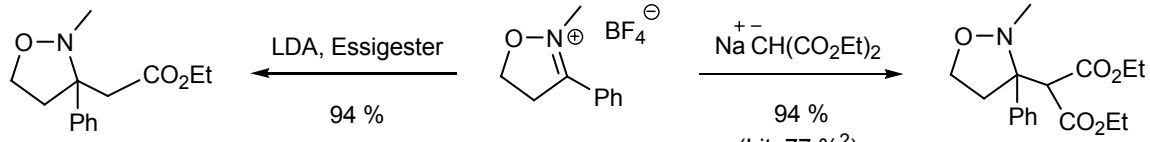
[a] Elementaranalyse leicht abweichend.

B) Reaktion der *N*-Methylisoxazolinium-Salze mit *C*-Nucleophilen

1. Addition von Malonsäurediethylester-Natrium-Salz und Lithiumessigesterenolat an N-Methylisoxazolinium-Salze

Die Verwendung von Malonsäurediethylester-Natrium-Salz und Lithiumessigesterenolat als *C*-nucleophile Reagenzien für verwandte Addukte wurde untersucht. Die Addition von Malonat an ein Modell-Isoxazolinium-Salz **3** wurde bereits von LeRoy in unserer Gruppe durchgeführt, was nun optimiert wurde. Die Addition eines neuen Esterenolats an das Isoxazolinium-Salz **3** erwies sich als glatte Umsetzung mit hoher Ausbeute (Gl. I).

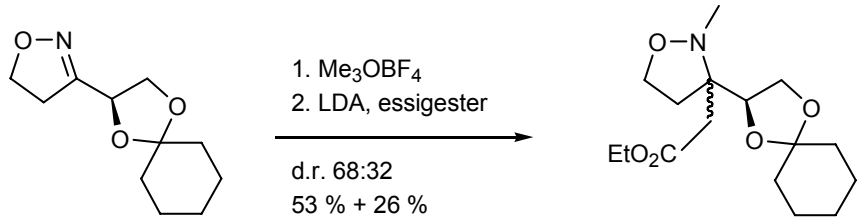
(I)



24 **3** **23**

In dieser Arbeit wurde das chirale *N*-Methylisoxazolinium-Salz **14** (aus **13**) bei der Enolat-Addition verwendet, was das entsprechende Addukt in guter Ausbeute, aber mäßiger Diastereoselektivität lieferte (Gl. II)

(II)

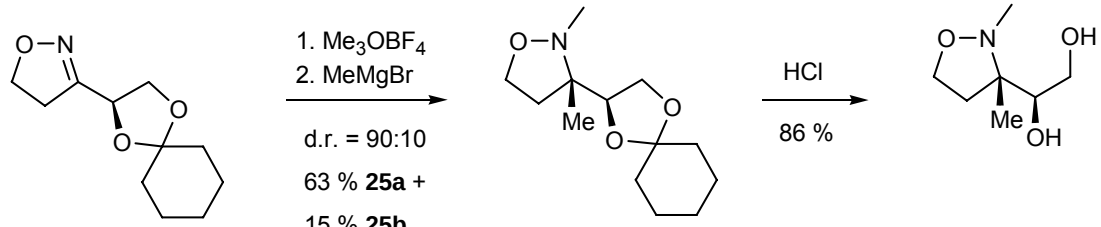


13 **26 a/b**

2. Addition von Metallorganylen an N-Methylisoxazolinium-Salze

In der vorausgehenden Dissertation unserer Gruppe auf diesem Gebiet hat Henneböhle die Addition verschiedener Grignard-Reagenzien an *N*-Methylisoxazolinium-Salze, wobei die Konfiguration der Addukte unbekannt blieb. Die Addition von Methylmagnesiumbromid an das *N*-Methylisoxazolinium-Salz **13** wurde nun wiederholt und das Addukt dann in das entsprechende Diol **52•HCl** überführt. Daraus wurde die Konfiguration durch eine Röntgenstrukturanalyse bestimmt, was auch die Bestimmung der bis dahin nicht bekannten Konfiguration an C-3 des Diols **52•HCl** und dessen Isoxazolidin-Vorläufer **25a** [Gl. III], erlaubte.

(III)



13 **25a** **52 • HCl**

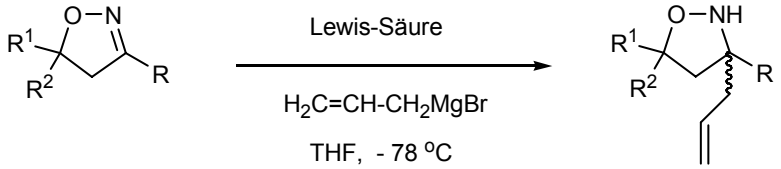
("X-ray")

C) Reaktion von Isoxazolinen mit *C*-Nucleophilen bei Anwesenheit von Lewis-Säure

1. Addition von Grignard-Reagenzien an Isoxazoline bei Anwesenheit von Lewis-Säure

Als alternative Route, um Isoxazoline als Akzeptoren für *C*-Nucleophile am C-3 zu aktivieren und die Anwesenheit einer Methylgruppe am Stickstoff des Isoxazolins, die durch die Aktivierung durch Meerwein-Salz auftritt, zu vermeiden, können spezielle *C*-Nucleophile auch durch vorausgehende Aktivierung durch Lewis-Säure an die Isoxazoline addiert werden, häufig mit sehr guten Diastereoselektivitäten und in hohen Ausbeuten (Tabelle III).

Tabelle III. Addition von Allylmagnesiumbromid an Isoxazoline in Gegenwart von Lewis-Säure



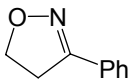
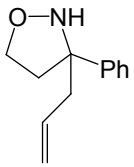
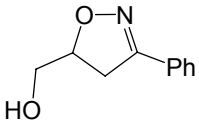
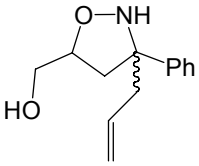
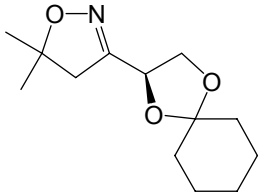
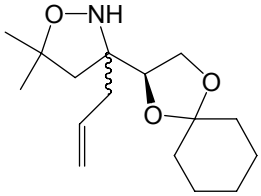
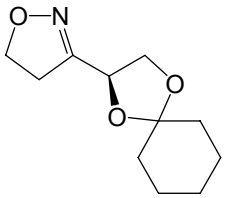
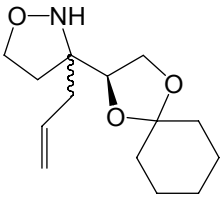
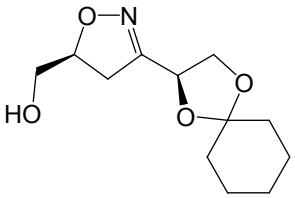
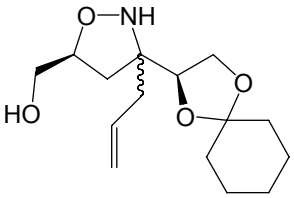
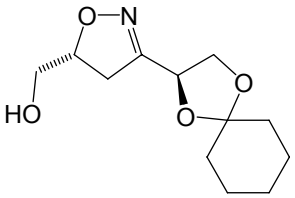
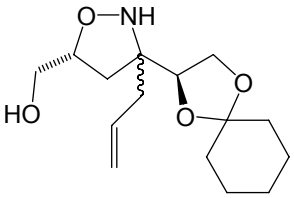
Nr.	Isoxazolin	Isoxazolidin	Lewis-Säure	d.r.[a]	Ausbeute[b] **a**	**b**	Σ
1			BF_3•OEt_2	-	-	-	65 %
2			$ZnBr_2$	-	-	-	76 %
3	**2**	**30**	$ZnCl_2$	-	-	-	59 %
4			$ZnBr_2$	85:15	-	-	63 %
	9	**31 a/b**					
5			$ZnBr_2$	88:12	73 %	11 %	84 %
6			$ZnCl_2$	87:13	67 %	9 %	76 %
7			BF_3•OEt_2	83:17	65 %	12 %	77 %
	22	**33 a/b**					

Tabelle III, Fortsetzung

Nr.	Isoxazolin	Isoxazolidin	Lewis-Säure	d.r.[a]	Ausbeute[b] **a**	**b**	Σ]
8	 **13**	 **34 a/b**	$ZnBr_2$	80:20	64 %	17 %	81 %
9	 **15/16** d.r. 87:13	 **35 a/b**	$ZnCl_2$	85:15	65 %	13 %	78 %
10			$ZnBr_2$	76:24	55 %	15 %	70 %
11			BF_3•OEt_2	77:23	47 %	16 %	63 %
12	 **15/16** d.r. 15:85	 **36 a/b**	$ZnCl_2$	81:19	61 %	19 %	80 %
13			$ZnBr_2$	78:22	61 %	17 %	78 %

[a] Die Bestimmung der Diastereomerenverhältnisse basiert auf den Intensitäten getrennter Signalpaare in den ^{13}C-NMR-Spektren der Rohprodukte. [b] Ausbeute berechnet über 2 Schritte ausgehend vom entsprechenden Isoxazolin; **a** : Hauptdiastereomer, **b** : Nebendiastereomer.

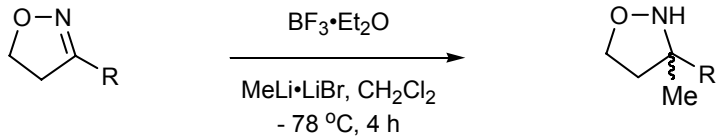
Der Einfluss von Temperatur und Lewis-Säure auf Ausbeute und Stereoselektivät der Addition wurde untersucht, es zeigte sich jedoch kein signifikanter Effekt. Bei diesen Versuchen was es nun möglich, die absolute Konfiguration der erhaltenen Isoxazolidine zu bestimmen, nachdem mehrere Kristallstrukturen erhalten werden konnten.

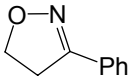
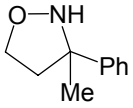
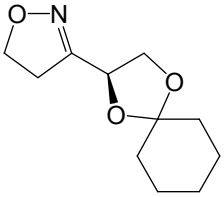
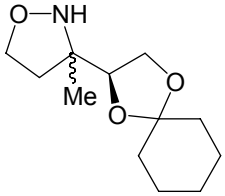
2. Addition von Alkyllithium-Lithiumbromid-Komplexen an Isoxazoline in Gegenwart von Lewis- Säure

Die Addition von *Alkyllithium-Lithiumbromid-Komplexen* an Isoxazoline wurde bislang nur selten untersucht. In der vorliegenden Arbeit wurde die Addition unter Verwendung von Methyllithium-Lithiumbromid in Gegenwart von Bortrifluorid-Etherat als Lewis-Säure

durchgeführt. Die Addukte wurden in hohen Ausbeuten erhalten, bei Verwendung des chiralen Isoxazolins **13** mit mäßigen Diastereoselektivitäten (Tabelle IV).

Tabelle IV. Addition des Methyllithium-Lithiumbromid-Komplexes an die Isoxazoline **2**, **13** in Gegenwart von Bortrifluorid-Etherat



Isoxazolin	Isoxazolidin	d.r.[a]	Ausbeute		
			a	**b**	Σ
 **2**	 **29**	-	-	-	83%
 **13**	 **32 a/b**	68:32	58 %	27 %	85 %

[a] Die Bestimmung der Diastereomereneverhältnisse basiert auf den Intensitäten getrennter Signalpaare in den ^{13}C-NMR-Spektren der Rohprodukte. **a** : Hauptdiastereomer, **b** : Nebendiastereomer.

C) Umwandlungen der Isoxazoline

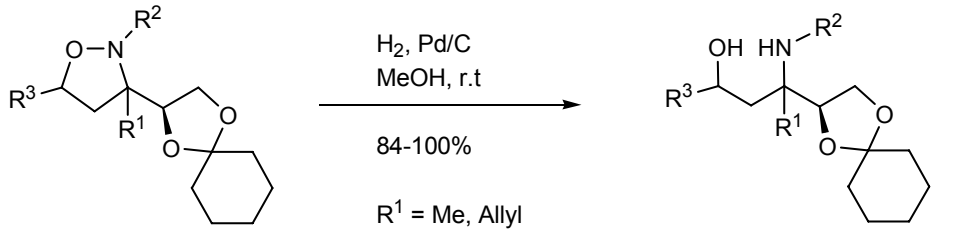
Ein Großteil dieser Arbeit befasste sich mit der Umwandlung der erhaltenen Isoxazolidine zu unterschiedlichen Zielstrukturen wie Aminoalkoholen and -polyolen oder α- and β-Aminosäuren, erstens, um die Konfiguration der Additionsprodukte zu bestimmen und zweitens um zu zeigen, dass Isoxazoline vielversprechende zwischenstufen bezüglich Synthesen von Aminosäuren sind.

1. Synthese von N-(un)substitutierten Aminoalkoholen and -polyolen

Um Aminoalkohole and -polyole ausgehend von den Isoxazolidinen zu erhalten, war es lediglich nötig, die N-O-Bindung der Isoxazolidine zu spalten. Hierzu erwies sich die

palladium-katalysierte Hydrierung als effektiv und lieferte die Zielstrukturen meistens in hoher Ausbeute [Gl. IV].

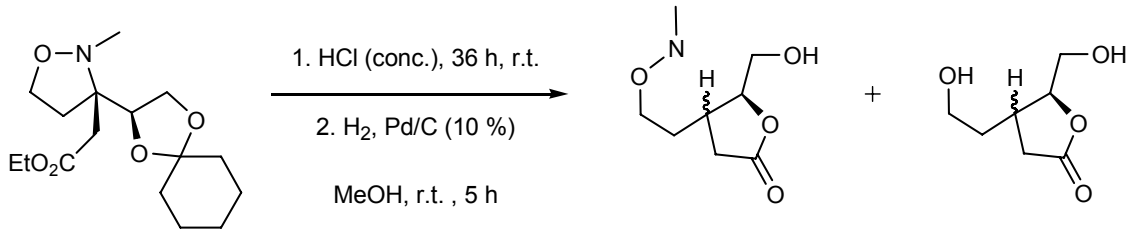
(IV)



25a, 25b, 32a, 34a, 34b, 35a, 35b, 52 **41, 42, 45, 47, 48,49, 50, 70**

Die absoluten Konfigurationen der dargestellten 3,3-disubstituierten Aminoalkohole and -polyole wurden basierend auf der relativen Konfiguration von entsprechenden Verbindungen der gleichen Serie, z. B. der 3,3-disubstituierten Isoxazolidine, von denen eine Kristallstruktur erhalten werden konnte, festgelegt. Ein abweichendes Verhalten wurde beobachtet, als ester-substituierte Isoxazolidine in der katalytischen Hydrierung untersucht wurden. Hier wurde zum Teil auch die C-N-Bindung statt der N-O-Bindung gespelten, wie das folgende Beispiel zeigt. [Gl. V]:

(V)

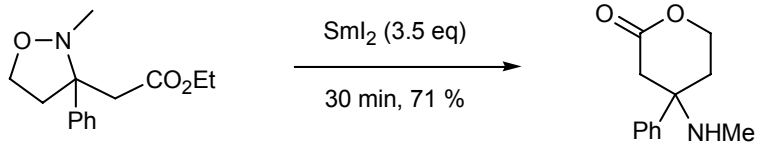


26a **57a/b** **58a/b**

74 % [*63*:*37*] 16 % [*65*:*35*]

Die Spaltung der N-O-Bindung wurde später durch eine Lösung von Samariumdiiodid in THF erreicht, wie in Gl. VI gezeigt, lieferte.

(VI)



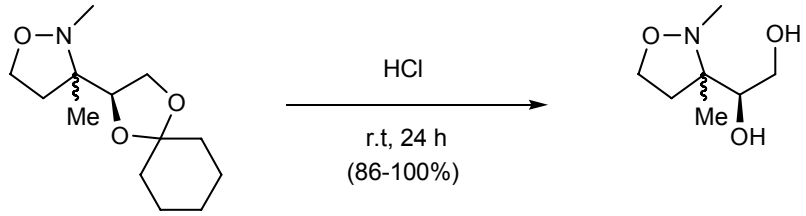
24 **37**

2. Hydrolyse der Isoxazolidin-Derivative: Acetale und Ester

Ein anderer Aspekt dieser Arbeit war, die Konfiguration der dargestellten Isoxazolidine zu bestimmen. Saure Hydrolyse des Isoxazolidins **25a** führte zum entsprechenden Diol **52•HCl**

in Form des Hydrochlorids [Gl. VII]. Die Struktur dieses Diols **52•HCl** wurde durch röntgenkristallographische Untersuchung bestätigt.

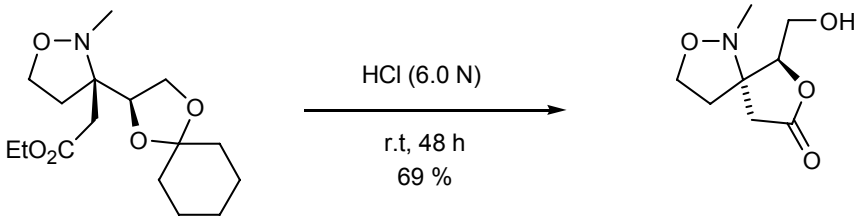
(VII)



25a **52 • HCl**

Auf gleiche Weise erfolgte die Hydrolyse des Isoxazolidinesters **26a** [Gl. VIII], wodurch das Isoxazolidinolacton **54** erhalten wurde; dessen Struktur wurde durch eine Röntgenstrukturanalyse bestätigt.

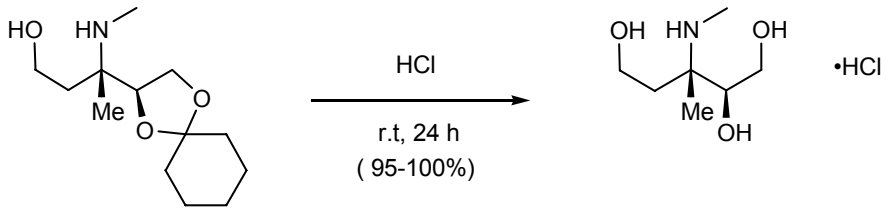
(VIII)



26a **54**

Interessanterweise wurden die *N*-Methylaminopolyole auf ähnlichem Weg problemlos dargestellt, wenn es auch teilweise schwierig war, korrekte Elementaranalysen zu erhalten. Auch hier war es möglich die Konfiguration eines Isoxazolidin (**25a**) durch Bestimmung der Kristallstruktur des Aminotriol-Hydrochlorids **70•HCl** [Gl. IX] aufzuklären.

(IX)



25a **70•HCl**

Abschließend sei gesagt, dass Transformationen zu einer Reihe solcher Strukturen durch einfache Schritte (katalytische Hydrierung, Hydrolyse) möglich waren, und damit die Vielseitigkeit dieses Zugangs zu den verschiedenen Zielstrukturen auf gezeigt werden könnte.

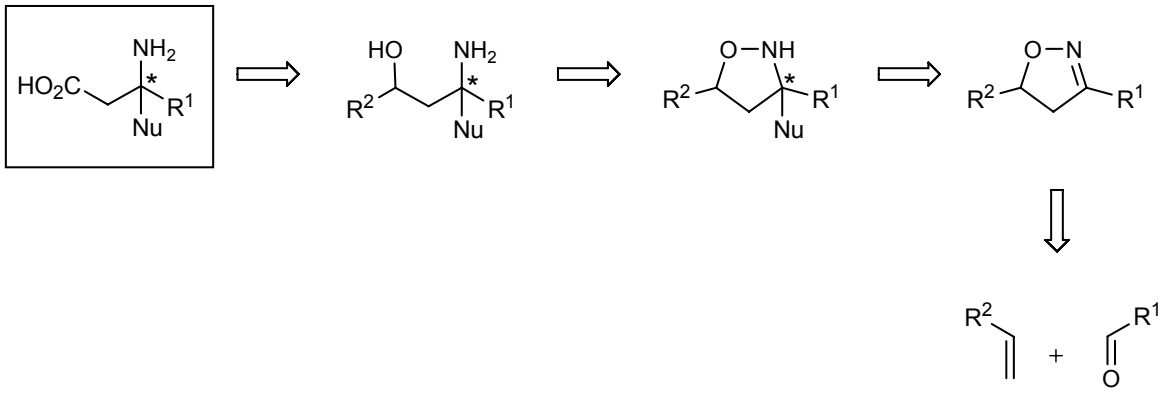
3. Synthese verzweigter β-Aminosäuren

Anlass zu dieser Studie war, einen neuen Zugang zu (verzweigten) Aminosäuren zu finden, was durch die Umsetzung von *N*-(un)substituierten Aminoalkoholen und -polyolen zu den entsprechenden Aminosäuren gelang.

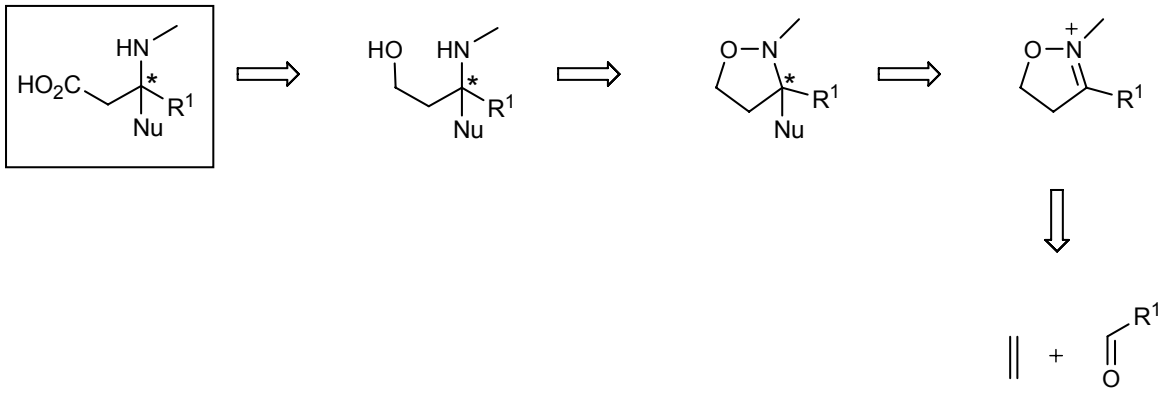
Dabei wurde nach dem Aufbau des "aktivierten Isoxazolin-Rings" eine Reihe von *C*-Nucleophilen addiert, was die entsprechenden Isoxazolidine in hoher Ausbeute und meistens mit hoher Selektivität lieferte. Nach katalytischer Hydrierung wurden die erhaltenen Aminoalkohole oder Aminopolyole geschützt und konnten nun zu einer Anzahl β-Aminosäuren durch Oxidation des primären Alkohols oder in einigen Fällen der Diol-Einheit, gefolgt von der Abspaltung der Schutzgruppe am Stickstoff, überführt werden (Schema I).

Schema I

A) Aktivierung durch Lewis-Säure

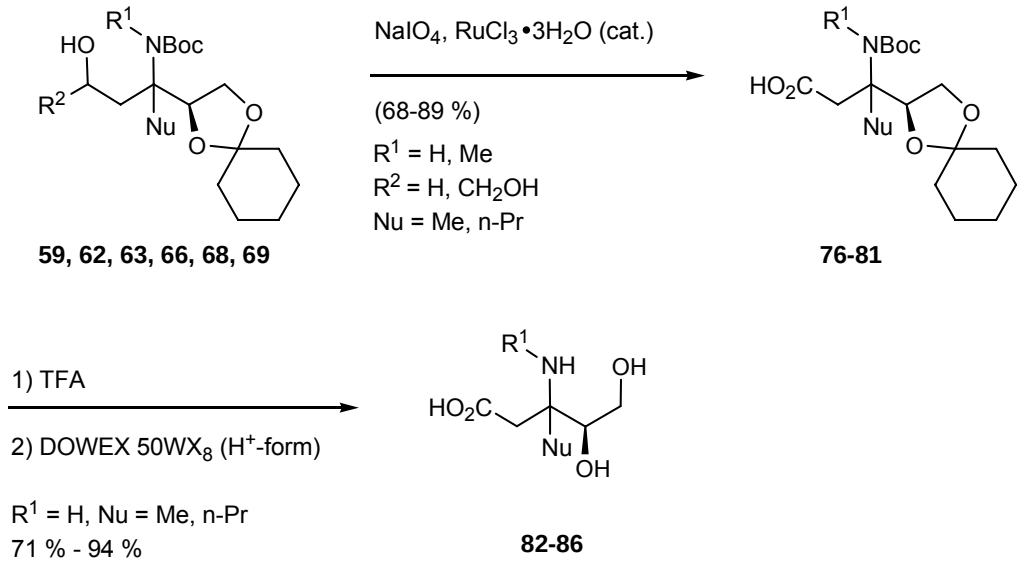


B) Aktivierung durch *N*-Methylierung



Mit der zuvor dargelegten Strategie war es naheliegend, die hochfunktionalisierten *N*-(un)substituierten Aminoalkohole und -polyole in die entsprechenden β-Aminosäuren zu überführen. Dazu wurden die *N*-(un)substituierten Aminoalkohole und -polyole als *N*-Boc-Derivative geschützt, die dann zu den geschützten β-Aminosäuren **76**-**81**. Nach Abspaltung der Schutzgruppen durch trifluoressigsäure und Reinigung am Ionenaustauscher wurden mehrere β-Aminosäuren in guter Gesamtausbeute erhalten. Die Konfiguration aller geschützten und ungeschützten β-Aminosäuren wurde durch Röntgenkristallographie von entsprechenden Verbindungen der gleichen Serie (Schema II) **82**-**86**.

Schema II



Somit wird ein vielseitiger und effizienter Weg zu verschiedenen Aminoalkoholen und -polyolen gezeigt. Die Synthese verläuft über chirale Isoxazolidine als Schlüsselzwichenstufen, zum Teil unter hoher Selektivität der 1,3-dipolaren Cycloaddition bei der Bildung weiterer Strukturen mit bis zu drei benachbarten stereogenen Zentren. Dadurch war es möglich, neue, flexible und effiziente Wege zu verzweigten *N*-(un)substituierten Aminoalkoholen bzw. -polyolen und zu β-Aminosäuren zu entwickeln. Insbesondere wurde gezeigt, dass Isoxazoline in hohem Maße brauchbare Vorläufer für Zielstrukturen mit tertiären und quartären stickstoffhaltigen Stereozentren darstellen, was sich in der Zukunft bei der Synthese anderer interessanter verzweigter Aminoverbindungen als nützlich erweisen sollte.

1. Introduction and Aims

The main aim of this work is the development of synthetic routes towards amino alcohols as well as branched α– and β–amino acids starting from achiral and chiral (racemic and optically active) isoxazolines **A** and *N*-methylisoxazolinium salts **B**.

A **B** **C** **D**

The isoxazolines were treated with a variety of Grignard reagents and organolithium complexes as *C*-nucleophiles. These results were comparable to the findings of analog additions to the ‘’activated’’ isoxazolines, that is, to the isoxazolinium salts **B**. The latter react smoothly with Grignard reagents, as well as with weaker *C*-nucleophiles such as sodium diethyl malonate or lithium ester enolate. At the same time it was observed, that the addition proceeds with -particly- good diastereoselectivity under mild reaction conditions, leading to good yields of the corresponding substituted isoxazolidines **C**.

Isoxazolines **A** and isoxazolinium salts **B** serve as versatile synthetic building blocks which were transformed into structurally very different, but nonetheless important target compounds. Related to this was the synthesis of amino alcohols and amino polyols, primarily by use of **B**. This approach required reductive opening of the N-O bond, and was achieved with almost quantitative yields through catalytic hydrogenation.

The synthesis of branched β-amino acids **D** was achieved via 1,3-aminoalcohols (-polyols), which were accessible with good yields and mostly high diastereoselectivity. After the introduction of the Boc protecting group at nitrogen, the amino alcohols were oxidized to carboxylic acids (cf. **B**). In some cases β-aminolactones were obtained instead of the open-chain β-amino hydroxy acids.

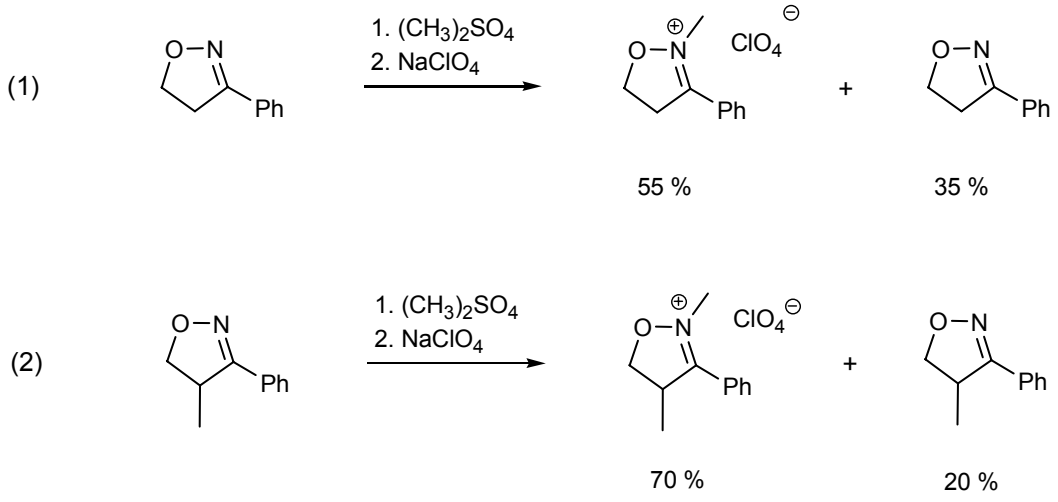
Attempts to N-demethylate the isoxazolidines remained unsuccessful. Therefore, later in this work, additions of a variety of *C*-nucleophiles to isoxazolines were performed using different Lewis acids to synthesize the required isoxazolidines in one step, thus avoiding the activation step of N-methylation with Meerwein salt. As done with the substituted isoxazolidines **C**, the isoxazolidines **E** were transformed into branched β-amino acids **F** through the cleavage of

the N-O bond followed by N-protection, which gave the possibility for alcohol or diol oxidation; the last step then was the removal of the Boc group.

E **F**

This work centered on the results of Hennböhle[1] and LeRoy[2], the first two dissertations in this project in our research group, in which the addition of several *C*-nucleophiles such as, metal organyls, cyanide reagents, sodium borohydride, Grignard reagents, sodium malonate and lithium methanenitronate were added to isoxazolinium salts. The transformation of the isoxazolidine **C** into the corresponding branched β-amino acid **D** was described.[1]

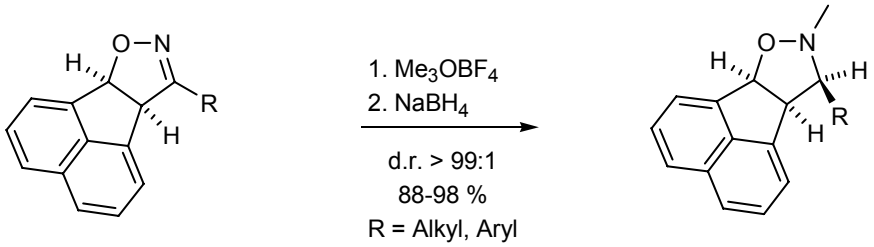
Apart from the previous research work in the Jäger group, very few examples of isoxazolinium salts can be found in the literature. The first isoxazolinium salt was reported in 1955.[3] In 1973, Belly et al. reported that isoxazolines can be methylated with dimethyl sulfate to produce the corresponding isoxazolinium salts [(Eq. 1) and (Eq. 2)].



During the last 40 years, several other alkylating agents were used to produce N-alkylisoxazolinium salts such as: methyl iodide,[4,5] dimethyl sulfate,[3,5,6,7] triethyloxonium[8] and trimethyloxonium tetrafluoroborate.[9,10]

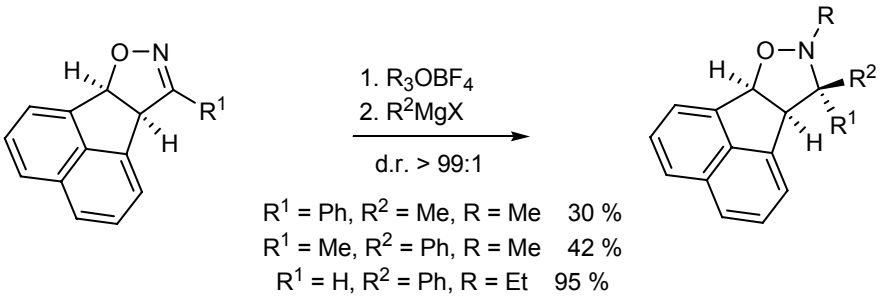
In 1974 Gandolfi et al. published their results on the addition of sodium borohydride to a *N*-methylisoxazolinium salt in which the diastereomeric ratio was cited as ‘’100%’’, and the yields were 88-98 % [Eq. (3)].[11]

(3)



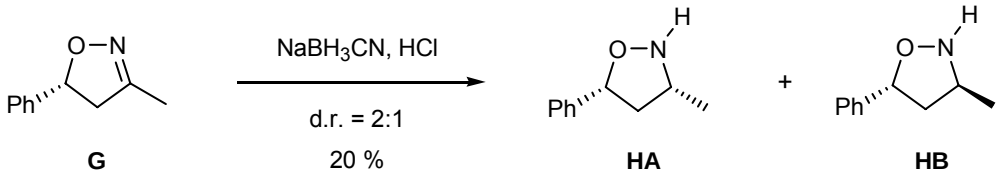
Additions of Grignard reagents were also reported, with excellent diastereoselectivity albeit unsatisfactory yields; when triethyloxonium tetrafluoroborate was used instead of trimethyloxonium tetrafluoroborate, the yield was improved in one case [Eq. (4)][11].

(4)

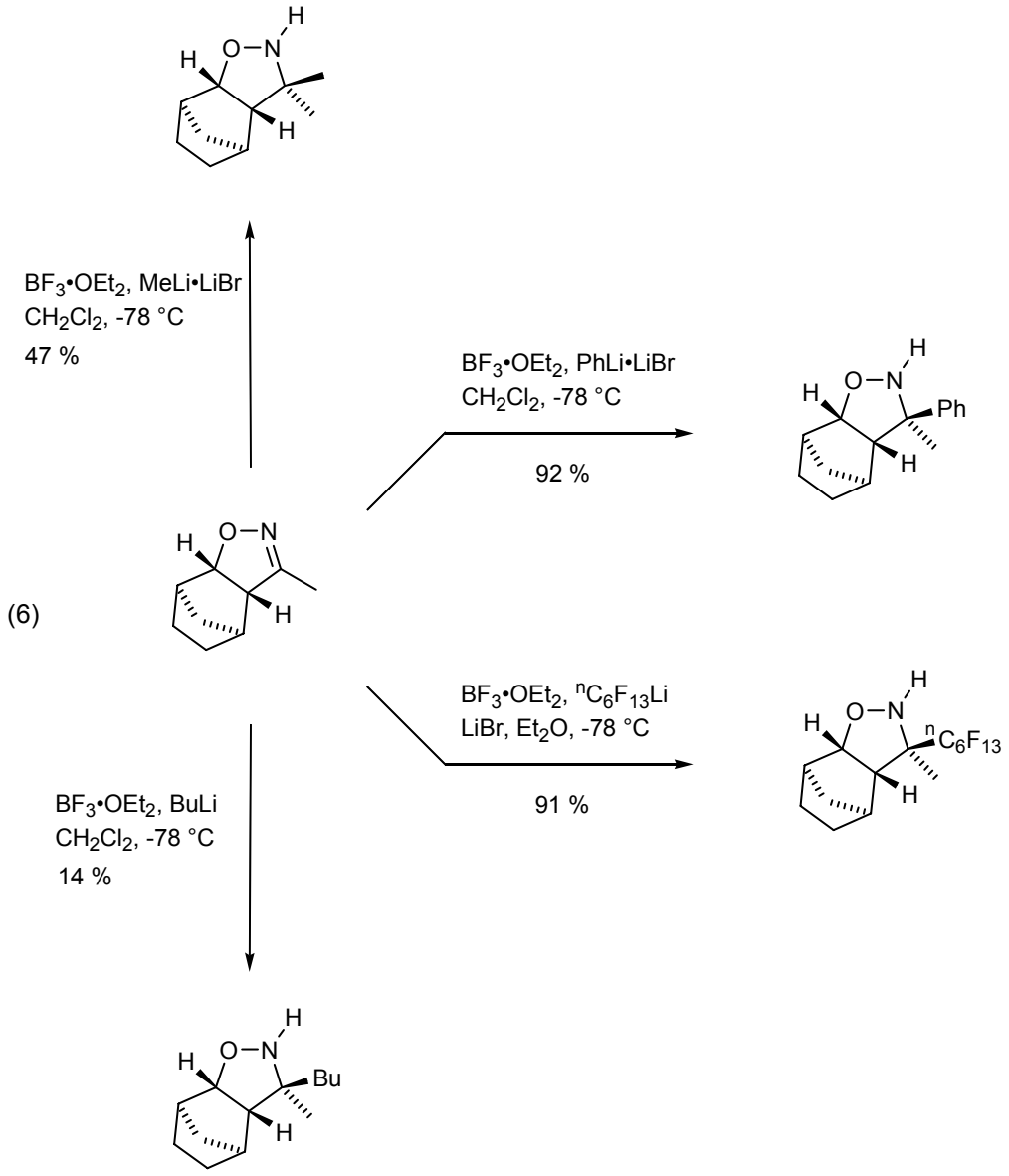


The addition of *C*-nucleophiles to the C=N bond of isoxazolines was also mentioned in the literature. In 1980, it was described the isoxazoline **G** by treatment with sodium cyanoborohydride under acidic conditions led to a 2:1 mixture of the two diastereomeric isoxazolidines **HA** and **HB**, but in poor yield [Eq. (5)].[12]

(5)

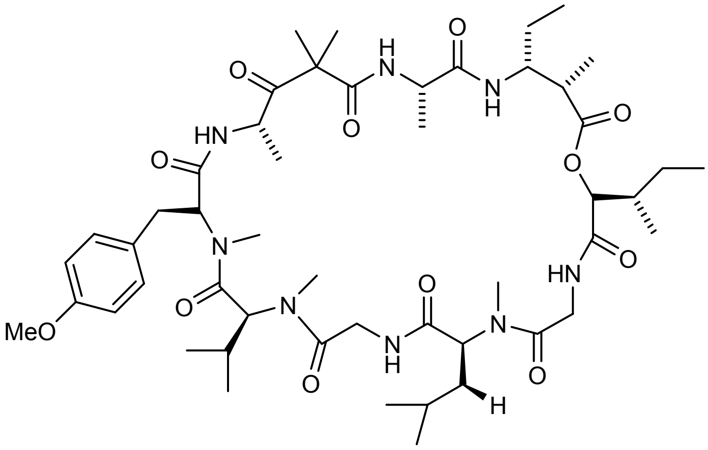


Better results have been disclosed by Uno et al. in 1989. The isoxazoline was first activated with borontrifluoride etherate $BF_3 \bullet OEt_2$, then the lithium organyls were added [Eq. (6)].[13] However, when *t*-butyllithium, lithium phenylacetylide, phenylmagnesium bromide or *n*-butylmagnesium bromide were used, no reaction was observed. Nevertheless, low to excellent yields were stated, for other cases [Eq. (6)].

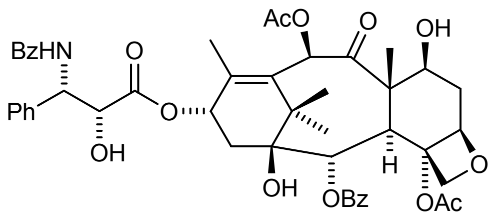


During the last few years, the preparation of enantiopure β-amino acids has emerged as an important and challenging synthetic endeavour. The increasing attention given to the chemistry of β-amino acids is partly due to the fact that they are components of a variety of natural products such as taxol,[14] the dolastatins 11,[15] and many others (Figure 1).[16]

Figure 1



Dolastatin 11



Taxol

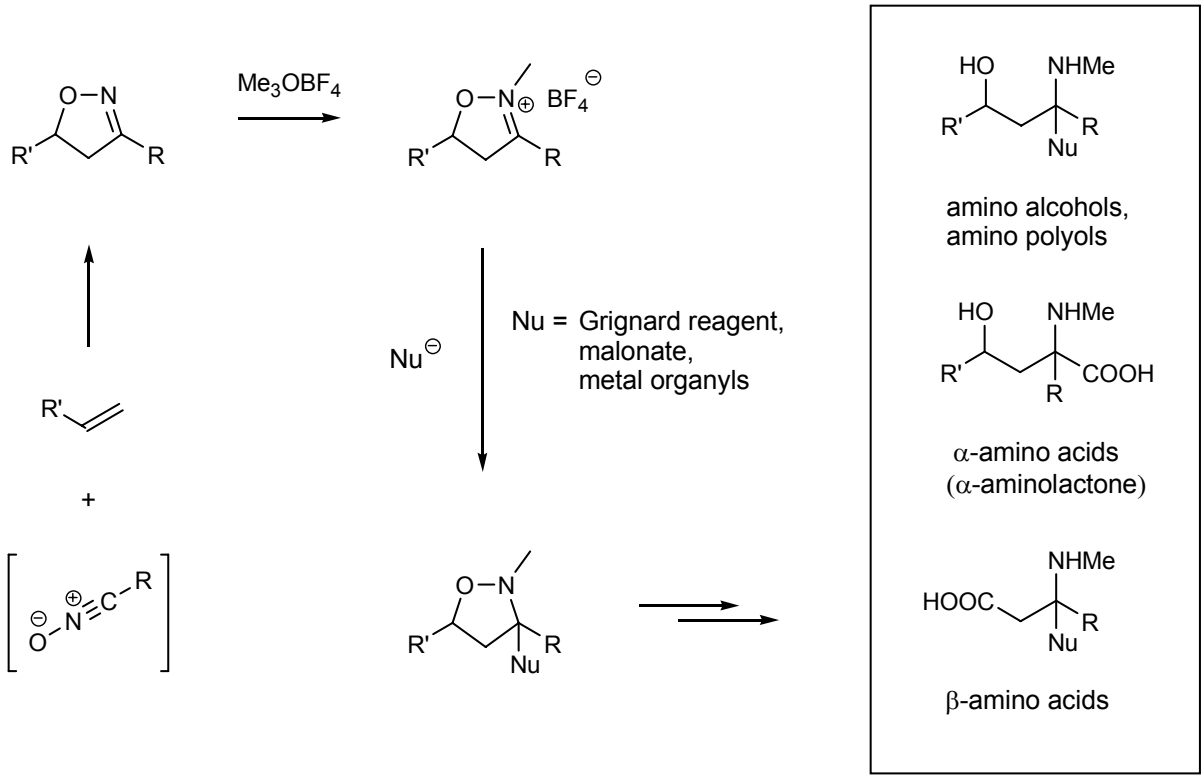
Also, a number of research groups have embarked on the synthesis of oligomers from β-amino acids which gives rise to stabilized helical structures that exhibit a resistance towards enzymatic hydrolysis.[17] Much of the work pertaining to enantioselective synthesis of β-amino acids has been reviewed.[18] Further remarkable applications of β-amino acids are the use as protease inhibitors,[19] as precursors for antibiotics,[20] and as building blocks in cryptophycins.[21]

To peruse this ambition of preparation of enantiopure β-amino acids,[1] amino polyols, lactones. The isoxazoline was built by cycloaddition of nitrile oxides with a variety of olefins, however, final introduction of a *C*-nucleophile is hampered by insufficient electrophilicity of the isoxazoline C=N bond.[22]

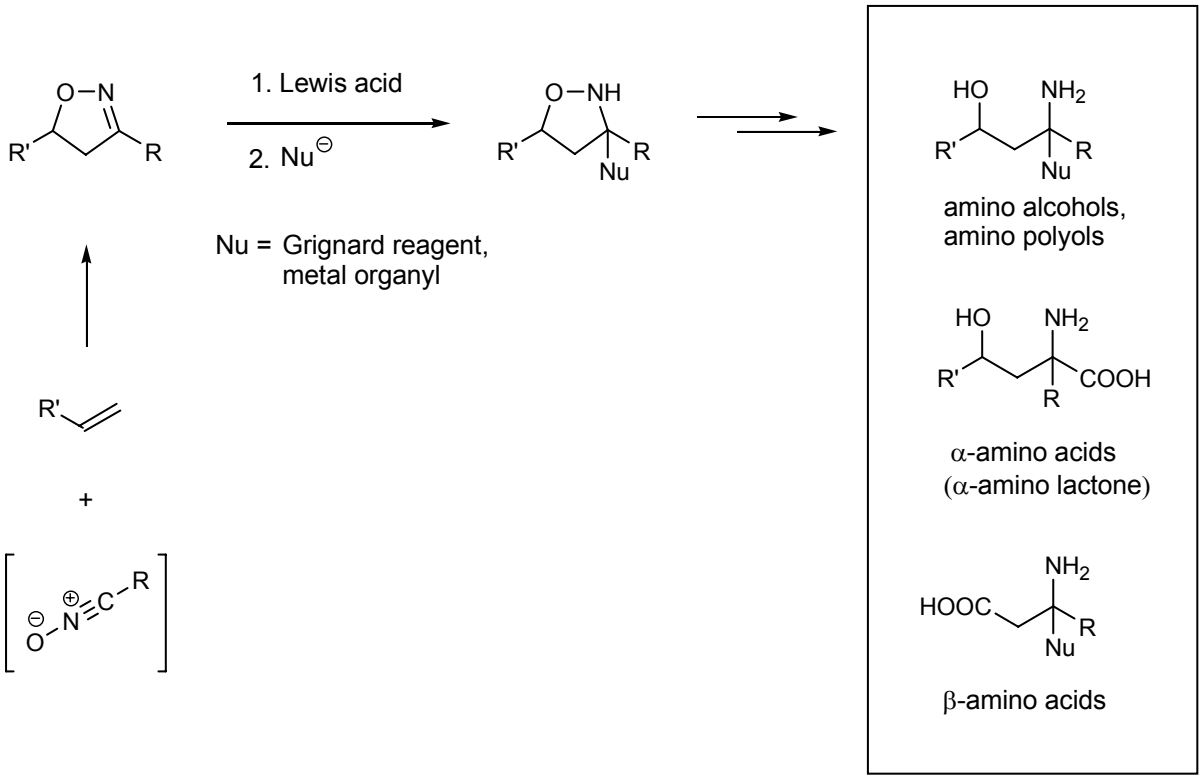
A general solution of this might be offered when ‘‘activated’’ derivatives, such as *N*-methylisoxazolinium salts, were employed. The strategy to use these cyclic oxy-iminium salts for synthesis of branched amino polyols, leading to branched α- and β-amino acids, is outlined in Scheme 1.

Because of the difficulty of removal of the *N*-methyl group from the isoxazolidines produced, an alternative way was sought using several Lewis acids to activate the isoxazolines used for addition of *C*-nucleophiles (Scheme 2).

Scheme 1. Isoxazolinium salts: Stratygy to build a variety of structures with an α-*tert*-alkylamine unit



Scheme 2. The isoxazoline route to build a variety of structures concerning enantiopure amino acids



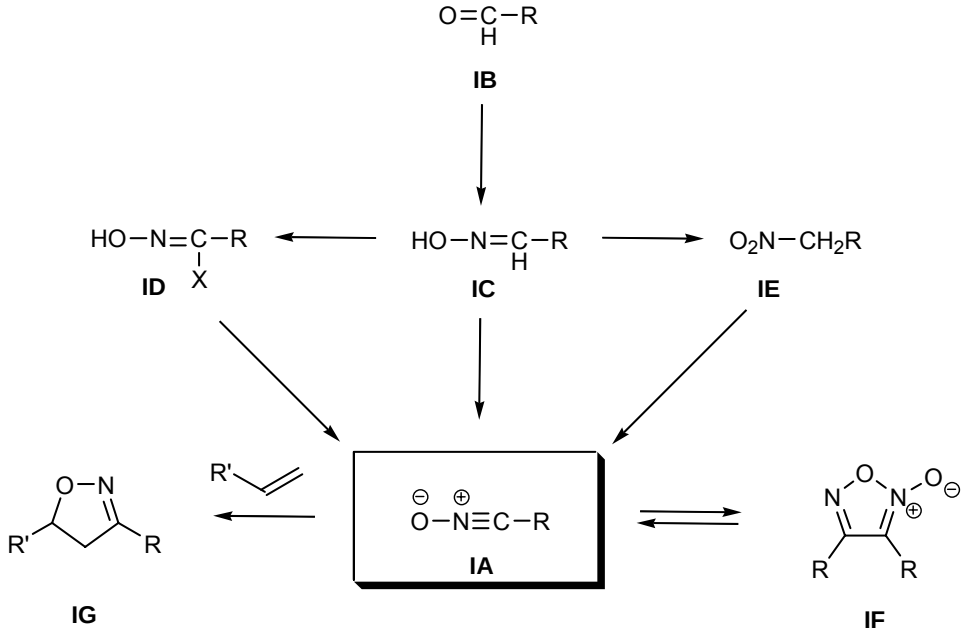
2 Preparation of Isoxazolines and *N*-Methylisoxazolinium Salts

In this chapter, preparation of isoxazolines and isoxazolinium salts will be described.

2.1 State of knowledge

2.1.1 Preparation of optically active isoxazolines by 1,3-dipolar nitrile oxide cycloaddition

The nitrile oxide cycloaddition has attracted much attention in synthetic organic chemistry. The value of this cycloaddition is ascribed mainly to the utility of the cycloaddition products as synthetic equivalents.[23] Generally, nitrile oxides are not isolable dipoles but are prepared *in situ* in the presence of a dipolarophile. A common source of nitrile oxides (**IA**) are aldehydes (**IB**) (chosen in this work, because of the availability of chiral, optically active derivatives) that are converted into the respective oximes (**IC**). From these, there is a choice concerning the actual precursor. A hydroximoyl halide (**ID**) or nitroalkane (**IE**) can be used. In most cases, the nitrile oxide (**IA**) tends to dimerize to produce a furoxan.[24]



Hydroximoyl halides (**ID**) are prepared by halogenation of the respective aldoxime (**IC**), for which a number of halogenating agents such as chlorine,[25] *tert*-butyl hypochlorite, *N*-chlorosuccinimide (NCS),[26] or *N*-bromosuccinimide (NBS)[27] have been employed.

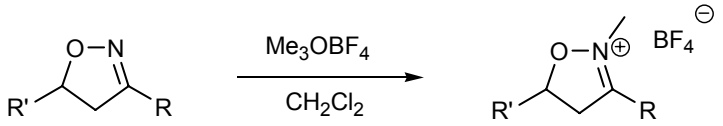
Nitrile oxides can be obtained from hydroximoyl halide (**ID**) by dehydrohalogenation with base. It must be underlined here that hydroximoyl halides are strong skin irritants and may cause abscess at the area of contact.[28]

2.1.2 Preparation of N-methylisoxazolinium salts

Based on the fact that isoxazolines are weak bases and weak *N*-nucleophiles,[29,30,31] alkylating agents can lead to activation by conversion to *N*-alkylisoxazolinium salts. Isoxazolinium salts represent potentially versatile intermediates for synthesis, even though relatively few transformations of these salts are known[1,2,32,11] and synthetic uses so far have been scarce.[1,2] A notable exception involves the use of an *N*-methylisoxazolinium salt: Its reduction to an isoxazolidine and subsequent cleavage to an *N*-methylaminoalcohol was used in a synthesis of paliclavine.[32]

In the present work, trimethyloxonium tetrafluoroborate Me_3OBF_4 was chosen as the alkylating agent to activate the isoxazolines used. The Meerwein salt was dissolved in dichloromethane (1.1 eq) with the isoxazoline at room temperature and kept with stirring overnight. After concentration of the solvent *in vacuo* the crude product was recrystallized from abs. ethanol to give the usually pure isoxazolinium salt in 79-96 % yield [Eq. (7)].

(7)



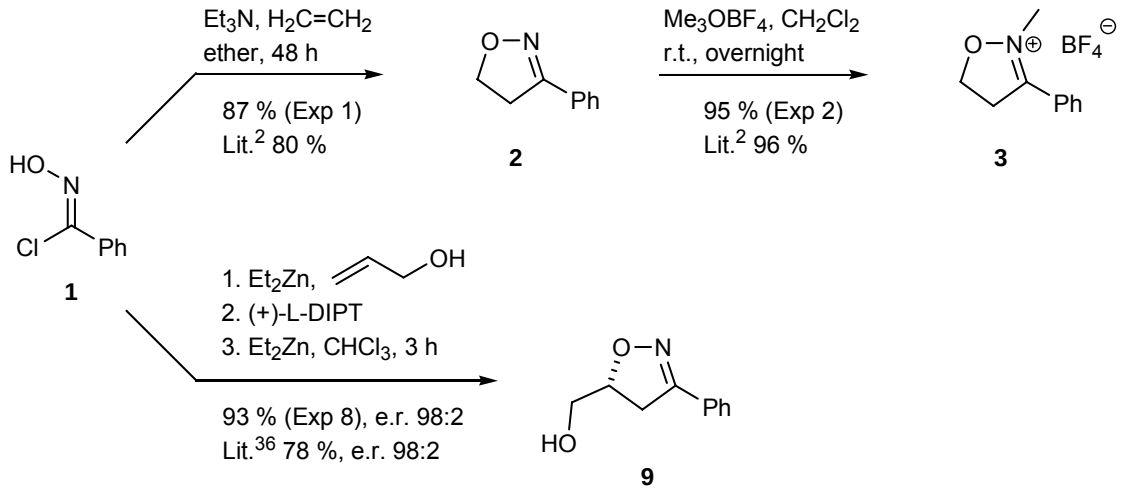
In comparison to other known alkylating agents in literature,[3,33,34] our experience has shown that Meerwein salts are the best alkylating agents for such isoxazolines.

2.2 Own results

The isoxazolinium salt **3** was prepared from the hydroximoyl chloride **1** which was obtained starting from benzaldehyde as described in literature.[35] The isoxazoline **2** prepared by reaction of **1** with ethylene in the presence of triethylamine as a base (Scheme 3) with good yield 87 % (lit.[36] 81 %). Next, the isoxazoline **2** was treated with 1.1 eq of trimethyloxonium tetrafluoroborate in abs. CH_2Cl_2 with stirring overnight. After evaporation of the solvent and recrystallization from ethanol the isoxazolinium salt **3** was obtained in 95 % yield (lit.[2] 96 %).
The isoxazoline **9** was prepared in an enantioselective manner according to Ukaji et al.[37] Allyl alcohol was treated with 1.1 eq of diethylzinc at 0 °C, followed by the addition of 1.1 eq of (+)-L-DIPT after 10 min; then another 1.1 eq of diethylzinc and hydroximoyl chloride were added. The enantiomeric ratio of the isoxazoline **9** obtained was 98:2 (see appendix 12.2.1 and 12.2.2), measured by means of GC for the crude isoxazoline **9**, with excellent yield 93 %.

The isoxazoline **9** was crystallized from petroleum ether/CH_2Cl_2 to give the pure enantiomer, the configuration of which was assigned to be (*5R*), by comparing the optical rotation of the sample obtained here with the known literature value (Scheme 3).[37]

Scheme 3. Preparation of the isoxazoline **9** and the *N*-methylisoxazolinium salt **3**



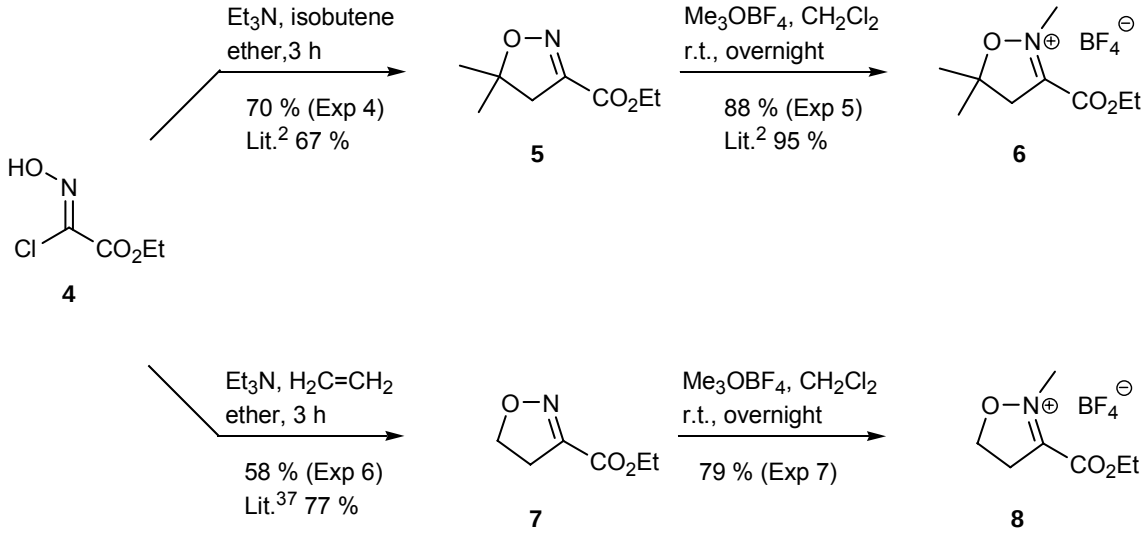
$[\alpha]_D^{20}$ = - 164.9 (*c* = 1.00, $CHCl_3$)

lit.[37] : $[\alpha]_D^{20}$ = - 164.0 (*c* = 0.70, $CHCl_3$)

The isoxazolinium salts **6** and **8** were prepared from the corresponding isoxazolines **5** and **7**, which in turn were available by reaction of chlorooximidoacetate **4** with isobutene and ethylene, respectively. The hydroximoyl chloride **4** was prepared by reaction of ethyl glycinate hydrochloride with sodium nitrite in acidic medium and was obtained **4** in 41 % yield (lit.[38] 54 %). In presence of triethylamine, the isoxazoline **5** was obtained from the corresponding hydroximoyl chloride **4**. Purification of the crude product by MPLC afforded the isoxazoline **5** in 70 % yield (lit.[2] 67 %). In the same manner the hydroximoyl chloride **4** was treated with ethylene with slowly dropping 1.1 eq of triethylamine into this solution. After purification by MPLC, the isoxazoline **7** was isolated in 58 % yield (lit.[39] 77 %).

Treatment of the isoxazolines **5** and **7**, respectively, with trimethyloxonium tetrafluoroborate in CH_2Cl_2 afforded after recrystallization from abs. ethanol 88 % (lit.[2] 95 %) of pure isoxazolinium salt **6**, and 79 % of spectroscopically pure, but analytically impure isoxazolinium salt **8** (Scheme 4).

Scheme 4. Preparation of *N*-methylisoxazolinium salts **6** and **8**

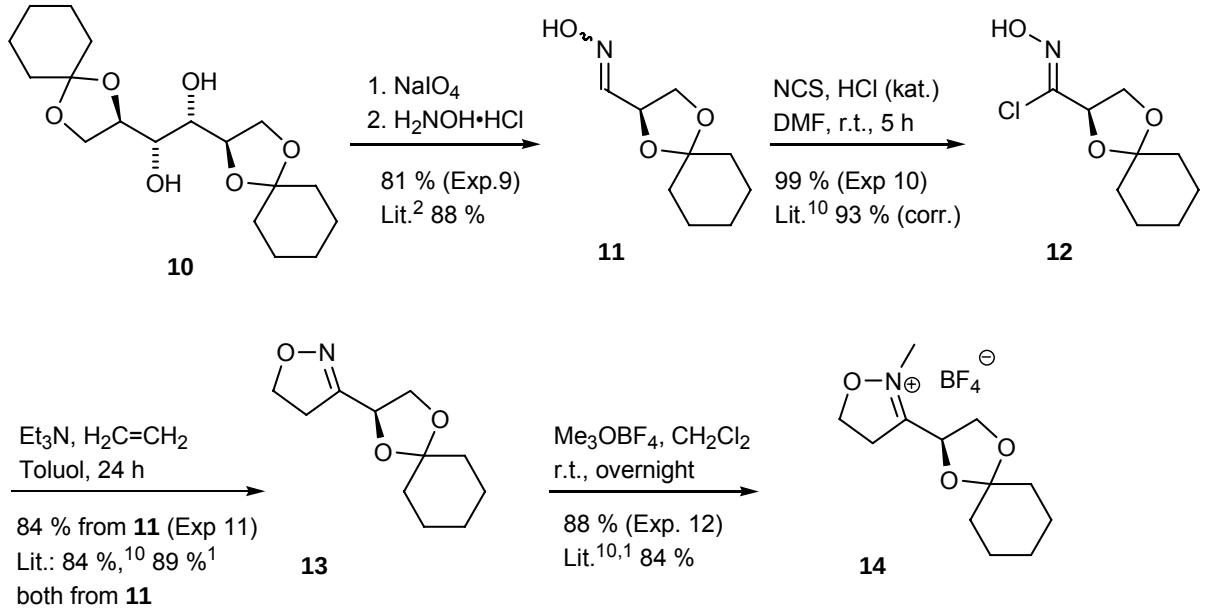


The synthesis of the *N*-methylisoxazolinium salt **14** was done according to the literature.[1,2,10] *D*-Mannitol was protected using cyclohexanone to afford 1,2:5,6-Di-*O*-cyclohexylidene-*D*-mannitol **10** in 57 % yield (lit.[40] 56 %), which in turn was transformed to the respective oxime by diol cleavage with sodium periodate, then treatment with hydroxylamine hydrochloride.

Purification by column chromatography afforded 2,3-*O*-cyclohexylidene-(*S*)-glyceraldoxime **11** in very good yield 81 % (lit.[2] 88 %). Treatment of **11** with *N*-chlorosuccinimide in DMF after introducing HCl gas into the solution and then leaving the reaction mixture with stirring for 3 h, gave 2,3-*O*-cyclohexylidene-D-glycerohydroximoyl chloride **12** in 99 % yield [(lit.[2] 99 % (corrected)] (Scheme 5).

Cycloaddition of the nitrile oxide derived from 2,3-*O*-cyclohexylidene-D-glycerohydroximoyl chloride **12** to ethylene in toluene with continuous dropping the triethylamine solution into the mixture during 24 h resulted in a yellowish oil. Recrystallization from hexane gave (1'*S*)-3-(1',2'-*O*-cyclohexylidenedioxyethyl)-4,5-dihydro-1,2-oxazole **13** in good yield 84 % (calculated from the oxime **11**) (lit.[10] 84 %). Methylating **13** with trimethyloxonium tetrafluoroborate in CH_2Cl_2, after evaporation of the solvent and recrystallization from abs. ethanol afforded (1'*S*)-3-(1',2'-*O*-cyclohexylidenedioxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate **14** in high yield 88 % (lit.[10] 84 %) (Scheme 5).

Scheme 5. Synthesis of the *N*-methylisoxazolinium salt **14**



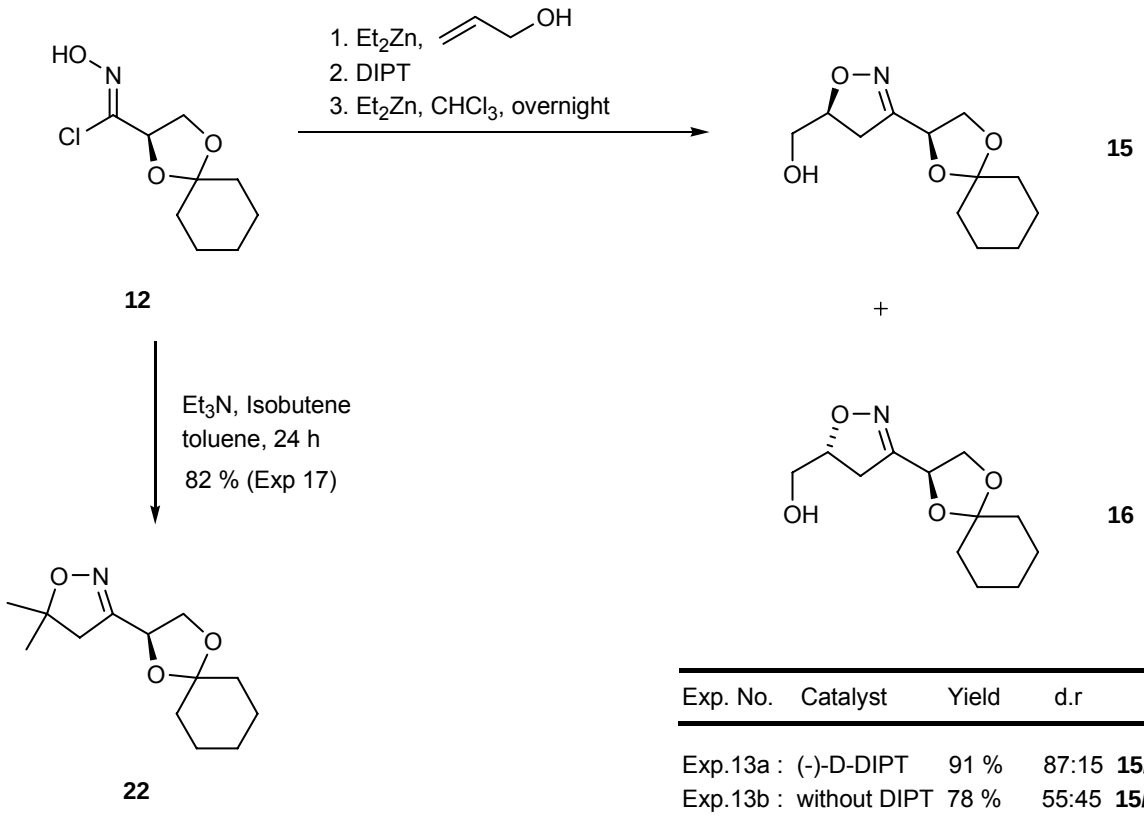
The cycloadditions of 2,3-*O*-cyclohexylidene-D-glyceronitrile oxide (from **12**) to allyl alcohol and isobutene were also carried out successfully. Allyl alcohol was first treated with diethylzinc (1.1 eq) in $CHCl_3$, followed by addition of 1.1 eq of (-)-D-DIPT and another 1.1 eq of diethylzinc and finally of the hydroximoyl chloride **12**. The ratio of the two resulting diastereomers was found as 87:13[a] for (5*R*, 1'*S*)- and (5*S*, 1'*S*)-3-(1',2'-*O*-cyclohexylidenedioxyethyl)-5-hydroxymethyl-2-isoxazoline **15** and **16**, respectively, with excellent yield 91 % (Scheme 6). Unfortunately, it was not possible to separate these diastereomers by MPLC.

When (+)-L-DIPT was used instead of (-)-D-DIPT, the isoxazolines **15** and **16** were obtained again, but now **16** constituted the major diastereomer (86 % yield, 15:85 diastereomeric ratio for **15**/**16**). When the same reaction was performed without (+)-L- or (-)-D-DIPT, the diastereomeric ratio of the isoxazolines **15**/**16** was 55:45 in 78 % yield. This clearly shows the effect of the chiral mediator DIPT on the diastereomeric ratio.

[a] The determinations of the diastereomeric ratios (d.r.) here are based on the intensities of the separated signals pairs in ^{13}C NMR spectra of the crude product **15**,**16**.

In a similar manner, when isobutene was introduced into the solution of hydroximoyl chloride **12** with continuous addition of triethylamine solution (1.0 N) in abs. toluene over 24 h, the isoxazoline **22** was obtained as a yellowish oily crude product. Recrystallization from hexane afforded (1'*S*)-3-(1',2'-*O*-cyclohexylidenedioxyethyl)-5,5-dimethyl-4,5-dihydroisoxazole **22** in good yield (82 %) as a colourless solid (Scheme 6).

Scheme 6. Synthesis of isoxazolines **15, 16, 22**

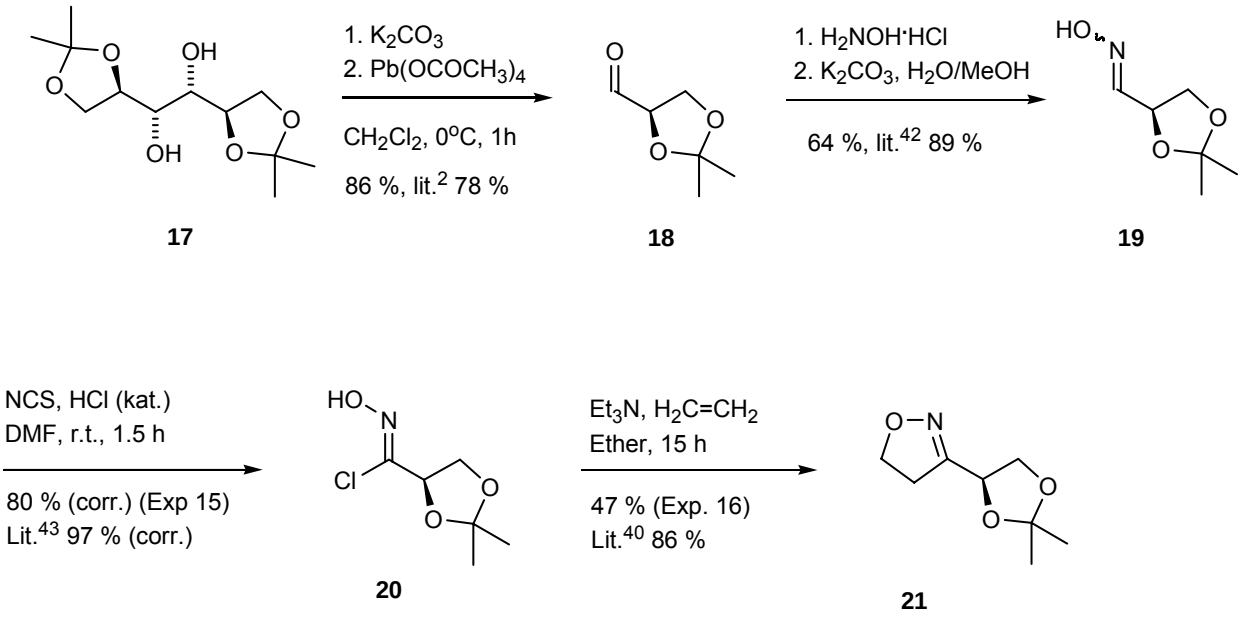


Exp. No.	Catalyst	Yield	d.r	
Exp.13a :	(-)-D-DIPT	91 %	87:15	**15/16**
Exp.13b :	without DIPT	78 %	55:45	**15/16**
Exp.14 :	(+)-L-DIPT	86 %	15:85	**15/16**

According to Henneböhle et al.[10,41] the isoxazoline **21** was prepared starting from D-mannitol, which was first protected using 2,2-dimethoxypropane in pyridine, to produce 1,2:5,6-Di-*O*-diisopropylidene-D-mannitol **17** in 65 % yield (lit.[42] 54 %) (Scheme 7).

Diol cleavage with lead(IV) tetraacetate and base gave the corresponding aldehyde[43], which was transformed into the respective hydroximoyl chloride in two steps[44]. Cycloaddition of 2,3-*O*-isopropylidene-D-glyceronitrile oxide **20** to ethylene afforded the corresponding (1'*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,5-dihydroisoxazole **21** in fair yield 57 % (lit.[10] 83 %) (Scheme 7).

Scheme 7. Synthesis of the isoxazoline **21**



2.3 NMR data of isoxazolines and N-methylisoxazolinium salts and assignment of configurations

^{1}H NMR data

Generally, the proton absorptions of the isoxazolinium salts show deshielding as compared to those of the corresponding isoxazolines (Tab. 1). As expected, the smallest deviation in the chemical shifts ($\Delta\delta$) was found for $CH_2C\underline{H}_3$ of the ester group of the compounds **5**-**8**, with a difference of 0.02-0.05 ppm. The highest deviation was observed for the 4-H signals with 0.69-0.80 ppm. In the case of 5-H the shift difference was 0.41-0.48 ppm, for the $C\underline{H}_2CH_3$ protons about 0.1 ppm only, and 0.21 ppm for the 3-phenyl groups. These deshieldings are due to the positively charged nitrogen atom (electronegativity effect).

It is important to be mentioned here that all isoxazolines were measured using $CDCl_3$ as a solvent, which was not the case with the corresponding isoxazolinium salts for which CD_3OD was used.

Coupling between the *N*-methyl group protons and 4-H was found.[10,1,2] This coupling over five bonds was detected in most isoxazolinium salts prepared, with values of 1.8 to 2.4 Hz. It was not possible, however, to detect this ^5J-coupling in case of isoxazolinium salt **8**. Henneböhle[1] had cited similar values of 1.8-2.1 Hz, also LeRoy[2] had found similar range of

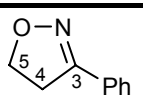
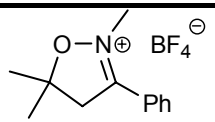
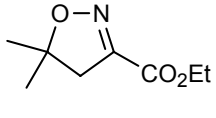
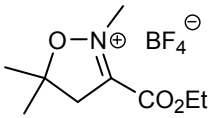
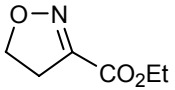
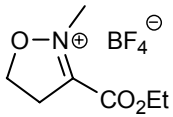
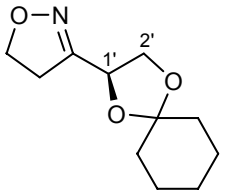
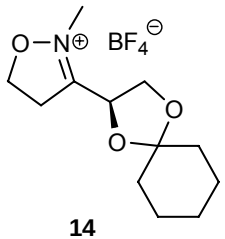
^5J = 1.6-2.4 Hz, depending on the isoxazolinium salt. Hence, the observed values in this work were in the same range. The homoallylic ^5J-coupling is also known from many other cases in the literature, with a range of 0-2.5 Hz.[45]

^{13}C NMR data

The chemical shifts of the carbon atoms of isoxazolinium salts also suffer deshielding as compared to the cases of the corresponding isoxazolines (Tab. 2). The differences in chemical shifts ($\Delta\delta$) were similar to those reported by Henneböhle[1] and LeRoy.[2] For C-3 the chemical shifts were shifted by 3.8-9.9 ppm, however, for C-4 this was less (in the range of 0.7 to 6.9 ppm) and for C-5 it was 1.7-5.9 ppm. The observed chemical shifts ($\Delta\delta$ values) reflect the transformation from imine to the iminium salt structure.[46]

Comparing the ^{13}C absorptions of *o*-, *m*-, *p*-C of the phenyl group in the isoxazoline **2** with those of the isoxazolinium salt **3**, we observed deshielding in the range of 3.6-7.2 ppm. In contrast to this, shielding of *i*-C of the phenyl group was observed with the isoxazolinium salt **3**, as compared to that of the corresponding isoxazoline **2** ($\Delta\delta$ = -3.6 ppm), which is difficult to interpret. Shifting of the carbonyl carbon to low-field of about 4.85 ppm was noticed also in case of the isoxazolines **6** and **8**.

Table 1. Selected ^{1}H NMR data (δ in ppm, *J* in Hz) of the isoxazolines and *N*-methylisoxazolinium salts prepared

Isoxazoline	*N*-Methylisoxaz-olinium Salt	No.	5-H	4-H	$(C\underline{H}_3)_2$	$(C\underline{H}_2CH_3)$	$(CH_2C\underline{H}_3)$	3-C_6H_5	N^+-CH_3	$^5J_{4,NMe}$
		**2**	4.47	3.34	-	-	-	7.54	-	-
		3	4.92	4.14	-	-	-	7.75	3.95	1.8
2	**3**	$\Delta\delta$	+0.45	+0.80	-	-	-	+0.21	-	-
		**5**	-	2.98	1.47	4.36	1.37	-	-	-
		6	-	3.76	1.66	4.47	1.42	-	4.17	2.4
5	**6**	$\Delta\delta$	-	+0.78	+0.19	+0.11	+0.05	-	-	-
		**7**	4.55	3.24	-	4.40	1.39	-	-	-
		8	4.96[a]	3.93[a]	-	4.48	1.41	-	4.17	[b]
7	**8**	$\Delta\delta$	+0.41	+0.69	-	+0.10	+0.02	-	-	-
					1'-H	2'-H_A	2'-H_B			
		**13**	4.37[a]	3.14[a]	4.97	3.99	4.22	-	-	-
		14	4.85[a]	3.85[a]	5.25	4.33	4.42	-	3.88	2.1
13	**14**	$\Delta\delta$	+0.48	+0.71	+0.28	+0.34	+0.20	-	-	-

[a] Signals were not identified, average of multiplet given. [b] Identification of $^5J_{4,1''}$ not possible.

Tab. 2. Selected ^{13}C NMR data (δ in ppm) of the isoxazolines and *N*-methylisoxazolinium salts prepared

Compound	C-5	C-4	C-3	$(\underline{C}H_3)_2$	$(\underline{C}H_2CH_3)$	*o*-, *m*-, *p*-C of 3-C_6H_5	*i*-C of 3-C_6H_5	N^+-CH_3
2	69.2	35.2	156.8	-	-	126.7, 128.7, 130.0	129.5	-
3	72.8	42.1	166.7	-	-	132.1, 132.3, 137.2	125.9	42.1
$\Delta\delta$	+3.6	+6.9	+9.9	-	-	[a]	-3.6	-
						$(CH_2\underline{C}H_3)$	C=O	
5	88.5	45.2	151.1	27.2	61.9	14.1	161.1	-
6	94.4	49.3	155.7	26.9	66.2	14.2	156.2	42.9
$\Delta\delta$	+5.9	+4.1	+4.6	-0.3	+4.3	+0.1	-4.9	-
7	71.4	33.8	151.9	-	62.1	14.1	160.7	-
8	73.6	38.0	155.7	-	66.2	14.2	155.9	42.2
$\Delta\delta$	+2.2	+4.2	+3.8	-	+4.1	+0.1	-4.8	-
				C-1’	C-2’			
13	68.8	35.9	158.4	70.7	66.8	-	-	-
14	70.5	36.6	166.7	69.5	66.5	-	-	39.4
$\Delta\delta$	+1.7	+0.7	+8.3	-1.2	-0.3	-	-	-

[a] *o*-, *m*-, *p*-C of C_5H_5 were not assigned.

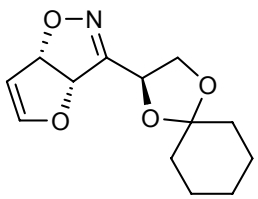
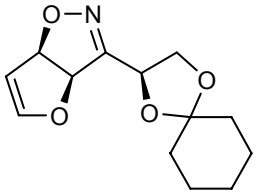
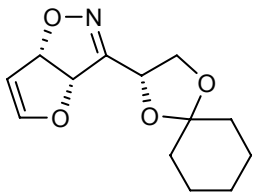
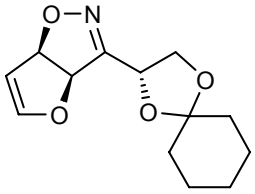
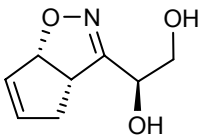
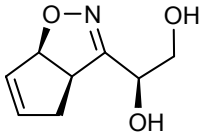
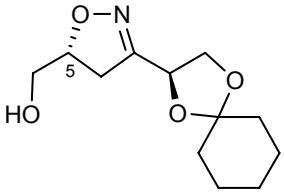
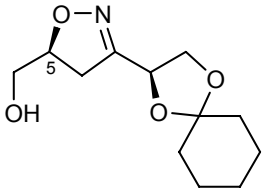
2.4 Correlation between the values of optical rotation and the absolute configuration of isoxazolines 15, 16

A correlation between optical rotation values / sign and the absolute configuration of selected isoxazolines was discussed in our research group. [44,48,49,47] For example, the optically active furoisoxazoline **JB** with (3a*R*,6a*R*,1'*S*)-configuration has a large optical rotation with positive sign (Tab. 3), while the furoisoxazoline **JA** with (3a*S*,6a*S*,1'*S*)-configuration shows a negative sign of a similarly large optical rotation.[48] The configuration at C-1' seems to have little influence on the sign of the optical rotation, i.e. the furoisoxazoline **JC** has a rotational value with negative sign, opposite to the furoisoxazoline **JD** which again shows a positive rotation.[44] The same behaviour was observed by Lee and Jäger[49] with the isoxazolines **JE**/**JF**.

Similarly, the isoxazoline **15** obtained here can be assigned the (5*S*)-configuration [$[\alpha]_D^{20}$ = +72.7 (mixture of **15**/**16** 87:13)], and the isoxazoline **16** should have the (5*R*)-configuration [$[\alpha]_D^{20}$ = - 63.0 (mixture of **15**/**16** 15:85)].

Transformation of isoxazolines **15**/**16** to the corresponding isoxazolidines **35a** and **35b** by the addition of allylmagnesium bromide led to the isoxazolidine **35a** (major product) a single crystal of which proved suitable for crystal structure analysis: This showed the configuration at C-5 to be (*S*), since the absolute configuration at C-1' is known from the mannitol precursor. This all correlates very well with the previous assignment for the isoxazolines **15** and **16**.

Table 3. Optical rotation values of selected isoxazolines.

Isoxazoline	$[\alpha]_D^{20}$	Ref.	Diastereomeric Isoxazoline	$[\alpha]_D^{20}$	Ref.
 **JA**	- 213	46	 **JB**	+ 185	46
 **JC**	- 172	43	 **JD**	+ 185	43
 **JE**	- 36.9	47	 **JF**	+ 135.3	47
 **15/16** = 15:85	- 63.0 [a]		 **15/16** = 87:13	+ 72.7 [b]	

[a] Measured value of mixture of isoxazolines **16**/**15** (85:15), see Exp. 14.

[b] Measured value of mixture of isoxazolines **15**/**16** (87:13), see Exp. 13a.

3 Addition of *C*-Nucleophiles to *N*-Methylisoxazolinium Salts

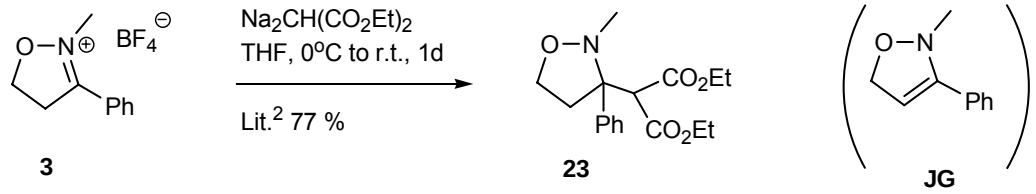
In this chapter, the addition of a variety of *C*-nucleophiles to *N*-methylisoxazolinium salts will be described.

3.1 Reaction of sodium diethyl malonate and lithium ester enolate with *N*-methylisoxazolinium salts

3.1.1 State of knowledge

The use of diethyl malonate as a *C*-nucleophile in addition to *N*-methylisoxazolinium salts was investigated only in our research group. LeRoy performed the addition of diethyl malonate in the presence of sodium hydride NaH as base to the model isoxazolinium salt **3** with good yield and without observing deprotonated product **JG** [Eq. (8)][2].

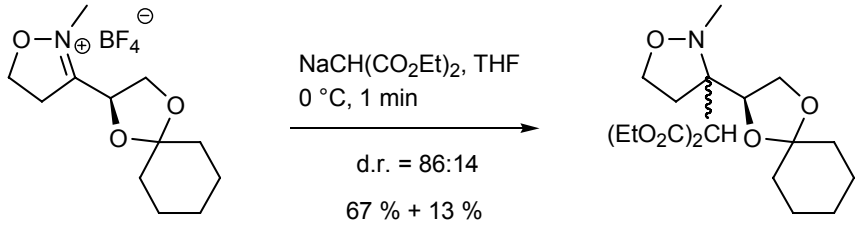
(8)



3 **23** **JG**

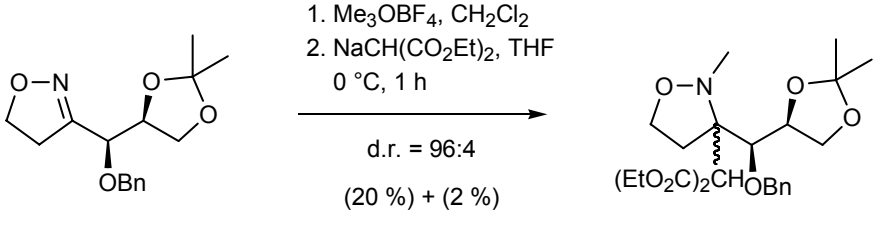
Henneböhle[1] studied the diastereoselectivity of this reaction with two isoxazolinium salts. He found good diastereomeric ratios of 86:14 to 96:4, with yields varying from 20 % to 80 % [Eq. (9) and (10)].

(9)



13 **Ka/b**

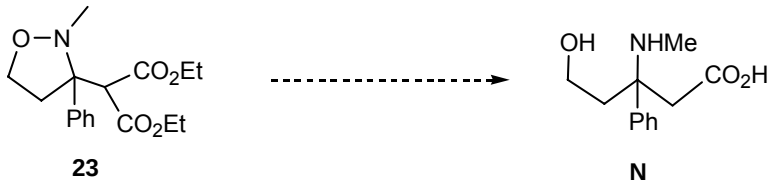
(10)



L **Ma/b**

The isoxazolidine **23** produced similarly could be a promising precursor for β-amino acids like **N**, this would be prepared by acidic hydrolysis decarboxylation followed by catalytic hydrogenation [Eq. (11)].

(11)



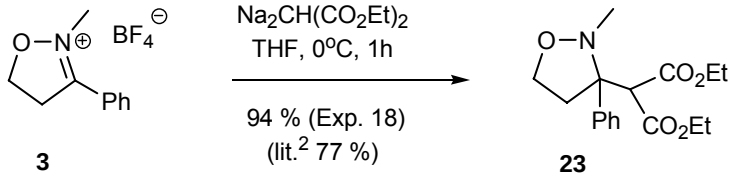
23 **N**

Addition of lithium ester malonate as a *C*-nucleophile is known in literature[50], But exclusively to aldehydes and ketones. However, Refomatskii reaction was applied to such additions.[51a-c] Additions of lithium ester enolate to isoxazolinium salts so far are unknown to the best of our knowledge.

3.1.2 Own results

The addition of sodium diethyl malonate to the model isoxazolinium salt **3** was repeated in this work to afford the corresponding isoxazolidine **23** in improved yield 94 %; the reaction time here was shorter (1 h instead of 1 d) than that used by LeRoy[2] [Eq. (12)].

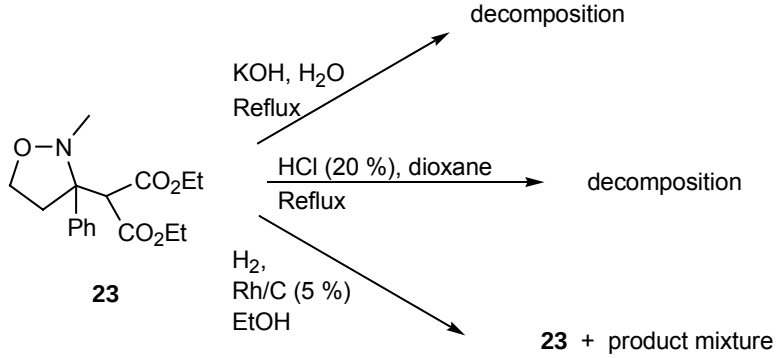
(12)



3 **23**

Aiming to prepare the β-amino acid **N**, tests were done with the isoxazolidine **23**, i.e. acidic and basic hydrolysis, catalytic hydrogenation, but all without success: This resulted either in decomposition or in a product mixture difficult to separate [Eq. (13)].

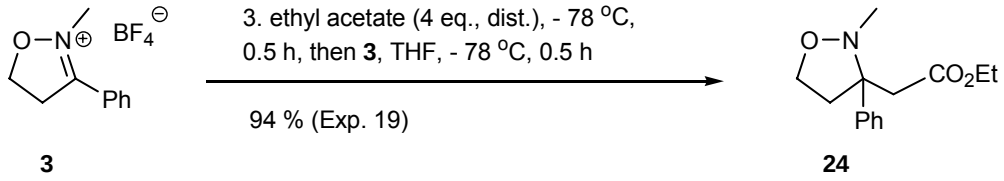
(13)



23

From the model isoxazolinium salt **3**, the corresponding isoxazolidine **24** was prepared by addition of lithium ester enolate in 94 % yield [Eq. (14)].

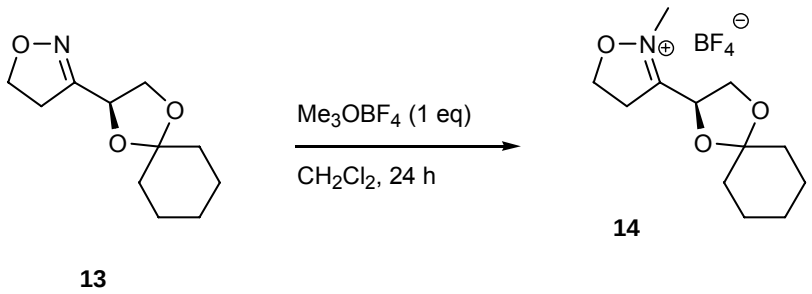
(14)



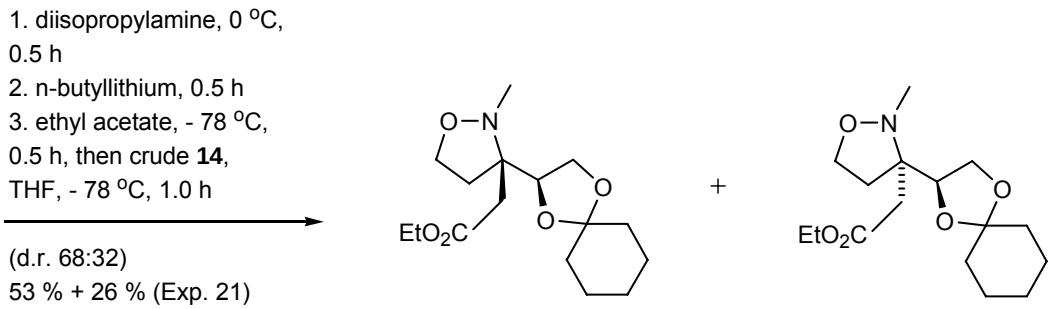
3 **24**

The diastereoselectivity of this was studied with the chiral isoxazolinium salt **14**, it proved moderate (d.r. 68:32). After MPLC the isoxazolidines **26a** and **26b** were obtained as pure diastereomers in good yield (79 %; 53 % + 26) [Eq. (15)].

(15)



13 **14**



26a **26b**

3.1.3 Assignment of configuration to ethyl *N*-methylisoxazolidinyl acetate 26a and 26b.

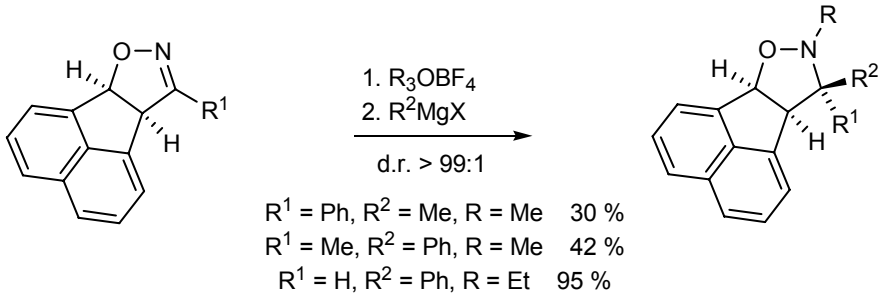
Acidic hydrolysis of the major diastereomer **26a** afforded the corresponding spirolactone **54** in the form of colourless crystals, suitable for crystal structure analysis; this confirmed the configuration at C-3 to be (3*R*) for the isoxazolidine **26a**, hence (3*S*) for the minor diastereomer **26b**.

3.2 Reaction of metal organyls with N-methylisoxazolinium salts

3.2.1 State of knowledge

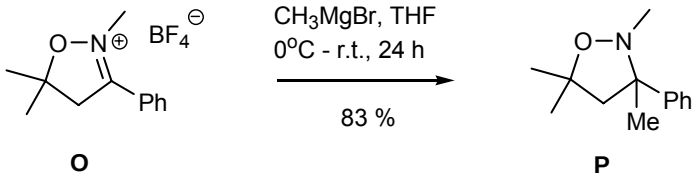
The addition of metal organyls to isoxazolinium salts has been studied earlier. Cerri et al. in 1974 have reported on the addition of methylmagnesium bromide to a tetracyclic isoxazolinium salt, with excellent diastereoselectivity but unsatisfactory yields. When triethyloxonium tetrafluoroborate Et_3OBF_4 was used instead of trimethyloxonium tetrafluoroborate Me_3OBF_4, the yield was improved [Eq. (16)].[11]

(16)



Additions of metal organyls to isoxazolinium salts were investigated by LeRoy, when methylmagnesium bromide was added to the isoxazolinium salt **O** to furnish the isoxazolidine **P** in good yield [Eq. (17)].[11]

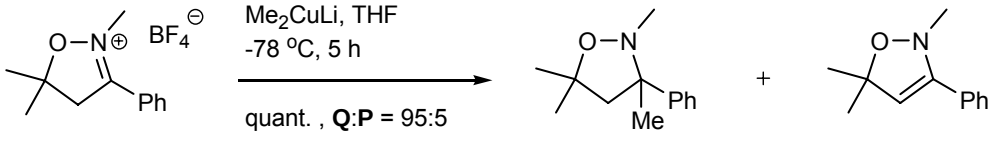
(17)



O **P**

However, copper organyls such as Me_2CuLi and $Me_2CuMgBr$ were also tested, The basic character of these organyls was the predominant, of which the ratio of the deprotonation product **Q** to the addition product **P** was (95:5, **Q**:**P**) in quantitative yield [Eq. (18)].[2]

(18)

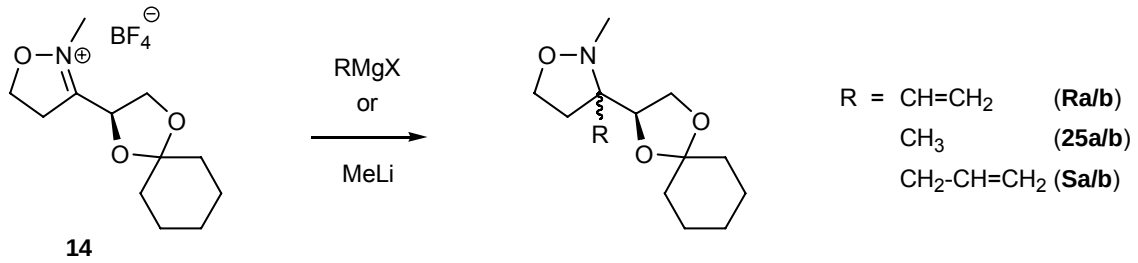


O **P** **Q**

Henneböhle studied the effects of temperature and solvent on the diastereoselectivity of this addition. Since there was only a very weak temperature effect observed, the solvent seems to have a more significant influence on the selectivity of the Grignard addition (Tab. 4).

In the dissertation of Henneböhle,[1] the addition of lithium organyls to chiral *N*-methylisoxazolinium salts was also investigated. Treatment of the isoxazolinium salt **14** with methyllithium afforded the corresponding 3-methylisoxazolidines **25a**/**b** in a non-stereoselective manner (d.r. ≈ 1:1, entry 3 in table 4) and with only 48 % yield.[1] Hence, the Grignard addition appeared much more suitable for the stereoselective synthesis of 3,3-disubstituted isoxazolidines, and this method was preferred in the present.

Table 4. Addition of Grignard reagents / lithium organyls to the *N*-methyl-isoxazolinium salt 14



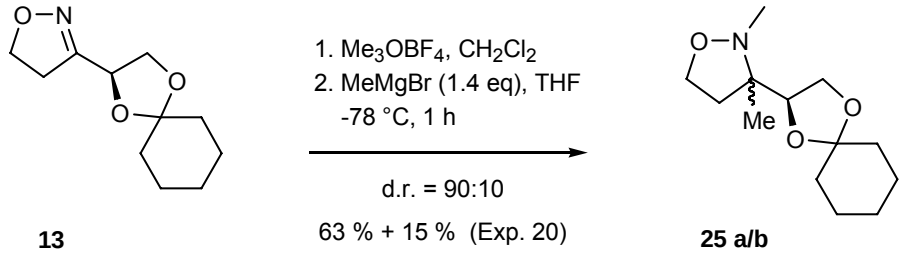
14

Entry	Reagent (RM)	Product	d.r.	Yield		
				a	**b**	Σ
1	H_2C=CHMgBr	**Ra**/**b**	67:33	59 %	26 %	85 %
2	MeMgBr	**25a**/**b**	88:12	64 %	7 %	71 %
3	MeLi	**25a**/**b**	47:53	23 %	25 %	48 %
4	H_2C=CH-CH_2MgCl	**Sa**/**b**	69:31	64 %	24 %	88 %

3.2.2 Own results

In this work the task concerning 3-methylisoxazolidine **25** was to assign the configuration at C-3, which had not been possible in the work of Henneböhle.[1] Therefore, (3*S*, 1'*S*)- and (3*R*, 1'*S*)-3-(1',2'-*O*-cyclohexylidenedioxyethyl)-2,3-dimethylisoxazolidines **25a** and **25b** were prepared from the corresponding isoxazoline **13** by treatment with Me_3OBF_4, then addition of methylmagnesium bromide in THF at – 78 °C, to afford the two diastereomers in 90:10 ratio and 78 % yield [Eq. (19)].

(19)

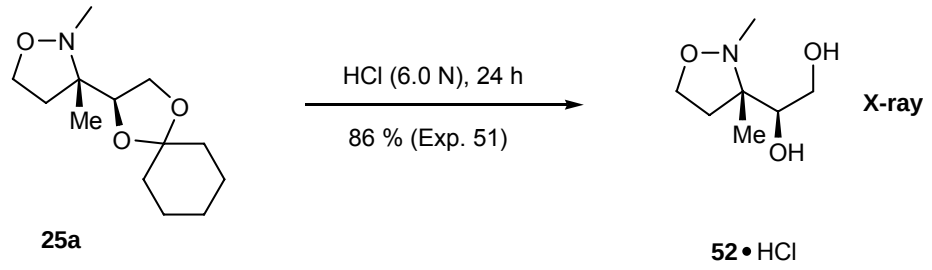


13 **25 a/b**

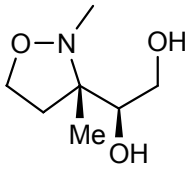
3.2.3 Assignment of configuration of 3-methylisoxazolidine 25a and 25 b.

The assignment of configuration at C-3 of the isoxazolinium salt **14** could not been done by Henneböhle because the isoxazolidines **25a** and **25b** had been obtained as oily substances. Acidic hydrolysis of **25a** now afforded the corresponding diol **52**•HCl (Eq. 20), which has (*S*)-configuration at C-3, this reflects on 3-methylisoxazolidine **25a** to have (3*S*, 1'*S*)-configuration. Hence, the 3-methylisoxazolidine **25b** has (3*R*, 1'*S*)-configuration.

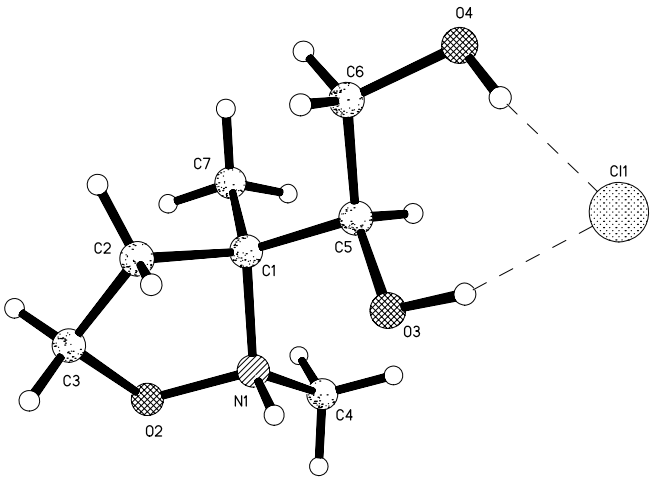
(20)



25a **52** • HCl



52 • HCl



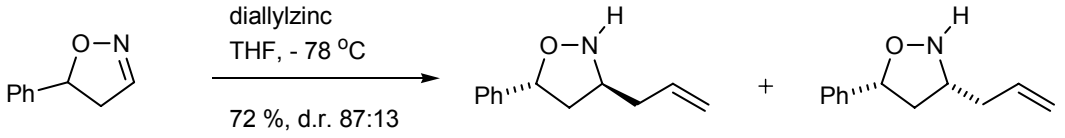
4 Addition of *C*-Nucleophiles to Isoxazolines

4.1 Reactions of Grignard reagents with isoxazolines

4.1.1 State of knowledge

Preparation of isoxazolidines by activation of the isoxazoline ring with Lewis acid followed by the addition of Grignard reagents was rarely studied in literature. In 1999, Castro et al.[52] cited the addition of diallylzinc to 5-phenyl-4,5-dihydroisoxazoline **R** to afford the isoxazolidines **S** and **T** with 87:13 diastereoselectivity and good yield [Eq. (19)].

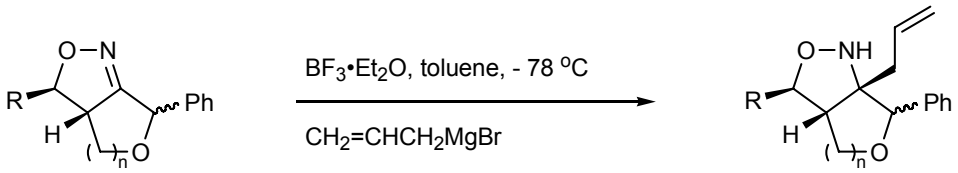
(19)



R **S** **T**

Kurth et al. reported on transformations of furanoisoxazolines **Ua-c** that led only to *cis*-fused allyl addition products **Va-c** by activation of the C=N bond with boron trifluoride etherate at – 78 °C, followed by addition of an etheral solution of allylmagnesium bromide (80 - 88 %) [Eq. (20)].[53]

(20)



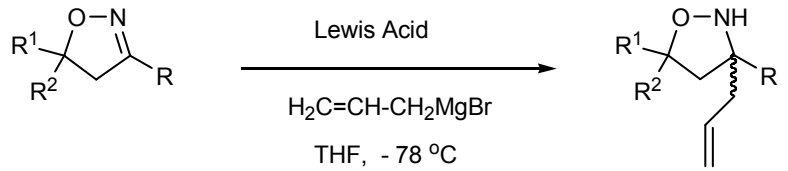
Ua-c **Va-c**

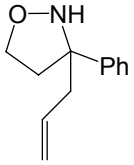
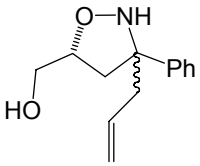
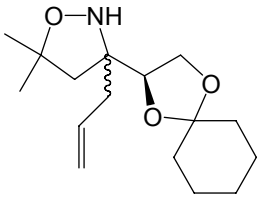
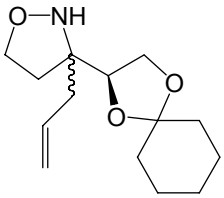
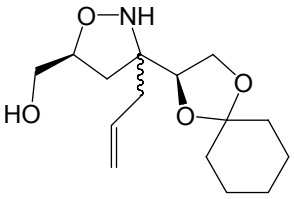
Ua, **Va** : n = 1, R = H, α-Ph, 88 %
Ub, **Vb** : n = 1, R = C_6H_5, α-Ph, 80 %
Uc, **Vc** : n = 2, R = H, β-Ph, 80 %

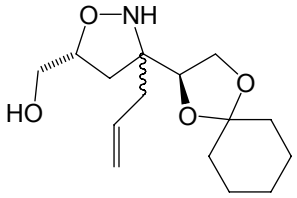
4.1.2 Own results

In this work, a variety of Grignard reagents were tested concerning the addition to isoxazolines. The best results were obtained when allylmagnesium bromide was used with a Lewis acid present. Table 5 illustrates the range of isoxazolines used and the respective isoxazolidines formed.

Table 5. Addition of allylmagnesium bromide to isoxazolines in the presence of a Lewis acid



Entry	Isoxazoline	Isoxazolidine	Lewis Acid	d.r.[a]	Yield[b] a	Yield[b] b	Yield[b] Σ	Exp. No.
1	**2**	 **30**	BF_3•OEt_2	-	-	-	65 %	25
2			$ZnBr_2$	-	-	-	76 %	25a
3			$ZnCl_2$	-	-	-	59 %	25b
4	**9**	 **31 a/b**	$ZnBr_2$	85:15	-	-	63 %	26
5	**22**	 **33 a/b**	$ZnBr_2$	88:12	73 %	11 %	84 %	28
6			$ZnCl_2$	87:13	67 %	9 %	76 %	28a
7			BF_3•OEt_2	83:17	65 %	12 %	77 %	28b
8	**13**	 **34 a/b**	$ZnBr_2$	80:20	64 %	17 %	81 %	29
9	**15/16** d.r. 87:13	 **35 a/b**	$ZnCl_2$	85:15	65 %	13 %	78 %	30
10			$ZnBr_2$	76:24	55 %	15 %	70 %	30a
11			BF_3•OEt_2	77:23	47 %	16 %	63 %	30b

12	**15/16**		$ZnCl_2$	81:19	61 %	19 %	80 %	31
13	d.r. 15:85		$ZnBr_2$	78:22	61 %	17 %	78 %	31a

36 a/b

[a] The determinations of the diastereomeric ratios are based on the intensities of separate signal pairs in the ^{13}C NMR spectra of the crude products. [b] Yields are calculated over two steps starting from the corresponding isoxazoline; **a** : major diastereomer, **b** : minor diastereomer.

The addition was first performed with the isoxazoline **2**, from which the isoxazolidine **30** was obtained. The reaction was done in absolute THF at – 78 ^{o}C in all cases. Three different Lewis acids were used: borontrifluoride etherate BF_3•OEt_2, zinc bromide $ZnBr_2$, and zinc chloride $ZnCl_2$. The results (entries 1-3 in Table 1) show almost no influence of the Lewis acid used, although the yields differ slightly (59% - 76%). It was easier to handle zinc bromide $ZnBr_2$ or zinc chloride $ZnCl_2$ as compared to the use of borontrifluoride etherate BF_3•OEt_2.

The addition was then carried out with (1,3-induction) isoxazoline **9**, in THF and zinc bromide as a Lewis acid. This afforded inseparable isoxazolidines **31a/b** in high diastereoselectivity (d.r. 85:15, entry 4 in Table 5). When the isoxazoline **22** (1,2-induction) was applied to the addition of allylmagnesium bromide, this resulted in a bit higher diastereoselectivity varying from 88:12 in the case of the Lewis acid zinc bromide, and 87:13 in the case of zinc chloride and little lower 83:17 when borontrifluoride etherate was used (entries 5-7 in Table 5).

Similar results were obtained when the isoxazoline **13** (1,2-induction) was added to allylmagnesium bromide in the presence of zinc bromide, to give the addition products: the isoxazolidines **34a** and **34b** in high yield (81 %) and 80:20 diastereomeric ratio (entry 8 in Table 5).

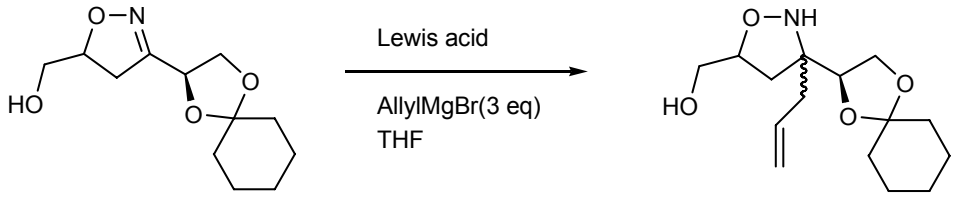
Comparing the effect of the isoxazoline **9** which shows 1,3-induction from C-5 and the isoxazolidines **13**, **22** (1,2-induction from C-1') on the diastereomeric ratios results of the additions products; proves no significant indifference between the two inductions available. Applying the isoxazolines **15**/**16** (87:13) with 1,2-induction from C-1' and 1,3-induction from C-5 to addition of allylmagnesium bromide in the presence of a Lewis acid, represented similar results. The additions were performed in THF in the presence of zinc chloride (entry 9 in Table 5), zinc bromide (entry 10 in Table 5), and borontrifluoride etherate (entry 11 in

Table 5). These additions led to almost the same results (compare entries 4-8 in Table 5), giving the isoxazolidines **35a** and **35b**.

This was proven again, when the same isoxazolines **15**/**16** (d.r. 15:85 in this case) were used, to afford in the presence of a Lewis acid the corresponding isoxazolidines **36a** and **36b** in a 81:19 diastereomeric ratio (entry 12 in Table 5) when zinc chloride was used as a Lewis acid, and in a 78:22 diastereomeric ratio (entry 13 in Table 5) in the case of the Lewis acid zinc bromide.

Changing the temperature of the addition reaction had almost no significant influence neither on the reaction yield nor the diastereoselectivity; this was investigated with the mixture of the isoxazolidines **15**/**16** (87:13) [Table 6].

Table 6. Effect of temperature on the addition of allylmagnesium bromide to the isoxazolines **15**/**16** (d.r. 85:15) in the presence of Lewis acids



15 / 16 **35 a/b**

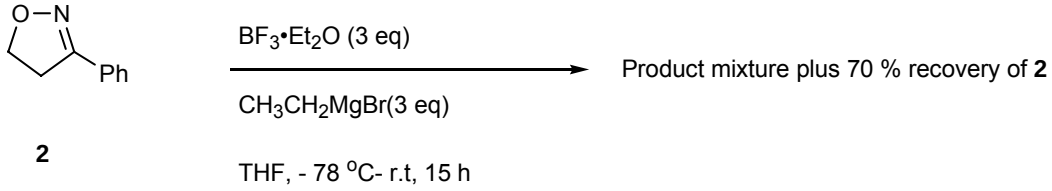
Entry	Temperature	Lewis acid	d.r.[a]	Exp. No.
1	0 °C	BF_3•OEt_2	85:15	30
2	0 °C	$ZnBr_2$	76:24	30a
3	- 78 °C	$ZnCl_2$	77:23	30b

[a] The determination of the diastereomeric ratios (d.r.) are is on the intensities of separate signal pairs in the ^{13}C NMR spectra of the crude products.

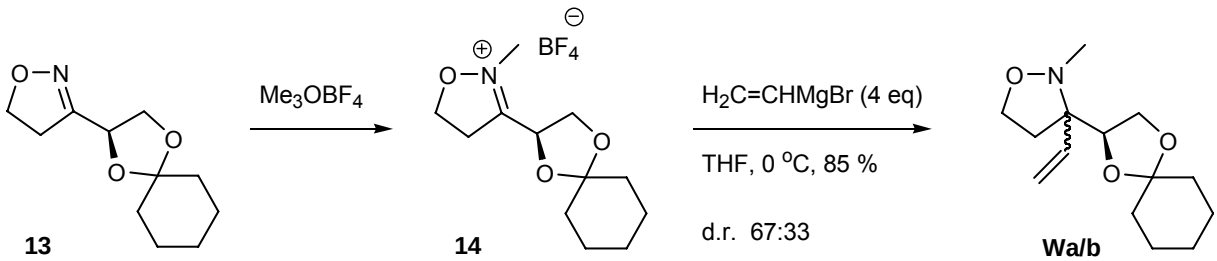
All additions, as already mentioned, were performed at – 78 °C, except for the case of the isoxazoline **15**, for which the yield of the isoxazolidines **35a/b** was somewhat better when the reaction was carried out at 0 °C (entries 9-11 in Table 5)

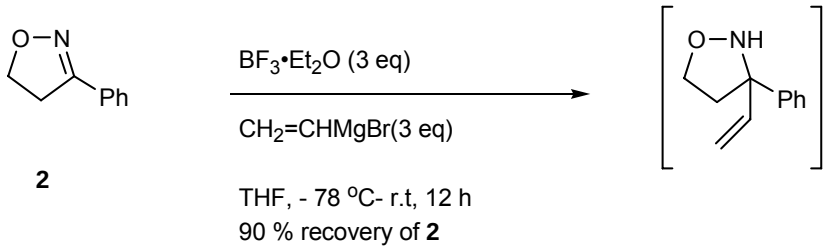
Other Grignard reagents were tested and normally used in excess (up to 4 eq), such as methylmagnesium bromide, ethylmagnesium bromide, vinylmagnesium bromide and isopropylmagnesium chloride. All there gave high recovery of at least 70 % of the isoxazoline used. Changing the temperature and the solvent did not enhance the conversion, and in

some cases led to decomposition when the reaction was performed at room temperature. One example is shown below.

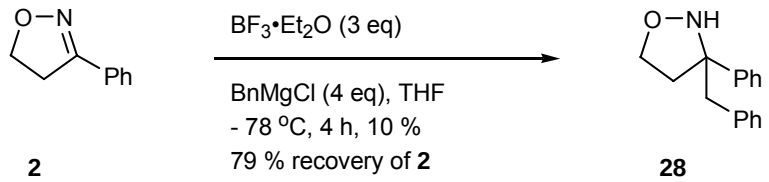


This can be compared with the isoxazolidines **Wa/b** obtained when Henneböhle[1] added vinylmagnesium bromide to the isoxazolinium salt **14**, to afford the respective isoxazolidines **Wa/b** under mild conditions and good yield (85 %). This proves high partial positive charge on C-3 in the isoxazolinium salt **14** compared with that of the isoxazoline **2**, activated by borontrifluoride etherate; this led to 90 % recovery of the starting material.





An exception was found with the isoxazoline **2** when benzylmagnesium chloride and borontrifluoride etherate were used at – 78 °C: This afforded the addition product **28** albeit in poor yield, with 79 % recovery of the isoxazoline **2**.



4.1.3 NMR data of 3-allylisoxazolidines 33a/b, 34a/b and 35a/b

The ^{1}H NMR spectra of the major and the minor diastereomers of the 3-allylisoxazolidines prepared show no significant difference of the chemical shifts (Table 7), which were ≤ 0.1 ppm. The ^{13}C NMR spectra of the 3-allylisoxazolidines present the same picture (Table 8). Here the chemical shifts are ≤ 1.0 ppm. Worth remarking is the difference in the chemical shifts of C-2' signals of the 3-allylisoxazolidines **33**-**35** ($\Delta\delta$= -2.5 to +2.7 ppm), and also that the difference in the chemical shifts of the major isoxazolidine **35a** and the minor one **35b** is 0.0 ppm.

In order to compare the effect of the acetal group on the chemical shifts of 4-H_a and 4-H_b in the 3-allylisoxazolidines prepared; the chemical shifts of the 3-allylisoxazolidines **34a/b**, are compared with those of the isoxazolidines **Wc/d** prepared by Henneböhle[1] by hydride addition to the N-methylisoxazolinium salt **14** in (Table 6a). Comparison according to Sustmann,[54] shows little influence of the acetal group on the chemical shift difference of 4-H_a and 4-H_b for the isoxazolidine **Wc** ($\Delta\delta$= 0.13 ppm) with stronger effect ($\Delta\delta$= 0.13 ppm) in the case of the isoxazolidine **Wd**. Lower chemical shift differences are observed in the case of the 3-allylisoxazolidine **34a** ($\Delta\delta$= 0.33 ppm) and the 3-allylisoxazolidine **34b** ($\Delta\delta$= 0.22 ppm).

Table 6a: Selected ^{1}H NMR data (δ in ppm) of 3-allylisoxazolidines **34a/b** and isoxazolidines **Wc/d**

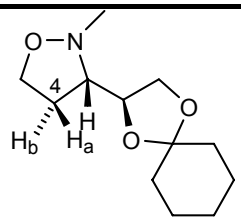
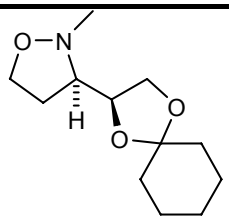
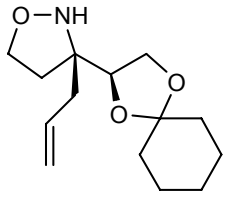
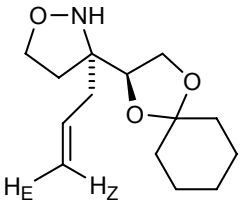
isoxazolidine	Compound	4-H_a	4-H_b
 **Wc**	**Wc**	2.30	1.89
 **Wd**	**Wd**	2.44	2.33
	$\Delta\delta$	0.13	0.44
 **34 a**	**34a**	1.93	2.05
 **34 b**	**34b**	2.26	2.27
	$\Delta\delta$	0.33	0.22

Table 7: Selected ^{1}H NMR data (δ in ppm) of the 3-allylisoxazolidines prepared

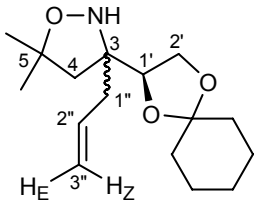
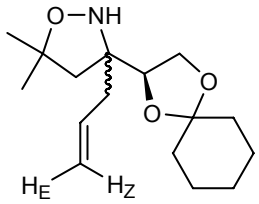
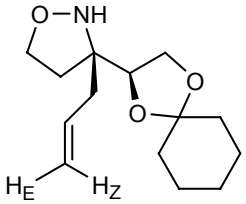
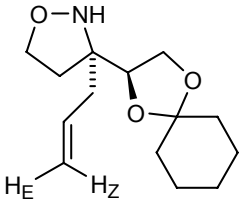
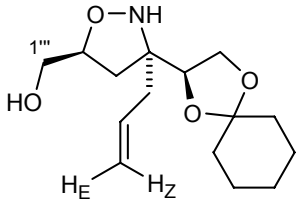
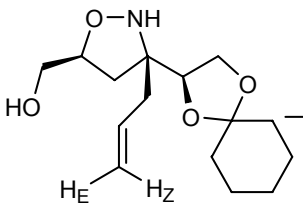
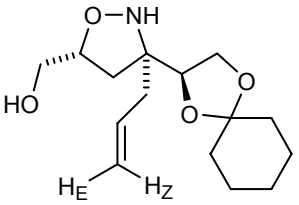
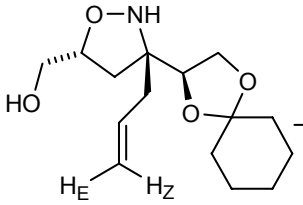
3-Allylisoxazolidine	Compound	1'''-H_a	1'''-H_b	5-$CH_{3(a)}$	5-$CH_{3(b)}$	4-H_a	4-H_b	1''-H_a	1''-H_b	2''-H	3''-H_E	3''-H_Z	1'-H	2'-H_a	2'-H_b
 **33 a**  **33 b**	**33a**	-	-	-	-	1.71	2.13	2.06	2.47	5.95	5.09[a]	5.09[a]	4.13	3.58[a]	4.04
	33b	-	-	-	-	1.91	2.11	2.28	2.44	5.85	5.15[a]	5.15[a]	4.17	3.86	4.01
	$\Delta\delta$	-	-	-	-	+0.20	-0.02	+0.22	-0.03	-0.10	+0.06	+0.06	+0.04	+0.28	-0.03
				5-H_a	5-H_b										
 **34 a**  **34 b**	**34a**	-	-	3.79[a]	3.95[a]	1.93[a]	2.26	2.10	2.42	5.91	5.09	5.13	4.16	3.68[a]	4.07
	34b	-	-	3.85	3.91	2.05	2.27	2.38	2.38	5.85	5.16	5.19	4.22	3.83	4.03
	$\Delta\delta$	-	-	+0.06	-0.04	+0.12	+0.01	-0.28	-0.04	-0.06	+0.07	+0.06	+0.06	+0.15	-0.04
 **35 a**  **35 b**	**35a**	3.64	3.70	4.14	-	2.05	2.14	2.34	2.34	5.85	5.18	5.18	4.20	3.90	4.03
	35b	3.62	3.82	4.10	-	1.74	2.34	2.10	2.44	5.92	5.10	5.10	4.13	3.66	4.06
	$\Delta\delta$	-0.02	+0.12	-0.04	-	-0.29	+0.20	-0.24	+0.10	+0.07	-0.08	-0.08	-0.07	-0.24	+0.03

Table 7: continue

3-Allylisoxazolidine	Compound	1'''-H_a	1'''-H_b	5-H_a	5-H_b	4-H_a	4-H_b	1''-H_a	1''-H_b	2''-H	3''-H_E	3''-H_Z	1'-H	2'-H_a	2'-H_b
 **36a**	**36a**	3.59	3.63	4.25	-	1.97	2.02	2.11	2.41	5.92	5.12[a]	5.12[a]	4.17	3.67	4.06
 **36b**	**36b**	3.59	3.70	4.16	-	2.05	2.14	2.34[a]	2.34[a]	5.85	5.17[a]	5.17[a]	4.19	3.89	4.03
	$\Delta\delta$	0.00	+0.07	-0.09	-	-0.08	+0.12	+0.23	-0.07	-0.07	+0.05	+0.05	+0.02	+0.22	-0.03

[a] Signals are not identified, average of multiplet are given.

Table 8: Selected ^{13}C NMR data (δ in ppm) of the 3-allylisoxazolidines prepared

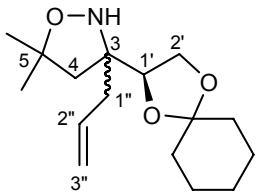
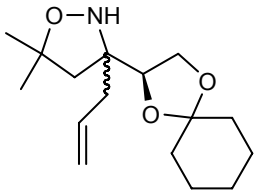
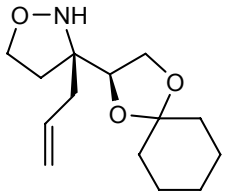
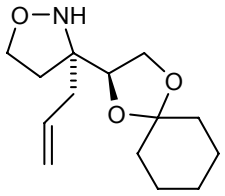
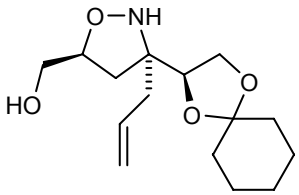
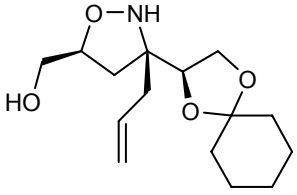
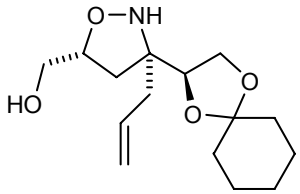
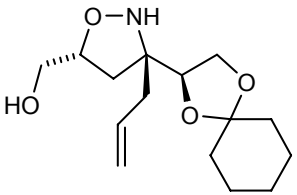
3-Allylisoxazolidine	Compound	C-1'''[a]	C-5	C-4	C-3	C-1'	C-2'	C-1''	C-2''	C-3''
 **33 a**	**33a**	-	84.9	46.6	70.9	74.9	66.6	42.5	134.6	118.0
 **33 b**	**33b**	-	84.9	48.0	68.8	77.6	65.6	41.5	133.8	119.5
	$\Delta\delta$	-	0.00	+1.4	-2.3	+2.7	-1.0	-1.0	-0.8	+1.5
 **34 a**	**34a**	-	72.1	35.2	68.7	76.1	66.8	41.0	134.1	118.9
 **34 b**	**34b**	-	72.2	36.0	67.3	78.8	65.7	40.8	133.1	120.0
	$\Delta\delta$	-	+0.1	+0.8	-1.4	+1.7	-1.1	-0.2	-1.0	+1.1
 **35 a**	**35a**	63.0	83.2	34.9	67.7	78.1	66.1	40.0	132.6	119.9
 **35 b**	**35b**	63.0	84.3	36.0	69.4	75.6	66.0	40.8	133.8	118.5
	$\Delta\delta$	0.0	+1.1	+1.1	+1.7	-2.5	-0.1	+0.8	+1.2	-1.4

Table 8: Continue

3-Allylisoxazolidine	Compound	C-1'''[a]	C-5	C-4	C-3	C-1'	C-2'	C-1''	C-2''	C-3''
 **36a**	**36a**	63.1	82.7	35.5	68.9	75.7	66.0	39.9	133.3	118.9
 **36b**	**36b**	63.4	83.5	37.1	67.9	76.9	65.5	40.2	132.9	120.1
	$\Delta\delta$	+0.3	+0.8	+1.6	-1.0	+1.2	-0.5	+0.3	-0.4	+1.2

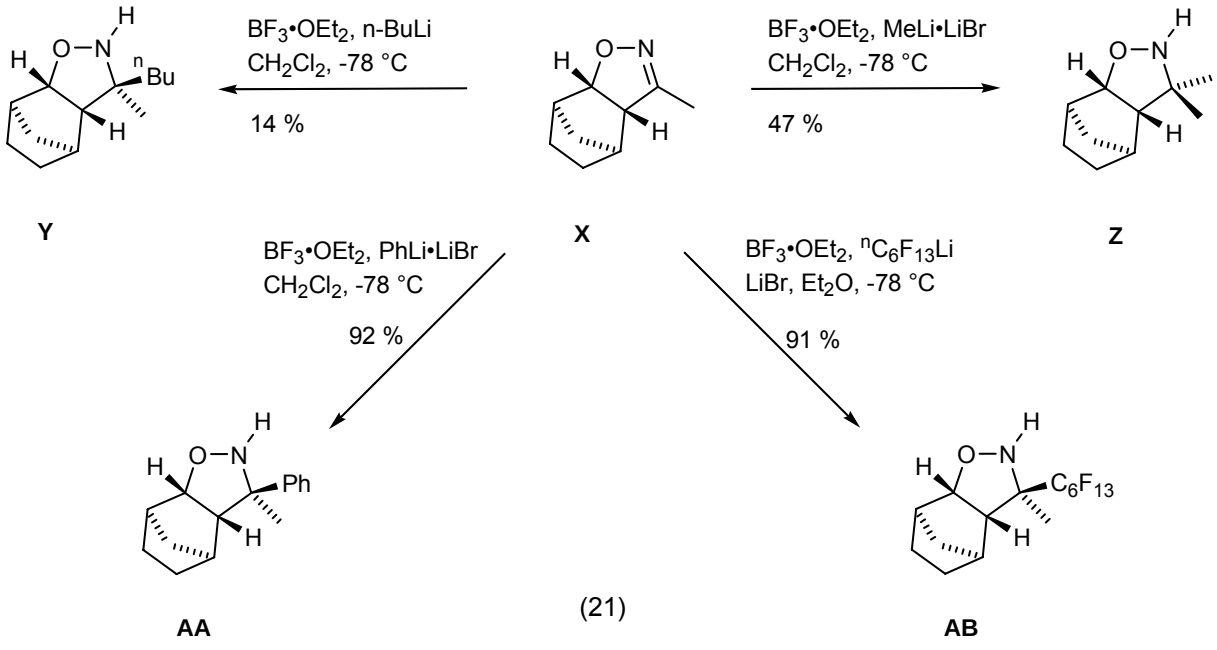
[a] In case of compounds **35a/b** and **36a/b**.

4.2 Reaction of organolithium compounds with isoxazolines: methyllithium and phenyllithium-lithium bromide complex

4.2.1 State of knowledge

In the literature, the addition of alkyl/aryllithium lithiumhalide complexes to isoxazolines has seldom been investigated. The only example in the literature is due to Uno et al,[13,55] who showed that in the presence of borontrifluoride etherate 3,4,5-tri-, 3,5,5-tri- and 3,5-disubstituted 2-isoxazolines underwent nucleophilic addition of alkyl- and aryllithiums to give the respective 3,3,4,5-, 3,3,3,5-, and 3,3,5-substituted isoxazolidines in moderate to good yield.

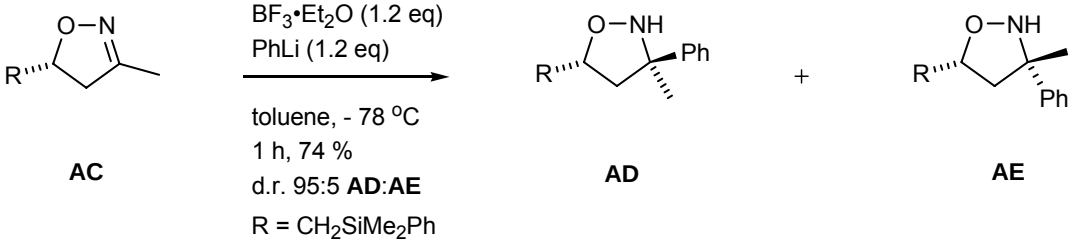
The isoxazoline **X** can easily be prepared from nitroethane and norbornene according to Hoshino and Mukaiyama.[56] High diastereoselectivity in the alkylation is anticipated because one face of the isoxazoline ring is completely blocked by the 4,5-substituents. The limitations reported by authors were that no reaction was observed when *t*-butyllithium, lithium phenylacetylide, phenylmagnesium bromide, or *n*-butylmagnesium bromide were employed [Eq. (21)].[55]



(21)

In each case the alkyl addition to a 4,5-disubstituted isoxazoline occurred from the opposite side of the substituents at C-4/C-5 to form one diastereomer. On the other hand, addition of phenyllithium to the 5-monosubstituted 2-isoxazoline in toluene also proceeded in a high stereoselective manner [Eq. (22)]. [13,55]

(22)



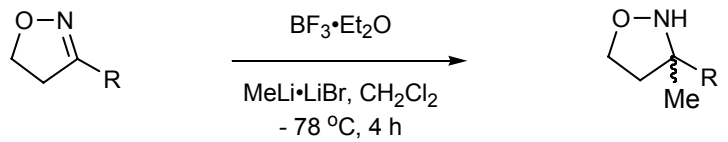
AC **AD** **AE**

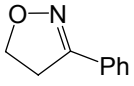
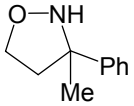
The diastereoselectivity of the addition of organolithium compounds to isoxazolines was studied by Uno[55] with the 3,5-disubstituted isoxazoline **AC**. Here a highly stereoselective reaction (>95:5 **AD**:**AE**) was observed using phenyllithium and borontrifluoride etherate to afford the isoxazolidines **AD** and **AE** in 74% combined yield [Eq. (22)]. Its worth mentioning that the two diastereomers obtained were inseparable, albeit they were detected and analyzed by means of NMR and elemental analysis. The diastereomeric ratio of the mixture obtained was estimated by ^{1}H NMR analysis.

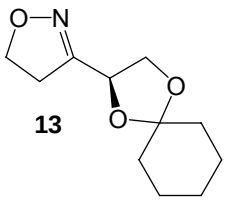
4.2.2 Own results

In this nucleophilic addition, methyllithium-lithium bromide complex was used to perform the addition to the isoxazolines **2** and **13**. The addition was performed in the presence of borontrifluoride etherate as a Lewis acid in abs. dichloromethane at – 78 °C [Table 9]; the diastereoselectivity of such addition was found to be moderate (68:32) when the chiral isoxazoline **13** used.

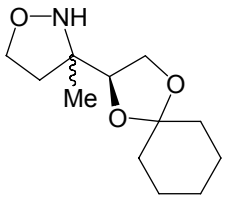
Table. 9. Addition of methyllithium-lithium bromide complex to the isoxazolines **2** and **13** in the presence of borontrifluoride etherate.



Entry	Isoxazoline	Isoxazolidine	d.r.[a]	Yield			Exp. No.
				a	**b**	Σ	
1	 **2**	 **29**	-	-	-	83%	24



13



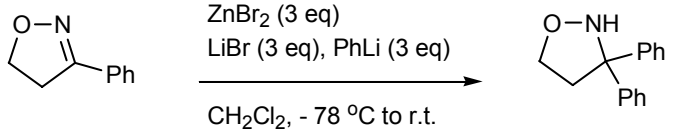
32 a/b

2	68:32	58 %	27 %	85 %	27	

[a] The determination of the diastereomeric ratios (d.r.) is based on the intensities of separate signal pairs in the ^{13}C NMR spectra of the crude products; **a** : major diastereomer, **b** : minor diastereomer.

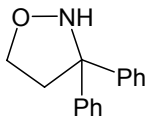
The addition of phenyllithium PhLi to the model isoxazoline **2** gave the corresponding 3,3-diphenylisoxazolidine **27**. The reaction was performed according to Uno's procedure, but using zinc bromide as a Lewis acid instead of borontrifluoride etherate. The yield was rather poor (5 %), even when the reaction temperature was allowed to rise to room temperature, after the addition of phenyllithium and lithium bromide at - 78 °C [Eq. 23].

(23)

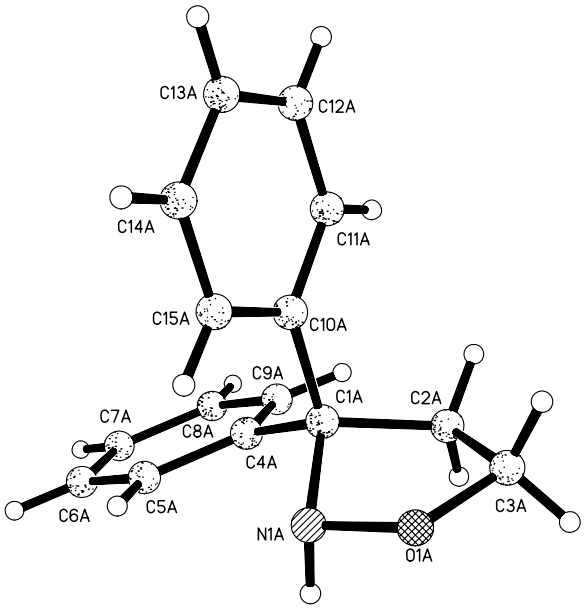


2 **27**

It was possible to obtain colourless crystals of the isoxazolidine **27**, which were suitable for crystal structure determination (see appendix 12.1).



27



4.2.3 NMR data of the 3-methylisoxazolidines 32a and 32b and assignment of configurations

Tables 10 and 11 show selected ^{1}H NMR and ^{13}C NMR data of the major and the minor diastereomer of the 3-methylisoxazolidines **32** prepared. The ^{1}H NMR chemical shifts of both diastereomers show no significant difference ($\Delta\delta \leq 0.11$ ppm). The ^{13}C NMR data show a similar picture, that is small chemical shift differences of $\Delta\delta \leq 2.2$ ppm.

Table 10: Selected ^{1}H NMR data (δ in ppm) of the 3-methylisoxazolidines **32**

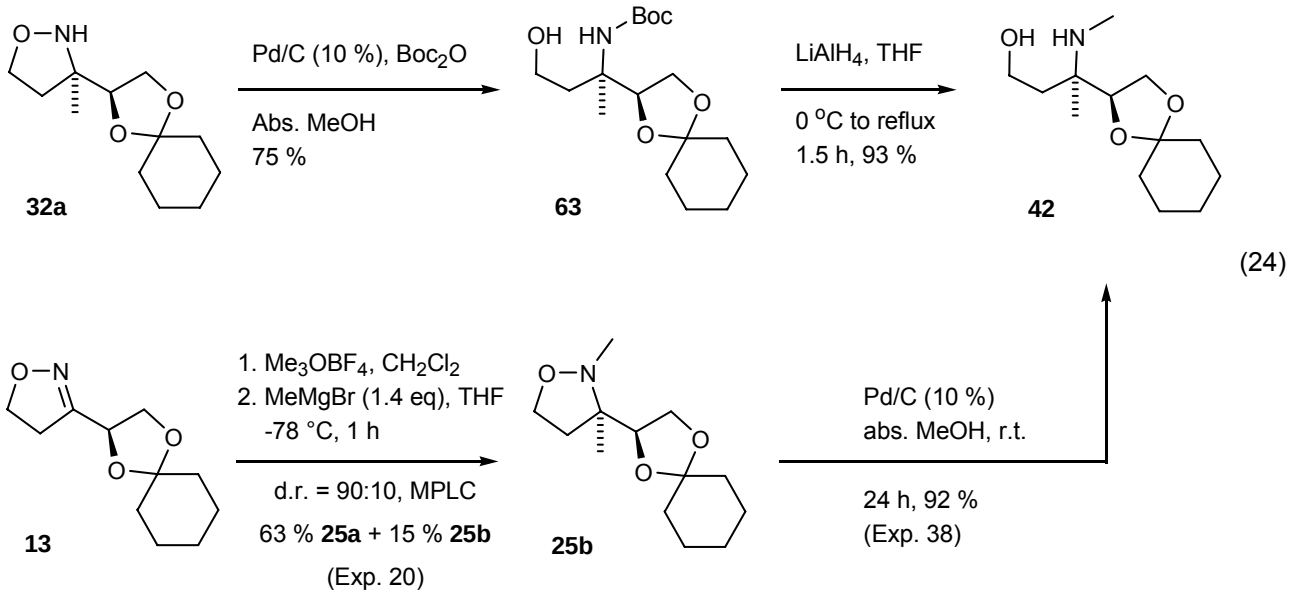
3-Methylisoxazolidine	5-H_a	5-H_b	4-H_a	4-H_b	1'-H	2'-H_a	2'-H_b	1''-H
32a	3.91[a]	3.91[a]	1.88	2.31	4.18	3.81	4.04	1.24
32b	3.86[a]	4.02[a]	1.84	2.31	4.13	3.74	4.09	1.17
$\Delta\delta$	-0.05	+0.11	-0.04	0.00	-0.05	-0.07	+0.05	-0.07

[a] Signals were not assigned, average of multiplet are given.

Table 11: Selected ^{13}C NMR data (δ in ppm) of the 3-methylisoxazolidines **32**

3-Methylisoxazolidine	C-5	C-4	C-3	C-1'	C-2'	C-1''
32a	65.6	38.5	64.7	79.1	71.5	22.5
32b	66.2	37.1	66.0	76.9	71.7	21.5
$\Delta\delta$	+0.6	-1.4	+1.3	-2.2	+0.2	-1.0

In order to assign the absolute configuration of the 3-methylisoxazolidine **32 a** and **32 b** obtained, catalytic hydrogenation of the diastereomer **32a** using palladium catalyst in the presence of *tert*-butyloxycarbonyl in methanol which transformed **32a** into the corresponding *N*-Boc-protected amino alcohol **64**. This, on $LiAlH_4$ reduction afforded the *N*-methyl-3-methyl amino alcohol **42** (which was previously prepared from the isoxazolidine **25b**), of which the absolute configuration had previously been confirmed to be (2*S*, 3*R*). This means that the 3-methylisoxazolidine **32a** has a (3*R*, 1'*S*)-configuration, and thence (3*S*, 1'*S*)-configuration for the isoxazolidine **32b** [Eq. 24]. The analytical data if the resulted *N*-methyl-3-methyl amino alcohol **42** (Exp. 39) was fully complied with those had been found for the *N*-methyl-3-methyl amino alcohol **42** afforded from N-O cleavage of the isoxazolidine **25b** (Exp. 38).


Pd/C (10 %), Boc2O
Abs. MeOH
75 %
LiAlH4, THF
0 °C to reflux
1.5 h, 93 %
32a
63
42
1. Me3OBF4, CH2Cl2
2. MeMgBr (1.4 eq), THF
-78 °C, 1 h
d.r. = 90:10, MPLC
63 % 25a + 15 % 25b
(Exp. 20)
13
25b
Pd/C (10 %)
abs. MeOH, r.t.
24 h, 92 %
(Exp. 38)

(24)

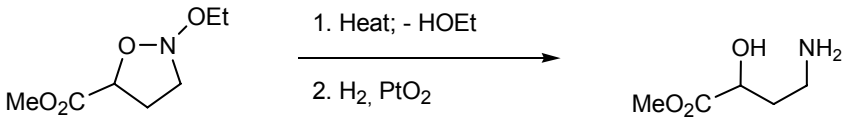
5 Catalytic Hydrogenation of Isoxazolidines and Isoxazolidinium Salts

5.1 Synthesis of *N*-methyl amino alcohols, amino alcohols, and amino polyols

5.1.1 State of knowledge

Over the years, a number of routes have been elaborated for the cleavage of the N-O bond of isoxazolidines, as a key step towards syntheses of amino alcohols, amino polyols, and many other important targets. The first known example of this, dates from 1975 when Sato et al.[57] effected a catalytic hydrogenation of an isoxazoline with platinum oxide PtO_2 as a catalyst, affording 4-amino-2-hydroxy-butyric acid methyl ester **AG**, no yield was given for this reaction as it was performed in multistep reaction [Eq. 25].

(25)



AF **AG**

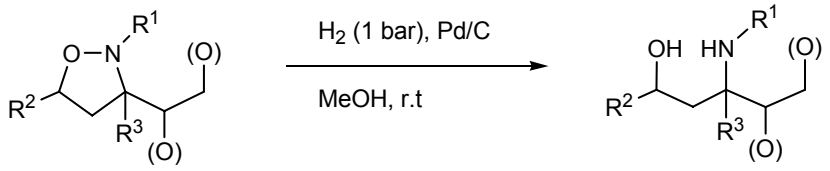
Catalytic hydrogenation was often performed over the last three decades using several catalysts such as palladium,[58] palladium on carbon, [1, 2, 10, 59, 60, 61] palladium hydroxide on carbon,[62,63,64] Raney Nickel,[65,66] platinum oxide,[67] rhodium on carbon,[68] molybdenum hexacarbonyl.[69] in our research group palladium on carbon (Pd/C) was often employed as the most convenient catalyst for N-O bond cleavage of isoxazolines[1,2,10] and isoxazolidines.[1,2,10]

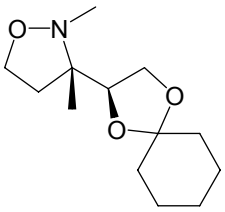
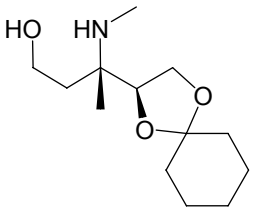
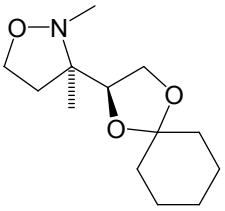
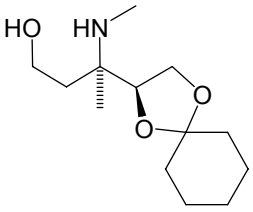
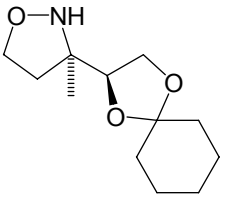
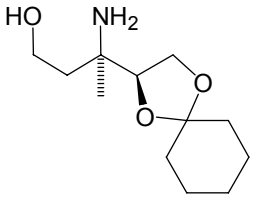
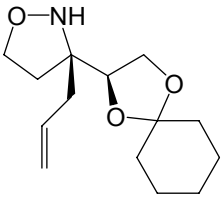
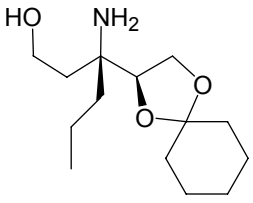
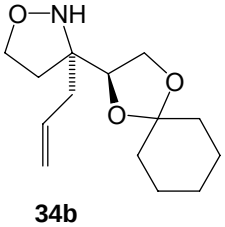
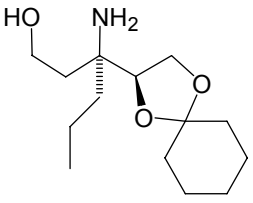
5.1.2 Own results

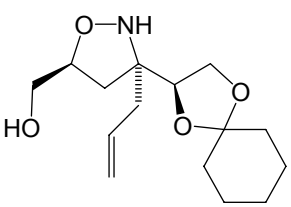
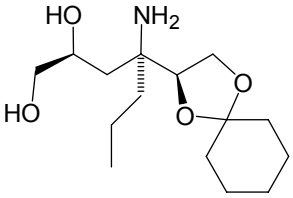
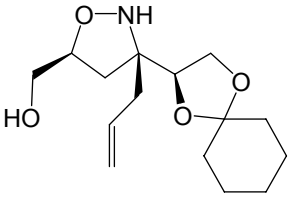
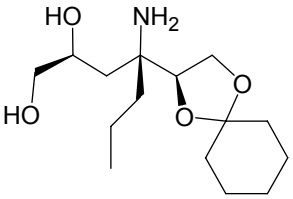
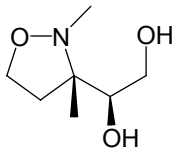
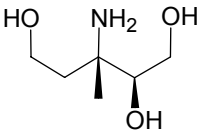
In this chapter, the synthesis of N-methylamino alcohols, amino alcohols, and amino polyols will be described. This catalytic hydrogenation of isoxazolidines using palladium on carbon is a typical procedure for N-O bond cleavage in our research group.[10] The hydrogenation can be taken place under different pressure of hydrogen. Fortunately, the catalytic hydrogenation of the isoxazolidines **25a/b**, **30**, **32a**, **34a/b**, **35a/b** and **52** presented here took place at 1 bar at room temperature and in methanol as a solvent. The yield of the hydrogenations mostly was very high (83 % - 100 %). Difficulties were encountered concerning correct elemental

analysis for the amino polyols **48**, **49**, **50**, albeit the samples were pure according to NMR (structures were ascertained by high resolution mass spectroscopy) [Table 12].

Table 12. Catalytic hydrogenation of isoxazolidines to give amino alcohols or polyols



Entry	Isoxazolidine	Amino alcohol or polyol	Yield	Exp. No.
1	 **25a**	 **41**	96 %	37
2	 **25b**	 **42**	92 %	38
3	 **32a**	 **45**	100 %	42
4	 **34a**	 **47**	84 %	44
5	 **34b**	 **48**	89 %	45

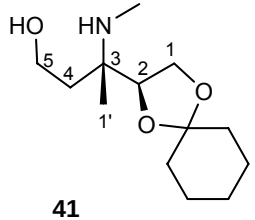
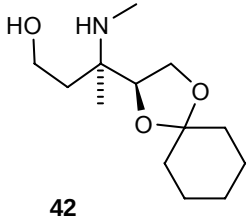
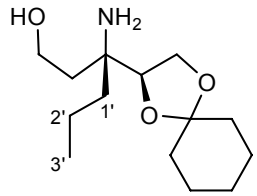
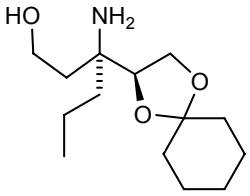
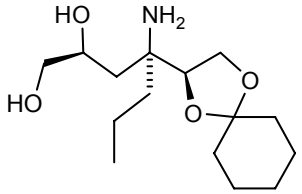
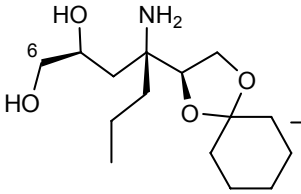
6	 **35a**	 **49**	97 %	46
7	 **35b**	 **50**	98 %	47
8	 **52**	 **70**	83 % lit. 99 %[1]	66

5.1.3 NMR data of *N*-methylamino alcohols, amino alcohols and amino polyols

An overview on tables 13 and 14, present small difference among the chemical shifts of the protons of the amino alcohols **41**, **47**, and their corresponding diastereomers obtained: the amino alcohols **42** and **48**, and similarly for the amino polyols **49** and **50**. The differences were only ≤0.20 ppm. One exception is the case of the 1-H_a signal of amino alcohols **49** and **50**, which has a difference ($\Delta\delta$) of 0.37 ppm.

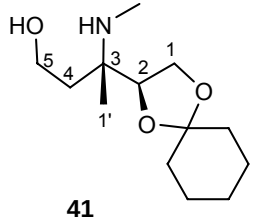
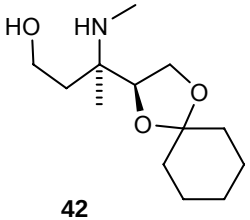
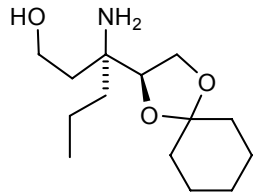
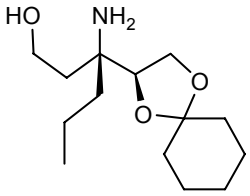
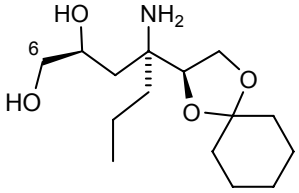
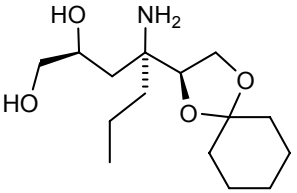
The ^{13}C NMR spectra of the corresponding amino alcohols and amino polyols present the same picture: no significant differences of the chemical shifts of diastereomeric pairs were observed, with two exceptions from this: In the case of the C-2 and the case of C-3 signals of the amino polyols **49** and **50**.

Table 13: Selected ^{1}H NMR data (δ in ppm) of the amino alcohols **41**, **42**, **47**, **48** and amino polyols **49**, **50**[a]

Amino alcohols, -polyols	Compound	6-H_a	6-H_b	5-H_a	5-H_b	4-H_a	4-H_b	2-H	1-H_a	1-H_b	1'-H	2'-H	3'-H	N-CH_3
 **41**	**41**	-	-	3.89	4.03	-[c]	-[c]	4.37	3.87	4.13	1.07	-	-	2.36
 **42**	**42**	-	-	3.73[b]	3.87[b]	-[c]	-[c]	4.21	3.71	3.97	1.10	-	-	2.39
	$\Delta\delta$	-	-	-0.16	-0.16	-	-	-0.16	-0.16	-0.16	+0.03	-	-	+0.03
 **47**	**47**	-	-	3.72[b]	3.89[b]	-[c]	-[c]	4.01	3.77	3.96	-[c]	-[c]	-	-
 **48**	**48**	-	-	3.73[b]	3.89[b]	-[c]	-[c]	4.04	3.68	3.94	-[c]	-[c]	-	-
	$\Delta\delta$	-	-	+0.01	0.00	-	-	+0.03	-0.09	-0.02	-	-	-	-
 **49**	**49**	3.46	3.58	3.99[b]	-	-[c]	-[c]	4.01	3.66	3.94	-[c]	-[c]	0.93	-
 **50**	**50**	3.55	3.68	4.14[b]	-	-[c]	-[c]	4.27	4.03	4.14	-[c]	-[c]	1.00	-
	$\Delta\delta$	+0.09	+0.10	+0.15	-	-	-	+0.26	+0.37	+0.20	-	-	+0.07	-

[a] $CDCl_3$ used as a solvent. [b] Signals were not assigned; centers of multiplets are given. [c] Signals were not identified due to overlap with the multiplet of $C(CH_2)_5$ protons.

Table 14: Selected ^{13}C NMR data (δ in ppm) of the amino alcohols **41**, **42**, **47**, **48** and amino polyols **49**, **50**[a]

Amino alcohols, -polyols	No.	C-6	C-5	C-3	C-2	C-1	C-1'	C-2'	C-3'	N-CH_3
 **41**  **42**	**41**	-	59.6	57.5	77.7	64.8	18.5	-	-	28.0
	42	-	59.5	57.0	78.2	65.0	18.6	-	-	28.1
	$\Delta\delta$	-	-0.1	-0.5	+0.5	+0.2	+0.1	-	-	+0.1
 **47**  **48**	**47**	-	59.1	56.1	79.6	64.3	-[b]	16.9	14.8	-
	48	-	59.2	55.3	80.2	63.6	-[b]	16.9	14.8	-
	$\Delta\delta$	-	+0.1	-0.8	+0.6	-0.7	-	0.0	0.0	-
 **49**  **50**	**49**	63.4	68.6	55.4	80.1	67.4	-[b]	17.1	14.8	-
	50	63.9	68.2	60.2	76.7	66.6	-[b]	16.9	14.5	-
	$\Delta\delta$	+0.5	-0.4	+4.8	-3.4	-0.8	-	-0.2	-0.3	-

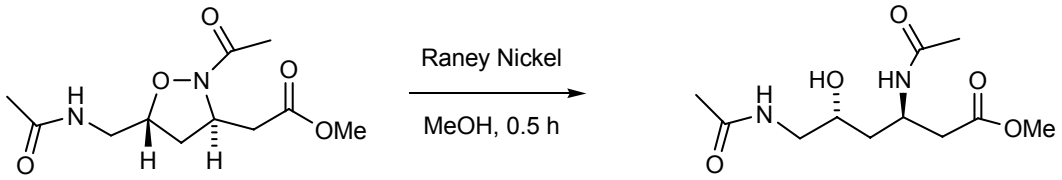
[a] $CDCl_3$ used as a solvent. [b] Not identified due to overlap by $C(CH_5)_2$ carbon signals.

5.2 Catalytic Hydrogenation of Isoxazolidine Esters

5.2.1 State of knowledge

Catalytic hydrogenation of isoxazolidine esters upon our knowledge has never been studied in literature. Screening the literature bring to Jurczak et al.,[70] who have published that the isoxazolidine **AH** can be hydrogenated in presence of Raney Nickel to give the respective bis-acetylamino-ester **AI**; the yield was not given [Eq. 26].

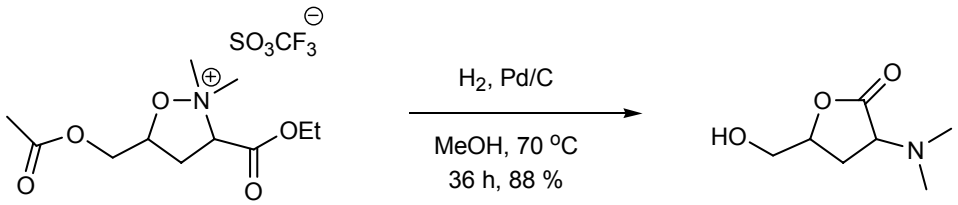
(26)



AH **AI**

Catalytic hydrogenation of the isoxazolidinium trifluoromethansufonate salt **AJ** with palladium on carbon according to Romeo, Uccella et al.[71] led to the lactone **AK** in 88 % yield [Eq. 27].

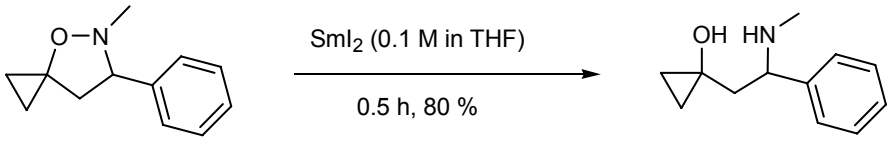
(27)



AJ **AK**

Samarium (II) iodide has found widespread use as a reducing agent;[72] it was as well revealed as a selective and mild reagent for the reduction for isoxazolidines. The yields of such reductions cited by Brandi et al.[73] vary between 55 and 98 % [Eq. 28].

(28)

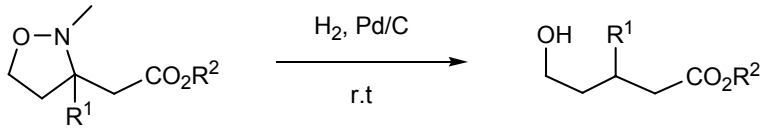


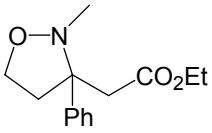
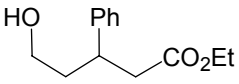
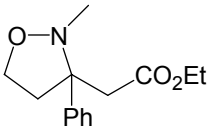
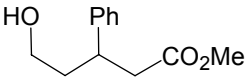
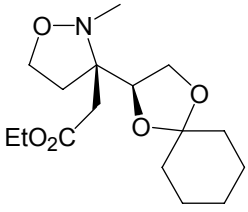
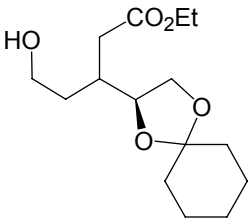
AL **AM**

5.2.2 Own results

Catalytic hydrogenation using palladium on carbon of the isoxazolidine esters **24**, **26a** unexpectedly afforded the corresponding esters **39**, **40**, **43**, by elimination of methylamine [Table 15]. The reactions carried out at room temperature and under 1 bar pressure of hydrogen. The esters **39**, **40** and **43** obtained in low yields, separated from mixture of products, could not be identified. The reaction progress was monitored by TLC and quenched when no more isoxazolidine remained.

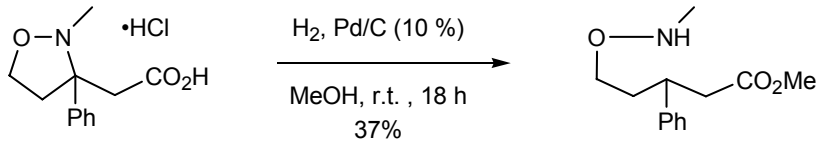
Table 15. Catalytic hydrogenation of isoxazolidine esters **24**, **26a**



Entry	Isoxazolidine	Deamination product	Solvent	Yield	Exp. No.
1	 **24**	 **39**	EtOH	35 %	35
2	 **24**	 **40**	MeOH	40 %	36
3	 **26a**	 **43**	EtOH	17 %	40

On the other hand, when the isoxazolidine **24** was first transformed to the isoxazolidinium salt **51** (see chapter 6.1.2) it was possible to reduce the resulting isoxazolidinium salt **51** with hydrogen/palladium on carbon (Pd/C) in MeOH for 18 hour which produced the *N*-methylaminoxy ester **77** in 37 % yield [Eq. 29].

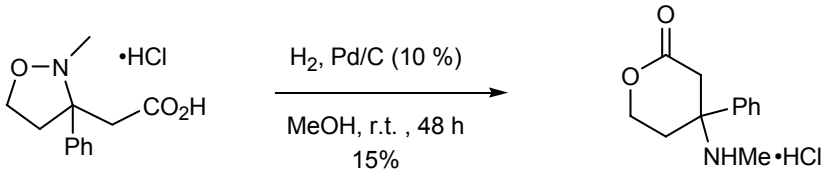
(29)



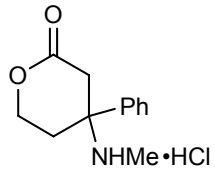
50 **78**

This suggests that in presence of an β-ester moiety in the isoxazolidine the cleavage of the β-C-N bond is preferred over that of the N-O bond. This will be discussed in detail in chapter 7. Fortunately, it was possible to isolate another product of from this reaction, the amino lactone **74** as a hydrochloride salt, after catalytic hydrogenation of the isoxazolidinium salt **51** by means of palladium on carbon (10 %) for 48 h. The yield here was poor; in spite of this it was possible to have an X-ray determination of the colourless crystals obtained [Eq. 30] (see appendix 12.8).

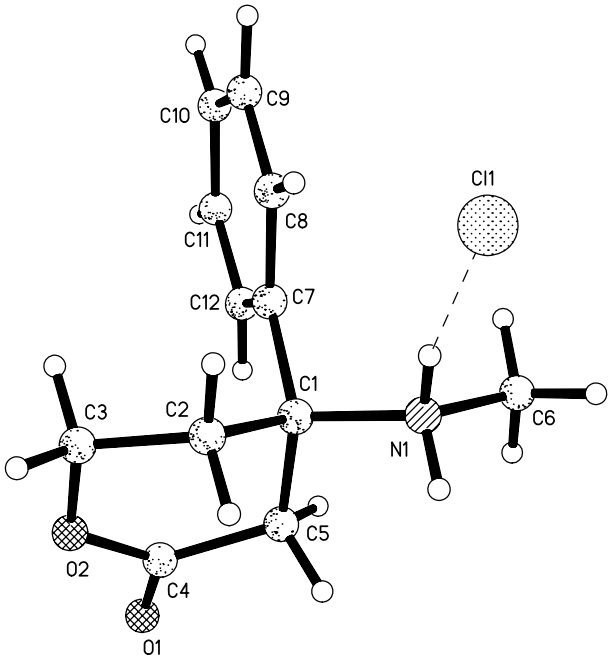
(30)



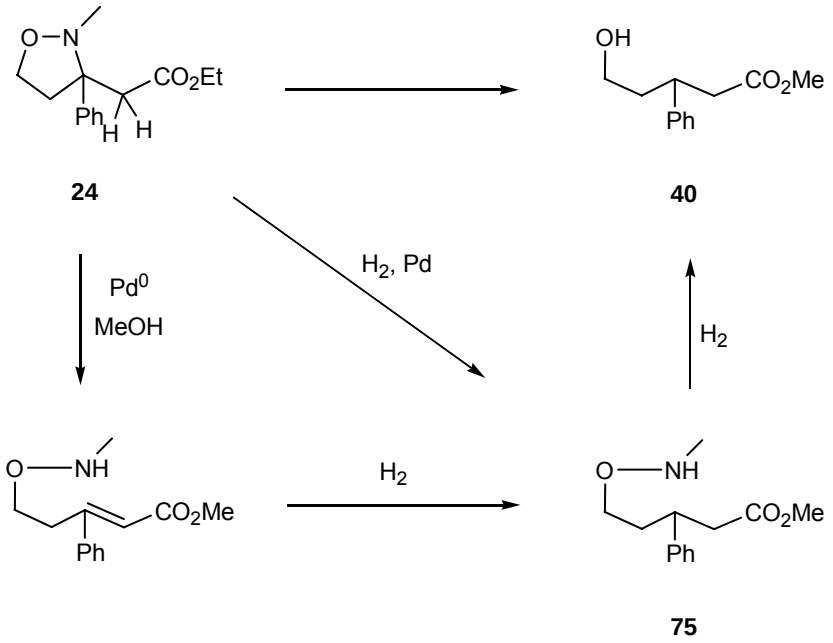
51 **74**



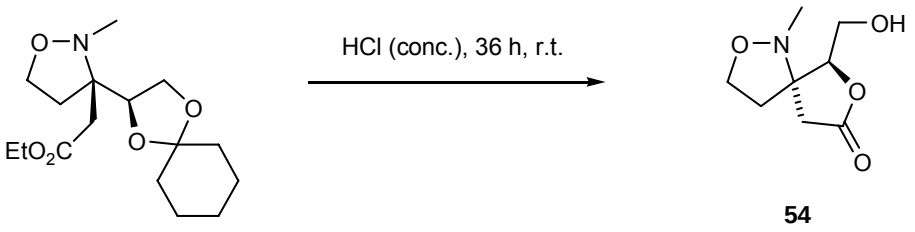
74



An interpretation of what is taking place in this catalytic hydrogenation can be given by the following sequence: The reduction of C-N bond β to the ester group is preferred in comparison with the N-O bond:

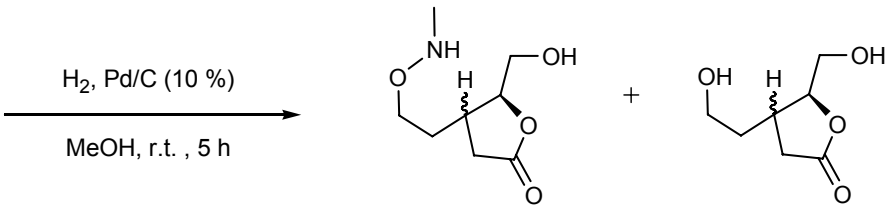


This was clarified again when the ethyl 2-methyl-3-isoxazolidinyl acetate **26a** was first hydrolyzed with hydrochloride (6.0 N) to give the corresponding isoxazolidinolactone **54**. Then catalytic hydrogenation was carried out with the crude product of **54** to afford the *N*-methylaminoxy-lactones **56a/b** as the major diastereomers. These two diastereomers could have been formed according to the mechanism suggested above, by hydrogenation of either the C-N bond or the temporary C=C bond. The other two diastereomers isolated were the dihydroxy-lactones **57a/b**, probably formed by cleavage of the N-O bond in **56a/b** that had remained. The diastereomeric ratio (d.r.) of the aminoxy-lactones **56a/b** was found as 63:37 and as 65:35 for the lactones **57a/b** [Eq. 31].



26a **54**

(31)

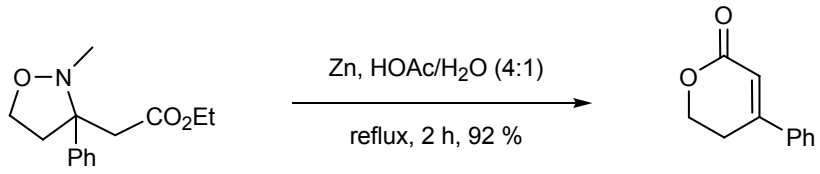


56a/b **57a/b**

74 % [*63*:*37*] 16 % [*65*:*35*]

Using other catalysts such as palladium hydroxide on carbon $Pd(OH)_2/C$, rhodium on carbon Rh/C, or rhuthinium (5 % on alumina) in the hydrogenation of isoxazolidine **24** led to decomposition. When activated zinc in $HOAc/H_2O$ (4:1) was employed, the lactone **38** was obtained in 92 % yield, this product probably transformed from **37** (produced first) by elimination of the acidic proton which will lead in methylamine removal to give **38** [Eq. 32].

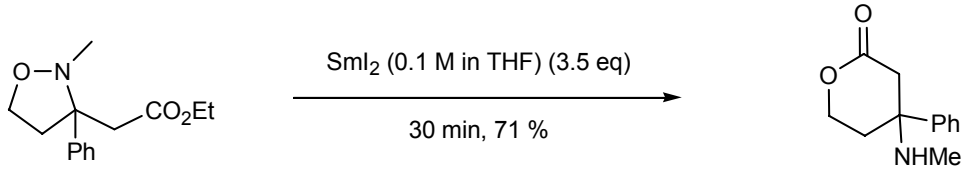
(32)



24 **38**

At the end of this work, in order to avoid the deamination, milder reduction conditions were sought and found by use of SmI_2: This finally gave the desired lactone **37** in 71 % yield [Eq. 33].

(33)



24 **37**

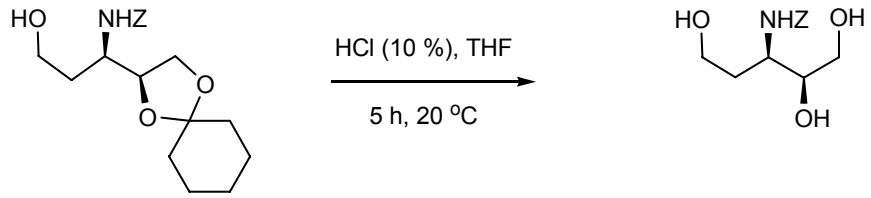
6 Hydrolysis of Isoxazolidine Acetals and Esters

6.1 Preparation of isoxazolidinium salts 51, 52•HCl, 53•HCl and diols 52, 53

6.1.1 State of knowledge

Within the scope of this work, acid-catalyzed hydrolysis was an important step on the way to prepare free amino polyols, and in the plan to obtain the target α-amino acids. Acetal hydrolysis is known in the literature using a variety of acids; in our research group Jäger et al.[1,10] cited the acetal hydrolysis of Z-protected amino alcohol **AN** with aqueous hydrochloric acid in THF [Eq. 34].

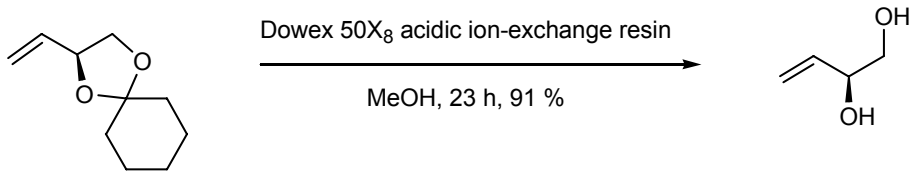
(34)



AN **AO**

Trifluoroacetic acid was used similarly in such hydrolyses, f.e. Sharma et al.[74] obtained (*S*)-5-bromopentane-1,2-diol from the protected diol in 72% yield. Other acids were also used, such as *p*-toluenesulfonic acid,[75] acetic acid,[76] Dowex 50X_8 acidic ion-exchange resin [Eq. 35],[77] or sulfuric acid.[78] Some other more selective hydrolysis used propane-1,3-dithiol in the presence of borontrifluoride etherate.[40]

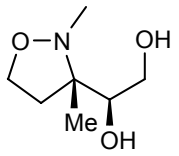
(35)



AP **AQ**

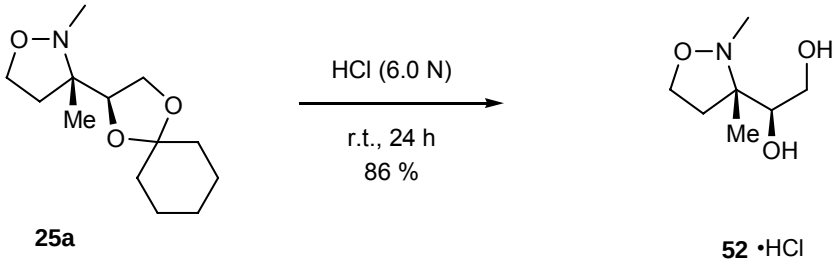
6.1.2 Own results

On the way to prepare the target β-amino acids and also in order to assign the configuration at C-3 of the isoxazolidines **25 a/b** prepared, it was first necessary to hydrolyze these isoxazolidines. Henneböhle[1] had done the hydrolysis of the diol **52** in 96 % yield, but the assignment of configuration at C-3 of the isoxazolidine was not possible in his work. This was solved in this work by repeating the reaction and excluding the neutralization step in the preparation of the diol **52**, to afford the isoxazolidinium salt **52•HCl** as colourless crystals, suitable for crystal structure determination [Eq. 36] (see appendix 12.5).

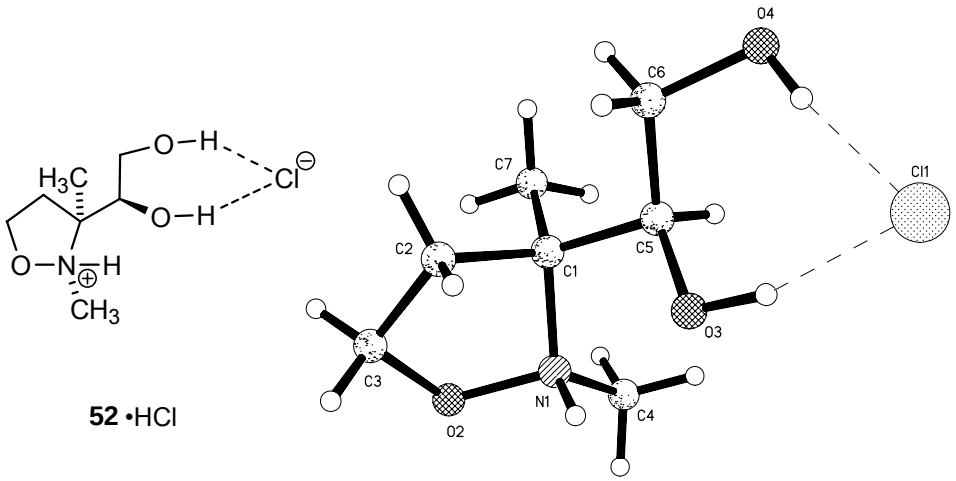


52

(36)

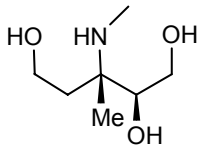


25a **52** •HCl



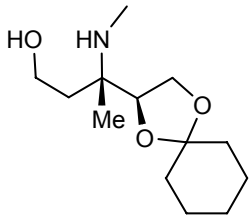
52 •HCl

In the same manner, the 3-methyl-3-methylamino alcohol **70** had been prepared by Henneböhle.[1] This was reproduced now starting from the amino alcohol **41** to give the hydrochloride salt **70•HCl**, collected as light-brown crystals, again suitable for crystal structure determination [Eq. 37] (see appendix 12.7).



70

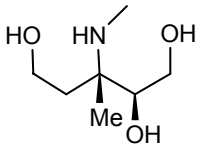
(37)



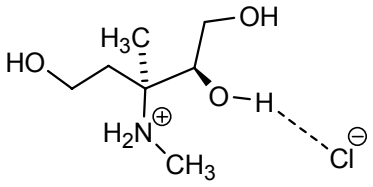
41

HCl (6.0 N)

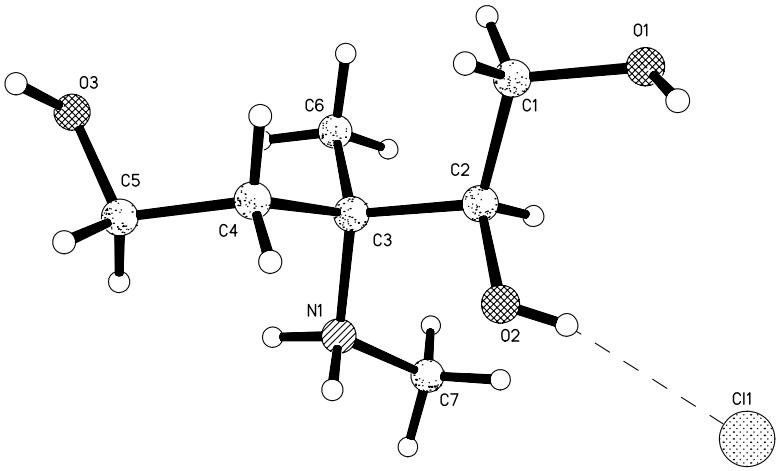
r.t., 24 h
quant.



70 •HCl

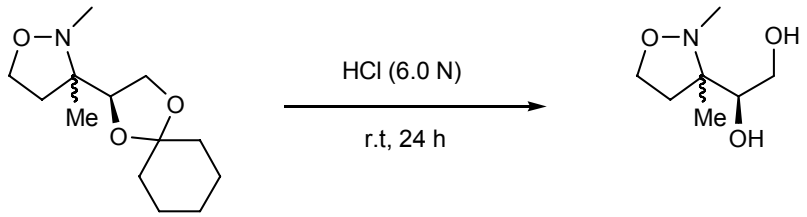


70 •HCl

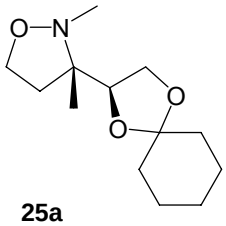
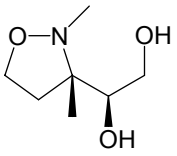
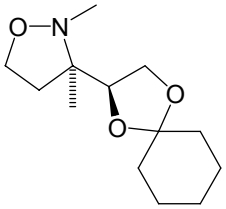
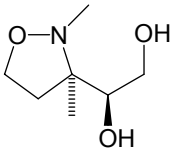
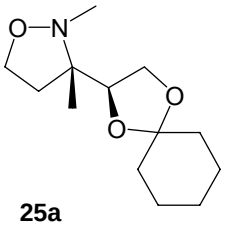
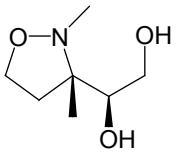
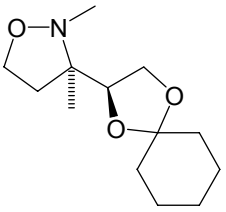
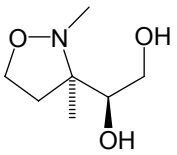


This procedure for acetal hydrolysis worked well in other cases, f.e. with the isoxazolidines **25 a/b** and the amino alcohols **41**, **42**, giving high yields of products (86%-100%). Tables 16 and 17 show the amino diols, and polyols obtained this way, and the exact configurations according to the X-ray structure determinations obtained for **52•HCl** and **70•HCl**.

Table 16. Acidic hydrolysis of the isoxazolidine acetals **25a/b**

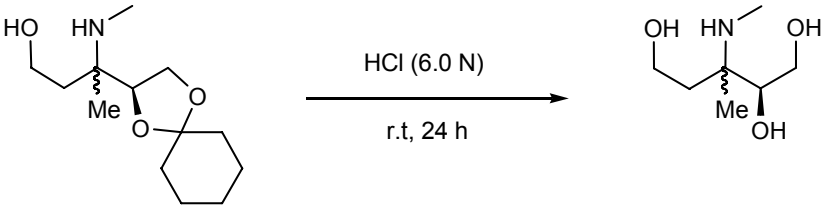


25a and 25b **52, 52•HCl, 53, 53•HCl**

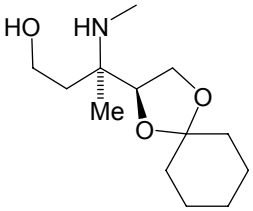
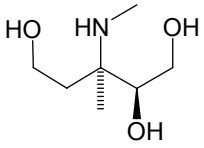
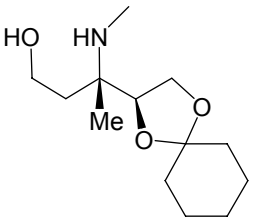
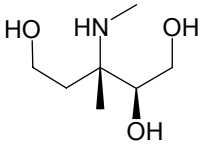
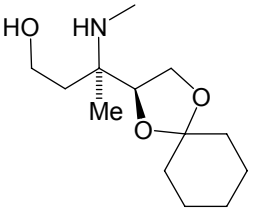
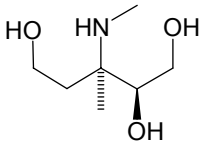
Entry	Isoxazolidine	Amino alcohol or polyol	Yield	Exp. No.
1	 **25a**	 **52**	93 % lit. 96 %[1]	49
2	 **25b**	 **53**	99 %	50
3	 **25a**	 **52** •HCl	86 %[a]	51
4	 **25b**	 **53** •HCl	89 %[a]	52

[a] It was not possible to have a correct elemental analysis, since the substance decomposes gradually.

Table 17. Acidic hydrolysis of the *N*-methylamino acetals **41**, **42**



41 and 42 **70•HCl, 71, 71•HCl**

Entry	*N*-Methylamino alcohols	*N*-Methylaminotriol	Yield	Exp. No.
1	 **42**	 **71**	95 %[a]	67
2	 **41**	 **70** •HCl	''100 %''	68
3	 **42**	 **71**•HCl	97 %[a]	69

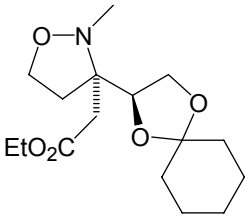
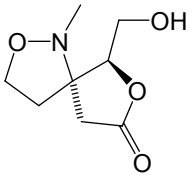
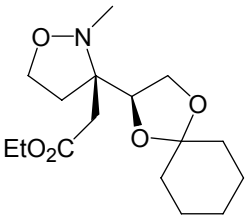
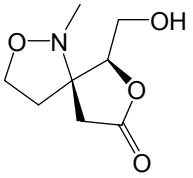
[a] it was not possible to have a correct elemental analysis.

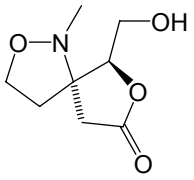
On acidic hydrolysis of the isoxazolidines **26a** and **26b**, the respective isoxazolidinolactones were obtained. Difficulties in the separations by thick layer chromatography led to moderate to poor yields. Table 18 contains the isoxazolidinolactones obtained.

The assignment of configuration at C-3 of the isoxazolidines **26a** and **26b** was done when it was possible to get an X-ray structure determination (see appendix 12.6, see also detailed discussion in Chapter 6.1.4) for the isoxazolidinolactone **54**. The absolute configuration of the isoxazolidinolactone **54** is (5*S*, 6*S*), which in turn leads to the (5*R*, 6*S*)-configuration for the epimer **55**. These results can be translated back to the (3*S*, 1'S)-configuration for the isoxazolidine **26a** and (3*R*, 1'S)-configuration for the isoxazolidine **26b**.

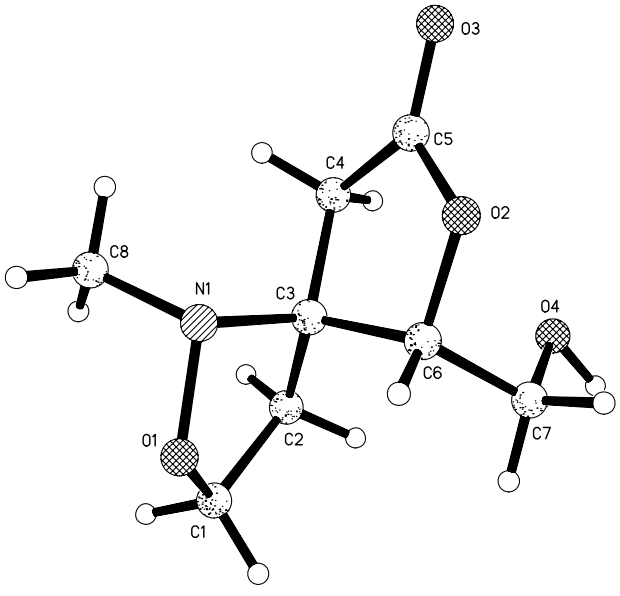
Table 18. Acidic hydrolysis of the isoxazolidines **26a** and **26b**

26a and 26b **54 and 55**

Entry	*N*-Methylisoxazolidine	Isoxazolidinolactone	Yield	Exp. No.
1	 **26a**	 **54**	69 %	53
2	 **26b**	 **55**	25 %	54

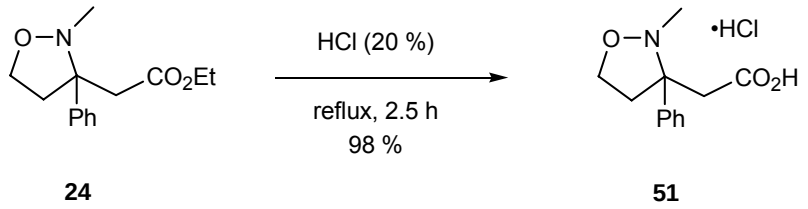


54

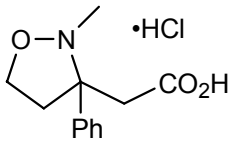


The isoxazolidinyl-ester **24** was hydrolyzed as well to give the isoxazolidinium salt **51** in excellent yield as colourless crystals, convenient to get an X-ray structure determination [Eq. 38] (see appendix 12.4).

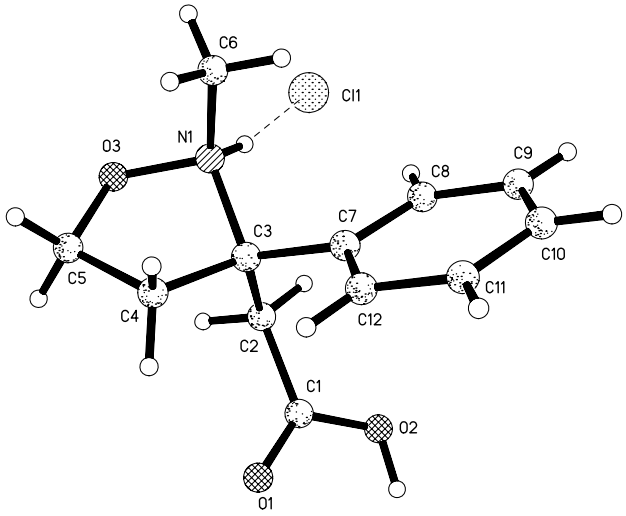
(38)



24 **51**



51



6.1.3 NMR data of diols 52, 52•HCl, 53, 53•HCl and *N*-methylamino triols 70, 70•HCl, 71, 71•HCl

The ^{1}H NMR spectra of the diol hydrochloride salts **52•HCl** and **53•HCl**, on comparison with those of the diols **52** and **53**, clearly show high-field shifts for all protons, with chemical shift differences varying from 0.0 ppm to 0.33 ppm in the case of the diol **52** and its salt **52•HCl**, and chemical shift differences varying from 0.0 to 0.65 ppm for the diol **53** and it's salt **53•HCl**. The same effects could be seen in the ^{13}C NMR spectra of corresponding pairs of compounds (Table 19).

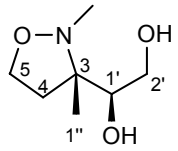
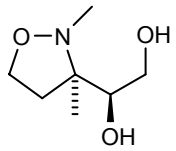
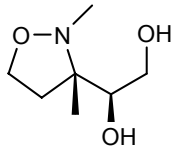
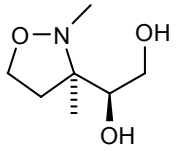
The ^{1}H NMR chemical shifts differences ($\Delta\delta$) between the signals of the diols **52** and **53** were small, as found for their salts **52•HCl** and **53•HCl**. The chemical shifts differences $\Delta\delta$ in the case of the diols **52** and **53** were ≤ 0.13 ppm, and almost the same for the salts **52•HCl** and **53•HCl** ($\Delta\delta \leq 0.15$ ppm) except for 4-H_a, 1'-H and N-CH_3 protons, of which chemical shifts

differences ($\Delta\delta$) rose to about 0.25 ppm. Coupling between 4-H and *N*-CH_3 (^4J) was not observed in the case of these polyols (Table 19), *cf.* Chapter **2.3**.

The same can be said about the ^{13}C NMR data, but with more exceptions: Chemical shifts differences ($\Delta\delta$) rise up to 6.0 ppm in the case of C-3 of the diols **52•HCl** and **53•HCl**, and to 5.5 ppm observed for the C-4 signals, and finally to 3.8 ppm for N$\underline{C}H_3$ of the same diols (Table 20).

The ^1H NMR spectra of the *N*-methylamino triols **70, 70•HCl, 71, 71•HCl**, however, show no significant differences of the chemical shifts recorded ($\Delta\delta \leq 0.08$ ppm), with only one exception of 1-H_a, for which $\Delta\delta = 0.18$ ppm was found (Table 21). A similar picture is shown by the ^{13}C NMR data; the differences in chemical shift values were $\Delta\delta = 0.3$-1.8 ppm (Table 22).

Table 19: Selected ^{1}H-NMR data (δ in ppm) of the diols **52**, **53**, **52•HCl**, **53•HCl**[a]

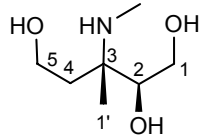
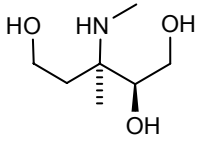
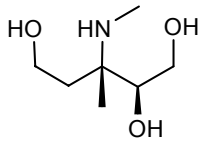
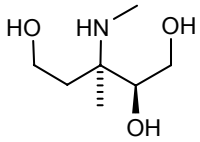
Diol	Compound	5-H_a	5-H_b	4-H_a	4-H_b	1'-H	2'-H_a	2'-H_b	1''-H	N-CH_3
 **52**	**52**	3.80	4.00	1.91	2.51	3.54	3.62	3.75	1.14	2.56
 **53**	**53**	3.93	4.09	2.04	2.41	3.48	3.68	3.77	1.17	2.56
	$\Delta\delta$	+0.13	+0.09	+0.13	-0.10	-0.06	+0.06	+0.02	+0.03	0.00
 **52** •HCl	**52•HCl**	4.16[b]	4.33[b]	2.26	2.79	3.76[b]	3.62	3.76[b]	1.36	2.94
 **53**•HCl	**53•HCl**	4.31[b]	4.42[b]	2.50[b]	2.69[b]	3.99[b]	3.76	3.76	1.48	3.21
	$\Delta\delta$	+0.15	+0.09	+0.24	-0.10	+0.23	+0.14	0.00	+0.12	+0.27

[a] $CDCl_3$ used as a solvent in the case of **52** and **53**, CD_3OD for **52•HCl** and **53•HCl** [b] Signals are not assigned, center of multiplet given.

Table 20: Selected ^{13}C NMR data (δ in ppm) of the diols **52**, **53**, **52•HCl**, **53•HCl**

Diol	C-4	C-5	C-3	C-1'	C-2'	C-1''	N-CH_3
52	36.7	65.2	68.5	73.5	63.7	16.6	37.7
53	39.2	66.0	69.7	77.4	65.0	16.0	38.5
$\Delta\delta$	+2.5	+0.8	1.2	+3.9	+1.3	-0.6	+0.8
52•HCl	35.3	69.6	72.3	75.4	64.2	16.5	37.1
53•HCl	40.8	71.5	78.3	75.5	64.5	15.7	40.9
$\Delta\delta$	+5.5	+1.9	+6.0	+1.1	+0.3	-0.8	+3.8

Table 21: Selected ^{1}H NMR data (δ in ppm) of the *N*-methylamino triols **70, 70•HCl, 71, 71•HCl**[a]

N-methylamino triol	Compund	5-H_a	5-H_b	4-H_a	4-H_b	2-H	1-H_a	1-H_b	1'-H	N-CH_3
 **70**  **71**	**70**	3.65	3.73	1.62	1.76	3.61[a]	3.52	3.69	1.09	2.28
	71	3.61	3.71	1.70	1.77	3.58	3.70	3.71	1.09	2.31
	$\Delta\delta$	-0.04	-0.02	+0.08	+0.01	-0.03	+0.18	+0.02	0.00	+0.03
 **70**•HCl  **71**•HCl	**70•HCl**	3.75[a]	3.75[a]	1.87	2.04	3.75[a]	3.75[a]	3.75[a]	1.36	2.62
	71•HCl	3.83[a]	3.83[a]	1.93	1.99	3.82	3.70	3.75	1.37	2.68
	$\Delta\delta$	+0.08	+0.08	+0.06	-0.05	+0.07	-0.05	0.00	+0.01	+0.06

[a] $CDCl_3$ used as a solvent in the case of **70** and **71**, CD_3OD for **70•HCl** and **71•HCl** [b] Signals are not assigned, center of multiplet given.

Table 22: Selected ^{13}C-NMR data (δ in ppm) of the *N*-methylamino triols **70, 70•HCl, 71, 71•HCl**

N-methylamino triol	C-5	C-4	C-3	C-2	C-1	C-1'	N-CH_3
70	60.5	38.9	60.0	77.1	65.8	21.8	28.1
71	59.3	37.1	59.1	75.4	64.5	20.0	27.8
$\Delta\delta$	-1.2	-1.8	-0.9	-1.7	-1.3	-1.8	-0.3
70•HCl	58.9	35.8	65.5	74.3	64.3	19.2	27.9
71•HCl	58.2	34.6	65.1	72.7	63.9	17.6	27.3
$\Delta\delta$	-0.7	-1.2	-0.4	-1.6	-0.4	-1.6	-0.6

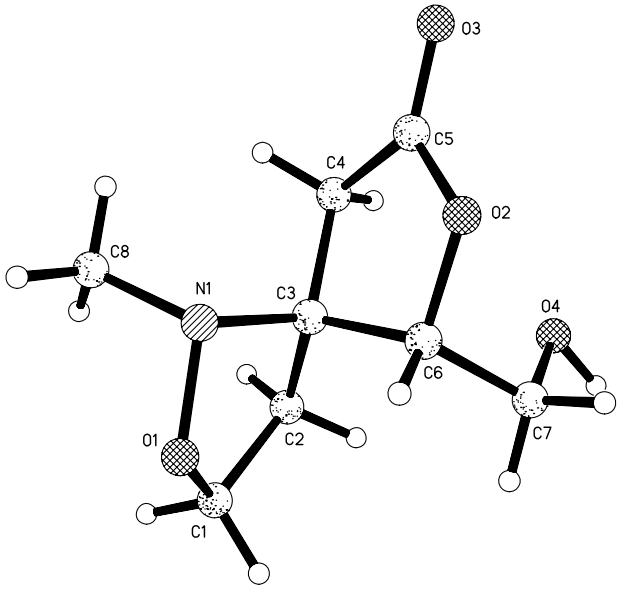
6.1.4 Discussion of the crystal structure data of the isoxazolidinolactone 54

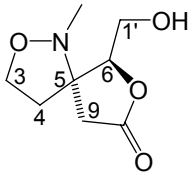
With all the NMR spectra of the enolate addition products, the isoxazolidines **26a** and **26b**, as well as of the spirolactones **54** and **55**, there was no possibility to assign the absolute configurations of these compounds at C-3. Isolation of flawless colourless crystals of the isoxazolidinolactone **54** changed the situation, since these were suitable to get a crystal structure determination (see appendix 12.6).

The configuration at C-5 of the isoxazolidinolactone **54** according to the X-ray data is (*S*), which automatically leads to the (*R*)-configuration of the 5-epimer **55**. Thence, the new stereogenic center of **26a** built by addition of the enolate to C-3 of the isoxazolidinium salt is established to have (*R*)-configuration, and therefore the (*S*)-configuration is present in the 3-epimer **26b**.

In the crystal structure of the isoxazolidine-spirolactone **54**, both five-membered ring systems have an envelope conformation, where the nitrogen N1 of the isoxazolidine moiety and the spirocarbon of the furanone system are out-of-plane. The molecules are arranged in chains along the b-axis in two orientations (180 deg) with C-8 atoms (chemical numbering, corresponding to C6 of structural numbering) superposing. In these columns the, molecules are tied together by intermolecular hydrogen bonds, where the hydroxy function acts as donor and the strongly pyrimidalized nitrogen (bond angles: C-8/N-1/C-3 115.2°, C-8/N-1/O-1 107.6°, O-1/N-1/C-3 101.4°) as acceptor. The H4···N1 distance is 2.0 Å and the OH-H4···N1 angle is 167 deg.

For the isoxazolidine ring, the C-3/C-4/C-5/O-2 torsional angle is 15.6°, for C-5/O-2/C-6/C-3 it is -20.9°, and for C-6/O-2/C-5/C-4 3.6°. In the furanone ring the C-3/N-1/O-1/C-1 torsional angle is -37.2°, for O-1/C-1/C-2/C-3 it is 8.1°, and for N-1/O-1/C-1/C-2 18.1°.





54

Table 23 gives a comparison of the torsional angles in the crystal with the ^{1}H NMR coupling constants found and transformed according to the Karplus equation[79] for estimation of the torsional angles. The values were taken from the ''middle'' Karplus curve (when ϕ = 0°, J = 11.1 Hz and when ϕ = 180°, J = 12.2 Hz) according to the electronegativity of the isoxazolidinolactone **54**.

Table 23. Comparison of the conformation of the isoxazolidinolactone **54** in solution and in the crystal

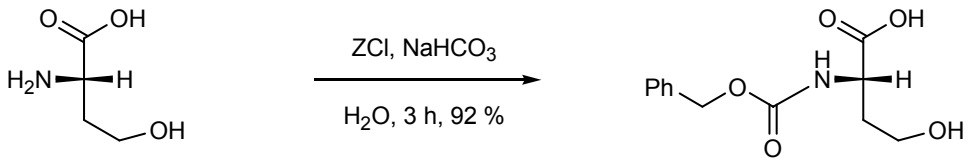
Dihedral angle	Crystal data		Solution data	
	Torsion angle in the crystal [°]	J estimated according to Karplus [Hz]	J measured in solution [Hz]	Torsion angle according to Karplus [°]
1-H_A/C-1/C-2/2-H_A	9	10.7	10.2	17
1-H_A/C-1/C-2/2-H_B	113	1.4	8.9	151
1-H_B/C-1/C-2/2-H_A	129	4.3	4.3	129
1-H_B/C-1/C-2/2-H_B	7	10.9	7.7	12
6-H/C-6/C-7/7-H_A	63	2.3	3.3	57
6-H/C-6/C-7/7-H_B	56	3.5	4.9	48

7 Synthesis of Protected Amino Alcohols and Polyols

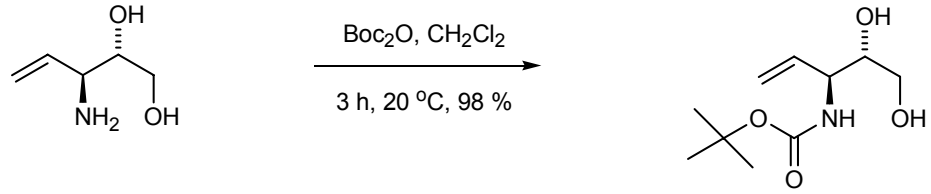
7.1 State of knowledge

The lone electron pair of the amino group of the amino alcohols and polyols obtained can easily be protonated and it generally is reactive towards electrophiles. In order to decrease the reactivity of such an amino group, it is commonly converted to an amide or carbamate. The benzyloxycarbonyl group [abbreviated Z or Cbz (in the older literature)] [Eq. 39][80] and the *tert*-butoxycarbonyl group (Boc) are the most frequently used amino-protecting group in organic synthesis [Eq. 40]. [81,82] Examples are:

(39)

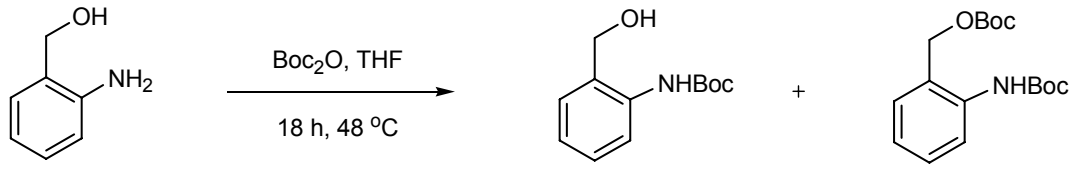


(40)



Tert-butoxycarbonyl protecting group (Boc) could overtake it is selectivity to amino groups, to protect any hydroxy group available. For example, Noe et al.[83] reported that during protection of (2-aminophenyl)-methanol **AR** with Boc_2O in THF the N-Boc derivative **AS** was separated in 91 % yield besides 5 % of N,O-Boc-protected derivative **AT** [Eq. 41].

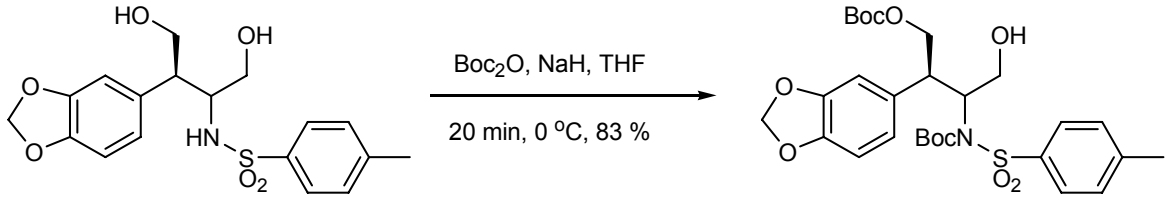
(41)



AR **AS** **AT**

Hudicky et al.[84] reported on the isolation of the doubly protected product **AV** in 83 % yield using *tert*-butoxycarbonyl for both nitrogen and oxygen transformation [Eq. 42].

(42)



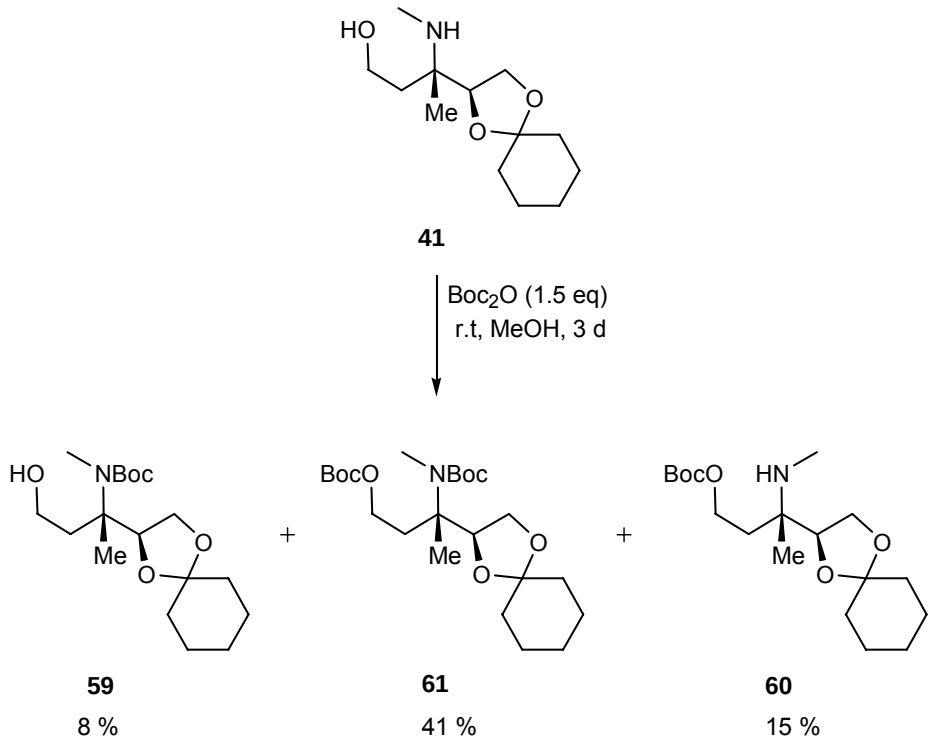
AU **AV**

7.2 Own Results

N-protection of the amino alcohols and amino triols of this work has faced some difficulties at the beginning. This problem was clearer with *N*-methylamino alcohols than with amino alcohols. The protection of the amino alcohol has to be selective with regard to the nitrogen atom, which is rivaled in some cases by the free primary hydroxy group.

Early in this work, benzylchloroformate was tested for N-protection of the amino alcohol **41**; the reaction was performed in absolute dichloromethane at 0 °C to produce Z-protected N-methylamino alcohol **58**, but in poor yield of 32 % only. Therefore, Boc_2O (*tert*-butoxycarbonyl) was chosen. When the same amino alcohol **41** was treated with 1.5 eq of Boc_2O, all three possible products were obtained, with the N-protected amino alcohol **59** isolated in 8 % yield only, the O-protected amino alcohol **60** in 41 % yield, and finally the N,O-protected amino alcohol **61** in 15 % yield [Eq. 43].

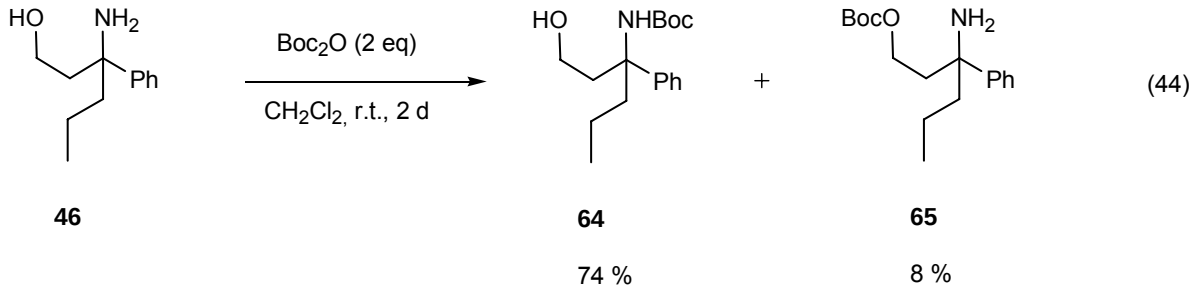
(43)



59 **61** **60**

8 % 41 % 15 %

This non-selectivity was improved and almost overcome when the solvent (methanol) was replaced by with dichloromethane. The amino alcohol **46** was treated with 2 eq of *tert*-butoxycarbonyl in dichloromethane and afforded 74 % of the required protected amino alcohol **64** and only 8 % of the O-protected amino alcohol **65** [Eq. 44].



Later-on in this work, the reaction of the amino alcohol **41** was repeated with *tert*-butoxycarbonyl (2.6 eq) in absolute ethyl acetate to give the corresponding *N*-protected *N*-methyl amino alcohol **59** in 75 % yield [Eq. 45].

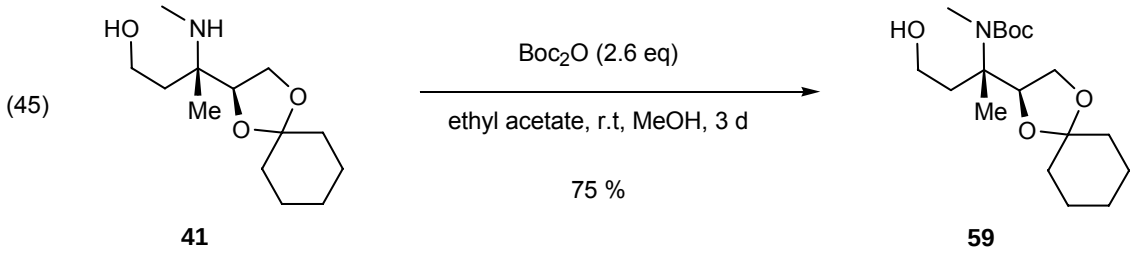


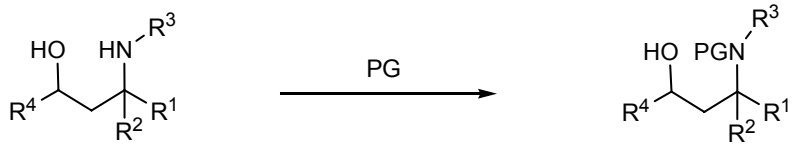
Table 24 gives the results of the use of benzyloxycarbonyl and Boc groups to protect amino alcohols and amino polyols with yields between 63 and 89 %. The protection was carried out using 2 equivalents of *tert*-butoxycarbonyl, the use of 2 equivalents is due to highest yield obtained, without the danger of O-protection. The reaction takes place in about 48 h in dichloromethane, then a short column chromatography is needed to obtain the *N*-protected amino alcohol or amino polyols in pure form.

It was possible to prepare the protected amino alcohols **68** and **69** in one step starting from the corresponding isoxazolidines **35a** and **35b**, f.e. when the isoxazolidine **35a** was mixed with 1.5 eq of *tert*-butoxycarbonyl and palladium on carbon (10 %) in methanol over 48 hours; this afforded the required protected amino alcohol **69**, after removal of the palladium on carbon in 77 % yield (entry 9 in Table 24).

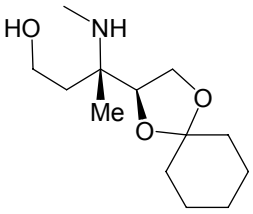
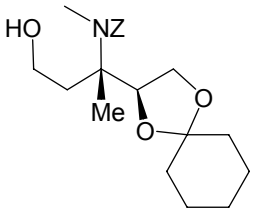
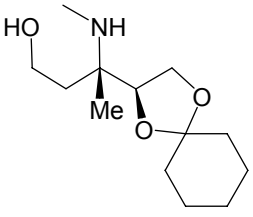
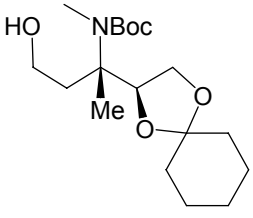
The assignments of the absolute configuration of the protected amino alcohols **58**, **59** and **63** were done according to the assignment obtained for the diol **52•HCl**. For the protected amino alcohol **66** and **67**, the absolute configuration is confirmed according to the assignment of configuration of the X-ray structure determination obtained for the protected amino hydroxy lactone **79**.

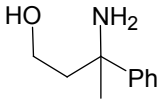
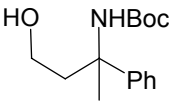
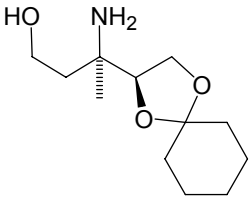
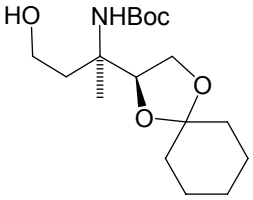
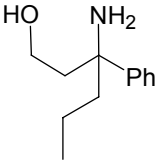
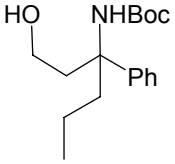
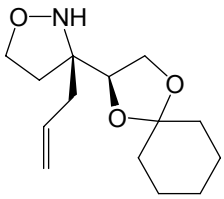
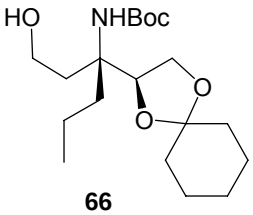
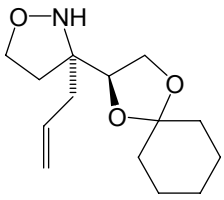
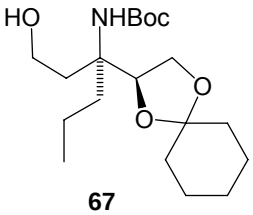
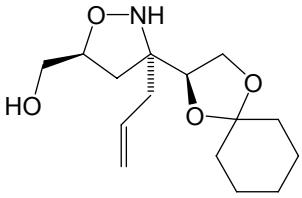
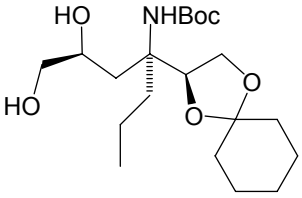
In addition, the exact configurations of the resulting protected amino alcohols **68** and **69** were assigned due to the absolute configuration of the isoxazolidine **35a**, also derived from crystal structure determination. The other protected amino alcohols **47**, **62** are racemic mixtures.

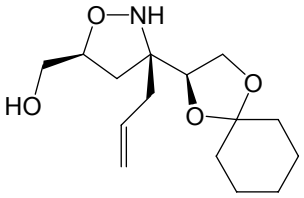
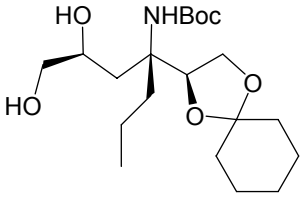
Table 24. Preparation of protected amino alcohols **58**, **59**, **62**-**64**, **66** and **67** and protected amino polyols **68** and **69**



41, 44-46, 34a/b, 35a/b **58, 59, 62-64, 66-69**

Entry	Amino alcohol or isoxazolidine[a]	Protected amino alcohol, polyol	Yield	Exp. No.
1	 **41**	 **58**	32 %	56
2	 **41**	 **59**	75 %	57

3	 **44**	 **63**	89 %	59
4	 **45**	 **63**	75 %	60
5	 **46**	 **47**	74 %	61
6	 **34 a**	 **66**	63 %	62
7	 **34 b**	 **67**	70 %	63
8	 **35 a**	 **69**	65 %	64

9	 **35 b**	 **69**	77 %	65

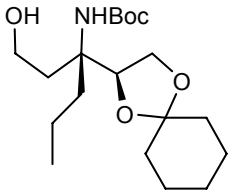
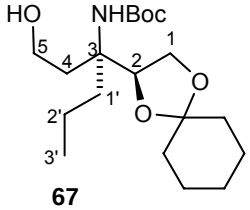
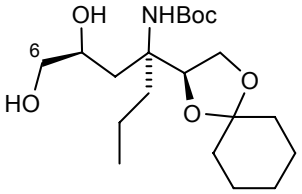
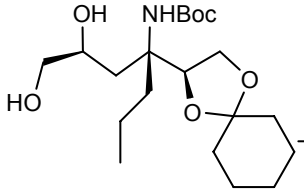
[a] In the case of protected amino alcohols **68**, **69** only: the products were obtained from the corresponding isoxazolidines **35a** and **35b**, through catalytic hydrogenatation and protection by Boc_2O in one pot.

7.3 NMR data of protected amino alcohols and polyols

The NMR data of the *N*-Boc-amino alcohols **66**, **67** and *N*-Boc-amino diols **68, 69** are collected in tables 25 and 26. The ^{1}H NMR data of the amino alcohols **66** and **67** as well as those of the *N*-Boc-aminodiols **68** and **69** show insignificant differences of the chemical shifts; f.e. the difference was ≤ 0.09 ppm for the chemical shifts of the diastereomers **66**/**67** and **68**/**69**. One exception was the shift difference of $\Delta\delta = 0.2$ ppm for of 1'-H signals of the protected amino alcohols **66** and **67**.

A similar picture is seen from the ^{13}C NMR spectra of the corresponding compounds; here the difference of chemical shifts was ≤ 1.3 ppm, with one larger value of 1.7 ppm for C-4 of the protected amino diols **68** and **69**. Larger values ($\Delta\delta = 2.6$ ppm) have been observed also for C-1', which could be interpreted according to its position next to the stereogenic center C-3.

Table 25: Selected ^{1}H NMR data (δ in ppm) of the *N*-Boc-amino alcohols **66**, **67** and *N*-Boc-amino diols **68, 69** [c]

Boc-Protected amino alcohols, -polyols	Compound	6-H_a	6-H_b	5-H_a	5-H_b	4-H_a	4-H_b	2-H	1-H_a	1-H_b	1'-H	3'-H
 **66**  **67**	**66**	-	-	3.75[a]	3.75[a]	-[b]	1.81[a]	4.37	3.85	3.98	2.00[a]	0.92
	67	-	-	3.75[a]	3.75[a]	-[b]	1.85	4.28	3.92	4.01	2.20[a]	0.92
	$\Delta\delta$	-	-	0.00	0.00	-	+0.04	-0.09	+0.07	+0.03	+0.20	0.00
 **68**  **69**	**68**	3.48	3.56	3.88[b]	-	-[b]	-[b]	4.35	3.92	4.02	2.19	0.91
	69	3.46	3.56	3.92	-	1.77	1.87	4.26	3.85	3.99	-[b]	0.92
	$\Delta\delta$	-0.02	0.00	+0.07	-	-	-	-0.09	-0.07	-0.03	-	+0.01

[a] Signals are not assigned, center of multiplet are given. [b] Signals not identified because of overlap with $C(CH_5)_2$ signals. [c] $CDCl_3$ used as a solvent.

Table 26: Selected ^{13}C NMR data (δ in ppm) of the *N*-Boc-amino alcohols **66**, **67** and *N*-Boc-amino diols **68, 69** [c]

Protected amino alcohols, -polyols	C-6	C-5	C-4	C-3	C-2	C-1	C-1'	C-2'	C-3'	C=O
66	-	59.0	36.9	58.2	79.6	65.2	37.3	17.0	14.9	155.7
67	-	58.9	36.9	57.6	80.2	65.2	38.6	17.5	15.1	155.6
$\Delta\delta$	-	-0.1	0.0	-0.6	+0.6	0.0	+1.3	+0.5	+0.2	-0.1
68	64.8	67.8	39.2	57.0	79.9	67.2	39.4	17.3	14.8	155.3
69	64.7	67.5	37.5	57.8	79.3	67.4	42.0	16.9	14.5	156.0
$\Delta\delta$	-0.1	-0.3	-1.7	+0.8	-0.6	+0.2	+2.6	-0.4	-0.3	+0.7

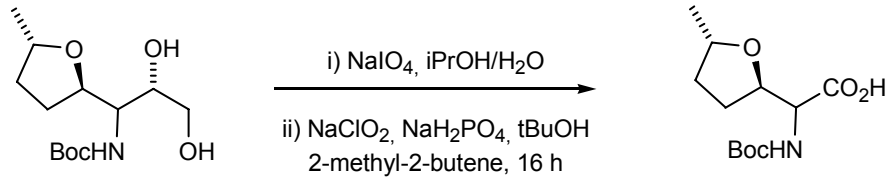
[c] $CDCl_3$ used as a solvent.

8 Preparation of Isoxazolidine-3-carbaldehydes

8.1 State of knowledge

As a typical means to oxidatively cleave a diol, sodium periodate ($NaIO_4$) is the reagent of choice where a variety of solvent systems can be employed. [85] For example, in our research group Jäger et al.[86] reported on the cleavage of diols using $NaIO_4$ in $iPrOH/H_2O$ followed by oxidation of the resulting aldehyde to afford the respective protected amino acid **AW**, with good yield (75 %) [Eq. 46].

(46)

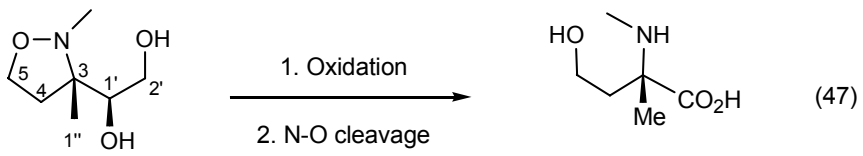


AW **AX**

Similar procedures were followed by Saita et al.[87] using dichloromethane. Cleavage of N-O bond of the resulted carbaldehyde -as will be described in this work- is unknown to our knowledge. Oxidation of a diol with an isoxazolidine moiety to the respective carboxylic acid is also unknown according to our knowledge.

8.2 Own results

As a last step to obtain the target α-amino acid **AY**, oxidation of the diol **52** followed by reduction of the N-O bond was envisaged [Eq. 47].

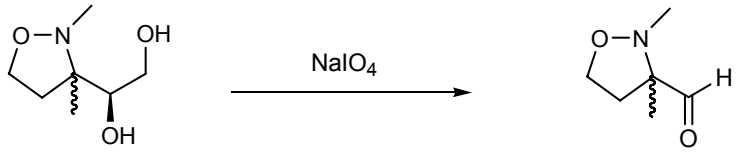


(47)

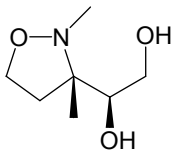
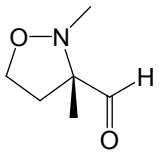
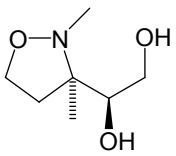
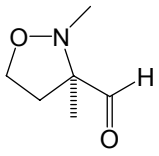
52 **AY**

The diol cleavage was successfully performed with sodium periodate ($NaIO_4$) in basic medium to give the corresponding isoxazolidine-3-carbaldehydes **72** and **73** in 56 % and 89 % yield respectively. It's worth mentioning that due to the volatile character of both aldehydes it was not possible to obtain correct elemental analysis (Table 27).

Table 27. Diol cleavage of isoxazolidine-1,2-diols **52** and **53**

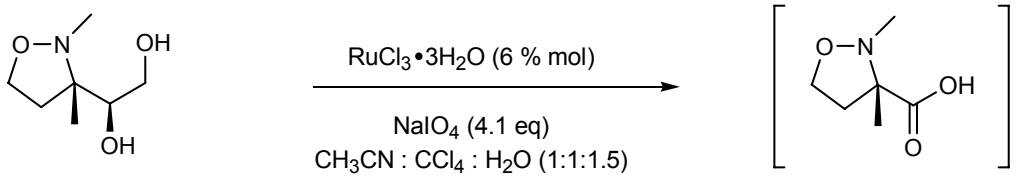


52, 53 **72, 73**

Entry	diol	carbaldehydes	Yield	Exp. No.
1			56 %	70
	52	**72**		
2			89 %	71
	53	**73**		

Other procedures were attempted, i.e. $RuCl_3 \bullet 3H_2O$ (6 % mol) with $NaIO_4$ were mixed with the diol **52**, and the reaction mixture was stirred for an hour; this resulted in decomposition [Eq. 49]. Sodium periodate with sodium bicarbonate and potassium permanganate as an oxidation reagent also led to decomposition.

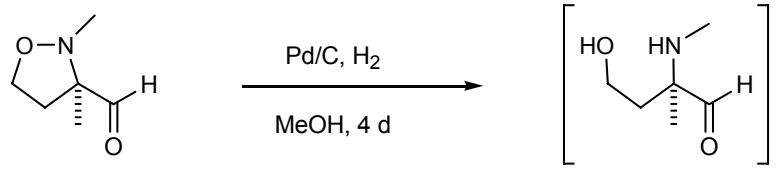
(49)



52 **AZ**

Efforts for catalytic hydrogenation of the aldehyde **73** failed [Eq. 48]; the products obtained from this reaction were inseparable and could not be identified.

(48)



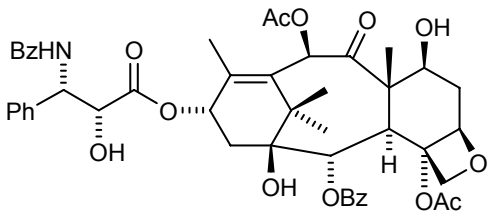
73 **BA**

9 Synthesis of Branched β-Amino Acids

9.1 State of knowledge

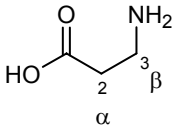
During the last decades, the preparation of enantiopure β-amino acids has emerged as an important and challenging synthetic endeavor. The increasing attention given to the chemistry of β-amino acids is partly due to the fact that they are constituents of several natural products (i.e. taxol,[14] dolastatin[15], and many others[16]). As well as pharmaceutical agents or valuable precursors to such structures as β-lactams.[18d,88,18e] The most well-known, medicinally important class of nonpeptidic β-amino acids are found in β-lactams. These include antibiotics,[89,90] β-lactamase inhibitors,[91] human leukocyte elastase inhibitors,[92] and cholesterol uptake inhibitors.[93] Also, a number of research groups have embarked on the synthesis of oligomers from β-amino acids, which gave rise to stabilized helical structures which can exhibit resistance to enzymatic hydrolysis.[17]

Recently, α-substituted β-amino acids have received greater scrutiny since they also serve as important segments of bioactive molecules. For example, one of the promising anti-tumor agents in cancer chemotherapy, Paclitaxol®, contains an α-hydroxy-β-amino acid side-chain as one of the key pharmacophores.[94]



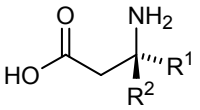
Paclitexol

In all of the β-amino acid applications, the substitution pattern and the configuration at the C2 and/or C3 position strongly influence both the structural characteristics and stability.[95] Thence, effective stereoselective synthetic approaches for β-amino acids remain highly sought-after.[18e, 96, 97, 98]



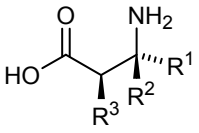
β-amino acid

Two particularly intriguing classes of β-amino acids are also among these challenging synthetic targets. The first of these contains geminal disubstitution at C2 and/or C3 such as the $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids.[98]



$\beta^{3,3}$-amino acid

,

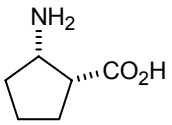


$\beta^{2,3,3}$-amino acid

Given the dense substitution pattern and their resistance to proteolytic degradation, this class of compounds provides excellent building blocks for bioactive molecules. Further, preliminary studies and predictive models indicate that the secondary structures adapted by β-peptides incorporating these amino acids will be unique and potentially quite stable.[98]

A second type of β-amino acids of particular interest includes cyclic proline analogues, cis-2-aminocyclopentanoic acid **BB** (Cispentacin), and trans-2-aminocyclopentanoic acid **BC** (Scheme 8).[99,100]

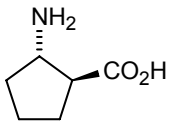
Scheme 8



BB

Cispentacin

,



BC

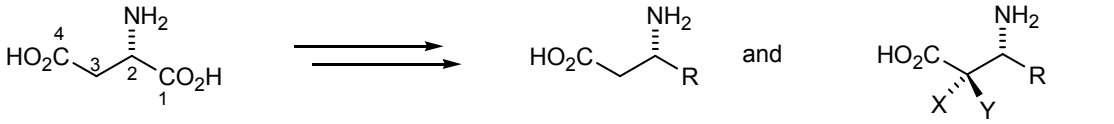
Illustrative of the relationship between stereochemistry and structure, oligomers of **BB** form strands,[101] whereas oligomers of **BC** form helices.[102] Due to their predictable and well-defined structural characteristics, this class of β-amino acids is expected to have enormous potential for the formation of higher-order structures, transitioning to protein-like structure and function for catalyst development and pharmaceutical applications.[103,104,105]

In the chemical literature, several diastereoselective methods have been reported for the synthesis of β-amino acids.[106] These include the elegant chemistry from the Davies group[107] with the addition of chiral nitrogen nucleophiles to enoates and addition of achiral amines to chiral enoates by d'Angelo et al..[108] Other diastereoselective methodologies for synthesis of

β-amino acids, which do not involve conjugate amine additions, have also been reported. Most notable of these are Davis chemistry[109] of chiral sulfinimines, Seebach's hydropyrimidines,[110] Juaristi's pyrimidinones,[111] and Konopelski's dihydropyrimidinones.[112]

L-aspartic acid **BD**, for example, is an ideal precursor of many enentiomerically pure β-amino acids **BE**, since it already possesses the butanoic backbone and only requires that the carbonyl group at C1 be differentiated from the other at C4 and transformed into the desired 4-alkyl or other substituted product (Scheme 9).[18d]

Scheme 9

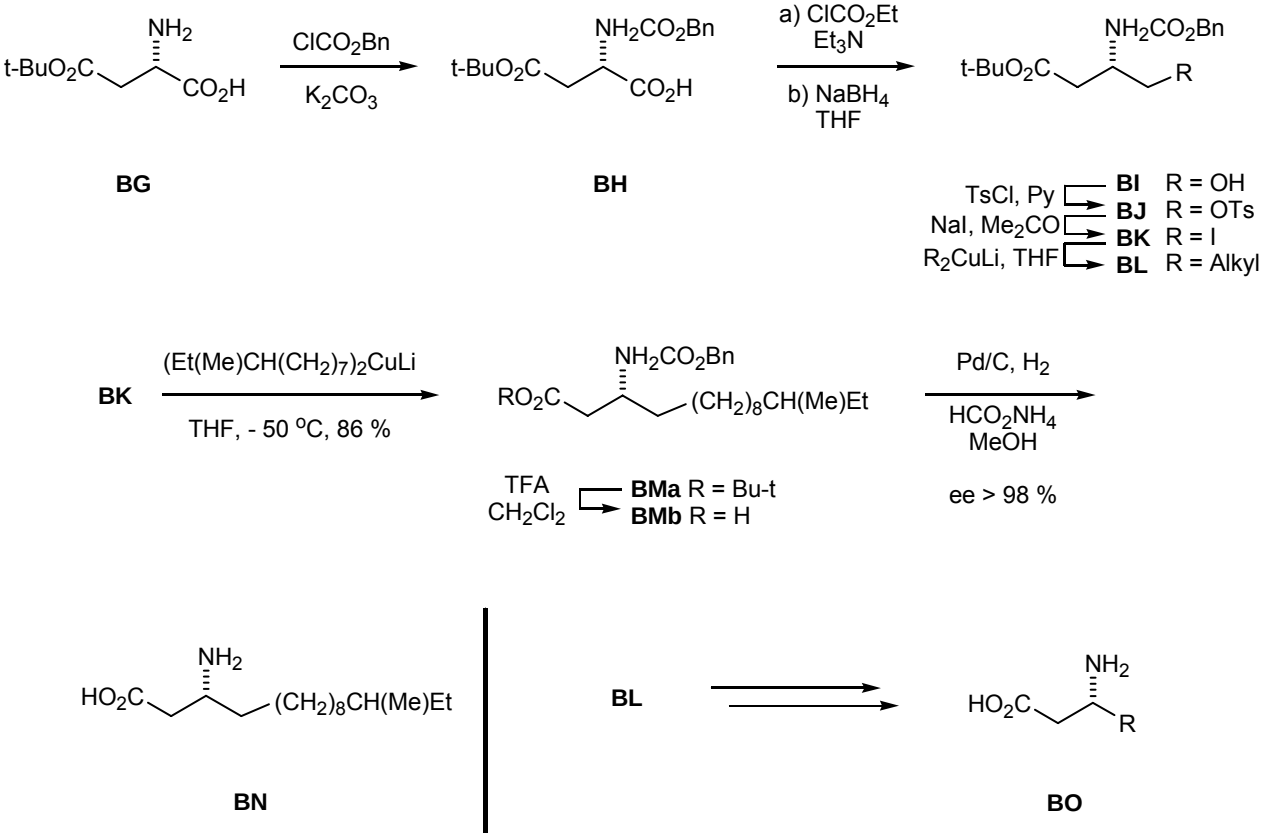


BD **BE** **BF**

syn X = substituent, Y = H
anti X= H, Y = substituent

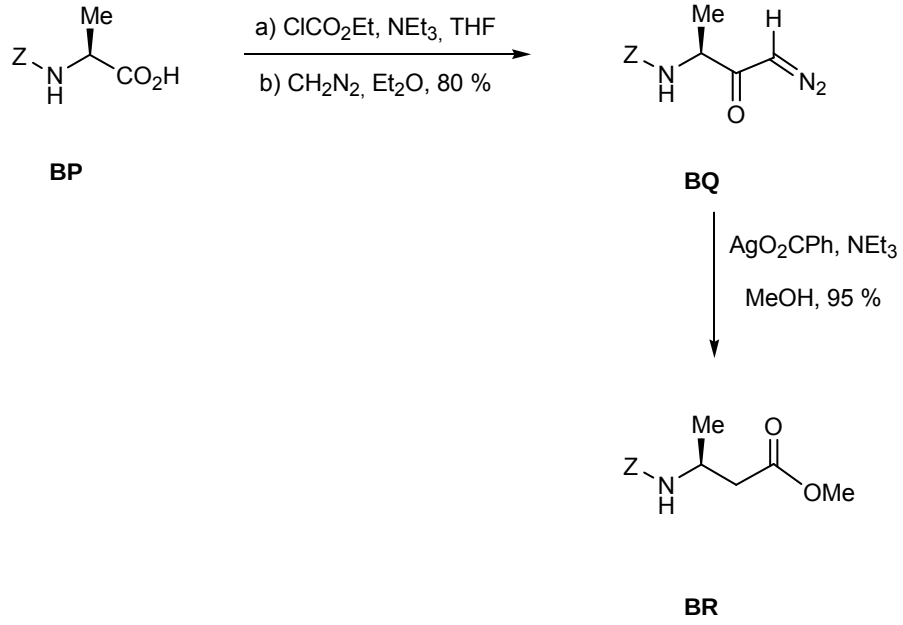
A typical approach starts with 4-*t*-butyl L-aspartate **BG** in which the free carboxyl function is ready to be transformed into the required group,[113,114] to furnish the β-amino acid **BN**, a component of the antifungal peptide, iturin A.[115] Hydrolysis and deprotonation of the other esters **BL** (where R = Bu or *i*-Pr) led to the corresponding (3*R*)-3-aminooctanoic and heptanoic acids **BO** in six steps from N-benzyloxycarbonyl derivative **BH** in 35-48 % overall yield (Scheme 10).

Scheme 10



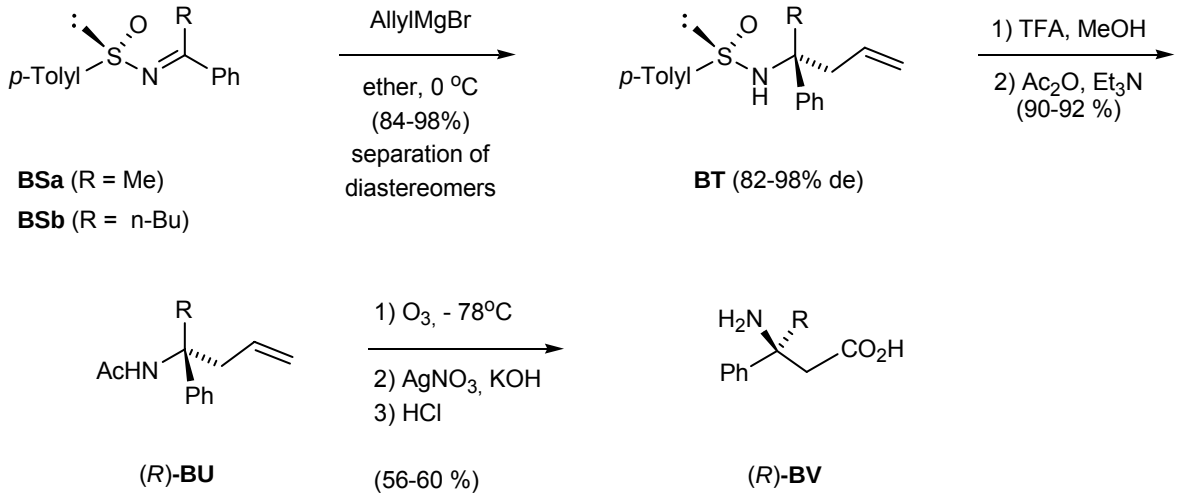
The large number of methodologies available for the synthesis of α-amino acids makes them ideal candidates for starting materials in the synthesis of β-amino acids.[116,117] This transformation, introduced by Arndt and Eistert, involves the formation of a diazoketone with subsequent loss of nitrogen and Wolff rearrangement under silver ion catalysis, photolysis, or less commonly, thermolysis[118,119] (Scheme 11).

Scheme 11



Hua et al. reported on the diastereoselective addition of allylmagnesium bromide to sulfinimines like **BSa** and **BSb** (R = Me, n-Bu) to give sulfinamides **BT** in 82 – 98 % d.r. and in 92 – 96 % yield.[120] Following separation of the diastereoisomers, the sulfinamides **BT** were hydrolyzed with trifluoroacetic acid (TFA), and the allylic amines were acetylated to furnish the *N*-acetyl derivatives **BU**. These acetamides were transformed into the free β-amino acids **BV** by ozonolysis, oxidation with $AgNO_3$, and deacetylation with HCl, as shown in Scheme 12.

Scheme 12

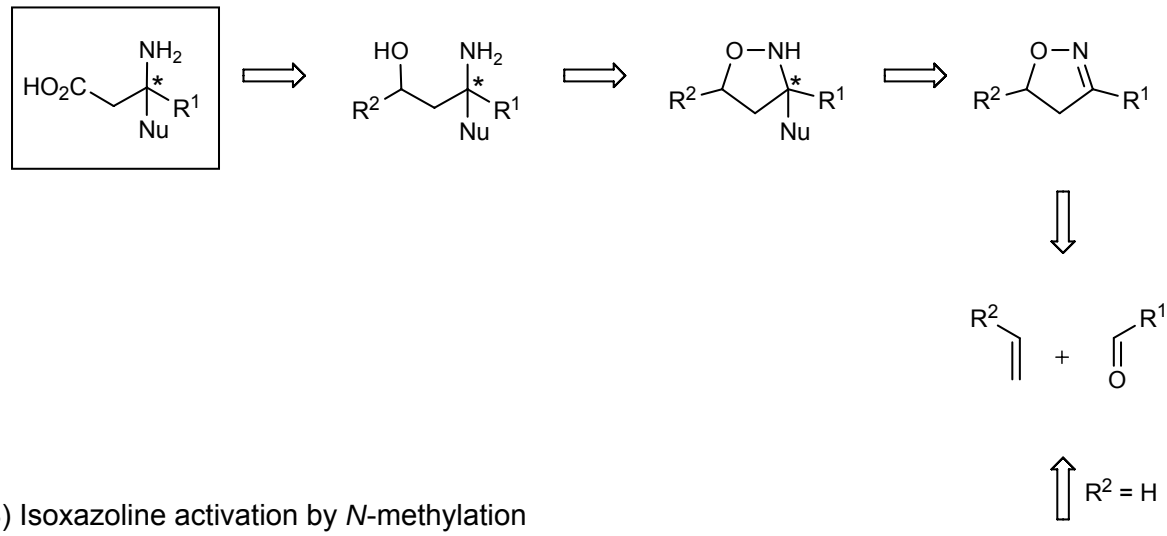


9.2 Own results

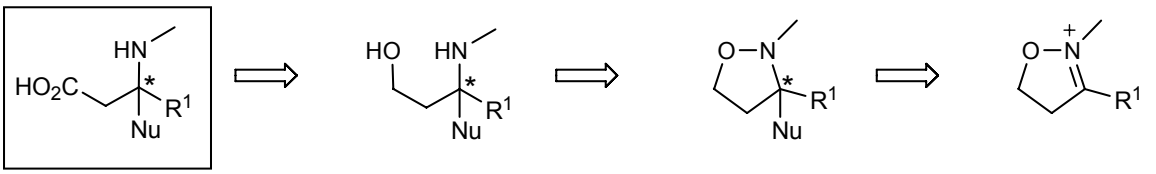
As previously described, the isoxazoline ring can be built in high yield and in high stereoselectivity in some cases by 1,3-dipolar cycloaddition of nitrile oxides to a variety of olefins. After activation of the isoxazoline ring either by Lewis acid or *N*-methylation with Meerwein salt, a variety of optically pure isoxazolidines was at hand, prepared with high selectivity. Through catalytic hydrogenation of the isoxazolidines followed by protection of the resulting amino alcohols or amino polyols, the latter are ready to be transformed into a new set of β-amino acids by oxidation of the primary alcohol or diol unit in some cases, completed by N-deprotection (Scheme 13).

Scheme 13

A) Isoxazoline activation by Lewis acid



B) Isoxazoline activation by *N*-methylation



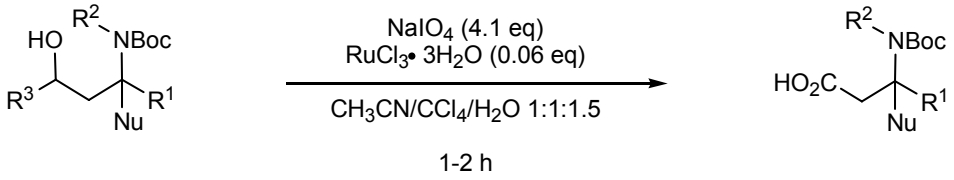
The isoxazoline route here offers an advantage, since the cycloaddition step joins two widely variable components, alkenes and nitrile oxides (with precursor nitroalkane or aldehyde, respectively). However, the final introduction of a *C*-nucleophile is hampered by insufficient electrophilicity of the C=N bond in the isoxazoline, which has been overcome by the different ways of activation mentioned previously.

To bring the retrosynthetic Scheme 13 to reality, an oxidation step is necessary with regard to the primary hydroxy group of the amino alcohols **59**, **62**, **63**, **66**, or oxidative diol cleavage of the amino polyols **68** and **69**, to afford in both cases the *N*-protected branched β-amino acids.

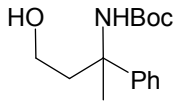
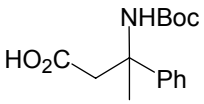
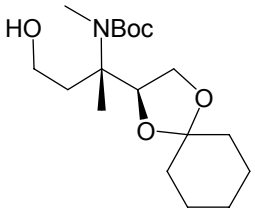
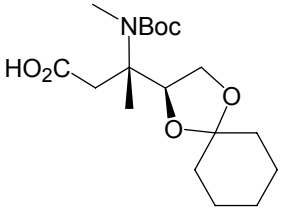
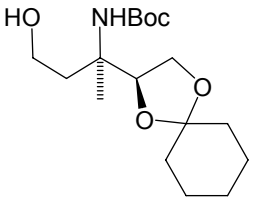
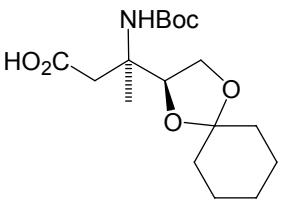
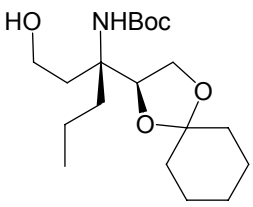
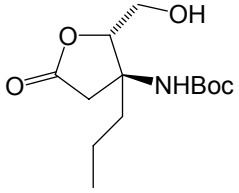
In Table 27 the β-amino acids obtained by oxidation of *N*-protected amino alcohols and polyols with 4.1 equivalents of sodium periodate ($NaIO_4$) in the presence of $RuCl_3 \bullet 3H_2O$ as a catalyst are shown with yields varying from 68 to 89 %. The oxidation was first performed with the N-protected amino alcohol **62**, and was done in a mixture of acetonitrile and carbon tetrachloride and water in 1 to 1 to 1.5 ratios. At room temperature sodium periodate and ruthenium trichloride (6 % mol) were added after one and a half hour, the catalyst was filtered off through celite and silica gel and the mixture was finally chromatographed to afford the *N*-protected amino acid **76** as a racemic mixture in high yield (84 %; entry 1 in Table 27). This was the model N-protected amino alcohol to be oxidized, in order to open the door to similar oxidations of the other *N*-protected amino alcohols and polyols.

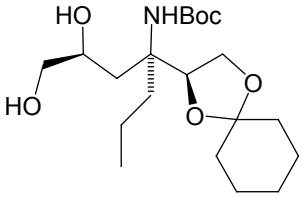
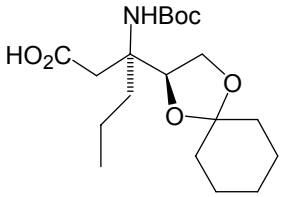
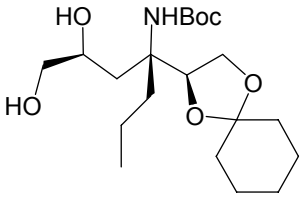
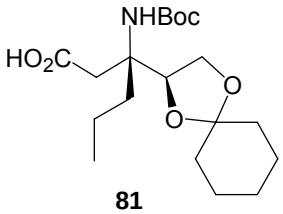
The oxidation was then performed similarly as described in the case of the preparation of the *N*-protected amino acid **76**, to afford the respective *N*-protected amino acids **77**, **78**, **80** and **81** (entries 2,3, 5 and 6 in Table 27), and in the case of the *N*-protected amino alcohol **66**, for which the oxidation was performed as before, followed by another deprotection for the acetal group available by addition of trifluoroacetic acid to the crude product, which led to the lactone **79** in 89 % over-all yield (entry 4 in Table 27).

Table 27. Synthesis of *N*-protected branched β-amino acids **76**-**81** from *N*-protected amino alcohol or polyols



59, 62, 63, 66, 68, 69 **76-81**

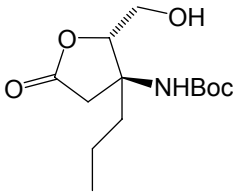
Entry	*N*-protected amino alcohol or polyol	*N*-protected β-amino acid	Yield	Exp. No.
1	 **62**	 **76**	84 %	74
2	 **59**	 **77**	76 %	75
3	 **63**	 **78**	89 %	76
4	 **66**	 **79**	89 %	77[a]

5	 **68**	 **80**	81 %[b]	78
6	 **69**	 **81**	68 %	79

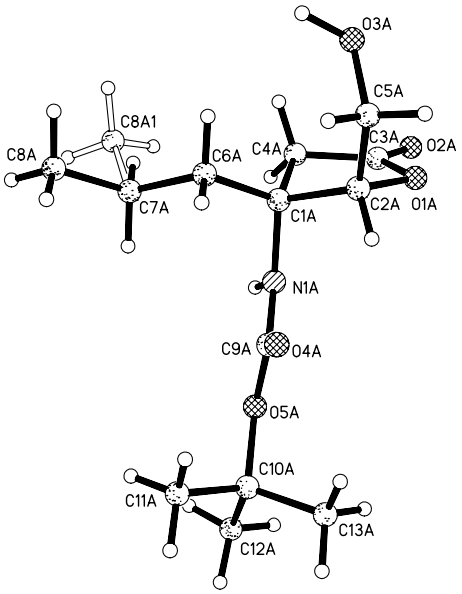
[a] The cyclohexylidene ring was cleaved by addition of 0.5 ml TFA to the crude product, which led to the lactone **79**.

[b] Volatile substance, it was not possible to have correct elemental analysis.

Assignment of configuration of the *N*-Boc-aminohydroxylactone **79** was possible due to a crystal structure analysis obtained (see appendix 12.9).



79

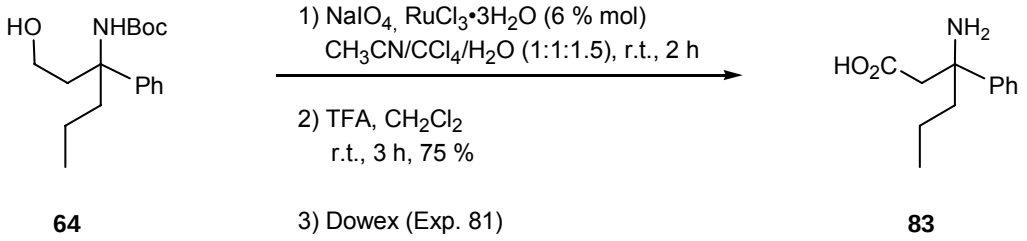


As a last step to reach the target structures, deprotection is needed; the use of hydrochloric acid in this step in some cases caused difficulties concerning the separation of the products. Therefore, CF_3COOH (TFA) was chosen; the hydrolysis was effected by stirring with the protected β-amino acid in dichloromethane overnight, followed by purification on ion exchange column [DOWEX $50WX_8$ (H^+-form)].

First of all, the deprotection of Boc group was performed for the N-protected amino acid **76**, by stirring it with 2 mL of trifluoroacetic acid in dichloromethane at room temperature for 18 hours. The crude product was then purified through ion exchange column, to afford the pure free β-amino acid **82** with the ammonia fraction of the ion exchange column in high yield (86 %) (entry 1 in Table 28).

In the case of the 3-amino-3-phenylhexanoic acid **83**, oxidation followed by deprotection of the resulting product was carried out, without separation of the N-protected β-amino acid, in 75 % yield [Eq. 49 and entry 2 in Table 28].

(49)

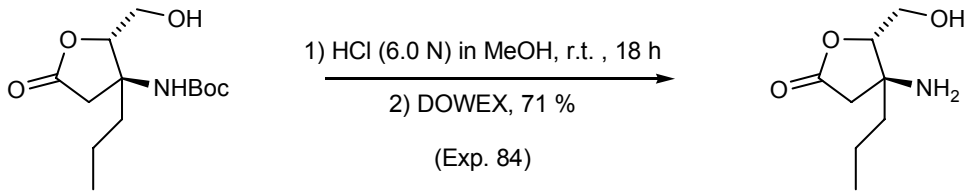


64 **83**

Similarly, the deprotection was carried out for the chiral N-protected amino acids **78** and **80**, to afford the corresponding branched free β-amino acids **84** and **85** successively, deprotected from both protection groups (Boc, acetal) in high yields (entries 3 and 4 in Table 28).

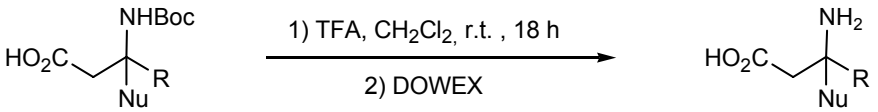
The β-amino acids **82**, **83**, **84**, **85** were obtained in yields of 71 to 94 %, they were isolated as solids except for the aminohydroxylactone **86**, which was oily and did not afford a correct elemental analysis [Eq. 50 and entry 5 in Table 28).

(50)

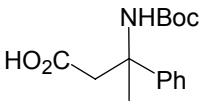
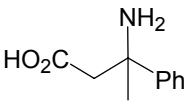
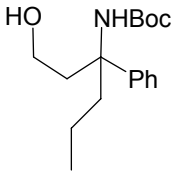
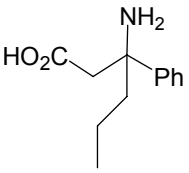
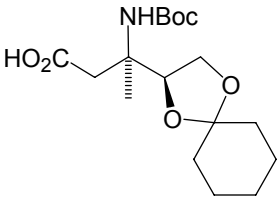
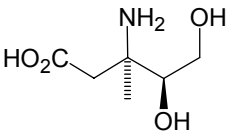
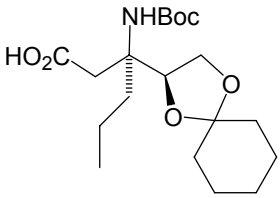
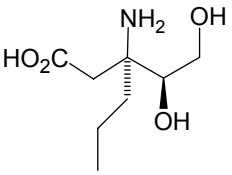
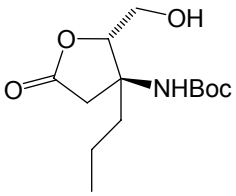
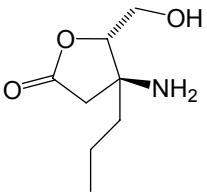


79 **86**

Table 28. Synthesis of branched β-amino acids **82**, **83**, **84**, **85** and **86**



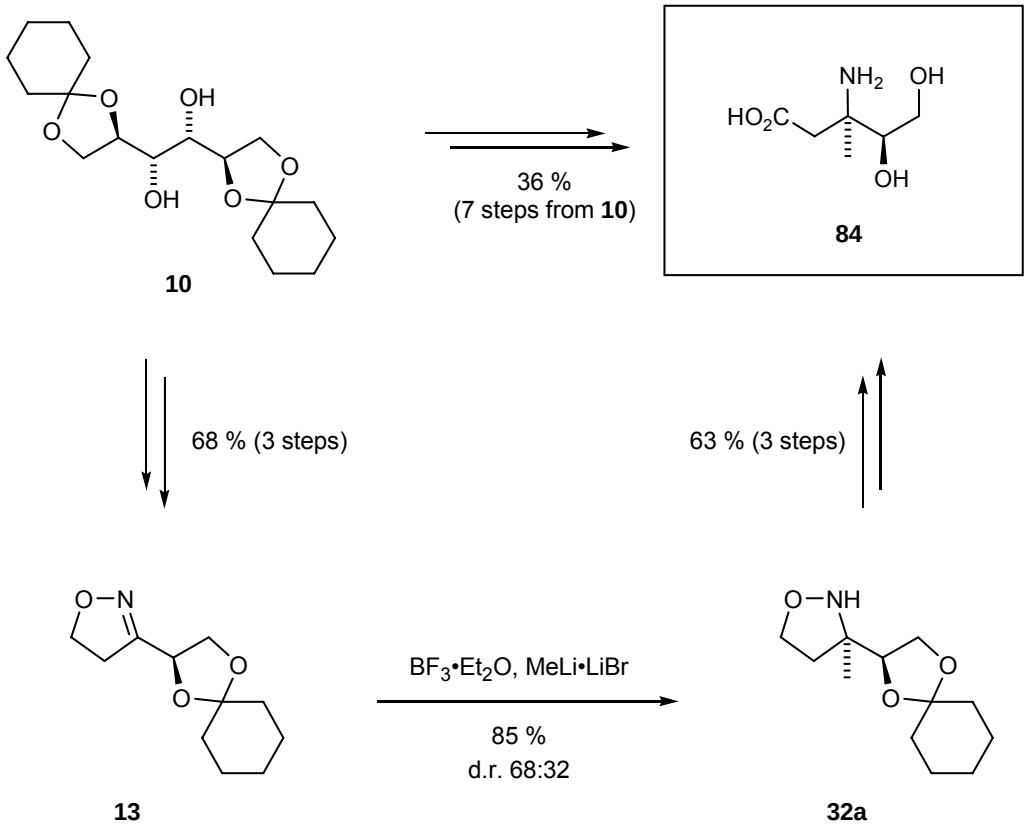
64, 76, 78-80 **82-86**

Entry	*N*-protected β-amino acid	β-amino acid	Yield	Exp. No.
1	 **76**	 **82**	86 %	80
2	 **64**	 **83**	75 %[a]	81
3	 **78**	 **84**	94 %	82
4	 **80**	 **85**	90 %	83
5	 **79**	 **86**	71 %	84

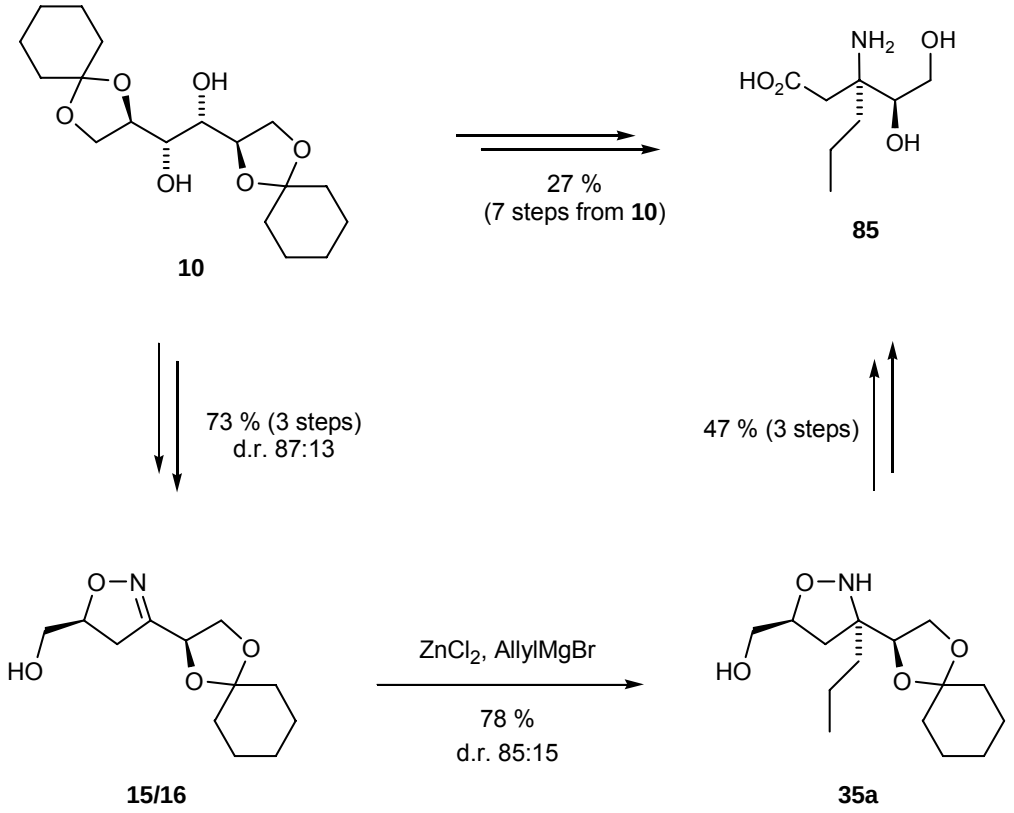
[a] In this case, oxidation was performed for the protected amino alcohol **64** followed by deprotection with TFA in one step, to yield the 3-amino-3-phenylhexanoic acid **83**.

The results presented above demonstrate the possibility to synthesize β-amino acids starting from D-mannitol by first building the isoxazoline ring, which upon activation with Lewis acid is ready to accept a variety of C-nucleophiles to give the corresponding isoxazolidines. These isoxazolidines by catalytic hydrogenation, then oxidation are transformed into the projected branched β-amino acids in an acceptable total yield of 36 % in the case of the β-amino acid **84** (Scheme 14), and 27 % over-all yield of the β-amino acid **85** (Scheme 15).

Scheme 14 Total synthesis of the β-amino acid **84**

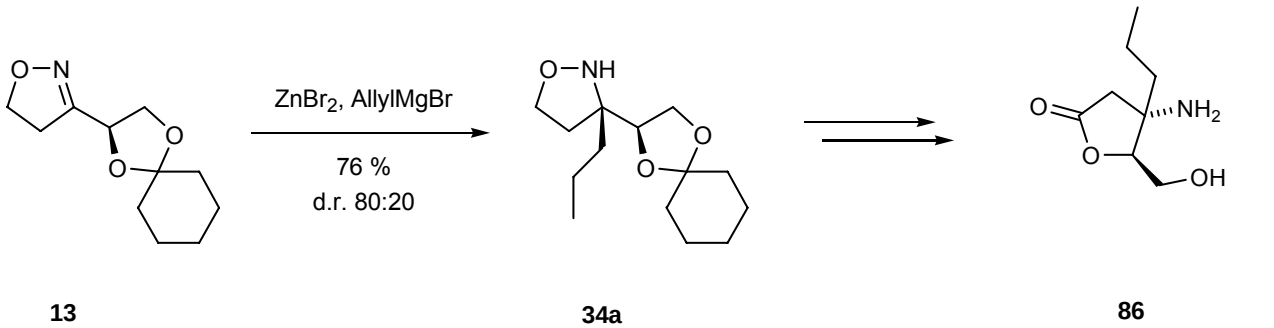


Scheme 15 Total synthesis of the β-amino acid **85**



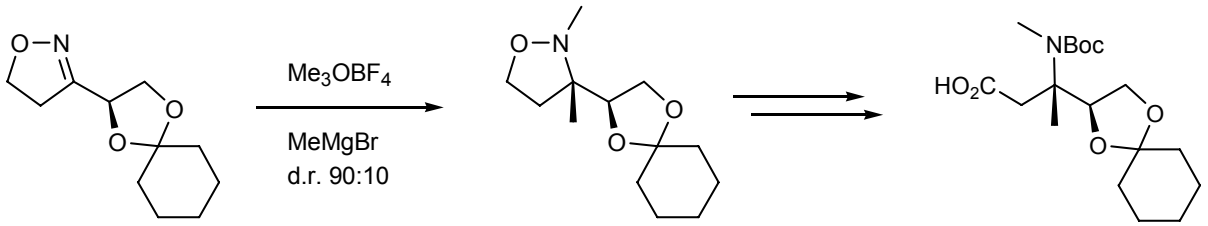
In addition, the aminohydroxylactone **86** was prepared, upon addition of allylmagnesium bromide with Lewis acid, to afford the isoxazolidine **34** in high selectivity, which was transformed in 3 steps into the more stable lactone **86** form of the target β-amino acid **86** (Scheme 16).

Scheme 16 Total synthesis of the amino hydroxy lactone **86**



The same strategy can be applied for the *N*-methylisoxazolidine **25a** which was obtained through activation of isoxazoline **13** with Meerwein salt. The protected branched β-amino acid **77** was produced on transformation of the isoxazolidine **25a** over 4 steps in 29 % overall yield (calculated from the protected D-mannitol **10**) (Scheme 17).

Scheme 17 Total synthesis of the protected branched β-amino acid **77**



13 **25a** **77**

Σ 29 % (7 steps from **10**)

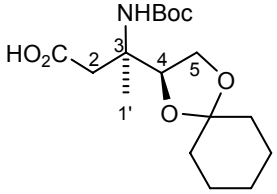
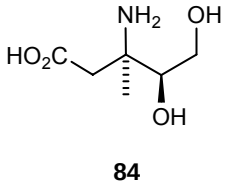
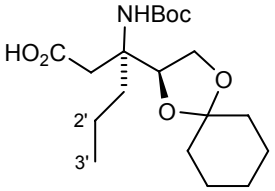
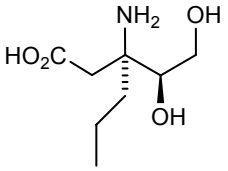
9.3 NMR data of branched β-amino acids 84 and 85

Table 29 compares the chemical shifts of the N-protected β-amino acids **78**, **80** with those of the deprotected compounds, the β-amino acids **84** and **85**. The ^{1}H NMR data show a systematic shift of all protons to low-field, on the average varying from 0.09 ppm in the case of 3'-H the most far proton to the center of the deprotection act took place, and maximum difference ($\Delta\delta$ = 0.75 ppm) for 4-H, the closest proton to the two sites where the protection groups have been removed.

The ^{13}C NMR data of the corresponding compounds reflect similar changes as seen in the ^{1}H NMR spectra. High-field shifts are clearly detected for C-3 of the β-amino acids **84**, **85** in comparison with their protected forms **78**, **80**. No significant difference was observed for the chemical shifts of propyl moiety. In contrast to this, notable differences were observed for the signals of carbon atoms closest to the two protection groups removed, of which the chemical shifts changed for 7.0 ppm to low-field in the case of the C-4 of the β-amino acid **85**.

The configuration of the branched β-amino acids **84** and **85** have been assigned according to the absolute configuration confirmed for the diol **52•HCl** (see chapter 6.1.2) and the isoxazolidine **35a** (see chapter 4.1.2).

Table 29: Selected ^{1}H NMR data (δ in ppm) of the branched β-amino acids **84** and **85**

branched β-amino acids	No.	2-H_a	2-H_b	4-H	5-H_a	5-H_b	1'-H	2'-H	3'-H
 **78**	**77**	2.72	2.86	4.37	3.86	4.01	-[b]	-	-
 **84**	**84**	2.21	2.53	3.61	3.57	3.68	1.30	-	-
	Δδ	-0.51	-0.33	-0.76	-0.29	-0.33	-	-	-
 **80**	**80**	2.58	2.90	4.46	3.92	4.01	2.03[a]	-[b]	0.92
 **85**	**85**	2.42	2.54	3.71	3.62	3.71	1.69	1.27[a]	0.83
	Δδ	-0.16	-0.36	-0.75	-0.30	-0.30	-0.34	-	-0.09

[a] D_2O used as a solvent. [b] Signals not identified because of overlap with $C(CH_5)_2$ signals. [c] Signals are not assigned, center of multiplet are given.

Table 30: Selected ^{13}C NMR data (δ in ppm) of the branched β-amino acids **84** and **85**[a]

branched β-amino acids	C-1(C=O)	C-2	C-3	C-4	C-5	C-1'	C-2'	C-3'
78	176.2	40.2	54.8	79.4	64.5	21.0	-	-
80	177.8	39.1	57.3	74.0	61.4	20.0	-	-
Δδ	+1.6	-1.1	+2.5	-5.4	-3.1	-1.0	-	-
80	176.8	38.0	57.6	79.2	64.8	38.6	17.0	14.2
85	178.1	39.2	59.9	72.2	61.5	34.7	16.2	13.7
Δδ	+1.3	+1.2	+2.3	-7.0	-3.3	-3.9	-0.8	-0.5

[a] D_2O used as a solvent.

10 Detailed Summary and Outlook

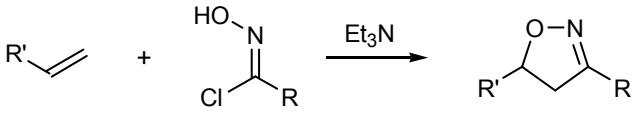
β-Amino acids are important synthetic targets due to their presence in a wide variety of natural products, pharmaceutical agents, and mimics of protein structural motifs. According to this importance of β-amino acids, this work consisted in the development of efficient routes to amino alcohols and polyols, and branched β-amino acids as a target compounds.

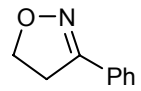
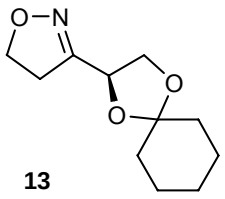
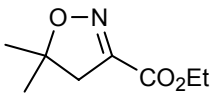
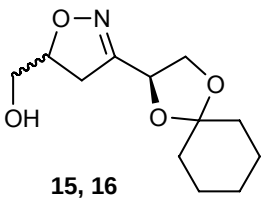
Isoxazolines are employed as key intermediates, transformed by activation either by Lewis acid or by conversion to the corresponding N-methylisoxazolinium salt. Next, highly stereoselective *C*-nucleophile additions to the "activated isoxazolines" were examined, followed by transformation to the target structures. The absolute configurations were assigned to the various enantiomerically pure compounds. The readily accessible, diversely substituted products are expected to facilitate future studies of the structure and function of this important class of molecules.

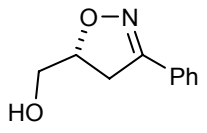
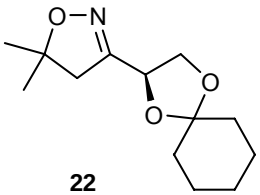
A) Preparation of Isoxazolines and *N*-Methylisoxazolinium Salts.

The isoxazolines were prepared by 1,3-dipolar cycloaddition of respective olefins and nitrile oxides obtained in situ from oximes via hydroximoyl chlorides, see Table 31.

Table 31. Preparation of Isoxazolines

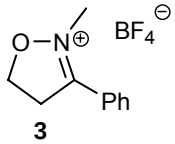
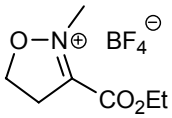
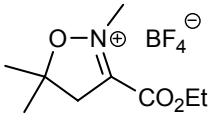
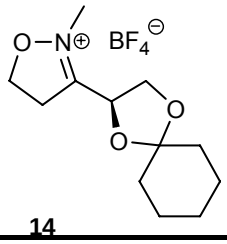


Cycloadduct	Yield	Cycloadduct	Yield
 **2**	87 %	 **13**	84 %
 **5**	70 %	 **15, 16**	91 %

3	 **9**	93 %	6	 **22**	82 %

One of the activation methods followed in this work is by *N*-alkylation of isoxazolines with Meerwein's salt (trimethyloxonium tetrafluoroborate), to form the respective isoxazolinium salt in high yield (Table 32).

Table 32. Preparation of Isoxazolinium Salts

Isoxazolinium salt	Yield	Isoxazolinium salt	Yield
 **3**	95 %	 **8**	(79 %)[a]
 **6**	88 %	 **14**	88 %

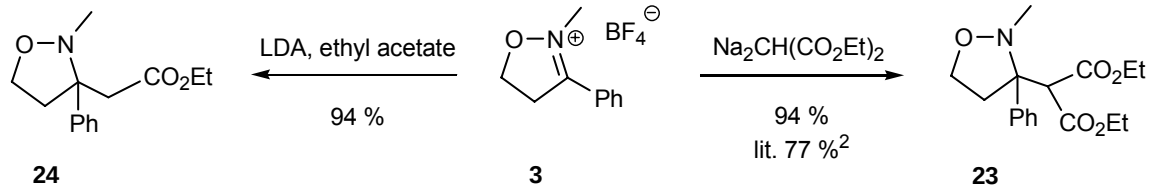
[a] It was not possible to have correct elemental analysis.

B) Reaction of *N*-Methylisoxazolinium Salts with *C*-Nucleophiles

Addition of sodium diethyl malonate and lithium ester enolate to N-methylisoxazolinium salts

The use of sodium diethyl malonate and lithium ester enolate as *C*-nucleophilic reagents for the related adducts has been explored. This addition of malonate to a model isoxazolinium salt **3** has already been done by LeRoy in our group.[2] This was now optimized. The new addition of an enolate to the isoxazolinium salt **3** also showed smooth conversion with high yield [Eq. 51].

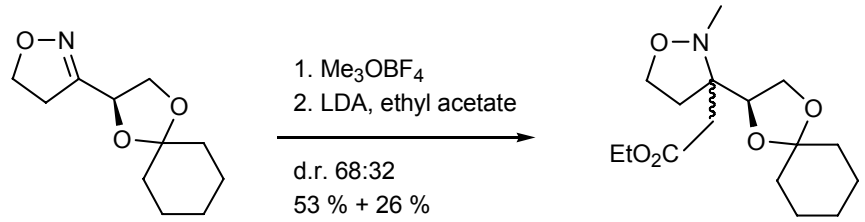
(51)



24 **3** **23**

In this work the chiral *N*-methylisoxazolinium salt **14** (from **13**) was applied in the enolate addition to give the corresponding adduct, in high yield, but with modest diastereoselectivity [Eq. 52].

(52)

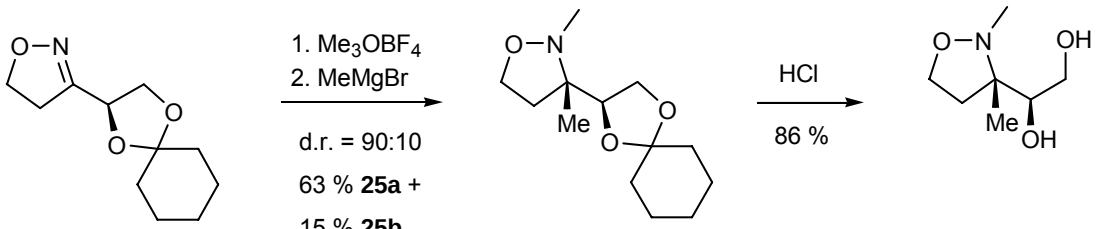


13 **26 a/b**

Addition of metal organyls to N-methyl-isoxazolinium salts

In the preceding dissertation in our research group in this field, Henneböhle has studied the addition of several Grignard reagents to *N*-methylisoxazolinium salts, wherein the configuration of adducts remained unknown. Now, the addition of methylmagnesium bromide to the *N*-methyl-isoxazolinium salt **13** was repeated, and the adduct was then transformed to the corresponding diol **52•HCl**. With this, the configuration was assigned by crystal structure determination, which allowed to further assign the hitherto unknown configuration at C-3 of the diol **52•HCl** and of the precursor isoxazoline **25a** [Eq. 53].

(53)



13 **25a** **52** • HCl

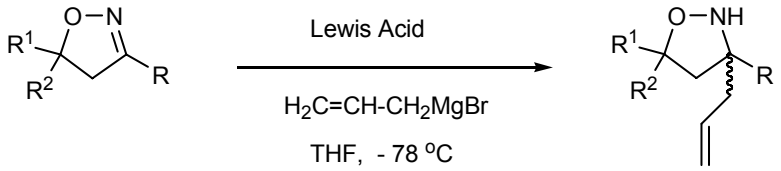
X-ray

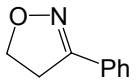
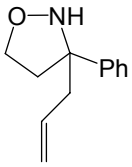
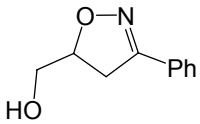
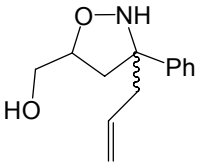
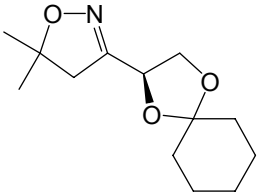
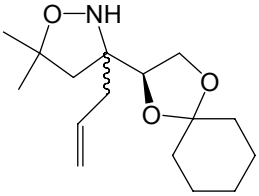
C) Reaction of isoxazolines with *C*-nucleophiles in the presence of Lewis acid

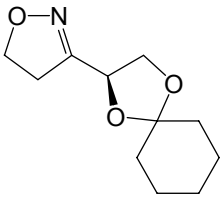
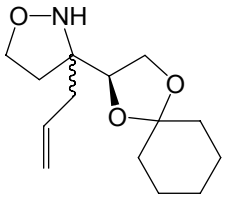
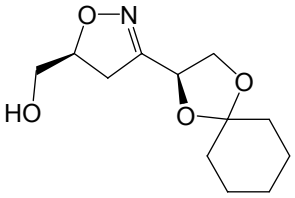
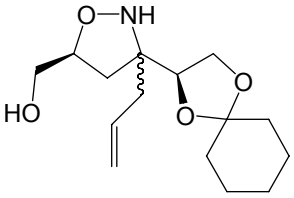
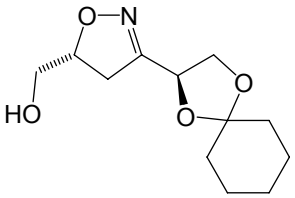
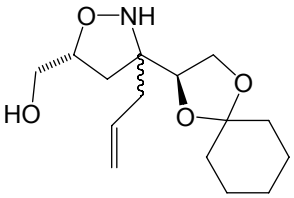
Addition of Grignard reagents to isoxazolines in the presence of Lewis acid

As an alternative route to activate isoxazoline to accept *C*-nucleophiles at C-3, and avoiding the presence of methyl group at the nitrogen atom of the activated isoxazoline; which formed by activation with trimethyloxonium tetrafluoroborate. Now it's possible to add *C*-nucleophiles to the isoxazolines, with prior activation by Lewis acid, with often excellent diastereoselectivities and high yields (Table 33).

Table 5. Addition of allylmagnesium bromide to isoxazoline in the presence of a Lewis acid



Entry	Isoxazoline	Isoxazolidine	Lewis Acid	d.r.[a]	Yield[b]		
					a	**b**	Σ
1			BF_3•OEt_2	-	-	-	65 %
2			$ZnBr_2$	-	-	-	76 %
3			$ZnCl_2$	-	-	-	59 %
	2	**30**					
4			$ZnBr_2$	85:15	-	-	63 %
	9	**31 a/b**					
5			$ZnBr_2$	88:12	73 %	11 %	84 %
6			$ZnCl_2$	87:13	67 %	9 %	76 %
7			BF_3•OEt_2	83:17	65 %	12 %	77 %
	22	**33 a/b**					

8	 **13**	 **34 a/b**	$ZnBr_2$	80:20	64 %	17 %	81 %
9	 **15/16** d.r. 87:13	 **35 a/b**		85:15	65 %	13 %	78 %
10			$ZnCl_2$	76:24	55 %	15 %	70 %
11			$ZnBr_2$	77:23	47 %	16 %	63 %
			BF_3•OEt_2				
12	 **15/16** d.r. 15:85	 **36 a/b**	$ZnCl_2$	81:19	61 %	19 %	80 %
13			$ZnBr_2$	78:22	61 %	17 %	78 %

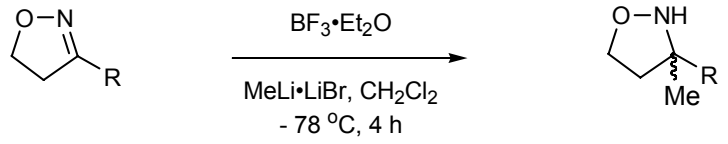
[a] The determinations of the diastereomeric ratios are based on the intensities of separate signal pairs in the ^{13}C NMR spectra of the crude products. [b] Yields are calculated over two steps starting from the corresponding isoxazoline; **a** : major diastereomer, **b** : minor diastereomer.

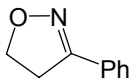
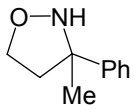
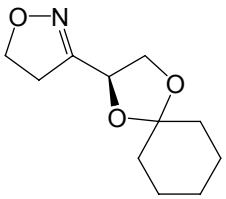
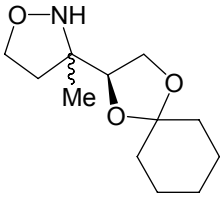
The effects of temperature and Lewis acid on the yield and stereoselectivity of the addition products were studied, but did not show a significant change. Nevertheless, it was possible to determine the absolute configuration of the isoxazolidines obtained, according to several crystal structures analysis that became available.

Addition of alkyllithium-lithium bromide complex to isoxazolines in the presence of Lewis acid

The addition of alkyl/aryllithium-lithium bromide complex to isoxazolines has rarely been studied. In the current work the addition was performed using methyllithium-lithium bromide in the presence of borontrifluoride etherate as a Lewis acid. The adducts were obtained in high yields, and with modest diastereoselectivity when the chiral isoxazoline **13** was used (Table 34).

Table 34. Addition of methyllithium-lithium bromide complex to the isoxazolines **2**, **13** in the presence of borontrifluoride etherate



Isoxazoline	Isoxazolidine	d.r.[a]	Yield **a**	Yield **B**	Yield Σ
		-	-	-	83%
2	**29**				
		68:32	58 %	27 %	85 %
13	**32 a/b**				

[a] The determination of the diastereomeric ratio (d.r.) is based on the intensities of separated signal pairs in the ^{13}C NMR spectra of the crude products. **a** : Major diastereomer, **b** : Minor diastereomer.

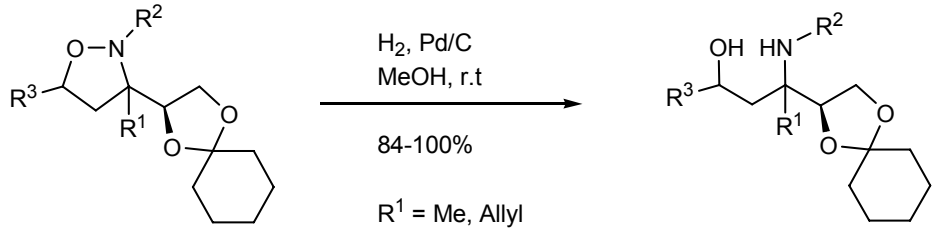
C) Transformation of isoxazolines

A major part of this work dealt with transformation of the isoxazolidines obtained into different target structures such as amino alcohols and polyols or α- and β-amino acids, first in order to assign the configuration of addition products, and secondly to demonstrate that isoxazolines are promising intermediates in field of amino acid synthesis.

Synthesis of N-(un)substituted amino alcohols and polyols

In order to obtain amino alcohols and polyols from the isoxazolidines, it was necessary to perform N-O bond cleavage of the isoxazolidine. For this, palladium-catalyzed hydrogenation proved effective, affording the respective target structures in mostly high yields [Eq. 54].

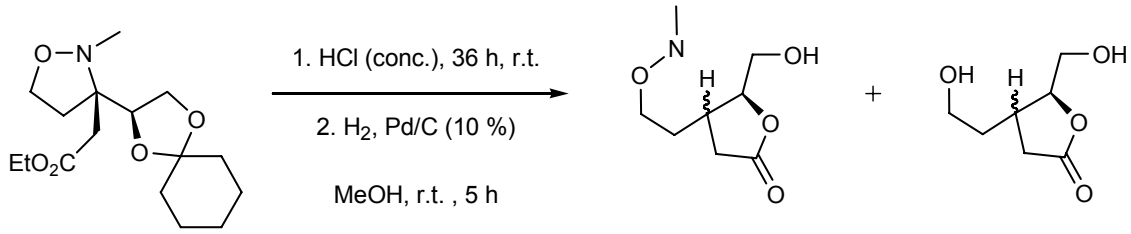
(54)



25a, 25b, 32a, 34a, 34b, 35a, 35b, 52 **41, 42, 45, 47, 48,49, 50, 70**

The absolute configurations of the 3,3-disubstituted amino alcohols and -polyols prepared were assigned according to the configurations of each of the 3,3-disubstituted isoxazolidines where crystal structure determinations had been obtained. A different behaviour was observed when ester-substituted isoxazolidines were examined in the catalytic hydrogenation. Here cleavage of the C-N bond prior to N-O bond fission was encountered, as seen with the following example [Eq. 55]:

(31)

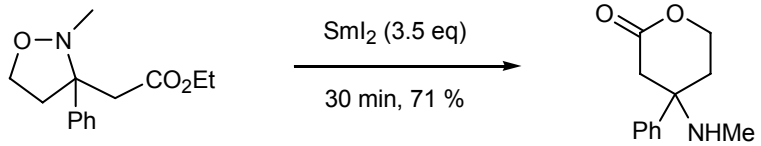


26a **57a/b** **58a/b**

74 % [*63*:*37*] 16 % [*65*:*35*]

Prior cleavage of the N-O bond has been achieved later in this work using samarium iodide solution in THF, to give the products of isoxazolidine ester, as illustrated in Eq. 56.

(56)

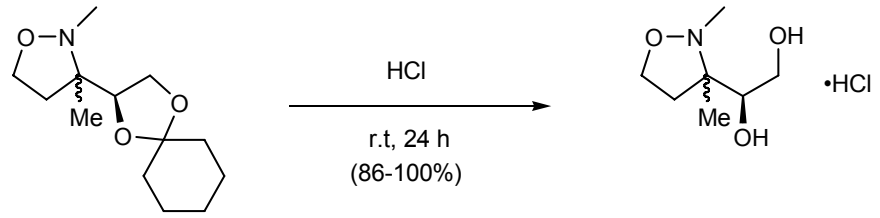


24 **37**

Hydrolysis of isoxazolidines derivatives: acetals and esters

Another aspect of this work was to assign the configuration of the isoxazolidines prepared. Acid hydrolysis performed on the isoxazolidine **25a** led to the respective diol **52•HCl** as a hydrochloride salt [Eq. 57]. The structure of this diol was confirmed by X-ray crystallographic analysis.

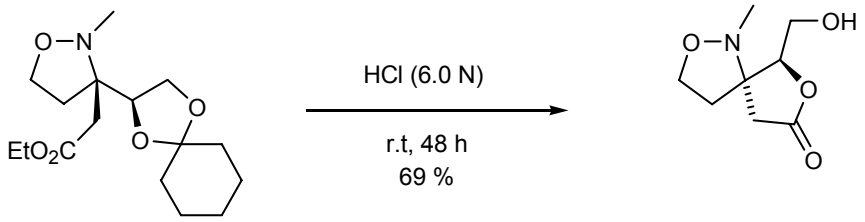
(57)



25a **52 • HCl**

In the same manner, the isoxazolidinolactone **54** was obtained on hydrolysis and its configuration was confirmed by X-ray crystallographic analysis. Thus, the absolute configuration of the isoxazolidine esters **26a** and **26b** were also known [Eq. 58].

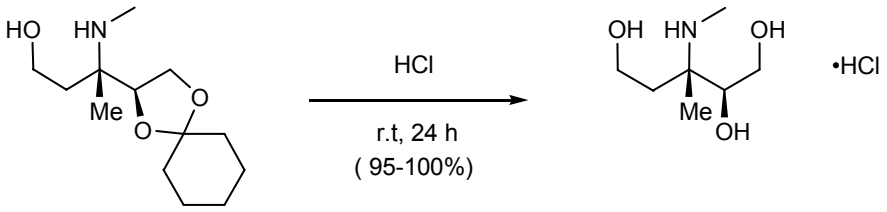
(58)



26a **54**

Interestingly *N*-methylamino polyols were similarly prepared smoothly, although in part with problems to get correct elemental analyses. Here it was as well possible to establish the configuration of the isoxazolidine **25a** by crystal structure determination of the aminotriol hydrochloride **70•HCl** [Eq. 59].

(59)



25a **70•HCl**

In summary, it is worth mentioning that transformations towards a variety of such structures by means of simple steps (catalytic hydrogenation, hydrolysis) were feasible, demonstrating the wide flexibility of this access to these types of compounds.

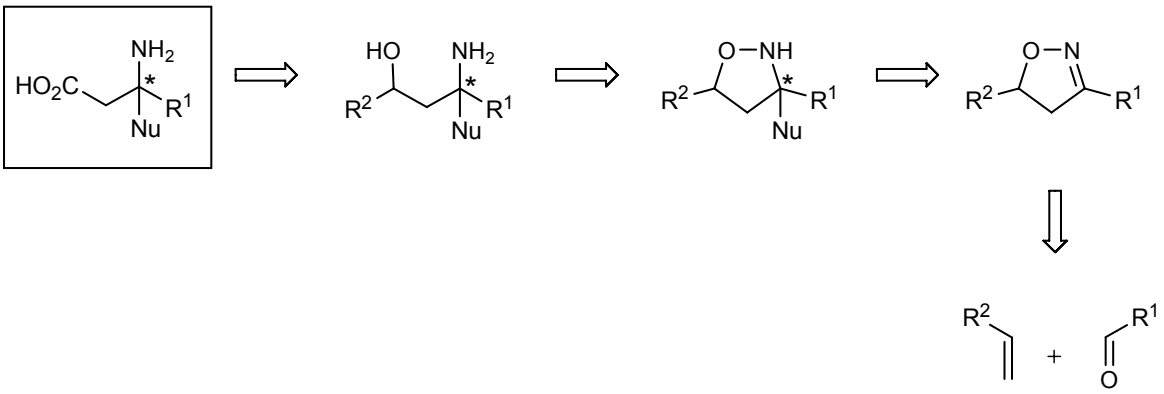
Synthesis of branched β-amino acids

One of the incentives to this study, a new approach to (branched) amino acids, was put into practice with the conversion of *N*-(un)substituted amino alcohols and polyols into the corresponding amino acids.

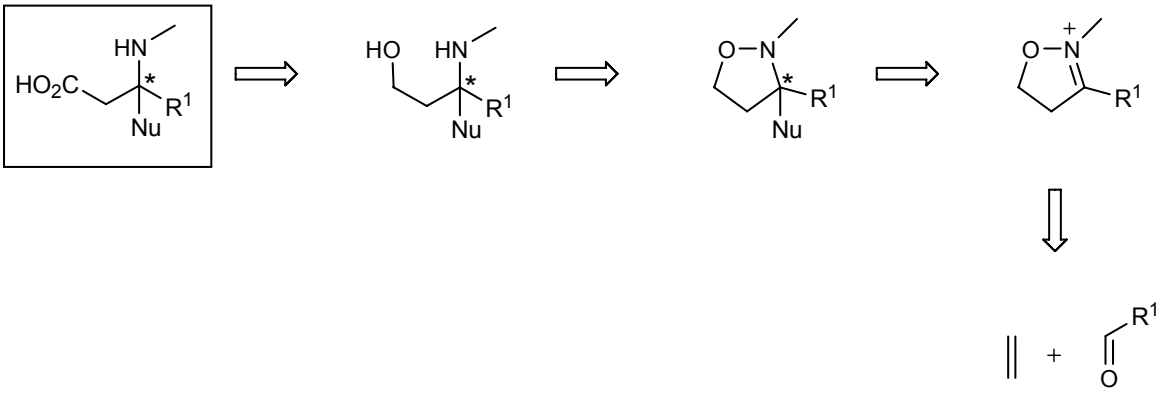
Here, after building the "activated isoxazoline" ring, a variety of *C*-nucleophiles was added to afford the respective isoxazolidines in high yield, and mostly with high selectivity, through catalytic hydrogenation of isoxazolidines followed by protection of the resulting amino alcohols or amino polyols. The latter are ready to be transformed into a new set of β-amino acids by oxidation of the primary alcohol or diol unit in some cases, completed by N-deprotection (Scheme 18).

Scheme 18

A) Activation by Lewis acid



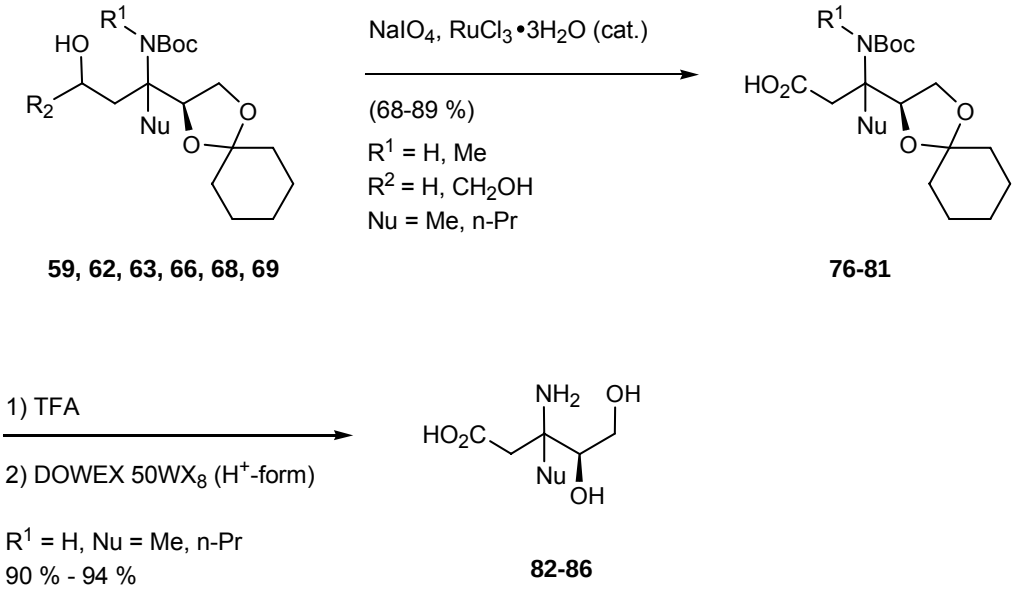
B) Activation by *N*-methylation



Using the strategy previously outlined, it was straightforward to convert the highly functionalized *N*-(un)substituted amino alcohols and polyols to the corresponding β-amino acids. First, the *N*-(un)substituted amino alcohols and polyols were protected as the *N*-Boc derivatives, which were then oxidized to give the protected β-amino acids. After deprotection by treatment with TFA and purification by ion exchange, several β-amino acids were obtained in good overall yields. The configuration of all protected and deprotected β-amino

acids in each case were confirmed by X-ray crystallography of related compounds in the same series (Scheme 19).

Scheme 19



In conclusion, a versatile and efficient approach for the synthesis of diverse amino alcohols and polyols and β-amino acids is demonstrated. The approach employs chiral isoxazolines as key intermediate, translating in part the high selectivity from the 1,3-dipolar cycloaddition reaction into the formation of further structures with up to three contiguous stereogenic centers. Thus, it was possible to develop new, flexible, and efficient routes to branched *N*-(un)substituted amino alcohols and polyols, respectively, and to β-amino acids. In particular, it was shown that isoxazolines are highly useful precursors for targets containing tertiary and quaternary amine-bearing stereocenters; this should be beneficial in the future for synthesis of other interesting branched amino compounds.

11 Experimental Part

11.1 General

Nuclear magnetic resonance spectroscopy

^{1}H NMR Spectra:	Bruker AC 250 (250.1 MHz)
	Bruker ARX 300 (300.1 MHz)
	Bruker ARX 500 (500.1 MHz)
^{13}C NMR Spectra:	Bruker AC 250 (62.90 MHz)
	Bruker ARX 300 (75.50 MHz)
	Bruker 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 the multiplicity 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 the diastereomeric ratios (d.r.) are based on the intensities of separated signal pairs in the ^{13}C NMR spectra. Assignment of the absorptions of carbon atoms - if not mentioned in text- has been done by means of C,H-COSY.

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 $\tilde{\nu}$ 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 from the Na_D absorption by means of the Drude equation by extrapolation of two Hg lines (546 and 578 nm):[121]

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

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 Analysis

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,[122] XRAY 76,[123] ORTEP II,[124] and FRIEDA[125] programmes.

Thin Layer Chromatography

Thin layer chromatography was performed on precoated aluminium sheets (silica 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.[126]

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 C columns filled with silica gel (column dimensions: 69 cm length x 5 cm width, pressure 15-20 bar, flow 50-60 mL/min, theoretical plate number 11500) were prepared according to G. Helmchen and B. Glatz.[127]

Gas Chromatography (GC)

For the GC analysis a HRGC 5300 (mega series) from Carlo Erba was used. One of the measurements was done with Amidex P22.10 column (glass capillary column length 20 m), FID as detector, and Thermo Finnigan (Chrom-Card) as integrator.

Solvents and Reagents

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

Filtration and 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 separately.

Purification by Acidic Ion Exchange Column Chromatography

Dowex 50WX8 (H^+-form, 200-400 mesh) purchased from Fluka was used for the acidic ion exchange column. The substance was filled into a glas frit (5 cm x 1 cm), then washed successively with 50 mL of the following solutions: demineralized water, ammonia (1.0 N), water till neutralization, HCl (1.0 N), water till neutralization, methanol, and water. The crude product was put on the column (dissolved in 10 mL water/MeOH) and washed successively with 50 mL of the following solitions: demineralized water, methanol, water. The product was finally collected by elution with 100 mL of ammonia (1.0 N).

Starting materials used and suppliers

Trimethyloxonium tetrafluoroborate (Me_3OBF_4): Aldrich Company.
Methyllithium-lithium bromide complex (MeLi•LiBr): Aldrich Company.
All Grignard reagents used in this work were purchased from Aldrich Company.
Pd/C (10 % and 5 %): Degussa Company.
Ethylene and isobutene: Linde Company.

Benzhydroximoyl chloride (**1**): prepared according to lit.[35] yield 67 %, m. p. 50-51 °C (lit. [128, 129]: yield 92 %, m.p. 50-51 °C).

1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol (**10**): Prepared according to lit.,[40] yield 57 %, m.p. 101-103 °C (lit.:[40] yield 56 %, m.p. 104-105 °C).

1,2:5,6-Di-*O*-diisopropylidene-D-mannitol (**17**) : Prepared according to lit.,[42] yield 65 % from D-Mannitol, m.p. 118 °C, $[\alpha]_D^{20}$ = 2.8 (*c* = 1.0, MeOH), [lit.:[42] yield 54 %, m.p. 122-123 °C, $[\alpha]_D^{20}$ = 1.9 (*c* = 1.74, MeOH)].

2,3-*O*-Isopropylidene-D-glyceraldehyde (**18**) : Prepared from 1,2:5,6-di-*O*-diisopropylidene-D-mannitol (**17**) according to lit.,[130] yield 86 % (lit.:[2] yield 78 %; lit.:[42] b.p. 72-74 °C (30 mmHg), $[\alpha]_D^{20}$ = 73.1 (*c* = 1.34, C_6H_6)).

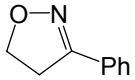
2,3-*O*-Isopropylidene-D-glyceraldoxime (*E*/*Z* = 65:35) (**19**): Prepared 1,2-O-isopropylidene-D-glyceraldehyde according to lit., [10, 43, 130] yield 64 % (lit. [130]: yield 62 %).

The numbers of the experiments are given in order. The code and number given in the brackets correspond to the number in the lab journal, YB meaning Yaser Bathich, MI for Mukhtar Imerhasan (Undergraduate research fellow, 2003).

11.2 Synthesis of Isoxazolines and *N*-Methylisoxazolinium Salts

Experiment 1 (YB 3)

3-Phenyl-4,5-dihydroisoxazole (2), cf. lit. [1,2,36,131]



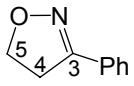
2

According to lit.[10], ethylene was bubbled into a solution of 16.65 g (106.5 mmol) of benzhydroximoyl chloride **1** in 450 mL ether at 0 °C for 30 min. The ethylene current was continued and 118 mL (1.00 M, 118 mmol) of triethylamine solution in ether was added dropwise with a rate of 3 to 4 drops/min within 48 h. The mixture was quenched with HCl (100 mL, 1.0 N), partitioned against ether (3 x 100 mL), and the combined organic phases were washed with $NaHCO_3$ (100 mL) and water (2 x 100 mL), then dried ($MgSO_4$), and concentrated *in vacuo* (50 mbar) to give a colourless solid. Crystallization from ether gave 13.34 g (87 %; lit.: 77 %,[10] 80 %,[2] 69 %,[131] 81 %[36]) of analytically and spectroscopically pure isoxazoline **2** in the form of colourless crystals (m. p. 62-64 °C; lit.: 63-66 °C,[10] 64-66 °C,[2] 66-67 °C[36]). The analytical and spectroscopic data fully complied with the literature values. [2, 10]

C_9H_9NO	calc.	C 73.45	H 6.16	N 9.52
(147.2)	found	C 73.25	H 6.21	N 9.47

IR (KBr): $\tilde{\nu}$ = 3061 (w), 2959 (w), 2891 (w), 1567 (w), 1499 (w), 1473 (w), 1449 (s), 1431 (m), 1354 (s), 1314 (w), 1079 (w), 1005 (w), 927 (s), 884 (vs), 856 (s), 761 (vs), 695 (vs), 663 (m) cm^{-1}.

^1H NMR (250.1 MHz, $CDCl_3$): δ = 3.34 (t, $J_{4,5}$ = 10.1 Hz, 2 H, 4-H), 4.47 (t, $J_{4,5}$ = 10.1 Hz, 2 H, 5-H), 7.37-7.70 (m, 5 H, C_6H_5)

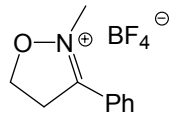


2

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.2 (t, C-4), 69.2 (t, C-5), 126.7, 128.7, 130.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 129.5 (s, *i*-C of C_6H_5), 156.8 (s, C-3).

Experiment 2 (YB 7)

2-Methyl-3-phenyl-4,5-dihydroisoxazol-2-ium tetrafluoroborate (3), cf. lit.[1,2]



3

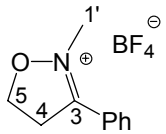
Typical Procedure TP 1 for Transformation of Isoxazolines to Isoxazolinium Salts

According to lit.,[1,2] 2.20 g (14.9 mmol, 1.1 eq) of Me_3OBF_4 was added with stirring to a solution of 2.00 g (13.6 mmol) of the isoxazoline **2** in 30 mL abs. CH_2Cl_2 at room temp. The mixture was left with stirring overnight, and then concentrated *in vacuo* (10 mbar) to give 3.65 g of a yellowish solid, which crystallized from abs. ethanol to afford 3.2 g (95 %; lit.: 90 %,[1] 96 %[2]) of pure isoxazolinium salt **3** in the form of colourless crystals (m. p. 103-104 °C; lit.: 104-106 °C[1], 103-104 °C[2]). The analytical and spectroscopic data fully complied with the values given in lit.[1,2]

$C_{10}H_{12}BF_4NO$	calc.	C 48.23	H 4.86	N 5.62
(249.0)	found	C 48.37	H 4.89	N 5.62

IR (KBr): $\tilde{\nu}$ = 3400 (m, b), 1651 (w, C=N$^+$), 1590 (m), 1440 (m), 1370 (m), 1100 (vs), 1083 (s), 1031 (s), 928 (m), 769 (m), 670 (s) cm^{-1}.

^{1}H NMR (250.1 MHz, CD_3OD): δ = 3.95 (t, $^5J_{4,1'}$ = 1.8 Hz, 3 H, NCH_3), 4.14 (qt, $J_{4,5}$ = 10.1, $^5J_{4,1'}$ = 1.8 Hz, 2 H, 4-H), 4.92 (t, $J_{4,5}$ = 10.1 Hz, 2 H, 5-H), 7.65-7.84 (m, 5 H, C_6H_5).

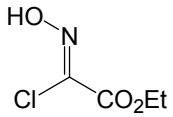


3

^{13}C NMR (62.9 MHz, CD_3OD): δ = 42.1 (q, NCH_3), 42.1 (t, C-4), 72.8 (s, C-5), 125.9 (s, *i*-C of C_6H_5), 132.1, 132.3, 137.2 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 166.7 (s, C-3).

Experiment 3 (MI 35)

Ethyl Chlorooximidoacetate (4), cf. lit.[2, 38]



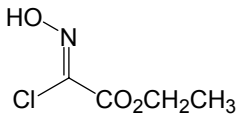
4

According to lit.[38] 69.7 g (503 mmol) of ethyl glycinate hydrochloride and 41.5 mL (494 mmol) of conc. HCl were added to 95 mL H_2O at – 5° C with stirring, and then 34.7 g (1 eq) of $NaNO_2$ (in 50 H_2O) was added. A second equivalent of hydrochloric acid (41.5 mL of conc. HCl, 494 mmol) and of sodium nitrite (34.7 g in 50 H_2O) was then added in the same manner. The reaction mixture was partitioned against ether (5 x 100 mL) and dried ($MgSO_4$), then concentrated *in vacuo* (4 mbar). Crystallization from hexane gave 31 g (41 %; lit.: 54 %[38]) of analytically and spectroscopically pure **4** as colourless crystals (m. p. 75-76 °C; lit.: 80 °C[38]).

$C_4H_6NO_3Cl$	calc.	C 31.70	H 3.99	N 9.24
(151.55)	found	C 32.22	H 3.98	N 9.29

IR (KBr) : $\tilde{\nu}$ = 3320 (s), 2970 (m), 1745 (s), 1720 (m), 1720 (m), 1615 (m), 1465 (m), 1440 (m), 1410 (m), 1375 (m), 1360 (m), 1290 (s), 1060 (s), 1040 (m), 980 (m), 840 (m), 800 (w), 780 (m), 735 (m) cm^{-1}.

^1H NMR (250.1 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.1 Hz, 3 H, $CH_2C\underline{H}_3$), 4.41 (q, *J* = 7.1 Hz, 2 H, $C\underline{H}_2CH_3$), 7.29 (s, 1 H, NO<u>H</u>).



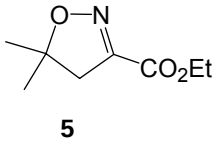
4

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 13.9 (q, $CH_2\underline{C}H_3$), 63.9 (t, $\underline{C}H_2CH_3$), 132.8 (s, <u>C</u>=N), 158.8 (s, C=O).

The spectroscopic data were in full agreement with those given in lit.[2]

Experiment 4 (MI 36)

Ethyl 5,5-dimethyl-4,5-dihydroisoxazole-3-carboxylate (5). cf. lit.[2,132]



5

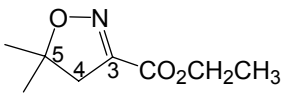
According to lit.[2] isobutene was introduced for 30 min into a solution of 7.0 g (46.2 mmol) of ethyl chlorooximidoacetate **4** in 150 mL ether at -15 °C. The isobutene current was continued and 50.8 mL (1.00 M, 5.14 g) of triethylamine solution in ether was added dropwise at a rate of 3 to 4 drops/min over 3 h. The mixture was left for 10 h with stirring at room temp., then

quenched with HCl (250 mL, 1.0 N), partitioned against ether (5 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo* (6 mbar) to give 7.0 g of a yellowish oil of **5**, which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1). Purification by MPLC (petroleum ether/ethyl acetate 7:3) gave 5.5 g (70 %; lit. [2]: 67 %) of an analytically impure but spectroscopically pure, light-yellow oil. The spectroscopic data were fully complied with those given in lit. [2]

$C_8H_{13}NO_3$	calc.	C 56.13	H 7.56	N 8.18
(171.2)	found	C 54.71	H 7.30	N 8.46

IR (film) : $\tilde{\nu}$ = 2960 (w), 2910 (w), 1735 (m), 1710 (s, C=O), 1660 (m), 1575 (s, C=N), 1460 (w), 1430 (w), 1395 (w), 1370 (m), 1360 (m), 1325 (m), 1275 (s), 1225 (s), 1115 (s), 1050 (w), 1000 (m), 930 (s), 840 (w), 740 (m), 725 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.1 Hz, 3 H, $CH_2C\underline{H}_3$), 1.47 [s, 6 H, $C(CH_3)_2$], 2.98 (s, 2 H, 4-H), 4.36 (q, *J* = 7.1 Hz, 2 H, $C\underline{H}_2CH_3$).

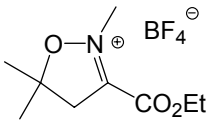


5

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (q, $CH_2\underline{C}H_3$), 27.2 [q, $C(\underline{C}H_3)_2$], 45.2 (t, C-4), 61.9 (t, $\underline{C}H_2CH_3$), 88.5 (s, C-5), 151.1 (s, C-3), 161.1 (s, C=O).

Experiment 5 (MI 43)

Ethyl 2,5,5-trimethyl-4,5-dihydro-2-isoxazolium-3-carboxylate tetrafluoroborate (6), cf. lit. [2]



6

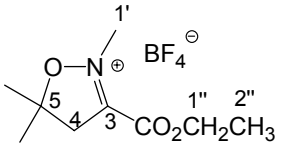
Scale: 2.00 g (11.7 mmol) isoxazoline **5**
1.90 g (12.9 mmol) Me_3OBF_4
50 mL abs. CH_2Cl_2

The reaction was performed according to TP 1 to afford a light-yellow solid of **6** (2.8 g, 88%; lit.[2]: 95 %) in the form of colourless crystals (m. p. 152-153 °C; lit.: 150-153 °C[2]) after crystalization from abs. ethanol. The spectroscopic data were fully complied with those given in lit.[2]

$C_9H_{16}NO_3BF_4$	calc.	C 39.59	H 5.91	N 5.13
(273.0)	found	C 39.02	H 5.73	N 5.09

IR (KBr) : $\tilde{\nu}$ = 2970 (m), 2910 (w), 2330 (w), 1740 (s, C=O), 1660 (m), 1460 (m), 1370 (m), 1320 (m), 1280 (m), 1250 (m), 1160 (m), 1090 (m), 1015 (vs), 950 (s), 920 (m), 840 (m), 740 (m) cm^{-1}.

^1H NMR (250 MHz, CD_3OD): δ = 1.42 (t, $J_{1',2'}$ = 7.1 Hz, 3 H, $CH_2C\underline{H}_3$), 1.66 [s, 6 H, $C(C\underline{H}_3)_2$], 3.76 (q, $^5J_{4,1'}$ = 2.4 Hz, 2 H, 4-H), 4.17 (s, 3 H, $NC\underline{H}_3$), 4.47 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, $C\underline{H}_2CH_3$).

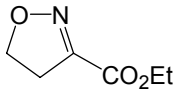


6

^{13}C NMR (62.9 MHz, CD_3OD): δ = 14.2 (q, $CH_2\underline{C}H_3$), 26.9 [q, $C(\underline{C}H_3)_2$], 42.9 (q, $N\underline{C}H_3$), 49.3 (t, C-4), 66.2 (t, $\underline{C}H_2CH_3$), 94.4 (s, C-5), 155.7 (s, C-3), 156.2 (s, C=O).

Experiment 6 (MI 37)

Ethyl 4,5-Dihydroisoxazole-3-carboxylate (7)



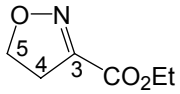
7

Ethylene was introduced into a solution of 7.0 g (46.2 mmol) of ethyl chlorooximidoacetate **4** in 150 mL ether at - 15 °C for 30 min. The ethylene current was continued and 50.8 mL (50.8 mmol, 1.00 M) of a triethylamine solution in ether was added dropwise at a rate of 3 to 4 drops/min over 3 h. The mixture was then left for 10 h with stirring at room temp., then was quenched with HCl (250 mL, 1.0 N). The mixture was partitioned against ether (5 x 100 mL), the organic solutions were dried ($MgSO_4$), and concentrated *in vacuo* (6 mbar) to give 7.0 g of a brownish oil, which was filtered through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to furnish 5.56 g of **7**. This was purified by MPLC (petroleum ether/ethyl acetate 7:3) to give 3.84 g (58 %; lit.[39]: 77 %) of **7** as an analytically and spectroscopically pure, light-brown oil.

$C_6H_9NO_3$	calc.	C 50.13	H 6.34	N 9.79
(143.1)	found	C 50.23	H 6.34	N 9.58

IR (KBr) : $\tilde{\nu}$ = 2970 (vs), 2920 (w), 2880 (w), 1730 (s, C=O), 1580 (s), 1460 (m), 1430 (s),1390 (s), 1370 (s), 1340 (m), 1320 (s), 1250 (vs), 1160 (m), 1110 (vs), 910 (vs), 840 (s), 805 (s), 760 (m), 730 (s).

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.39 (t, J = 7.2 Hz, 3 H, $CH_2C\underline{H}_3$), 3.24 (t, $J_{4,5}$ = 10.7 Hz, 2 H, 4-H), 4.40 (q, J = 7.2 Hz, 2 H, $C\underline{H}_2CH_3$), 4.55 (t, $J_{4,5}$ = 10.7 Hz, 2 H, 5-H).

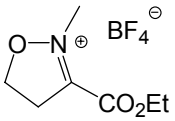


7

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (q, $CH_2\underline{C}H_3$), 33.8 (t, C-4), 62.1 (t, $\underline{C}H_2CH_3$), 71.4 (t, C-5), 151.9 (s, C-3), 160.7 (s, C=O).

Experiment 7 (YB 316)

Ethyl 2-methyl-4,5-dihydro-2-isoxazolium-3-carboxylate tetrafluoroborate (8)



8

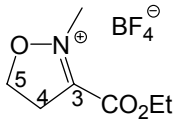
Scale: 39 mg (0.27 mmol) isoxazoline **7**
44 mg (0.30 mmol) Me_3OBF_4
5 mL abs. CH_2Cl_2

The reaction was performed according to TP 1 to afford a light-yellow oil of crude **8** afforded 53 mg (''79 %'') of a yellowish oil as spectroscopically pure isoxazolinium salt **8** but analytically impure.

$C_7H_{12}BF_4NO_3$	calc.	C 34.32	H 4.94	N 5.71
(245.0)	Found	C 29.69	H 5.24	N 5.12

IR (KBr) : $\tilde{\nu}$ = 2970 (s), 2920 (m), 1740 (s, C=O), 1460 (m),1435 (m), 1410 (w), 1365 (s), 1340 (m), 1260 (s), 1190 (w), 1050 (s), 1010 (m), 745 (m), 730 (w) cm^{-1}.

^{1}H NMR (250 MHz, CD_3OD): δ = 1.41 (t, $J_{1',2'}$ = 7.1 Hz, 3 H, $CH_2C\underline{H}_3$), 4.17 (s, 3 H, $NC\underline{H}_3$), 3.86-4.00 (m, 2 H, 4-H), 4.48 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, $C\underline{H}_2CH_3$), 4.92-5.00 (m, 2 H, 5-H).

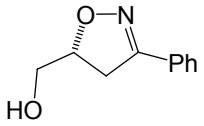


8

^{13}C NMR (62.9 MHz, CD_3OD): δ = 14.2 (q, $CH_2\underline{C}H_3$), 38.0 (t, C-4), 42.2 (q, $N\underline{C}H_3$), 66.2 (t, $\underline{C}H_2CH_3$), 73.6 (t, C-5), 155.7 (s, C-3), 155.9 (s, C=O).

Experiment 8 (YB 273)

(5*R*)-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (9) cf. lit.[37]



9

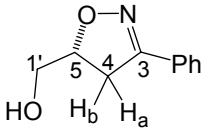
Similar to a procedure given by Ukaji,[37] to a solution of allyl alcohol (0.44 g, 7.5 mmol) in $CHCl_3$ (15 mL) diethylzinc (7.6 mL of a 1.0 M solution in hexane, 7.6 mmol) was added at 0 °C under nitrogen, and the mixture was stirred for 10 min. Next, a solution of (+)-L-DIPT (1.78 g, 7.60 mmol) in $CHCl_3$ (15 mL) was added and the mixture was stirred for 1 h. Diethylzinc (8.2 mL, 8.2 mmol) and a solution of hydroximoylchloride **1** (1.16 g, 7.5 mmol, 1 eq) in $CHCl_3$ (15 mL) were added successively, and the resulting solution was stirred for 3 h room temp.

The reaction was quenched by addition of a sat. NH_4Cl solution, then the mixture was extracted with ether (3 x 40 mL). The organic solutions were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar, 20 °C) to give 1.41 g (e.r. 98:2)[a] of crude **9**. Crystallization from petroleum ether/CH_2Cl_2 produced 1.23 g (93 %) of **9** as colourless crystals (m.p. 75-77 °C; lit.[133] 78-79 °C).

$[\alpha]_D^{20}$ = - 164.9 (*c* = 1.000, $CHCl_3$) lit. : - 164.0 (*c* = 0.700, $CHCl_3$)[37]

$C_{10}H_{11}NO_2$	calc.	C 67.78	H 6.26	N 7.87
(177.2)	found	C 67.59	H 6.29	N 7.90

IR : $\tilde{\nu}$ = 3469 (sb, OH), 2940 (w), 2868 (w), 1757 (w), 1433 (w), 1361 (s), 1115 (s), 1033 (s), 896 (vs), 608 (vs) cm^{-1}.



9

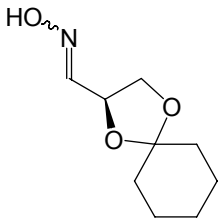
^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.84 (s, 1 H, OH), 3.28 (dd, $J_{4a,4b}$ = 16.6, $J_{4a,5}$ = 7.8 Hz, 1 H, 4-H_a), 3.39 (dd, $J_{4a,4b}$ = 16.6, $J_{4a,5}$ = 10.8 Hz, 1 H, 4-H_b), 3.69 (dd, $J_{1'a,1'b}$ = 12.2, $J_{5,1'a}$ = 4.7 Hz, 1 H, 1'-H_a), 3.88 (dd, $J_{1'a,1'b}$ = 12.2, $J_{5,1'b}$ = 3.2 Hz, 1 H, 1'-H_b), 4.87 ("dddd", $J_{4a,5}$ = 7.8 Hz, $J_{4a,5}$ = 10.9, $J_{5,1'a}$ = 4.7 Hz, $J_{5,1'b}$ = 3.2 Hz, 1 H, 5-H), 7.38-7.69 (m, 5 H, C_6H_5).

[a] GC analyses with 0.4 bar H_2; the sample was injected on column starting with 40 °C, first min, then the temperature was increased by 4 °C/min till 200 °C. Appendix 12.2.1 illustrates the diagram of the racemic mitxure of **9** (has been prepared following the same procedure without DIPT; appendix 12.2.2 illustrates the GC diagram of the mixture of **9** in e.r 98:2.

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.3 (t, C-4), 63.7 (t, C-6), 81.2 (d, C-5), 126.7, 128.7, 130.2 (3 d, *o-, m-, p*-C of C_6H_5), 129.3 (s, *i*-C of C_6H_5), 157.5 (s, C-3).

Experiment 9 (YB 202)

2,3-*O*-Cyclohexylidene-(*S*)-glyceraldoxime (11), cf. lit. [1,2,40,134]



11

To a mixture of H_2O/ethyl acetate (3:1, 500 mL) 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol **10** (30.0 g, 87.6 mmol) was added and the pH adjusted to 8-9 by addition of NaOH solution (ca. 3 mL, 1.0 N). Next, sodium periodate (18.73 g, 87.60 mmol) was added portionwise, then the mixture was stirred at room temp. for 2.5 h. The organic phase was extracted with ethyl acetate (5 x 75mL) and the combined organic solutions were dried ($MgSO_4$) to give, after evaporating the solvent (50 mbar), 29.2 g ("98%") of a colourless oil.

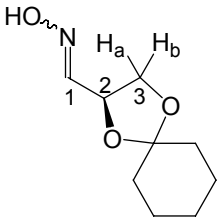
The oil was dissolved in 400 mL MeOH and 90.0 g (378 mmol) of K_2CO_3 and 23.1 g (333 mmol) of $NH_4OH{\cdot}HCl$ (dissolved in 400 mL H_2O) were added at 0 °C. The mixture was stirred overnight. The total volume was then reduced to one third by evaporation (15 mbar, 50 °C) followed by extraction with CH_2Cl_2 (5 x 60 mL). The combined organic solutes were dried ($MgSO_4$) and concentrated *in vacuo* (5 mbar), then the residual oil was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) to yield 26.24 g of the oxime **11** as a colourless oil (81%, E:Z = 60:40; lit.: 87 %, *E*/*Z* = 65:35;[1] 88 %, *E*/*Z* = 70:30[2]). The analytical and spectroscopic data were in accordance with the literature values.[2,40,134]

$[\alpha]_D^{20}$ = 55.3 (*c* = 1.00, $CHCl_3$) lit. : $[\alpha]_D^{20}$ = 55.0 (*c* = 1.35, $CHCl_3$)[1]

$[\alpha]_D^{20}$ = 51.6 (*c* = 1.58, $CHCl_3$)[2]

IR (neat): $\tilde{\nu}$ = 3350 (sb), 2920 (vs), 2845 (s), 1650 (w), 1440 (s), 1355 (s), 1320 (m), 1270 (s), 1240 (m), 1220 (m), 1150 (s), 1130 (m), 1085 (s), 1120 (s), 950 (m), 915 (s), 835 (s), 815 (m), 760 (w), 680 (w), 640 (w) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$, *E*:*Z* = 60:40) : δ = 1.42-1.63 (m, C(C<u>H</u>$_2$)$_5$), 3.87, 3.80 (A for ABX, 3-H_a), 4.17, 4.35 (B for ABX, 3-H_b), 4.65, 5.08 (dX for ABX, 2-H), 7.39, 6.96 (d, 1-H), 9.1, 9.35 (sb, 1 H, NOH).

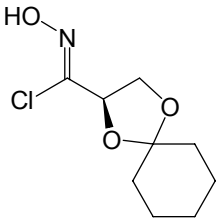


11

^{13}C NMR (62.9 MHz, $CDCl_3$, *E*:*Z* = 60:40) : (*E*) Isomer : δ = 23.8, 23.9, 25.0, 35.0, 36.2 (5 t, C(<u>C</u>H$_2$)$_5$), 67.0 (t, C-3), 72.9 (d, C-2), 111.0 (s, *i*-C), 149.8 (d, C-1). (*Z*) Isomer : δ = 34.8, 35.7 (5 t, C(<u>C</u>H$_2$)$_5$), 67.5 (t, C-3), 70.3 (d, C-2), 110.4 (s, *i*-C), 153.0 (d, C-1); the other signals were overpalled by those of the major diastereomer.

Experiment 10 (YB 203)

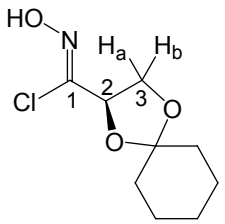
2,3-*O*-Cyclohexylidene-D-glycerohydroximoyl chloride (12), cf. lit.[1,35,40,134,48]



12

According to lit.[1,35], 10.4 g (77.94 mmol) of NCS was added portionwise to a solution of 26.24 g (141.7 mmol) 2,3-*O*-cyclohexylidene-D-glyceraldoxime **11** in 200 mL of abs. DMF. HCl gas (from HCl vapor on bottle with conc. HCl 37%) was then introduced by means of a syringe into the solution several times until the reaction started (the colour changed to green). After 5 min, a second portion of NCS (10.4 g, 77.94 mmol) was added and the reaction was kept with stirring for 3 h at room temp. To this mixture 500 mL of ice water was added, then it was extracted with ether (5 x 75 mL). The extracts were washed with water (2 x 100 mL) and dried ($MgSO_4$). Finally, the solvent was evaporated (10 mbar) to afford 30.87 g of the hydroximoyl chloride **12** (99 %; lit.: 99 %[2], 96 %[1]) as a green oil. The analytical data complied with the literature values. [1,2,10]

^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.40-1.79 [m, C(C<u>H</u>$_2$)$_5$], 4.14 (dd, $J_{2,3a}$ = 5.8, $J_{3a,3b}$ = 8.7 Hz, 1 H, 3-H_a), 4.20 (dd, $J_{2,3b}$ = 6.7, $J_{3a,3b}$ = 8.7 Hz, 1 H, 3-H_b), 4.83 (dd, $J_{2,3a}$ = 5.8, $J_{2,3b}$ = 6.7 Hz, 1 H, 2-H), 9.75 (sb, 1 H, NOH).

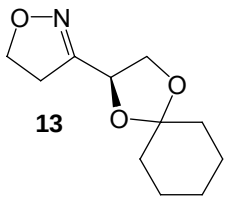


12

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.81, 23.83, 25.0, 35.0, 35.5 (5 t, C($\underline{C}H_2)_5$), 66.6 (t, C-3), 75.9 (d, C-2), 112.1 (s, *i*-C), 139.4 (d, C-1).

Experiment 11 (YB 6)

(1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-4,5-dihydro-1,2-oxazole (13), cf. lit. [1,2,10,135]



13

In analogy to lit.[10] 10.80 g (49.17 mmol) of hydroximoyl chloride **12** at 0 °C was dissolved in 250 mL of abs. toluene. Ethylene was bubbled into the solution till saturation (30 min), then 53.8 mL (1.00 N in toluene, 53.8 mmol) of triethylamine was added dropwise at a rate of 3 to 4 drops/min over 24 h. The mixture was then quenched by addition of HCl (150 mL, 1.0 N) and partitioned against ether (4 x 60 mL). The combined organic phases were washed with $NaHCO_3$ (100 mL) and water (2 x 100 mL), then dried ($MgSO_4$), and concentrated *in vacuo* (15 mbar) to give a yellowish oil. Crystallization from hexane gave analytically and spectroscopically pure isoxazoline **13** (9.00 g, 84 % from 2,3-O-cyclohexylidene-D-glyceraldoxime; lit.: 89 %[1], 65 %[2], 63 %[135]) as a colourless solid (m.p. 38-40 °C; lit. : 45 °C[1], 40 °C[2]).

$[\alpha]_D^{20}$ = -3.9 (*c* = 1.00, CH_2Cl_2) lit.: $[\alpha]_D^{20}$ = -4.0 (*c* = 0.49, CH_2Cl_2) [2]

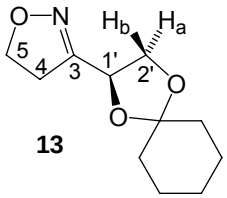
$[\alpha]_D^{20}$ = -3.7 (*c* = 0.50, CH_2Cl_2) [2]

$[\alpha]_D^{20}$ = -4.1 (*c* = 0.60, CH_2Cl_2) [135]

$C_{11}H_{17}NO_3$	calc.	C 62.54	H 8.11	N 6.63
(211.3)	found	C 62.55	H 8.09	N 6.56

IR (KBr): $\tilde{\nu}$ = 2920 (vs), 2830 (s), 1610 (w), 1435 (m), 1350 (m), 1325 (w), 1270 (w), 1220 (w), 1150 (s), 1080 (vs), 1060 (w), 1030 (m), 910 (s), 890 (w), 850 (vs), 810 (w) cm^{-1}.

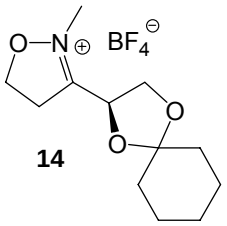
^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.40-1.65 [m, 10 H, $C(CH_2)_5$], 2.93-3.14 (m, 2 H, 4-H), 3.99 (dd, $J_{1',2'a}$ = 6.0 , $^2J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_a), 4.22 (dd, $J_{1',2'b}$ = 6.8, $^2J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_b), 4.33-4.41 (m, 2 H, 5-H), 4.97 (dd, $J_{1',2'a}$ = 6.0, $J_{1',2'b}$ = 6.8 Hz, 1 H, 1'-H).



13

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 23.8, 24.0, 25.0, 34.1, 34.6 [5 t, $C(\underline{C}H_2)_5$], 35.9 (t, C-4), 66.8 (t, C-2'), 68.8 (t, C-5), 70.7 (d, C-1'), 111.0 [s, $\underline{C}(CH_2)_5$], 158.4 (s, C-3).
The analytical and spectroscopic data complied with the literature values. [1,2,10]

Experiment 12 (YB 9)
(1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-2-methyl-4,5-dihydro-1,2-oxazolium tetrafluoroborate (14), cf. lit. [1,2,10]



14

Scale : 500 mg (2.37 mmol) isoxazoline **13**
390 mg (2.60 mmol) Me_3OBF_4
25 mL abs. CH_2Cl_2

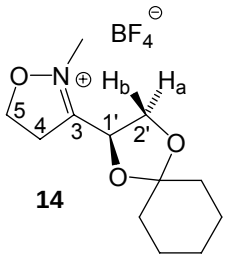
This reaction was performed according to TP 1. This led to a brownish solid, which after crystallization from ethanol gave 650 mg (88 %; lit.1 84 %) of analytically and spectroscopically pure isoxazolinium salt **14** in the form of a colourless solid (m. p. 96-97 °C; lit. 105-106 °C[1]).

$[\alpha]_D^{20}$ = -12.9 (*c* = 1.00, CH_2Cl_2); lit. $[\alpha]_D^{20}$ = -12.9 (*c* = 0.96, CH_2Cl_2)[1]

$C_{12}H_{20}BF_4NO_3$	calc.	C 46.03	H 6.44	N 4.47
(313.1)	found	C 45.84	H 6.56	N 4.40

IR (KBr): $\tilde{\nu}$ = 2920 (s), 2830 (w), 1625 (w, C=N$^+$), 1440 (m), 1360 (m), 1320 (w), 1275 (m), 1225 (m), 1150 (s), 1100 (vs), 1070 (vs), 1040 (vs), 1020 (vs), 800 (s), 830 (w), 810 (w) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.35-1.76 [m, 10 H, $C(CH_2)_5$], 3.68-3.85 (m, 2 H, 4-H), 3.88 (t, $^5J_{4,1'}$ = 2.1 Hz, 3 H, NCH_3), 4.33 (dd, $J_{1'',2''a}$ = 4.1, $^2J_{2''a,2''b}$ = 10.1 Hz, 1 H, 2'-H_a), 4.42 (dd, $J_{1'',2''b}$ = 6.9, $^2J_{2''a,2''b}$ = 10.1 Hz, 1 H, 2'-H_b), 4.78-4.92 (m, 2 H, 5-H), 5.25 (dd, $J_{1'',2''a}$ = 4.1, $J_{1'',2''b}$ = 6.9 Hz, 1 H, 1'-H).

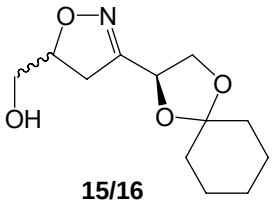


14

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 23.6, 23.9, 24.8, 33.7, 35.6 [5 t, $C(\underline{C}H_2)_5$], 36.6 (t, C-4), 39.4 (q, NCH_3), 66.5 (t, C-2'), 69.5 (d, C-1'), 70.5 (t, C-5), 113.4 [s, $\underline{C}(CH_2)_5$], 166.7 (s, C-3).

Experiment 13a-b

(5*S*, 1'*S*) and (5*R*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethyl-2-isoxazoline (15) and (16).



15/16

<u>a) Experiment 13a (YB 132):</u>

Reaction of hydroximoyl chloride **12** with allyl alcohol and diethylzinc in the presence of (-)-D-DIPT in $CHCl_3$.

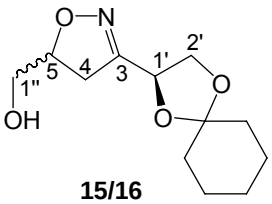
In analogy to lit[37], diethylzinc (7.6 mmol, 7.6 mL of 1.0 M solution in hexane) at 0 °C was added to a $CHCl_3$ (15 mL) solution of allyl alcohol (436 mg, 7.50 mmol) under nitrogen, and the mixture was stirred for 10 min. To this, a solution of (-)-D-DIPT (1.78 g, 7.60 mmol) in $CHCl_3$ (15 mL) was added and the mixture was stirred for 1 h. Diethylzinc (8.2 mL, 8.2 mmol) and a $CHCl_3$ (15 mL) solution of the hydroximoyl chloride **12** (4.11 g, 18.8 mmol, 2.5 eq) were added successively, and the resulting mixture was stirred at r.t. overnight. The reaction was quenched afterwards by addition of a sat. NH_4Cl solution (30 mL), then the mixture was partitioned against ether (3 x 100 mL). The solutes were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar, 20 °C) to give 5.0 g (d.r. 87:13)[a] of crude product **15/16**, which was chromatographed (SiO_2, column 3 cm x 15 cm, petroleum ether/ethyl acetate 1:1) to yield 1.64 g (91 %) of analytically and spectroscopically pure isoxazolines **15/16** as a colourless oil (d.r. 87:13 after purification).

$[\alpha]_D^{20}$ = 72.7 (*c* = 1.00, CH_2Cl_2)

[a] The determinations of the diastereomeric ratios (d.r.) here are based on the intensities of the separated signals pairs in ^{13}C NMR spectra of the crude product **15/16**.

$C_{12}H_{19}NO_4$	calc.	C 59.74	H 7.94	N 5.81
(241.3)	Found	C 59.59	H 8.02	N 5.62

IR : $\tilde{\nu}$ = 3420 (vs, OH), 2918 (s), 2840 (vs), 1740 (w), 1615 (m, C=N), 1440 (w), 1360 (w), 1325 (m), 1270 (m), 1220 (m), 1150 (vs), 1130 (m), 1090 (vs), 1060 (m), 910 (vs), 890 (vs), 1270 (m), 1220 (m), 1150 (vs), 1130 (m), 1090 (vs), 1060 (m), 910 (vs), 890 (vs), 870 (vs), 830 (m), 760 (m), 710 (m) cm^{-1}.



15/16

^{1}H NMR (500.1 MHz, $CDCl_3$, mixture of **15**/**16** = 85:13) : δ = 1.39-1.66 [m, 10 H, $C(CH_2)_5$], 2.66 (sb, 1 H, OH), 2.95 (dd, $J_{4a,4b}$ = 17.3, $J_{4a,5}$ = 7.4 Hz, 1 H, 4-H_a), 3.14 (dd, $J_{4a,4b}$ = 17.3, $J_{4b,5}$ = 11.0 Hz, 1 H, 4-H_b), 3.57 (dd, $J_{1''a,1''b}$ = 12.3, $J_{5,1''a}$ = 4.4 Hz, 1 H, 1''-H_a) , 3.78 (dd, $J_{1''a,1''b}$ = 12.3, $J_{5,1''b}$ = 3.1 Hz, 1 H, 1''-H_b), 3.98 (dd, $J_{2'a,2'a}$ = 8.6, $J_{1',2'a}$ = 5.8, 1 H, 2'-H_a), 4.20 (dd, $J_{2'a,2'a}$ = 8.6, $J_{1',2'b}$ = 6.8, 1 H, 2'-H_b), 4.73 ("dddd", $J_{4b,5}$ = 11.0, $J_{4a,5}$ = 7.4, $J_{5,1''a}$ = 4.1, $J_{5,1''b}$ = 3.6, 1 H, 5-H), 4.92 (t, $J_{1',2'b}$ = $J_{1',2'a}$ = 6.3 Hz, 1 H, 1'-H). -The signals of the minor diasteromer were overlapped by those of the major one.

^{13}C NMR (125.8 MHz, $CDCl_3$, mixture of **15**/**16** = 87:13) :
Major diastereomer: δ = 24.1, 24.3, 25.4, 35.0, 35.5 [5 t, $C(\underline{C}H_2)_5$], 36.2 (t, C-4), 63.8 (t, C-1''), 67.0 (t, C-2'), 71.1 (d, C-1'), 81.2 (d, C-5), 111.4 [s, $\underline{C}(CH_2)_5$], 159.2 (s, C-3).
Minor diastereomer: δ = 63.6 (t, C-1''), 66.8 (t, C-2'), 70.9 (d, C-1'), 81.4 (d, C-5), the other signals were overlapped by those of the major one.

b) Experiment 13b (YB 317):

Reaction of hydroximoyl chloride **12** with allyl alcohol and diethylzinc without DIPT in $CHCl_3$

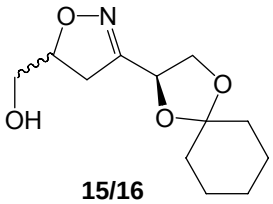
Diethylzinc (8.0 mmol, 8.0 mL of 1.0 M solution in hexane) at 0 °C was added to a $CHCl_3$ (15 mL) solution of allyl alcohol (436 mg, 7.50 mmol) under nitrogen, and the mixture was stirred for 15 min. Then diethylzinc (8.0 mL, 8.0 mmol) and a solution of hydroximoylchloride **12** (4.11 g, 18.8 mmol, 2.5 eq) in $CHCl_3$ (15 mL) were added successively, and the resulting solution was stirred at r.t. overnight.
The reaction was quenched with sat. NH_4Cl solution and then partitioned against ether (2 x 50 mL). The organic solutes were dried ($MgSO_4$) and concentrated *in vacuo* (5 mbar, 20 °C) to give 4.3 g (d.r. 45:55) of crude product **15/16**, which was chromatographed (SiO_2, column

3 cm x 13 cm, petroleum ether/ethyl acetate 6:4) to afford 1.41 g (78 %, d.r. 42:58 after purification) of analytically and spectroscopically pure isoxazolines **15/16** as a yellowish oil.

$[\alpha]_D^{20}$ = - 21.5 (*c* = 1.00, CH_2Cl_2)

c) Experiment 14 (MI 31, YB 311)

Reaction of hydroximoyl chloride **12** with allyl alcohol and diethylzinc in the presence of (+)-L-DIPT in $CHCl_3$.



15/16

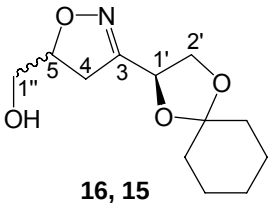
In analogy to lit.[37] diethylzinc (7.6 mmol, 7.6 mL of 1.0 M solution in hexane) at 0 °C was added to a $CHCl_3$ (15 mL) solution of allyl alcohol (436 mg, 7.50 mmol) under nitrogen, and the mixture was stirred for 10 min. then, solution of (+)-L-DIPT (1.78 g, 7.60 mmol) in $CHCl_3$ (15 mL) was added and the mixture was stirred for 1 h. Diethylzinc (8.2 mL, 8.2 mmol) and hydroximoylchloride **12** (4.11 g, 18.8 mmol, 2.5 eq) in $CHCl_3$ (15 mL) were added successively, and the resulting solution was stirred at r.t. overnight.

The reaction was quenched with sat. NH_4Cl solution and then partitioned against ether (3 x 100 mL). The organic solutes were dried ($MgSO_4$) and concentrated *in vacuo* (5 mbar, 20 °C) to give 2.92 g (d.r. 15:85) of crude products **15/16**, which was chromatographed (SiO_2, column 3 cm x 15 cm, petroleum ether/ethyl acetate 1:1) to afford 1.55 g (86 %, d.r. 15:85 after purification) of analytically and spectroscopically pure isoxazolines **15/16** as a yellowish oil.

$[\alpha]_D^{20}$ = - 63.0 (*c* = 1.00, CH_2Cl_2)

$C_{12}H_{19}NO_4$	calc.	C 59.74	H 7.94	N 5.81
(241.3)	Found	C 59.20	H 8.14	N 5.73

IR : $\tilde{\nu}$ = 3420 (vs), 2918 (s), 2840 (vs), 1740 (w), 1615 (m), 1440 (w), 1360 w), 1325 (m), 1270 (m), 1220 (m), 1150 (vs), 1130 (m), 1090 (vs), 1060 (m), 910 (vs), 890 (vs), 870 (vs), 830 (m), 760 (m), 710 (m) cm^{-1}.



16, 15

^{1}H NMR (250.1 MHz, $CDCl_3$, mixture of **15**/**16** = 15:85) : δ = 1.25-1.65 [m, 10 H, $C(CH_2)_5$], 2.28 (sb, 1 H, OH), 2.97 (ddd, $J_{4a,4b}$ = 17.3, $J_{4a,5}$ = 8.4, $J_{4a,1'}$ = 0.8 Hz, 1 H, 4-H_a), 3.14 (ddd, $J_{4a,4b}$ = 17.3, $J_{4b,5}$ = 10.3, $J_{4b,1'}$ = 0.8 Hz, 1 H, 4-H_b), 3.62 (dd, $J_{1''a,1''b}$ = 12.2, $J_{5,1''a}$ = 4.9 Hz, 1 H, 1''-H_a), 3.78 (dd, $J_{1''a,1''b}$ = 12.2, $J_{5,1''b}$ = 3.3 Hz, 1 H, 1''-H_b), 3.99 (dd, $J_{2'a,2'b}$ = 8.5, $J_{1',2'a}$ = 5.9, 1 H, 2'-H_a), 4.21 (dd, $J_{2'a,2'b}$ = 8.5, $J_{1',2'b}$ = 6.7, 1 H, 2'-H_b), 4.72 ("dddd", $J_{4b,5}$ = 10.3, $J_{4a,5}$ = 8.4, $J_{5,1''a}$ = 4.9, $J_{5,1''b}$ = 3.3, 1 H, 5-H), 4.92 (dd, $J_{1',2'b}$ = 6.7, $J_{1',2'a}$ = 5.9 Hz, 1 H, 1'-H). -The signals of the minor diasteromer were overlapped by those of the major one.

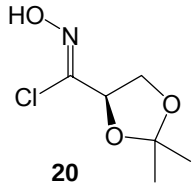
^{13}C NMR (125.8 MHz, $CDCl_3$, mixture of **15**/**16** = 15:85) :

Minor diastereomer **15**: δ = 63.7 (t, C-1''), 66.7 (t, C-2'), 70.8 (d, C-1'), 80.8 (d, C-5), the other signals were overlapped by those of the major one.

Major diastereomer **16**: δ = 23.8, 23.9, 25.0, 34.6, 35.3 [5 t, $C(\underline{C}H_2)_5$], 35.9 (t, C-4), 63.6 (t, C-1''), 66.7 (t, C-2'), 70.7 (d, C-1'), 81.0 (d, C-5), 111.1 [s, *i*-C of $C(\underline{C}H_2)_5$], 158.9 (s, C-3).

Experiment 15 (MI 41)

2,3-*O*-Isopropylidene-D-glycerohydroximoyl chloride (20), cf. lit. [1,10,41]

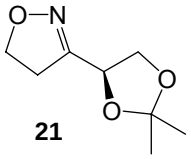


20

According to lit.[1], to a solution of 8.40 g (57.9 mmol) of 2,3-*O*-isopropylidene-D-glyceraldoxime **19** in 150 mL of abs. DMF one third of 8.51 g (63.7 mmol) of NCS was added portionwise. HCl gas (from HCl vapor on bottle with conc. HCl 37%) was then introduced into the solution several times, until the reaction started. After 5 min the rest of NCS was added and the reaction was kept with stirring for 1.5 h at room temp. To this mixture 150 mL of ice water was added, then it was extracted with ether (5 x 75 mL), washed with water (100 mL), the combined organic fractions were dried ($MgSO_4$). Finally, the solvent was evaporated (10 mbar) to yield 9.00 g ("87 %") of a yellowish oil which showed in according to NMR analysis the presence of ca. 2.5 % DMF and 0.6 % ether corresponding to 80 % yield (corrected, lit.[10] 89 %) of hydroximoyl chloride **20**, which was used without further purification for the next reaction. The analytical data fully complied with the literature values.[1,39,41]

Experiment 16 (MI 42)

(1'S)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4,5-dihydroisoxazole (21), cf. lit.[1,10,41]



21

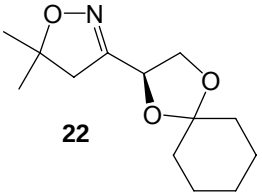
According to lit.[1] 9.00 g (50.1 mmol) of the hydroximoyl chloride **20** at - 10 °C was dissolved in 500 mL ether and ethylene was bubbled into the solution till saturation (40 min). The ethylene current was continued and 55 mL of a triethylamine solution in ether (1.0 M, 55 mmol) was added dropwise at a rate of 3 to 4 drops/min over 15 h. The mixture was quenched by addition of HCl (1.0 N, 200 mL), partitioned against ether (5 x 100 mL), and the combined organic phases were washed with water (200 mL), then dried ($MgSO_4$), and concentrated *in vacuo* (15 mbar) to give 4.60 g of a yellowish oil. This was filtered through silica gel (column 2 cm × 5 cm, petroleum ether/ethyl acetate 3:7) to afford 4.00 g (47 %; lit.: 83 %,[2] 86 %[41]) of the isoxazoline **21** as an analytically pure, bright-yellow oil. The spectroscopic and analytical data complied well with the literature values. 1,2,41

$[\alpha]_D^{20}$ = - 5.7 (*c* = 1.00, $CHCl_3$), lit. : $[\alpha]_D^{20}$ = - 5.8 (*c* = 2.56, $CHCl_3$) [10]

$[\alpha]_D^{20}$ = - 4.85 (*c* = 2.59, $CHCl_3$) [41]

Experiment 17 (YB 267)

(1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5,5-dimethyl-4,5-dihydroisoxazole (22)



22

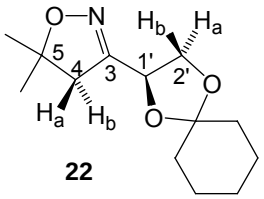
6.90 g (28.7 mmol) of the hydroximoyl chloride **12** at 0 °C was dissolved in 150 mL of abs. toluene. Ethylene was bubbled into the solution till saturation (30 min), then 31.55 mL of a triethylamine solution (31.55 mmol, 1.0 N in toluene) was added dropwise at a rate of 3 to 4 drops/min within 24 h. The mixture was quenched by addition of HCl (1.0 N, 100 mL) and partitioned against ether (4 x 60 mL); the combined organic phases were washed with $NaHCO_3$ (100 mL) and water (2 x 100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) to give a yellowish oil. Crystallization from hexane gave analytically and spectroscopically pure isoxazoline **22** (5.65 g, 82%) as a colourless soild (m.p. 65-67 °C).

$[\alpha]_D^{20}$ = - 2.3 (*c* = 1.00, CH_2Cl_2)

$C_{13}H_{21}NO_3$	calc.	C 65.24	H 8.84	N 5.85
(239.3)	found	C 65.12	H 8.87	N 5.74

IR (KBr): $\tilde{\nu}$ = 2920 (vs), 2840 (s), 1435 (m), 1360 (m), 1310 (m), 1270 (m), 1150 (s), 1080 (s), 1020 (m), 910 (m), 880 (mw) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.39, 1.43 (2 s, 3 H each, 5-C$\underline{H}_3$), 1.39-1.64 [m, 10 H, C$(CH_2)_5$], 2.75 (d, $J_{4a,4b}$ = 17.1 Hz, 1 H, 4-H_a), 2.86 (d, $J_{4a,4b}$ = 17.2 Hz, 1 H, 4-H_b), 3.96 (dd, $J_{1',2'a}$ = 6.1, $^2J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_a), 4.20 (dd, $J_{1',2'b}$ = 6.8, $^2J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_b), 4.91 (dd, $J_{1',2'a}$ = 6.1, $J_{1',2'b}$ = 6.8 Hz, 1 H, 1'-H).



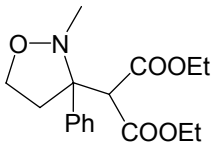
22

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 23.8, 23.9, 25.0, 34.6, 35.9 [5 t, C($\underline{C}H_2)_5$], 27.1 (2 q, 2 5-$\underline{C}H_3$), 45.4 (t, C-4), 66.7 (t, C-2'), 71.2 (d, C-1'), 110.8 [s, $\underline{C}(CH_2)_5$], 158.1 (s, C-3).

11.3 Addition of *C*-Nucleophiles to *N*-Methylisoxazolinium Salts

Experiment 18 (YB 8)

Diethyl 2-(2-Methyl-3-phenylisoxazolidin-3-yl)-malonate (23)



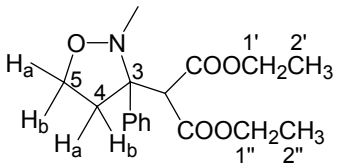
23

According to lit.,[2] 210 mg of NaH (55% in paraffin oil, 4.80 mmol) was added to 40 mL abs. THF under nitrogen at 0 °C, then 840 mg (5.26 mmol) of diethyl malonate in 5 mL THF was added dropwise over 5 min The mixture was stirred for 1 h, then 1.0 g (4.0 mmol) of isoxazolinium salt **3** was added. After 1 h of stirring at 0 °C, 20 mL of a sat. NH_4Cl solution was added, then the mixture was partitioned against ether (4 x 40 mL). The combined organic phases were washed with sat. $NaHCO_3$ solution (30 mL) and dried ($MgSO_4$) to give a yellowish oil. Crystallization from petroleum ether produced 1.21 g (94 %; lit.[2] 77 %) of analytically and spectroscopically pure isoxazolidine **23** in the form of colourless crystals (m. p. 43-45 °C, lit.[2] : 43-45 °C).

$C_{17}H_{23}NO_5$	calc.	C 63.54	H 7.21	N 4.36
(321.4)	found	C 63.27	H 7.26	N 4.23

IR (KBr): $\tilde{\nu}$ = 2948 (m), 1748 (vs, C=O), 1709 (s), 1436 (m), 1358 (m), 1310 (s), 1185 (m), 1120 (m), 1077 (m), 998 (m), 742 (m), 681 (m) cm^{-1}.

^1H NMR (250.1 MHz, $CDCl_3$): δ = 0.97 (t, $J_{1',2'}$ = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.3 (t, $J_{1'',2''}$= 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 2.27 (s, 3 H, $NC\underline{H}_3$), 2.82 (ddd, $J_{4a,4b}$ = 13.0, $J_{4a,5a}$ = 6.2, $J_{4a,5b}$ = 10.2 Hz, 1 H, 4-H_a), 3.66 (ddd, $J_{4a,4b}$ = 13.0, $J_{4b,5a}$ = 9.5, $J_{4b,5b}$ = 5.0 Hz, 1 H, 4-H_b), 3.90 (q, $J_{1',2'}$ = 7.2, 2 H, $OC\underline{H}_2CH_3$), 4.01 (ddd, $J_{4a,5a}$ = 6.2, $J_{4b,5a}$ = 9.5, $J_{5a,5b}$ = 7.6 Hz, 1 H, 5-H_a), 4.12 [s, 1 H, $C\underline{H}(CO_2Et)_2$], 4.14 (ddd, $J_{4a,5b}$ = 10.2, $J_{4b,5b}$ = 5.0, $J_{5a,5b}$= 7.6 Hz, 1 H, 5-H_b), 4.20 (t, $J_{1'',2''}$ = 7.2 Hz, 2 H, $OC\underline{H}_2CH_3$), 7.27-7.41 (m, 5 H, C_6H_5).

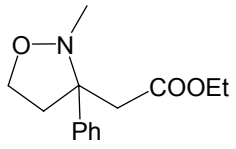


23

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7, 14.1 (2 q, 2 $OCH_2\underline{C}H_3$), 32.7 (t, C-4), 39.4 (q, NCH_3), 60.2 [d, $\underline{C}H(CO_2Et)_2$], 61.0, 61.7 (2 t, $O\underline{C}H_2CH_3$), 65.8 (t, C-5), 76.4 (s, C-3), 127.9, 128.1, 128.4 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 139.0 (s, *i*-C of C_6H_5), 166.9, 167.6 (2 s, 2 $\underline{C}O_2Et$).
The analytical and spectroscopic data complied with the literature values.[2]

Experiment 19 (YB 10)

3-Ethoxycarbonylmethyl-2-methyl-3-phenylisoxazolidine (24).



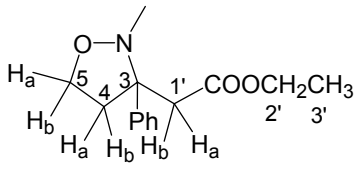
24

To a solution of diisopropylamine (abs. dist.; 1.2 mL, 8.0 mmol) in dry THF (20 mL) at 0 °C was added 5.2 mL of n-butyllithium (1.6 M, 8.0 mmol). The mixture was stirred for 0.5 h, then the solution was cooled to – 78° C and ethyl acetate (0.8 mL, 8.0 mmol) was added, followed after 0.5 h by addition of the isoxazolinium salt **3** (0.50 g, 2.0 mmol). The mixture was stirred at – 78 °C for 0.5 h and quenched with aqueous HCl (40 mL, 20 %). The mixture was added to water (40 mL), partitioned against ether (4 x 40mL), then washed with sat. NaCl solution (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* (5 mbar) to yield 470 mg (94 %, m. p. 42-43 °C) of analytically and spectroscopically pure isoxazolidine **24** as a colourless solid. Crystallization from petroleum ether gave colourless crystals, m. p. 42 °C.

$C_{14}H_{19}NO_3$	calc.	C 67.45	H 7.68	N 4.65
(249.31)	found	C 67.43	H 7.77	N 4.42

IR (KBr): $\tilde{\nu}$ = 2950 (m), 2860 (m), 1715 (vs, C=O), 1570 (w), 1480 (w), 1450 (s), 1440 (s), 1380 (m), 1360 (s), 1310 (vs), 1250 (m), 1210 (s), 1190 (m), 1160 (m), 1135 (s), 1110 (m), 1085 (m), 1070 (s), 1035 (m) cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.99 (t, $J_{2',3'}$ = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 2.35 (s, 3 H, $NC\underline{H}_3$), 2.79 (ddd, $J_{4a,4b}$ = 12.6, $J_{4a,5a}$ = 7.1, $J_{4a,5b}$ = 10.1 Hz, 1 H, 4-H_a), 2.85 (d, $J_{1'a,1'b}$= 14.3 Hz, 1 H, 1'-H_a), 2.88 (d, $J_{1'a,1'b}$ = 14.3 Hz, 1 H, 1'-H_b), 3.00 (m, 1 H, 4-H_b), 3.88 (q, $J_{2',3'}$ = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 4.10 (ddd, $J_{4a,5a}$ = 7.2, $J_{4b,5a}$ = 7.8, $J_{5a,5b}$ = 8.9 Hz, 1 H, 5-H_a), 4.23 (m, 1 H, 5-H_b), 7.25-7.40 (m, 5 H, C_6H_5).

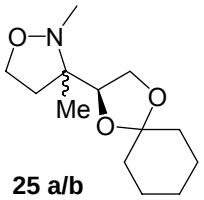


24

^{13}C NMR (250.1 MHz, $CDCl_3$): δ = 13.9 (q, $OCH_2\underline{C}H_3$), 34.1 (q, NCH_3), 39.4 (t, C-4), 60.2 (t, $O\underline{C}H_2CH_3$), 65.5 (t, C-5), 72.6 (t, $\underline{C}H_2CO_2Et$), 76.6 (s, C-3), 127.6, 127.7, 128.3 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 140.0 (s, *i*-C of C_6H_5), 170.9 (s, $\underline{C}O_2Et$).

Experiment 20 (YB 79)

(3*S*, 1'*S*)- and (3*R*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-2,3-dimethylisoxazolidine (25a and 25b), cf. lit.[1]



25 a/b

According to lit.[1] , to 50 mL abs. CH_2Cl_2 2.45 g (11.6 mmol) of the isoxazoline **13** and 1.89 g (12.5 mmol) of Me_3OBF_4 were added with stirring at room temp. overnight. The mixture was then concentrated *in vacuo* (10 mbar) to give 3.88 g of a brownish solid, which was dissolved in 30 mL of abs. THF. To this, 5.92 mL (17.8 mmol, 3.00 M, 1.4 eq) of MeMgBr in ether (Aldrich) was added under N_2 at – 78 °C. After stirring for 1 h, the mixture was hydrolyzed with sat. NH_4Cl solution (50 mL), poured into water (50 mL), and partitioned against ether (4 x 50 mL) The ether extracts were washed with sat. $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), and then concentrated *in vacuo* to give 4.12 g of a yellowish oil (d.r. 90:10), which was filtered through silica gel (2 cm × 5 cm, petroleum ether/ethyl acetate 1:1) to give 3.98 g of crude product with the isoxazolidines **25a/b**. Finally, the two diastereomers were separated by MPLC (petroleum ether/ethyl acetate 75:25), to yield 1.92 g (69 %) of (3*S*, 1'*S*)-3-methylisoxazolidine **25a** and 0.26 g (9 %) of (3*R*, 1'*S*)-3-methylisoxazolidine **25b** as analytically and spectroscopically pure, colourless oils in 78% yield (lit. 82 %[1]),

corresponding to a d.r. of 88:12 (lit.[1] 88:12). The analytical data fully complied with the values given in lit.[1]

A) Major diastereomer

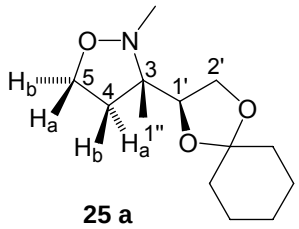
(3*S*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-2,3-dimethylisoxazolidine (25 a)

$[\alpha]_D^{20}$ = - 46.2 (*c* = 1.00, CH_2Cl_2) lit. : $[\alpha]_D^{20}$ = - 47.7 (*c* = 0.94, CH_2Cl_2)[1]

$C_{13}H_{23}NO_3$	calc.	C 64.70	H 9.61	N 5.80
(241.3)	found	C 64.79	H 9.61	N 5.58

IR (Film): $\tilde{\nu}$ = 2920 (vs), 2865 (vs), 1440 (s), 1390 (w), 1355 (s), 1320 (m), 1270 (s), 1240 (m), 1220 (m), 1150 (vs), 1140 (w), 1085 (vs), 1050 (m), 1025 (s), 1005 (s), 940 (w), 920 (s), 890 (w), 830 (w), 810 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.14 (s, 3 H, 1"-H), 1.34-1.65 [m, 10 H, $C(CH_2)_5$], 1.99 (ddd, $^2J_{4a,4b}$ = 12.4, $J_{4a,5a}$ = 6.8, $J_{4a,5b}$ = 9.8 Hz, 1 H, 4-H_a), 2.48 (ddd, $^2J_{4a,4b}$ = 12.4, $J_{4b,\,5a}$ = 9.3, $J_{4b,\,5b}$ = 5.1 Hz, 1 H, 4-H_b), 2.55 (s, 3 H, NCH_3), 3.84 (dd, $J_{1',2'a}$ = 6.4, $^2J_{2'a,2'b}$ = 8.5 Hz, 2'-H_a) and 3.87-3.92 (m, 5-H_a; together 2 H); 4.02 (dd, $J_{1',2'b}$ = 6.9, $^2J_{2'a,2'b}$ = 8.5 Hz, 2'-H_b and 4.05 ("ddd", $J_{4a,5b}$ = 9.7, $J_{4b,5b}$ = 5.1, $^2J_{5a,5b}$ = 7.9 Hz, 5-H_b; together 2 H); 4.10 ("dd", $J_{1',2'a}$ = 6.4, $J_{1',2'b}$ = 6.9 Hz, 1 H, 1'-H).



25 a

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.6 (q, C-1"), 24.1, 24.4, 25.6, 34.6, 36.3 [5 t, $C(\underline{C}H_2)_5$], 37.7 (t, C-4), 39.4 (q, NCH_3), 65.4 (t, C-5), 65.9 (t, C-2'), 68.3 (s, C-3), 78.2 (d, C-1'), 110.1 [s, $\underline{C}(CH_2)_5$].

B) Minor diastereomer

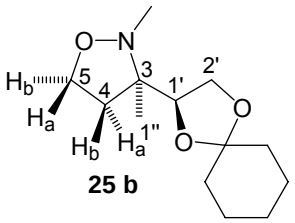
(3*R*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-2,3-dimethylisoxazolidine (25 b)

$[\alpha]_D^{20}$ = 31.2 (*c* = 0.960, CH_2Cl_2) lit. : $[\alpha]_D^{20}$ = 36.9 (*c* = 0.41, CH_2Cl_2)[1]

$C_{13}H_{23}NO_3$	calc.	C 64.70	H 9.61	N 5.80
(241.3)	found	C 64.58	H 9.45	N 5.72

IR (Film): $\tilde{\nu}$ = 2920 (vs), 2865 (vs), 1440 (s), 1390 (w), 1355 (s), 1320 (m), 1270 (s), 1240 (m), 1220 (m), 1150 (vs), 1140 (w), 1090 (vs), 1050 (m), 1025 (s), 1005 (s), 940 (w), 920 (s), 890 (w), 830 (w), 810 (m) cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$) : δ = 1.19 (s, 3 H, 1"-H), 1.39-1.71 [m, 10 H, $C(CH_2)_5$], 1.92 (ddd, $^2J_{4a,4b}$ = 12.5, $J_{4a,5a}$ = 6.0, $J_{4a,5b}$ = 9.3 Hz, 1 H, 4-H_a), 2.14 (ddd, $^2J_{4a,4b}$ = 12.4, $J_{4b,5a}$ = 9.4, $J_{4b,5b}$ = 5.8 Hz, 1 H, 4-H_b), 2.63 (s, 3 H, NCH_3), 3.72 (dd, $J_{1',2'a}$ = 7.2, $^2J_{2'a,2'b}$ = 8.5 Hz, 1 H, 2'-H_a), 3.80 (ddd, $J_{4a,5a}$ = 6.0, $J_{4b,5a}$ = 9.5, $^2J_{5a,5b}$ = 8.0 Hz, 1 H, 5-H_a), 3.92-3.97 (m, 1 H, 5-H_b), 4.01 (dd, $J_{1',2'b}$ = 6.7, $^2J_{2'a,2'b}$ = 8.4 Hz, 1 H, 2'-H_b), 4.07-4.10 (m, 1 H, 1'-H).

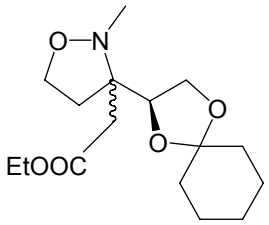


25 b

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 16.1 (q, C-1"), 24.2, 24.4, 25.6, 34.9, 36.4 [5 t, $C(\underline{C}H_2)_5$], 38.2 (t, C-4), 38.9 (q, NCH_3), 65.1 (t, C-5), 66.4 (t, C-2'), 67.2 (s, C-3), 77.8 (d, C-1'), 110.2 [s, $\underline{C}(CH_2)_5$].

Experiment 21 (YB 205)

(3*R*, 1'*S*)- and (3*S*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-3-ethoxycarbonylmethyl-2-methylisoxazolidine (26a and 26b)



26 a/b

2.00 g (9.47 mmol) of the isoxazoline **13** and 1.54 g (10.4 mmol) of Me_3OBF_4 under nitrogen were added to 40 mL abs. CH_2Cl_2 at room temp. and left with stirring overnight. The mixture was then concentrated *in vacuo* (room temp./10 mbar) to give a brownish solid of the isoxazolinium salt **14**. Next, in a separate flask diisopropylamine (abs., dist.) (4.8 mL, 32 mmol) in dry THF (35 mL) and n-butyllithium (1.6 M, 20.8 mL, 32 mmol) under nitrogen were mixed at 0 °C with stirring for 0.5 h. The solution was cooled to – 78 °C and ethyl acetate (3.2 mL, 32 mmol) was added, which after 0.5 h was followed by addition of the crude isoxazolinium salt in 20 mL of THF. The mixture was stirred at – 78 °C for 1.0 h, quenched with HCl (40 mL, 20 %), then poured into water (40 mL) and partitioned against ether (5 x 40mL). The combined organic phases were washed with sat. NaCl solution (40 mL), dried ($MgSO_4$), and then concentrated *in vacuo* to give 2.90 g of a yellowish oil (d.r. 68:32 from ^{13}C NMR), which was filtered through silica gel (column 2 cm × 5 cm, petroleum ether/ethyl acetate 4:6). The two diastereomers were then separated by MPLC (column petroleum

ether/ethyl acetate 4:1) to yield 1.58 g (55 %) of (3*R*,1'*S*)-isoxazolidine **26a** and 0.77 g (27 %) of (3*S*,1'*S*)-isoxazolidine **26b** as analytically and spectroscopically pure, colourless oils. The diastereomeric ratio after MPLC separation was 67:33, combined yield 82 %.

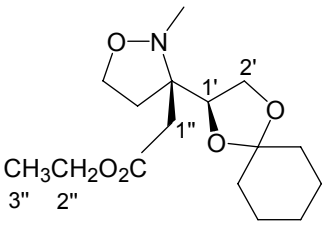
a) Major diastereomer

(3*R*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)- 3-ethoxycarbonylmethyl-2-methylisoxazolidine (26a)

$[\alpha]_D^{20}$ = - 21.2 (*c* = 1.00, CH_2Cl_2)

$C_{16}H_{27}NO_5$	calc.	C 61.32	H 8.68	N 4.47
(301.4)	found	C 61.28	H 8.73	N 4.19

IR (KBr): $\tilde{\nu}$ = 2920 (vs), 2870 (s), 2840 (s), 1740 (vs, C=O), 1450 (w), 1440 (m), 1355 (s), 1320 (m), 1270 (m), 1290 (m), 1150 (s), 1090 (vs), 1055 (m), 1015 (vs), 920 (s), 890 (w), 830 (m), 715 (m) cm^{-1}.



26 a

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27 (t, $J_{2'',3''}$ = 7.1Hz, 3 H, $OCH_2C\underline{H}_3$), 1.36-1.69 [m, 10 H, $C(CH_2)_5$], 2.21 (ddd, $J_{4a,4b}$ = 12.6, $J_{4a,5a}$ = 9.0, $J_{4a,5b}$= 5.2 Hz, 1 H, 4-H_a); 2.52 (ddd, $J_{4a,4b}$ = 12.6, $J_{4b,5a}$ = 6.8, $J_{4b,5b}$ = 9.1 Hz, 4-H_b) and 2.53 (d, $J_{1''a,1''b}$= 14.3 Hz, 1"-H_a; together 2 H); 2.70 (d, $J_{1''a,1''b}$ = 14.3 Hz, 1"-H_b) and 2.70 (s, $NC\underline{H}_3$; together 4 H); 3.84 (ddd, $J_{4b,5a}$ = 6.8, $J_{4a,5a}$ = 9.0, $J_{5a,5b}$ = 7.8 Hz, 1 H, 5-H_a), 3.90 (ddd, $J_{4a,5b}$ = 5.2, $J_{4b,5b}$ = 9.1, $J_{5a,5b}$ = 7.8 Hz, 1 H, 5-H_b), 3.96 (dd, $J_{1',2'a}$ = 7.9, $J_{2'a,2'b}$ = 15.7 Hz, 1 H, 2'-H_a), 4.03 (dd, $J_{1',2'b}$ = 6.5 Hz, $J_{2'a,2'b}$ = 14.4, 1 H, 2'-H_b), 4.14 (q, $J_{2'',3''}$ = 7.1, 2 H, $OC\underline{H}_2CH_3$), 4.43 (dd, $J_{1',2'a}$ = 7.9 Hz, $J_{1',2'b}$ = 6.5 Hz, 1 H, 1'-H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.1 (q, $OCH_2\underline{C}H_3$), 23.8, 24.0, 25.2, 34.3, 35.8 [5 t, $C(CH_2)_5$], 36.0 (t, $\underline{C}H_2CO_2Et$), 36.3 (t, C-4), 39.9 (q, NCH_3), 60.6 (t, $O\underline{C}H_2CH_3$), 64.8 (t, C-5), 65.0 (t, C-2'), 66.9 (s, C-3), 77.5 (d, C-1'), 109.9 [s, $\underline{C}(CH_2)_5$], 171.5 (s, $\underline{C}O_2Et$).

b) Minor diastereomer

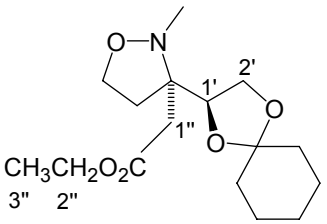
(3*S*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)- 3-ethoxycarbonylmethyl-2-methylisoxazolidine (26b)

$[\alpha]_D^{20}$ = 2.73 (*c* = 0.75, CH_2Cl_2)

$C_{16}H_{27}NO_5$	calc.	C 61.32	H 8.68	N 4.47
(301.39)	found	C 61.13	H 8.64	N 4.27

IR (KBr): $\tilde{\nu}$ = 2920 (vs), 2870 (s), 2840 (s), 1735 (vs, C=O), 1450 (w), 1440 (m), 1355 (s), 1320 (m), 1270 (m), 1290 (m), 1120 (s), 1090 (vs), 1055 (m), 1015 (vs), 920 (s), 890 (w), 830 (m), 715 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27 (t, $J_{2'',3''}$ = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.30-1.62 [m, 10 H, $C(CH_2)_5$], 2.11 (ddd, $J_{4a,4b}$ = 12.7, $J_{4a,5a}$ = 9.5, $J_{4a,5b}$ = 6.4 Hz, 1 H, 4-H_a), 2.52 (d, $J_{1''a,1''b}$ = 13.9 Hz, 1 H, 1"-H_a), 2.68 (d, $J_{1''a,1''b}$ = 13.9 Hz, 1"-H_b) and 2.70 (ddd, $J_{4a,4b}$ = 12.7, $J_{4b,5a}$ = 5.4, $J_{4b,5b}$ = 9.0 Hz, 4-H_b) and 2.72 (s, $NC\underline{H}_3$; together 5 H); 3.79 (ddd, $J_{4b,5a}$ = 5.4, $J_{4a,5a}$ = 9.4, $J_{5a,5b}$ = 7.8 Hz, 5-H_a) and 3.79 (dd, $J_{1',2'a}$ = 7.0, $J_{2'a,2'b}$ = 8.7 Hz, 2'-H_a; together 2 H); 3.85 (ddd, $J_{4a,5b}$ = 6.3, $J_{4b,5b}$ = 9.0, $J_{5a,5b}$ = 7.8 Hz, 1 H, 5-H_b), 4.01 (dd, $J_{1',2'b}$ = 6.9, $J_{2'a,2'b}$ = 8.7 Hz, 1 H, 2'-H_b), 4.14 (q, $J_{2'',3''}$ = 7.2, 2 H, $OC\underline{H}_2CH_3$), 4.21 (dd, $J_{1',2'a}$ = 7.1, $J_{1',2'b}$ = 6.9 Hz, 1 H, 1'-H).



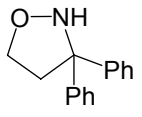
26 b

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.5 (q, $OCH_2\underline{C}H_3$), 24.1, 24.4, 25.5, 34.6, 36.3 [5 t, $C(CH_2)_5$], 35.5 (t, C-4), 36.0 (t, $\underline{C}H_2CO_2Et$), 38.2 (q, NCH_3), 60.9 (t, $O\underline{C}H_2CH_3$), 65.4 (t, C-5), 66.2 (t, C-2'), 68.7 (s, C-3), 78.0 (d, C-1'), 110.4 [s, $\underline{C}(CH_2)_5$], 172.0 (s, $\underline{C}O_2Et$).

11.4 Addition of *C*-Nucleophiles to Isoxazolines

Experiment 22 (YB 263)

3,3-Diphenylisoxazolidine (27).



27

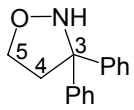
In analogy to lit [55a,136], to a solution of 500 mg (3.40 mmol) of isoxazoline **2** in abs. CH_2Cl_2 (40 mL) 2.30 (10.2 mmol, 3 eq) of $ZnBr_2$ was added under nitrogen at – 78 °C, followed by addition of 886 mg (10.2 mmol, 3 eq) of lithium bromide (LiBr) and 5.37 mL (10.2 mmol, 3 eq)

of phenyllithium (PhLi) successively at the same temperature. The mixture was left with stirring overnight and the temperature was allowed to rise to room temp.. Then sat. $NaHCO_3$ solution (30 mL) was added; the mixture was partitioned against ether (3 x 40 mL), washed with brine (50 mL), then dried ($MgSO_4$), and concentrated *in vacuo* (10 mbar/20 °C) to give 900 mg of a yellowish oil. This was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 7:3), concentrated again *in vacuo*, and then purified by MPLC (petroleum ether/ethyl acetate 85:15) to afford 455 mg of starting material **2** and 40 mg (5 %) of analytically and spectroscopically pure isoxazolidine **27** as a colourless solid (m.p. 90-92 °C), Crystallization from petroleum ether gave colourless crystals, suitable for crystal structure determination (see Appendix 12.1.1).

$C_{15}H_{15}NO$	calc.	C 79.98	H 6.71	N 6.22
(225.3)	found	C 79.74	H 6.75	N 5.96

IR (KBr): $\tilde{\nu}$ = 2955 (w), 2888 (w), 1489 (m), 1449 (m, C=N), 1405 (w), 1267 (w), 1059 (m), 1032 (m), 748 (s), 693 (vs), 658 (s), 594 (s) cm^{-1}.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.91 (t, $J_{4,5}$ = 7.3 Hz, 2 H, 4-H), 4.00 (t, $J_{4,5}$ = 7.3 Hz, 2 H, 5-H), 7.19-7.51 (m, 5 H, C_6H_5).

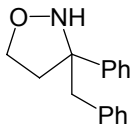


27

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.7 (t, C-4), 69.5 (s, C-5), 72.5 (s, C-3), 126.2, 126.8, 128.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 142.8 (s, *i*-C of C_6H_5).

Experiment 23 (YB 158)

3-Benzyl-3-phenyl-isoxazolidine (28).



28

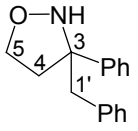
To a stirred solution of the isoxazoline **2** (630 mg, 4.28 mmol) and BF_3•OEt_2 (1.60 mL, 12.8 mmol, 3 eq) in abs. THF (30 mL), BenzylMgCl (12.83 mL, 12.83 mmol, 3 eq) was added at – 78 °C over 10 min. The mixture was left with stirring for 4 h and the reaction temperature was allowed to increase to room temp., then the mixture was quenched with sat. $NaHCO_3$ solution (20 mL) and extracted with ether (3 x 40 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* (10 mbar, 20 °C) to

give 1.7 g of crude product. Purification was perfomed by MPLC (petroleum ether/ethyl acetate 7:3) to afford 500 mg of the starting material **2** and 100 mg (10 %) of analytically and spectroscopically pure isoxazolidine **42** as a colourless solid (m. p. 79-80 °C).

$C_{16}H_{17}NO$	calc.	C 80.30	H 7.16	N 5.85
(239.3)	found	C 80.20	H 7.22	N 5.49

IR (KBr): $\tilde{\nu}$ = 3030 (w), 2873 (w), 1704 (w), 1496 (w), 1274 (m), 1208 (w), 1015 (vs), 735 (s), 697 (vs) cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$) : δ = 2.39 (ddd, $J_{4a,4b}$ = 12.1, $J_{4a,5a}$ and $J_{4a,5b}$ = 9.2 and 6.5 Hz, 1 H, 4-H_a), 2.51 (ddd, $J_{4a,4b}$ = 12.1, $J_{4a,5a}$ and $J_{4a,5b}$ = 8.7 and 6.2 Hz, 1 H, 4-H_b), 3.01 (d, $J_{1'a,1'b}$ = 13.4 Hz, 1 H, 1'-H_a), 3.13 (d, $J_{1'a,1'b}$ = 13.4 Hz, 1 H, 1'-H_b), 3.84-3.93 (m, 1 H, 5-H_a), 4.04-4.11 (m, 1 H, 5-H), 6.82-7.35 (m, 10 H, 2 C_6H_5).

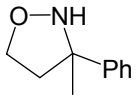


28

^{13}C NMR (125.7 MHz, $CDCl_3$) : δ = 39.7 (t, C-4), 46.1 (t, C-1'), 70.5 (t, C-5), 71.1 (s, C-3), 127.0, 127.1, 127.6, 128.3, 128.6, 131.0 (6 d, *o-, m-, p*-C of 2 C_6H_5), 137.0, 141.5 (s, *i*-C of 2 C_6H_5).

Experiment 24 (YB 225)

3-Methyl-3-phenyl-isoxazolidine (29)



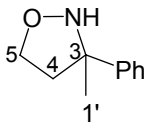
29

To a solution of 1.30 g (8.83 mmol) of the isoxazoline **2** in abs. CH_2Cl_2 (20 mL) 2.8 mL (22 mmol, 2.5 eq) of BF_3•OEt_2 was added and kept with stirring for 10 min at – 78 °C under nitrogen. Then 14.7 mL (22.1 mmol, 2.5 eq) of MeLi·LiBr was added and the temperature was allowed to rise to room temp. within 4 h. The mixture was quenched with sat. $NaHCO_3$ solution (30 mL), partitioned against ether (3 x 40 mL), dried ($MgSO_4$), and concentrated in vacuo (10 mbar, 20 °C) to give 1.6 g of yellowish oil. This was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) and then purified by MPLC (petroleum ether/ethyl acetate 7:3) to afford, after evaporation of solvent, 1.19 g (83 %) of analytically and spectroscopically pure isoxazolidine **29** as colourless oil.

$C_{10}H_{13}NO$	calc.	C 73.59	H 8.18	N 8.56
(163.2)	found	C 73.39	H 8.03	N 8.58

IR : $\tilde{\nu}$ = 2971 (m), 2876 (m), 1495 (w), 1446 (m), 1055 (w), 853 (w), 765 (m), 702 (s), 631 (vs) cm^{-1}.

^1H NMR (300.1 MHz, $CDCl_3$) : δ = 1.51 (s, 3 H, 1'-H), 2.34 (ddd, $J_{4a,4b}$ = 12.0, $J_{4a,5a}$ = 6.3, $J_{4a,5b}$ = 8.8 Hz, 1 H, 4-H_a), 2.53 (ddd, $J_{4a,4b}$ = 12.0, $J_{4b,5a}$ = 8.9, $J_{4b,5b}$ = 6.1 Hz, 1 H, 4-H_b), 3.90 (ddd, $J_{5a,5b}$ = 7.7, $J_{5a,4a}$ = 6.3, $J_{4b,5a}$ = 8.9 Hz, 1 H, 5-H_a), 4.07 (ddd, $J_{5a,5b}$ = 7.7, $J_{4a,5b}$ = 8.8, $J_{4b,5b}$ = 6.1 Hz, 1 H, 5-H_b), 7.24-7.49 (m, 5 H, C_6H_5).

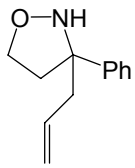


29

^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 27.4 (q, C-1'), 43.0 (t, C-4), 66.9 (s, C-3), 70.5 (t, C-5), 125.7, 127.0, 128.4 (3 d, *o-, m-, p*-C of C_6H_5), 144.8 (s, *i*-C of C_6H_5).

Experiment 25 (YB 142)

3-Allyl-3-phenylisoxazolidine (30)



30

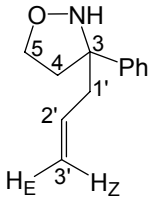
Typical Procedure TP 2, Addition of Allylmagnesium Bromide to Isoxazolines

To a solution of the isoxazoline **2** (500 mg, 3.40 mmol) in abs. THF (30 mL), 2.15 mL (20.5 mmol, 5.0 eq) of BF_3•OEt_2 (Aldrich) was added with stirring at – 78 °C for 10 min. Then 20.5 mL (20.5 mmol, 5.0 eq) of allylmagnesium bromide (1.0 M, Aldrich) was added within 5 min. The mixture was left with stirring 5 h (controlled by TLC) and the temperature was allowed to rise to 0 °C, quenched with sat. $NaHCO_3$ solution (30 mL) and then partitioned against ether (3 x 40 mL), washed with brine (30 mL), dried ($MgSO_4$), and then concentrated *in vacuo* (room temp./10 mbar) to give 730 mg of the crude isoxazolidine **30** as a yellowish oil. This was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) and then purified by MPLC (petroleum ether/ethyl acetate 4:1) to afford after evaporation of solvent 420 mg (65 %) of analytically and spectroscopically pure isoxazolidine **30** as a colourless solid (m. p. 29-30 °C). Crystallization from hexane produced colourless crystals of **30** (m.p. 30 °C, see Appendix 12.1.2).

$C_{12}H_{15}NO$	calc.	C 76.16	H 7.99	N 7.40
(189.2)	found	C 75.95	H 8.03	N 7.24

IR : $\tilde{\nu}$ = 3196 (w), 3061 (w), 2976 (w), 2878 (w), 1638 (w), 1494 (m), 1447 (m), 1316 (w), 1052 (m), 997 (m), 915 (s), 860 (m), 762 (s), 634 (vs), 599 (w) cm^{-1}.

^{1}H NMR (500.2 MHz, $CDCl_3$) : δ = 2.44-2.54 (m, 2 H, 4-H), 2.54-2.60 (m, 2 H, 1'-H) 2.89-2.93 (m, 1 H, 5-H_a), 4.04-4.06 (m, 1 H, 5-H_b), 5.00-5.05 (m, 2 H, 3'-H), 5.62 ("dddd", $J_{1'a,2'}$ = 7.1, $J_{1'b,2'}$ = 7.5, $J_{2',3'E}$ = 10.2, $J_{2',3'Z}$ = 14.7 Hz, 1 H, 2'-H), 7.24-7.42 (m, 5 H, C_6H_5).



30

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 40.0 (t, C-4), 44.5 (t, C-1'), 69.7 (s, C-3), 70.5 (t, C-5), 118.6 (t, C-3'), 126.3, 127.1, 128.3 (3 d, *o-, m-, p*-C of C_6H_5), 133.4 (d, C-2'), 142.9 (s, *i*-C of C_6H_5).

Experiment 25a (YB 243)

Preparation of **3-Allyl-3-phenylisoxazolidine (30)** using $ZnBr_2$ as a Lewis acid

Scale: 1.00 g (6.80 mmol) isoxazoline **2**
4.60 g (20.4 mmol, 3 eq) $ZnBr_2$
20.4 mL (20.4 mmol, 3 eq) allylmagnesium bromide (1.0 M in THF, Aldrich)
30 mL abs. THF

The reaction was performed according to TP 2, work-up was done after stirring for 3.5 h and the temperature was left to raise to room temperature, to afford 1.25 g of a yellowish oil, which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 1.08 g of crude **30**. Purification by MPLC (petroleum ether/ethyl acetate 7:3) afforded, after evaporating the solvent, 980 mg (76 %) of analytically and spectroscopically pure isoxazolidines **30** as a colourless soild (m. p. 29-30 °C).

Experiment 25b (YB 169)

Preparation of **3-Allyl-3-phenylisoxazolidine (30)** using $ZnCl_2$ as a Lewis acid

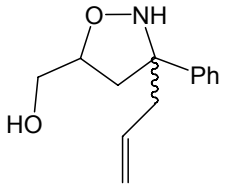
Scale: 1.00 g (6.80 mmol) isoxazoline **2**
0.93 g (6.8 mmol, 1 eq) $ZnCl_2$

13.6 mL (13.6 mmol, 2 eq) allylmagnesium bromide (1.0 M in THF, Aldrich)
30 mL abs. THF

The reaction was performed according to TP 2 using $ZnCl_2$ at –78 °C, work-up was done after stirring overnight and the temperature was left to raise to room temperature, to afford 980 mg of a yellowish oil, which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 890 mg of crude **30**. Purification by MPLC (petroleum ether/ethyl acetate 85:15) afforded, after evaporating the solvent, 760 mg (59 %) of pure isoxazolidines **30** as a colourless soild (m. p. 28-30 °C).

Experiment 26 (YB 269)

(3-Allyl-5-hydroxymethyl-3-phenylisoxazolidine (31a/b, cis and trans)



31

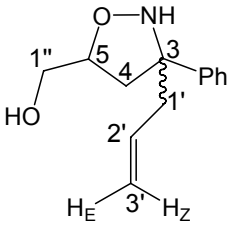
Scale: 790 mg (4.49 mmol) isoxazoline **9**
3.01 g (13.4 mmol, 3 eq) $ZnBr_2$
13.4 mL (13.4 mmol, 3 eq) allylmagnesium bromide (1.0 M in THF, Aldrich)
40 mL abs. THF

The reaction was performed according to TP 2 with $ZnBr_2$ instead of BF_3•OEt_2, work-up was done after stirring overnight to afford 1.31 g of a yellowish oil (d.r. 86:14), which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) to give 1.09 g of crude **31**. Purification by MPLC (petroleum ether/ethyl acetate 7:3) afforded, after evaporating the solvent, 619 mg (63 %, d.r. 85:15) of analytically and spectroscopically pure cis/trans-isoxazolidines **31** as colourless oil.

$C_{13}H_{17}NO_2$	calc.	C 71.21	H 7.81	N 6.39
(219.3)	found	C 71.36	H 8.02	N 6.06

IR: $\tilde{\nu}$ = 3370 (sb), 2697 (w), 1735 (m), 1639 (w), 1495 (m), 1243 (m), 1043 (s), 999 (m), 915 (s), 849 (m), 812 (s), 762 (s), 700 (vs) cm^{-1}.

^{1}H NMR (500.2 MHz, $CDCl_3$, mixture 85:15) : δ = 2.17 (dd, $J_{4a,4b}$ = 12.3, $J_{4a,5}$ = 7.5 Hz, 1 H, 4-H_a), 2.54 (dt, $J_{1',2'}$ = 7.5, $J_{1',3'}$ = 1.2 Hz, 2 H, 1'-H), 2.60 (dd, $J_{4a,4b}$ = 12.3, $J_{4b,5}$ = 8.0 Hz, 1 H, 4-H_b), 3.47 (dd, $J_{5,\ 1''a}$ = 5.7, $J_{1''a,1''b}$ = 12.2 Hz, 1 H, 1''-H_a), 3.65 (dd, $J_{5,1''a}$ = 3.1, $J_{1''a,1''b}$ = 12.2 Hz, 1 H, 1''-H_b), 3.88 (ddt, $J_{4,5}$ = 7.7, $J_{5,1''a}$ = 5.7, $J_{5,1''b}$ = 3.0 Hz, 1 H, 5-H), 4.95-5.03 (m, 2 H, 3'-H), 5.56 (''dddd'', $J_{1'a,2'}$ = 7.2, $J_{1'b,2'}$ = 7.4, $J_{2',3'E}$ = 10.5, $J_{2',3'Z}$ = 14.6 Hz, 1 H, 2'-H), 7.20-7.42 (m, 5 H, C_6H_5).



31

The signals of the minor diasteromer were completely overlapped by those of the major one.

^{13}C NMR (75.5 MHz, $CDCl_3$, mixture 85:15) :

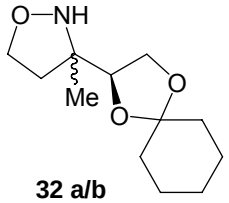
A) Major diastereomer **31a** : δ = 40.8 (t, C-4), 44.5 (t, C-1'), 63.7 (t, C-6), 70.6 (s, C-3), 82.2 (t, C-5), 118.7 (t, C-3'), 126.4, 127.3, 128.3 (3 d, *o-, m-, p*-C of C_6H_5), 133.5 (d, C-2'), 142.5 (s, *i*-C of C_6H_5).

B) Minor diastereomer 31b **: δ = 63.5 (t, C-6), 70.3 (s, C-3), 118.8 (t, C-3'), 126.2, 127.0 (2 d, *o-, m-, p*-C of C_6H_5), 133.1 (d, C-2'), 143.1 (s, *i*-C of C_6H_5).**

The other signals coincided with those of the major diastereomer.

Experiment 27 (YB 236)

(3*R*, 1'*S*)- and (3*S*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-3-methylisoxazolidine (32a and 32b)



32 a/b

To a solution of 360 mg (1.49 mmol) of the isoxazoline **13** in abs. CH_2Cl_2 (15 mL) 0.57 mL (4.5 mmol, 3.0 eq) of BF_3•OEt_2 was added and the mixture was kept with stirring for 10 min at – 78 °C under nitrogen. To this mixture 3.0 mL (4.5 mmol, 3.0 eq) of MeLi·LiBr (1.5 M in ether, Aldrich) was added and then the temperature was allowed to rise to room temp. within 4 h. The mixture was then quenched with sat. $NaHCO_3$ solution (20 mL), partitioned against ether (3 x 40 mL), dried ($MgSO_4$), and concentrated *in vacuo* (10 mbar, 20 °C) to give 370 mg of yellowish oil (d.r. 68:32, taken from ^{13}C NMR spectrum of the crude product). This was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) and then purified by MPLC (petroleum ether/ethyl acetate 8:2) to afford, after evaporating the solvent, 224 mg (58 %) of analytically and spectroscopically pure isoxazolidine **32a** as a colourless oil, and 106 mg (27 %) of analytically and spectroscopically pure isoxazolidine **32b**, also as a colourless oil, in 85 % total yield; d.r. after MPLC separation was 68:32.

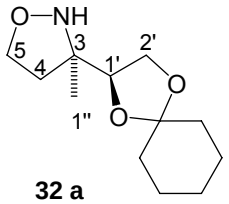
A) Major diastereomer

(3*R*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-3-methylisoxazolidine (32a)[a]

$[\alpha]_D^{20}$ = - 8.90 (*c* = 1.00, CH_2Cl_2)

$C_{12}H_{21}NO_3$	calc.	C 63.41	H 9.31	N 6.16
(227.3)	found	C 63.39	H 9.37	N 6.21

IR : $\tilde{\nu}$ = 2932 (s), 2860 (m), 1448 (m), 1365 (m), 1252 (m), 1144(s), 1098 (vs), 1038 (s), 847 (s), 650 (m), 622 (s) cm^{-1}.



32 a

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.24 (s, 3 H, 1"-H), 1.31-1.64 [m, 10 H, $C(CH_2)_5$], 1.88 (ddd, $J_{4a,4b}$ = 12.2, $J_{4a,5a}$ and $J_{4a,5b}$ = 5.4 and 8.1 Hz, 1 H, 4-H_a), 2.31 (ddd, $J_{4a,4b}$ = 12.2, $J_{4b,5a}$ and $J_{4b,5b}$ = 7.8 and 8.4 Hz, 1 H, 4-H_b), 3.81 (dd, $J_{1',2'a}$ = 7.3, $J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_a), 3.87-3.95 (m, 2 H, 5-H), 4.04 (dd, $J_{1',2'b}$ = 6.7, $J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_b), 4.18 (t, $J_{1',2'}$ = 7.0 Hz, 1 H, 1'-H).

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 22.5 (q, C-1"), 23.8, 24.0, 25.2, 34.6, 36.0 [5t, $C(\underline{C}H_2)_5$], 38.5 (t, C-4), 64.7 (s, C-3), 65.6 (t, C-5), 71.5 (t, C-2'), 79.1 (d, C-1'), 109.7 [s, *i*-C of $C(\underline{C}H_2)_5$].

B) Minor diastereomer

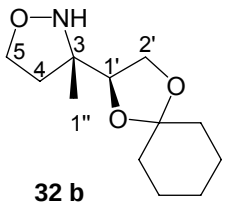
(3*S*, 1'*S*)-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-3-methylisoxazolidine (32b)

$[\alpha]_D^{20}$ = 3.40 (*c* = 1.00, CH_2Cl_2)

$C_{12}H_{21}NO_3$	calc.	C 63.41	H 9.31	N 6.16
(227.3)	found	C 63.30	H 9.30	N 6.11

IR : $\tilde{\nu}$ = 2935 (m), 2887 (m), 2857 (w), 1442 (m), 1366 (m), 1279 (m), 1165(m), 1096 (vs), 1032 (s), 851 (s) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.17 (s, 3 H, 1"-H), 1.31-1.68 [m, 10 H, C(CH_2)$_5$], 1.84 (ddd, $J_{4a,4b}$ = 11.9, $J_{4a,5a}$ and $J_{4a,5b}$ = 6.4 and 8.6 Hz, 1 H, 4-H_a), 2.31 (ddd, $J_{4a,4b}$ = 11.9, $J_{4b,5a}$ and $J_{4b,5b}$ = 6.0 and 9.0 Hz, 1 H, 4-H_b), 3.74 (dd, $J_{1',2'a}$ = 5.6, $J_{2'a,2'b}$ = 7.3 Hz, 1 H, 2'-H_a), 3.79-3.92 (m, 1 H, 5-H_a), 3.98-4.05 (m, 1 H, 5-H_b), 4.09 (dd, $J_{1',2'b}$ = 5.6, $J_{2'a,2'b}$ = 7.3 Hz, 2'-H_b) and 4.13 (t, $J_{1',2'}$ = 5.6 Hz, 1'-H; together 2 H).

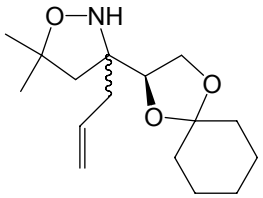


32 b

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 21.5 (q, C-1"), 23.7, 24.0, 25.2, 34.3, 36.0 [5 t, C($\underline{C}H_2$)$_5$], 37.1 (t, C-4), 66.0 (s, C-3), 66.2 (t, C-5), 71.7 (t, C-2'), 76.9 (d, C-1'), 110.3 [s, *i*-C of C($\underline{C}H_2$)$_5$].

Experiment 28 (YB 270)

(3*R*, 1'*S*)- and (3*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5,5-dimethylisoxazolidine (33a and 33b)



33 a/b

Scale: 500 mg (2.09 mmol) isoxazoline **22**
1.41 g (6.27 mmol, 3 eq) $ZnBr_2$
6.27 mL (6.27 mmol, 3 eq) allylmagnesium bromide
30 mL abs. THF

The reaction was performed according to TP 2 with $ZnBr_2$ instead of BF_3•OEt_2; work-up was done after stirring overnight to afford 680 mg of a yellowish oil (d.r. 88:12, from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 610 mg and then purified by MPLC (petroleum ether/ethyl acetate 9:1) to afford, after evaporation of the solvent, 495 mg (73 %) of analytically and spectroscopically pure isoxazolidine **33a** as a colourless oil, and 78 mg (11 %) of analytically and spectroscopically pure isoxazolidine **33b**, also as a colourless oil, in 84 % total yield (d.r. 87:13).

A) Major diastereomer **33a**

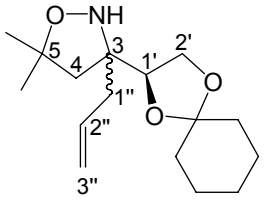
$[\alpha]_D^{20}$ = - 42.6 (*c* = 0.540, CH_2Cl_2)

[a] Assignment of configuration done by treatment of 64 with $LiAlH_4$ to afford 41, see Exp. 39.

$C_{16}H_{27}NO_3$	calc.	C 68.29	H 9.67	N 4.98
(281.4)	found	C 68.32	H 9.63	N 4.92

IR : $\tilde{\nu}$ = 3199 (m), 2933 (s), 2862 (m), 1685 (w), 1448 (m), 1433 (w), 1366 (m), 1332 (w), 1162 (s), 1104 (vs), 1042 (s), 927 (vs), 847 (w), 808 (m) cm^{-1}.

^{1}H NMR (300.1 MHz, $CDCl_3$) : δ = 1.28-1.68 [m, 16 H, $C(CH_2)_5$, $C(CH_3)_2$], 1.71 (d, $J_{4a,4b}$ = 12.1 Hz, 1 H, 4-H_a), 2.06 (ddt, $J_{1"a,1"b}$ = 14.1, $J_{1"a,2"}$ = 8.2, $J_{1"a,3"E}$ = $J_{1"a,3"Z}$ = 1.0 Hz, 1"-H_a) and 2.13 (d, $J_{4a,4b}$ = 12.1 Hz, 4-H_b; together 2 H); 2.47 (ddt, $J_{1"a,1"b}$ = 14.1, $J_{1"b,2"}$ = 6.3, $J_{1"b,3"E}$ = $J_{1"b,3"Z}$ = 1.4 Hz, 1"-H_b), 3.55-3.60 (m, 1 H, 2'-H_a), 4.04 (dd, $J_{2'b,2'b}$ = 8.1, $J_{1',2'b}$ = 6.8 Hz, 1 H, 2'-H_b), 4.13 (t, $J_{1',2'b}$ = 6.9 Hz, 1 H, 1'-H), 5.04-5.13 (m, 2 H, 3"-H), 5.95 ("dddd", $J_{1"a,2"}$ = 8.3, $J_{1"b,2"}$ = 6.3, $J_{2",3"E}$ = 10.3, $J_{2",3"Z}$ = 16.7, 1 H, 2"-H).



33a

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 24.1, 24.3, 25.5, 34.8, 36.4 [5 t, C(<u>C</u>$H_2)_5$] , 26.7, 27.5 [2 q, C(<u>C</u>$H_3)_2$], 42.5 (t, C-1"), 46.6 (t, C-4), 66.6 (t, C-2'), 70.6 (s, C-3), 74.9 (d, C-1'), 84.9 (s, C-5), 110.3 [s, <u>C</u>$(CH_2)_5$], 118.0 (t, C-3"), 134.6 (d, C-2").

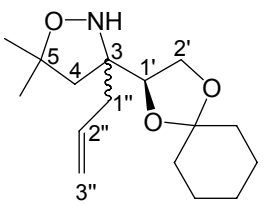
<u>B) Minor diastereomer **33b**</u>

$[\alpha]_D^{20}$ = 14.2 (*c* = 1.00, CH_2Cl_2)

$C_{16}H_{27}NO_3$	calc.	C 68.29	H 9.67	N 4.98
(281.4)	found	C 68.29	H 9.72	N 4.89

IR: $\tilde{\nu}$ = 2933 (s), 2861 (m), 1685 (w), 1448 (m), 1367 (m), 1162 (s), 1144 (s), 1100 (vs), 1040 (s), 927 (v), 847 (w), 788 (w) cm^{-1}.

^{1}H NMR (300.1 MHz, $CDCl_3$) : δ = 1.26-1.68 [m, 16 H, $C(CH_2)_5$, $C(CH_3)_2$], 1.91 (d, $J_{4a,\ 4b}$ = 12.6 Hz, 1 H, 4-H_a), 2.11 (d, $J_{4b,\ 4a}$ = 12.6 Hz, 1 H, 4-H_b), 2.22-2.33 (m, 1 H, 1"-H_a), 2.44 (ddt, $J_{1"a,1"b}$ = 14.2, $J_{1"b,2"}$ = 7.4, $J_{1"b,3"E}$ = $J_{1"b,3"Z}$ = 1.3 Hz, 1"-H_b), 3.83-3.89 (m, 1 H, 2'-H_a), 4.01 (dd, $J_{2'a,2'b}$ = 8.5, $J_{1',2'b}$ = 6.6 Hz, 1 H, 2'-H_b), 4.17 (dd, $J_{1',2'a}$ = 7.8, $J_{1',2'b}$ = 6.6 Hz, 1 H, 1'-H), 5.11-5.20 (m, 2 H, 3"-H), 5.85 ("dddd", $J_{1"a,2"}$ = 10.5, $J_{1"b,2"}$ = 7.4, $J_{2",3"E}$ = 14.9, $J_{2",3"Z}$ = 16.7 Hz, 1 H, 2"-H).



33b

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 24.2, 24.4, 25.6, 35.1, 36.5 [5 t, C($\underline{C}H_2)_5$], 26.7 [2 q, C($\underline{C}H_3)_2$], 41.5 (t, C-1"), 48.0 (t, C-4), 65.6 (t, C-2'), 68.8 (s, C-3), 77.6 (d, C-1'), 84.9 (s, C-5), 109.7 [s, $\underline{C}(CH_2)_5$], 119.5 (t, C-3"), 133.8 (d, C-2").

Experiment 28a (YB 271)

Preparation of **(3*R*, 1'*S*)- and (3*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5,5-dimethylisoxazolidine (33a and 33b)** using $ZnCl_2$ as a Lewis acid

Scale: 500 mg (2.09 mmol) isoxazoline **22**
0.855 g (6.27 mmol, 3 eq) $ZnCl_2$
6.27 mL (6.27 mmol, 3 eq) allylmagnesium bromide
30 mL abs. THF

The reaction was performed according to TP 2 with $ZnCl_2$; work-up was done after stirring overnight to afford 630 mg of a yellowish oil (d.r. 87:13, from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 572 mg and then purified by MPLC (petroleum ether/ethyl acetate 9:1) to afford, after evaporation of the solvent, 460 mg (67 %) of analytically and spectroscopically pure isoxazolidine **33a** as a colourless oil, and 63 mg (9 %) of analytically and spectroscopically pure isoxazolidine **33b**, also as a colourless oil, in 76 % total yield (d.r. 88:12).

Experiment 28b (YB 144)

Preparation of **(3*R*, 1'*S*)- and (3*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5,5-dimethylisoxazolidine (33a and 33b)** using BF_3•OEt_2 as a Lewis acid

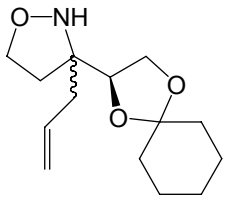
Scale: 275 mg (1.15 mmol) isoxazoline **22**
0.36 ml (3.5 mmol, 3 eq) BF_3•OEt_2
3.5 mL (3.5 mmol, 3 eq) allylmagnesium bromide
20 mL abs. THF

The reaction was performed according to TP 2 with BF_3•OEt_2; work-up was done after stirring for 4 h to afford 405 mg of a yellowish oil (d.r. 83:17, from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) to give 370 mg and then purified by MPLC (petroleum ether/ethyl acetate 8:2) to

afford, after evaporation of the solvent, 209 mg (65 %) of pure isoxazolidine **33a** as a colourless oil, and 40 mg (12 %) of pure isoxazolidine **33b**, also as a colourless oil, in 77 % total yield (d.r. 84:16).

Experiment 29 (YB 151)

(3*S*, 1'*S*)- and (3*R*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl) isoxazolidine (34a and 34b)



34 a/b

Scale: 1.00 g (4.73 mmol) isoxazoline **13**
3.19 g (14.2 mmol, 3 eq) $ZnBr_2$
14.2 mL (14.2 mmol, 3 eq) allylmagnesium bromide
50 mL abs. THF

The reaction was performed according to TP 2 with $ZnBr_2$ instead of BF_3•OEt_2; work-up was done after stirring the reaction mixture for 4 h to afford 1.59 g of a yellowish oil (d.r. 80:20; from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 1.37 g of crude isoxazolines **34a/b**. This was purified by MPLC (petroleum ether/ethyl acetate 9:1) to afford, after evaporation of the solvent, 766 mg (64 %) of analytically and spectroscopically pure isoxazolidine **34a** as a colourless oil, and 204 mg (17 %) of analytically and spectroscopically pure isoxazolidine **34b**, a colourless oil likewise, in 81 % total yield (d.r. 79:21).

Major diastereomer

(3*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl) isoxazolidine (34a)[a]

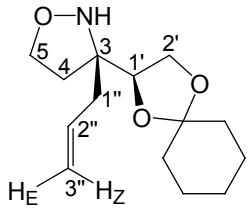
$[\alpha]_D^{20}$ = - 24.1 (*c* = 0.58, CH_2Cl_2)

$C_{14}H_{23}NO_3$	calc.	C 66.37	H 9.15	N 5.53
(253.3)	found	C 66.53	H 9.18	N 5.43

IR : $\tilde{\nu}$ = 2932 (s), 2860 (m), 1638 (w), 1447 (m), 1365 (m), 1332 (w), 1281 (m), 1252 (w), 1232 (w), 1162 (m), 1099 (vs), 1040 (s), 1001 (m), 926 (vs), 909 (s), 880 (m), 847 (w) cm^{-1}.

[a] Assignments done by assignment of configuration at C-3 of **79** by crystal structure determination. see Exp. 77.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.39-1.64 [m, 10 H, $(CH_2)_5$], 1.86-1.99 (m, 1 H, 4-H_a), 2.10 (dd, $J_{1"a,1"b}$ = 14.0, $J_{1"a,2'}$ = 8.3 Hz, 1 H, 1"-H_a), 2.26 (ddd, $J_{4a,4b}$ = 11.7, $J_{4b,5a}$ = 8.9, $J_{4a,5b}$ = 5.5 Hz, 1 H, 4-H_b), 2.42 (dd, $J_{1"b,1"a}$ = 13.9, $J_{1"b,2'}$ = 5.9 Hz, 1 H, 1"-H_b), 3.61-3.75 (m, 2'-H_a) and 3.75-3.82 (m, 5-H_a; together 2 H); 3.86-4.03 (m, 1 H, 5-H_b), 4.07 (dd, $J_{1',2'b}$ = 6.8, $J_{2'b,2'a}$ = 8.3 Hz, 1 H, 2'-H_b), 4.16 (t, $J_{1',2'}$ = 6.9 Hz, 1 H, 1'-H), 5.09 ("d", $J_{2",3"Z}$ = 17.0 Hz, 3"-H_z) and 5.13 ("d", $J_{2",3"E}$ = 10.4 Hz, 3"-H_E; togther, 2 H), 5.91 ("dddd", $J_{1"a,2"}$ = 8.3, $J_{1"b,2"}$ = 6.3, $J_{2",3"E}$ = 10.2, $J_{2",3"Z}$ = 16.8 Hz, 1 H, 2"-H).



34a

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 24.1, 24.3, 25.5, 34.8, 36.5 [5 t, C($\underline{C}H_2)_5$], 35.2 (t, C-4), 41.0 (t, C-1"), 66.4 (t, C-2'), 68.7 (s, C-3), 72.1 (t, C-5), 76.1 (d, C-1'), 110.4 [s, $\underline{C}(CH_2)_5$], 118.9 (t, C-3"), 134.1 (d, C-2").

Minor diastereomer

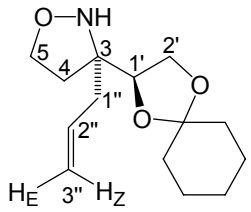
(3*R*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl) isoxazolidine (34b)

$[\alpha]_D^{20}$ = 3.9 (*c* = 0.57, CH_2Cl_2)

$C_{14}H_{23}NO_3$	calc.	C 66.37	H 9.15	N 5.53
(253.3)	found	C 66.04	H 9.23	N 5.22

IR : $\tilde{\nu}$ = 2932 (s), 2860 (m), 1638 (w), 1447 (m), 1365 (m), 1332 (w), 1281 (m), 1252 (w), 1232 (w), 1162 (m), 1099 (vs), 1040 (s), 1001 (m), 926 (vs), 909 (s), 880 (m), 847 (w) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.38-1.63 [m, 10 H, $(CH_2)_5$], 2.05 (ddd, $J_{4a,4b}$ = 12.4, $J_{4a,5b}$ and $J_{4a,5b}$ = 7.9 and 5.4 Hz, 1 H, 4-H_a), 2.27 (ddd, $J_{4a,4b}$ = 12.5, $J_{4b,5a}$ and $J_{4b,5b}$ = 7.8 and 8.1 Hz, 1 H, 4-H_b), 2.38 (d, $J_{1",2"}$ = 7.3, 2 H, 1"-H), 3.81-3.87 (m, 5-H_a) and 3.83 (dd, $J_{1',2'a}$ = 7.4, $J_{2'a,2'b}$ = 8.5 Hz, 2'-H_a) and 3.86-3.96 (m, 5-H_b; together 3 H); 4.03 (dd, $J_{1',2'b}$ = 6.7, $J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_b), 4.22 (t, $J_{1',2'}$ = 7.0 Hz, 1 H, 1'-H), 5.16 ("ddt", $J_{1"a,3"Z}$ = $J_{1"b,3"Z}$ = 1.4, $J_{2",3"Z}$ = 16.8, $J_{3"E,3"Z}$ = 3.4 Hz, 3"-H_Z) and 5.19 ("ddt", $J_{1"a,3"E}$ = $J_{1"b,3"E}$ = 1.0, $J_{2",3"E}$ = 10.2, $J_{3"E,3"Z}$ = 2.0 Hz, 3"-H_E; together 2 H); 5.85 (ddt, $J_{1"a,2"}$ = $J_{1"b,2"}$ = 7.5, $J_{2",3"E}$ = 10.3, $J_{2",3"Z}$ = 16.9 Hz, 1 H, 2"-H).

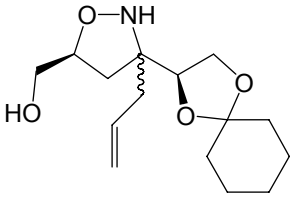


34b

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 24.1, 24.3, 25.6, 34.9, 36.5 [5 t, C($\underline{C}H_2)_5$], 36.0 (t, C-4), 40.8 (t, C-1"), 65.7 (t, C-2'), 67.3 (s, C-3), 72.2 (t, C-5), 78.8 (d, C-1'), 109.8 [s, $\underline{C}(CH_2)_5$], 120.0 (t, C-3"), 133.1 (d, C-2").

Experiment 30 (YB 191)

(3*R*, 5*S*, 1'*S*)- and (3*S*, 5*S*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (35a and 35b).



35 a/b

Scale: 1.71 g (7.10 mmol) isoxazoline **15/16** (mixture 87:13)
2.90 g (21.3 mmol, 3 eq) $ZnCl_2$
21.3 mL (21.3 mmol, 3 eq) allylmagnesium bromide
50 mL abs. THF

The reaction was performed according to TP 2 with $ZnCl_2$ instead of BF_3•OEt_2 and at 0 °C. Work-up was done after stirring for 12 h to afford 2.04 g of a yellowish oil (d.r. 85:15), this was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:9) to give 1.96 g of crude **35a/b** and then purified by MPLC (petroleum ether/ethyl acetate 6:4).
This afforded, after evaporation of the solvent, 1.30 g (65 %) of analytically and spectroscopically pure isoxazolidine **35a** as a colourless solid (m. p. 92-93 °C), and 260 mg (13 %) of analytically and spectroscopically pure isoxazolidine **35b**, also as a colourless oil, in 78 % total yield (d.r. 85:15). Crystallization of **35a** from hexan/chloroform gave colourless crystals (m. p. 92 °C), suitable for crystal structure analysis, from which the relative and absolute configuration of **35a** was derived (see appendix 12.1.3 for data).

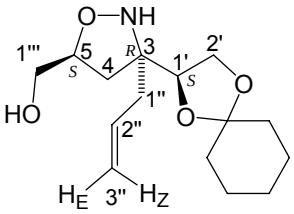
Major diastereomer

(3*R*, 5*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (35a)

$[\alpha]_D^{20}$ = 15.6 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{25}NO_4$	calc.	C 63.58	H 8.89	N 4.94
(283.4)	found	C 63.57	H 8.78	N 4.89

IR : $\tilde{\nu}$ = 3487 (b, w), 3239 (w), 2933 (s), 2887 (m), 2846 (m), 1640 (w), 1485 (m), 1450 (m), 1433 (m), 1284 (m), 1163 (m), 1143 (vs), 1070 (s), 1055 (s), 969 (m), 935 (s), 914 (vs), 827 (s), 770 (w), 696 (s) cm^{-1}.



35a

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.39-1.64 [m, 10 H, $(CH_2)_5$], 2.05 (dd, $J_{4a,4b}$ = 12.7, $J_{4a,5}$ = 7.8 Hz, 1 H, 4-H_a), 2.14 (dd, $J_{4b,4a}$ = 12.7, $J_{4b,5}$ = 7.7 Hz, 1 H, 4-H_b), 2.34 (d, $J_{1",2"}$ = 6.7, 2 H, 1"-H), 3.64 (dd, $J_{5,\ 1'''a}$ = 6.4, $J_{1'''a,1'''b}$ = 12.3 Hz, 1 H, 1'''-H_a), 3.70 (dd, $J_{5,1'''b}$ = 3.1, $J_{1'''a,1'''b}$ = 12.3 Hz, 1 H, 1'''-H_b), 3.90 (dd, $J_{1',2'a}$ = 7.3, $J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_a), 4.03 (dd, $J_{1',2'b}$ = 6.7, $J_{2'b,2'a}$ = 8.6 Hz, 1 H, 2'-H_b), 4.10-4.17 (m, 1 H, 5-H), 4.20 (dd, $J_{1',2'a}$ = 7.3, $J_{1',2'b}$ = 6.7 Hz, 1 H, 1'-H), 5.15-5.21 (m, 2 H, 3"-H), 5.85 (ddt, $J_{1"a,2"}$ = $J_{1"b,2"}$ = 7.5, $J_{2",3"E}$ = 10.2, $J_{2",3"Z}$ = 16.9 Hz, 1 H, 2"-H).

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 23.7, 23.8, 25.2, 34.5, 35.9 [5 t, C($\underline{C}H_2)_5$], 34.9 (t, C-4), 40.0 (t, C-1"), 63.0 (t, C-1'''), 66.1 (t, C-2'), 67.7 (s, C-3), 78.1 (d, C-1'), 83.2 (d, C-5), 109.7 [s, $\underline{C}(CH_2)_5$], 119.9 (t, C-3"), 132.6 (d, C-2").

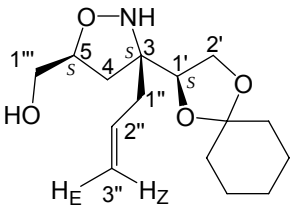
Minor diastereomer

(3*S*, 5*S*, 1'*S*)-3-Allyl-3-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (35b)

$[\alpha]_D^{20}$ = - 48.3 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{25}NO_4$	calc.	C 63.58	H 8.89	N 4.94
(283.4)	found	C 63.35	H 8.89	N 4.78

IR : $\tilde{\nu}$ = 3378 (b, m), 2932 (s), 2860 (m), 1638 (w), 1448 (m), 1366 (m), 1282 (m), 1162 (s), 1100 (vs), 1044 (s), 926 (s), 848 (w), 631 (vs) cm^{-1}.



35b

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.40-1.67 [m, 10 H, $(CH_2)_5$], 1.74 (dd, $J_{4a,4b}$ = 12.1, $J_{4a,5}$ = 8.2 Hz, 1 H, 4-H_a), 2.10 (ddt, $J_{1"a,1"b}$ = 14.2, $J_{1"a,2"}$ = 8.2, $J_{1"a,3"E}$ = $J_{1"a,3"Z}$ = 1.1 Hz, 1 H, 1"-H_a), 2.34 (dd, $J_{4b,4a}$ = 12.1, $J_{4b,5}$ = 8.3 Hz, 1 H, 4-H_b), 2.44 (ddt, $J_{1"a,1"b}$ = 14.2, $J_{1"b,2"}$ = 6.4 Hz, $J_{1"b,3"E}$ = $J_{1"b,3"Z}$ = 1.5 Hz, 1 H, 1"-H_b); 3.62 (dd, $J_{5,1'''a}$ = 5.6, $J_{1'''a,1'''b}$ = 12.3, 1'''-H_a) and 3.66 (dd, $J_{1',2'a}$ = 7.0, $J_{2'a,2'b}$

= 8.3, Hz, 2'-H_a; together 2 H); 3.81 (dd, $J_{5,1'''b}$ = 2.8, $J_{1'''a,1'''b}$ = 12.3 Hz, 1 H, 1'''-H_b); 4.06 (dd, $J_{1',2'b}$ = 6.8, $J_{2'a,2'b}$ = 8.3 Hz, 2'-H_b) and 4.10 ("dddd", $J_{4a,5}$ = 8.1, $J_{4b,5}$ = 8.2, $J_{5,1'''a}$ = 5.5, $J_{5,1'''b}$ = 2.7 Hz, 5-H) and 4.13 (t, $J_{1',2'}$ = 6.9 Hz, 1'-H; together 3 H); 5.07-5.13 (m, 2 H, 3"-H), 5.92 (dddd, $J_{1''a,2''}$ = 8.3, $J_{1''b,2''}$ = 6.4, $J_{2'',3''E}$ = 10.2, $J_{2'',3''Z}$ = 16.6 Hz, 1 H, 2"-H).

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 23.7, 24.0, 25.0, 34.4, 36.1 [5 t, C($\underline{C}H_2)_5$], 36.0 (t, C-4), 40.8 (t, C-1"), 63.0 (t, C-1'''), 66.0 (t, C-2'), 69.4 (s, C-3), 75.6 (d, C-1'), 84.3 (d, C-5), 110.1 [s, $\underline{C}(CH_2)_5$], 118.5 (t, C-3"), 133.8 (d, C-2").

Experiment 30a (YB 189)

Preparation of **(3*R*, 5*S*, 1'*S*)- and (3*S*, 5*S*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (35a and 35b)** using $ZnBr_2$ as a Lewis acid

Scale: 600 mg (2.49 mmol) isoxazoline **15/16** (mixture 80:20)
1.12 g (4.97 mmol, 2 eq) $ZnBr_2$
7.46 mL (7.46 mmol, 3 eq) allylmagnesium bromide
30 mL abs. THF

The reaction was performed according to TP 2 with $ZnBr_2$ as a Lewis acid at 0 °C. Work-up was done after stirring overnight to afford 705 mg of a yellowish oil (d.r. 76:24), this was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:9) to give 655 mg of crude **35a/b** and then purified by MPLC (petroleum ether/ethyl acetate 7:3).
This afforded, after evaporation of the solvent, 385 mg (55 %) of pure isoxazolidine **35a** as a colourless solid (m. p. 92-94 °C), and 109 mg (15 %) of pure isoxazolidine **35b**, as a colourless oil, in 70 % total yield (d.r. 78:22).

Experiment 30b (YB 187)

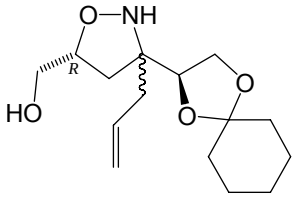
Preparation of **(3*R*, 5*S*, 1'*S*)- and (3*S*, 5*S*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (35a and 35b)** using BF_3•OEt_2 as a Lewis acid

Scale: 850 mg (3.52 mmol) isoxazoline **15/16** (mixture 80:20)
1.11 g (10.6 mmol, 3 eq) BF_3•OEt_2

10.6 mL (10.6 mmol, 3 eq) allylmagnesium bromide
30 mL abs. THF

The reaction was performed according to TP 2 with BF_3•OEt_2 as a Lewis acid at – 78 °C. Work-up was done after stirring for 4 h to afford 1.13 g of a yellowish oil (d.r. 77:23), this was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 1:9) to give 1.04 g of crude **35a/b** and then purified by MPLC (petroleum ether/ethyl acetate 7:3).
This afforded, after evaporation of the solvent, 470 mg (47 %) of pure isoxazolidine **35a** as a colourless solid (m. p. 92-93 °C), and 155 mg (16 %) of pure isoxazolidine **35b**, as a colourless oil, in 63 % total yield (d.r. 75:25).

Experiment 31 (YB 188)
(3*R*, 5*R*, 1'*S*)- and (3*S*, 5*R*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine (36a and 36b).



36 a/b

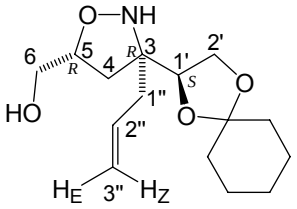
Scale: 465 mg (1.93 mmol) Isoxazolines **15/16** (mixture 15:85)
526 mg (3.85 mmol, 2 eq) $ZnCl_2$
5.8 mL (5.8 mmol, 3 eq) AllylMgBr
30 mL abs. THF

The reaction was performed according to TP 2 with $ZnCl_2$ instead of BF_3•OEt_2 and at 0 °C, work-up was done after stirring overnight to afford 500 mg of a yellowish oil (d.r. 85:15, taken from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 1:1) to give 485 mg of crude product **36a/b**. This was purified by MPLC (petroleum ether/ethyl acetate 7:3) to afford after evaporation of the solvent, 335 mg (61 %) of analytically and spectroscopically pure isoxazolidine **36a** as a colourless oil, and 103 mg (19 %) of analytically and spectroscopically pure isoxazolidine **36b**, also as a colourless oil, in 80 % total yield (d.r. 81:19).

A) Major diastereomer (3*R*, 5*R*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine 36a

$[\alpha]_D^{20}$ = - 48.8 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{25}NO_4$	calc.	C 63.58	H 8.89	N 4.94
(283.4)	found	C 63.64	H 8.95	N 4.79



36a

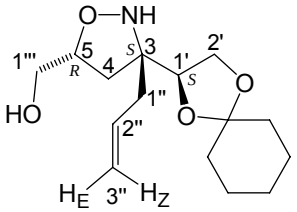
^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.25-1.69 [m, 10 H, $(CH_2)_5$], 1.97 (dd, $J_{4a,4b}$ = 12.4, $J_{4a,5}$ = 7.0 Hz, 4-H_a), and 2.02 (dd, $J_{4b,4a}$ = 12.4, $J_{4b,5}$ = 6.8 Hz, 4-H_b; together 2 H), 2.11 (ddt, $J_{1"a,1"b}$ = 14.2, $J_{1"a,2"}$ = 8.2, $J_{1"a,3"E}$ = $J_{1"a,3"Z}$ = 1.2 Hz, 1 H, 1"-H_a), 2.41 (ddt, $J_{1"a,1"b}$ = 14.2, $J_{1"b,2"}$ = 6.5 Hz, $J_{1"b,3"E}$ = $J_{1"b,3"Z}$ = 1.4 Hz, 1 H, 1"-H_b), 3.57-3.61 (m, 1'"-H_a) and 3.60-3.65 (m, 1'"-H_b) and 3.67 (dd, $J_{1',2'a}$ = 6.9, $J_{2'a,2'b}$ = 8.2, Hz, 2'-H_a; together, 3 H), 4.06 (dd, $J_{1',2'b}$ = 6.8, $J_{2'a,2'b}$ = 8.2 Hz, 2'-H_b), 4.17 (t, $J_{1',2'}$ = 6.9 Hz, 1'-H) and 4.20-4.29 (m, 5-H; together 2 H), 5.06-5.17 (m, 2 H, 3"-H), 5.92 (dddd, $J_{1",2"}$ = 8.2, $J_{1"b,2"}$ = 6.4, $J_{2",3"E}$ = 10.4, $J_{2",3"Z}$ = 16.8 Hz, 1 H, 2"-H).

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 23.8, 23.9, 25.1, 34.3, 35.8 [5 t, C($\underline{C}H_2)_5$], 35.5 (t, C-4), 39.9 (t, C-1"), 63.1 (t, C-1'"), 66.0 (t, C-2'), 68.9 (s, C-3), 75.7 (d, C-1'), 82.7 (d, C-5), 110.2 [s, $\underline{C}(CH_2)_5$], 118.9 (t, C-3"), 133.3 (d, C-2").

B) Minor diastereomer (3*S*, 5*R*, 1'*S*)-3-Allyl-(1',2'-*O*-Cyclohexylidenedioxyethyl)-5-hydroxymethylisoxazolidine 36b

$[\alpha]_D^{20}$ = 14.9 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{25}NO_4$	calc.	C 63.58	H 8.89	N 4.94
(283.4)	Found	C 63.87	H 8.98	N 4.87



36b

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.32-1.68 [m, 10 H, $(CH_2)_5$], 2.05 (dd, $J_{4a,4b}$ = 12.5, $J_{4a,5}$ = 7.9 Hz, 1 H, 4-H_a), 2.14 (dd, $J_{4b,4a}$ = 12.4, $J_{4b,5}$ = 7.9 Hz, 1 H, 4-H_b), 2.34 (d, $J_{1",2"}$ = 6.6, 2 H, 1"-H), 3.59 (dd, $J_{5,1'"a}$ = 6.7, $J_{1'"a,1'"b}$ = 12.3 Hz, 1 H, 1'"-H_a), 3.70 (dd, $J_{5,1'"b}$ = 3.0, $J_{1'"a,1'"b}$ = 12.3 Hz, 1 H, 1'"-H_b), 3.89 (dd, $J_{1',2'a}$ = 6.9, $J_{2'a,2'b}$ = 8.6 Hz, 1 H, 2'-H_a), 4.03 (dd, $J_{1',2'b}$ = 6.7, $J_{2'b,2'a}$ = 8.6 Hz, 1 H, 2'-H_b), 4.10-4.21 (m, 1 H, 5-H), 4.19 (dd, $J_{1',2'a}$ = 7.3, $J_{1',2'b}$ = 6.7 Hz, 1 H, 1'-H), 5.11-5.23 (m, 2 H, 3"-H), 5.85 (ddt, $J_{1",2"}$ = $J_{1"b,2"}$ = 7.3, $J_{2",3"E}$ = 10.1, $J_{2",3"Z}$ = 17.0 Hz, 1 H, 2"-H).

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 24.1, 24.3, 25.5, 35.0, 36.2 [5 t, C($\underline{C}H_2)_5$], 37.1 (t, C-4), 40.2 (t, C-1"), 63.4 (t, C-1'"), 65.5 (t, C-2'), 67.9 (s, C-3), 76.9 (d, C-1'), 83.5 (d, C-5), 110.1 [s, $\underline{C}(CH_2)_5$], 120.1 (t, C-3"), 132.9 (d, C-2").

Experiment 31a (YB 313)

Preparation of **((3*RS*,5*RS*)-3-Allyl-3-(*S*)-1,4-dioxa-spiro[4.5]dec-2-yl-isoxazolidin-5-yl)-methanol (35 a/b)** using $ZnBr_2$ as Lewis acid

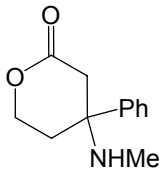
Scale: 550 mg (2.30 mmol) Isoxazolines **16/15** (mixture 85:15)
1.55 mg (4.90 mmol) $ZnBr_2$
9.2 mL (9.2 mmol) AllylMgBr
30 mL abs. THF

The reaction was performed according to TP 2 with $ZnBr_2$ at 0 °C, work-up was done after stirring overnight to afford 645 mg of a yellowish oil (d.r. 78:22, taken from ^{13}C NMR spectrum of the crude product), which was filtered through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 4:6) to give 605 mg of crude product **35a/b**. This was purified by MPLC (petroleum ether/ethyl acetate 7:3) to afford after evaporation of the solvent, 395 mg (61 %) of analytically and spectroscopically pure isoxazolidine **35b** (as the major diastereomer here) as a colourless oil, and 110 mg (17 %) of analytically and spectroscopically pure isoxazolidine **35a** (as the minor diastereomer here), also as a colourless oil, in 78 % total yield (d.r. 78:22).

11.5 Catalytic Hydrogenation of Isoxazolidines

Experiment 32 (YB 293)

4-Methylamino-4-phenyltetrahydropyran-2-one (36).



37

In analogy to lit.[73] A 100 mL-flask charged with the isoxazolidine **24** (500 mg, 2.00 mmol) under nitrogen was treated with 70 mL (7.0 mmol, 3.5 eq) of a 0.1 M THF solution of SmI_2 (Aldrich) at room temp. The resulting blue solution was stirred for 0.5 h. A 1.0 M solution of NH_3 in MeOH (30 mL) was added and the mixture was left with stirring for 20 min. Finally the

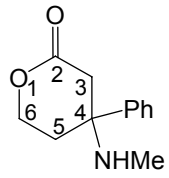
mixture was washed with the saturated $Na_2S_2O_3$ solution and extracted with ether (3 x 40 mL). The combined organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to afford 505 mg of a yellowish oil, which was chromatographed through silica gel (column 2 cm x 15 cm, CH_2Cl_2/MeOH 95:5) to give 293 mg of spectroscopically pure lactone **37** (71 %) as a colourless oil.

$C_{12}H_{15}NO_2$	calc.	C 70.22	H 7.37	N 6.28
(205.2)	found	C 68.59	H 7.43	N 6.34

HRMS (ES, *m/z*): calc. $C_{12}H_{15}NO_2$ 205.1102, found 205.1102

IR (Film): $\tilde{\nu}$ = 3391 (m, b), 2925 (w), 1720 (vs, C=O), 1496 (w), 1412 (m), 1045 (m), 1001 (w), 763 (m), 701 (s) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 2.32 (dt, $J_{5a,5b}$ = 13.0, $J_{5a,6}$ = 6.5 Hz, 1 H, 5-H_a), 2.49 (dt, $J_{5a,5b}$ = 13.4, $J_{5b,6}$ = 6.7 Hz, 1 H, 5-H_b), 2.87 (s, 3 H, NCH_3), 3.04 (d, $J_{3a,3b}$ = 14.7 Hz, 1 H, 3-H_a), 3.32 (d, $J_{3a,3b}$ = 14.7 Hz, 1 H, 3-H_b), 3.70 (dt, $J_{5,6a}$ = 6.6, $J_{6a,6b}$ = 10.8 Hz, 1 H, 6-H_a), 3.77 (dt, $J_{5,6b}$ = 6.6, $J_{6a,6b}$ = 10.8 Hz, 1 H, 6-H_b), 7.31-7.41 (m, 5 H, $C_6\underline{H}_5$).



37

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 26.1 (q, NCH_3), 38.1(t, C-5), 50.2 (t, C-3), 58.5 (t, C-6), 61.5 (s, C-4), 125.4, 127.8, 128.9 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 141.1 (s, *i*-C of C_6H_5), 167.6 (s, C=O).

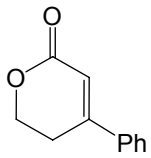
Experiment 33 (YB 75)

4-Methylamino-4-phenyltetrahydropyran-2-one (37)

500 mg (2.00 mmol) of isoxazolidine **24** and 250 mg of $Pd(OH)_2$ were added oo abs. ethanol (15 mL). The mixture was stirred under hydrogen (1 bar) for 24 h, then centrifuged to separate the catalyst by decantation, and concentrated *in vacuo* (10 mbar) to afford 425 mg of the crude lactone product. This was chromatographed throught silica gel (column 3 cm x 15 cm, CH_2Cl_2/MeOH 9:1) to give 60 mg of analytically and spectroscopically pure lactone **37** (15 %) as a colourless oil. The analytical data fully complied with the data given in Exp. 32.

Experiment 34 (YB 276)

4-Phenyl-5,6-dihydropyran-2-one (38)



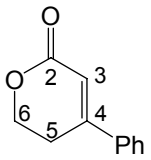
38

To a solution of HOAc/MeOH (20 mL, 4:1) 450 mg (1.80 mmol) of the isoxazolidine **24** and 690 mg of activated zinc[a] (10.56 mmol, 5.85 eq) were added. The mixture was refluxed for 2 h, and then concentrated *in vacuo* (30 °C/10 mbar) to afford 315 mg of crude lactone product. Filtration through silica gel (colomn, 2 cm x 5 cm, petroleum ether/ethyl acetate 4:6) gave 290 mg (92 %) of analytically and spectroscopically pure lactone **38** as a colourless solid (m.p = 56-57 °C, lit.: 57 °C)[137]

$C_{11}H_{10}O_2$	calc.	C 75.58	H 5.79
(174.2)	Found	C 75.72	H 5.90

IR (Film): $\tilde{\nu}$ = 1723 (w), 1695 (vs, C=O), 1610 (m), 1496 (m), 1462 (m), 1444 (m), 1341 (m), 1227 (s), 1215 (s), 1084 (s), 1049 (m), 886 (s), 766 (s) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 2.86 ("ddd", $J_{3,5a}$ = 1.8, $J_{5a,5b}$ = 7.8, $J_{5a,6}$ = 6.0 Hz, 5-H_a) and 2.89 ("ddd", $J_{3,5b}$ = 1.4, $J_{5a,5b}$ = 7.7, $J_{5b,6}$ = 6.4 Hz, 5-H_b; together 2 H); 4.54 ("ddd", $J_{3,6}$ = 0.5, $J_{5a,6}$ = 6.0, $J_{5b,6}$ = 6.4 Hz, 2 H, 6-H), 6.38 ("ddd", $J_{3,5a}$ = 1.8, $J_{3,5b}$ = 1.4, $J_{3,6}$ = 0.5, Hz, 1 H, 3-H), 7.43-7.57 (m, 5 H, $C_6\underline{H_5}$).

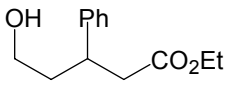


38

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.4 (t, C-5), 66.0 (t, C-6), 115.1 (d, C-3), 126.0, 129.0, 130.7 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 136.0 (s, *i*-C of C_6H_5), 155.3 (s, C-4), 165.0 (s, C=O).

Experiment 35 (YB 58)

Ethyl 5-hydroxy-3-phenylpentanoate (39)



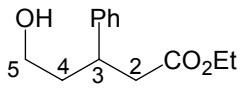
39

To abs. ethanol (10 mL) 250 mg (1.00 mmol) of isoxazolidine **24** and 100 mg of 10% Pd/C were added. The mixture was left with stirring for 4 h under hydrogen (1 bar), then it was centrifuged to separate the catalyst, decanted, and concentrated *in vacuo* (roomtemp./10 mbar) to afford 200 mg of the crude ester **39**. After purification by MPLC (petroleum ether/ethyl acetate 3:7) 77 mg (35 %) of **39** as a colourless slightly pure oil was obtained.

[a] Pretreated with HCl and throughly washed with water and ether prior to use.

$C_{13}H_{18}O_3$	Cal.	C 70.24	H 8.14
(222.28)	Fon.	C 69.53	H 8.34

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, $OCH_2C\underline{H}_3$), 1.90 (m, 2 H, 4-H), 2.64 (t, 2 H, 2-H), 3.29 (m, 1 H, 3-H), 3.51 (m, 2 H, 5-H), 4.04 (m, 2 H, $OC\underline{H}_2CH_3$), 7.20-7.31 (m, 5 H, $C_6\underline{H}_5$).

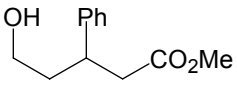


39

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.1 (q, $OCH_2\underline{C}H_3$), 38.7 (d, C-3), 39.0 (t, C-4), 41.6 (t, C-2), 60.4 (t, $O\underline{C}H_2CH_3$), 60.6 (t, C-5), 126.7, 127.5, 128.6 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 143.5 (s, *i*-C of C_6H_5), 172.5 (s, C=O).

Experiment 36 (YB 13)

Methyl 5-hydroxy-3-phenylpentanoate (40)



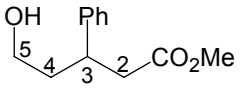
40

250 mg (1.00 mmol) of isoxazolidine **24** and 200 mg of 10 % Pd/C were added to MeOH (15 mL), and the mixture was left with stirring for 4 d under hydrogen (4 bar). The reaction mixture was then centrifuged to separate the catalyst, decanted, and concentrated *in vacuo* (room temp./10 mbar) to afford 219 mg of the crude ester **39**, which after purification by MPLC (petroleum ether/ethyl acetate 1:1) gave 83 mg (40 %) of **40** as a colourless, analytically and spectroscopically pure oil.

HRMS (ES, *m/z*): calc. $C_{12}H_{16}O_3$ 208.1099, found 208.1099

$C_{12}H_{16}O_3$	calc.	C 69.21	H 7.74
(208.25)	found	C 69.53	H 7.79

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.86 ("dddd", $J_{3,4a}$ = 5.4, $J_{4a,4b}$ = 13.8, $J_{4a,5a}$ = 6.0, $J_{4a,5b}$ = 5.9 Hz, 4-H_a) and 1.93 ("dddd", $J_{3,4b}$ = 5.4, $J_{4a,4b}$ = 13.8, $J_{4b,5a}$ = 7.4, $J_{4b,5b}$ = 6.7 Hz, 4-H_b); together 2 H); 2.62 (dd, $J_{2a,2b}$ = 15.5, $J_{2a,3}$ = 7.6 Hz, 2-H_a) and 2.67 (dd, $J_{2a,2b}$ = 15.5, $J_{2a,3}$ = 7.4 Hz, 2-H_b; together 2 H); 3.29 ("ddt", $J_{2a,3}$ = $J_{2b,3}$ = 7.5, $J_{3,4}$ = 5.4 Hz, 1 H, 3-H); 3.47 (ddd, $J_{4a,5a}$ = 6.2, $J_{4b,5a}$ = 7.4, $J_{5a,5b}$ = 10.8 Hz, 5-H_a) and 3.53 (ddd, $J_{4a,5b}$ = 5.7, $J_{4b,5b}$ = 6.6, $J_{5a,5b}$ = 10.8 Hz, 5-H_a; together 2 H); 3.59 (s, 3 H, $OC\underline{H}_3$), 7.19-7.31 (m, 5 H, C_6H_5).

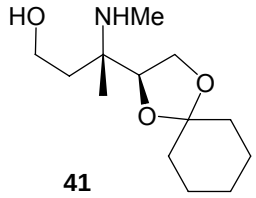


40

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 39.0 (d, C-3), 39.3 (t, C-2), 41.8 (t, C-4), 52.0 (s, O<u>C</u>H$_3$), 60.9 (t, C-5), 127.1, 127.8, 129.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 143.8 (s, *i*-C of C_6H_5), 173.3 (s, C=O).

Experiment 37 (YB 20)

(2*S*, 3*S*)-1,2-*O*-Cyclohexylidenedioxyethyl)-3-methyl-3-methylamino-1,2,5-pentanetriol (41) by catalytic hydrogenation of the isoxazoline 25a, cf. lit.[1]



41

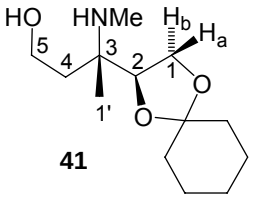
In analogy to lit.[1] 150 mg of the isoxazolidine **25a** and 80 mg of Pd/C (10%) were added to 5 mL methanol. The mixture was left with stirring overnight under hydrogen (1 bar) at room temp., then Pd/C was filtered off through celite and the solution was concentrated *in vacuo* (30 °C/10 mbar) to give 145 mg of the amino alcohol **41** as a colourless oil with slightly deviating elemental analysis (96%, lit. 96%[1]). The analytical data complied well with the literature values.[1]

$[\alpha]_D^{20}$ = - 14.7 (*c* = 1.00, CH_2Cl_2); lit. : $[\alpha]_D^{20}$ = - 14.9 (*c* = 0.99, CH_2Cl_2)[1]

$C_{13}H_{25}NO_3$	calc.	C 64.16	H 10.36	N 5.76
(243.3)	found	C 63.29	H 10.23	N 5.53

IR (Film): $\tilde{\nu}$ = 3400 (m, b; NH, OH), 2925 (vs), 2865 (vs), 2840 (m), 1440 (s), 1367 (s), 1333 (m), 1282 (s), 1252 (m), 1231 (m), 1164 (s), 1144 (s), 1105 (s), 1071 (s), 1042 (s), 970 (m), 938 (s), 909 (m), 848 (m), 830 (m), 777 (w), 738 (w) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.07 (s, 3 H, 1'-H), 1.32-1.65 [m, 12 H, 4-H, C$(CH_2)_5$], 2.36 (s, 3 H, NC<u>H</u>$_3$), 3.52 (sb, 2 H, NH, OH); 3.87 (dd, $^2J_{1a,1b}$ = 8.2, $J_{1a,2}$ = 7.4 Hz, 1-H$_a$) and 3.89 (ddd, $J_{4a,5a}$ and $J_{5a,4b}$ = 4.2, 6.0, $^2J_{5a,5b}$ = 11.3 Hz, 5-H$_a$; togethor, 2 H), 4.03 (ddd, $J_{4a,5b}$ and $J_{4b,5b}$ = 3.7 and 8.6, $^2J_{5a,5b}$ = 11.3 Hz, 1 H, 5-H$_b$), 4.13 (dd, $^2J_{1a,1b}$ = 8.1, $J_{1b,2}$ = 6.7 Hz, 1 H, 1-H$_b$), 4.37 (dd, $J_{1a,2}$ = 7.5, $J_{1b,2}$ = 6.7 Hz, 1 H, 2-H).

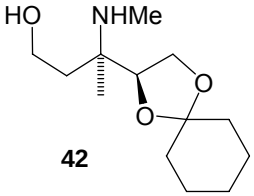


41

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 18.5 (q, C-1'), 23.9, 24.0, 25.3, 34.0, 34.2, 35.9 [6 t, C-4, C($\underline{C}H_2)_5$], 28.0 (q, $NHCH_3$), 57.5 (s, C-3), 59.6 (t, C-5), 64.8 (t, C-1), 77.7 (d, C-2), 109.7 [s, $\underline{C}(CH_2)_5$].

Experiment 38 (YB 107)

(2*S*, 3*R*)-1,2-*O*-Cyclohexylidenedioxyethyl)-3-methyl-3-methylamino-1,2,5-pentanetriol (42) by catalytic hydrogenation of the isoxazoline 25b



42

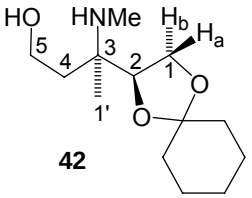
In analogy to lit.[1] 270 mg of the isoxazolidine **25b** and 100 mg of Pd/C (10%) were added to a solution of 10 mL methanol. The mixture was left under H_2 (1 bar) at room temp. with stirring overnight, and then Pd/C was filtered off on celite. The resulting solution was concentrated *in vacuo* (room temp./10 mbar) to give 250 mg of the aminoalcohol **42** as a colourless, analytically pure oil (92 %; lit. : 92 %[1]). The analytical data fully complied with the literature values.[1]

$[\alpha]_D^{20}$ = - 10.6 (*c* = 1.00, CH_2Cl_2) lit. : $[\alpha]_D^{20}$ = - 10.9 (*c* = 1.00, CH_2Cl_2)[1]

$C_{13}H_{25}NO_3$	calc.	C 64.16	H 10.36	N 5.76
(243.3)	found	C 64.13	H 10.07	N 5.21

IR (neat): $\tilde{\nu}$ = 3319 (sb), 2931 (vs), 2857 (s), 1448 (w), 1367 (w), 1333 (m), 1282 (w), 1163 (m), 1102 (vs), 1071 (m), 1042 (m) 937 (m) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 1'-H), 1.39-1.69 [m, 12 H, 4-H, C($C\underline{H}_2)_5$], 2.39 (s, 3 H, $NC\underline{H}_3$), 3.71 (dd, $J_{1a,1b}$ = 8.2, $J_{1a,2}$ = 7.4 Hz, 1-H_a) and 3.68-3.78 (m, 5-H_a; together, 2 H), 3.82-3.91 (m, 5-H_b) and 3.97 (dd, $J_{1a,1b}$ = 8.2, $J_{1b,2}$ = 6.7 Hz, 1-H_b; together, 2 H), 4.21 (dd, $J_{1a,2}$ = 7.6, $J_{1b,2}$ = 6.6 Hz, 1 H, 2-H).



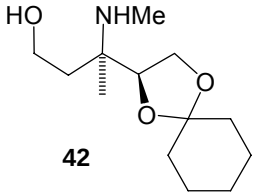
42

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.6 (q, C-1'), 23.8, 24.0, 25.2, 34.4, 35.8 [5 t, C($\underline{C}H_2)_5$], 28.1 (q, $NHCH_3$), 34.4 (t, C-4), 57.0 (s, C-3), 59.5 (t, C-5), 65.0 (t, C-1), 78.9 (d, C-2), 109.6 [s, $\underline{C}(CH_2)_5$].

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

Experiment 39 (YB 315)

(2*S*, 3*R*)-1,2-*O*-Cyclohexylidenedioxyethyl)-3-methyl-3-methylamino-1,2,5-pentanetriol (42) by $LiAlH_4$ reduction of the N-Boc-protected amino alcohol 62



42

In analogy to lit.[138], under nitrogen a $LiAlH_4$-THF solution (22.8 mL, 0.20 M, 4.6 mmol) at 0 °C was added drop by drop to a solution of 300 mg (0.91 mmol) of the protected amino alcohol **63** in 50 mL abs. THF.

The mixture was refluxed for 1.5 h and then cooled to 0 °C. The excess of $LiAlH_4$ was quenched by adding 0.5 mL of water, 1 mL of NaOH (5% in water, w/w), and 1 mL of water successively. The precipitated $Al(OH)_3$ was filtered off and washed three times with hot chloroform (3 x 10 mL).

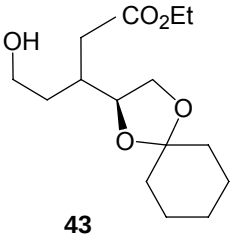
The combined organic phases were dried over $MgSO_4$ and the solvent was removed under vacuum (30 °C/20 mbar) to give 206 mg of analytically and spectroscopically pure, as a colourless amino alcohol **42** in 93 % yield. The analytical data fully complied with those given in Exp. 38.

$[\alpha]_D^{20}$ = - 11.1 (*c* = 1.00, CH_2Cl_2)

$C_{13}H_{25}NO_3$	calc.	C 64.16	H 10.36	N 5.76
(243.3)	found	C 64.24	H 10.11	N 5.22

Experiment 40 (YB 67)

4,5-*O*-Cyclohexylidenedioxyethyl)-3-(1-hydroxyethyl)-pentanoate (43).



43

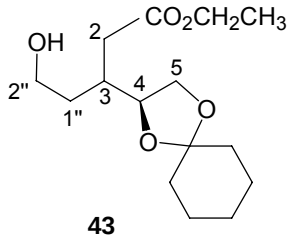
323 mg (1.03 mmol) of the isoxazolidine **26a** and 200 mg of 10% Pd/C were added to abs. ethanol (10 mL). The mixture was kept stirring under hydrogen (1 bar) for 3 d, then centrifuged to separate the catalyst, and concentrated *in vacuo* (20 °C/10 mbar) to afford 224 mg of the crude ester **43** (d.r. 70:30). Purification by MPLC (petroleum ether/ethyl acetate 1:9) gave 50 mg of the analytically pure ester **43** as colourless oil in 17 % yield.

$[\alpha]_D^{20}$ = - 21.1 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{26}O_5$	calc.	C 62.91	H 9.15
(286.35)	found	C 62.60	H 8.92

IR (KBr) : $\tilde{\nu}$ = 3539 (b, m), 2935 (m), 2860 (w), 1724 (vs, C=O), 1449 (w), 1399 (w), 1283 (w), 1161 (m), 1084 (s), 1045 (m), 924 (m), 883 (w), 848 (w) cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.27 (t, $J_{1',2'}$ = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.38-1.61 [m, 10 H, $(CH_2)_5$], 1.52 (m, 1 H, 3-H), 1.69 (m, 1 H, 1"-H_a), 2.26 (m, 1 H, 1"-H_b), 2.33 (dd, $J_{3,2a}$ = 8.3, $J_{2a,2b}$ = 16.1 Hz, 1 H, 2-H_a), 2.60 (dd, $J_{3,2b}$ = 4.0, $J_{2a,2b}$ = 16.1 Hz, 1 H, 2-H_b); 3.60-3.67 (m, 2"-H_a, 5-H_a) and 3.68-3.75 (m, 5-H_b; together 3 H); 4.04-4.11 (m, 2 H, 2"-H_b, 4-H) and 4.15 (q, $J_{1',2'}$ = 7.1 Hz, $OC\underline{H}_2CH_3$; together 4 H).

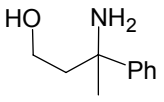


43

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.2 (q, $OCH_2\underline{C}H_3$), 23.8, 24.0, 25.1, 34.5, 36.2 [5 t, $(\underline{C}H_2)_5$], 34.7 (t, C-1"), 35.0 (t, $\underline{C}H_2OEt$), 35.2 (d, C-3), 59.9 (t, C-2"), 60.7 (t, $O\underline{C}H_2CH_3$), 67.3 (t, C-5), 78.0 (d, C-4), 109.6 [s, $\underline{C}(CH_2)_5$], 173.8 (s, C=O).

Experiment 41 (YB 228)

3-Amino-3-phenylbutan-1-ol (44)



44

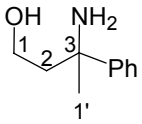
Typical Procedure TP 3 for the Catalytic Reduction of Isoxazolidines to Amino alcohols.

0.42 g (2.58 mmol) of the isoxazolidine **29** and 200 mg of Pd/C (10%) were added to 25 mL of MeOH. The mixture was left with stirring overnight under hydrogen (1 bar) at room temp. Then Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to afford 424 mg of analytically and spectroscopically pure amino alcohol **44** in quantitative yield ("100 %") as a colourless solid (m.p. 75-77 °C; lit. : 77-78 °C[139]). The analytical data complied fully with the values given in lit.[139]

$C_{10}H_{15}NO$	calc.	C 72.69	H 9.15	N 8.48
(165.2)	found	C 72.57	H 9.17	N 8.32

IR : $\tilde{\nu}$ = 3346 (m), 3290 (m), 3049 (b), 2920 (w), 2812 (w), 1594 (m), 1494 (m), 1440 (m), 1372 (m), 1167 (s), 1097 (s), 1079 (s), 1029 (vs), 765 (vs), 695 (vs) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, 1'-H), 2.00 (t, $J_{1,2}$ = 7.1 Hz, 2 H, 2-H), 3.41 (t, $J_{1,2}$ = 7.1 Hz, 2 H, 1-H), 7.18-7.46 (m, 5 H, C_6H_5).

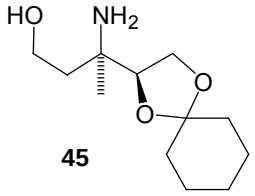


44

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.7 (q, C-1'), 47.7 (t, C-2), 56.4 (s, C-3), 60.7 (t, C-1), 126.8, 128.0, 129.9 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 149.8 (s, *i*-C of C_6H_5).

Experiment 42 (YB 231)

(2*S*, 3*R*)-3-Amino-1,2-*O*-(Cyclohexylidene)-3-methyl-1,2,5-pentanetriol (45)



45

Scale: 270 mg (1.19 mmol) Isoxazolidine **32a**
100 mg of Pd/C (10 %)
20 mL abs. MeOH

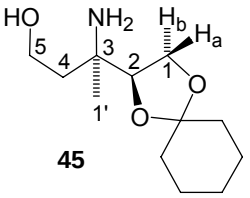
The reaction was performed according to TP 3 to afford 272 mg of analytically and spectroscopically pure amino alcohol **45** in quantitative yield ("100 %") as colourless oil.

$[\alpha]_D^{20}$ = - 3.9 (*c* = 1.00, MeOH)

$C_{12}H_{23}NO_3$	calc.	C 62.85	H 10.11	N 6.11
(229.3)	Found	C 62.96	H 10.17	N 5.88

IR: $\tilde{\nu}$ = 3357 (b; NH, OH), 2931 (vs), 2857 (s), 1594 (w), 1448 (m), 1366 (m), 1333 (w), 1281 (w), 1162 (vs), 1069 (s), 909 (s), 848 (m) cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$) : δ = 1.05 (s, 3 H, 1'-H), 1.33-1.68 [m, 11 H, 4-H_a, $C(CH_2)_5$], 1.71-1.76 (m, 1 H, 4-H_b), 3.71 (ddd, $J_{4a,5a}$ and $J_{4b,5a}$ and $^2J_{5a,5b}$ = 10.9 and 7.5 and 5.5 Hz, 1 H, 5-H_a), 3.75-3.81 (m, 2 H, 5-H_b, 1-H_a), 3.96 (dd, $^2J_{1a,1b}$ = 8.1, $J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.00 (t, $J_{1,2}$ = 6.9 Hz, 1 H, 2-H).

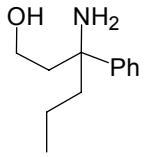


45

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.6 (q, C-1'), 24.8, 25.0, 26.3, 35.5, 37.1[5 t, $C(\underline{C}H_2)_5$], 42.4 (t, C-4), 53.6 (s, C-3), 59.2 (t, C-5), 65.4 (t, C-1), 82.7 (d, C-2), 110.1 [s, $\underline{C}(CH_2)_5$].

Experiment 43 (YB 143)

3-Amino-3-phenyl-hexan-1-ol (46)



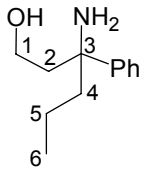
46

Scale: 235 mg (1.24 mmol) Isoxazolidine **30**
110 mg of Pd/C (10 %)
20 mL abs. MeOH

The reaction was performed according to TP 3. Column chromatography was done on silica gel (column 2 cm x 10 cm, MeOH/CH_2Cl_2 9:1) to afford 214 mg (90 %) of analytically and spectroscopically pure amino alcohol **46** as a colourless soild (m.p. 71-72 °C).

$C_{12}H_{19}NO$	calc.	C 74.57	H 9.91	N 7.25
(193.3)	found	C 74.15	H 9.71	N 7.09

IR : $\tilde{\nu}$ = 3355 (m), 3287 (m), 3113 (sb), 3052 (m), 2924 (m), 2868 (s), 1586 (s), 1493 (m), 1444 (s), 1166 (s), 1051 (vs), 963 (vs), 947 (s), 832 (s), 768 (vs) cm^{-1}.



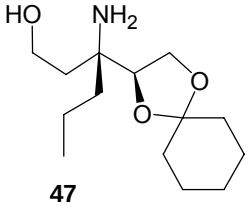
46

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 0.85 (t, $J_{5,6}$ = 7.2 Hz, 3 H, 6-H), 0.95 (m, 1 H, 5-H_a), 1.19 (m, 1 H, 5-H_b), 1.69 (ddd, $J_{4a,4b}$ = 13.6, $J_{4a,5a}$ = 12.2, $J_{4a,5b}$ = 4.5 Hz, 1 H, 4-H_a), 1.85 (ddd, $J_{1a,2a}$ = 3.1, $J_{1b,2a}$ = 5.6, $J_{2a,2b}$ = 8.8 Hz, 1 H, 2-H_a), 1.93 (ddd, $J_{4a,4b}$ = 13.4, $J_{4b,5a}$ = 12.9, $J_{4b,5b}$ = 4.3 Hz, 1 H, 4-H_b), 2.01 (ddd, $J_{1a,2b}$ = 9.1, $J_{1b,2b}$ = 3.8, $J_{2a,2b}$ = 9.0 Hz, 1 H, 2-H_b), 2.96 (sb, 3 H, NH_2, OH), 3.43 (ddd, $J_{1a,1b}$ = 9.5, $J_{1a,2a}$ = 3.1, $J_{1a,2b}$ = 9.1 Hz, 1 H, 1-H_a), 3.64 (ddd, $J_{1a,1b}$ = 9.5, $J_{1b,2a}$ = 5.6, $J_{1b,2b}$ = 3.8 Hz, 1 H, 1-H_b), 7.22-7.36 (m, 5 H, C_6H_5)

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 14.4 (q, C-6), 16.4 (t, C-5), 43.4 (t, C-2), 46.8 (t, C-4), 59.5 (s, C-3), 60.1(t, C-1), 125.3, 126.4, 128.4 (3 d, *o-, m-, p*-C of C_6H_5), 145.5 (s, *i*-C of C_6H_5).

Experiment 44 (YB 166)

(2*S*, 3*S*)-3-Amino-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5-pentanetriol (47)



47

Scale: 270 mg (1.07 mmol) Isoxazolidine **34a**
100 mg of Pd/C (10 %)
15 mL abs. MeOH

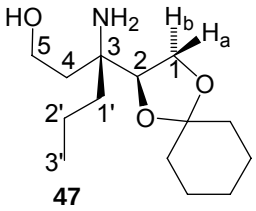
The reaction was performed according to TP 3 to afford 230 mg (84 %) of analytically and spectroscopically pure aminoalcohol **47** as colourless oil.

$[\alpha]_D^{20}$ = 5.3 (*c* = 0.49, CH_2Cl_2)

$C_{14}H_{27}NO_3$	calc.	C 65.33	H 10.57	N 5.44
(257.4)	Found	C 65.02	H 10.48	N 5.16

IR: $\tilde{\nu}$ = 3346, 3292 (2 b, m), 2931 (s), 2862 (m), 1591 (w), 1365 (m), 1281 (m), 1163 (m), 1101 (vs), 1069 (s), 1035 (vs), 936 (s), 848 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 0.96 (t, $J_{2',3'}$ = 7.0 Hz, 3 H, 3'-H), 1.26-1.66 [m, 16 H, C(C<u>H</u>$_2$)$_5$, 4-H, 1'-H, 2'-H), 3.2 (sb, 3 H, NH_2, OH), 3.68-3.76 (m, 5-H_a) and 3.77 (dd, $J_{1a,1b}$ = 6.8, $J_{1a,2}$ = 5.6 Hz, 1-H_a; together, 2 H), 3.82-3.95 (m, 5-H_b) and 3.96 ("t", $J_{1a,1b}$ = 6.7 Hz, $J_{1b,2}$ = 6.6 Hz, 1-H_b) and 4.01 ("dd", $J_{1a,2}$ = 6.2, $J_{1b,2}$ = 6.6 Hz, 1 H, 2-H; together, 3 H)

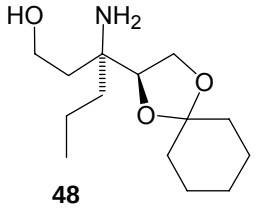


47

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 14.8 (q, C-3'), 16.9 (t, C-2'), 23.9, 24.0, 25.2, 34.3, 34.5, 36.0, 38.3 [7 t, C(CH_2)$_5$, C-4, C-1'], 56.1 (s, C-3), 59.1 (t, C-5), 64.3 (t, C-1), 79.6 (d, C-2), 109.3 [s, <u>C</u>(CH_2)$_5$].

Experiment 45 (YB 167)

(2*S*, 3*R*)-3-Amino-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5-pentanetriol (48)



48

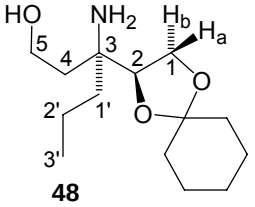
Scale: 150 mg (0.59 mmol) Isoxazolidine **34b**
50 mg of Pd/C (10 %)
10 mL abs. MeOH

The reaction was performed according to TP 3 to afford 136 mg (89 %) of analytically and spectroscopically pure aminoalcohol **48** as colourless oil.

$[\alpha]_D^{20}$ = - 6.1 (*c* = 1.19, CH_2Cl_2)

$C_{14}H_{27}NO_3$	calc.	C 65.33	H 10.57	N 5.44
(257.4)	Found	C 64.81	H 10.56	N 5.12

IR: $\tilde{\nu}$ = 3359 (sb), 2931 (s), 2861 (m), 1589 (w), 1448 (m), 1365 (m), 1281 (w), 1231 (w), 1162 (m), 1100 (vs), 1068 (m), 1036 (s), 930 (vs), 908 (vs), 847 (m) cm^{-1}.



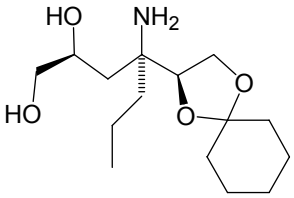
48

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 0.93 (t, $J_{2',3'}$ = 7.0 Hz, 3 H, 3'-H), 1.26-1.66 [m, 16 H, C(C<u>H</u>$_2$)$_5$, 4-H, 1'-H, 2'-H], 3.2 (sb, 3 H, NH_2, OH), 3.68 ("t", $J_{1a,1b}$ = 7.9, 1-H_a) and 3.68-3.77 (m, 5-H_a; together, 2 H), 3.84-3.94 (m, 5-H_b) and 3.94 (dd, $J_{1a,1b}$ = 8.0, $J_{1b,2}$ = 6.6 Hz, 1-H_b; together, 2 H), 4.04 (dd, $J_{1a,2}$ = 7.7, $J_{1b,2}$ = 6.6 Hz, 1 H, 2-H).

^{13}C NMR (250.1 MHz, $CDCl_3$) : δ = 14.8 (q, C-3'), 16.9 (t, C-2'), 23.7, 23.9, 25.1, 34.6, 36.1, 37.0, 38.2 [7 t, $(CH_2)_5$, C-4, C-1'], 55.3 (s, C-3), 59.2 (t, C-5), 63.6 (t, C-1), 80.2 (d, C-2), 109.6 [s, <u>C</u>$(CH_2)_5$].

Experiment 46 (YB 197)

(2*S*, 3*R*, 5*S*)-3-Amino-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5,6-hexanetetraol (49)



49

Scale: 190 mg (0.67 mmol) Isoxazolidine **35a**
60 mg of Pd/C (10 %)
15 mL abs. MeOH

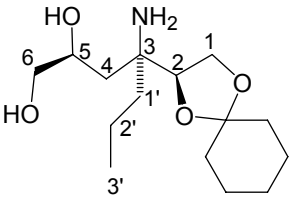
The reaction was performed according to TP 3 to afford 185 mg (97 %) of analytically and spectroscopically pure aminoalcohol **49** as colourless oil.

$[\alpha]_D^{20}$ = - 3.6 (*c* = 1.00, CH_2Cl_2)

$C_{15}H_{29}NO_4$	calc.	C 62.69	H 10.17	N 4.87
(287.4)	found	C 62.14	H 10.05	N 4.45

IR: $\tilde{\nu}$ = 3410 (sb, OH), 2931 (vs), 2862 (m), 1695 (w), 1580 (w), 1448 (m), 1364 (w), 1251 (w), 1143 (w), 1098 (vs), 960 (s), 848 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 0.93 (t, $J_{2',3'}$ = 7.2 Hz, 3 H, 3'-H), 1.07-1.86 [m, 16 H, 2'-H, 4-H, 1'-H, C(C<u>H</u>$_2$)$_5$], 3.46 (dd, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.1 Hz, 1 H, 6-H$_a$), 3.58 (dd, $J_{5,6b}$ = 3.6, $J_{6a,6b}$ = 11.1 Hz, 1 H, 6-H$_b$), 3.66 ("dd", $J_{1a,1b}$ and $J_{1a,2}$ = 8.0 Hz, 1 H, 1-H$_a$); 3.94 (dd, $J_{1a,1b}$ = 8.2, $J_{1b,2}$ = 6.6 Hz, 1-H$_b$) and 3.96-4.02 (m, 5-H) and 4.01 (dd, $J_{1a,2}$ = 7.6, $J_{1b,2}$ = 6.6 Hz, 2-H; together 3 H).

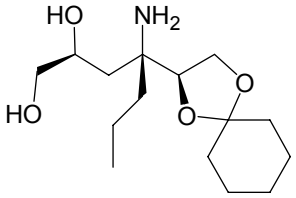


49

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.8 (q, C-3'), 17.1 (t, C-2'), 23.7, 23.9, 25.1, 34.5, 36.1, 36.8, 37.9 [7 t, C-4, C-1', C(<u>C</u>H$_2$)$_5$], 55.4 (s, C-3), 63.4 (t, C-6), 67.4 (t, C-1), 68.6 (d, C-5), 80.1 (d, C-2), 109.7 [s, <u>C</u>(CH$_2$)$_5$].

Experiment 47 (YB 198)

(2*S*, 3*S*, 5*S*)-3-Amino-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5,6-hexanetetraol (50)



50

Scale: 445 mg (1.57 mmol) isoxazolidine **35b**
150 mg of Pd/C (10 %)
25 mL abs. MeOH

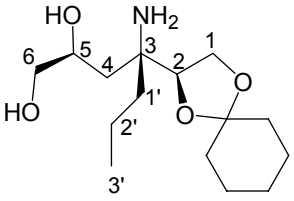
The reaction was performed according to TP 3 to afford 443 mg (98 %) of spectroscopically pure, analytically impure aminoalcohol **50** as colourless oil.

$[\alpha]_D^{20}$ = 13.3 (*c* = 1.00, MeOH)

MS (*m/z*): calc. $C_{15}H_{29}NO_4$ 287.4, found 287.2 (molecular peak).

IR: $\tilde{\nu}$ = 3280 (sb, OH), 2931 (vs), 2860 (m), 1504 (w), 1448 (w), 1282 (w), 1144 (m), 1095 (vs), 1071 (s), 1034 (vs), 926 (s), 910 (m), 848 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.00 (t, $J_{2',3'}$ = 7.1 Hz, 3 H, 3'-H), 1.12-2.08 [m, 16 H, 2'-H, 4-H, 1'-H, C(C<u>H</u>$_2$)$_5$], 3.55 (dd, $J_{5,6a}$ = 6.2, $J_{6a,6b}$ = 11.7 Hz, 1 H, 6-H$_a$), 3.68 (dd, $J_{5,6b}$ = 2.8, $J_{6a,6b}$ = 11.5 Hz, 1 H, 6-H$_b$), 4.03 (dd, $J_{1a,1b}$ = 9.0, $J_{1a,2}$ = 6.8 Hz, 1H, 1-H$_a$); 4.14 (dd,



50

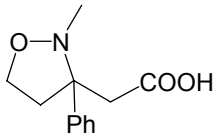
$J_{1a,1b}$ = 9.2, $J_{1b,2}$ = 7.0 Hz, 1-H_b) and 4.11-4.16 (m, 5-H; together 2 H); 4.27 (t, $J_{1,2}$ = 6.9 Hz, 1 H, 2-H).

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.5 (q, C-3'), 16.9 (t, C-2'), 23.7, 24.0, 25.1, 32.6, 34.1, 35.5, 35.6 [7 t, C-4, C-1', C($\underline{C}H_2)_5$], 60.2 (s, C-3), 63.9 (t, C-6), 66.6 (t, C-1), 68.2 (d, C-5), 76.7 (d, C-2), 110.5 [s, $\underline{C}(CH_2)_5$].

11.6 Hydrolysis of Isoxazolidines.

Experiment 48 (YB 17)

2-methyl-3-phenyl-2-isoxazolidineacetic acid; hydrochloride (51).



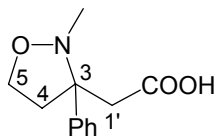
51 · HCl

300 mg (1.2 mmol) of isoxazolidine **24** was added to HCl (40 mL, 20 %). The mixture was refluxed for 2.5 h, then the solvent was evaporated to give 305 mg (98 %) of analytically and spectroscopically pure isoxazolinium salt **51** as a colourless solid (m. p. 185 °C decom.). Crystallization from abs. ethanol gave **51** in the form of colourless crystals, suitable for crystal structure determination (see appendix 12.1.4).

$C_{12}H_{16}NO_3Cl$	calc.	C 55.89	H 6.26	N 5.43	Cl 13.76
(257.7)	found	C 55.98	H 6.35	N 5.32	Cl 14.00

IR (Film): $\tilde{\nu}$ = 2950 (m, b), 2360 (s, b), 1725 (vs), 1640 (w), 1480 (w), 1455 (m), 1445 (w), 1430 (w), 1415 (w), 1370 (w), 1340 (w), 1300 (m), 1260 (w), 1270 (m), 1260 (m), 1250 (m), 1100 (w), 1075 (w), 1040 (w), 1025 (w), 980 (w), 825 (m), 740 (m), 690 (m), 600 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, D_2O): δ = 2.49 (s, 3 H, NC$\underline{H}_3$), 2.96 (m, 1 H, 4-H_a); 3.20 (d, $J_{1'a,1'b}$ = 16.1 Hz, 1'-H_a) and 3.23 (m, 4-H_b; together 2 H); 3.37 (d, $J_{1'a,1'b}$ = 14.3 Hz, 1 H, 1'-H_b), 4.41 (m, 1 H, 5-H_a), 4.57 (m, 1 H, 5-H_b), 7.36-7.49 (m, 5 H, C_6H_5).

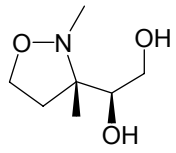


51 · HCl

^{13}C NMR (125.8 MHz, D_2O): δ = 35.2 (t, C-4), 39.4 (q, NCH_3), 40.1 (t, $\underline{C}H_2CO_2H$), 70.3 (t, C-5), 77.2 (s, C-3), 126.2, 128.4, 129.9, 130.0, 130.9 (5 d, *o*-, *m*-, *p*-C of C_6H_5), 133.0 (s, *i*-C of C_6H_5), 172.6 (s, $\underline{C}O_2H$).

Experiment 49 (YB 25)

(*S*)-3-((*S*)-1,2-Dihydroxyethyl)-2,3-dimethyl-2-isoxazolidine (52), cf. lit.[1]



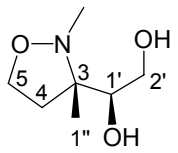
52

According to lit.[1] to 570 mg (2.36 mmol) of isoxazolidine **25a**, 20 mL of HCl (6.0 N) was added. The reaction mixture was left with stirring for 24 h at room temp., then the solvent was concentrated *in vacuo* (60 °C/20 mbar) to give brownish oil. This was neutralized with sat. $NaHCO_3$ solution (25 mL), 5 gram of silica gel was added to mixture, and then concentrated *in vacuo* (60 °C/20 mbar), which purified by column chromatography (2 cm x 15 cm, CH_2Cl_2/ MeOH 85:15) to afford 354 mg of **52** (93%; lit. 96 %[1]) as a colourless soild (m.p. 46-48 °C). The analytical data complied fully with the literature values.[1]

$[\alpha]_D^{20}$ = - 70.4 (*c* = 1.00, CH_2Cl_2), lit. : $[\alpha]_D^{20}$ = - 72.8 (*c* = 1.05, CH_2Cl_2)[1]

$C_7H_{15}NO_3$	calc.	C 52.16	H 9.38	N 8.69
(161.2)	found	C 52.04	H 9.40	N 8.27

IR (Film): $\tilde{\nu}$ = 3367 (s, b; OH), 2968 (s), 2884 (s), 1445 (m), 1404 (m), 1093 (s), 1069 (s), 1024 (vs), 942 (m), 882 (m) cm^{-1}.



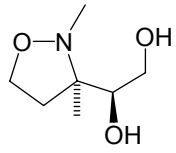
52

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.14 (s, 3 H, 1"-H), 1.91 (ddd, $J_{4a,4b}$ = 12.5, $J_{4a,5a}$ = 6.8, $J_{4a,5b}$ = 9.5 Hz, 1 H, 4-H_a), 2.51 (ddd, $^2J_{4a,4b}$ = 12.5, $J_{4b,5a}$ = 9.3, $J_{4b,5b}$ = 5.1 Hz, 1 H, 4-H_b), 2.56 (s, 3 H, NCH_3), 3.54 (sb, 2 OH) and 3.54 (dd, $J_{1',2'a}$ = 6.2, $J_{1',2'b}$ = 4.3 Hz, 1'-H; together 3 H); 3.62 (dd, $J_{1',2'a}$ = 6.3, $^2J_{2'a,2'b}$ = 11.4 Hz, 1 H, 2'-H_a), 3.75 (dd, $J_{1',2'b}$ = 4.3, $^2J_{2'a,2'b}$ = 11.4 Hz, 1 H, 2'-H_b), 3.80 (ddd, $J_{4a,5a}$ = 6.7, $J_{4b,5a}$ = 9.4, $^2J_{5a,5b}$ = 8.0 Hz, 1 H, 5-H_a), 4.00 (ddd, $J_{4a,5b}$ = 9.5, $J_{4b,5b}$ = 5.1, $^2J_{5a,5b}$ = 7.9 Hz, 1 H, 5-H_b).

^{13}C-NMR (125.8 MHz, $CDCl_3$) : δ = 16.6 (q, C-1"), 36.7 (t, C-4), 37.7 (q, N-CH_3), 63.7 (t, C-2'), 65.2 (t, C-5), 68.5 (s, C-3), 73.5 (d, C-1').

Experiment 50 (YB 108)

(*R*)-3-((*S*)-1,2-Dihydroxyethyl)-2,3-dimethyl-2-isoxazolidine (52).



53

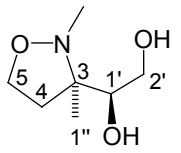
According to lit.[1] to 750 mg (3.11 mmol) of isoxazolidine **25b** 30 mL of HCl (6 N) was added and left with stirring for 48 h at room temp., then the solvent was concentrated *in vacuo* (20 mbar/ 60°C) to give a brownish oil. This was neutralized with sat. $NaHCO_3$ solution (25 mL), to this mixture 5 gram of silica gel was added, and then the mixture was concentrated *in vacuo* (60 °C/20 mbar). Purification with column chromatography through silica gel (2 cm x 15 cm, CH_2Cl_2/ MeOH 9:1) afforded 490 mg of analytically pure diol **53** (99 %) as a colourless oil.

$[\alpha]_D^{20}$ = 39.9 (*c* = 1.00, MeOH)

$C_7H_{15}NO_3$	calc.	C 52.16	H 9.38	N 8.69
(161.2)	Found	C 52.46	H 9.10	N 8.16

IR (Film): $\tilde{\nu}$ = 3440 (s, b; OH), 2959 (s), 2870 (s), 2218 (m), 1455 (m), 1431 (m), 1395 (m), 1161 (m), 1075 (s), 1035 (s), 1008 (s), 955 (m), 915 (m) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$) : δ = 1.17 (s, 3 H, 1"-H), 2.04 (ddd, $J_{4a,4b}$ = 12.4, $J_{4a,5a}$ = 6.3, $J_{4a,5b}$ = 9.9 Hz, 1 H, 4-H_a), 2.41 (ddd, $J_{4a,4b}$ = 12.4, $J_{4b,5a}$ = 9.4, $J_{4b,5b}$ = 5.6 Hz, 1 H, 4-H_b), 2.56 (2, 3 H, NCH_3), 3.41 (sb, 2 H, 2 OH), 3.48 (dd, $J_{1',2'a}$ = 3.5, $J_{1',2'b}$ = 5.5 Hz, 1 H, 1'-H), 3.68 (dd, $J_{1',2a'}$ = 3.5, $J_{2'a,2'b}$ = 11.5 Hz, 2'-H_a) and 3.77 (dd, $J_{1',2'b}$ = 5.5, $J_{2'a,2'b}$ = 11.5 Hz, 2'-H_b); together 2 H); 3.93 (ddd, $J_{4a,5a}$ = 6.3, $J_{4b,5b}$ = 9.5, $J_{5a,5b}$ = 7.9 Hz, 1 H, 5-H_a), 4.09 (ddd, $J_{4a,5b}$ = 9.9, $J_{4b,5b}$ = 5.6, $J_{5a,\,5b}$ = 7.9 Hz, 1 H, 5-H_b).

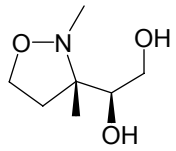


53

^{13}C NMR (500.1 MHz, $CDCl_3$) : δ = 16.0 (q, C-1"), 39.2 (t, C-4), 38.5 (q, N-CH_3), 65.0 (t, C-2'), 66.0 (t, C-5), 69.7 (s, C-3), 77.4 (d, C-1').

Experiment 51 (YB 68)

(*S*)-3-((*S*)-1,2-Dihydroxyethyl)-2,3-dimethyl-2-isoxazolidine; hydrochloride (53).



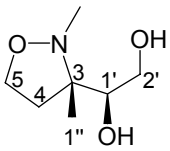
52 ▪ HCl

444 mg (1.84 mmol) of the isoxazolidine **25a** was added to 20 mL of HCl (6.0 N). The mixture was kept with stirring for 24 h at room temp. Then the solvent was concentrated *in vacuo* (60 °C/20 mbar) to give brownish oil, which purified by column chromatography (SiO_2, 2 cm x 15 cm, CH_2Cl_2/ MeOH 85:15 to 1:1) to yield 254 mg (86 %) spectroscopically pure diol **52•HCl** as a colourless soild (m. p. 118-120 °C). Crystallization from ethanol/petroleum ether gave colourless crystals, suitable for crystal structure determination (m. p. 118 °C, see appendix 12.1.5).

$[\alpha]_D^{20}$ = - 60.8 (*c* = 1.00, MeOH)

IR : $\tilde{\nu}$ = 3380 (s, b; OH), 2968 (s), 2893 (s), 1501 (w), 1489 (m), 1445 (m), 1404 (m), 1097 (s), 1061 (vs), 1024 (vs), 942 (m), 882 (m), 798 (w) cm^{-1}.

^{1}H NMR (500.1 MHz, CD_3OD): δ = 1.36 (s, 3 H, 1"-H), 2.26 ("ddd", $J_{4a,4b}$ = 12.9, $J_{5a,4a}$ and $J_{4a,5b}$ = 5.1 and 8.6 Hz, 1 H, 4-H_a), 2.79 (ddd, $^2J_{4a,4b}$ = 12.9, $J_{4b,5a}$ and $J_{4b,5b}$ = 7.2 and 9.6 Hz, 1 H, 4-H_b), 2.94 (s, 3 H, NCH_3), 3.62 (dd, $J_{1',2'a}$ = 5.6, $^2J_{2'a,2'b}$ = 11.4 Hz, 1 H, 2'-H_a), 3.70-3.81 (m, 2 H, 2'-H_b, 1'-H), 4.11-4.21 (m, 1 H, 5-H_a), 4.29-4.37 (m, 1 H, 5-H_b).

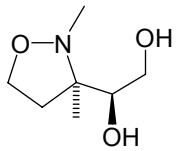


52 ▪ HCl

^{13}C NMR (125.8 MHz, CD_3OD): δ = 16.5 (t, C-1"), 35.3 (t, C-4), 37.1 (q, NCH_3), 64.2 (t, C-2'), 69.6 (t, C-5), 72.3 (s, C-3), 75.4 (d, C-1').

Experiment 52 (YB 174)

(*R*)-3-((*S*)-1,2-Dihydroxyethyl)-2,3-dimethyl-2-isoxazolidine; hydrochloride (53•HCl).



53 ▪ HCl

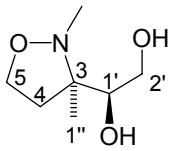
950 mg (3.94 mmol) of the isoxazolidine **25b** was added to 40 mL of HCl (6.0 N). The reaction mixture was kept with stirring for 24 h at room temp., then the solvent was concentrated *in vacuo* (60 °C/20 mbar) to give brownish oil, then purified by column

chromatography (SiO_2, 2 cm x 15 cm, CH_2Cl_2/ MeOH 85:15 to 1:1) to yield 695 mg (89 %) spectroscopic pure diol **53•HCl** as a colourless oil.

$[\alpha]_D^{20}$ = 34.3 (*c* = 1.00, MeOH)

IR: $\tilde{\nu}$ = 3324 (vs, b), 2953 (w), 2534 (m), 1634 (m), 1449 (s), 1388 (m), 1227 (w), 1188 (w), 1094 (s), 1058 (vs), 1008 (m), 968 (w), 881 (w) cm^{-1}.

^{1}H NMR (500.1 MHz, CD_3OD): δ = 1.48 (s, 3 H, 1"-H), 2.46-2.53 (m, 1 H, 4-H_a), 2.66-2.72 (m, 1 H, 4-H_b), 3.21 (s, 3 H, NCH_3), 3.67 (d, $J_{1',2'}$ = 4.5 Hz, 2 H, 2'-H), 3.96-4.02 (m, 1 H, 1'-H), 4.28-4.33 (m, 1 H, 5-H_a), 4.39.4.44 (m, 1 H, 5-H_b).

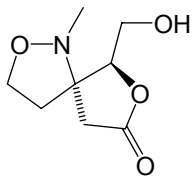


53 • HCl

^{13}C NMR (125.8 MHz, CD_3OD): δ = 15.7 (t, C-1"), 40.8 (t, C-4), 40.9 (q, NCH_3), 64.5 (t, C-2'), 71.5 (t, C-5), 75.5 (d, C-1'), 78.3 (s, C-3).

Experiment 53 (YB 209, MI 22)

(5*S*,6*S*)-6-Hydroxymethyl-1-methyl-2,7-dioxa-1-azaspiro[4.4]nonan-8-one (55).



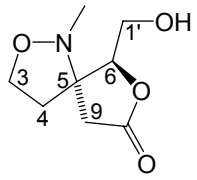
54

To 500 mg (1.60 mmol) of isoxazolidine **26a**, 15 mL of HCl (1.4 M in MeOH) was added and left with stirring for 48 h at room temp., then the solvent was concentrated *in vacuo* (10 mbar/ 30 °C) to give 400 mg of a yellowish oil, which was neutralized with sat. $NaHCO_3$ solution (25 mL), to this mixture 5 gram of silica gel was added, and then concentrated *in vacuo* (20 mbar/ 60°C), then purified by column chromatography (SiO_2, 2 cm x 20 cm, CH_2Cl_2/ MeOH 9:1) to afford 205 mg of the isoxazolidinolactone **54** (69 %) as a colourless oil. Crystallization from ethanol/petroleum ether gave a colourless crystals (m.p. 101-103 °C), suitable for crystal structure determination (m.p. 102 °C, see appendix 12.1.6).

$[\alpha]_D^{20}$ = - 68.1 (*c* = 1.00, CH_2Cl_2)

$C_8H_{13}NO_4$	calc.	C 51.33	H 6.99	N 7.48
(187.2)	found	C 51.43	H 7.00	N 7.37

IR (KBr) : $\tilde{\nu}$ = 3405 (vs), 2930 (m), 2900 (m), 2890 (m), 2840 (m), 1760 (vs), 1475 (m), 1462 (w), 1395 (w), 1370 (s), 1275 (w), 1345 (s), 1285 (s), 1230 (m), 1170 (vs), 1110 (m), 1090 (w), 1060 (m), 1035 (m), 1015 (vs), 990 (s), 910 (s), 880 (m), 850 (m), 810 (m), 775 (s) cm^{-1}.



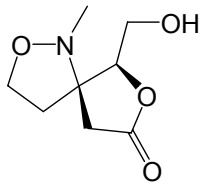
54

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.39 (ddd, $J_{3a,4a}$ = 7.7, $J_{3b,4a}$ = 10.2, $J_{4a,4b}$ = 12.7 Hz, 1 H, 4-H_a), 2.49 (d, $J_{9a,9b}$ = 17.1 Hz, 1 H, 9-H_a), 2.55 ("ddd", $J_{3a,4b}$ = 8.9, $J_{3b,4b}$ = 4.3, $J_{4a,4b}$ = 12.8 Hz, 1 H, 4-H_b), 2.60 (s, 3 H, NC$\underline{H}_3$), 3.04 (d, $J_{9a,9b}$ = 17.1 Hz, 1 H, 9-H_b), 3.83 (dd, $J_{6,1'a}$ = 4.9, $J_{1'a,1'b}$ = 12.6 Hz, 1 H, 1'-H_a), 3.94 (dd, $J_{6,1'b}$ = 3.3, $J_{1'a,1'b}$ = 12.6 Hz, 1 H, 1'-H_b), 4.02 (dt, $J_{3a,3b}$ = 8.8, $J_{3a,4a}$ = $J_{3a,4b}$ = 7.9 Hz, 1 H, 3-H_a), 4.19 (dd, $J_{6,1'a}$ = 4.9, $J_{6,1'b}$ = 3.3 Hz, 1 H, 6-H), 4.28 (ddd, $J_{3a,3b}$ = 10.1, $J_{3b,4a}$ = 4.2, $J_{3b,4b}$ = 8.2 Hz, 1 H, 3-H_b).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 35.1 (t, C-9), 38.2 (t, C-4), 40.8 (q, N$\underline{C}H_3$), 61.5 (t, C-1'), 65.3 (t, C-3), 71.9 (s, C-5), 86.6 (d, C-6), 173.0 (s, $\underline{C}$=O).

Experiment 54 (MI 26)

(5*R*,6*S*)-6-Hydroxymethyl-1-methyl-2,7-dioxa-1-azaspiro[4.4]nonan-8-one (55).



55

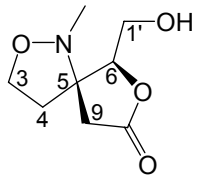
To 567 mg (1.80 mmol) of isoxazolidine **26b**, 40 mL of HCl (6 N) was added and left stirring over 29 h at room temp., then the solvent was concentrated *in vacuo* (10 mbar/ 60 °C) to give a yellowish oil, which was neutralized with sat. $NaHCO_3$ solution (25 mL), and then concentrated *in vacuo* (20 mbar/ 60°C) to give 290 mg of 37, which purified through silica gel plates (Silica gel 60 F_{254} 20 × 20 thickness 0.25 mm) to afford 85 mg of the isoxazolidinolactone **55** (25 %) as colourless crystals (m.p. 118-119 °C).

$[\alpha]_D^{20}$ = 12.4 (*c* = 1.00, CH_2Cl_2)

$C_8H_{13}NO_4$	calc.	C 51.33	H 6.99	N 7.48
(187.2)	found	C 51.19	H 6.98	N 7.32

IR (KBr) : $\tilde{\nu}$ = 3270 (vs), 2950 (m), 2900 (m), 2870 (m), 2810 (m), 1770 (s), 1470 (m), 1440 (m), 1385 (m), 1340 (w), 1275 (w), 1240 (m), 1180 (vs), 1110 (m), 1095 (w), 1040 (m), 1025 (vs), 940 (w), 895 (m), 835 (m), 760 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.40 (ddd, $J_{4a,4b}$ = 13.0, $J_{4a,3b}$ and $J_{4a,3a}$ = 9.5 and 6.1 Hz, 1 H, 4-H_a); 2.58 (s, NC$\underline{H}_3$) and 2.51-3.02 (m, 9-H, 4-H_b; together 6 H); 3.81 (dd, $J_{6,1'a}$ = 2.6, $J_{1'a,1'b}$ = 12.7 Hz, 1 H, 1'-H_a), 3.92 (ddd, $J_{3a,3b}$ = 9.4, $J_{3b,4a}$ and $J_{3b,4b}$ = 7.9 and 6.1 Hz, 1 H, 3-H_a); 3.96-4.08 (m, 6-H) and 4.03 (dd, $J_{6,1'b}$ = 3.2, $J_{1'a,1'b}$ = 12.8 Hz, 1 H, 1'-H_b; together 2 H); 4.46 (m, 1 H, 3-H_b).

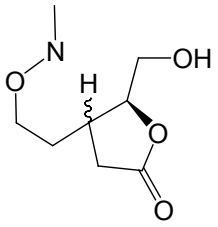


55

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 33.9 (t, C-9), 36.5 (t, C-4), 37.7 (q, N$\underline{C}H_3$), 62.2 (t, C-1'), 64.7 (t, C-3), 71.3 (s, C-5), 86.3 (d, C-6), 175.2 (s, $\underline{C}$=O).

Experiment 55 (YB 216)

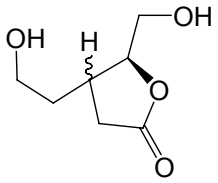
(4*RS*,5*S*)-5-Hydroxymethyl-4-[2-(*N*-methylaminooxy)-ethyl]-dihydrofuran-2-one (56)



56

and

(4*RS*,5*S*)-4-(2-Hydroxyethyl)-5-hydroxymethyldihydrofuran-2-one (57)



57

0.71 g (2.27 mmol) of isoxazolidine **26a** was added to conc. HCl (20 mL). The mixture was left with stirring for 36 h at room temp., and then concentrated *in vacuo* (60 °C/15 mbar) to give 0.58 g which was neutralized with sat. $NaHCO_3$ solution up to pH 9, then concentrated again, and then filtered through silica gel (SiO_2, 2 cm x 5 cm, CH_2Cl_2/MeOH 9:1) to yield 450 mg. To this crude product in 25 mL of MeOH 200 mg of 10% Pd/C was added. The mixture was kept with stirring for 5 h under hydrogen (1 bar) at room temp., then concentrated *in vacuo* (30 °C/10 mbar) to give a yellowish oil, which was chromatographed (SiO_2, 2 cm x 15 cm, CH_2Cl_2/MeOH 9:1 then 4:6) to afford 318 mg of the spectroscopically pure lactone **56** (74

%, d.r. 63:37) as a colourless oil and 60 mg of the slightly pure lactone **57** (16%, d.r. 65:35), also as a colourless oil.

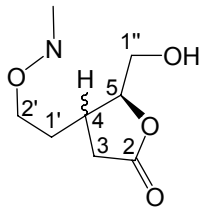
A) (4*RS*,5*S*)-5-Hydroxymethyl-4-[2-(*N*-methylaminooxy)-ethyl]-dihydrofuran-2-one (56)

$C_8H_{17}NO_4$	calc.	C 50.25	H 8.96	N 7.32
(191.2)	found	C 48.70	H 8.90	N 6.91

IR : $\tilde{\nu}$ = 3276 (sb, OH), 2930 (w), 1745 (vs, C=O), 1420 (w), 1358 (w), 1181 (m), 1029 (vs), 936 (m), 799 (w) cm^{-1}.

MS (*m/z*): calc. $C_8H_{17}NO_4$ 191.2, found 191.2 (molecular peak).

^{1}H NMR (500.1 MHz, CD_3OD) : δ = 1.47-1.55 (m, 1 H, 1'-H_a), 1.70 (ddt, $J_{1'a,1'b}$ = 11.8, $J_{4,1'b}$ and ($J_{1'b,2'a}$ = $J_{1'b,2'b}$) = 4.7 and 7.0 Hz, 1 H, 1'-H_b), 2.11-2.18 (m, 1 H, 4-H), 2.22 (dd, $J_{3a,3b}$ = 14.4, $J_{3a,4}$ = 6.9 Hz, 1 H, 3-H_a), 2.38 (dd, $J_{3a,3b}$ = 14.5, $J_{3b,4}$ = 6.8 Hz, 1 H, 3-H_b), 2.71 (s, 3 H, NCH_3), 3.48-3.64 (m, 5 H, 1"-H, 5-H, H-2').



56

The peaks of the minor diasteromer were totally overlaped with the major one.

I) Major diastereomer **56**:

^{13}C NMR (125.8 MHz, CD_3OD) : δ = 28.0 (s, NCH_3), 36.6 (d, C-1'), 38.3 (d, C-4), 40.4 (t, C-1'), 62.7 (t, C-2'), 66.8 (t, C-1"), 76.9 (d, C-5), 177.7 (s, C=O).

II) Minor diastereomer **56**:

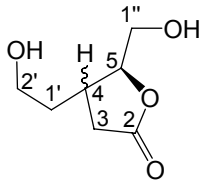
^{13}C NMR (125.8 MHz, CD_3OD) : δ = 28.0 (s, NCH_3), 36.8 (d, C-2'), 37.8 (d, C-3), 38.5 (t, C-2'), 62.5 (t, C-1'), 66.5 (t, C-5), 76.4 (d, C-4), 178.1 (s, C=O).

B) (4*RS*,5*S*)-4-(2-Hydroxyethyl)-5-hydroxymethyldihydrofuran-2-one (57)

$C_7H_{12}O_4$	calc.	C 52.49	H 7.55
(160.2)	found	C 51.51	H 7.56

IR: $\tilde{\nu}$ = 3408 (sb), 2930 (w), 1745 (vs, C=O), 1358 (w), 1181 (m), 1029 (vs), 936 (m), 799 (w) cm^{-1}.

I) Major diastereomer **57**:

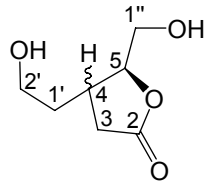


57

^{1}H NMR (500.1 MHz, CD_3OD) : δ = 1.70 (ddt, $J_{4,1'a}$ and $J_{1'a,2'}$ = 9.0 and 6.0, $J_{1'a,1'b}$ = 11.9 Hz, 1 H, 1'-H_a), 1.79-1.90 (m, 1 H, 1'-H_b), 2.43 (dd, $J_{3a,3b}$ = 17.6, $J_{3a,4}$ = 8.3 Hz, 1 H, 3-H_a), 2.56-2.65 (m, 1 H, 4-H), 2.83 (dd, $J_{3a,3b}$ = 17.6, $J_{3b,4}$ = 8.9 Hz, 1 H, 3-H_b), 3.60-3.73 (m, 3 H, 2'-H, 1"-H_a), 3.88 (dd, $J_{5,1"b}$ = 2.8, $J_{1"a,1"b}$ = 12.6 Hz, 1 H, 1"-H_b), 4.35 ("ddd", $J_{4,5}$ and $J_{5,1"a}$ = 7.2 and 4.6, $J_{5,1"b}$ = 2.8 Hz, 1 H, 5-H).

^{13}C NMR (125.8 MHz, CD_3OD) : δ = 35.0 (d, C-4), 36.1 (t, C-3), 36.9 (t, C-1'), 60.8 (t, C-2'), 63.4 (t, C-1"), 87.9 (d, C-5), 179.4 (s, C=O).

II) Minor diastereomer **57**:



57

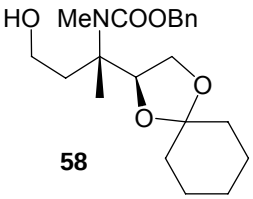
^{1}H NMR (500.1 MHz, CD_3OD) : δ = 1.77-1.84 (m, 1 H, 1'-H_a), 1.89-1.97 (m, 1 H, 1'-H_b), 2.55 (dd, $J_{3a,3b}$ = 17.2, $J_{3a,4}$ = 10.9 Hz, 1 H, 3-H_a), 2.61 (dd, $J_{3a,3b}$ = 17.1, $J_{3b,4}$ = 8.9 Hz, 1 H, 3-H_b), 2.84-2.92 (m, 1 H, 4-H), 3.60-3.73 (m, 3 H, 2'-H, 1"-H_a), 3.86 (dd, $J_{5,1"b}$ = 3.3, $J_{1"a,1"b}$ = 12.5 Hz, 1 H, 1"-H_b), 4.64 (dt, $J_{4,5}$ = 6.6, $J_{5,1"a}$ = $J_{5,1"b}$ = 3.3 Hz, 1 H, 5-H).

^{13}C NMR (125.8 MHz, CD_3OD) : δ = 32.7 (t, C-1'), 35.6 (t, C-3), 36.5 (d, C-4), 61.5 (t, C-2'), 62.1 (t, C-1"), 84.5 (d, C-5), 180.0 (s, C=O).

11.7 Synthesis of Protected Amino Alcohols and Protected Polyols

Experiment 56 (YB 87)

(2*S*, 3*S*)-3-(*N*-Benzyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriol (58)



58

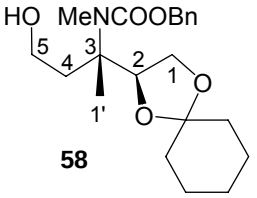
490 mg (2.01 mmol) of aminoalcohol **41** and 224 mg (2.22 mmol, in 3 mL CH_2Cl_2) of triethylamine were added to 15 mL of abs. CH_2Cl_2 at 0 °C. To this mixture 376 mg (2.22

mmol, in 3 mL CH_2Cl_2) of benzylchloroformate was added. The reaction mixture was kept with stirring for 24 h, the temperature was allowed to rise to room temp. Then the mixture was quenched with water (50 mL), partitioned against CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with sat. NaCl solution (40 mL), then dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) to give 750 mg of protected amino alcohol **58**. This filtered through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 1:9) to give 550 mg as yellowish oil. This was purified by MPLC (petroleum ether/ethyl acetate 1:1) to yield 230 mg (32 %) of analytical pure alcohol **59** as colourless oil.

$[\alpha]_D^{20}$ = - 6.20 (*c* = 0.33, CH_2Cl_2)

$C_{21}H_{31}NO_5$	calc.	C 66.81	H 8.28	N 3.71
(377.5)	found	C 66.34	H 8.34	N 3.64

IR : $\tilde{\nu}$ = 3365 (m, b; OH), 2931 (s), 2855 (m), 1745 (w), 1680 (s, C=O), 1449 (m), 1365 (w), 1162 (m), 1099 (vs), 1070 (vs), 1038 (vs), 936 (s), 733 (m), 699 (s) cm^{-1}.



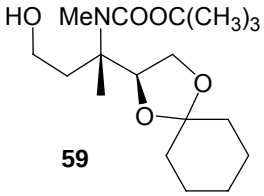
58

^{1}H NMR (500.1 MHz, $CDCl_3$, rotamer ratio 84:16) : δ = 1.04 (s, 3 H, 1'-H) 1.32-1.68 [m, 10 H, $C(CH_2)_5$], 1.79-1.84 (m, 1 H, 4-H_a), 1.91-1.96 (m, 1 H, 4-H_b), 3.34 (s, 3 H, NC$\underline{H}_3$), 3.79 (dd, $^2J_{1a,1b}$ = 8.3, $J_{1a,2}$ = 7.5 Hz, 1-H_a), 3.96 (dd, $^2J_{1a,1b}$ = 8.3, $J_{1b,2}$ = 7.1 Hz, 1 H, 1-H_b), 4.07 (t, $J_{1,2}$ = 7.0 Hz, 1 H, 2-H), 4.28-4.36 (m, 2 H, 5-H), 5.17 (s, 2 H, CH_2Ph), 7.33-7.41 (m, 5 H, C_6H_5)

^{13}C NMR (125.1 MHz, $CDCl_3$, rotamer ratio 84:16) : δ = 19.9 (q, C-1'), 23.9, 24.0, 25.2, 33.3, 34.3, 35.9 [6 t, C-4, C($\underline{C}H_2)_5$], 28.5 (q, NHCH_3), 55.3 (s, C-3), 64.8, 65.0 (2 t, C-5, C-1), 69.5 (t, CH_2Ph), 79.7 (d, C-2), 109.5 [s, $\underline{C}(CH_2)_5$], 128.3, 128.5, 128.6 (3 d, *o-, m-, p*-C of C_6H_5), 135.3 (s, *i*-C of C_6H_5), 155.2 (s, C=O).

Experiment 57 (YB 247)

(2*S*, 3*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriol (59)



59

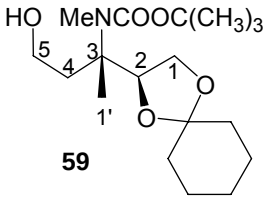
To a solution of the aminoalcohol **41** (260 mg, 1.07 mmol) in 20 mL of abs. ethyl acetate, 606 mg (2.78 mmol, 2.6 eq) of *tert*-butyloxycarbonyl (Boc_2O, Fluka) was added at room temp.

The mixture was left with stirring for 3 d, and then concentrated *in vacuo* (30 °C/10 mbar) to give 560 mg of protected amino alcohol **59**. Then was filtered through silica gel (2 cm x 5 cm, petroleumether/ethyl acetate 3:7) to give 510 mg of crude **59**. This was purified by MPLC (petroleum ether/ethyl acetate 1:1) to give 198 mg (75 %) of analytically pure protected amino alcohol **59** as colourless oil.

$[\alpha]_D^{20}$ = - 5.00 (*c* = 1.00, CH_2Cl_2)

$C_{18}H_{33}NO_5$	calc.	C 62.94	H 9.68	N 4.08
(343.4)	found	C 62.73	H 9.71	N 3.99

IR: $\tilde{\nu}$ = 3454 (sb, OH), 2934 (s), 2862 (w), 1688 (vs), 1447 (m), 1364 (vs), 1251 (m), 1156 (vs), 1098 (vs), 1037 (vs), 961 (m) cm^{-1}.



59

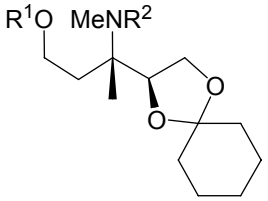
^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.33 (s, 1'-H) and 1.45 (s, $C(C\underline{H}_3)_3$) and 1.35-1.68 [m, $C(C\underline{H}_2)_5$]; together 22 H); 2.16-2.23 (m, 2 H, 4-H), 2.50 (sb, 1 H, OH), 2.87 (s, 3 H, $NC\underline{H}_3$), 3.66-3.78 (m, 5-H) and 3.74 (dd, $^2J_{1a,1b}$ = 8.3, $J_{1a,2}$ = 6.9 Hz, 1-H_a; together 3 H); 3.98 (dd, $^2J_{1a,1b}$ = 8.4, $J_{1b,2}$ = 7.0 Hz, 1 H, 1-H_b), 5.08 (t, $J_{1,2}$ = 6.9 Hz, 1 H, 2-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.0 (q, C-1'), 23.8, 24.0, 25.2, 34.2, 35.7 [5 t, $C(\underline{C}H_2)_5$], 28.5 [q, $C(C\underline{H}_3)_3$], 32.6 (q, $NHCH_3$), 40.2 (t, C-4), 59.2 (t, C-5), 61.5 (s, C-3), 65.4 (t, C-1), 78.5 (d, C-2), 80.1 [s, $\underline{C}(CH_3)_3$], 110.1 [s, $\underline{C}(CH_2)_5$], 155.8 (s, C=O).

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

Experiment 58 (YB 97)

(2*S*, 3*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriol (59)



59 R^1 = H, R^2 = $COOC(CH_3)_3$
60 R^1 = $COOC(CH_3)_3$, R^2 = H
61 R^1 = $COOC(CH_3)_3$, R^2 = $COOC(CH_3)_3$

5-*tert*-Butyl (2*S*, 3*S*)-3-(*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriolcarbonate (60)

5-*tert*-Butyl (2*S*, 3*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriolcarbonate (61)

740 mg (3.39 mmol, 1.5 eq) of *tert*-butyloxycarbonyl (Boc_2O, Fluka) was added to 550 mg (2.26 mmol) of the amino alcohol **41** in 20 mL MeOH at room temp. The reaction mixture was left with stirring for 3 d, and then concentrated *in vacuo* (30 °C/10 mbar) to give 1.21 g of yellowish oil. This was chromatographed through silica gel (3 cm x 15 cm, petroleum ether/ethyl acetate 6:4) to give 150 mg of slightly pure protected amino alcohol **61** (15 %) as a colourless oil, and 60 mg (8 %) of analytically and spectroscopically pure protected amino alcohol **59** and finally 320 mg (41 %) of analytically and spectroscopically pure protected aminoalocohol **60** successivly, also as a colourless oil.

A) (2*S*,3*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriol (59)

$[\alpha]_D^{20}$ = - 5.0 (*c* = 1.00, CH_2Cl_2)

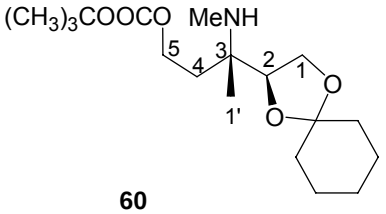
The analytical analysis fully complied with those given in Exp. 57.

B) 5-*tert*-Butyl (2*S*,3*S*)-3-(*N*-methylamino)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriolcarbonate (60)

$[\alpha]_D^{20}$ = - 4.0 (*c* = 1.00, CH_2Cl_2)

$C_{18}H_{33}NO_5$	calc.	C 62.94	H 9.68	N 4.08
(343.4)	found	C 62.86	H 9.78	N 4.07

IR : $\tilde{\nu}$ = 3419 (b, OH), 3299 (b, w), 2975 (vs), 2936 (vs), 2861 (vs), 2781 (m), 1739 (vs, C=O), 1478 (s), 1450 (s), 1394 (m), 1368 (s), 1279 (vs), 1255 (s), 1163 (m), 1101 (m), 937 (m), 862 (m), 794 (m) cm^{-1}.



60

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, 1'-H), 1.48 (s, C(C<u>H</u>$_3$)$_3$) and 1.35-1.68 (m, $C(CH_2)_5$; together 19 H); 1.79 (ddd, $J_{4a,4b}$ = 14.2, $J_{4a,5a}$ = 6.8, $J_{4a,5b}$ = 8.5 Hz, 1 H, 4-H_a), 1.92 ("ddd", $J_{4a,4b}$ = 14.2, $J_{4b,5a}$ = 8.4, $J_{4b,5b}$ = 6.6 Hz, 1 H, 4-H_b), 2.34 (s, 3 H, NC<u>H</u>$_3$), 3.79 (dd, $^2J_{1a,1b}$ = 8.2, $J_{1a,2}$ = 7.3 Hz, 1-H_a), 3.98 (dd, $^2J_{1a,1b}$ = 8.2, $J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.06 (t, $J_{1,2}$ = 7.0 Hz, 1 H, 2-H), 4.21 (ddd, $J_{5a,5b}$ = 9.0, $J_{5a,4a}$ = 6.6, $J_{5b,4b}$ = 8.4 Hz, 5-H_a) and 4.18-4.24 (m, 5-H_b; together 2 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.0 (q, C-1'), 23.8, 24.0, 25.2, 34.4, 36.0 [5 t, C(<u>C</u>H$_2$)$_5$], 27.8 [q, C(C<u>H</u>$_3$)$_3$], 28.5 (q, $NHCH_3$), 33.3 (t, C-4), 55.4 (s, C-3), 63.8 (t, C-5), 64.9 (t, C-1), 79.8 (d, C-2), 81.9 [s, <u>C</u>(CH$_3$)$_3$], 109.6 [s, <u>C</u>(CH$_2$)$_5$], 153.6 (s, C=O).

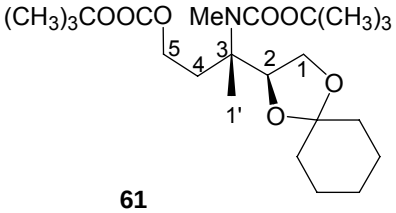
The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

C) 5-*tert*-Butyl(2*S*, 3*S*)-3-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino)-1,2-*O*-cyclohexylidene -3-methyl-1,2,5-pentanetriolcarbonate (61)

$[\alpha]_D^{20}$ = - 11.5 (*c* = 1.00, CH_2Cl_2)

$C_{18}H_{33}NO_5$	calc.	C 62.28	H 9.32	N 3.16
(343.4)	found	C 61.65	H 9.46	N 2.92

IR : $\tilde{\nu}$ = 2975 (m), 2934 (s), 2862 (m), 1738 (vs, OC=O), 1691 (NC=O), 1478 (w), 1450 (m), 1392 (m), 1366 (s), 1277 (vs), 1253 (vs), 1159 (vs), 1098 (vs), 1037 (m), 938 (m), 909 (w), 864 (m), 628 (s) cm^{-1}.



61

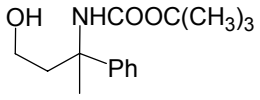
^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.34 (s, 1'-H) and 1.45, 1.45 (2 s, $NCOOC(C\underline{H}_3)_3$, $OCOOC(C\underline{H}_3)_3$) and 1.33-1.68 (m, $C(CH_2)_5$; together 31 H); 1.79 (ddd, $J_{4a,4b}$ = 14.4, $J_{4a,5a}$ = 8.0, $J_{4a,5b}$ = 6.6 Hz, 1 H, 4-H_a), 1.92 ("ddd", $J_{4a,4b}$ = 14.4, $J_{4b,5a}$ = 6.7, $J_{4b,5b}$ = 7.7 Hz, 1 H, 4-H_b), 2.87 (s, 3 H, $NC\underline{H}_3$), 3.71 (dd, $^2J_{1a,1b}$ = 8.6, $J_{1a,2}$ = 6.6 Hz, 1-H_a), 3.94 (dd, $^2J_{1a,1b}$ = 8.6, $J_{1b,2}$ = 7.0 Hz, 1 H, 1-H_b), 4.13 (ddd, $J_{5a,5b}$ = 11.6, $J_{5a,4a}$ = 8.0, $J_{5b,4b}$ = 6.5 Hz, 5-H_a) and 4.11-4.17 (m, 5-H_b; together 2 H); 4.95 (t, $J_{1,2}$ = 6.8 Hz, 1 H, 2-H),

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 19.2 (q, C-1'), 23.8, 24.1, 25.3, 34.2, 35.8 [5 t, $C(\underline{C}H_2)_5$], 27.8, 28.5 [2 q, $NCO_2C(\underline{C}H_3)_3$, $OCO_2C(\underline{C}H_3)_3$], 33.0 (q, $NHCH_3$), 35.9 (t, C-4), 60.9 (s, C-3), 63.7 (t, C-5), 65.1 (t, C-1), 78.7 (d, C-2), 80.0, 81.8 [2 s, $NCO_2\underline{C}(CH_3)_3$, $OCO_2\underline{C}(CH_3)_3$], 110.1 [s, $\underline{C}(CH_2)_5$], 153.7 (s, OC=O), 155.6 (s, NC=O).

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

Experiment 59 (YB 235)

1-(Amino-*N*-*tert*-butyloxycarbonyl)-3-hydroxy-1-methyl-1-phenylpropane (62)



62

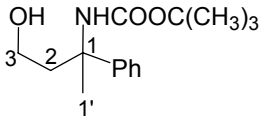
Scale: 450 mg (3.06 mmol) isoxazolidine **44**
125 mg of Pd/C (10 %)
20 mL abs. MeOH
900 mg (4.59 mmol, 3 eq) Boc_2O

The reaction was performed according to TP 3 with addition of Boc_2O to the mixture. This was kept with stirring for 40 h, to afford 920 mg of crude protected amino alcohol **62**. Filtration through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 4:6) gave 810 mg of crude **62**. This was purified by MPLC (petroleum ether/ethyl acetate 7:3) to afford after evaporation of solvent 650 mg (89 %) of analytically and spectroscopically pure protected amino alcohol **62** as a colourless solid (m. p. 79-81 °C). Crystallization from petroleum ether produced **62** in the form of white hair.

$C_{15}H_{23}NO_3$	calc.	C 67.90	H 8.74	N 5.28
(265.3)	found	C 67.66	H 8.89	N 5.24

IR: $\tilde{\nu}$ = 3351 (m, OH), 3299 (m), 2920 (w), 1707 (vs, C=O), 1595 (m), 1494 (s), 1439 (m), 1429 (w), 1372 (m), 1172 (s), 1099 (s), 1028 (vs), 766 (vs) cm^{-1}.

?!1!H NMR (300 MHz, $CDCl_3$): δ = 1.25 [s, 9 H, C(C<u>H</u>$_3$)$_3$], 1.75 (s, 3 H, 1'-H), 2.00 (sb, 2 H, 2-H), 2.38 (sb, 1 H, NH), 3.53 (sb, 1 H, 3-H_a), 3.65 (sb, 1 H, 3-H_b), 6.11 (sb, 1 H, OH), 7.19-7.37 (m, 5 H, C_6H_5).

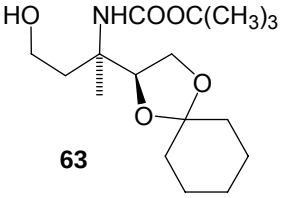


62

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.7 (q, C-1'), 28.3 [s, C(<u>C</u>H$_3$)$_3$], 45.3 (t, C-2), 57.8 (s, C-1), 59.2 (t, C-3), 79.1 [s, <u>C</u>(CH$_3$)$_3$], 125.1, 126.3, 128.2 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 146.2 (s, *i*-C of C_6H_5), 154.7 (s, C=O)

Experiment 60 (YB 237)

(2*S*, 3*R*)-3-(Amino-*N*-*tert*-butyloxycarbonyl)-1,2-*O*-cyclohexylidene-3-methyl-1,2,5-pentanetriol (63)



63

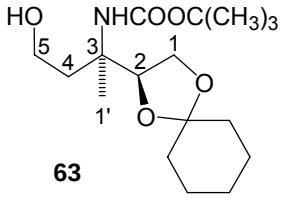
250 mg of the amino alcohol **45** (1.09 mmol) and Boc_2O (380 mg, 1.74 mmol, 1.6 eq) were added to abs. MeOH (20 mL). The mixture was left with stirring for 48 h at room temp., then concentrated in vacuo (30 °C/10 mbar) to give 450 mg of crude **63** as a yellowish oil. Filtration through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 95:5 then 4:6) gave 350 mg. This was purified by MPLC (petroleum ether/ethyl acetate 7:3) to afford after evaporation of the solvent 270 mg (75 %) of analytically and spectroscopically pure protected amino alcohol **63** as a colourless oil.

$[\alpha]_D^{20}$ = - 2.6 (*c* = 1.00, CH_2Cl_2)

$C_{17}H_{31}NO_5$	calc.	C 61.98	H 9.49	N 4.25
(329.4)	found	C 61.96	H 9.47	N 4.16

IR: $\tilde{\nu}$ = 3401 (sb, OH), 2934 (s), 1712 (s, C=O), 1498 (s), 1449 (m), 1365 (vs), 1281 (m), 1251 (m), 1161 (vs), 1097 (vs), 1070 (vs), 1047 (vs), 937 (m), 848 (w), 780 (w) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.34 (s, 1'-H) and 1.42 (s, $C(C\underline{H}_3)_3$) and 1.35-1.67 (m, $C(CH_2)_5$; together 22 H); 1.80-1.87 (m, 1 H, 4-H_a), 2.05-2.16 (m, 1 H, 4-H_b), 2.93 (sb, 1 H, OH), 3.66-3.71 (m, 5-H_a) and 3.73-3.79 (m, 5-H_b) and 3.86 (dd, $J_{1a,1b}$ = 8.4, $J_{1a,2}$ = 7.4, 1-H_a; together 3 H); 4.00 (dd, $J_{1a,1b}$ = 8.4, $J_{1b,2}$ = 6.6 Hz, 1 H, 1-H_b), 4.15 (dd, $J_{1a,2}$ = 7.4, $J_{1b,2}$ = 6.6 Hz, 1 H, 2-H).

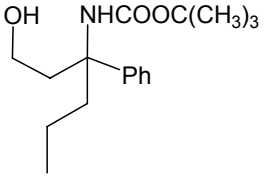


63

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.8 (q, C-1'), 23.7, 23.9, 25.0, 34.3, 35.9 [5 t, $C(\underline{C}H_2)_5$], 28.4 [q, $C(C\underline{H}_3)_3$], 40.7 (t, C-4), 54.7 (s, C-3), 58.7 (t, C-5), , 64.9 (t, C-1), 79.3 [s, $\underline{C}(CH_3)_3$], 80.7 (d, C-2), 110.2 [s, $\underline{C}(CH_2)_5$], 155.5 (s, C=O).

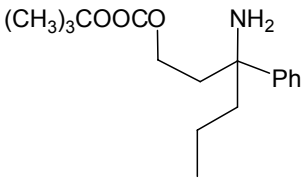
Experiment 61 (YB 147)

1-(Amino-*N*-*tert*-butyloxycarbonyl-2-hydroxyethyl)-1-phenylbutane (64)



64

***tert*-Butyl 3-amino-3-phenylhexane carbonate (65)**



65

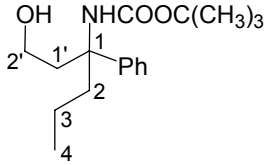
170 mg of the amino alcohol **46** (0.880 mmol) and Boc_2O (384 mg, 1.76 mmol, 2.0 eq) were added to abs. CH_2Cl_2 (30 mL). The mixture was left with stirring for 48 h at room temperature, then concentrated *in vacuo* (10 mbar) to give 440 mg of crude products as a yellowish oil, which filtered through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 95:5 then 1:1) to afford after evaporation of the solvent 190 mg (74 %) of analytically and spectroscopically pure protected amino alcohol **64** as a colourless oil, and 21 mg (8 %) of protected amino alcohol **65**, also as a colourless oil.

A) 1-(Amino-*N*-*tert*-butyloxycarbonyl-2-hydroxyethyl)-1-phenylbutane (64)

$C_{17}H_{27}NO_3$	calc.	C 69.59	H 9.28	N 4.77
(293.39)	found	C 69.24	H 9.22	N 4.65

IR: $\tilde{\nu}$ = 3327 (m, OH), 3291 (m), 1709 (vs, C=O), 1601 (s), 1491 (s), 1439 (m), 1429 (w), 1381 (m), 1199 (w), 769 (m), 766 (s), 699 (vs), 639 (m), 580 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 0.88 (t, $J_{3,4}$ = 7.3, 3 H, 4-H), 1.12-1.46 [m, 12 H, 2-H_a, 3-H, C(C$\underline{H}_3$)$_3$], 1.81-1.85 (m, 1 H, 1'-H_a), 2.05-2.25 (m, 3 H, NH, 2-H_b, 1'-H_b), 3.49-3.61 (m, 2 H, 2'-H), 5.52 (sb, 1 H, OH), 7.18-7.31 (m, 5 H, C_6H_5).



64

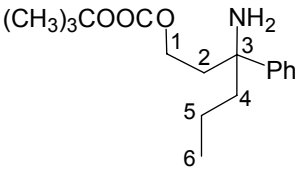
^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.7 (q, C-4), 17.4 (t, C-3), 28.7 [q, C(C$\underline{H}_3$)$_3$], 41.4, 42.3 (2 t, C-2, C-1'), 59.5 (t, C-2'), 60.8 (s, C-1), 79.5 [s, $\underline{C}$(CH$_3$)$_3$], 125.8, 126.8, 128.5 (3 d, *o-, m-, p-*C of C_6H_5), 145.3 (s, *i*-C of C_6H_5), 155.1 (s, C=O).

B) *tert*-Butyl 3-amino-3-phenylhexane carbonate (65)

$C_{17}H_{27}NO_3$	calc.	C 69.59	H 9.28	N 4.77
(293.39)	found	C 70.12	H 8.75	N 4.77

IR: $\tilde{\nu}$ = 2963 (s), 2932 (m), 2873 (m), 1716 (vs, C=O), 1692 (vs), 1494 (w), 1448 (m), 1391 (vs), 1252 (m), 1156 (vs), 1099 (vs), 1032 (w), 1014 (w), 889 (w), 761 (m), 701 (s), 662 (vs) cm^{-1}.

^{1}H NMR (300.1 MHz, $CDCl_3$) : δ = 1.02 (t, $J_{5,6}$ = 7.3, 3 H, 6-H), 1.29 [s, 9 H, C(C$\underline{H}_3$)$_3$], 1.43-1.53 (m, 2 H, 5-H), 2.14-2.23 (m, 1 H, 4-H_a), 2.28-2.38 (m, 1 H, 4-H_b), 2.48 (ddd, $J_{2a,2b}$ = 12.3, $J_{1a,2a}$ and $J_{1b,2a}$ = 6.3 and 7.1 Hz, 1 H, 2-H_a), 2.67 (dt, $J_{2a,2b}$ = 12.3, $J_{1a,2b}$ = $J_{1b,2b}$ = 7.1 Hz, 1 H, 2-H_b), 4.01-4.06 (m, 2 H, 1-H), 7.22-7.41 (m, 5 H, C_6H_5).

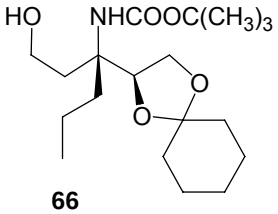


65

^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 14.8 (q, C-6), 17.7 (t, C-5), 28.5 [q, C(C$\underline{H}_3$)$_3$], 40.1, 45.1 (2 t, C-2, C-4), 66.5 (t, C-1), 69.0 (s, C-3), 81.4 [s, $\underline{C}$(CH$_3$)$_3$], 125.6, 127.1, 128.6 (3 d, *o-, m-, p-*C of C_6H_5), 147.1 (s, *i*-C of C_6H_5), 153.3 (s, C=O).

Experiment 62 (YB 170)

(2*S*, 3*S*)-3-(Amino-*N*-*tert*-butyloxycarbonyl)-1,2-*O*-cyclohexylidene-3-propyl-1,2,5-pentanetriol (66)



66

To 560 mg (2.22 mmol) of the isoxazolidine **34a** in MeOH (30 mL), 200 mg of Pd/C (10 %) and 976 mg of Boc_2O (4.44 mmol, 2.0 eq) were added. The reaction mixture was left with

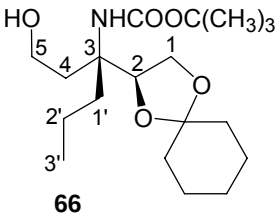
stirring under hydrogen (1 bar) for 36 h. The Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to give 910 mg of crude product **66**. This was purified through silica gel (2 cm x 5 cm, petroleum ether/ether acetate 9:1 then 4:6) to afford 498 mg (63 %) of analytically and spectroscopically pure protected amino alcohol **66** as a colourless oil.

$[\alpha]_D^{20}$ = - 11.1 (*c* = 1.00, CH_2Cl_2)

$C_{19}H_{35}NO_5$	calc.	C 63.83	H 9.87	N 3.92
(357.5)	found	C 63.44	H 9.77	N 3.76

IR : $\tilde{\nu}$ = 4319 (b, OH), 3357 (b, m), 2933 (s), 2872 (m), 1714 (s, C=O), 1505 (s), 1448 (m), 1332 (s), 1280 (m), 1245 (m), 1164 (vs), 1099 (vs), 1036 (vs), 937 (m), 928 (m), 830 (w), 779 (w), 701 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 0.92 (t, $J_{3',2'}$ = 7.2 Hz, 3 H, 3'-H), 1.25-1.63 [m, 2'-H, 4-H_a, C(C$\underline{H}_2$)$_5$] and 1.42 (s, C(C$\underline{H}_3$)$_3$; together 22 H); 1.73-1.88 (m, 1 H, 4-H_b), 1.96-2.04 (m, 2 H, 1'-H), 3.15 (sb, 1 H, NH), 3.70-3.80 (m, 2 H, 5-H), 3.85 (dd, $J_{1a,1b}$ = 8.3, $J_{1a,2}$ = 7.9 Hz, 1 H, 1-H_a), 3.98 (dd, $J_{1a,1b}$ = 8.4, $J_{1b,2}$ = 6.7 Hz, 1H, 1-H_b), 4.37 ("t", $J_{1,2}$ = 7.1 Hz, 1 H, 2-H), 5.05 (sb, 1 H, OH).

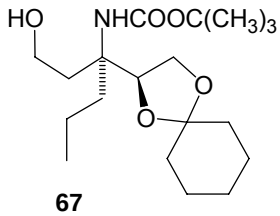


66

^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 14.9 (q, C-3'), 17.0 (t, C-2'), 24.1, 24.3, 25.5, 34.7, 36.2 [5 t, C(C$\underline{H}_2$)$_5$], 36.9 (t, C-4), 37.3 (C-1'), 28.7 [s, C(C$\underline{H}_3$)$_3$], 58.2 (s, C-3), 59.0 (t, C-5), 65.2 (t, C-1), 79.6 (d, C-2), 79.6 [s, C$\underline{(CH_3)_3}$], 110.0 [s, C$\underline{(CH_2)_5}$], 155.7 (s, C=O).

Experiment 63 (YB 172)

(2*S*, 3*R*)-3-(Amino-*N*-*tert*-butyloxycarbonyl)-1,2-*O*-cyclohexylidene-3-propyl-1,2,5-pentanetriol (67)



67

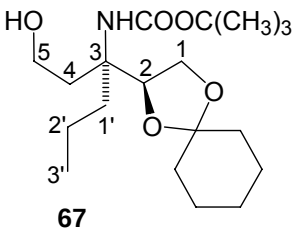
To 305 mg (1.21 mmol) of the isoxazolidine **34b** in MeOH (20 mL), 150 mg of Pd/C (10 %) and 528 mg of Boc_2O (2.42 mmol, 2.0 eq) were added. The reaction mixture was left with stirring under hydrogen (1 bar) for 36 h. The Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to give 360 mg of crude product **67**. This was purified

by column chromatography (SiO_2, 2 cm x 5 cm petroleum ether/ethyl acetate 9:1 then 4:6) to afford 303 mg (70 %) of analytically and spectroscopically pure protected amino alcohol **67** as colourless oil.

$[\alpha]_D^{20}$ = 4.40 (*c* = 1.00, CH_2Cl_2)

$C_{19}H_{35}NO_5$	calc.	C 63.83	H 9.87	N 3.92
(357.5)	found	C 63.64	H 9.76	N 3.85

IR : $\tilde{\nu}$ = 4318 (b, OH), 3357 (b, m), 2933 (s), 2871 (m), 1714 (s, C=O), 1504 (s), 1449 (m), 1332 (s), 1280 (m), 1245 (m), 1161 (vs), 1095 (vs), 1036 (vs), 937 (m), 928 (m), 830 (w), 703 (m) cm^{-1}.



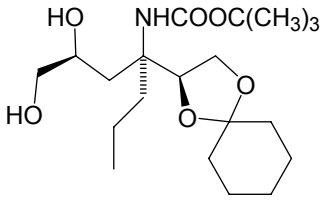
67

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 0.92 (t, $J_{3',2'}$ = 7.2 Hz, 3 H, 3'-H), 1.30-1.65 [m, 2'-H, 4-H_a, C(C$\underline{H}_2$)$_5$] and 1.42 [s, C(C$\underline{H}_3$)$_3$; together 22 H]; 1.85 (ddd, $J_{4a,4b}$ = 12.6, $J_{4b,5a}$ and $J_{4b,5b}$ = 5.1 and 7.5 Hz ,1 H, 4-H_b), 2.15-2.24 (m, 2 H, 1'-H), 3.23 (sb, 1 H, NH), 3.66-3.83 (m, 2 H, 5-H), 3.92 (dd, $J_{1a,1b}$ = 8.5, $J_{1a,2}$ = 7.7 Hz, 1 H, 1-H_a), 4.01 (dd, $J_{1a,1b}$ = 8.5, $J_{1b,2}$ = 6.5 Hz, 1 H, 1-H_b), 4.28 (dd, $J_{2,1a}$ = 7.1, $J_{2,1a}$ = 6.5 Hz, 1 H, 2-H), 5.13 (sb, 1 H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 15.1 (q, C-3'), 17.5 (t, C-2'), 24.1, 24.3, 25.5, 34.7, 36.2 [5 t, C($\underline{C}H_2$)$_5$], 36.9 (t, C-4), 38.6 (C-1'), 28.7 [s, C($\underline{C}H_3$)$_3$], 57.6 (s, C-3), 58.9 (t, C-5), 65.2 (t, C-1), 79.5 [s, $\underline{C}$(CH$_3$)$_3$], 80.2 (d, C-2), 110.2 [s, $\underline{C}$(CH$_2$)$_5$], 155.6 (s, C=O).

Experiment 64 (YB 285)

(2*S*, 3*R*, 5*S*)- 3-(Amino-*N*-*tert*-butyloxycarbonyl)-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5,6-hexanetetraol (68)



68

910 mg (3.21 mmol) of the isoxazolidine **35a** and 500 mg of Pd/C (10 %) and 1404 mg of Boc_2O (6.43 mmol, 2.0 eq) were added in MeOH (40 mL). The reaction mixture was left with stirring under hydrogen (1 bar) for 48 h. The Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to give 905 mg of crude product **68**. Filtration through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 9:1 then 4:6) and then purification by

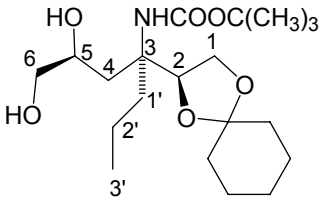
MPLC (petroleum ether/ethyl acetate 1:1) afforded 905 mg (65 %) of analytically and spectroscopically slightly impure protected amino alcohol **68** as colourless oil.

$[\alpha]_D^{20}$ = - 11.8 (*c* = 1.00, CH_2Cl_2)

$C_{20}H_{32}NO_6$	calc.	C 61.99	H 9.62	N 3.61
(387.5)	Found	C 61.24	H 9.27	N 3.50

IR: $\tilde{\nu}$ = 3410 (sb, OH), 2933 (s), 2889 (w), 1711 (s, C=O), 1450 (w), 1391 (s), 1282 (w), 1245 (vs), 1093 (vs), 1031 (vs), 937 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 0.91 (t, $J_{3',2'}$ = 7.3 Hz, 3 H, 3'-H), 1.23-1.36 (m, 2'-H) and 1.42 [s, C(C<u>H</u>$_3$)$_3$] and 1.38-1.72 [m, 4-H, C(C<u>H</u>$_2$)$_5$; together 23 H]; 2.17-2.21 (m, 2 H, 1'-H), 2.59 (sb, 1 H, NH), 3.48 (dd, $J_{5,6a}$ = 7.6, $J_{6a,6b}$ = 10.9 Hz, 1 H, 6-H_a), 3.56 (dd, $J_{5,6b}$ = 3.8, $J_{6a,6b}$ = 10.9 Hz, 1 H, 6-H_b), 3.86-3.90 (m, 1 H, 5-H), 3.92 (dd, $J_{1a,1b}$ = 8.7, $J_{1a,2}$ = 7.5 Hz, 1 H, 1-H_a), 4.02 (dd, $J_{1a,1b}$ = 8.7, $J_{1b,2}$ = 6.6 Hz, 1 H, 1-H_b), 4.35 (t, $J_{1,2}$ = 7.0 Hz, 1 H, 2-H).



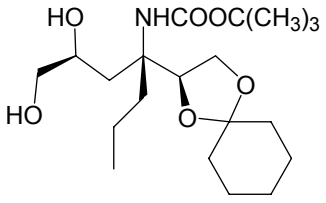
68

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.8 (q, C-3'), 17.3 (t, C-2'), 23.7, 23.9, 25.0, 34.3, 35.8 [5 t, C(<u>C</u>H$_2$)$_5$], 39.2 (t, C-4), 39.4 (t, C-1'), 28.4 [s, C(<u>C</u>H$_3$)$_3$], 57.0 (s, C-3), 64.8 (t, C-6), 67.2 (t, C-1), 67.8 (d, C-5), 79.4 [s, <u>C</u>(CH$_3$)$_3$], 79.9 (d, C-2), 110.2 [s, <u>C</u>(CH$_2$)$_5$], 155.3 (s, C=O).

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

Experiment 65 (YB 277)

(2*S*, 3*S*, 5*S*)- 3-(Amino-*N*-*tert*-butyloxycarbonyl)-1,2-*O*-(Cyclohexylidene)-3-propyl-1,2,5,6-hexanetetraol (69)



69

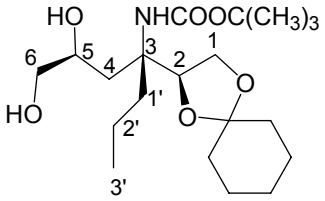
100 mg (0.350 mmol) of the isoxazolidine **35b** and 50 mg of Pd/C (10 %) and 144 mg of Boc_2O (0.53 mmol, 1.5 eq) were added in MeOH (20 mL). The reaction mixture was left with stirring under hydrogen (1 bar) for 48 h. Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to give 195 mg of crude product **69**. Filtration through silica gel (2 cm x 5 cm, petroleum ether/ethyl acetate 9:1 then 4:6) then purification by MPLC (petroleum

ether/ethyl acetate 1:1) afforded 105 mg (77 %) of analytically and spectroscopically pure protected amino alcohol **69** as a colourless oil.

$[\alpha]_D^{20}$ = 7.8 (*c* = 1.00, CH_2Cl_2)

$C_{20}H_{32}NO_6$	calc.	C 61.99	H 9.62	N 3.61
(387.5)	found	C 61.97	H 9.54	N 3.43

IR : $\tilde{\nu}$ = 3413 (sb, OH), 2933 (s), 2871 (w), 1716 (s), 1504 (w), 1449 (w), 1365 (m), 1242 (s), 1162 (vs), 1095 (vs), 1041 (vs), 936 (m) cm^{-1}.



69

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 0.92 (t, $J_{3',2'}$ = 7.3 Hz, 3 H, 3'-H), 1.22-1.30 (m, 2'-H_a) and 1.43 [s, C(C<u>H</u>$_3$)$_3$] and 1.34-1.70 [m, 1'-H_a, 2'-H_b, $C(CH_2)_5$; together 22 H]; 1.77 (dd, $J_{4a,4b}$ = 15.3, $J_{4a,5}$ = 2.2 Hz, 1 H, 4-H_a), 1.87 (dd, $J_{4a,4b}$ = 15.3, $J_{4b,5}$ = 8.8 Hz, 4-H_b) and 1.82-1.89 (m, 1'-H_b; together 2 H); 3.46 (dd, $J_{5,6a}$ = 7.0, $J_{6a,6b}$ = 10.9 Hz, 1 H, 6-H_a), 3.56 (dd, $J_{5,6b}$ = 3.8, $J_{6a,6b}$ = 10.9 Hz, 1 H, 6-H_b), 3.92 ("dddd", $J_{4a,5}$ = 2.2, $J_{4b,5}$ = 9.0, $J_{5,6a}$ = 7.0, $J_{5,6b}$ = 3.8 Hz, 1 H, 5-H), 3.85 (dd, $J_{1a,1b}$ = 8.7, $J_{1a,2}$ = 7.3 Hz, 1 H, 1-H_a), 3.99 (dd, $J_{1a,1b}$ = 8.6, $J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.26 (t, $J_{1,2}$ = 7.0 Hz, 1 H, 2-H).

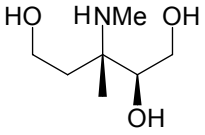
^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.5 (q, C-3'), 16.9 (t, C-2'), 23.7, 23.9, 25.1, 34.2, 35.8 [5 t, C(<u>C</u>H$_2$)$_5$], 37.5 (t, C-4), 42.0 (t, C-1'), 28.3 [s, C(<u>C</u>H$_3$)$_3$], 57.8 (s, C-3), 64.7 (t, C-6), 67.4 (t, C-1), 67.5 (d, C-5), 79.3 (d, C-2), 79.8 [s, <u>C</u>(CH$_3$)$_3$], 109.9 [s, <u>C</u>(CH$_2$)$_5$], 156.0 (s, C=O).

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

11.8 Synthesis of Amino Polyols

Experiment 66 (YB 80)

(2*S*,3*S*)-3-Methyl-3-methylaminopentane-1,2,5-triol (70), cf. lit.[12]

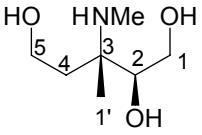


70

In analogy to lit.[1] 235 mg (1.45 mmol) of the isoxazolidine **52** and 100 mg of Pd/C (10%) were added in MeOH (15 mL). The mixture was left with stirring overnight under hydrogen (1 bar) at room temp. Pd/C was filtered off through celite and concentrated *in vacuo* (30 °C/10 mbar) to give 195 mg of amino polyol **70** as colourless oil (83 %; lit. 96 %[1]). The analytical data complied with the literature values.[1]

$[\alpha]_D^{20}$ = 14.3 (*c* = 1.00, MeOH) lit. : $[\alpha]_D^{20}$ = 22.0 (*c* = 0.88, MeOH)[1]

IR: $\tilde{\nu}$ = 3287 (b, vs; OH), 2941 (s), 2879 (s), 2506 (w), 1651 (w), 1467 (m), 1381 (w), 1034 (s), 891 (s) cm^{-1}.



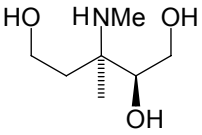
70

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.09 (s, 3 H, 1'-H), 1.62 (ddd, $J_{4a,4a}$ = 14.5, $J_{4a,5a}$ = 5.5, $J_{4a,5b}$ = 6.2 Hz, 1 H, 4-H_a), 1.76 (ddd, $J_{4a,4a}$ = 14.5, $J_{4b,5a}$ = 6.7, $J_{4b,5b}$ = 7.9 Hz, 1 H, 4-H_b), 2.28 (s, 3 H, NHC$\underline{H}_3$), 3.52 (dd, $J_{1a,1b}$ = 8.9, $J_{1a,2}$ = 7.1 Hz, 1-H_a), 3.58-3.64 (m, 2-H) and 3.65 (ddd, $J_{4a,5a}$ = 5.5, $J_{4b,5a}$ = 6.7, $J_{5a,5b}$ = 11.0 Hz, 5-H_a) and 3.69 (dd, $J_{1a,1b}$ = 8.9, $J_{1b,2}$ = 2.3 Hz, 1-H_b) and 3.73 (ddd, $J_{4a,5b}$ = 6.2, $J_{4b,5b}$ = 7.9, $J_{5a,5b}$ = 11.0 Hz, 5-H_b; together 4 H).

^{13}C-NMR (125.8 MHz, CD_3OD) : δ = 21.8 (q, C-1'), 28.1 (q, $NHCH_3$), 38.9 (t, C-4), 60.0 (s, C-3), 60.5 (t, C-5), 65.8 (t, C-1), 77.1 (d, C-2).

Experiment 67 (YB 296)

(2*S*,3*R*)-3-Methyl-3-methylamino-pentane-1,2,5-triol (71)



71

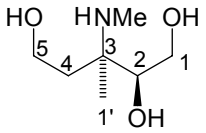
In analogy to lit.[1] to 80 mg (0.33 mmol) of the aminoalcohol **42** 5 mL of HCl (conc.) was added at room temp. and kept with stirring overnight. The solvent was removed *in vacuo* (40 °C/10 mbar) to give 89 mg of brownish oil, which was chromatographed through silica gel

(column 2.5 cm x 10 cm, MeOH/CH_2Cl_2 15:85) to give 51 mg of analytically impure but spectroscopically pure amino polyol **71** as a colourless oil (95 %).

$[\alpha]_D^{20}$ = 4.20 (*c* = 1.00, MeOH)

IR: $\tilde{\nu}$ = 3292 (b, vs; OH), 2939 (s), 2879 (s), 1465 (m), 1380 (w), 1061 (m), 1053 (s), 1043 (m), 632 (vs) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.09 (s, 3 H, 1'-H), 1.70 (ddd, $J_{4a,4a}$ = 14.3, $J_{4a,5a}$ = 7.0, $J_{4a,5b}$ = 7.1 Hz, 4-H_a) and 1.77 (ddd, $J_{4a,4a}$ = 14.3, $J_{4b,5a}$ = 7.7, $J_{4b,5b}$ = 6.6 Hz, 4-H_b; together, 2 H), 2.31 (s, 3 H, NHC$\underline{H}_3$), 3.58 ("dd", $J_{1a,2}$ = 8.1, $J_{1b,2}$ = 5.9 Hz, 2-H) and 3.61 ("ddd", $J_{4a,5a}$ = 7.0, $J_{4b,5a}$ = 7.6, $J_{5a,5b}$ = 13.5 Hz, 5-H_a; together, 2 H), 3.70 (dd, $J_{1a,1b}$ = 9.0, $J_{1a,2}$ = 5.9 Hz, 1-H_a) and 3.71 ("dd", $J_{1a,1b}$ = 8.9, $J_{1b,2}$ = 8.0 Hz, 1-H_b) and 3.71 ("ddd", $J_{4a,5b}$ = 7.0, $J_{4b,5b}$ = 6.7, $J_{5a,5b}$ = 13.5 Hz, 5-H_b; together 3 H).

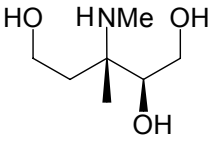


71

^{13}C-NMR (125.8 MHz, CD_3OD) : δ = 20.0 (q, C-1'), 27.8 (q, $NHCH_3$), 37.1 (t, C-4), 59.1 (s, C-3), 59.3 (t, C-5), 64.5 (t, C-1), 75.4 (d, C-2).

Experiment 68 (YB 134)

(2*S*,3*S*)-3-Methyl-3-methylaminopentane-1,2,5-triol; hydrochloride (70•HCl)



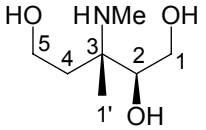
70·HCl

To 780 mg (3.21 mmol) of amino alcohol **41**, 30 mL of HCl (6.0 N) was added at room temp. The reaction mixture was left with stirring for 24 h. The solvent was evaporated *in vacuo* (60 °C/20 mbar) to give 640 mg of analytically and spectroscopically pure amino polyol **70•HCl** as a brownish oil in quantitative yield. Crystallization from MeOH/ethyl acetate gave amino triol **70•HCl** as light-brownish crystals, suitable for crystal structure determination (m.p. 103 °C, see appendix 12.1.7).

$[\alpha]_D^{20}$ = 6.10 (*c* = 1.00, MeOH)

$C_7H_{18}NO_3Cl$	calc.	C 42.10	H 9.09	N 7.02	Cl 17.78
(199.67)	found	C 42.02	H 9.02	N 6.85	Cl 17.88

IR (KBr): $\tilde{\nu}$ = 3349 (vs, b; NH, 3 OH), 2960 (sb), 1580 (m), 1455 (s), 1408 (m), 1378 (m), 1112 (m), 1066 (s), 1016 (s), 879 (w) cm^{-1}.



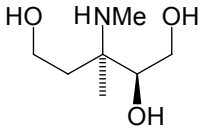
70·HCl

^{1}H NMR (500.1 MHz, CD_3OD): δ = 1.36 (s, 3 H, 1'-H), 1.87 ("ddd", $^2J_{4a,4b}$ = 15.0, $J_{4a,5a}$ and $J_{4a,5b}$ = 11.2 and 5.5 Hz, 1 H, 4-H_a), 2.04 (ddd, $^2J_{4a,4b}$ = 15.1, $J_{4b,5a}$ and $J_{4b,5b}$ = 7.9 and 5.9 Hz, 1 H, 4-H_b), 2.62 (s, 3 H, NCH_3), 3.65-3.85 (m, 5 H, 1-H, 2-H, 5-H).

^{13}C NMR (125.1 MHz, CD_3OD) : δ = 19.2 (q, C-1'), 27.9 (q, N-CH_3), 35.8 (t, C-4), 58.9 (t, C-5), 64.3 (t, C-1), 65.5 (s, C-3), 74.3 (d, C-2).

Experiment 69 (YB 173)

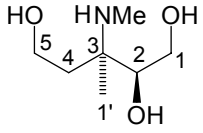
(2*S*,3*R*)-3-Methyl-3-methylaminopentane-1,2,5-triol; hydrochloride (71•HCl)



71·HCl

To 1.35 g (5.55 mmol) of amino alcohol **42**, 50 mL of HCl (6.0 N) was added at room temp. The mixture was left with stirring for 24 h. The solvent was evaporated *in vacuo* (60 °C/20 mbar) to give 1.11 g brownish oil, which was chromatographed through silica gel (2 cm x 6 cm, CH_2Cl_2/MeOH, 9:1 then 1:1) to give 1.07 g of amino triol **71•HCl** (97 %) as a colourless oil.

IR: $\tilde{\nu}$ = 3351 (vs, b, 3 OH), 2960 (sb), 1599 (w), 1580 (m), 1458 (s), 1409 (m), 1377 (m), 1111 (s), 1069 (vs), 1017 (vs), 968 (w), 878 (w) cm^{-1}.



71·HCl

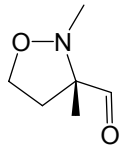
^{1}H NMR (500.1 MHz, CD_3OD): δ = 1.37 (s, 3 H, 1'-H), 1.93 ("ddd", $^2J_{4a,4b}$ = 15.2, $J_{4a,5a}$ and $J_{4a,5b}$ = 7.3 and 5.9 Hz, 1 H, 4-H_a), 1.99 ("ddd", $^2J_{4a,4b}$ = 15.2, $J_{4b,5a}$ and $J_{4b,5b}$ = 11.5 and 5.7 Hz, 1 H, 4-H_b), 2.68 (s, 3 H, NCH_3), 3.70 (dd, $J_{1a,1b}$ = 11.6, $J_{1a,2}$ = 5.6 Hz, 1 H, 1-H_a), 3.75 (dd, $J_{1a,1b}$ = 11.6, $J_{1b,2}$ = 3.8 Hz, 1 H, 1-H_b), 3.82 (dd, $J_{1a,2}$ = 5.7, $J_{1b,2}$ = 3.9 Hz, 2-H) and 3.80-3.85 (m, 5-H; together 3 H).

^{13}C NMR (125.8 MHz, CD_3OD) : δ = 17.6 (q, C-1'), 27.3 (q, N-CH_3), 34.6 (t, C-4), 58.2 (t, C-5), 63.9 (t, C-1), 65.1 (s, C-3), 72.7 (d, C-2).

11.9 Oxidation of isoxazoline-1,2-diols.

Experiment 70 (YB 101)

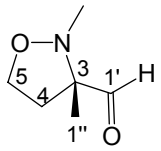
(*S*)-2,3-Dimethyl-isoxazolidine-3-carbaldehyde (72).



72

280 mg (1.74 mmol) of the diol **52** was dissolved in 10 mL of water/ethyl acetate (3:1). The pH adjusted to 8-9 by addition of NaOH solution (ca. 3 mL, 1.0 N), then 372 mg (1.74 mmol, 1 eq) of sodium periodate ($NaIO_4$) was added. The mixture was left with stirring for 1.5 h at room temp. The organic phase was partitioned against ethyl acetate (4 x 30 mL). The organic solutes were dried ($MgSO_4$) to give after evaporation of the solvent (20 °C/10 mbar) 160 mg of aldehyde **72**, which was filtered through silica gel (2 cm x 6 cm, petroleum ether/ethyl acetate 7:3) to yield 125 mg (56 %) of the aldehyde **72** as a volatile colourless oil.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, 1"-H), 2.06 (dddd, $^2J_{4a,4b}$ = 12.5, $J_{4a,5a}$ = 6.4, $J_{4a,5b}$ = 9.7, $^4J_{4a,1'}$ = 0.9 Hz, 1 H, 4-H_a), 2.68 (ddd, $^2J_{4a,4b}$ = 12.5, $J_{4b,5a}$ = 9.3, $J_{4b,5b}$ = 5.2 Hz, 1 H, 4-H_b), 2.62 (s, 3 H, NCH_3), 3.93 (ddd, $J_{4a,5a}$ = 6.4, $J_{4b,5b}$ = 9.4, $J_{5a,5b}$ = 7.9 Hz, 1 H, 5-H_a), 4.09 (ddd, $J_{4a,5b}$ = 9.7, $J_{4b,5b}$ = 5.2, $J_{5a,5b}$ = 7.9 Hz, 1 H, 5-H_b), 9.48 (s, 1 H, CHO).

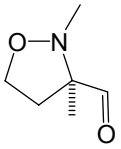


72

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.1 (t, C-1'), 34.8 (t, C-4), 37.9 (q, NCH_3), 65.2 (t, C-5), 74.1 (s, C-3), 202.9 (s, C=O).

Experiment 71 (YB 109)

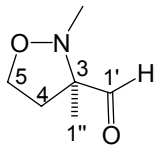
(*R*)-2,3-Dimethyl-isoxazolidine-3-carbaldehyde (73).



73

490 mg (3.04 mmol) of the diol **53** was dissolved in 20 mL of H_2O/ethyl acetate (3:1). The pH adjusted to 8-9 by addition of NaOH solution (ca. 4 mL, 1.0 N), then 650 mg (3.04 mmol, 1 eq) of sodium periodate ($NaIO_4$) was added. The reaction mixture was left with stirring for 1.5 h at room temp. The organic phase was extracted with ethyl acetate (4 x 30 mL) and dried ($MgSO_4$) to give after evaporation of the solvent (30 °C/60 mbar) 390 mg of aldehyde **73**. Filtration through silica gel (2 cm x 6 cm, petroleum ether/ethyl acetate 7:3) yielded 350 mg (89 %) of the aldehyde **76** as volatile colourless oil.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 1"-H), 2.09 (dddd, $^2J_{4a,4b}$ = 12.5, $J_{4a,5a}$ = 6.4, $J_{4a,5b}$ = 9.7, $^4J_{4a,1'}$ = 0.9 Hz, 1 H, 4-H_a), 2.65 (s, 3 H, NCH_3), 2.71 (ddd, $^2J_{4a,4b}$ = 12.5, $J_{4b,5a}$ = 9.3, $J_{4b,5b}$ = 5.2 Hz, 1 H, 4-H_b), 3.84 (ddd, $J_{4a,5a}$ = 6.4, $J_{4b,5b}$ = 9.4, $J_{5a,5b}$ = 7.9 Hz, 1 H, 5-H_a), 4.09 (ddd, $J_{4a,5b}$ = 9.7, $J_{4b,5b}$ = 5.2, $J_{5a,\,5b}$ = 7.9 Hz, 1 H, 5H_b), 9.52 (s, 1 H, CHO).



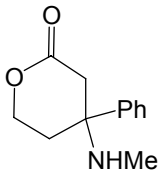
73

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.1 (t, C-1'), 34.8 (t, C-4), 37.9 (q, NCH_3), 65.2 (t, C-5), 74.2 (s, C-3), 202.9 (s, C=O).

11.10 Catalytic hydrogenation of isoxazolidinium salts.

Experiment 72 (YB 21)

4-Methylamino-4-phenyltetrahydropyran-2-one hydrochloride (74)

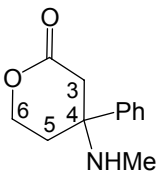


74·HCl

To 500 mg (1.94 mmol) of the isoxazolinium salt **51** in MeOH (20 mL) 250 mg of 10% Pd/C was added. The mixture was left with stirring for 48 h under hydrogen (1 bar). Then centrifuged to separate the catalyst, and concentrated *in vacuo* (10 mbar) to afford 415 mg. To this 20 mL of NaOH (1.0 M) was added, and the organic solutes was partitioned against ethyl acetate (3 x 30 mL), then was acidified with HCl (1.0 M) to give colourless solid which was collected by rextraction with water to give 200 mg. Recrystallization from ethanol/petroleum ether produced 70 mg of the lactone **74** (15 %) as a colourless crystals, suitable for crystal structure determination (see appendix 12.1.8).

IR (Film): $\tilde{\nu}$ = 2924 (m), 2860 (m), 1708 (vs, C=O), 1615 (w), 1495 (w), 1448 (w), 1399 (w), 1261 (w), 1223 (s), 1087 (vs), 1049 (m), 724 (m), 605 (vs) cm^{-1}.

^{1}H NMR (500.1 MHz, D_2O) : δ = 2.69 (s, 3 H, NCH_3), 2.92 (m, 1 H, 5-H_a), 3.09 (m, 1 H, 5-H_b), 3.64 (d, 1 H, 3-H_a), 4.01 (d, 1 H, 3-H_b), 4.26 (m, 1 H, 6-H_a), 4.80 (m, 1 H, 6-H_b), 7.75-7.85 (m, 5H, $C_6\underline{H_5}$).

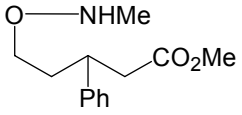


74·HCl

^{13}C NMR (125.8 MHz, D_2O) : δ = 27.3 (q, NCH_3), 31.7 (t, C-5), 37.1 (t, C-3), 61.1 (s, C-4), 66.6 (t, C-6), 127.1, 130.5, 131.1 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 132.9 (s, *i*-C of C_6H_5), 171.1 (s, C=O).

Experiment 73 (YB 261)

Methyl 5-(*N*-methylaminoxy)-3-phenylpentanoate (75).

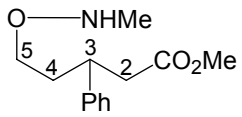


75

To 410 mg (1.59 mmol) of isoxazolidinium salt **51** in MeOH (30 mL) 110 mg of 10% Pd/C were added. The mixture was left with stirring overnight under hydrogen (1 bar), then concentrated *in vacuo* (roomtemp./10 mbar), and filtered through silica gel (SiO_2, 2 cm x 5 cm, petroleum ether/ethyl acetate 3:7) to afford 240 mg of the crude ester **75**. Purification by MPLC (petroleum ether/ethyl acetate 7:3) afforded 140 mg of analytically pure ester **75** (37 %) as colourless oil.

$C_{13}H_{17}NO_3$	calc.	C 65.80	H 8.07	N 5.90
(237.3)	found	C 66.11	H 8.11	N 5.69

IR : $\tilde{\nu}$ = 2950 (w), 2866 (w), 1734 (vs, C=O), 1454 (w), 1435 (m), 1257 (m), 1196 (m), 1161 (s), 1050 (m), 761 (m), 701 (vs) cm^{-1}.



75

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 1.80 (dddd, $J_{3,4a}$ = 9.9, $J_{4a,4b}$ = 11.4, $J_{4a,5a}$ = 6.4, $J_{4a,5b}$ = 5.1 Hz, 1 H, 4-H_a), 2.00 (dddd, $J_{3,4b}$ = 5.1, $J_{4a,4b}$ = 11.4, $J_{4b,5a}$ = 7.7, $J_{4b,5b}$ = 6.8 Hz, 1 H, 4-H_b), 2.61 (dd, $J_{2a,2b}$ = 15.4, $J_{2a,3}$ = 8.0 Hz, 1 H, 2-H_a), 2.66 (s, NCH_3) and 2.67 (dd, $J_{2a,2b}$ = 15.4, $J_{2b,3}$ = 7.4 Hz, 2-H_a; together 4 H); 3.26 ("dddd", $J_{2b,3}$ = 7.6, $J_{3,4a}$ = 9.9, $J_{3,4b}$ = 5.2 Hz,1 H, 3-H), 3.49 (ddd, $J_{4a,5a}$ = 6.3, $J_{4b,5a}$ = 7.7, $J_{5a,5b}$ = 10.2 Hz, 5-H_a) and 3.54 (ddd, $J_{4a,5b}$ = 5.1, $J_{4b,5b}$ = 7.0, $J_{5a,5b}$ = 10.2 Hz, 5-H_b) and 3.58 (s, $CO_2C\underline{H}_3$; together 5 H); 7.19-7.30 (m, 5 H, $C_6\underline{H}_5$).

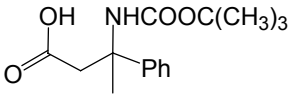
^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 34.8 (t, C-4), 38.8 and 39.1 (2 s, $N\underline{C}H_3$ and $CO_2\underline{C}H_3$), 41.4 (t, C-2), 51.4 (d, C-3), 70.8 (t, C-5), 126.5, 127.4, 128.4 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 143.3 (s, *i*-C of C_6H_5), 172.6 (s, C=O).

The assignment was confirmed by means of DEPT-, H,H-COSY, C,H-COSY spectra.

11.11 Synthesis of protected branched β-amino acids

Experiment 74 (YB 239)

3-*tert*-Butyloxycarbonylamino-3-phenyl-butanoic acid (76)



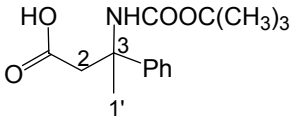
76

In analogy to lit.[140] to a solution of protected amino alcohol **62** (500 mg, 1.88 mmol) in 28 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temp. 1.66 g (7.73 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 30 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 1 h. Finally, 30 mL of CH_2Cl_2 was added, and then partitioned against CH_2Cl_2 (2 x 40 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar). This was filtered off through two layers of silica gel and celite (silica gel was added to the column first) (2 cm x 8 cm, petroleum ether/ethyl acetate 3:7), then concentrated to give 550 mg of a colourless solid. This was chromatographed (SiO_2, column 3 cm x 12 cm, petroleum ether/ethyl acetate 4:6). After evaporation of the solvents *in vacuo* (10^{-1} mbar) 440 mg (84 %) was obtained of analytically and spectroscopically pure protected amino acid **76** as a colourless soild (m.p. 85-86 °C).

$C_{15}H_{21}NO_4$	Calc.	C 64.50	H 7.58	N 5.01
(279.3)	found	C 64.39	H 7.56	N 4.93

IR : $\tilde{\nu}$ = 3333 (sb), 2967 (w), 1704 (vs, C=O), 1647 (vs, C=O), 1445 (w), 1394 (vs), 1367 (vs), 1163 (vs), 1106 (m), 1079 (m), 1064 (m), 1030 (w), 917 (m), 775 (m), 761 (s), 696 (vs) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.23 [s, 9 H, C($C\underline{H}_3)_3$], 1.73 (s, 3 H, 1'-H), 2.83 (d, $J_{2a,2b}$ = 13.3 Hz, 1 H, 2-H_a), 3.24 (d, $J_{2a,2b}$ = 13.3 Hz, 1 H, 2-H_b), 7.19-7.38 (m, 5 H, C_6H_5), 10.29 (s, 1 H, OH).

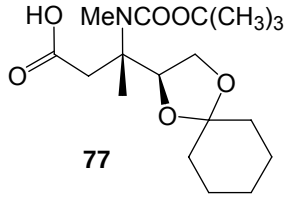


76

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 27.9 [s, $C(\underline{C}H_3)_3$], 29.5 (q, C-1'), 44.3 (t, C-2), 56.4 (s, C-3), 81.6 [s, $\underline{C}(CH_3)_3$], 124.5, 126.6, 128.3 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 147.2 (s, *i*-C of C_6H_5), 157.3 (s, C=O of Boc), 175.5 (s, C=O).

Experiment 75 (YB 251)

(3*S*, 4*S*)-3-(*tert*-Butyloxycarbonylmethylamino)-4,5-cyclohexylidenedioxy-pentanoic acid (77).



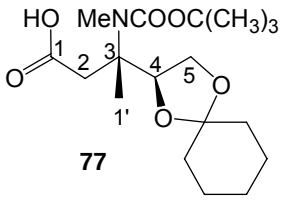
77

In analogy to lit.[140] to a solution of protected aminoalcohol **59** (130 mg, 0.38 mmol) in 28 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temp. 332 mg (1.55 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 6 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 2 h. Finally, 30 mL of CH_2Cl_2 was added, partitioned against CH_2Cl_2 (2 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) This was filtered off through two layers of silica gel and celite (silica gel was added to the column first) (2 cm x 8 cm, petroleum ether/ethyl acetate 3:7), then concentrated again to give 118 mg of colourless oil. This oil was purified by column chromatography (SiO_2, column 3 cm x 12 cm, petroleum ether/ethyl acetate 4:6). After evaporation of the solvent *in vacuo* (10^{-1} mbar) 102 mg (76 %) of analytically pure protected amino acid **77** was obtained as a colourless oil.

$[\alpha]_D^{20}$ = - 14.3 (*c* = 1.00, CH_2Cl_2)

$C_{18}H_{31}NO_6$	calc.	C 60.48	H 8.74	N 3.92
(357.4)	found	C 60.31	H 8.83	N 3.66

IR : $\tilde{\nu}$ = 3140 (sb, OH), 2934 (m), 2860 (w), 1732 (m, C=O) 1688 (vs, C=O), 1449 (w), 1365 (vs), 1252 (m), 1146 (vs), 1094 (vs), 1043 (m), 926 (s) cm^{-1}.



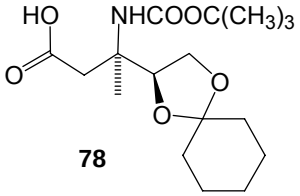
77

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.43 (s, 1'-H) and 1.45 (s, $C(C\underline{H}_3)_3$) and 1.35-1.67 [m, $C(CH_2)_5$; together 22 H]; 2.61 (d, $J_{2a,2b}$ = 15.2 Hz, 1 H, 2-H_a), 2.90 (s, 3 H, $NC\underline{H}_3$), 3.64 (d, $J_{2a,2b}$ = 15.2 Hz, 1 H, 2-H_b), 3.74 (dd, $J_{4,5a}$ = 6.1, $^2J_{5a,5b}$ = 8.7 Hz, 5-H_a), 3.96 (dd, $J_{4,5b}$ = 7.2, $^2J_{5a,5b}$ = 8.7 Hz, 1 H, 5-H_b), 5.08 (t, $J_{4,5}$ = 6.5 Hz, 1 H, 4-H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 18.6 (q, C-1'), 23.8, 24.0, 25.2, 34.0, 35.7 [5 t, $C(\underline{C}H_2)_5$], 28.4 [q, $C(C\underline{H}_3)_3$], 33.2 (q, $NHCH_3$), 41.1 (t, C-2), 60.5 (s, C-3), 64.8 (t, C-5), 77.9 (d, C-4), 80.3 [s, $\underline{C}(CH_3)_3$], 110.4 [s, $\underline{C}(CH_2)_5$], 155.8 (s, C=O of Boc), 176.7 (s, C=O).

Experiment 76 (YB 288)

(3*R*, 4*S*)-3-(*tert*-Butyloxycarbonylamino)-4,5-cyclohexylidenedioxy-pentanoic acid (78).



78

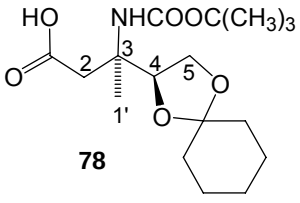
To a solution of protected amino alcohol **63** (795 mg, 2.41 mmol) in 56 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temp. 2.12 g (9.89 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 37 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 2 h. Finally, 40 mL of CH_2Cl_2 was added, and then partitioned against CH_2Cl_2 (2 x 50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar), This was filtered off through two layers of silica gel and celite (silica gel was added to the column first) (2 cm x 8 cm, petroleum ether/ethyl acetate 3:7). The solvent was evaporated to give 790 mg of yellowish oil. This oil was purified by MPLC (petroleum ether/ethyl acetate 65:35). After evaporation of the solvents *in vacuo* (10^{-1} mbar) 738 mg (89 %) of analytical pure protected amino acid **78** was obtained as a colourless oil.

$[\alpha]_D^{20}$ = - 7.20 (*c* = 1.00, CH_2Cl_2)

$C_{17}H_{29}NO_6$	calc.	C 59.46	H 8.51	N 4.08
(343.4)	found	C 59.21	H 8.74	N 3.73

IR: $\tilde{\nu}$ = 2934 (m), 1709 (vs, 2 C=O), 1503 (m), 1448 (m), 1366 (s), 1235 (m), 1161 (vs), 1096 (vs), 1071 (s), 927 (m), 848 (w), 776 (w) cm^{-1}.

^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.26-1.65 [m, 22 H, C($C\underline{H}_2$)$_5$, 1'-H, C($C\underline{H}_3$)$_3$], 2.72 (d, $J_{2a,2b}$ = 14.4 Hz, 1 H, 2-H_a), 2.86 (d, $J_{2a,2b}$ = 14.4 Hz, 1 H, 2-H_b), 3.86 (dd, $J_{4,5a}$ = 6.6, $J_{5a,5b}$ = 8.6 Hz, 1H, 5-H_a), 4.01 (dd, $J_{4,5b}$ = 6.8, $J_{5a,5b}$ = 8.6, Hz, 1 H, 5-H_b), 4.37 (t, $J_{4,5}$ = 6.6 Hz, 1 H, 4-H), 5.21 (sb, 1 H, OH).

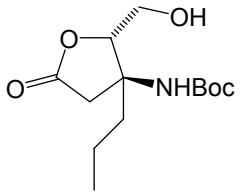


78

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (q, C-1'), 23.6, 23.9, 25.1, 34.0, 35.9 [5 t, C($\underline{C}H_2$)$_5$], 28.4 [q, C($C\underline{H}_3$)$_3$], 40.5 (t, C-2), 54.8 (s, C-3), 64.5 (t, C-5), 79.4 (d, C-4), 79.7 [s, $\underline{C}(CH_3)_3$], 110.3 [s, $\underline{C}(CH_2)_5$], 155.5 (s, C=O of Boc), 176.2 (s, C=O).

Experiment 77 (YB 190)

(4*S*, 5*S*)-4-(Amino-*N*-*tert*-butyloxycarbonyl)-5-hydroxymethyl-4-propyltetrahydrofuran-2-one (79)



79

To a solution of protected amino alcohol **66** (450 mg, 1.26 mmol) in 35 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temperature 1.10 g (5.17 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 20 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 2 h. Finally, 20 mL of CH_2Cl_2 was added, and then partitioned against CH_2Cl_2 (3 x 30 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) to give 565 mg of crude amino acid **79** as a yellowish oil. This was filtered off through two layers of silica gel and celite (silica gel was added to the column first) (2 cm x 8 cm, petroleum ether/ethyl acetate 4:6), then concentrated *in vacuo* and 0.5 mL of CF_3COOH was added to oil and dissolved in 15 mL of CH_2Cl_2 and kept stirring at room temp. for 1 h.

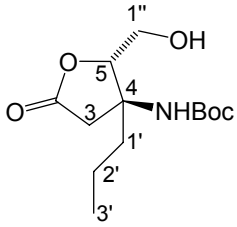
The solvent was evaporated, then filtered off through silica gel (2 cm x 6 cm, petroleum ether/ethyl acetate 1:1), then concentrated and purified by MPLC (petroleum ether/ethyl acetate 7:3). After evaporation of the solvents *in vacuo* (10^{-1} mbar) 445 mg (89 %) of analytically pure protected amino acid **79** was obtained as a colourless solid (m.p. 115-116 ^oC). Crystallization from hexan/chloroform gave **79** as colourless crystals, suitable for crystal structure determination (m.p. 115 ^oC, see appendix 12.1.9).

$[\alpha]_D^{20}$ = - 28.9 (c = 1.00, CH_2Cl_2)

$C_{13}H_{23}NO_5$	calc.	C 57.13	H 8.48	N 5.13
(273.31)	found	C 57.01	H 8.40	N 5.07

IR : $\tilde{\nu}$ = 3300 (sb, OH), 2952 (w), 2931 (w), 2894 (w), 1780 (m), 1754 (s, C=O), 1672 (vs, C=O), 1523 (vs), 1412 (w), 1365 (m), 1281 (s), 1253 (m), 1159 (vs), 1131 (w), 1084 (vs), 1028 (s), 936 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$) : δ = 0.99 (t, $J_{3',2'}$ = 7.2 Hz, 3 H, 3'-H), 1.22-1.46 (m, 2'-H) and 1.42 [s, C(C<u>H</u>$_3$)$_3$; together 11 H]; 1.70-1.76 (m, 1 H, 1'-H_a), 2.11-2.29 (m, 1 H, 1'-H_b), 2.57 (d, $J_{3a,3b}$ = 17.4 Hz ,1 H, 3-H_a), 2.80 (d, $J_{3a,3b}$ = 17.5 Hz ,1 H, 3-H_b), 3.47 (sb, 1 H, NH), 3.85 ("d", $J_{1''a,1''b}$ = 12.2 Hz, 1 H, 1''-H_a), 3.95 (dd, $J_{5,\ 1''b}$ = 3.2, $J_{1''a,\ 1''b}$ = 12.8, Hz, 1 H, 1''-H_b), 4.85 (sb, 1 H, 5-H), 5.08 (sb, 1 H, OH).

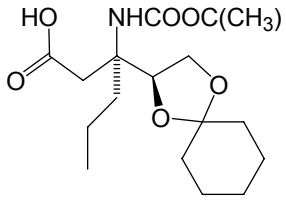


79

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.2 (q, C-3'), 17.9 (t, C-2'), 28.4 [s, C(<u>C</u>H$_3$)$_3$], 33.7 (t, C-3), 41.4 (t, C-1'), 60.7 (t, C-1''), 61.7 (s, C-4), 80.1 [s, <u>C</u>(CH$_3$)$_3$], 86.6 (d, C-5), 154.7 (s, C=O of Boc), 176.1 (s, C=O).

Experiment 78 (YB 287)

(3*R*, 4*S*)-3-(*tert*-Butyloxycarbonylamino)-4,5-cyclohexylidenedioxy-3-propylpentanoic acid (80).



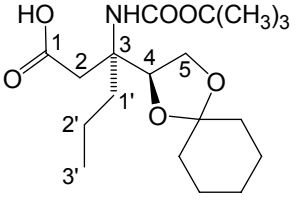
80

To a solution of protected amino alcohol **68** (600 mg, 1.55 mmol) in 56 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temperature 1.36 g (6.35 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 24 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 2 h. Finally, 30 mL of CH_2Cl_2 was added, and then partitioned against CH_2Cl_2 (3 x 30 mL), the combined organic solutes were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) to give 573 mg of crude amino acid **80** as a yellowish oil. This was chromatographed through silica gel (3 cm x 10 cm, petroleum ether/ethyl acetate 7:3). After evaporation of the solvents *in vacuo* (10^{-1} mbar) 465 mg (81 %) of spectroscopically pure protected amino acid **80** was obtained as a volatile colourless oil.

$[\alpha]_D^{20}$ = - 6.90 (c = 1.00, CH_2Cl_2)

IR: $\tilde{\nu}$ = 3416 (b, w), 2933 (s), 2866 (m), 1713 (vs, 2 C=O), 1504 (s), 1449 (m), 1392 (m), 1366 (s), 1279 (m), 1248 (m), 1160 (vs), 1095 (vs), 1035 (m), 927 (s), 848 (w), 776 (w) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$) : δ = 0.92 (t, $J_{3',2'}$ = 7.2 Hz, 3 H, 3'-H), 1.23-1.74 [m, 2'-H, C(C<u>H</u>$_2$)$_5$, 1'-H_a] and 1.42 [s, C(C<u>H</u>$_3$)$_3$; together 22 H]; 1.97-2.08 (m, 1 H, 1'-H_b), 2.58 (d, $J_{2a,2b}$ = 14.6 Hz, 1 H, 2-H_a),



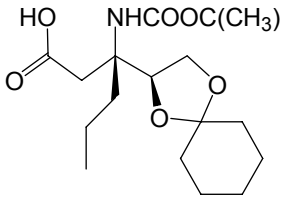
80

2.90 (d, $J_{2a,2b}$ = 14.6 Hz, 1 H, 2-H_b), 3.92 (dd, $J_{4,5a}$ = 6.7, $J_{5a,5b}$ = 8.8 Hz, 1 H, 5-H_a), 4.01 (dd, $J_{4,5b}$ = 6.7, $J_{5a,5b}$ = 8.8 Hz, 1 H, 5-H_b), 4.46 ("t", $J_{4,5}$ = 6.7 Hz, 1 H, 4-H).

^{13}C NMR (62.9 MHz, $CDCl_3$) : δ = 14.2 (q, C-3'), 17.0 (t, C-2'), 21.1, 23.7, 25.2, 34.0, 35.8, [5 t, C($\underline{C}H_2)_5$], 38.0 (t, C-2), 38.6 (t, C-1'), 28.4 [s, C($\underline{C}H_3)_3$], 57.6 (s, C-3), 64.8 (t, C-5), 79.2 (d, C-4), 79.6 [s, $\underline{C}(CH_3)_3$], 109.9 [s, $\underline{C}(CH_2)_5$], 155.5 (s, C=O of Boc), 176.8 (s, C=O).

Experiment 79 (YB 248)

(3*S*, 4*S*)-3-(*tert*-Butyloxycarbonylamino)-4,5-cyclohexylidenedioxy-3-propylpentanoic (81).



81

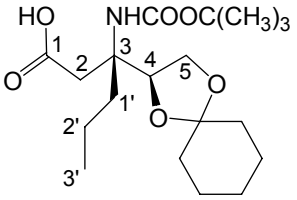
To a solution of protected amino alcohol **69** (290 mg, 0.750 mmol) in 28 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temperature 656 mg (3.07 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 12 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 90 min. Finally, 20 mL of CH_2Cl_2 was added, and the mixture was partitioned against CH_2Cl_2 (3 x 30 mL), the combined organic solutes were dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar) to give 260 mg of crude amino acid **81** as a yellowish oil. This was chromatographed on silica gel (2 cm x 10 cm, petroleum ether/ethyl acetate 6:4). After evaporation of the solvents *in vacuo* (10^{-1} mbar) 190 mg (68 %) of slightly pure protected amino acid **81** was obtained as a colourless oil.

$[\alpha]_D^{20}$ = 6.4 (c = 1.00, CH_2Cl_2)

$C_{19}H_{33}NO_6$	calc.	C 61.43	H 8.95	N 3.77
(271.5)	found	C 60.49	H 8.80	N 3.67

IR : $\tilde{\nu}$ = 3358 (b, w; OH), 2933 (s), 2868 (m), 1709 (vs, 2 C=O), 1504 (m), 1449 (w), 1392 (w), 1366 (s), 1280 (s), 1248 (s), 1161 (vs), 1095 (vs), 1035 (m), 928 (s), 848 (w), 778 (w), 739 (w) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 0.92 (t, $J_{3',2'}$ = 7.3 Hz, 3 H, 3'-H), 1.25-1.79 [m, 2'-H, C(C<u>H</u>$_2$)$_5$, 1'-H] and 1.42 [s, C(C<u>H</u>$_3$)$_3$; together 23 H]; 2.72 (d, $J_{2a,2b}$ = 14.6 Hz, 1 H, 2-H_a), 2.88 (d, $J_{2a,2b}$ = 14.6 Hz, 1 H, 2-H_b), 3.82 (dd, $J_{4,5a}$ = 7.5, $J_{5a,5b}$ = 8.5 Hz, 1 H, 5-H_a), 4.00 (dd, $J_{4,5b}$ = 6.6, $J_{5a,5b}$ = 8.5 Hz, 1 H, 5-H_b), 4.39 (dd, $J_{4,5a}$ = 7.5, $J_{4,5b}$ = 6.6 Hz, 1 H, 4-H).



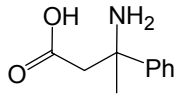
81

^{13}C NMR (125.8 MHz, $CDCl_3$) : δ = 14.4 (q, C-3'), 16.8 (t, C-2'), 23.7, 23.9, 25.1, 34.2, 35.6 [5 t, C(<u>C</u>H$_2$)$_5$], 38.0, 38.5 [2 t, C-2, C-1'], 28.3 [s, C(<u>C</u>H$_3$)$_3$], 57.5 (s, C-3), 64.8 (t, C-5), 78.9 (d, C-4), 80.0 [s, <u>C</u>(CH$_3$)$_3$], 110.0 [s, <u>C</u>(CH$_2$)$_5$], 155.8 (s, C=O of Boc), 175.3 (s, C=O).

11.12 Synthesis of Branched β-Amino Acids

Experiment 80 (YB 306)

3-Amino-3-phenyl-butyric acid (82)

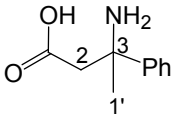


82

To a solution of 40 mg (0.14 mmol) of protected amino acid **76** in CH_2Cl_2 (10 mL) 2 mL of CF_3COOH were added. The mixture was kept with stirring overnight at room temp., then concentrated *in vacuo* (40 °C/10 mbar) to give 45 mg of a yellowish oil. This was purified with Dowex 50WX8 (H^+-Form, 200-400 mesh) to afford 22 mg (86 % yield) of amino acid **82** as a colourless solid (m. p. 223-224 °C; lit. : 225 °C[141]).

IR: $\tilde{\nu}$ = 2858 (b, m; OH, NH_2), 1983 (w), 1671 (s, C=O), 1561 (s), 1448 (vs), 1384 (vs), 1319 (w), 1197 (s), 1129 (vs), 908 (w), 834 (m), 764 (s), 720 (m), 695 (vs) cm^{-1}.

^{1}H NMR (500.1 MHz, CD_3OD): δ = 1.68 (s, 3 H, 1'-H), 2.73 (d, $J_{2a,2b}$ = 16.4 Hz, 1 H, 2-H_a), 2.83 (d, $J_{2a,2b}$ = 16.4 Hz, 1 H, 2-H_b), 7.32-7.47 (m, 5 H, C_6H_5).

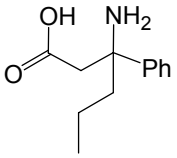


82

^{13}C NMR (125.8 MHz, CD_3OD): δ = 27.2 (q, C-1'), 46.3 (t, C-2), 58.1 (s, C-3), 125.7, 129.2, 130.1 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 143.1 (s, *i*-C of C_6H_5), 177.3 (s, C=O).

Experiment 81 (YB 182)

3-Amino-3-phenyl-hexanoic acid (83)



83

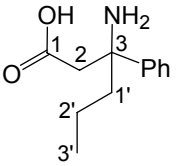
To a solution of protected amino alcohol **64** (670 mg, 2.28 mmol) in 35 mL of $CCl_4/CH_3CN/H_2O$ 1:1:1.5 at room temp. 2.00 g (9.36 mmol, 4.1 eq) of sodium periodate ($NaIO_4$) was added, followed by addition of 36 mg (6 % mol) of $RuCl_3 \bullet 3H_2O$, then the mixture was left with stirring for 2 h. 30 mL of CH_2Cl_2 was added, and the organic solutes were partitioned against CH_2Cl_2 (3 x 30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* (10 mbar). This was filtered off through two layers of silica gel and celite (silica gel was added to the column first) (2 cm x 8 cm, petroleum ether/ethyl acetate 3:7), then concentrated again to give 700 mg of crude colourless oil.

To this oil 3 mL of CF_3COOH in CH_2Cl_2 (40 mL) was added. The mixture was stirred for 3 h at room temp. to give after concentration *in vacuo* (30 °C/10 mbar) 800 mg of oily product. This was purified by ion exchange column to yield 337 mg of analytically and spectroscopically pure amino acid **83** (75 %) in the form of a colourless solid (m. p. 221-222 °C).

$C_{12}H_{17}NO_2$	calc.	C 69.54	H 8.27	N 6.76
(207.26)	found	C 69.11	H 8.26	N 6.69

IR : $\tilde{\nu}$ = 2959 (sb, OH, NH_2), 2873 (sb), 1568 (sb, C=O), 1468 (s), 1385 (vs), 1201 (w), 768 (m), 742 (w), 697 (vs), 639 (m), 577 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d^6): δ = 0.86 (t, $J_{3',2'}$ = 7.2 Hz, 3 H, 3'-H), 1.04-1.14 (m, 2 H, 2'-H), 1.93-2.04 (m, 2 H, 1'-H), 2.81 (d, $J_{2a,2b}$ = 16.5 Hz , 2-H_a) and 2.90 (d, $J_{2a,2b}$ = 16.5 Hz, 2-H_b; together 2 H); 7.44-7.57 (m, 5 H, C_6H_5).

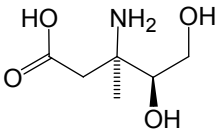


83

^{13}C NMR (75.5 MHz, DMSO-d^6) : δ = 13.8 (q, C-3'), 16.4 (t, C-2'), 41.7, 43.0 (2 t, C-2, C-1'), 59.9 (s, C-3), 125.0, 128.2, 129.1 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 139.6 (s, *i*-C of C_6H_5), 175.6 (s, C=O).

Experiment 82 (YB 289)

(3*R*,4*S*)-3-Amino-4,5-dihydroxy-3-methylpentanoic acid (84)



84

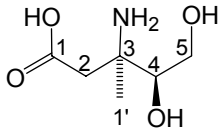
To a solution of 620 mg (1.81 mmol) of protected amino acid **78** in CH_2Cl_2 (50 mL) 5 mL of CF_3COOH was added. The reaction mixture was kept with stirring overnight at room temp. Then concentrated *in vacuo* (40 °C/10 mbar) to give 390 mg of a yellowish oil. This was purified by ion exchange column to afford 245 mg (94 % yield) of analytically and spectroscopically pure amino acid **84** as a colourless solid (m.p. 185-186 °C).

$[\alpha]_D^{20}$ = - 14.1 (*c* = 0.950, MeOH)

$C_6H_{13}NO_4$	calc.	C 44.16	H 8.03	N 8.58
(163.2)	found	C 44.13	H 7.98	N 8.42

IR : $\tilde{\nu}$ = 3456 (w, OH), 3253 (mb, OH), 2980 (wb), 1617 (s, C=O), 1562 (w), 1532 (s), 1407 (vs), 1314 (w), 1205 (m), 1073 (w), 1044 (m), 918 (w), 644 (m) cm^{-1}.

^{1}H NMR (500.1 MHz, D_2O): δ = 1.30 (d, $J_{2b,1'}$ = 0.8 Hz, 3 H, 1'-H), 2.21 (d, $J_{2a,2b}$ = 16.2 Hz, 1 H, 2-H_a), 2.53 (dd, $J_{2a,2b}$ = 16.2, $J_{2b,1'}$ = 0.8 Hz, 1 H, 2-H_b), 3.57 (dd, $J_{4,5a}$ = 6.6, $J_{5a,5b}$ = 11.3 Hz, 1 H, 5-H_a), 3.61 (dd, $J_{4,5a}$ = 6.6, $J_{4,5b}$ = 2.8 Hz, 1 H, 4-H), 3.68 (dd, $J_{4,5b}$ = 2.8, $J_{5a,5b}$ = 11.2 Hz, 1 H, 5-H_b).

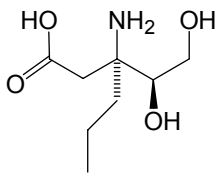


84

^{13}C NMR (125.8 MHz, D_2O): δ = 20.0 (q, C-1'), 39.1 (t, C-2), 57.3 (s, C-3), 61.4 (t, C-5), 74.0 (d, C-4), 177.8 (s, C=O).

Experiment 83 (YB 290)

(3*R*, 1′*S*)-3-Amino-3-[(*S*)-1,2-dihydroxyethyl)]-hexanoic acid (85)



85

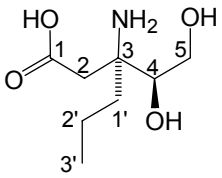
To a solution of 430 mg (1.16 mmol) of protected amino acid **80** in CH_2Cl_2 (40 mL) 4 mL of CF_3COOH was added, and kept with stirring overnight at room temp., and then concentrated *in vacuo* (10 mbar) to give 235 mg of a yellowish oil. This was purified by ion exchange

column to afford 180 mg (90 % yield) of analytically and spectroscopically pure amino acid **85** as a colourless solid (m. p. 170-171 °C).

$[\alpha]_D^{20}$ = 22.7 (*c* = 1.00, MeOH)

$C_8H_{17}NO_4$	calc.	C 50.25	H 8.96	N 7.33
(191.2)	found	C 50.12	H 8.89	N 7.03

IR : $\tilde{\nu}$ = 3109 (sb, OH), 2961 (m), 2873 (m), 1565 (sb, C=O), 1455 (s), 1386 (vs), 1183 (m), 1081 (s), 1041 (s), 922 (w), 883 (w), 737 (w) cm^{-1}.



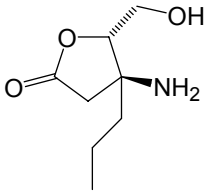
85

^{1}H NMR (500.1 MHz, D_2O): δ = 0.83 (t, $J_{2',3'}$ = 7.3 Hz, 3 H, 3'-H), 1.21-1.32 (m, 2 H, 2'-H), 1.54 (dddd, $J_{2b,1'a}$ = 0.8, $J_{1'a,1'b}$ = 14.3, $J_{1'a,2'a}$ and $J_{1'a,2'b}$ = 11.4 and 6.6 Hz, 1 H, 1'-H_a), 1.69 (ddd, $J_{1'a,1'b}$ = 14.3, $J_{1'b,2'a}$ and $J_{1'b,2'b}$ = 11.5 and 6.5 Hz, 1 H, 1'-H_b), 2.42 (d, $J_{2a,2b}$ = 16.4 Hz, 1 H, 2-H_a), 2.54 (dd, $J_{2a,2b}$ = 16.4, $J_{2b,1'}$ = 0.9 Hz, 1 H, 2-H_b), 3.62 (dd, $J_{4,5a}$ = 6.9, $J_{5a,5b}$ = 12.4 Hz, 1 H, 5-H_a), 3.71 (dd, $J_{4,5a}$ = 7.1, $J_{4,5b}$ = 3.1 Hz, 4-H) and 3.71 (dd, $J_{4,5b}$ = 2.9, $J_{5a,5b}$ = 12.4 Hz, 5-H_b; together 2 H).

^{13}C NMR (125.8 MHz, D_2O): δ = 13.7 (q, C-3'), 16.2 (t, C-2'), 34.7 (t, C-1'), 39.2 (t, C-2), 59.9 (s, C-3), 61.5 (t, C-5), 72.2 (d, C-4), 178.1 (s, C=O).

Experiment 84 (YB 199)

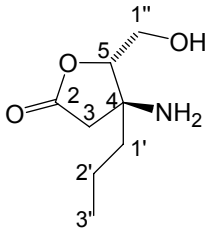
(4*S*, 5*S*)-4-Amino-5-hydroxymethyl-4-propyldihydrofuran-2-one (86)



86

155 mg (0.57 mmol) of protected amino acid **79** was dissolved in 15 mL HCl (6.0 N in MeOH). The mixture was kept with stirring overnight at room temp. The solvent was evaporated *in vacuo* (50 °C/ 10 mbar) to give 100 mg of a colourless oil. This was purified by ion exchange column to afford 69 mg (71%) of analytically impure, but spectroscopically pure amino acid **86**.

^{1}H NMR (300 MHz, CD_3OD) : δ = 0.99 (t, $J_{2',3'}$ = 7.2 Hz, 3 H, 3'-H), 1.29-1.76 (m, 4 H, 2'-H, 1'-H) 2.28 (d, $J_{3a,3b}$ = 17.0 Hz ,1 H, 3-H_a), 2.70 (d, $J_{3a,3b}$ = 17.0 Hz ,1 H, 3-H_b), 3.73 (dd, $J_{5,1''a}$ = 3.7, $J_{1''a,1''b}$ = 12.6 Hz, 1 H, 1''-H_a), 3.80 (dd, $J_{5,1''b}$ = 3.1, $J_{1''a,1''b}$ = 12.6 Hz, 1 H, 1''-H_b), 4.19 ("t", $J_{5,1''}$ = 3.4 Hz,1 H, 5-H).



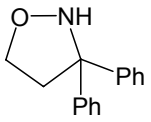
86

^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 15.5 (q, C-3'), 19.0 (t, C-2'), 39.8 and 44.2 (2 t, C-3 and C-1'), 60.8 (t, C-1''), 62.0 (s, C-4), 91.8 (d, C-5), 179.4 (s, C=O).

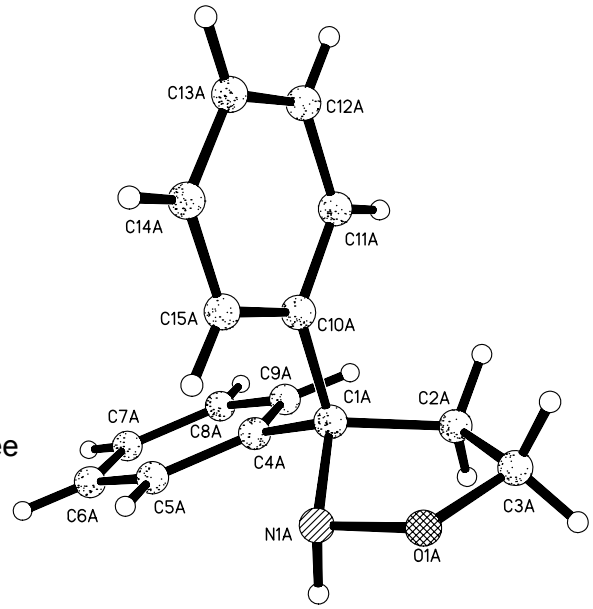
12.1 Crystal Structure Data

12.1.1 3,3-Diphenyl-isoxazolidine (27).

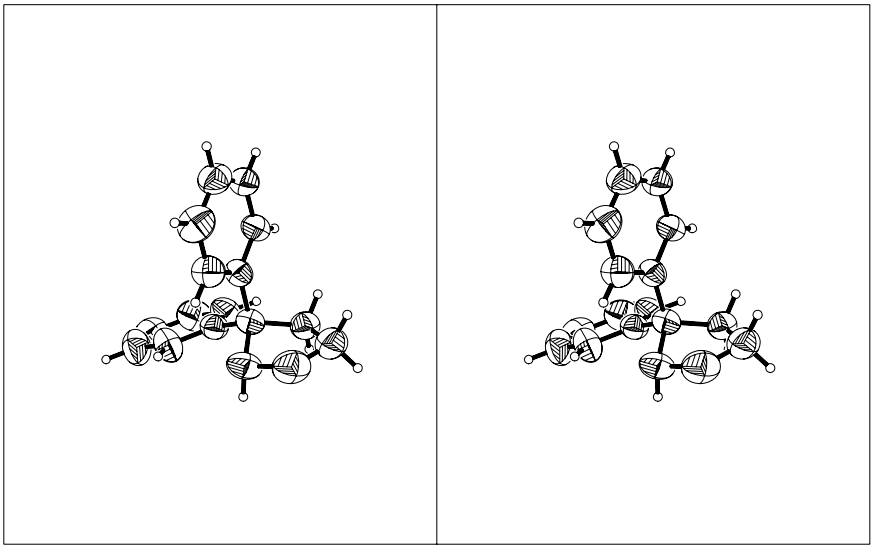
$C_{15}H_{15}NO$
Triclinic, P-1
a = 6.1257(3) Å
b = 8.7113(5) Å
c = 24.0652(9) Å
α = 98.502(4)°
β = 93.050(5)°
γ = 107.668(5)°
V = 1203.59(10) Å^3
Z = 4, *R(F)* = 0.0692
$R_W(F^2)$ = 0.1855
Crystal size: 0.25 x 0.25 x 0.10 mm
Calculated density : 1.243 g/cm^3
Theta range for data collection: 7.63 - 67.98 degree
Unigue reflections: 3808
Observed reflections: 2268
No. of contributed reflections to refinement: 3808
No. of refined parameters: 316



27

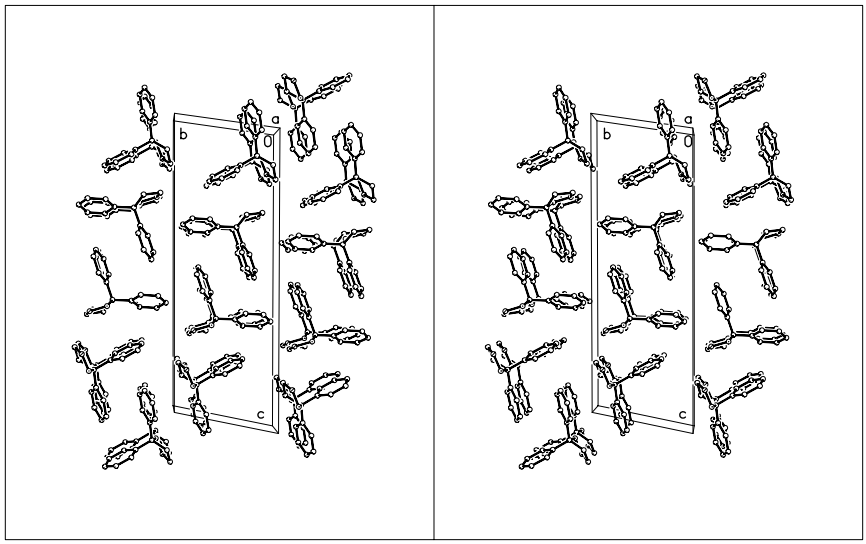


Stereoview of the structure with displacement parameters:

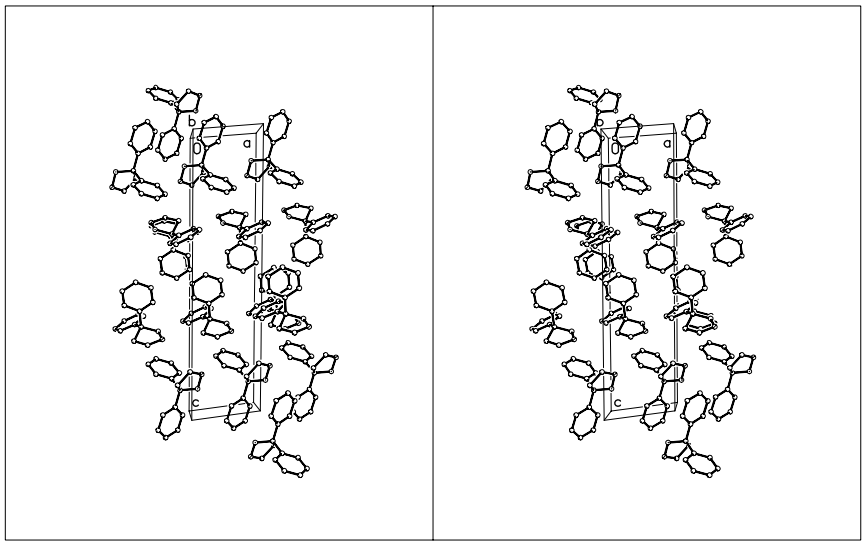


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

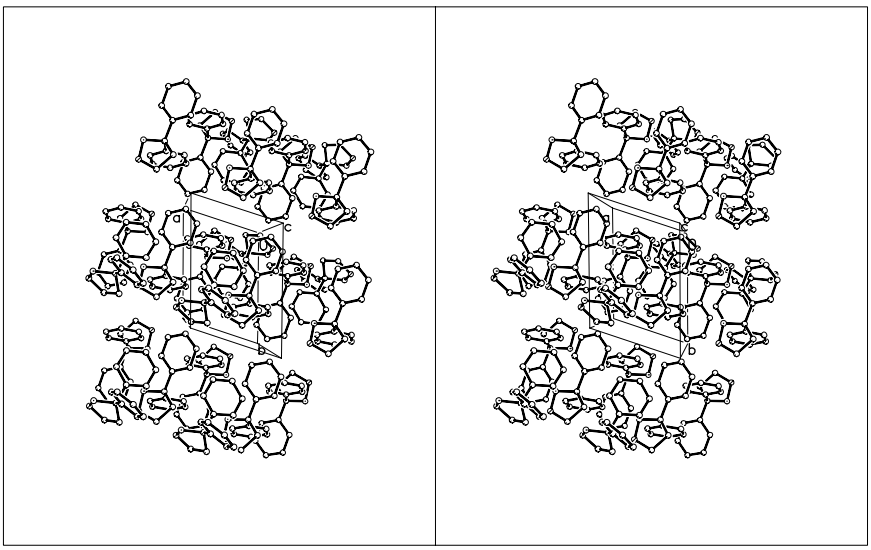
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

O(1A)-N(1A)	1.444(4)
O(1A)-C(3A)	1.452(5)
C(1A)-N(1A)	1.485(3)
C(1A)-C(4A)	1.519(4)
C(1A)-C(10A)	1.529(4)
C(1A)-C(2A)	1.533(4)
N(1A)-H(1A)	1.01(5)
C(2A)-C(3A)	1.514(5)
C(2A)-H(2A1)	0.9700
C(2A)-H(2A2)	0.9700
C(3A)-H(3A1)	0.9700
C(3A)-H(3A2)	0.9700
C(4A)-C(5A)	1.378(4)
C(4A)-C(9A)	1.382(4)
C(5A)-C(6A)	1.379(5)
C(5A)-H(5A)	0.9300
C(6A)-C(7A)	1.366(5)
C(6A)-H(6A)	0.9300
C(7A)-C(8A)	1.360(6)
C(7A)-H(7A)	0.9300
C(8A)-C(9A)	1.382(5)
C(8A)-H(8A)	0.9300
C(9A)-H(9A)	0.9300
C(10A)-C(11A)	1.392(4)
C(10A)-C(15A)	1.395(4)
C(11A)-C(12A)	1.388(4)
C(11A)-H(11A)	0.9300
C(12A)-C(13A)	1.365(5)
C(12A)-H(12A)	0.9300
C(13A)-C(14A)	1.373(5)
C(13A)-H(13A)	0.9300
C(14A)-C(15A)	1.388(5)
C(14A)-H(14A)	0.9300
C(15A)-H(15A)	0.9300
O(1B)-C(3B)	1.428(4)
O(1B)-N(1B)	1.451(4)
C(1B)-N(1B)	1.488(3)
C(1B)-C(10B)	1.516(4)
C(1B)-C(4B)	1.529(4)
C(1B)-C(2B)	1.533(4)
N(1B)-H(1B)	0.95(5)
C(2B)-C(3B)	1.512(4)
C(2B)-H(2B1)	0.9700
C(2B)-H(2B2)	0.9700
C(3B)-H(3B1)	0.9700
C(3B)-H(3B2)	0.9700
C(4B)-C(5B)	1.379(4)
C(4B)-C(9B)	1.394(4)
C(5B)-C(6B)	1.398(5)
C(5B)-H(5B)	0.9300
C(6B)-C(7B)	1.362(5)
C(6B)-H(6B)	0.9300
C(7B)-C(8B)	1.371(6)
C(7B)-H(7B)	0.9300
C(8B)-C(9B)	1.372(5)
C(8B)-H(8B)	0.9300
C(9B)-H(9B)	0.9300
C(10B)-C(15B)	1.383(4)
C(10B)-C(11B)	1.391(4)
C(11B)-C(12B)	1.385(5)
C(11B)-H(11B)	0.9300
C(12B)-C(13B)	1.370(5)
C(12B)-H(12B)	0.9300
C(13B)-C(14B)	1.352(5)
C(13B)-H(13B)	0.9300
C(14B)-C(15B)	1.389(5)
C(14B)-H(14B)	0.9300
C(15B)-H(15B)	0.9300
N(1A)-O(1A)-C(3A)	108.9(2)
N(1A)-C(1A)-C(4A)	108.4(2)
N(1A)-C(1A)-C(10A)	109.7(2)
C(4A)-C(1A)-C(10A)	109.0(2)
N(1A)-C(1A)-C(2A)	101.6(2)
C(4A)-C(1A)-C(2A)	115.9(2)
C(10A)-C(1A)-C(2A)	111.9(2)
O(1A)-N(1A)-C(1A)	104.2(2)
O(1A)-N(1A)-H(1A)	109(3)
C(1A)-N(1A)-H(1A)	109(2)
C(3A)-C(2A)-C(1A)	102.5(3)
C(3A)-C(2A)-H(2A1)	111.3
C(1A)-C(2A)-H(2A1)	111.3
C(3A)-C(2A)-H(2A2)	111.3
C(1A)-C(2A)-H(2A2)	111.3
H(2A1)-C(2A)-H(2A2)	109.2
O(1A)-C(3A)-C(2A)	106.0(3)
O(1A)-C(3A)-H(3A1)	110.5
C(2A)-C(3A)-H(3A1)	110.5
O(1A)-C(3A)-H(3A2)	110.5
C(2A)-C(3A)-H(3A2)	110.5
H(3A1)-C(3A)-H(3A2)	108.7
C(5A)-C(4A)-C(9A)	117.5(3)
C(5A)-C(4A)-C(1A)	120.9(3)
C(9A)-C(4A)-C(1A)	121.6(3)
C(4A)-C(5A)-C(6A)	121.6(3)
C(4A)-C(5A)-H(5A)	119.2
C(6A)-C(5A)-H(5A)	119.2
C(7A)-C(6A)-C(5A)	120.0(4)
C(7A)-C(6A)-H(6A)	120.0
C(5A)-C(6A)-H(6A)	120.0
C(8A)-C(7A)-C(6A)	119.5(4)
C(8A)-C(7A)-H(7A)	120.3
C(6A)-C(7A)-H(7A)	120.3
C(7A)-C(8A)-C(9A)	120.7(4)
C(7A)-C(8A)-H(8A)	119.7
C(9A)-C(8A)-H(8A)	119.7
C(4A)-C(9A)-C(8A)	120.8(3)
C(4A)-C(9A)-H(9A)	119.6
C(8A)-C(9A)-H(9A)	119.6
C(11A)-C(10A)-C(15A)	118.0(3)
C(11A)-C(10A)-C(1A)	120.4(3)
C(15A)-C(10A)-C(1A)	121.5(3)
C(12A)-C(11A)-C(10A)	120.9(3)
C(12A)-C(11A)-H(11A)	119.6
C(10A)-C(11A)-H(11A)	119.6
C(13A)-C(12A)-C(11A)	120.5(3)
C(13A)-C(12A)-H(12A)	119.8

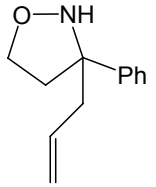
C(11A)-C(12A)-H(12A)	119.8
C(12A)-C(13A)-C(14A)	119.5(3)
C(12A)-C(13A)-H(13A)	120.2
C(14A)-C(13A)-H(13A)	120.2
C(13A)-C(14A)-C(15A)	120.9(3)
C(13A)-C(14A)-H(14A)	119.6
C(15A)-C(14A)-H(14A)	119.6
C(14A)-C(15A)-C(10A)	120.2(3)
C(14A)-C(15A)-H(15A)	119.9
C(10A)-C(15A)-H(15A)	119.9
C(3B)-O(1B)-N(1B)	109.5(2)
N(1B)-C(1B)-C(10B)	107.2(2)
N(1B)-C(1B)-C(4B)	109.7(2)
C(10B)-C(1B)-C(4B)	110.6(2)
N(1B)-C(1B)-C(2B)	102.0(2)
C(10B)-C(1B)-C(2B)	116.1(2)
C(4B)-C(1B)-C(2B)	110.8(2)
O(1B)-N(1B)-C(1B)	104.7(2)
O(1B)-N(1B)-H(1B)	104(3)
C(1B)-N(1B)-H(1B)	101(2)
C(3B)-C(2B)-C(1B)	101.9(2)
C(3B)-C(2B)-H(2B1)	111.4
C(1B)-C(2B)-H(2B1)	111.4
C(3B)-C(2B)-H(2B2)	111.4
C(1B)-C(2B)-H(2B2)	111.4
H(2B1)-C(2B)-H(2B2)	109.3
O(1B)-C(3B)-C(2B)	106.7(3)
O(1B)-C(3B)-H(3B1)	110.4
C(2B)-C(3B)-H(3B1)	110.4
O(1B)-C(3B)-H(3B2)	110.4
C(2B)-C(3B)-H(3B2)	110.4
H(3B1)-C(3B)-H(3B2)	108.6
C(5B)-C(4B)-C(9B)	117.7(3)
C(5B)-C(4B)-C(1B)	122.8(3)
C(9B)-C(4B)-C(1B)	119.6(2)
C(4B)-C(5B)-C(6B)	120.5(3)
C(4B)-C(5B)-H(5B)	119.7
C(6B)-C(5B)-H(5B)	119.7
C(7B)-C(6B)-C(5B)	120.5(3)
C(7B)-C(6B)-H(6B)	119.7
C(5B)-C(6B)-H(6B)	119.7
C(6B)-C(7B)-C(8B)	119.6(3)
C(6B)-C(7B)-H(7B)	120.2
C(8B)-C(7B)-H(7B)	120.2
C(9B)-C(8B)-C(7B)	120.3(3)
C(9B)-C(8B)-H(8B)	119.9
C(7B)-C(8B)-H(8B)	119.9
C(8B)-C(9B)-C(4B)	121.4(3)
C(8B)-C(9B)-H(9B)	119.3
C(4B)-C(9B)-H(9B)	119.3
C(15B)-C(10B)-C(11B)	118.2(3)
C(15B)-C(10B)-C(1B)	121.9(3)
C(11B)-C(10B)-C(1B)	119.9(2)
C(12B)-C(11B)-C(10B)	120.6(3)
C(12B)-C(11B)-H(11B)	119.7
C(10B)-C(11B)-H(11B)	119.7
C(13B)-C(12B)-C(11B)	120.0(3)
C(13B)-C(12B)-H(12B)	120.0
C(11B)-C(12B)-H(12B)	120.0
C(14B)-C(13B)-C(12B)	120.1(3)
C(14B)-C(13B)-H(13B)	119.9
C(12B)-C(13B)-H(13B)	119.9
C(13B)-C(14B)-C(15B)	120.7(3)
C(13B)-C(14B)-H(14B)	119.6
C(15B)-C(14B)-H(14B)	119.6
C(10B)-C(15B)-C(14B)	120.3(3)
C(10B)-C(15B)-H(15B)	119.8
C(14B)-C(15B)-H(15B)	119.8

Torsionangles[°].

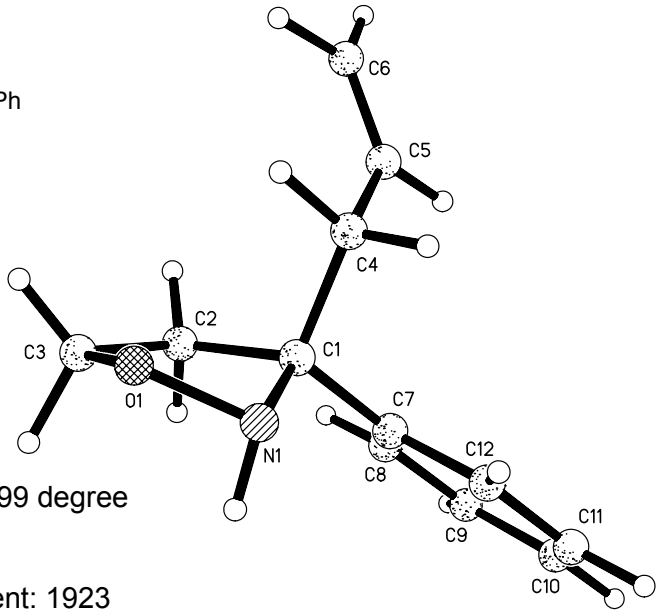
C(3A)-O(1A)-N(1A)-C(1A)	-27.8(3)
C(4A)-C(1A)-N(1A)-O(1A)	162.7(2)
C(10A)-C(1A)-N(1A)-O(1A)	-78.5(3)
C(2A)-C(1A)-N(1A)-O(1A)	40.1(3)
N(1A)-C(1A)-C(2A)-C(3A)	-37.3(3)
C(4A)-C(1A)-C(2A)-C(3A)	-154.6(3)
C(10A)-C(1A)-C(2A)-C(3A)	79.7(3)
N(1A)-O(1A)-C(3A)-C(2A)	3.4(4)
C(1A)-C(2A)-C(3A)-O(1A)	21.3(3)
N(1A)-C(1A)-C(4A)-C(5A)	37.6(4)
C(10A)-C(1A)-C(4A)-C(5A)	-81.7(3)
C(2A)-C(1A)-C(4A)-C(5A)	151.0(3)
N(1A)-C(1A)-C(4A)-C(9A)	-144.1(3)
C(10A)-C(1A)-C(4A)-C(9A)	96.6(3)
C(2A)-C(1A)-C(4A)-C(9A)	-30.7(4)
C(9A)-C(4A)-C(5A)-C(6A)	-1.3(5)
C(1A)-C(4A)-C(5A)-C(6A)	177.0(3)
C(4A)-C(5A)-C(6A)-C(7A)	0.7(6)
C(5A)-C(6A)-C(7A)-C(8A)	-0.4(6)
C(6A)-C(7A)-C(8A)-C(9A)	0.7(6)
C(5A)-C(4A)-C(9A)-C(8A)	1.6(5)
C(1A)-C(4A)-C(9A)-C(8A)	-176.7(3)
C(7A)-C(8A)-C(9A)-C(4A)	-1.4(6)
N(1A)-C(1A)-C(10A)-C(11A)	161.0(3)
C(4A)-C(1A)-C(10A)-C(11A)	-80.5(3)
C(2A)-C(1A)-C(10A)-C(11A)	48.9(4)
N(1A)-C(1A)-C(10A)-C(15A)	-22.1(4)
C(4A)-C(1A)-C(10A)-C(15A)	96.4(3)
C(2A)-C(1A)-C(10A)-C(15A)	-134.2(3)
C(15A)-C(10A)-C(11A)-C(12A)	0.8(5)
C(1A)-C(10A)-C(11A)-C(12A)	177.9(3)
C(10A)-C(11A)-C(12A)-C(13A)	-0.2(5)
C(11A)-C(12A)-C(13A)-C(14A)	-0.4(5)
C(12A)-C(13A)-C(14A)-C(15A)	0.3(6)
C(13A)-C(14A)-C(15A)-C(10A)	0.4(6)
C(11A)-C(10A)-C(15A)-C(14A)	-1.0(5)
C(1A)-C(10A)-C(15A)-C(14A)	-177.9(3)
C(3B)-O(1B)-N(1B)-C(1B)	-21.4(3)
C(10B)-C(1B)-N(1B)-O(1B)	158.7(2)
C(4B)-C(1B)-N(1B)-O(1B)	-81.1(3)
C(2B)-C(1B)-N(1B)-O(1B)	36.3(3)
N(1B)-C(1B)-C(2B)-C(3B)	-37.4(3)
C(10B)-C(1B)-C(2B)-C(3B)	-153.5(2)
C(4B)-C(1B)-C(2B)-C(3B)	79.4(3)
N(1B)-O(1B)-C(3B)-C(2B)	-3.1(3)
C(1B)-C(2B)-C(3B)-O(1B)	25.3(3)
N(1B)-C(1B)-C(4B)-C(5B)	-6.0(4)
C(10B)-C(1B)-C(4B)-C(5B)	112.0(3)

C(2B)-C(1B)-C(4B)-C(5B)	-117.9(3)	C(4B)-C(1B)-C(10B)-C(15B)	106.0(3)
N(1B)-C(1B)-C(4B)-C(9B)	173.9(3)	C(2B)-C(1B)-C(10B)-C(15B)	-21.3(4)
C(10B)-C(1B)-C(4B)-C(9B)	-68.0(3)	N(1B)-C(1B)-C(10B)-C(11B)	45.3(3)
C(2B)-C(1B)-C(4B)-C(9B)	62.1(3)	C(4B)-C(1B)-C(10B)-C(11B)	-74.3(3)
C(9B)-C(4B)-C(5B)-C(6B)	0.3(5)	C(2B)-C(1B)-C(10B)-C(11B)	158.5(3)
C(1B)-C(4B)-C(5B)-C(6B)	-179.8(3)	C(15B)-C(10B)-C(11B)-C(12B)	1.8(5)
C(4B)-C(5B)-C(6B)-C(7B)	-0.5(6)	C(1B)-C(10B)-C(11B)-C(12B)	-178.0(3)
C(5B)-C(6B)-C(7B)-C(8B)	0.5(6)	C(10B)-C(11B)-C(12B)-C(13B)	-0.4(5)
C(6B)-C(7B)-C(8B)-C(9B)	-0.3(6)	C(11B)-C(12B)-C(13B)-C(14B)	-1.3(6)
C(7B)-C(8B)-C(9B)-C(4B)	0.2(6)	C(12B)-C(13B)-C(14B)-C(15B)	1.5(6)
C(5B)-C(4B)-C(9B)-C(8B)	-0.2(5)	C(11B)-C(10B)-C(15B)-C(14B)	-1.6(5)
C(1B)-C(4B)-C(9B)-C(8B)	179.9(3)	C(1B)-C(10B)-C(15B)-C(14B)	178.2(3)
N(1B)-C(1B)-C(10B)-C(15B)	-134.5(3)	C(13B)-C(14B)-C(15B)-C(10B)	0.0(5)

12.1.2 3-Allyl-3-phenyl-isoxazolidine (30).

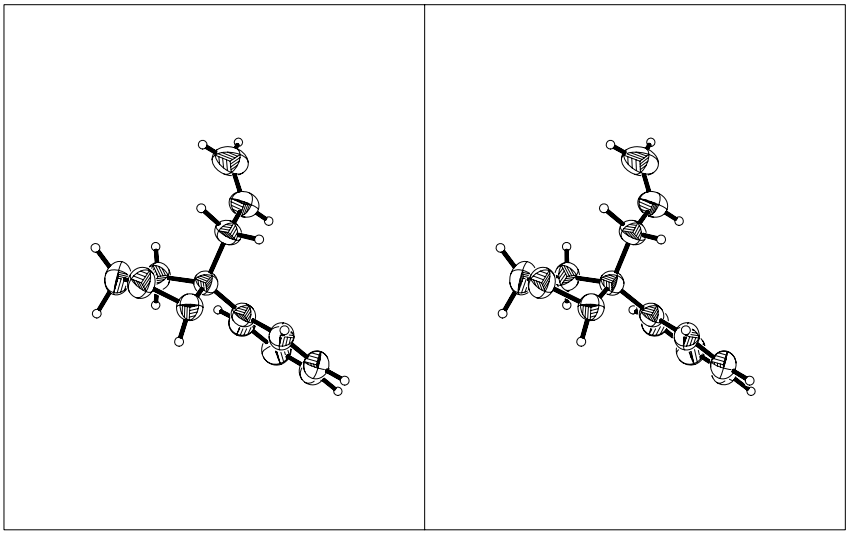


30



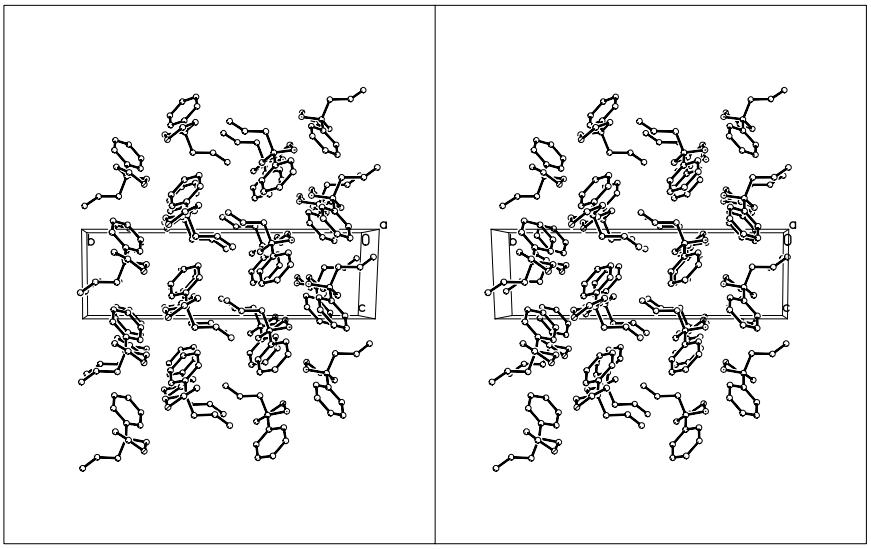
$C_{12}H_{15}NO$
monoclinic, P2(1)/c
a = 9.1243(6) Å
b = 19.8216(12) Å
c = 6.3163(4) Å
α = 90°
β = 107.662(5)°
γ = 90°
V = 1088.51(12) Å^3
Z = 4, *R(F)* = 0.0827
$R_W(F^2)$ = 0.2255
Crystal size: 0.75 x 0.20 x 0.15 mm
Calculated density : 1.155 g/cm^3
Theta range for data collection: 4.46-67.99 degree
Unigue reflections: 1923
Observed reflections: 1322
No. of contributed reflections to refinement: 1923
No. of refined parameters: 188

Stereoview of the structure with displacement parameters:

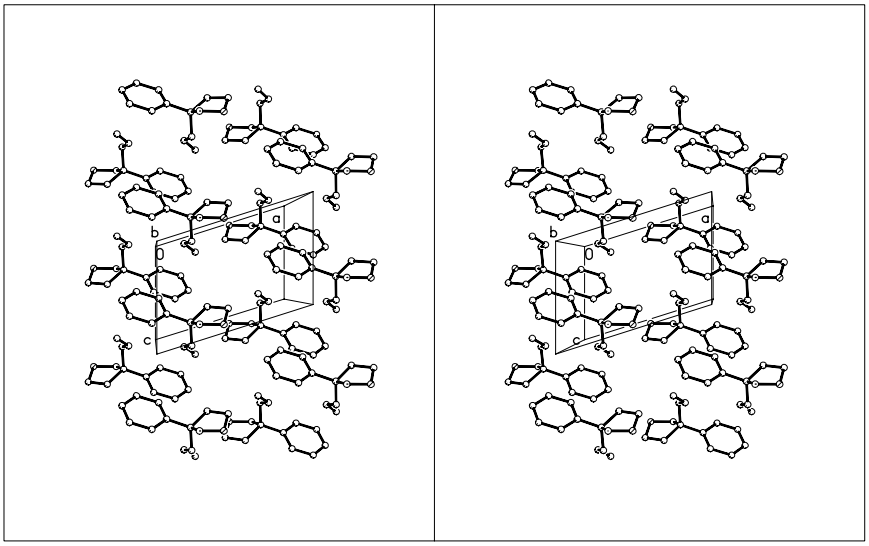


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

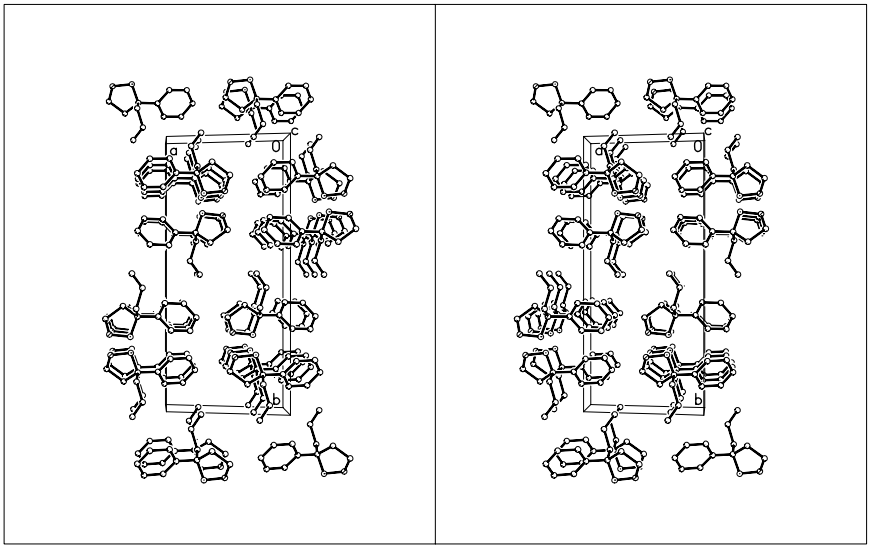
(a)



(b)



(c)



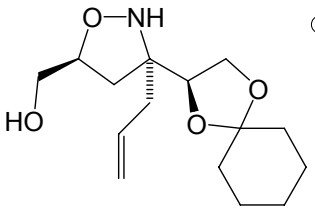
Bond lengths [Å] and angles [°].

C(1)-N(1)	1.478(3)
C(1)-C(7)	1.519(3)
C(1)-C(2)	1.543(4)
C(1)-C(4)	1.543(3)
O(1)-C(3)	1.423(4)
O(1)-N(1)	1.451(3)
N(1)-H(1)	0.99(4)
C(2)-C(3)	1.518(5)
C(2)-H(2A)	1.02(3)
C(2)-H(2B)	1.04(5)
C(3)-H(3A)	1.02(4)
C(3)-H(3B)	1.14(5)
C(4)-C(5)	1.496(4)
C(4)-H(4A)	1.10(3)
C(4)-H(4B)	1.04(4)
C(5)-C(6)	1.308(5)
C(5)-H(5)	0.99(4)
C(6)-H(6A)	1.01(6)
C(6)-H(6B)	1.05(5)
C(7)-C(8)	1.377(4)
C(7)-C(12)	1.395(4)
C(8)-C(9)	1.401(4)
C(8)-H(8)	1.01(4)
C(9)-C(10)	1.381(5)
C(9)-H(9)	1.01(5)
C(10)-C(11)	1.365(5)
C(10)-H(10)	1.08(4)
C(11)-C(12)	1.386(4)
C(11)-H(11)	0.99(4)
C(12)-H(12)	1.06(3)
N(1)-C(1)-C(7)	108.87(18)
N(1)-C(1)-C(2)	103.7(2)
C(7)-C(1)-C(2)	115.5(2)
N(1)-C(1)-C(4)	106.1(2)
C(7)-C(1)-C(4)	111.0(2)
C(2)-C(1)-C(4)	111.0(2)
C(3)-O(1)-N(1)	106.6(2)
O(1)-N(1)-C(1)	103.27(18)
O(1)-N(1)-H(1)	102(2)
C(1)-N(1)-H(1)	107(2)
C(3)-C(2)-C(1)	103.2(2)
C(3)-C(2)-H(2A)	111.4(19)
C(1)-C(2)-H(2A)	117(2)
C(3)-C(2)-H(2B)	111(3)
C(1)-C(2)-H(2B)	107(3)
H(2A)-C(2)-H(2B)	107(3)
O(1)-C(3)-C(2)	107.2(2)
O(1)-C(3)-H(3A)	107(3)
C(2)-C(3)-H(3A)	116(3)
O(1)-C(3)-H(3B)	108(2)
C(2)-C(3)-H(3B)	106(2)
H(3A)-C(3)-H(3B)	113(3)
C(5)-C(4)-C(1)	114.0(2)
C(5)-C(4)-H(4A)	105.2(16)
C(1)-C(4)-H(4A)	111.8(16)
C(5)-C(4)-H(4B)	109.7(19)
C(1)-C(4)-H(4B)	106.2(19)
H(4A)-C(4)-H(4B)	110(2)
C(6)-C(5)-C(4)	126.0(4)
C(6)-C(5)-H(5)	121(3)
C(4)-C(5)-H(5)	113(2)
C(5)-C(6)-H(6A)	130(3)
C(5)-C(6)-H(6B)	117(3)
H(6A)-C(6)-H(6B)	112(4)
C(8)-C(7)-C(12)	118.4(3)
C(8)-C(7)-C(1)	122.6(2)
C(12)-C(7)-C(1)	118.9(2)
C(7)-C(8)-C(9)	120.3(3)
C(7)-C(8)-H(8)	126(2)
C(9)-C(8)-H(8)	114(2)
C(10)-C(9)-C(8)	120.2(3)
C(10)-C(9)-H(9)	130(3)
C(8)-C(9)-H(9)	110(3)
C(11)-C(10)-C(9)	119.9(3)
C(11)-C(10)-H(10)	122(2)
C(9)-C(10)-H(10)	119(2)
C(10)-C(11)-C(12)	120.0(3)
C(10)-C(11)-H(11)	118(2)
C(12)-C(11)-H(11)	121(2)
C(11)-C(12)-C(7)	121.1(3)
C(11)-C(12)-H(12)	119.5(17)
C(7)-C(12)-H(12)	119.4(17)

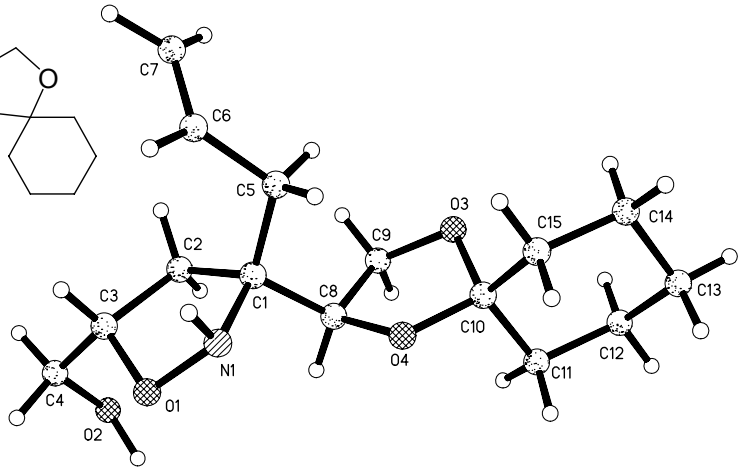
Torsion angles [°].

C(3)-O(1)-N(1)-C(1)	40.2(3)
C(7)-C(1)-N(1)-O(1)	-160.6(2)
C(2)-C(1)-N(1)-O(1)	-37.1(3)
C(4)-C(1)-N(1)-O(1)	79.9(2)
N(1)-C(1)-C(2)-C(3)	21.2(3)
C(7)-C(1)-C(2)-C(3)	140.3(3)
C(4)-C(1)-C(2)-C(3)	-92.3(3)
N(1)-O(1)-C(3)-C(2)	-26.3(4)
C(1)-C(2)-C(3)-O(1)	2.6(4)
N(1)-C(1)-C(4)-C(5)	-178.4(2)
C(7)-C(1)-C(4)-C(5)	63.5(3)
C(2)-C(1)-C(4)-C(5)	-66.4(3)
C(1)-C(4)-C(5)-C(6)	124.4(4)
N(1)-C(1)-C(7)-C(8)	137.9(3)
C(2)-C(1)-C(7)-C(8)	21.8(3)
C(4)-C(1)-C(7)-C(8)	-105.7(3)
N(1)-C(1)-C(7)-C(12)	-43.7(3)
C(2)-C(1)-C(7)-C(12)	-159.8(3)
C(4)-C(1)-C(7)-C(12)	72.7(3)
C(12)-C(7)-C(8)-C(9)	0.5(4)
C(1)-C(7)-C(8)-C(9)	178.9(3)
C(7)-C(8)-C(9)-C(10)	0.4(5)
C(8)-C(9)-C(10)-C(11)	-0.8(6)
C(9)-C(10)-C(11)-C(12)	0.4(5)
C(10)-C(11)-C(12)-C(7)	0.5(5)
C(8)-C(7)-C(12)-C(11)	-0.9(4)
C(1)-C(7)-C(12)-C(11)	-179.4(2)

12.1.3 ((3*R*,5*S*)-3-Allyl-3-(*S*)-1,4-dioxa-spiro[4.5]dec-2-yl-isoxazolidin-5-yl)-methanol (35a).

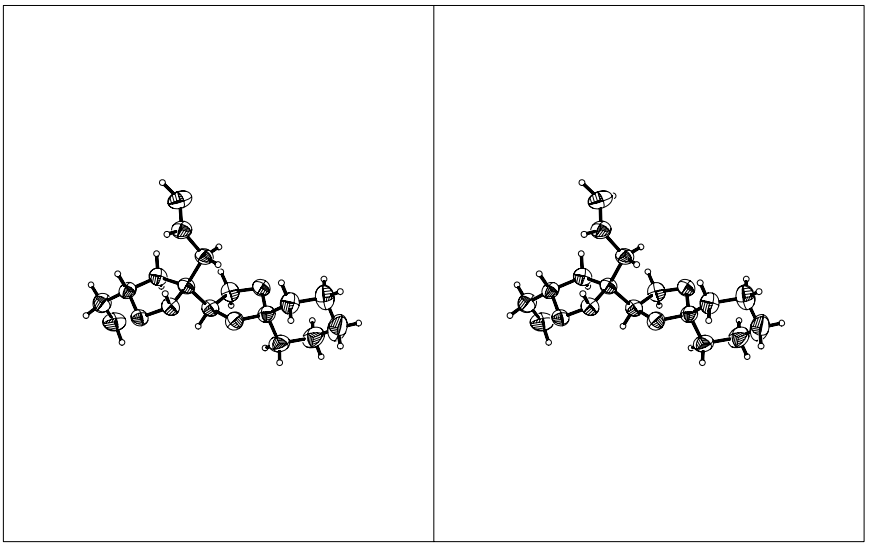


35a



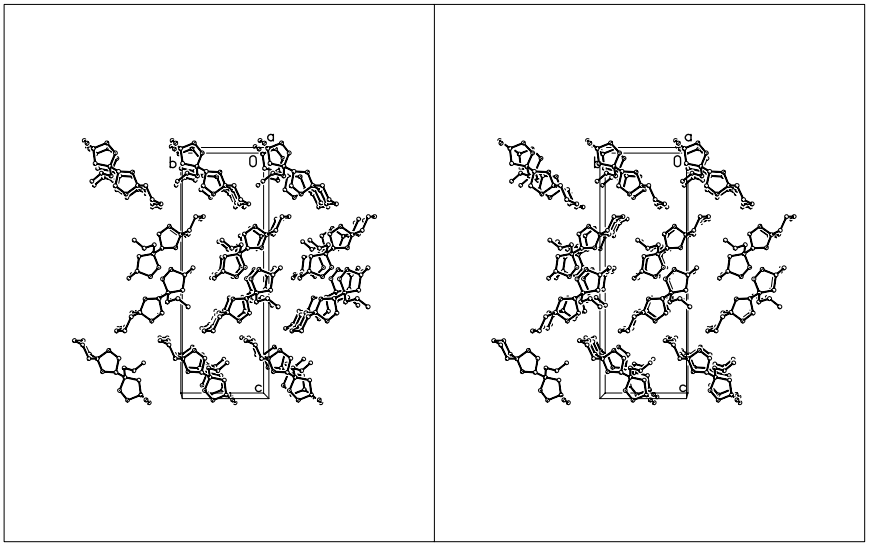
$C_{15}H_{25}NO_4$
orthorhombic,
P2(1)2(1)2(1)
a = 7.0599(3) Å
b = 8.5951(5) Å
c = 24.9282(13) Å
α = 90°
β = 90°
γ = 90°
V = 1512.66(13) Å^3
Z = 4, *R(F)* = 0.0493
$R_W(F^2)$ = 0.1313
Crystal size: 1.2 x 0.3 x 0.15 mm
Calculated density : 1.244 g/cm^3
Theta range for data collection: 3.55 - 67.99 degree
Unigue reflections: 2428
Observed reflections: 2092
No. of contributed reflections to refinement: 2428
No. of refined parameters: 202

Stereoview of the structure with displacement parameters:

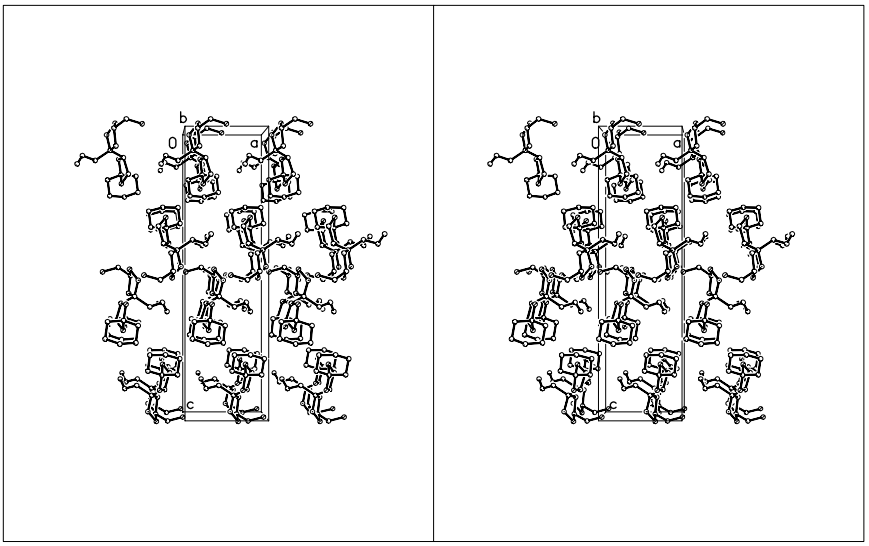


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

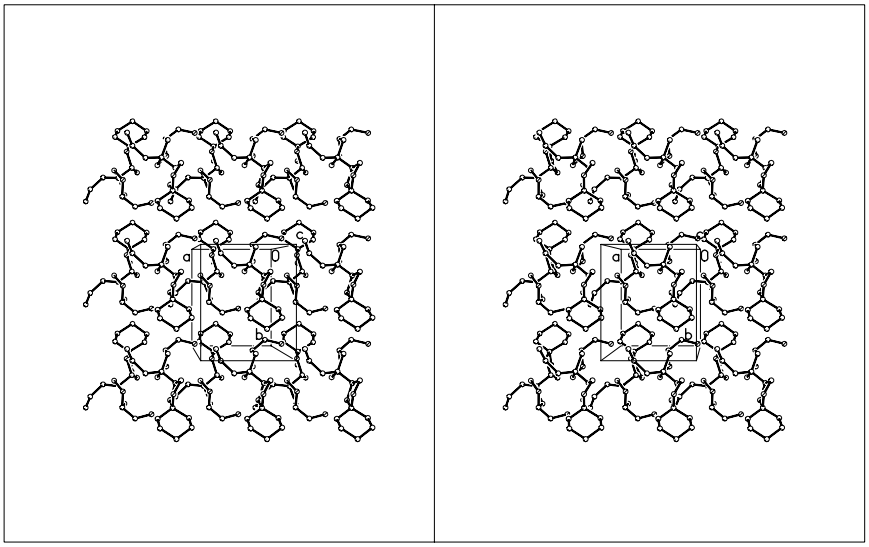
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

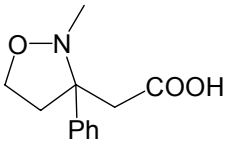
O(1)-N(1)	1.442(3)
O(1)-C(3)	1.444(3)
N(1)-C(1)	1.498(3)
N(1)-H(1)	0.91(3)
C(1)-C(8)	1.522(4)
C(1)-C(2)	1.537(4)
C(1)-C(5)	1.544(4)
O(2)-C(4)	1.411(4)
O(2)-H(2)	0.98(7)
C(2)-C(3)	1.517(4)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
O(3)-C(9)	1.422(4)
O(3)-C(10)	1.430(3)
C(3)-C(4)	1.510(4)
C(3)-H(3)	0.9800
O(4)-C(8)	1.430(3)
O(4)-C(10)	1.432(3)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-C(6)	1.486(4)
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-C(7)	1.310(5)
C(6)-H(6)	1.02(5)
C(7)-H(7A)	0.95(5)
C(7)-H(7B)	1.04(5)
C(8)-C(9)	1.530(4)
C(8)-H(8)	0.9800
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-C(15)	1.499(5)
C(10)-C(11)	1.518(4)
C(11)-C(12)	1.523(5)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-C(13)	1.523(7)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-C(14)	1.522(6)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-C(15)	1.521(5)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
N(1)-O(1)-C(3)	105.86(18)
O(1)-N(1)-C(1)	105.55(19)
O(1)-N(1)-H(1)	106.6(18)
C(1)-N(1)-H(1)	109.8(17)
N(1)-C(1)-C(8)	106.4(2)
N(1)-C(1)-C(2)	104.7(2)
C(8)-C(1)-C(2)	110.6(2)
N(1)-C(1)-C(5)	107.9(2)
C(8)-C(1)-C(5)	111.6(2)
C(2)-C(1)-C(5)	115.0(2)
C(4)-O(2)-H(2)	111(5)
C(3)-C(2)-C(1)	104.7(2)
C(3)-C(2)-H(2A)	110.8
C(1)-C(2)-H(2A)	110.8
C(3)-C(2)-H(2B)	110.8
C(1)-C(2)-H(2B)	110.8
H(2A)-C(2)-H(2B)	108.9
C(9)-O(3)-C(10)	106.6(2)
O(1)-C(3)-C(4)	108.5(2)
O(1)-C(3)-C(2)	103.7(2)
C(4)-C(3)-C(2)	116.7(3)
O(1)-C(3)-H(3)	109.2
C(4)-C(3)-H(3)	109.2
C(2)-C(3)-H(3)	109.2
C(8)-O(4)-C(10)	109.6(2)
O(2)-C(4)-C(3)	114.2(3)
O(2)-C(4)-H(4A)	108.7
C(3)-C(4)-H(4A)	108.7
O(2)-C(4)-H(4B)	108.7
C(3)-C(4)-H(4B)	108.7
H(4A)-C(4)-H(4B)	107.6
C(6)-C(5)-C(1)	114.8(2)
C(6)-C(5)-H(5A)	108.6
C(1)-C(5)-H(5A)	108.6
C(6)-C(5)-H(5B)	108.6
C(1)-C(5)-H(5B)	108.6
H(5A)-C(5)-H(5B)	107.6
C(7)-C(6)-C(5)	125.2(4)
C(7)-C(6)-H(6)	116(3)
C(5)-C(6)-H(6)	119(3)
C(6)-C(7)-H(7A)	118(3)
C(6)-C(7)-H(7B)	121(3)
H(7A)-C(7)-H(7B)	119(4)
O(4)-C(8)-C(1)	109.9(2)
O(4)-C(8)-C(9)	104.1(2)
C(1)-C(8)-C(9)	115.8(2)
O(4)-C(8)-H(8)	109.0
C(1)-C(8)-H(8)	109.0
C(9)-C(8)-H(8)	109.0
O(3)-C(9)-C(8)	104.1(2)
O(3)-C(9)-H(9A)	110.9
C(8)-C(9)-H(9A)	110.9
O(3)-C(9)-H(9B)	110.9
C(8)-C(9)-H(9B)	110.9
H(9A)-C(9)-H(9B)	108.9
O(3)-C(10)-O(4)	104.6(2)
O(3)-C(10)-C(15)	108.9(3)
O(4)-C(10)-C(15)	109.6(3)
O(3)-C(10)-C(11)	110.9(3)
O(4)-C(10)-C(11)	110.4(2)
C(15)-C(10)-C(11)	112.1(2)
C(10)-C(11)-C(12)	111.1(3)
C(10)-C(11)-H(11A)	109.4
C(12)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
C(12)-C(11)-H(11B)	109.4

H(11A)-C(11)-H(11B)	108.0
C(11)-C(12)-C(13)	111.1(3)
C(11)-C(12)-H(12A)	109.4
C(13)-C(12)-H(12A)	109.4
C(11)-C(12)-H(12B)	109.4
C(13)-C(12)-H(12B)	109.4
H(12A)-C(12)-H(12B)	108.0
C(14)-C(13)-C(12)	110.6(3)
C(14)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13A)	109.5
C(14)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	108.1
C(15)-C(14)-C(13)	110.7(4)
C(15)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14A)	109.5
C(15)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	108.1
C(10)-C(15)-C(14)	111.9(3)
C(10)-C(15)-H(15A)	109.2
C(14)-C(15)-H(15A)	109.2
C(10)-C(15)-H(15B)	109.2
C(14)-C(15)-H(15B)	109.2
H(15A)-C(15)-H(15B)	107.9

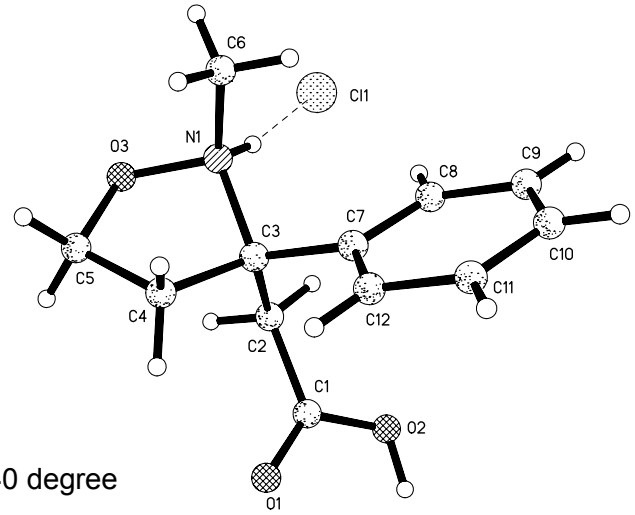
Torsion angles [°].

C(3)-O(1)-N(1)-C(1)	-37.7(3)
O(1)-N(1)-C(1)-C(8)	-97.3(2)
O(1)-N(1)-C(1)-C(2)	19.8(3)
O(1)-N(1)-C(1)-C(5)	142.8(2)
N(1)-C(1)-C(2)-C(3)	3.9(3)
C(8)-C(1)-C(2)-C(3)	118.1(3)
C(5)-C(1)-C(2)-C(3)	-114.4(3)
N(1)-O(1)-C(3)-C(4)	164.3(2)
N(1)-O(1)-C(3)-C(2)	39.7(3)
C(1)-C(2)-C(3)-O(1)	-26.0(3)
C(1)-C(2)-C(3)-C(4)	-145.2(3)
O(1)-C(3)-C(4)-O(2)	-71.1(3)
C(2)-C(3)-C(4)-O(2)	45.4(4)
N(1)-C(1)-C(5)-C(6)	-73.3(3)
C(8)-C(1)-C(5)-C(6)	170.1(2)
C(2)-C(1)-C(5)-C(6)	43.1(4)
C(1)-C(5)-C(6)-C(7)	-114.1(4)
C(10)-O(4)-C(8)-C(1)	-126.8(2)
C(10)-O(4)-C(8)-C(9)	-2.2(3)
N(1)-C(1)-C(8)-O(4)	-58.2(3)
C(2)-C(1)-C(8)-O(4)	-171.3(2)
C(5)-C(1)-C(8)-O(4)	59.3(3)
N(1)-C(1)-C(8)-C(9)	-175.7(2)
C(2)-C(1)-C(8)-C(9)	71.2(3)
C(5)-C(1)-C(8)-C(9)	-58.2(3)
C(10)-O(3)-C(9)-C(8)	31.6(3)
O(4)-C(8)-C(9)-O(3)	-17.8(3)
C(1)-C(8)-C(9)-O(3)	102.8(3)
C(9)-O(3)-C(10)-O(4)	-33.3(3)
C(9)-O(3)-C(10)-C(15)	-150.4(2)
C(9)-O(3)-C(10)-C(11)	85.7(3)
C(8)-O(4)-C(10)-O(3)	21.4(3)
C(8)-O(4)-C(10)-C(15)	138.1(3)
C(8)-O(4)-C(10)-C(11)	-97.9(3)
O(3)-C(10)-C(11)-C(12)	67.9(4)
O(4)-C(10)-C(11)-C(12)	-176.6(3)
C(15)-C(10)-C(11)-C(12)	-54.1(4)
C(10)-C(11)-C(12)-C(13)	55.1(5)
C(11)-C(12)-C(13)-C(14)	-56.6(5)
C(12)-C(13)-C(14)-C(15)	56.2(5)
O(3)-C(10)-C(15)-C(14)	-68.7(3)
O(4)-C(10)-C(15)-C(14)	177.4(3)
C(11)-C(10)-C(15)-C(14)	54.5(4)
C(13)-C(14)-C(15)-C(10)	-55.4(4)

12.1.4 3-Carboxymethyl-2-methyl-3-phenyl-isoxazolidin-2-ium; chloride (51).

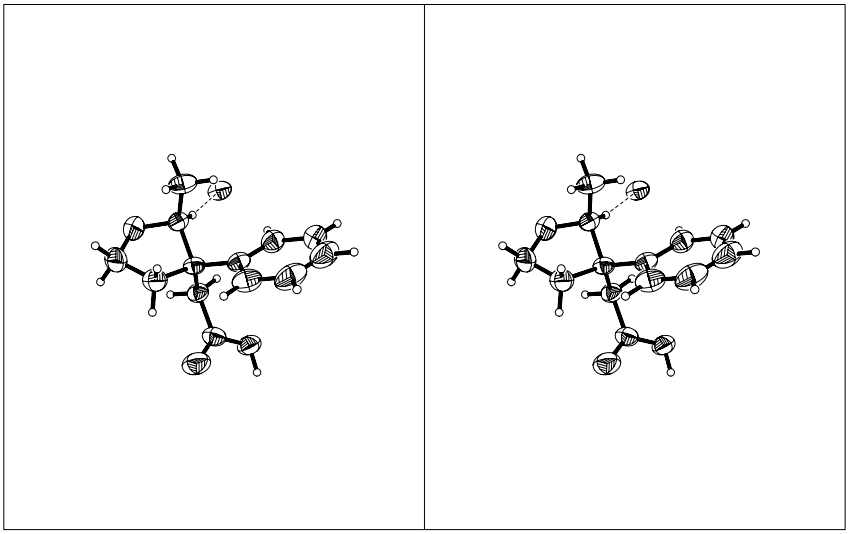


51 · HCl



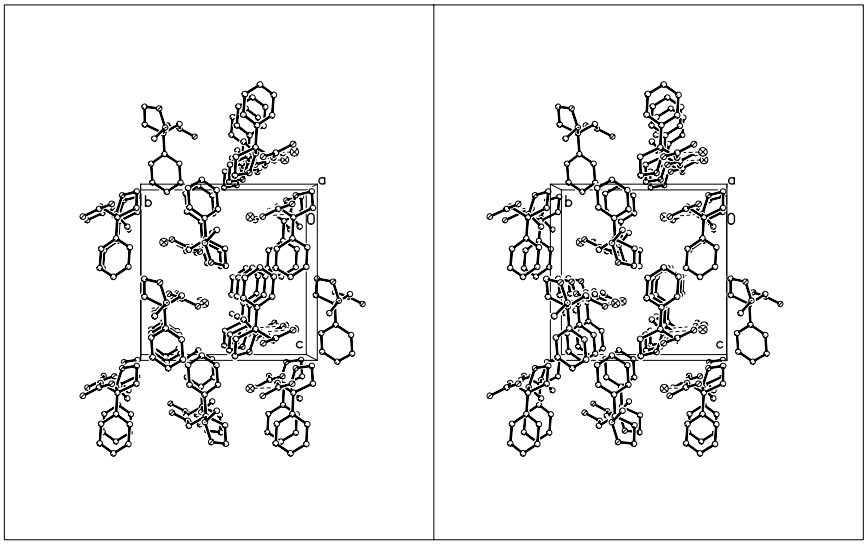
$C_{12}H_{16}ClNO_3$
orthorhombic,
P2(1)2(1)2(1)
a = 8.1632(5) Å
b = 12.4642(6) Å
c = 12.4641(6) Å
α = 90°
β = 90°
γ = 90°
V = 1268.19(12) Å^3
Z = 4, *R(F)* = 0.0537
$R_W(F^2)$ = 0.1324
Crystal size: 0.2 x 0.12 x 0.10 mm
Calculated density : 1.350 g/cm^3
Theta range for data collection: 5.02 - 62.40 degree
Unigue reflections: 1826
Observed reflections: 1473
No. of contributed reflections to refinement: 1826
No. of refined parameters: 159

Stereoview of the structure with displacement parameters:

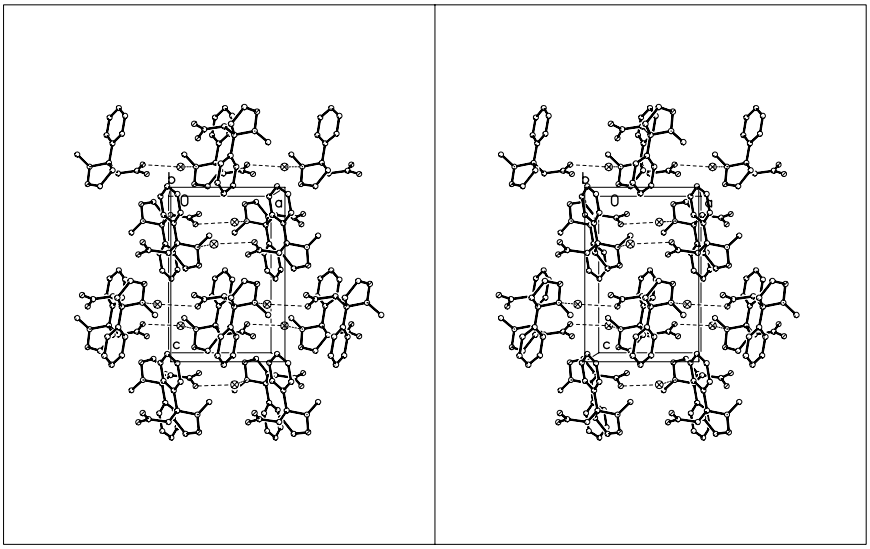


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

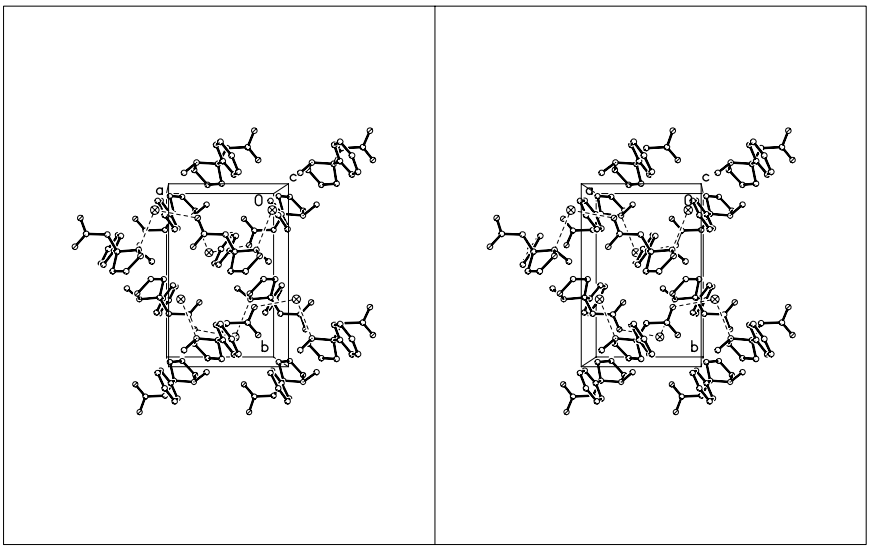
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

N(1)-O(3)	1.434(5)
N(1)-C(6)	1.489(6)
N(1)-C(3)	1.527(5)
N(1)-H(1)	0.9100
O(1)-C(1)	1.218(6)
C(1)-O(2)	1.316(6)
C(1)-C(2)	1.483(7)
O(2)-H(2)	0.87(8)
C(2)-C(3)	1.540(7)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-C(7)	1.524(6)
C(3)-C(4)	1.541(7)
O(3)-C(5)	1.454(7)
C(4)-C(5)	1.535(8)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(7)-C(8)	1.382(7)
C(7)-C(12)	1.393(7)
C(8)-C(9)	1.393(8)
C(8)-H(8)	0.9300
C(9)-C(10)	1.380(10)
C(9)-H(9)	0.9300
C(10)-C(11)	1.369(10)
C(10)-H(10)	0.9300
C(11)-C(12)	1.391(9)
C(11)-H(11)	0.9300
C(12)-H(12)	0.9300

O(3)-N(1)-C(6)	109.9(4)
O(3)-N(1)-C(3)	104.4(3)
C(6)-N(1)-C(3)	116.7(4)
O(3)-N(1)-H(1)	108.5
C(6)-N(1)-H(1)	108.5
C(3)-N(1)-H(1)	108.5
O(1)-C(1)-O(2)	121.8(5)
O(1)-C(1)-C(2)	124.0(5)
O(2)-C(1)-C(2)	114.2(5)
C(1)-O(2)-H(2)	110(5)
C(1)-C(2)-C(3)	112.8(4)
C(1)-C(2)-H(2A)	109.0
C(3)-C(2)-H(2A)	109.0
C(1)-C(2)-H(2B)	109.0
C(3)-C(2)-H(2B)	109.0
H(2A)-C(2)-H(2B)	107.8
C(7)-C(3)-N(1)	110.5(3)
C(7)-C(3)-C(2)	110.7(4)
N(1)-C(3)-C(2)	106.2(4)
C(7)-C(3)-C(4)	116.1(4)
N(1)-C(3)-C(4)	100.0(4)
C(2)-C(3)-C(4)	112.4(4)
N(1)-O(3)-C(5)	107.5(4)
C(5)-C(4)-C(3)	103.3(4)
C(5)-C(4)-H(4A)	111.1
C(3)-C(4)-H(4A)	111.1
C(5)-C(4)-H(4B)	111.1
C(3)-C(4)-H(4B)	111.1
H(4A)-C(4)-H(4B)	109.1
O(3)-C(5)-C(4)	106.8(4)
O(3)-C(5)-H(5A)	110.4
C(4)-C(5)-H(5A)	110.4
O(3)-C(5)-H(5B)	110.4
C(4)-C(5)-H(5B)	110.4
H(5A)-C(5)-H(5B)	108.6
N(1)-C(6)-H(6A)	109.5
N(1)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
N(1)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(8)-C(7)-C(12)	118.9(5)
C(8)-C(7)-C(3)	120.2(4)
C(12)-C(7)-C(3)	120.9(5)
C(7)-C(8)-C(9)	121.0(5)
C(7)-C(8)-H(8)	119.5
C(9)-C(8)-H(8)	119.5
C(10)-C(9)-C(8)	119.1(6)
C(10)-C(9)-H(9)	120.4
C(8)-C(9)-H(9)	120.4
C(11)-C(10)-C(9)	120.7(6)
C(11)-C(10)-H(10)	119.6
C(9)-C(10)-H(10)	119.6
C(10)-C(11)-C(12)	120.2(6)
C(10)-C(11)-H(11)	119.9
C(12)-C(11)-H(11)	119.9
C(11)-C(12)-C(7)	120.0(6)
C(11)-C(12)-H(12)	120.0
C(7)-C(12)-H(12)	120.0

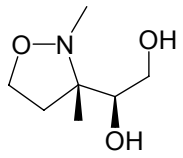
Torsion angles [°].

O(1)-C(1)-C(2)-C(3)	60.1(8)
O(2)-C(1)-C(2)-C(3)	-120.7(5)
O(3)-N(1)-C(3)-C(7)	-165.5(4)
C(6)-N(1)-C(3)-C(7)	-44.0(6)
O(3)-N(1)-C(3)-C(2)	74.3(4)
C(6)-N(1)-C(3)-C(2)	-164.2(4)
O(3)-N(1)-C(3)-C(4)	-42.6(4)
C(6)-N(1)-C(3)-C(4)	78.8(5)
C(1)-C(2)-C(3)-C(7)	58.5(6)
C(1)-C(2)-C(3)-N(1)	178.5(4)
C(1)-C(2)-C(3)-C(4)	-73.2(5)
C(6)-N(1)-O(3)-C(5)	-91.1(4)
C(3)-N(1)-O(3)-C(5)	34.8(5)
C(7)-C(3)-C(4)-C(5)	153.0(4)
N(1)-C(3)-C(4)-C(5)	34.2(5)
C(2)-C(3)-C(4)-C(5)	-78.1(5)
N(1)-O(3)-C(5)-C(4)	-12.0(5)
C(3)-C(4)-C(5)-O(3)	-15.1(5)
N(1)-C(3)-C(7)-C(8)	-54.2(6)
C(2)-C(3)-C(7)-C(8)	63.1(5)

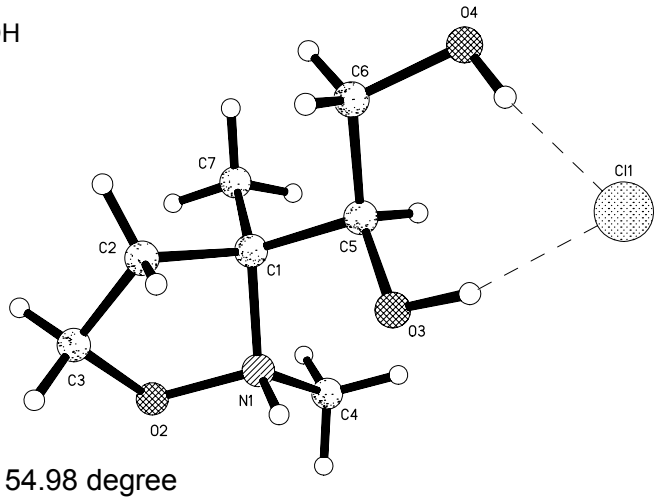
C(4)-C(3)-C(7)-C(8)	-167.1(4)	C(7)-C(8)-C(9)-C(10)	0.5(9)
N(1)-C(3)-C(7)-C(12)	127.6(5)	C(8)-C(9)-C(10)-C(11)	0.5(10)
C(2)-C(3)-C(7)-C(12)	-115.0(5)	C(9)-C(10)-C(11)-C(12)	-0.3(10)
C(4)-C(3)-C(7)-C(12)	14.8(6)	C(10)-C(11)-C(12)-C(7)	-0.9(9)
C(12)-C(7)-C(8)-C(9)	-1.7(8)	C(8)-C(7)-C(12)-C(11)	1.9(8)
C(3)-C(7)-C(8)-C(9)	-179.8(5)	C(3)-C(7)-C(12)-C(11)	-180.0(5)

12.1.5 (*S*)-3-((*S*)-1,2-Dihydroxy-ethyl)-2,3-dimethylisoxazolidin-2-ium; chloride (52•HCl).

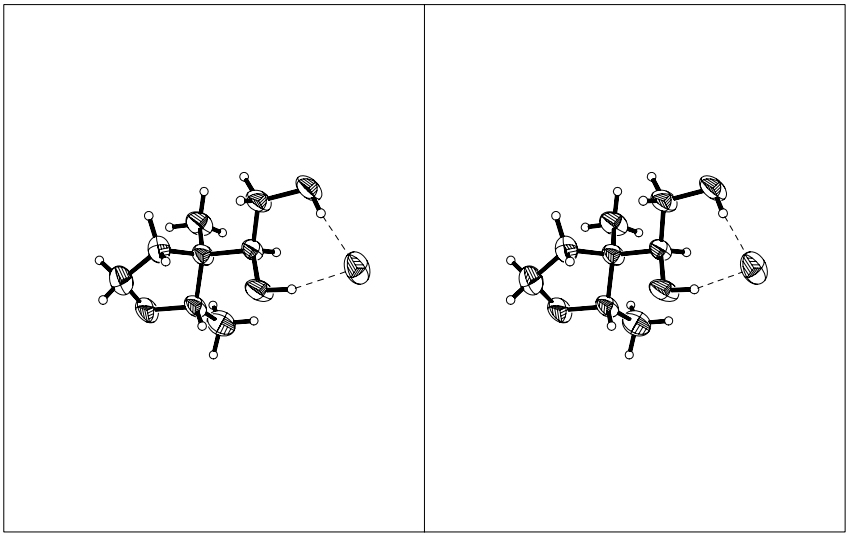
$C_7H_{16}ClNO_3$
orthorhombic,
P2(1)2(1)2(1)
a = 8.1100(10) Å
b = 9.846(2) Å
c = 12.1560(10) Å
α = 90°
β = 90°
γ = 90°
V = 970.7(2) Å^3
Z = 4, *R(F)* = 0.0374
$R_W(F^2)$ = 0.0940
Crystal size: 0.5 x 0.4 x 0.4 mm
Calculated density : 1.353 g/cm^3
Theta range for data collection: 6.56 to 54.98 degree
Unigue reflections: 632
Observed reflections: 1010
No. of contributed reflections to refinement: 632
No. of refined parameters: 112



52 · HCl

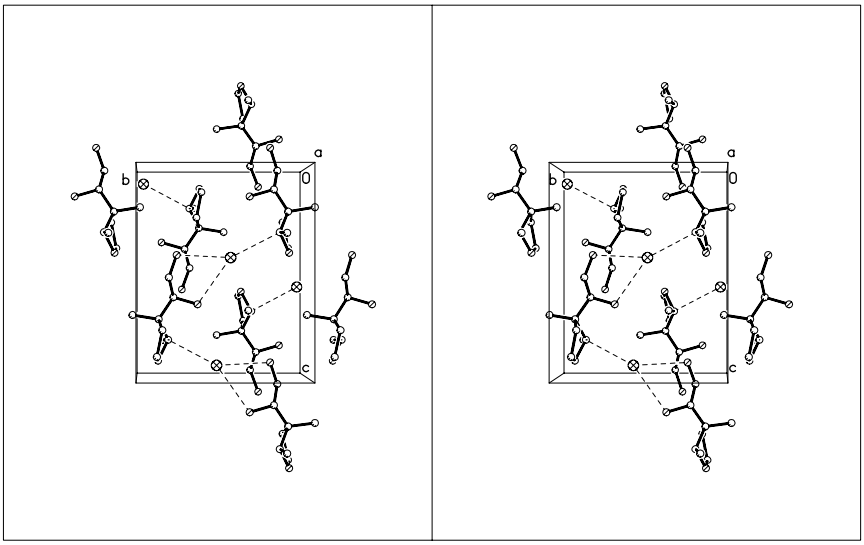


Stereoview of the structure with displacement parameters:

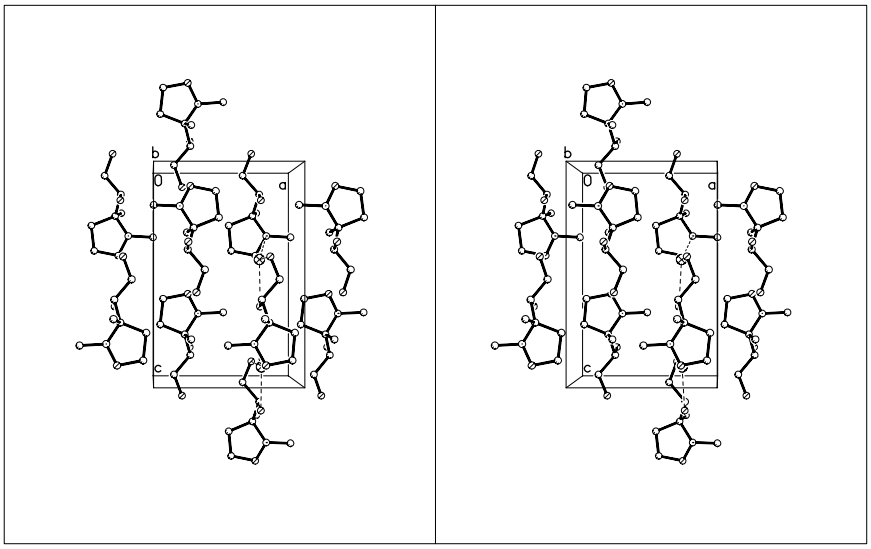


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

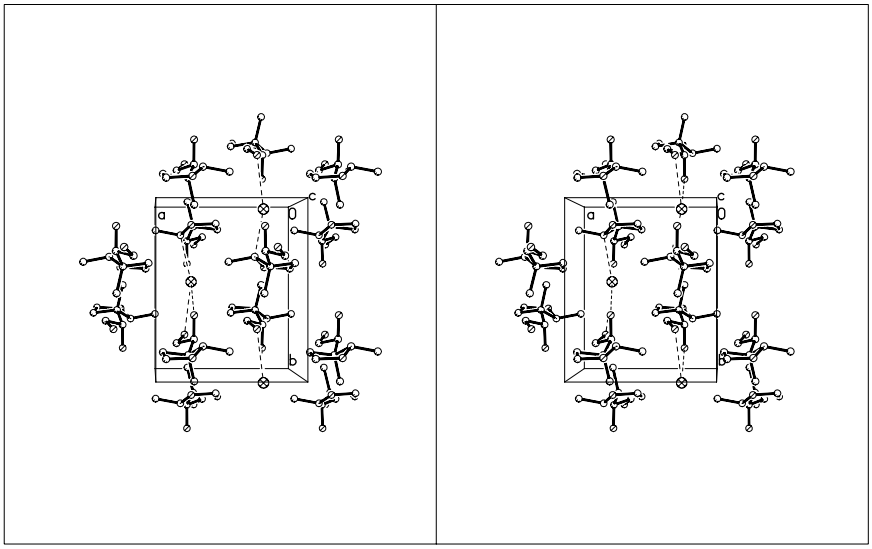
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

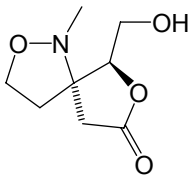
C(1)-N(1)	1.524(6)
C(1)-C(2)	1.526(8)
C(1)-C(5)	1.528(6)
C(1)-C(7)	1.530(7)
N(1)-O(2)	1.420(5)
N(1)-C(4)	1.477(7)
N(1)-H(1)	0.9100
O(2)-C(3)	1.452(9)
C(2)-C(3)	1.527(8)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
O(3)-C(5)	1.423(6)
O(3)-H(3)	1.02(8)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
O(4)-C(6)	1.416(6)
O(4)-H(4)	0.92(10)
C(4)-H(4A)	0.9600
C(4)-H(4B)	0.9600
C(4)-H(4C)	0.9600
C(5)-C(6)	1.497(7)
C(5)-H(5)	0.9800
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600

N(1)-C(1)-C(2)	98.0(4)
N(1)-C(1)-C(5)	108.7(4)
C(2)-C(1)-C(5)	116.2(5)
N(1)-C(1)-C(7)	110.3(4)
C(2)-C(1)-C(7)	112.3(5)
C(5)-C(1)-C(7)	110.6(4)
O(2)-N(1)-C(4)	107.6(4)
O(2)-N(1)-C(1)	105.5(4)
C(4)-N(1)-C(1)	118.4(4)
O(2)-N(1)-H(1)	108.3
C(4)-N(1)-H(1)	108.3
C(1)-N(1)-H(1)	108.3
N(1)-O(2)-C(3)	106.3(4)
C(1)-C(2)-C(3)	104.0(5)
C(1)-C(2)-H(2A)	111.0
C(3)-C(2)-H(2A)	111.0
C(1)-C(2)-H(2B)	111.0
C(3)-C(2)-H(2B)	111.0
H(2A)-C(2)-H(2B)	109.0
C(5)-O(3)-H(3)	114(4)
O(2)-C(3)-C(2)	106.4(5)
O(2)-C(3)-H(3A)	110.5
C(2)-C(3)-H(3A)	110.5
O(2)-C(3)-H(3B)	110.5
C(2)-C(3)-H(3B)	110.5
H(3A)-C(3)-H(3B)	108.6
C(6)-O(4)-H(4)	104(6)
N(1)-C(4)-H(4A)	109.5
N(1)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
N(1)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
O(3)-C(5)-C(6)	112.4(4)
O(3)-C(5)-C(1)	107.3(4)
C(6)-C(5)-C(1)	111.3(4)
O(3)-C(5)-H(5)	108.6
C(6)-C(5)-H(5)	108.6
C(1)-C(5)-H(5)	108.6
O(4)-C(6)-C(5)	113.2(5)
O(4)-C(6)-H(6A)	108.9
C(5)-C(6)-H(6A)	108.9
O(4)-C(6)-H(6B)	108.9
C(5)-C(6)-H(6B)	108.9
H(6A)-C(6)-H(6B)	107.7
C(1)-C(7)-H(7A)	109.5
C(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5

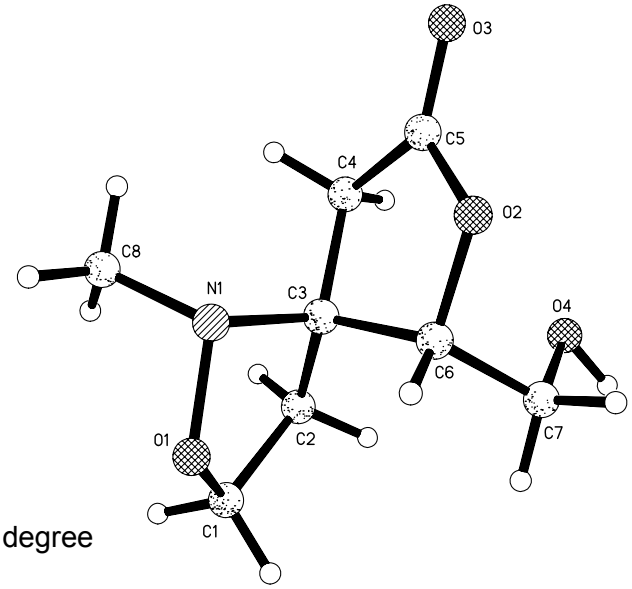
Torsion angles [°].

C(2)-C(1)-N(1)-O(2)	44.7(5)
C(5)-C(1)-N(1)-O(2)	165.9(4)
C(7)-C(1)-N(1)-O(2)	-72.7(5)
C(2)-C(1)-N(1)-C(4)	165.0(5)
C(5)-C(1)-N(1)-C(4)	-73.8(6)
C(7)-C(1)-N(1)-C(4)	47.7(6)
C(4)-N(1)-O(2)-C(3)	-163.3(5)
C(1)-N(1)-O(2)-C(3)	-36.1(5)
N(1)-C(1)-C(2)-C(3)	-35.8(6)
C(5)-C(1)-C(2)-C(3)	-151.2(5)
C(7)-C(1)-C(2)-C(3)	80.0(6)
N(1)-O(2)-C(3)-C(2)	11.6(7)
C(1)-C(2)-C(3)-O(2)	16.7(8)
N(1)-C(1)-C(5)-O(3)	-43.6(6)
C(2)-C(1)-C(5)-O(3)	65.7(6)
C(7)-C(1)-C(5)-O(3)	-164.8(6)
N(1)-C(1)-C(5)-C(6)	-166.9(4)
C(2)-C(1)-C(5)-C(6)	-57.6(6)
C(7)-C(1)-C(5)-C(6)	71.9(6)
O(3)-C(5)-C(6)-O(4)	76.3(6)
C(1)-C(5)-C(6)-O(4)	-163.4(5)

12.1.6 (1*S*,6*S*)-6-Hydroxymethyl-1-methyl-2,7-dioxa-1-azaspiro[4.4]nonan-8-one (54).

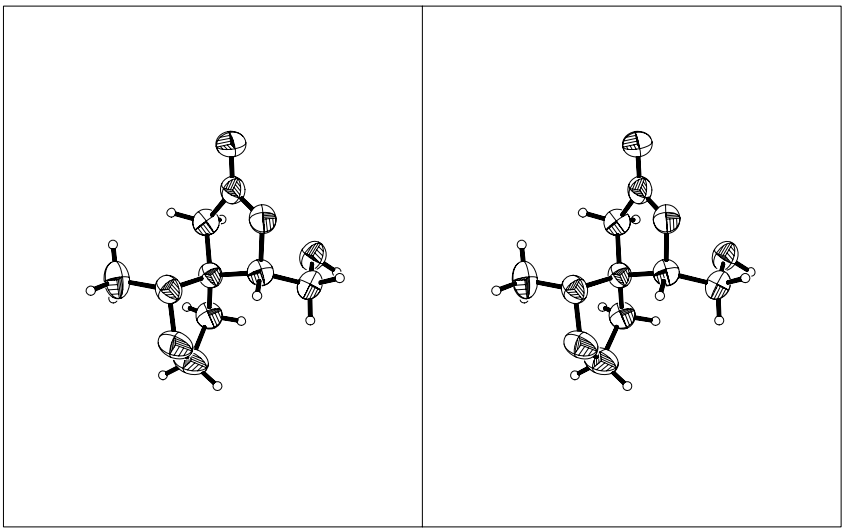


54



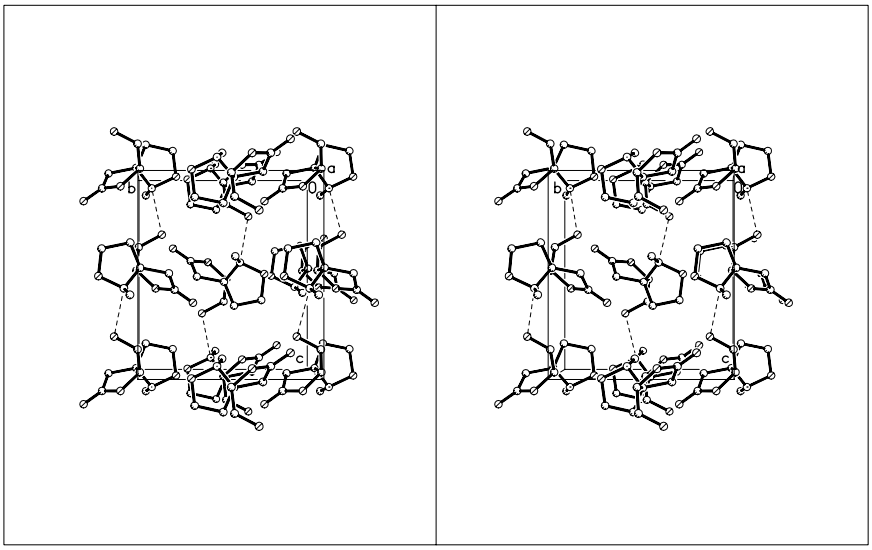
$C_8H_{13}NO_4$
Orthorhombic,
P2(1)2(1)2(1)
a = 8.8739(5) Å
b = 9.5664(5) Å
c = 10.7489(6) Å
α = 90°
β = 90°
γ = 90°
V = 912.49(9) Å^3
Z = 4, *R(F)* = 0.0515
$R_W(F^2)$ = 0.1428
Crystal size: 0.4 x 0.4 x 0.2 mm
Calculated density : 1.363 g/cm^3
Theta range for data collection: 6.19-67.98 degree
Unigue reflections: 1389
Observed reflections: 1304
No. of contributed reflections to refinement: 1389
No. of refined parameters: 123

Stereoview of the structure with displacement parameters:

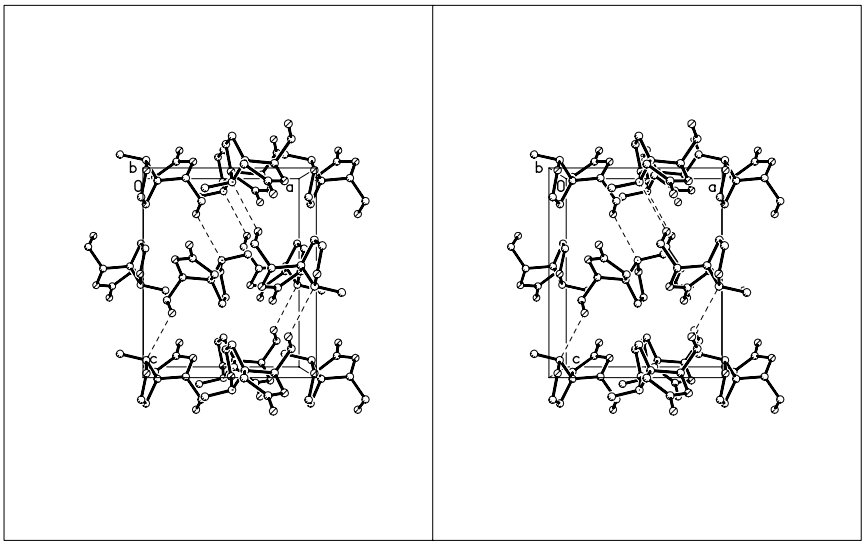


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

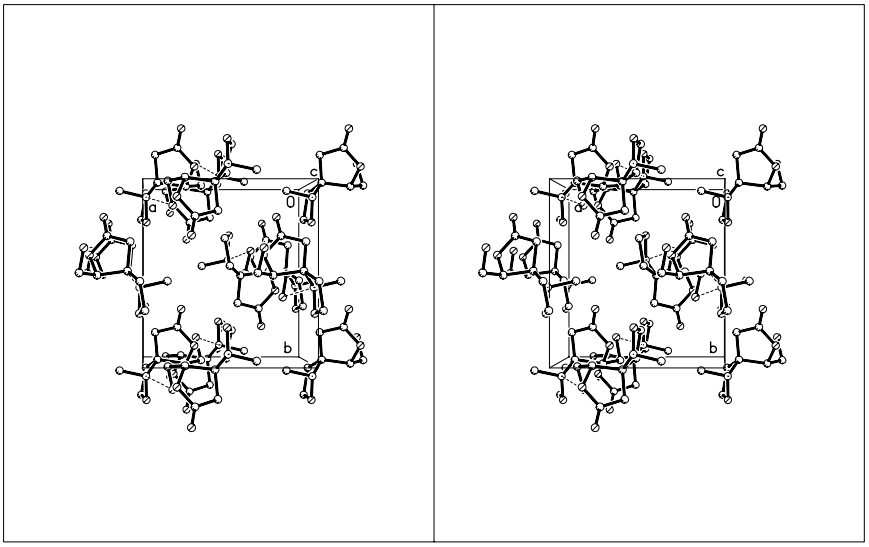
(a)



(b)



(c)



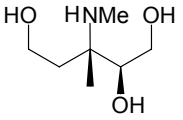
Bond lengths [Å] and angles [°].

N(1)-O(1)	1.454(3)
N(1)-C(8)	1.480(4)
N(1)-C(3)	1.481(3)
O(1)-C(1)	1.453(4)
C(1)-C(2)	1.514(5)
C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700
C(2)-C(3)	1.527(4)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
O(2)-C(5)	1.339(4)
O(2)-C(6)	1.458(3)
O(3)-C(5)	1.208(4)
C(3)-C(4)	1.518(4)
C(3)-C(6)	1.549(4)
O(4)-C(7)	1.419(4)
O(4)-H(4)	0.96(5)
C(4)-C(5)	1.495(4)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(6)-C(7)	1.513(4)
C(6)-H(6)	0.9800
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-H(8A)	0.9600
C(8)-H(8B)	0.9600
C(8)-H(8C)	0.9600
O(1)-N(1)-C(8)	107.6(2)
O(1)-N(1)-C(3)	101.4(2)
C(8)-N(1)-C(3)	115.2(2)
C(1)-O(1)-N(1)	107.9(2)
O(1)-C(1)-C(2)	106.4(3)
O(1)-C(1)-H(1A)	110.4
C(2)-C(1)-H(1A)	110.4
O(1)-C(1)-H(1B)	110.4
C(2)-C(1)-H(1B)	110.4
H(1A)-C(1)-H(1B)	108.6
C(1)-C(2)-C(3)	102.7(2)
C(1)-C(2)-H(2A)	111.2
C(3)-C(2)-H(2A)	111.2
C(1)-C(2)-H(2B)	111.2
C(3)-C(2)-H(2B)	111.2
H(2A)-C(2)-H(2B)	109.1
C(5)-O(2)-C(6)	110.5(2)
N(1)-C(3)-C(4)	112.4(2)
N(1)-C(3)-C(2)	104.1(2)
C(4)-C(3)-C(2)	117.1(2)
N(1)-C(3)-C(6)	105.7(2)
C(4)-C(3)-C(6)	101.5(2)
C(2)-C(3)-C(6)	115.7(2)
C(7)-O(4)-H(4)	106(3)
C(5)-C(4)-C(3)	104.3(2)
C(5)-C(4)-H(4A)	110.9
C(3)-C(4)-H(4A)	110.9
C(5)-C(4)-H(4B)	110.9
C(3)-C(4)-H(4B)	110.9
H(4A)-C(4)-H(4B)	108.9
O(3)-C(5)-O(2)	120.9(3)
O(3)-C(5)-C(4)	128.6(3)
O(2)-C(5)-C(4)	110.5(3)
O(2)-C(6)-C(7)	108.8(2)
O(2)-C(6)-C(3)	104.4(2)
C(7)-C(6)-C(3)	118.4(2)
O(2)-C(6)-H(6)	108.3
C(7)-C(6)-H(6)	108.3
C(3)-C(6)-H(6)	108.3
O(4)-C(7)-C(6)	110.2(2)
O(4)-C(7)-H(7A)	109.6
C(6)-C(7)-H(7A)	109.6
O(4)-C(7)-H(7B)	109.6
C(6)-C(7)-H(7B)	109.6
H(7A)-C(7)-H(7B)	108.1
N(1)-C(8)-H(8A)	109.5
N(1)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
N(1)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5

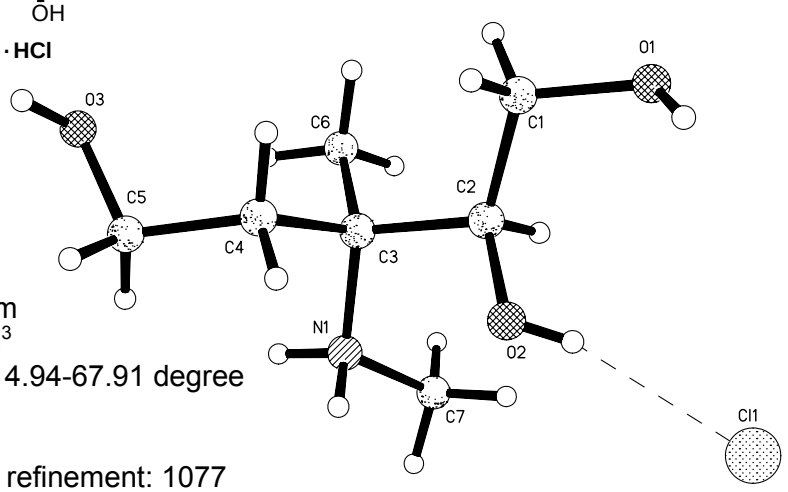
Torsion angles [°].

C(8)-N(1)-O(1)-C(1)	84.1(3)
C(3)-N(1)-O(1)-C(1)	-37.2(3)
N(1)-O(1)-C(1)-C(2)	18.1(4)
O(1)-C(1)-C(2)-C(3)	8.1(4)
O(1)-N(1)-C(3)-C(4)	169.2(2)
C(8)-N(1)-C(3)-C(4)	53.4(3)
O(1)-N(1)-C(3)-C(2)	41.5(3)
C(8)-N(1)-C(3)-C(2)	-74.3(3)
O(1)-N(1)-C(3)-C(6)	-80.8(2)
C(8)-N(1)-C(3)-C(6)	163.3(3)
C(1)-C(2)-C(3)-N(1)	-30.7(3)
C(1)-C(2)-C(3)-C(4)	-155.4(3)
C(1)-C(2)-C(3)-C(6)	84.9(3)
N(1)-C(3)-C(4)-C(5)	86.0(3)
C(2)-C(3)-C(4)-C(5)	-153.5(2)
C(6)-C(3)-C(4)-C(5)	-26.5(3)
C(6)-O(2)-C(5)-O(3)	-176.5(3)
C(6)-O(2)-C(5)-C(4)	3.6(3)
C(3)-C(4)-C(5)-O(3)	-164.2(3)
C(3)-C(4)-C(5)-O(2)	15.6(3)
C(5)-O(2)-C(6)-C(7)	106.4(2)
C(5)-O(2)-C(6)-C(3)	-20.9(3)
N(1)-C(3)-C(6)-O(2)	-88.7(3)
C(4)-C(3)-C(6)-O(2)	28.8(3)
C(2)-C(3)-C(6)-O(2)	156.7(2)
N(1)-C(3)-C(6)-C(7)	150.2(2)
C(4)-C(3)-C(6)-C(7)	-92.3(3)
C(2)-C(3)-C(6)-C(7)	35.6(4)
O(2)-C(6)-C(7)-O(4)	-66.2(3)
C(3)-C(6)-C(7)-O(4)	52.6(3)

12.1.7 [(1*S*,2*S*)-2,3-Dihydroxy-1-(2-hydroxyethyl)-1-methylpropyl]-methylammonium; chloride (70•HCl).

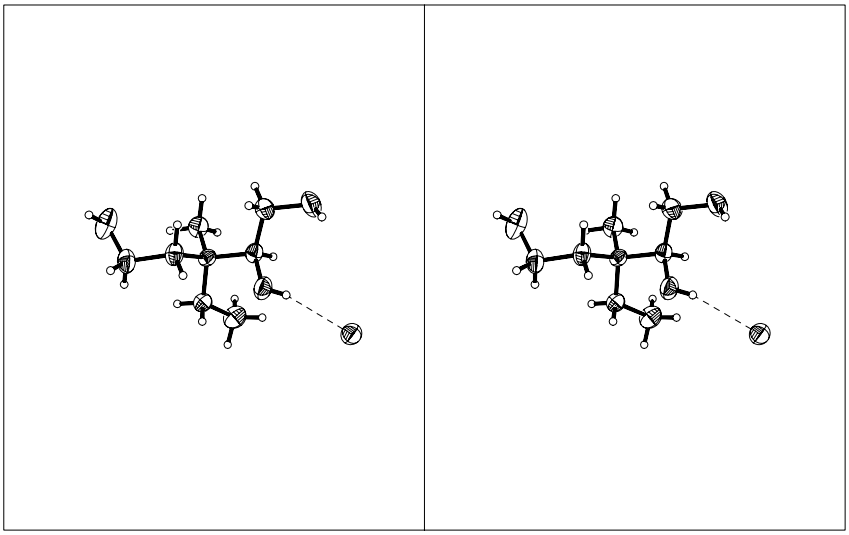


70 · HCl



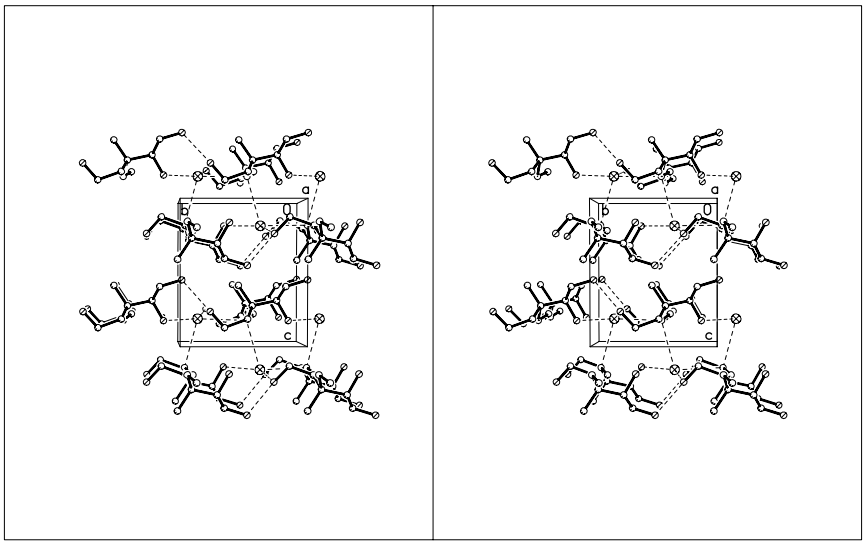
$C_7H_{18}ClNO_3$
monoclinic, P2(1)
a = 7.3469(4) Å
b = 7.6564(5) Å
c = 8.9565(4) Å
α = 90°
β = 92.792(5)°
γ = 90°
V = 503.21(5) Å^3
Z = 2, *R(F)* = 0.0379
$R_W(F^2)$ = 0.0997
Crystal size: 0.4 x 0.35 x 0.2 mm
Calculated density : 1.318 g/cm^3
Theta range for data collection: 4.94-67.91 degree
Unigue reflections: 1077
Observed reflections: 1037
No. of contributed reflections to refinement: 1077
No. of refined parameters: 122

Stereoview of the structure with displacement parameters:

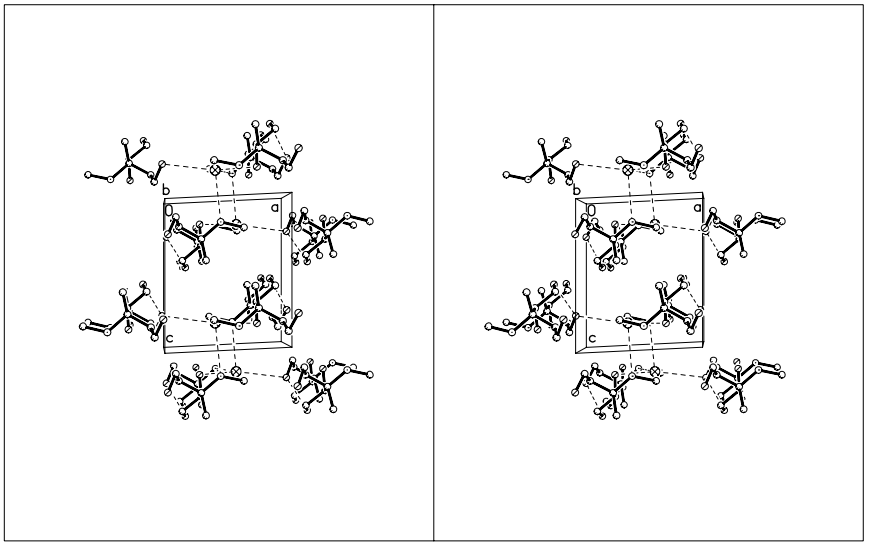


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

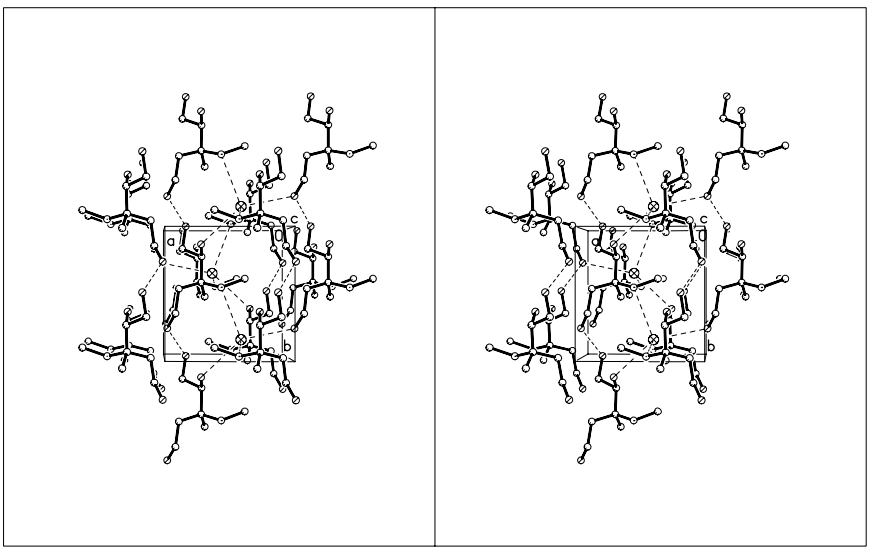
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

N(1)-C(7)	1.492(4)
N(1)-C(3)	1.521(4)
N(1)-H(1A)	0.9000
N(1)-H(1B)	0.9000
O(1)-C(1)	1.413(6)
O(1)-H(1)	0.92(7)
C(1)-C(2)	1.510(5)
C(1)-H(1C)	0.9700
C(1)-H(1D)	0.9700
C(2)-O(2)	1.426(5)
C(2)-C(3)	1.538(5)
C(2)-H(2A)	0.9800
O(2)-H(2)	0.74(5)
C(3)-C(6)	1.520(5)
C(3)-C(4)	1.532(4)
O(3)-C(5)	1.419(6)
O(3)-H(3)	0.86(8)
C(4)-C(5)	1.511(6)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600

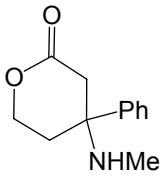
C(7)-N(1)-C(3)	118.8(3)
C(7)-N(1)-H(1A)	107.6
C(3)-N(1)-H(1A)	107.6
C(7)-N(1)-H(1B)	107.6
C(3)-N(1)-H(1B)	107.6
H(1A)-N(1)-H(1B)	107.0
C(1)-O(1)-H(1)	114(4)
O(1)-C(1)-C(2)	111.1(4)
O(1)-C(1)-H(1C)	109.4
C(2)-C(1)-H(1C)	109.4
O(1)-C(1)-H(1D)	109.4
C(2)-C(1)-H(1D)	109.4
H(1C)-C(1)-H(1D)	108.0
O(2)-C(2)-C(1)	110.2(3)
O(2)-C(2)-C(3)	107.5(3)
C(1)-C(2)-C(3)	114.5(3)
O(2)-C(2)-H(2A)	108.2
C(1)-C(2)-H(2A)	108.2
C(3)-C(2)-H(2A)	108.2
C(2)-O(2)-H(2)	104(4)
C(6)-C(3)-N(1)	108.3(3)
C(6)-C(3)-C(4)	113.2(3)
N(1)-C(3)-C(4)	106.3(3)
C(6)-C(3)-C(2)	111.2(3)
N(1)-C(3)-C(2)	107.3(3)
C(4)-C(3)-C(2)	110.2(3)
C(5)-O(3)-H(3)	103(5)
C(5)-C(4)-C(3)	119.3(3)
C(5)-C(4)-H(4A)	107.5
C(3)-C(4)-H(4A)	107.5
C(5)-C(4)-H(4B)	107.5
C(3)-C(4)-H(4B)	107.5
H(4A)-C(4)-H(4B)	107.0
O(3)-C(5)-C(4)	113.0(4)
O(3)-C(5)-H(5A)	109.0
C(4)-C(5)-H(5A)	109.0
O(3)-C(5)-H(5B)	109.0
C(4)-C(5)-H(5B)	109.0
H(5A)-C(5)-H(5B)	107.8
C(3)-C(6)-H(6A)	109.5
C(3)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
C(3)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
N(1)-C(7)-H(7A)	109.5
N(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
N(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5

Torsion angles [°].

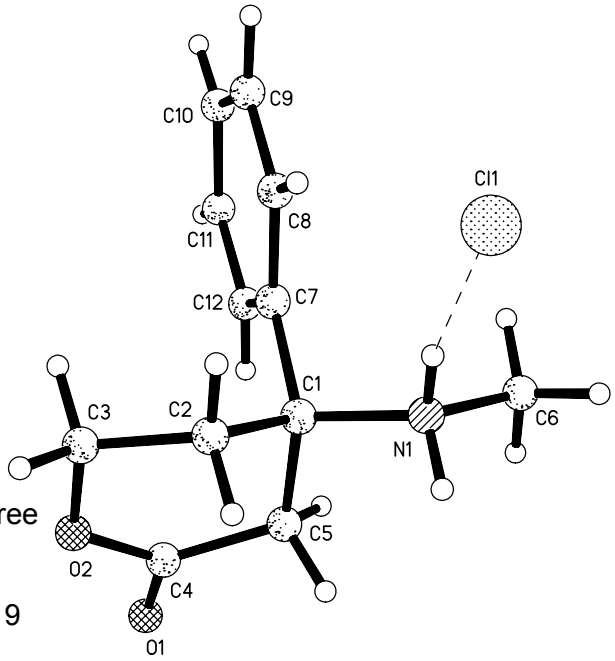
O(1)-C(1)-C(2)-O(2)	67.0(5)
O(1)-C(1)-C(2)-C(3)	-171.7(4)
C(7)-N(1)-C(3)-C(6)	69.8(4)
C(7)-N(1)-C(3)-C(4)	-168.3(3)
C(7)-N(1)-C(3)-C(2)	-50.3(4)
O(2)-C(2)-C(3)-C(6)	-172.7(3)
C(1)-C(2)-C(3)-C(6)	64.6(4)
O(2)-C(2)-C(3)-N(1)	-54.4(4)
C(1)-C(2)-C(3)-N(1)	-177.2(3)
O(2)-C(2)-C(3)-C(4)	60.9(4)
C(1)-C(2)-C(3)-C(4)	-61.8(4)
C(6)-C(3)-C(4)-C(5)	59.2(5)
N(1)-C(3)-C(4)-C(5)	-59.5(4)
C(2)-C(3)-C(4)-C(5)	-175.5(3)
C(3)-C(4)-C(5)-O(3)	-82.8(4)

12.1.8 Methyl-(2-oxo-4-phenyl-tetrahydro-pyran-4-yl)-ammonium; chloride (74•HCl).

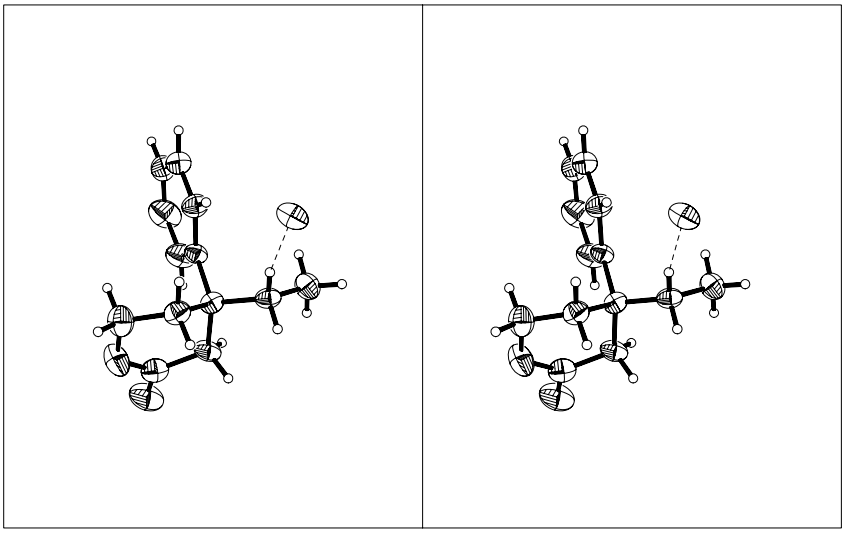
$C_{12}H_{16}ClNO_2$
Orthorhombic, Pbca
a = 9.9256(6) Å
b = 11.0569(6) Å
c = 22.383(2) Å
α = 90°
β = 90°
γ = 90°
V = 2456.4(3) Å^3
Z = 8, *R(F)* = 0.0530
$R_W(F^2)$ = 0.1436
Crystal size: 0.5 x 0.3 x 0.07 mm
Calculated density : 1.307 g/cm^3
Theta range for data collection: 3.95-67.95 degree
Unigue reflections: 2019
Observed reflections: 1509
No. of contributed reflections to refinement: 2019
No. of refined parameters: 146



74·HCl

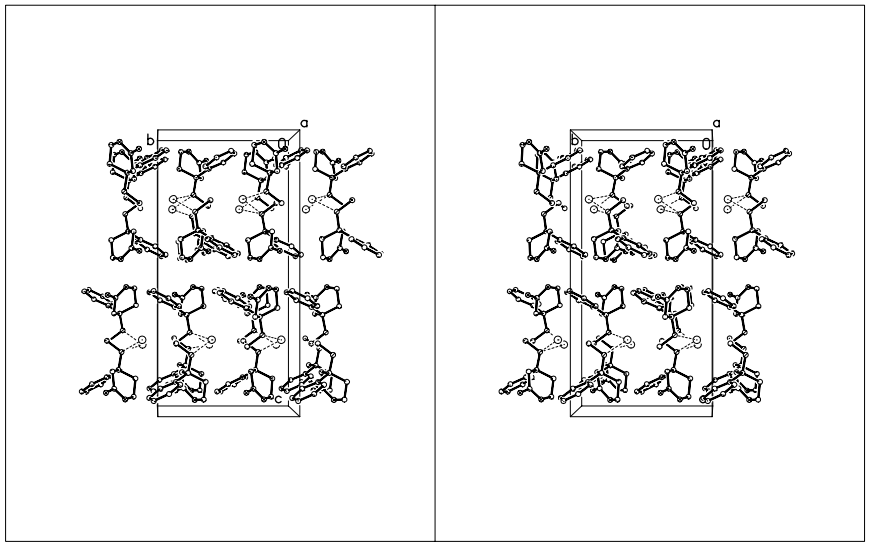


Stereoview of the structure with displacement parameters:

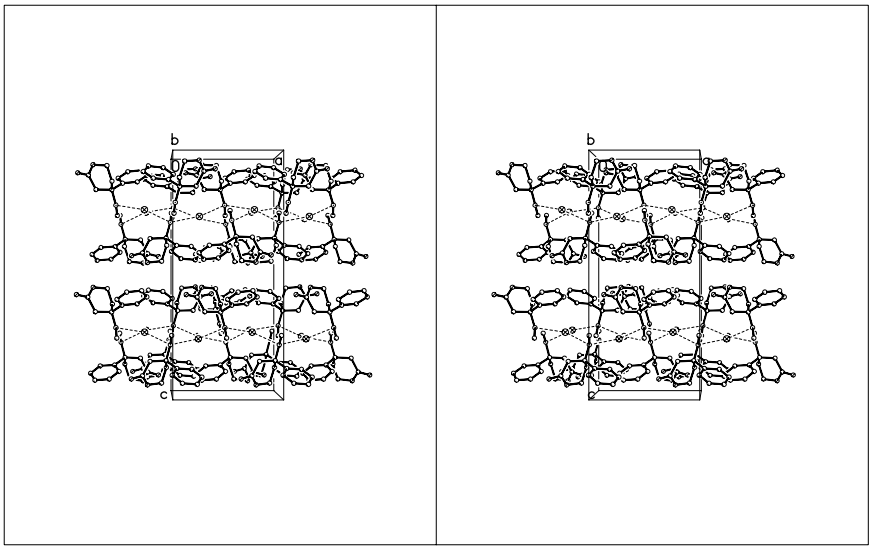


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

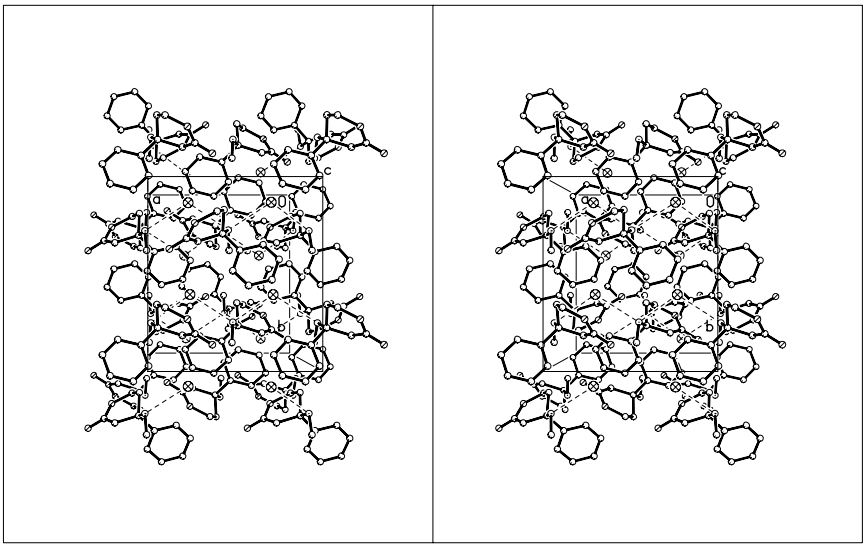
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

O(1)-C(4)	1.200(4)
C(1)-N(1)	1.518(3)
C(1)-C(5)	1.522(4)
C(1)-C(7)	1.524(3)
C(1)-C(2)	1.527(3)
N(1)-C(6)	1.490(3)
N(1)-H(1A)	0.9000
N(1)-H(1B)	0.9000
O(2)-C(4)	1.340(4)
O(2)-C(3)	1.450(4)
C(2)-C(3)	1.501(4)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(5)	1.509(4)
C(5)-H(5A)	0.9700
C(5)-H(5B	0.9700
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(7)-C(12)	1.390(4)
C(7)-C(8)	1.400(4)
C(8)-C(9)	1.382(4)
C(8)-H(8)	0.9300
C(9)-C(10)	1.380(5)
C(9)-H(9)	0.9300
C(10)-C(11)	1.365(5)
C(10)-H(10)	0.9300
C(11)-C(12)	1.393(4)
C(11)-H(11)	0.9300
C(12)-H(12)	0.9300

N(1)-C(1)-C(5)	107.6(2)
N(1)-C(1)-C(7)	110.00(19)
C(5)-C(1)-C(7)	114.6(2)
N(1)-C(1)-C(2)	105.84(18)
C(5)-C(1)-C(2)	106.2(2)
C(7)-C(1)-C(2)	112.1(2)
C(6)-N(1)-C(1)	116.63(19)
C(6)-N(1)-H(1A)	108.1
C(1)-N(1)-H(1A)	108.1
C(6)-N(1)-H(1B)	108.1
C(1)-N(1)-H(1B)	108.1
H(1A)-N(1)-H(1B)	107.3
C(4)-O(2)-C(3)	122.5(2)
C(3)-C(2)-C(1)	109.9(2)
C(3)-C(2)-H(2A)	109.7
C(1)-C(2)-H(2A)	109.7
C(3)-C(2)-H(2B)	109.7
C(1)-C(2)-H(2B)	109.7
H(2A)-C(2)-H(2B)	108.2
O(2)-C(3)-C(2)	113.5(2)
O(2)-C(3)-H(3A)	108.9
C(2)-C(3)-H(3A)	108.9
O(2)-C(3)-H(3B)	108.9
C(2)-C(3)-H(3B)	108.9
H(3A)-C(3)-H(3B)	107.7
O(1)-C(4)-O(2)	118.5(3)
O(1)-C(4)-C(5)	122.0(3)
O(2)-C(4)-C(5)	119.4(3)
C(4)-C(5)-C(1)	115.2(2)
C(4)-C(5)-H(5A)	108.5
C(1)-C(5)-H(5A)	108.5
C(4)-C(5)-H(5B)	108.5
C(1)-C(5)-H(5B)	108.5
H(5A)-C(5)-H(5B)	107.5
N(1)-C(6)-H(6A)	109.5
N(1)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
N(1)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(12)-C(7)-C(8)	118.0(3)
C(12)-C(7)-C(1)	121.7(3)
C(8)-C(7)-C(1)	120.1(2)
C(9)-C(8)-C(7)	120.7(3)
C(9)-C(8)-H(8)	119.6
C(7)-C(8)-H(8)	119.6
C(10)-C(9)-C(8)	120.2(3)
C(10)-C(9)-H(9)	119.9
C(8)-C(9)-H(9)	119.9
C(11)-C(10)-C(9)	120.1(3)
C(11)-C(10)-H(10)	120.0
C(9)-C(10)-H(10)	120.0
C(10)-C(11)-C(12)	120.3(3)
C(10)-C(11)-H(11)	119.9
C(12)-C(11)-H(11)	119.9
C(7)-C(12)-C(11)	120.7(3)
C(7)-C(12)-H(12)	119.7
C(11)-C(12)-H(12)	119.7

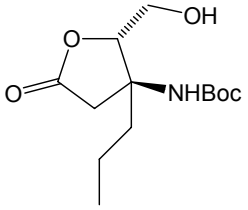
Torsion angles [°].

C(5)-C(1)-N(1)-C(6)	69.4(3)
C(7)-C(1)-N(1)-C(6)	-56.1(3)
C(2)-C(1)-N(1)-C(6)	-177.4(2)
N(1)-C(1)-C(2)-C(3)	-176.4(2)
C(5)-C(1)-C(2)-C(3)	-62.2(3)
C(7)-C(1)-C(2)-C(3)	63.6(3)
C(4)-O(2)-C(3)-C(2)	-27.0(4)
C(1)-C(2)-C(3)-O(2)	52.5(3)
C(3)-O(2)-C(4)-O(1)	-172.2(3)
C(3)-O(2)-C(4)-C(5)	12.6(4)
O(1)-C(4)-C(5)-C(1)	160.3(3)
O(2)-C(4)-C(5)-C(1)	-24.7(4)
N(1)-C(1)-C(5)-C(4)	161.4(2)
C(7)-C(1)-C(5)-C(4)	-75.9(3)
C(2)-C(1)-C(5)-C(4)	48.4(3)
N(1)-C(1)-C(7)-C(12)	121.9(3)
C(5)-C(1)-C(7)-C(12)	0.4(3)
C(2)-C(1)-C(7)-C(12)	-120.7(3)
N(1)-C(1)-C(7)-C(8)	-62.1(3)
C(5)-C(1)-C(7)-C(8)	176.5(2)
C(2)-C(1)-C(7)-C(8)	55.4(3)
C(12)-C(7)-C(8)-C(9)	-0.4(4)

C(1)-C(7)-C(8)-C(9)	-176.5(2)	C(1)-C(7)-C(12)-C(11)	176.0(3)
C(7)-C(8)-C(9)-C(10)	1.7(4)	C(10)-C(11)-C(12)-C(7)	-0.8(5)
C(8)-C(9)-C(10)-C(11)	-2.5(5)		
C(9)-C(10)-C(11)-C(12)	2.1(5)		
C(8)-C(7)-C(12)-C(11)	-0.1(4)		

12.1.9 ((2*S*,3*S*)-2-Hydroxymethyl-5-oxo-3-propyl-tetrahydro-furan-3-yl)-carbamic acid *tert*-butyl ester (79).

$C_{13}H_{23}NO_5$
Orthorhombic,
P2(1)2(1)2(1)
a = 11.198(2) Å
b = 16.442(4) Å
c = 17.551(4) Å
α = 90°
β = 90°
γ = 90°
V = 3231.5(12) Å^3
Z = 8, *R(F)* = 0.0758
$R_W(F^2)$ = 0.1390
Crystal size: 0.9 x 0.5 x 0.3 mm
Calculated density : 1.124 g/cm^3
Theta range for data collection: 1.70-27.50 degree
Unigue reflections: 4138
Observed reflections: 2358
No. of contributed reflections to refinement: 4138
No. of refined parameters: 369



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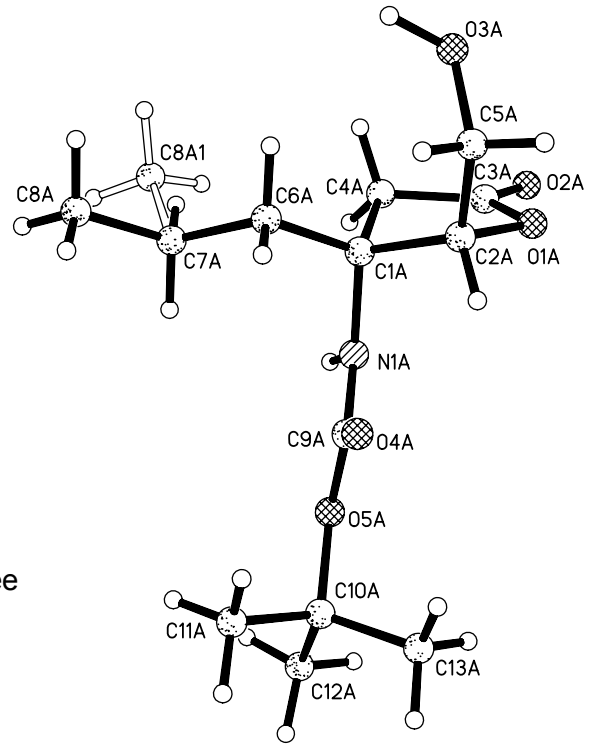
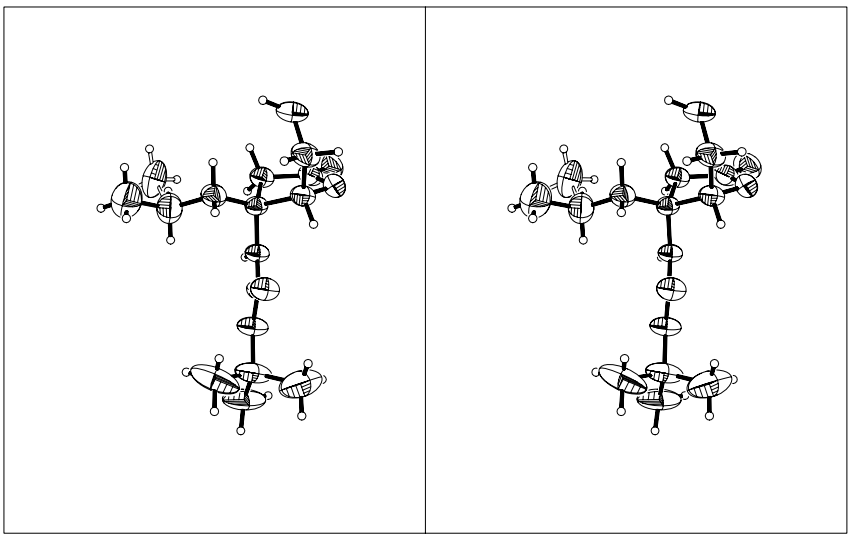
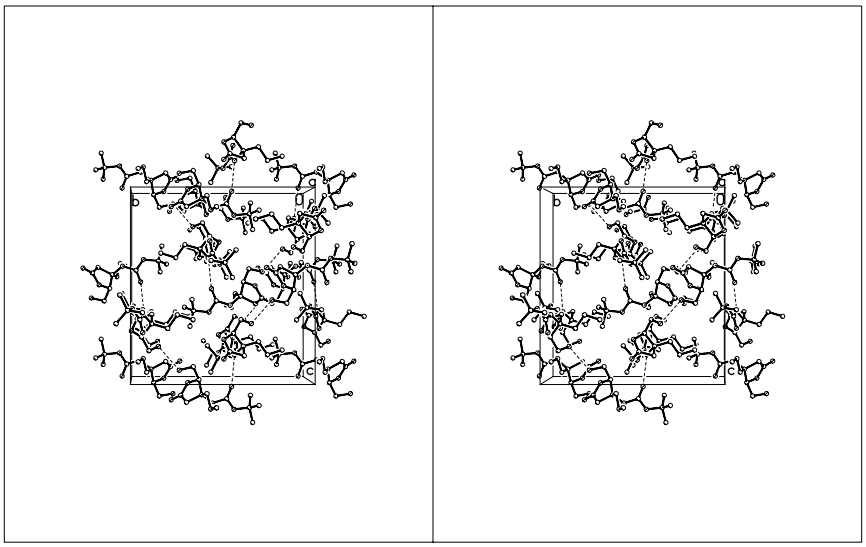


Stereoview of the structure with displacement parameters:

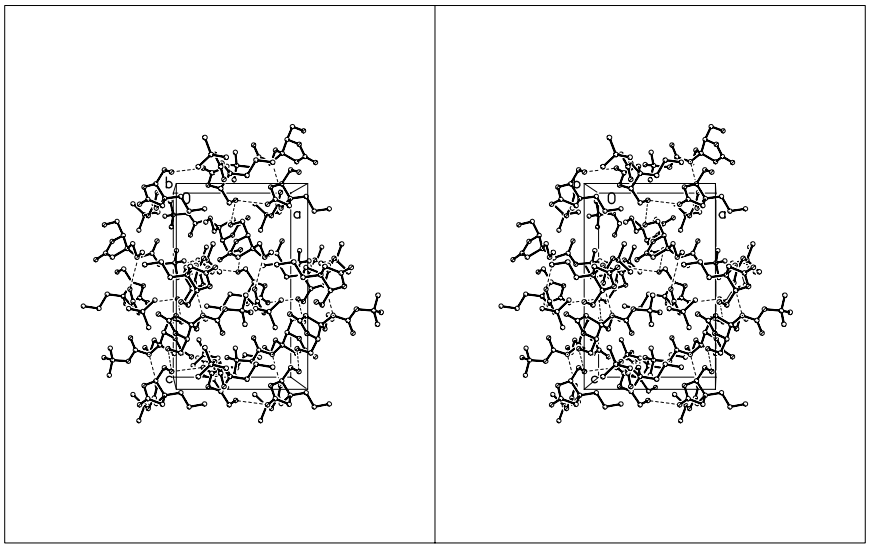


Elemente cells : (a) view to bc plane, (b) view to ac plane, (c) view to ab plane:

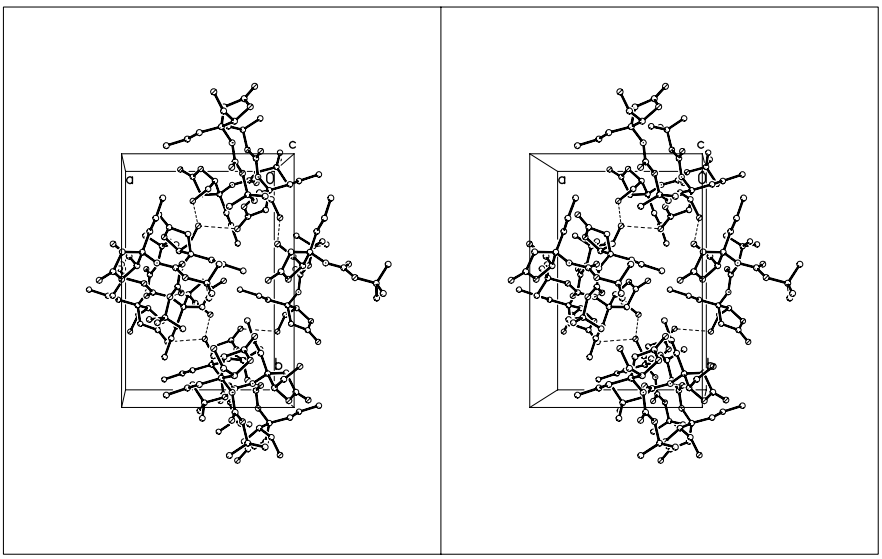
(a)



(b)



(c)



Bond lengths [Å] and angles [°].

N(1A)-C(9A)	1.357(6)
N(1A)-C(1A)	1.481(5)
N(1A)-H(1A)	0.97(4)
O(1A)-C(3A)	1.333(6)
O(1A)-C(2A)	1.467(6)
C(1A)-C(6A)	1.517(7)
C(1A)-C(4A)	1.542(6)
C(1A)-C(2A)	1.544(6)
C(2A)-C(5A)	1.519(7)
C(2A)-H(2A)	0.9800
O(2A)-C(3A)	1.214(6)
O(3A)-C(5A)	1.430(7)
O(3A)-H(3A)	0.95(7)
C(3A)-C(4A)	1.484(7)
O(4A)-C(9A)	1.210(5)
C(4A)-H(4A1)	0.9700
C(4A)-H(4A2)	0.9700
O(5A)-C(9A)	1.334(5)
O(5A)-C(10A)	1.470(6)
C(5A)-H(5A1)	0.9700
C(5A)-H(5A2)	0.9700
C(6A)-C(7A)	1.529(8)
C(6A)-H(6A1)	0.9700
C(6A)-H(6A2)	0.9700
C(7A)-C(8A)	1.487(8)
C(7A)-C(8A1)	1.544(10)
C(7A)-H(7A1)	0.9700
C(7A)-H(7A2)	0.9700
C(8A)-H(8A1)	0.9600
C(8A)-H(8A2)	0.9600
C(8A)-H(8A3)	0.9600
C(8A1)-H(8A4)	0.9600
C(8A1)-H(8A5)	0.9600
C(8A1)-H(8A6)	0.9600
C(10A)-C(11A)	1.481(11)
C(10A)-C(13A)	1.505(10)
C(10A)-C(12A)	1.530(9)
C(11A)-H(11A)	0.9600
C(11A)-H(11B)	0.9600
C(11A)-H(11C)	0.9600
C(12A)-H(12A)	0.9600
C(12A)-H(12B)	0.9600
C(12A)-H(12C)	0.9600
C(13A)-H(13A)	0.9600
C(13A)-H(13B)	0.9600
C(13A)-H(13C)	0.9600
N(1B)-C(9B)	1.345(6)
N(1B)-C(1B)	1.465(6)
N(1B)-H(1B)	0.93(4)
O(1B)-C(3B)	1.323(8)
O(1B)-C(2B)	1.455(6)
C(1B)-C(2B)	1.535(7)
C(1B)-C(4B)	1.538(7)
C(1B)-C(6B)	1.539(7)
C(2B)-C(5B)	1.500(7)
C(2B)-H(2B)	0.9800
O(2B)-C(3B)	1.210(7)
O(3B)-C(5B)	1.418(7)
O(3B)-H(3B)	0.81(5)
C(3B)-C(4B)	1.496(10)
O(4B)-C(9B)	1.214(5)
C(4B)-H(4B1)	0.9700
C(4B)-H(4B2)	0.9700
O(5B)-C(9B)	1.333(5)
O(5B)-C(10B)	1.484(6)
C(5B)-H(5B1)	0.9700
C(5B)-H(5B2)	0.9700
C(6B)-C(7B)	1.515(9)
C(6B)-H(6B1)	0.9700
C(6B)-H(6B2)	0.9700
C(7B)-C(8B)	1.487(11)
C(7B)-H(7B1)	0.9700
C(7B)-H(7B2)	0.9700
C(8B)-H(8B1)	0.9600
C(8B)-H(8B2)	0.9600
C(8B)-H(8B3)	0.9600
C(10B)-C(13B)	1.494(8)
C(10B)-C(12B)	1.508(7)
C(10B)-C(11B)	1.510(9)
C(11B)-H(11D)	0.9600
C(11B)-H(11E)	0.9600
C(11B)-H(11F)	0.9600
C(12B)-H(12D)	0.9600
C(12B)-H(12E)	0.9600
C(12B)-H(12F)	0.9600
C(13B)-H(13D)	0.9600
C(13B)-H(13E)	0.9600
C(13B)-H(13F)	0.9600
C(9A)-N(1A)-C(1A)	122.7(4)
C(9A)-N(1A)-H(1A)	118(2)
C(1A)-N(1A)-H(1A)	115(2)
C(3A)-O(1A)-C(2A)	109.9(4)
N(1A)-C(1A)-C(6A)	111.9(4)
N(1A)-C(1A)-C(4A)	106.1(4)
C(6A)-C(1A)-C(4A)	115.3(4)
N(1A)-C(1A)-C(2A)	107.6(4)
C(6A)-C(1A)-C(2A)	114.7(4)
C(4A)-C(1A)-C(2A)	100.2(4)
O(1A)-C(2A)-C(5A)	108.1(4)
O(1A)-C(2A)-C(1A)	105.5(4)
C(5A)-C(2A)-C(1A)	117.5(4)
O(1A)-C(2A)-H(2A)	108.5
C(5A)-C(2A)-H(2A)	108.5
C(1A)-C(2A)-H(2A)	108.5
C(5A)-O(3A)-H(3A)	108(4)
O(2A)-C(3A)-O(1A)	121.0(6)
O(2A)-C(3A)-C(4A)	127.9(6)
O(1A)-C(3A)-C(4A)	111.2(5)
C(3A)-C(4A)-C(1A)	104.2(4)
C(3A)-C(4A)-H(4A1)	110.9
C(1A)-C(4A)-H(4A1)	110.9
C(3A)-C(4A)-H(4A2)	110.9
C(1A)-C(4A)-H(4A2)	110.9
H(4A1)-C(4A)-H(4A2)	108.9
C(9A)-O(5A)-C(10A)	121.4(4)
O(3A)-C(5A)-C(2A)	112.2(4)

O(3A)-C(5A)-H(5A1)	109.2	C(9B)-N(1B)-C(1B)	123.9(4)
C(2A)-C(5A)-H(5A1)	109.2	C(9B)-N(1B)-H(1B)	121(3)
O(3A)-C(5A)-H(5A2)	109.2	C(1B)-N(1B)-H(1B)	115(3)
C(2A)-C(5A)-H(5A2)	109.2	C(3B)-O(1B)-C(2B)	110.7(5)
H(5A1)-C(5A)-H(5A2)	107.9	N(1B)-C(1B)-C(2B)	107.7(4)
C(1A)-C(6A)-C(7A)	114.2(5)	N(1B)-C(1B)-C(4B)	106.8(4)
C(1A)-C(6A)-H(6A1)	108.7	C(2B)-C(1B)-C(4B)	100.7(5)
C(7A)-C(6A)-H(6A1)	108.7	N(1B)-C(1B)-C(6B)	112.3(5)
C(1A)-C(6A)-H(6A2)	108.7	C(2B)-C(1B)-C(6B)	114.6(4)
C(7A)-C(6A)-H(6A2)	108.7	C(4B)-C(1B)-C(6B)	114.0(5)
H(6A1)-C(6A)-H(6A2)	107.6	O(1B)-C(2B)-C(5B)	108.2(5)
C(8A)-C(7A)-C(6A)	112.8(8)	O(1B)-C(2B)-C(1B)	105.1(4)
C(8A)-C(7A)-C(8A1)	93.7(11)	C(5B)-C(2B)-C(1B)	117.9(5)
C(6A)-C(7A)-C(8A1)	118.6(10)	O(1B)-C(2B)-H(2B)	108.4
C(8A)-C(7A)-H(7A1)	109.0	C(5B)-C(2B)-H(2B)	108.4
C(6A)-C(7A)-H(7A1)	109.0	C(1B)-C(2B)-H(2B)	108.4
C(8A1)-C(7A)-H(7A1)	15.5	C(5B)-O(3B)-H(3B)	105(4)
C(8A)-C(7A)-H(7A2)	109.0	O(2B)-C(3B)-O(1B)	121.5(9)
C(6A)-C(7A)-H(7A2)	109.0	O(2B)-C(3B)-C(4B)	127.8(8)
C(8A1)-C(7A)-H(7A2)	112.7	O(1B)-C(3B)-C(4B)	110.7(6)
H(7A1)-C(7A)-H(7A2)	107.8	C(3B)-C(4B)-C(1B)	103.7(5)
C(7A)-C(8A)-H(8A1)	109.5	C(3B)-C(4B)-H(4B1)	111.0
C(7A)-C(8A)-H(8A2)	109.5	C(1B)-C(4B)-H(4B1)	111.0
H(8A1)-C(8A)-H(8A2)	109.5	C(3B)-C(4B)-H(4B2)	111.0
C(7A)-C(8A)-H(8A3)	109.5	C(1B)-C(4B)-H(4B2)	111.0
H(8A1)-C(8A)-H(8A3)	109.5	H(4B1)-C(4B)-H(4B2)	109.0
H(8A2)-C(8A)-H(8A3)	109.5	C(9B)-O(5B)-C(10B)	121.3(4)
C(7A)-C(8A1)-H(8A4)	109.5	O(3B)-C(5B)-C(2B)	110.7(5)
C(7A)-C(8A1)-H(8A5)	109.5	O(3B)-C(5B)-H(5B1)	109.5
H(8A4)-C(8A1)-H(8A5)	109.5	C(2B)-C(5B)-H(5B1)	109.5
C(7A)-C(8A1)-H(8A6)	109.5	O(3B)-C(5B)-H(5B2)	109.5
H(8A4)-C(8A1)-H(8A6)	109.5	C(2B)-C(5B)-H(5B2)	109.5
H(8A5)-C(8A1)-H(8A6)	109.5	H(5B1)-C(5B)-H(5B2)	108.1
O(4A)-C(9A)-O(5A)	126.4(4)	C(7B)-C(6B)-C(1B)	112.5(5)
O(4A)-C(9A)-N(1A)	124.8(4)	C(7B)-C(6B)-H(6B1)	109.1
O(5A)-C(9A)-N(1A)	108.8(4)	C(1B)-C(6B)-H(6B1)	109.1
O(5A)-C(10A)-C(11A)	110.0(7)	C(7B)-C(6B)-H(6B2)	109.1
O(5A)-C(10A)-C(13A)	109.2(6)	C(1B)-C(6B)-H(6B2)	109.1
C(11A)-C(10A)-C(13A)	113.8(7)	H(6B1)-C(6B)-H(6B2)	107.8
O(5A)-C(10A)-C(12A)	101.5(5)	C(8B)-C(7B)-C(6B)	112.1(8)
C(11A)-C(10A)-C(12A)	110.9(7)	C(8B)-C(7B)-H(7B1)	109.2
C(13A)-C(10A)-C(12A)	110.8(7)	C(6B)-C(7B)-H(7B1)	109.2
C(10A)-C(11A)-H(11A)	109.5	C(8B)-C(7B)-H(7B2)	109.2
C(10A)-C(11A)-H(11B)	109.5	C(6B)-C(7B)-H(7B2)	109.2
H(11A)-C(11A)-H(11B)	109.5	H(7B1)-C(7B)-H(7B2)	107.9
C(10A)-C(11A)-H(11C)	109.5	C(7B)-C(8B)-H(8B1)	109.5
H(11A)-C(11A)-H(11C)	109.5	C(7B)-C(8B)-H(8B2)	109.5
H(11B)-C(11A)-H(11C)	109.5	H(8B1)-C(8B)-H(8B2)	109.5
C(10A)-C(12A)-H(12A)	109.5	C(7B)-C(8B)-H(8B3)	109.5
C(10A)-C(12A)-H(12B)	109.5	H(8B1)-C(8B)-H(8B3)	109.5
H(12A)-C(12A)-H(12B)	109.5	H(8B2)-C(8B)-H(8B3)	109.5
C(10A)-C(12A)-H(12C)	109.5	O(4B)-C(9B)-O(5B)	126.2(5)
H(12A)-C(12A)-H(12C)	109.5	O(4B)-C(9B)-N(1B)	124.8(5)
H(12B)-C(12A)-H(12C)	109.5	O(5B)-C(9B)-N(1B)	109.1(4)
C(10A)-C(13A)-H(13A)	109.5	O(5B)-C(10B)-C(13B)	110.2(5)
C(10A)-C(13A)-H(13B)	109.5	O(5B)-C(10B)-C(12B)	102.1(5)
H(13A)-C(13A)-H(13B)	109.5	C(13B)-C(10B)-C(12B)	110.9(5)
C(10A)-C(13A)-H(13C)	109.5	O(5B)-C(10B)-C(11B)	108.1(5)
H(13A)-C(13A)-H(13C)	109.5	C(13B)-C(10B)-C(11B)	113.9(6)
H(13B)-C(13A)-H(13C)	109.5	C(12B)-C(10B)-C(11B)	110.9(6)

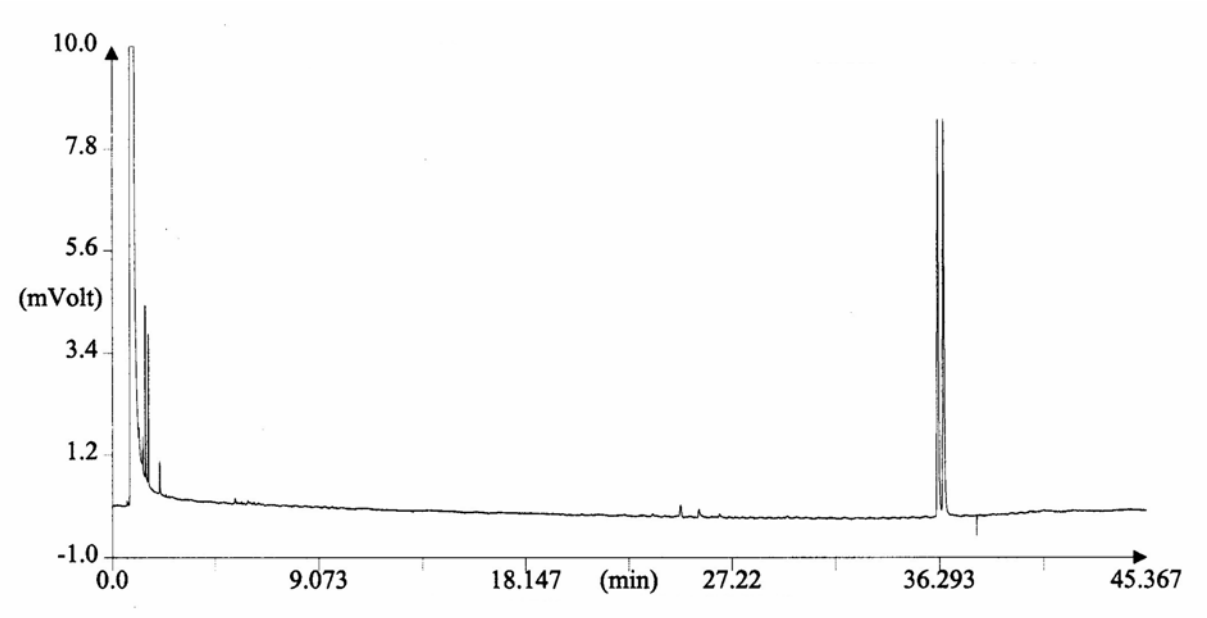
C(10B)-C(11B)-H(11D)	109.5
C(10B)-C(11B)-H(11E)	109.5
H(11D)-C(11B)-H(11E)	109.5
C(10B)-C(11B)-H(11F)	109.5
H(11D)-C(11B)-H(11F)	109.5
H(11E)-C(11B)-H(11F)	109.5
C(10B)-C(12B)-H(12D)	109.5
C(10B)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
C(10B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(10B)-C(13B)-H(13D)	109.5
C(10B)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13E)	109.5
C(10B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5

Torsion angles [°].

C(9A)-N(1A)-C(1A)-C(6A)	-61.3(6)
C(9A)-N(1A)-C(1A)-C(4A)	172.2(5)
C(9A)-N(1A)-C(1A)-C(2A)	65.6(6)
C(3A)-O(1A)-C(2A)-C(5A)	-107.0(4)
C(3A)-O(1A)-C(2A)-C(1A)	19.5(5)
N(1A)-C(1A)-C(2A)-O(1A)	82.1(4)
C(6A)-C(1A)-C(2A)-O(1A)	-152.7(4)
C(4A)-C(1A)-C(2A)-O(1A)	-28.6(4)
N(1A)-C(1A)-C(2A)-C(5A)	-157.4(4)
C(6A)-C(1A)-C(2A)-C(5A)	-32.1(6)
C(4A)-C(1A)-C(2A)-C(5A)	91.9(5)
C(2A)-O(1A)-C(3A)-O(2A)	179.3(5)
C(2A)-O(1A)-C(3A)-C(4A)	-0.8(5)
O(2A)-C(3A)-C(4A)-C(1A)	161.7(5)
O(1A)-C(3A)-C(4A)-C(1A)	-18.2(5)
N(1A)-C(1A)-C(4A)-C(3A)	-84.2(4)
C(6A)-C(1A)-C(4A)-C(3A)	151.4(4)
C(2A)-C(1A)-C(4A)-C(3A)	27.7(4)
O(1A)-C(2A)-C(5A)-O(3A)	60.2(6)
C(1A)-C(2A)-C(5A)-O(3A)	-59.0(7)
N(1A)-C(1A)-C(6A)-C(7A)	-53.3(6)
C(4A)-C(1A)-C(6A)-C(7A)	68.1(6)
C(2A)-C(1A)-C(6A)-C(7A)	-176.3(5)
C(1A)-C(6A)-C(7A)-C(8A)	177.8(7)
C(1A)-C(6A)-C(7A)-C(8A1)	-74.3(13)
C(10A)-O(5A)-C(9A)-O(4A)	0.3(9)
C(10A)-O(5A)-C(9A)-N(1A)	178.6(6)
C(1A)-N(1A)-C(9A)-O(4A)	-10.1(8)
C(1A)-N(1A)-C(9A)-O(5A)	171.6(4)
C(9A)-O(5A)-C(10A)-C(11A)	60.7(8)
C(9A)-O(5A)-C(10A)-C(13A)	-64.8(8)
C(9A)-O(5A)-C(10A)-C(12A)	178.1(6)
C(9B)-N(1B)-C(1B)-C(2B)	66.2(7)
C(9B)-N(1B)-C(1B)-C(4B)	173.6(5)
C(9B)-N(1B)-C(1B)-C(6B)	-60.9(7)
C(3B)-O(1B)-C(2B)-C(5B)	-105.6(5)
C(3B)-O(1B)-C(2B)-C(1B)	21.2(5)
N(1B)-C(1B)-C(2B)-O(1B)	82.4(5)
C(4B)-C(1B)-C(2B)-O(1B)	-29.2(5)
C(6B)-C(1B)-C(2B)-O(1B)	-151.9(4)
N(1B)-C(1B)-C(2B)-C(5B)	-157.0(5)
C(4B)-C(1B)-C(2B)-C(5B)	91.4(5)
C(6B)-C(1B)-C(2B)-C(5B)	-31.4(7)
C(2B)-O(1B)-C(3B)-O(2B)	178.5(5)
C(2B)-O(1B)-C(3B)-C(4B)	-2.9(6)
O(2B)-C(3B)-C(4B)-C(1B)	162.0(6)
O(1B)-C(3B)-C(4B)-C(1B)	-16.4(6)
N(1B)-C(1B)-C(4B)-C(3B)	-85.2(5)
C(2B)-C(1B)-C(4B)-C(3B)	27.1(5)
C(6B)-C(1B)-C(4B)-C(3B)	150.3(5)
O(1B)-C(2B)-C(5B)-O(3B)	66.1(6)
C(1B)-C(2B)-C(5B)-O(3B)	-52.8(7)
N(1B)-C(1B)-C(6B)-C(7B)	-55.2(7)
C(2B)-C(1B)-C(6B)-C(7B)	-178.5(6)
C(4B)-C(1B)-C(6B)-C(7B)	66.3(7)
C(1B)-C(6B)-C(7B)-C(8B)	-179.3(8)
C(10B)-O(5B)-C(9B)-O(4B)	6.2(9)
C(10B)-O(5B)-C(9B)-N(1B)	-174.9(5)
C(1B)-N(1B)-C(9B)-O(4B)	-1.3(9)
C(1B)-N(1B)-C(9B)-O(5B)	179.8(5)
C(9B)-O(5B)-C(10B)-C(13B)	-64.1(7)
C(9B)-O(5B)-C(10B)-C(12B)	178.1(5)
C(9B)-O(5B)-C(10B)-C(11B)	61.0(7)

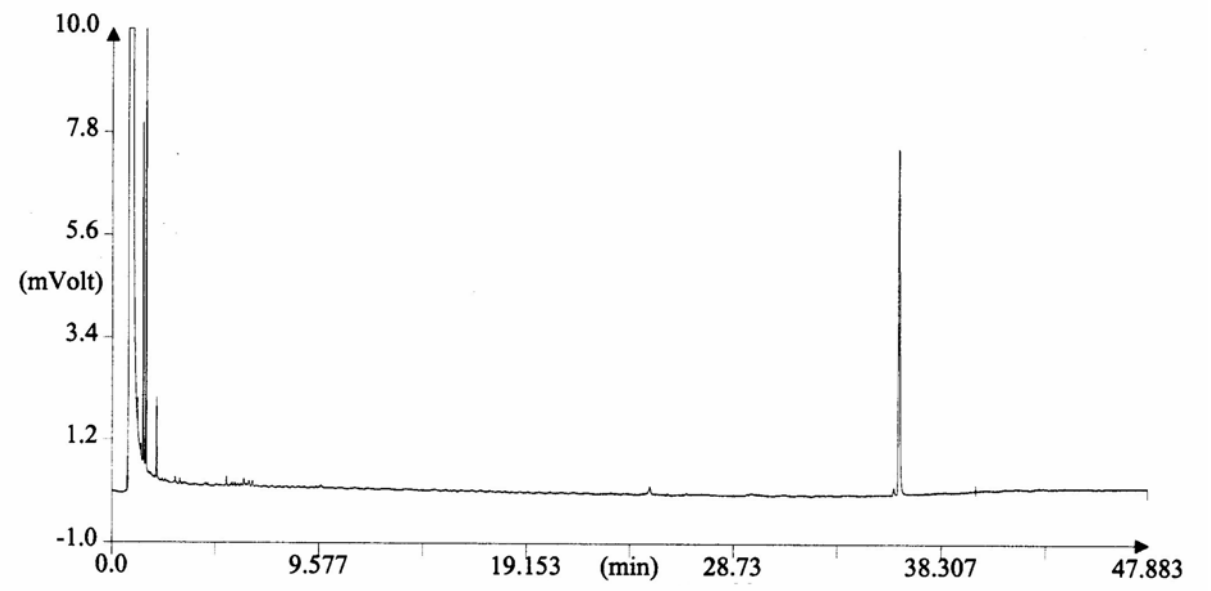
12.2 Crystal Structure Data and Selected NMR Specta

12.2.1 GC diagram of the racemic mixture of the isoxazoline 9



Peak Number (#)	Retention Time (min)	Area (.1*uV*sec)	Area % (%)	Peak Type	Width at (sec)
1	1.453	41760	4.849	Fused	1.1
2	1.587	42753	4.965	Fused	1.3
3	2.093	12472	1.448	Resolved	1.7
4	24.960	8308	0.965	Resolved	3.6
5	36.227	377100	43.789	Fused	4.1
6	36.473	378784	43.984	Fused	4.1
		861176			

12.2.2 GC diagram of the isoxazoline mixture 9, with e.r. 98:2



Peak Number (#)	Retention Time (min)	Area (.1*uV*sec)	Area % (%)	Peak Type	Width at (sec)
1	0.720	6519	1.105	Resolved	1.0
2	1.447	78516	13.308	Fused	1.1
3	1.580	132690	22.490	Fused	1.3
4	2.067	29916	5.071	Resolved	1.6
5	24.887	5303	0.899	Resolved	3.9
6	36.138	6479	1.098	Manual integ.	4.1
7	36.367	330562	56.029	Manual integ.	4.1
		589985			

13 References

1) Henneböhle, M. *Dissertation*, Universität Stuttgart, **2002**.

2) LeRoy, P.-Y. *Dissertation*, Universität Stuttgart, **1997**.

3) Blatt, A. H.; Gross, N. *J. Am. Chem. Soc.* **1955**, *77*, 5424-5425.

4) Dauzonne, D.; Demerseman, P.; Royer, R.; *J. Heterocycl. Chem.* **1982**,*19*, 693-694.

5) Jacquier, R.; *Bull. Soc. Chim.* **1974**, 1651-1655.

6) Isager, P.; Thomsen, I.; Torssell, K. B. G.; *Acta Chem. Scand.* **1990**, *44*, 806-813.

7) Kwiatkowski, S. *J. Chem. Soc. Chem. Commun.* **1987**, *19*, 1496-1498.

8) Shatzmiller, S.; Shalom, E.; Lidor, R.; Tartkovski, E.; *Liebigs Ann. Chem.* **1983**, *6*, 906-912.

9) Fray, M. J.; Thomas, E. J.; *Tetrahedron* **1984**, *40*(4), 673-680.

10) Henneböhle, M.; Le Roy P.-Y. ; Hein, M. ; Ehrler, R. ; Jäger, V. *Z. Naturforsch.* **2004**, *59b*, 451-467.

11) Cerri, A.; De Micheli, C.; Gandolfi, R. *Synthesis* **1974**, 710-712.

12) Jäger, V.; Buß, V. *Liebigs. Ann. Chem.* **1980**, 101-121.

13) Uno, H.; Terakawa, T.; Suzuki, H. *Chem. Lett.* **1989**, *6*, 1079-1082.

14) Ojima, I.; Lin, S.N.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927.

15) Bates, R.B.; Brusoe, K.G. Burns, J.J.; Caldera, S.; Cui, W.; Gangwar S.; Gramme, M.R.; McClure, K.J.; Rouen, G.P.; Shadow, H.; Stessman, C.C.; Taylor, S.R.; Vu, V.H.; Yarick, G.V. Zhang, J.X.; Pettit, G.R.; Bontems, R. *J. Am. Chem. Soc.* **1997**, *119*, 2111.

16) (*R*)-dopa in mushrooms; see: von Nussbaum, F.; Spiteller, P.; Ruth, M. Steglich, W.; Wanner, G.; Gamblin, B.; Stievano, L.; Wagner, F.E. *Angew. Chem. Int. Ed.*, **1998**, *37*, 3292.

17) (a) Seebach, D.; Gademann, K.; Ernst, M.; Hoyer, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 1223.
(b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

18) (a) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim.Acta* **1994**, *27*, 3.
(b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *23*, 117.
(d) Juaristi, E., *Enantioselective Synthesis of α-Amino Acids*; Wiley: New York, 1997.
(e) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983-1004.

19) Takashiro, E.; Hayakawa, L.; Nitta, T.; Kasuya, A.; Miyamoto, S.; Ozawa, Y.; Yagi, R.; Yamamoto, I., Shibayama, T.; Nakagawa, A.; Yabe, Y. *Bioorg. & Med. Chem.* **1999**, *7*, 2063-2072.

20) Tymiak, A. A.; McCormick, T. J.; Unger, S. E. *J. Org. Chem.* **1989**, *54*, 1149-1157.

21) a) Eggen, M.; Nair, S. K.; Georg, G. I. *Org. Lett.* **2001**, *12*, 1813-1815. , b) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206.

22) a) Jäger, V.; Grund, H. *Liebigs Ann. Chem.* **1980**, 80-100.
b) Jäger, V.; Buß, V.; Schwab, W. *Liebigs Ann. Chem.* **1980**, 122-139.

23) For reviews on the synthetic versatility of the nitrile oxide cycloaddition, see (a) Desmoni, G.; Tacconi, G.; Baro, A.; Pollini, G. P. *Natural Product Synthesis Through Pericyclic Reaction* ; ACS Monograph: Washington, U. S. A., 1983; pp 91-108. (b) Kozikowski , A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (c) Curran, D. P. *In Advances in Cycloaddition*; Curran, D. P. Ed.; JAI Press Inc.: London, U. K., 198 8; vol 1, pp 129-189.

24) Jäger, V.; Colinas P. A. Nitrile Oxides : Synthetic applications of 1,3-dipolar cycloaddition chemistry towards heterocyclic and natural products. Edited by A. Padwa and W. H. Person. Chapter 6, 2002, p. 363-365.

25) Chiarino, D.; Napoletano, M.; and Sala. A. *Synth. Commun.* **1998**, *18*, 1171.

26) Hallig, K.; Torssel, K. B. G; Hazell, R. G. *Acta. Chem. Scand.* **1991**, *45*, 736.

27) Tsuge, O.; Kanemasa, S; Suga, H. *Chem. Lett.* **1986**, 183.

28) Jäger, V. and co-workers, observations over ~ 29 years.

29) Grünanger, P.; Vita-Finzi P. in: *Isoxazoles*, in: the Chemistry of Heterocyclic Compounds, Vol. 49, Pt. 1, Taylor, E. C.; Weissberger, A., Wiley, Toronto, **1991**, S. 417-647.

30) Jäger, V. *Synthesen mit Isoxazolinen - Neue Wege zum Aufbau funktionalisierter Kohlenstoffgerüste*, Habilitationsschrift, Gießen, **1979**.

31) Quilico, A.; Weissberger, A. *The Chemistry of Heterocyclyc Compounds*, Five- and Six-membered Compounds with Nitrogen and Oxygen, Interscience Publishers, New York, **1962**, S. 1-151.

32) Kozikowski, A. P.; Chen, Y.-Y.; Wang, B. C.; Xu, Z.-B. *Tetrahedron* **1984**, *40*, 2345-2358.

33) Belly, A.; Petrus, C.; Petrus, F. *Bull. Soc. Chim. Fr.* **1973**, 1390-1395.

34) Olivé, J. L.; Jacquier, R.; Pétrus, C.; Pétrus, F. *Bull. Soc. Chim. Fr.* **1974**, 1651-1655.

35) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916-3918.

36) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258-3290.

37) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Letters* **1993**, *11*, 1847-50.

38) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366-372.

39) Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, *116*; 6513-6520.

40) Yin, H.; Franck, R. W.; Chen, S.-L.; Quigley, G. J.; Todardo, L. *J. Org. Chem.* **1992**, *57*, 644-651.

41) Ehrler, R. *Dissertation*, Universität Würzburg, **1985**.

42) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Philips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L., Vianco, C. S. *J. Org. Chem.* **1991**, *56* (12), 4056-4058.

43) a) Häfele, B. *Dissertation*, Universität Würzburg, **1987**.
b) Häfele, B. *Diplomarbeit*, Universität Würzburg, **1983**.

44) Zimmermann, P. J. *Dissertation*, Universität Stuttgart, **2000**.

45) Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 5. Auflage, Thieme Verlag, Stuttgart, **1995**.

46) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3. Auflage, Weinheim; New York: VCH, **1987**.

47) Müller, R. *Dissertation*, Universität Würzburg, **1992**.

48) Leibold, T. *Dissertation*, Universität Stuttgart, **1995**.

49) Lee, J- Y., *Dissertation*, Universität Stuttgart, **2004**.

50) White, J. D.; Avery, M. A.; Carter, J. P. *J. Am. Chem. Soc.*, **1982**, *104*, 5486-5489.

51) a) Rathke, M. W. *J. Am. Chem. Soc.*, **1970**, 3222-3223.
b) Courtois, G., Miginiac, L. *J. Organomet. Chem.*, **1993,** *452*, 5-12.
c) Pini, D.; Mastantuono, A.; Salvadori, P. *Tetrahedron asymmetry*, **1994**, *5*,1875-1876.

52) Castro, J. F.; Vila, M. M.; Jenkins, P.R.; Sharma, M.L.; Tustin, G.; Fawcett, J.; Russell, D.R. *Synlett* **1999**, *6*, 798-800.

53) Huang, K. S-L.; Lee E. H.; Olmstead M. M.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 499-503.

54) Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802-1813.

55) Uno, H.; Terakawa, T.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2730-2737.

56) Mukaiyama, T.; Hoshino, T. *J Amer Chem Soc.* **1960**, *82*, 5339-5342

57) Sato, H. *Chem. Lett.* **1975**; 965-966.

58) Hjeds, H.; Honore,T. *Acta Chem. Scand. Ser. B* **1978**, *32*, 187-192.

59) Honore,T. *Eur. J. Med. Chem. Chim. Ther.* **1978**, 13, 429-434.

60) Iida, H.; Kasahara, K.; Kibayashi, C.; *J. Am. Chem. Soc.* **1986**, *108*(15), 4647-4648.

61) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*(9), 2225-2233.

62) Krol, W. J.; Mao, S.; Steele, D. L.; Townsend, C. A. *J. Org. Chem.* **1991**, *56*(18), 728-731.

63) Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Drake, D. J.; Fujishima, Y. *J. Chem. Soc. Chem. Commun.* **1994**, *9*, 1133-1134.

64) Wityak, J.; Gould, S. J.; Hein, S. J.; Keszler, D. A. *J. Org. Chem.* **1987**, *52*(11), 2179-2183.

65) Tanaka, K.; Sugimoto, Y.; Okafuji, Y.; Tachikawa, M.; Mitsuhashi, K.; *J. Heterocycl. Chem.* **1989**, *26*, 381-385.

66) Socha, D.; Jurczak, M.; Chmielewski, M. *Tetrahedron Lett.* **1995**, *36*, 135-138.

67) Kametani, T.; Chu, S.-D.; Honda, T. *Heterocycles* **1987**, *25*, 241-244.

68) Vasella, A.; Voeffray, R. *J. Chem. Soc. Chem. Commun.* **1981**, *3*, 97-98.

69) Kudoh, T.; Ishikawa, T.; Shimizu, Y.; Saito, S.; *Org. Lett.* **2003**, *5*, 3875 - 3878.

70) Socha, D.; Jurczak, M.; Chmielewski, M.; *Tetrahedron Lett.* **1995**, *36,* 135-138.

71) a) Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28-36.

b) Chiacchio, U.; Piperino, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1998**, *54*, 5695-5708.

72) Molander, G. A. *Org. React.* **1994**, *46*, 211-367.

73) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, 45, 8375-8377.

74) Sharma, A.; Iyer, P.; Gamre, S.; Chattopadhyay, S. *Synthesis* **2004**, *7*, 1037 - 1040.

75) Xu, Y.; Qian, L.; Prestwich, G. D.; *Org. Lett.* **2003**, *5*, 2267 - 2270.

76) Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem*. **2000**, *65*(8), 2599 - 2602.

77) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852 - 2859.

78) Haudrechy, A.; Picoul, W.; Langlois, Y. *Tetrahedron Asymmetry* **1997**, *8*, 139-148.

79) Macomber, R. S. *A Complete Introduction to Modern NMR Spectroscopy*, Wiley-Interscience, **1998**.

80) Pellicciari, R.; Natalini, B.; Marinozzi, M.; *Synth. Commun.* **1988**, *18*, 1715-1722.

81) Kirschbaum, B.; Stahl, U.; Jäger, V. *Bull. Soc. Chim. Belg.* **1994**, *103*, 425-432.

82) Kocieński, P. J. Protecting groups **1994**, Foundation of organic chemistry series (Thieme), p. 192.

83) Noe, C. R.; Knollmueller, M.; Schoedl, C.; Berger, M. L. *Sci. Pharm.* **1996**, *64*, 577-590.

84) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726 - 8743.

85) Xiang, Y.; Gong, Y.; Zhao, K. *Tetrahedron Lett.* **1996**, *37*, 4877-4880.

86) Zimmermann, P. J.; Lee, J-Y.; Hlobilova, I.; Endermann, R.; Häbich, D.; Jäger, V. *Eur. J. Org. Chem.* **2005**, 2450-3460.

87) Saita, M. G.; Chiacchio, U.; Iannazzo, D.; Corsaro, A.; Merino, P.; Piperno, A.; Previtera, T.; Rescifina, A.; Romeo, G.; Romeo, R.; *Nucleosides Nucleotides* **2003**, *22*, 739 - 742.

88) Juaristi, E.; Gutiérrez-Gutiérrez, V. M.; Rayers-Rangel, G.; Muñoz-Muñoz, R. *J. Braz. Chem. Soc.*, **2001**, *12(5)*, 652-660.

89) Morin, R. B.; Gorman, M.; Eds., *Chemistry and Biology of β-Lactam Antibiotics*, Academic, New York, 1982.

90) For review see: Lukacs, G.; Ohno, M.; Eds. *Recent Progress in the Chemical Synthesis of Antibiotics and Related Natural Products*, Springer, Berlin, 1990.

91) For review see: Cherry, P.C.; Newall, C. E. *Chemistry and Biology and β-Lactam Antibiotics*, Morin, R. B.; Gorman, M.; Eds., Academic, New York, 1982, Vol. 2, p. 361.

92) Georg, G. I, *Med. Chem. Lett.* **1993**, *3*, 2135-2486.

93) Burnett, D.; Caplen, M. A.; Davis, H. R.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733.

94) (a) Guérnard, D.; Guéritte-Voegelein F.; Potier, P. *Acc. Chem Res.* **1993**, *26*, 160. (b) Potier, P., *Chem. So.c. Rev.*, **1992**, *21*, 113.

95) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Amer. Chem. Soc.* **2005**, *127*, 5376-5383.

96) Liu, M.; Sibi, M.P. *Tetrahedron* **2002**, *58*, 7991-8035.

97) a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517-9582.
b) Sewald, N. *Angew. Chem.*, Int. Ed. **2003**, *42*, 5794-5795.

98) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1-15.

99) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181-2204.

100) Leplae, P.R.; Umezawa, N.; Lee, H. S.; Gellman, S.H. *J. Org. Chem.* **2001**, *66*, 5629-5632.

101) Martinek, T.A.; Tóth, G.k.; Vass, E.; Hollósi, M.; Fülöp, F.; *Angew. Chem., int. Ed.* **2002**, *41*, 1718.

102) Appella, D.H.; Christianson, L. A.; Klein, D. A.; Powell, D.R., Huang, X. L., Barchi, J. J.; Gellman, S. H. Nature **1997**, *387*, 381-384.

103) Kimmerlin, T.; Namoto, K.; Seebach, D. *Helv. Chim. Aca* **2003**, *86*, 2104-2109.

104) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223-1226.

105) Kritzer, J. A.; Lear, J. D.; Hodsdon, M. E., Schepartz, A. *J. Amer. Chem. Soc.* **2004**, *126*, 9468-9496.

106) See for example: Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed.* **1995**, *34*, 455.

107) Brackenridge, I.; Davies, S. G.; Fenwick, D. T.; Ichihara, O.; Polywka, M.E.C. *Tetrahedron* **1999**, *55*, 533 and references therein.

108) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293.

109) Davis, F.W.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.***1998**, *27*, 13 and reference therein.

110) a) Seebach, D.; Boog, A.; Schweizer, W.E. *Eur. J. Org. Chem.* **1999**, 335.
b) Hintermann T.; Seebach, D. *Synlett* **1997**, 337.
c) Seebach. D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103.

111) Juaristi, E.; Quintana, B.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.

112) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N. –T.; Olmstead, M. M. *J. Amer. Chem. Soc.* **1992**, *114*, 1800-1812.

113) Coleman, D. *J. chem. Soc.* **1951**, 2294-2295.

114) El Marini, A.; Roumestant M. L.; Viallefont, P.; Razafindranboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.

115) Peypoux, F.; Guinand, M.; Michel, G.; Delcambe, L.; Das, B. C.; Vareune, P.; Lederer, E. *Tetrahedron Lett.* **1995**, *36*, 381.

116) Arndt, F.; Ernst, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1364.

117) Balenović, K.; Cerar, D.; Fuks, Z. *J. Chem. Soc.* **1952**, 3316.

118) Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217.

119) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

120) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4-6

121) Flügge, J. *Grundlagen der Polarimetrie*, de Gruyter-Verlag, Berlin, **1970**, 16.

122) Sheldrick, G., *Program SHELXS-86* und *SHELXL-93*, Institut für Anorganische Chemie der Universität Göttingen, **1986**, **1993**.

123) Stewart, J. M.; Dickinson, P. A.; Ammon, H. L.; Flach, H.; Heck, H., *Programm XRAY-76*, Tech. Rep. TR-446, University of Maryland, Computer Center, College Park MD, **1976**.

124) Johnson, C. K., *Programm ORTEP II*, Tech. Rep. ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, **1971**.

125) Hildenbrand, T., *Programm FRIEDA*, Universität Stuttgart, unpublished.

126) Jork, H.; Funk, W.; Fischer, W.; Wimmer, H. *Dünnschicht-Chromatographie, Reagenzien und Nachweismethoden*, Bd. 1a, VCH, Weinheim, **1989**.

127) Helmchen, G.; Glatz, B. *Ein apparativ einfaches System und Säulen höchster Trenn-leistung zur präparativen Mitteldruckchromatographie*, Anhang zur Habilitationsschrift, Stuttgart, **1978**.

128) Chiang, Y. H. *J. Org. Chem.* **1971**, *36*, 2146-2155.

129) Matsuo, K.; Sunago, M.; Okutani, N.; Takagi, T.; Nakamoto, H.; Kobayashi, M. *Chem. Pharm. Bull.* **1995**, *43(10)*,1643-1646.

130) Carl, T., *Diplomarbeit*, Universität Stuttgart, **1999**.

131) Schwab, W. *Dissertation*, Universität Gießen, **1981**.

132) Kai, H.; Matsumoto, H.; Hattori, N.; Takase, A.; Fujiwara, T.; Sugimoto, H. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1997 - 2000.

133) Kanemasa, S.; Onimura, K. *Tetrahedron*, **1992**, *48*, 8642-8658.

134) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 6291-6292.

135) Hein, M. *Dissertation*, Universität Stuttgart **1996**.

136) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846-6847.

137) Stewart, J. M.; Woolley, D. W. *Biochemistry* (Moscow, Russian Federation) Rockefeller Inst., New York, NY, **1964**, *3*, 1998-2004.

138) Dorn, I. T.; Neumaier, K. R.; Tampé, R. *J. Amer. Chem. Soc.* **1998**, *120*, 2753-2763.

139) Portnyagin, Y. M. *J. Org. Chem. USSR* (EN) **1974**, *10*, 96-98.

140) Carlsen, P.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3638.

141) Posner, T. *Justus Liebigs Ann. Chem.* **1912**, *389*, 111.

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And many others,

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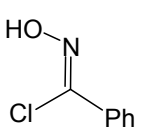
since Nov. 2003	Wissenschaftlicher Angestellter (BAT IIa) am Institut für Organische Chemie der Universität Stuttgart

16 Formula Tables of Structures Prepared



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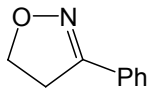

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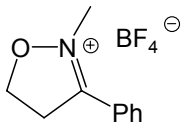

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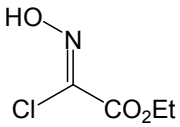

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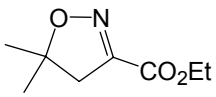

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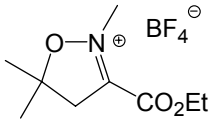

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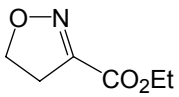

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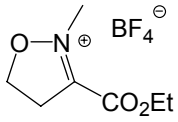

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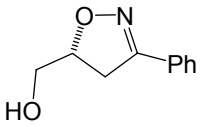

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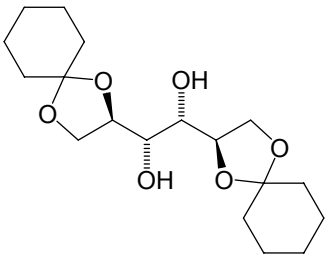

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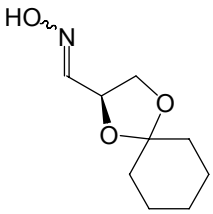

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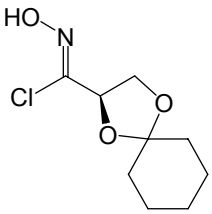

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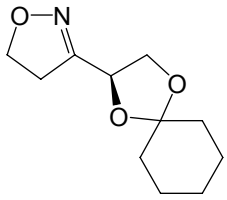

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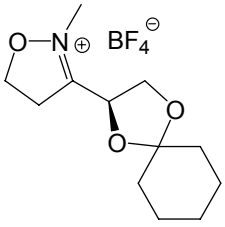

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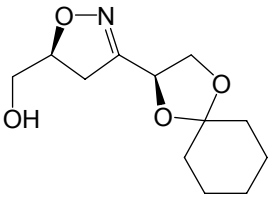

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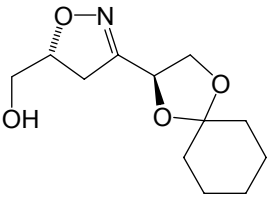

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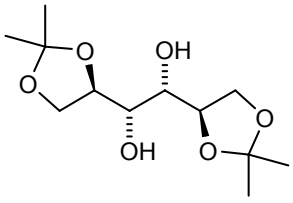

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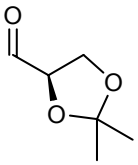

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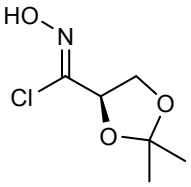

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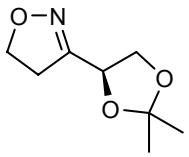

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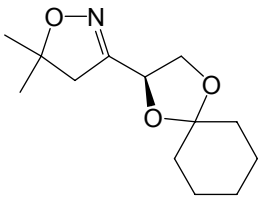

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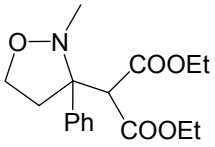

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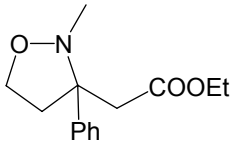

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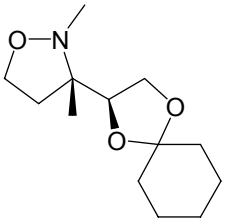

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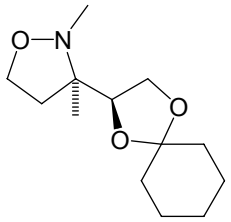

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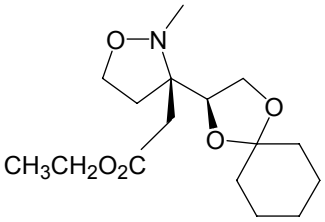

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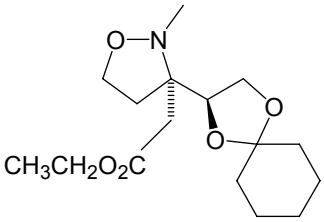

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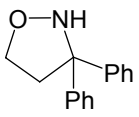

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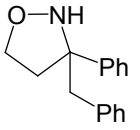

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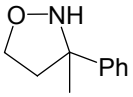

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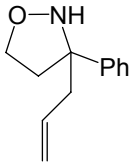

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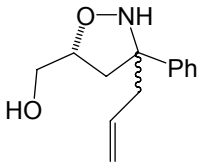

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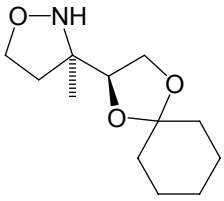

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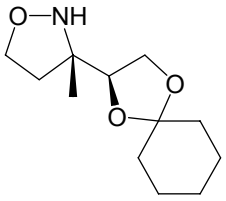

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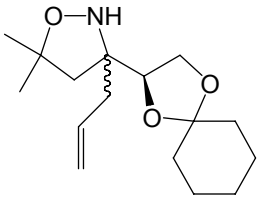

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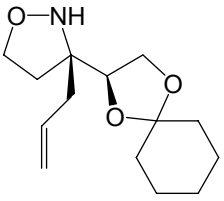

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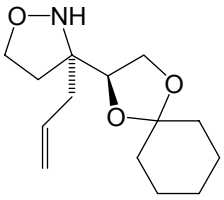

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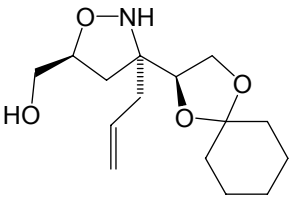

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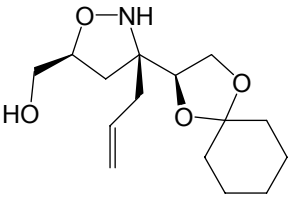

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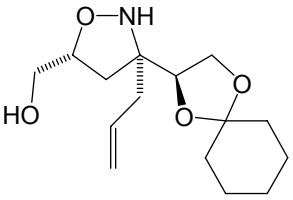

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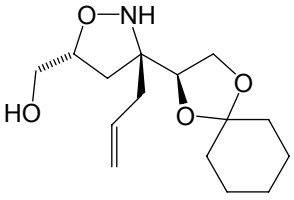

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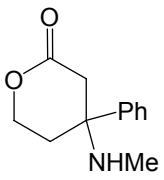

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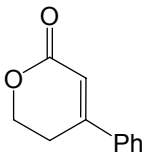

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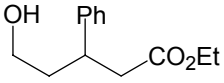

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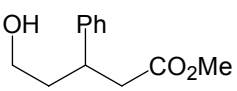

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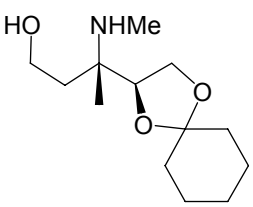

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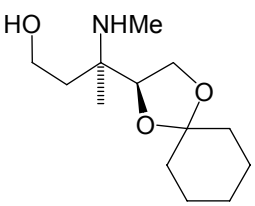

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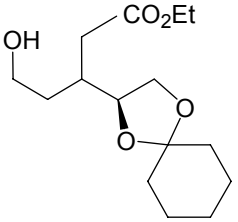

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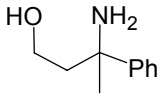

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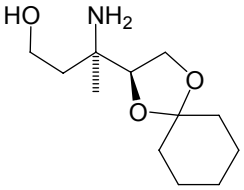

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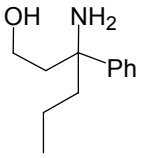

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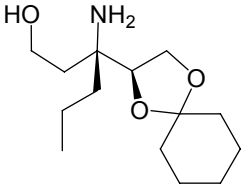

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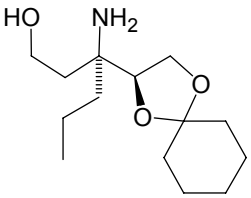

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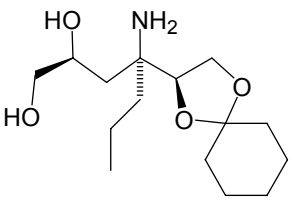

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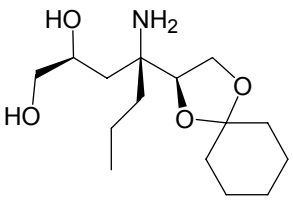

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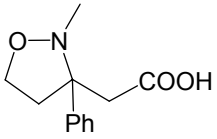

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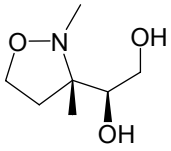

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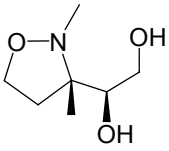

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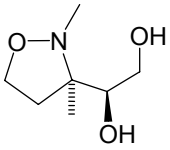

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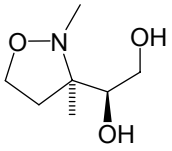

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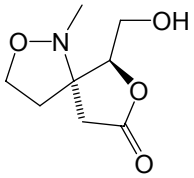

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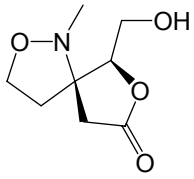

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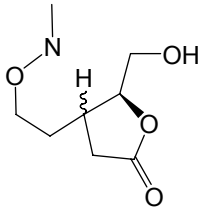

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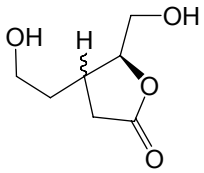

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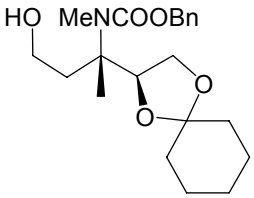

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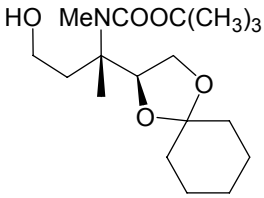

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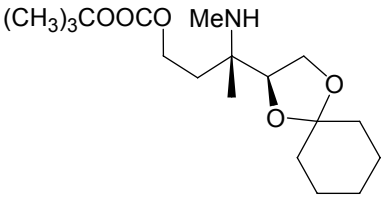

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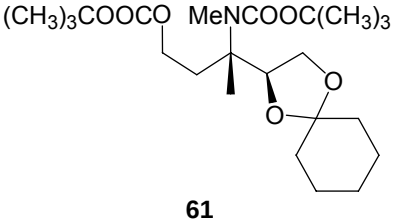

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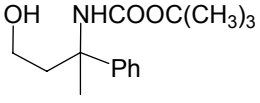

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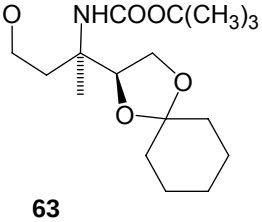

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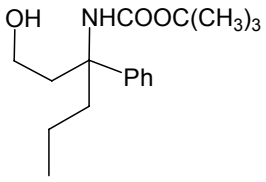

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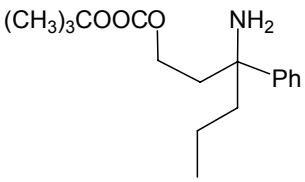

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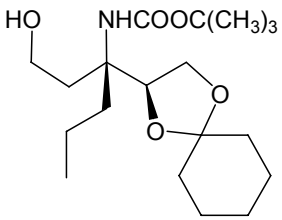

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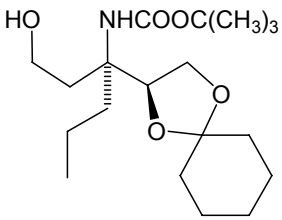

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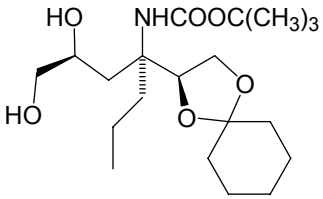

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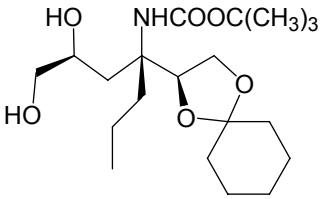

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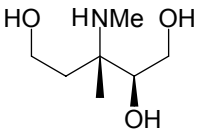

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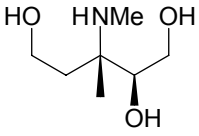

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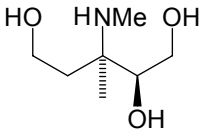

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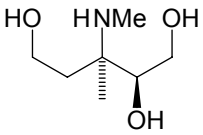

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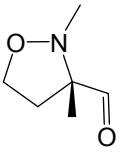

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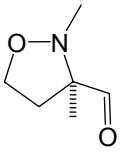

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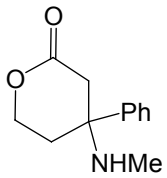
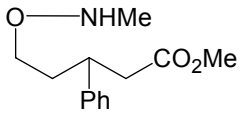


74·HCl



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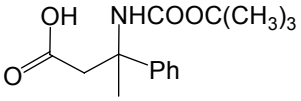

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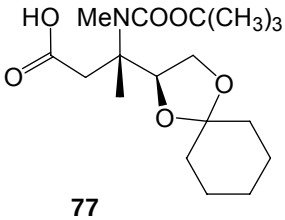

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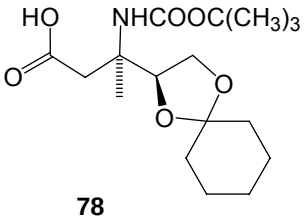

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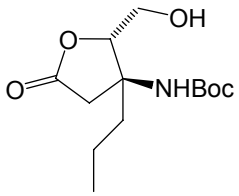

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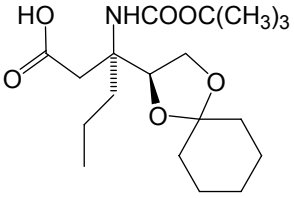

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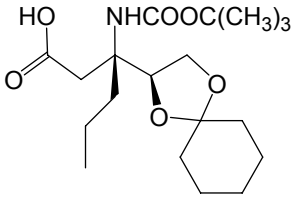

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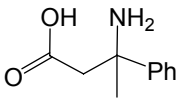

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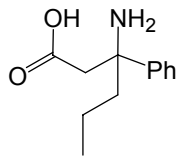

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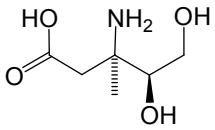

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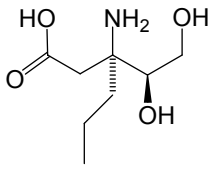

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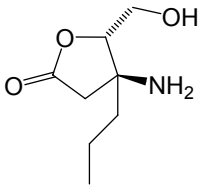

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