Synthesis of conformationally restricted amino acids – Highly versatile scaffolds

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Meinen Eltern

Experience is the name everyone
gives to their mistakes.

Oscar Wilde,
Lady Windermere's Fan, 1892, Act III

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Abbreviations

Ala	alanine
β-ACC	β-amino cyclopropanecarboxylic acid
Asp	asparagine
Bn	benzyl
Boc	tert-butyloxycarbonyl
Cbz	carboxybenzyloxy
CD	circular dichroism
CH_3CN	acetonitrile
DABCO	1,4-diazabicycl[2.2.2]octane
d.e.	diastereoisomeric excess
d.r.	diastereoisomeric ratio
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexyl carbodiimide
DCM	dichloromethane
DIBAL-H	diisobutyl aluminium hydride
DIC	*N*,*N*'-diisopropyl carbodiimide
DIPEA	diisopropylethylamine
DKP	diketopiperazine
DMAP	dimethylaminopyridine
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EDC	*N*-ethyl-*N*'-dimethylaminopropyl carbodiimide
Fmoc	9-fluorenylmethyl chloroformate
GABA	γ-amino butyric acid
Gln	glutamine
Gly	glycine
HATU	2-(7-aza-benzotriazole-1-l)-1,1,3,3-tetramethyluronium) hexafluorophosphate
HBTU	*O*-benzotriazole-N,N,N',N'-tetramethyluronium hexafluoro phosphate
HOAt	hydroxyazabenzotriazole
HOBt	hydroxybenzotriazole
LAH	lithium aluminiumhydride
LDA	lithium diisopropylamide
Me	methyl
NPY	neuropeptide Y
Ph	phenyl
ppb	part per billion
ppm	part per million
Pro	proline
RNA	ribonucleic acid
Ser	serine
SPPS	Solid phase peptide synthesis
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpyridine-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TMEDA	tetramethylethylendiamine
Tyr	tyrosine
Val	valine

A. Introduction

A. 0. Preface

Small molecules played the crucial role in the beginning of life.

Hence, of course also amino acids are basic building blocks of all vital existence. This appears to be the appropriate expression since only 20 different amino acids display the smallest unit of peptides and proteins which are responsible for innumerable various activities. They are the monomers of entities that build up and maintain life's structure and are involved in coordination of almost all physiological processes. Consequently, they give the cell structure and stability through proteins like collagen or elastin. Furthermore, amino acids build up macro biopolymers like enzymes as well as many other peptides which play important roles in coordination and maintenance of living organisms. Peptides, but also amino acids themselves, as well as biogenic amines (generally derived from amino acids) are the major substrates for targets like enzymes and receptors.

Amino acids are naturally synthesised from intermediates of the major metabolic pathways like glycolysis or the citric acid cycle. Here α-keto acids like α-ketoglutarate are converted to the corresponding α-amino acids by transfer of ammonia catalysed by enzymes, e.g. glutaminase to produce glutamate. Other amino acids can be synthesised by transaminases in the presence of glutamate or aspartate as amine source.

The first laboratory preparation of an amino acid was accomplished by *Adolph Strecker* (**Figure 1**) in 1850. In his pioneering work he was able to synthesise α-amino acids from simple readily available building blocks which will be described in the next chapter.

Figure 1. Oil painting of *Adolph Strecker*.[1]

Currently, amino acids are industrially produced *via* fermentation or chemical synthesis in thousand ton scale per year. They are mainly used as food additives and in cosmetics but also as precursors for various other chemical syntheses.

Moreover, the synthesis of unnatural amino acids is also of high interest. They can serve as building blocks for the preparation of foldamers with new interesting secondary structures and as subunits in peptidomimetics as well as in α-peptide analogues. Moreover, they are utilised as appropriately labelled compounds, e.g. ^{18}F-labelled amino acids in diagnostics of cerebral gliomas.[2]

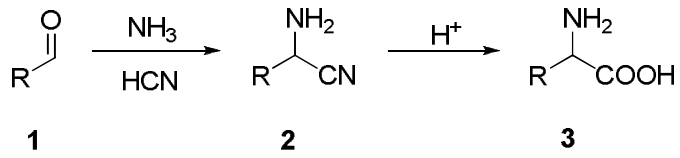
The development of methods for the synthesis of amino acids (including complex unnatural β- and γ-amino acids), starting from the first syntheses of racemic natural α-amino acids and their fields of application will be briefed in the following chapter.

A. 1. Synthetic strategies towards α-amino acids

A. 1.1 Racemic syntheses of α-amino acids

The first methodology for the synthesis of α-amino acids was developed in 1850 by *A. Strecker*[3] (**Scheme 1**). Here, aldehyde **1** is condensed with ammonia in the presence of hydrocyanic acid, giving rise to an α-amino nitrile **2** which can be hydrolysed to the corresponding α-amino acid **3**.

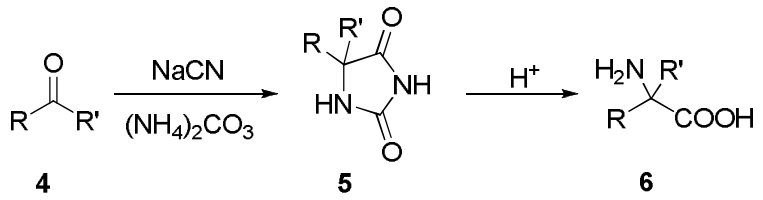
Scheme 1. Outline of the *Strecker* synthesis.



1 **2** **3**

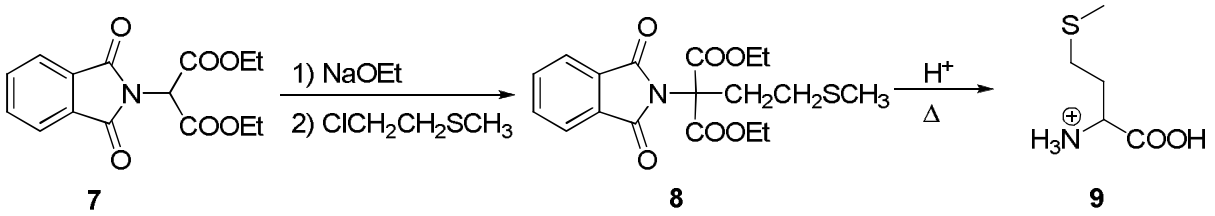
Another, quite old strategy is the amino acid synthesis via hydantoin intermediates (*Bucherer-Bergs* reaction) which is still used by companies like SEKISUI Medical Co., Ltd.[4] The hydantoin **5** is formed from an aldehyde or ketone **4**, sodium cyanide and ammonium carbonate. Upon hydrolysis of heterocycle **5**, amino acids like **6** can be obtained (**Scheme 2**).

Scheme 2. Hydantoin approach towards α-amino acids.



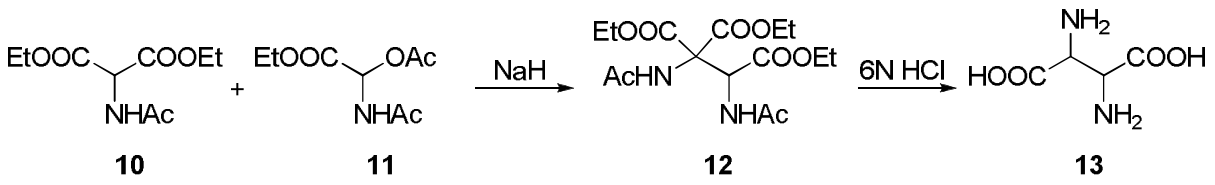
Furthermore, α-amino acids are accessible via a *Gabriel*-malonic ester synthesis as shown for methionine in **Scheme 3.**[5] Compound **7** can be obtained from diethyl malonic ester which is converted to the corresponding α-bromo malonate using a *Hell-Volhard-Zelinsky* transformation followed by the bromide substitution with phthalimide. Subsequently, the side chain of methionine was introduced using 2-chloroethyl methyl sulfide in the presence of a base to obtain **8**. Decarboxylation and ester cleavage gives free methionine **9**.

Scheme 3. *Gabriel*-malonic ester synthesis of methionine.



Another interesting methodology utilises *N*-acylaminomalonates which can be transformed, as shown by *Matsumoto et al.* from Tanabe Seiyaku Co., Ltd. to 3-substituted aspartic acids (**Scheme 4**).[6]

Scheme 4. Synthesis of 3-amino aspartic acid.



Malonate **10** is reacted with ethyl 2-acetoxyglycinate (**11**; prepared by anodic oxidation of another equivalent of ethyl *N*-acetylaminomalonate) to afford the corresponding *N*-acetyl-3-substituted aspartic acid derivative **12**. Hydrolysis with hydrochloric acid gives rise to 2,3-diaminosuccinic acid (**13**). Another, more sophisticated modification of this method uses microwave irradiation.[7]

These reactions give just a glimpse of the broad spectrum of possibilities of syntheses known for α-amino acids.

The disadvantage of all the aforementioned reactions is their stereochemical outcome as racemic products. Therefore, various methods for the resolution of racemic mixtures have been developed.

The classical ways for these resolutions are:

(1) Derivatisation of the racemate by another chiral reagent and separation of the resulting diastereomers followed by reversal of the derivatisation.

(2) The use of suitable enzymes which convert only one enantiomer of the racemate, e.g. by acetylation. Separation from the unreacted enantiomer followed by its hydrolysis yields amino acids in high optical purity. In the case of α-amino acids, this proves to be an especially useful approach since they are the natural substrates of enzymes.

Nevertheless, strategies are needed to produce amino acids in optical pure form without any resolution process and without production of the undesired second enantiomer. A brief overview of some of the most interesting methods will be given in the next chapter.

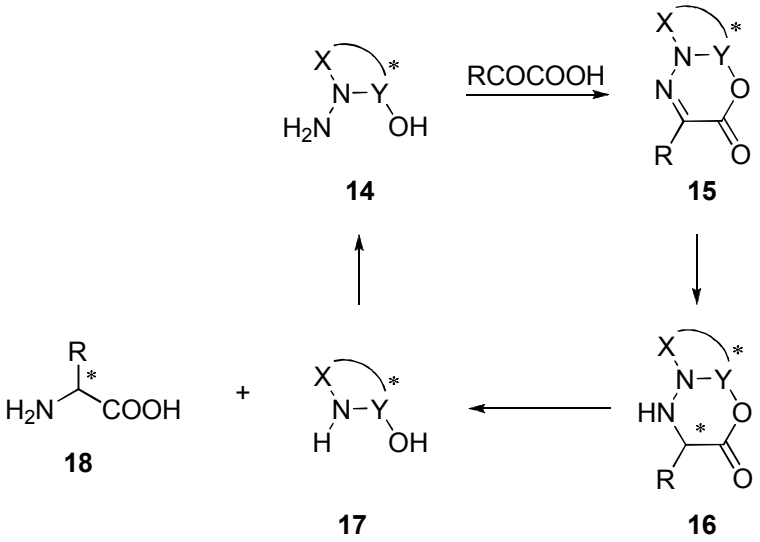
A. 1.2 Asymmetric syntheses of α-amino acids

Using the aforementioned methodologies enantiopure amino acids can only be accessed after a resolution process of the racemic material. Therefore, many asymmetric syntheses were developed for the preparation of amino acids as single enantiomers.[8]

The first synthesis of α-amino acids using a chiral reagent which can be recovered was developed by *Corey et al.*[9] in 1970 based on former investigations by *Kagan et al.*[10] *Corey's* synthesis starts from a α-keto acid which is converted to the hydrazonolactone **15** using the chiral hydrazine reagent **14**. The C=N double bond of the hydrazonolactone can than be reduced to yield intermediate **16** with the desired stereochemistry at the later α-C of the amino acid. Hydrogenolytic cleavage of the N-N bond, followed by an ester saponification

gave the corresponding amino alcohol **17** of the chiral hydrazine and the α-amino acid **18** with selectivities up to 97% *ee* (**Scheme 5**).

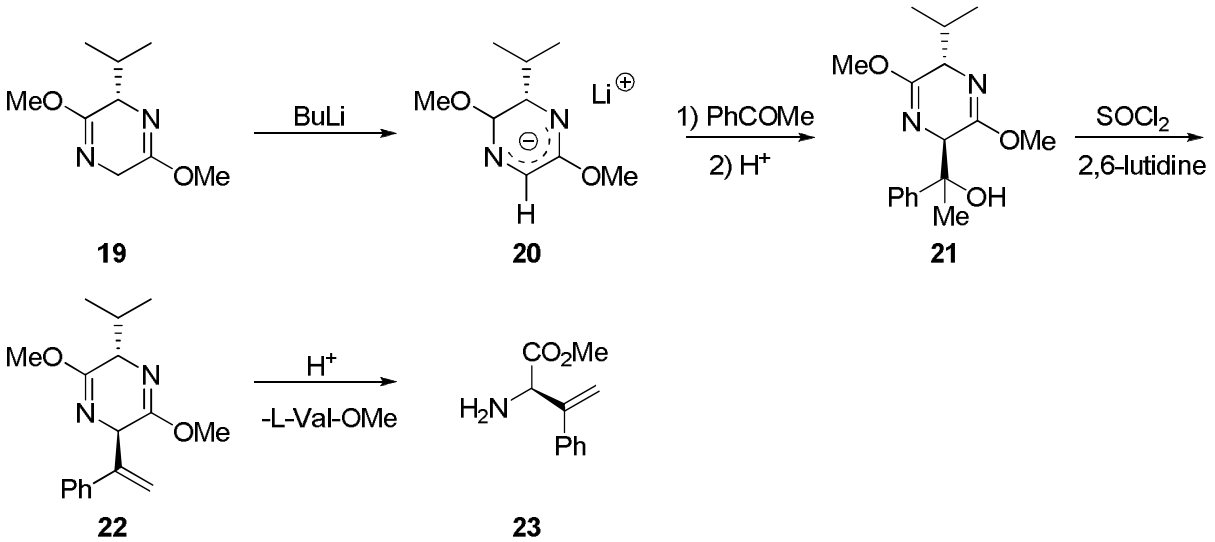
Scheme 5. Outline of *Corey's* methodology.



* Asterisk signifies a chiral group or centre

Another approach referred to as intraannular chirality transfer, was introduced by *Schöllkopf et al.* in 1984 for the synthesis of α-vinyl amino acids (**Scheme 6**).[11]

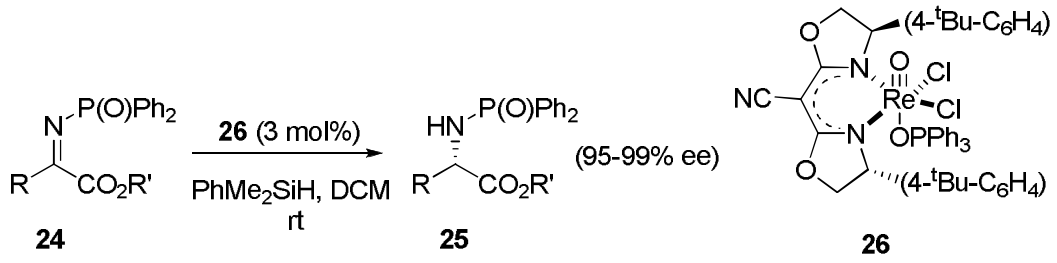
Scheme 6. Synthesis of α-vinyl amino acid **23** according to *Schöllkopf et al.*



Here, glycine is condensed with (*L*)-valine as chiral auxiliary followed by methylation giving the bislactim ether **19**. Deprotonation of **19** with butyl lithium gives rise to monoanion **20** which is then reacted with acetophenone to yield **21**. The subsequent reaction with thionyl chloride in the presence of 2,6-lutidine gave **22** as the major product, which on hydrolysis with hydrochloric acid affords the desired α-vinyl amino acid ester **23**. It was demonstrated that this method can be applied for a broad variety of aldehydes and ketones in the synthesis of different natural and unnatural substituted α-amino acids.

Moreover, catalytic reduction using transition metal catalysts in the presence of chiral ligands is another very popular approach. One possibility is the enantioselective introduction of the α-hydrogen using α,β-dehydro-α-amino acids to create the chiral centre selectively.[12] Since the pioneering work of *Knowles et al.*[13] in the synthesis of *L*-Dopa, one of the most common systems is rhodium (I) in the presence of phosphine ligands, to hydrogenate C=C double bonds. An additional strategy is the stereoselective reduction of C=N double bonds of α-imino esters like **24** from α-keto esters (this somehow mimicks the natural process of amino acid synthesis with the help of enzymes as chiral catalyst). A recent example is the hydrosilylation by a Re(V)-oxo complex **26** coordinated by a cyano bis(oxazoline) ligand, introduced by *Toste et al.*, which furnished *N*-phosphinyl arylglycines (**25**) in excellent enantioselectivities (**Scheme 7**).[14]

Scheme 7. Re(V)-catalysed C=N reduction.



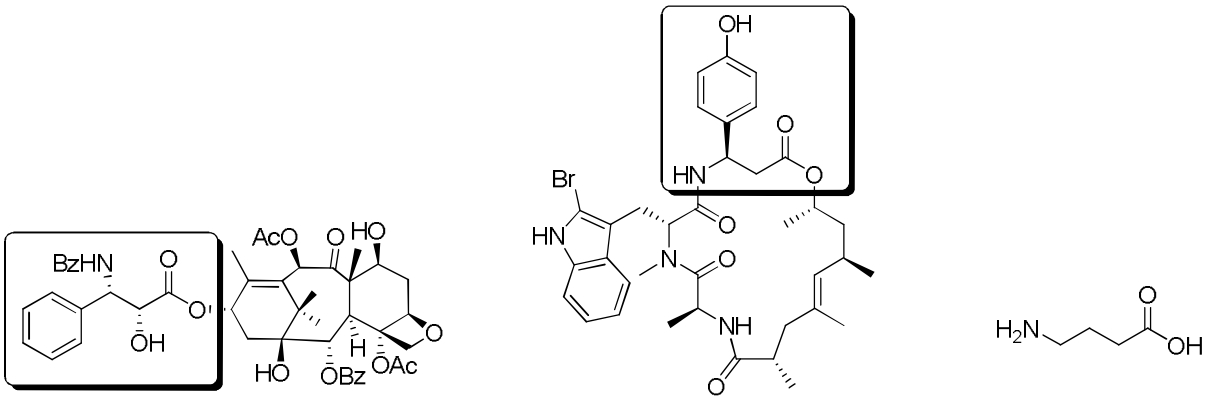
All the introduced methods allow the stereoselective synthesis of naturally occurring as well as novel, differently substituted α-amino acids. For the preparation of β-, γ- or higher homologated amino acids different methods need to be utilised.

A. 2. Synthetic strategies towards β- and γ-amino acids

The synthesis of new β- and γ-amino acids is always a remunerative challenge since they display important subunits in bioactive compounds, like the highly active anticancer agent taxol[15] **27** (containing a phenylisoserine) or Jasplakinolide **28 (**containing a β-tyrosine) which has insecticidal, antifungal, and antihelminthic properties[16] (**Figure 2**).

The most prominent example for a naturally occurring γ-amino acid is GABA (**29**; γ-amino butyric acid), being an important inhibitory neurotransmitter in the central nervous system.

Figure 2. Naturally occurring β- and γ-amino acids in: Taxol **27**; Jasplakinolide **28**; GABA **29**.

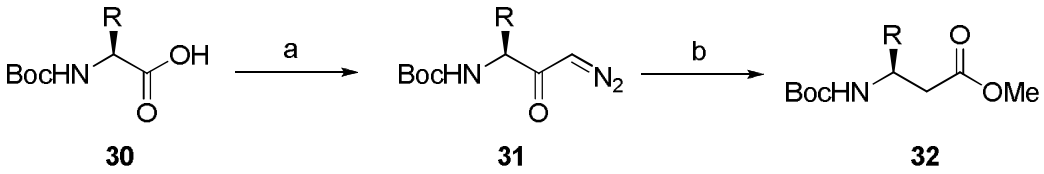


27 **28** **29**

These types of amino acids often have many beneficial properties such as a higher proteolytic stability compared to α-amino acids as well as the ability to induce discrete and predictable folding properties in polymers. Hence, they are utilised in the preparation of foldamers, as surrogates for natural amino acids in biologically active peptides to study structure-activity relationships and as potential therapeutics. The pioneering work of *Gellman* and *Seebach* starting in the middle of the 1990s in the field of foldamers showed the conformational preferences imposed by these unnatural amino acids in oligomers.[17] However, the monomeric building blocks of these highly interesting oligomers need to be synthesised before.

One of the simplest methods for the preparation of β-amino acids is the synthesis from the natural (*L*)-α-amino acid by an *Arndt-Eistert* homologation (**Scheme 8**).[18]

Scheme 8. *Arndt-Eistert* homologation of α-amino acids.

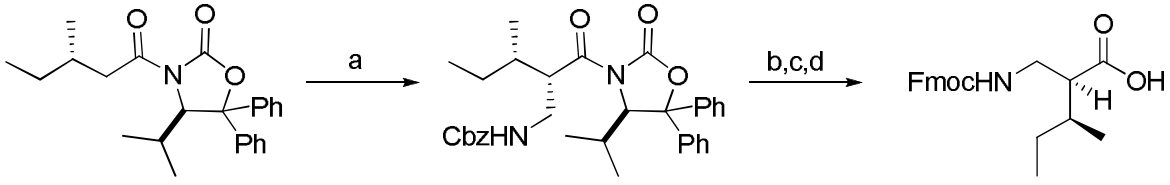


30 **31** **32**

Reagents and conditions: (a) i. $Et_3N/ClCO_2Et$, -15° C; ii. CH_2N_2, -5° C - rt. (b) Cat. $PhCO_2Ag$ in Et_3N/MeOH.

In the first step carboxylic acid **30** is activated and directly converted to the corresponding diazoketone **31** using diazomethane. **31** can then undergo a *Wolff* rearrangement which is conducted in the presence of catalytic amounts of Ag(I)-salts and methanol to give the homologated β-amino ester **32**. By this homologation β^3-amino acids[19] can be obtained.
Furthermore, *Seebach et al.* reported the synthesis of β^2-amino acids, like for instance Fmoc protected homo-isoleucine[20] (**Scheme 9**). **33** can be prepared by the standard *Evans* protocol which involves acylation of the lithiated (*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one ((*R*)-DIOZ) with an acid chloride like (*S*)-3-methylpentanoic acid. The acyl-DIOZ can then be enolised and amidomethylated to give **34**. After removal of the auxiliary with LiOH and hydrogenolysis of the Cbz group the final Fmoc protection gave β^2-isoleucine (**35**).

Scheme 9. *Seebach's* synthesis of Fmoc-protected β^2-amino acids.



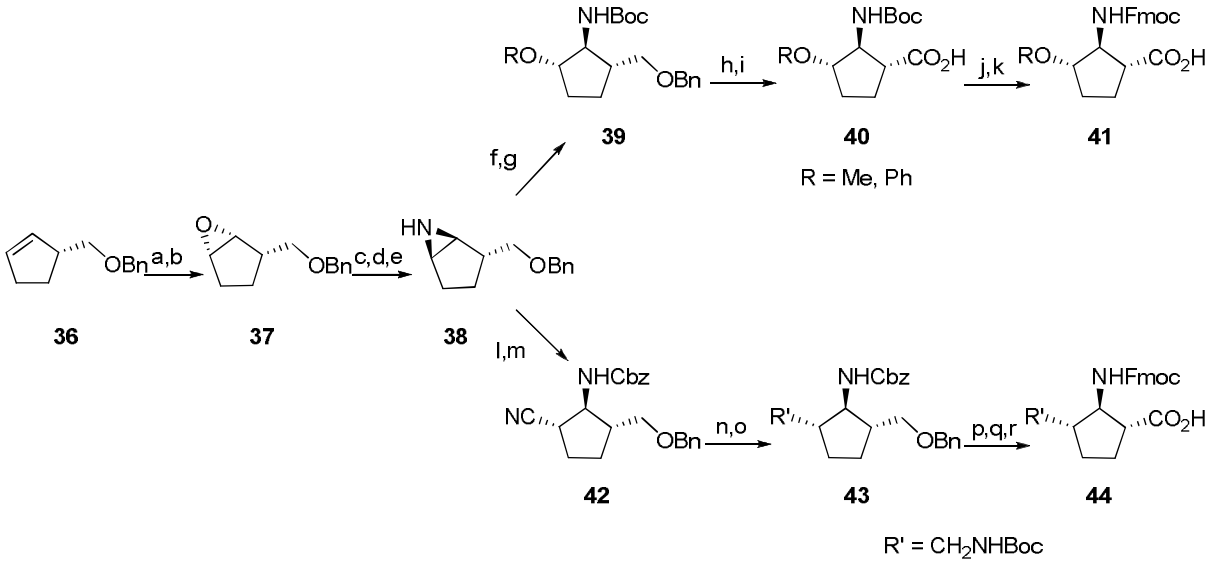
33 **34** **35**

Reagents and conditions: (a) i. $TiCl_4/NEt_3$, CH_2Cl_2; ii. $CbzNHCH_2OMe$, $TiCl_4$, 66% (96 % dr). (b) LiOH, THF/H_2O, 66%. (c) H_2/Pd-C, MeOH. (d) FmocOSu, aq. Na_2CO_3, acetone, 90% (over two steps).

However, not only linear amino acids but also cyclic β-amino acids, being more conformationally restricted are of substantial interest.
The first examples by *Gellman et al.* for cyclic β-amino acids that can be successfully utilised in foldamers were *trans*-ACPC (*trans*-2-aminocyclopentanecarboxylic acid) and *trans*-ACHC

(*trans*-2-aminocyclohexanecarboxylic acid) and some of their derivatives. The general synthetic approach of *Gellman* for different *trans*-ACPCs is given in **Scheme 10**.[21] In the first step the homoallylic benzylalcohol **36** is epoxidised to **37**. This epoxide is then converted, in a three step procedure, to the corresponding aziridine **38** having the inverse stereochemistry. At this point the synthetic route was diverging. On the one hand, the tricycle of the aziridine was opened with alcohols and the free amine was Boc protected giving **39**. After removal of the benzyl group, the primary alcohol can be oxidised to the corresponding carboxylic acid by Jones oxidation yielding β-amino acid **40**. A two step substitution of the Boc- to the corresponding Fmoc-protecting group gives rise to **41**. In the second route, aziridine **38** was opened using potassium cyanide and the resulting free amine was protected with CbzCl to **42**. After reduction of the nitrile the resulting primary amine is Boc protected to **43**. Finally, the Cbz- as well as the Bn-group were removed, the corresponding amino function Fmoc-protected and the primary alcohol oxidised yielding **44**.

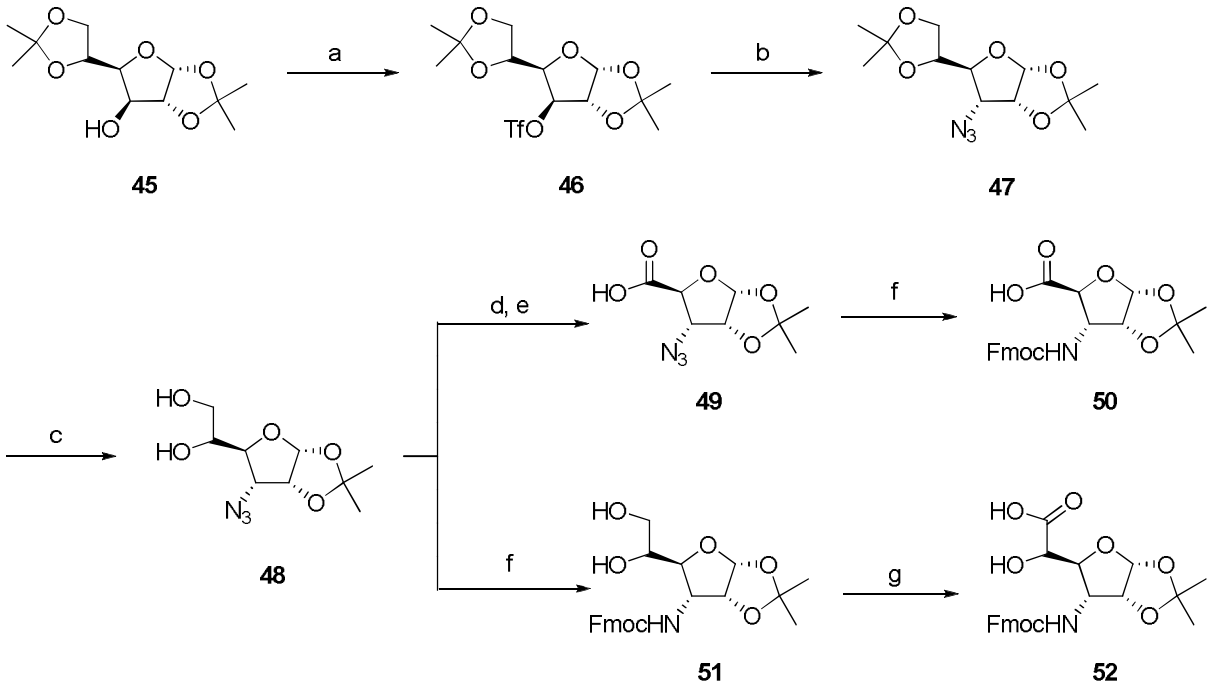
Scheme 10. Synthesis of *trans*-ACPC derivatives by *Gellman et al.*



Reagents and conditions: (a) $TiCl_4$/TBHP, CH_2Cl_2, 30 min, -78 °C. (b) KOtBu, benzene, rt, 3 h, 85% (over two steps). (c) NaN_3/NH_4Cl, MeOH/H_2O, reflux, 12 h, 85%. (d) MsCl, pyridine, 0 °C, 2 h. (e) LAH, THF, 0 °C to rt, 2 h, 84% (over two steps). (f) Boc_2O/NEt_3, MeOH, rt, 2 h, 84%. (g) $BF_3{\cdot}OEt_2$/ROH, CH_2Cl_2, -78 °C, 15 min, 71-87%. (h) 10% Pd/C, NH_4HCO_2, MeOH, reflux, 10 h, 93%. (i) Jones reagent, acetone, 0 °C, 2 h, 73-89%. (j) 4 N HCl, dioxane, rt, 1 h. (k) Fmoc-OSu/$NaHCO_3$, acetone/H_2O, rt, 12 h, 61-74% (over two steps). (l) Cbz-Cl/NEt_3, CH_2Cl_2, 0 °C, 2 h, 93%. (m) KCN/18-crown-6, DMSO, 80 °C, 2 h, 90%. (n) $BH_3{\cdot}$THF, THF, rt, 4 h. (o) Boc_2O/NEt_3, MeOH, rt, 2 h, 75% (over two steps). (p) Na/NH_3, -78 °C, 30 min. (q) Fmoc-OSu/$NaHCO_3$, acetone/H_2O, rt, 12 h, 47% (over two steps). (r) TEMPO/NaClO, CH_2Cl_2/H_2O, 0 °C, 30 min, 57%.

Another highly interesting approach towards the enantioselective synthesis of cyclic β- as well as γ-amino acids is the use of carbohydrates for the preparation of sugar derived amino acids introduced by the groups of *Fleet*,[22] *Kessler*,[23] *Chakraborty*[24] and many others. In the synthesis of *Kessler et al.* diacetone glucose (**45**) gives rise to β- and γ-amino acids (**Scheme 11).** Triflyl activated diacetone glucose **46** is converted to azide **47** in DMF accompanied by inversion of configuration. After azidolysis, the exocyclic hydroxyl group is deprotected by acetic acid yielding **48**. In the first route towards the β-sugar amino acid the diol **48** can be cleaved oxidatively to **49** followed by a one-pot reaction, where the azide is reduced and simultaneously Fmoc protected to β-amino acid **50**. For the preparation of **52**, a different route was used in which a similar one-pot reaction like in the first route can be applied to yield the Fmoc protected intermediate **51**. The selective oxidation of the primary alcohol with TEMPO, sodium hypochlorite and KBr provides γ-sugar amino acid **52**.

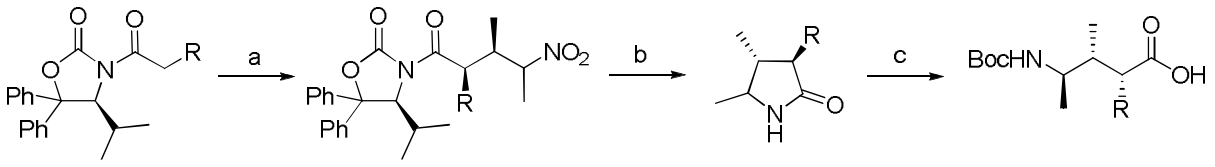
Scheme 11. Synthesis of β- and γ-amino acids derived from *D*-glucose.



Reagents and conditions: (a) Tf_2O, pyridine, -10 °C, CH_2Cl_2. (b) NaN_3, Bu_4NCl (cat), 50 °C, DMF. (c) 77% HOAc, 3 h, 65 °C. (d) $NaIO_4$, 5 h, 10 °C, MeOH. (e) $KMnO_4$, 50% HOAc, rt. (f) H_2, Pd/C, MeOH, FmocCl, $NaHCO_3$, pH 8 - 9, THF, MeOH, rt, 90%. (g) NaOCl, TEMPO (cat), KBr, CH_2Cl_2, sat. aq. $NaHCO_3$, Bu_4NCl, 62%.

Naturally, like in the case of β-amino acids, also linear γ-amino acids can be prepared. Very simple acyclic γ-amino acids were prepared by *Hanessian et al.* who reported γ-peptides derived by homologation of (*L*)-alanine and (*L*)-valine to form stable right-handed helical secondary structures.[25] Besides the facile homologation many other syntheses for γ-amino acids with different substitution patterns are in the literature, e.g. the methodology developed by *Seebach et al.* for 2, 3, 4-substituted γ-amino acids (**Scheme 12**).[26] Here the amino acid is prepared stereoselectively by a Michael addition of the modified Evans acyloxazolidinone **53** to nitrobutene, yielding **54**. After reductive cleavage the cyclised pyrrolidone **55** can be obtained, which upon hydrolysis and *N*-Boc protection gives γ-amino acid **56**.

Scheme 12. Synthesis of 2, 3, 4-substituted γ-amino acids *by Seebach et al.* [26]

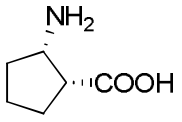


Reagents and conditions: (a) i. $TiCl_4$/DIPEA; ii. Nitrobutene, $TiCl_4$. (b) Raney-Ni/H_2. (c) i. 6M HCl; ii. Boc_2O, Na_2CO_3.

A. 2.1 Applications of β- and γ-amino acids

As described before there are some examples in nature for β- and γ-amino acids, but there is also a large number of new synthetic cyclic as well as acyclic amino acids for a broad range of applications. A very interesting β-amino acid is cispentacin **57** and its derivatives since it has highly antifungal properties which make it a useful tool as a fungicide in crop protection.[27] Two other prominent examples for the application of γ-amino acids employed as therapeutics are vigabatrin **58** which is used as anticonvulsant and baclofen **59** which is a $GABA_B$ receptor agonist and is applied in the treatment of spasticity (**Figure 3**).

Figure 3. Biologically active β- and γ-amino acids.



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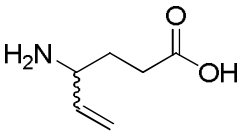

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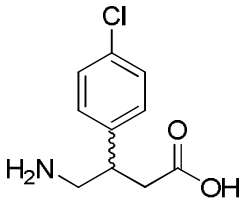

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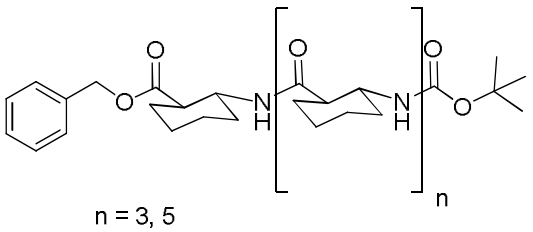
Furthermore, β- as well as γ-amino acids can be applied in homo- and heterooligomers (foldamers), mimicking natural secondary structures like helices or sheets. Since biological systems rely almost exclusively on polymers, the intention of foldamer design is to have analogue capabilities, like peptides or proteins from unnatural polymers, which are able to fold into compact and specific conformations.[28] One of the first foldamers that strongly favour a helical structure (14-helix) were tetramer and hexamer structures of *trans*-ACHC **60** by *Gellman et al.*[29] However, not only homooligomers but also heterooligomers are able to show discrete secondary structures. *Reiser et al.* showed that α/β-alternating peptides using 3-amino-cyclopropane-1,2-dicarboxylic acid monomethyl ester (**61**;β-ACC) and alanine give surprisingly stable helical conformations.[30]

Figure 4. Examples for foldamers giving stable secondary structures.



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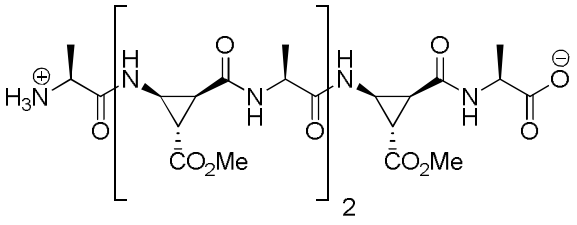


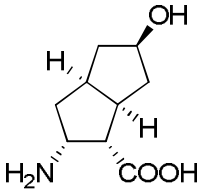
61

In addition, many foldamers from unnatural amino acids were found to possess highly interesting physiological properties. For instance, some arginine rich β-peptides were used to investigate the entry process of peptides into HeLa cells in order to gain insight into the correlation between structure and endocytic uptake.[31] Furthermore, different α,β-peptides

were found to have antimicrobial activity[32] or to have the ability to disrupt protein-protein interactions.[33]

Moreover, unnatural amino acids are effective as building blocks in the design of functional peptides by substitution of α-amino acids in natural α-peptides. This alteration can have many beneficial effects for incorporated peptides, like higher stability to proteolytic hydrolysis or the possibility to control the conformation and thereby modify its function. Herein, especially discrete structure inducing conformationally restricted amino acids are a useful tool to investigate how secondary structures can affect activity. This can help to get a deeper insight into structure-activity-relationships (SARs) and give the possibility to alter its function. Very often unnatural amino acids are used as turn inducers in peptide analogues, e.g. for the gonadotropin releasing hormone. Here, *Mulzer et al.* could show the turn inducing effect for cispentacin derivative[34] **62** whereas *Nagai et al.* reported similar effects for the bicyclic amino acid **63**.[35]

Figure 5. Examples for various turn inducing amino acids.



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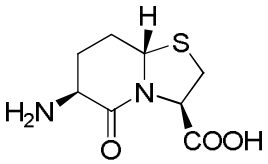

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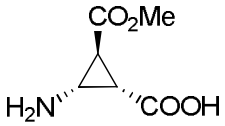


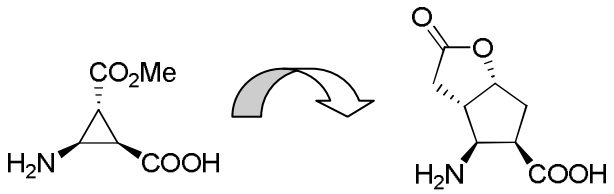
64

Moreover, the incorporation of β-ACC (**64**) as constrained β-alanine analogue was successfully carried out in the group of *Reiser*. These modified peptides were very useful in receptor-ligand interaction studies on neuropeptide Y (NPY),[36] Calcitonin gene related peptide[37] and orexin peptides.[38] In the case of the NPY receptor, truncated NPY analogues (residues 25-36) containing β-ACCs in different combinations in close proximity to the two *C*-terminal arginines were synthesised. Some of these NPY fragments showed nanomolar affinity towards the Y_1 and the Y_5 receptor with a good selectivity for the Y_1 receptor.

Thus, the incorporation of conformationally restricted β-amino acids into biologically active peptides as well as their application in foldamers is a promising objective. Hence, different derivatives of β-ACCs with α-amino acid side chain functionality were prepared.[39] Unfortunately, many of these compounds were not stable or require very special conditions in

peptide coupling reactions. This drawback makes it necessary to synthesise *cis*-β-amino acids with a similar stereochemical structure that are able to induce comparable conformational properties in peptides, but having a higher stability. Cispentacin derivatives like **65** with its annulated γ-butyrolactone moiety as "side chain", thus allowing a wide range of modifications were envisaged to be a worthwhile approach. The lactone can be easily diversified in many different ways like opening by hydrolysis and reduction respectively or enolisation.

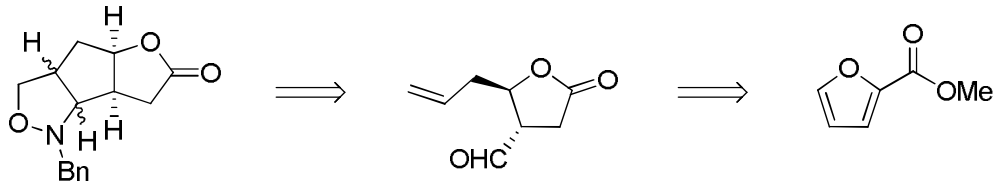
Figure 6. Outline for a new modifiable β-amino acid lactone 'side chain' with comparable stereochemical configuration like (+)-β-ACC **64**.



64 **65**

The aim of this work was to develop new unnatural conformationally restricted β- and γ-amino acids and to investigate their potential applications. These various amino acids were derived from the intramolecular 1,3-dipolar cycloaddition products which were obtained as diastereomers **66a** and **66b** ascribed to γ-butyrolactone **67**. The synthesis of **67** starting from 2-furoic methyl ester (**68**) and its value in the synthesis of different natural products had been described before.[40]

Scheme 13. Retrosynthetic scheme to the two diastereomeric nitrone cycloaddition products **66a/b**.



66a/b **67** **68**

The two diastereomers **66a** and **66b** can be transformed to a broad variety of β-amino acids as well as γ-amino acids. Cispentacin derivatives with an annelated lactone as well as open chain products modified with protected alcohol groups and/or protected guanidinium group can be obtained. Furthermore, isomer **66a** gives rise to a *trans*-γ-amino acid with a cyclopentane backbone and a free alcohol group which allows for further modifications. The second diastereomer **66b** can be converted to a bicyclic β-amino acid.

[1] Picture taken from: http://www.uni-tuebingen.de/ziegler/history/chemists_tuebingen.htm

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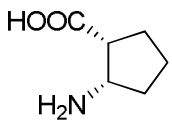
B. Main part

B. 1. Development of conformationally constrained β-amino acids – New cispentacin derivatives

Cispentacin (**57**) was first isolated independently in 1989 by two distinct Japanese groups from *Bacillus cereus* and *Streptomyces setonii* respectively and revealed very potent antifungal activity.[1] Since then, it has gained relevance in agrochemical research,[2] but was also described to exhibit activity against human pathogens.[3] However, not only cispentacin but also different analogues are currently under investigation by pharmaceutical companies for the treatment of various yeast infections.[4]

Their mode of action is based on the inhibition of prolyl-*t*-RNA synthetase and isoleucyl-*t*-RNA synthetase after being transported and accumulated in fungal cells by proline permease and other amino acid permeases.[5] The interaction with synthetases results then in inhibition of protein synthesis and therefore cell growth.

Figure 7. Cispentacin (**57**) and several highly active antifungal derivatives; PLD-118 (**69**) and Amipurimycin **70**.



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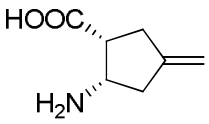

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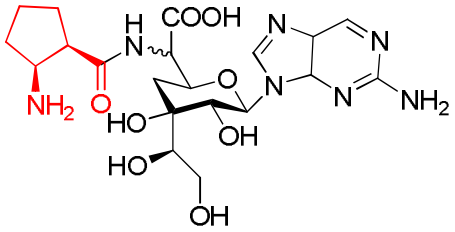


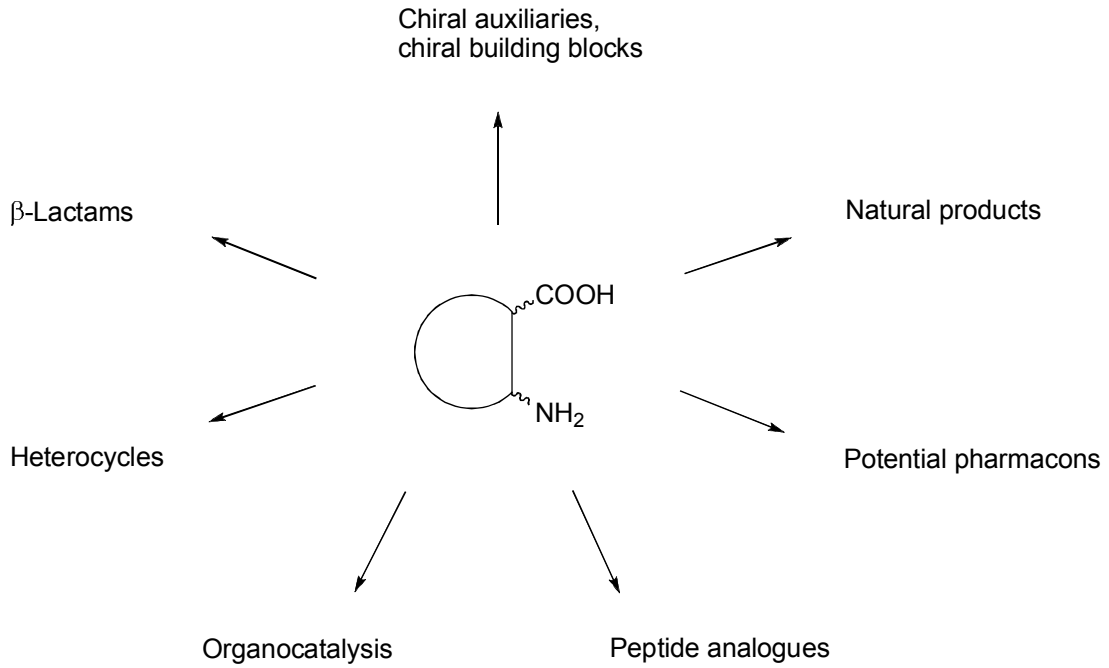
70

B. 1. 1. Cispentacin and other cyclic β-amino acids - Highly versatile scaffolds

Besides their pharmacological properties, cispentacin derivatives were also introduced into peptides modifying their biological activity.[6] In this context, e.g. the turn inducing properties of a bicyclic cispentacin derivative in gonadotropin-releasing hormone (GnRH) analogues was studied by *Mulzer et al.*[7]

Furthermore, cispentacin was also applied as organocatalyst in the *Hajos-Perrish-Eder-Wichert-Sauer* reaction by *Davies et al.*[76]

Figure 8. Different areas of application of 2-aminocycloalkanecarboxylic acids.[8]



All these examples show the enormous potential of cispentacin and its derivatives in different fields, thus making the development of new analogues for various applications, as depicted in **Figure 8**, a promising objective.

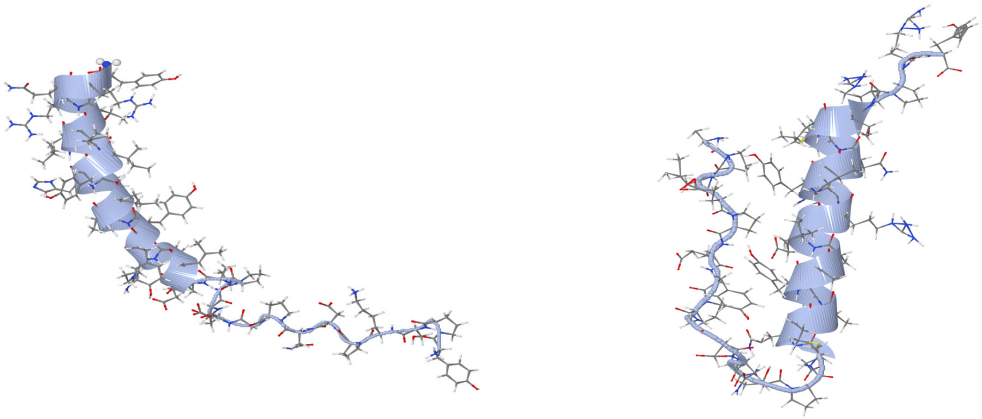
B. 1. 1. 2. Structure inducing amino acids in Neuropeptide Y (NPY) analogues

Neuropeptide Y is a *C*-terminally amidated 36 amino acid peptide and was first isolated from porcine brain in 1982 by *Tatemoto et al.*[9] It belongs to a peptide family consisting of peptide YY (PYY), pancreatic polypeptide (PP) and NPY itself. These peptides exert most of their biological effects through five G-protein coupled receptors (GPCRs) Y_1, Y_2, Y_4, Y_5 and y_6. However, there are reports that there might be many more subtypes[10] whereas the Y_3 receptor continues to be an enigma since it was cloned and shortly afterwards concluded not be a NPY receptor.[11]

NPY and PYY have a high affinity to Y_1, Y_2 and Y_5 whereas PP prefers the Y_4 receptor.[12] The PP and the PYY are mainly synthesised and released by intestinal and pancreatic cells whereas NPY is distributed in the central nervous system. In the periphery it is ubiquitous in the symphatic nervous system and it is also expressed in liver, heart spleen and in endothelial cells of blood vessels.[13]

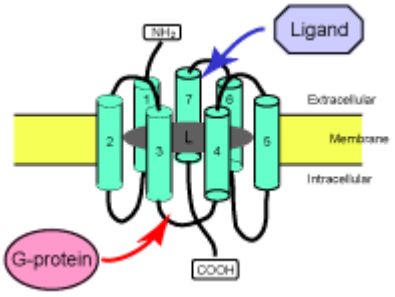
This peptide family was assumed to have a similar secondary structure due to its high sequence homology. The first three-dimensional structure of avian PP was determined by X-ray crystallography.[14] In this structure, which is called PP-fold, a type II β-turn connects a type II polyproline helix to an amphiphilic α-helix (**Figure 9**; *right*) forming a hairpin fold (PP-fold). In contrast, NMR studies have shown that the *N*-terminal segment of NPY bound to the membrane mimetic dodecylphosphocholine micelles extends like a flexible tail (**Figure 9**; *left*).[15]

Figure 9. Structures of NPY in the presence of micelles (left) and the PP-fold of bovine pancreatic polypeptide.[16]



The cloned Y_1, Y_2, Y_4 and Y_5 are all coupled to G_i and therefore mediate external stimuli by inhibition of cAMP synthesis. Their general structure is depicted in **Figure 10**. Furthermore, NPY receptors are reported to couple to phospholipase C and thus increase the intracellular calcium concentration by release of Ca^{2+} from intracellular stores.[17]

Figure 10. Structure of a GPCR.[18]



These different subtypes of NPY receptors play an important role in many different physiological processes like food intake, regulation of blood pressure, depression and many more (**Table 1**). However, the role of each receptor and its mediated physiological function is still not completely understood. Therefore, subtype selective agonists as well as antagonists are rewarding targets. There is already a quite large number of more or less selective, nonpeptidic as well as peptidic, ligands known.[19] They are very useful pharmaceutical tools in diagnostics as well as in therapy of many diseases since NPY is such a highly abundant peptide and is connected to a broad range of ailments.[20] Moreover, these selective ligands can contribute to the better understanding of the effects mediated by certain subtypes of receptors.

Table 1. Potential physiological roles of NPY and the receptors proposed to mediate those effects.[21]

Main physiological implications	Receptor(s) liable
Regulation of blood pressure	Y_1, Y_2
Food intake	Y_1, Y_2, Y_4, Y_5
Seizure regulation	Y_1, Y_2, Y_5
Anxiety	Y_1, Y_2, Y_5
Hypothalamic regulation of bone formation	Y_2
LH secretion	Y_1
Pain sensitivity	Y_1, Y_2
Depression	Y_1, Y_2
Regulation of GI motility	Y_2, Y_4
Angiogenesis	Y_1, Y_2
Ethanol consumption	Y_1

As incipiently mentioned, β-ACC units were already applied successfully as building blocks in biological active analogues of NPY and RGD peptides, inducing a particular spatial orientation of important side chain moieties for their interaction with the respective receptor.[22] Biological testing of these peptides showed receptor subtype selectivity with a still high affinity for some of the derivatives. Conformational investigations could help to get a deeper insight into structure-activity-relationships of these peptides and their targets.

Especially, the introduction of (+)-β-ACC in the *C*-terminal part of truncated NPY analogues (NPY^{25-36}) led to peptides with good NPY Y_1 receptor selectivity.

The consideration to synthesise NPY analogues with unnatural amino acids was based on Ala scans showing the high importance of Arg^{33} and/or Arg^{35}. The replacement of these two arginine residues as well as of the *C*-terminal tyrosineamide using an (*L*)-alanine scan leads to significant decrease or complete loss of affinity.[23] Furthermore, other previous reports by *Beck-Sickinger* and *Cabrele*, who described different NPY analogues by changing different amino acids, also emphasise the importance of this prominent region.[24]

All these reports gave motivation to investigate different new unnatural amino acids in NPY analogues and furthermore to combine the principle of conformational influence of a restricted β-amino acid with a variety of side chains in one amino acid.

B. 1. 2. Synthesis of new cispentacin derivatives

B. 1. 2. 1. Synthesis of the γ-butyrolactone framework

In the synthetic efforts towards new amino acid structures the γ-butyrolactone scaffold was envisaged to be an appropriate moiety for the syntheses of new β- and γ-amino acids, since lactones have a high potential for various modifications by different ways of ring opening giving rise to many alterations.

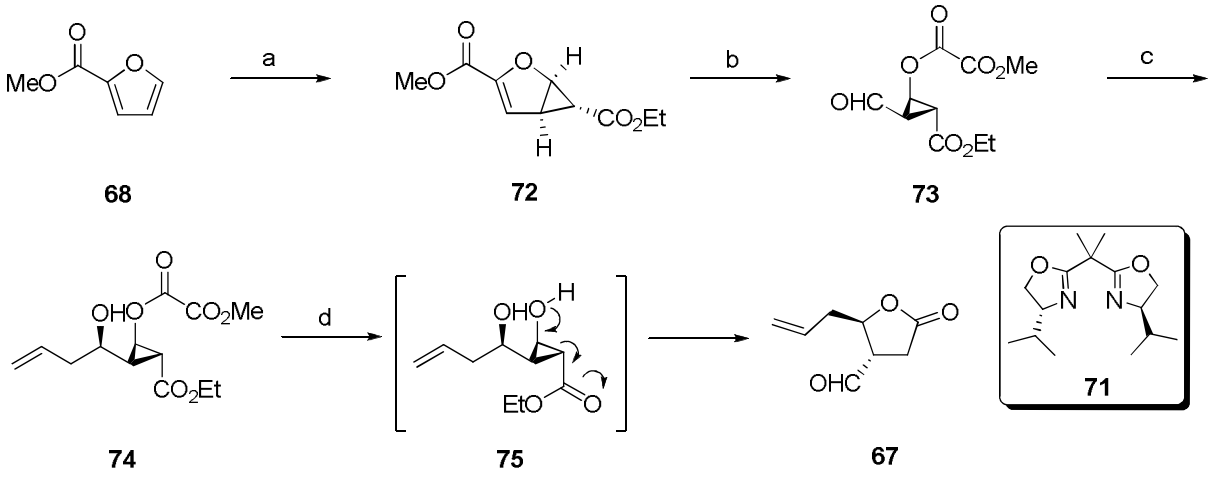
γ-Butyrolactones are a widely spread structural motif in numerous natural products. Therefore many synthetic approaches towards diverse mono- and polycyclic γ-butyrolactone scaffolds are known.[25]

A very elaborate strategy en route to monocyclic *anti*-4,5-disubstituted γ-butyrolactone aldehydes (**Scheme 14**) was first reported in 2001 by *Reiser et al.* in the synthesis of (-)-roccellaric acid using an asymmetric cyclopropanation of furans as one of the keysteps.[26] The possibility of introducing various allylic side chains as well as the high modification potential of the aldehyde functionality makes it an interesting and versatile building block. Therefore, this scaffold was chosen for the preparation of various new amino acids.

The initial step of this synthesis is the copper(I)-catalysed cyclopropanation of 2-furoic methyl ester (**68**) using ethyl diazoacetate (EDA) in the presence of the C_2 symmetric bis(oxazoline) ligand **71** affords bicyclic **72** in 36 % yield with an enantiomeric excess of > 99 % after crystallisation. Ozonolytic cleavage of the remaining double bond in the bicyclic compound **72**, followed by a reductive workup, results in cyclopropane carbaldehyde **73** in

92% yield after recrystallisation from diethyl ether. The aldehyde functionality of **73** is then subjected to a *Sakurai* allylation using trimethylallylsilane, giving rise to **74** which is the stereoelectronic favoured diastereomer following the rules of *Felkin* and *Ahn*.[27] Subsequent treatment with a base gives the free cyclopropane alcohol intermediate **75**, being a donor-acceptor substituted cyclopropane hence highly unstable and collapses by forming an aldehyde via opening of the three-membered ring. A retro-aldol-lactonisation-cascade reaction yields the *trans*-substituted lactone **67** in 41 %. The rearrangement to **67** is reported to be initiated by *Okawara's* tetrabutyldistannoxane catalyst[28] or $Ba(OH)_2 \cdot 8H_2O$.[29]

Scheme 14. Synthesis of *anti*-4,5-disubstituted γ-butyrolactone aldehyde according to *Reiser et al.*



Reagents and conditions: (a) 0.75 mol% $Cu(OTf)_2$, 1 mol% **71**, $PhNHNH_2$, ethyl diazoacetate (10% – 15% solution in CH_2Cl_2, 1.3 equiv), 0 °C, 45%, after recrystallization 36 % (99% ee). (b) O_3, DMS (5.5 equiv), CH_2Cl_2, -78 °C → rt, 24 h, 92 %. (c) Allyl trimethylsilane (1.3 equiv), $BF_3 \cdot OEt_2$ (1.1 equiv), CH_2Cl_2, -78 °C. (d) $Ba(OH)_2 \cdot 8H_2O$ (0.51 equiv), MeOH, 0 °C, 24 h (41 %).

However, the commonly used barium hydroxide procedure is often problematic because of the formation of an emulsion during workup and the associated laborious extraction procedure. Facing this problem, some investigations on different reagents, in order to improve this step, were carried out. In here, the focus was on various basic ion exchange resins as well as organic bases. The results are summarised in **Table 2**.

Table 2. Overview of different reagents for the lactonisation of **74**.

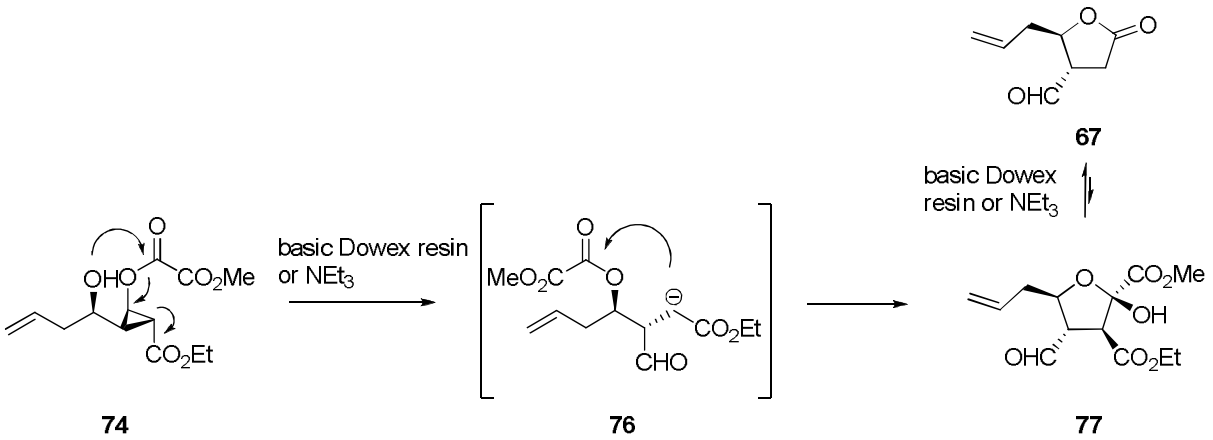
entry	solvent	reagent (properties)	yield [%]
1	methanol	$Ba(OH)_2 * 8H_2O$	41 - 63
2	methanol	Dowex® 1x2, (strong basic IER)	65
3	methanol	Amberlite® IRA-400, (strong basic IER)	a)
4	methanol	Amberlyst A21, (weak basic IER)	- b)
5	methanol	Amberlite® IRA-68, (weak basic IER)	a)
6	methanol	Dowex® 1x8 (strong basic IER)	a)
7	methanol	Ionenaustauscher III (strong basic IER)	a)
8	methanol	Amberlyst 15 (strong acidic IER)	- b)
9	methanol	Amberlite IR 120 plus (strong acidic IER)	- b)
10	methanol	DMAP	a)
11	methanol	triethylamine	69
12	methanol	DBU	a)
13	methanol	DABCO	a)
14	methanol	TMEDA	a)
15	methanol	p-TosOH	- b)
16	ethyl acetate	triethylamine	- b)
17	dichloromethane	triethylamine	- b)
18	diethylether	triethylamine	- b)
19	ethanol	triethylamine	a)
20	methanol (anhydr.)	triethylamine (anhydr.)	68

The solvents were, if not otherwise indicated, used without any purification. All reactions were conducted at 0 °C. (a) no complete conversion after 24 h (TLC control); yield was not determined. (b) no conversion.

It could be shown, that triethylamine in methanol (entry **11** and **20**) is as effective as barium hydroxide concerning the yield, but allows a simplified workup. In this reaction a solid by-product was isolated and indentified as a mixture of oxalic esters which were not, like in the reaction with barium hydroxide hydrolysed to the corresponding oxalic acid. The use of basic Dowex resin (entry **2**) gave good yields on a small scale. During scale up of the reactions the yields dropped tremendously.

Moreover, the lactonisation with triethylamine as well as with basic Dowex resin were shown to give a by-product **77** which is claimed to be in an equilibrium with the desired product **67**[30] and can therefore be transformed to the very. The proposed mechanism of the formation of this secondary product starts with a shift of the oxalic ester moiety to **76** which is followed by the formation of acetal **77** as a diastereomeric mixture (80:20).

Scheme 15. Proposed mechanism of the formation of the by-product in the lactonisation reaction using triethylamine or basic Dowex ion exchange resin.



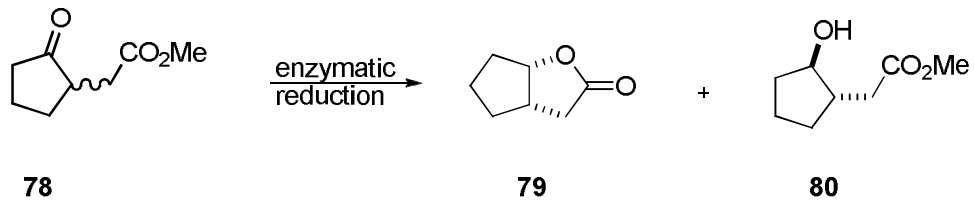
Due to all these problematic side products and side reactions the 'classic' barium hydroxide procedure was applied on large scale lactonisation reactions.

The aldehyde in this final *anti*-4,5-disubstitued γ-butyrolactone **67** is now assumed to give rise to the desired cispentacin precursors via an intramolecular [3+2] nitrone cycloaddition.

B. 1. 2. 2. Synthesis of lactone fused cyclopentanes

There is only a rather limited number of possibilities in the literature for the direct construction of lactone fused cyclopentanes. Apparently, the intramolecular esterification is the simplest approach. Thus, a very straightforward strategy is the selective reduction of racemic γ-ketoester **78** either by metal catalysts[31] or enzymes[32] followed by lactonisation to **79** or the resolution of the corresponding *trans*-γ-hydroxyester (**80**) followed by epimerisation and lactonisation (**Scheme 16**).[33]

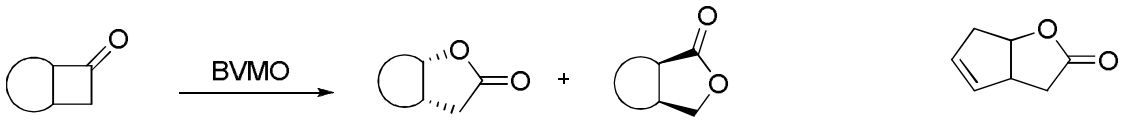
Scheme 16. Conversion of γ-ketoester to a fused cyclopentane.



78 **79** **80**

Furthermore, the desired bicyclic lactones can be obtained by a Baeyer-Villiger oxidation of bicyclic butenones as described in the synthesis of the *Grieco* lactone[34] **81** which is a commercially available starting material for many natural product syntheses especially for eicosanoides like prostaglandin and thromboxane derivatives.[35] A related methodology utilises the Baeyer-Villiger monooxygenase (BVMO), an enzyme mediating a regiodivergent biooxidation of fused bicyclic ketones. Here, racemic starting material is converted to two regioisomers, in which either the more substituted or the less substituted carbon centre can undergo migration thus leading to the 'normal' or the 'abnormal' lactone (**Scheme 17**).[36]

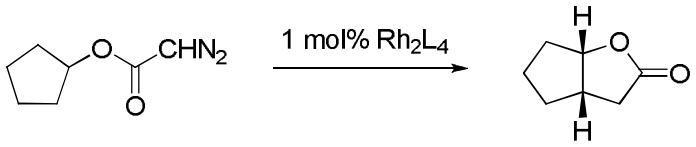
Scheme 17. Regioselective enzymatic Baeyer-Villiger oxidation of fused bicyclic ketones; *Grieco* lactone **81**.



'normal' 'abnormal' **81**

Another interesting approach is a carbon-hydrogen insertion of cyclopentyl diazoacetate catalysed by dirhodium(II) carboxamidates as reported by *Doyle et al.* in 2005.[37] Here, the *cis*-fused lactone cyclopentanes were synthesized in good yield with an enantiomeric excess of 93% (**Scheme 18**). Moreover, there are some other methods in the literature including radical cyclisation using tributyltin hydride[38] or catalytic asymmetric cyclocarbonylation.[39]

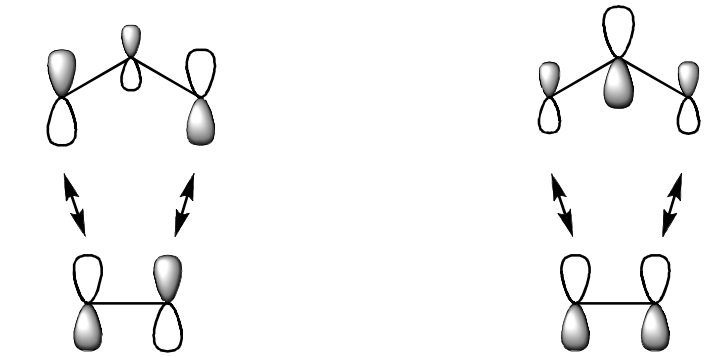
Scheme 18. Dirhodium mediated C-H insertion in the synthesis of lactone fused cyclopentanes.



Another quite common methodology to build up bicyclic frameworks utilises cycloaddition reactions.

Cycloaddition reactions are among the most useful and elegant types of reactions to increase intricacy[40] in molecules by a quite simple transformation. 1,3-dipolar cycloadditions[41] are reactions that follow a $[\pi 4_s + \pi 2_s]$ paradigm and proceed through a 6π-electron 'aromatic' transition state, means concerted. These reactions between the 4π component (1,3-dipole) and the 2π component (dipolarophile) lead to five-membered heterocycles.[42] They are mainly controlled by HOMO (dipole) - LUMO (dipolarophile) or HOMO (dipolarophile) – LUMO (dipole) interactions as depicted in **Figure 11**. Moreover, these interactions can be classified as so-called *Sustmann* types depending on the electron demand of the dipole as well as of the dipolarophile.[43]

Figure 11. Frontier molecular orbital (FMO) interactions in 1,3-dipolar cycloadditions.



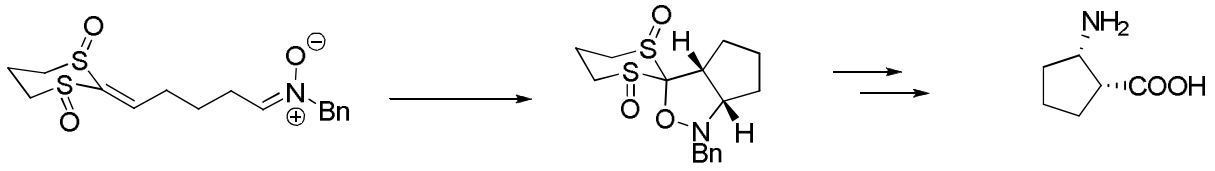
HOMO Nitrone
LUMO double bond

LUMO Nitrone
HOMO double bond

In the case of nitrones this cycloaddition leads to the formation of an isoxazolidine which can be easily converted to amino alcohols, amino acids and other derivatives. This methodology was already used by *Aggarwal et al.* in the synthesis of (-)-cispentacin (**Scheme 19**).[44] In here,

the ketene dithioacetal **82** undergoes a cycloaddition to afford isoxazolidine **83**. This intermediate could than be easily transformed to cispentacin (**57**). However, the derivatisation of this cispentacin core is not trivial.

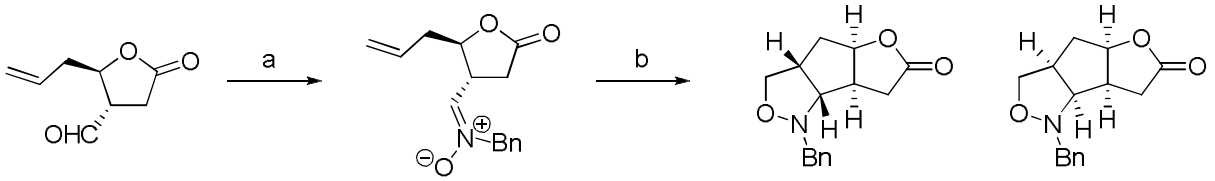
Scheme 19. Keystep in *Aggarwal's* synthesis of (-)-cispentacin (**57**).



82 **83** **57**

In the approach towards β- and γ-amino acids the highly functionalising intramolecular 1,3-dipolar cycloaddition reaction was applied as well. In this course, γ-butyrolactone **67** was treated with *N*-benzylhydroxylamine hydrochloride in the presence of $NaOAc \cdot 3H_2O$ in an aqueous ethanolic solution to afford **84**. This nitrone intermediate could not be purified because of its instability on silica gel and its poor crystallisation properties. Attempts to cyclise the intermediate by heating in ethanolic solution, directly after nitrone formation, were not successful. Hence, the crude **84** after strict removal of water dissolved in anhydrous benzene and refluxed for 20 hours under nitrogen atmosphere to afford a diastereomeric mixture of *fused* cycloadducts **66a** and **66b** in a 3:1 ratio (**Scheme 20**). It is not surprising that *bridged* cycloadduct was not detected.

Scheme 20. Cycloaddition of nitrone **84**.



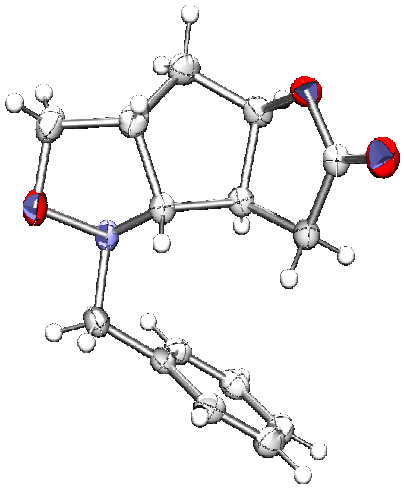
67 **84** **66a** **66b**

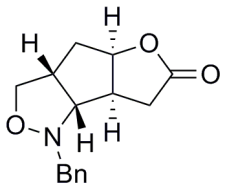
Reagents and conditions: (a) *N*-benzylhydroxylamine hydrochloride, $NaOAc \cdot 3H_2O$, ethanol/water (4:1), r.t., 2h. (b) Benzene, reflux, 20 h, 55%.

In both diastereomers all three five-membered rings are annulated in a *cis* fashion, but the quite high flexibility of the nitrone as well as of the terminal double bond allows the formation of two diastereomers in favour of the thermodynamically preferred **66a**. The ratio of 78:22 is in the range of comparable intramolecular nitrone cycloaddition (INC) reactions whereas it is suggested that the solvent and the reaction temperature play a crucial role[45] though this effect was not investigated in detail so far.

It should be mentioned that an epimerisation occurred during the cycloaddition at the 4a-*H* which is the most labile and therefore prone to isomerisation. First investigations of the two diastereomers using two-dimensional NMR spectroscopy already suggested that there is an inversion at one of the stereocenters since only a *cis* relationship of 4a-*H* to 5a-*H* adjacent to the lactone was detected. Hence, only a relative correlation determination of the stereocenters was possible. This observation was further confirmed by X-ray crystallography (**Figure 12**).

Figure 12. Determination of the relative stereochemistry by X-ray structure analysis of the major cycloadduct **66a**.



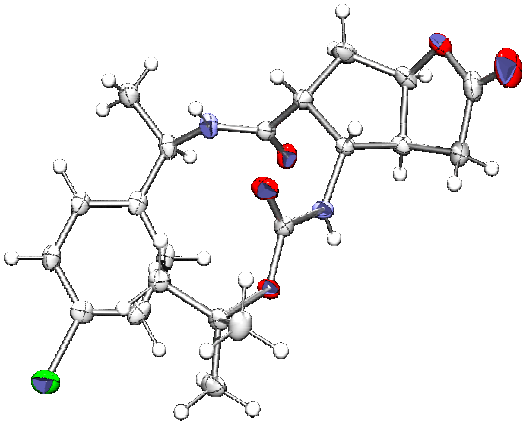


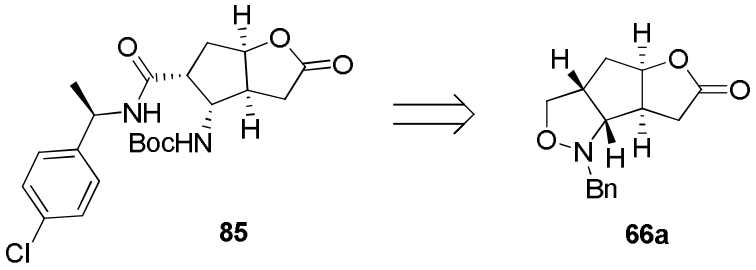
66a

Nevertheless, not only relative but also absolute stereochemistry needed to be determined. For that reason, a modified derivative of **66a** was prepared and coupled to (*R*)-1-(4-chlorophenyl)ethanamine which fortunately could be crystallised to give the desired information about the absolute stereochemistry of both **66a** (**Figure 13**) and **66b** taking in addition the two-dimensional NMR spectra into consideration. The X-ray structure proofed

the assumption that the α proton to the aldehyde and nitrone respectively is the most labile and is epimerised to give the less strained *cis* cycloaddition products.

Figure 13. X-ray structure of **85**.





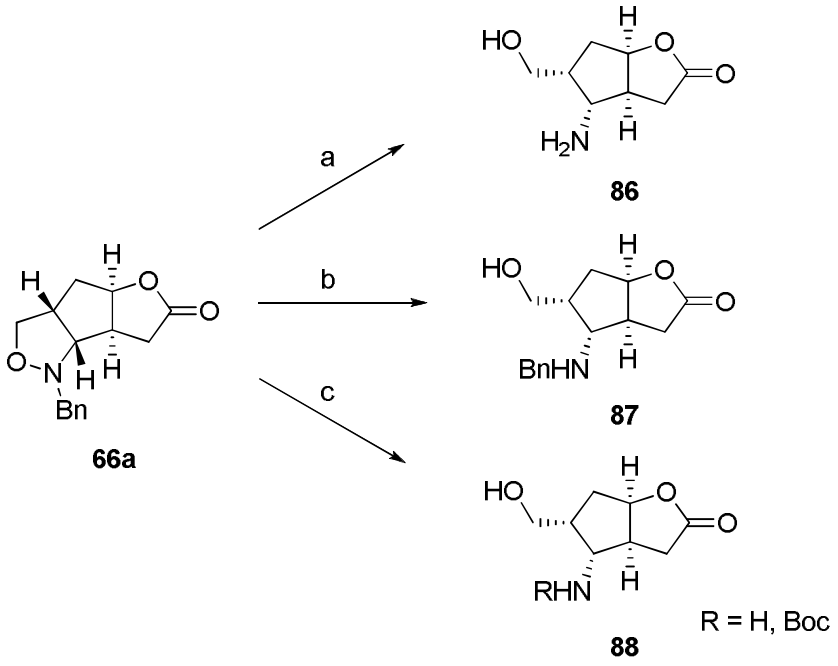
Having this valuable framework in hands a broad range of various cispentacin derivatives are accessible. Besides the formation of the desired scaffold, this valuable method provides also an amine as well as a carboxylic acid functionality precursor masked as isoxazolidine unit. Therefore, the conversion to the bicyclic cispentacin analogue can be achieved in a quite straightforward manner.

As mentioned before the isoxazolidine moiety can be easily transformed into the corresponding amino acid. Consequently, the lactone annelated cispentacin is accessible by a hydrogenation, protection and oxidation sequence.

Isoxazolidines are generally stable to hydrogenation conditions and furthermore benzyl protecting groups on amines are often difficult to remove too. Thus, it was not surprising, that hydrogenation with 10% Pd/C (atmospheric as well as higher pressures) did not affect the isoxazolidine moiety. Moreover, these building blocks are stable to a broad variety of other hydrogenation catalysts as well as to sodium amalgam or diimide.[46] Nevertheless, three

methods were applied that showed to be successful in *N-O* bond cleavage and debenzylation of the amine. The first nicely performing method was the use of ammonium formate in the presence of Pd/C which needed to be heated in refluxing methanol for 20 hours. In another successful methodology zinc and copper(II)acetate in acetic acid were utilised to selectively cleave the *N-O* bond without removal of the benzyl group on the amine. However, these two approaches need very harsh conditions like high temperature or the use of neat acetic acid. Due to these drastic reaction parameters the formation of by-products and some decomposition was observed. Furthermore, they are not really suitable for more sensitive functional groups. This fact made it necessary to find easier and milder methods. The mildest and also the most yielding conditions were found to be the use of $Pd(OH)_2/C$ (*Pearlman's* catalyst)[47] under atmospheric hydrogen pressure which also provides the possibility of an *in situ* Boc protection of the free amine, whereas the protection with different activated Fmoc species in one pot failed. The Pd(II) species in *Pearlman's* catalyst is reduced with hydrogen *in situ* and gives an extremely active catalyst. The high activity of *Pearlman's* catalyst is due to his quite high loading (20% $Pd(OH)_2/C$), which is very often advantageous for problematic debenzylations.[48] It is also reported to be highly selective for *N*-debenzylation, which can also be performed in presence of benzyl ethers.[49]

Scheme 21. Three pathways to the desired amino alcohols.



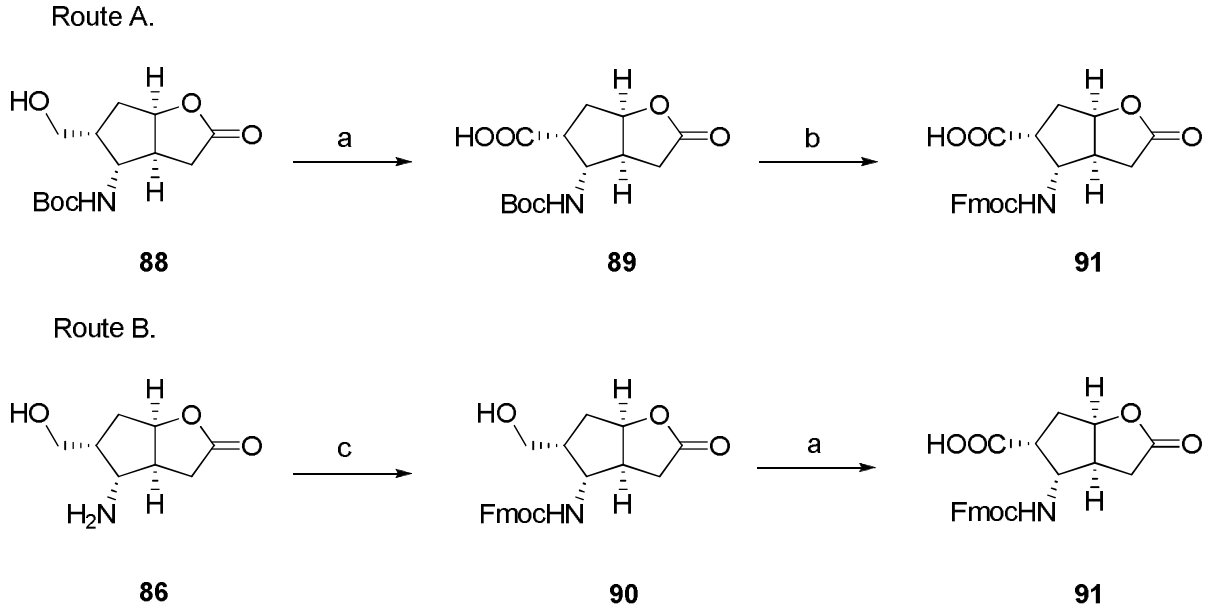
Reagents and conditions: (a) $Pd(OH)_2$-C, H_2, MeOH, overnight, quant. yield. (b) Zn/$Cu(OAc)_2$, AcOH, reflux, 5 h, 70 %. (c) Pd/C, NH_4CHOO, Boc_2O, MeOH, reflux, overnight, 76%.

For the synthesis of the various β-amino acids containing a cispentacin core it was necessary to think about further applications, and hence to choose the suitable protecting groups accordingly for the amine or the carboxylic acid respectively. Here, the synthesis of Boc protected β-amino cyclopentane carboxylic acid (β-APC), as well as the preparation of the Fmoc protected analogue will be described. Like it was shown before the Boc amino alcohol can be easily prepared *in situ* during hydrogenation in good yields.

For the preparation of Fmoc β-APC two routes are conceivable. On the one hand, simply by protecting the free amino alcohol and on the other hand the transposition of the Boc group by an Fmoc group. During first synthetic approaches the second, more extensive strategy was preferred since Fmoc chloride did not give satisfactory yields in the protection of amino alcohol **86** but of the corresponding amino acid (**Scheme 22**, Route A). However, Fmoc succinimide was applied successfully in the protection of the amino alcohols and therefore made the change of protecting groups redundant (**Scheme 22**, Route B). Unfortunately, an *in situ* Fmoc protection of the amino alcohol during the hydrogenation like reported by *Kessler et al.*[50] for a similar system was not successful.

The protected amino alcohols **88** and **90** now needed to be converted to the final target molecules.

Scheme 22. Two routes towards Fmoc β-APC.



Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O, 0°C to r.t., 90% (for **88**); 75% (for **90**). (b) (i) HCl/EtOAc, 0°C to r.t., quant. yield. (ii) FmocOSu, $NaHCO_3$, acetone/water, 24 h, 93 %. (c) FmocOSu, $NaHCO_3$, acetone/water, 73 % over two steps.

The oxidation to the carboxylic acid can be achieved by a two step process via the aldehyde using methods like *Dess-Martin* periodinane or *Swern* oxidation followed by treatment with $NaClO_2$. These methods provided the product in reasonable yields. However, a conversion in one step would be favourable. Unfortunately, there are only a quite limited number of methods known which often involve toxic Cr(VI) compounds under harsh conditions like in the Jones oxidation, which are incompatible to the sensitive functionalities in the molecule. A classical and mild method is the use of molecular oxygen in the presence of a platinum catalyst that should also be selective for primary alcohols.[51] Regrettably, this approach did not show satisfactory results. The method of choice upon this was the employment of RuO_4[52] which was generated from catalytic amounts of $RuCl_3$ in the presence of the stoichiometric oxidant sodium metaperiodate. Here, the methodology of *Sharpless et al.*, avoiding the formation of lower valent ruthenium carboxylate complexes, was employed.[53]

This sequence gave rise to Fmoc-β-ACP (**91**) from **67** in 55%, and to Boc-β-ACP (**89**) in 68% overall yield.

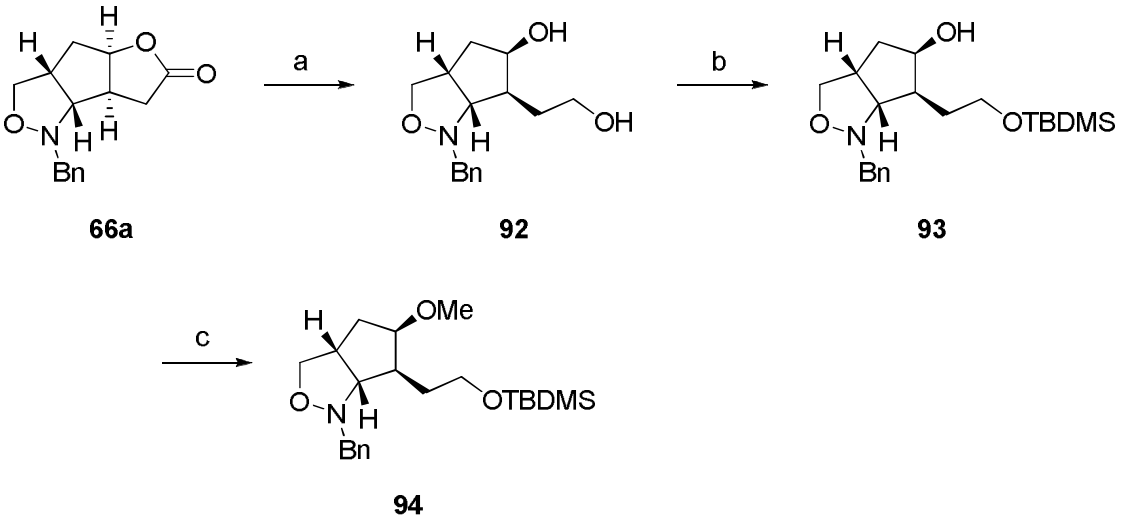
B. 1. 3 Modification of the lactone moiety – Synthetic access to different α-amino acid side chains

Having this lactone annelated cispentacin in hand there are now a variety of conceivable modifications. For this purpose, the lactone moiety is a very versatile building block since it can be enolised, hydrolysed or reduced to the corresponding aldehyde or diol respectively. These transformations allow a broad range of alterations. However, basic hydrolysis of the lactone was not possible because of relactonisation upon acidic workup. Furthermore, attempts using boron triiodide-*N*,*N*-diethylaniline complex[54] or hydrobromic acid under various conditions[55] failed. For different modifications, reduction of the lactone to the corresponding diol was envisaged to be the method of choice.

The synthesis of the hydroxyl β-APC started from the cycloaddition product **66a**. For the reduction lithium aluminiumhydride was used obtaining **92** in quantitative yield. For the aqueous extraction a *Rochelle*'s salt solution was helpful to remove all formed aluminates. The reduction was followed by a selective protection of the primary alcohol. This was achieved using TBDMS chloride in the presence of triethylamine and a catalytic amount of DMAP. This selective protection yielded **93** in 92 % yield. The TBDMS group was chosen because of its good stability towards basic and slightly acidic conditions but nevertheless easy removability under strong acidic conditions or in presence of fluoride ions which have a high affinity for silicon.

The protection of the secondary alcohol was accomplished using iodomethane in the presence of sodium hydride as a base to **94** (**Scheme 23**).

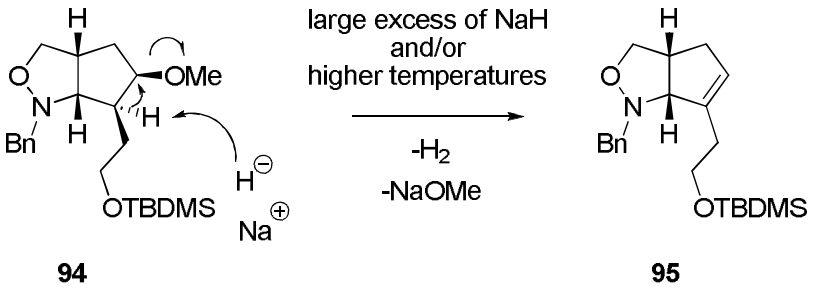
Scheme 23. Synthesis of the doubly protected diol **94**.



Reagents and conditions: (a) LAH, THF, 0°C, 1h, 98%. (b) TBDMSCl, NEt_3, DMAP, CH_2Cl_2, 18 h, 92%. (c) MeI, NaH, THF, 86%.

During this reaction elimination product **95** was observed occasionally. Therefore, the reaction conditions, namely the amount of sodium hydride and especially the temperature needed to be monitored carefully. An elimination product was observed when a large excess of sodium hydride was used or at temperatures above 30 °C. The formation of this elimination product is depicted in **Scheme 24**.

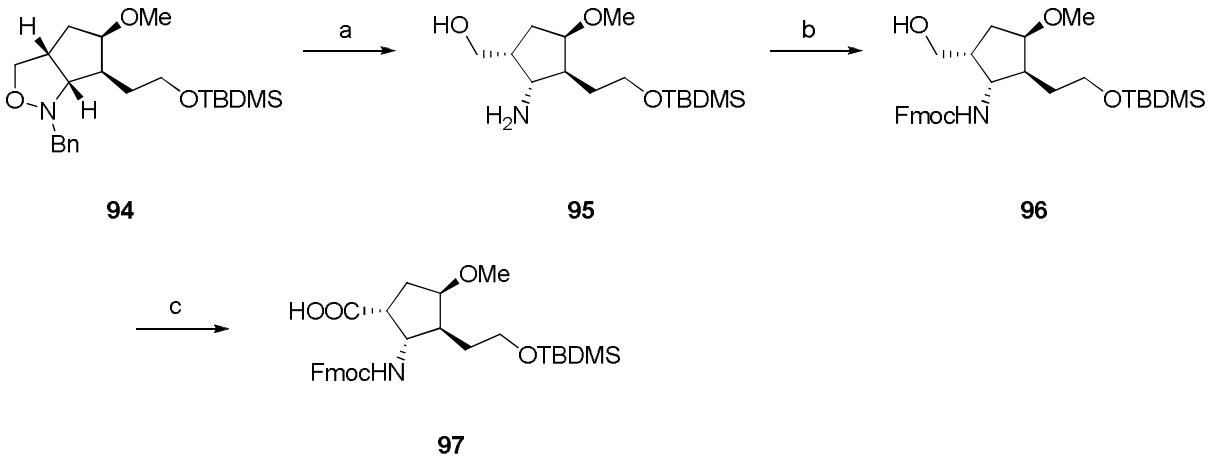
Scheme 24. By-product formation during the protection of the secondary alcohol in **94**.



However, using 1.5 equivalents of sodium hydride and 5 equivalents of iodomethane the protected product can be isolated in 86 %.

The additional steps of the synthesis including hydrogenolytic *N-O* and *N*-benzyl cleavage followed by Fmoc protection and oxidation were performed accordingly to the abovementioned protocol (**Scheme 25**).

Scheme 25. Final steps of the synthesis of the doubly protected hydroxyl β-ACP.



94 **95** **96**

97

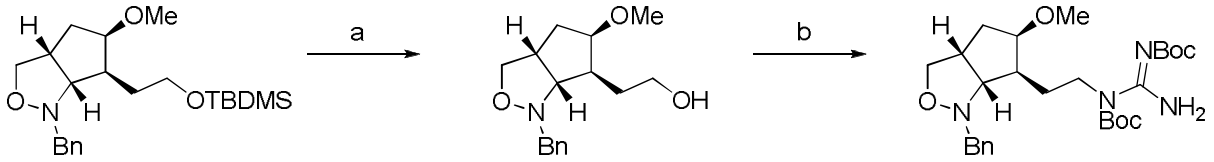
Reagents and conditions: (a) $Pd(OH)_2$-C, H_2, MeOH, overnight, quant. yield. (b) FmocOSu, $NaHCO_3$, acetone/water, 24 h, 86%. (c) $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O, 0°C to r.t., 74%.

Naturally, the methodology of modifying the side chain of the cispentacin scaffold can be further exploited. Demonstrating this high versatility, a conformationally restricted homoarginine derivative with a β-APC backbone was prepared. For this purpose, a similar route as in the synthesis of hydroxyl β-APC was chosen diverging at the stage of protected isoxazolidine **94**.

The acid lability of the silyl protecting group was utilised to selectively deprotect the primary alcohol of **94** using acetic acid.[56] The hydroxyl group now needs to be converted to a guanidine. There are several methods and reagents for the preparation of guanidines[57] but almost all of them involve the conversion of an amine to a guanidine. For this purpose a broad range of reagents is available but their utility is limited by the availability of the starting amines. However, there is a very efficient and mild method for the preparation of guanidines without using amines as a starting material. Employing a Mitsunobu protocol and *N*,*N*-bis(*tert*-butyloxycarbonyl)guanidine or *N*,*N*-bis(benzyloxycarbonyl)guanidine as nucleophiles protected guanidines can be generated starting from an alcohol.[58] In this synthesis the

deprotected primary alcohol (**98**) was reacted with a doubly Boc protected guanidine which was prepared from guanidinium hydrochloride and Boc_2O giving **99** in 76% yield.[59]

Scheme 26. Acidic deprotection of the TBDMS alcohol followed by guanidinylation using a Mitsunobu protocol.

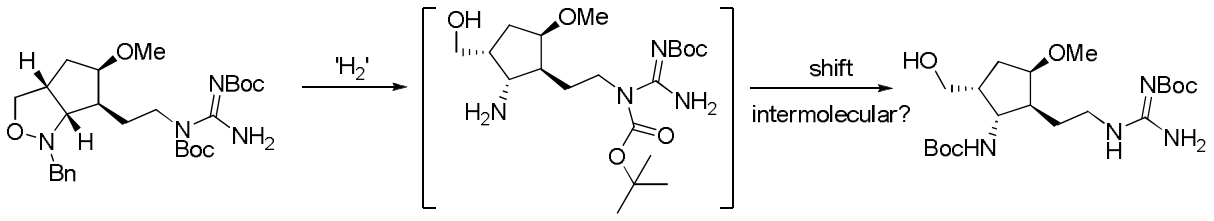


94 **98** **99**

Reagents and conditions: (a) AcOH, THF/water, 0°C to r.t., 88%. (b) *N*,*N*-bis(*tert*-butyloxycarbonyl)guanidine, PPh_3, DEAD, THF, 0°C to r.t., 76%.

The synthesis of the cispentacin arginine analogue was subjected to similar conditions like in the aforementioned protocols. The opening of the isoxazolidine and the debenzylation with $Pd(OH)_2$ under hydrogen at atmospheric pressure was followed by Fmoc protection. However, during the hydrogenolytic formation of the free amine **100** an undesired carbamate shift of the Boc group of ε-*N* in guanidine to the free amine occurred. The following addition of FmocOSu then gave rise to a mixed Boc, Fmoc protected guanidine **101** in 69% yield.

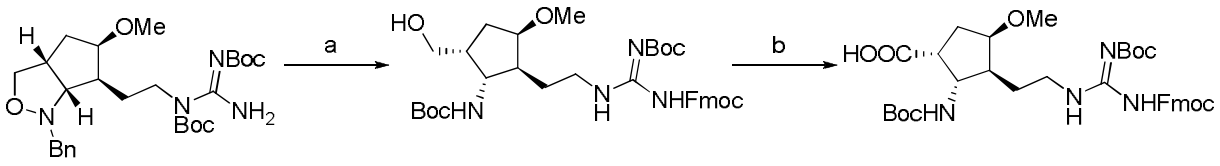
Scheme 27. Boc-shift during hydrogenation.



99 **100** **101**

This lability of δ-N-Boc groups in arginine and its tendency to migrate was already reported by *Goodman et al.*[59] This observation suggests that this shift is an intermolecular process due to quite high spatial distance between the β- and the ε-Boc-*N*.

Scheme 28. Synthesis of mixed Fmoc, Boc protected guanidinium β-APC.



99 **101** **102**

Reagents and conditions: (a) $Pd(OH)_2$-C, H_2, MeOH, overnight, quant. yield. (b) FmocOSu, $NaHCO_3$, acetone/water, 5 h, 69%. (c) $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O, 0°C to r.t., 65%.

The final oxidation of compound **101** using $RuCl_3$ afforded **102** in 65% yield.

B. 1. 4. Application of new cispentacin analogues in peptides

B. 1. 4. 1. Solid phase peptide synthesis (SPPS)

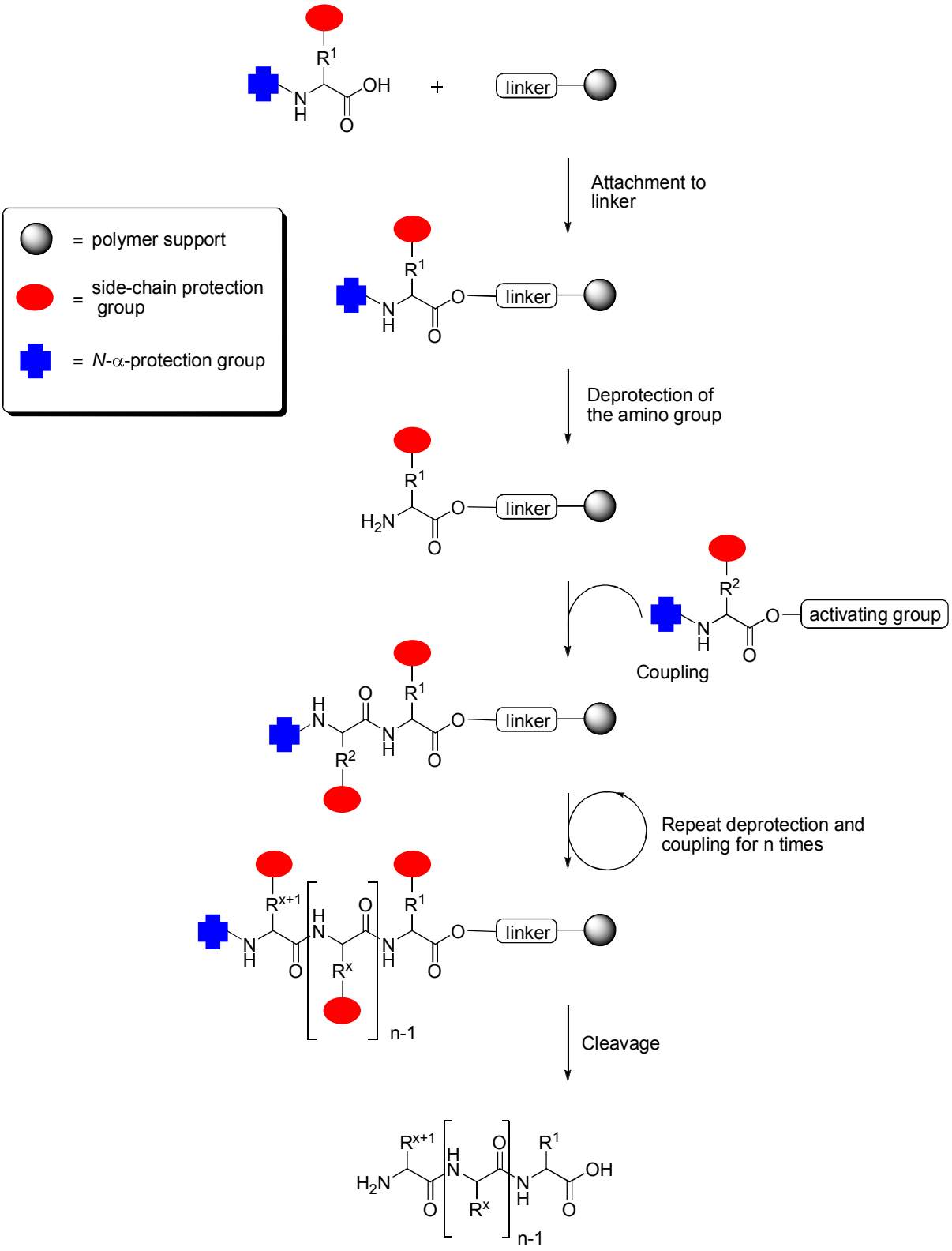
"*To equal Nature […] I therefore foresee the day when physiological chemistry will not only make extensive use of the natural enzymes as agents, but when it will also prepare synthetic ferments for its purposes.*"[60]

This dream of *E. Fischer*, which he envisioned in his Nobel lecture in 1902, made him one of the first chemists thinking of the artificial preparation of large biological active macromolecules. However, it took until the early 1950s when *Vigneaud et al.* initiated a new era in biology and chemistry by the isolation, determination of structure and, most important, synthesis of oxytocin and analogues.[61] The work in this field was also honoured with the Nobel price in 1955. During this period more and more peptides were characterized but could be isolated often enough only in small quantities. This development, and in addition the need of peptide analogues to study structure-activity-relationships (SAR), made it necessary to synthesise these desired compounds. With increasing intricacy of the peptides the classical method of solution phase peptide synthesis met its limits, since the coupling reactions gave only moderate overall yields which were often contaminated with side products. These problems stimulated many scientists to think of more sophisticated techniques to produce peptides. The breakthrough was the work of *R. B. Merrifield* who conceived and elaborated the solid-phase alternative. In his approach the synthesis is still carried out in solution but the growing peptide chain is anchored on an insoluble solid support. The improved yields are due

to high excess of soluble reagents which can be removed simply by washing and filtration retaining the nascent peptide on the solid support.

The protection of the amino acids that are attached stepwise need a special orthogonal protection scheme. Two kinds of protection groups are required, on the one hand a temporary protection group which can be removed after each coupling step to free a reactive group that can then undergo the next coupling. On the other hand, there is a need for 'permanent' protection groups for the side chains of the amino acids which are stable to the coupling conditions but can be selectively cleaved at the end of the synthesis to gain the free peptide. Most established is the Fmoc/^{t}Bu chemistry,[62] what means that the amino group that needs to be coupled is protected with the base labile Fmoc group and can be easily removed *in situ* by using piperidine. Therefore, the side chains of the amino acids having reactive functional groups demand a base stable protecting group. Generally, acid labile protecting groups are chosen (e.g. ^{t}Bu and Boc) to afford the free peptide in one step contemporaneous to the cleavage from the resin which can be achieved under acidic conditions as well. This mild Fmoc strategy is favoured over the Boc SPPS since the repetitive TFA acidolysis of the Boc group can lead to decomposition or alterations of sensitive peptides. Furthermore, this approach often needs dangerous HF for deprotection and cleavage from the resin.

Scheme 29. General scheme of SPPS.[63]

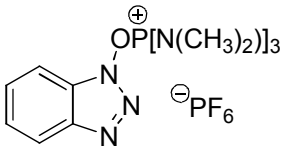


The solid support resins for SPPS need to be of small, low cross-linked particles which can swell more then 6-fold in volume giving the possibility for a fast diffusion of reagents. The simplest used resins are polystyrenes like chloro- or aminomethylpolystyrene which are crosslinked (~ 1% cross-linked) with divinylbenzene. However, these materials where supplanted by polystyrene-polyethylene glycol graft polymers (PEG-PS, TentaGel or NovaSyn® TG) and polyethylene glycol dimethyl acrylamide co-polymers (PEGA) with a loading capacity between 0.2 and 0.8 mmol per g depending on the degree of branching.
For SPPS these polymers need to be functionalised with different linkers depending on the applied requirements and coupling strategy. For the Fmoc/^{t}Bu strategy the commonly used resins can be divided into four subgroups:[64]

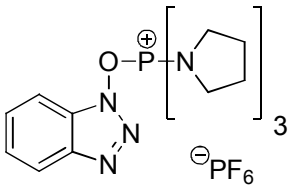
a. The Wang linker (4-Alkoxybenzyl alcohol resin)
b. The more acid-labile SASRIN^{TM} linker (2-Methoxy-4-alkoxybenzyl alcohol resin) having the same structure like the Wang resin but with the addition of a methoxy group, which leads to the free peptide acids.
c. Fmoc-amide resin (2,4-Dimethoxy-4'-[carboxymethyloxy]-benzhydrylamine linked to amino methyl resin) and the Rink amide linker which lead to C-terminal amidated peptides.
d. Traceless linker like the silyl linkers, which gained their name from the fact, that the final compound does not reveal the point of linkage to the solid phase.

As a matter of course many combinations and subtypes of these basic subtypes are commercially available.
The coupling of the amino acids to the resin starts with the modification of the resin and linker respectively in a way that a free accessible functionality is gained whereon the first (*C*-terminal activated) Fmoc-amino acid is coupled. After this initial step the *N*-terminal Fmoc group is removed by treatment of solutions of piperidine and/or DBU to free the amino group which is then prone to the attachment of the next Fmoc-amino acid. Activation of these amino acids can be accomplished by using carbodiimides, preformed symmetrical anhydrides or active esters like OBt or OPfp esters. However, the most commonly used strategy in SPPS is the *in situ* activation of the carboxylic acids. For this process a wide range of activation reagents is known (**Figure 14**). These reagents are extremely helpful in forming HOBt, succinimidyl or other active esters.

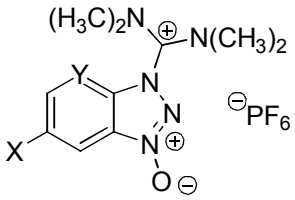
Figure 14. Coupling reagents in SPPS.



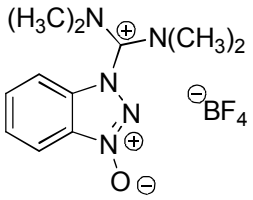
BOP



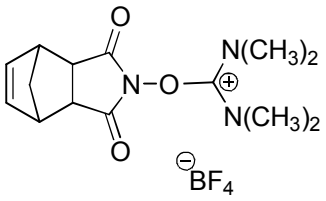
PyBOP®



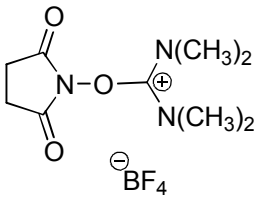
X=H, Y=CH: **HBTU**; X=H, Y=N: **HATU**; X=Cl, Y=CH: **HCTU**



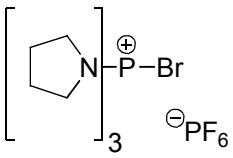
TBTU



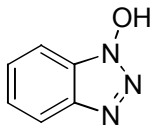
TNTU



TSTU



PyBrOP®

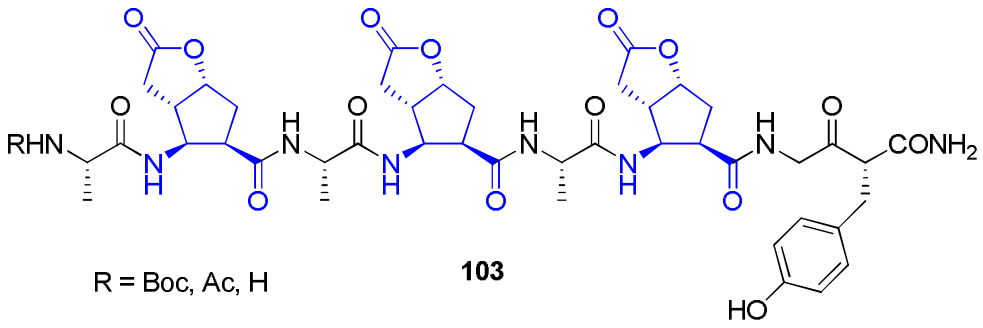


HOBt

The abovementioned β-amino acids were investigated concerning their behaviour in peptides. Therefore, some of the cispentacin analogues were coupled in a SPPS approach.

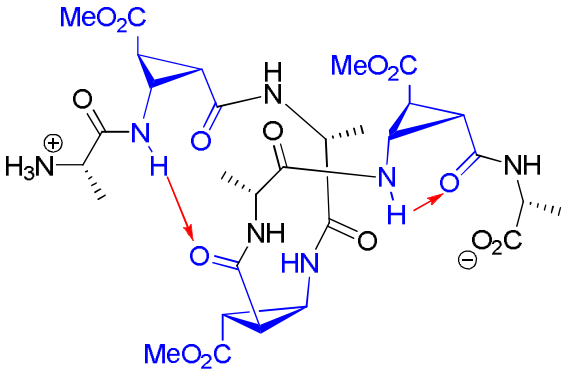
The primarily approach was the synthesis of a α-β-alternating peptide of **91** and (*L*)-Ala (**Figure 15**).

Figure 15. α-β-Alternating peptide from **65** and (*L*)-Ala.



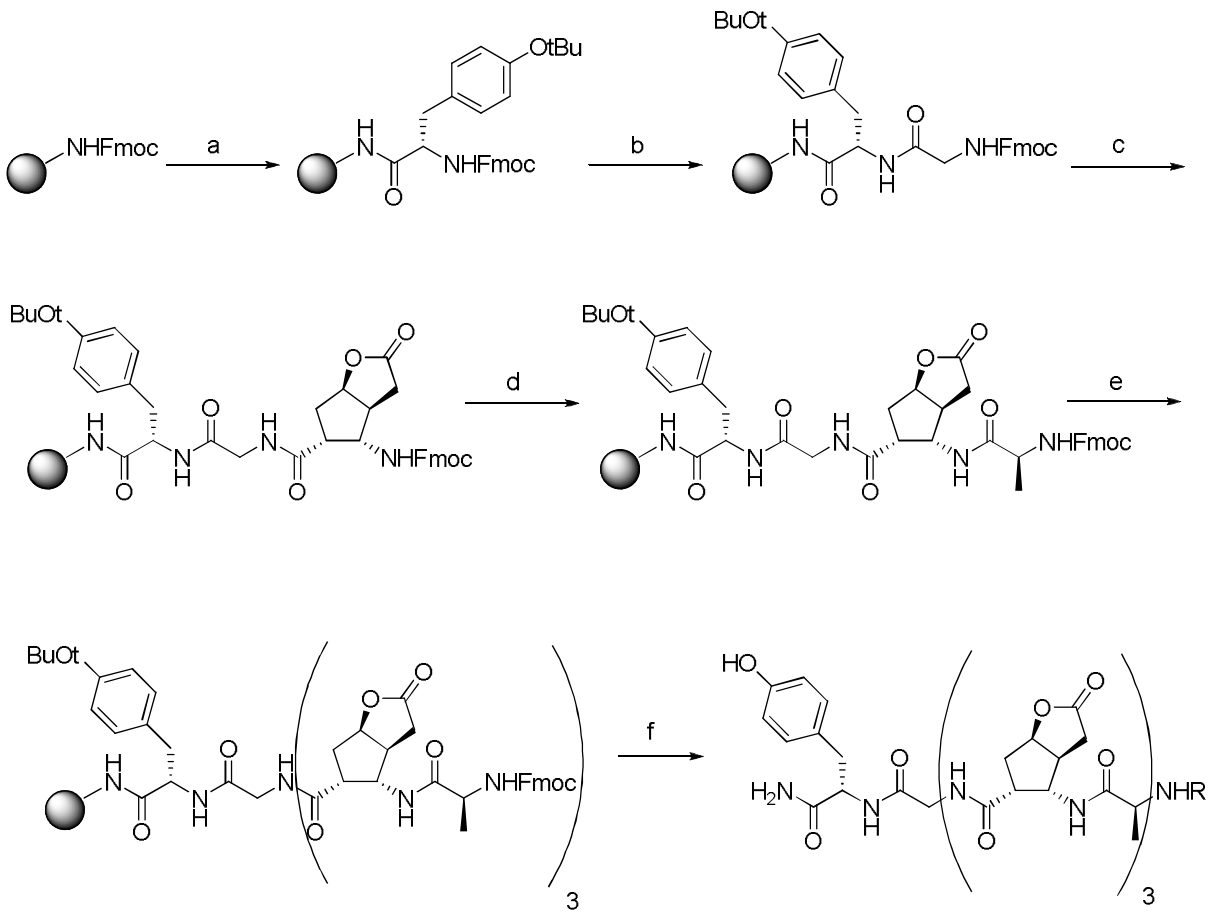
This sequence was chosen to examine the coupling performance of **91** in SPPS and as potential new foldamers building block akin to the α-β-peptides of β-ACC which were shown to adopt a helical conformation (**Figure 16**).[65]

Figure 16. Helical conformation of short (*L*)-Ala-β-ACC peptide.



Fortunately, this synthesis showed that the standard coupling procedures for SPPS could be applied and no racemisation or ring opening of the lactone occurred. The synthesis was performed on the commercially available Fmoc-protected Rink amide MBHA resin with a loading of 0.64 mmol/g (**Scheme 29**). Cleavage of the Fmoc group with piperidine provided the free amine which was subsequently coupled with the first amino acid, Fmoc-Tyr(OtBu)-OH. In the following steps the same deprotection-coupling protocol was applied. Finally the peptide was removed from the resin with a 'cleavage cocktail' (TFA/TIS/H_2O 90:5:5) providing the three differently *N*-terminal modified peptides of **103**.

Scheme 29. Synthesis of α-β-alternating peptides.



Reagents and conditions: (a) (i) 40% Piperidine in DMF/NMP (80:20), (2 x 5 min). (ii) Fmoc-Tyr(OtBu)-OH (5 equiv), HBTU (5 equiv), DIPEA (10 equiv), DMF, 1 hr. (b) (i) 40% Piperidine in DMF/NMP (80:20), (2 x 5 min). (ii) Fmoc-Gly-OH (5 equiv), HBTU (5 equiv), DIPEA (10 equiv), DMF, 1 hr. (c) (i) 40% Piperidine in DMF/NMP (80:20), (2 x 5 min). (ii) Fmoc-Acp-OH (3 equiv), HBTU (3 equiv), DIPEA (6 equiv), DMF, 1.5 hr. (e) (i) 40% Piperidine in DMF/NMP (80:20), (2 x 5 min). (ii) Fmoc-Ala-OH (5 equiv), HBTU (5 equiv), DIPEA (10 equiv), DMF, 1 hr. (iii) repeat (c) and (d) twice. (f) TFA/TIS/H_2O, 1.5 hr.

1. 4. 2. Structural investigations of α-β-peptides and biological activity of NPY analogues

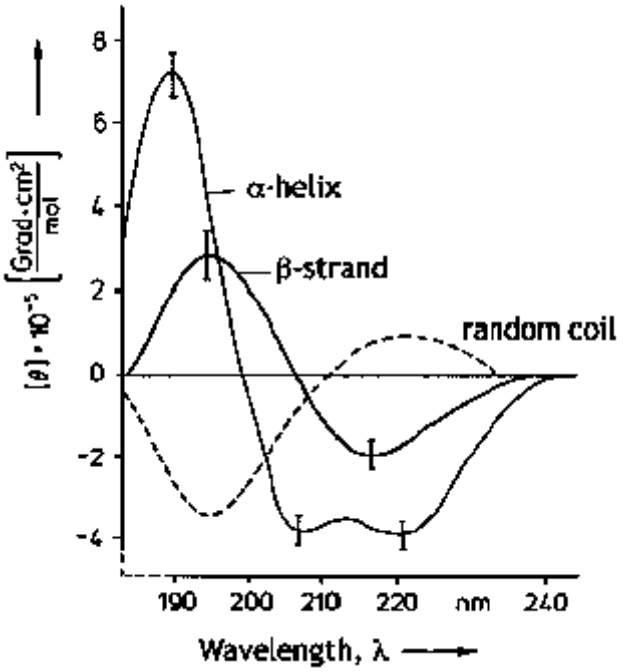
All of the three peptides were purified by preparative HPLC and subsequently investigated by CD- as well as two-dimensional NMR spectroscopy.

CD spectroscopy is a common method to investigate secondary structures in peptides and proteins. Circular polarised light interacts with optically active molecules depending on their secondary structure. When the optical active chromophore interacts with planar polarised

light, consisting of left and right circular polarised light, some parts of the spectrum are absorbed resulting in elliptically polarised light. The extent of this ellipticity can be measured after recombination of the left and right polarised light. The absorbance values of peptidic chromophores are due to a low energy nπ* transition centred around 220 nm and a higher energy ππ* transition around 190 nm.[66]

The typical CD spectra for α-peptides are shown in **Figure 17**.

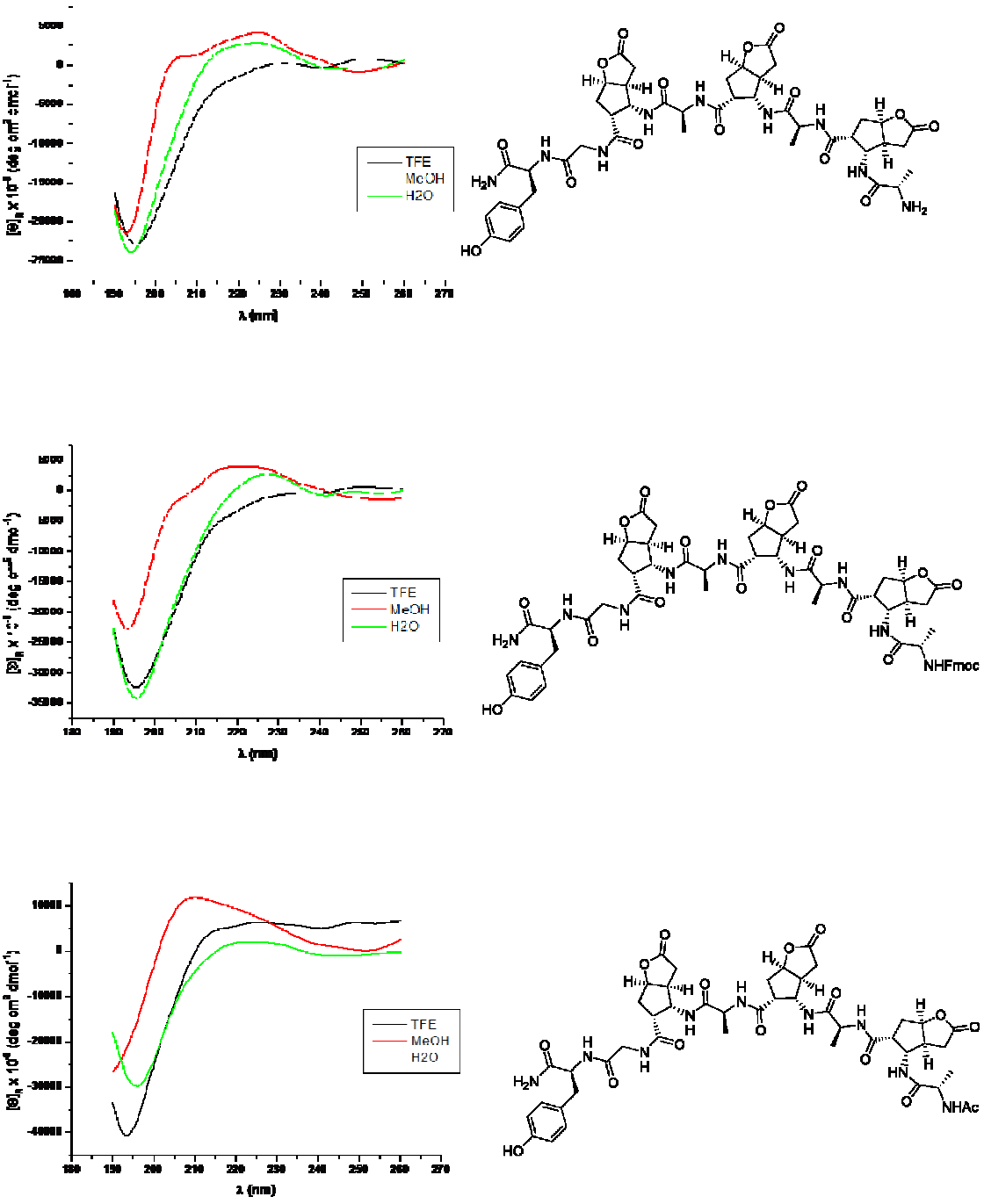
Figure 17. CD spectra of the common secondary structures seen for α-peptides.[67]



The CD spectra of α-peptides and proteins are well established but there are of course also examples for CD spectra of α-β-alternating and unnatural amino acid containing peptides respectively.[65]

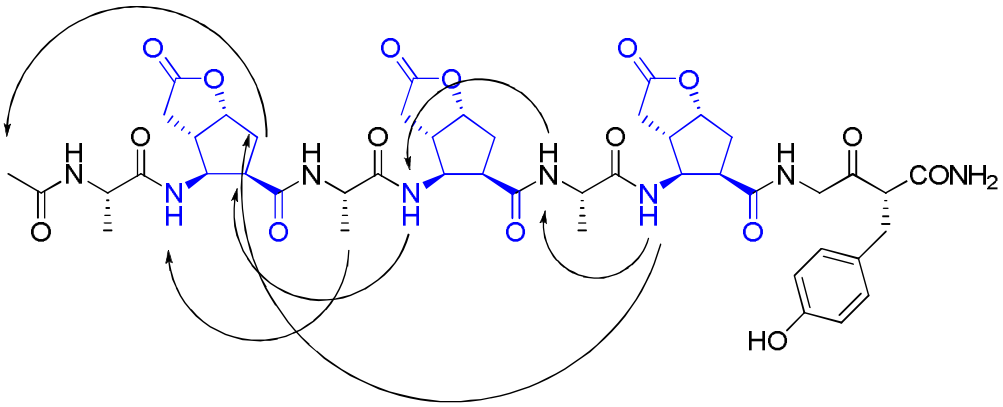
The three investigated peptides showed to be quite similar concerning their CD profile (**Figure 18**). The shapes of the graphs are comparable to the spectra of (*L*)-Ala-β-ACC alternating hepta- and nonapeptides which were shown to have a 3_{13} helical fold.[68] Moreover, the structure seems to be quite independent of the solvent having similar shapes in methanol, water and the helix promoting solvent TFE.

Figure 18. CD spectra of the three differently *N*-terminal modified α-β-peptides.



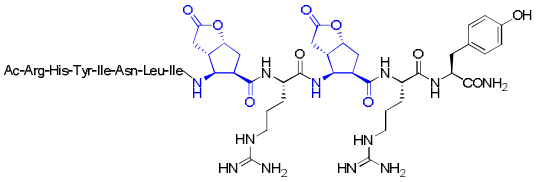
However, the quite high variability of the temperature coefficient (Δδ/ΔT) of the amide protons as well as the most prominent long range couplings in NOE spectroscopy (**Figure 19**) suggest that a well ordered structure was not present in this α-β-peptide.

Figure 19. Most prominent NOE contacts in peptide **103** (R=Ac).

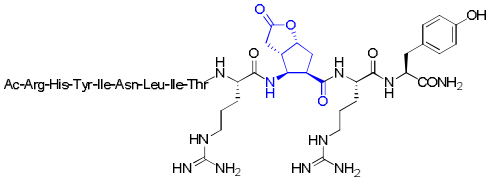


In the same way like shown in **Scheme 29** some NPY analogues were prepared. In this context, similar to β-ACC containing NPY analogues like **106** the cispentacin containing β-amino acids were incorporated into the peptide, namely in position 34 and 32 (in terms of the numbering of the natural peptide; **104** and **105**). These positions are of high importance since they are adjacent to the Arg33 and Arg35 which were shown to be highly important for activity as well as selectivity.[24] The substitution or removal of the *C*-terminal arginines were shown to be detrimental or resulted in complete loss of activity.

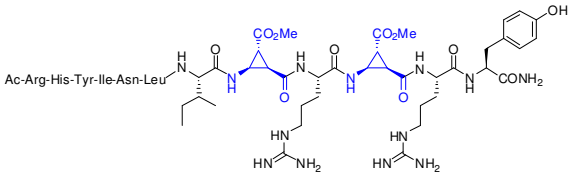
Figure 20. NPY analogues containing cispentacin derivative **65** (*left*) and containing β-ACC (*right*).



104



105



106

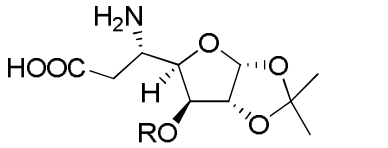
All cispentacin containing peptides were tested at the Department of Pharmaceutical/Medicinal Chemistry II, University of Regensburg concerning their affinity towards Y^1, Y^4 and Y^5 receptors using Ca^{2+} assay as well as fluorescence activated cell sorting (FACS). Unfortunately, their affinities were found to be only in a high micromolar range and therefore are not useful for any further pharmacological experiments.
Ultimately, the lactone fused and other cispentacin derivatives seem to have neither a similar nor beneficial effect when compared to β-ACCs.

B. 2. Preparation of a bicyclic β-proline derivative as potential new organocatalyst

B. 2. 1. Introduction

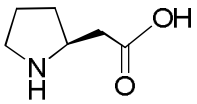
Since the pioneering work of *List et al.*[69] in the field of organocatalysis using proline in aldol reactions this field has emerged tremendously. Ever since, not only proline but an enormous number of amino acids and related compounds were utilised for various transformations in synthetic chemistry.[70] However, not only α-amino acid derivatives but also β-amino acids have attracted chemists and were successfully applied.
Interesting examples are the glycosyl-β-amino (**107**) acids derived from sugars which were applied in aldol reactions.[71] Moreover, the organocatalytic properties of (*S*)-homoproline (**108**),[72] homoproline tetrazole (**109**)[73] and homoproline sulfonamides[74] derivatives in various reactions are under investigation by several groups. Very recently, the constrained β-proline analogue and **110** was applied in organocatalytic Aldol reactions by *Armstrong et al.*[75] In their work they studied the influence of the acid geometry in the aforementioned reactions.
Even cispentacin (**57**) was shown to be a highly active and selective catalyst in the *Hajos-Perrish-Sauer-Eder-Wiechert* reaction.[76] The activity of the lactone *cis*-fused cispentacin derived from **66b**, which is described in this work, was also investigated in a quite limited preliminary study concerning its catalytic behaviour in this reaction and showed comparable results. Therefore, the lactone moiety blocking one side of the molecule did not show any effect to improve this reaction.

Figure 21. β-Amino acids in organocatalysis.



R = Me, Bn

107



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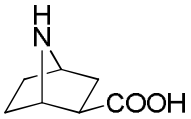
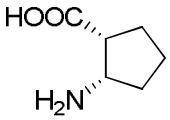
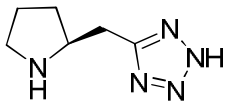


110



57



109

Nevertheless, restricting and sterically shielding fragments in organocatalysts are envisioned to be valuable for selectivity in catalysis.

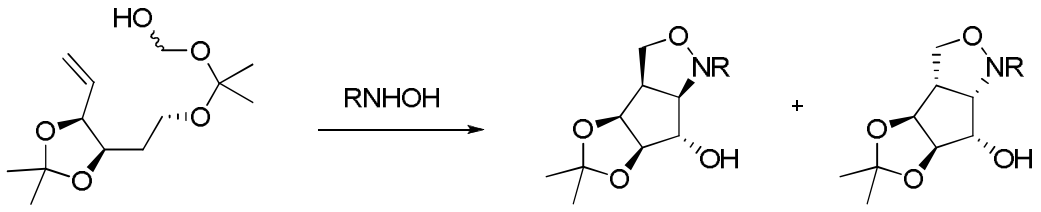
B. 2. 2. Synthesis of bicyclic homoproline

The substantial capability of the nitrone cycloaddition product **66a** was already shown for cispentacin derivatives with different side chains. Moreover, not only cycloadduct **66a** but also the second diastereomer **66b** is a quite versatile building block. It can give rise to similar β-amino acids as shown in the abovementioned examples with an all-*cis* configuration.

However, **66b** is only be obtained as a minor diastereomer in the cycloaddition reaction under the herein applied conditions.

Hence, methods need to be developed to increase the amount of the minor diastereomer. In this regard, *Jäger et al.* could show that the ratio of *syn*- to *anti*-cyclopentanoisoxazolidines **112** and **113** in the cycloaddition of **111** depends strongly on the choice of solvent.[77] In polar solvents like methanol the *syn*-tricycle was preferred whereas nonpolar solvents like chloroform favoured the formation of the *anti* isomer. The values for these reactions ranged from 87:13 to a complete inverse ratio of 5:95 (*syn*/*anti*).

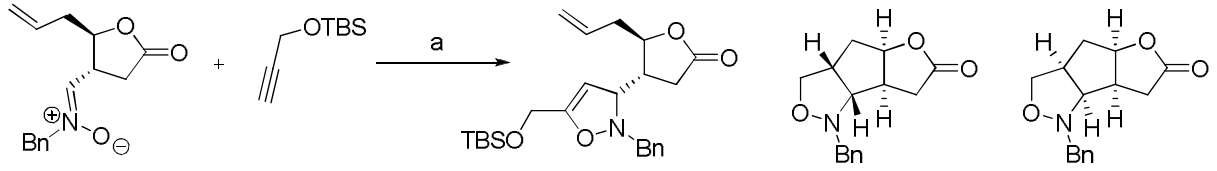
Scheme 30. Intramolecular nitrone cycloaddition step in the synthesis of amino(hydroxymethyl)cyclopentanetriols according to *Jäger et al.*[77]



111 **112** **113**

Moreover, it was shown by *M. Kuhn*[78] that the diastereomeric ratio in the case of γ-butyrolactone nitrones can be modified by the use of a different solvent as well as the addition of acids or bases. This accidental result was observed in attempts to alkylate the nitrone in the presence of zinc(II)-triflate and *Hünig's* base in dichloromethane (**Scheme 31**). In these reactions the desired alkylation product was not formed, but inter- and intramolecular cycloaddition products **115** and **66a/b** instead. Here, the correlation changed from about 3:1 in benzene to 2:1 under the conditions of this reaction. This result suggests that it is possible to alter the diastereomeric ratio of this transformation by using different solvents and/or other additives. The influence of the aforementioned factors still needs to be examined in detail.

Scheme 31. Unanticipated results in the attempts to alkylate the nitrone in **84**.



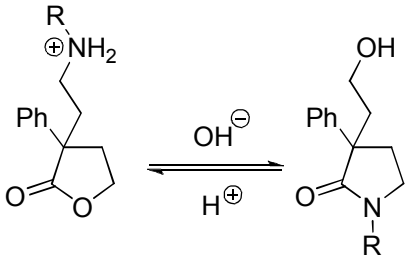
84 **114** **115** **66a** **66b**

Reagents and conditions: (a) Zinc(II)-triflate (10 mol%), DIPEA (25 mol%), CH_2Cl_2, r.t. for 48 h then 50 °C for 16 h, 28% for **115**, 37% for **66a/66b** (*dr* 2:1).

In contrast to **66a**, the stereochemical correlations in **66b** can give rise to different transformation pathways like a rearrangement of the lactone moiety to the corresponding lactame. To obtain lactame **116** the *N-O* bond of the isoxazolidine needs to be cleaved. In the present case it can be achieved using the $Zn/Cu(OAc)_2$ system in acetic acid at elaborate

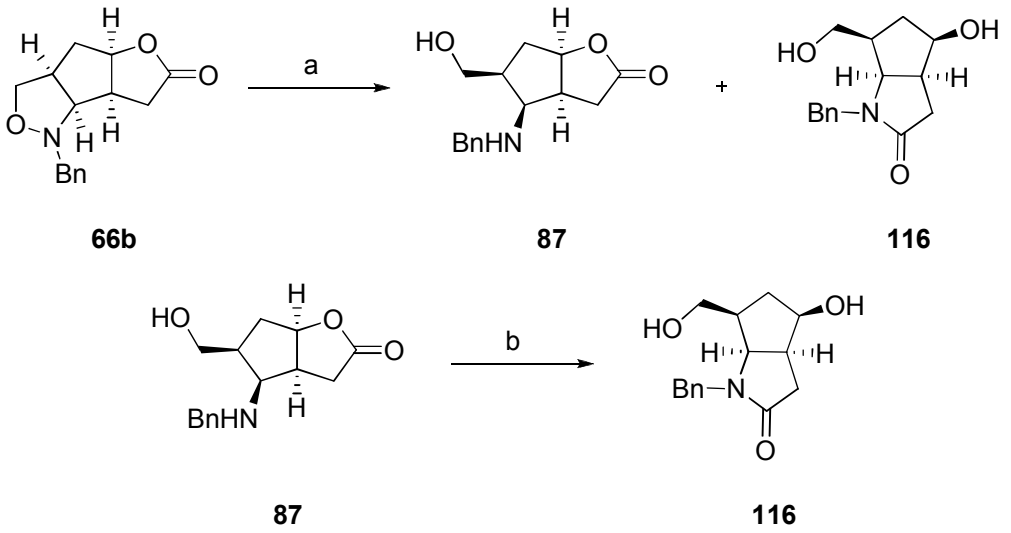
temperatures. These conditions allow an opening of the heterocycle without removing the benzyl group on the amine and are frequently applied for breaking *N-O* bonds in nitrones and isoxazolidines.[79] During the course of the reaction the formation of the desired product as well as of a secondary product was observed. This 'by-product' was identified as the lactame rearrangement product. After purification on silica gel the two products were obtained as a mixture of lactone and rearranged lactame in varying ratios. The remaining benzyl amino alcohol lactone **87** was then subjected to basic conditions to be rearranged to lactame **116**.
These *N-O* acyl migrations are already known since the early 20th century. This is especially true for the transformation from lactones to lactames (**Scheme 32**). Sometimes it was shown, that this rearrangement is in a pH dependent equilibrium and was utilised in several natural product syntheses.[80]

Scheme 32. First example of the rearrangement from lactones to lactames by *Walton* and *Green*[81].



For this transformation from lactone to the lactame different basic conditions with inorganic bases like LiOH and organic bases like triethylamine in different solvent mixtures were screened. However, the best base proved to be DBU, what was already shown for similar lactone rearrangements by *G. Geyer*[82] (**Scheme 33**).

Scheme 33. Hydrogenolytic cleavage of the *N-O* bond and rearrangement from lactone **87** to lactame **116**.



Reagents and conditions: (a) Zn/Cu(OAc)$_2$, AcOH, Δ, 2 hr, quant. (mixture of **87** and **116**). (b) DBU, MeOH, 5 hr, 0°C - r.t., 81%.

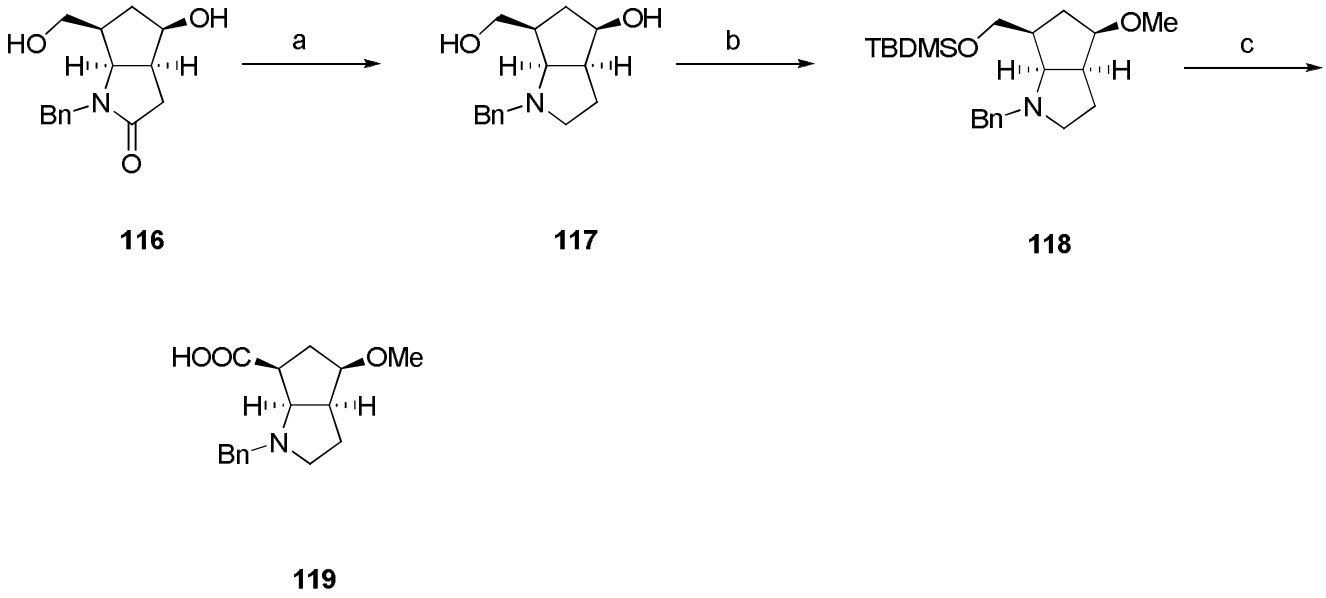
Lactame **116** now needs to be reduced to the corresponding amine. The most commonly used reagent for this reduction is LAH[83] but also other reagents and methods were applied like DIBALH[84], rhodium- and platinum-catalysed silane reductions[85] or lithium aminoborohydrides.[86] In this synthesis another classical method was employed, namely the use of boranes.[87] The BH_3·DMS complex in THF was successfully applied in the conversion of the lactame to amine **117** in excellent yield. However, due to quite long reaction times, LAH was used affording **117** in 81% yield.

The diol of the benzylated amino alcohol now needs to be properly orthogonally protected to be prepared for further modifications. For that reason the primary alcohol was protected in a similar way as in the syntheses of the previous amino acids by TBDMS chloride in the presence of triethylamine to give **118**. The secondary alcohol can now be variously altered by S_N reactions or oxidations and further transformations. This position would of course also allow a ether formation with propargyl bromide which then could arise the possibility of immobilisation on various solid supports using 'click-chemistry'.

However, it was decided to protect the alcohol by methylation. This was again achieved by the use of iodomethane in presence of NaH yielding **119**. Finally, the conversion of the primary silyl ether was necessary. Deprotection and *in situ* oxidation to the carboxylic acid

was performed under the acidic conditions of a Jones oxidation following a slightly modified protocol of *Evans et al.*[88] to give **120** in good yield. This method was preferred over the method by *Liu* and *Han*[89] who additionally used potassium fluoride, which was shown to be superfluous.

Scheme 34. Final steps in the synthesis of β-proline analogue **119**.



116 **117** **118**

119

Reagents and conditions: (a) LAH, THF, r.t., 81%. (b) TBDMSCl, NEt_3, DMAP, CH_2Cl_2, 18 h, 79%. (c) MeI, NaH, THF, 12 h, 77%. (c) Jones reagent, acetone, 0 °C – r.t., 83%.

The application of this reaction in aldol as well as in conjugate additions is currently under investigation in the *Reiser* group.

B. 3. Conformationally restricted γ-amino acids

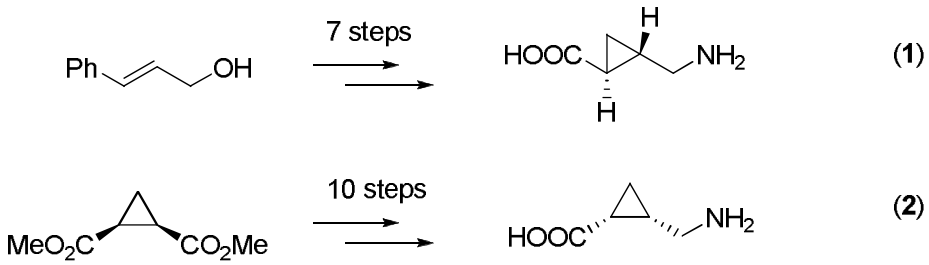
B. 3. 1. Introduction

γ-Amino acids are undoubted a very important class of amino acids and were intensively studied with the intent to generate new GABA analogues, turn inducing building blocks in peptides or peptidomimetics and to study their properties in foldamers.[90]

However, γ-peptides are comparatively not so well studied like their β- and, of course, α-peptide counterparts. Nevertheless, they also show an ability to fold into defined secondary

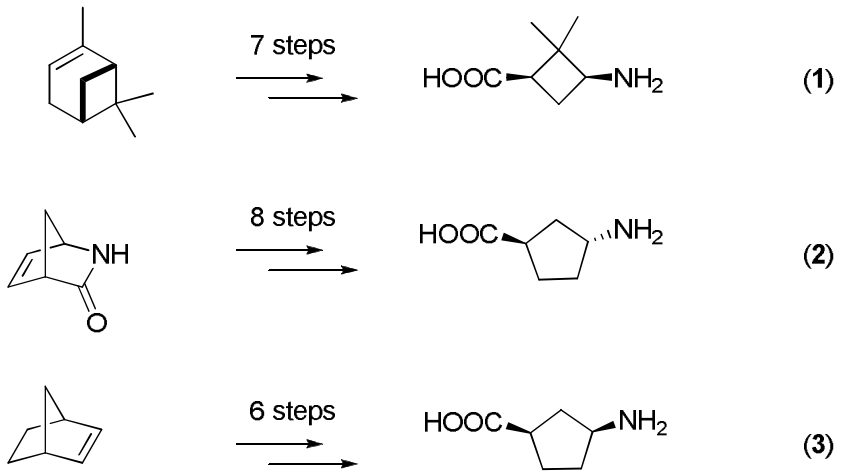
structures which are reported to have interesting biologic activities.[91] Therefore, over the last few years the stereoselective synthesis of new linear as well as cyclic γ-amino acids and their application as GABA analogues as well as in γ-peptides gained significant interest.[90b] As already outlined in the introduction of this work there are quite a number of different approaches towards various γ-amino acids. This includes also the synthesis of cyclic γ-amino acid derivatives ($C^n_{\alpha,\beta}$, $C^n_{\alpha,\gamma}$ and $C^n_{\beta,\gamma}$; *n* indicates the ring size and the Greek letters indicate the position of the junction atoms of the cycle).[90b] An interesting approach was published by *Mohapatra* starting from *trans*-cinnamyl alcohol to *trans*-$C^3_{\alpha,\beta}$ amino acids (rct 1; **Scheme 35**). Another synthesis of cyclopropane containing compounds was described by *Ley et al.* [92] who applied an enzymatic desymmetrisation of cyclopropane dicarbonic acid methyl ester using pig liver esterase yielding *cis*-$C^3_{\alpha,\beta}$ amino acids (rct 2; **Scheme 35**). Furthermore, there are also a various number of syntheses for $C^4_{\alpha,\gamma}$ and $C^5_{\alpha,\gamma}$ amino acids.

Scheme 35. Syntheses of different $C^3_{\alpha,\beta}$ amino acids.



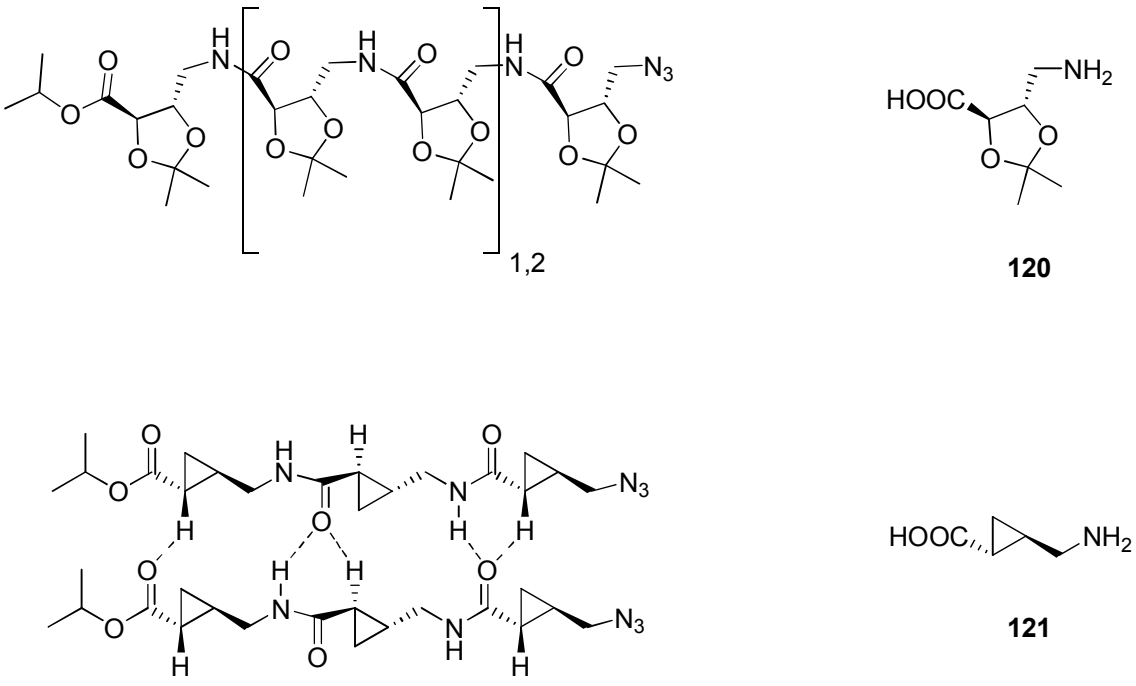
In this context, *López et al.* recently described a stereoselective synthesis of cyclobutane containing amino acids starting from commercially available α-pinene (rct. 1; **Scheme 36**).[93] The synthesis of *cis* and *trans*-cyclopentane γ-amino acids is also reported starting from 2-azabicyclo[2.2.1]hept-5-en-3-one or simple norbornene (rct.2 and 3; **Scheme 36**).[94]

Scheme 36. Syntheses of different $C^4_{\alpha,\gamma}$ and $C^5_{\alpha,\gamma}$ amino acids.



However, the synthesis of foldamers from cyclic γ-amino acids remains quite neglected and only view examples are known.[95] A remarkable synthesis was reported by *Smith et al.* who described γ-peptides which fold into parallel sheet structures as well as into bend-ribbons (**Figure 22**). The building blocks used in these syntheses are $C^5_{\alpha,\beta}$ (**120**) a $C^3_{\alpha,\beta}$ (**121**) amino acids.

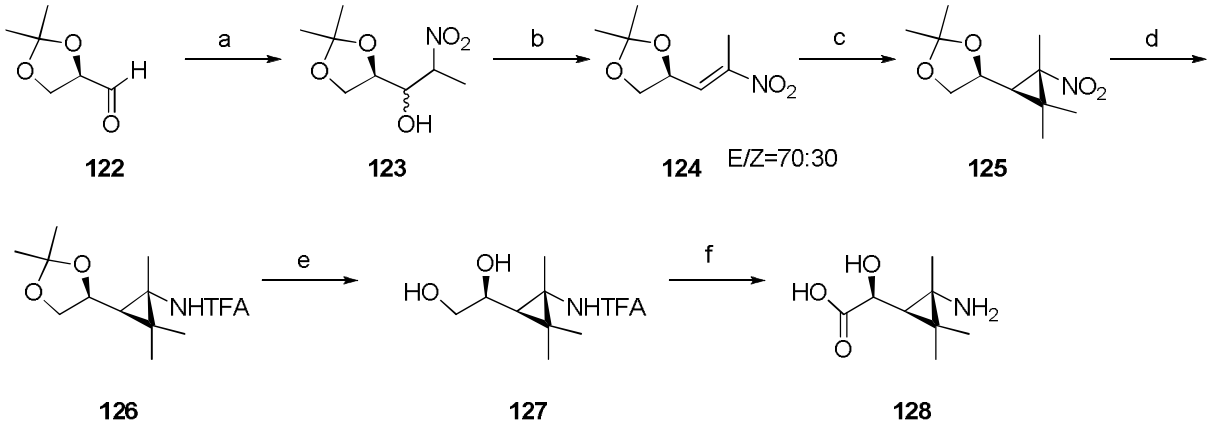
Figure 22. Foldamers of cyclic γ-amino acids according to *Smith et al.*



B. 3. 2. Synthesis of new trans $C^5_{\beta,\gamma}$ amino acids

As mentioned in the previous chapter there are quite a number of syntheses for γ-amino acids. However, the construction of $C^5_{\beta,\gamma}$ scaffolds is not as well investigated like for the other frameworks. One possibility was shown by *Pätzel et al.* who derived cyclopropane γ-amino acids from optically active nitroalkenes.[96] In their approach, nitroethane was added to an acetonide of (*R*)-glyceraldehyde (**122**) affording the nitroaldol adduct **123**, which can be dehydrated to nitroalkene **124**. Cyclopropanation of **125** using a diphenylsulfur ylide gave the cyclopropane derivative **126**, which by catalytic hydrogenation and *N*-protection with TFAA yielded **127**. Finally, the cleavage of the acetonide was followed by an oxidation of the primary alcohol and a TFA deprotection affording α-hydroxy-γ-amino acid **128**.

Scheme 37. Synthesis of γ-amino acids from the acetonide of (*R*)-glyceraldehyde **122**.

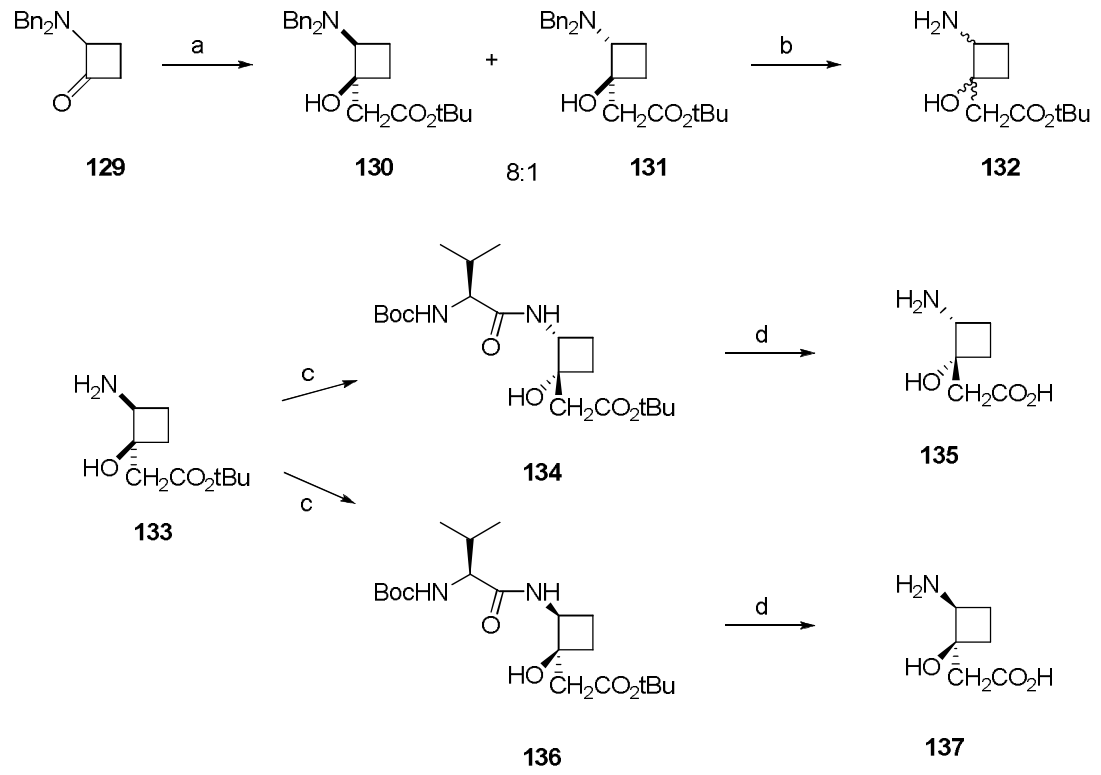


Reagents and conditions: (a) Nitroethane, KF (cat.), neat, r. t., 18 h, 62-95% (b) DCC (1.2 equiv), CuCl(cat.), Et_2O, r. t., 24–100 h; 14–70%. (c) PhS-CMe_2 (1.2 equiv), DME, -70°C – r.t., 18 h; 74%, d.r. 94:6. (d) (i) H_2 (10–15bar), Pd–C (cat.), MeOH, r. t., 48 h; 74%; (ii) $TFAO_2$ (e) *p*-TsOH·$1H_2O$ (cat.) MeOH/H_2O (10:1), r. t., 18 h, 97%. (f) (i) Et_3SiCl (3.0 equiv), NEt_3 (4.0 equiv), CH_2Cl_2, DMAP (cat.), -18°C – r. t., 18 h, 97%. (ii Swern oxidation, 77%. (iii) $NaOCl_2$ (1.4 equiv), H_2O (1.05 equiv), NaH_2PO_4 (cat.), MeCN/H_2O (2:1), 0°C to r. t., 1 h, 42%; (iv) $Ba(OH)_2 \cdot 8H_2O$ (4.8 equiv), MeOH, r. t. for 24 h then reflux for 2 h, 96%.

A different synthetic approach towards cyclobutane γ-amino acids was reported by *Baldwin et al.*[97] Here, 2-(dibenzylamino)-cyclobutanone **129** was reacted with *tert*-butyl bromoacetate under *Reformatsky* conditions affording the racemic mixture of **130** and **131** (8:1). Debenzylation gave the corresponding amino alcohol **132** which upon coupling with Boc-(*S*)-valine in the presence of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) yielded a

diastereomeric mixture of **134** and **136**. After separation of the diastereomers the final treatment under acidic conditions afforded 1-hydroxy-2-aminocyclobutane-1-acetic acids **135** and **137**.

Scheme 38. Synthesis of γ-amino acids from 2-(dibenzylamino)-cyclobutanone **129**.

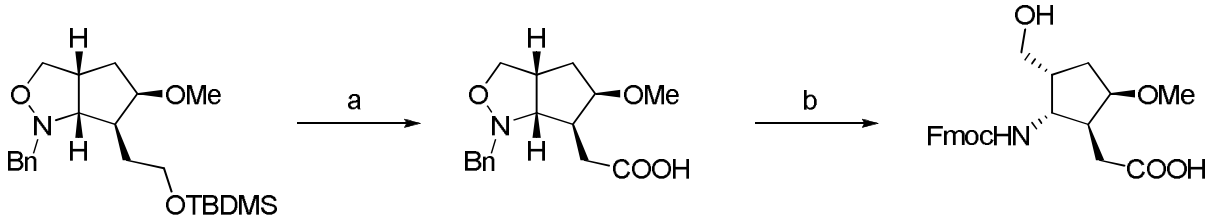


Reagents and conditions: (a) $BrCH_2CO_2{}^tBu$, Zn, THF, reflux, 1.5 h, 70%. (b) Pd/C, H_2 (1 atm), MeOH, r. t., 78%. (c) EEDQ, CH_2Cl_2, 24 h, 69 %. (d) 2 N HCl, reflux, 10-20 h.

However, until today - to the best of knowledge of the author - there is no synthesis reported for *trans* or *cis* $C^5_{\beta,\gamma}$ γ-amino acids. A new approach towards these γ-amino acids highlights once again the versatility of cycloadducts **66a** and **66b**. The before described doubly protected diol intermediate **94** can be deprotected and oxidised in one pot under Jones oxidation conditions yielding carboxylic acid **138**. During this reaction the acidic conditions will initially provoke a cleavage of the silyl ether which is then followed by the Cr(IV) mediated oxidation. Subsequently, the isoxazoline moiety of **138** is opened by a reduction using hydrogen at atmospheric pressure catalysed by $Pd(OH)_2$-C which once again also removes the benzyl group of the amine. The resulting free amine can now be protected by FmocOSu under

basic conditions affording the γ-amino acid **139** with a free hydroxyl group which gives the possibility for further derivatisation obtaining differently substituted γ-amino acids (**Scheme 39**).

Scheme 39. Synthetic scheme towards the *trans* $C^5_{\beta,\gamma}$ γ-amino acid

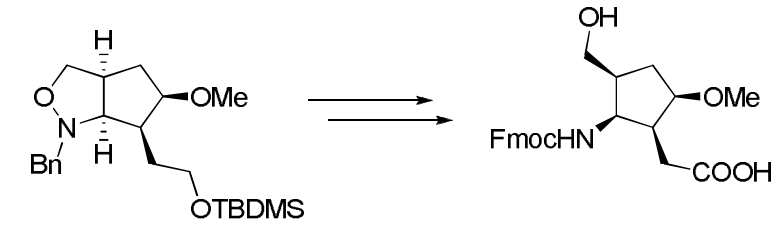


94 **138** **139**

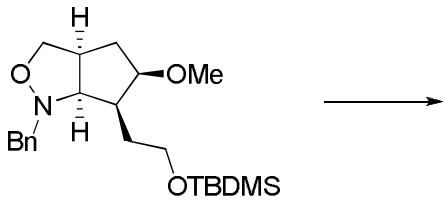
Reagents and conditions: (a) Jones oxidation, acetone, 0°C – r. t., 86%. (b) (i) $Pd(OH)_2$-C, H_2, MeOH, overnight, 86%. (ii) FmocOSu, $NaHCO_3$, acetone/water, 24 h, 58%.

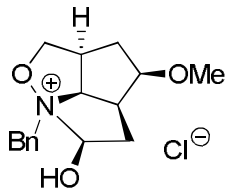
It is worth mentioning, that the preparation of the *cis* analogue **141** of this γ-amino acid failed using selfsame synthetic route. In the case of **140**, Jones oxidation afforded the tricyclic intermediate **142** which was inert towards further oxidation and conversion to **141**.

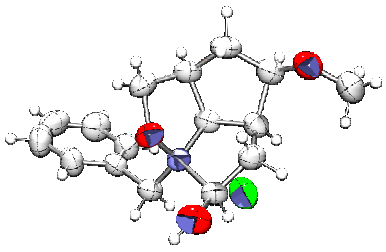
Scheme 40. Failure in the attempt to synthesise **141** due to formation of inert intermediate **142** (*left*); X-ray structure of tricyclic oxidation intermediate **142** (*right*).



140 **141**







140 **142**

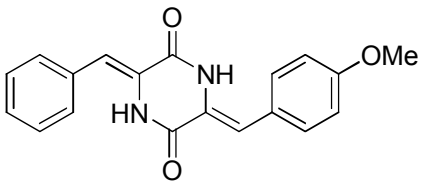
The behaviour of **139** in Homo- and Heteropolymers as well as in other peptides is currently under in investigation in the *Reiser* group.

B. 4. Preparation of Diketopiperazine (DKP) amino acids and their application in organocatalysis

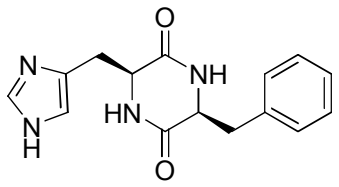
B. 4. 1. Introduction

DKPs are cyclic dipeptides composed of two α-amino acids. These scaffolds are a common motif in natural products and have a broad range of applications in various fields. Their structure was first reported by *Corey* in 1938 who elucidated them via X-ray crystallography.[98] Especially, many of their chemical features make them highly beneficial for medicinal chemistry, such as high resistance to proteolysis, the possibility of mimicking peptidic pharmacophoric groups, conformational rigidity, their quite simple preparation and many others.[99] Hence, they have been used as PAI-1 inhibitors (**143**), antiarrhythmic agents for the treatment of cardiovascular dysfunctions (**144**), as analogues of pyrimidinic bases in antiviral agents (**145**) and also showed activity in antimicrobial testing (**146**) (**Figure 23**).

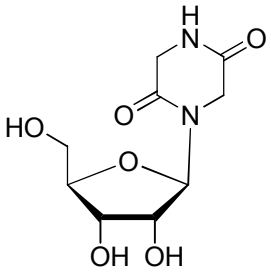
Figure 23. Various biologically active compounds containing a DKP motif.



143



144



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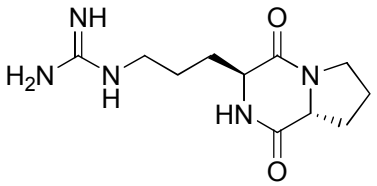


146

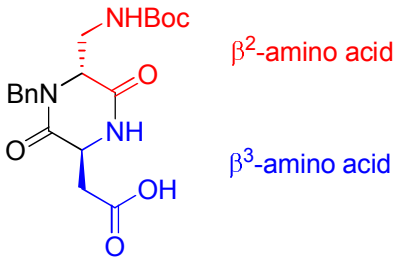
Furthermore, DKPs were successfully applied as peptidomimetics by *Piarulli et al.*[100] who used a new bifunctional diketopiperazine scaffold as a β-hairpin inducer, and in selective

peptide recognition using DKP receptors by *Wennemers et al.*[101] Another application is the introductorily mentioned *Schöllkopf* synthesis which allows an intra-annular chirality transfer in the synthesis of natural and unnatural α-amino acids. All these results are an encouraging starting point for further investigations.

B. 4. 2. Synthesis of trans-DKP scaffold

The scaffold which was chosen for different new applications is a DKP composed of (*R*)-2,3-diaminopropionic acid and (*L*)-aspartic acid. This combination gives rise to a cyclic β^2/β^3 amino acid having the amino functionality and the carboxylic acid in a *trans* configuration (**Figure 24**).

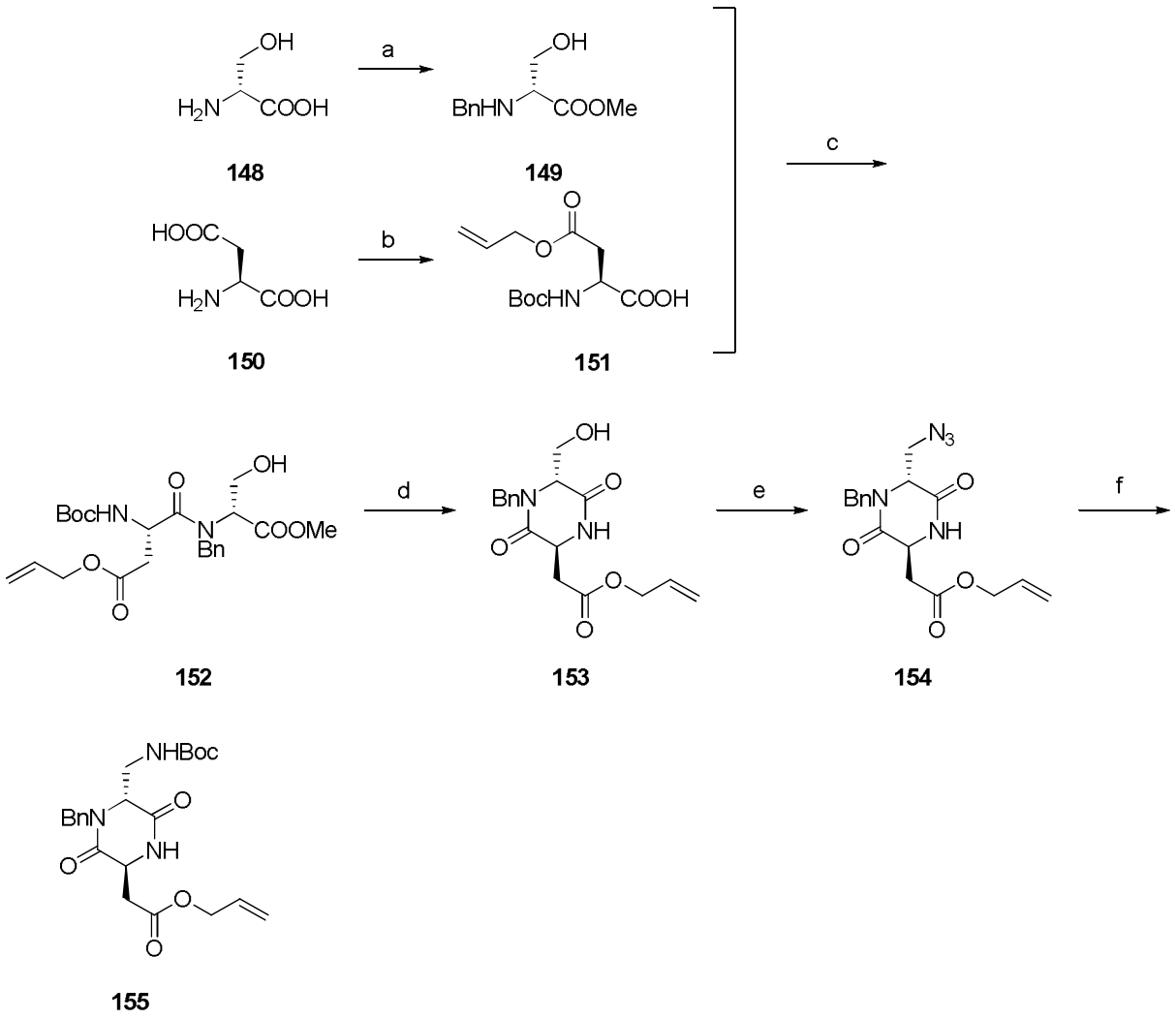
Figure 24. Structure of *trans*-DKP **147**.



147

The synthesis of **155** was accomplished similar to a known strategy.[100,30] (*D*)-Serine (**148**) was converted to its methyl ester followed by a benzyl protection of the amine functionality under reductive amination conditions using benzaldehyde to yield **149**. In the second amino acid, (*L*)-aspartic acid (**150**), the carboxylic acid of the side chain could be selectively protected as an allyl ester, followed by a *N*-Boc protection under standard conditions to form **151**. These two orthogonally protected amino acids were then coupled to form dipeptide **152** using HBTU. After Boc deprotection of **152** with trifluoroacetic acid the corresponding TFA salt was stirred in a 1:1 mixture of ethyl acetate and saturated $NaHCO_3$, leading to cyclisation and formation of DKP **153**. Introduction of the azide functionality to **154** was accomplished under Mitsunobu conditions using hydrazoic acid. Subsequently, azide **154** can be converted to a Boc protected amine in a one pot reaction applying a Staudinger reduction in the presence of BocON [2-(tert-butoxycarbonyloxyimino)-2-phenyl-acetonitile] to yield **155**.

Scheme 41. Preparation of Boc-*trans*-DKP-OAllyl.



Reagents and conditions: (a) (i) AcCl, MeOH, 65%. (ii) PhCHO, NEt_3, MeOH, then $NaBH_4$, 71%. (b) (i) Allylalcohol, AcCl, 71%. (ii) NEt_3, Boc_2O, dioxane/H_2O, 88%. (c) HBTU, DIPEA, DCM, 78%. (d) (i)TFA, DCM. (ii) Sat. $NaHCO_3$, EtOAc, 87% over two steps. (e) HN_3·toluene, PPh_3, DIAD, toluene/DCM, -20 °C, 91%. (f) Me_3P, Boc-ON, toluene, -20 °C, 79%.

B. 4. 3. Pro-trans-DKP esters and amides in organocatalysis

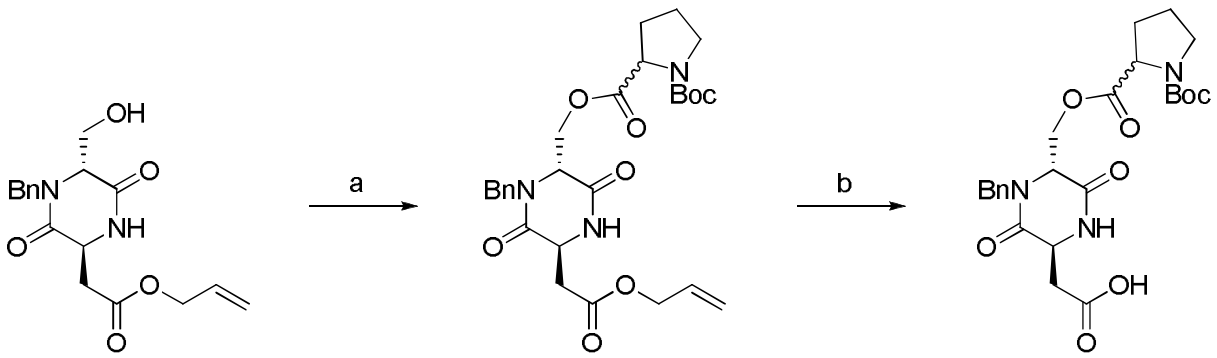
Not only amino acids - as already addressed in chapter B. 2. 1. of this work – but also peptides are highly useful organocatalysts. Thanks to the recent investigations of *Wennemers et al.* this field has becoming increasingly popular.[102] The *Wennemers* group was able to identify new organocatalysts from a pool of almost 3500 tripeptides using a catalyst-substrate coimmobilisation in split-and-mix libraries.[103] These tripeptide scaffolds, and particular the

H-Pro-Pro-Asp-NH_2 sequence, showed to be highly effective concerning yield and selectivity in the aldol condensation of acetone and aromatic and aliphatic aldehydes[104]- as well as in conjugate additions[105] showing its enormous potential. The secondary amine of proline at the *N*-terminus and the carboxylic acid functionality of the aspartic acid side chain are crucial for the catalytic activity suggesting that the mechanism is similar to enamine activation proposed for proline catalysis. Moreover, a defined turn structure within the peptide was demonstrated to be essential.[106] The importance of these features was also demonstrated by the *Reiser* group by introduction of the turn inducing β-ACC in between to proline units which was successfully applied in aldol reactions.[107]

Even though these results show that there is a quite limited space of variation in the peptide sequence and substitution pattern, these results led to the hypothesis that coupling of proline to DKP scaffolds **153** or **155** (after *N*-deprotection) might lead to interesting organocatalysts. In fact, the Pro-DKP derivatives provide the secondary amine of the proline moiety and a free carboxylic acid connected by a shape inducing element, the DKP itself. In this way up to four different organocatalyst precursors could be formed by coupling either enantiomer of Boc-proline with in turn the hydroxy-derived DKP **153** and the amino functionalised DKP **155**.

The Pro-DKP esters were prepared by esterification of Boc-Pro-OH to the hydroxyl functionality of DKP **153** using a standard EDC, HOBt protocol. After deallylation of **156** Boc-Pro-DKP (**157**) esters were obtained (**Scheme 42**).

Scheme 42. Preparation of Boc-Pro-O-DKP esters.

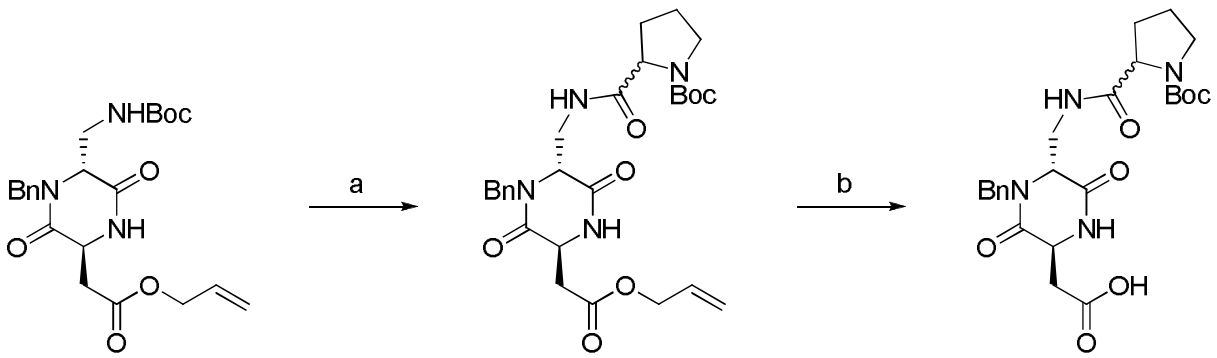


153 **156** **157**

Reagents and conditions: (a) Boc-Pro-OH, EDC, HOBt, DMAP, DCM/THF, 5 h, 0°C – r. t., 96 % (for (*D*)-Pro). (b) $Pd(Ph_3)_4$, PPh_3, pyrrolidine, DCM, 3 h, 0°C – r.t., 77% (for Boc-(*L*)-Pro-O-DKP-OH) and 98% (for Boc-(*D*)-Pro-O-DKP-OH).

The analogous Pro-DKP amides were prepared by a peptide coupling of Boc-Pro-OH to Boc deprotected **155** using HBTU to yield **158**. Again, deallylation afforded the Boc protected organocatalyst precursor **159** (**Scheme 43**).

Scheme 43. Preparation of Boc-Pro-DKP amides.



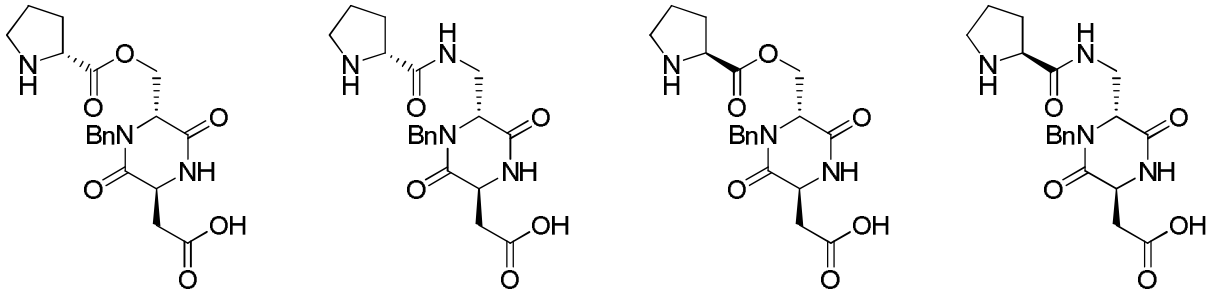
155 **158** **159**

Reagents and conditions: (a) (i) TFA/DCM (1:1), 0°C – r.t., 30 min. (ii) Boc-Pro-OH, HBTU, collidine, MeCN, overnight, 0°C – r. t., 98% (for (*L*)-Pro) and 97% (for (*D*)-Pro). (b) $Pd(Ph_3)_4$, PPh_3, pyrrolidine, DCM, 3 h, 0°C – r.t., 74% (for Boc-(*L*)-Pro-O-DKP-OH) and 93% (for Boc-(*D*)-Pro-O-DKP-OH).

In this regard, it should be mentioned that both enantiomers of proline were applied in the synthesis. In addition, also the *cis*-DKP counterparts of the aforementioned DKP esters and peptides were synthesised in the *Piarulli* group in order to have a small library of compounds for the testing of their catalytic activity.

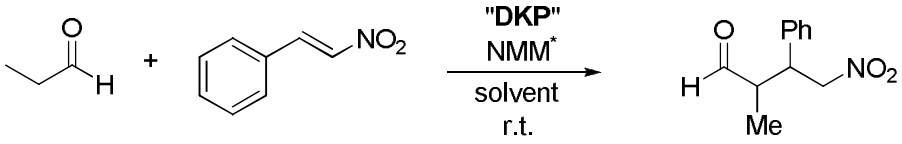
The final Boc deprotection of the amide and ester precursors gave the TFA salts of catalysts **160**, **161**, **162** and **163**.

Figure 25. Applied catalysts in addition of aldehydes and ketones to β-nitrostyrene.



As a benchmark reaction to test the effectiveness of all these catalysts, the conjugate addition of propanal and β-nitrosytrene was chosen. The reaction conditions and the results are summarised in **Table 3**.

Table 3. Addition of propanal to β-nitro styrene using DKP catalysts.



*equivalent amount of base corresponding to "**DKP**" (TFA salt) was used

Entry	Cat.	Solvent	t [h]	yield [%]	*syn*:*anti*	*ee* [%]	Abs. Conf.
1	(L)-Pro	CH_2Cl_2	24	88	4:1	23	(*R*, *S*)
2	**A** [a] (10 mol%)	CH_2Cl_2	24	49	11:1	52	(*S*, *R*)
3	**B** [a] (10 mol%)	CH_2Cl_2	24	62	20:1	83	(*S*, *R*)
4	**C** [a] (10 mol%)	CH_2Cl_2	24	63	4:1	30	(*R*, *S*)
5	**D** [a] (10 mol%)	CH_2Cl_2	12	95	3:1	60	(*R*, *S*)
6	**A** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	5	96	n.d.	53	(*S*, *R*)
7	**B** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	4	98	n.d.	89	(*S*, *R*)
8	**C** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	5	95	n.d.	29	(*R*, *S*)
9	**D** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	4	89	n.d.	86	(*R*, *S*)
10 [b]	**B** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	9	93	n.d.	89	(*S*, *R*)
11 [b]	**D** [a] (10 mol%)	$CHCl_3$/^{i}PrOH (9:1)	9	95	n.d.	91	(*R*, *S*)
12 [b]	**B** [a] (5 mol%)	$CHCl_3$/^{i}PrOH (9:1)	24	93	n.d.	91	(*S*, *R*)
13 [b]	**D** [a] (5 mol%)	$CHCl_3$/^{i}PrOH (9:1)	24	91	20:1	84	(*R*, *S*)

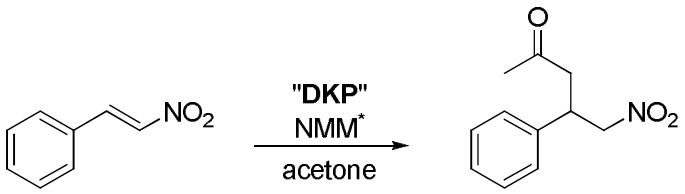
(a) An equal amount of N-methylmorpholine was added to the reaction mixture as the trifluoroacetate of the catalyst was used; (b) reactions were carried out at 0 °C.

The scope of this reaction was further investigated using other aldehydes. The 'amide' catalysts **161** and **163** were used, due to their higher activity and selectivity in the reaction with propanal.

Some preliminary results in these reactions show the high potential of both (*L*)-Pro-DKP and (*D*)-Pro-DKP in the addition of aldehydes to nitroolefins giving the opposite absolute configuration. The amount of catalyst can be reduced to only 5 mol% giving high yields with a fast conversion and excellent selectivity already at 20°C.

The scope and the universal application of the reactions between various aldehydes and nitroolefins is under investigation in *Piarulli* group at the moment.

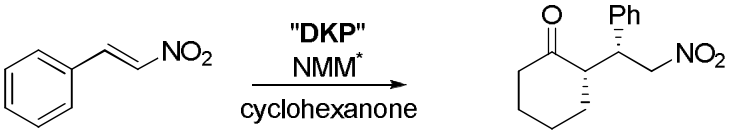
However, not only the addition of aldehydes but also the addition of ketones to nitroolefines is an extremely interesting transformation which recently showed good results in selected cases.[108] For that purpose, again β-nitrostyrene was chosen and reacted with acetone and cyclohexanone. The first attempts using neat acetone showed a quite fast conversion (12 h) with a very low stereoinduction for the Pro-DKP esters. Interestingly, both diastereomeric catalysts gave the same enantiomer.
On the other hand, the Pro-DKP amides showed a very slow conversion and only moderate yields. Furthermore, also here the selectivity was very low.



*equivalent amount of base corresponding to "**DKP**" (TFA salt) was used

Entry	Cat.	t [h]	Conv. [%]	*ee* [%]
1	**A** (10 mol%)	12	quant.[a]	6
2	**B** (10 mol%)	12	42	-6
3	**C** (10 mol%)	72	quant.[a]	-6
4	**D** (10 mol%)	72	42	0

(a) full consumption of starting material on TLC.



*equivalent amount of base corresponding to "**DKP**" (TFA salt) was used

Entry	Cat.	t [h]	Conv. [%]	*ee* [%]
1	**A** (10 mol%)	72	92	15
2	**B** (10 mol%)	72	49	2
3	**C** (10 mol%)	72	97	-7
4	**D** (10 mol%)	72	41	2

In summary, Pro-DKP peptides were shown to be quite active and selective catalysts in the conjugate addition of aliphatic or β-branched aldehydes to nitroolefins. Some preliminary experiments suggest that α-branched aldehydes need a higher catalyst loading and were extremely slow at temperatures lower than room temperature.

The conjugate addition of ketones to nitroolefins did show only a low stereoinduction with moderate to good yields. However, it should be mentioned that the DKP-ester catalysts are more active and also selective compared to DKP-amides, which might be due to lower solubility. Hence, further studies on this unexpected result need to be carried out in order to understand this observation. The scope of these catalysts is currently under further investigation in the *Piarulli* group.

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C. Experimental part

Instruments and general techniques

^{1}H-NMR spectra were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shifts are reporter in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d6, 2.49 ppm), methanol-d3 or methanol-d4 (CD_3OH, 3.34 ppm). The spectra were analysed by first order, the coupling constant (*J*) are reported in Hertz (Hz). Characterisation of signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bm = broad multiplet, dd = double doublet, dt = double triplet, ddd = double double doublet. Integration is determined as the relative number of atoms. Diastereomeric ratios were determined by comparing the integrals of corresponding protons in the 1H-NMR spectra.

^{13}C-NMR spectra were recorded on Bruker AC 250 (62.9 MHz), Bruker Avance 300 (75.5 MHz), Bruker Avance 400 (100.6 MHz) and Bruker Avance 600 (150.9 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77 ppm), dimethylsulfoxide (DMSO-d6, 39.52 ppm), methanol-d3 or methanol-d4 (CD_3OH, 49 ppm).

2D-NMR spectra (COSY, NOESY, ROESY, TOCSY, HETCORR, HMBC, HSQC) were recorded on Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz).

IR spectra were recorded with a Bio-Rad Excalibur series FT-IR.

MS spectra were recorded in the mass spectroscopy department of the University of Regensburg.

Optical rotations were measured on a Perkin-Elmer-polarimeter 241 with sodium lamp at 589 nm in the specified solvent. Concentration is indicated as [g/100ml].

CD spectra were measured on a JASCO model J-710/720 at the Institute of Analytical Chemistry of the University of Regensburg at 21°C between 250 and 190 nm in the specified solvent, with 10 scans. The length of the rectangular cuvette was 0.1 mm, the resolution was

0.2 nm, the band width 1.0 nm, the sensitivity 10-20 mdeg, the response 2.0 s, the speed 10 nm/min. The background was substracted for each spectrum. The absorption value is measured as molar ellipticity per residue (deg.cm2.dmol-1). The spectra were smoothed by adjacent averaging algorithm or FFT filter with the Origin 6.0 program.

Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm) or glass plates coated with flash chromatography silica gel (Merck silica gel 60 F 254, layer thickness 0.25 mm). Visualisation was accomplished by UV light (wavelength λ= 254 nm), permanganate solution, ninhydrin/acetic acid solution, vanillin/H_2SO_4 solution, anisaldehyde solution or Draggendorf-Munier reagent.

HPLC-chromatography analytical and preparative reverse Phase HPLC was performed on Agilent equipment (Böblingen, Germany) by using the columns: Luna C18(2), 3 µm, 4.60 x 150 mm and the Luna C18(2), 90 µm, 21.2 x 250 mm (Phenomenex, Aschaffenburg, Germany). The flow rate was 1 mL/min for the analytical HPLC runs and 21 mL/min for preparative applications. The binary solvent system (A/B) was: (A) ACN, (B) 0.0059% TFA in water. The absorbance was detected at 220 nm.

BF_3•Et_2O was distilled under nitrogen and stored in a Schlenk flask under nitrogen in the refrigerator. Diethyl ether, dichloromethane and THF were purified by a solvent purification system apparatus. In Como, all dry solvents were obtained from sealed bottles under nitrogen purchased from Aldrich.

Solid phase peptide synthesis

General procedure for the preparation of peptides on a Rink-amide resin

The syntheses were carried out by manual coupling using Fmoc/^{t}Bu strategy on the acid labile HMPA-AM resin pre-modified with an Fmoc protecting group (loading 0.64 mmol/g). The Fmoc group was removed by treatment with 20% piperidine in DMF, one cycle of and one of 15 minutes. The first amino acid (5 equiv), was attached activating the carboxylic function with HBTU (5 equiv) and HOBt (5 equiv) in the presence of DIPEA (10 equiv) in NMP/DMF for 2 hours. This deprotection/coupling strategy was applied for each step, besides the amount

of the unnatural amino acids (3 equiv) and the amount of coupling reagents respectively. The cleavage of the peptide from the resin with simultaneous side chains deprotection was achieved by treatment with a TFA/water/TIS mixture (95:5:5) for 2.5 hours. The peptide was precipitated from ice-cold diethyl ether and recovered by centrifugation. The purification was achieved by using RP-preparative HPLC and the products were characterized by analytical HPLC and MALDI-MS spectroscopy.

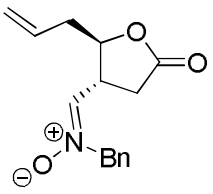
Catalysis

General procedure for addition of aldehydes to nitroolefins

The catalyst (5 mol%, 10 mol%) was dissolved in the appropriate solvent (500 µl, 1 ml; solvent contained equal amount of *N*-methylmorpholine corresponding to the catalyst (TFA salt)) and stirred for 5 minutes. To that solution was added the nitroolefin (1 equiv) and the aldehyde (3 equiv) and stirred for the indicated time. Purification was accomplished using flash column chromatography on flash silica gel eluting with mixtures of hexanes and EtOAc. The d.r. was determined by NMR and the e.e. was determined by HPLC (for propanal Hexane/^{i}Propanol 99.3:0.7, flow 0.6 ml/min on Chiracel AD-H. The isomeric products were detected at 254 nm at 36.3 and 42.1 min)

General procedure for addition of ketones to nitroolefins

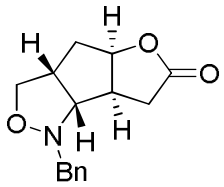
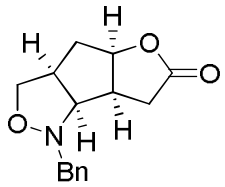
The catalyst (10 mol%) was dissolved in the appropriate ketone (1 ml; solvent contained equal amount of *N*-methylmorpholine corresponding to the catalyst (TFA salt)) and stirred for 5 minutes. To that solution was added the nitroolefin (1 equiv) stirred for the indicated time. Purification was accomplished using flash column chromatography on flash silica gel eluting with mixtures of hexanes and EtOAc.



(E)-*N*-(((2*R*,3*R*)-2-allyl-5-oxotetrahydrofuran-3-yl)methylene)-1-phenylmethanamine oxide (84)

A mixture of (2*R*,3*S*)-2-Ally-5-oxo-tetrahydro-furan-3-carbaldehyde **67** (0.5 g, 3.24 mmol, 1 equiv), $NaOAc \cdot 3H_2O$ (1.32 g, 9.73 mmol, 3 equiv) and *N*-benzylhydroxylamine hydrochloride (0.78 g, 4.86 mmol, 1.5 equiv) in 10 ml of an 80% ethanol/water mixture was stirred at room temperature for 1 hour (TLC control). Ethanol was removed under reduced pressure, the aqueous solution was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic layers were washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$ and evaporated to give a brown sticky oil (710 mg, 2.74 mmol, 85 %) which was used for the next step without further purification.

R_f = 0.17 (hexanes/ethyl acetate 1:1). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 2.50 (m, 2H), 2.54 (dd, *J* = 17.9, 7.5 Hz, 1H), 2.84 (dd, 1H, *J* = 17.8, 9.4 Hz), 3.55 (m, 1H), 4.47 (dd, 1H, *J* = 12.2, 5.9 Hz), 4.87 (s, 2H), 5.07-5.14 (m, 1H), 5.14-5.23 (m, 1H), 5.66-5.80 (m, 1H), 6.72 (d, 1H, *J* = 6.31 Hz), 7.30-7.44 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 31.96 (-, 1C), 37.97 (+, 1C), 39.17 (-, 1C), 69.58 (-, 1C), 81.38 (+, 1C), 119.76 (-, 1C), 129.15 (+, 1C), 129.35 (+, 2C), 131.30 (+, 2C), 132.22 (1C), 135.94 (+, 1C), 175.14 (1C). – **IR** (film): $\tilde{\nu}$ = 3366, 3273, 3078, 2934, 1775, 1639, 1602, 1495, 1450, 1422, 1205, 1169, 995, 915, 703.

(3a*R*,4a*R*,7a*S*,7b*R*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (66a; major)

(3a*S*,4a*R*,7a*S*,7b*S*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (66b; minor)

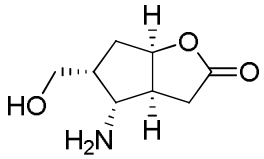
A solution of crude nitrone **84** (710 mg, 2.74 mmol, 1 equiv) in 20 ml anhydrous benzene was refluxed for 20 hours under nitrogen (TLC). After coming to room temperature benzene was removed under reduced pressure to give a black sticky oil. The two isomers where seperated by chromatography on silica gel (5-20 % ethyl acetate in hexanes) yielding a yellowish oil which was crystallized from ethylacetate/hexane giving a colourless crystalline solid (508 mg, 1.96 mmol, 55 %, *dr* (**major/minor**) = 78:22).

66a; major:

$\mathbf{R}_f$ = 0.37 (hexanes/ethyl acetate 1:1). – $[\alpha]^{20}$ = +26.3 (c = 0.13, CH_2Cl_2). – **mp**: +78 °C. – **^{1}H NMR** (600 MHz, $CDCl_3$): δ_H = 2.02 (m, 1H), 2.15 (dd, 1H, *J* = 1.5, 18.0 Hz), 2.41 (dd, 1H, *J* = 8.2, 14.7 Hz), 2.60 (dd, 1H, *J* = 9.3, 18.0 Hz), 2.74 (m, 1H), 3.21 (dd, 1H, *J* = 3.0, 7.9 Hz), 3.34 (dq, 1H, *J* = 3.1, 8.3 Hz), 3.71 (dd, 1H, *J* = 3.0, 8.6 Hz), 3.80 (d, 1H, *J* = 12.6 Hz), 4.12 (d, 1H, *J* = 12.6 Hz), 4.20 (m, 1 H), 5.02 (t, 1H, *J* = 5.1 Hz), 7.35 (m, 5H). – **^{13}C NMR** (150.9 MHz, $CDCl_3$): δ_C = 34.76 (-, 1C), 37.76 (-, 1C), 45.54 (+, 1C), 47.88 (+, 1C), 61.17 (+, 1C), 71.75 (+, 1C), 78.49 (+, 1C), 88.48 (+, 1C),127.81 (+, 1C), 128.57 (+, 2C), 129.18 (+, 2C), 136.26 (1C), 176.33 (1C). – IR (KBr) = $\tilde{\nu}$ = 3503, 3440, 3028, 2940, 2874, 2360, 1762, 1360, 1171, 1028, 754, 702. – **MS** (EI-MS): m/z (%) = 91.1 (100) [$C_7H_7^+$], 259 (17) [$M^{+\cdot}$]. – **HRMS** (HR-EI, 70 eV): 259.1206 ($C_{15}H_{17}NO_3$ [$M^{+\cdot}$]: calcd. 259.1208). – **Elemental analysis** calcd. (%) for $C_{15}H_{27}NO_3$ (259.12): C 69.48, H 6.61, N 5.40, found C 69.42, H 6.61, N 5.35.

66b; minor:

R_f = 0.29 (hexanes/ethyl acetate 1:1). – **[α]^{20}** = -36.0 (c = 0.11, CH_2Cl_2). – **mp**: +108 °C. – **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 1.97 (ddd, 1H, *J* = 5.0, 7.6, 13.1 Hz), 2.31 (d, 1H, *J* = 15.3 Hz), 2.46 (dd, 1H, *J* = 9.5, 17.6 Hz), 2.80 (ddt, 1H, *J* = 1.1, 5.9, 9.6 Hz), 3.17 (dd, 1H, *J* = 1.0, 17.6 Hz), 3.33 (m, 1H), 3.66-3.72 (m, 1H), 3.66-3.76 (m, 1H), 3.72 (d, 1H, *J* = 12.8 Hz), 4.05 (d, 1H, *J* = 12.8 Hz), 4.15 (m, 1H), 4.88 (t, 1H, *J* = 5.3 Hz), 7.31-7.37 (m, 5H). – **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ_C = 29.71 (-, 1C), 30.58 (-, 1C), 42.45 (+, 1C), 46.65 (+, 1C), 60.12 (-, 1C), 70.31 (+, 1C), 70.99 (-, 1C), 86.30 (+, 1C), 127.56 (+, 1C), 128.50 (+, 2C), 128.90 (+, 2C), 136.99 (1C), 177.53 (1C). – **IR** (KBr): $\tilde{\nu}$ = 3353, 3030, 2956, 2878, 1960, 1753, 1495, 1452, 1360, 1331, 1200, 1165, 1203, 974, 913, 893, 724, 698 656. – **MS** (EI-MS): m/z (%) = 91.1 (100) [$C_7H_7^+$], 259.1 (24) [$M^{+\cdot}$]. – **HRMS** (HR-EI, 70 eV): 259.121 ($C_{15}H_{17}NO_3$ [$M^{+\cdot}$]: calcd. 259.1208). – **Elemental analysis** calcd. (%) for $C_{15}H_{17}NO_3$ (259.12): C 69.48, H 6.61, N 5.40, found C 69.31, H 6.93, N 5.36.

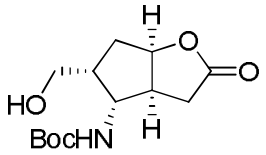


(3a*S*,4*R*,5*R*,6a*R*)-4-amino-5-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (86)

To a solution of (3a*R*,4a*R*,7a*S*,7b*R*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (**66a**, 250 mg, 0.96 mmol, 1 equiv) in 18 ml anhydrous MeOH was added 10% Pd/C (40 mg) and ammonium formate (304 mg, 4.82 mmol, 5 equiv). After refluxing for 2 hours the solution was filtered through celite yielding a slightly yellow sticky solid (164 mg, 0.96 mmol, quant. yield).

R_f = 0.84 (DCM/MeOH 9:1). – **[α]^{20}** = +4.8 (c = 0.03, MeOH). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 2.00 (broad m, 5H), 2.23-2.32 (m, 1H), 2.38 (dd, 1H, *J* = 3.1, 18.4 Hz), 2.68 (ddd, 1H, *J* = 3.3, 6.7, 10.4 Hz), 2.85 (dd, 1H, *J* = 10.7, 18.3 Hz), 3.37 (dd, 1H, *J* = 3.4, 5.6 Hz), 3.64-3.72 (m, 1H), 3.83 (dd, 1H, *J* = 4.4, 11.1 Hz), 5.08 (td, 1H, *J* = 3.7, 7.2 Hz). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 33.35 (-, 1C), 34.16 (-, 1C), 42.68 (+, 1C), 47.85 (+, 1C),

60.52 (+, 1C), 62.05 (-, 1C), 84.84 (+, 1C), 177.01 (1C). – **IR** (film): $\tilde{\nu}$ = 3353, 3300, 2931, 1760, 1643, 1555, 1359, 1187, 1017, 753. – **MS** (CI-MS): m/z (%) = 172.1 (100) [MH^+], 189.1 (39) [$M+NH_4^+$]. – **HRMS** (HR-EI, 70 eV): 171.0894 ($C_8H_{13}NO_3$ [$M^{+\cdot}$]: calcd. 171.0895).



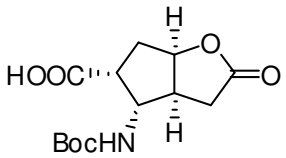
***tert*-butyl[(3a*S*,4*R*,5*R*,6a*R*)-5-(hydroxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl]carbamate (88)**

Procedure A: (3a*S*, 4*R*, 5*R*, 6a*R*)-4-Amino-5-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (**66a**) (96 mg, 0.56 mmol, 1 equiv) was dissolved in 5 ml dry MeOH under nitrogen. To that solution di-*tert*-butyl dicarbonate (132 µl, 0.62 mmol, 1.1 equiv) and a catalytic amount of 4-dimethylamino pyridine (6 mg, 0.05 mmol, 0.1 equiv) was added. After stirring for 2 h the reaction mixture was added 2 ml 1N HCl and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with 60 % ethyl acetate in hexanes gave a colourless solid (114 mg, 0.42 mmol, 75%).

Procedure B: Cycloadduct **66a** (500 mg, 1.93 mmol, 1 equiv) was dissolved in 20 ml dry MeOH under nitrogen. To that solution di-*tert*-butyl dicarbonate (631 mg, 2.89 mmol, 1.5 equiv) and $Pd(OH)_2$-C (150 mg) was added. After stirring overnight under a hydrogen atmosphere the reaction mixture was filtered through celite. The solution was concentrated under reduced pressure. Chromatography on silica gel eluting with 60 % ethyl acetate in hexanes gave a colourless solid (396 mg, 1.46 mmol, 76%).

$\mathbf{R_f}$ = 0.66 (DCM/MeOH 9:1). – $\mathbf{[\alpha]^{20}}$ = - 8.4 (c = 0.7, MeOH). – **mp**: +137 °C. – **^{1}H NMR** (300 MHz, D_2O): δ_H = 1.27 (s, 9H), 1.60-1.78 (m, 1H), 1.96 (dd, 1H, *J* = 6.6, 14.8 Hz), 2.27 (tt, 1H, *J* = 6.5, 12.8 Hz), 2.41 (dd, 1H, *J* = 2.5, 18.1 Hz), 2.75-2.85 (m, 1H), 2.90 (dd, 1H, *J* = 11.1, 18.1 Hz), 3.42 (dd, 1H, *J* = 6.6, 11.3 Hz), 3.50 (dd, 1H, *J* = 8.4, 15.4 Hz), 3.75 (m, 1H), 5.06 (t, 1H, *J* = 6.1 Hz). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 28.29 (+, 3C), 33.18 (-, 1C),

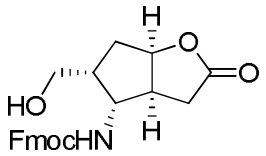
34.24 (-, 1C), 42.83 (+, 1C), 45.56 (+, 1C), 59.57 (+, 1C), 60.89 (-, 1C), 80.65 (1C), 83.62 (+, 1C), 156.57 (1C), 176.38 (1C). – **IR** (KBr): $\tilde{\nu}$ = 3349, 3272, 3047, 2974, 2932, 2360, 1801, 1674, 1553, 1186, 1024. – **MS** (ES-MS): m/z (%) = 272.1 [MH^+], 289.1 [$M+NH_4^+$], 543.4 ($2MH^+$), 560.4 ($2M+NH_4^+$), 565.4 ($2M+Na^+$). – **Elemental analysis** calcd. (%) for $C_{13}H_{23}NO_6$ (289.32): C 57.55, H 7.80, N 5.16, found C 57.63, H 7.90, N 4.74.



(3a*S*,4*S*,5*R*,6a*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid (89)

Aminoalcohol **88** (92 mg, 0.32 mmol) was dissolved in a 1:1:2 mixture of CCl_4-CH_3CN-H_2O and cooled to 0°C. After addition of $RuCl_3 \cdot 3H_2O$ (3.3 mg, 0.02 mmol, 5mol%) and $NaIO_4$ (340 mg, 1.59 mmol, 5 equiv) the mixture was stirred for 19 h at room temperature. The mixture was quenched with H_2O and extracted with CH_2Cl_2 (4x10ml). The resulting black sticky oil was recrystallized from ethyl acetate/hexane giving a white solid (83 mg, 0.29 mmol, 90%).

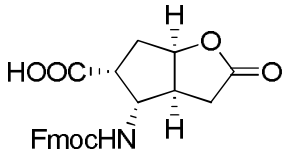
R_f = 0.18 (DCM/MeOH 9:1). – **$[\alpha]^{20}$** = - 33.9 (c = 0.53, MeOH). – **mp**: +161 °C. – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.45 (s, 9H), 2.18 (ddd, 1H, *J* = 2.26, 8.16, 15.44 Hz), 2.45-2.61 (m, 2H), 2.85 (dd, 1H, *J* = 9.06, 17.84 Hz), 2.84 (m, 1H), 3.32 (dt, 1H, *J* = 3.91, 11.34 Hz), 3.87 (m, 1H), 5.06 (dt, 1H, *J* = 2.47, 6.72 Hz), 7.06 (d, 1H, *J* = 7.68 Hz), 10.50-13.00 (1H, bs). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 28.17 (+, 3C), 33.98 (-, 1C), 34.02 (+, 1C), 44.48 (+, 1C), 47.06 (+, 1C), 59.93 (+, 1C), 82.95 (-, 1C), 83.42 (+, 1C), 158.30 (1*C*), 175.96 (1C), 177.59 (1C).– **IR** (KBr): $\tilde{\nu}$ = 3397, 3226, 2980, 2938, 1757, 1728, 1697, 1530, 1163,1001, 924, 775, 596. – **MS** (CI-MS): m/z (%) = 247.1 (100) [$M+NH^+-C_4H_8$], 286.1 (4) [MH^+], 303.1 (73) [$2M+NH_4^+$]. – **Elemental analysis** calcd. (%) for $C_{13}H_{23}NO_6$ (289.32): C 54.73, H 6.71, N 4.91, found C 54.83, H 6.71, N 4.92.



(9*H*-fluoren-9-yl)methyl (3a*S*,4*R*,5*R*,6a*R*)-5-(hydroxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-ylcarbamate (90)

66a (600 mg, 2.31 mmol, 1 equiv) was dissolved in 20 ml anhydrous methanol, 150 mg of $Pd(OH)_2$-C were added and the resulting suspension was stirred under hydrogen atmosphere overnight. After filtration through celite the methanol was removed under reduced pressure giving the crude amino alcohol in quantitative yield. The crude intermediate was dissolved in 10 ml of an acetone/water mixture (1:1) and subsequently $NaHCO_3$ (1.94 g, 23.14 mmol, 10 equiv) and FmocOSu (1.64 mg, 4.86 mmol, 2.1 equiv) were added. After stirring for 24 h acetone was removed under reduced, 5 ml of saturated NH_4Cl solution was added and the aqueous solution was extracted with ethyl acetate (3 x 30 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel eluting with 5% MeOH in dichloromethane gave a white solid (663 mg, 1.69 mmol, 73 %).

R_f = 0.65 (DCM/MeOH 9:1). – **$[\alpha]^{20}$** = - 8.4 (c = 0.7, MeOH). – **mp**: +158 °C. – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.81-1.97 (m, 2H), 2.19 (m, 1H), 2.41 (dd, 1H, *J* = 16.91, 1.65 Hz), 2.70-2.94 (m, 2H), 3.20-3.54 (m, 3H), 3.80 (m, 1H), 4.17-4.59 (broad m, 4H), 4.98 (m, 1H), 7.30-7.46 (m, 4H), 7.64-7.73 (m, 2H), 7.86-7.94 (m, 2H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 33.53 (-, 1C), 33.81 (-, 1C), 42.47 (+, 1C), 44.70 (+, 1C), 46.65 (+, 1C), 58.80 (+, 1C), 59.87 (-, 1C), 65.27 (-, 1C), 83.60 (-, 1C), 120.04 (+, 2C), 125.02 (+, 2C), 126.97 (+, 2C), 127.53 (+, 2C), 140.65 (2C), 143.72 (2C), 155.84 (1C), 176.76 (1C). – **IR** (KBr): $\tilde{\nu}$ = 3266, 1790, 1684, 1561, 1449, 1272, 1252, 1147, 1012. – **MS** (EI-MS): m/z (%) = 178.0 (100) [$C_{14}H_{10}^{+\cdot}$], 393.1 (0.5) [$M^{+\cdot}$]. – **HRMS** (EI-MS): 393.1569 ($C_{23}H_{23}NO_5$ [$M^{+\cdot}$]: calcd. 393.1576).



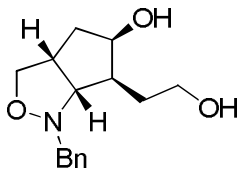
(3a*S*,4*S*,5*R*,6a*R*)-4-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid (91)

Procedure A: 89 (605 mg, 2.12 mmol) was dissolved in ethyl acetate saturated with HCl at 0°C and stirred for 1 h (TLC control). After removing the solvent under reduced pressure the hydrochloride salt of (3a*S*,4*S*,5*R*,6a*R*)-4-amino-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid was isolated as a white solid. The hydrochloride salt was then dissolved in a 2:1 mixture of acetone/water and cooled to 0°C. After addition of $NaHCO_3$ (1.07 g, 12.7 mmol, 6 equiv) and *N*-(9-Fluorenylmethoxycarbonyloxy)-succinimide (720 mg, 2.12 mmol, 1 equiv) the mixture was stirred for 2 h at 0°C and then for 24 h at room temperature. Acetone was removed under reduced pressure and 60 ml water and 60 ml diethyl ether were added and additionally stirred for 1 h. The layers were separated and the aqueous layer was extracted with 50 ml of diethyl ether. The aqueous layer was adjusted to pH 2 and extracted with ethyl acetate (4 x 80 ml). The combined organic layers were washed with 30 ml 1N HCl and brine, dried over MgSO4 filtered and concentrated. Chromatography on silica gel eluting with 10 % methanol in chloroform gave a white foaming solid (805 mg, 1.98 mmol, 93%).

Procedure B: Aminoalcohol **90** (92 mg, 0.32 mmol) was dissolved in a 1:1:2 mixture of CCl_4-CH_3CN-H_2O and cooled to 0°C. After addition of $RuCl_3 \cdot 3H_2O$ (3.3 mg, 0.02 mmol, 5 mol%) and $NaIO_4$ (340 mg, 1.59 mmol, 5 equiv) the mixture was stirred for 19 h at room temperature. The mixture was added H_2O and extracted with CH_2Cl_2 (4x10ml). The resulting black foam was purified by chromatography on silica gel eluting with 5% MeOH in dichloromethane gave a white solid (78 mg, 0.27 mmol, 72%)

R_f = 0.28 (DCM/MeOH 9:1). – **$[\alpha]^{20}$** = - 13.2 (c = 0.83, MeOH). – **mp**: +173 °C. – **^{1}H NMR** (300 MHz, DMSO): δ_H = 1.93 (m, 1H), 2.29-2.56 (m, 2H), 2.77-2.95 (m, 2H), 3.07 (m, 1H), 4.07 (m, 1H), 4.13-4.36 (m, 3H), 5.03 (m, 1H), 7.29-7.95 (m, 9H), 12.24 (1H, bs). – **^{13}C NMR** (75.5 MHz, DMSO): δ_C = 33.14 (-, 1C), 33.25 (-, 1C), 44.25 (+, 1C), 45.60 (+, 1C), 46.55 (+, 1C), 59.10 (+, 1C), 65.50 (-, 1C), 82.99 (+, 1C), 120.02 (+, 2C), 125.10 (+, 2C),

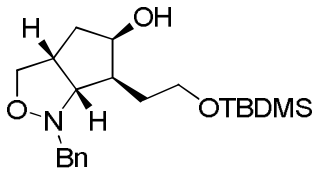
126.99 (+, 2C), 127.54 (+, 2C), 140.60 (2C), 143.59 (1C), 143.85 (1C), 155.47 (2C), 172.72 (1C), 176.72 (1C).– **IR** (KBr): $\tilde{\nu}$ = 3368, 3068, 2959, 2363, 2200, 1752, 1695, 1560, 1541, 1416, 1244, 1161, 1032, 736. – **MS** (NI-LSIMS) (MeOH/glycerol): m/z (%) = 406.1 [$(M\text{-}H^+)^-$], 498.3 [$(M\text{-}H^+)^-$+Gly^-], 590.2 [$(M\text{-}H^+)^-$+2Gly^-]. – **HRMS** (NI-LSIMS): 406.1285 ($C_{23}H_{21}NO_6$ [$M^{+\cdot}$]: calcd. 406.1291).



(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-(2-hydroxyethyl)hexahydro-1*H*-cyclopenta[*c*]isoxazol-5-ol (92)

To a solution of LAH (77 mg, 2.0 mmol, 5 equiv) in 10 ml anhydrous THF under nitrogen was slowly added **66a** (105 mg, 0.4 mmol) in 5 ml anhydrous THF at -10 °C. After stirring for 30 min the reaction mixture was quenched with 6 ml EtOAc. The reaction mixture was filtered through celite and concentrated under reduced pressure yielding a colourless solid (103 mg, 0.39 mmol, 98%).

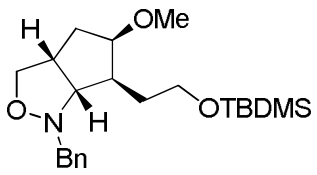
R_f = 0.40 (DCM/MeOH 9:1). – **$[\alpha]^{20}$** = -8.2 (c = 0.11, CH_2Cl_2). – **mp**: +83 °C. – **^{1}H NMR** (300 MHz, MeOD): δ_H = 1.48 (m, 1H), 1.55-167 (m, 2H), 1.69-1.80 (m, 1H), 2.10 (ddd, 1H, *J* = 1.5, 8.6, 13.6 Hz), 3.24-3.37 (m, 1H), 3.43-3.53 (m, 3H), 3.58 (dd, 1H, *J* = 2.2, 8.8 Hz), 3.75 (d, 1H, *J* = 12.6 Hz), 3.97 (d, 1H, *J* = 12.6 Hz), 4.16 (m, 1H), 4.23 (dd, 1H, *J* = 7.4, 8.8 Hz), 7.20-7.39 (m, 5H). – **^{13}C NMR** (75.5 MHz, MeOD): δ_C = 31.84 (-, 1C), 42.02 (-, 1C), 45.61 (+, 1C), 49.34 (+, 1C) 61.04 (-, 1C), 61.70 (-, 1C), 73.04 (-, 8C), 75.82 (+, 5C), 76.65 (+, 1C), 128.65 (+, 1C), 129.42 (+, 2C), 130.85 (+, 2C), 138.22 (1C), 177.53 (1C). – **IR** (film): $\tilde{\nu}$ = 3420, 2932, 2390, 2221, 1580, 1427, 1078, 1039, 868, 731, 509. – **MS** (EI-MS): m/z (%) = 91.1 (100) [$C_7H_7^+$], 263.3 (24) [$M^{+\cdot}$]. – **HRMS** (HR-EI, 70 eV): 263.15208 ($C_{15}H_{17}NO_3$ [$M^{+\cdot}$]: calcd. 263.1521).



(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-[2-(*tert*-butyldimethylsiloxy)ethyl]hexahydro-1*H*-cyclopenta[*c*]isoxazol-5-ol (93)

Diol **92** (3.5g, 13.30 mmol) was dissolved 180 ml DCM and *tert*-butyltrimethylsilyl chloride (2.20g, 14.62 mmol, 1.1 equiv), triethylamine (2.3 ml, 15.95 mmol, 1.2 equiv) and DMAP (0.16 g, 1.33 mmol, 0.1 equiv) were added and stirred overnight (18 h). After addition of 10 ml saturated NH_4Cl solution the layers were separated and the aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate in hexanes (2:1) gave a colourless oil (4.6 g, 12.18 mmol, 92 %).

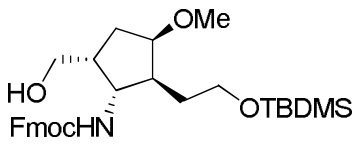
R_f = 0.43 (hexanes/ethyl acetate 1:1). – $[\alpha]^{20}$ = - 18.6 (c = 0.54, MeOH). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.49 (m, 1H), 1.62 (dt, 1H, *J* = 2.3, 5.0 Hz), 1.68 (m, 1H), 1.81 (m, 1H), 2.21 (m, 1H), 3.18 (s, 1H), 3.32 (m, 1H), 3.40 (m, 1H), 3.52 (m, 1H), 3.64 (m, 2H), 3.71 (d, 1H, *J* = 12.3 Hz), 4.05 (d, 1H, *J* = 12.3 Hz), 4.23 (m, 1H), 4.31 (m, 1H), 7.26-7.39 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.64 (+, 1C), -5.59 (+, 1C), 18.14 (1C), 25.85 (+, 3C), 31.03 (-, 1C), 39.96 (-, 1C), 44.59 (+, 1C), 50.99 (+, 1C), 60.52 (-, 1C), 62.60 (-, 1C), 72.47 (-, 1C), 75.15 (+, 1C), 75.58 (+, 1C), 127.44 (+, 1C), 128.36 (+, 1C), 129.41 (+, 1C), 137.16 (1C).– **IR** (film): $\tilde{\nu}$ = 3437, 3031, 2954, 2858, 2200, 1463, 1254, 1087, 1005, 835, 777. – **MS** (EI-MS): m/z (%) = 91.1 (100) [$C_7H_7^+$], 106.1 (21), 320.2 (21) [M^+-C_4H_9], 377.2 (10) [M^+]. – **HRMS** (HR-EI, 70 eV): 377.2384 ($C_{21}H_{35}NO_3Si$ [$M^{+\cdot}$]: calcd. 377.2386).



(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-[2-(*tert*-butyldimethylsiloxy)ethyl]-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazole (94)

To a solution of alcohol **93** (4.36 g, 11.55 mmol) in 100 ml anhydrous THF was added NaH (60 % suspension in paraffin oil, 0.51 g, 12.71 mmol, 1.1 eq) at 0 °C. After stirring for 1 hour methyl iodide (3.6 ml, 57.73 mmol, 5 equiv) was added and stirred overnight (14 h). Subsequently 10 ml of saturated NH_4Cl solution was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate in hexanes (1:10) gave a colourless oil (3.9 g, 9.96 mmol, 86 %).

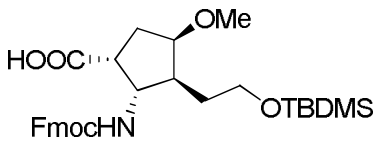
R_f = 0.64 (hexanes/ethyl acetate 1:1). – $[\alpha]^{20}$ = - 29.4 (c = 0.38, MeOH). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 1.35-151 (m, 2H), 1.63 (m, 1H), 1.84 (m, 1H), 2.16 (ddd, 1H, *J* = 3.16, 8.64, 13.58 Hz), 3.10 (m, 1H), 3.22 (s, 3H), 3.29 (m, 1H), 3.55 (m, 3H), 3.71 (d, 1H, *J* = 12.90), 3.75 (m, 1H), 3.94 (d, 1H, *J* = 12.90), 4.13 (m, 1H), 7.18-7.36 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.20 (+, 1C), -5.17 (+, 1C), 18.39 (1C), 26.04 (+, 1C), 30.42 (-, 1C), 35.74 (-, 1C), 44.14 (+, 1C), 45.82 (+, 1C), 56.69 (+, 1C), 60.39 (-, 1C), 62.36 (-, 1C), 72.05 (-, 1C), 77.50 (+, 1C), 83.61 (+, 1C), 127.35 (+, 1C), 128.35 (+, 2C), 129.18 (+, 2C), 137.39 (1C).– **IR** (film): $\tilde{\nu}$ = 3030, 2951, 2928, 2857, 2200, 1462, 1358, 1252, 1090, 835, 776, 728, 697. – **MS** (EI-MS): m/z (%) = 91.1 (100) [$C_7H_7^+$], 334.2 (28) [$MH^{\cdot+}$-C_4H_9], 360.2 (4) [$MH^{\cdot+}$-OMe], 376.3 (6) [$MH^{\cdot+}$-CH_3], 391.3 (22) [$MH^{\cdot+}$]. – **HRMS** (HR-EI, 70 eV): 391.2547 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 391.2543).



(9*H*-fluoren-9-yl)methyl (1*R*,2*S*,3*R*,5*R*)-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-(hydroxymethyl)-3-methoxycyclopentylcarbamate (96)

94 (500 mg, 1.28 mmol, 1 equiv) was dissolved in 20 ml anhydrous methanol, 100 mg of $Pd(OH)_2$-C were added and the resulting suspension was stirred under hydrogen atmosphere overnight. After filtration through celite the methanol was removed under reduced pressure giving the crude amino alcohol in quantitative yield. The crude intermediate was dissolved in 10 ml of an acetone/water mixture (1:1) and subsequently $NaHCO_3$ (1.08 g, 12.80 mmol, 10 equiv) and FmocOSu (907 mg, 2.69 mmol, 2.1 equiv) were added. After stirring for 24 h acetone was removed under reduced, 5 ml of saturated NH_4Cl solution was added and the aqueous solution was extracted with ethyl acetate (3 x 20 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel eluting with 2% MeOH in dichloromethane gave a white solid (580 mg, 1.10 mmol, 86 %).

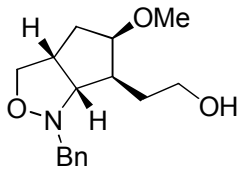
R_f = 0.48 (DCM/MeOH 95:5). – $[\alpha]^{20}$ = - 45.6 (c = 0.10, MeOH). mp = 87 °C. – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 0.05 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.50-1.70 (m, 2H), 1.73-1.93 (m, 2H), 1.99 (ddd, 1H, , *J* = 13.86, 8.37, 0.99 Hz), 2.28 (broad s, 1H), 2.48 (m, 1H), 3.26 (s, 3H), 3.47-3.77 (m, 5H), 4.00 (m, 1H), 4.22 (m, 1H), 4.33-4.55 (m, 2H), 5.26 (d, 1H, *J* = 8.23 Hz), 7.27-7.44 (m, 4H), 7.60 (m, 2H), 7.76 (m, 2H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.27 (+, 1C), -5.23 (+, 1C), 18.35 (1C), 26.01 (+, 3C), 30.22 (-, 1C), 31.16 (-, 1C), 40.13 (+, 1C), 47.36 (+, 1C), 47.68 (+, 1C), 56.49 (+, 1C), 56.89 (+, 1C), 61.70 (-, 1C), 62.51 (-, 1C), 66.62 (-, 1C), 80.56 (+, 1C), 119.95 (+, 1C), 119.98 (+, 1C), 125.03 (+, 1C), 125.10 (+, 1C), 127.07 (+, 2C), 127.86 (+, 2C), 141.34 (2C), 143.99 (2C), 157.23 (1C).– **IR** (film): $\tilde{\nu}$ = 3307, 2933, 2859, 1969, 1686, 1547, 1258, 1081. – **MS** (PI-LSIMS): m/z (%) = 526.6 [MH^+], 304.4 [MH^+-Fmoc]. – **HRMS** (HR-FAB): 526.29775 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 391.2989).



(1*R*,2*S*,3*S*,4*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-methoxycyclopentanecarboxylic acid (97)

$RuCl_3$ hydrate (35-40 % Ru; 17 mg, 0.03 mmol, 5 mol%) and $NaIO_4$ (610 mg, 2.85 mmol, 5 equiv) were dissolved in 14 ml of a CCl_4/CH_3CN/water (2:2:3) mixture and cooled to 0 °C. To that solution **96** (300 mg, 0.57 mmol, 1 equiv) in 3 ml CH_3CN was added and stirred at 0°C until the starting material was consumed (TLC control). After addition of 10 ml of diethylether and 5 ml of brine the layers were separated and the aqueous layer was extracted with diethylether (5 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with 5% MeOH in dichloromethane gave a white solid (228 mg, 0.42 mmol, 74 %).

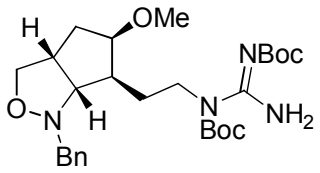
R_f = 0.16 (DCM/MeOH 95:5). – $[\alpha]^{20}$ = - 59.3 (c = 0.78, MeOH). mp: 115 °C. – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 0.07 (s, 6H), 0.91 (s, 9H), 1.70 (m, 1H), 1.83 (m, 1H), 2.00 (m, 1H), 2.06-2.21 (m, 2H), 3.26 (m, 1H), 3.31 (s, 3H), 3.70 (m, 3H), 4.16-4.46 (m, 4H), 5.51 (d, 1H, *J* = 5.50 Hz), 7.27-7.45 (m, 4H), 7.58-7.44 (m, 2H), 7.74 (m, 2H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.31 (+, 1C), -5.22 (+, 1C), 18.37 (1C), 26.04 (+, 3C), 29.39 (-, 1C), 31.51 (-, 1C), 44.37 (+, 1C), 45.88 (+, 1C), 47.01 (+, 1C), 56.49 (+, 1C), 57.79 (+, 1C), 62.02 (-, 1C), 68.20 (-, 1C), 80.53 (+, 1C), 119.95 (+, 2C), 125.19 (+, 1C), 125.30 (+, 1C), 127.09 (+, 2C), 127.67 (+, 2C), 141.27 (2C), 143.69 (2C), 143.94 (1C), 158.96 (1C), 178.04 (q).– **IR** (film): $\tilde{\nu}$ = 2857, 1704, 1661, 1420, 1336, 1082. – **MS** (PI-LSIMS): m/z (%) = 540.5 [MH^+], 318.4 [MH^+-Fmoc]. – **HRMS** (HR-FAB): 540.27908 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 540.2781).



2-[(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl]ethanol (98)

To solution of **94** (1.94 g, 4.95 mmol, 1 equiv) in 9 ml THF was added 18 ml of water and the solution was cooled to 0°C. Subsequently, 36 ml of AcOH were slowly added and the resulting mixture was allowed to come to ambient temperature and stirred for 6 hours. The solvent mixture was removed under reduced pressure and the residue was chromatographed on silica gel eluting with ethyl acetate in hexanes (2:1) giving a colourless solid (1.21 g, 4.36 mmol, 88%).

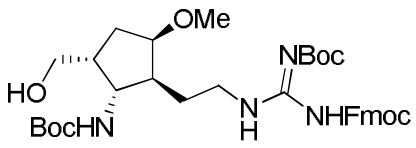
R_f = 0.12 (ethyl acetate/hexanes 1:1). – $[\alpha]^{20}$ = - 4.7 (c = 0.74, CH_2Cl_2). mp: 57 °C. – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.49 (dddd, 1H, *J* = 13.98, 7.58, 3.70, 0.35 Hz), 1.63 (m, 1H), 1.81 (m, 1H), 1.99 (m, 1H), 2.41 (ddd, 1H, *J* = 13.86, 8.92, 0.96 Hz), 3.16-3.30 (m, 1H), 3.27 (s, 3H), 3.47 (m, 1H), 3.54-3.66 (m, 3H), 3.70 (m, 1H), 3.75 (d, 1H, *J* = 12.91 Hz), 3.99 (d, 1H, *J* = 12.90 Hz), 4.21 (m, 1H), 7.23-7.40 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 30.70 (-, 1C), 36.30 (-, 1C), 43.94 (+, 1C), 47.45 (+, 1C), 56.62 (+, 1C), 59.62 (-, 1C), 61.13 (-, 1C), 72.09 (-, 1C), 75.28 (+, 1C), 85.59 (+, 1C), 127.70 (+, 1C), 128.51 (+, 2C), 129.39 (+, 2C), 136.40 (1C).– **IR** (film): $\tilde{\nu}$ = 3267, 2927, 2882, 1735, 1455,1440, 1077, 1053. – **MS** (EI-MS): m/z (%) = 277.2 [$MH^{+\cdot}$], 262 [MH^+-CH_3], 246.2 [MH^+-OCH_3], 91.0 [$C_7H_7^+$]. – **HRMS** (EI-MS, 70 eV): 277.16747 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 277.1678).



***tert*-butyl {(*Z*)-amino[{2-[(3a*R*,5*R*,6*S*,6a*R*)1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl]ethyl}(*tert*-butoxycarbonyl)amino]methylidene}carbamate (99)**

Alcohol **98** (1.7 g, 6.13 mmol), PPh_3 (2.41 g, 9.19 mmol, 1.5 equiv) and *tert*-butyl {(*Z*)-amino[(*tert*-butoxycarbonyl)amino]methylidene}carbamate (2.38 g, 9.19 mmol, 1.5 equiv) were dissolved in 80 ml anhydrous THF and cooled to 0 °C. To the solution was slowly added DEAD (1.45 ml, 9.19 mmol, 1.5 equiv) in 10 ml anhydrous THF and the resulting mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was treated with 200 ml of pentane/ethyl acetate (9:1) mixture, filtered through celite and concentrated. Chromatography on silica gel eluting with ethyl acetate in hexanes (gradient from 10% - 30 % ethyl acetate) gave a colourless oil (2.42 g, 4.66 mmol, 76 %).

R_f = 0.50 (ethyl acetate/hexanes 1:1). – $[\alpha]^{20}$ = - 7.7 (c = 1.2, CH_2Cl_2).- **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.43 (s, 9H), 1.45-1.53 (m, 2H), 1.51 (s, 9H), 1.66-1.89 (m, 2H), 2.25 (ddd, 1H, *J* = 13.58, 8.78, 2.88 Hz), 3.17 (m, 1H), 3.29 (s, 3H), 3.48 (m, 1H), 3.59 (dd, 1H, *J* = 8.78, 2.47 Hz), 3.77-3.89 (m, 2H), 3.93 (d, 2H, *J* = 5.21 Hz), 4.06 (m, 1H), 4.16 (m, 1H), 7.19-7.41 (m, 5H), 9.24 (broad s, 1H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 26.76 (-, 1C), 28.07 (+, 3 C), 28.28 (+, 3C), 35.92 (-, 1C), 43.58 (-, 1C), 44.45 (+, 1C), 46.98 (+, 1C), 56.75 (+, 1C), 59.97 (-, 1C), 71.56 (-, 1C), 75.66 (+, 1C), 78.31 (1C), 83.43 (1C), 83.83 (+, 1C), 127.19 (+, 1C), 128.25 (+, 2C), 129.39 (+,2C), 137.80 (1C), 155.13 (1C), 160.51 (1C), 163.83 (1C).– **IR** (film): $\tilde{\nu}$ = 3383, 2975, 2932, 1710, 1607,1270, 1249, 1143, 1116. – **MS** (LSIMS): m/z (%) = 519.3 [MH^+], 419.3 [MH^+-Boc], 319.3 [MH^+-2Boc]. – **HRMS** (LSIMS): 519.31685 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 519.3183).



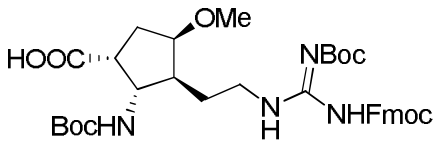
***Tert*-butoxy-(1*R*,2*S*,3*R*,5*R*)-2-(2-(1-(*tert*-butoxycarbonyl)-2-(9*H*-fluoren-9-yl)-guanidino) ethyl)-5-(hydroxymethyl)-3-methoxycyclopentylcarbamate (101)**

99 (3.25 g, 6.27 mmol, 1 equiv) was dissolved in 60 ml anhydrous methanol, 600 mg of $Pd(OH)_2$-C was added and the resulting suspension was stirred under hydrogen atmosphere for 9 hours. After filtration through celite methanol was removed under reduced pressure giving the crude amino alcohol in quantitative yield. The crude intermediate was dissolved in 120 ml of an acetone/water mixture (1:1) and subsequently $NaHCO_3$ (5.27 g, 62.70 mmol, 10 equiv) and FmocOSu (4.44 g, 13.17 mmol, 2.1 equiv) were added. After stirring for 24 h acetone was removed under reduced pressure, 15 ml of saturated NH_4Cl solution was added and the aqueous solution was extracted with ethyl acetate (4 x 60 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel eluting with ethyl acetate in hexanes (1:2) gave a white solid foam (2.82 g, 4.31 mmol, 69 %).

NMR spectra showed a mixture of rotamers (92:8, assigned by ratio of amide peaks at 8.27 and 8.49); High temperature NMR experiments failed due to decomposition Assignment was possible only for the major isomer)

R_f = 0.30 (ethyl acetate/hexanes 1:1). – $[\alpha]^{20}$ = - 28.8 (c = 0.8, CH_2Cl_2). – mp: ~88 °C (decomposition). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.44 (s, 9H), 1.47-1.55 (m, 1H), 1.51 (s, 9H), 1.61-1.68 (m, 1H), 1.85-2.04 (m, 3H), 2.65 (m, 1H), 3.13-3.26 (m, 2H), 3.31 (s, 3H), 3.55 (m, 1H), 3.64 (m, 1H), 3.80 (m, 1H), 4.25-4.34 (m, 3H), 4.41 (m, 1H), 4.76 (broad s, 1H), 7.28-7.42 (m, 4H), 7.66 (m, 2H), 7.55 (m, 2H), 8.50 (d, 1H, *J* = 7.9), 9.39 (broad s, 1H), 11.37 (s, 1H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 28.02 (+, 3C), 28.23 (-, 1C), 28.43 (+, 3C), 31.14 (-, 1C), 39.70 (-, 1C), 42.10 (+, 1C), 47.10 (+, 1C), 50.02 (+, 1C), 56.54 (+, 1C), 57.37 (+, 1C), 61.80 (-, 1C), 67.81 (-, 1C), 78.98 (1C), 80.23 (+, 1C), 83.92 (1C), 119.84 (+, 2C), 125.40 (+, 1C), 125.48 (+, 1C), 127.11 (+, 1C), 127.15 (+, 1C), 127.59 (+, 2C), 141.17 (1C), 141.22 (1C), 144.10 (1C), 144.13 (1C), 153.14 (1C), 156.03 (1C), 156.91 (1C), 163.30 (1C).– **IR** (film): $\tilde{\nu}$ = 3370, 3321, 2977, 2935, 2364, 1713, 1612, 1249, 1148, 1108. – **MS**

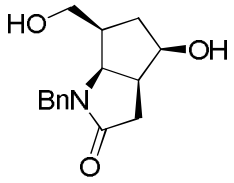
(LSIMS): m/z (%) = 653.4 [MH^+], 553.4 [MH^+-Boc], 453.4 [MH^+-2Boc], 431.5 [MH^+-Fmoc]. – **HRMS** (LSIMS): 653.35464 ($C_{22}H_{37}NO_3Si$ [$M^{+\cdot}$]: calcd. 653.3550).



(1*R*,2*S*,3*S*,4*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(2-(2,3-bis(*tert*-butoxycarbonyl)guanidino)ethyl)-4-methoxycyclopentanecarboxylic acid (102)

$RuCl_3 \cdot H_2O$ (35 mg, 0.06 mmol, 5mol%) was dissolved in 3ml CCl_4 and cooled in an ice bath. To this solution were subsequently added $NaIO_4$ (1.26 g, 5.87 mmol, 5 equiv) in 7 ml H_2O and alcohol **101** (767 mg, 1.17 mmol, 1 equiv) in 5 ml of a CH_3CN and the resulting mixture was stirred for 5 h. Addition of 5 ml of water as followed by extraction with CH_2Cl_2 (4 x 20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. A quick chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate (5:1) was performed, which was followed by chromatography on neutral alumina eluting with CH_2Cl_2/MeOH/H_2O (75:20:5) giving a white foam (568 mg, 0.85 mmol, 73%).

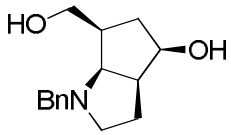
R_f = 0.12 (CH_2Cl_2/MeOH 95:5). – $[\alpha]^{20}$ = - 39.0 (c = 0.8, MeOH). – mp: ~99 °C. – **^{1}H NMR** (600 MHz Kryo, MeOD): δ_H = 1.41 (s, 9H), 1.50 (s, 9H), 1.58 (m, 1H), 1.78 (m, 1H), 2.08-2.16 (m, 2H), 2.24 (m, 1H), 3.03-3.17 (m, 2H), 3.27 (m, 1H), 3.32 (s, 3H), 3.85 (m, 1H), 4.24-4.38 (m, 3H), 4.73 (m, 1H), 7.30 (m, 2H), 7.37 (m, 2H), 7.66 (m, 2H), 7.78 (m, 2H). – **^{13}C NMR** (150.9 MHz Kryo, MeOD): δ_C = 27.82 (1C), 28.24 (3C), 28.82 (3C), 34.04 (1C), 39.94 (1C), 45.85 (1C), 48.32 (1C), 48.47 (1C), 56.84 (1C), 57.22 (1C), 69.24 (1C), 79.88 (1C), 81.22 (1C), 84.83 (1C), 120.90 (1C), 120.91 (1C), 126.32 (1C), 126.39 (1C), 128.16 (2C), 128.72 (1C), 128.74 (1C), 142.52 (1C), 142.56 (1C), 145.41 (1C), 145.47 (1C), 153.89 (1C), 158.22 (1C), 158.53 (1C), 164.97 (1C), 178.06 (1C).– **IR** (film): $\tilde{\nu}$ 3350, 2976, 2933, 1710, 1609, 1249, 1108. – **MS** (ESIMS): m/z (%) = 667.2 [MH^+], 576.3 [MH^+-Boc], 467.1 [MH^+-2Boc], 2 isomers due to Boc migration at 13.34 min and 13.93 min.



(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-4-hydroxy-6-(hydroxymethyl)hexahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (116)

A mixture of zinc dust (1.16 g, 17.7 mmol, 5 equiv) in 5ml acetic acid was added copper(II) acetate (5.5 mg, 0.03 mmol, 0.8 mol%) and stirred for 15 minutes. To that mixture was added **66b** (879 mg, 3.39 mmol, 1 equiv) in 3 ml AcOH/H_2O (2:1) and the solution was heated to 80°C until starting material was consumed (TLC control). After cooling to room temperature EDTA (0.4 g) were added and stirred for additional 15 minutes. Upon addition of 4M NaOH the pH of the solution was adjusted to pH 10 and subsequently extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture (900 mg) was obtained as a mixture of **87** and **116** was therefore used in the next step without further purification. The crude mixture was dissolved in 5 ml MeOH, upon addition of DBU (1.5 ml, 10.17 mmol, 3equiv) the mixture was stirred overnight. After addition of EtOAc the organic layers were washed with KHSO4 solution, dried over MgSO4, filtered and concentrated under reduced pressure. Chromatography on silica gel eluting with 5% MeOH in CH_2Cl_2 gave white solid foam (712 g, 2.75 mmol, 81 %).

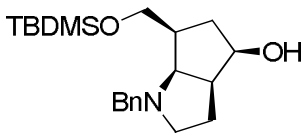
R_f = 0.27 (CH_2Cl_2/MeOH 9:1). – $[\alpha]^{20}$ = - 48.2 (c = 0.8, MeOH).– **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.67 (m, 1H), 1.99 (m, 1H), 2.20 (m, 1H), 2.36 (dd, 1H, *J* = 13.3, 19.9 Hz), 2.85 (m, 1H), 3.68 (dd, 1H, *J* = 6.2, 10.8 Hz), 3.77 (dd, 1H, *J* = 4.4, 10.8 Hz), 3.90 (m, 1H), 4.04 (d, 1H, *J* = 14.7 Hz), 4.21 (m, 1H), 5.22 (d, 1H, *J* = 14.7 Hz), 7.23-7.35 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 30.02 (-, 1C), 36.94 (+, 1C), 40.17 (-, 1C), 43.05 (-, 1C), 46.28 (+, 1C), 61.67 (+, 1C), 62.00 (-, 1C), 70.67 (+, 1C), 127.64 (+, 1C), 128.31 (+, 2C), 128.71 (+, 2C), 136. 63 (q, 1C), 176.86 (q, 1C).– **IR**: $\tilde{\nu}$ = 3399, 2892, 2977, 1651, 1451, 1423, 1255, 1074, 1052, 1014. – **MS** (EI-MS): m/z (%) = 261.1 (23.7) [$M^{+\cdot}$], 244.1 (7.4) [$M^{+\cdot}$–OH], 91.1 (100) [$C_7H_7^+$]. – **HRMS** (EI-MS): 261.1366 ($C_{15}H_{19}NO_3$ [$M^{+\cdot}$]: calcd. 261.1368).



(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-(hydroxymethyl)octahydrocyclopenta[*b*]pyrrol-4-ol (117)

To a solution of LAH (241 mg, 6.36 mmol, 3 equiv) in 15 ml anhydrous THF under nitrogen was slowly added **116** (554 mg, 2.12 mmol, 1 equiv) in 10 ml anhydrous THF at 0 °C. After stirring for 45 min the reaction mixture was quenched with 10 ml EtOAc. The reaction mixture was filtered through celite and concentrated under reduced pressure yielding a colourless solid (422 mg, 1.71 mmol, 81%).

R_f = 0.14 (CH_2Cl_2/MeOH 9:1). – $[\alpha]^{20}$ = - 41.1 (c = 0.3, MeOH). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.68 (m, 1H), 1.98 (m, 1H), 2.19 (m, 1H), 2.34 (dd, 1H, *J* = 13.3, 19.9 Hz), 2.83 (m, 2H), 3.62-3.77 (m, 3H), 3.88 (m, 1H), 4.02 (d, 1H, *J* = 14.8 Hz), 4.18 (m, 2H), 5.17 (d, 1H, *J* = 14.8 Hz), 7.22-7.34 (m, 5H) . – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 23.39 (-, 1C), 39.63 (+, 1C), 39.85 (-, 1C), 49.38 (+, 1C), 56.52 (-, 1C), 62.04 (-, 1C), 63.46 (-, 1C), 71.13 (+, 1C), 71.69 (+, 1C), 127.54 (+, 1C), 128.59 (+, 2C), 129.16 (+, 2C), 137.95 (1C).– **IR** (film): $\tilde{\nu}$ = 3290, 3267, 2922, 2849, 2785, 1728, 1453, 1331, 1050, 1029, 1002, 751. – **MS** (EI-MS): m/z (%) = 247.2 [$M^{+\cdot}$], 230.2 [$M^{+\cdot}$-$OH^{\cdot}$], 91.1 [$C_7H_7^+$]. – **HRMS** (EI-MS): 247.1566 ($C_{15}H_{21}NO_2$ [$M^{+\cdot}$]: calcd. 247.1572).

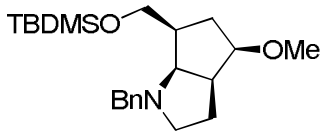


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-((tert-butyldimethylsilyloxy)methyl)octahydrocyclopenta [*b*]pyrrol-4-ol (118)

Diol **117** (600 mg, 2.43 mmol, 1 equiv) was dissolved in 20 ml DCM and *tert*-butyltrimethylsilyl chloride (403 mg, 2.67 mmol, 1.1 equiv), triethylamine (406 µl, 2.92 mmol, 1.2 equiv) and DMAP (30 mg, 0.24 mmol, 0.1 equiv) were added and stirred overnight (18 h). After addition of 5 ml saturated NH_4Cl solution the layers were separated and the

aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with 5% MeOH in CH_2Cl_2 gave a colourless oil (690 mg, 1.91 mmol, 79 %).

R_f = 0.27 (ethyl acetate/hexanes 1:1). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = -0.06 (s, 3H), 0.00 (s, 9H), 1.54 (m, 2H), 1.77 (m, 2H), 1.93 (m, 2H), 2.09 (m, 1H), 2.73 (p, 1H, *J* = 8.5 Hz), 2.92 (m, 1H), 3.15 (m, 2H), 3.68 (dd, 1H, *J* = 5.6, 10.0 Hz), 3.98 (m, 1H), 4.08 (ddd, 1H, J = 5.8, 7.9, 9.5 Hz), 4.31 (d, 1H, *J* = 13.6 Hz), 7.17-7.31 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.37 (+, 2C), 18.22 (1C), 24.56 (-, 1C), 25.90 (+, 3C), 35.02 (-, 1C), 43.50 (+, 1C), 47.46 (+, 1C), 55.20 (-, 1C), 62.59 (-, 1C), 68.16 (+, 1C), 72.89 (+, 1C), 128.16 (4C), 128.48 (2C). – **IR** (film): $\tilde{\nu}$ = 3289, 2856, 2791, 1453, 1253, 1089, 1059, 833. – **MS** (ESIMS): m/z = 376.1 [MH^+]. – **HRMS** (EI-MS): 375.2588 ($C_{22}H_{37}NO_2Si$ [$M^{+\cdot}$]: calcd. 375.2594).

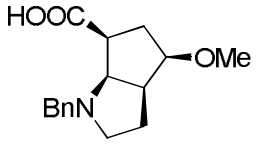


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-((tert-butyldimethylsilyloxy)methyl)-4-methoxyoctahydrocyclopenta[*b*]pyrrole (118)

To a solution of alcohol **118** (20 mg, 0.05 mmol, 1 equiv) in 5 ml anhydrous THF was added NaH (60 % suspension in paraffin oil, 5 mg, 0.11 mmol, 2.2 equiv). After stirring for 1 hour methyl iodide (16 µl, 0.25 mmol, 5 equiv) was added and stirred overnight (18 h). Subsequently 2 ml of half saturated NH_4Cl solution was and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate in hexanes (1:10) gave a colourless oil (14 mg, 0.04 mmol, 77 %).

R_f = 0.53 (ethyl acetate/hexanes 1:1). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = -0.06 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 1.44 (m, 1H), 1.59 (m, 1H), 1.69-1.94 (m, 3H), 2.02 (ddd, 1H, *J* = 5.5, 8.7, 12.0 Hz), 2.82 (m, 2H), 3.08 (dd, 1H, *J* = 6.0, 8.4 Hz), 3.16 (d, 1H, *J* = 13.7 Hz), 3.30 (s, 3H), 3.63 (m, 2H), 4.00 (dd, 1H, *J* = 8.2, 9.8 Hz), 4.29 (d, 1H, *J* = 13.7 Hz), 7.17-7.32 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = -5.37 (+, 2C), 18.22 (1C), 24.89 (-, 1C), 25.91 (+,

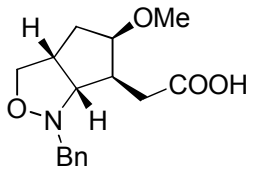
3C), 31.15 (-, 1C), 43.37 (+, 1C), 44.80 (+, 1C), 54.95 (-, 1C), 57.32 (+, 1C), 60.53 (-, 1C), 62.58 (-, 1C), 67.39 (+, 1C), 81.57 (+, 1C), 126.46 (+, 1C), 128.10 (+, 2C), 128.43 (+, 2C), 140.51 (1C).– **IR** (film): $\tilde{\nu}$ = 2927, 2855, 2791, 1462, 1357, 1253, 1091, 836. – **MS** (ESIMS): m/z = 362.1 [MH^+]. – **HRMS** (ES-MS): 361.2431 ($C_{21}H_{35}NO_2Si$ [$M^{+\cdot}$]: calcd. 361.2437).



(3aS,4R,6S,6aR)-1-benzyl-4-methoxyoctahydrocyclopenta[b]pyrrole-6-carboxylic acid (119)

To a solution of **118** (200 mg, 0.53 mmol, 1 equiv) in 5 ml acetone was added 1 ml of Jones reagent at 0°C and stirred for 5 hours at room temperature. After addition of 2 ml isopropanol and 30 ml of ethylacetate the mixture of organic solvents was washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with 2% MeOH in DCM giving a colourless solid (120 mg, 0.44 mmol, 83 %).

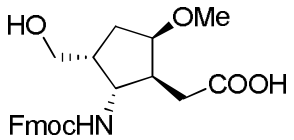
R_f = 0.18 (CH_2Cl_2/MeOH 1:1). – $[\alpha]^{20}$ = - 2.6 (c = 0.3, MeOH). – **^{1}H NMR** (300 MHz, MeOD): δ_H = 1.94-2.21 (m, 4H), 2.68 (m, 1H), 3.11-3.26 (m, 2H), 3.29 (s, 1H), 3.77 (m, 1H), 4.07 (m, 1H), 4.16 (d, 1H, *J* = 12.8 Hz), 4.38 (d, 1H, *J* = 12.8 Hz), 7.43 (m, 3H), 7.53 (m, 2H). – **^{13}C NMR** (75.5 MHz, MeOD): δ_C = 24.40 (-, 1C), 36.48 (-, 1C), 42.24 (+, 1C), 47.46 (+, 1C), 55.34 (-, 1C), 57.62 (+, 1C), 59.98 (-, 1C), 71.94 (+, 1C), 81.25 (+, 1C), 130.37 (+, 2C), 130.71 (+, 1C), 131.45 (+, 2C), 133.14 (1C), 180.08 (1C).– **IR** (neat): $\tilde{\nu}$ = 3412, 2977, 2934, 1602, 1457, 1370, 1205, 1107, 1205, 1107, 1041, 936, 762. – **MS** (EI-MS): m/z (%) = 275.1 (11.9) [$M^{+\cdot}$], 91.0 (100) [$C_7H_7^+$]. – **HRMS** (EI-MS, 70 eV): 275.1514 ($C_{16}H_{21}NO_4$ [$M^{+\cdot}$]: calcd. 275.1521).



[(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl]acetic acid (138)

To a solution of **94** (550 mg, 1.40 mmol, 1 equiv) in 10 ml acetone was added 2 ml of Jones reagent at 0°C and stirred for 2 hours at room temperature. After addition of 5ml isopropanol and 60 ml of ethylacetate the mixture of organic solvents was washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel eluting with 2% MeOH in DCM giving an colorless oil (350 mg, 1.20 mmol, 86 %).

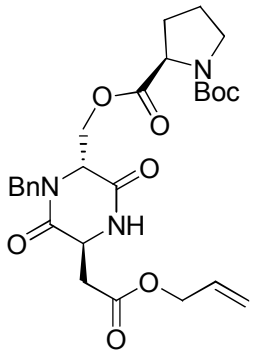
R_f = 0.14 (ethyl acetate). – $[\alpha]^{20}$ = - 44.1 (c = 0.07, MeOH). – **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 1.57 (ddd, 1H, *J* = 4.1, 6.8, 14.0 Hz), 2.26 (m, 3H), 2.57 (dd, 1H, *J* = 6.6, 16.5 Hz), 3.16 (m, 1H), 3.25 (s, 3H), 3.46 (m, 2H), 3.64 (dd, 1H, *J* = 2.9, 8.9 Hz), 3.77 (d, 1H, *J* = 12.8 Hz), 3.85 (m, 1H), 3.99 (d, 1H, *J* = 12.8 Hz), 4.21 (m, 1H), 7.27-7.37 (m, 5H). – **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ_C = 32.98 (-, 1 C), 35.77 (-, 1 C), 43.70 (+, 1 C), 44.66 (+, 1 C), 56.81 (+, 1 C), 59.78 (-, 1 C), 72.66 (-, 1 C), 74.95 (+, 1 C), 83.78 (+, 1 C), 127.78 (+, 1 C), 128.54 (+, 2 C), 129.30 (+, 2 C), 136.10 (1 C), 176.96 (1 C).– **IR** (film): $\tilde{\nu}$ = 2932, 2882, 1706, 1455, 1255, 1177, 1131, 1083. – **MS** (EI-MS): m/z (%) = 291.1 (22.4) [$M^{+\cdot}$], 276.1 (13.7) [M^+-CH_3], 260.1 (4.3), [M^+-COOH], 246.1 (3.1) [M^+-OCH_3], 91.0 (100)[$C_7H_7^+$]. – **HRMS** (EI-MS, 70 eV): 291.1469 ($C_{16}H_{21}NO_4$ [$M^{+\cdot}$]: calcd. 291.1481).



2-((1*S*,2*R*,3*R*,5*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(hydroxymethyl)-5-methoxycyclopentyl)acetic acid (139)

138 (1.1 g, 3.78 mmol, 1 equiv) was dissolved in 25 ml anhydrous methanol, 150 mg of $Pd(OH)_2$-C were added and the resulting suspension was stirred under hydrogen atmosphere overnight. After filtration through celite the methanol was removed under reduced pressure giving the crude amino alcohol in quantitative yield. The crude intermediate was dissolved in 20 ml of an acetone/water mixture (1:1) and subsequently $NaHCO_3$ (2.95 g, 37.80 mmol, 10 equiv) and FmocOSu (2.67 g, 7.94 mmol, 2.1 equiv) were added. After stirring for 24 h acetone was removed under reduced, 15 ml of saturated NH_4Cl solution was added and the aqueous solution was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel eluting with 5% MeOH in dichloromethane gave a white solid (930 mg, 2.19 mmol, 58 %).

R_f = 0.25 (DCM/MeOH 95:5). – $[\alpha]^{20}$ = - 55.7 (c = 0.73, MeOH). mp: 133 °C. – **^{1}H NMR** (300 MHz, DMSO): δ_H = 1.63 (m, 1H), 1.95 (m, 1H), 2.10-2.35 (m, 2H), 2.38 (m, 1H), 3.13 (s, 3H), 3.28-3.49 (m, 2H), 3.76 (m, 2H), 4.19-4.45 (m, 3H), 7.05 (d, 1H, *J* = 5.35 Hz), 7.33-7.50 (m, 4H), 7.75 (m, 2H), 7.93 (m, 1H). – **^{13}C NMR** (75.5 MHz, DMSO): δ_C = 31.40 (-, 1 C), 31.73 (-, 1 C), 39.01 (+, 1 C), 44.99 (+, 1 C), 46.69 (+, 1 C), 55.43 (+, 1 C), 55.93 (+, 1 C), 61.24 (-, 1 C), 65.22 (-, 1 C), 79.40 (+, 1 C), 120.01 (+, 2 C), 125.11 (+, 2 C), 126.93 (+, 2 C), 127.52 (+, 2 C), 140.61 (2 C), 143.70 (1 C), 143.83 (1 C), 150.89 (1 C), 173.97 (1 C).– **IR** (film): $\tilde{\nu}$ = 3312, 2935, 2361, 1683, 1539,1450, 1262, 1082, 1021. – **MS** (PI-LSIMS): m/z = 426.3 [MH^+], 851.3 [2 x MH^+]. – **HRMS** (PI-LSIMS): 426.1915 ($C_{24}H_{27}NO_6$ [MH^+]: calcd. 426.1913).

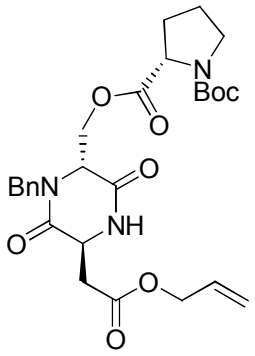


(*R*)-2-((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methyl 1-tert-butyl pyrrolidine-1,2-dicarboxylate (156a)

Under nitrogen at 0 °C were dissolved Boc-(*D*)-Pro (320 mg, 1.53 mmol, 1.5 equiv), EDC (270 µl, 1.53 mmol, 1.5 equiv), HOBt (201 mg, 1.53 mmol, 1.5 equiv) and DMAP (364 mg, 3.05 mmol, 3 equiv) in 14 ml DCM/THF (5:2). After 30 minutes were added alcohol **153** (330 mg, 1.02 mmol, 1 equiv) and the reaction was stirred at room temperature for 5 hours. The reaction mixture was poured into 100 ml EtOAc and washed successively with 1 M $KHSO_4$, sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 1 % MeOH in DCM to afford **156a** (510 mg, 0.70 mmol, 96 %).

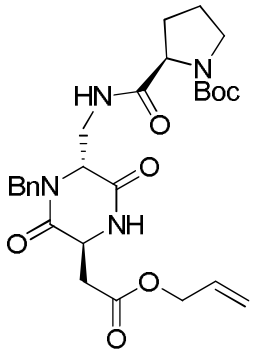
NMR spectra showed a double set of signal for most proton peaks and carbon peaks respectively.

R_f = 0.52 (ethyl acetate). – **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 1.40+1.46 (s, 9H), 1.70 (broad s, 1H), 1.92 (broad m, 3H), 2.20 (m, 1H), 2.80 (m, 1H), 3.28-3.57 (m, 3H), 4.04 (m, 2H), 4.21-4.70 (m, 6H), 5.32 (m, 2H), 5.91 (m, 1H), 7.30 (bs, 1H), 7.23-7.36 (m, 5H). – **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ_C = 23.77+24.51 (1C), 28.29+28.42 (3C), 29.97+30.97 (1C), 37.34+37.38 (1C), 46.35+46.64 (1C), 47.40 (1C), 50.91 (1C), 58.16+58.43 (1C), 58.75+58.93 (1C), 62.79+63.03 (1C), 65.94+66.03 (1C), 80.18+80.32 (1C), 119.09+119.13 (1C), 128.21+128.39 (2C), 129.11+129.15 (2C), 131.39+46 (1C), 134.80+134.93 (1C), 153.56+154.36 (1C), 165.48+165.69 (1C), 165.78+165.87 (1C), 170.59+170.86 (1C), 172.31+172.68 (1C).



(*S*)-2-((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methyl 1-tert-butyl pyrrolidine-1,2-dicarboxylate (156b)

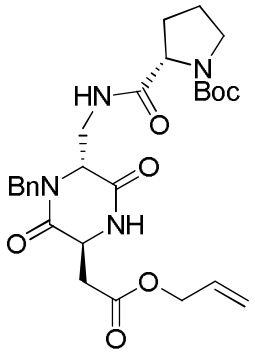
Under nitrogen at 0 °C were dissolved Boc-(*L*)-Pro (162 mg, 0.75 mmol, 1.5 equiv), DCC (156 mg, 0.75 mmol, 1.5 equiv), HOBt (103 mg, 0.75 mmol, 1.5 equiv) and DMAP (184 mg, 1.5 mmol, 3 equiv) in 7ml DCM/THF (5:2). After 30 minutes were added alcohol **153** (165 mg, 0.50 mmol, 1 equiv) and the reaction was stirred at room temperature for 5 hours. The reaction mixture was poured into 80 ml EtOAc and washed successively with 1 M $KHSO_4$, sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 2 % MeOH in DCM to afford **156b** (370 mg, 0.70 mmol, 140 %). Even after chormoatography the NMR spectra showed the presence of DCU which could not be removed and therefore the mixture was used for the next step without further purification.



(*R*)-*tert*-butyl 2-(((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (158a)

155 (320 mg, 0.74 mmol, 1 equiv) was dissolved in 7 ml DCM and added 7 ml TFA at 0°C and stirred for 30 minutes. The solution was concentrated under reduced pressure and the residue was treated with EtO_2 to provoke precipitation of the TFA salt. Boc-(*D*)-Pro (230 mg, 1.11 mmol, 1.5 equiv) was dissolved in 15 ml acetonitrile and added HBTU (406 mg, 1.11 mmol, 1.5 equiv) and collidine (0.38 ml, 2.97 mmol, 4 equiv) at 0°C under N_2. After stirring for 30 minutes the TFA salt was added and the mixture was continued stirring for overnight at room temperature. The reaction mixture was poured in to 100 ml of EtOAc and washed with 1 M $KHSO_4$, sat. $NaHCO_3$ and brine. The organic layer was dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 1 % MeOH in DCM to yield **158a** (380 mg, 0.72 mmol, 97 %).

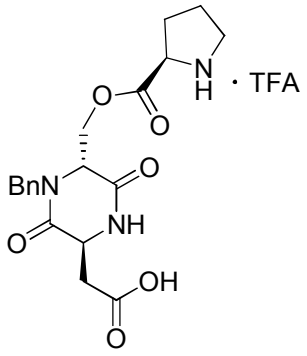
R_f = 0.26 (ethyl acetate). – **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 1.46 (s, 9H), 1.86 (broad m, 2H), 2.34 (broad s, 1H), 2.60 (s, 1H), 2.79 (m, 1H) 3.26 (dd, 1H, *J* = 17.52, 1.52 Hz), 3.31–3.52 (broad m, 3H), 3.86 (broad s, 1H), 4.05-4.75 (broad m, 3H), 4.61-4.80 (m, 3 H), 5.28 (m, 2H), 5.50 (m, 1H), 5.89 (m, 1H), 6.72 (broad s, 1H), 7.18 (broad s, 1H), 7.25 – 7.41 (m, 5H). – **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ_C = 24.50 (1C), 28.40 (3C), 28.58 (1C), 37.78 (1C), 38.61 (1C), 39.21 (1C), 47.03 (1C), 47.36 (1C), 50.80 (1C), 58.61 (1C), 60.31 (1C), 65.86 (1C), 80.66 (1C), 119.00 (1C), 128.02 (1C), 128.38 (2C), 128.68 (2C), 131.47 (1C), 135.43 (1C), 165.00 (1C), 166.68 (1C), 170.71 (1C), 173.15 (1C).



(*S*)-*tert*-butyl2-(((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (158b)

155 (325 mg, 0.75 mmol, 1 equiv) was dissolved in 6 ml DCM and added 6ml TFA at 0°C and stirred for 30 minutes. The solution was concentrated under reduced pressure and the residue was treated with EtO_2 to provoke precipitation of the TFA salt. Boc-(*L*)-Pro (230 mg, 1.11 mmol, 1.5 equiv) was dissolved in 15 ml acetonitrile and added HBTU (406 mg, 1.11 mmol, 1.5 equiv) and collidine (0.38 ml, 2.97 mmol, 4 equiv) at 0°C under N_2. After stirring for 30 minutes the TFA salt was added and the mixture was continued stirring for overnight at room temperature. The reaction mixture was poured in to 100 ml of EtOAc and washed with 1 M $KHSO_4$, sat. $NaHCO_3$ and brine. The organic layer was dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 2 % MeOH in DCM to yield **158b** (390 mg, 0.74 mmol, 98%).

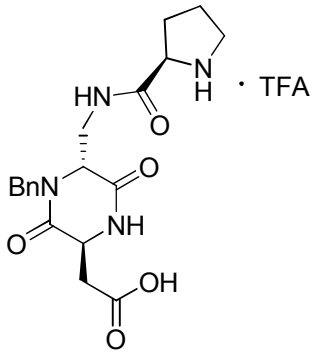
R_f = 0.26 (ethyl acetate). – **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.88 (broad m, 2H), 2.08 (broad m, 1H), 2.81 (broad m, 2H), 3.22 (dd, 1H, *J* = 17.57, 3.12 Hz), 3.33 (broad m, 1H), 3.41 (broad m, 1H), 3.58 (broad m, 1H), 3.88 (broad s, 1H), 3.95 (broad m, 1H), 4.21 (d, 1H, *J* = 15.17 Hz), 4.30 (broad s, 1H), 4.55-4.63 (m, 3 H), 5.28 (ddd, 2H, *J* = 30.17, 17.20, 1.16 Hz), 5.43 (d, 1H, *J* = 15.16 Hz), 5.89 (m, 1H), 6.97 (broad s, 1H), 7.27 – 7.35 (m, 5H), 7.51 (broad m, 1H). – **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 24.54 (-, 1C), 28.40 (+, 3C), 28.62 (-, 1C), 37.55 (-, 1C), 39.21 (-, 1C), 47.06 (-, 1C), 47.44 (-, 1C), 50.69 (+, 1C), 59.04 (+, 1C), 59.84 (+, 1C), 65.81 (-, 1C), 80.63 (1C), 118.92 (-, 1C), 127.93 (+, 1C), 128.43 (+, 2C), 128.90 (+, 2C), 131.48 (+, 1C), 135.61 (1C), 164.81 (1C), 167.03 (1C), 170.68 (1C), 173.85 (1C).



2-((2*S*,5*R*)-4-benzyl-3,6-dioxo-5-(((*R*)-pyrrolidine-2-carbonyloxy)methyl)piperazin-2-yl)acetic acid (160)

To a solution of **156a** (490 mg, 0.67 mmol, 1 equiv) in 7 ml of DCM were subsequently added pyrrolidine (91 µl, 0.81 mmol, 1.2 equiv), PPh_3 (44 mg, 0.12 mmol, 0.18 equiv) and $Pd(PPh_3)_4$ (44 mg, 0.03 mmol, 0.04 equiv) at 0 °C and additionally stirred at room temperature for 2-3 hours. The reaction mixture was poured into 120 ml of EtOAc and extracted with ml of sat. $NaHCO_3$. The organic layers were discarded and the pH of the aqueous solution was carefully adjusted to 2 by addition of 1 M $KHSO_4$. The acidified aqueous solution was extracted with DCM (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 5 % MeOH in DCM to yield **157a**. Subsequently, **157a** was dissolved in 5 ml DCM and added 5 ml TFA to yield TFA salt **160** (321 mg, 0.66 mmol, 98 %).

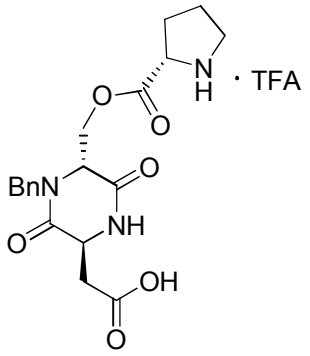
$R_f \approx 0.05$ (CH_2Cl_2/MeOH). – **^{1}H NMR** (300 MHz, D_2O): δ_H = 1.78-1.96 (m, 3H), 2.28 (m, 1H), 2.82 (dd, 1H, *J* = 4.9, 17.8 Hz), 3.01 (dd, 1H, *J* = 4.4, 17.7 Hz), 3.24 (m, 2H), 4.31-4.40 (m, 3H), 4.46-4.51 (m, 3H), 4.70 (d, 1H, *J* = 15.5 Hz), 7.19-7.30 (m, 5H). – **^{13}C NMR** (75.5 MHz, D_2O): δ_C = 23.36 (-, 1C), 28.12 (-, 1C), 35.84 (-, 1C), 46.25 (-, 1C), 48.67 (-, 1C), 50.81 (+, 1C), 59.06 (+, 1C), 59.53 (+, 1C), 64.87 (-, 1C), 127.71 (+, 2C), 128.16 (+, 1C), 129.04 (+, 2C), 135.43 (1C), 167.49 (1C), 168.32 (1C), 169.09 (1C), 173.66 (1C).



2-((2*S*,5*R*)-4-benzyl-3,6-dioxo-5-(((*R*)-pyrrolidine-2-carboxamido)methyl)piperazin-2-yl)acetic acid (161)

To a solution of **158a** (370 mg, 0.70 mmol, 1 equiv) in 6 ml of DCM were subsequently added pyrrolidine (70 µl, 0.84 mmol, 1.2 equiv), PPh_3 (33 mg, 0.13 mmol, 0.18 equiv) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol, 0.04 equiv) at 0 °C and additionally stirred at room temperature for 2-3 hours. The reaction mixture was poured into ml of EtOAc and extracted with ml of sat. $NaHCO_3$. The organic layers were discarded and the pH of the aqueous solution was carefully adjusted to 2 by addition of 1 M $KHSO_4$. The acidified aqueous solution was extracted with DCM (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 5 % MeOH in DCM to yield **159a**. Subsequently, **159a** was dissolved in 5 ml DCM and added 5 ml TFA to yield TFA salt **161** (315 mg, 0.65 mmol, 93 %).

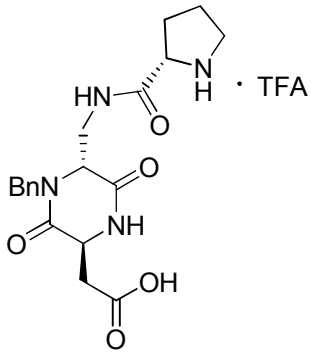
$R_f \approx 0.05$ (CH_2Cl_2/MeOH). – **^{1}H NMR** (300 MHz, D_2O): δ_H = 1.69-2.10 (m, 3H), 2.33 (m, 1H), 2.83 (dd, 1H, *J* = 4.8, 17.7 Hz), 3.02 (dd, 1H, *J* = 4.4, 17.7 Hz), 3.31 (m, 2H), 3.57 (dd, 1H, *J* = 2.4, 14.1 Hz), 4.00 (m, 2H), 4.14 (d, 1H, *J* = 15.5 Hz), 4.24 (t, 1H, *J* = 7.8 Hz), 4.41 (t, 1H, *J* = 4.5 Hz), 5.13 (d, 1H, *J* = 15.5 Hz), 7.24-7.35 (m, 5H). – **^{13}C NMR** (75.5 MHz, D_2O): δ_C = 23.71 (-, 1C), 29.66 (-, 1C), 35.83 (-, 1C), 39.50 (-, 1C), 46.73 (-, 1C), 47.76 (-, 1C), 50.71 (+, 1C), 59.24 (+, 1C), 59.76 (+, 1C), 127.83 (+, 2C), 128.17 (+, 1C), 129.02 (+, 2C), 129.07 (1C), 167.88 (1C), 168.18 (1C), 170.17 (1C), 173.56 (1C).



2-((2*S*,5*R*)-4-benzyl-3,6-dioxo-5-(((*S*)-pyrrolidine-2-carbonyloxy)methyl)piperazin-2-yl)acetic acid (162)

To a solution of crude **156b** (370 mg, 0.70 mmol, 1 equiv) in 6 ml of DCM were subsequently added pyrrolidine (70 µl, 0.84 mmol, 1.2 equiv), PPh_3 (33 mg, 0.13 mmol, 0.18 equiv) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol, 0.04 equiv) at 0 °C and additionally stirred at room temperature for 2-3 hours. The reaction mixture was poured into 100 ml of EtOAc and extracted with ml of sat. $NaHCO_3$. The organic layers were discarded and the pH of the aqueous solution was carefully adjusted to 2 by addition of 1 M $KHSO_4$. The acidified aqueous solution was extracted with DCM (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 5 % MeOH in DCM to yield **162**. Subsequently, **157b** was dissolved in 4 ml DCM and added 4 ml TFA to yield TFA salt **162** (238 mg, 0.49 mmol, 77 %).

$R_f \approx 0.05$ (CH_2Cl_2/MeOH). – **^{1}H NMR** (300 MHz, D_2O): δ_H = 1.90-2.06 (m, 3H), 2.33 (m, 1H), 2.88 (dd, 1H, *J* = 4.7, 17.8 Hz), 3.07 (dd, 1H, *J* = 4.5, 17.8 Hz), 3.30 (m, 2H), 4.33-4.55 (m, 6H), 4.86 (d, 1H, *J* = 15.8 Hz), 7.22-7.35 (m, 5H). – **^{13}C NMR** (75.5 MHz, D_2O): δ_C = 23.31 (-, 1C), 28.02 (-, 1C), 35.88 (-, 1C), 46.28 (-, 1C), 48.26 (-, 1C), 50.76 (+, 1C), 59.11 (+, 1C), 59.28 (+, 1C), 64.75 (-, 1C), 127.55 (+, 2C), 128.11 (+, 1C), 128.99 (+, 2C), 135.21 (1C), 167.33 (1C), 168.20 (1C), 169.05 (1C), 173.69 (1C).



2-((2*S*,5*R*)-4-benzyl-3,6-dioxo-5-(((*S*)-pyrrolidine-2-carboxamido)methyl)piperazin-2-yl)acetic acid (163)

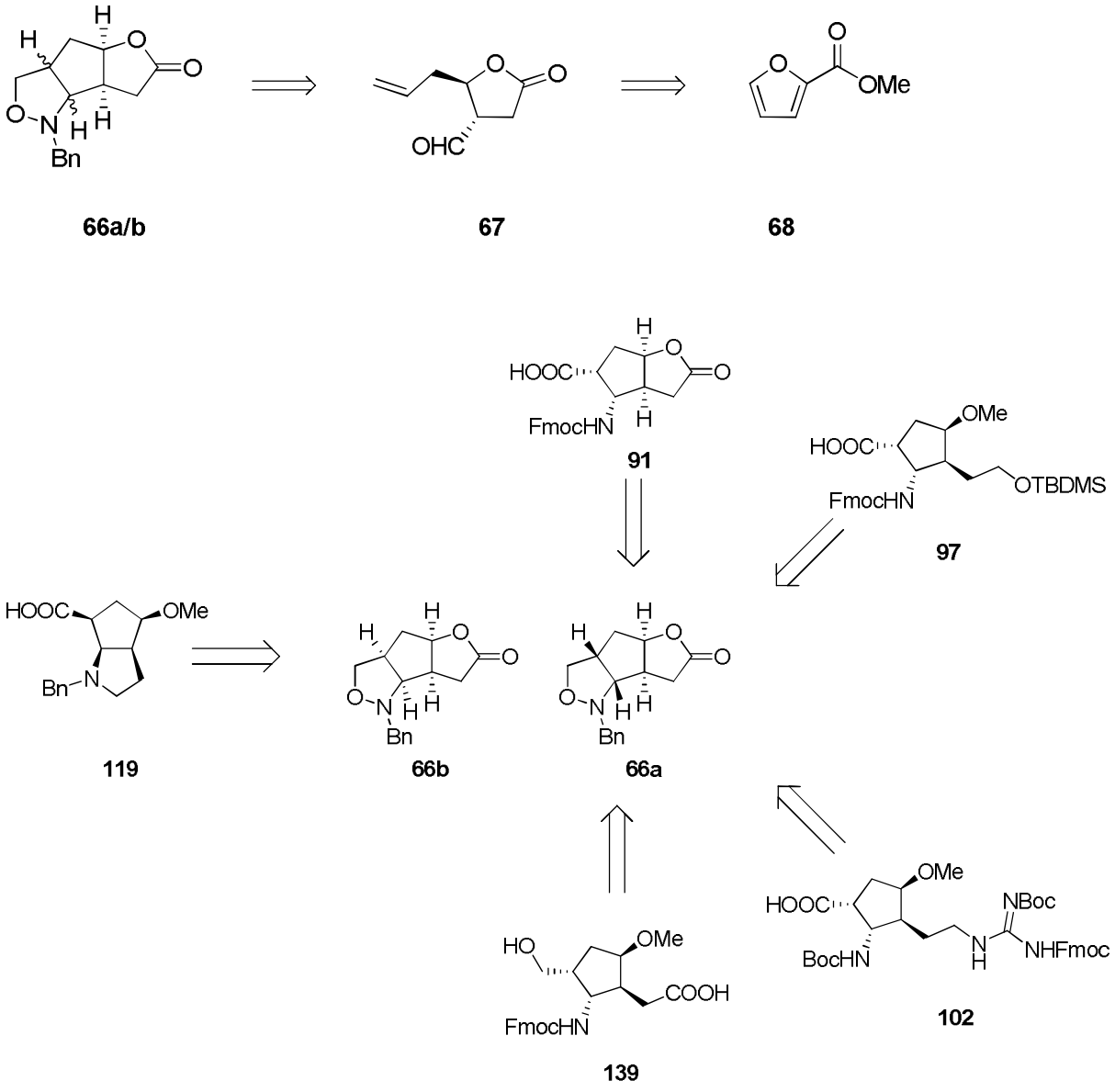
To a solution of **158b** (350 mg, 0.66 mmol, 1 equiv) in 5 ml of DCM were subsequently added pyrrolidine (65 µl, 0.79 mmol, 1.2 equiv), PPh_3 (32 mg, 0.12 mmol, 0.18 equiv) and $Pd(PPh_3)_4$ (32 mg, 0.03 mmol, 0.04 equiv) at 0 °C and additionally stirred at room temperature for 2-3 hours. The reaction mixture was poured into ml of EtOAc and extracted with ml of sat. $NaHCO_3$. The organic layers were discarded and the pH of the aqueous solution was carefully adjusted to 2 by addition of 1 M $KHSO_4$. The acidified aqueous solution was extracted with DCM (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 5 % MeOH in DCM to yield **159b**. Subsequently, **159b** was dissolved in 5 ml DCM and added 5 ml TFA to yield TFA salt **163** (237 mg, 0.49 mmol, 74 %).

$R_f \approx 0.05$ (CH_2Cl_2/MeOH). – **^{1}H NMR** (300 MHz, D_2O): δ_H = 1.83-2.01 (m, 3H), 2.34 (m, 1H), 2.83 (dd, 1H, *J* = 4.8, 17.8 Hz), 3.03 (dd, 1H, *J* = 4.4, 17.8 Hz), 3.30 (m, 2H), 3.80 (dd, 1H, *J* = 5.0, 14.7 Hz), 3.71 (dd, 1H, *J* = 3.4, 14.7 Hz), 4.03 (t, 1H, *J* = 3.9 Hz), 4.13 (d, 1H, *J* = 15.5 Hz), 4.24 (m, 1H), 4.42 (t, 1H, *J* = 4.5 Hz), 5.16 (d, 1H, *J* = 15.5 Hz), 7.30 (m, 5H). – **^{13}C NMR** (75.5 MHz, D_2O): δ_C = 23.77 (-, 1C), 29.64 (-, 1C), 35.94 (-, 1C), 39.49 (-, 1C), 46.36 (-, 1C), 47.82 (-, 1C), 50.77 (+, 1C), 59.24 (+, 1C), 59.78 (+, 1C), 127.84 (+, 2C), 128.15 (+, 1C), 129.01 (+, 2C), 134.91 (1C), 167.85 (1C), 168.19 (1C), 170.26 (1C), 173.57 (1C).

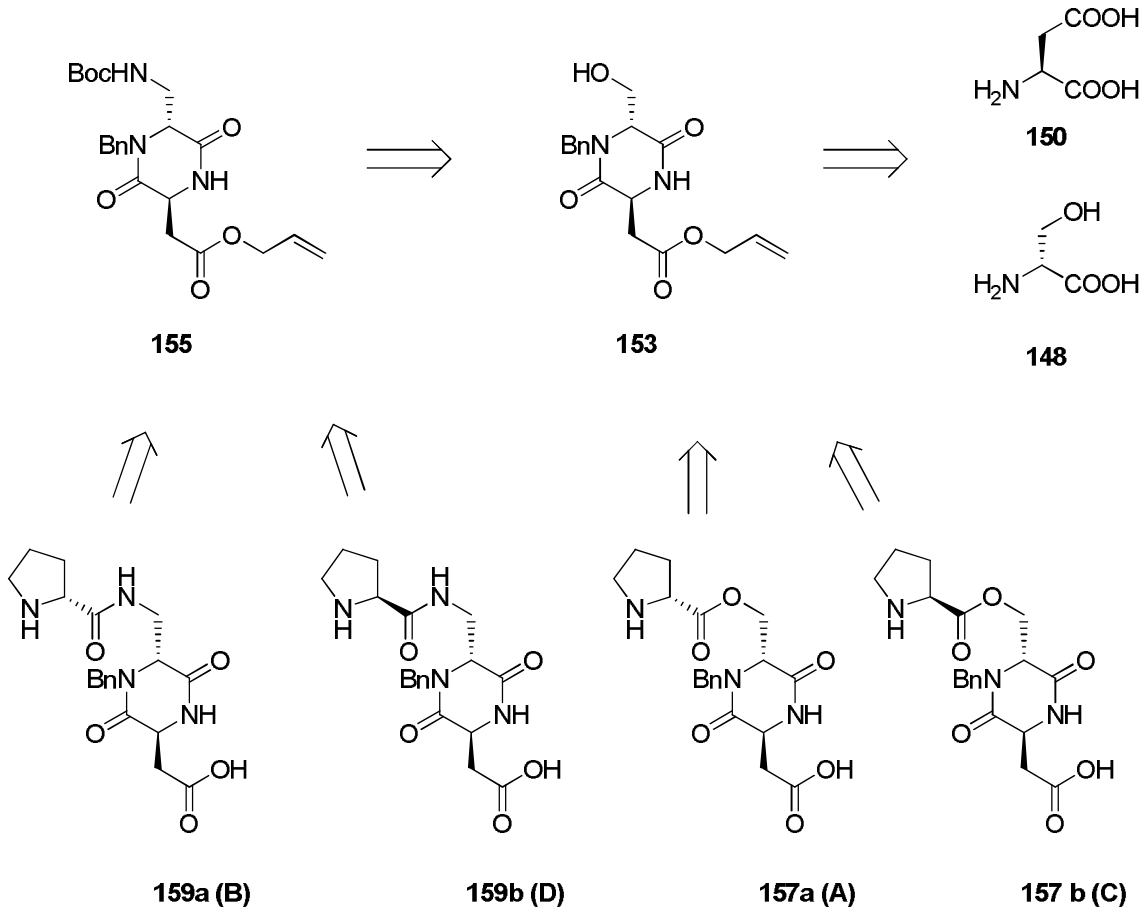
D. Summary

The synthesis of different cispentacin derivatives (**91**, **97**, **102** and **119**) as well as of conformational restricted γ-amino acid **139** was accomplished starting from furan methyl ester (**68**) and the thereof derived *trans*-substituted γ-butyrolactone **67** respectively.

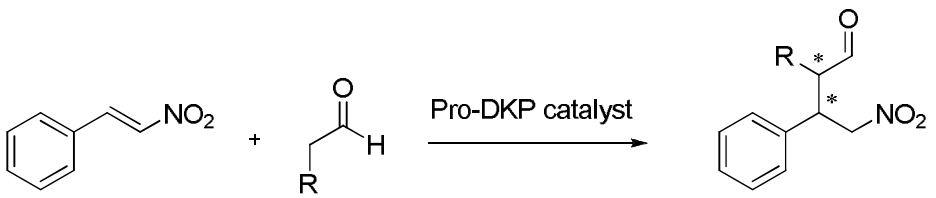
The keystep in this synthetic approach is a [3+2]-nitrone-cycloaddition reaction affording the diastereomeric products **66a** and **66b** which were subsequently transformed in a straightforward manner. These amino acids have a broad range of potential applications like in the field of medicinal chemistry as new antiviral agents (cispentacin analogues), in organocatalysis, as constricting elements in peptides and as building blocks for foldamers.



Furthermore, four different proline-diketopiperazine esters (**157a/157b**) and the related amides (**159a/159b**) were prepared. In this course, differently protected Asp and Ser derivatives were condensed to DKP **153**, which can be subsequently transformed to the corresponding DKP **155**. Adducts of these to DKPs with (*L*)-and (*D*)-proline were applied as novel organocatalysts in the conjugate addition of aldehydes and ketones to nitroolefines.



Especially, the proline DKP amides were shown to be highly active and selective in the reaction of aldehydes.



However, the addition of ketones (acetone and cyclohexanone respectively were utilised and also used as neat solvent) were achieved in reasonable to good yields with comparably low stereoinduction. The potentially beneficial effect of additives or other solvents was not investigated so far.

Due to the promising results in the addition of aldehydes, the scope of these catalysts is currently under further investigation in the *Piarulli* group.

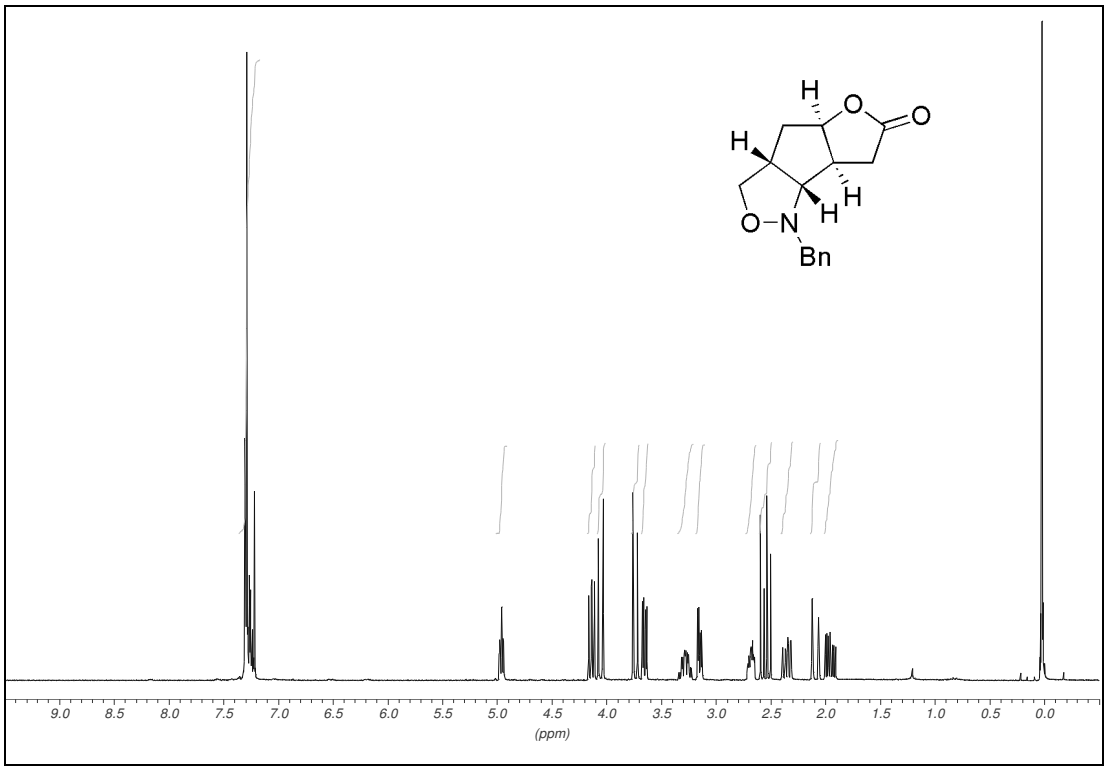
E. Appendix

E. 1. NMR spectroscopic data

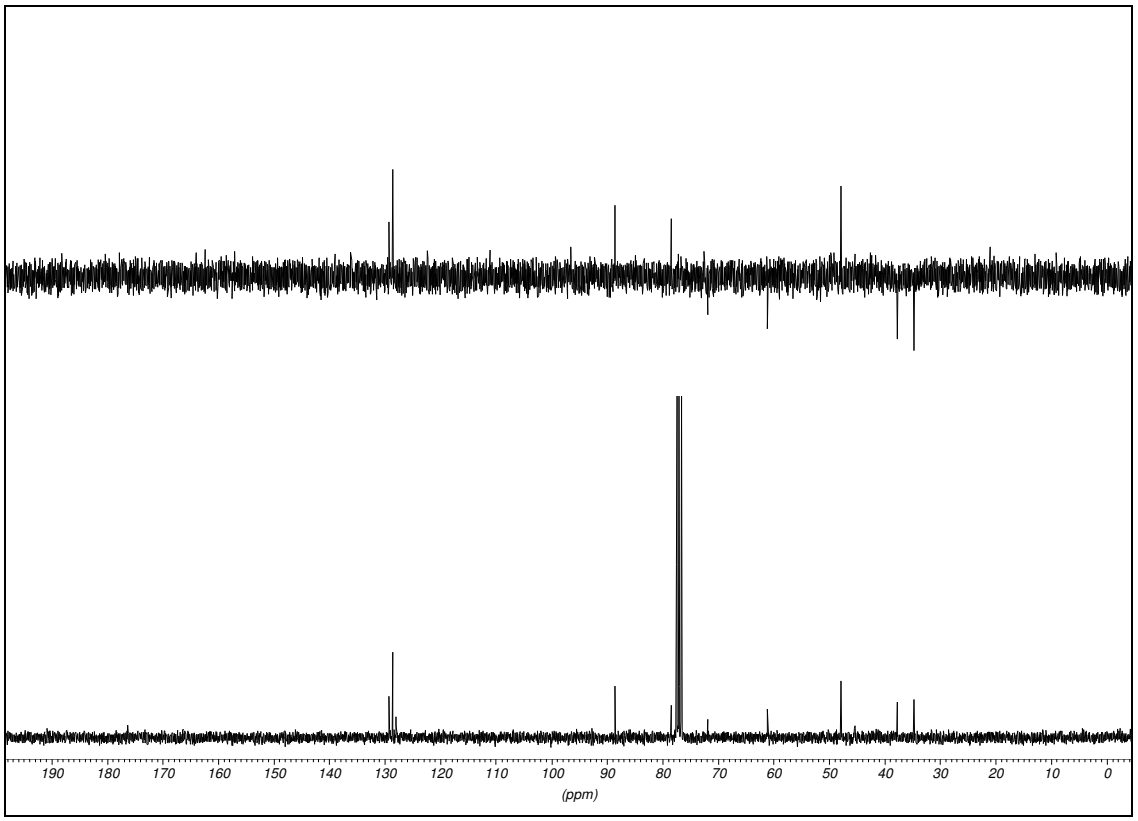
Nuclei, solvents and type of experiment are indicated separately for each spectrum.

(3a*R*,4a*R*,7a*S*,7b*R*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (66a)

^{1}H-NMR (300 MHz, $CDCl_3$)

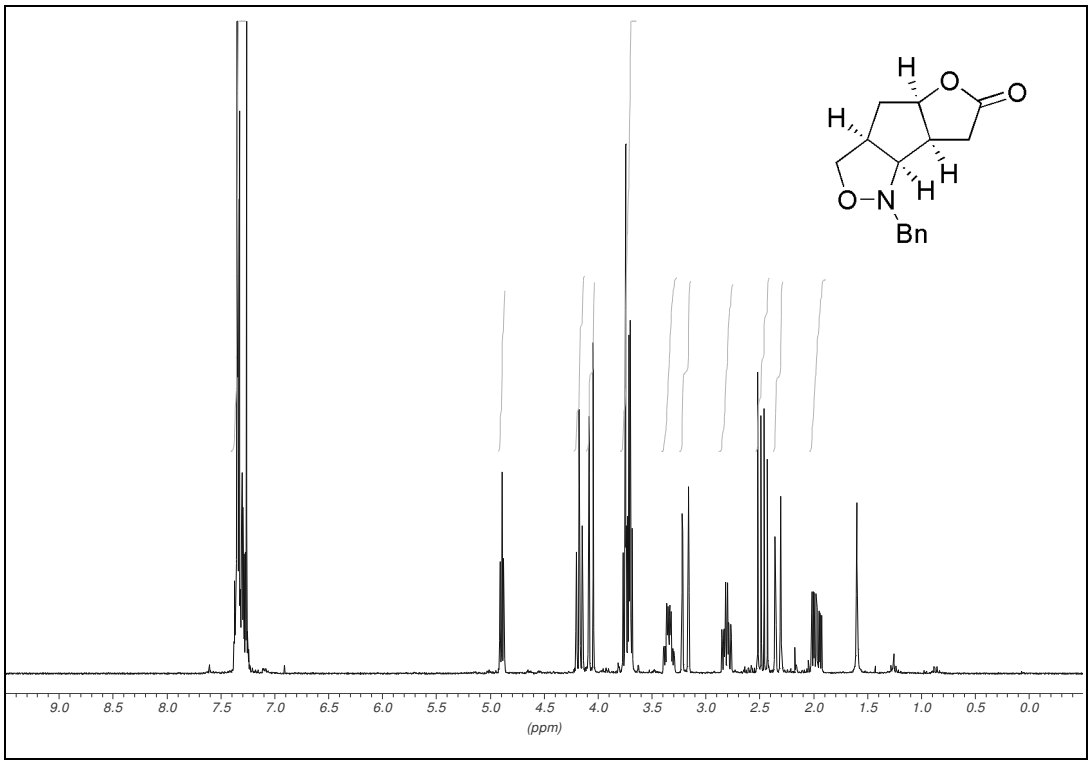


^{13}C NMR (75.5 MHz, $CDCl_3$)

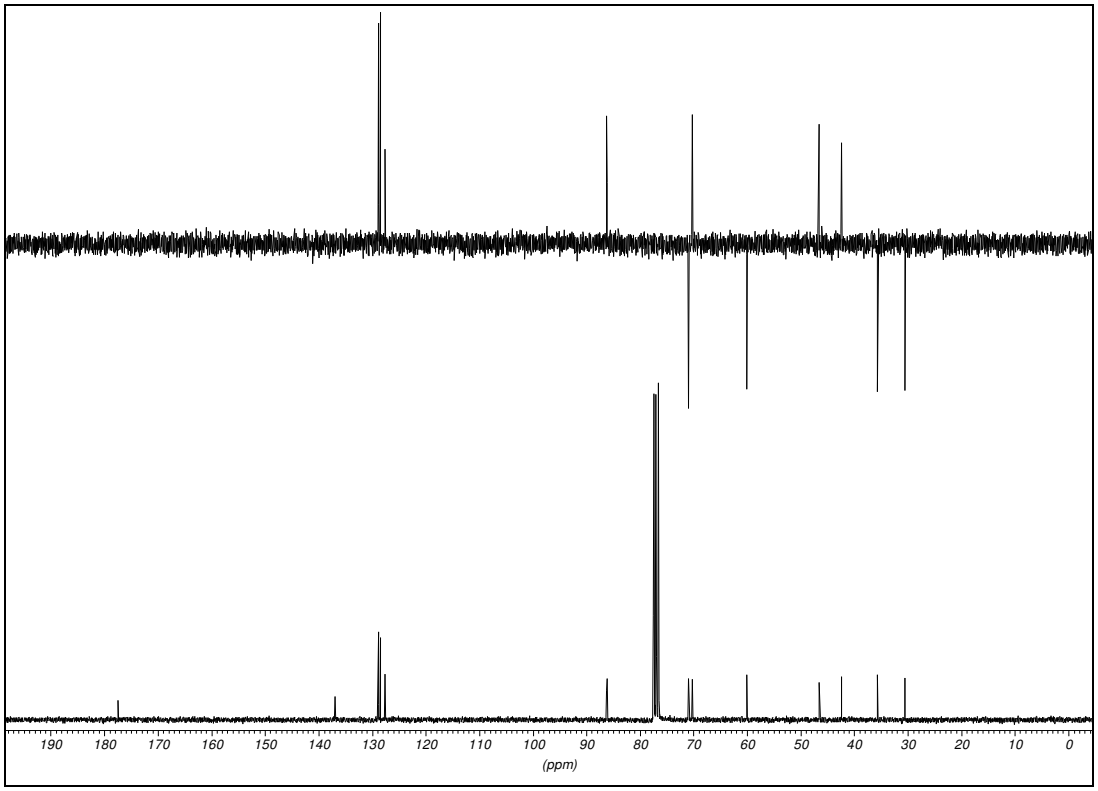


(3a*S*,4a*R*,7a*S*,7b*S*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (66b)

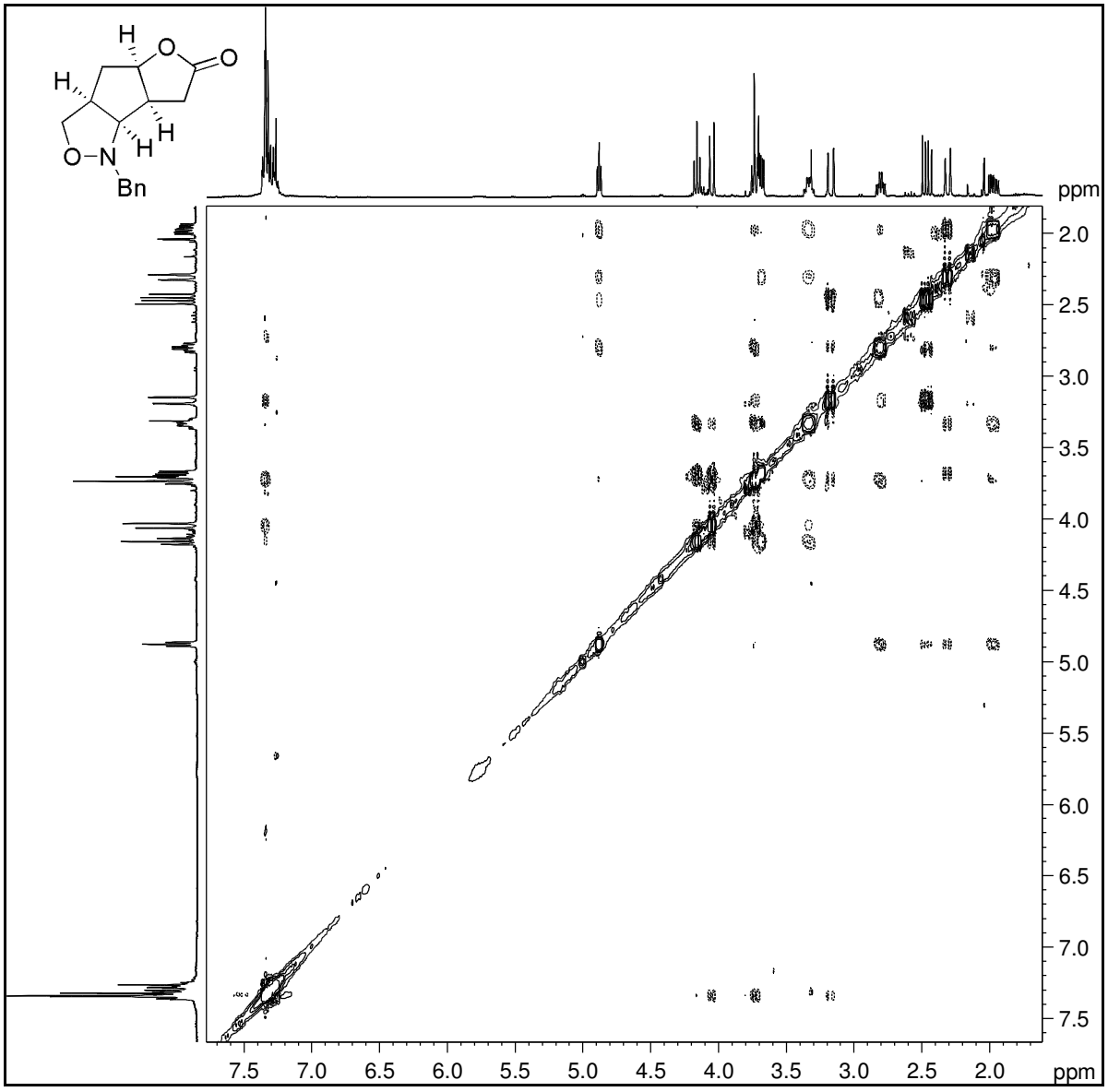
^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75.5 MHz, $CDCl_3$)

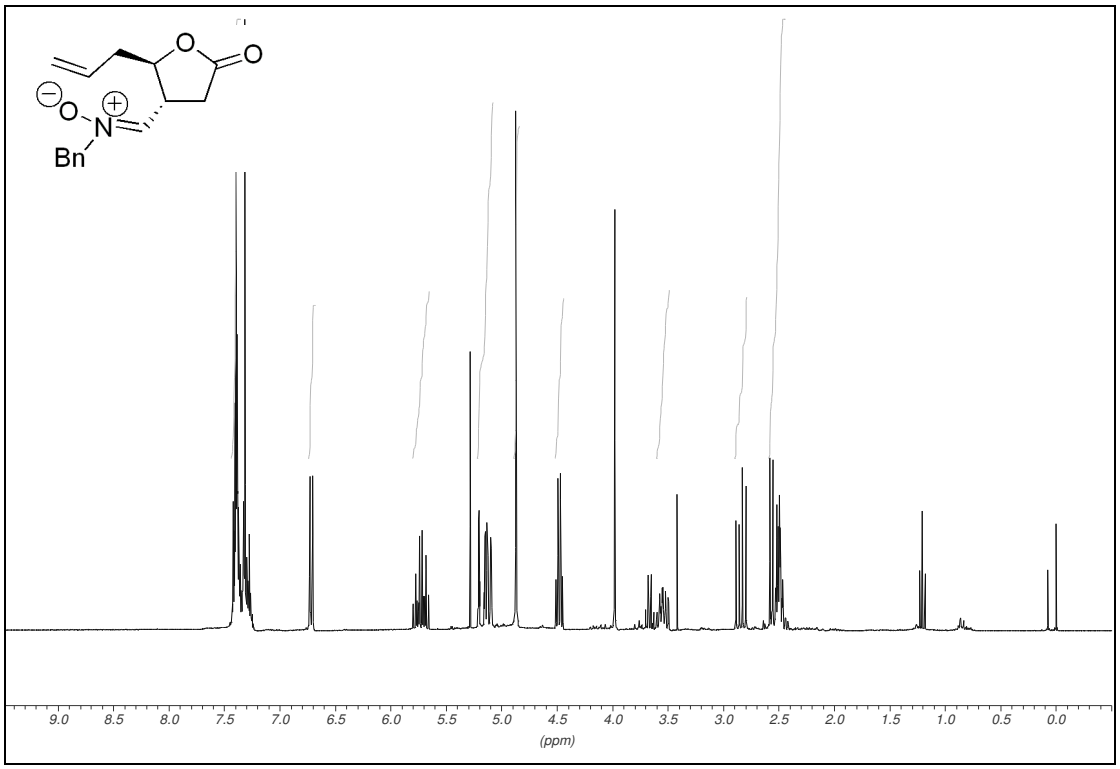


NOESY (400 MHz)

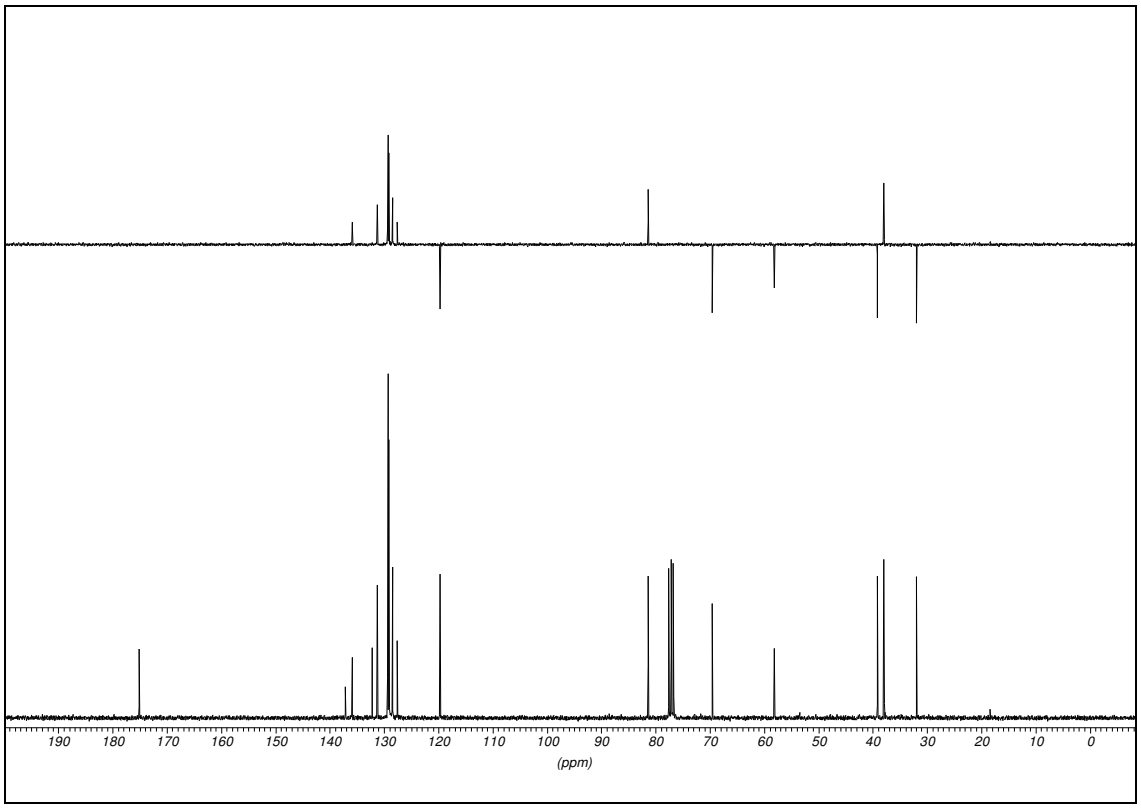


(E)-*N*-(((2*R*,3*R*)-2-allyl-5-oxotetrahydrofuran-3-yl)methylene)-1-phenylmethanamine oxide (84)

^{1}H-NMR (300 MHz, $CDCl_3$)

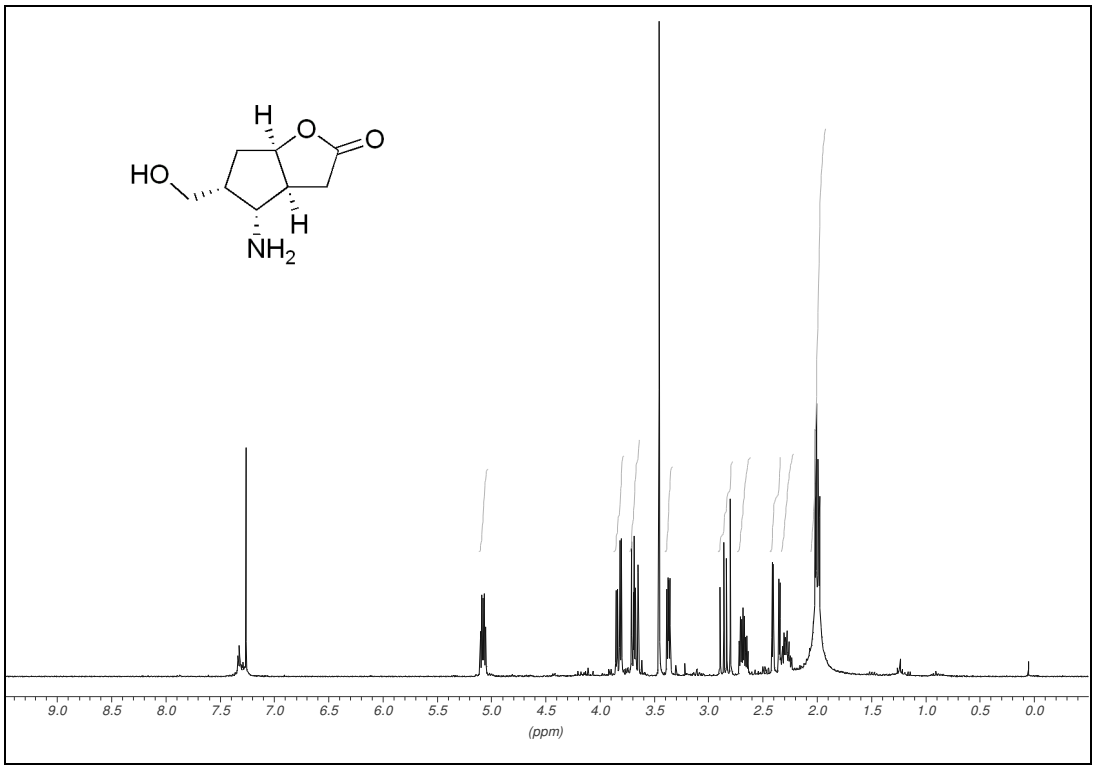


^{13}C NMR (75.5 MHz, $CDCl_3$)

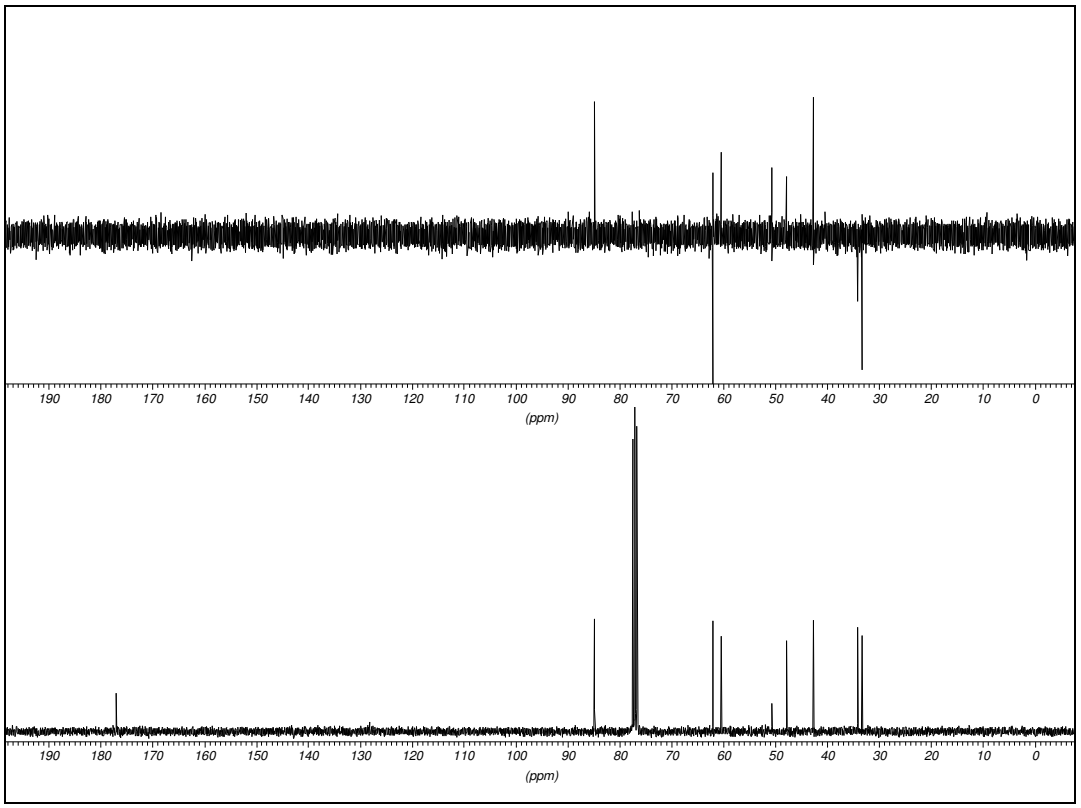


(3a*S*,4*R*,5*R*,6a*R*)-4-amino-5-(hydroxymethyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (86)

^{1}H-NMR (300 MHz, $CDCl_3$)

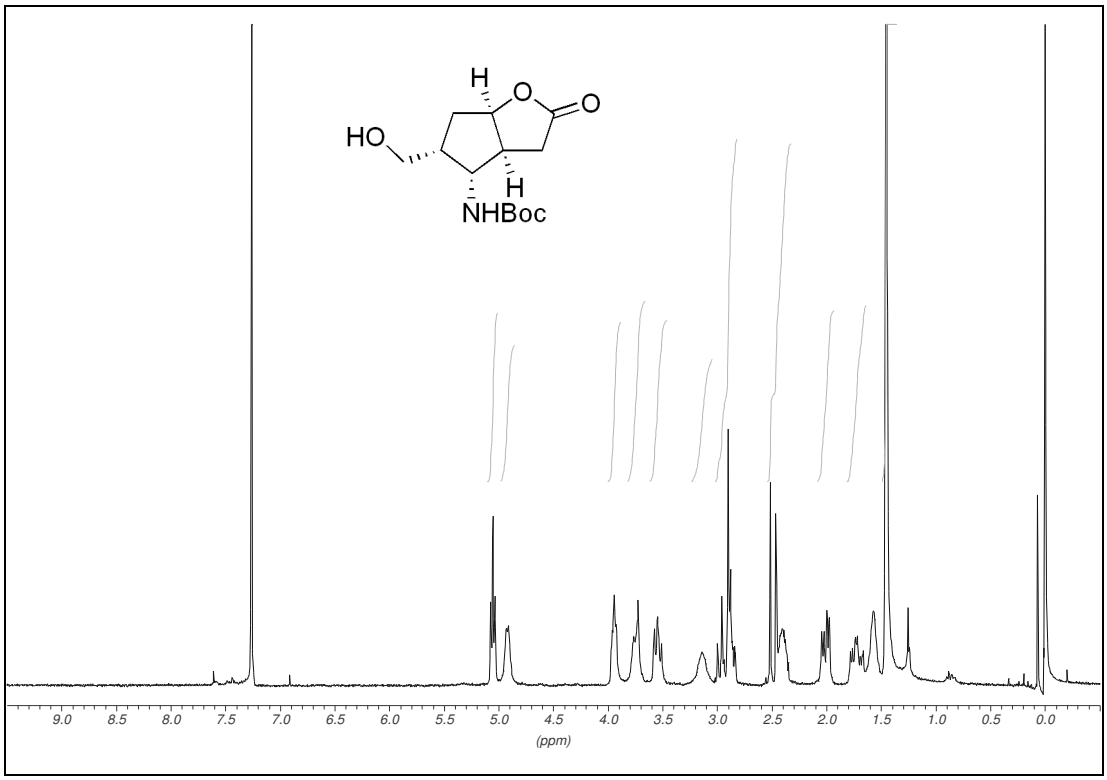


^{13}C NMR (75.5 MHz, $CDCl_3$)

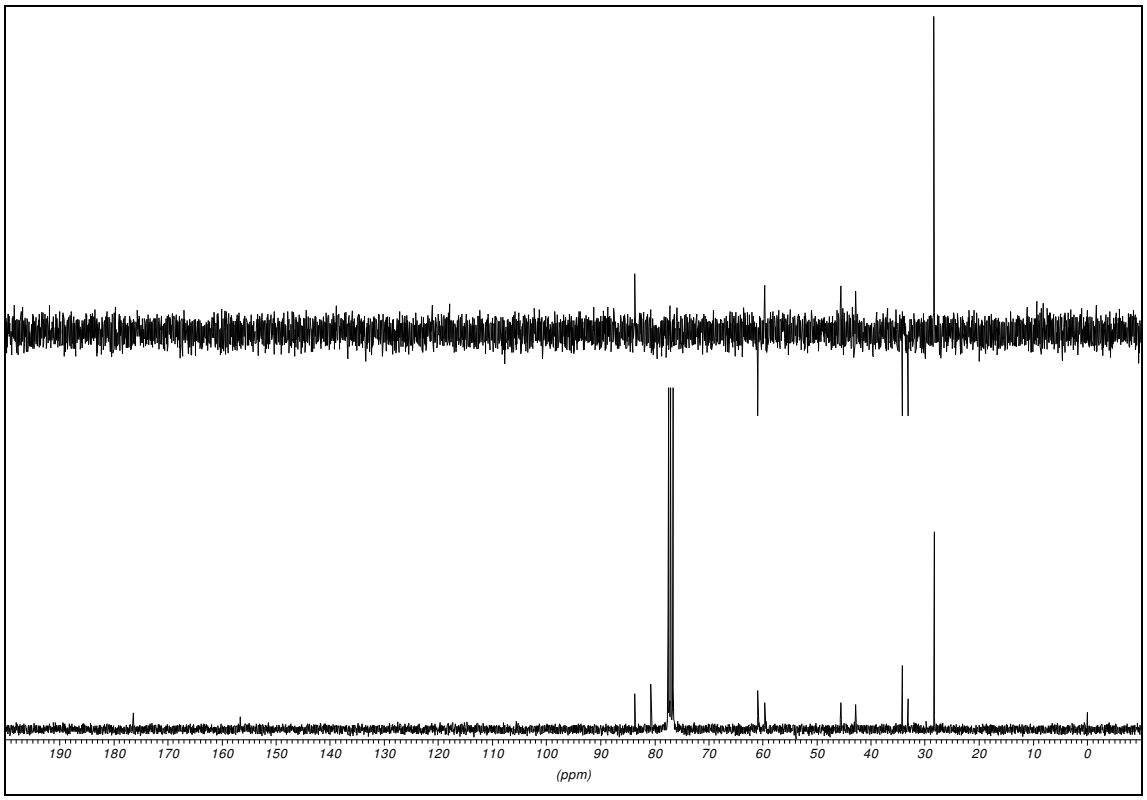


tert-butyl [(3a*S*,4*R*,5*R*,6a*R*)-5-(hydroxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl]carbamate (88)

^{1}H-NMR (300 MHz, $CDCl_3$)

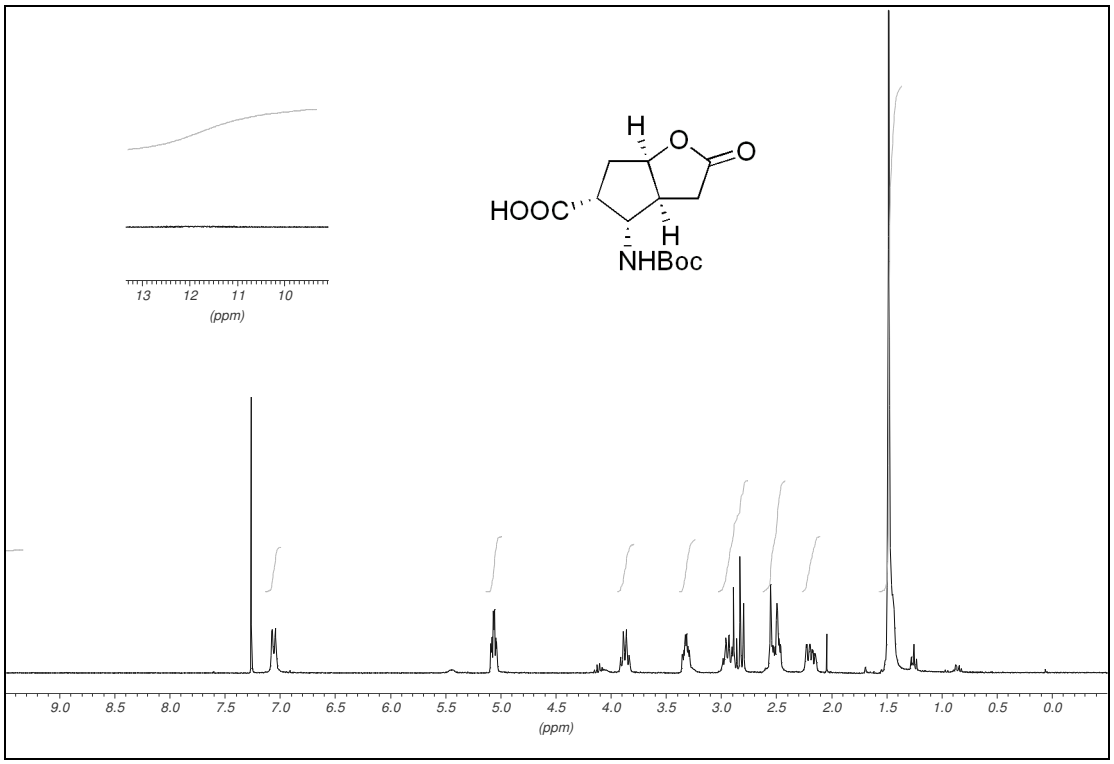


^{13}C NMR (75.5 MHz, $CDCl_3$)

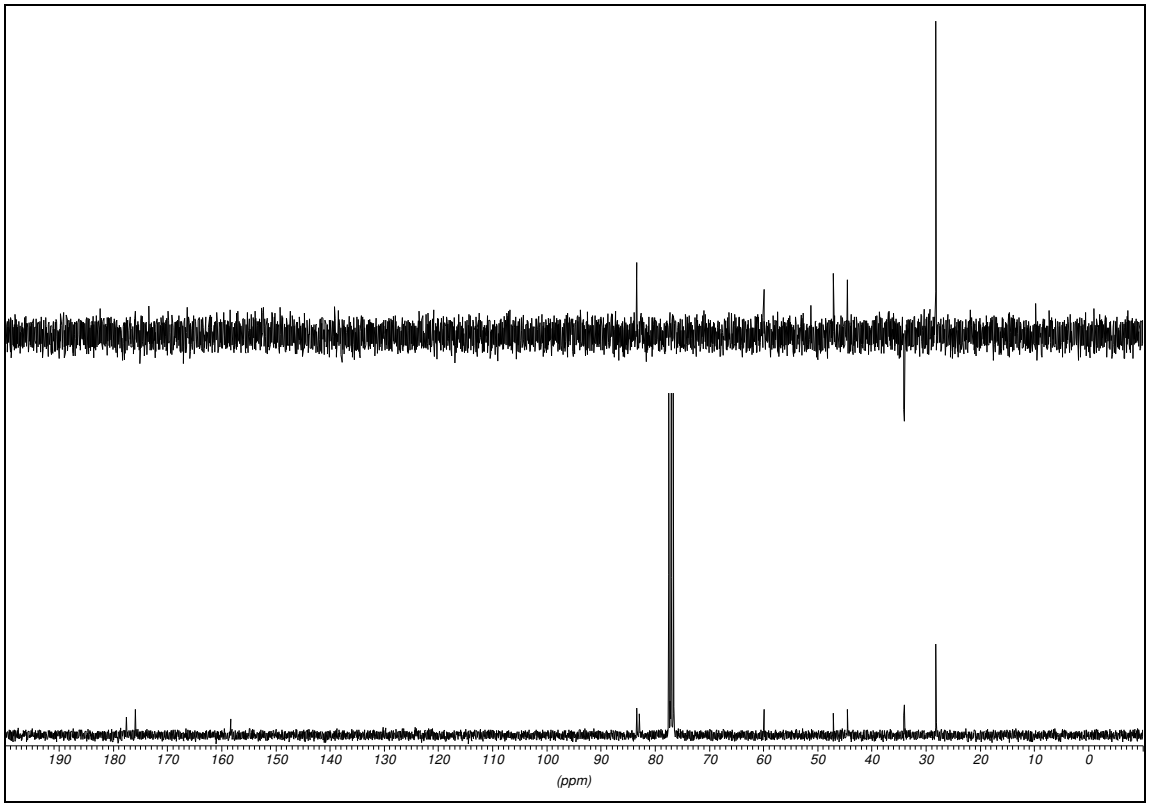


(3a*S*,4*S*,5*R*,6a*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid (89)

^{1}H-NMR (300 MHz, $CDCl_3$)

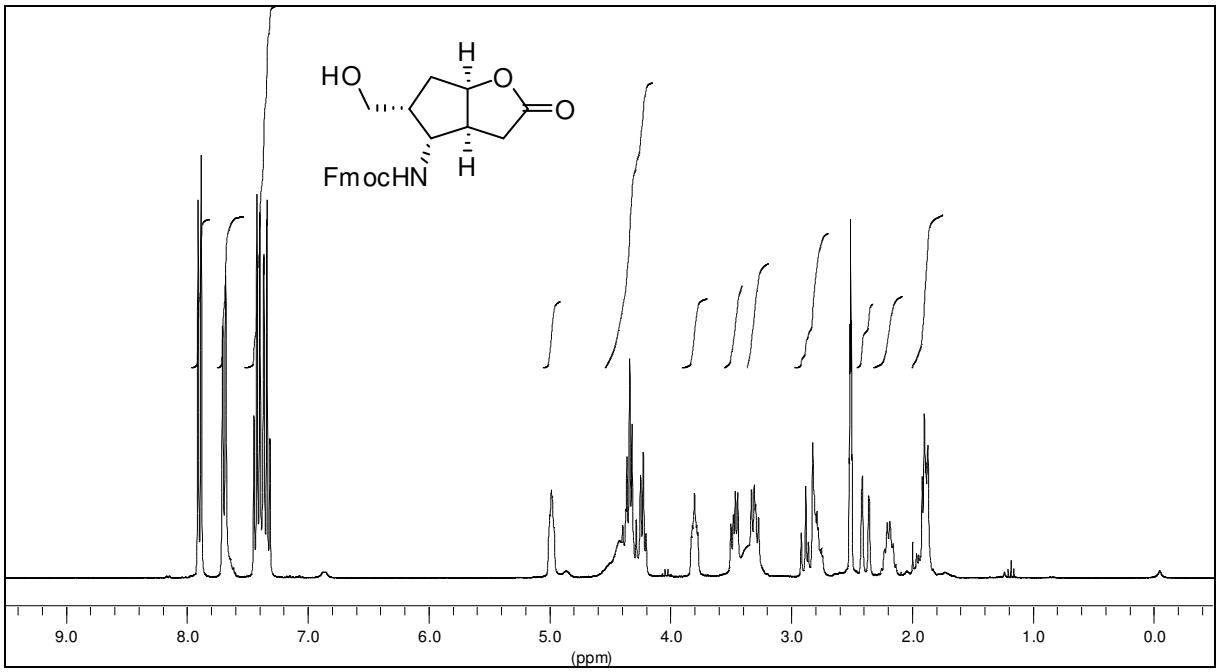


^{13}C NMR (75.5 MHz, $CDCl_3$)

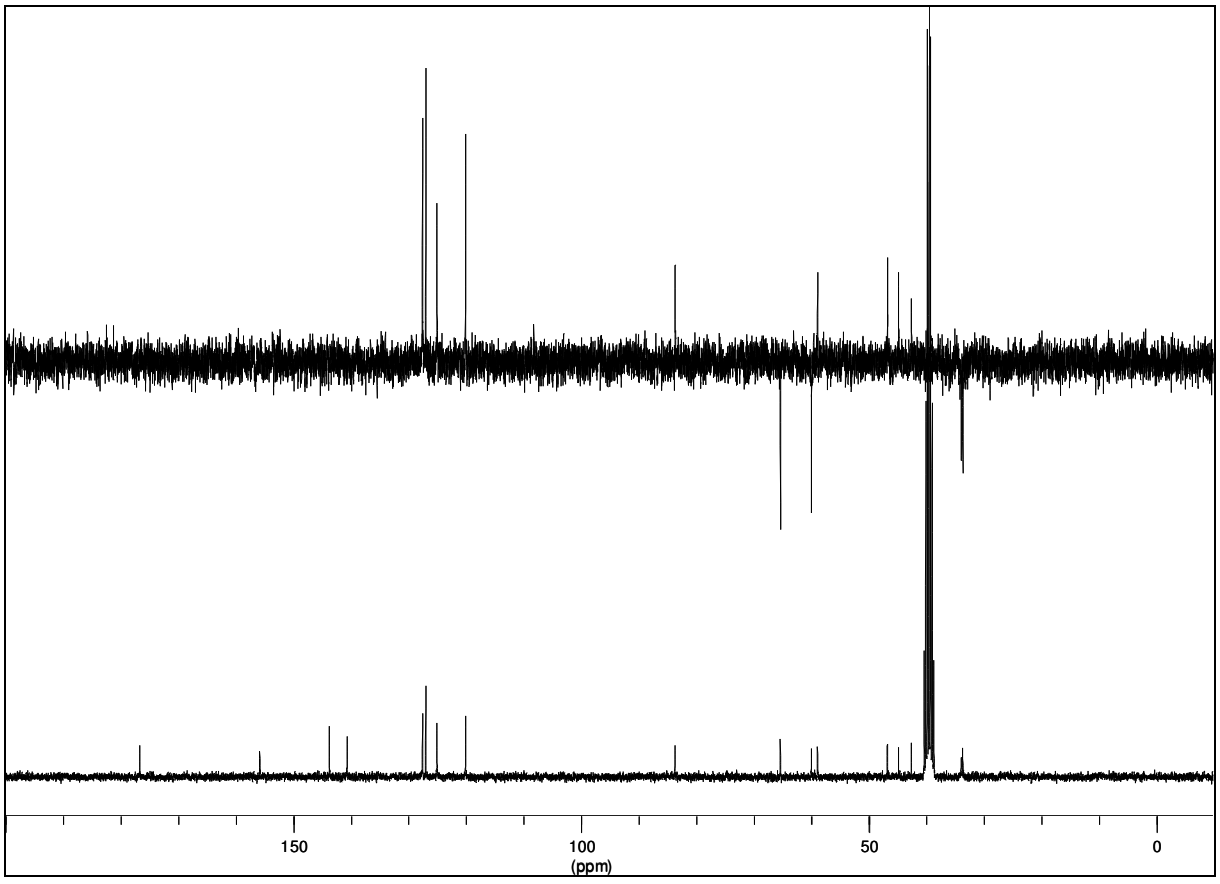


(9*H*-fluoren-9-yl)methyl (3a*S*,4*R*,5*R*,6a*R*)-5-(hydroxymethyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-ylcarbamate (90)

^{1}H-NMR (300 MHz, MeOD)

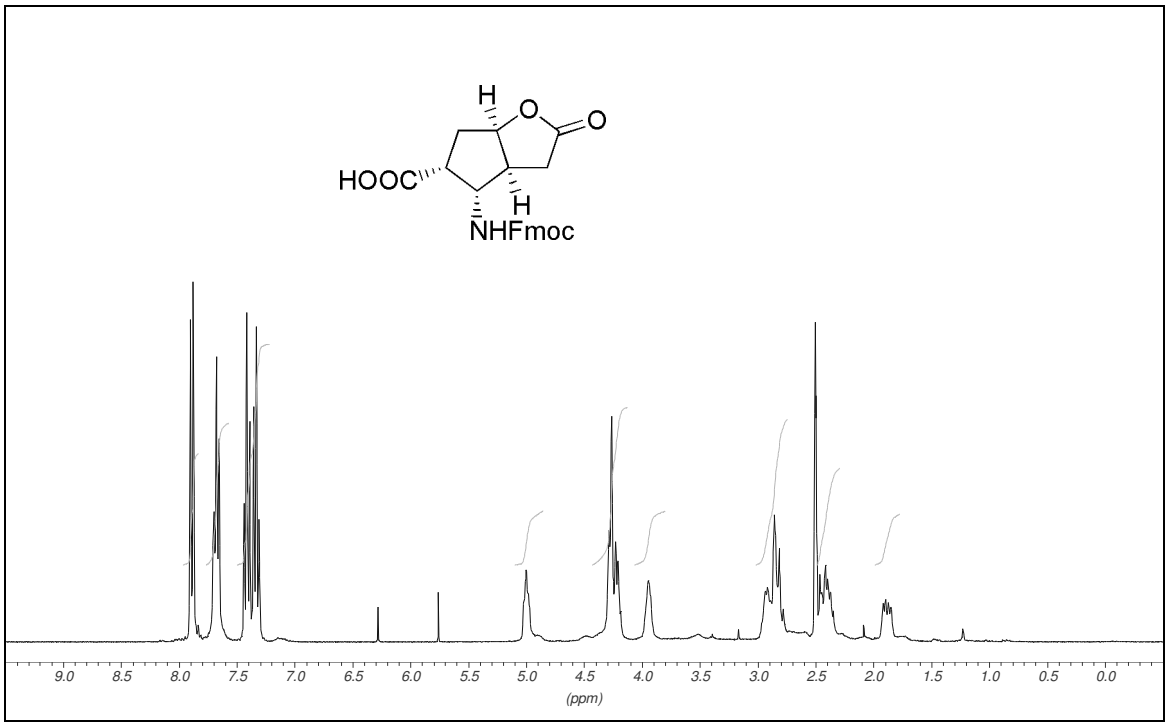


^{13}C NMR (75.5 MHz, MeOD)

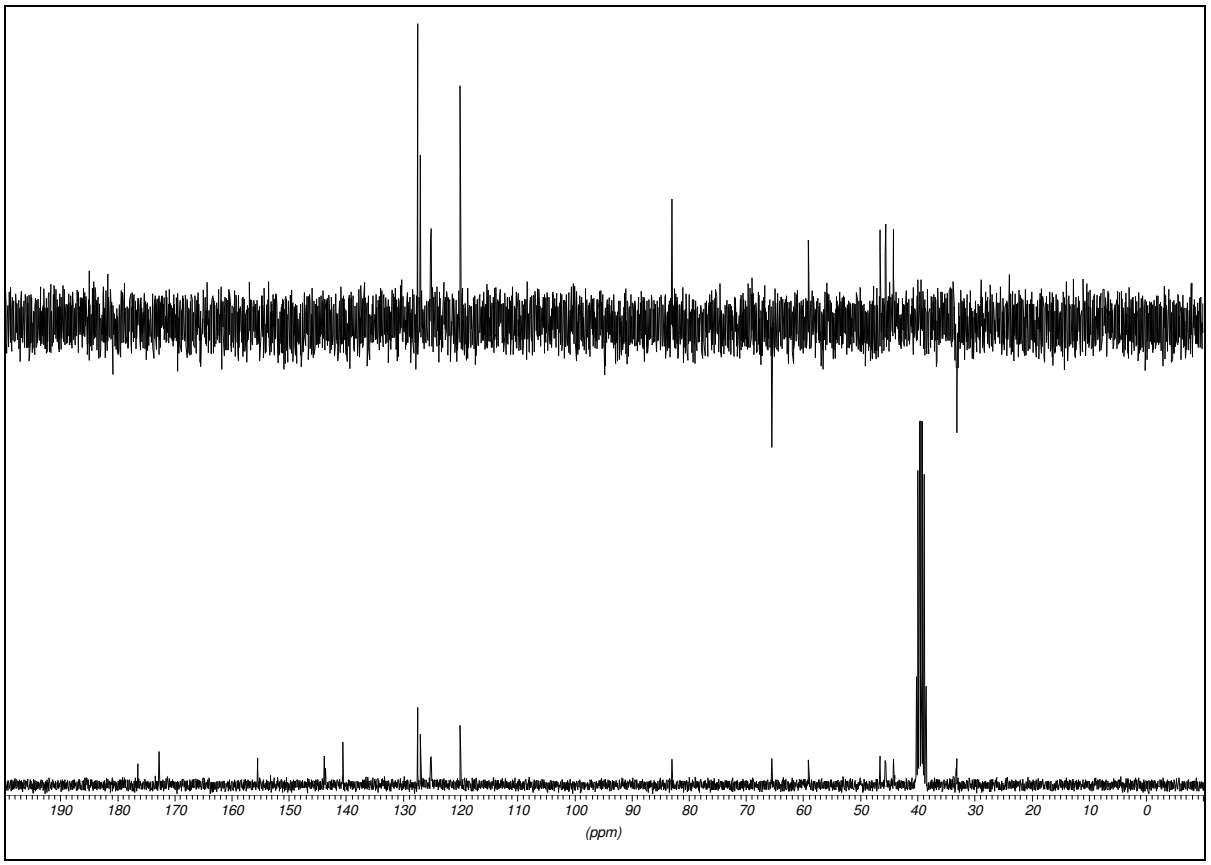


(3a*S*,4*S*,5*R*,6a*R*)-4-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-carboxylic acid (91)

^{1}H-NMR (300 MHz, DMSO+D_2O)

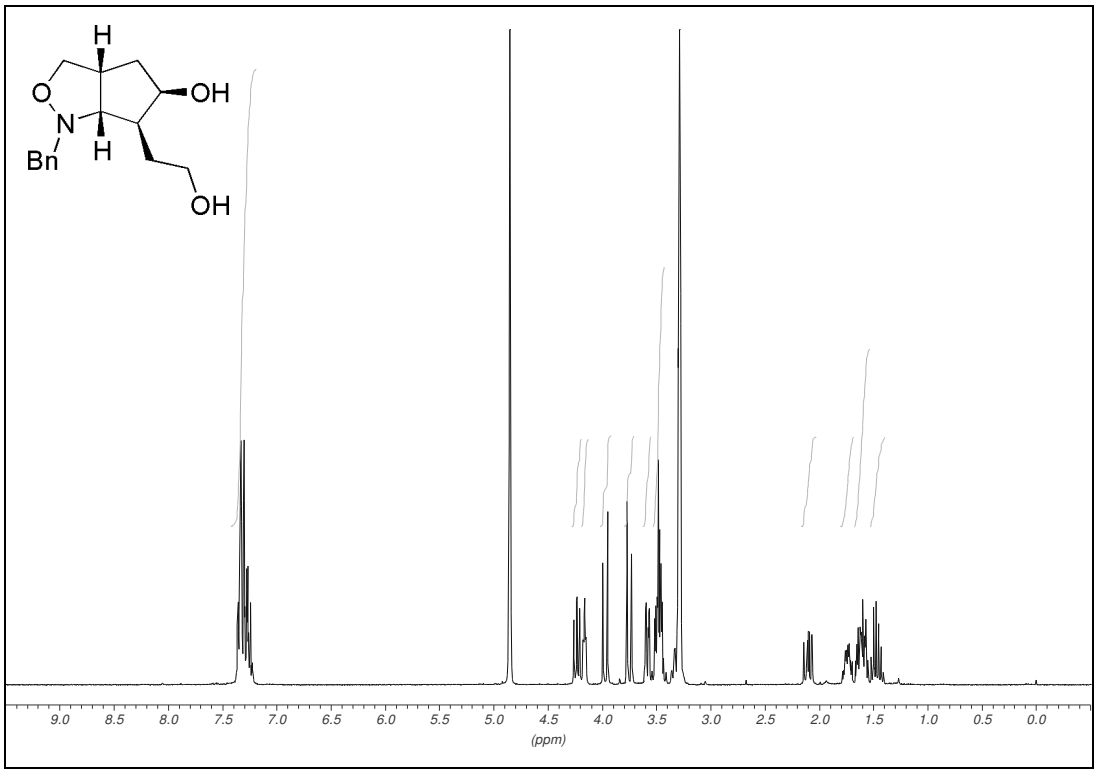


^{13}C NMR (75.5 MHz, DMSO+D_2O)

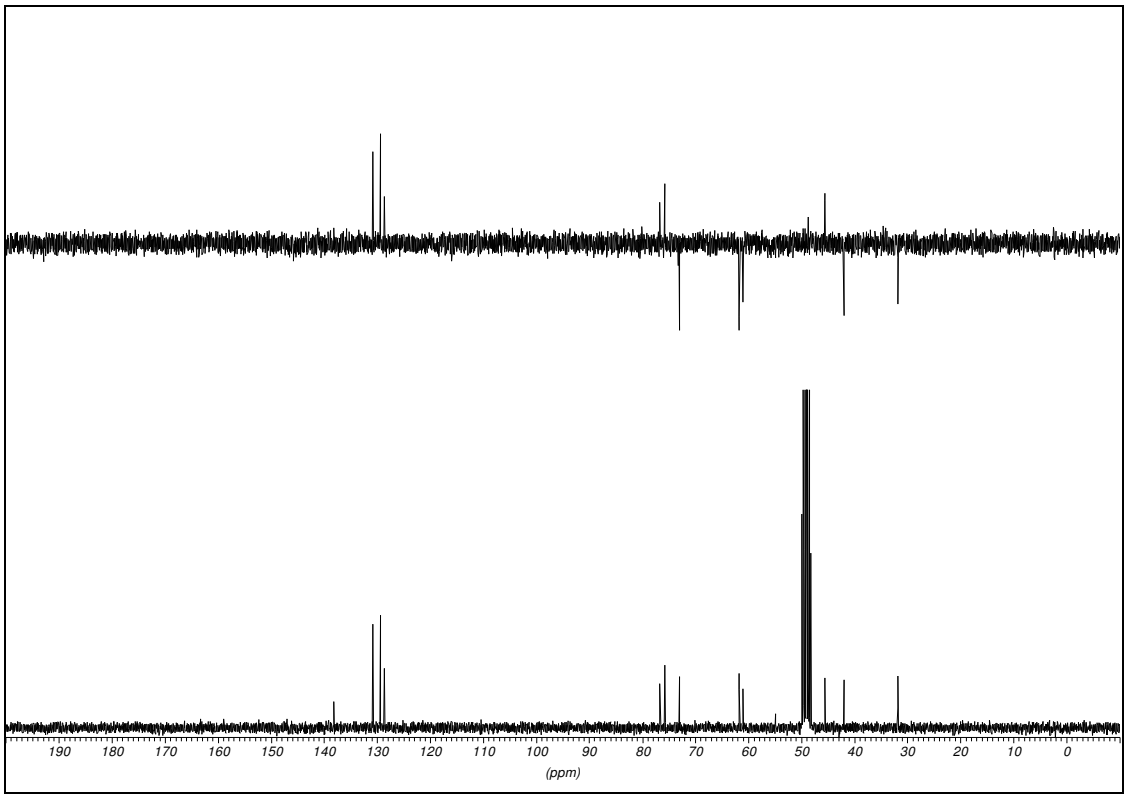


(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-(2-hydroxyethyl)hexahydro-1*H*-cyclopenta[*c*]isoxazol-5-ol (92)

^{1}H-NMR (300 MHz, MeOD)

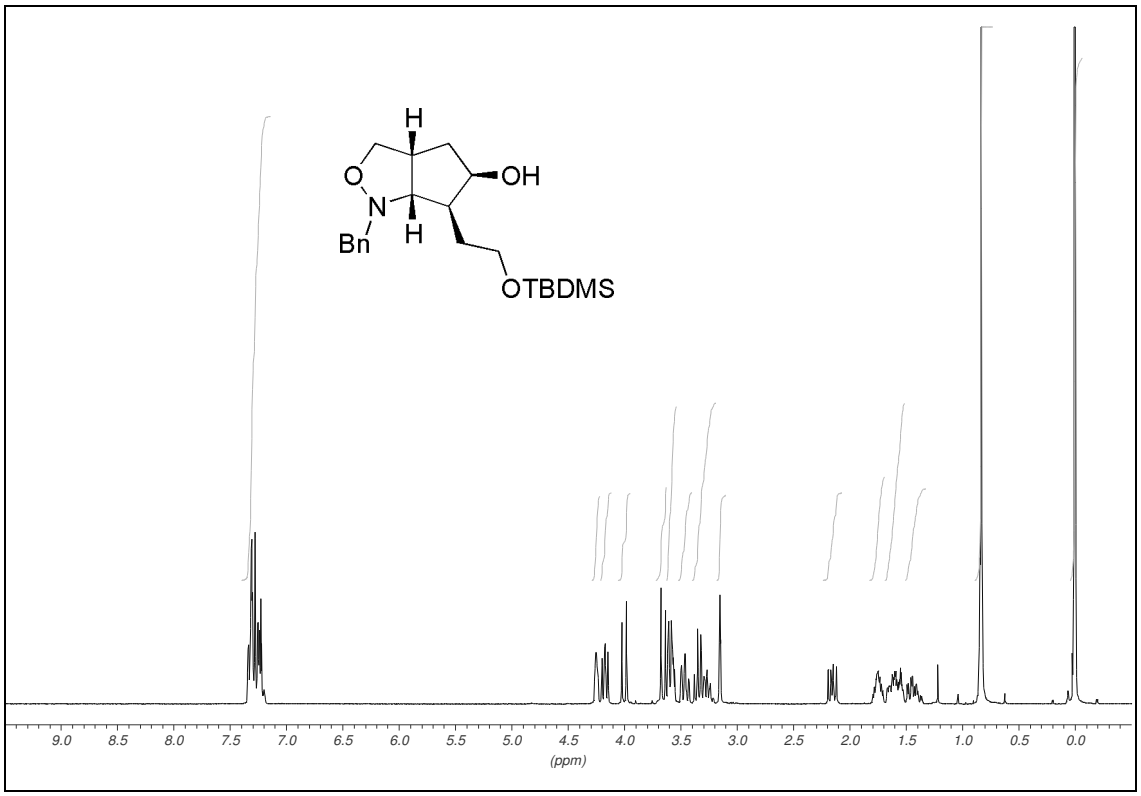


^{13}C NMR (75.5 MHz, MeOD)

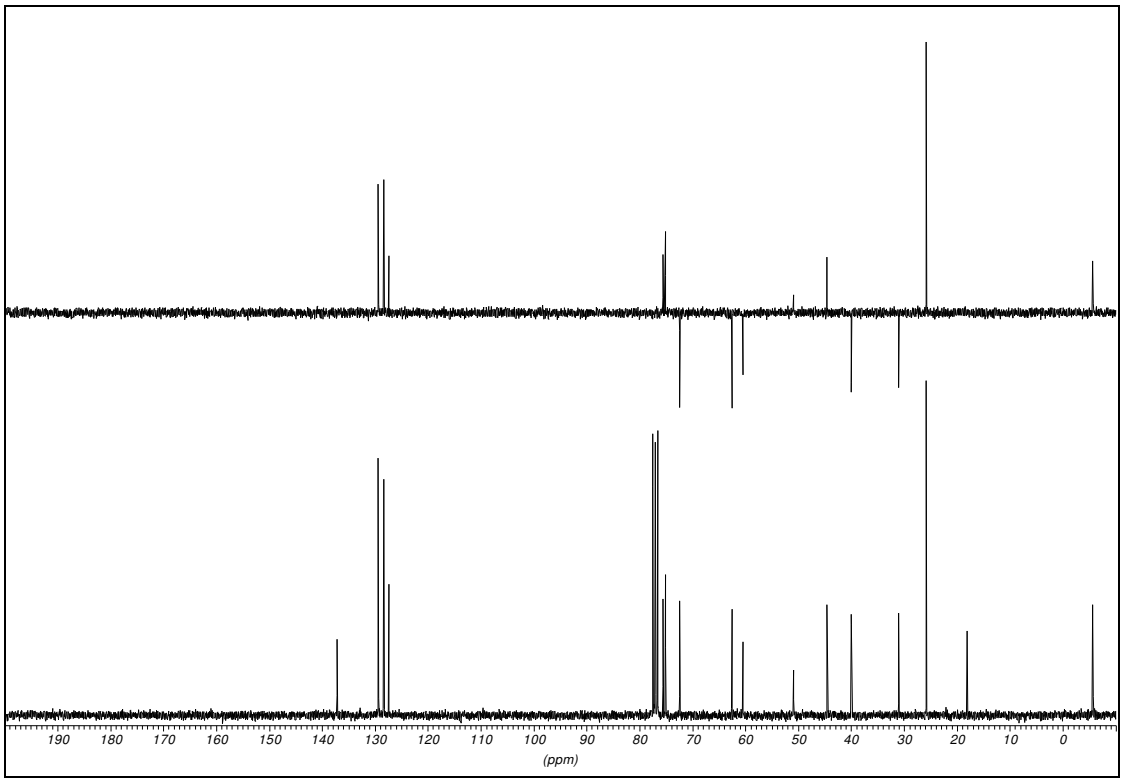


(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-[2-(*tert*-butyldimethylsiloxy)ethyl]hexahydro-1*H*-cyclopenta[*c*]isoxazol-5-ol (93)

^{1}H-NMR (300 MHz, $CDCl_3$)

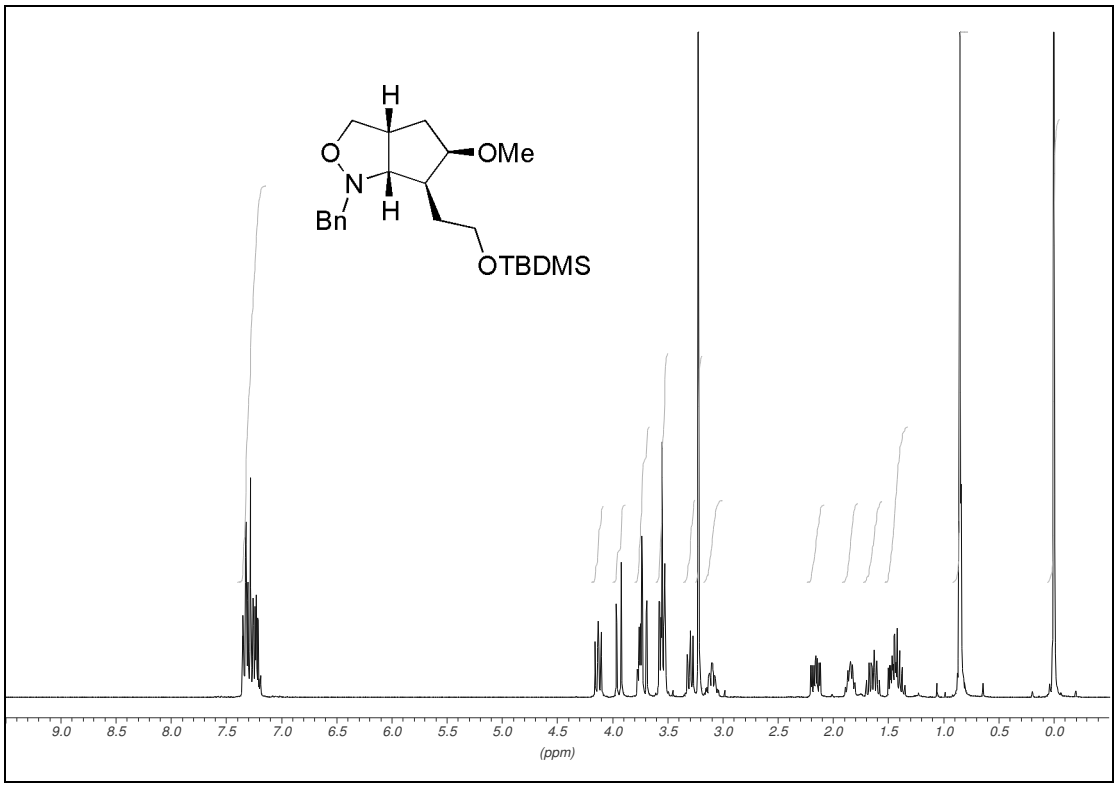


^{13}C NMR (75.5 MHz, $CDCl_3$)

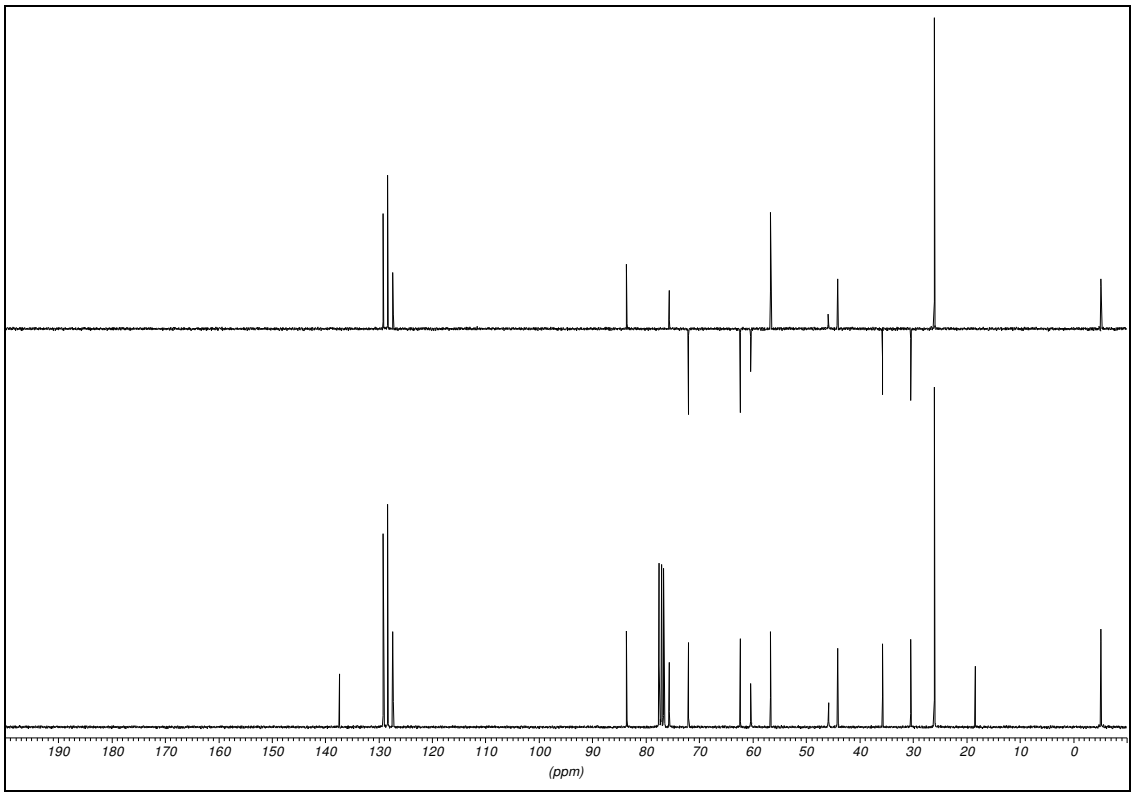


(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-6-[2-(*tert*-butyldimethylsiloxy)ethyl]-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazole (94)

^{1}H-NMR (300 MHz, $CDCl_3$)

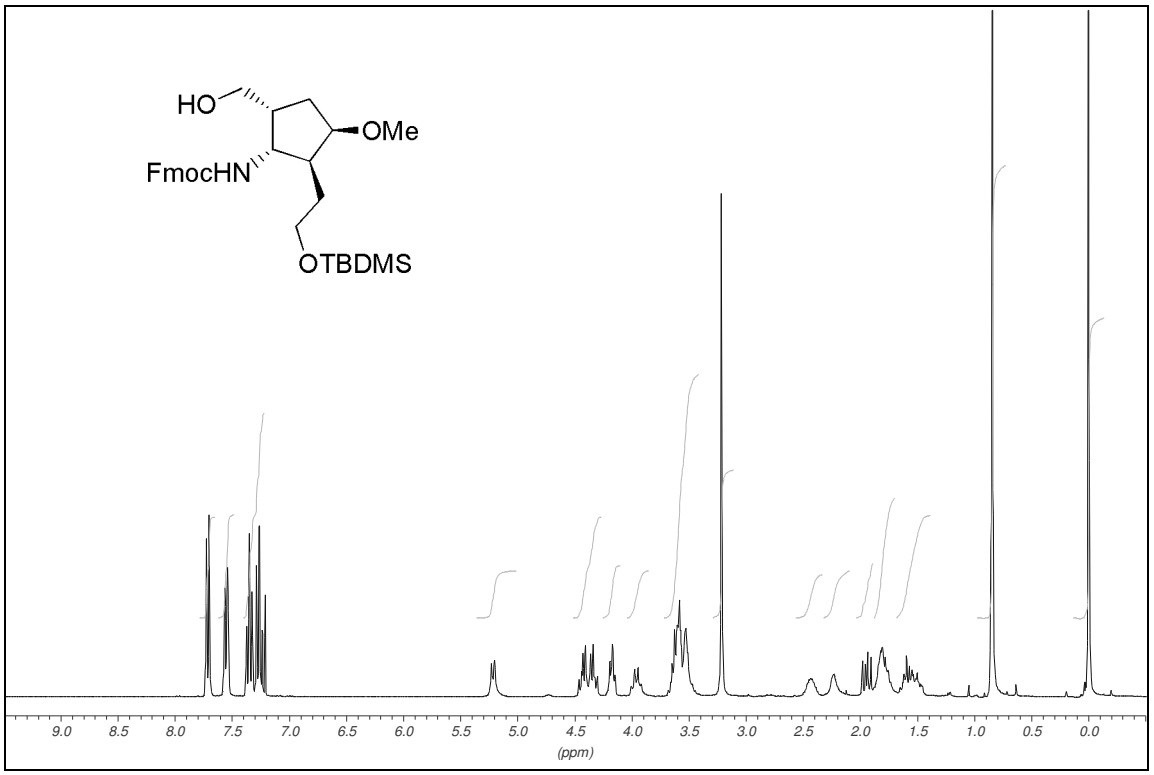


^{13}C NMR (75.5 MHz, $CDCl_3$)

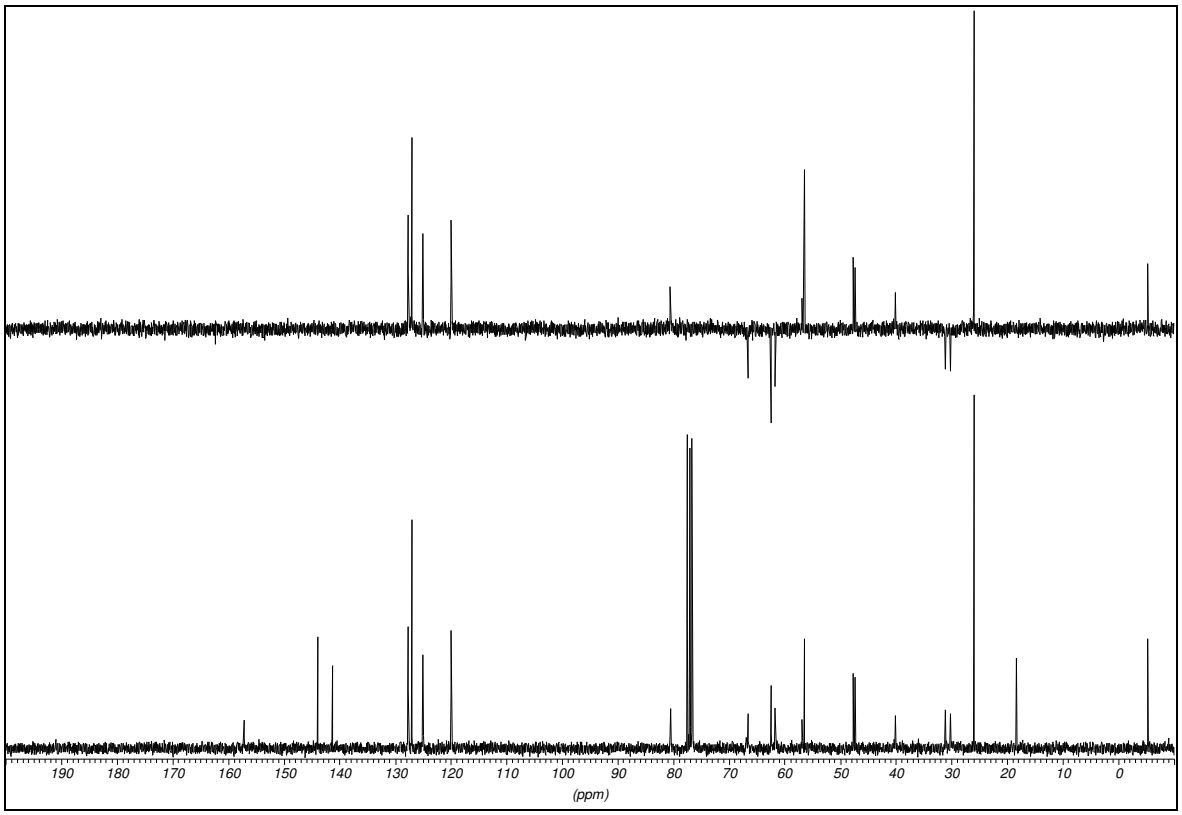


(9*H*-fluoren-9-yl)methyl (1*R*,2*S*,3*R*,5*R*)-2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-(hydroxymethyl)-3-methoxycyclopentylcarbamate (96)

^{1}H-NMR (300 MHz, $CDCl_3$)

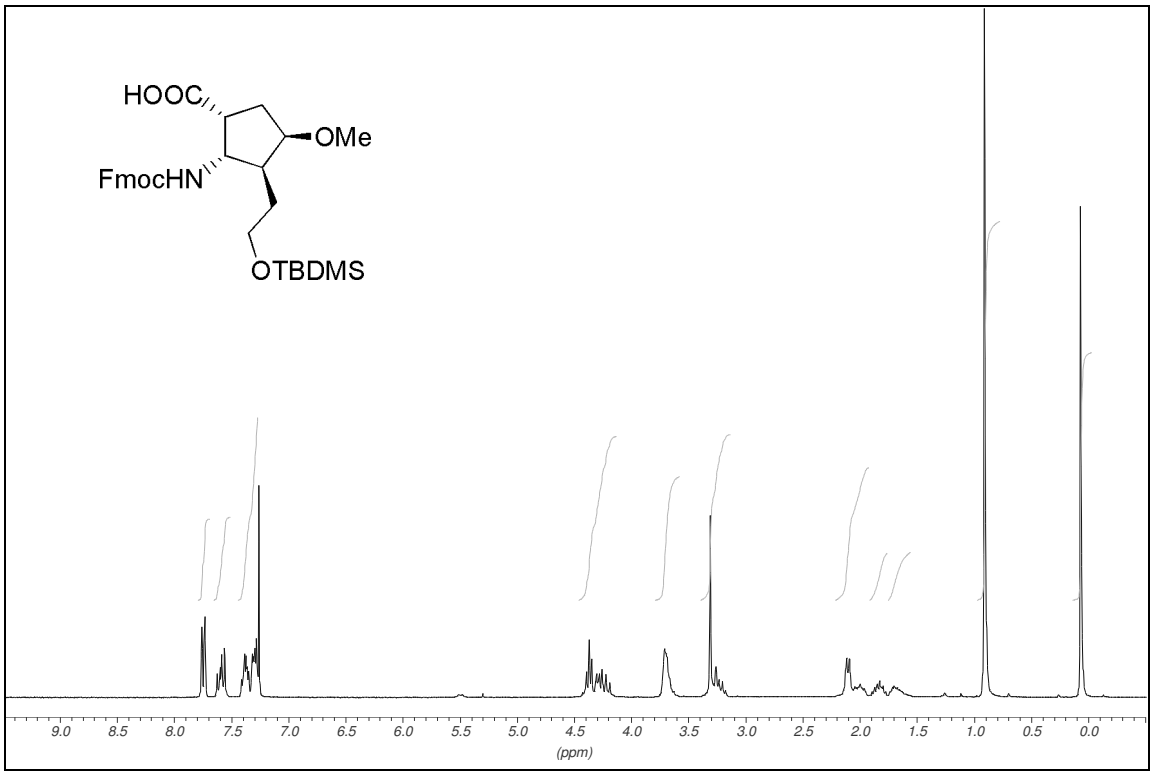


^{13}C NMR (75.5 MHz, $CDCl_3$)

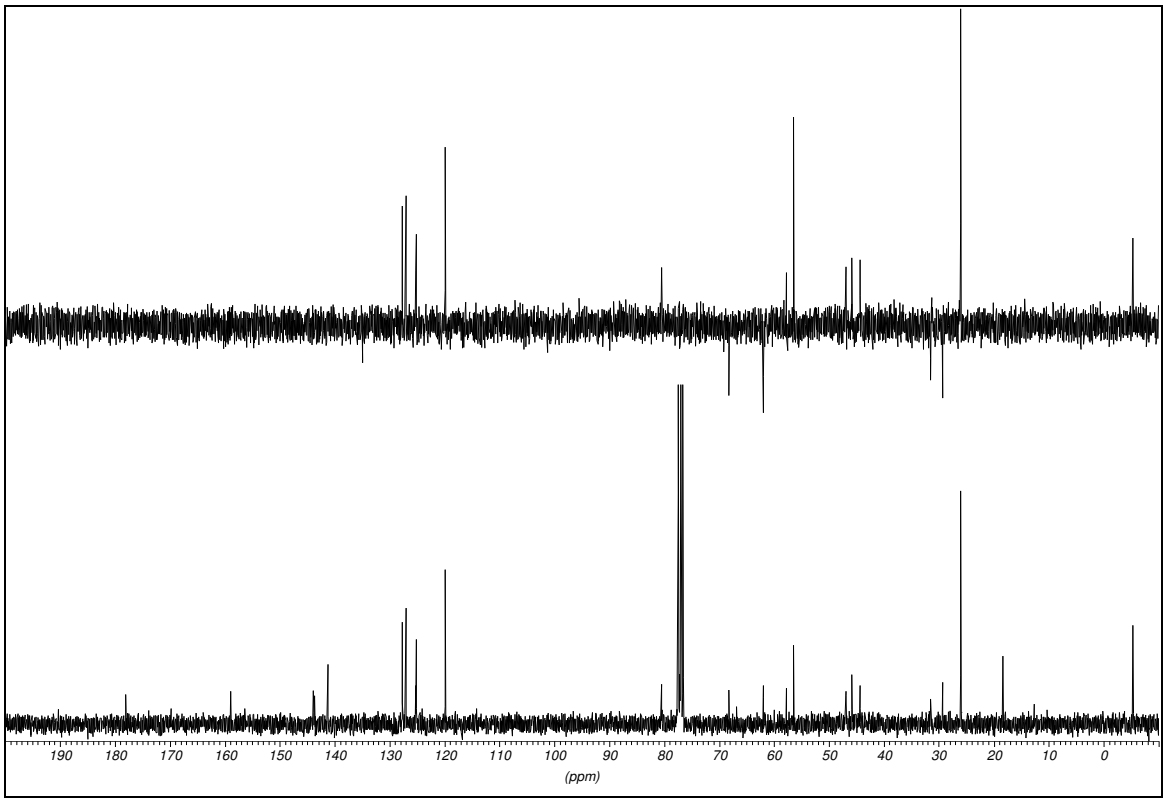


(1*R*,2*S*,3*S*,4*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-methoxycyclopentanecarboxylic acid (97)

^{1}H-NMR (300 MHz, $CDCl_3$)

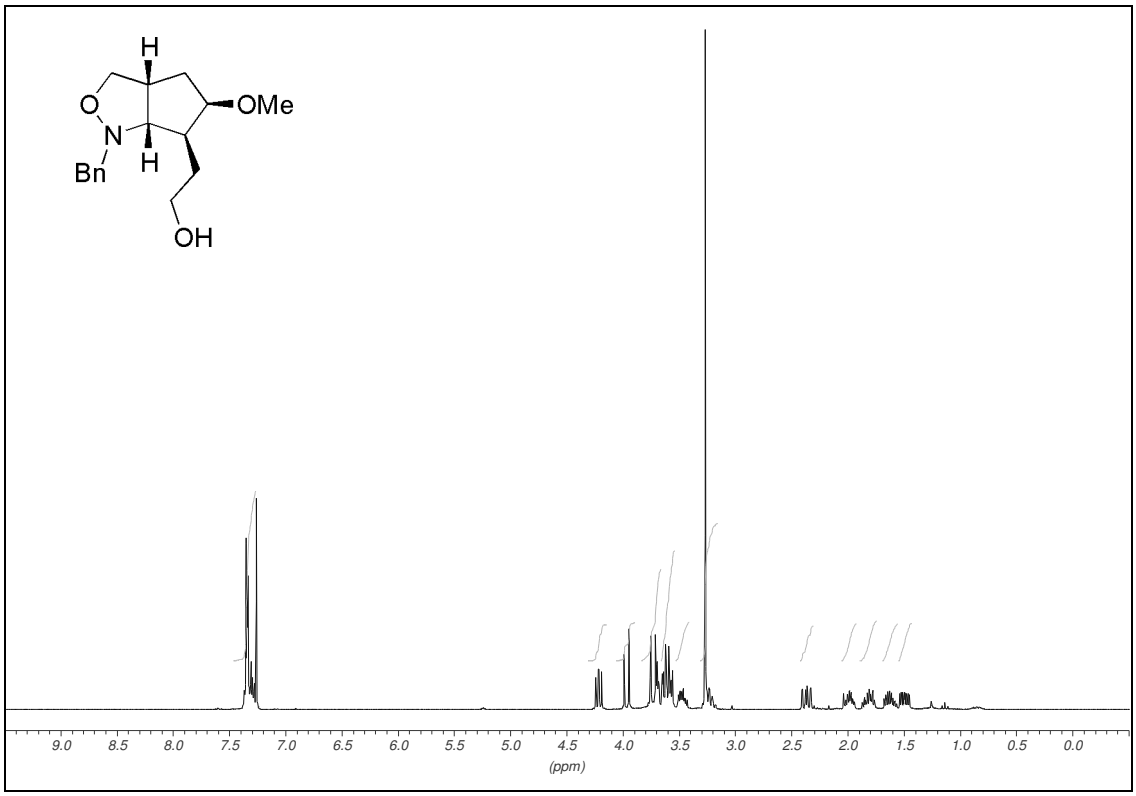


^{13}C NMR (75.5 MHz, $CDCl_3$)

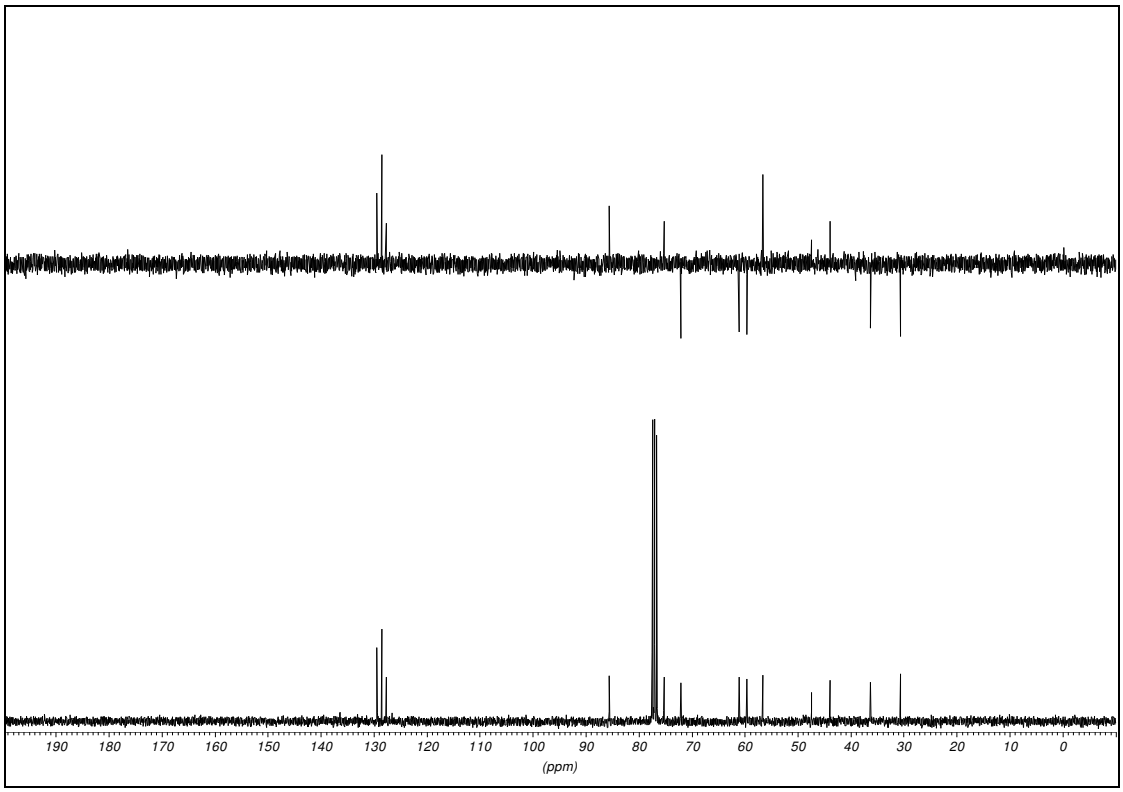


2-[(3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl]ethanol (98)

^{1}H-NMR (300 MHz, $CDCl_3$)

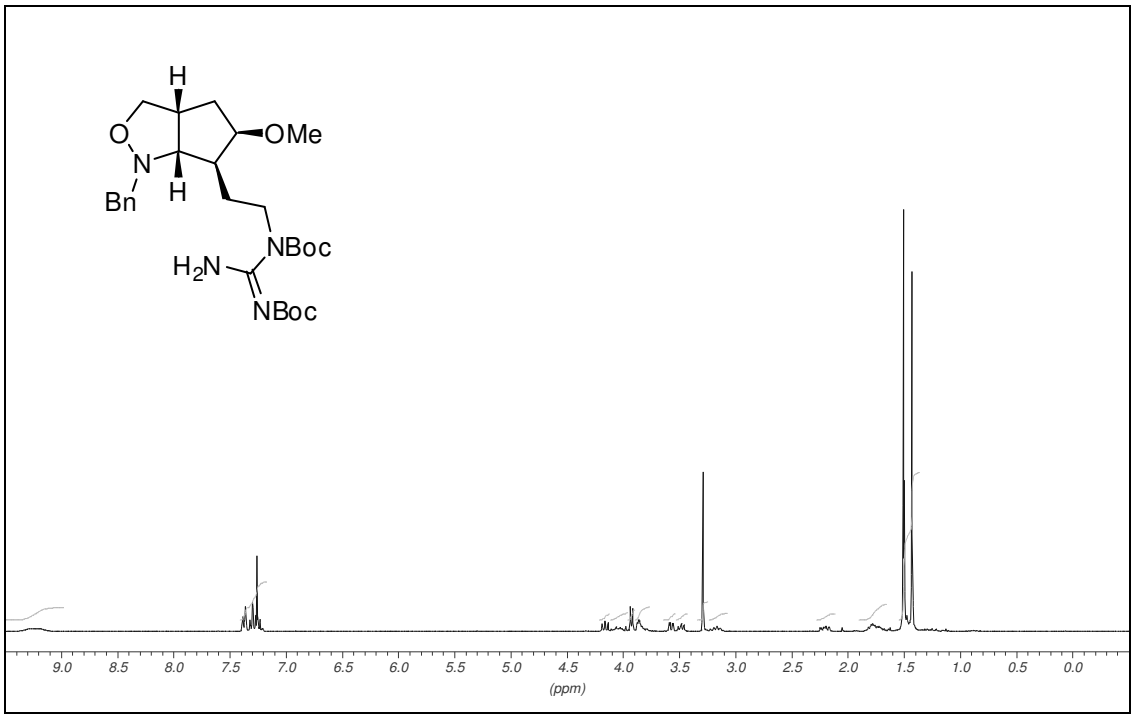


^{13}C NMR (75.5 MHz, $CDCl_3$)

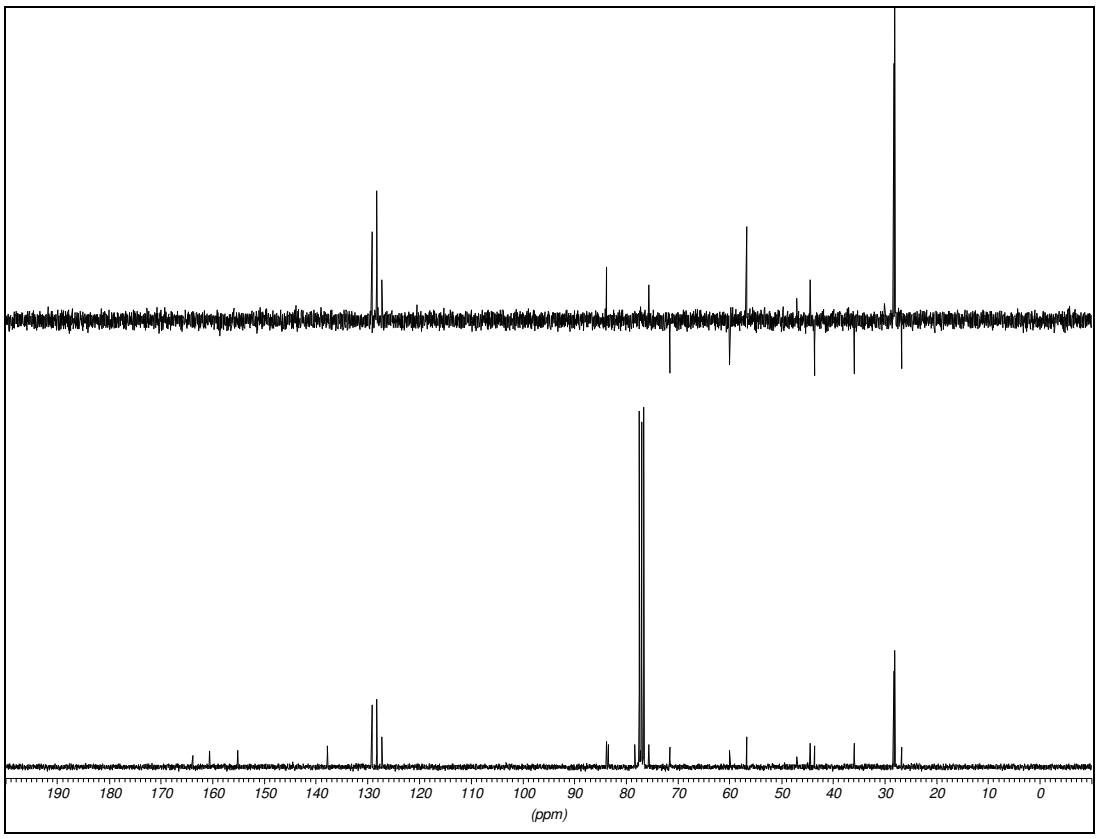


tert-butyl 2-((3a*S*,5*R*,6*S*,6a*S*)-1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl)ethyl(*N*-(*tert*-butoxycarbonyl)carbamimidoyl)carbamate (99)

^{1}H-NMR (300 MHz, $CDCl_3$)

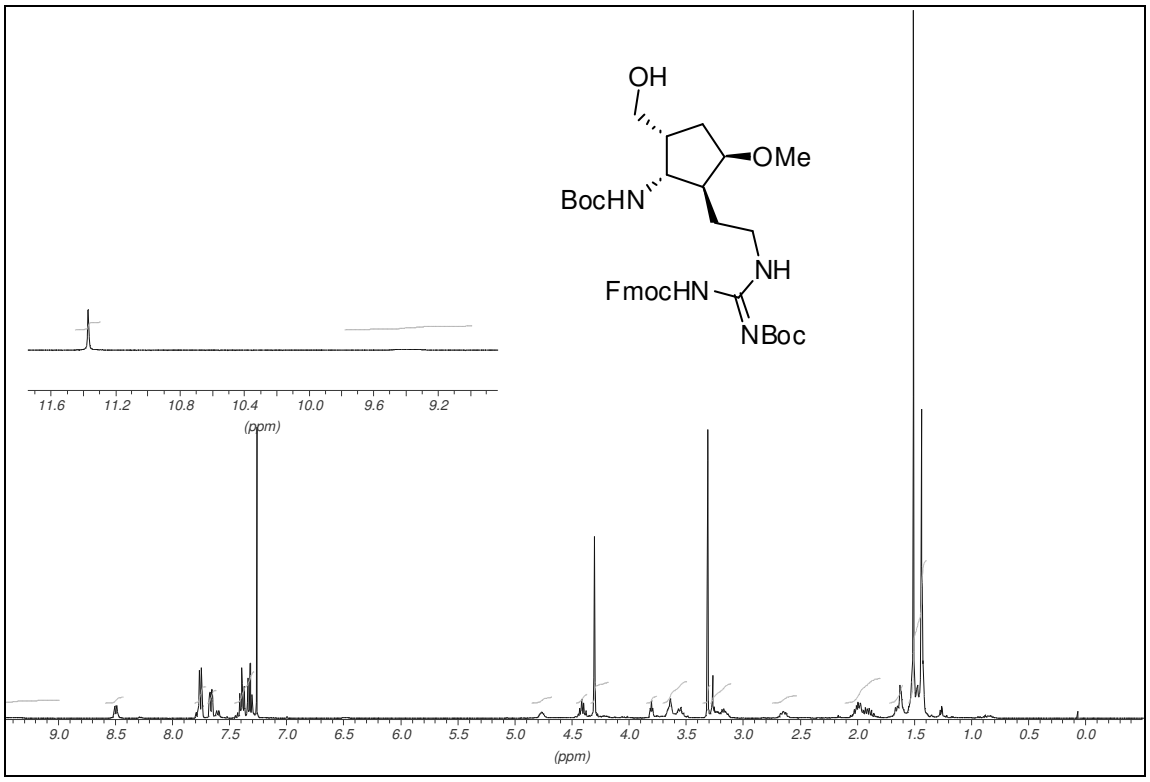


^{13}C NMR (75.5 MHz, $CDCl_3$)

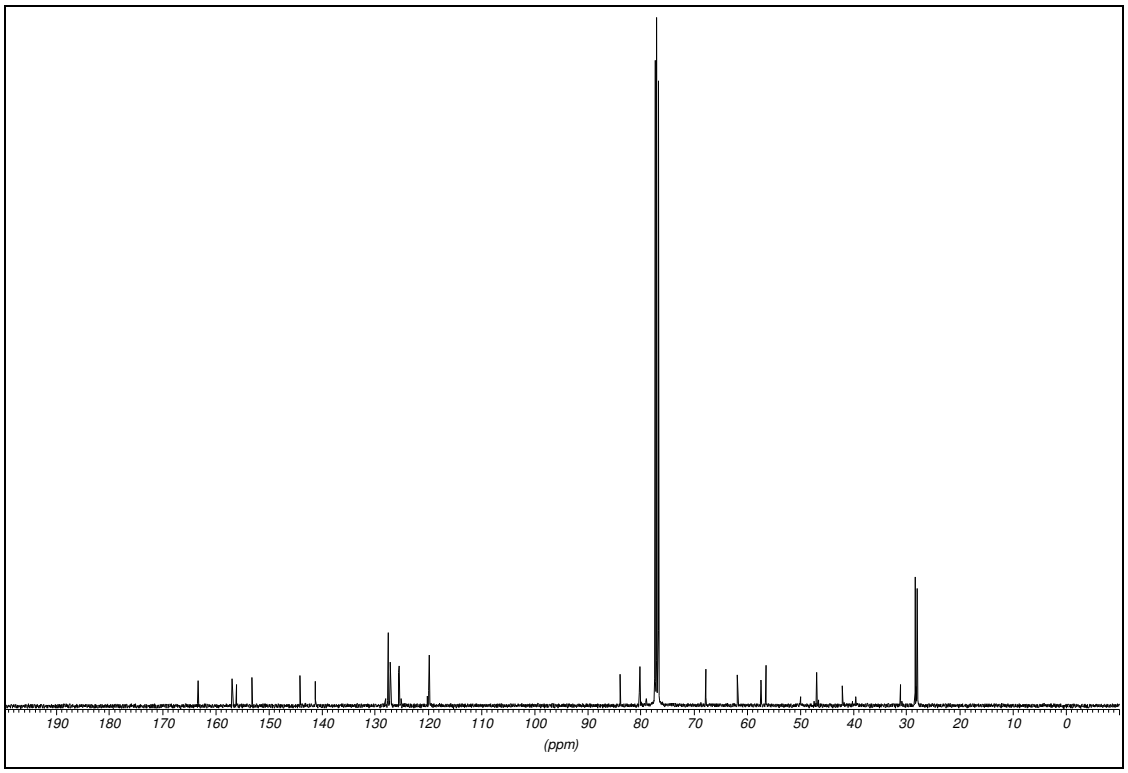


***tert*-butyl (1*R*,2*S*,3*R*,5*R*)-2-(2-(3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-2-(*tert*-butylcarboxy)guanidino)ethyl)-5-(hydroxymethyl)-3-methoxycyclopentylcarbamate (101)**

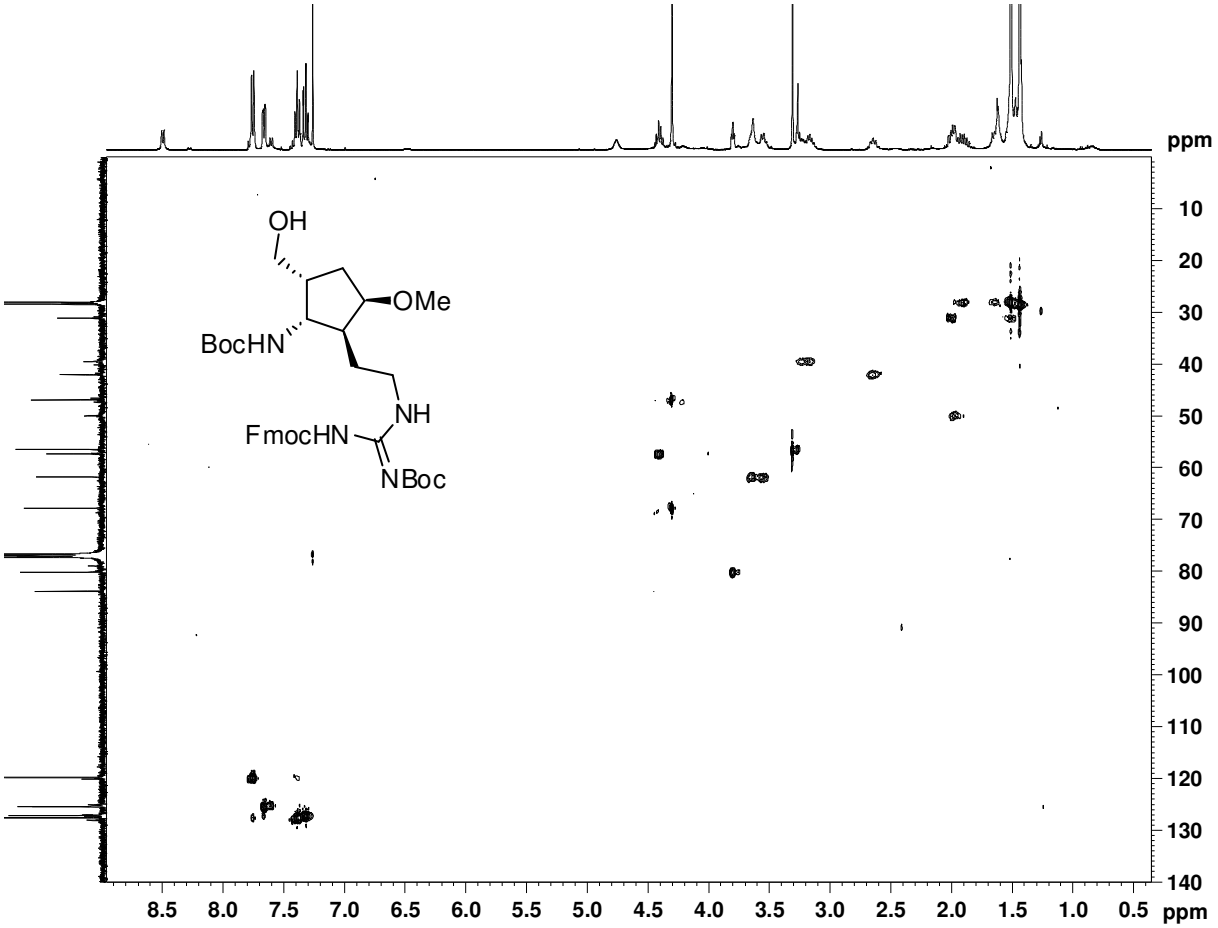
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

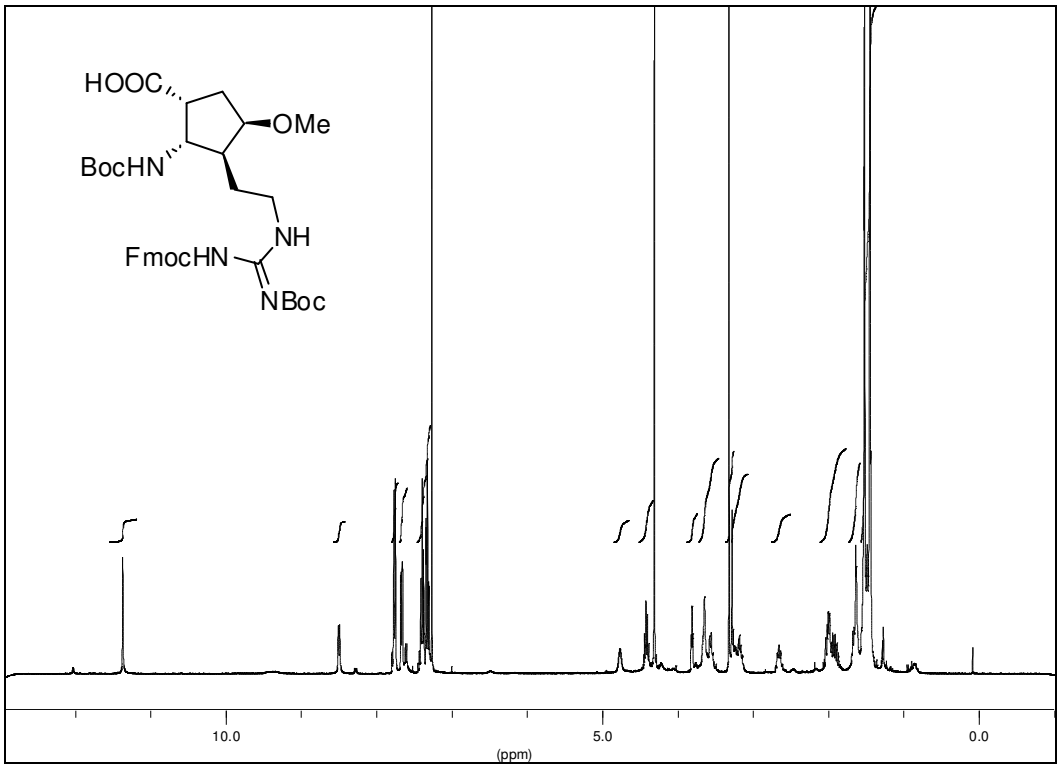


HSQC (400MHz)

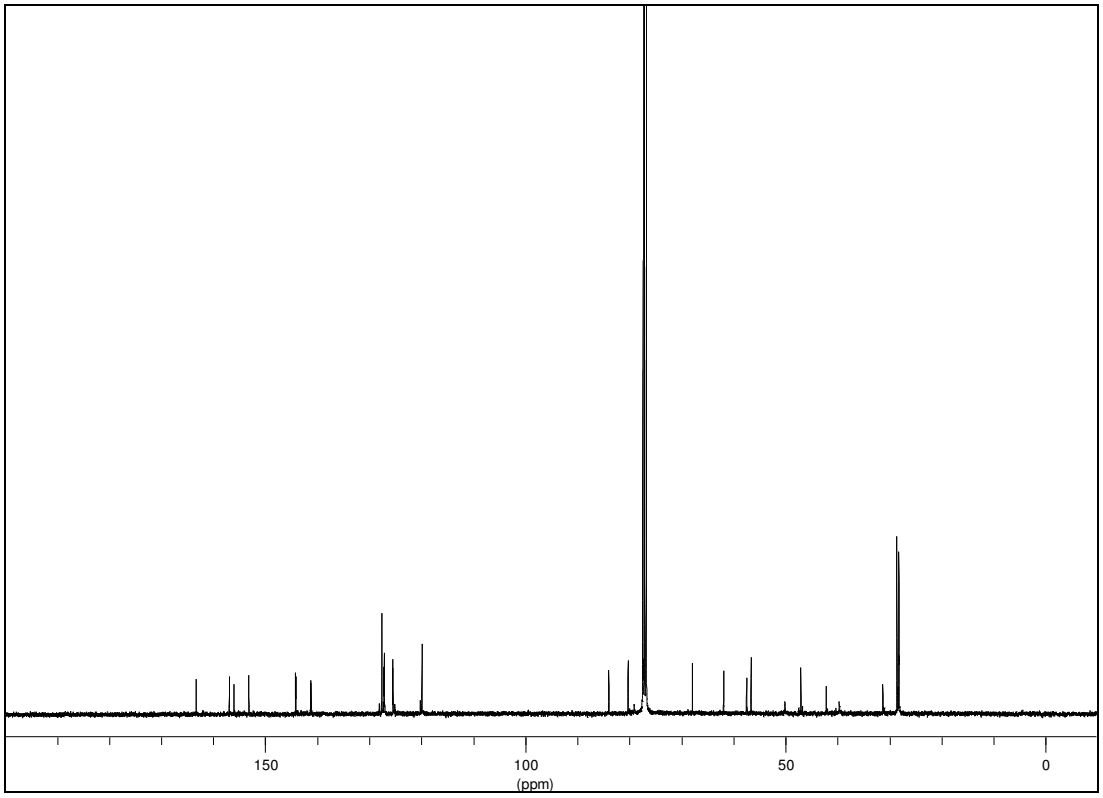

OH
OMe
BocHN
NH
FmocHN
NBoc
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

(1*R*,2*S*,3*S*,4*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(2-(1,2-bis(tert-butoxycarbonyl)guanidino)ethyl)-4-methoxycyclopentanecarboxylic acid (102)

^{1}H-NMR (600 MHz, $CDCl_3$)

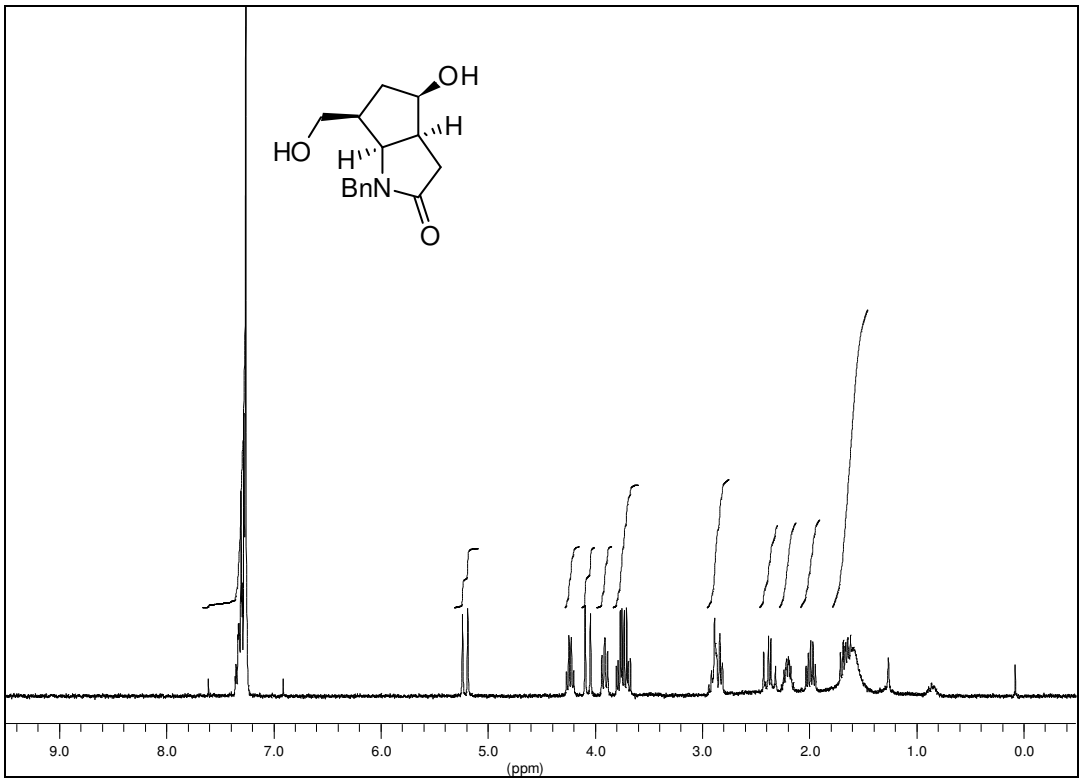


^{13}C NMR (151 MHz, $CDCl_3$)

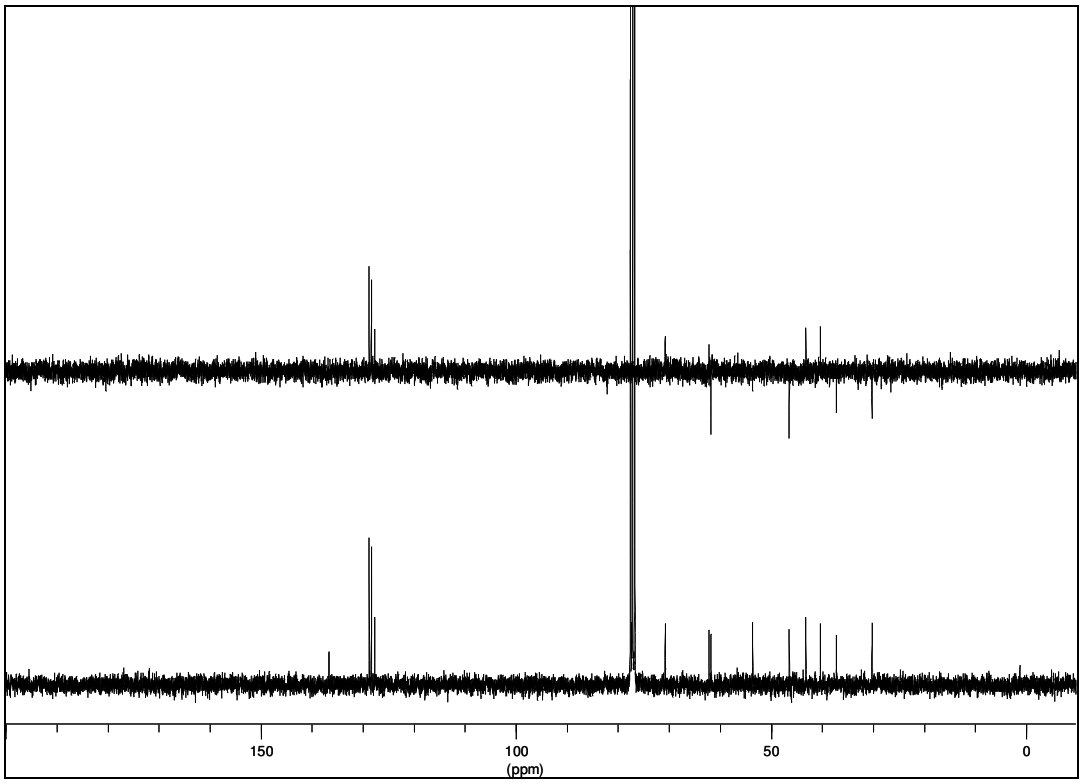


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-4-hydroxy-6-(hydroxymethyl)hexahydrocyclopenta[*b*]pyrrol-2(1H)-one (116)

^{1}H-NMR (300 MHz, $CDCl_3$)

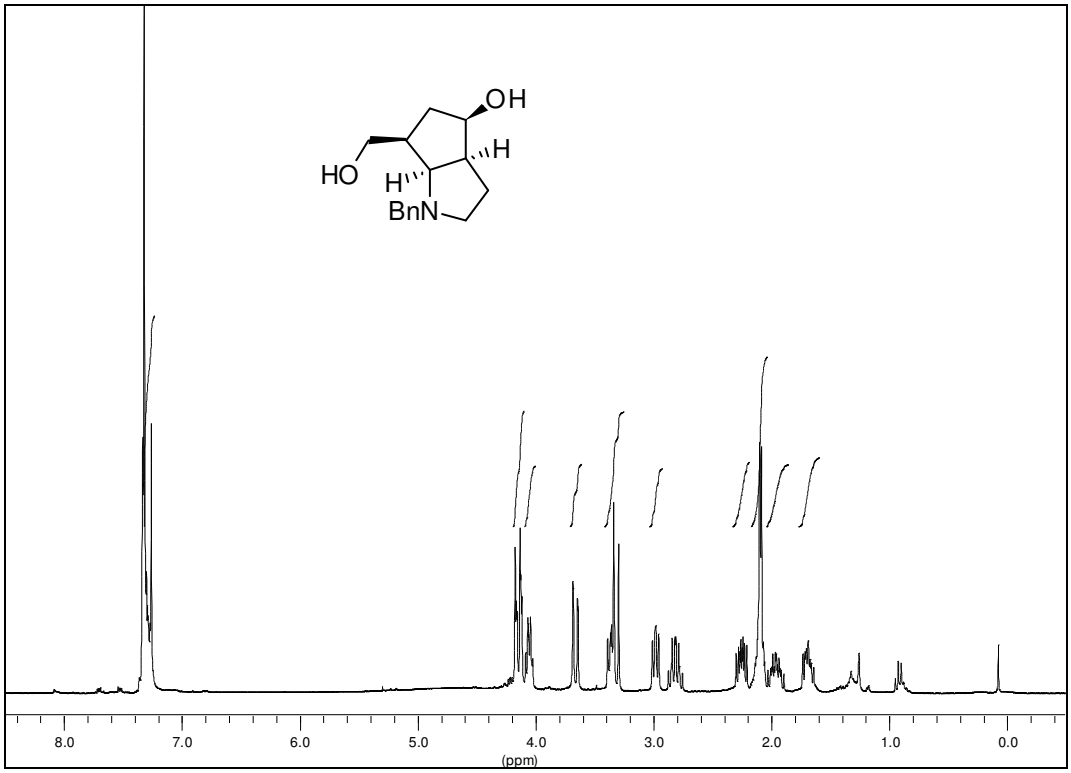


^{13}C NMR (75.5 MHz, $CDCl_3$)

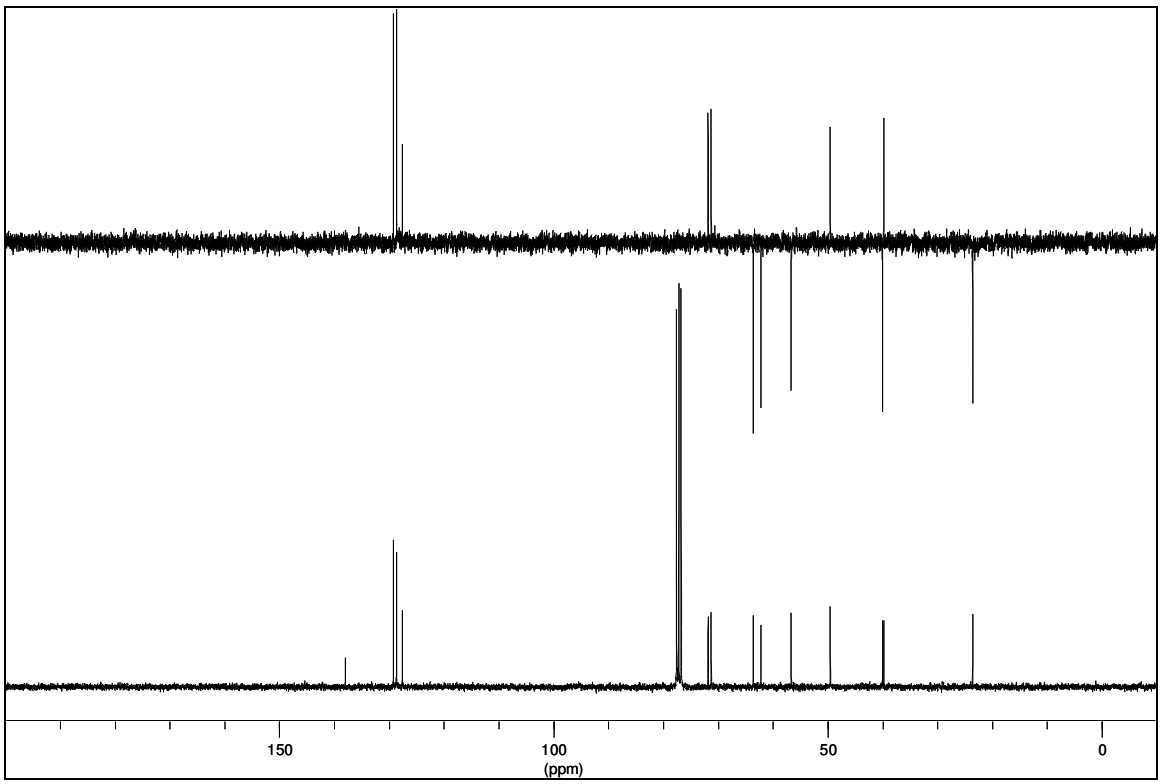


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-(hydroxymethyl)octahydrocyclopenta[*b*]pyrrol-4-ol (117)

^{1}H-NMR (300 MHz, $CDCl_3$)

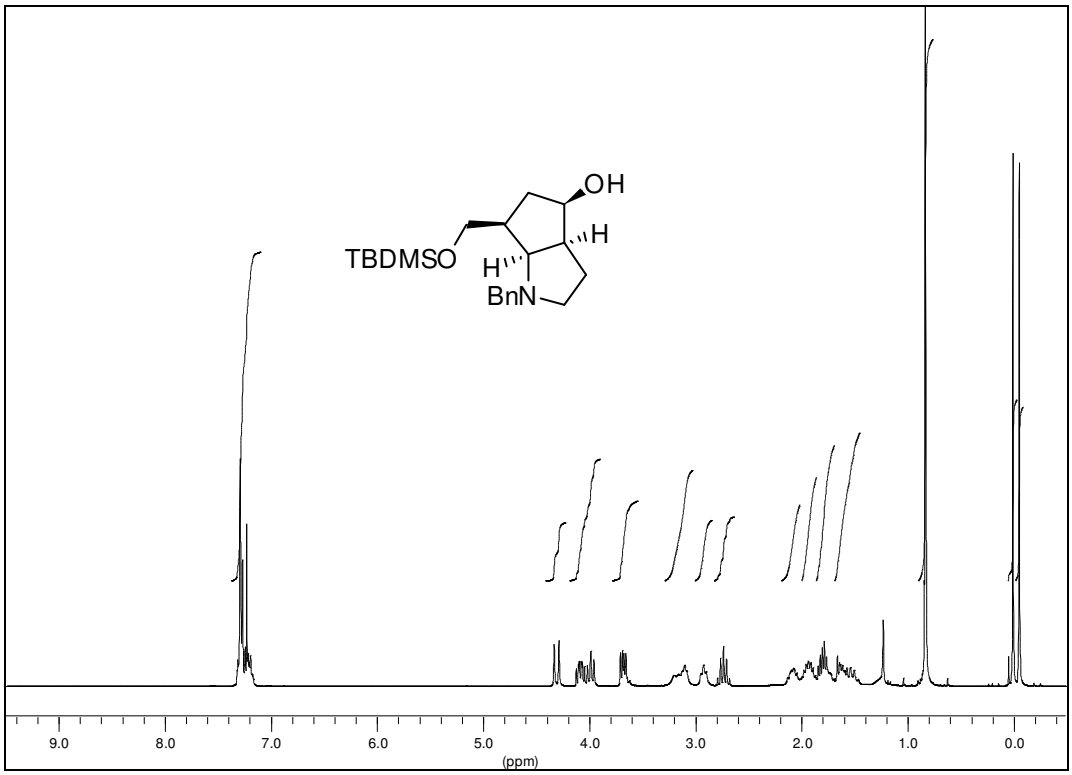


^{13}C NMR (75.5 MHz, $CDCl_3$)

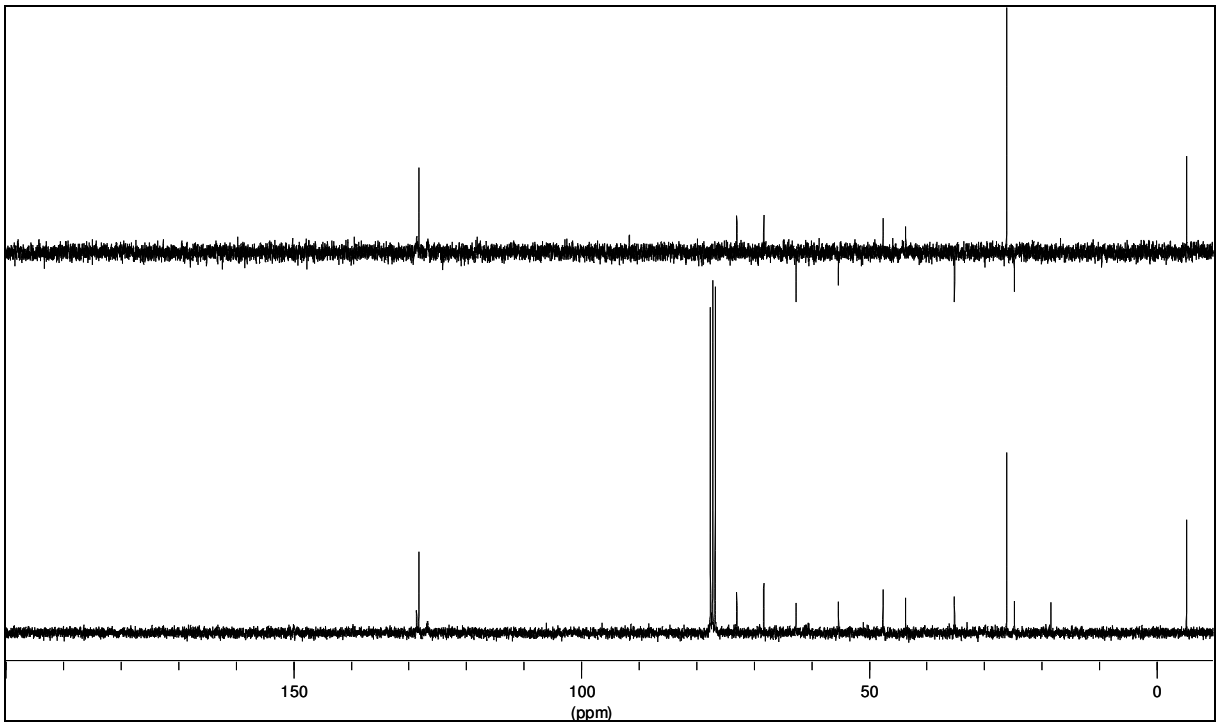


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-((*tert*-butyldimethylsilyloxy)methyl) octahydrocyclopenta[*b*]pyrrol-4-ol

^{1}H-NMR (300 MHz, $CDCl_3$)

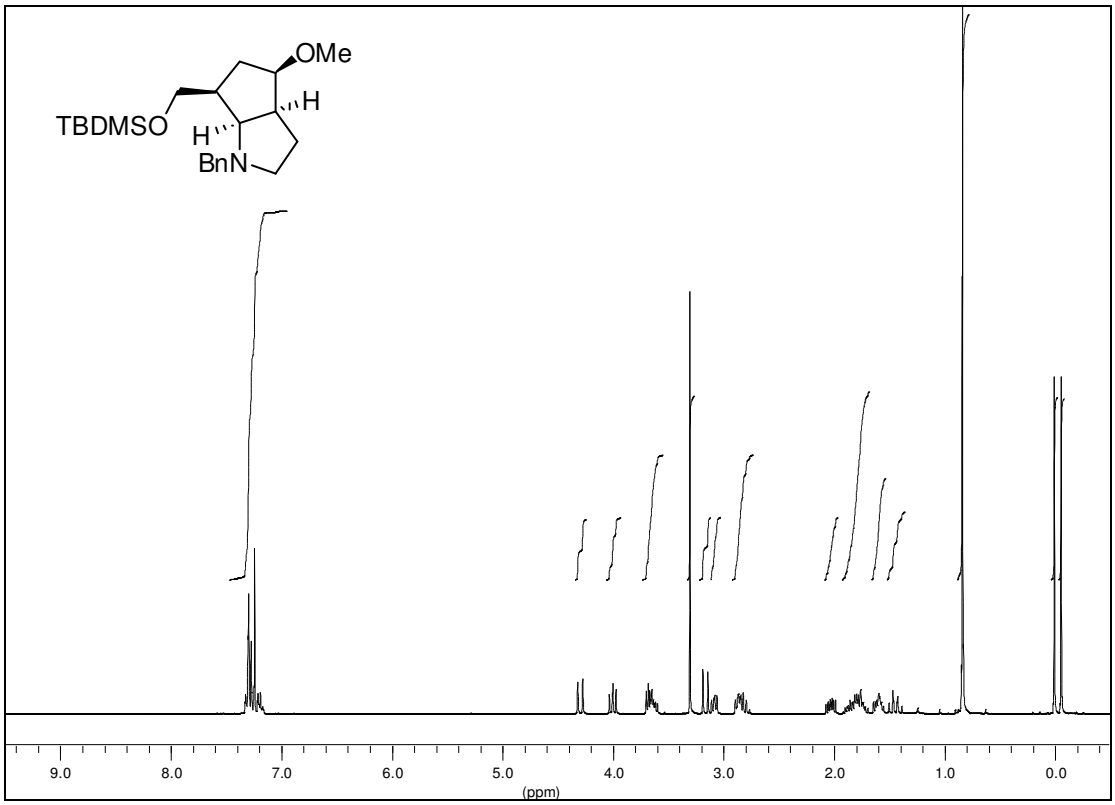


^{13}C NMR (75.5 MHz, $CDCl_3$)

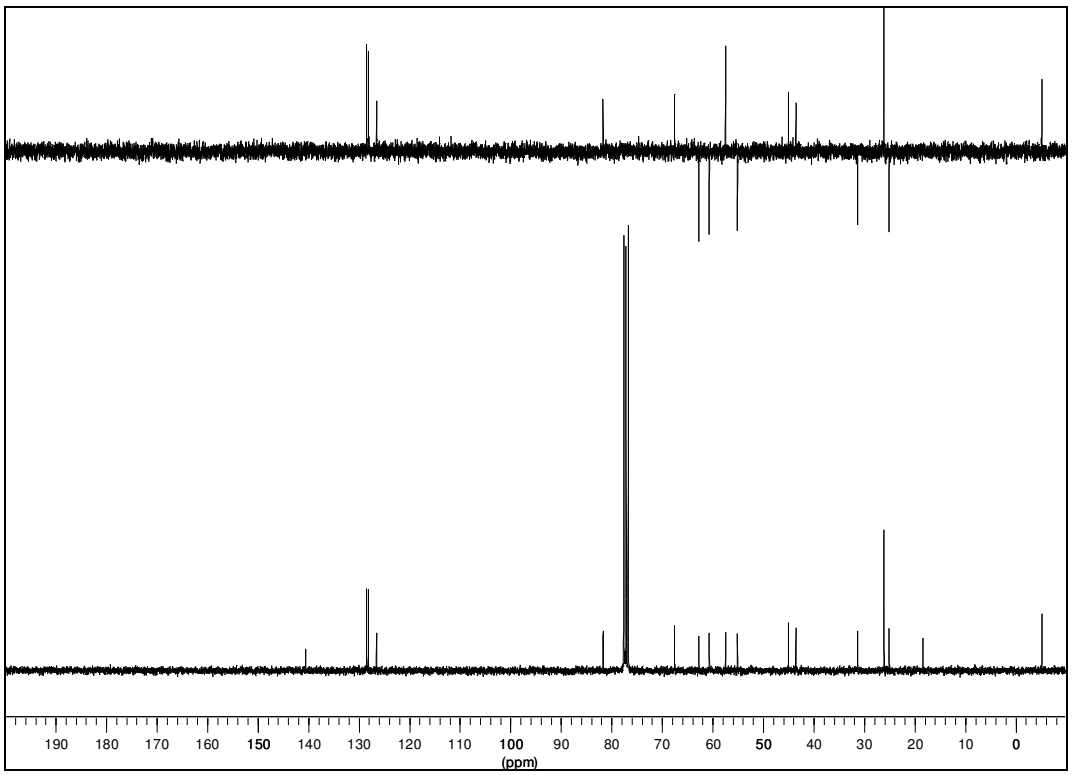


(3a*S*,4*R*,6*S*,6a*S*)-1-benzyl-6-((*tert*-butyldimethylsilyloxy)methyl)-4-methoxy-octahydrocyclopenta[*b*]pyrrole (118)

^{1}H-NMR (300 MHz, $CDCl_3$)

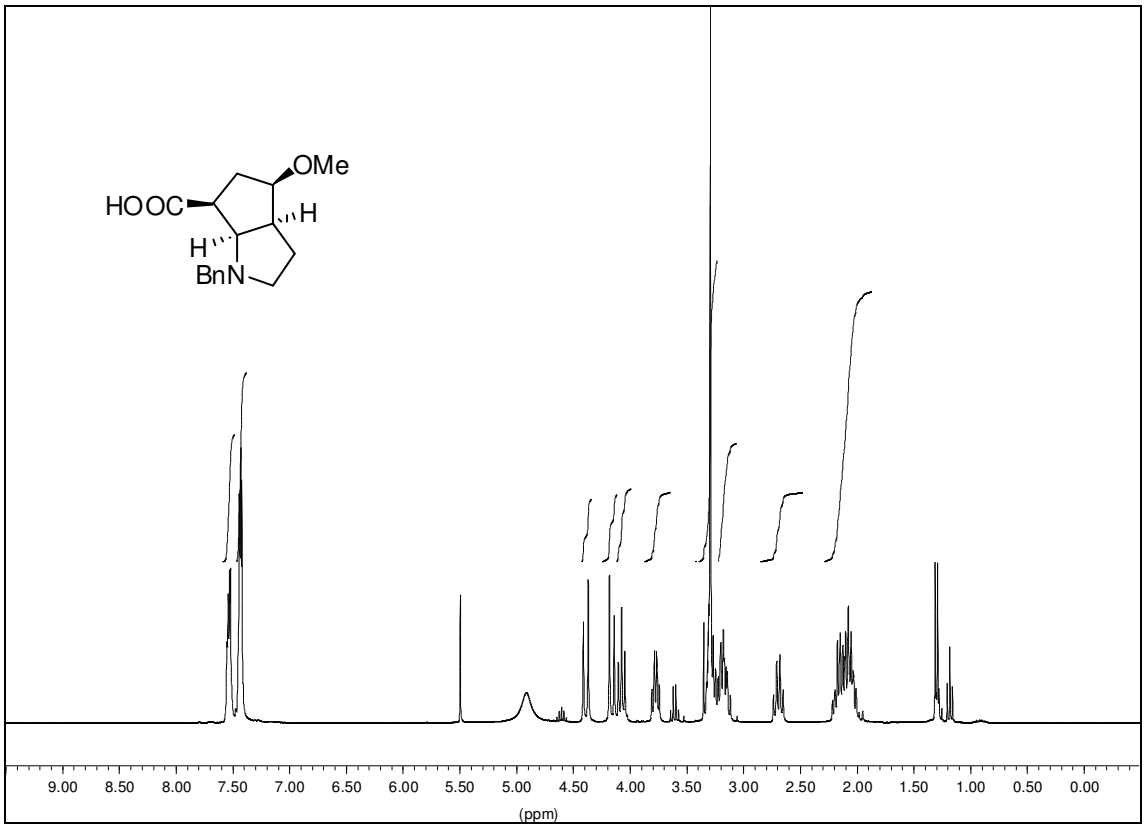


^{13}C NMR (75.5 MHz, $CDCl_3$)

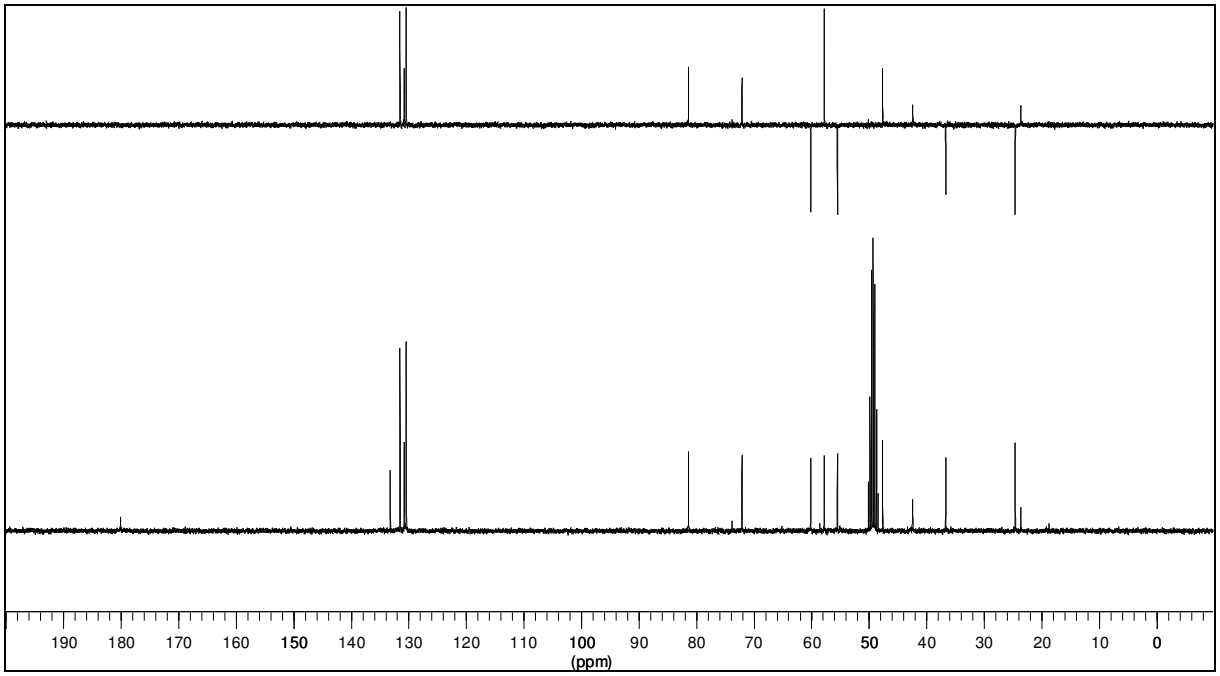


(3a*S*,4*R*,6*S*,6a*R*)-1-benzyl-4-methoxyoctahydrocyclopenta[*b*]pyrrole-6-carboxylic acid (119)

^{1}H-NMR (300 MHz, MeOD)

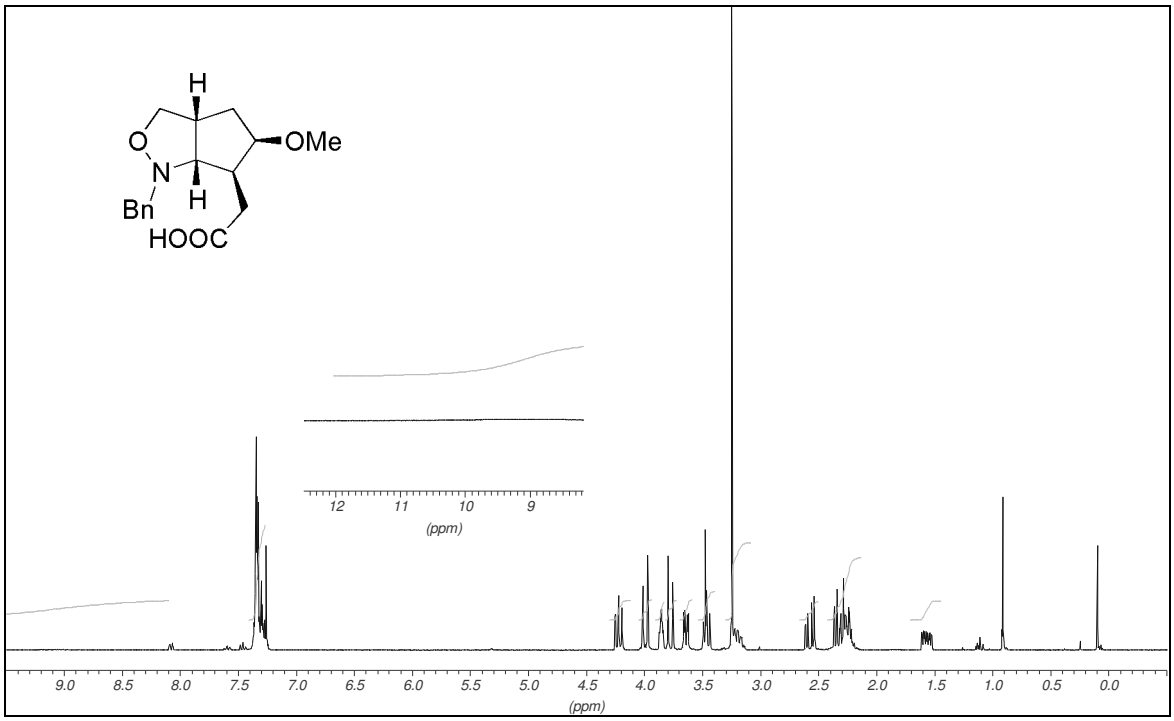


^{13}C NMR (75.5 MHz, MeOD)

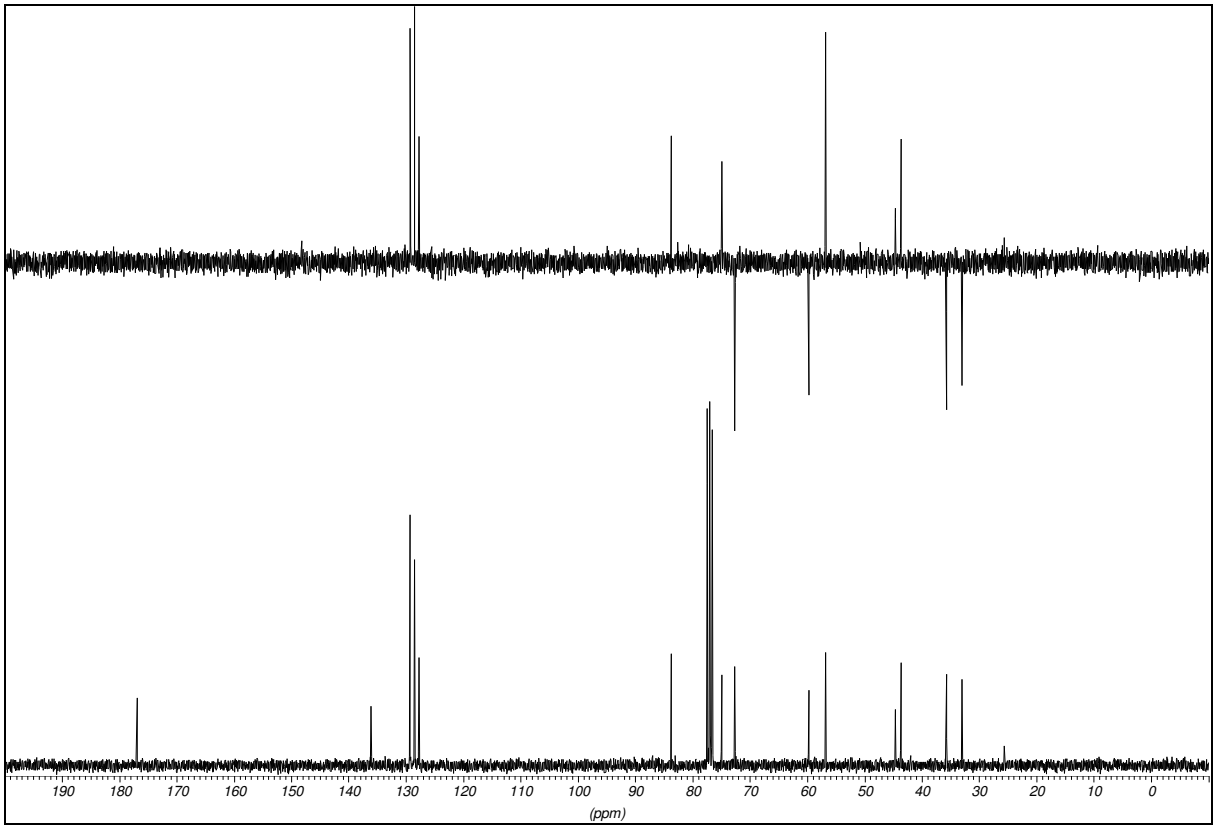


2-((3a*R*,5*R*,6*S*,6a*R*)-1-benzyl-5-methoxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl)acetic acid (138)

^{1}H-NMR (300 MHz, $CDCl_3$)

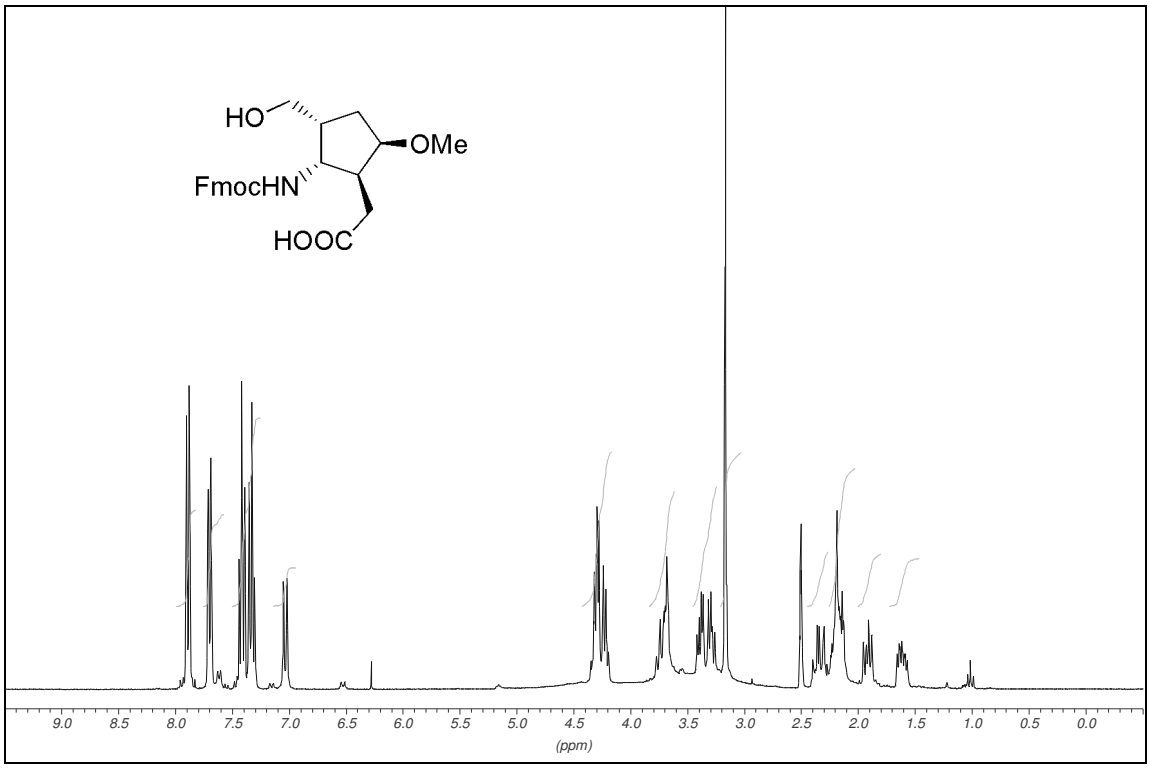


^{13}C NMR (75.5 MHz, $CDCl_3$)

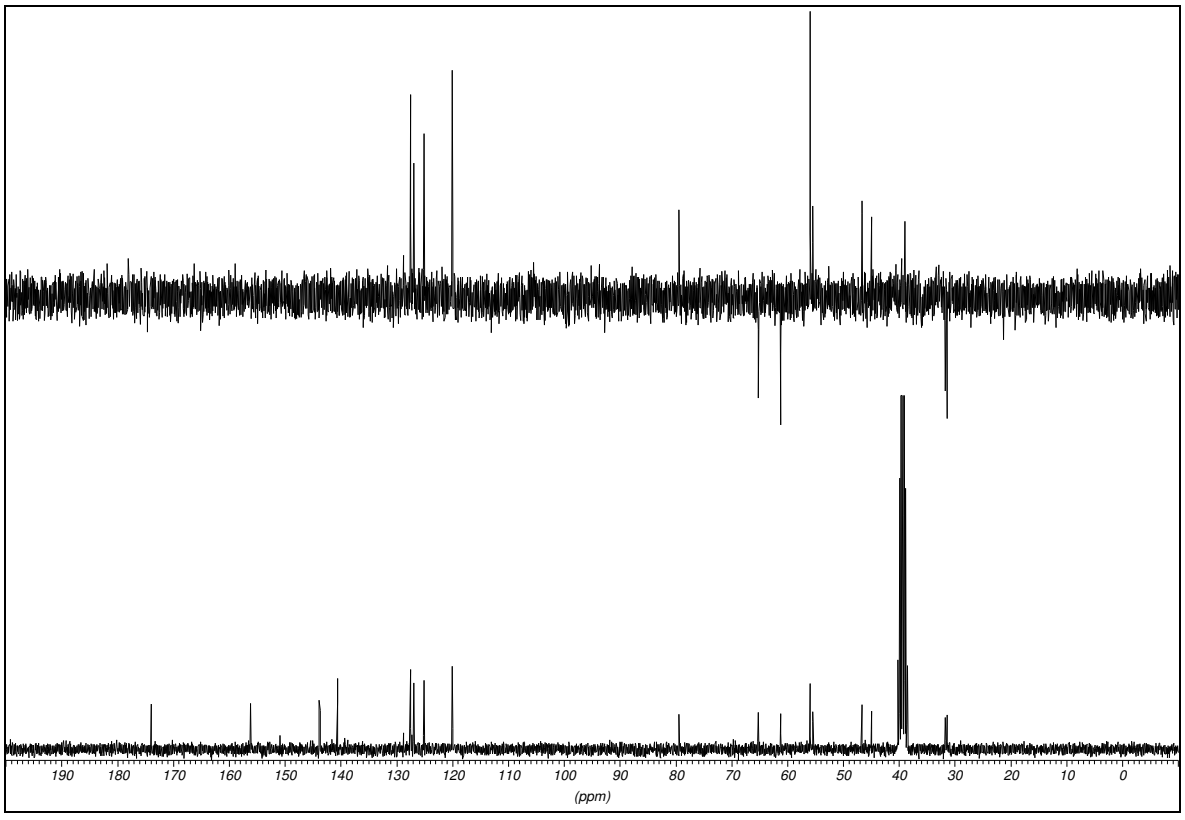


2-((1*S*,2*R*,3*R*,5*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-(hydroxymethyl)-5-methoxycyclopentyl)acetic acid (139)

^{1}H-NMR (300 MHz, DMSO)

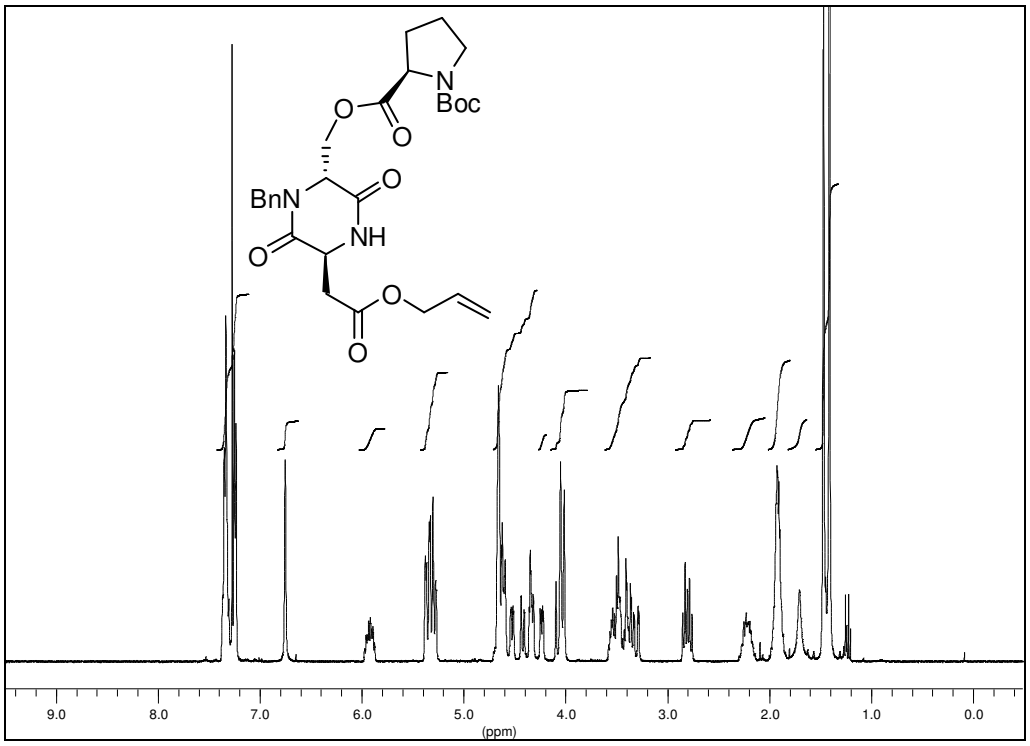


^{13}C NMR (75.5 MHz, $CDCl_3$)

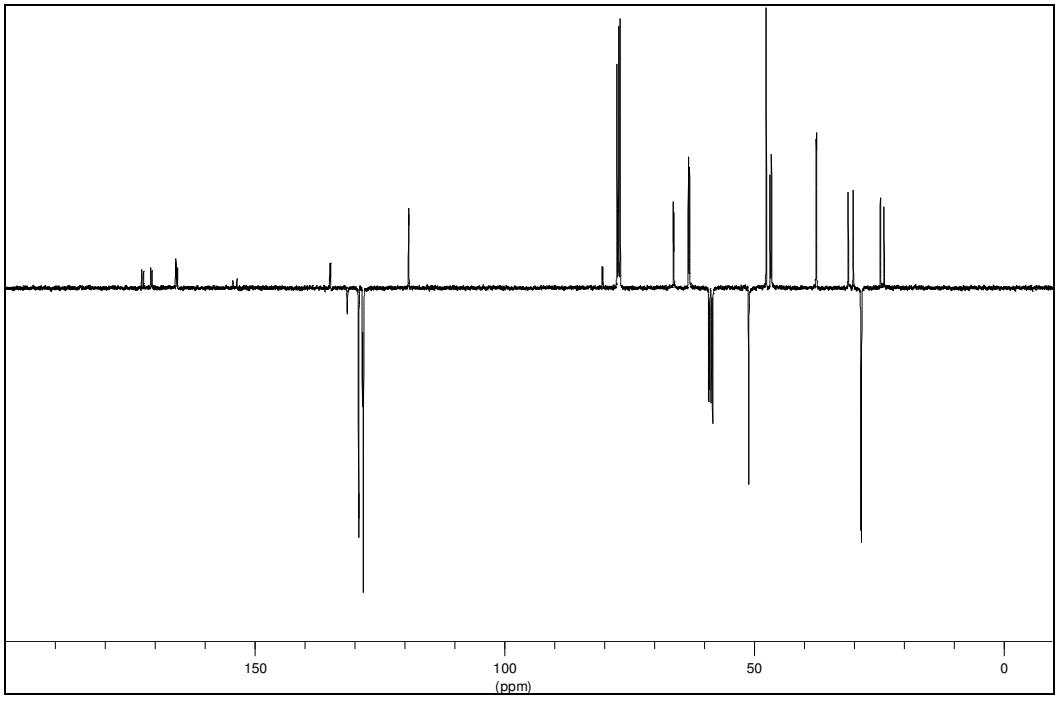


(*R*)-2-((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methyl 1-tert-butyl pyrrolidine-1,2-dicarboxylate (156a)

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

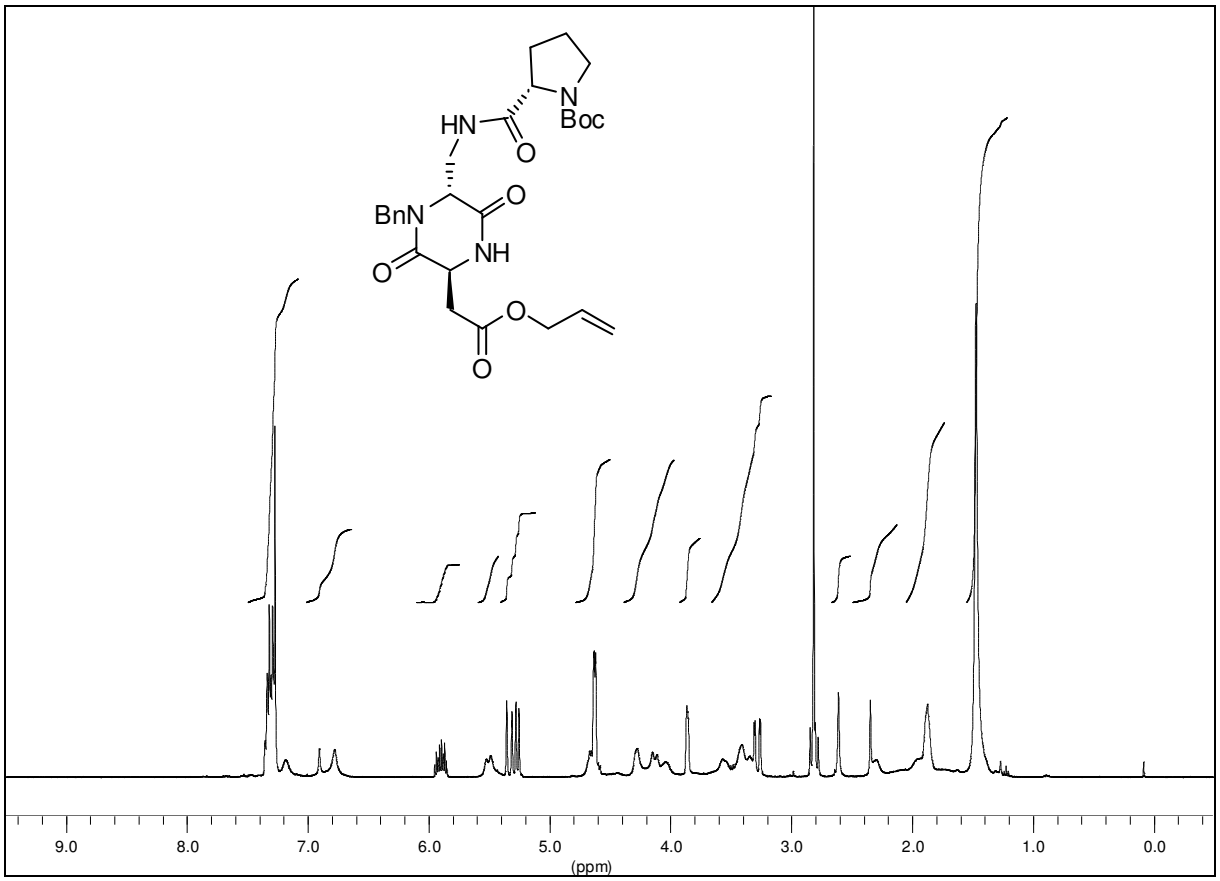


^{13}C NMR (APT, 101 MHz, $CDCl_3$)

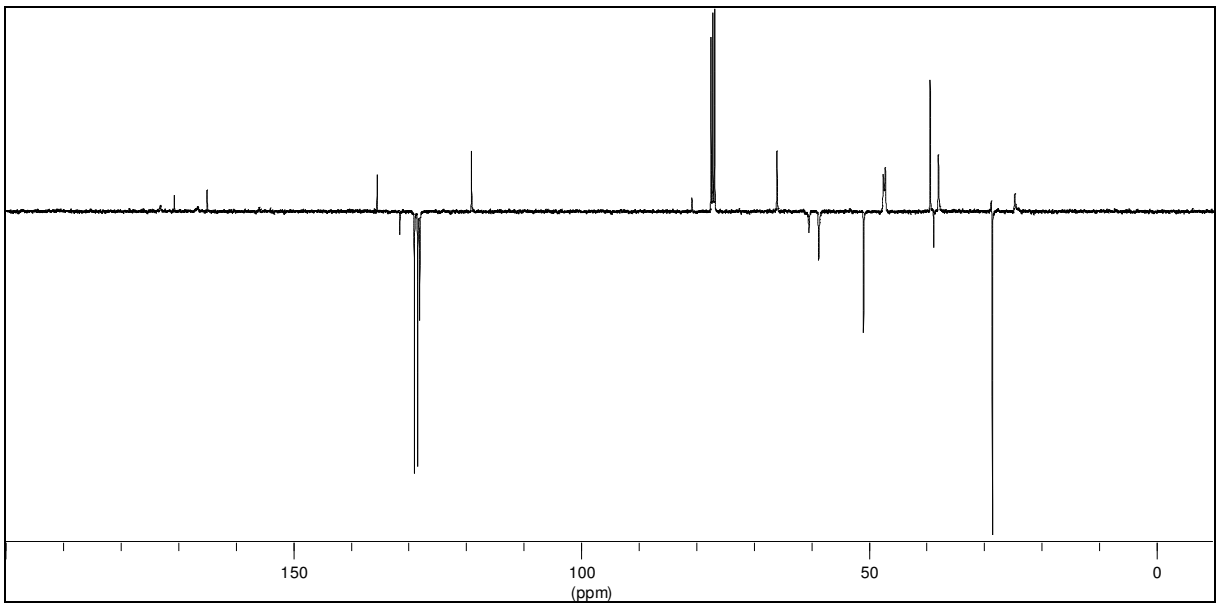


(*S*)-*tert*-butyl-2-(((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (158a)

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

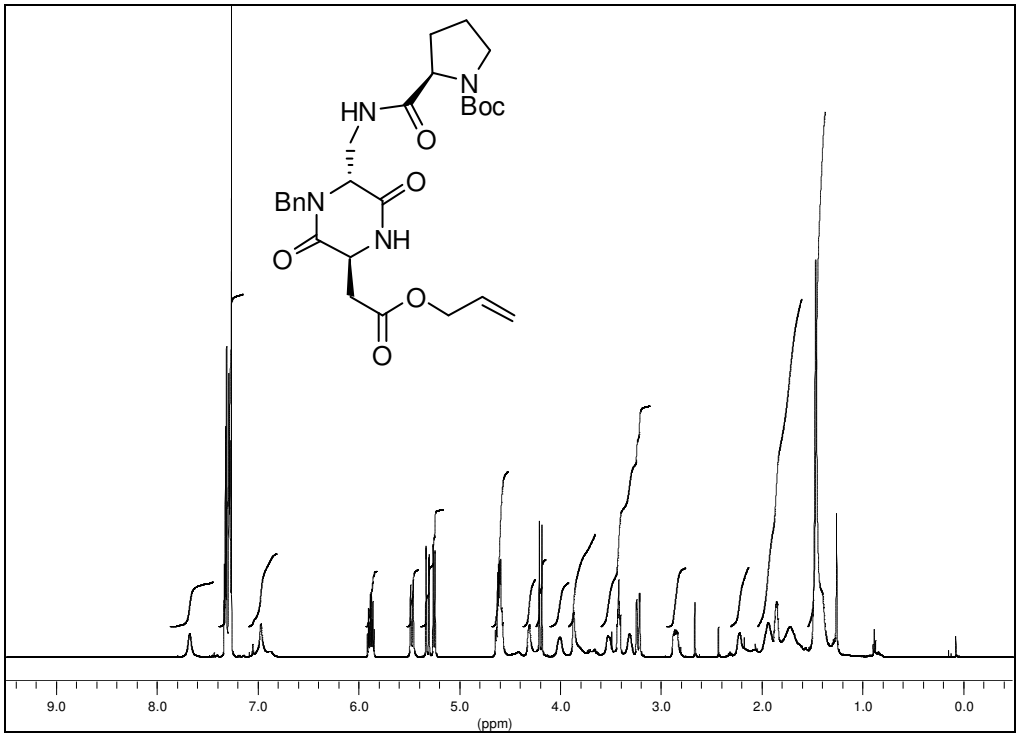


^{13}C NMR (APT, 101 MHz, $CDCl_3$)

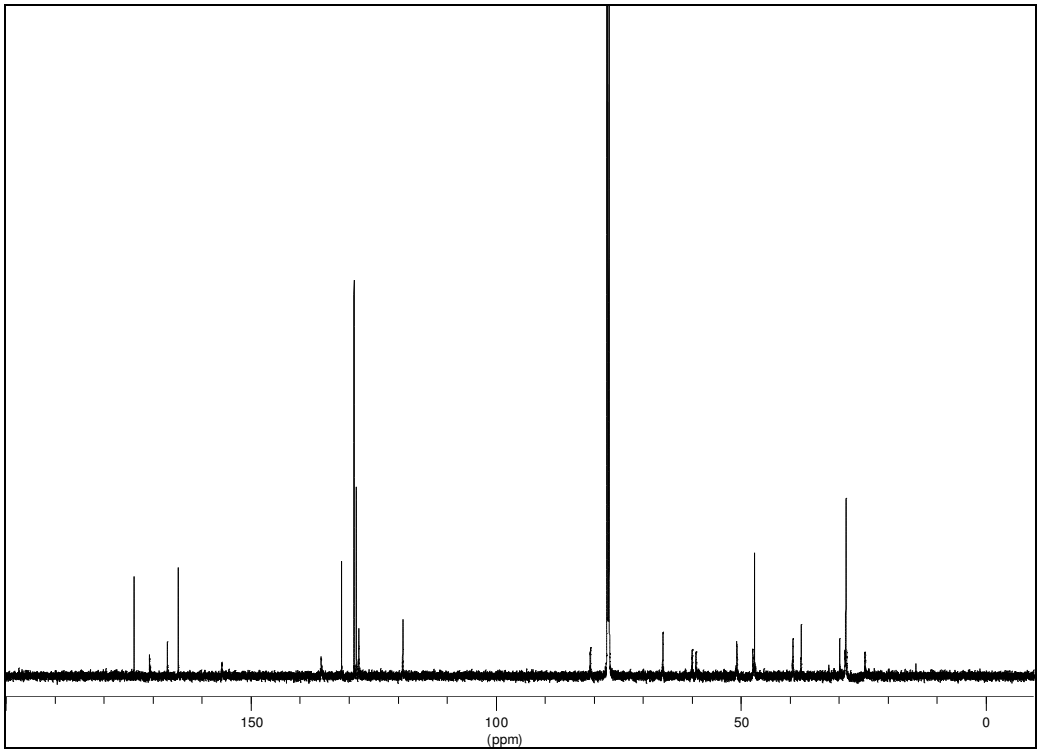


(*R*)-tert-butyl 2-(((2*R*,5*S*)-5-(2-(allyloxy)-2-oxoethyl)-1-benzyl-3,6-dioxopiperazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (158b)

^{1}H-NMR (600 MHz, $CDCl_3$)

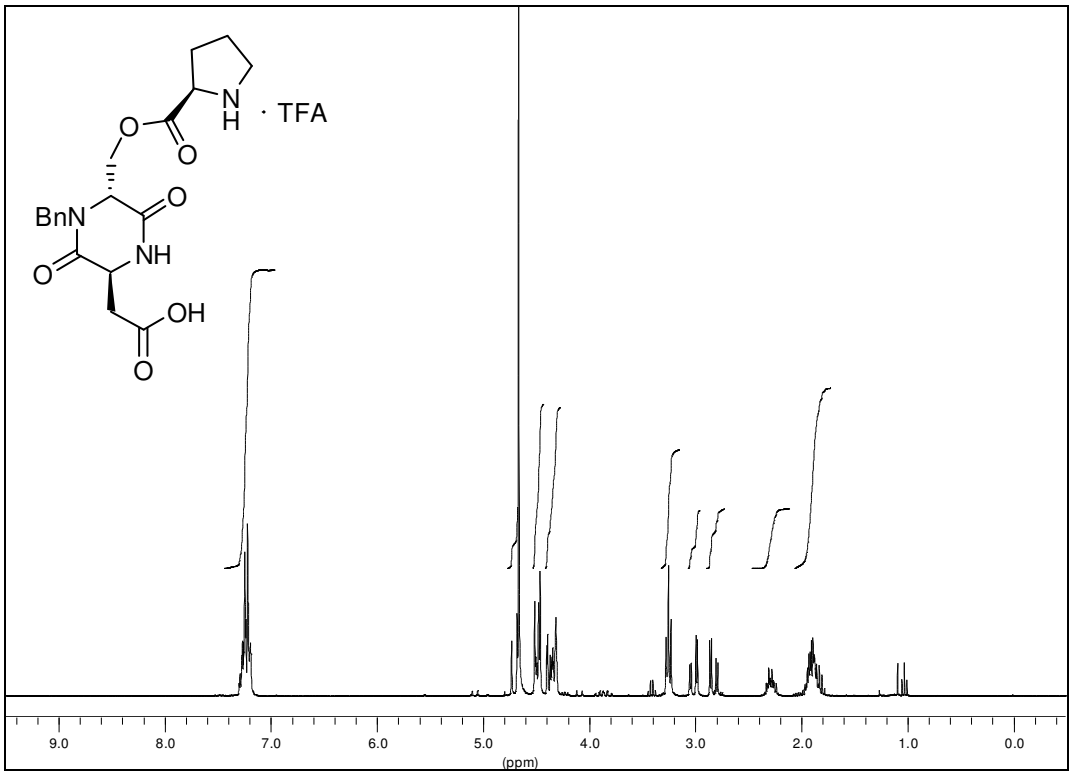


^{13}C NMR (151 MHz, $CDCl_3$)

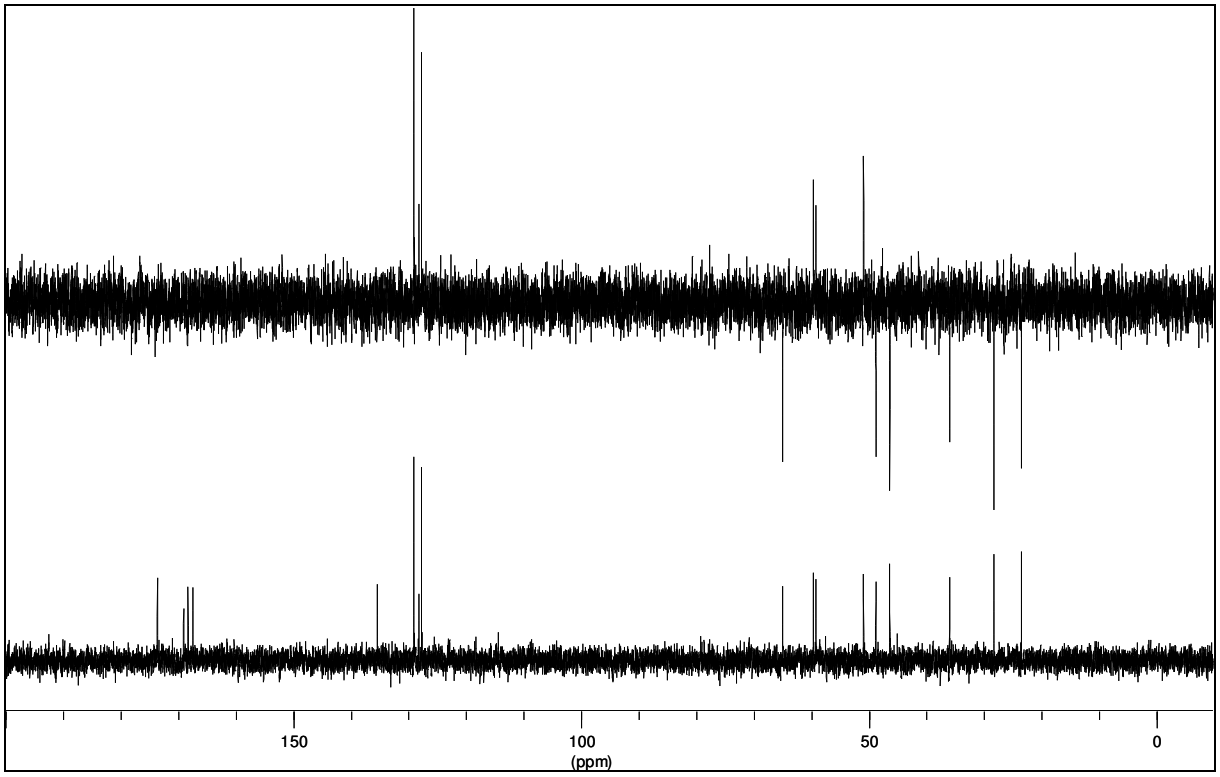


2-((2S,5R)-4-benzyl-3,6-dioxo-5-(((R)-pyrrolidine-2-carbonyloxy)methyl)piperazin-2-yl)acetic acid (160)

^{1}H-NMR (300 MHz, D_2O)

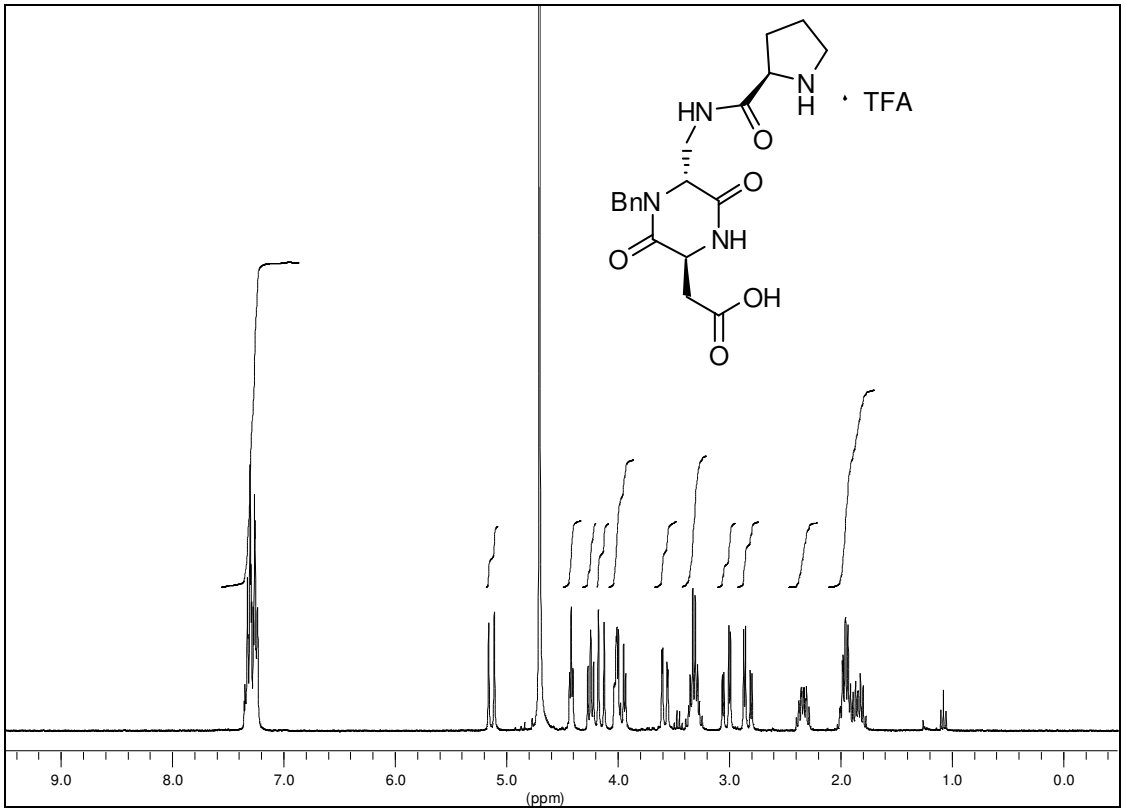


^{13}C NMR (75.5 MHz, D_2O)

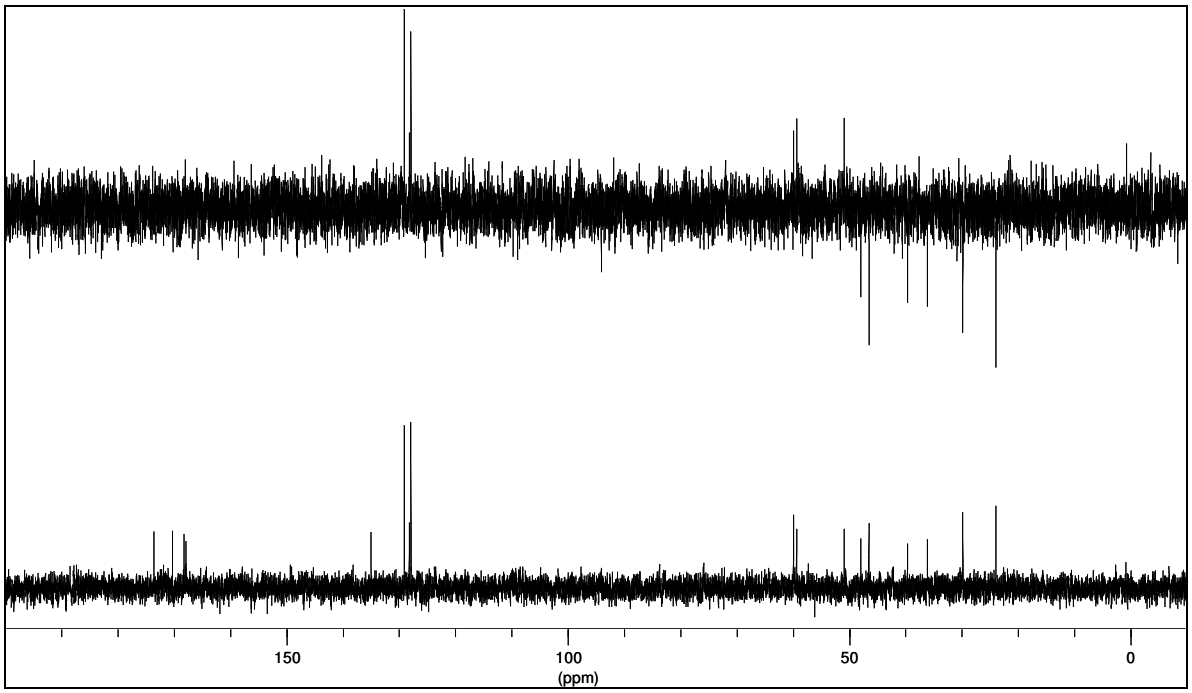


2-((2S,5R)-4-benzyl-3,6-dioxo-5-(((R)-pyrrolidine-2-carboxamido)methyl)piperazin-2-yl)acetic acid (161)

^{1}H-NMR (300 MHz, D_2O)

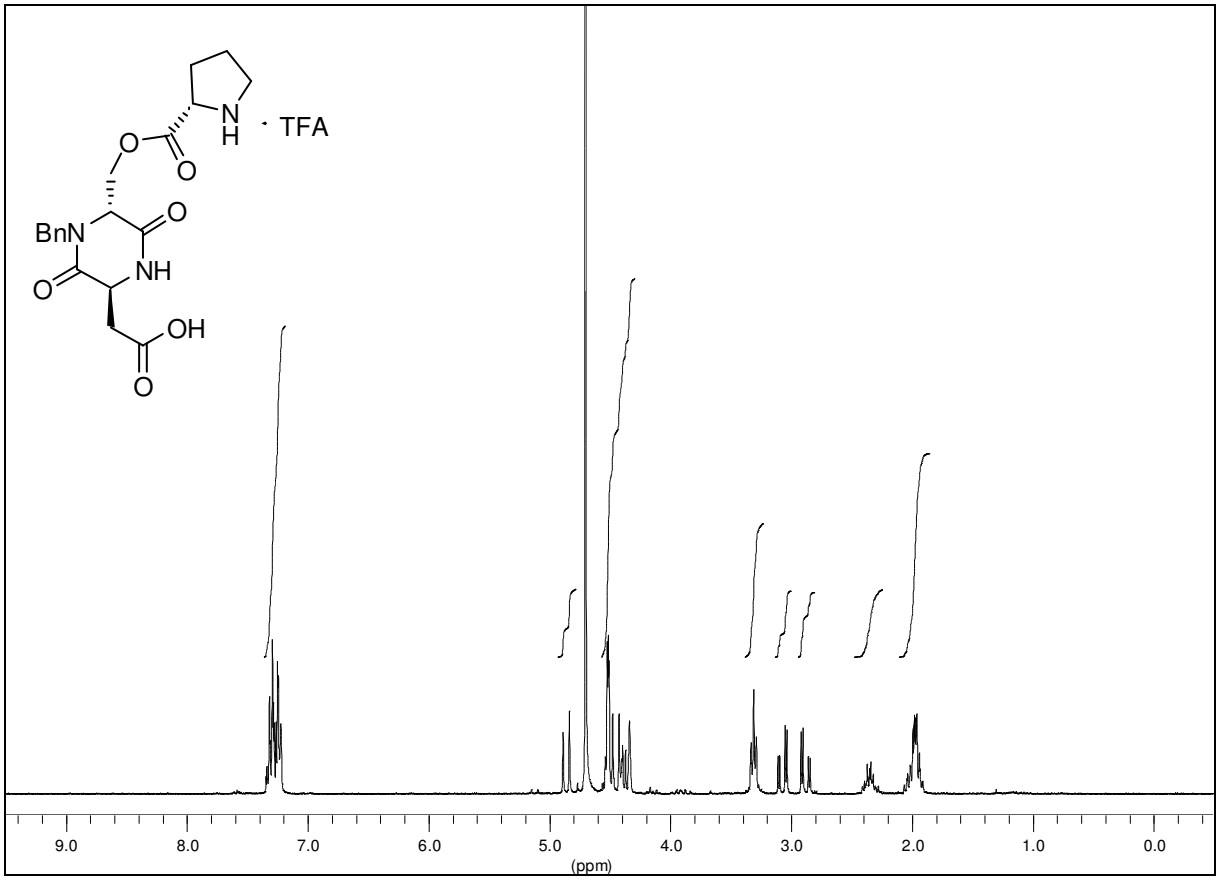


^{13}C NMR (101 MHz, D_2O)

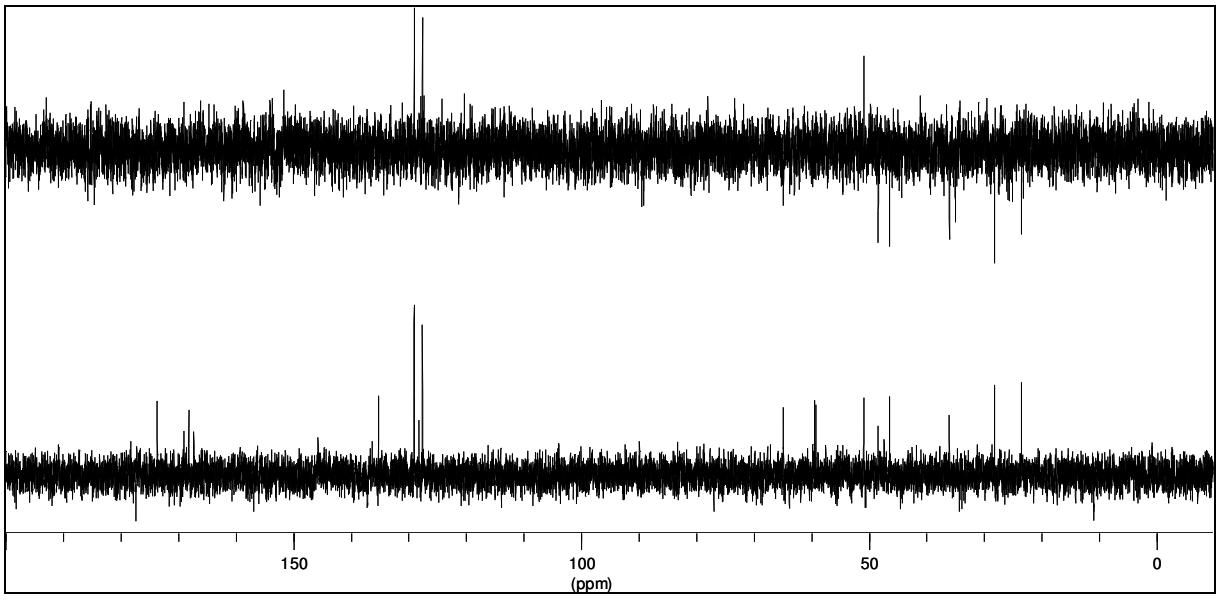


2-((2S,5R)-4-benzyl-3,6-dioxo-5-(((S)-pyrrolidine-2-carbonyloxy)methyl)piperazin-2-yl)acetic acid (162)

^{1}H-NMR (300 MHz, D_2O)

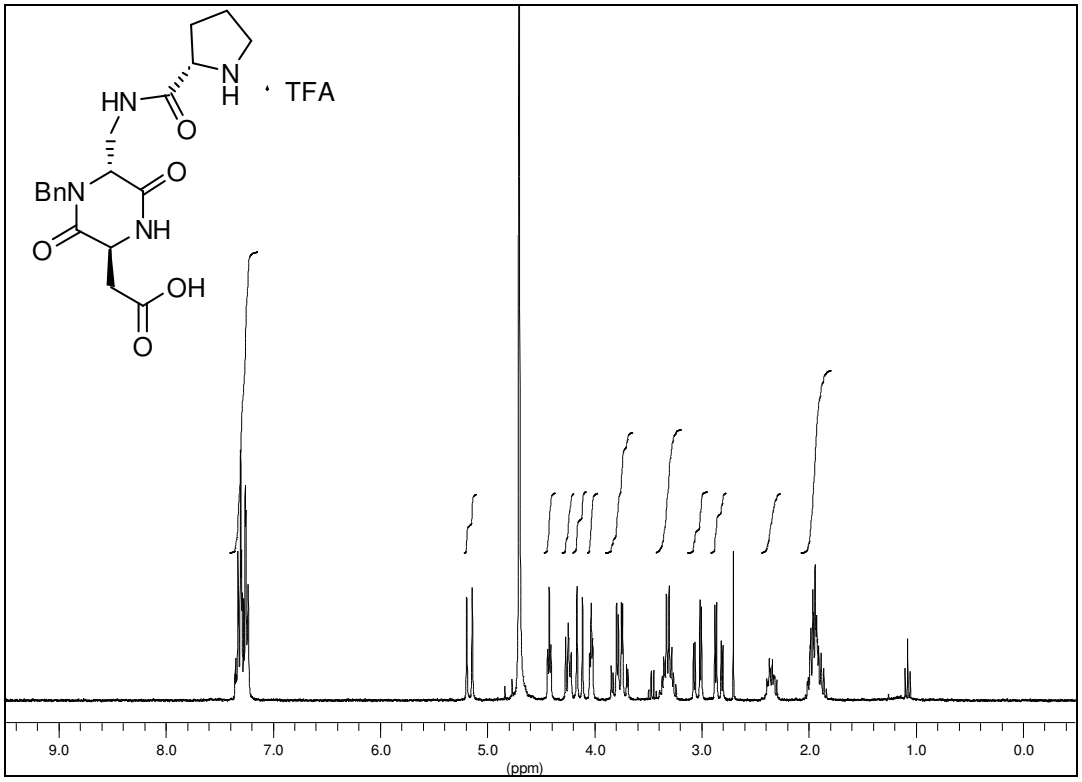


^{13}C NMR (75.5 MHz, D_2O)

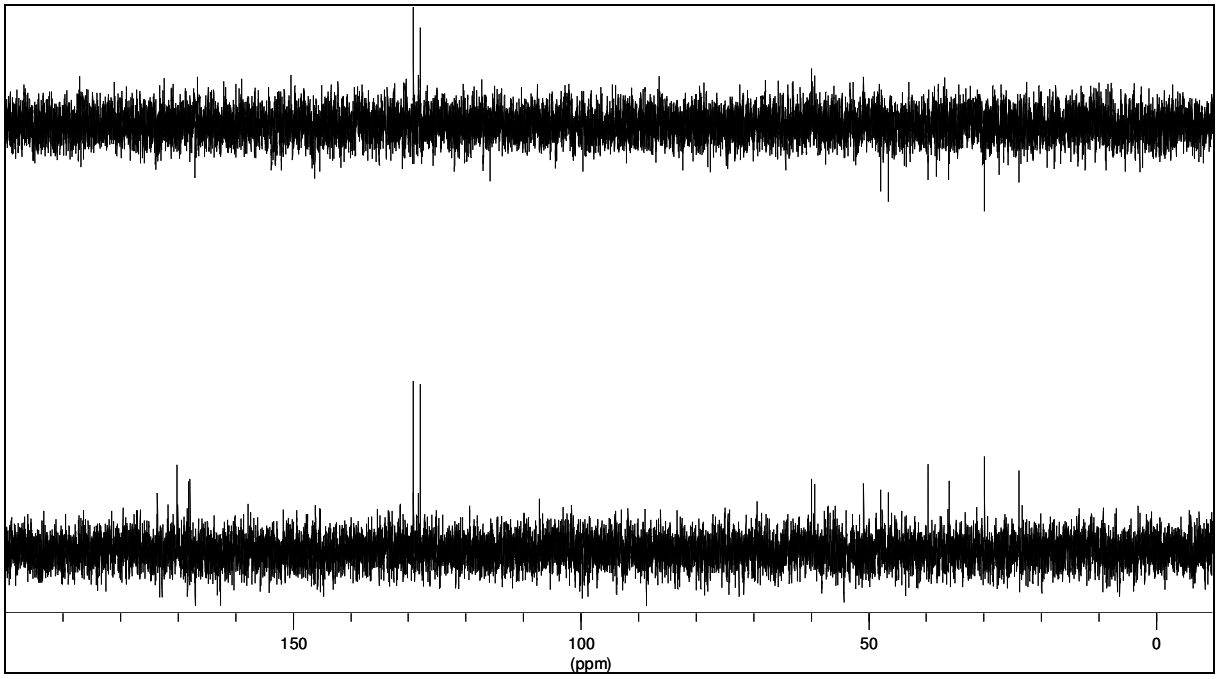


2-((2S,5R)-4-benzyl-5-(((S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)methyl)-3,6-dioxopiperazin-2-yl)acetic acid (163)

^{1}H-NMR (300 MHz, D_2O)

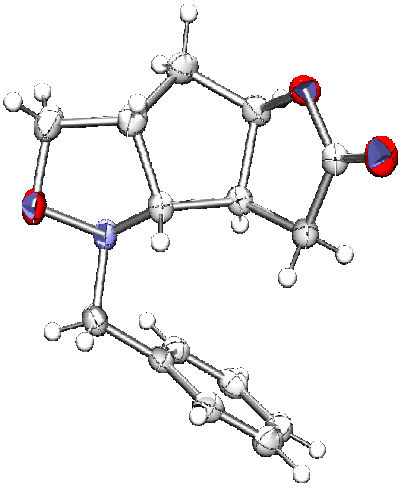


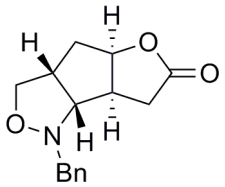
^{13}C NMR (75.5 MHz, D_2O)



E. 2. X-ray crystallographic data

(3a*R*,4a*R*,7a*S*,7b*R*)-1-benzyloctahydro-6*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]isoxazol-6-one (66a)





66a

Crystal data and structure refinement for **66a**.

Empirical formula	$C_{15}H_{17}NO_3$
Formula weight	259.30
Crystal size	0.36 x 0.28 x 0.06 mm
Crystal description	platelike
Crystal colour	colourless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.7077(7) Å alpha = 90 deg. b = 9.8447(10) Å beta = 90 deg. c = 13.7934(10) Å gamma = 90 deg.
Volume	1318.23(19) $Å^3$
Z, Calculated density	4, 1.306 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	552
Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	123(1) K
Wavelength	0.71073 A
Monochromator	graphite
Theta range for data collection	2.54 to 26.84 deg.
Index ranges	-12<=h<=12, -12<=k<=12, -17<=l<=17
Reflections collected / unique	19567 / 2822 [R(int) = 0.0577]
Reflections greater I>2\s(I)	2581

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2822 / 0 / 172
Goodness-of-fit on F^2	1.092
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0775
R indices (all data)	R1 = 0.0335, wR2 = 0.0792
Absolute structure parameter	-0.2(8)
Largest diff. peak and hole	0.196 and -0.141 e. $Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **66a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	1476(1)	7241(1)	9334(1)	30(1)
O(2)	3302(1)	5862(1)	9414(1)	36(1)
O(3)	1535(1)	10624(1)	6415(1)	35(1)
N(1)	2227(1)	10829(1)	7357(1)	26(1)
C(1)	2847(1)	6996(1)	9315(1)	25(1)
C(2)	3632(1)	8311(1)	9162(1)	24(1)
C(3)	2536(1)	9323(1)	8828(1)	23(1)
C(4)	2358(1)	9400(1)	7709(1)	24(1)
C(5)	921(1)	8806(1)	7463(1)	30(1)
C(6)	107(1)	8872(1)	8415(1)	33(1)
C(7)	1174(1)	8695(1)	9210(1)	26(1)
C(8)	394(2)	9752(2)	6651(1)	42(1)
C(9)	3556(1)	11436(1)	7066(1)	30(1)
C(10)	4457(1)	11729(1)	7935(1)	24(1)
C(11)	4120(1)	12770(1)	8585(1)	26(1)
C(12)	4942(1)	13025(1)	9390(1)	31(1)
C(13)	6120(1)	12241(1)	9559(1)	33(1)
C(14)	6468(1)	11207(1)	8918(1)	35(1)
C(15)	5644(1)	10954(1)	8106(1)	30(1)
O(1)	1476(1)	7241(1)	9334(1)	30(1)
O(2)	3302(1)	5862(1)	9414(1)	36(1)
O(3)	1535(1)	10624(1)	6415(1)	35(1)
N(1)	2227(1)	10829(1)	7357(1)	26(1)
C(1)	2847(1)	6996(1)	9315(1)	25(1)
C(2)	3632(1)	8311(1)	9162(1)	24(1)
C(3)	2536(1)	9323(1)	8828(1)	23(1)
C(4)	2358(1)	9400(1)	7709(1)	24(1)
C(5)	921(1)	8806(1)	7463(1)	30(1)
C(6)	107(1)	8872(1)	8415(1)	33(1)

Bond lengths [Å] and angles [deg] for **66a**.

O(1)-C(1)	1.3534(15)	N(1)-C(4)-C(5)	101.97(9)
O(1)-C(7)	1.4710(14)	C(3)-C(4)-C(5)	107.41(9)
O(2)-C(1)	1.2082(14)	C(4)-C(5)-C(6)	105.04(10)
O(3)-N(1)	1.4770(14)	C(4)-C(5)-C(8)	103.28(10)
O(3)-C(8)	1.4388(19)	C(6)-C(5)-C(8)	115.11(11)
N(1)-C(4)	1.4937(15)	C(5)-C(6)-C(7)	105.19(10)
N(1)-C(9)	1.4771(17)	O(1)-C(7)-C(3)	104.92(9)
C(1)-C(2)	1.5165(16)	O(1)-C(7)-C(6)	109.38(10)
C(2)-C(3)	1.5293(16)	C(3)-C(7)-C(6)	106.85(10)
C(3)-C(4)	1.5537(16)	O(3)-C(8)-C(5)	105.62(12)
C(3)-C(7)	1.5519(16)	N(1)-C(9)-C(10)	111.48(10)
C(4)-C(5)	1.5506(18)	C(9)-C(10)-C(11)	120.81(11)
C(5)-C(6)	1.534(2)	C(9)-C(10)-C(15)	120.39(11)
C(5)-C(8)	1.543(2)	C(11)-C(10)-C(15)	118.80(11)
C(6)-C(7)	1.5182(19)	C(10)-C(11)-C(12)	120.62(11)
C(9)-C(10)	1.5114(18)	C(11)-C(12)-C(13)	120.19(12)
C(10)-C(11)	1.4013(17)	C(12)-C(13)-C(14)	119.78(13)
C(10)-C(15)	1.4027(17)	C(13)-C(14)-C(15)	120.06(12)
C(11)-C(12)	1.3905(19)	C(10)-C(15)-C(14)	120.54(12)
C(12)-C(13)	1.3987(19)	C(1)-C(2)-H(2A)	110.85
C(13)-C(14)	1.390(2)	C(1)-C(2)-H(2B)	110.89
C(14)-C(15)	1.398(2)	C(3)-C(2)-H(2A)	110.90
C(2)-H(2A)	0.9893	C(3)-C(2)-H(2B)	110.88
C(2)-H(2B)	0.9897	H(2A)-C(2)-H(2B)	108.89
C(3)-H(3)	10.005	C(2)-C(3)-H(3)	111.24
C(4)-H(4)	10.003	C(4)-C(3)-H(3)	111.25
C(5)-H(5)	0.9994	C(7)-C(3)-H(3)	111.24
C(6)-H(6A)	0.9901	N(1)-C(4)-H(4)	111.59
C(6)-H(6B)	0.9901	C(3)-C(4)-H(4)	111.59
C(7)-H(7)	0.9995	C(5)-C(4)-H(4)	111.60
C(8)-H(8A)	0.9898	C(4)-C(5)-H(5)	110.99
C(8)-H(8B)	0.9894	C(6)-C(5)-H(5)	110.97
C(9)-H(9A)	0.9900	C(8)-C(5)-H(5)	111.01
C(9)-H(9B)	0.9902	C(5)-C(6)-H(6A)	110.70
C(11)-H(11)	0.9504	C(5)-C(6)-H(6B)	110.67
C(12)-H(12)	0.9501	C(7)-C(6)-H(6A)	110.72
C(13)-H(13)	0.9502	C(7)-C(6)-H(6B)	110.74
C(14)-H(14)	0.9506	H(6A)-C(6)-H(6B)	108.81
C(15)-H(15)	0.9493	O(1)-C(7)-H(7)	111.78
C(1)-O(1)-C(7)	111.54(9)	C(3)-C(7)-H(7)	111.78
N(1)-O(3)-C(8)	103.43(10)	C(6)-C(7)-H(7)	111.80
O(3)-N(1)-C(4)	101.31(8)	O(3)-C(8)-H(8A)	110.64
O(3)-N(1)-C(9)	102.29(9)	O(3)-C(8)-H(8B)	110.60
C(4)-N(1)-C(9)	113.29(10)	C(5)-C(8)-H(8A)	110.62
O(1)-C(1)-O(2)	121.45(10)	C(5)-C(8)-H(8B)	110.64
O(1)-C(1)-C(2)	110.16(9)	H(8A)-C(8)-H(8B)	108.71
O(2)-C(1)-C(2)	128.39(11)	N(1)-C(9)-H(9A)	109.31
C(1)-C(2)-C(3)	104.40(9)	N(1)-C(9)-H(9B)	109.31
C(2)-C(3)-C(4)	114.13(9)	C(10)-C(9)-H(9A)	109.37
C(2)-C(3)-C(7)	103.33(9)	C(10)-C(9)-H(9B)	109.32
C(4)-C(3)-C(7)	105.21(9)	H(9A)-C(9)-H(9B)	107.97
N(1)-C(4)-C(3)	112.24(9)	C(10)-C(11)-H(11)	119.66

C(12)-C(11)-H(11)	119.72
C(11)-C(12)-H(12)	119.92
C(13)-C(12)-H(12)	119.89
C(12)-C(13)-H(13)	120.10
C(14)-C(13)-H(13)	120.12
C(13)-C(14)-H(14)	119.99
C(15)-C(14)-H(14)	119.95
C(10)-C(15)-H(15)	119.74
C(14)-C(15)-H(15)	119.72
O(1)-C(1)	1.3534(15)
O(1)-C(7)	1.4710(14)
O(2)-C(1)	1.2082(14)
O(3)-N(1)	1.4770(14)
O(3)-C(8)	1.4388(19)
N(1)-C(4)	1.4937(15)
N(1)-C(9)	1.4771(17)
C(1)-C(2)	1.5165(16)
C(2)-C(3)	1.5293(16)
C(3)-C(4)	1.5537(16)
C(3)-C(7)	1.5519(16)
C(4)-C(5)	1.5506(18)
C(5)-C(6)	1.534(2)
C(5)-C(8)	1.543(2)
C(6)-C(7)	1.5182(19)
C(9)-C(10)	1.5114(18)
C(10)-C(11)	1.4013(17)
C(10)-C(15)	1.4027(17)
C(11)-C(12)	1.3905(19)
C(12)-C(13)	1.3987(19)
C(13)-C(14)	1.390(2)
C(14)-C(15)	1.398(2)
C(2)-H(2A)	0.9893
C(2)-H(2B)	0.9897
C(3)-H(3)	1.0005
C(4)-H(4)	1.0003
C(5)-H(5)	0.9994
C(6)-H(6A)	0.9901
C(6)-H(6B)	0.9901
C(7)-H(7)	0.9995
C(8)-H(8A)	0.9898
C(8)-H(8B)	0.9894
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9902
C(11)-H(11)	0.9504
C(12)-H(12)	0.9501
C(13)-H(13)	0.9502
C(14)-H(14)	0.9506
C(15)-H(15)	0.9493
C(1)-O(1)-C(7)	111.54(9)
N(1)-O(3)-C(8)	103.43(10)
O(3)-N(1)-C(4)	101.31(8)
O(3)-N(1)-C(9)	102.29(9)
C(4)-N(1)-C(9)	113.29(10)
O(1)-C(1)-O(2)	121.45(10)
O(1)-C(1)-C(2)	110.16(9)
O(2)-C(1)-C(2)	128.39(11)
C(1)-C(2)-C(3)	104.40(9)
C(2)-C(3)-C(4)	114.13(9)
C(2)-C(3)-C(7)	103.33(9)
C(4)-C(3)-C(7)	105.21(9)
N(1)-C(4)-C(3)	112.24(9)

Anisotropic displacement parameters (A^2 x 10^3) for **66a**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U12].

	U11	U22	U33	U23	U13	U12
O(1)	26(1)	25(1)	38(1)	7(1)	1(1)	-1(1)
O(2)	41(1)	24(1)	44(1)	5(1)	-4(1)	6(1)
O(3)	43(1)	36(1)	25(1)	7(1)	-12(1)	-8(1)
N(1)	30(1)	25(1)	22(1)	4(1)	-6(1)	-3(1)
C(1)	27(1)	25(1)	22(1)	2(1)	-1(1)	1(1)
C(2)	25(1)	24(1)	23(1)	1(1)	-1(1)	0(1)
C(3)	26(1)	21(1)	21(1)	-3(1)	1(1)	1(1)
C(4)	28(1)	21(1)	22(1)	-1(1)	-1(1)	2(1)
C(5)	34(1)	23(1)	32(1)	1(1)	-7(1)	-3(1)
C(6)	25(1)	31(1)	42(1)	5(1)	-1(1)	4(1)
C(7)	26(1)	24(1)	29(1)	2(1)	6(1)	5(1)
C(8)	46(1)	39(1)	40(1)	10(1)	-21(1)	-14(1)
C(9)	33(1)	33(1)	24(1)	6(1)	-1(1)	-5(1)
C(10)	26(1)	23(1)	24(1)	5(1)	2(1)	-4(1)
C(11)	26(1)	21(1)	32(1)	5(1)	3(1)	-2(1)
C(12)	38(1)	24(1)	32(1)	-1(1)	4(1)	-6(1)
C(13)	33(1)	35(1)	31(1)	6(1)	-7(1)	-8(1)
C(14)	27(1)	33(1)	45(1)	9(1)	-2(1)	2(1)
C(15)	30(1)	25(1)	35(1)	1(1)	5(1)	2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **66a**.

	x	y	z	U(eq)
H(2A)	4354	8197	8663	29
H(2B)	4068	8617	9773	29
H(3)	2698	10244	9112	27
H(4)	3111	8903	7364	28
H(5)	1000	7849	7227	36
H(6A)	-367	9758	8479	39
H(6B)	-589	8138	8442	39
H(7)	873	9125	9831	32
H(8A)	107	9218	6078	50
H(8B)	-401	10293	6880	50
H(9A)	3382	12291	6708	36
H(9B)	4043	10805	6624	36
H(11)	3322	13308	8474	32
H(12)	4703	13733	9827	37
H(13)	6680	12416	10110	40
H(14)	7266	10671	9032	42
H(15)	5891	10251	7668	35
H(2A)	4354	8197	8663	29
H(2B)	4068	8617	9773	29
H(3)	2698	10244	9112	27
H(4)	3111	8903	7364	28
H(5)	1000	7849	7227	36
H(6A)	-367	9758	8479	39

H(6B)	-589	8138	8442	39
H(7)	873	9125	9831	32
H(8A)	107	9218	6078	50
H(8B)	-401	10293	6880	50

Torsion angles [deg] for **66a**.

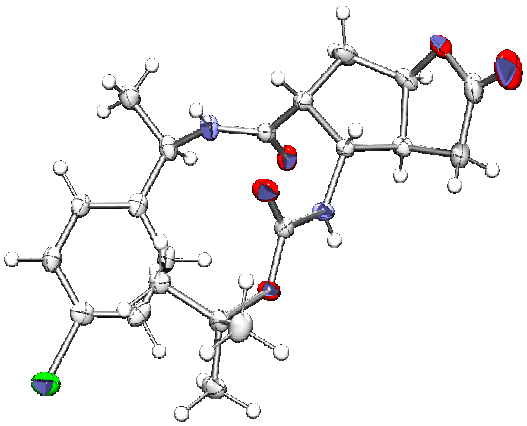
C(1)-O(1)-C(7)-C(6)	129.33(11)
C(1)-O(1)-C(7)-C(3)	15.02(12)
C(7)-O(1)-C(1)-O(2)	179.31(11)
C(7)-O(1)-C(1)-C(2)	-0.51(13)
N(1)-O(3)-C(8)-C(5)	-34.84(13)
C(8)-O(3)-N(1)-C(9)	166.94(10)
C(8)-O(3)-N(1)-C(4)	49.80(11)
C(4)-N(1)-C(9)-C(10)	-71.41(12)
O(3)-N(1)-C(4)-C(5)	-43.59(10)
O(3)-N(1)-C(9)-C(10)	-179.60(10)
C(9)-N(1)-C(4)-C(5)	-152.40(10)
O(3)-N(1)-C(4)-C(3)	-158.24(9)
C(9)-N(1)-C(4)-C(3)	92.95(11)
O(2)-C(1)-C(2)-C(3)	165.80(12)
O(1)-C(1)-C(2)-C(3)	-14.40(12)
C(1)-C(2)-C(3)-C(7)	22.23(11)
C(1)-C(2)-C(3)-C(4)	-91.45(11)
C(2)-C(3)-C(4)-C(5)	111.86(11)
C(2)-C(3)-C(7)-O(1)	-22.75(11)
C(7)-C(3)-C(4)-C(5)	-0.69(11)
C(2)-C(3)-C(4)-N(1)	-136.85(10)
C(4)-C(3)-C(7)-C(6)	-18.83(12)
C(7)-C(3)-C(4)-N(1)	110.59(10)
C(4)-C(3)-C(7)-O(1)	97.23(10)
C(2)-C(3)-C(7)-C(6)	-138.82(10)
N(1)-C(4)-C(5)-C(6)	-98.58(10)
C(3)-C(4)-C(5)-C(6)	19.58(12)
C(3)-C(4)-C(5)-C(8)	140.57(10)
N(1)-C(4)-C(5)-C(8)	22.41(12)
C(4)-C(5)-C(8)-O(3)	7.26(13)
C(8)-C(5)-C(6)-C(7)	-144.12(11)
C(4)-C(5)-C(6)-C(7)	-31.25(12)
C(6)-C(5)-C(8)-O(3)	121.16(12)
C(5)-C(6)-C(7)-C(3)	31.36(12)
C(5)-C(6)-C(7)-O(1)	-81.69(12)
N(1)-C(9)-C(10)-C(11)	-70.30(15)
N(1)-C(9)-C(10)-C(15)	109.38(13)
C(11)-C(10)-C(15)-C(14)	0.73(18)
C(9)-C(10)-C(11)-C(12)	179.18(12)
C(15)-C(10)-C(11)-C(12)	-0.49(18)
C(9)-C(10)-C(15)-C(14)	-178.94(12)
C(10)-C(11)-C(12)-C(13)	0.09(19)
C(11)-C(12)-C(13)-C(14)	0.07(19)
C(12)-C(13)-C(14)-C(15)	0.2(2)
C(13)-C(14)-C(15)-C(10)	-0.6(2)
C(1)-O(1)-C(7)-C(6)	129.33(11)

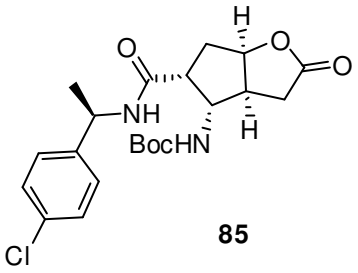
C(1)-O(1)-C(7)-C(3)	15.02(12)
C(7)-O(1)-C(1)-O(2)	179.31(11)
C(7)-O(1)-C(1)-C(2)	-0.51(13)
N(1)-O(3)-C(8)-C(5)	-34.84(13)
C(8)-O(3)-N(1)-C(9)	166.94(10)
C(8)-O(3)-N(1)-C(4)	49.80(11)
C(4)-N(1)-C(9)-C(10)	-71.41(12)
O(3)-N(1)-C(4)-C(5)	-43.59(10)
O(3)-N(1)-C(9)-C(10)	-179.60(10)

Hydrogen-bonds for **66a** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2B)...O(3)#1	0.9900	24.600	3.2831(16)	141.00
C(12)-H(12)...O(2)#2	0.9500	25.600	3.2151(16)	126.00

tert-butyl (3a*S*,4*S*,5*R*,6a*R*)-5-((*R*)-1-(4-chlorophenyl)ethylcarbamoyl)-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-ylcarbamate (85)





85

Crystal data and structure refinement for **85**.

Empirical formula	$C_{21}H_{27}ClN_2O_5$
Formula weight	422.90
Crystal size	0.42 x 0.22 x 0.06 mm
Crystal description	flat prism
Crystal colour	colourless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.1731(4) Å alpha = 90 deg. b = 18.9784(15) Å beta = 90 deg. c = 21.737(2) Å gamma = 90 deg.
Volume	2134.1(3) $Å^3$
Z, Calculated density	4, 1.316 Mg/m^3
Absorption coefficient	0.213 mm^{-1}
F(000)	896
Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	123(1) K
Wavelength	0.71073 A
Monochromator	graphite
Theta range for data collection	2.15 to 26.88 deg.
Index ranges	-6<=h<=6, -24<=k<=24, -27<=l<=27
Reflections collected / unique	31067 / 4589 [R(int) = 0.0545]
Reflections greater I>2\s(I)	3794
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4589 / 0 / 266

Goodness-of-fit on F^2	0.931
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0667
R indices (all data)	R1 = 0.0447, wR2 = 0.0689
Absolute structure parameter	0.02(5)
Largest diff. peak and hole	0.251 and -0.153 e. $Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **85**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cl(1)	1415(1)	4150(1)	-378(1)	36(1)
O(11)	-3293(2)	2603(1)	2682(1)	26(1)
O(15)	-1216(3)	3174(1)	4844(1)	32(1)
O(17)	-594(3)	4177(1)	5362(1)	54(1)
O(23)	3408(2)	4325(1)	2873(1)	28(1)
O(24)	377(2)	4819(1)	2241(1)	22(1)
N(9)	814(3)	2436(1)	2340(1)	24(1)
N(21)	-880(3)	4122(1)	2999(1)	20(1)
C(1)	1064(4)	3565(1)	241(1)	25(1)
C(2)	2895(3)	3043(1)	324(1)	24(1)
C(3)	2604(3)	2576(1)	812(1)	23(1)
C(4)	530(3)	2627(1)	1216(1)	22(1)
C(5)	-1267(4)	3167(1)	1122(1)	26(1)
C(6)	-1029(4)	3637(1)	635(1)	26(1)
C(7)	120(4)	2111(1)	1747(1)	24(1)
C(8)	1571(4)	1414(1)	1675(1)	30(1)
C(10)	-941(3)	2632(1)	2762(1)	20(1)
C(12)	226(4)	2879(1)	3370(1)	21(1)
C(13)	-878(4)	2447(1)	3917(1)	32(1)
C(14)	-2587(4)	2937(1)	4291(1)	25(1)
C(16)	-1522(4)	3880(1)	4927(1)	32(1)
C(18)	-3135(4)	4182(1)	4410(1)	27(1)
C(19)	-2986(3)	3610(1)	3917(1)	20(1)
C(20)	-534(3)	3655(1)	3523(1)	17(1)
C(22)	1184(3)	4414(1)	2713(1)	20(1)
C(25)	2282(3)	5140(1)	1811(1)	21(1)
C(26)	541(4)	5469(1)	1326(1)	29(1)
C(27)	3989(3)	4574(1)	1528(1)	22(1)
C(28)	3843(4)	5704(1)	2146(1)	28(1)

Bond lengths [Å] and angles [deg] for **85**.

Cl(1)-C(1)	1.7538(17)	C(27)-H(27A)	0.9800
O(11)-C(10)	1.2304(19)	C(27)-H(27B)	0.9800
O(15)-C(14)	1.467(2)	C(27)-H(27C)	0.9800
O(15)-C(16)	1.360(2)	C(28)-H(28A)	0.9800
O(17)-C(16)	1.201(2)	C(28)-H(28B)	0.9800
O(23)-C(22)	1.2136(19)	C(28)-H(28C)	0.9800
O(24)-C(22)	1.3468(19)	C(14)-O(15)-C(16)	110.74(14)
O(24)-C(25)	1.4890(19)	C(22)-O(24)-C(25)	120.41(12)
N(9)-C(7)	1.472(2)	C(7)-N(9)-C(10)	123.31(15)
N(9)-C(10)	1.344(2)	C(20)-N(21)-C(22)	120.82(14)
N(21)-C(20)	1.454(2)	C(7)-N(9)-H(9)	118.00
N(21)-C(22)	1.355(2)	C(10)-N(9)-H(9)	118.00
N(9)-H(9)	0.8800	C(22)-N(21)-H(21)	120.00
N(21)-H(21)	0.8800	C(20)-N(21)-H(21)	120.00
C(1)-C(2)	1.383(2)	Cl(1)-C(1)-C(6)	119.50(14)
C(1)-C(6)	1.386(3)	C(2)-C(1)-C(6)	121.65(16)
C(2)-C(3)	1.389(2)	Cl(1)-C(1)-C(2)	118.85(14)
C(3)-C(4)	1.391(2)	C(1)-C(2)-C(3)	118.81(15)
C(4)-C(7)	1.528(2)	C(2)-C(3)-C(4)	121.47(15)
C(4)-C(5)	1.398(3)	C(3)-C(4)-C(5)	118.12(16)
C(5)-C(6)	1.391(3)	C(3)-C(4)-C(7)	122.72(16)
C(7)-C(8)	1.529(3)	C(5)-C(4)-C(7)	119.16(15)
C(10)-C(12)	1.526(2)	C(4)-C(5)-C(6)	121.47(17)
C(12)-C(13)	1.553(2)	C(1)-C(6)-C(5)	118.48(18)
C(12)-C(20)	1.562(2)	N(9)-C(7)-C(4)	111.07(15)
C(13)-C(14)	1.519(3)	C(4)-C(7)-C(8)	114.11(14)
C(14)-C(19)	1.529(2)	N(9)-C(7)-C(8)	109.37(14)
C(16)-C(18)	1.512(3)	O(11)-C(10)-C(12)	121.85(14)
C(18)-C(19)	1.527(2)	N(9)-C(10)-C(12)	114.16(14)
C(19)-C(20)	1.533(2)	O(11)-C(10)-N(9)	123.97(14)
C(25)-C(28)	1.524(2)	C(10)-C(12)-C(20)	111.96(14)
C(25)-C(26)	1.520(2)	C(13)-C(12)-C(20)	104.01(13)
C(25)-C(27)	1.521(2)	C(10)-C(12)-C(13)	110.86(15)
C(2)-H(2)	0.9500	C(12)-C(13)-C(14)	107.54(14)
C(3)-H(3)	0.9500	O(15)-C(14)-C(13)	110.22(16)
C(5)-H(5)	0.9500	O(15)-C(14)-C(19)	104.18(14)
C(6)-H(6)	0.9500	C(13)-C(14)-C(19)	107.76(13)
C(7)-H(7)	1.0000	O(15)-C(16)-C(18)	109.83(15)
C(8)-H(8A)	0.9800	O(17)-C(16)-C(18)	128.9(2)
C(8)-H(8B)	0.9800	O(15)-C(16)-O(17)	121.30(18)
C(8)-H(8C)	0.9800	C(16)-C(18)-C(19)	102.99(15)
C(12)-H(12)	1.0000	C(18)-C(19)-C(20)	113.23(14)
C(13)-H(13A)	0.9900	C(14)-C(19)-C(18)	103.09(13)
C(13)-H(13B)	0.9900	C(14)-C(19)-C(20)	103.42(14)
C(14)-H(14)	1.0000	N(21)-C(20)-C(19)	111.69(13)
C(18)-H(18A)	0.9900	C(12)-C(20)-C(19)	105.96(14)
C(18)-H(18B)	0.9900	N(21)-C(20)-C(12)	116.03(13)
C(19)-H(19)	1.0000	O(23)-C(22)-O(24)	126.24(14)
C(20)-H(20)	1.0000	O(23)-C(22)-N(21)	123.96(15)
C(26)-H(26A)	0.9800	O(24)-C(22)-N(21)	109.80(13)
C(26)-H(26B)	0.9800	C(26)-C(25)-C(28)	110.91(15)
C(26)-H(26C)	0.9800	C(27)-C(25)-C(28)	112.40(14)

C(26)-C(25)-C(27)	110.63(13)
O(24)-C(25)-C(26)	102.20(13)
O(24)-C(25)-C(27)	110.43(13)
O(24)-C(25)-C(28)	109.83(13)
C(1)-C(2)-H(2)	121.00
C(3)-C(2)-H(2)	121.00
C(2)-C(3)-H(3)	119.00
C(4)-C(3)-H(3)	119.00
C(4)-C(5)-H(5)	119.00
C(6)-C(5)-H(5)	119.00
C(1)-C(6)-H(6)	121.00
C(5)-C(6)-H(6)	121.00
N(9)-C(7)-H(7)	107.00
C(4)-C(7)-H(7)	107.00
C(8)-C(7)-H(7)	107.00
C(7)-C(8)-H(8A)	109.00
C(7)-C(8)-H(8B)	109.00
C(7)-C(8)-H(8C)	109.00
H(8A)-C(8)-H(8B)	109.00
H(8A)-C(8)-H(8C)	110.00
H(8B)-C(8)-H(8C)	109.00
C(10)-C(12)-H(12)	110.00
C(13)-C(12)-H(12)	110.00
C(20)-C(12)-H(12)	110.00
C(12)-C(13)-H(13A)	110.00
C(12)-C(13)-H(13B)	110.00
C(14)-C(13)-H(13A)	110.00
C(14)-C(13)-H(13B)	110.00
H(13A)-C(13)-H(13B)	108.00
O(15)-C(14)-H(14)	111.00
C(13)-C(14)-H(14)	111.00
C(19)-C(14)-H(14)	111.00
C(16)-C(18)-H(18A)	111.00
C(16)-C(18)-H(18B)	111.00
C(19)-C(18)-H(18A)	111.00
C(19)-C(18)-H(18B)	111.00
H(18A)-C(18)-H(18B)	109.00
C(14)-C(19)-H(19)	112.00
C(18)-C(19)-H(19)	112.00
C(20)-C(19)-H(19)	112.00
N(21)-C(20)-H(20)	108.00
C(12)-C(20)-H(20)	108.00
C(19)-C(20)-H(20)	108.00
C(25)-C(26)-H(26A)	110.00
C(25)-C(26)-H(26B)	109.00
C(25)-C(26)-H(26C)	109.00
H(26A)-C(26)-H(26B)	109.00
H(26A)-C(26)-H(26C)	109.00
H(26B)-C(26)-H(26C)	109.00
C(25)-C(27)-H(27A)	110.00
C(25)-C(27)-H(27B)	110.00
C(25)-C(27)-H(27C)	109.00
H(27A)-C(27)-H(27B)	109.00
H(27A)-C(27)-H(27C)	110.00
H(27B)-C(27)-H(27C)	109.00
C(25)-C(28)-H(28A)	109.00
C(25)-C(28)-H(28B)	109.00
C(25)-C(28)-H(28C)	109.00
H(28A)-C(28)-H(28B)	109.00
H(28A)-C(28)-H(28C)	109.00
H(28B)-C(28)-H(28C)	109.00

Anisotropic displacement parameters (A^2 x 10^3) for **85**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U12].

	U11	U22	U33	U23	U13	U12
Cl(1)	45(1)	28(1)	36(1)	6(1)	-3(1)	1(1)
O(11)	19(1)	33(1)	25(1)	-6(1)	-1(1)	0(1)
O(15)	40(1)	41(1)	16(1)	1(1)	-5(1)	9(1)
O(17)	56(1)	72(1)	33(1)	-25(1)	-11(1)	3(1)
O(23)	17(1)	40(1)	29(1)	12(1)	-2(1)	1(1)
O(24)	16(1)	27(1)	23(1)	9(1)	2(1)	0(1)
N(9)	18(1)	36(1)	19(1)	-6(1)	-1(1)	-2(1)
N(21)	15(1)	24(1)	20(1)	5(1)	-2(1)	2(1)
C(1)	30(1)	22(1)	23(1)	-4(1)	-6(1)	-4(1)
C(2)	22(1)	29(1)	22(1)	-8(1)	1(1)	0(1)
C(3)	20(1)	29(1)	20(1)	-6(1)	-3(1)	3(1)
C(4)	20(1)	27(1)	20(1)	-9(1)	-4(1)	-2(1)
C(5)	18(1)	31(1)	27(1)	-12(1)	2(1)	-1(1)
C(6)	22(1)	23(1)	34(1)	-9(1)	-7(1)	4(1)

C(7)	19(1)	33(1)	19(1)	-5(1)	1(1)	-3(1)
C(8)	35(1)	31(1)	24(1)	-1(1)	4(1)	1(1)
C(10)	22(1)	18(1)	19(1)	1(1)	-2(1)	1(1)
C(12)	23(1)	22(1)	19(1)	0(1)	-3(1)	4(1)
C(13)	55(1)	20(1)	22(1)	4(1)	-2(1)	4(1)
C(14)	30(1)	28(1)	18(1)	5(1)	-2(1)	-6(1)
C(16)	29(1)	47(1)	22(1)	-10(1)	3(1)	4(1)
C(18)	27(1)	30(1)	25(1)	-3(1)	5(1)	4(1)
C(19)	17(1)	24(1)	18(1)	2(1)	-3(1)	-2(1)
C(20)	17(1)	19(1)	17(1)	1(1)	-2(1)	0(1)
C(22)	20(1)	20(1)	19(1)	1(1)	1(1)	1(1)
C(25)	17(1)	22(1)	24(1)	5(1)	4(1)	-1(1)
C(26)	23(1)	32(1)	31(1)	14(1)	6(1)	2(1)
C(27)	21(1)	22(1)	23(1)	1(1)	0(1)	-1(1)
C(28)	25(1)	23(1)	37(1)	-4(1)	6(1)	-2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **85**.

	x	y	z	U(eq)
H(2)	4326	3004	52	29
H(3)	3850	2215	870	27
H(5)	-2682	3214	1398	31
H(6)	-2273	3998	572	32
H(7)	-1768	1999	1763	29
H(8A)	3435	1500	1701	36
H(8B)	1158	1206	1274	36
H(8C)	1048	1090	2003	36
H(9)	2461	2504	2422	29
H(12)	2151	2831	3356	25
H(13A)	-1898	2043	3763	38
H(13B)	549	2263	4175	38
H(14)	-4273	2709	4397	30
H(18A)	-2403	4631	4260	33
H(18B)	-4942	4261	4543	33
H(19)	-4589	3590	3660	24
H(20)	868	3858	3786	21
H(21)	-2450	4215	2866	24
H(26A)	-498	5100	1130	34
H(26B)	1605	5704	1015	34
H(26C)	-605	5814	1521	34
H(27A)	5312	4431	1825	27
H(27B)	4826	4761	1158	27
H(27C)	2928	4166	1417	27
H(28A)	2663	6048	2330	34
H(28B)	4985	5942	1852	34
H(28C)	4883	5483	2469	34

Torsion angles [deg] for **85**.

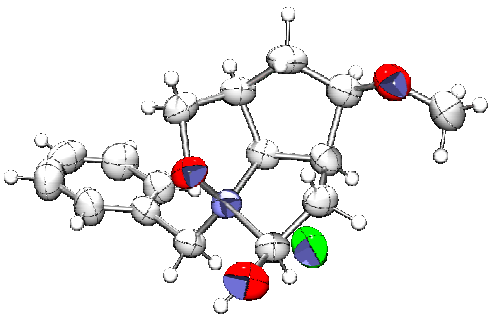
C(16)-O(15)-C(14)-C(19)	19.45(19)
C(16)-O(15)-C(14)-C(13)	134.81(16)
C(14)-O(15)-C(16)-O(17)	178.43(18)
C(14)-O(15)-C(16)-C(18)	-1.1(2)
C(22)-O(24)-C(25)-C(27)	56.14(17)
C(25)-O(24)-C(22)-O(23)	7.4(2)
C(25)-O(24)-C(22)-N(21)	-173.60(13)
C(22)-O(24)-C(25)-C(28)	-68.37(18)
C(22)-O(24)-C(25)-C(26)	173.86(13)
C(7)-N(9)-C(10)-C(12)	173.37(15)
C(10)-N(9)-C(7)-C(8)	-125.69(18)
C(7)-N(9)-C(10)-O(11)	-4.7(3)
C(10)-N(9)-C(7)-C(4)	107.48(18)
C(22)-N(21)-C(20)-C(19)	158.46(14)
C(20)-N(21)-C(22)-O(24)	179.51(13)
C(20)-N(21)-C(22)-O(23)	-1.5(2)
C(22)-N(21)-C(20)-C(12)	-79.97(19)
C(6)-C(1)-C(2)-C(3)	0.5(3)
C(2)-C(1)-C(6)-C(5)	0.0(3)
Cl(1)-C(1)-C(2)-C(3)	-179.49(13)
Cl(1)-C(1)-C(6)-C(5)	-179.98(14)
C(1)-C(2)-C(3)-C(4)	-0.3(3)
C(2)-C(3)-C(4)-C(5)	-0.4(2)
C(2)-C(3)-C(4)-C(7)	178.46(16)
C(3)-C(4)-C(7)-N(9)	104.75(19)
C(3)-C(4)-C(7)-C(8)	-19.4(2)
C(5)-C(4)-C(7)-C(8)	159.40(17)
C(7)-C(4)-C(5)-C(6)	-177.96(17)
C(3)-C(4)-C(5)-C(6)	0.9(3)
C(5)-C(4)-C(7)-N(9)	-76.4(2)
C(4)-C(5)-C(6)-C(1)	-0.7(3)
O(11)-C(10)-C(12)-C(13)	54.0(2)
O(11)-C(10)-C(12)-C(20)	-61.7(2)
N(9)-C(10)-C(12)-C(20)	120.15(16)
N(9)-C(10)-C(12)-C(13)	-124.19(16)
C(13)-C(12)-C(20)-N(21)	-152.00(14)
C(10)-C(12)-C(20)-C(19)	92.34(15)
C(13)-C(12)-C(20)-C(19)	-27.42(17)
C(10)-C(12)-C(20)-N(21)	-32.2(2)
C(10)-C(12)-C(13)-C(14)	-110.61(16)
C(20)-C(12)-C(13)-C(14)	9.89(19)
C(12)-C(13)-C(14)-O(15)	-101.85(16)
C(12)-C(13)-C(14)-C(19)	11.2(2)
O(15)-C(14)-C(19)-C(18)	-29.15(17)
O(15)-C(14)-C(19)-C(20)	89.01(15)
C(13)-C(14)-C(19)-C(18)	-146.23(15)
C(13)-C(14)-C(19)-C(20)	-28.07(18)
O(17)-C(16)-C(18)-C(19)	162.9(2)
O(15)-C(16)-C(18)-C(19)	-17.6(2)
C(16)-C(18)-C(19)-C(20)	-82.98(17)
C(16)-C(18)-C(19)-C(14)	28.07(18)
C(14)-C(19)-C(20)-N(21)	161.46(13)

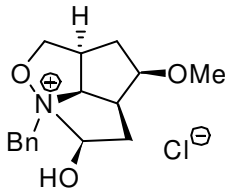
C(18)-C(19)-C(20)-C(12)	145.07(14)
C(14)-C(19)-C(20)-C(12)	34.23(16)
C(18)-C(19)-C(20)-N(21)	-87.70(16)

Hydrogen-bonds for **85** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(9)-H(9)...O(11)#1	0.8800	22.800	3.1540(19)	175.00
N(21)-H(21)...O(23)#2	0.8800	21.500	2.9926(19)	159.00
C(7)-H(7)...O(11)	1.0000	24.300	2.849(2)	104.00
C(14)-H(14)...O(15)#3	1.0000	25.600	3.391(2)	141.00
C(19)-H(19)...O(23)#2	1.0000	24.400	3.236(2)	136.00
C(26)-H(26B)...O(17)#4	0.9800	25.100	3.417(3)	153.00
C(27)-H(27A)...O(23)	0.9800	24.900	2.977(2)	110.00
C(28)-H(28C)...O(23)	0.9800	24.900	3.065(2)	118.00

Tricyclic intermediate during Jones oxidation 142





142

Crystal data and structure refinement for **142**.

Empirical formula	$C_{16}H_{22}NO_3$,Cl
Formula weight	311.80
Crystal size	0.220 x 0.120 x 0.060 mm
Crystal description	prism
Crystal colour	translucent, colourless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.0050(9) Å alpha = 90 deg. b = 10.7653(12) Å beta = 90 deg. c = 16.745(2) Å gamma = 90 deg.
Volume	1623.3(3) $Å^3$
Z, Calculated density	4, 1.276 Mg/m^3
Absorption coefficient	0.245 mm^{-1}
F(000)	664
Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	297(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	2.25 to 25.31 deg.
Index ranges	-10<=h<=10, -12<=k<=12, -20<=l<=20
Reflections collected / unique	12705 / 2926 [R(int) = 0.0891]
Reflections greater I>2\s(I)	1723
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2926 / 0 / 190
Goodness-of-fit on F^2	0.834
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.0866

R indices (all data)	R1 = 0.0839, wR2 = 0.0965
Absolute structure parameter	0.05(10)
Largest diff. peak and hole	0.389 and -0.165 e. $Å^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **142**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-2096(3)	-5255(2)	-7053(2)	72(1)
O(2)	-5798(3)	-2649(2)	-5337(2)	71(1)
O(3)	-4325(2)	-4293(2)	-7907(1)	53(1)
N(1)	-3193(3)	-3437(2)	-7654(1)	42(1)
C(1)	-2719(3)	-2663(3)	-9067(2)	47(1)
C(2)	-2797(4)	-1389(3)	-9172(2)	59(1)
C(3)	-3313(5)	-900(4)	-9873(2)	73(2)
C(4)	-3735(4)	-1644(5)	-10489(3)	82(2)
C(5)	-3649(5)	-2895(5)	-10407(3)	81(2)
C(6)	-3137(4)	-3399(4)	-9695(2)	65(1)
C(7)	-2102(3)	-3207(3)	-8321(2)	48(1)
C(8)	-2372(3)	-4060(3)	-6925(2)	48(1)
C(9)	-3403(4)	-3790(3)	-6253(2)	55(1)
C(10)	-3887(3)	-2451(3)	-6396(2)	51(1)
C(11)	-5465(4)	-2154(3)	-6103(2)	59(1)
C(12)	-6453(3)	-2712(4)	-6733(2)	63(1)
C(13)	-5647(3)	-2501(3)	-7526(2)	53(1)
C(14)	-3997(3)	-2335(3)	-7307(2)	46(1)
C(15)	-4900(5)	-2150(5)	-4722(2)	91(2)
C(16)	-5637(3)	-3563(3)	-8105(2)	57(1)
Cl(1)	-807(1)	-560(1)	-7177(1)	84(1)
O(1)	-2096(3)	-5255(2)	-7053(2)	72(1)
O(2)	-5798(3)	-2649(2)	-5337(2)	71(1)
O(3)	-4325(2)	-4293(2)	-7907(1)	53(1)
N(1)	-3193(3)	-3437(2)	-7654(1)	42(1)
C(1)	-2719(3)	-2663(3)	-9067(2)	47(1)
C(2)	-2797(4)	-1389(3)	-9172(2)	59(1)
C(3)	-3313(5)	-900(4)	-9873(2)	73(2)
C(4)	-3735(4)	-1644(5)	-10489(3)	82(2)

Bond lengths [Å] and angles [deg] for **142**.

O(1)-C(8)	1.327(4)	C(8)-N(1)-C(14)	105.2(2)
O(2)-C(11)	1.420(4)	O(3)-N(1)-C(14)	106.1(2)
O(2)-C(15)	1.416(5)	C(2)-C(1)-C(6)	117.5(3)
O(3)-N(1)	1.438(3)	C(2)-C(1)-C(7)	121.0(3)
O(3)-C(16)	1.457(3)	C(6)-C(1)-C(7)	121.3(3)
O(1)-H(1O)	0.8200	C(1)-C(2)-C(3)	120.5(3)
N(1)-C(8)	1.576(4)	C(2)-C(3)-C(4)	121.3(4)
N(1)-C(14)	1.506(4)	C(3)-C(4)-C(5)	119.5(5)
N(1)-C(7)	1.508(4)	C(4)-C(5)-C(6)	119.6(5)
C(1)-C(6)	1.369(5)	C(1)-C(6)-C(5)	121.6(4)
C(1)-C(7)	1.488(4)	N(1)-C(7)-C(1)	116.3(2)
C(1)-C(2)	1.385(5)	O(1)-C(8)-C(9)	115.3(3)
C(2)-C(3)	1.368(5)	N(1)-C(8)-C(9)	102.1(2)
C(3)-C(4)	1.360(6)	O(1)-C(8)-N(1)	112.1(3)
C(4)-C(5)	1.356(8)	C(8)-C(9)-C(10)	104.1(3)
C(5)-C(6)	1.389(6)	C(9)-C(10)-C(14)	104.6(3)
C(8)-C(9)	1.489(5)	C(11)-C(10)-C(14)	103.9(2)
C(9)-C(10)	1.525(5)	C(9)-C(10)-C(11)	114.3(3)
C(10)-C(14)	1.535(4)	O(2)-C(11)-C(10)	113.9(3)
C(10)-C(11)	1.537(5)	C(10)-C(11)-C(12)	103.9(3)
C(11)-C(12)	1.505(5)	O(2)-C(11)-C(12)	111.0(3)
C(12)-C(13)	1.531(4)	C(11)-C(12)-C(13)	105.6(3)
C(13)-C(14)	1.541(4)	C(12)-C(13)-C(16)	116.8(3)
C(13)-C(16)	1.499(5)	C(14)-C(13)-C(16)	103.7(2)
C(2)-H(2)	0.9300	C(12)-C(13)-C(14)	105.5(2)
C(3)-H(3)	0.9300	N(1)-C(14)-C(10)	106.8(2)
C(4)-H(4)	0.9300	C(10)-C(14)-C(13)	106.8(2)
C(5)-H(5)	0.9300	N(1)-C(14)-C(13)	106.3(2)
C(6)-H(6)	0.9300	O(3)-C(16)-C(13)	105.6(2)
C(7)-H(7A)	0.9700	C(1)-C(2)-H(2)	120.00
C(7)-H(7B)	0.9700	C(3)-C(2)-H(2)	120.00
C(8)-H(8)	0.9800	C(2)-C(3)-H(3)	119.00
C(9)-H(9A)	0.9700	C(4)-C(3)-H(3)	119.00
C(9)-H(9B)	0.9700	C(3)-C(4)-H(4)	120.00
C(10)-H(10)	0.9800	C(5)-C(4)-H(4)	120.00
C(11)-H(11)	0.9800	C(4)-C(5)-H(5)	120.00
C(12)-H(12A)	0.9700	C(6)-C(5)-H(5)	120.00
C(12)-H(12B)	0.9700	C(1)-C(6)-H(6)	119.00
C(13)-H(13)	0.9800	C(5)-C(6)-H(6)	119.00
C(14)-H(14)	0.9800	N(1)-C(7)-H(7A)	108.00
C(15)-H(15A)	0.9600	N(1)-C(7)-H(7B)	108.00
C(15)-H(15B)	0.9600	C(1)-C(7)-H(7A)	108.00
C(15)-H(15C)	0.9600	C(1)-C(7)-H(7B)	108.00
C(16)-H(16A)	0.9700	H(7A)-C(7)-H(7B)	107.00
C(16)-H(16B)	0.9700	O(1)-C(8)-H(8)	109.00
C(11)-O(2)-C(15)	113.2(3)	N(1)-C(8)-H(8)	109.00
N(1)-O(3)-C(16)	107.22(19)	C(9)-C(8)-H(8)	109.00
C(8)-O(1)-H(1O)	109.00	C(8)-C(9)-H(9A)	111.00
O(3)-N(1)-C(7)	110.4(2)	C(8)-C(9)-H(9B)	111.00
O(3)-N(1)-C(8)	106.72(19)	C(10)-C(9)-H(9A)	111.00
C(7)-N(1)-C(8)	109.7(2)	C(10)-C(9)-H(9B)	111.00
C(7)-N(1)-C(14)	118.0(2)	H(9A)-C(9)-H(9B)	109.00

C(9)-C(10)-H(10)	111.00
C(11)-C(10)-H(10)	111.00
C(14)-C(10)-H(10)	111.00
O(2)-C(11)-H(11)	109.00
C(10)-C(11)-H(11)	109.00
C(12)-C(11)-H(11)	109.00
C(11)-C(12)-H(12A)	111.00
C(11)-C(12)-H(12B)	111.00
C(13)-C(12)-H(12A)	111.00
C(13)-C(12)-H(12B)	111.00
H(12A)-C(12)-H(12B)	109.00
C(12)-C(13)-H(13)	110.00
C(14)-C(13)-H(13)	110.00
C(16)-C(13)-H(13)	110.00
N(1)-C(14)-H(14)	112.00
C(10)-C(14)-H(14)	112.00
C(13)-C(14)-H(14)	112.00
O(2)-C(15)-H(15A)	109.00
O(2)-C(15)-H(15B)	109.00
O(2)-C(15)-H(15C)	109.00
H(15A)-C(15)-H(15B)	109.00
H(15A)-C(15)-H(15C)	109.00
H(15B)-C(15)-H(15C)	110.00
O(3)-C(16)-H(16A)	111.00
O(3)-C(16)-H(16B)	111.00
C(13)-C(16)-H(16A)	111.00
C(13)-C(16)-H(16B)	111.00
H(16A)-C(16)-H(16B)	109.00
O(1)-C(8)	1.327(4)
O(2)-C(11)	1.420(4)
O(2)-C(15)	1.416(5)
O(3)-N(1)	1.438(3)
O(3)-C(16)	1.457(3)

O(1)-H(1O)	0.8200
N(1)-C(8)	1.576(4)
N(1)-C(14)	1.506(4)
N(1)-C(7)	1.508(4)
C(1)-C(6)	1.369(5)
C(1)-C(7)	1.488(4)
C(1)-C(2)	1.385(5)
C(2)-C(3)	1.368(5)
C(3)-C(4)	1.360(6)
C(4)-C(5)	1.356(8)
C(5)-C(6)	1.389(6)
C(8)-C(9)	1.489(5)
C(9)-C(10)	1.525(5)
C(10)-C(14)	1.535(4)
C(10)-C(11)	1.537(5)
C(11)-C(12)	1.505(5)
C(12)-C(13)	1.531(4)
C(13)-C(14)	1.541(4)
C(13)-C(16)	1.499(5)
C(2)-H(2)	0.9300
C(3)-H(3)	0.9300
C(4)-H(4)	0.9300
C(5)-H(5)	0.9300
C(6)-H(6)	0.9300
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-H(8)	0.9800
C(9)-H(9A)	0.9700

Anisotropic displacement parameters (A^2 x 10^3) for **142**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U12].

	U11	U22	U33	U23	U13	U12
O(1)	64(2)	63(2)	88(2)	14(1)	13(1)	2(1)
O(2)	57(1)	96(2)	60(2)	11(2)	15(1)	3(2)
O(3)	45(1)	40(1)	73(2)	-2(1)	-9(1)	-7(1)
N(1)	39(1)	37(1)	50(1)	-1(1)	-3(1)	-3(1)
C(1)	45(2)	48(2)	47(2)	0(2)	8(2)	3(2)
C(2)	64(2)	55(2)	59(2)	2(2)	2(2)	1(2)
C(3)	79(3)	70(3)	71(3)	21(2)	3(2)	4(2)
C(4)	58(3)	124(4)	63(3)	29(3)	-1(2)	3(3)
C(5)	83(3)	105(4)	54(2)	-13(2)	1(2)	-11(3)
C(6)	79(3)	59(2)	57(2)	-8(2)	0(2)	6(2)
C(7)	42(2)	51(2)	52(2)	3(2)	4(2)	5(2)
C(8)	41(2)	47(2)	57(2)	6(2)	0(2)	4(1)
C(9)	48(2)	64(2)	52(2)	14(2)	2(2)	4(2)
C(10)	47(2)	53(2)	53(2)	-2(2)	9(2)	-3(2)

C(11)	55(2)	59(2)	62(2)	5(2)	7(2)	5(2)
C(12)	39(2)	74(2)	75(2)	11(2)	9(2)	7(2)
C(13)	41(2)	54(2)	64(2)	8(2)	4(2)	8(2)
C(14)	45(2)	37(2)	55(2)	6(2)	8(2)	-1(1)
C(15)	75(3)	139(4)	59(3)	-4(3)	13(2)	14(3)
C(16)	41(2)	68(2)	63(2)	6(2)	-9(2)	-5(2)
Cl(1)	65(1)	95(1)	93(1)	-28(1)	19(1)	-35(1)
O(1)	64(2)	63(2)	88(2)	14(1)	13(1)	2(1)
O(2)	57(1)	96(2)	60(2)	11(2)	15(1)	3(2)
O(3)	45(1)	40(1)	73(2)	-2(1)	-9(1)	-7(1)
N(1)	39(1)	37(1)	50(1)	-1(1)	-3(1)	-3(1)
C(1)	45(2)	48(2)	47(2)	0(2)	8(2)	3(2)
C(2)	64(2)	55(2)	59(2)	2(2)	2(2)	1(2)
C(3)	79(3)	70(3)	71(3)	21(2)	3(2)	4(2)
C(4)	58(3)	124(4)	63(3)	29(3)	-1(2)	3(3)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **142**.

	x	y	z	U(eq)
H(1O)	-1518	-5327	-7428	86
H(2)	-2496	-862	-8762	71
H(3)	-3376	-42	-9929	88
H(4)	-4080	-1297	-10963	98
H(5)	-3932	-3413	-10825	97
H(6)	-3076	-4258	-9644	78
H(7A)	-1333	-2656	-8123	58
H(7B)	-1631	-3990	-8454	58
H(8)	-1431	-3625	-6832	58
H(9A)	-2901	-3872	-5743	66
H(9B)	-4250	-4347	-6262	66
H(10)	-3163	-1863	-6177	61
H(11)	-5605	-1252	-6094	70
H(12A)	-7415	-2306	-6736	75
H(12B)	-6597	-3592	-6637	75
H(13)	-6024	-1749	-7787	64
H(14)	-3595	-1545	-7502	55
H(15A)	-3874	-2315	-4837	109
H(15B)	-5162	-2527	-4223	109
H(15C)	-5054	-1269	-4690	109
H(16A)	-6530	-4060	-8048	69
H(16B)	-5580	-3261	-8650	69
H(1O)	-1518	-5327	-7428	86
H(2)	-2496	-862	-8762	71
H(3)	-3376	-42	-9929	88
H(4)	-4080	-1297	-10963	98
H(5)	-3932	-3413	-10825	97

Torsion angles [deg] for **142**.

C(15)-O(2)-C(11)-C(10)	63.4(4)
C(15)-O(2)-C(11)-C(12)	-179.8(3)
C(16)-O(3)-N(1)-C(14)	28.2(3)
C(16)-O(3)-N(1)-C(7)	-100.8(3)
C(16)-O(3)-N(1)-C(8)	140.0(2)
N(1)-O(3)-C(16)-C(13)	-34.9(3)
C(7)-N(1)-C(8)-C(9)	159.9(2)
C(14)-N(1)-C(8)-C(9)	32.0(3)
C(14)-N(1)-C(7)-C(1)	-61.8(3)
O(3)-N(1)-C(8)-O(1)	43.5(3)
C(7)-N(1)-C(8)-O(1)	-76.2(3)
C(14)-N(1)-C(8)-O(1)	156.0(2)
O(3)-N(1)-C(8)-C(9)	-80.5(3)
O(3)-N(1)-C(7)-C(1)	60.4(3)
C(8)-N(1)-C(7)-C(1)	177.8(3)
C(7)-N(1)-C(14)-C(10)	-132.6(2)
C(8)-N(1)-C(14)-C(10)	-9.9(3)
O(3)-N(1)-C(14)-C(10)	103.0(2)
C(8)-N(1)-C(14)-C(13)	-123.7(2)
C(7)-N(1)-C(14)-C(13)	113.6(3)
O(3)-N(1)-C(14)-C(13)	-10.8(3)
C(2)-C(1)-C(7)-N(1)	89.6(3)
C(2)-C(1)-C(6)-C(5)	-1.2(5)
C(7)-C(1)-C(6)-C(5)	-177.0(3)
C(6)-C(1)-C(7)-N(1)	-94.8(3)
C(6)-C(1)-C(2)-C(3)	1.7(5)
C(7)-C(1)-C(2)-C(3)	177.5(3)
C(1)-C(2)-C(3)-C(4)	-1.3(6)
C(2)-C(3)-C(4)-C(5)	0.3(6)
C(3)-C(4)-C(5)-C(6)	0.2(6)
C(4)-C(5)-C(6)-C(1)	0.3(6)
N(1)-C(8)-C(9)-C(10)	-41.6(3)
O(1)-C(8)-C(9)-C(10)	-163.4(3)
C(8)-C(9)-C(10)-C(11)	149.1(3)
C(8)-C(9)-C(10)-C(14)	36.1(3)
C(9)-C(10)-C(11)-C(12)	-77.1(3)
C(9)-C(10)-C(11)-O(2)	43.7(4)
C(9)-C(10)-C(14)-N(1)	-15.3(3)
C(11)-C(10)-C(14)-C(13)	-22.0(3)
C(9)-C(10)-C(14)-C(13)	98.1(3)
C(11)-C(10)-C(14)-N(1)	-135.4(2)
C(14)-C(10)-C(11)-O(2)	157.0(3)
C(14)-C(10)-C(11)-C(12)	36.2(3)
C(10)-C(11)-C(12)-C(13)	-36.8(3)
O(2)-C(11)-C(12)-C(13)	-159.6(3)
C(11)-C(12)-C(13)-C(14)	22.9(4)
C(11)-C(12)-C(13)-C(16)	137.4(3)
C(12)-C(13)-C(14)-N(1)	113.6(3)
C(12)-C(13)-C(14)-C(10)	-0.1(3)
C(16)-C(13)-C(14)-N(1)	-9.7(3)
C(16)-C(13)-C(14)-C(10)	-123.4(3)
C(12)-C(13)-C(16)-O(3)	-89.0(3)

C(14)-C(13)-C(16)-O(3)	26.6(3)
C(15)-O(2)-C(11)-C(10)	63.4(4)
C(15)-O(2)-C(11)-C(12)	-179.8(3)

Hydrogen-bonds for **142** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...Cl(1)#1	0.8200	22.100	2.933(3)	147.00
C(7)-H(7A)...Cl(1)	0.9700	28.000	3.626(3)	144.00
C(13)-H(13)...O(1)#2	0.9800	23.500	3.236(4)	150.00
C(14)-H(14)...Cl(1)	0.9800	27.800	3.457(3)	127.00
O(1)-H(1O)...Cl(1)#1	0.8200	22.100	2.933(3)	147.00
C(7)-H(7A)...Cl(1)	0.9700	28.000	3.626(3)	144.00
C(13)-H(13)...O(1)#2	0.9800	23.500	3.236(4)	150.00
C(14)-H(14)...Cl(1)	0.9800	27.800	3.457(3)	127.00

Curriculum vitae

Personal information

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Marital status	Unmarried
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Education

- *April – June 2009*: Research project at the **Università dell' Insubria, Como, Italy** in the group of Prof. Umberto Piarulli in the field of Organocatalysis using diketopiperazine-proline adducts

- *November 2005 - March 2009*: PhD thesis at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser supported by the DFG within the **Graduiertenkolleg GRK 760** (Research Training Group) Medicinal Chemistry: Molecular Recognition – Ligand-Receptor Interactions
  "Synthesis of conformationally restricted amino acids – Highly versatile scaffolds"

- *September 2005*: **Graduation**: Diplom-Chemiker (diploma in chemistry) with additional qualification in Medicinal Chemistry

- *January-September 2005*: Diploma thesis in the research group of Prof. Dr. Oliver Reiser **"Stereoselective Synthesis of Unnatural Amino Acids"**; diploma thesis was carried out as a cooperative project between the University of Regensburg and the **University of Pune, India** including an three-month-stay in Pune, India

- *September 2003-September 2005*: Vertiefungstudiengang (advanced studies) **"Medicinal Chemistry"**

- *September 2002 – February 2003*: Studies at the **University of Vienna, Austria** within the ERASMUS/SOCRATES program including an internship in the research group of Prof. Dr. Johann Mulzer

- *September 2002*: **Vordiplom** (intermediate examination),

- *September 2000*: start of studies in chemistry at the **University of Regensburg**
- *August 1999 – July 2000*: **Zivildienst** (civil service)
- *1990 – 1999*: **Von-Müller-Gymnasium, Regensburg** (secondary school); Abitur (A-levels)
- *1986 – 1990*: primary school (Grundschule St. Wolfgang, Regensburg)

Qualifications

Additional lab courses	Molecular modelling in drug research
	Combinatorial chemistry and solid phase synthesis
	Special aspects of NMR spectroscopy
Languages	German(native)/English(fluent)/French(intermediate)
Memberships	Gesellschaft deutscher Chemiker (GdCh)

Conferences and Courses

- ***2nd International Conference on Organic Synthesis and Process Chemistry(OSPC-2005)***
  Indian Institute of Chemical Technology, Hyderabad (India), April 1-3, 2005
- ***3rd Summer School Medicinal Chemistry***
  University of Regensburg, Regensburg (Germany), September 25-27, 2006
  Foldamers from unnatural amino acids as selective ligands for neuropeptide Y (NPY) receptors
- ***Intensive Course Medicinal Chemistry***
  University of Natural Sciences, Ho-Chi-Minh-City (Vietnam), October 31st – November 3rd, 2006
  Foldamers from unnatural amino acids as selective ligands for neuropeptide Y (NPY) receptors (including a short oral poster presentation)

- ***Joint Meeting of the Graduate Colleges GRK 677 and GRK 760*** Nürnberg (Germany), October 8-10, 2007
  Synthesis of new unnatural amino acids for various applications

- ***Annual Meeting Frontiers in Medicinal Chemistry*** University of Regensburg, Regensburg (Germany), March 2-5, 2008
  Synthesis of new unnatural amino acids for foldamers and neuropeptide Y (NPY) analogs as selective ligands for NPY receptors

- ***116th International Summer Course (BASF)*** Business-Hotel René Bohn, Ludwigshafen (Germany), August 11-22, 2008

- ***2nd EuCheMS Chemistry Congress*** Lingotto Conference Center, Turin (Italy), September 16-30, 2008
  Synthesis of new unnatural amino acids for foldamers

- ***4th Summer School Medicinal Chemistry*** University of Regensburg, Regensburg (Germany), September 29 – October 1, 2008
  Synthesis of new cispentacin analogues

Fellowships and Grants

'Marie Curie Actions' supported research (April 09 – June 09)

PhD Scholarship, Graduate College GRK760 "Medicinal Chemistry: Molecular Recognition - Ligand-Receptor Interactions" (November 05 – November 09)

Travel Fellowship "Karl-Ziegler-Stiftung"/GdCh (September 08)

Travel Fellowship Asia Link Medicinal Chemistry (November 06)

Travel Fellowship "Fonds Hochschule International" (March 05)

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