Enantioselective synthesis of new conformationally constrained sugar-like γ-, δ-, ε-amino acids, δ-peptides and nucleoside amino acids

Dissertation

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to my parents, my wife Salma and my son Redwan

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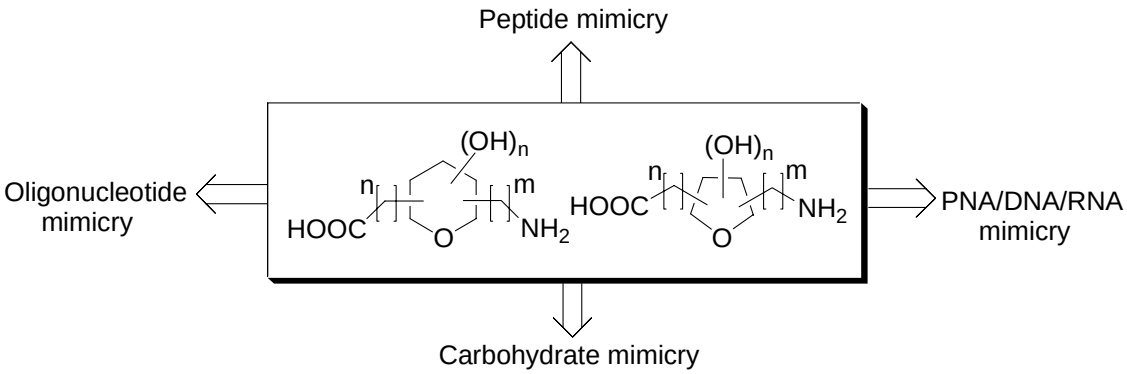
Abbreviations

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
CAN	Cerium (IV) diammonium nitrate
Cbz	Benzyloxycarbonyl
CD	Circular Dichroism
COSY	Correlation Spectroscopy
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIC	Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EDC	Ethyl-N,N-dimethyl-3-aminopropylcarbodiimide
ee	Enantiomeric excess
EI	Electron Impact
Et	Ethyl
equiv.	equivalents
Fmoc	9-Fluorenylmethoxycarbonyl
h	hour(s)
HBTU	O-benzotriazole-N,N,N',N' tetramethyluronium-hexafluoro-phosphate
HB	Hydrogen Bond
HFA	Hexafluoroacetone
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
IR	Infrared Spectroscopy
LDA	Lithium diisopropylamide
Me	Methyl
MeOH	Methanol
min	minutes
m.p.	Melting Point
MS	Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
OAc	Acetate
PNA	Peptide Nucleic Acid
PG	Protecting group
Py	Pyridine
quant.	quantitative
PMB	4-Methoxybenzyl
RMSD	Root Mean Square Deviation
RNA	Ribonucleic Acid
ROESY	Rotating Frame NOE spectroscopy
R.T.	room temperature
sat.	saturated
TBDMS	*tert*-Butyldimethylsilyl
tert	tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
TOCSY	Total Correlation Spectroscopy
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
Ts	*para*-Toluenesulfonyl

Introduction

1. Sugar amino acids

Sugar amino acids were designed and synthesized as new non-peptide peptidomimetics utilizing carbohydrates as peptide building blocks. Generally they present suger-like ring structures which carry an amino and a carboxylic functional group (Scheme-1) and have a specific conformational influence on the backbone of peptide due to their distinct substitution patterns in rigid pyranose and furanose sugar rings.[2-4]

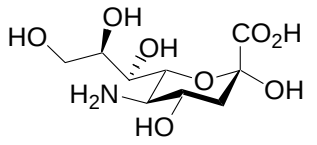


Scheme 1. Sugar amino acids as structural scaffolds, as carbohydrate mimetics, as peptide mimetics, and as oligonucleotide mimetics.

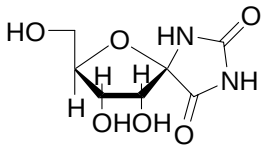
The interest in a rational design of amino acid and peptide mimetics has extensively grown due to the pharmacological limitations of bioactive peptides. A large variety of modifications of peptide structures has been used for conformationally directed drug design to investigate the active peptide receptor binding conformation.[2] Conformationally constrained amino acids provide access to short sequences of peptide mimetics with secondary structure and thus may generate new opportunities for the design of antagonists and agonists of specific protein-protein interections. Carbohydrates present as an attractive option for non-peptide scaffolding as they contain well-defined and readily convertible substituents with a rigid pyran or furan

ring.[4] Carbohydrates are frequently found in proteins as a result of enzyme-mediated glycosylation in post-translational modification processes.[5]

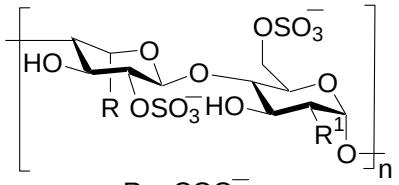
Sugar amino acids specially occur in nature as construction elements.[6-8] The most common example is sialic acid often located peripherically on glycoproteins. This familly of natural sugar amino acids consists of *N*- and *O*- acyl derivatives of neuraminic acid **1** (Scheme 2). In nature sugar amino acids are found not only in monomeric form but also in dimer as well as polysaccharide such as Heparin **2** (Scheme 2). Natural sugar amino acids are also found in nucleoside antibiotics,[10] in cell walls of bacteria (muraminic acid). The furanoid sugar amino acid (+)-Hydantocidin **3** (Scheme 2), which represents a spirohydanthion derivative,[11,12] exhibits herbicidal activity. Siastatin B **4** (Scheme 2) is among the class of sugar amino acids in which the nitrogen is located within the pyranoid ring structure. This inhibitor for both β-glucuronidase and *N*-acetylneuraminidase was isolated from a *Streptomyces* culture.[13]



Neuraminic acid **1**



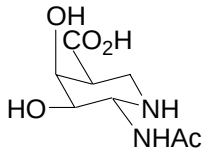
Hydantocidin **3**



R = COO^-

R^1= $NHSO_3^-$

Heparin **2**



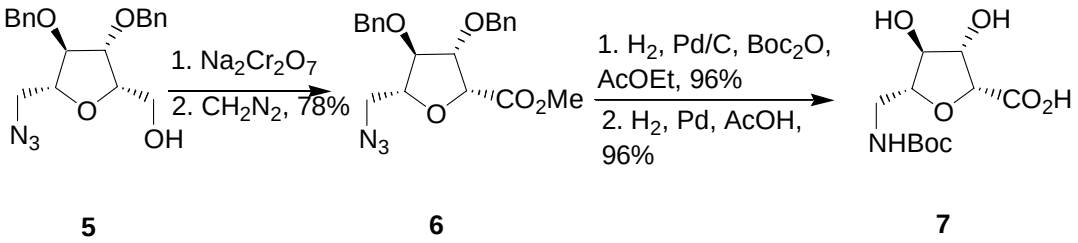
Siastatin B **4**

Scheme 2. Naturally occuring sugar amino acids.

The synthesis of sugar amino acids is easily accomplished in a few steps starting from commercially available or easily accessible glucose, glucosamine, diacetone glucose, galactose, etc. The amino functionality of the sugar amino acid can be introduced as an

azide, cyanide or nitromethane equivalent, followed by subsequent reduction. The carboxylic function is introduced directly as CO_2, or hydrolyzable cyanide, by a Wittig reaction and subsequent oxidation or by selective oxidation of a primary alcohol.[6-9]

In 1995 *Pointout, Le Merrer and Depezay* at first synthesized a furanoid sugar amino acid.[14] Here they synthesized azidomethyl-tetrahydrofuran **5** from D-Mannitol in five steps. The primary alcohol function of the **5** was oxidized to the carboxylic acid by $Na_2Cr_2O_7$ which was treated with an excess of diazomethane to give **6** in 78% overall yield. The sugar amino acid **7** was achieved by hydrogenolysis of azido ester **6** in presence of di-*tert*butyldicarbonate, followed by deprotection of benzyl group in high yield (Scheme 3).[14]



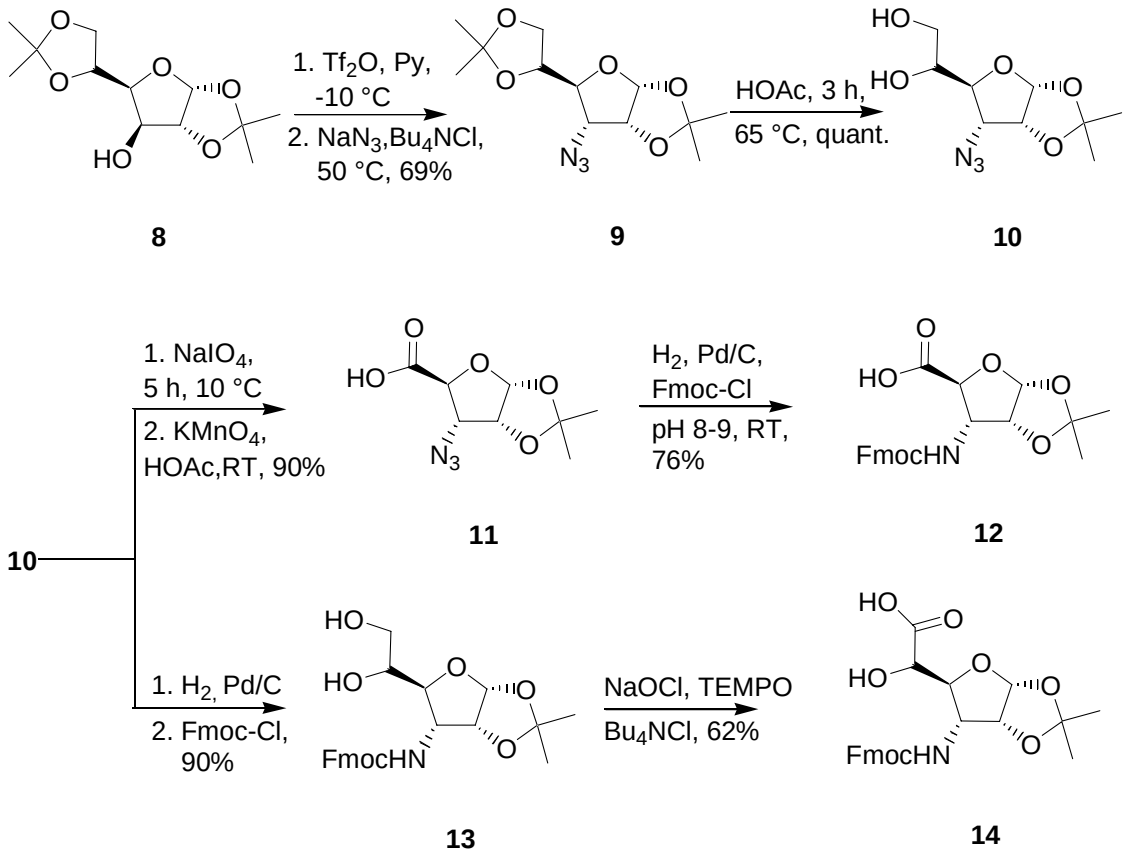
5 **6** **7**

Scheme 3. Synthesis of *Le Merrer's* δ-sugar amino acid **7**.

Several derivatives with an α-amino acid moiety at the anomeric position of the sugar were synthesized by *Fleet et al*., and *Dondoni et al*. including glucose, rhamnose, galactose and mannose derivatives.[15] These types of sugar amino acids have also been employed as precursors to five- and six-membered spiroheterocyclic derivatives of carbohydrates such as the rhamnose functionality, required for enhanced activity analogues of hydantocidine **3**[11,12] exhibits herbicidal activity.

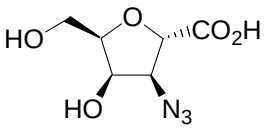
Kessler et al. synthesized β-sugar amino acid **12** and γ-sugar amino acid **14** as turn mimetics[16] from commercially available diacetone-glucose **8** in good yield of 47% for **12** and 39% for **14** (Scheme 3). The azidolysis of the triflate activated diacetone-glucose **9** and followed by quantitative deprotection of exocyclic hydroxyl group using concentrated acetic acid to yield **10**. Subsequently, the diol **10** is oxidatively cleaved using $NaIO_4/KMnO_4$ to **11**. Finally the amino acid **12** was synthesized by

hydrogenolysis of azide group and followed by Fmoc-protection in one-pot reaction. Alternatively reduction of the azide group and followed by Fmoc-protection to give **13** in 90% yield which was subjected to TEMPO mediated NaOCl oxidation to give sugar amino acid **14** in 62% yield.



Scheme 4. Synthesis of β- and γ-sugar amino acid **12** and **14** by *Kessler's et al*.

Fleet et al. published the synthesis of several azid precursors to β- and γ-sugar amino acids (Scheme 5)[17,21-26].



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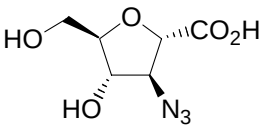

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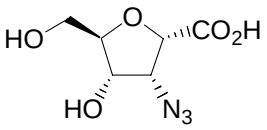

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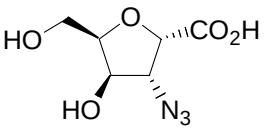

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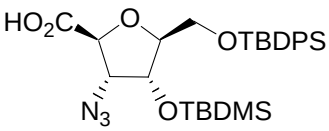

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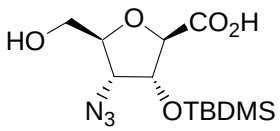

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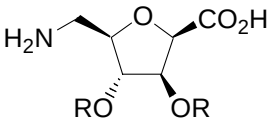
Scheme 5. *Fleet's* large collection of azides, used as *β*- and *γ*-sugar amino acid precursors.

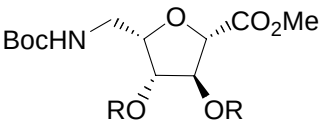
At the same time Fleet's group also synthesized several *δ*-sugar amino acids **21, 24, 25** and **26** (Scheme 6), those provide access to short sequences of peptide mimetics with secondary structure.[17]



R = H, Bn, Ac

21

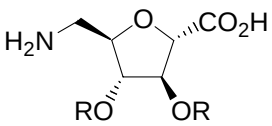
Fleet
Le Merrer
Chakraborty



R = H, Bn

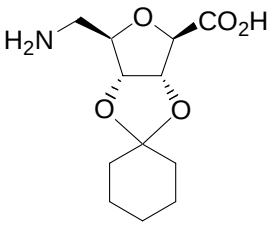
22

Le Merrer



23

Chakraborty
Fleet



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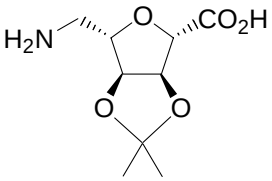
Fleet



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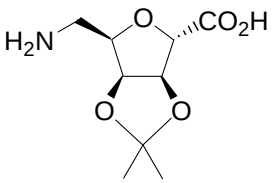
Fleet

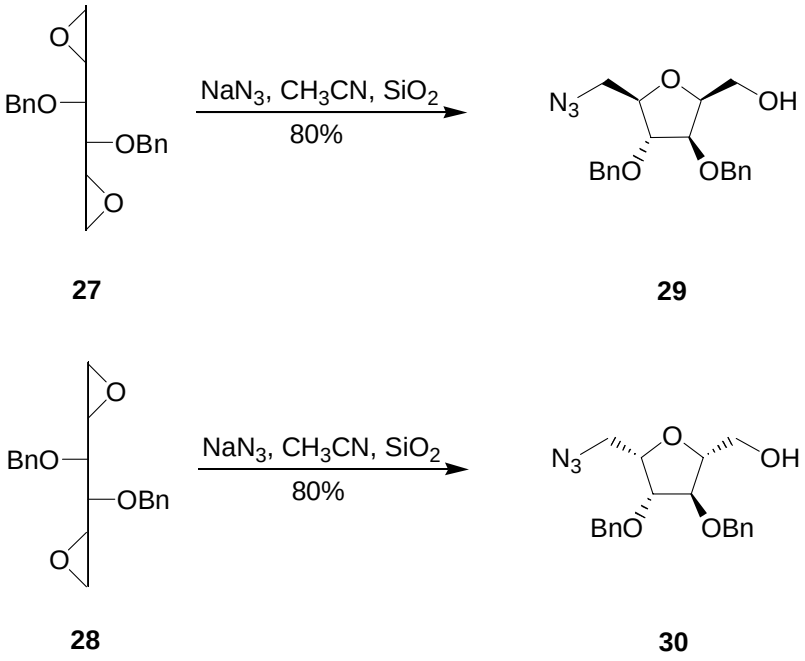


26

Fleet

Scheme 6. Furanoid *δ*-sugar amino acids of *Le Merrer's, Fleet's and Chakraborty's.*

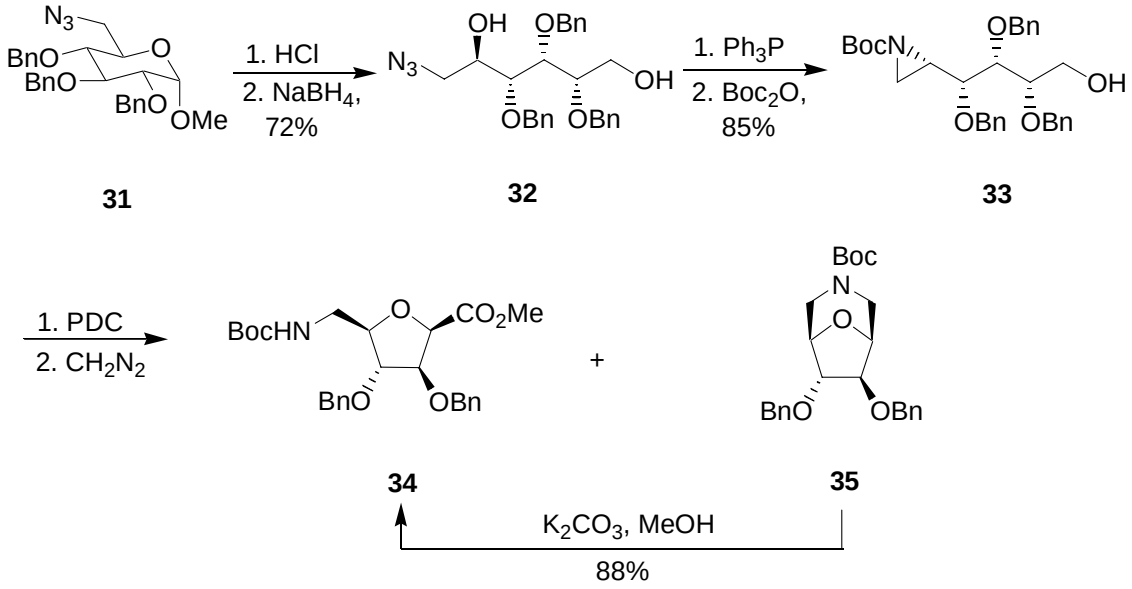
Le Merrer et al. also synthesized some δ-sugar amino acids **22** and **23** (Scheme 6),[14] as dipeptide isosteres for the incorporation into peptide based drugs. The benzylated derivatives were designed as mimics for hydrophobic amino acids, and unprotected sugar amino acids as mimics for hydrophilic amino acids.[14] Key step of their synthesis was the one-pot silica gel assisted azidolysis followed by *O*-ring closure of the bis-epoxides **27** and **28** (Scheme 7) to yield **29** and **30** respectively. For the synthesis of sugar amino acids **22** and **23** from azido compound **29** and **30**, reaction-sequences were described in Scheme 3.



Scheme 7. Key step of *Le Merrer's* synthesis of **22** and **23**.

Chakraborty et al. also synthesized several δ-sugar amino acids (Scheme 6) by an intramolecular 5-exo S_N2 opening of the hexose-derived terminal aziridin ring and their incorporation into Leu-enkephalin in its Gly-Gly position as dipeptide isosteres leading to the formation of peptidomimetic analogues with secondary structure.[18] Here they synthesized diol **32** from azido glucopyranoside **31**, in two steps in 72% yield. Treatment of **32** with Ph_3P led to the formation of an aziridine ring, which was protected in situ to give **33** in 85% yield. The Boc-protected aziridinyl **33** transformed

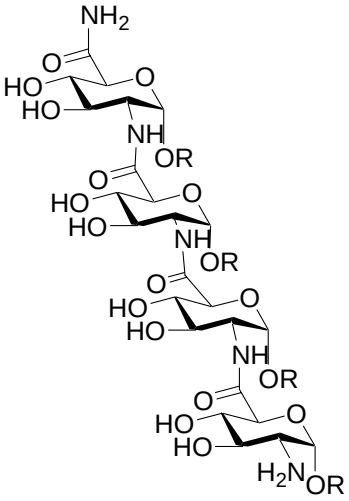
into thermodynamically stable 5-ring sugar amino acid **34** along with another bicyclic compound **35** which was converted to **34** in presence of K_2CO_3/MeOH (Scheme 8).[18]



Scheme 8. Synthesis of *Chakraborty's* furanoid δ- sugar amino acid **34**.

1.1 Carbohydrate-Based Peptidomimetics

During the past few years chemists have developed a large variety of oligomeric compounds that mimic biopolymers.[27] These synthetic oligomers are composed of unnatural and yet nature-like monomeric building blocks assembled together by iterative synthetic processes that are amenable to combinatorial strategies. The main objective in developing such oligomers is to mimic the ordered secondary structures displayed by the biopolymers and their functions. They are also expected to be more stable toward proteolytic cleavage in physiological systems than their natural counterparts. Sugar amino acids can adopt robust secondary turn or helical structures and thus may allow one to mimic helices or sheets. They can be used as substitutes for single amino acids or dipeptide isosters. The first oligomers were synthesized in solutions by *fuchs* and *Lehmann*, although they did only characterize the individual products by mass spectroscopy.[28] More recently, oligomers were synthesized both in solution[29] and on solid phase[30] and have been proposed to mimic oligosaccharide (**36**)[30] backbone structures via amide bond linkages (Scheme 9).



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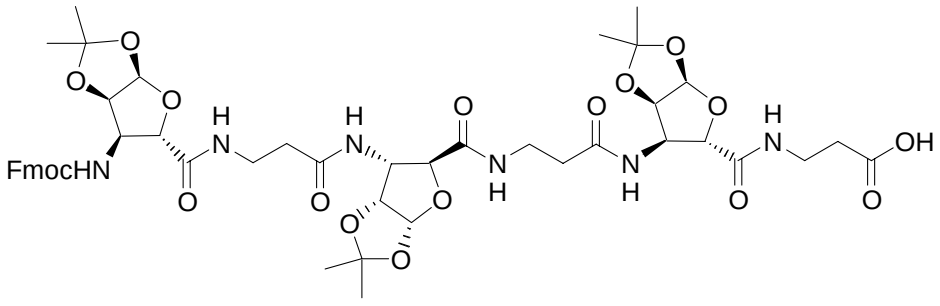
Scheme 9. *K. C. Nicolaou's* Oligosaccharide.

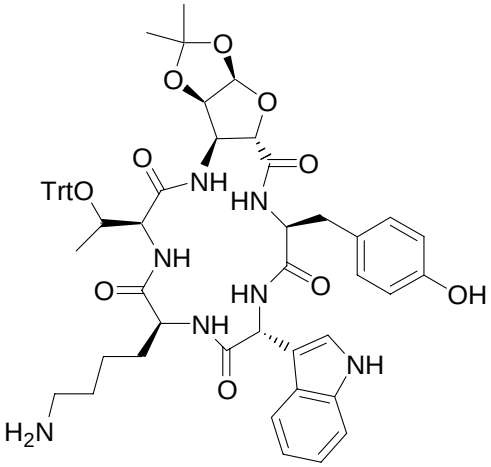
Kessler et al. synthesized sugar amino acid **12** and **14** containing mixed linear and cyclic oligomers those provide access to short sequences of peptide mimetics with secondary structure.[9,16] β-alanine and γ-aminobuteric acid were used as amino acid counterpart, because they represent likewise to β- and γ-sugar amino acid **12** and **14** and they are completely unsubstituted, thus secondary structure results exclusively from the sugar amino acid incorporated. The β-sugar amino acid **12** containing linear oligomer **37** in CH_3CN exhibited 12/10/12-helical structure (Scheme 10).



37

Scheme 10. *Kessler's* linear oligomer **37**.

Kessler et al. also synthesized biologically active cyclic somatostatine analogues **38,**[16] and **39** (Scheme 11) by using sugar amino acid **12**, which exhibit strong antiproliferative and apoptotic activity against multidrug-resistant hepatoma carcinoma cells.[16] Somatostatin is a 14-residue cyclic hormone formed in the Hypothalamus which also plays an impotant role in a large number of physiological actions. For instance it inhibits the release of growth hormon,[19] and plays a role in the inhibition of insulin secretion.[19]



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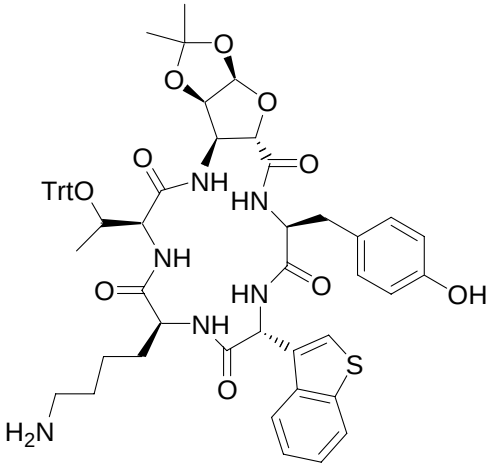

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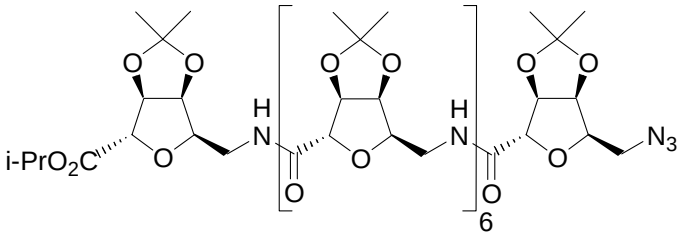
Scheme 11. *Kessler's* Cyclic Peptide, somatostatin analogue **38** and **39**.

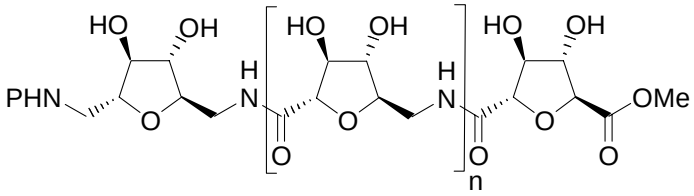
For the peracetylated tetramers of sugar amino acid **21** (Scheme 6) as well as for the sugar amino acids **24** and **25**, Fleet et al. observed a repeating β-turn like bond structure by a combination of solution and IR techniques.[21-24] All of the oligomers adopt a repeating 10-membered hydrogen-bonded ring structure. These results show that protecting groups and substitution patterns of the hydroxyl groups in the sugar ring do not significantly influence the secondary structure of their homooligomers. On the basis of their solution NMR studies, *Fleet et al.* observed a left-handed helical secondary structure stabilized by 16-membered (i, i – 3) interresidue hydrogen bonds, for the octamer **40** of sugar amino acid **26** (Scheme 12).[17,22,25,26]



40

Scheme 12. *Fleet's* sugar amino acid **26** containing octamer **40**

Chakraborty et al. also investigated several protected and unprotected oligomers **41** of sugar amino acid **23** (Scheme 13). The unprotected octamer shows a strong positive band in its CD spectra in MeOH and TFE, which might hint at a possible presence of a distinct secondary structure. However, the ^{1}H NMR spectra in various solvent did not show dispersed chemical shifts for the amide protons.[27]



n = 0-6

P = H or Boc

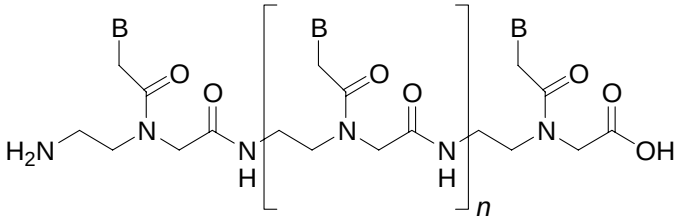
41

Scheme 13. *Chakraborty's* sugar amino acid **23** containing oligomers **41**.

1.2 Carbohydrate-Based Peptide Nucleic Acid (PNA) mimetics

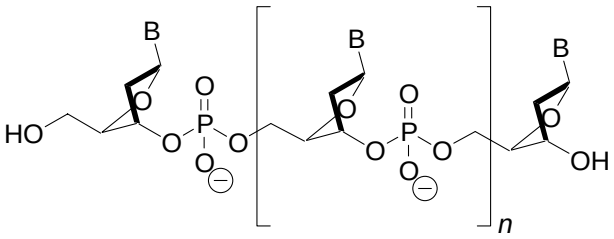
The most important molecular recognition event in nature is the base-pairing of nucleic acids, which guarantees the storage, transfer, and expression of genetic information in living systems. The highly specific recognition through the natural pairing of the nucleobase has become increasingly important for the development of DNA diagnostics and for oligonucleotide therapeutics in the form of antisense and antigene

oligonucleotides.[33-34] In the last couple of years, many attempts to optimize the properties of oligonucleotides have resulted in the synthesis and analysis of a huge variety of new oligonucleotide derivatives[35] with modifications to the phosphate group, the ribose, or the nucleobase. The most radical change to the natural structure, however, was made by *Nielsen et al.*[36-39] in 1991, who replaced the entire sugar-phosphate backbone (Scheme 14) by an *N*-(2-aminoethyl)glycine-based polyamide structure. The interesting that these polyamide or peptide nucleic acids (PNAs) bind with higher affinity to complementary nucleic acids than their natural counterparts.[40]



PNA

42



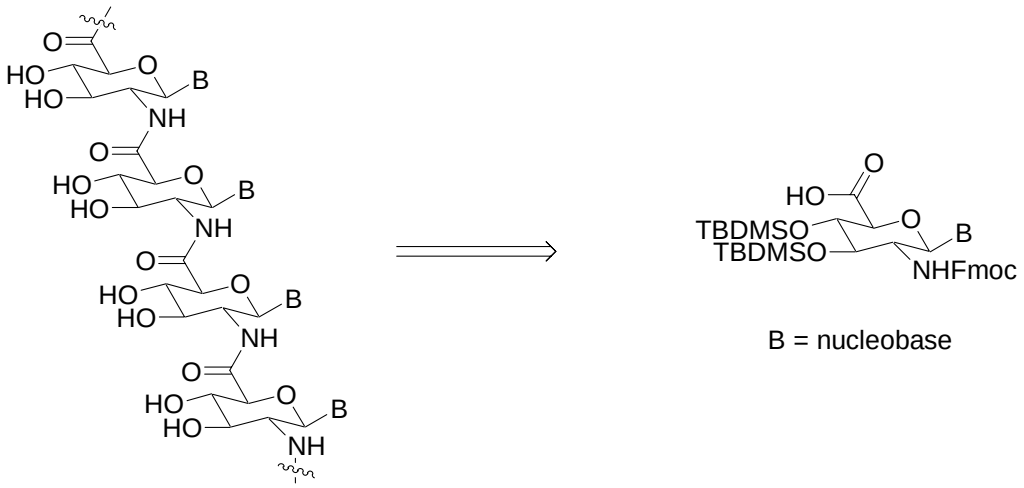
DNA

43

Scheme 14. Chemical structures of PNA **42** and DNA **43**. B = nucleobase.

Actually PNA was designed and developed as a mimic of a DNA-recognizing, major-groove-binding, triplexforming oligonucleotide.[36-38] However, the pseudopeptide (polyamide) backbone of PNA (Scheme 14) has proven to be a surprisingly good structural mimic of the ribose phosphate backbone of nucleic acids. Therefore, PNA has attracted wide attention in medicinal chemistry for the development of gene therapeutic (antisense and antigene) drugs, and in genetic diagnostics. However, while PNA is conceptually a DNA mimic, it is chemically a pseudopeptide (polyamide), and this fact makes PNA of interest for more basic questions regarding DNA structure, evolution, and function.[36-43]

More recently, PNA oligomers were synthesized in solution and solid phase[42,43] and have been proposed to mimic of oligonucleotide (so-called GNA, glycopyranosyl nucleic amide) backbone structures via amide bond linkages. The aim of GNA development was to improve the properties of the presently most useful class of antisense agents the phosphorothioates.[44] By the following idea of PNA, *Goodnow et al.*[45] presented oligomers **45** of Gum as novel antisense agents with the nucleobases attached *via N*-glycosidic linkage at the anomeric center, which showed similar selectivities and binding affinities as DNA and RNA (Scheme 15).

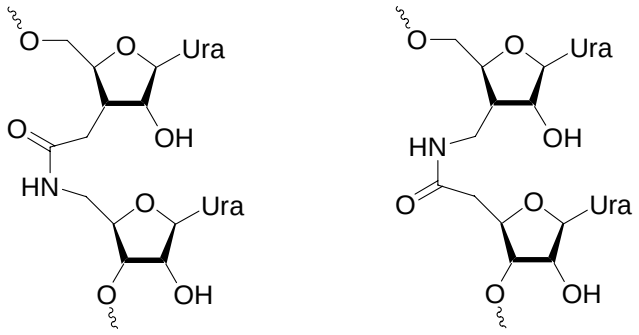


45

44a : B = Thymine
44b : B = Cytosine
44c : B = Adenine
44d : B = Guanine

Scheme 15. *Goodnow's* oligonucleotide **45.**

Rozner et al. also synthesized oligoribonucleotide analogues **45** and **46** (Scheme 16) having amide internucleoside linkage at selected position, exhibit interesting properties, similarly to peptide nucleic acids which are very promising candidates for medicinal applications.[46] They also found that oligoribonucleotides where selected phosphodiester bonds were replaced by formacetal linkages had increased affinity to the complementary RNA fragments compared to unmodified oligoribonucleotides.[41]

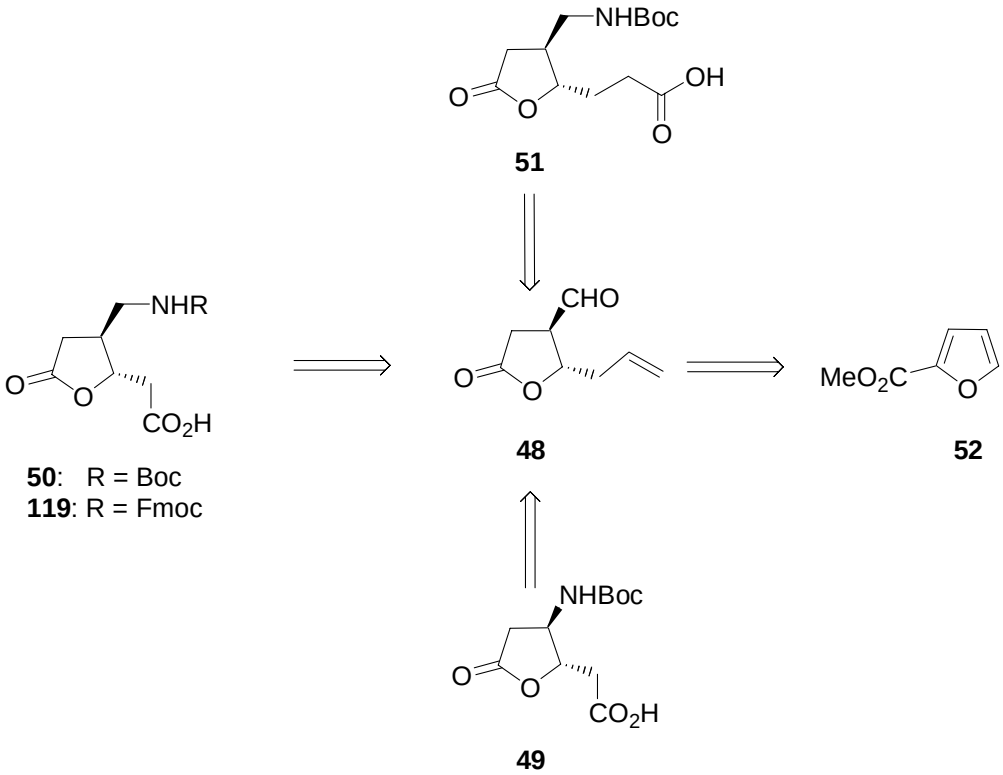


46 **47**

Scheme 16. *Rozner's* oligoribonucleotide **46** and **47**.

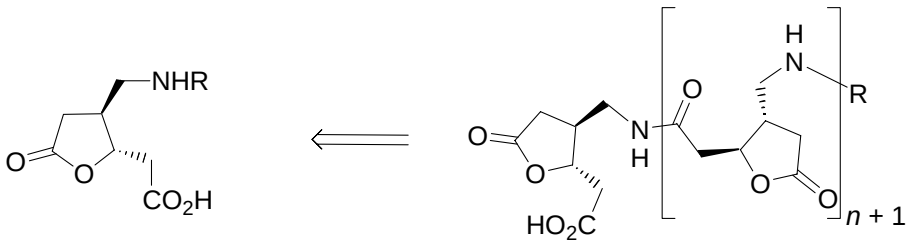
1.3 Aim of this work

In view of the above importance of carbohydrate and peptide based sugar amino acids, I would like to culminate in the development of a new strategy for the stereoselective synthesis of γ-, δ-, and ε-amino acids **49**, **50**, **119** and **51** respectively (Scheme 17) from *trans*-disubstituted γ-butyrolactonaldehyde **48**.



Scheme 17. Retrosynthetic strategy for the stereoselective synthesis of γ-, δ- and ε-amino acids **49**, **50, 119** and **51**.

Here, the γ-amino acid **49** was envisioned to be synthesized from γ-butyrolacton-aldehyde **48** through oxidation of the aldehyde, Curtius rearrangement and finally ruthenium catalyzed oxidation of the allylic double bond. The δ-amino acid **50** was envisioned to be synthesized from γ-butyrolactonaldehyde **48** through reductive amination, Boc protection, oxidative removal of PMB and finally ruthenium catalyzed oxidation of the allylic double bond. The ε-amino acid **51** was envisioned to be synthesized from the carbamate **117** through ruthenium catalyzed hydroboration of the allylic double bond and finally TEMPO mediated oxidation of the primary alcohol. The *trans* disubstituted γ-butyrolactonaldehyde **48** and (ent)-**48** were synthesized from furan **52** through asymmetric cyclopropanation of **52** followed by ozonolysis of bicyclic compound, diastereoselective addition of nucleophile and finally by retroaldol-lactonization sequences. The oligopeptide **53** and **54** was envisioned to be synthesized from conformationally constrained δ-amino acid **50** by standard solid or solution phase peptide coupling methods (Scheme 18). The main objective in developing such oligomer is to mimic the ordered secondary structure displayed by the biopolymers and their functions.

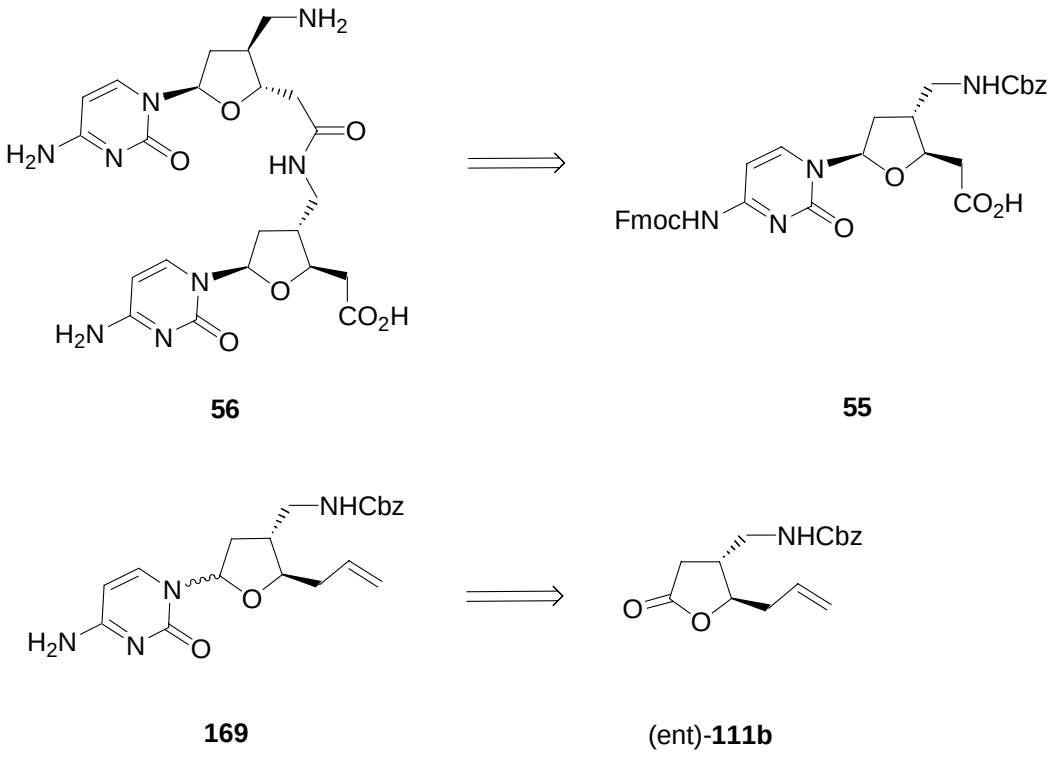


50: R = Boc
119: R = Fmoc

53 (*n* = 2): R = Boc
54 (*n* = 2): R = Fmoc

Scheme 18. Retrosynthetic strategy for oligopeptide **53** and **54**.

The PNA analouge **56** was envisioned to be synthesized from nucleoside amino acid **55** by standard solution phase peptide coupling methods (Scheme 19). The nucleoside amino acid **55** was envisioned to be synthesized from the amine (ent)-**111b** through Cbz-protection, reduction of lactone followed by acetylation, Lewis acid mediated coupling with nucleobase, oxidative removal of PMB and finally ruthenium catalyzed oxidation of the allylic double bond (Scheme 19).



Scheme 19. Retrosynthetic strategy for PNA analogues **56**.

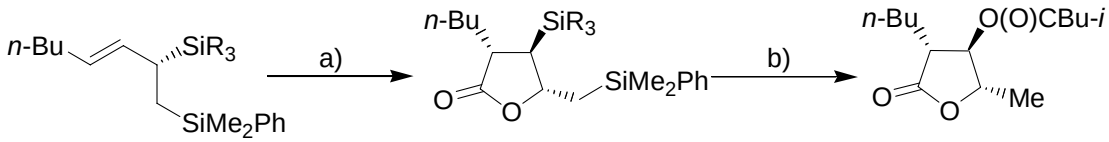
Chapter 1

Enantioselective synthesis of new conformationally constrained sugar-like γ-, δ-, and ε-amino acids.

1.1 γ-Butyrolactonaldehyde

1.1.1 Synthetic strategy of substituted γ-butyrolactonaldehyde

Functionalized chiral γ-buryrolactone skeletons represent an important core structure in many biologically active natural products[47] and also useful synthetic building blocks[48] in organic synthesis. Consequently, the development of new methods for the synthesis of γ-butyrolactone, particularly in a stereocontrolled fashion, has received considerable attention.[48,49] A good example was presented by *K. A. Woerpel et al.* for the total synthesis of (+)-Blastmycinone **59**. As the key step they synthesized γ-butyrolactone **58** by the [3 + 2] annulation reaction of substituted allylic silanes **57** with *N*-chlorosulfonyl isocyanate (Scheme 20).

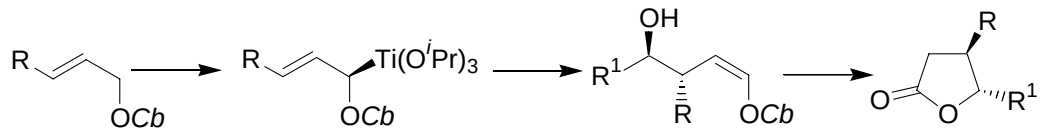


57 **58** **59**

Reagent and Conditions: a) CSI, CH_2Cl_2; HCl, THF-H_2O, 72%; b) *i*) CsF; H_2O_2, 81%; *ii*) ^{i}BuCOCl, Et_3N, DMAP, 89%; *iii*) KBr, AcOOH, 73%; *iv*) CBr_4, PPh_3; Bu_3SnH, AIBN, 79%.

Scheme 20. Total synthesis of (+)-Blastmycinone **59** by *K. A. Woerpel et al.*

D. Hoppe et al.[50] synthesized disubstituted γ-butyrolactone **63** from carbamate **60**. After initial deprotonation of the carbamate **60** with lithiumbase and (-)-sparteine, the allyltitanium intermediate **61** was generated by metal exchange with inversion of configuration. Trapping of **61** with aldehydes gave enantioselective homoaldol adducts **62** which were transformed to *trans*-disubstituted γ-butyrolactone **63** (Scheme 21).

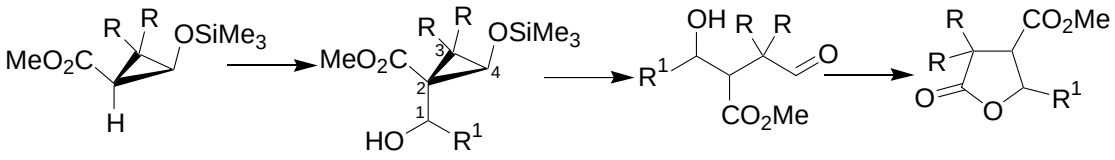


60 **61** **62** **63**

Scheme 21. Synthesis of substituted γ-butyrolactone **63** by *D. Hoppe et al*.[50]

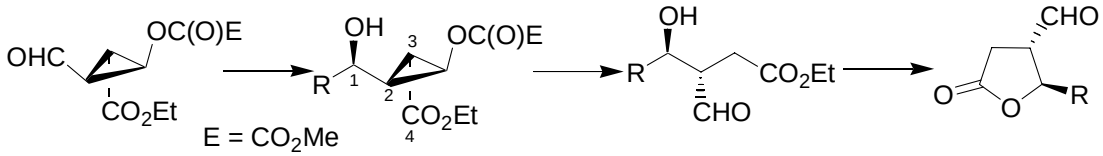
Cyclopropane derivatives substituted by donor and acceptor groups are particularly suitable for synthetic applications, since electronic effects of these substituents guarantee activation of the cyclopropanes and high versatility of the products after ring cleavage.[51]

H.-U. Reißig et al.



(*rac*)-**64** (*rac*)-**65** (*rac*)-**66** (*rac*)-**67**

O.Reiser et al.

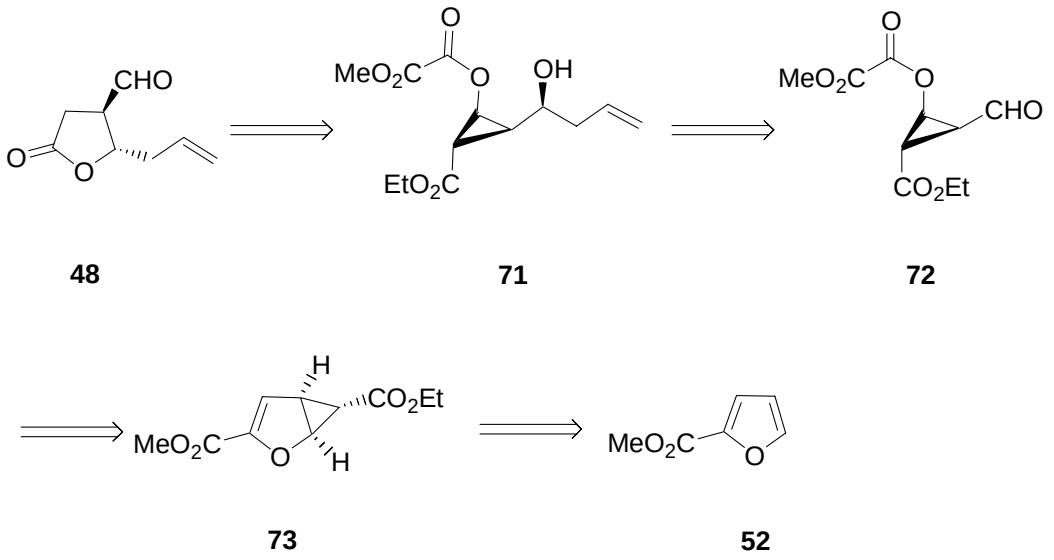


68 **69** **70** (ent)-**48**

Scheme 22. Synthesis of substituted γ-butyrolactone by *H.-U. Reißig and O. Reiser*.

H.-U. Reißig et al.[51-53] and *O. Reiser et al.* [54] used cyclopropane derivatives (*rac*)-**64** and **68** for the synthesis of substituted γ-butyrolactone (Scheme 22). *Reißig et al*. synthesized (*rac*)-**67** by deprotection of methyl 2-siloxycyclopropane (*rac*)-**64** in the presence of lithiumbase and reaction of the resultant enolate with carbonyl compound gave cyclopropanol (*rac*)-**65**, which under lactonization gave (*rac*)-**67** in good yield. *Reiser et al.* synthesized (ent)-**48** in good yield by diastereoselective nucleophilic addition with cyclopropanecarbaldehyde **68** gave cyclopropanol **69** which under base mediatated retroaldol-lactonisation sequences. Following *Reiser* strategy,[54] the initial

work was aimed to synthesize the key intermediate *trans*-disubstituted γ-butyrolactonaldehyde **48** (Scheme 23) diastereo- and enantioselectively, using a copper (I)-catalyzed asymmetric cyclopropanation of furan-2-carboxylic methyl ester **52** followed by ozonolysis, Sakurai allylation with allyltrimethylsilane and finally base mediated retroaldol-lactonisation sequences.



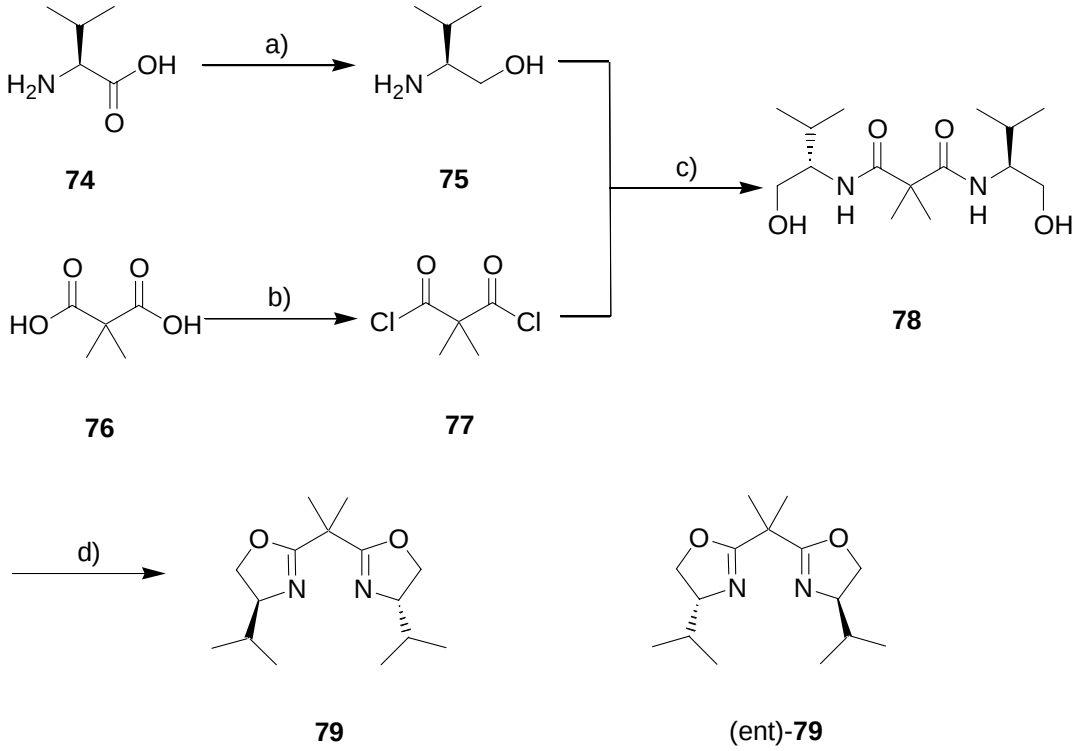
Scheme 23. Retrosynthetic strategy of *trans*-disubstituted γ-butyrolactonaldehyde **48**.

1.1.2 Asymmetric Cyclopropanation and Ozonolysis

Substituted cyclopropanes are an important class of compounds because of their occurance in numerous natural products and drugs[54] and also useful synthetic building blocks in organic synthesis.[55] As a result, the development of new methods for the synthesis of substituted cyclopropanes, particularly in a stereocontrolled fashion, has received wide attention.[56] Vicinally donor and acceptor substituted cyclopropanes[55] are particularly useful, since they easily undergo ring opening, giving rise to reactive intermediates for many synthetically valuable transformations. In 1966 *Nozaki et al.*[57] first reported the stereoselective [2 + 1]-cycloaddition of carbenes to olefins in the presence of a chiral (salicylaldiminato)copper complex. Although the optical yields were low, these findings were of considerable consequence for the development of enantioselective catalysis, since they demonstrated the general principle that a homogeneous metal catalyst can be rendered enantioselective by complexation with a chiral ligand. Subsequently, a number of research groups tried to improve the selectivity of this synthetically useful (C-C)-bond-forming reaction.

1.1.2.1 Cyclopropanation of furan-2-carboxylic methyl ester

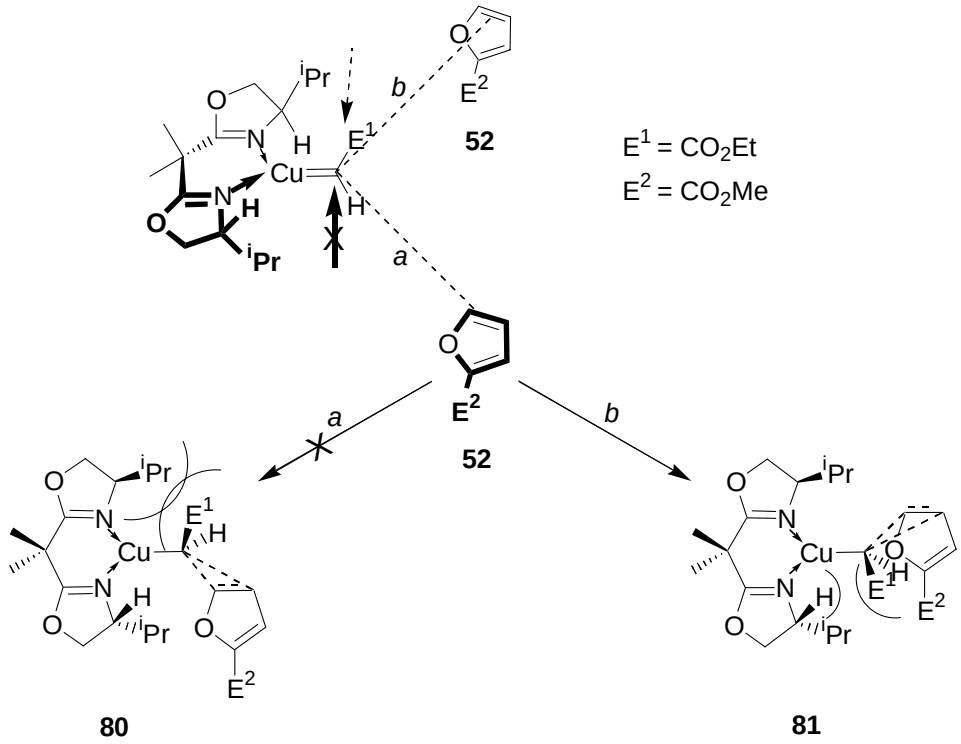
The initial work was aimed to improve on the copper(I) catalyzed asymmetric cyclopropanation of furan-2-carboxylic methyl ester **52** with ethyl diazoacetate. The absolute stereochemistry was controlled by using chiral bisoxazoline ligand **79**, which was synthesized from the readily available amino acid L-valine **74** by using the methodology developed by *D. A. Evans*.[58] L-valine was reduced to the corresponding amino alcohol **75** by using $NaBH_4$ and I_2, followed by acylation with dimethylmalonyl dichloride **77** which was prepared from diacid **76** using oxalyl chloride to give diamide **78**. The diamide **78** was cyclized to bisoxazoline **79** in 58% via the bistosylate (Scheme 24). The corresponding bisoxazoline (ent)-**79**[58,59] was also synthesized from D-valine, which was used in synthesis of PNA analogues (Chapter 3).



Reagent and Conditions: a) $NaBH_4$ (2.5 equiv.), I_2 (1.0 equiv.), THF, 21 h, 91%; b) **76** (1.0 equiv.), oxalyl chloride (3.0 equiv.), CH_2Cl_2, 19 h, 82%; c) **75** (1.0 equiv.), **77** (0.5 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, 45 min, 71%; d) DMAP (0.1 equiv.), Et_3N (4.4 equiv.), *p*-Tosylchloride (2.0 equiv.), CH_2Cl_2, 48 h. 67%.

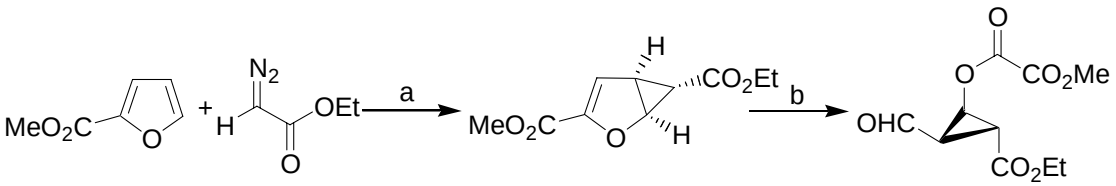
Scheme 24. Synthesis of bisoxazoline ligand **79**.

The stereoselectivity of the copper-bisoxazoline catalyzed cyclopropanation of furan-2-carboxylic methyl ester **52** with ethyl diazoacetate was explained using model proposed by *A. Pfaltz*[58] (Scheme 25). The (bisoxazoline)copper(I) complex first reacts with the ethyl diazoacetate to form a metal-carbene intermediate in which one of the two enantiotopic faces of the trigonal carbene C-atom is shielded by the chiral bisoxazoline ligand such that the double bond of furan preferentially approaches from the less hindered side. Depending on the direction of attack, the ester group at the carbenoid center either moves forward or backward relatively to the plane bisecting the bisoxazoline ligand (Scheme 25, Pathway *a* and *b* respectively). In the case of pathway *a*, a repulsive steric interaction builds up between the ester group and the isopropyl group of the bisoxazoline ligand. Therefore, pathway *b* is expected to be favoured over *a*.



Scheme 25. The mechanistic pathway of the stereoselective cyclopropanation of furan-2-carboxylic methyl ester **52**.

The cyclopropanation of **52** with ethyl diazoacetate **82** in the presence of $Cu(OTf)_2/PhNHNH_2$ as catalyst, proceeds regioselectively and diastereoselectively at the less substituted double bond with the ester group orienting onto the convex face of the bicyclic adduct **73** in upto 54% yield and 91% *ee*. (Scheme 26). The enantiopurity was improved to >99% *ee* by a single recrystallization from *n*-pentane/dichloromethane. It was observed that the chemical yield of **73** was dependant on addition time and concentration of ethyl diazoacetate **82**. When 1.0 equivalent of ethyl diazoacetate **82** was added the bicyclic aduct **73** was obtained in 36% yield. When an excess (1.5-2.67 equiv.) of ethyl diazoacetate **82** was added the yield improved. An optimum was found with 2.67 equivalent of ethyl diazoacetate **82** under slow addition to give **73** in 54% yield. Upon ozonolysis the double bond of bicyclic adduct **73** followed by reductive workup with DMS gave the highly functionalized 1, 2, 3-trisubstituted cyclopropanecarbaldehyde **72** in 94% yield.



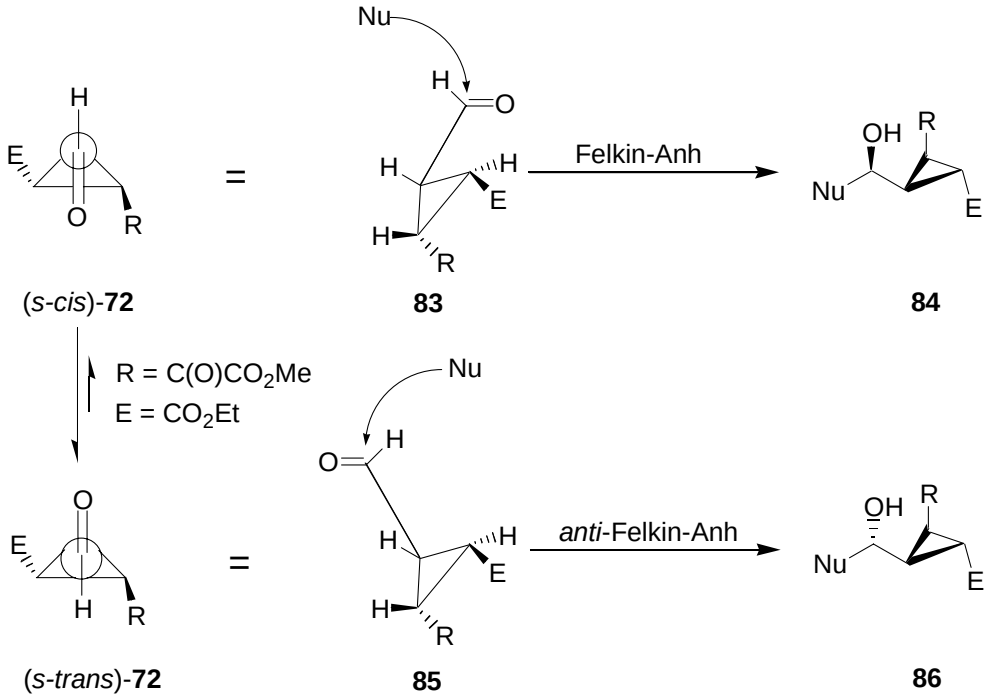
52 **82** **73** **72**

Reagent and Conditions: a) **79** (0.8 mol%), $Cu(OTf)_2$ (0.66 mol%), $PhNHNH_2$ (0.9 mol%), **82** (2.67 equiv.), CH_2Cl_2, 0 °C, 5 days, 54%, 91% *ee*; recrystallization from *n*-pentane/ dichloromethane (20:1) at –27 °C, 38%, >99% *ee*; b) O_3, DMS (5.0 equiv.), CH_2Cl_2, –78 °C to RT, 22 h, 94%.

Scheme 26. Enantioselective cyclopropanation of **52** and Ozonolysis of **73**.

1.1.3 Sakurai allylation and retroaldol-lactonization

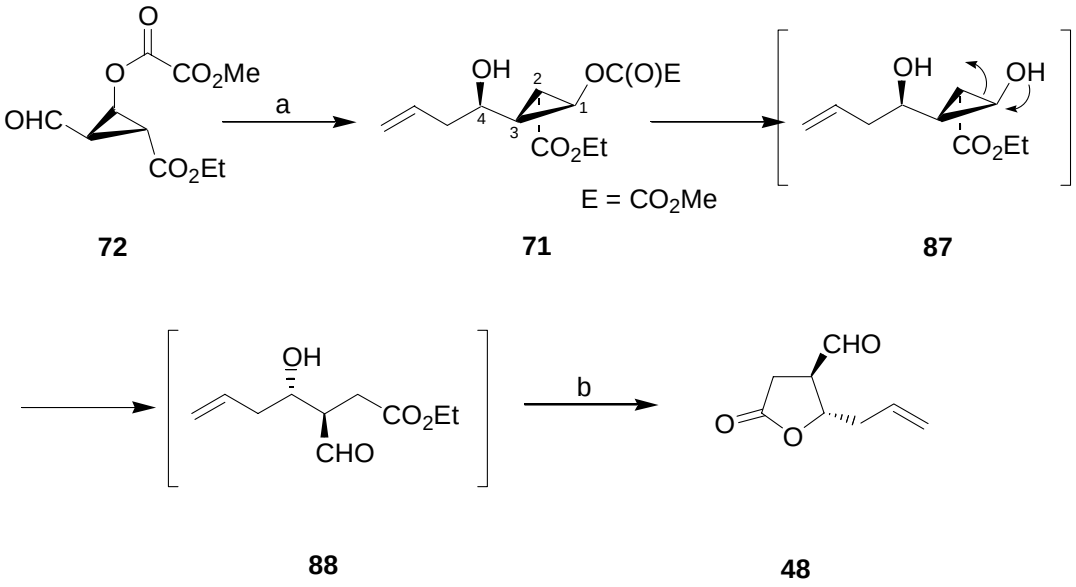
The stereoselectivity in the addition of nucleophiles to α-chiral carbonyl compound was postulated by *D. J. Cram*[60] and the idea was improved by *Felkin and Anh.*[60] Due to stereoelectronic reasons, cyclopropyl-substituted carbonyl compounds are most stable in bisected conformations. On the basis of this preference, a model was postulated by *S. Satoshi* for the nucleophilic attack to α-chiral cyclopropyl carbaldehydes.[61a] Of the two possible bisected conformations, the *s-cis* conformation **72** is disfavoured in cyclopropyl carbaldehydes because of steric interections with the cyclopropyl moiety (Scheme 27). The attack of the nucleophile is therefore thought to occur in the preferred *s-trans* conformation **72** of the cyclopropyl compound from the sterically less shielded side, predicting **86** is the major diastereomer. However, in this case, the trajectory of the nucleophile is interfering with the cyclopropane ring corresponding to an *anti*-Felkin-Anh attack. But in accordance with the Felkin-Anh rule, one would postulate a transition state resulting from the conformation **83** as most favorable, giving rise to **84** as the major diastereomer[62a] which is indeed the experimentally observed result.[54,62b] Based on these results, *S. Satoshi* and co-workers recently revised their model.[61b]



Scheme 27. Transition state of the nucleophilic attack to substituted cyclopropyl carbaldehyde.

1.1.3.1 Addition of allyl trimethyl silane and retroaldol-lactonization

The nucleophile, allyltrimethyl silane was added to cyclopropyl carbaldehyde **72** selectively to give **71** following the Felkin-Anh rule.[62] The cyclopropane **71** has several interesting characteristics that prove useful for further synthetic transformations. The hydroxy group at C-4, which was created by addition of the allyltrimethylsilane, is located in a γ-position to the ester group at C-2 of the cyclopropane moiety, Furthermore, the vicinal donor-acceptor relationship between the hydroxyl group at C-1 and the ester group at C-2 should make ring opening of the cyclopropane feasible.[63] These two features opened up the possibility to develope a retroaldol/lactonization sequences of **71** to *trans*-disubstituted γ-butyrolactone **48**. The ring opening of **71** occured in the presence of barium hydroxide followed by retroaldol reaction to give homoaldolderivative **88** which undergoes lactonization to give **48** in a single step (Scheme 28), having a unprotected aldehyde group available for further synthetic transformation.



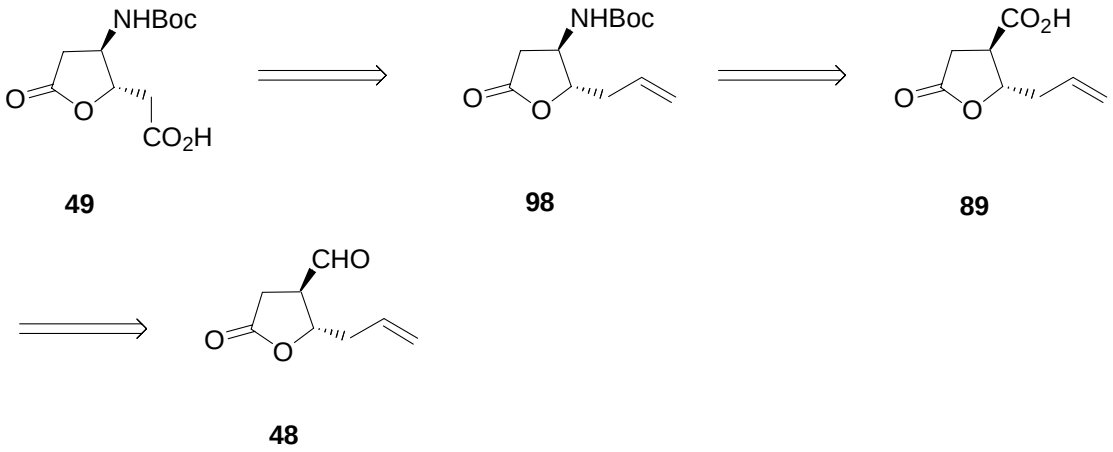
Reagent and Conditions: a) Allyltrimethylsilane (1.1 equiv.), $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2, –78 °C, 12 h, *dr*. 95:5; b) $Ba(OH)_2{\cdot}8H_2O$ (1.1 equiv.), MeOH, 0 °C, 5 h, 67%, *dr*. 95:5.

Scheme 28. Synthesis of *trans*-disubstituted *γ*-butyrolactonaldehyde **48** from cyclopropane carbaldehyde **72** via Sakurai allylation.

1.2 Synthesis of γ-amino acid

1.2.1 Synthetic strategy of γ-amino acid

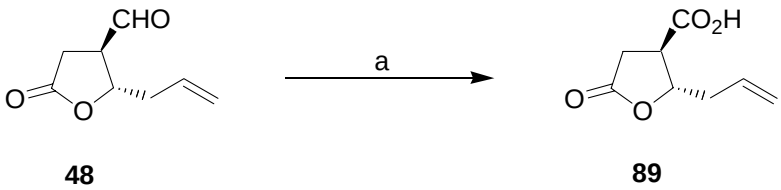
The γ-amino acid **49** was envisioned to be synthesized from γ-butyrolactonaldehyde **48** (Scheme 29) by oxidation of the aldehyde group, followed by Curtius rearrangement, and oxidative cleavage of the allylic double bond as the key steps.



Scheme 29. Retrosynthetic strategy of γ-amino acid **49**.

1.2.2 Oxidation of γ-butyrolactonaldehyde

The aldehyde group of lactone **48** was oxidized by using known methodology.[66] When γ-butyrolactone **48** was treated with $NaClO_2$, KH_2PO_4 and 30% H_2O_2 in acetonitrile at 0 °C to give the corresponding acid **89** (Scheme 30) in 87% yield.



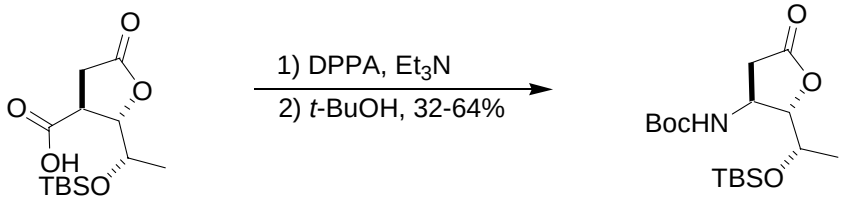
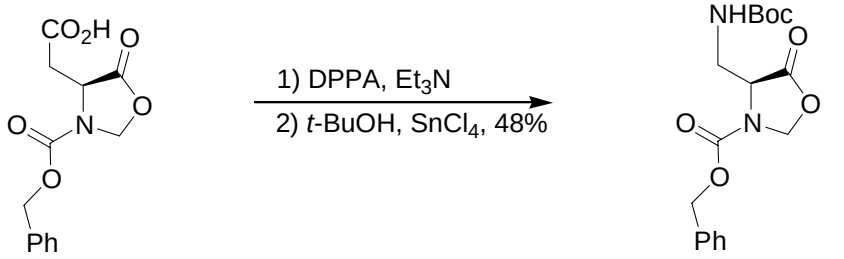
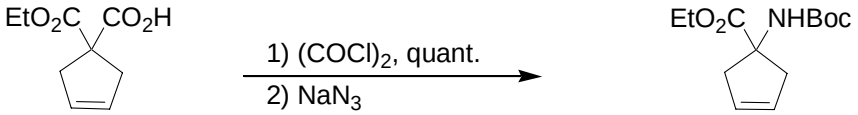
Reagent and Conditions: a) *i*) $NaClO_2$ (0.6 equiv.), KH_2PO_4 (0.6 equiv.), 30% H_2O_2 (1.6 equiv.), CH_3CN, 4.0 h, 0 °C; *ii*) Na_2SO_3, 1.5 h, 0 °C; *iii*) $KHSO_4$, pH 2, 87%.

Scheme 30. Synthesis of acid **89** from γ-butyrolactonaldehyde **48**.

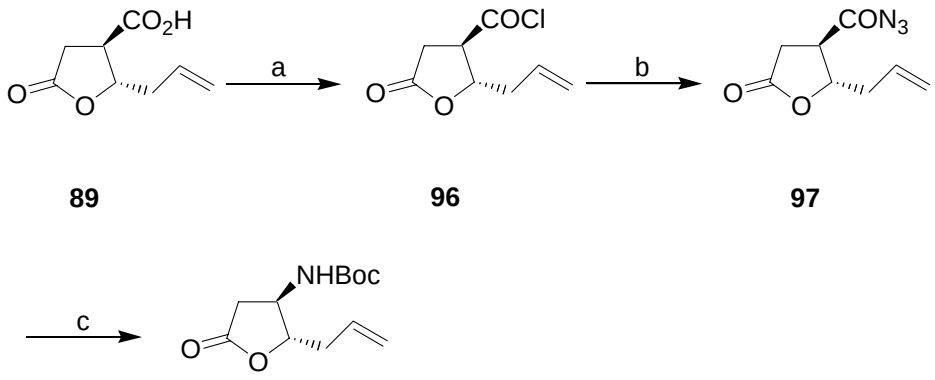
1.2.3 Curtius rearrangement

The key step for *γ*-amino acid **49** synthesis was the synthesis of the carbamate **98** using the Curtius rearrangement.[64] Curtius rearrangement has an valuable aspects in organic synthesis (Table 1).[67]

Table 1. Some examples of Curtius rearrangement

Entry	Reactions
1[67a]	 **90** **91**
2[67b]	 **92** **93**
3[67c]	 **94** **95**

Hodgson et al.[67c] reported that the Lewis acid mediated Curtius rearrangement of acid **94** to give correseponding amino compound **95** in 71% yield (Table 1, entry 3). Following this protocol the acid **89** was treated with oxalyl chloride to give acid chloride **96** in 99% (crude) yield, which was converted to azide **97** in 98% (crude) yield in the presence of NaN_3. Then the azide **97** was subsequently treated with *t*-BuOH and catalytic amount of $SnCl_4$, however **98** was obtained in only 28% yield over 3 steps (Scheme 31). Due to low chemical yield of carbamate **98** the DPPA protocol[67a] was tested as an alternative for the synthesis of carbamate **98**.

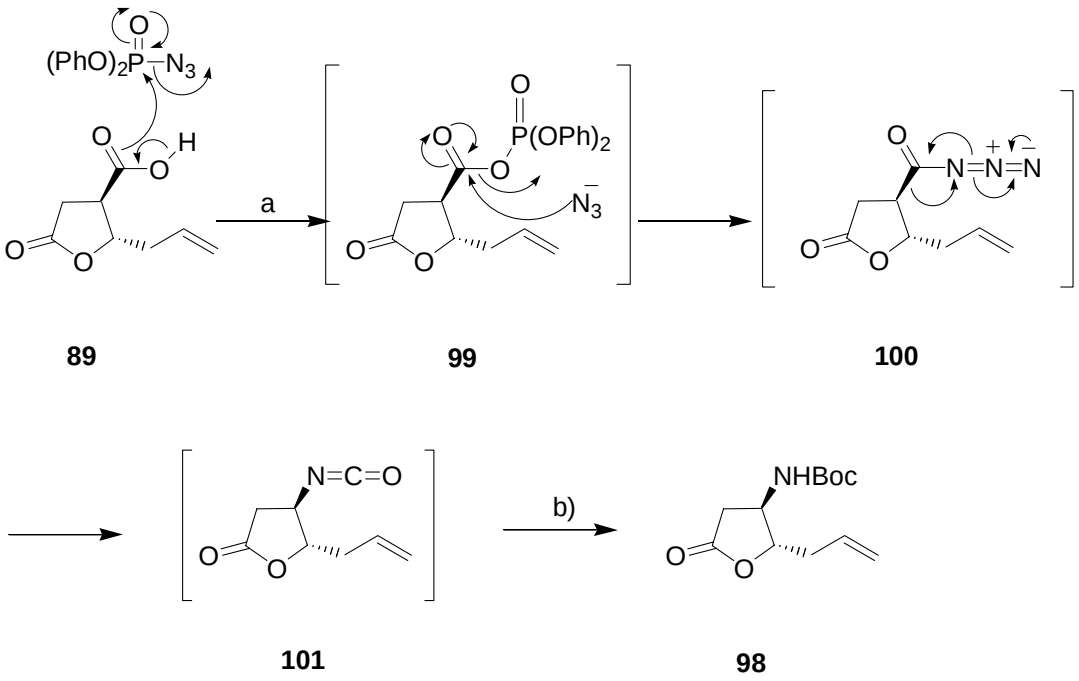


Reagent and Conditions: a) Oxalyl chloride (1.2 equiv.), DMF (cat.), CH_2Cl_2, 20 h, RT 99% (crude); b) NaN_3 (1.6 equiv.), Acetone/H_2O, 1 h, 0 °C, 98% (crude); c) abs. *t*-BuOH, $SnCl_4$ (cat.), 17 h, 28% (3 steps).

Scheme 31. Synthesis of carbamate **98** in the presence of Lewis acid.

Curtius rearrangement with DPPA

Diphenylphosphoryl azide (DPPA) has been established as a reagent of choice for the preparation of acyl azides from carboxylic acids.[65] It has been established in the literature that the conversion of an acid to the corresponding amino compound requires refluxing an equimolar mixture of the carboxylic acid, DPPA and Et_3N in the presence of alcohol (2.0 equiv.). However applying this protocol to acid **89,** the carbamate **98** was obtained in only 28% yield. Following preceded by *Sibi et al*.[67a] it was found that when the reaction was carried out in a mixed solvent with equal amounts of toluene and *t*-BuOH at elevated temperature (120 °C), the chemical yield of the desired carbamate **98** increased dramatically upto 51%. (Scheme 32).

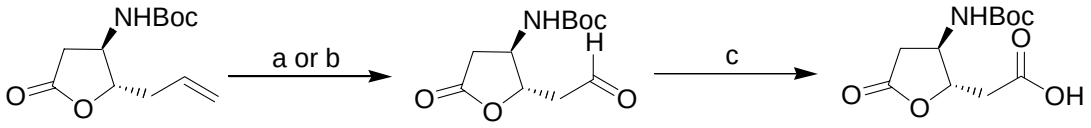


Reagent and Conditions: a) Et_3N (1.15 equiv.), DPPA (1.1 equiv.), Toluene; b) *t*-BuOH, reflux, overnight, 51%.

Scheme 32. Curtius rearrangement for the synthesis of carbamate **98** in the presence of DPPA.

1.2.4 Oxidative cleavage of the allylic double bond

Oxidations of C=C double bond to ketones, aldehydes or carboxylic acids are fundamental transformations in synthetic organic chemistry. Many reagents are known for these conversions such as $KMnO_4$,[86] OsO_4,[87] O_3,[88] $RuCl_3/NaIO_4$.[76] When the carbamate **98** was treated with O_3 at –78 °C followed by reductive workup with DMS it was observed that resulting aldehyde **102** was not stable on chromatography. Therefore, the crude aldehyde **102** was oxidized *in situ* in the presence of $NaClO_2$, KH_2PO_4 and 30% H_2O_2 to give *γ*-amino acid **49** in 32% yield over 2 steps (Scheme 33). It was also carried out another oxidising agent OsO_4[87] in the presence of $NaIO_4$ in dioxane/H_2O which gave same result. Due to low chemical yield of *γ*-amino acid **49**, $RuCl_3$[76] was found as a good alternative for the synthesis of *γ*-amino acid **49**.



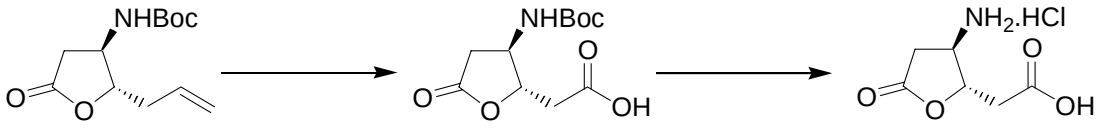
98 **102** **49**

Reagent and Conditions: a) O_3, DMS, CH_2Cl_2, −78 °C to RT, 21 h, 98% (crude); b) OsO_4 (1.5 mol%), $NaIO_4$ (5.6 equiv.), dioxane/H_2O (3:1), 18 h, 99% (crude); c) *i*) $NaClO_2$ (0.6 equiv.), KH_2PO_4 (0.6 equiv.), 30% H_2O_2 (1.6 equiv.), CH_3CN, 4.0 h, 0 °C; *ii*) Na_2SO_3, 1.5 h, 0 °C; *iii*) $KHSO_4$, pH 2, 32% (two steps).

Scheme 33. Synthesis of *γ*-amino acid **49**.

1.2.5 Ruthenium catalyzed oxidative cleavage of the allylic double bond

The oxidative cleavage of the allylic double bond was done by using the methodology.[76] It was observed that when the carbamate **98** was treated with $NaIO_4$ in the presence of catalytic amount of $RuCl_3{\cdot}3H_2O$ in CH_3CN-CCl_4-H_2O the *γ*-amino acid **49** was obtained in 79% yield (Scheme 34). Deprotection to the free *γ*-amino acid **103**[77] was achieved using saturated HCl in dry ethyl acetate in nearly quantitative yield. The Boc deprotection was also carried out with 10 to 20% TFA in dry CH_2Cl_2. However, in these cases it was observed that the *γ*-amino acid **49** was partially opened on followed to some extent by elimination of water.



98 **49** **103**

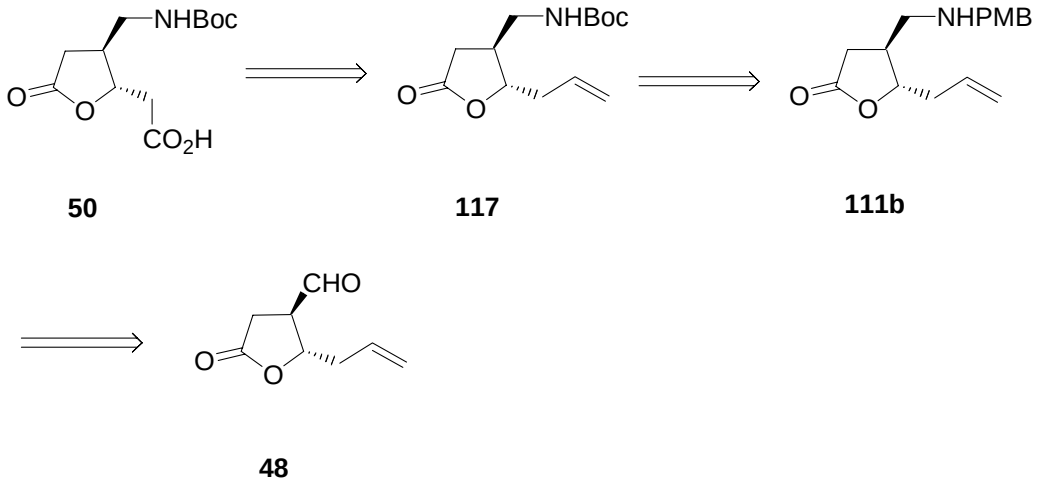
Reagent and Conditions: a) $RuCl_3{\cdot}H_2O$ (6.3 mol%), $NaIO_4$ (4.0 equiv.), CH_3CN-CCl_4-H_2O (1:1:1.5), 42 h, 79%; b) HCl/EtOAc, 0 °C, 3 h, quant.

Scheme 34. Synthesis of Boc-substituted *γ*-amino acid **49** and free *γ*-amino acid **103**.

1.3 Synthesis of δ-amino acids

1.3.1 Synthetic strategy of δ-amino acid

The δ-amino acid **50** was envisioned to be synthesized from γ-butyrolactonaldehyde **48** (Scheme 35) by reductive amination and ruthenium catalyzed oxidative cleavage of the allylic double bond as the key steps.

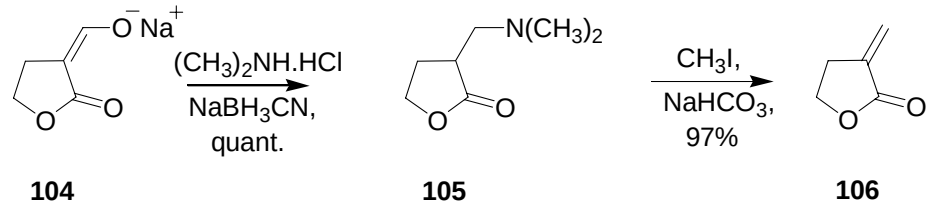
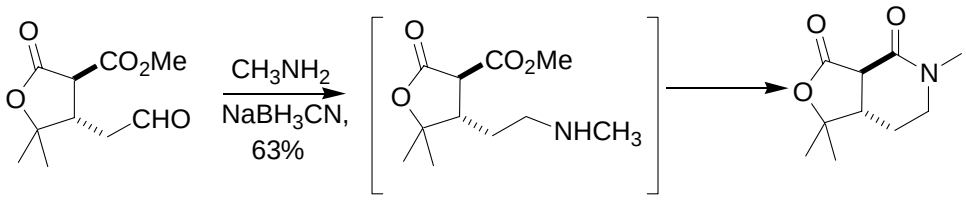


Scheme 35. Retrosynthetic straregy of Boc-δ-amino acid **50**.

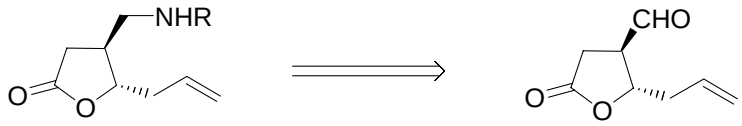
1.3.2 Reductive amination of γ-butyrolactonaldehyde

The reductive amination of aldehyde represents a possible complement to the more conventional approaches toward amine synthesis. Despite the apparent simplicity of the transformation there are few efficient methods currently available for the reductive amination of γ-butyrolactonaldehydes and related compounds. In 1974 *Hutchinson et al.*[70a] synthesized the antifungal agent **106** from α-formyl-γ-butyrolactone **104** with dimethylamine and $NaBH_3CN$ in quantitative yield (Table 2, entry 1). *Matsuo et al.*[70b] also synthesized the alkaloids **109** from **107** by using methylamine and $NaBH_3CN$ in 63% yield (Table 2, entry 2). Generally imines are reduced to amines using reducing agents such as $NaBH_4$,[69] $NaBH_3CN$,[70] Pyridine-Borane,[71] $LiAlH_4$.[69]

Table 2. Some examples of reductive amination.

Entry	Reactions
1[70a]	 **104** **105** **106**
2[70b]	 **107** **108** **109**

By applying above concept a simple and mild reductive amination protocol was developed for the synthesis of **111** from *γ*-butyrolactonaldehyde **48** (Scheme 36).

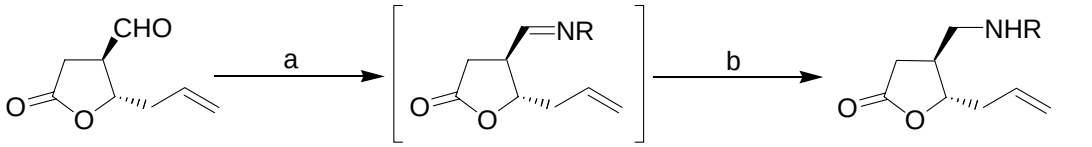


111 **48**

Scheme 36. Retrosynthetic strategy for reductive amination of *γ*-butyrolactonaldehyde **48**.

1.3.2.1 Reductive amination with 4-Methoxybenzylamine

The reductive amination of *γ*-butyrolactonaldehyde **48** with benzylamine or 4-methoxybenzylamine in CH_2Cl_2 gave the corresponding imine **110**, which was reduced to amine **111** in 89% yield by using $NaBH_4$ and MeOH (Scheme 37). While the reductive amination was run in CH_2Cl_2 it was observed that the subsequent reduction of the imines was significantly faster in MeOH. The corresponding amine (ent)-**111b** was also synthesized from *γ*-butyrolactonaldehyde (ent)-**48**, which was used in synthesis of PNA analogues (Chapter 3).



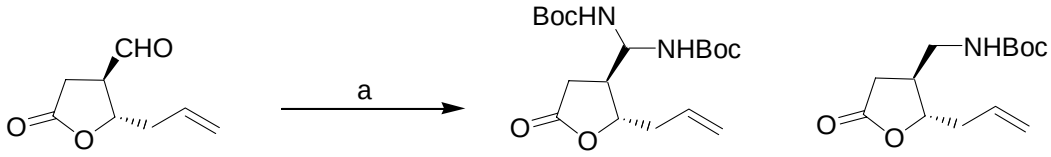
48 **110a:** R = $PhCH_2$ **111a:** R = $PhCH_2$
110b: R = 4-MeO-$PhCH_2$ **111b:** R = 4-MeO-$PhCH_2$

Reagent and Conditions: a) 4-MeO-$PhCH_2$-NH_2 (1.3 equiv.), 4 Å molecular sieve, CH_2Cl_2, RT, 15 h.; b) $NaBH_4$ (2.0 equiv.), MeOH, H_2O, 0°C, 80 min, 89%.

Scheme 37. Reductive amination of γ-butyrolactonaldehyde **48** with 4-methoxy-benzylamine or benzylamine.

1.3.3 Reductive *N*-alkylation of aldehyde with TFE/Et_3SiH

In 1999 *Dube et al.*[72] reported that a variety of aldehydes (aromatic and aliphatic), amides and other analogs like thioamides, carbamates and ureas can be mono N-alkylated products by using TFA/Et_3SiH in good yields. However, applying this protocol to γ-butyrolactonaldehyde **48** by treatment with Boc-amine (3.0 equiv.), Et_3SiH (3.0 equiv.) and TFA (2.0 equiv.) in CH_3CN an undesirable compound **112** was obtained in 65% yield with no observable formation of *N*-alkylated compound **113**. To minimize this problem, the reaction was carried out with 1.0 equivalent of Boc-amine which also gave **112** in only 31% yield (Scheme 38).



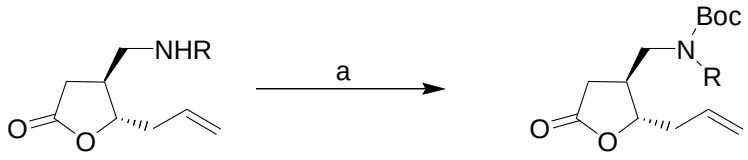
48 **112** **113**

Reagent and Conditions: a) *t*-$BuOCONH_2$ (3.0 equiv.), Et_3SiH (3.0 equiv.), TFE (3.0 equiv.), CH_3CN, RT, 20 h, 65%.

Scheme 38. Reductive amination of γ-butyrolactonaldehyde **48** with Boc amine.

1.3.4 Protection of amine 111

The *t*-butoxy carbonyl group is an easily removable protecting group which is useful in the synthesis of peptide in solution phase, therefore, the amine **111** was protected with a *t*-butoxy carbonyl group.[92] When the amine **111** was treated with di-*tert*-butyldicarbonate and catalytic amounts of DMAP the protected amine **114** were obtained in 71% yield (Scheme 39). It was observed that the reaction also proceeds in the absence of DMAP but longer reaction time were necessary and the yield was also lower by 15%.



111

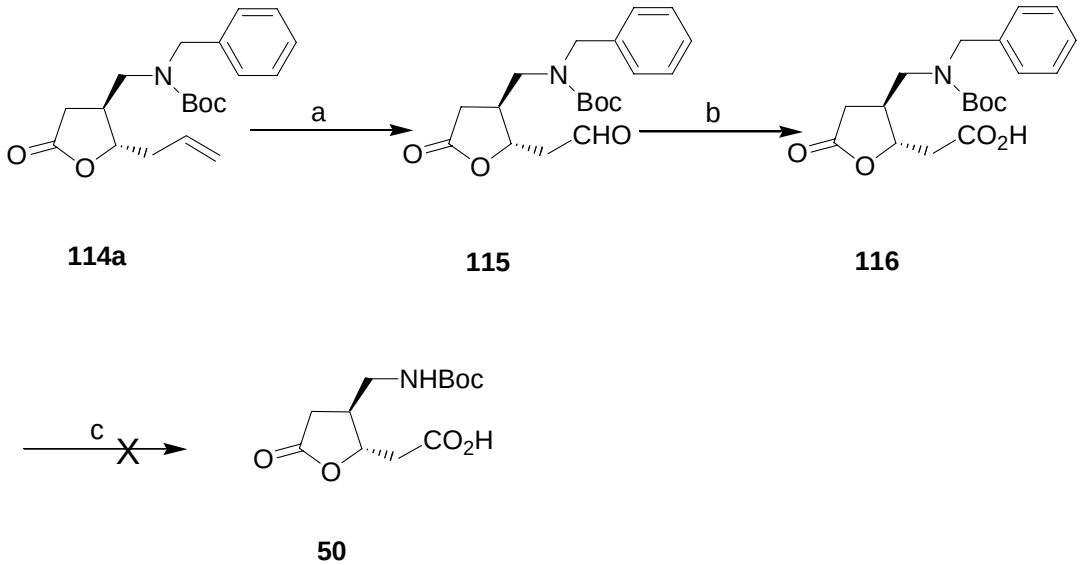
114a: R = $PhCH_2$
114b: R = 4-MeO-$PhCH_2$

Reagent and Conditions: a) $(Boc)_2O$ (2.0 equiv.), DMAP (cat.), CH_2Cl_2, RT, 36 h, 71%.

Scheme 39. Boc protection of amine **111**.

1.3.5 Oxidation of allylic double bond

The protected amine **114a** was treated with O_3 at –78 °C followed by reductive workup with DMS at room temperature for 21 h to give aldehyde **115**. It was observed that aldehyde **115** was not stable on chromatography. Therefore, the crude aldehyde **115** was oxidized *in situ* in the presence of $NaClO_2$, KH_2PO_4 and 30% H_2O_2 to give the substituted δ-amino acid **116** in 36% yield (Scheme 40). To obtain the free amino acid **50**, however, deprotection of the benzyl group turned out to be problematic, which was carried out under various hydrogenation protocols even under high pressure (70 bar) unsuccessfully. Due to this problem the PMB group was found as an alternative to the benzyl group which could be easily deprotected by CAN in high yield.

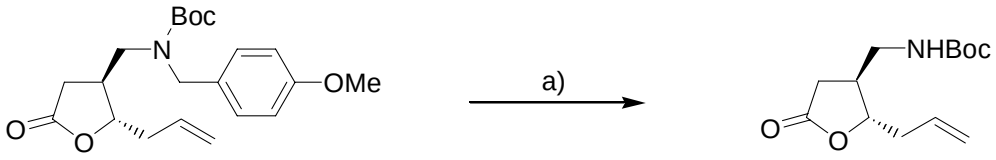


Reagent and Conditions: a) O_3, DMS, CH_2Cl_2, –78 °C to RT, 21 h, 98% (crude); b) *i*) $NaClO_2$ (0.6 equiv.), KH_2PO_4 (0.6 equiv.), 30% H_2O_2 (1.6 equiv.), CH_3CN, 4.0 h, 0 °C; *ii*) Na_2SO_3, 1.5 h, 0 °C; *iii*) $KHSO_4$, pH 2, 36% (over two steps); c) Pd-C, MeOH; Pd-C, MeOH, 5 to 70 bar, 40 °C; $Pd(OH)_2$, MeOH; $Pd(OH)_2$, 5 to 70 bar, 40 °C.

Scheme 40. Synthesis of δ-amino acid **50**.

1.3.6 Deprotection of PMB group by CAN

The PMB group of **114b** was oxidatively removed by using methodology developed by Yoshimura.[73] The fully protected amine **114b** was treated with CAN (3.5 equiv.) in CH_3CN-H_2O gave corresponding amine **117** in upto 94% yield (Scheme 41). It was observed that this reaction was influenced by reaction time and concentration of CAN. It was found that the oxidation of **114b** in aqueous acetonitrile with 1.0 equivalent of CAN gave **117** in only 45% yield. To optimize the conditions the reaction was carried out under various concentration (2 - 3.5 equiv.) of CAN under various time. Finally, it was found that when the amine **114b** was treated with 3.5 equiv. of CAN in 2 h gave best (94%) yield.



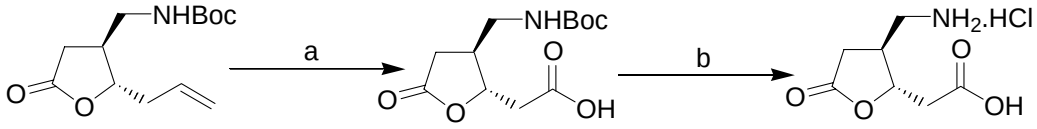
114b **117**

Reagent and Conditions: a) CAN (3.5 equiv.), CH_3CN-H_2O (3:1), 0 °C, 2 h, 94%.

Scheme 41. Deprotection of PMB group by using CAN.

1.3.7 Ruthenium catalyzed oxidative cleavage of the allylic double bond

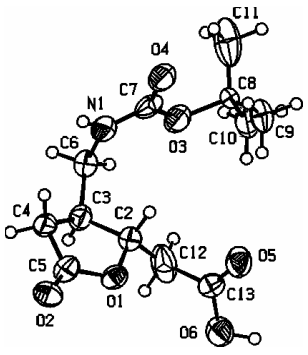
For the synthesis of δ-amino acid **50,** ruthenium catalyzed[76] oxidative cleavage of the allylic double bond of **117** has been done by using γ-amino acid protocol (Scheme 34) in 81% yield (Scheme 42) and the free amino acid **118** was achieved by using saturated HCl in dry ethyl acetate in nearly quantitative yield.



117 **50** **118**

Reagent and Conditions: a) $NaIO_4$ (4.0 equiv.), $RuCl_3 \cdot H_2O$ (6.3 mol%), CH_3CN-CCl_4-H_2O (1:1:1.5), 36 h, 81%; b) HCl/EtOAc, 0 °C, 3 h, quant.

Scheme 42. Synthesis of Boc-substituted δ-amino acid **50** and free δ-amino acid **118**.



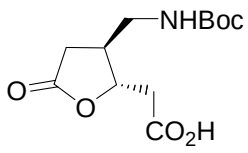
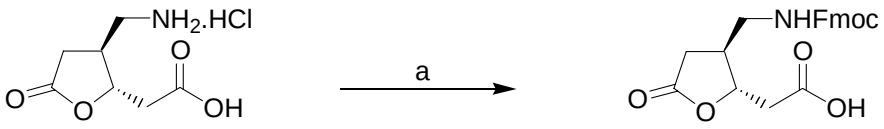


Figure 1. Crystal structure of Boc-δ-amino acid **50**.

1.4 Synthesis of Fmoc protected δ-amino acid

The Fmoc protected δ-amino acid **119** was synthesized using the methodology developed by *Rosowsky*.[74] When **118** was treated with 9-fluorenylmethyl chloroformate in dioxane-1M K_2CO_3 the corresponding Fmoc protected amino acid **119** was afforded in 67% yield (Scheme 43). This reaction was also carried out by the methodology developed by *Chamber et al.*,[75] but when **118** was treated with 9-fluorenylmethyl chloroformate in dry pyridine the protected amine **119** was obtained in only 50% yield.



118 **119**

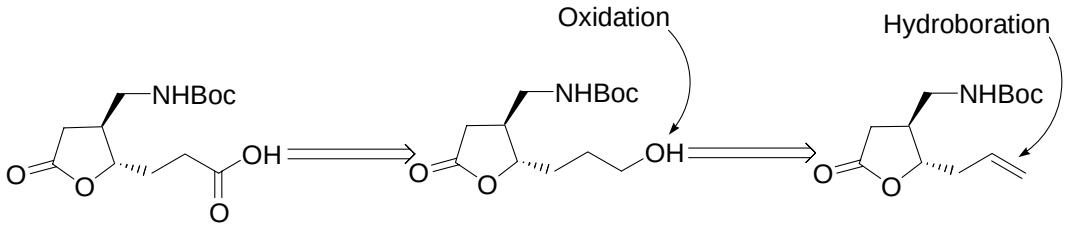
Reagent and Conditions: a) Fmoc-Cl (1.1 equiv.), dioxane- 1M K_2CO_3 (1:2), 0 °C to RT, 67%.

Scheme 43. Synthesis of Fmoc protected δ-amino acid **119**.

1.5 Synthesis of ε-amino acid

1.5.1 Synthetic strategy of ε-amino acid

The ε-amino acid **51** was envisioned to be synthesized from the carbamate **117** (Scheme 44) using a hydroboration of allylic double bond and oxidation as the key steps.

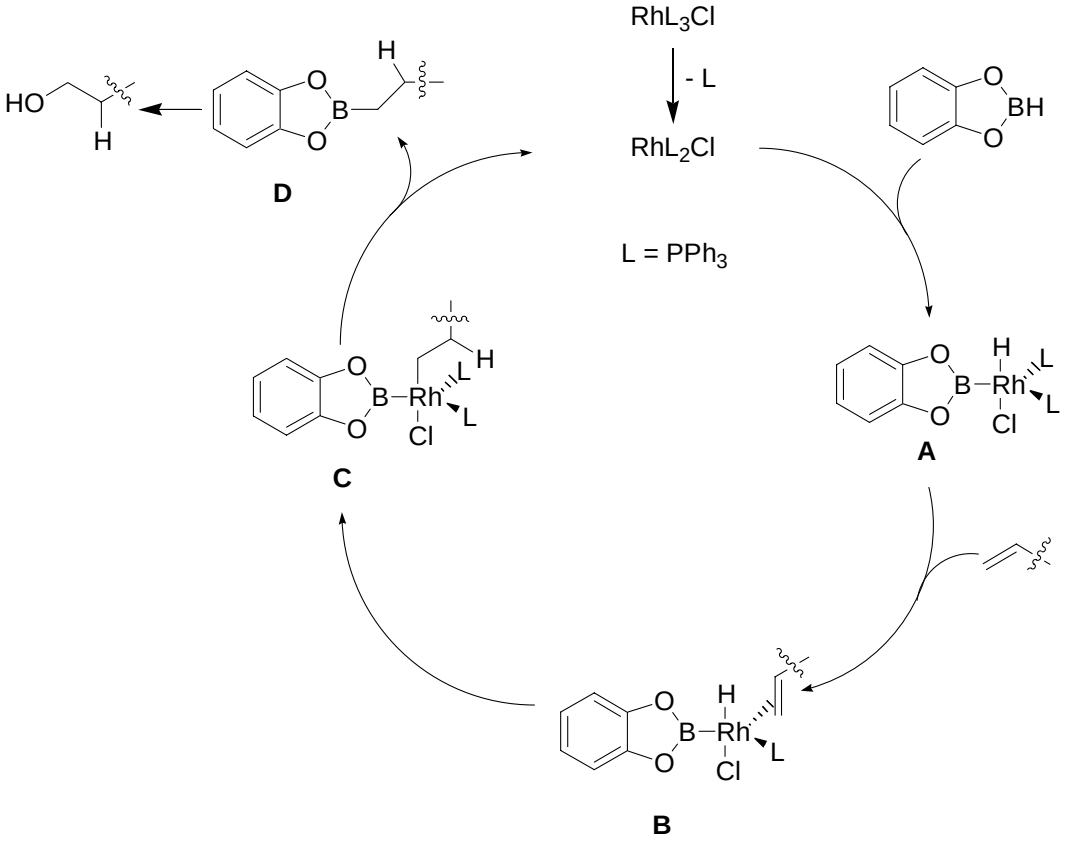


51 **123** **117**

Scheme 44. Retrosynthetic strategy of ε-amino acid **51.**

1.5.2 Hydroboration of allylic double bond

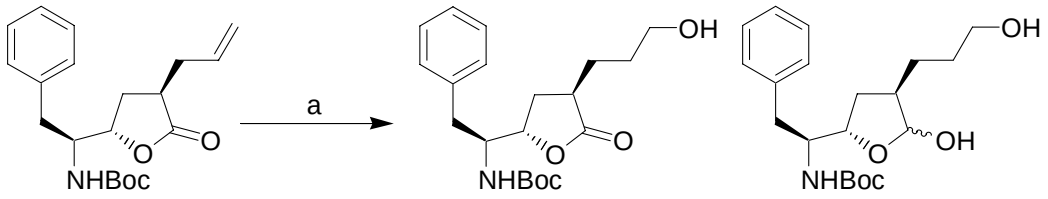
The transition metal catalyzed hydroboration of double bond represent a possible complement to the more conventional approaches towards regioselective alcohol synthesis. Despite the apparent simplicity of the transformation there are few efficient methods currently available for the rhodium-catalyzed olefin addition reactions.[78] The reaction mechanism of the rhodium-catalyzed hydroboration is proposed[78] (Scheme 45). **A** is formed by the oxidative addition of RhL_2Cl and catecholborane. Coordination of the alkene to **B** followed by addition and to form complex **C** which undergoes reductive elimination to regenerate RhL_2Cl and alkylboronate **D**, which is converted to alcohol via oxidation.



Scheme 45. Mechanism of the $Rh(Ph_3P)_3Cl$-catalyzed hydroboration of allylic double bond with catecholborane.

Daniel H. Rich.[79] reported that conversions of lactone **120** to alcohol **121** by hydroboration using disiamylborane, 9-BBN, dicyclohexylborane and (*S*)-alpineborane followed by oxidation is problematic. They found low yield due to competitive

reduction of the γ-lactone to its corresponding hemiacetal **122**. However, they found that the rhodium catalyzed hydroboration using catecholborane followed by oxidation gave alcohol **121** in 70% yield with no observable formation of **122** (Scheme 46).

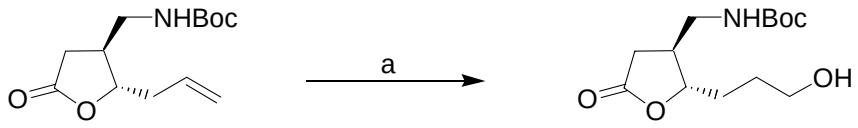


120 **121** **122**

Reagent and Conditions: a) $Rh(Ph_3P)_3Cl$, catecholborane, THF, 0 °C, then RT, 30 min; 30% H_2O_2, THF:EtOH (1:1), pH 7.2 buffer, RT, overnight, 70%.

Scheme 46. $Rh(Ph_3P)_3Cl$ catalyzed hydroboration using catecholborane by *Rich et al.*[79]

Following this protocol, when the carbamate **117** was treated with freshly prepared catecholborane[89] in the presence of $Rh(Ph_3P)_3Cl$ followed by oxidation with 30% H_2O_2 the primary alcohol **123** was obtained in 71% yield (Scheme 47).



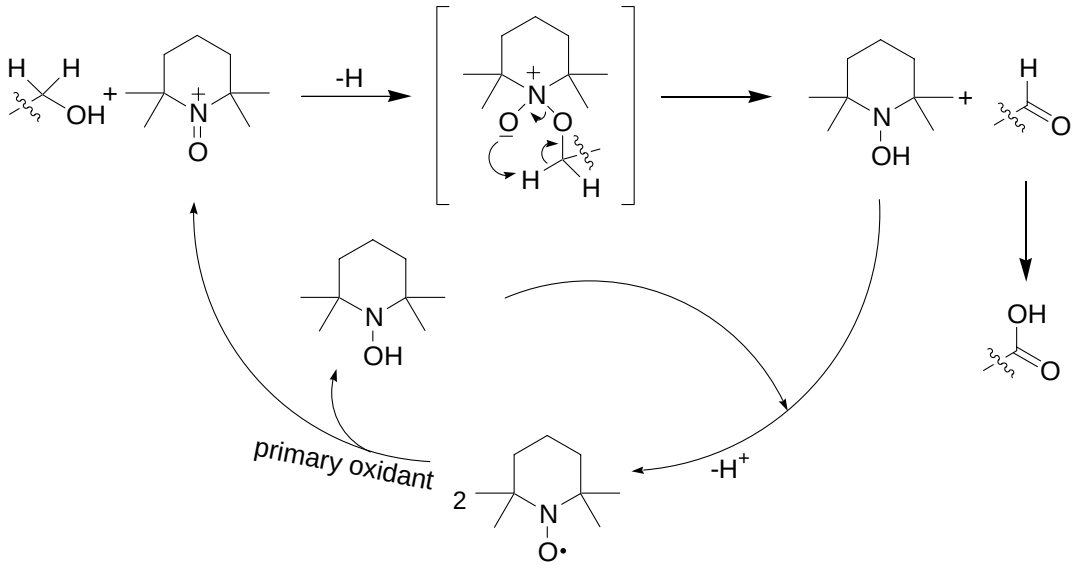
117 **123**

Reagent and Conditions: a) i) $Rh(Ph_3P)_3Cl$ (2.0 mol%), catecholborane (1.1 equiv.), THF, 0 °C, 45 min; ii) 30% H_2O_2, phosphatbuffer (pH 7.2), THF:EtOH (1:1), RT, overnight, 71%.

Scheme 47. $Rh(Ph_3P)_3Cl$-catalyzed hydroboration of allylic double bond with catecholborane.

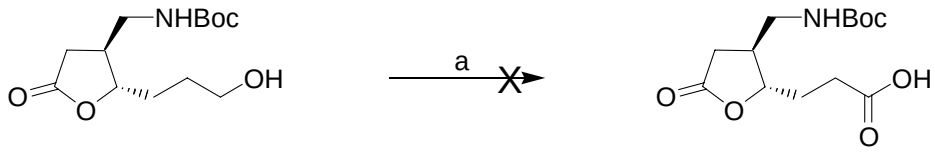
1.5.3 TEMPO mediated Oxidation of Primary alcohol

Oxidations of alcohols to ketones, aldehydes or carboxylic acids are fundamental transformations in synthetic organic chemistry. Many reagents are known for these conversions such as chromium (vi) oxides,[80] dipyridine chromium (vi) oxides,[81] pyridinium chlorochromate.[82] Relatively recent the use of nonconjugated stable organic nitroxyl radicals as catalyst in the oxidation of alcohols was discovered as a promising alternative. Nitroxyl radicals are componds containing the *N*,*N*-disubstituted NO-group with one unpaired electron. The most simple radical of this class, 2,2,6,6-tetramethylpiperidin-1-oxyl more commonly known as TEMPO, was the first nonconjugated nitroxyl radical to be applied. The mechanism of the TEMPO mediate oxidation between the oxoammonium salt and the alcohol is still unclear, but a reaction mechanistic cycle was proposed[83] (Scheme 48). It was also reported that when a primary alcohol was oxidized in an organic solvent, the reaction stops at the aldehyde stage, implying that the oxoammonium salt itself is not able to oxidize an aldehyde but under two phase (organic-aqueous) conditions, hydrophilic substrates were over-oxidized to carboxylic acids.[84]



Scheme 48. Mechanistic cycle of the TEMPO mediated oxidation of primary alcohol **123**.

Following a protocol by *Field and Nepogodiev et al.*[84] when the alcohol **123** was treated with TEMPO, NaOCl and KBr in H_2O could not identify any corresponding acid (Scheme 49), nevertheless, on TLC it was observed that starting material completely disappeared in 2 h. ^{1}H NMR showed some aldehyde and unidentified byproducts.

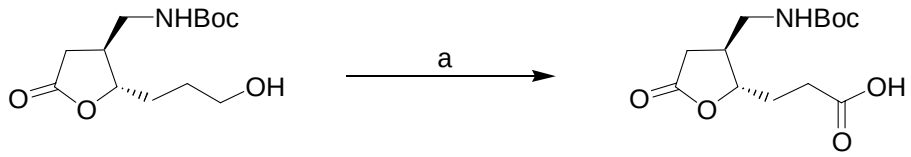


123 **51**

Reagent and Conditions: a) TEMPO (0.06 equiv.), KBr (3.0 equiv.), NaOCl (14 equiv.), acetone, 0 °C , 6 h.

Scheme 49. TEMPO mediated oxidation of alcohol **123** to ε-amino acid **51**.

However, it was found an efficient protocol by *Giacomelli et al.*[85] When the alcohol **123** was treated with 15% $NaHCO_3$, NaBr, TEMPO and trichloroisocyanuric acid the ε-amino acid **51** was obtained in 83% yield (Scheme 50).



123 **51**

Reagent and Conditions: a) 15% $NaHCO_3$, NaBr (0.2 equiv.), TEMPO (0.02 equiv.), trichloroisocyanuric acid (2.0 equiv.), acetone, 0 °C to RT, 6 h, 83%.

Scheme 50. TEMPO mediated oxidation of alcohol **123** to ε-amino acid **51**.

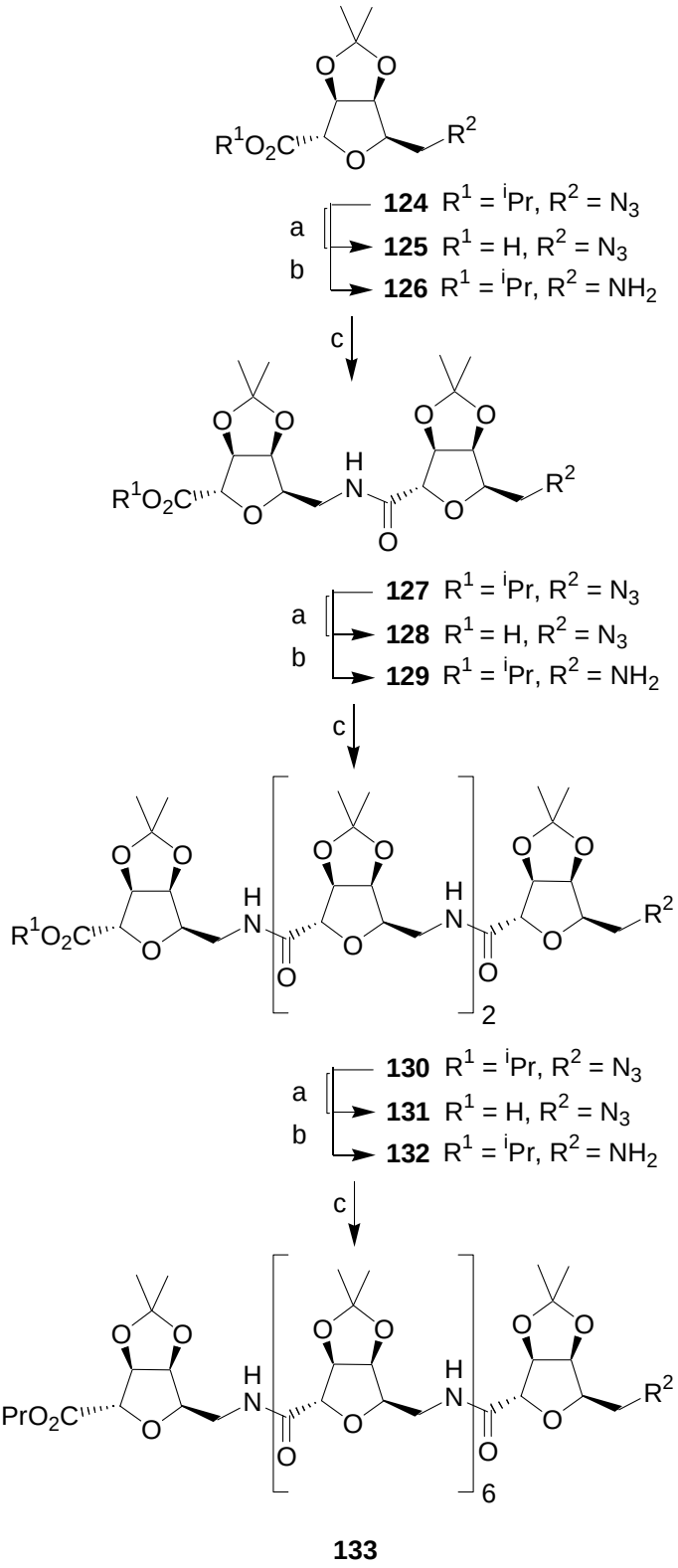
Chapter 2

2.1 Synthesis of Oligopeptide in general

Sugar amino acids constitute an important class of synthetic monomers that have been used recently by several groups to construct oligomeric libraries.[17-31] The development of sugar amino acids as a class of unique building blocks with the facile incorporation of these species, using their carboxyl and amino termini for attachments by well-developed solid- or solution-phase peptide synthesis methods, to make many well defined molecular frameworks.

Since proteins exhibit their biological activity through only small regions of their folded surfaces, their functions could in principle be reproduced in much smaller designed molecules that retain these crucial surfaces. There are many possibilities for modifications, such as introduction of constraints, cyclization, and/or replacement of the peptidic backbone or part of it. Sugar amino acids can adopt robust secondary turn or helical structures and thus may allow one to mimic helices or sheets.[17-27, 95,97]

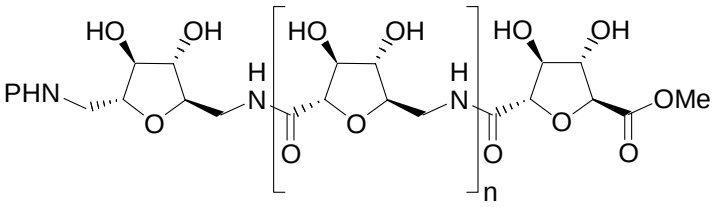
Fleet et al.[17] synthesized tetrameric and octameric chains of *C*-glycosyl α-D-*lyxo*furanose configured tetrahydrofuran amino acids and they observed that the tetramer **130** does not adopt a hydrogen-bonded configuration wherease the octamer **133** populates a well-defined helical secondary structure. They synthesized D-lyxo-configured THF amino acid derivatives **124** via short route from D-galactone.[90] The isopropyl ester **124** was converted to its corresponding acid **125** using aqueous NaOH and amine **126** using hydrogenation in the presence of Pd/C. The acid **125** and the amine **126** were coupled to give the isopropylidene protected dimer **127** in 74% yield. By applying above sequence they synthesized the tetrameric oligomer **130** from dimer **127** and the octamer **133** from tetramer **130** respectively (Scheme 51).



Reagent and Conditions: a) H_2, Pd/C, IPA; b) 0.5 M NaOH (aq), dioxane; then Amberlite IR 120 (H^+); c) EDCI, HOBt, $(i\text{-}Pr)_2NEt$, CH_2Cl_2,

Scheme 51. Carbohydrate amino acid oligomers by *Fleet et al*.

Chakraborty et al.[27] also synthesized oligomers of **41** from sugar amino acid **23** (Scheme 52) by standard solution phase peptide coupling methods in high yield.

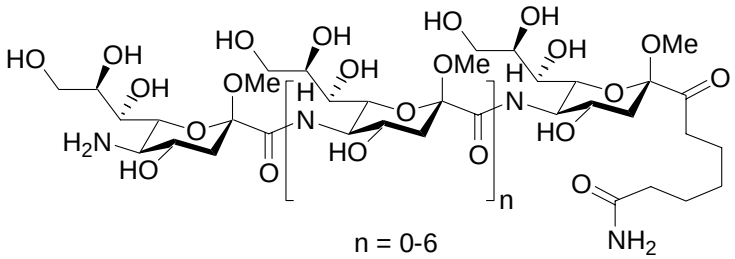


n = 0-6
P = H or Boc

41

Scheme 52. Synthesis of oligomers **41** by *Chakraborty et al.*

Gervay et al.[91] synthesized oligomers **134** (Scheme 53) which were analyzed in solution by NMR and circular dichroism spectroscopy to reveal preferred secondary structures.



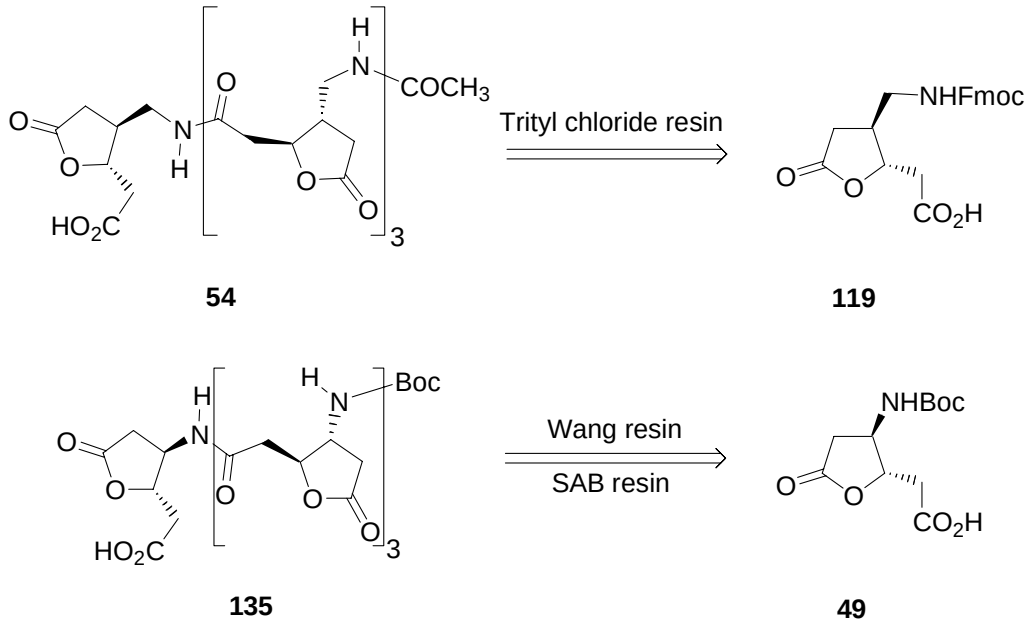
n = 0-6

134

Scheme 53: Sialooligomers **134** by *Gervay et al.*

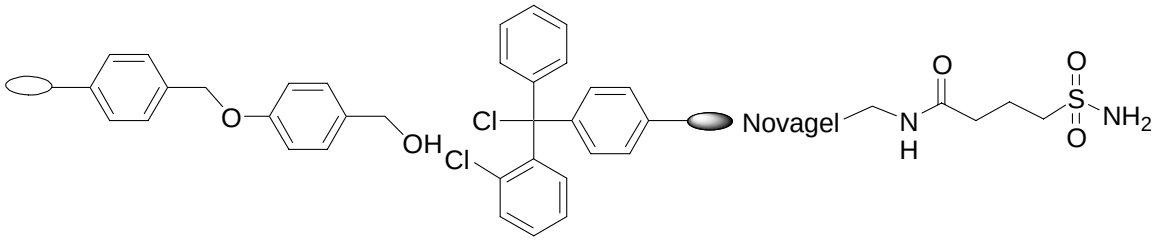
2.1.1 Synthetic strategy for oligopeptide 54 and 135 using solid-phase protocol

The initial work was aimed to the synthesis of tetramer **54** and **135** from Fmoc-δ-amino acid **119** and Boc-γ-amino acid **49** by using solid support such as 2-chlorotrityl chloride, Wang and SAB resin (Scheme 54).



Scheme 54. Retrosynthetic strategy of tetramer **54** and **135** using solid suport.

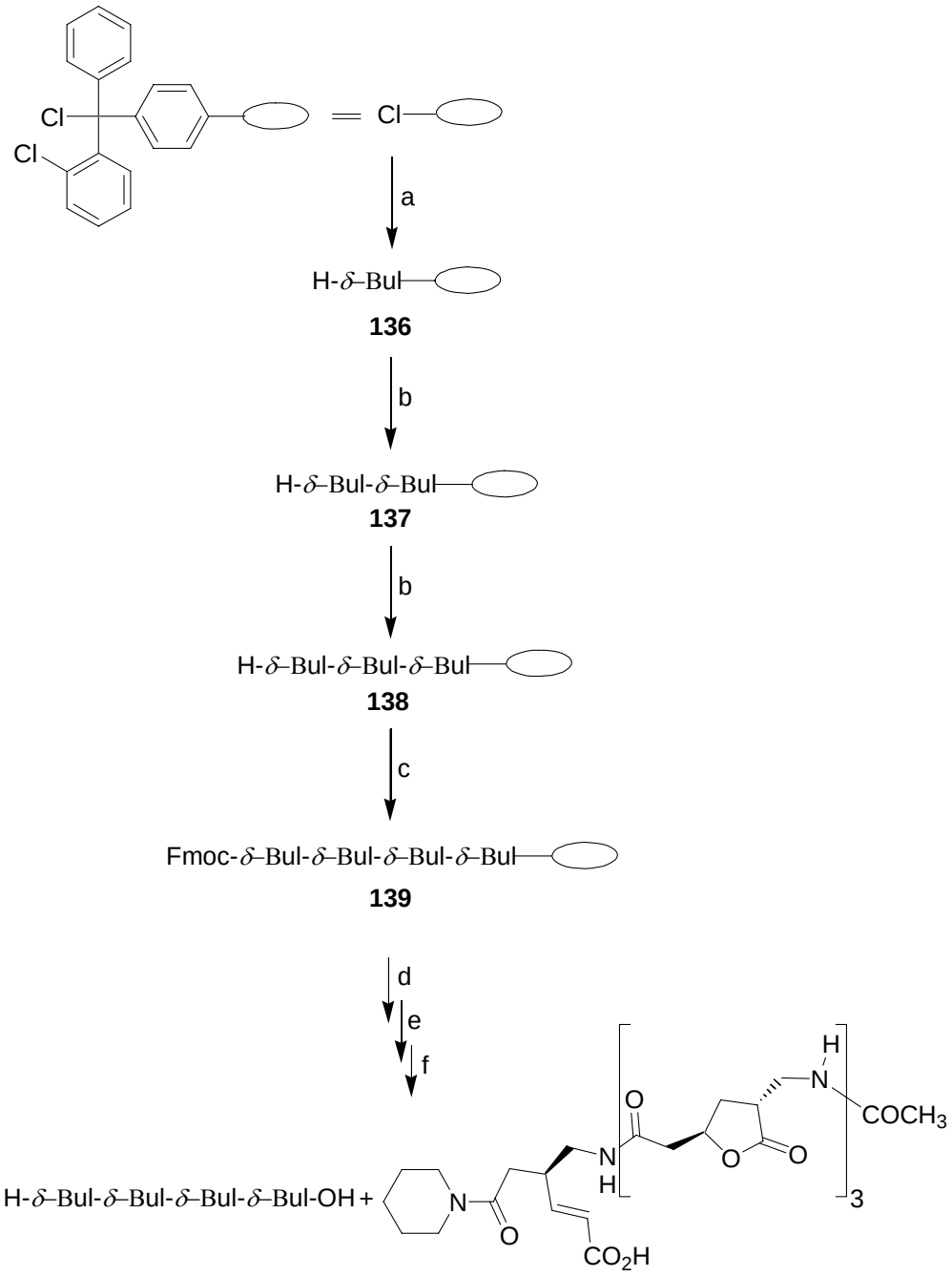
The solid phase synthesis can be performed by two alternative protecting group (PG) strategies: Boc (temporary PG)/Bn (permanent PG) and Fmoc (temporary PG)/Bn (permanent PG). Generally the Boc strategy is less suitable for solid phase synthesis due to highly acidic conditions that are necessary for the cleavage from the resin. In contrast, in the Fmoc strategy the cleavage of the peptide from the resin occurs under milder conditions (50% TFA for Wang linker and 1% TFA for Trityl linker) (Figure 1), and for this reason Fmoc protection is widely used in solid phase synthesis. To make use of the sugar amino acids on a acid labile resins a *N*-protecting group is required to be cleaved under neutral or weakly basic conditions, and the protecting group should also allow *in situ* deprotection or coupling to prevent ring opening of the lactone moiety by the free amino group.



Wang linker 2-Chlorotrityl chloride linker SAB linker

Figure 1. Various types of linkers for solid phase synthesis.

For the solid phase synthesis of **135** and **54**, the first attempt was to load Boc-γ-amino acid **49** on Wang resin and it was found that the loading was in only 0.1 mmol/g (Std. loading 1.13 mmol/g). Alternatively, the SAB resin was also used, but did not improve the loading. However, treatment of Fmoc-δ-amino acid **119** with 2-chlorotrityl chloride PS resin (TrtR-Cl)[92] in the presence of DIPEA provided a better loading of 0.74 mmol/g (Std. loading 1.0-1.6 mmol/g). To obtain *N*-free amino acid **136** the loaded resin was treated with piperidine. Subsequently, **136** was coupled with Fmoc-δ-Bul-amino acid **119**. The synthesis was then continued as usual by cleaving the Fmoc-group and treating with Fmoc-δ-Bul-amino acid **119**. Finally, acetylation of the *N*-terminus and cleavage from the resin using TFA (Scheme 55) to give **54** and **140**. However, on controll by HPLC/MALDI-TOF, it was found that the expected tetramer **54** was the minor product while the unexpected byproduct was the major one, which can be explained by the ring opening of the terminal lactone ring as depicted in **140**. In order to controll each coupling, it was observed that the ring opening problem arises from second coupling.

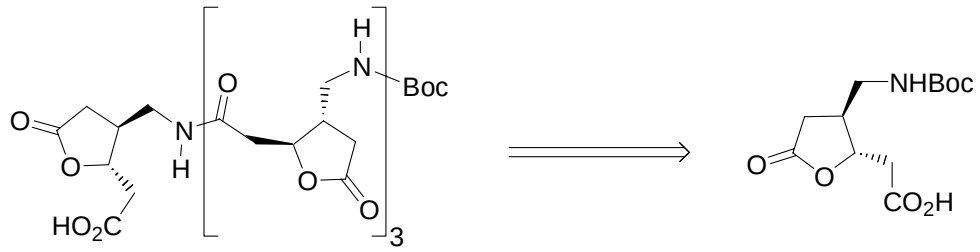


Reagent and conditions: a) i) **119** (1.2 equiv.), DIPEA (6.0 equiv.), DMF, ii) 20% piperidine/DMF; Loading 0.74 mmol/g; b) i) **119** (2.8 equiv.), HOBt/HBTU (3 equiv.), DIPEA (6.0 equiv.), DMF; ii) 20% piperidine/DMF; c) **119** (2.8 equiv.), HOBt/HBTU (3 equiv.), DIPEA (6.0 equiv.), DMF; d) Ac_2O/DIPEA, DMF; e) 20% piperidine/DMF; f) 1% TFA, 5% TIS, CH_2Cl_2.

Scheme 55. Synthesis of tetramer **54** using 2-chlorotrityl chloride resin.

2.1.2 Synthetic strategy of oligopeptide 53 using solution phase protocol

Due to the problems with the solid phase synthesis described above the oligopeptide **53** was envisioned to be synthesized in solution from Boc-δ-amino acid **50** via an iterative peptide coupling procedure using Boc strategy (Scheme 56).

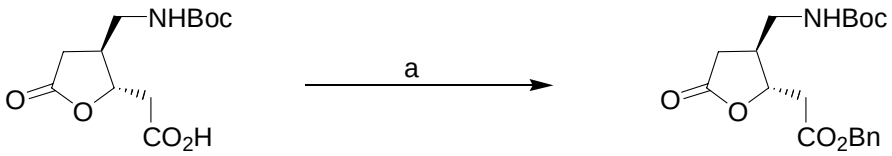


53 **50**

Scheme 56. Retrosynthetic strategy of oligopeptide **53**.

2.1.2.1 Benzyl Protection of Boc-δ-amino acid 50

The initial work was aimed to protect the free carboxylic acid of **50**. Since the benzyl group is an easily removable protecting group therefore the Boc-δ-amino acid **50** was protected with BnBr[93] to give **141** in 70% yield. (Scheme 57).



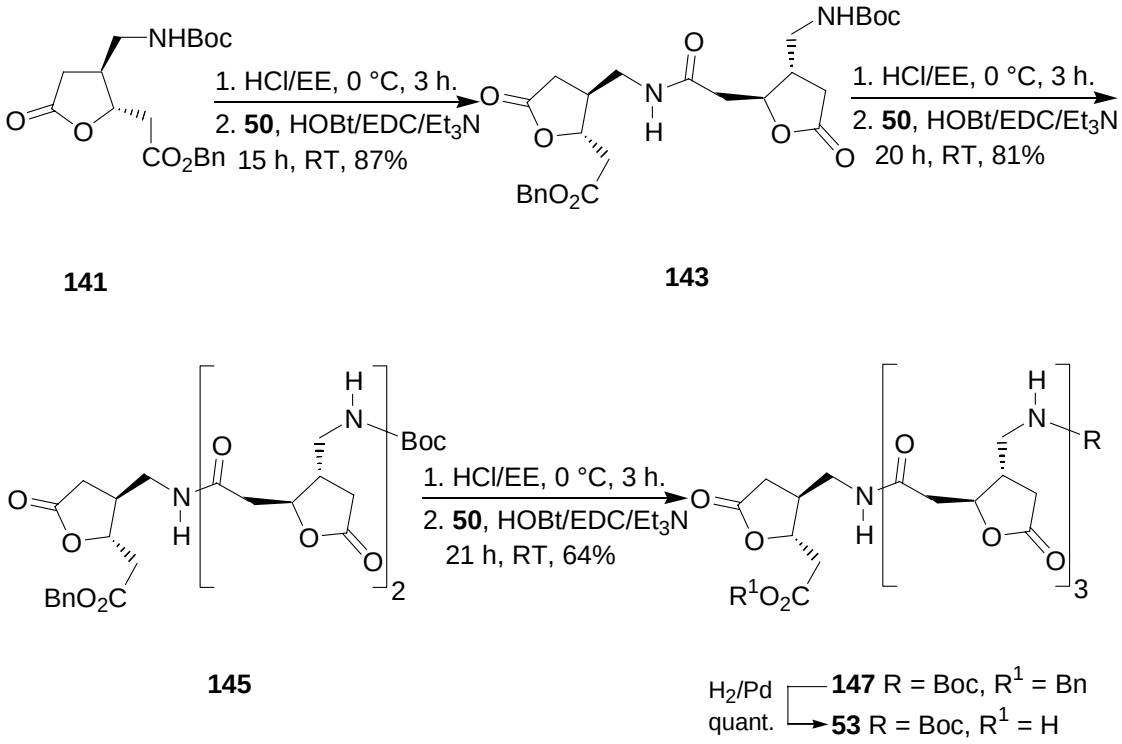
50 **141**

Reagent and Conditions: a) K_2CO_3 (1.8 equiv.), BnBr (1.6 equiv.), DMF, RT, 36 h, 70%.

Scheme 57. Synthesis of Bn-protected Boc-δ-amino acid **141**.

2.1.2.2 Synthesis of δ-peptide (tetramer) from Boc-δ-amino acid 50

For the synthesis of δ-peptide, the *tert*-butoxycarbonyl group of **141** was converted to its corresponding ammonium salt **142** using saturated solution of HCl in dry ethyl acetate. Subsequently, the ammonium salt **142** was coupled in the presence of Et_3N with preactivated Boc-δ-amino acid **50** using HOBt/EDC in CH_2Cl_2 to yield the dimer **143** in 87% yield. An iterative coupling procedure was employed to synthesize the trimer **145** in 81% yield from the dimer **143** and the tetramer **147** in 64% yield from the trimer **145** respectively. Hydrogenation of the Bn-protected tetramer **147** in MeOH and CH_2Cl_2 (1:1) in the presence of Pd/C (10 mol%) afforded tetramer **53** in quant. yield (Scheme 58).



Scheme 58. Synthesis of tetramer **53** from Boc-δ-amino acid **50**.

During hydrogenation, it was found that solvents play an important role. In the case of CH_2Cl_2, could not observed any conversion even in 5 days.

2.1.3 Structure investigation of oligopeptide

During the past couple of years, many examples of unnatural oligomeric sequences have been found that fold into well defined conformations in solutions,[17-29] in general such oligomers are known as foldamers.[94] Studies on oligomers of β- and γ- amino acids (β- and γ-peptides) represented their ability to adopt ordered secondary structures, e.g. helices, strands and turns.[95] Presently, some experimental reports are available for the formation of ordered structures in oligomers of δ-amino acids (δ-peptides),[97] but detailed conformation is still unclear.

2.1.3.1 Secondary structure of peptides and proteins: in general

The three-dimensional structure of peptides and proteins is governed by several factors, such as hydrogen bonding, hydrophobic interactions, electrostatic interections and van der Waals forces. Hydrogen bonding is one of the most impotant interactions related to peptides and proteins folding. The formation of secondary structural elements is mainly guided by hydrogen-bonding patterns. The secondary structure of peptide and proteins are classified into two regular structures, α- helix and β- sheet and two non-regular structures, loops and turns. The α- helix is a secondary structural element in which the polypeptide backbone adopts a coiled arrangement that is stabilized by a repeating i←i+4 hydrogen bond (the residue i represents as hydrogen bond donor with its amide N-H, and i+4 represents as hydrogen bond acceptor with its C=O). Genarally, β- sheets are stabilised by intra- and inter- strand hydrogen bond which could be aligned in the same (parallel) or in opposite (antiparallel) direction. The parallel and antiparallel β-sheets are folded with the α-carbon atoms alternating along the strands slightly above and below the plane of the sheet. The inter-strand hydrogen bonds for antiparallel β-sheet produce alternating 10- and 14-member rings and for parallel β-sheet produce 12-member rings (Figure 2).

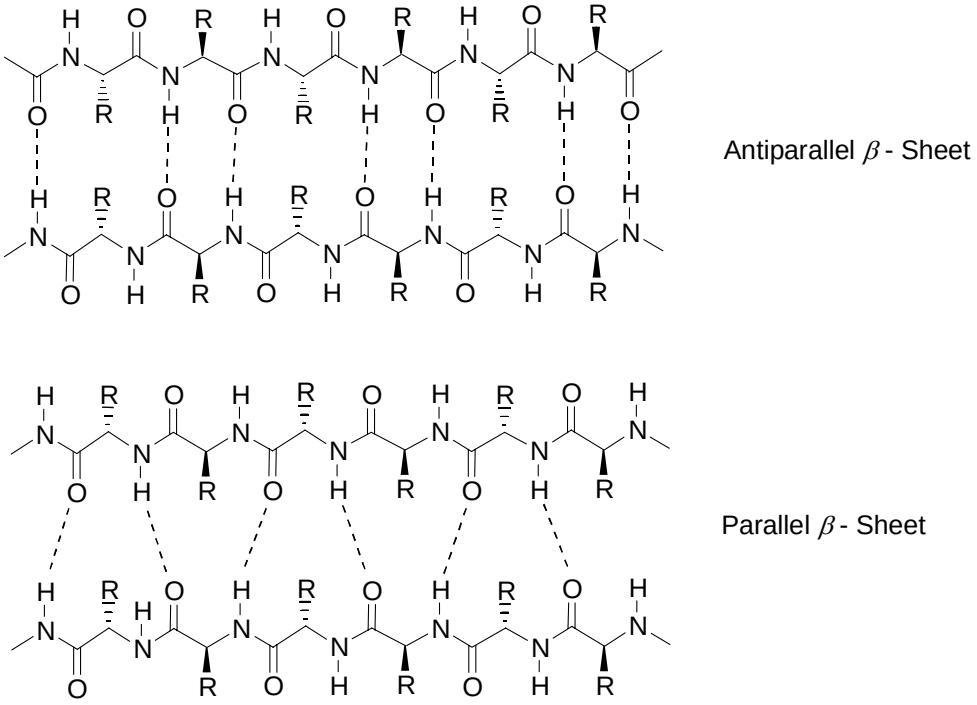


Figure 2. Schematic representation of parallel and antiparallel β-sheet[98].

Normally three to five residues forming a loop are found on the surface of a protein, while are as the polypeptide chain reverses its overall direction are called turns. The three residue γ-turn is stabilised by a i←i+2 hydrogen bond (forming a seven membered ring) while the four residue β-turn is stabilized by a i←i+3 hydrogen bond (forming a ten membered ring also designated C_{10}) (Figure 3). There are many types of β-turn but type I, II, and III right handed and type I`, II`, and III` left handed are mostly common in peptides and proteins and these are determined by the dihedral angles ϕ (rotation around the C_α-N bond) and ψ (rotation around the C_α-C=O).

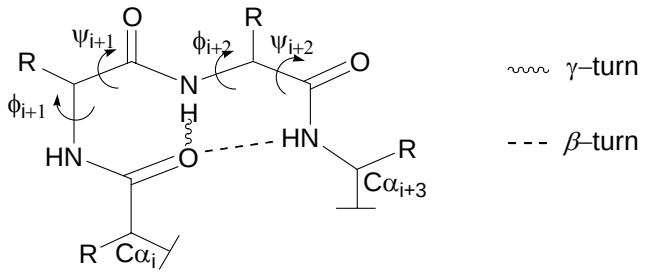


Figure 3. Schematic representation of β-turn and γ-turn.[99]

2.1.3.2 Circular Dichroism: an introduction

Circular dichroism (CD) spectroscopy is a powerful technique to detect the secondary structure of proteins and peptides.[100] It is based on the property of asymmetric chromophores or symmetric chromophores in asymmetric environments to absorb differently right- and left- circular polarized light. The peptide bond is the main chromophore in peptides and proteins, beside the aromatic side chains. It is surrounded by an asymmetric environment due to the stereocenters of the amino acids but mainly due to the three-dimensional arrangement of the peptide backbone (ϕ and ψ dihedral angles). As a result, the CD absorption of the peptide bond is highly sensitive to the peptide secondary structure. Normally the peptide bond absorption occours between 180-300 nm. The lowest energy transition of the peptide chromophore occurs between 210 and 220 nm and represents the n→π* transition involving non-bonding electrons of the carbonyl group. The second transition is observed around 190 nm and describes the π→π* transition involving the π electrons of the carbonyl group. The intensity and energy of these transitions depend on the ϕ and ψ dihedral angles, which relates to the secondary structure.

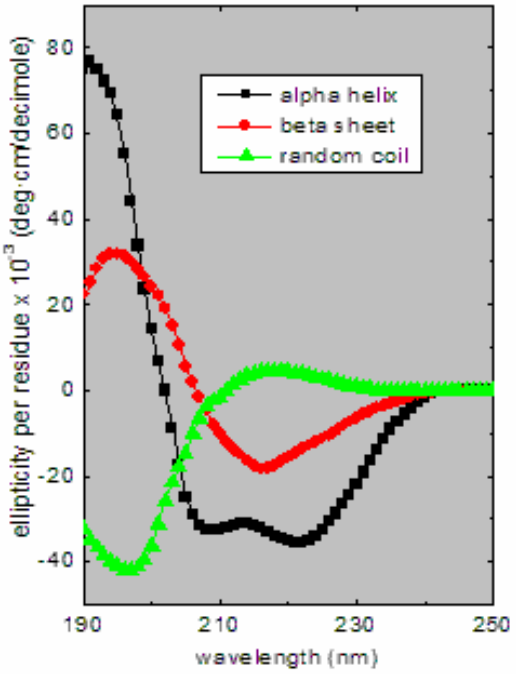


Figure 4. Characteristic CD signals for certain secondary structures in proteins.

2.1.3.3 CD spectra of tetramer 53 (δ-peptide) containing Boc-δ-amino acid 50

Circular dichroism (CD) spectra of the δ-peptide **53** were recorded in the far-UV region (190-260 nm) at the concentration of 5 mM in TFE, methanol and methanol/water 60:40 (v/v) (Figure 4). In TFE the CD spectrum was characterized by a positive band at 191 nm and by a negative broad band centered at 214 nm, with a crossover at 204 nm. The positive peak was four times more intensive than the negative one. Changing TFE with methanol doubled the intensity of the negative band, while maintaining the shape and position. The region below 200 nm could not be observed due to the cutoff of the solvent. The intensity of the negative band further increased in the mixture methanol/water, becoming more than two and four times higher than in 100 % methanol and TFE, respectively. Again, the shape of the band remained more or less constant, but a better-defined minimum was present at 214 nm and a shoulder near 221 nm was also visible. Although the ellipticity values of the δ-peptide **53** in all the three solvents were much lower than those usually found for stable secondary structures of α- and β-peptides, they were perfectly distinguished from the noise and were reproducible. Moreover, the CD spectrum of tetramer **53** was completely different from that of the monomer **50** (Figure 4) form in methanol, which was characterized by a positive signal in the region 200-260 nm. Therefore, the ellipticity of the peptide **53** reflects a chiral geometry of the amide-bond chromophores.

The fact that the CD spectra were solvent-dependent indicates that the conformational properties of the peptide are influenced by the environment. In the field of the α- and β-peptides, the increase in the intensity of their typical CD bands generally corresponds to an improved structural stability; for the δ-peptide a stabilization effect was observed in methanol rather than in TFE, and in the presence of water rather than in 100 % methanol. This behavior is quite unusual, as the conformation of peptides containing α- or β-amino acids is very often negatively affected by water that is a strong H-bond donor and acceptor and, thus, can prevent the formation of intramolecular H-bonds. In contrast, TFE is a well-known secondary structure stabilizer, being a strong H-bond donor but a weak H-bond acceptor (pK_a ~ 12) and, consequently, it largely interacts only with the carbonyl groups of the peptides, which are able to build bifurcated H-bonds without the necessity of breaking the intramolecular H-bonds. These are even stabilized, as TFE has the property of replacing the coordination water molecules and

creating a hydrophobic sphere surrounding the peptide.[101] On the other hand, experimental data and computational studies have pointed out the interaction of water molecules with the peptide carbonyl groups to be an important factor for the energetics of protein folding and stabilization.[102]

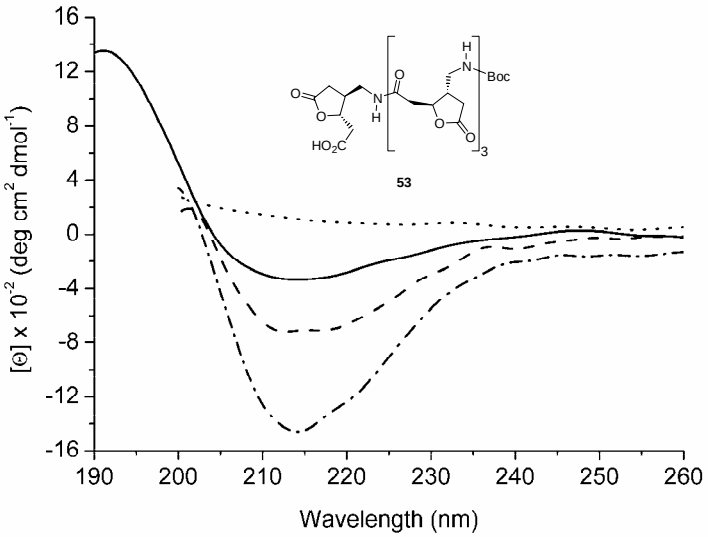


Figure 4. CD spectra of the N^{δ}–Boc-protected monomer **50** in methanol (dots) and of the δ-peptide **53** in TFE (solid), methanol (dashes) and methanol/water 60:40 (dot-dash). Both compounds were measured at the concentration of 5 mM.

Fleet et al.[17] also recorded CD spectra of tetramer **130** (Figure 5) in TFE and they found a negative peak with two separate maxima at 221 and 201nm which has been shown regular rigid conformation rather than irregular conformation. NMR and IR studies in $CHCl_3$ rather TFE indicate that the most populated conformer of the tetramer **130** is not stabilized by hydrogen bonds due to short length. Finally they suggested that the tetramer **130** may adopt an extended helical conformation. In case of tetramer **53**, the CD pattern is solvent-dependent and, therefore, the fact that solute and solvent molecules interact with each other is not really surprising, considering that the capability of the δ-peptide **53** to form intramolecular H-bonds is limited by the low content of H-bond donors with respect to the H-bond acceptors and by their distance along with the backbone. However, considering the fleet tetramer **130**, it is conceivable that the tetramer **53** may adopt extended helical conformation. Unfortunately, the ^{1}H-NMR spectra of the tetramer **53** in CD_3OH does not represent any significant dispersion

of the amide proton. Then next attempt was made to study IR technique, but it was also failed due to solubility problem.

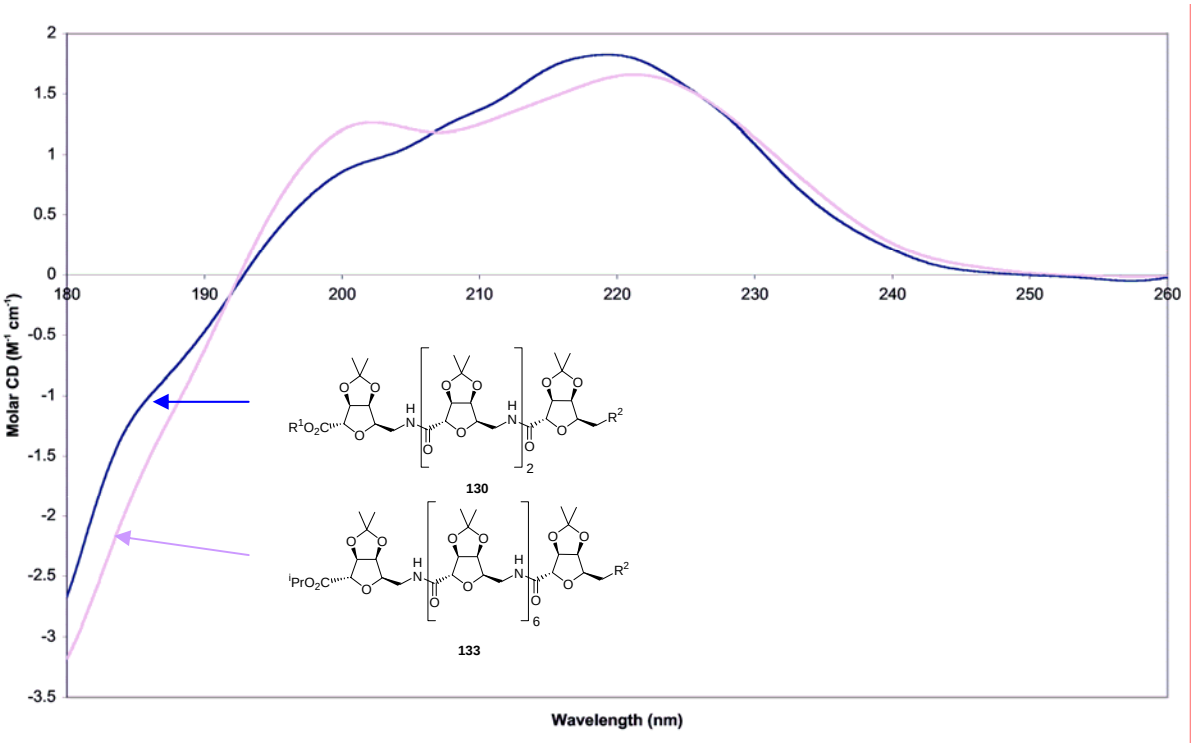


Figure 5. CD spectra of tetramer **130** and octamer **133** in TFE by *Fleet et al.*

Chapter 3

3.1 Synthesis of Peptide Nucleic Acid analogues

In 1991 *Nielsen et al.* first described a most interesting new entity, a polyamide or peptide nucleic acid (PNA), in which the entire sugar-phosphate backbone is replaced by an *N*-(2-aminoethyl)glycine polyamide structure. Though even minor structural changes in oligonucleotides, such as the replacement of an oxygen atom by sulfur(phosphorothioates), or by a neutral methyl group (methyl phosphonates), result in a decrease in binding affinity, it was interesting to find that the drastic structural changes in PNA results in nucleic acid mimetics with higher binding-affinity to complementary DNA and RNA than unmodified nucleotides. For this reason the surprising binding properties of PNA are rapidly expanding a new field of research, where the targets are the synthesis of PNA analogues, and their application as gene therapeutics (antisense and antigene), drugs, genetic diagnostics and tools in biotechnology.[36-41]

3.1.1 Monomeric Building Blocks for the synthesis of PNAs

A variety of different monomeric building blocks have been used for the synthesis of PNAs and their structural analogues. These differ from each other in the type of protecting group (PG) for the amino function of the backbone and/or for the nucleobase, and also in the structure of the backbone (Figure 1).

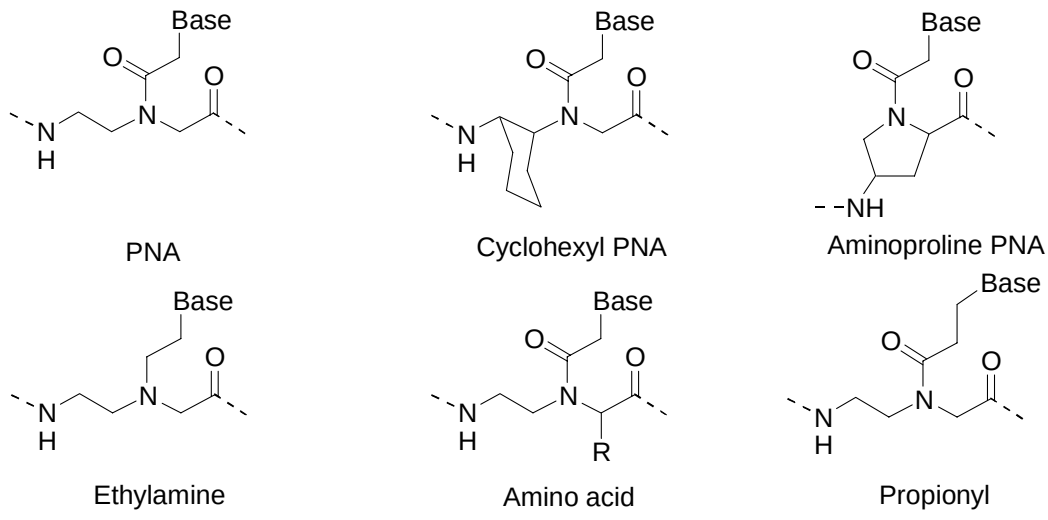
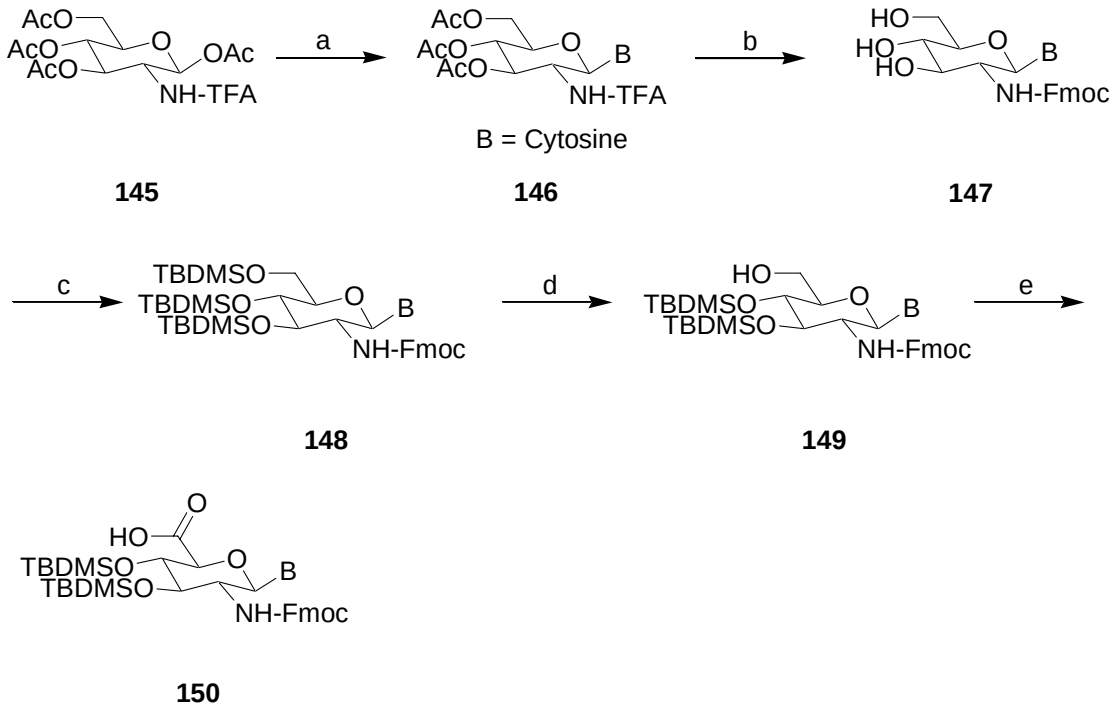


Figure 1. Chemical structures of a selection of some PNA monomer units.[41]

3.1.2 Synthesis of nucleoside amino acid

Godnow et al.[45] synthesized various nucleoside amino acid building blocks such as **150** for construction of novel oligonucleotide backbone analogues **45** (Scheme 15). For the synthesis of the pyranosyl cytosine nucleoside amino acid **150**, they treated carbohydrate **145** with persilylated cytosine to give nucleoside **146**. They exchanged the protecting group from TFA to Fmoc **147**. The 3‘, 4‘, and 6‘ hydroxyl groups of **147** were protected as *tert*-butyldimethylsilyl ethers **148** which was converted to the primary alcohol **149** followed by TEMPO mediated oxidation to give rise to the nucleoside amino acid **150** (Scheme 59).



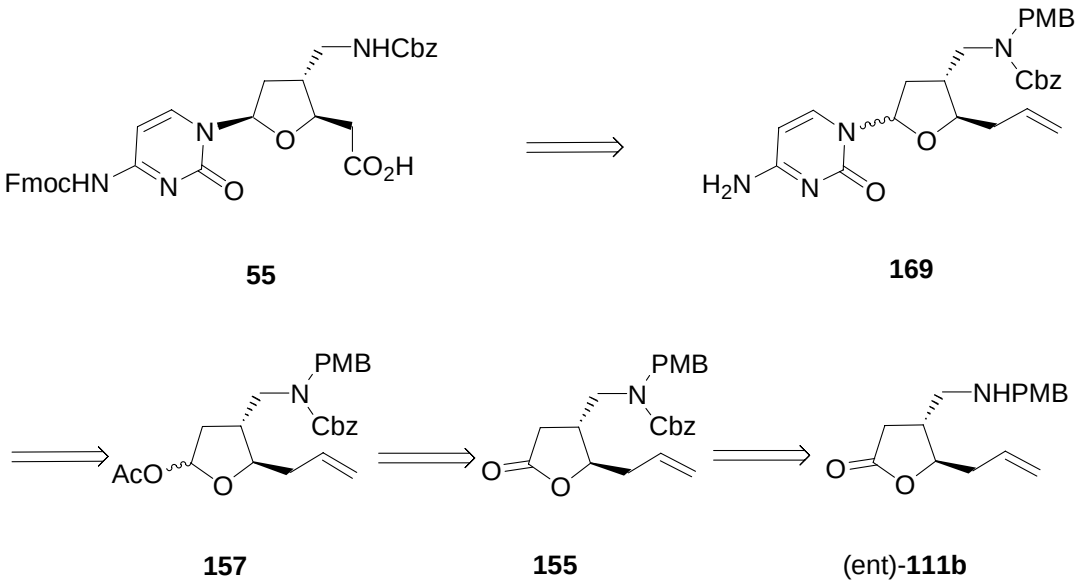
Reagent and Conditions: a) *N*, *O*-Bis(trimethylsilyl)acetamide, *N*-benzoylcytosine, $ClCH_2CH_2Cl$, $SnCl_4$, 85%; b) i) Et_3N, H_2O, MeOH (1:4:5 by vol), 70-100%; ii) NH_4OH, 70%; iii) Fmoc-succinimide, $NaHCO_3$, H_2O, dioxane, 60%; c) *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine, CH_2Cl_2, 70%; d) Camphor sulfonic acid, CH_3OH/CH_2Cl_2 (1:1), 70%; e) i) TEMPO, KBr, $(Bu_4N)_2SO_4$, NaOCl, NaCl, $NaHCO_3$, H_2O; ii) $NaClO_2$, NaH_2PO_4,H_2O, 50%.

Scheme 59. Synthesis of nucleoside amino acid by *Goodnow et al.*

Taking into account the *Godnow* strategy out lined above, the development of a versatile route to the nucleoside amino acid **55**, was developed.

3.2 Synthetic Strategy towards nucleoside amino acid 55

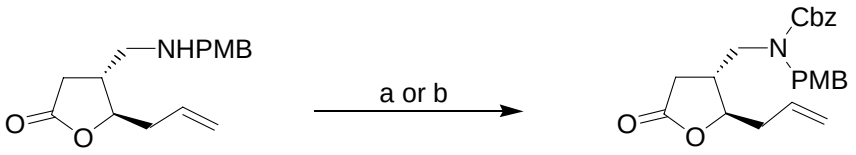
The nucleoside amino acid **55** was envisioned to be synthesized from the amine (ent)-**111b** (Scheme 60). As key steps the introduction of pyrimidine base onto the lactone **155** was planed, followed by subsequent transformation of the allyl into a carboxylic acid group.



Scheme 60. Retrosynthetic strategy for nucleoside amino acid **55**.

3.2.1 Benzyloxycarbonyl protection of amine (ent)-111b.

During acetylation of the corresponding lactol (ent)-**111b** was problematic. According to crude NMR and Mass spectrometry it was found in only di-acetylated compound along with unidentified byproducts. Therefore, the amine (ent)-**111b** was protected with benzyloxycarbonyl group[103] which could be useful in the synthesis of nucleoside amino acid and oligonucleotides in solution phase.[45] Treatment of (ent)-**111b** with benzyl chloroformate in NaOH/H_2O to give protected amine **155** in 71% yield (Scheme 61). However it was also tried with another solvent dioxane/H_2O[103] and Et_3N to give **155** in only 60% yield.



(ent)-**111b** **155**

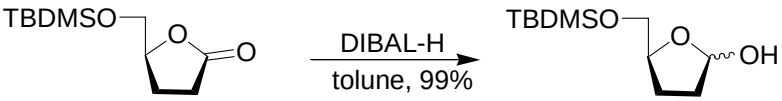
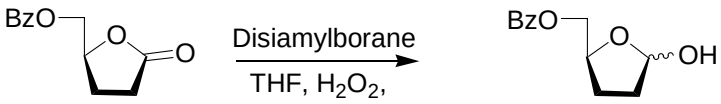
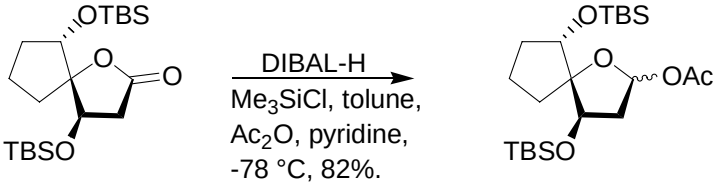
Reagent and conditions: a) Cbz-Cl (1.3 equiv.), NaOH/H_2O (pH 8.5), 0° C, 45 min, then RT, 2 h, 71%; b) Cbz-Cl (1.3 equiv.), dioxane/H_2O, NH_3, RT, 3 h, 60%.

Scheme 61. Synthesis of protected amine **155** from amine (ent)-**111b**.

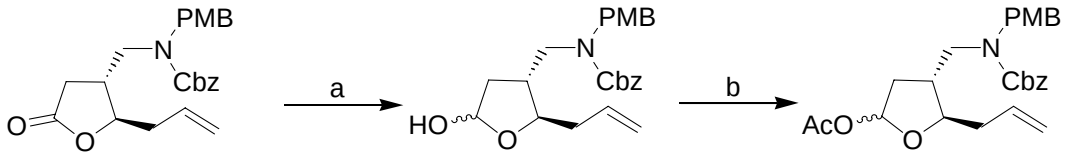
3.2.2 Reduction of lactone to lactol followed by acetylation

The reduction of lactones offers a facile access toward the synthesis of lactol. Despite the apparent simplicity of the transformation there are few efficient methods currently available for the reduction of *γ*-butyrolactone derivatives (Table 1).

Table 1. Some examples for the reduction of lactones to lactoles.

Entry	Reactions
1[104a]	 **158** **159**
2[104b]	 **160** **161**
3[104c]	 **162** **163**

A good example was presented by *Okabe et al.*[104a] for the reduction of lactone to lactol. They synthesized lactol **159** in 99% (crude) yield from lactone **158** using DIBAL-H. *Farina et al.*[104b] synthesized lactol **161** in 94% yield from lactone **160** by using disiamylborane and H_2O_2. Following the first protocol,[104a] treatment of protected amine **155** with diisobutylaluminium hydride the corresponding lactol **156** was obtained in 98% yield. Acetylation to give the acetate **157**[106] as an inseparable mixture of anomers (1:1.5) in 92% yield (Scheme 62).



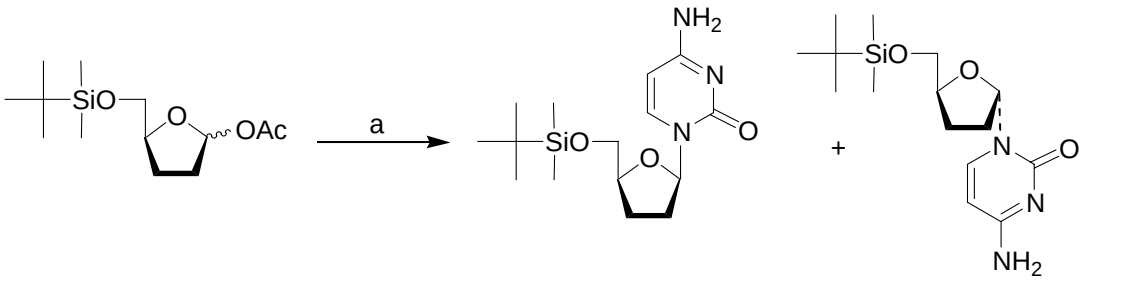
155 **156** **157**

Reagent and Conditions: a) DIBAL-H (1.1 equiv.), CH_2Cl_2, –78 °C, 20 min, MeOH, 98%; b) Ac_2O (1.1 equiv.), pyridine, DMAP (cat.), 15 h, 92% (1: 1.5 mixture of α/β-anomer).

Scheme 62. Reduction of lactone **155** followed by acetylation.

3.2.3 Glycosylation of 157 with persilylated cytosine

2`, 3`-Dideoxynucleosides have found utility mainly as reagents for DNA sequencing.[107] Since only the β-isomers generally exhibit useful biological activity[107], a general and economically attractive synthesis of β-dideoxynucleosides has therefore become an considerable attention. Lewis acid mediated glycosylation is a key step for the synthesis of nucleoside amino acids. *Okaba et al*.[104a] synthesized the furanosyl cytosine nucleoside **166** and **167** from acetate **164** and silylated cytosine using various lewis acid such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $TMSOTf_2$ and $EtAlCl_2$. They found that $EtAlCl_2$ gave best results yielding a 2:3 α/β-anomeric mixture in 71% yield (Scheme 63).

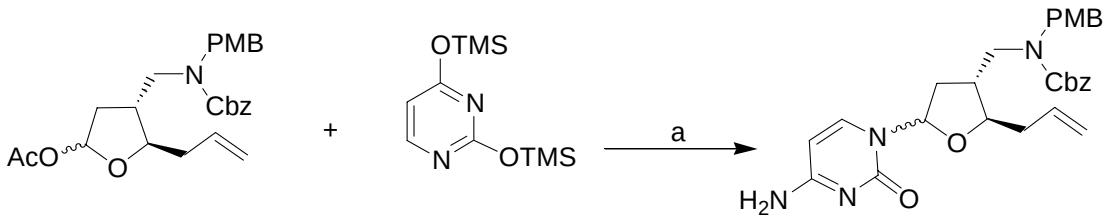


164 **166** (β–*anomer*) **167** (α–*anomer*)

Reagent and conditions: a) Silylated cytosine (1.0 equiv.), $EtAlCl_2$ (1.0 equiv.), CH_2Cl_2, 4 h, 71%.

Scheme 63. Synthesis of furanosyl cytosine nucleoside **165** and **166** by *Okaba et al.*

Following this protocol, the acetate **157** was treated with freshly prepared silylated cytosine **168**[104a] in the presence of $EtAlCl_2$ to give the furanosyl cytosine nucleoside **169** as an inseparable mixture of anomers (1:1.2) in 84% yield (Scheme 64).



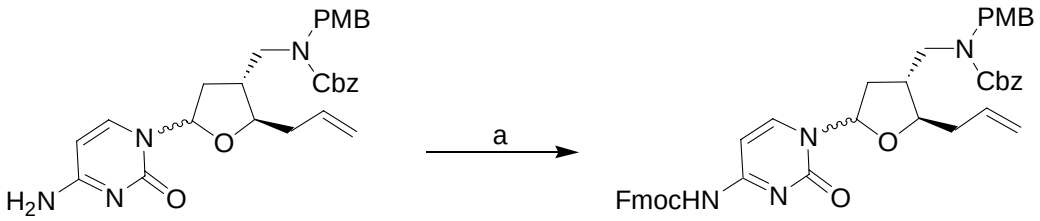
157 **168** **169**

Reagent and conditions: a) silylated cytosine **168** (2.0 equiv.), $EtAlCl_2$ (2.0 equiv.), CH_2Cl_2, –5 °C→RT for 6 h, 84%.

Scheme 64. Synthesis of furanosyl cytosine nucleoside **169**.

3.2.4 Fmoc-protection of furanosyl cytosine nucleoside 169

Taking into account the coupling strategy of PNA analogues, the exocyclic amino function of cytosyl nucleoside **169** was protected with Fmoc group which can be easily cleaved with piperidine. Therefore, the nucleoside **169** was converted to its corresponding Fmoc-protected derivative **170**[75] using 9-fluorenylmethyl chloroformate to provide an inseparable mixture of anomers (1:1.2) in 87% yield (Scheme 65).



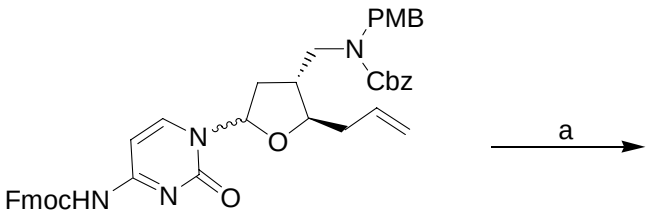
169 **170**

Reagent and conditions: a) 9-fluorenylmethyl chloroformate (1.1 equiv.), pyridine, RT, overnight, 87%.

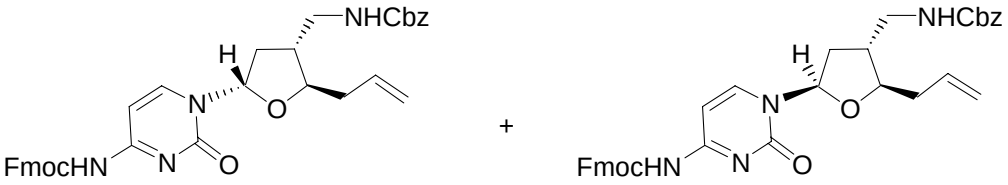
Scheme 65. Synthesis of Fmoc-protected nucleoside **170**.

3.2.5 Oxidative removal of PMB group by CAN

In order to remove the 4-methoxy benzyl group, nucleoside **170** was treated with CAN (3.5 equiv.) in CH_3CN-H_2O (3:1), but no conversion even in 2 days. Therefore deprotection was tried with DDQ,[96] but again, no conversion observed. However another efficient protocol was found,[84] where deprotection of PMB group with excess (6.0 equiv.) of CAN in CH_3CN-H_2O (9:1). Following this protocol, the protected nucleoside **170** was successful afforded α-and β- nucleoside **171** (34%) and **172** (41%) respectively, which can be separated on chromatography (Scheme 66).



170

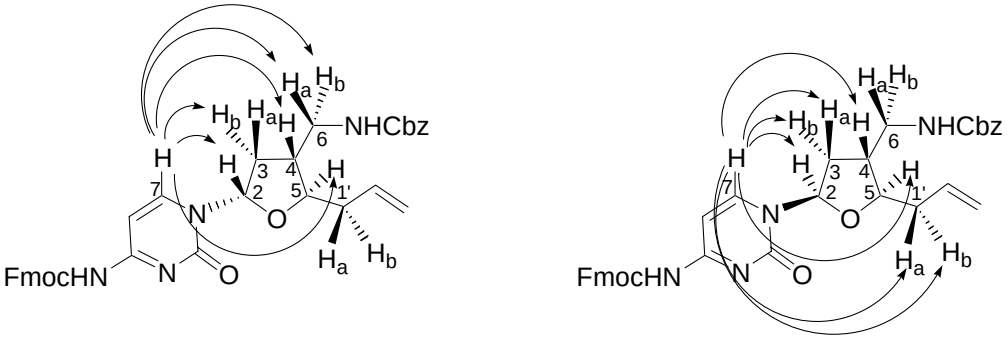


171 **172**

Reagent and Conditions: a) CAN (6.0 equiv.), CH_3CN-H_2O (10:1), 0 °C, 2 h, **171** (34%), **172** (41%).

Scheme 66. Deprotection of PMB group of **170** by CAN.

The stereochemistry of nucleosides **171** and **172** were assigned on the basis of their ROESY spectra. The ROESY spectra of the compound **171** (Figure 1) shows that the 7-position proton (δ 7.97) and 1`ab, 3a protons are located at different side because no ROESY effect exists between these protons. Moreover 7-H proton correlates with 5-H proton very strongly it shows that the two protons are located in same side. While the ROESY spectra of the compound **172** (Figure 2) shows that the 7-H (δ 8.05) proton correlate with 5-H proton weakly compare to **171**, it shows that the two protons are located in oposite side. Moreover, 7-H proton and 6ab protons are located in oposite side because no ROESY effect exists between these protons.



171 **172**

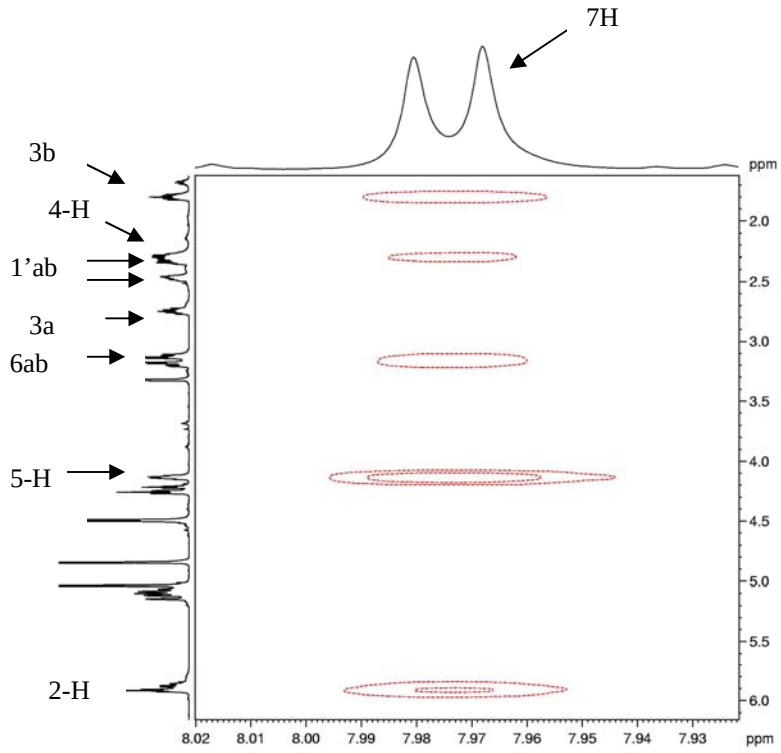


Figure 1. ROESY spectra of the cytosyl α-nucleoside **171**.

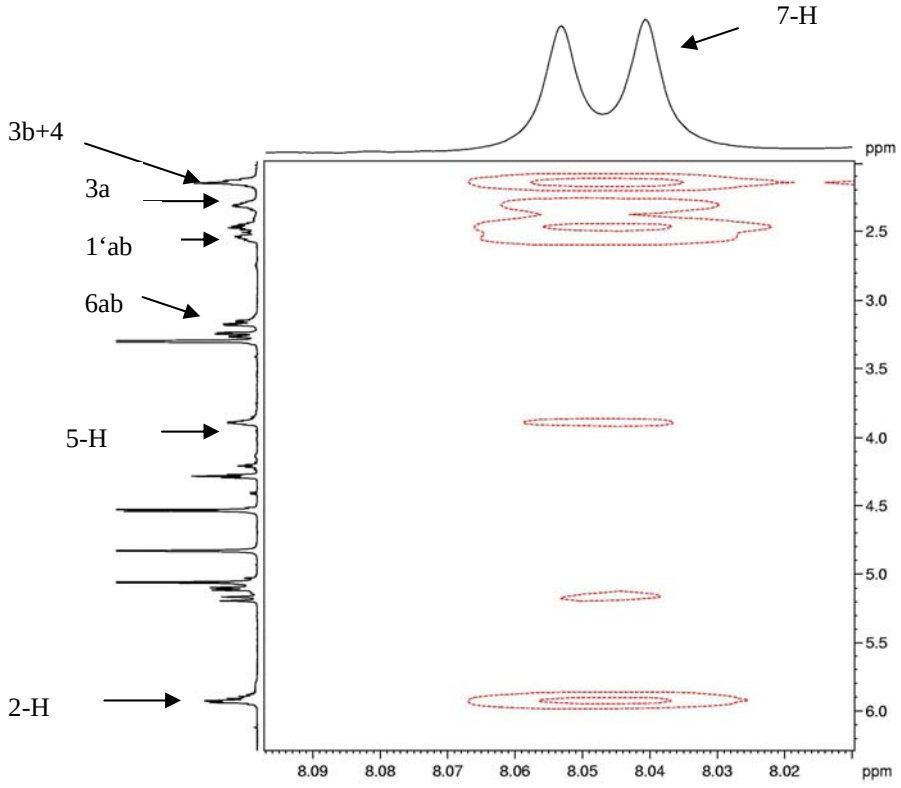
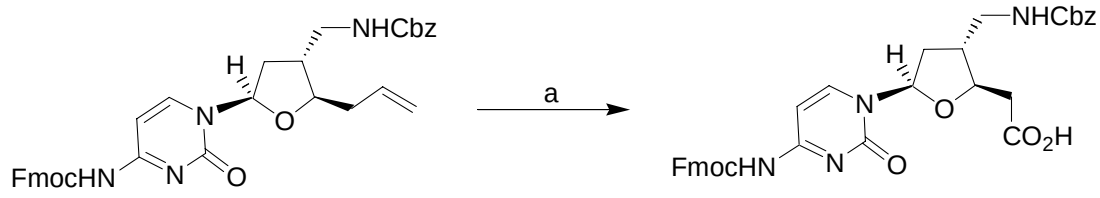


Figure 2: ROESY spectra of the cytosyl *β*-nucleoside 172.

Based on the chemistry of DNA[107] the β-nucleoside **172** can be useful synthetic building block for the synthesis of PNA analogues.

3.2.6 Ruthenium catalyzed oxidative cleavage of the allylic double bond

Therefore, Furanosyl cytosine nucleoside **172** was converted to its corresponding nucleoside amino acid **55** by ruthenium catalyzed[76] oxidative cleavage of the allylic double bond in the presence of $NaIO_4$ in 61% yield (Scheme 67).



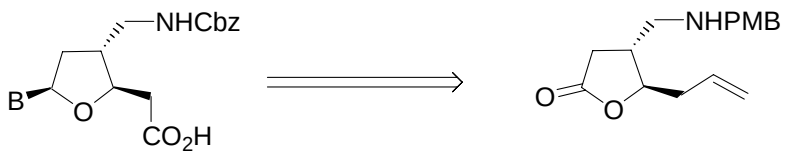
172 **55**

Reagent and Conditions: a) $NaIO_4$ (4.0 equiv.), $RuCl_3 \cdot 3H_2O$ (6.3 mol%), CH_3CN-CCl_4-H_2O (1:1:1.5), 0 °C, 40 h, 61%.

Scheme 67. Synthesis of furanosyl cytosine nucleoside amino acid **55**.

3.3 Model study towards the synthesis of PNA analogues

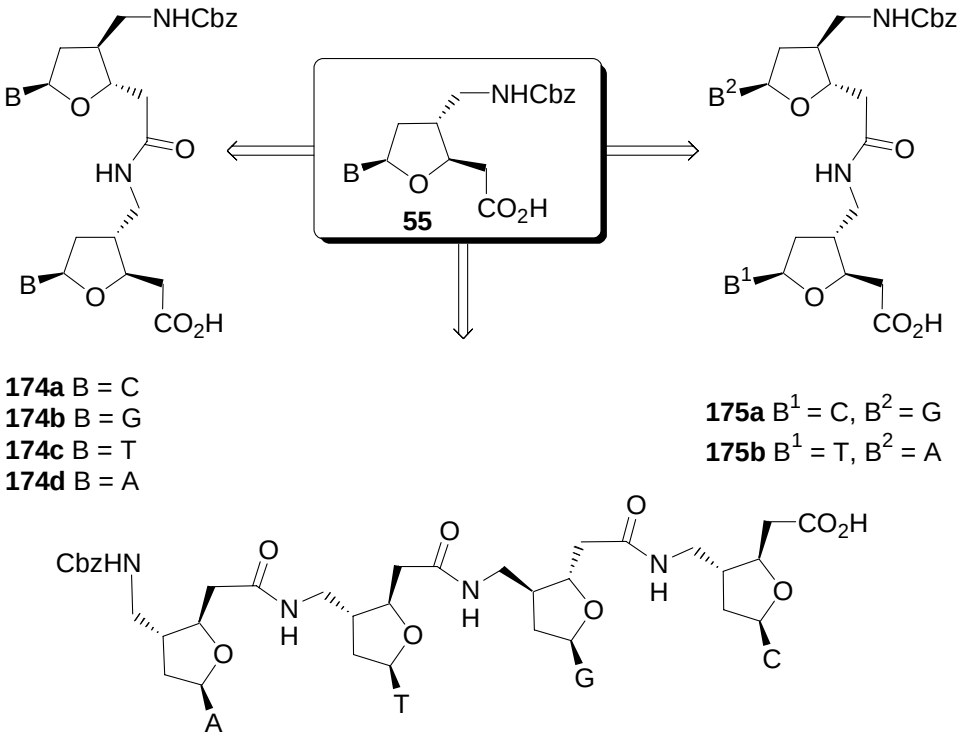
Following above the synthetic strategy of **55**, it can be also synthesize guanine, adenine and thymine containing nucleoside amino acids **173** from the amine (ent)-**111b** (Scheme 68). The PNA analogues **174**, **175** and **176** can be synthesized from nucleoside amino acid **55** or **173** (Scheme 69) by using the standard solution or solid phase coupling methods.



B = Thymine, Adenine, Guanine

173 (ent)-**111b**

Scheme 68. Retrosynthetic strategy of nucleoside amino acids **173**.



174a B = C
174b B = G
174c B = T
174d B = A

175a B^1 = C, B^2 = G
175b B^1 = T, B^2 = A

A = Adenine, T = Thymine, G = Guanine, C = Cytosine

176

Scheme 69. Retrosynthetic strategy of PNA analogues **174**, **175** and **176**.

Experimental Part

1. Instruments and general techniques

^{1}H NMR-Spectra were recorded on Bruker AC 250 (250 MHz), Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d_6, 2.49 ppm), methanol-d_4 (CD_3OD, 3.34 ppm) and tetramethylsilane (TMS, 0.00 ppm) as an internal standard. The spectra were analysed by first order, the coupling constants (*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 douplet, dt = double triplet, ddd = double double douplet, Integration is determined as the relative number of atoms. Diastereomeric ratios were determined by comparing the integrals of corresponding protons in the ^{1}H 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 ($CDCl_3$, 77.0 ppm), dimethylsulfoxide (DMSO-d_6, 39.52 ppm), methanol-d_4 (CD_3OD, 49.0 ppm) and tetramethylsilane (TMS, 0.00 ppm) as an internal standard.

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

Melting points (m.p.) were determined with a Buchi SMP 20 and are uncorrected.

IR-Spectra were recorded with an AT1 Mattson Genesis Series FT-IR or a Bio-Rad Excalibur series FT-IR.

MS-Spectra were recorded in Finnigan MAT 95, Varian MAT 311A and Finnigan TSQ 7000.

Elemental analysis: Microanalytical 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.

CD-Spectra were measured on a JASCO model J-710/720 at the institute of Bioanalytic and Sensoric of the University of Regensburg at 21 °C between 300 and 180 nm in the specified solvent, the number of scans ranging between 10 and 20. The length of the cylindrical cuvettes was 1.0 or 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 subtracted to each spectrum. The absorption value is measured as Molar Ellipticity per residue (deg cm^2 $dmol^{-1}$). The spectra were smoothed by the adjacent averaging algorithm with the Origin 6.0 program.

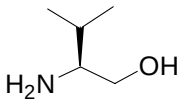
Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualisation was accomplished by UV-light (wavemength λ = 254 nm), Mostain, Molybdatophosphoric acid and a vanillin/sulphuric acid solution.

Column chromatography was performed on silica gel (Merck Geduran 60, 0.063-0.0200 mm mesh) and flash-silica gel 60 (0.040-0.063 mm mesh).

Solvents were purified according to standard laboratory methods. THF, diethyl ether and toluene were distilled over sodium/benzophenone before use. Dichloromethane was distilled over calcium hydride. Methanol was refluxed with Mg/I_2 for 2 h, distilled and stored under nitrogen over 4Å molecular sieves. Acetic anhydride was refluxed with P_2O_5 for 2h, distilled and stored under nitrogen. All solvents were distilled before use. All reactions with oxygen or moisture sensitive reactant were performed under nitrogen/Argon atmosphere.

2. Synthesis of compounds

2.1 γ-Butyrolactonaldehyde

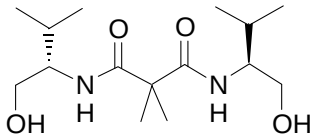


75

(L)-2-Amino-3-methylbutan-1-ol (75):[58]

To a solution of $NaBH_4$ (8.1 g, 214.0 mmol, 2.5 equiv.) in dry THF (135 mL) was added L-valine (10.0 g, 85.3 mmol, 1.0 equiv.) under argon atmosphere. The reaction mixture was cooled to 0 °C in an ice bath and a solution of iodine (21.6 g, 85.3 mmol, 1.0 equiv.) in dry THF (50 mL) was slowly added over 1 h, resulting in evolution of hydrogen. After gas evolution had ceased, the reaction mixture was refluxed for 20 h and then cooled to room temperature. Methanol was added cautiously until the stirred solution became clear. The solution was stirred for 30 min and concentrated in vacuo to give a white paste, which was dissolved in 20% aqueous KOH (50 mL). The solution was further stirred for 4 h and extracted with CH_2Cl_2 (3 x 140 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford **75** (8.15 g, 92%) as a colorless oil.

^{1}H NMR (250 MHz, CDCl3): δ = 0.91 (d, *J* = 6.8 Hz, 3H, *CH_3*), 0.93 (d, *J* = 6.8 Hz, 3H, *CH_3*), 1.5-1.7 (m, 1H, *CH*(CH_3)$_2$), 2.20 (bs, 2H, *NH_2*), 2.57 (ddd, *J* = 8.6, 6.4, 3.9 Hz, 1H, 2-H), 3.31 (dd, *J* = 106, 8.7 Hz, 1H, CH_2), 3.64 (dd, *J* = 106, 8.7 Hz, 1H, CH_2).

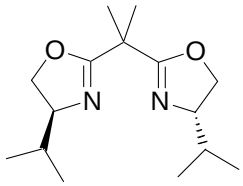


78

(–)-(*S*,*S*)-N,N'-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalonamide (78):[58]

To a cold (0 °C) solution of (L)-valinol (**75**, 15.4 g, 150.0 mmol, 2.0 equiv.) in dry CH_2Cl_2 (150 ml) were slowly added triethyl amine (52.3 mL, 375.0 mmol, 5.0 equiv.) and a solution of 2,2-dimethylmalonyl dichloride (**77**, 10 mL, 75.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (70 mL). Then the ice bath was removed and the reaction mixture was stirred for 45 min to room temperature, resulting in a colorless precipitate which was dissolved again by addition of dry CH_2Cl_2 (350 mL). After addition of 1N HCl (100 mL) the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Crystallization of the crude product from ethyl acetate (100 mL) and subsequent recrystallization of the residue of the mother liquor afforded **78** (18.76 g, 83%) as colorless crystals.

R_f = 0.26 (SiO_2, EtOAc/MeOH 95:5); m.p. = 98 - 99 °C; $[\alpha]_D^{20}$ = – 6.3 (c = 0.50, CH_2Cl_2); **^{1}H-NMR** (250 MHz, $CDCl_3$)): δ = 6.41 (d, *J* = 8.8 Hz, 2 H, *NH*), 3.84-3.72 (m, 4 H, C*H*$_2$OH), 3.56-3.48 (m, 2 H, 1-H), 3.21 (bs, 2 H, OH), 1.80 (hept, *J* = 6.8 Hz, 2 H, C*H*$(CH_3)_2$), 1.49 (s, 6 H, C$(CH_3)_2$), 0.95 (d, *J* = 6.74 Hz, 6 H, CH$(CH_3)_2$), 0.92 (d, *J* = 6.74 Hz, 6 H, CH$(CH_3)_2$).; **^{13}C-NMR** (62.9 MHz, $CDCl_3$): δ = 174.6 (C_{quart}, CO), 64.0 (CH_2OH), 57.2 (1-C), 50.1 (C_{quart}, $C(CH_3)_2$), 29.1 ($CH(CH_3)_2$), 23.6 ($C(CH_3)_2$), 19.7 ($CH(CH_3)_2$), 18.8 ($CH(CH_3)_2$). **IR** (KBr): $\tilde{\nu}$ = 3326, 2963, 2877, 1642, 1543, 1391, 1368, 1287, 1186, 1071, 1024, 899, 651 cm^{-1}. **MS** (DCI, NH_3): m/z (%) = 304.5 (16), 303.5 (100) $[M + H^+]$.

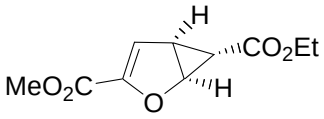


79

(–)-(*S*,*S*)-*iso*-Propylbisoxazoline (79):[58]

To a mixture of (–)-(*S*,*S*)-N,N'-Bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethyl-malonamide (**78**, 18.76 g, 620.0 mmol, 1.0 equiv.) and 4-dimethylamino pyridine (0.75 g, 6.2 mmol, 0.1 equiv.) in dry CH_2Cl_2 (400 mL) was slowly added triethyl amine (37.6 mL, 270.0 mmol, 4.4 equiv.) over 15 min. Subsequently a solution of tosyl chloride (23.65 g, 124.0 mmol, 2.0 equiv.) in dry CH_2Cl_2 (50 mL) was added dropwise *via* the addition funnel. The reaction mixture was stirred for additional 48 h at room temperature where the color changed to yellow and cloudy precipitate occurred. The precipitate was dissolved in CH_2Cl_2 (150 mL). The reaction mixture was then washed with saturated NH_4Cl (250 mL) followed by water (150 mL) and saturated $NaHCO_3$ (200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and concentration in vacuo the residue was purified by hot n-pentane extraction to afford **79** (7.466 g, 44%) as a colorless oil.

R_f = 0.26 (SiO_2, CH_2Cl_2/MeOH 19:1); $[\alpha]_D^{20}$ = – 108.1 (c = 1.01, CH_2Cl_2).; **^{1}H-NMR** (250 MHz, $CDCl_3$): δ = 4.27-4.09 (m, 2 H, 4-H, 4'-H), 4.04-3.92 (m, 4 H, 5-H, 5'-H), 1.91-1.72 (m, 2 H, C*H*$(CH_3)_2$), 1.52 (s, 6 H, C(C*H*$_3)_2$), 0.92 (d, *J* = 6.84 Hz, 6 H, CH(C*H*$_3)_2$), 0.85 (d, *J* = 6.79 Hz, 6 H, CH(C*H*$_3)_2$); **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 168.8 (C_{quart}, O*C*N), 71.5 (4-C), 69.9 (3-C), 38.6 (C_{quart}, *C*$(CH_3)_2$), 32.2 (*C*H$(CH_3)_2$), 24.4 (C(*C*H$_3)_2$), 18.5 (CH(*C*H$_3)_2$), 17.3 (CH(*C*H$_3)_2$); **IR** (Film): $\tilde{\nu}$ = 3411, 3225, 2960, 1660, 1468, 1385, 1352, 1301, 1247, 1146, 1109, 980, 925, 795, 737 cm^{-1}.; **MS** (DCI, NH_3): m/z (%) = 391.6 (7), 313.5 (7), 268.4 (17), 267.4 (100) [M + NH_4^+].

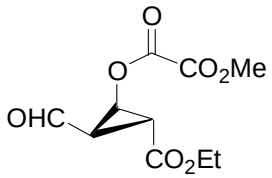


73

(*1S,5S,6S*)-(–)-2-Oxa-bicyclo[3.1.0]hex-3-en-3,6-dicarbonicacid-6-ethylester-3-methyl-ester (73):

A solution of **52** (12.0 g, 95.0 mmol, 1 equiv.) in dry CH_2Cl_2 (15 mL) was cooled to 0 °C and followed by addition of $Cu(OTf)_2$ (227.2 mg, 0.66 mol%), chiral bisoxazolin (–)-**79** (211.0 mg, 0.80 mmol) and 3 drops of phenylhydrazine were stirred for 30 min gave a brown-red solution. Then a solution of ethyldiazoacetate **82** (28.94 g, 253.6 mmol, 2.67 equiv.) in CH_2Cl_2 (400 mL) was added dropwise over 5 days. The reaction mixture was filtered through a short pad of alumina (basic, activity-I), washed with CH_2Cl_2 (300 mL) and concentrated in vacuo. The unreactive ester was removed under reduced pressure distilation (0.1 mbar, b.p. 63-64°C). The brown residue was purified by column chromatography on silica (hexanes:ethylacetate 9:1) to afford **73** (10.8 g, 53%, 89% *ee*) as a yellowish oil which was recrystallized from n-pentane/CH_2Cl_2 at – 27 °C to afford **73** (7.7 g, 38%, >99% *ee*) as a colorless crystal.

R_f = 0.29 (SiO_2, hexanes/ethylacetate 5:1), m.p. 42-43 °C; $[\alpha]_D^{20}$ = – 272 (c = 1.0, CH_2Cl_2).; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 6.40 (d, *J* = 3.0 Hz, 1H, 4-H), 4.98 (dd, *J* = 5.2, 1.1 Hz, 1H, 1-H), 4.17 (q, *J* = 7.1 Hz, 2H, *CH_2*), 3.82 (s, 3H, *OCH_3*), 2.89-2.86 (m, 1H, 5-H), 1.28 (t, *J* = 7.1 Hz, 3H, *CH_3*), 1.17 (dd, *J* = 2.6, 1.1 Hz, 1H, 6-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 171.8 (C_{quart}, CO), 159.6 (C_{quart}, CO), 149.2 (C_{quart}, 3-C), 116.2 (4-C), 67.6 (1-C), 61.1 (CH_2), 52.3 (OCH_3), 32.0 (5-C), 21.5 (6-C), 14.2 (CH_3); **MS** (EI, 70 eV): m/z (%) = 212.3 (9.09) [M^+], 153.2 (10.83) [M^+-CO_2CH_3], 139.2 (100) [M^+-CO_2Et], 125.2 (20.65), 97.2 (27.40), 79.2 (9.82), 59.2 (6.35), 52.2 (9.81); **HRMS** (EI, 70 eV): Calculated for [$C_{10}H_{12}O_5$]: 212.0685, found 212.0686 [M^+].

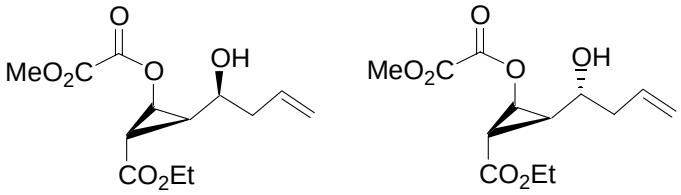


72

(*1S,2S,3S*)-(–)-Oxalicacid-(2-formyl-3-ethoxycarbonyl)-cyclopropylestermethylester (72):

A solution of **73** (14.2 g, 66.91 mmol, 1 equiv) in dry CH_2Cl_2 (200 mL) was cooled to –78 °C and treated with ozone until the mixture turned deep blue, excess ozone was expelled by passing oxygen through the solution, followed by addition of DMS (24.43 mL, 334.57 mmol, 5.0 equiv.). The mixture was warm to room temperature and stirred for 22 h. The reaction mixture was subsequently washed with saturated $NaHCO_3$ (75 mL) and water (75 mL). Dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized from diethylether at – 27 °C to afford **72** (15.35 g, 94%) as a colorless solid.

m.p. 51-52 °C; $[\alpha]_D^{20} = -37.6$ (c = 1.0, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 9.45 (d, *J* = 4.0 Hz, 1H, CHO), 4.83 (dd, *J* = 7.3, 3.6 Hz, 1H, 1-H), 4.20 (q, *J* = 7.1 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 2.90 (dd, *J* = 6.0, 3.6 Hz, 1H, 3-H), 2.8 (ddd, *J* = 7.3, 6.0, 4.0 Hz, 1H, 2-H), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 192.7 (CHO), 168.1 (C_{quart}, CO_2Et), 156.9 (C_{quart}, CO), 156.6 (C_{quart}, CO), 62.0 (CH_2CH_3), 58.9 (1-C), 54.0 (CO_2CH_3), 34.9 (2-C), 26.4 (3-C), 14.1 (CH_3); **MS** (DCI, NH_3): m/z (%) = 262.0 (100) [M+NH_4^+], 176.0 (20), 160.0 (55), 120.9 (15).; elemental analysis calcd (%) for $C_{10}H_{12}O_7$ (244.20): C 49.18, H 4.95; found C 48.87, H 4.98.

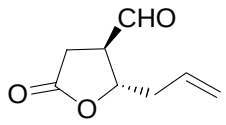


71

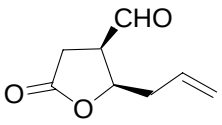
(*1S,1'S/R,2S,3S*)-Oxalicacid-hydroxy-but-3'-enyl)-3-ethoxycarbonyl-cyclopropylester methylester (71):

A solution of **72** (9.0 g, 36.8 mmol, 1 equiv) in dry CH_2Cl_2 (100 mL) was treated with $BF_3.Et_2O$ (5.14 ml, 40.5 mmol, 1.1 equiv.) at –78 °C. After 30 min allyltrimethylsilane (6.47 ml, 40.54 mmol, 1.1 equiv) was slowly added and further stirred for 15 h. The reaction mixture was quenched with saturated $NaHCO_3$ (7.5 mL) and the mixture was warm to 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the corresponding alcohol **71** (10.54 g, 100% crude yield, *dr*. 95:5) as a colorless oil which was used for next step without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.93-5.76 (m, 1H, 3'-H), 5.25-5.15 (m, 2H, 4'-H), 4.76 (dd, *J* = 7.3, 2.8 Hz, 1H, 1-H), 4.23-4.10 (m, 2H, CO_2 CH_2CH_3), 3.91 (s, 3H, CO_2CH_3), 3.80-3.76 (m, 1H, 1'-H), 2.55-2.31 (m, 2H, 2'-H), 2.20 (dd, *J* = 5.9, 2.8 Hz , 1H, 3-H), 1.98-1.85 (m, 1H, 2-H),1.28 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), Characteristic signal for diastereomers: δ = 4.70 (dd, *J* = 6.9, 3.0 Hz, 1H, 1-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 170.6 (C_{quart}, CO_2CH_3),157.1 (C_{quart}, CO), 133.3 (3'-C), 118.9 (4'-C), 67.7 (1'-C), 61.3 ($CO_2CH_2CH_3$), 58.8 (1-C), 53.9 (CO_2CH_3), 41.7 (2'-C), 31.2 (2-C), 24.6 (3-C), 14.1 (CH_3), Characteristics signal for diastereomers: δ = 133.4 (3'-C), 118.6 (4'-C), 58.7 (1-C), 53.8 (CO_2CH_3), 41.3 (2'-C), 25.0 (3-C); **MS** (DCI, NH_3): m/z (%) = 304.2 (100) [$M+NH_4^+$], 287.2 (2.53) [MH^+], 269.1 (9.90) [MH^+-H_2O], 200.1 (8.24).



48



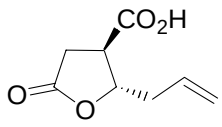
48a

(*2S/R,3R*)-(–)-3-Formyl-5-oxo-2-(propen-2‘-yl)-tetrahydrofuran (48):

To a cold (0 °C) solution of **71** (10.54 g, 36.85 mmol, 1.0 equiv.) in MeOH (100 mL) was slowly added a solution of $Ba(OH)_2 \cdot 8H_2O$ (5.81 g, 18.42 mmol, 0.5 equiv.) in MeOH (300 mL), stirred for 6 h at 0 °C. MeOH was removed in vacuo, CH_2Cl_2 (150 mL) and water (100 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (hexanes/ethylacetate 1:1) to afford **48** (3.8 g, 67%, *dr* = 95:5) as a colorless oil.

R_f = 0.17 (SiO_2, hexanes/ethylacetate 1:1); $[\alpha]_D^{20}$ = – 27.4 (c = 1.01, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 9.70 (d, *J* = 1.6 Hz, 1H, CHO), 5.75 (dddd, *J* = 17.2, 10.0, 7.1, 3.6 Hz, 1H, 2‘-H), 5.30-5.10 (m, 2H, 3‘-H), 4.75 (dd, *J* = 12.1, 6.1 Hz, 1H, 2-H), 3.23-3.13 (m, 1H, 3-H), 2.90 (dd, *J* = 17.9, 7.5 Hz, 1H, 4-H), 2.71 (dd, *J* = 17.7, 10.1 Hz, 1H, 4-H), 2.63-2.43 (m, 2H, 1‘-H); Characteristic signal for **48a** (minor): δ = 9.86 (d, *J* = 1.6 Hz, 1H, CHO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 197.3 (CHO), 174.0 (CO), 130.9 (2‘-C), 120.5 (3‘-C), 78.0 (2-C), 51.3 (3-C), 39.2 (1‘-C), 28.9 (4-C), Characteristic signals for **48a** (minor): δ = 198.0 (CHO), 131.3 (2‘-C), 120.0 (3‘-C), 49.6 (3-C), 39.4 (1‘-C), 28.7 (4-C); **MS** (EI, 70 eV): m/z (%) = 154.2 (5) [M^+], 113.1 (100) [M – C_3H_5], 85.1 (95), 57.1 (9); elemental analysis calcd (%) for $C_8H_{10}O_3$ (154.2): C 62.33, H 6.54; found C 62.37, H 6.81.

2.2 γ-amino acid

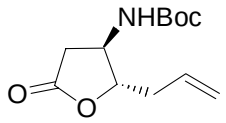


89

(*2S,3R*)-(–)-Tetrahydro-5-oxo-2-(propen-2‘-yl)-3-furancarbonicacid (89):

To a cold (0 °C) solution of **48** (210.0 mg, 1.36 mmol, 1.0 equiv.) in CH_3CN (15 mL) were added sequentially KH_2PO_4 (111.0 mg, 0.82 mmol, 0.6 equiv.) in H_2O (4 mL), $NaClO_2$ (196 mg, 2.18 mmol, 1.6 equiv.) and 30% H_2O_2 (220 µL, 1.6 equiv.) dropwise. The bright yellowish reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was quenched with Na_2SO_3 (34.0 mg, 2.72 mmol, 2.0 equiv.) and further stirred for 90 min at 0 °C. The reaction mixture was acidified with aqueous $KHSO_4$ (1N) and maintained to pH 2, water (20 mL) was added and extracted with CH_2Cl_2 (6 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallized from ethylacetate to afford **89 (**201.0 mg, 87%) as a colorless solid.

m.p. 62-64 °C; $[\alpha]_D^{20}$ = – 37.0 (c = 0.5, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 11.9-9.75 (bs, 1H, OH), 6.00-5.65 (m, 1H, 2‘-H), 5.30-5.10 (m, 2H, 3‘-H), 4.79-4.69 (m, 1H, 2-H), 3.20 (ddd, *J* = 9.8, 8.2, 6.8 Hz, 1H, 3-H), 2.95 (dd, *J* = 18.1, 8.1 Hz, 1H, 4-H), 2.82 (dd, *J* = 18.1, 9.8 Hz, 1H, 4-H), 2.66-2.43 (m, 2H, 1‘-H). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.8 (C_{quart}, CO), 173.8 (C_{quart}, COOH), 129.9 (2‘-C), 118.7 (3‘-C), 79.5 (2-C), 42.9 (3-C), 37.7 (4-C), 30.7 (1‘-C); **IR** (KBr): $\tilde{\nu}$ = 3439, 3085, 2928, 2593, 1983, 1747, 1643, 1427, 1356, 1234, 1196, 1109, 1059, 975, 918, 862, 670 cm^{-1}, **MS** (CI, NH_3): m/z (%) = 190.1 (48), 189.1 (10), 188.1 (100) [$M+NH_4^+$], 172.1 (1), 144.1 (18).

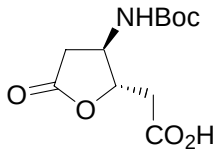


98

(*2S,3R*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-yl)-carbamic acid-*tert*-butylester (98):

In a flame-dried three necked 50 mL round bottom flask equipped with condenser was added a solution of **89** (150.0 mg, 0.88 mmol, 1 equiv.) in dry toluene (5 mL) and dry *t*-BuOH (5 mL) under N_2. Freshly distilled triethylamine (140 µL, 1.01 mmol., 1.15 equiv.) was added dropwise under stirring at room temperature over 5 min. The solution was immediately heated to reflux in a preheated oil bath at 120°C. DPPA (210 µL, 0.97 mmol, 1.1 equiv.) was added dropwise in 5 min. The resuling yellow-red solution was refluxed overnight. The solvent was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and subsequently washed with a 10% $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a brown residue which was purified by flash chromatography on silica (hexanes/ethylacetate 4:1) to afford **98** (109.0 mg, 51%) as a colorless solid.

R_f = 0.30 (SiO_2, hexanes/ethylacetate 3:1), m.p. 71-72 °C, $[\alpha]_D^{20} = -28.4$ (c = 0.1, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 5.88-5.74 (m, 1H, 2‘-H), 5.25-5.18 (m, 2H, 3‘-H), 4.85 (bs, 1H, N-H), 4.45-4.35 (m, 1H, 2-H), 4.18 (m, 1H, 3-H), 2.90 (dd, *J* = 18.1, 8.4 Hz, 1H, 4-H), 2.59-2.40 (m, 2H, 1‘-H), 2.44 (dd, *J* = 18.1, 5.7 Hz, 1H, 4-H), 1.45 (s, 9H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 174.3 (C_{quart}, CO), 154.9 (C_{quart}, CO), 131.4 (2‘-C), 119.7 (3‘-C), 84.9 (2-C), 80.6 (C_{quart}, Boc-C), 51.2 (3-C), 37.6 (4-C), 35.3 (1‘-C), 28.3 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3411, 3371, 2980, 2935, 2361, 1772, 1684, 1527, 1454, 1369, 1332, 1251, 1209, 1171, 980, 920, 654 cm^{-1}; **MS** (CI, NH_3): m/z (%) 259.3 (100) [$M+NH_4^+$], 242.3 (0.96) [$M + H^+$], 203.2 (91.74), 186.2 (5.65), 159.2 (5.12); **HRMS** (CI, NH_3): Calculated for [$C_{12}H_{19}NO_4 + H^+$] 242.1392, found 242.1397 [$M + H^+$]; elemental analysis calcd (%) for $C_{12}H_{29}NO_4$ (241.15): C 59.73, H 7.94, N 5.81; found: C 59.77, H 8.08, N 5.76.



49

(*2S,3R*)-(–)-(3-*tert*-Butoxycarbonylamino-5-oxo-tetrahydro-furan-2-yl)-acetic acid (49):

Method 1.

A solution of **98** (200.0 mg, 0.83 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) was cooled to –78 °C and treated with ozone until the mixture turned deep blue, excess ozone was expelled by passing oxygen through the solution, followed by addition of DMS (303 μL, 4.15 mmol, 5.0 equiv.). The mixture was warm to room temperature and stirring was continued for 21 h. The reaction mixture was subsequently washed with saturated $NaHCO_3$ (25 mL) and water (20 mL). Dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford aldehyde **102** (201.0 mg) in 95% (crude) yield. Then a cold (0 °C) solution of **102** (201.0 mg, 0.827 mmol, 1.0 equiv.) in CH_3CN (15 mL) were added sequentially KH_2PO_4 (67.5 mg, 0.50 mmol, 0.6 equiv.) in H_2O (2.5 mL), $NaClO_2$ (119.6 mg, 1.32 mmol, 1.6 equiv.) and 30% H_2O_2 (212 μL, 1.6 equiv.) dropwise. The bright yellowish reaction mixture was stirred for 4 h at 0°C. The reaction mixture was quenched with Na_2SO_3 (208.0 mg, 1.65 mmol, 2.0 equiv.) and further stirred for 90 min at the same temperature. The reaction mixture was acidified with aqueous $KHSO_4$ (1N) and maintained to pH 2, water (10 mL) was added and extracted with CH_2Cl_2 (6 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (ethylacetate/MeOH 10:1) to afford **49** (69 mg, 32 %) as a colorless solid.

Method 2.

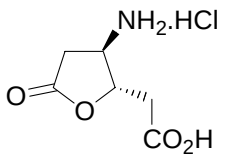
To a solution of **98** (200.0 mg, 0.83 mmol, 1 equiv) in dioxane-H_2O (3:1, 40 mL) were subsequently added $K_2O_4Os.2H_2O$ (4.6 mg, 1.3 mol%) and $NaIO_4$ (993.0 mg, 4.64 mmol, 5.6 equiv.) portion-wise over 5 min. The mixture was stirred at room temperature for 21 h, water (10 ml) was added and extracted with CH_2Cl_2 (3 x 40 mL), dried over anhydrous

$MgSO_4$, filtered and concentrated in vacuo to afford aldehyde **102** (205.0 mg) in 99% crude yield. Then a cold (0 °C) solution of **102** (201.0 mg, 0.827 mmol, 1.0 equiv.) in CH_3CN (15 mL) were added sequentially KH_2PO_4 (67.5 mg, 0.496 mmol, 0.6 equiv.) in H_2O (2.5 mL), $NaClO_2$ (119.6 mg, 1.32 mmol, 1.6 equiv.) and 30% H_2O_2 (212 µL, 1.6 equiv.) dropwise. The bright yellowish reaction mixture was stirred for 4 h at 0°C. The reaction mixture was quenched with Na_2SO_3 (208.0 mg, 1.65 mmol, 2.0 equiv.) and further stirred for 90 min at the same temperature. The reaction mixture was acidified with aqueous $KHSO_4$ (1N) and maintained to pH 2, water (10 mL) was added and extracted with CH_2Cl_2 (6 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (ethylacetate/MeOH 10:1) to afford **49** (70.0 mg, 33 %) as a colorless solid.

Method 3.

To a cold (0 °C) solution of **98** (350.0 mg, 1.45 mmol, 1 equiv.) in CCl_4-CH_3CN-H_2O (1:1:2, 45 mL) were added $RuCl_3 \cdot 3H_2O$ (2.4 mg, 6.3 mol%), $NaIO_4$ (1.24 g, 5.80 mmol, 4.0 equiv.) portion-wise, stirred for 42 h at 0°C. Water (20 mL) was added and extracted with CH_2Cl_2 (6 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give 354.0 mg of a crude brown oil which was recrystallized from ethylacetate-pentane afforded **49** (297.0 mg, 79%) as a colorless solid.

R_f = 0.75 (SiO_2, ethylacetate/MeOH 6:1); m.p. 132-133 °C; $[\alpha]_D^{20}$ = – 30.4 (c = 0.13, DMSO); **^{1}H-NMR** (300 MHz, DMSO): δ = 12.6 (s, 1H, OH), 7.35 (d, *J* = 6.59 Hz, 1H, NH), 4.46 (ddd, *J* = 13.4, 4.7, 4.1 Hz, 1H, 2-H), 4.06-3.99 (m, 1H, 3-H), 2.83 (dd, *J* = 17.7, 8.6 Hz, 1H, 4-H), 2.69 (dd, *J* = 16.5, 3.8 Hz, 1H, 1‘-H), 2.54 (dd, *J* = 16.5, 8.5 Hz, 1H, 1‘-H), 2.39 (dd, *J* = 11.9, 5.6 Hz, 1H, 4-H), 1.34 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, DMSO-d_6): δ = 174.4 (C_{quart}, CO), 171.0 (C_{quart}, COOH), 155.0 (C_{quart}, CO), 81.2 (2-C), 78.4 (C_{quat}, Boc-C), 50.7 (3-C), 37.8 (1‘-C), 33.9 (4-C), 28.0 (Boc-C); IR (KBr): $\tilde{\nu}$ = 3342, 3101, 2989, 1757, 1718, 1667, 1522, 1367, 1348, 1269, 1194, 1163, 1004 cm^{-1}; **MS** [CI, NH_3]: m/z (%) 277.2 (91.0) [$M+NH_4^+$], 260.2 (3.4) [$M + H^+$]; **HRMS** (CI, NH_3): Calculated for [$C_{11}H_{17}NO_6 + H^+$]: 260.1134, found 260.1135 [$M + H^+$].



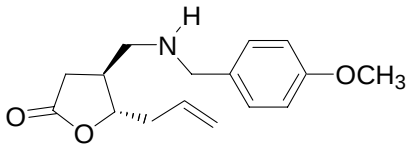
103

(*2S,3R*)-(3-amino-5-oxo-tetrahydro-furan-2-yl)-acetic acid mono hydro-chloride (103):

The compound **49** (50.0 mg, 0.19 mmol, 1.0 equiv.) was treated with saturated HCl in dry ethylacetate (15 mL) at 0 °C for 3 h, and solvent was removed in vacuo, dried on oil pump overnight to afford **103** (37.0 mg , 97%) as a brown solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.80-11.96 (bs, 1H,OH), 8.35 (s, 3H, NH_2.HCl), 4.80-4.68 (m, 1H, 2-H), 3.89-3.87 (m, 1H, 3-H), 3.18 (dd, *J* = 18.1, 8.4Hz. 1H, 4-H), 2.95-2.55 (m, 3H, 4-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, DMSO-d_6): δ = 173.4 (C_{quart}, CO), 170.9 (C_{quart}, COOH), 78.6 (2-C), 49.6 (3-C), 37.5 (1‘-C), 32.7 (4-C); **MS** [CI, NH_3]: m/z (%) 160.0 (100) [M + H^+], 177.1 (32.74) [M + NH_4^+]; **HRMS** (EI, 70 eV): Calculated for [$C_6H_9NO_4$]: 159.0531, found 159.0533 [M^+].

2.3 δ-amino acids



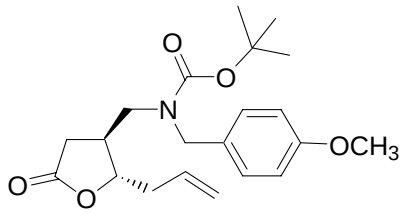
111b

(*4S,5S*)-(–)-(5-Allyl-4-[(4-methoxy-benzylamino)-methyl]-dihydro-furan-2-one (111b):

To a solution of **48** (450.0 mg, 2.90 mmol, 1.0 equiv.) in dry CH_2Cl_2 (32 mL) were added sequentially 1.0 g of powdered and activated 4Å molecular sieves, 4-methoxybenzylamine (570 µL, 4.37 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 16 h. The resulting brownish mixture was cooled to 0 °C in an ice bath, $NaBH_4$ (220.0 mg, 5.84 mmol, 2.0 equiv.) and dry MeOH (8 mL) were added slowly over 15 min. The

reaction mixture was further stirred for 90 min at 0 °C, H_2O (10 mL) was added and stirred for 15 min, filtered and washed with brine (2 x 15 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (ethylacetate) to afford **111b (**710.0 mg, 89%) as a colorless oil.

R_f = 0.40 (SiO_2, ethylacetate); $[\alpha]_D^{20}$ = – 19.42 (c = 1.04 , CH_2Cl_2) ; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 11.5, 8.5 Hz, 2H, PMB-H), 6.89-6.81 (m, 2H, PMB-H), 5.79 (dddd, *J* = 16.9, 10.9, 6.8, 6.8 Hz, 1H, 2‘-H), 5.20-5.13 (m, 2H, 3‘-H), 4.34 (dd, *J* = 11.7, 5.4 Hz, 1H, 5-H), 3.80 (s, 3H, OCH_3), 3.71 (s, 2H, PMB-*CH_2*), 2.73-2.61 (m. 2H, *CH_2*-NHPMB), 2.53-2.20 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 176.4 (C_{quart}, CO), 158.8 (C_{quart}, PMBn), 132.4 (PMB-C), 132.0 (C_{quart}, PMB-C), 129.2 (2‘-C), 119.0 (3‘-C), 113.9 (PMB-C), 83,1 (5-C), 55.3 (OCH_3), 53.3 (CH_2-PMB), 51.4 (CH_2-NHPMB), 39.9 (4-C), 39.1 (3-C), 33.2 (1‘-C); **IR** (KBr): $\tilde{\nu}$ = 3329, 3070, 2924, 2831, 2357, 2057, 1772, 1679, 1611, 1508, 1454, 1288, 1246, 1176, 1029, 985, 918, 819 cm^{-1}; **MS** (CI, NH_3): m/z (%) = 276.3 (100) [M + H^+]**; HRMS** (EI, 70 eV): Calculated for [$C_{16}H_{21}NO_3$]: 275.1521, found 275.1515 [M^+].



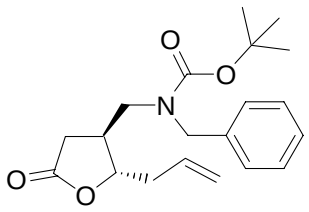
114b

(*2S,3S*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid *tert*-butylester (114b):

To a solution of **111b** (710.0 mg, 2.58 mmol, 1.0 equiv.) in dry CH_2Cl_2 (25 mL) was added di-*tert*-butyldicarbonate (1.13 g, 5.16 mmol, 2.0 equiv.), and catalytic amount of DMAP (1.0 mg). The reaction mixture was stirred at room temperature for 36 h, washed subsequently with 5% aqueous citric acid (15 mL) and brine (15 mL). The aqueous layer

was separated and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by chromatography (hexanes/ethylacetate 4:1) to give **114b (**690.0 mg, 71%) as a colorless oil.

R_f = 0.35 (SiO_2, hexanes/ethylacetate 3:1); $[\alpha]_D^{20}$ = – 10.37 (c = 0.96, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.20-7.11 (m. 2H, PMB-H), 6.91-6.84 (m, 2H, PMB-H), 5.85-5.67 (m, 1H, 2‘-H), 5.23-5.10 (m, 2H, 3‘-H), 4.40 (s, 2H, PMB-*CH_2*), 4.24 (bs, 1H, 2-H), 3.80 (s, 3H, OCH_3), 3.26 (bs, 2H, *CH_2*-NR_2), 2.59-2.22 (m, 5H, 4-H, 3-H, 1‘-H), 1.5 (s, 9H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.7 (C_{quart}, CO), 159.1 (C_{quart}, PMB), 155.8 (C_{quart}, CO), 132.1 (C_{quart}, PMB-C), 129.6 (2’-C), 128.8 (PMB-C), 119.1 (3‘-C), 114.1 (PMB-C), 82.5 (2-C), 80.7 (C_{quart}, Boc-C), 55.3 (OCH_3), 48.4 (($PMB-CH_2$), 39.9 (3-C), 38.6 (CH_2-NR_2), 33.0 (4-C), 28.4 (Boc-C); **IR** (Film): $\tilde{\nu}$ = 3076, 2976, 2931, 2837, 2372, 1778, 1690, 1612, 1512, 1462 1413, 1365, 1124, 1034, 984, 917, 815 cm^{-1}; **MS** (EI, 70 eV): m/z (%) = 375.3 [M^+]; **HRMS** (EI, 70 eV): Calculated for [$C_{21}H_{29}NO_5$]: 375.2046, found 375.2046 [M^+].



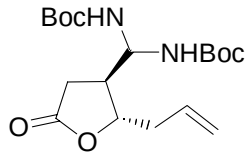
114a

(*2S,3S*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-benzyl)-carbamic acid *tert*-butyl ester (114a):

To a solution of **48** (500.0 mg, 3.24 mmol, 1.0 equiv.) in dry CH_2Cl_2 (32 mL) were added sequentially 1.0 g of powdered and activated 4Å molecular sieves and benzylamine (530 μL, 4.86 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 16 h. The resulting brownish mixture was cooled to 0 °C in an ice bath, $NaBH_4$ (250.0 mg, 6.48 mmol, 2.0 equiv.) and dry MeOH (15 mL) were added slowly over 15 min. The reaction mixture was further stirred for 90 min at 0 °C, H_2O (15 mL) was added and stirred for 15

min, filtered and washed with brine (2 x 25 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford crude amine **111a (**715.0 mg, 90%) as a colorless oil. Then to a solution of **111a** (715.0 mg, 2.07 mmol, 1.0 equiv.) in dry CH_2Cl_2 (25 mL) was added di-*tert*-butyldicarbonate (903.0 mg, 4.14 mmol, 2.0 equiv.) portion-wise. The reaction mixture was stirred at room temperature for 36 h, washed subsequently with 5% aqueous citric acid (15 mL) and brine (25 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by chromatography (hexanes/ethylacetate 3:1) to afford **114a (**501.0 mg, 70%) as a colorless oil.

R_f = 0.17 (SiO_2, hexanes/ethylacetate 4:1); $[\alpha]_D^{20}$ = – 11.3 (c = 0.48, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.37-7.26 (m. 5H, Ph), 5.81-5.67 (m, 1H, 2‘-H), 5.16-5.10 (m, 2H, 3‘-H), 4.44 (s, 2H, Ph-*CH_2*), 4.25 (bs, 1H, 2-H), 3.29 (bs, 2H, *CH_2*-NR_2), 2.60-2.17 (m, 5H, 4-H, 3-H, 1‘-H), 1.48 (s, 9H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.7 (C_{quat}, CO), 155.8 (C_{quart}, CO), 137.6 (C_{quart}, Ph-C), 132.1 (2’-C), 128.8 (Ph-C), 127.6 (Ph-C), 127.3 (Ph-C), 119.1 (3‘-C), 82. (2-C), 80.7 (C_{quart}, Boc-C), 48.7 (Ph-CH_2), 38.9 (3-C), 38.6 (4-C), 33.1 (CH_2-NR2), 28.4 (Boc-C); **IR** (Film): $\tilde{\nu}$ = 3072, 2976, 2930, 2837, 2337, 1778, 1692, 1512, 1455, 1455, 1370, 1248, 1167, 1074, 1036, 985, 916, 875, 700 cm^{-1}; **MS** (CI, NH_3): m/z (%) = 363.3 (52.7) [M + NH_4^+], 346.2 (1.2) [M + H^+], 307.2 (100) [M + NH_4^+ – C_4H_8], 290.1 (29.3) [M + H^+ – C_4H_8].

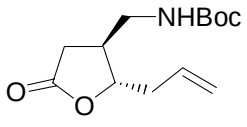


112

(*2S,3S*)-(–)-[(2-Allyl-5-oxo-tetrahydro-furan-3-yl)-*tert*-butoxycarbonylaminomethyl]-carbamic acid *tert*-butyl ester (112):

To a solution of **48** (160.0 mg, 1.04 mmol, 1.0 equiv.) in CH_3CN (10 ml) was added Boc-amine (360.0 mg, 3.12 mmol, 3.0 equiv.) followed by triethylsilane (490 µL, 3.12 mmol, 3.0 equiv.) and TFA (160 µL, 2.08 mmol, 2.0 equiv.). The reaction mixture was stirred for 20 h at room temperature. Then washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by chromatography on silica (hexanes/ethylacetate 3:1) to afford **112 (**250.0 mg, 65%) as a colorless solid.

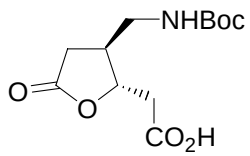
R_f (SiO_2, hexanes/ethylacetate 3:1) = 0.22; m.p. 143-144 °C; $[\alpha]_D^{20}$ = – 9.2 (c = 0.50, CH_2Cl_2**); ^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 5.85-5.67 (m, 1H, 2‘-H), 5.57 (bs, 2H, N-H), 5.20-5.10 (m, 2H, 3‘-H), 4.73 (bs, 1H, *CH*$(NHBoc)_2$, 4.47-4.41 (m, 1H, 2-H), 3.08 (bs, 1H, 3-H), 2.66 (dd, *J* = 18.3, 9.4 Hz, 1H, 4-H), 2.54-2.31 (m, 3H, 4-H, 1‘-H), 1.41 (2s, 18H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.4 (C_{quart}, CO), 155.1 (C_{quart}, CO), 131.8 (2‘-C), 119.5 (3‘-C), 81.7 (2-C), 80.7 (C_{quart}, Boc-C), 61.7 $CH(NHBoc)_2$, 39.1 (1’-C), 38.7 (3-C), 30.4 (4-C), 28.3 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3430, 3286, 2981, 2937, 1781, 1691, 1557, 1509, 1366, 1311, 1253, 1172, 1046, 1013, 870, 766, 671 cm^{-1}; **MS** (CI, NH_3): m/z (%) = 371.2 (14.02) [M + H^+], 388.3 (67.69) [M+NH_4^+].



(*2S,3S*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-carbamic acid *tert*-butylester (117):

To a cold (0 °C) solution of **114b** (360.0 mg, 0.96 mmol, 1.0 equiv.) in CH_3CN (24 mL) was added slowly a solution of CAN (1.84 g, 3.36 mmol, 3.5 equiv.) in H_2O (8 mL) over 15 min. The resulting bright yellow reaction mixture was stirred for 2 h at 0 °C, H_2O (15 mL) was added and extracted with ethylacetate (3 x 40 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ (40 mL) and water (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica (hexanes/ethylacetate 3:1) to afford **117** (227.0 mg, 93%) as a colorless solid.

R_f (SiO_2, hexanes/ethylacetate 3:1) = 0.29; m.p. 72-73 °C; $[\alpha]_D^{20}$ = – 21.58 (c = 1.01, CH_2Cl_2**);** ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ = 5.81 (ddd, *J* = 17.8, 16.5, 7.1 Hz, 1H, 2‘-H), 5.25-5.15 (m, 2H, 3‘-H), 4.73 (bs, 1H, N-H), 4.31 (dd, *J* = 11.8, 5.8 Hz, 1H, 2-H), 3.33-3.17 (m, 2H, *CH*$_2$-NHBoc), 2.68 (dd, *J* = 17.2, 8.1 Hz, 1H, 4-H), 2.59-2.42 (m, 3H, 3-H, 1‘-H), 2.34 (dd, *J* = 17.3, 7.1 Hz, 1H, 4-H), 1.41 (s, 9H, Boc-H); ^{13}**C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.7 (C_{quart}, CO), 156.0 (C_{quart}, CO), 131.0 (2‘-C), 119.3 (3‘-C), 82.3 (2-C), 80.0 (C_{quart}, Boc-C), 40.2 (3-C), 38.7 (4-C), 38.5 (1‘-C), 28.3 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3474, 2979, 1778, 1682, 1523, 1446, 1265, 1168, 1067, 995, 910, 855 cm^{-1}; **MS** (CI, NH_3): m/z (%) = 273.2 (71.32) [$M+NH_4^+$], 256.1 (1.07) [$M + H^+$], 256.1 (100) [($M+NH_4^+$) – C_4H_8]; elemental analysis calcd (%) for $C_{13}H_{21}NO_4$ (255.15): C 61.16, H 8.29, N 5.49; found: C 61.04, H 7.86, N 5.35.

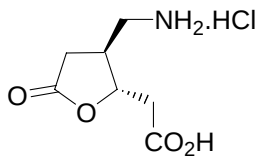


50

(*2S,3S*)-(–)-[3-(tert-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid (50):

To a cold (0 °C) solution of **117** (112.0 mg, 0.44 mmol, 1.0 equiv.) in CCl_4-CH_3CN-H_2O (1:1:2, 14 mL) were added sequentially $RuCl_3 \cdot 3H_2O$ (0.7 mg, 6.3 mol%), $NaIO_4$ (380.0 mg, 1.75 mmol, 4.0 equiv.) portion-wise and stirred for 36 h at 0 °C, water (15 mL) was added and extracted with CH_2Cl_2 (6 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give 224.0 mg of a brown oil which was purified by column chromatography on silica (ethylacetate/methanol 6:1) to afford **50** (97.0 mg, 81%) as a colorless solid.

R_f = 0.67 (SiO_2, hexanes/ethylacetate 6:1); m.p. 138-139 °C; $[\alpha]_D^{20}$ = – 7.41 (c = 0.4, DMSO); **^{1}H-NMR** (300 MHz, DMSO-d_6): δ = 12.75-12.20 (bs, 1H, OH), 7.07 (t, *J* = 5.9 Hz, 1H, NH), 4.55 (ddd, *J* = 8.4, 5.4, 4.5 Hz, 1H, 2-H), 3.15-2.96 (m, 2H, *CH_2*-NHBoc), 2.74-2.25 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, DMSO-d_6): δ = 175.8 (C_{quart}, CO), 171.3 (C_{quart}, COOH), 155.8 (C_{quart}, CO), 78.9 (2-C), 77.8 (C_{quart}, Boc-C), 41.3 (CH_2-NHBoc), 39.8 (3-C), 39.0 (1‘-C), 31.6 (4-C), 28.0 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3327, 3101, 2989, 2938, 2569, 1783, 1716, 1658, 1534, 1477, 1419, 1369, 1348, 1256, 1022, 1089, 952, 930 cm^{-1}; **MS** [ESI, (CH_2Cl_2/MeOH + 10 mmol/l NH_4Ac)NH_3]: m/z (%) = 290.8 (100) [M + NH_4^+], 273.7 (4.7) [M + H^+]; elemental analysis calcd (%) for $C_{12}H_{19}NO_6$ (273.12): C 52.74, H 7.01, N 5.13; found: C, 52.40, H 6.73, N, 5.03.

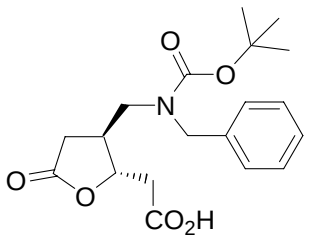


118

(*2S,3S*)-(–)-(3-Aminomethyl-5-oxo-tetrahydro-furan-2-yl)-acetic acid monohydro-chloride (118):

The compound **50** (50.0 mg, 0.18 mmol, 1.0 equiv.) was treated with saturated HCl in dry ethylacetate (10 mL) at 0 °C for 3 h, and solvent was removed in vacuo, dried on oil pump overnight to afford **118** (37.0 mg, 97%) as a colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.80-11.96 (bs, 1H,OH), 8.25 (bs, 3H, NH_2.HCl), 4.65-4.55 (m, 1H, 2-H), 3.15-2.96 (m, 2H, *CH_2*-NH_2.HCl), 2.94-2.55 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, DMSO-d_6): δ = 175.2 (C_{quart}, COOH), 171.2 (C_{quart}, CO), 78.1 (2-C), 39.9 (CH_2-NH_2.HCl), 39.6 (1‘-C), 37.8 (3-C), 32.6 (4-C); MS (CI, NH_3): m/z (%) = 174 (92) [M + H^+], 155.9 (39.35) [(M + H^+) - H_2O]; **HRMS** (EI, 70 eV): calculated for [$C_7H_{11}NO_4$]: 173.0688, found 173.0687 [M^+].



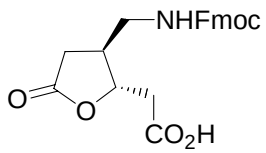
116

(*2S,3S*)-(–)-{3-[(Benzyl-*tert*-butoxycarbonyl-amino)-methyl]-5-oxo-tetrahydro-furan-2-yl}-acetic acid (116):

A solution of **114a** (200.0 mg, 0.577 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) was cooled to –78 °C and treated with ozone until the mixture turned deep blue, excess ozone was expelled by passing oxygen through the solution, followed by addition of DMS (211 µL, 2.88 mmol, 5.0 equiv.). The mixture was warm to room temperature and stirred for 21 h. The reaction mixture was subsequently washed with saturated $NaHCO_3$ (25 mL) and water

(20 mL). Dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford aldehyde **115** (201.0 mg) in 95% (crude) yield. Then a cold (0 °C) solution of **115** (201.0 mg, 0.575 mmol, 1.0 equiv.) in CH_3CN (15 mL) were added sequentially KH_2PO_4 (47.0 mg, 0.345 mmol, 0.6 equiv.) in H_2O (1.5 mL), $NaClO_2$ (83 mg, 0.917 mmol, 1.6 equiv.) and 30% H_2O_2 (90 µL, 1.6 equiv.) dropwise. The bright yellowish reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was quenched with Na_2SO_3 (144.0 mg, 1.15 mmol, 2.0 equiv.) and further stirred for 90 min at the same temperature. The reaction mixture was acidified with aqueous $KHSO_4$ (1N) and maintained to pH 2, water (10 mL) was added and extracted with CH_2Cl_2 (6 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (ethylacetate/MeOH 10:1) to afford **116** (76.0 mg, 36%) as a colorless solid.

R_f = 0.35 (SiO_2, ethylacetate/MeOH 3:1); $[\alpha]_D^{20}$ = – 5.31 (c = 0.26, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 10.8-9.75 (bs. 1H, OH), 7.41-7.12 (m, 5H, Bn), 4.60 (s, 1H, 2-H), 4.42 (s, 2H, Bn-CH_2), 3.36-3.28 (bm, 2H, *CH_2*-NR_2), 2.82-2.20 (m, 5H, 4-H, 3-H, 1‘-H), 1.46 (s, 9H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 174.4 (C_{quat}, CO), 172.9 (C_{quat}, COOH), 154.9 (C_{quart}, CO), 136.5 (C_{quart}, Bn-C), 127.8 (Bn-C), 126.7 (Bn-C), 126.3 (Bn-C), 80.1 (2-C), 77.8 (C_{quart}, Boc-C), 50.8 (Bn-CH_2), 47.6 (CH_2-NR_2), 38.4 (3-C), 37.8 (4-C), 31.8 (1‘-C), 27.3 (Boc-C); **IR** (Film): $\tilde{\nu}$ = 3175, 3065, 2976, 2932, 2635, 1781, 1735, 1690, 1454, 1418 1413, 1368, 1251, 1162, 1076, 1015, 984, 930, 874, 739, 701 cm^{-1}; **MS** (CI, NH_3): m/z (%) = 391.3 (12) 381.3 (39) [M + NH_4^+]; **HRMS** (EI, 70 eV): Calculated for [$C_{21}H_{29}NO_5$]: 375.2046, found 375.2046 [M^+].



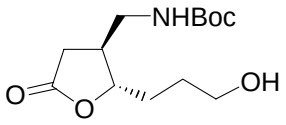
119

(*2S,3S*)-(–)-{3-[9*H*-Fluoren-9-ylmethoxycarbonylamino)-methyl]-5-oxo-tetrahydro-furan-2-yl}-acetic acid (119):

The compound **50** (238.0 mg, 0.18 mmol, 1.0 equiv.) was treated with saturated HCl in dry ethylacetate (20 mL) at 0 °C for 3 h. The solvent was removed in vacuo, dried on oil pump overnight to afford **118** (208.2 mg) as a colorless solid. To a cold (0 °C) solution of **118** (208.2 mg, 0.99 mmol, 1.0 equiv.) in dioxane-H_2O (1:2, 20 ml) was slowly added a solution of Fmoc-Cl (308.1 mg, 1.19 mmol, 1.2 equiv.) in dioxane (5 mL) within 10 min at 0 °C. Then the reaction mixture was stirred for 15 h at room temperature and diluted with CH_2Cl_2 (20 mL), wahsed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford an oil which was purified by column chromatography on silica (CH_2Cl_2/MeOH 5:1) to afford **119** (263.0 mg, 67%) as a colorless solid.

R_f = 0.29 (SiO_2, CH_2Cl_2/MeOH 3:1); m.p. 86-87 °C; $[\alpha]_D^{20}$ = – 8.41 (c = 0.4, DMSO); **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 14.20-9.55 (bs. 1H, OH), 7.89 (d, *J* = 7.45 Hz, 2H, Fmoc-H), 7.68 (d, *J* = 7.45 Hz, 2H, Fmoc-H), 7.54 (t, *J* = 5.7 Hz, 1H, N-H), 7.41 (t, *J* = 7.56 Hz, 2H, Fmoc-H), 7.33 (t, *J* = 7.34 Hz, 2H, Fmoc-H), 4.59-4.54 (m, 1H, 2-H), 4.32 (d, *J* = 6.80 Hz, 2H, Fmoc-CH_2), 4.22 (t, *J* = 6.80 Hz, 1H, Fmoc-H), 3.18-3.06 (m, 2H, CH_2-NHFmoc), 2.69-2.25 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (100.6 MHz, DMSO-d_6): δ = 175.9 (C_{quart}, CO), 172.0 (C_{quart}, COOH), 156.4 (C_{quart}, CO), 143.8 (Fmoc-C), 140.6 (Fmoc-C), 127.5 (Fmoc-C), 127.0 (Fmoc-C), 125.0 (Fmoc-C), 120.0 (Fmoc-C), 79.4 (2-C), 65.3 (Fmoc-CH_2), 46.6 (C_{quart}, Fmoc), 41.9 (CH_2-NR_2), 39.8 (4-C), 39.6 (3-C), 31.7 (1‘-C); **IR** (Film): $\tilde{\nu}$ = 3402, 3065, 2948, 2605, 1776, 1708, 1538, 1471, 1446, 1420, 1334, 1257, 1195, 1152, 1080, 1014, 984, 934, 741, 645 cm^{-1}; **MS** (ESI): m/z (%) = 395.5 (29) [$M+H^+$], 413.0 (100) [$M + NH_4^+$]; **HRMS** (EI, 70 eV): Calculated for [$C_{22}H_{21}NO_6$]: 395.1369, found 395.1368 [M^+].

2.4 ε-amino acids



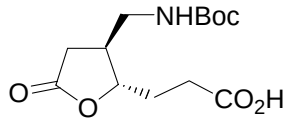
123

(*2S,3S*)-(–)-[2-(3-Hydroxy-propyl)-5-oxo-tetrahydro-furan-3-ylmethyl]-carbamic acid *tert*-butyl ester (123):

A solution of catecholborane (940.0 mg, 7.83 mmol, 2.0 equiv.) in dry THF (6 mL) was added dropwise to a cold (0 °C) mixture of **117** (1.0 g, 3.92 mmol, 1.0 equiv.) and $Rh(PPh_3)_3Cl$ (73.0 mg, 2 mol%) in dry THF (20 mL). The reaction mixture was stirred at room temperature for 1 h, and further cooled to 0 °C, were added sequentially a mixture (1:1) of THF and EtOH (10 mL), phosphate buffer (pH 7.2, 10 mL), and 30% H_2O_2 (10 mL). The reaction mixture was warm to room temperature, stirred overnight, and concentrated in vacuo. The residue was diluted with ethylacetate, wahsed with brine (20 mL). The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with a 10% Na_2CO_3 until the aqueous layer remain colorless. The organic phase was washed with brine (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford an oil which was purified by column chromatography on silica (hexanes/ethylacetate 1:1) to afford **123** (762.0 mg, 71%) as a white solid.

R_f = 0.34 (SiO_2, ethylacetate); m.p. 54-55 °C; $[\alpha]_D^{20}$ = – 25.83 (c = 0.96 , CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 4.86 (bs, 1H, NH), 4.30-4.27 (m, 1H, 2-H), 3.73-3.66 (m, 2H, 3‘-H), 3.27-3.21 (m, 2H, *CH_2*-NHBoc), 2.64(dd, *J* = 20.9, 12.1 Hz, 1H, 4H), 2.43-2.34 (m, 2H, 3-H, 4-H), 1.91-1.66 (m, 4H, 1‘-H, 2‘-H), 1.44 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.8 (C_{quart}, CO), 156.3 (C_{quart}, CO), 82.6 (2-C), 80.2 (C_{quart}, Boc-C), 61.5 (3’-C), 41.8 (3-C), 41.5 (CH_2-NHBoc), 32.5 (4-C), 30.9 (1’-C), 28.5 (2’-C), 28.3 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3364, 3268, 2937, 2872, 2575, 2383, 2200, 1779, 1682, 1529, 1447, 1368, 1333, 1269, 1170, 1096, 1066, 985, 889, 851, 782, 725, 690, 653; **MS** (CI, NH_3): m/z (%) =

291.1 (61) [M + NH_4^+], 235.0 (100) [(M+NH_4^+) – C_4H_8], 217.1 (35) [(M + NH_4^+) - C_4H_8 - H_2O], 191.0 (3) [(M+NH_4^+) – H_2O] ; **HRMS** (LSI): Calculated for [$C_{13}H_{23}NO_5$ + H^+]: 274.1648, found 274.1647 [M + H^+].



51

(*2S,3S*)-(–)-3-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-propionic acid (51):

To a cold (0 °C) solution of **123** (72.3 mg, 0.26 mmol, 1 equiv.) in acetone (10 mL) were added 15% $NaHCO_3$ solution (300µL), NaBr (5.4 mg,0.05 mmol, 0.2 equiv.) and TEMPO (0.8 mg, 0.005 mmol, 0.02 equiv.). Trichloroisocyanuric acid (122.0 mg, 0.53 mmol, 2.0 equiv.) was slowly added within 10 min at 0 °C. The reaction mixture was stirred at room temperature for 6 h, 2-propanol (300 µL) was added, filtered through celite and concentrated in vacuo. The residue was treated with saturated Na_2CO_3 (5 mL). The aqueous phase was treated with 1N HCl, extracted with ethylacetate (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (ethylacetate/methanol 6:1) to afford **51** (62.0 mg, 83%) as a colorless solid.

R_f = 0.28 (SiO_2, ethylacetate/methanol 6:1); m.p. 127-130 °C; $[\alpha]_D^{20}$ = – 17.2 (c = 0.55, DMSO); **^{1}H-NMR** (300 MHz, DMSO-d_6): δ = 13.8-10.7 (bs, 1H, OH), 7.09 (t, *J* = 5.9 Hz, 1H, NH), 4.21 (dd, *J* = 8.2, 4.7 Hz, 1H, 2-H), 3.05-2.95 (m, 2H, *CH*$_2$-NHBoc), 2.63 (dd, *J* = 19.5, 10.9 Hz, 1H, 4-H), 2.38-2.16 (m, 4H, 4-H, 3-H, 2‘-H), 1.98-1.70 (m, 2H, 1‘-H), 1.38 [s, 9H, C(CH_3)$_3$]; **^{13}C-NMR** (150.9 MHz, DMSO-d_6): δ = 175.9 (C_{quart}, CO), 174.6 (C_{quart}, COOH), 155.8 (C_{quart}, CO), 82.2 (2-C), 77.8 (C_{quart}, Boc-C), 41.7 (CH_2-NHBoc), 39.8 (3-C), 31.9 (4-C), 30.8 (2’-C), 30.0 (1’-C), 28.1 [C(CH_3)$_3$]; **IR** (KBr): $\tilde{\nu}$ = 3409, 2976, 2932, 2779, 2538, 2199, 1772, 1710, 1527, 1442, 1408, 1367, 1274, 1253, 1169, 1039, 950, 897, 858, 783 cm^{-1}; **MS** [ES, (CH_2Cl_2/MeOH + 10 mmol/l NH_4Ac)NH_3]: m/z (%) = 310.0 [M +

Na^+], 305 (100) [M + NH_4^+]; **HRMS** (LSI): Calculated for [$C_{13}H_{21}NO_6$ + H^+]: 288.1447, found 288.1448 [M + H^+].

2.5 δ-peptides

General procedure for solid phase loading GP 1

Wang resin

The resin was swelled in CH_2Cl_2 for 30 min. The mixture was drained and Boc-γ-amino acid **49** (4.0 equiv.), HOBt (4.0 equiv.), DIC (4.0 equiv.), DIPEA (4.0 equiv.) were added in CH_2Cl_2 and DMF (4:1, 12 mL/g). The resin was agitated at room temperature overnight. The mixture was drained and the resin was washed with DMF (5 x 15 mL/g of resin), CH_2Cl_2 (5 x 15 mL/g of resin), and diethyl ether (5 x 15 mL/g of resin). The resin was dried under vacuum at room temperature overnight. The loading of the resin was estimated from the weight gain of the resin.

SAB resin

The resin was swelled in CH_2Cl_2 for 30 min. The mixture was drained and Boc-γ-amino acid **49** (4.0 equiv.), DIC (4.0 equiv.), MeIm (4.0 equiv.) were added in CH_2Cl_2 and DMF (4:1, 12 mL/g). The resin was agitated at room temperature overnight. The mixture was drained and the resin was washed with DMF (5 x 15 mL/g of resin). CH_2Cl_2 (5 x 15 mL/g of resin), and diethyl ether (5 x 15 mL/g of resin), The resin was dried under vacuum at room temperature overnight. The loading of the resin was estimated from the weight gain of the resin.

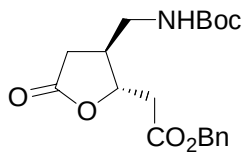
2-chlorotrityl chloride resin

The resin was swelled in CH_2Cl_2 for 30 min. The mixture was drained and Fmoc-δ-amino acid **50** (4.0 equiv.), DIPEA (4.0 equiv.) were added in CH_2Cl_2 and DMF (1:1, 12 mL/g). The resin was agitated at room temperature for 2-5 h. The mixture was drained and the resin was washed with DMF (5 x 15 mL/g of resin), CH_2Cl_2 (5 x 15 mL/g of resin), and diethyl ether (5 x 15 mL/g of resin). The resin was dried under vacuum at room temperature

overnight. The loading of the resin was estimated from the weight gain of the resin; spectrophotometrically from the amount of Fmoc released from a weighed sample of the resin and by estimation of the amount of amino acid released by cleavage from the resin.

General procedure for solid phase coupling of Fmoc-δ-amino acid on Fmoc-δ-amino acid loaded on a 2-chlorotrityl chloride resin. GP 2

The loaded resin was swelled in CH_2Cl_2 for 20 min (15 mL/g of resin). The mixture was drained and capped with CH_2Cl_2/MeOH/DIPEA (17:2:1). The mixture was drained and the resin was washed with DMF (10 x 15 mL/g of resin). The capped resin was agitated with 20% piperidine in DMF (15 mL/g of resin) for 10-20 min. The mixture was drained, the resin was washed with DMF (10 x 15 mL/g of resin) to give *N*-free amino acid **136** and couple with a solution of Fmoc-δ-amino acid **50** (3.0 equiv.), HOBt (3.0 equiv.), HBTU (3.0 equiv.) and DIPEA (6.0 equiv.) in DMF. The resin was agitated for 2 h at room temperature. The mixture was drained and the resin was washed with DMF (10 x 15 mL/g of resin). The synthesis was then continued as usual by cleaving the Fmoc-group and couple with Fmoc-δ-amino acid **50** in twice. Acetylated with Ac_2O/DIPEA in DMF for 15 min. The mixture was drained and the resin was washed with DMF (5 x 15 mL/g of resin). Then treated with 20% piperidine, washed with DMF (6 x 15 mL/g of resin), CH_2Cl_2 (5 x 15 mL/g of resin), and diethyl ether (5 x 15 mL/g of resin). Finally cleavage of the resin with 1% TFA and 5% TIS in CH_2Cl_2 to afford tetramer **54** (minor) and **140** (major).

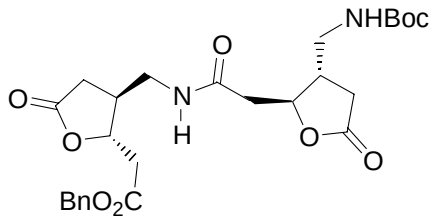


141

(*2S,3S*)-(–)-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydrofuran-2-yl]-acetic acid benzyl ester (141):

To a solution of **50** (945.0 mg, 3.46 mmol, 1.0 equiv.) in dry DMF (40 mL) were added successively anhydrous K_2CO_3 (860.0 mg, 6.22 mmol, 1.8 equiv.) and BnBr (660 µL, 5.53 mmol, 1.6 equiv.) at room temperature. The reaction mixture was stirred for 36 h, DMF was removed under reduced-pressure distilation (1 mbar Hg, 25 °C). The residue was dissolved in CH_2Cl_2 (50 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica (hexanes/ethylacetate 1:2) to afford **141** (884.0 mg, 70%) as a colorless oil.

R_f = 0.67 (SiO_2, hexanes/ethylacetate 1:2); $[\alpha]_D^{20}$ = – 24.92 (c = 0.97, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.40-7.31 (m, 5H, Bn), 5.16 (s, 2H, Bn-CH_2), 4.82 (bs, 1H, NH), 4.66 (dd, *J* = 12.3, 6.3 Hz, 1H, 2-H), 3.30-3.15 (m, 2H, CH_2-NHBoc), 2.82-2.75 (m, 2H, 1'H), 2.67 (dd, J = 17.2, 8.6 Hz, 1H, 4-H), 2.57-2.47 (m, 1H, 3-H), 2.37 (dd, J = 17.0, 7.1 Hz, 1H, 4-H), 1.42 (s, 9H, Boc-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.1 (C_{quart}, CO), 168.5 (C_{quart}, CO), 156.1 (C_{quart}, Boc-CO), 135.2 (C_{quart}, Bn), 128.6 (Bn-C), 128.5 (Bn-C), 128.4 (Bn-C), 80.1 (C_{quart}, Boc), 78.5 (2-C), 66.9 (Bn-CH_2), 41.9 (CH2-NHBoc), 40.9 (3-C), 39.2 (4-C), 32.2 (1'-C), 28.3 (Boc-C); **IR** (KBr): $\tilde{\nu}$ = 3369, 2976, 2932, 2199, 1782, 1710, 1520, 1454, 1392, 1367, 1252, 1161, 1074, 1012, 967, 923, 857, 752, 699 cm^{-1}; **CI-MS** (NH_3): m/z (%) = 381.1 (100) [M + NH_4^+], 325.0 (45) [(M + NH_4^+) - C_4H_4]; **HRMS** (LSI): Calculated for [$C_{19}H_{25}NO_6$ + H^+]: 364.1760, found 364.1760 [M + H^+].

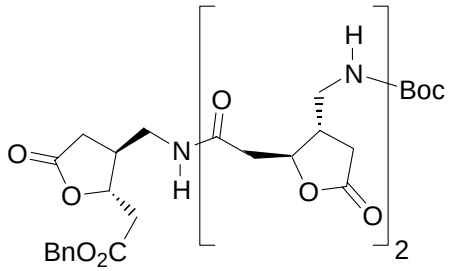


143

[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetyl-amino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (143):

The compound **141** (325.4 mg, 0.90 mmol, 1.0 equiv.) was treated with saturated HCl in ethylacetate (25 mL) at 0 °C for 3 h. The solvent was removed in vacuo, the residue was dried on oil pump overnight to give the hydrochloride salt of **142** (302.4 mg) as a colorless solid. To a solution of **50** (330.0 mg, 1.21 mmol, 1.2 equiv.) in dry CH_2Cl_2 (15 mL) at 0 °C were added sequentially HOBt (177.2 mg, 1.31 mmol, 1.3 equiv) and EDC (251.0 mg, 1.31 mmol, 1.3 equiv.). After 20 min the reaction mixture was added to a solution of **142** (302.4 mg, 1.01 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL). Et_3N (209 µL, 1.51 mmol, 1.51 equiv.) was added and stirred for 15 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 1M $KHSO_4$ (15 mL) and 5% $NaHCO_3$ (15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark-yellow oil which was purified by column chromatography on silica (CH_2Cl_2/MeOH 40:1) to afford **143** (455.1 mg, 87% yield) as an amorphous white solid.

R_f (SiO_2, ethylacetate/methanol 14:1) = 0.54; m.p. 50-52 °C; $[\alpha]_D^{20}$ = – 43.04 (c = 0.92, MeOH); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.41-7.30 (m, 5H), 6.64 (t, *J* = 5.61, 1H), 5.14 (s, 2H), 5.05 (t, *J* = 6.17, 1H), 4.68-4.59 (m, 2H), 3.43-3.31 (m, 2H), 3.29-3.16 (m, 2H), 2.88-2.32 (m, 10H), 1.48 (s, 9H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.4, 175.4, 169.9, 167.7, 156.3, 135.2, 128.7, 128.6, 128.4, 80.03, 79.7, 78.6, 67.1, 41.7, 41.3, 41.2, 41.1, 40.0, 39.1, 32.3, 32.0, 28.3; **IR** (KBr): $\tilde{\nu}$ = 3387, 2974, 2929, 2199, 1780, 1741, 1707, 1668, 1534, 1452, 1367, 1253, 1170, 1076, 1004, 929, 748, 699 cm^{-1}; **MS** [EI, 70 eV]: m/z (%) = 518.1 (13) [M^+], 462.1 (15) [M^+ - C_4H_8], 418.1 (37) [M^+ - Boc]; **HRMS** (EI, 70 eV): Calculated for [$C_{26}H_{34}N_2O_9$]: 518.2264, found 518.2266 [$M^{+\cdot}$].



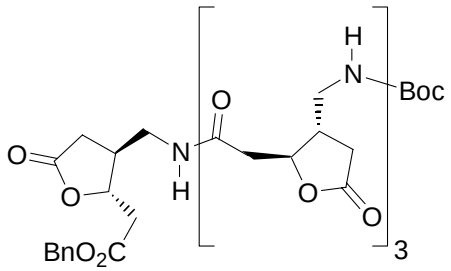
145

[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetyl-amino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (145):

The compound **143** (368.6 mg, 0.71 mmol) was treated with saturated HCl in ethylacetate (25 mL) at 0 °C for 3 h. The solvent was removed in vacuo, the residue was dried on oil pump overnight to give the hydrochloride salt of **144** (369.0 mg) as a colorless solid. To a solution of **50** (265.7 mg, 0.97 mmol, 1.2 equiv.) in dry CH_2Cl_2 (15 mL) at 0 °C were added sequentially HOBt (142.4 mg, 1.05 mmol, 1.3 equiv.) and EDC (202.1 mg, 1.05 mmol, 1.3 equiv.). After 20 min the reaction mixture was added to a solution of **144** (369.0 mg, 0.81 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL), Et_3N (168 µL, 1.21 mmol, 1.5 equiv.) was added and stirred for 20 h at room temparature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 1M $KHSO_4$ (20 mL) and 5% $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark-brown oil which was purified by column chromatography on silica (dichloromethane/methanol 20:1) to afford **145** (443.6 mg, 81%) as an amorphous white solid.

R_f (SiO_2, dichloromethane/methanol 8:1) = 0.52; m.p. 72-73°C; $[\alpha]_D^{20}$ = – 39.87 (c = 0.75, MeOH); **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 8.16-8.12 (m, 2H), 7.43-7.30 (m, 5H), 7.03 (t, *J* = 5.79, 1H), 5.13 (s, 2H), 4.63-4.65 (m, 3H), 3.26-2.91 (m, 7H), 2.88-2.31 (m, 14H),1.37 (s, 9H); ^{13}C-NMR (150.9 MHz, DMSO-d_6): δ = 175.85, 175.68,169.68, 169.10, 169.00, 155.86, 135.90, 128.40, 128.02, 127.92, 79.42, 79.38, 78.59, 77.78, 65.63, 41.48, 40.26, 40.18, 39.90, 39.78, 39.76, 39.64, 39.61, 38.67, 33.56, 31.92, 31.76, 28.09; **IR** (KBr): $\tilde{\nu}$ = 3404, 3088, 2974, 2930, 2306, 1779, 1663, 1541, 1439, 1367, 1252, 1170, 1070, 1005, 929, 748, 699 cm^{-1}; **MS** [ESI, (CH_2Cl_2 /MeOH + 10 mmol/l NH_4Ac)NH_3]: m/z

(%) = 691.3 (100) [M + NH_4^+], 674.3 (15) [M + H^+], 618.2 (9) [(M + H^+) - C_4H_8], 574.1 (5) [(M + H^+) - Boc]; **HRMS** (LSI): Calculated for [$C_{33}H_{43}N_3O_{12}$ + H^+]: 674.2925, found 674.2918 [M + H^+].



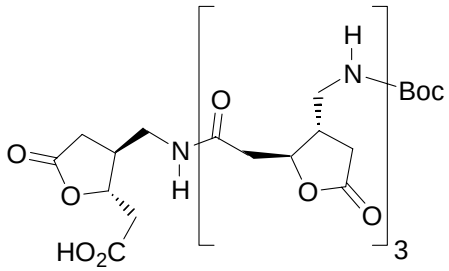
147

[3-({2-[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-ace-tylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (147):

The compound **145** (113.2 mg, 0.17 mmol) was treated with saturated HCl in ethylacetate (25 mL) at 0 °C for 4 h. The solvent was removed in vacuo, the residue was dried on oil pump overnight to give the hydrochloride salt of **146** (112.0 mg) as a colorless solid. To a solution of **50** (60.2 mg, 0.22 mmol, 1.2 equiv.) in dry CH_2Cl_2 (15 mL) at 0 °C were added sequentially HOBt (24.6 mg, 0.18 mmol, 1.3 equiv.) and EDC (45.7 mg, 0.24 mmol, 1.3 equiv.). After 20 min the reaction mixture was added to a solution of **146** (112.0 mg, 0.18 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL), Et_3N (38.1 µL, 0.28 mmol, 1.5 equiv.) was added and stirred for 21 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 1M $KHSO_4$ (15 mL) and 5% $NaHCO_3$ (15 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark-brown oil which was purified by column chromatography on silica (dichloromethane/methanol 15:1) to afford **147** (98.0 mg, 64%) as an amorphous colorless solid.

R_f (SiO_2, dichloromethane/methanol 4:1) = 0.68; m.p. 157-158 °C; $[\alpha]_D^{20}$ = – 34.6 (c = 0.78, DMSO); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.16-8.15 (m, 3H), 7.39-7.30 (m, 5H), 7.05 (t, *J*

= 5.90, 1H), 5.14 (s, 2H), 4.63-4.53 (m, 4H), 3.27-2.92 (m, 9H), 2.78-2.29 (m, 19H), 1.37 (s, 9H); **^{13}C-NMR** (100.6 MHz, DMSO-d_6): δ = 175.79, 175.66, 175.65, 175.63, 175.62, 169.05, 168.98, 168.95, 155.80, 135.83, 128.33, 127.96, 127.85, 79.42, 79.38, 79.36, 78.60, 77.78, 65.63, 41.48, 40.17, 40.09, 39.90, 39.78, 39.76, 39.75, 39.72, 39.69, 39.64, 39.61, 38.67, 31.92, 31.91, 31.76, 31.75, 28.09 C); **IR** (KBr): $\tilde{\nu}$ = 3369, 3068, 2934, 2199, 1776, 1660, 1539, 1366, 1255, 1172, 1074, 1006, 927, 747, 698, 659 cm^{-1}; **MS** [ESI, (CH_2Cl_2 /MeOH + 10 mmol /l NH_4Ac)NH_3]: m/z (%) = 846.4 (100) [M + NH_4^+], 829.4 (29) [M + H^+], 773.3 [(M + H^+) - C_4H_8], 729.3 [(M + H^+) - Boc]; **HRMS** (LSI): Calculated for [$C_{40}H_{52}N_4O_{15}$ + H^+]; 829.3507, found 829.3500 [M + H^+].



53

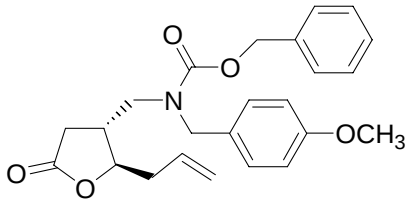
[3-({2-[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-ace-tylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid (53):

To a solution of **147** (98.0 mg, 0.16 mmol) in dry CH_2Cl_2 and MeOH (1:1, 15 mL) was added Pd-C (10 mol%). The reaction mixture was stirred overnight under H_2 (1 atm.) at room temperature, filtered through celite, concentrated in vacuo, to give a crude residue (105.0 mg) which was purified by column chromatography on silica (dichloromethane/methanol 1:1) to afford **53** (95.6 mg, 98%) as a colorless solid.

R_f (SiO_2, dichloromethane/methanol 1:1) = 0.10; m.p. 202-203 °C; $[\alpha]_D^{20}$ = – 26.5 (c = 0.75, MeOH); **^{1}H-NMR** (400 MHz, CD_3OH): δ = 8.35-8.28 (m, 3H), 7.88 (m, 1H), 4.66-4.60 (m, 4H), 3.49-3.10 (m, 8H), 2.89-2.33 (m, 20H), 1.41 (s, 9H); **^{13}C-NMR** (100.6 MHz, CD_3OH): δ = 178.79, 178.21, 178.11, 178.05, 172.53, 172.47, 172.43, 158.69, 83.04,

81.82, 81.71, 80.39, 40.85, 42.91, 42.24, 42.12, 42.10, 41.99, 41.98, 41.86, 33.39, 33.33, 33.29, 33.21, 27.78; **MS** (LSI): m/z (%) = 739.7 (31) [M + H^+], 683.7 (5) [(M + H^+) - C_4H_8], 639.6 (100) [(M + H^+) - Boc]; **HRMS** (LSI): Calculated for [$C_{33}H_{46}N_4O_{15}$ + H^+]: 739.3038, found 739.3039 [M + H^+].

2.6 Nucleoside amino acids



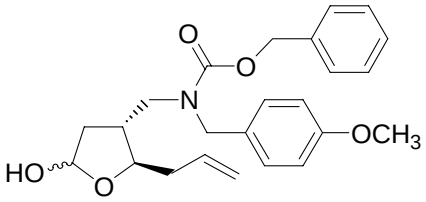
155

(*2R,3R*)-(+)-2-allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid benzyl ester (155):

To a cold (0 °C) solution of (ent)-**111b** (5.6 g, 20.35 mmol, 1.0 equiv.) in H_2O/NaOH (200 mL, pH 8.5) was slowly added benzylchloroformate (3.76 mL, 26.44 mmol, 1.3 equiv.) over 10 min. The reaction mixture was stirred for 1 h at 0 °C, then further stirred for 3 h to room temperature, extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica (hexanes/ethylacetate 3:1) to afford **155 (**5.7 g, 71%) as a colorless oil.

R_f = 0.29 (SiO_2, hexanes/ethylacetate 2:1); $[\alpha]_D^{20}$ = + 9.83 (c = 1.01, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.40-7.28 (m. 5H, Cbz-H), 7.23-7.0 (m, 2H, PMB-H), 6.92-6.75 (m, 2H, PMB-H), 5.67 (bs, 1H, 2‘-H), 5.18 (s, 2H, PMB-CH_2), 5.17-5.01 (m, 2H, 3‘-H), 4.53-4.36 (dd, 2H, Cbz-CH_2), 4.29-4.09 (bm, 1H, 2H), 3.80 (s, 3H, OCH_3), 3.41-3.18 (bm, 2H, CH_2-NR_2), 2.68-2.12 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 175.6 (C_{quart}, CO), 159.3 (C_{quart}, PMB), 156.5 (C_{quart}, CO), 136.3 (C_{quart}, PMB), 132.0 (2’-C), 129.4 (PMB-C), 128.9 (Cbz-C), 128.7 (Cbz-C), 128.4 (Cbz-C), 119.2 (3’-C), 114.2 (PMB-C), 82.3 (2-C), 67.8 (Cbz-CH_2), 55.3 (OCH_3), 50.8 (PMB-CH_2), 49.1 (CH_2-NR_2), 38.8 (3-C), 38.5 (1’-C), 33.0 (4-C); **IR** (Film): $\tilde{\nu}$ = 3506, 3066, 2935, 2836, 1776, 1697,

1611, 1585, 1512, 1446, 1417, 1363, 1298, 1246, 1175, 1118, 1032, 985, 915, 817, 750, 699 cm^{-1}; **MS** (EI, 70 eV): m/z (%) = 409.2 (2.3) [M^+]; **HRMS** (EI, 70 eV): Calculated for [$C_{24}H_{27}NO_5$]: 409.1889, found 409.1891 [M^+].



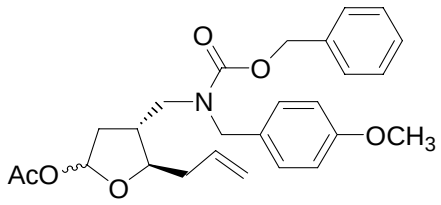
156

(*2R,3R*)-(2-Allyl-5-hydroxy-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid benzyl ester (156):

To a cold (-78 °C) solution of **155** (540.0 mg, 1.36mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was slowly added a 1 M solution of DIBAL-H in CH_2Cl_2 (1.36 mL, 1.5 mmol, 1.1 equiv.) over 20 min. After being stirred for an additional 30 min, the reaction mixture was quenched with MeOH (1.5 mL) and warm to room temperature. Then CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (1.0 ml) were added and the mixture was further stirred for 2.0 h. Na_2SO_4 (10.0 g) was added and again stirred for 2 h, filtered through celite and concentrated in vacuo to give an oil which was purified by column chromatography (hexanes/ethylacetate 2:1) to afford lactol **156 (**531.0 mg, 98%) as a colorless oil.

R_f = 0.51 (SiO_2, hexanes/ethylacetate 1:1); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.35 (bs. 5H, Cbz-H), 7.24-7.05 (m, 2H, PMB-H), 6.85 (bs, 2H, PMB-H), 5.88-5.55 (bm, 1H, 2‘-H), 5.52-5.38 (m, 1H, 5-H), 5.20 (s, 2H, Cbz-*CH_2*), 5.17-4.97 (bm, 2H, 3‘-H), 4.45 (s, 2H, PMB-*CH_2*), 4.05-3.80 (bm, 1H, 2-H), 3.80 (s, 3H, OCH_3), 3.55-3.15 (bm, 2H, *CH_2*-NR_2), 2.81 (bs, 1H, OH), 2.60-1.60 (m, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 159.0 (C_{quart}, PMB), 156.5 (C_{quart}, CO), 136.5 (C_{quart}, PMB), 134.4 (2‘-C), 129.4 (PMB-C), 129.3 (Cbz-C), 128.8 (Cbz-C), 128.5 (Cbz-C), 128.1 (Cbz-C), 117.4 (3‘-C), 114.0 (PMB-C), 97.9 (5-C), 82.5 (2-C), 67.5 (Cbz-CH_2), 55.3 (OCH_3), 50.4 (PMB-CH_2), 49.9 (CH_2-NR_2), 40.7 (3-C), 38.9 (1’-C), 36.8 (4-C); Characteristic signals for diastereomer: **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 134.6 (2‘-C), 117.3 (3‘-C), 98.3 (5-C), 80.8 (2-C), 68.2

(Cbz-CH_2); **IR** (Film): $\tilde{\nu}$ = 3417, 3069, 2934, 1689, 1612, 1512, 1417, 1361, 1298, 1246, 1176, 1126, 1033, 979, 916, 817, 750, 699 cm^{-1}.



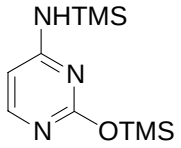
156

(*4R,5R*)-Acetic acid 5-allyl-4-{[benzyloxycarbonyl-(4-methoxy-benzyl)-amino]-methyl}-tetrahydro-furan-2-yl ester (157):

To a cold (0 °C) solution of **156** (531.0 mg, 1.34 mmol, 1.0 equiv.) in dry pyridine (15 mL) were slowly added dry acetic anhydride (140 µL, 1.48 mmol, 1.1 equiv.) over 2 min and catalytic amount of DMAP (12.0 mg). After being stirred for an additional 20 min, the reaction mixture was warm to room temperature and stirred for overnight. Pyridine was removed in vacuo and diluted with CH_2Cl_2 (15 mL) and H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography (hexanes/ethylacetate 2:1) to afford **157 (**551.0 mg, 92%) as a colorless oil.

R_f = 0.51 (SiO_2, hexanes/ethylacetate 2:1); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.35 (bs. 5H, Cbz-H), 7.24-7.05 (m, 2H, PMB-H), 6.85 (bs, 2H, PMB-H), 6.26-6.15 (m, 1H, 2-H), 5.88-5.55 (bm, 1H, 2‘-H), 5.18 (s, 2H, Cbz-CH_2), 5.17-4.97 (m, 2H, 3‘-H), 4.45 (s, 2H, PMB-CH_2), 4.09-3.82 (bm, 1H, 5-H), 3.80 (s, 3H, OCH_3), 3.45-3.13 (bm, 2H, CH_2-NR_2), 2.55-2.15 (m, 3H, 3-H, 4-H), 2.05 (s, 3H, OAc), 1.95-1.71 (bm, 2H, 1‘-H); **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ = 170.2 (C_{quart}, CO), 159.1 (C_{quart}, PMB), 156.4 (C_{quart}, CO), 136.5 (C_{quart}, PMB), 133.9 (2‘-C), 129.4 (PMB-C), 129.3 (Cbz-C), 128.7 (Cbz-C), 128.5 (Cbz-C), 128.2 (Cbz-C), 117.6 (3‘-C), 114.1 (PMB-C), 98.2 (2-C), 83.5 (5-C), 67.6 (Cbz-CH_2), 55.3 (OCH_3), 50.2 (PMB-CH_2), 48.7 (CH_2-NR_2), 40.1 (4-C), 38.9 (1’-C), 37.7 (3-C), 21.4 (OAc); Characteristic signals for diastereomer: ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ = 117.9 (3‘-C), 98.7 (2-C), 82.7 (5-C); **IR** (Film): $\tilde{\nu}$ = 3069, 2936, 1729, 1694, 1612, 1512, 1464,

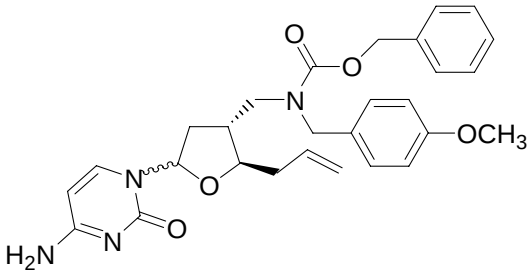
1417, 1367, 1242, 1176, 1118, 981, 918, 840, 750, 699 cm^{-1}; **MS** (LSI): m/z (%) = 453.3 (48) [M^+]; **HRMS** (LSI): Calculated for [$C_{26}H_{31}NO_6$]: 453.2151, found 453.2155 [M^+].



168

2,4-Bis(trimethylsilyl)cytosine (168):[104a]

A mixture of cytosine (500.0 mg, 4.5 mmol), hexamethyl disilazane (4 mL), and catalytic amount of $(NH_4)_2SO_4$ (1.0 mg) was refluxed for 80 min and then cooled to room temperature. The mixture was concentrated in vacuo, and the residue was coevaporated twice with dry toluene to afford **168** as a white solide, which was used for the next step without purification.



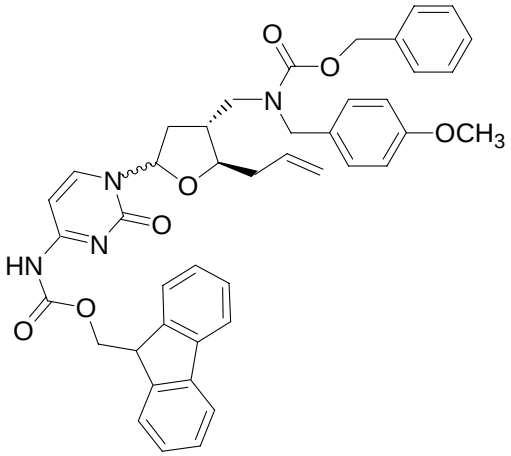
169

(*2R,3R*)-[2-Allyl-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-tetrahydro-furan-3-ylmethyl]-(4-methoxy-benzyl)- carbamic acid benzyl ester (169):

To a cold (-5 °C) mixture of **157** (443.0 mg, 0.98 mmol, 1.0 equiv.), and **168** (499.0 mg, 1.95 mmol, 2.0 equiv.) in dry CH_2Cl_2 (30 mL) was slowly added $EtAlCl_2$ (340 µL, 1.95 mmol, 2.0 equiv.) over 15 min. After the completion of the addition, the mixture was stirred at room temperature for 6 h and then slowly poured into an ice-cold mixture of CH_2Cl_2 (30 mL) and saturated $NaHCO_3$ (20 mL). The mixture was further stirred for 5 min and filtered through a celite pad. The organic layer was washed with saturated $NaHCO_3$ (30

mL) and brine (30 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give an oil which was purified by column chromatography (ethylacetate/methanol 5:1) to afford **169 (**415.0 mg, 84%) as an amorphous white solid.

R_f = 0.62 (SiO_2, ethylacetate/methanol 4:1); m.p. 70-72 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.64-7.46 (m, 1H, Cyto.CH), 7.33 (bs. 5H, Cbz-H), 7.21-7.05 (m, 2H, PMB-H), 6.87-6.78 (m, 2H, PMB-H), 6.05-5.85 (m, 1H, 5-H), 5.81-5.60 (m, 2H, 2‘-H, Cyto.CH), 5.18 (s, Cbz-*CH_2*), 5.11-5.06 (m, 2H, 3’-H), 4.65-4.27 (m, 2H, PMB-*CH_2*), 4.12-3.88 (bm, 1H, 2H), 3.80 (s, 3H, OCH_3), 3.46-3.09 (bm, 2H, *CH_2*-NR_2), 2.79-1.53 (bm, 5H, 4-H, 3-H, 1‘-H); **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ = 165.8 (C_{quart}, Cyto. CO), 159.1 (C_{quart}, PMB), 156.4 (C_{quart}, Cbz, CO), 155.8 (C_{quart}, Cyto-C), 140.4 (Cyto-C),136.4 (C_{quart}, PMB), 133.7 (2’-C), 129.3 (PMB-C), 128.7 (Cbz-C), 128.5 (Cbz-C), 128.2 (Cbz-C), 128.0 (Cbz-C), 117.6 (3‘-C), 114.1 (PMB-C), 93.7 (Cyto-C), 87.2 (5-C), 83.5 (2-C), 67.5 (Cbz-CH_2), 55.3 (OCH_3), 50.2 (PMB-CH_2), 48.8 (CH_2-NR_2), 40.2 (3-C), 39.0 (1’-C), 37.7 (4-C); **IR** (Film): $\tilde{\nu}$ = 3343, 3198, 3077, 2934, 1693, 1645, 1510, 1485, 1416, 1359, 1282, 1244, 1175, 1117, 1031, 985, 914, 789, 750, 699 cm^{-1}; **MS** (EI, 70 eV): m/z (%) = 504.4 (45) [M^+]; **HRMS** (EI): Calculated for [$C_{28}H_{32}N_4O_5$]: 504.2373, found 504.2367 [M^+].



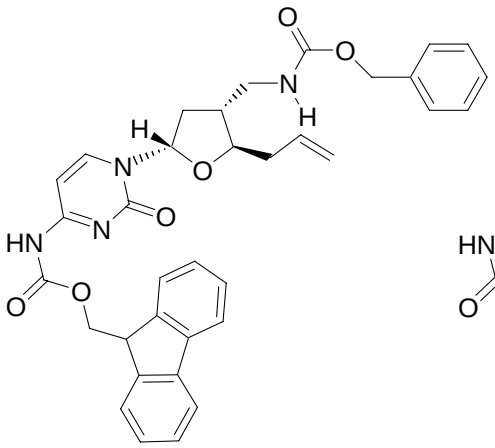
170

(*4R,5R*)-[1-(5-Allyl-4-{[benzyloxycarbonyl-(4-methoxy-benzyl)-amino]methyl}tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester (170):

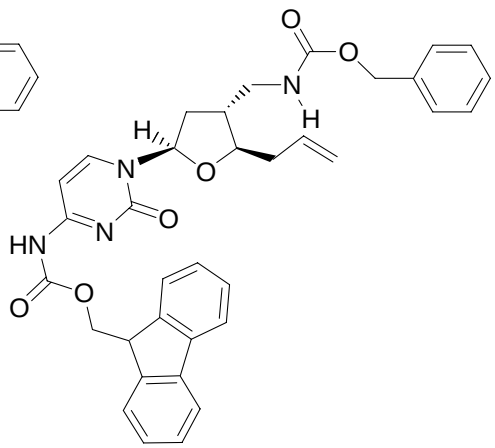
To a solution of **169** (947.0 mg, 1.88 mmol, 1.0 equiv.) in dry Pyridine (30 mL) was slowly added 9-fluorenylmethyl chloroformate (534.0 mg, 2.06 mmol, 1.1 equiv.) portion-wise. The mixture was stirred at room temperature overnight, removed pyridine in vacuo to give an oil which was diluted with CH_2Cl_2 (30 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 65 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica (hexanes/ethylacetate 1:2) to afford **170** (1.18 g, 87%) as a white solid.

R_f (SiO_2, hexanes/ethylacetate 1:4) = 0.43; m.p. 74-76 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.90 (bs, 1H, Cyto.H), 7.77 (d, *J* = 7.41, 2H, Fmoc-H), 7.57 (d, *J* = 7.41, 2H, Fmoc-H), 7.42 (t, *J* = 7.54, 2H, Fmoc-H), 7.40-7.27 (m, 8H, Cbz-H, Fmoc-H), 7.23-6.97 (bm, 3H, PMB-H, Cyto-H), 6.82 (bs, 2H, PMB-H), 5.97-5.60 (bm, 2H, 2‘-H, 2-H), 5.28-5.06 (m, 4H, Cbz-*CH_2*, 3’-H), 4.65-4.40 (m, 3H, PMB-CH_2, 5-H), 4.36-4.20 (m, 2H, Fmoc-CH_2), 3.78 (s, 3H, OCH_3), 3.47-2.91 (bm, 2H, *CH_2*- NHCbz), 2.59-1.54 (bm, 5H, 3-H, 4-H, 1‘-H); **^{13}C-NMR** (150.9 MHz, CD_3OD): δ = 162.1 (C_{quart}, Cyto. CO), 159.2 (C_{quart}, PMB), 156.3 (C_{quart}, Cbz, CO), 152.3 (C_{quart}, Fmoc, CO), 143.23 (Cyto-C), 143.2 (Fmoc-C), 141.3 (Fmoc-C), 133.5 (2’-C), 129.3 (Cbz-C), 128.6 (Fmoc-C), 128.0 (Cbz-C), 127.2 (Cbz-C), 124.9 (Fmoc-C), 120.2 (Fmoc-C), 118.4 (3‘-C), 114 (PMB-C), 94.0 (Cyto-C), 88.0 (2-C),

83.5 (5-C), 68.0 (Fmoc-CH_2), 67.6 (Cbz-CH_2), 50.3 (OCH_3), 50.8 (PMB-CH_2), 48.0 (CH_2-NHCbz), 46.7 (Fmoc-C), 41.5 (4-C), 38.8 (1'-C), 38.3 (3-C); **IR** (Film): $\tilde{\nu}$ = 3447, 2929, 1743, 1693, 1663, 1622, 1558, 1506, 1444, 1322, 1223, 1106, 1033, 992, 916, 789, 741, 699 cm^{-1}; **MS** (ES): m/z (%) = 727.4 (100) [$M+H^+$]; **HRMS** (LSI): Calculated for [$C_{43}H_{42}N_4O_7 + H^+$]: 727.3132, found 727.3135 [$M+H^+$].



171



172

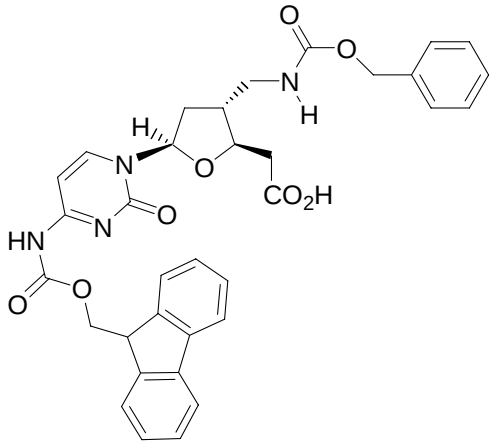
(*2R,4R,5R*)-{1-[5-Allyl-4-(benzyloxycarbonylamino-methyl)-tetrahydro-furan-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (171 and 172):

To a cold (0 °C) solution of 170 (525.0 mg, 723 mmol, 1.0 equiv.) in CH_3CN (100 mL) was slowly added a solution of CAN (2.38 g, 4.33 mmol, 6 equiv.) in H_2O (10 mL) over 5 min. After the completion of the addition, the resulting bright yellow reaction mixture was stirred at room temperature for 2 h, water (15 mL) was added and extracted with CH_2Cl_2 (4 x 60 mL). The combined extracts were successively washed with saturated $NaHCO_3$ (150 mL) and water (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica (hexanes/ethylacetate 1:1 followed by 1:2) to afford 264.0 mg (34%) of α-anomer **171**, and 315.0 mg (41%) of β-anomer **172** as a colorless solid.

Compound 171: R_f (SiO_2, hexanes/ethylacetate 1:4) = 0.33; m.p. 109-110 °C; $[\alpha]_D^{20}$ = – 30.10 (c = 1.03, CH_3OH); **^{1}H-NMR** (600 MHz, CD_3OD): δ = 7.97 (d, *J* = 7.45 Hz, 1H, Cyto.CH), 7.79 (d, *J* = 7.45 Hz, 2H, Fmoc), 7.67 (d, *J* = 7.45 Hz, 2H, Fmoc), 7.38 (*t*, *J* = 7.45 Hz, 2H, Fmoc), 7.37-7.21 (m, 7H, Cbz-H, Fmoc-H), 5.91 (t, *J* = 6.25 Hz, 1H, 2-H), 5.90-5.82 (m, 1H, 2‘-H), 5.15-5.06 (m, 2H, 3’-H), 5.04 (s, 2H, Cbz-CH_2), 4.49 (d, J = 6.58 Hz, 2H, Fmoc-CH_2), 4.26 (t, *J* = 6.69 Hz, 1H, Fmoc), 4.15-4.12 (m, 1H, 5-H), 3.19 (dd, *J* = 13.9, 6.0 Hz, 1H, CH_2- NHCbz), 3.12 (dd, *J* = 13.9, 6.2 Hz, 1H, CH_2- NHCbz), 2.77-2.72 (m, 1H, 3-H), 2.48-2.45 (m, 1H, 1‘-H), 2.35-2.27 (m, 2H, 1’-H, 4-H), 1.82-1.77 (m, 1H, 3-H); **^{13}C-NMR** (150.9 MHz, CD_3OD): δ = 164.8 (C_{quart}, Cyto. CO), 158.9 (C_{quart}, Cyto), 157.7(C_{quart}, Cbz, CO), 154.5 (C_{quart}, Fmoc, CO), 144.9 (Fmoc-C), 144.8 (Fmoc-C), 144.7 (+, Cyto-C), 135.1 (2’-C), 132.4 (C_{quart}, Cbz-C), 129.8 (Cbz-C), 129.4 (Fmoc-C), 129.0 (Fmoc-C), 128.9 (Cbz-C), 128.8 (Fmoc-C), 128.2 (Cbz-C), 126.1 (Fmoc-C), 121.0 (Fmoc-C), 118.3 (3‘-C), 96.7 Cyto-C), 89.5 (2-C), 84.6 (5-C), 68.6 (Fmoc-CH_2), 67.5 (Cbz-CH_2), 48.0 (Fmoc-C), 44.8 (4-C),), 42.7 (CH_2- NHCbz), 39.7 (1’-C), 38.6 (3-C); **IR** (Film): $\tilde{\nu}$ = 3417, 3245, 3066, 2929, 2503, 1702, 1656, 1624, 1560, 1505, 1448, 1409, 1325, 1230, 1206, 1069, 993, 919, 790, 739, 697 cm^{-1}; **MS** (LSI): m/z (%) = 607.3 (16) [M+H^+], 629.3 [M+Na^+]; **HRMS** (LSI): Calculated for [$C_{35}H_{34}N_4O_6$+H]: 607.2541, found 607.2540 [M+H^+].

Compound 172: R_f(SiO_2, hexanes/ethylacetate 1:4) = 0.27; m.p. 116-117 °C; $[\alpha]_D^{20}$ = + 38.32 (c = 1.07, CH_3OH); **^{1}H-NMR** (600 MHz, CD_3OD): δ = 8.05 (d, *J* = 7.45 Hz, 1H, Cyto.CH), 7.79 (d, *J* = 7.45 Hz, 2H, Fmoc), 7.67 (d, *J* = 7.45 Hz, 2H, Fmoc), 7.38 (*t*, *J* = 7.45 Hz, 2H, Fmoc), 7.38-7.18 (m, 7H, Cbz-H, Fmoc-H), 5.94-5.87 (m, 2H, 2-H, 2‘-H), 5.19-5.07 (m, 3H, 3’-H, Cyto.CH), 5.06 (s, 2H, Cbz-*CH_2*), 4.53 (d, *J* = 6.58 Hz, 2H, Fmoc-*CH_2*), 4.25 (t, *J* = 6.47 Hz, 1H, Fmoc), 3.90-3.85 (m, 1H, 5-H), 3.25 (dd, *J* = 13.92, 5.81 Hz, 1H, *CH_2*- NHCbz), 3.16 (dd, *J* = 14.03, 5.9 Hz, 1H, *CH_2*-NHCbz), 2.57-2.43 (m, 2H, 1’-H,), 2.34-2.28 (m, 1H, 3-H), 2.18-2.11 (m, 2H, 3-H, 4-H); **^{13}C-NMR** (150.9 MHz, CD_3OD): δ = 164.8 (C_{quart}, Cyto. CO), 159.0 (C_{quat}, Cyto), 157.7(C_{quat}, Cbz, CO), 154.5 (C_{quat}, Fmoc, CO), 144.9 (Cyto-C), 142.7 (Fmoc-C), 138.4 (Fmoc-C), 135.5 (2’-C), 132.4 (C_{quart}, Cbz-C), 129.8 (Cbz-C), 129.4 (Fmoc-C), 130 (Fmoc-C), 128.9 (Cbz-C), 128.2 (Cbz-C), 126.1 (Fmoc-C), 121.0 (Fmoc-C), 118.3 (3‘-C), 95.7 (Cyto-C), 88.4 (2-C), 85.0 (5-C),

68.6 (Fmoc-CH_2), 67.5 (Cbz-CH_2), 48.1 (Fmoc-C), 43.1 (4-C),), 42.5 (CH_2- NHCbz), 40.2 (1'-C), 38.3 (3-C); **IR** (Film): $\tilde{\nu}$ = 3417, 3245, 3066, 2929, 2503, 1702, 1656, 1624, 1560, 1505, 1448, 1409, 1325, 1230, 1206, 1069, 993, 919, 790, 739, 697 cm^{-1}; **MS** (LSI): m/z (%) = 607.3 (16) [$M+H^+$], 629.3 [$M+Na^+$]; **HRMS** (HR-LSI): Calculated for [$C_{35}H_{34}N_4O_6$+H]: 607.2541, found 607.2540 [$M+H^+$].



173

(*2R,3R,5R*)-(+)-{3-(Benzyloxycarbonylamino-methyl)-5-[4-(9*H*-fluoren-9-ylmethoxy-carbonylamino)-2-oxo-2*H*-pyrimidin-1-yl]-tetrahydro-furan-2-yl}-acetic acid (173):

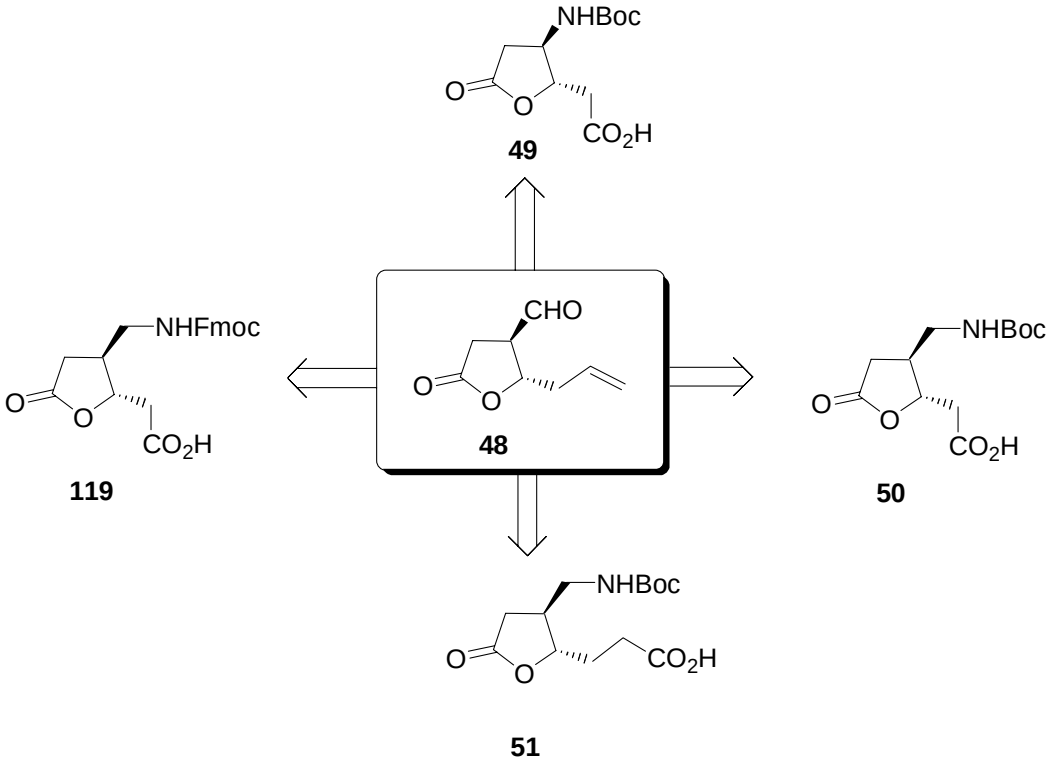
To a cold (0 °C) solution of **172** (149.0 mg, 0.25 mmol, 1.0 equiv.) in CCl_4-CH_3CN-H_2O (1:1:1.5, 35 mL) were added sequentially $RuCl_3 \cdot 3H_2O$ (0.04 mg, 6.3 mol%), $NaIO_4$ (211 mg, 0.98 mmol, 4.0 equiv.) portion-wise and stirred for 40 h at 0 °C. H_2O (10 mL) was added and extracted with CH_2Cl_2 (5 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give 160.0 mg of a brown oil which was purified by column chromatography on silica (dichloromethane/methanol 15:1) to afford **173** (95.0 mg, 62%) as a colorless solid.

R_f (SiO_2, ethylacetate/MeOH 15:1) = 0.55; m.p. 147-148 °C; $[\alpha]_D^{20}$ = + 20.3 (c = 0.75, DMSO); **^{1}H-NMR** (400 MHz, DMSO-d_6): δ = 8.08 (d, *J* = 7.45 Hz, 1H, Cyto.CH), 7.90 (d, *J* = 7.45 Hz, 2H, Fmoc), 7.82 (d, *J* = 7.67 Hz, 2H, Fmoc), 7.43 (m, 3H, Fmoc), 7.36-7.08 (m, 8H, Cbz, Fmoc, 2N-H), 7.00 (d, *J* = 7.67 Hz, 1H, Cyto-H), 5.87 (t, *J* = 6.25 Hz, 1H, 5-

H), 4.39-4.27 (m, 4H, 2-H, Fmoc), 3.17-3.03 (2H, *CH*$_2$-NHCbz), 2.68-2.59 (m, 2H, 1'-H), 2.40 (dd, *J* = 15.89, 8.44 Hz, 1H, 4-H,), 2.22 (m, 1H, 3-H), 1.80-1.73 (m, 1H, 4-H); **^{13}C-NMR** (100.6 MHz, DMSO-d_6): δ = 172.9 (C_{quart}, COOH), 165.5 (C_{quart}, Cyto. CO), 162.7 (C_{quart}, Cyto), 156.2 (C_{quart}, Cbz, CO), 155.0 (C_{quart}, Fmoc, CO), 153.1 (Cyto-C), 143.9 (Fmoc-C), 140.6 (Fmoc-C), 137.0 (C_{quart}, Cbz-C), 128.8 (Cbz-C), 128.2 (Fmoc-C), 127.7 (Fmoc-C), 127.6 (Cbz-C), 127.5 (Cbz-C), 125.4 (Fmoc-C), 120.0 (Fmoc-C), 118.3 (3'-C), 93.9 (Cyto-C), 86.8 (5-C), 79.9 (2-C), 66.8 (Fmoc-CH_2), 65.1 (Cbz-CH_2), 46.1 (Fmoc-C), 43.4 (3-C),), 41.0 (*CH*$_2$-NHCbz), 40.5 (1'-C), 40.1 (4-C); IR (Film): $\tilde{\nu}$ = 3406, 3062, 2948, 2888, 2827, 2512, 1714, 1647, 1560, 1500, 1444, 1401, 1327, 1232, 1207, 1099, 994, 847, 789, 741, 699 cm^{-1}; **MS** (LSI): m/z (%) = 625.3 (100) [M+H$^+$]; **HRMS** (LSI): Calculated for [$C_{35}H_{34}N_4O_6$+H]: 625.2298, found 625.2285 [M+H$^+$].

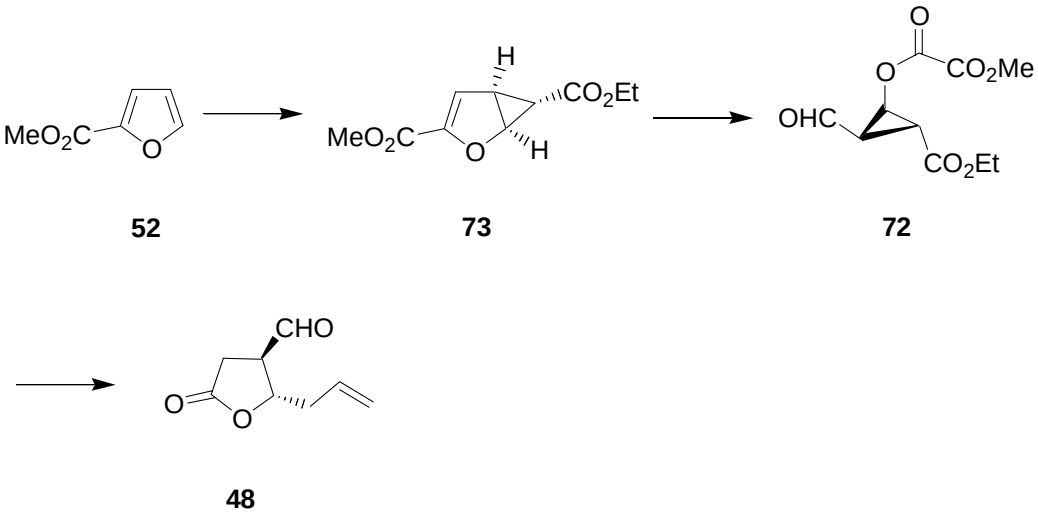
Summary

In this work, new conformationally constrained sugar-like γ-, δ-, and ε-amino acids **49**, **50, 119** and **51** respectively were synthesized in enantiomerically pure in an efficient manner from *trans*-2,3-disubstituted γ-butyrolactone **48** (Scheme 70). These novel amino acids can serve as useful templates to induce interesting secondary structures in peptides.



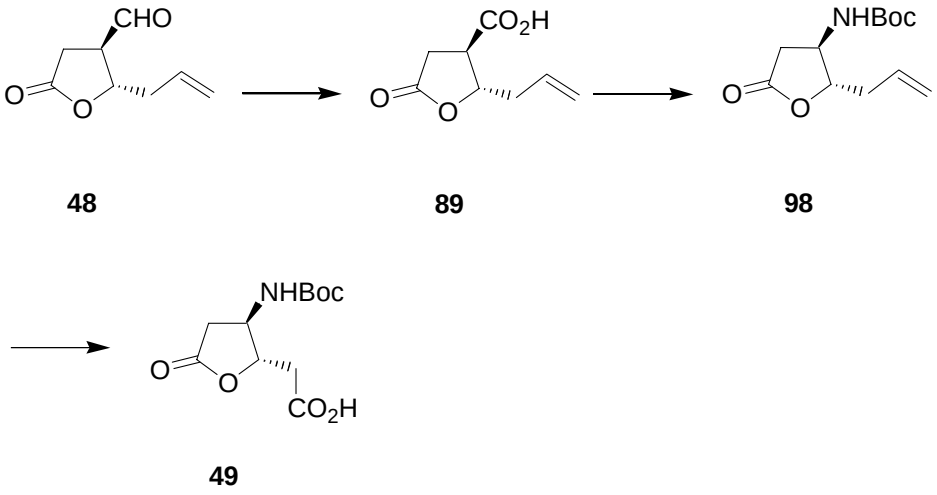
Scheme 70. Synthesis of furanoid sugar-like γ-, δ-, and ε-amino acids **49**, **50, 119** and **51** respectively from *trans*-2,3-disubstituted γ-butyrolactone aldehyde **48**.

The key intermediate γ-butyrolactone **48** was synthesized from readily available furan-2-carboxylic methyl ester **52** (Scheme 71) by using a copper (I)-catalyzed asymmetric cyclopropanation to afford bicyclic derivative **73**. Ozonolysis of the C=C double bond followed by reductive work up gave cyclopropanecarbaldehyde **72**, which undergoes diastereoselective Sakurai-allylation with allylsilane to give cyclopropanol and finally under a base mediated retroaldol-lactonisation sequence to the γ-butyrolactonaldehyde **48** in good yield.



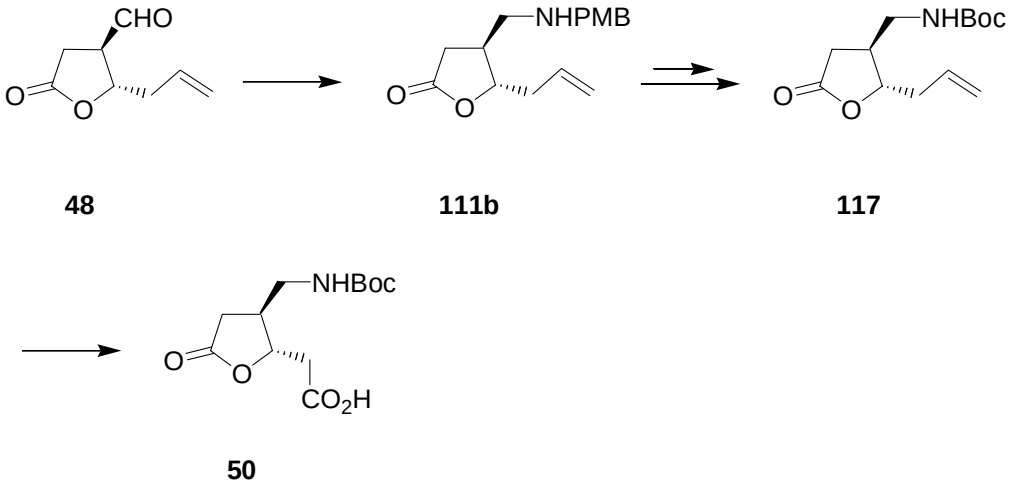
Scheme 71. Synthesis of *trans*-2,3-disubstituted *γ*-butyrolactone **48**.

Firstly, an efficient route leading to *γ*-amino acid **49** was successfully developed from *trans*-2,3-disubstituted *γ*-butyrolactone **48** by oxidation of the aldehyde group to give the acid **89**, followed by Curtius rearrangement to carbamate **98** and ruthenium-catalyzed oxidative cleavage of the allylic double bond to give the Boc-*γ*-amino acid **49** in high yield (Scheme 72).



Scheme 72. Synthesis of Boc-*γ*-amino acid **49** from *γ*-butyrolactonaldehyde **48**.

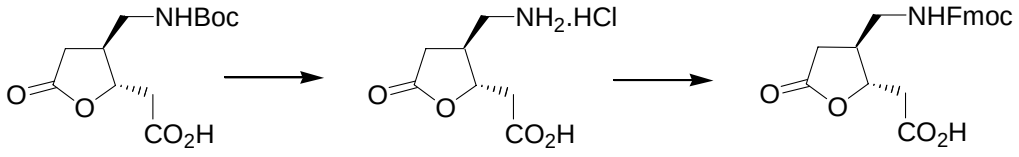
Secondly, a simple and short synthetic strategy leading to Boc-δ-amino acid **50** was successfully developed from γ-butyrolactone **48** by reductive amination to provide the amine **111b** followed by Boc protection and PMB deprotection to give the carbamate **117**. Ruthenium-catalyzed oxidative cleavage of the allylic double bond afforded the Boc-δ-amino acid **50** in high yield (Scheme 73).



48 **111b** **117** **50**

Scheme 73. Synthesis of Boc-δ-amino acid **50** from γ-butyrolactone **48**.

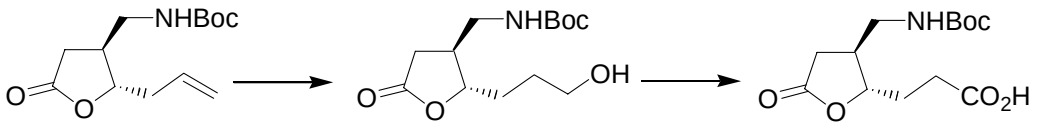
Thirdly, a short synthetic strategy was developed for the synthesis of Fmoc-δ-amino acid **119** from Boc-δ-amino acid **50**. Deprotection of the Boc group afforded the free amine **118** followed by re-protection with Fmoc-Cl, to give the Fmoc-δ-amino acid **119** in high yield (Scheme 74).



50 **118** **119**

Scheme 74. Synthesis of Fmoc-δ-amino acid **119** from Boc-δ-amino acid **50**.

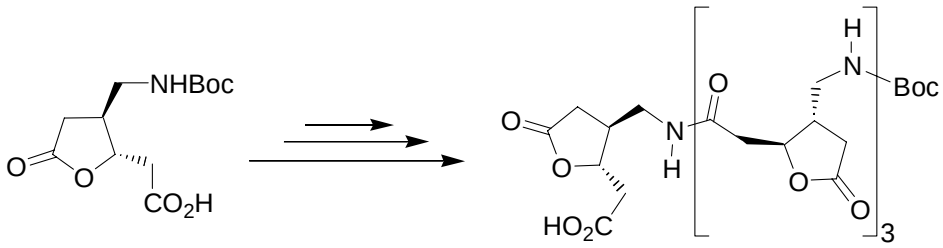
Fourthly, a simple and efficient route was successfully developed leading to ε-amino acids **51** from the carbamate **117** by using a regioselective ruthenium-catalyzed hydroboration of the allylic double bond to give the primary alcohol **123** which under TEMPO mediated oxidation gave the ε-amino acid **51** in high yield (Scheme 75).



117 **123** **51**

Scheme 75. Synthesis of ε-amino acid **51** from carbamate **117**.

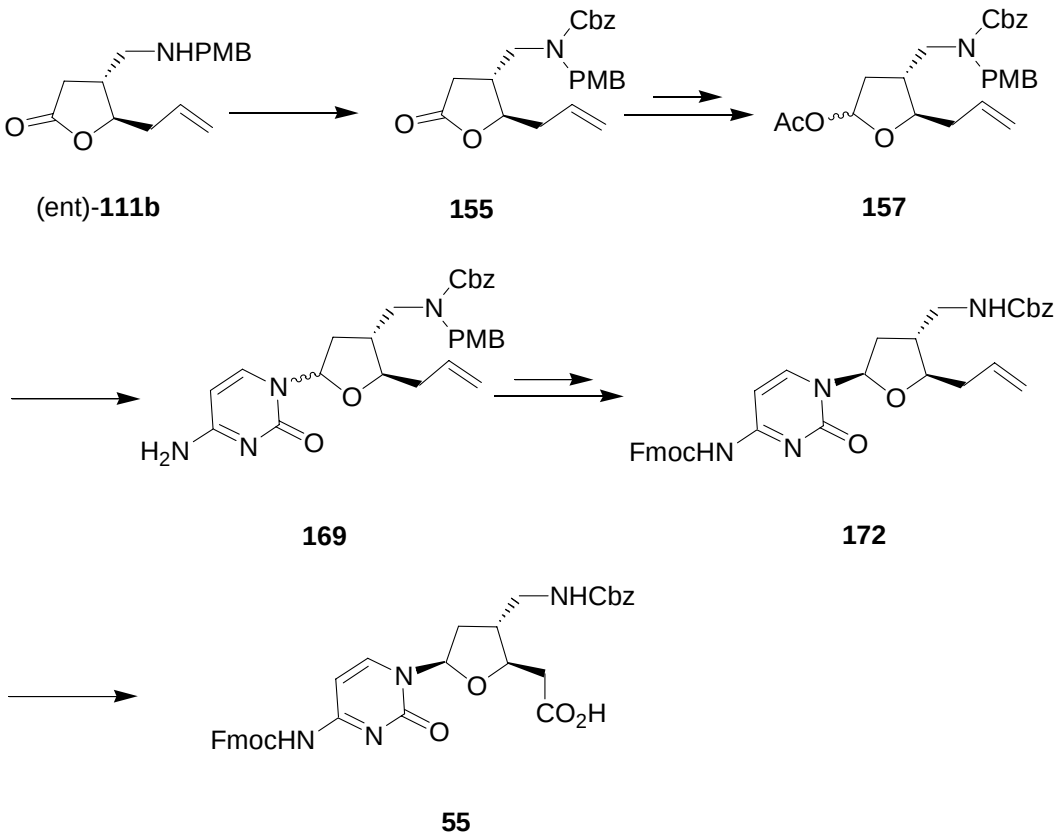
Furthermore, an efficient protocol leading to the oligopeptide **53** was successfully developed from conformationally constrained Boc-δ-amino acid **50** (Scheme 76) in good yield.



50 **53**

Scheme 76. Synthesis of oligopeptide **53** from Boc-δ-amino acid **50**.

Finally, a simple and efficient synthetic strategy was successfully developed leading to the nucleoside amino acid **55** from the amine (ent)-**111b**. Cbz protection gave protected amine **155** which was reduced to the corresponding lactol followed by acetylation to give **157** in high yield. Lewis acid mediated coupling with persilylated cytosine gave furanosyl cytosine nucleoside **169** as an inseparable mixture of anomers (1:1.2) in high yield. Then Fmoc protection and deprotection of the PMB yielded chromatographically separable β-nucleoside **172**. Finally, ruthenium-catalyzed oxidative cleavage of the allylic double bond of **172** gave furanosyl cytosine nucleoside amino acid **55** in good yield (Scheme 77).



Scheme 77. Synthesis of furanosyl cytosine nucleoside amino acid **55**.

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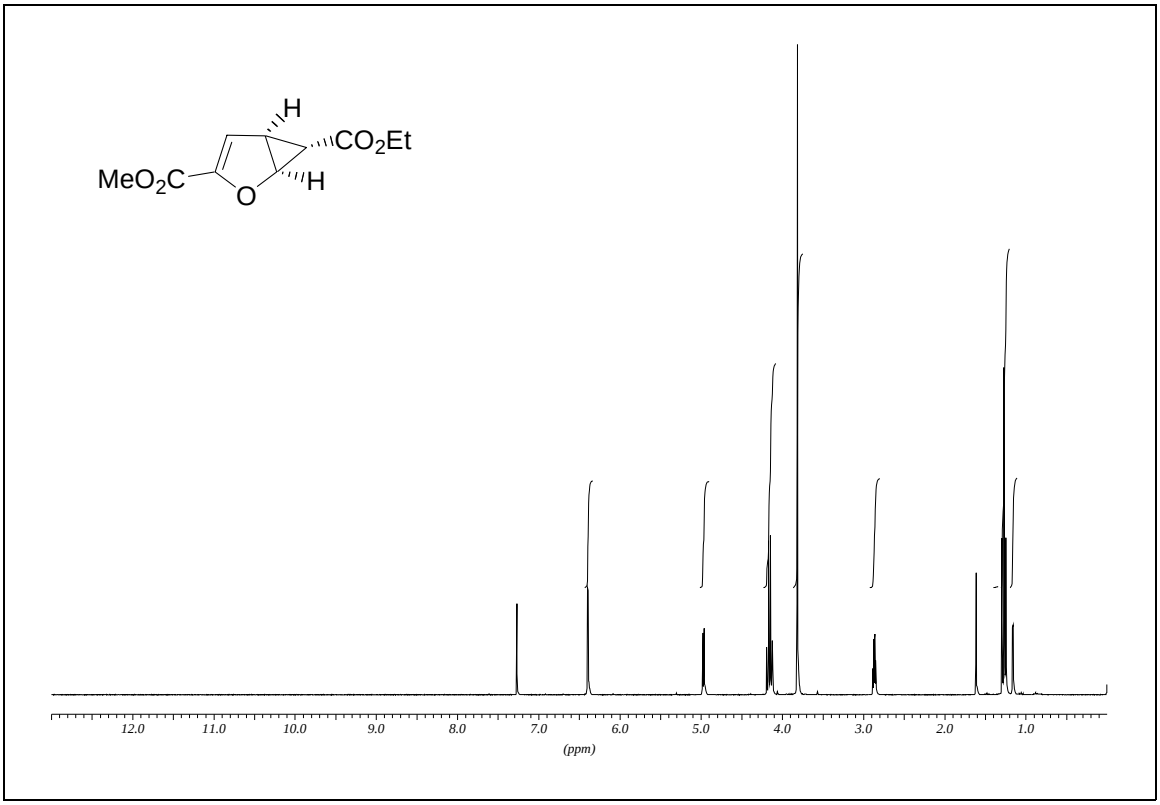
Appendix of NMR and X-ray Data

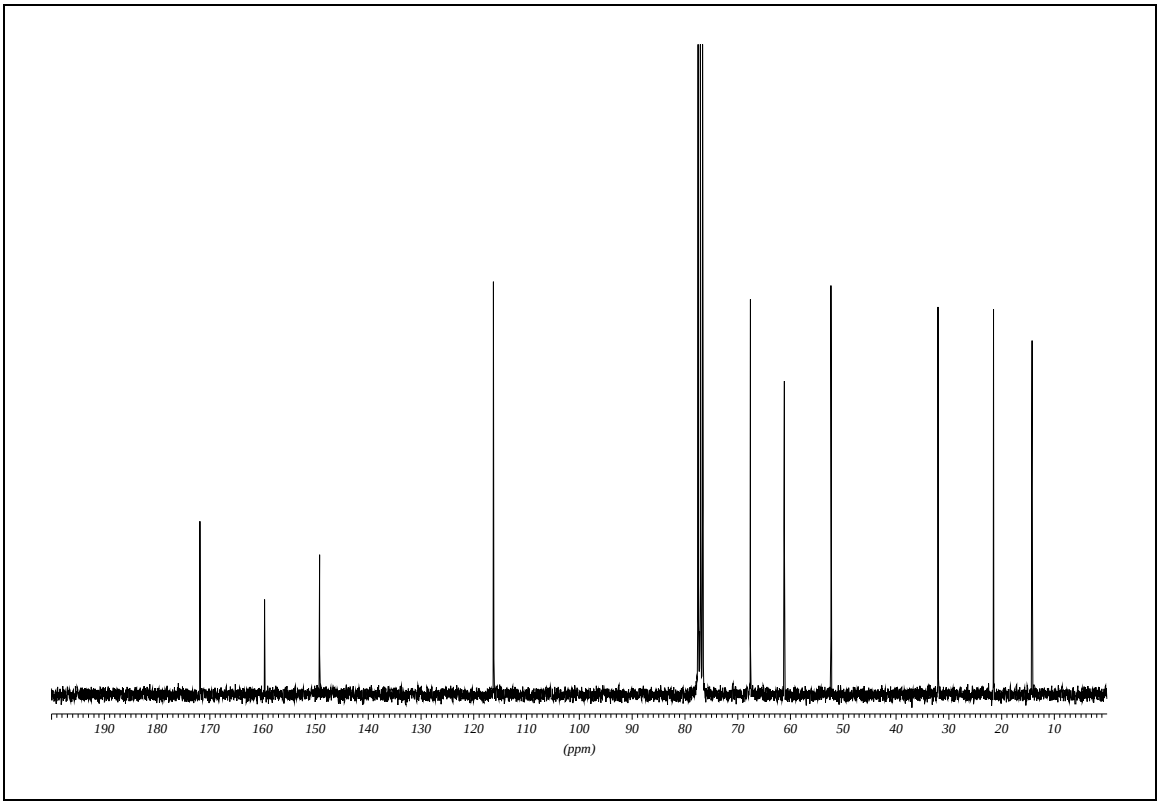
NMR

^{1}H-Spectra (top of the page)

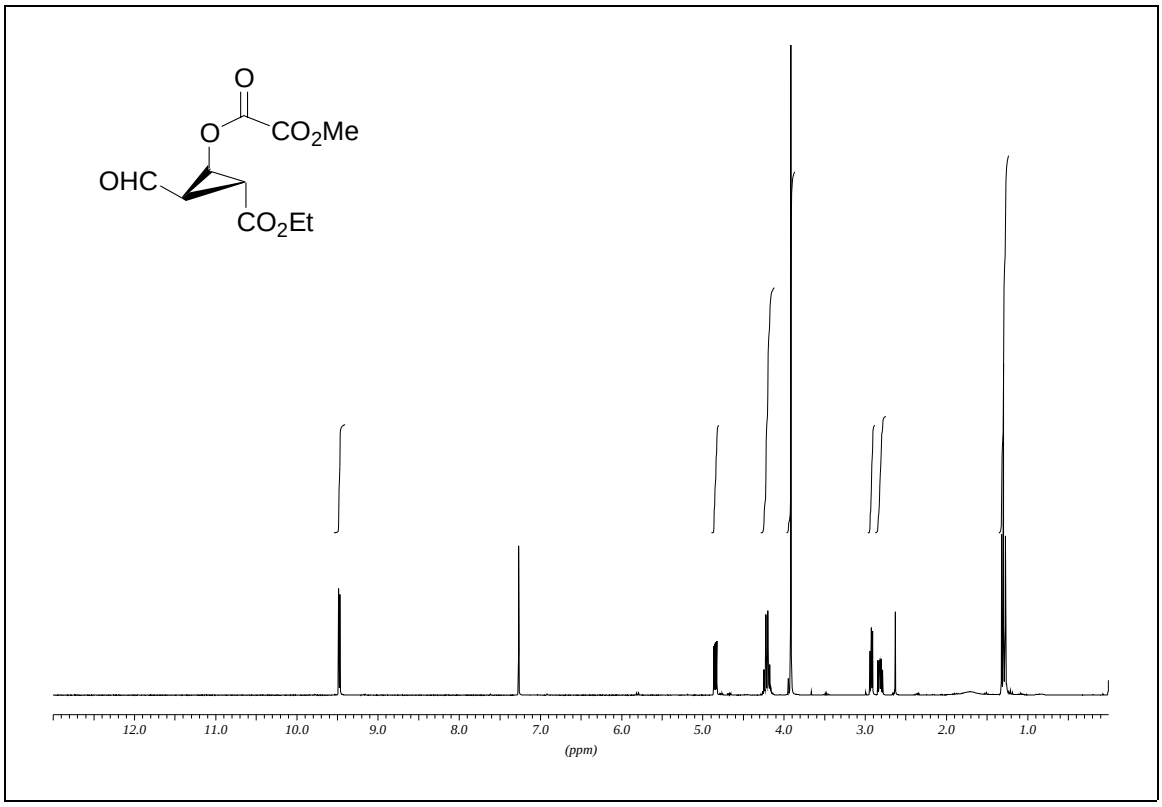
^{13}C-Spectra (bottom of the page)

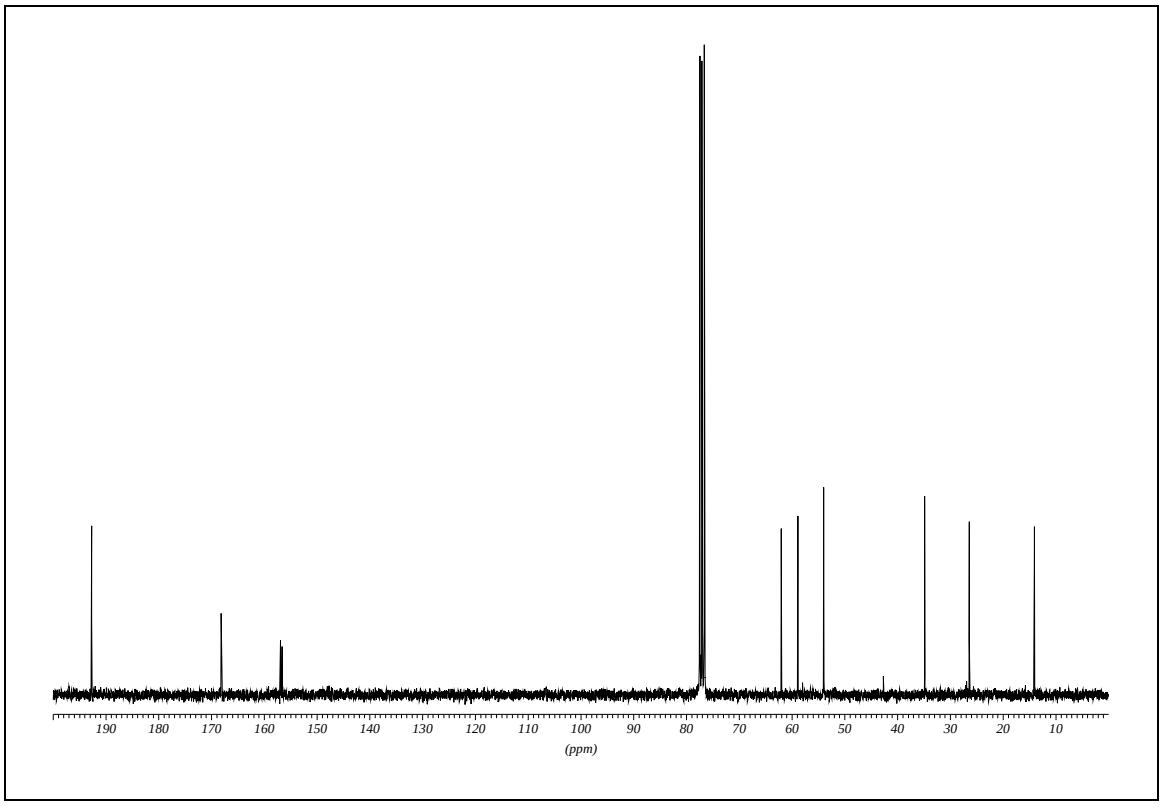
(*1S,5S,6S*)-(–)-2-Oxa-bicyclo[3.1.0]hex-3-en-3,6-dicarbonicacid-6-ethylester-3-methyl-ester (73, $CDCl_3$)



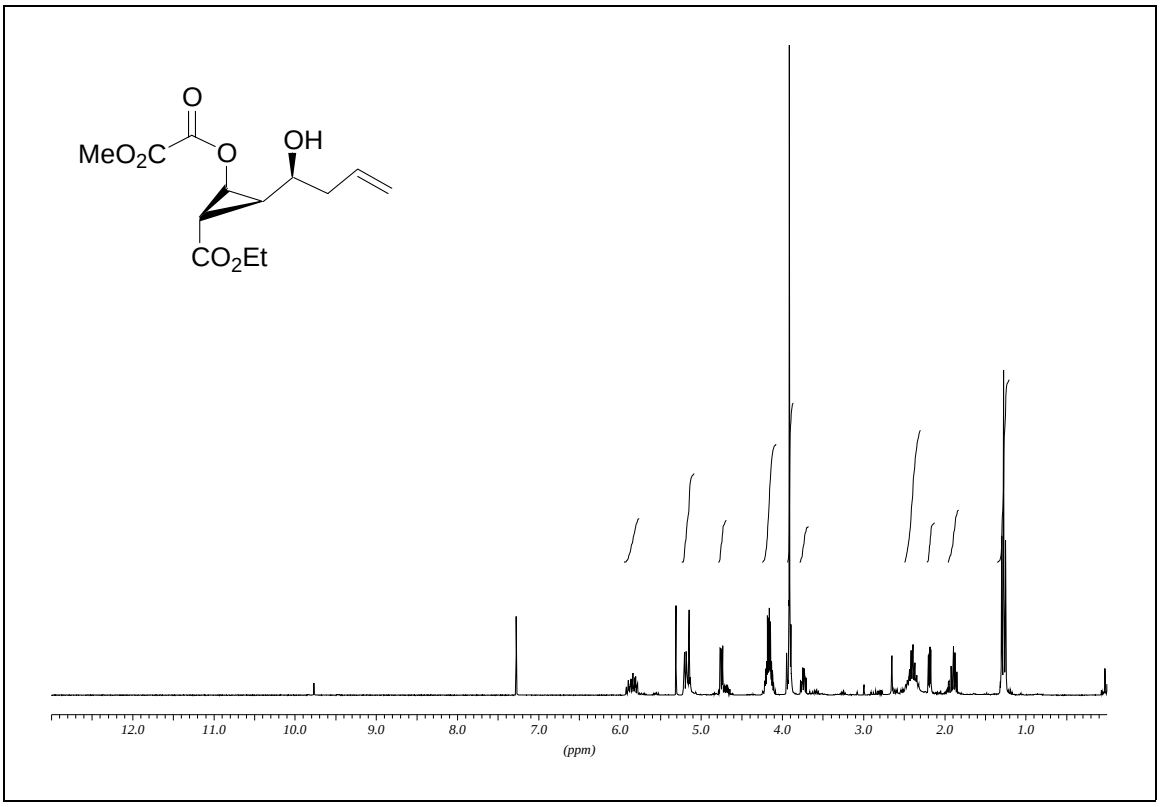


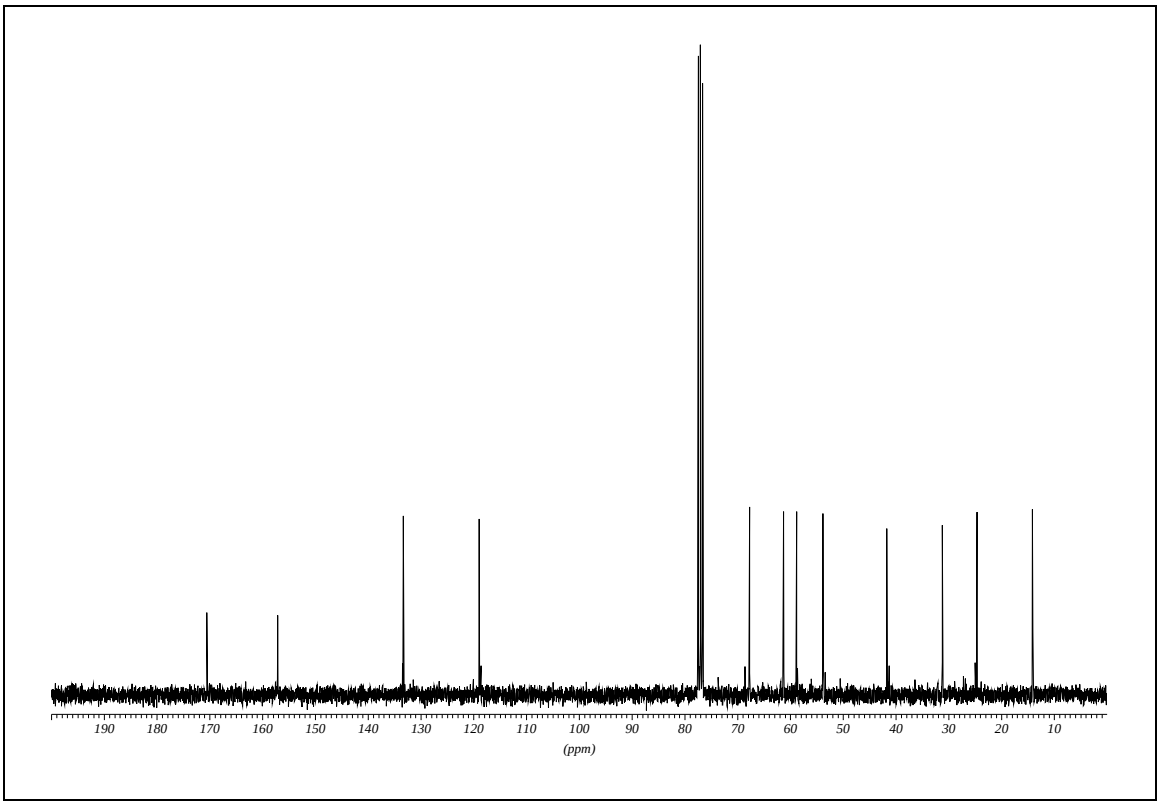
(*1S,2S,3S*)-(–)-Oxalicacid-(2-formyl-3-ethoxycarbonyl)-cyclopropylestermethyl-ester (72, $CDCl_3$):



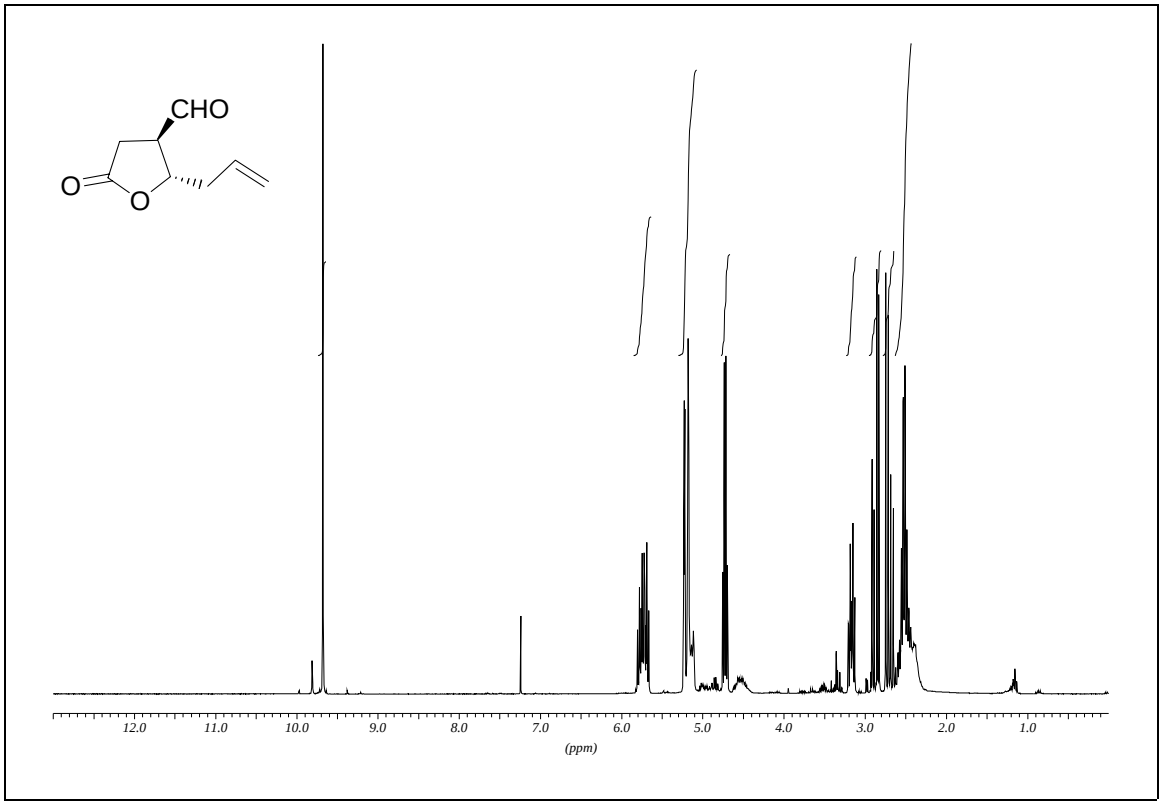


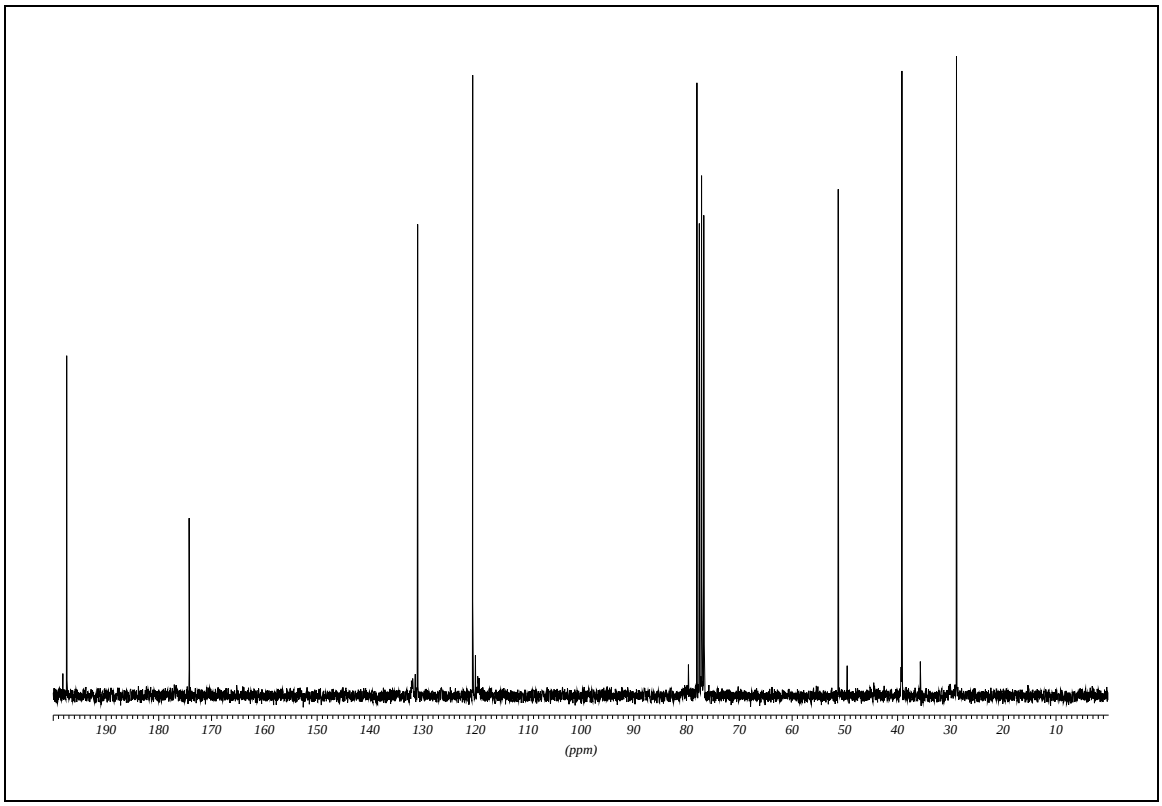
(*1S,1'S/R,2S,3S*)-Oxalicacid-hydroxy-but-3'-enyl)-3-ethoxycarbonyl-cyclopropyl-estermethylester (71, $CDCl_3$):



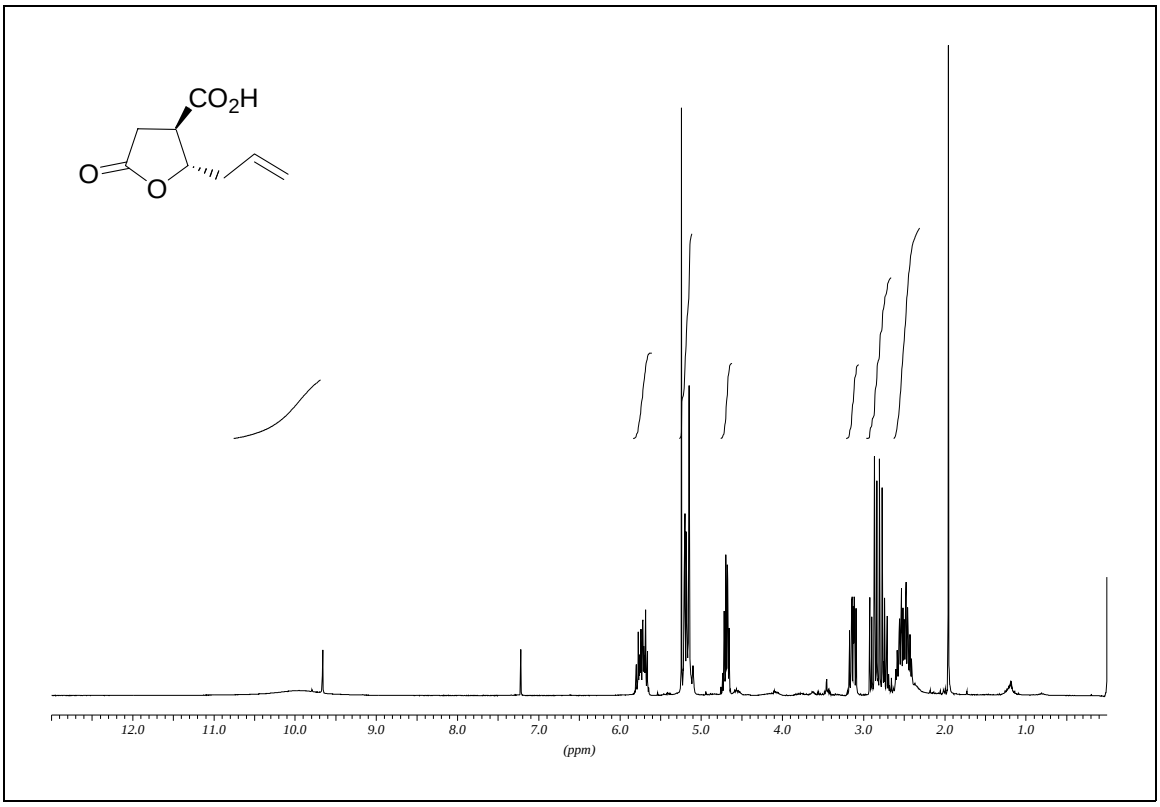


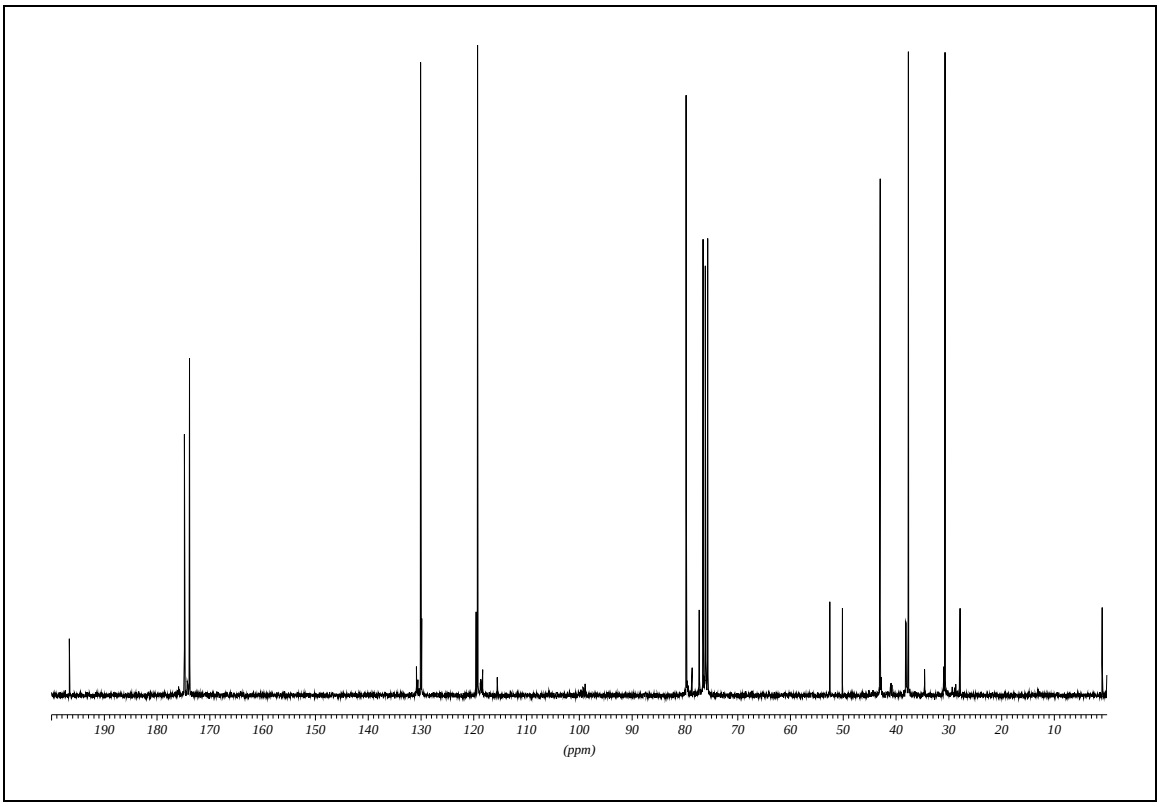
(*2S/R,3R*)-(–)-3-Formyl-5-oxo-2-(propen-2‘-yl)-tetrahydrofuran (48, $CDCl_3$):



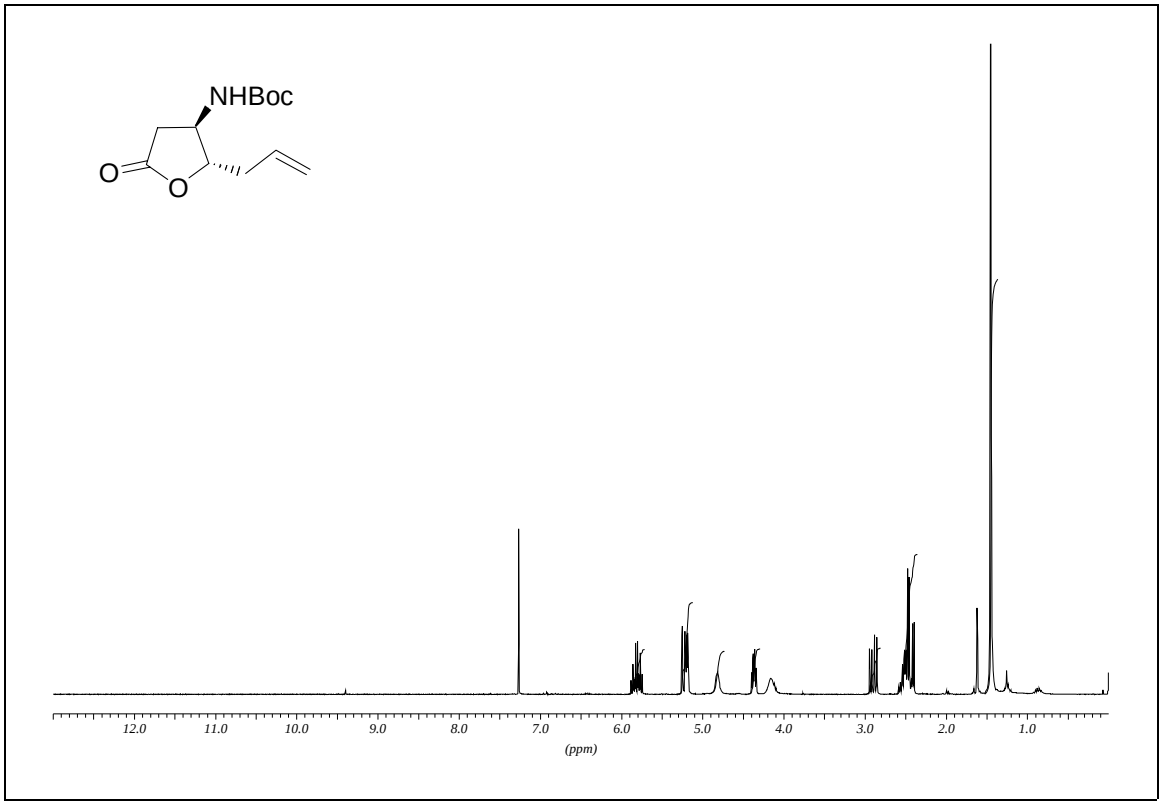


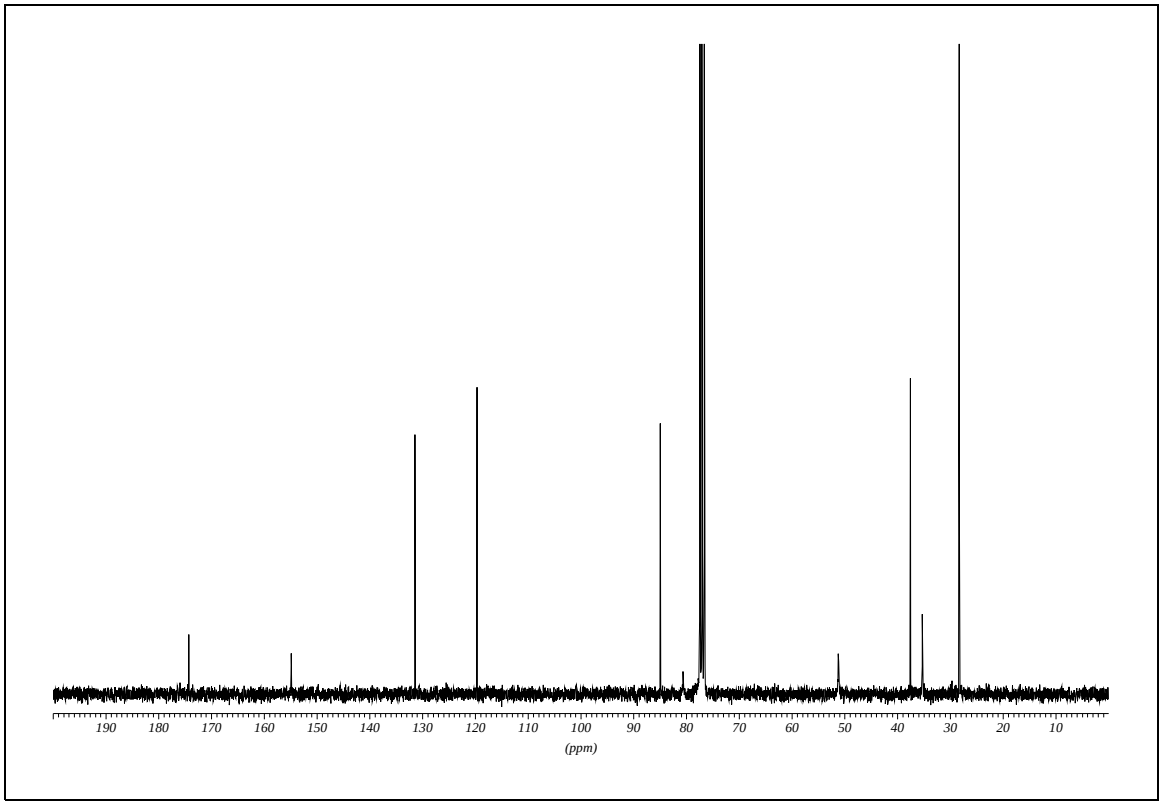
(*2S,3R*)-(–)-Tetrahydro-5-oxo-2-(propen-2‘-yl)-3-furancarbonicacid (89, $CDCl_3$):



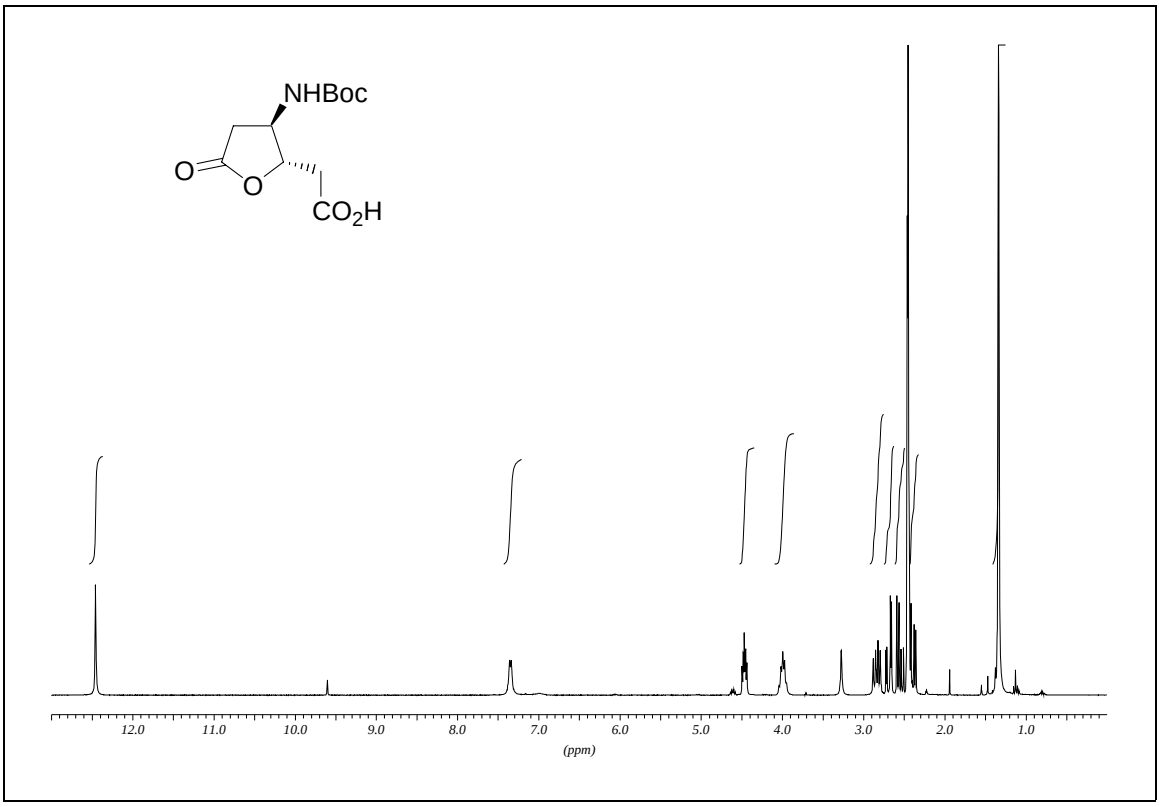


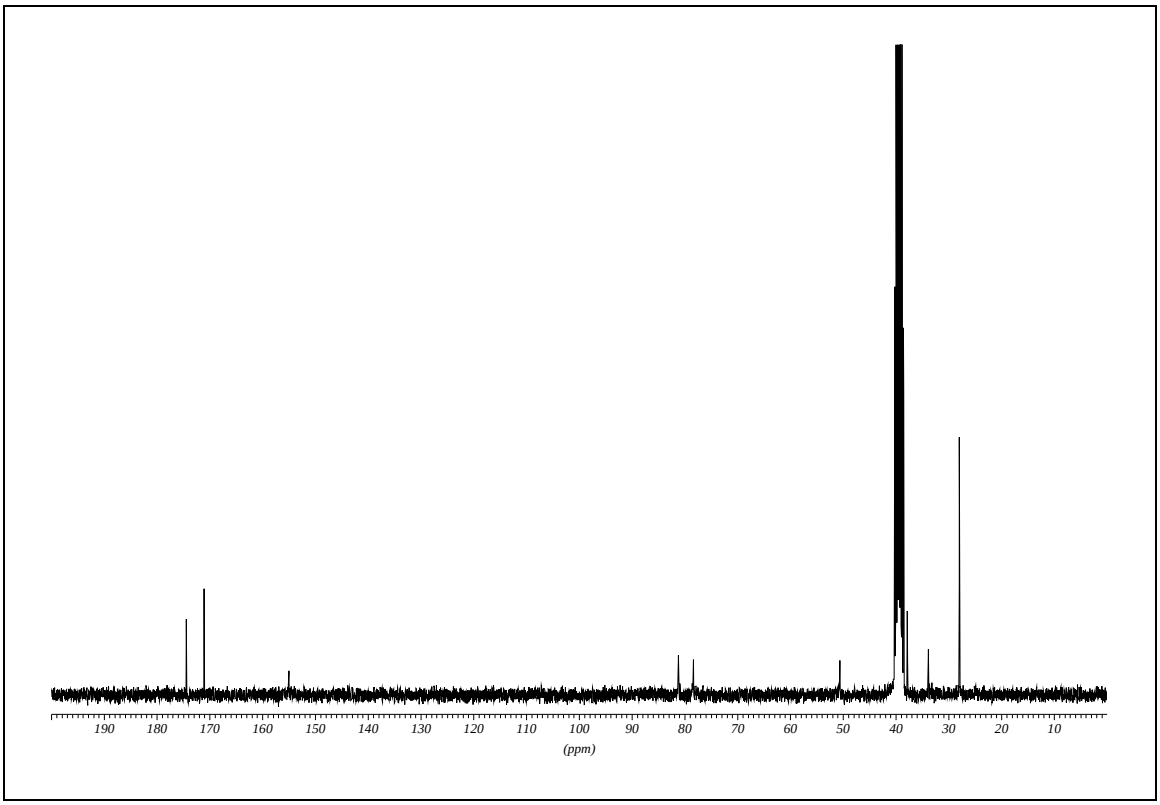
(*2S,3R*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-yl)-carbamic acid-*tert*-butylester (98, $CDCl_3$):



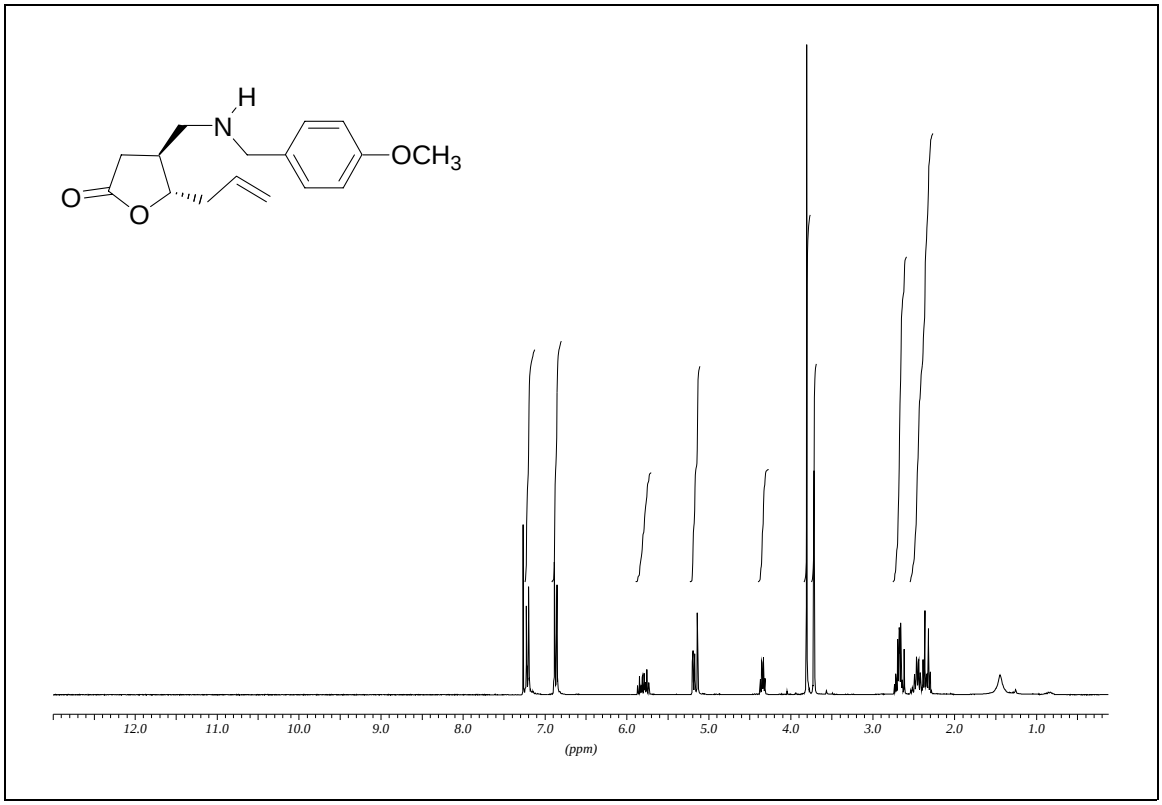


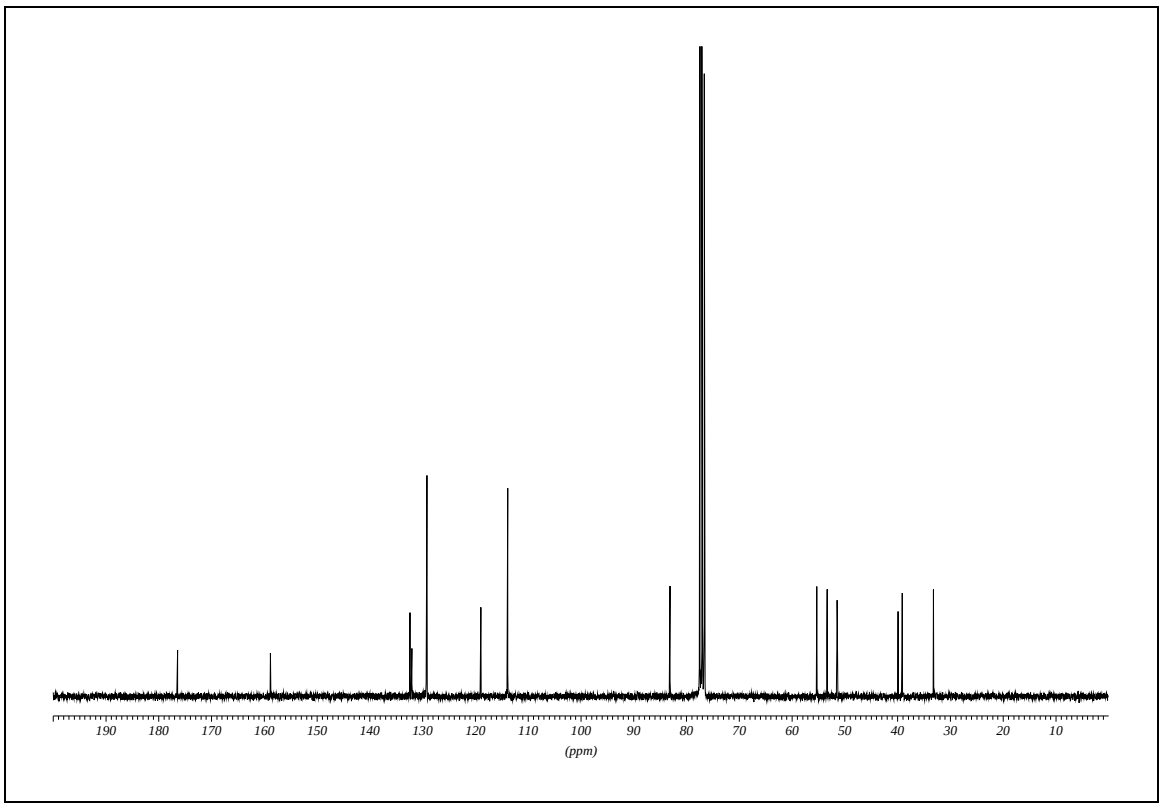
(*2S,3R*)-(–)-(3-*tert*-Butoxycarbonylamino-5-oxo-tetrahydro-furan-2-yl)-acetic acid (49, DMSO-d_6):



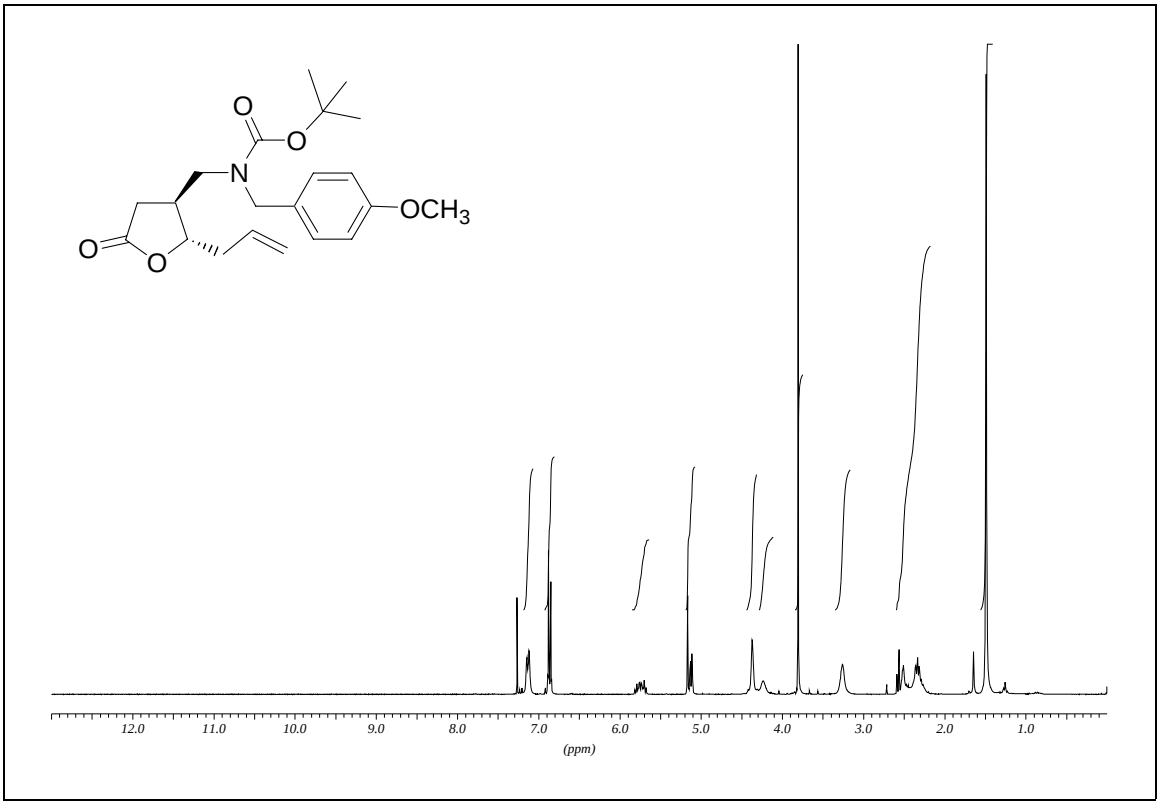


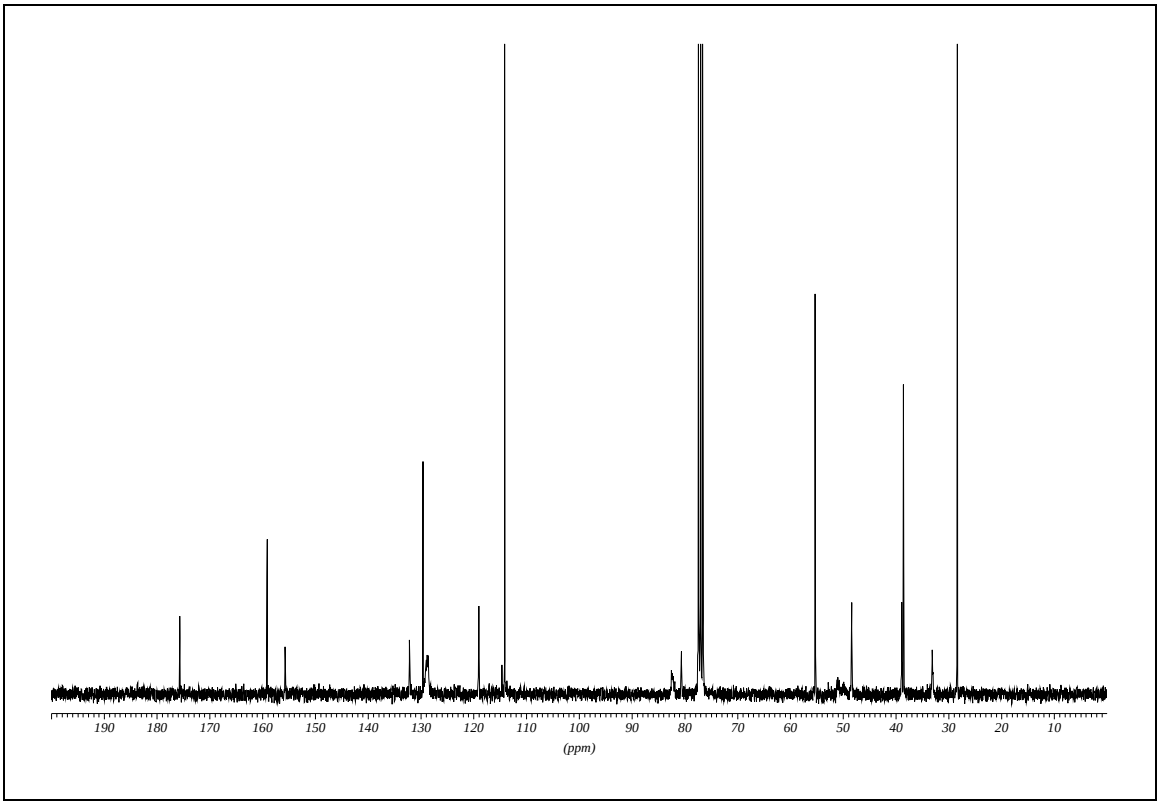
(*2S,3R*)-(–)-(5-Allyl-4-[(4-methoxy-benzylamino)-methyl]-dihydro-furan-2-one (111b, $CDCl_3$):



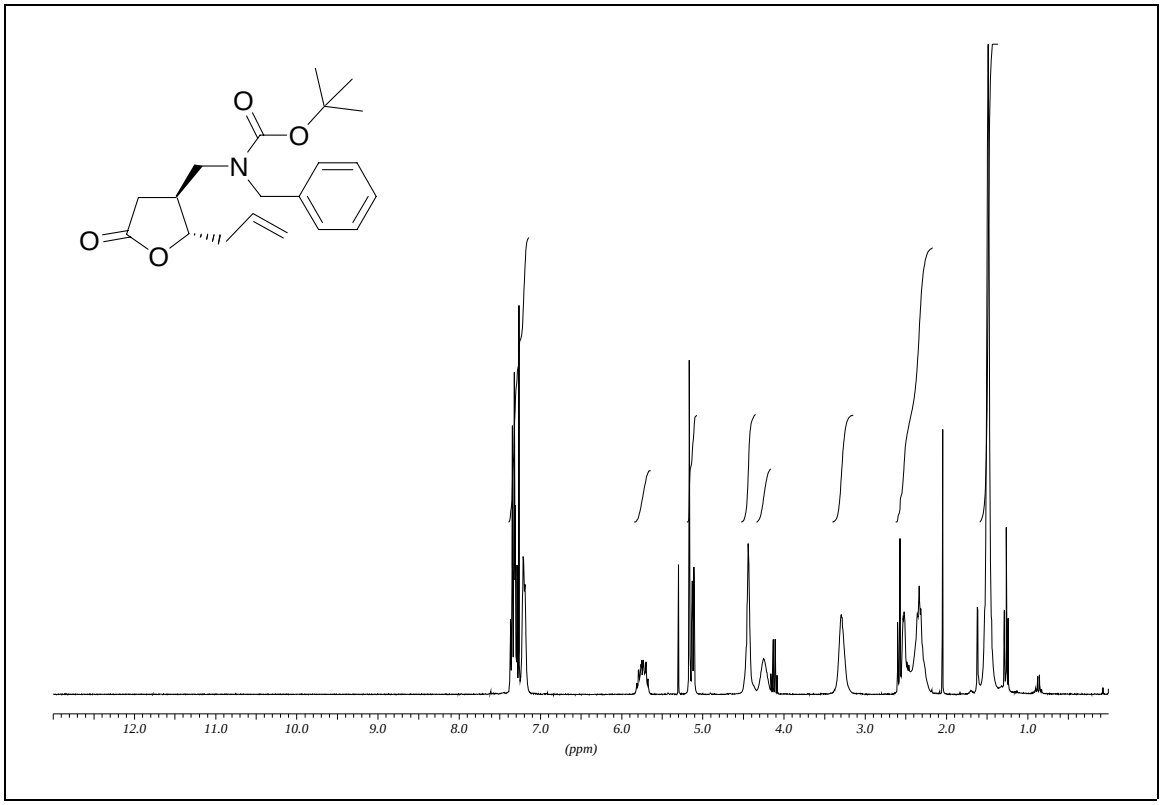


(*2S,3S*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid *tert*-butylester (114b, $CDCl_3$):

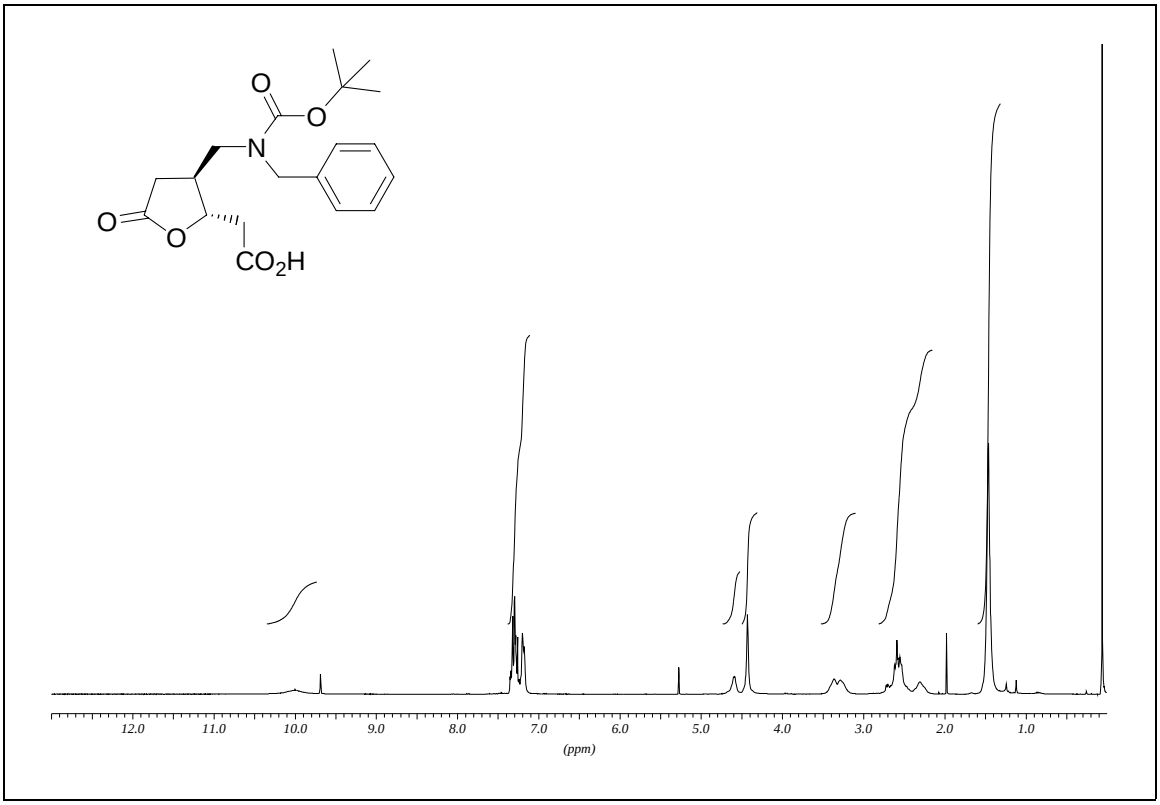


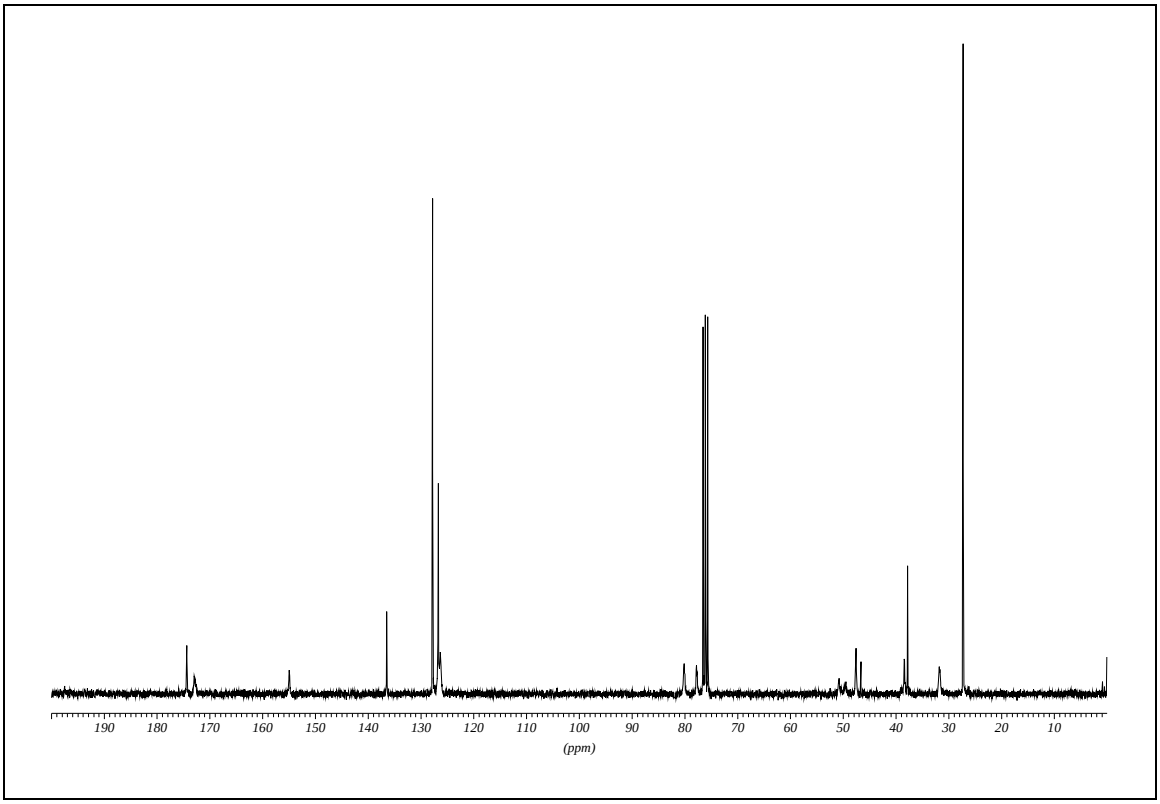


(*2S,3S*)-(–)-(2-Allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-benzyl)-carbamic acid *tert*-butyl ester (114a, $CDCl_3$):

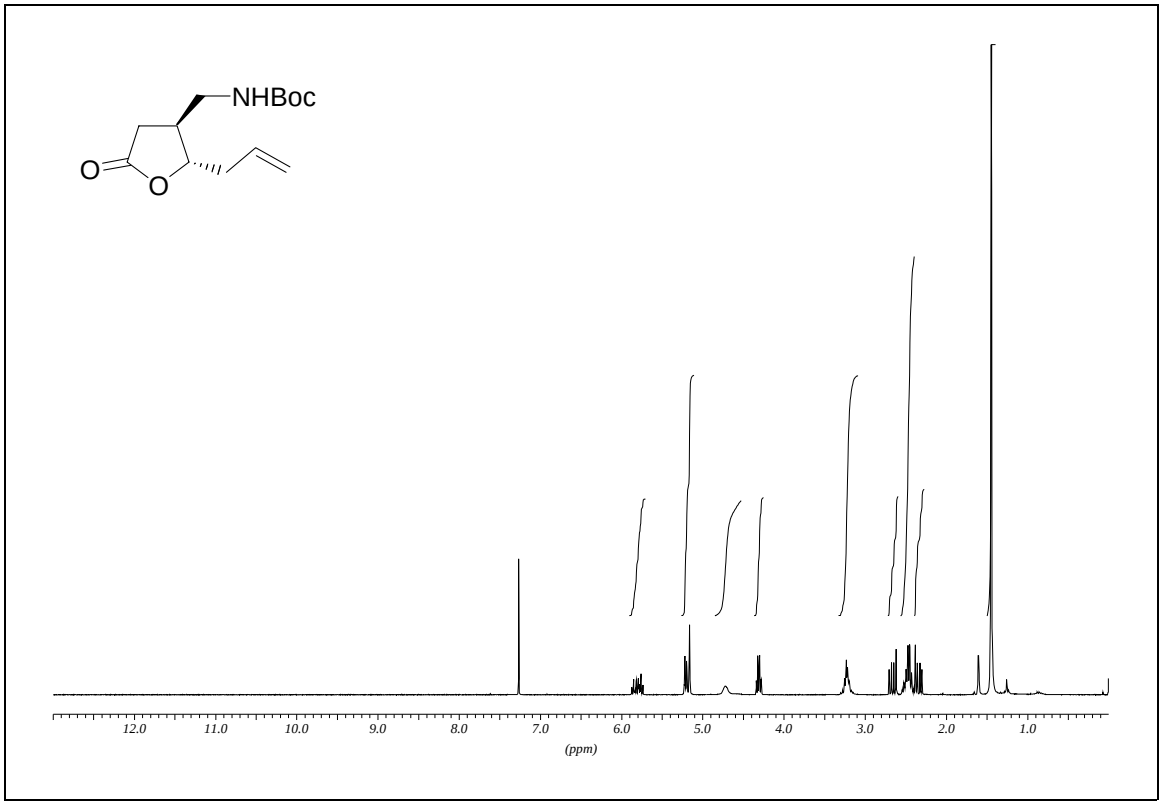


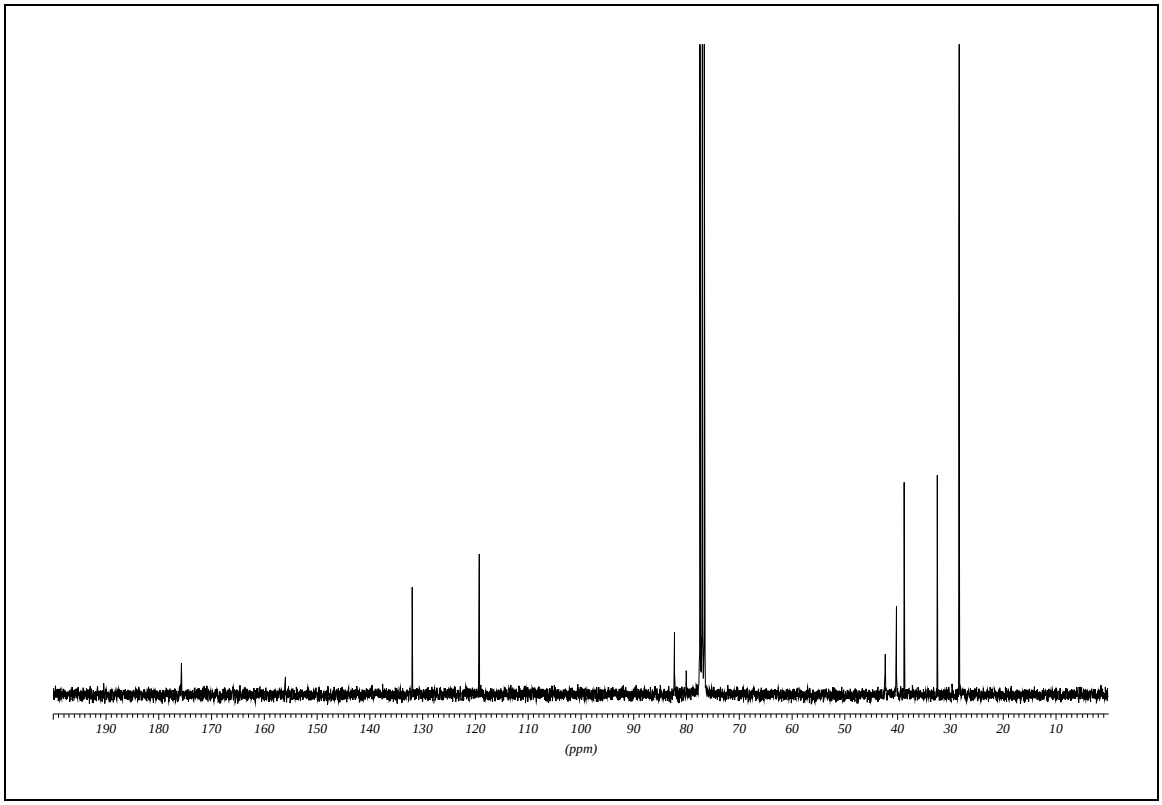
(*2S,3S*)-(–)-[Benzyl-*tert*-butoxycarbonyl-amino)-methyl]-5-oxo-tetrahydro-furan-2-yl}-acetic acid (116, $CDCl_3$):



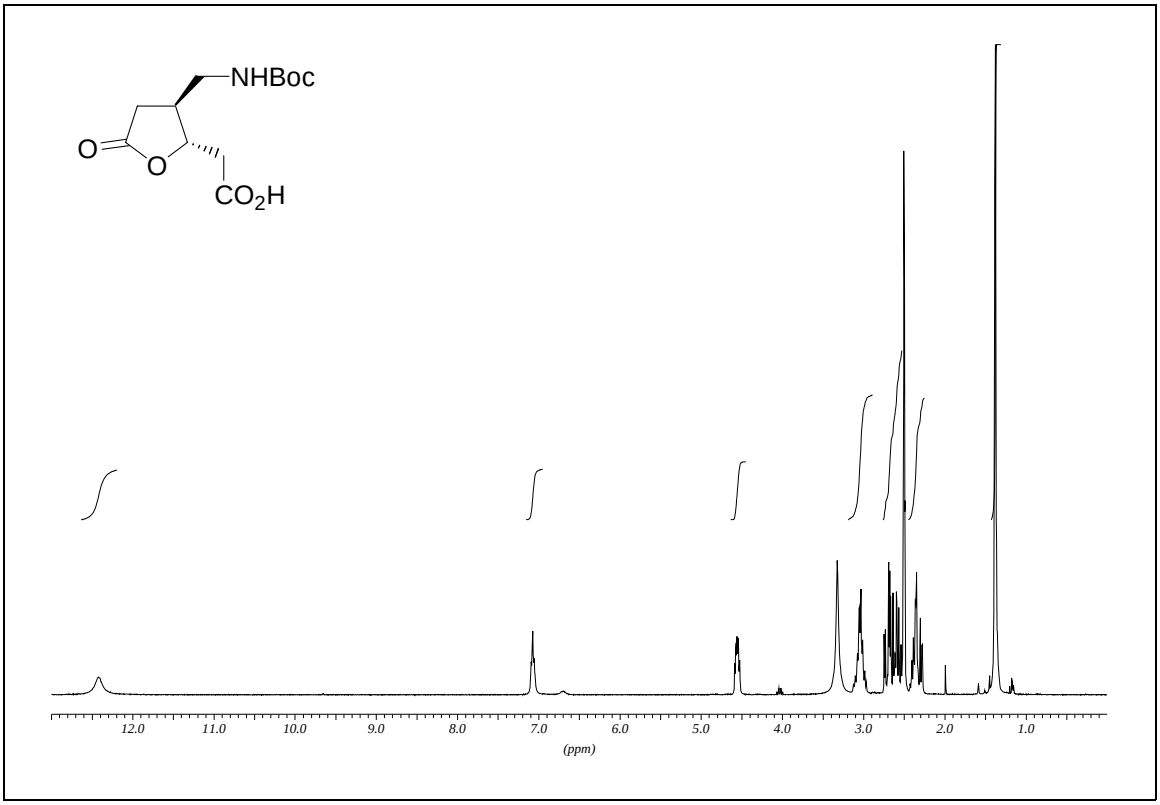


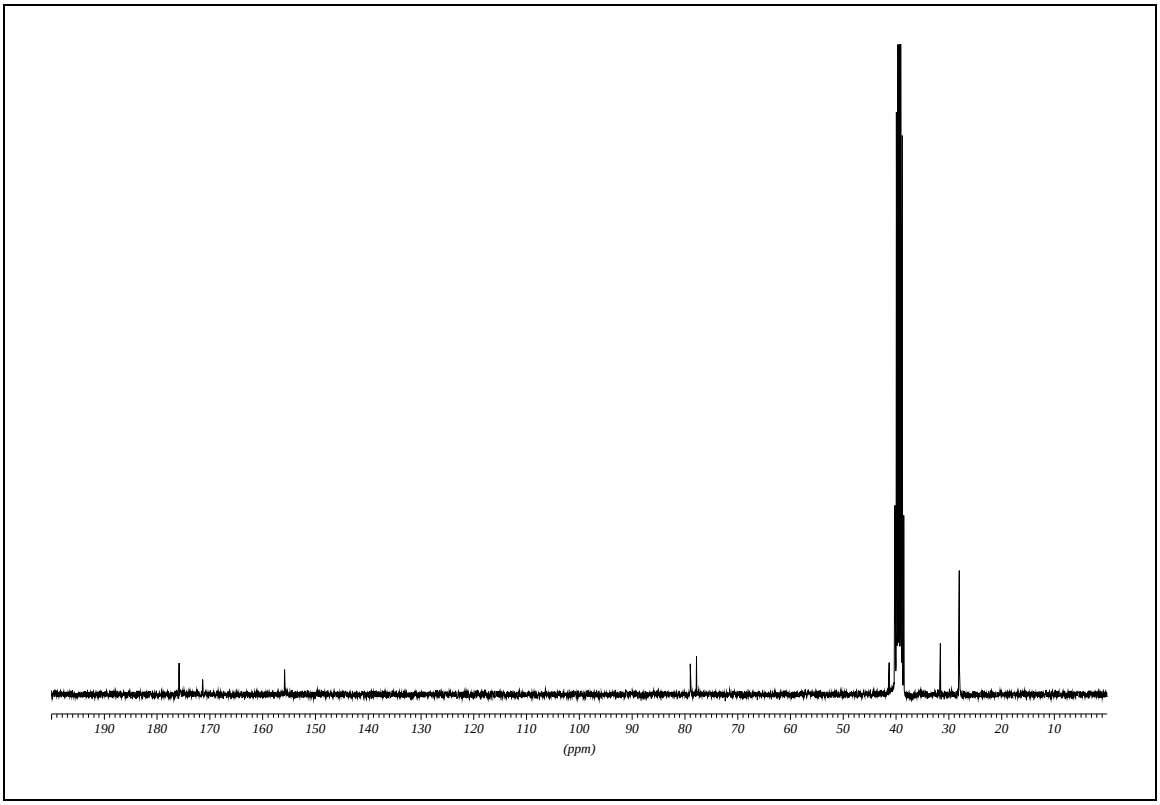
(*1S,5S,6S*)-(–)-2-Oxa-bicyclo[3.1.0]hex-3-en-3,6-dicarbonicacid-6-ethylester-3-methyl-ester (117, $CDCl_3$)



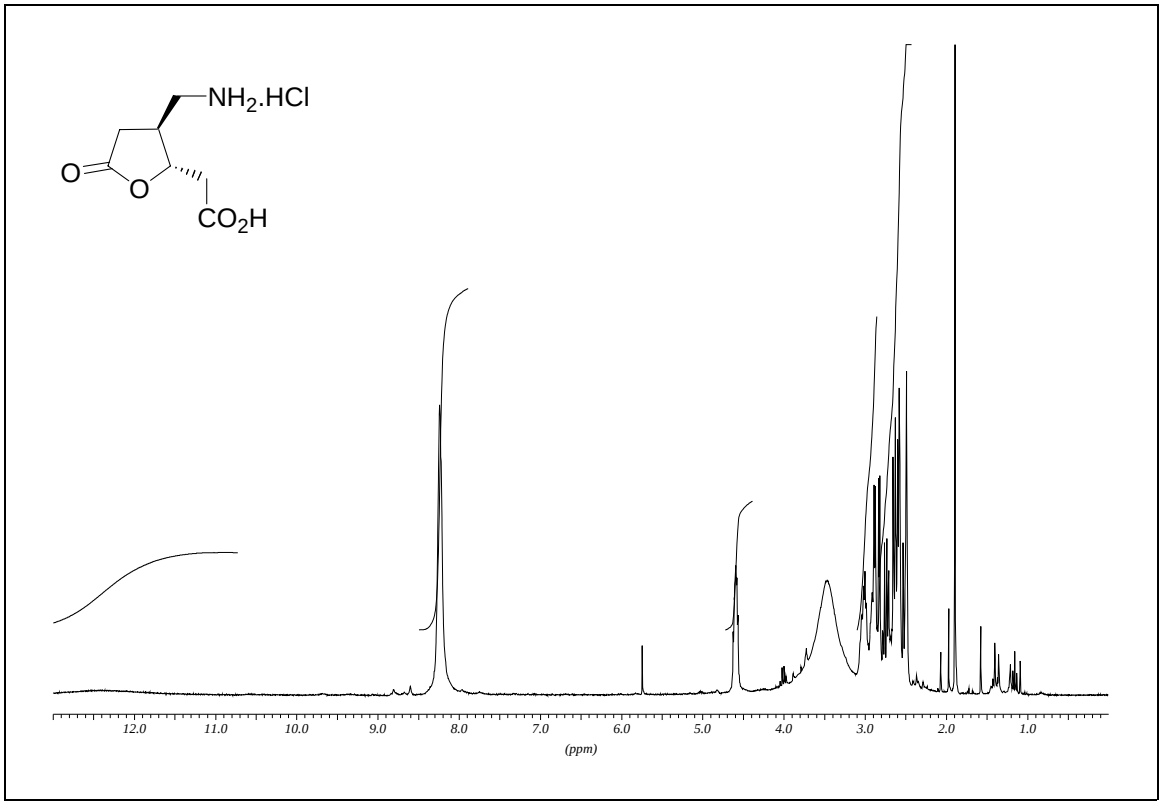


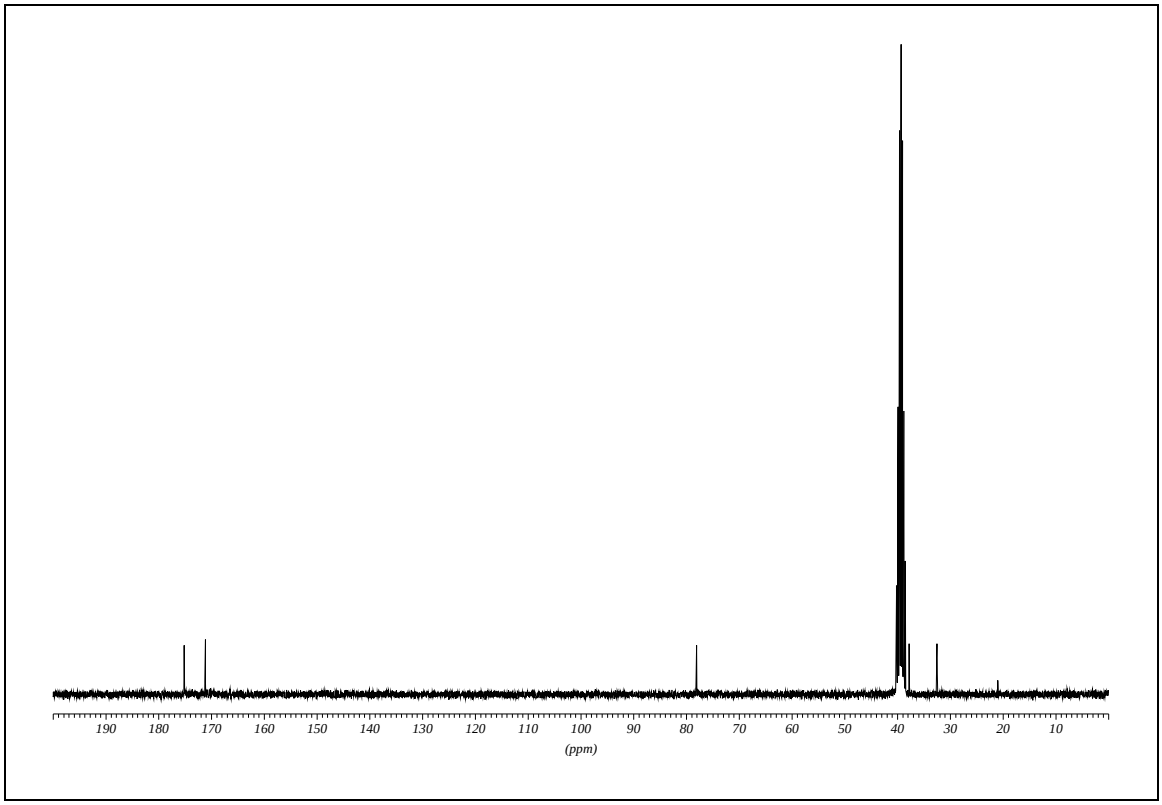
(*2S,3S*)-(–)-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid (50, DMSO-d_6):



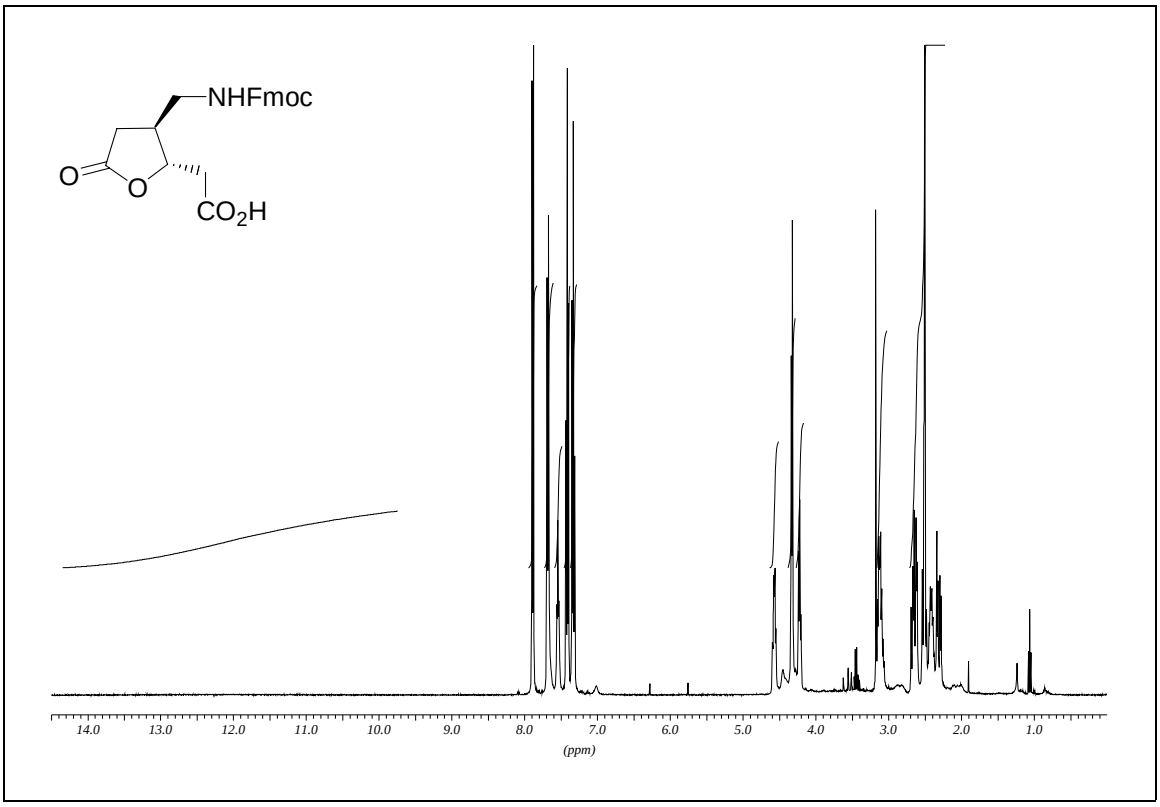


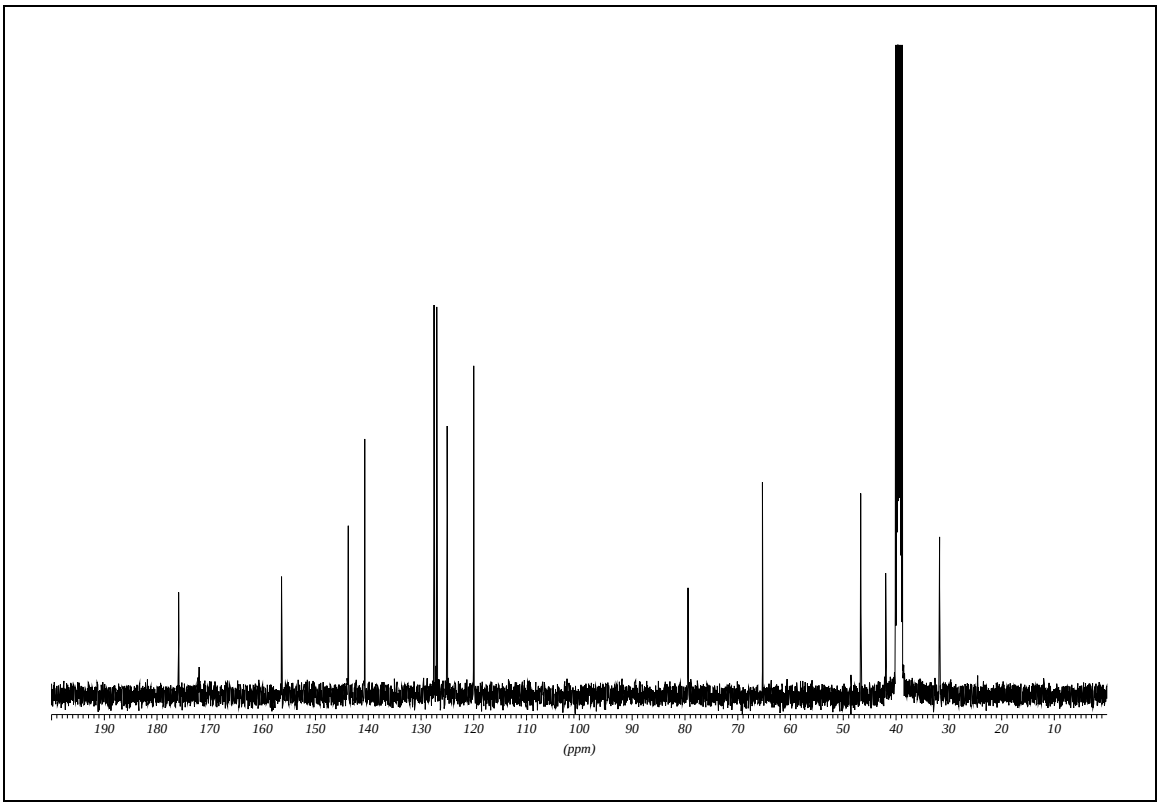
(*2S*,*3S*)-(–)-(3-Aminomethyl-5-oxo-tetrahydro-furan-2-yl)-acetic acid monohydrochloride (118, DMSO-d_6):



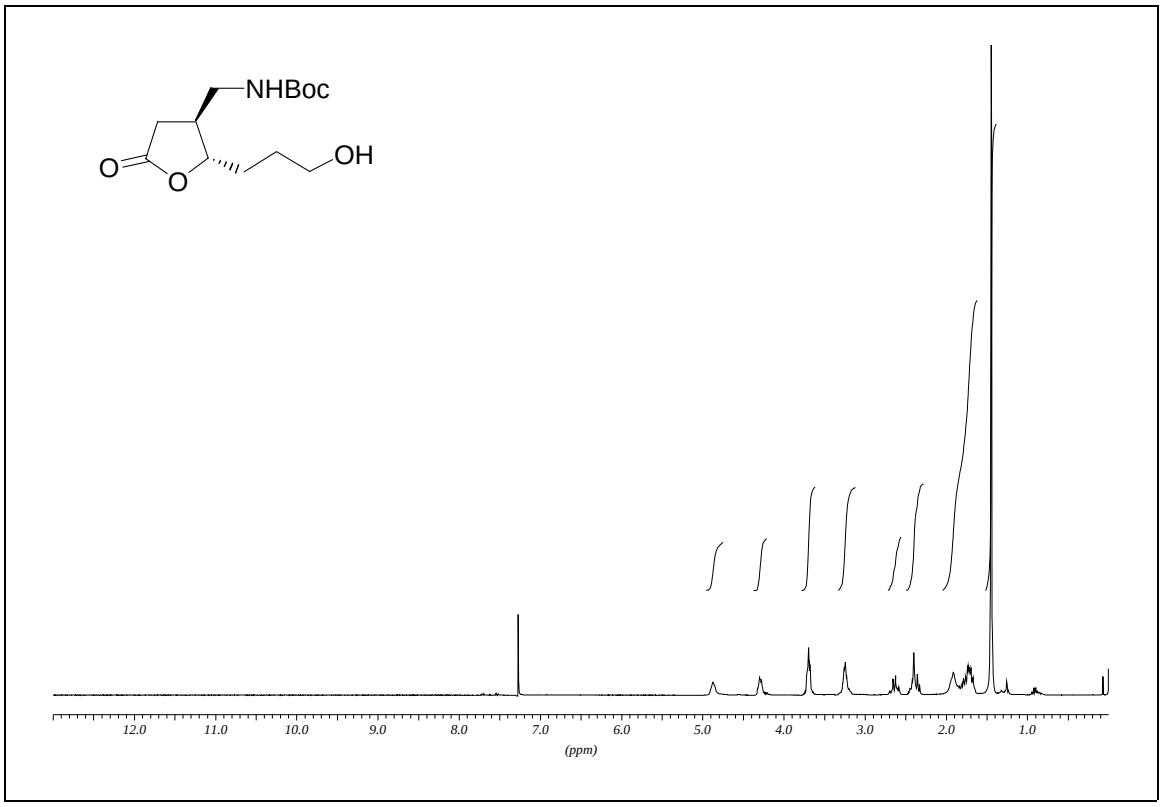


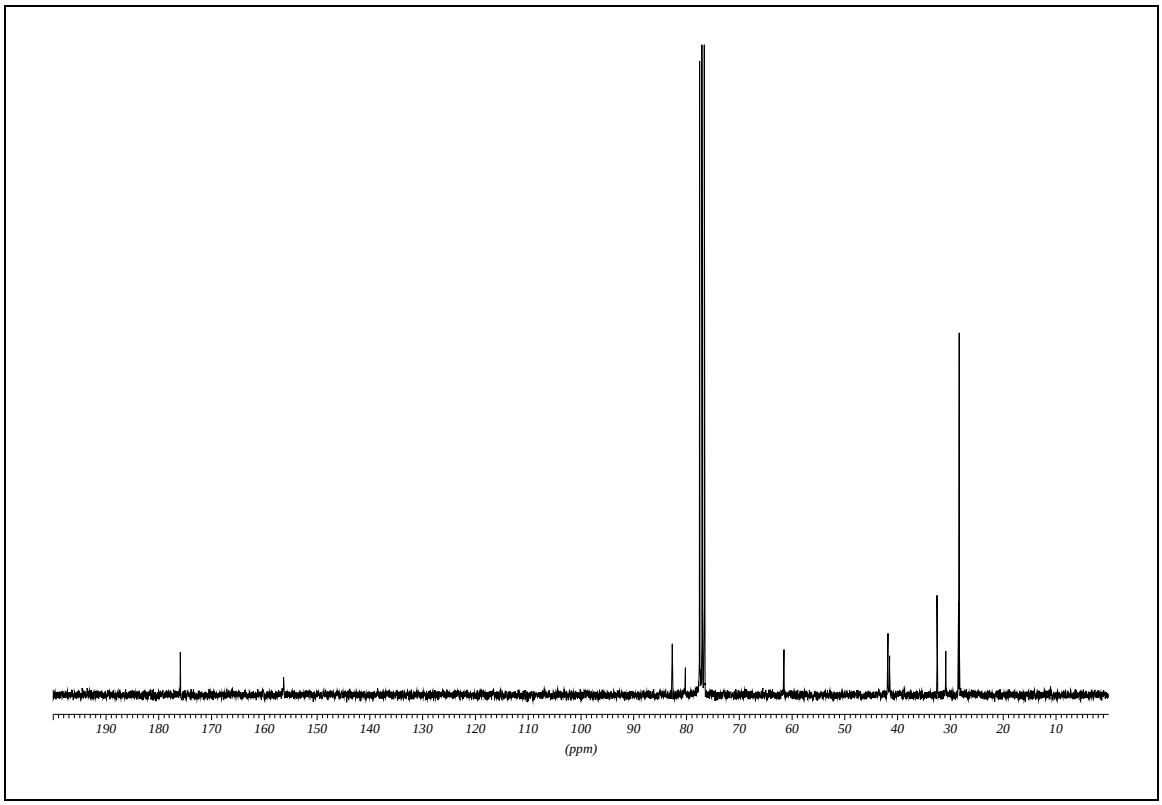
(*2S,3S*)-(–)-{3-[9*H*-Fluoren-9-ylmethoxycarbonylamino)-methyl]-5-oxo-tetra-hydro-furan-2-yl}-acetic acid (119, DMSO-d_6):



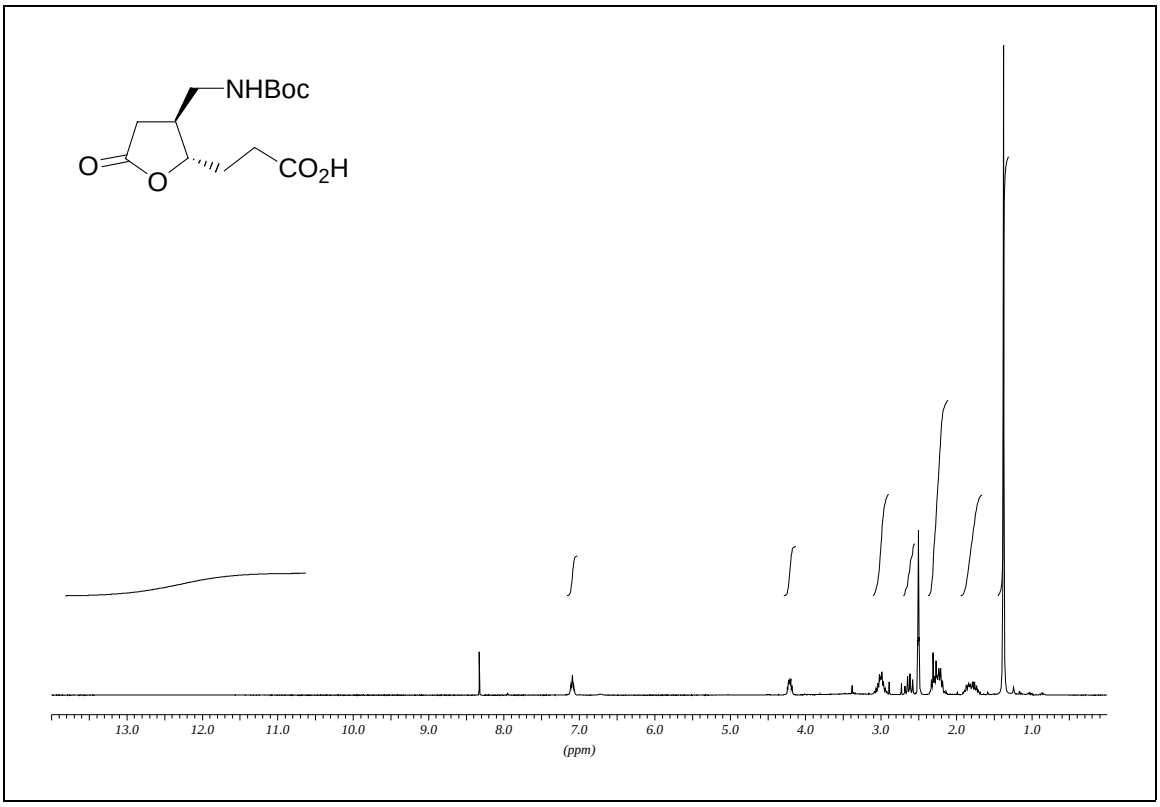


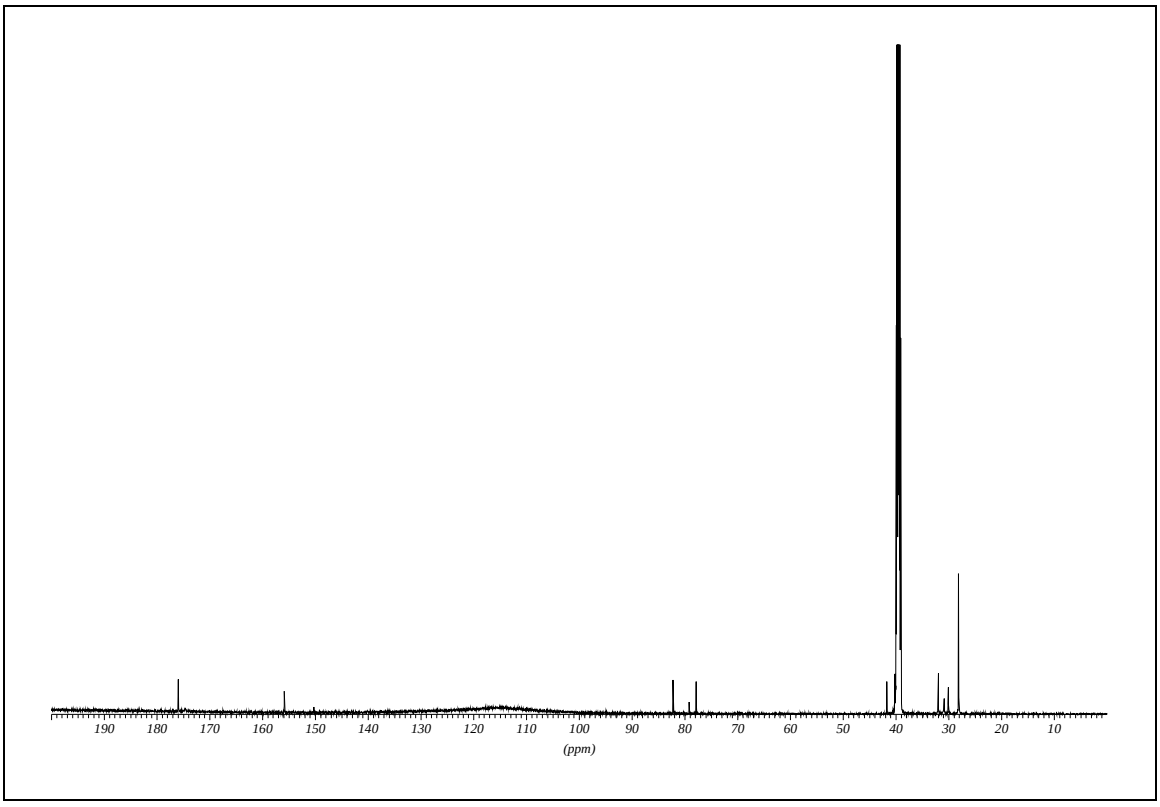
(*2S,3S*)-(–)-[2-(3-Hydroxy-propyl)-5-oxo-tetrahydro-furan-3-ylmethyl]-carbamic acid *tert*-butyl ester (123, $CDCl_3$):



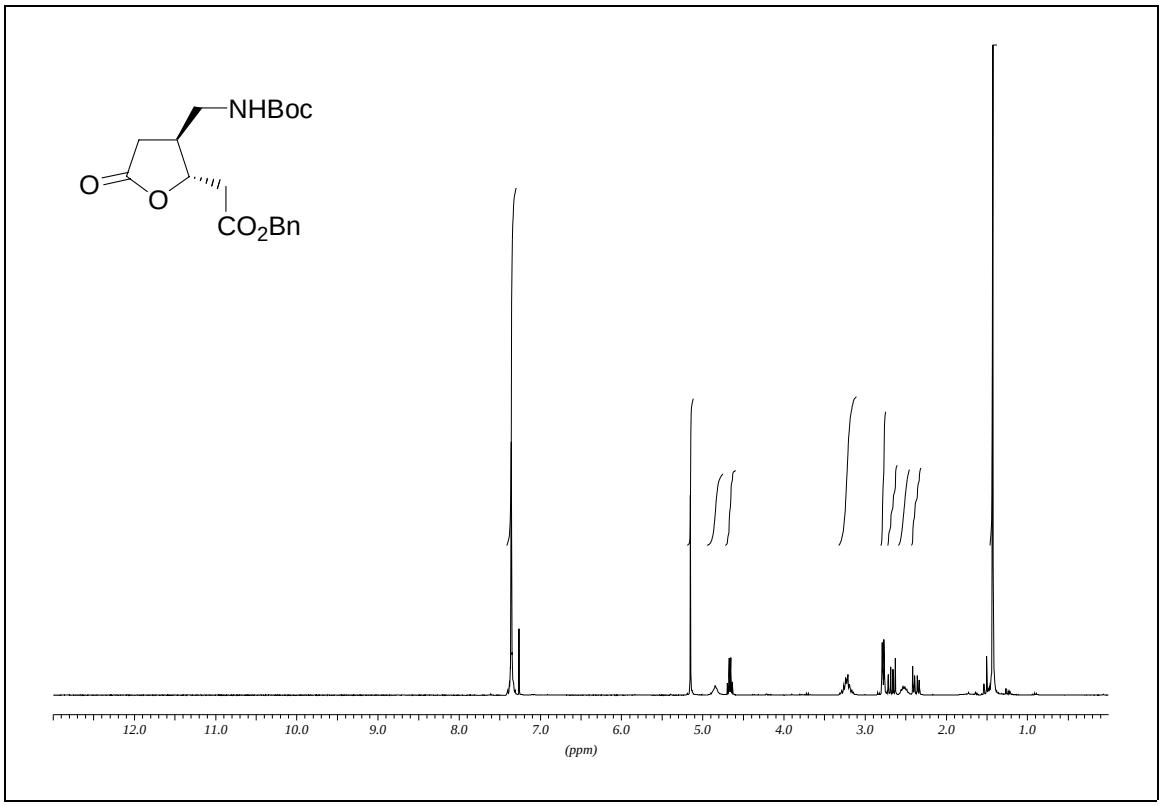


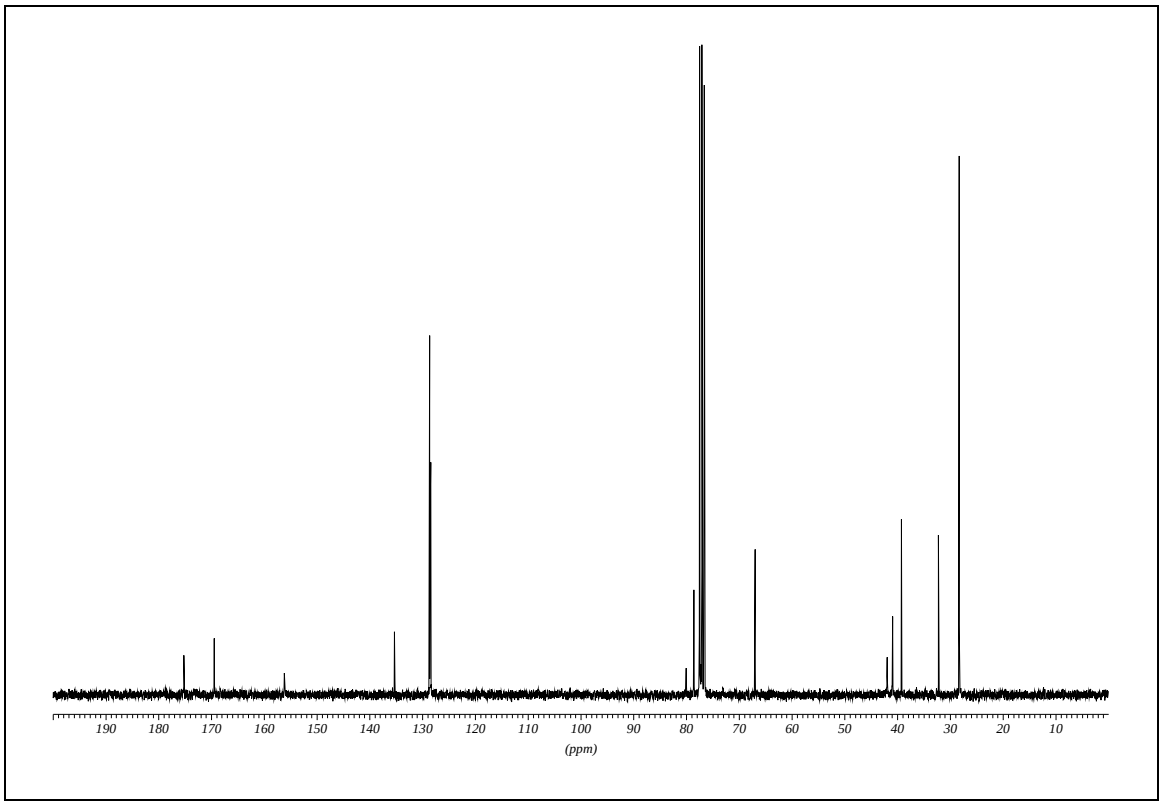
(*2S,3S*)-(–)-3-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-propionic acid (51, DMSO-d_6):



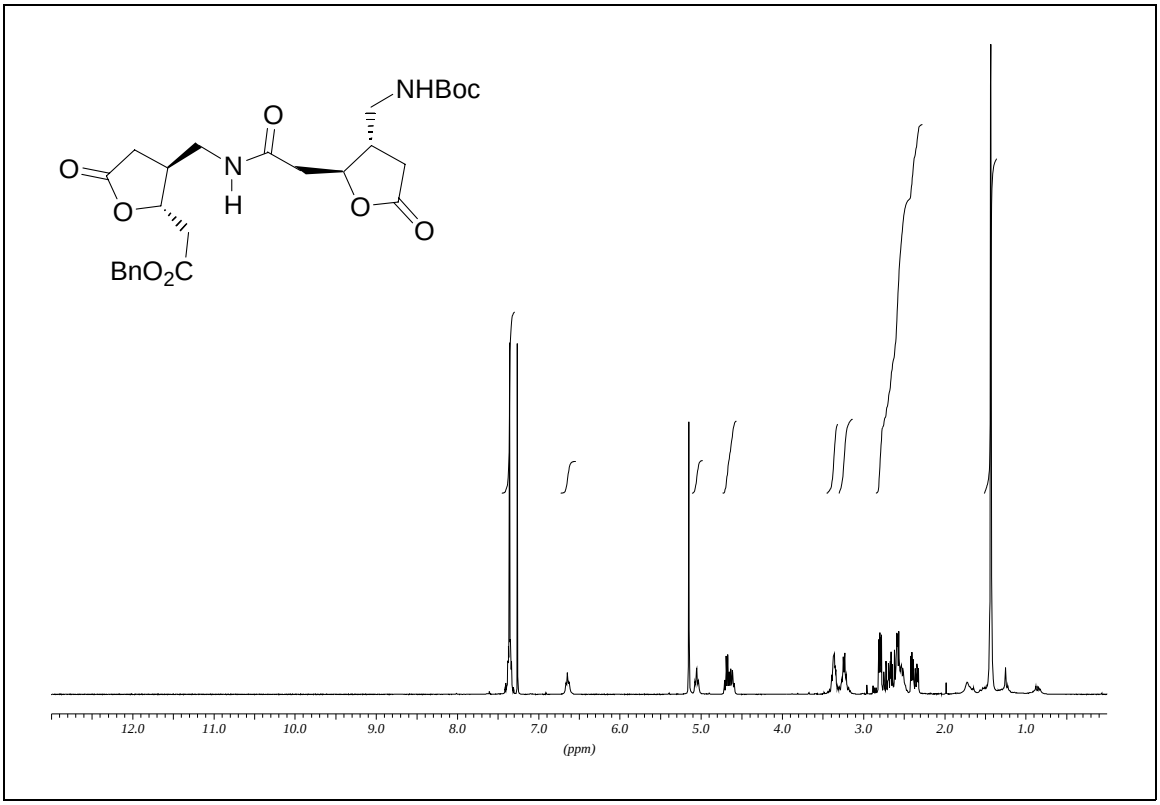


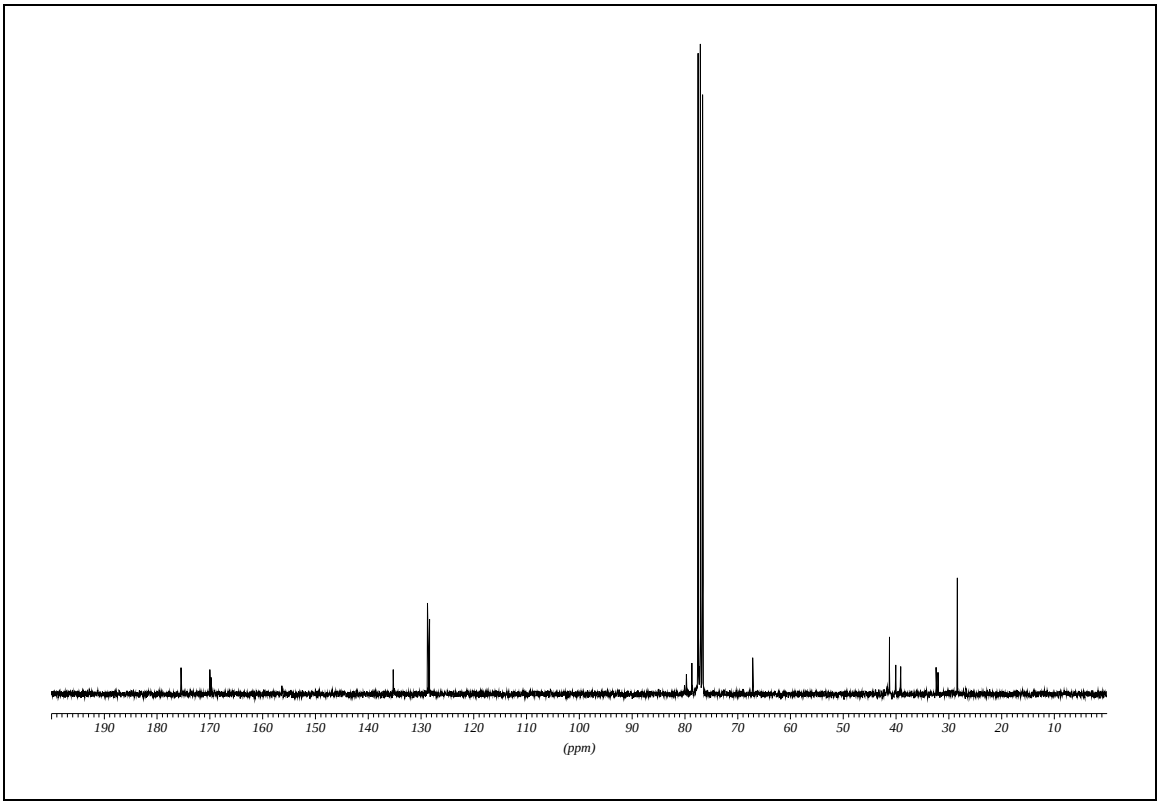
(*2S,3S*)-(–)-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydrofuran-2-yl]-acetic acid benzyl ester (141, $CDCl_3$):



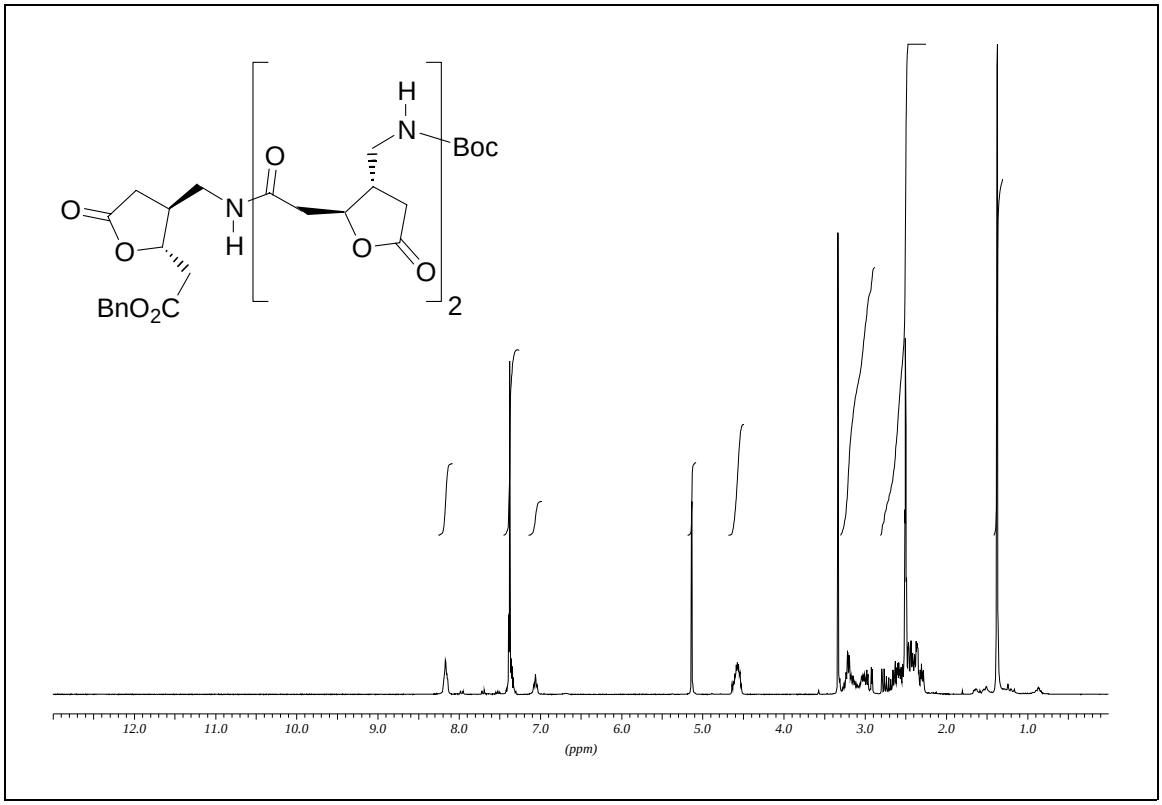


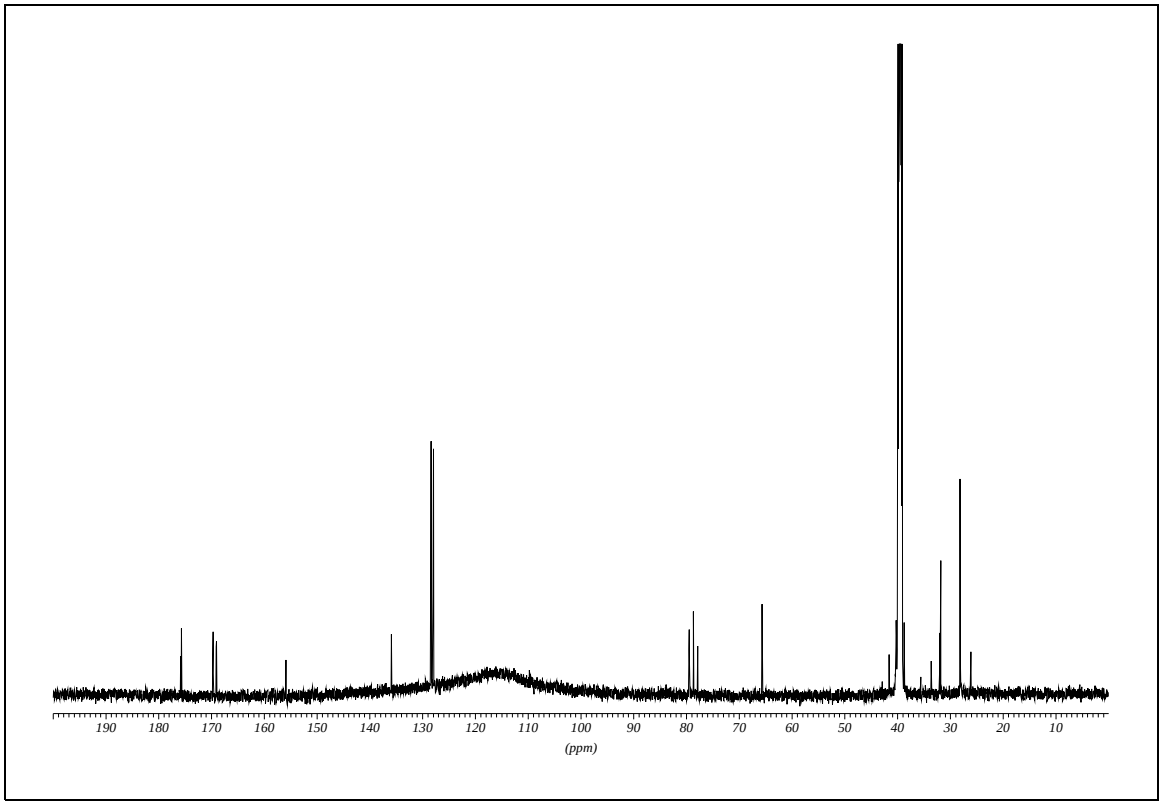
[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetyl-amino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (143, $CDCl_3$):



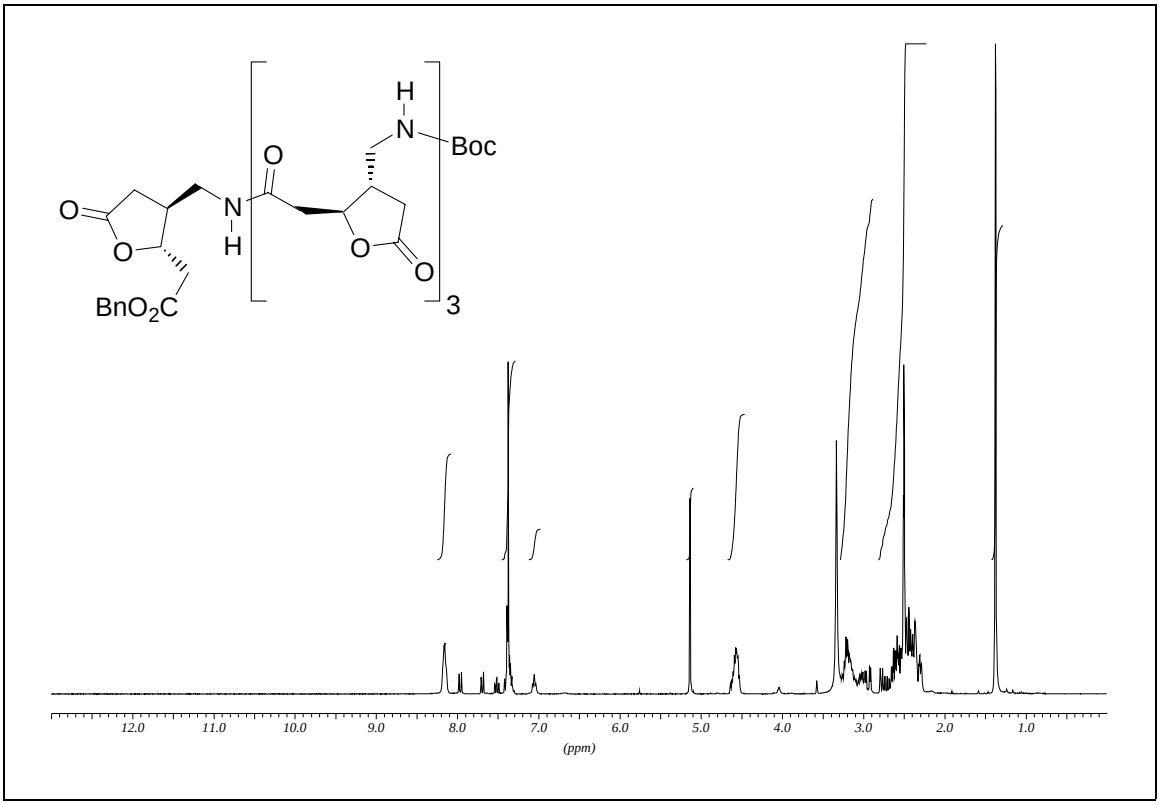


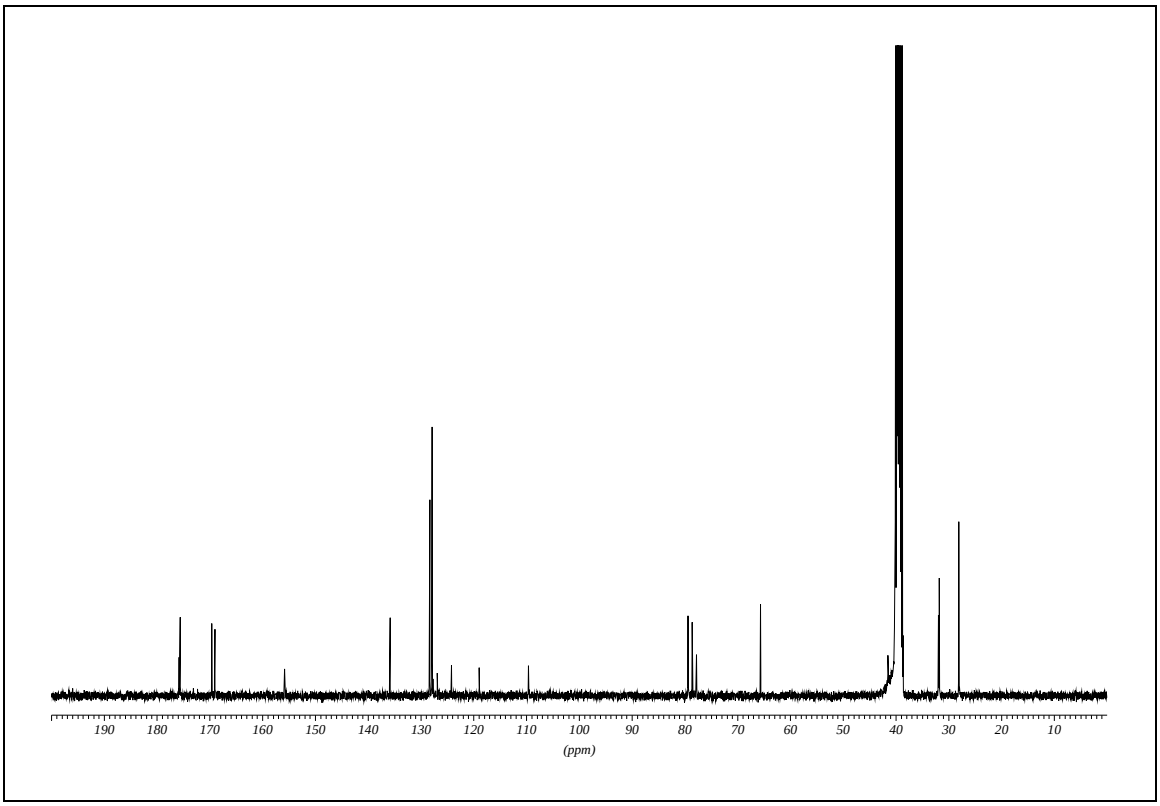
[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetyl-amino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)- 5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (145, DMSO-d_6):



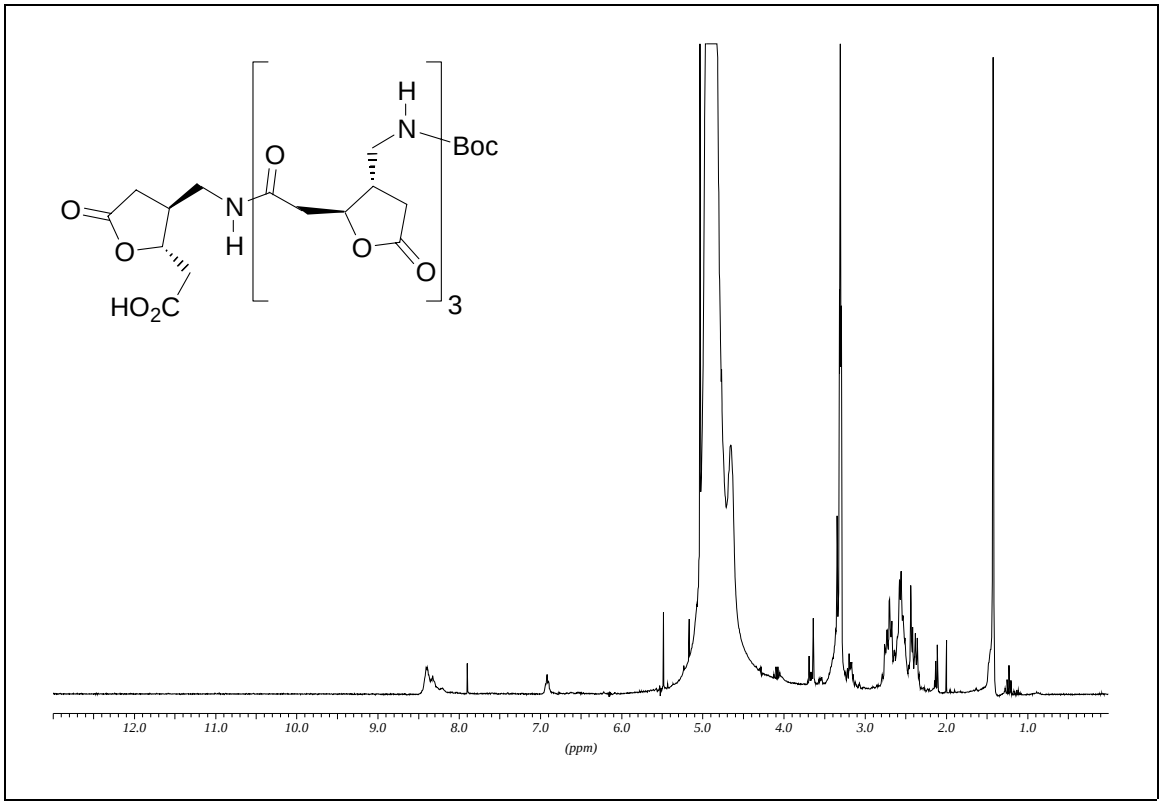


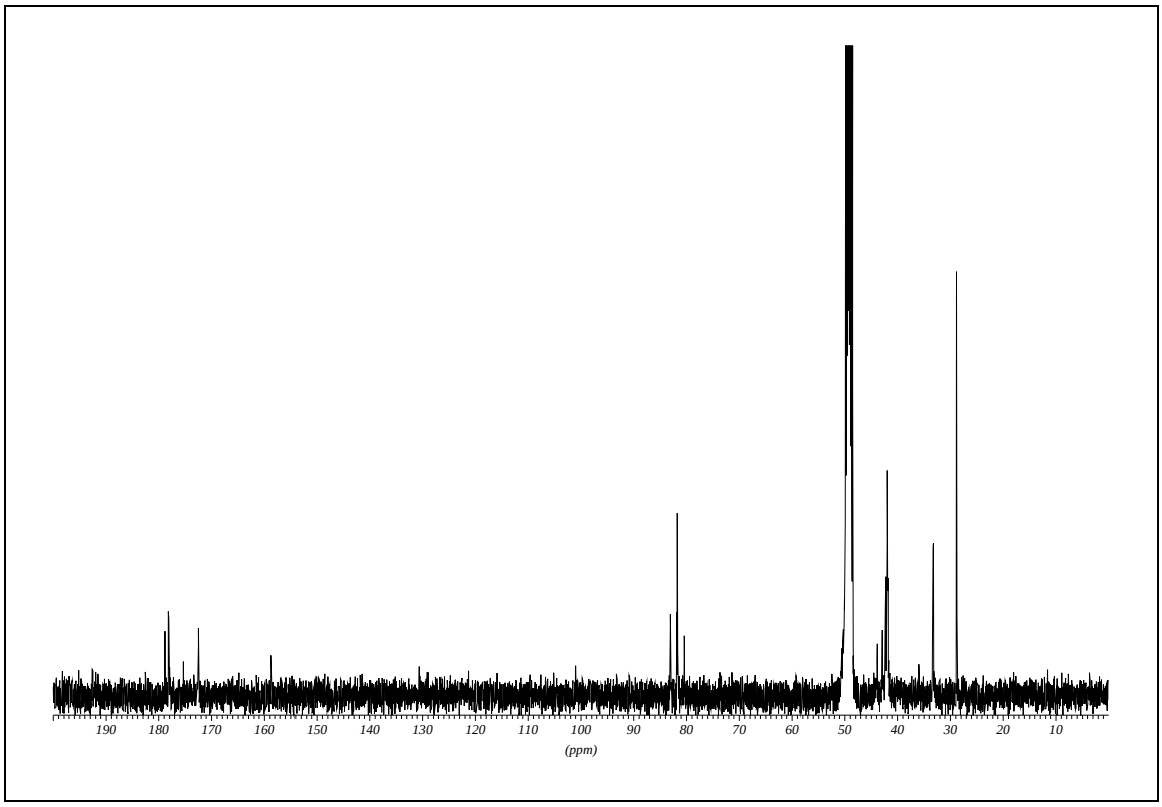
[3-({2-[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-ace-tylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid benzyl ester (147, DMSO-d_6):



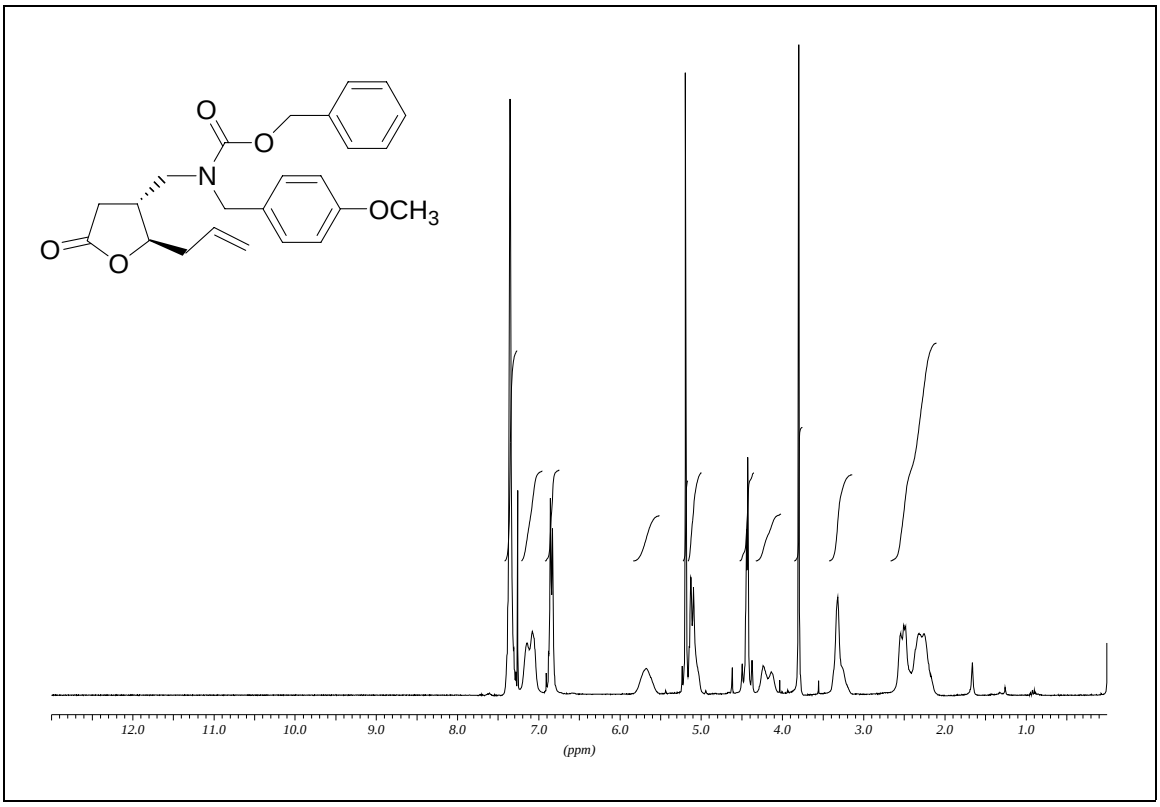


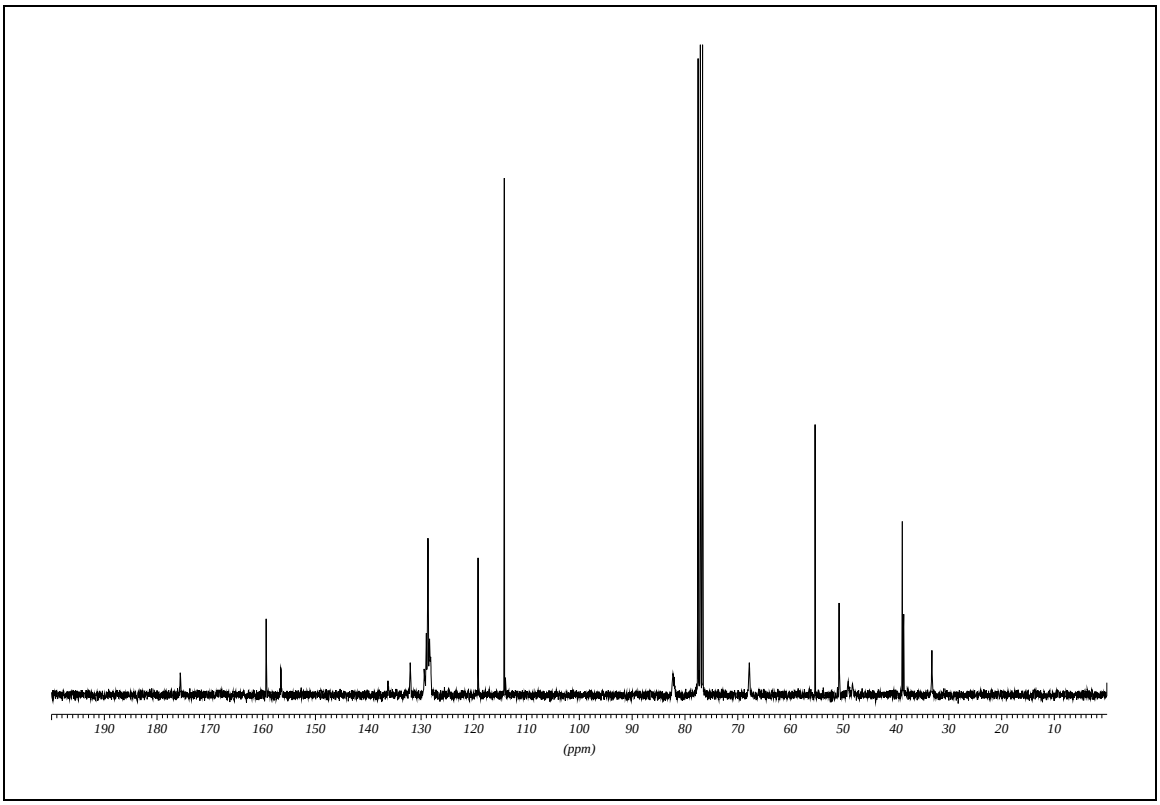
[3-({2-[3-({2-[3-({2-[3-(*tert*-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-ace-tylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetylamino}-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid (53, CD_3OH):



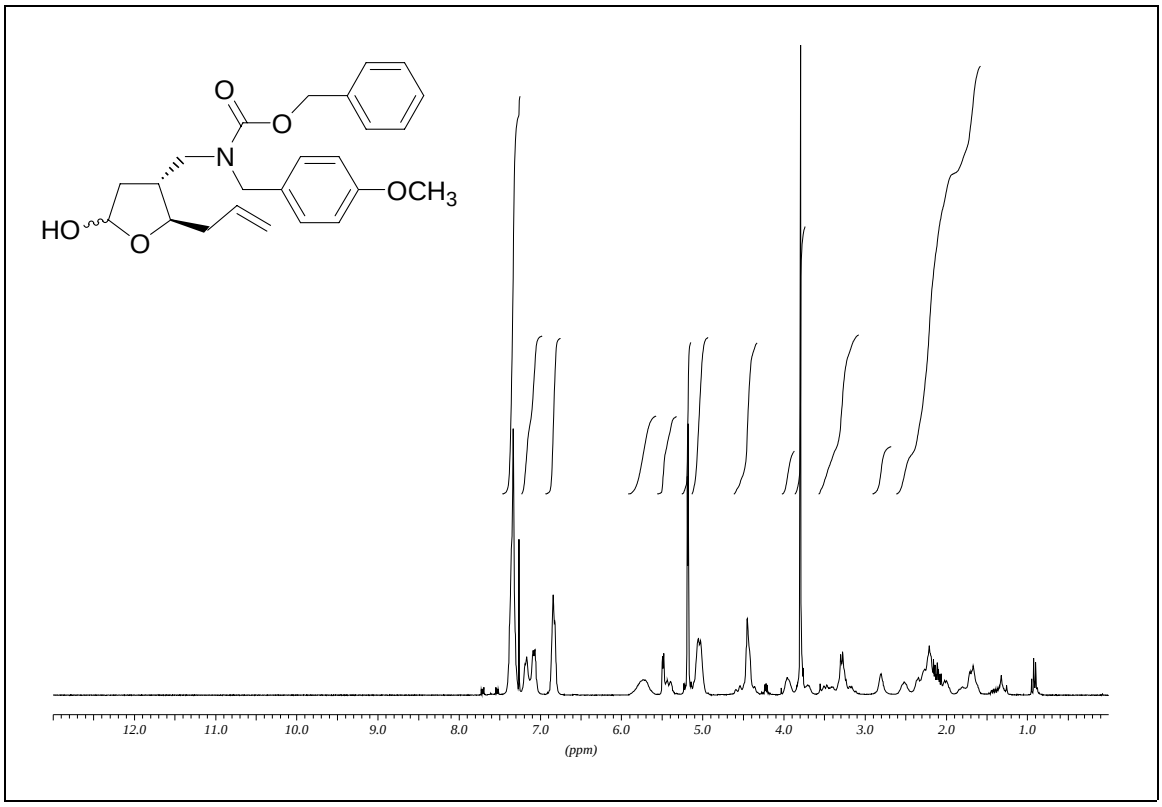


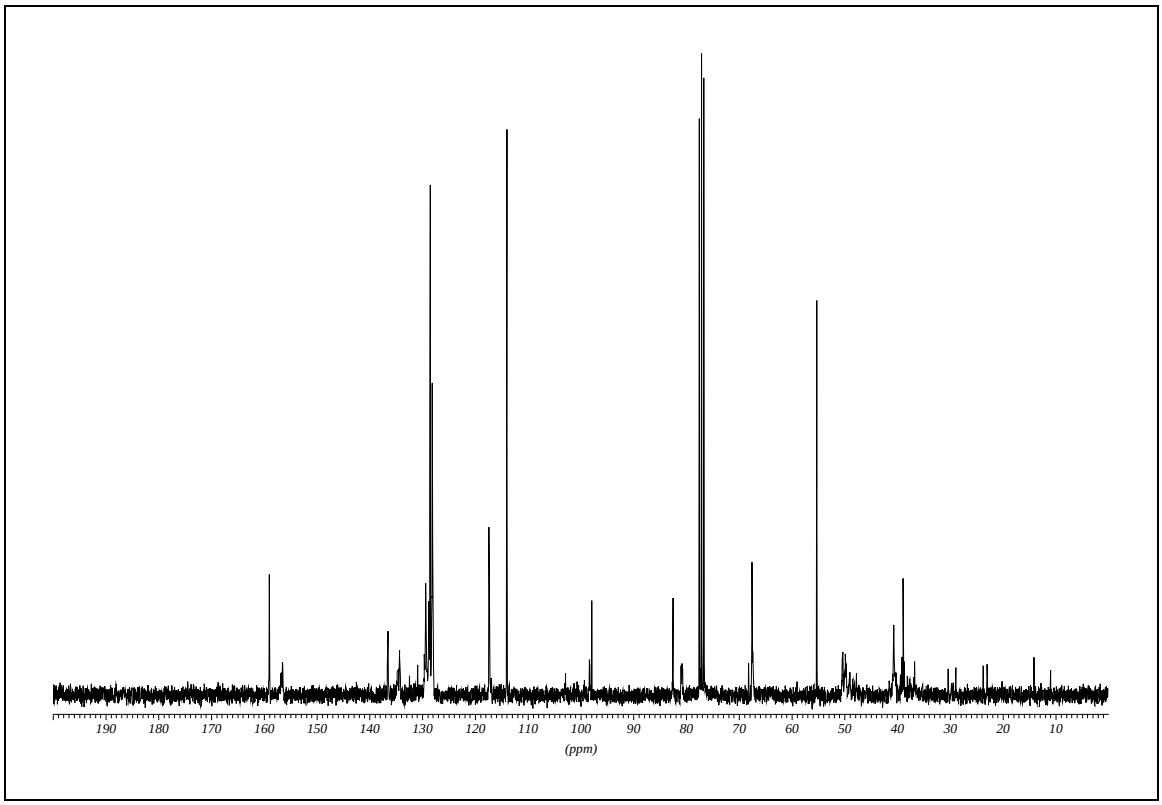
(*2R,3R*)-(+)-2-allyl-5-oxo-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid benzyl ester (155, $CDCl_3$):



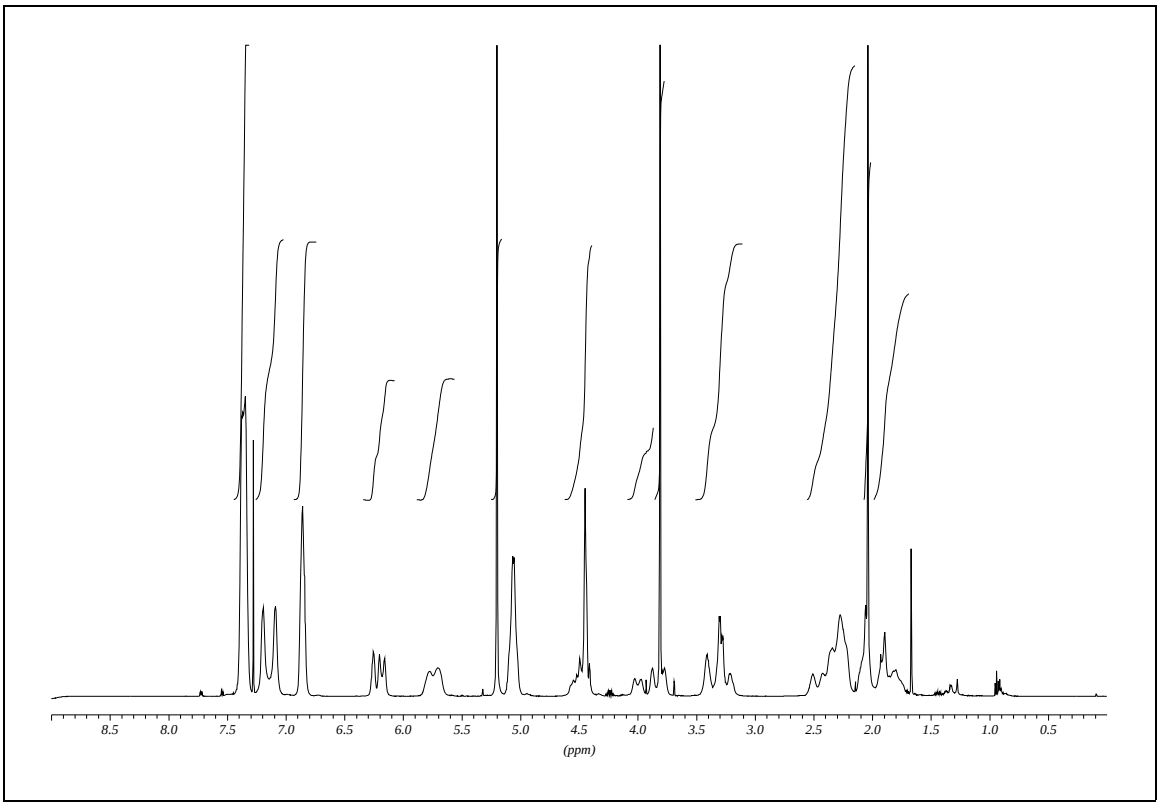


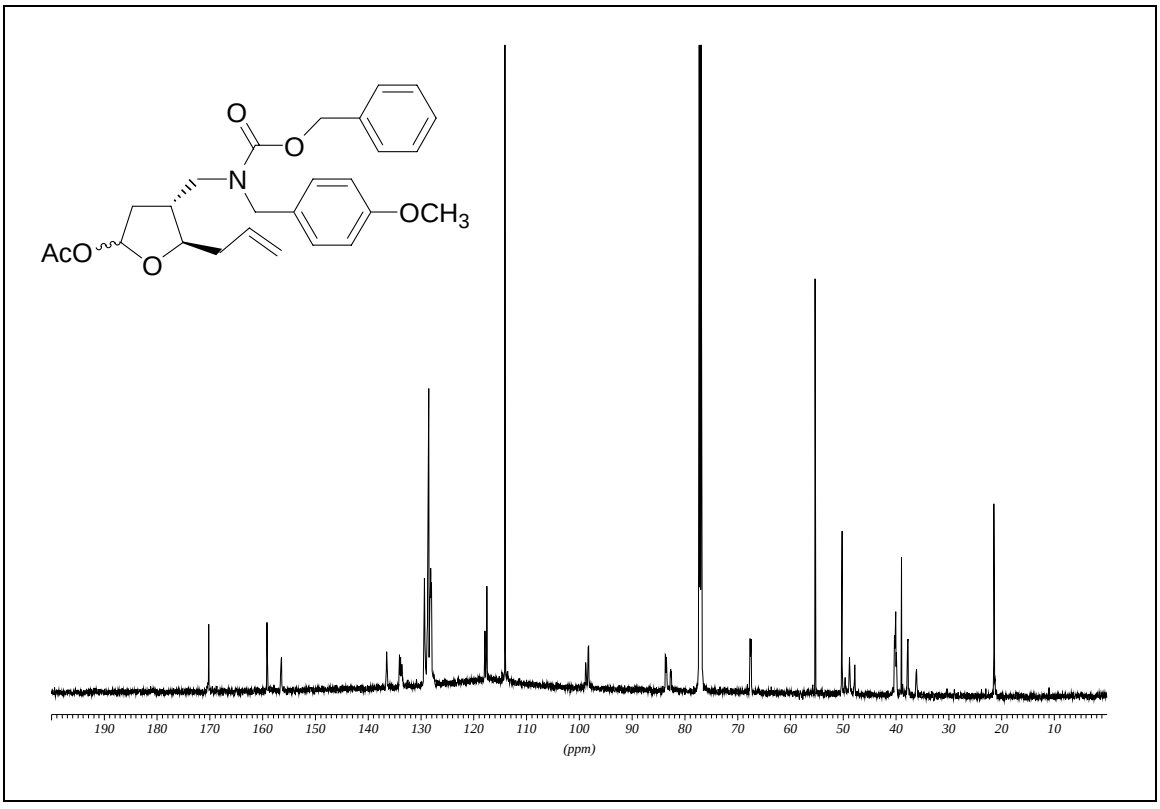
(*2R,3R*)-(2-Allyl-5-hydroxy-tetrahydro-furan-3-ylmethyl)-(4-methoxy-benzyl)-carbamic acid benzyl ester (156, $CDCl_3$):



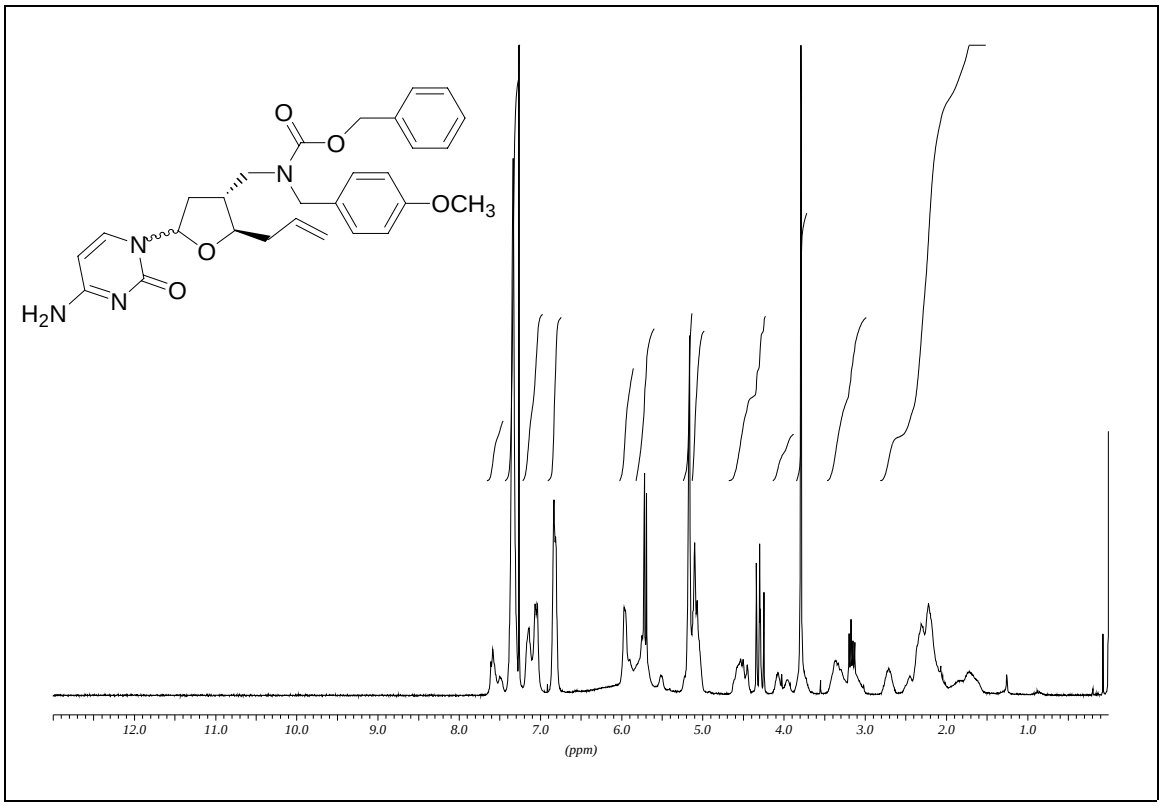


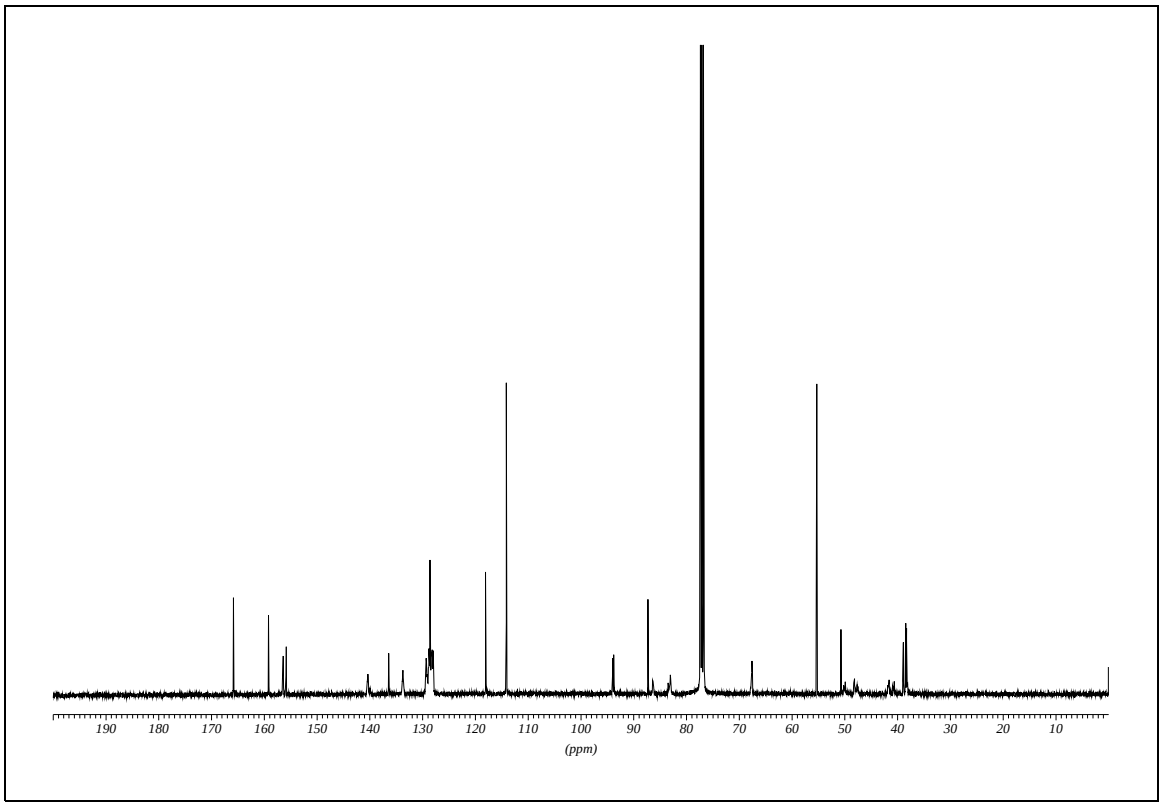
(*4R,5R*)-Acetic acid 5-allyl-4-{[benzyloxycarbonyl-(4-methoxy-benzyl)-amino]-methyl}-tetrahydro-furan-2-yl ester (157, $CDCl_3$):



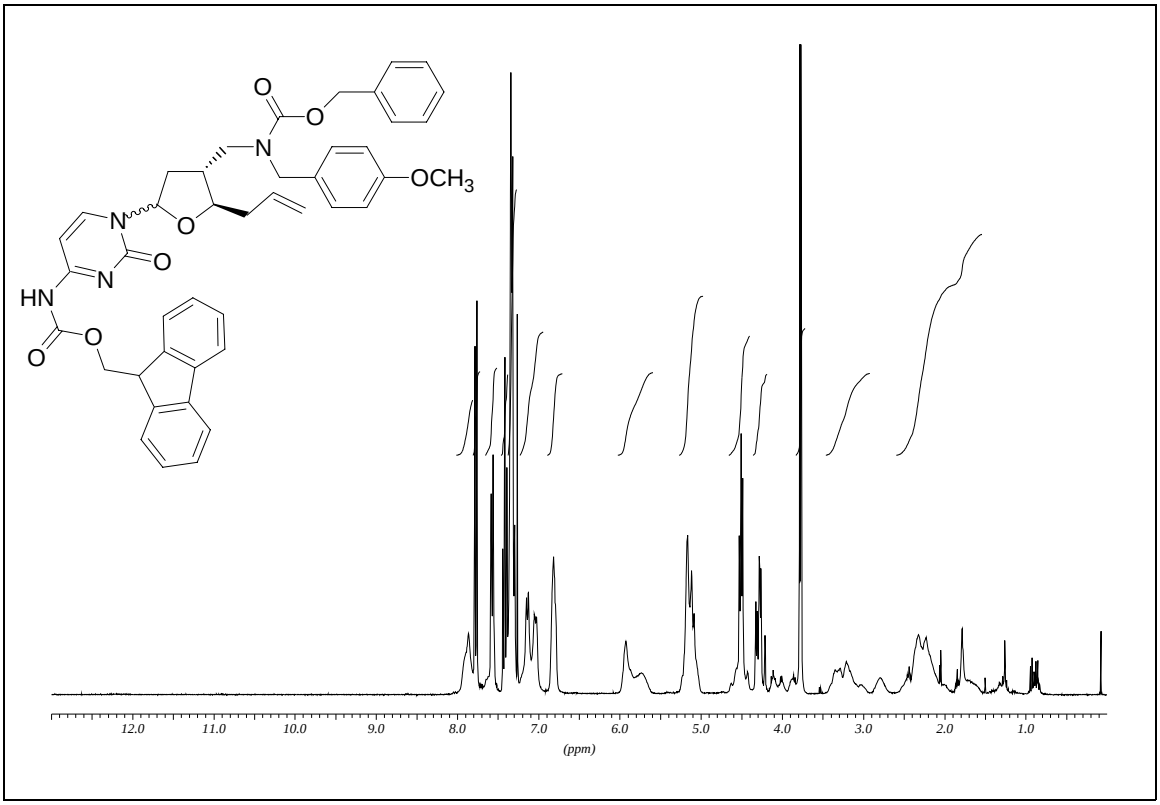


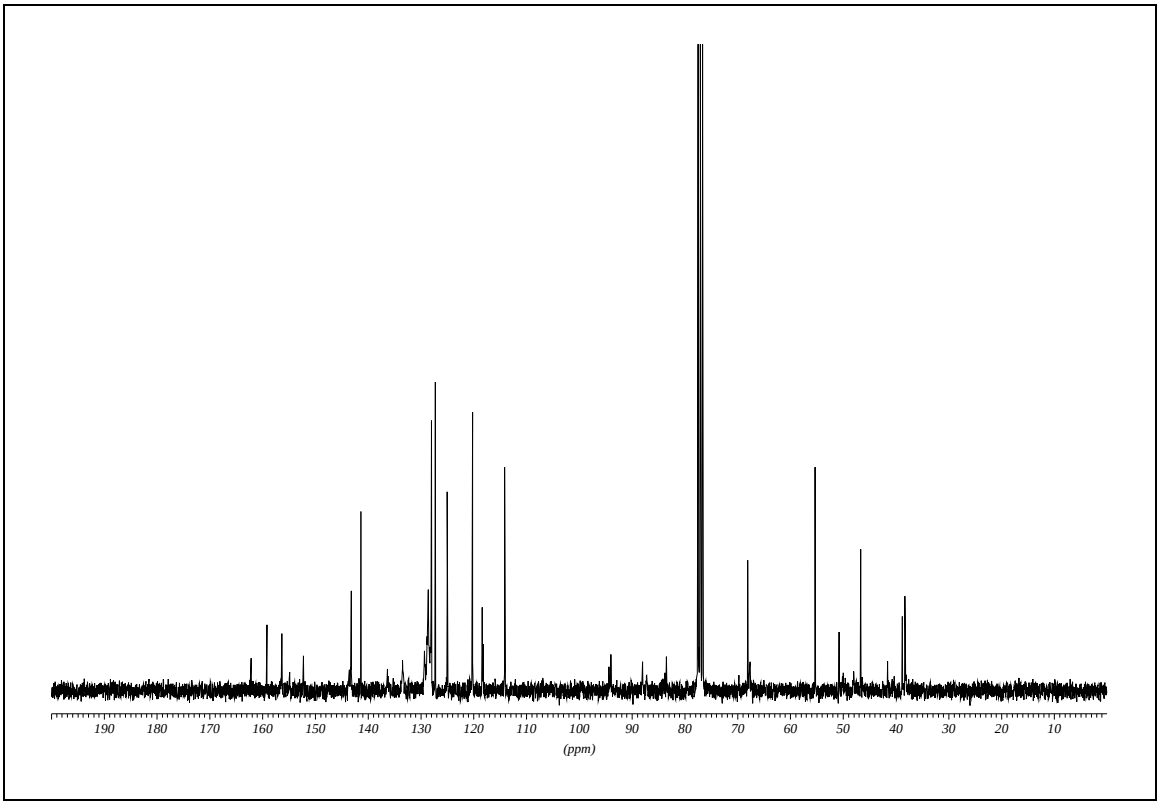
(*2R,3R*)-[2-Allyl-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-tetrahydro-furan-3-ylmethyl]-(4-methoxy-benzyl)- carbamic acid benzyl ester (169, $CDCl_3$):



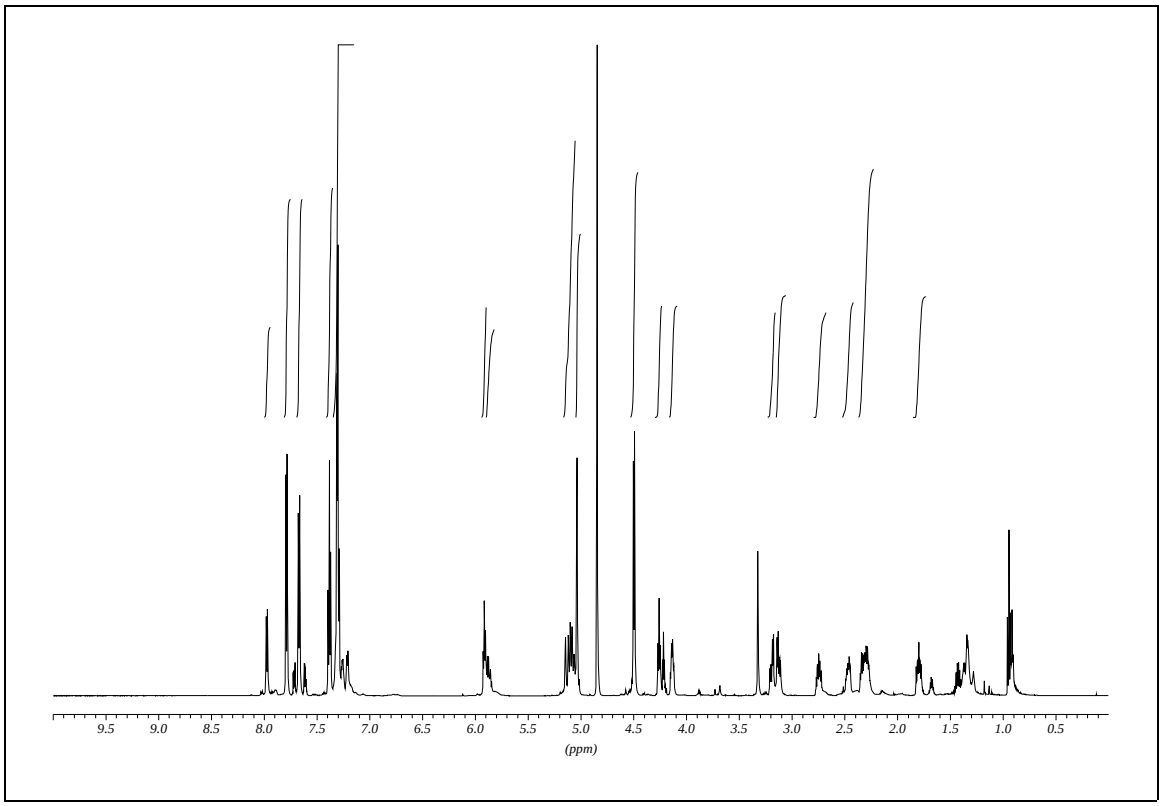


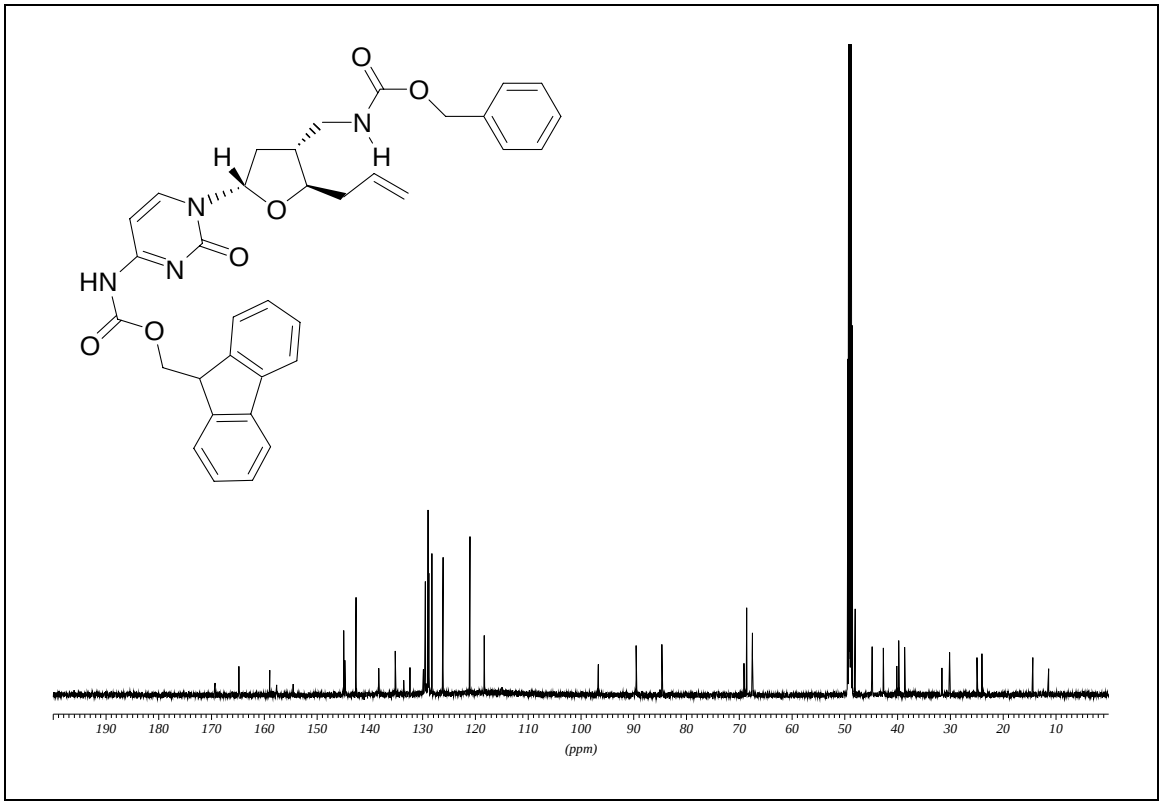
(*4R*,*5R*)-[1-(5-Allyl-4-{[benzyloxycarbonyl-(4-methoxy-benzyl)-amino] methyl}-tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester (170, $CDCl_3$):



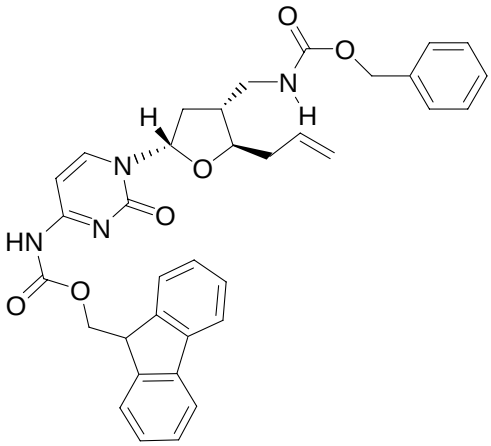


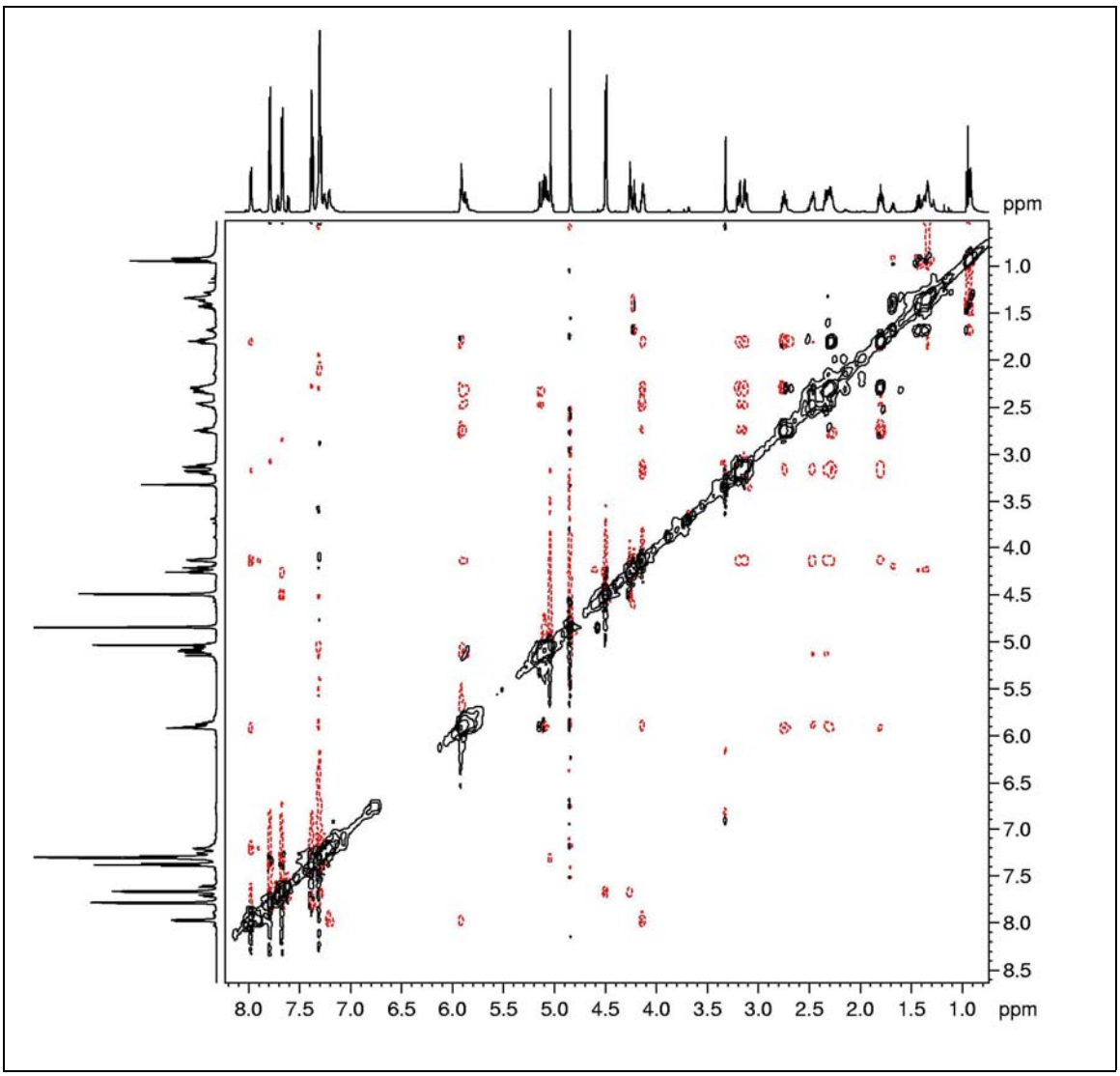
(*2R,4R,5R*)-(–)-{1-[5-Allyl-4-(benzyloxycarbonylamino-methyl)-tetrahydro-furan-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (171, CD_3OD):



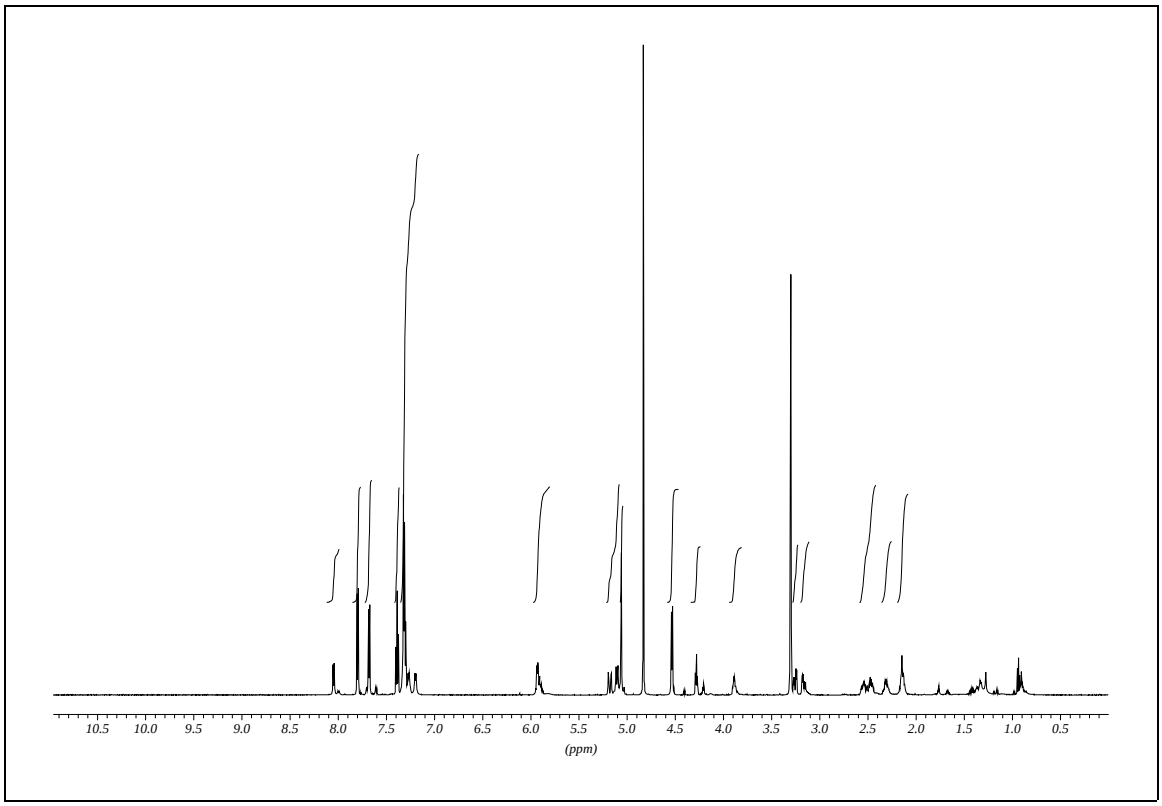


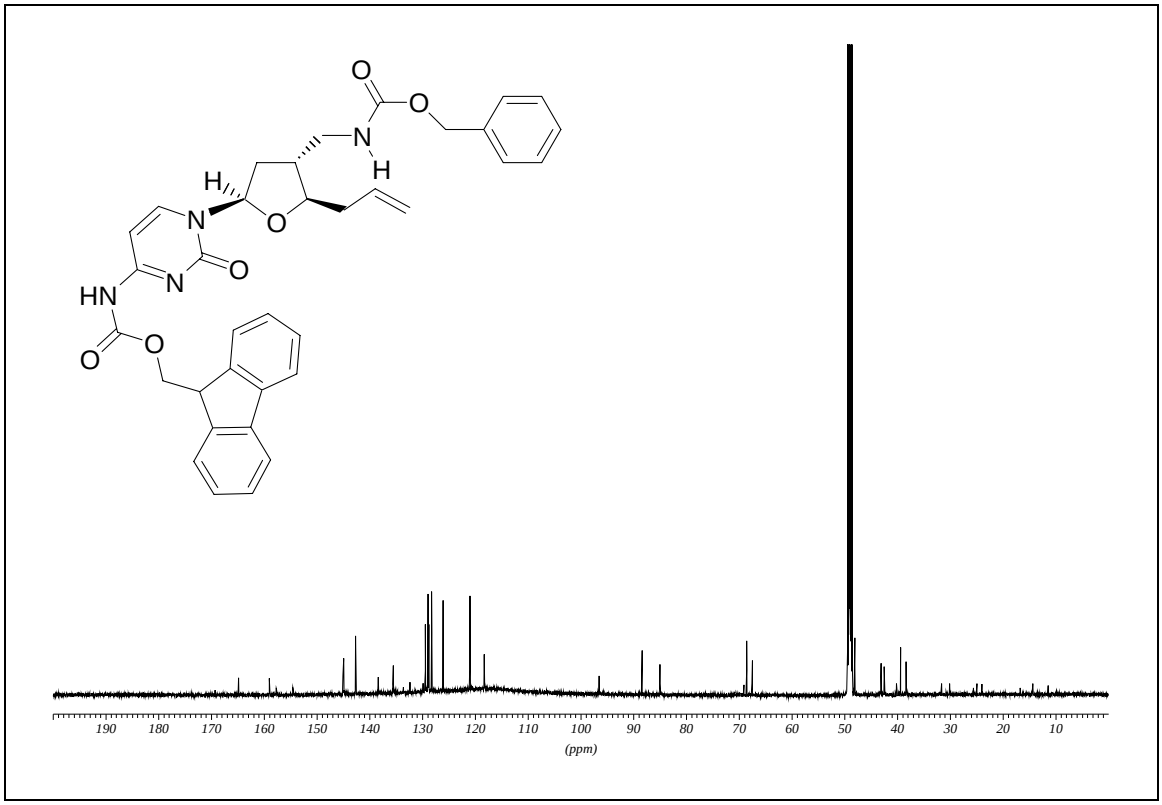
(*2R,4R,5R*)-(–)-{1-[5-Allyl-4-(benzyloxycarbonylamino-methyl)-tetrahydro-furan-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (171, CD_3OD): ROESY



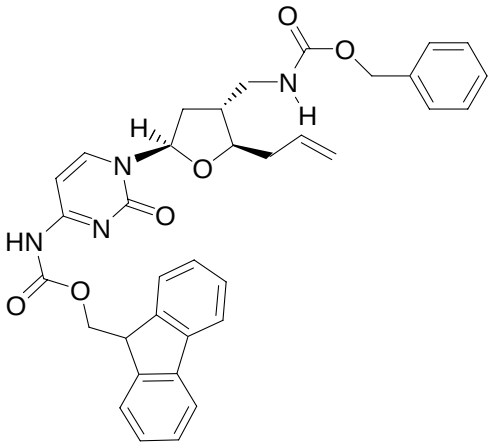


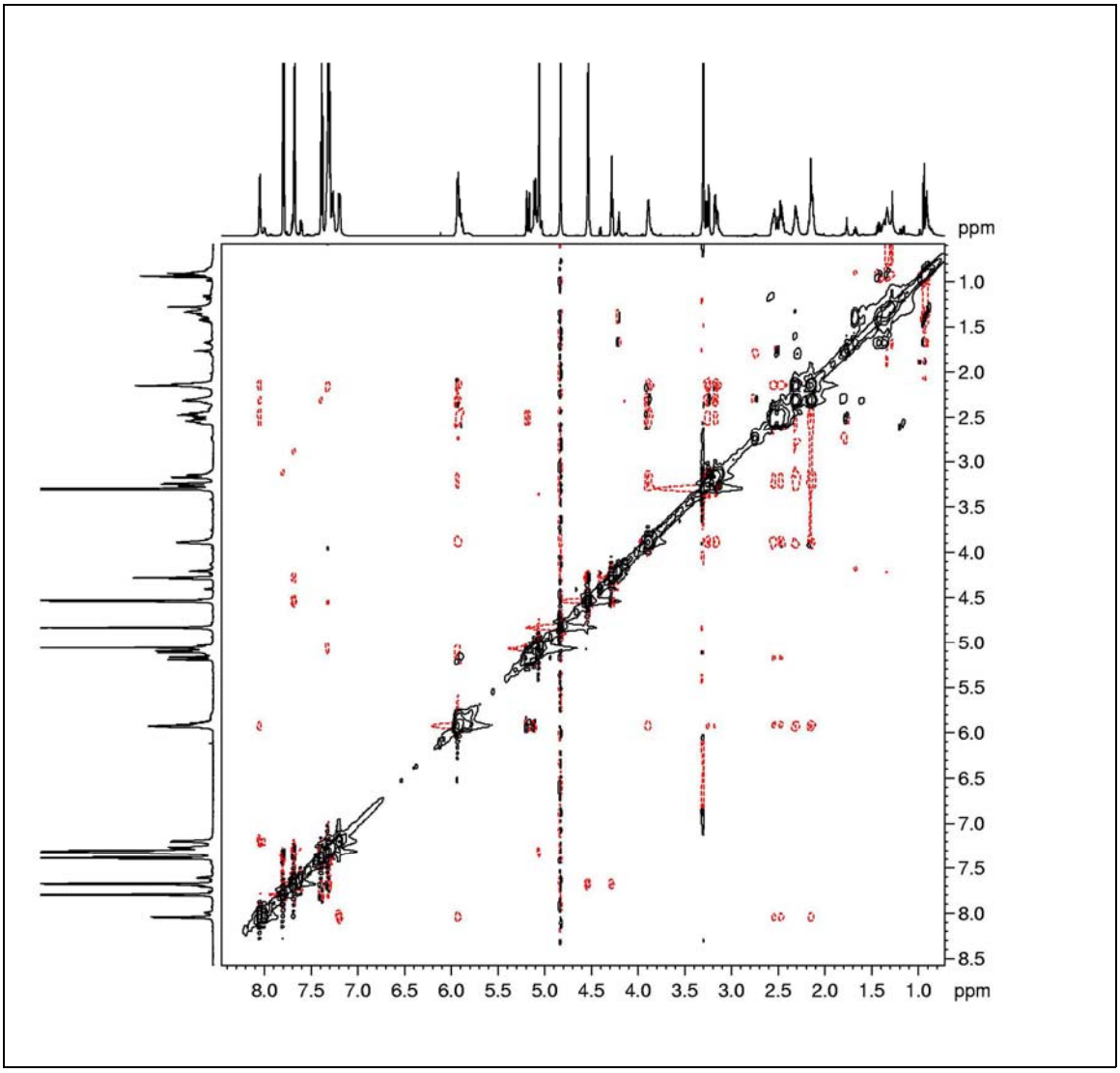
(*2R,4R,5R*)-(+)-{1-[5-Allyl-4-(benzyloxycarbonylamino-methyl)-tetrahydro-furan-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (172, CD_3OD):



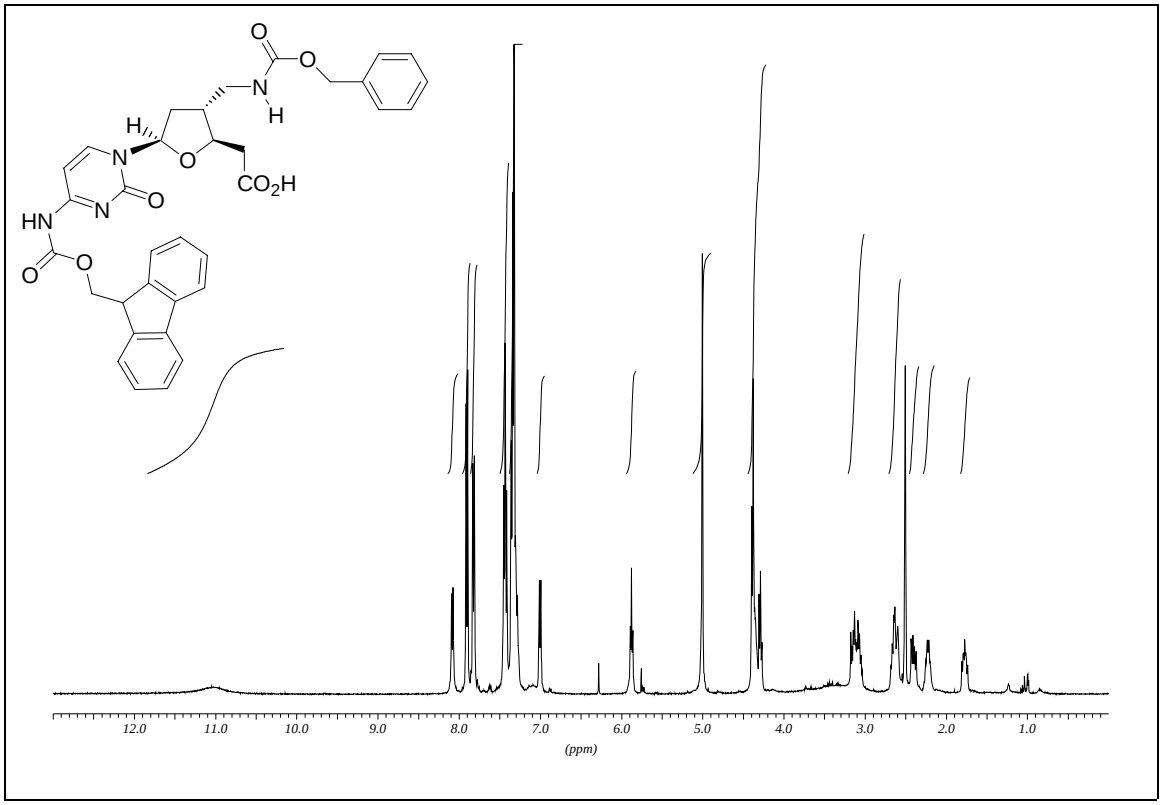


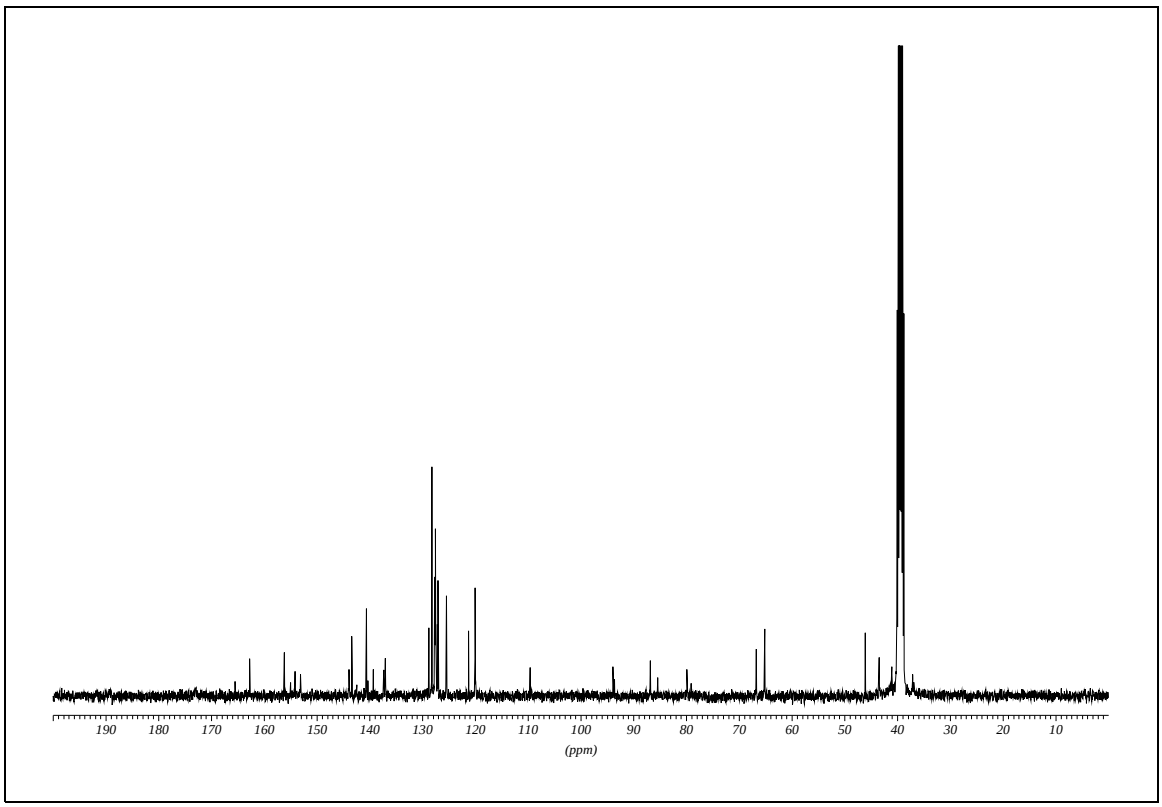
(*2R,4R,5R*)-(+)-{1-[5-Allyl-4-(benzyloxycarbonylamino-methyl)-tetrahydro-furan-2-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (172, CD_3OD): ROESY





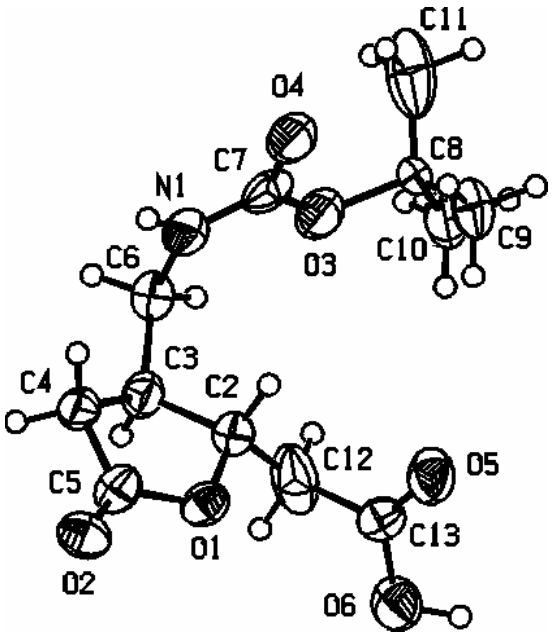
(*2R*,*3R*,*5R*)-(+)-{3-(Benzyloxycarbonylamino-methyl)-5-[4-(9*H*-fluoren-9-yl-methoxy-carbonylamino)-2-oxo-2*H*-pyrimidin-1-yl]-tetrahydro-furan-2-yl}-acetic acid (55, DMSO-d_6):





X-ray data of compound 50

(*2S,3S*)-(–)-[3-(tert-Butoxycarbonylamino-methyl)-5-oxo-tetrahydro-furan-2-yl]-acetic acid (50):



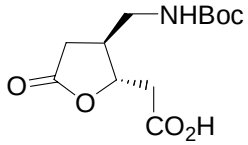


Table-1. Crystal data and structure refinement for **50.**

Identification code	c183f
Empirical formula	C_{12} H_{19} N O_6
Formula weight	273.28
Crystal size	0.08 x 0.08 x 0.04 mm
Crystal description	prism
Crystal colour	colorless
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 10.512(2) Å α = 92.61(2) deg.
	b = 11.903(2) Å β = 110.71(2) deg.
	c = 13.312(2) Å γ = 113.77(2) deg.
Volume	1391.0(6) A^3
Z, Calculated density	4, 1.305 Mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	584

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	Rotation
Temperature	173(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	1.92 to 25.80 deg.
Index ranges	-11<=h<=12, -14<=k<=14, -15<=l<=16
Reflections collected/unique	6314 / 4446 [R(int) = 0.0779]
Reflections greater I>2\\s(I)	1313
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4446 / 0 / 351
Goodness-of-fit on F^2	0.703
Final R indices [I>2sigma(I)]	R1 = 0.0547, wR2 = 0.0816
R indices (all data)	R1 = 0.2020, wR2 = 0.1094
Largest diff. peak and hole	0.246 and -0.144 e. $Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 50. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4509(4)	582(3)	1227(3)	44(1)
O(2)	2519(5)	-723(3)	-291(3)	52(2)
O(3)	6984(5)	5276(4)	2608(3)	56(2)
O(4)	4609(5)	5180(4)	2102(3)	58(2)
O(5)	6327(5)	1839(3)	3951(3)	63(2)
O(6)	7540(5)	765(4)	3678(3)	61(2)
N(1)	5166(5)	4193(4)	946(4)	53(2)
C(2)	5607(6)	1930(5)	1602(4)	45(2)
C(3)	5596(7)	2351(5)	539(4)	45(2)
C(4)	4029(7)	1476(5)	-297(4)	41(2)
C(5)	3556(7)	308(5)	152(4)	49(2)
C(6)	6128(7)	3799(5)	648(4)	41(2)
C(7)	5516(7)	4897(4)	1899(4)	49(3)
C(8)	7564(8)	6046(6)	3731(5)	38(2)
C(9)	6712(8)	5318(5)	4363(5)	59(3)
C(10)	9183(9)	6217(8)	4214(6)	62(3)
C(11)	7474(9)	7265(5)	3641(5)	99(3)
C(12)	7088(7)	2043(5)	2425(4)	84(3)

Table 3. Bond lengths [Å] and angles [deg]

O(1)-C(2)	1.477(7)	C(12)-H(12B)	0.9916
O(1)-C(5)	1.356(6)	C(12)-H(12A)	0.9894
O(2)-C(5)	1.201(7)	C(14)-C(18)	1.517(7)
O(3)-C(7)	1.359(8)	C(14)-C(15)	1.517(9)
O(3)-C(8)	1.492(7)	C(15)-C(20)	1.512(7)
O(4)-C(7)	1.236(9)	C(15)-C(16)	1.533(7)
O(5)-C(13)	1.234(9)	C(16)-C(17)	1.487(9)
O(6)-C(13)	1.303(9)	C(18)-C(19)	1.488(10)
O(6)-H(6O)	1 .04(10)	C(22)-C(25)	1.485(12)
O(7)-C(17)	1.349(7)	C(22)-C(23)	1.498(8)
O(7)-C(14)	1.465(7)	C(22)-C(24)	1.522(9)
O(8)-C(17)	1.209(7)	C(14)-H(14)	1.0006
O(9)-C(19)	1.198(9)	C(15)-H(15)	1.0002
O(10)-C(19)	1.341(6)	C(16)-H(16A)	0.9891
O(11)-C(22)	1.480(8)	C(16)-H(16B)	0.9909
O(11)-C(21)	1.329(6)	C(18)-H(18A)	0.9909
O(12)-C(21)	1.247(7)	C(18)-H(18B)	0.9897
O(10)-H(10O)	1.09(11)	C(20)-H(20A)	0.9900
N(1)-C(7)	1.331(7)	C(20)-H(20B)	0.9900
N(1)-C(6)	1.431(10)	C(23)-H(23A)	0.9805
N(1)-H(1N)	0.8800	C(23)-H(23B)	0.9793
N(2)-C(20)	1.439(8)	C(23)-H(23C)	0.9804
N(2)-C(21)	1.328(8)	C(24)-H(24A)	0.9798
N(2)-H(2N)	0.8805	C(24)-H(24B)	0.9805
C(2)-C(3)	1.520(7)	C(24)-H(24C)	0.9798
C(2)-C(12)	1.501(9)	C(25)-H(25A)	0.9795
C(3)-C(6)	1.564(8)	C(25)-H(25B)	0.9794
C(3)-C(4)	1.500(9)	C(25)-H(25C)	0.9802
C(4)-C(5)	1.505(8)		
C(8)-C(11)	1.499(10)	C(2)-O(1)-C(5)	111.1(4)
C(8)-C(10)	1.512(13)	C(7)-O(3)-C(8)	119.4(6)
C(8)-C(9)	1.495(10)	C(13)-O(6)-H(6O)	102(7)
C(12)-C(13)	1.517(8)	C(14)-O(7)-C(17)	110.3(4)
C(2)-H(2)	1.0008	C(21)-O(11)-C(22)	122.6(4)
C(3)-H(3)	1.0004	C(19)-O(10)-H(10O)	106(4)
C(4)-H(4B)	0.9893	C(6)-N(1)-C(7)	127.4(6)
C(4)-H(4A)	0.9908	C(6)-N(1)-H(1N)	116.27
C(6)-H(6A)	0.9903	C(7)-N(1)-H(1N)	116.38
C(6)-H(6B)	0.9897	C(20)-N(2)-C(21)	126.3(4)
C(9)-H(9C)	0.9798	C(21)-N(2)-H(2N)	116.80
C(9)-H(9B)	0.9800	C(20)-N(2)-H(2N)	116.87
C(9)-H(9A)	0.9796	C(3)-C(2)-C(12)	117.3(6)
C(10)-H(10A)	0.9803	O(1)-C(2)-C(3)	103.7(4)
C(10)-H(10C)	0.9804	O(1)-C(2)-C(12)	108.0(4)
C(10)-H(10B)	0.9805	C(4)-C(3)-C(6)	117.9(5)
C(11)-H(11B)	0.9799	C(2)-C(3)-C(6)	113.2(4)
C(11)-H(11C)	0.9791	C(2)-C(3)-C(4)	103.4(5)
C(11)-H(11A)	0.9801	C(3)-C(4)-C(5)	104.9(5)

O(1)-C(5)-C(4)	108.6(4)	H(12A)-C(12)-H(12B)	107.75
O(2)-C(5)-C(4)	130.0(5)	C(2)-C(12)-H(12A)	109.00
O(1)-C(5)-O(2)	121.4(5)	C(13)-C(12)-H(12A)	109.02
N(1)-C(6)-C(3)	111.9(6)	C(13)-C(12)-H(12B)	109.00
O(4)-C(7)-N(1)	123.5(6)	C(2)-C(12)-H(12B)	108.90
O(3)-C(7)-N(1)	112.0(6)	O(7)-C(14)-C(15)	105.8(4)
O(3)-C(7)-O(4)	124.4(5)	O(7)-C(14)-C(18)	107.7(4)
O(3)-C(8)-C(10)	100.9(6)	C(15)-C(14)-C(18)	115.8(5)
O(3)-C(8)-C(9)	110.4(5)	C(16)-C(15)-C(20)	116.0(4)
C(9)-C(8)-C(11)	112.4(7)	C(14)-C(15)-C(16)	102.7(5)
C(10)-C(8)-C(11)	112.8(7)	C(14)-C(15)-C(20)	114.5(5)
O(3)-C(8)-C(11)	109.7(5)	C(15)-C(16)-C(17)	104.4(5)
C(9)-C(8)-C(10)	110.1(6)	O(7)-C(17)-O(8)	120.7(6)
C(2)-C(12)-C(13)	113.0(6)	O(7)-C(17)-C(16)	110.6(5)
O(6)-C(13)-C(12)	113.5(6)	O(8)-C(17)-C(16)	128.7(6)
O(5)-C(13)-O(6)	123.4(5)	C(14)-C(18)-C(19)	112.2(5)
O(5)-C(13)-C(12)	123.0(6)	O(10)-C(19)-C(18)	112.1(6)
O(1)-C(2)-H(2)	109.19	O(9)-C(19)-C(18)	125.4(5)
C(12)-C(2)-H(2)	109.12	O(9)-C(19)-O(10)	122.4(7)
C(3)-C(2)-H(2)	109.23	N(2)-C(20)-C(15)	115.3(5)
C(6)-C(3)-H(3)	107.27	O(11)-C(21)-O(12)	122.9(6)
C(4)-C(3)-H(3)	107.24	O(11)-C(21)-N(2)	114.3(5)
C(2)-C(3)-H(3)	107.27	O(12)-C(21)-N(2)	122.7(5)
H(4A)-C(4)-H(4B)	108.81	O(11)-C(22)-C(25)	109.4(5)
C(3)-C(4)-H(4A)	110.73	C(23)-C(22)-C(25)	110.7(6)
C(3)-C(4)-H(4B)	110.84	C(24)-C(22)-C(25)	112.9(6)
C(5)-C(4)-H(4B)	110.82	C(23)-C(22)-C(24)	112.3(5)
C(5)-C(4)-H(4A)	110.73	O(11)-C(22)-C(23)	102.7(5)
N(1)-C(6)-H(6A)	109.18	O(11)-C(22)-C(24)	108.3(6)
N(1)-C(6)-H(6B)	109.21	O(7)-C(14)-H(14)	109.05
H(6A)-C(6)-H(6B)	107.91	C(15)-C(14)-H(14)	109.10
C(3)-C(6)-H(6A)	109.24	C(18)-C(14)-H(14)	109.09
C(3)-C(6)-H(6B)	109.28	C(14)-C(15)-H(15)	107.76
C(8)-C(9)-H(9A)	109.50	C(16)-C(15)-H(15)	107.72
H(9A)-C(9)-H(9B)	109.43	C(20)-C(15)-H(15)	107.71
C(8)-C(9)-H(9B)	109.42	C(15)-C(16)-H(16A)	110.91
C(8)-C(9)-H(9C)	109.46	C(15)-C(16)-H(16B)	110.86
H(9B)-C(9)-H(9C)	109.48	C(17)-C(16)-H(16A)	110.93
H(9A)-C(9)-H(9C)	109.53	C(17)-C(16)-H(16B)	110.83
H(10B)-C(10)-H(10C)	109.44	H(16A)-C(16)-H(16B)	108.88
C(8)-C(10)-H(10B)	109.48	C(14)-C(18)-H(18A)	109.19
C(8)-C(10)-H(10A)	109.49	C(14)-C(18)-H(18B)	109.17
H(10A)-C(10)-H(10C)	109.45	C(19)-C(18)-H(18A)	109.17
C(8)-C(10)-H(10C)	109.46	C(19)-C(18)-H(18B)	109.18
H(10A)-C(10)-H(10B)	109.50	H(18A)-C(18)-H(18B)	107.86
H(11A)-C(11)-H(11B)	109.46	N(2)-C(20)-H(20A)	108.44
C(8)-C(11)-H(11A)	109.49	N(2)-C(20)-H(20B)	108.43
C(8)-C(11)-H(11B)	109.44	C(15)-C(20)-H(20A)	108.45
C(8)-C(11)-H(11C)	109.52	C(15)-C(20)-H(20B)	108.45
H(11A)-C(11)-H(11C)	109.47	H(20A)-C(20)-H(20B)	107.51
H(11B)-C(11)-H(11C)	109.45	C(22)-C(23)-H(23A)	109.42

C(22)-C(23)-H(23B)	109.45	H(24A)-C(24)-H(24B)	109.50
C(22)-C(23)-H(23C)	109.47	H(24B)-C(24)-H(24C)	109.41
H(23A)-C(23)-H(23B)	109.49	C(22)-C(25)-H(25A)	109.45
H(23A)-C(23)-H(23C)	109.46	C(22)-C(25)-H(25B)	109.47
H(23B)-C(23)-H(23C)	109.54	C(22)-C(25)-H(25C)	109.43
C(22)-C(24)-H(24A)	109.53	H(25A)-C(25)-H(25B)	109.49
C(22)-C(24)-H(24B)	109.45	H(25A)-C(25)-H(25C)	109.48
C(22)-C(24)-H(24C)	109.46	H(25B)-C(25)-H(25C)	109.51

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3). 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)	43(3)	38(2)	49(2)	17(2)	20(2)	15(2)
O(2)	50(3)	40(2)	62(3)	6(2)	23(2)	16(2)
O(3)	62(3)	66(2)	50(3)	23(2)	23(2)	36(3)
O(4)	65(3)	69(3)	54(3)	25(2)	28(2)	40(3)
O(5)	61(3)	89(3)	45(3)	9(2)	13(2)	47(3)
O(6)	53(3)	72(3)	52(3)	2(2)	8(2)	34(3)
N(1)	55(4)	53(3)	43(3)	10(3)	8(3)	28(3)
C(2)	55(5)	47(3)	38(3)	12(3)	20(3)	27(3)
C(3)	46(4)	53(3)	36(3)	12(3)	13(3)	25(3)
C(4)	46(5)	52(4)	40(3)	15(3)	21(3)	32(4)
C(5)	51(4)	51(3)	47(4)	20(3)	21(3)	22(3)
C(6)	32(4)	47(3)	39(3)	9(3)	14(3)	13(3)
C(7)	61(5)	62(4)	58(4)	40(3)	42(4)	42(4)
C(8)	53(4)	31(3)	26(3)	1(2)	10(3)	20(3)
C(9)	51(5)	71(4)	36(4)	-3(3)	8(3)	20(4)
C(10)	70(6)	72(4)	40(4)	3(3)	19(4)	32(4)
C(11)	49(6)	153(7)	50(4)	-18(5)	0(4)	25(6)
C(12)	102(7)	53(4)	50(4)	-5(3)	30(5)	-6(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3).

	x	y	z	U(eq)
H(1N)	4238	3940	442	63
H(2)	5218	2391	1967	47
H(3)	6332	2152	348	54
H(4A)	4047	1281	-1022	54
H(4B)	3322	1852	-382	54
H(6A)	7184	4259	1214	58
H(6B)	6126	4017	-61	58
H(6O)	7430(120)	600(80)	4410(80)	170(40)
H(9A)	6796	4529	4396	75
H(9B)	5638	5131	3995	75
H(9C)	7142	5817	5111	75
H(10A)	9710	6640	3762	119
H(10B)	9177	5392	4228	119
H(10C)	9712	6730	4966	119
H(11A)	6406	7097	3277	101
H(11B)	8028	7699	3208	101
H(11C)	7929	7796	4378	101
H(12A)	7850	2938	2660	59
H(12B)	7459	1570	2065	59
H(2N)	6345	1282	-4508	49
H(10O)	12990(100)	4630(70)	1190(60)	120(30)
H(14)	9258	2631	-2221	50
H(15)	6973	3132	-1943	48
H(16A)	7243	3408	-3979	55
H(16B)	6663	4133	-3329	55
H(18A)	9220	3703	-261	57
H(18B)	8881	2268	-583	57
H(20A)	6405	1015	-2454	52
H(20B)	5245	1394	-3337	52
H(23A)	7908	-1108	-1281	82
H(23B)	9517	70	-1002	82
H(23C)	9352	-1330	-1169	82
H(24A)	6933	-2133	-4097	87
H(24B)	6400	-2467	-3116	87
H(24C)	7739	-2742	-3187	87
H(25A)	10539	489	-2368	92
H(25B)	9558	-298	-3613	92
H(25C)	10318	-911	-2681	92

Table 6. Torsion angles [deg].

C(5)-O(1)-C(2)-C(3)	-20.2(7)
C(5)-O(1)-C(2)-C(12)	-145.3(5)
C(2)-O(1)-C(5)-O(2)	-175.3(7)
C(2)-O(1)-C(5)-C(4)	3.5(8)
C(8)-O(3)-C(7)-O(4)	2.5(8)
C(8)-O(3)-C(7)-N(1)	-178.3(5)
C(7)-O(3)-C(8)-C(9)	62.5(7)
C(7)-O(3)-C(8)-C(10)	179.0(5)
C(7)-O(3)-C(8)-C(11)	-61.8(8)
C(14)-O(7)-C(17)-C(16)	0.6(7)
C(17)-O(7)-C(14)-C(15)	-16.0(6)
C(14)-O(7)-C(17)-O(8)	177.0(6)
C(17)-O(7)-C(14)-C(18)	-140.5(5)
C(21)-O(11)-C(22)-C(23)	177.8(5)
C(21)-O(11)-C(22)-C(24)	-63.3(7)
C(22)-O(11)-C(21)-O(12)	0.5(9)
C(22)-O(11)-C(21)-N(2)	179.8(5)
C(21)-O(11)-C(22)-C(25)	60.2(6)
C(7)-N(1)-C(6)-C(3)	110.7(6)
C(6)-N(1)-C(7)-O(4)	-178.6(5)
C(6)-N(1)-C(7)-O(3)	2.2(7)
C(20)-N(2)-C(21)-O(12)	173.7(6)
C(21)-N(2)-C(20)-C(15)	107.7(6)
C(20)-N(2)-C(21)-O(11)	-5.6(9)
C(3)-C(2)-C(12)-C(13)	-177.7(5)
O(1)-C(2)-C(3)-C(6)	156.8(6)
O(1)-C(2)-C(3)-C(4)	28.0(7)
O(1)-C(2)-C(12)-C(13)	-61.1(6)
C(12)-C(2)-C(3)-C(4)	146.9(5)
C(12)-C(2)-C(3)-C(6)	-84.3(7)
C(2)-C(3)-C(6)-N(1)	-60.6(7)
C(2)-C(3)-C(4)-C(5)	-26.3(7)
C(6)-C(3)-C(4)-C(5)	-152.0(6)
C(4)-C(3)-C(6)-N(1)	60.2(7)
C(3)-C(4)-C(5)-O(2)	-166.4(8)
C(3)-C(4)-C(5)-O(1)	14.9(8)
C(2)-C(12)-C(13)-O(6)	129.9(6)
C(2)-C(12)-C(13)-O(5)	-48.3(8)
O(7)-C(14)-C(15)-C(20)	150.3(4)
C(18)-C(14)-C(15)-C(16)	143.0(5)
O(7)-C(14)-C(18)-C(19)	-59.6(6)
C(15)-C(14)-C(18)-C(19)	-177.8(5)
C(18)-C(14)-C(15)-C(20)	-90.4(6)
O(7)-C(14)-C(15)-C(16)	23.7(5)
C(16)-C(15)-C(20)-N(2)	54.5(8)
C(14)-C(15)-C(20)-N(2)	-64.9(6)
C(14)-C(15)-C(16)-C(17)	-23.0(6)
C(20)-C(15)-C(16)-C(17)	-148.7(6)
C(15)-C(16)-C(17)-O(7)	14.7(7)

C(15)-C(16)-C(17)-O(8)	-167.9(7)
C(14)-C(18)-C(19)-O(9)	-44.4(8)
C(14)-C(18)-C(19)-O(10)	135.9(5)

Table 7. Hydrogen-bonds [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(9)#1	0.8800	2.1300	2.987(7)	165.00
N(2)-H(2N)...O(5)#2	0.8800	2.1800	3.030(5)	162.00
O(6)-H(6O)...O(12)#3	1.04(10)	1.63(9)	2.605(5)	154(8)
O(10)-H(10O)...O(4)#4	1.09(11)	1.54(9)	2.551(8)	151(8)
C(2)-H(2)...N(1)	1.0000	2.6000	3.028(8)	106.00
C(3)-H(3)...O(2)#5	1.0000	2.4600	3.360(9)	149.00
C(6)-H(6A)...O(3)	0.9900	2.2900	2.712(7)	105.00
C(6)-H(6A)...O(7)#6	0.9900	2.6000	3.520(8)	155.00
C(9)-H(9B)...O(4)	0.9800	2.3800	2.988(8)	120.00
C(11)-H(11A)...O(4)	0.9800	2.3100	2.928(8)	120.00
C(12)-H(12A)...O(8)#6	0.9900	2.4300	3.221(8)	136.00
C(12)-H(12B)...O(2)#5	0.9900	2.5400	3.414(8)	147.00
C(18)-H(18B)...O(2)#5	0.9900	2.4800	3.386(7)	153.00
C(20)-H(20A)...O(11)	0.9900	2.3300	2.732(8)	103.00
C(24)-H(24A)...O(12)	0.9800	2.3500	2.977(7)	121.00
C(25)-H(25B)...O(12)	0.9800	2.3100	2.938(9)	121.00

Publications

1) Bend Nosse, Eva Jezek, Mohammad Mahbubul Haque, Rakeshwar Bandichhor, K. A. woerpal, David A. Evans, Oliver Reiser – *Synthesis of (–)-(S,S)-iso-propyl-bis(oxazoline)*, submitted in Organic Synthesis, **2004**.

2) Bend Nosse, Schall Andreas, Mohammad Mahbubul Haque, Eva Jezek, Rakeshwar Bandichhor, Oliver Reiser – *Synthesis of (1S,2S,3S)-(–)-Oxalic acid 2-ethoxycarbonyl-3-formyl-cyclopropyl ester by asymmetric cyclopropanation of furan-2-carboxylic methyl ester catalyzed by bisoxazoline with $Cu(OTf)_2$ followed by ozonolysis*, submitted in Organic Synthesis, **2004**.

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