SYNTHESIS OF (-)-GEISSMAN WAISS LACTONE, *cis* γ- BUTYROLACTONE DERIVATIVES AND γ-PEPTIDES

Dissertation

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Dedicated to my family

A Introduction

B. Enantioselective synthesis of (-)-Geissman Waiss Lactone as Synton to Retronecine

C. Enantioselective synthesis of functionalized *cis* γ-butyrolactone derivatives.

D. Synthesis of peptides from sugar amino acid

2. X-ray diffraction structure

3. Acknowledgements

Abbreviations

Ac	Acetyl	Fmoc	9-Fluorenlmethoxycarbonyl
Ar	Aryl		
Bn	Benzyl	h	hour(s)
Boc	*tert*-Butoxycarbonyl	HBTU	O-benzotriazole-N,N,N N',N' tetramethyluronium hexafluoro-phosphate
Cbz	Benzyloxycarbonyl		
CD	Circular Dichroism		
COSY	Correlation Spectroscopy	HOBt	Hydroxybenzotriazole
DIPEA	Diisopropylethylamine	IR	Infrared Spectroscopy
DMAP	Dimethylaminopyridine	Me	Methyl
DMF	Dimethylformamide	MeOH	Methanol
DMSO	Dimethylsulfoxide	min	minutes
EDC	Ethyl-N,N-dimethyl-3-aminopropyl Carbodiimide	m.p.	Melting point
		MS	Mass Spectroscopy
		NMR	Nuclear Magnetic Resonance
ee	Enantiomeric excess		
EI	Electron impact	NOE	Nuclear Overhauser Effect
Et	Ethyl	OAc	Acetate
Equiv.	Equivalents	PNA	Peptide Nucleic Acid
		PG	Protecting group

quant.	Quantitative
ROESY	Rotating Frame NOE Spectroscopy
rt.	room temperature
tert	tertiary
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
Ts	*para*-Toluenesulonyl

A Introduction

1. The Importance of Drug Discovery

To meet the growing demands of molecules for the discovery of new drugs, organic chemists have developed novel techniques and explored new reaction mechanisms and strategies to efficiently carry out organic transformations. Based on the vast traditional practice to combat a variety of malignant and infectious diseases, natural products play a pivotal role in the search and development of new drugs entities. From their vast repertoire, organic chemists have been able to invent, design and synthesize unnatural molecules to predict their properties in *vivo* or *vitro*, and subsequently providing modern therapeutic drugs in highly effective ways.

The need to discover drugs and to create *de novo* designer molecules is steadily growing. It is noteworthy to realize that instead of creating new molecules in million by combinatorial chemistry, it is better to design new molecules by emulating the basics of information showed provided by nature.[1] Moreover chemical synthesis will be a key technology of progress in medicine and human health during the 21st century.[2]

Therefore studies in the area of chemical syntheses and drug discovery will make enormous contributions to human health.

1.1 Oxygen Heterocycles with γ-butyrolactone

Heterocyclic compounds are present in a majority of natural products. Most of natural products with heterocyclic ring structures exhibit biological activity. Oxygen heterocyclic compounds bearing a γ-butyrolactone ring system have attracted

considerable attention during the last two decades due to their diverse medicinal properties such as antibiotic,[3] antitumor,[4] antifungal, antibacterial,[5] antileukemia[6] , glaucoma [7] and many more.

γ-butyrolactone are also versatile synthons for synthesizing more complex medicinally important compounds such as bacilosarsin A[8], an antibiotic with potent herbicidal activity, *trans*-burseran[9] for antileukemia treatment and microsclerodermins which display potent antifungal and antiproliferative activities. Some natural products with γ-butyrolactone ring system are depicted in **Figure 1**.

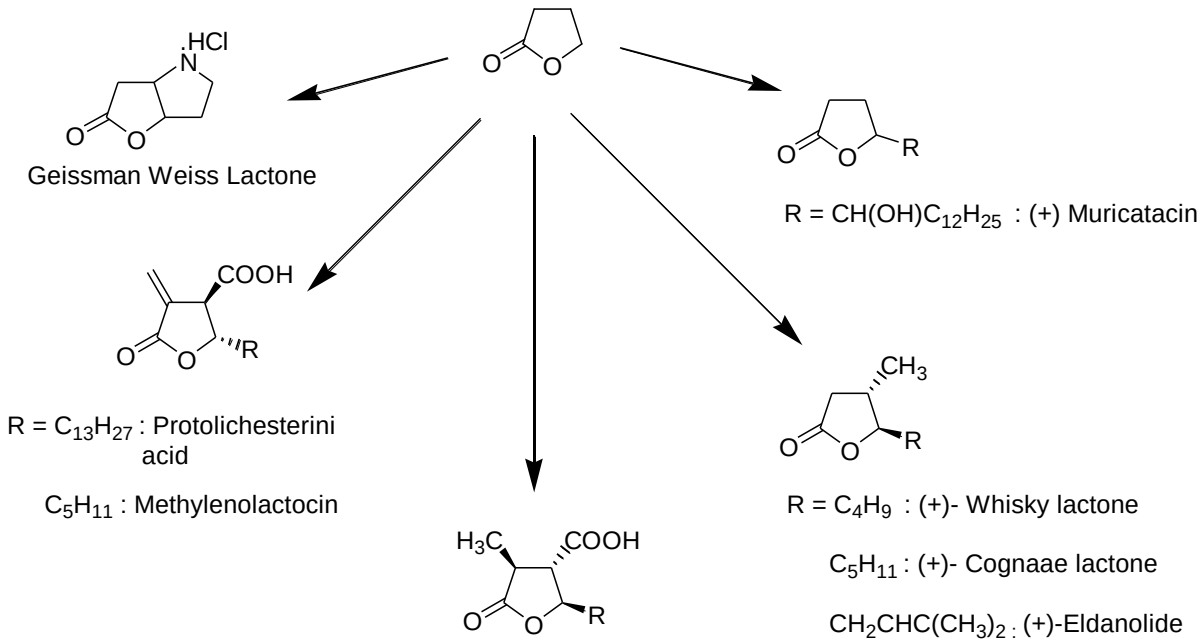
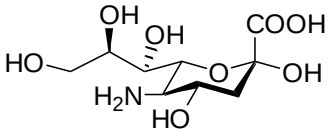


Figure 1: Compounds with γ-butyrolactone ring system

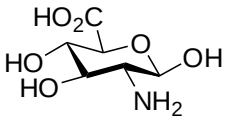
1.2 Sugar Amino Acids

Carbohydrate scaffolds with both a carboxylic acid and an amine functionality, the so-called sugar amino acids (SAAs) have served as building blocks for the synthesis of oligopeptides.[8]

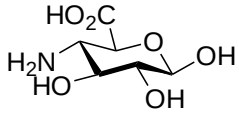
Sugar amino acids are present in nature as construction elements in bacteria. The most abundant naturally occurring SAAs is sialic acid which is often located in the periphery of glycoproteins. These natural SAAs consist of *N*- and *O*-acyl derivatives of neuraminic acid derivatives **1**. Several others example of natural SAAs are glucosaminuronic acid **2**, found in bacterial cell walls,[9] 4-amino-4-deoxy-glucuronic acid **3**, found in antibiotic isolated from *Streptomyces* bacteria[10] and (+)-hydantocidin **4**, which represents a spirohydanthion derivatives[11] and siastatin **5** which was isolated from a *Streptomyces* culture[12], act as inhibitor for both β -glucuronidase and *N*-acetylneuraminidase. Their molecule structures are depicted in **Figure 2**.



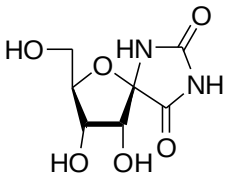
Neuraminic acid **1**



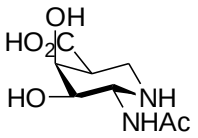
Glucosaminuronic acid **2**



4-Amino-4-deoxy-glucuronic acid **3**



(+)- Hydantocidin **4**



Siastatin B **5**

Figure 2: Natural occurring of sugar amino acids

Fleet and coworkers reported the synthesis of α-SAAs **6, 7, 8, 9**, several azide precursors of β-SAAs **10, 11, 12, 13** and γ-SAAs **15, 16** as depicted in **Figure 3**.

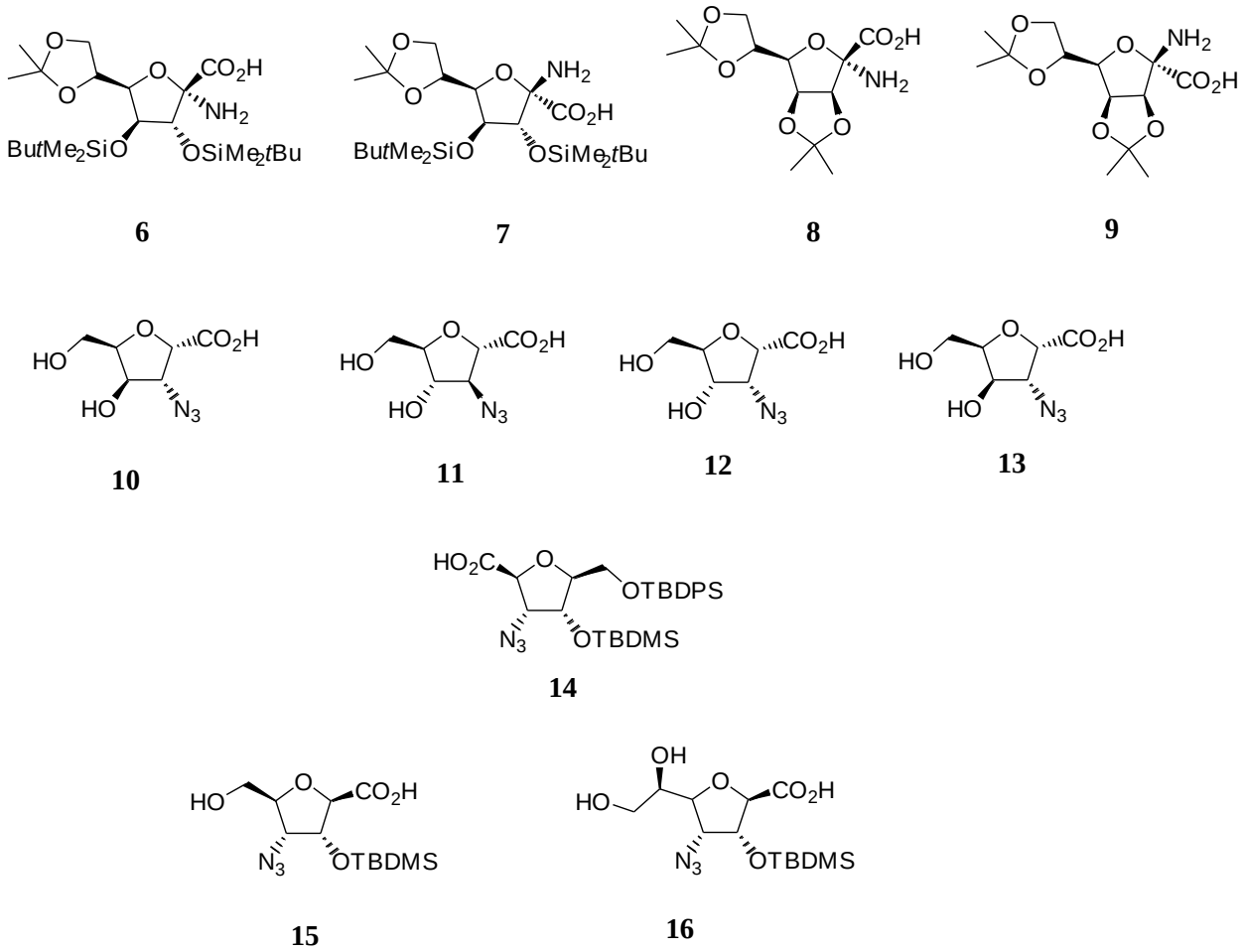
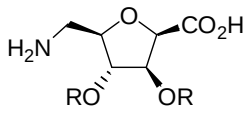


Figure 3: Fleet's large collection of α,β and γ-SAAs

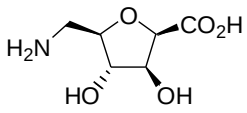
Several research groups have also synthesized furanoid δ- SAAs such as Le Merrer's,[13] Fleet's[14] and Charkraborty's [15] and their molecules structure are depicted in **Figure 4**.



R = H, Bn, Ac

17

Le Merrer
Charkraborty
Fleet



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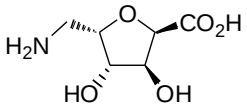
Charkraborty
Fleet



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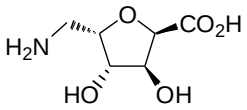
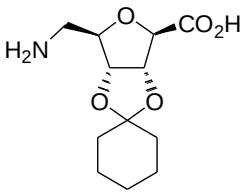
Charkraborty



R = H, Bn

20

Le Marrer



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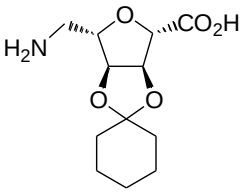
Fleet



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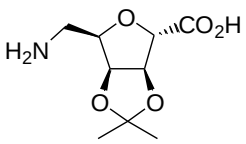

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Fleet

Figure 4: Some of Le Merrer's, Fleet's and Charkraborty's furanoid δ- SAAs

There are several advantages of SAAs as building blocks: Firstly, the rigid conformations of SAAs make them ideal candidates as non-peptide scaffolds in peptidomimetics where they can be incorporated into linear or cyclic oligopeptides by using their carboxyl and amino termini. Secondly, the presence of several chiral centers

in furanoid SAAs, can give rise to a large number of possible isomers that can be used to create combinatorial libraries of SAAs. Finally, the protected or unprotected hydroxyl

groups of SAAs rings can also influence the hydrophobic or hydrophilic nature of the molecules.[16] Incorporation of SAAs in a peptide chain, or for instance as a replacement of a natural peptide segment, may create a more stable unnatural peptide under physiologic conditions since peptidases and proteases do not recognize those.

1.3 Objectives of Research

The aim of this study is to develop a novel *cis*-γ-butyrolactone amino acid and its utilization as a building block in peptides, moreover, the syntheses of chiral intermediates being relevant for natural products synthesis is also intended. Therefore, the objectives of this study are as follows:

(1) To develop new methodology for the synthesis of (-)-Geissman Waiss Lactone (GWL).

(2) To synthesize *cis*-γ-butyrolactone amino esters and their corresponding amino acids.

(3) To synthesize dipeptides and tetrapeptides based on a *cis*-*γ*-butyrolactone scaffold.

(4) To evaluate the antituberculosis ability of some of the synthesized *cis*-γ-butyrolactone amino type compounds.

1.5 References

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B. Enantioselective synthesis of (-)- Geissman Waiss Lactone as Synton to Retronecine

1. Introduction

Retronecine is found widely in numerous alkaloids such as senecionine, seneciphylline and retrorsine. It belongs to the pyrrolizidine type alkaloids, which are also found in many plants. Extracts of plants containing these alkaloids have been used in traditional herbal medicine.[1] Many of these alkaloids show interesting biological activities including hepatotoxic, antitumor, hypotensive, anti-inflammatory and antispasmolytic activities.[2] In addition, a epimer of retronecine found in nature is heliotridine with an invered configuration on C-8 (Figure 5). Other known necine bases of interest are turneforcidine, platynecine and coralbinecine.

Due to the intriguing diverse chemical structures and their characteristic pharmacologic bioactivities, a lot of efforts have been directed towards the synthesis of these alkaloids (Figure 5).

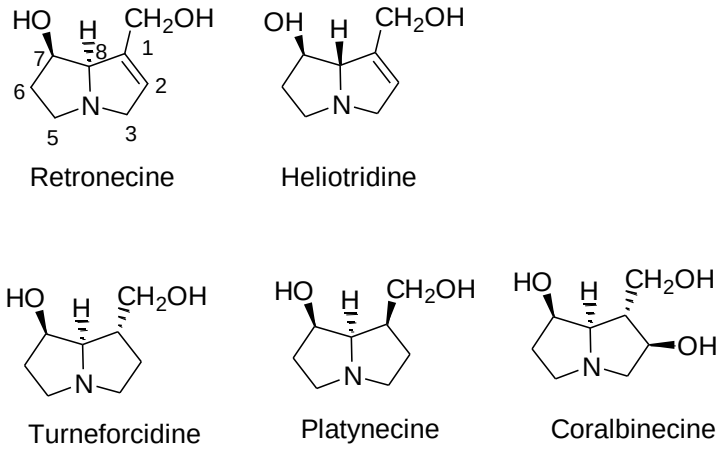
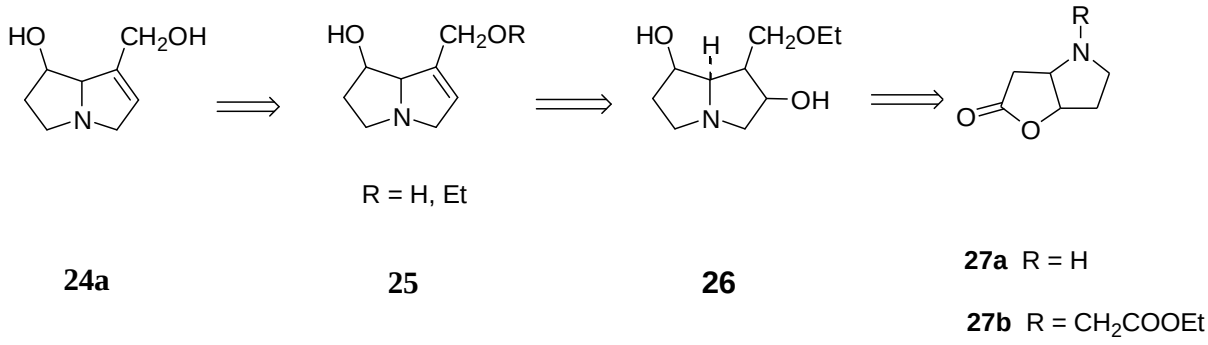


Figure 5: Examples of pyrrolizidine bases with retronecine backbone.

2. Synthesis of Retronecine

Syntheses of retronecine have been reported by different research groups led by Geissman, Naraska and Ruger. In 1962, Geissman reported the synthesis of racemic retronecine ±-**24a** from racemic GWL ±-**27a**.[3] Geissman showed that retronecine ±-**24a** could be derived from 7-hydroxypyrrolizidine-1-carboxylate ±-**25**, which could be in turn be prepared from ethyl-2,7-dihydroxypyrrolizidine-1-carboxylate ±-**26.** N-protected (±)-GWL ±-**27b** could be used to prepare ±-**26** (Scheme 1)**.**



Scheme 1: Retrosynthesis towards retronecine developed by Geissman

Rueger and co-workers reported a new approach towards the syntheses of retronecine **24a**, coralbinecine **24c** and platynecine **24d**. Rueger showed that these necine bases could be derived from the very versatile building block lactone known as (+)-Geissman-Waiss Lactone **27a**.[4]

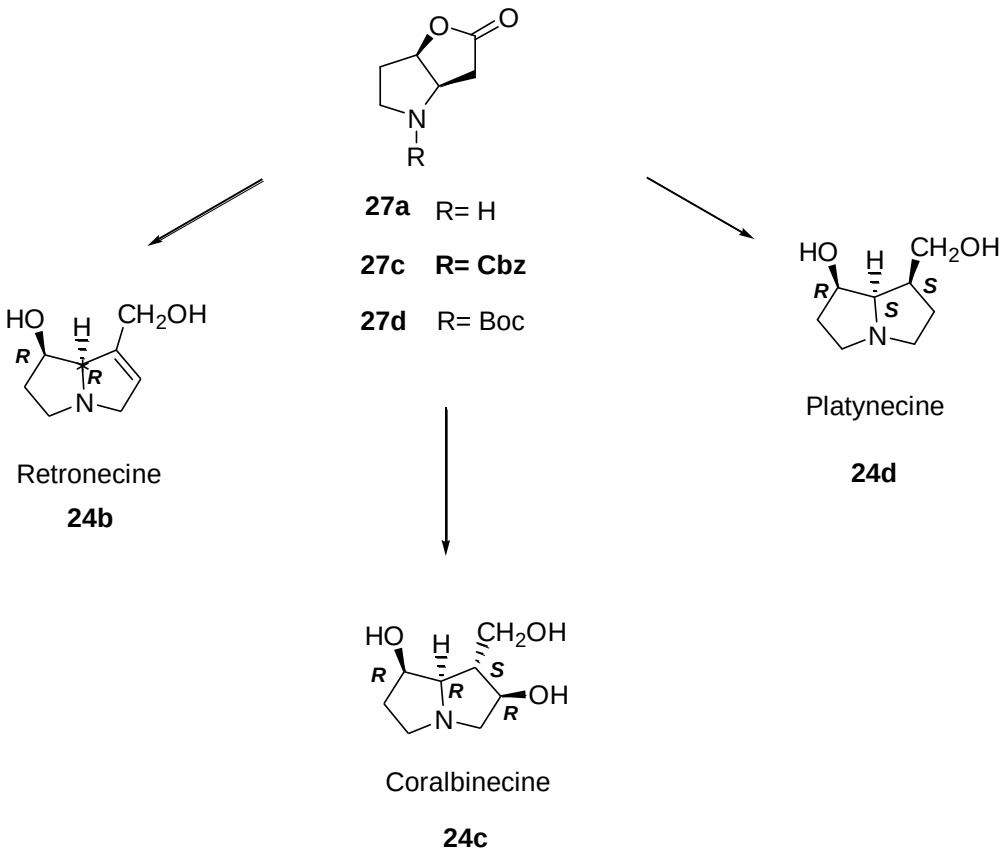
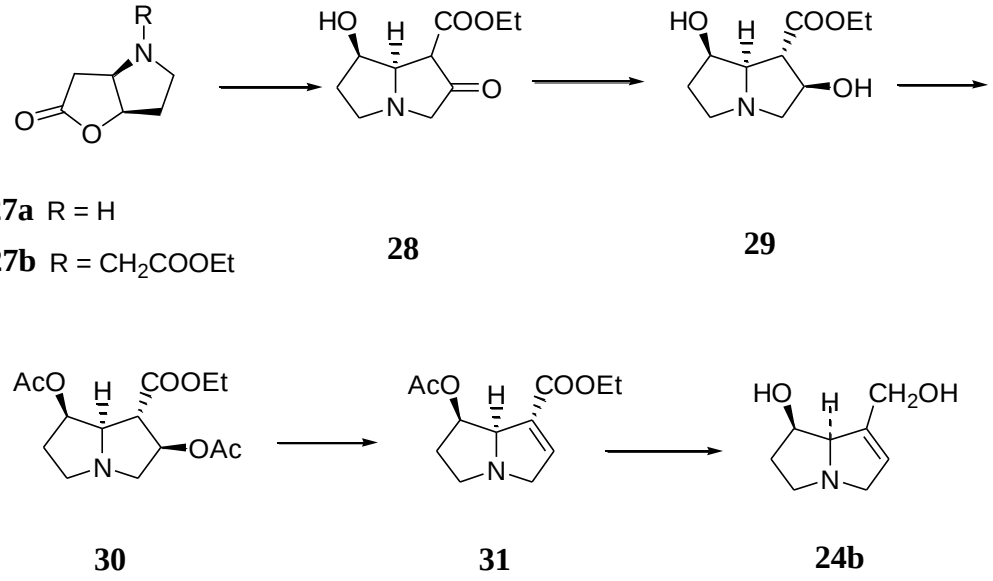


Figure 6: Necine bases synthesized from Geissman-Weiss Lactone developed by Rueger.

In this route, Rueger demonstrated that alkylation of (+)-GWL **27a** gives *N*-alkylated GWL **27b**, which was then subjected to Dieckmann condensation followed by catalytic hydrogenation to afford dihydroxy ester **29**. Treatment of dihydroxy ester **29** with acetic anhydride to protect the hydroxyl groups gave **30**, followed by base induced elimination to **31**. Saponification and reduction finally to give the corresponding retronecine **24b** (Scheme 2).



27a R = H

27b R = CH_2COOEt

28

29

30

31

24b

Scheme 2: Synthesis of retronecine developed by Rueger et. al

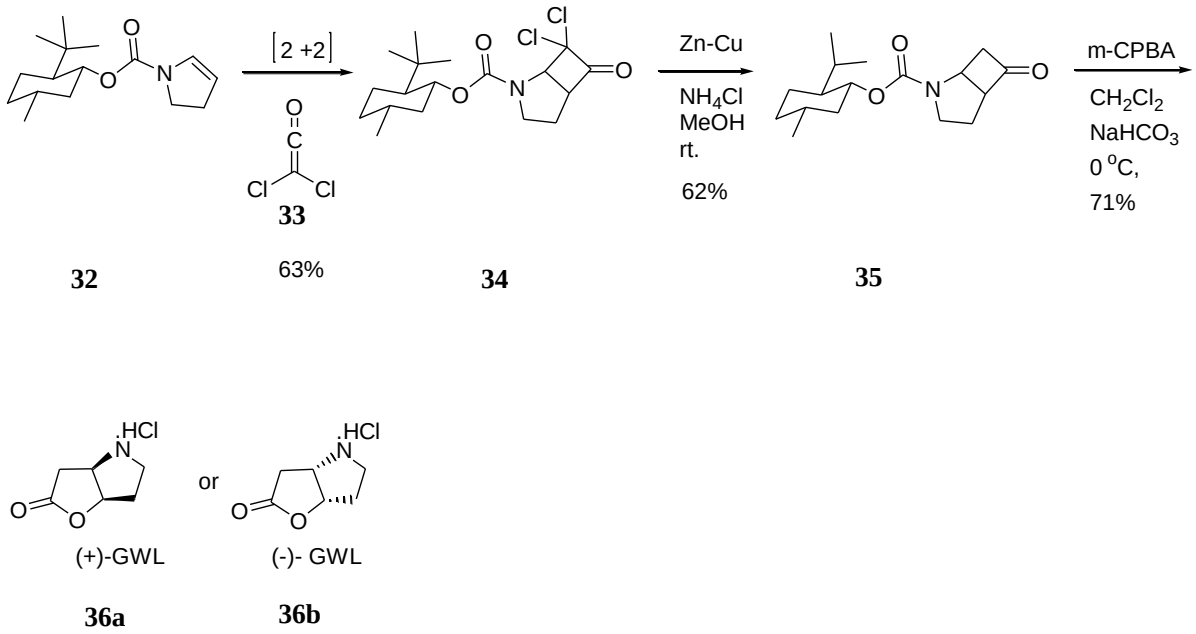
3. Several known synthetic strategy to (-)- Geissman Weiss Lactone

GWL was first synthesized in 1962 by Geissman and Waiss,[3] from α,β-unsaturated ester and amino ester. However they only synthesized racemic GWL and racemic retronecine.

Consequently, the development of new methods for the synthesis of GWL has received considerable attention. In 1999, the syntheses of two diastereoisomers of GWL *ie* (+)-GWL **36a** and (-)-GWL **36b** were achieved *via* Miranda methodology by applying a [2+2] cycloaddition reaction in the presence of chiral auxiliaries on enecarbamate.[5]

Enecarbamate **32** after treatment with dichloroketene **33** via [2+2] cycloaddition reaction in triethylamine was transformed into aza-bicyclic cyclobutanones **34** in 63% yield.

Subsequently dechlorination and ring expansion of **35** through Bayer Villager oxidation to provide the corresponding GWL **36a** or **36b** in 71% as depicted in Scheme 3.

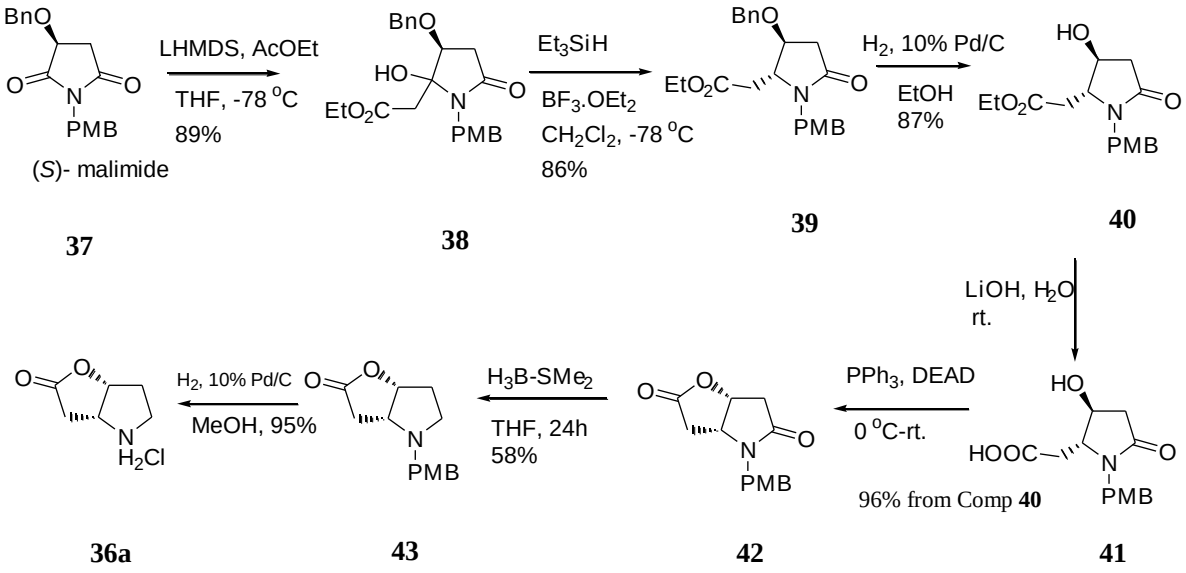


Scheme 3: Syntheses of (+) and (-)-GWL developed by Miranda et al.

Huang et al. developed a methodology to (+)-GWL starting from (*S*)-malimide **37**.[6] Selective reductive alkylation of protected (S)-malimide **37** by organolithium in ethyl acetate, gave **38** in high C-2 regioselectivity. Treatment of *N,O*-acetal **38** with $BF_3.OEt_2$/triethylsilane led to lactam **39**. Subsequent debenzylation of **39** under hydrogenation conditions afforded hydroxyl lactam **40**. Successive saponification of **40**

and intramolecular Mitsunobu reaction (PPh_3, DEAD, CH_2Cl_2) gave lactone **42**. The chemoselective deoxygenation reduction of **42** was achieved by treating with borane

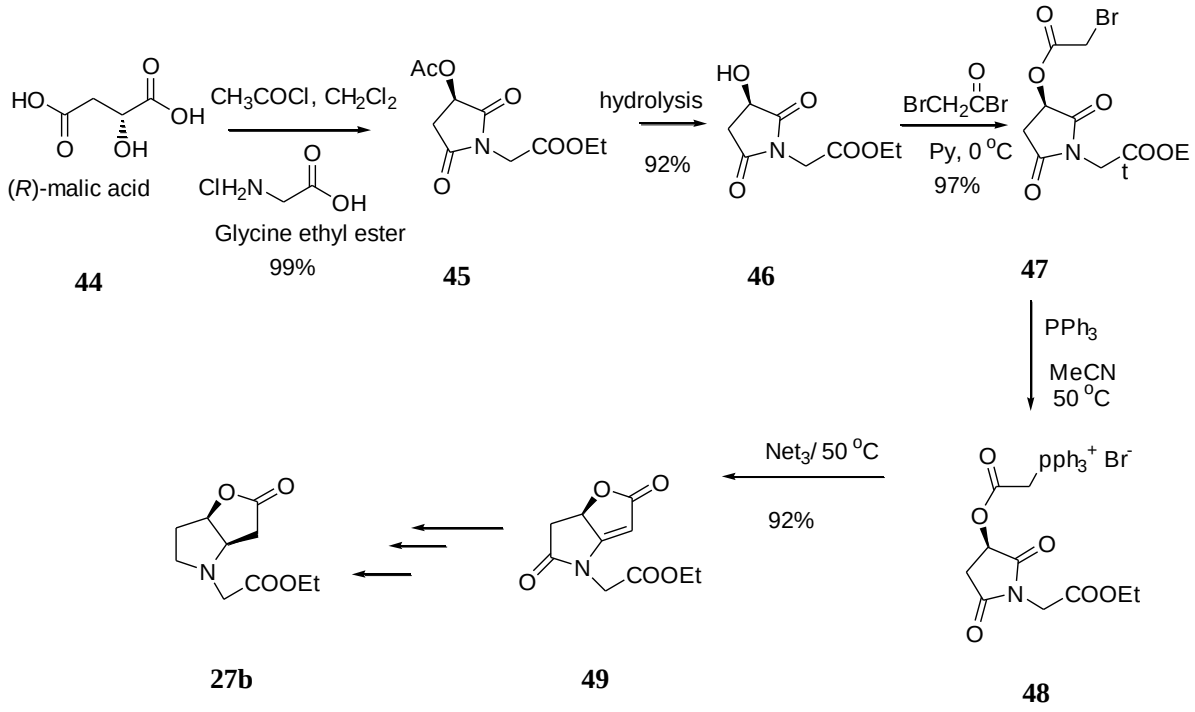
dimethylsulfide in THF yielding *cis*-pyrolidine lactone **43** in 58%. The (+)-GWL **36a** was obtained by deprotection of PMB with Pd/C under hydrogenolytic conditions (Scheme 4).



Scheme 4: Synthesis of (+)-GWL from (S)-malimide

Niwa *et al*. synthesized (-)-*N*-(ethoxycarbonyl) methyl GWL **27b** starting from *R*-(+)-malic acid **44**.[7] Treatment of malic acid **44** with acetyl chloride and glycine ethyl ester afforded imide **45** followed by hydrolysis to give the hydroxyl imide **46**. Bromoacetylation of **46** in ether gave bromoacetoxy imide **47**. Reaction of **47** with triphenylphosphine in acetonitrile furnished phosphonium salt **48**, which was treated with triethylamine to give lactone **49**. Hydrogenation of **49** afforded the lactone lactam, which

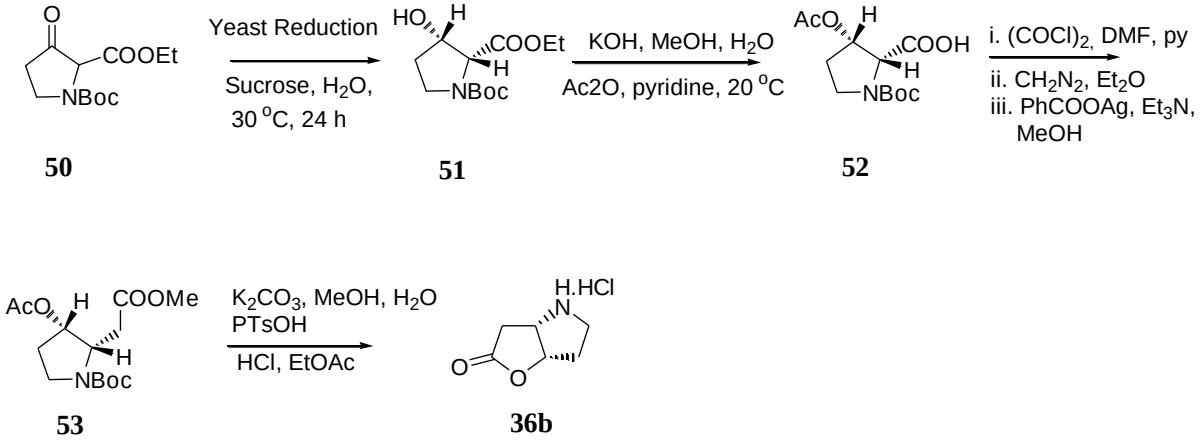
by reduction of the lactam group using Lawesson reagent gave the thiolactam which then undergoes reduction with triethyloxonium tetrafluroborate and sodium cyanoborohydrate to give the product as depicted in Scheme 5.



Scheme 5: Synthesis of (+)-GWL **27b** developed by Niwa and coworkers.

Cooper and co-workers reported that (-)-GWL **36b** could be derived from keto proline **50**. According to their report, yeast reduction (dried Baker yeast, sucrose, water, 30 ^{o}C, 24 h) yielded hydroxy proline **51** in 75% and in single diastereoisomer.[8] Acetylation of **51**, followed by Arndt-Eistert homologation provided the homologous ester **53**, which

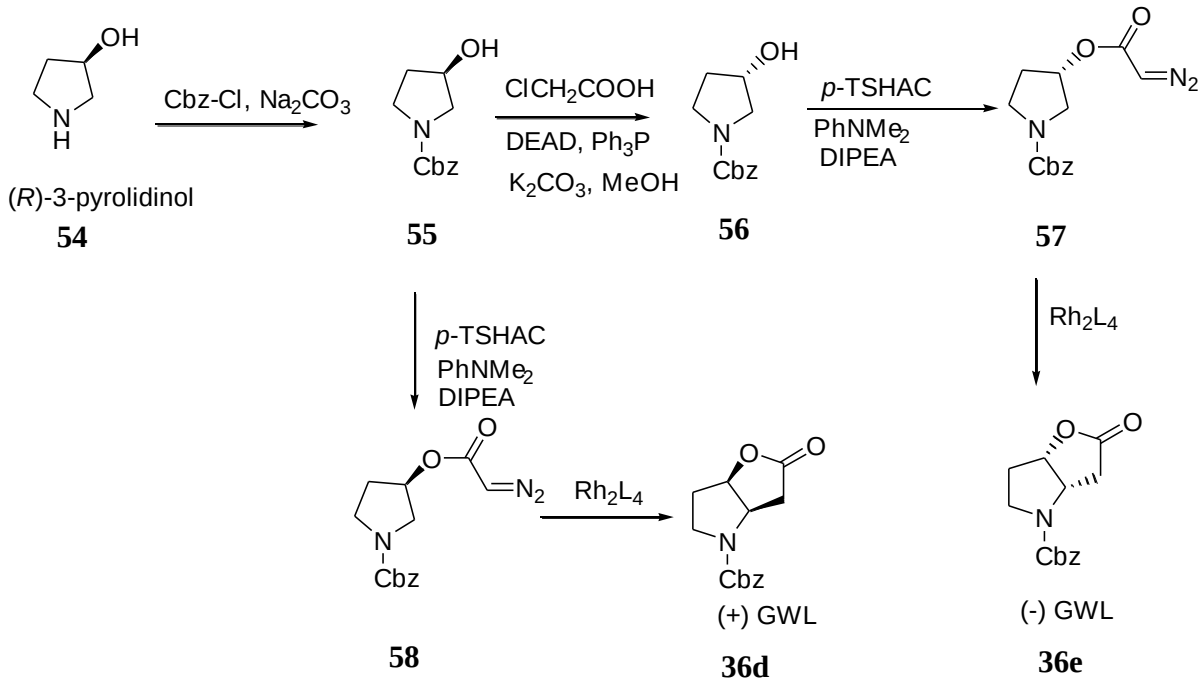
upon base hydrolysis of **53** followed by treatment with the acid furnished (-)-GWL **36b** as depicted in Scheme 6.



Scheme 6: Synthesis of (-) GWL from keto proline developed by Cooper and coworkers.

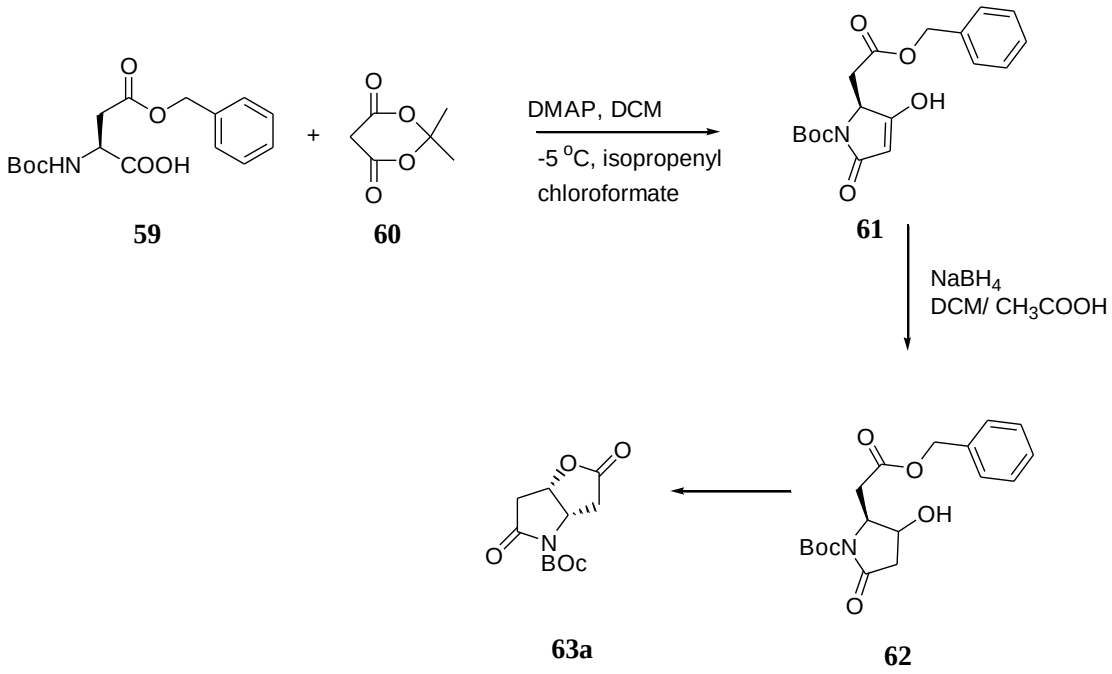
Also in this regard, Wee reported intramolecular C-H insertion reaction of chiral diazoacetates catalyzed by dirohodium-(II) tetrakis[methyl (5R and 5S)-3 phenylpropanoyl-2 imidazolidinone-5-carboxylate][9] for the synthesis of (-) and (+) GWL as depicted in Scheme 7. Wee et al synthesized (-)-GWL starting from (*R*)-3-pyrolidinol **54**. Treatment of (*R*)-3-pyrolidinol **54** with benzyl chloroformate to protect *N* terminal gave *N*-Cbz-3- hydroxy pyrroline **55**. Inversion of hydroxyl group of **55** under Mitsonobu condition afforded **56** and acylation of the latter by Corey-Myers method gave

diazoacetate **57**. By applying Rh(II) catalyzed reaction, **57** could be transformed to (-)-GWL. The (+)-GWL also could be envisioned by this protocol.



Scheme 7: Synthesis of (+) and (-) GWL *via* intramolecular C-H insertion developed by Wee

Lactone lactam is a useful synton for the synthesis of GWL. Jouin *et al* discovered that lactone lactam could be obtained form *N*-protected amino acid .[10] The reaction between *N*-protected amino acid **59** and cyclic diester **60** afforded the tetramic **61**, which was then transformed to cyclic statine **62** by hydrogenation. The latter was transformed spontaneously to *N*-protected lacton lactam **63a** as depicted in Scheme 8.

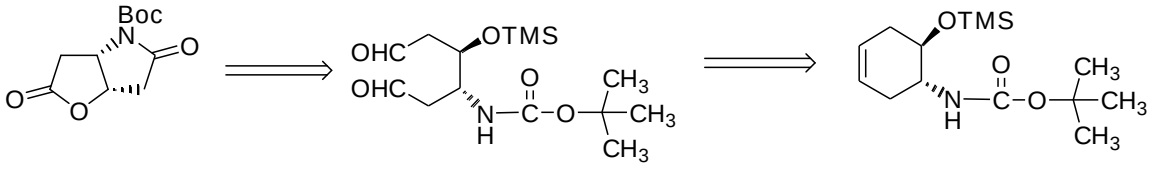


Scheme 8: Synthesis of lactone lactam from *N*-protected amino acid

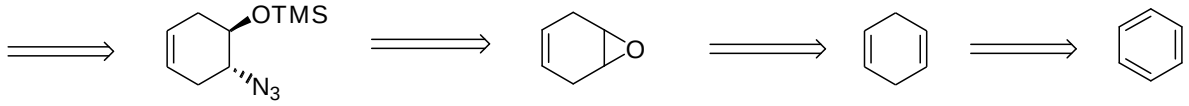
4. Retrosynthesis analysis of (-)- lacton lactam 63a

The (-)-lactone lactam **63a,** can in principle be derived from benzene **69.** Benzene was envisioned to be transformed to 1,4–cyclohexadiene **68**, then epoxidation of - 1,4-cyclohexadiene **68**, followed by enantioselective asymmetric ring opening of the epoxide **67,** reduction amination sequence and Boc protection of **66.** Ozonolysis of *N*-Boc protected amine **65** should give dialdehyde **64 w**hich is then easily converted into the desired (-)- lactone lactam **63a** by Jones oxidation (Scheme 9).

First strategy



63a **64** **65**



66 **67** **68** **69**

Scheme 9. Retrosynthetic analysis of (-)- lacton lactam

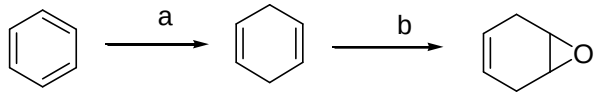
Second strategy towards (-)-lactone lactam can also be synthesized from *N*-Boc protected amine **65.** Oxidative cleavage of **65** by ruthenium tetraoxide in the presence of sodium periodate should give spontaneously (-)-lactone lactam **63a**.

5. Synthesis outline towards (-)-lactone lactam 63a

5.1 Birch reduction and epoxidation

Benzene **69** was reduced into 1,4–cyclohexadiene **68** *via* Birch reduction with liquid NH_3 and sodium metal. Epoxidation of 1,4–cyclohexadiene **68** with m-CPBA (1 equiv.) in the

presence of K_2HPO_4 yielded 1,4-cyclohexadiene monoxide **67** as the major product (89%), while the corresponding diepoxide[11] was found in minor amounts (8%) as depicted in Scheme 10. Epoxides are valuble intermediates for the stereocontrolled synthesis of complexs natural products compounds. Havingsuccessfully prepared epoxide **67**, our next attempt was to open the epoxide ring enantioselectively to obtain the requisite olefinic product **66**.



69 **68** **67**

Reagent and condition : (a) Na, Liq. NH_3, EtOH, -78 ^oC to r.t, 40.1% (b) mCPBA (1 equiv), K_2HPO_4 (1 equiv.), CH_2Cl_2, 0 ^oC, 20 h, 88.9%

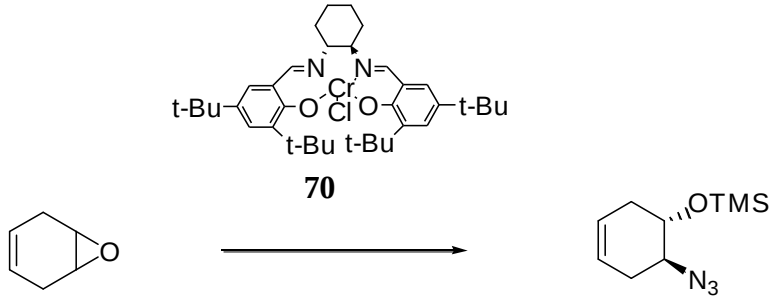
Scheme 10: Synthesis o 1,4-cyclohexadiene and 1,4-cyclohexadiene monoxide

5.2 Enantioselective epoxide ring opening

Organic azides are an important class of compounds, particulary for producing primary amines. Moreover, they are involved in many synthetic reactions such as "*clicked*" reactions[12a], intramolecular cycloadditions of nitrenes[12b], *Staudinger* reductions[12c], *Curtius rearrangement*[12d] and many more. Jacobsen et al. reported in 1995, the asymmetric ring-opening (ARO) of epoxide **67** catalyzed by (salen)Cr(III) complex **70** giving the corresponding azido silyl ether **66** in 72% and 81% ee.[13]

Following this protocol, the enantioselective asymmetric ring opening of the epoxide **67** using Salen catalyst complex **70** with trimethylsilylazide furnished the azido

trimethylsiloxy cyclohexene in 68% and 86% ee as depicted in Scheme 11. Jacobsen rationalized this transformation by the formation of a chromium-azide coordinated species as the active catalyst[13a,b] which could be driving the enantioselection of this process, affording the preferred *trans*- azido silyl ether **66** (Scheme 12). The corresponding racemic azido silyl ether was also synthesized.

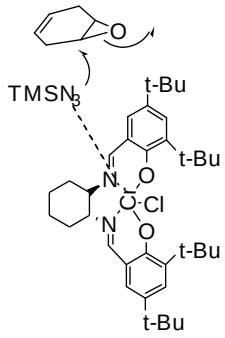


70

67 **66**

Reagent and conditions: (a) Salen complex (2 mol%), $TMSN_3$ (1.05 equiv.), Et_2O, rt, 46 h, 68%, 86% ee

Scheme 11: Epoxide ring opening by salen complex

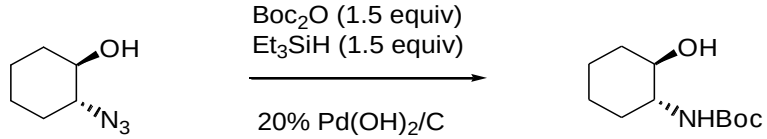
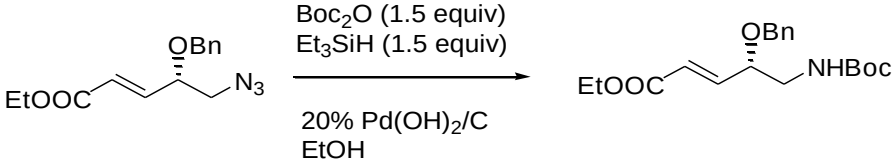


Scheme 12: Epoxide activation by (salen)Cr(III) complex

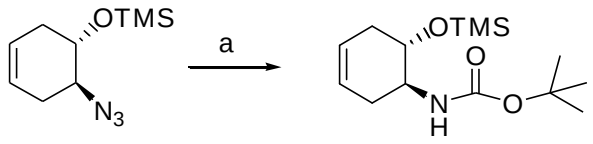
5.3 Reductive amination and Boc protection of 66

In principle, the *tert*-butoxy carbonyl protecting group can be easily and quantitatively introduced under mild conditions. Facile cleavage of this protecting group by TFA in DCM or concentrated HCl in ethyl acetate is a useful criteria for application in peptide synthesis. The combination of azide reduction and *N*-Boc protection in a one-pot reaction, offers an efficient approach for the synthesis of suitably protected amino acid. In 1997, Katsuki *et al*. developed a facile method for the chemoselective reductive transformation of several azides **71** and **73** to *N*-(*tert*-butoxycarbonyl) amines **72** and **74**.[14a,b] Some examples of this transformation are tabulated in Table 1.

Table 1: Some examples of reductive amination

Entry	Reaction
1.	 **71** 76% **72**
2.	 **73** 84% **74**

By applying the same procedure, azide reduction and *in situ* amine protection of azido trimethylsiloxy cyclohexene **66** with $Pd(OH)_2/C$ and di-*tert*-butyl dicarbonate (Boc anhydride) as trapping agent in ethanol and followed by addition of with triethylsilane as proton donors gave **65** in 88% yield as depicted in Scheme 13.



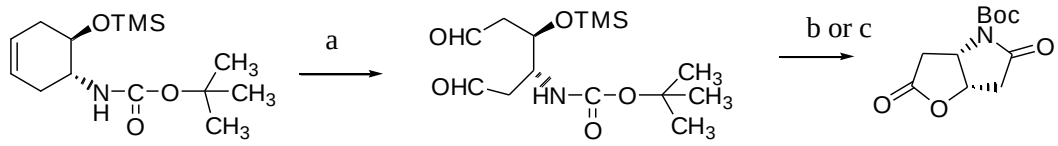
66 **65**

Reagent and condition: Boc_2O (1.5 equiv), $Pd(OH)_2/C$, Et_3SiH (1.5 equiv.), EtOH, r.t, 20 hrs, 88%

Scheme 13: Reduction amination and Boc protection

5.4 Oxidation of double bond by ozonolysis and lactonisation

The protected amine **65** was subjected to ozonolysis at –78 °C followed by reductive workup with DMS at room temperature for 20 h to give dialdehyde **64** in 62% yield. The dialdehyde **64** was then transformed to the corresponding carboxylic acid using Jones' reagent in which dicarboxylic acid spontaneously undergoes lactonization to give the (-)-**63a** lactone lactam in 59% yield. When dialdehyde **64** was oxidized with sodium chlorite in the presence of hydrogen peroxide and potassium dihydrogen phosphate in acetonitrile, the (-) lacton lactam **63a** was only obtained in 23% yield (Scheme 14).



65 **64** **63a**

Reagent and condition : (a) O_3, DMS, CH_2Cl_2, -78 ^oC to rt, 20 h, 62% (b) Jones reagent, AcOH, 10 ^oC, 15 min, 59% (c) i. $NaClO_2$ (0.6 equiv), KH_2PO_4 (0.6 equiv), 30% H_2O_2 (1.6 equiv), CH_3CN, 3 h, 0 ^oC, ii. Na_2SO_3, 2 h, 0 ^oC. iii. $KHSO_4$, pH2, 23%

Scheme 14: Synthesis of (-) lactone lactam

5.5 Ruthenium catalyzed oxidative cleavage of double bond in 65

Ruthenium tetraoxide (RuO_4) has been used mainly as a strong oxidizing agent for alcohol[15], aldehydes[15a], alkenes[16] and alkynes[17]. Being less toxic and less volatile than OsO_4, RuO_4 has been used also as catalyst for selective dihydroxylation of olefins[18] and for cleavage reactions[19]. RuO_4 can be generated from $RuCl_3$ or RuO_2 in the presence of an appropriate oxidant, such $NaIO_4$, NaOCl, $NaBrO_3$, Oxone, O_3, $Ce(SO_4)_2$ and $K_2S_2O_8$ [20].

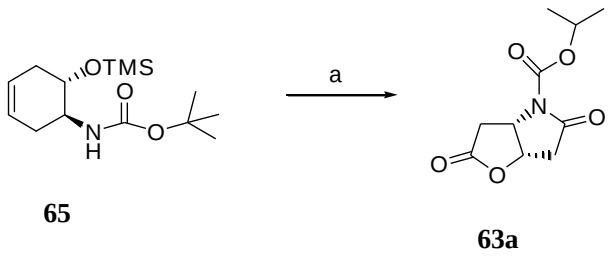
Applying RuO_4 it was envisioned to cleave the double bond in **65** directly to give rise to the dicarboxylic acid **63b** and to obtain the requisite lactone lactam **63a** *via* lactonization. Lactonization is an intramolecular cyclization to form five membered ring units. The double bond cleavage is accompanied by the deprotection of trimethylsilyl (TMS) group

since ruthenium tetraoxide can behave as a weak acid as suggested by Martin in 1954 as show in equation below:[21]

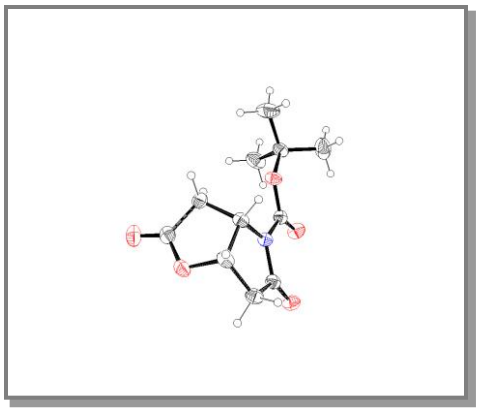
$$[RuO_4] + H_2O \rightleftharpoons [H_2RuO_5]$$

$$[H_2RuO_5] + H_2O \rightleftharpoons H_3O^+ + [HRuO_5]$$

Treatment of **65** with ruthenium tetraoxide and sodium periodate gave spontaneously rise to **63a**. We postulate that once the lactone is formed, ring closure is facilitated by the formation of hydrogen bonding from migrating hydrogen atom to the hydroxyl functionality. Nucleophilic attack of the nitrogen lone pair onto the carbonyl group afforded lactone **63a**. The structure was confirmed by X-ray crystallographic analysis.

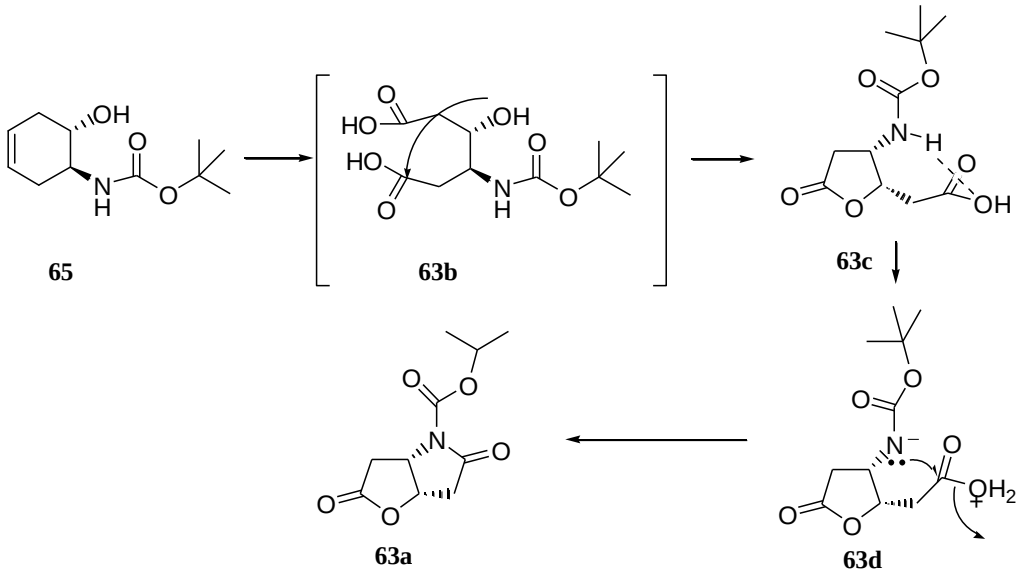


65 **63a**



Reagent and condition: $RuCl_3.3H_2O$ (8.3 %mol), $NaIO_4$ (4.1equiv.), CCl_4:CH_3CN, H_2O (1:1:2), 0 ^oC, 62%

Scheme 15: Synthesis of (-)-lactone lactam **63a** by ruthenium catalyzed oxidative cleavage

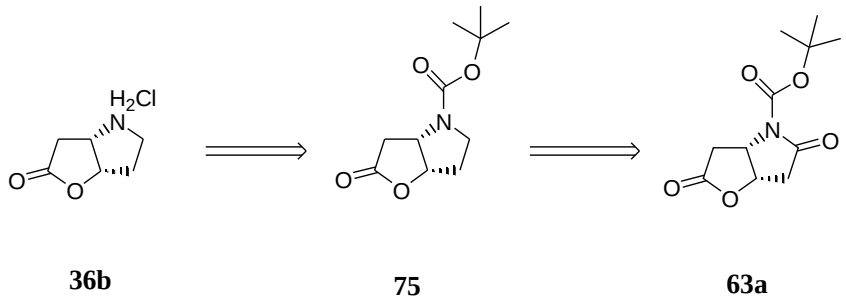


Scheme 16: Proposed mechanism of lactonization after oxidative cleavage by ruthenium tetraoxide

6.0 Synthesis towards (-)-GWL

6.1 Retrosynthesis towards (-)-GWL 36b

The (-)-GWL **36b** can be envisioned from *N*-protected GWL **75**, by removing the *N*-Boc group. Compound **75**, can then be derived by chemoselective reduction of the lactam carbonyl group of **63a** as depicted in Scheme 17.

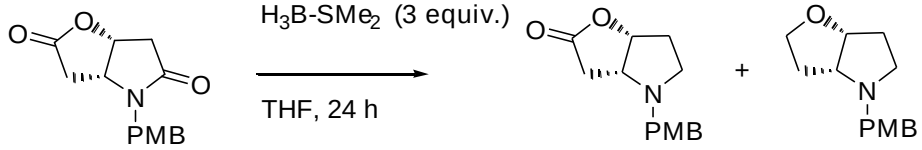


Scheme 17: Retrosynthetic analysis to (-)-GWL **36b**

6.2 Synthetic outline towards (-)-GWL

6.2.1 Selective reduction of carbonyl group and deprotection

In an effort towards the synthesis of (-)-GWL **36b**, the next step is to reduce the lactam of **63a** to arrive at **36b**. Several methodologies for the chemoselective reduction of lactams to pyrrolidines in the presence of lactone, have been developed. In 2004, Huang et al reported that the chemoselective deoxygenation[22] reduction of **76** could be achieved by treating **76** with three equivalent of borane dimethylsulfide in THF at room temperature for 24 hours to give lactone **77** in 58% and the fully reduced **78** in 10% yield (Scheme 18).

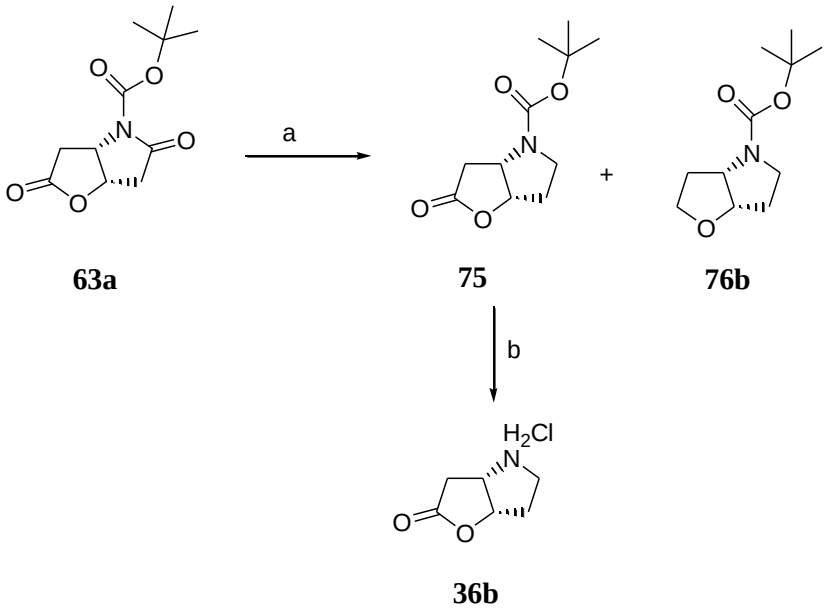


42 **43** **76a**

Scheme 18: Chemoselective reduction of carbonyl lactam with boron dimethylsulfide

Selective reduction of carbonyl group near to amide functionality of (-)-lactone lactam **63a** by borane dimethylsulfide gave **75** in 53% yield**.** Analysis of the product by HPLC

showed only a single peak with retention time at 25 min indicating that its stereoisomeric purity. Subsequent deprotection of the latter compound by hydrogenation furnished exclusively the *cis* (-)-Gaissman Waiss Lactone (Scheme 19).

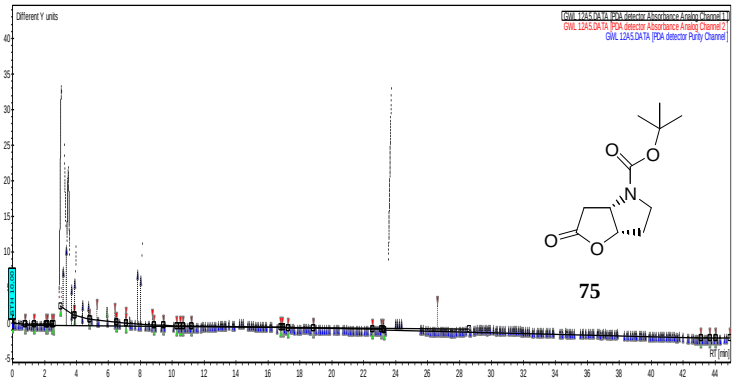


63a **75** **76b**

36b

Reagent and condition: **:** a. H_3B-SMe_2 (3.0 equiv.), THF, 24 h, (**75** : 53% ; **76b** : 11%). b. HCl / EtOAc: quant.

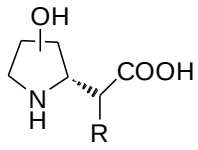
Scheme 19: Synthesis of *cis* (-)-Gaissman Waiss Lactone



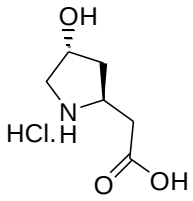
HPLC condition: Chiral column OD, 215+254 nm, solvent system 20% isopropanol in heptane, flow rate: 1 ml/min

7.0 Conclusion

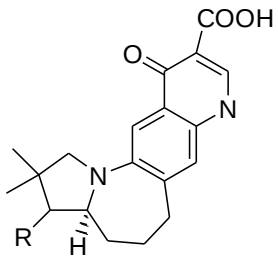
The synthesis of (-)-GWL from benzene disclosed here is an easy and short route, but low overall yield was achieved (13%) for the synthesis of key intermediate lactone lactam **63a** from benzene compared to 34% overall yield synthesized from *N*-protected amino acid developed by Jouin et al.[10] Nevertheless this approach differs from others known strategy, since compound **63a** can be used as a versatile intermediate especially for synthesizing more complex medicinally important compounds such as Tiagabine **77** (GABA transporter), a building block for anti Hepatitis C **78** and fluoroquinolone **79** for anti bacteria (Figure 6b).



77



78



79

Figure 6b: Medicinally important compounds

8.0 References

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25. Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc. Perkin Trans 1*, **1993**, *12*, 1313-1317.

C. Enantioselective synthesis of functionalized *cis* γ-butyrolactone derivatives.

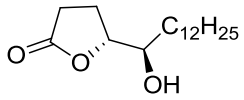
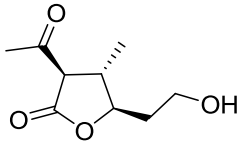
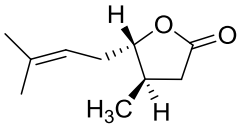
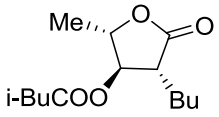
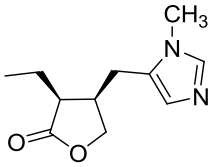
1. Introduction

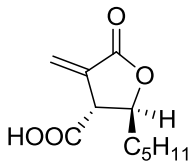
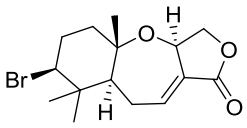
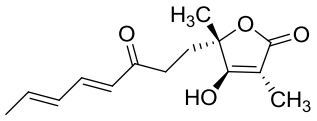
γ-Butyrolactone, a five membered ring lactone, has served a pivotal role as an interesting synthon in the design and construction of a variety of biologically active natural product compounds based on natural occurring substances.[1a] Thus employing butyrolactone moiety in the design and construction of new natural products, significantly contributes to the enrichment of existing pool of known biologically active substances.

Many functionalized γ-butyrolactone have been identified as versatile intermediates for synthesizing complex medicinally important compounds such as ionomycin, lasalocid A, elaiophylin, calcimycin, carbapenam alkaloids,[1a] ellipticine,[1b] (+)- grandisol,[1c] bacilosarcin B [1d] and many more.

The above compounds with the basic γ-butyrolactone scaffold have received much attention due to their diverse medicinal properties such as antibiotic, antitumor, antifungus, pheromone, etc. Some of the corresponding molecular structure and biological activity of compounds containing γ-butyrolactone scaffold are tabulated in Table 2.

Table 2: Molecular structure and biological activity of compounds containing γ-butyrolactone scaffold

Name	Molecular Structure	Biological activities
(-) Muricatacin		Antitumor[1e]
11-Deoxyprostaglandins		Anti-inflammatory, anti-apoptotic, anti asmthmatic agents
Eldanolide		Phermone
(+) Blastmycinone		Antifungal agents
Pilocarpine		Commonly used in the treatment of glaucoma.[1f]

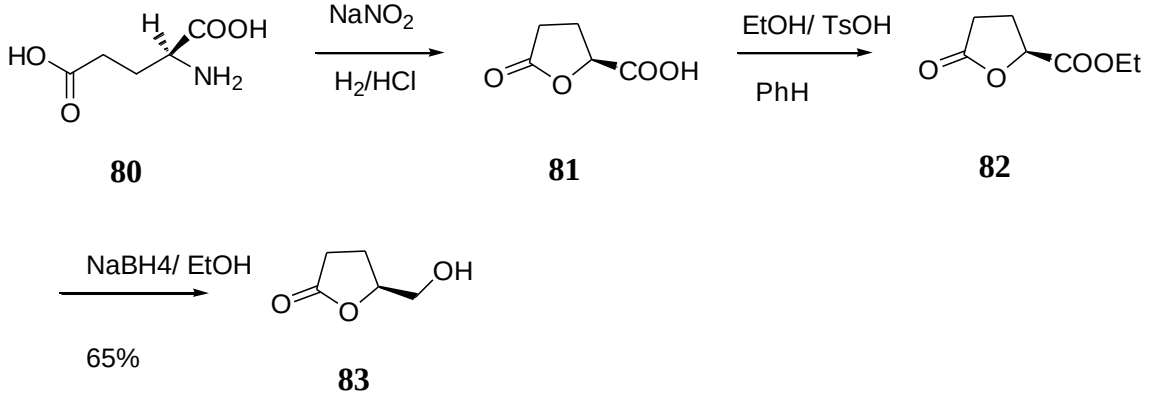
(-)-Methylenolactocin		Antitumor, antibiotic
(-)Aplysistatin		Anti-neoplastic agent
(-) Vertinolide		Antibiotic, insecticidal, herbicidal [1g, 1h]

Based on their notable therapeutic properties, the design and synthesis of γ-butyrolactone analogs should undoubtedly lead to the development of novel pharmaceutical agents.

2. Synthesis of γ-Butyrolactone

Several stereoselective approaches towards the synthesis of (+) or (-)-γ-butyrolactone have been published. Taniguchi et al. reported the synthesis of (+)-γ-butyrolactone from L-glutamic acid.[2] The requisite (+)-γ-butyrolactone was prepared in three steps as

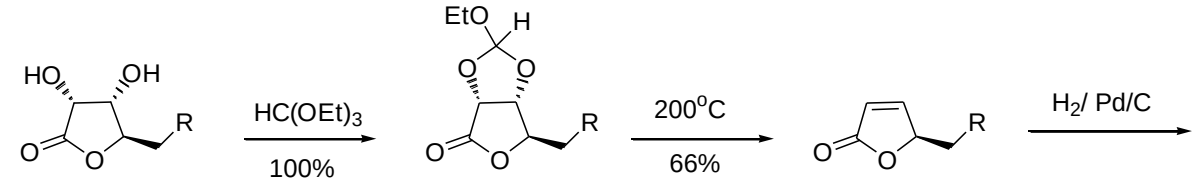
depicted in Scheme 20. Glutamic acid **80** was converted to γ- carboxylic-butyrolactone **81** by deamination in aqueous nitrous acid. Subsequent esterification in ethanol, followed by reduction with $NaBH_4$, giving rise to (+)-γ-butyrolactone **83** in 65%.



80 **81** **82** **83**

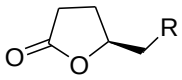
Scheme 20: Synthesis of (+)-γ-butyrolactone developed by Taniguchi and coworkers

Camps et al described an efficient transformation of D-ribonolactone **84** into (+)-γ-butyrolactone as depicted in Scheme 21.[3] According to Camps, protection of dihydroxyl group of D- ribonolactone **84** by $HC(OEt)_3$ to give cyclic orthoformate **85**, which was converted into butenolide **86**, by pyrolysis. Hydrogenation of the enone afforded (+)-γ-butyrolactone **87**.



R = H, Me, Bn, Ph_3C

84 **85** **86**

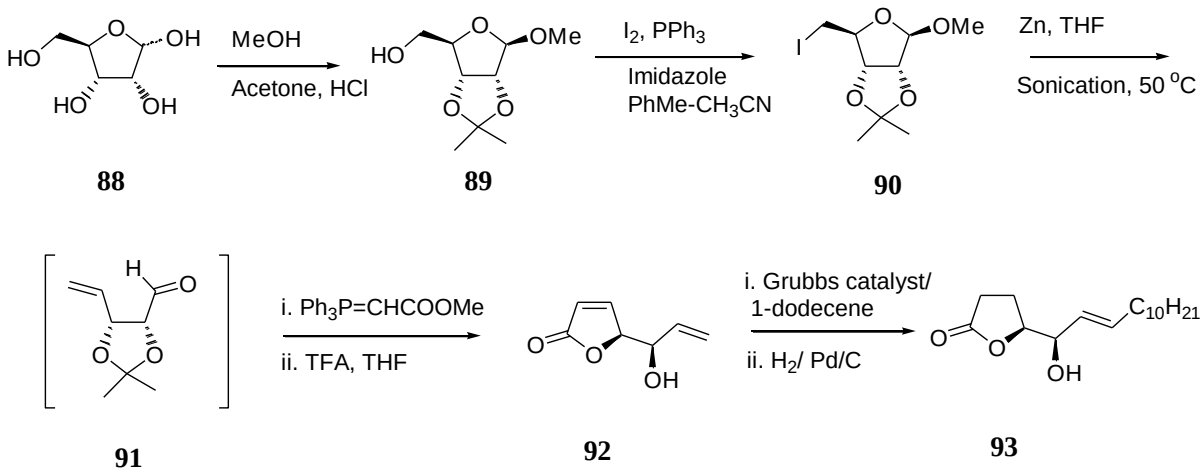


(+) GWL

87

Scheme 21: Synthesis of (+)-γ-butyrolactone developed by Camps and coworkers

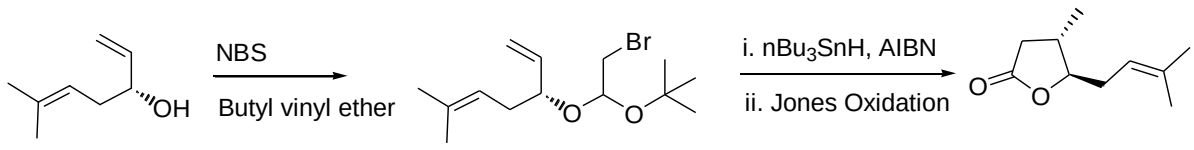
Ghosal et al showed (+)-γ-butyrolactone [4], could be derived from commercially available and inexpensive D-ribose as depicted in Scheme 22. In this route, Ghosal claimed that an appropriate precursor or key intermediate, butenolide could be accessible through D-ribose **88** in five steps. Protection and methylation of D- ribose **88** followed by iodination of **89** gives **90**. Applying Boord reaction or alkoxy-halo elimination of **90** gave aldehyde **91**. Treating the corresponding aldehyde **91** with phosphine ester through Wittig reaction, followed by deprotection and hydrolysis of methyl group gave the butenolide **92**. By applying RCM methodology on the latter, followed by hydrogenation could afforded (+)-γ-butyrolactone **93**.



Scheme 22: Synthesis of (+)-γ-butyrolactone developed by Ghosal and coworkers

3. Synthesis of β- Substituted γ-Butyrolactone

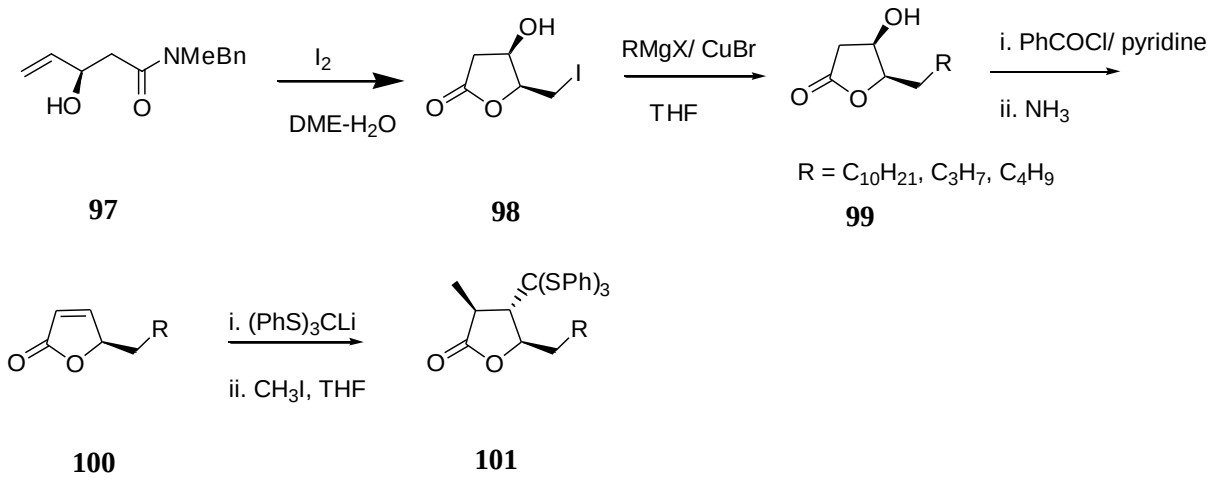
In the forward sense, functionalized (+)-γ-butyrolactone have served as key building blocks in the synthesis of many types of natural products. Much researched has been performed to functionalize (+)-γ-butyrolactone, especially at the β- position. Toshiyuki and co-workers reported a new approach towards the synthesis of β-substituted γ-butyrolactone, *ie* (+) eldanolide via intramolecular radical cyclization methodology ad depicted in Scheme 23.[5] They showed that (+)-eldanolide **96**, could be derived from butyl acetal **95**, which could be in turn be prepared from allyl alcohol **94**.



94 **95** **96**

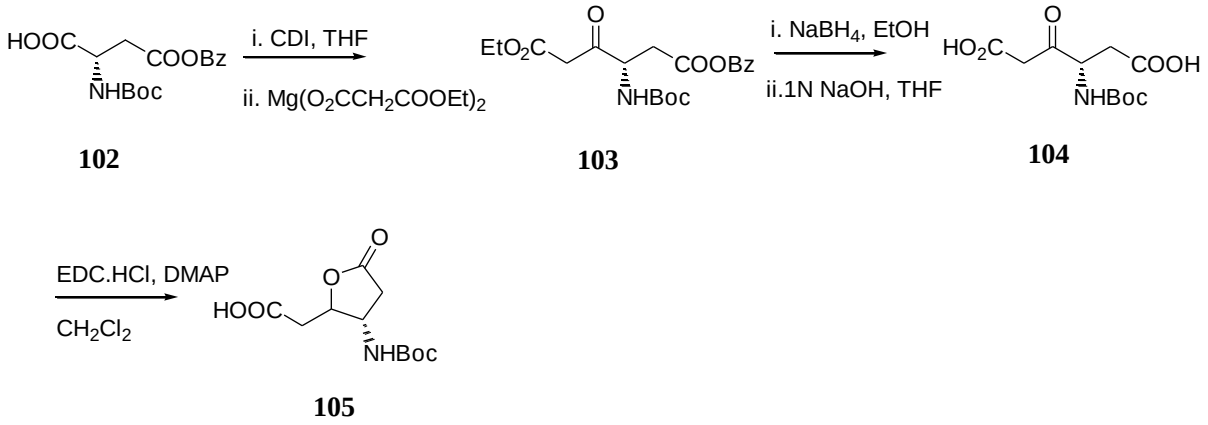
Scheme 23: Synthesis of β-hydroxy γ-butyrolactone developed Toshiyuki and co-workers

Takahata et al discovered a new method to functionalized (+)-γ-butyrolactone, at β-position through iodolactonation of homo chiral *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide as depicted in Scheme 24.[6] In this route, Takahata claimed that an appropriate precursor of β- substituted γ-butyrolactone could be accessible through intramolecular iodolactonization of **97** to provide directly lactone **98**, with high diastereoselectivity (8:1 = *cis*:*trans*) ratio due to direction by an allylic hydroxyl. Compound **98** could be transformed into β-hydroxy γ-butyrolactone **101** *via* cross coupling with Grignard derived cuprates, followed by elimination with ammonia in methanol to give butenolide **100**. In addition, the conjugate addition of tris(phenylthio)methyllithium and quenching with methyl iodide gave the α,β-substituted γ-butyrolactone **101**.



Scheme 24: Synthesis of β-hydroxy γ-butyrolactone and α,β-substituted γ-butyrolactone developed Takahata and coworkers

In the synthesis of biologically active aquatic natural peptide for example micro-sclerodermins has attract much attention because of their potent towards anti-fungal and anti proliferative activities. One of the requisite building blocks to synthesize the compound is a γ-butyrolactone moiety. Takayuki et. al. synthesized this amino acid in three steps from *N*- Boc (*S*) - aspartic acid 4 - benzyl ester **102**. Takayuki showed that homologation of the later with 1,1-carbonyldiimidazole (CDI) to give β- keto ester **103**, which was transformed to dicarboxylic acid **104**. Lactonization of **104** with EDC gave β –substituted γ-butyrolactone acid **105**.[7]

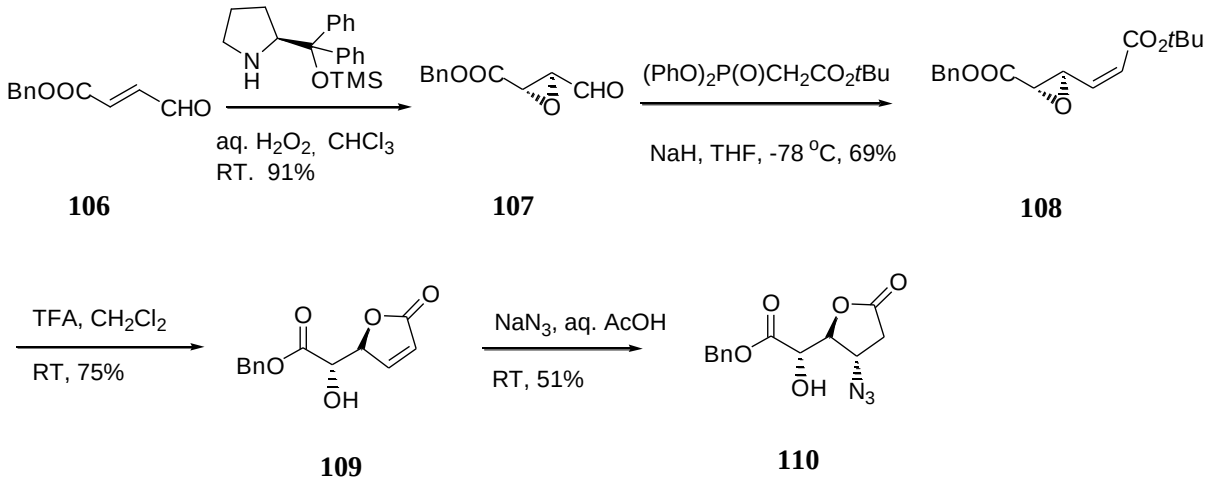


102 **103** **104**

105

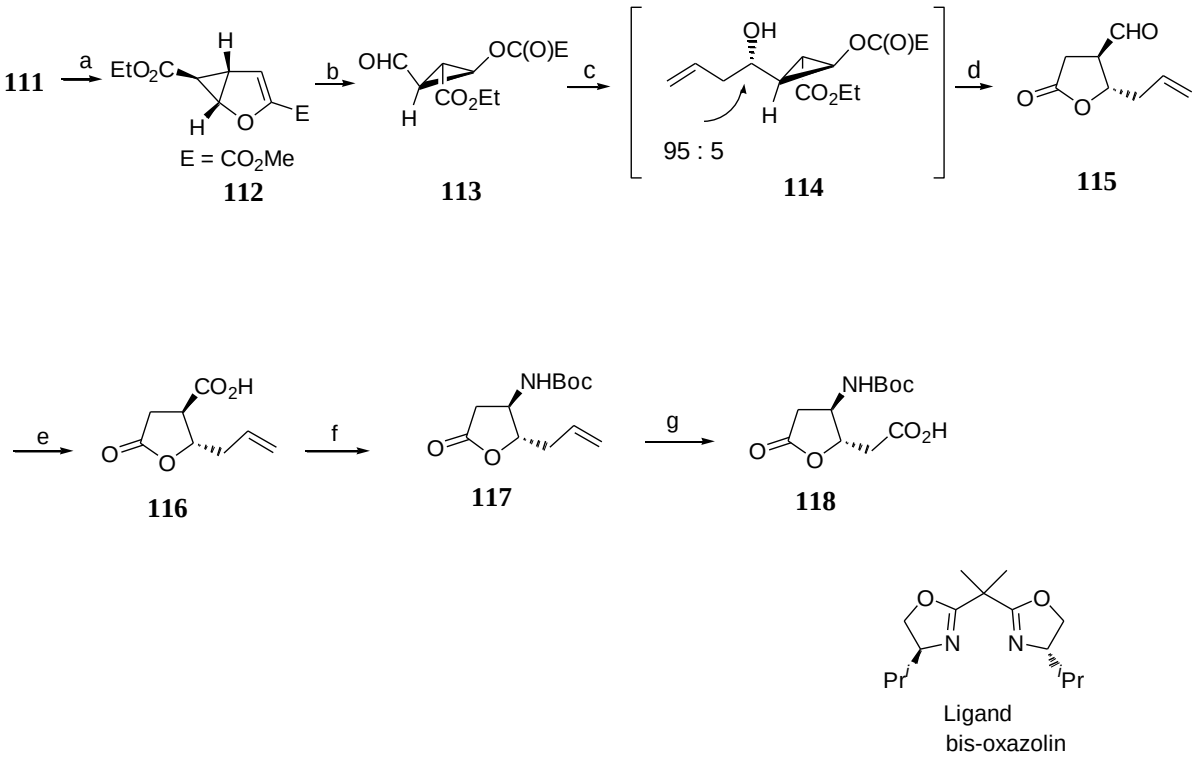
Scheme 25: Synthesis of β,γ-butyrolactone amino acid

Masaru[1d] described the synthesis of β-substituted γ-butyrolactone starting from aldehyde **106** as depicted in Scheme 26. Asymmetric epoxidation of aldehyde **106** under the organocatalytic condition proceeded smoothly to give epoxy **107**. Subsequent chain elongation through Wittig reaction afforded epoxy- α,β-unsaturated ester **108**, which could be transformed into hydroxy lactone **109** by intramolecular epoxide ring opening reaction after treatment with TFA. Then subsequent conjugate addition of **109** with sodium azide gave the corresponding β-azido γ-butyrolactone **110**.



Scheme 26: Synthesis of β-azido,γ-butyrolactone ester

Mahbbobul et al. used furan-2-carboxylic methyl ester **2** to synthesized *trans*-γ-butyrolactone amino acid (Scheme 27). The copper (I) bis(oxazoline)-catalysed asymmetric cyclopropanation[8] afforded **112**, which was recrystalized from pentane in >99% ee. Ozonolysis of **117** followed by reductive workup led to aldehyde **113** in diastero- and enatiomerically pure form. Boron trifluoride mediated addition of allyltrimethylsilane yielded **114** as a 95 : 5 diastereomeric mixture, which was used for further reaction without purification, directly transformed on a retro-aldol/lactonization cascades under basic condition to generate lactone **115**. The aldehyde functionality of **115** was oxidized to the corresponding acid **116** followed by Curtius rearrangement of the latter by diphenylphosphoryl azide (DPPA) to give carbamate **117**. Oxidative cleavage of the allylic double bond of **117** furnished γ- amino acid **118**.



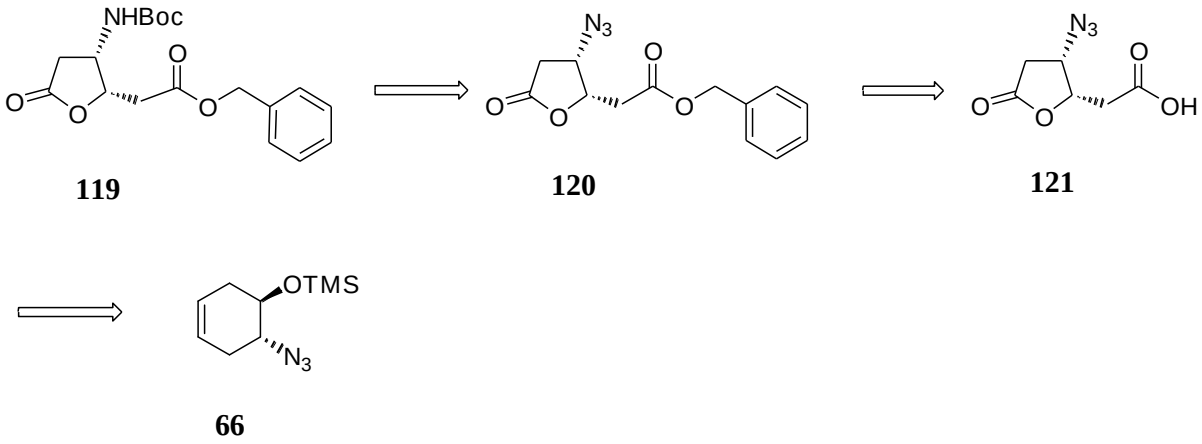
Reagent and condition : (a) (i) ethyl diazoacetate (1.6 equiv), $Cu(OTf)_2$ (0.66 mol%), (-)-**10** (0.83 mol%), $PhNHNH_2$ (0.83 mol%), CH_2Cl_2, 95% ee; (ii) recrystallization (pentane), >99% ee, 53%. (b) (i) O_3, CH_2Cl_2, -78 ^oC; (ii) dimethyl sulfide, 94%. (c) (i) $BF_3{\cdot}OEt_2$, -78 ^oC; (ii) allyltrimethylsilane. (d) $Ba(OH)_2{\cdot}8H_2O$, MeOH, 0 ^oC, 64%. (e) $NaClO_2$ (1.6 equiv), H_2O_2 (1.6 equiv), KH_2PO_4 (0.6 equiv), CH_3CN-H_2O, 0 ^oC, 87%. (f) DPPA (1.1 equiv), Et_3N (1.1 equiv), ^{t}BuOH, reflux, 20 h, 52%. (g) $RuCl_3{\cdot}3H_2O$ (6.3 mol%), $NaIO_4$ (4.0 equiv), CCl_4-CH_3CN-H_2O (1 : 1 : 2), 0 ^oC, 42 h, 79%.

Scheme 27: Synthesis of *trans* γ-butyrolactone amino acid

4. Synthesis of *cis* γ-butyrolactone amino esters

4.1 Retrosynthetic analysis of *N*-Boc protected *cis* γ-butyrolactone amino ester

N-Boc protected *cis* γ-butyrolactone amino ester **119** can be envisioned from azido trimethylsiloxy cyclohexene **66**. Oxidative cleavage of **66** by ruthenium tetraoxide catalysis give azido carboxylic acid **121**, benzyl protection at carboxyl functionality, reduction amination of azide to amide followed by *in situ* protection of the amine group should afford **119**.

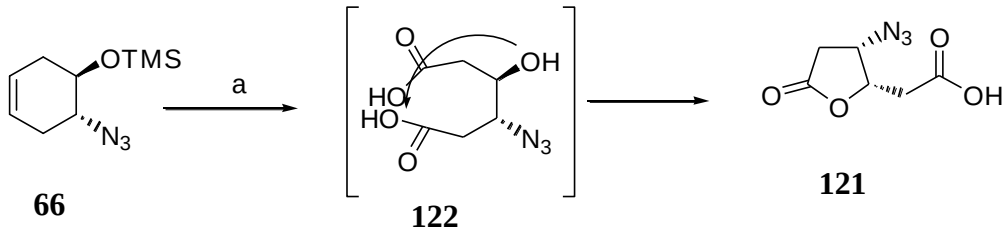


Scheme 28: Retrosynthetic strategy of *N*-Boc protected *cis* γ-butyrolactone amino ester

4.2 Synthesis of *N*-Boc protected *cis* γ-butyrolactone amino ester

4.2.1 Oxidative cleavage by ruthenium

Azido trimethylsiloxy cyclohexene **66** undergoes lactonisation by ruthenium tetraoxide in the presence of sodium periodate[9] through intermediate **122** to give the corresponding azido carboxylic acid **121** in 62% as depicted in Scheme 29.

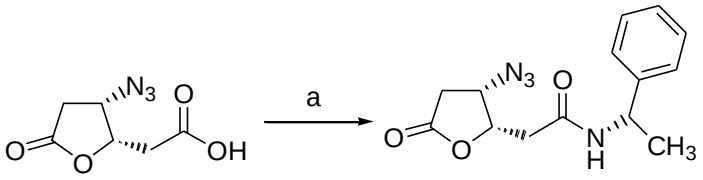


Reagent and condition : d) $RuCl_3.3H_2O$ (8.3 %mol), $NaIO_4$ (4.1equiv.), CCl_4:CH_3CN, H_2O (1:1:2), 0 ^oC, 62%

Scheme 29: Synthesis of azido acid **121**

4.3 Determination the purity of azido acid 121 by coupling with chiral amine

The purity of azido acid **121** was determined by coupling the carboxyl group of azido acid with (*R*)-phenylethanamine[10] to give dipeptide **123** (Scheme 30). Analysis of the crude product by HPLC showed only single peak at retention time 31 min indicating that a single enantiomer was produced during the lactonization. So we assume that the azido acid **121** purity is more than 99% (Figure 7). The corresponding racemic dipeptide was also synthesized for comparison. Ebata T et al. synthesized *cis* γ- lactonic carboxylic acid from (1*S*,2*S*) 1-benzoyloxy-2-methyl-4-cyclohexene **124**. Oxidative cleavage using ruthenium oxide in the presence of sodium periodate in biphasic solution of CCl_4, MeCN and water gave the corresponding dicarboxylic acid **125**. Subsequent lactonization with concentrated acid furnished *cis* -γ- lactonic carboxylic acid[11] **126** (Scheme 31).



121 **123**

HPLC : OD column, 20% isopropanol

Reagent and condition : (a) (*R*)-phenylethylamine (1.1 equiv.), HOBt (1.1 equiv.), HBTU (1.3 equiv.), THF, 48%

Scheme 30: Coupling reaction of azido acid **121** with chiral amine

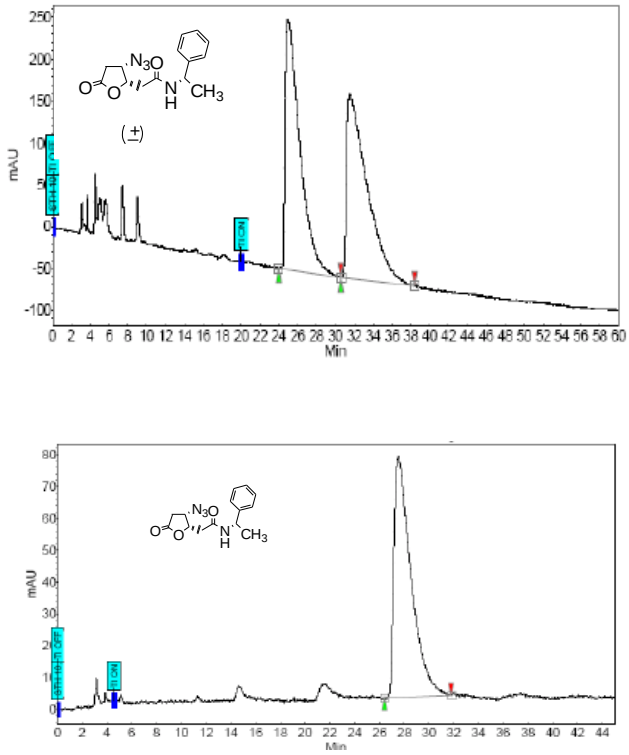
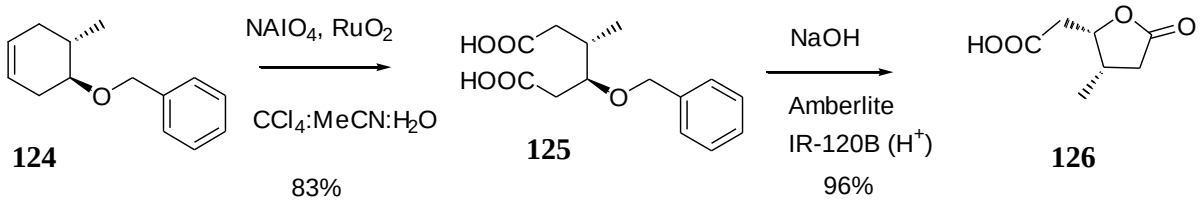


Figure 7: HPLC spectrum for dipeptide **123** and racemic dipeptide

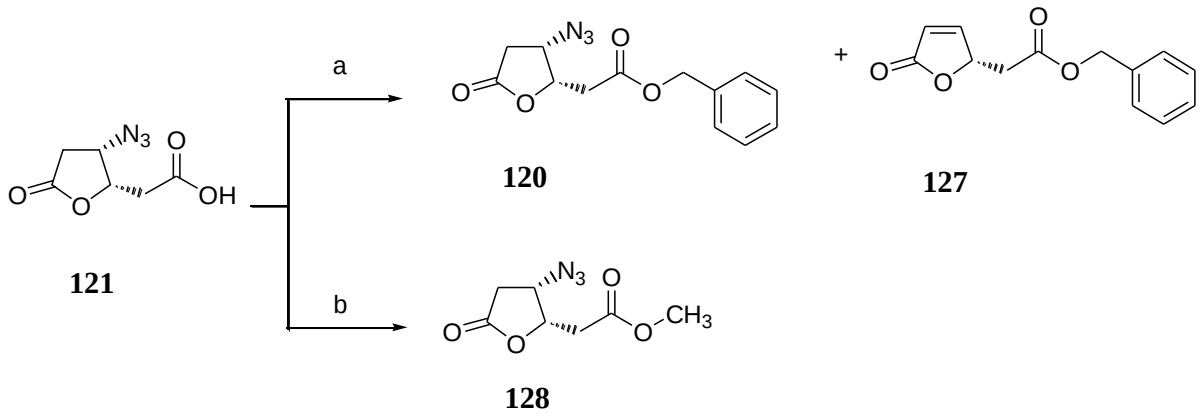


124 **125** **126**

Scheme 31: The synthesis of *cis* γ- lactonic carboxylic acid from (1*S*,2*S*) 1-benzoyloxy-2-methyl-4-cyclohexene developed by Ebata et al.

4.4 Synthesis of γ-butyrolactone ester derivatives

Benzylic protection[12] of carboxylic acid **121** gave ester **120.** This was accomplished by treatment with benzyl bromide together with side product **127** due to azide elimination (Scheme 32). Compound **127** could be used as an intermediate compound to synthesize micromolide which showed good in vitro anti-TB activity (MIC: 1.5 μg/mL)[13]. In addition, esterification of **121** with diazomethane to give ester **128** also was performed in good yield (89%).



120 **127**

121

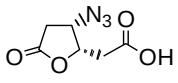
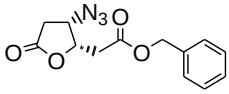
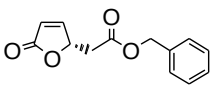
128

Reagent and condition : (a) BnBr (1.6 equiv.), $NaHCO_3$ (6 equiv.), DMF, 43 h, rt. 69% b. CH_2N_2 (excess), Et_2O, 89%

Scheme 32: Synthesis of γ-butyrolactone ester

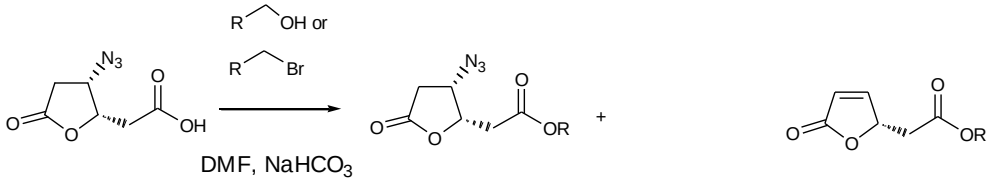
By using different bases in the reaction, different product yields could be obtained. For instance, a strong base, potassium carbonate could afford more elimination product as depicted in Table 3.

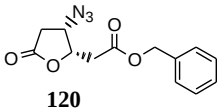
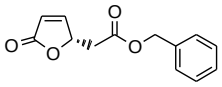
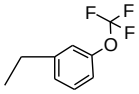
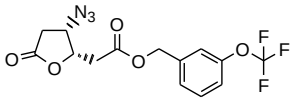
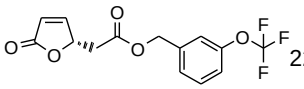
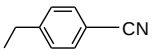
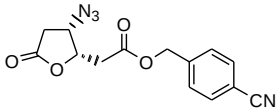
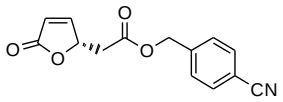
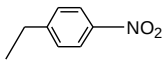
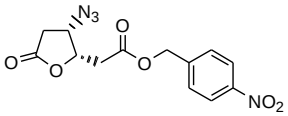
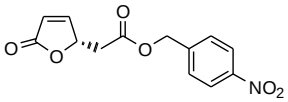
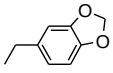
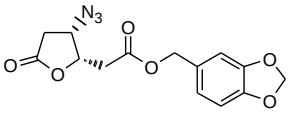
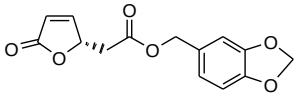
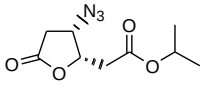
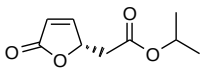
Table 3: Effect of base in esterification of azido acid **121**

Entry	Base	 **121**	BnBr, DMF RT. 20 h	Yield (%)  **120**	+  **127**
1	triethylamine			40	20
2	K_2CO_3			6	60

By allowing this transformation strategy to take place, a wide range of *cis* γ-butyrolactone ester derivatives could be synthesized as depicted in Table 4.

Table 4: *cis*γ-Butyrolactone ester derivatives and butenolide: their antituberculosis cytotoxicity activity.



Entry	R		MIC(μg/ml)	IC_{50} (ug/ml)[a]		MIC(μg/ml)[b]	IC_{50} (ug/ml)
1		 **120**	**11.1**	>20 (0%)	 **127**	**8.4**	>20 (0%)
2		 **129**	46.9	79.51	 **130**	22.7	90.37
3		 **131**	49.5	>100 (41%)	 **132**	48.4	83.3
4		 **133**	47.9	79.62	 **134**	45.5	94.32
5		 **135**	49.9	79.62	 **136**	43.7	94.32
6	-CH(CH 3)2	 **137**	>100	-	 **138**	>100	-

a: antituberculosis activity value b: cytotoxicity value

In this study, we wanted to test whether our synthesized compounds have anti-TB abilities. Therefore, thirteen of the synthesized compounds were chosen and tested to determine their ability to inhibit H_{37}Rv *Mycobacterium tuberculosis* strain.

In this biological study, the inhibitory activity of compounds against *M. tuberculosis* were evaluated by the MABA (microplate Almar Blue assay) method. MABA is sensitive, rapid, inexpensive and non-radiometric method which is able to screen a large number of antimicrobial compounds against slow-growing mycobacteria. The Alamar blue reagent, an oxidation-reduction dye is a general indicator of cellular growth and viability. After reduction, the blue which is non-fluorescent and the oxidized form becomes pink and fluorescent. Growth can be analyzed using a fluorimeter or spectrophotometer or determined by a visual color change. The minimum inhibitory concentration (MIC) is defined as the lowest drug concentration effecting growth inhibition of >90% relative to the growth for the drug-free control.

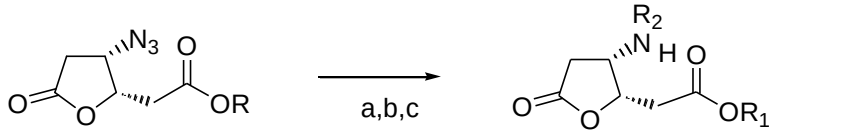
The MIC values using the MABA assay for these compounds are presented in **Table 4**.
In general, the azido *cis* γ-butyrolactone ester analogs are less active than their corresponding butenolide benzyl ester analogs. Compound **120**, without any substituent on the benzyl ring showed the high activity (MIC= 11.1 μg/ml). This data suggest that in the presence of electron withdrawing group (EWG) at meta position (compound **129**) or para position (compound **131**, **133**) and electron donating group (compound **135**) on the benzyl ring results in reduced activity., while no significant activity was observed for the branched isopropyl group (compound **137**).

According to Table 4, most of the butenolide benzyl esters showed considerably reduced activity except for butenolide **127** which shows higher MIC value (8.4 μg/ml) and **130** with 22.7 μg/ml MIC value.

In conclusion, compounds **120** and **127** tested for antituberculosis activity and were determined to be non-toxic on mammalian cell line (IC_{50} >20 (0%)).

4.5 Synthesis of *cis* γ-N-Boc butyrolactone derivatives and *cis* γ-butyrolactone amino acid

Reductive transformation of the azide **120 or 128** was performed using Boc_2O in the presence of $Pd(OH)_2/C$ and triethyl silane as proton donor which yielded the *N*- (*tert*-butoxycarbonyl) amino lactone **139** or **140.** Deprotection of benzylic group in **139** by Pd/C afforded amino acid **141** (Scheme 33).



120 R : Bn
128 R : Me

139 R_1 : Bn R_2 : Boc
139a R_1 : Bn R_2 : TFA
140 R_1 : Me R_2 : Boc
141 R_1 : H R_2 : Boc

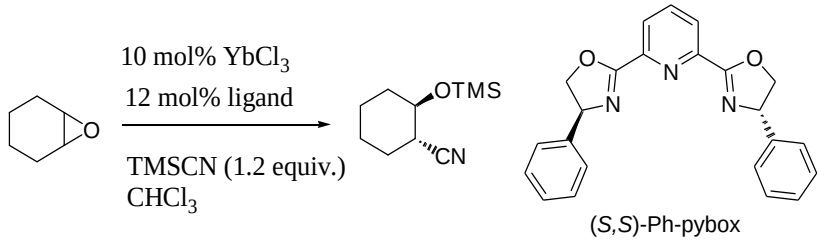
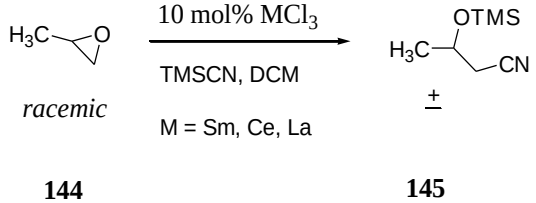
Reagent and condition : (a) Boc_2O (1.5 equiv), $Pd(OH)_2/C$, Et_3SiH (1.5 equiv.), EtOH, r.t, 20 h, (**139:** 71**%** %) (**140**:74 %) (b) TFA, DCM, quant. (c) a. Pd/C, H_2, MeOH, 84 %

Scheme 33: *cis* γ-*N*-Boc butyrolactone derivatives

5. Synthesis of cyanotrimethyl silane

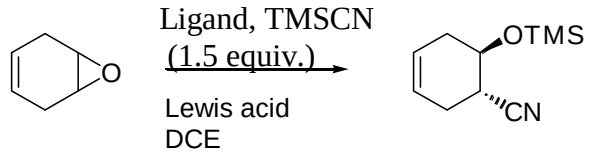
Cyanotrimethyl silane derived from asymmetric ring opening (ARO) of meso epoxide with TMSCN and catalyzed by chiral complexes ligand, can be used as a synton to synthesize novel *cis* δ–amino acids. Jacobsen et al reported the possibility of effecting cyanide ARO reaction with lanthanide- base catalyst.[14] They found that (pybox)$YbCl_3$, effectively promote the ring opening of epoxide **142** to yield cyanotrimethyl silane **143** as tabulated in Table 5 (entry 1). Kagan et al. reported that lanthanide chloride salts also promote ARO of epoxide **144** with TMSCN in good yield to give cyanotrimethyl silane **145** adduct but no selectivity (Table 5, entry 2)

Table 5: Asymmetric ring opening (ARO) of meso epoxide with TMSCN and catalyzed by chiral complexes ligand

Entry	Reaction	Ligand	yield (%)	ee (%)
1	 **142** **143**		90	91 (1*S*, 2*R*)
2	 *racemic* **144** **145**	–	Sm = 88 Ce = 85 La = 77	*racemic*

Inspired by the above discovery, we conducted several screening ARO of racemic epoxide **67** with TMSCN catalyzed by (pybox)$YbCl_3$ or (pybox)$YbCl_3.6H_2O$ to give cyanotrimethyl silane **146** as tabulated in Table 6).

Table 6: ARO of racemic epoxide 67 with TMSCN catalyzed by (pybox)$YbCl_3$ or (pybox)$YbCl_3.6H_2O$



67 **146**

Entry	(*S*,*S*)-ph-pybox	Lewis acid	Conditions	Yield %[a]	$[\alpha]_D^{20}$	ee (%)[b]
1	-	5 mol% $YbCl_3.\ 6H_2O$	reflux, 5 h	65	0	0
2	10 mol%	5 mol% $YbCl_3.6H_2O$	reflux, 5 h	69	-5	3
3	12 mol%	5 mol% $YbCl_3.6H_2O$	reflux, 5 h	54	-9	4
4	10 mol%	12 mol% $YbCl_3.6H_2O$	0°C, 4 d	23	-3	0
5	-	$YbCl_3$	RT, 24 h	65	0	0
6	10 mol%	12 mol% $YbCl_3$	reflux, 5 h	40	-14	10
7	10 mol%	12 mol% $YbCl_3$	reflux, 24 h	75	-6	3
8	10 mol%	12 mol% $YbCl_3$	reflux, 4 d	52	-8	4

[a] isolated yield, [b] determined by chiral GC

ARO of cyclohexene oxide with TMSCN in DCE and catalyzed by chiral (pybox)$YbCl_3$ complexes or (pybox)$YbCl_3.6H_2O$ did not show good enantioselectivity. Only entry 6 gave highest enantioselectivity, *ie* 10%. However in this reaction, by employing 10 mol% (*S,S*)-ph-pybox and 12 mol% $YbCl_3$, the decrease in yield was observed. By lowering the reaction temperature to 0^oC or increase the lewis acid, did not help to improve the enantioselectivity. When the reaction was carried out in DCM or THF, the product was not observed.

6. Conclusion

In summary, a convenient and facile strategy for the synthesis of enantiopure azido acid bearing γ-butyrolactone scaffold **121**, was developed. Several *cis* γ-butyrolactone ester derivatives and their corresponding butenolide ester were synthesized. Some of them exhibited good in vitro anti-tuberculosis (TB) activity. This results open furthermore the possibility to design a new anti-TB compounds based on *cis* γ-butyrolactone scaffold.

7. References

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D. Synthesis of peptides from sugar amino acid

1. Introduction

Sugar amino acid (SAAs) is grouped into one of the glycosamino acids. The carboxylic acid and amino functionality are incorporated directly into a cyclic five or six membered ring of a carbohydrate skeleton, which produces restrict conformation.[1] General structure of SAAs is depicted in Figure 7.

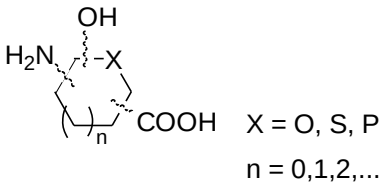
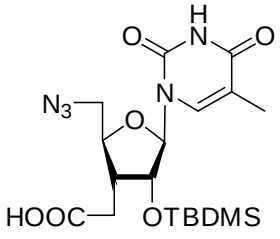
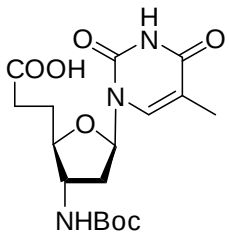


Figure 7: General structure of SAAs

The rigidity of SAAs is an important factor to generate secondary structure in oligomers or short peptides. Several SAAs have served as building blocks for the synthesis of furanoside- based antisence oligonucleotides **147** and **148** as depicted in Figure 8.[2]



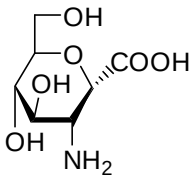
147



148

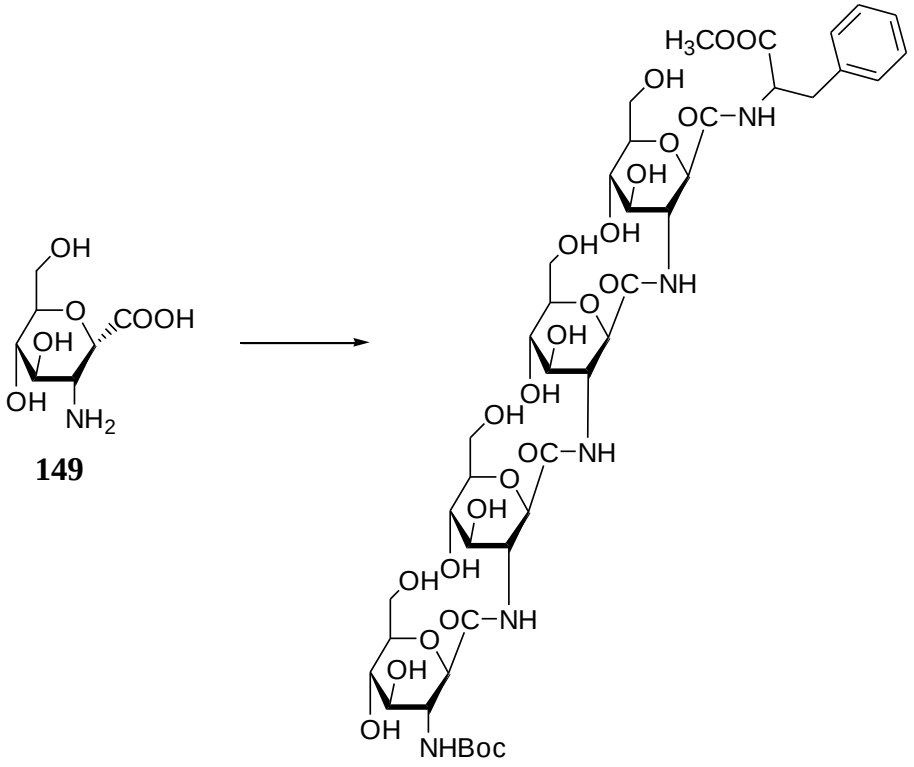
Figure 8: Examples of building blocks used in the synthesis of furanoside- based antisence oligonucleotides

SAAs **149**, adopt a secondary structure *ie*, mimic β and γ-turn when incorporated into a short peptide sequence.[3]



149

Due to its ability to form restricted conformation in peptides, SAAs have been used as oligosaccharide mimics. In 1996, Ichikawa et al reported the first characterized carbopeptides by using D-glucoseamine- derived SAAs building block **149** as a key building block[4] as depicted in Scheme 34. Elongation of **149**, afforded the tetramer **150**, in which after O-sulfation showed a strong inhibitory potency against HIV infection of CD_4 cell.

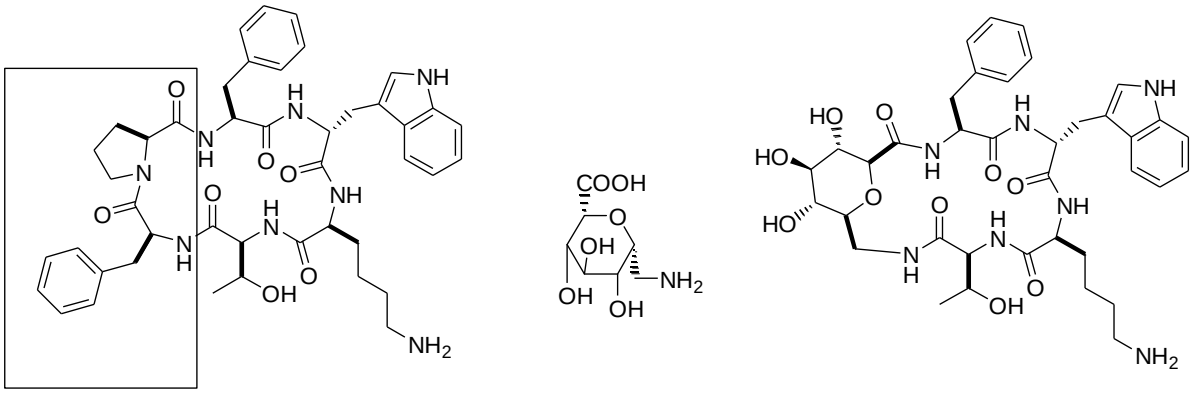


149

150

Scheme 34: Carbopeptides synthesized from D-glucoseamine- derived SAAs building block

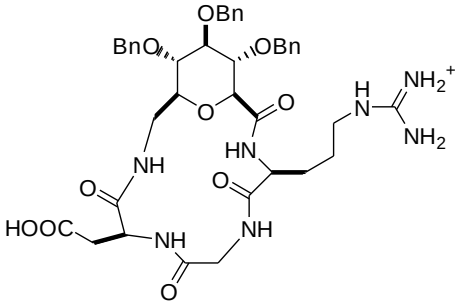
Over the last two decades, there have been dramatic increase in the field of peptidomimetic, in which SAAs is oligomerized into other amino acid. Kessler and co-workers were the first to demonstrate the potential of SAAs as peptidomimetics.[5] They claimed that, the Pro-Phe dipeptide sequence in the somatostatine analog cyclo (Pro-Phe-D- Trp-Lys-Thr-Phe) **151**, was replaced by the dipeptide isosteres **152** to give the potent hexapeptide mimetic somatostatine analog **153** as depicted in Figure 9. Somatostatine is a 14-residue cyclic peptide hormone formed in the hypothalamus, which plays an important role in a lots number of physiological actions, for instance, it inhibits the release of growth hormone,[6] insulin secretion[7], tumor cells and it induces apoptosis.[8]



151 **152** **153**

Figure 9: Hexapeptide mimetic somatostatine analog synthesized by Kessler et al

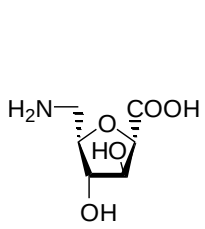
The same group was also able to manipulate the cyclic pentapeptide cyclo (Arg-Gly-Asp-D-Phe-Val) structure. This cyclic pentapeptide binds selectively to the $\alpha_v\beta_3$ receptor of the integrin family. They incorporate the SAAs **152** analog into cyclic peptides that contain RGD (Arg-Gly-Asp) motif. Replacement of D-Phe-Val sequence with isostere **152** analog furnished the potent peptidomimetic **154** with high $\alpha_v\beta_3$ receptor activity (IC_{50} = 25 nM)[9] as depicted in Figure 10.



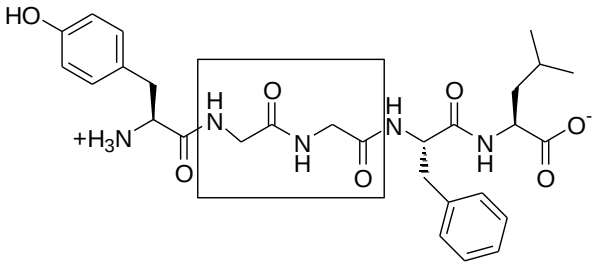
154

Figure 10: Peptidomimetic RGD analog synthesized by Kessler et al

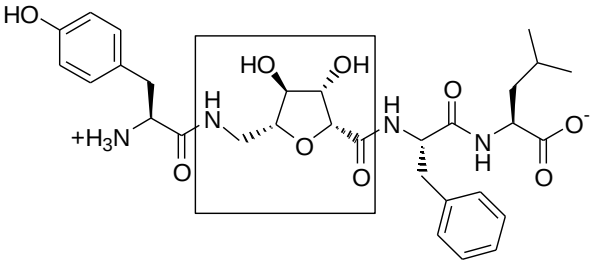
On the other hand, Chakraborty and co-worker, incorporated the furanoid SAAs **155**, into Leu-enkephalin sequence **156**.[10] Replacement of the Gly-Gly sequence in Leu-enkephalins **156** by the isosteres **155** afforded the biologically active peptide **157** as depicted in Figure 11.



155



156



157

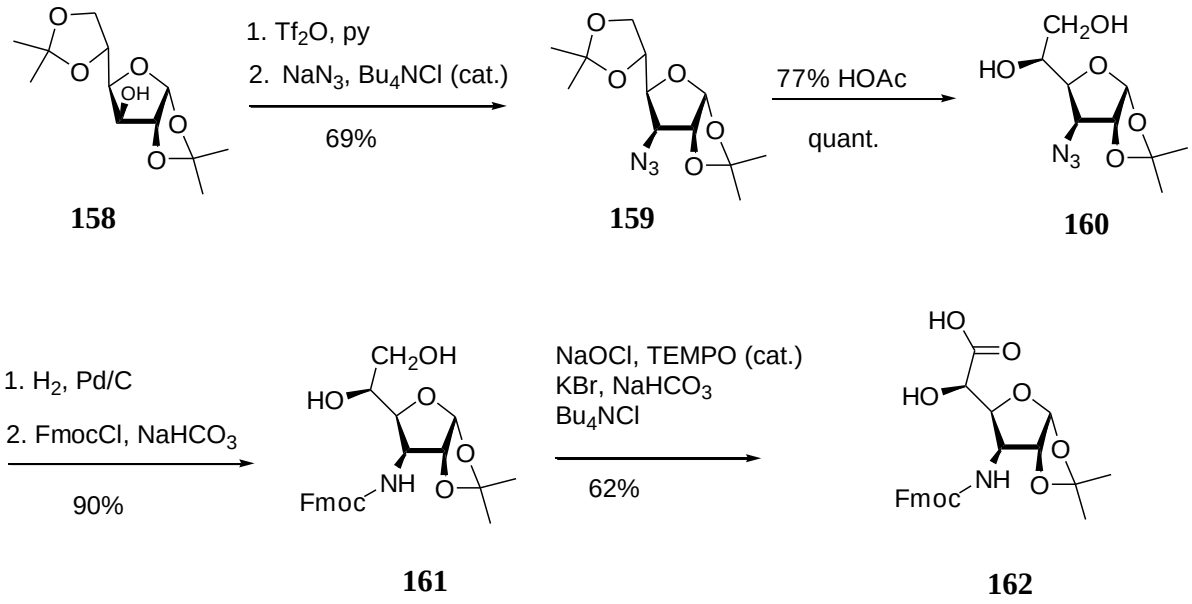
Figure 11: Peptidomimetic Leu-enkephalins analog synthesized by Chakraborty et al

2. Synthesis of γ- Sugar Amino Acids

Fleet et al reported the synthesis of γ- SAAs as depicted in Scheme 35. They used monosaccharides which commercially available, as the starting material.[11]

They converted **158**, into their corresponding azide **159** by addition of catalytic amount of Bu_4NCl.[12] Subsequent deprotection of the exocyclic hydroxyl **159** with acetic acid

yielded diol **160**. Azide reduction of the latter and Fmoc protection in one pot reaction, gave rise to *N*-Fmoc diol **161**, which was then converted to the desired γ- SAAs **162** after primary alcohol oxidation mediated by TEMPO.

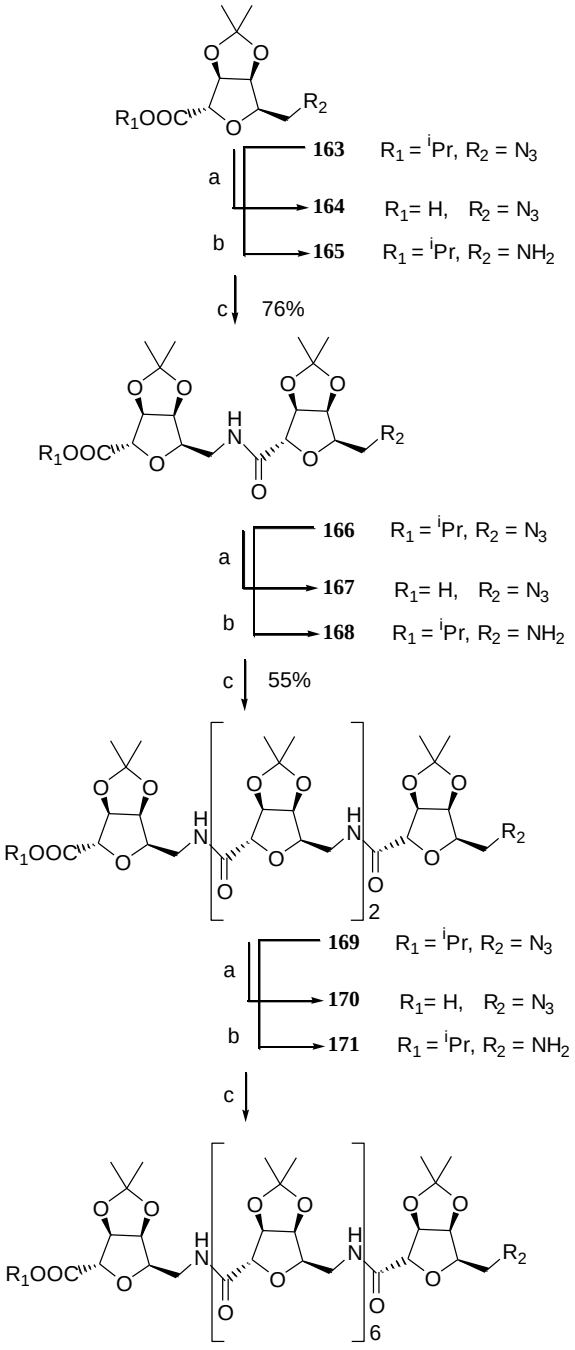


Scheme 35: Synthesis of Fmoc-Protected SAAs developed by Fleet et al.

3. Synthesis of Homooligomer

SAAs have also served as candidates for biopolymer scaffolds to mimic oligosaccharide and polysaccharides structure. Several research groups have developed libraries of oligomers based on SAAs monomers. Fleet et al reported the syntheses of tetramer **171** and octamer **172** from carbohydrate-like tetrahydrofuran **163** as building blocks. This

monomer could be envisioned from commercially available D-glucono- 1,4- lactone.[13] They claimed that tetramer **171** exhibits no conformational preferences (no secondary structure) whereas the octamer **172** exhibits a well- defined left handed-helical conformation stabilized by hydrogen bonding. In their route, the isopropyl ester, D-talo **163** was transformed into the corresponding acid **164** after ester hydrolysis by aqueous NaOH. The azide group in D-talo **164** was reduced into the corresponding amine **165** by hydrogenation in the presence of Pd/C. The acid **164** and amine **165** were coupled to give dimer **166**. From dimer **166**, tetramer **169** and octamer **172** were synthesized by applying the same methodology as depicted in Scheme 36.



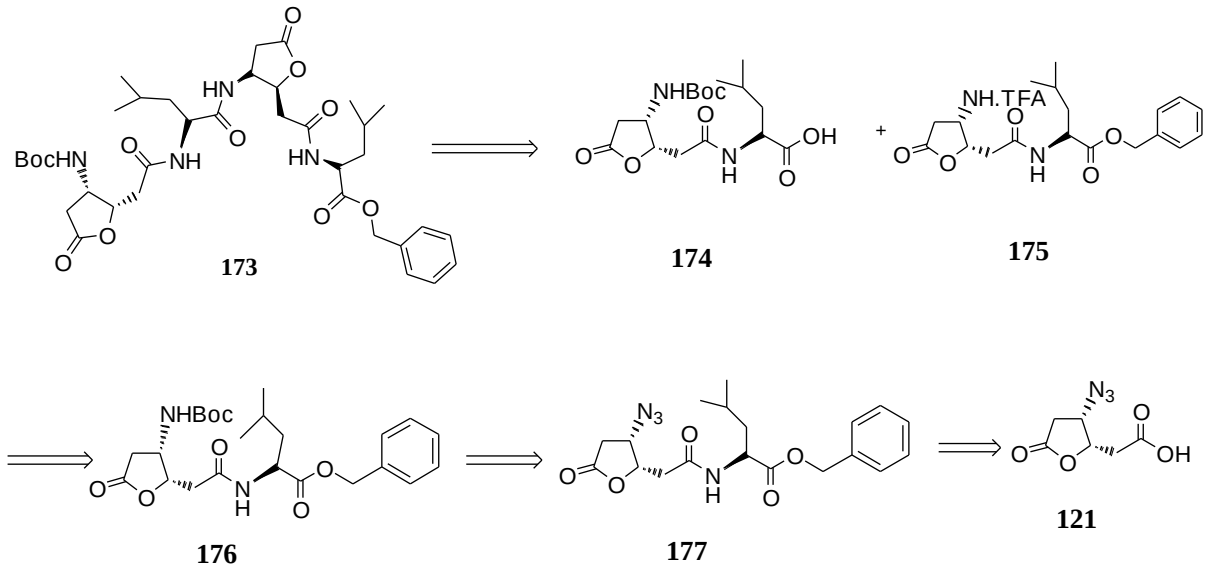
172

Reagent and conditions: a) 0.5 M NaOH (aq), dioxane; Amberlite IR 120 (H^+). b) H_2, Pd/C. c) EDC, HOBt, ($^i pr$)$_2$Net, CH_2Cl_2

Scheme 36: Carbohydrate-like tetrahydrofuran homooligomers by Fleet et al

4. Retrosynthesis strategy of tetrapeptide 173 using solution phase procedure

In an effort to synthesize tetrapeptide **173**, we decided to carry out the synthesis in solution phase rather than in a solid phase synthesis protocol. Tetrapeptide **173** was envisioned to be synthesized in solution from azido carboxylic acid **121** *via* an iterative peptide coupling procedure as depicted in Scheme 37.

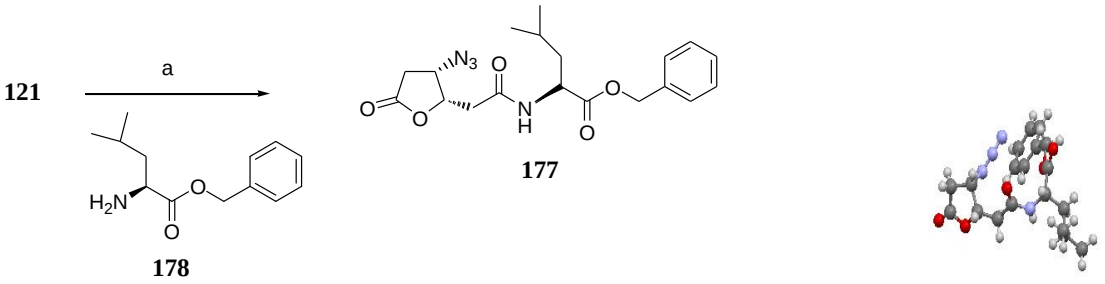


Scheme 37 : Retrosynthetic strategy of tetrapeptide **173**

4.1 Synthesis of dipeptide 177

Due to the leaving group characteristic of the azide group at γ position in γ–butyrolactone acid **121**, treating with a strong base would easily remove the azide group. Our initial attempt was aimed to synthesize the dipeptide **177** from azido carboxylic acid **121** (Scheme 38)**.** Coupling the azido carboxylic acid **121** with amine **178** in the presence of coupling reagent HOBt/EDC in CH_2Cl_2 and DIPEA did not give the

dipeptide product. In that case, the conversion could not be observed. However, we managed to produce dipeptide **177** in 60% yield by dissolving γ–butyrolactone acid **121**



Reagent and conditions : a) amine **178**, HOBt, HBTU, 0 ^{o}C- rt, THF, 24 h, 60%.

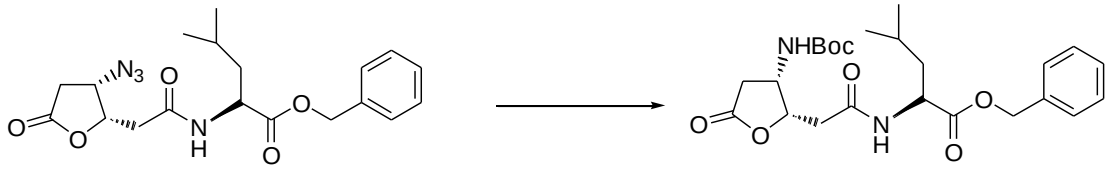
Scheme 38: Synthesis of dipeptide **177** from γ–butyrolactone acid **121**

and coupling reagents (HOBt and HBTU) in dry THF prior to treating them gradually with amine **178** without presence any base.

4.2 Reductive amination and *N*-Boc protection

The *tert*-butoxycarbonyl group is one of the protecting groups used frequently in organic synthesis. Being stable towards catalytic hydrogenation, basic reagents and nucleophilic reagents, this protecting group is considered as an ideal partner to benzyl ester and carbamates used in peptide synthesis.[14]

When dipeptide **177** in methanol was treated with $Pd(OH)_2/C$ in the presence of Boc_2O, followed by sequentially addition of triethylsilane, the *N*- (*tert*- butoxycarbonyl) dipeptide **176** was yielded (Scheme 39).



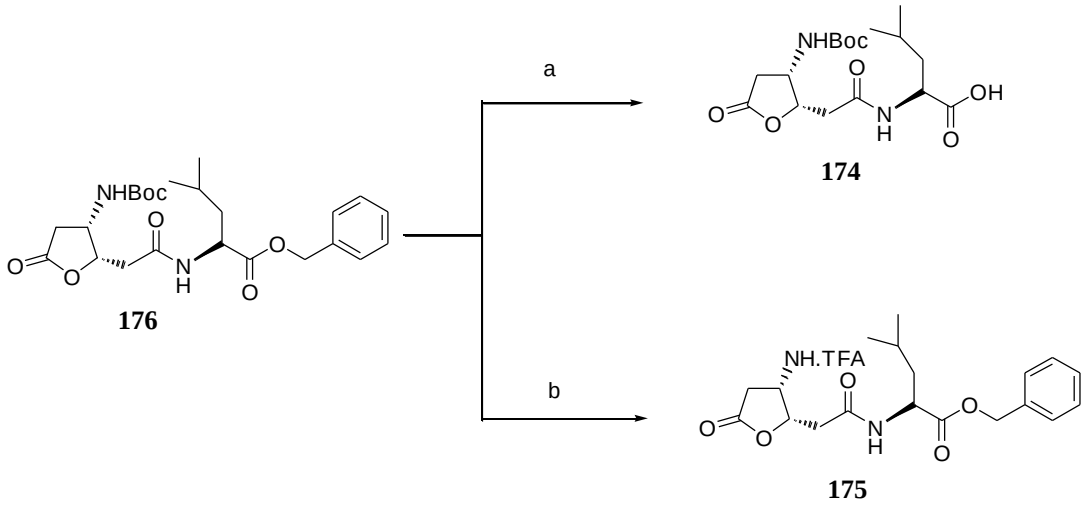
177 **176**

Reagent and condition: (a) Boc_2O (1.5 equiv), $Pd(OH)_2/C$, Et_3SiH (1.5 equiv.), MeOH, rt, 1.5 h

Scheme 39: *N*-Boc protection of dipeptide **176**

4.3 Synthesis of tetrapeptide 173

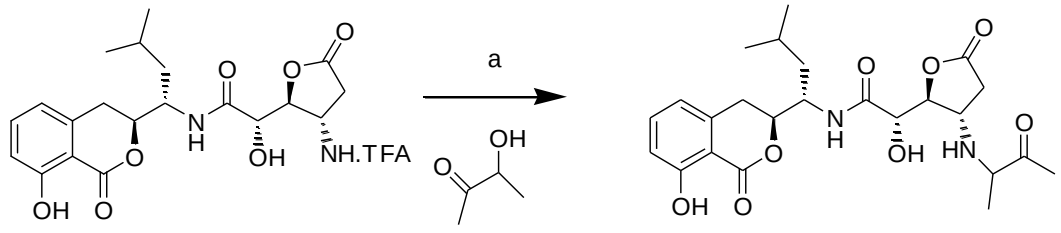
Prior to the synthesis of tetrapeptide **173**, the *tert*-butoxycarbonyl group of *N*-Boc dipeptide **176**, has to be initially removed using 30% of TFA in CH_2Cl_2 to give its corresponding ammonium salt **175**. On the other hand, catalytic hydrogenation of benzyl group using Pd/C in EtOH afforded the free carboxylic acid **174** (Scheme 40). Subsequently, the ammonium salt **175** was coupled with preactivated dipeptide acid **174**, using HOBt/EDC in CH_2Cl_2 in the presence of DIPEA, however there was no conversion observed, even after two days reaction. Then we carried out the coupling reaction using a different coupling reagent *ie*. HOBt/HBTU in CH_2Cl_2, in the presence of DIPEA, but in this case, after two days no conversion was observed.



Reagent and condition: (a) Pd/C in EtOH, quant. (b) 30% of TFA in CH_2Cl_2

Scheme 40: Deprotection of *tert*-butoxycarbonyl and benzyl ester in **176**

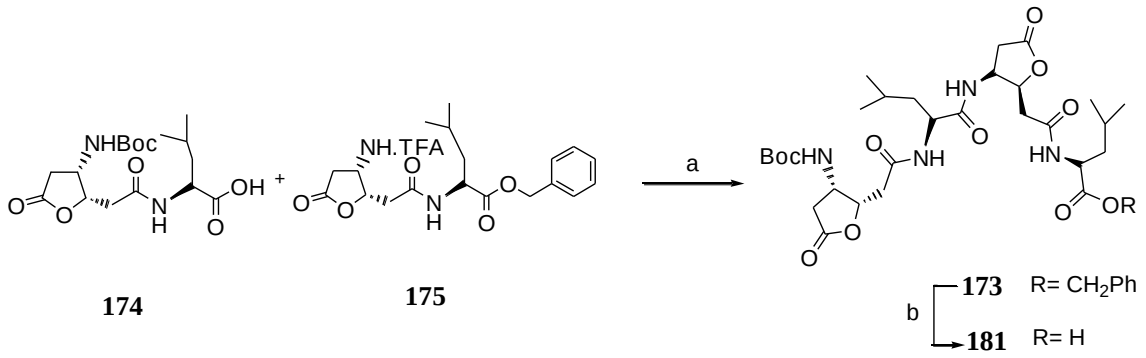
In 2009, Kuwahara et al. reported the *N*-alkylation of γ–butyrolactone **179** with 3-hydroxy-2-butanone in acetonitrile[15]. They used one equivalent of $NaHCO_3$ and five equivalent of $MgSO_4$ to give the N-alkylated product **180** as depicted in Scheme 41.



Reagent and condition : a) $MgSO_4$ (5 equiv.), $NaHCO_3$ (1 equiv.), CH_3CN, 75 ^oC, 72%

Scheme 41: N-alkylation of lactone **179** with 3-hydroxy-2-butanone developed by Kuwahara et al.

By applying the above procedure, in which dipeptide acid **174** was pre-activated with coupling reagent, HOBt/HBTU in dry THF, followed by treatment with solution of dipeptide amine salt **175**, $NaHCO_3$ and $MgSO_4$ in CH_3CN at 0 ^oC to room temperature. The tetrapeptide **173** was obtained in 95 % yield after four days reaction time (Scheme 42). Catalytic hydrogenation of **173** in EtOH afforded tetrapeptide acid **181**.



174 **175**

Reagent and condition: a) HOBt/HBTU, $MgSO_4$ (5 equiv.), $NaHCO_3$ (1 equiv.), THF:CH_3CN (1:1) (b) Pd/C, H_2, EtOH, 6 h

Scheme 42: Synthesis of α,γ- tetrapeptide **173** and α,γ- tetrapeptide acid **181**

4.4 Structural investigations of α,γ- tetrapeptide acid 181

Circular dichorism (CD) is based on the differential in absorption of let-handed and right handed circularly polarized light. Therefore, the spectra of chromophores can be positive and negative bands in the observed wavelength range (far UV). The spectra is displayed using mean residue weight ellipticity [Θ].

The amide chromophore (restricted rotation) in peptides or proteins are due to the low energy n $\longrightarrow \pi^*$ transition and higher energy $\pi \longrightarrow \pi^*$ transition. Therefore bonds such as RC_α-NH (ϕ) bond and CO- C_α (ψ) are responsible for the CD spectra.

The observed bands in the CD spectra can be used as a primary indicator to predict the secondary structure in peptides or proteins. Each secondary structures will gives specific CD spectrum such as β-turn, β–sheet, α-helix and random coil as depicted in Figure 12.

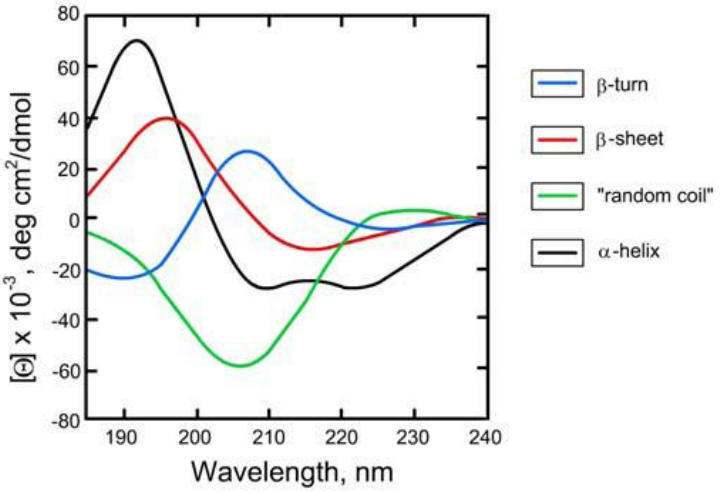


Figure 12 : CD spectra of the common secondary structures[16]

In β-turns (Figure 13), peptides with four amino acid residues connected by the amide bond. Secondary structure of peptide with β-turns occurs when hydrogen bonds are forming between the C=O backbone and NH ($i + 3$).

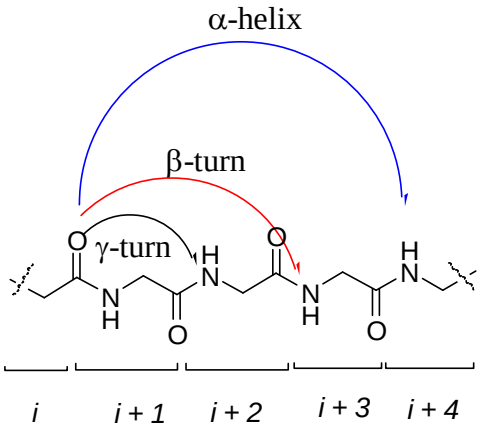


Figure 13 : Schematic representation of the intramolecular hydrogen bond

Secondary structure with γ-turn occurs when hydrogen bonding is forming between the C=O group of one residue and the NH of the (*i + 2*). Whereas α-helix is defined by the formation of hydrogen bonding between the C=O group of one residue and the NH of the (*i + 4*).

The *α,γ*- tetrapeptide acid **181** was characterized by CD spectroscopy in methanol. The CD spectrum was positive between 198 nm and 260 nm, with crossover at 218 nm. Two negative bands were observed in **181**, centered at 203 nm and 213 nm with crossover at 198 nm as depicted in Figure **14**. This was the result of exiton splitting which lead to splitting of the $\pi \longrightarrow \pi^*$ transition. The CD spectrum results, allow us to suggest that *α,γ*- tetrapeptide acid **181** was able to induce a stable helical conformation with a well-defined arrangement of the side chains.

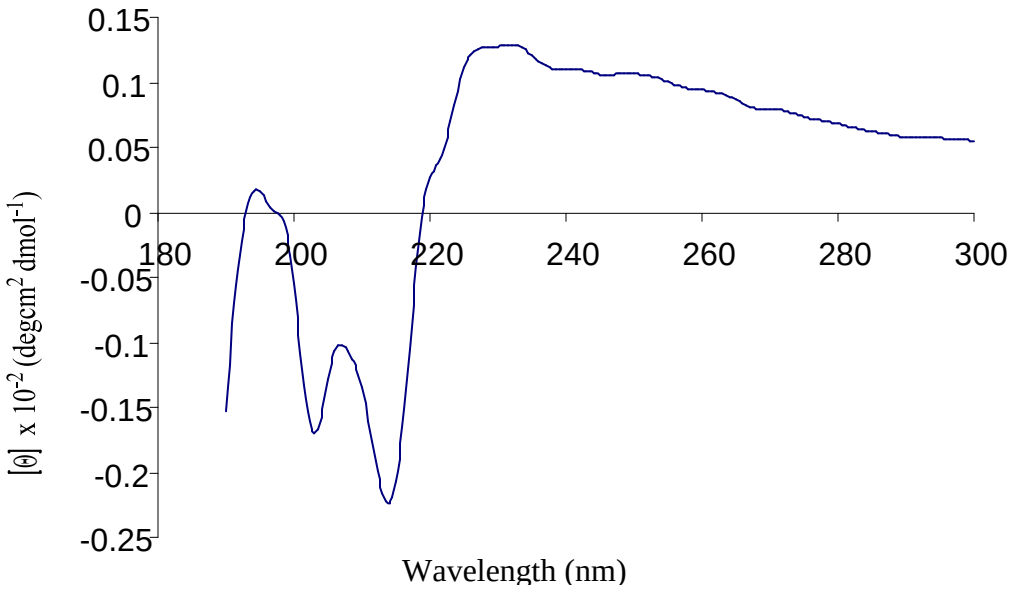


Figure 14: CD spectra α,γ- tetrapeptide acid **181** in methanol

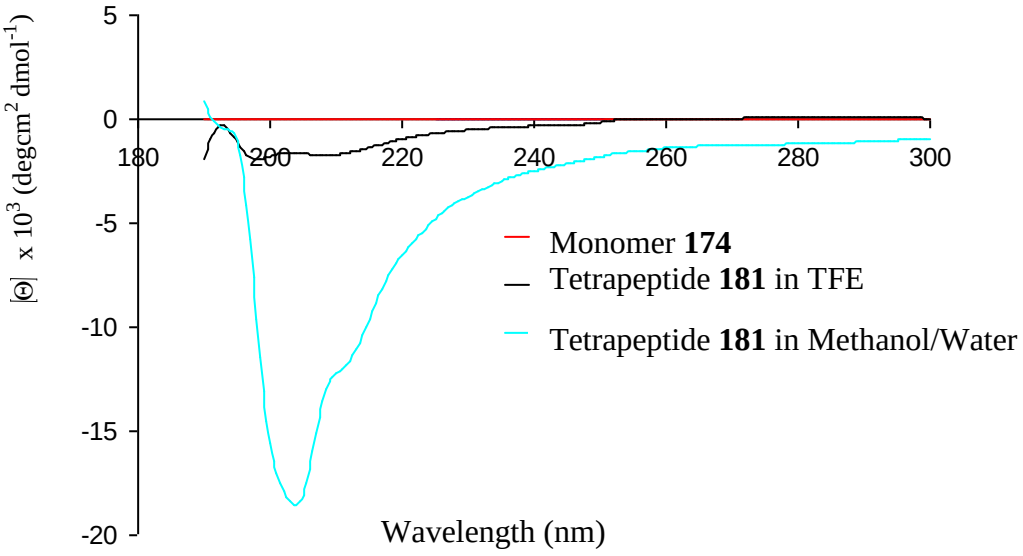
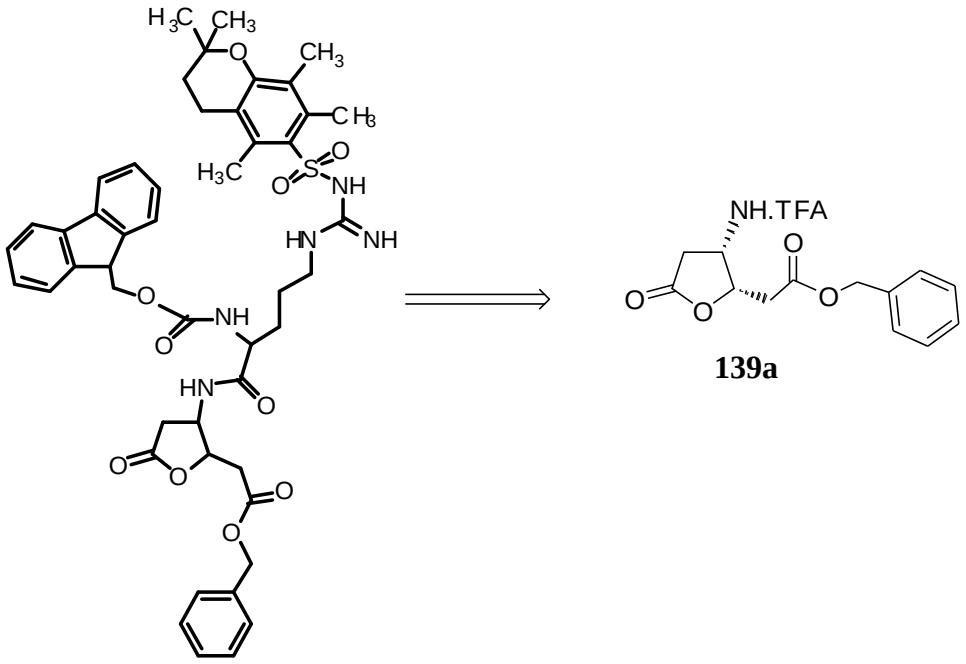


Figure 15: CD spectra of monomer 175 in methanol and α,γ- tetrapeptide acid **181** in methanol, TFE and methanol/water. All compounds were measured at the concentration of 0.3 mM.

In order to see if the conformational properties of α,γ- tetrapeptide acid **181** is dependent on the solvent, the CD spectra of the α,γ- tetramer acid dissolved in TFE and methanol/water were recorded. In TFE, a well-known secondary structure stabilizer, two negative bands were observed, centered at 210 nm and 197 nm, with crossover at 192 nm. The band shape remained the same in methanol. Changing TFE with methanol/water, increased the intensity of the negative band centered at 204 nm with a crossover at 190 nm. The exciton splitting was observed for the α,γ- tetrapeptide acid **181** dissolved in methanol or TFE, but disappeared in methanol/water, suggesting that a more open conformation was observed (Figure 15). The CD intensity was reduced especially in methanol/water rather than TFE. This might due to their ability to form more favourable hydrogen bonding.

5. The synthesis of NFmoc-Arginine-γ-butyrolactone dipeptide as a useful scaffold for NPY analogs

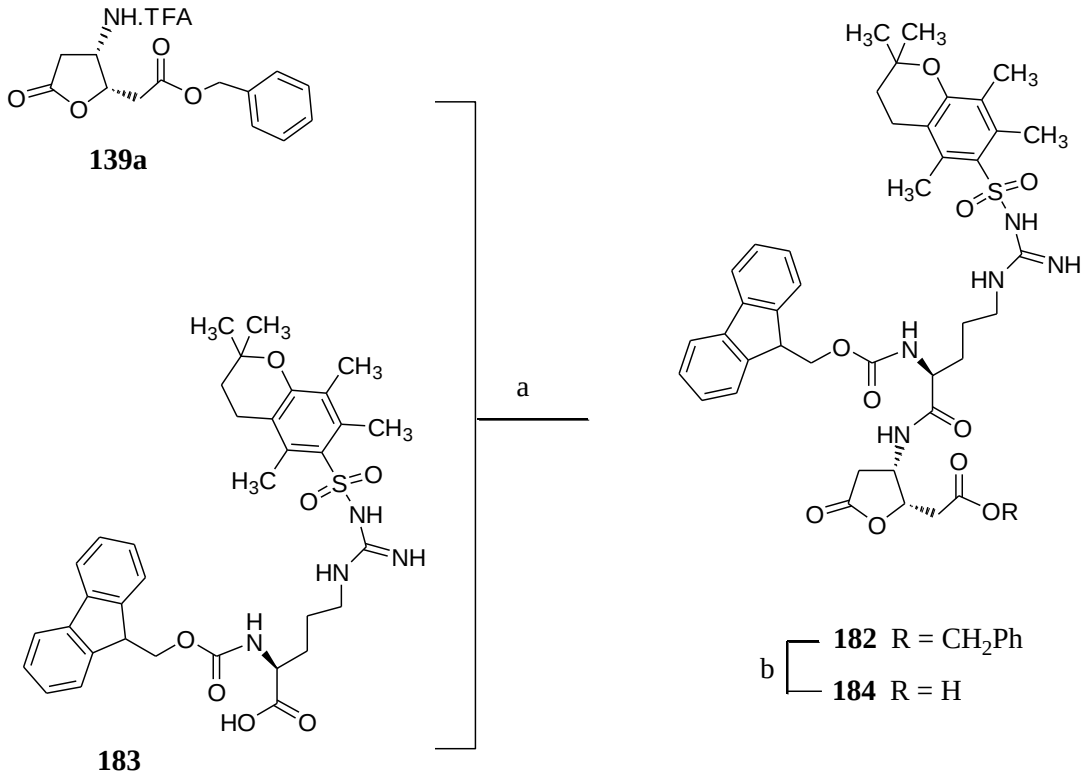
NFmoc-Arginine-γ-butyrolactone **182** was envisioned to be synthesized from **139a** in solution phase strategy (Scheme 43).



182 **139a**

Scheme 43: Retrosynthetic strategy of dipeptide **182.**

The ammonium salt **139a** was coupled with Fmoc-L-Arg(Pmc)-OH **183** in the presence of DIPEA using HOBt/HBTU in THF to yield the dipeptide **182** as depicted in Figure 17. Hydrogenation of the benzyl protected dipeptide **182** in EtOH in the presence of Pd/C (10 mol%) furnished *N*-Fmoc-Arginine-γ-butyrolactone acid **184** (Scheme 44).



Reagent and condition : a) HOBt/HBTU, DIPEA, THF, 68 % (b) Pd/C, H_2, EtOH, 6 h, 95 %.

Scheme 44: Synthesis of *N*-Fmoc-Arginine-γ-butyrolactone **182** and **183**

6. Conclusion

Azido acid bearing γ-butyrolactone scaffold **121,** could serve as useful building block for peptide synthesis either in solution phase nor solid phase protocols. We have synthesized for the first time, tetrapeptide **173** and dipeptide NFmocArg-γ-butyrolactone **182** in the solution phase protocol. With these results, a wide range of unnatural peptides can be synthesized which lead to the exploration of conformational study of foldamers which may demonstrate high stability, affinity and selectivity towards natural occurring peptides

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7. References

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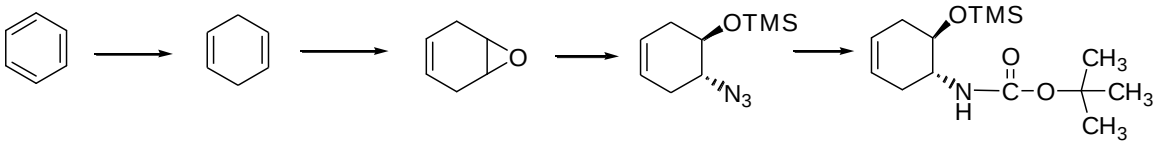
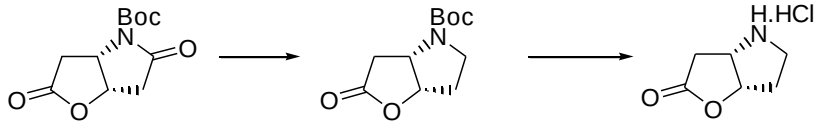
D. SUMMARY

5.1 Synthesis of (-) GWL

In this work, new methodology towards the synthesis of (-) GWL **36b** was synthesized in enantiomerically pure from benzene **69** in seven steps through lactonization of **65** as the key steps.



69 **68** **67** **66** **65**



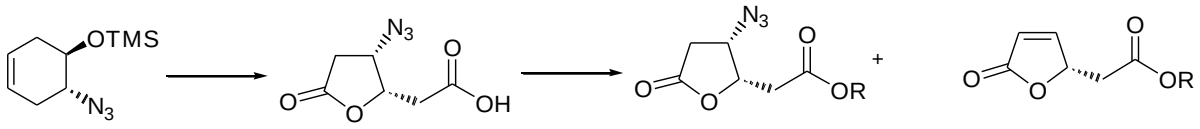
63a **75** **36b**

The key intermediate azido trimethylsiloxy cyclohexene **66**, was synthesized from benzene **69**. By birch reduction protocol, benzene **66** was transformed to 1,4-cyclohexadiene **68**, followed by *m*-CPBA epoxidation of **68** to afford epoxide **67**. Subsequently enantioselective asymmetric ring opening of the epoxide **67** catalyzed by salen Cr (III) complex **70** to give the azido trimethylsiloxy cyclohexene **66** (in 68%, 86% ee). Reduction amination of compound **66** furnished N-Boc protected amine **65**, which undergoes lactonization by ruthenium catalyzed oxidative cleavage of double bond to

give lactone lactam **63a**. Finally in two steps, (-)-GWL was obtained via chemoselective reduction of lactone lactam carbonyl group in **63** and deprotection of Boc group **75**.

5.2 Synthesis of *cis* γ-butyrolactone ester analogs

We have also developed a series of novel *cis* γ-butyrolactone ester analogs derived from azido carboxylic acid **121**.



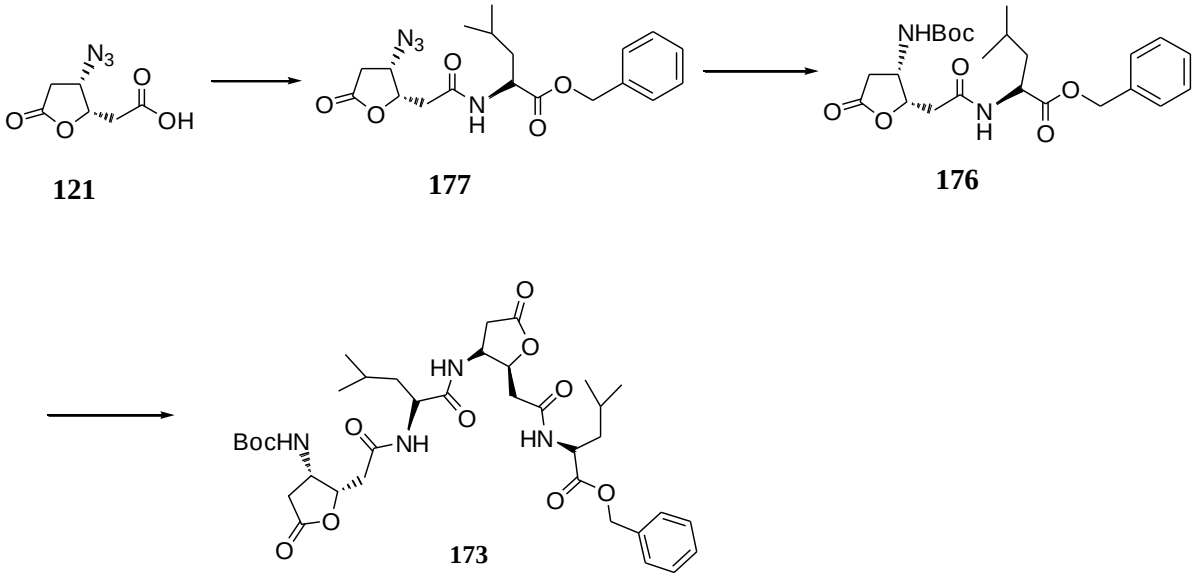
66 **121** **120, 127-139**

The key step was lactonisation of azido trimethylsiloxy cyclohexene **66** by ruthenium catalyzed oxidative cleavage of double bond to give azido carboxylic acid **121**. Treatment of compound **121** with several functionalized aromatic bromide under base condition or diazomethane or esterification with alkyl alcohol afforded *cis* γ-butyrolactone ester analogs

120,127-139. Most of the synthesized compounds (**129, 130, 131, 132, 133, 134, 135** and **136**) showed moderate MIC activities and compounds **130, 139** showed a very modest MIC value. The most active one among the synthesized analogs is compound **127**.

5.3 Synthesis of dipeptide and tetrapeptides

We have also successfully achieved the synthesis of novel dipeptide **176**, **177**, **182**,**184** and tetrapeptide **173**, **181**. Coupling of azido acid **121** and amine **178** using standard coupling procedure without base afforded dipeptide **177**. Subsequent reduction amination and protection in one step gave *N*-Boc protected dipeptide **176**. Coupling of free carboxylic acid **174** and amine salt **175** using standard coupling method furnished tetramer **173**, which could be transformed into their corresponding acid **181** by catalytic hydrogenation of **173**. In the forward sense, *N*-Fmoc-Arginine-γ-butyrolactone **182** also could be envisioned from **139a** using the same protocols.



Experimental Part

1. Instruments and general techniques

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

^{13}C NMR-Spectra were on 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 ($CDCl_3$, 77.0 ppm), dimethlsulfoxide (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, HMBC, HSQC) were recorded on Bruker Avance 600 (600 MHz).

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

IR-Spectra were recorded on a Bio-Rad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System.

Mass spectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. High resolution mass spectroscopy (HRMS): The molecular formula was proven by the calculated mass.

Optical rotation was measured at rt on a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm or 0.1 dm cell.

CD-Spectra were measured on a JASCO model J-710/720 at the institute of Bioanalytic and Sensoric, University of Regensburg at 21 ^{o}C between 300 and 180 nm in the specific solvent, the number of scans ranging from 5 to 10. The length of the cylindrical cuvettes was 1.0 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 (degcm^{2} dmol^{-1}). The spectra were smoothed by the adjacent averaging algorithm with the Origin 6.0 program.

X-ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH).

Antituberculosis assay was performed in the Institute for Tuberculosis Research, College of Pharmacy, University of Illinois, Chicago, USA.

Mycobacterium tuberculosis. The inhibitory activity of fractions and compounds against M. tuberculosis was determined using the microplate Alamar Blue assay and the low oxygen-recovery assay. Virulent H37Rv strain was used in both assays.

Cytotoxicity was evaluated using green monkey kidney cells (Vero). Cell viability was measured using the CellTiter 96 aqueous nonradioactive cell proliferation assay.

Chiral HPLC was performed in the Institute of Organic Chemistry, University of Regensburg on a Kontron Instruments 325 System (HPLC 335 UV detector, λ = 254 nm, Chiracel OD/OD-H, OJ as chiral stationary phase.

Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualization was accomplished by UV-light (wavelength λ = 254 nm), vanillin/sulphuric acid and ninhydrin stain.

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

Solvents were performed according to standard laboratory methods. THF, diethyl ether, ethanol and DMF were distilled before used. Dichloromethane was distilled over calcium hydride. Methanol or ethanol was refluxed with Mg/I_2 for 3 h, distilled and stored under nitrogen over 4 ^{o}A molecular sieves. Acetic anhydride was refluxed with P_2O_5 for 2 h, distilled and stored under nitrogen. All reactions with oxygen or moisture sensitive reactant were performed under nitrogen atmosphere.

1. Synthesis of compounds

2.1 (-)-Geissmann Weiss Lactone (GWL)

68

Cyclohexa-1,4-diene (**68**)

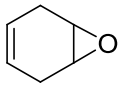
To a two liter three neck round bottom flask equipped with mechanical stirrer and under N_2 atmosphere was flowed in 750 mL ammonia at -78 ^{o}C. With vigorously stirred, dry benzene 100 mL (88.2 g, 1.13 mol) was added slowly using dropping funnel into the liquid ammonia until white precipitate formed.

Sodium metal (40 g) was then added in small quantities within 1 h and the reaction mixture became deep blue during this periods. The mixture was allowed to stir for another 2 h. Ethanol (150 mL) was then added into the reaction mixture and the mixture was keep stirring for overnight.

500 mL cooled H_2O was added into white precipitate solution, slowly by dropping funnel.

The organic layer was collected and washed with 500 mL H_2O, the aqueous layer was extracted back with 50 mL of n-pentane and the combined organic layer was dried with $MgSO_4$, filtered to give 70.1 g (40.1%) of 1,4–cyclohexadiene (**68**).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.70 (s, 4H), 2.60 (s, 4H). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 128.3 (C=C), 124.4 (C=C), 25.8 (CH_2).

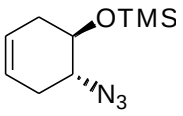


67

7-Oxabicyclo [4.1.0]hept-3-ene (**67**)

To a 1 liter round- bottom flask with a magnetic bar was charge with 1,4–cyclohexadiene **68** (3.38 g, 42.1 mmol, 1.1 equiv.), 300 mL of DCM and K_2HPO_4 (3.61 g, 20.7 mmol, 1equiv.) in 2 mL of H_2O. The flask was placed in ais bath (0 ^oC) and *m*-CPBA (70%, 10.2 g, 41.3 mmol, 1 equiv.) was added portion wise in small quantities. The white solution was stirred for several hours and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was stirred for another 18 h at room temperature. The white solid was filtered by vacum filtration and the filtrate was washed with 50 mL of saturated $NaHCO_3$, 50 mL of 5% Na_2SO_3, 50 mL of saturated $NaHCO_3$, water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated under vacuo to afford 3.58 g, (88.9%) of desired product as colourless oil . The product could be purified by distillation (23 mmHg, 60 ^oC).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.48 (s, 2H), 3.73 (s, 2H), 2.56 (d, *J*= 17.6, 2H), 2.45 (d, 2H, *J* = 17.6, 2H). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 121.6 (C=C), 51.3 (CH), 24.9 (CH_2). **IR** (Film): $\tilde{\nu}$ = 2993, 2891, 2824, 1429, 1349, 1214, 1183, 864, 737, 650 cm^{-1}.



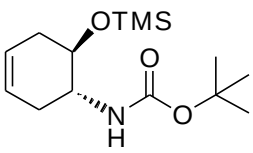
66

(1*R*,6*R*)-6- Azidocyclohex-3-enyloxy trimethylsilane (66)

To a mixture of epoxide **67** (0.61 g, 6.32 mmol, 1 equiv.) in 2.1 mL of Et_2O was added catalyst complex **70** (0.088 mg, 0.126 mmol, 2 mol%). The mixture was stirred for 15 minutes and subsequently trimethylsilylazide (0.88 mL, 6.63 mmol, 1.05 equiv.) was added slowly. After the mixture was stirred for 46 h at room temperature then the solvent was evaporated under reduced pressure to give yellowish crude product, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 9:1) to yield 0.84 g (68 %) of **66** as yellowish oil.

R_f = 0.83 (SiO_2, hexanes/ethyl acetate 9:1); $[\alpha]_D^{20}$ = -14.8 (c = 0.4, CH_2Cl_2), 86 % ee; (Lit[13a]: 72%, 81% ee)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.48-5.61 (m, 2H, C*H* Olefin), 3.73-3.84 (m, 1H, $(CH_3)SiOCH$), 3.49-3.59 (m, 1H, N_3CH), 2.32-2.48 (m, 2H, N_3CHCH_2), 2.08-2.20 (m, 1H, $(CH_3)SiOCHCH_2$), 1.90-2.03 (m, 1H, $(CH_3)SiOCHCH_2$), 1.98 (s, 9H, TMSO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 124.6 (C=C), 123.9 (C=C), 71.9 (C_{quart}), 62.9 (C_{quart}), 34.7 (CH_2), 30.9 (CH_2), 0.0 (TMSO-C); **IR** (Film): $\tilde{\nu}$ = 2957, 2905, 2107, 1438, 1250, 1140, 881, 840, 748, 667 cm^{-1}. **MS** [CI, NH_3]: m/z (%) = 212.1 (11) [M + H^+], 184.1 (29.9) [(M + H^+) – N_2].



65

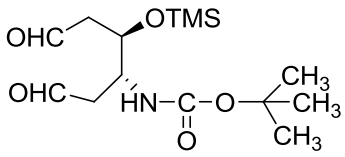
***tert*-Butyl (1*S*,6*S*)-6-(trimethylsilyloxy) cyclohex-3-enylcarbamate** (**65**)

To a stirred mixture of azido trimethylsiloxy cyclohexene **66** (0.2 g, 1.02 mmol, 1 equiv.) in 3.4 mL ethanol, was added *tert*-butoxycarbonyl (Boc_2O) (0.45 g, 2.04 mmol, 2 equiv.) and 20% $Pd(OH)_2/C$ (10.2 mg) at room temperature. Then to this mixture, triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.) was added sequentially and the mixture was stirred for 20 h under N_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated under reduce pressure to remove the solvent to give yellowish solid which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 15:0.5) to yield 0.26 g (88%) of **65** as yellowish solid and 0.017 mg (8%) of **16** as white solid.

R_f = 0.75 (SiO_2, hexanes/ethyl acetate 21:7) m.p. 79-81 °C $[\alpha]_D^{20}$ = +35.5 (c = 0.4, CH_2Cl_2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.46-5.57 (m, 2H, C*H* olefin), 4.45 (bs, IH, NH), 3.67-3.76 (m, 1H, C*H*OSi$(CH_3)_3$), 3.53-3.65 (m, 1H, C*H*NBoc), 2.55 (m, 1H, CH_2CHNBoc), 2.26 (m, 1H, CH_2CHNBoc), 2.05 (m, 1H, CH_2CHOSi$(CH_3)_3$), 1.88 (m, 1H, (CH_2CHOSi$(CH_3)_3$), 1.48 (s, 9H, Boc), 0.90 (s, 9H, TMSO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 155.5 (CO, Boc), 124.2 (C=C), 78.9 (C_{quart}, *C*HOTMS) ,68.9 (C_{quart}, Boc-C), 50.8 (C_{quart}, *C*HNBoc), 32.9 (*C*H_2CHOTMS), 29.9 (*C*H_2CHNBoc), 28.2 (Boc-C), 0.0 (TMSO-C); **IR** (Film): $\tilde{\nu}$ = 3340, 2976, 1689, 1531, 1366, 1309, 1249, 1170, 1102, 1067, 887, 840, 749, 661 cm^{-1}.

MS [CI, NH_3] m/z (%) = 285.1 (100); **HRMS** (Cl, NH_3); Calculated for [$C_{14}H_{27}NO_3Si$: 285.1760, found 285.1758.



64

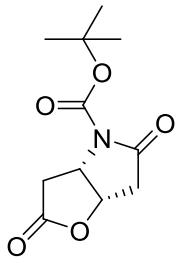
***tert*-Butyl(3*R*,4*R*)-1,6-dioxo-4-(trimethylsiloxy)hexan-3-ylcarbamate(64)**

To a stirred solution of *N*-Boc-trimethylsiloxy cyclohexene amine (1.016 g, 3.56 mmol, 1 equiv.), $NaHCO_3$ (0.03 g, 0.36 mmol, 0.1 equiv.) and methanol (0.36 ml, 8.9 mmol) in DCM (4.5 mL) was treated with ozone at -78 ^oC. Subsequently, dimethyl sulfide (0.54 mL, 7.33 mmol) was added and the reaction mixture was allowed to warm up to room temperature and stirred for 12 h at room temperature. Then, the mixture was extracted with water for three times (6 mL of water each), dried over MgSO4, filtered and concentrated under reduce pressure to give the crude dialdehyde, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate, 15 : 3) to afford 0.70 g (62.0%) of **64** as colorless oil.

R_f = 0.24 (SiO_2, hexanes/ethylacetate 15:3); $[\alpha]_D^{20}$ = +20.5 (c = 0.4, CH_2Cl_2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.78 (t, 1H, C*H*O), 9.72 (t, 1H , C*H*O), 5.41 (d, 1H, *J* = 4.1, NH), 4.63-4.74 (m, 1-H, (CH_3)SiOC*H*), 4.38-4.51 (m, 1-H, BoCNHC*H*), 2.60-2.78 (m,

1H, $(CH_3)SiOCHCH_2$), 2.35-2.45 (m, 1H, $(CH_3)SiOCHCH_2$), 2.02-2.42 (m, 1H, $BoCNHCHCH_2$), 1.81-1.98 (m, 1H, $BoCNHCHCH_2$), 1.49 (s, 9-H, BoC), 0.11 (s, 9-H, TMSO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 221.7 (2CHO), 154.1 (CO, BoC), 73.3 (C_{quart}, Boc-C), 70.2 (C_{quart}, TMSOC), 56.9 (C_{quart}, Boc-NHC), 42.3 (Boc-$NHCHCH_2$), 41.3 ($TMSOCHCH_2$), 28.6 (Boc-C), 0.0 (TMSO-C); **MS** [CI, NH_3] : m/z (%) = 259.1 (45), 159.1 (100) [$M - C_4H_8 + CO_2$].



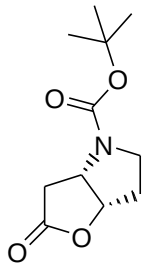
63a

(3*aS*, 6*aS*)-*tert*-Butoxycarbonyl-cis-dihydrofuro(3,2-b) pyrrole-2,5-dione (63a)

To a stirred solution of **65** (0.530 g, 1.8 mmol) in 55 mL of biphasic solution of CCl_4:MeCN:H_2O (1:1:2) was added $RuCl_3.3H_2O$ (0.032 g, 8.3 mol%) at 0 ^oC, followed by $NaIO_4$ (1.588 g, 4.1 equiv.) portion wise. The reaction mixture was stirred for 8 h at 0 ^oC. Then the mixture was diluted with 30mL of water and extracted with DCM (15 mL x 3), followed by 1-butanol (15 mL x 3). The combined organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give brownish crude product, which was purified by column chromatography on silica gel (ethyl acetate:methanol, 9:1) to yield 0.268 g (62 %) of **63a** as a white solid.

R_f = 0.71 (SiO_2, ethylacetate/methanol 9:1); m.p. 162-164 °C (lit[10], m.p 163-164 °C), $[\alpha]_D^{20}$ = +53.8 (c = 0.4, DMF) (lit[10], $[\alpha]_D^{20}$ = +61.7 (c = 1, DMF)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.01-5.09 (ddd, *J* = 5.1, 5.5, 2.7, 1H, C*H*OCO), 4.74-4.81 (ddd, *J* = 4.8, 6.0, 2.2, 1H , C*H*NBoc), 2.89-2.98 (m, 4H,CH_2CONBoc, CH_2CHNBoc), 1.51 (s, 9H, BoC); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 173.7 (C_{quart}, CO), 169.8 (C_{quart}, CONBoc), 149.8 (C_{quart}, CO-Boc), 84.7 (*C*HOCO), 73.5 (C_{quart}, Boc-C), 57.9 (*C*HNBoc), 38.6 (*C*H_2CONBoc), 35.6 (*C*H_2NBoc), 28.0 (Boc-C); **IR** (Film): $\tilde{\nu}$ = 1781, 1768, 1721, 1356, 1324, 1251, 1225, 1186, 1149, 1047, 1022, 933, 907, 836 cm^{-1}.**MS** [CI, NH_3] : m/z (%) = 259.1 (44) [M + NH_4^+]; Elemental analysis calcd (%) for $C_{11}H_{15}NO_5$ (241.1): C 54.9, H 6.3, N 5.9 ; found C 54.99, H 6.36, N 5.44.



75

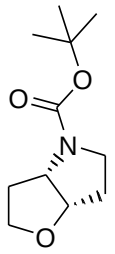
(3*aS*,6*aS*)-*tert*-Butyl 2- oxotetrahydro-2*H*-furo(3,2-b) pyrrole-4(5*H*) carboxylate (75)

To a stirred solution of **63** (0.10 g, 0.41 mmol) in 10 ml dry THF was added borane DMS (0.12 mL, 1.24 mmol, 3 equiv.) dropwise at 0 ^oC to room temperature, then the mixture was leaved stirred for 17 h under N_2 atmosphere. MeOH (2 mL) was added until no evolution of gas, then the solvent was removed by rotary evaporator (repeated 3 times). Organic layer

was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give white solid product, which was purified by column chromatography on silica gel (ethyl acetate:methanol, 4:6) to yield g 0.056 g (53%) of **75** as white solid and side product **79** (10 mg) 11% also as white solid.

R_f = 0.57 (SiO_2, hexane/ethyl acetate 4:6); m.p. 105-107°C, lit[23]: 106-107°C; $[\alpha]_D^{20}$ = +95.0 (c = 0.4, MeOH), lit[23]: $[\alpha]_D^{20}$ = +96.0 (c = 0.4, MeOH)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.01-5.10 (m, 1H, C*H*OCO), 4.38-4.50 (m, 1H, C*H*NBoc), 3.61-3.86 (m, 1H, CH_2NBoc), 3.29-3.42 (m, 1H, CH_2NBoc), 2.72-2.88 (m, 2H, CH_2CHNBoc), 2.28-2.40 (dd, *J* = 14, 6.2 Hz, 1H, CH_2CHO), 1.96-2.12 (m,1H, CH_2CHO), 1.45 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 176.45 ((C_{quart}, CO), 154.52 (C_{quart}, CO-Boc), 83.12 (*C*HOCO), 80.52 ((C_{quart}, Boc-C), 57.87 (*C*HNBoc), 44.26 (*C*H_2NBoc), 36.64 (*C*H_2COO), 30.70 (*C*H_2CHO), 28.42 (Boc-C);); **IR** (Film): $\tilde{\nu}$ = 2978, 2933, 2872, 1766, 1698, 1394, 1366, 1230, 1160, 1116, 1092, 1036, 982, 904, 843, 774 cm^{-1}. **MS** [CI, NH_3] : m/z (%) = 227.1 [M^+].

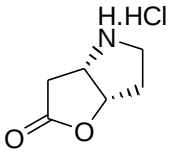


79

(3*aS*,6*aS*)-*tert*-Butyl tetrahydro-2*H*-furo(3,2-b) pyrrole-4(5*H*) carboxylate (79)

R_f = 0.42 (SiO_2, hexane/ethylacetate 4:6); m.p. 83-85 °C $[\alpha]_D^{20}$ = +10.8 (c = 0.4, CH_2Cl_2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.28-4.36 (m, 1H, C*H*OCH_2), 3.85-3.92 (bs, 1H, C*H*NBoc), 3.55- 3.72 (m, 2H, CH_2O), 3.20-3.35 (m, 2H, CH_2NBoc), 3.55-2.02 (m, 4H, CH_2CHO, CH_2CH_2O), 1.38 (s, 9H, Boc); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 155.88 (C_{quart}, CO-Boc), 79.97 (*C*HO), 70.66 (C_{quart}, Boc-C), 59.00 (*C*HNBoc), 57.84 (*C*H_2O), 43.49 (*C*H_2NBoc), 31.06 (*C*H_2CHNBoc), 30.75 (*C*H_2CHO), 28.43 (Boc). **IR** (Film): $\tilde{\nu}$ = 2976, 2938, 2888, 1650, 1410, 1366, 1251, 1162, 1128, 1068, 1013, 980, 866, 770 cm^{-1}. **MS** [CI, NH_3] : m/z (%) = 213.1 [M^+].



36b

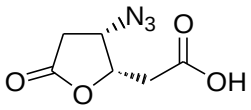
(3*aS*,6*aS*)-Hexahydro-2*H*-furo[3,2-b]pyrrol-2-one hydrochloride (36b)

To a compound **75** (31 mg, 0.14 mmol) was treated with saturated HCl in dry ethylacetate (8 mL) at 0 ^{o}C for 3 h. Then the solvent was removed in vacuo, dried on oil pump overnight to afford **36b** (68%) as a white solid.

R_f = (SiO_2, hexane/ethyl acetate 4:6); m.p. 181-183 °C, lit[23]: 182-184 ^{o}C; $[\alpha]_D^{20}$ = -40.0 (c = 0.4, MeOH), lit[23]: $[\alpha]_D^{20}$ = -42.0 (c = 0.4, MeOH)

^{1}H-NMR (300 MHz, DMSO): δ = 9.65 (bs, 2H, N*H*$_2$Cl), 5.15 (m, 1H, C*H*O), 4.34 (ddd, *J* = 1.6, 2.4, 1.9 Hz, 1H, C*H*N), 3.24-3.44 (m, 2H, C*H*$_2$N), 3.05-3.16 (m, 2H, C*H*$_2$COO), 2.02-2.20 (m, 2H, C*H*$_2$CH$_2$N); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 174.30 (C_{quart}, CO), 82.12 (*C*HO), 57.57 (*C*HN), 43.01 (N*C*H$_2$), 31.77 (*C*H$_2$COO), 30.57 (NCH$_2$*C*H$_2$). **IR** (Film): $\tilde{\nu}$ = 3300, 2923, 1771, 1723, 1389, 1201, 1165, 1108, 1039, 1023, 991, 906, 801, 670, 615, 582,543 cm^{-1}. **MS** [CI, NH_3] : m/z (%) = 113.1 [M^{+}].

2.2 *cis* (-)-γ-butyrolactone derivatives



121

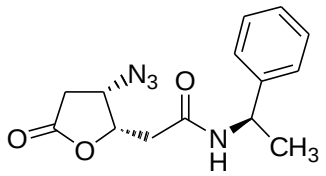
2-(2*S*,3*S*)- 3-Azido-5-oxotetrahydrofuran-2-yl) acetic acid (121)

To a stirred solution of **66** (2.73 g, 13.9 mmol) in 400 mL of biphasic solution of CCl_4: MeCN: H_2O (1:1:2) was added $RuCl_3.3H_2O$ (0.241 g, 8.3 mol%) at 0 ^oC, followed by $NaIO_4$ (12.256 g, 4.1 equiv.) portion wise. The reaction mixture was stirred for 19 h at 0 ^oC. Then the mixture was diluted with 30 mL of water and extracted with DCM (15 mL x 3), followed by 1-butanol (15 mL x 3). The combined organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give brownish crude product, which was purified by column chromatography on silica gel (ethyl acetate:methanol, 9:1) to yield 1.593 g (61 %) of **121** as yellowish solid. The product could be recrystallized by dissolving in (DCM:EtOAc, 1:1) to give pure azido carboxylic acid.

R_f = 0.33 (SiO_2, ethyl acetate/methanol 9:1); m.p. 126-128 °C $[\alpha]_D^{20}$= +15.6 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, DMSO): δ = 12.66 (s, 1H, OH), 4.88-4.95 (m, 1H, CH_2CHO), 4.65-4.72 (m, 1H, N_3CH), 3.15 (dd, *J* = 17.6, 6.4 Hz, 1H, N_3CHCH_2), 2.65-2.88 (dddd, *J* = 16.9, 6.2, 7.7, 7.7 Hz, 2H, CH_2COOH), 2.59 (dd, *J* = 17.7, 1.2 Hz, 1H, N_3CHCH_2); **^{13}C-NMR**

(75.5 MHz, DMSO): δ = 174.03 (C_{quart}, CO), 170.88 (C_{quart}, COOH), 78.29 (CH_2CHO), 60.12 (N_3CH), 35.56 (N_3CHCH_2), 34.28 (CH_2COOH); **IR** (Film): $\tilde{\nu}$ = 2920, 2098, 1776, 1717, 1409, 1356, 1283, 1215, 1187, 1158, 1064, 1020, 996, 919, 878, 785, 654 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 185.0; **HRMS** (Cl, NH_3); Calculated for [$C_6H_7N_3O_4$]: 185.0437, found 185.0440.



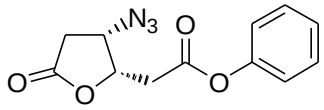
123

2-((2*S*,3*S*)-3- Azido-5-oxotetrahydrofuran-2-yl)-*N*-(1-phenylethyl)acetamide (123)

To a stirred solution of azido carboxylic acid **121** (30.0 mg, 0.16 mmol) in dry THF (2 mL) was added HOBt (24.1 mg, 1.1 equiv.), DCC (43.5 mg, 1.3 equiv.) and (*R)*-phenylethylamine (22.7 μL, 1.1 equiv.) at 0 ^{o}C. Then the ice bath was removed and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed by rotary evaporator. Then the white solid was dissolved in 5 mL EtOAc and filtered. The filtrate was washed with 1 M HCl (2 mL), saturated $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give white solid crude product, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 4:6) to yield 24.6 mg (55 %) of **123** as white solid.

R_f = 0.48 (SiO_2, petroleum ether: ethyl acetate, 4:6); $[\alpha]_D^{20}$ = +59.1 (c = 0.4, CH_2Cl_2)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.40 (m, 5H, Ph), 5.94 (bs, NH), 5.08-5.18 (m, 1H, CH_2CHO), 4.88-4.97 (m,1H, N_3CH), 4.59 (t, 1H, CH_3CHPh), 2.63-2.95 (m, 4H, CH_2CHN_3, CH_2CON); ^{13}C-NMR (75.5 MHz, DMSO): δ = 176.36 (C_{quart}, CO), 175.4 (C_{quart}, CO), 128.3 (C_{quart},Bz-C), 126.12 (Ph-C), 77.8 (CH_2CHO), 60.16 (CH_3CHPh), 49.19 (N_3CHCH_2), 36.05 (N_3CHCH_2), 33.97 (CH_2CON), 21.81 (CH_3). **IR** (Film): $\tilde{\nu}$ = 3300, 2929, 2111, 1777, 1645, 1541, 1260, 1196, 1152, 1018, 763, 700; MS [Cl, NH_3]: m/z (%) 306.1 [M + NH_4^+], 289.1 [M + H^+]; HRMS (Cl, NH_3); Calculated for [$C_{14}H_{16}N_4O_3$]: 288.1222, found 288.1222.



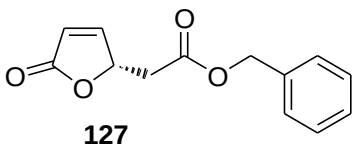
120

Benzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl) acetate (120)

To a stirred solution of azido carboxylic acid **121** (152 mg, 0.82 mmol) in dry DMF (6 mL) was added $NaHCO_3$ (414.0 mg, 6 equiv.), followed by benzyl bromide (157.0 μL, 1.6 equiv.) sequentially at room temperature. The reaction mixture was stirred for 43 h at room temperature. Then the mixture was diluted with 4 mL of EtOAc: H_2O (1:1) solution and the solution was separated. The aqueous layer extracted with EtOAc and the combined organic

layer was dried over by $MgSO_4$, concentrated under reduced pressure to give yellowish crude oil product, which was purified by column chromatography on silica gel (petroleum:ethyl acetate, 6:4) to yield 50.1 mg (69 %) of **120** as yellowish oil and side product **127,** 8.0 mg (12%) as white solid.

R_f = 0.51 (SiO_2, ethyl acetate/methanol 9:1); m.p. 76-78 °C $[\alpha]_D^{20}$ = +34.4 (c = 0.4, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.33-7.41 (m,5H, Ph), 5.17(s, 2H, C*H*$_2$Ph), 4.85-4.93 (m,1H, CH_2CHO), 4.52-4.58 (ddd, *J* = 1.4, 1.6, 1.4 Hz, 1H, N_3CH), 2.85-3.05 (m, 3H, C*H*$_2$CHN$_3$, C*H*$_2$COOBz), 2.68 (dd, *J* = 17.8, 1.4 Hz, C*H*$_2$CN$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.88 (C_{quart}, CO), 169.34 (C_{quart}, COOBz), 135.19 (C_{quart}, Bz), 128.72 (Ph-C), 128.61 (Ph-C), 128.40 (Ph-C), 78.04 (CH_2CHO), 67.08 (*C*H$_2$Ph), 59.61(*C*HN$_3$), 35.66 (*C*H$_2$CHN$_3$), 34.26 (*C*H$_2$COOBz); **IR** (Film): $\tilde{\nu}$ = 2100, 1776, 1717, 1421, 1396, 1342, 1311, 1275, 1196, 1151, 1121, 1031, 990, 937, 899, 741, 700 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 293.1 [M + NH_4^+]; **HRMS** (Cl, NH_3); Calculated for [$C_{13}H_{13}N_3O_4$]: 275.0906, found 275.0901.

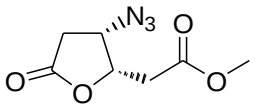


127

(*S*)-Benzyl 2-(5-oxo-2,5-dihydrofuran-2-yl) acetate (127)

R_f = 0.35 (SiO_2, petroleum ether/ethyl acetate 6:4); $[\alpha]_D^{20}$ = +47.6 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 5.6, 1.5 Hz, 1H, C*H*CHCO), 7.30-7.38 (m, 5H, Ph-H), 6.14 (dd, *J* = 5.8, 1.9 Hz, 1H, C*H*CO), 5.39-5.44 (m, 1H, C*H*CH_2CO), 5.16 (s, 1H, C*H*$_2$Ph), 2.88 (dd, *J* = 16.5, 7.3 Hz, 1H, C*H*$_2$COO), 2.68 (dd, *J* = 16.5, 7.1 Hz, 1H, C*H*$_2$COO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.29 (C_{quart}, COOBn), 168.80 (C_{quart}, CO), 155.38 (C=C), 135.16 (C_{quart}, Bn), 128.71 (Ph-C), 128.61 (Ph-C), 128.45 (Ph-C), 122.19 (C=C), 78.9 (*C*HCH_2CO), 67.13 (*C*H$_2$-Ph), 37.81 (*C*H$_2$COO); **IR** (Film): $\tilde{\nu}$ = 1760, 1730, 1498, 1456, 1389, 1335, 1268, 1155, 1108, 1080, 1041, 923, 815, 739, 697 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 232.1; **HRMS** (Cl, NH_3); Calculated for [$C_{13}H_{12}O_4$]: 232.0736, found 232.0732.

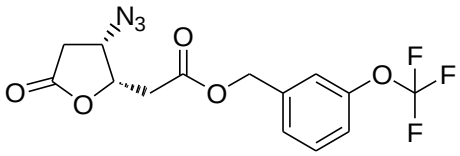


128

Methyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (128)

To a stirred solution of azido carboxylic acid **121** (100 mg, 0.54 mmol) in dry Et_2O (5 mL) was added freshly prepared diazomethane (5 mL in diethyl ether) (in excess) at 0 ^oC to room temperature, then the mixture was leaved stirred for overnight. The reaction mixture was diluted with 5 mL of diethyl ether and subsequently, 10% of aqueous acetic acid was added to remove an excess of diazomethane. The layer was separated and the aqueous layer was extracted with diethyl ether (5 mL x 3) and the combined organic layer was washed with saturated $NaHCO_3$, dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give brownish crude product, which was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 6:4) to yield 99.1 mg (92 %) of **128** as yellowish oil.

R_f = 0.53 (SiO_2, petroleum ether/ethylacetate 6:4); $[\alpha]_D^{20}$ = +55.2 (c = 0.4, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$):): δ = 4.82-4.92 (m, 1H, CH_2CHO), 4.55 (ddd, 1.6,1.6, 1.6 Hz, 1H, CHN_3), 3.66 (s,3H, OCH_3), 2.94 (d, *J* = 6.7 Hz, 1H, CH_2CHN_3), 2.82-2.88 (m, 2H, CH_2COOCH_3), 2.62 (dd, *J* = 17.8, 1.4 Hz, 1H, CH_2CHN_3); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.05 (C_{quart}, CO), 168.96 (C_{quart}, COOMe), 77.11 (CH_2CHO), 58.66 (OCH_3), 51.22 (CH_2CHN_3), 34.66 (CH_2CHN_3), 32.99 (CH_2COOMe); **IR** (Film): $\tilde{\nu}$ = 2958, 2107, 1787, 1732, 1438, 1280, 1151, 1023, 999, 667, 553cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 217.0 [M + NH_4^+] ; **HRMS** (Cl, NH_3); Calculated for [$C_7H_9N_3O_4$: 199.0422 , found 199.0593.



129

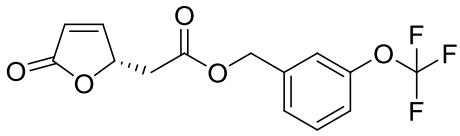
3-(Trifluoromethoxy)benzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (129, $CDCl_3$)

To a stirred solution of azido carboxylic acid **121** (60.0 mg, 0.32 mmol) in dry DMF (2 mL) was added $NaHCO_3$ (163.0 mg, 6 equiv.), followed by trifluoromethoxy benzyl bromide (84.0 μL, 1.6 equiv.) sequentially at room temperature. The reaction mixture was stirred for 48 h at room temperature. Then the mixture was diluted with 4 mL of DCM: H_2O (1:1) solution and the solution was separated. The aqueous layer extracted with DCM and the combined organic layer was dried over by $MgSO_4$, concentrated under reduced pressure to give yellowish crude oil product, which was purified by column chromatography on silica gel (petroleum:ethyl acetate, 6:4) to yield 62.1 mg (54 %) of **121** as yellowish oil and side product **130** 8.0 mg (3%) as yellowish oil.

R_f = 0.45 (SiO_2, petroleum:ethylacetate 6:4); $[\alpha]_D^{20}$ = +19.3 (c = 0.3, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.37-7.45 (dd, *J* = 7.8, 7.7 Hz, 1H, Ar), 7.25-7.34 (dd, *J* = 7.3, 3.8 Hz, Ar), 7,16-7.24 (m, 2H, Ar), 5.18 (s, 2H, C*H*$_2$Ar), 4.55-4.95 (m,1H, CH_2CHO), 4.51-4.59 (m, 1H, N_3CH), 2.87-3.06 (m, 3H, CH_2CHN_3, CH_2COOBz), 2.68 (dd, *J* = 17.9, 1.3 Hz, CH_2CN_3); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.84 (C_{quart}, CO), 169.23 (C_{quart}, COOAr), 149.40 (C_{quart}, Ar), 137.49 (C_{quart}, Ar), 130.16 (Ar-C), 126.46 (C_{quart},CF_3), 122.13 (Ar-C), 120.91 (Ar-C) 120.66 (Ar-C), 77.91 (CH_2CHO), 65.96 (CH_2Ph), 59.54 (CHN_3),

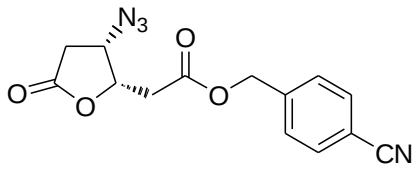
35.57 (CH_2CHN_3), 34.20 (CH_2COOAr); **IR** (Film): $\tilde{\nu}$ = 2110, 1784, 1737, 1428, 1313, 1144, 1022, 867, 797, 701, 633 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 359.00 [$M^{+\cdot}$]; **HRMS** (Cl, NH_3); Calculated for [$C_{13}H_{13}N_3O_4$]: 359.0729, found 359.0737.



130

(*S*)-3-(Trifluoromethoxy)benzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (130, $CDCl_3$)

R_f = 0.40 (SiO_2, petroleum ether/ethylacetate 6:4); $[\alpha]_D^{20}$ = +75.0 (c = 0.15, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.57-7.68 (dd, *J* = 5.8, 1.6 Hz, 1H, C*H*CHCO), 7.30-7.38 (m, 1H, Ar-H), 7.27-7.32 (m, 1H, Ar-H), 7.17-7.24 (m, 2H, Ar-H), 6.14-6.20 (dd, *J* = 5.6, 2.0 Hz, 1H, C*H*CO), 5.36-5.46 (m, 1H, C*H*CH_2CO), 2.88-3.14 (dd, *J* = 16.5, 7.3 Hz, 1H, C*H*$_2$COO), 2.66-2.70 (dd, *J* = 16.6, 7.3 Hz, 1H, C*H*$_2$COO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 170.7 (C_{quart}, COOAr), 168.60 (C_{quart}, CO), 160.18 (C_{quart}, Ar), 155.05 (C_{quart}, olefin) (130.19 (C_{quart}, Ar), 126.55 (Ar-C), 122.39 (C=C), 120.98 (Ar-C), 78.9 (*C*HCH_2CO), 66.09 (*C*H_2-Ar), 37.77 (*C*H_2COO); **IR** (Film): $\tilde{\nu}$ = 1809, 1738, 1453, 1389, 1247, 1213, 1151, 1110, 1081, 1042, 1002, 863, 818, 795, 703, 634 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 334.06 [M + NH_4^+]; Elemental analysis calcd (%) for $C_{14}H_{11}F_3O_5$ (316.23): C 53.17, H 3.51, F 18.02; found C 54.19, H 4.13, F 17.99. **HRMS** (Cl, NH_3); Calculated for [$C_{14}H_{11}F_3O_5$]: 316.0559, found 316.0560.



131

4-Cyanobenzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (131, $CDCl_3$)

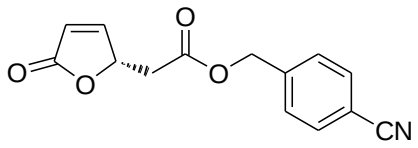
To a stirred solution of azido carboxylic acid **121** (60.0 mg, 0.32 mmol) in dry DMF (2 mL) was added $NaHCO_3$ (181.0 mg, 4 equiv.), followed by 4-bromo methyl benzonitrile, (102.0 mg, 1.6 equiv.) sequentially at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 24 h. Then the mixture was diluted with 4 mL of DCM: H_2O (1:1) solution and the solution was separated. The aqueous layer extracted with DCM and the combined organic layer was dried over by $MgSO_4$, concentrated under reduced pressure to give yellowish crude oil product, which was purified by column chromatography on silica gel (petroleum:ethyl acetate, 6:4) to yield 58.0 mg (60%) of **131** as yellowish oil and side product **132** 3.0 mg (4%) as yellowish oil

R_f = 0.20 (SiO_2, petroleum: ethyl acetate 6:4); $[\alpha]_D^{20}$ = +20.0 (c = 0.2, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.62-7.69 (dd, *J* = 8.23, 1.7 Hz, 2H, Ar), 7.42-7.49 (dd, *J* = 8.51, 1.4 Hz, 2H, Ar), 5.21(s, 2H, C*H*$_2$Ar), 4.86-4.95 (m,1H, CH_2C*H*O), 4.54-4.59 (m, 1H, N_3C*H*), 2.87-3.06 (m, 3H, C*H*$_2$CHN_3, C*H*$_2$COOAr), 2.68 (dd, *J* = 18.11, 1.4 Hz, C*H*$_2$CN_3);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 172.81 (C_{quart}, CO), 169.20 (C_{quart}, COOAr), 140.49

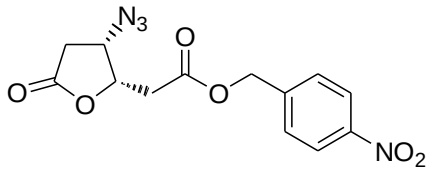
(C_{quart}, Ar), 132.50 (Ar-C), 128.82 (Ar-C), 118.49 (C_{quart}, Ar), 112.26 (CN), 77.80 (CH_2CHO), 65.70 (CH_2Ar), 59.51 (CHN_3), 35.56 (CH_2CHN_3), 34.24 (CH_2COOAr); **IR** (Film): $\tilde{\nu}$ = 2229, 2109, 1782, 1734, 1412, 1345, 1268, 1147, 1020, 928, 818, 735, 710, 547 cm^{-1}. MS [Cl, NH_3]: m/z (%) 300.0 [$M^{+\cdot}$]; HRMS (Cl, NH_3); Calculated for [$C_{14}H_{12}N_4O_4$]: 300.0859, found 300.0863.



132

(*S*)-4-Cyanobenzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (132, $CDCl_3$)

R_f = 0.16 (SiO_2, petroleum: ethylacetate 6:4); m.p. 72-74 °C $[\alpha]_D^{20}$ = +40.6 (c = 0.2, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.61-7.65 (dd, *J* = 8.00, 1.5 Hz, 2H, Ar), 7.60-7.77 (d, *J* = 6.06, 1H, Olefin), 7.44-7.59 (dd, *J* = 8.45, 1.5 Hz, 2H, Ar), 6.15-6.23 (d, *J* = 7.06, 1H, Olefin), (5.21 (s, 2H, CH_2Ar), 5.41-5.62 (m,1H, CH_2CHO), 2.78-3.05 (m, 2H, CH_2CHN_3); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.31 (C_{quart}, CO), 154.22 (C_{quart}, COOAr), 132.50 (Ar-C), 128.82 (Ar-C), 112.26 (CN), 78.80 (CH_2CHO), 65.40 (CH_2Ar), 38.16 (CH_2CHN_3), 35.22 (CH_2COOAr); **IR** (Film): $\tilde{\nu}$ = 2924, 2229, 2200, 1738, 1612, 1389, 1270, 1158, 1109, 817, 548 cm^{-1}. MS [Cl, NH_3]: m/z (%) 257.0 [$M^{+\cdot}$]; HRMS (Cl, NH_3); Calculated for [$C_{14}H_{11}NO_4$]: 257.0690, found 257.0688.



133

4-Nitrobenzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (133, $CDCl_3$)

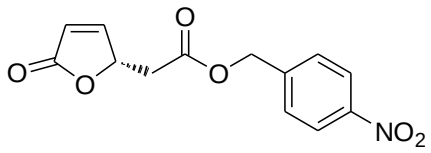
To a stirred solution of azido carboxylic acid **121** (50.0 mg, 0.27 mmol) in dry DMF (2 mL) was added $NaHCO_3$ (90.7 mg, 4 equiv.), followed by 4-nitro bromo benzyl (93.3 mg, 1.6 equiv.) sequentially at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature. Then the mixture was diluted with 4 mL of DCM: H_2O (1:1) solution and the solution was separated. The aqueous layer extracted with DCM and the combined organic layer was dried over by $MgSO_4$, concentrated under reduced pressure to give yellowish crude oil product, which was purified by column chromatography on silica gel (petroleum:ethyl acetate, 6:4) to yield 35.0 mg (41%) of **133** as white solid and side product **134** 7.0 mg (10%) as yellowish oil

R_f = 0.24 (SiO_2, petroleum:ethyl acetate 6:4); m.p. 80-82 °C $[\alpha]_D^{20}$ = +47.7 (c = 0.34, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21-8.34 (dd, *J* = 8.78, 1.6 Hz, 2H, Ar), 7.51-7.57 (dd, *J* = 8.78, 1.3 Hz, 2H, Ar), 5.27(s, 2H, C*H*$_2$Ar), 4.87-4.95 (m,1H, CH_2C*H*O), 4.55-4.60 (m, 1H, N_3C*H*), 2.87-3.06 (m, 3H, C*H*$_2$CHN_3, C*H*$_2$COOAr), 2.68 (dd, *J* = 17.8, 1.4 Hz, C*H*$_2$CN_3);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 172.67 (C_{quart}, CO), 169.19 (C_{quart}, COOAr), 147.86 (C_{quart}, Ar), 142.37 (C_{quart}, Ar), 128.72 (Ar-C), 123.93 (Ar-C), 77.80 (CH_2*C*HO), 67.08

(CH_2Ar), 59.48 (CHN_3), 35.56 (CH_2CHN_3), 34.22 (CH_2COOAr); **IR** (Film): $\tilde{\nu}$ = 2142, 2106, 1771, 1728, 1608, 1521, 1414, 1346, 1315, 1287, 1200, 1151, 1120, 992, 848, 741, 692 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 264.9 [M + $HCOO^-$]; **HRMS** (Cl, NH_3); Calculated for [$C_{13}H_{12}N_4O_6$]: 320.2611, found 320.2601.

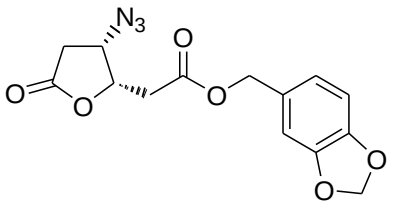


134

(*S*)-4-Nitrobenzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (134, $CDCl_3$)

R_f = 0.20 (SiO_2, petroleum ether/ethylacetate 6:4); $[\alpha]_D^{20}$ = +26.4 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.21-8.29 (dd, *J* = 8.78, 1.6 Hz, 2H, Ar), 7.61-7.64 (dd, 1H, *J* = 4.8, 1.7 Hz, 1H, C*H*CHCO), 7.52-7.58 (dd, *J* = 8.78, 1.4 Hz, 2H, Ar), 6.15-6.20 (dd, *J* = 5.8, 1.9 Hz, 1H, C*H*CO), 5.25 (s, 2H, CH_2Ar), 4.55-4.65 (m,1H, CH_2CHO), 2.87 (dd, *J* = 16.4, 7.3 Hz, 1H, CH_2COO), 2.69 (dd, *J* = 16.6, 7.1 Hz, 1H, CH_2COO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.58 (C_{quart}, CO), 169.19 (C_{quart}, COOAr), 154.87 (C_{quart}, Olefin), 147.86 (C_{quart}, Ar), 142.37 (C_{quart}, Ar), 128.72 (Ar-C), 123.95 (Ar-C), 122.52 (C_{quart}, Olefin), 78.65 (CH_2CHO), 65.57 (CH_2Ar), 34.22 (CH_2COOAr);; **IR** (Film): $\tilde{\nu}$ = 2109, 1738, 1606, 1519, 1345, 1270, 1152, 1110, 1024, 925, 849, 817, 739, 693 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 295.00 [M + NH_4^+]; Elemental analysis calcd (%) for $C_{13}H_{11}NO_6$ (277.23): C 56.32, H 4.04, N 5.05; found C 55.89, H 4.13, N 5.23.



135

Benzo[d][1,3]dioxol-5-ylmethyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (135, $CDCl_3$)

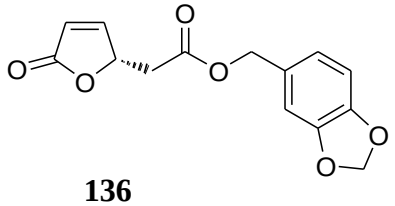
R_f = 0.34 (SiO_2, petroleum ether:ethyl acetate:6:41); m.p. 66-68 °C $[\alpha]_D^{20}$ = +52.7 (c = 0.15, CH_2Cl_2);

To a stirred solution of azido carboxylic acid **121** (50.0 mg, 0.27 mmol) in dry DMF (2 mL) was added $NaHCO_3$ (90.7 mg, 4 equiv.), followed by methylene dioxibromobenzene (185.0 mg, 1.6 equiv.) sequentially at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature. Then the mixture was diluted with 4 mL of DCM: H_2O (1:1) solution and the solution was separated. The aqueous layer extracted with DCM and the combined organic layer was dried over by $MgSO_4$, concentrated under reduced pressure to give yellowish crude oil product, which was purified by column chromatography on silica gel (petroleum:ethyl acetate, 6:4) to yield 42.0 mg (50%) of **135** as white solid and side product **136** 10.0 mg (14%) as yellowish oil.

R_f = 0.36 (SiO_2, petroleum ether:ethyl acetate:6:41); m.p. 66-68 °C $[\alpha]_D^{20}$ = (c = 0.35, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.76 (m, 3H, Ar), 5.98 (s, 2H, acetal-CH_2), 5.20 (s, 2H, CH_2Ar), 4.84-4.92 (m,1H, CH_2C*H*O), 4.52-4.56 (m, 1H, N_3C*H*), 2.86-3.12 (m, 3H,

CH_2CHN$_3$, CH_2COOAr), 2.64-2.72 (dd, J = 17.8, 1.4 Hz, CH_2CN$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.84 (C_{quart}, CO), 169.31 (C_{quart}, COOAr), 147.86 (C_{quart}, Ar), 128.72 ($C_{quart,}$ Ar-C), 122.60 (Ar-C), 109.16 (Ar-C), 108.35 (Ar-C), 101.29 (acetal-CH$_2$), 78.03 (CH$_2$$C$HO), 67.08 ($CH_2$Ar), 59.61 ($CHN_3$), 35.66 ($CH_2CHN_3$), 34.26 ($CH_2$COOAr); **IR** (Film): $\tilde{\nu}$ = 2132, 2098, 1777, 1720, 1501, 1443, 1411, 1348, 1311, 1276, 1249, 1191, 1150, 1121, 1029, 932, 823, 786 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 319.0 [$M^{+\cdot}$]; **HRMS** (Cl, NH_3); Calculated for [$C_{14}H_{13}N_3O_6$]: 319.0804, found 319.0850.

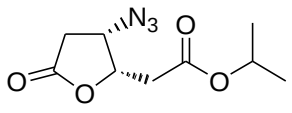


136

R_f = 0.31 (SiO_2, petroleum ether:ethyl acetate:6:4); $[\alpha]_D^{20}$ = +2.7 (c = 0.35, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.54-7.60 (dd, J = 5.6, 1.5 Hz,1H, CHCHCO), 6.75-6.79 (m, 3H, Ar), 6.16-6.18 (dd, J = 6.16, 2.0 Hz,1H, CHCO), 5.98 (s, 2H, acetal-CH_2), 5.38-5.45 (m,1H, CH$_2$CHO), 5.20 (s, 2H, CH_2Ar), 2.86-2.90 (dd, dd, J = 16.6, 7.3 Hz, 1H, CH_2COOAr), 2.64-2.72 (dd, J = 17.8, 1.4 Hz, CH_2COOAr); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.79 (C_{quart}, CO), 169.30 (C_{quart}, COOAr), 155.28 ($C_{quart,}$ olefin), 147.86 (C_{quart}, Ar), 128.72 ($C_{quart,}$ Ar-C), 122.60 (Ar-C), 122.2 ($C_{quart,}$ olefin), (109.21 (Ar-C), 109.17 (Ar-C), 109.16 (Ar-C), 101.29 (acetal-CH$_2$), 78.84 (CH$_2$$C$HO), 67.10 ($CH_2$Ar), 35.66 ($CH_2$COOAr); **IR** (Film): $\tilde{\nu}$ = 2132, 2098, 1777, 1720, 1501, 1443, 1411, 1348, 1311, 1276, 1249, 1191,

1150, 1121, 1029, 932, 823, 786 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 276.0 [$M^{+\cdot}$]; **HRMS** (Cl, NH_3); Calculated for [$C_{14}H_{12}O_6$]: 276.0634, found 276.0632.



137

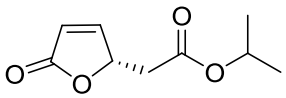
Isopropanol2-((2*S*,3*S*)-3- Azido-5-oxotetrahydrofuran-2-yl)-*N*-(1-phenylethyl)acetamide (137)

To a stirred solution of azido carboxylic acid **121** (50.0 mg, 0.27 mmol) in isopropanol (5 mL) was added concentrated H_2SO_4 (catalytic amount) and the reaction mixture was refluxed for 2 h. The solvent was removed by rotary evaporator. Then the reaction mixture was dissolved in CH_2Cl_2 (5 mL), washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give yellowish oily crude product, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 6:4) to yield 54.0 mg (90%) of **137** as colorless oil and side product 2 mg (5%) **138** as yellowish oil.

R_f = 0.62 (SiO_2, petroleum ether: ethyl acetate, 6:4); $[\alpha]_D^{20}$ = +17.7 (c = 0.4, CH_2Cl_2);

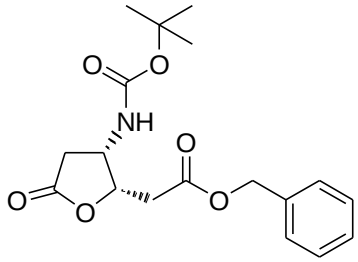
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.00-5.10 (m, 1H, C*H*CH_3), 4.83-4.92 (m, 1H, CH_2C*H*O), 4.54-4.60 (m, 1H, C*H*N_3), 2.63-2.95 (m, 4H, C*H*$_2$$CHN_3$, C*H*$_2$CON), 1.26 (d, *J* = 6.6 Hz,

C*H*$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.98 (C_{quart}, CO), 169.00 (C_{quart}, CO), 78.27 (CH_2*C*HO), 68.98 (C_{quart},CH_3-*C*), 59.78 (CH_2*C*HN_3), 35.73 (*C*H_2CHN_3), 34.52 (*C*H_2CHO), 21.74 (CH_3); **IR** (Film): $\tilde{\nu}$ = 2983, 2104, 1781, 1721, 1309, 1268, 1182, 1148, 1104, 1021, 962, 668, 548 **MS** [Cl, NH_3]: m/z (%) 228.1 [M + H^+]; **HRMS** (Cl, NH_3); Calculated for [$C_{14}H_{16}N_4O_3$]: 227.2172, found 227.0984.



138

R_f = 0.2 (SiO_2, petroleum ether: ethyl acetate, 6:4); $[\alpha]_D^{20}$ = +30.2 (c = 0.3, CH_2Cl_2); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.58-7.62 (dd, *J* =5.76, 1.4 Hz, 1H), 6.16-6.20 (dd, *J* = 5.62, 2.1 Hz, 1H), 5.32-5.44 (m, 1H, C*H*COO), 4.83-4.92 (m, 1H, CH_2C*H*O), 2.87- 29.2 (m, 1H, C*H*(CH_3)$_2$), 2.87-2.92 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.59-2.69 (dd, *J* = 16.3, 7.0 Hz, 1H) 1H, C*H*$_2$COO), 1.82-1.89(d, *J* = 6.6 Hz, C*H*$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 172.06 (C_{quart}, CO), 165.30 (C_{quart}, CO), 158.43 (C_{quart}, CO), 122.56 (CH-Olefin), 78.24 (CH_2*C*HO), 67.96 (C_{quart},CH_3-*C*), 30.91 (*C*H_2CHO), 21.04 (CH_3), 14.18 (CH_3); **IR** (Film): $\tilde{\nu}$ = 2983, 2104, 1781, 1721, 1680, 1268, 1182, 1148, 1104, 1021, 962, 668, 548 **MS** [Cl, NH_3]: m/z (%) 185.1 [M + H^+];



139

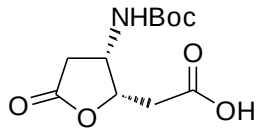
Benzyl 2-((2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl) acetate (139)

To a stirred mixture of azido benzyl ester **120** (128.0 mg, 0.11 mmol, 1 equiv.) in 2 mL dry ethanol, was added *tert*-butoxycarbonyl (Boc_2O) (35.6 mg, 0.16 mmol, 1.5 equiv.) and 20% $Pd(OH)_2/C$ (1.2 mg) at room temperature. Then to this mixture, triethylsilane (30.0 μL, 0.19 mmol, 1.7 equiv.) was added sequentially and the mixture was stirred for 20 h under N_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated under reduce pressure to remove the solvent to give white solid which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate,) to yield 48.2 mg (71%) of **139** as white solid.

R_f = 0. 51 (SiO_2, petroleum ether/ethyl acetate 6:4); m.p. 122-124 °C $[\alpha]_D^{20}$ = -31.4 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.30-7.55 (m, 5H, Ph), 5.15 (d, *J* = 2.2 Hz, 2H, C*H*$_2$Ph), 4.97-5.35 (m, 1H, C*H*OCO), 4.86-4.95 (m, 1H, C*H*NBoc), 4.65 (bs, 1H, NH), 2.93-3.05 (m,

1H, C*H*$_2$CHNBoc), 2.89 (dd, *J* = 7.1, 3.6 Hz, 1H, C*H*$_2$COBz), 2.81 (dd, *J* = 6.3, 1.9 Hz, 1H, C*H*$_2$COBz), 2.48 (dd, *J* = 17.8, 3.0 Hz, 1H, C*H*$_2$CHNBoc), 1.43 (s, 9H, Si(CH$_3$)$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 169.61 (C_{quart}, CO), 169.34 (C_{quart}, COBz), 157.4 (C_{quart}, Boc), 135.28 (C_{quart}, Ph), 128.72 (Ph-C), 128.67 (Ph-C), 128.62 (Ph-C), 12.52 (Ph-C), 128.44 (Ph-C), 79.13 (*C*HOCO), 78.04 ($C_{quart,}$ Boc), 67.08 (*C*H$_2$Ph), 59.59 (*C*HNBoc), 35.96 (*C*H$_2$CHNBoc), 34.52 (*C*H$_2$COBz), 28.24 (Si(*C*H$_3$)$_3$); **IR** (Film): $\tilde{\nu}$ = 2133, 2100, 1774, 1717, 1680, 1421, 1311, 1275, 1238 1202, 1151, 1123, 989, 964, 938, 899, 751, 711 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 367.0 [M + NH_4^+], 350.0 [M + H^+] ; Elemental analysis calcd (%) for $C_{18}H_{23}NO_6$ (349.38): C 61.88, H 6.64, N 4.01; found C 62.04, H 6.74, N 3.94.



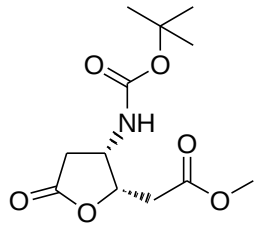
141

2-((2*S*,3*S*)3-(*tert*-Butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetic acid (141)

To a solution of **139** (100.0 mg, 0.11 mmol) in dry EtOH (5 mL) was added Pd/C (1.2 mg, 10 mol%). The reaction mixture was stirred for 8 h under H_2 (1 atm.) at room temperature, filtered through celite, dried over $MgSO_4$, concentrated in vacuo to give a crude residue which was purified by column chromatography on silica (ethyl acetate/methanol, 1:1) to afford 75.3 mg of **141** (95 %) as colorless solid.

R_f = 0. 14 (SiO_2, petroleum ether/ethylacetate 6:4); m.p. 156-158 °C $[\alpha]_D^{20}$ = +10.0 (c = 0.2, DMSO)

^{1}H-NMR (300 MHz, D_2O): δ = 4.91 (m, 1H, $CHCH_2COOH$), 4.39 (m, 1H, C*H*NBoc), 2.41-2.45 (m, 4H, CH_2COOH, CH_2CO), 1.34 (s, 9H, Boc). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): **IR** (Film): $\tilde{\nu}$ = 3362, 2982, 2930, 1773, 1737, 1681, 1522, 1368, 1246, 1154, 1043, 934, 852 cm^{-1}.**MS** [Cl, NH_3]: m/z (%) 259.0[$M^{+\cdot}$]; **HRMS** (Cl, NH_3); Calculated for [$C_{17}H_{17}NO_6$]: 259.01103, found 259.01113.



140

Methyl 2-((2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl) acetate (140)

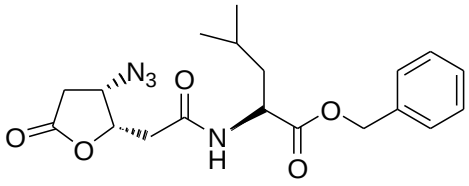
To a stirred mixture of azido methyl ester **128** (236 mg, 1.18 mmol, 1 equiv.) in 13 mL dry ethanol, was added *tert*-butoxycarbonyl (Boc_2O) (647 mg, 2.96 mmol, 2.5 equiv.) and 20 % $Pd(OH)_2/C$ (11.8 mg) at room temperature. Then to this mixture, triethylsilane (0.28 ml, 1.80 mmol, 1.5 equiv.) was added sequentially and the mixture was stirred for 24 h under N_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated under reduce pressure to remove the solvent to give white solid which was purified by column

chromatography on silica gel (petroleum ether: ethyl acetate, 4:6) to yield 239.9 mg (74%) of **140** as white solid.

R_f = 0.66 (SiO_2, petroleum ether/ethyl acetate 6:4); m.p. 119-121 °C $[\alpha]_D^{20}$ = -42.1 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.14 (d, *J* = 8.8 Hz, 1H, C*H*OCO), 4.97 (m, 1H, C*H*NBoc), 4.62 (bs, 1H, NH), 3.72 (s, 3H, OCH_3), 2.90-2.98 (dd, *J* = 18.3, 8.4 Hz, 1H, C*H*$_2$CHNBoc), 2.77 (d, *J* = 6.6, Hz, 2H, C*H*$_2$COOCH_3), 2.49 (dd, *J* = 18.1, 3.3 Hz, 1H, C*H*$_2$CHNBoc), 1.43 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 174.33 (C_{quart}, CO), 170.21 (C_{quart}, COOCH_3), 157.0 (C_{quart}, CO-Boc), 80.52 (*C*HOCO), 79.28 (C_{quart}, Boc), 52.20 (*C*HNBoc), 49.48 (OCH_3), 35.95 (*C*H$_2$CHNBoc), 34.26 (*C*H$_2$COOCH_3), 28.24 (Si(*C*H$_3$)$_3$); **IR** (Film): $\tilde{\nu}$ = 3359, 3010, 1774, 1735, 1681, 1522, 1356, 1296, 1249, 1180, 1051, 935, 853, 779, 617 cm^{-1}. **MS** [Cl, NH_3]: m/z (%) 291.1 [M + NH_4^+], 274.0 [M + H^+]; **HRMS** (Cl, NH_3); Calculated for [$C_{12}H_{19}NO_6$: 273.1212, found 273.1209.

2.3 Synthesis of dipeptide and tetramer



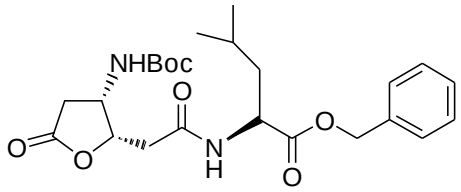
177

Benzyl2-(2-((*2S,3S*))-3-Azido-5-oxotetrahydrofuran-2-yl)acetamido)-4-ethylpentanoate (177)

To a stirred solution of azido carboxylic acid **121** (157.0 mg, 0.85 mmol) in dry THF (4 mL) was added HOBt (125.6 mg, 1.1 equiv.), HBTU (417.2 mg, 1.3 equiv.) and amine **178** (0.299 mg, 1.1 equiv.) at 0 ^{o}C. Then the ice bath was removed and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed by rotary evaporator. Then the reaction mixture was dissolved in CH_2Cl_2 (5 mL), washed with 1 M $KHSO_4$ (5 mL), 5% $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give white solid crude product, which was purified by column chromatography on silica gel (ethyl acetate: methanol, 14:1) to yield 0.190 mg (60%) of **177** as crystalline solid.

R_f = 0.88 (SiO_2,); (ethyl acetate: methanol, 14:1) m.p. 126-128 ^oC $[\alpha]_D^{20}$ = +20.9 (c = 0.4, CH_2Cl_2);

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.40 (m, 5H, Ph), 6.17 (d, 1H, *J* = 9.3 Hz, NH), 5.16 (d, 2H, *J* = 2.2 Hz, 2H, C*H*$_2$Ph), 4.85-4.93 (m, 1H, C*H*NH), 4.62-4.71 (m, 1H, CH_2C*H*O), 4.45-4.60 (m, 1H, CH_2C*H*N_3), 2.62-2.93 (m, 4H, C*H*$_2$$CHN_3$, C*H*$_2$CON), 1.52-1.71 (m, 3H, C*H*CH_3, C*H*$_2$$CHCH_3$), 0.92 (d, *J* = 6.0 Hz, C*H*$_3$); ^{13}C-NMR (75.5 MHz, DMSO): δ = 173.03 (C_{quart}, CO), 172.55 (C_{quart}, CO), 168.18 (C_{quart}, CO), 135.28 (C_{quart}, Ph), 128.64 (Ph-C), 128.51 (Ph-C), 128.30 (Ph-C), 78.94 (CH_2*C*HO), 67.24 (*C*H_2Ph), 59.86 (CH_2*C*HNH), 51.03 (CH_2*C*HN_3), 41.38 (*C*$H_2$$CHCH_3$), 36.07 (*C*$H_2$$CHN_3$), 35.88 (*C*$H_2$CHO), 24.86 (*C*H$CH_3$), 22.76 (*C*$H_3$), 21.87 (*C*$H_3$); **IR** (Film): $\tilde{\nu}$ =3360, 2955, 2133, 2097, 1778,1708,1668, 1536, 1288, 1256, 1150, 1028, 999, 739 cm^{-1}. MS [Cl, NH_3]: m/z (%) 389.0 [M + H^+]; **HRMS** (Cl, NH_3); Calculated for [$C_{19}H_{24}N_4O_5$]: 388.1735, found 388.1747.



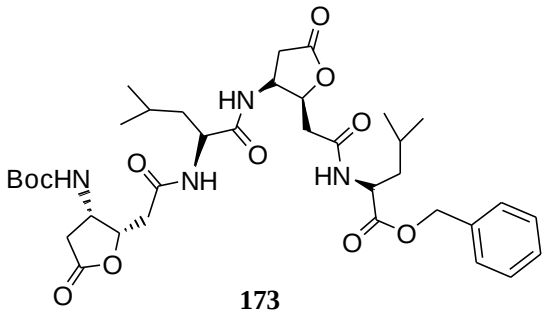
176

Benzyl2-(2-((*2S,3S*))-3-Azido-5-oxotetrahydrofuran-2-yl)acetamido)-4-ethylpentanoate (176)

To a stirred mixture of azido ester **177** (236 mg, 1.18 mmol, 1 equiv.) in 13 mL dry ethanol, was added *tert*-butoxycarbonyl (Boc_2O) (647 mg, 2.96 mmol, 2.5 equiv.) and 20%

$Pd(OH)_2/C$ (11.8 mg) at room temperature. Then to this mixture, triethylsilane (0.28 mL, 1.80 mmol, 1.5 equiv.) was added sequentially and the mixture was stirred for 24 h under N_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated under reduce pressure to remove the solvent to give white solid which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 4:6) to yield 239.9 mg (74%) of **176** as yellowish oil

R_f = 0.65 (SiO_2,); (petroleum ether: ethyl acetate, 2:8) $[\alpha]_D^{20}$ = -20.9 (c = 0.3, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.30-7.40 (m, 5H, Ph), 6.58-6.70 (d, 1H, *J* = 9.0 Hz, NH), 5.60-5.71 (d, 1H, *J* = 10.1 Hz, NH), 5.17 (s, 2H, C*H*$_2$Ph), 4.81-4.90 (m, 1H, C*H*O), 4.51-4.71 (m, 1H, CH_2C*H*COO, CH_2C*H*NHBoc), 2.40-2.93 (m, 4H, C*H*$_2$CHN$_3$, C*H*$_2$CON), 1.52-1.71 (m, 3H, C*H*CH_3, C*H*$_2$CHC*H*$_3$), 1.40 (s, 9H, $(CH_3)_3$), 0.92 (d, *J* = 6.0 Hz, C*H*$_3$); ^{13}C-NMR (75.5 MHz, DMSO): δ = 174.40 (C_{quart}, CO), 169.08 (C_{quart}, CO), 168.27 (C_{quart}, CO), 168.18 (C_{quart}, CO), 135.28 (C_{quart}, Ph), 128.64 (Ph-C), 128.35 (Ph-C), 128.30 (Ph-C), 85.22 (CH_2*C*HO), 79.74 (C_{quart}, Boc), 67.22 (*C*H_2Ph), 59.86 (*C*HNHBoc), 51.22 (CH_2*C*HO), 41.34 (*C*H_2CHCH$_3$), 36.54 (*C*H_2CHNHBoc), 35.92 (*C*H_2CHO), 28.31 (Si(*C*H_3)$_3$, 24.84 (*C*HCH$_3$), 22.80 (*C*H$_3$), 21.80 (*C*H$_3$); **IR** (Film): $\tilde{\nu}$ =3310, 2924, 2855, 1737,1661,1535, 1457, 1366, 1253, 1165, 1028, 743, 687 cm^{-1}. MS [Cl, NH_3]: m/z (%) [M + H$^+$]; **HRMS** (Cl, NH_3); Elemental analysis calcd (%) for $C_{24}H_{34}N_2O_7$ (241.1): C 62.3, H 7.41, N 6.06 ; found C 61.52, H 7.73, N 5.86.



173

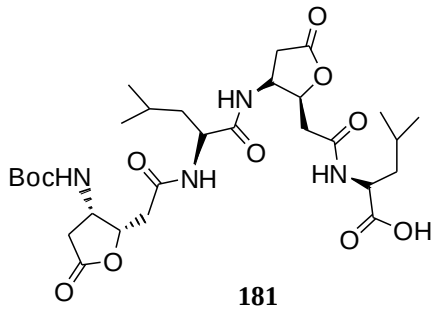
(*R*)-Benzyl2-(2-((2*S*,3*R*)-3-((*R*-2-(2-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanamido)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoate (173)

To a stirred solution of **174** (25.0 mg, 0.067 mmol, 1 equiv.) in dry THF (3 mL) at 0 ^{o}C was added sequentially HBTU (27.9 mg, 0.087 mmol, 1.3 equiv.) and HOBt (11.8 mg, 0.087 mmol, 1.1 equiv.). After 30 min, to this reaction mixture was added a solution of **175** (25.5 mg, 0.073 mmol, 1.1 equiv.), $MgSO_4$ (200 mg, 1.67 mmol, 25 equiv.), $NaHCO_3$ (500 mg, 5.9 mmol, 88.0 equiv.) in CH_3CN (3 mL) and stirred for 3 d at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1 M $KHSO_4$ (5 mL), saturated $NaHCO_3$ (15 mL) and saturated NaCl (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give yellowish oil which was purified by column chromatography on silica (ethyl acetate/ methanol 1:1) to afford **173** (45.2 mg, 95 %) as an amorphous solid.

R_f = 0.29 (SiO_2,); (ethyl acetate, methanol 14:1) m.p. 110-112 ^{o}C $[\alpha]_D^{20}$ = -16.0 (c = 0.1, MeOH);

^{1}H-NMR (300 MHz, MeOD): δ = 8.67-8.31 (m, 2H, NH), 8.21-8.15 (d, 1H, *J* = 6.3 Hz, NH), 7.42-7.44 (m, 1H, NH), 7.29-7.39 (m, 5H, Ph), 5.13 (s, 2H, C*H*$_2$Ph), 4.98-5.06 (m, 2H, C*H*O), 4.65-4.55 (m, 1H, C*H*CH$_2$CO), 4.43-4.20 (m, 3H, C*H*CH$_2$CO, CH$_2$C*H*NH), 3.02-2.80

(m, 2H, CH_2CHO), 2.64-2.20 (m, 6H, CH_2CHO, CH_2CHN), 178-1.58 (m, 6H, CHCH$_3$, CH_2CHCH$_3$), 1.28 (s, 9H, (CH$_3$)$_3$), 0.83-1.00 (m, CH_3); ^{13}C-NMR (75.5 MHz, MeOD): δ = 174.83 (C_{quart}, CO), 174.73 (C_{quart}, CO), 172.45 (C_{quart}, CO), 172.25 (C_{quart}, CO), 169.00 (C_{quart}, CO), 168.80 (C_{quart}, CO), 155.22 (C_{quart}, CO-Boc), 135.81 (C_{quart}), 128.33 (C_{quart}, Ph), 127.93 (Ph-C), 127.66 (Ph-C), 79.58 (CH$_2$*C*HO), 79.26 (CH$_2$*C*HO), 78.18 (C_{quart}-Boc), 65.79 (*C*H$_2$Ph), 59.65 (*C*HNH), 50.84 (CH$_2$*C*HN), 47.89 (CH$_2$*C*HN), 40.67 (*C*H$_2$NH), 40.19 (*C*H$_2$NH), 35.34 (*C*H$_2$CHNH), 34.72 (*C*H$_2$CONH) 34.62 (*C*H$_2$CONH), 28.04 (*C*H(CH$_3$)$_2$, 23.04 (*C*H$_3$), 22.56 (*C*H$_3$), 21.46 (*C*H$_3$), 21.19 (*C*H$_3$), 13.97 (Si(*C*H$_3$)$_3$; **IR** (Film): $\tilde{\nu}$ =3433, 1650, 1539, 1419, 1325, 1157, 1041, 818, 753, 559 cm^{-1}. MS [Cl, NH$_3$]: m/z (%) 717.4 [M + H$^+$]; HRMS, (Cl, NH$_3$); Calculated for [$C_{36}H_{52}N_4O_{11}$]: 716.8201, found 716.8210.



181

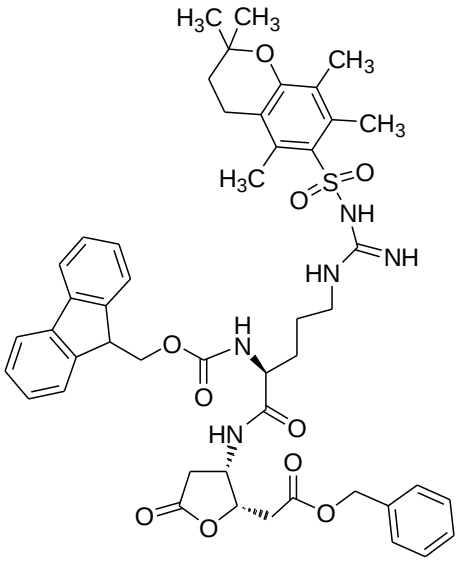
(*R*)-2-(2-((2*S*,3*R*)-3-((*R*)-2-(2-((2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl) acetamido)-4-methylpentanamido)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoic acid (181)

To a solution of **173** (25.0 mg, 0.035 mmol) in dry EtOH (4 mL) was added Pd/C (10 mol %). The reaction mixture was stirred for 8 h under H_2 (1 atm.) at room temperature, filtered through celite, dried over $MgSO_4$, concentrated in vacuo to give a crude residue which was

purified by column chromatography on silica (dichloromethane/methanol 1:1) to afford 28.8 mg (90 %) of **181** as colorless solid.

R_f = 0.23 (SiO_2,); (ethyl acetate, methanol 14:1) m.p. 154-158 °C $[\alpha]_D^{20}$ = +24.4 (c = 0.1, DMSO);

^{1}H-NMR (300 MHz, MeOD): δ = 5.06-5.12 (m, 1H, C*H*O), 4.97-4.87 (m, 1H, C*H*O), 4.79-4.97 (m, 2H, C*H*CH_2CO), 4.40-4.58 (m, 2H, C*H*NH), 3.01-3.20 (m, 2H, CH_2CHN), 2.62-2.88 (m,6, CH_2CHN, CH_2CON), 1.50-1.78 (m, 6H, C*H*CH_3, CH_2CHCH_3), 1.28 (s, 9H, $(CH_3)_3$), 0.83-1.00 (m, CH_3); ^{13}C-NMR (75.5 MHz, MeOD): δ = 170.31 (C_{quart}, CO), 167.26 (C_{quart}, CO), 166.21 (C_{quart}, CO), 164.52 (C_{quart}, CO), 129.60 (C_{quart}, Ph), 129.38 (Ph-C), 129.05 (Ph-C), 80.66 (CH_2*C*HO), 78.13 (CH_2*C*HO), 52.33 (*C*HNH), 52.34 (CH_2*C*HCOO), 51.62 (CH_2*C*HCOO), 49.42 (*C*HNH), 33.02 (*C*H_2CONH), 30.82 (*C*H$(CH_3)_2$, 29.80 (*C*H$(CH_3)_2$, 23.72 (*C*H_3), 23.33 (*C*H_3), 22.21 (*C*H_3), 21.52 (*C*H_3), 14.45 (Si(*C*$H_3)_3$; **IR** (Film): $\tilde{\nu}$ =3433, 2901, 1650, 1539, 1419, 1325, 1157, 1041, 818, 753, 559 cm^{-1}. MS [Cl, NH_3]: m/z (%) 627.32 [M + H^+];



182

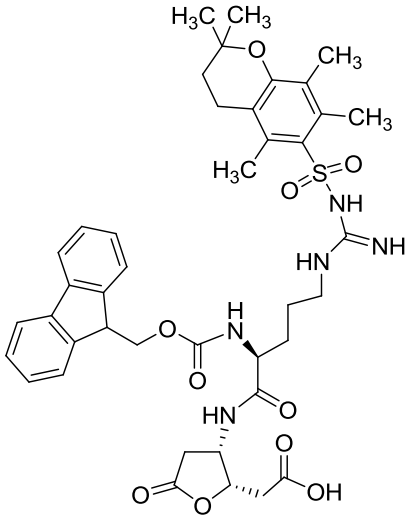
Benzyl2-(3-(2-((9H-fluoren-9-yl)methoxy)carbonylamino)-5-(3-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidino)pentanamido)-5-oxotetrahydrofuran-2-yl)acetate (182)

The compound **139** (45.0 mg, 0.12 mmol) was treated with TFA in dichloromethane (2 mL, 30 %) at 0 ^{o}C for 3 h. The solvent was removed in vacuo, to give the salt of **139a** as colorless solid. To a stirred solution of NFmocArgnine acid **183** (109.0 mg, 164 mmol, 1 equiv.) in dry THF (2 mL at 0 ^{o}C was added sequentially HBTU (79.8 mg, 0.21 mmol, 1.3 equiv.) and HOBt (24.0 mg, 0.18 mmol, 1.1 equiv.). After 30 min, to this reaction mixture was added a solution of **139a** (30.5 mg, 0.064 mmol, 1.1 equiv.) in CH_3CN (2 mL) followed by DIPEA (0.05 mL) and stirred for overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1 M $KHSO_4$ (5 mL), saturated $NaHCO_3$ (15 mL) and saturated NaCl (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give white

solid which was purified by column chromatography on silica (ethyl acetate/ methanol 1:1) to afford **182** (101.0 mg, 68 %) as an amorphous white solid.

R_f = 0.24 (SiO_2,); (ethyl acetate, petroleum ether 8:2) m.p. 152-154 °C $[\alpha]_D^{20}$ = +17.0 (c = 0.1, MeOH);

^{1}H-NMR (300 MHz, MeOD): δ = ^{1}H-NMR (300 MHz, MeOD): δ = 7.70-7.85 (d, 2H, *J* = 7.1 Hz, Ar), = 7.67-7.73 (d, 2H, *J* = 6.9 Hz, Ar), 7.15-7.43 (m, 9H, Ar), 5.10-5.23 (s, 2H, C*H*$_2$Ph), 5.10-5.35 (m, 1H, C*H*O), 4.66-4.76 (m, 1H, C*H*Ar), 4.28-4.44 (m, 2H, C*H*$_2$Ar), 4.15-4.20 (m, 2H, CH_2CHNH, $CHCH_2CH_2$), 2.95-3.22 (m, 3H, CH_3), 2.43-2.74 (m, 10H, C*H*$_2$CHN, C*H*$_2$CON,C*H*$_2$C(CH_3)$_2$, C*H*$_2$CH$_2$C(CH_3)$_2$), C*H*$_2$NH), 1.72-1.81 (m, 2H, C*H*$_2$CH$_2$NH), 1.43-1.60 (m, 2H, C*H*$_2$CH$_2$CH$_2$NH), 1.20-1.34 (m, 12H, C*H*$_3$); ^{13}C-NMR (75.5 MHz, MeOD): δ = 173.06 (C_{quart}, CO), 167.43 (C_{quart}, CO), 167.26 (C_{quart}, CO), 154.70 (C_{quart}, CO), 142.64 (C-Ar), 136,59 (C-Ar), 136.08 (C-Ar), 129.60 (C-Ar), 129.53 (C-Ar), 129.37 (C-Ar), 129.20 (C-Ar), 128.85 (C-Ar), 128.25 (C-Ar), 126.24, (C-Ar) 125.03 (C-Ar), 120.98 (C-Ar), 119.03 (C-Ar), 81.35 (C_{quart}), 79.44 (CH_2CHO), 74.89 (*C*H$_2$-Fmoc), 68.08 (*C*H$_2$Ph), 67.81 (*C*HNH), 64.57 (C_{quart}.) 58.84 (*C*HNH), 49.93, (*C*H-Fmoc), 33.67 (CH_2), 31.66 (CH_2), 27.00 (CH_2), 22.40 (CH_2), 20.97 (CH_2), 19.08 (CH_3), 18.00 (CH_3), 17.82 (CH_3), 14.46 (CH_3) , 12.38 (CH_3); **IR** (Film): $\tilde{\nu}$ =3488, 1623, 1703, 1632, 1546, 1421, 1330, 1165, 1107, 1040, 818, 741, 597 cm^{-1}. MS [Cl, NH_3]: m/z (%) 804.4 [M + H$^+$]; **IR** (Film): $\tilde{\nu}$ =3488, 1703, 1623, 1546, 1421, 1330, 1165, 1107, 1040, 818, 741, 658 cm^{-1}. MS [Cl, NH_3]: m/z (%) 894.4 [M + H$^+$];



184

2-(3-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-5-(3-(2,,2,5,7,8-pentamethylchroman-6-yl sulfonyl)guanidine)pentanamido)-5-oxotetrahydrofuran-2-yl)acetic acid (184)

To a solution of **182** (100.0 mg, 0.11 mmol) in dry EtOH (5 mL) was added Pd/C (1.2 mg, 10 mol%). The reaction mixture was stirred for 8 h under H_2 (1 atm.) at room temperature, filtered through celite, dried over $MgSO_4$, concentrated in vacuo to give a crude residue which was purified by column chromatography on silica (ethyl acetate/methanol, 1:1) to afford 67.3 mg of **184** (95 %) as colorless solid.

R_f = 0.23 (SiO_2,); (ethyl acetate, methanol 14:1) m.p. 184-186 ^oC $[\alpha]_D^{20}$ = +8.3 (c = 0.1, DMSO);

^{1}H-NMR (300 MHz, DMSO): δ = 7.71-7.84 (d, 2H, *J* = 7.1 Hz, Ar), 7.65-7.74 (d, 2H, *J* = 6.9 Hz, Ar), 7.25-7.33 (m, 4H, Ar), 5.11-5.23 (m, 1H, C*H*O), 4.65-4.76 (m, 1H, C*H*Ar), 4.27-4.46 (m, 2H, CH_2Ar), 4.15-4.19 (m, 2H, CH_2CHNH, $CHCH_2CH_2$), 2.94-3.22 (m, 3H, CH_3), 2.42-2.79 (m, 10H, CH_2CHN, CH_2CON,$CH_2C(CH_3)_2$, $CH_2CH_2C(CH_3)_2$), CH_2NH),

1.73-1.84 (m, 2H, C*H*$_2$CH$_2$NH), 1.42-1.61 (m, 2H, C*H*$_2$CH$_2$CH$_2$NH), 1.21-1.36 (m, 12H, C*H*$_3$); ^{13}C-NMR (75.5 MHz, MeOD): δ = 173.07 (C_{quart}, CO), 167.41 (C_{quart}, CO), 167.25 (C_{quart}, CO), 154.70 (C_{quart}, CO), 142.56 (C-Ar), 136,49 (C-Ar), 136.05 (C-Ar), 128.76 (C-Ar), 128.15 (C-Ar), 126.17 (C-Ar), 124.94 (C-Ar), 120.87 (C-Ar), 119.36 (C-Ar), 81.32 (C_{quart}), 79.43 (CH$_2$*C*HO), 74.82 (*C*H$_2$-Fmoc), 67.81 (*C*HNH), 58.8 (*C*HNH), 49.84 (*C*H-Fmoc), 33.69 (CH_2), 30.66 (CH_2), 26.88 (CH_2), 22.30 (CH_2), 20.83 (CH_2), 18.92 (CH_3), 18.31 (CH_3), 17.83 (CH_3), 14.41 (CH_3) , 12.20 (CH_3); **IR** (Film): $\tilde{\nu}$ =3487, 1623, 1543, 1448, 1325, 1158, 1108, 1041, 813, 742, 567 cm^{-1}. MS [Cl, NH_3]: m/z (%) 804.4 [M + H$^+$];

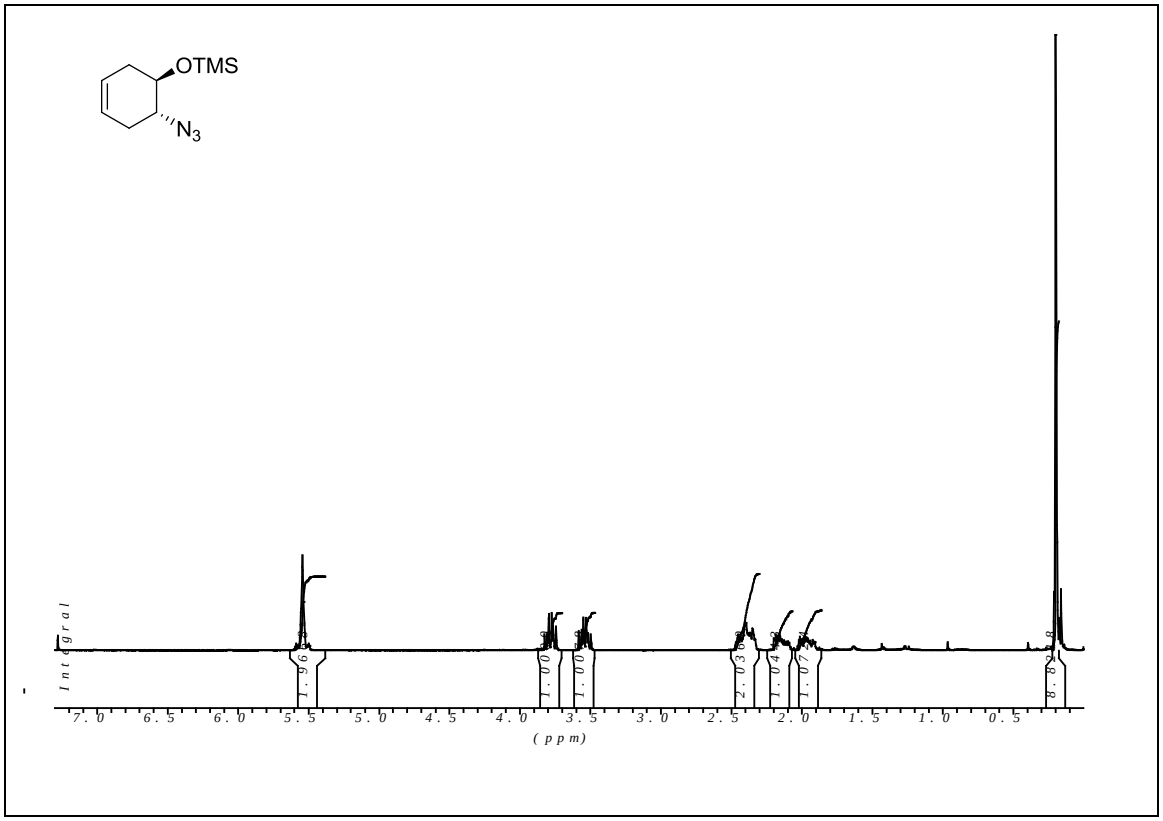
Appendix of NMR

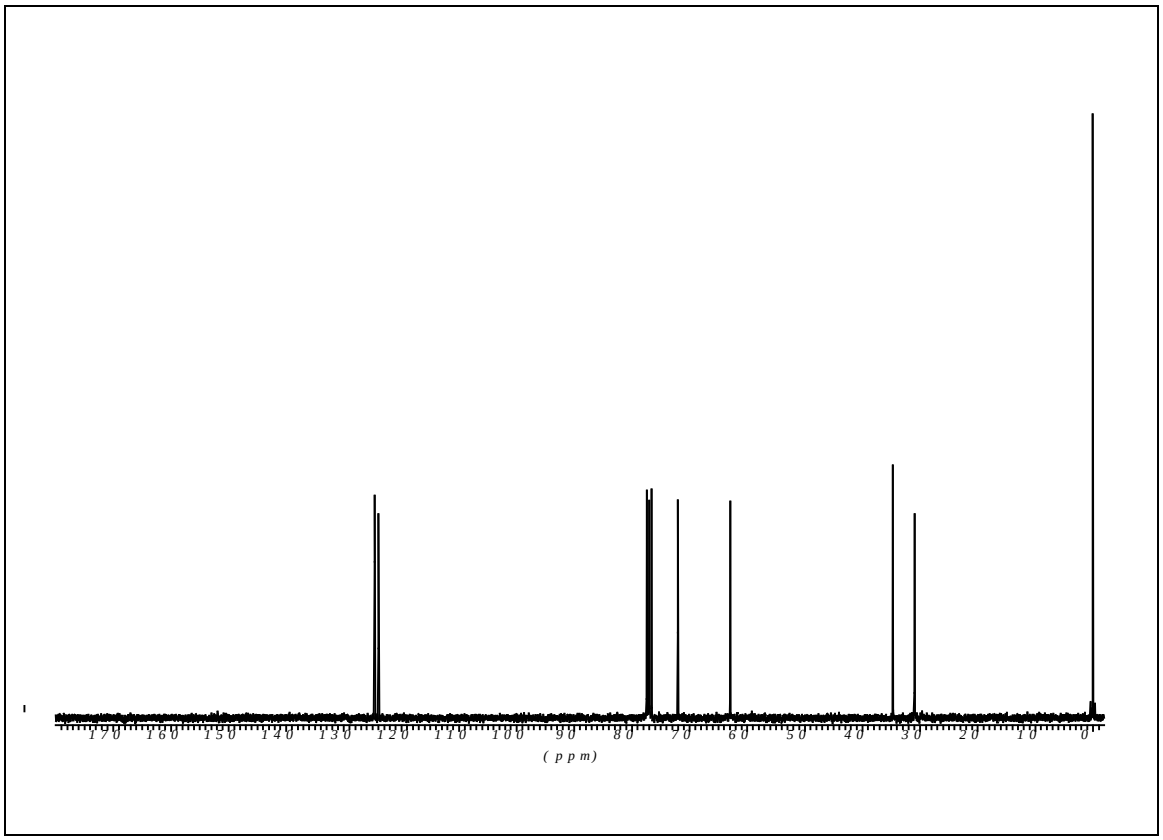
NMR

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

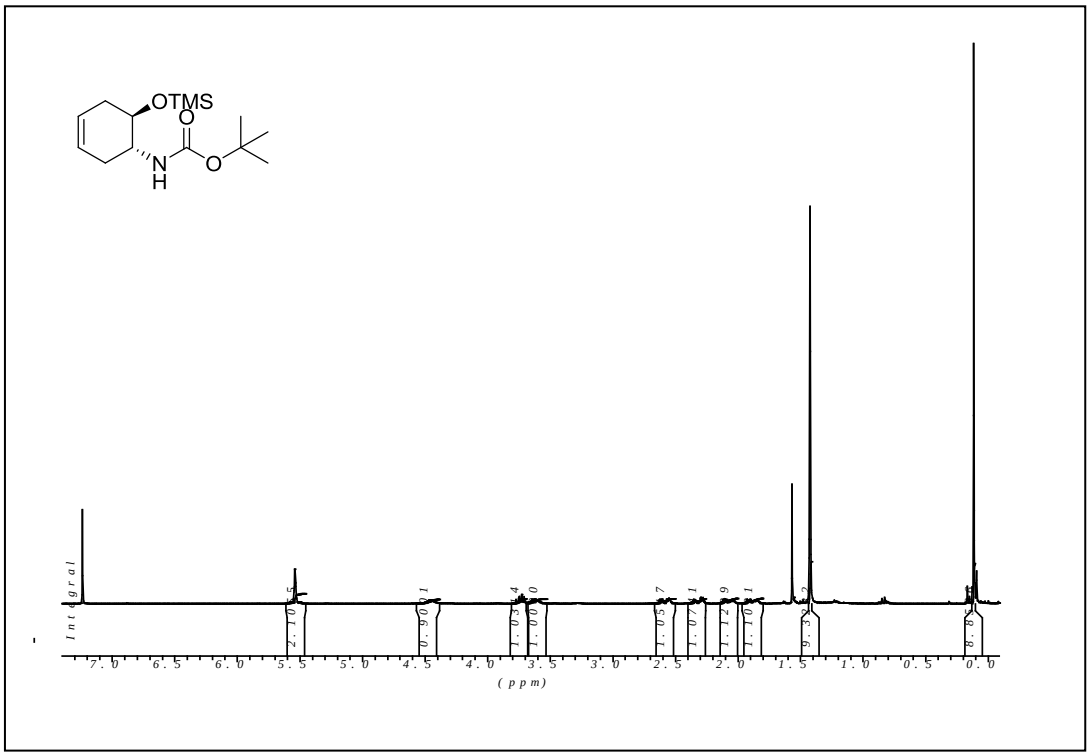
^{13}C-Spectra (bottom of the page)

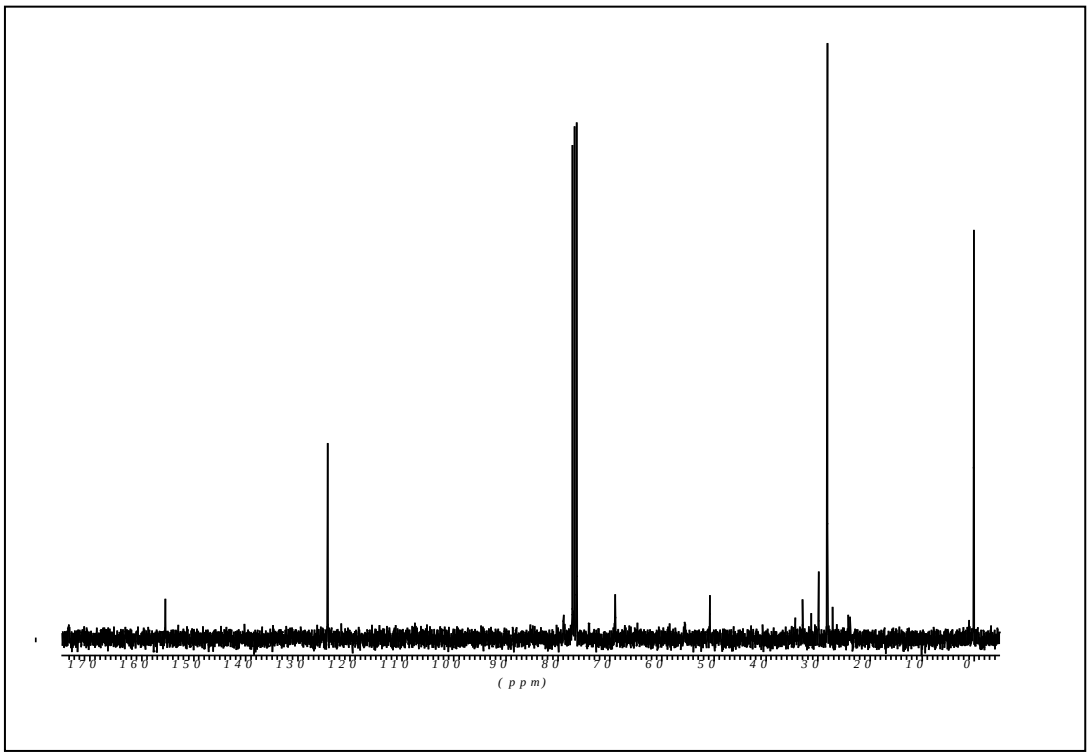
((1*R*,6*R*)-6-Azidocyclohex-3-enyloxy)trimethylsilane (66, $CDCl_3$):



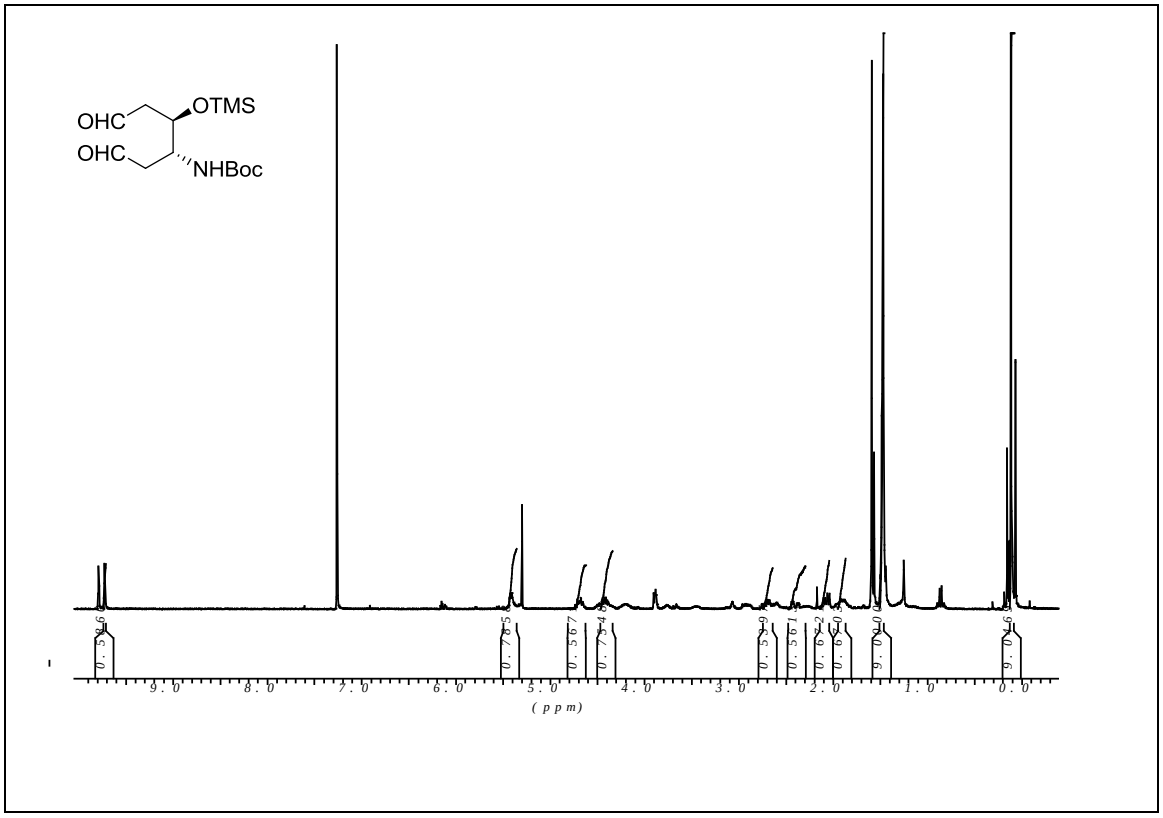


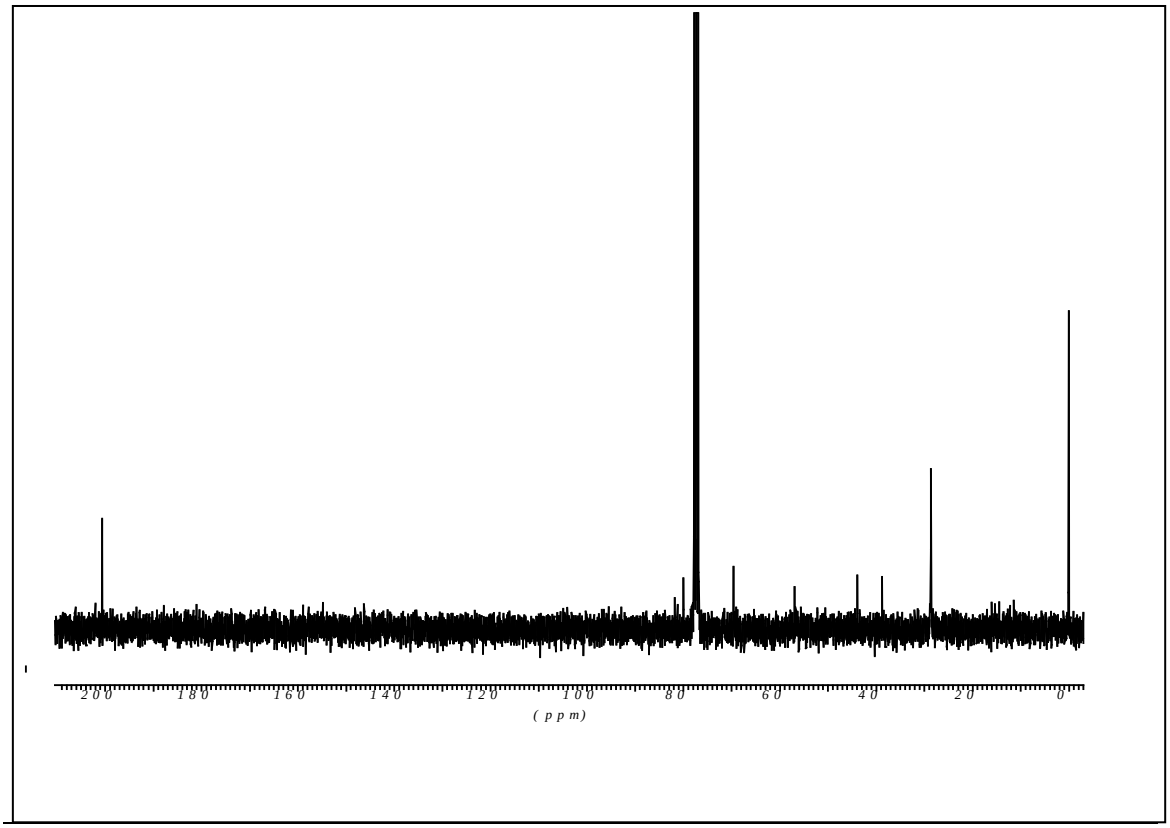
***Tert*-butyl (1*R*,6*R*)-6-(trimethylsilyloxy)cyclohex-3-enylcarbamate (65, $CDCl_3$):**



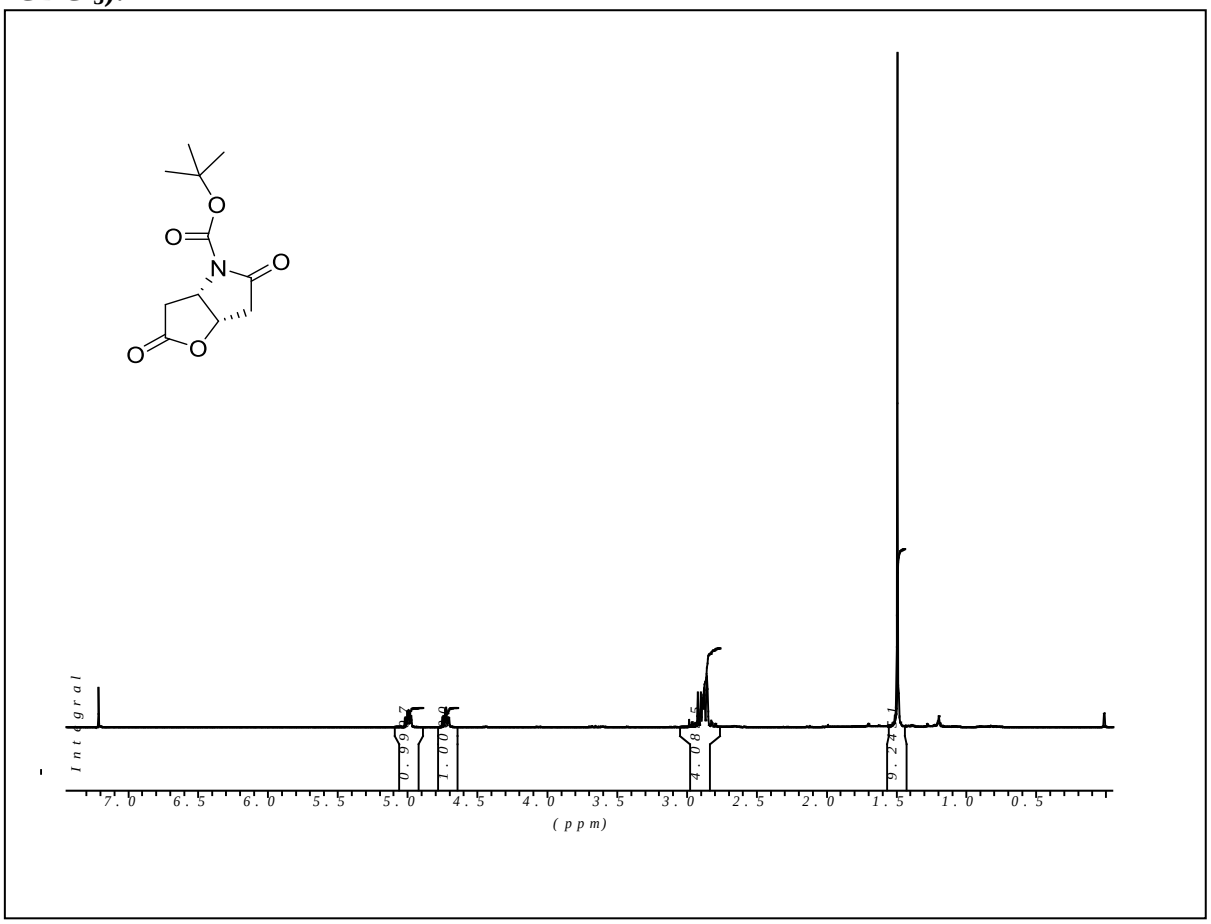


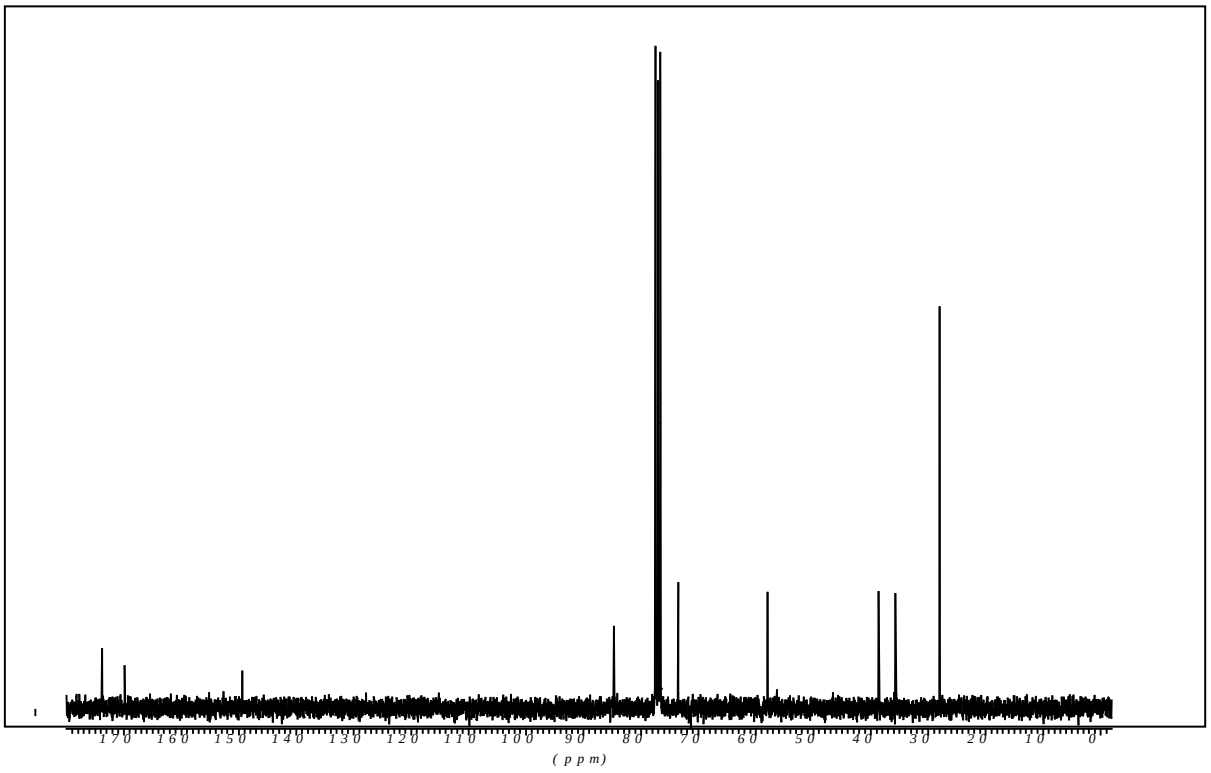
Tert-butyl (3R,4R)-1,6-dioxo-4-(trimethylsilyloxy)hexan-3-ylcarbamate (64, $CDCl_3$)



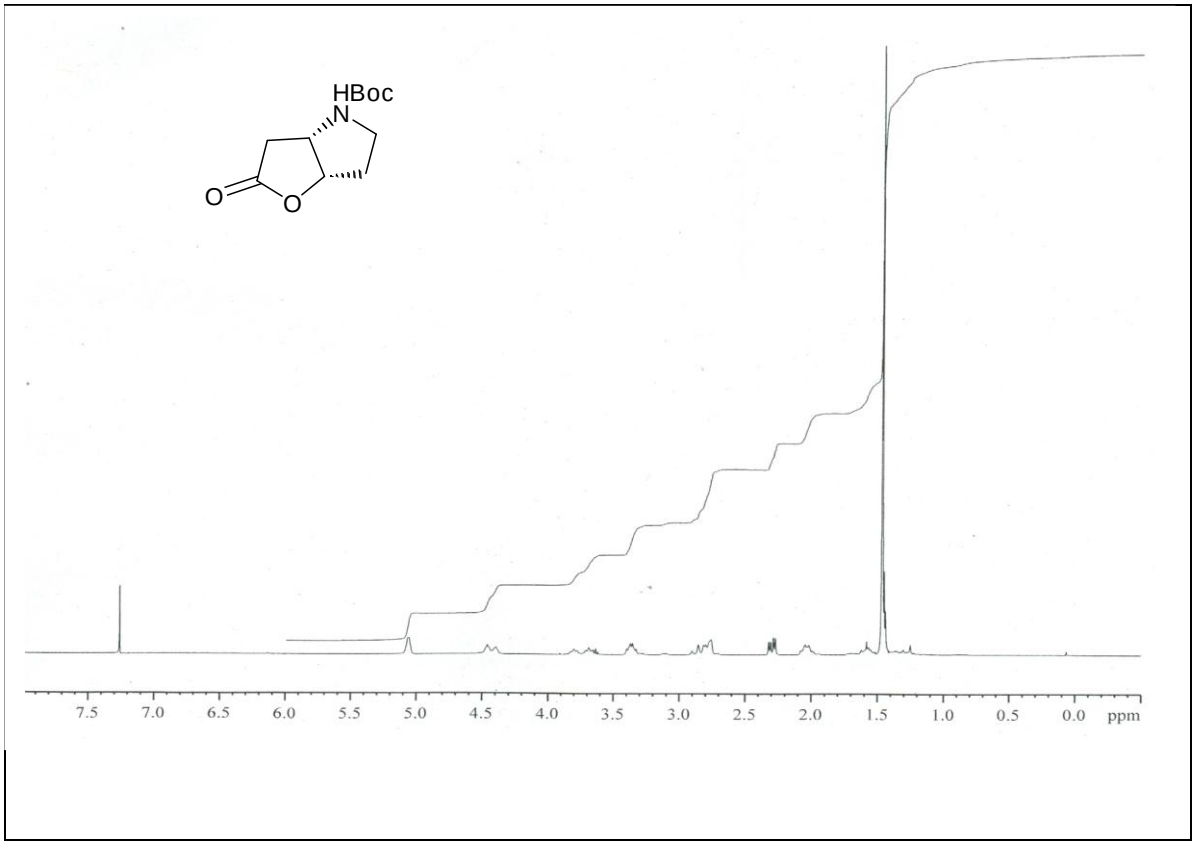


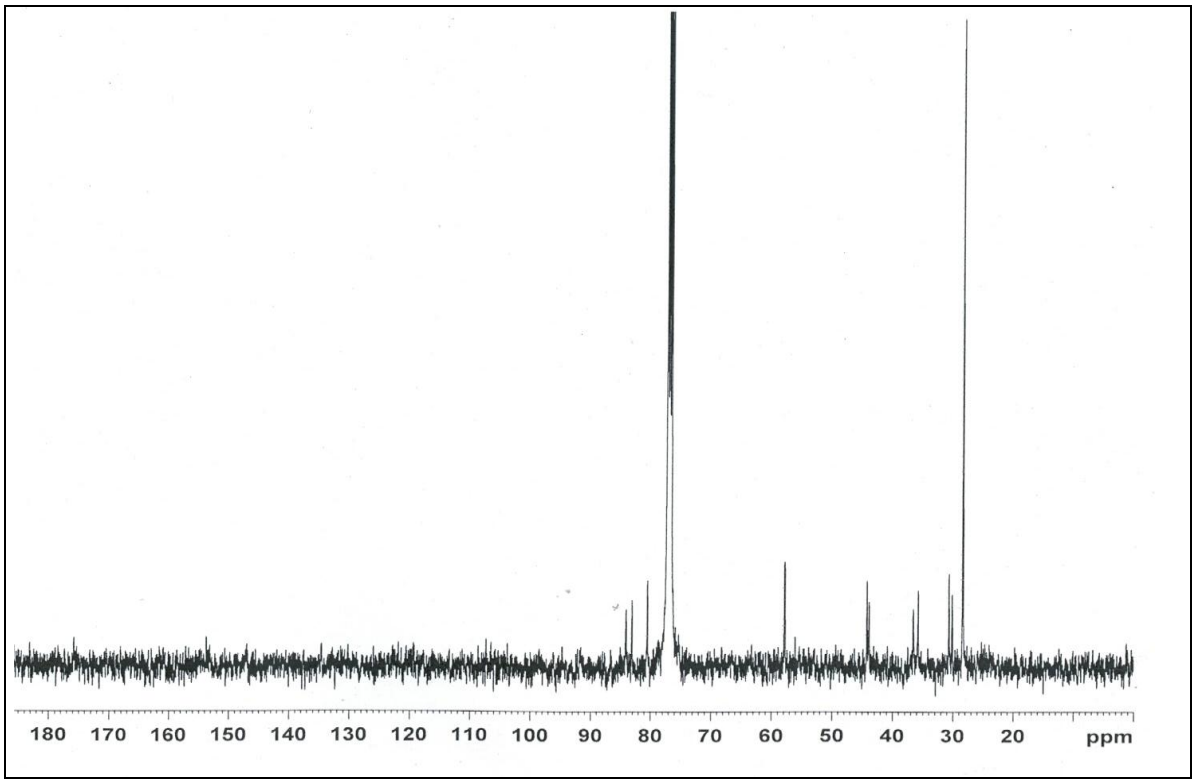
(3a*S*,6a*S*)-*Tert*- butyl 2,5-dioxotetrahydro-2*H*-furo[3,2-b]pyrrole-4(5*H*)-carboxylate (63a, $CDCl_3$):



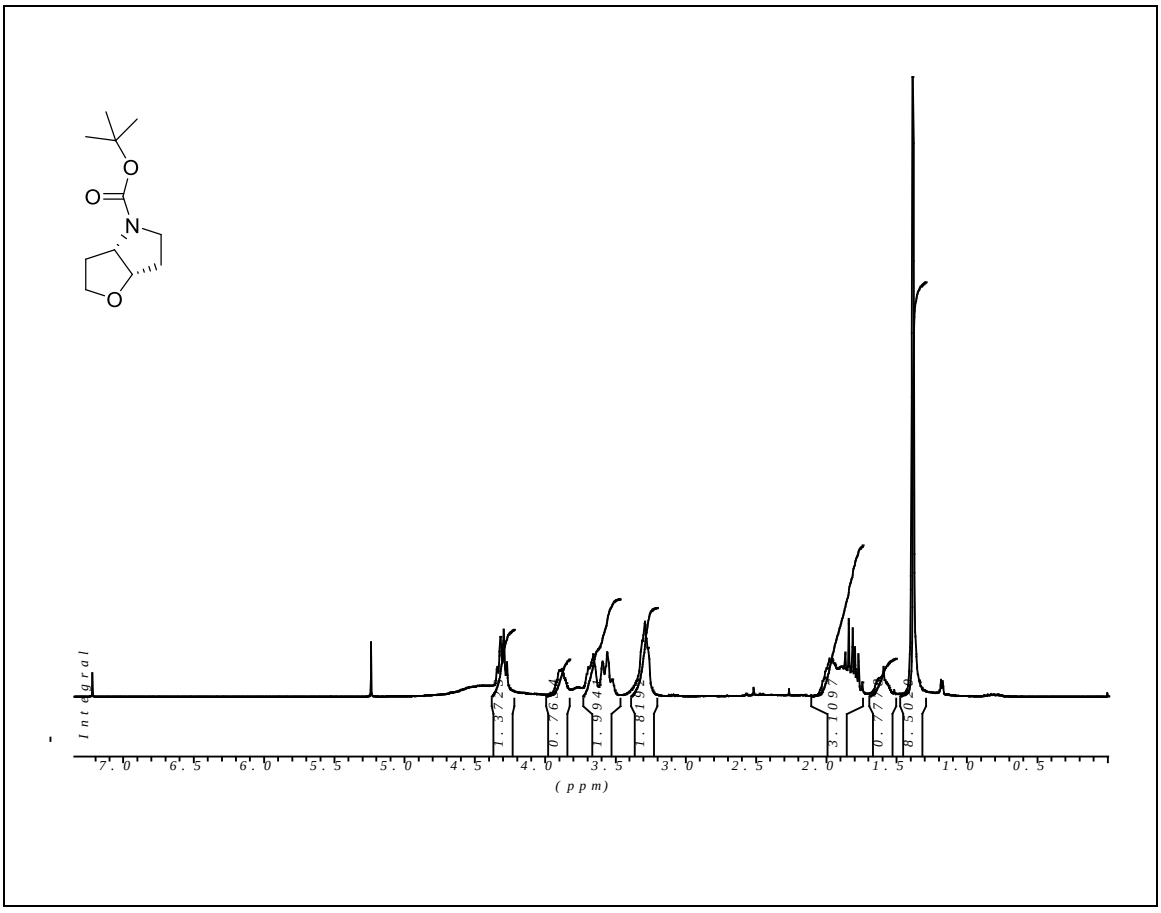


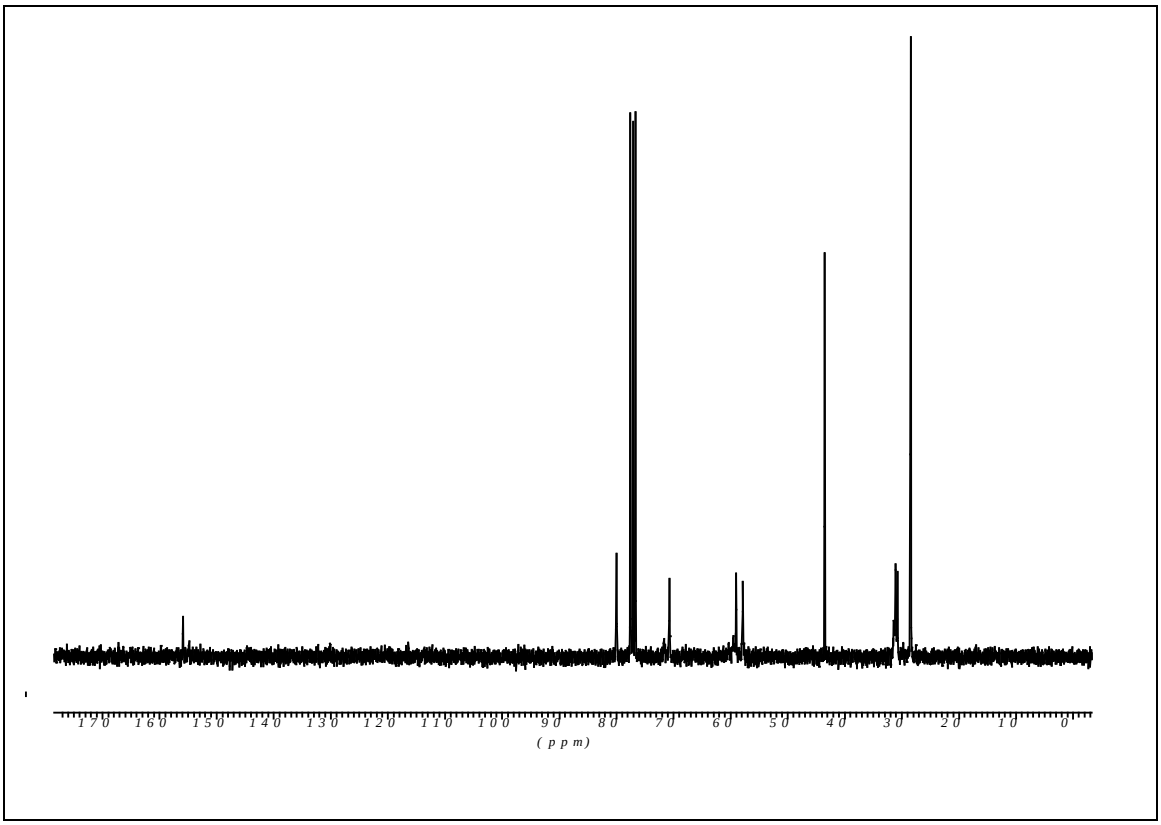
(3aS,6aS)-tert-butyl 2-oxotetrahydro-2H-furo[3,2-b]pyrrole-4(5H)-carboxylate (75, CDCl3)



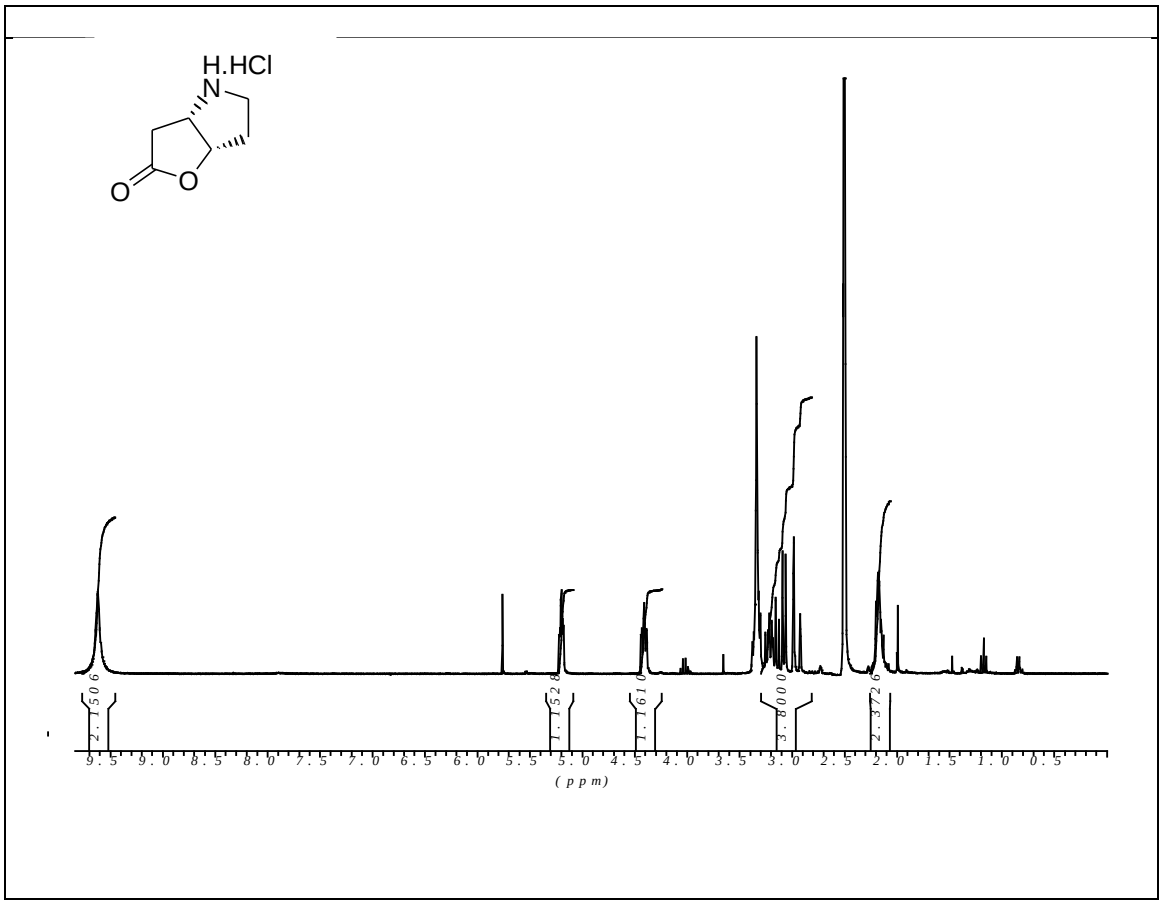


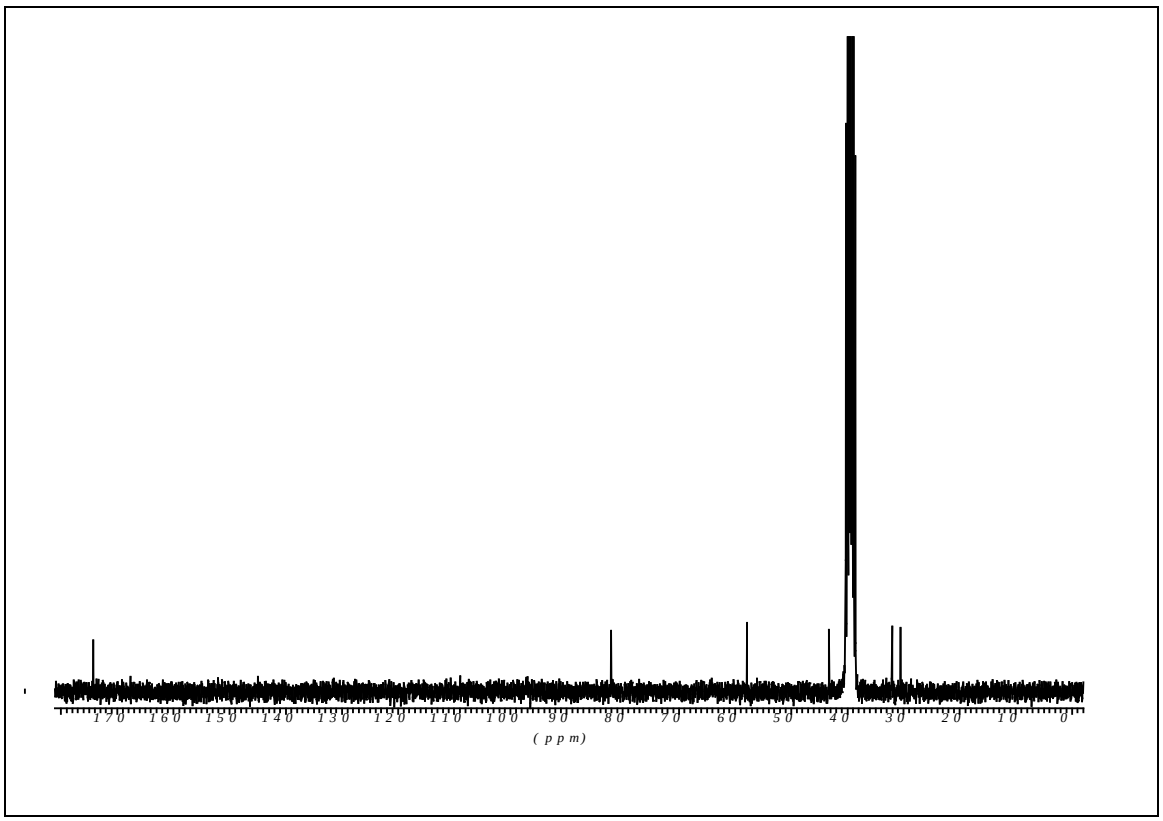
(3aS,6aS)-tert-butyl tetrahydro-2H-furo[3,2-b]pyrrole-4(5H)-carboxylate (79, $CDCl_3$)



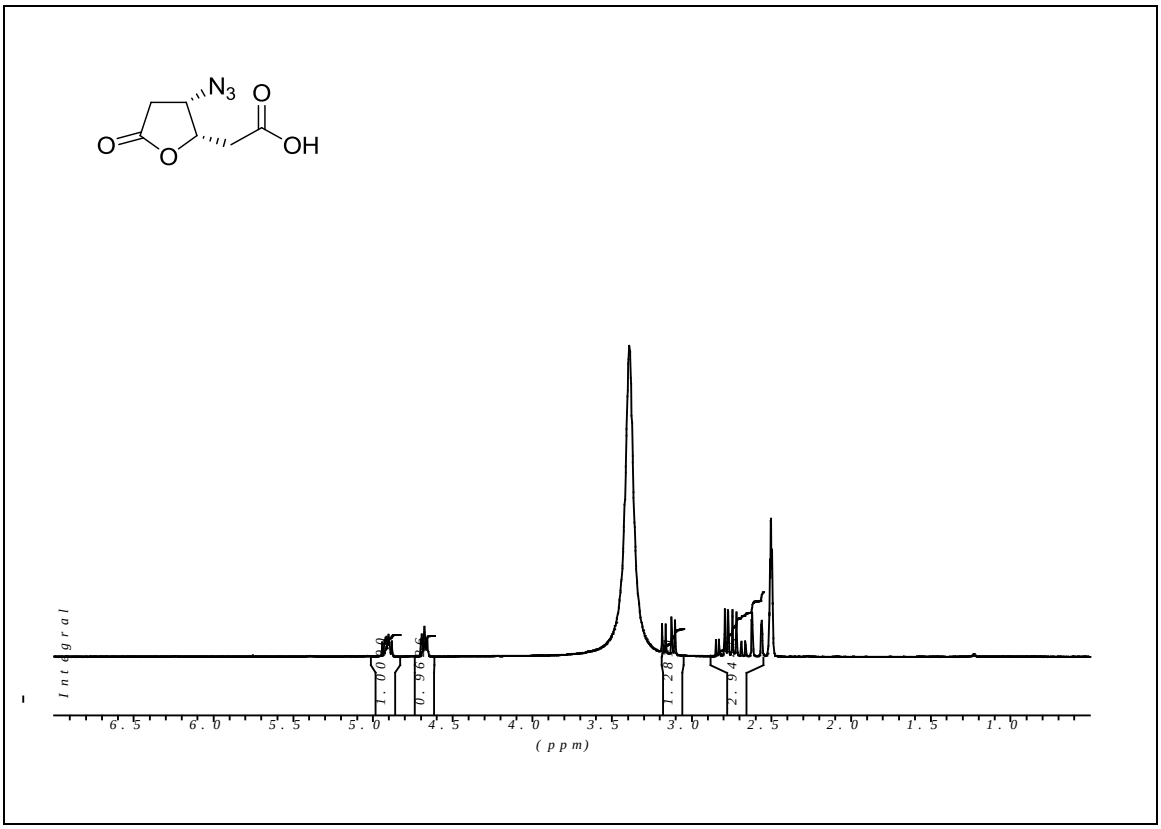


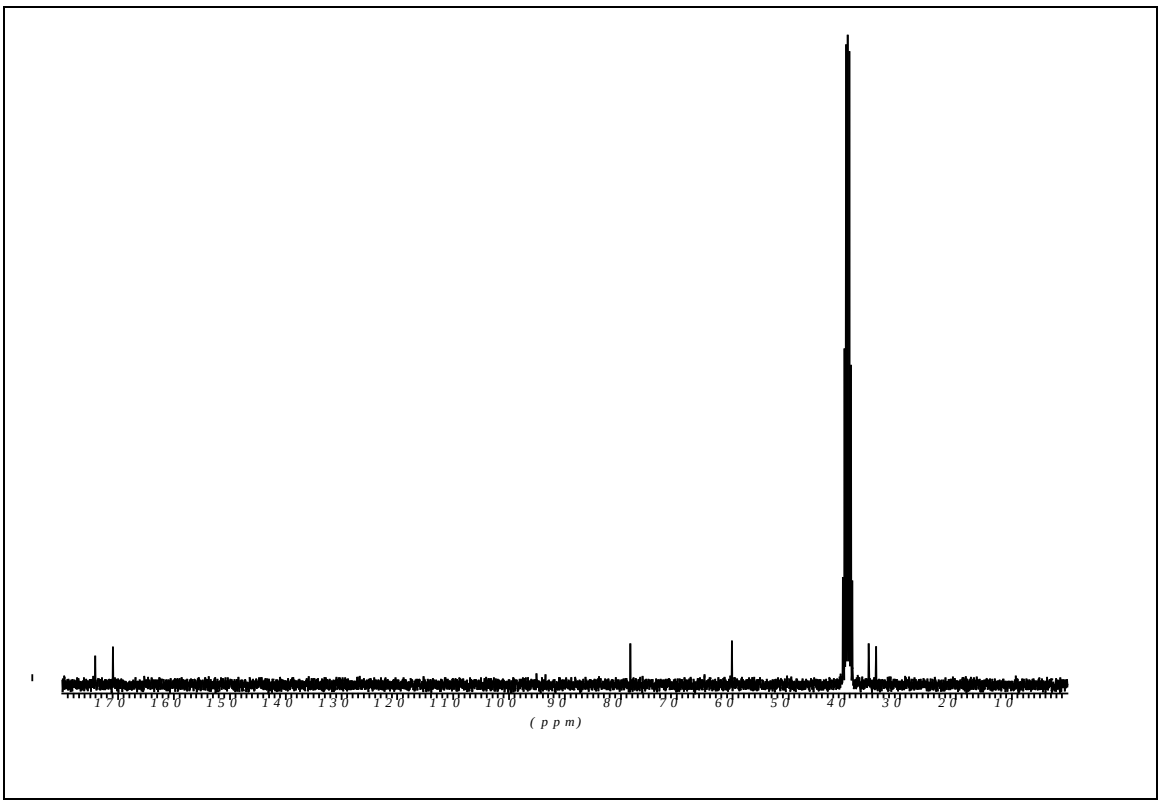
(3a*S*,6a*S*)-hexahydro-2H-furo(3,2-b)pyrrole hydrochloride (36b, MeOD)



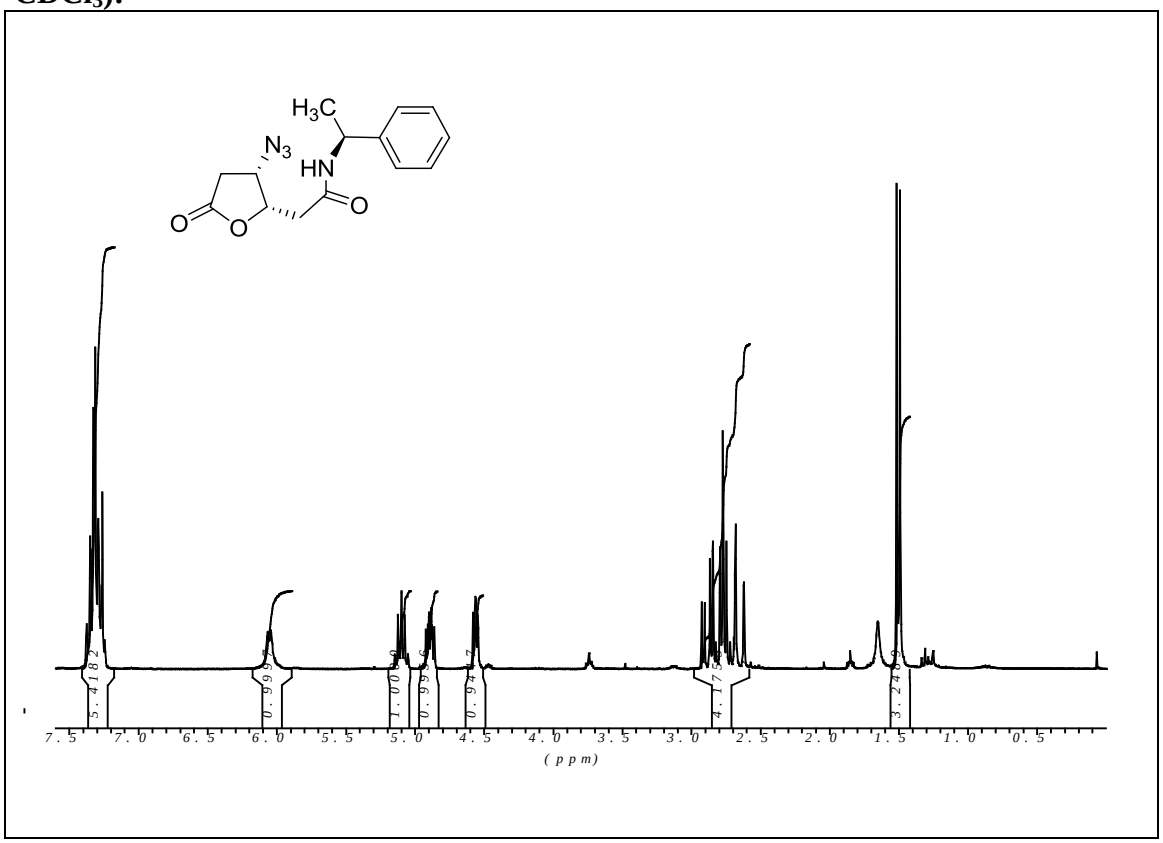


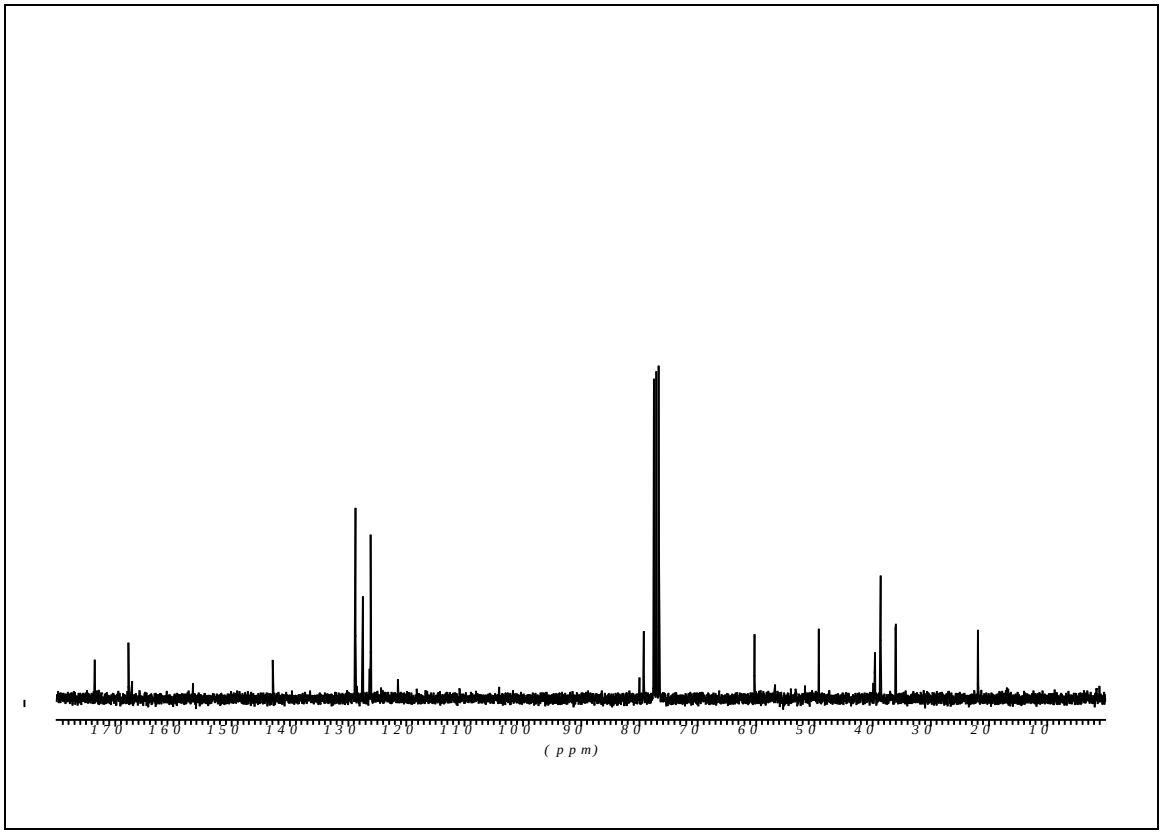
2-((2*S*,3*S*)-3-Azido-5-oxotetrahydrofuran-2-yl)acetic acid (121, DMSO):



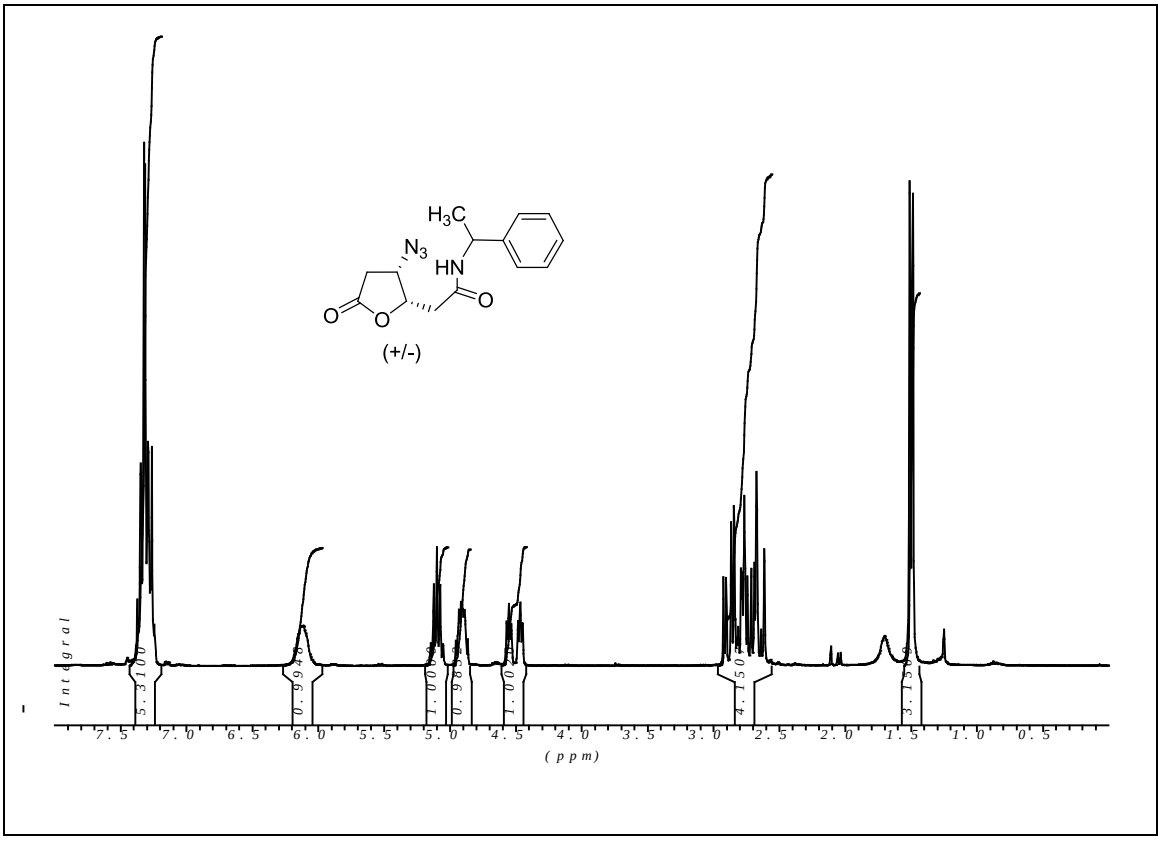


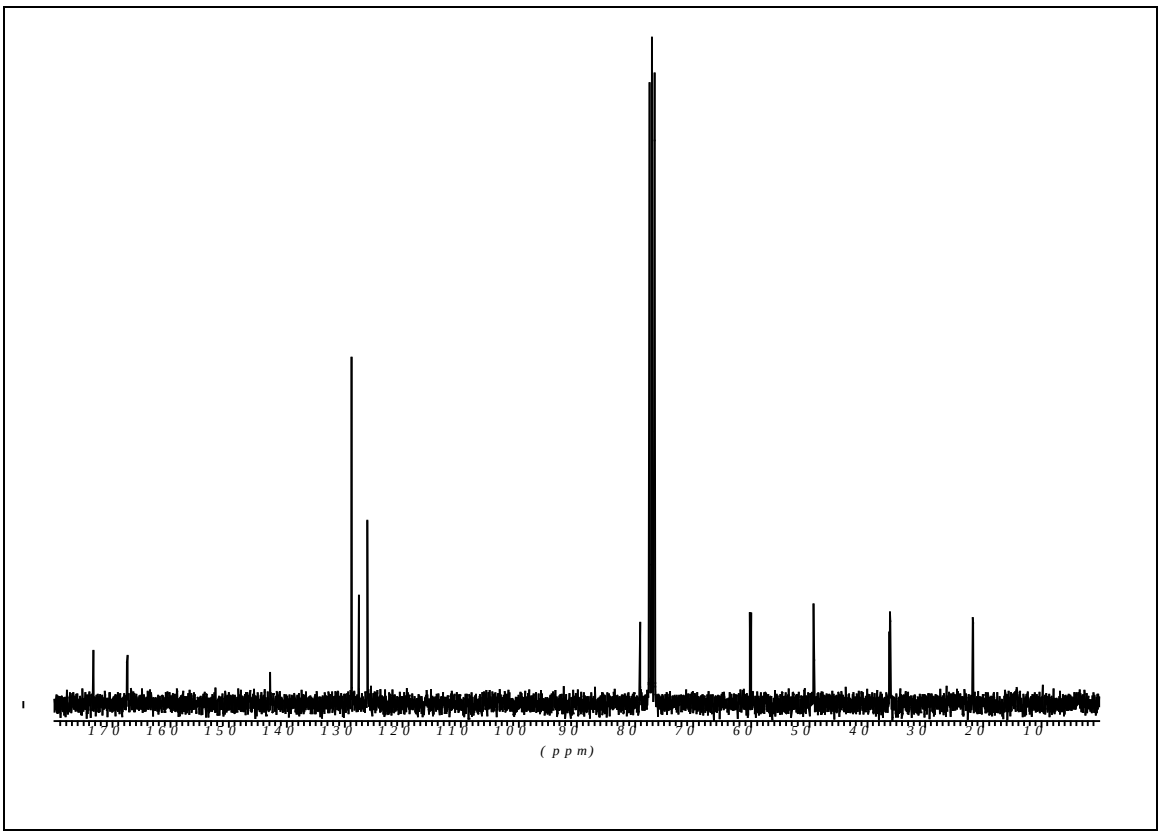
2-((2*S*,3*S*)-3-Azido-5-oxotetrahydrofuran-2-yl)-*N*-(1-phenylethyl)acetamide (123, $CDCl_3$):



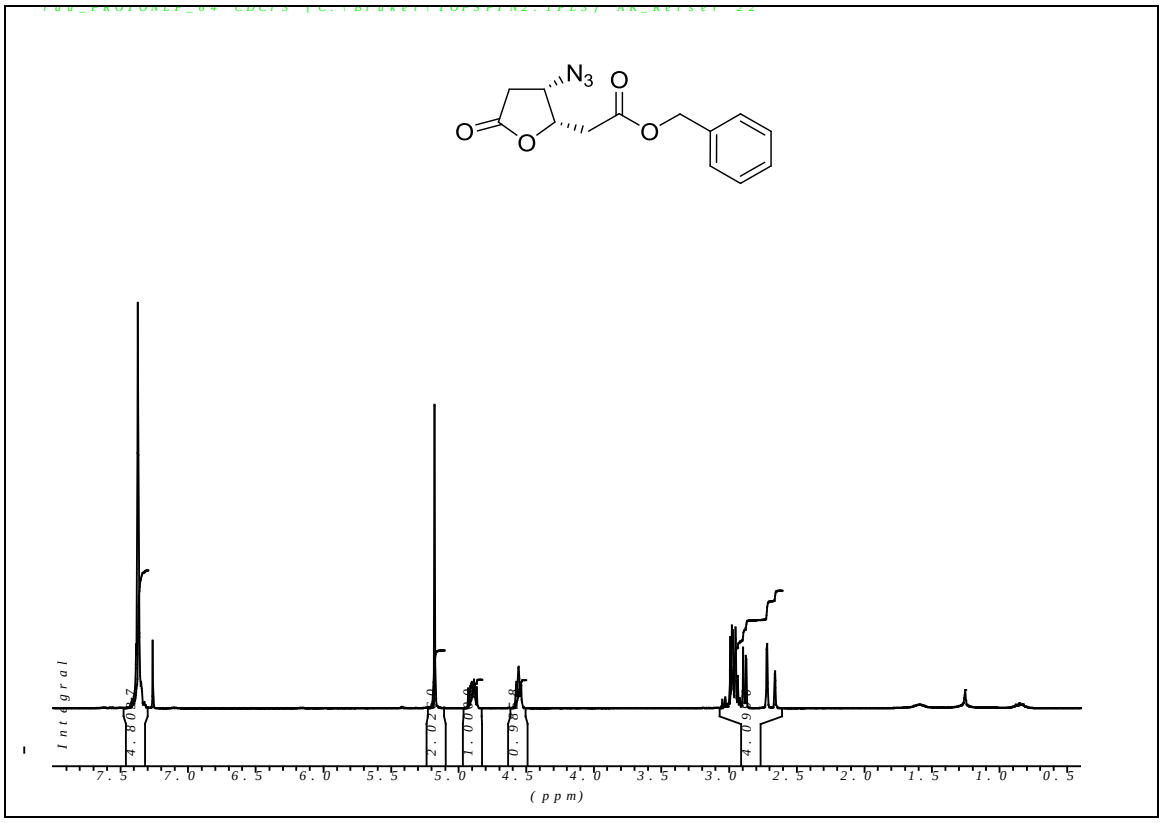


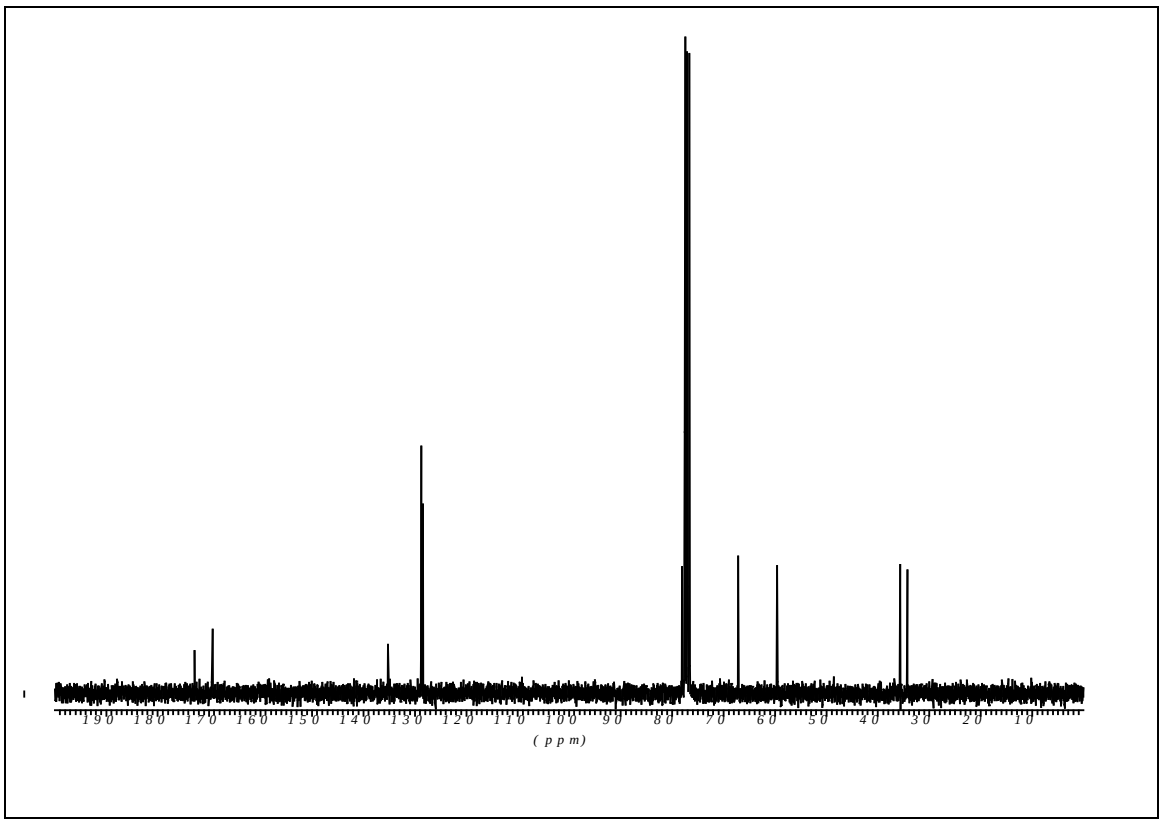
2-((2*S*,3*S*)-3-Azido-5-oxotetrahydrofuran-2-yl)-*N*-(1-phenylethyl)acetamide (123 (*Racemic*), $CDCl_3$



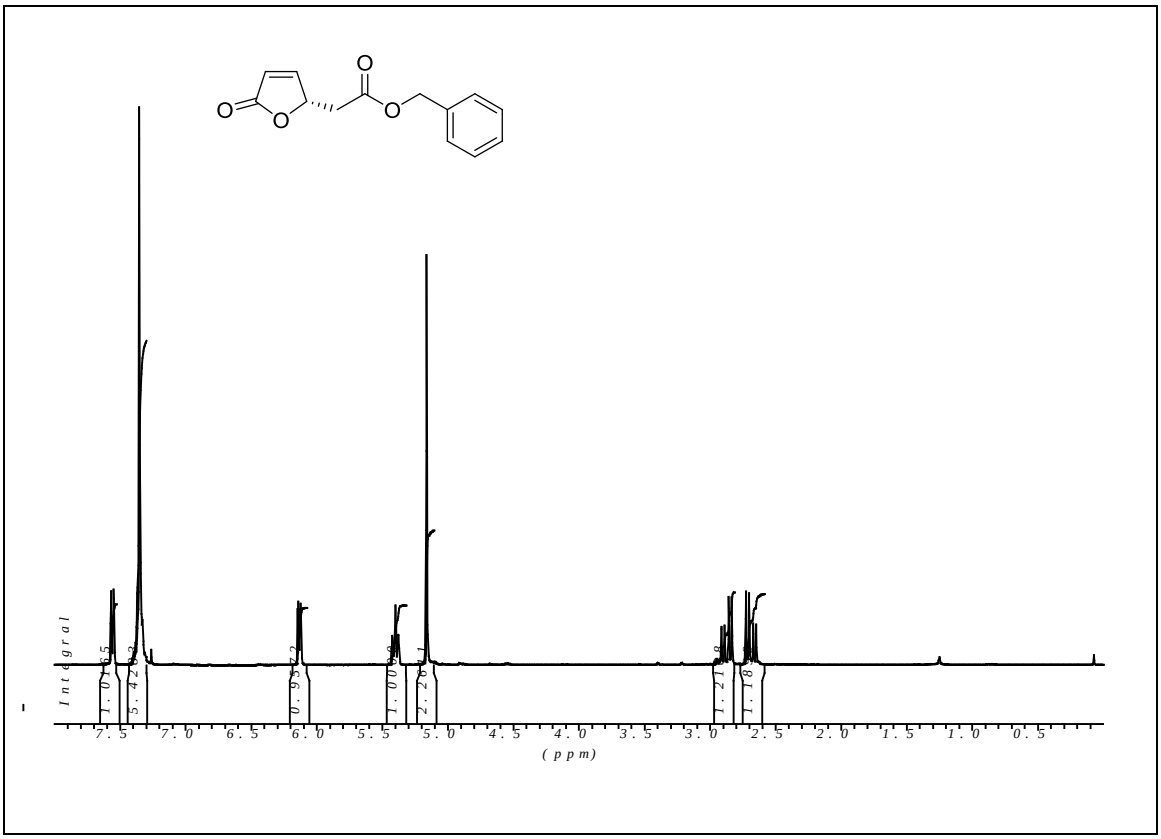


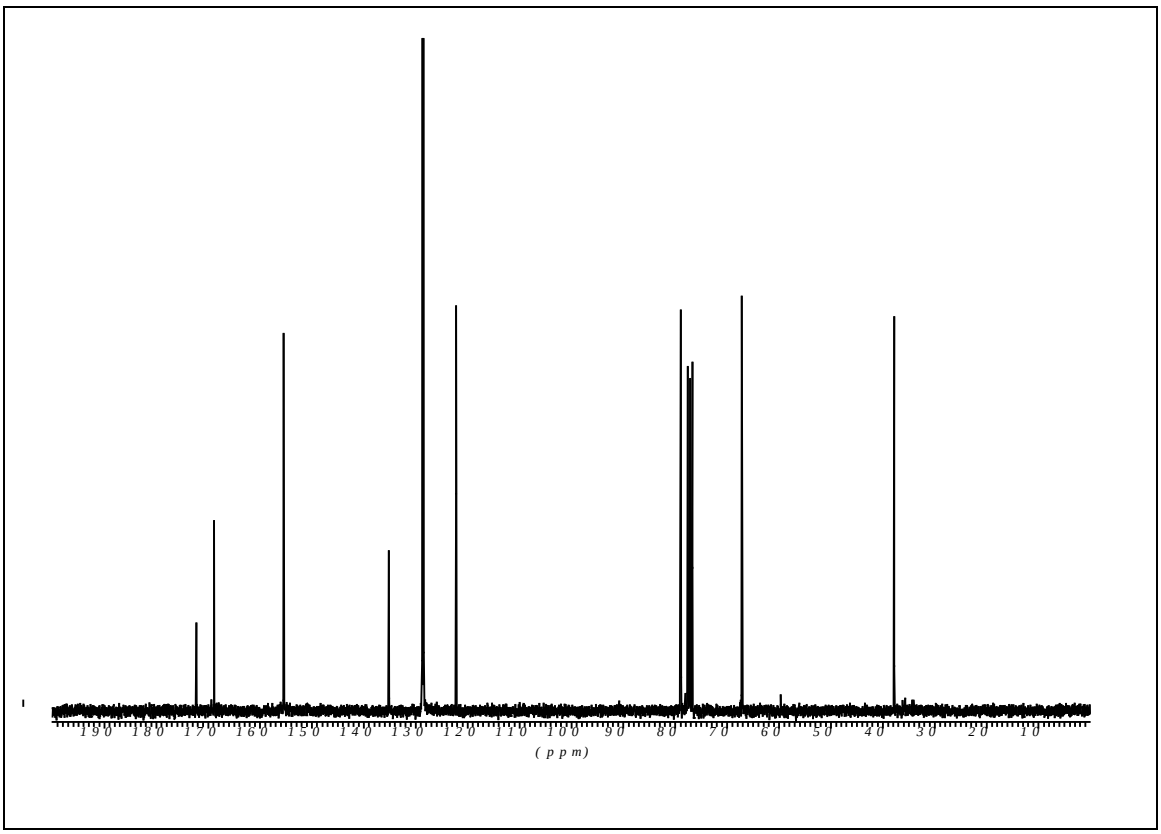
Benzyl 2-((*2S,3S*))-3-Azido-5-oxotetrahydrofuran-2-yl)acetate (120, $CDCl_3$):



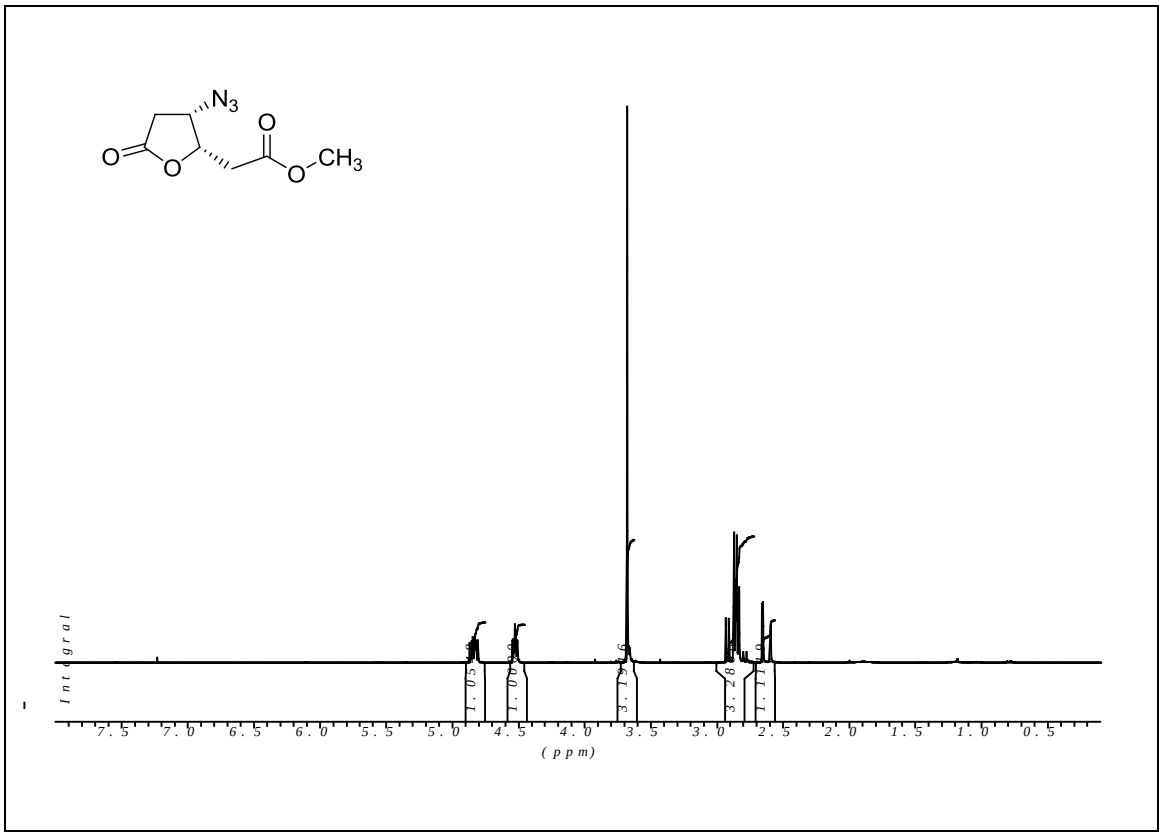


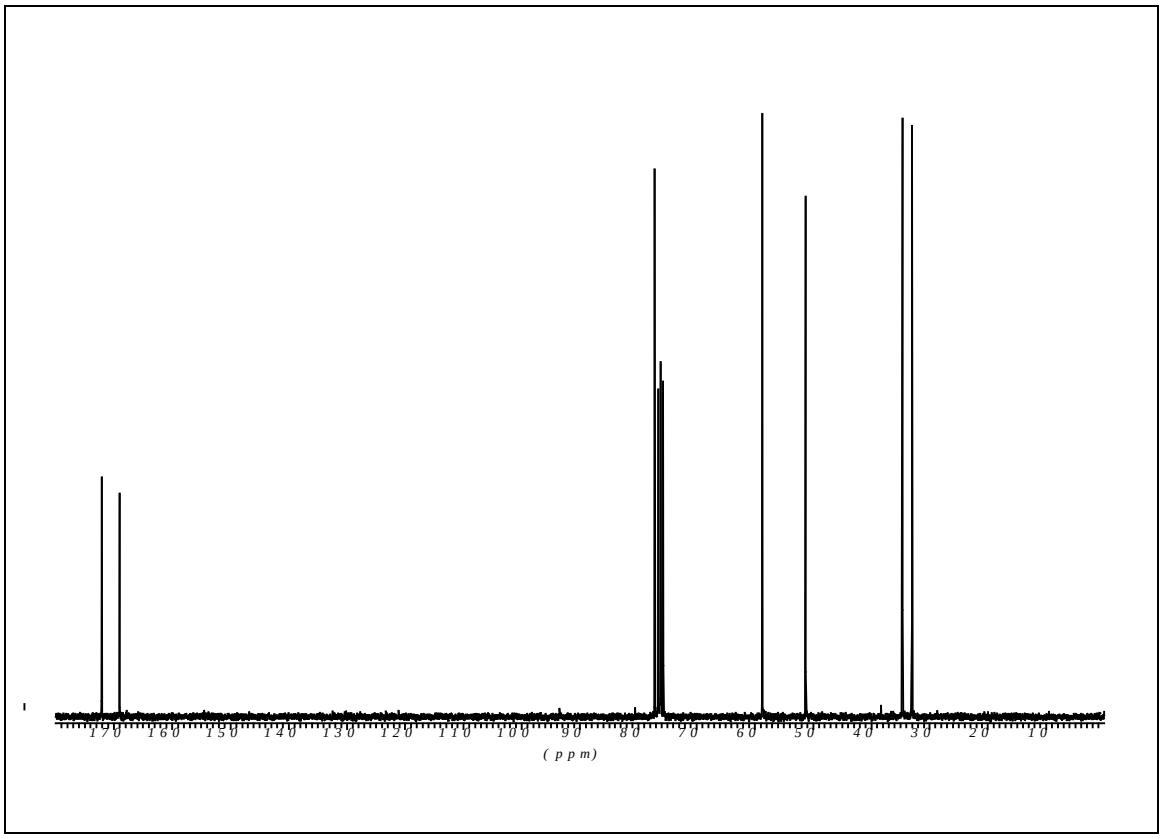
(*S*)-Benzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (127, $CDCl_3$):



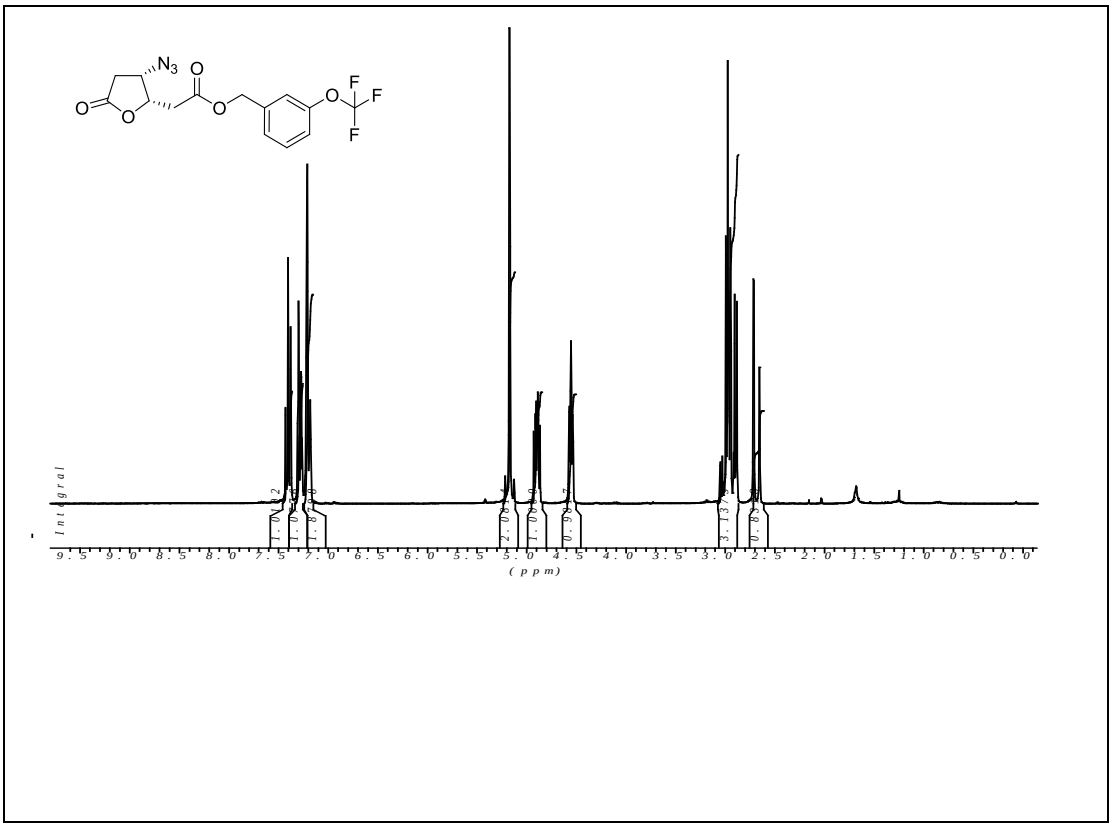


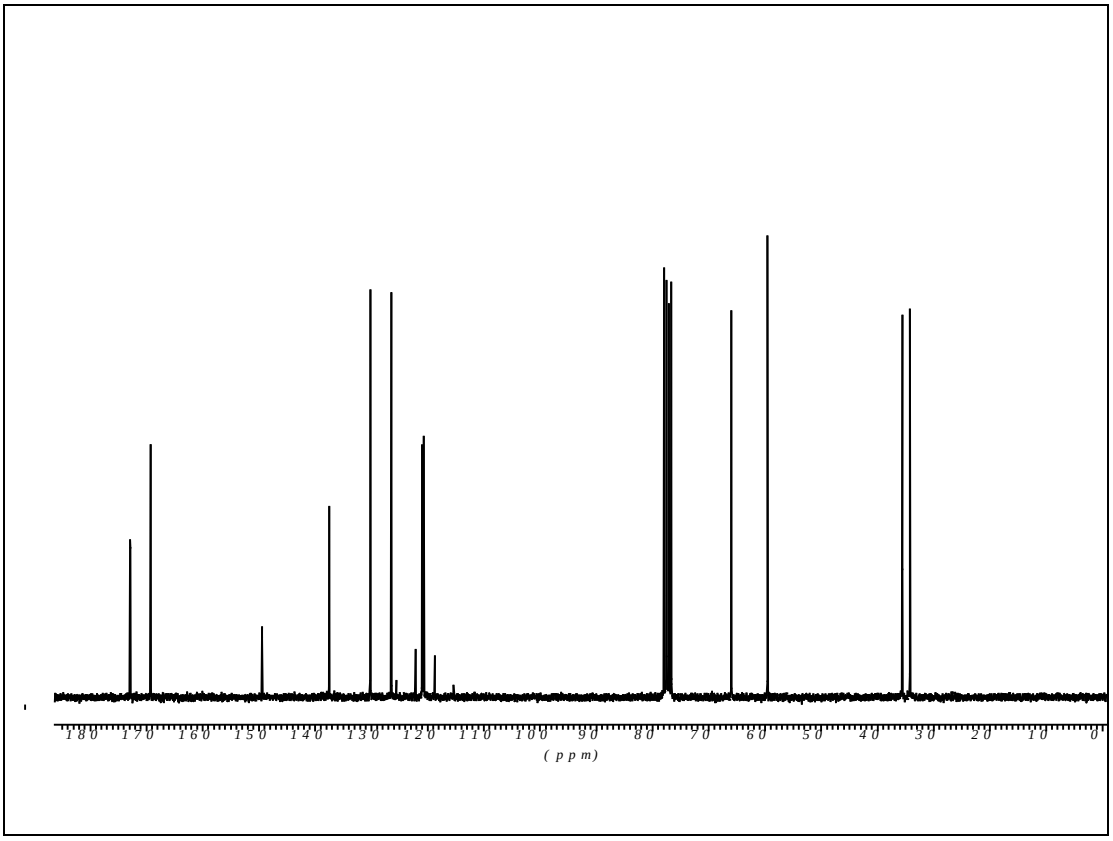
Methyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (128, $CDCl_3$):



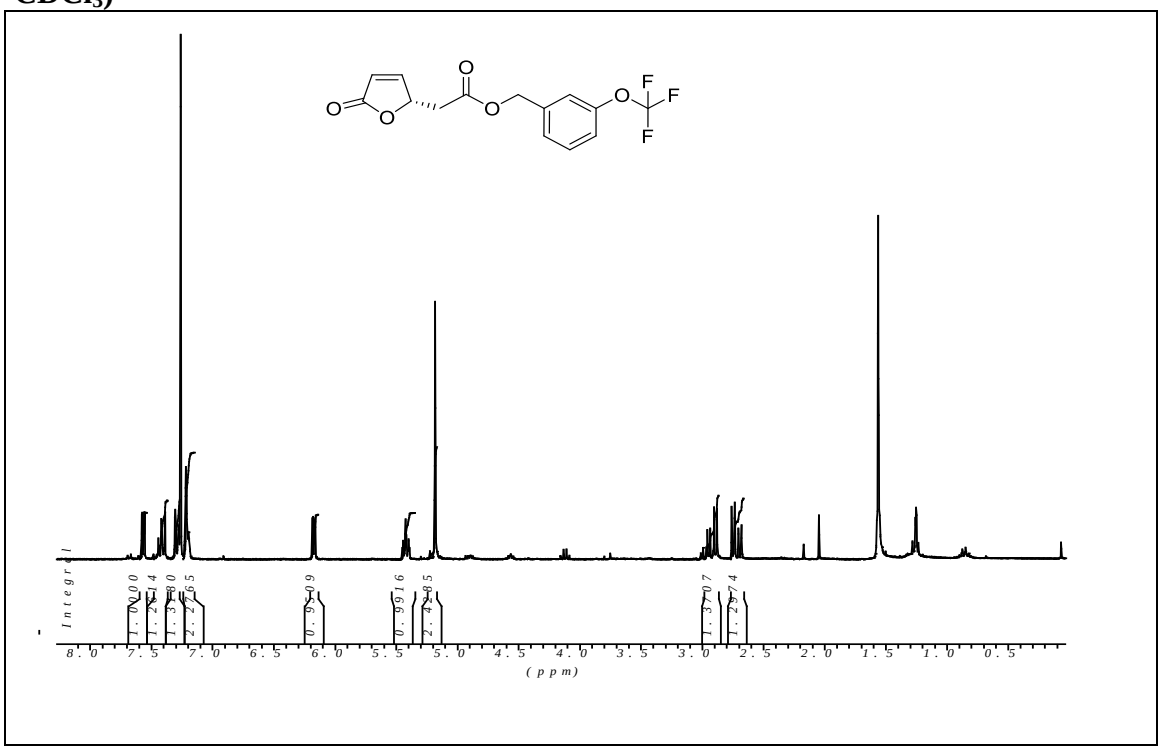


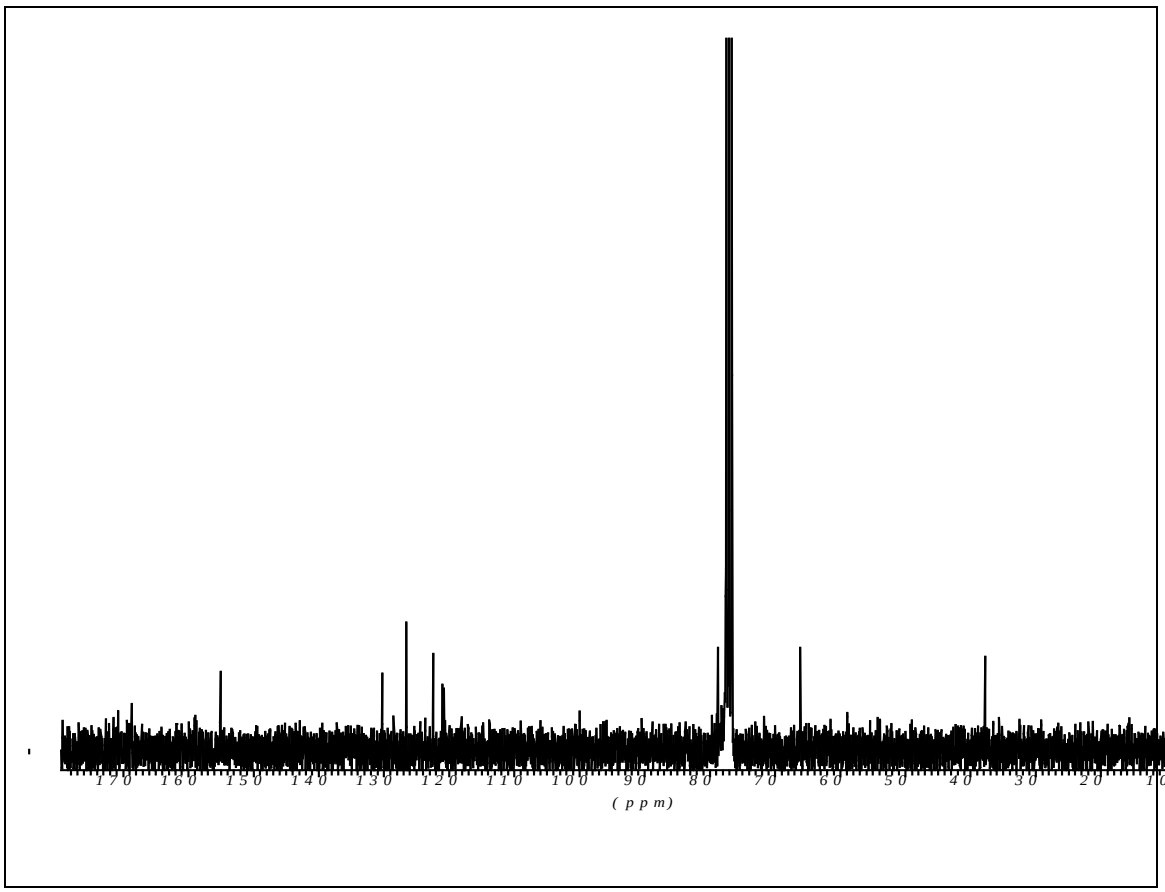
3-(Trifluoromethoxy)benzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (129, $CDCl_3$)



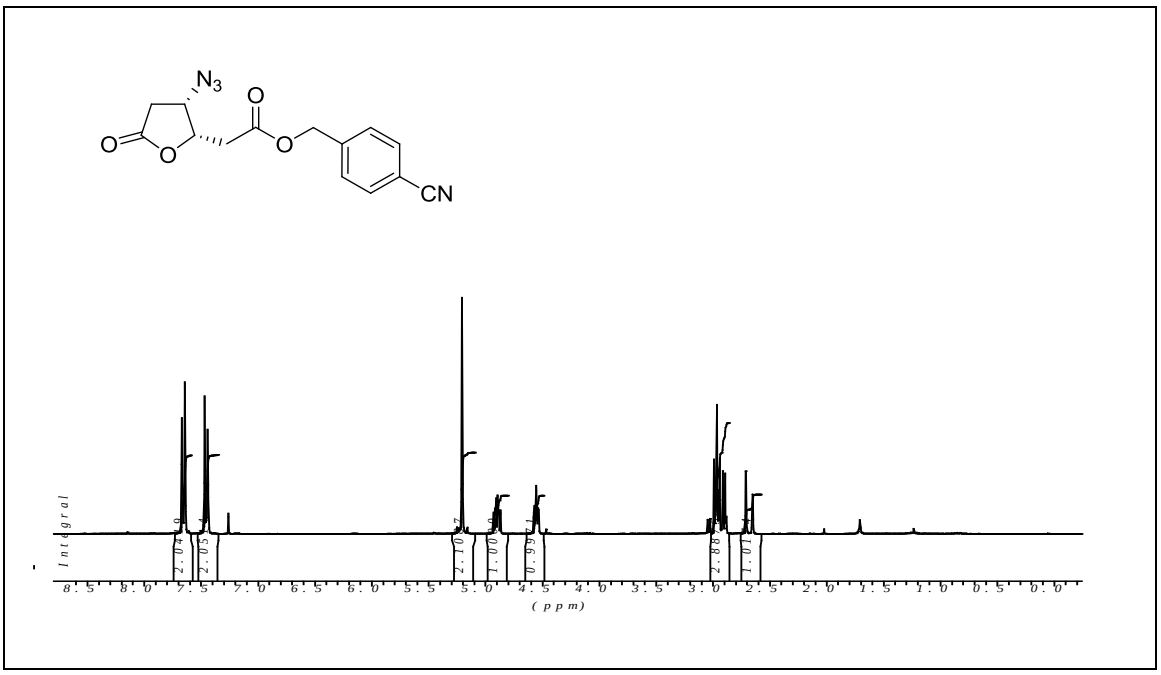


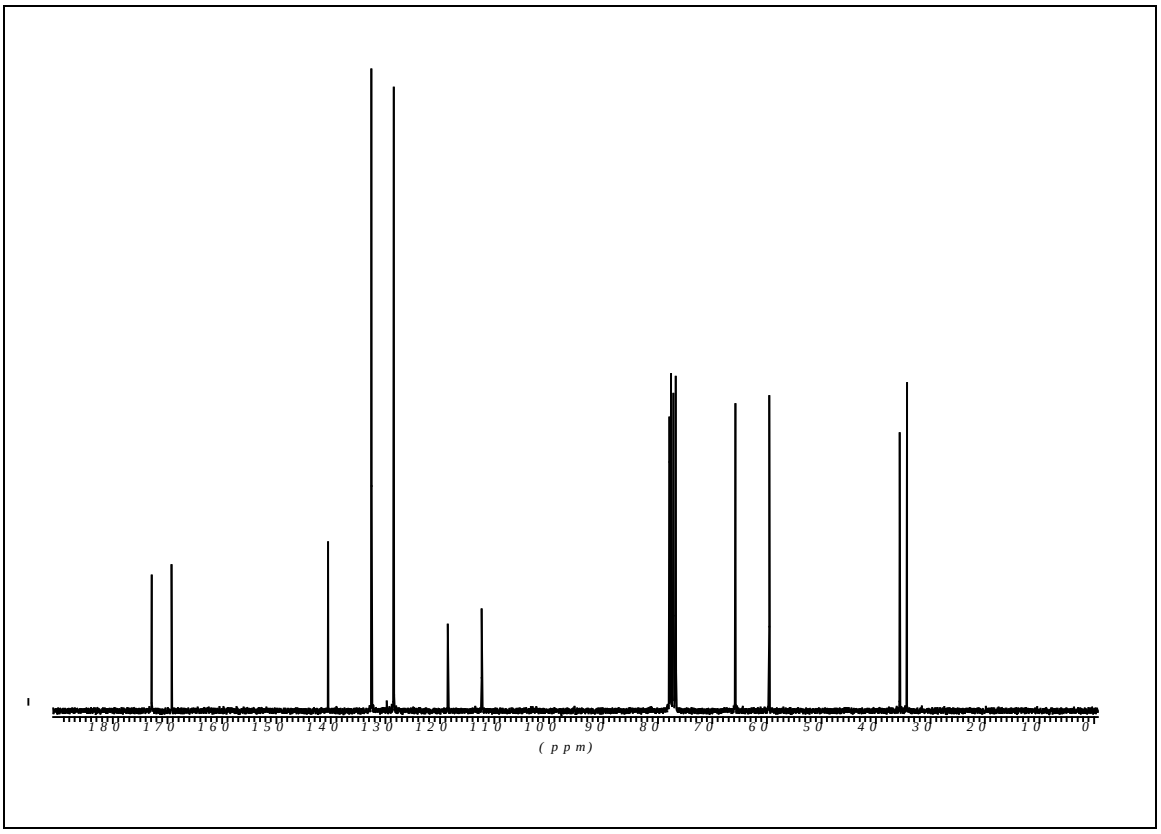
(*S*)-3-(Trifluoromethoxy)benzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (130, $CDCl_3$)



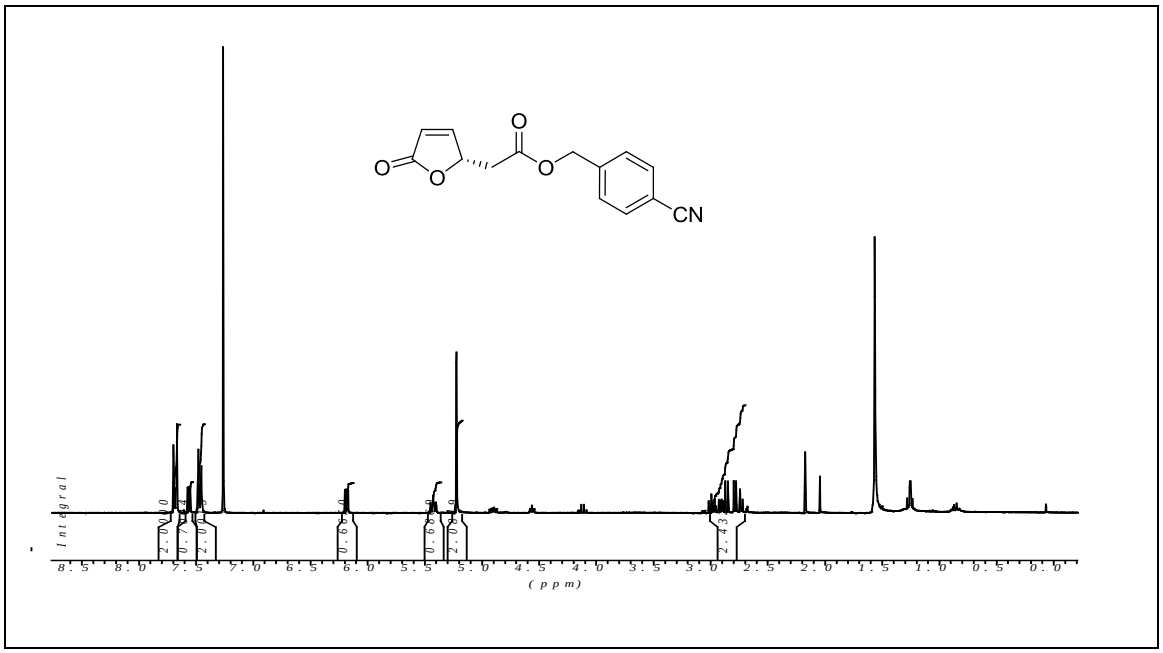


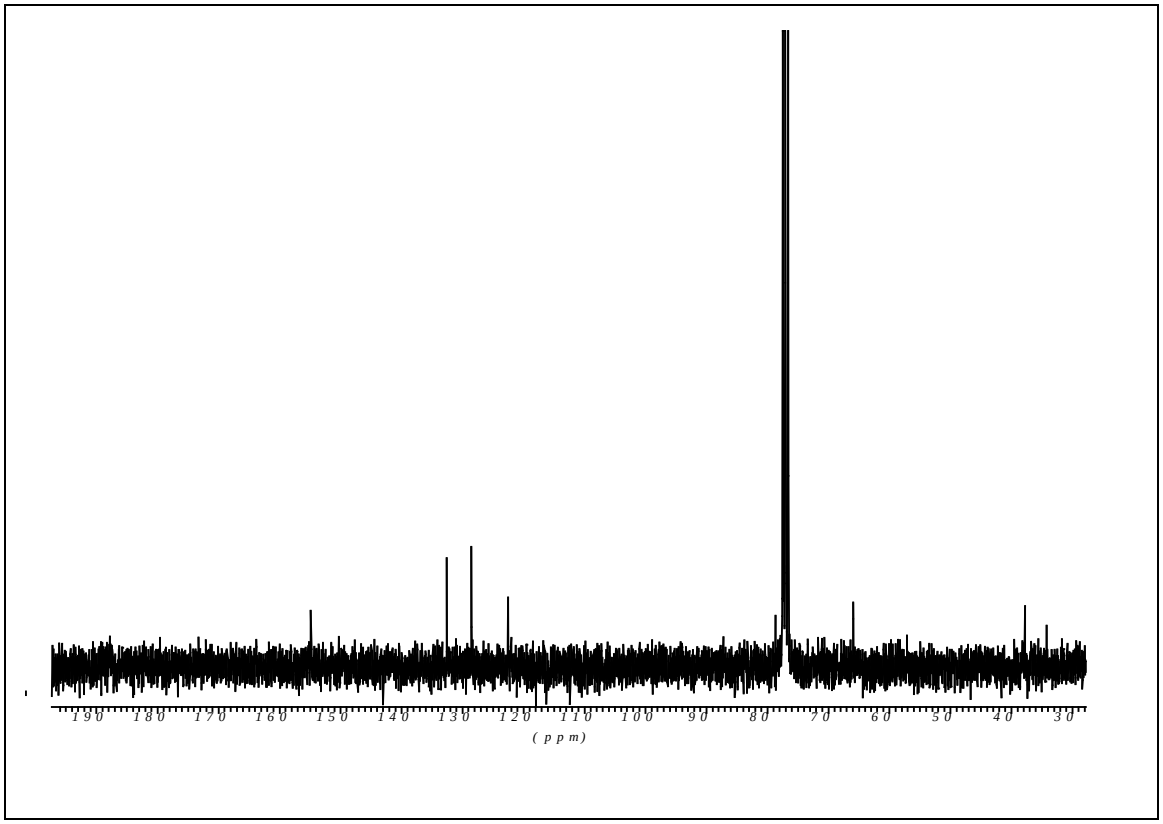
4-Cyanobenzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (131, $CDCl_3$)



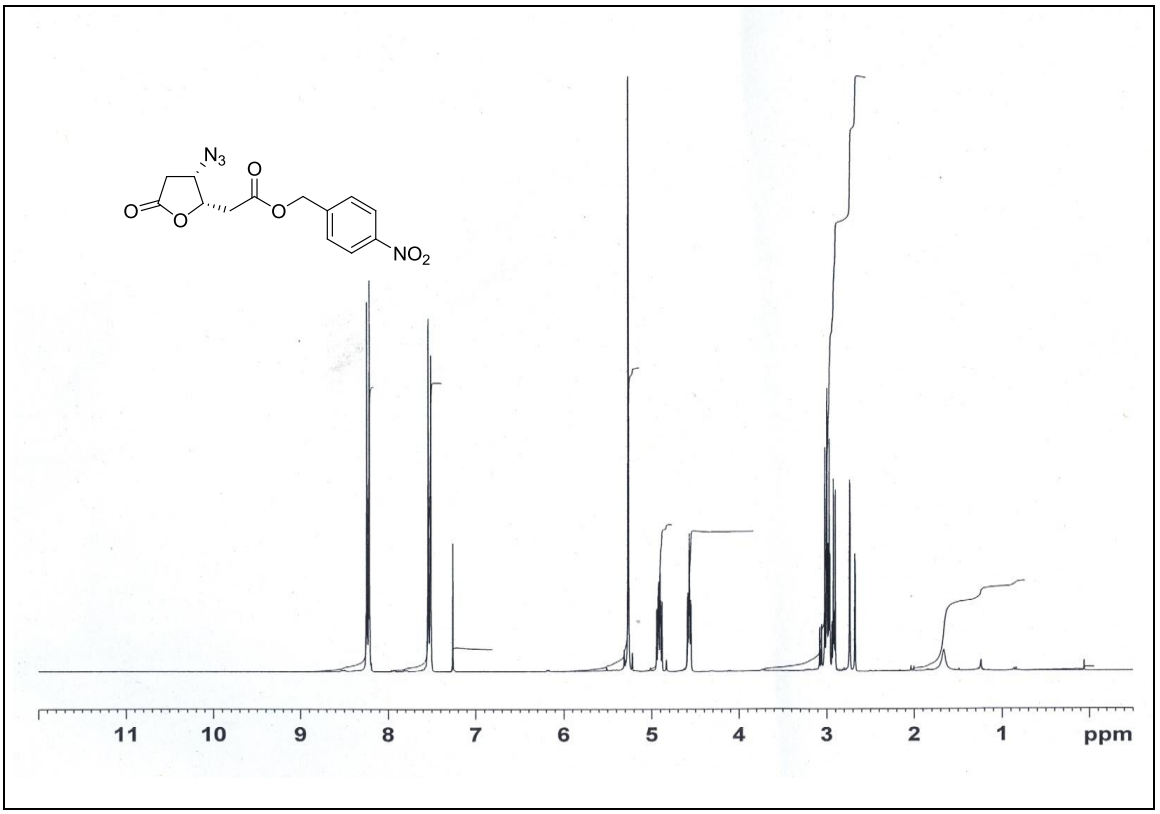


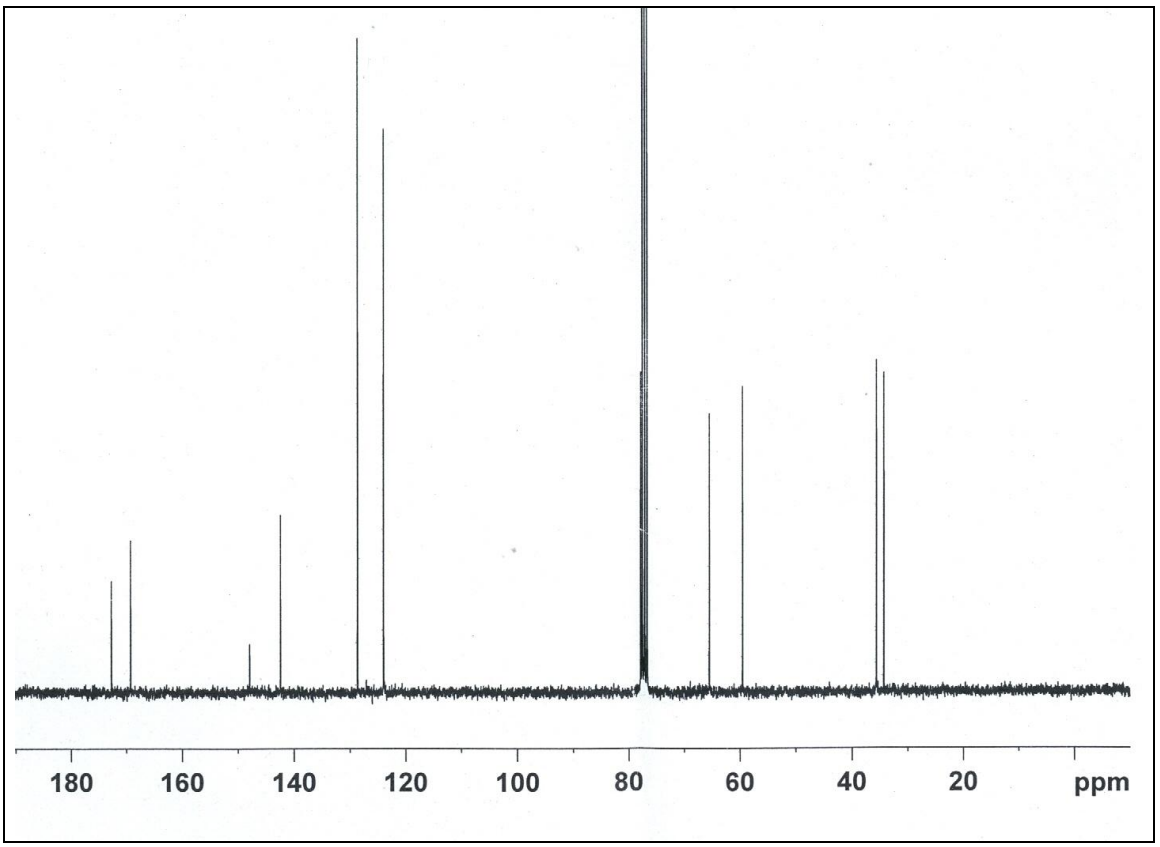
(*S*)-4-Cyanobenzyl 2-(5-oxo-2,5-dihydrofuran-2-ylIacetate (132, $CDCl_3$)



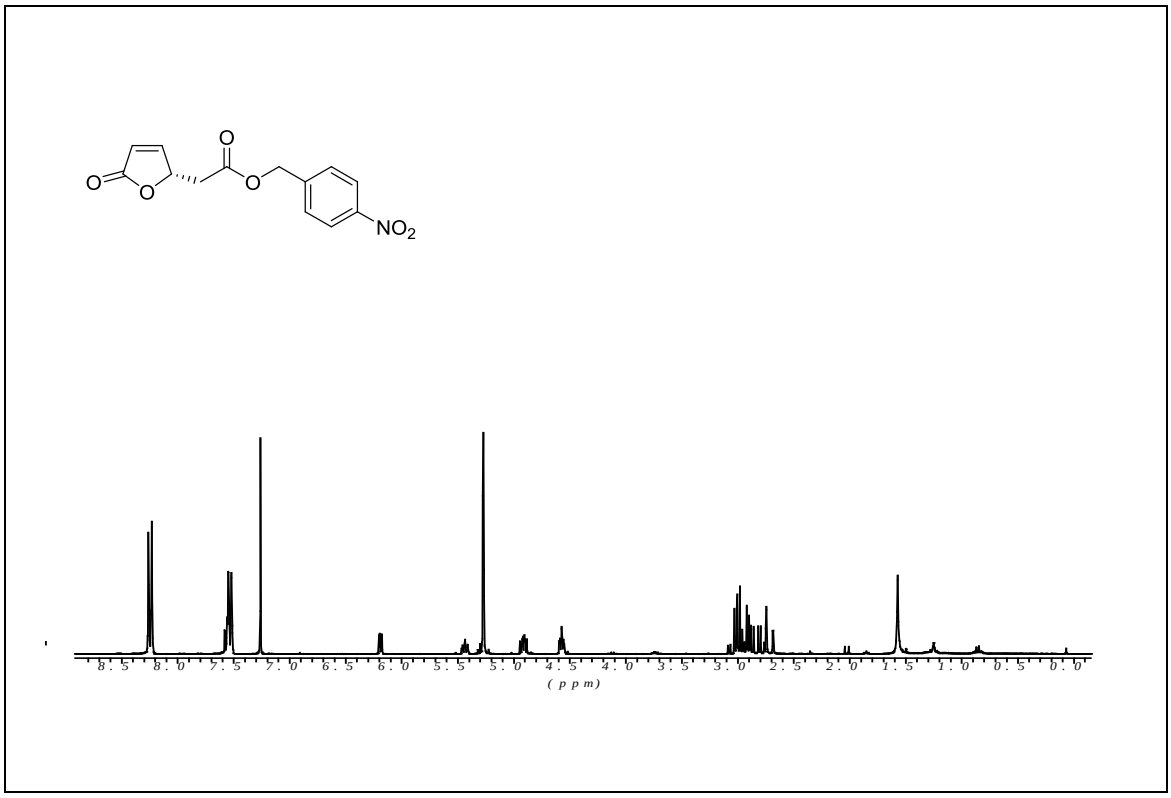


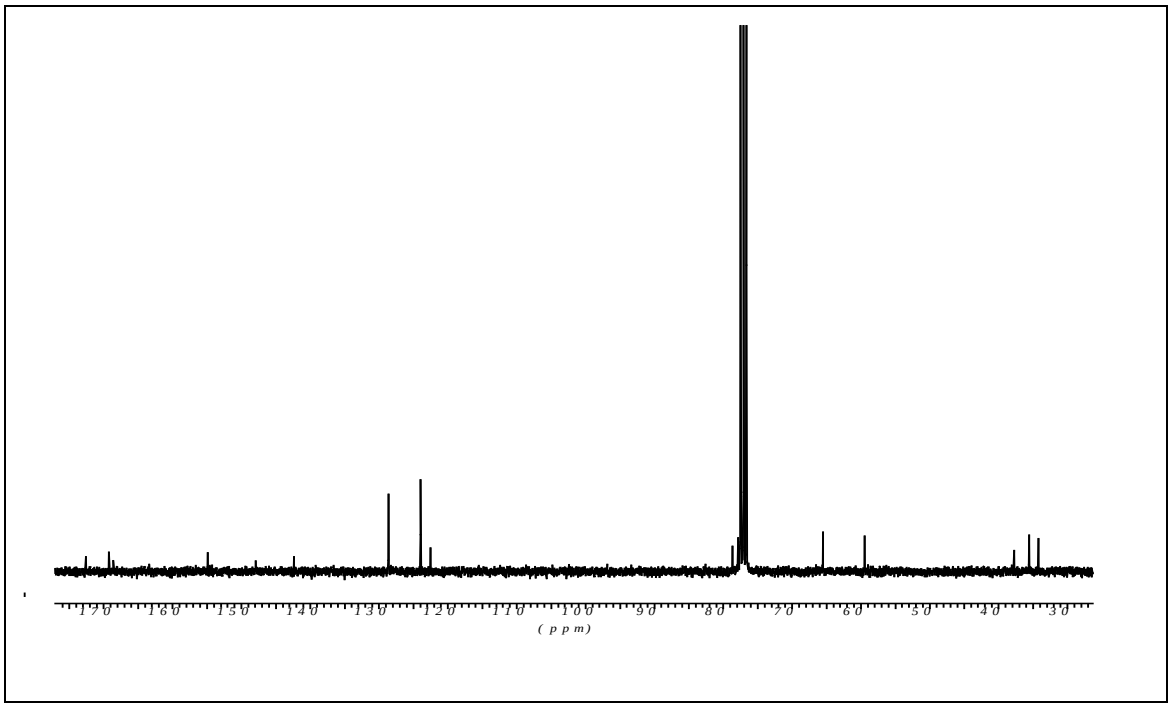
4-Nitrobenzyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (133, $CDCl_3$)



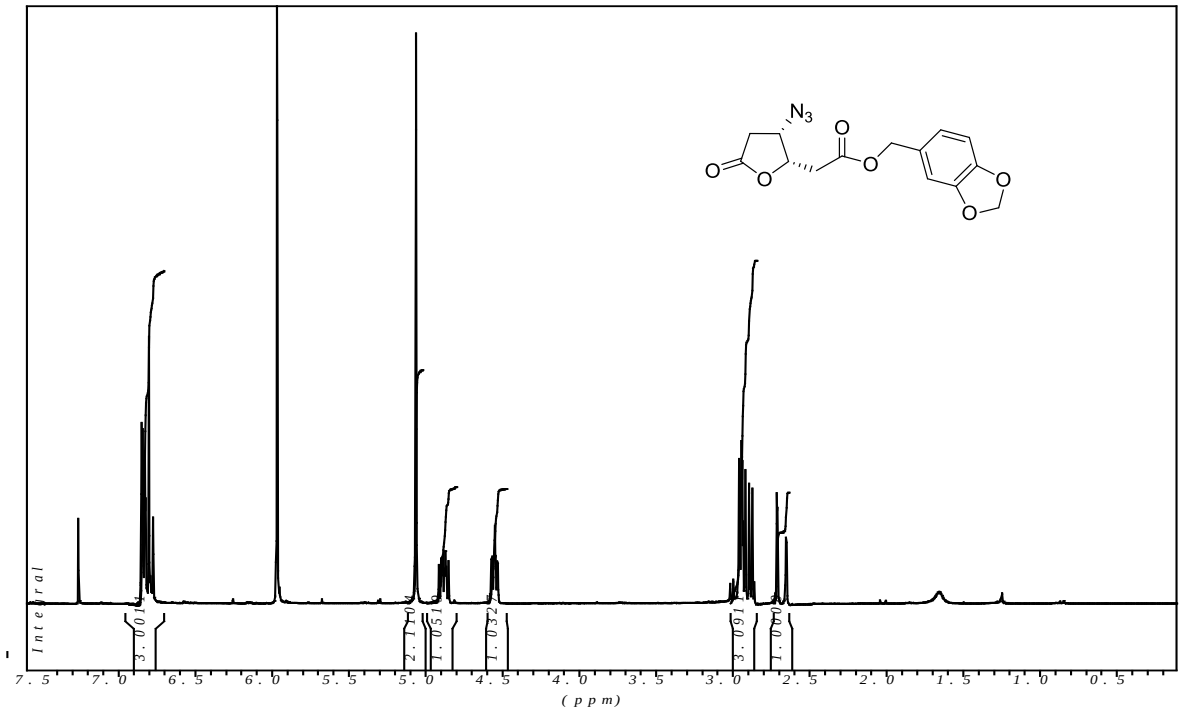


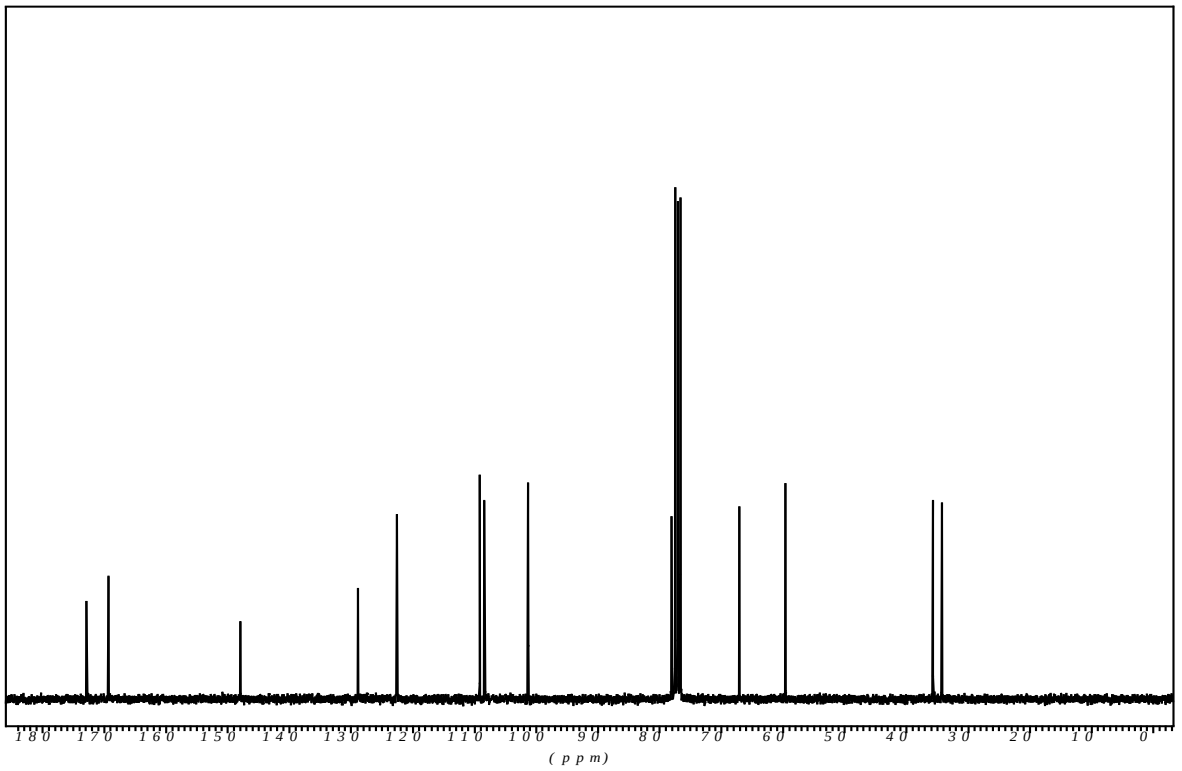
(*S*)-4-Nitrobenzyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (134, $CDCl_3$)



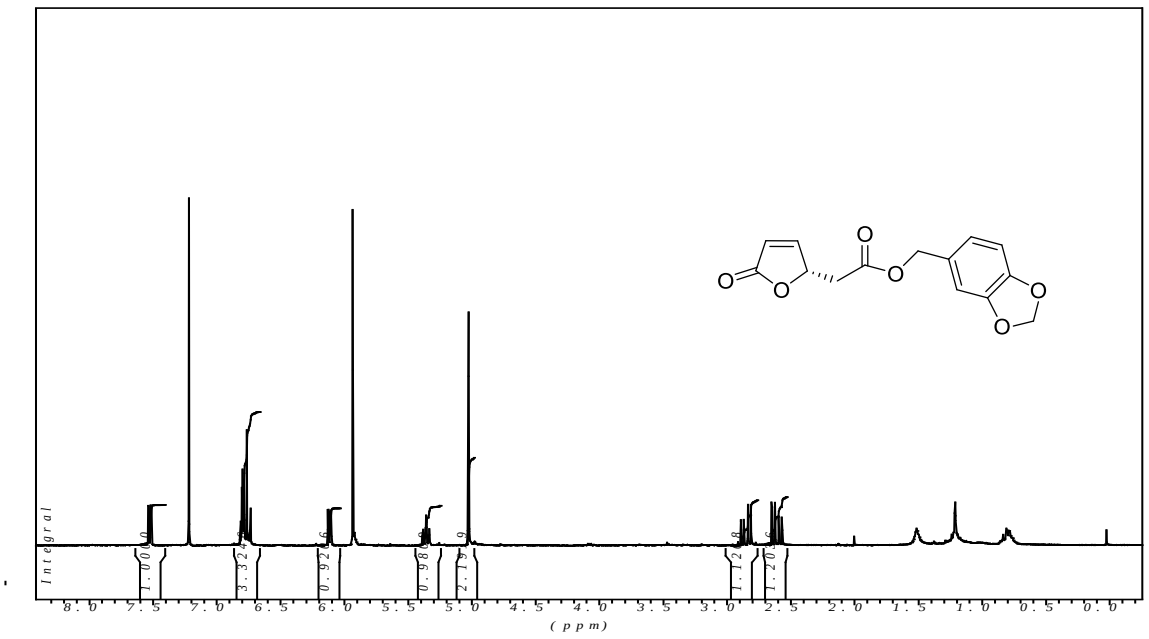


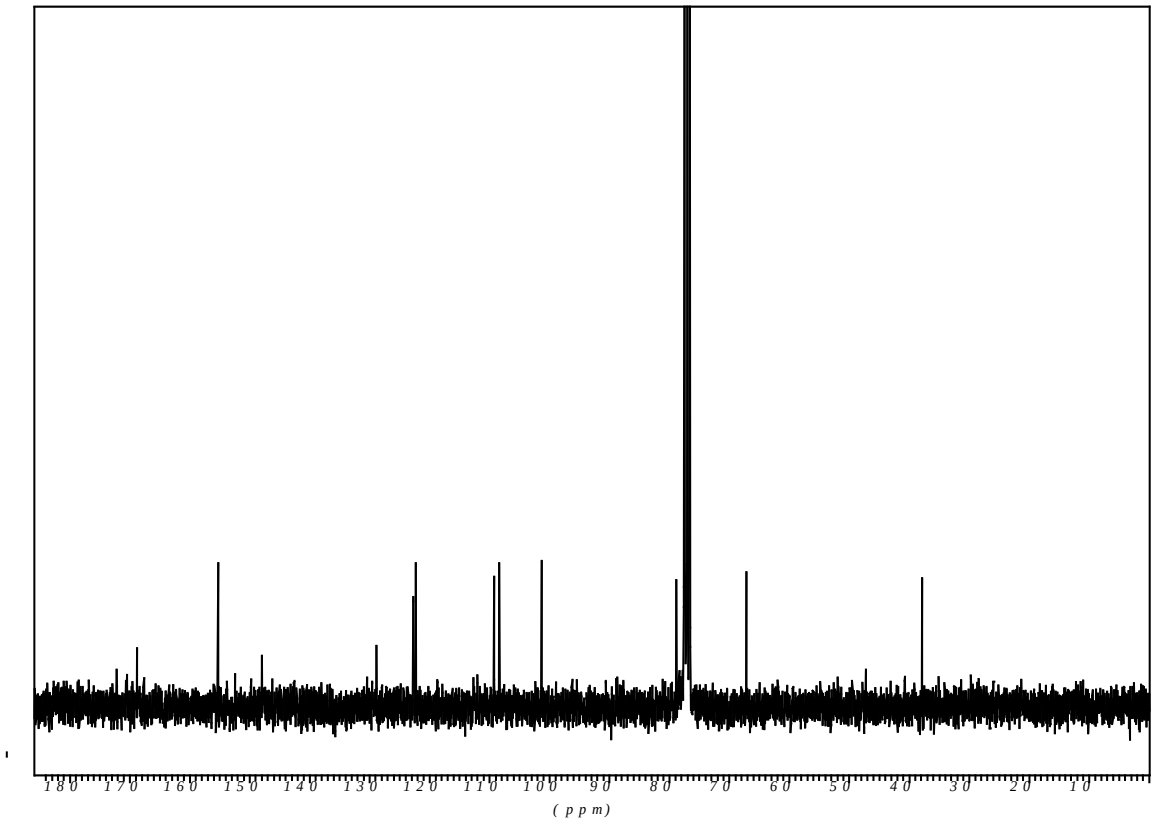
Benzo[d][1,3]dioxol-5-ylmethyl 2-((2S,3S)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (135, $CDCl_3$)



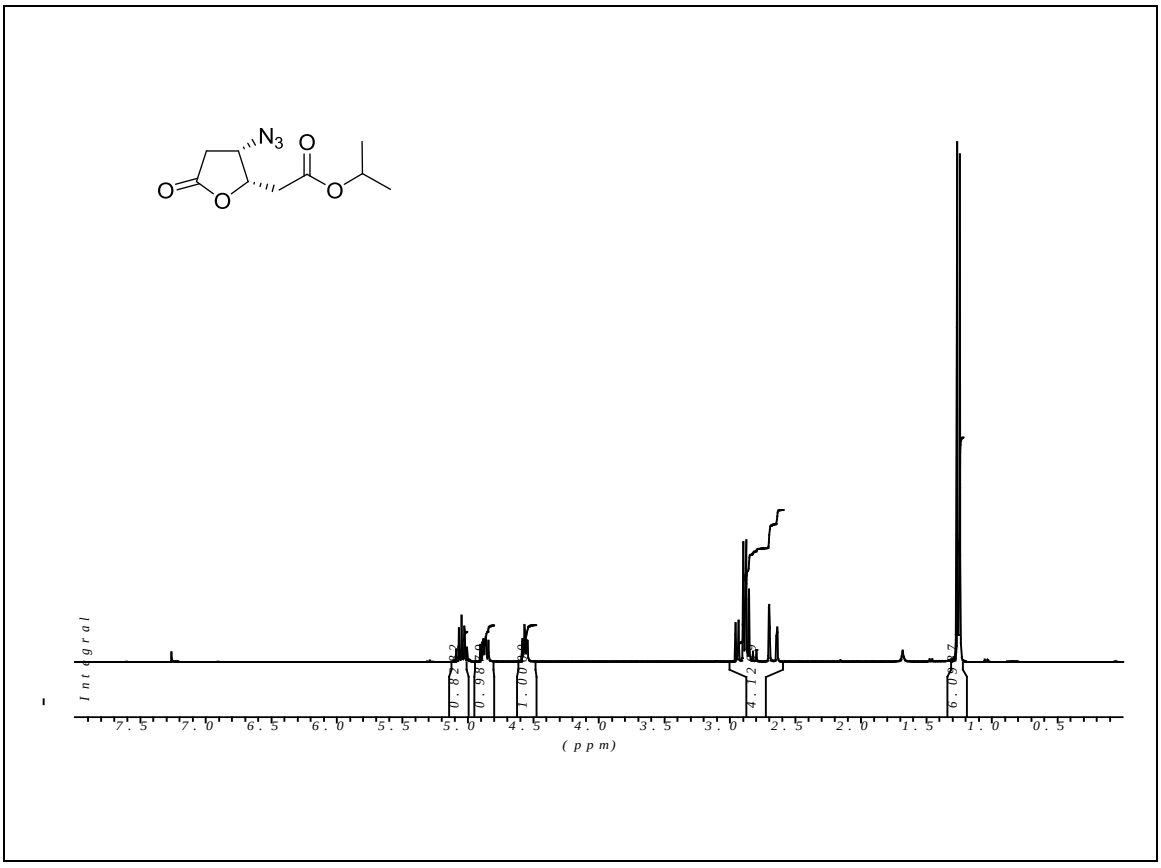


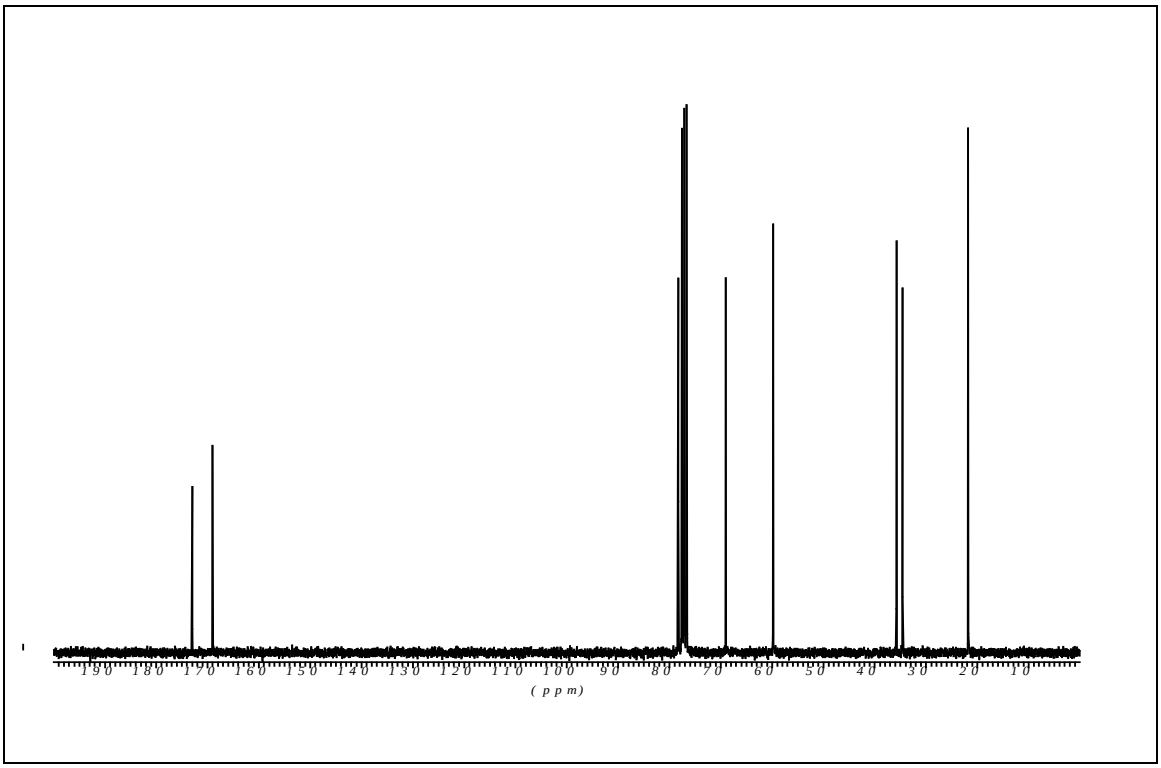
Benzo(d)(1,3)dioxol- 5-ylmethyl 2-((2*S*,3*S*)-3 azido-5-oxotetrahydrofuran-2-yl)acetate (136, $CDCl_3$)



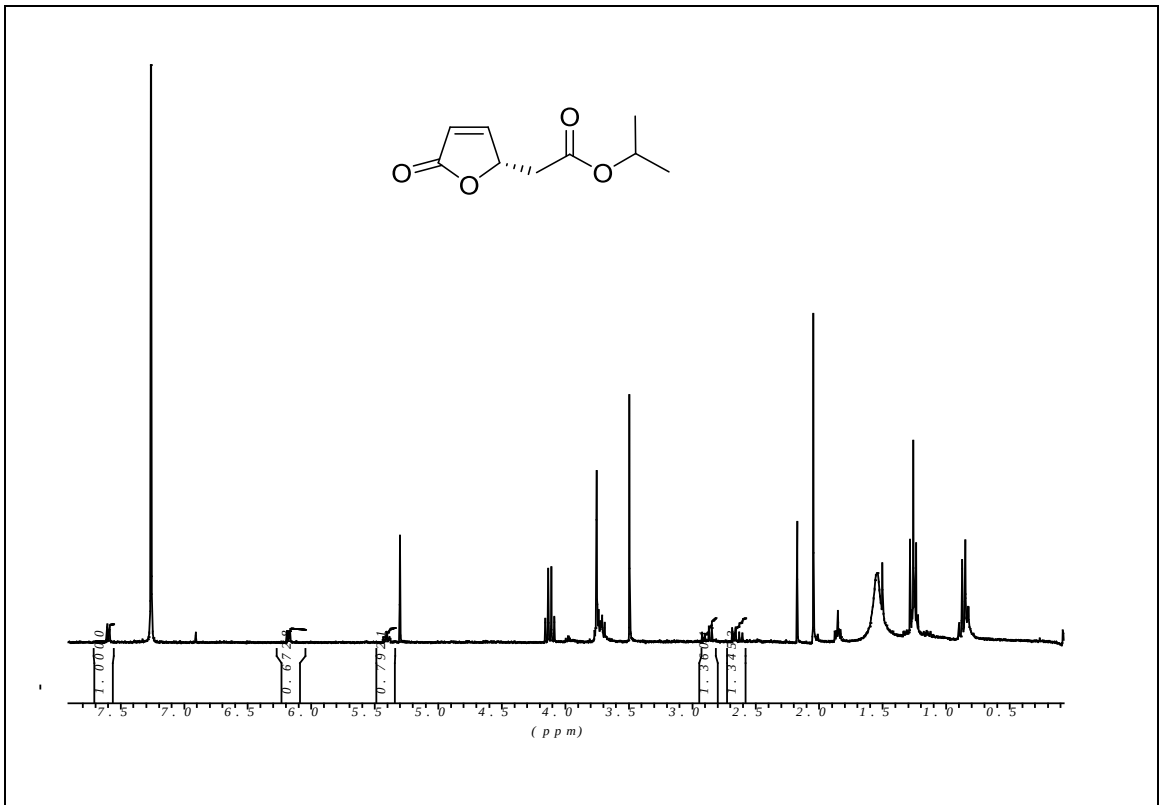


Isopropyl 2-((2*S*,3*S*)-3-azido-5-oxotetrahydrofuran-2-yl)acetate (137, $CDCl_3$):

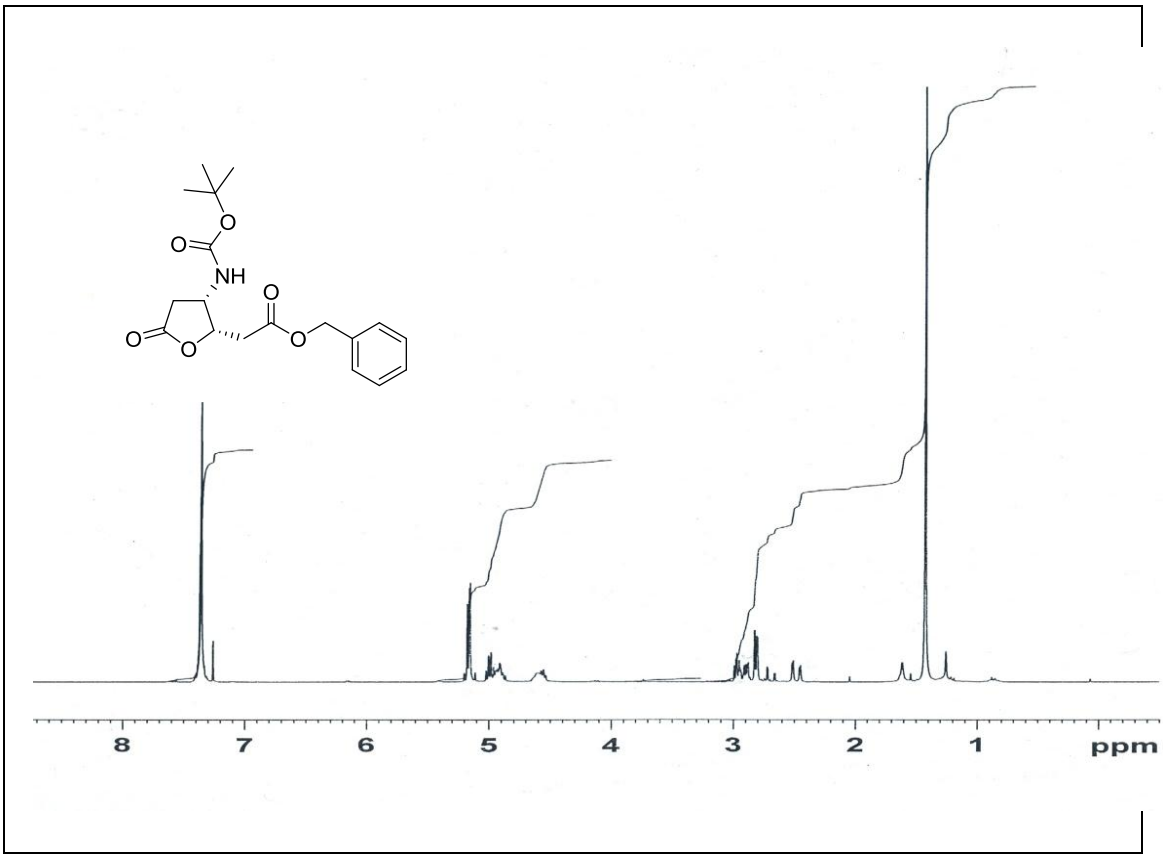


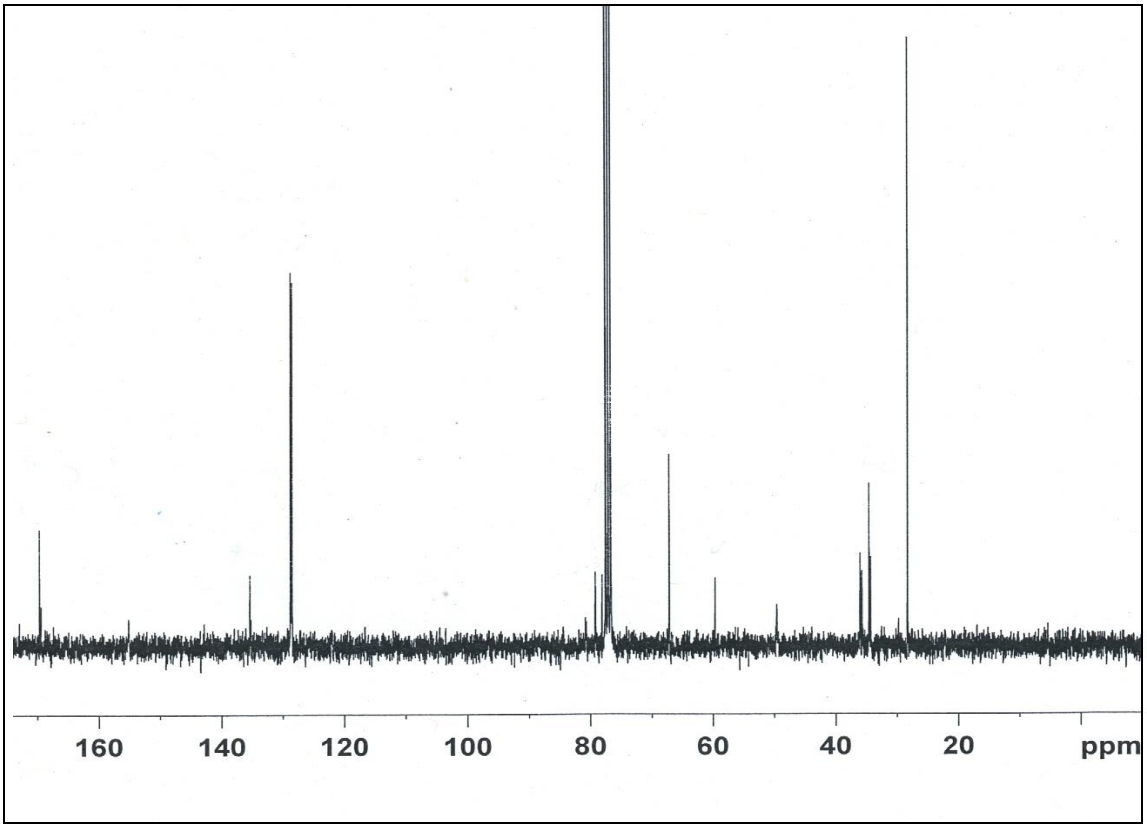


(*S*)-Isopropyl 2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (137, $CDCl_3$)

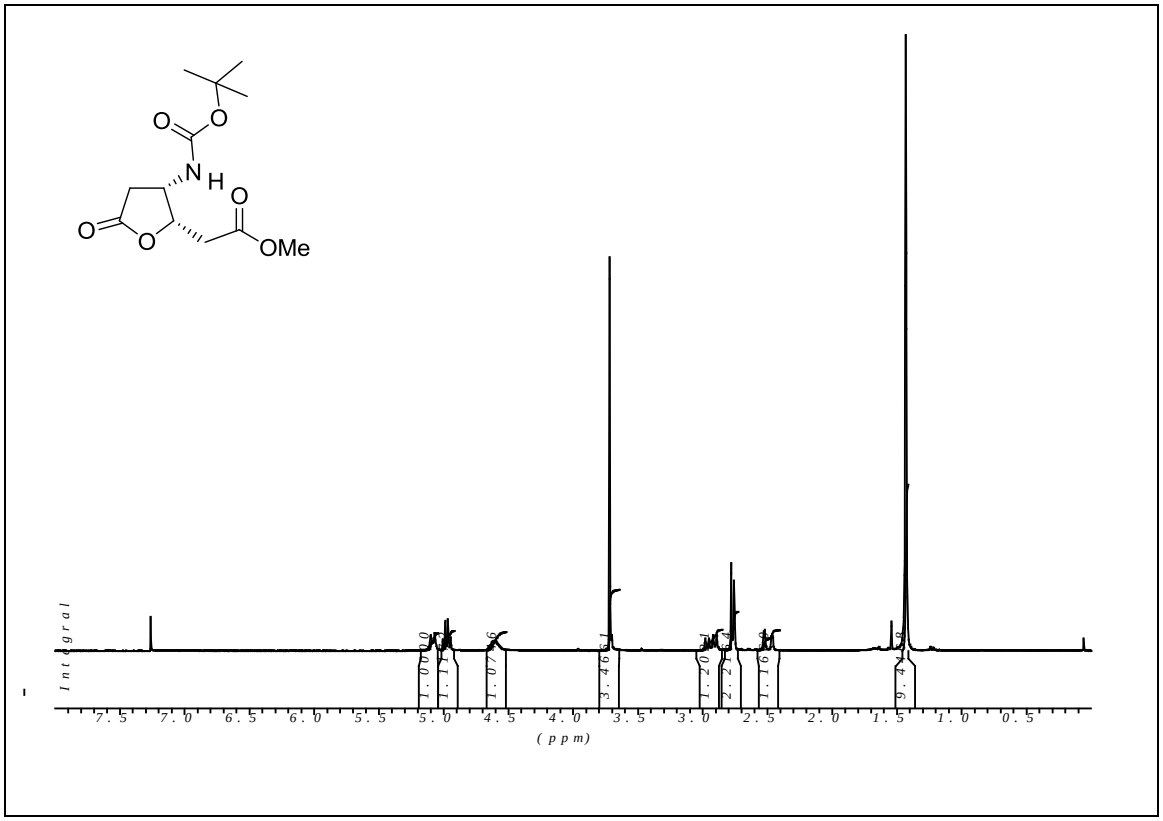


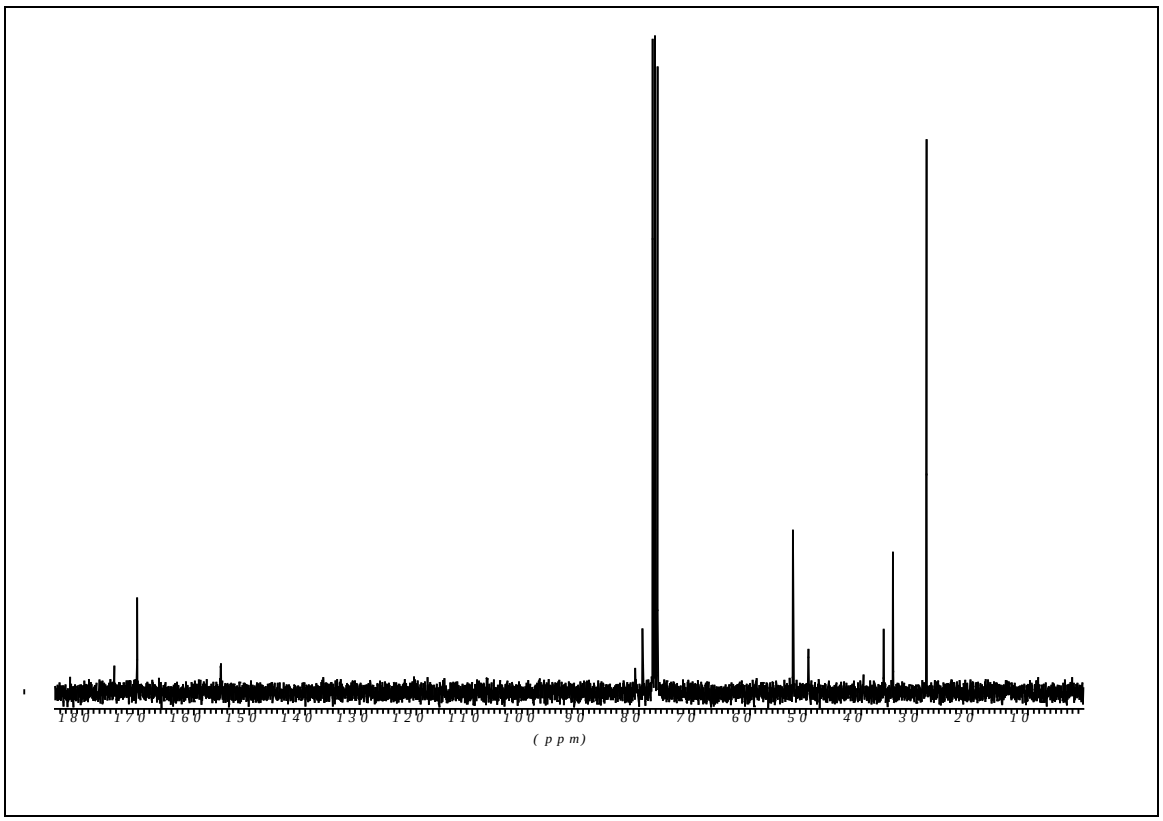
Benzyl 2-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetate (139, $CDCl_3$)



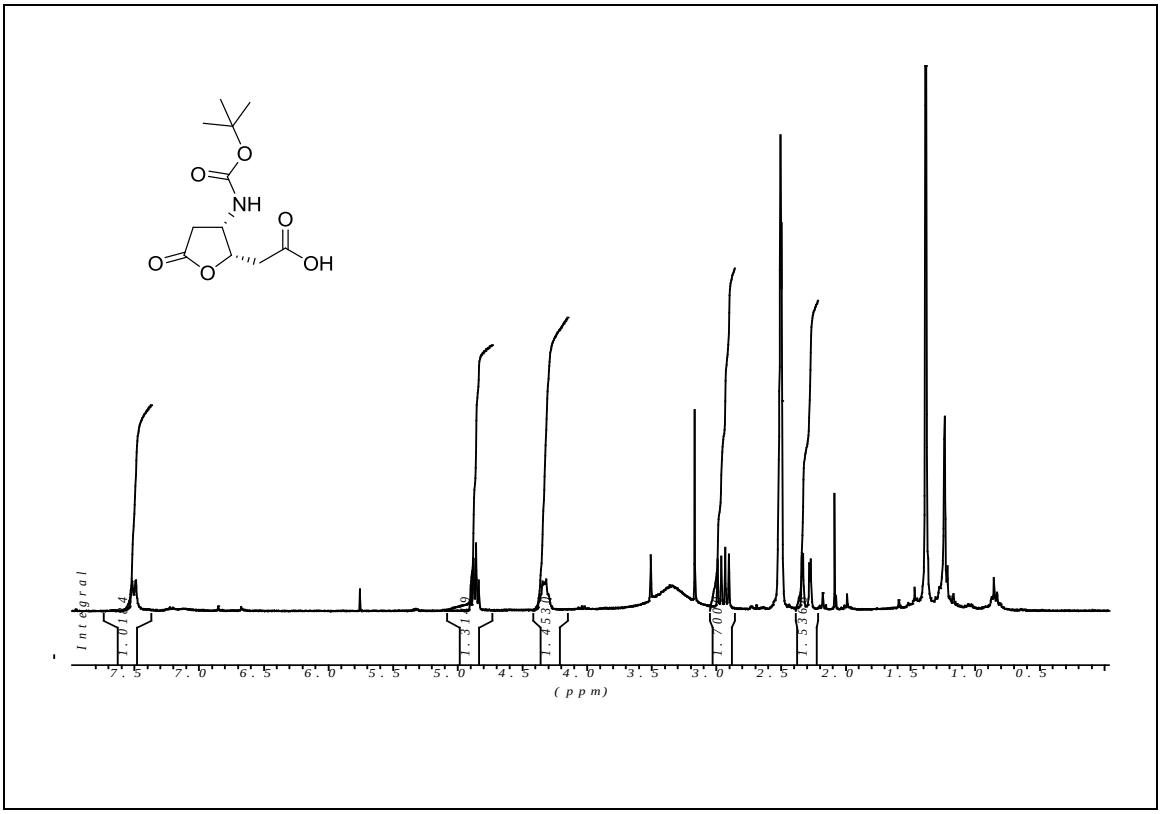


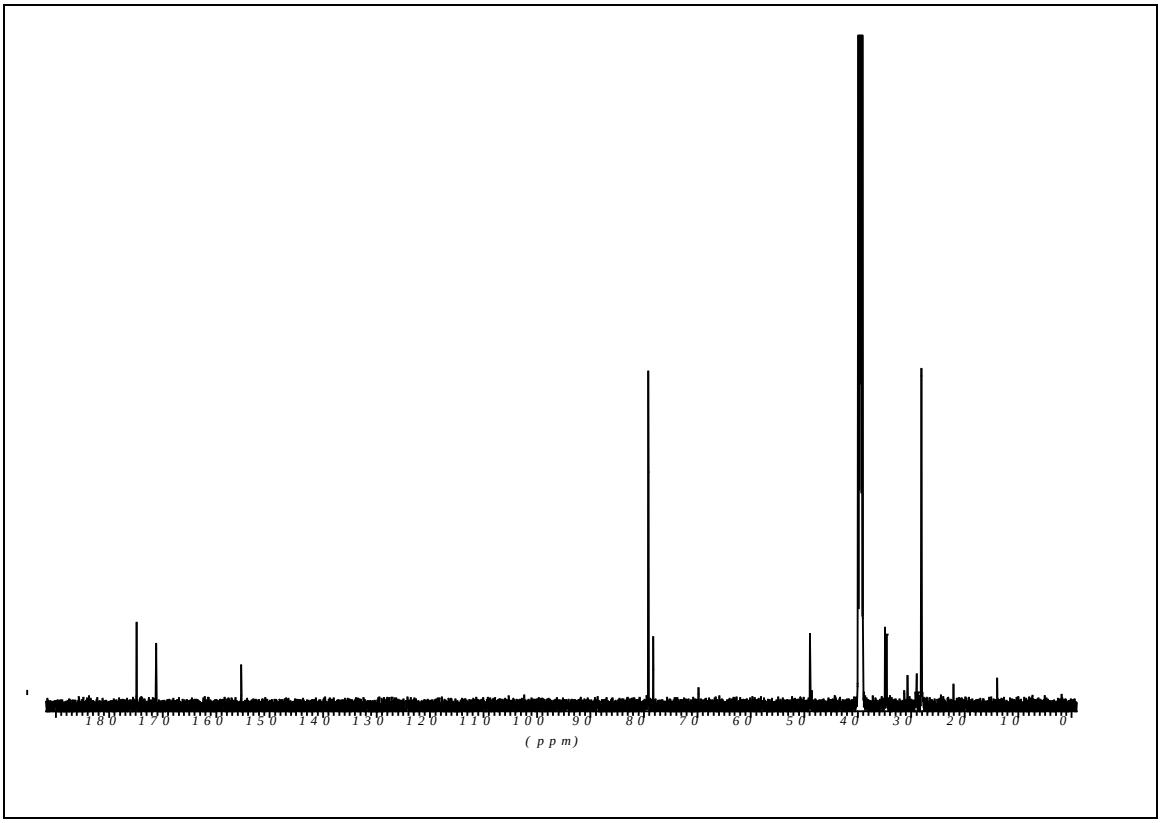
Methyl 2-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetate (140, $CDCl_3$):



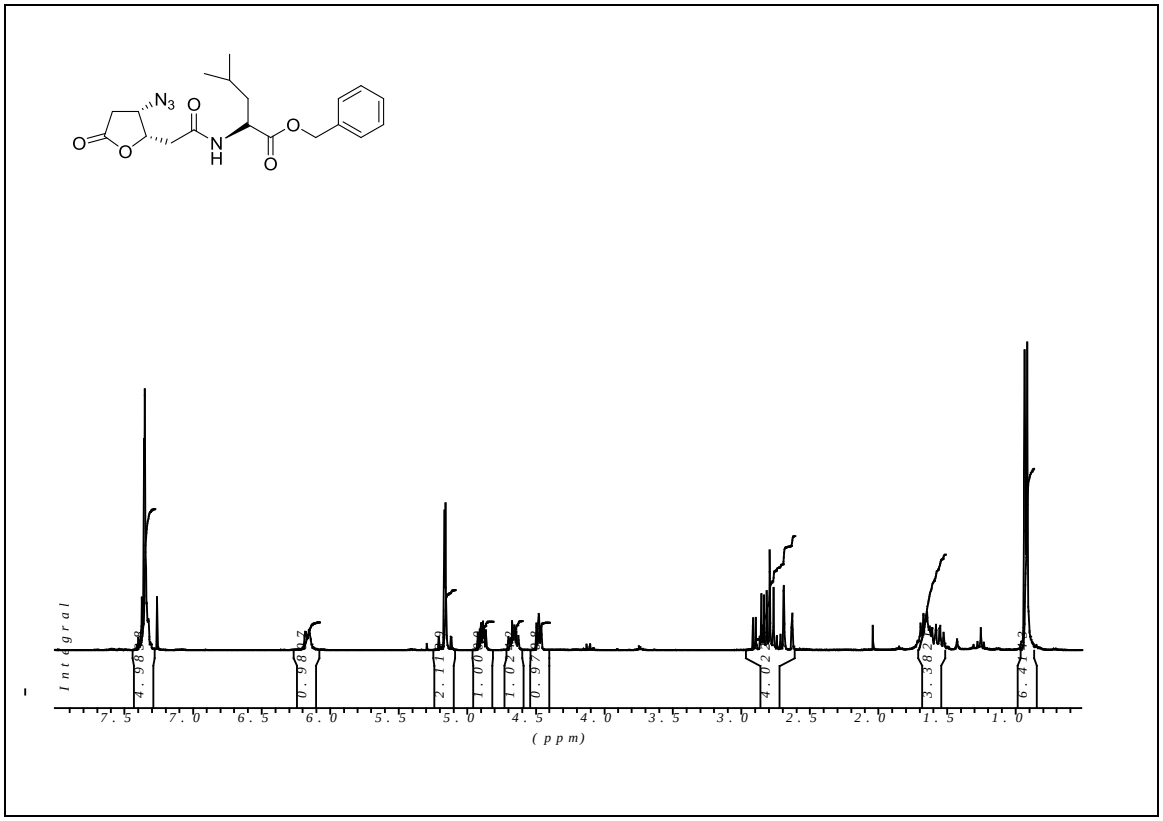


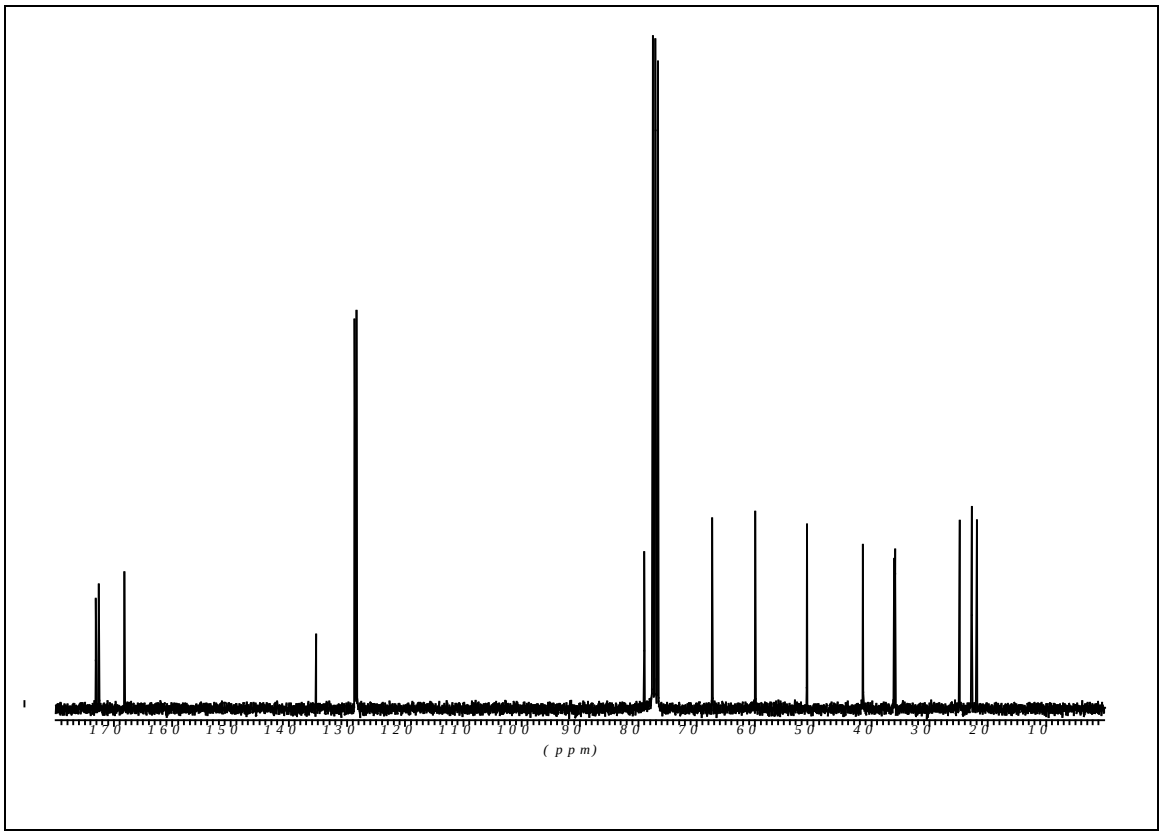
2-(2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetic acid (141, $CDCl_3$)

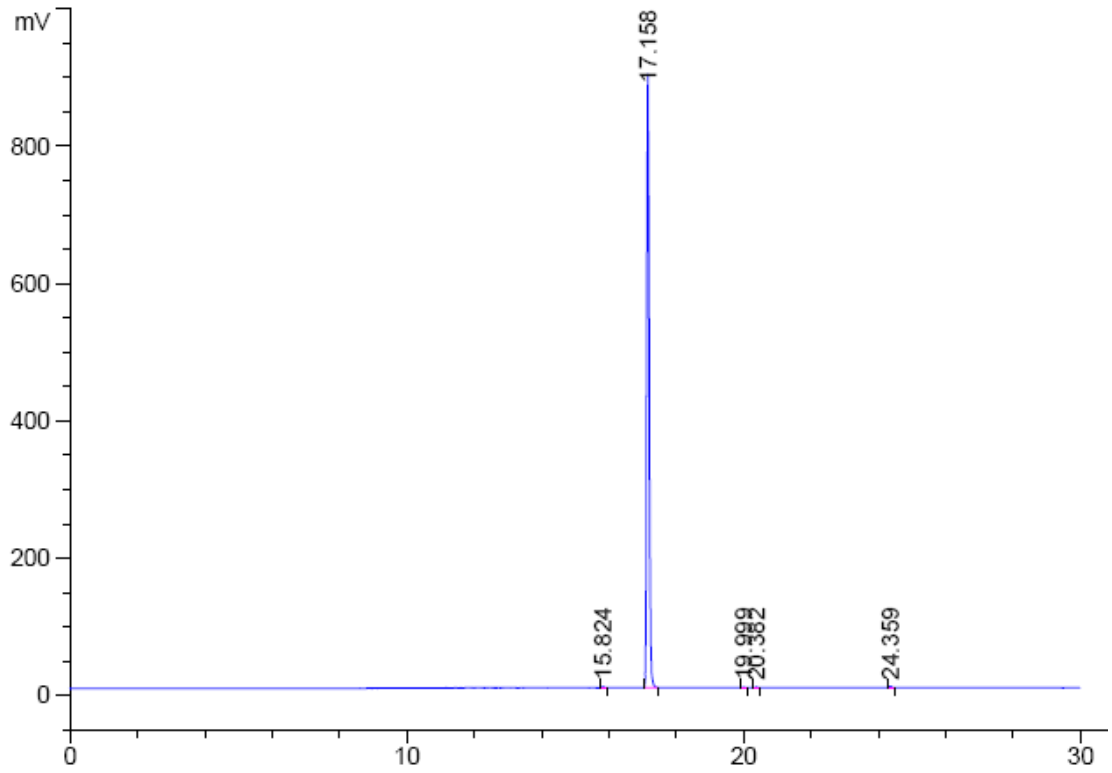




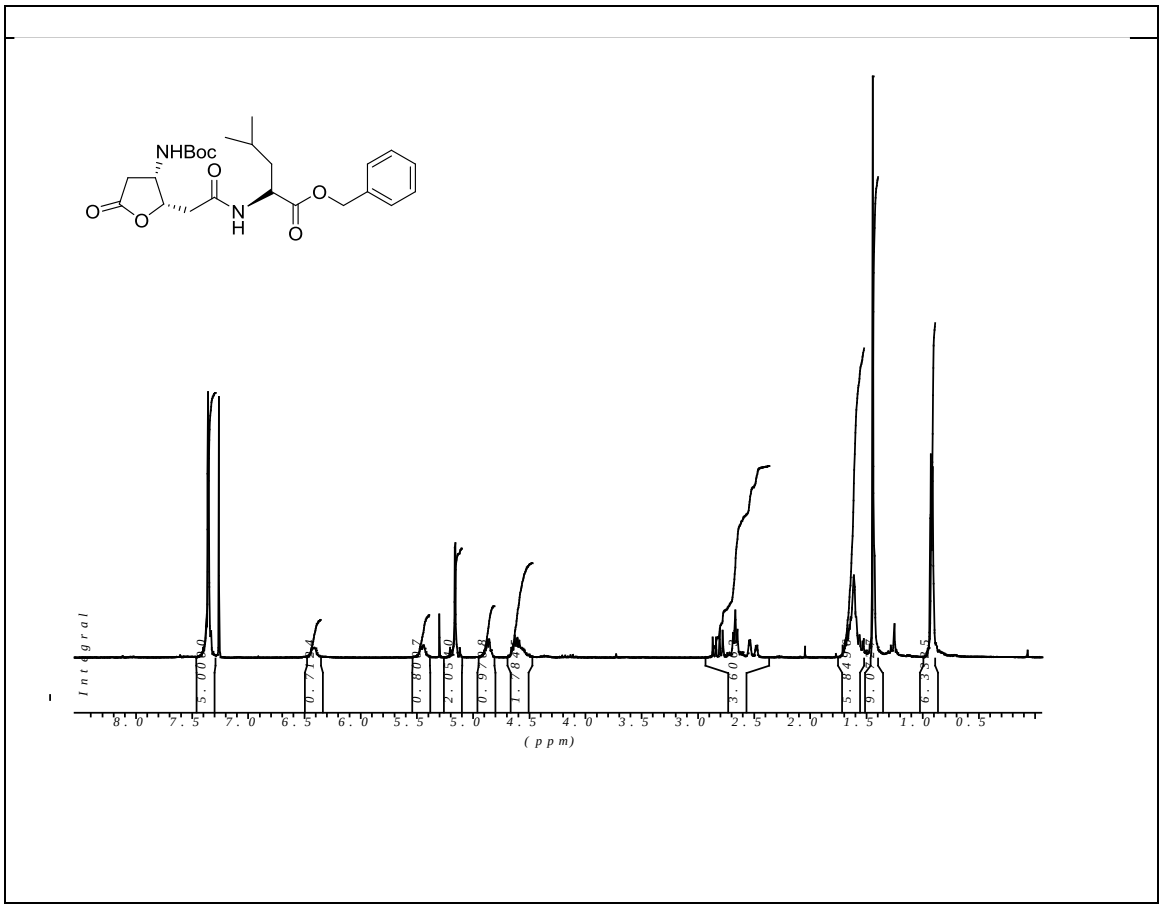
Benzyl 2-(2-((2*S*,3*S*))-3-Azido-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoate (177, $CDCl_3$):

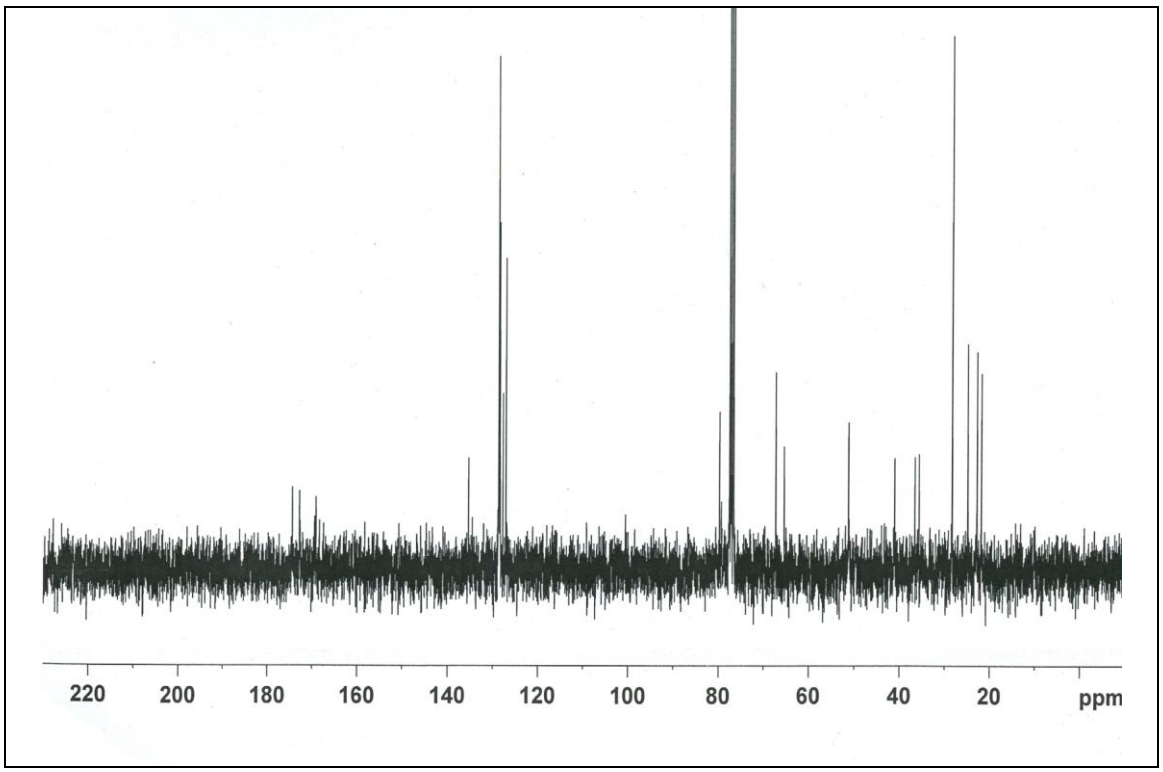




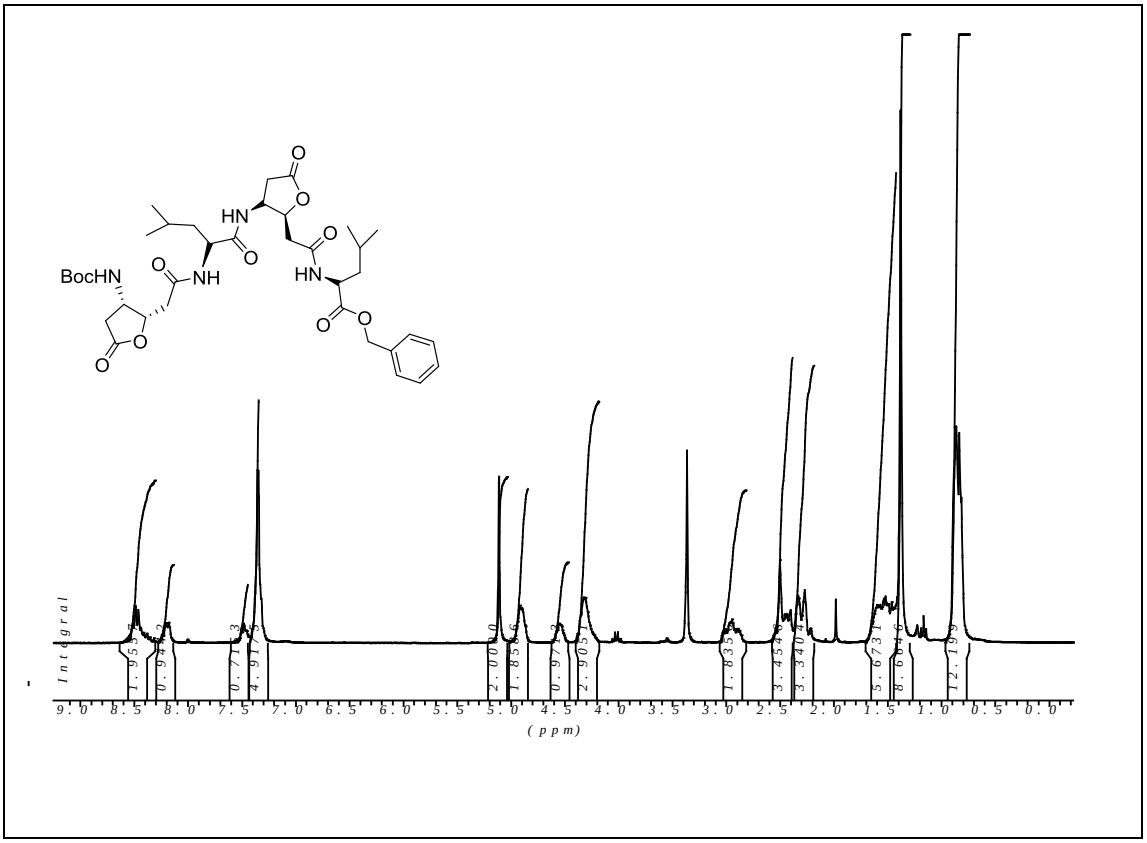

mV
800
600
400
200
0
17.158
15.824
24.359
0
10
20
30

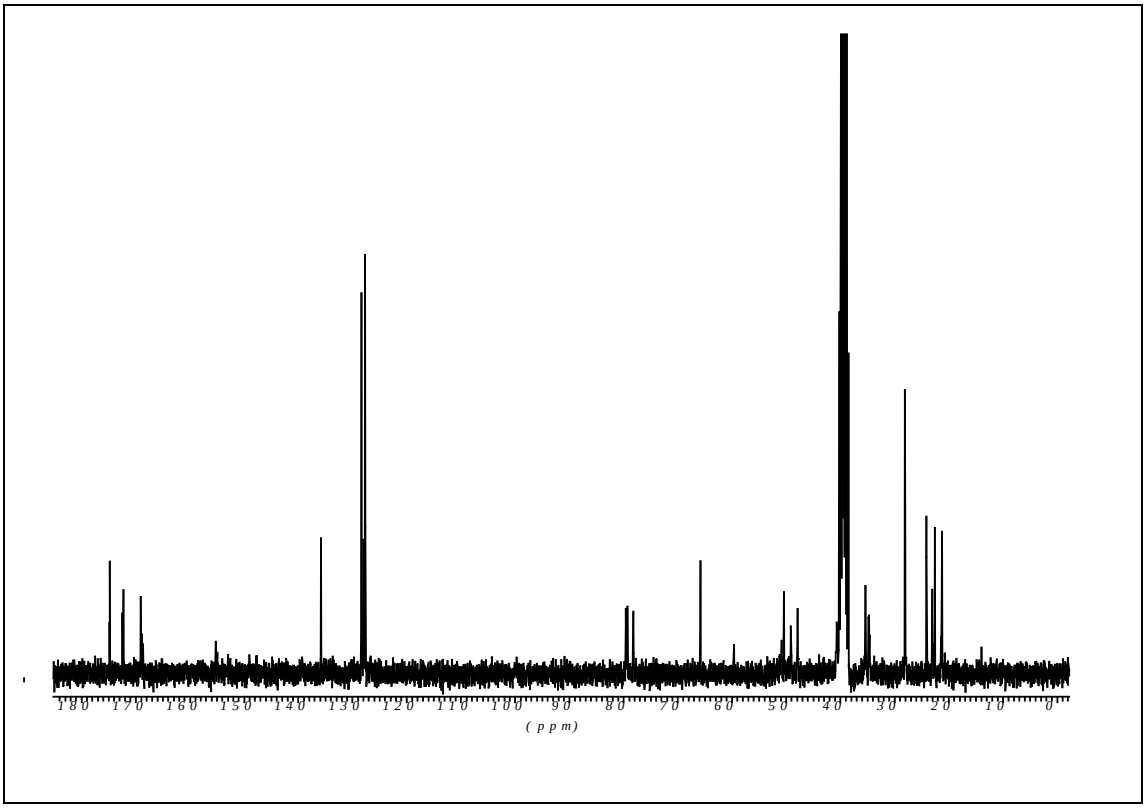
(*R*)-benzy2-(2-((2*S*,3*S*)-3-(tert-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoate (176, $CDCl_3$)



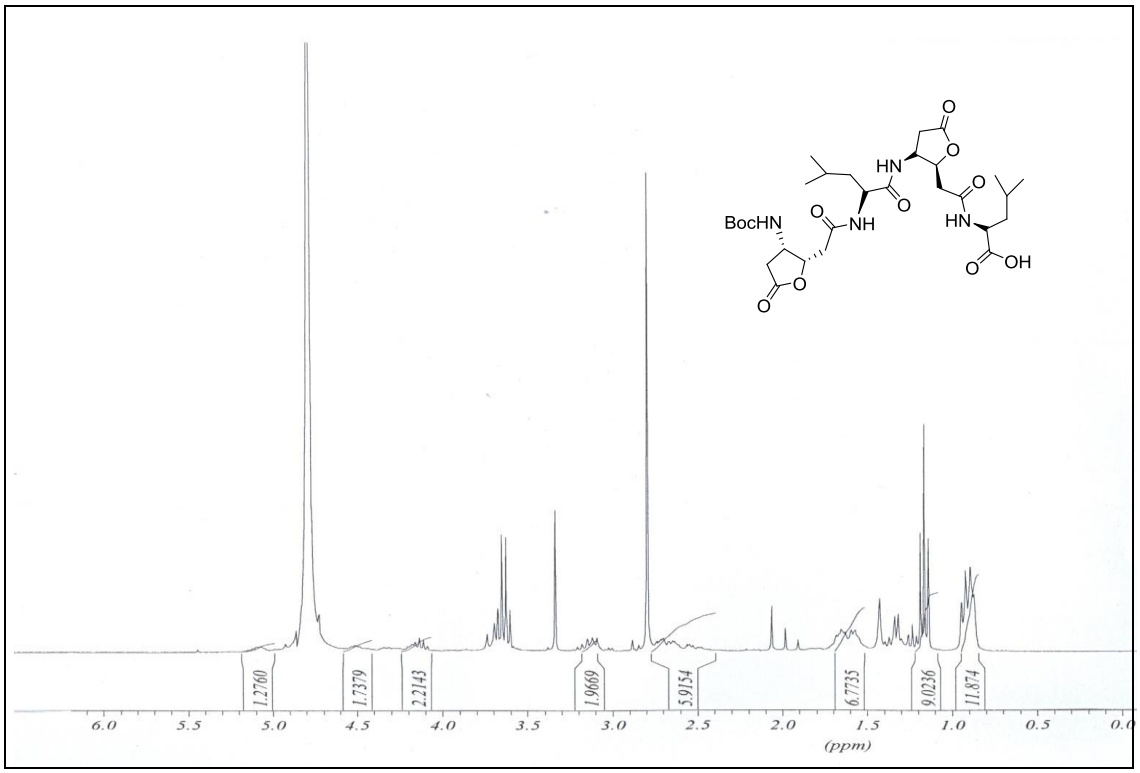


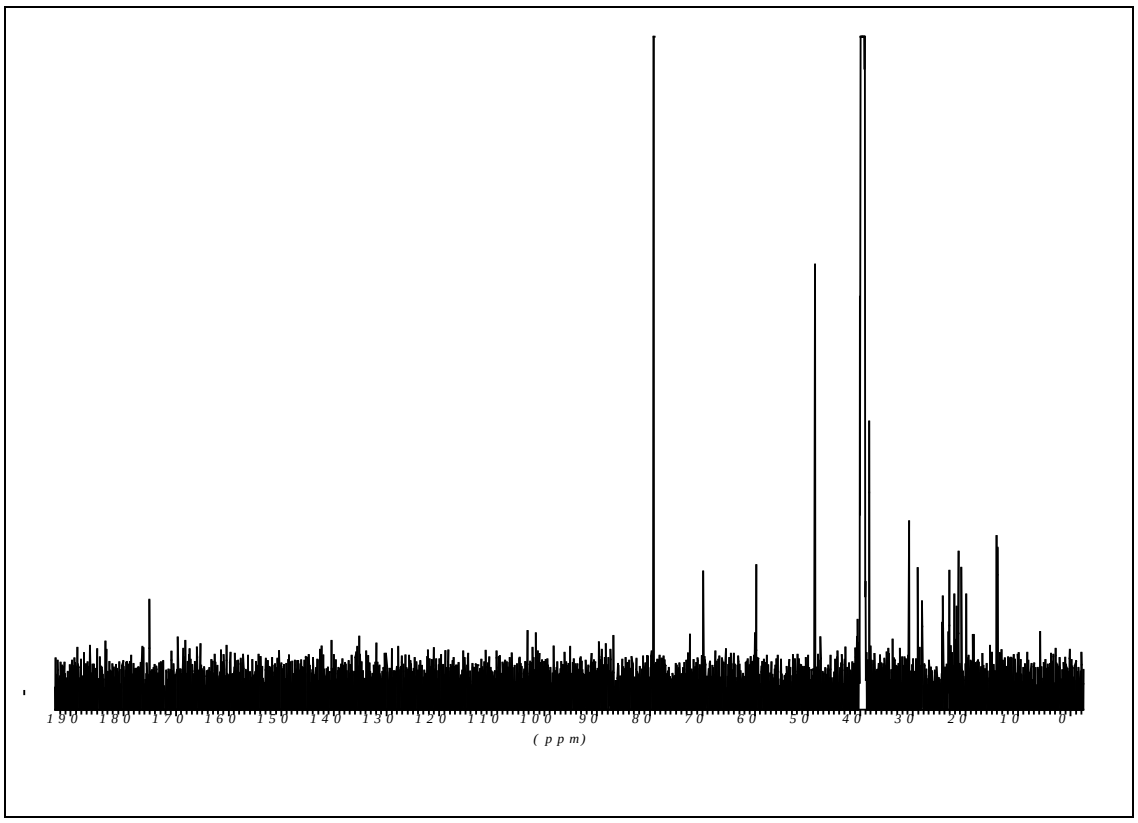
(*R*)-Benzyl2-(2-((2*S*,3*R*)-3-((*R*-2-(2-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanamido)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoate (173, DMSO)



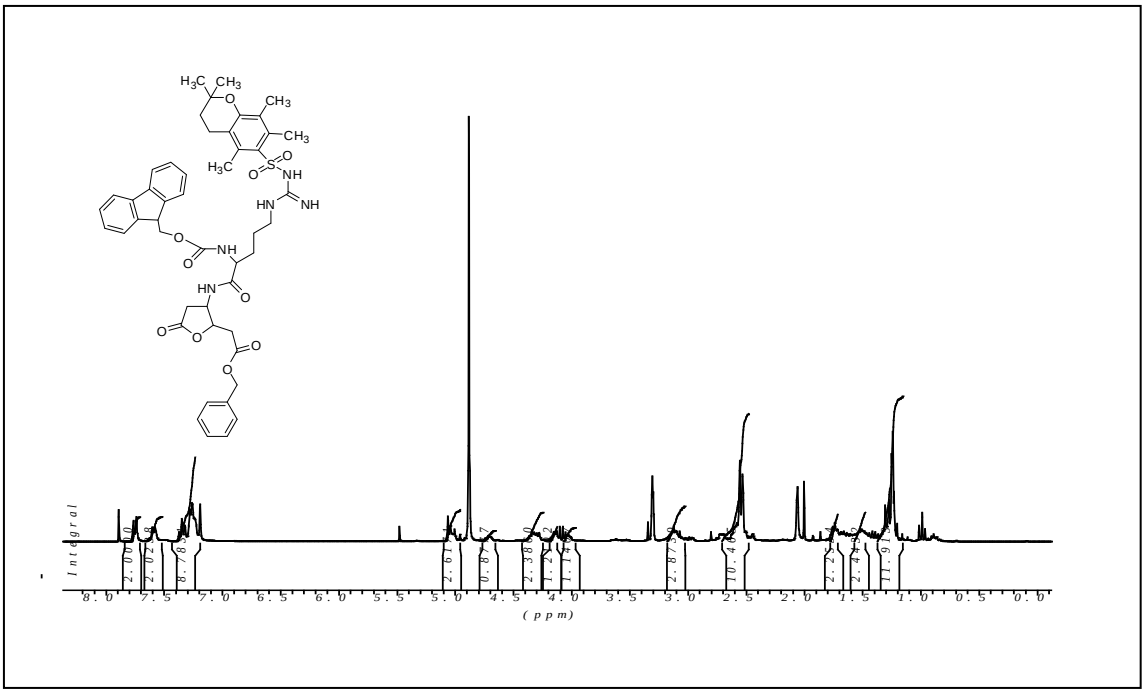


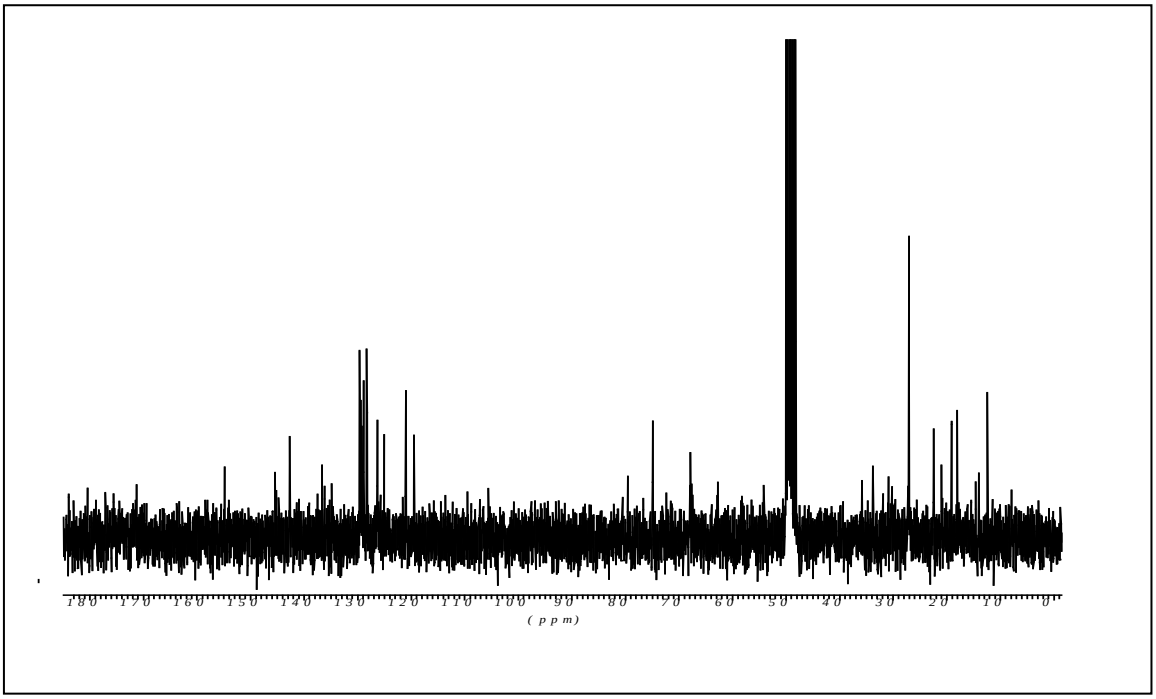
(*R*)- 2-(2-((2*S*,3*R*)-3-((*R*)-2-(2-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanamido)-5-oxotetrahydrofuran-2-yl)acetamido)-4-methylpentanoic acid (181, DMSO)



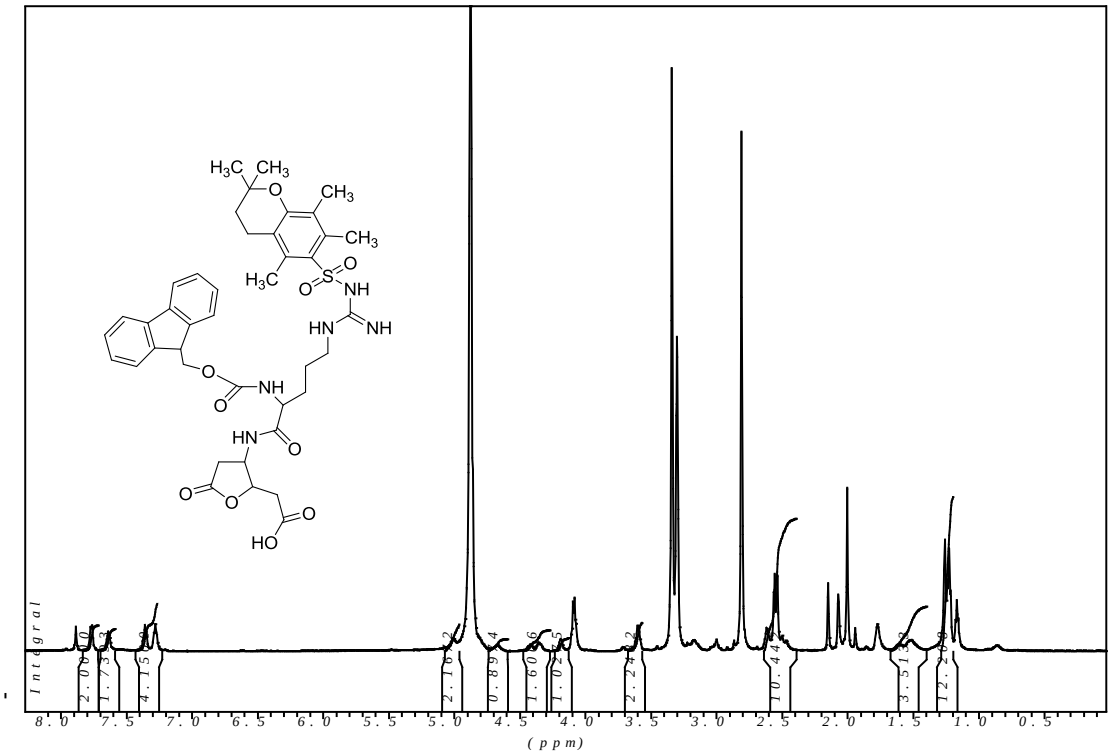


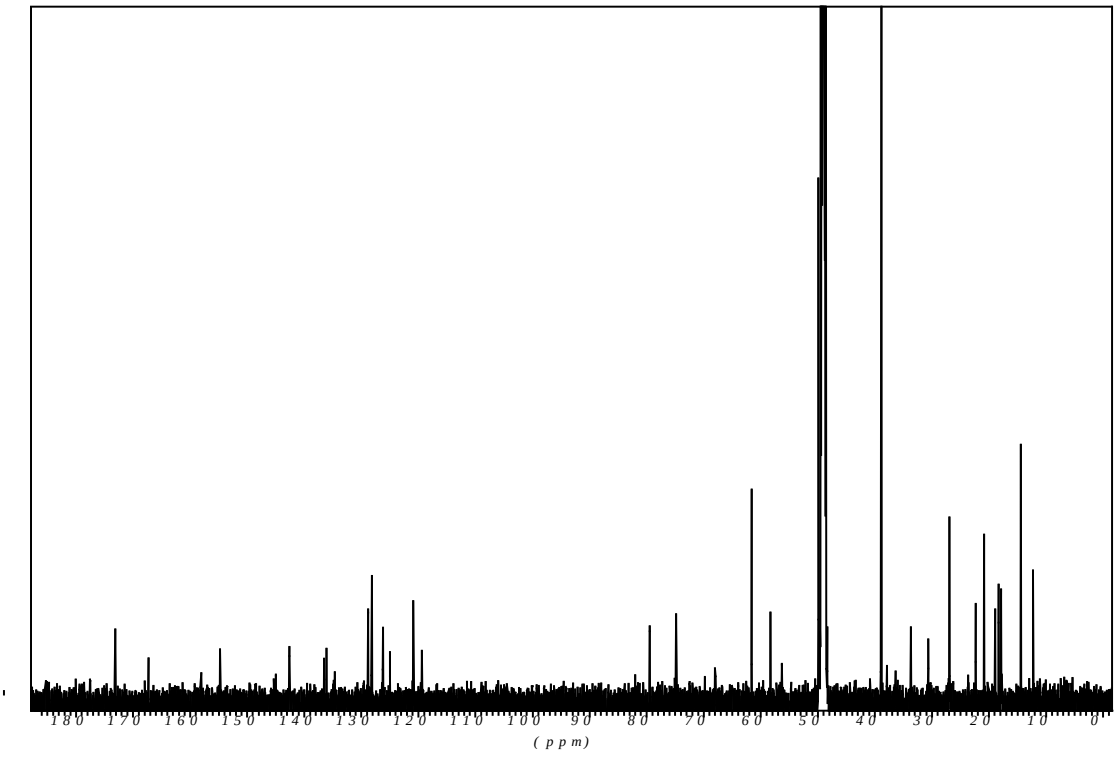
Benzyl2-(3-(2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-5-(3-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidine)pentanamido)-5-oxotetrahydrofuran-2-yl)acetate (182, MeOD)

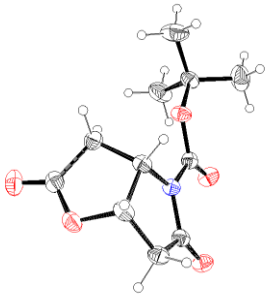


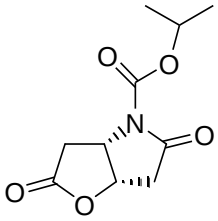


2-(3-(2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-5-(3-(2,2,5,7,8-pentamethylchroman-6-ylsulfonyl)guanidino)pentanamido)-5-oxotetrahydrofuran-2-yl)acetic acid (184, DMSO)









63

Table 1. Crystal data and structure refinement for gaa.

Crystal Data ;

Empirical formula ;C11 H15 N O5

Formula weight ;241.24

Crystal size ;0.570 x 0.130 x 0.060 mm

Crystal description ;stick

Crystal colour ;translucent colourless

Crystal system;Orthorhombic

Space group ;P 21 21 21

Unit cell dimensions ;a = 6.38405(13) A alpha = 90 deg.
;b = 10.35543(18) A beta = 90 deg.
;c = 17.7328(3) A gamma = 90 deg.

Volume ;1172.31(4) A^3

Z, Calculated density ;4, 1.367 Mg/m^3

Absorption coefficient ;0.918 mm^-1

F(000) ;512

Data Collection ;

Measurement device type ;Goniometer Xcalibur, detector: Ruby (Gemini ultra Mo)

Measuremnet method ;\w scans

Temperature ;123 K

Wavelength ;1.54184 A

Monochromator ; graphite

Theta range for data collection ;4.95 to 66.65 deg.

Index ranges ;-7<=h<=4, -12<=k<=12, -20<=l<=20

Reflections collected / unique ;6308 / 2049 [R(int) = 0.0333]

Reflections greater I>2\s(I);2018

Absorption correction ;Semi-empirical from equivalents

Max. and min. transmission ;1.00000 and 0.80965

Refinement ;

Refinement method ;Full-matrix least-squares on F^2

Hydrogen treatment ;:

Data / restraints / parameters ;2049 / 0 / 154

Goodness-of-fit on F^2 ;1.073

Final R indices [I>2sigma(I)] ;R1 = 0.0311, wR2 = 0.0811

R indices (all data) ;R1 = 0.0316, wR2 = 0.0820

Absolute structure parameter ;-0.01(17)

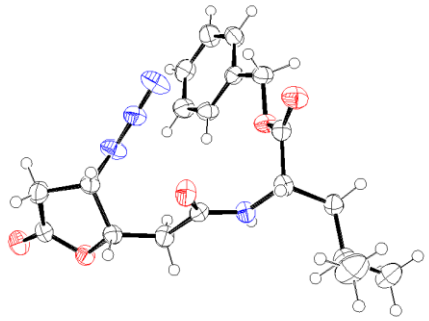
Largest diff. peak and hole ;0.158 and -0.190 e.A^-3

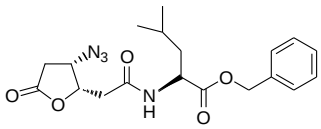
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for gaa. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

;x ;y ;z ;U(eq)

O(1);-2420(2);-1514(1);-5368(1);30(1)
O(2);-7446(2);1048(1);-5593(1);30(1)
O(3);-7134(2);3083(1);-5205(1);39(1)
O(4);-1430(2);-712(1);-3901(1);31(1)
O(5);-4350(2);-72(1);-3280(1);26(1)
N(1);-4617(2);-523(1);-4497(1);21(1)

C(1);-4111(2);-1083(1);-5188(1);24(1)
C(2);-6065(2);-1106(2);-5663(1);27(1)
C(3);-7604(2);-242(1);-5268(1);26(1)
C(4);-7221(2);1954(2);-5053(1);29(1)
C(5);-7126(2);1326(1);-4289(1);27(1)
C(6);-6831(2);-107(1);-4449(1);23(1)
C(7);-3256(2);-453(1);-3883(1);23(1)
C(8);-3299(2);268(1);-2562(1);28(1)
C(9);-1836(3);1384(2);-2692(1);42(1)
C(10);-2219(4);-900(2);-2230(1);48(1)
C(11);-5145(3);651(2);-2073(1);48(1)





177

Table 1. Crystal data and structure refinement for j177.

Crystal Data ;

Empirical formula ;C19 H24 N4 O5

Formula weight ;388.42

Crystal size ;0.3912 x 0.1675 x 0.0177 mm

Crystal description ;small plate

Crystal colour ;colourless

Crystal system;Monoclinic

Space group ;P 21

Unit cell dimensions ;a = 5.55990(9) A alpha = 90 deg.
;b = 15.95341(19) A beta = 100.6484(14) deg.
;c = 11.20045(15) A gamma = 90 deg.

Volume ;976.37(2) A^3

Z, Calculated density ;2, 1.321 Mg/m^3

Absorption coefficient ;0.806 mm^-1

F(000) ;412

Data Collection ;

Measurement device type ;SuperNova, Single source at offset), Atlas

Measuremnet method ;\w scans

Temperature ;173 K

Wavelength ;1.54184 A

Monochromator ; graphite

Theta range for data collection ;4.02 to 71.34 deg.

Index ranges ;-6<=h<=6, -19<=k<=19, -13<=l<=13

Reflections collected / unique ;9063 / 3543 [R(int) = 0.0212]

Reflections greater I>2\s(I);3421

Absorption correction ;Analytical

Max. and min. transmission ;0.985 and 0.843

Refinement ;

Refinement method ;Full-matrix least-squares on F^2

Hydrogen treatment ;:

Data / restraints / parameters ;3543 / 1 / 256

Goodness-of-fit on F^2 ;1.068

Final R indices [I>2sigma(I)] ;R1 = 0.0247, wR2 = 0.0647

R indices (all data) ;R1 = 0.0257, wR2 = 0.0652

Absolute structure parameter ;0.08(12)

Largest diff. peak and hole ;0.115 and -0.130 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for j177. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

;x ;y ;z ;U(eq)

O(1);-3392(2);480(1);-10316(1);33(1)
O(2);-7236(2);738(1);-11266(1);41(1)
O(3);-3724(2);2814(1);-10360(1);38(1)
O(4);4600(2);3962(1);-6304(1);42(1)
O(5);2842(2);3639(1);-8193(1);33(1)
N(1);-1681(2);1853(1);-11252(1);30(1)
N(2);-1064(2);2395(1);-7578(1);42(1)
N(3);-3028(2);2023(1);-7805(1);36(1)
N(4);-4706(2);1610(1);-7956(1);52(1)
C(1);-2247(2);-306(1);-8467(1);30(1)

C(2);-130(2);169(1);-8193(1);36(1)
C(3);1662(3);-27(1);-7194(1);41(1)
C(4);1355(3);-700(1);-6457(1);43(1)
C(5);-755(3);-1173(1);-6727(1);47(1)
C(6);-2547(3);-980(1);-7717(1);40(1)
C(7);-4272(2);-120(1);-9521(1);34(1)
C(8);-5062(2);866(1);-11130(1);30(1)
C(9);-3893(2);1468(1);-11915(1);29(1)
C(10);-3319(2);990(1);-13013(1);32(1)
C(11);-2426(3);1538(1);-13964(1);40(1)
C(12);-4401(4);2123(1);-14598(2);65(1)
C(13);-1447(3);986(1);-14877(2);54(1)
C(14);-1786(2);2489(1);-10476(1);27(1)
C(15);658(2);2765(1);-9754(1);34(1)
C(16);400(2);3467(1);-8881(1);28(1)
C(17);-1168(2);3295(1);-7916(1);30(1)
C(18);156(3);3797(1);-6847(1);42(1)
C(19);2770(2);3812(1);-7018(1);31(1)

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