STUDIES TOWARD THE TOTAL SYNTHESIS OF ACULEATIN A, B, E, F AND SACIDUMLIGNAN D & SYNTHESIS OF FURANO-β-AMINO ACIDS (β-FAA) AND THEIR HOMO-OLIGOMER

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OCTOBER–2010

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A THESIS
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BY

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(Research Guide)

ORGANIC CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE–411008

OCTOBER–2010

DEDICATED
TO
MY PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled **"Studies Toward the Total Synthesis of Aculeatins A, B, E, F and Sacidumlignan D & Synthesis of Furano β-Amino Acids (β-FAA) and Their Homo-Oligomers"** has been carried out under my supervision and is a bonafide work of **Mr. Sunil Kumar Pandey**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
October –2010

Dr. C. V. Ramana
(Research Guide)

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Sunil Kumar Pandey

DEFINATIONS AND ABBREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AIBN	–	Azobisisobutyronitrile
aq.	–	Aqueous
Bn	–	Benzyl
BnBr	–	Benzyl bromide
DCM	–	Dichloro methane
DCE	–	1,2-Dichloro ethane
DEAD	–	Diethyl azodicarboxylate
DIP-Cl	–	Diisopinocampheyl chloroborane
Cat.	–	Catalytic/catalyst
TsCl	–	Tosyl chloride
Conc.	–	Concentrated
CD	–	Circular dichroism
COSY	–	Correlation spectroscopy
DCC	–	N,N'-Dicyclohexylcarbodiimide
DIBAL-H	–	Diisobutylaluminiumhydride
DIPEA	–	Diisopropylethyl amine
DDQ	–	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	–	Diethyl tartrate
DIPT	–	Diisopropyl tartrate
DMP	–	2,2'-Dimethoxypropane
DMF	–	*N*,*N*-Dimethylformamide
DMAP	–	*N*,*N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et_3SiH	–	Triethylsilyl hydride
Et_2O	–	Diethyl ether
EtOAc	–	Ethyl acetate
Et_3N	–	Triethylamine
EDCI.HCl	–	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HMPA	–	Hexamethylphosphoramide
HSQC	–	Heteronuclear Single Quantum Coherence
HMBC	–	Hetronuclear Multiple Bond Coherence
HOBT	–	1-Hydroxybenzotriazole
LAH	–	Lithium aluminium hydride
LiHMDS	–	Lithium1,1,1,3,3,3-hexamethyldisilazane
LDA	–	Lithium diisopropyamide
Ms/Mesyl	–	Methanesulfonyl
MTPA	–	α-Methoxytrifluorophenylacetic acid
NBS	–	*N*-bromosuccinamide
NMO	–	*N*-Methylmorpholine N-oxide
NOESY	–	Nuclear overhauser effect spectroscopy
ORTEP	–	Oak Ridge Thermal Ellipsoid Plot
Pd/C	–	Palladium on Carbon
PCC	–	Pryridinium chlorochromate
PIDA	–	Phenyliodine(III) diacetate
PIFA	–	Phenyliodine(III) bis-(trifluoroacetate)
PPTS	–	Pyridine *p*-Toluenesulpfonate
PMBCl	–	*p*-Methoxy benzyl chloride
TBSCl	–	*tert*-Butyldimethylsilyl chloride
TBAF	–	*tetra*-*n*-butylammonium fluoride
TBDMS	–	*tert*-Butyldimethyl chlorosilane
t-BuOOH	–	*tert*-Butyl hydroperoxide
TPP	–	Triphenylphosphine
TBAI	–	*tetra*-Butylammonium iodide
Tf_2O	–	Triflic anhydride
t-BuOK	–	Potassium tertiary butoxide
TFA	–	Trifloroacetic acid
TFE	–	Trifluoroethanol

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, and DRX–125 MHz spectrometer.
- EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

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ABSTRACT

ABSTRACT

The thesis entitled **"Studies Toward the Total Synthesis of Aculeatins A, B, E, F and Sacidumlignan D & Synthesis of Furano β-Amino Acids (β-FAA) and Their Homo-Oligomers"** consists of three chapters. The first chapter describes the total syntheses of Aculeatins A, B, E and F. The second chapter deals with the synthesis of Sacidumlignan D. The third chapter presents the synthesis of cis- and trans-furano β-amino acids and their homo-oligomers and the secondary structural analysis.

Chapter 1: Total Synthesis of Aculeatins A, B, E, F and 5-*epi*-aculeatins E and F

Introduction

In 2000, Heilmann *et. al* reported the isolation of three biologically active metabolites aculeatins A–C from the petroleum ether extract of the rhizomes of *Amomum aculeatum* ROXB, a plant used in the folk medicine of Papua New Guinea against fever and malaria. In 2007, Kinghorn *et. al* reported the isolation of related metabolites aculeatols A – D; the C(9) hydroxylated aculeatins A or B having either the same or two carbon truncated side chains. Subsequently, the isolation of truncated aculeatins A and D named respectively as aculeatins F (**6**) and E (**5**), were reported by the same group. The structural similarity present in aculeatins A, B and D–F and their promising biological activity provides an opportunity to explore a modular assembly of aculeatins and related derivatives.

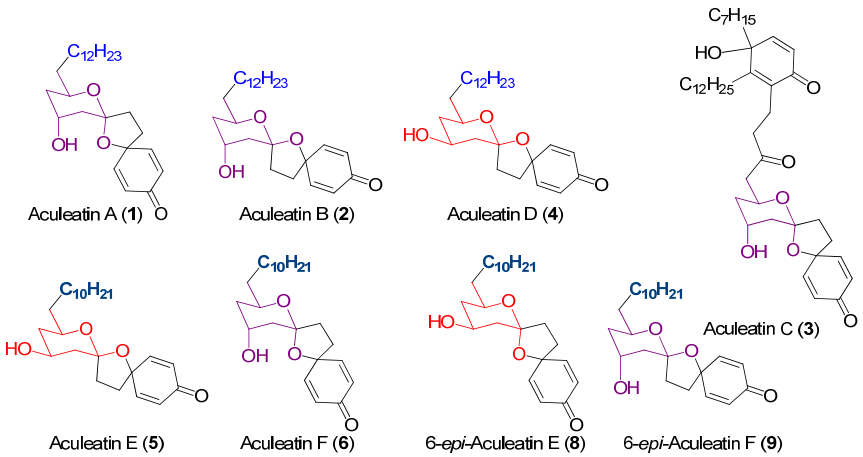


Figure 1. *Natural aculeatins A–F (**1**–**6**) and the unnatural 6-epi-aculeatins E (**8**) and F (**9**)*

Results and Discussion

Our retrosynthetic disconnections are outlined in Figure **2**. The construction of the central tricyclic core was the final event which was planned through the global deprotection of a differentially protected keto 3,5-diol unit and subsequent phenol oxidative spiroketalization. To allow for maximum flexibility, the key disconnection of the aculeatin's carbon-frame was made at two places resulting in two simple

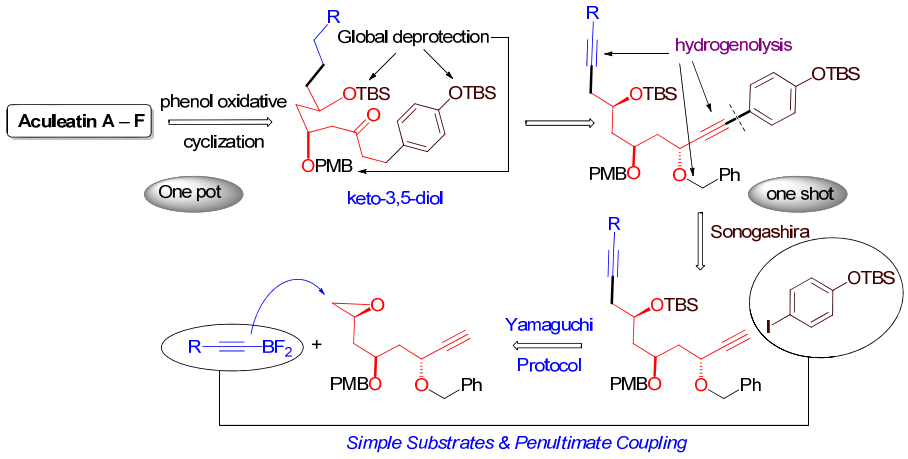


Figure 2. *Key retrosynthetic disconnections and penultimate flexibility*

appending units and an epimeric pair of functionalized building blocks (Figure 2). Considering the fact that several of the analogues of these two appending units are

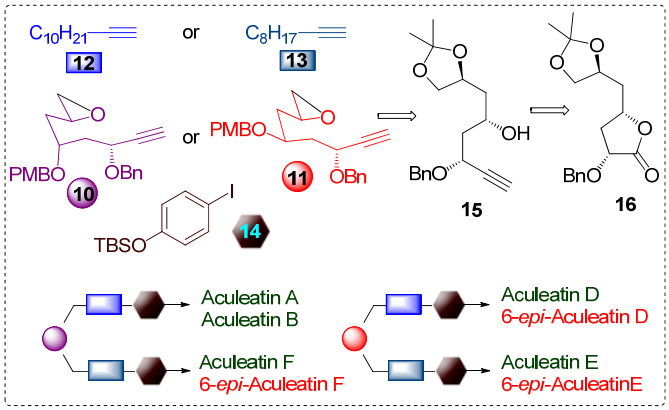
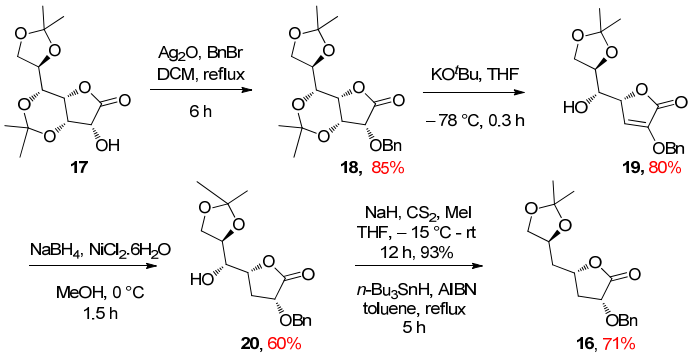


Figure 3. *Key building blocks for the synthesis of aculeatins A - F*

commercially available or that one can access their functionalized analogues very easily, the additions were planned at an advanced stage. As given in Figure **3**, the diastereomeric alkyne epoxides **10** and **11** were identified as the central chirons, respectively for the aculeatins A,/B,/F (**1,/2,/6**) and for the aculeatins E (**5**). The

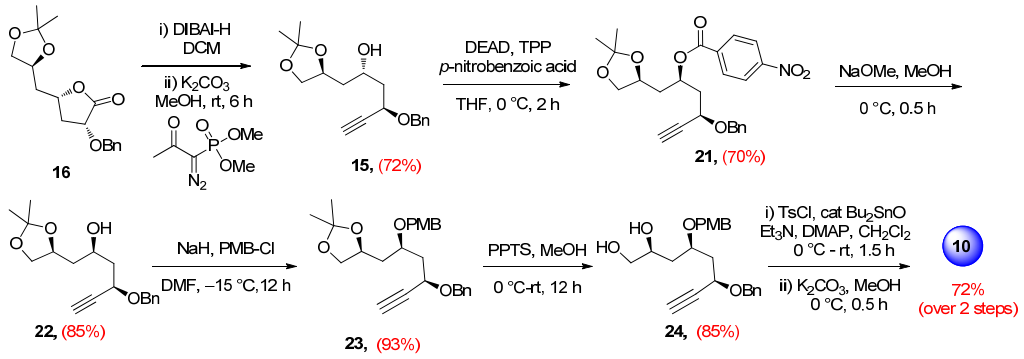
synthesis of oxiranes **10** and **11** was planned from the alkynol **15** which in turn can be accessed from the lactone **16** by controlled lactone reduction to lactol and subsequent Ohira-Bestmann alkyne synthesis. The synthesis of lactone **16** has been earlier reported from our laboratory from commercially available D-glucono-heptono-γ-lactone.

The synthesis started with the preparation of the γ-lactone **16** following the procedures developed in our lab. The diacetonide of commercially available α-D-glucoheptonic-γ-lactone would be an ideal starting point.



Scheme 1. *Synthesis of the Lactone*

The controlled DIBAL-H reduction of the γ-lactone **16** in CH_2Cl_2 at –78 °C followed by alkynylation intermediate lactol using the Ohira-Bestmann reagent resulted in the alkynol **15** in 72% yield. To access the oxirane **10** with the central *syn*,*syn* 1,3-polyol configuration, the configuration at the C(4) center had to be inverted. The Mitsunobu inversion of alkynol **15** by using DEAD, TPP could be



Scheme 2. *Synthesis of the syn,syn-oxiranes **10***

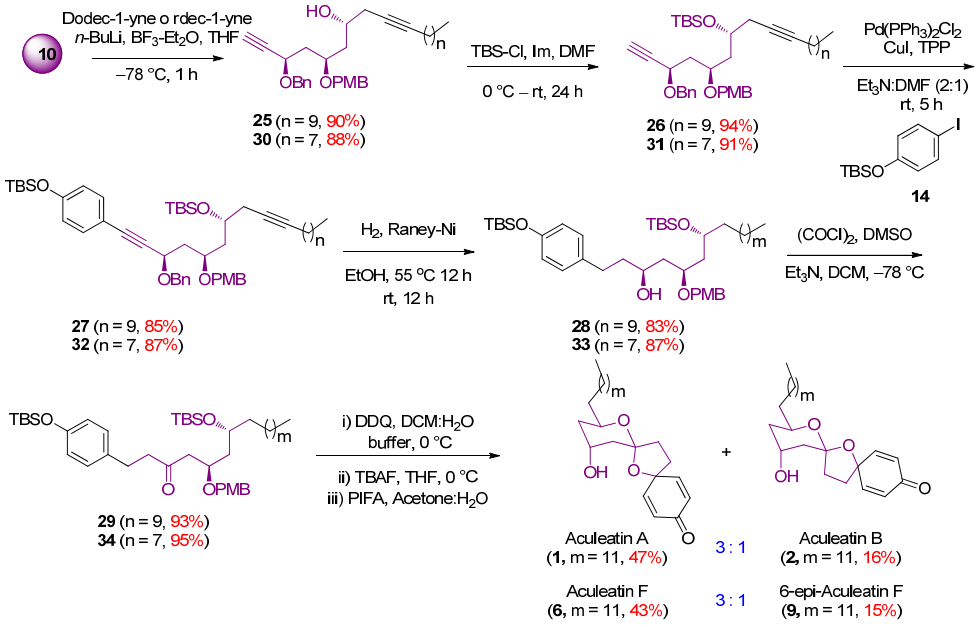
conducted in good yield by employing the *p*-nitrobenzoic acid as the nucleophile to afford the corresponding nitrobenzoate **21**. Saponification of nitrobenzoate ester **21**

with NaOMe in MeOH secured the required *syn,syn*-alkynol **22** having physical data different from that of the starting alkynol **15**.

The free hydroxyl group of alkynol **22** was protected as its PMB ether by employing NaH and PMB-Cl in DMF at –15 °C. Subsequently, the isopropylidene group of the resulting compound **23** was deprotected by employing PPTS in methanol to afford the diol **24**. The primary hydroxyl group of diol **24** was selectively tosylated by treating with *p*-TsCl, catalytic Bu_2SnO, DMAP and triethylamine in CH_2Cl_2 and the resulting tosylate was used without any purification for the oxirane formation using K_2CO_3 in methanol to furnish the epoxide **10**.

Synthesis of aculeatins A, B, F and 6-*epi*-F

We next proceeded for the synthesis of aculeatins A, B, and F by selecting the *syn*,*syn*-oxirane **10** as the common starting point. The regioselective opening of epoxide **10** with either dodec-1-yne (**12**) or dec-1-yne (**13**) gave the diynes **25** and **30**



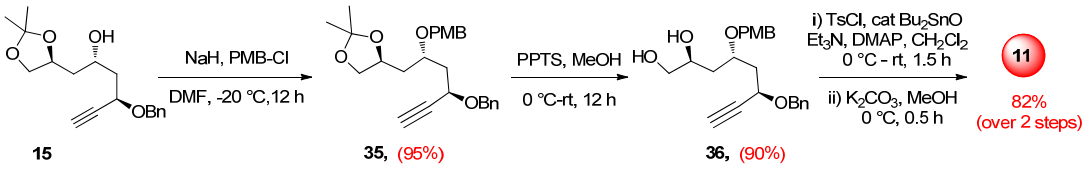
Scheme 3. *Synthesis of the Aculeatin A (**1**), B (**2**), F (**6**) and 6-epi-F (**9**)*

respectively. The resulting alkynes were subsequently converted to the corresponding TBS ethers **26** and **31** by treating with TBSCl/imidazole in DMF. The Sonogashira coupling of **26** or **31** with aryliodide **14** was best effected by a thorough degassing of the reaction mixture prior to the addition of CuI and gave the coupled products **27** (85%) and **32** (87%).

To this end, the hydrogenolysis of both the alkyne groups and selective debenzylation of compounds **27** and **32** were carried out by using Raney Ni/H_2 (20 psi) at 55 °C in

good yields. The free C(6)–OH of the resulting products **28** and **33** was oxidized under Swern conditions to afford the protected keto 3,5-diols **29** and **34**. Finally, compound **29** was subjected for a sequential deprotection of PMB ether by employing DDQ (CH_2Cl_2, pH 7.0 phosphate buffer, 0 °C) followed by TBS ether deprotection using TBAF (THF at 0 °C) produce the completely deprotected keto 3,5-diol which, upon the oxidative spiroketalization using PIFA (10:1, v/v acetone:water, rt, under dark) afforded the aculeatins A (**1**) and B (**2**) (3:1) in 63% overall yield. The spectral and the analytical data of **1** and **2** were in good agreement with data reported for natural aculeatins A and B. Similarly, the keto 3,5-diol **34**, upon one pot sequential deprotection and oxidative phenol cyclization, afforded a 2.5:1mixture of aculeatin F (**6**) and its 6-epimer **9**. The spectral data of **6** was in agreement with the data reported for the natural aculeatin F and the specific rotation measured confirmed its assigned absolute configuration.

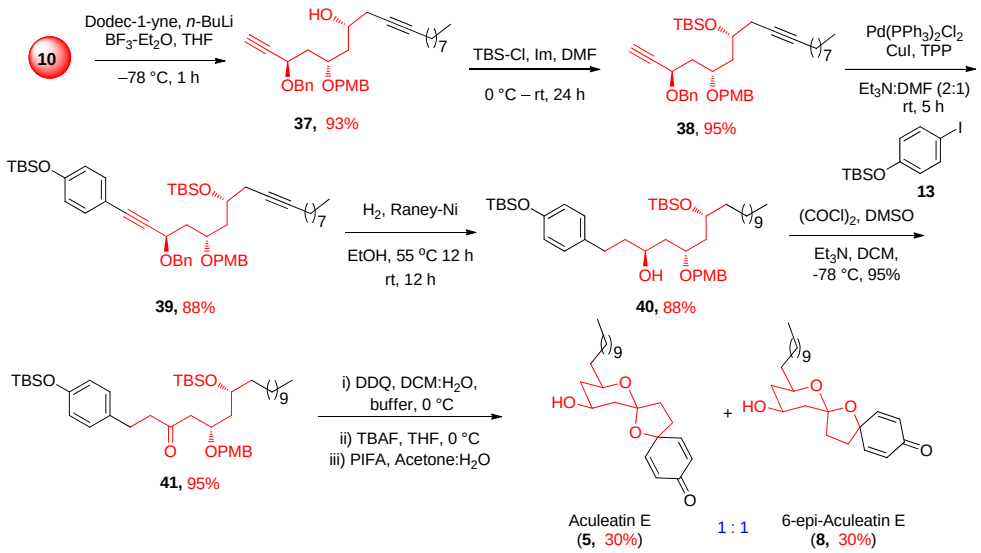
Next, we focused on the synthesis of aculeatin E (**5**) from the oxirane **11** (Scheme 4). The synthesis of the *anti,anti*-configured oxirane **11** commenced with the PMB protection of free hydroxyl group present in **15** by using NaH, PMB–Cl in DMF at 0 °C to secure **35**. The isopropylidene group of **35** was hydrolyzed in the presence of PPTS in methanol and the resulting diol **36** was converted to the corresponding oxirane **11** following the established conditions for selective 1-OH tosylation and subsequent treatment of the intermediate tosylate with K_2CO_3 in methanol.



Scheme 4. *Synthesis of the anti,anti-oxiranes **11***

The opening of the oxirane **11** with dec-1-yne, gave **37**. The free C(5)-OH in **37** was protected as TBS-ether and then subjected to Sonogashira coupling with **14** to afford the diynes **39**. Subsequently, the diynes **39** was advanced to the key keto-1,5-diols **41,** by hydrogenolysis with Raney Ni/H_2 followed by the Swern oxidation. The final stage of the synthesis, sequential deprotection of the TBS and PMB ethers of **41** and oxidative phenolcyclization of the intermediate ketodiols, provided the aculeatin E (**5**) along with its spiroepimer **8**. The comparison of the ^{1}H and ^{13}C NMR spectra with the

natural aculeatines D and E established their structure and the observed similar specific rotation of the synthetic aculeatin E confirmed its assigned absolute configuration.



Scheme 5. *Synthesis of the Aculeatin E (**4**), and 6-epi-E (**7**)*

Conclusion:

A flexible approach for the total syntheses of aculeatins has been documented. Central to the success of our approach is a dual-end disconnection of the aculeatin's core leading to three segments in which the two terminal segments are easily available and are amicable towards alterations for the synthesis of aculeatin like small molecule libraries.

Chapter 2: Total synthesis of Sacidumlignan D

Introduction

Recently, Jain-Min Yue *et al.* isolated four new lignans, namely, sacidumlignans A–D (Figure 4) from the ethanolic extract of the whole plant of *Sarcostemma acidum* collected from Hainan Island of China. The structures and the relative configuration of these new compounds were elucidated on the basis of spectroscopic and chemical data, especially 2D NMR techniques. Sacidumlignan D, with a novel rearranged lignan skeleton showed antimicrobial activities against Grampositive bacteria in vitro.

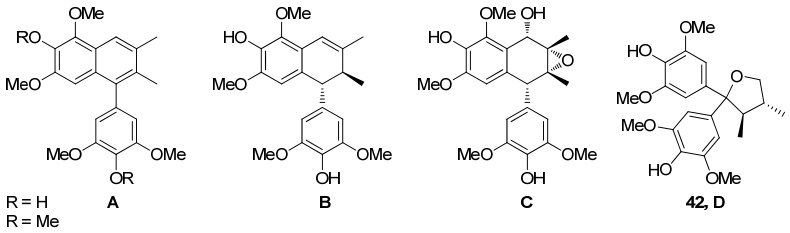


Figure 4. *Structures of Sacidumlignans A – D*

Retrosynthetic analysis: The planned total synthesis of sacidumlignan D involves diastereoselective methylation of lactone **44** as a key step. The resulting fully elaborated key lactone **43** can be transformed to sacidumulignan D (**42)** by carbonyl

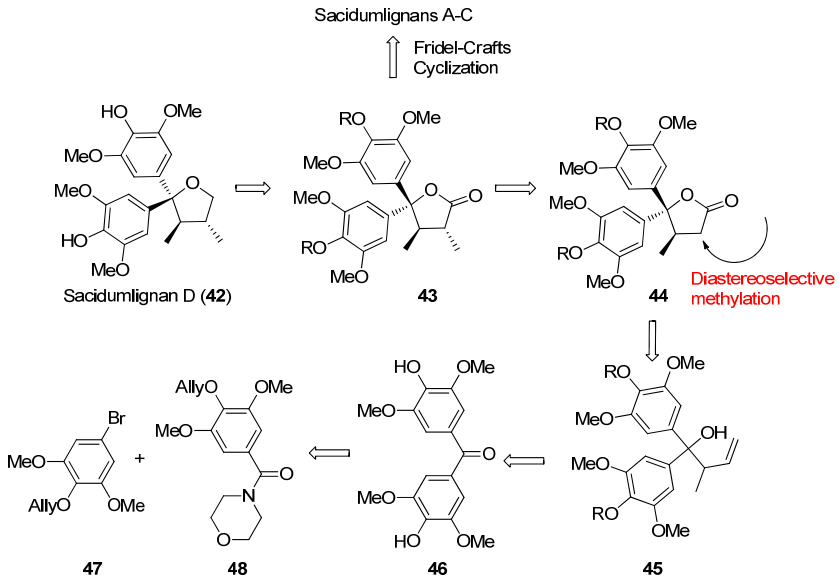


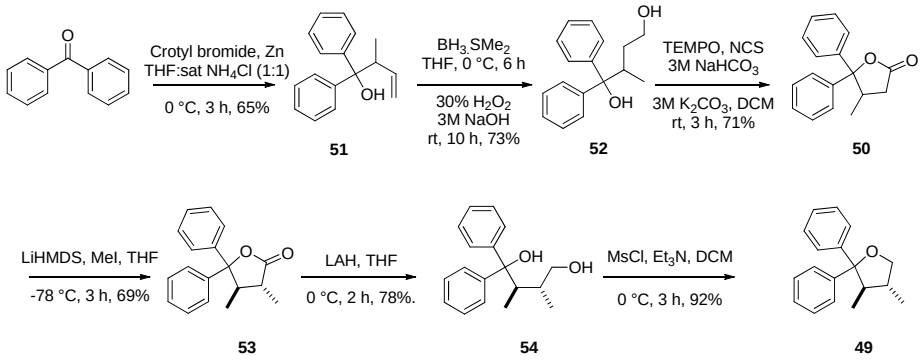
Figure 5. *Retrosynthetic strategy of Sacidumlignan D*

reduction and cyclization. On the other hand, subjecting **43** under Friedel-Crafts

conditions, di- and tetrahydronapthalenes were anticipated which could be used for the synthesis of other sacidumulignans. The synthesis of benzophenone derivative **46** has been identified as the intermediate goal in the synthesis of sacidumlignans A–D. Allyl protection was opted for in regard that it is stable under a variety of conditions. The synthesis of di-*O*-allyl-**46** was intended from the addition of lithiated **47** to amide **48**. We initially opted for the construction of the central core from easily available benzophenone.

Synthesis of the central core of sacidumlignan D:

According to the retrosynthetic strategy as depicted in Figure 5, the model study for the synthesis of the central core of sacidumlignan D (**42**) started with the crotylation of benzophenone under Barbier conditions followed by hydroboration oxidation of resulting homoalkyl alcohol **51** gave **52**. Oxidation of **52** with NCS and TEMPO provided the lactone **50** in good yield.

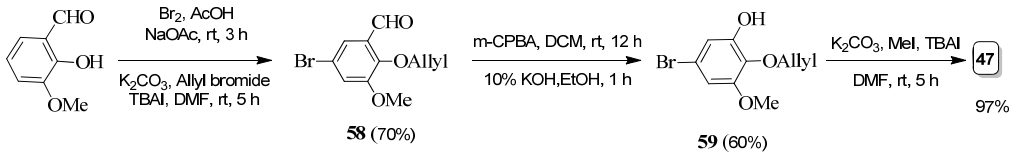


Scheme 6. *Synthesis of the central core of sacidumlignan D*

After having made lactone **50**, we next performed the diastereoselective methylation at C(3) was using LiHMDS-MeI to afford **53**. The coupling constant (J = 9.6) of the C(3) and C(4) protons clearly indicates that they are *trans* to each other. The reduction of **53** using $LiAlH_4$ and the subsequent ring closure gave **49** with the central core of sacidumlignan D.

Synthesis of bromo partner 47:

The bromination of *o*-vanillin followed by the protection of free -OH by using allyl bromide and K_2CO_3 in the presence of phase transfer catalyst (TBAI) afforded **58**. The Baeyer-Villiger oxidation of **58** was achieved by employing *m*-CPBA and the

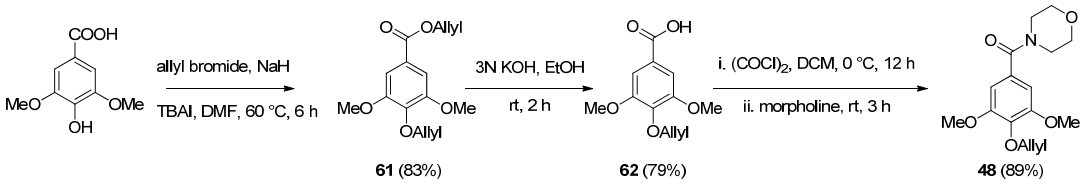


Scheme 7. *Synthesis of the coupling partner **47***

desired phenol **59** was obtained in excellent yields. Treatment of **59** with K_2CO_3 and MeI afforded the key bromo derivative **47**.

Synthesis of Amide Partner 48:

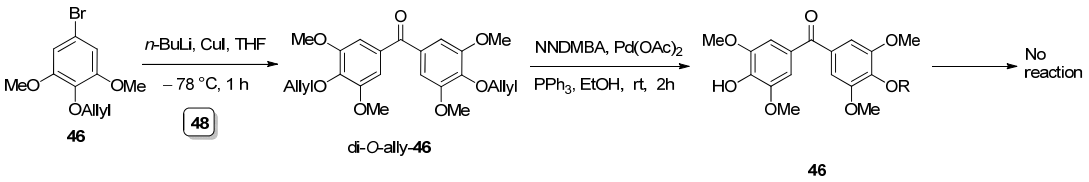
Synthesis of the compound **48** was started from commercially available syringic acid. Syringic acid was treated with allyl bromide and NaH in the presence of



Scheme 8. *Synthesis of the amide **48***

a phase transfer catalyst (TBAI) to afford the **61**. Hydrolysis of **61** with aq. KOH followed by coupling of the resulting acid **62** with morpholine gave the key amide partner **48**.

After having an easy access for both coupling partners **47** and **48** our next concern was the synthesis of di-*O*-ally-**46**. The treatment of **47** with ^{n}BuLi followed

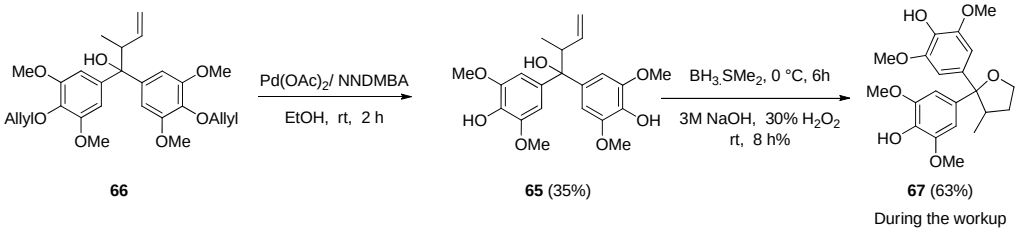


Scheme 9. *Coupling between **46** and **48***

by addition of the amide **48** in excess (5 eq.) afforded the required benzophenone derivative di-*O*-ally-**46**. The deallylation of compound di-*O*-ally-**46** using *N*,*N*'-dimethylbarbituric acid in the presence of $Pd(OAc)_2$ and triphenylphosphine afforded **46** in good yields. Surprisingly, the attempted crotylation of **46** under standard Barbier

conditions was sluggish and even after prolonged exposure, the ketone **46** was found to be intact.

Next, the crotylation of di-*O*-ally-**46** was attempted under standard Barbier conditions to afford the homoallylic alcohol **66** in moderate yields. Deallylation of compound **66** was carried out employing $Pd(OAc)_2$ and *N,N'*-dimethylbarbituric acid

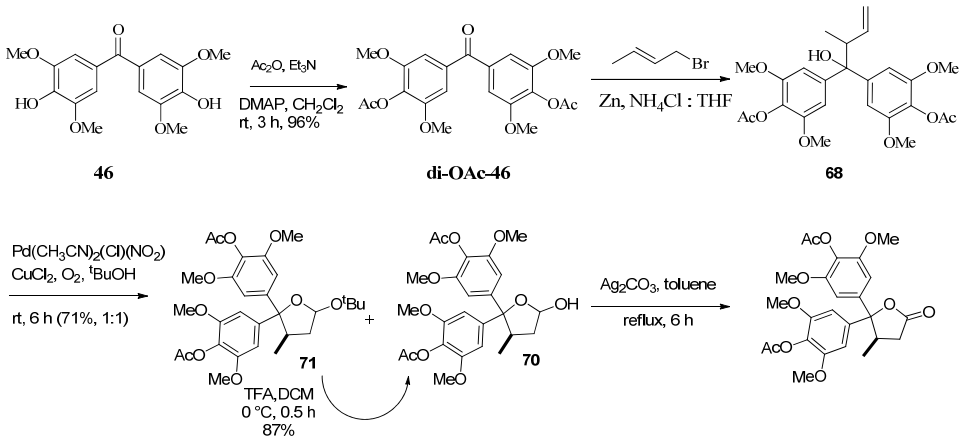


Scheme 10. *Attempt for hydroboration-oxidation*

in the presence of triphenylphosphine to afford **65** in moderate yields. The next task was the hydroboration-oxidation to procure the diol. Surprisingly, during the hydroboration-oxidation of **65**, the furan derivatve **67** (des-sacidumulignan D) was obtained as the major product. This undesired cyclization prior to the oxidation has prompted us to modify the retro-synthetic strategy.

The free hydroxyl groups of **46** were protected as acetates by using Ac_2O, Et_3N in the presence of DMAP to procure the di-*O*-Ac-**46** which was subjected to Barbier conditions to afford the homoallylic alcohol **68**.

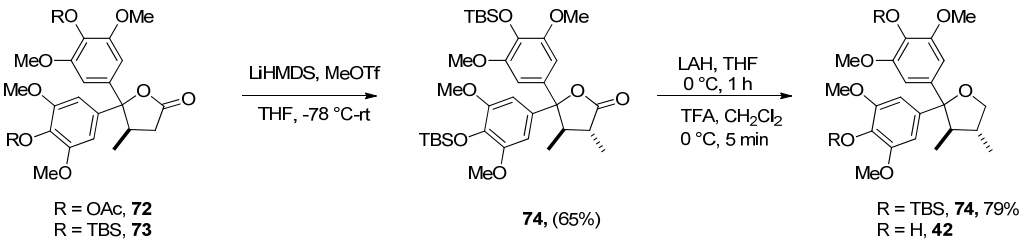
Next task was the regioselective Wacker oxidation of **68**. Amongst various Pd(II)-



Scheme 11. *Attempt reverse Wacker-oxidation*

reagents employed, the regioselectivity of the Wacker oxidation of **68** was found to be promising with $Pd(CH_3CN)_2(Cl)(NO_2)$, $CuCl_2$, O_2. However, the reaction gave a 1:1

mixure of lactol **70** and its *t*-Bu acetal **71**. The acetal **71** was hydrolyzed with TFA in CH_2Cl_2 to afford the lactol **70**. The oxidation of lactol **71** was carried out by celite supported silver carbonate to procure the lactone **72**. Our next target was diastereoselective methylation of lactone **72**. Our initial attempts of methylation using the diacetate **72** were turned out to be unsuccessful because of the presence of the base susceptible acetate protecting group. To prevail over this, we subjected **72** for the deacetylation using K_2CO_3 in methanol and reprotected as it di-O-TBS ether **73**. We next performed the diastereoselective methylation at C(3) by using LiHMDS-MeOTf



Scheme 12. *Synthesis of Sacidumlignan D*

to afford **74**. The final stage of the synthesis, sequential reduction of the lactone, cyclisation and deprotection of the TBS ethers of **74** provided the sacidumlignan D (**42**). The spectral and the analytical data of **42** were in good agreement with data reported for natural sacidumlignan D.

Conclusion:

The first total synthesis of *rac*-sacidumlignan D has been completed. The adopted approach employs the reverse Wacker oxidation of terminal olefin and diastereoselective methylation of lactone as key reactions.

Chapter 3: Synthesis of furano β-amino acids and their homo-oligomers.

Intoduction:

In recent years, several approaches have been put forward to address the mimicking of the secondary structures of the peptides on one hand and the *in-vitro* stability of synthetic peptides for medicinal applications on the other. Seebach and Gellman groups have introduced the *β*-peptides as expeditious tools in this context. The nature of the secondary structure of their homo-oligomers seems to depend mainly upon i. the relative stereochemistry of the amine and acid groups, ii. ring atoms and iii. the ring size. For example, the homo-oligomers constructed by the

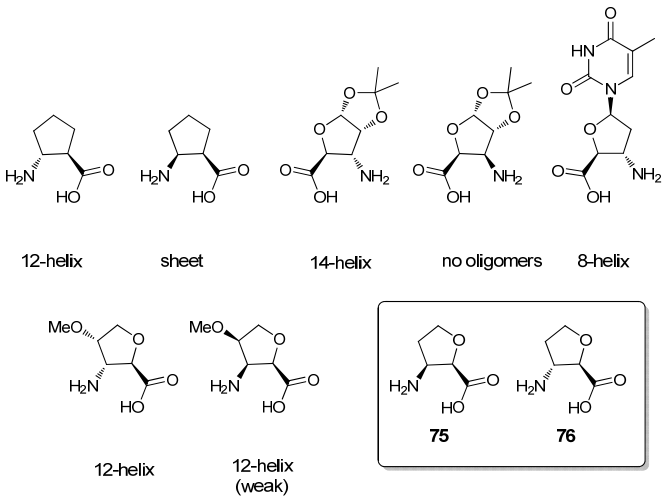


Figure 6. Five member ring constrained *β*-amino acids and the secondary structures reported for the corresponding homo-oligomers and the simple cis-/trans- furanoid-*β*-aminoacids.

trans-2-aminocyclopentane carboxylic (*trans*-ACPC) acid form a stable 12-helix whereas the homo-oligomers derived from the *cis*-2-aminocyclopentane carboxylic acid (*cis*-ACPC) form a sheet-like structure.

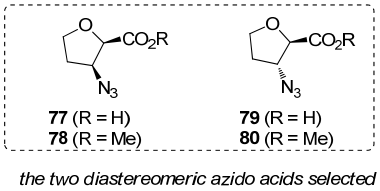


Figure 7: *Structures of β-amino acids synthesized by Fleet and selected β-amino acids for synthesis*

A close examination of the *β*-peptides of furanoamino acids reported reveal a random selection of monomers. This necessitates the structural analysis of the homo-

oligomers of simple unsubstituted furan constrained-*β*-amino acids to understand

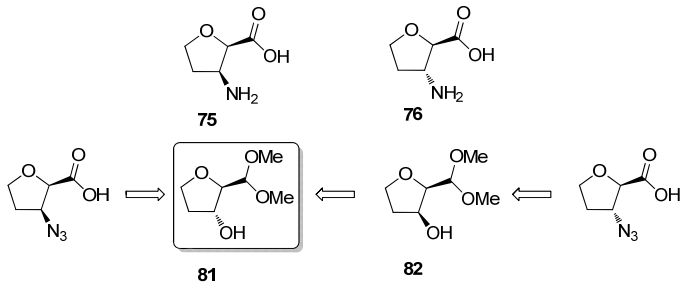


Figure 8: *Designed β-amino acids and the intended synthetic strategy*

whether the diversity in their secondary structure was either due to the substituents present on the furan ring or due to the ring oxygen. In this context, we have identified the azido acids/esters **77**–**80** as suitable precursors for the synthesis of the corresponding homo-oligomers. Figure 10 provides a retrosynthetic strategy for the

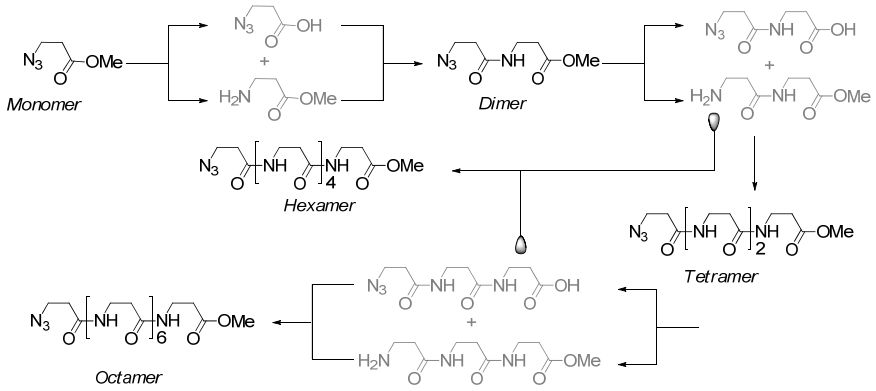


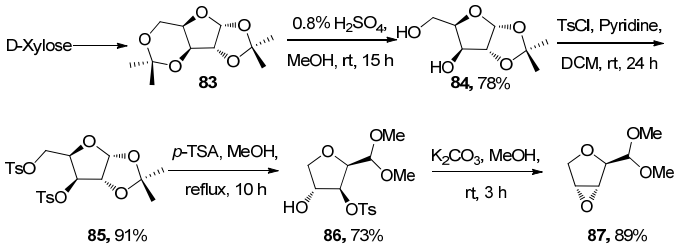
Figure 9: *β-Amino acid, and retrosynthetic scheme and flow diagram for synthesis of homo-oligomers*.

building blocks synthesis and a protocol for the solution phase synthesis of homo-oligomers.

We have designed a set of two diastereomeric furanoid *β*-amino acids and intended to synthesize their homo-oligomers. To start in this direction, first we have selected the *cis*-and *trans*-furanoid *β*-azido acids **77** and **79** and their corresponding methyl esters **78** and **80** as suitable precursors for the iterative synthesis of the corresponding *β*-peptides. A representative protocol for the synthesis of homo-oligomers is given in figure 11.

Synthesis of dimethylacetal oxirane 87

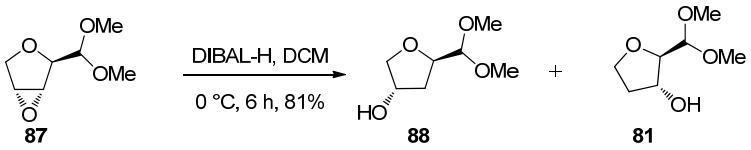
The synthetic endeavor began with the conversion of D-xylose into D-xylose



Scheme 13. *Dimethylacetal oxirane 87*

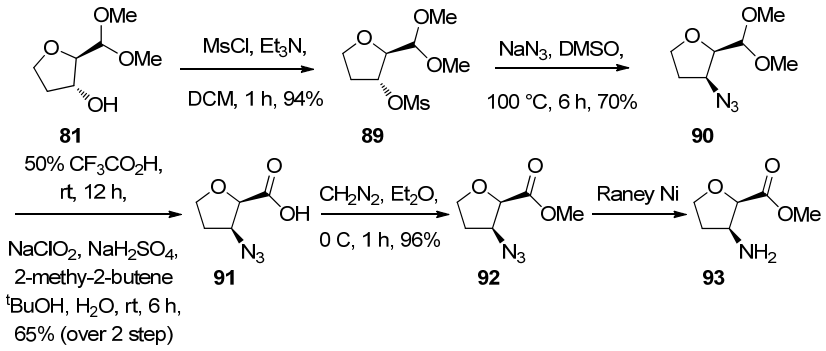
diacetonide **78** (prepared from D-xylose by treating it with conc. H_2SO_4, anhydrous $CuSO_4$, in acetone). Selective deprotection of 3,5-isopropylidene group by using 0.8% H_2SO_4 in methanol gave diol **79**. The diol **79** was protected with tosyl by treated with tosyl chloride in pyridine to procure the compound **76**. Having the tosyl protected compound **76** in hand, the next task was acid mediated acetonide deprotection with concomitant 2,5-ring closure to give dimethylacetal **80** which on base treatment gave **75**.

Synthesis of *β*-amino acid:



Scheme 14: *Reduction of epoxide*

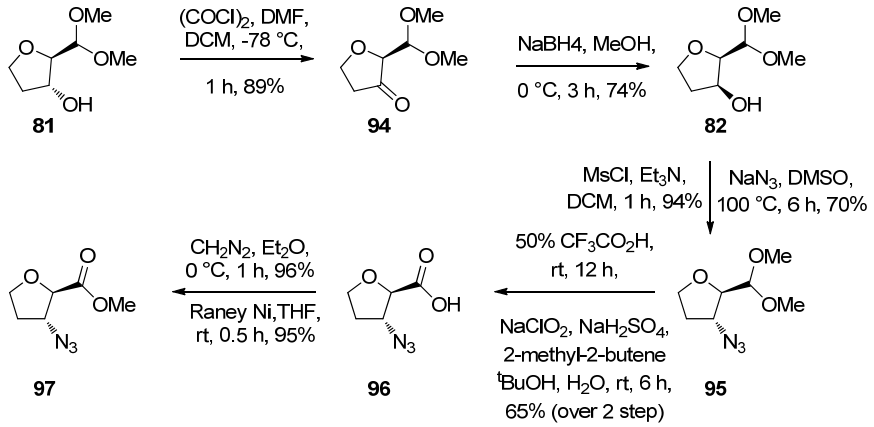
The compound **87** was treated with DIBAL-H in DCM to get the regiomeric mixture of **88** and **81** in 1:7 ratios. The hydroxyl group of **81** was mesylated gave **89**, mesyl group of **89** was displaced with azide by using NaN_3. The acetal group of **90** was



Scheme 15: *Synthesis of cis-β-amino acid*

deprotected and resultant aldehyde was oxidized to acid **91** by treating with sodium chlorite and sodium dihydrogen phosphate in ^{t}BuOH and water in the presence of 2-methy-2-butene as a scavenger. Acid **91** was converted to ester **92**, which was then converted to second monomer **93** using Raney Ni in EtOH.

The compound **81** was oxidized into **94**, followed by sodium borohydride reduction to procure **82**. The hydroxyl group of **82** was transformed to the corresponding azide by treatment with MsCl in Et_3N followed by reacting the intermediate mesylate with NaN_3 in DMF to give the **95**. Dimethyl acetal was

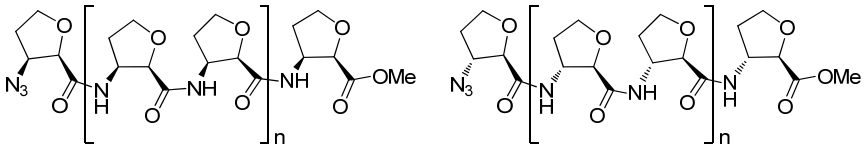


Scheme 16: *Synthesis of trans-β-amino acid*

converted to aldehyde followed by acid formation using sodium chlorite and sodium dihydrogen phosphate in *t*-BuOH and water to give **96**. Monomer **96** was converted to ester **97**, which was then converted to second monomer amine using Raney Ni in EtOH.

Synthesis of *cis* and *trans*-homo–oligomers:

We have synthesized the homo-oligomers of *β*-FAA in solution phase by using standard coupling protocol where EDCI and HOBt combination was used for peptide coupling.



n = 0, Dipeptide **98**
n = 1, Tetrapeptide **99**
n = 2, Hexapeptide **100**
n = 3, Octapeptide **101**

n = 0, Dipeptide **102**
n = 1, Tetrapeptide **103**
n = 2, Hexapeptide **104**

Scheme 17: *Synthesis of cis-FAA-homo-oligomer*

Once we have the Oligomers **98**–**104** in our hand to examine existence of secondary structure resulting from the intra-strand hydrogen bonding. Indeed the CD spectra of oligomers as shown in (figure 12), suggest the existence of a distinctive secondary structure in solution.

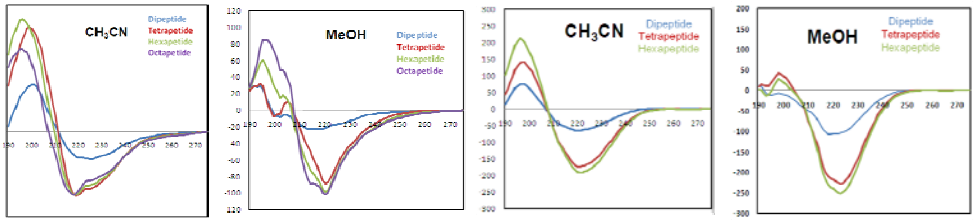


Figure 12: *The CD Spectral graph of cis and trans-β-FAA oligomer in different solvents*

The secondary structures of *cis*-*β*-FAA were confirmed with the help of the inter-residue *nOes* noticed. Amongst the various *nOes* observed in the NOESY of the *cis*-tetramer **99**, the inter-residue $C_{\beta}H_i/NH_{(i+3)}$, $C_{\alpha}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$, $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, and $NH_{(i+2)}$/Me of ester (Figure 14) indicates the presence of a three 12-helix pitch.

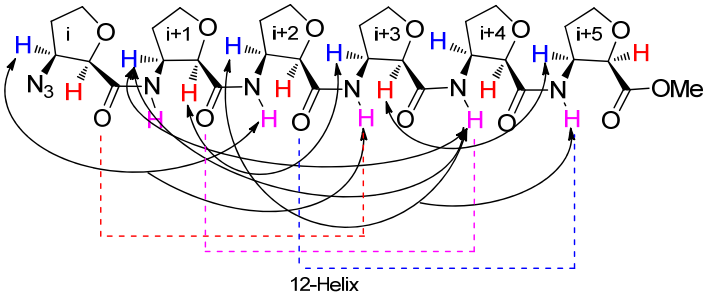


Figure 15: *Characteristic nOes supporting a 12-helix*

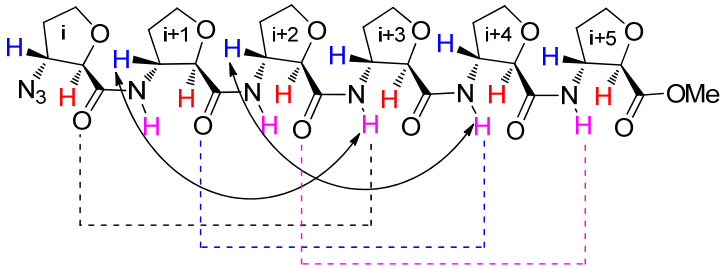


Figure 95: *Characteristic nOes supporting a 12-helix*

NOESY data of **99**, **100**, **101**, **103** and **104** revealed several medium and long-range backbone *nOes* between $C_{\beta}H_i/NH_{i+2}$, $C_{\beta}H_i/C_{\alpha}H_{i+2}$ and $C_{\beta}H_i/NH_{i+3}$ which are

characteristic for the 12-helix. For the *cis*/*trans*-tetramer, the one *nOes* signals between $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$ are well resolved. Several of the peaks which are characteristics *nOes* for the higher oligomers confirmed the 12-helix.

Conclusion:

The secondary structural analysis of native *cis*- and *trans*- furanoid-*β*-amino acids reveals that the all adopt left handed 12-helix structures in solution. The temperature dependent deviation in the chemical shifts indicate that the *trans*-*β*-FAA homo-oligomers form a robust left handed 12-helix ($\Delta\delta < 6$ ppb/°C) whereas the *cis*-*β*-FAA homo-oligomers form a week left handed 12-helix ($\Delta\delta > 4$ ppb/°C)**.**

CHAPTER-I

Total Synthesis of Aculeatins A, B, E, F and 5-*epi*-aculeatins E and F

Introduction

Introduction:

Spiroketals occur in nature predominant as a sub-units of naturally occurring substances from many resources, including insects, microbes, plants, fungi, and marine organisms[1]. It is a cyclic ketal in which two rings are joined by a single atom, the spiro atom, and the two ketal oxygens flanking the spiro atom, each belonging to one of the rings. There are an enormous range of structural complexity ranging from the relatively simple fly pheromones to the intricate frameworks of the polyether antibiotics and the spiroketal macrolides. Several of these have potent pharmacological activity. Four different types of spiroketal ring systems are known (Figure 1)[2].

Figure 1: *Representative spiroketal ring systems*

In a several cases, the spiroketal structure itself is directly associated with the biological activity. Some representative biologically active natural products containing the spiroketal motifs were given in Figure 2.[3] Talaromycin is a small spiroketal natural product that is a potent mycotoxin. In addition, spiroketals represent an important class of insect pheromones, demonstrating the ability of even simple spiroketals to bind to biological receptors. For example, both the enantiomers of Olean are produced by the female olive fly, but their chemo-attractant activities are gender-specific, with the *R*-enantiomer active on males, and the *S*-enantiomer active on females (Figure 2). The exocyclic spiroketal in the avermectin class of anti-parasitic compounds exhibits a pronounced, narrow structure-activity relationship profile, indicating that it is likely the spiroketal unit directly involved in target binding.

Reveromycins A and B are the members of a novel family of bioactive spiroketal containing natural product isolated from a soil actinomycete belonging to the *Streptomyces* genus. Reveromycin A is an inhibitor of the mitogenic activity of epidermal growth factor (EFG) and may represent a new class of antitumor agents. In addition, reveromycin A also exhibits antifungal activity (MIC) 2.0 μg mL^{-1}, pH 3)

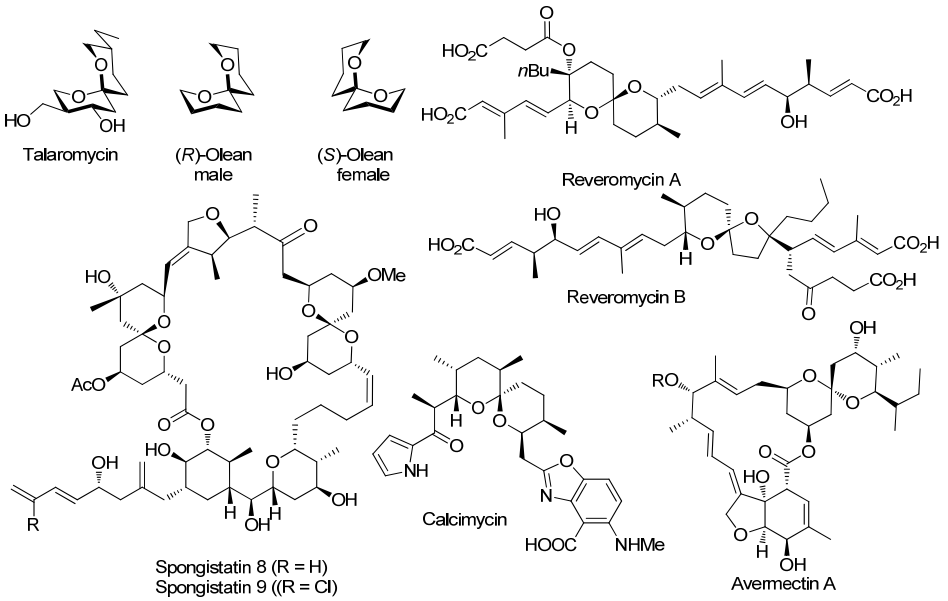


Figure 2: *Spiroketal-containing natural products*

and it has been identified as a specific inhibitor of *Saccharomyces cerevisiae* isoleucyl-*t*RNA synthetase (IleRS). Calcimycin has been shown to be an ionophore antibiotic. It selectively transports divalent cations, and has been used for specific perturbation of transmembrane Ca^{2+} gradients in complex systems such as cells.

The spiroketal unit in several natural products has been also identified as rigid scaffolds that can display complex side chains along various well-defined three-dimensional vectors.[4] The spongistatins 8 and 9, are the classical examples. They have been found to be inhibiting tubulin protein-protein interactions. However, some recent reports indicate that simple spiroketal analogs of spongistatin exhibit a similar activity of their own.[5] The increasing pharmacological importance of compounds containing spiroketal assemblies has ascertained importance of spiroketals as valuable pharmacophore and has attracted considerable attention in both target- and diversity-oriented synthesis.[6] In the latter context, spiroketals present an excellent opportunity

to exploit stereochemical diversity, wherein these rigid scaffolds can be used to display substituents along various well-defined three-dimensional vectors.[7]

- **Conformational analyses of spiroketals**

The conformational analyses of spiroketals of 1,7-dioxaspiro[5.5]undecane system has been well documented in the literature, by virtue of its frequent occurrence. Studies by Deslongchamps[8] have determined that 1,7-dioxaspiro[5.5]undecane **A** exists exclusively in conformation $\mathbf{A_1}$ (Figure 3). This experimental observation has been explained by the fact that conformation $\mathbf{A_1}$ is stereoelectronically and sterically more stable than conformations $\mathbf{A_2}$ and $\mathbf{A_3}$ which were estimated to be less stable by a value of 2.4 and 4.8 Kcal/mol, respectively.

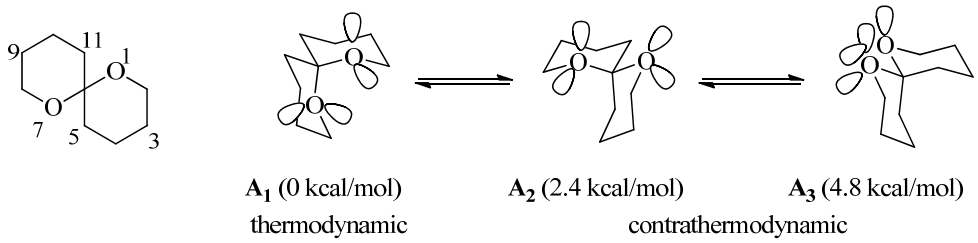


Figure 3: *Relative energies of the three possible chair-chair conformations of* ***A***

Spiroketals are readily formed by the acid-catalyzed convergence of two tethered alcohols onto a central ketone. During this process, only a single spiroacetal conformation is formed *i.e* conformer $\mathbf{A_1}$. Conformer $\mathbf{A_1}$ can be considered a *thermodynamic* spiroketal due to the existence of two anomeric stabilizing interactions wherein both acetal oxygen atoms have a set of lone pairs able to mutually donate into the C-O σ* of the other oxygen. Conformers $\mathbf{A_2}$ and $\mathbf{A_3}$, which are not formed under these conditions, can be considered *contrathermodynamic* spiroketals because they lack atleast one anomeric stabilizing effect. Representative examples (Figure 4) are the ABCD subunit of azaspiracid 1, dianomycin, leuseramycin, aplysiatoxin, spirofungin A, BCD subunit of salinomycin, ABC subunit of (+)-pinnatoxin and the CD subunit of spongistatins 8 and 9 (Figure 4).[9]

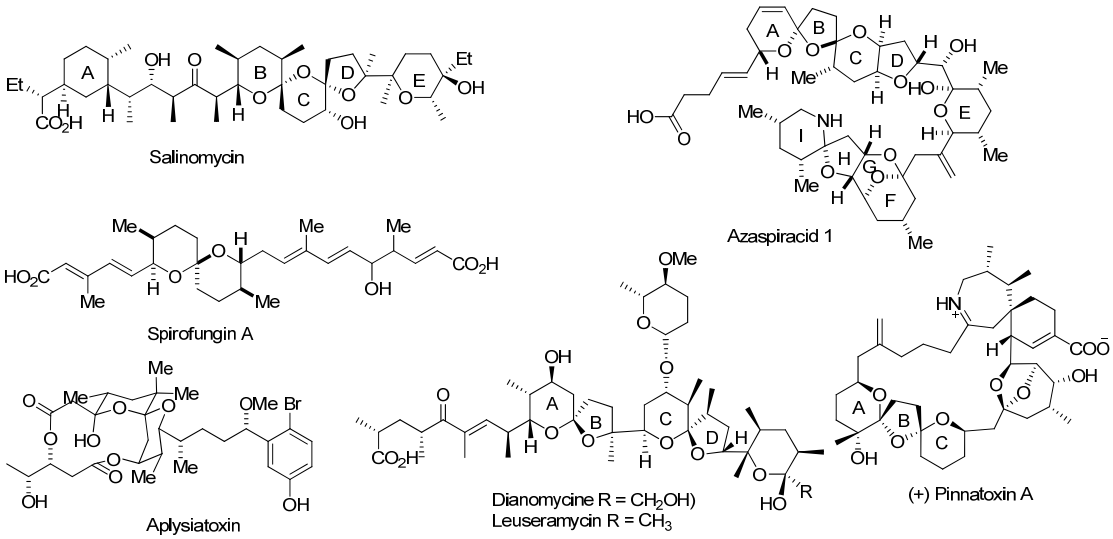


Figure 4: *Contrathermodynamic spiroketal motifs in natural products*

Aculeatins: Natural products with unique [6,5]-spiroketal tricyclic ring system:

Aculeatins A–D (**1**–**4**, respectively) were isolated from the petroleum ether extracts of the rhizomes of *Amomum aculeatum*. With the help of extensive 2D-NMR experiments, the structures of aculeatins A–D were characterized by the presence of a fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture.[10] Aculeatin D (**4**) showed the remarkably high cytotoxicity, anti-bacterial and anti-protozoal

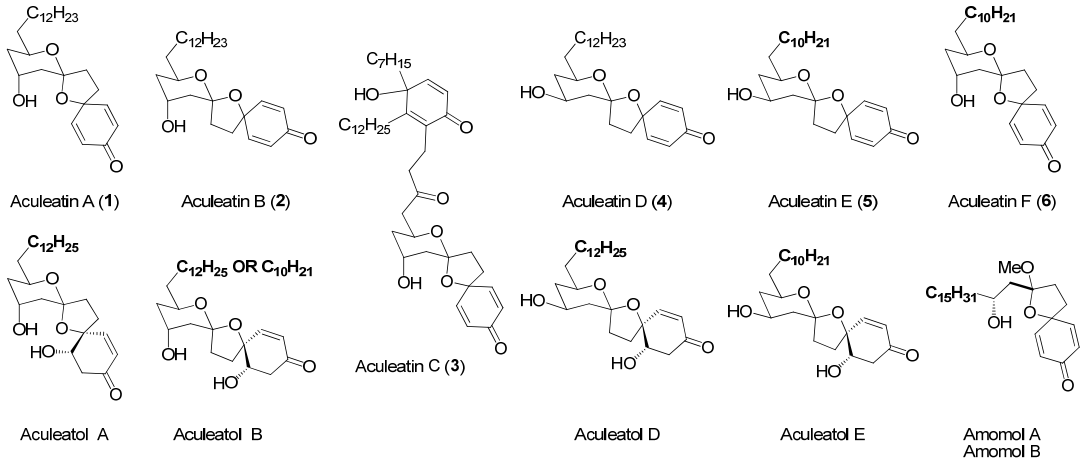
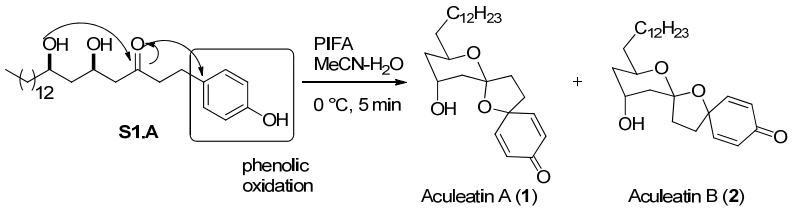


Figure 5. *Natural aculeatins A–F (**1**–**6**), aculeatols A– E and amomols A/B*

activities. In 2007, Kinghorn *et.al* reported the isolation of related metabolites aculeatols A–D; the *C*(9) hydroxylated aculeatins A or B having either the same or two carbon truncated side chains.[11] Subsequently, the isolation of truncated aculeatins A and D, named respectively as aculeatins F (**6**) and E (**5**), were reported by the same group. Having the novel dioxadispirocyclic architecture present in aculeatins and showing the broad spectrum of biological activity, many synthetic efforts have been reported to the construction of their unusual architecture, involving a final key oxidative spirocyclisation of phenolic precursors.

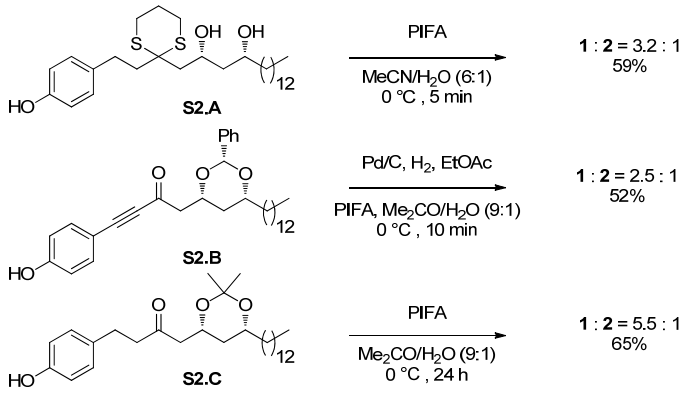
Total Synthesis of Aculeatins

Wong *et al*. reported the first total synthesis of aculeatins A (**1**) and B (**2**) by employing the spiroketalisation as the key transformation and PIFA as the reagent of choice (Scheme 1). The initial success of this reaction has been accepted as the key disconnection approach in the syntheses of aculeatins reported later by other groups. The key retron used for this particular transform was a 1,3-diol-5-ketone and synthesis of which has been designated as the essence of various aculeatins total syntheses documented.



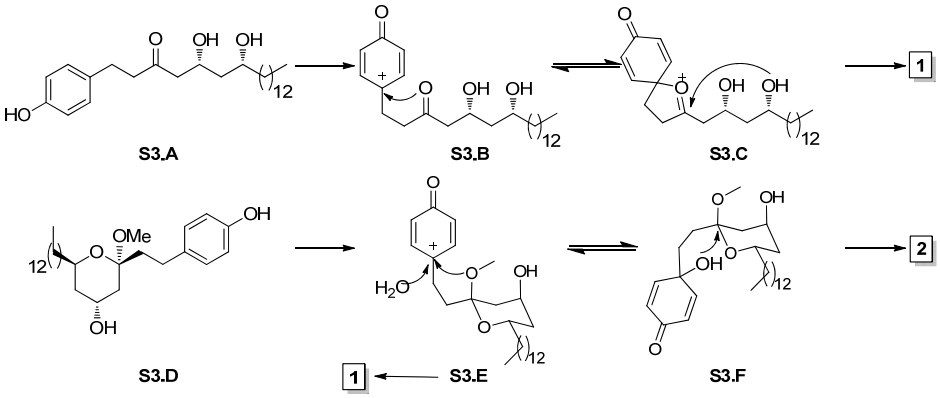
Scheme 1. *Spiroketalization to the aculeatin A and B*

The inaugural synthesis of aculeatins A and B by Wong *et al*. involves the treatment of thioacetal **S2.A** with phenyliodine bis(trifluoroacetate) (PIFA) giving a 3.2:1 ratio of epimeric aculeatins A (**1**) and B (**2**), in favor of the stable spiroketal structure. Longer reaction times increased the proportion of the stable spiroketal as illustrated by Marco *et al*. on the protected diol **S2.C** which afforded a 5.5:1 ratio of **1** and **2**.



Scheme 2. *Synthetic approaches towards the total synthesis of aculeatin A and B*

A rationalization for the stereochemical outcome of the oxidative spirocyclization to aculeatins has put forward by Wong *et al*. recently. The linear precursor S**3.A** led to a mixture of epimers in favor of the anomeric spiroketal **1** through a pathway involving the bicyclic oxycarbenium cation intermediate **S3.C**. Starting from methyl acetal **S3.D**, the authors assumed that the methyl ether was less prone to direct attack on the cation intermediate **S3.E**, thus favoring water addition to produce the tertiary alcohol **S3.F**. Nucleophilic displacement of the methoxy group then led to the contrathermodynamic spiroketal **2**.

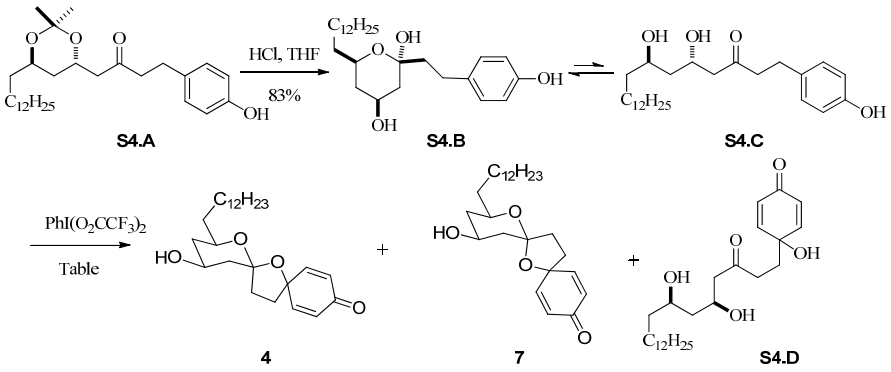


Scheme 3. *Mechanism of oxidative spirocyclization according to Wong et al.*

Biomimetic synthesis of (±)-aculeatin D (Baldwin *et al.* 2005)

Baldwin's group explored the synthesis of aculeatin D (**4**) from dihydroxy ketone **S4.A** (Scheme 4). Acid mediated removal of the acetonide delivered hemiketal **S4.B** which in solution is in equilibrium with the linear ketone **S4.C**. Further

oxidative spirocylization afforded a mixture of (**4**) and (**7**) and the open chain derivative **S4.D**. The ratio depends on the solvent. In acetonitrile, only 6-*epi*-acuelatin D (**7**) was formed in 33% yield. In acetone and wet acetone, aculeatin D (**4**) was formed and was isolated in up to 19% yield. In acetonitrile, hemiketal intermediate **S4.D** is observed whereas in acetone, a mixture of hemiketal **S4.D** and open chain derivative **S4.C** is observed (Scheme 4). After oxidation, the hemiketal **S4.D** can directly react with the phenoxycarbenium cation to deliver the 6-*epi*-aculeatin D (**7**), whereas two pathways are possible for the open chain carbocation intermediate giving also access to the expected less stable aculeatin D (**4**).

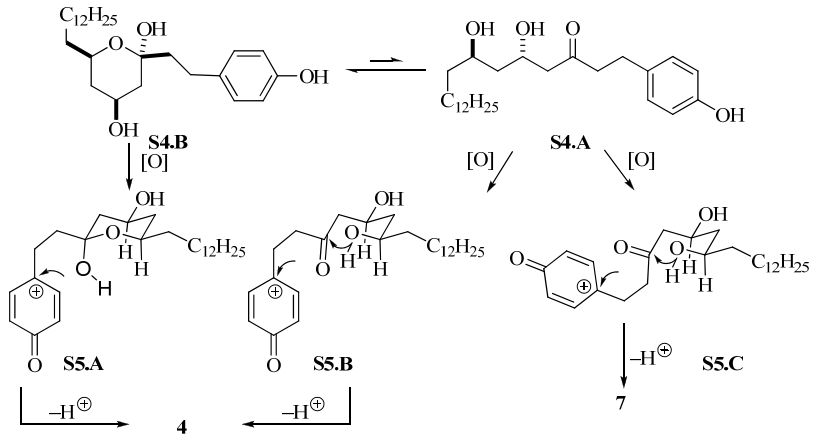


Conditions	Yield of **(±)-4** (%)	Yield of **(±)-7** (%)	Yield of **(±)-S4.D** (%)
MeCN, 0 °C, 1 h	0	33	15
MeCN/H_2O (6:1 v/v), 0 °C, 1 h	0	29	44
Acetone, rt, 20 min	11	40	20
Acetone/H_2O (9:1 v/v), rt, 20 min	19	43	27

Scheme 4. *Synthesis of aculeatin D (**4**) and 6-epi-aculeatin D (**7**) according to Baldwin et al*.

Baldwin *et al*. proposed a mechanistic rationale for the dramatic influence of the nature of the solvent on the product distribution on the oxidative cyclisation (Scheme 5). The cyclisation precursor was found to exist as an equilibrium mixture of the cyclic compound **S4.B** and the open-chain compound **S5.A** in solution (*vide supra*). In deuterated acetone the equilibrium ratio of **S4.B**: **S5.A** was shown to be 2:1 (by 500 MHz NMR analysis), whereas in deuterated acetonitrile compound **S4.B** was present almost exclusively [**S4.B**:**S5.A** > 95:5]. This suggests that the partitioning between **S4.B** and **S5.A** is likely to be due to hydrogen-bonding effects, since acetone would be expected to stabilize intermolecular hydrogen bonds [and thus favour the open-chain compound **S5.A**] to a greater extent than would acetonitrile. Greater

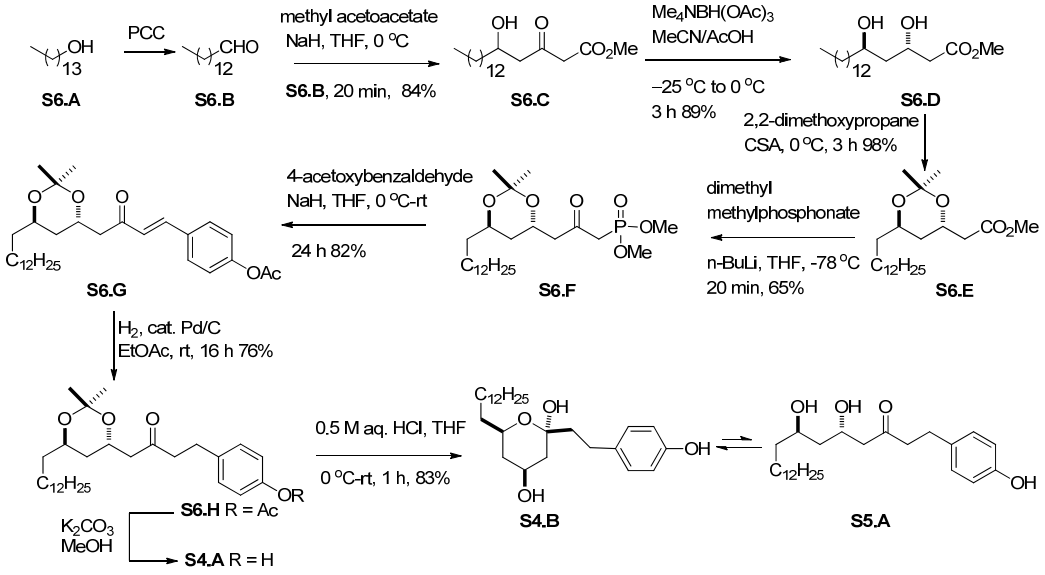
solvent polarity would thus be expected to increase the proportion of aculeatin D (**4**) formed in the reaction, as observed experimentally. It is possible to speculate that metal ion coordination could favour the open-chain structure **S4.C** (required for formation of aculeatin D (**4**) over the cyclic compound **S4.B**, thus increasing the proportion of **4** formed during the oxidative cyclisation.



Scheme 5. *Mechanistic proposal for the oxidative spirocyclization by Baldwin et al.*

Baldwin *et al*. started the synthesis of aculeatin D (**4**) with the oxidation of commercially available 1-tetradecanol **S6.A** using PCC to obtain the corresponding aldehyde **S6.B** (Scheme 6), then selective γ-alkylation of the dianion of methyl acetoacetate gave racemic alcohol **S6.C** in good overall yield. Following the Evans' protocol, treatment of compound **S6.C** with tetramethylammonium triacetoxyborohydride resulted in a chemo- and diastereoselective reduction of the ketone group resulting in formation of a 95:5 mixture of 1,3-*anti*-/1,3-*syn*-diol products, and a single recrystallisation gave the pure 1,3-*anti* product **S6.D** in excellent yield. The diol **S6.D** was converted into the acetonide derivative **S6.E** and treated with α-lithio methyl phosphonoacetate to give phosphonate **S6.F**. Wadsworth–Emmons olefination of phosphonate **S6.F** with commercially available 4-acetoxybenzaldehyde proceeded efficiently at room temperature to afford alkene **S6.G** in good yield (Scheme 6), and exclusively as the (*E*)-isomer. The palladium-catalyzed hydrogenation of alkene **S6.G** and subsequent cleavage of the acetate group gave phenol **S4.A**. The acetonide protecting group was then cleanly removed from phenolic ketone **S4.A** under aqueous acidic conditions. The product was formed as a white

solid in good yield, and was shown to be the cyclic compound **S4.B**. However, in solution this material was found to equilibrate to a mixture of cyclic compound **S4.B** and the open chain derivative **S5.A**; in deuterated acetone a 2:1 equilibrium mixture of compounds **S4.B**: **S5.A** was formed within 3 h at room temperature.

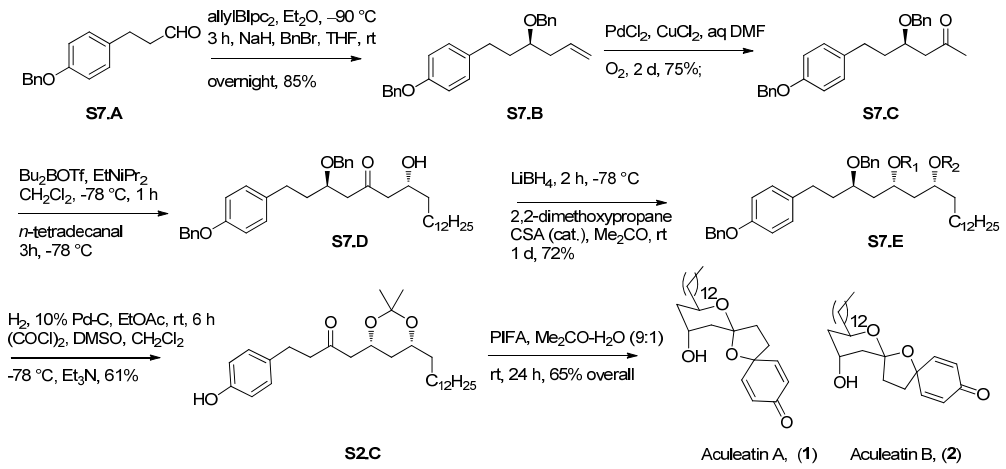


Scheme 6. *Synthesis of aculeatin D and its 6-epimer*

Treatment of a mixture of **S4.B** and **S5.A** with PIFA in MeCN at 0 °C led to the rapid consumption of the starting material, and the formation of two new products in moderate yield (Scheme 5), spectroscopic analysis revealed that these two compounds were tricyclic compound **7** and ketone **S4.D**. The next conditions attempted were the use of aqueous acetonitrile as the solvent for the oxidation of phenol **S4.B** and **S5.A**, however it did not produce any of the desired aculeatin D (**4**), but instead merely increased the yield of ketone **S4.D**. After extensive variation of the reaction conditions, it was found that performing the oxidation in acetone resulted in the formation of an additional third product, isolated in 11% yield, found to be the desired racemic aculeatin D (**4**). The relative stereochemistry of the spiroacetal ring system in **4** was confirmed by NOE analysis. Further optimization of reaction conditions, it was found that using an acetone/water (9:1 v/v) solvent system for the reaction maximized the yield of aculeatin D (**4**) (19%), the proportion of the desired product **4** is (**4**:**7**:**S4.D** 1.0:2.4:1.5) and also the overall yield of the reaction (89%).

Enantioselective synthesis of aculeatins Aculeatin A (1) and B (2) by Falomir et al. 2006

Falomir and coworkers described the enantioselective synthesis of aculeatins A, B, D and *epi*-D by using asymmetric allylations. A further key step was a stereoselective aldol reaction with remote stereochemical induction. The absolute configurations of the natural products have been established and an erroneous structural assignment has been corrected. The synthesis starts with asymmetric allylation of 3-(*p*-benzyloxyphenyl)propanal **S7.A** using the chiral allylborane prepared from allylmagnesium bromide and (–)-DIP-Cl [(–)-diisopinocamphenylchloroborane] leading to homoallyl alcohol with 96% ee which



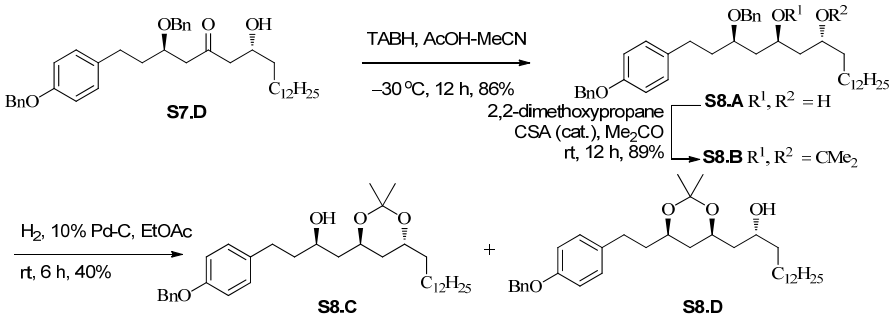
Scheme 7. *Synthesis of aculeatins A and B.*

was benzyleted to get **S7.B**. Wacker oxidation of followed by boron aldol reaction of allyl alcohol **S7.C** provides the desired aldol **S7.D** as a single disastereomer. The aldol is then reduced *in situ* to the monobenzylated *anti*, *syn*-1,3,5-triol with $LiBH_4$ followed by acetonide protection of the two free hydroxyl groups by using dimethoxy propane gave the **S7.E**. The hydrogenolytic debenzylation which is under Swern oxidation furnishes ketone **S2.C**. The ketone **S2.C** is then subjected to hydrolytic cleavage of the acetonide moiety but the yield of expected β,δ-dihydroxy ketone is low (< 35%). The treatment of acetonide **S2.C** with phenyliodonium bis(trifluoroacetate) not only causes the desired phenolic oxidation, but also acetonide hydrolysis and subsequent spiroacetalization (Scheme 7). This cleanly gives a 5.5:1

mixture of two optically active products with spectral properties identical to those reported for aculeatins A (**1**) and B (**2**).

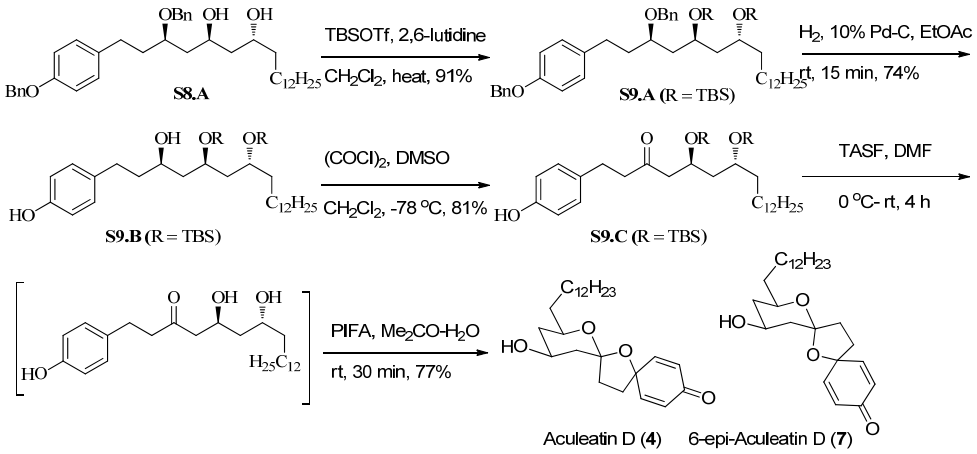
Synthesis of Aculeatin D (4) and 6-*epi*-D (7)

The synthesis of aculeatin D and 6-*epi*-aculeatin D is achieved by inversion of configuration at C-4. Thus, aldol **S7.D** is stereoselectively reduced with TABH to afford the expected *anti*-1,3-diol **S8.A**. In this case the free hydroxyl groups of **S8.A** are not protected as an acetonide because it gives unwanted rearranged acetonide **S8.C** as major product (Scheme 8).



Scheme 8. *Attempted synthesis of aculeatins D and 6-epi-D*

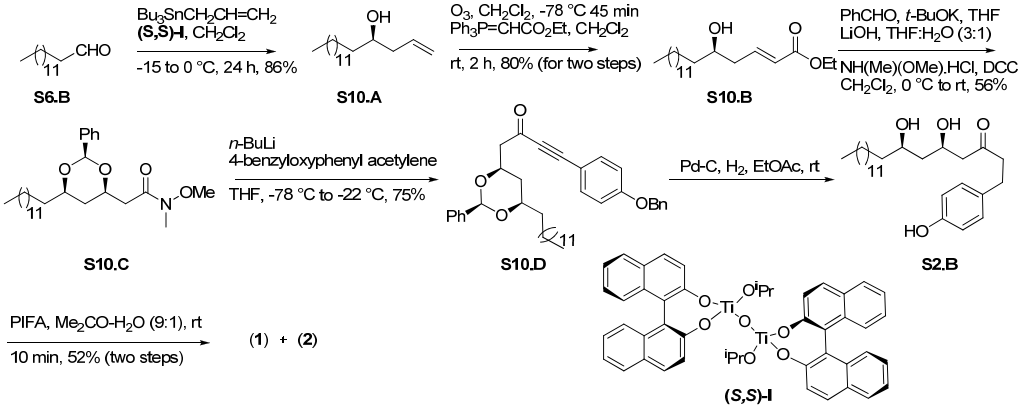
This problem was solved by double silylation of diol **S8.A** with TBSOTf, and subsequent hydrogenolysis to give compound **S9.B**. Swern oxidation and desilylation of **S9.B** under mild conditions with TASF affords the diol which immediately subjected to oxidative spiroacetalization with $PhI(OCOCF_3)_2$ to yield a 2.7:1 mixture of natural aculeatin D (**4**) and 6-*epi*-aculeatin D (**7**).



Scheme 9. *Synthesis of aculeatins D and 6-epi-D*

Chandrasekhar's Synthesis of aculeatins A and B via a oxa-Michael approach (2007)

Chandrasekhar *et al*. reported the synthesis of aculeatins A and B starting from the tetradecanal (**S6.B**) *via* a tethered oxa-Michael approach. The homoallylic alcohol **S10.B** is synthesized from aldehyde (**S6.B**) using a Maruoka allylation. This compound is then converted to unsaturated ester **S10.B** by ozonolysis and subsequent two-carbon homologation and is used for the tethered intramolecular oxa- Michael



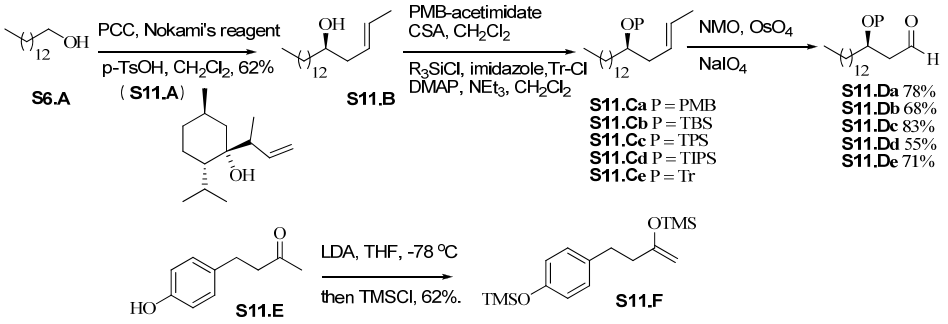
Scheme 10. *Synthesis of aculeatin A and B*

reaction to install the second stereocenter. Thus, reaction of **S10.B** with benzaldehyde and potassium *tert*-butoxide affords benzylidene acetal with 95% diastereoselectivity favouring the more stable *syn*-isomer. Acetal is converted to Weinreb amide **S10.C**,

which upon treatment with lithiated 4-benzyloxyphenylacetylene affords fragment alkynone **S10.D**. Catalytic hydrogenation of **S10.D** gives intermediate **S2.B**, which on treatment with phenyliodonium (III) bis(trifluoroacetate) (PIFA) affords aculeatins A (**1**) and B (**2**) as a 5:2 mixture (Scheme 10).

Diastereodivergent synthesis of aculeatins by Wong *et. al*. 2007

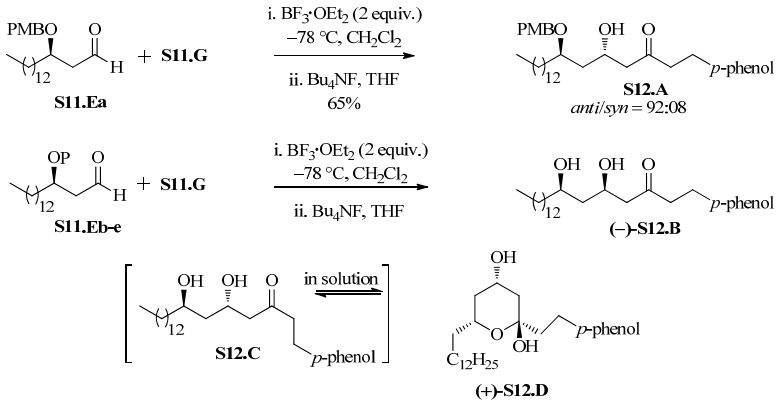
Wong *et al.* reported a concise and stereocontrolled syntheses of aculeatins (–)-A, (+)-B, (+)-D, and (+)-6-*epi*-D. The diastereodivergent 1,3-inductions in Mukaiyama aldol coupling contribute to reduce steps and to increase flexibility with reactants having sterically restricted proximal substituents (-CH_2), involving either a good *anti* or a moderate *syn* 1,3-induction, depending on the nature of protecting group (P). In addition, the 3,5-*syn*-diol-ketone resulting from concomitant deprotection of the β-alkoxy (Tr = trityl) group proves to be remarkably stable whereas the 3,5-*anti* diastereoisomer cyclizes spontaneously to the corresponding tetrahydropyran hemiketal, thus enabling a useful and facile separation. The second part of study is devoted to improving the yield and the diastereoselectivity of the final phenolic oxidation reaction leading to aculeatins. Several hydroxy-protected aldehydes **S11.E** were prepared starting from alcohol **S6.A** using Nokami's enantioselective crotylation, protection and oxidation sequence (Scheme 11). On the other hand the enolsilane **S11.F** was synthesized from ketone **S11.E**. It was observed that the aldol reaction of **S11.F** and aldehyde **S11.D** having a PMB protecting group proceeded with a good 1,3-*anti* induction (dr = 92:08) to give *anti* product, whereas



Scheme 11. *Syntheses of **S11.Ea–e** and **S11.G***

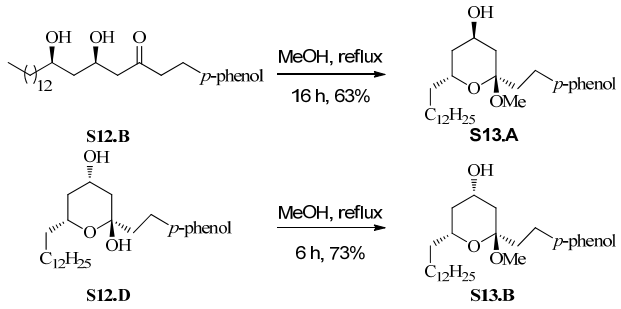
with bulky silyl ether dramatically reduce the 1,3-*anti* induction. For TBS ether the *anti*/*syn* ratio is 60:40 and for TPS and TIPS there is no 1,3-induction. During the

aldol reaction, the two compounds **S12.A** and **(+)-S12.D** are isolated. Here the aldol product **S12.A** does not undergo cyclization due to the strong hydrogen bonding. Whereas, compound (+)-**S12.D** is formed from the cyclization of *anti* isomer **S12.C**, which lack of hydrogen bonding (Scheme 12).



Scheme 12. *Syntheses of keto-diol*

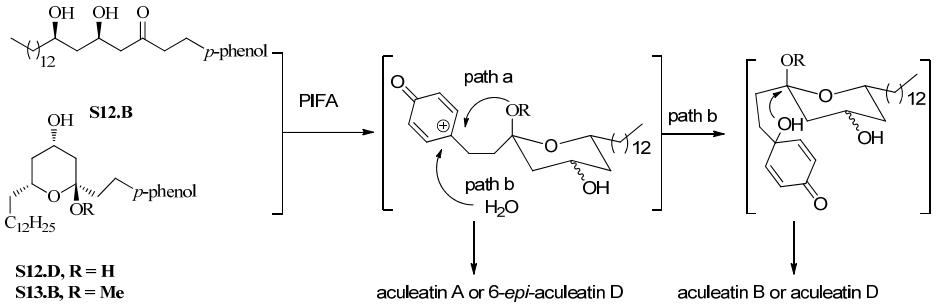
Next the compounds **S12.B** and (+)-**S12.D** are converted to methoxy-protected ketals **S13.A** and **S13.B** (Scheme 13). Finally the compounds **S12.A**, **S12.D**, **S13.A** and **S13.B** are subjected to spirocyclization in different conditions to give aculeatins A, B, D and 6- *epi*-aculeatin D.



Scheme 13. *Syntheses of **S13.A** and **S13.B***

For instance, presence of water in the medium was necessary to get high yield of aculeatins. In addition, they observed that running the reaction at higher concentration (0.04 M) using PIFA in acetone/H_2O (10:1) at room temperature in darkness for only 15 min allows the corresponding aculeatins to be isolated in good yields. The yield was improved by adding additional TFA (CF_3CO_2H, optimized at

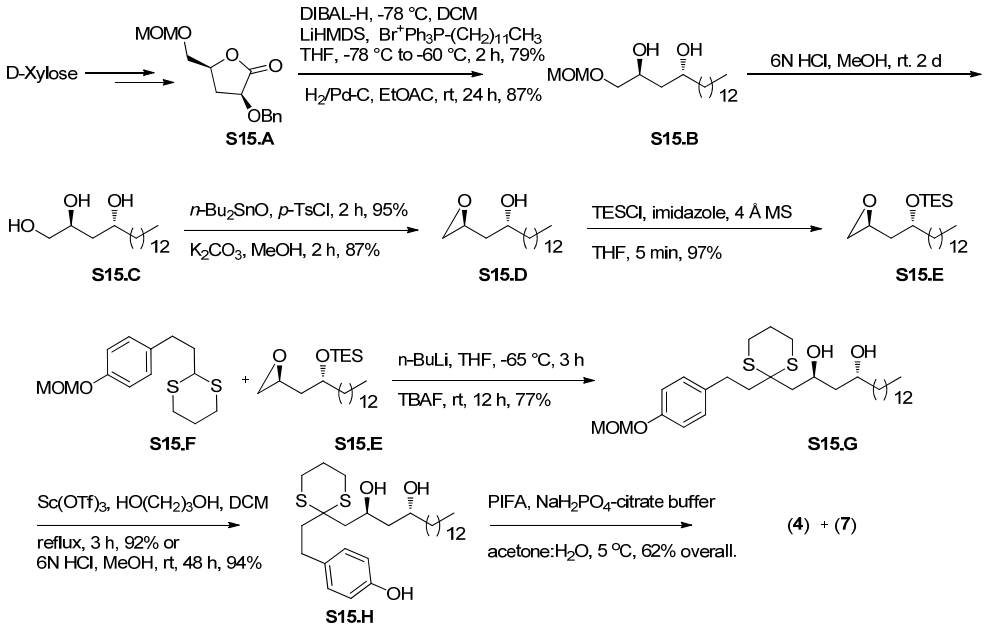
0.4 equiv) beyond that generated in situ from the PIFA reagent. Concerning the stereocontrol in the syntheses of aculeatins (–)-A and (+)-B, typically 3:2 selectivity in favor of (–)- aculeatin A was observed with the linear 3,5-*syn*-diol-ketone **S12.B** as precursor, whereas with the cyclic tetrahydropyran methoxy ketal **S13.A**, a ratio of about 1:1 was obtained. Similarly, the product distribution of (+)- 6-*epi*-aculeatin D and (+)-aculeatin D starting from the tetrahydropyran hemiketal **S12.D** as precursor led to a preference in the formation of (+)-6-*epi*-aculeatin D (ratio of 6-*epi*-D/D 3:2). In contrast, the use of the tetrahydropyran-methoxy ketal **S13.B** gave a ratio of 1:1. Addition of the Lewis acid $ZnCl_2$ as the chelating agent had no influence over the diastereoselectivity of the resulting bis-spiroketal structure.



Scheme 14. *Total synthesis of aculeatin A, B, D and 6-epi-aculeatin D*

A Chiron Approach to the Total Synthesis of (+)-Aculeatin D (Y. Wu *et al.* 2008)

Yikang Wu *et al.* documented the total synthesis of aculeatin D (**4**) from D-xylose. They prepared **S15.A** from D-xylose through literature procedure in a 6 steps. The controlled DIBAL-H reduction of the lactone **S15.A** followed by 12C-wittig salt ($Br^{+}Ph_3P^{-}(CH_2)_{11}CH_3$) resulted in the olefin which on palladium catalyzed hydrogenation gave the **S15.B**. The MOM group of **S15.B** was deprotected followed by resulting triol of **S15.C** was selectively tosylated and treated with base to furnish the epoxide **S15.D** which was silylated to procure the **S15.E**. The epoxide **S15.E** was opened by dithiane and subjected for silyl deprotection to procure the **S15.G**. Exclusive formation of **7** in the PIFA-mediated oxidative spirocyclization was reported by the author for the first time which indicated that it is thermodynamically more favored. Finally, a citrate-phosphate buffer system was introduced in the spirocyclization, which effectively raised the content of the desired yet thermodynamically less favored **4** in the product mixture from 0 to 50%.

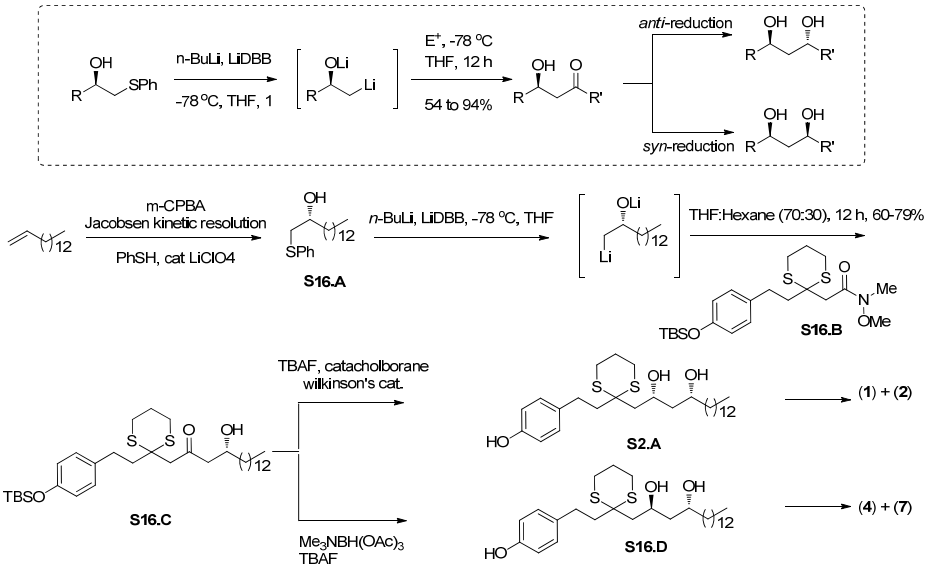


Scheme 15. *Total Synthesis of Aculeatins D and 6-epi-D by Wu and Co-workers*

Syntheses of Aculeatins A, B, and D (Scot D Rychnovsky *et al*. 2009)

Rychnovsky *et al*. developed a new method to synthesize the *β*-hydroxy ketone by using a non-aldol route. The *β*-phenylthio alcohols were prepared from optically pure oxiranes. Deprotonation and reductive lithiation generated the key intermediate, a *β*-oxyanionic alkyllithium reagent, addition of which to a Weinreb amide produced the *β*-hydroxy ketone. Stereoselective reduction of the ketone led to either the *syn*- or *anti*-1,3-diol. By employing this simple, convergent strategy, they synthesized the aculeatins A, B, and D from a common intermediate. The journey of synthesis started with the epoxidation of 1-pentadodecene followed by the Jacobsen kinetic resolution to get the chiral epoxide which was treated with thiophenol to obtain **S16.A**. The lithiation of **S16.A** followed by the addition of Weinreb amide **S16.B** delivered the aldol adduct **S16.C**. The ketone **S16.C** was the common intermediate for all three aculeatins. Anti reduction using Evan's method and deprotection led to *anti*-1,3-diol **S16.D** as a 10:1 dr in very good yield. The final oxidative cyclization of **S16.D** was conducted under citrate-buffered conditions to generate aculeatin D in 30% yield, accompanied by the separable C6 epimer in 35% yield. Without the added buffer, only the C-6 epimer was produced. Selective *syn*-

reduction of **S16.C** followed by a similar sequence of reactions, aculeatin A (38%) and aculeatin B (20%) have been synthesized by Rychnovsky.



Scheme 16. *The stereodivergent approach for syn- and anti-1,3-diols and* the total *synthesis of Aculeatins A, B, D and 6-epi-D*

Thus the examination of the available synthesis of aculeatins reveals that in majority of the cases they are linear in nature and the options for the synthesis of analogues are limited. Considering the promising biological activities reported for the aculeatins, we were interested to develop a modular strategy to provide the flexibility in changing the either end of the aculeatins and also the stereochemical diversity at the central spirobicyclic system.The details of our efforts in this direction will be discussed in the next part of this Chapter.

Present Work

Present Work:

Access to a collection of distinctive small molecules is an important aspect in the realm of chemical genetics and for identifying new therapeutic candidates.[16] Several philosophies addressing the target molecules ensemble either in a forward or the backward sense have been put forward, with the ultimate aim of providing flexible and diverse routes with the potential of addressing both the number and function with ease.[17–19] Concepts founded upon designing of and around the synthesis of natural products and natural products like small molecules have provided a direct entry of "total synthesis programs" into medicinal chemistry research. Development of synthetic methods that are efficient and the design of strategies that are modular with a flexibility window was a prerequisite for the synthesis of natural product derived and inspired compound collections.[20]

Bio-activity guided isolation from herbaceous plants which have their origin in folk medicine is one of the reliable approaches in identifying new drugs of natural origin. In 2000, Heilmann *et. al* reported the isolation of three biologically active metabolites: aculeatins A–C from the petroleum ether extract of the rhizomes of *Amomum aculeatum* ROXB, a plant used in the folk medicine of Papua New Guinea against fever and malaria.[10a] The aculeatins A–C were identified as potent inhibitors of the human tumor KB cell line and also displayed promising activity against the Plasmodium falciparum strains K1 and NF54.[21] With the help of extensive 2D-NMR experiments, the structures of aculeatins A–C were characterized by the presence of a fascinating 1,7-dioxadispiro[5.1.5.2]-pentadecane spirocyclic architecture. Soon afterwards, the same group added aculeatin D (**4**) to this family and reported remarkably high cytotoxicity along with anti-bacterial and anti-protozoal activities.

In 2007, Kinghorn *et.al* reported the isolation of related metabolites aculeatols A–D; the *C*(9) hydroxylated aculeatins A or B having either the same or two carbon truncated side chains.[11a] Subsequently, the isolation of truncated aculeatins A and D, named respectively as aculeatins F (**6**) and E (**5**), were reported by the same group.[11b] The structural similarity present in aculeatins A, B and D–F and their promising biological activity provides an opportunity to explore a modular assembly of

aculeatins and related derivatives. A modular total synthesis of aculeatins would lead to the achievement of the library of aculeatins like compounds in addition to a

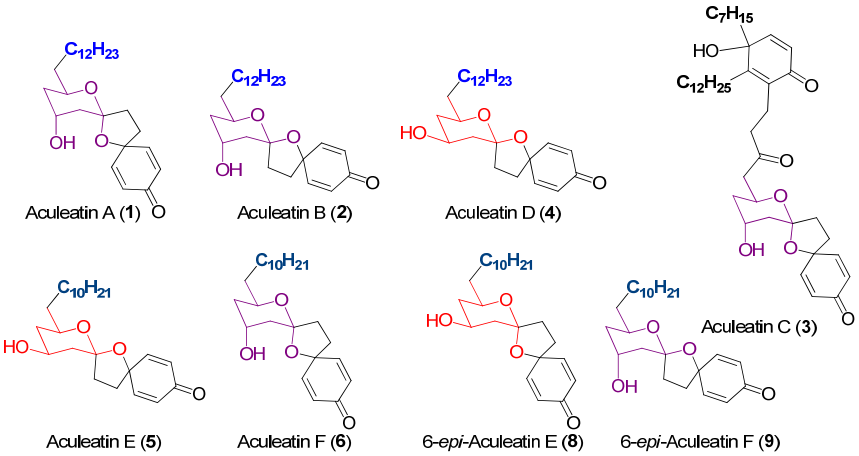


Figure 6. *Natural aculeatins A–F (**1**–**6**) and the unnatural 6-epi-aculeatins E (**8**) and F (**9**)*

cyclohexadienone unit and/or the alterations on the aliphatic side chain should give access to various synthetic analogues for structure-activity studies.

Our retrosynthetic disconnections are outlined in Figure **7**. The construction of the central tricyclic core was the final event which was planned through the global deprotection of a differentially protected keto 3,5-diol unit and subsequent phenol oxidative spiroketalization. To allow for maximum flexibility, the key disconnection of the aculeatins carbon-frame was made at two places resulting in two simple appending units and an epimeric pair of functionalized building blocks (Figure 7).

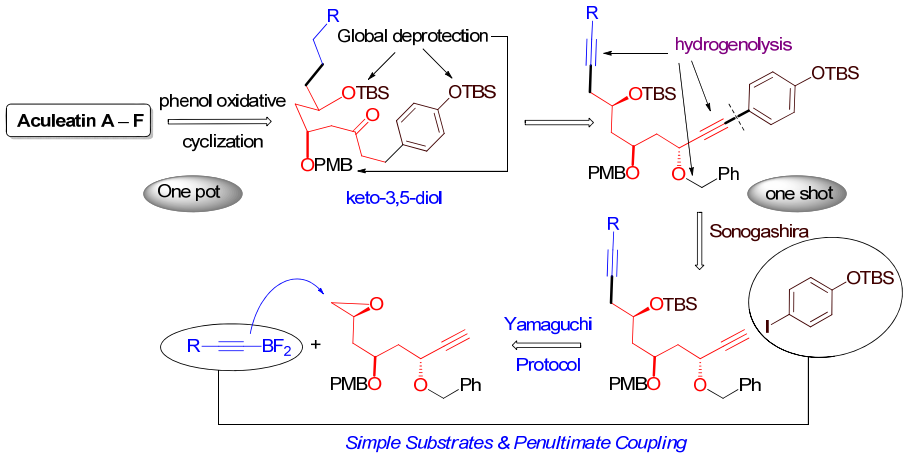


Figure 7. *Key retrosynthetic disconnections and penultimate flexibility*

Considering the fact that several of the analogues of these two appending units are commercially available or that one can access their functionalized analogues very easily, the additions were planned at an advanced stage. As given in Figure **8**, the diastereomeric alkyne epoxides **10** and **11**[14b] were identified as the central chirons, respectively for the aculeatins A,/B,/F (**1,/2,/6**) and for the aculeatins E (**5**). The synthesis of oxiranes **10** and **11** was planned from the alkynol **15** which in turn can be accessed from the lactone **16** by controlled lactone reduction to lactol and subsequent Ohira-Bestmann alkyne synthesis. The advantages with this lactone **16** is that one can also access the unnatural enantiomers of the aculeatins by simple Wittig homologation of the intermediate lactols with the requisite long chain alkyl phosphonium salts and the opening of the epoxide with a suitable substituted benzyl Grignard. The synthesis of lactone **16** has been earlier reported from our laboratory from commercially available D-glucono-heptono-γ-lactone.[22]

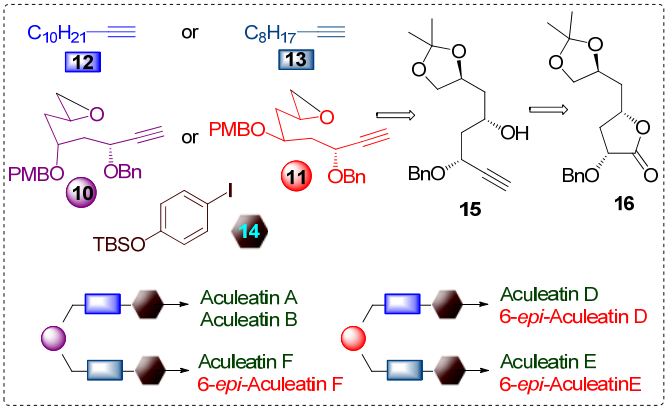
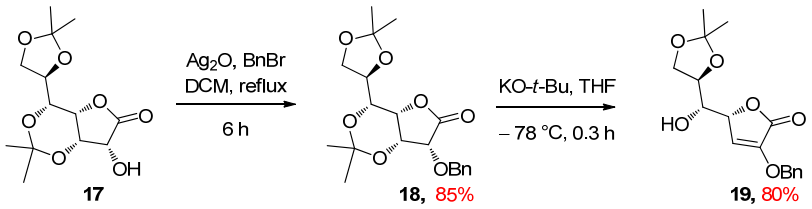


Figure 8. *Key building blocks for the synthesis of aculeatins A - F*

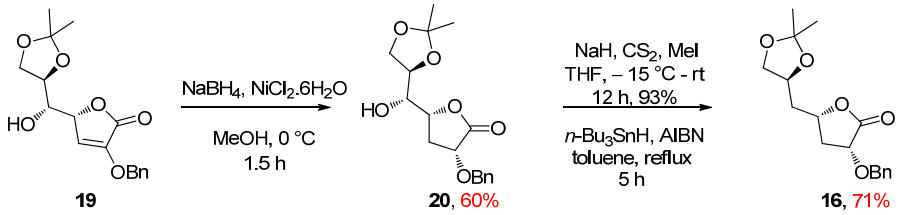
The synthesis started with the preparation of the γ-lactone **16** by using the procedure developed in our lab. The commercially available α-D-glucoheptonic-γ-lactone was transformed to the diacetonide **17** following the known procedures. Protection of the hydroxyl group at C-2 with silver oxide and benzyl bromide gave the benzyl ether **18**. The structure of benzyl ether **18** was well supported by ^{1}H, ^{13}C NMR spectrum and elemental analysis.

The chemoselective stereocontrolled conjugate reduction of the lactone **19** with the -OBn intact was achieved with $NiCl_2$−$NaBH_4$ in methanol at 0 °C to furnish the hydroxy lactone **20**. The stereochemistry of C-2 was as expected the spectral and analytical data of **20** were in agreement with the assigned structure. Signals corresponding to *endo* methylene protons were observed separately at 2.51, 2.30 ppm



Scheme 17. *Synthesis of the α,β-unsaturated Lactone **19***

as a doublet of doublet of doublet and a doublet of triplet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum C-3 carbon resonated at δ 31.1 as a triplet. The deoxygenation at C-5 of hydroxylactone **20** was achieved by employing the Barton- McCombie protocol as shown in Scheme 18. The treatment of compound **20** with NaH, CS_2, followed by MeI in THF furnished xanthate ester in nearly quantitative yield. The presence of xanthate ester was well supported by the spectral and analytical data. In the ^{1}H NMR spectrum of xanthate, the H–C(5) resonated relatively down field at 5.99

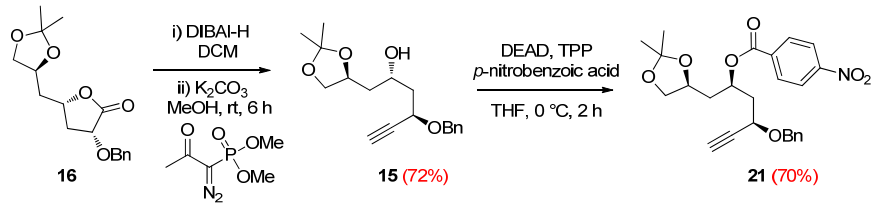


Scheme 18. *Synthesis of the Lactone **16***

ppm (J = 7.9, 1.7 Hz) as a doublet of doublet and a singlet for three protons at 2.54 ppm due to the S–CH_3. In the ^{13}C NMR spectrum, the thio carbonyl was located as a singlet at δ 216.8 and a quartet at δ 19.3 for S–CH_3 indicating the presence of xanthate ester. Treatment of xanthate with *n*-Bu_3SnH and catalytic AIBN in refluxing toluene afforded the key intermediate: the fully functionalized *anti*, *anti*-1,3,5-triol lactone **16**. The signals corresponding to methylene protons appeared at 2.61 ppm as a ddd for one proton and at 2.03−1.81 ppm multiplet for three protons in the ^{1}H NMR spectrum.

In the ^{13}C NMR spectrum, the signals at δ 36.0, 40.2 resonated as triplets indicating the presence of two methylene units.

The controlled DIBAL-H reduction of the γ-lactone **16** in CH_2Cl_2 at –78 °C followed by alkynylation of the intermediate lactol using the Ohira-Bestmann reagent resulted in the alkynol **15** in 72% yield.[14b, 23] The structure of the alkyne **15** was well supported by its ^1H, ^{13}C NMR spectra and elemental analysis. In the ^1H NMR spectrum of **15**, the isopropylidene groups resonated at δ 1.34, 1.39 as singlets, the alkyne C–H was located at 2.53 ppm as a doublet (J = 2.1 Hz) and aromatic protons were observed at 7.28–7.36 ppm as a multiplet. In the ^{13}C NMR spectrum, alkyne carbons resonated at δ 74.7, 82.0 as a doublet and singlet respectively. In the IR spectrum of **15**, the O–H stretching was observed at 3486 cm^{-1} and C≡C stretching was observed at 2126 cm^{-1}. To access the oxirane **10** with the central *syn*, *syn* 1,3-polyol configuration, the configuration at the C(4) center had to be inverted. The Mitsunobu inverstion of alkynol **15** by using DEAD, TPP could be conducted in good yields by employing the *p*-nitrobenzoic acid as the nucleophile to afford the corresponding nitrobenzoate **21**.[24] The presence of benzoate ester was evidenced by the appearance of additional signals in the aromatic region. The corresponding ester attached proton resonated at 5.57−5.51 ppm as a multiplet in the ^1H NMR spectrum. In the ^{13}C NMR spectrum, the carbonyl ester resonated at δ 164.0 as a singlet. The characteristic of benzoate **21**, C=O stretching was observed at 1724 cm^{-1} in the IR

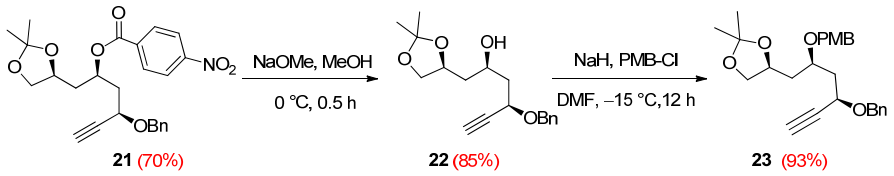


16 **15** (72%) **21** (70%)

Scheme 19. *Synthesis of the fully protected syn-syn-1,3-poly derivative **21***

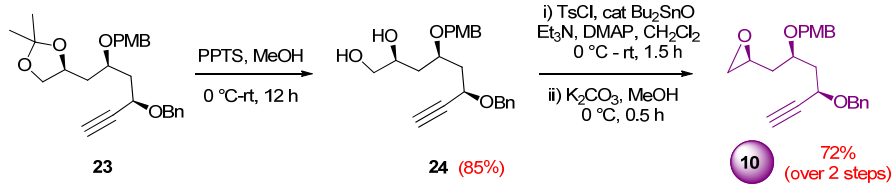
spectrum. In the ESI-MS of benzoate **62**, the characteristic peaks at 476.1 (100%, $[M+Na]^+$), 492.1(28%, $[M+K]^+$), 454.2 (14%, $[M+1]^+$) confirmed the assigned constitution.

Saponification of nitrobenzoate ester **21** with NaOMe in MeOH secured the required *syn,syn*-alkynol **22** having physical data different from that of the starting alkynol **15**. The isopropylidene methyl groups were located at δ 1.41, 1.36 as singlets and the alkyne C–H was located at 2.53 ppm as a doublet (J = 2.0 Hz) in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, alkyne carbons resonated at δ 75.0, 82.1 ppm as



Scheme 20. *Synthesis of* ***23***

a doublet and singlet respectively. In the IR spectrum, the O–H stretching was observed at 3486 cm^{-1}. In the mass spectrum, the peaks corresponding to m/z 327.1 (100%, $[M+Na]^+$), 343.1(19%, $[M+K]^+$), 305.2 (4%, $[M+1]^+$), 277.1 (15%, $[M+1–H_2O]^+$) were found. The free hydroxyl group of alkynol **22** was protected as its PMB ether by employing NaH and PMB-Cl in DMF at –15 °C to afford the differentially protected 1,3-polyol **23**. Subsequently, the isopropylidene group of the resulting compound **23** was deprotected by employing PPTS in methanol at 0 °C–rt to procure the terminal diol **24**. The structure of **24** was confirmed by spectral and analytical data. In the IR spectrum of **24**, O–H stretching was observed at 3423 cm^{-1} and C≡C stretching was observed at 2112 cm^{-1}. In the ^{1}H NMR spectrum, the methyl peaks of



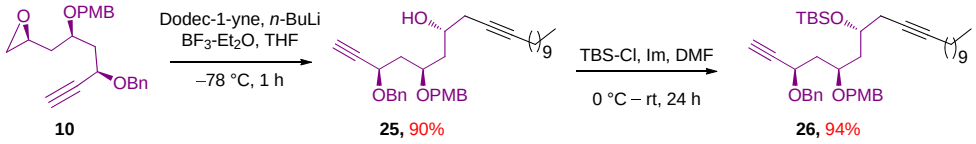
Scheme 21. *Synthesis of the oxirane* ***10***

isopropylidene group were seen to disappear and other peaks matched with the assigned structure of diol **24**. The primary hydroxyl group of diol **24** was selectively tosylated by using Martinelli's (*n*-Bu_2SnO/*p*-TsCl/Et_3N/CH_2Cl_2) protocol and the resulting tosylate was used without any purification for the oxirane formation using K_2CO_3 in methanol to furnish the epoxide **10**. The assigned structure for **10** was well

supported by spectral and analytical data. In the ^{1}H NMR spectrum of **10**, all three oxirane protons separately resonated relatively upfield at 3.03–2.99 (m), 2.72 (br t, J = 4.7 Hz) and 2.42 (dd, J = 4.9, 2.5 Hz) ppm and the alkyne C–H resonated at 2.50 (d, J = 1.8 Hz) ppm. In the ^{13}C NMR spectrum of **10**, the oxirane carbons were observed at δ 46.8 as a triplet and δ 49.2 as a doublet. The presence of peaks at m/z 405.3 (28%, $[M + K]^+$), 389.3 (100%, $[M + Na]^+$) in the ESI-MS spectrum supported the structure of **10**.

Synthesis of aculeatins A and B

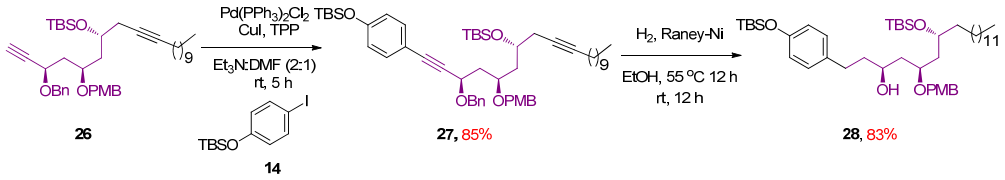
We next proceeded for the synthesis of aculeatins A, B, and F by selecting the *syn*,*syn*-oxirane **10** as the common starting point. The regioselective opening of epoxide **10** with dodec-1-yne (**12**) in the presence of *n*-BuLi, $BF_3{\cdot}Et_2O$ in THF at –78 °C gave the diyne **25** in near quantitative yields.[25] In the ^{1}H NMR spectrum of **25,** the propargylic CH_2 protons were located at δ 2.29–2.26, 2.14–2.09 as two multiplets and the terminal methyl were observed at 0.88 (t, J = 7.0 Hz) ppm. In the ^{13}C NMR spectrum of **25**, the alkyne carbons appeared at δ 75.5 ppm (doublet), δ 76.1, 82.4, 82.8 ppm (singlets), propargylic carbons appeared at δ 40.1, 41.2 ppm as triplets and



Scheme 22. *Synthesis of* ***26***

the terminal methyl resonated at δ 14.1 as a quartet. The structure of **25** was further supported by ESI-MS where the peaks corresponding to m/z 571.6 (26%, $[M + K]^+$), 555.6 (100%, $[M+Na]^+$), 533.6 (7%, $[M + 1]^+$) appeared. The free hydroxyl group present in **25** was protected as its TBS ether with TBS-Cl, imidazole in DMF to afford the TBS-ether derivative **26** in excellent yields.

Having the complete aliphatic skeleton in hand, our next concern was the extension of the terminal alkyne end in **26** through the Sonogashira coupling with a *p*-iodophenol derivative **14**. Keeping our experience with the synthesis of aculeatin D in mind, we have employed the TBS protected *p*-iodophenol **14**, as it gave better yields in coupling reactions and also since phenol protection is essential for the selective



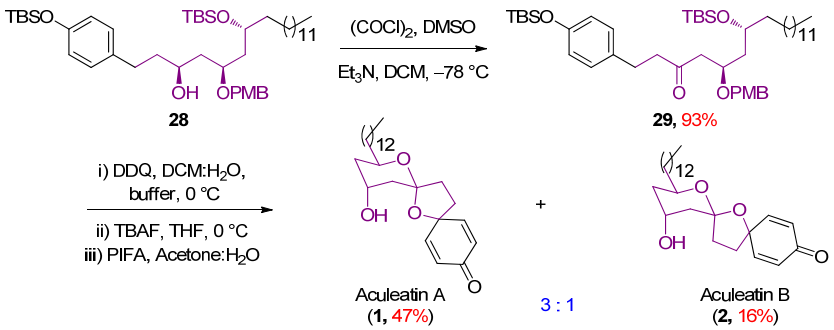
Scheme 23. *Sonogashira coupling and hydrogenolysis*

propargylic debenzylation during the hydrogenolysis of the alkyne units. Thus the Sonogashira coupling of **26** with **14** was best effected by a thorough degassing of the reaction mixture prior to the addition of CuI and gave the coupled product **27** (85%).[26] The formation of coupled moiety **27** was ascertained from its ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of **27**, the aromatic protons appeared at δ 7.30 and 7.22 as a doublet (J = 8.5 Hz). In the ^{13}C NMR spectrum of **27** alkyne carbons appeared at δ 75.5, δ 76.1, 82.4, 82.8 ppm as singlets, the phenolic carbon resonated at δ 115.6, 155.9 ppm as singlets and at 120.1, 133.2 ppm as doublets. In the ESI-MS of **27**, the characteristic peak at *m/z* 876.3 (100%, $[M+Na]^{+}$) supported the assigned constitution.

After this extension at both the ends, the remaining exercise was the synthesis of the advanced keto 3,5-diol **29** and its one pot sequential TBS and PMB ethers deprotection followed by key phenol oxidative spiroketalization, to complete the synthesis of aculeatins A and its spiroepimer aculeatin B. To this end, the hydrogenolysis of both the alkyne groups and selective debenzylation of compound **27** was carried out by using Raney Ni/H_2 (20 psi) at 55 °C in good yields. The assigned structure for **28** was well supported by spectral and analytical data. In the IR spectrum of **28**, O–H stretching was observed at 3480 cm^{-1}. In the ^{1}H and ^{13}C NMR spectrum of **28**, the benzyl protons, benzyl carbons and propagylic carbon (δ 75.5, δ 76.1, 82.4, 82.8 ppm) were seen to disappear. Also, the mass peak at m/z 793.98 (100%, $[M+Na]^{+}$) agreed with the structure of **28**. The free C(6)–OH of the resulting product **28** was oxidized under Swern condition (oxalyl chloride, DMSO and Et_3N in DCM at –78 °C) to afford the protected keto 3,5-diol **29**. The structure of **29** was ascertained by spectral and analytical data. In the ^{13}C NMR spectrum of **29**, the carbonyl carbon resonated at 208.9 ppm as a singlet. In the IR spectrum, the C=O

stretching was observed at 1718 cm^{-1}. Further supplementary proof such as CHN and the mass peak noticed at *m/z* 792.3 (100, $[M+Na]^+$) corroborate the assigned structure.

After having the well functionalized **29** in hand, our next concern was its global deprotection and subsequent oxidative phenol cyclization to complete the total



Scheme 24. *Synthesis of the Aculeatins A and B*

synthesis of aculeatins A and B. Our optimized conditions involving a sequential deprotection of PMB ether by employing DDQ (CH_2Cl_2, pH 7.0 phosphate buffer, 0 °C) followed by TBS ether deprotection using TBAF (THF at 0 °C) produced the completely deprotected keto 3,5-diol which, upon the oxidative spiroketalization using PIFA (10:1, v/v acetone:water, rt, under dark) afforded the corresponding epimeric aculeatins A/B mixture. Thus, following this protocol, aculeatins A (**1**) and B (**2**) (3:1) were prepared in 63% overall yield from the keto 3,5-diol **29**. Our scale-up syntheses involve proceeding with the alcohol *via* oxidation, two sequential deprotections and oxidative cyclization without the purification of any of the intermediates and isolation of the corresponding natural products without any compromise on the final yields. The spectral and the analytical data of **1** and **2** were in good agreement with data reported for natural aculeatins A and B (Tables 1 & 2).

Aculeatin A: In the ^1H NMR spectrum of **1**, conjugated olefinic protons resonated at δ 6.85 (dd, *J* = 10.0, 3.0 Hz, 1H) and 6.76 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.15 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.12 (dd, *J* = 10.0, 2.0 Hz, 1H). In the ^{13}C NMR spectrum, conjugated carbonyl carbon was observed at δ 185.3 as a singlet. In the IR spectrum, O–H stretching was observed at 3495 cm^{-1} and C=O stretching was observed at 1674 cm^{-1}. The optical rotation observed for synthetic aculeatin A is –4.7 (*c* = 2.0, $CHCl_3$),

comparable with the litarature value for natural aculeatin A. lit.[12] $[\alpha]_D^{23}$ = –5.3 (*c* = 0.9, $CHCl_3$).

Table 1. *Comparative ^{1}H NMR data of natural and synthetic Aculeatin A*

ISOLATION 500 MHz ***Aculeatin A***	Marco 500 MHz ***Aculeatin A***	Wong 400 MHz ***Aculeatin A***	Ramana 400 MHz ***Aculeatin A***
4.10 (m)	4.15-4.10 (m)	4.16-4.07 (m)	4.16-4.07 (m)
1.79 (ddd, *J* =13.7, 5.1, 2.1), 1.42 (m)	1.79 (br dd, *J* = 13.7, 2.0 Hz), 1.60-1.40 (m)	1.83-1.77 (m), 1.39-1.55 (m)	1.79 (br ddd, *J* = 13.7, 5.0, 2.1 Hz), 1.50-1.39 (m)
4.12 (m)	4.15-4.10 (m)	4.16-4.07 (m)	4.16-4.07 (m)
2.00 (m), 1.93 (m)	2.05-2.00 (m)	1.98-2.05 (m), 1.90-1.97 (m)	2.05-1.98 (m), 1.93 (br dt, *J* =14.0, 2.1 Hz)
6.79 (dd, *J* = 10.0, 2.9)	6.76 (dd, *J* = 10.0, 3.0 Hz)	6.76 (dd, *J* = 10.0, 3.0 Hz)	6.76 (dd, *J* = 10.0, 3.0 Hz)
6.11 (dd, *J* = 10.0, 2.0)	6.10 (dd, *J* = 10.0, 1.7 Hz)	6.12 (dd, *J* = 10.0, 2.0 Hz)	6.12 (dd, *J* = 10.0, 2.0 Hz)
6.14 (dd, *J* = 10.0, 2.0)	6.14 (dd, *J* = 10.0, 1.7 Hz)	6.15 (dd, *J* = 10.0, 2.0 Hz)	6.15 (dd, *J* = 10.0, 2,0 Hz)
6.85 (dd, *J* = 10.0, 2.9)	6.85 (dd, *J* = 10.0, 3.0 Hz)	6.85 (dd, *J* = 10.0, 3.0 Hz)	6.85 (dd, *J* = 10.0, 3.0 Hz)
2.37 (m), 2.00 (m)	2.38 (m), 2.05-2.00 (m)	2.43-2.33 (m), 2.05-1.98 (m)	2.43-2.33 (m), 2.05-1.98 (m)
2.37 (m), 2.22 (m)	2.24 (m), 2.05-2.00 (m)	2.24 (dd, *J* = 10.8, 7.8 Hz), 1.98-2.05 (m)	2.24 (dd, *J* = 10.8, 7.7 Hz) 2.05-1.98 (m)

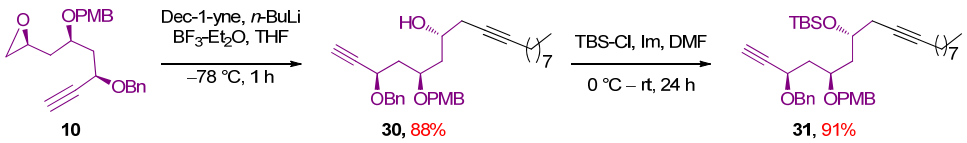
Aculeatin B: In the ^{1}H NMR spectrum of **2**, conjugated olefinic protons resonated at δ 6.99 (dd, *J* = 10.0, 3.0 Hz, 1H) and 6.78 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.14 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.11 (dd, *J* = 10.0, 2.0 Hz, 1H). In the ^{13}C NMR spectrum, the conjugated carbonyl carbon was observed at δ 185.7 as a singlet. In the IR spectrum, O–H stretching was observed at 3521 cm^{-1} and C=O stretching was observed at 1664 cm^{-1}. The optical rotation observed for synthetic aculeatin B is $[\alpha]_D^{26}$ = +46.8 (*c* 1.0, $CHCl_3$) and the reported value for aculeatin B is $[\alpha]_D^{23}$ = +50.0 (*c* 0.2, $CHCl_3$).[12]

Table 2. *Comparative ^{1}H NMR data of natural and synthetic Aculeatins B*

ISOLATION 500 MHz ***Aculeatin B***	Marco 500 MHz ***Aculeatin B***	Wong 400 MHz ***Aculeatin B***	Ramana 400 MHz ***Aculeatin B***
3.86 (m)	3.86 (m)	3.91-3.82 (m)	3.91-3.82 (m)
1.62 (m), 1.52 (m)	1.60–1.40 (m)	1.65-1.53 (m)	1.65-1.53 (m)
4.35 (m)	4.36 (quintuplet)	4.39-4.34 (m)	4.39-4.35 (m)
2.08 (m), 1.88 (m)	2.10-2.00 (m), 1.95–1.85 (m)	2.11-2.02 (m), 1.98-1.86 (m)	2.11-2.02 (m), 1.98-1.86 (m)
6.78 (dd, *J* = 10.0, 2.9)	6.77 (dd, *J* = 10, 2.9 Hz,)	6.78 (dd, *J* = 10.0, 3.2 Hz)	6.78 (dd, *J* = 10.0, 3.0 Hz
6.11 (dd, *J* = 10.0, 2.0)	6.10 (dd, *J* = 10, 2.0 1H)	6.11 (dd, *J* = 10.0, 2.0 Hz)	6.11 (dd, *J* = 10.0, 2.0 Hz)
6.13 (dd, *J* = 10.0, 2.0)	6.13 (dd, *J* = 10, 2.0 Hz)	6.14 (dd, *J* = 10.0, 2.0 Hz)	6.14 (dd, *J* = 10.0, 2.0 Hz)
6.99 (dd, *J* = 10.0, 2.9)	6.99 (dd, *J* = 10, 2.9 Hz,)	6.99 (dd, *J* = 10.0, 3.2 Hz)	6.99 (dd, *J* = 10.0, 3.0 Hz)
2.30 (m), 2.04 (m)	2.30 (dd, *J* = 12.3, 7.2 Hz) 2.10-2.00 (m)	2.35-2.26 (m), 2.11-2.02 (m)	2.29 (dt, *J* = 12.3, 7.3 Hz), 2.11-2.02 (m),
2.69 (ddd, 12.1, 6.2, 1.2), 1.92 (m)	2.68 (br dd, *J* = 12.8, 7.2 Hz), 1.95–1.85 (m),	2.69 (ddd, *J* = 13.2, 7.6, 1.6 Hz), 1.98-1.86 (m)	2.69 (ddd, *J* = 13.1, 7.4, 1.6 Hz), 1.98-1.86 (m)

Synthesis of aculeatins F and 6-*epi*-F:

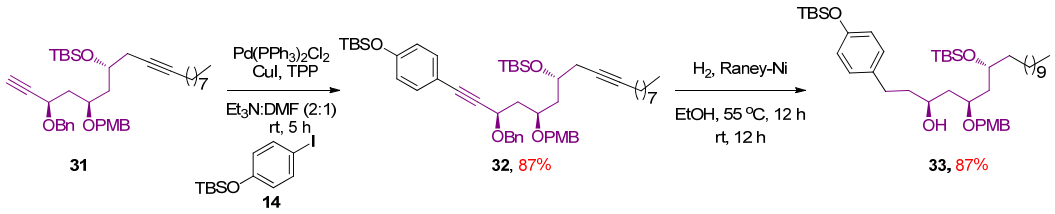
After successfully completing the total synthesis of aculeatin A and B, we next focused on the synthesis of the truncated analogue aculeatin F (**6**) from the oxirane **10** which has the central *syn*,*syn* 1,3-polyol configuration. The opening of the oxirane **10** with dec-1-yne **13** gave **30**. Compound **30** has shown data similar to that of **25**. In the mass spectrum, the peaks corresponding to m/z 527.6 (100%, $[M+Na]^+$), 543.6 (37%, $[M+K]^+$), 505.7(8%, $[M+1]^+$) were observed. The resulting alkynes **30** were subsequently converted to the corresponding TBS ethers **31** by treating with TBSCl/imidazole in DMF.



Scheme 25. *Opening of epoxide under Yamaguchi conditions*

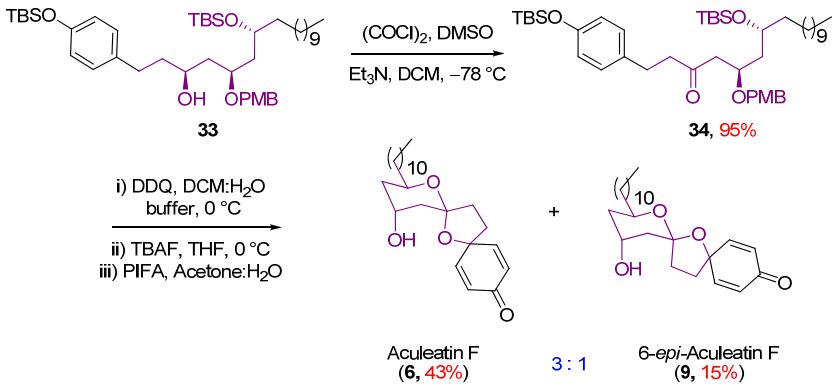
The Sonogashira coupling of **31** with aryliodide **14** gave the coupled product **32** (87%). The structure of **32** was well supported by ^{1}H, ^{13}C NMR and mass spectrum analysis. For example, in the ^{1}H NMR spectrum, peaks corresponding to aromatic protons resonated at δ 7.38–7.30 (m, 2H), 6.78 (d, J = 7.2 Hz, 2H) and the absence of the alkyne proton which should have been located at 2.46 ppm. In the ^{13}C NMR spectrum, the alkyne carbons resonated at δ73.2 (s), 82.3 (s), 86.6 (s), 86.7 (s) and the aromatic carbon appeared at δ 115.6 (s) 120.1 (d, 2C), 133.2 (d, 2C), 155.9 (s). Presence of a strong peak of highest m/z 848.3 (100%, $[M+Na]^{+}$) supported the struture of **32**. To this end, the hydrogenolysis of both the alkyne groups and selective debenzylation of compounds **32** was carried out by using Raney Ni/H_2 (20 psi) at 55 °C in good yields.

The structure of **33** was confirmed by its ^{1}H, ^{13}C NMR, mass spectra and



Scheme 26. *Sonogashira coupling and hydrogenolysis*

elemental analysis. In the ^{1}H NMR, ^{13}C NMR spectrum of **33**, the benzyl group was absent. In the IR spectrum of **33**, O–H stretching was observed at 3480 $cm^{-1}$and the mass spectrum showed peaks at *m*/*z* 766.2 (100%, $[M+Na]^{+}$), 782.4 (35%, $[M+K]^{+}$),



Scheme 27. *Synthesis of the Aculeatin F (**6**) and 6-epi-F (**9**)*

744.4 (35%, [M+1] $^{+}$). The free C(6)–OH group of the resulting products **33** was oxidized under Swern condition to afford the protected keto 3,5-diols **34**. The structure of **34** was fully supported by spectral and analytical data. In the ^{13}C NMR spectrum of **34**, the keto carbonyl resonated at 208.9 ppm as a singlet. In the IR spectrum, C=O stretching was observed at 1713 cm^{-1}. In the mass spectrum, the peaks related to m/z *m*/*z* 764.4 (100%, $[M+Na]^+$), 780.6 (56%, $[M+K]^+$), 759.6 (20%, $[M+H_2O]^+$), 743.6 (15%, $[M+2]^+$), 741.6 (11%, $[M+1]^+$) were observed.

Finally, compound **34** was subjected to a sequential deprotection of PMB ether by the employment of DDQ (CH_2Cl_2, pH 7.0 phospate buffer, 0 °C) followed by TBS ether deprotection using TBAF (THF at 0 °C) followed by oxidative spiroketalization using PIFA (10:1, v/v acetone:water, rt, under dark) to afford the aculeatin F (**6**) and its spiroepimer 6-*epi*-F (**9**) (3:1) in (58%) overall yield. The spectral and the analytical data of **6** were in good agreement with data reported for natural aculeatin F. (Table 3).

Aculeatin F: In the ^{1}H NMR spectrum of **6**, conjugated olefinic protons resonated at δ 6.85 (dd, J = 10.0, 2.8 Hz, 1H); 6.76 (dd, J = 10.0, 2.8 Hz, 1H), 6.15 (dd, $J \approx$ 10.0, 1.8 Hz, 1H), 6.12 (dd, $J \approx$ 10.0, 1.8 Hz, 1H). In the ^{13}C NMR spectrum, conjugated keto carbonyl was observed at δ 185.3 as a singlet. In the IR spectrum O–H stretching was observed at 3494 cm^{-1} and C=O stretching was observed at 1677 cm^{-1}. The optical rotation observed for synthetic aculeatin F is $[\alpha]_D^{26}$ = –4.7 (*c* 2.0, $CHCl_3$) and the literature value for natural aculeatin F is lit.[11b] $[\alpha]_D^{23}$ = –5.3 (*c* 0.9, $CHCl_3$).

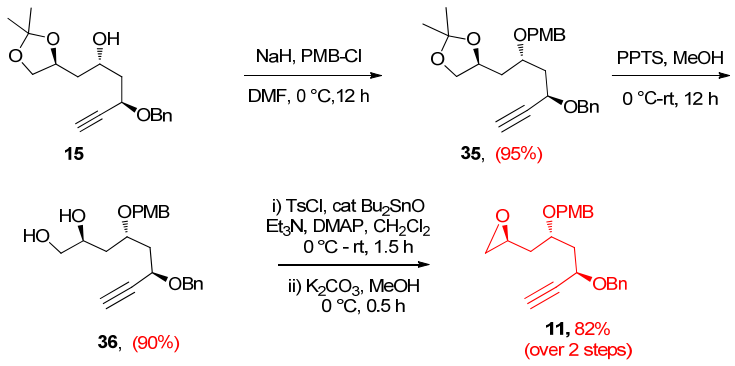
6-*epi*-Aculeatin F: In the ^{1}H NMR spectrum of **9**, conjugated olefinic protons resonated at δ 6.99 (dd, J = 10.0, 3.0 Hz, 1H) and 6.78 (dd, J = 10.0, 3.0 Hz, 1H), 6.14 (dd, J = 10.0, 2.0 Hz, 1H), 6.11 (dd, J = 10.0, 2.0 Hz, 1H). In the ^{13}C NMR spectrum, the conjugated carbonyl carbon was observed at δ 185.7 as a singlet. In the IR spectrum, O–H stretching was observed at 3520 cm^{-1} and C=O stretching was observed at 1664 cm^{-1}. The optical rotation observed for the 6-*epi*-aculeatin F is $[\alpha]_D^{26}$ = +46.8 (*c* 1.0, $CHCl_3$).

Table 3. *Comparative ^1H NMR data of natural and synthetic Aculeatins F and 6-epi-F*

ISOLATION ***Aculeatin F*** (400 MHz)	Ramana ***Aculeatin F*** (500 MHz)	Ramana ***6-epi-Aculeatin F*** (500 MHz)
4.13 (m)	4.17-4.06 (m)	3.91-3.83 (m)
1.80 (br d, J =13.7), 1.41 (m)	1.80 (br d, J = 13.2), 1.54-1.39 (m)	1.64-1.52 (m, 2H)
4.13 (m)	4.17-4.06 (m)	4.39-4.35 (m)
2.00 (m), 1.94 (m)	2.05-1.98 (m), 1.94 (br t, J = 14.0 Hz)	2.10-2.01 (m), 1.97-1.85 (m)
6.77 (dd, J = 10.0, 2.9)	6.76 (dd, J = 10.0, 2.8 Hz)	6.78 (dd, J = 10.0, 3.0 Hz)
6.11 (dd, J = 9.9, 1.8)	6.12 (dd, $J \approx$ 10.3, 1.8 Hz)	6.12 (dd, = 10.0, 2.0 Hz)
6.15 (dd, J = 10.0, 1.8)	6.15 (dd, $J \approx$ 10.3, 1.8 Hz)	6.14 (dd, J = 10.0, 2.0 Hz)
6.86 (dd, J = 10.0, 2.9)	6.85 (dd, J = 10.0, 2.8 Hz)	6.99 (dd, = 10.0, 3.0 Hz)
2.37 (m), 2.00 (m)	2.42-2.34 (m), 2.05-1.98 (m)	2.29 (dt, J = 12.3, 7.4 Hz), 2.10-2.01 (m)
2.24 (m), 2.00 (m)	2.24 (dd, J = 10.3, 8.1 Hz), 2.05-1.98 (m)	2.69 (br dd, J = 12.9, 7.2 Hz), 1.97-1.85 (m)

Synthesis of aculeatin E and 6-*epi*-E:

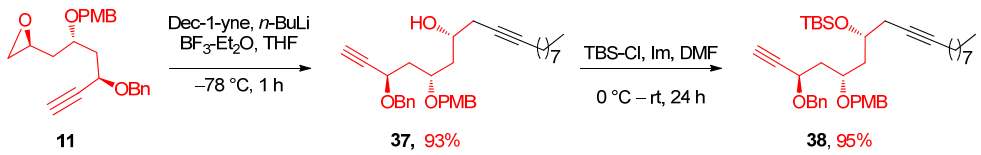
To prove the generality and modularity of our strategy, we next took up the synthesis of the truncated analogue aculeatin E. The synthesis of aculatin E was started with the use of alkyne **15** having *anti*, *anti*-1,3-polyol configuration. Treatment of **15** with PMB chloride in the presence of NaH in DMF at 0 °C–rt furnished the PMB-ether **35**. The 1,2-isopropylidene methyl group was hydrolyzed in the presence of PPTS in methanol in the range of 0 °C–rt to obtain the terminal diol **36**. The



Scheme 28. *Synthesis of the oxiranes **11***

assigned structure for **36** was confirmed by spectral and analytical data. In the IR spectrum of **36**, O–H stretching was observed at 3411 cm^{-1} and C≡C stretching was observed at 2110 cm^{-1}.

The primary hydroxyl group of **36** was selectively tosylated by treating with TsCl, catalytic Bu_2SnO and triethylamine in dichloromethane to obtain the primary tosylate, which was further used for the next reaction without any chromatographic purification. Oxirane formation was facile with K_2CO_3 in methanol to furnish the epoxide **11** (82% over two steps). The formation of epoxide **11** was ascertained from its ^1H, ^{13}C NMR spectrum and elemental analysis. In the ^1H NMR spectrum of **11**, all three oxirane protons separately resonated relatively upfield at 3.03 (ddt, J = 5.8, 3.9, 2.7 Hz), 2.78 (dd, J = 5.0, 4.0 Hz) and 2.49 (dd, J = 5.0, 2.7 Hz) ppm and alkyne C–H resonated at 2.47 (d, J = 2.1 Hz) ppm. In the ^{13}C NMR spectrum of **11**, the oxirane carbons were observed at δ 47.3 as a triplet and δ 49.2 as a doublet.

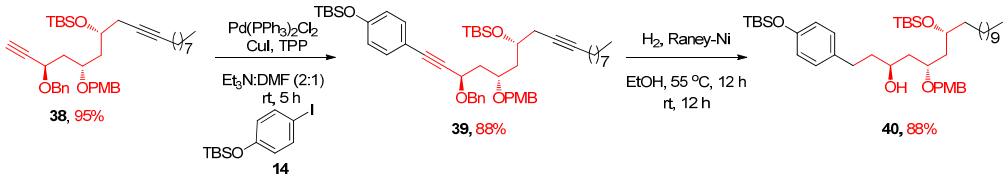


11 **37**, 93% **38**, 95%

Scheme 29. *Opening of epoxide **10** with dec-1-yne*

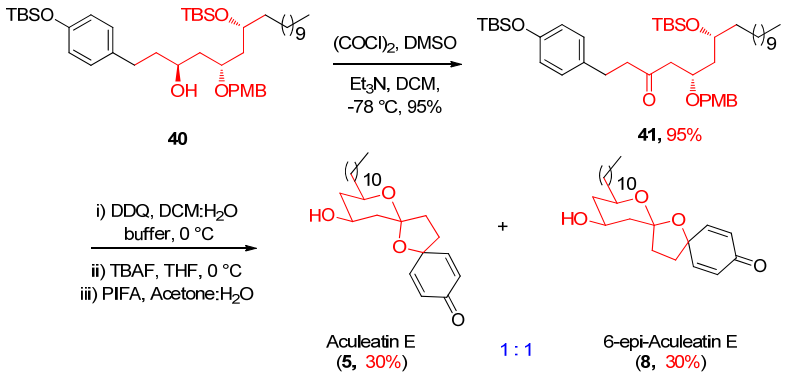
The opening of the oxirane **11** with dec-1-yne **13** under the Yamaguchi protcol gave **37** in good yield. In the ^1H NMR spectrum, propargylic CH_2 protons resonated at δ 2.34−2.30 (m, 2H), 2.17−2.07 (m, 2H) and the terminal methyl resonated at δ 0.88 (t, J = 6.9 Hz) of **37**. In the ^{13}C NMR spectrum of **37**, the alkyne carbons were located at δ 74.0 ppm (doublet), 76.0, 82.8, 83.0 (singlet), propargylic carbons appeared at δ 39.2, 40.1 as triplets and the terminal methyl resonated at δ 14.1 as a quartet. In the IR spectrum, O−H stretching was observed at 3469 cm^{-1}. In the mass spectrum, peaks corresponding to m/z 527.6 (100%, $[M+Na]^+$), 543.6 (36%, $[M+K]^+$), 505.7(7%, $[M+1]^+$). 407.5 (46%, $[M–97]^+$), 383.4 (74%, $[M–115]^+$) were noticed. The free hydroxyl group present in **37** was protected as TBS-ether. The diyne **38** was subjected to Sonogashira coupling with TBS ether of *p*-iodophenol **14**, in the presence of $Pd(PPh_3)_2Cl_2$, CuI in triethylamine/DMF at rt to obtain the required coupling product **39**. Coupling was evidenced from the appearing of additional signals in the aromatic

region in the ^{1}H and ^{13}C NMR spectrum. The structure of **39** was further supported by mass spectrum (ESI-MS: *m/z* 848.3 (100%, $[M+Na]^{+}$) and elemental analysis. The hydrogenolysis of both the alkyne groups and selective debenzylation of compounds **39** was carried out by using Raney Ni/H_2 (20 psi) at 55 °C to produce **40** in good yields.



Scheme 30. *Sonogashira coupling and hydrogenolysis*

Subsequently, the oxidation of **40** under Swern conditions in the presence of [$(COCl)_2$, DMSO, Et_3N in dichloromethane at –78 °C] afforded the advanced keto-3,5-diol **41**. The structure of **41** was fully supported by spectral and analytical data. In the ^{13}C NMR spectrum of **41**, the keto carbonyl resonated at 208.6 ppm as a singlet and in the IR spectrum, the C=O stretching was observed at 1715 cm^{-1}. Mass spectrum showed the signals of *m/z* 764.5 (100%, $[M + Na]^{+}$), 777.5 (56%, $[M+K]^{+}$), 742.5 (11%, $[M+1]^{+}$) which further supported the assigned structure.



Scheme 31 *Synthesis of the Aculeatin E (**5**) and 6-epi-E (**8**)*

The final stage of the synthesis are sequential deprotection of the TBS and PMB ethers of **41** and oxidative phenolcyclization of the intermediate ketodiols, providing the aculeatin E (**5**), along with its unnatural spiroepimer **8**. The natural product and its epimer were obtained in almost equal ratio, which is similar to the

observation with related aculeatin D synthesis. The comparison of the ^{1}H and ^{13}C NMR spectra of **5** with the natural aculeatin D and E (Table 4 & 5) established its structure and the observed similar specific rotation of the synthetic aculeatin E values confirmed its assigned absolute configuration ($[\alpha]_D^{25}$ = +47.7 (*c* = 1, $CHCl_3$); lit.[9b] $[\alpha]_D^{23}$ = +46.5 (*c* = 1, $CHCl_3$).

Aculeatin E: In the ^{1}H NMR spectrum of **5**, conjugated olefinic protons resonated at δ 6.99 (dd, *J* = 10.3, 3.0 Hz, 1H), 6.78 (dd, *J* = 10.3, 3.0 Hz, 1H), 6.14 (dd, *J* = 10.0, 1.7 Hz, 1H) and 6.12 (dd, *J* = 10.0, 1.7 Hz, 1H). In the ^{13}C NMR spectrum, conjugated keto carbonyl was observed at δ 185.5 as a singlet. In the IR spectrum, O–H stretching was observed at 3410 cm^{-1} and C=O stretching was observed at 1665 cm^{-1}. In the mass spectrum, the strong peak was observed of m/z at ESI-MS: *m*/*z* 413.5 (100%, $[M + Na]^+$), 429.5 (33%, $[M+K]^+$), 391.5 (26%, $[M+1]^+$), 373.5 (18%, $[M+1-H_2O]^+$). The optical rotation observed for synthetic aculeatin E is $[\alpha]_D^{25}$ = +47.7 (*c* = 1, $CHCl_3$), and the reported value for natural aculeatin E is $[\alpha]_{23}^{D}$ = +46.5 (*c* = 1, $CHCl_3$).[11b]

Table 4. *Comparative ^{1}H NMR data of natural and synthetic Aculeatin E*

ISOLATION (400 MHz) ***Aculeatin E***	Ramana (500 MHz) ***Aculeatin E***
3.36 (m)	3.40-3.34 (m)
1.96 (m), 1.23 (m)	1.96 (br ddd, *J* = 12.3, 4.4, 2.0 Hz), 1.33-1.23 (m)
3.85 (tt, *J* = 11.2, 4.4 Hz)	3.85 (tt, *J* = 11.2, 4.4 Hz)
2.12 (m), 1.78 (m)	2.13 (ddd, *J* = 12.3, 4.3, 1.8 Hz), 1.79 (t, 11.9 Hz)
6.79 (dd, *J* = 10.0, 2.9 Hz)	6.78 (dd, *J* = 10.3, 3.0 Hz)
6.13 (dd, *J* = 10.0, 1.8 Hz)	6.12 (dd, *J* = 10.0, 1.7 Hz)
6.14 (dd, *J* = 10.4, 1.8 Hz)	6.15 (dd, *J* = 10.0, 1.7 Hz)
6.99 (dd, *J* = 10.4, 2.9 Hz)	6.99 (dd, *J* = 10.3, 3.0 Hz)
2.28 (m), 2.06 (m)	2.27 (br ddd, *J* = 12.5, 11.2, 7.5 Hz), 2.07 (ddd, *J* = 12.5, 8.2, 1.9 Hz).
2.39 (m), 1.83 (m)	2.39 (ddd, *J* = 12.7, 7.5, 2.0 Hz), 1.84 (dt, *J* = 12.2, 8.5 Hz)

6-*epi*-Aculeatin E: In the ^{1}H NMR spectrum of **8**, conjugated olefinic protons resonated at δ 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.76 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.12 (dd, *J* = 10.1, 1.9 Hz, 1H) and 6.10 (dd, *J* = 10.1, 1.9 Hz, 1H). In the ^{13}C NMR

spectrum, conjugated keto carbonyl was observed at δ 185.4 as a singlet. In the IR spectrum, O–H stretching was observed at 3412 cm^{-1} and C=O stretching was observed at 1662 cm^{-1}. In the mass spectrum , the peak corresponding to m/z ESI-MS: *m*/*z* 413.5 (100%, $[M + Na]^+$), 429.5 (22%, $[M+K]^+$), 391.5 (24%, $[M+1]^+$), 373.5 (22%, $[M+1-H_2O]^+$) were observed. The optical rotation observed for synthetic 6-*epi*-aculeatin E is $[\alpha]_D^{25} = +14.6$ (*c* = 0.2, $CHCl_3$).

Table 5. *Comparative ^1H NMR data of unnatural 6-epi-Aculeatin D and E*

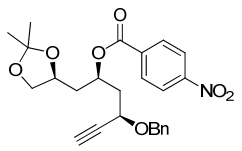
Marco (500 MHz C_6D_6) **6-*epi*-Aculeatin D**	Wong (400 MHz) **6-*epi*-Aculeatin D**	Ramana (500 MHz) **6-*epi*-Aculeatin D**	Ramana (500 MHz) **6-*epi*-Aculeatin E**
3.70 (m)	3.84-3.77 (m)	3.83-3.75 (m)	3.83-3.78 (m)
1.65 (m), 1.55 (m)	1.65 (dd, *J* = 11.6, 11.6 Hz) 1.52-1.42 (m)	1.62 (dd, *J* = 11.8, 11.8 Hz) 1.52-1.41 (m)	1.65 (t, *J* = 11.8 Hz), 1.57-1.51 (m)
3.90 (m)	4.05 (m)	4.15-4.02 (m)	4.10 (tt, *J* = 11.2, 4.8 Hz)
1.87 (m) 1.50-1.20 (m)	2.07-1.94 (m, 2H) 1.52-1.42 (m)	2.04-1.94 (m), 1.52-1.41 (m)	2.12-2.08 (m), 2.04-2.01 (m).
6.68 (dd, *J* = 10, 3.2 Hz)	6.76 (dd, *J* = 10.2, 3.0 Hz)	6.76 (dd, *J* = 10.4, 3.2 Hz)	6.76 (dd, *J* = 10.2, 3.2 Hz)
6.01 (dd, *J* = 10, 2.0 1H)	6.13 (dd, *J* = 10.2, 2.0 Hz)	6.11 (dd, *J* = 10.1, 1.9 Hz)	6.10 (dd, *J* = 10.1, 1.9 Hz)
6.15- 6.10 (m)	6.13 (dd, *J* = 10.2, 2.0 Hz)	6.11 (dd, *J* = 10.1, 1.9 Hz)	6.12 (dd, *J* = 10.1, 1.9 Hz)
6.15- 6.10 (m)	6.81 (dd, *J* = 10.2, 3.0 Hz)	6.81 (dd, *J* = 10.4, 3.2 Hz)	6.82 (dd, *J* = 10.2, 3.2 Hz)
1.87 (m), 1.50-1.20 (m)	2.25 (dd, *J* = 10.8, 8.0 Hz) 2.07-1.94 (m)	2.24 (dd, *J* = 10.3, 8.2 Hz), 2.08 (ddd, *J* = 12.4, 4.7, 1.6 Hz)	2.25 (dd, *J* ≈ 10.9, 7.8 Hz), 2.04-2.01 (m)
2.00 (m), 1.07 (q, *J* = 12 Hz)	2.44-2.33 (m), 1.19 (ddd, *J* = 11.6, 11.6, 11.6 Hz)	2.42-2.32 (m), 1.18 (ddd, *J* = 11.6, 11.6, 11.6 Hz)	2.43-2.35 (m), 1.18 (q, *J* = 11.8 Hz)

Conclusion: A modular approach for the total synthesis of aculeatins has been documented. Central to the success of our approach is a dual-end disconnection of the aculeatins core leading to three segments in which the two terminal segments are easily available and are amicable toward the alterations for the synthesis of aculeatin like small molecule libraries.

Experimental

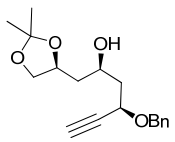
Experimental:

(2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-4-*O*-(4-nitrobenzoyl)-6-*O*-benzyl-oct-7-yne-1,2,4,6-tetraol (21):



To a solution of alcohol **15**[12b] (500 mg, 1.64 mmol) in dry THF (5 mL), TPP (517 mg, 1.97 mmol) and DEAD (343 mg, 1.97 mmol) were added at 0 °C and stirred for 15 min, followed by *p*-nitrobenzoic acid (330 mg, 1.97 mmol). After stirring for additional 2 h at 0 °C, the reaction mixture was quenched by adding sat. $NaHCO_3$, poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried over (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (13% ethyl acetate in petroleum ether) gave the **21** (520 mg, 70%) as colorless oil. *Rf* = 0.50 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ = +23.9 (c = 1, $CHCl_3$). IR ($CHCl_3$): ν 3291, 2931, 2852, 2110, 1724, 1528, 1455, 1350, 1274, 1102, 872, 839, 752, 699, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (dt, *J* = 8.8, 2.0 Hz, 2H), 8.09 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.30–7.26 (m, 5H), 5.57–5.51 (m, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.26 (ddd, *J* = 8.5, 6.5, 2.0 Hz, 1H), 4.19 (ddd, *J* = 12.8, 6.5, 5.8 Hz, 1H), 4.05 (dd, *J* = 8.1, 5.8 Hz, 1H), 3.53 (t, *J* = 7.7 Hz, 1H), 2.50 (d, *J* = 2.0 Hz, 1H), 2.36 (ddd, *J* = 14.4, 8.1, 7.0 Hz, 1H), 2.17 (ddd, *J* = 14.4, 6.3, 4.6 Hz, 1H), 2.06 (dt, *J* = 14.5, 7.3 Hz, 1H), 1.92 (dt, *J* = 14.5, 5.8 Hz, 1H), 1.34 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5 (q), 26.8 (q), 37.9 (t), 39.8 (t), 65.6 (d), 69.3 (t), 70.6 (t), 70.9 (d), 72.7 (d), 74.9 (d), 81.5 (s), 109.0 (s), 123.3 (d, 2C), 127.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 130.6 (d, 2C), 135.7 (s), 137.2 (s), 150.3 (s), 164.0 (s) ppm. ESI-MS: m/z 476.1 (100%, $[M+Na]^+$), 492.1(28%, $[M+K]^+$), 454.2 (14%, $[M+1]^+$). Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00, N; 3.09. Found: C, 65.81; H, 5.94, N; 3.2.

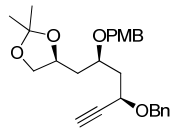
(2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-6-*O*-benzyl-oct-7-yne-1,2,4,6-tetraol (22):



A solution of benzoate **21** (300 mg, 0.66 mmol) and NaOMe (35 mg, 0.66 mmol) in MeOH (5 mL) was stirred at 0 °C for 0.5 h. Several drops of CH_3COOH were added to the reaction

mixture to adjust the pH to 7. The solution was diluted with water (20 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification of the crude by column chromatography (20% ethyl acetate in petroleum ether) yielded the alcohol **22** (171 mg, 85%) as colorless oil. *Rf* = 0.50 (Petether/EtOAc 1:1), $[\alpha]_D^{25}$ = –8.7 (*c* = 2, $CHCl_3$). IR ($CHCl_3$): ν 3486, 3308, 2923, 2852, 2110, 1730, 1463, 1378, 1215, 1157, 1071, 760, 698, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.36 (dt, *J* = 7.1, 1.9 Hz, 1H), 4.30–4.24 (m, 1H), 4.08 (dd, *J* = 8.1, 6.0 Hz, 2H), 3.54 (t, *J* = 7.7 Hz, 1H), 3.42 (s, 1H), 2.53 (d, *J* = 2.0 Hz, 1H), 2.05 (ddd, *J* = 13.8, 9.0, 7.3 Hz, 1H), 1.86 (ddd, *J* = 13.8, 6.5, 3.2 Hz, 1H), 1.77–1.65 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (q), 26.8 (q), 40.4 (t), 42.7 (t), 67.1 (d), 68.4 (d), 69.6 (t), 70.8 (t), 74.5 (d), 75.0 (d), 82.1 (s), 109.2 (s), 127.9 (d), 128.1 (d, 2C), 128.5 (d, 2C), 137.3 (s) ppm. ESI-MS: *m/z* 327.1 (100%, $[M+Na]^+$), 343.1(19%, $[M+K]^+$), 305.2 (4%, $[M+1]^+$), 277.1 (15%, $[M+1–H_2O]^+$). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.85; H, 7.94.

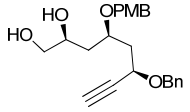
(2*S*,4*S*,6*R*)-1,2-*O*-isopropylidene-4-*O*-benzyl-6-*O*-(4-methoxybenzyl)-oct-7-yne-1,2,4,6-tetraol (23):



To a solution of alcohol **22** (500 mg, 1.64 mmol) in dry DMF (2 mL), NaH (78 mg, 1.97 mmol) was added portionwise at –15 °C and stirred for 15 min, followed by *p*-methoxybenzyl chloride (0.28 mL, 1.97 mmol). After stirring for additional 6 h at –15 °C, the reaction mixture was quenched by adding sat. Na_2SO_4, poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (15% ethyl acetate in petroleum ether) gave the PMB derivative **23** (634 mg, 93%) as colorless oil. *Rf* = 0.4 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ = +30.4 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): ν 3305, 3012, 2932, 2870, 2115, 1720, 1612, 1586, 1513, 1455, 1380, 1370, 1302, 1248, 1216, 1173, 1158, 1086, 1059, 823, 756, 699, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.27 (m, 5H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.41 (br s, 2H), 4.31 (dt, *J* = 7.3, 1.8 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 1H), 3.91 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.43 (t, *J* = 7.8 Hz, 1H), 2.50 (d, *J* = 1.9 Hz, 1H), 2.18 (dt,

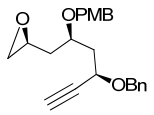
J = 13.9, 7.2 Hz, 1H), 1.98–1.90 (m, 2H), 1.73 (dt, *J* = 13.4, 6.0 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (q), 26.9 (q), 37.5 (t), 40.1 (t), 55.2 (q), 66.0 (d), 69.6 (t), 70.7 (t, 2C), 72.8 (d), 73.0 (d), 74.5 (d), 82.5 (s), 108.5 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.4 (s), 137.6 (s), 137.6 (s), 159.2 (s) ppm. ESI-MS: *m/z* 463.2 (21%, $[M+K]^+$), 447.3 (100%, $[M+Na]^+$), 425.3 (8%, $[M+H]^+$). Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.45; H, 7.55.

(2*S*,4*S*,6*R*)-4-*O*-benzyl-6-*O*-(4-methoxybenzyl)-oct-7-yne-1,2,4,6-tetraol (24):



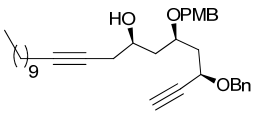
A solution of PMB-derivative **23** (500 mg, 1.17 mmol) in methanol (20 mL) was cooled to 0 °C, PPTS (44 mg, 0.17 mmol) was added in portions, and the reaction mixture was warmed to rt, stirred for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue obtained was purified by column chromatography (60% ethyl acetate in petroleum ether) to afford the diol **24** (380 mg, 85%) as colorless oil. *Rf* = 0.30 (Petether/EtOAc 2:3), $[\alpha]_D^{25}$ = –16.0 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): ν 3423, 3291, 2919, 2850, 2112, 1717, 1612, 1514, 1463, 1451, 1305, 1249, 1069, 1028, 822, 752, 699, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.28 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 4.21 (dt, *J* = 7.4, 1.8 Hz, 1H), 3.91 (br s, 1H), 3.78–3.77 (m, 4H), 3.55 (br s, 1H), 3.49 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.35 (dd, *J* = 11.0, 6.4 Hz, 1H), 2.53 (s, 1H), 2.40 (br s, 1H), 2.24 (ddd, *J* = 14.0, 7.4, 5.4 Hz, 1H), 1.92 (dd , *J* = 14.0, 6.1 Hz, 1H), 1.68 (dt, *J* = 14.6, 8.9 Hz, 1H), 1.55 (dt, *J* = 14.5, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.3 (t), 39.9 (t), 55.2 (q), 65.3 (d), 66.7 (t), 70.6 (t, 2C), 71.0 (d), 74.5 (d), 75.5 (d), 82.3 (s), 113.9 (d, 2C), 127.9 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.7 (s), 137.3 (s), 159.3 (s) ppm. ESI-MS: *m/z* 423.4 (28%, $[M+K]^+$), 407.4 (100%, $[M+Na]^+$), 402.5 (14%, $[M+18]^+$) 385.4 (7%, $[M+1]^+$),.Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.96; H, 7.26.

(*S*)-2-((2*S*,4*R*)-4-(Benzyloxy)-2-(4-methoxybenzyloxy)-hex-5-ynyl)oxirane (10):



To a solution of diol **24** (600 mg, 1.56 mmol) in dry CH_2Cl_2 (15 mL) were added Bu_2SnO (7 mg) and *p*-TsCl (327 mg, 1.71 mmol) followed by triethylamine (435 μL, 3.12 mmol) and DMAP (20 mg) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and extracted. The combined organic phases were washed with water and brine, dried over (Na_2SO_4), and concentrated. The crude tosylate (840 mg) was dissolved in methanol (20 mL) and stirred with anhydrous K_2CO_3 (270 mg) for 30 min at 0 °C and concentrated. The crude was dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (18% ethyl acetate in petroleum ether) gave the epoxide **10** (410 mg, 72% for two steps) as a colorless oil. *Rf* = 0.50 (Petether/EtOAc 1:1), $[\alpha]_D^{25}$ = –13.2 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *v* 3304, 3010, 2923, 2110, 1720, 1612, 1586, 1514, 1248, 1070, 822, 757, 698, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 4.33 (ddd, *J* = 8.3, 6.5, 2.0 Hz, 1H), 3.87 (ddd, *J* = 10.5, 8.3, 5.5 Hz, 1H), 3.80 (s, 3H), 3.03–2.99 (m, 1H), 2.72 (br t, *J* ≈ 4.7 Hz, 1H), 2.50 (d, *J* = 1.8 Hz, 1H), 2.42 (dd, *J* = 4.9, 2.5 Hz, 1H), 2.22 (ddd, *J* = 14.2, 8.3, 6.3 Hz, 1H), 1.98 (ddd, *J* = 13.2, 8.2, 4.7 Hz, 1H), 1.77 (t, *J* = 5.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 36.9 (t), 40.4 (t), 46.8 (t), 49.2 (d), 55.3 (q), 66.1 (d), 70.7 (t), 70.9 (t), 73.7 (d), 74.5 (d), 82.5 (s), 113.8 (d, 2C), 127.8 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.4 (s), 137.6 (s), 159.2 (s) ppm. ESI-MS: *m*/*z* 405.3 (28%, $[M + K]^+$), 389.3 (100%, $[M + Na]^+$), 384.3 (14%$^+$). Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.30; H, 7.28.

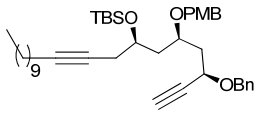
(3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-ol (25):



Dodec-1-yne (816 mg, 4.91 mmol) was taken in a flame dried two-necked round bottom flask (50 mL) and dissolved in anhydrous THF (15 mL). The reaction mixture was cooled to −78 °C, treated with *n*-BuLi (2.1 mL, 4.91 mmol, 2.34 M in hexane) drop wise and stirred for 15 min, to this $BF_3.Et_2O$ (0.55 mL, 4.36 mmol) was

added and stirring was continued for an additional 15 minutes. A solution of epoxide **10** (400 g, 1.09 mmol) in anhydrous THF (10 mL) was added and stirred for 30 min at −78 °C. The reaction mixture was quenched at −78 °C by addition of sat. Na_2SO_4 (20 mL), diluted with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **25** (512 mg, 90%) as colorless oil. *Rf* = 0.40 (Petether/EtOAc 3:2) , $[\alpha]_D^{25}$ = –19.8 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): ν 3469, 3308, 2922, 2851, 2111, 1738, 1612, 1588, 1514, 1463, 1248, 1089, 1031, 823, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.28 (m, 5H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.26 (br ddd, 7.3, 6.3, 1.9 Hz, 1H), 3.94–3.88 (m, 1H), 3.83–3.81 (m, 1H), 3.78 (s, 3H), 3.19 (br s, 1H), 2.51 (d, *J* = 2.0 Hz, 1H), 2.29–2.26 (m, 2H), 2.22 (ddd, *J* = 14.1, 7.2, 5.9 Hz, 1H), 2.14−2.09 (m, 2H), 1.96 (dt, *J* = 14.0, 6.2 Hz, 1H), 1.82 (ddd, *J* = 14.4, 4.5, 3.2 Hz, 1H), 1.73 (br dt, *J* = 14.6, 8.5 Hz, 1H), 1.46 (br dt, *J* = 14.6, 7.2 Hz, 2H), 1.35–1.25 (br s, 14H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 18.7 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 40.1 (t), 40.2 (t), 55.2 (q), 65.7 (d), 69.3 (d), 70.6 (t), 70.7 (t), 74.4 (d), 75.5 (d), 76.1 (s), 82.4 (s), 82.8 (s), 113.9 (d, 2C), 127.8 (d), 128.0 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.9 (s), 137.5 (s), 159.3 (s) ppm. ESI-MS: *m/z* 571.6 (26%, $[M + K]^+$), 555.6 (100%, $[M+Na]^+$), 533.6 (7%, $[M + 1]^+$). Anal. Calcd for $C_{35}H_{48}O_4$: C, 78.91; H, 9.08; Found: C, 78.67; H, 9.22.

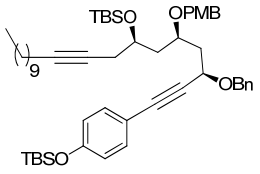
((3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)icosa-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethyl-silane (26):



A solution of alcohol **25** (1 g, 1.87 mmol) in dry DMF (4 mL) was cooled to 0 °C, imidazole (766 mg, 11.26 mmol) followed by TBS-Cl (848 mg, 5.63 mmol) were added and stirring was continued at rt for 24 h. The reaction mixture was partitioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. Combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded

TBS-derivative **26**(1.14 g, 94%) as colorless oil. *Rf* = 0.45 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$ = +11.0 (*c* = 2, $CHCl_3$). IR ($CHCl_3$): ν 3308, 2926, 2855, 2110, 1614, 1514, 1463, 1249, 1095, 836, 776, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.28 (m, 5H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.39 (br ddd, *J* = 8.7, 5.9, 2.0 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 3.84–3.81 (m, 2H), 3.80 (s, 3H), 2.47 (d, *J* = 2.0 Hz, 1H), 2.29–2.27 (m, 2H), 2.13−2.10 (m, 2H), 2.04 (br s, 1H), 1.58 (br s, 1H), 1.49–1.42 (m, 3H), 1.27–1.25 (m, 15H), 0.89 (s, 9H), 0.87 (t, *J* = 4.0 Hz, 3H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q), −4.3 (q), 14.1 (q), 14.2 (q), 18.0 (s), 18.8 (t), 22.7 (t), 25.9 (q, 2C), 28.1 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 40.8 (t), 41.3 (t), 55.3 (q), 66.5 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.1 (d), 74.5 (d), 76.9 (s), 82.4 (s), 82.8 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.8 (s), 137.8 (s), 159.1 (s) ppm. ESI-MS: *m/z* 669.7 (100%, $[M+Na]^+$), 685 (29%, $[M + K]^+$), 647.7 (26%, $[M + 1]^+$). Anal. Calcd for $C_{41}H_{62}O_4Si$: C, 76.11; H, 9.66. Found: C, 76.32; H, 9.85.

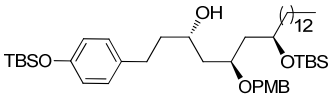
((3*R*,5*S*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethylsilyloxy)phenyl)-5-(4-methoxy-benzyloxy)icosa-1,9-diyn-7-yloxy)(tert-butyl)dimethylsilane (27):



To a solution of alkyne **26** (300 mg, 0.46 mmol), TBS-iodophenol **14** (310 mg, 0.93 mmol) in Et_3N (8 mL) and DMF (4 mL), TPP (12 mg, 0.046 mmol) and $Pd(PPh_3)_2Cl_2$ (32 mg, 0.046 mmol), were added and degassed with argon for 30 min. CuI (9 mg, 0.046 mmol) was added and degassed with argon for 10 min and stirred at rt for 5 h. The reaction mixture was partitioned between ethyl acetate and water. Organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated and the residue obtained was purified by column chromatography (5% → 10% ethyl acetate in petroleum ether) to afford **27** (340 mg, 85%) as colorless oil. *Rf* = 0.45 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$ = +49.2 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): ν 3436, 2928, 2224, 1603, 1507, 1251, 1096, 911, 837, 778, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.31 (m, 5H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 3.89–3.82 (m, 2H), 3.78 (s, 3H), 2.29–2.27 (m, 2H), 2.16−2.09 (m, 3H), 2.05 (ddd, *J*

= 13.3, 9.2, 4.2 Hz, 1H), 1.96 (ddd, *J* = 14.0, 4.2, 5.0 Hz, 1H), 1.85 (ddd, *J* = 14.0, 7.4, 4.6 Hz, 1H), 1.45 (dd, *J* = 14.8, 7.4 Hz, 2H), 1.36–1.30 (m, 2H), 1.25 (m, 10H), 0.98 (s, 9H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.83 (s, 9H), 0.20 (s, 6H), 0.06 (s, 6H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (q), −4.4 (q, 2C), –4.3 (q), 14.1 (q), 17.9 (s), 18.2 (s), 18.8 (t), 22.7 (t), 25.6 (q, 3C), 25.8 (q, 3C), 28.1 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (t), 31.9 (t), 41.1 (t), 41.4 (t), 55.2 (q), 67.2 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.2 (d), 76.7 (s), 82.3 (s), 86.6 (s), 86.7 (s), 113.7 (d, 2C), 115.6 (s) 120.1 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 129.5 (d, 2C), 130.8 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.1 (s) ppm. ESI-MS: *m/z* 876.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{53}H_{80}O_5Si_2$: C, 74.59; H, 9.45. Found: C, 74.82; H, 9.31.

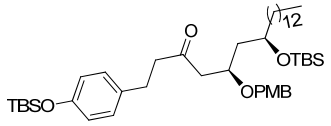
(3*S*,5*S*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)icosane-3,5,7-triol (28):



A suspension of di-TBS derivative **27** (150 mg, 0.174 mmol) and Raney-Ni (300 mg) in ethanol (10 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at 55 °C for 12 h and then stirred at rt for 12 h. The reaction mixture was filtered through a plug of filter aid, washed with ethyl acetate thoroughly (3 × 20 mL), and concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **28** (100 mg, 83%) as a colorless oil. *Rf* = 0.45 (Petether/EtOAc 8:2), $[\alpha]_{25}^{D}$ = –5.1 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *ν* 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.29 (d, *J* ≈ 8.5 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 4.59 (d, *J* = 10.9 Hz, 1H), 4.36 (d, *J* = 10.9 Hz, 1H), 3.84 (br s, 1H), 3.82 (s, 3H), 3.80–3.76 (m, 1H), 3.72–3.66 (m, 1H), 2.71 (ddd, *J* = 13.8, 10.2, 5.5 Hz, 1H), 2.60 (ddd, *J* = 13.8, 10.0, 6.5 Hz, 1H), 1.94 (ddd, *J* = 13.8, 8.2, 3.5 Hz, 1H), 1.78–1.74 (m, 2H), 1.68–1.63 (m, 5H), 1.51–1.41 (m, 3H), 1.25 (br s, 20H), 0.96 (s, 9H), 0.87 (s, 12H), 0.170 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* –4.5 (q), –4.4 (q, 2C), –4.1 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t), 25.0 (t), 25.7 (q, 3C), 25.9 (q, 3C) 29.4 (t), 29.7 (t, 6C), 29.8 (t), 30.9 (t), 31.9 (t), 37.9 (t), 39.7 (t), 41.0 (t), 41.3 (t), 55.3 (q), 69.5 (d), 71.1 (t), 71.2 (d), 77.7 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.6 (d, 2C), 129.9

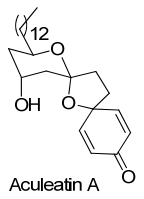
(s), 135.0 (s), 153.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 793.98 (100, $[M + Na]^+$). Anal. Calcd for $C_{46}H_{82}O_5Si_2$: C, 71.63; H, 10.72. Found: C, 71.79; H, 10.91.

(5*R*,7*R*)-5-(4-Methoxybenzyloxy)-7-(*tert*-butyldimethylsilyloxy-1-(4-*tert*-butyldimethyl silyloxyphenyl)icosan-3-one (29):



In a flame-dried, two necked, round-bottom flask (25 mL) was dissolved oxalyl chloride (34 μL, 0.39 mmol) under N_2 atmosphere in dry CH_2Cl_2 (5 mL). After the solution was cooled to –78 °C, dry DMSO (50 μL, 0.71 mmol) was added drop-wise with stirring for 15 min. A solution of alcohol **28** (100 mg, 0.12 mmol) in dry CH_2Cl_2 (5 mL) was added drop-wise and stirred for 30 min. To this was added Et_3N (108 μL, 0.78 mmol) and stirring continued for 15 min at –78 °C. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by column chromatography (5% ethyl acetate in petroleum ether) afforded ketone **29** (93 mg, 93%) as a colorless oil. *Rf* = 0.50 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$ = –4.5 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *v* 3432, 2927, 2955, 2854, 1718, 1611, 1510, 1252, 1081, 1040, 836, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.5, Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.05–3.99 (m, 1H), 3.79 (s, 3H), 3.70 (dd, *J* = 11.2, 5.7 Hz, 1H), 2.80 (t, *J* = 7.1 Hz, 2H), 2.70 (br d, *J* ≈ 7.1 Hz, 2H), 2.64 (d, *J* = 7.8 Hz, 1H), 1.42 (br s, 4H), 1.29 (br s, 5H), 1.26 (s, 18H), 0.97 (s, 9H), 0.88 (s, 12H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.5 (q, 3C), –4.3 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t, 2C) 25.2 (t), 25.8 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.4 (t, 2C), 29.7 (t, 3C), 29.8 (t), 31.9 (t, 2C), 37.2 (t), 41.9 (t), 45.8 (t), 48.3 (t), 55.2 (q), 69.4 (d), 71.1 (t), 72.8 (d), 113.7 (d, 2C), 120.0 (d, 2C), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.7 (s), 153.8 (s), 159.1 (s), 208.9 (s) ppm. ESI-MS: *m*/*z* 792.3 (100, $[M + K]^+$). Anal. Calcd for $C_{46}H_{80}O_5Si_2$: C, 71.82; H, 10.48. Found: C, 71.99; H, 10.76.

Aculeatins A (1) and B (2):

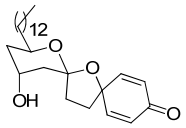


Aculeatin A

To a solution of PMB ether **29** (80 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) and buffer (2 mL) was added DDQ (26 mg, 0.11 mmol) portion-wise at 0 °C and stirring continued for another 30 min at the same temperature. The reaction mixture was filtered through a plug of filter aid. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude (72 mg) was dissolved in dry THF (5 mL) and treated with TBAF (222 μL of 1 M solution in THF, 0.22 mmol) at 0 °C. After the mixture was stirred for 15 min at the same temperature, solvent was evaporated under reduced pressure. The crude ketal (38 mg) was dissolved in acetone/H_2O (2.5 mL, 10:1 v/v solution), and PIFA (50 mg, 0.117 mmol) was added in single portion at room temperature. After the mixture was stirred for 15 min in darkness, a saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the resulting mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (30% and 35% ethyl acetate in petroleum ether) to afford **1** (23 mg, 47%) and **2** (9 mg, 16%) as colorless oils.

Aculeatin A (1): *Rf* = 0.25 (Petether/EtOAc 7:3) $[\alpha]_D^{25}$ = –4.7 (*c* = 2.0, $CHCl_3$); lit.[10] $[\alpha]_D^{23}$ = –5.3 (*c* = 0.9, $CHCl_3$). IR (neat): ν 3495, 2926, 2855, 1674, 1634, 1100, 1047, 999, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.76 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.15 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.12 (dd, *J* = 10.0, 2.0 Hz, 1H) 4.16–4.07 (m, 2H), 3.37 (d, *J* = 9.9 Hz, 1H), 2.43–2.33 (m, 1H), 2.24 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.05–1.98 (m, 3H), 1.96–1.90 (m, 1H), 1.80 (ddd, *J* = 13.6, 5.4, 2.5 Hz, 1H), 1.50–1.39 (m, 4H), 1.30–1.23 (s, 21H), 0.88 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t, 6C), 31.9 (t), 34.1 (t), 35.9 (t), 37.9 (t), 39.1 (t), 64.8 (d), 65.3 (d), 72.2 (t), 79.7 (s), 109.1 (s), 127.1 (d), 127.3 (d), 148.7 (d), 150.9 (d), 185.3 (s) ppm. ESI-MS: *m*/*z* 860 (47%, $[2M+Na]^+$), 441 (36%, $[M+Na]^+$), 419 (48%, $[M+1]^+$), 507.4 (100%). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.47; H, 10.34.

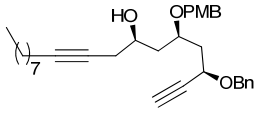
Aculeatin B (2):



Aculeatin B

Rf = 0.20 (Petether/EtOAc 7:3); $[\alpha]_D^{26}$ = +46.8 (*c* 1.0, $CHCl_3$); lit.[10] $[\alpha]_D^{23}$ = +50.0 (*c* 0.2, $CHCl_3$). IR (neat): ν 3521, 2916, 2849, 1665, 1621, 1068, 1020, 1005, 854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.78 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.14 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.11 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.39–4.35 (m, 1H), 3.91–3.82 (m, 1H), 2.69 (ddd, *J* = 13.1, 7.4, 1.6 Hz, 1H), 2.31 (dt, *J* = 12.3, 7.3 Hz, 1H), 2.11–2.02 (m, 2H), 1.98–1.86 (m, 2H), 1.65–1.53 (m, 2H), 1.49–1.42 (m, 4H), 1.23–1.33 (s, 21H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.9 (t), 29.4 (t, 2C), 29.6 (t, 3C), 29.7 (t, 3C), 31.9 (t), 35.3 (t), 35.4 (t), 35.7 (t), 37.9 (t), 40.6 (t), 65.2 (d), 69.4 (d), 77.6 (s), 108.5 (s), 127.1 (d), 149.1 (d), 152.2 (d), 185.7 (s). ESI-MS: *m*/*z* 441 (100% $[M+Na]^+$), 419 (44% $[M+1]^+$). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.52; H, 10.31.

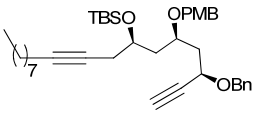
(3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-ol (30):



The similar procedure as in the preparation of **25** was used to open epoxide **10** (400 mg, 1.09 mmol) with the dec-1-yne (680 mg, 4.91 mmol) affording **30** (484 mg, 88%) as colorless oil. *Rf* = 0.45 (Petether/EtOAc 3:2) $[\alpha]_D^{25}$ = –101.4 (*c* = 1.6, $CHCl_3$). IR ($CHCl_3$): ν 3439, 3152, 2917, 2857, 2111, 1613, 1403, 1216, 1085, 1039, 757, 669 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.28 (m, 5H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.26 (dd, *J* = 6.3, 2.0 Hz 1H), 3.87 (ddd, *J* = 14.0, 10.8, 5.8 Hz, 1H), 3.85−3.81 (m, 1H), 3.80 (s, 3H), 3.21 (d, *J* = 2.5 Hz, 1H), 2.52 (d, *J* = 2.0 Hz, 1H), 2.28 (ddd, *J* = 8.0, 4.7, 2.0 Hz, 2H), 2.23 (ddd, *J* = 13.9, 7.2, 5.9 Hz, 1H), 2.12 (tt, *J* = 7.2, 2.3 Hz, 2H), 1.96 (dt, *J* = 14.0, 6.2 Hz, 1H), 1.81 (ddd, *J* = 14.5, 4.7, 3.2 Hz, 1H), 1.73 (dt, *J* = 14.5, 8.8 Hz, 1H), 1.46 (br dt, *J* ≈ 14.5, 6.9 Hz, 2H), 1.37−1.31 (m, 3H), 1.26 (br s, 7H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 18.8 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.8 (t), 40.1 (t), 40.2 (t), 55.2 (q), 65.7 (d), 69.4 (d), 70.7 (t), 70.7 (t), 74.4 (d), 75.5 (d), 76.1 (s), 82.4 (s), 82.8 (s), 113.9 (d, 2C), 127.8 (d), 128.1 (d,

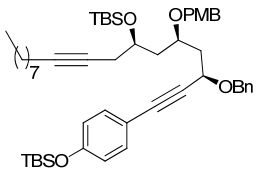
2C), 128.4 (d, 2C), 129.6 (d, 2C), 129.9 (s), 137.5 (s), 159.3 (s) ppm. ESI-MS: *m/z* 527.6 (100%, $[M+Na]^+$), 543.6 (37%, $[M+K]^+$), 505.7(8%, $[M+1]^+$). Anal. Calcd for $C_{33}H_{44}O_4$: C, 78.53; H, 8.79. Found: C, 78.80; H, 9.04.

((3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethyl-silane (31):



The same procedure as in the preparation of **26** was used with the alcohol **31** (500 mg, 1.0 mmol) affording TBS-derivative **31** (554 mg, 91%) as colorless oil. *Rf* = 0.50 (Petether/EtOAc 4:1), $[\alpha]_D^{25}$ = +53.6 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): ν 3308, 2929, 2856, 2110, 1613, 1514, 1463, 1361, 1248, 1091, 1039, 835, 775, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.41–4.37 (m, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 3.86–3.82 (m, 1H), 3.80 (s, 3H), 2.46 (d, *J* = 1.9 Hz, 1H), 2.28 (dd, *J* = 4.7, 2.2 Hz, 2H), 2.12 (tt, *J* = 7.0, 2.4 Hz, 2H), 2.06–1.90 (m, 3H), 1.85–1.78 (m, 1H), 1.49–1.42 (m, 2H), 1.37–1.33 (m, 3H), 1.26 (s, 8H), 0.89 (s, 9H), 0.87 (t, *J* = 4.0 Hz, 3H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ − 4.5 (q), − 4.2 (q), 14.1 (q), 18.0 (s), 18.8 (t), 22.6 (t), 25.9 (q, 3C), 28.1 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 29.7 (t), 31.9 (t), 40.8 (t), 41.3 (t), 55.3 (q), 66.5 (d), 68.6 (d), 70.6 (t), 70.8 (t), 73.1 (d), 74.6 (s), 82.4 (s), 82.7 (s), 113.7 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.4 (d, 2C), 130.7 (s), 137.8 (s), 159.1 (s) ppm. ESI-MS: *m/z* 641.9 (100%, [M+Na]+), 657.9(66%, $[M+K]^+$), 619.9 (25%, $[M+1]^+$). Anal. Calcd for $C_{39}H_{58}O_4Si$: C, 75.68; H, 9.44. Found: C, 75.52; H, 9.51.

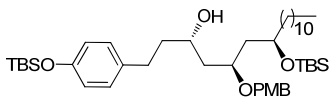
((3*R*,5*S*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethylsilyloxy)phenyl)-5-(4-methoxy-benzyloxy)octadeca-1,9-diyn-7-yloxy)(tert-butyl)dimethylsilane (32):



The similar procedure as in the preparation of **27** was used with the alkyne **31** (400 mg, 0.65 mmol). The crude was purified by column chromatography (5% → 10% ethyl acetate in petroleum ether) to afford **32** (465 mg, 87% yield) as colorless oil. *Rf* = 0.40

(Petether/EtOAc 4:1), $[\alpha]_D^{25}$ = +49.2 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): ν 3436, 2929, 2857, 2224, 1603, 1507, 1463, 1251, 1096, 911, 837, 777, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.30 (m, 7H), 7.22 (d, *J* = 7.2 Hz, 2H), 6.83 (d, *J* = 7.4 Hz, 2H), 6.78 (d, *J* = 7.2 Hz, 2H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 10.7 Hz, 1H), 4.41 (d, *J* = 10.7 Hz, 1H), 3.89–3.81 (br s, 2H), 3.79 (s, 3H), 2.29 (s, 2H), 2.12 (s, 3H), 2.05 (br s, 1H), 1.98–1.90 (m, 1H), 1.89–1.86 (m, 1H), 1.46 (t, *J* = 6.4 Hz, 2H), 1.35 (br s, 2H), 1.30–1.22 (br s, 9H), 0.99 (s, 9H), 0.87 (t, *J* = 6.85 Hz, 3H), 0.83 (s, 9H), 0.21 (s, 6H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5 (q), −4.4 (q, 2C), −4.3 (q), 14.1 (q), 17.9 (s), 18.2 (s), 18.8 (t), 22.6 (t), 25.6 (q, 3C), 25.8 (q, 3C), 25.9 (s), 28.1 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.9 (t), 41.1 (t), 41.4 (t), 55.2 (q), 67.2 (d), 68.7 (d), 70.6 (t), 70.7 (t), 73.2 (d), 82.3 (s), 86.6 (s), 86.7 (s), 113.7 (d, 2C), 115.6 (s) 120.1 (d, 2C), 127.6 (d), 128.1 (d, 2C), 128.3 (d, 2C), 129.5 (d, 2C), 130.8 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.1 (s) ppm. ESI-MS: *m/z* 848.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{51}H_{76}O_5Si_2$: C, 74.22; H, 9.28. Found: C, 74.38; H, 9.16.

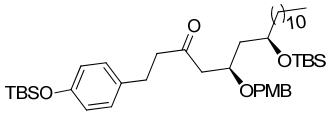
(3*S*,5*S*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)octadecane-3,5,7-triol (33):



The same procedure as in the preparation of **28** was used with the di-TBS derivative **32** (180 mg, 0.22 mmol) to procure **33** as colorless oil (142 mg, 87% yield). *Rf* = 0.40 (Petether/EtOAc 8:2), $[\alpha]_{25}^D$ = –5.1 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *v* 3480, 2928, 2855, 1611, 1509, 1470, 1252, 1040, 836, 775, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.46 (d, *J* = 10.7 Hz, 1H), 3.94 (br s, 1H), 3.91(s, 3H), 3.90–3.87 (m, 1H), 3.80 (br s, 1H), 2.80 (ddd, *J* = 14.4, 9.9, 5.1 Hz, 1H), 2.70 (ddd, *J* = 14.4, 9.9, 5.8 Hz, 1H), 2.04 (ddd, *J* = 13.1, 8.3, 3.7 Hz, 1H), 1.85 (d, *J* = 14.3 Hz, 2H), 1.80–1.62 (m, 4H), 1.57 (br s. 2H), 1.38 (br s, 18H), 1.09 (s, 9H), 1.00 (s, 12H), 0.30 (s, 6H), 0.17 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* –4.5 (q), –4.5 (q, 2C), –4.1 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t), 25.0 (t), 25.7 (q, 3C), 25.9 (q, 3C) 29.3 (t), 29.6 (t, 4C), 29.8 (t), 30.9 (t), 31.9 (t), 37.9 (t), 39.6 (t), 40.9 (t), 41.3 (t), 55.2 (q), 69.4 (d), 70.1 (t), 71.2 (d), 77.7 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.6 (d, 2C), 130.0 (s), 135.0

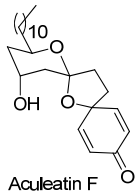
(s), 153.5 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 766.2 (100%, $[M + Na]^+$), 782.4 (35%, $[M+K]^+$), 744.4 (35%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{78}O_5Si_2$: C, 71.10; H, 10.58. Found: C, 71.06; H, 10.76.

(5*R*,7*R*)-5-(4-Methoxybenzyloxy)-7-(*tert*-butyldimethylsilyloxy-1-(4-*tert*-butyldimethyl silyloxyphenyl)octadecan-3-one (34):



The same procedure as in the preparation of **29** was used with the alcohol **33** (120 mg, 0.49 mmol) affording **34** (114 mg, 95% yield) as colorless oil. *Rf* = 0.45 (Petether/EtOAc 4:1), $[\alpha]_{25}^{D} = -4.5$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *v* 3432, 2928, 2855, 1713, 1611, 1510, 1251, 1039, 916, 836, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.5, Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.01 (ddd, *J* = 13.7, 6.7, 4.2 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, *J* = 11.6, 5.8 Hz, 1H), 2.80 (t, *J* ≈ 7.4 Hz, 2H), 2.70 (t, *J* ≈ 7.4 Hz, 2H), 2.65 (d, *J* = 7.9 Hz, 1H), 2.54 (dd, *J* = 15.9, 4.4 Hz, 1H), 1.83–1.78 (m, 1H), 1.54–1.49 (m, 1H), 1.39 (br s, 2H), 1.29 (br s, 3H), 1.26 (s, 15H), 0.97 (s, 9H), 0.88 (s, 12H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.5 (q, 3C), –4.3 (q), 14.1 (q), 18.0 (s), 18.2 (s), 22.7 (t) 25.2 (t), 25.7 (q, 3C), 25.9 (q, 3C), 28.7 (t), 29.4 (t), 29.7 (t, 4C), 29.8 (t), 31.9 (t), 37.2 (t), 41.9 (t), 45.8 (t), 48.3 (t), 55.2 (q), 69.4 (d), 71.1 (t), 72.8 (d), 113.7 (d, 2C), 119.9 (d, 2C), 129.1 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.7 (s), 153.8 (s), 159.1 (s), 208.9 (s) ppm. ESI-MS: *m*/*z* 764.4 (100%, $[M+Na]^+$), 780.6 (56%, $[M+K]^+$), 759.6 (20%, $[M+H_2O]^+$), 743.6 (15%, $[M+2]^+$), 741.6 (11%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{76}O_5Si_2$: C, 71.30; H, 10.33. Found: C, 71.47; H, 10.35.

Aculeatin F (6) and 6-*epi*-aculeatin F (9):

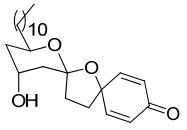


The similar procedure as in the preparation of aculeatin A/B was used with the ketone **34** (100 mg, 0.13 mmol) to afford **6** (21 mg, 43%) and **9** (8 mg, 15%) as colorless oils.

Aculeatin F (6): *Rf* = 0.24 (Petether/EtOAc 7:3). $[\alpha]_D^{26} = -4.7$ (*c* 2.0, $CHCl_3$); lit.[9b] $[\alpha]_D^{23} = -5.3$ (*c* 0.9, $CHCl_3$). IR (neat): ν 3494, 2927, 2854,

1677, 1633, 1100, 1046, 998, 852 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, J = 10.0, 2.8 Hz, 1H); 6.76 (dd, J = 10.0, 2.8 Hz, 1H), 6.15 (dd, $J \approx$ 10.0, 1.8 Hz, 1H), 6.12 ((dd, $J \approx$ 10.0, 1.8 Hz, 1H), 4.17–4.06 (m, 2H), 3.38 (d, J = 10.0 Hz, 1H), 2.42–2.34 (m, 1H), 2.24 (dd, J = 10.3, 8.1 Hz, 1H), 2.05–1.98 (m, 3H), 1.94 (br t, J = 14.0 Hz, 1H), 1.80 (d, J = 13.5 Hz, 1H), 1.54–1.39 (m, 4H), 1.29 (s, 17H), 0.88 (t , J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.6 (t), 29.3 (t), 29.6 (t), 29.7 (t, 4C), 31.9 (t), 34.1 (t), 35.9 (t), 37.9 (t), 39.0 (t), 39.1 (t), 64.8 (d), 65.3 (d), 79.7 (s), 109.1 (s), 127.0 (d), 127.3 (d), 148.8 (d), 150.9 (d), 185.3 (s). ESI-MS: m/z 804.0 (47% $[2M+Na]^+$), 413.5 (36% $[M+Na]^+$), 491.5 (48% $[M+1]^+$), 507.4 (100%). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.69; H, 9.94.

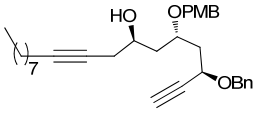
6-*epi*-Aculeatin F (9):



6-*epi*-Aculeatin F

Rf = 0.18 (Petether/EtOAc 7:3). $[\alpha]_D^{26}$ = +46.8 (c 1.0, $CHCl_3$), IR ($CHCl_3$): ν 3520, 2916, 2848, 1664, 1620, 1067, 1020, 1004, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 10.0, 3.0 Hz, 1H), 6.78 (dd, J = 10.0, 3.0 Hz, 1H), 6.14 (dd, J = 10.0, 2.0 Hz, 1H), 6.11 (dd, J = 10.0, 2.0 Hz, 1H), 4.39–4.35 (m, 1H), 3.91–3.83 (m, 1H), 2.69 (br dd, J = 12.3, 7.4, Hz, 1H), 2.31 (dt, J = 12.3, 7.4 Hz, 1H), 2.10–2.01 (m, 2H), 1.97–1.85 (m, 2H), 1.64–1.52 (m, 3H), 1.49–1.39 (m, 3H), 1.29 (s, 17H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t, 4C), 31.9 (t), 35.3 (t, 2C), 35.7 (t), 37.9 (t), 40.5 (t), 65.2 (d), 69.4 (d), 77.6 (s), 108.5 (s), 127.1 (d, 2C), 149.2 (d), 152.3 (d), 185.7 (s). ESI-MS: m/z 413.5 (100% $[M+Na]^+$), 429.5 (22% $[M+K]^+$), 491 (24% $[M+1]^+$), 373.5 (22%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.97; H, 9.88.

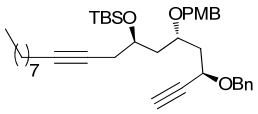
(3*R*,5*S*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-ol (37):



The same procedure as in the preparation of **25** was used to couple the dec-1-yne (**12**) and oxirane **11** (400 mg, 1.1 mmol) to procure the diyne **37** (500 mg, 91%) as colorless oil. *Rf* = 0.30 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$ = +79.7 (c = 2.0, $CHCl_3$). IR ($CHCl_3$): ν 3469, 3305, 2930, 2857, 2111, 1612, 1586, 1513, 1455,

1249, 1216, 1069, 1034, 822, 756, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 4H), 7.32−7.28 (m, 1H), 7.14 (ddd, *J* = 8.6, 2.9, 2.0 Hz, 2H), 6.82 (ddd, *J* = 8.6, 2.9, 2.0 Hz, 2H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.27−4.23 (m, 1H), 4.02−3.91 (m, 2H), 3.76 (s, 3H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.34−2.30 (m, 2H), 2.17−2.07 (m, 3H), 1.97 (ddd, *J* = 14.5, 9.4, 3.9 Hz, 1H), 1.84 (ddd, *J* = 14.5, 9.7, 3.9 Hz, 1H), 1.72 (ddd, *J* = 14.5, 6.0, 2.7 Hz, 1H), 1.48 (dt, *J* = 7.0, 1.2 Hz, 2H), 1.39−1.32 (m, 2H), 1.31−1.21 (br s, 9H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 18.7 (t), 22.6 (t), 27.8 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.8 (t), 39.2 (t), 41.1 (t), 55.2 (q), 65.0 (d), 67.4 (d), 70.6 (t), 71.5 (t), 73.1 (d), 74.0 (d), 76.0 (s), 82.8 (s), 83.0 (s), 113.8 (d, 2C), 127.8 (d), 128.2 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 130.1 (s), 137.6 (s), 159.3 (s) ppm. ESI-MS: *m/z* 527.6 (100%, $[M+Na]^+$), 543.6 (36%, $[M+K]^+$), 505.7(7%, $[M+1]^+$). 407.5 (46%, $[M–97]^+$), 383.4 (74%, $[M–115]^+$). Anal. Calcd for $C_{33}H_{44}O_4$: C, 78.53; H, 8.79. Found: C, 78.88; H, 9.02.

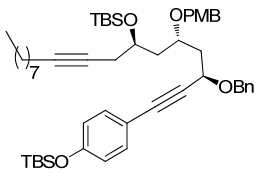
((3*R*,5*R*,7*R*)-3-(Benzyloxy)-5-(4-methoxybenzyl-oxy)octadeca-1,9-diyn-7-yloxy)(*tert*-butyl)-dimethyl-silane (38):



A solution of alcohol **37** (500 g, 0.99 mmol) in anhydrous DMF (3 mL) was cooled to 0 °C, imidazole (404 mg, 5.94 mmol) followed by TBS-Cl (447 mg, 2.97 mmol) were added and stirring was continued at rt for 24 h. The reaction mixture was portioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded TBS-derivative **38** (563 mg, 92%) as colorless oil. *Rf* = 0.40 (Petether/EtOAc 7:3) $[\alpha]_D^{25}$ = +24.2 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): ν 3308, 2928, 2856, 2110, 1613, 1514, 1463, 1248, 1091, 1039, 835, 775, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.28 (m, 5H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 10.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 10.5 Hz, 1H), 4.27 (dt, *J* = 6.9, 2.0 Hz, 1H), 3.99−3.92 (m, 1H), 3.90–3.83 (m, 1H), 3.76 (s, 3H), 2.47 (d, *J* = 2.0 Hz, 1H), 2.33−2.30 (m, 2H), 2.13 (tt, *J* = 7.0, 2.3 Hz, 2H), 2.05−1.97 (m, 3H), 1.64 (ddd, *J* = 14.2, 8.0, 4.8 Hz, 1H), 1.50−1.43

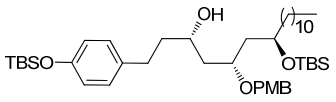
(m, 2H), 1.38–1.34 (m, 2H), 1.246 (s, 8H),0.89 (s, 9H), 0.86 (t, *J* = 5.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6 (q), −4.1 (q), 14.1 (q), 18.1 (s), 18.8 (t), 22.7 (t), 25.9 (q, 3C), 28.2 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.9 (t), 41.8 (t), 42.2 (t), 55.2 (q), 65.3 (d), 68.6 (d), 70.4 (t), 70.6 (t), 72.1 (d), 73.8 (d), 76.6 (s), 82.5 (s), 83.0 (s), 113.7 (d, 2C), 127.7 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 130.8 (s), 137.8 (s), 159.0 (s) ppm. ESI-MS: *m/z* 641.8 (23%, $[M+Na]^+$), 657.9 (14%, $[M+K]^+$), 429.5 (73%, $[M–189]^+$), 421.5 (100%, $[M–197]^+$). Anal. Calcd for $C_{39}H_{58}O_4Si$: C, 75.68; H, 9.44. Found: C, 75.51; H, 9.67.

((3*R*,5*R*,7*R*)-3-(Benzyloxy)-1-(4-(*tert*-butyl-dimethylsilyloxy)phenyl)-5-(4-methoxy-benzyloxy)octadeca-1,9-diyn-7-yloxy)(tert-butyl)dimethylsilane (39):



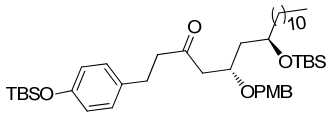
The coupling of alkyne **33** (200 mg, 0.32 mmol) and the iodo derivative **13** was carried out according to the procedure used for the preparation of **27**. Purification of the crude by column chromatography (5% ethyl acetate in petroleum ether) gave **39** (180 mg, 90%) as a colorless syrup. *Rf* = 0.60 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ = +26.1 (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$): ν 3351, 2929, 2224, 1603, 1507, 1217, 1094, 838, 759, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 7H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.49−4.46 (m, 1H), 4.44 (d, *J* = 10.8 Hz, 1H),4.35 (d, *J* = 10.8 Hz, 1H), 4.00−3.88 (m, 2H), 3.77 (s, 3H), 2.32 (ddd, *J* = 5.3, 2.2 Hz, 2H), 2.17−2.05 (m, 4H), 2.01 (ddd, *J* = 14.1, 7.7, 3.8 Hz, 1H), 1.68 (ddd, *J* = 14.1, 8.0, 4.7 Hz, 1H), 1.64−1.57 (br s, 1H), 1.50−1.43 (m, 2H), 1.38−1.33 (m, 2H), 1.25 (s, 7H), 0.98 (s, 9H), 0.89 (s, 9H), 0.86 (t, *J* = 5.0 Hz, 3H), 0.20 (s, 6H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.6 (q), −4.5 (q, 2C), −4.1 (q), 14.1 (q), 18.1 (s), 18.2 (s), 18.8 (t), 22.6 (t), 25.6 (q, 3C), 25.9 (q, 3C), 28.3 (t), 28.9 (t), 29.0 (t), 29.2 (t), 29.3 (t), 31.9 (t), 41.9 (t), 42.3 (t), 55.2 (q), 66.1 (d), 68.6 (d), 70.3 (t), 70.6 (t), 72.4 (d), 77.2 (s), 82.4 (s), 85.9 (s), 87.1 (s), 113.7 (d, 2C), 115.6 (s), 120.1 (d, 2C), 127.6 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.2 (d, 2C), 131.0 (s), 133.2 (d, 2C), 138.1 (s), 155.9 (s), 159.0 (s) ppm. ESI-MS: *m/z* 848.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{51}H_{76}O_5Si_2$: C, 74.22; H, 9.28. Found: C, 74.09; H, 9.15.

(3*S*,5*R*,7*R*)-5-*O*-(4-Methoxybenzyl)-7-*O*-*tert*-butyldimethylsilyl-1-(4-*tert*-butyldimethyl-silyloxyphenyl)octadecane-3,5,7-triol (40):



The same procedure as in the preparation of **28** was used with the di-TBS derivative **39** (140 mg, 0.17 mmol) affording **40** (105 mg, 84% yield) as colorless oil. *Rf* = 0.30 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ –5.1 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): *v* 3480, 2855, 1611, 1510, 1252, 1039, 836, 758, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2H), 7.04 (dt, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.52 (d, *J* = 10.9 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 3.94−3.90 (br s, 1H), 3.84−3.81 (m, 2H), 3.80 (s, 3H), 3.13 (br s, 1H), 2.72 (ddd, *J* = 14.6, 9.7, 5.4 Hz, 1H), 2.54 (ddd, *J* = 15.8, 9.7, 6.3 Hz, 1H), 1.91−1.81 (m, 2H), 1.79−1.72 (m, 1H), 1.67−1.59 (m, 1H), 1.58−1.52 (m, 2H), 1.45−1.40 (m, 2H), 1.26 (s, 18H), 0.98 (s, 9H), 0.87 (s, 9H), 0.87 (t, *J* = 5.0 Hz, 3H), 0.18 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ − 4.5 (q, 2C), − 4.4 (q), − 4.1 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t, 2C), 24.7 (t), 25.7 (q, 3C), 25.9 (q, 3C), 29.3 (t), 31.1 (t, 2C), 31.9 (t), 37.7 (t, 2C), 39.5 (t, 2C), 39.8 (t), 41.5 (t), 55.2 (q), 68.1 (d), 69.7 (d), 70.7 (t, 2C), 74.9 (d), 113.9 (d, 2C), 119.8 (d, 2C), 129.2 (d, 2C), 129.4 (d, 2C), 130.2 (s), 134.9 (s), 153.6 (s), 159.3 (s) ppm. ESI-MS: *m*/*z* 766.1 (80%, $[M + Na]^+$), 779.1 (10%, $[M+K]^+$), 565.5 (100%). Anal. Calcd for $C_{44}H_{78}O_5Si_2$: C, 71.10; H, 10.58. Found: C, 71.25; H, 10.64.

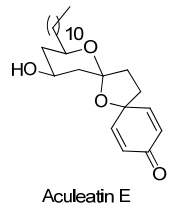
(5*S*,7*R*)-5-(4-Methoxybenzyloxy)-7-(*tert*-butyldimethylsilyloxy-1-(4-*tert*-butyldimethyl silyloxyphenyl)octadecan-3-one (41):



The Swern oxidation of the alcohol **40** (100 mg, 0.14 mmol) was carried out as described for the preparation of **29** and the ketone **41** (93 mg, 93%) was obtained as a colorless syrup after usual workup and purification by column chromatography (5% ethyl acetate in petroleum ether). *Rf* = 0.50 (Petether/EtOAc 8:2), $[\alpha]_D^{25}$ = –4.5 (c = 1). $CHCl_3$). IR ($CHCl_3$): ν 3415, 2927, 1715, 1612, 1511, 1252, 1040, 836, 759, 686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (br.d, *J* = 8.7 Hz, 2H), 6.99 (br.d, *J* = 8.3 Hz, 2H), 6.85 (br.d, *J* = 8.7 Hz, 2H), 6.73 (br.d, *J* = 8.3 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H),

4.39 (d, *J* = 11.0 Hz, 1H), 4.08 –4.02 (m, 1H), 3.84–3.73 (m, 1H), 3.79 (s, 3H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.71 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.49 (dd, *J* = 15.6, 5.1 Hz, 1H), 1.76–1.69 (m, 1H), 1.52–1.41 (m, 3H), 1.25 (br. s, 18H), 0.97 (s, 9H), 0.88 (s, 9H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.17 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.5 (q, 3C), –4.0 (q), 14.1 (q), 18.1 (s), 18.2 (s), 22.7 (t) 24.7 (t), 25.3 (t), 25.7 (q, 3C), 25.8 (q, 3C), 28.7 (t), 29.3 (t), 29.6 (t, 2C), 29.8 (t), 31.9 (t), 37.3 (t), 40.4 (t), 41.7 (t), 45.6 (t), 48.8 (t), 55.2 (q), 69.4 (d), 71.1 (t), 73.1 (d), 113.9 (d, 2C), 120.0 (d, 2C), 129.2 (d, 2C), 129.5 (d, 2C), 130.6 (s), 133.6 (s), 153.8 (s), 159.1 (s), 208.6 (s) ppm. ESI-MS: *m*/*z* 764.5 (100%, $[M + Na]^+$), 777.5 (56%, $[M+K]^+$), 742.5 (11%, $[M+1]^+$). Anal. Calcd for $C_{44}H_{76}O_5Si_2$: C, 71.30; H, 10.33. Found: C, 71.16; H, 10.52.

Aculeatin E (5) and 6-*epi*-Aculeatin E (8):



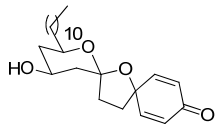
Aculeatin E

The same sequence of procedures as in the preparation of aculeatin A/B were used with the ketone **41** (90 mg, 0.122 mmol) affording an easily seperable mixture of (flash column chromatography, 30% ⟶35% ethyl acetate in petroleum ether) aculeatin E (**5**) (16 mg, 30%) and 6-*epi*-aculeatin E (**8**) (15 mg, 30%) as colorless oils.

Aculeatin E (5): *Rf* = 0.20 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ = +47.7 (*c* = 1, $CHCl_3$); lit.[9b] $[\alpha]_{23}^{D}$ = +46.5 (*c* = 1, $CHCl_3$). IR (neat): *v* 3410, 2916, 2849, 1665, 1628, 1057, 1009 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (dd, *J* = 10.3, 3.0 Hz, 1H), 6.78 (dd, *J* = 10.3, 3.0 Hz, 1H), 6.14 (dd, *J* = 10.0, 1.7 Hz, 1H), 6.12 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.85 (tt, *J* = 11.2, 4.4 Hz, 1H), 3.40–3.34 (m, 1H), 2.39 (ddd, *J* = 12.7, 7.5, 2.0 Hz, 1H), 2.27 (br ddd, *J* = 12.5, 11.2, 7.5 Hz, 1H), 2.13 (ddd, *J* = 12.3, 4.3, 1.8 Hz, 1H), 2.07 (ddd, *J* = 12.5, 8.2, 1.9 Hz, 1H), 1.96 (br ddd, *J* = 12.3, 4.4, 2.0 Hz, 1H), 1.84 (dt, *J* = 12.5, 8.5 Hz, 2H), 1.67–1.57 (m, 3H), 1.50–1.48 (m, 2H), 1.26 (s, 17H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 25.9 (t), 29.3 (t), 29.4 (t), 29.6 (t, 4C), 31.9 (t), 33.4 (t), 34.9 (t), 35.7 (t), 40.8 (t), 43.6 (t), 66.8 (d), 71.6 (d), 78.1 (s), 109.2 (s), 127.2 (d), 127.4 (d), 148.8 (d), 151.6 (d), 185.5 (s) ppm. ESI-MS: *m*/*z* 413.5 (100%, $[M + Na]^+$), 429.5 (33%, $[M+K]^+$), 391.5 (26%, $[M+1]^+$),

373.5 (18%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.08; H, 10.02.

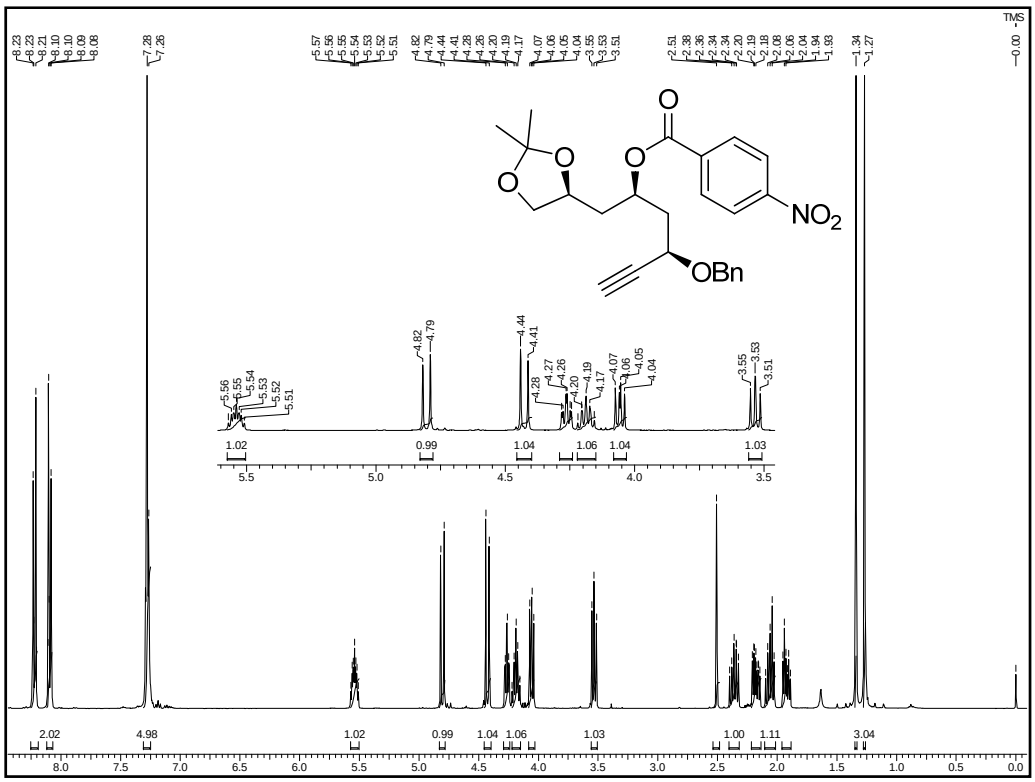
6-*epi*-Aculeatin E (8):



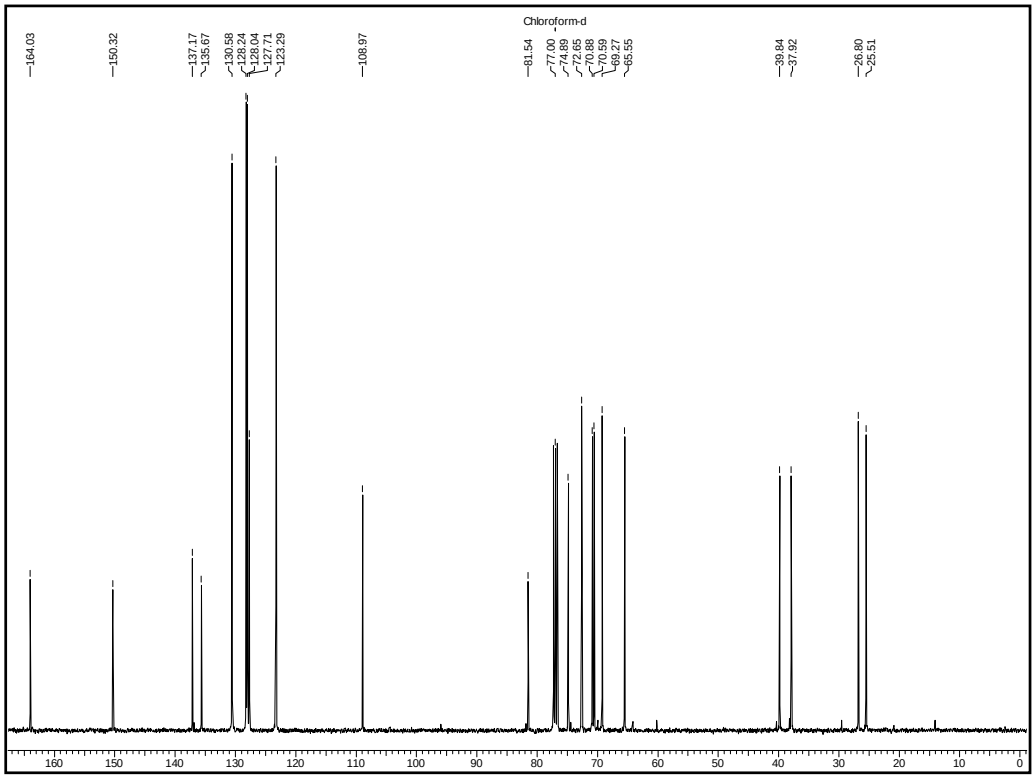
6-epi-Aculeatin E

Rf = 0.25 (Petether/EtOAc 7:3), $[\alpha]_D^{25}$ = +14.6 (*c* = 0.2, $CHCl_3$). IR (neat): *v* 3412, 2915, 2848, 1662, 1627, 1052, 1004 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *δ* 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.76 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.12 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.10 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.10 (tt, *J* = 12.2, 4.8 Hz, 1H), 3.83–3.77 (m, 1H), 2.43–2.35 (m, 1H), 2.25 (dd, *J* ≈ 10.9, 7.8 Hz, 1H), 2.10 (ddd, *J* = 12.4, 4.8, 1.8 Hz, 1H), 2.06–2.00 (m, 2H), 1.97 (ddd, *J* = 12.3, 4.4, 1.9 Hz, 1H), 1.65 (t, *J* = 11.8 Hz, 1H), 1.57–1.51 (m, 1H), 1.49–1.41 (m, 2H), 1.32–1.22 (m, 18H), 1.18 (q, *J* = 11.8 Hz, 1H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.1 (q), 22.7 (t), 25.7 (t), 29.3 (t), 29.6 (t, 5C), 31.9 (t), 34.6 (t), 35.9 (t), 38.8 (t), 40.6 (t), 43.0 (t), 65.3 (d), 69.1 (d), 79.0 (s), 109.0 (s), 127.0 (d), 127.1 (d), 149.2 (d), 151.4 (d), 185.4 (s) ppm. ESI-MS: *m/z* 413.5 (100%, $[M + Na]^+$), 429.5 (22%, $[M+K]^+$), 391.5 (24%, $[M+1]^+$), 373.5 (22%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.77; H, 10.09.

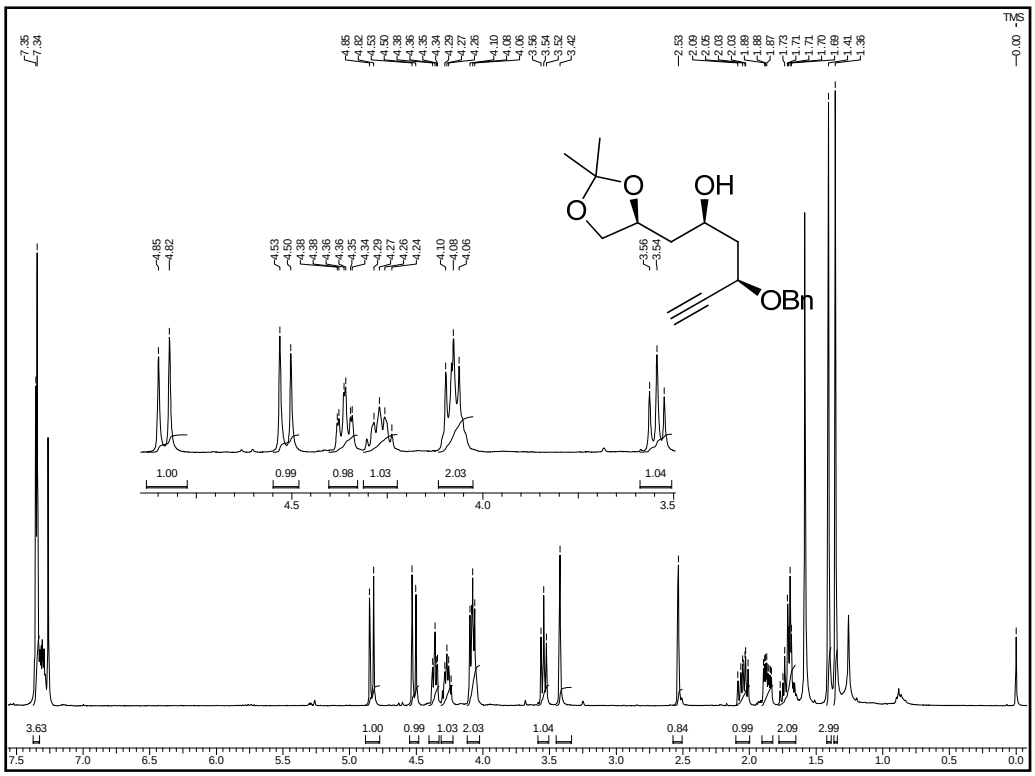
Spectroscopic Data



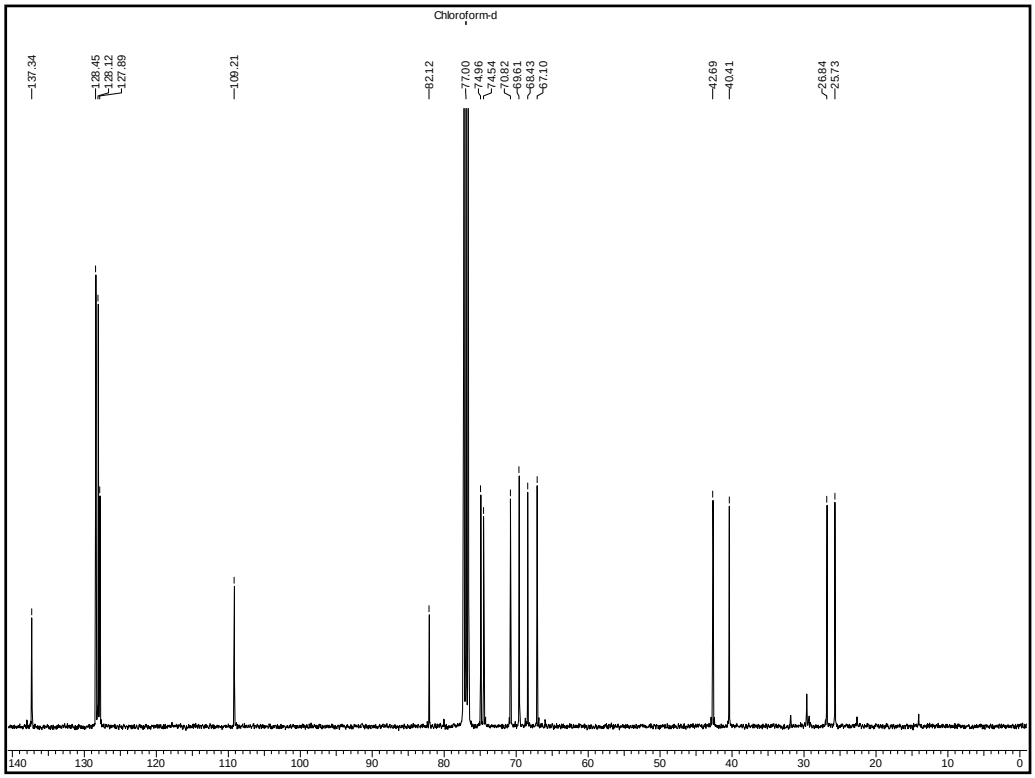
^{1}H NMR Spectrum of 21 in $CDCl_3$



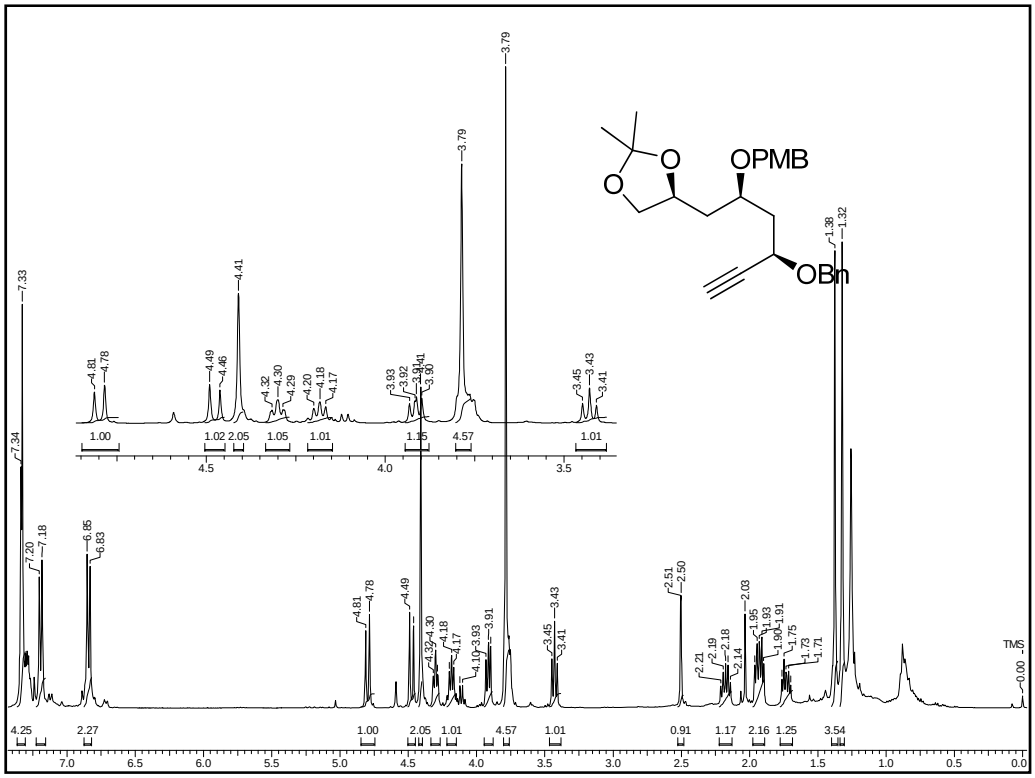
^{13}C NMR Spectrum of 21 in $CDCl_3$



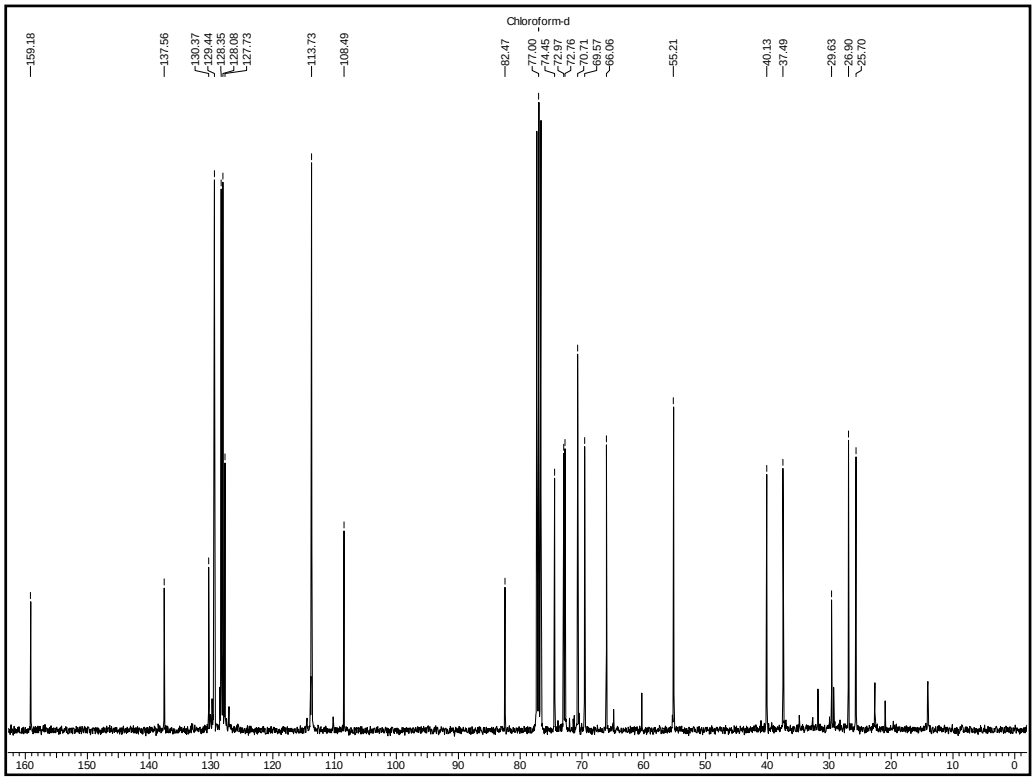
^{1}H NMR Spectrum of 22 in $CDCl_3$



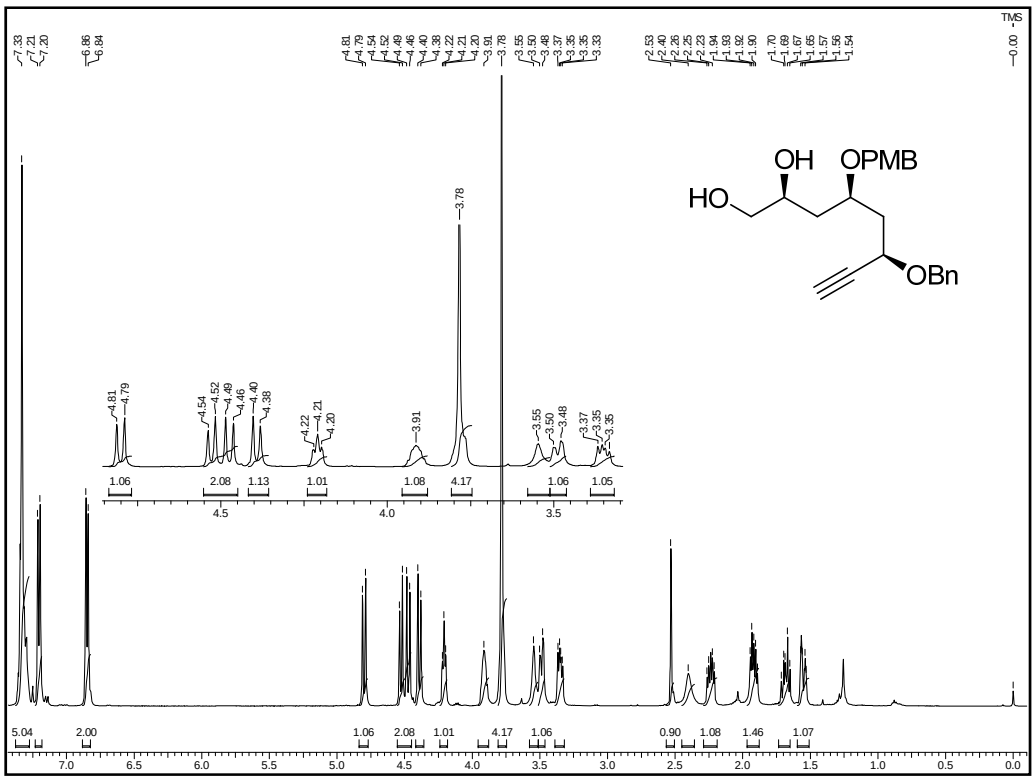
^{13}C NMR Spectrum of 22 in $CDCl_3$



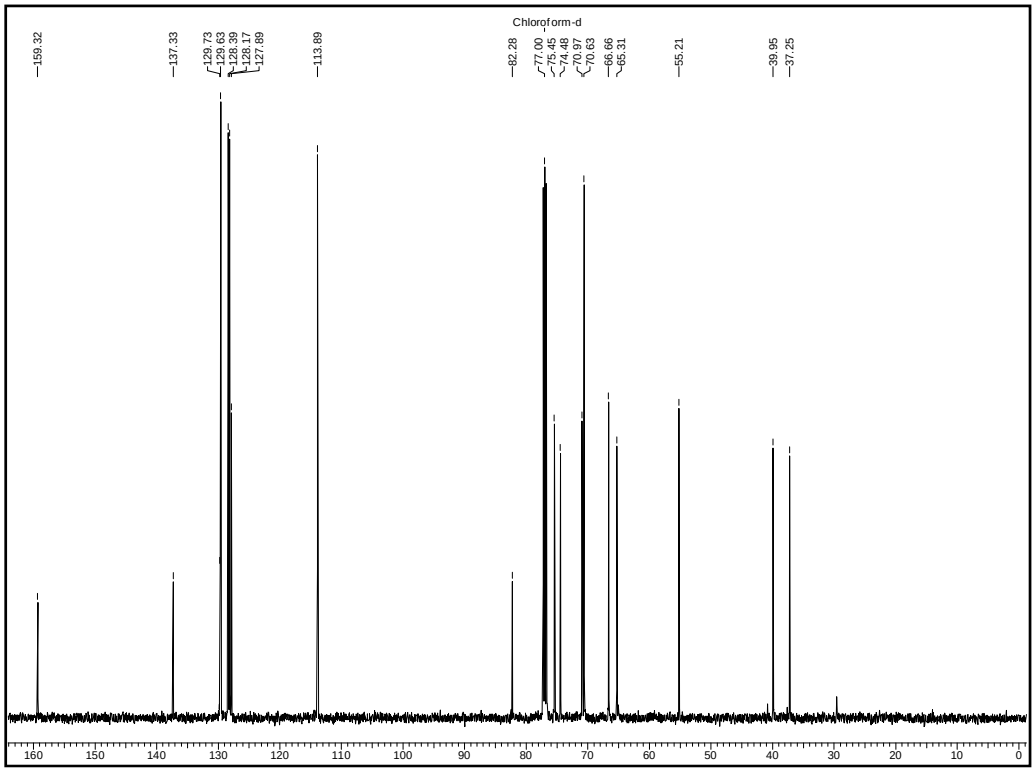
^{1}H NMR Spectrum of 23 in $CDCl_3$



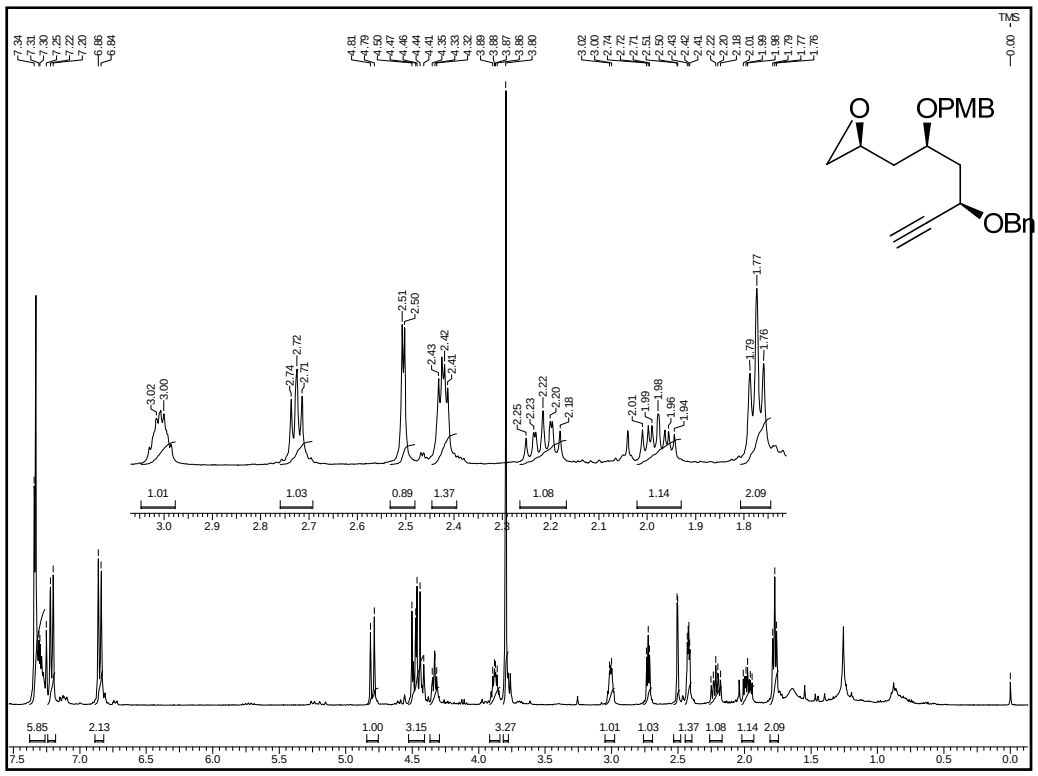
^{13}C NMR Spectrum of 23 in $CDCl_3$



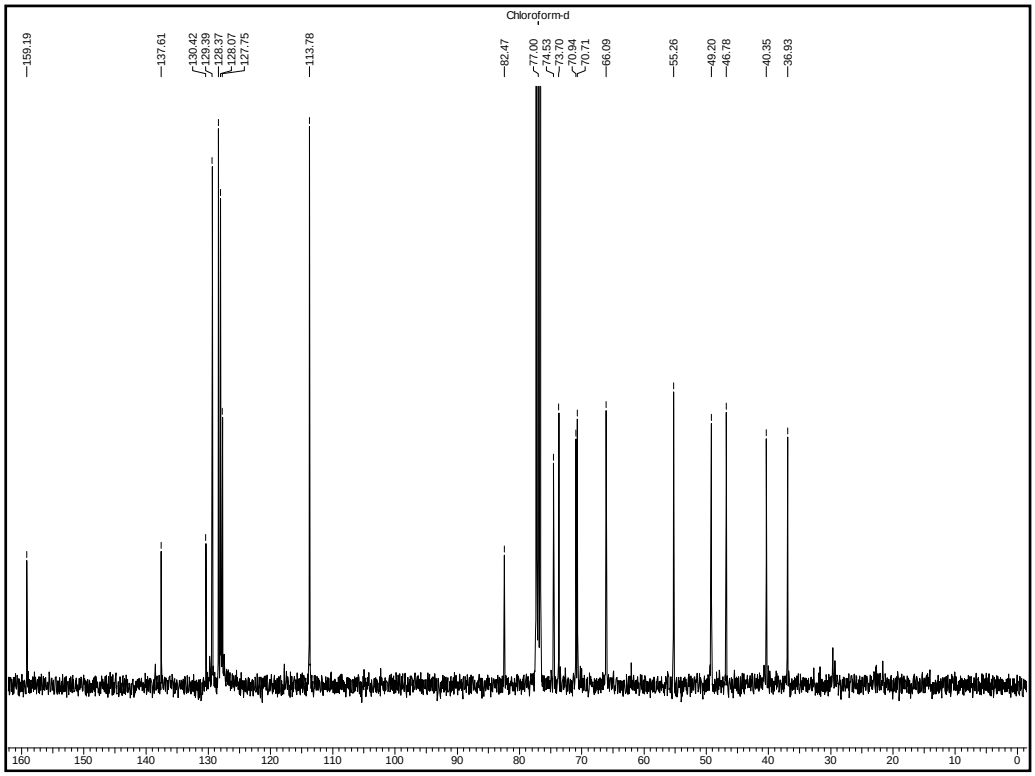
^{1}H NMR Spectrum of 24 in $CDCl_3$



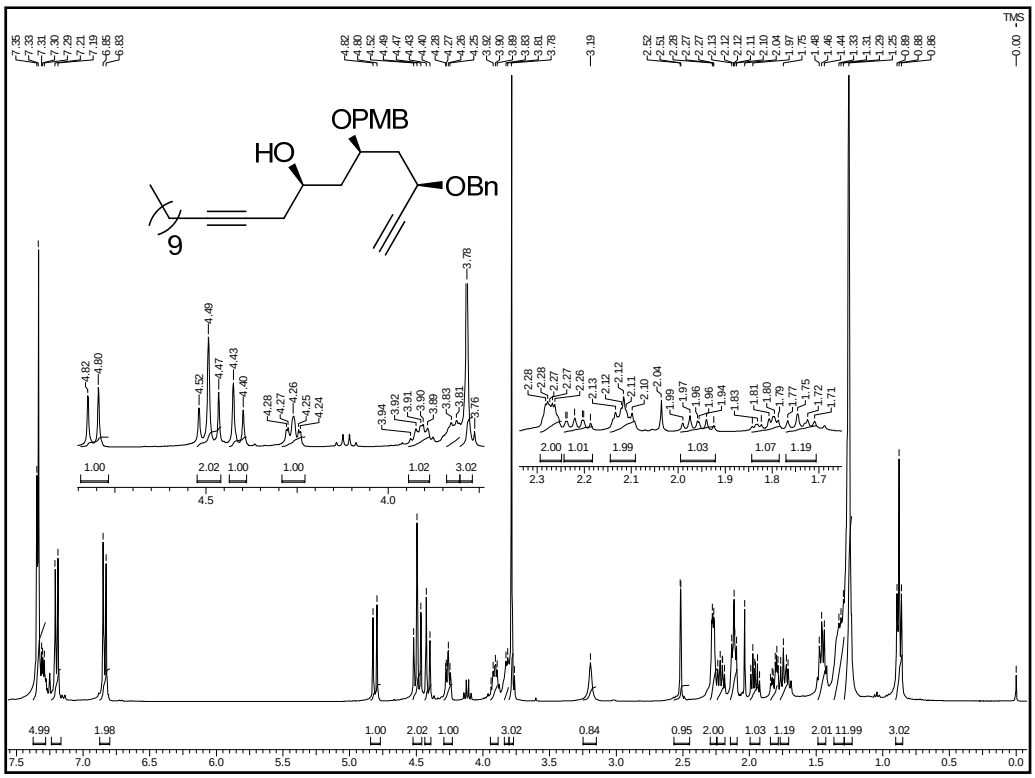
^{13}C NMR Spectrum of 24 in $CDCl_3$



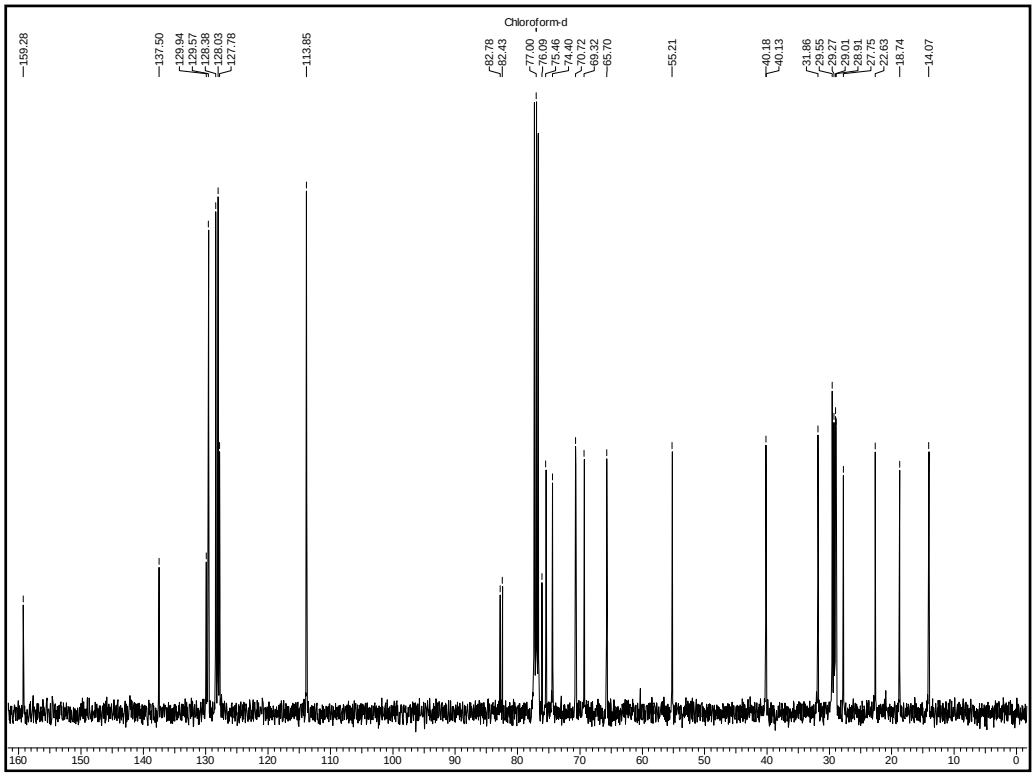
^{1}H NMR Spectrum of 10 in $CDCl_3$



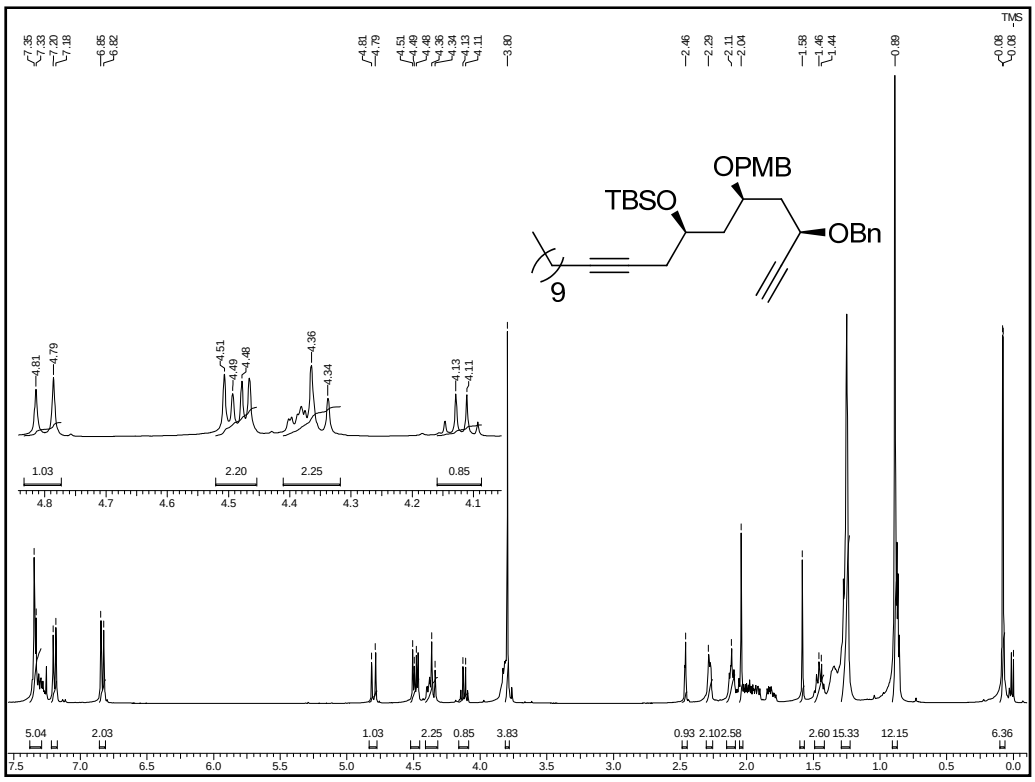
^{13}C NMR Spectrum of 10 in $CDCl_3$



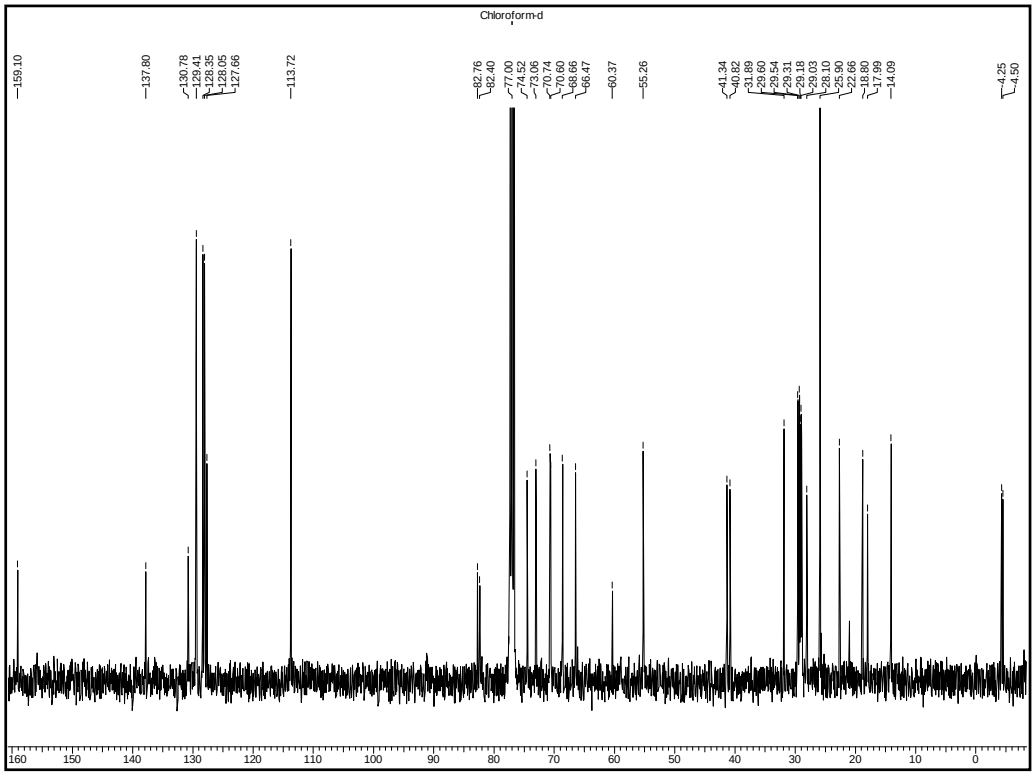
^{1}H NMR Spectrum of 25 in $CDCl_3$



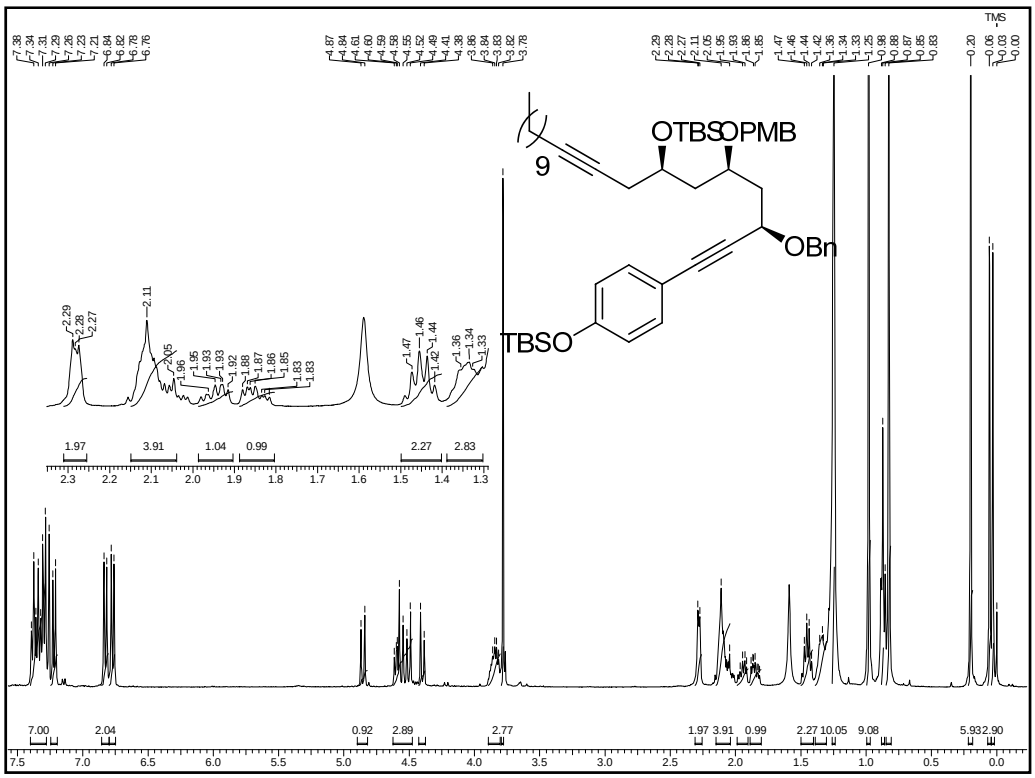
^{13}C NMR Spectrum of 25 in $CDCl_3$



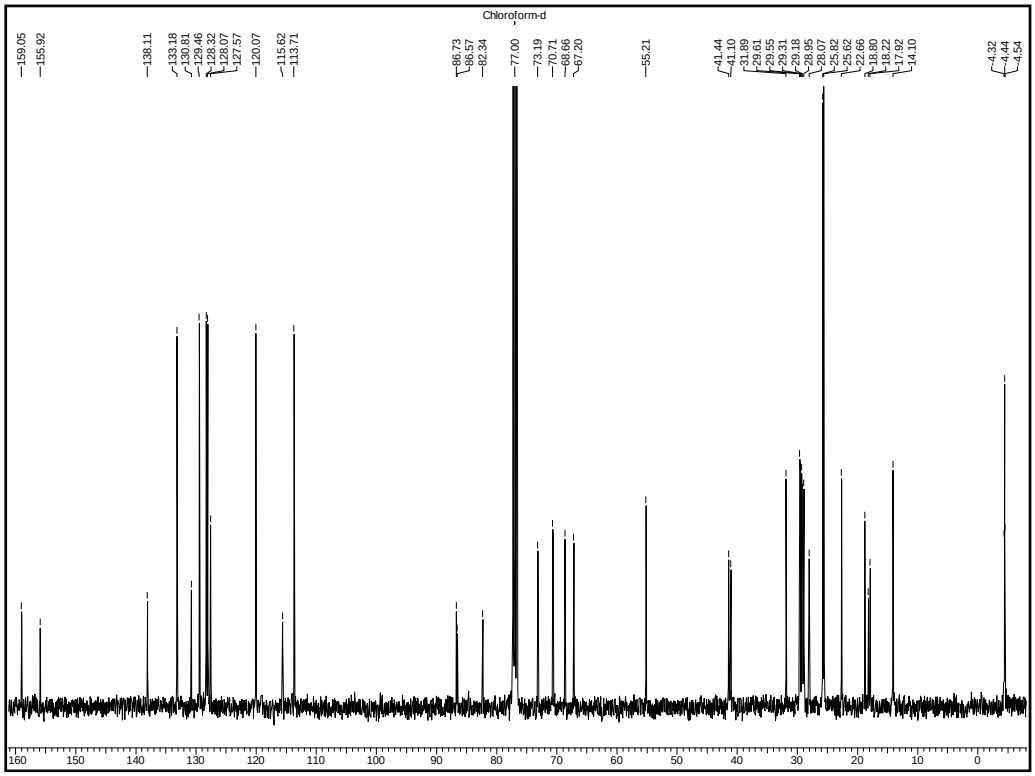
^{1}H NMR Spectrum of 26 in $CDCl_3$



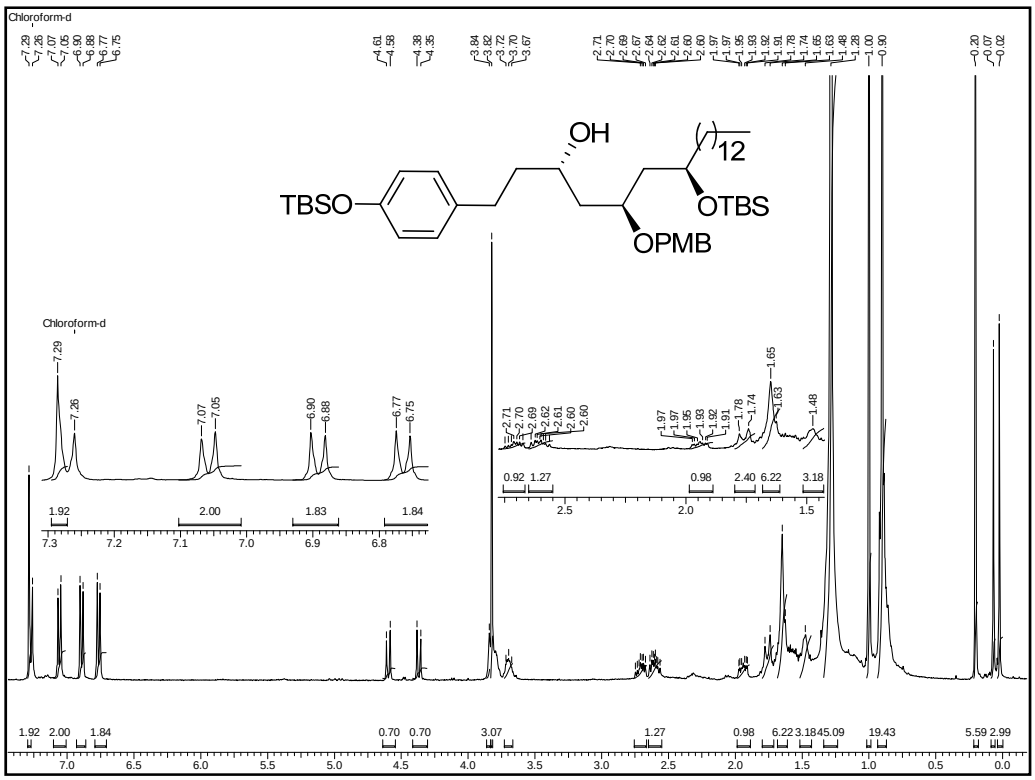
^{13}C NMR Spectrum of 26 in $CDCl_3$



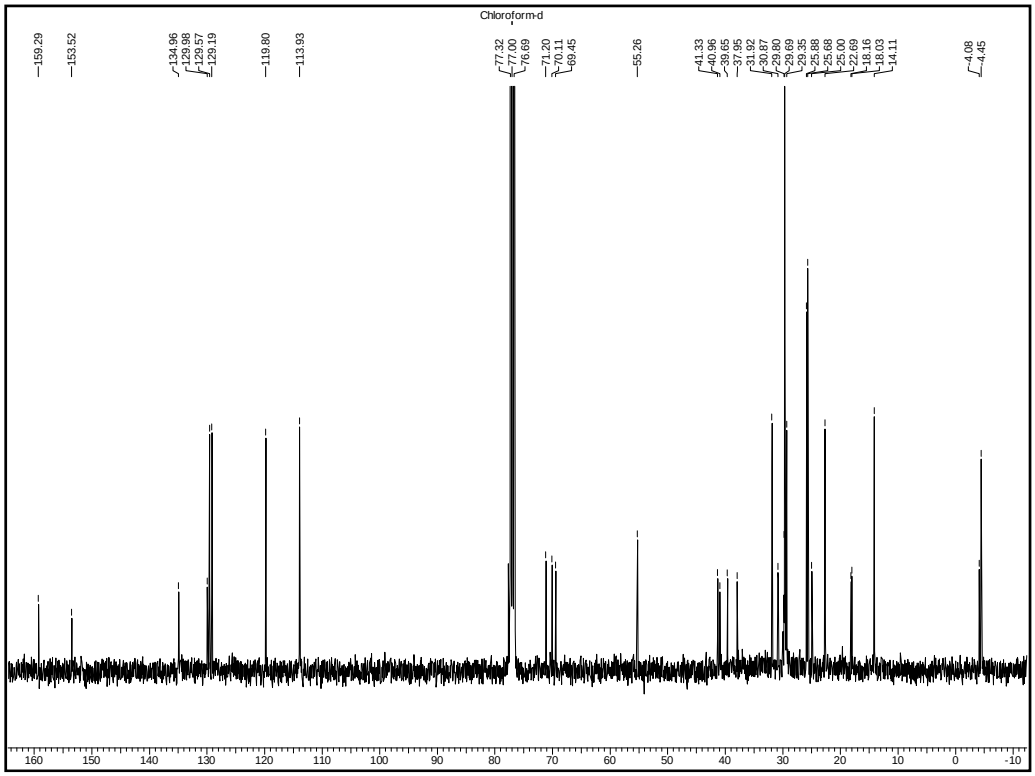
^{1}H NMR Spectrum of 27 in $CDCl_3$



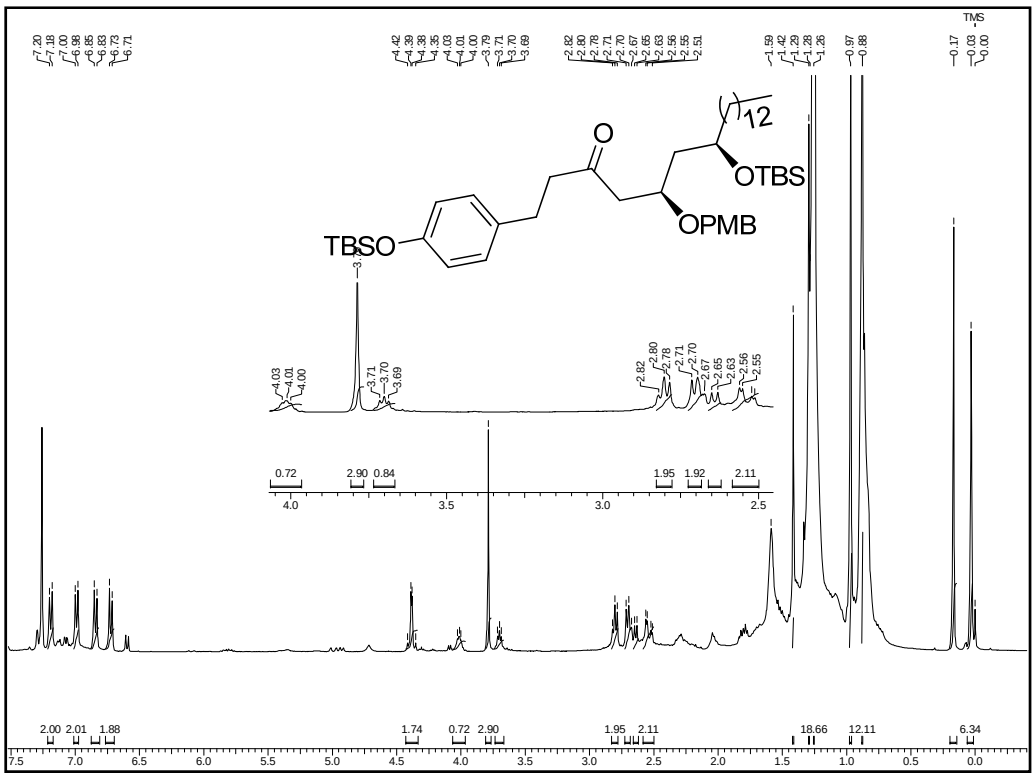
^{13}C NMR Spectrum of 27 in $CDCl_3$



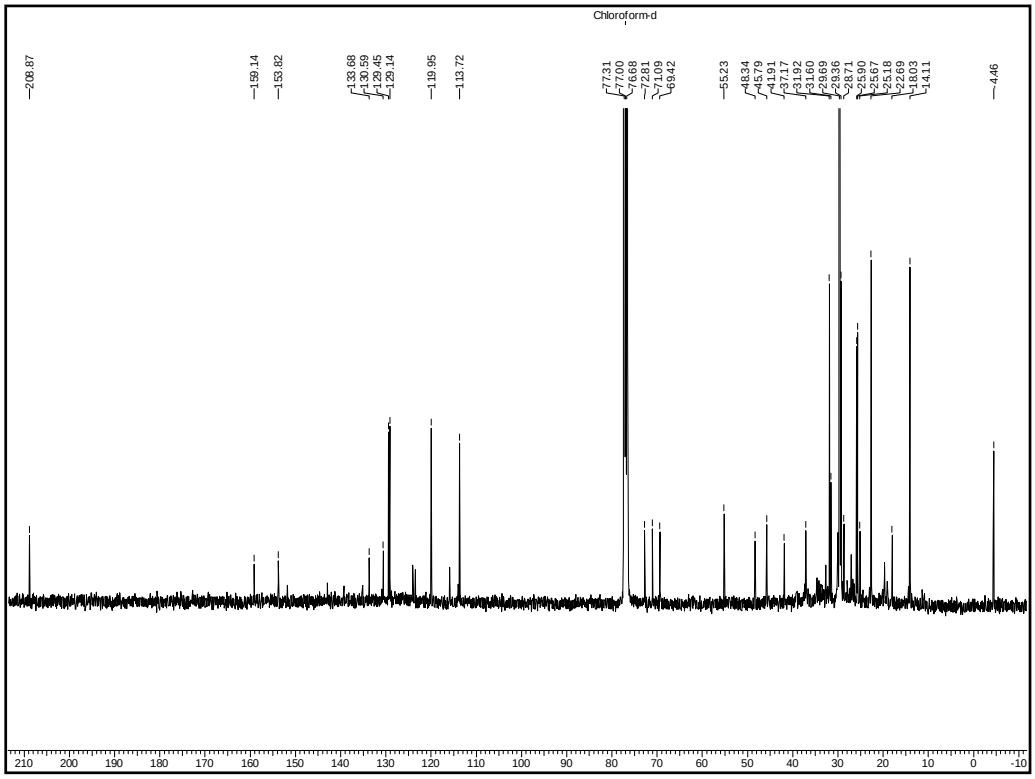
^{1}H NMR Spectrum of 28 in $CDCl_3$



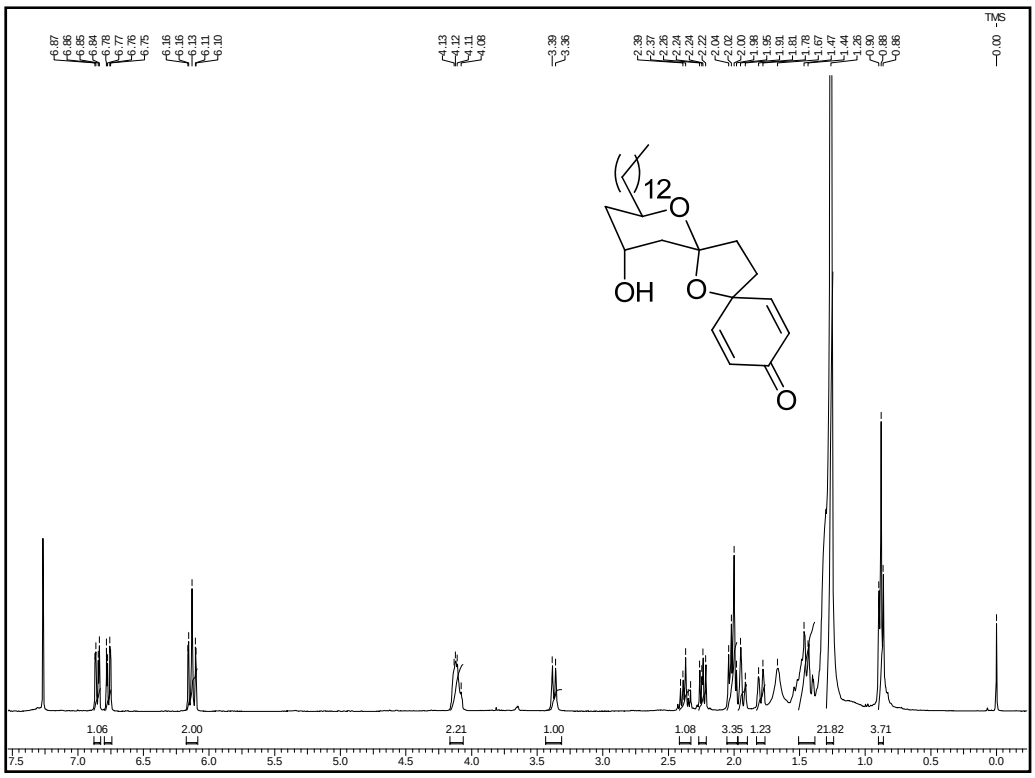
^{13}C NMR Spectrum of 28 in $CDCl_3$



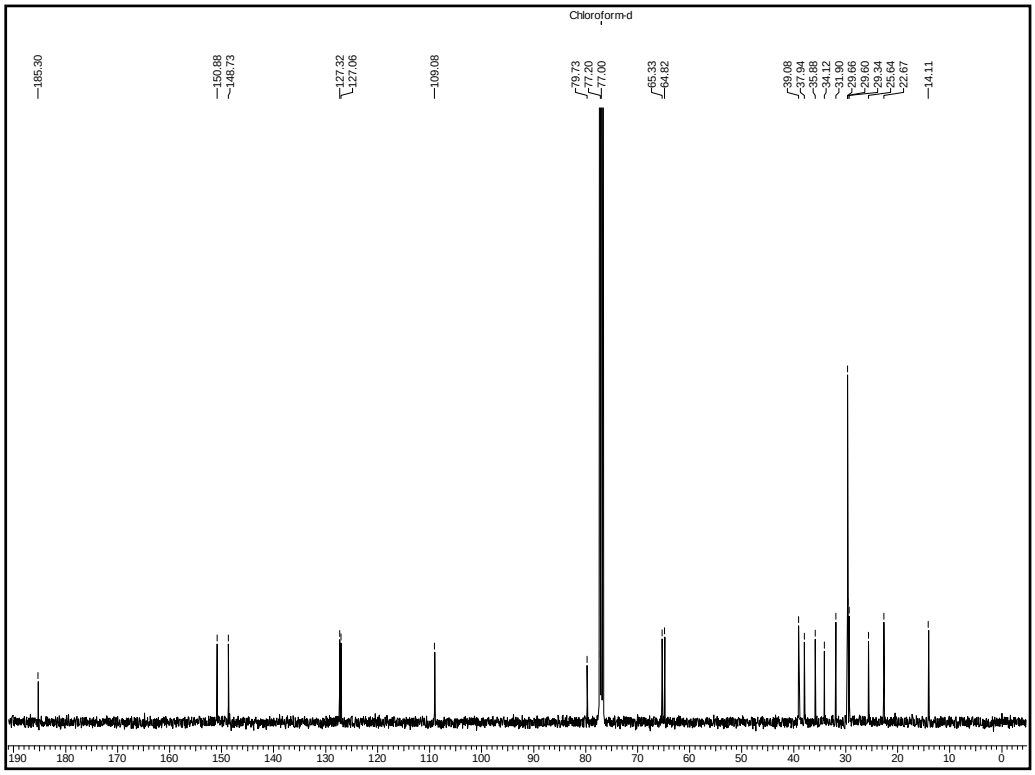
^{1}H NMR Spectrum of 29 in $CDCl_3$



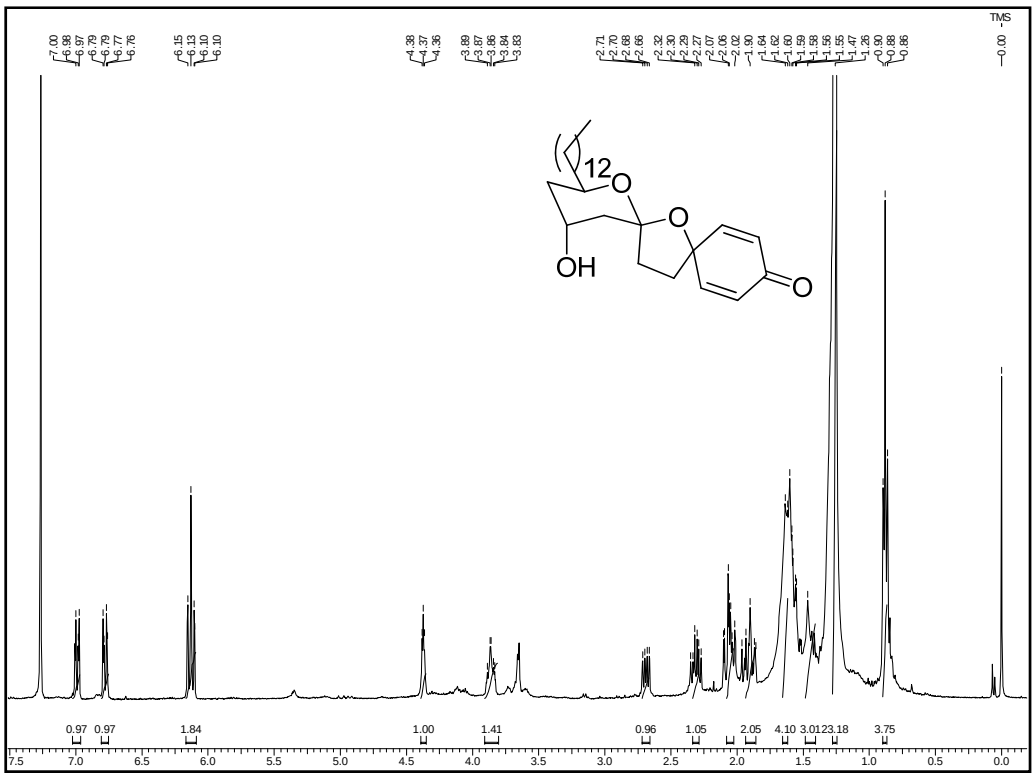
^{13}C NMR Spectrum of 29 in $CDCl_3$



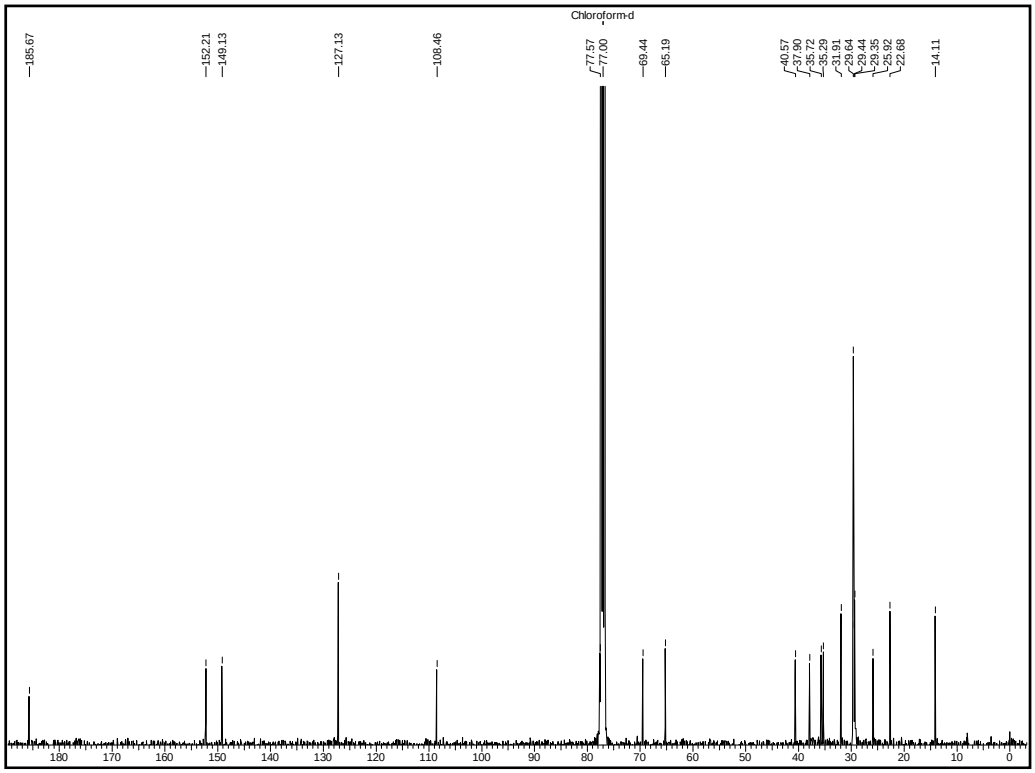
^{1}H NMR Spectrum of 1 in $CDCl_3$



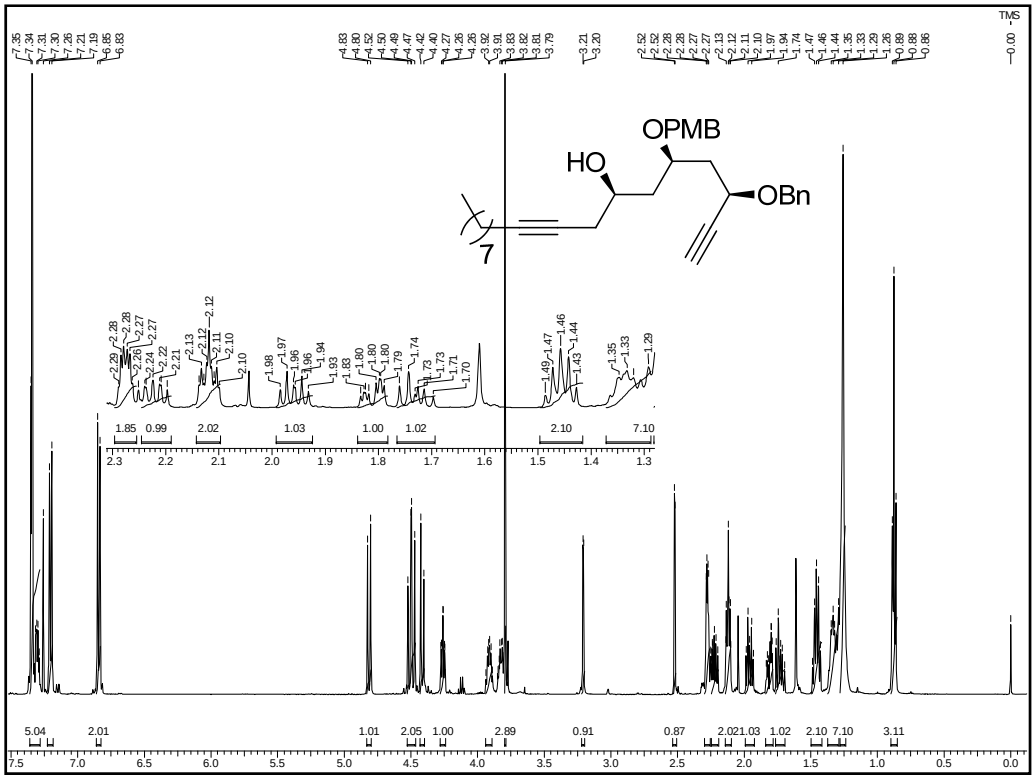
^{13}C NMR Spectrum of aculeatin A (1) in $CDCl_3$



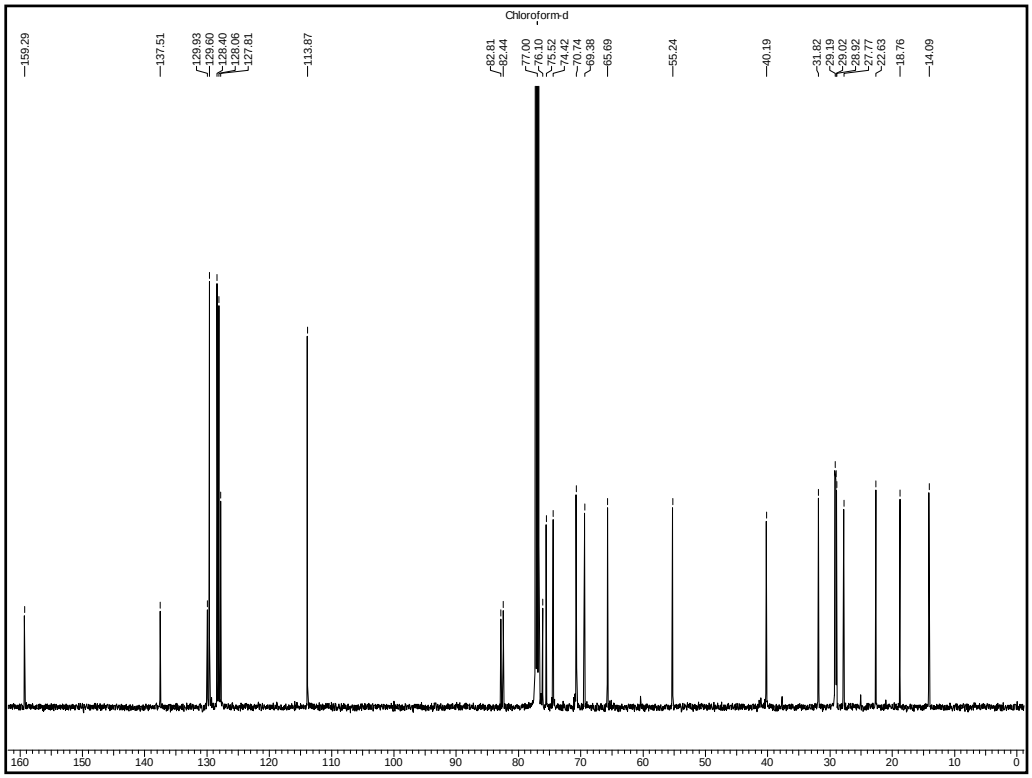
^{1}H NMR Spectrum of aculeatin B (2) in $CDCl_3$



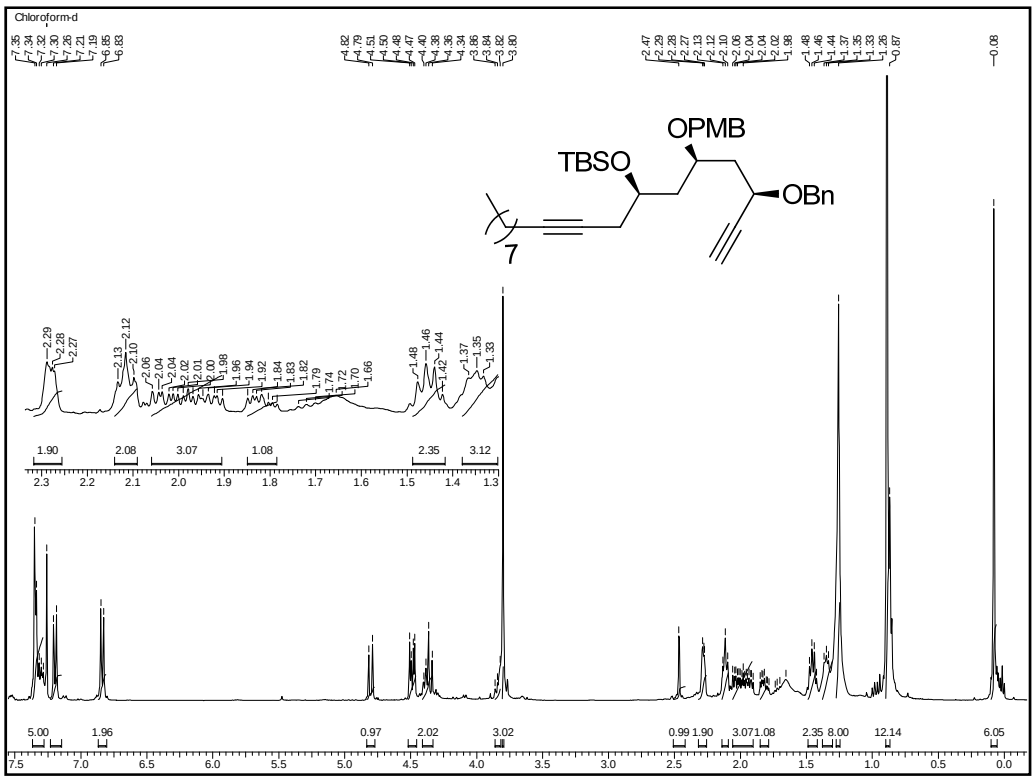
^{13}C NMR Spectrum of 2 in $CDCl_3$



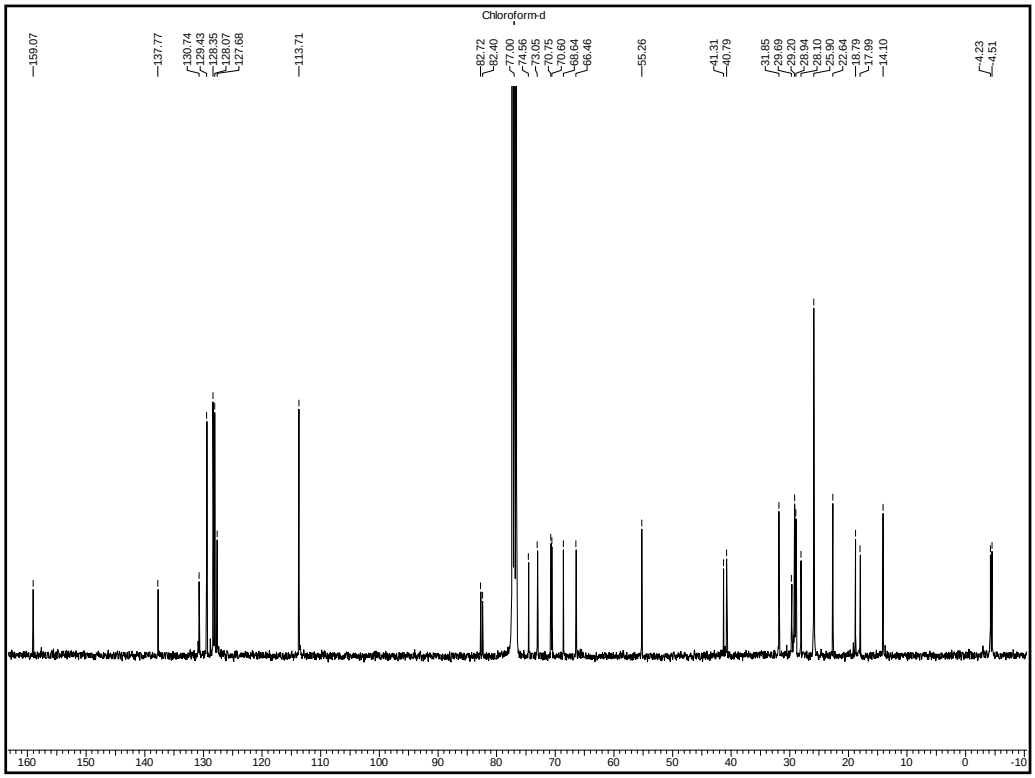
^{1}H NMR Spectrum of 30 in $CDCl_3$



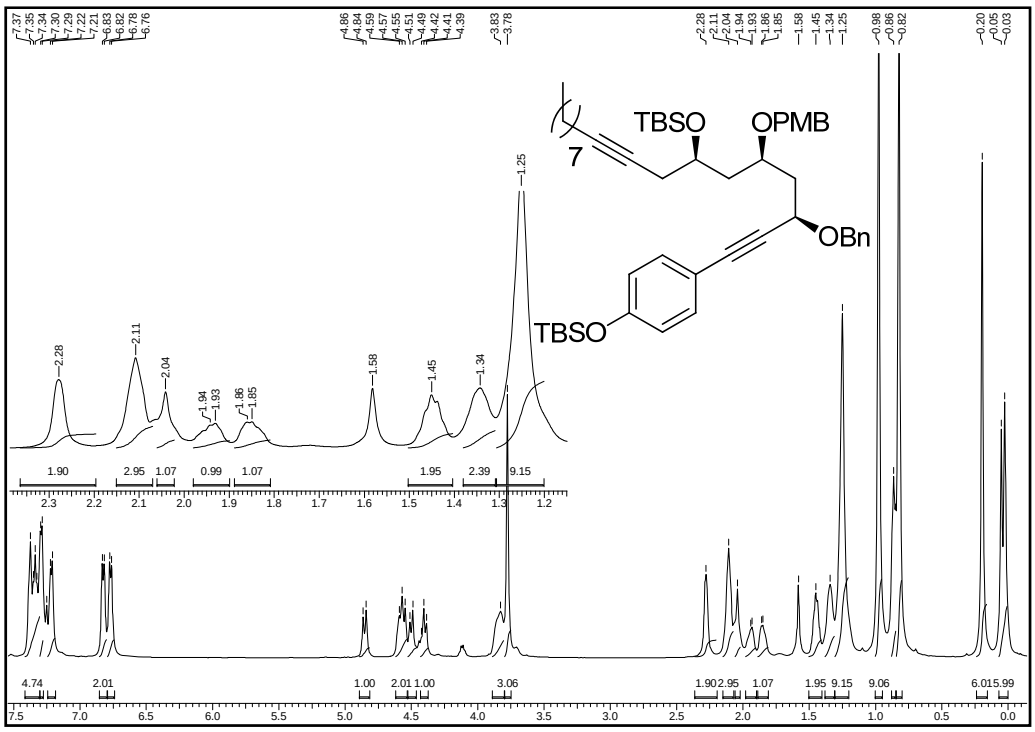
^{13}C NMR Spectrum of 30 in $CDCl_3$



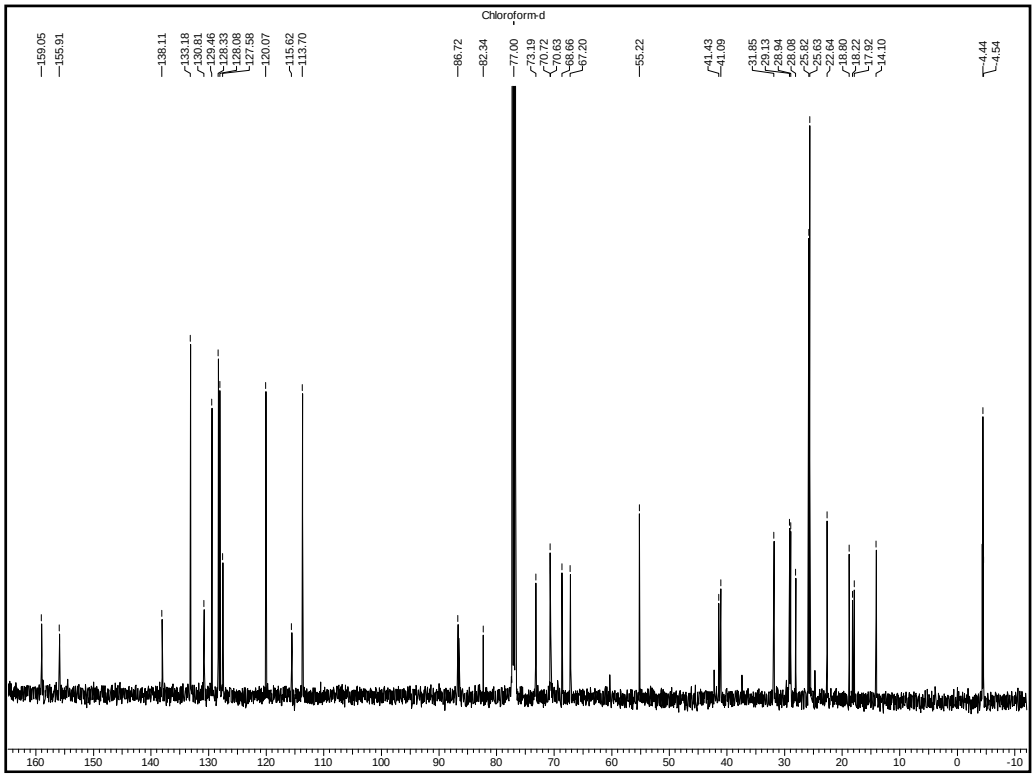
^{1}H NMR Spectrum of 31 in $CDCl_3$



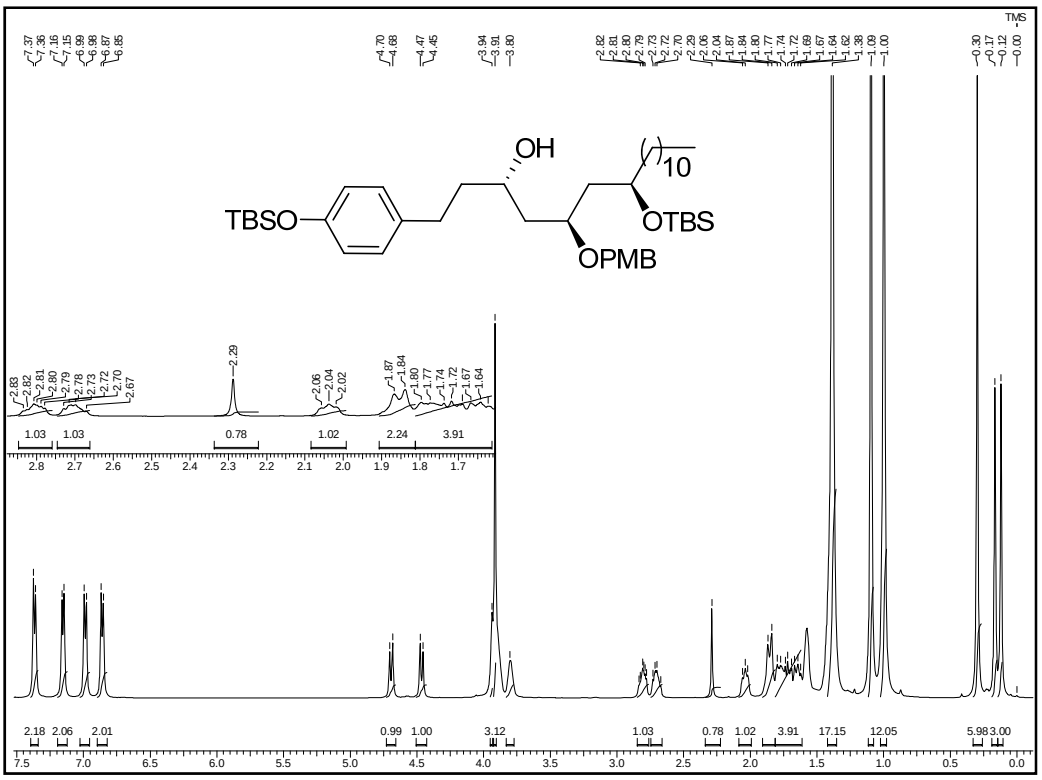
^{13}C NMR Spectrum of 31 in $CDCl_3$



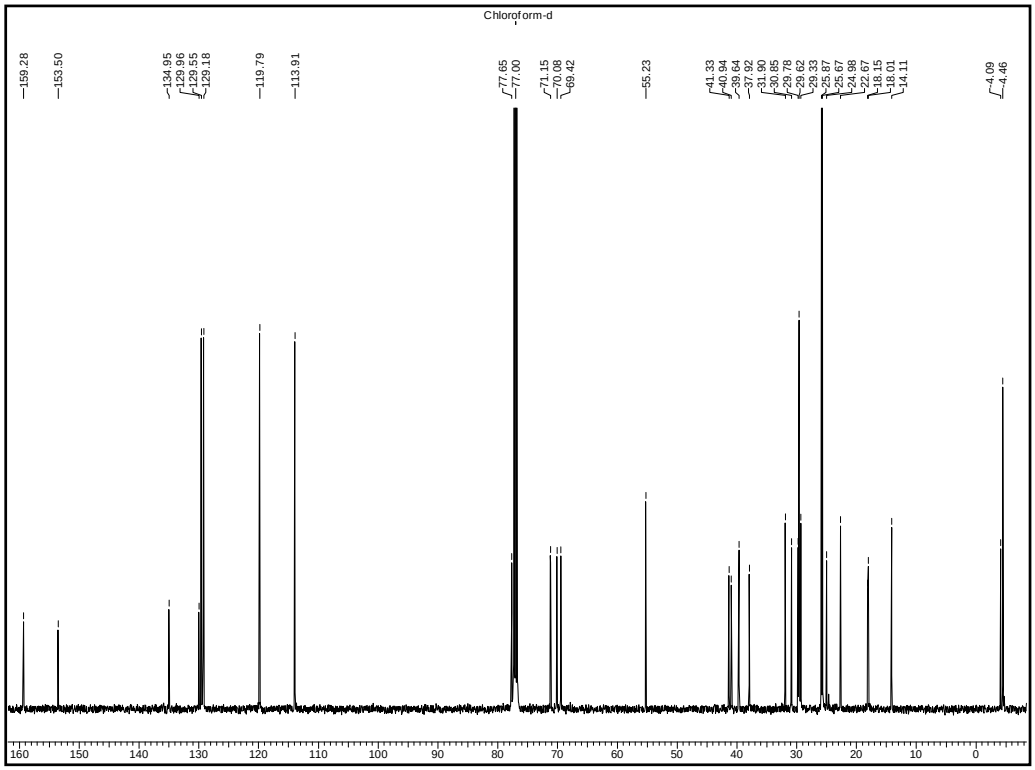
^{1}H NMR Spectrum of 32 in $CDCl_3$



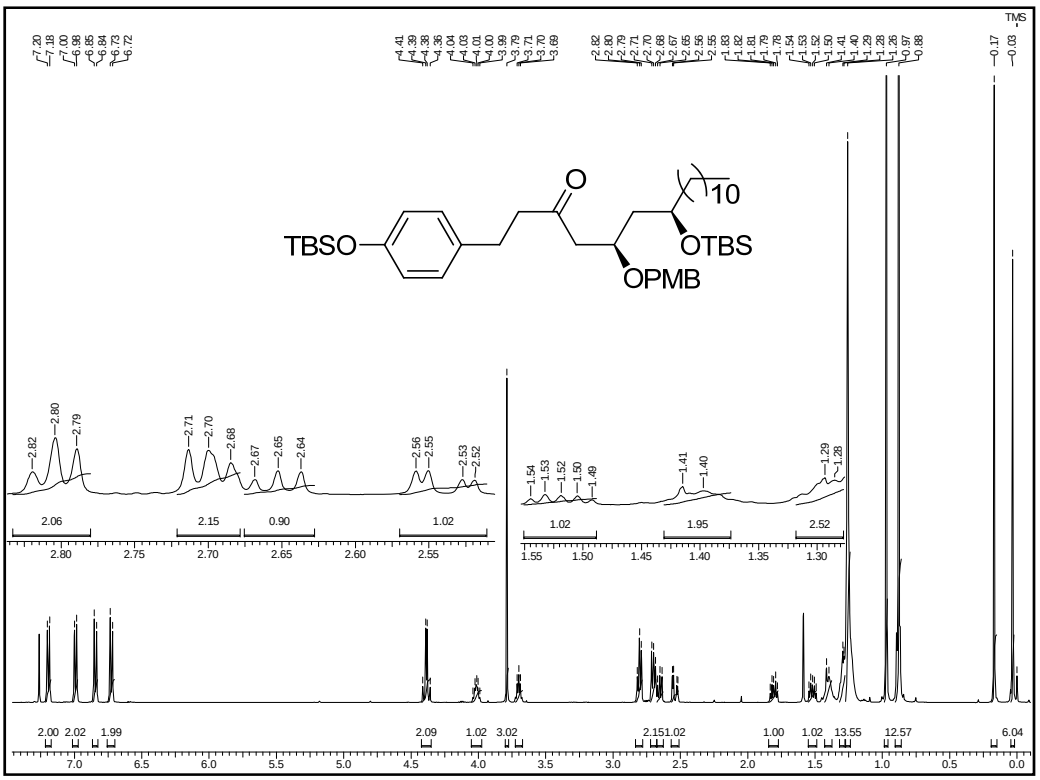
^{13}C NMR Spectrum of 32 in $CDCl_3$



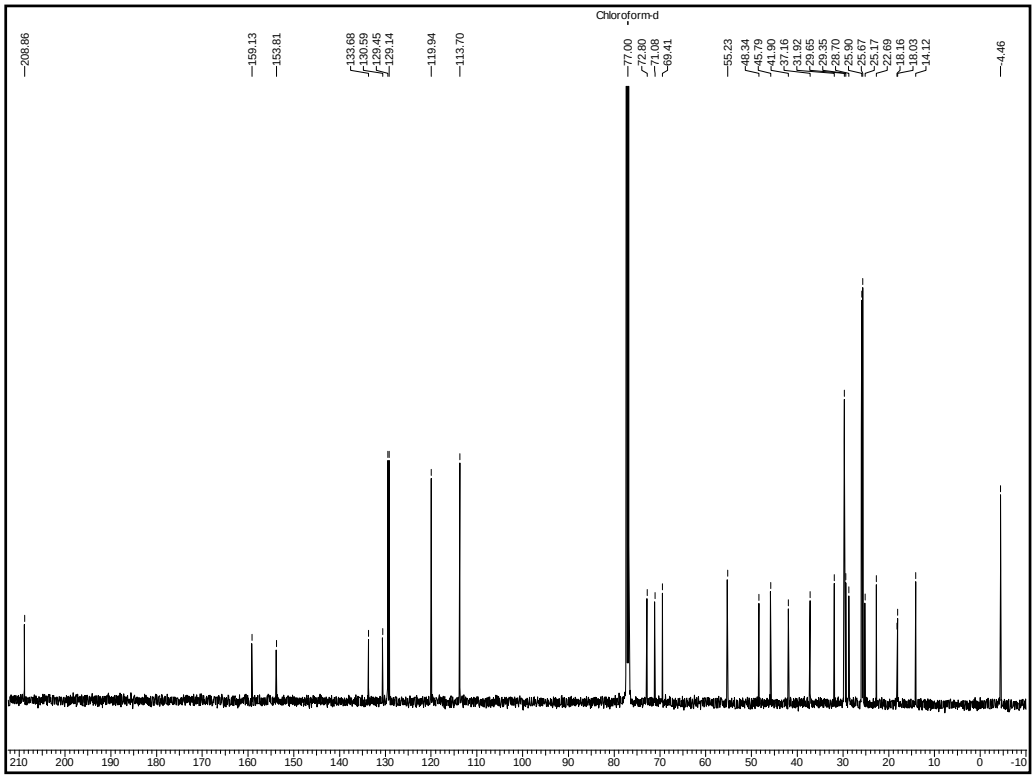
^{1}H NMR Spectrum of 33 in $CDCl_3$



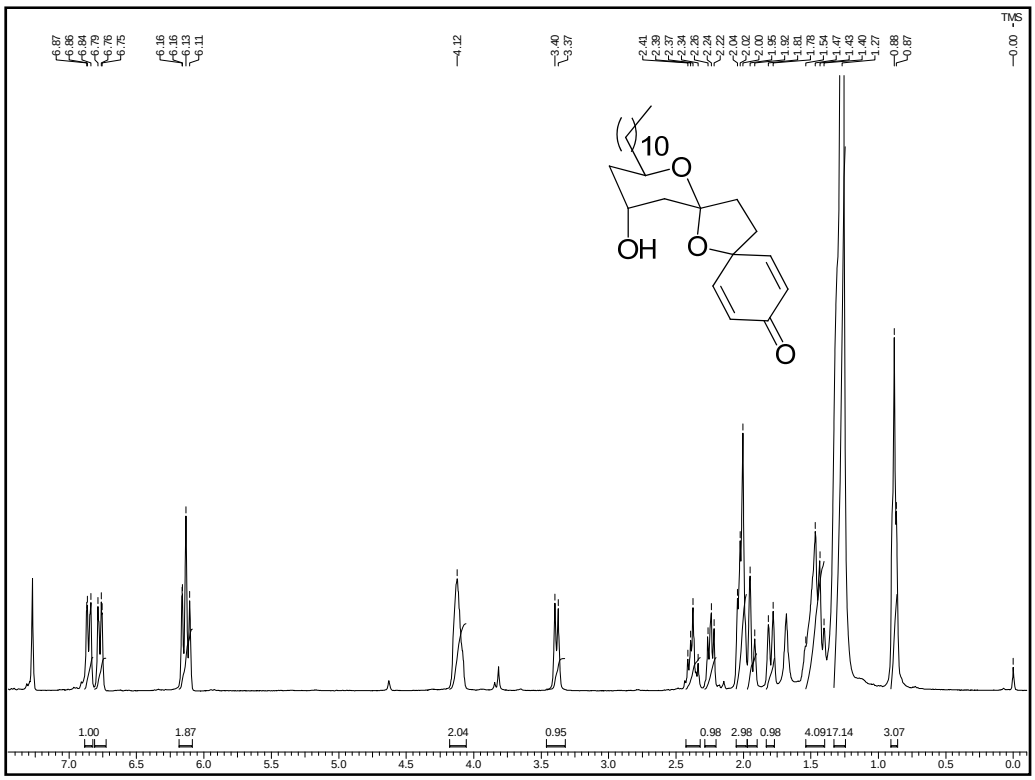
^{13}C NMR Spectrum of 33 in $CDCl_3$



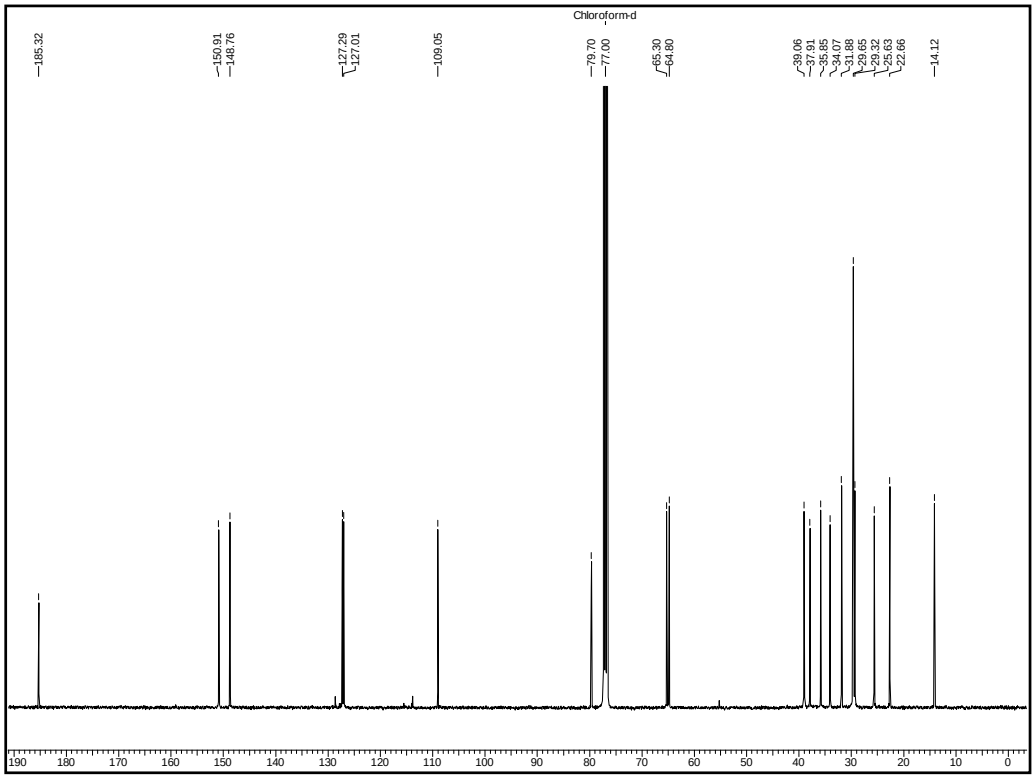
^{1}H NMR Spectrum of 34 in $CDCl_3$



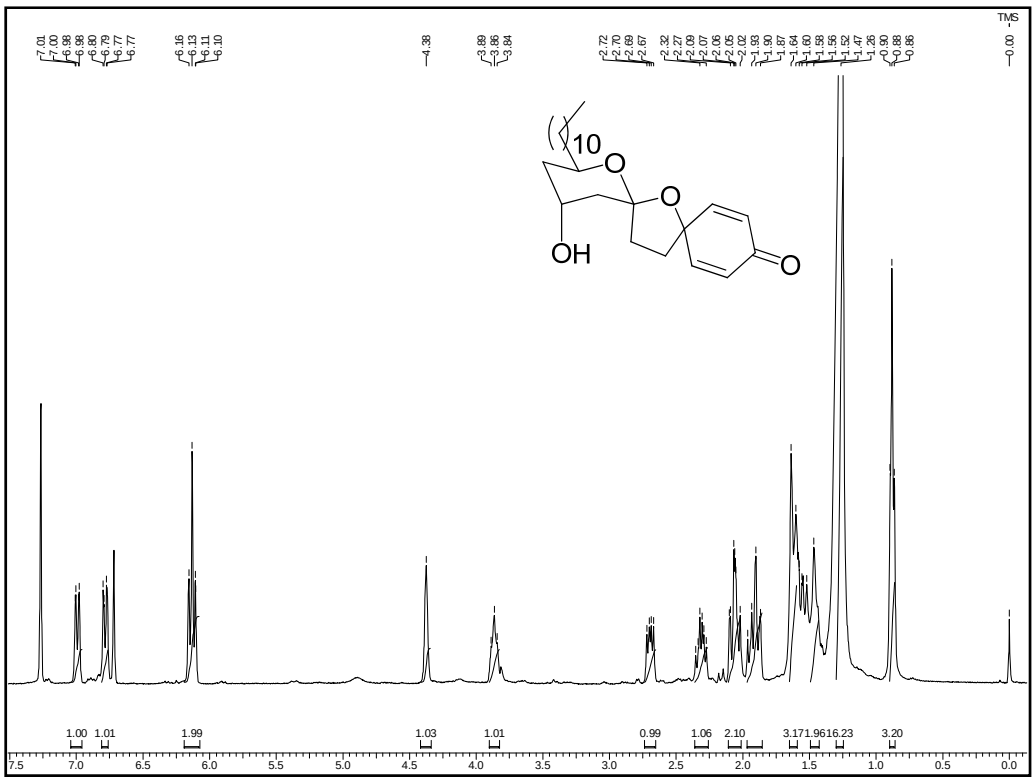
^{13}C NMR Spectrum of 34 in $CDCl_3$



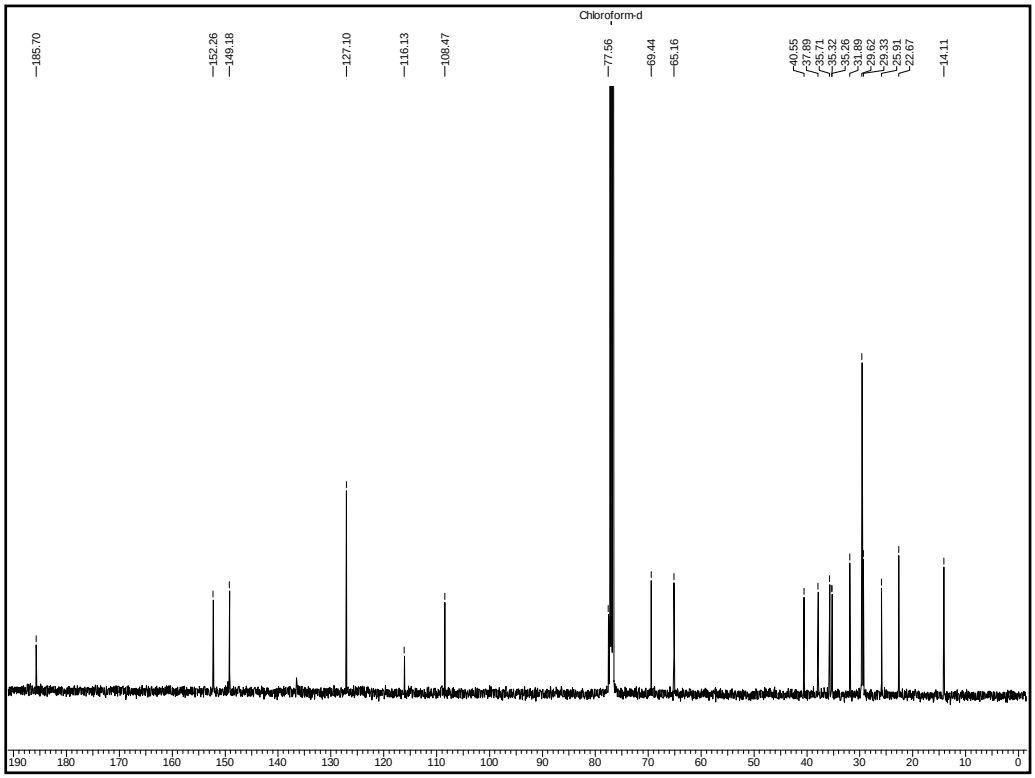
^{1}H NMR Spectrum of aculeatin F (6) in $CDCl_3$



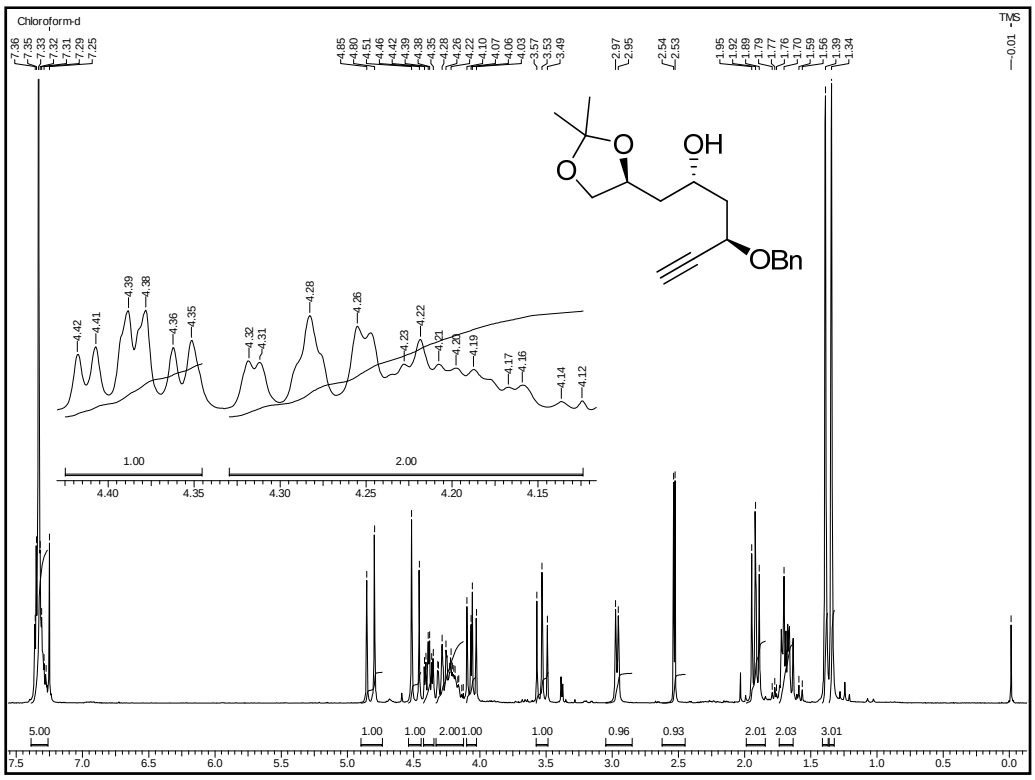
^{13}C NMR Spectrum of 6-*epi*-aculeatin F (6) in $CDCl_3$



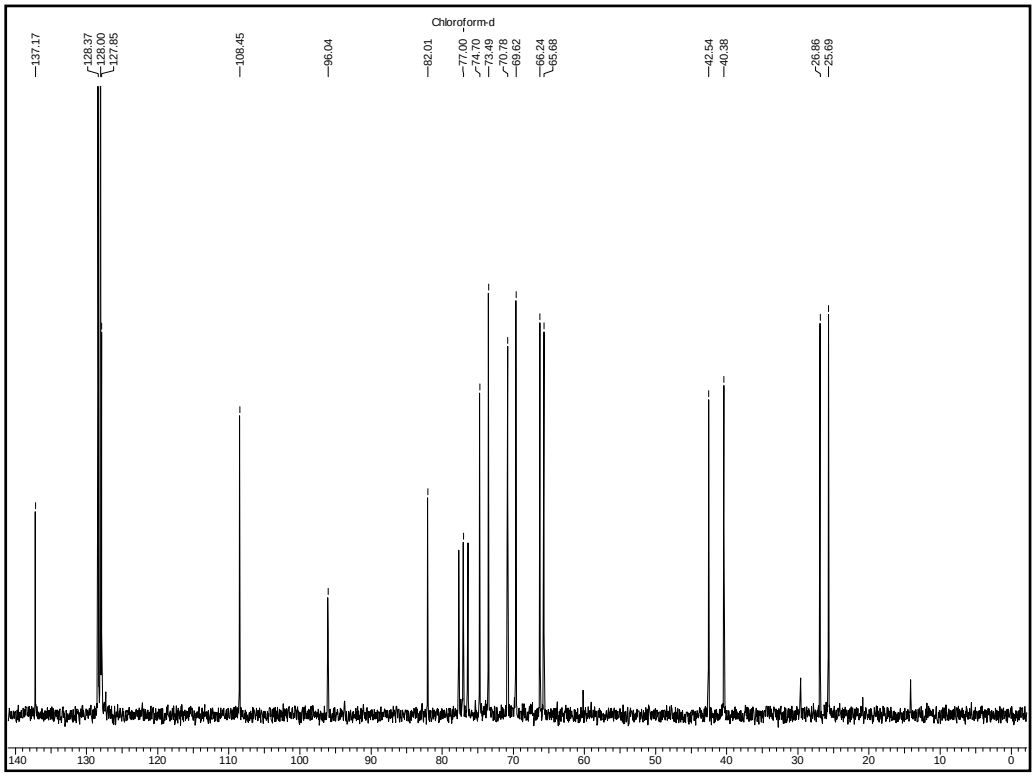
^{1}H NMR Spectrum of 6-*epi*-aculeatin F in $CDCl_3$



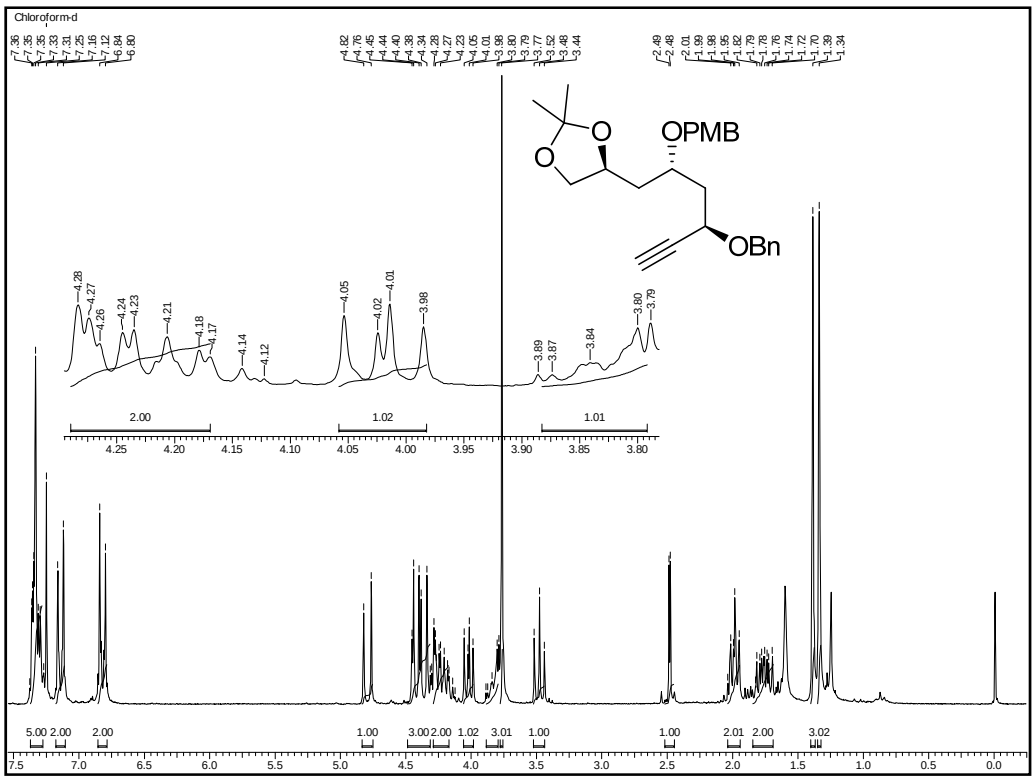
^{13}C NMR Spectrum of 6-*epi*-aculeatin F in $CDCl_3$



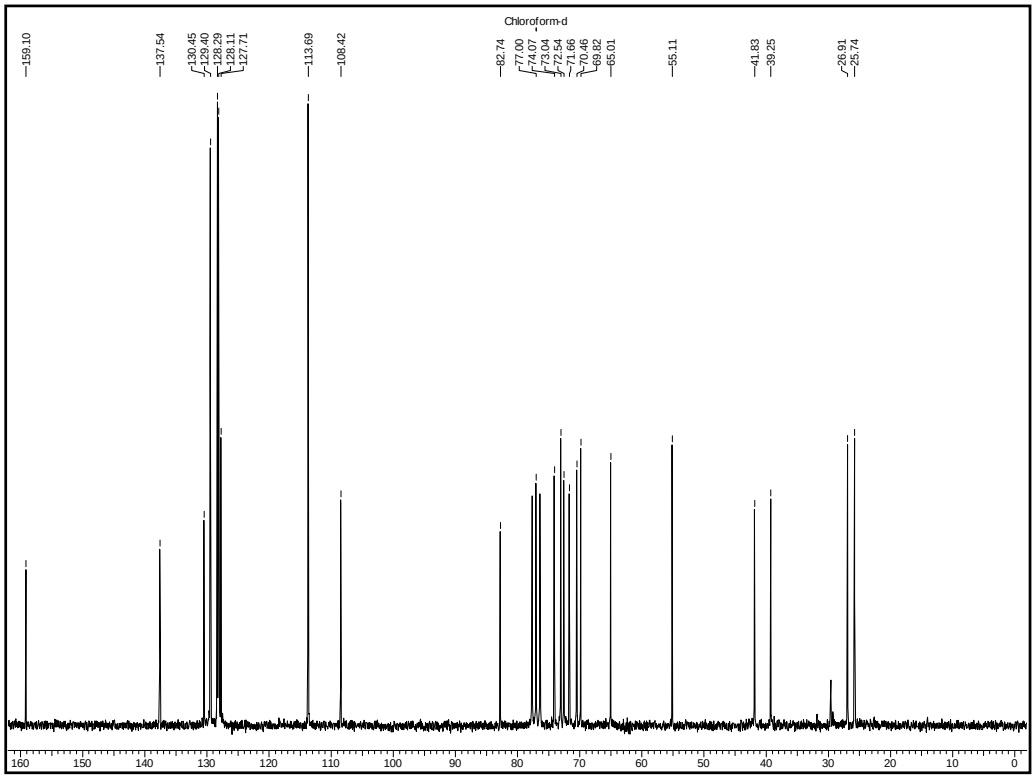
^{1}H NMR Spectrum of 15 in $CDCl_3$



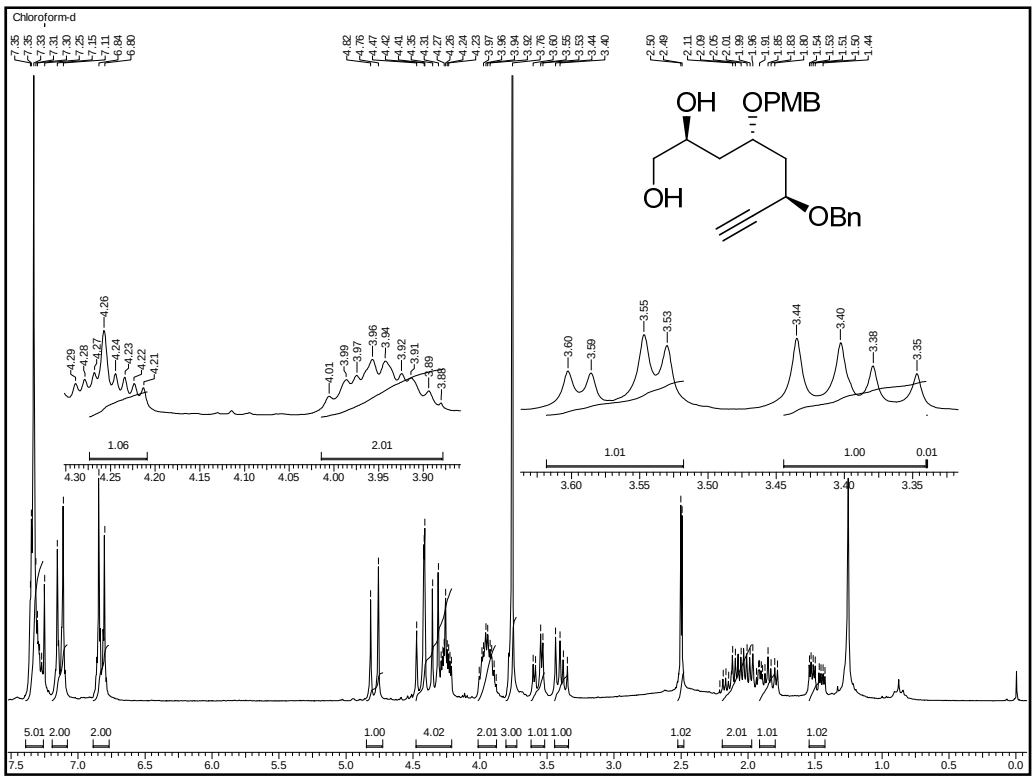
^{13}C NMR Spectrum of 15 in $CDCl_3$



^{1}H NMR Spectrum of 35 in $CDCl_3$



^{13}C NMR Spectrum of 35 in $CDCl_3$



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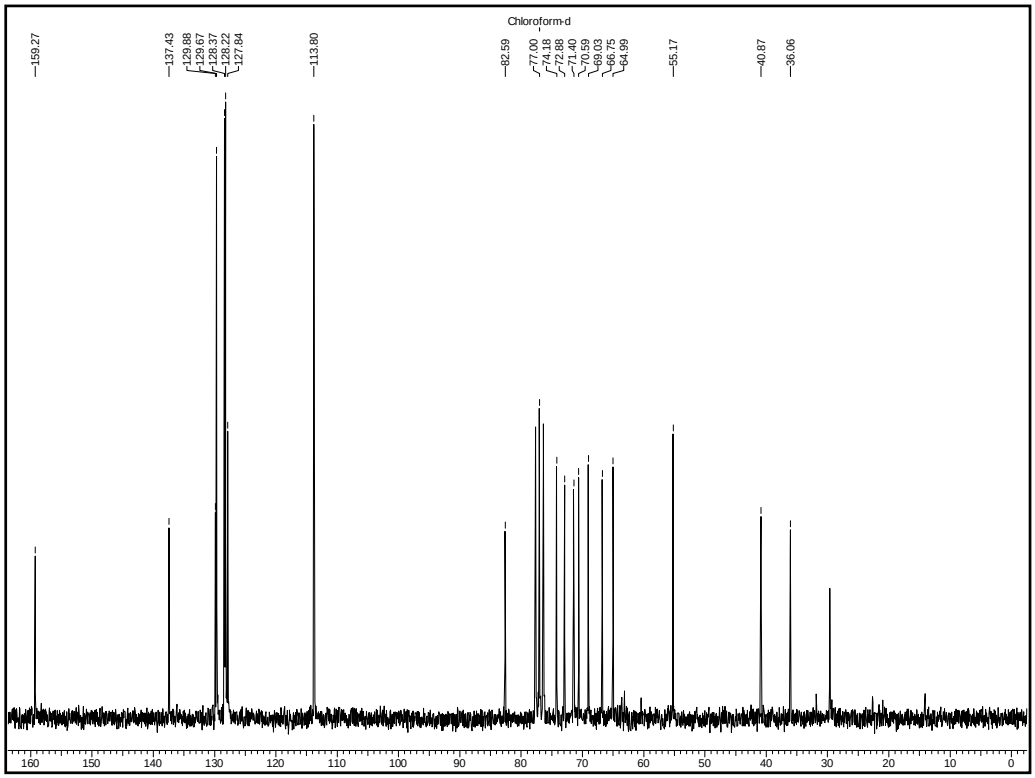
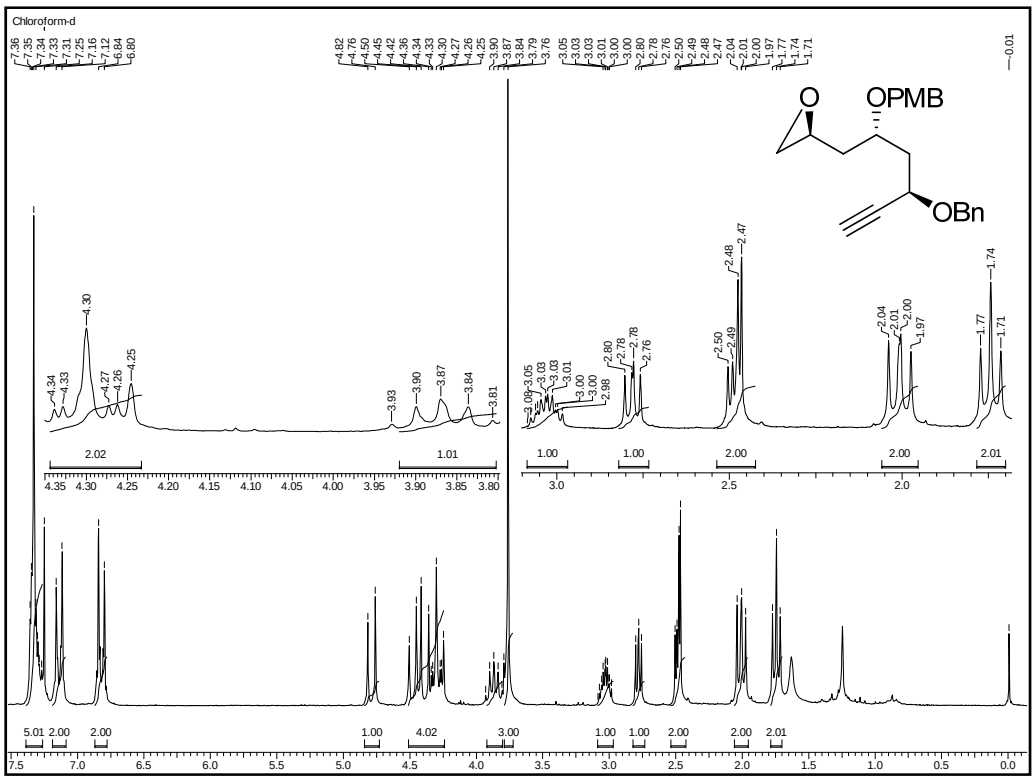
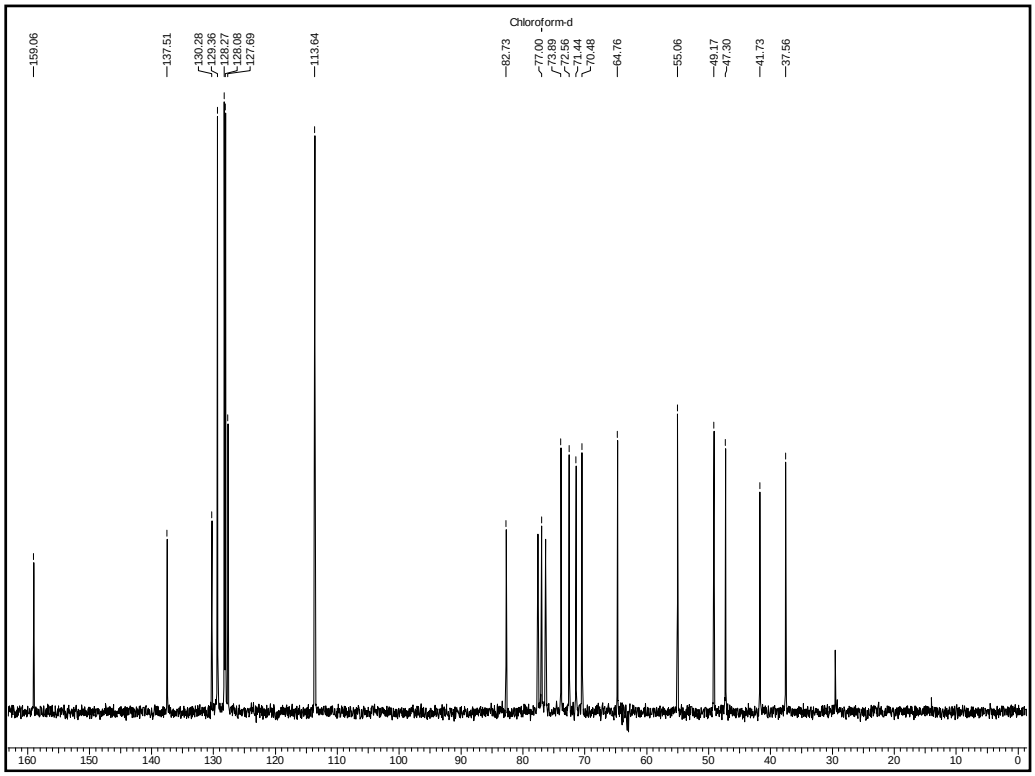


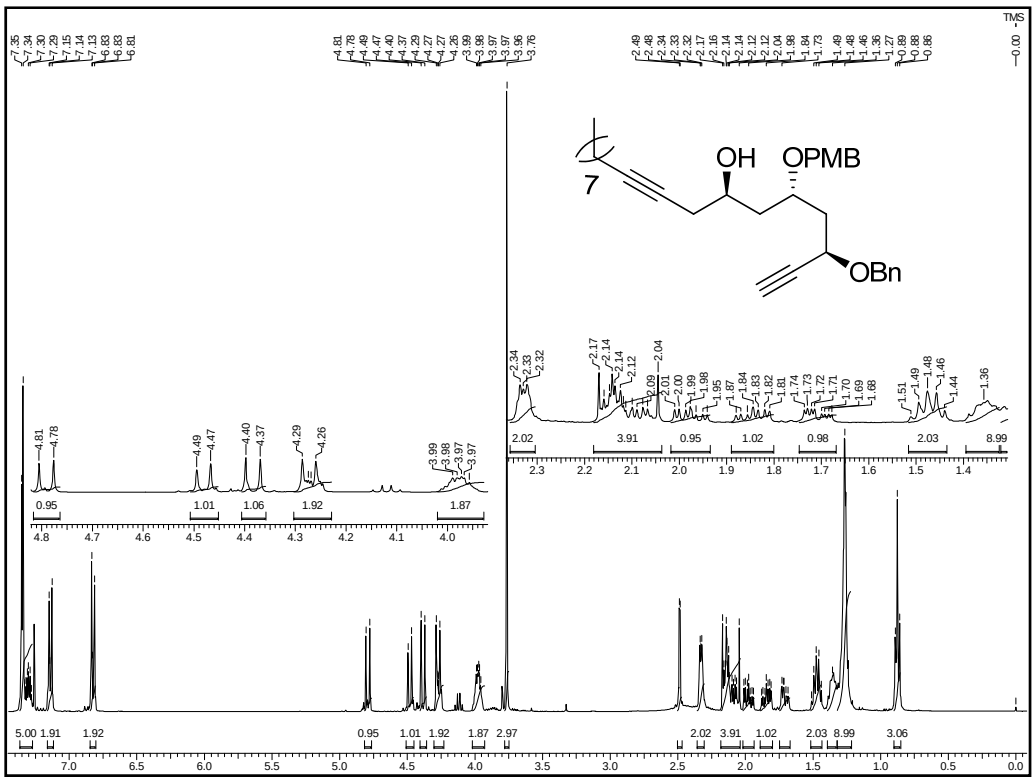
^{13}C NMR Spectrum of 36 in $CDCl_3$



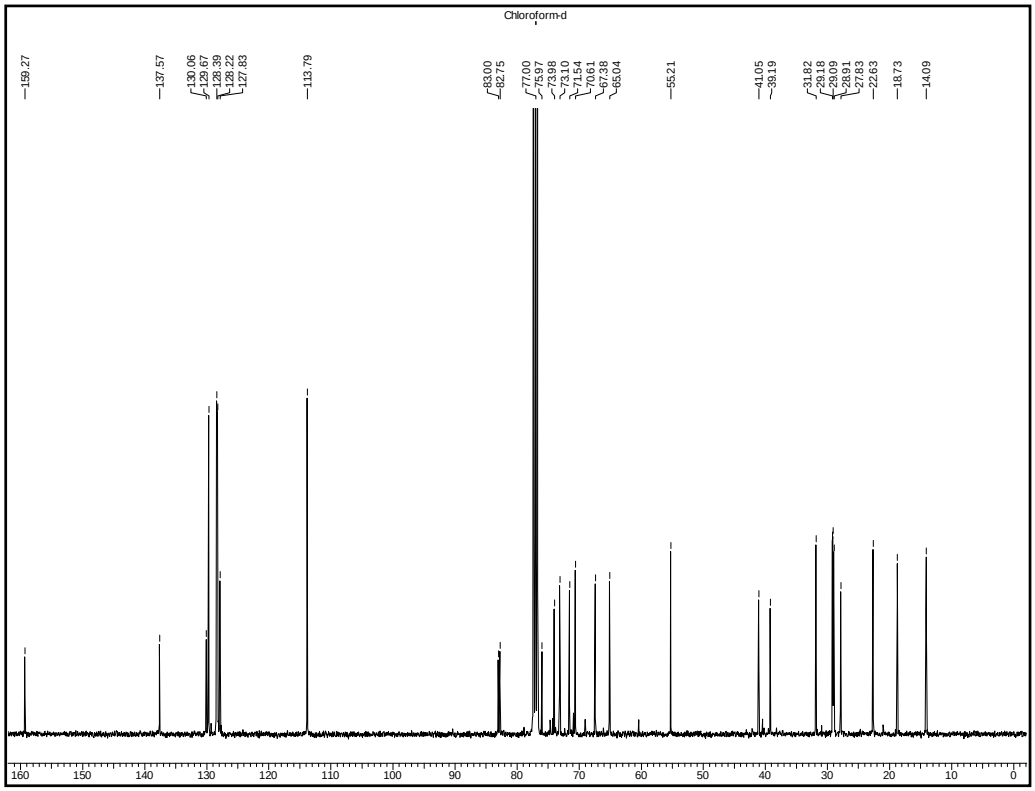
^{1}H NMR Spectrum of 11 in $CDCl_3$



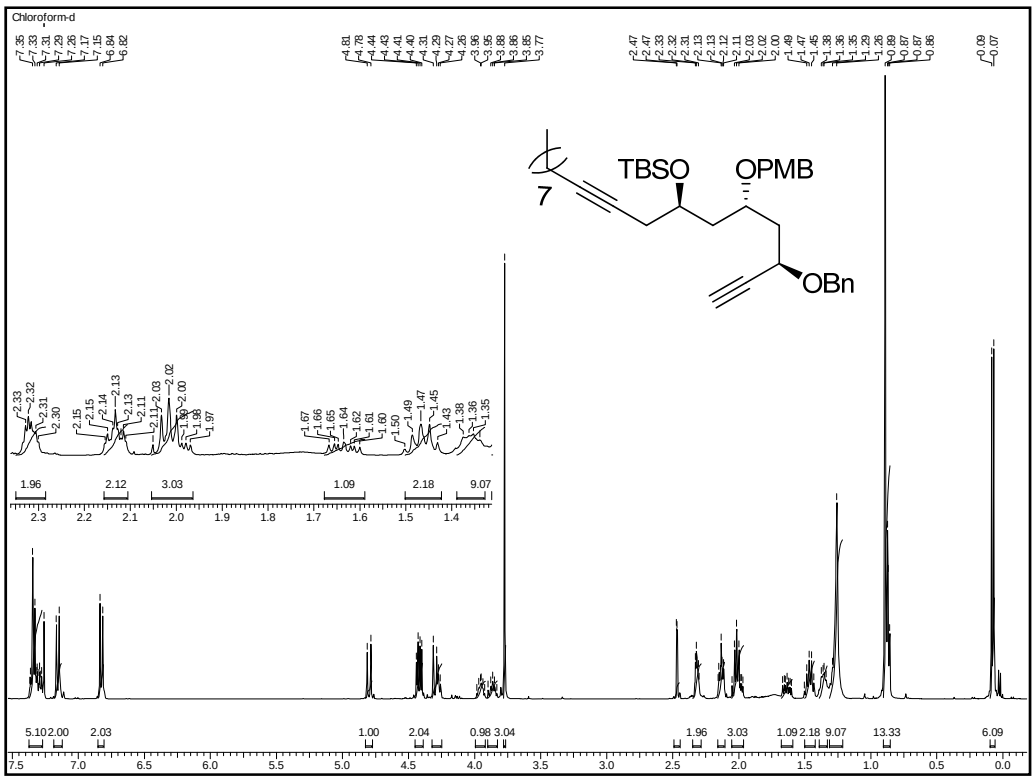
^{13}C NMR Spectrum of 11 in $CDCl_3$



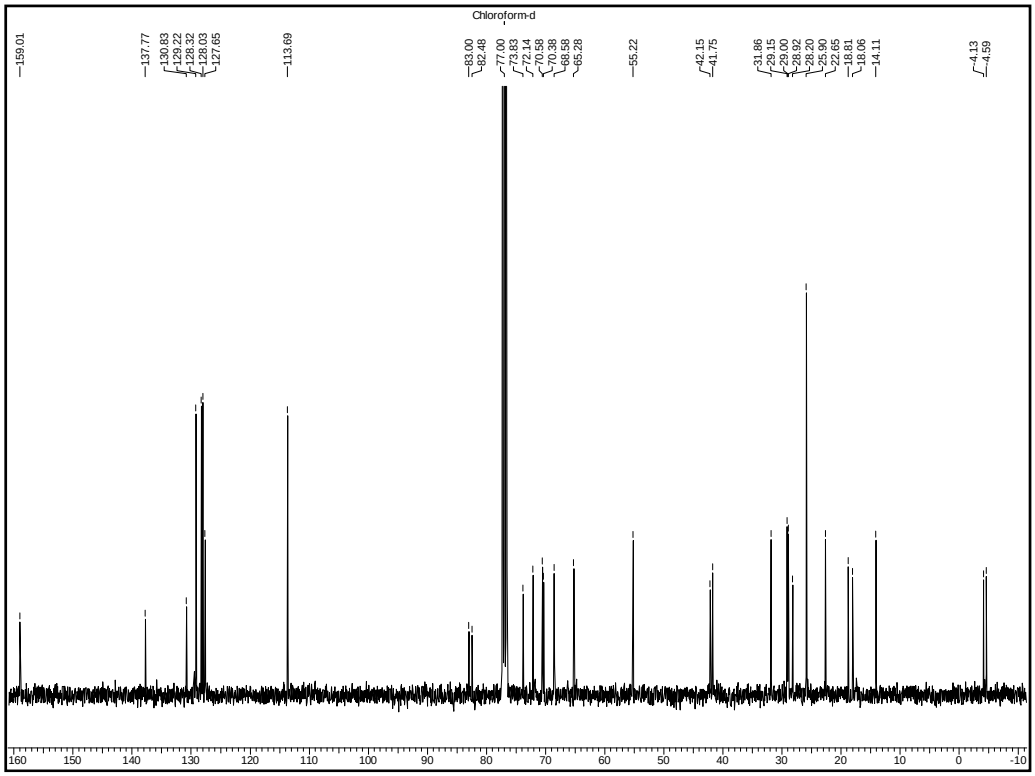
^{1}H NMR Spectrum of 37 in $CDCl_3$



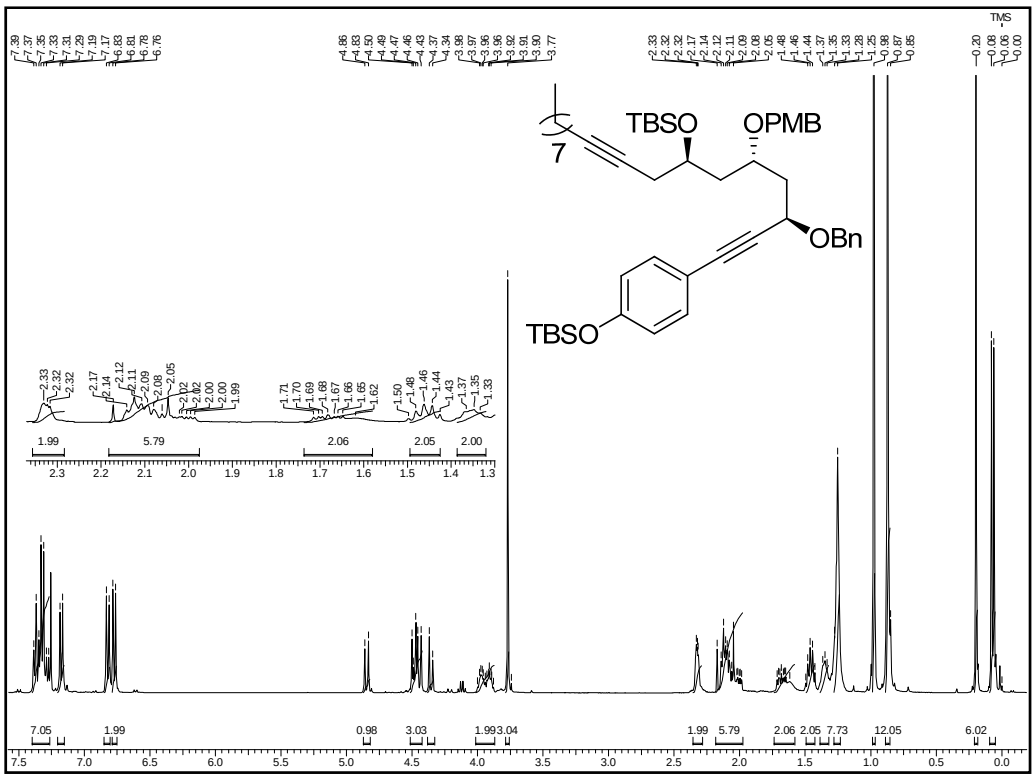
^{13}C NMR Spectrum of 37 in $CDCl_3$



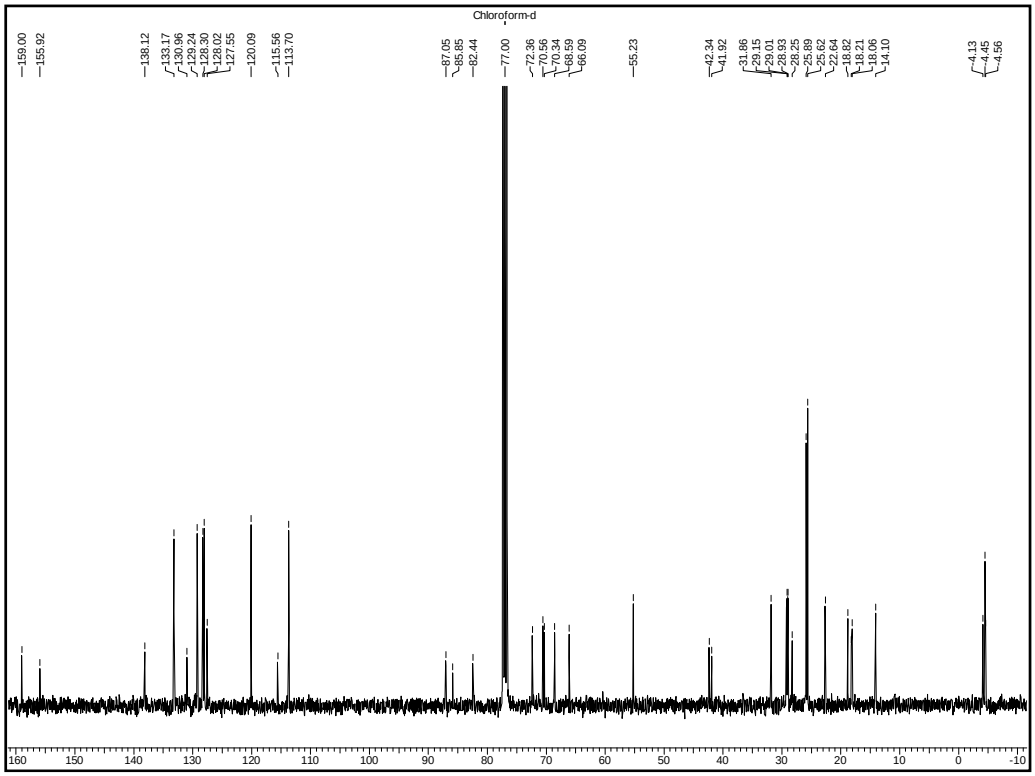
^{1}H NMR Spectrum of 38 in $CDCl_3$



^{13}C NMR Spectrum of 38 in $CDCl_3$



^{1}H NMR Spectrum of 39 in $CDCl_3$



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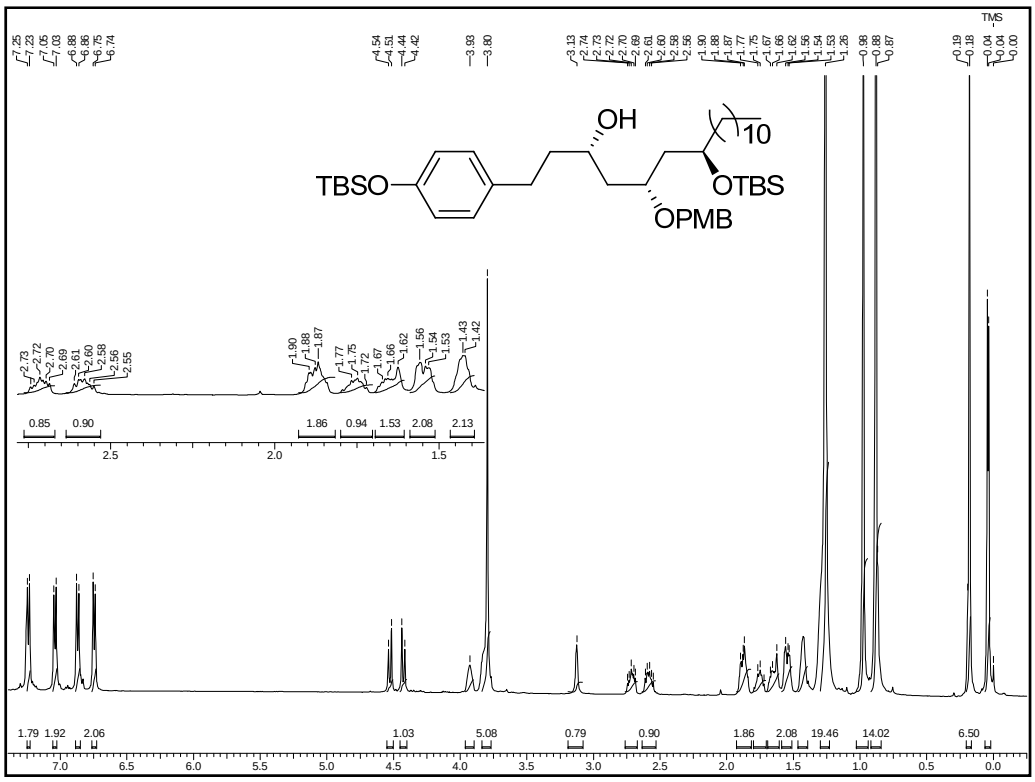
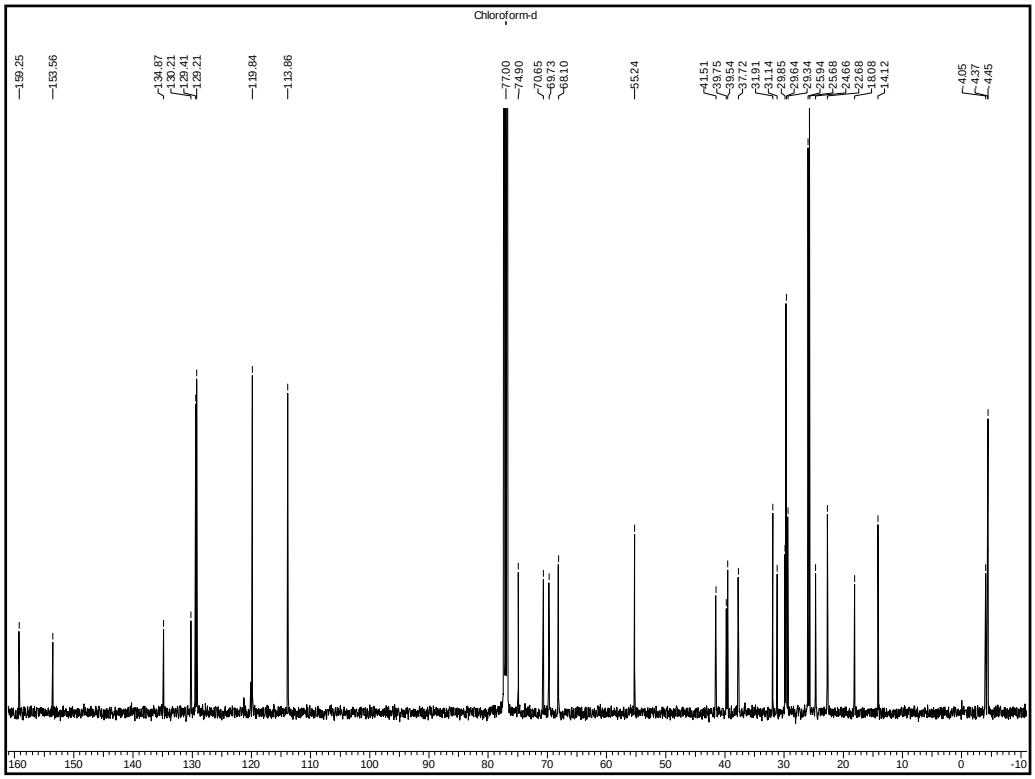
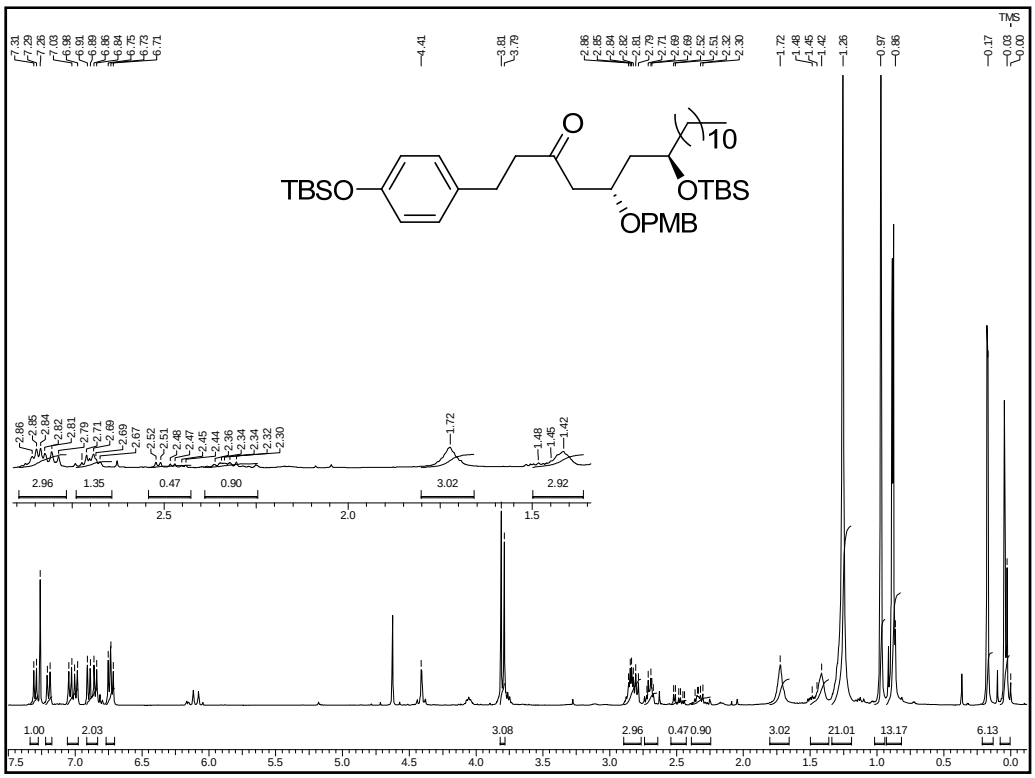


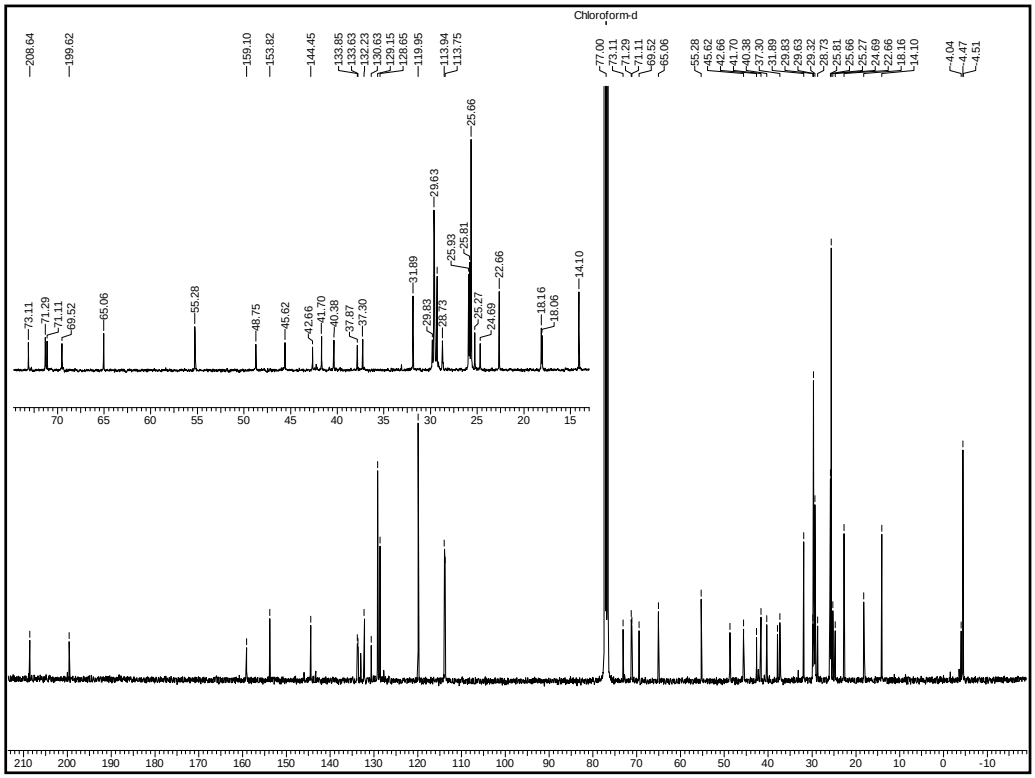
^{1}H NMR Spectrum of 40 in $CDCl_3$



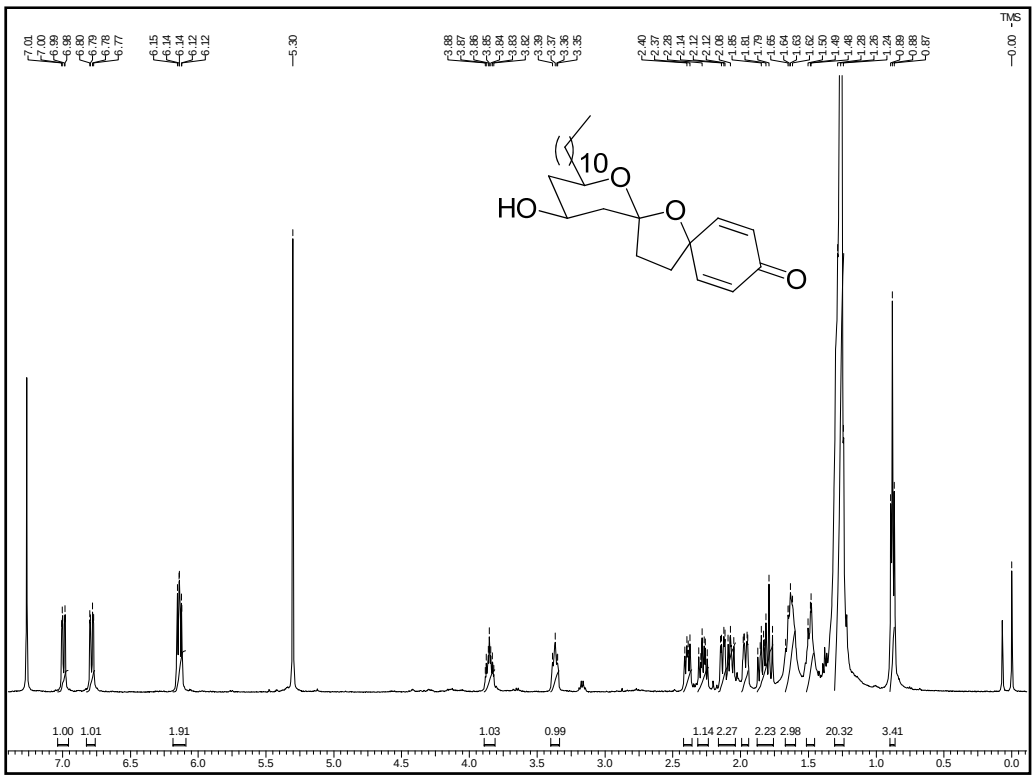
^{13}C NMR Spectrum of 40 in $CDCl_3$



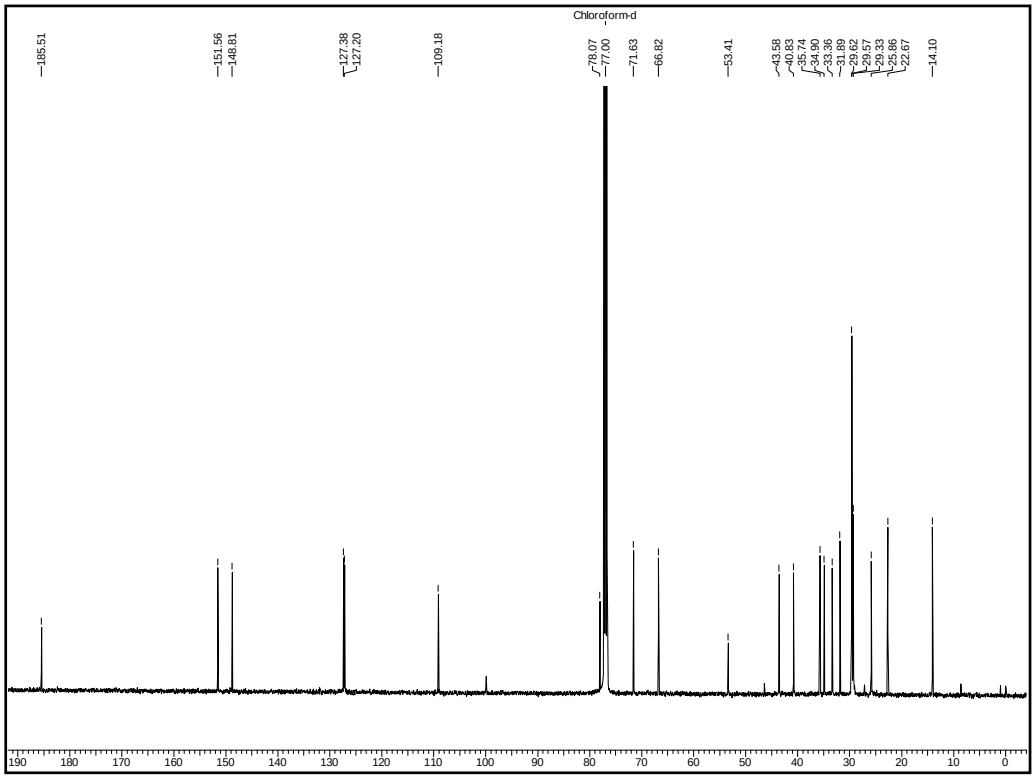
^{1}H NMR Spectrum of 41 in $CDCl_3$



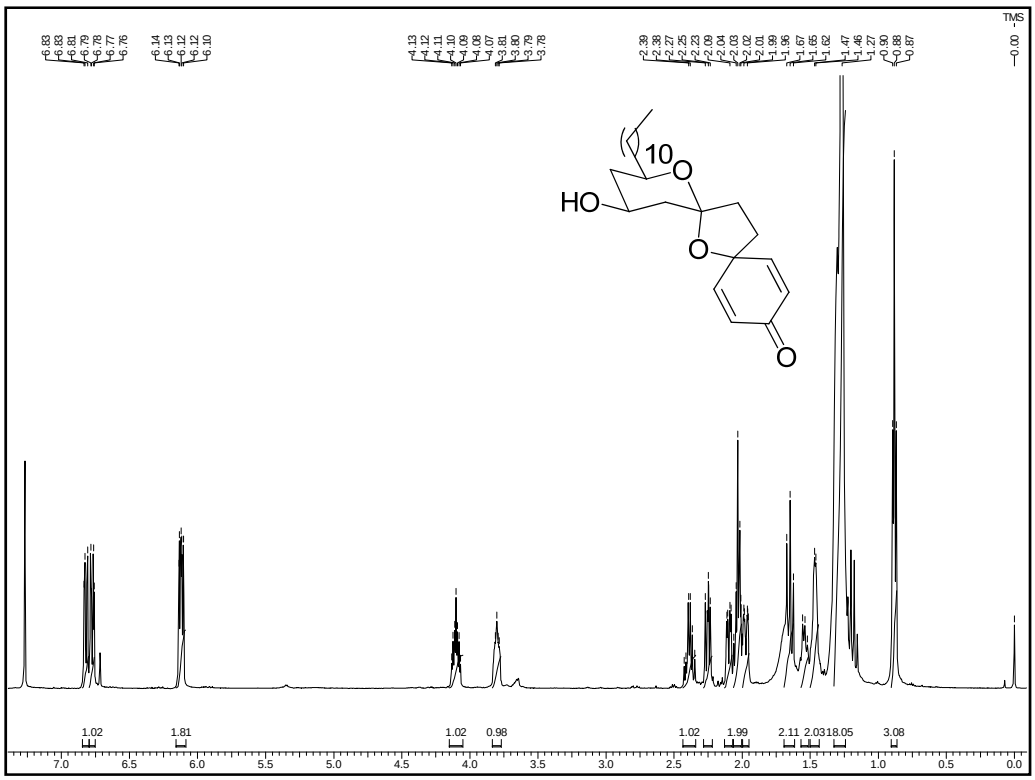
^{13}C NMR Spectrum of 41 in $CDCl_3$



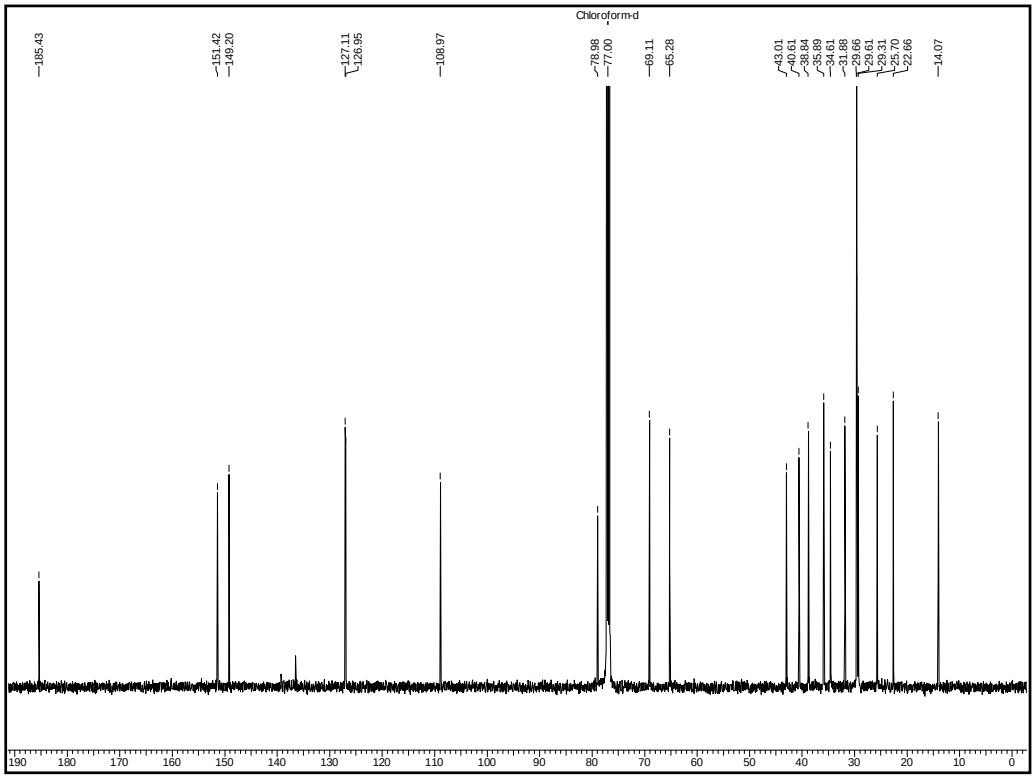
^{1}H NMR Spectrum of aculeatin E (5) in $CDCl_3$



^{13}C NMR Spectrum of aculeatin E (5) in $CDCl_3$



^{1}H NMR Spectrum of 6-*epi*-aculeatin E (8) in $CDCl_3$



^{13}C NMR Spectrum of 6-*epi*-aculeatin E (8) in $CDCl_3$

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CHAPTER-II

Total synthesis of Sacidumlignan D

Introduction

Introduction:

Lignans are a class of secondary metabolites widely encountered in the plant kingdom and have been found in species belonging to more than seventy families. The term 'lignan', reflecting the woody tissue from which many examples derive, was introduced by Haworth.[1] The formation of lignans is done biogenetically through the shikimate pathway. The frequent occurrence of this linkage can be ascribed to *β–β′* coupling of radicals derived by oxidation of, for example, a *p*-hydroxycinnamyl precursor. Lignans are characterized by the coupling of two C_6C_3 units. For nomenclature purposes the C_6C_3 unit is treated as propylbenzene and numbered from 1 to 6 in the ring, starting from the propyl group, and with the propyl group numbered from 7 to 9, starting from the benzene ring. With the second C_6C_3 unit, the numbers are primed. When the two C_6C_3 units are linked by a bond between positions 8 and 8' or also referred to as the *β–β′* linkage, the compound is referred to and named as a lignan. In the absence of the C-8 to C-8' bond, and where the two C_6C_3 units are linked by a carbon-carbon bond, it is referred to and named as a neolignan. The linkage with neolignans may include C-(8) or C-(8'). Where there are no direct carbon-carbon bonds between the C_6C_3 units and they are linked by an ether oxygen atom, the compound is named as an oxyneolignan. Coming to the higher homologues, the sesquineolignans have three C_6C_3 units and dineolignans have four C_6C_3 units.

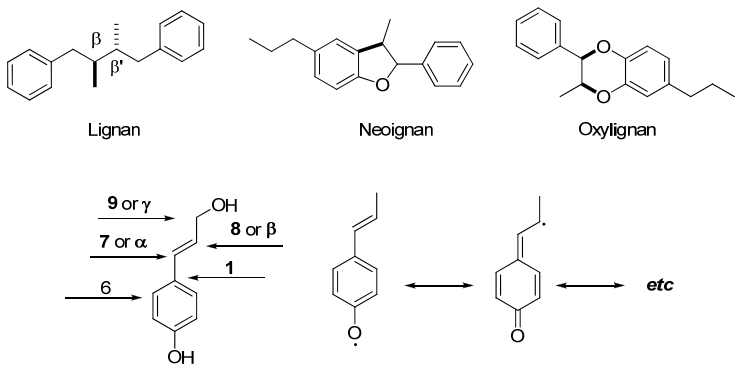


Figure 9. *Representative of Lignan linkages & and radical oxidative coupling*

These are mostly present in nature either in free form or as their glycoside derivatives.

The main source of lignans are fiber-rich plants, including grains such as wheat, barley and oats; legumes such as beans, lentils and soybeans; and vegetables such as garlic, asparagus, broccoli and carrots. These show an enormous structural diversity, although their molecular backbone consists only of two phenylpropane (C6–C3) units.

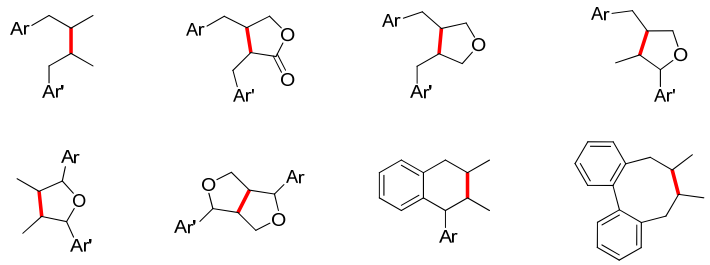


Figure 10. *Different types of Lignans which are showing β-β′ coupling*

As mentioned above, traditionally, these are classified mainly in two class, viz. classical lignans (or lignins) and neolignans which also include the oxylignans. Classical lignans are phenylpropane dimers linked in a β–β′ (8–8′) fashion, while

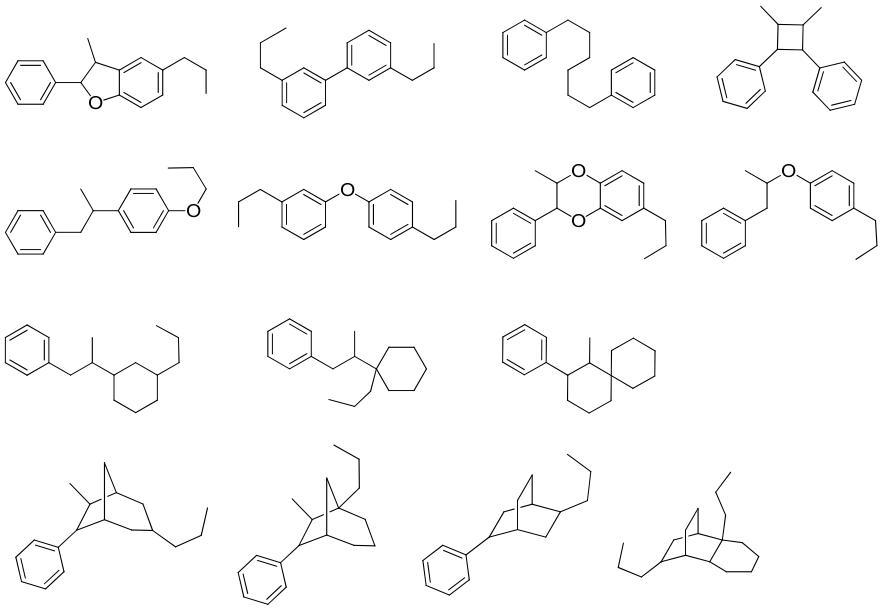


Figure 11. *Different types of Neolignans*

neolignans are those dimers whose coupling patterns differ from such a β–β′ linkage. Classical lignans include six sub-types: dibenzylbutanes (CL1), dibenzylbutyrolactones (CL2), arylnaphthalenes (CL3), dibenzocyclooctadienes

(CL4), substituted tetrahydrofurans (CL5a-c) and 2,6-diarylfurofurans (CL6) (Fig. 10), and neolignans consist of fifteen subtypes (NL1 to NL15) (Fig. 11).[2] Besides classical lignan and neolignan, other types of lignans, such as oligomeric lignans, hybrid lignans and norlignans, have been reported. The dibenzylbutanes have C_6C_3 units linked β–β′ only; the lactones, furans and furofurans have an additional oxygen bridge, and the arylnaphthalenes and bridged biphenyls have a second C–C link.

Structural Diversity and Pharmaceutical Importance:

A broad range of biological activities has been associated with lignans, including antitumor, antimiotic, antimicrobial, antiviral, antifeedant and insecticidal activities. From a pharmacological point of view, these compounds display a wide array of interesting biological activities and have a long and fascinating history beginning with their use as folk remedies by many different cultures. In the course of the last five decades, a large number of publications have appeared on the subject, including several books.[3] Continued research is currently focused on the structure optimization of the active natural lignans to generate derivatives with superior pharmacological profiles as well as a broader therapeutic scope. Some examples of the structural diversity of neolignans, norlignans, and related phenolics in plants are presented in Figure 4 and a brief summary of their biological activities follows.

Brevitaxin, first known as terpenolignan, was isolated from the twigs of the Himalayan yew *T. brevifolia* which has a diterpene-lignan structure.[4] Brevitaxin showed cytotoxicity in the NCI 60-cell line assay. Selectivity within the prostate cancer panel was observed with the DU 145 cell line, with an ED value of 6.8 μM. The (–)-sesquipinsapol B pentaacetate and (+)-Sesquimarocanol B hexaacetates showed the cytotoxicity against the cancer lines P-388, A-549, HT-29 and MEL-28 (human melanoma).[5]

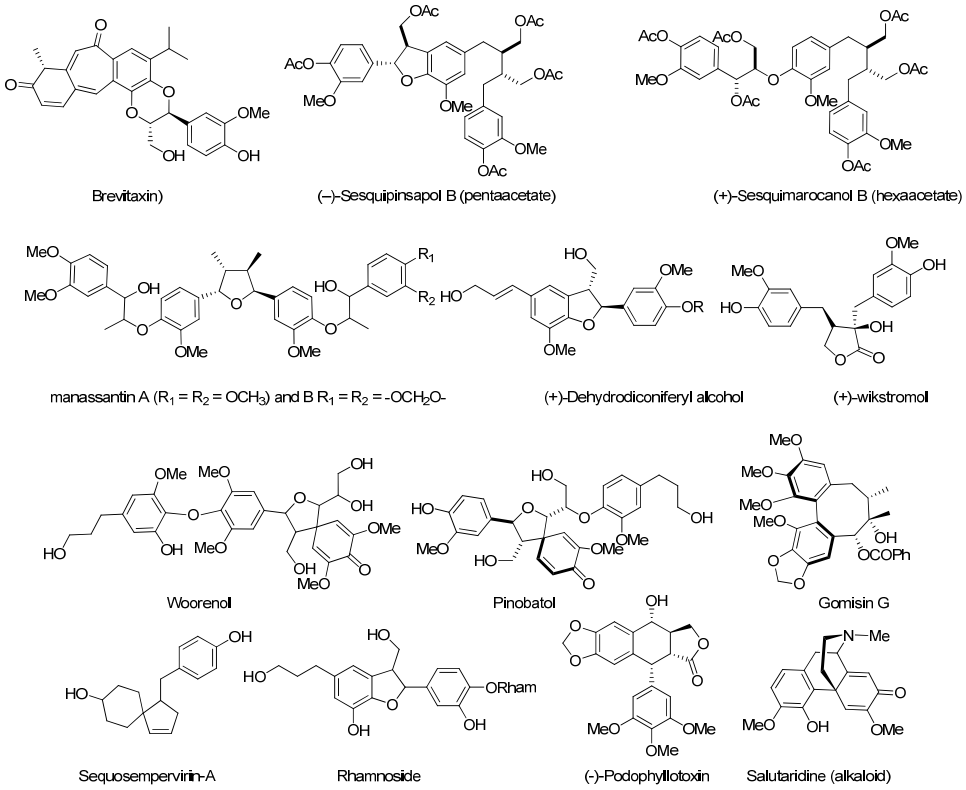


Figure 12. *Some examples of neolignans, norlignans, and sesquineolignan*

Some examples of unique dineolignans from manassantin group have been structurally related and isolated from active root extracts of *Saururus cernuus* L. (Saururaceae), also referred to as "lizard tail".[6] Many medically relevant activities have been associated with manassantin A and B in particular. For example, manassantin B was found to be a potent inhibitor of the key transcription factor HIF-1 (hypoxia-inducible factor-1). Remarkably, manassantins A and B are also identified to inhibiting PC-3 prostate cancer cell growth and other cell lines with IC_{50} values superior to those for *cis* platin and doxorubicin. Inhibition of TNF-R in conjunction with *E*-selective expression may have relevance in the prevention of atherosclerosis and endothelial activation. Manassantin A has also been associated with selective neuroleptic activity. The dehydrodiconiferyl alcohol was isolated either in free form or its glycosidate and exhibited potent antiplasmodial activity.[7] The wikstromol or (+)-nortrachelogenin belongs to the class of the relatively rare R-hydroxylated lactone lignans and exhibits several biological activities,[8,9] among which the antileukemic activity *in vivo* is most important.[9b]

Woorenol[10] and pinobatol represent novel sesquineolignans with a unique spirodienone system. These compounds are isolated from the rhizomes of *Coptis japonica* var. *dissecta* and the Pine (Pinus sylvestris L.) and shown to have anti-inflammatory activity.[11] This activity has been attributed to the inhibition of the production of two proinflammatory mediators, nitric oxide and prostaglandin E2. Sequosempervirin A, the first naturally occurring norlignan containing one spirocycle with a C6 (cyclohexane)–C2–C3–C6 skeleton, was isolated from the branches and leaves of *Sequoia sempervirens* a species of the taxodiaceae family and exhibited useful bioactivity.

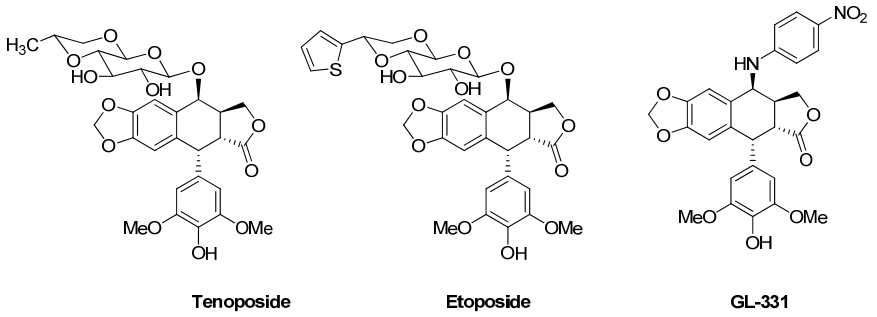


Figure 13. *Modified phdophylytoxi analogues used in the cancer treatment*

The aryltetralin lactone (–)-podophyllotoxin, has been under continued investigation due to its significant pharmacological activity.[12] The action of podophyllotoxin basically consists in disrupting the dynamic equilibrium of assembled and disassembled microtubules *in vitro* and *in vivo*. The net result is the destruction of the cytoskeletal framework in the cytoplasm and in the spindle fibres causing inhibition of cell division in the metaphase. As a result, the cell duplication at the miotic stage is impeded. However, since podophyllotoxin attacks both normal and cancerous cells, the toxic side effect has limited its application as a drug in cancer therapy. Therefore, analogues of phodophyllotoxin have been prepared in order to reduce its toxic properties and to enhance its pharmacological profile. Particularly successful have been tenoposide and etoposide, two semi-synthetic derivatives currently used in treatment of small cell lung cancer, testicular carcinoma, lymphoma and Kaposi´s sarcoma.[13] Another podophyllotoxin derivative, GL-331, was undergoing phase II clinical trials for treatment of various cancers.[14]

Unusual nor-lignans with γ-butyrolactone moiety

The Australian shrub *Eupomatia Bennettii* F. Muell is a source of rich variety of lignans like eupomatenoids, eupodienones, eupobennettin, bennettinone and eupomatilones.[15] The Eupomatilones are a family of seven degraded lignans. The eupomatilones are unusual among the lignan family in that the Cα-phenyl linkage in one of the phenylpropanoid units has been cleaved. Their relative stereochemistry has been assigned to be as shown in Figure 14 based on NOE studies. They also possess a biaryl system with a γ-lactone ring attached to one of the aryl rings. Eupomatilones 5,6 and 7-exhibited atropisomerism. The majority of the family members possess C(4)-C(5) *cis*-stereochemistry in the butyrolactone ring. In the paper describing the isolation, the relative stereochemistry of the methyl groups of butylactone ring in eupomatilones 4, 6 and 7 has been proposed to be *cis*.

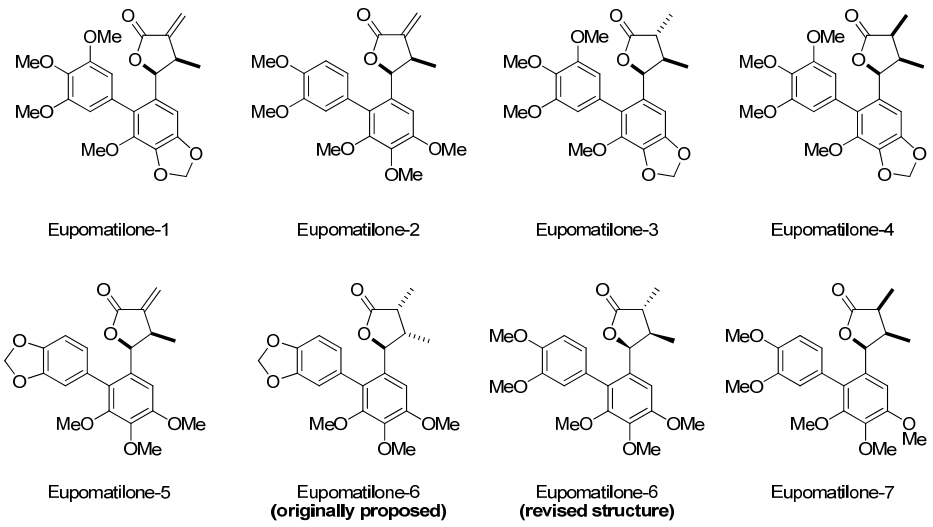


Figure 14. *Representative natural eupomatilones*

Considering the unprecedented lignan skeleton present in eupomatilones, they have been recognized as simple yet challenging goals for the total synthesis. Our intial total synthesis of eupomatilone-6 has resulted in as concluding that its structure has been wrongly assigned. Later we have fixed the relative and absolute configuration of eupomatilones-6 as shown in Figure 14, by accomplishing its racemic as well as asymmetric total synthesis.[16]

Very recently, Yue and co-workers reported the isolation of a rearranged lignan with an unprecedented skeleton and named it as sacidumulignan D (**42**) (Figure 15).[17] The plant *Sarcostemma acidum* (Roxb.), which grows in and over trees and shrubs near the seashore of Hainan Island of China, is a sturdy, succulent, and leafless creeper and is applied in folklore medicine to remedy chronic cough and postnatal hypogalactia. Along with several known compounds, four new lignans, namely, sacidumlignans A−D, and two new degraded lignan derivatives have been isolated. The structures and relative configurations of these new compounds were elucidated on the basis of spectroscopic and chemical data, especially 2D NMR techniques. Sacidumlignan D (**42**) was assigned as a rearranged tetrahydrofuran lignan with an unprecedented skeleton.

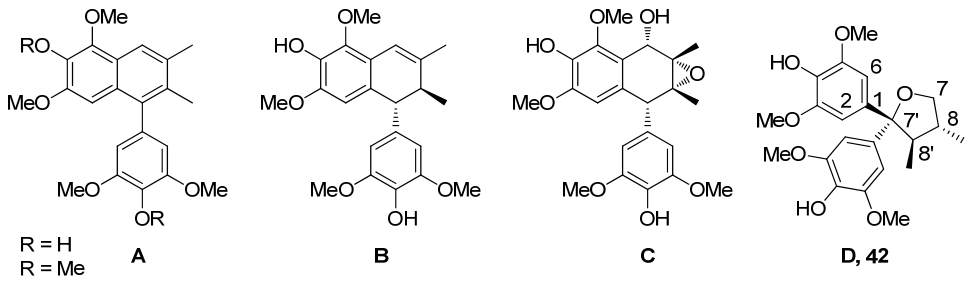


Figure 15. *Structures of Sacidumlignans A–D*

Sacidumlignan D (**42**) showed moderate antimicrobial activities against two Gram-positive bacteria *in vitro*. The assigned *trans*-configuration of the two methyl groups of tetrahydrofuran has attracted our attention, since a similar configuration has been established for eupomatilones-6 and because we have provided a classical diastereoselective methylation of lactone as a key step in our inaugural synthesis of naturally occurring eupomatilone-6.[16]

Diastereoselective mehtylation and the total synthesis of eupomatilone-6

The unprecedented skeleton of the eupomatilones and the lack of their absolute stereochemistry had prompted us to attempt the total synthesis of eupomatilones-6. To address the relative cis-streochemistry of C2 and C3 and the trans-stereochemistry of C3 and C4, we have opted for the diastereoselective hydrogenation of the corresponding butenolide as the key step. This proposal has successfully been realized

to accomplish the putative structure of the eupomatilone-6. After comparing the spectral data reported for various eupomatilones, we realized a *trans-trans* stereochemistry, similar to eupomatilone 3. However in order to verify it, the synthesis of the two possible eupomatilone-6 derivatives i.e. cis/trans and trans/trans isomers has been undertaken.The key retrosynthetic disconnections for the synthesis of putative structure of eupomatilones-6 and its new variants are given in Figure 16.

The synthesis was started with the crotylation of the known aldehyde **S32.A** with crotyl bromide in the presence of zinc and ammonium chloride giving an

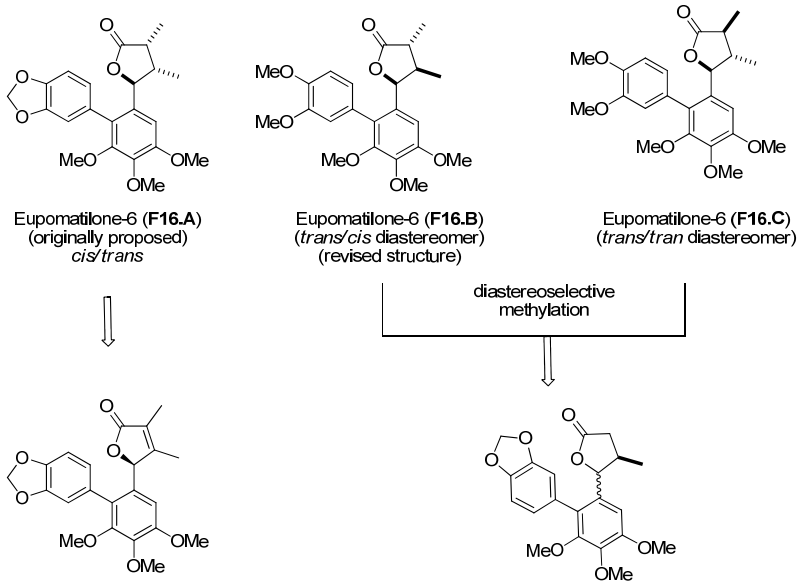
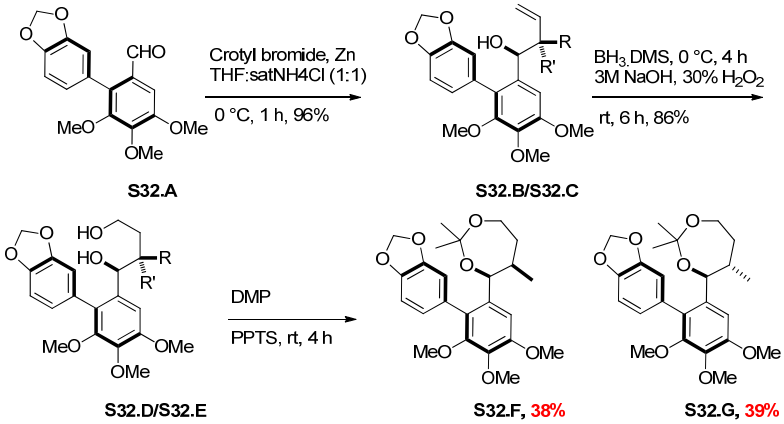
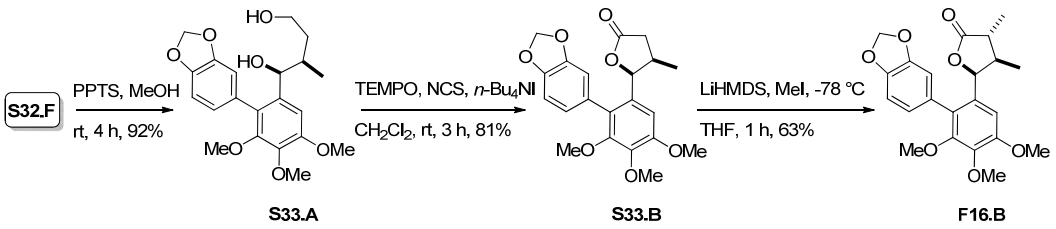


Figure 16. *Key reactions for establishing either cis- or trans-stereochemistry of the C2 and C3 centers of the butrylactone ring*



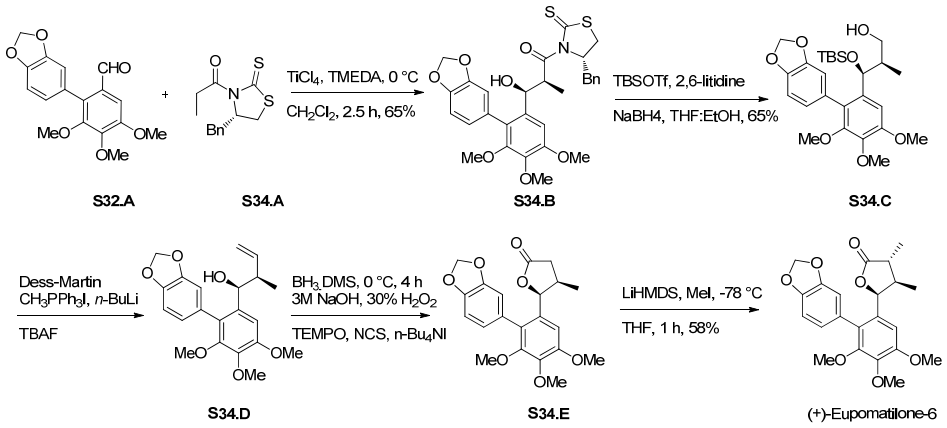
Scheme 32. *Synthesis of 1,4-Diol*

inseparable 1:1 mixture of *syn*- and *anti*-homoallylic alcohols **S32.B** and **S32.C**. Subsequent hydroboration-oxidation of **S32.B**/**S32.C** followed by acetonide protection gave the acetonidies **S32.F** and **S32.G** which were separated by silica gel chromatography and the relative stereochemistry was established with the help of 2D NMR studies.



Scheme 33: *Synthesis of (±)-Eupomatilone-6* ***F16.B***

The *Syn* acetonide **S32.F** was deprotected by PPTS in methanol and the *syn* diol **S33.A** was oxidized with NCS-TEMPO to obtain the corresponding γ-butyrolactones **S33.B** in good yields. The diastereoselectivity of methylation at C-3 was done with the help of LiHMDS-MeI to produce the racemic *cis-trans* eupomatilone-6 diastereomer (**F16.B**), the spectral data of which was identical with that of the data reported for the natural product.

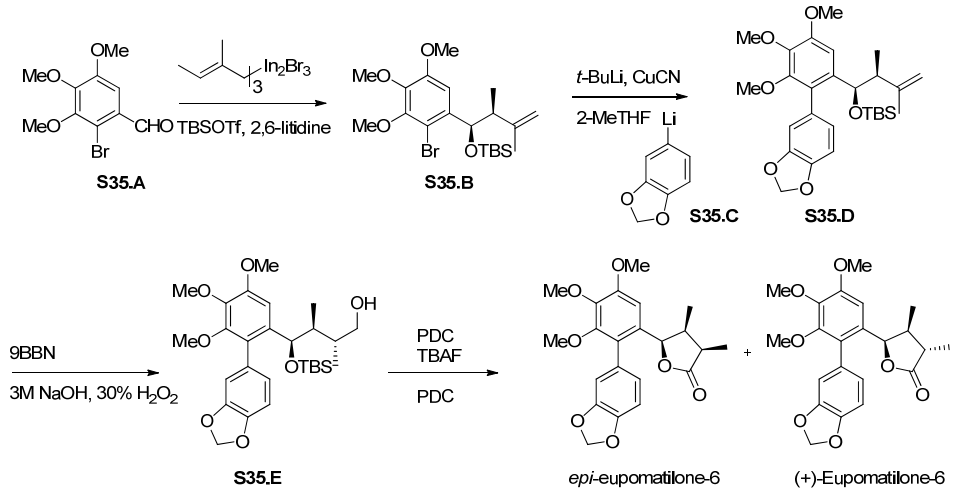


Scheme 34: *Synthesis of (+)-Eupomatilone-6*

After completing the racemic synthesis of eupomatilone-6, next the asymmetric total synthesis eupomatilone-6 was undertaken. The synthesis began with aldol condensation of *N*-propionyl-thiazolidinethione **S34.A** with aldehyde **S32.A**. The free hydroxyl group of resulting aldol adduct **S34.B** was protected as its TBS-ether followed by the removal of the thiazolidinethione auxiliary by treatment it with $NaBH_4$ to afford primary alcohol **S34.C**. The alcohol **S34.C** was subjected to Dess-Martin periodinane oxidation to aldehyde followed by one carbon Wittig homologation by using $PPh_3{=}CH_2$ giving the olefine derivative **S34.D**. The compound **S34.D** was subjected to TBS deprotection and successive hydroboration-oxidation to give the diol, which was subjected to selective oxidation and lactonization to afford the lactone derivative **S34.E** The methylation of **S34.E** was executed by using LiHMDS and MeI to give (3*R*,4*R*,5*S*)-eupomatilone-6. Two other synthesis of eupomatilone-6 was reported in literature by Coleman *et al*. and Hall *et al*. in which the stereochemistry of the two methyl groups was achieved by either hydroborarion-oxidation or reduction of *exo*-methylene group.

- **Coleman's Approach:**

The synthetic strategy of Colleman was based on a Lipshutz oxidative biarylcuprate cross-coupling and the diastereoselective hydroboration/oxidation.[18] The synthesis began with the addition of *tris*-[(*E*)-2-methyl-2-buten-1-yl]-

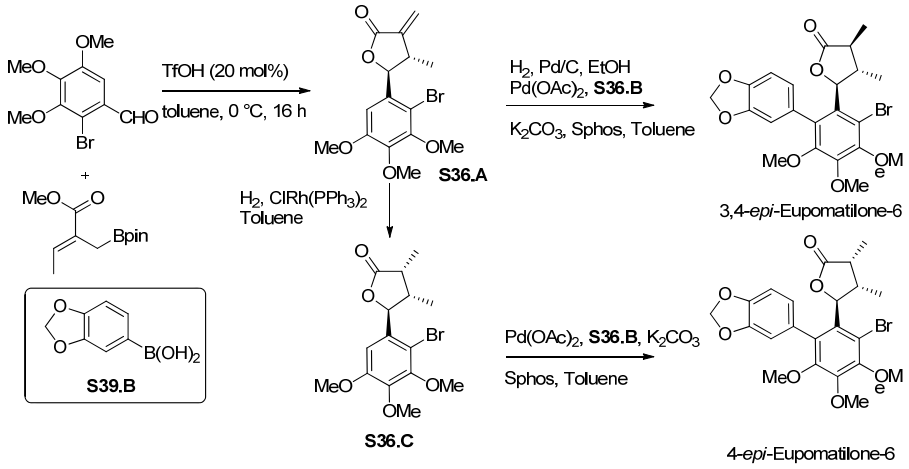


Scheme 35: *Synthesis of (+)-Eupomatilone-6*

indiumtribromide to aldehyde **S35.A** and the intermediate was converted to its silyl ether **S35.B**. Lipshutz oxidative biarylcuprate cross coupling of **S35.B** with **S35.C** and oxidation of this species formed the biaryl compound **S35.D**. The hydroboration/oxidation of **S35.D** gave the corresponding primary alcohol **S35.E** which was oxidized with pyridinium dichromate to afford the corresponding aldehyde. The fluoride-mediated deprotection of the silyl ether followed by oxidation of lactol to lactone produced a 3:1 mixture of eupimatiolone-6 and its C-3-*epimer*.

- **Hall's Approach:**

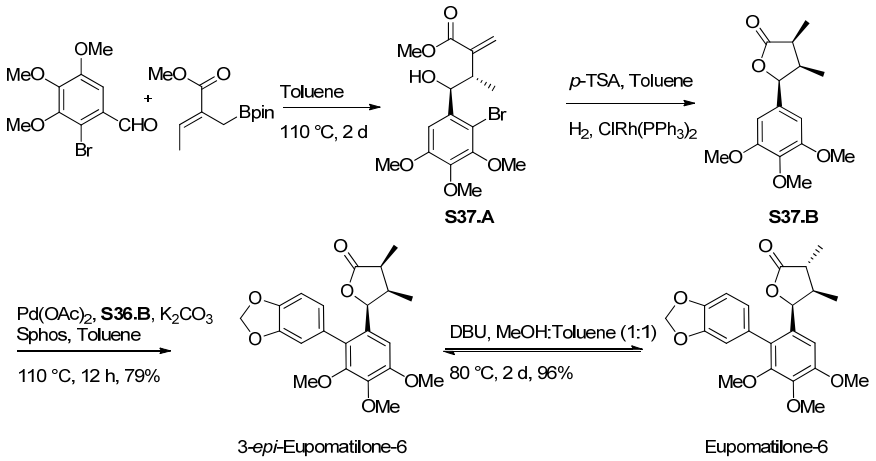
Hall *et al.* reported the synthesis of all four diastereomers of eupomatilone-6 by employing the acid catalyzed addition of allylboronates to aldehydes **S35.A** and the



Scheme 36: *Synthesis of 3,4-epi-eupomatilone and epi-eupomatilone*

diastereoselective reduction of *exo*-methylene as key steps.[19] The reduced product of **S36.A** and **S36.C** were coupled with boronic acid under Buchwald's conditions to give 4-*epi*-Eupomatilone-6 and 3, 4-*epi*-Eupomatilone-6.

To synthesize the two other diastereomers, a thermal addition of allylboronates with aldehyde **S35.A** gave the *syn*-hydroxy ester **S37.A**. The ester was lactonized under mildly acidic conditions and the resultant lactone was reduced in diastereocontrolled fashion to yield **S37.B**. The compound **S37.B** coupled with boronic acid and isomerized with the help of DBU in methanol to afford a 1:1 mixture of 3-*epi*-eupomatilone-6 and eupomatilone-6 in 1:1 ratio.



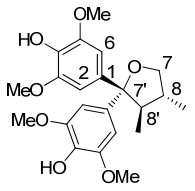
Scheme 37. *Synthesis of eupomatilone-6*

As described above, amongst the various available syntheses of eupomatilones, the one developed in our group is particularly attractive in terms of the simple reactions and complete stereoselectivity. The sacidumulignan D (**42**, Figure 15) with an unprecedented skeleton has been identified as a suitable target to extend the scope our synthetic strategy. The details of our efforts in this direction will be discussed in the next part of this Chapter.

Present Work

Present Work:

Lignans are fairly widespread throughout the plant kingdom and have been documented in species belonging to up to seventy plant families. Lignans are the dimers of phenylpropanoid (C6-C3) units linked by the central carbons of their side chains C(8)-C(8') (Figure 1). Naturally occurring dimers that exhibit linkages other than this C(8)-C(8') type linkage are known as neolignans and are more limited in number and phylogenetic distribution. In 2005, four new lignans, namely sacidumlignans A–D from the ethanolic extract of the whole plant of *Sarcostemma acidum* were collected from the Hainan Island of China.[17a] The structure and the relative configuration of these four new compounds were elucidated by employing extensive 2D NMR spectroscopic techniques. Sacidumlignan C was identified with a novel rearranged lignan skeleton and showed promising antimicrobial activities against Grampositive bacteria *in vitro*.



Sacidumlignan-D, 42

Figure 17. *Structure of Sacidumlignan D*

Stimulated by the novel structures and biological activity of these compounds, we initiated a program to synthesize sacidumlignans A–D. Our retrosynthetic strategy for sacidumlignans in general and for sacidumlignan D in particular is depicted in Scheme 34. Two contiguous stereogenic carbons, C(8) and C(8'), make the synthesis challenging, particularly the C(7') which is a quaternary carbon center.

Retrosynthetic analysis: The planned total synthesis of sacidumlignan D involves diastereoselective methylation of lactone **44** as a key step.[20,21] The resulting fully elaborated key lactone **43** can be transformed to sacidumulignan D (**42**) by carbonyl reduction and cyclization. On the other hand, subjecting **43** to Friedel-Crafts conditions, di- and tetrahydronapthalenes were anticipated which could be used for

the synthesis of other sacidumulignans. The synthesis of benzophenone derivative **46** has been identified as the intermediate goal in the synthesis of sacidumlignans A–D. The diacetate of **46** itself is a natural product and the synthesis of the same has not yet been reported. We opted for various protecting groups at 4 and 4'-hydroxy as the reactivity of benzophenone towards the organo Zn intermediates could be altered by

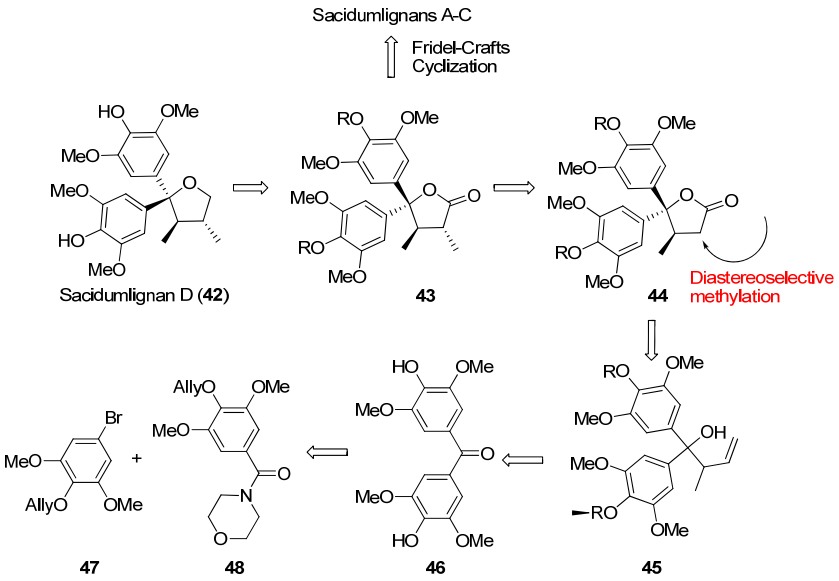


Figure 18. *Retrosynthetic strategy of Sacidumlignan D*

the nature of the protecting group and its influence on the developing positive charge at the benzylic position during the cyclization. Considering these issues, we initially opted for a robust protecting group that can be selectively removed under neutral conditions and thus the resulting dihydroxy derivative **46** can be re-protected with other protecting groups. Allyl protection was opted for in this regard as it is stable under a variety of conditions. The synthesis of di-*O*-allyl-**46** was intended from the addition of lithiated **47** to amide **48**.

Although the key intermediates and a proper retrosynthetic strategy was designed for sacidumlignans, in order to validate the key alkylation reaction and also to cross-check the assigned relative stereochemistry of the central furan unit in **42**, we initially opted for the construction of the central core from easily available benzophenone (Figure 19).

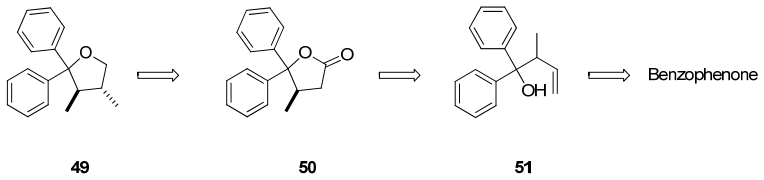
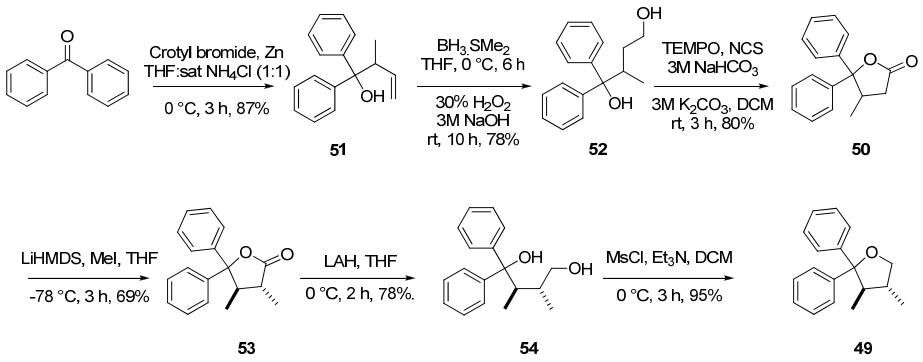


Figure 19. *Retrosynthetic strategy of the central core of Sacidumlignan D*

Synthesis of the central core of sacidumlignan D:

According to the retrosynthetic strategy as depicted in Figure 19, the model studied for the synthesis of the central core of sacidumlignan D (**42**) started with the crotylation of benzophenone under Barbier conditions.[22] The reaction was found to show only 65% conversion and demonstrated no improvement either by the use of excess Zn or the addition of excess crotyl bromide. The separation of the resulting homoallylalcohol **51** from the unreacted benzophenone was found to be tedious. However, the corresponding hydroboration product **52** could be separated easily and it was characterized by its ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of diol **52**, two methylene group (CH_2) resonated at δ 3.82–3.57 and 1.74–1.43 as a multiplet. In the IR spectrum, the O–H stretching was observed at 3392 cm^{-1}. Oxidation of **52** with NCS and TEMPO provided the lactone **50** in good yield.[18,23] The structure of **50** was fully confirmed by ^{1}H and ^{13}C NMR analysis. In the ^{13}C NMR spectrum, the characteristic lactone carbonyl resonated at δ 175.7 as a

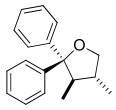
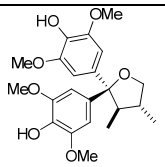


Scheme 38. *Synthesis of the central core of sacidumlignan D*

singlet and C=O absorption was observed at 1778 cm^{-1}.

After having made lactone **50**, we next investigated its proposed stereoselective 3,4-*anti*-methylation. After screening several reagents, we observed that the diastereoselectivity of methylation at C(3) was highest with LiHMDS-MeI and afforded **53** in excellent yield.[20,21] The structure of compound **53** was determined by ^{1}H NMR spectrum where the newly formed methyl group resonated at δ 1.27 ppm as doublet and all other signals were in good agreement with the assigned structure. The coupling constant (J = 9.6) of the C(3) and C(4) protons clearly indicates that they are *trans* to each other. The structure was further confirmed by ^{13}C NMR. The methylation exclusively occurred *anti* to the existing methyl. After achieving the fully elaborated central core of sacidumlignan D, we next focused on the reduction of **53** and the subsequent ring closure to get the requisite tetrahydrofuran unit. Reduction of **53** with LAH gave the diol **54**.

Table 6. *Comparative δ and J (Hz) of* ***42*** *and* ***49***

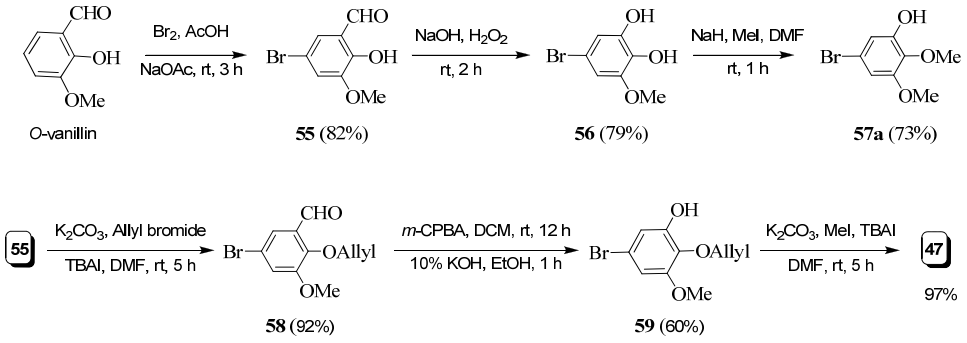
Sr. No.	**^{1}H NMR**		
1	Me–8′	0.87 (d, J = 6.8 Hz, 3H)	0.85 (d, J = 6.9 Hz, 3H)
2	Me–8	1.0 (d, J = 6.5 Hz, 3H)	0.96 (d, J = 6.5 Hz, 3H)
3	H–8	2.11–1.91 (m, 1H)	2.00 (m, 1H)
4	H–8′	2.45 (dq, J = 10.5, 6.8 Hz, 1H)	2.45 (dq, J = 9.6, 6.9 Hz, 1H)
5	H–7	3.47 (dd, J = 10.5, 8.1 Hz, 1H)	3.2 (dd, J = 10.0, 8.0 Hz, 1H)
6	H–7	4.45 (t, J = 7.8 Hz, 1H)	4.25 (dd, J = 8.0, 7.7 Hz, 1H)

The formation of diol **54** was ascertained by its ^{1}H, ^{13}C NMR spectra and elemental analysis. In the ^{1}H NMR spectrum of **54** the CH_2 proton was seen to resonate at δ 3.43–3.40 as a doublet and in the ^{13}C NMR spectrum the characteristic methylene resonated at δ 67.4 as a triplet. As anticipated, mesylation of the resulting diol **54** provided directly the requisite sacidumlignan analogue **49**. The chemical shift and coupling constants (Table 6) of the central furan unit of **49** are in agreement with that of sacidumlignan D (**42**), which established that the proposed relative stereochemistry of **42** is indeed correct.

After the synthesis of the central core of sacidumlignan D and confirmation of its relative stereochemistry, we next proceeded further for accessing the key benzophenone derivative **46** which was planned via the coupling of compounds **47** and **48**.

Synthesis of bromo partner 47.

The synthesis of the key bromo partner **47** was begun from the commercially available *o*-vanillin. The bromination of *o*-vanillin[24] by using Br_2 /NaOAc in AcOH gave the brominated compound **55** which was subjected to the Baeyer-Villiger oxidation[25] condition by employing alkaline H_2O_2 to produce the diol **56**. Though we subjected the resulting diol **56** for selective mono methylation by treating with NaH and limited amount of MeI, after extensive NMR studies, the resulting product was found to be the unwanted regiomer **57**. Considering the undesired selectivity in methylation, we changed the sequence of reactions. The initially obtained bromination product **55** was protected as its allyl ether **58** by treatment with allyl bromide and K_2CO_3 in the presence of TBAI. [26] The structure of allyl ether **58** was well supported by ^1H, ^{13}C NMR spectra and elemental analysis. In the ^1H NMR spectrum of **58**, the



Scheme 39. *Synthesis of bromo partner **47***

terminal olefinic protons resonated at δ 5.41–5.24 as multiplet and the internal proton appeared as a ddd at δ 6.03ppm. A triplet in the ^{13}C NMR spectrum at δ 117 ppm confirmed the presence of a methylene carbon in the compound **58**.

The crucial Baeyer-Villiger oxidation of **58** was evaluated by using a variety of reagents and under different conditions (Table 7). We successfully brought about the

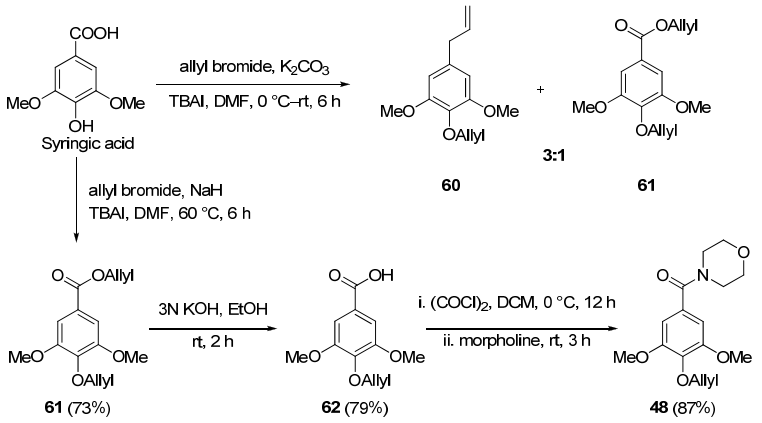
requisite transformation by using *m*-CPBA in DCM at rt and the desired phenol **59** was obtained in excellent yields. The ^{1}H, ^{13}C NMR and IR spectra of **59** revealed the presence of the phenolic OH group. In the IR spectrum, the O–H stretching was observed at 3500 cm^{-1}. Treatment of **59** with K_2CO_3 and MeI afforded the key bromo partner **47**. The structural integrity of the bromo partner **47** was established with the help of NMR, IR and mass spectral analysis. In the ^{1}H NMR spectrum, the six methoxy protons showed a broad singlet at δ 3.82 ppm and two aromatic protons showed a singlet at δ 6.70 ppm.

Table 7. *Optimisation of the Baeyer-Villiger oxidation of **58**.*

S.No	Reagents & Conditions	Observations
1	NaOH, H_2O_2, rt 3 h	Starting recovered
2	H_3BO_3, H_2O_2, THF, 60°C[27]	End product was carboxylic acid
3	H_2O_2, $KHSO_4$, MeOH, rt[28]	Oxidized to methyl ester
4	H_3BO_3, H_2O_2, H_2SO_4, THF, rt	Same observation as entry 2.
5	(i) *m*-CPBA, DCM, rt, 12h (ii) 10% KOH, EtOH, 1/2h[29].	Expected product along with trace amount of carboxylic acid

Synthesis of amide partner 48.

The synthesis of compound **48** was began with the allylation of commercially available syringic acid. Our initial allylation attempts using K_2CO_3 and allyl bromide



Scheme 40. *Synthesis of amide partner **48***

in DMF resulted in the isolation of a *C*-allylated product **60** along with the desired *O*-

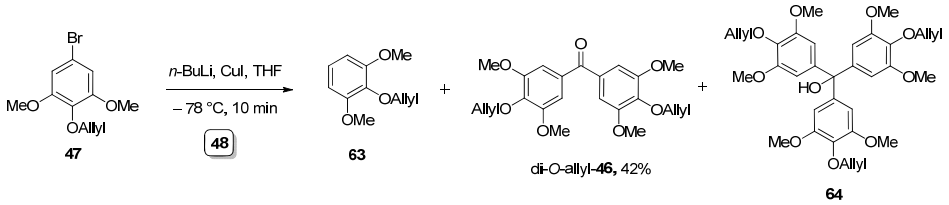
allylated product **61** in a 2:1 ratio. The structure of *C*-allylated product **60** was established with the help of spectral and mass analysis. In ^{1}H NMR spectrum of **60**, four olefinic protons resonated at δ 5.35–5.05 ppm which was terminal and the two internal protons appeared as ddd in the δ 6.05 ppm. The two methylene protons resonated at δ 4.49 and 3.32 as doublet of triplet. In ^{1}H NMR spectrum of **61**, the two methylene protons resonated at δ 4.76 and 4.54 as a doublet of triplet. In the ^{13}C NMR spectrum the characteristic ester carbonyl resonated at δ 165.3 ppm as a singlet and C=O absorption was observed at 1718 cm^{-1}.

After screening various bases, we concluded that the competitive *C*-allylation could be avoided by using NaH in the presence of a phase transfer catalyst TBAI, **61** was obtained exclusively. Hydrolysis of **61** using aq. KOH followed by coupling of the resulting acid **62** with morpholine using oxallyl chloride (see table 8) gave the key partner **48**.[30] In the ^{1}H NMR of amide **48**, the eight protons of the morpholine unit appeared as multiplet ranging from δ 3.75−3.50 ppm and the aromatic protons resonated at δ 6.56 as a singlet. The carbon of amide carbonyl appeared in ^{13}C NMR at δ 169.5 ppm. The structure of amide **48** was further supported by ESI-MS and elemental analysis.

Table 8. *Attempted conditions for the formation of morpholine amide **48**.*

Sr .No	**Reaction Conditions**	**Observations**
1	$SOCl_2$, neat, reflux, 2 h	Complex mixture
2	$SOCl_2$, Toluene, 80 °C, 3 h	Complex mixture
3	$SOCl_2$, DCM, reflux, Morpholine, 3 h	Starting intact
4	$(COCl)_2$, DCM, 0°C, 6 h, Morpholine, rt 2 h[12]	**48** obtained

After having an easy access for both coupling partners **47** and **48**, we next focused on their coupling to prepare the key benzophenone intermediate di-*O*-allyl-**46**. After a careful optimization of molar ratios of reagents and various bases, we concluded that the treatment of **47** with *n*-BuLi followed by addition of the amide **48** in excess (5 eq.) afforded the required benzophenone derivative di-*O*-allyl-**46** along with the dehalogenated product **63** and the triaryl carbinol **64**. The structure of di-*O*-allyl-**46** was established with the help of spectral and analytical data. For example, in the IR spectrum of di-*O*-allyl-**46**, a band at 1585 cm^{-1} corresponding to the C=O stretching



Scheme 41. *Coupling of **47** and **48***

was noticed. In the ^{13}C NMR spectrum, the carbonyl carbon resonated at δ 194.9 ppm as a singlet, thus confirming the presence of a ketone group in di-*O*-allyl-**46**. Based on the solvent of crystallization, we could isolate about 6 different polymorphs of di-*O*-allyl-**46** the structural features of which were analyzed with the help of single crystal *X*-ray diffraction studies.

The deallylation of compound di-*O*-ally-**46** using *N*,*N*'-dimethylbarbituric acid in the presence of $Pd(OAc)_2$ and triphenylphosphine afforded **46** in good yields.[31] In the IR spectrum of **46**, the O−H stretching was observed at 3393 cm^{-1}.

Surprisingly, the attempted crotylation of **46** under standard Barbier conditions was sluggish and even after prolonged exposure, the ketone **46** was found to be intact. Next various alternative procedures/reagents reported for the Barbier reaction were explored and in all the cases crotylation of **46** turned out to be a difficult proposition.

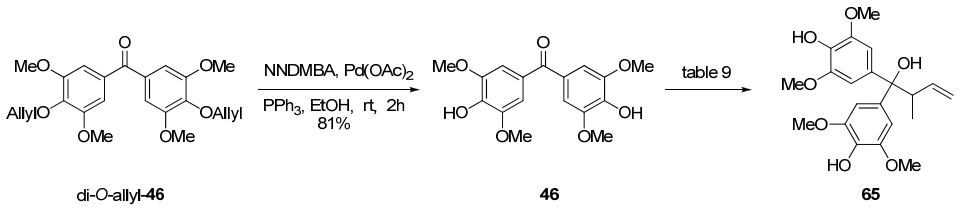
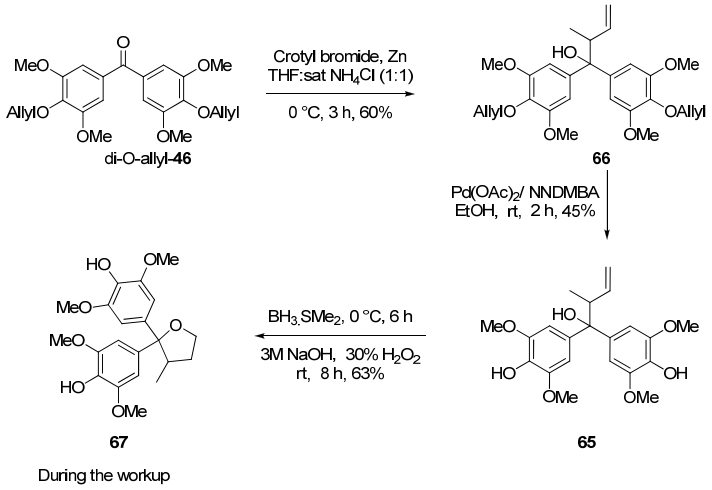


Table 9. *Attempted conditions for the crotylation of* **46**.

Sr. No	Reaction conditions	Observations
1	Crotyl bromide, Zn , sat NH_4Cl : THF[2]	Starting material recovered
2	Crotyl Bromide, In, DMF : H_2O[14]	Starting material recovered
3	Crotyl Bromide, In, THF : H_2O, NH_4Cl	Starting material recovered
4	Crotyl bromide, $SnCl_4$, In, H_2O	Starting material decomposed

As the intended crotylation of **46** was found to be a difficult task, we explored the Zn-mediated crotylation of the initial prepared di-*O*-allyl-**46**. The crotylation of di-*O*-Allyl-**46** under standard Barbier conditions gave the homoallylic alcohol **66** in moderate yields. The structure of **66** was established by spectral data and elemental analysis. In the ^{1}H NMR spectrum of **66**, three internal olefinic protons resonated at δ 6.19–5.80 as a multiplet. The six terminal olefinic protons appeared in between δ 5.24–5.10 as a multiplet. The four allylic methylene protons resonated at δ 4.61 as a doublet of triplet. In the ^{13}C NMR spectrum, the methyl carbon was located at δ 13.4 as a quartet and the methine carbon attached to this methyl group resonated at δ 44.9



Scheme 42. *Attempt for hydroboration-oxidation*

as a doublet. In the IR spectrum of **66**, O–H stretching was observed at 3513 cm^{-1}. In the mass spectrum, a peak corresponding to m/z 493.3 (100%, $[M+Na]^{+}$) was observed. Deallylation of compound **66** was carried out by employing $Pd(OAc)_2$ and *N,N'*-dimethylbarbituric acid in the presence of triphenylphosphine to afford **65** in moderate yield. The deallylated product **65** was confirmed with the help of ^{1}H, ^{13}C NMR, IR spectra and mass analysis. In ^{1}H NMR spectrum of **65**, the internal olefinic proton resonated at δ 5.99–5.80 as a multiplet and the terminal protons appeared at δ 5.22–5.12 as a multiplet. In the ^{13}C NMR spectrum, the methyl resonated at δ 13.5 as a quartet, the methine carbon attached to the methyl resonated at δ 44.9 as a doublet, two methylene carbons resonated at δ 117.1 and 139.6 ppm as triplets and the tertiary alcohol carbon was located at δ 79.3 as a singlet. The O–H absorption was observed at 3539 cm^{-1} in the IR spectrum of **65**.

After having the fully characterized homoallylic alcohol **65** in hand, the next task was the hydroboration-oxidation to prepare the diol. Surprisingly, when the hydroboration-oxidation of **65** was attempted under standard conditions, the furan derivatve **67** (des-methylsacidumulignan D) was obtained as the major product. The structure of the **67** was analyzed with the help of NMR, IR, mass spectra and elemental analysis. The ^{1}H NMR spectrum of compound **67** showed the methylene protons resonated at δ 4.15 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.83–3.81 (m, 1H) and other two methylene protons resonated at up field δ 1.98–1.60 as a multiplet. The assigned structure of **67** was further supported by the ^{13}C NMR spectrum where the signals of methylene carbons resonated as a triplet at δ 33.6, 65.2 ppm, quaternary carbon and methine carbon resonated at δ 90.0 ppm as a singlet and δ 44.8 ppm as doublet respectively. IR (O–H), Mass (m/z 413.2, 100%, $[M+Na]^{+}$) and elemental analysis further supported the assigned constitution for compound **67**. Attempted oxidation of intermediate diol (without purification) using NCS and TEMPO or other reagents resulted in a complex reaction mixture. The formation of the furan from the diol can be explained by double M+ stabilization of the benzylic position with the 4-OH groups. This undesired cyclization prior to the oxidation has prompted us to modify the retro-synthetic strategy. In the current strategy, the reverse Wacker oxidation[32] of terminal olefin has been planned as a alternative for the hydroboration-oxidation to get the lactol which could be oxidized into lactone **44**.

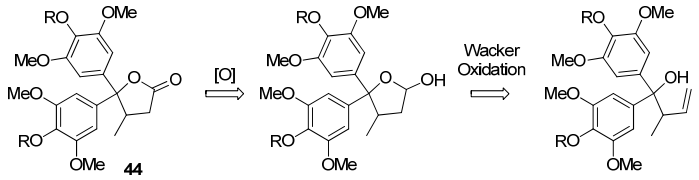
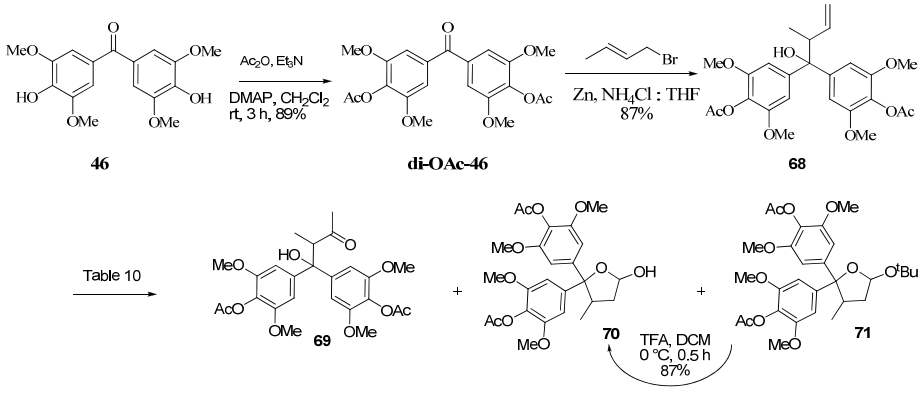


Figure 20. *Revised plan for the synthesis of intermediate lactone **44***

In our earlier attempt, we performed the Barbier reaction with di-*O*-allyl-**46** followed by the deallylation of the resulting product but in both the steps, the yields were poor and the scale up was also found to be tedious. Keeping this fact in mind, we revised our synthetic plan. The free hydroxyl groups of **46** were protected as acetates by using Ac_2O, Et_3N in the presence of DMAP to procure the di-*O*-Ac-**46**. The ^{1}H, ^{13}C NMR and IR spectrum of di-*O*-Ac-**46** revealed the presence of two acetate groups. In the ^{1}H NMR spectrum of di-*O*-Ac-**46**, two methyl protons appeared

as a singlet at 2.37 ppm. The carbonyl carbon of acetate was found to resonate at δ 168.0 ppm as a singlet in the ^{13}C NMR spectrum. The di-*O*-Ac-**46** was subjected to crotylation under Barbier conditions using Zn and crotyl bromide to furnish homoallylic alcohol **68** in excellent yields (89%). The spectral and analytical data of **68** were in agreement with the assigned structure. Signals corresponding to the olefinic protons resonated at δ 5.85 (ddd, J = 17.1, 10.3, 5.8 Hz, 1H), 5.16 (dt, J = 6.3, 1.5 Hz, 2H), methyl proton located at δ 0.92 as doublet and methine proton attached to methyl group appeared at δ 3.36−3.22 as a multiplet in ^{1}H NMR spectrum.

The next task was the regioselective Wacker oxidation of **68**. Amongst various Pd(II)-reagents employed (Table 10), the regioselectivity of the Wacker oxidation of **68** was found to be promising with $Pd(CH_3CN)_2(Cl)(NO_2)$, $CuCl_2$, O_2. However, the reaction gave a 1:1 mixure of lactol **70** and its *t*-Bu acetal (**71**).



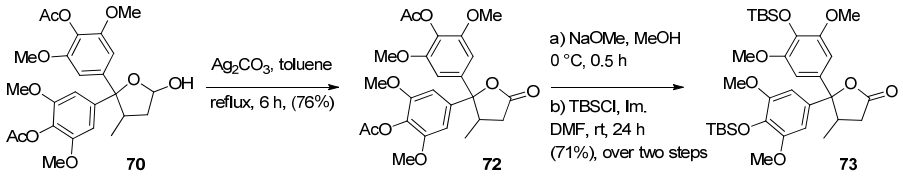
Scheme 43. *Reverse Wacker oxidation of olefin*.

Table 10. *Reagents and conditions explored for the Wacker oxidation of* **68**.

Sr. No	Reaction conditions	Observations
1	$PdCl_2$, *p*-benzoquinone, DMF:H_2O	Methyl ketone
2	$Pd(CH_3CN)_2Cl_2$, CuCl, $CuCl_2$, LiCl, *t*-BuOH, O_2, 60 °C, 2 h	Methyl ketone
3	$PdCl_2$, CuCl, NaCl, *t*-BuOH, O_2, 60 °C, 3 h	Methyl Ketone
4	$Pd(CH_3CN)_2(Cl)(NO_2)$, $CuCl_2$, O_2, *t*-BuOH, rt, 6 h[32b]	lactol + acetal (1 :1)

The formation of *t*-Bu acetal (**71**) was ascertained by its ^{1}H, ^{13}C NMR, IR, Mass spectra and elemental analysis. In the ^{1}H NMR spectrum of **71**, the olefinic protons disappeared and anomeric protons was seen to resonate at δ 5.70 (dd, J = 5.0, 2.8 Hz,

0.7H), 5.48 (t, J = 5.7 Hz, 0.3H) as its α and β anomeric mixture. The two methyl groups of *t*-Bu were located at δ 1.22 as a singlet and the third methyl group of *t*-Bu resonated at 1.34, the methylene protons appeared at 1.43 (d, J = 7.5 Hz, 1H), 1.25 (s, 1H) ppm and the methine proton resonated at δ 3.28–3.13 as a multiplet. In the ^{13}C NMR spectrum of **71**, the anomeric carbon was observed at δ 97.8 & 97.9 ppm as a doublet, the methylene carbon located at δ 40.9 & 41.5 ppm as a triplet and the methine carbon attached to methyl appeared at δ 40.2 & 40.3 as a doublet. The acetal



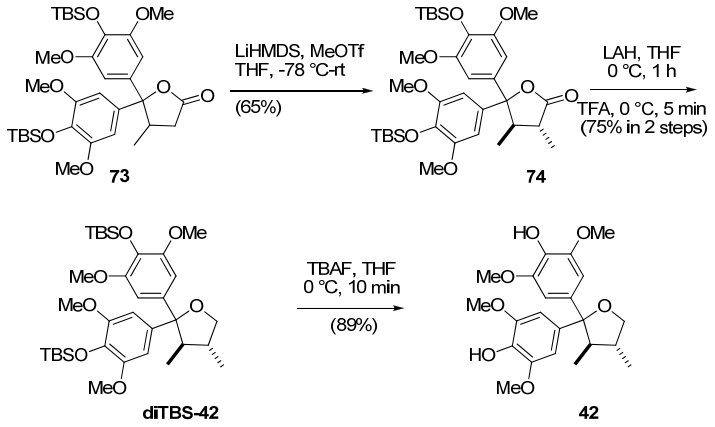
Scheme 44. *Synthesis of Lactone **73***

71 was hydrolyzed with TFA in CH_2Cl_2 to afford the lactols **70**. In the ^1H NMR of **70**, the anomeric proton resonated downfield at δ 5.85–5.72 (m, 0.7H), 5.68–5.54 (m, 0.3H). In the ^{13}C NMR spectrum of **70**, the anomeric carbon was observed at δ 97.8 & 97.9 as a doublet, methylene carbon rsonated at δ 40.7 & 41.6 as a triplet and the methine carbon attached to methyl appeared at δ 39.5 & 40.1 as a doublet. Other peaks in ^1H, ^{13}C NMR spectral and analytical data of **70** were in good agreement with the assigned structure. The oxidation of lactols **70** under Fétizon's reaction conditions employing Ag_2CO_3/*Celite* gave the lactone **72**. The structure of **72** was fully confirmed by ^1H and ^{13}C NMR analysis. In the ^{13}C NMR spectrum, the characteristic lactone carbonyl resonated at δ 175.3 ppm as a singlet and C=O absorption was observed at 1778 cm^{-1} in the IR spectrum.

After having synthesized the lactone **72**, our next target was its diastereoselective C(2)-methylation. Our initial attempts of methylation using the diacetate **72** were found to be unsuccessful because of the presence of the base susceptible acetate protecting group. To prevail over this, we have subjected **72** for the deacetylation using Na in methanol and reprotected it as their TBS ether **73**. We could successfully achieve diastereoselective methylation of lactone **73** after a careful optimization of molar ratios of reagents and various bases. We concluded that the treatment of **73** with LiHMDS (6 eq.) followed by the addition of the MeOTf (1.0 eq.)

afforded the required diastereselective methylated lactone **74** in good yield. The presence of a methyl group in **74** is evidence of the appearance of additional signals of methyl group at δ 1.28 as a doublet in the ^{1}H NMR spectrum. The coupling constant (J = 9.6 Hz) of the C(8) and C(8′) protons in the skeleton clearly indicates that they are *trans* to each other. The methylation exclusively occurred *anti* to the existing methyl group. Results from ^{1}H, ^{13}C NMR, IR, Mass Spectra and elemental analysis were in accordance with the assigned structure of **74**.

Having the complete skeleton in hand, now the stage was set to complete the total synthesis of sacidumlignan D. Our next objective was to reduce the carbonyl group of **74** to methylene and attempt a ring closure to get the requisite tetrahydrofuran unit. Reduction of **74** with LAH obtained the diol which was cyclized during the work-up to afford diTBS-**42**. The formation of diTBS-**42** was confirmed by its ^{1}H, ^{13}C NMR spectrum and elemental analysis. In the ^{1}H NMR spectrum of diTBS



Scheme 45. *Synthesis of* (±)-*sacidumlignan D*

-42, the CH_2 proton was seen to resonated at δ 4.30 (t, J = 7.8 Hz, 1H) & 3.48 (dd, J = 10.5, 8.3 Hz, 1H). In the ^{13}C NMR spectrum the characteristic methylene resonated at δ 73.9 ppm as a triplet. In the IR spectrum of diTBS-**42**, the disappearance of carbonyl carbon and O–H absorption band and other data of diTBS-**42** were in good agreement with the assigned structure. Finally, the deprotection of the TBS ethers of diTBS-**42** with TBAF provided the sacidumlignan D (**42**). The spectral and the analytical data of **42** were in good agreement with data reported for natural sacidumlignan D.

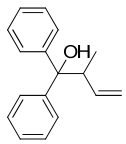
Conclusion:

The first total synthesis of (±)-sacidumlignan D has been completed. The adopted approach employs the reverse Wacker oxidation of terminal olefin and diastereoselective methylation of lactone as the key reactions.

Experimental

Experimental:

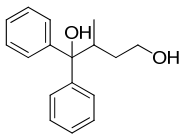
2-Methyl-1,1-diphenyl-but-3-ene-1-ol (51)



To a ice cooled suspension of benzophenone (5.0 g, 27.4 mmol), crotyl bromide (5.6 mL, 54.9 mmol), aqueous saturated NH_4Cl (15 mL) and THF (30 mL) was added Zn dust (3.56 g, 54.9 mmol) over a period of 30 min and the contents were stirred vigorously for 3 h. The reaction mixture was filtered through celite and the filtrate was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel (230–400 mesh) column chromatography (1% of ethyl acetate in pet ether as eluent) to afford the homoallylic alcohol **51** as a colorless solid (5.90 g, 87%).

IR ($CHCl_3$): ν 3558, 3019, 1657, 1599, 1493, 1448, 1319, 1279, 1215, 1177, 1083, 1031, 1012, 981, 941, 920, 703, 669, 638, 506 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$)** δ: 7.64–7.44 (m, 8H), 7.83–7.78 (m, 2H), 5.87 (ddd, *J* = 17.5, 10.6, 6.1 Hz, 1H), 5.17 (dt, *J* = 17.5, 1.6 Hz, 1H), 5.17 (dt, *J* = 10.6, 1.6 Hz, 1H), 3.61–3.47 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz)** δ: 13.3 (q), 44.2 (d), 79.1 (s), 117.0 (t), 125.6 (d), 125.8 (d), 126.2 (d), 126.4 (d), 127.9 (d), 128.0 (d), 128.1 (d), 129.9 (d), 132.3 (d), 137.4 (d), 139.2 (d), 145.6 (s), 146.6 (s) ppm. **ESI-MS *m/z***: 261.1 (80%, $[M+Na]^+$) 277.1(19%, $[M+K]^+$), 205.0 (100%, $[M–33]^+$). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.81; H, 7.91.

2-Methyl-1,1-diphenyl-butane-1,4-diol (52)

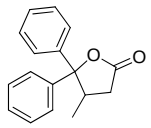


At 0 °C, a solution of **51** (4.5 g, 18.9 mmol) in anhydrous THF (25 mL) was treated with borane-methyl sulfide complex (1.62 mL, 18.9 mmol) and stirred for 6 h at 0 °C. To this, were introduced 3M NaOH solution (19 mL, 57.0 mmol) and 30% H_2O_2 (6.5 mL, 57.0 mmol) and stirring was continued for additional 6 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic phase was dried over

sodium sulphate, concentrated and the crude residue was purified by silica gel (100–200 mesh) column chromatography (20% EtOAc in pet ether) to procuer **52** (2.78 g, 78%) as a colorless solid.

M.P. 106–107 °C. **IR ($CHCl_3$)**: ν 3392, 3018, 2925, 2855, 1597, 1491, 1448, 1377, 1349, 1311, 1249, 1220, 1179, 1142, 1055, 1009, 985, 967, 943, 916, 896, 853, 767, 747, 720, 697, 639, 543, 525 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ**: 7.57–7.49 (m, 4H), 7.34–7.24 (m, 4H), 7.21–7.11 (m, 2H), 3.82–3.57 (m, 2H), 3.06–2.90 (m, 1H), 1.76–1.43 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 13.7 (q), 33.8 (t), 37.4 (d), 60.0 (t), 80.3 (s), 125.6 (d, 2C), 125.8 (d, 2C), 126.2 (d), 126.3 (d), 128.0 (d, 2C), 128.1 (d, 2C), 146.5 (s), 147.0 (s) ppm. **ESI-MS *m/z***: 279.1 (100%, $[M+Na]^+$), 239.1(29%, $[M+1-H_2O]^+$). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.91; H, 7.97.

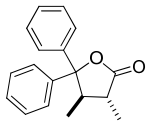
4-Methyl-5,5-diphenyl-dihydro-furan-2-one (50)



A biphasic mixture of diol **52** (2 g, 7.8 mmol), TEMPO (122 mg, 0.78 mmol), *n*-Bu_4NI (290 mg, 0.78 mmol) and *N*-chlorosuccinimide (3.17 g, 23.4 mmol), aqueous $NaHCO_3$ (0.5M, 15 mL), aqueous K_2CO_3 (0.5M, 15 mL) and DCM (20 mL) was vigorously stirred for 3 h at rt. The organic layer was separated, and the aqueous phase was extracted with DCM. The combine organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc in pet ether) to afford **50** (1.6 g, 80%) as a colorless solid.

M.P. 108–109 °C. **IR ($CHCl_3$)**: ν 3086, 3057, 3026, 2923, 2855, 1957, 1888, 1778, 1599, 1493, 1462, 1450, 1415, 1380, 1312, 1296, 1223, 1194, 1169, 1162, 1117, 1101, 1085, 1074, 1053, 1031, 1001, 970, 927, 904, 884, 865, 855, 775, 747, 701, 665, 640, 563, 543, 527 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ**: 7.55–7.48 (m, 2H), 7.41–7.20 (m, 8H), 3.51–3.34 (m, 1H), 2.72 (dd, *J* = 17.2, 7.4 Hz, 1H), 2.32 (dd, *J* = 17.2, 5.0 Hz, 1H), 0.91 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 17.1 (q), 37.5 (t), 38.0 (d), 92.2 (s), 125.6 (d, 2C), 126.1 (d, 2C), 127.4 (d), 128.0 (d), 128.1 (d, 2C), 128.5 (d, 2C), 140.5 (s), 142.8 (s), 175.7 (s) ppm. **ESI-MS *m/z***: 291.0 (10%, $[M+K]^+$), 275.0 (100%, $[M+Na]^+$), 270 (73%, $[M+H_2O]^+$), 253 (47%, $[M+H]^+$). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.99; H, 6.57.

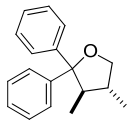
(*3R/S,4S/R*)-3,4-Dimethyl-5,5-diphenyl-dihydro-furan-2-one. (53)



A solution of **50** (500 mg, 1.3 mmol) in anhydrous THF (5 mL) was cooled to –78 °C and treated with LiHMDS (1M solution in THF, 1.55 mL) and the reaction mixture was allowed to stirr at the same temperature for 1 h and then treated with MeI (0.09 mL, 1.45 mmol) and the stirring was continued for additional 1h at –78 °C and the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate, dried (sodium sulphate) and concentrated. The crude residue was purified by silica gel chromatography (10% EtOAc in pet ether) to afford **53** (360 mg, 69%) as a colorless solid.

M.P. 110–111 °C. **IR ($CHCl_3$)**: ν 3068, 3044, 2926, 2854, 1968, 1898, 1771, 1599, 1490, 1448, 1376,1336, 1324, 1309, 1251, 1230, 1197, 1185, 1156, 1114, 1078, 1050, 1032, 977, 920, 896, 849, 831, 769, 745, 701, 681, 665, 632, 610, 585, 501cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ**: 7.48–7.27 (m, 8H), 7.11–7.05 (m, 2H), 2.93 (dq, *J* = 12.1, 6.8 Hz, 1H), 2.37 (dq, *J* = 12.1, 7.0 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 13.0 (q), 16.0 (q), 40.9 (d), 46.0 (d), 90.4 (s), 126.7 (d, 2C), 126.8 (d, 2C), 127.6 (d), 127.9 (d, 2C), 128.2 (d), 128.3 (d, 2C), 140.0 (s), 143.0 (s), 178.4 (s) ppm. **ESI-MS *m/z***: 289.1 (100%, $[M+Na]^+$), 284.1 (17%, $[M+H_2O]^+$), 267.1 (33%, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.49; H, 6.97.

(*3R/3S, 4S/4R*)-3,4-Dimethyl-2,2-diphenyl-tetrahydro-furan. (49)



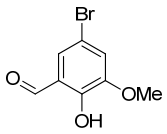
To a solution of **53** (200 mg, 0.75 mmol) in anhydrous THF (4 mL) at 0 °C, was slowly added LAH (57 mg, 1.50 mmol) and stirred for 30 min. After completion, the reaction mixture was quenched with saturated ammonium chloride solution and filtered through celite. The filtrate was washed with water and extracted with ethyl acetate, dried over sodium sulphate and concentrated. The resulting crude diol was used for next the step.

At 0 °C, a solution of the diol **54** (150 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (3 mL) was treated with Et_3N (75 µL, 0.101 mmol), MsCl (50 µL, 1.7 mmol) and stirred for 3 h at rt. The reaction mixture was partitioned between CH_2Cl_2 and water and extracted with

CH_2Cl_2. The combined organic phase was dried (sodium sulphate) and concentrated under reduced pressure. The crude residue was purified by flash silica gel (230–400 mesh) chromatography (20% EtOAc in pet ether) to give **49** (135 mg, 95%) as a colorless solid.

M.P. 91–93 °C. **IR ($CHCl_3$)**: ν 3019, 2966, 2931, 2875, 2400, 1710, 1620, 1585, 1491, 1446, 1408, 1384, 1338, 1297, 1215, 1226, 1083, 1051, 1030, 972, 928, 890, 847, 758, 703, 669, 625, 561, 526 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 7.46–7.27 (m, 4H), 7.25–7.11 (m, 6H), 4.43 (t, *J* = 7.8 Hz, 1H), 3.48 (dd, *J* = 10.5, 8.1 Hz, 1H), 2.46 (dq, *J* = 10.6, 6.9 Hz, 1H), 2.11–1.91 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (100 MHz) δ**: 14.5 (q), 15.7 (q), 40.5 (d), 49.2 (d), 73.9 (t), 90.6 (s), 126.5 (d), 126.9 (d), 127.0 (d), 127.2 (d), 127.3 (d), 127.4 (d), 127.5 (d), 127.6 (d), 128.0 (d), 128.1 (d), 145.0 (s), 147.2 (s) ppm. **ESI-MS *m/z***: 275.1 (100%, $[M+Na]^+$), 270 (9%, $[M+H_2O]^+$), 253.1 (10%, $[M+H]^+$). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.49; H, 7.7.

5-Bromo-2-hydroxy-3-methoxy-benzaldehyde (55)

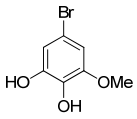


To a suspension of *o*-vanallin (10 g, 65.7 mmol) and sodium acetate (8.63 g, 105.2 mmol) in acetic acid (200 mL), was added a solution of bromine (3.38 mL, 65.7 mmol) in acetic acid (15 mL). The resulting yellow solution was stirred at room temperature for 2 h and the reaction mixture was quenched with water (500 mL) and the contents were extracted with toluene (5 X 300 mL). The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in reduced pressure (water bath temp 40 °C) to leave a brown solid. Recrystallization from acetic acid/water gave **55** (12.4 g, 82%) as a yellow needles, mp: 126 °C in literature and found 125–126 °C.

M.P. 125–126 °C, (Lit. 126 °C). **IR ($CHCl_3$):** ν 2982, 1651, 1581, 1463, 1389, 1258, 1202, 959, 848, 760, 745, 707, 577 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 11.02 (s, 1H), 9.86 (s, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR (50 MHz) δ**: 56.4 (q), 110.9 (s), 120.7 (d), 121.1 (s), 149.3 (s), 151.0 (s), 126.0 (d), 195.1 (d) ppm. **ESI-MS *m/z***: 256.7 (100%, $[M+Na]^+$), 258.6 (100%, $[M+Na]^+$).

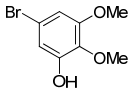
5-Bromo-3-methoxybenzene-1,2-diol (56)

At 0 °C, a solution of aldehyde **55** (200 mg, 0.87 mmol) in water (1 mL) was treated with 3M NaOH (0.6 mL) solution and 30% H_2O_2 (0.16 mL) and stirred for 3 h at rt. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated sodium sulfite, brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude was purified by column chromatography (20% EtOAc in pet ether) to procure the diol **56** (179 mg, 79%) as a colorless solid.



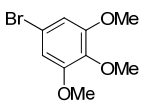
IR ($CHCl_3$): ν 3485, 2980, 1648, 1578, 1460, 1387, 1260, 120, 960, 847, 762, 745, 705, 578 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.77 (d, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 5.33 (br s, 2H), 3.87 (s, 3H).

5-Bromo-2,3-dimethoxyphenol (57a and 57b)



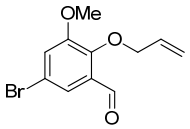
At 0 °C, a solution of diol **56** (50 mg, 0.23 mmol) in dry DMF (1 mL) was treated with 50% NaH (11 mg, 0.23 mmol) followed by MeI (14 mmL, 0.23 mmol) and the reaction mixture was stirred for 6 h at rt. The reaction mixture was quenched by adding sat. salution of Na_2SO_4, poured into water and extracted with ethyl acetate. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatgrphy (10% EtOAc in pet ether) gave a mixture of **57a** and **57b**.

Compound 57a: IR ($CHCl_3$): ν 3300, 2979, 1653, 1578, 1460, 1387, 1259, 1201, 957, 849, 762, 747, 705, 576 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.75 (d, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 5.33 (br s, 1H), 3.86 (s, 3H), 3.84 (s, 3H).



Compound 57b: IR ($CHCl_3$): ν 3078, 2933, 2860, 1587, 1494, 1220, 1189, 1125, 985, 920, 844, 785, 650 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.70 (s, 2H), 3.85 (s, 6H), 3.81 (s, 3H).

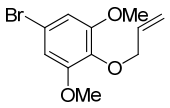
2-Allyloxy-5-bromo-3-methoxy-benzaldehyde (58)



To an ice cooled solution of 5-Bromo-2-hydroxy-3-methoxy-benzaldehyde **55** (12 g, 51.9 mmol) in dry DMF (150 mL) were added K_2CO_3 (10.8 g, 77.9 mmol) in portion wise and allyl bromide (6.3 mL, 72.7 mmol) and stirred 6 h at rt. After completion, the reaction mixture was filtered through celite and the filtrate was diluted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (3% EtOAc in pet ether) to procure the **58** (12.9 g, 92%) as a colorless solid.

M.P. 99–100 °C. **IR ($CHCl_3$):** ν 3020, 2927, 2855, 1688, 1577, 1478, 1262, 1216, 1074, 848, 758, 668 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 10.33 (s, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 1H), 6.03 (ddd, *J* = 12.2, 10.2, 6.1 Hz, 1H), 5.41–5.24 (m, 2H), 4.64 (dt, *J* = 6.1, 1.1 Hz, 2H), 3.91 (s, 3H). **^{13}C NMR (50 MHz) δ:** 56.1 (q), 75.1 (t), 116.2 (s), 119.3 (t), 120.7 (d), 121.7 (d), 130.9 (s), 132.8 (d), 150.3 (s), 153.8 (s), 188.5 (d) ppm. **ESI-MS *m/z***: 292.98 (100%, $[M+Na]^+$), 294.96 (100%, $[M+Na]^+$). Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.44; H, 4.23.

2-Allyloxy-5-bromo-1,3-dimethoxy-benzene (47)



At 0 °C, a solution of 2-alloxy-5-bromo-3-methoxy benzaldehyde **58** (12.0 g, 44.3 mmol) in CH_2Cl_2 (100 mL) was treated with *m*-CPBA (10.9 g, 48.7 mmol) and the contents were stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated under reduced pressure.

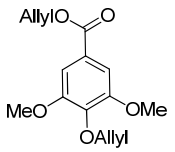
The crude residue was dissolved in EtOH (100 mL) and treated with 10% KOH (27 mL) and the reaction mixture was stirred for 10 min at rt. After completion as indicated by TLC, the reaction mixture was neutralized with 1N HCl and EtOH was removed under reduced pressure. The residue was dissoved in EtOAc (200 mL) and washed with brine,

dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (4% EtOAc in pet ether) to procure the 2-alloxy-5-bromo-3-methoxyphenol **59** (5.7 g, 60%) as a reddish syrup.

To an ice cooled solution of above crude product **59** (5.5 g, 21.3 mmol) in DMF (25 mL) was added K_2CO_3 (4.12 g, 29.8 mmol), TBAI (catalytic amount) and methyl iodide (2.0 mL, 31.98 mmol) and the contents were stirred for 3 h at rt. After completion, the reaction mixture was filtered through celite, diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatgrphy (3% EtOAc in pet ether) to afford the bromo derivative **47** (5.4 g, 58% from **58**) as a syrup.

IR ($CHCl_3$): ν 3081, 2937, 2865, 2349, 1689, 1646, 1587, 1494, 1455, 1408, 1306, 1226, 1186, 1127, 987, 928, 843, 812, 785, 650 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.70 (s, 2H), 6.07 (ddd, *J* = 12.2, 10.2, 6.1 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.1 Hz, 1H), 4.47 (dt, *J* = 6.2, 1.2 Hz, 2H), 3.82 (s, 6H). **^{13}C NMR (50 MHz) δ:** 56.1 (q, 2C), 73.9 (t), 108.9 (d, 2C), 116.0 (s), 117.6 (t), 134.2 (d), 135.9 (s), 154.0 (s, 2C) ppm. **ESI-MS *m/z***: 294.8 (100%, $[M+Na]^+$), 296.96 (85%, $[M+Na]^+$), 272.8 (62%, $[M]^+$), 274.8 (57%, $[M]^+$), 289.8 (26%, $[M+NH_4]^+$), 291.8 (25%, $[M+NH_4]^+$). Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 43.37; H, 4.80. Found: C, 43.49; H, 4.67.

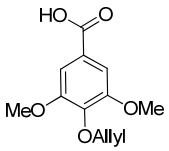
4-Allyloxy-3,5-dimethoxy-benzoic acid allyl ester (61)



To a solution of syringic acid (5 g, 21.5 mmol) in dry DMF (50 mL) was added 50% NaH (3.0 g, 64.36 mmol) portion wise at 0 °C and stirred it for 15 min and the allyl bromide (6.5 mL, 75.09 mmol) was added slowly and the contents were stirred for 3 h at rt. After completion, the reaction mixture was quenched by adding sat. Na_2SO_4, poured into water and extracted with ethyl acetate. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The resulting crude was purified by column chromatgrphy (15% EtOAc in pet ether and 100–200 mesh silica gel) to afford diallyl compound **61** (10.2 g, 73%) as a colorless thick syrup.

IR ($CHCl_3$): ν 3082, 2940, 2876, 2840, 1718, 1647, 1590, 1500, 1460, 1415, 1363, 1332, 1215, 1183, 1128, 1035, 987, 929, 864, 817, 766 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 7.32 (s, 2H), 5.95–6.19 (m, 2H), 5.41 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.34 (dq, *J* = 5.2, 1.3 Hz, 1H), 5.27 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.19 (dq, *J* = 10.2, 1.1 Hz, 1H), 4.82 (dt, *J* = 5.7, 1.4 Hz, 2H), 4.60 (dt, *J* = 6.1, 1.2 Hz, 2H), 3.90 (s, 6H). **^{13}C NMR (50 MHz) δ:** 56.9 (q, 2C), 63.3 (t), 73.7 (t), 106.6 (d, 2C), 117.6 (t), 118.0 (t), 124.9 (s), 132.1 (d), 133.9 (d), 140.7 (s), 152.9 (s, 2C), 165.3 (s). **ESI-MS *m/z***: 300.9 (40%, $[M+Na]^+$), 279.0 (100%, $[M+H]^+$). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.89; H, 6.63.

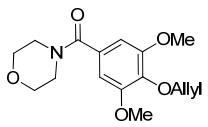
4-Allyloxy-3,5-dimethoxy-benzoic acid (62)



At 0 °C, a solution of diallyl ester **61** (10 g, 35.9 mmol) in ethanol (80 mL) was treated with the 3N KOH solution (15.7 mL, 46.7 mmol) and the reaction mixture was stirred for 1 h at rt. After completion, as indicated with TLC, the reaction mixture was neutralized by 2N HCl and EtOH was removed under reduced pressure. The content was extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (100–200 mesh silica gel, 25% EtOAc in pet ether to obtain acid **62** (6.67 g, 79%) as a white solid.

M.P. 115–117 °C. **IR ($CHCl_3$):** ν 2940, 2654, 1682, 1587, 1504, 1455, 1416, 1332, 1286, 1227, 1184, 1129, 985, 942, 865, 813, 767, 726, 682 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 7.37 (s, 2H), 6.09 (ddd, *J* = 17.2, 10.2, 6.1 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.2, 1.1 Hz, 1H), 4.62 (dt, *J* = 6.1, 1.1 Hz, 2H), 3.91 (s, 6H). **^{13}C NMR (50 MHz) δ:** 56.1 (q, 2C), 74.0 (t), 107.4 (d, 2C), 118.0 (t), 124.2 (s), 134.0 (d), 141.6 (s), 153.1 (s, 2C), 171.8 (s). **ESI-MS *m/z***: 276.8 (10%, $[M+K]^+$), 260.8 (100%, $[M+Na]^+$), 238.8 (58%, $[M+H]^+$). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.29; H, 6.10.

(4-Allyloxy-3,5-dimethoxy-phenyl)-morpholin-4-yl-methanone (48)

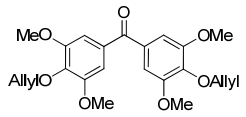


To a solution of oxalyl chloride (2.8 mL, 32.7 mmol) in DCM (50 mL) was added the DMF (50 µL) at 0 °C and stirred the mixture for 15 minutes. To this, a solution of acid **62** (6.5 g, 27.3 mmol)

in 30 mL of dry DCM was added slowly over 30 minutes. The content was stirred for 6 h at 0 °C. To this, the morpholin (4.8 mL, 54.6 mmol) was added slowly and the reaction mixture was warmed up to rt and stirred for 2 h. The reaction mixture was quenched by adding saturated NH_4Cl and extracted with DCM. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in *vaccuo*. The crude residue was purified by column chromatography (60% EtOAc in pet ether) to get morpholine amide **48** (7.3 g, 87%) as a thick syrup.

IR ($CHCl_3$): ν 3481, 3079, 2965, 2856, 1630, 1583, 1503, 1461, 1420, 1327, 1272, 1238, 1218, 1187, 1127, 987, 962, 924, 861, 759, 665 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.56 (s, 2H), 6.02 (ddd, *J* = 17.2, 10.3, 6.1 Hz 1H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dq, *J* = 10.3, 1.1 Hz, 1H), 4.47 (dt, *J* = 6.1, 1.2 Hz, 2H), 3.91 (s, 6H), 3.75−3.50 (m, 8H). **^{13}C NMR (50 MHz) δ:** 56.7 (q, 2C), 66.3 (t, 2C), 73.5 (t, 2C), 104.1 (d, 2C), 117.2 (t), 130.1 (s), 133.8 (d, 2C), 137.6 (s), 153.0 (s, 2C), 169.5 (s). **ESI-MS *m/z***: 330.0 (30%, $[M+Na]^+$), 308.3 (100%, $[M+H]^+$). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; N, 4.56; H, 6.89. Found: C, 62.39; N, 4.47; H, 6.51.

Preparation of Benzophenone di-*O*-allyl-46:

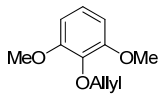


At –78 °C, a solution of **47** (500 mg, 1.83 mmol) in anhydrous THF (15 mL) was treated with *n*-BuLi (0.82 mL of 2.34 M solution in hexane, 1.92 mmol) and the contents were stirred for 30 min. The CuI (70 mg, 0.37 mmol) was introduced to the reaction mixture at the same temperature and a solution of the amide **48** (2.81 g, 2.8 mmol) in anhydrous THF (15 mL) was added to the contents and it was stirred for 5 min at –78 °C. After completion, the reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (15% ethyl acetate in pet ether) afforded ketone di-*O*-allyl-**46** (42%, m.p. 127 °C) along with dehalogenated **63** (liquid) and alcohol **64** (m.p. 105 °C).

Di-O-allyl-46: M.P. 127–128 °C. **IR ($CHCl_3$):** ν 3093, 3013, 2940, 2839, 1732, 1645, 1581, 1500, 1455, 1412, 1336, 1233, 1177, 1127, 984, 929, 867, 761, 666 cm^{-1}. **^{1}H NMR**

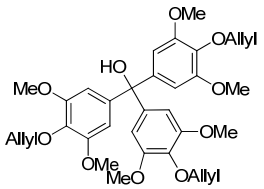
(200 MHz, $CDCl_3$) δ: 7.04 (s, 4H), 6.19–5.99 (m, 2H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 2H), 5.20 (dquin, *J* = 10.3, 1.1 Hz, 2H), 4.61 (dt, *J* = 6.1, 1.5 Hz, 4H), 3.81 (s, 12H). **^{13}C NMR (50 MHz) δ:** 55.3 (q, 4C), 74.2 (t, 2C), 107.5 (d, 4C), 118.2 (t, 2C), 132.7 (s, 2C), 134.0 (d, 2C), 140.5 (s, 2C), 153.0 (s, 4C), 194.9 (s) ppm. **ESI-MS *m/z***: 437.2 (100%, $[M+Na]^+$), 453.3 (41%, $[M+K]^+$), 415 (77%, $[M+H]^+$). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.47; H, 6.65.

63: colorless liquid. IR ($CHCl_3$): ν 3081, 2938, 2837, 1596, 1492, 1477, 1297, 1254, 1219, 1112, 991, 926, 775, 730 cm^{-1}.



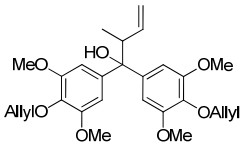
^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.95 (dt, *J* = 8.5, 1.0 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 2H), 6.20–6.00 (m, 1H), 5.32 (dq, *J* = 17.2, 2.3 Hz, 1H), 5.20 (dq, *J* = 10.3, 1.1 Hz, 1H), 4.61 (m, 2H), 3.84 (s, 6H). **ESI-MS *m/z***: 191.2 (100%, $[M+Na]^+$). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.21. Found: C, 68.31; H, 7.34.

64: M.P. 104–105 °C. IR ($CHCl_3$): ν 3462, 2936, 2838, 1588, 1501, 1462, 1413, 1324, 1238, 1127, 988, 926, 843 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.98 (s, 6H), 6.13–5.93 (m, 3H), 5.26 (dq, *J* = 17.2, 1.5 Hz, 3H), 5.14 (dq, *J* = 10.3, 0.8 Hz, 3H), 4.61 (dt, *J* = 6.0, 1.5 Hz, 6H), 3.81 (s, 18H). **^{13}C NMR (50 MHz) δ:** 55.9 (q, 6C), 74.0 (t, 3C), 74.1 (s), 103.3 (d, 4C), 105.5 (d, 2C), 117.6 (t, 3C), 134.5 (d, 3C), 135.5 (s, 3C), 143.4 (s, 3C), 152.6 (s, 4C), 152.8 (s, 2C) ppm. **ESI-MS *m/z***: 631.1 (10%, $[M+K]^+$), 607.8 (5%, $[M–H]^+$), 413.5 (100%, $[M–195]^+$). Anal. Calcd for $C_{34}H_{40}O_{10}$: C, 43.75; H, 4.49. Found: C, 43.49; H, 4.67.



1,1-Bis[4-(allyloxy)-3,5-dimethoxyphenyl)]-2-methylbut-3-en-1-ol (66)

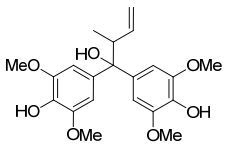
A solution of 4,4′-*O*-diallyl-**46** (1 g, 2.4 mmol), crotyl bromide (0.72 mL, 7.2 mmol) and aqueous saturated NH_4Cl (5 mL) in THF (10 mL) was cooled to 0 °C and treated with Zn dust (0.78 g, 12.1 mmol) over a period of 20 min. After an hour, the reaction mixture was filtered through celite and the contents were extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by



silica gel (230–400 mesh) column chromatography (10% of acetone in pet ether as eluent) to obtain the homoallylic alcohol **66** (680 mg, 60%) as a colorless solid.

M.P. 142–144 °C. IR ($CHCl_3$): ν 3513, 2925, 2853, 1602, 1588, 1462, 1415, 1330, 1204, 1129, 923, 755 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.75 (s, 2H), 6.70 (s, 2H), 6.19–5.80 (m, 3H), 5.24–5.10 (m, 6H), 4.61 (dt, *J* = 6.1, 1.5 Hz, 4H), 3.45–3.30 (m, 2H), 3.83 (s, 6H), 3.81 (s, 6H), 0.89 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 13.4(q), 44.9 (d), 56.2 (q, 4C), 73.9 (t, 2C), 79.3 (s), 103.5 (d, 2C), 103.9 (d, 2C), 117.1 (t), 117.2 (t, 2C), 134.6 (d, 2C), 135.5 (s), 135.7 (s), 139.3 (d), 141.0 (s), 141.9 (s), 152.9 (s, 2C), 153.0 (s, 2C) ppm. **ESI-MS *m/z***: 493.2 (100%, $[M+Na]^+$). Anal. Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28. Found: C, 68.76; H, 7.13.

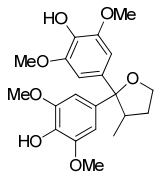
1,1-Bis[4-Hydroxy-3,5-dimethoxyphenyl]-2-methylbut-3-en-1-ol (65)



To a suspension of 1,3-Dimethylbarbituric acid (NDMBA) (200 mg, 1.3 mmol), palladium acetate (11 mg, 4.0 mol %) and PPh_3 (27 mg, 8 mol%) in absolute ethanol (15 mL) was added **66** (600 mg, 1.3 mmol) and stirred for 2 h at rt. After completion of the reaction as indicated by TLC, The contents were filtered through celite, concentrated. The crude was purified by column chromatography (40% EtOAc in Pet ether) to afford the **65** (370 mg, 45%) as a solid.

M.P. 159–161 °C. IR ($CHCl_3$): ν 3539, 3020, 2939, 1618, 1515, 1463, 1423, 1322, 1215, 1116, 756, 668 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.75 (s, 2H), 6.70 (s, 2H), 5.99–5.80 (m, 1H), 5.22–5.12 (m, 2H), 3.45–3.30 (m, 1H), 3.85 (s, 12H), 0.89 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 13.5 (q), 44.9 (d), 55.2 (q, 2C), 55.3 (q, 2C), 79.3 (s), 103.1 (d, 2C), 103.4 (d, 2C), 117.1 (t), 133.5 (s), 133.6 (s), 136.9 (s), 137.7 (s), 139.6 (d), 146.6 (s, 2C), 146.7 (s, 2C) ppm. **ESI-MS *m/z***: 429.0 (33%, $[M+K]^+$), 413.0 (100%, $[M+Na]^+$). Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.83; H, 6.79.

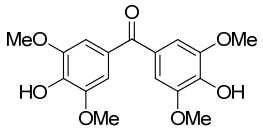
4,4'-(3-Methyltetrahydrofuran-2,2-diyl)bis(2,6-dimethoxyphenol) (67)



At 0 °C, a solution of **66** (50 mg, 0.128 mmol) in anhydrous THF (25 mL) was treated with borane-methyl sulfide complex (0.02 mL, 0.256 mmol) and stirred for 6 h at 0 °C. To this introduced (1 mL, 0.38 mmol) and 30% H_2O_2 (1 mL) and stirring continued for additional 6 h at rt. The reaction mixture was quenched with saturated ammonium chloride, extracted with ethyl acetate. The combined organic phase was dried over sodium sulphate and concentrated. The crude residue was purified by silica gel (100–200 mesh) column chromatography (50% EtOAc in pet ether) to give **67** (33 mg, 63%) as a colorless solid.

IR ($CHCl_3$): ν 3673, 2928, 1611, 1516, 1462, 1423, 1215, 1116, 668 cm^{-1}. **^{1}H NMR (200 MHz, $DMSOd_6$) δ:** 6.71 (s, 2H), 6.53 (s, 2H), 5.43 (br. s, 1H), 5.36 (br. s, 1H), 4.15 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.83–3.81 (m, 1H), 3.88 (s, 6H) 3.83 (s, 6H), 2.13–2.00 (m, 1H), 1.98–1.60 (m, 2H), 0.89 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz) δ**: 17.5 (q), 33.6 (t), 44.8 (d), 56.2 (q, 2C), 56.4 (q, 2C), 65.2 (t), 90.0 (s), 103.4 (d, 2C), 103.6 (d, 2C), 133.2 (s), 134.0 (s), 135.5 (s), 137.6 (s), 146.3 (s, 2C), 146.7 (s, 2C) ppm. **ESI-MS *m/z***: 413.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.41; H, 6.91.

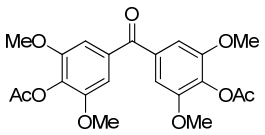
Bis-(4-hydroxy-3,5-dimethoxy)-benzophenone (46)



The similar procedure as used in the preparation of **65** was used for deallylation of 4,4′-*O*-diallyl-**46** (300 mg, 1.9 mmol) having palladium acetate (27 mg, 0.12 mmol, 5.0 mol %) and PPh_3 (64 mg, 0.24 mmol, 10 mol %) to procure **46** (195 mg, 81%) as colorless solid.

M.P. 163–165°C. **IR ($CHCl_3$):** ν 3393, 2938, 2841, 1585, 1515, 1462, 1421, 1336, 1207, 1178, 1114, 1034,755, 731, 696, 665 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 7.08 (s, 4H), 5.92 (s, 2H), 3.89 (s, 12H). **^{13}C NMR (50 MHz) δ:** 56.4 (q, 4C), 107.5 (d, 4C), 128.9 (s, 2C), 138.9 (s, 2C), 146.5 (s, 4C), 194.4 (s) ppm. **ESI-MS *m/z***: 357.1 (100%, $[M+Na]^+$). Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 61.23; H, 5.37.

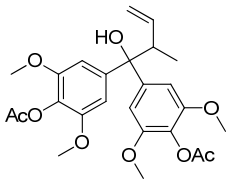
Acetic acid 4-(4-acetoxy-3,5-dimethoxy-benzoyl)-2,6-dimethoxy-phenyl ester (di-*O*-Ac-46)



At 0 °C, a solution of 4,4′-dihydroxy benzophenone derivative **46** (2 g, 5.98 mmol) in dry CH_2Cl_2 (10 mL) was treated with Et_3N (4.7 mL, 35.9 mmol) followed by Ac_2O (2.3 mL, 25.5 mmol), DMAP (50 mg) and the contents were stirred for 6 h at rt. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc in pet ether) to obtain the di-*O*-Ac-**46** (2.3 g, 89%) as a colorless solid.

IR ($CHCl_3$): ν 3093, 3013, 2940, 2839, 1730, 1645, 1581, 1500, 1455, 1412, 1336, 1233, 1177, 1127, 984, 929, 867, 761, 666 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 7.09 (s, 4H), 3.85 (s, 12H), 2.37 (s, 6H). **^{13}C NMR (50 MHz) δ**: 20.2 (q, 2C), 55.2 (q, 4C), 106.8 (d, 4C), 132.2 (s, 2C), 135.0 (s, 2C), 151.9 (s, 4C), 168.0 (s, 2C), 194.0 (s) ppm. **ESI-MS *m/z***: 457 (15%, $[M+K]^+$), 441.1 (100%, $[M+Na]^+$), 419 (10%, $[M+H]^+$). Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30 Found: C, 60.43; H, 5.21.

1,1-Bis[4-(acetoxy)-3,5-dimethoxyphenyl)]-2-methylbut-3-en-1-ol (68):

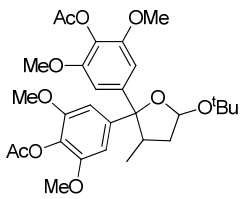


At 0 °C, a suspension of di-*O*-Ac-**46** (2.2 g, 5.26 mmol), crotyl bromide (1.62 mL, 15.8 mmol), saturated NH_4Cl (15 mL) and THF (20 mL) was treated with Zn dust (2.4 g, 36.8 mmol) over a period of 30 min. After an hour, the reaction mixture was filtered through celite and the content was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel (100–200 mesh) column chromatography (10% of acetone in pet ether) to afford the homoallylic alcohol **68** (2.17 g, 87%) as a colorless solid.

M.P. 167–169 °C. **IR ($CHCl_3$):** ν 3444, 2927, 1732, 1634, 1413, 1167, 1131, 1018, 770 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.73 (s, 2H), 6.67 (s, 2H), 5.85 (ddd, J = 17.1,

10.3, 5.8 Hz, 1H), 5.16 (dt, *J* = 6.3, 1.5 Hz, 2H), 5.11−5.07 (m, 1H), 3.71 (s, 12H), 3.36−3.22 (m, 1H), 2.24 (s, 6H), 0.92 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (50 MHz) δ:** 13.3 (q), 20.5 (d), 44.7 (d), 56.2 (q, 4C), 79.4 (s), 102.8 (d, 2C), 103.2 (d, 2C), 117.6 (t), 127.3 (s), 127.5 (s), 139.0 (d, 2C), 143.5 (s), 144.4 (s), 151.7 (s, 4C), 168.7 (s, 2C). **ESI-MS *m/z***: 497.2 (100%, $[M+Na]^+$). Anal. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37. Found: C, 64.14; H, 6.51.

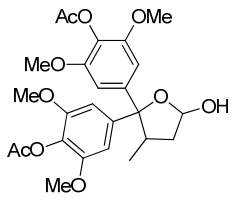
4,4'-(5-tert-Butoxy-3-methyl-tetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene) diacetate (71)



A suspension of 5 mol% $Pd(NO_2)Cl(CH_3CN)_2$ and 20 mol% $CuCl_2$ in *t*-BuOH was stirred under oxygen atmosphere for 2 h at 55 °C. The reaction mixture was cooled to 30 °C and the substrate **68** (1 g, 2.11 mmol) was added and the reaction contents were stirred for 5 h at 30 °C. The reaction mixtures were filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography (15% ethylacetate in pet ether) to procure the *t*-Bu ether **71** (860 mg, 75%) as colourless solid.

M.P. 179–180 °C. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.81 (s, 1.3H), 6.75 (s, 0.6H), 6.74 (s, 0.6H), 6.49 (s, 1.3 H), 5.70 (dd, *J* = 5.0, 2.8 Hz, 0.7H), 5.48 (t, *J* = 5.7 Hz, 0.3H), 3.80 (s, 6H), 3.75 (s, 6H), 3.28–3.13 (m, 1H), 3.10 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.34–2.32 (br s, 6H), 1.43 (d, *J* = 7.5 Hz, 1H), 1.37 (s, 0.5H), 1.34 (s, 2.5H), 1.25 (s, 1H), 1.22 (s, 5H), 0.88 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (50 MHz) δ:** 17.3, 17.5 (q), 20.4 (q, 2C), 28.9 (q), 29.0 (q, 2C), 40.2, 40.3 (d), 40.9, 41.5 (t), 56.0 (q, 2C), 56.2 (q, 2C), 74.1, 74.5 (s), 90.5 (s), 97.8, 97.9 (d), 103.6, 103.9 (d, 2C), 104.1, 104.6 (d, 2C), 127.3, 127.5 (s, 2C), 142.2 (s, 2C), 145.5 (s, 2C), 151.0, 151.2 (s), 151.3, 151.5 (s), 168.7 (s, 2C). **ESI-MS *m/z***: 585 (13%, $[M+K]^+$), 569.3 (100%, $[M+Na]^+$). Anal. Calcd for $C_{29}H_{38}O_{10}$: C, 63.72; H, 7.01 Found: C, 63.91; H, 6.94.

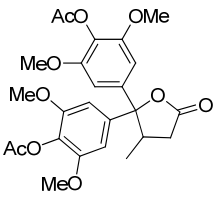
4,4'-(5-hydroxy-3-methyl-tetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene) diacetate (70)



At 0 °C, a solution of *t*-Bu ether **71** (800 mg, 1.46 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (1 mL) slowly and was stirred for 30 min at the same temperature. The reaction mixture was quenched with sat. $NaHCO_3$ and the organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by flash column chromatography (45% ethyl acetate in pet ether) to afford the lactols **70** (620 mg, 87%) as colorless solid.

M.P. 199–200 °C. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.78 (s, 1.3H), 6.74 (s, 0.7H), 6.72 (s, 0.8H), 6.44 (s, 1.2H), 5.85–5.72 (m, 0.7H), 5.68–5.54 (m, 0.3H), 3.81 (s, 5H), 3.79 (s, 1H), 3.78–3.77 (m, 1H), 3.75 (s, 2H), 3.73 (s, 4H), 2.33 (s, 3H), 2.32 (s, 3H), 2.17–1.88 (m, 2H), 1.64 (br s, 1H), 0.96 (d, *J* = 7.0 Hz, 1H), 0.89 (d, *J* = 7.0 Hz, 2H). **^{13}C NMR (50 MHz) δ:** 17.0, 17.7 (q), 20.3 (q, 2C), 39.5, 40.1 (d), 40.7, 41.6 (t), 55.9 (q, 2C), 56.1 (q, 2C), 91.0, 91.4 (s), 97.8, 97.9 (d), 103.3 (d), 103.6 (d), 104.1 (d, 2C), 127.2, 127.3 (s), 127.7 (s), 141.4, 141.5 (s), 144.3, 145.1 (s), 151.1, 151.2 (s, 2C), 151.6 (s, 2C), 168.5 (s), 168.6 (s). **ESI-MS *m/z***: 513.1 (100%, $[M+Na]^+$). Anal. Calcd for $C_{25}H_{30}O_{10}$: C, 61.22; H, 6.16. Found: C, 61.08; H, 6.31.

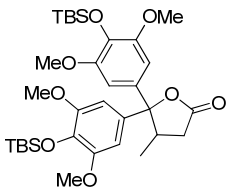
4,4'-(3-methyl-5-oxo-tetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene) diacetate (72)



A suspension of lactols **70** (800 mg, 1.63 mmol) and Ag_2CO_3 impregnated on Celite (1.35 g, 4.89 mmol, contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent) in toluene (40 mL) was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite and the Celite pad was washed with ethyl acetate (3 × 30 mL). The combined filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (35% ethyl acetate in petroleum ether) to afford lactone **72** (600 mg, 76%) as a white crystalline solid.

M.P. 211–212 °C. **IR ($CHCl_3$):** ν 3020, 2941, 2842, 1767, 1605, 1508, 1463, 1417, 1369, 1338, 1211, 1176, 1133, 759, 666 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.77 (s, 2H), 6.55 (s, 2H), 3.82 (s, 6H), 3.77 (s, 6H), 3.39–3.30 (m, 1H), 2.77 (dd, *J* = 12.8, 3.5 Hz, 1H), 2.35 (m, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (50 MHz) δ:** 17.1 (q), 20.3 (q, 2C), 37.5 (t), 38.3 (d), 56.1 (q, 2C), 56.2 (q, 2C), 91.8 (s), 102.2 (d, 2C), 103.0 (d, 2C), 127.8 (s), 128.5 (s), 138.3 (s), 140.6 (s), 151.8 (s, 2C), 152.0 (s, 2C), 168.4 (s), 168.4 (s), 175.3 (s). **ESI-MS *m/z***: 511.2 (100%, $[M+Na]^+$), 527 (14%, $[M+K]^+$) 506 (9%, $[M+H_2O]^+$), 469 (29%, $[M–H–H_2O]^+$). Anal. Calcd for $C_{25}H_{28}O_{10}$: C, 61.47; H, 5.78. Found: C, 61.53; H, 5.91.

5,5-bis(4-(tert-butyldimethylsilyloxy)-3,5-dimethoxyphenyl)-4-methyl-dihydrofuran-2(3H)-one (73)



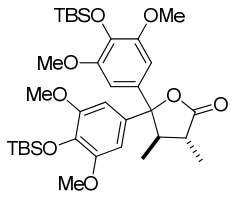
At 0 °C, a solution of the 4,4′-diacetate lactone derivative **72** (600 mg, 1.02 mmol) in dry methanol (15 mL) was treated with Na (47 mg, 2.05 mmol) and the resulting reaction mixture was stirred at 0 °C being monitored by TLC. After 30 min, the reaction mixture was neutralized with AcOH at 0 °C, MeOH was evaporated under reduced pressure, diluted with EtOAc and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was used for next step without any further purification.

At 0 °C, a solution of above crude product in dry DMF (15 mL) was treated with imidazole (418 mg, 6.1 mmol) followed by TBS-Cl (462 mg, 3.1 mmol) and the contents were stirred for 24 h at rt. The reaction mixture was partitioned between ethyl acetate and water, organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water (5 x 15 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) gave diTBS-derivative **73** as a solid.

M.P. 169–171 °C. **IR ($CHCl_3$):** ν 3020, 2929, 2856, 1765, 1588, 1514, 1463, 1415, 1338, 1247, 1128, 918, 838, 781 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.64 (s, 2H), 6.36 (s, 2H), 3.76 (s, 6H), 3.69 (s, 6H), 3.33–3.24 (m, 1H), 2.77 (d, *J* = 17.2, 7.4 Hz, 1H), 2.77

(d, *J* = 17.2, 5.1 Hz, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.10 (s, 6H), 0.08 (s, 6H). **^{13}C NMR (50 MHz) δ:** −4.7 (q, 4C), 17.2 (q), 18.6 (s, 2C), 25.7 (q, 6C), 37.7 (t), 38.3 (d), 55.7 (q, 2C), 56.0 (q, 2C), 92.7 (s), 103.1 (d, 2C), 104.1 (d, 2C), 133.1 (s), 133.5 (s), 134.4 (s), 135.1 (s), 151.1 (s, 2C), 151.3 (s, 2C), 176.1 (s). **ESI-MS *m/z***: 671.0 (10%, $[M+K]^+$), 655.3 (100%, $[M+Na]^+$), 633.1 (12%, $[M+H]^+$) Anal. Calcd for $C_{33}H_{52}O_8Si_2$: C, 62.62; H, 8.28. Found: C, 62.81; H, 8.2.

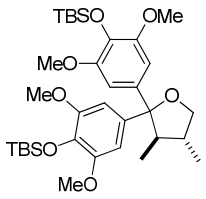
5,5-bis(4-(tert-butyldimethylsilyloxy)-3,5-dimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2(3H)-one (74)



At –78 °C, a solution of diTBS-derivative **73** (100 mg, 0.158 mmol) in anhydrous THF (1 mL) was treated with LiHMDS (1M solution in THF, 1.55 mL) and contents were stirred at the same temperature for 1 h and treated with MeOTf (18 μL, 0.158 mmol), the stirring was continued for additional 2 h at –78 °C. The reaction mixture was warmed up to rt and quenched with saturated ammonium chloride, extracted with ethyl acetate, washed with brine, dried (sodium sulphate) and concentrated. The crude residue was purified by silica gel chromatography (pet ether:ethyl acetate, 9:1) to afford **74** (66 mg, 65%) as a crystalline solid.

M.P. 174 °C. **IR ($CHCl_3$):** ν 3023, 2930, 2850, 1760, 1590, 1515, 1465, 1412, 1334, 1248, 1126, 780 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.61 (s, 2H), 6.20 (s, 2H), 3.76 (s, 6H), 3.67 (s, 6H), 2.86 (dq, *J* = 11.8, 6.7 Hz, 1H), 2.43 (dq, *J* = 11.8, 7.0 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), –0.13 (s, 6H), –0.11 (s, 6H). **^{13}C NMR (50 MHz) δ:** –4.7 (q, 4C), 13.2 (q), 16.2 (q), 18.7 (s, 2C), 25.7 (q, 6C), 41.1 (d), 46.2 (d), 55.7 (q, 2C), 56.0 (q, 2C), 91.0 (s), 104.1 (d, 2C), 104.8 (d, 2C), 132.7 (s), 133.7 (s), 134.5 (s), 135.5 (s), 150.9 (s, 2C), 151.2 (s, 2C), 178.8 (s). **ESI-MS *m/z***: 669.4 (100%, $[M+Na]^+$). Anal. Calcd for $C_{34}H_{54}O_8Si_2$: C, 63.12; H, 8.41. Found: C, 63.42; H, 8.29.

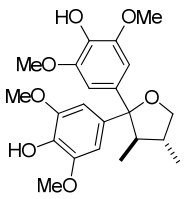
diTBS-42:



To a solution of diTBS lactone **74** (100 mg, 154.6 μmol) in anhydrous THF (2mL) at 0 °C was slowly added LAH (26 mg, 0.62 mmol). The reaction mixture was vigorously stirred 30 min. The reaction mixture was quenched with saturated ammonium chloride and filtered through celite and the filtrate was diluted by EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated. At 0 °C, a solution of above crude product in dry CH_2Cl_2 (2 mL) was treated with TFA (20 μL) and the contents were stirred for 5 min. The reaction mixture was quenched with sat. $NaHCO_3$ and the organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (pet ether:ethyl acetate, 9:1) to give cyclized product (30 mg, 78%) as a white solid.

IR ($CHCl_3$): ν 3019, 2966, 2931, 2875, 1620, 1583, 1489, 1446, 1383, 1335, 1223, 1082, 1048, 1030, 928, 845, 757, 669 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$) δ:** 6.62 (s, 2H), 6.32 (s, 2H), 4.30 (t, *J* = 7.8 Hz, 1H), 3.76 (s, 6H), 3.67 (s, 6H), 3.48 (dd, *J* = 10.5, 8.4 Hz, 1H), 2.37 (dq, *J* = 10.6, 6.8 Hz, 1H), 2.04 (ddq, *J* = 13.6, 10.6, 7.1 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H), –0.13 (s, 6H), –0.09 (s, 6H). **^{13}C NMR (50 MHz) δ:** –4.7 (q, 4C), 14.5 (q), 15.6 (q), 18.7 (s, 2C), 25.8 (q, 6C), 40.6 (d), 49.6 (d), 55.6 (q, 2C), 56.0 (q, 2C), 73.9 (t), 90.9 (s), 104.8 (d, 2C), 105.0 (d, 2C), 132.9 (s), 133.5 (s), 137.7 (s), 139.5 (s), 150.5 (s, 2C), 151.0 (s, 2C) ppm. **ESI-MS *m/z***: 655.3 (18%, $[M+Na]^+$). Anal. Calcd for $C_{34}H_{56}O_7Si_2$: C, 64.51; H, 8.92. Found: C, 64.63; H, 8.79.

(±)-Sacidumlignan D

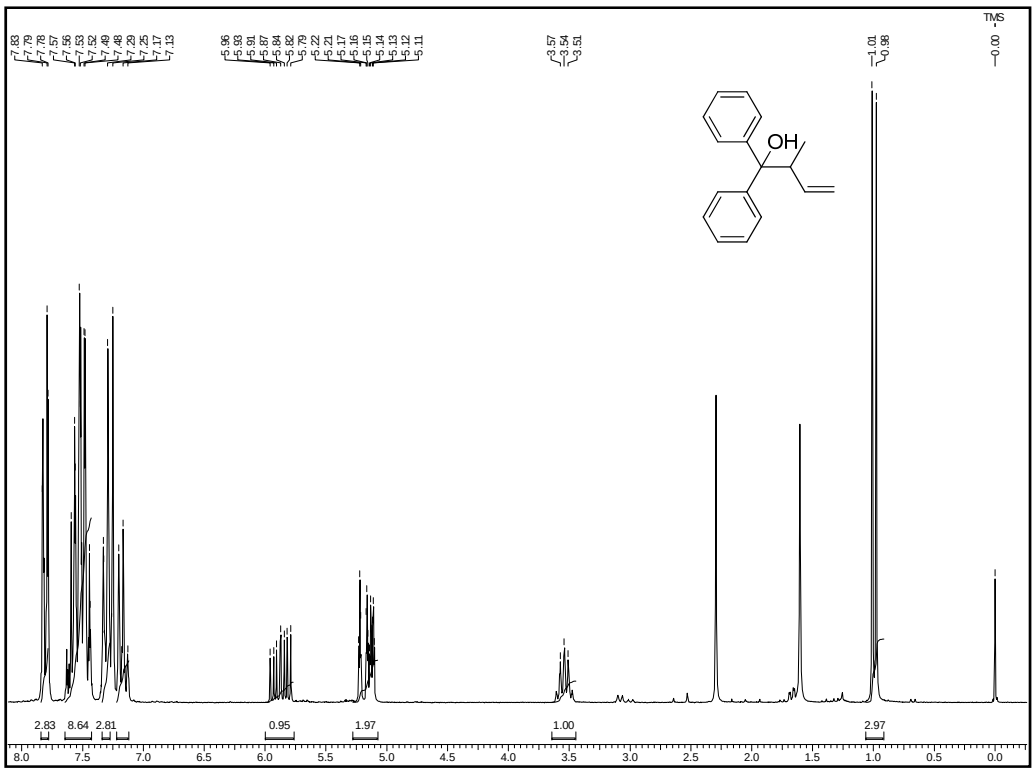


The diTBS-**42** (30 mg) was dissolved in dry THF (0.5 mL) and treated with TBAF (27 mg 0.66 mmol) at 0 °C. After the mixture was stirred for 15 min at the same temperature, after completion of reaction, the reaction mixture was quenched with saturated ammonium chloride, extracted with EtOAc (2 x 5 mL), washed with brine dried over Na_2SO_4 and solvent was

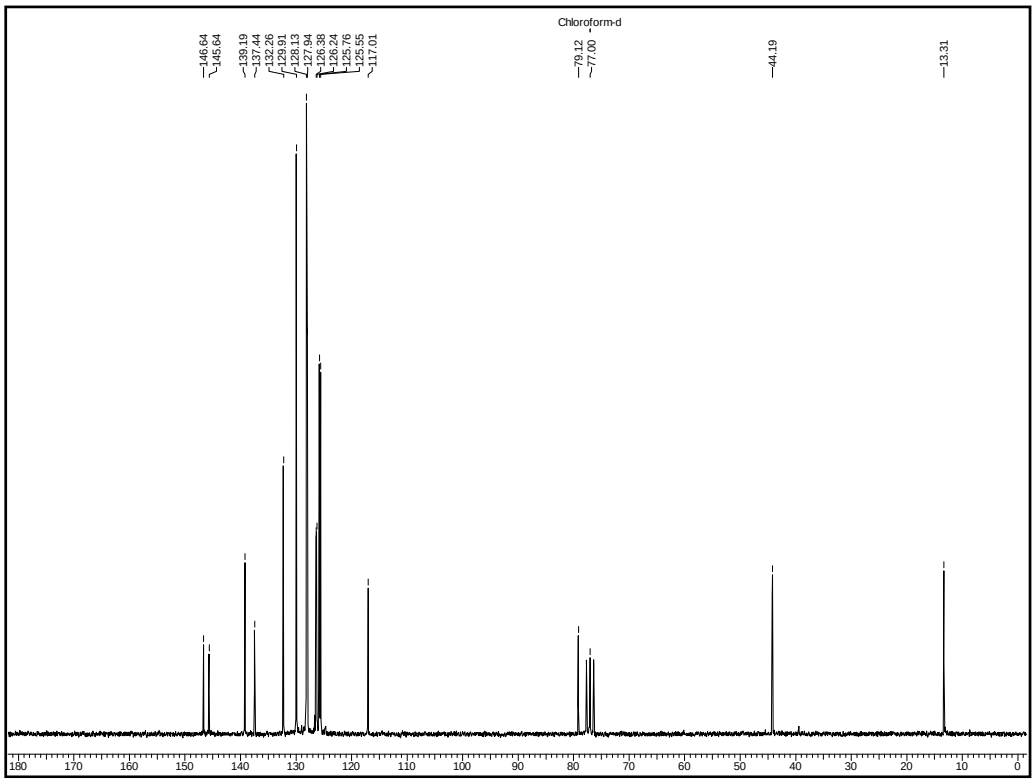
evaporated under reduced pressure. The crude residue was purified by silica gel chromatography by eluting with light pet ether/ethyl acetate (6:4) to procure sacidumlignan D (15 mg, 89%) as a solid crystalline.

IR ($CHCl_3$): ν 3025, 2927, 2847, 1565, 1514, 1457, 1406, 1327, 1253, 1121, 785 cm^{-1}. **^{1}H NMR (400 MHz, CD_3COCD_3)** δ: 7.21 (s, 1H), 7.11 (s, 1H), 6.79 (s, 2H), 6.54 (s, 2H), 4.30 (t, *J* = 7.7 Hz, 1H), 3.81 (s, 6H), 3.74 (s, 6H), 3.34 (dd, *J* = 10.1, 8.2 Hz, 1H), 2.43 (dq, *J* = 9.6, 6.9 Hz, 1H), 2.04–1.94 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CD_3COCD_3)** δ: 15.4 (q), 17.1 (q), 42.3 (d), 51.2 (d), 56.9 (q, 2C), 57.1 (q, 2C), 74.3 (t), 91.5 (s), 106.0 (d, 2C), 106.4 (d, 2C), 135.7 (s), 136.2 (s), 137.1 (s), 139.4 (s), 148.0 (s, 2C), 148.4 (s, 2C) ppm. ESI-MS *m/z*: 427.2 (100%, $[M+Na]^+$). Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.22; H, 7.11.

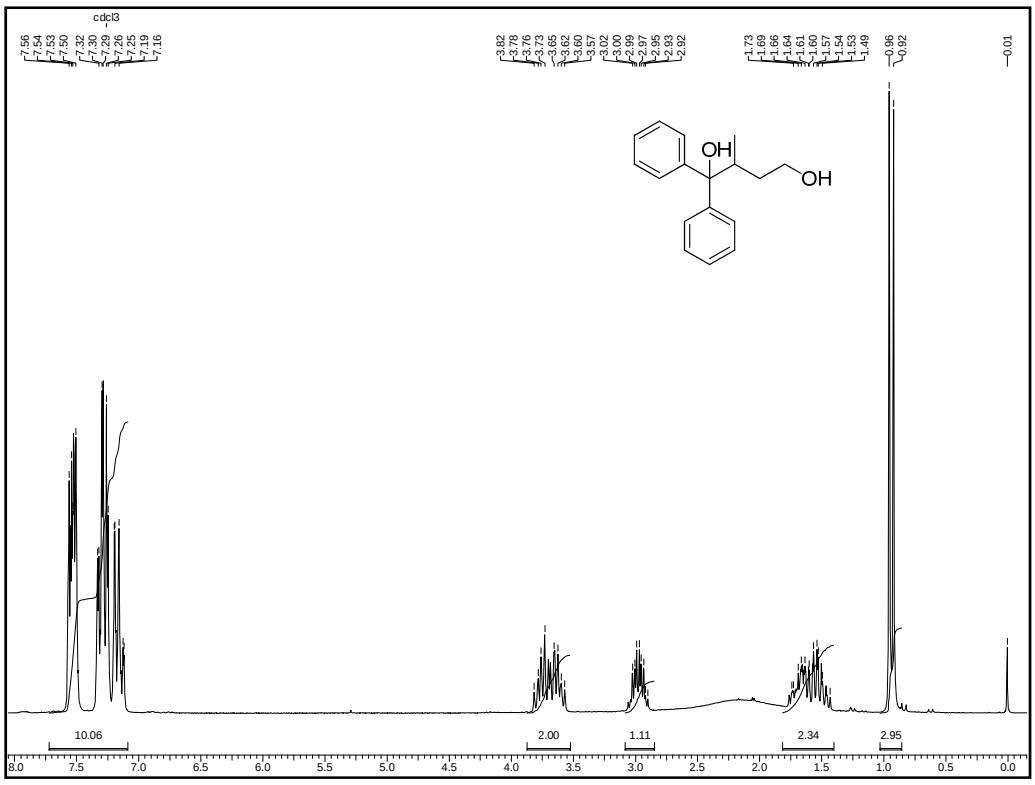
Spectroscopic Data



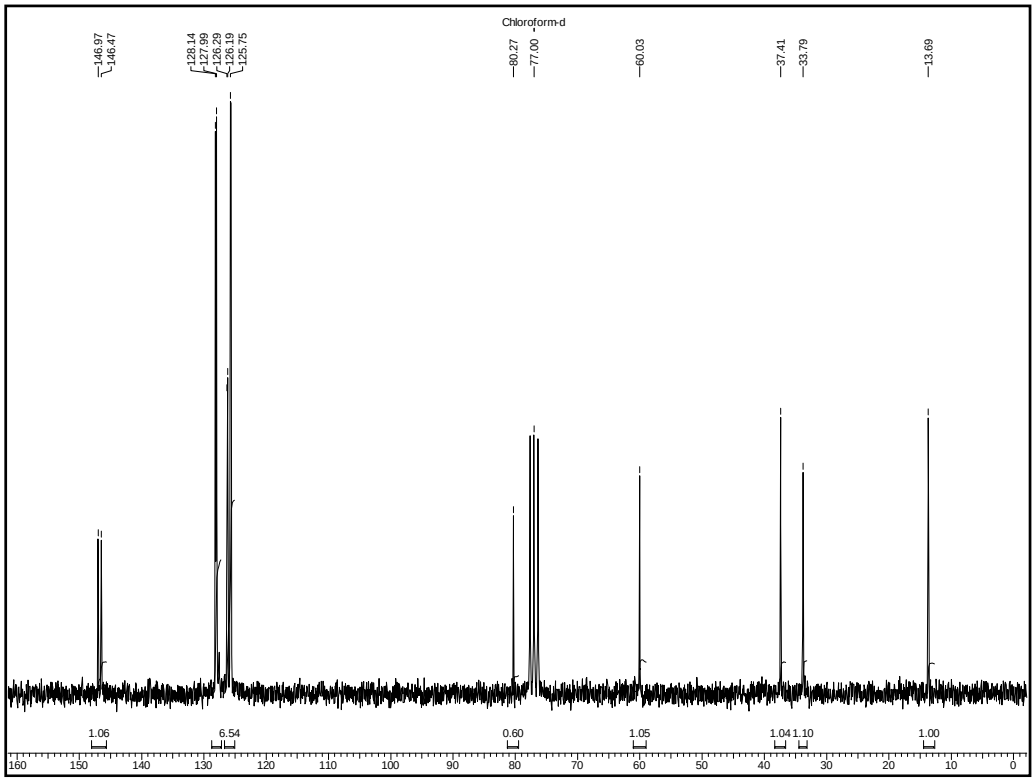
^{1}H NMR Spectrum of 51 in $CDCl_3$



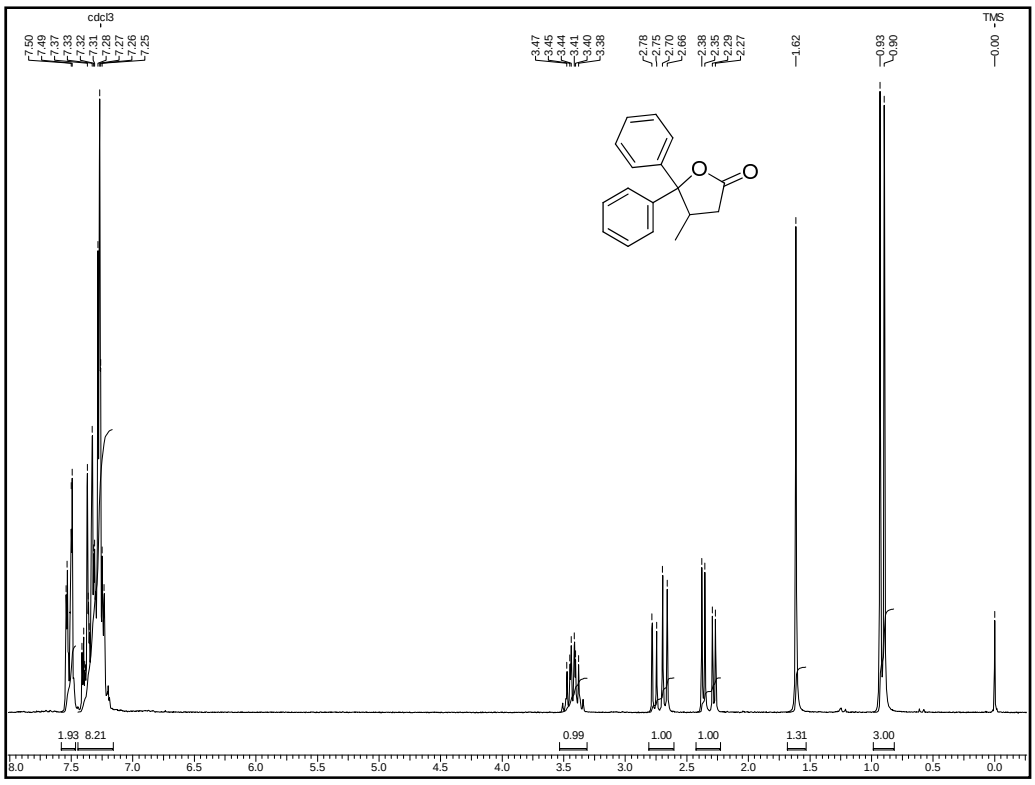
^{13}C NMR Spectrum of 51 in $CDCl_3$



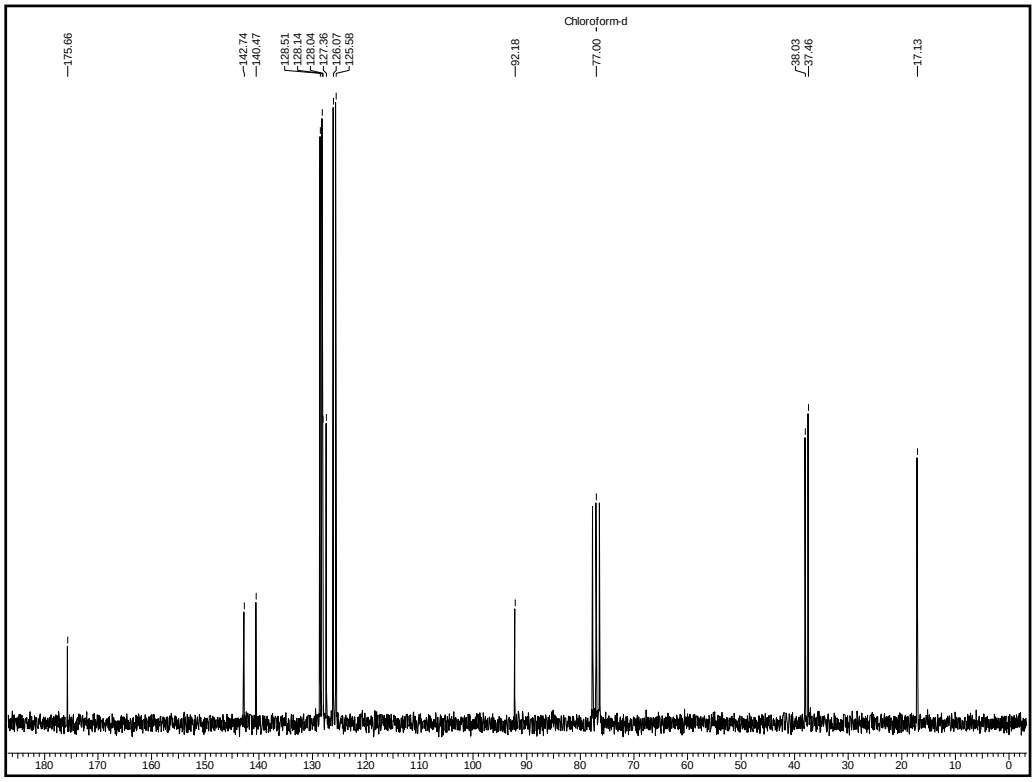
^{1}H NMR Spectrum of 52 in $CDCl_3$



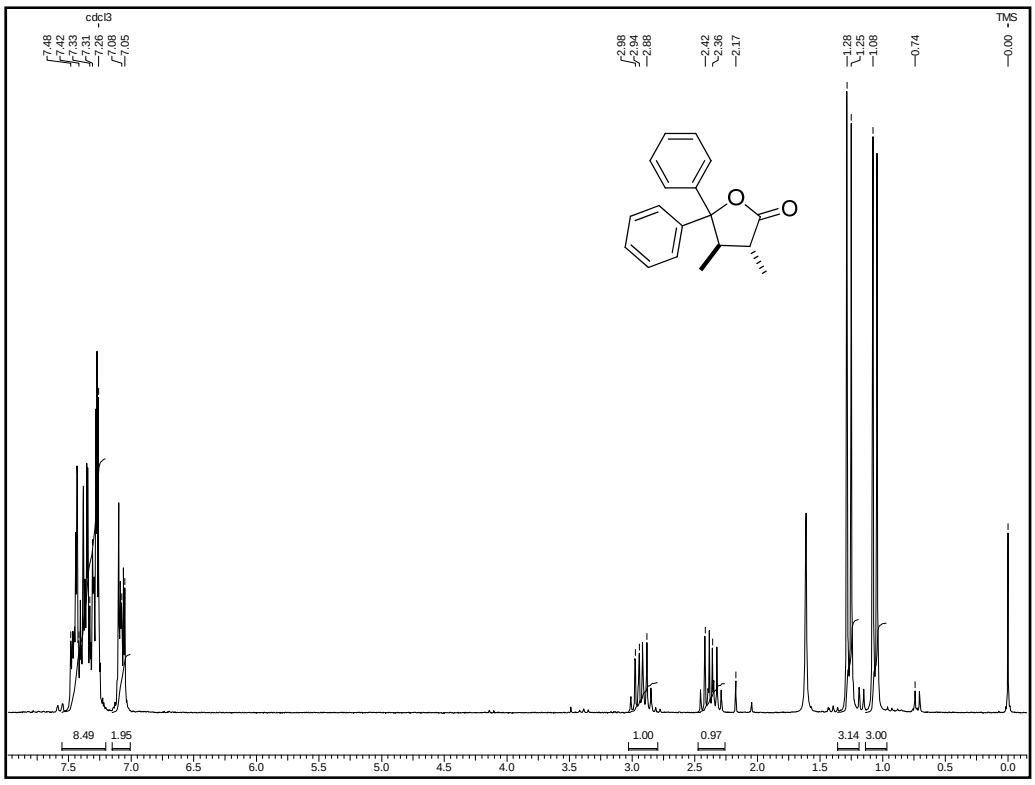
^{13}C NMR Spectrum of 52 in $CDCl_3$



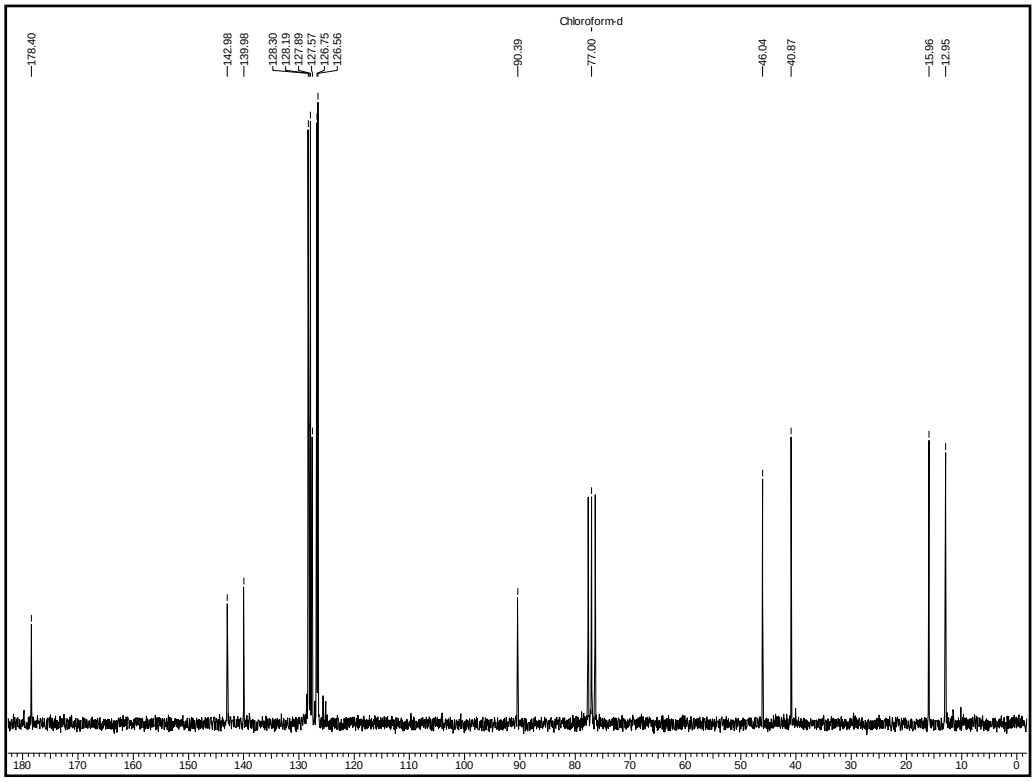
^{1}H NMR Spectrum of 50 in $CDCl_3$



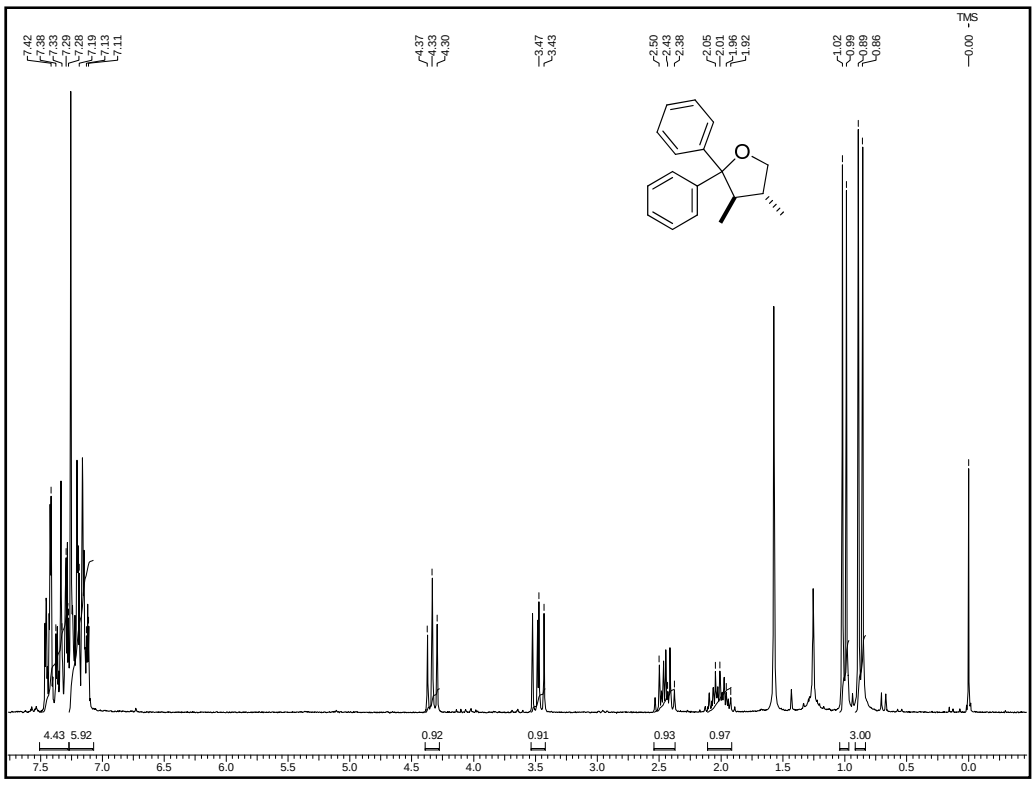
^{13}C NMR Spectrum of 50 in $CDCl_3$



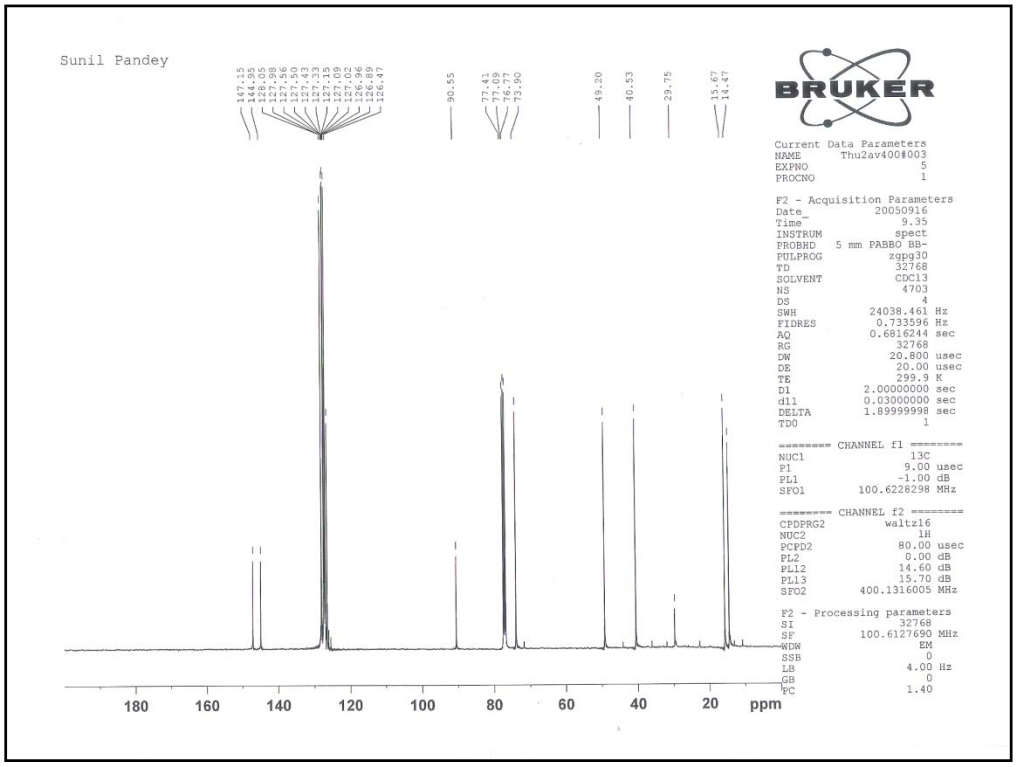
^{1}H NMR Spectrum of 53 in $CDCl_3$



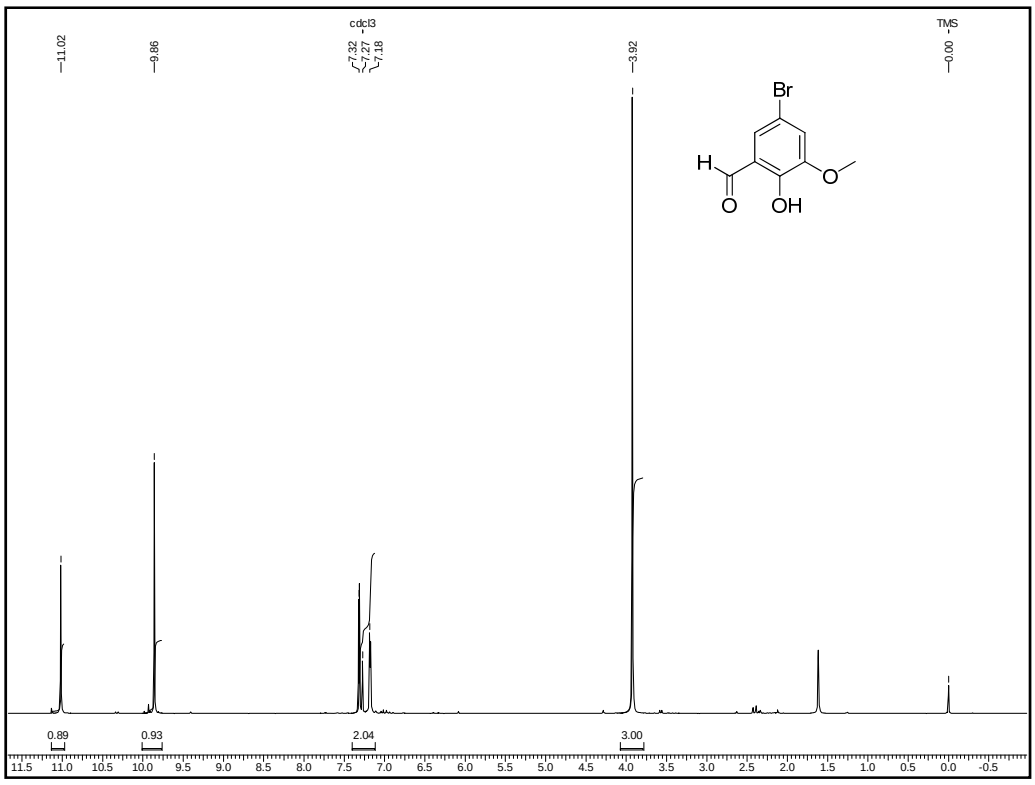
^{13}C NMR Spectrum of 53 in $CDCl_3$



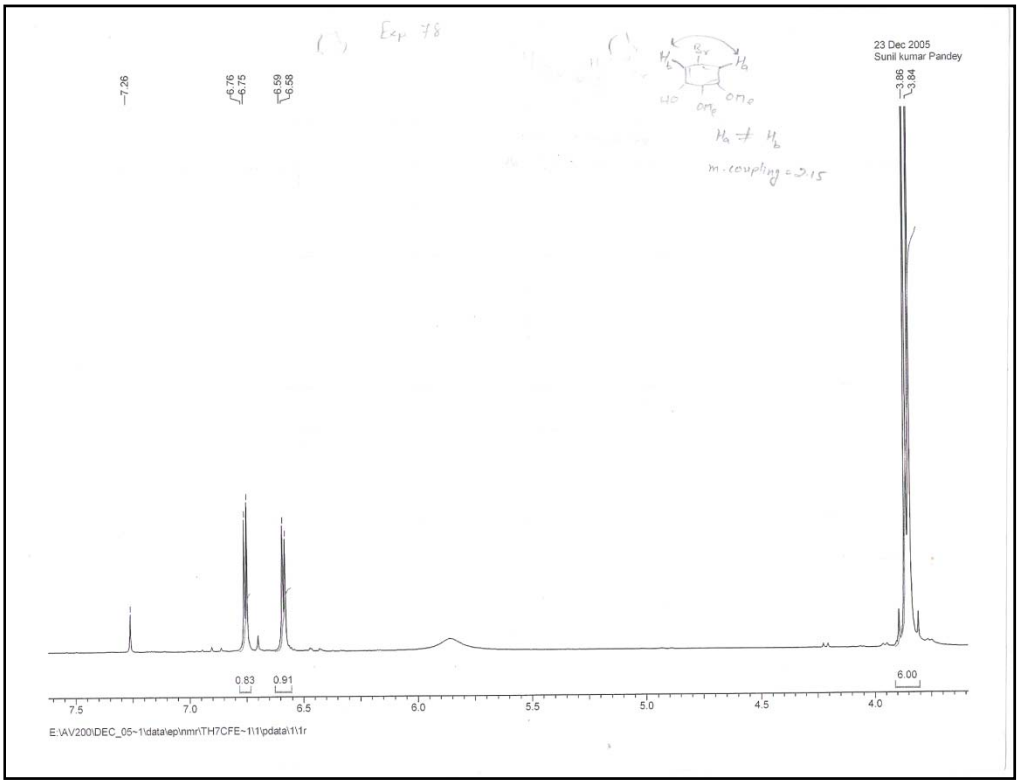
^{1}H NMR Spectrum of 49 in $CDCl_3$



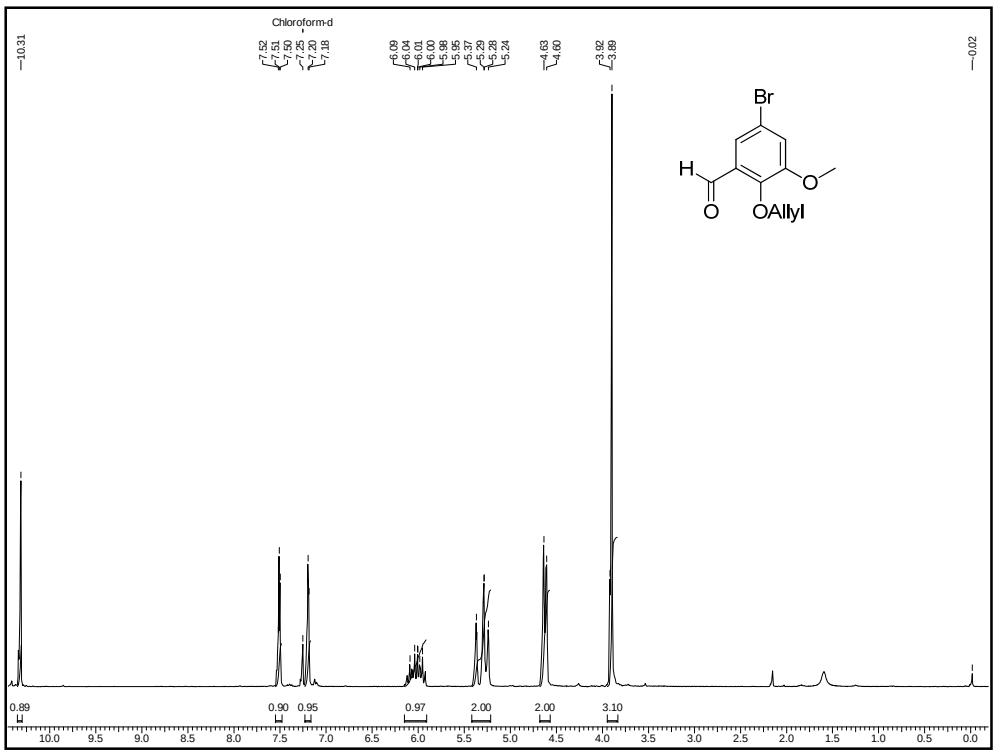
^{13}C NMR Spectrum of 49 in $CDCl_3$



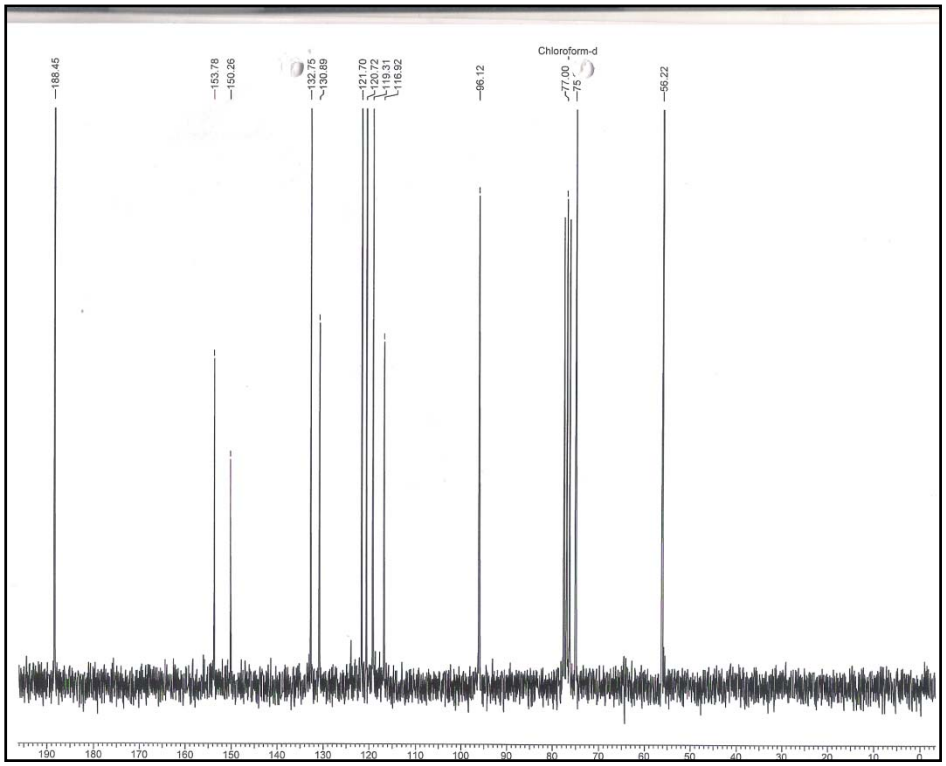
^{1}H NMR Spectrum of 55 in $CDCl_3$



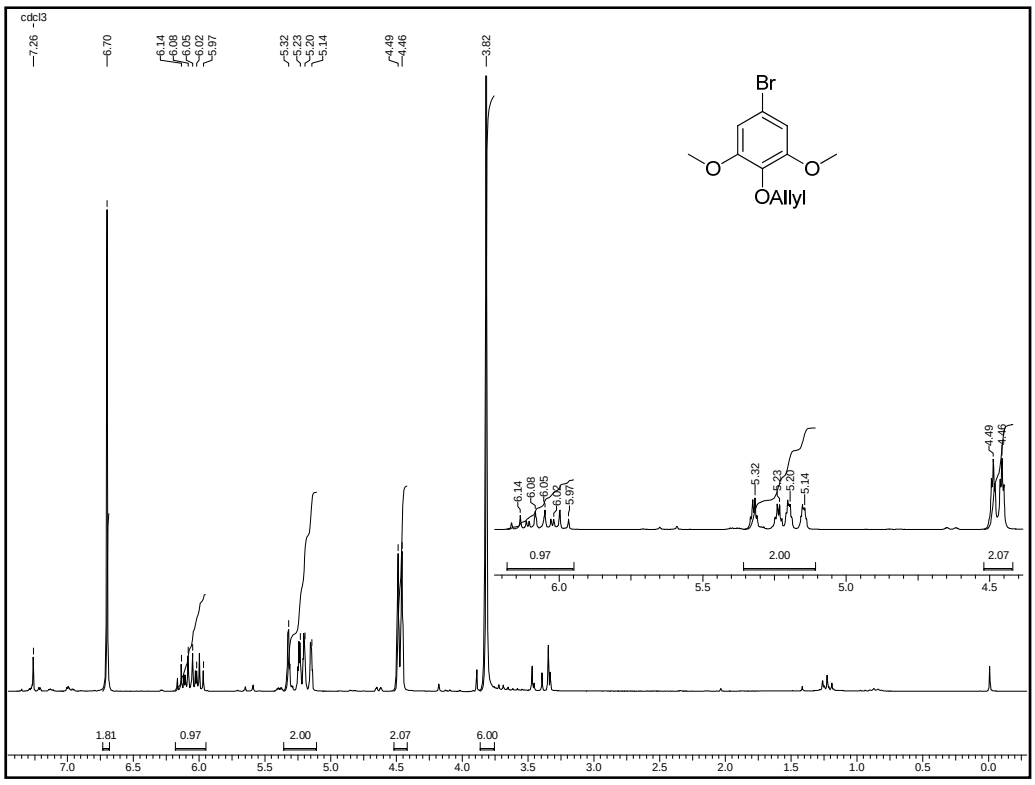
^{1}H NMR Spectrum of 57a in $CDCl_3$



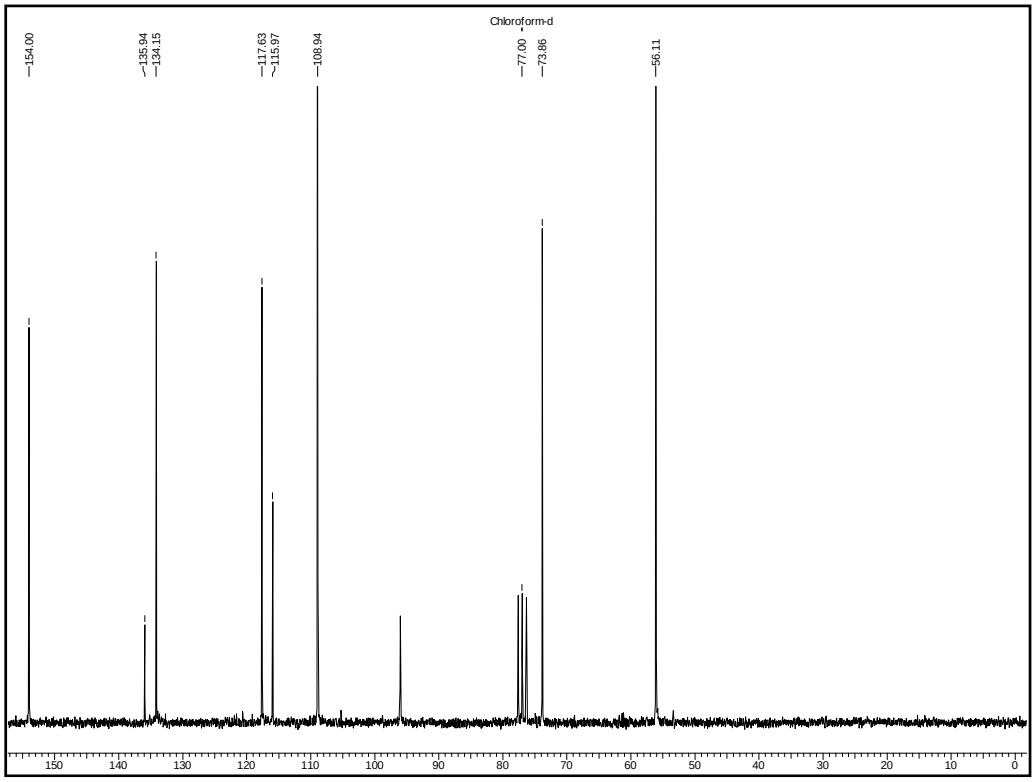
^{1}H NMR Spectrum of 58 in $CDCl_3$



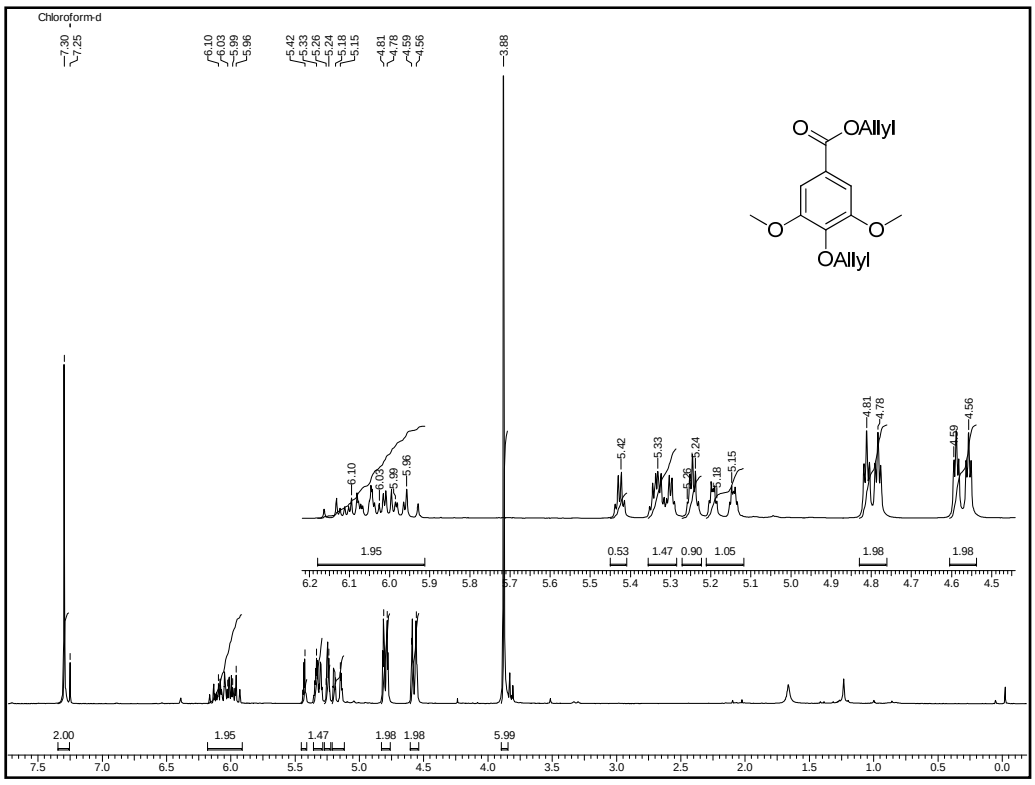
^{13}C NMR Spectrum of 58 in $CDCl_3$



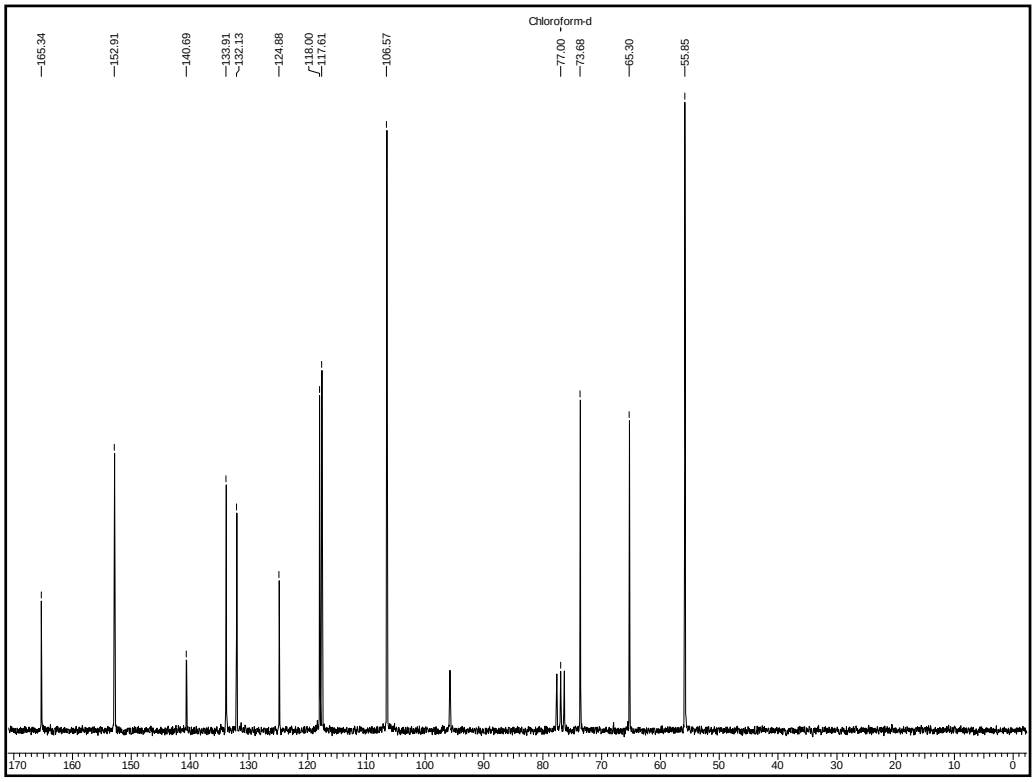
^{1}H NMR Spectrum of 47 in $CDCl_3$



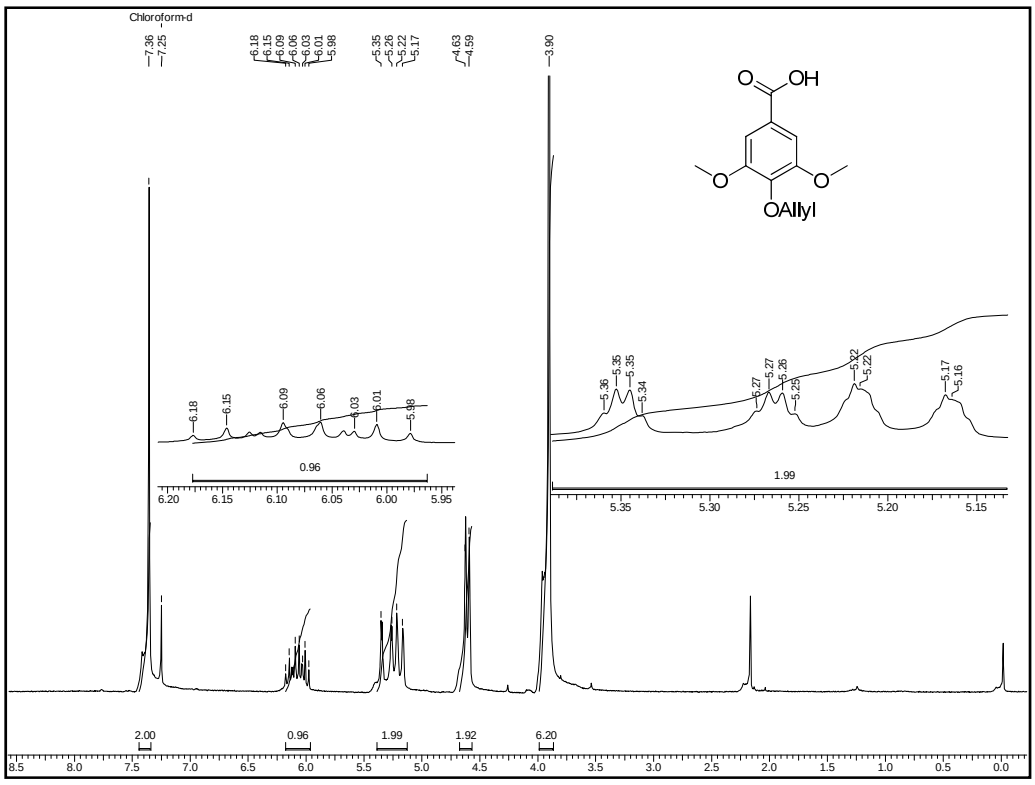
^{13}C NMR Spectrum of 47 in $CDCl_3$



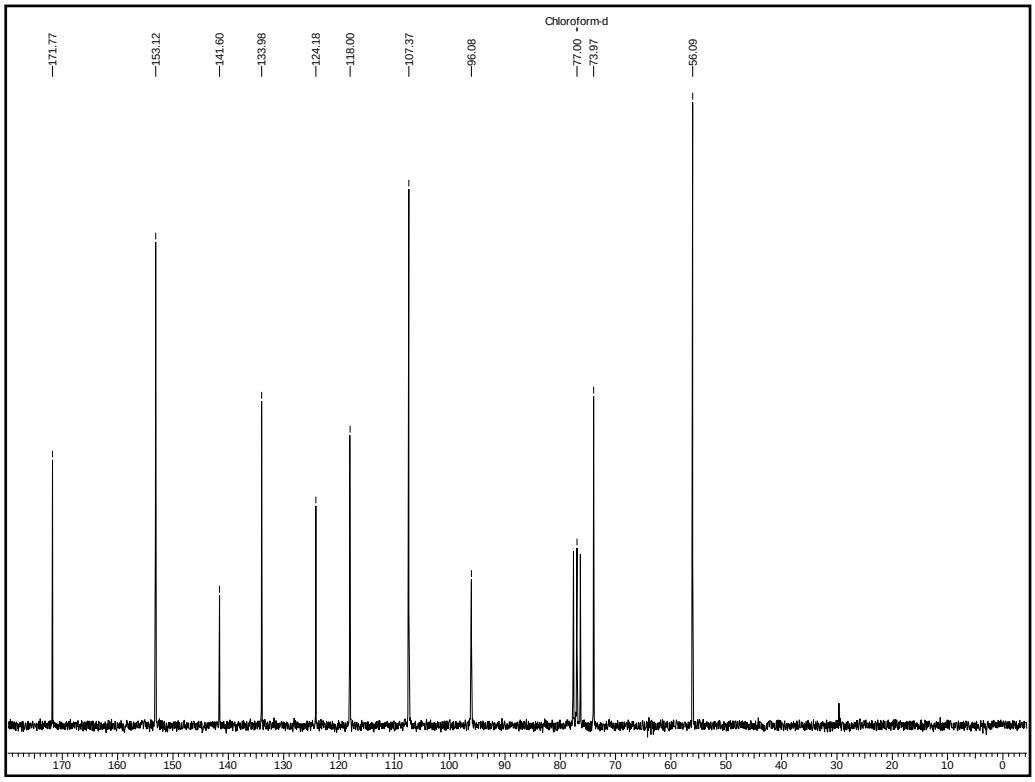
^{1}H NMR Spectrum of 61 in $CDCl_3$



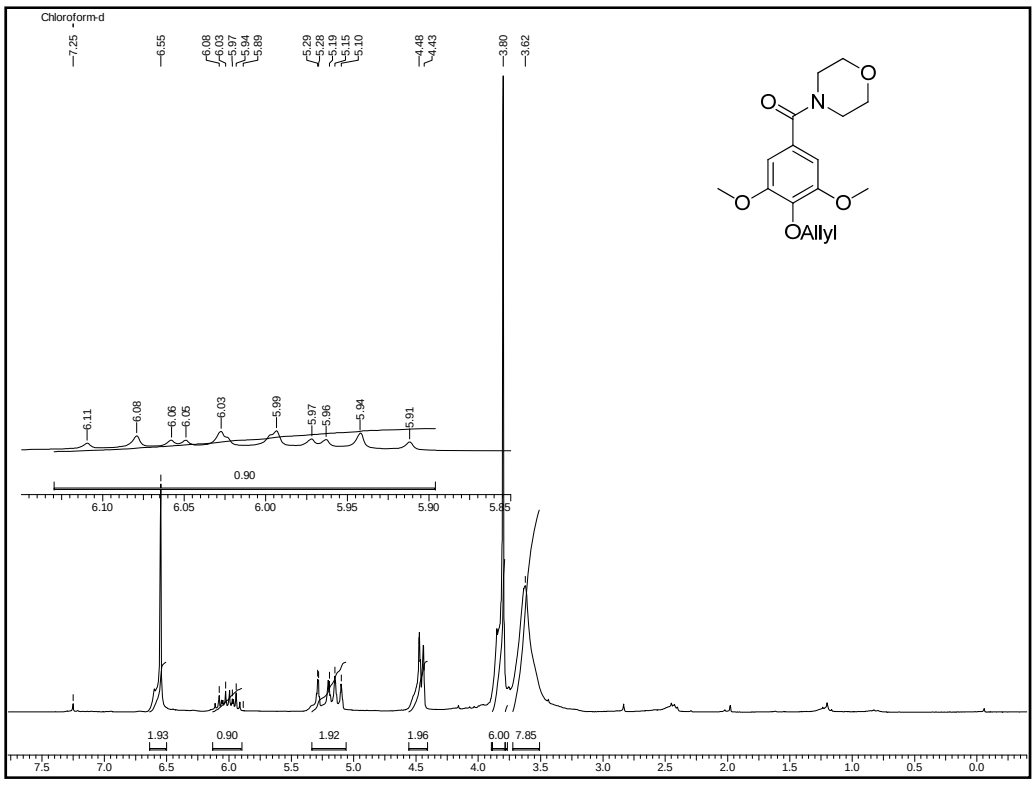
^{13}C NMR Spectrum of 61 in $CDCl_3$



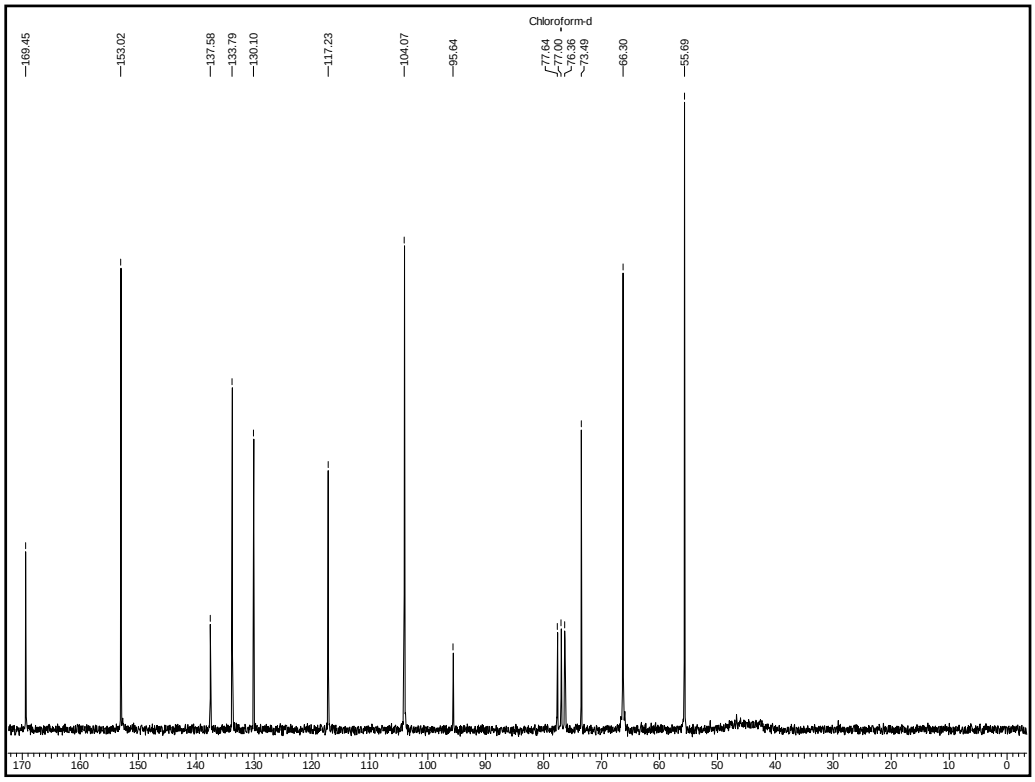
^{1}H NMR Spectrum of 62 in $CDCl_3$



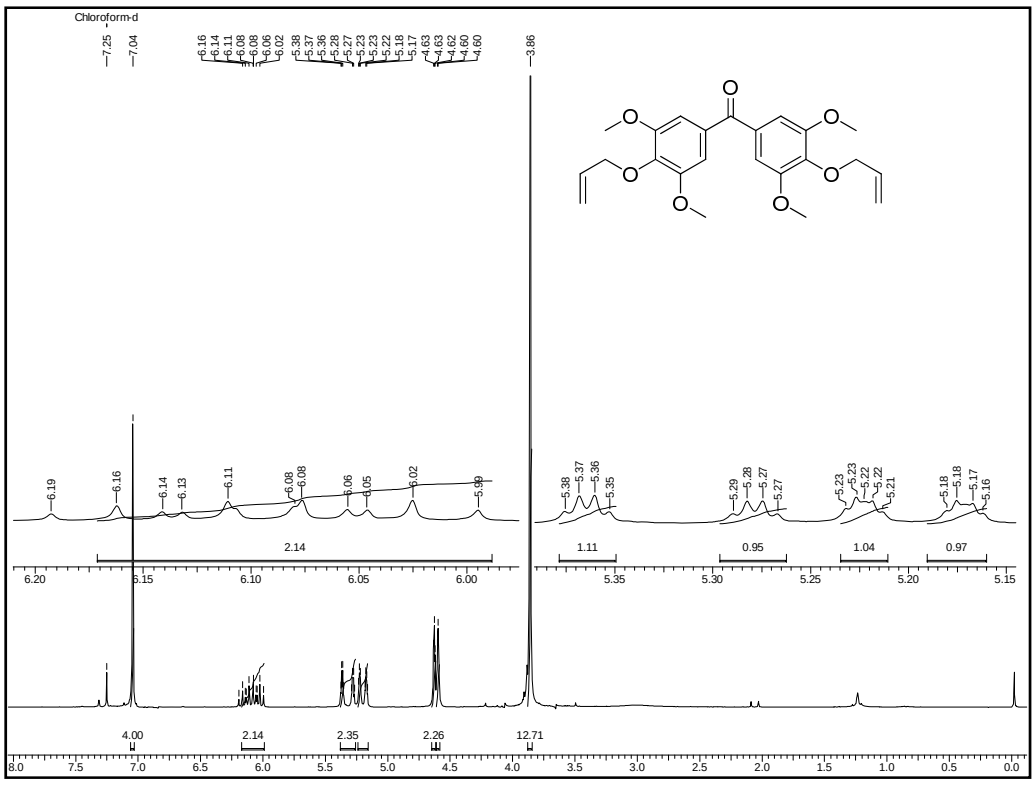
^{13}C NMR Spectrum of 62 in $CDCl_3$



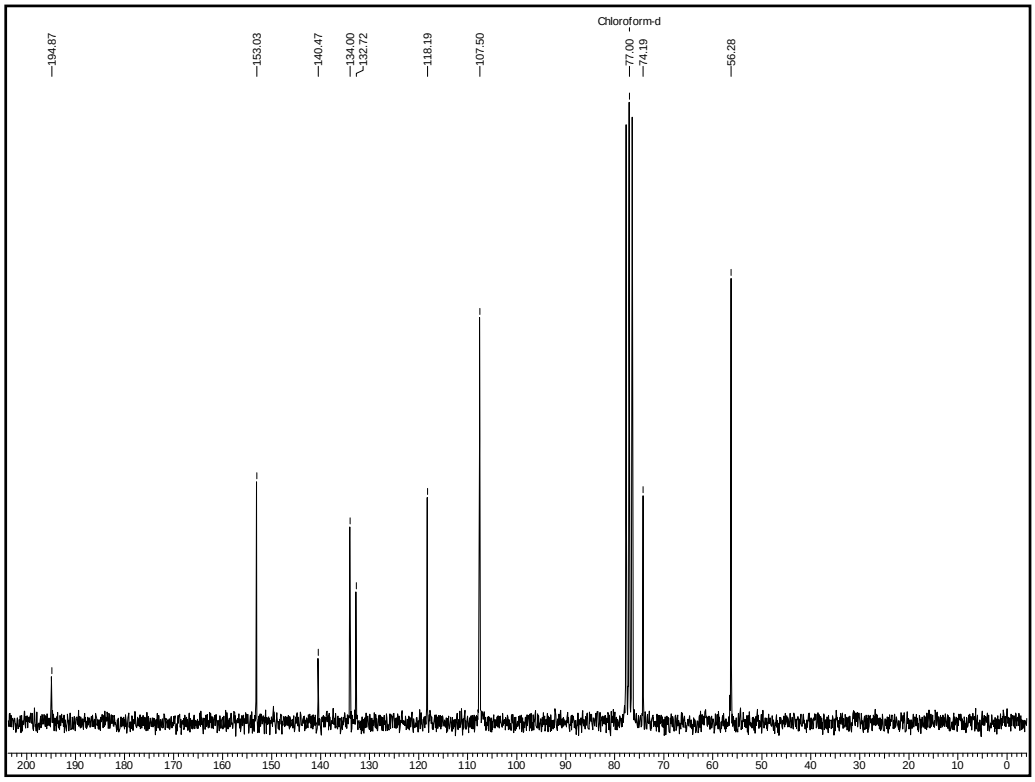
^{1}H NMR Spectrum of 48 in $CDCl_3$



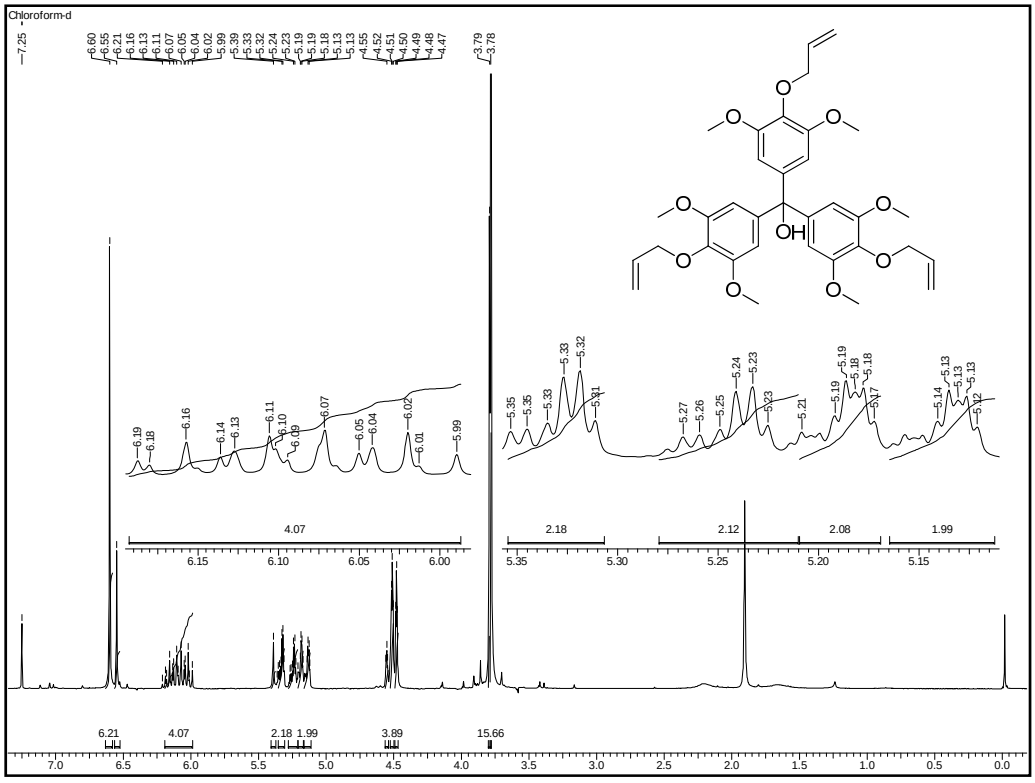
^{1}H NMR Spectrum of 48 in $CDCl_3$



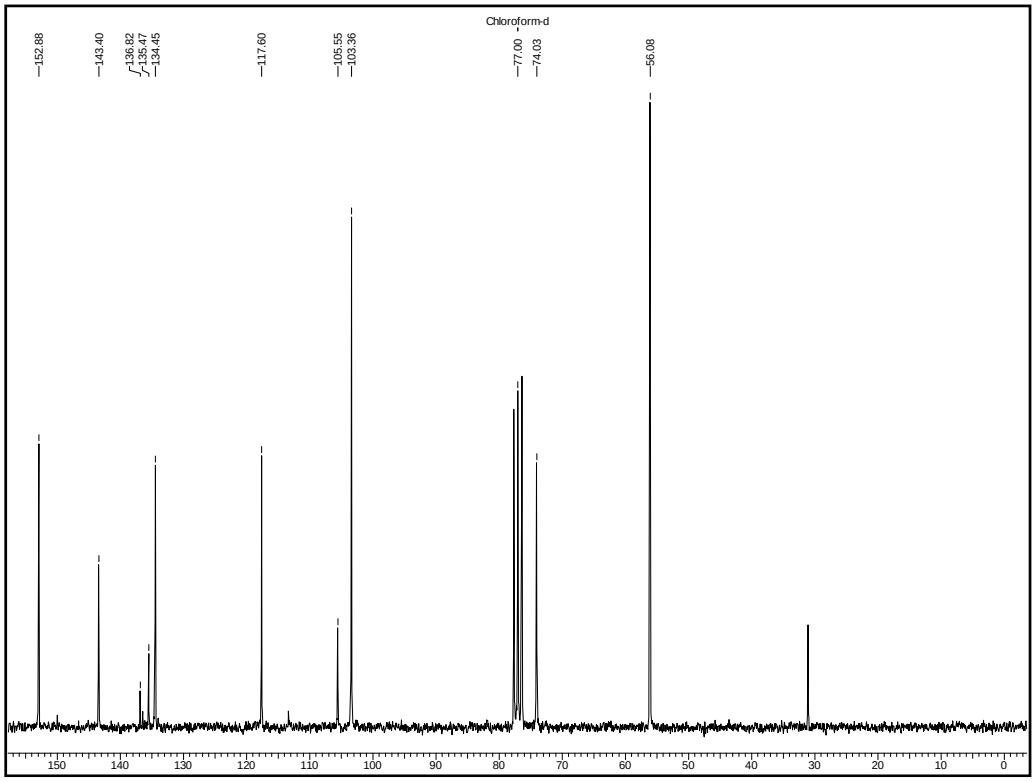
^{1}H NMR Spectrum of di-O-allyl-46 in $CDCl_3$



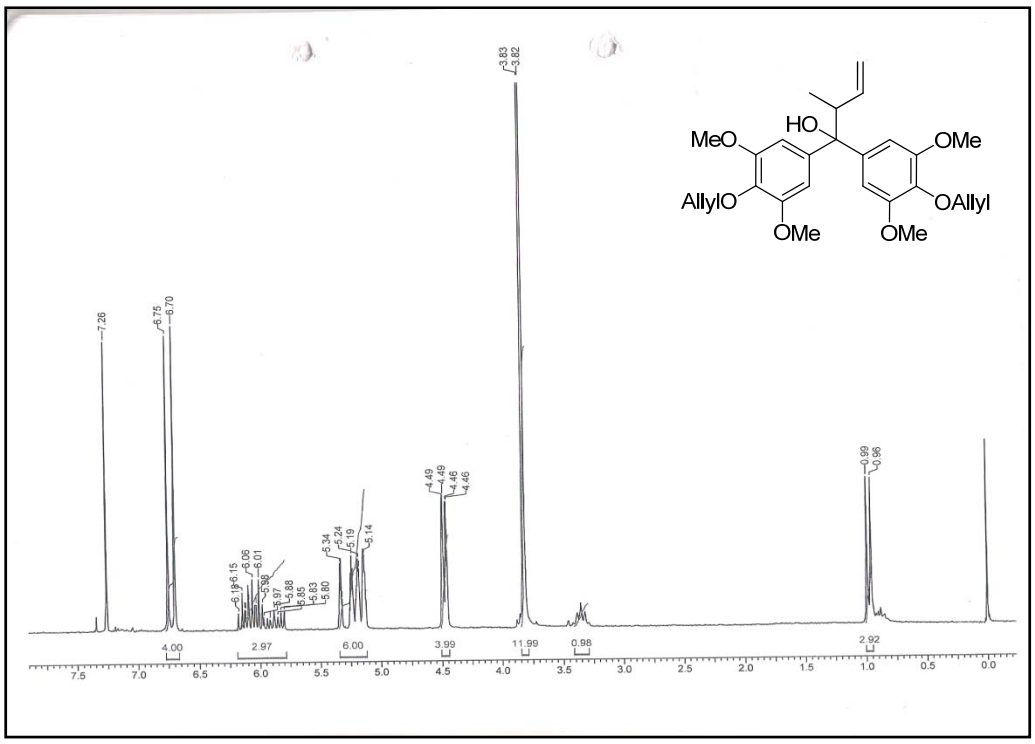
^{1}H NMR Spectrum of di-O-allyl-46 in $CDCl_3$



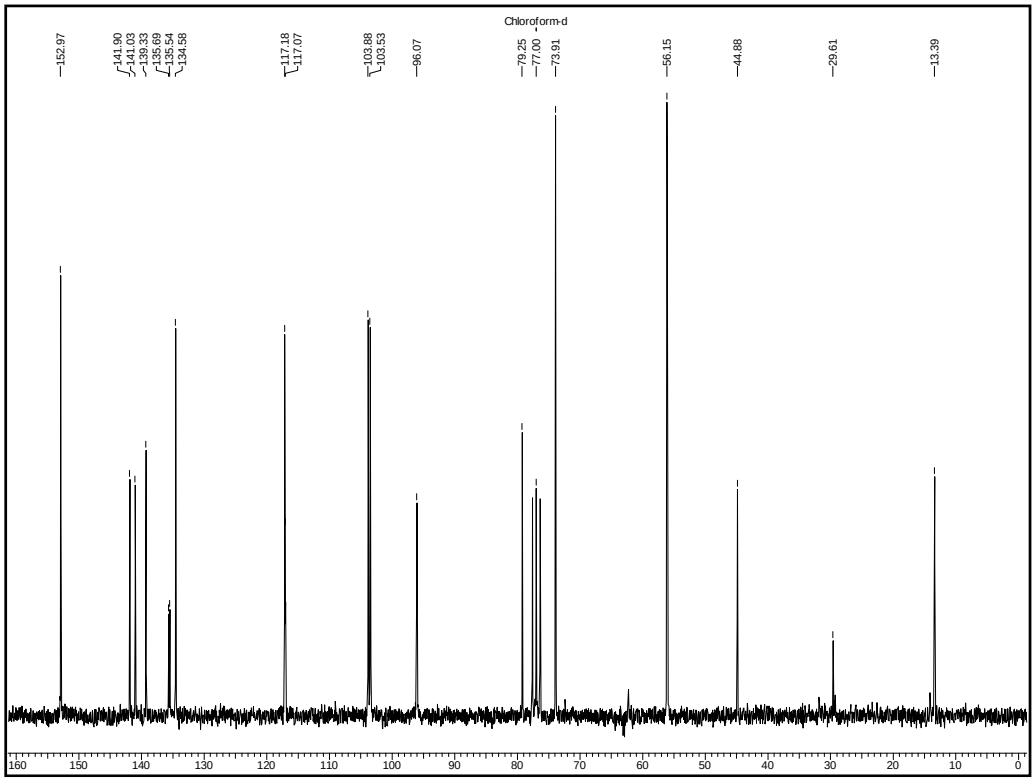
^{1}H NMR Spectrum of 64 in $CDCl_3$



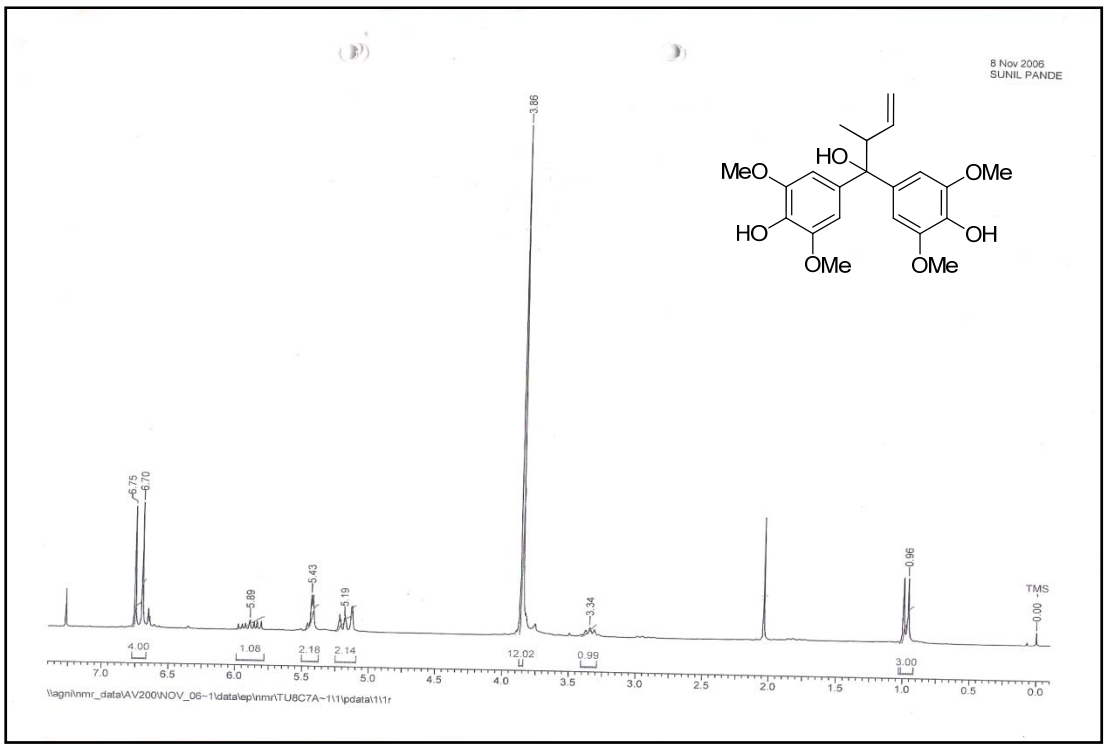
^{13}C NMR Spectrum of 64 in $CDCl_3$



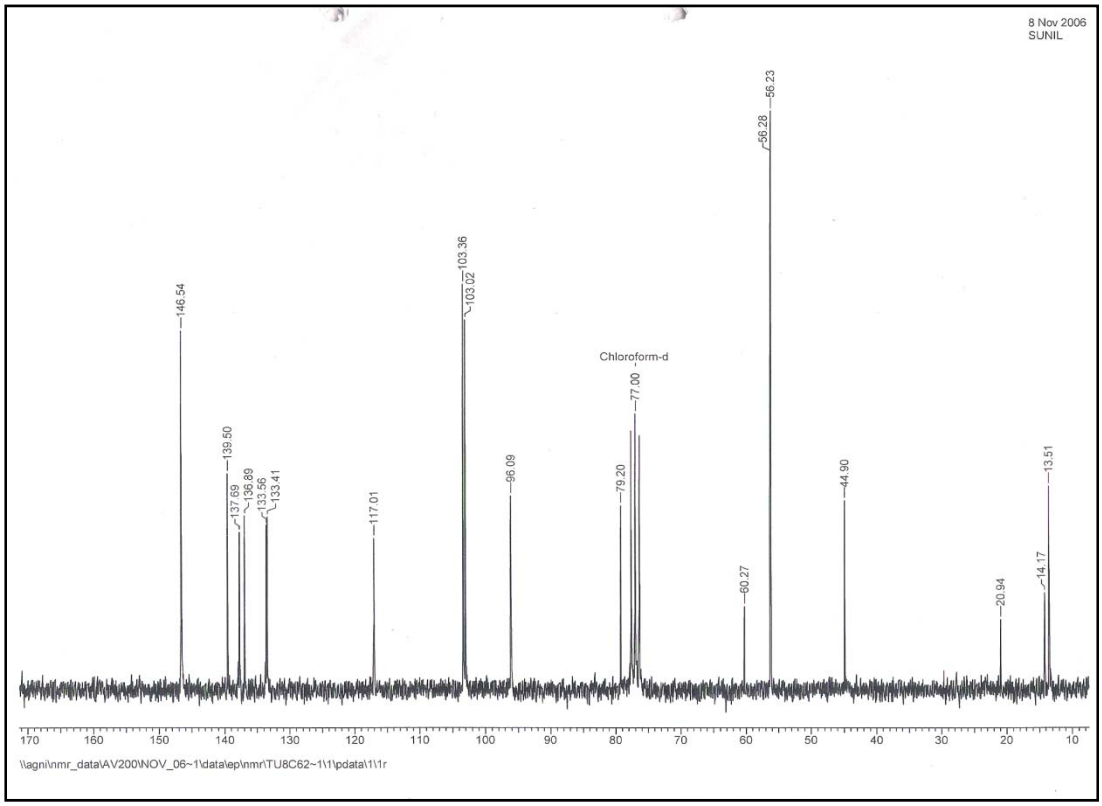
^{1}H NMR Spectrum of 66 in $CDCl_3$



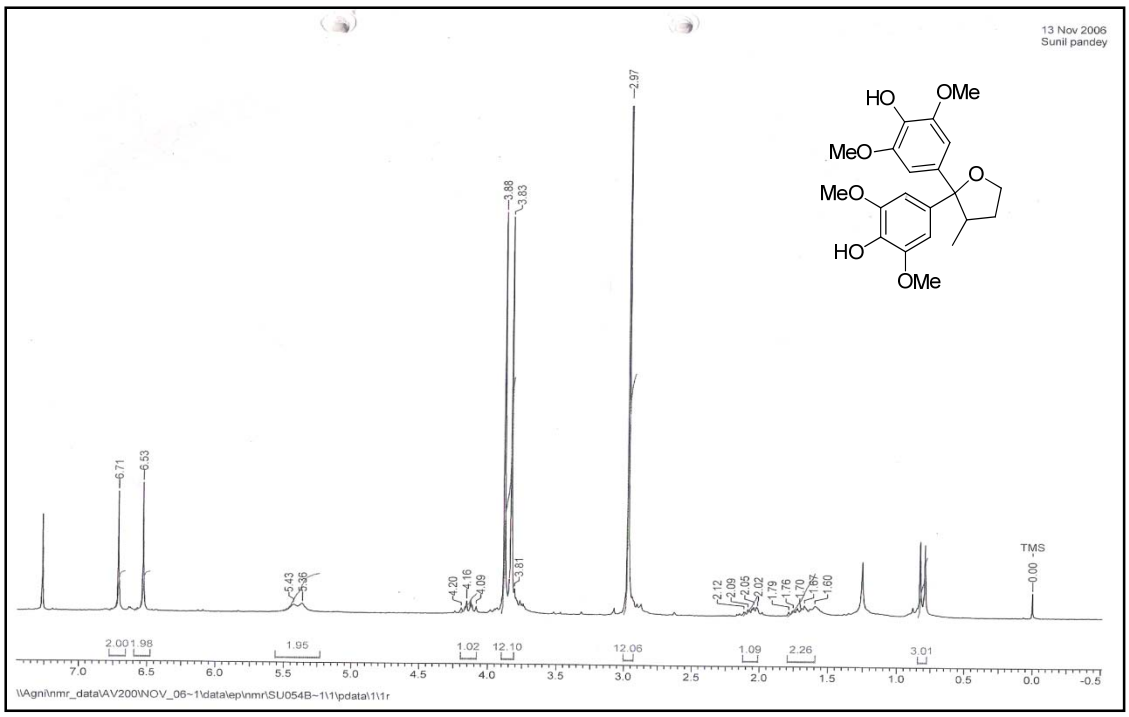
^{13}C NMR Spectrum of 66 in $CDCl_3$



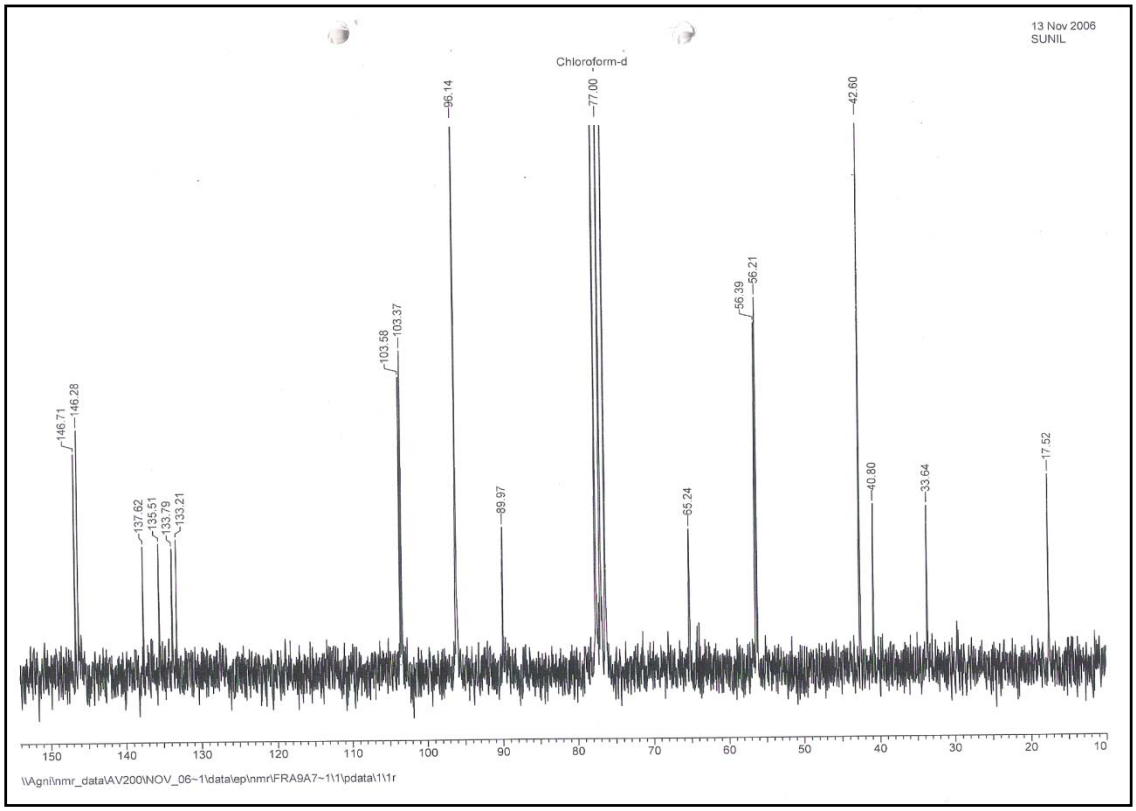
^{1}H NMR Spectrum of 65 in $CDCl_3$



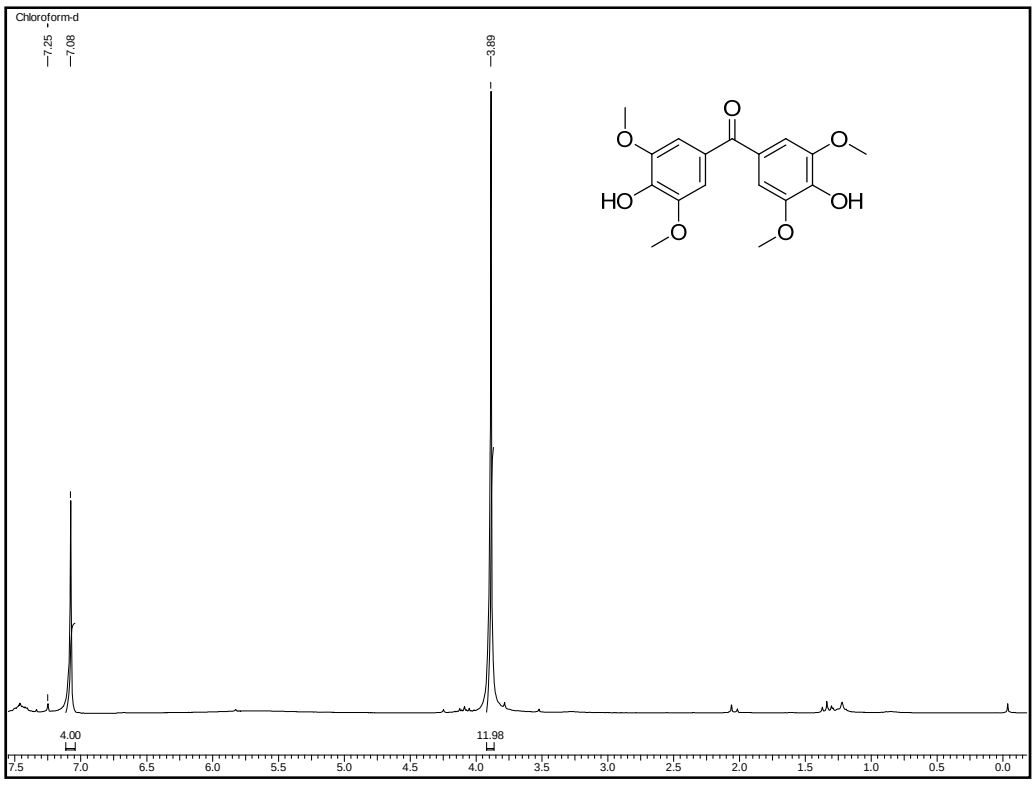
^{13}C NMR Spectrum of 65 in $CDCl_3$



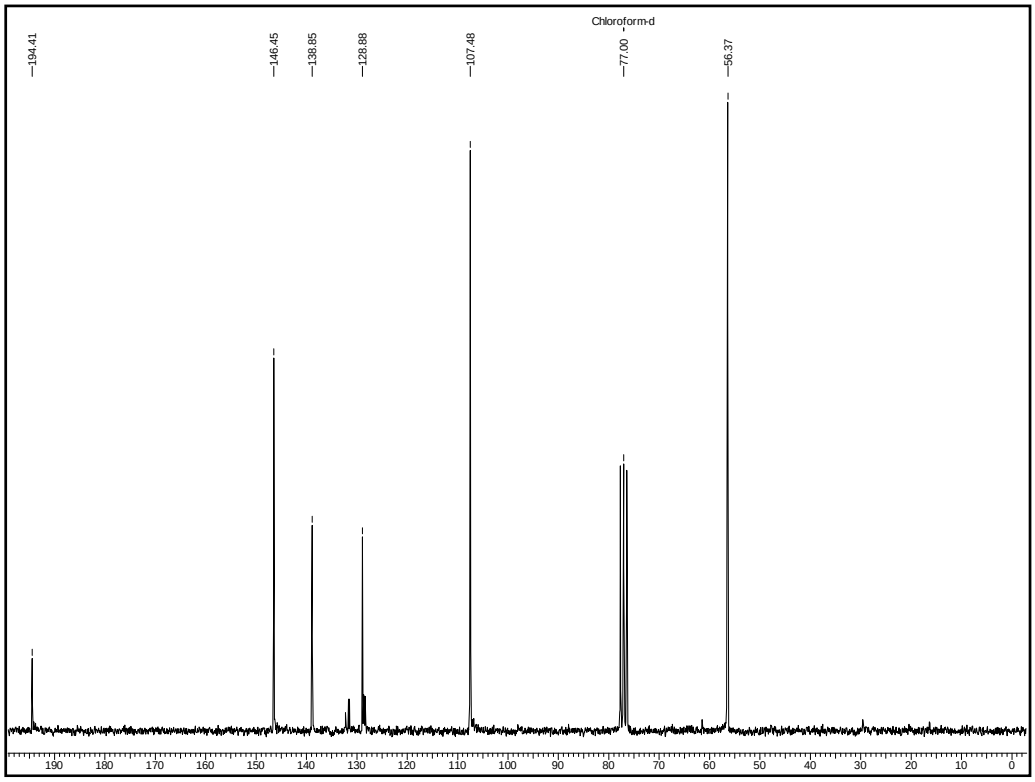
^{1}H NMR Spectrum of 67 in $CDCl_3$



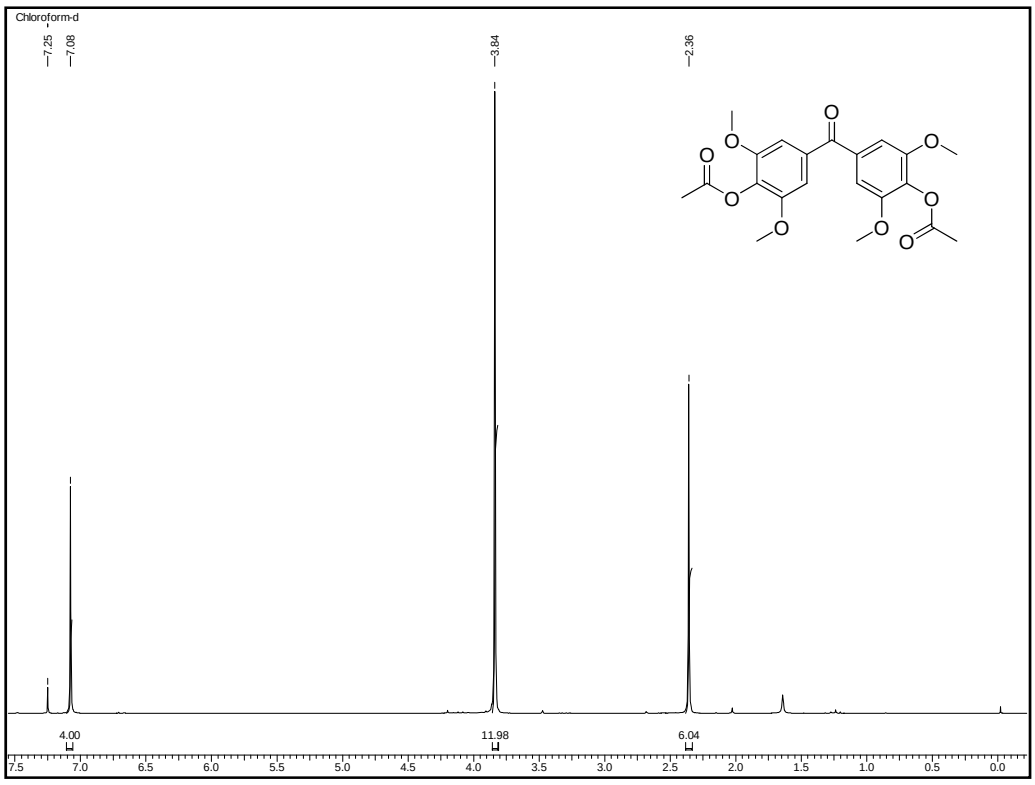
^{13}C NMR Spectrum of 67 in $CDCl_3$



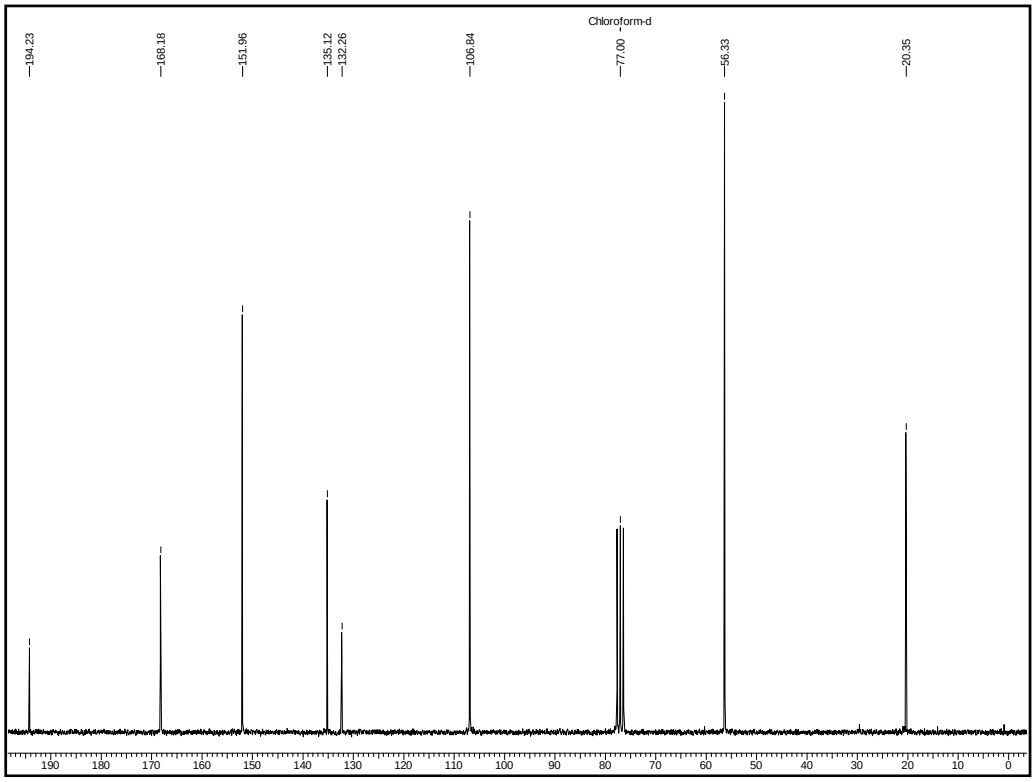
^{1}H NMR Spectrum of 46 in $CDCl_3$



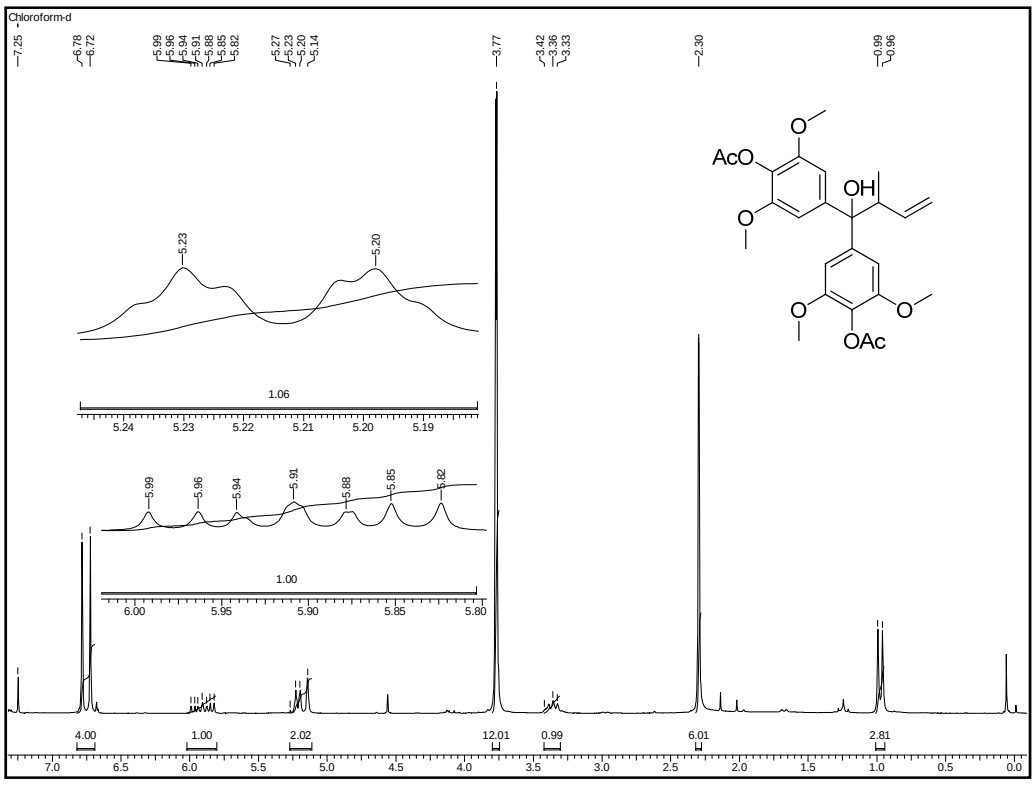
^{13}C NMR Spectrum of 46 in $CDCl_3$



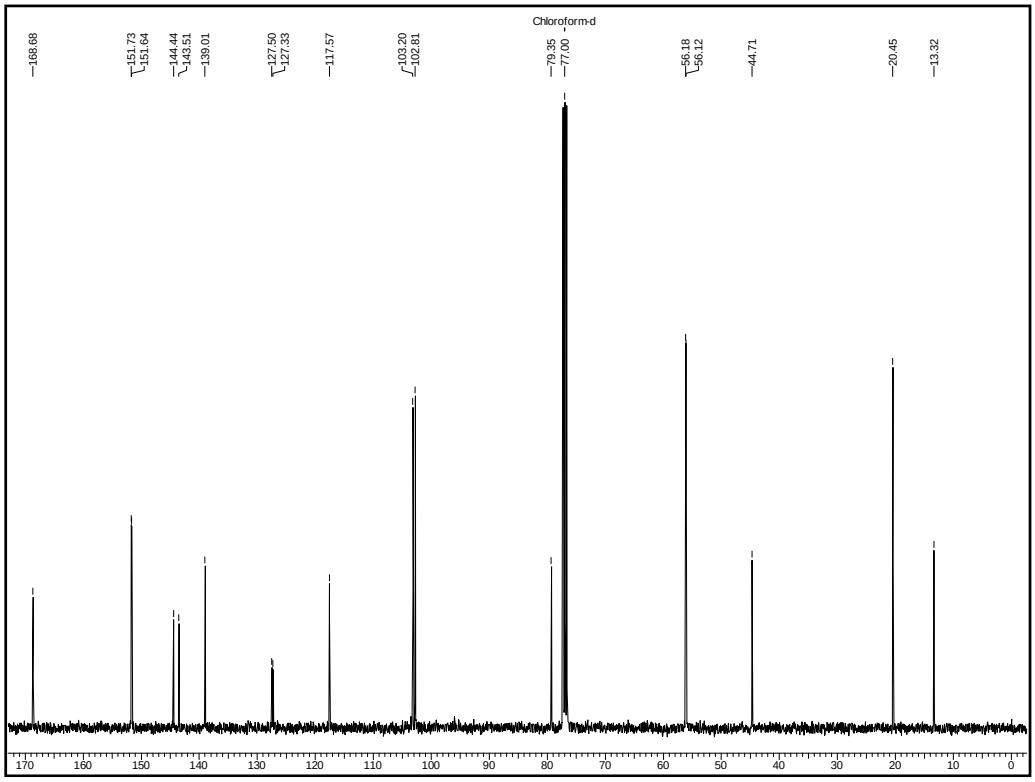
^{1}H NMR Spectrum of di-OAc-46 in $CDCl_3$



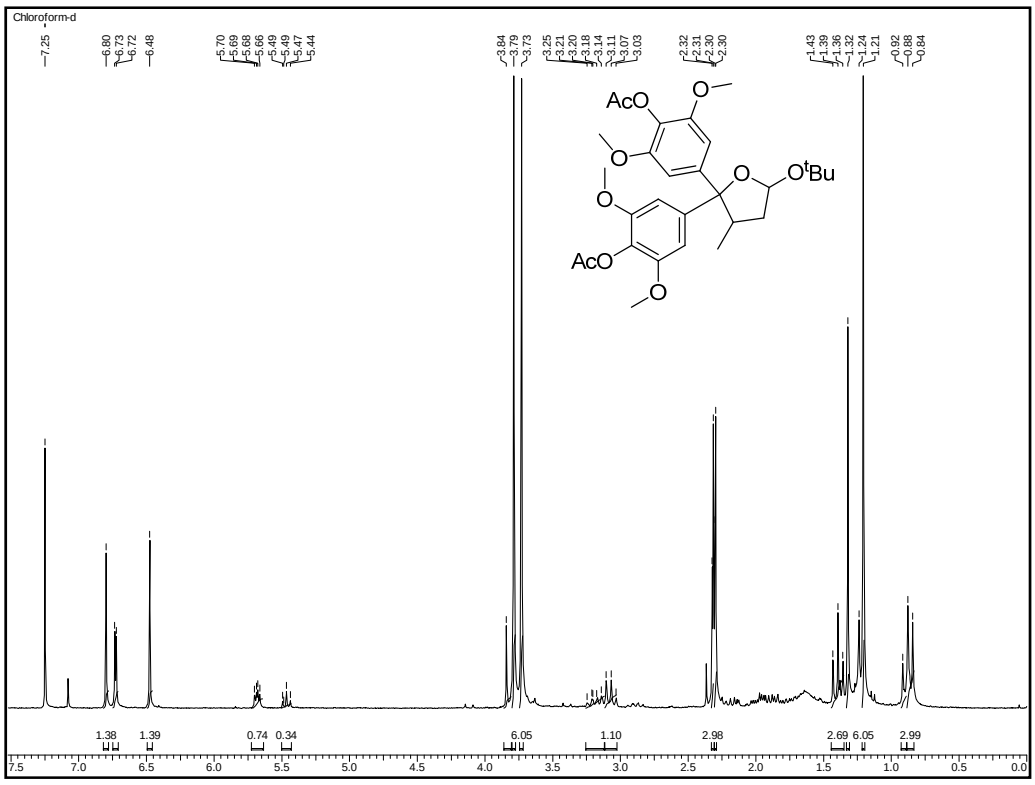
^{13}C NMR Spectrum of di-OAc-46 in $CDCl_3$



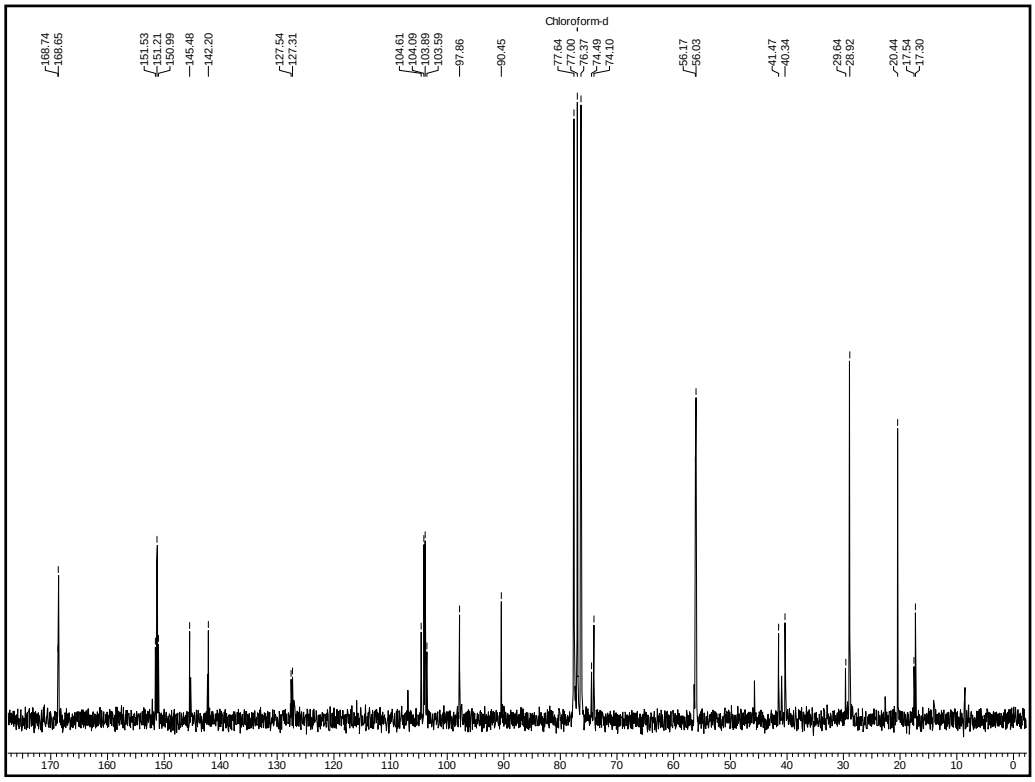
^{1}H NMR Spectrum of 68 in $CDCl_3$



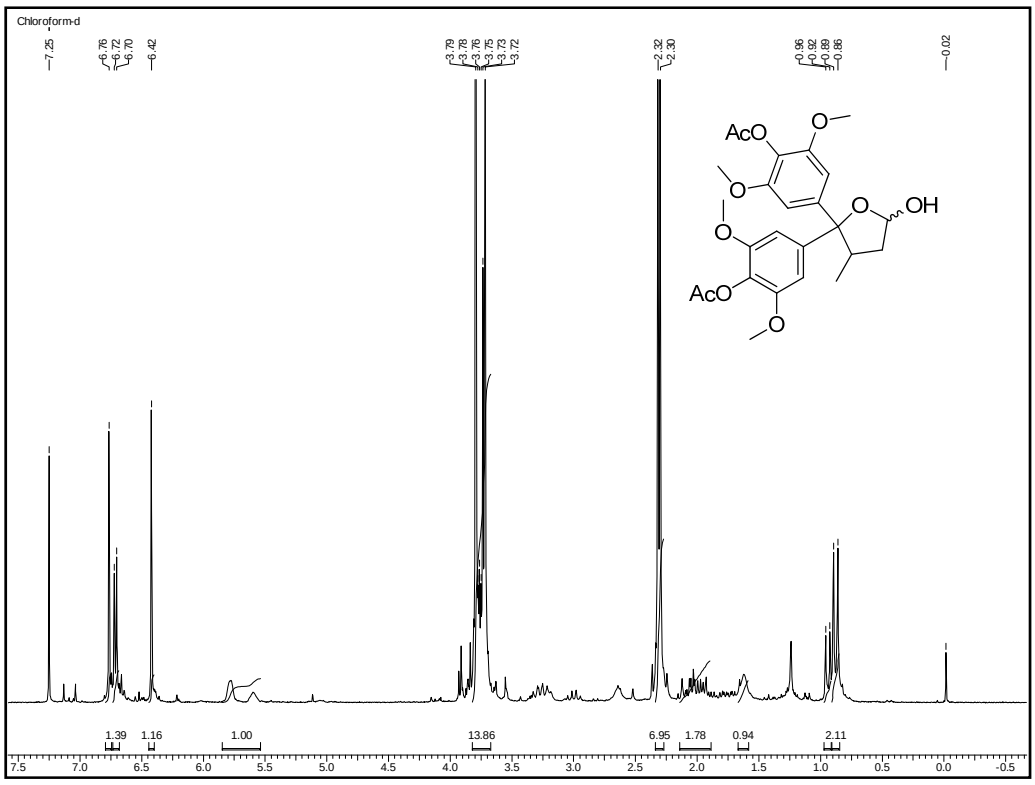
^{13}C NMR Spectrum of 68 in $CDCl_3$



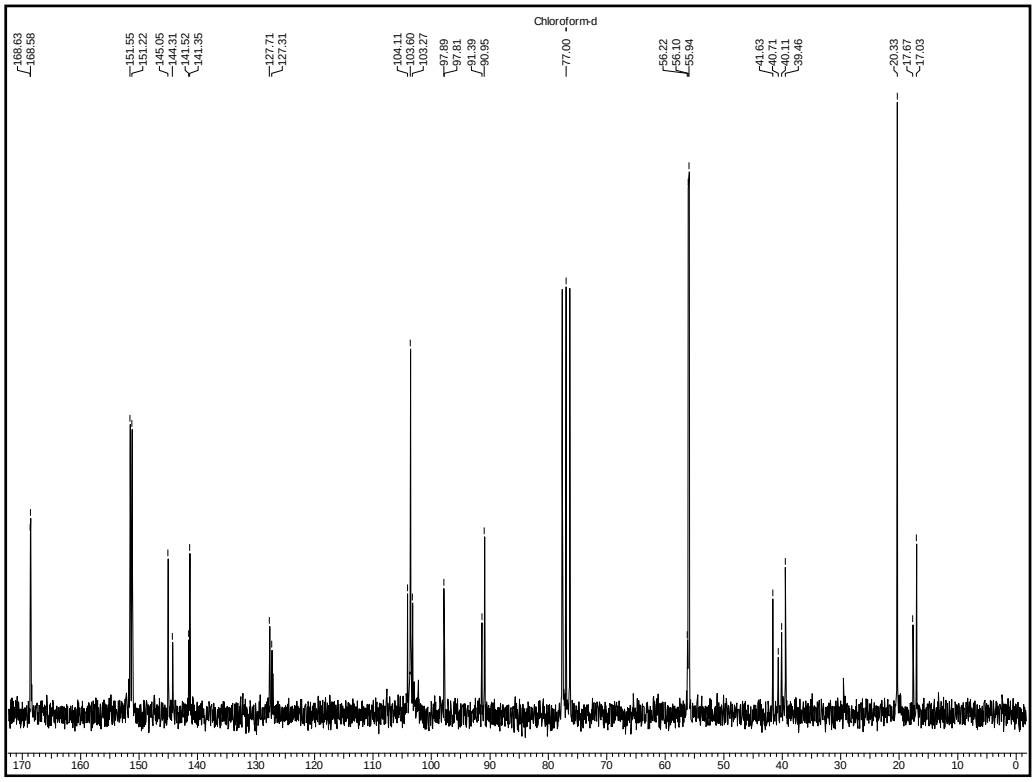
^{1}H NMR Spectrum of 71 in $CDCl_3$



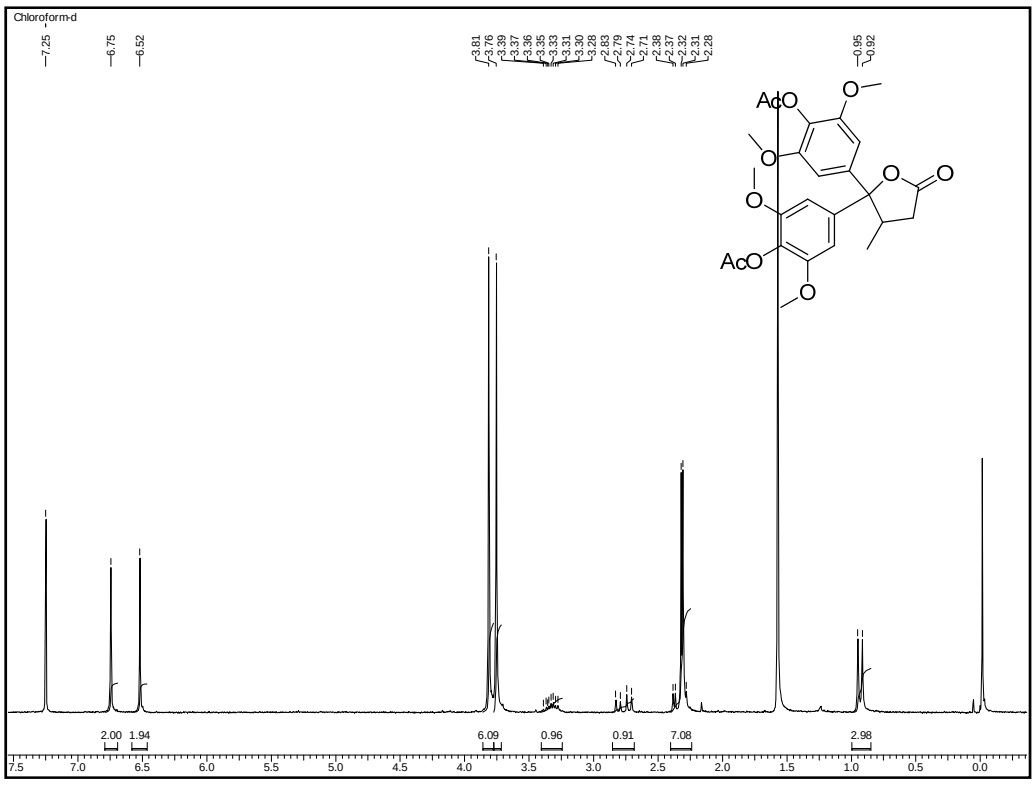
^{13}C NMR Spectrum of 71 in $CDCl_3$



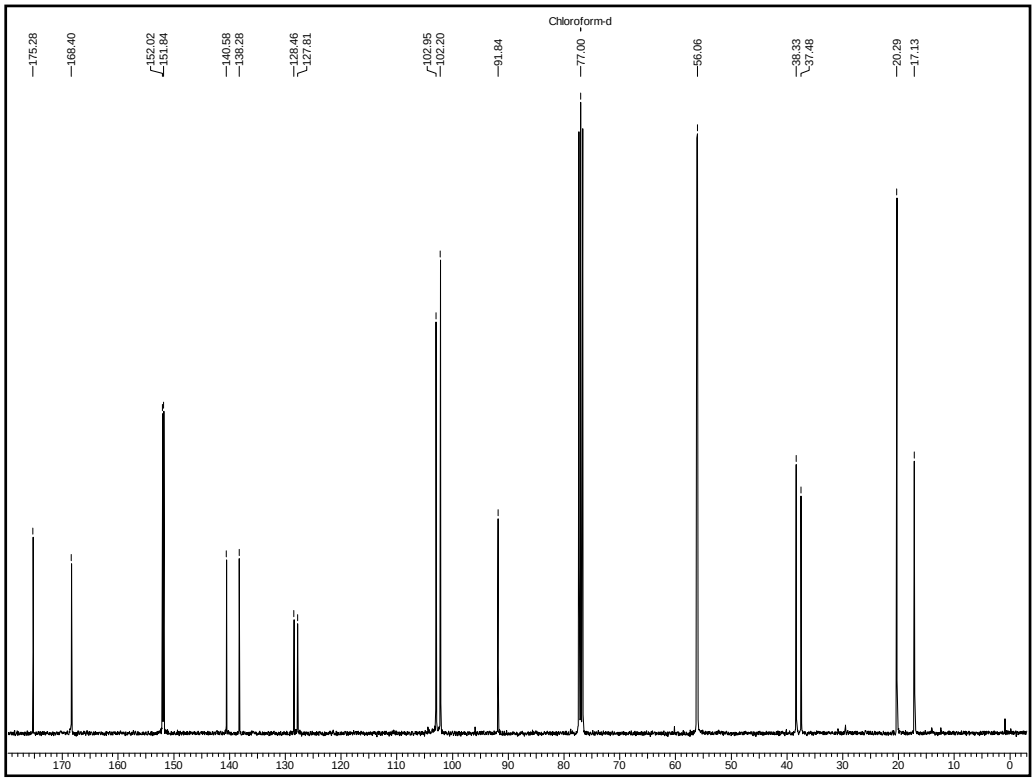
^{1}H NMR Spectrum of 70 in $CDCl_3$



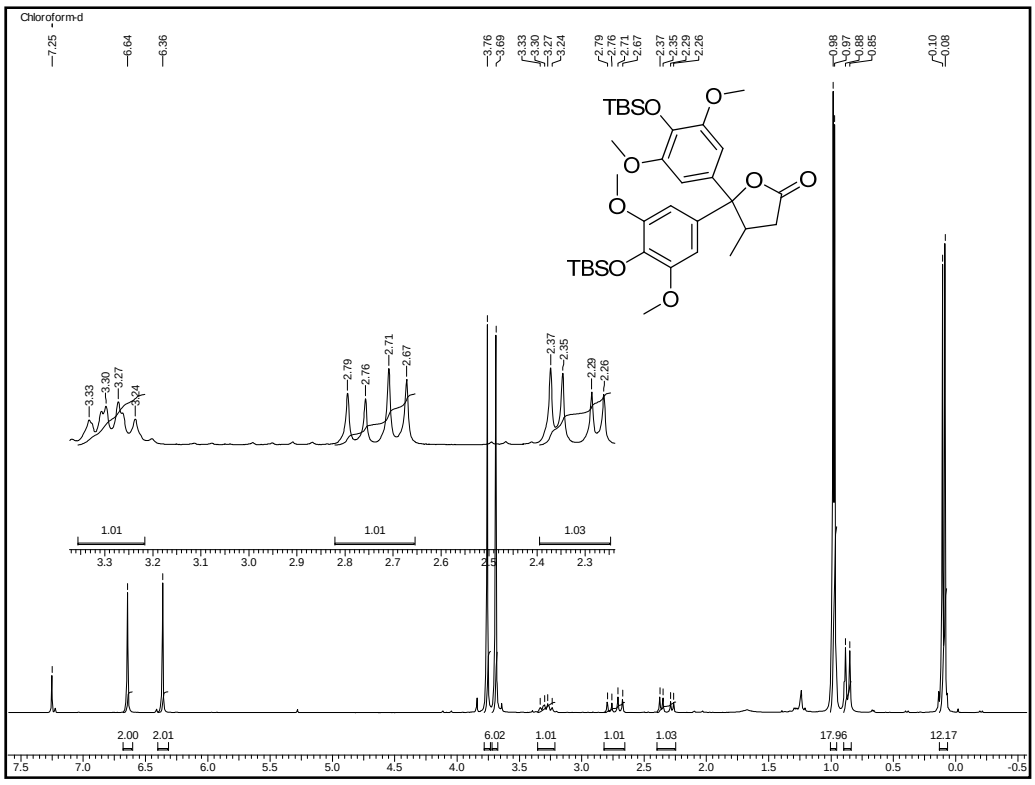
^{13}C NMR Spectrum of 70 in $CDCl_3$



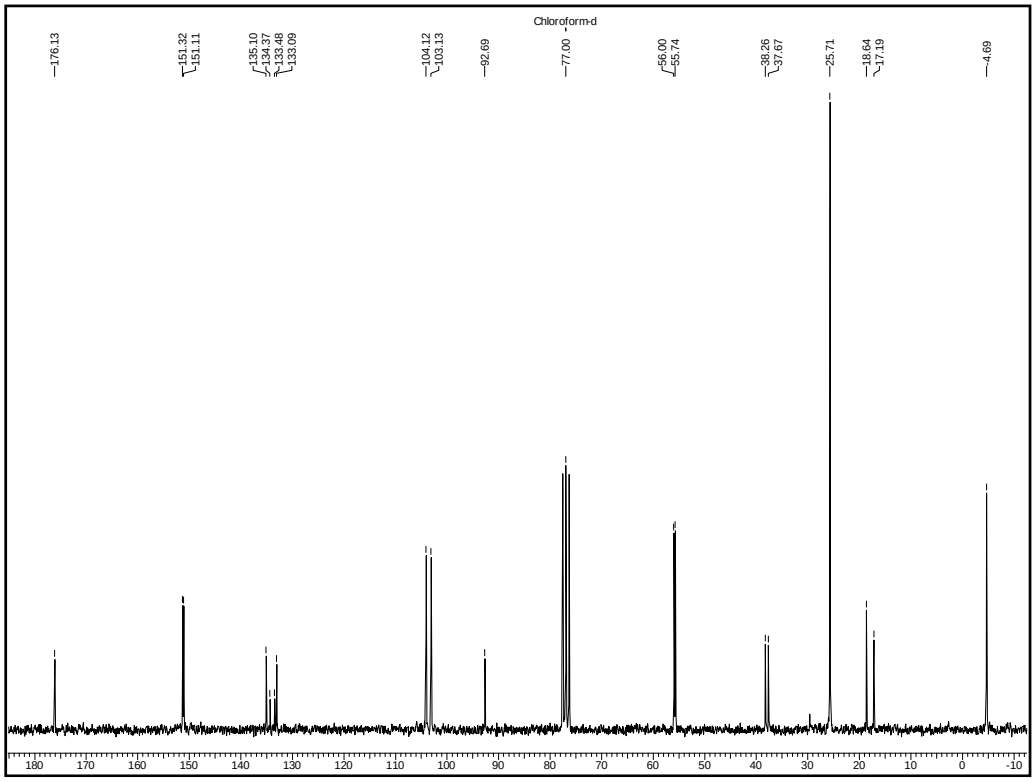
^{1}H NMR Spectrum of 72 in $CDCl_3$



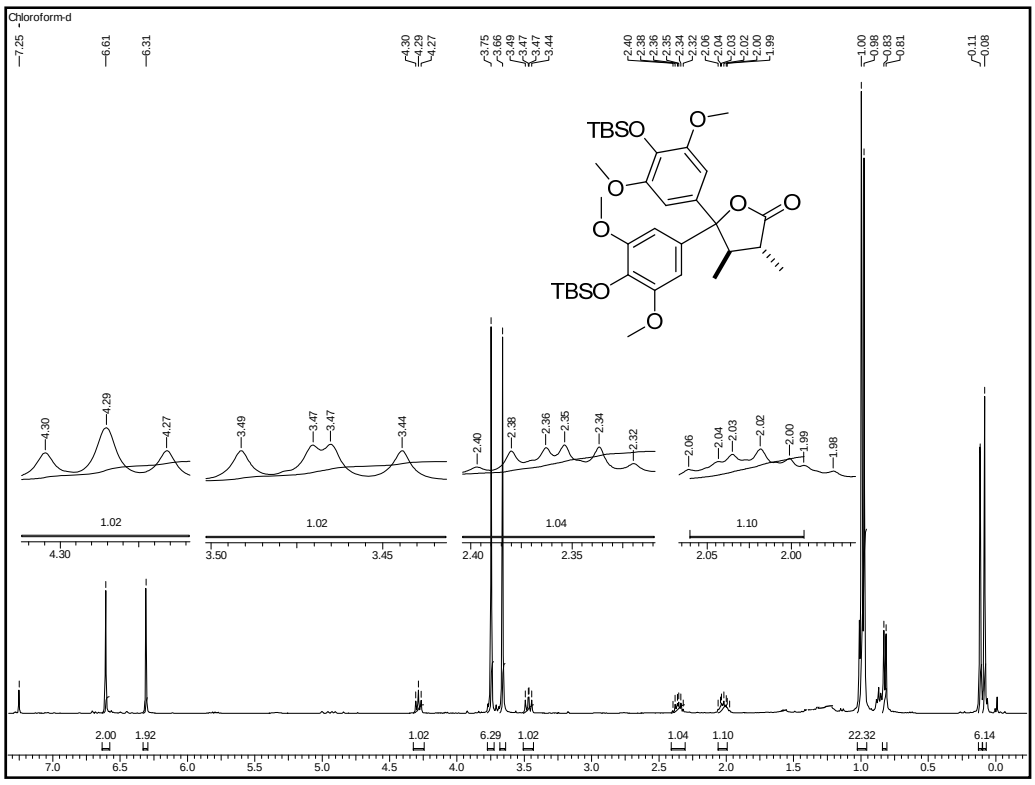
^{13}C NMR Spectrum of 72 in $CDCl_3$



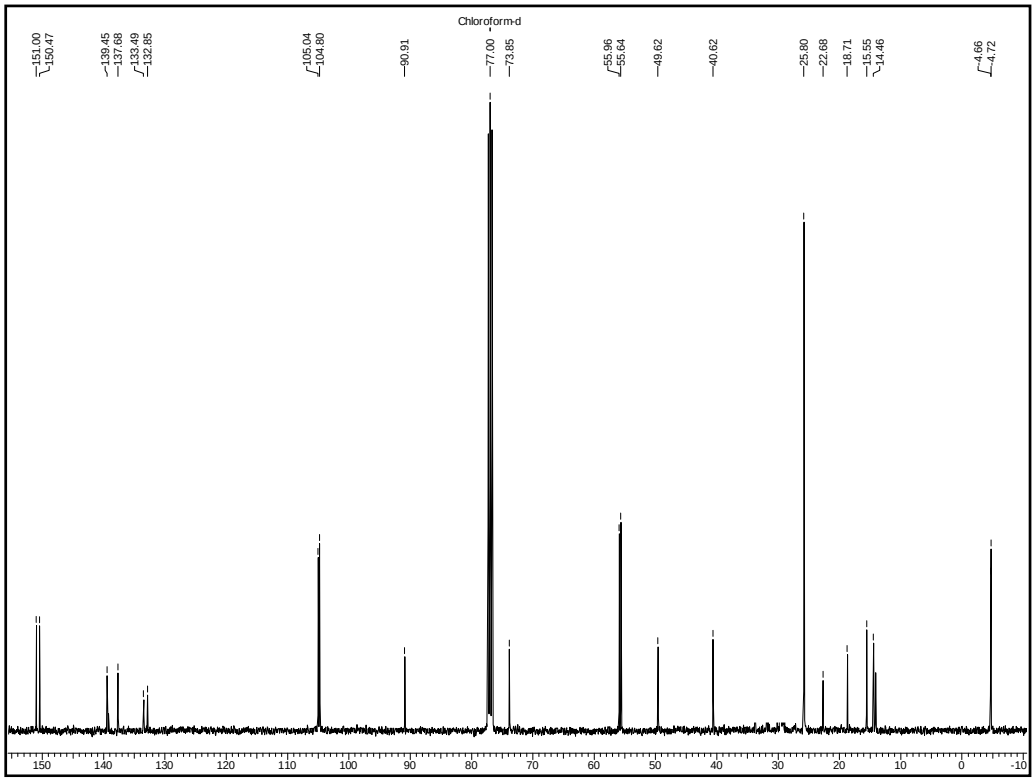
^{1}H NMR Spectrum of 73 in $CDCl_3$



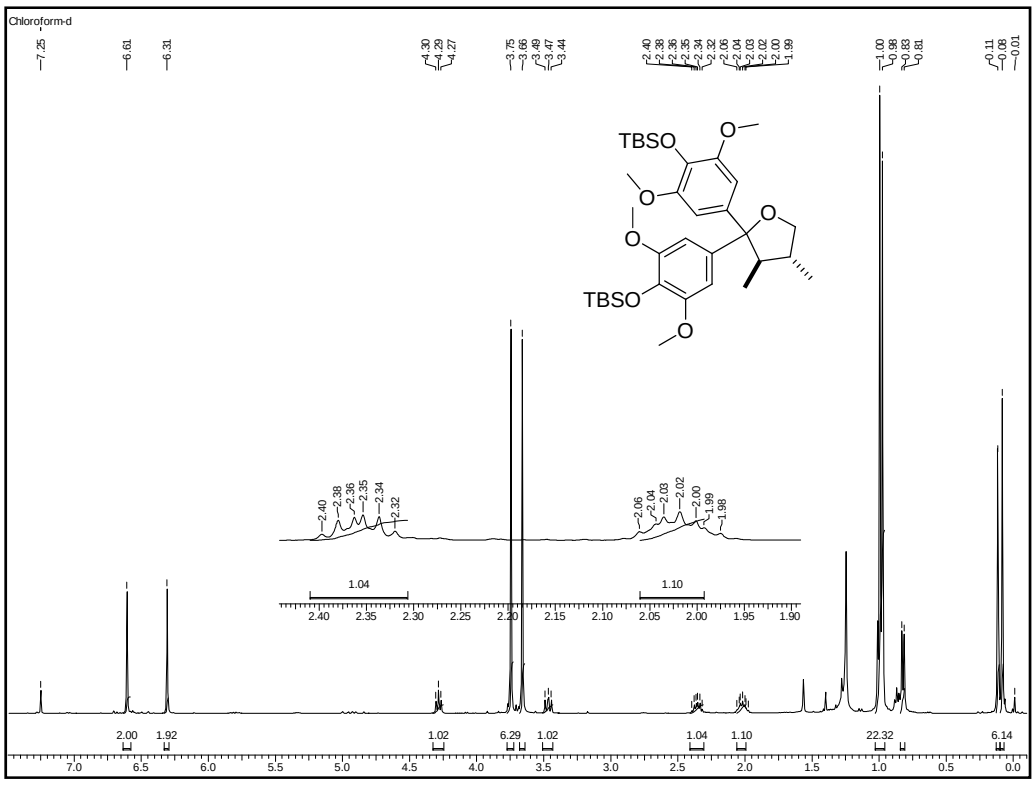
^{13}C NMR Spectrum of 73 in $CDCl_3$



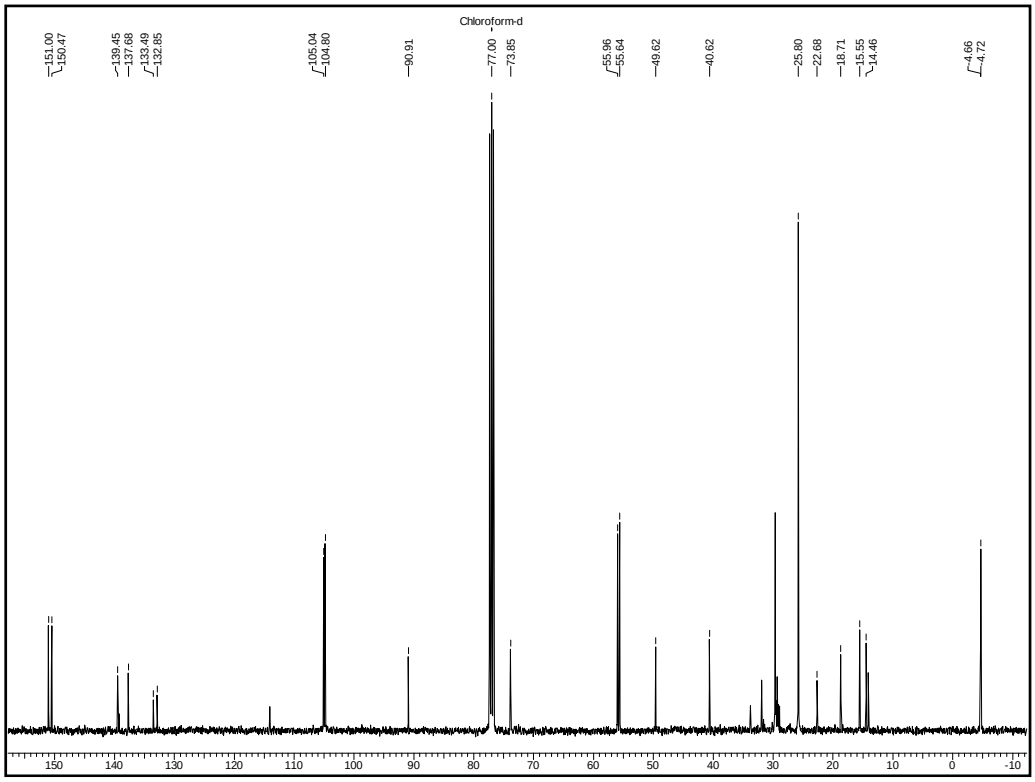
^{1}H NMR Spectrum of 74 in $CDCl_3$



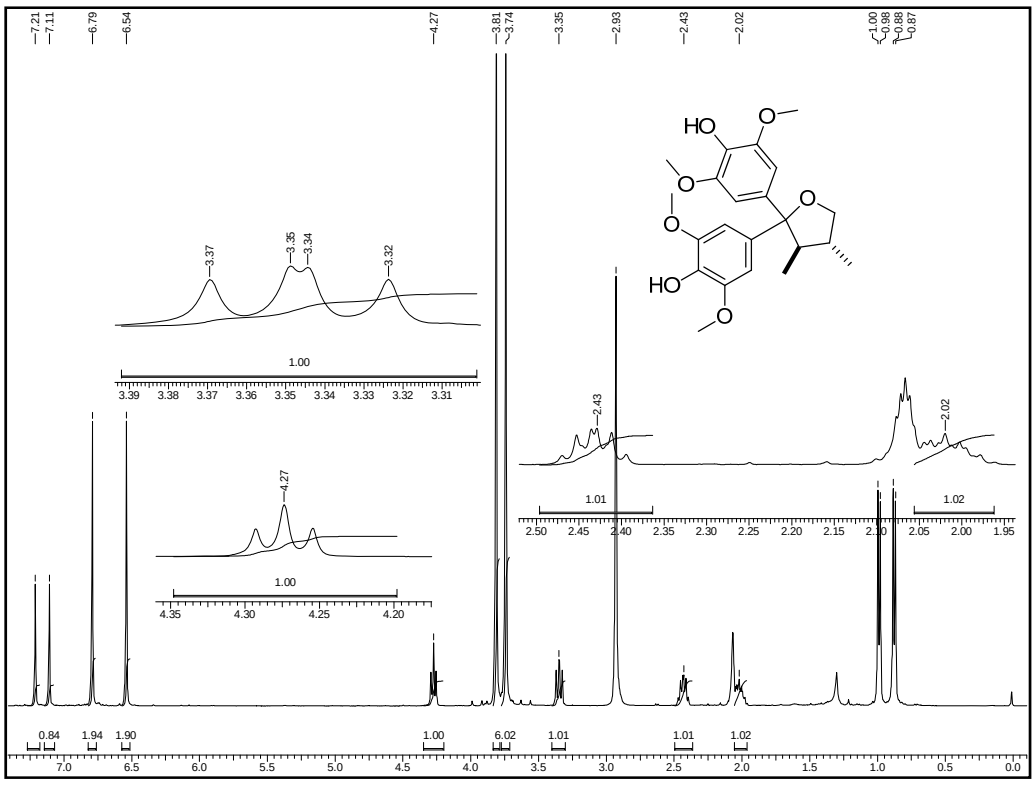
^{13}C NMR Spectrum of 74 in $CDCl_3$



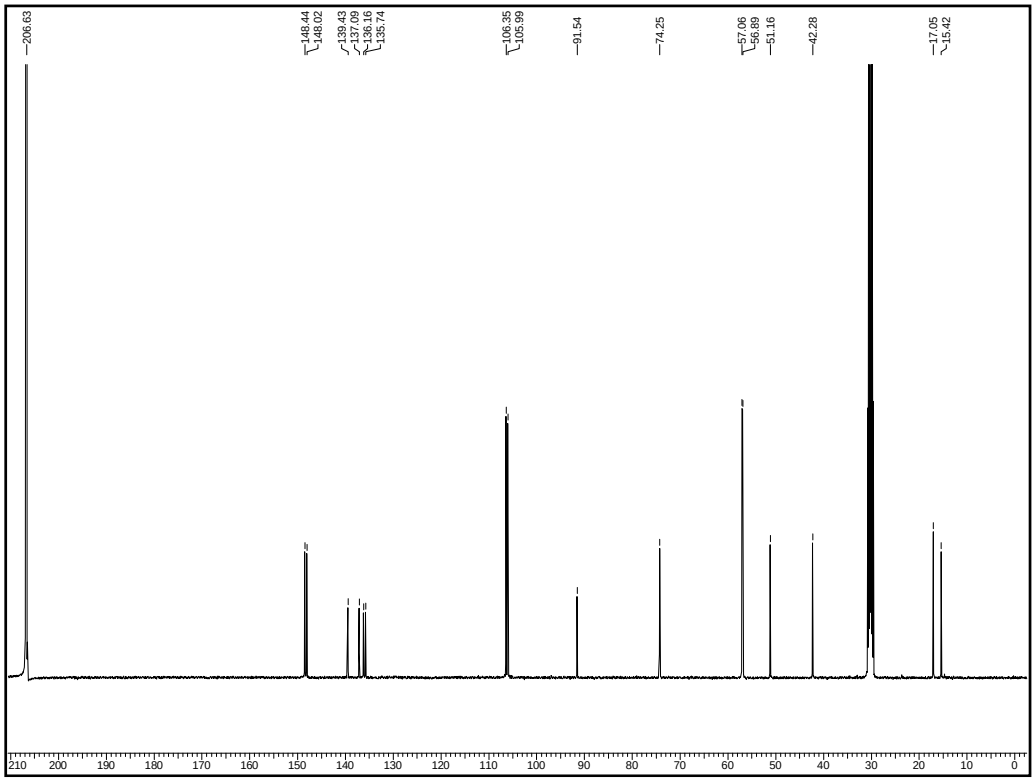
^{1}H NMR Spectrum of di-TBS-42 in $CDCl_3$



^{13}C NMR Spectrum of di-TBS-42 in $CDCl_3$



^{1}H NMR Spectrum of 42 in CD_3COCD_3



^{13}C NMR Spectrum of 42 in CD_3COCD_3

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CHAPTER-III

Synthesis of furano β-amino acids and their homo-oligomers

Introduction

Introduction:

An important objective in modern bioorganic and medicinal chemistry concerns the design of synthetic models that mimic various aspects of biologically active molecules. The correct folding of these biopolymers is an important and crucial element, since any kind of interaction is observed only if the reactive groups are positioned in the correct spatial orientation to each other. In this context, mimicking the functions of biopolymers with help of unnatural oligomers with backbones of discrete and predictable folding patterns ("foldamers") has emerged an important area during the last two decades. Amongst the three major biopolymers – *i.e* nucleic acids, polypeptides and carbohydrates, mimicking the secondary structures of peptides is one of the well explored areas. A number of very important physiological and biochemical functions of life are influenced by peptide. Peptides are the only biopolymers which have been well explored in medicinal chemistry and the number of drugs which consist of (modified) peptides or of peptide-related compounds are constantly increasing. However, the use of peptides as drugs is limited, because each living system employs several defense mechanisms preventing external peptides to get into the metabolism. In recent years, several approaches have been documented to address the mimicking of the secondary/tertiary structures of biopolymers on the one hand and the *in-vitro* stability of this synthetic backbone for medicinal applications on the other. In this context, *β*-peptides have been developed as the potential peptidomimetics with highly organized secondary structures and bio-compatibility. Various groups have established that the resulting *β*-peptides have superior stability against proteolytic degradation *in vitro* and *in vivo*. For example, *β*-Peptides have been used to mimic natural peptide-based antibiotics such as magainins. Magainin peptides are highly potent but difficult to use as drugs because they are degraded by proteolytic enzymes in the body. The use of *β*-Peptides and mixed α/*β*-peptides as stable mimics of natural peptides with applications ranging antibiotic,[1] anticancer,[2] anti-HIV functions,[3] DNA[4] and RNA[5] binding and cell penetration[6] has been well explored. A brief introduction and the secondary structures noticed in various *β*-peptides in general and of the *β*-peptides derived from the cyclic *β*-amino acids in particular, will be provided in the following sections.

β-Amino acids and Their Secondary Structures

Seebach and Gellmann groups introduced the *β*-amino acids as elegant alternatives to *α*-amino acids (Figure 1). With extensive structural analysis of their homo- and hetero oligomers, it has been shown that *β*-peptides form the more stable and diverse secondary structures. For example, *β*-Peptides have been identified for different helical secondary structures (14-helix, 12-helix and 10/12 helix, 10-helix and 8-helix). Most importantly, unlike the *α*-Peptides which only form distinct stable secondary structures in solution when they consist of at least 15–20 amino acids, even a simple *β*-hexapeptide can form a stable helical structure in solution. Indeed in recent years, it has been shown that even tetramer could form the stable single turn helix.

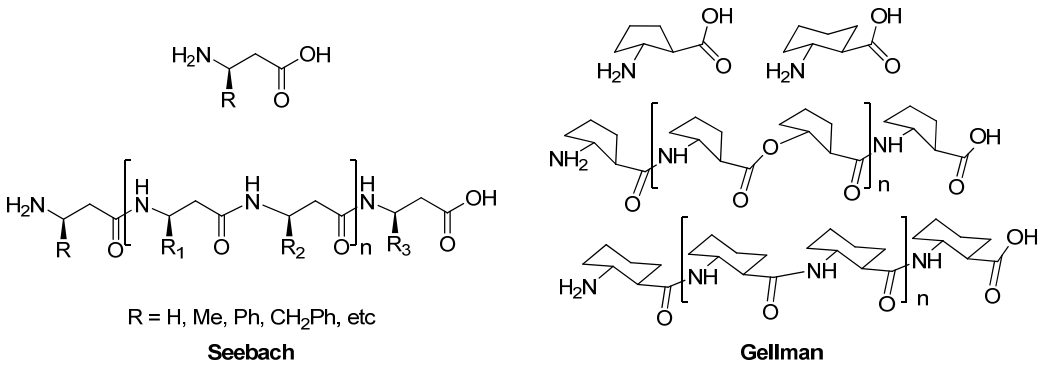


Figure 21: *The inaugural β-amino acids, β-peptides introduced by Seebach and Gellman*

- **Nomenclature of *β*-peptides:**

The nomenclatures of *β*-peptide conformations have been introduced by various groups and are summarized in Table 11. The IUPAC–IUB was recommended the notation as *gauche plus* (*g*+), *anti* (*a*) and *gauche minus* (*g*–) which could be used for the conformers. The nomenclature of helical conformations has varied widely in the literature.[7] Gellmans nomenclature is more commonly used that depends on the number of atoms involved in the hydrogen bonded ring formed between donor and acceptor atoms.

Table 11. *Nomenclatures of β-peptide by various groups*

Helix nom	Applequist	Gellman	Seebach	Hofmann I	Hofmann II	IUPAC	Perczel
2_6	R_0	6	2_1	H^I_6	U_1	$g^+[g^+]a$	$Z6^i_{PM}$
–	–	–	–	C_8	U_7	$g^+[g^+]g^-$	$Z8^{i-2}_{PM}$
2_g	R_{-2}	8	2_1	H^I_8	U_2	$g^-[a]g^-$	$H8^{i-2}_{PM}$
2.5_{10}	R_{+1}	10	2.5_1	H_{10}	N/A	$g^+[g^+]g^+$	$H10^{i+1}_{PM}$
2.5_{12}	R_{-3}	12	2.5_1	H_{12}	U_6	$g^-[g^+]g^-$	$H12^{i-3}_{PM}$
3_{14}	R_{+2}	14	3_1	H_{14}	U_{10}	$a[g^-]a$	$H14^{i+2}_{PM}$
–	–	–	–	H_E	U_4	$g^-[a]a$	S_{PM}
2_6	R_0	6	$(M)2_1$	H^I_6	B4	$g^+[g^+]a$	$Z6^I_M$
2_6	L_0	6	$(P)2_1$	H^I_6	B1	$g^-[g^-]a$	$Z6^I_P$
2_6	R_0	6	$(M)2_1$	H^{II}_6	B5	$a\,[g^+]\,g^+$	$Z6^{*I}_M$
–	–	–	–	C_8, $H8^{III}$	B3	$g^-[g^-]g^+$	$Z8^{i-2}_P$
–	–	–	–	C_8, $H8^{III}$	B3’	$g^+[g^+]g_l^-$	$Z8^{i-2}_M$
–	–	–	–	–	B9	$g^-[g^+]\,g^+$	$Z8^{*i-2}_M$
2_8	R_{-2}	8	$(P)2_1$	H^I_8	B2	$g^-[a]g^-$	$H8^{i-2}_P$
2_8	L_{-2}	8	$(M)2_1$	H^I_8	B2’	$g^+[a]g^+$	$H8^{i-2}_M$
2.5_{10}	R_{+1}	10	$(P)2.5_1$	H_{10}	B18	$g^+[g^+]g^+$	$H10^{i+1}_P$
2.5_{10}	L_{+1}	10	$(M)2.5_1$	H_{10}	B18’	$g^-[g^-]g^-$	$H10^{i+1}_M$
2.5_{12}	R_{-3}	12	$(P)2.5_1$	H_{12}	B11	$g^-[g^+]g^-$	$H12^{i-3}_P$
2.5_{12}	L_{-3}	12	$(M)2.5_1$	H_{12}	B11’	$g^+[g^-]g^+$	$H12^{i-3}_M$
3_{14}	L_{+2}	14	$(M)3_1$	H_{14}	B10	$a[g^+]a$	$H14^{i+2}_M$
–	–	–	–	–	B14	$g^+[g^+]g_2^-$	H_M
–	–	–	–	–	B7	$g^-[a]a$	S_P
–	–	–	–	–	B8	$g^+[a]a$	S_M

- **Helices:**

The *β*-peptides can form different type of helices by changing *β*-amino acid residue. Unlike the α-peptides, where the secondary structures are significantly affected by side chain properties, in *β*-peptides the secondary structure appears to be determined mainly by substitution patterns. considering the content of our work that deals mainly with the homo-oligomers, the further discussion will focus mainly on the studies of the structures of homo-oligomers of cyclic *β*-amino acids.

α-peptides *β*-peptides

α-helix (3.6_{13}) 14-helix (3_1) 12-helix (2.5_1)

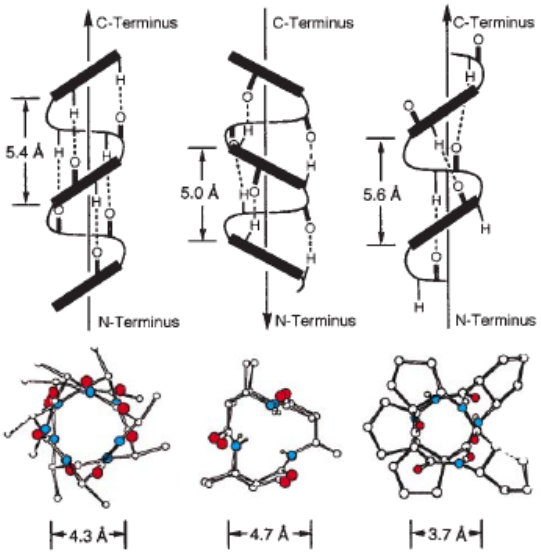


Figure 22: *Polarities, pitches, diameters and positioning of the side chain in α and β-peptide helices*

- **14-Helix:**

The 14-helix (also called 3_1 helix) depicted in Figure 3 was discovered almost simultaneously by Gellman's and Seebach's groups.[8–14] The short oligomers of the *β*-amino acids *trans*-2-aminocyclohexanecarboxylic acid (*trans*-ACHC) favor the 14-helix. It is characterized by a 14-membered ring hydrogen bond between an amide

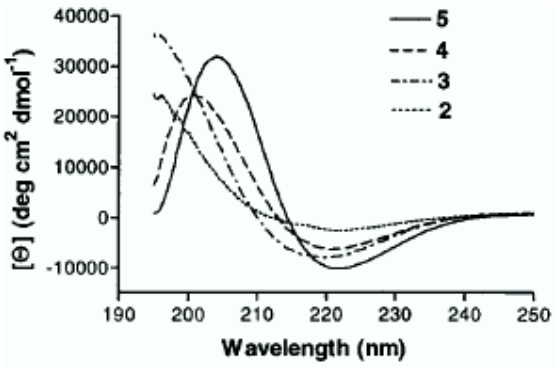


Figure 23*: CD-spectra of the trans-2-aminocyclopentane carboxylic acid showing the 12-helix*

proton and a carbonyl. The side chains of the *β*-amino acids *i* and *i*+3 reside above each other in close proximity on the outside of the helix. The CD pattern is diagnostic for the presence of a left- or right handed 14-helix. The CD spectra of 14-helix peptides show a maximum at 195 nm and a minimum at 215 nm. The pitch of an α-helix is 5.4 Å wide and its diameter is 4.3 Å, whereas the pitch of the 14-helix is only 5.0 Å wide. However the diameter is 4.7 Å (Figure 3). Only three *β*-amino acid

residues are needed for a 14-helix, while 3.6 α-amino acids are required for a single winding of the α-helix. The amide carbonyl and NH groups project toward the N- and C-terminus respectively in the 14-helix, resulting in a net dipole opposite to that of the α-helix. The helicity and dipole moment of the L- *β*-peptides are in the opposite direction compared to that of the α-helix formed by the corresponding α-peptides.

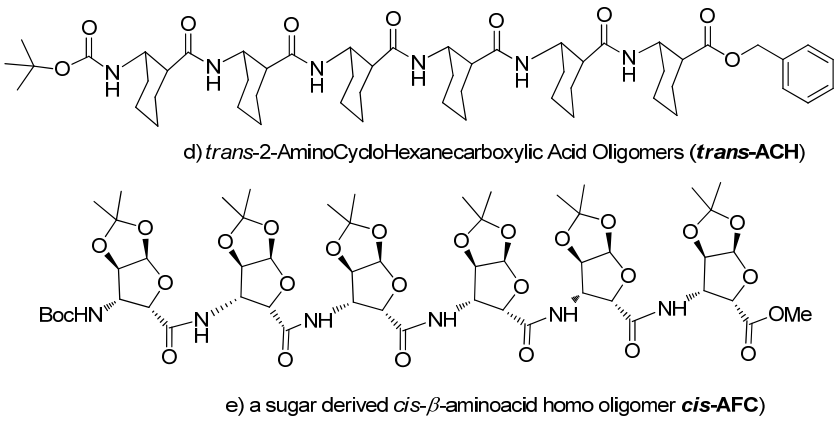


Figure 24: *Observed 14-helix in β-peptides derived from acyclic β-amino acid oligomers*

There are couple of reports which demonstrate that even favorable secondary interactions between the helix dipole and salt bridges does stabilize a 14-helix in water. Interestingly, Gellman has shown that the salt bridge formation is not required

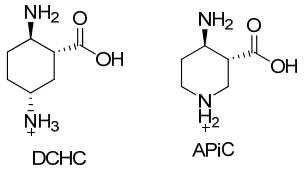


Figure 25: *Cationic cyclically constrained β-amino acids that adopt 14-helical conformation*

for secondary structure stabilization by incorporation of constrained *β*-amino acid containing ACHC residues anticipating the need for salt bridges to promote folding in aqueous solution and folding displays no pH dependence (Figure 25).[15]

- **12-Helix**

The 12-helix is also called as a 2.5_1-helix and it repeats approximately every 2.5 residues. The *trans*-2-aminocyclopentanecarboxylic acid (*trans*-ACPC)[16] (Figure 26) adopt a 12-membered helical structure both in organic solution as well as in the solid state. The CD spectra of 12-helix peptides show a maximum at 207 nm and a

minimum at 222 nm. The *β*-peptides of *trans*-3-amino-pyrrolidine-4-carboxylic acid (*trans*-APC) (2*R*,3*R*)-amino proline (AP),[17] *β*-peptides of the 3-substituted *trans*-ACPC and *β*-peptides containing *trans*-ACPC and *trans*-APC units also found to adopt a 12-helix in aqueous solution[18] (Figure 26).

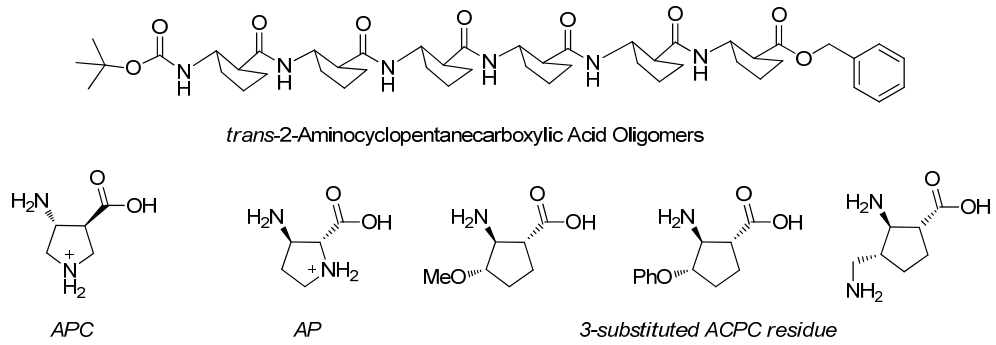


Figure 26: Monomers of the *12-helix of β-peptides*

A 12-helix is formed by contiguous 12-membered hydrogen bonds between the amide carbonyl groups of the ith residue and an amide proton of $i+3^{th}$ residue. The amide carbonyl and NH groups orient themselves toward the C- and N- termini respectively, giving rise to a net helix dipole with the same directionality as the *α*-helix. The characteristic interaction of a 12-helix in a NOESY are $C_\beta H_i$-NH_{i+2}, $C_\beta H_i$-$C_\alpha H_{i+2}$ and $C_\beta H_i$-NH_{i+3}. Recently, Aitken *et al*. reported that hexa- and octamer of *trans*-2-aminocyclobutanecarboxylic acid (*trans*-ACBA) have been shown to adopt a 12-helix conformation,[19] although in its di-and tetramer present 8-helix conformations.[20]

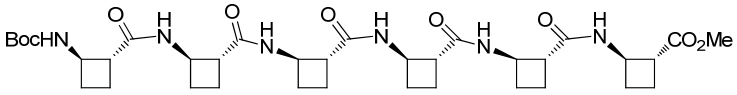


Figure 27: *12-helix of β-peptides of trans-2-aminocyclobutanecarboxylic acid*

- **10/12-helix**

In the 10/12 helix, C=O and N-H bonds point alternatively up and down along the axis of the helix, thus the net dipole is almost zero. As in the 14-helix, side chains of the *β*-amino acids *i* and *i*+3 reside above each other. The major difference between those two helices is the polarity. The 10/12 helix has almost no resulting dipole moment of the molecule, while the 14-helix has one with the positive end at the C-

and the negative at the N-terminus.[21] The 14-helix consists of only one type of 14-membered turn whereas in the 10/12 helix has two different turns, the central 10-membered- and the two terminal 12-membered turns. Seebach group reported the CD spectra of 10/12-helix peptides shows intense signal peak at 205 nm.[8] Fülöp *et al.* reported 10/12 helix in which alternate backbone heterochiral of *cis*-2-aminocyclopentane carboxylic acid oligomer.[22]

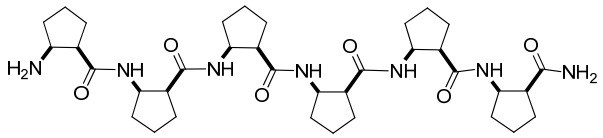


Figure 28: *Observered 10/12-helix of β-peptides*

- **10-Helix**

Fleet's[23] group reported the secondary structure of *β*-hexapeptide stabilization by 10-membered hydrogen bonded rings in which the peptide backbone is formed by *cis*-substituted oxetane rings (Figure 13). This secondary structure was confirmed by

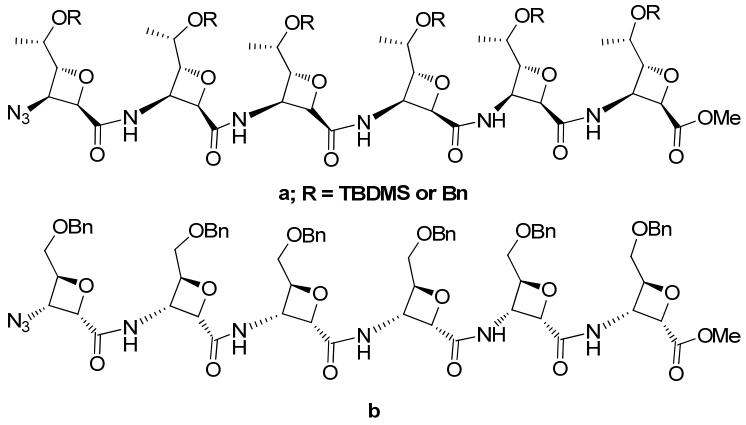


Figure 29: *β-Peptide that adopts a 10-helix conformation*

NMR analysis in nonpolar solvents. Molecular mechanics assisted conformational analysis of *β*-hexapeptide show left-handed helical structure (figure 13a) and right-handed helical structure (Figure 13b). S. Chandrasekhar *et al*. reported that a mixed oligomer with alternating *cis*-*β*-norbornene amino acid and *cis*-*β*-furanoid sugar amino acid. The *cis*-*β*-norbornene amino acid is showing a highly robust 6-strand

motif which transforms into a right-handed 10-helix through the substitution of 14-helical nucleating residues.[24]

- **8-Helix**

Crystal structure of the trimer and tetramer of achiral monomer 1-(aminomethyl)cyclopropanecarboxylic acid revealed a regular 8-helix,[25] having approximately two residues per turn (Figure 15). In an 8-helix, the amide carbonyl group is gauche to the two C_α–H bonds. Simple alkyl substituents do not favor the 8-helix. This conformational preference is mainly due to a hyper-conjugative interaction between the cyclopropane and the carbonyl group, instead of the steric effect.

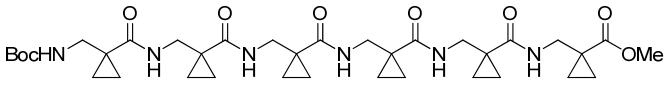


Figure 30: *β-Peptide that adopt 8-helix conformation*

R. Cosstick *et al*. prepared peptide of nucleoside *β*-amino acids revealed that these homo-oligomers adopt a distinct 8-helix conformation.[26]

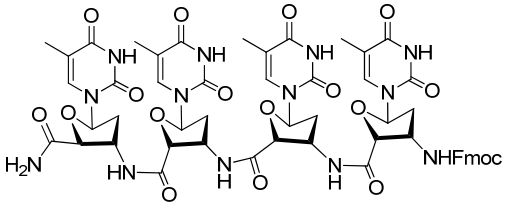


Figure 31: *Observed 8-helix of β-peptides*

Pleated sheet

The sheet structures in *β*-peptides has extensively dealt by Seebach and co-workers. Mainly, two types of sheet structures are observed. One in which each residue has an anti C^2–C^3 torsion angle and another in which each residue has a gauche C^2–C^3 torsion angle. Theoretical analysis of the dipeptide model indicates that the intrinsic hydrogen bond strength is large for both parallel and antiparallel sheets and affected little by substituents. $\beta^{2,3}$-peptides have much stronger sheet forming abilities. The *β*-sheets formed by the α-peptides have little or no net dipole because the backbone carbonyls alternate in direction along each strand. In contrast, in *β*-peptide sheets, where C=O and N-H bonds point up and down alternatively, the

resulting pleated sheet is polar, since all carbonyls point in one direction, while all N-H bonds point in the opposite direction (Figure 32).[22,27,28]

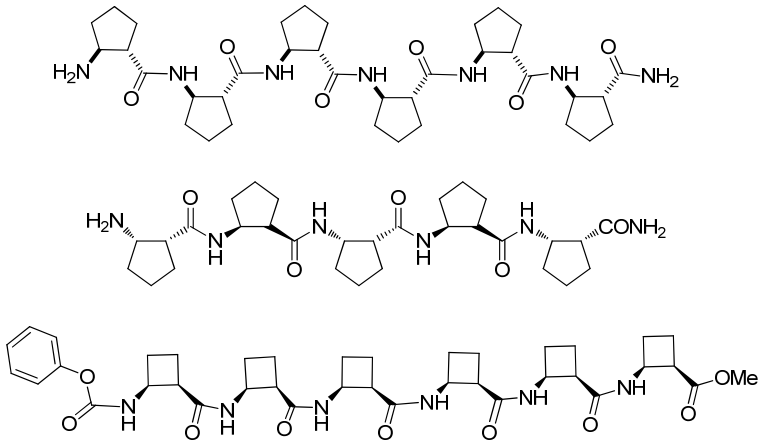


Figure 32: *β-Peptides that adopt a sheet conformation*

Torsion angles Conformational properties of β-amino acids

According to the convention of Balaram, the conformational studies of *β*-peptides analyzed in terms of the main chain torsional angles, which are designated the angles *ω, φ, θ* and *ψ* respectively (Figure 33a).[30] These torsion angles mainly depend on the substituents at the β^2 and β^3-positions. The substituents at β^2 or β^3-monosustituted and β^2, β^3-disustituted amino acids preferred gauche conformation about the C^2–C^3 bond.

Cyclic *β*-amino acids and their secondary structures:

The *trans*-2-aminocyclohexane carboxylic acid, *trans*-2,5-diaminocyclohexanecarboxylic acid, *trans*-2-aminocyclopentanecarboxylic acid and *trans*-3-aminopyrrolidine-4-carboxylic acid strongly favor to a gauche type conformation about β^2─β^3 torsional bond (Figure 33b)[31]. When the substituents at β^2 and β^3 are *syn,* a *trans*-conformation about the β^2─β^3 bond is favored (Figure 33c), which encourages the formation of sheet like structure.[32] After extensive theoretical investigations, Wu and Wang proposed that in *β*-dipeptides, a gauche conformation about the *θ* torsional angle defined by β^2─β^3 bond is a prerequisite to form folded helical and turn like conformations (Figure 33b).[33]

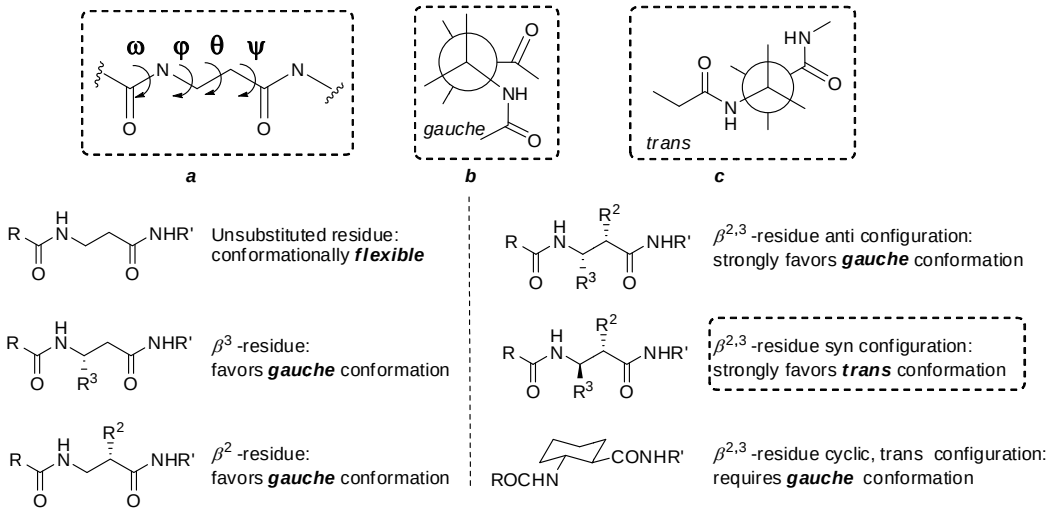


Figure 33: *Torsion angles in β-peptide and effect of substitution on the torsional angles*

Circular Dichroism spectroscopy

Circular dichroism (CD) is a useful tool to determine the secondary structure of peptides in the "far-UV" spectral region (190–250 nm). At these wavelengths the chromophore is the peptide bond, and the signal arises when it is located in a regular, folded environment. There are three main classes of secondary structure of *β*-peptide: the alpha helix, the beta sheet, and the random coil. The *α*-helix produces the most distinctive CD spectrum: a very strong positive band near 192 nm, which corresponds to (π–π) transitions, and two negative maxima of approximately equal intensity near 222 nm (n–π) and 208 nm (π–π).

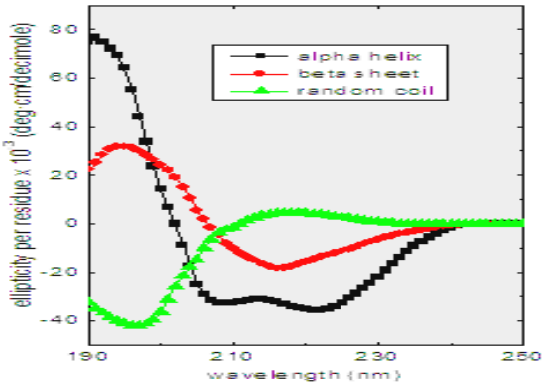


Figure 34: *CD-spectra of the β-Peptide that adopts a secondary conformation*

The β-sheet exhibits a single negative band near 217 nm, representing (π–π^*). The random coil exhibits a strong negative band at 197 nm (n–π^*) and a small positive band at 217 nm (π–π^*). The CD spectra of several hexa- and hepta-β-peptides, which adopt left-handed 14-helices as determined by NMR or crystallography, show a maximum near 195 nm and a minimum near 215 nm (or vice versa for right-handed helices).

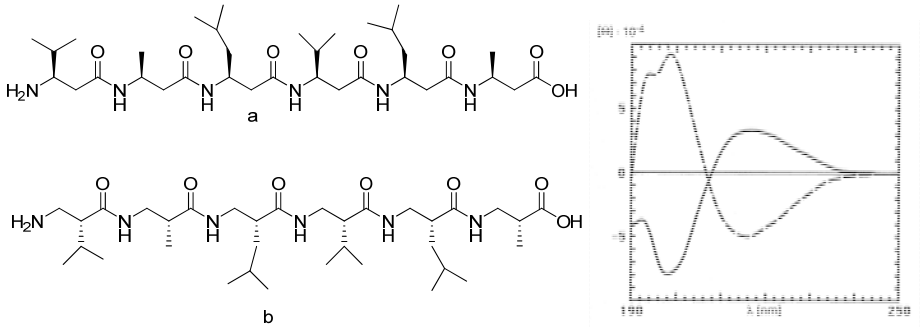
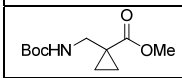
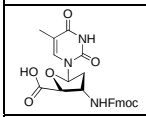
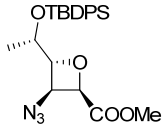
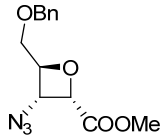
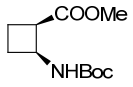
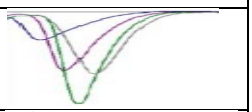
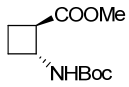
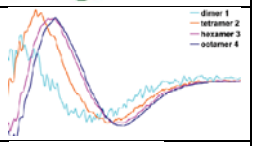
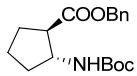
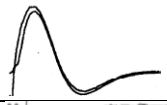
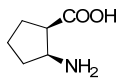
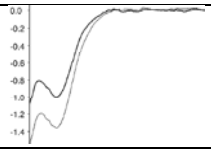
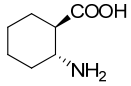
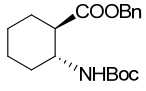
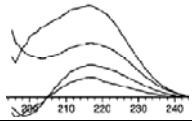
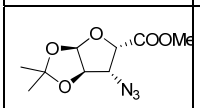
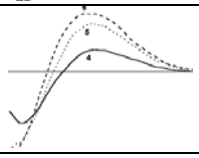


Figure 35: *CD-spectra of the β^3-hexapeptide **a** forming a left-handed 14-helix and of the β^2-hexapeptide **b** forming a right-handed 14-helix in methanol*

The intensity of the CD spectrum of the α-helix is known to depend on chain length, becoming more intense as the helix is lengthened. Similar behavior appears to be found for 14-helices. The CD spectra of many 10–15-residue peptides, which have been designed to adopt a 14-helical conformation, are more intense than their shorter counterparts. The CD spectrum of the 12-helix is similar in shape to that of the 14-helix but that the sign is reversed for a given helical handedness and the splitting between the parallel and perpendicular bands are greater. The left-handed 12-helix is consistent with this analysis, showing a maximum near 205 nm and a negative band is observed near 220 nm, which is probably associated with the (n-π^*) transition. The circular dichroism spectrum of the right-handed 10/12-helical conformation shows an intense single peak near 205 nm.

Table 12. *Characteristic features of CD-graph recorded by various cyclic β-peptide*

Monomer	Secondary Structure	Characteristic CD peaks in nm			CD Graph
			Zero crossing		
	8–helix				
	8–helix				
	10–(LH)helix				CD not given
	10-(RH)helix				CD not given
	Strand	210		225	
	12-(LH)helix	209		227	
	12-(LH)helix	204	214	221	
	Sheet like	203			
	*Tetramer* 10-(LH)helix *Petamer and hexamer* 14-(RH)helix	197	207	217	
	14-(RH)helix			217	
	14-(RH)helix	198	209	218	

The studies on *β*-amino acids derived from conformationally restrained five membered systems such as cyclopentane and furanoid show that they can adopt helical structures. The *β*-peptides derived from *trans*-2-aminocyclopentanecarboxylic acid (*trans*-ACPC) adopt a 12-helix whereas the *β*-peptides prepared from *cis*-2-aminocyclopentanecarboxylic acid (*cis*-ACPC), form a sheet like structure. Fülöp *et al*. postulated that might be the relative configuration of the ACPC residues provides an efficient control on the secondary structures of their homo-oligomer. In contrast, the *cis*-*β*-furanoid amino acid oligomers are found adopt the right-handed 14-helical conformation as revealed by Chandrasekhar *et al*. Very recently, Fisher *et al*. documented that a *trans*-*β*-furanoid amino acid homo-oligomer with a nucleobase

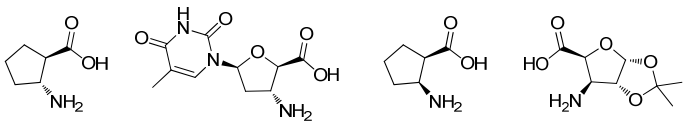


Figure 36: *Different type of five membered β-amino acids*

substituent favor an 8-helix conformation where an unsusbstituted cyclopentane or the pyrrolidine oligomers exhibit a 12-helix.

These results are quite interesting and reveal that at least in furanoid amino acids a systematic investigation is lacking. In this context it was quite interesting to note that the homo-oligomers of the parent *β*-aminofuranoid acids have neither synthesized nor their secondary structures have been probed by the theoretical investigations. This has prompted us to undertake the synthesis and the secondary

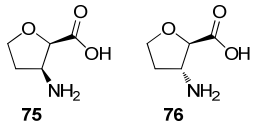


Figure 37: *Designed diastereomeric furano-β-amino acids building blocks*

structural analysis of the simple *cis*- and *trans*- furano-*β*- amino acids **75** and **76** respectively.

The silent features of investigations will be discussed in the next section of this chapter.

Present Work

Present Work:

In recent years, several approaches have been put forward to address the mimicking of the secondary structures of the peptides on one hand and the *in-vitro* stability of synthetic peptides for medicinal applications on the other.[1–7] Seebach and Gellman groups have introduced the *β*-peptides as expeditious tools in this context.[8–10] Through the extensive structural analysis of their homo- and hetero oligomers, *β*-peptides have been shown to adopt stable and diverse secondary structures (helices, sheets and turns) and form interesting molecular architectures via self assembly. The homo-oligomers derived from the conformationally constrained (*via* ring-annulations at C_α-C_β bond) *β*-amino acids have been the subject of extensive structural investigations.[5] The nature of the secondary structure of their homo-oligomers seems to depend mainly upon (i) the relative stereochemistry of the amine and acid groups, (ii) ring atoms and (iii) the ring size. For example, the homo-oligomers constructed by the *trans*-2-aminocyclopentane carboxylic acid (*trans*-ACPC) form a stable 12-helix whereas the homo-oligomers derived from the *cis*-2-aminocyclopentane carboxylic acid (*cis*-ACPC) form a sheet-like structure.[16,27]

Quite interestingly, the homo-oligomers of the **F38.C** adopt a stable 14-membered helix,[11] unlike the sheet structure by *cis*-ACPC homo-oligomers.[27] The synthesis of the corresponding *trans*-*β*-aminofuranose acid **F38.D** has been reported, however, no attempts of the synthesis and structural analysis of its homo-oligomers has been documented.[11] Very recently, the Cosstick documented the synthesis of the oligomers of nucleic acid derived furanoid-*β*-amino acid **F38.E** and showed that they adopt an unusual 8-membered helix, which has partly been attributed to the β^4-carbon substituent.[26] Whereas for the same tetramer, Chandrasekhar's *et al.* group reported a 12-helix solution structure.[34] We have synthesized the homo-oligomers of diastereomeric *cis*- and *trans*-furanoid-*β*-aminoacids **F38.F** and **F38.G**. The structural investigations of these homo-oligomers revealed that the *trans*-FAA oligomers adopt a robust 12-helix. Whereas, in solution, the NMR structural investigations have revealed that the *cis*-FAA oligomers seem to adopt a 12-helix conformation which either rapidly unfolds or is in equilibrium with an unfolded structure.

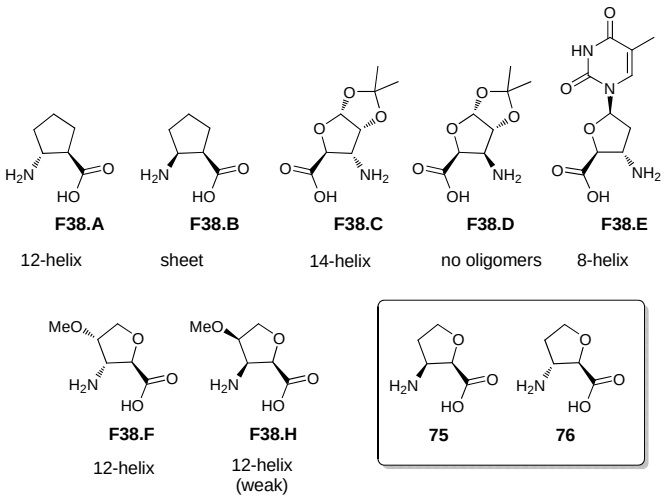


Figure 38. Five member ring constrained *β*-amino acids and the secondary structures reported for the corresponding homo-oligomers and the simple cis-/trans- furanoid-*β*-aminoacids

A close examination of the *β*-peptides of furanoamino acids reported reveals a random selection of monomers. This necessitates the structural analysis of the homo-oligomers of simple unsubstituted furan constrained-*β*-amino acids to understand whether the diversity in their secondary structure was either due to the substituents present on the furan ring or due to the ring oxygen. In this context, we have identified the azido acids/esters **77-79** as suitable precursors for the synthesis of the corresponding homo-oligomers. Figure 39 provides a retrosynthetic strategy for the building blocks synthesis and Figure 40 presents a protocol for the solution phase syntheses of homo-oligomers.

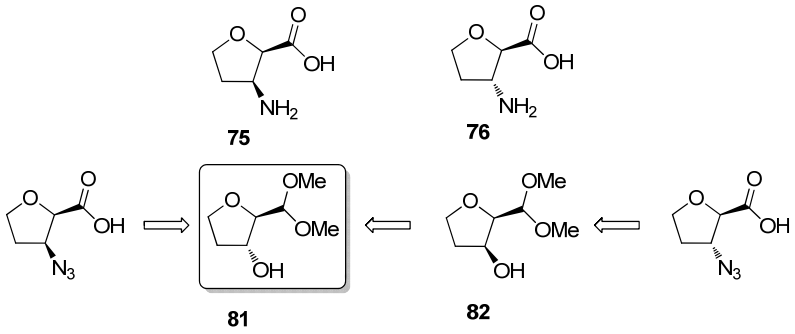


Figure 39: *Designed β-amino acids and the intended synthetic strategy*

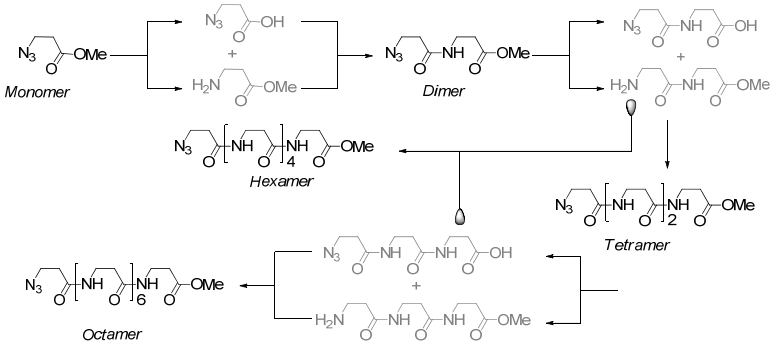
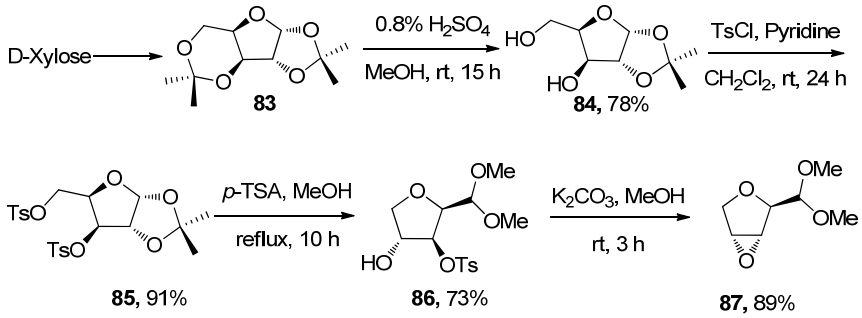


Figure 40: *β-Amino acid, and retrosynthetic scheme and flow diagram for synthesis of homo-oligomers*

Synthesis of dimethylacetal oxirane 87

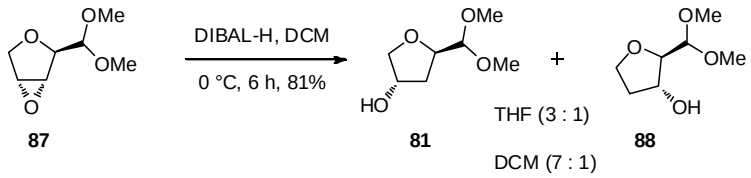
The synthetic endeavor began with the conversion of D-xylose into D-xylose diacetonide **83**. The selective deprotection of 3,5-*O*-isopropylidene group by using 0.8% H_2SO_4 in methanol gave the diol **84**. The diol **84** on was converted to ditosylate **85** by treating with tosyl chloride in pyridine. The acid mediated acetonide deprotection with concomitant 2,5-ring closure of the ditosylate was carried out with cat. *p*-toluenesulfonic acid in a solution of methanol at reflux temperature and the dimethylacetal **86** was obtained in quantitative yields. The resulting dimethyl upon basic treatment, gave the oxirane **87**. In the ^{1}H NMR spectrum of **87**, the signal corresponding to acetal was seen to be located at δ 4.28 as a doublet and the the two methyene protons of oxirane are located at 3.97 and 3.83 as doublets. Other analytical data such as mass, ^{13}C NMR spectrum and CHN were in accordance with the proposed structure of **87**.



Scheme 46: *Synthesis of acetal oxirane **87***

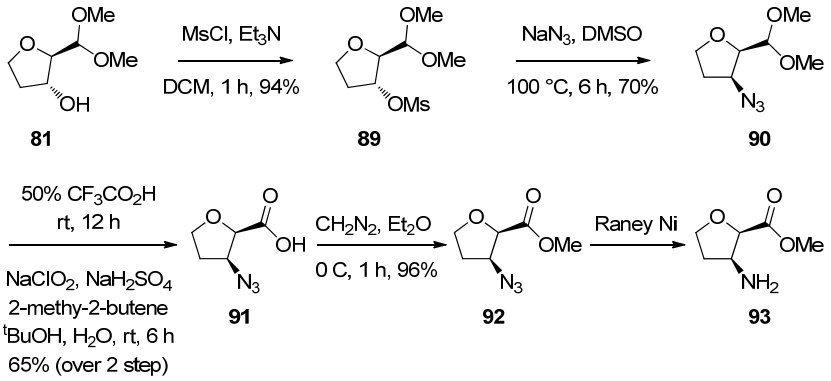
Synthesis of *cis*-*β*-azido acid 91 and *cis*-*β*-aminomethyl ester 93:

Next the opening of the epoxide **87** with hydride nucleophile was studied. The regiochemistry of the epoxide opening with diisobutylaluminum hydride (DIBAL-H) was found to be solvent dependent. As shown in Scheme 47, in CH_2Cl_2 the regioselectivity was high and obtained the required isomer **81** along with its regiomer **88** in a 7 : 1 ratio. The free hydroxyl group of **81** was converted to the corresponding mesylate **89** by treating with mesyl chloride in the presence of triethyl amine in dichloromethane. In the ^{1}H NMR spectrum of **89**, the presence of mesyl group was evident from the appearance of methyl singlets at δ 3.00 and 2.99 and other analytical data such as mass, ^{13}C NMR spectrum and CHN were in accordance with the proposed structure **89**.



Scheme 47: *Reduction of epoxide*

Next, the displacement of mesyl group of **89** with azide nucleophile was carried out by treating it with sodium azide in DMSO at 100 °C and the azidoacetal **90** was obtained in 70% yield. In the ^{1}H NMR spectrum of **90**, the methyl signals corresponding to the mesyl group was disappeared. The azide functionality was confirmed by a characteristic band at 2105 cm^{-1} in the IR spectrum of **90**. The highest mass peak at *m/z* 210.3 (100%, $[M+Na]^+$) and elemental analysis supported the assigned structure of **90**. The acetal group of **90** was deprotected by employing 50% TFA at 0 °C–rt and resultant crude aldehyde was oxidized to acid **91** by treating with sodium chlorite and sodium dihydrogen phosphate in *t*-BuOH and water in the presence of 2-methy-2-butene as a scavenger. The azido acid was purified by column chromatography and characterized by spectral data. In the IR spectrum of **91** the O–H stretching band was observed at 3354 cm^{-1} and C=O stretching at 1730 cm^{-1}. The carbonyl group was observed at 172.4 ppm in the ^{13}C NMR spectrum of compound **91**. The other analytical and spectral data such as mass and CHN were matched with the proposed structure of **91**.



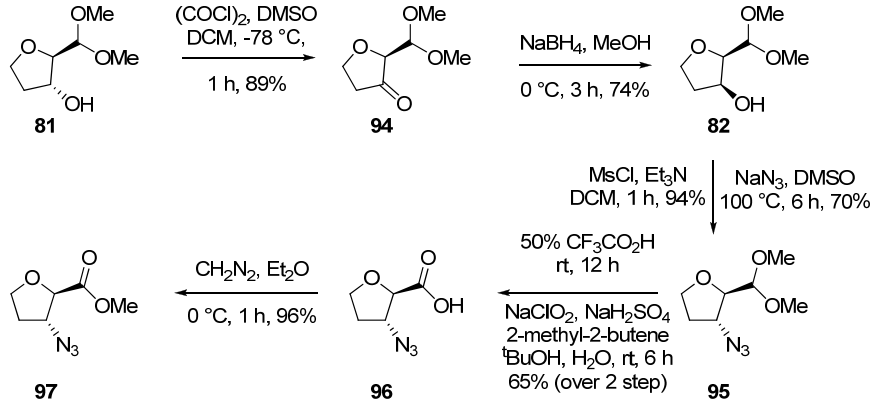
Scheme 48: *Synthesis of cis-β-amino acid*

Next, esterification of acid **91** carried out by treating **91** with diazomethane in CH_2Cl_2:ether at 0 °C and the methyl ester **92** was obtained in 96% yield. The structure of **92** was supported by ^{1}H NMR and IR spectra. The presence of methyl ester was evident from the ^{1}H NMR spectrum where an additional singlet at δ 3.83 integrating for three protons was seen to be appeared. In the IR spectrum, the O–H stretching disappeared and a C=O stretching band was observed at 1745 cm^{-1}. The carbonyl group was observed at 168.8 ppm in ^{13}C NMR spectrum. In the mass spectrum the characteristic mass peak at *m/z* 194.3 (100% $[M+Na]^+$) confirmed the proposed constitution of **92**.

Synthesis of *trans*-*β*-azido acid 96 and *trans*-*β*-azidomethyl ester 97:

The free C(3)–OH of the **81** was oxidized under Swern conditions (oxalyl chloride, DMSO and Et_3N in CH_2Cl_2 at –78 °C) to afford the ketone **94**. The ketone **94** was reduced with sodium borohydride in MeOH to procure **82**. The hydroxyl group of **82** was transformed to the corresponding azide by treatment with MsCl in Et_3N followed by reacting the intermediate mesylate with NaN_3 in DMSO at 100 °C gave the azido acetal **95**. The structure of **95** was well supported by ^{1}H, ^{13}C NMR and mass spectrum analysis. For example, in the ^{1}H NMR spectrum, peaks corresponding to furan ring were resonated at δ 4.10 (dd, *J* = 7.5, 3.8 Hz, 1H), 4.01–3.92 (m, 1H), 3.88 (ddd, *J* = 11.2, 8.4, 7.5 Hz, 2H), 2.15 (ddd, *J* = 15.9, 13.1, 7.5 Hz, 1H) and 1.89 (dddd, *J* = 13.1, 11.1, 4.5, 4.0 Hz, 1H). In the ^{13}C NMR spectrum, the methylene carbon was seen to be located at δ 32.5 and 67.5 as triplet; methyl carbon resonated at δ 54.4 and 56.0 as quartet and methyne carbons were seen to be located at δ 61.9, 83.4 and 104.3 as doublets. The azide functionality was confirmed by a characteristic band

at 2101 cm^{-1} in the IR spectrum of **95**. The highest mass peak at *m/z* 210.3 (100%, $[M+Na]^+$) and elemental analysis supported the assigned structure of **95**. The dimethyl acetal of **95** was deprotected to procure the aldehyde which was further converted to the acid using sodium chlorite and sodium dihydrogen phosphate in the presence of 2-methyl-2-butene in *t*-BuOH and water to give **96**. The acid monomer **96** was converted to corresponding ester **97** by employing diazomethane in CH_2Cl_2:ether at 0 °C in excellent yields.

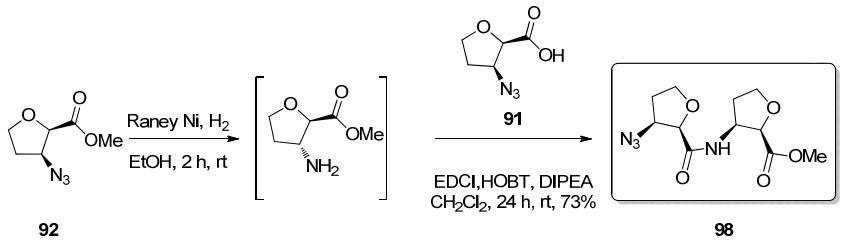


Scheme 49: *Synthesis of trans-β-amino acid*

The structure of **97** was supported by ^1H NMR and IR spectra. The presence of methyl ester was evident from the ^1H NMR spectrum where an additional singlet at δ 3.77 integrating for three protons was seen to be appeared. In the IR spectrum, C=O stretching band was observed at 1740 cm^{-1}. The carbonyl group was observed at 170.9 ppm in ^{13}C NMR spectrum. In the mass spectrum the characteristic mass peak at *m/z* 194.3 (100% $[M+Na]^+$) confirmed the proposed constitution of **97**.

Synthesis of homo–oligomers from *cis*-*β*-azido acid 91 and its methyl ester 92 in Liquid phase:

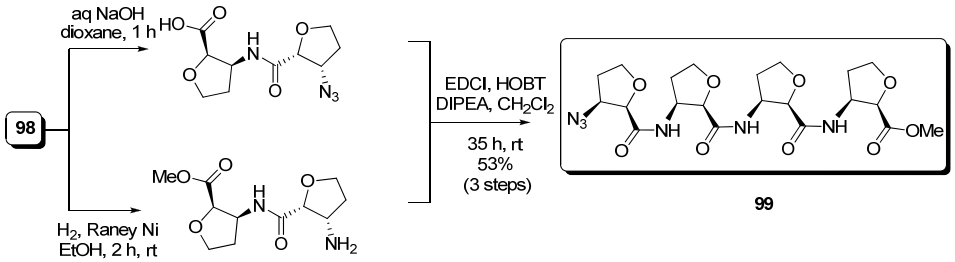
After having the necessary building blocks **91** and **92** in our hand, the remaining exercise was the synthesis of the corresponding oligomers. The synthesis of dimer was achieved in two steps. In the first step, the reduction of azide group of **92** was carried out by employing Raney nickel in EtOH in hydrogen atmosphere at rt to obtain the corresponding amine which was coupled immediately with the acid **91** by using EDCI and HOBt, DIPEA in CH_2Cl_2 at rt to afford the dimer **98** in 73% yield (Scheme 53).[37]



Scheme 50: *Synthesis of cis-β-FAA Dimer*

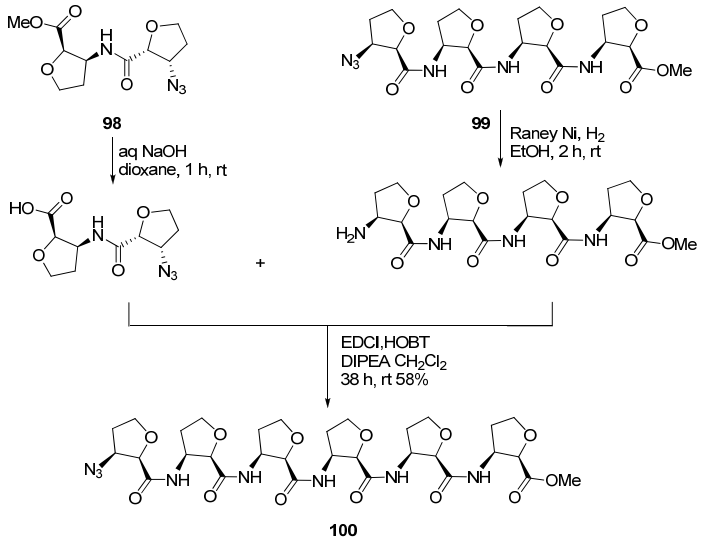
The presence of an amide proton was evident from the ^{1}H NMR spectrum where a doublet at δ 6.99 (J = 8.6 Hz) integrating for one proton was seen. In the ^{13}C NMR spectrum, ester carbonyl appeared at δ 170.1 as s singlet and amide carbonyl appeared at 167.9 as a singlet. The ester functionality was confirmed by characteristic band at 1745 cm^{-1} and the amide functionality was confirmed by the characteristic band at 1667 cm^{-1} in the IR spectrum. The highest mass peak at *m/z* 307.1 (100%, $[M+H]^{+}$) supported the assigned structure of **98**.

The tetramer synthesis commenced with the conversion of the dimer to the two requisite acid and amine units. The treatment of *cis*-dimer **98** with aqueous sodium hydroxide solution in dioxane afforded the intermediate dimer-acid. The Raney nickel mediated hydrogenolysis of azide **98** in EtOH gave the intermediate dimer-amine. Finally, the coupling of these acid and amines partner was done by employing EDCI, HOBt and DIPEA at rt in CH_2Cl_2. The tetramer **99** was purified by column chromatography and characterized by spectral and analytical data. The presence of three amide protons as doublet at δ 8.06, 7.72 and 7.10 ppm in ^{1}H NMR spectrum confirmed the structure of **99** as a tetramer. The four quaternary carbon singlets were seen to be appeared in the ^{13}C NMR spectrum of tetramer **99**, one at δ 170.50 corresponding to carbonyl of ester and three at δ 168.6, 170.4 and 170.5 ppm corresponding to the amide carbonyls confirmed the needful coupling. Absorptions due to the ester and amide carbonyl functionalities were seen separately in the IR spectrum, respectively at 1729 cm^{-1} and 1668 cm^{-1}. Mass spectra showed a peak at *m/z* 633.2 (100%, $[M+Na]^{+}$) which corresponds to the tetramer structure **99**.



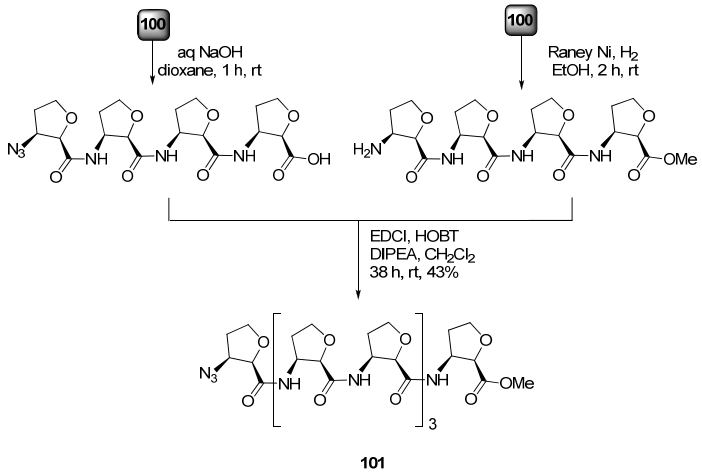
Scheme 51: *Synthesis of cis-β-FAA Tetramer 99*

Having the tetramer in our hand, we turned to synthesize higher oligomers. The synthesis of *cis*-hexamer **100** was carried out by coupling tetramer-amine crude (prepared by the hydrogenolysis of tetramer **99**) product, with dimer-acid (prepared by hydrolysis of methyl ester with aq. sodium hydroxide in dioxane) using EDCI and HOBt, DIPEA in CH_2Cl_2 at rt (Scheme 52). The formation of hexamer **100** was confirmed by the presence of five amide protons at δ 8.20, 8.10, 7.87, 7.12 and 6.86 as doublets in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, the characteristic ester carbonyl signal appeared at δ 171.1 and five amide carbonyls appeared at δ 168.8, 169.6, 170.3, 170.4 and 170.7 ppm as singlets. In the IR spectrum, absorption due to ester C=O stretching band appeared at 1728 cm^{-1} and the C=O stretching band of amide functionality were seen at 1665, 1660 and 1651 cm^{-1} and the characteristic peak at 2113 cm^{-1} justified the presence of azide group. Further supplementations such as CHN and the mass peak noticed at *m/z* 759.5 (100%, $[M+Na]^+$) agreed with the assigned structure of **100**.



Scheme 52: *Synthesis of cis-β-FAA Hexamer*

Next, we focused to synthesize the *cis*-octamer. For this intend, the methyl ester of *cis*-tetramer **99** was hydrolyzed with aqueous sodium hydroxide in dioxane and the



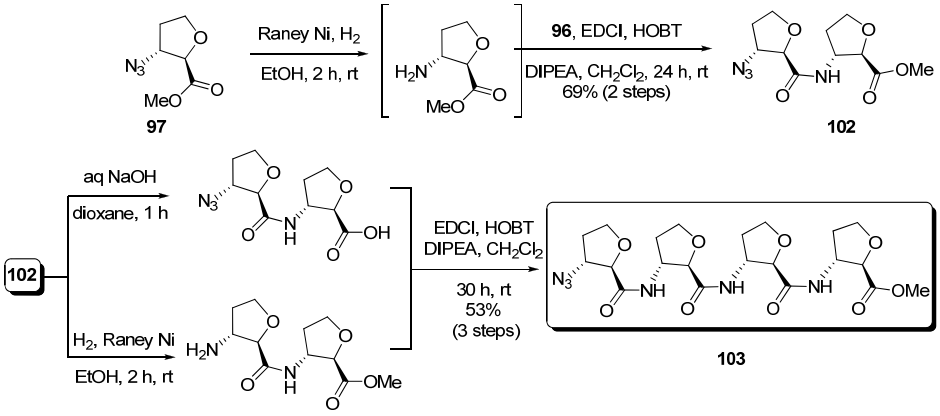
Scheme 53: *Synthesis of cis-β-FAA Octamer **101***

resulting tetramer-acid was coupled with the *cis*-tetramer-amine (prepared by the hydrogenolysis of *cis*-tetramer **99**) employing EDCI, HOBT and DIPEA in CH_2Cl_2 at rt to afford *cis*-octamer **101** (Scheme 53).

The constitution of the *cis*-octamer **101** was investigated with the help of spectral and analytical data. In the ^{1}H NMR spectrum of octamer **101**, seven characteristic amide protons are present as doublets at δ 8.28, 8.22, 8.13, 8.03, 7.89, 7.10 and 6.83 each integrating for one proton. The ^{13}C NMR spectrum showed corresponding carbonyl singlets at δ 168.9, 169.6, 170.2, 170.5, 170.6, 170.8, 171.1 and 171.3 ppm. The IR spectrum showed the C=O stretching of ester at 1725 cm^{-1} and the C=O stretching of amide carbonyl at 1661, 1656, 1653 and 1649 cm^{-1}. The azide functionality was confirmed by characteristic band at 2112 cm^{-1}. Also mass peak at *m/z* 985.4 (100%, $[M+H]^+$) agreed with the structure **101**.

Synthesis of homo–oligomers from *trans*-*β*-azido acid (96) and its methyl ester (97) in Liquid phase:

To synthesize the homo-oligomer of *trans*-*β*-furano-Amino Acid, we carried a similar set of reactions which were used in the synthesis of homo-oligomer of *cis*-*β*-furano-Amino Acid. The synthesis of *trans*-dimer **102** was achieved by coupling the intermediate monomer-amine (prepared by the hydrogenolysis of the azide **97** using Raney nickel) and acid **96** by employing EDCI, HOBt and DIPEA in CH_2Cl_2 at rt (Scheme 54). The structure of dimer **102** was confirmed with the help of ^{1}H NMR,



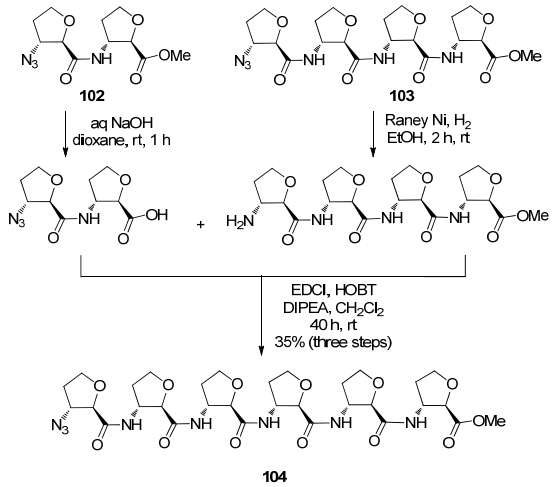
Scheme 54: *Synthesis of cis-β-FAA dimer* **102** *and cis-β-FAA tetramer **103***

^{13}C NMR, IR and mass spectral data analysis. In the ^{1}H NMR of dimer **102**, the distinguishing amide proton appeared as a doublet at δ 6.88 with J = 6.9 Hz. In ^{13}C NMR spectrum, ester carbonyl carbon singlet appeared at δ 171.1 ppm and the amide carbonyl carbon appeared at 169.7 ppm. Absorption due to ester and amide carbonyl functionalities was seen in the IR spectrum at 1746 cm^{-1} and 1667 cm^{-1} respectively. The characteristic peak at 2107 cm^{-1} indicated the presence of the azide group.

To synthesize the *trans*-tetramer **103**, *trans*-dimer-acid was prepared by saponification of *trans*-dimer **102** and *trans*-dimer-amine was prepared by reduction of azide unit of the same compound. The coupling of these two partners in the presence of EDCI and HOBt, DIPEA in CH_2Cl_2 procured the *trans*-tetramer **103** in 53% overall yield (Scheme 49). The assigned structure of *trans*-tetramer **103** was well supported by spectral data. In the ^{1}H NMR spectrum of *trans*-tetramer **103**, the amide protons were appeared as doublets at δ δ 7.40 (d, J = 6.5 Hz, 1H), 7.22 (d, J = 7.6 Hz,

1H) and 7.06 (d, J = 5.8 Hz, 1H). The carbonyl of ester appeared as a singlet at δ 171.4 ppm and the amide carbonyls appeared as singlets at δ 170.3, 170.8 and 170.9 ppm. In the IR spectrum of *trans*-tetramer **103**, C=O stretching of ester and amide were observed at 1744 cm^{-1} and 1667 cm^{-1} respectively and the azide functionality of **103** appeared at 2111 cm^{-1}.

We next proceeded for the synthesis of *trans*-hexamer **104** from the product of hydrogenolysis of the *trnas*-tetramer **103** and the *trans*-dimer-acid (saponification of



Scheme 55: *Synthesis of cis-β-FAA hexamer **104***

trans-dimer **102**). The coupling of acid and amine partner was carried out by employing EDCI, HOBt and DIPEA in CH_2Cl_2 at rt to procure the *trans*-hexamer **104** (Scheme 58). The *trans*-hexamer product was confirmed by ^1H NMR, ^{13}C NMR, IR and mass spectrum. In the ^1H NMR spectrum of hexamer **104**, the amide protons were seen to be located as multiplet at δ 7.53–7.49 (m, 3H) and as a doublet at δ 7.30 (d, J = 7.5 Hz, 1H) and 7.05 (d, J = 6.6 Hz, 1H). In the IR spectrum, the absorption band due to ester C=O stretching appeared at 1744 cm^{-1} and C=O stretching of amide functionality was seen at 1672, 1667 and 1656 cm^{-1}, and the azide functionality was confirmed by characteristic band at 2106 cm^{-1} in the IR spectrum. The mass peak at *m/z* 759.5 (100%, $[M+Na]^+$) supported for the assigned structure of **104**.

Next we tackled the *trans*-octamer synthesis by employing the amine and acids of the *trans*-tetramer following to the standard protocols. However we could not obtain the required product. We also tried to synthesize the *trans*-octamer by using the *trans*-

dimer acid and *trans*-hexamer amine or vice versa. However our all efforts were unsuccessful, probably the failure was partly due to the poor solubility of hexa-homomer.

Once we have the oligomers **98**–**104** in our hand, next we proceeded to examine the existence of secondary structure resulting from the intra-strand hydrogen bonding.

Secondary structural analysis of *β-FAA*-oligomer oligomers:

The analysis of the secondary structure of *cis*-*β*-FAA homo-oligomers started with the recording of the CD spectra of *cis*-dimer **98**, *cis*-tetramer **99**, *cis*-hexamer **100** and *cis*-octamer **101**. The CD spectra of these four oligomers were recorded in

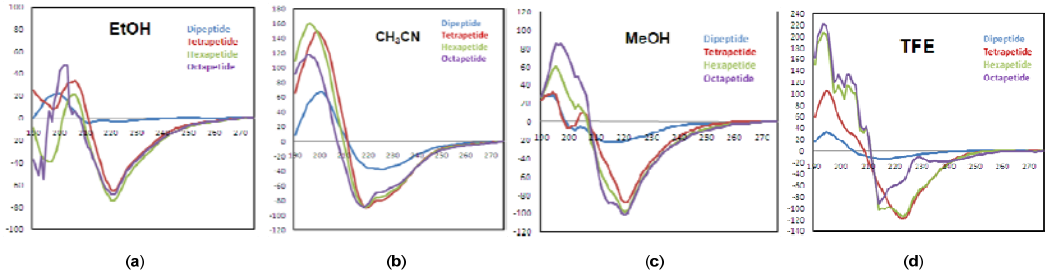


Figure 41: *The CD Spectral graph of di, tetra, hexa and octamers in different solvents of cis-β-FAA oligomer*

four different solvent viz ethanol, acetonitrile, methanol and trifluoroethanol at 0.1 mmol concentrations. The CD spectra of *cis*-dimer **98** did not show any significant ellipticity. The CD spectrum for each of the *cis*-tetramer **99**, *cis*-hexamer **100** and *cis*-octamer **101** suggested a distinct secondary structure and the sign and magnitude of the CD were found to be dependent on the nature of the solvents. In the EtOH the CD spectra of *cis*-tetramer **99**, *cis*-hexamer **100** and *cis*-octamer **101** show the maxima at

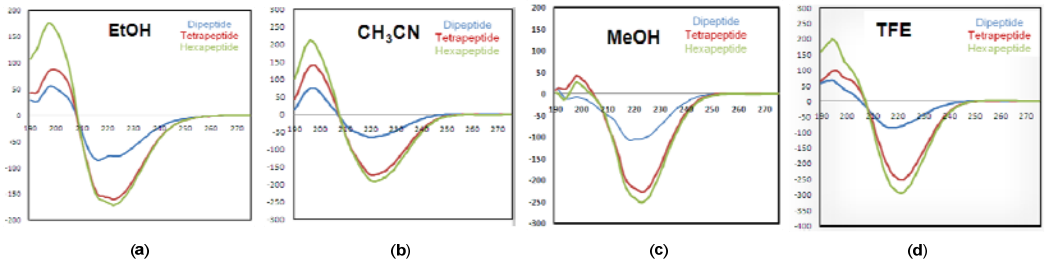


Figure 42: *The CD Spectral graph of di, tetra and hexa in different solvents of trans-β-FAA oligomer*

206, 206 and 203 nm, zero crossing at 211, 210 and 208 nm and minima at 221 nm respectively. Similarly, CD spectra of *trans*-tetramer **103** and *trans*-hexamer **104** showed a maxima at 200 nm, zero crossing at 211 nm and minima at 220 nm (Figure 42). This CD pattern suggested a left-handed 12-helix in these two homo-oligomers which indeed is similar to that of *trans*-aminocyclopentane carboxylic acid (*trans*-ACPC) and also cyclic pyrrolidne based t*rans-β*-amino acid homo-oligomers.

Secondary Structural Analysis of *cis-β-FAA*-oligomer by 2D NMR

The secondary structural analysis of oligo-peptides has been well established by 2D-NMR techniques. Though, the 1D NMR techniques like ^{1}H, ^{13}C and DEPT help to get the intra-residual connectivity to some extent, however, extensive 2D-NMR (HSQC and HMBC) analysis is required to get the inter-residue connectivity. We have used COSY, HSQC and HMBC to characterize first the primary structure of these peptides and which has been cross checked to get the proximal through spatial connectivity with the help of NOESY such as the cross talk between the $C_{\alpha}H_{(i)}/NH_{(i+2)}$, $NH_{(i)}/NH_{(i+1)}$, and $C_{\beta}H_{(i)}/NH_{(i+2)}$. Inter-residue n*O*es are also present in most of the spectra. Additional n*O*es are observed in spectra of those peptides for which lower tempered coefficients implicate amide protons involved in intramolecular H-bonding interaction and there exists a defined secondary structure. In case of *α*-peptides, characteristic n*O*e connectivities include $NH_{(i)}/NH_{(i+1)}$, $C\alpha H_{(i)}/NH_{(i+2)}$, and $C_{\beta}H_{(i)}/NH_{(i+2)}$. Whereas, *β*-peptides with defined secondary structure show long range n*O*es like $NH_{(i)}/NH_{(i+1)}$, $NH_{(i)}/C_{\beta}H_{(i+1)}$, $NH_{(i)}/C_{\beta}H_{(i+2)}$, $NH_{(i)}/C_{\beta}H_{(i+3)}$, $C_{\alpha}H_{(i)}/C_{\beta}H_{(i+3)}$, $C_{\alpha}H_{(i)}/C_{\beta}H_{(i+2)}$.

***Secondary structural analysis of cis-β-FAA dimer* 98**

i) COSY of cis-β-FAA dimer **98***:* The detailed analysis of the COSY spectrum (Figure 43) of *cis*-dimer **98** has been given and the inter-residue connectivities are shown in Figure 44.

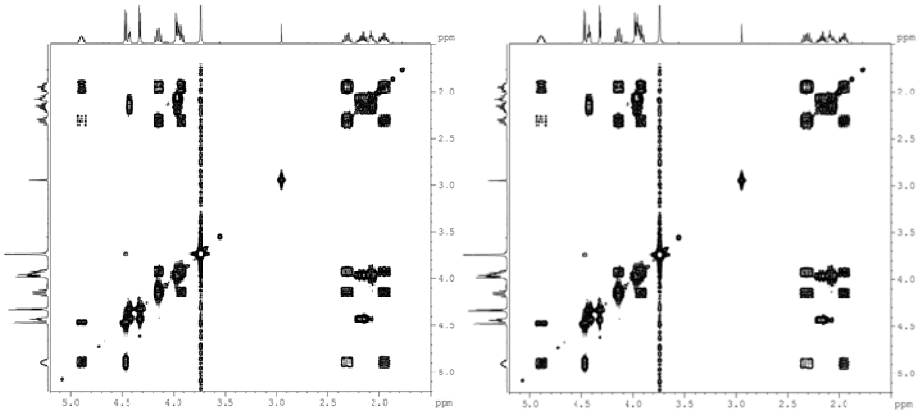


Figure 43: *Expansion of COSY spectrum of cis-dimer* **98**

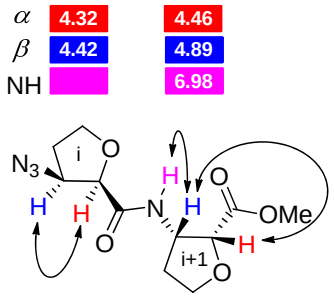
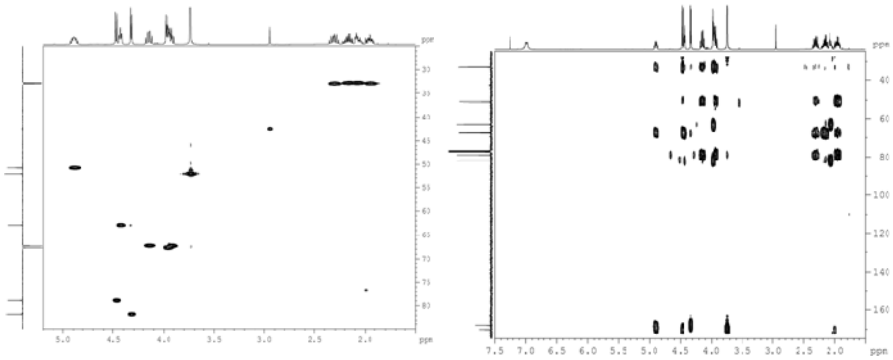


Figure 44: *Skeletal presentation of the cis-dimer* ***98*** *obtained from COSY experiment*

II) HSQC of cis-β-FAA dimer ***98*****:** This experiment identified the carbon and ^{1}H which are connected to each other through single bond. Figure 46 shows the $^{1}J_{C\text{-}H}$ couplings of *cis*-dimer **98**.

iii) HMBC of cis-β-FAA dimer ***98*****:** This experiment (Figure 45) identified the carbon and proton which are separated by two/three bonds depending on the coupling constant and dihedral angles. Figure 45 shows some of the characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *cis*-dimer **98** observed.



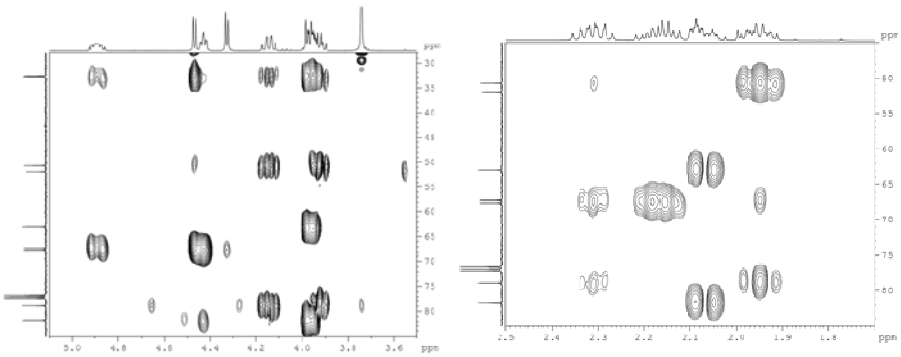


Figure 45: *Expansion of HSQC and HMBC spectrum of cis-dimer* ***98***

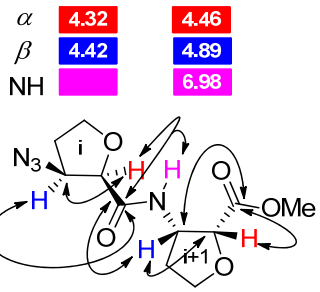


Figure 46: *Skeletal representation of the cis-dimer* ***98*** *obtained from HMBC and HSQC experiment*

iv) NOESY Spectrum of cis-dimer ***98****:* The Figure 47 shows some of the characteristic n*O*es of dimer **98** and Figure 49 shows the skeletal presentation.

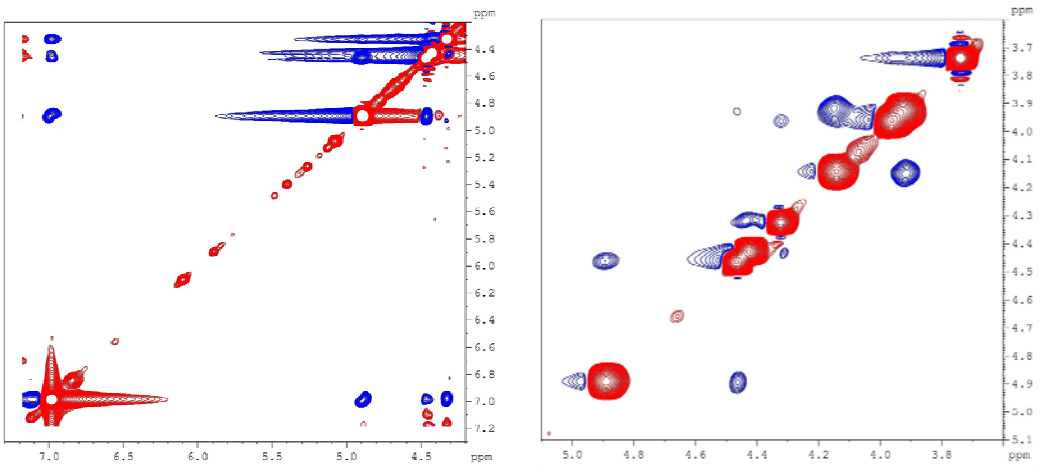


Figure 47: *Expansion of NOESY spectrum of cis-dimer* ***98***

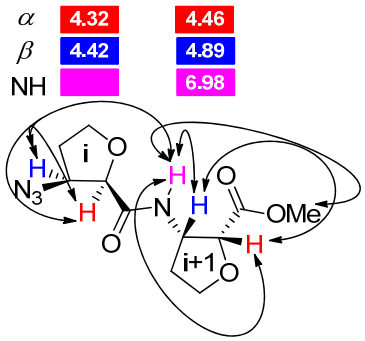


Figure 48: *Skeletal presentation of the cis-dimer **98** obtained from nOe experiment*

The NOESY spectrum of the *cis*-dimer **98** some notable interactions are $C_{\alpha}H_i/C_{\beta}H_i$, $NH_{(i+1)}/C_{\beta}H_i$, $C_{\alpha}H_{(i+1)}/C_{\beta}H_{(i+1)}$, $NH_{(i+1)}/C_{\alpha}H_{(i+1)}$, $NH_{(i+1)}/C_{\beta}H_{(i+1)}$, $NH_{(i+1)}$/OMe.

Table 13: *^1H NMR chemical shift (δ in ppm) is in $CDCl_3$ for cis-dimer **98***

Monomer → / Proton ↓	(i)	(i+1)
NH		6.98
α	4.32	4.46
β	4.42	4. 89

Secondary structural analysis of *cis*-β-AFA tetramer 99

*i) COSY of cis-Tetramer **99**:* Majority of inter residual connectivities are characterized with the help of the COSY spectrum of *cis*-tetramer (Figure 49) and the representative connectivities and peak assignments are given in the Figure 50.

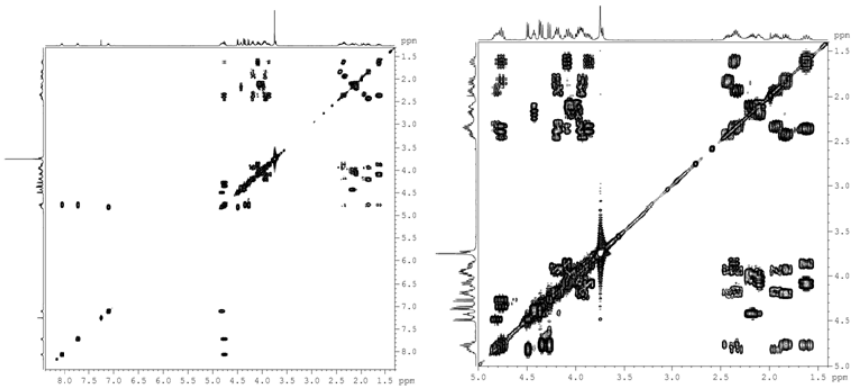


Figure 49: *Expansion of COSY spectrum of cis-tetramer **99***

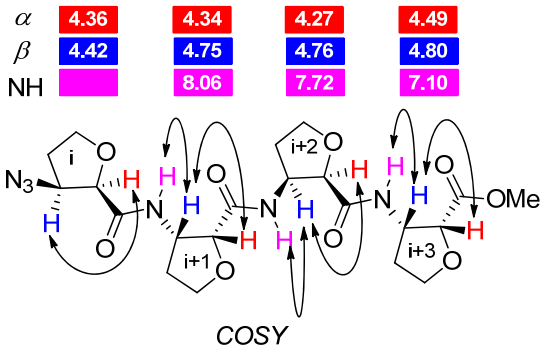


Figure 50: *Skeletal presentation of the cis-tetramer **99** obtained from COSY experiment*

*ii) HSQC of cis-Tetramer **99**:* This experiment identified the carbon and ^{1}H which are connected to each other through single bond. Figure 52 shows the $^{1}J_{C\text{-}H}$ couplings of *cis*-tetramer **99**.

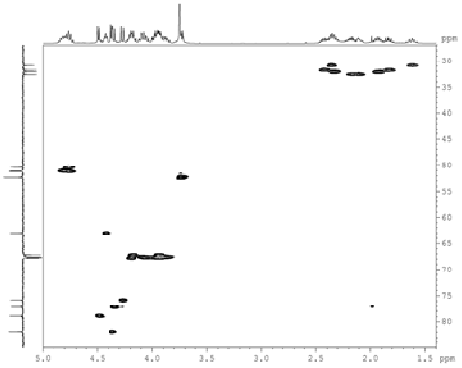


Figure 51: *HSQC spectrum of cis-tetramer **99***

*iii) HMBC of cis-Tetramer **99**:* The HMBC spectrum (Figure 52) and characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *cis*-tetramer **99** (Figure 53) are given below.

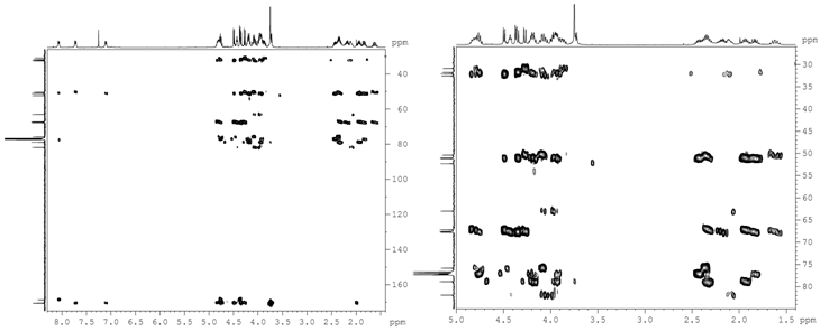


Figure 52: *Expansion of HMBC spectrum of cis-tetramer **99***

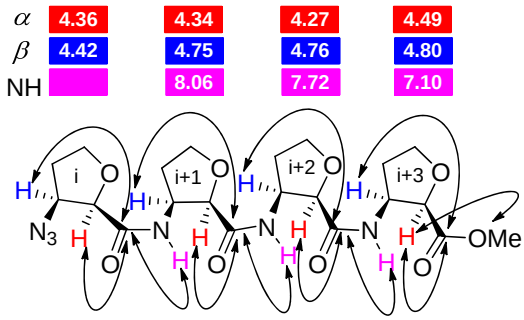


Figure 53: *Skeletal presentation of the cis-tetramer **99** obtained from HMBC experiment*

*iv) NOESY analysis of cis-Tetramer **99**:* The NOESY of *cis*-tetramer **99** and the characteristic through spatial connectives are given in Figures 54 and 55 respectively.

The *cis*-tetramer **99** shows n*O*es between $C_{\alpha}H_{(i+3)}/NH_{(i+3)}$, $C_{\beta}H_{(i+3)}/C_{\alpha}H_{(i+3)}$, $C_{\beta}H_{(i+2)}/NH_{(i+2)}$, $C_{\alpha}H_{(i+2)}/NH_{(i+2)}$, $C_{\alpha}H_{(i+1)}/C_{\beta}H_{(i+1)}$, $NH_{(i+1)}/C_{\alpha}H_{(i+1)}$, $NH_{(i+1)}/C_{\beta}H_{(i+1)}$ and $C_{\alpha}H_i/C_{\beta}H_i$ which are the intra-residue n*O*es.

The observed inter-residue n*O*es of *cis*-tetramer **99** are between $C_{\beta}H_i/NH_{(i+3)}$, $C_{\alpha}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$, $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, and $NH_{(i+2)}$/Me of ester.

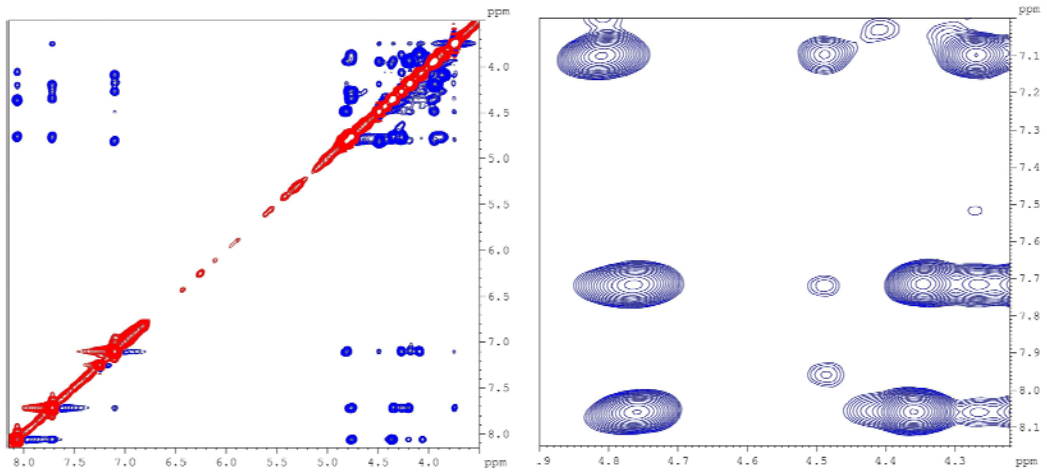


Figure 54*: Expansion of nOes spectrum of cis-tetramer **99***

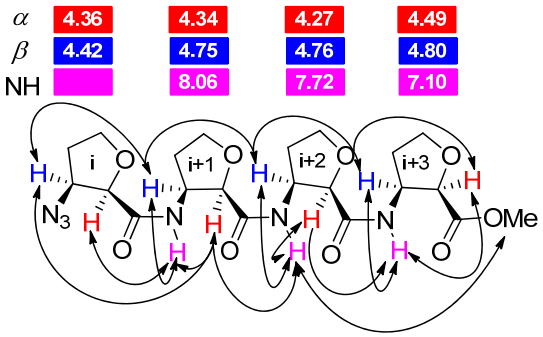


Figure 55: *Skeletal presentation of the tetramer **99** obtained from nOes experiment*

Table 14: *^{1}H NMR chemical shift (δ in ppm) is in $CDCl_3$ for cis-tetramer **99***

Monomer → / Proton ↓	(i)	(i+1)	(i+2)	(i+3)
NH		8.06	7.72	7.10
α	4.36	4.34	4.26	4.49
β	4.42	4.75	4.76	4.80

Secondary structural analysis of cis-β-FAA hexamer 100

*i) COSY of cis-hexamer **100**:* Majority of inter residual connectivities of hexamer **100** are characterized with the help of the COSY spectrum (Figure 56) and the representative connectivities and peak assignments are given in the Figure 57.

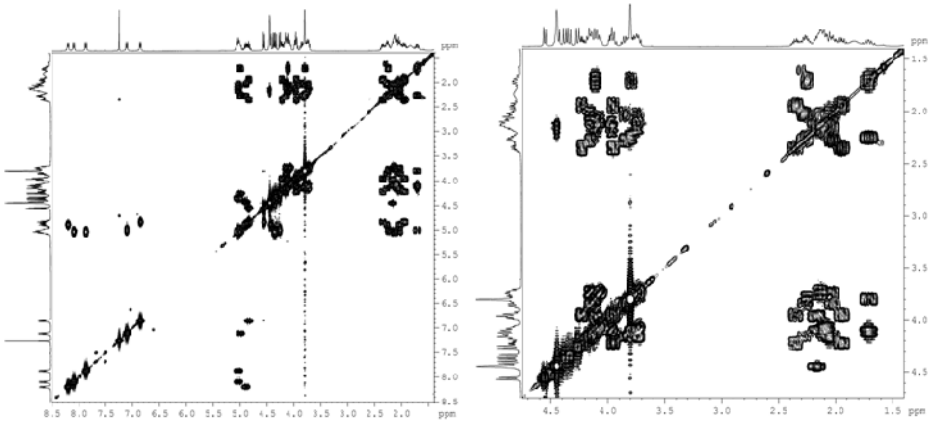


Figure 56: *Expansion of COSY spectrum of cis-hexamer **100***

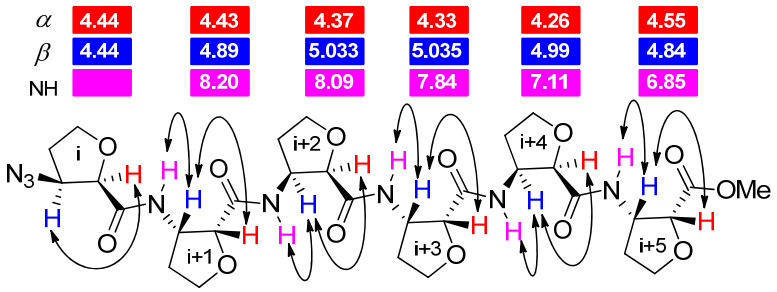


Figure 57: *Skeletal presentation of the cis-hexamer **100** obtained from COSY experiment*

*ii) HSQC analysis of cis-hexamer **100**:* This experiment identified the carbon and ^{1}H which are connected to each other through a single bond. Figure 58 shows the $^{1}J_{C\text{-}H}$ couplings of *cis*-hexamer **100**.

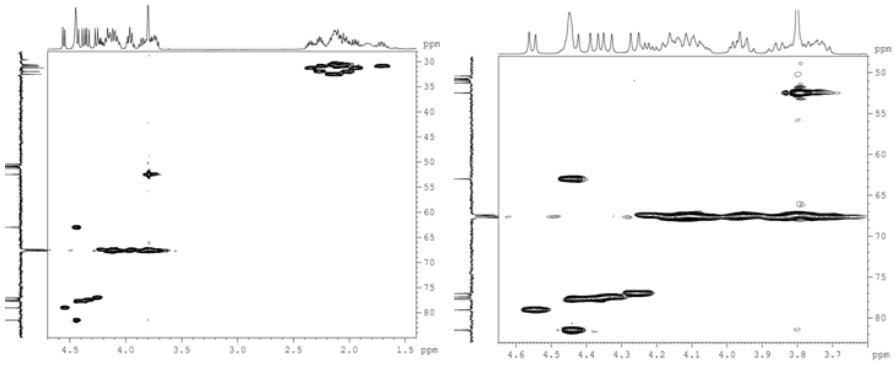
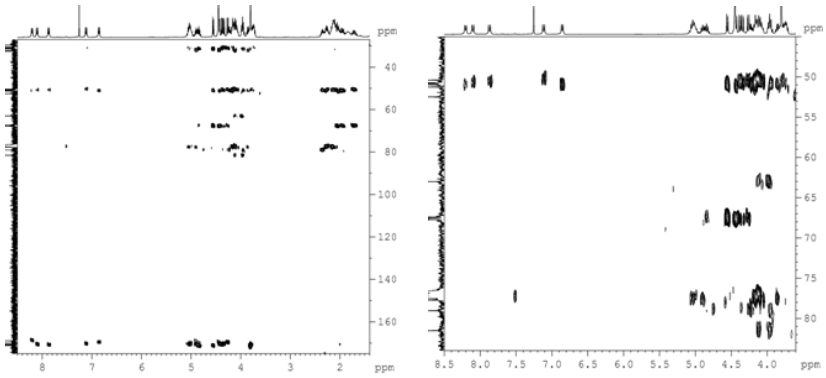


Figure 58: *HSQC spectrum of cis-hexamer **100***

*iii) HMBC anylysis of cis-hexamer **100**:* The HMBC spectrum (Figure 59) and characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *cis*-hexamer **100** (Figure 60) are given below.



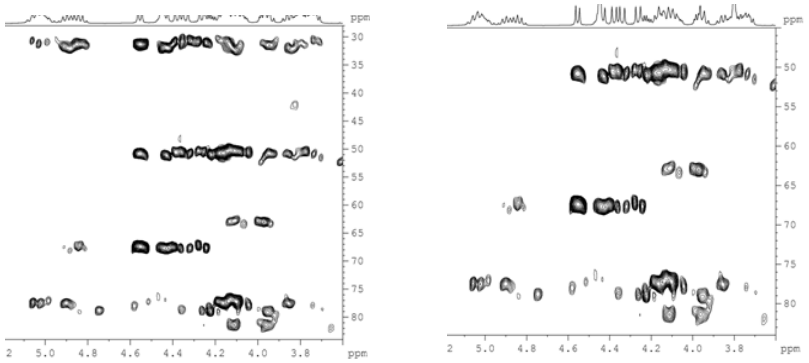


Figure 59: *Expansion of HMBC spectrum of cis-hexamer **100***

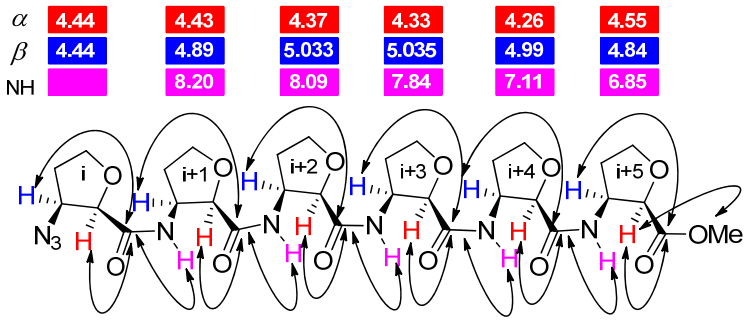


Figure 60: *Skeletal presentation of the cis-hexamer **100** obtained from HMBC experiment*

*iv) NOESY of cis-hexamer **100**:* The NOESY of *cis*-hexamer **100** and the characteristic through spatial connectives are given in Figures 61 and 62 respectively.

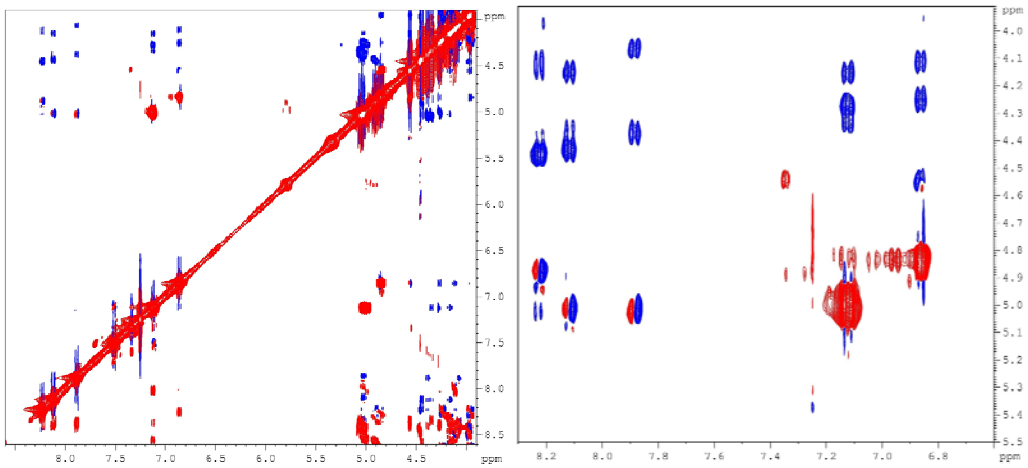


Figure 61: *Expansion of ROESY spectrum of cis-hexamer **100***

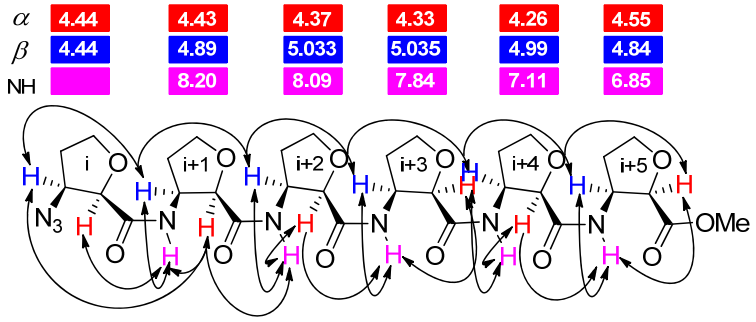


Figure 62: *Skeletal presentation of the cis-hexamer **100** obtained from NOESY experiment*

The *cis*-hexamer **100** shows intraresidue n*O*es between $C_{\alpha}H_{(i+5)}/C_{\beta}H_{(i+5)}$, $C_{\beta}H_{(i+5)}/NH_{(i+5)}$, $C_{\beta}H_{(i+5)}/C_{\alpha}H_{(i+5)}$, $C_{\alpha}H_{(i+4)}/C_{\beta}H_{(i+4)}$, $C_{\beta}H_{(i+4)}/NH_{(i+4)}$, $NH_{(i+4)}/C_{\alpha}H_{(i+4)}$, $C_{\alpha}H_{(i+3)}/C_{\beta}H_{(i+3)}$, $C_{\beta}H_{(i+3)}/NH_{(i+3)}$, $NH_{(i+3)}/C_{\alpha}H_{(i+3)}$, $C_{\alpha}H_{(i+2)}/C_{\beta}H_{(i+2)}$, $C_{\beta}H_{(i+2)}/NH_{(i+2)}$, $NH_{(i+2)}/C_{\alpha}H_{(i+2)}$, $C_{\alpha}H_{(i+1)}/C_{\beta}H_{(i+1)}$, $C_{\beta}H_{(i+1)}/NH_{(i+1)}$, $C_{\alpha}H_{(i+1)}$ /$NH_{(i+1)}$, and $C_{\alpha}H_i/C_{\beta}H_i$.

The inter-residue n*O*es of *cis*-hexamer are $C_{\beta}H_i/NH_{(i+2)}$, $C_{\beta}H_i/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+3)}$, $C_{\beta}H_{(i+2)}/NH_{(i+4)}$, $C_{\beta}H_{(i+3)}/NH_{(i+5)}$, $C_{\beta}H_{(i+3)}/NH_{(i+6)}$, $C_{\beta}H_{(i+4)}/NH_{(i+6)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$ and $NH_{(i+1)}/C_{\beta}H_{(i+4)}$.

Table 14: *^{1}H NMR chemical shift (δ in ppm) in $CDCl_3$ for cis-hexamer **100***

Monomer → / Proton ↓	(i)	(i+1)	(i+2)	(i+3)	(i+4)	(i+5)
NH		8.20	8.09	7.84	7.11	6.85
α	4.44	4.43	4.37	4.33	4.26	4.55
β	4.44	4.89	5.03349	5.03525	4.99	4.84

Secondary structural analysis of *cis*-β-FAA octamer 101

i) COSY of cis-octamer ***101***: Majority of inter residual connectivities of *cis*-octamer **101** are established with the help of the COSY spectrum (Figure 63) and the representative connectivities and peak assignments are given in the Figure 64.

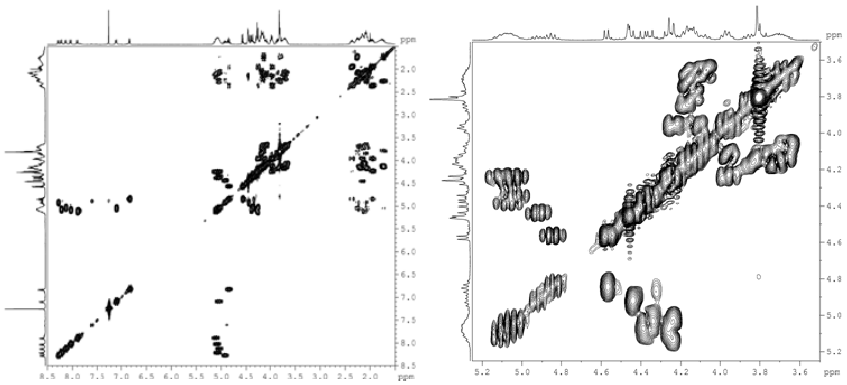


Figure 63: *Expansion of COSY spectrum of cis-octamer* ***101***

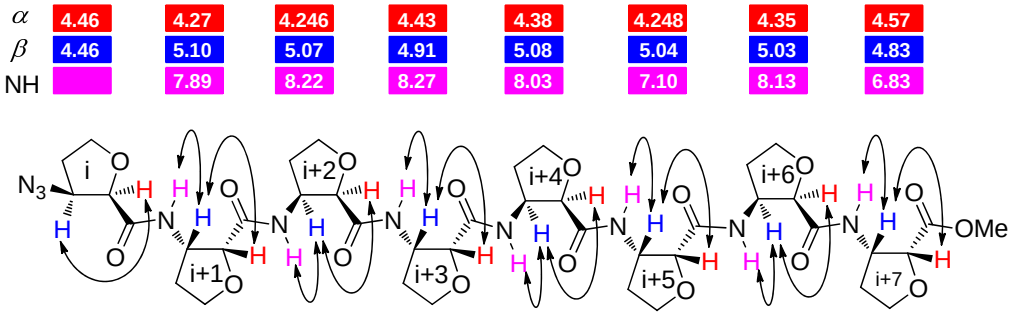


Figure 64: *Skeletal presentation of the cis-octamer* ***101*** *obtained from COSY experiment*

ii) HSQC analysis of cis-octamer ***101****:* This experiment identified the carbon and ^{1}H which are connected to each other through single bond. Figure 65 shows the $^{1}J_{C\text{-}H}$ couplings of *cis*-octamer **101**.

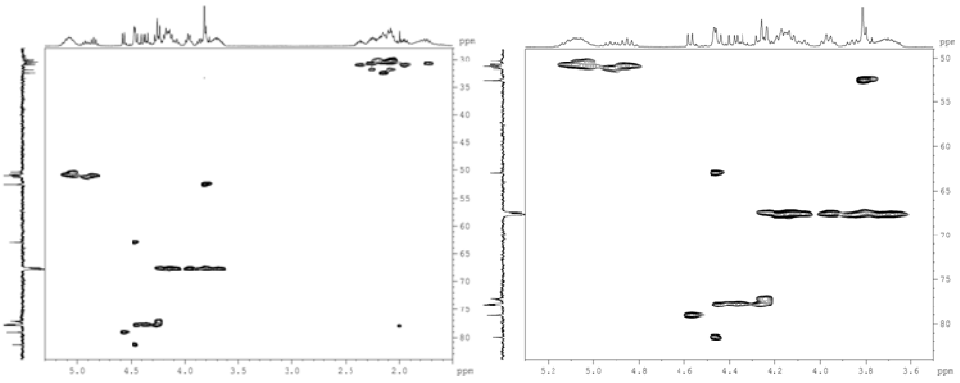


Figure 65: *Expansion of HSQC spectrum of cis-octamer* ***101***

iii) HMBC analysis of cis-octamer ***101****:* The HMBC spectrum (Figure 66) and characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *cis*-octamer **101** (Figure 67) are given below.

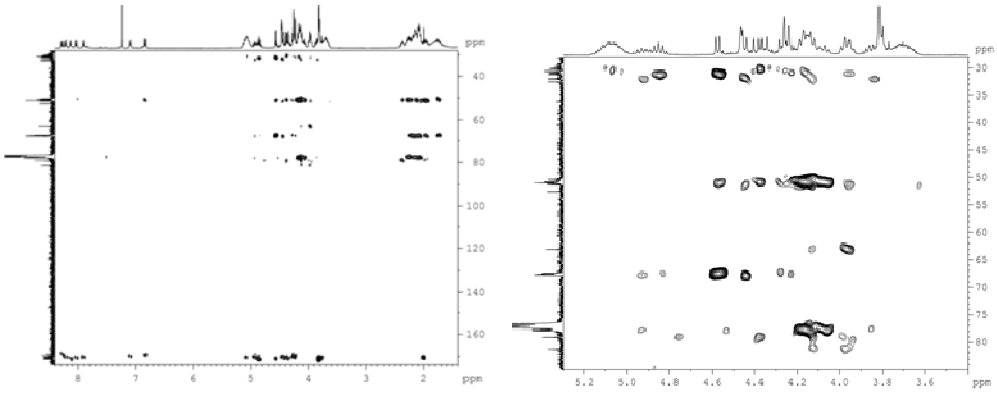


Figure 66: *Expansion of HMBC spectrum of cis-octamer **101***

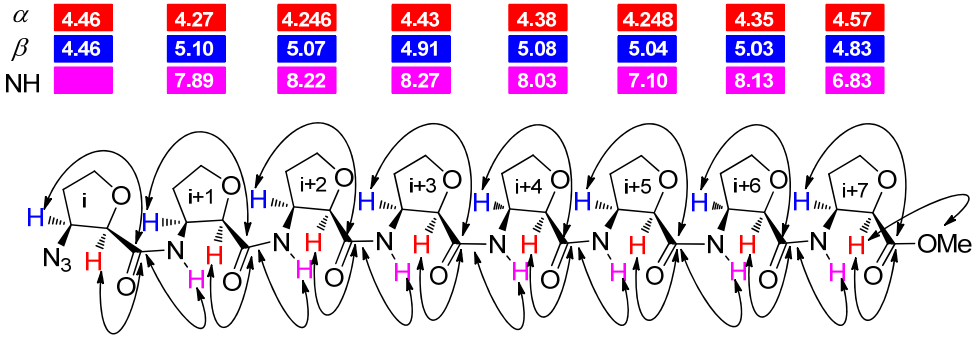


Figure 67: *Skeletal presentation of the cis-octamer **101** obtained from HMBC experiment*

*iv) NOESY analysis of cis-octamer **101**:* The NOESY of *cis*-octamer **101** and the characteristic through spatial connectives are given in Figures 68 and 69 respectively.

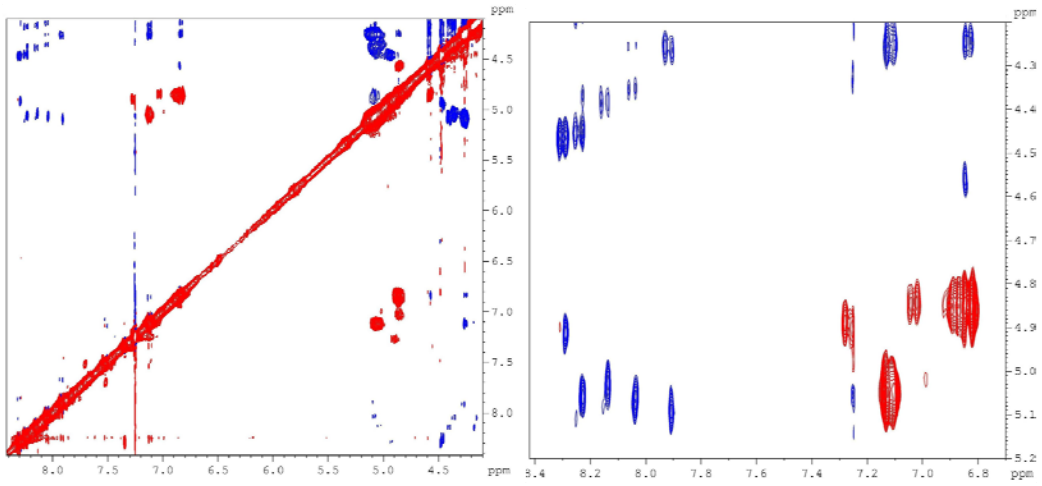


Figure 68: *Expansion of ROESY spectrum of cis-octamer **101***

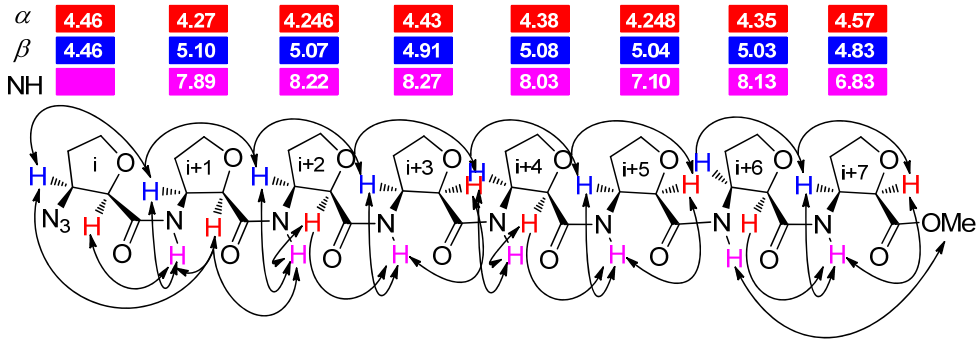


Figure 69 *Skeletal presentation of the cis-octamer **101** obtained from nOe experiment*

The *cis*-octamer **101** shows intraresidue n*O*es between $C_{\alpha}H_{(i+7)}/C_{\beta}H_{(i+7)}$, $C_{\beta}H_{(i+7)}/NH_{(i+7)}$, $C_{\alpha}H_{(i+6)}/C_{\beta}H_{(i+6)}$, $C_{\beta}H_{(i+6)}/NH_{(i+6)}$, $C_{\alpha}H_{(i+6)}/NH_{(i+6)}$, $C_{\alpha}H_{(i+5)}/C_{\beta}H_{(i+5)}$, $C_{\beta}H_{(i+5)}/NH_{(i+5)}$, $C_{\beta}H_{(i+5)}/\ NH_{(i+5)}$, $C_{\alpha}H_{(i+4)}/C_{\beta}H_{(i+4)}$, $C_{\beta}H_{(i+4)}/NH_{(i+4)}$, $NH_{(i+4)}/C_{\alpha}H_{(i+4)}$, $C_{\alpha}H_{(i+3)}/C_{\beta}H_{(i+3)}$, $C_{\beta}H_{(i+3)}/NH_{(i+3)}$, $NH_{(i+3)}/C_{\alpha}H_{(i+3)}$, $C_{\alpha}H_{(i+2)}/C_{\beta}H_{(i+2)}$, $C_{\beta}H_{(i+2)}/NH_{(i+2)}$, $NH_{(i+2)}/C_{\alpha}H_{(i+2)}$, $C_{\alpha}H_{(i+1)}/C_{\beta}H_{(i+1)}$, $C_{\beta}H_{(i+1)}/NH_{(i+1)}$, $C_{\alpha}H_{(i+1)}\ /NH_{(i+1)}$, and $C_{\alpha}H_{i}/C_{\beta}H_{i}$.

The inter-residue n*O*es of *cis*-octamer **101** are $C_{\beta}H_{i}/NH_{(i+2)}$, $C_{\beta}H_{i}/C_{\alpha}H_{(i+2)}$, $C_{\beta}H_{i}/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/C_{\alpha}H_{(i+4)}$, $C_{\beta}H_{(i+3)}/NH_{(i+5)}$, $C_{\beta}H_{(i+3)}/C_{\alpha}H_{(i+5)}$, $C_{\beta}H_{(i+4)}/NH_{(i+6)}$, $C_{\beta}H_{(i+5)}/NH_{(i+7)}$, $C_{\beta}H_{(i+5)}/C_{\alpha}H_{(i+7)}$ $NH_{(i+1)}/C_{\beta}H_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+4)}$, $NH_{(i+2)}/C_{\beta}H_{(i+5)}$, $NH_{(i+3)}/C_{\beta}H_{(i+5)}$, and $NH_{(i+5)}/C_{\beta}H_{(i+7)}$.

Table 15: *^{1}H NMR chemical shift (δ in ppm) in $CDCl_3$ for cis-octamer **101***

Monomer → / Proton ↓	(i)	(i+1)	(i+2)	(i+3)	(i+4)	(i+5)	(i+6)	(i+7)
NH		7.89	8.22	8.27	8.03	7.10	6.83	8.13
α	4.46	4.27	4.2661	4.43	4.38	4.2487	4.57	4.33
β	4.46	5.10	5.07	4.91	5.08	5.04	4.83	5.03

Secondary structural analysis of trans-β-FAA dimer 102

*i) COSY of trans-dimer **102**:* The detailed analysis of the COSY spectrum (Figure 70) of *trans*-dimer **102** has been given and the inter-residue connectivities are shown (Figure 71) below.

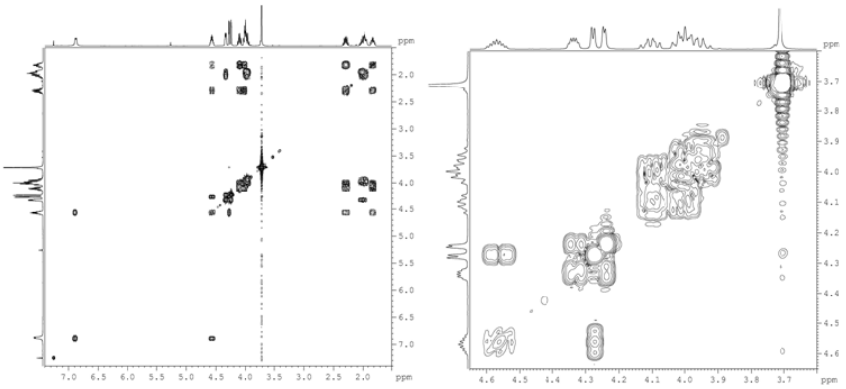


Figure 70: *Expansion of COSY spectrum of trans-dimer* ***102***

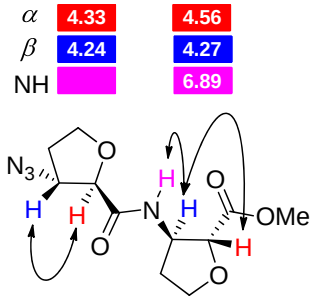


Figure 71: *Skeletal presentation of the cis-octamer* ***101*** *obtained from COSY experiment*

II) HSQC analysis of trans-dimer ***102*****:** This experiment identifies the carbon and ^{1}H which are connected to each other through a single bond. Figure 73 shows the $^{1}J_{C\text{-}H}$ couplings of *trans*-dimer **102**.

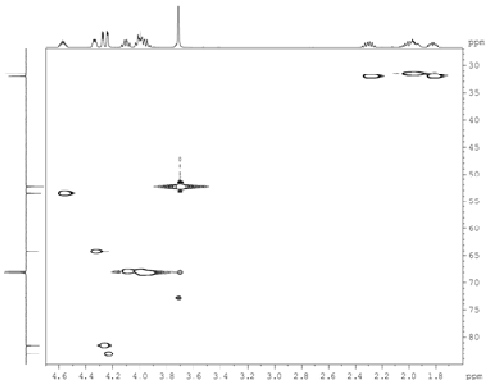


Figure 72: *Expansion of HSQC spectrum of trans-dimer****102***

iii) HMBC of trans-dimer ***102*****:** This experiment (Figure 73) identified the carbon and proton which are separated by two/three bonds depending on the coupling constant

and dihedral angles. Figure 74 shows some of the characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *trans*-dimer **102** observed.

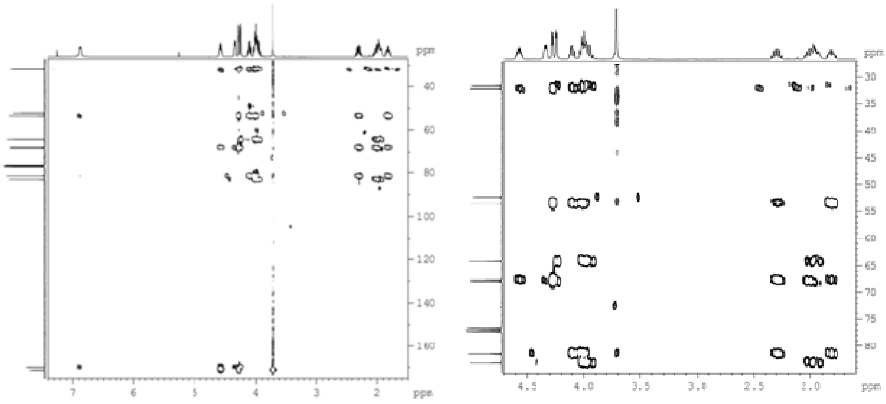


Figure 73: *Expansion of HMBC spectrum of trans-dimer **102***

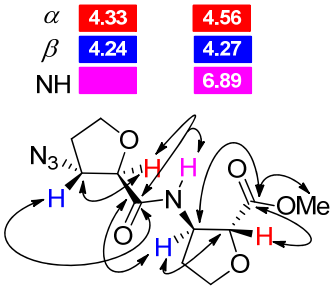


Figure 74: *Skeletal representation of the trans-dimer **102** obtained from HMBC*

*iv) NOESY analysis of dimer **102**:* The Figure 75shows some of the characteristic n*O*es of dimer **102** and Figure 76 shows the skeletal presentation.

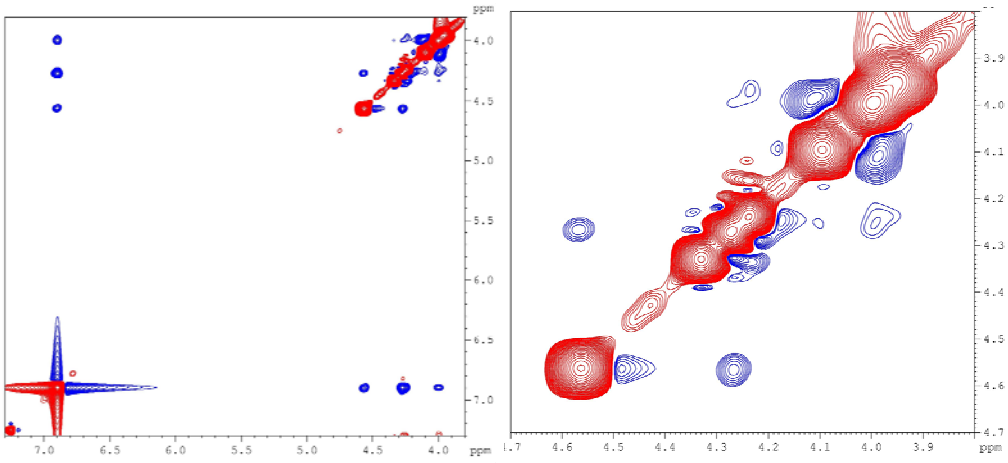


Figure 75: *Expansion of nOe spectrum of trans-dimer **102***

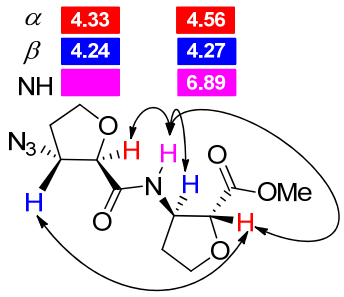


Figure 76: *Skeletal presentation of the trans-dimer **102** obtained from nOe experiment*

The *trans*-dimer **102** shows intra-residue n*O*es between $C_{\alpha}H_{(i+1)}/NH_{(i+1)}$, $C_{\beta}H_{(i+1)}/NH_{(i+1)}$, the inter-residue n*O*es is $C_{\beta}H_i/C_{\alpha}H_{(i+1)}$.

Table 16: *^{1}H NMR chemical shift (δ in ppm) in $CDCl_3$ for trans-dimer **102***

Monomer → / Proton ↓	(i)	(i+1)
NH		6.89
α	4.24	4.27
β	4. 33	4.56

Secondary structural analysis of trans-tetramer 103

*i). COSY of trans-tetramer **103**:* A majority of inter residual connectivities are characterized with the help of the COSY spectrum of tetramer (Figure 77) and the representative connectivities and peak assignments are given in the Figure 78.

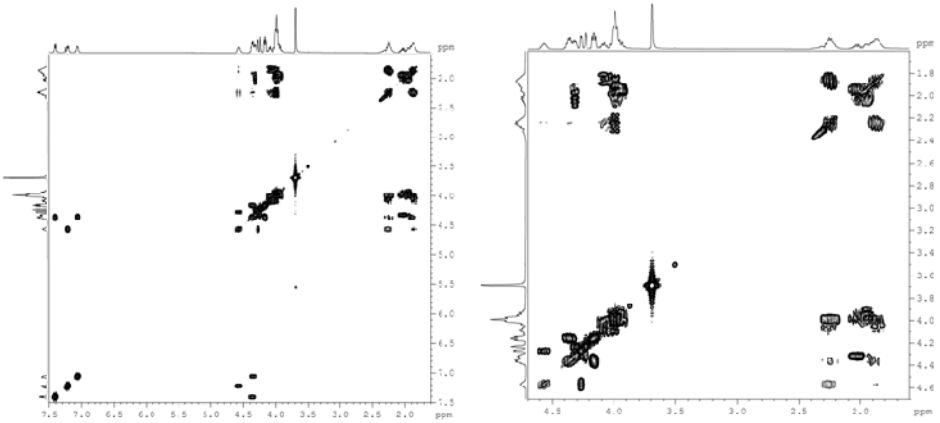


Figure 77: *Expansion of COSY spectrum of tetramer **103***

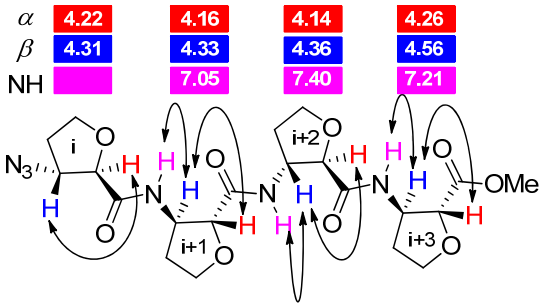


Figure 78: *Skeletal presentation of the trans-tetramer **103** obtained from COSY experiment*

*ii) HSQC analysis of trans-tetramer **103**:* This experiment identified the carbon and ^{1}H which are connected to each other through single bond. Figure 80 shows the $^{1}J_{C\text{-}H}$ couplings of tetramer **103**.

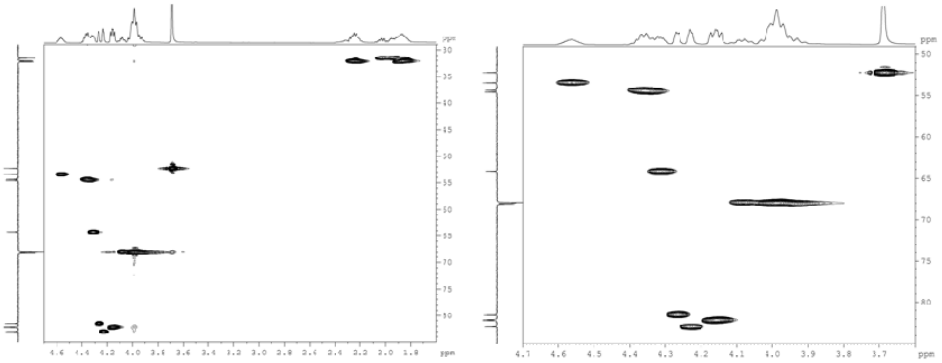


Figure 79: *Expansion of HSQC spectrum of trans-tetramer **103***

*iii) HMBC analysis of tetramer **103**:* The HMBC spectrum (Figure 80) and characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of tetramer **103** (Figure 81) are given below.

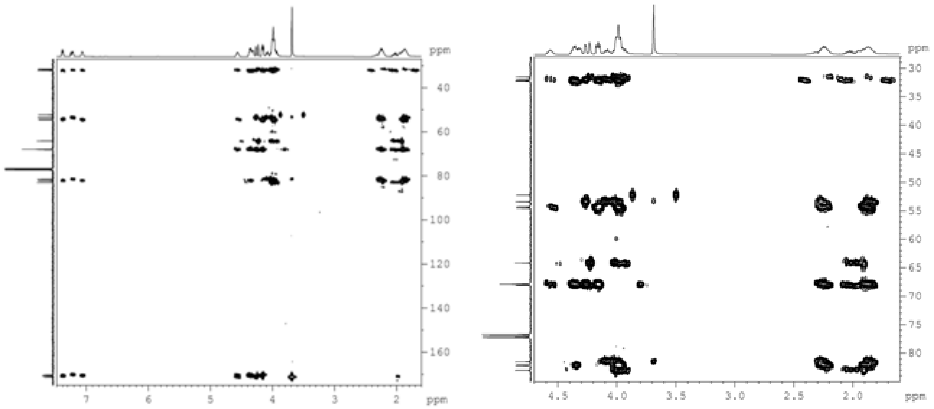


Figure 80: *Expansion of HMBC spectrum of trans-tetramer **103***

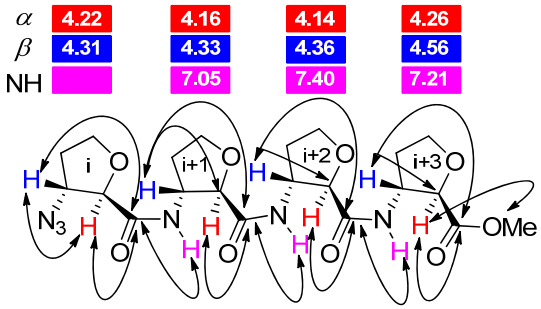


Figure 81: *Skeletal presentation of the trans-tetramer **103** obtained from HMBC experiment*

*iv) NOESY analysis of trans-tetramer **103**:* The NOESY of *trans*-tetramer **103** and the characteristic through spatial connectives are given in Figures 83 and 84 respectively.

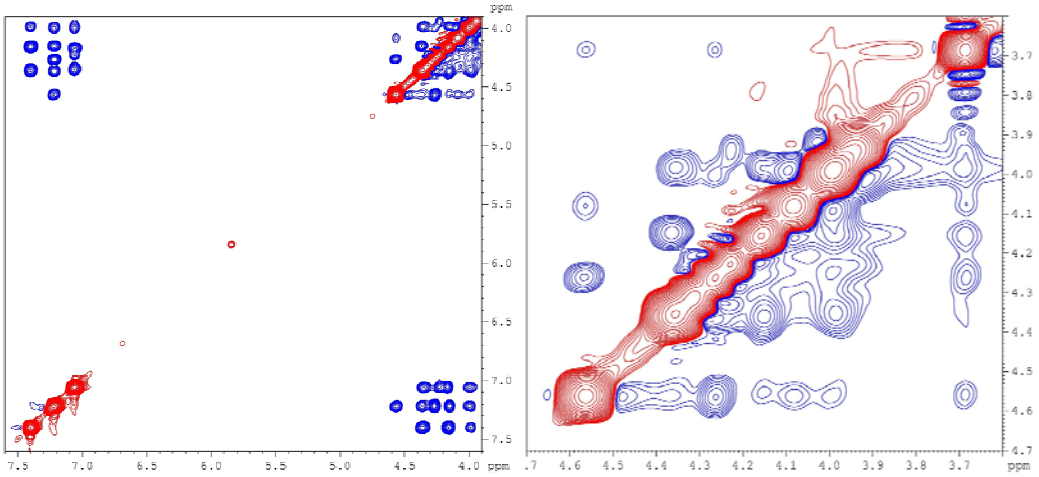


Figure 82: *Expansion of nOe spectrum of trans-tetramer **103***

The n*O*es of *trans*-tetramer **103**, $C_{\beta}H_i/NH_{(i+2)}$, $C_{\beta}H_i/NH_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$ were observed.

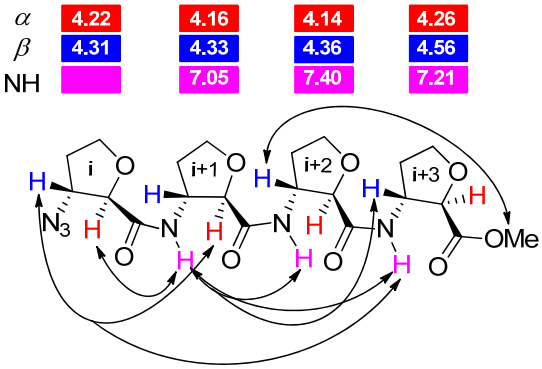


Figure 83: *Skeletal presentation of the trans-tetramer **103** obtained from nOe experiment*

Table 17: *^{1}H NMR chemical shift (δ in ppm) in $CDCl_3$ for trans-tetramer* ***103***

Monomer → / Proton ↓	(i)	(i+1)	(i+2)	(i+3)
NH		7.05	7.40	7.21
α	4.22	4.16	4.14	4.26
β	4.31	4.33	4.36	4.56

Secondary structural analysis of trans-hexamer 104

i). COSY of trans-hexamer ***104****:* A majority of inter residual connectivities are characterized with the help of the COSY spectrum of tetramer (Figure 84) and the representative connectivities and peak assignments are given in the Figure 85.

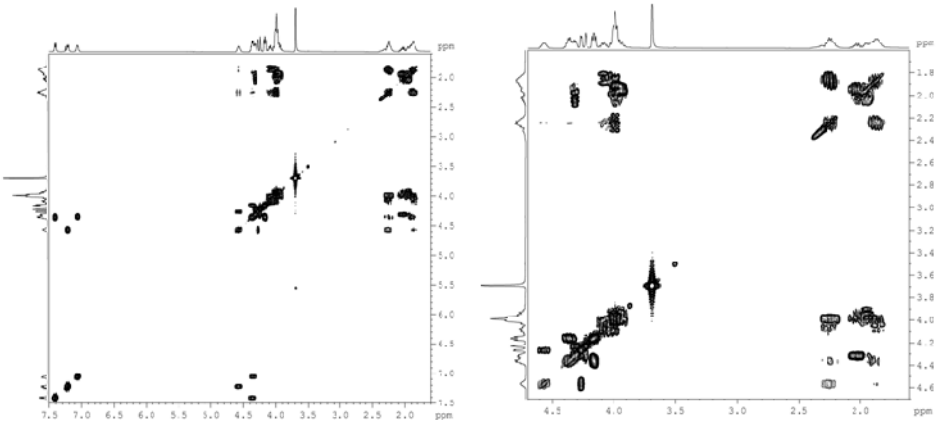


Figure 84: *Expansion of COSY spectrum of trans-hexamer* ***104***

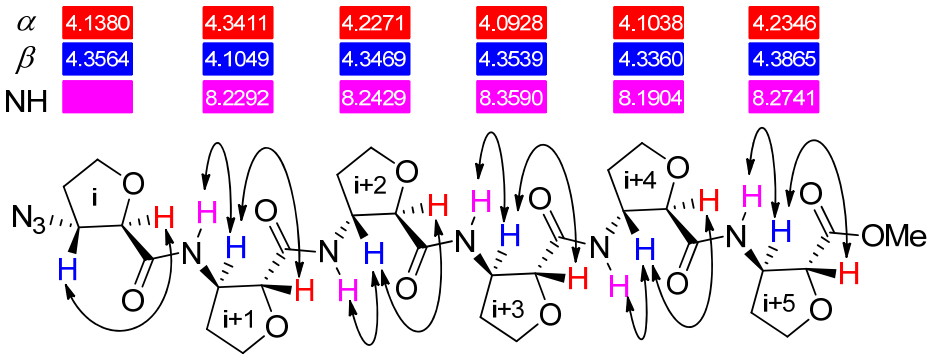


Figure 85: *Skeletal presentation of the trans-hexamer* ***104*** *obtained from COSY experiment*

ii) HSQC analysis of trans-hexamer ***104****:* This experiment identified the carbon and ^{1}H which are connected to each other through single bond. Figure 86 shows the $^1J_{C\text{-}H}$ couplings of *trans*-hexamer **104**.

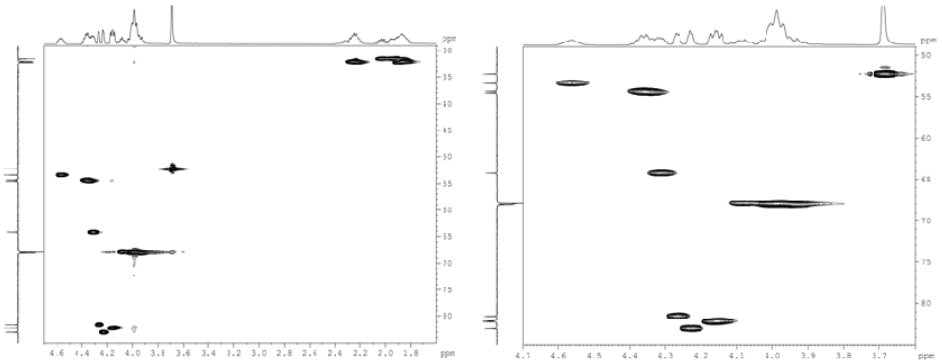


Figure 86: *Expansion of HSQC spectrum of trans-hexamer **104***

*iii) HMBC analysis of trans-tetramer **104**:* The HMBC spectrum (Figure 86) and characteristic $^{2}J_{C\text{-}H}/^{3}J_{C\text{-}H}$ couplings of *trans*-hexamer **104** (Figure 87) are given below.

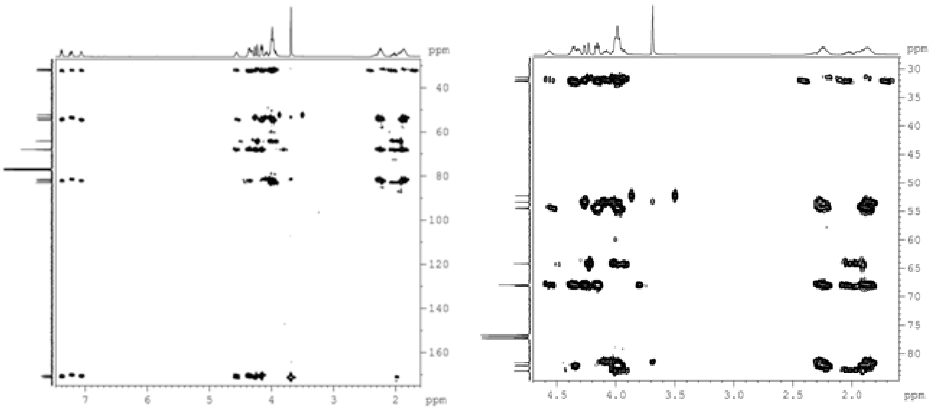


Figure 87: *Expansion of HMBC spectrum of trans-hexamer **104***

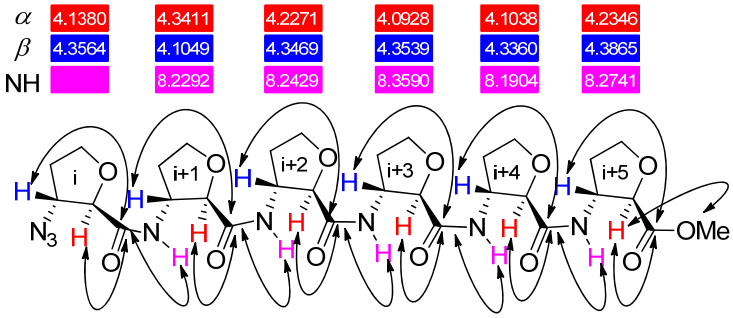


Figure 88: *Skeletal presentation of the trans-hexamer **104** obtained from HMBC experiment*

*iv) NOESY analysis of trans-hexamer **104**:* The NOESY of *trans*-hexamer **104** and the characteristic through spatial connectives are given in Figures 88 and 89 respectively.

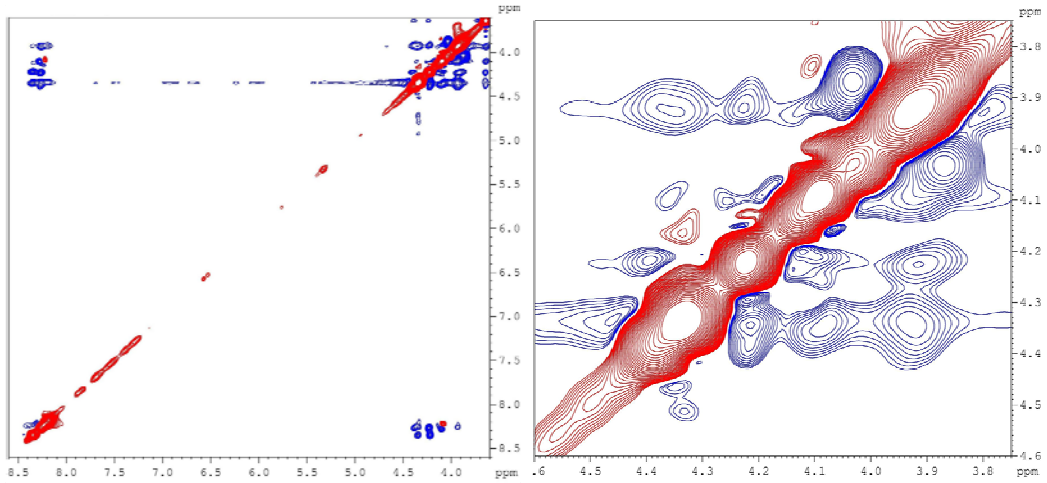


Figure 89: *Expansion of nOe spectrum of trans-hexamer **104***

The n*O*es of *trans*-hexamer **104**, $C_{\beta}H_i/NH_{(i+2)}$, $C_{\beta}H_i/NH_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$ were observed.

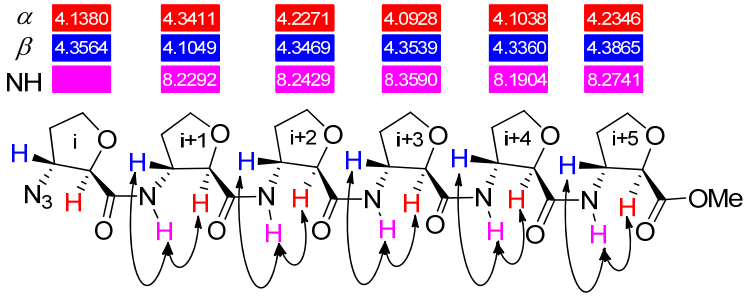


Figure 90: *Skeletal presentation of the trans-hexamer **104** obtained from nOe experiment*

Table 17: *^1H NMR chemical shift (δ in ppm) in $CDCl_3$ for trans-hexamer **104***

Monomer → / Proton ↓	(i)	(i+1)	(i+2)	(i+3)	(i+4)	(i+5)
NH		8.2292	8.2429	8.3590	8.1904	8.2741
α	4.1380	4.1049	4.2271	4.0928	4.1028	4.2346
β	4.3564	4.3411	4.3469	4.3539	4.3360	4.3865

Discussion and Conclusion

The secondary structures of *cis*-*β*-FAA were confirmed with the help of the inter-residue n*O*es noticed. Amongst the various n*O*es observed in the NOESY of the *cis*-tetramer **98**, the inter-residue $C_{\beta}H_i/NH_{(i+3)}$, $C_{\alpha}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, $NH_{(i+1)}/C_{\beta}H_{(i+3)}$, $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, and $NH_{(i+2)}$/Me of ester (Figure 36) indicates the presence of a three 12-helix pitchs. The CD spectra of *cis*-tetramer **99** shows maxima at 205 nm, zero crossing at 210 nm and minima at 222 nm. This CD pattern suggested a left-handed

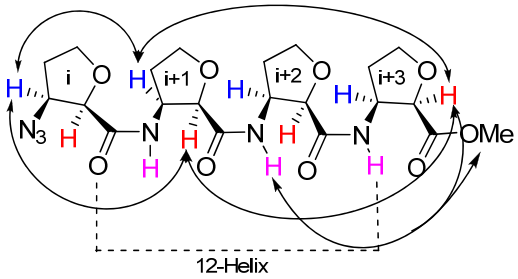


Figure 91: *Characteristic nOes supporting a 12-helix of cis-tetramer **99***

12-helix in *cis*-tetramer **99** which indeed has been observed with the *trans*-aminocyclopentane carboxylic acid (*trans*-ACPC) and also cyclic pyrrolidne based *β*-amino acid homo-oligomers.

Temp (°C)	NH_{i+1}	NH_{i+2}	NH_{i+3}
0	8.16	7.80	7.12
5	8.14	7.78	7.12
10	8.12	7.77	7.11
15	8.10	7.75	7.11
20	8.09	7.74	7.11
25	8.08	7.74	7.10
30	8.05	7.71	7.10
35	8.03	7.69	7.10
40	8.02	7.68	7.09
45	8.00	7.67	7.09
50	7.98	7.65	7.08
Δδ/ppb/°C	**3.60**	**3.0**	**2.0**

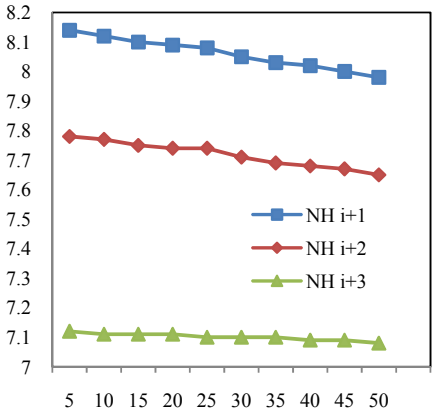


Figure 92: *Temperature-dependent chemical shifts of NH protons of **99** in $CDCl_3$ solution*

% DMSO-d6 (v/v)	NH_{i+1}	NH_{i+2}	NH_{i+3}
0	8.07	7.73	7.1
25	7.97	7.61	7.14
50	7.9	7.54	7.15
100	7.8	7.44	7.2
150	7.72	7.35	7.22
200	7.66	7.29	7.24
250	7.61	7.25	7.26
300	7.57	7.21	7.27
Δδ ppm	**0.50**	**0.52**	**– 0.16**

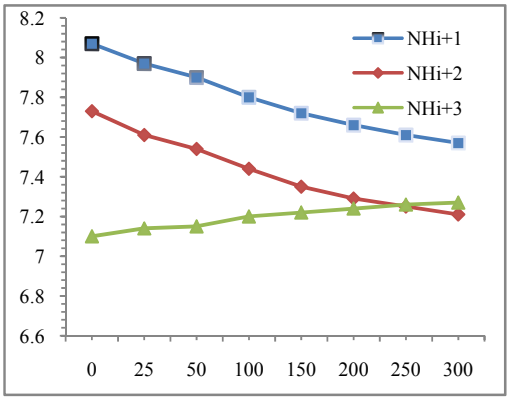


Figure 93: The *NH chemical shifts variation on the addition of DMSO-d6 for cis-tetramer **99***

The ^{1}H NMR spectrum of **99** shows the well resolved backbone proton signals as well as low field amide protons resonance which indicates the involvement of these NH groups in H-bonding. These bonding were further confirmed by solvent titration studies (Figure 92) and temperature dependent deviation of chemical shift of amide protons (Figure 93).

Next, we analyzed the various inter-residue n*O*es observed in the NOESY of the *cis*-hexamer **100** (Figure 94). Seven characteristic n*O*es $C_{\beta}H_{(i+0)}/NH_{(i+2)}$, $C_{\beta}H_{(i+0)}/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/NH_{(i+5)}$, and $C_{\beta}H_{(i+3)}/NH_{(i+5)}$

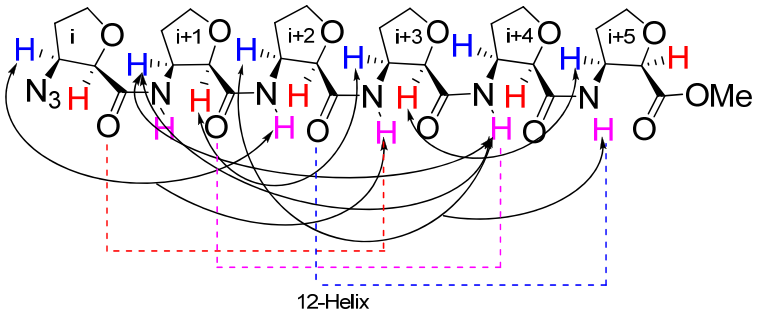


Figure 94: *Characteristic nOes supporting a 12-helix*

Temp (°C)	NH_{i+1}	NH_{i+2}	NH_{i+3}	NH_{i+4}	NH_{i+5}
0	8.32	8.18	7.96	7.16	6.82
5	8.30	8.16	7.94	7.15	6.83
10	8.28	8.15	7.93	7.14	6.83
15	8.25	8.14	7.91	7.13	6.84
20	8.23	8.12	7.89	7.12	6.85
25	8.21	8.10	7.87	7.11	6.85
30	8.19	8.09	7.85	7.11	6.86
35	8.16	8.07	7.83	7.10	6.87
40	8.14	8.05	7.82	7.10	6.87
45	8.12	8.03	7.79	7.10	6.88
50	8.10	8.01	7.77	7.10	6.89
Δδ/ppb/°C	4.40	3.40	3.80	1.20	1.4

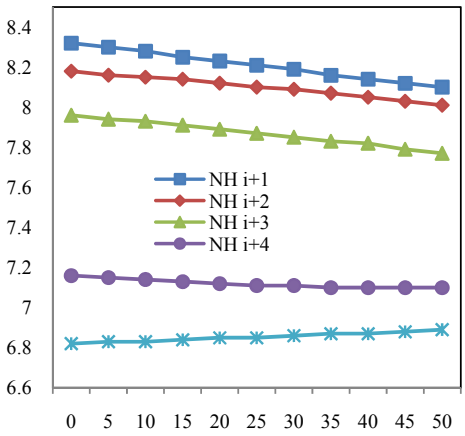


Figure 95: *Temperature-dependent chemical shifts of NH protons of* ***102*** *in* $CDCl_3$ *solution*

were found that indicated the presence of a left-handed 12-helix, which was further confirmed by the CD maxima and minima recorded for this *cis*-hexamer **100**. The solvent titration studies and temperature dependent deviation in amide proton confirm the presence of secondary structure in **100**.

% DMSO-d6 (v/v)	NH_{i+1}	NH_{i+2}	NH_{i+3}	NH_{i+4}	NH_{i+5}
0	8.21	8.11	7.88	7.12	6.86
25	8.14	8.06	7.85	7.1	6.94
50	8.08	8.01	7.82	7.08	7
75	8.04	7.98	7.77	7.04	7.06
100	7.99	7.93	7.72	7.03	7.08
125	7.91	7.86	7.65	6.99	7.14
150	7.84	7.8	7.67	6.96	7.18
200	7.78	7.74	7.63	6.93	7.2
250	7.73	7.71	7.59	6.9	7.22
300	7.66	7.68	7.56	6.87	7.24
Δδ ppm	**0.55**	**0.43**	**0.32**	**0.25**	**–0.38**

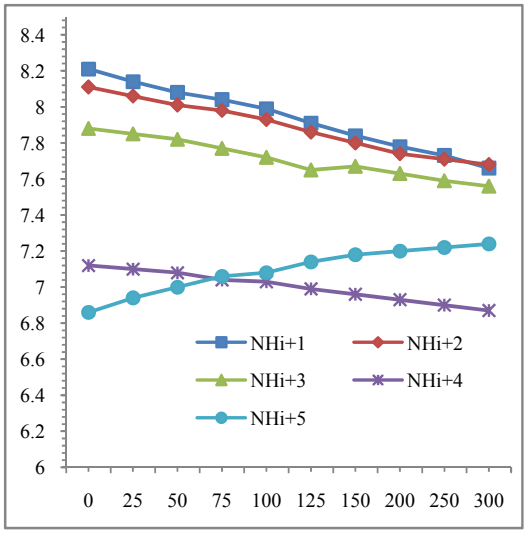


Figure 96: The *NH chemical shifts variation on the addition of DMSO-d6 for cis-hexamer* **100**

The inter-residue n*O*es observed in the NOESY of the *cis*-octamer **101** are given in Figure 95 which indicated the strong hydrogen bonding pattern governing to the left-handed 12-helix. The inter-residue n*O*es of *cis*-octamer **101** are $C_{\beta}H_i/NH_{(i+2)}$, $C_{\beta}H_i/C_{\alpha}H_{(i+2)}$, $C_{\beta}H_i/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+3)}$, $C_{\beta}H_{(i+1)}/C_{\alpha}H_{(i+3)}$, $C_{\beta}H_{(i+1)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/NH_{(i+4)}$, $C_{\beta}H_{(i+2)}/C_{\alpha}H_{(i+4)}$, $C_{\beta}H_{(i+3)}/NH_{(i+5)}$, $C_{\beta}H_{(i+3)}/C_{\alpha}H_{(i+5)}$, $C_{\beta}H_{(i+4)}/NH_{(i+6)}$, $C_{\beta}H_{(i+5)}/NH_{(i+7)}$, $C_{\beta}H_{(i+5)}/C_{\alpha}H_{(i+7)}$ are the characteristic peak for 12-helix (Figure 97).

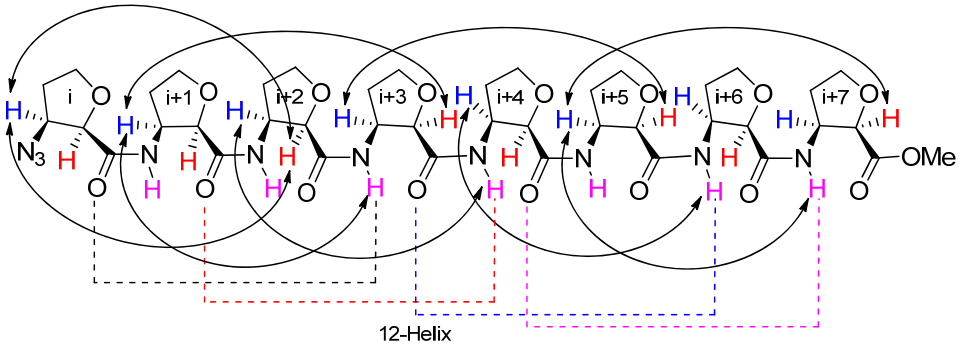


Figure 97: *Characteristic nOes supporting a 12-helix* **101**

The ^{1}H NMR spectrum of **101** shows the secondary structure in which the amide protons resonated at down field. The H-bonding was further supported by solvent titration studies and temperature dependent deviation

Temp (°C)	NH_{i+3}	NH_{i+2}	NH_{i+6}	NH_{i+4}	NH_{i+1}	NH_{i+5}	NH_{i+7}
0	8.38	8.27	8.195	8.115	8.01	7.19	6.82
5	8.36	8.26	8.18	8.10	7.99	7.17	6.82
10	8.34	8.25	8.17	8.085	7.97	7.15	6.825
15	8.32	8.24	8.16	8.07	7.945	7.13	6.83
20	8.30	8.235	8.15	8.05	7.92	7.115	6.83
25	8.28	8.22	8.14	8.035	7.90	7.10	6.83
30	8.26	8.21	8.12	8.015	7.875	7.085	6.84
35	8.24	8.20	8.105	8.01	7.85	7.07	6.84
40	8.22	8.19	8.09	7.98	7.83	7.06	6.845
45	8.20	8.18	8.075	7.96	7.815	7.05	6.85
50	8.18	8.165	8.06	7.94	7.78	7.04	6.86
Δδ/ppb/°C	**4.00**	**2.10**	**2.70**	**3.50**	**4.60**	**3.00**	**0.08**

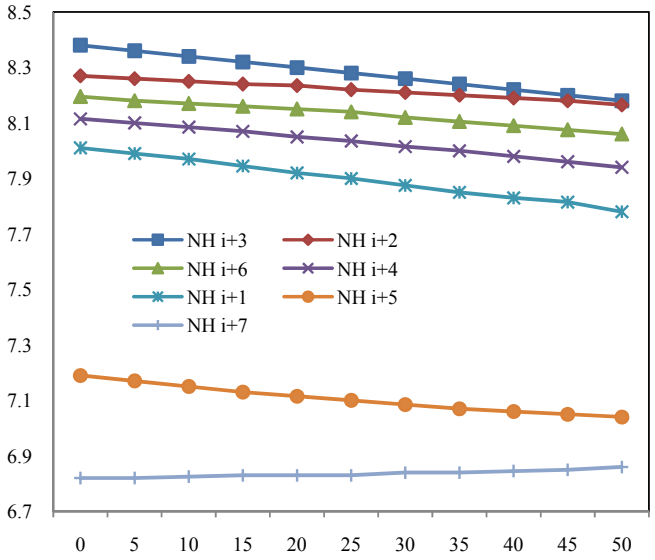


Figure 98: *Temperature-dependent chemical shifts of NH protons of **102** in $CDCl_3$ solution*

% DMSO-d6 (v/v)	NH_{i+3}	NH_{i+2}	NH_{i+7}	NH_{i+4}	NH_{i+1}	NH_{i+5}	NH_{i+6}
0	8.28	8.23	8.14	8.04	7.91	7.11	6.84
25	8.22	8.21	8.11	8.01	7.89	7.1	6.92
50	8.15	8.19	8.08	7.98	7.87	7.09	6.99
75	8.11	8.14	8.05	7.95	7.84	7.08	7.04
125	8.08	8.1	8.02	7.91	7.82	7.06	7.08
150	8.03	8.07	7.99	7.89	7.80	7.04	7.11
200	7.97	7.99	7.98	7.83	7.75	7.01	7.17
250	7.9	7.92	7.88	7.77	7.70	6.97	7.22
300	7.81	7.83	7.78	7.67	7.61	6.91	7.25
Δδ ppm	**0.47**	**0.40**	**0.36**	**0.37**	**0.30**	**0.20**	**–0.41**

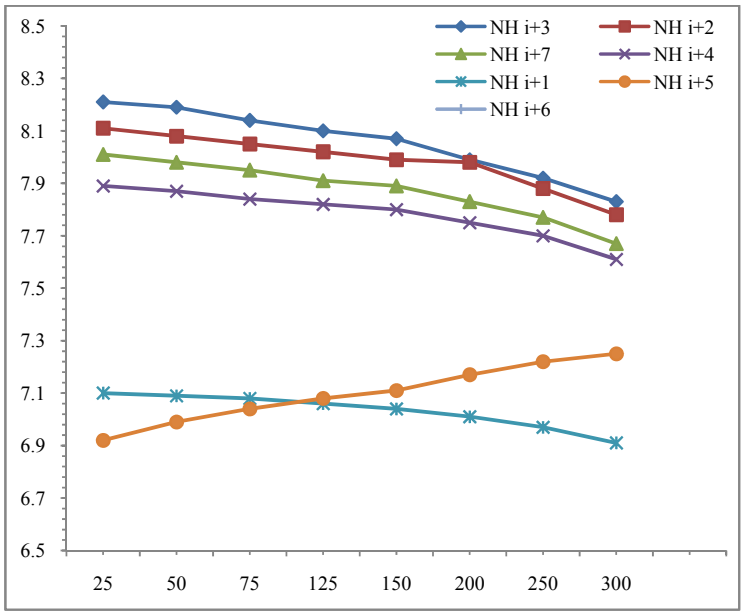


Figure 99: The *NH chemical shifts variation on the addition of DMSO-d6 for cis-octamer* **101**

The secondary structures of *trans-β*-FAA oligomers were assigned with the help of observed inter-residue n*O*es noticed. All protons at $C_{\beta}H$ and NH of each residue were well separated of **102** and **103**. The *trans*-dimer **102** was showing eight membered hydrogen bonding. The *trans*-tetramer **103** was showing strong secondary structural feature and the various n*O*es confirmed the 12 helix. One characteristic n*O*e *i.e.* $NH_{(i+1)}/C_{\beta}H_{(i+3)}$ indicated the presence of a left-handed 12-helix. The ^{1}H NMR spectrum of **103** shows the low field amide protons resonance which indicates the involvement of these NH groups in H-bonding. These bonding were further confirmed by solvent titration studies and temperature dependent deviation chemical shifts of amide protons.

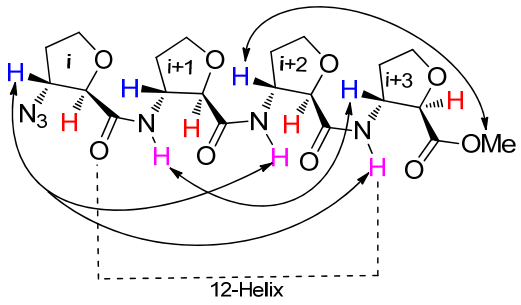


Figure 100: *Characteristic nOes supporting a 12-helix* ***103***

Temp (°C)	NH_{i+2}	NH_{i+3}	NH_{i+1}
0	7.58	7.35	7.13
5	7.53	7.32	7.12
10	7.5	7.29	7.09
15	7.46	7.26	7.08
20	7.42	7.23	7.06
25	7.39	7.2	7.04
30	7.36	7.17	7.03
35	7.32	7.15	7.01
40	7.29	7.12	7.01
45	7.26	7.1	6.99
Δδ/ppb/°C	**7.11**	**5.55**	**3.11**

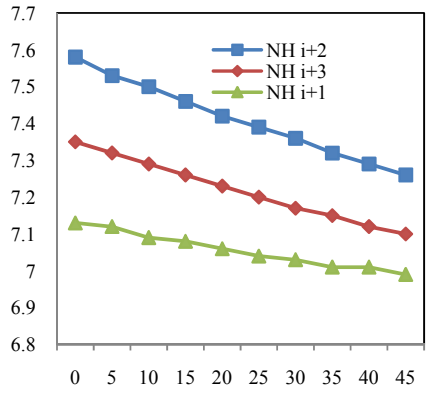


Figure 101: *Temperature-dependent chemical shifts of NH protons of **103** in $CDCl_3$ solution*

% DMSO-d6 (v/v)	NH_{i+2}	NH_{i+3}	NH_{i+1}
0	7.42	7.24	7.07
25	7.51	7.38	7.27
50	7.53	7.43	7.35
75	7.54	7.48	7.4
100	7.54	7.49	7.44
150	7.55	7.53	7.49
200	7.56	7.54	7.51
250	7.57	7.55	7.53
300	7.56	7.54	7.52
350	7.56	7.53	7.51
Δδ ppm	**0.14**	**–0.29**	**–0.44**

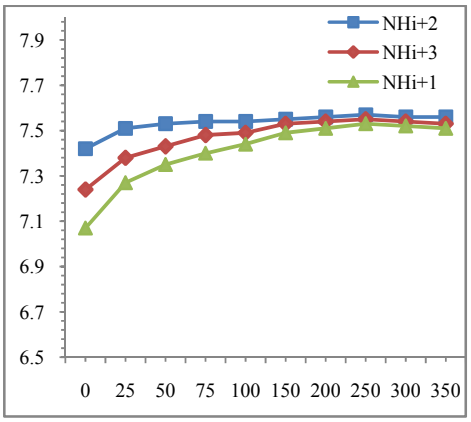


Figure 102: The *NH chemical shifts variation on the addition of DMSO-d6 for trans-tetramer* **103**

The important inter-residue n*O*es observed in the NOESY of the *trans*-hexamer **104** are given in Figure 103. The interpretation of some of the observed long-range n*O*es is complicated by the overlapping of two of the five NH protons, the characteristic n*O*es were found which indicated the presence of a left-handed 12-helix (Figure 95).

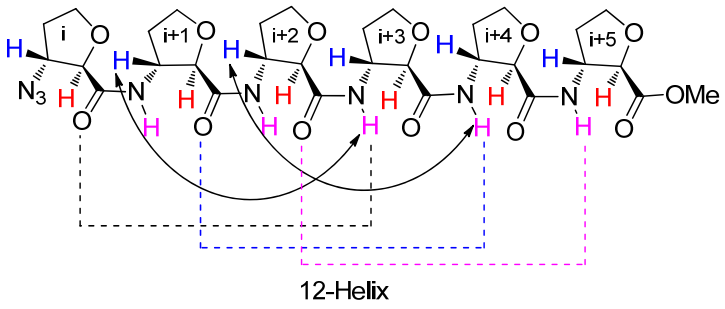


Figure 103: *Characteristic nOes supporting a 12-helix*

Temp (°C)	NH_{i+3}	NH_{i+5}	NH_{i+2}	NH_{i+1}	NH_{i+4}
20	8.39	8.33	8.32	8.29	8.25
25	8.38	8.33	8.31	8.28	8.24
30	8.32	8.28	8.26	8.23	8.19
40	8.26	8.22	8.2	8.17	8.13
50	8.20	8.16	8.14	8.11	8.08
60	8.14	8.10	8.08	8.05	8.02
70	8.09	8.05	8.03	8.00	7.97
80	8.03	8.00	7.98	7.93	7.92
Δδ/ppb/°C	6.00	5.50	5.67	6.00	5.50

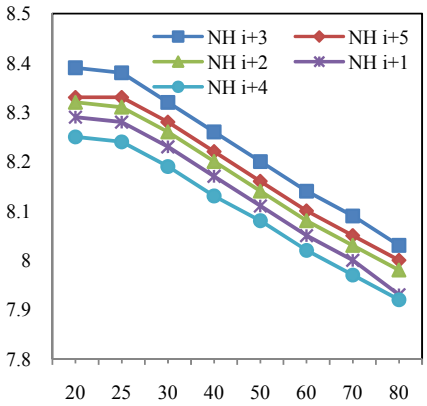


Figure 104: *Temperature-dependent chemical shifts of NH protons of **104** in DMSO-d6 solution*

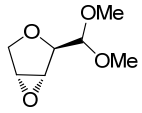
NOESY data of **99, 100, 101**, **103** and **104** revealed several medium and long-range backbone n*O*es between $C_\beta H_i/NH_{i+2}$, $C_\beta H_i/C_\alpha H_{i+2}$ and $C_\beta H_i/NH_{i+3}$ which are characteristic for the 12-helix. For the *cis*/*trans*-tetramer, the one n*O*e signals between $C_\beta H_{(i+1)}/C_\alpha H_{(i+3)}$ are well resolved. Several of the peaks which are characteristics n*O*e for the higher oligomers confirmed the 12-helix.

The secondary structural analysis of native *cis*- and *trans*- furanoid-*β*-amino acids reveals that the all adopt left handed 12-helix structures in solution. The temperature dependent deviation in the chemical shifts indicate that the *trans*-*β*-FAA homo-oligomers form a robust left handed 12-helix (Δδ from 3.11–7.11 ppb/°C except NH_{i+1} of **103**) whereas the *cis*-*β*-FAA homo-oligomers form a week left handed 12-helix (Δδ from 0.80–4.60 ppb/°C).

Experimental

Experimental:

3,4-Epoxy-5-*(R-trans)*-dimethoxymethyl-tetrahydrofuran (87):



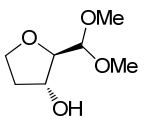
A solution of ditosyl compound **85** (50 g, 100.0 mmol) was dissolved in MeOH (400 mL) and treated with catalytic amount of *p*-toluene sulphonic acid (1.6 g, 10.0 mmol) and heated to reflux for 24 h. After completion, the reaction mixture was cooled to 0 °C and added the potassium carbonate (34.6 g, 0.25 mol) and stirred at rt for 1 h. The reaction mixture was filtered (celite), neutralized (1N HCl) and concentrated under reduced pressure. The crude product was extracted with EtOAc and the ethyl acetate layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude was purified on silica gel column chromatography to give **87** (12.36 g 77% in two steps).

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.28 (d, J = 4.5 Hz, 1H), 4.08 (d, J = 4.5 Hz, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.83 (d, J = 10.3 Hz, 1H), 3.82 (d, J = 3.0, 0.8 Hz, 1H), 3.78 (dd, J = 3.0, 0.8 Hz, 1H), 3.46 (s, 3H), 3.44 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 54.8 (q), 55.8 (q), 56.0 (d), 56.3 (d), 67.5 (t), 77.4 (d), 104.6 (d) ppm. **ESI-MS *m/z***: 183.1 (100%, $[M+Na]^+$). **Anal. Calcd for**: C, 51.49; H, 7.55; Found: C, 51.73; H, 7.53

Reduction of epoxide (87) by diisobutylaluminium hydride:

At 0 °C, a solution of **87** (12 g, 75 mmol) in dry CH_2Cl_2 (200 mL) was added diisobutylaluminium hydride (60 mL, 2.5 M solution in toluene, 150 mmol) and the reaction mixture was stirred until compound **87** was consumed. The reaction mixture was cooled to −10 °C and quenched by adding MeOH (5 mL) and saturated sodium potassium tartrate. The resulting suspension was filtered, dried (Na_2SO_4) and concentrated. The crude was subjected for chromatographic purification (25% ethylacetate in petroleum ether) to yield **83** (9.0 g, 74%) and the regiomer **88** (2.5 g, 19%) as colorless oils.

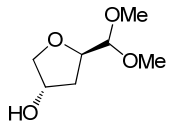
(2R,3R)-2-(dimethoxymethyl)-tetrahydrofuran-3-ol (83):



$[\alpha]_D^{25}$ = –28.8 (c 2.0, MeOH). **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.27 (dt, J = 5.5, 2.5 Hz, 1H), 4.15 (d, J = 5.7 Hz, 1H), 3.87 (dd, J

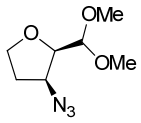
= 8.2, 5.7 Hz, 2H), 3.67 (dd, *J* = 5.7, 3.5 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.03 (ddd, *J* = 12.8, 8.1, 6.9 Hz, 1H), 1.81 (dddd, J = 12.8, 9.4, 5.7, 3.7 Hz, 1H). **ESI-MS (m/z):** 131 $[M–OCH_3]^+$. **Anal. calcd for** $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.69; H, 8.61.

(3S,5R)-5-(dimethoxymethyl)-tetrahydrofuran-3-ol (88):



$[\alpha]_D^{25}$ = –1.9 (c 1.5, MeOH). **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.42 (ddd, *J* = 5.8, 3.8, 1.8 Hz, 1H), 4.17 (d, *J* = 6.7 Hz, 1H), 3.86 (dd, *J* = 6.7, 3.8 Hz, 2H), 3.70 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.36 (s, 6H), 1.94–1.86 (m, 2H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 36.3 (t), 53.9 (q), 55.0 (q), 71.6 (d), 75.5 (t), 77.1 (d), 105.6 (d) ppm. **ESI-MS *m/z***: 185.07 (100%, $[M+Na]^+$). **Anal. Calcd for**: C, 51.84; H, 8.70 Found: C, 51.73; H, 8.54.

(2R,3S)-3-azido-2-(dimethoxymethyl)-tetrahydrofuran (90):



A solution of **83** (9.0 g, 55.6 mmol) and Et_3N (15.5 mL, 0.11 mol) in CH_2Cl_2 (80 mL) was treated with mesyl chloride (5.3 mL, 67 mmol) at 0 °C and stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with cold water, washed with water and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the intermediate mesylate (12.50 g, 94%) as a liquid. A portion of the mesylate **83-OMs** was purified by column chromatography for the analytical data. Otherwise the crude mesylate was directly subjected to azidation reaction.

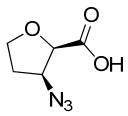
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.18–5.10 (m, 1H), 4.23 (dd, *J* = 4.2, 1.0 Hz, 1H), 4.05–3.96 (m, 2H), 3.86 (ddd, *J* = 8.3, 7.8, 1.3 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 2.99 (s, 3H), 2.22–2.12 (m, 2H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 33.8 (t), 37.6 (q) 54.6 (q), 56.3 (q), 67.2 (t), 82.0 (d), 83.6 (d), 103.8 (d) ppm. **ESI-MS *m/z***: 263.1 (100%, $[M+Na]^+$).

The mesylate **83-OMs** (13 g, 50 mmol) was dissolved in dry DMSO (180 mL) and sodium azide (9.75 g, 150.0 mmol) was added. The contents were stirred at 100 °C for 12 h. The reaction mixture was diluted with EtOAc (450 mL), washed with water (3 x 80 mL). The organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel

column chromatography (10→20% EtOAc in pet ether) to obtained **90** (7.7 g, 83%) as a colorless oil.

$[\alpha]_D^{25}$ = +46.8 (c = 1, $CHCl_3$). **IR** ($CHCl_3$): ν 3352, 2939, 2888, 2833, 2514, 2105, 1634, 1445, 1401, 1333, 1274, 1192, 1144, 1083, 1018, 977, 959, 931, 873, 757, 666 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.47 (d, J = 7.5 Hz, 1H), 4.10 (ddd, J = 5.6, 3.9, 1.7 Hz, 1H), 4.04–3.92 (m, 1H), 3.88 (dd, J = 8.6, 4.2 Hz, 1H), 3.76 (dd, J = 7.5, 3.9 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.29–2.00 (m, 2H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 32.4 (t), 53.5 (q), 55.0 (q), 62.7 (d), 66.7 (t), 80.7 (d), 103.2 (d) ppm. **ESI-MS *m/z***: 210.1 (100%, $[M+Na]^+$), 226.0 (65%, $[M+K]^+$), 188.2 (45%, $[M+1]^+$). **Anal. Calcd for $C_7H_{13}N_3O_3$**: C, 44.91; H, 7.00; Found: C, 44.83; H, 6.89.

(2R,3S)-3-azido-tetrahydrofuran-2-carboxylic acid (77):



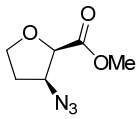
A suspension of azido-acetal **90** (2.5 g, 13.4 mmol) in trifluoroacetic acid (50%, 25 mL) was stirred at rt for 6 to 10 h. The reaction mixture was cooled to 0 °C, CH_2Cl_2 (100 mL) was introduced and neutralized with sodium bicarbonate and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude aldehyde was used directly for the next step without any further purification.

To a cooled solution of above aldehyde in *t*-BuOH and H_2O (2:1, 25 mL), $NaH_2PO_4.2H_2O$ (0.8 g, 6.7 mmol dissolved in 15 mL water, pH 7) was added. Sodium chlorite (80%, 6 g, 40 mmol) was added slowly and the resulting mixture was stirred at rt for 10 h. After the reaction was complete, solid $NaHCO_3$ was added. The reaction mixture was extracted with CH_2Cl_2 (2 x 50 mL) and the CH_2Cl_2 layer was discarded. The aqueous layer was neutralized with conc. HCl and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography (silica gel 20→40% EtOAc in pet ether) to procure acid **91** (1.53 g, 73% over 2 step) as colorless oil.

$[\alpha]_D^{25}$ = +70.5 (c = 1.5, $CHCl_3$). **IR ($CHCl_3$):** ν 2960, 2560, 2115, 1746, 1483, 1330, 1272, 1113, 1085, 1026, 967, 937, 871, 789, 759, 698, 665 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 8.69 (br s, 1H), 4.54 (d, J = 5.1 Hz, 1H), 4.38 (ddd, J = 7.7, 5.2, 2.6 Hz, 1H), 4.42–3.99 (m, 2H), 3.79 (s, 3H), 2.33–2.11 (m, 2H). **^{13}C NMR (50 MHz,**

$CDCl_3$+CCl_4): δ 31.1 (t), 62.8 (d), 67.6 (t), 78.0 (d), 172.4 (s) ppm. **ESI-MS *m/z***: 180.1 (100%, $[M+Na]^+$), 196.3 (53%, $[M+K]^+$), 168.1 (32%, $[M+1]^+$). **Anal. Calcd for $C_5H_7N_3O_3$**: C, 38.22; H, 4.49; Found: C, 38.31; H, 4.41.

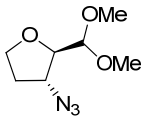
(2*R*,3*S*)-Methyl 3-azido-tetrahydrofuran-2-carboxylate (78):



At 0 °C, a solution of acid **77** (1.5 g, 9.5 mmol) in CH_2Cl_2 (15 mL) and was treated with a solution of diazomethane in ether (30 mL) until the color of the diazomethane persist. The solution was kept standing for 30 minutes and treated with few drops of acetic acid to quench the residual diazomethane. The solvent was removed and the residue was purified by silica gel column chromatography (silica gel 15→25% EtOAc in pet ether) to afford **92** (1.57 g, 96%) as colorless syrup.

$[\alpha]_D^{25}$ = +10.4 (c = 1.0, $CHCl_3$). **IR ($CHCl_3$):** ν 3359, 2956, 2894, 2560, 2112, 1760, 1439, 1326, 1268, 1113, 1033, 1013, 924, 869, 795, 745 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.49 (d, *J* = 5.3 Hz, 1H), 4.38 (ddd, *J* = 8.2, 5.3, 2.8 Hz, 1H), 4.13 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.97 (ddd, *J* = 12.7, 8.2, 4.5 Hz, 1H), 3.79 (s, 3H), 2.34–2.10 (m, 2H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 31.5 (t), 51.5 (q), 62.6 (d), 67.1 (t), 79.8 (d), 168.8 (s) ppm. **ESI-MS *m/z***: 194.1 (100%, $[M+Na]^+$), 233.0 (35%, $[M+K]^+$), 195.1 (15%, $[M+1]^+$). **Anal. Calcd for $C_6H_9N_3O_3$**: C, 42.10; H, 5.30; Found: C, 42.19; H, 5.37.

(2*R*,3*R*) 3-azido-tetrahydrofuran-2-carboxylic acid (93):



In a flame-dried, two necked, round-bottom flask (250 mL) was dissolved oxalyl chloride (8 mL, 93 mmol) under N_2 atmosphere in dry CH_2Cl_2 (150 mL). After the solution was cooled to –78 °C, dry DMSO (8.75 mL, 123 mmol) was added drop-wise with stirring for 15 min. To this, solution of alcohol **83** (5 g, 30.8 mmol) in dry CH_2Cl_2 (40 mL) was added drop-wise and stirred for 30 min at the same temperature and treated with Et_3N (25.8 mL, 185 mmol) and stirred for additional 30 min at –78 °C. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude by

column chromatography (15% ethyl acetate in petroleum ether) afforded ketone **92** as a colorless oil which was used for next step without any purification.

At 0 °C, a solution of the crude ketone **92** in methanol (100 mL) was treated with $NaBH_4$ (3.26 g, 92.5 mmol) in three portions with a 10 minutes interval. After completing the additions, stirring was continued for another 30 min at 0 °C. The contents were filtered (Celite), concentrated and dissolved in ethylacetate (25 mL). The ethyl acetate solution was washed with water, brine, dried (Na_2SO_4) and concentrated to get a syrup like compound **82** which was used directly for the next step.

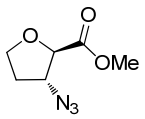
At 0 °C, a solution of the crude alcohol **82** and Et_3N (12.9 mL, 92.5 mmol) in CH_2Cl_2 (50 mL) was treated with mesyl chloride (2.62 mL, 33.9 mmol) and stirred for 30 min at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with cold water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford crude mesylated compound.

A solution of above crude mesylate in DMSO (100 mL) was treated with sodium azide (6.0 g, 92.5 mmol) and the contents were stirred at 100 °C for 5 h. The reaction mixture was cooled to rt and diluted with EtOAc (200 mL), washed with water (3 x 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10→20% EtOAc in petroleum ether) to obtain **93** (2.78 g, 48%) as a colorless oil.

IR ($CHCl_3$): ν 3400, 3083, 3015, 2937, 2866, 2835, 2110, 1588, 1494, 1462, 1443, 1408, 1306, 1226, 1186, 1129, 986, 930, 843, 814, 756, 666 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.25 (d, J = 4.9 Hz, 1H), 4.10 (dd, J = 7.5, 3.8 Hz, 1H), 4.01–3.92 (m, 1H), 3.88 (ddd, J = 11.2, 8.4, 7.5 Hz, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.15 (ddd, J = 15.9, 13.1, 7.5 Hz, 1H), 1.89 (dddd, J = 13.1, 11.1, 4.5, 4.0 Hz, 1H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 32.5 (t), 54.4 (q), 56.0 (q), 61.9 (d), 67.5 (t), 83.4 (d), 104.3 (d) ppm. **ESI-MS *m/z***: **ESI-MS *m/z***: 210.1 (100%, $[M+Na]^+$), 226.0 (39%, $[M+K]^+$), 188.2 (19%, $[M+1]^+$). **Anal. Calcd for**: C, 44.91; H, 7.00; N, 22.45; Found: C, 44.83; H, 7.12; N, 22.17.

(2R,3R)-methyl 3-azido-tetrahydrofuran-2-carboxylate (80):

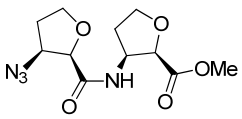
The esterification of acid **79** (2 g, 10.69 mmol) using diazomethane following procedure used in the preparation of **93**, gave **80** (1.3 g, 71% in three step) as colorless oil.



IR ($CHCl_3$): ν 3020, 2974, 2874, 2842, 2112, 1753, 1655, 1598, 1504, 1479, 1463, 1415, 1342, 1215, 1134, 1113, 1028, 928, 889, 866, 756, 668 cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.38 (d, J = 3.0 Hz, 1H), 4.26 (dd, J = 6.5, 3.2 Hz, 1H), 4.13 (dd, J = 8.5, 4.3 Hz, 1H), 4.04–3.96 (m, 1H), 3.77 (s, 3H), 2.28–2.17 (m, 1H), 2.08–1.94 (m, 1H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 31.5 (t), 52.5 (q), 64.3 (t), 68.1 (d), 81.7 (d), 170.9 (s) ppm. **ESI-MS *m/z***: 210.2 (100%, $[M+Na]^+$). **ESI-MS *m/z***: 194.1 (100%, $[M+Na]^+$), 233.0 (31%, $[M+K]^+$), 195.1 (11%, $[M+1]^+$). **Anal. Calcd for**: C, 42.10; H, 5.30; N, 24.55 Found: C, 42.31; H, 7.18; N, 24.19.

Synthesis of *cis*-dipeptide (94):

A solution of azido ester **78** (1 g, 5.84 mmol) in EtOH (20 mL) was stirred under an atmosphere of hydrogen in the presence of Raney nickel (0.5 g,) for 1 h. After the completion of reaction as indicated by TLC, the reaction mixture was filtered through celite and the solvent removed under reduced pressure to obtain crude amine.

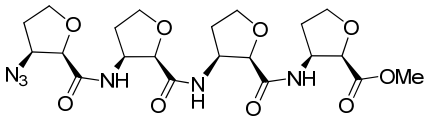


A solution of acid **77** (1.0 g, 6.4 mmol), 1-hydroxybenzotriazole (950 mg, 7.0 mmol) and diisopropylethylamine (2.54 mL, 14.6 mmol) in dry CH_2Cl_2 (20 mL) was treated with EDCI.HCl [1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] (1.1 g, 7.0 mmol) and stirred for 30 min. After that a solution of crude amine in CH_2Cl_2 (7 mL) was added and reaction mixture was stirred for 24 h at rt. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified over a silica gel column chromatography (50→60% ethyl acetate in petroleum ether) to obtain the dimer **94** (1.2 g, 73%) as thick syrup.

$[\alpha]_D^{25}$ = –24.2 (c = 1.0, $CHCl_3$). **IR ($CHCl_3$):** ν 3338, 2956, 2107, 1745, 1667, 1532, 1440, 1266, 1098, 728 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.99 (d, J = 8.6 Hz, 1H), 4.89 (ddd, J = 10.6, 6.2, 4.9 Hz, 1H), 4.47 (d, J = 5.9 Hz, 1H), 4.43 (dt, J = 4.9, 1.3 Hz, 1H), 4.33 (d, J = 4.5 Hz, 1H), 4.15 (dt, J = 8.3, 6.9 Hz, 1H), 3.99–3.90 (m,

3H), 3.74 (s, 3H), 2.32 (ddt, *J* = 13.6, 8.3, 6.9 Hz, 1H), 2.17 (ddt, *J* = 13.6, 9.2, 5.2 Hz, 1H), 2.07 (dddd, *J* = 10.3, 5.2, 4.1, 1.3 Hz, 1H), 1.96 (dddd, *J* = 13.6, 10.3, 5.9, 4.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 32.7 (t), 32.9 (t), 50.7 (d), 51.9 (d), 62.9 (q), 67.3 (t), 67.7 (t), 78.9 (d), 81.8 (d), 167.9 (s), 170.1 (s) ppm. **ESI-MS *m/z***: 307.2 (100%, $[M+Na]^+$) 323.1(32%, $[M+K]^+$), 285.2 (29%, $[M+1]^+$), 301 (15%, $[M-1+H_2O]^+$). **Anal. Calcd for $C_{11}H_{16}N_4O_5$**: C, 46.48; H, 5.67; N, 19.71. Found: C, 46.39; H, 5.58; N, 19.63.

Synthesis of *cis*-tetrapeptide (95):



To a solution of dimer **94** (500 mg, 1.76 mmol) in EtOH (15 mL) was added Raney nickel (400 mg,) and stirred under an atmosphere of hydrogen for 1 h. The reaction mixture was filtered through celite and concentrated under reduced pressure.

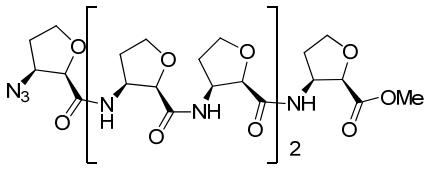
To a stirred solution of dimer **94** (500 mg, 1.76 mmol) in dioxane water 9:1 (14 mL), aqueous sodium hydroxide (3.0 mL, 2M) was added at 0 °C and the reaction mixture was stirred for 1h at rt. The reaction mixture was neutralized with 2N HCl and concentrated under reduced pressure. The crude residue was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried (Na_2SO_4) and solvent was removed under reduced pressure to procure the dimer acid.

At 0 °C a solution of crude *cis*-dimer acid, 1-hydroxybenzotriazole (285 mg, 2.11 mmol) and diisopropylethylamine (0.8 mL, 4.40 mmol) in dry CH_2Cl_2 (15 mL) was treated with 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (330 mg, 2.11 mmol) and stirred for 30 min, a solution of crude amine in CH_2Cl_2 (5 mL) was introduced and resulting reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with H_2O (20 mL, 3 times). The organic phase was dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified over a silica gel column chromatography (1→3% methanol in CH_2Cl_2) obtained the tetramer **5** (560 mg, 62%) as colorless amorphous solid.

$[\alpha]_D^{25}$ = –52.3 (c = 1.0, $CHCl_3$). **IR ($CHCl_3$):** ν 3383, 2925, 2113, 1729, 1668, 1520, 1451, 1271, 1219, 1085, 1027, 1007, 759, 728 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ

8.06 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 4.85–4.73 (m, 3H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.43 (dt, *J* = 6.0, 4.5, 1.8 Hz, 1H), 4.37 (d, *J* = 4.5 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.27 (d, *J* = 8.2 Hz, 1H), 4.21 (dd, *J* = 8.2, 4.5 Hz, 1H), 4.17 (dd, *J* = 8.2, 6.2 Hz, 1H), 4.09 (ddd, *J* = 10.8, 8.5, 2.3 Hz, 1H), 4.06 (dd, *J* = 9.1, 6.7 Hz, 1H), 3.98 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.96–3.90 (m, 3H), 3.86 (d, *J* = 10.2, 8.9, 6.2 Hz, 1H), 3.75 (s, 3H), 2.47–2.29 (m, 1H), 2.23–2.15 (m, 1H), 2.13–2.07 (m, 1H), 1.96–1.90 (m, 1H), 1.86–1.79 (m, 1H), 1.67–1.57 (m, 1H). **^{13}C NMR (100 MHz , $CDCl_3$):** 30.9 (t), 31.8 (t), 32.1 (t), 32.6 (t), 50.4 (d), 51.1 (d), 51.2 (d), 52.3 (d), 63.0 (d), 67.2 (t), 67.6 (t), 67.7 (t), 67.8 (t), 75.8 (d), 77.2 (d), 78.9 (d), 81.9 (d), 168.6 (s), 170.4 (s), 170.5 (s, 2C). **ESI-MS *m/z***: 533.5 (100%, $[M+Na]^+$) 549.5 (31%, $[M+K]^+$), 511.5 (63%, $[M+1]^+$). **Anal. Calcd for $C_{21}H_{30}N_6O_9$**: C, 49.41; H, 5.92; N, 16.46; Found: C, 49.39; H, 5.97; N, 16.39.

Synthesis of *cis*-hexapeptide (96):

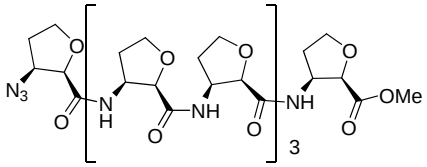


The similar procedure used for the synthesis of tetrapeptide **94** was followed to prepare the hexapeptide **96**. The amine partner was made via the reduction of azide group of *cis*-tetramer **95** (100 mg, 0.193 mmol) and acid partner obtained from ester hydrolysis of *cis*-dimer **94** (60 mg, 0.21 mmol). The crude product was purified by column chromatography (5→10% methanol in CH_2Cl_2) obtained the *cis*-hexamer **96** (82 mg, 57%) as colorless amorphous solid.

$[\alpha]_D^{25}$ = –65.3 (c = 0.5, $CHCl_3$). **IR ($CHCl_3$):** ν 3324, 2925, 2846, 2113, 1728, 1665, 1660, 1651, 1520, 1274, 1083, 991, 758, 729 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.20 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 9.5 Hz, 1H), 7.87 (d, *J* = 9.7 Hz, 1H), 7.12 (d, *J* = 9.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.08–4.98 (m, 3H), 4.94–4.81 (m, 2H), 4.56 (d, *J* = 7.3 Hz, 1H), 4.48–4.41 (m, 3H), 4.38 (d, *J* = 8.9 Hz, 1H), 4.34 (d, *J* = 9.3 Hz, 1H), 4.27 (d, *J* = 9.0 Hz, 1H), 4.22 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.18–4.05 (m, 5H), 3.99–3.93 (m, 2H), 3.88–3.81 (m, 2H), 3.80 (s, 3H), 3.78–3.71 (m, 2H), 2.39–2.31 (m, 1H), 2.29–2.22 (m, 2H), 2.18–2.01 (m, 7H), 1.99–1.92 (m, 2H). **^{13}C NMR (100 MHz , $CDCl_3$):** 30.6 (t), 30.9 (t), 30.9 (t), 31.3 (t), 32.0 (t), 32.5 (t), 50.4 (d), 50.7 (d), 50.8 (d), 51.0 (d), 51.2 (d), 52.5 (d), 63.0 (d), 67.4 (t), 67.5 (t), 67.6 (t), 67.7 (t), 67.7 (t), 67.7 (t), 77.0 (d),77.2 (d), 77.4 (d), 77.7 (d, 2C), 79.0 (d), 81.5 (d), 168.8 (s), 169.6

(s), 170.3 (s), 170.4 (s), 170.7 (s), 171.1 (s). **ESI-MS *m/z***: 759.5 (10%, $[M+Na]^+$), 775.4 (7%, $[M+K]^+$), 301.2 (100%, $[M–435]^+$). **Anal. Calcd for $C_{31}H_{44}N_8O_{13}$**: C, 50.54; H, 6.02; N, 15.21; Found: C, 50.59; H, 5.99; N, 15.27.

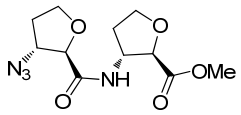
Synthesis of *cis*-octapeptide (97):



The preparation of octamer **97** was carried out as described for the preparation of *cis*-teramer **95**. Both the coupling partners were obtained from the *cis*-tetramer **95**. The amine partner made via the reduction of azide group of tetramer **95** (60 mg, 0.117 mmol) and acid partner obtained from ester hydrolysis of tetramer **95** (60 mg, 0.117 mmol) and coupled to obtain the octamer **97** (46 mg, 41%) as amorphous solid after usual workup and purification by column chromatography (10→15% methanol in CH_2Cl_2). *Rf* = 0.25 (MeOH/DCM 1:9).

$[\alpha]_D^{25}$ = –144–155 (c = 0.1, $CHCl_3$). **IR ($CHCl_3$):** ν 3324, 2925, 2854, 2112, 1725, 1717, 1661, 1656, 1653, 1649, 1523, 1459, 1082, 987, 728 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28 (d, *J* = 8.5 Hz, 1H), 8.22 (d, *J* = 9.8 Hz, 1H), 8.13 (d, *J* = 9.6 Hz, 1H), 8.03 (d, *J* = 9.7 Hz, 1H), 7.89 (d, *J* = 9.9 Hz, 1H), 7.10 (d, *J* = 9.7 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.13–5.01 (m, 5H), 4.94–4.81 (m, 3H), 4.57 (d, *J* = 7.4 Hz, 1H), 4.46 (br s, 2H), 4.44 (d, *J* = 7.8 Hz, 1H), 4.39 (d, *J* = 9.2 Hz, 1H), 4.35 (d, *J* = 9.5 Hz, 1H), 4.25 (br d, *J* = 8.6, 3H), 4.19–4.09 (m, 7H), 4.07 (t, *J* = 7.7 Hz, 1H), 3.96 (ddd, *J* = 12.9, 7.3, 1.4 Hz, 3H), 3.85 (dd, *J* = 6.7, 1.4 Hz, 1H), 3.81 (s, 3H), 3.73–3.65 (m, 4H), 2.38–2.33 (m, 2H), 2.29–2.22 (m, 3H), 2.19–2.12 (m, 5H), 2.10–2.05 (9m, 5H), 1.96–1.92 (m, 1H). **^{13}C NMR (100 MHz , $CDCl_3$):** 30.0 (t), 30.2 (t), 30.6 (t), 30.9 (t), 30.9 (t), 31.1 (d), 32.0 (t), 32.5 (t), 50.4 (d), 50.6 (d), 50.8 (d), 51.0 (d), 51.1 (d, 2C), 51.3 (d), 52.5 (d), 63.0 (d), 67.4 (t), 67.5 (t), 67.6 (t), 67.7 (t, 2C), 67.8 (t), 77.2 (d), 77.7 (d, 2C), 77.8 (d), 79.1 (d), 81.4 (d), 168.9 (s), 169.6 (s), 170.2 (s), 170.5 (s), 170.6 (s), 170.8 (s), 171.1 (s), 171.3 (s) ppm. **ESI-MS *m/z***: 985.7 (7%, $[M+Na]^+$), 963.7 (5%, $[M+H]^+$), 549.4 (100%, [M–413], 492 (63%, [M–470]. **Anal. Calcd for $C_{41}H_{58}N_{10}O_{17}$**: C, 51.14; H, 6.07; N, 14.55; Found: C, 51.23; H, 6.11; N, 14.49.

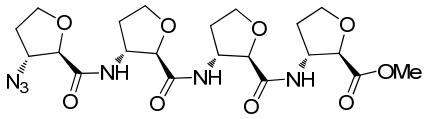
Synthesis of *trans*-dipeptide (98):



The same sequence of procedures as in the preparation of *cis-FAA* dimer **94** were used with the acid **79** (808 mg, 5.14 mmol) and monomer-amine (prepared by the hydrogenolysis of the azide **80** using Raney nickel, 800 mg, 4.67 mmol) to afford *trans-FAA* dimer **98** (915 mg, 69%) as colorless syrup.

$[\alpha]_D^{25}$ = – 141.4 (c = 2.0, $CHCl_3$). **IR ($CHCl_3$): IR ($CHCl_3$):** ν 3341, 2955, 2890, 2107, 1746, 1667, 1532, 1439, 1267, 1212, 1098, 924, 729 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.88 (d, J = 6.9 Hz, 1H), 4.63 (ddd, J = 11.2, 7.5, 3.8 Hz, 1H), 4.39 (dt, J = 2.9, 5.9 Hz, 1H), 4.33 (d, J = 3.4 Hz, 1H), 4.30 (d, J = 2.8 Hz, 1H), 4.20–4.11 (m, 1H), 4.09–3.98 (m, 3H), 3.77 (s, 3H), 2.40–2.31 (m, 1H), 2.11–1.98 (m, 2H), 1.91–1.83 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 31.3 (t), 31.8 (t), 52.1 (d), 53.3 (d), 64.0 (q), 67.6 (t), 67.9 (t), 81.2 (d), 82.8 (d), 169.7 (s), 171.1 (s) ppm. **ESI-MS *m/z***: 307.2 (100%, $[M+Na]^+$) 323.1(31%, $[M+K]^+$), 285.2 (30%, $[M+1]^+$), 301 (14%, $[M–1+H_2O]^+$). **Anal. Calcd for $C_{11}H_{16}N_4O_5$**: C, 46.48; H, 5.67; N, 19.71. Found: C, 46.53; H, 5.61; N, 19.67.

Synthesis of *trans*-tetrapeptide (99):

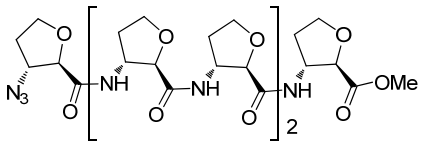


The procedures used in the preparation of *cis-FAA* tetramer **95** were followed. Coupling of the dimer acid (prepared by alkaline hydrolysis of **98**, 400 mg, 1.41 mmol) and dimer-amine (prepared by the hydrogenolysis of the azide **98** using Raney nickel, 400 mg, 1.41 mmol) using the standard coupling protocol gave the *trans-FAA* tetramer **99** (365 mg, 51%) as colorless amorphous soild.

$[\alpha]_D^{25}$ = – 101.3 (c = 2.0, $CHCl_3$). **IR ($CHCl_3$):** ν 3301, 2955, 2890, 2106, 1744, 1667, 1524, 1267, 1218, 1086, 759, 729 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, J = 6.5 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 5.8 Hz, 1H), 4.60–4.53 (m, 1H), 4.39–4.30 (m, 3H), 4.29–4.25 (m, 1H), 4.24–4.22 (m, 1H), 4.16 (dd, J = 7.1, 5.0 Hz, 2H), 4.08 (dd, J = 7.9, 2.0 Hz, 1H), 4.02–3.96 (m, 6H), 3.69 (s, 3H), 2.29–2.20 (m, 3H), 2.08–1.99 (m, 1H), 1.96–1.81 (m, 4H). **^{13}C NMR (100 MHz , $CDCl_3$):** 31.5 (t), 32.0 (t), 32.2 (t), 32.2 (t), 52.3 (d), 53.4 (d), 54.5 (d), 54.6 (d), 64.2 (d), 67.9 (t,

2C), 68.0 (t), 68.1 (t), 81.5 (d), 82.1 (d), 82.2 (d), 83.0 (d), 170.3 (s), 170.8 (s), 170.9 (s), 171.4 (s) ppm. **ESI-MS *m/z***: 533.0 (100%, $[M+Na]^+$) 549.0 (33%, $[M+K]^+$), 511.0 (30%, $[M+1]^+$), 301 (13%, $[M-1+H_2O]^+$). **Anal. Calcd for $C_{21}H_{30}N_6O_9$**: C, 49.41; H, 5.92; N, 16.46; Found: C, 49.39; H, 5.99; N, 16.51.

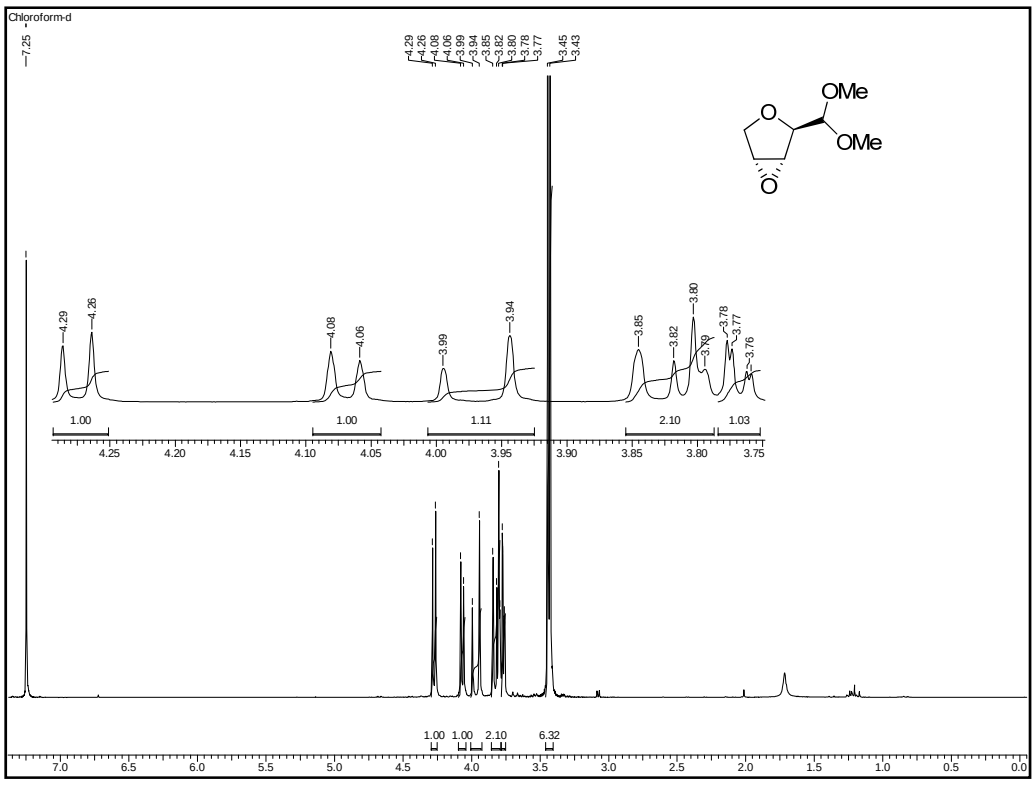
Synthesis of *trans*-hexapeptide (100):



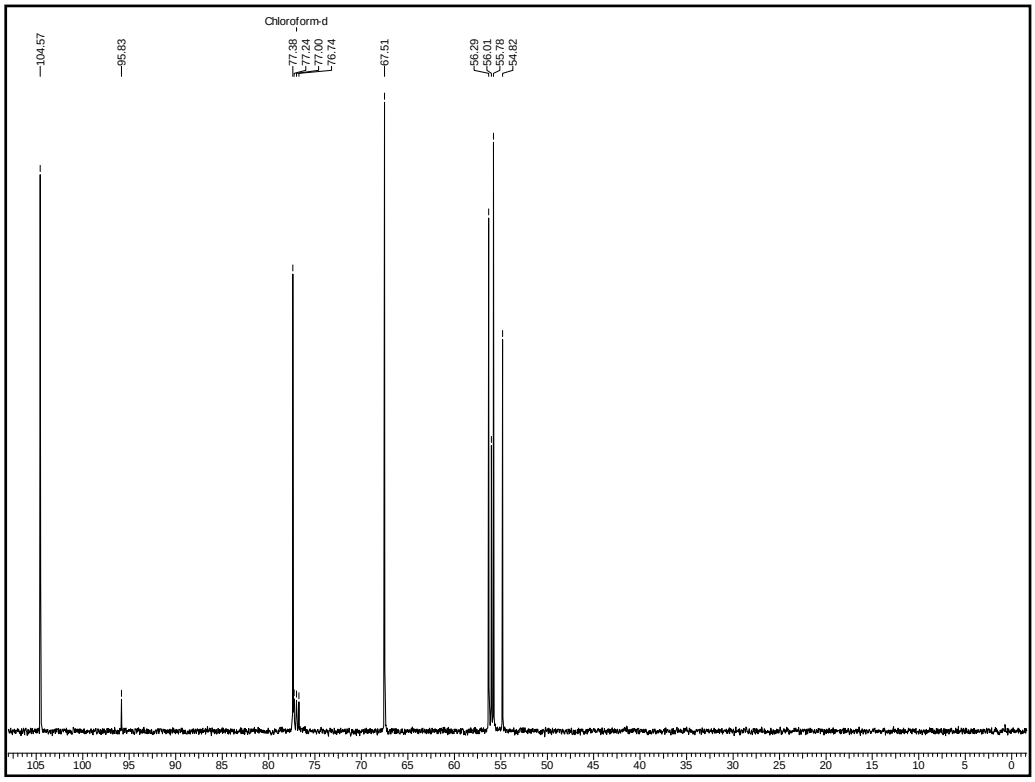
The same sequence of procedures as used in the preparation of *cis-FAA* hexamer **96** was followed. The dimer acid (prepared by alkaline hydrolysis of **98**, 70 mg, 0.245 mmol) and tetramer-amine (prepared by the hydrogenolysis of the azide **99** using Raney nickel, 100 mg, 0.195 mmol) gave *trans-FAA* hexamer **100** (53 mg, 37%) as colorless amorphous solid.

$[\alpha]_D^{25}$ = – 79.4 (c = 0.5, $CHCl_3$). **IR ($CHCl_3$):** ν 3301, 2955, 2106, 1744, 1672, 1667, 1656, 1648, 1528, 1521, 1269, 1085, 729 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53–7.49 (m, 3H), 7.30 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 6.6 Hz, 1H), 4.64 (ddd, J = 11.0, 7.5, 4.0 Hz, 1H), 4.49–4.40 (m, 4H), 4.39–4.35 (m, 1H), 4.33 (d, J = 3.3 Hz, 1H), 4.17–4.13 (m, 1H), 4.29 (d, J = 2.8 Hz, 1H), 4.24–4.18 (m, 4H), 4.10–4.01 (m, 11H), 3.75 (s, 3H), 2.38–2.28 (m, 5H), 2.03–1.88 (m, 7H). **^{13}C NMR (100 MHz , $CDCl_3$):** 31.9 (t), 32.1 (t), 32.2 (t, 2C), 32.3 (t, 2C), 52.4 (d), 53.5 (d), 54.5 (d), 54.6 (d), 54.7 (d, 3C), 64.3 (d), 68.0 (t, 2C), 68.1 (t, 2C), 68.2 (t), 81.6 (d), 82.2 (d), 82.3 (d), 82.4 (d), 83.1 (d, 2C), 170.5 (s), 171.0 (s), 171.2 (s), 171.3 (s, 2C), 171.5 (s) ppm. **ESI-MS *m/z***: 759.5 (22%, $[M+Na]^+$), 775.4 (11%, $[M+K]^+$), 633.5 (77%, $[M-203]^+$), 533. (100%, $[M-203]^+$). **Anal. Calcd for $C_{31}H_{44}N_8O_{13}$**: C, 50.54; H, 6.02; N, 15.21; Found: C, 50.63; H, 6.09; N, 15.18.

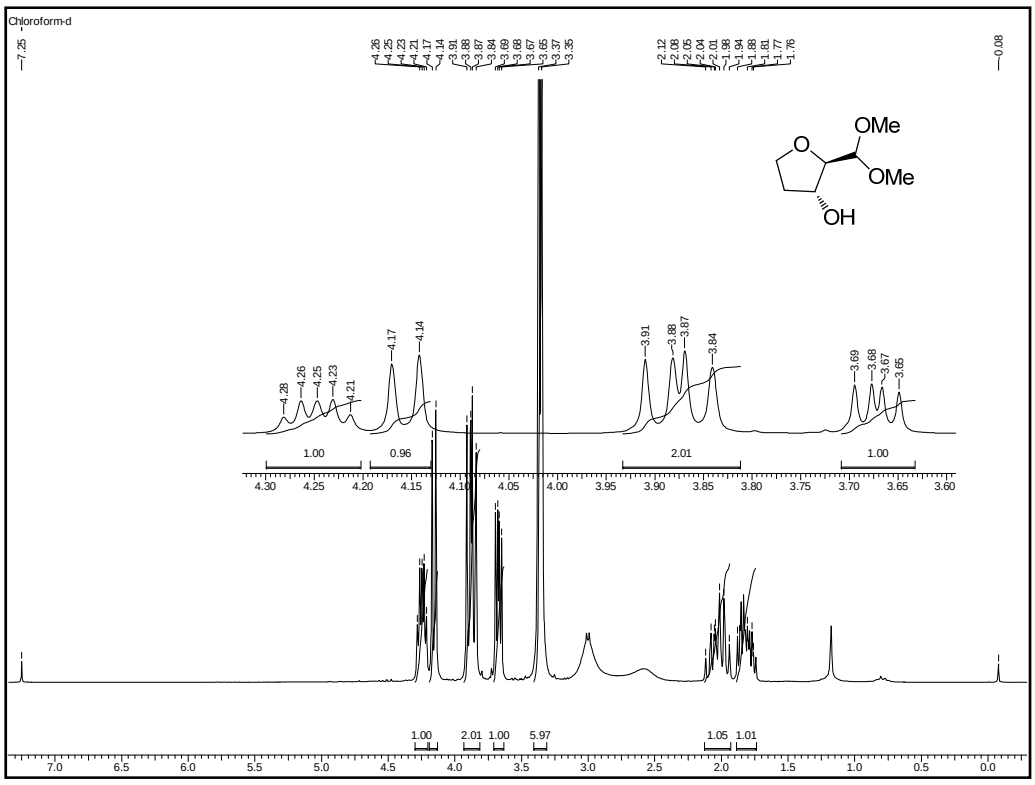
Spectroscopic Data



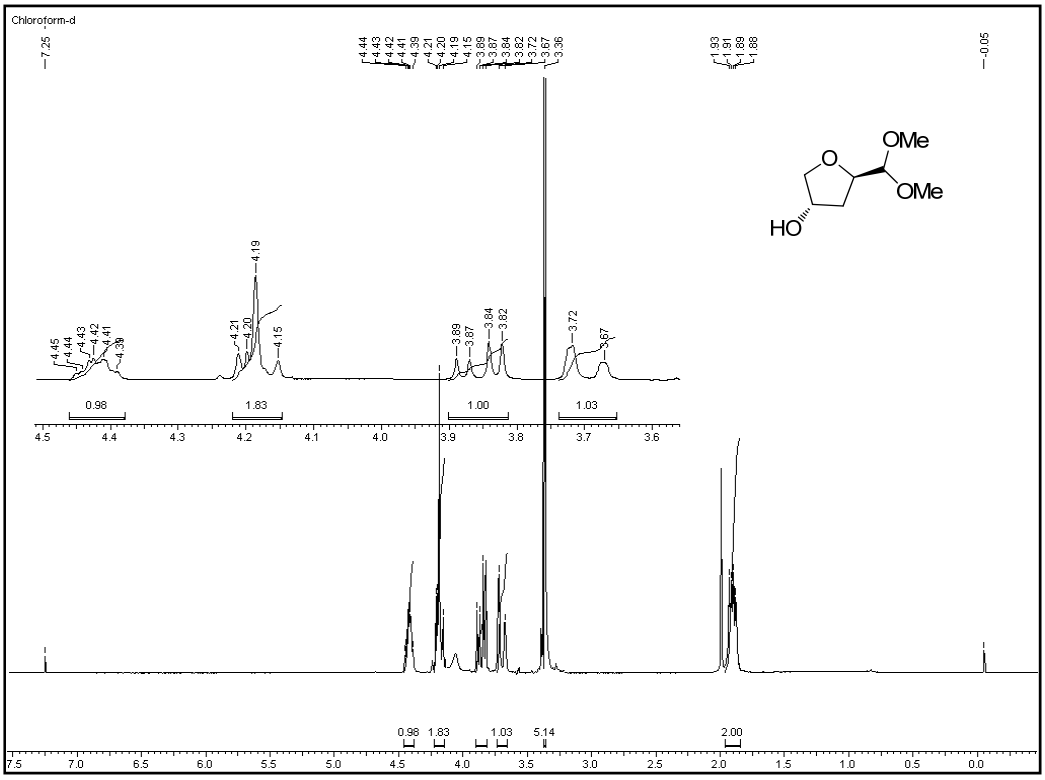
^{1}H NMR Spectrum of 87 in $CDCl_3$



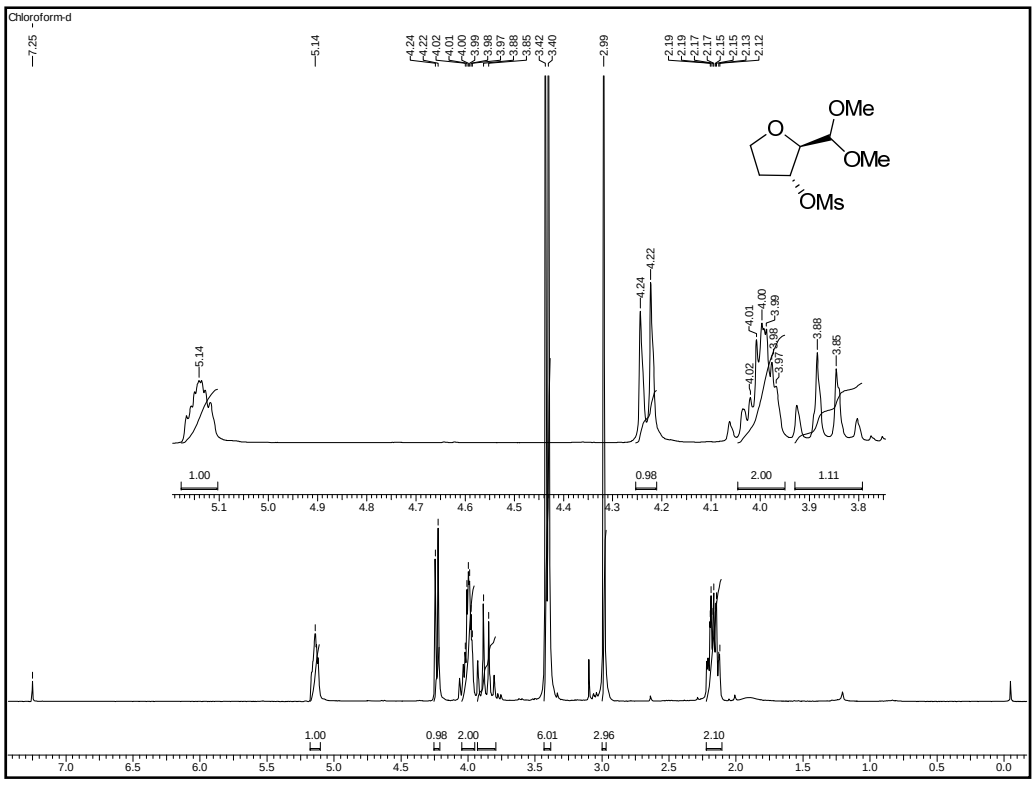
^{13}C NMR Spectrum of 87 in $CDCl_3$



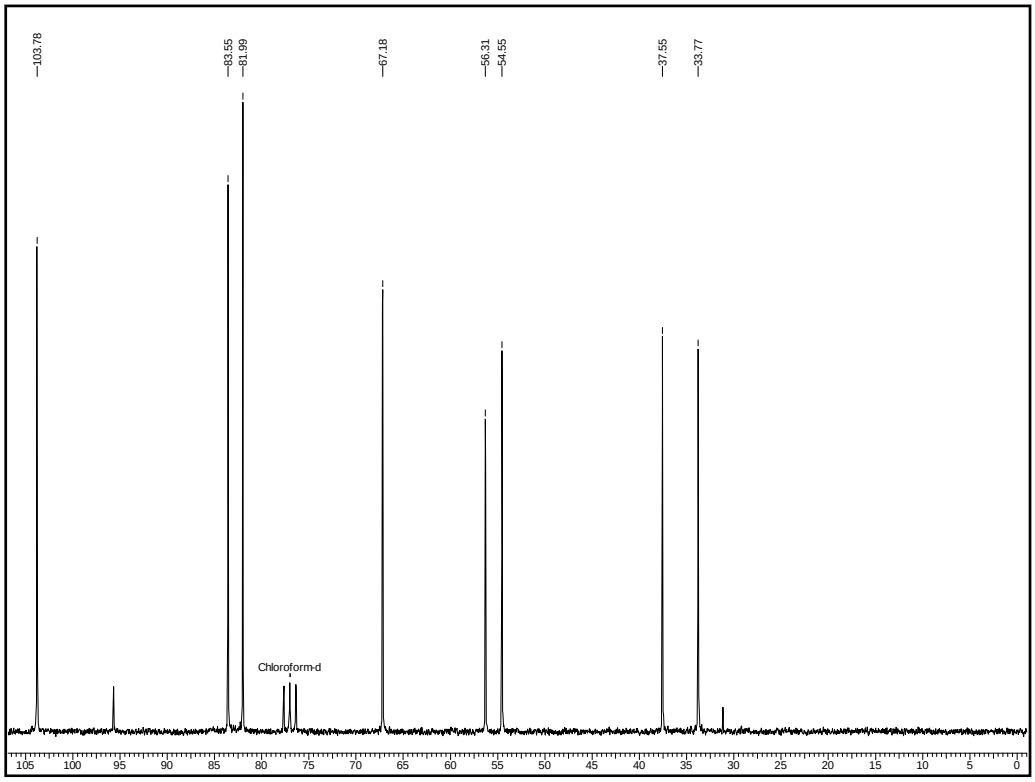
^{1}H NMR Spectrum of 83 in $CDCl_3$



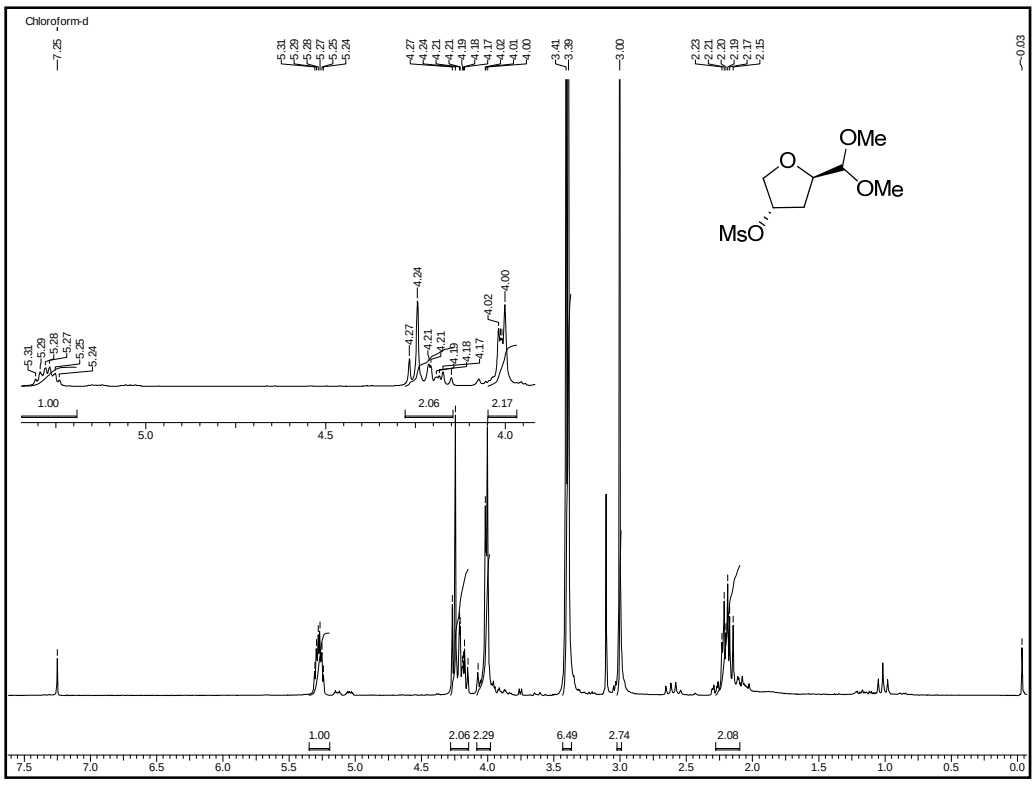
^{1}H NMR Spectrum of 88 in $CDCl_3$



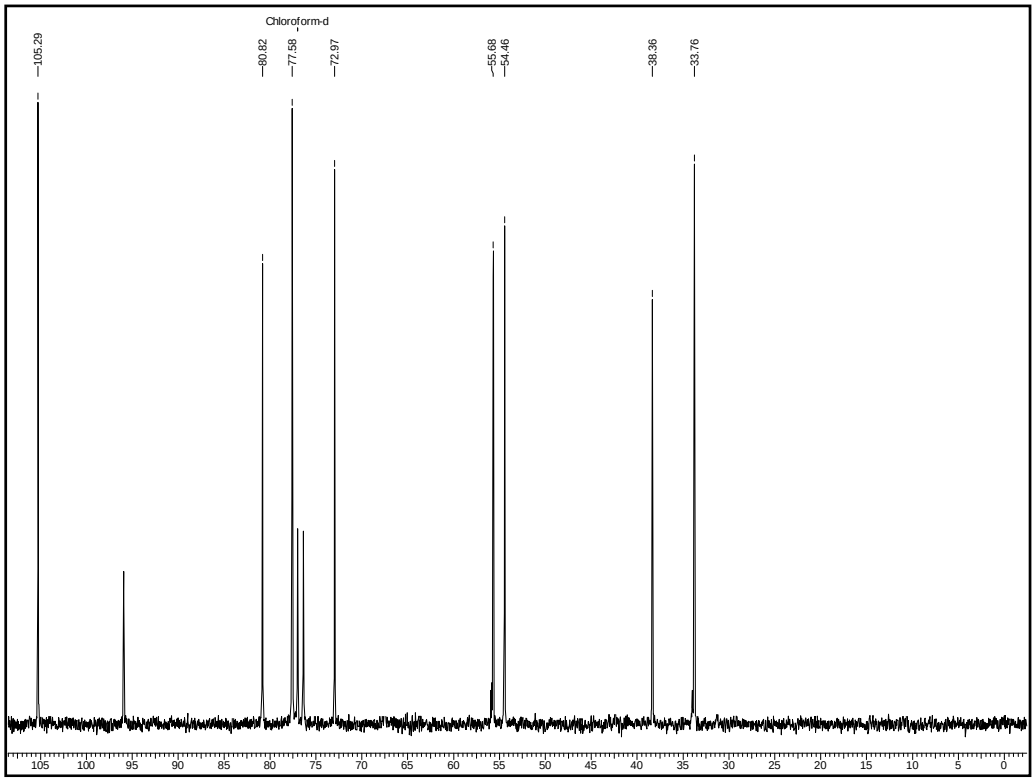
^{1}H NMR Spectrum of MsO-83 in $CDCl_3$



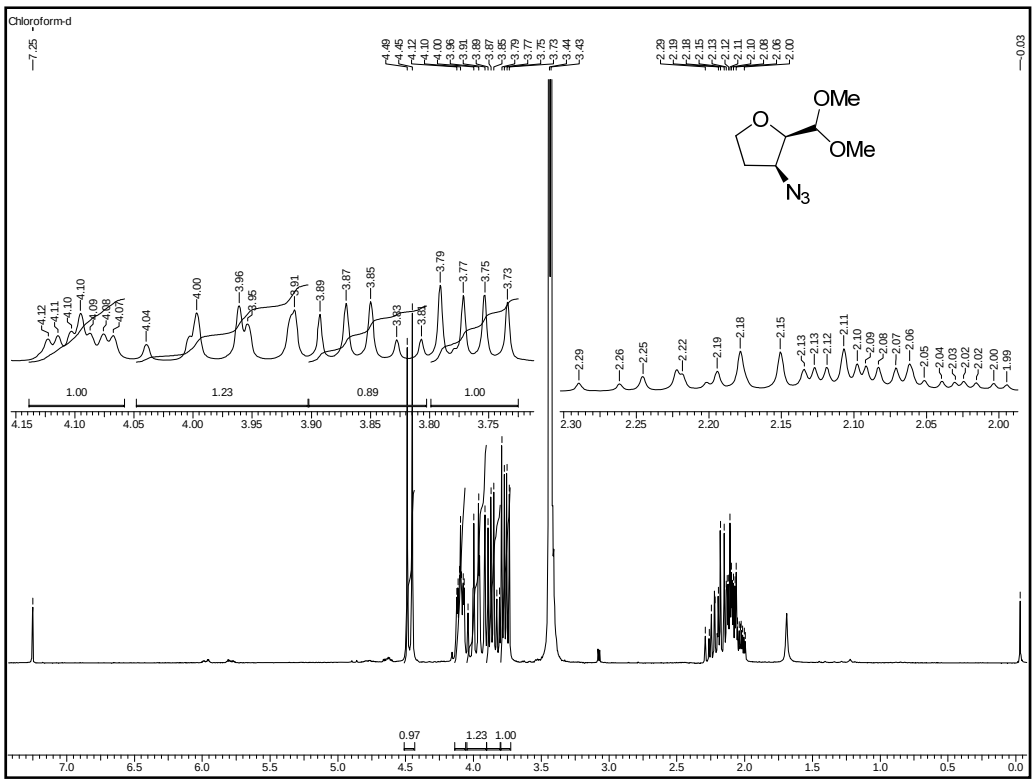
^{13}C NMR Spectrum of MsO-83 in $CDCl_3$



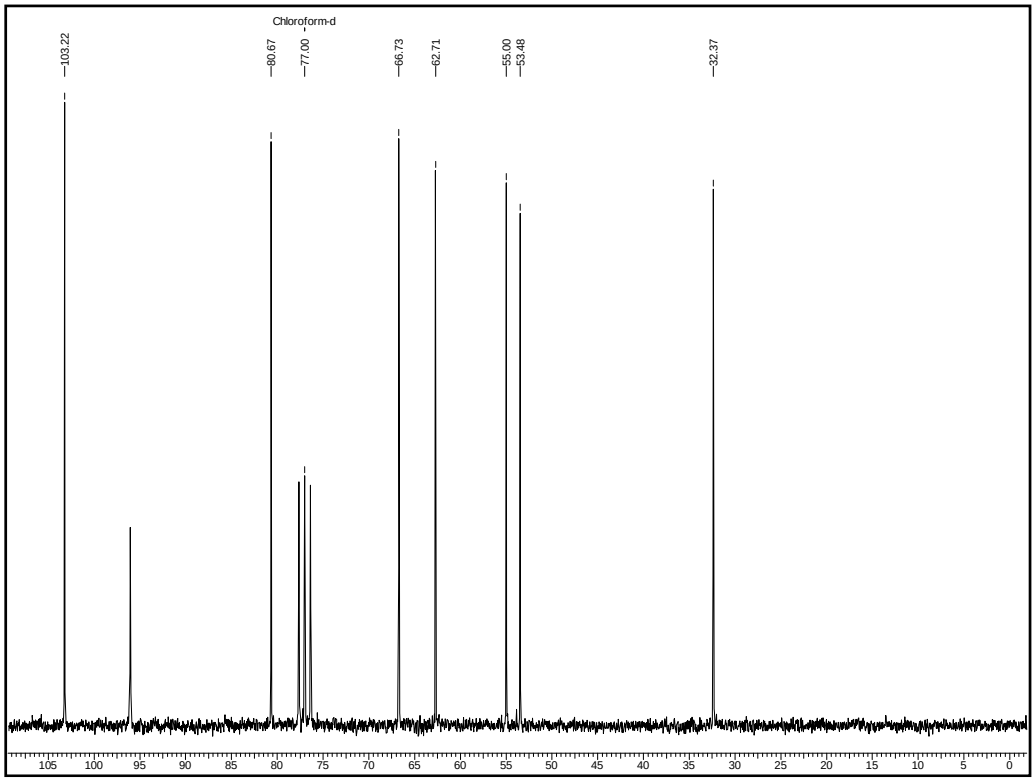
^{1}H NMR Spectrum of MsO-88 in $CDCl_3$



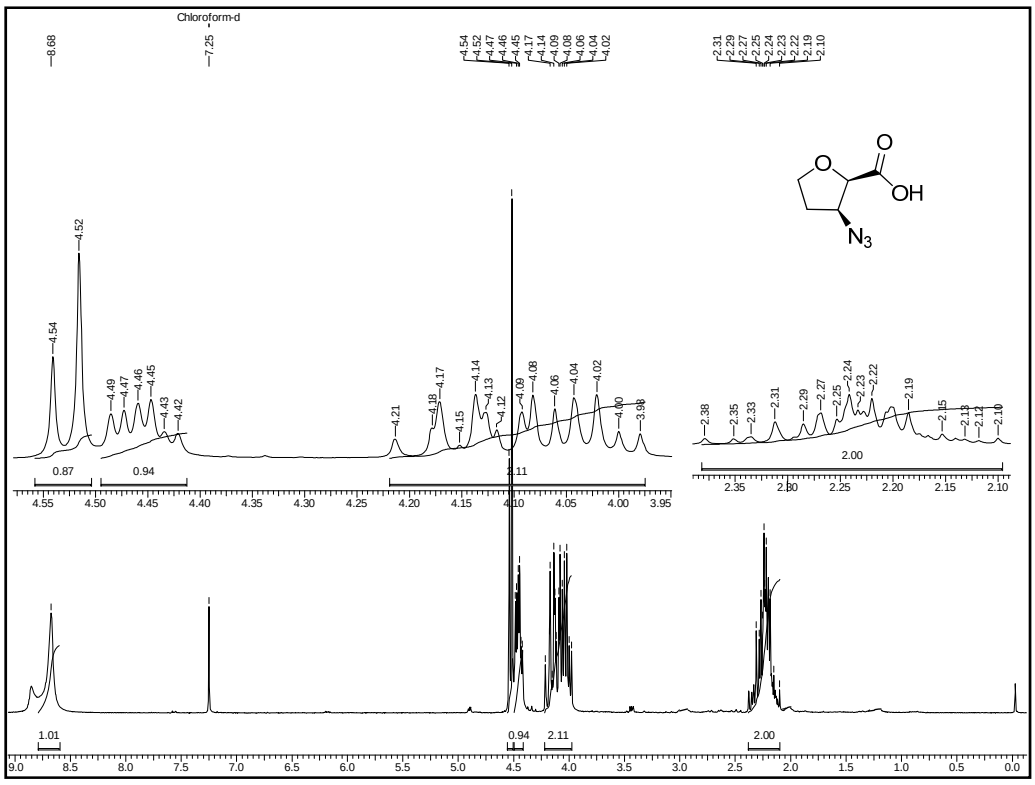
^{13}C NMR Spectrum of MsO-88 in $CDCl_3$



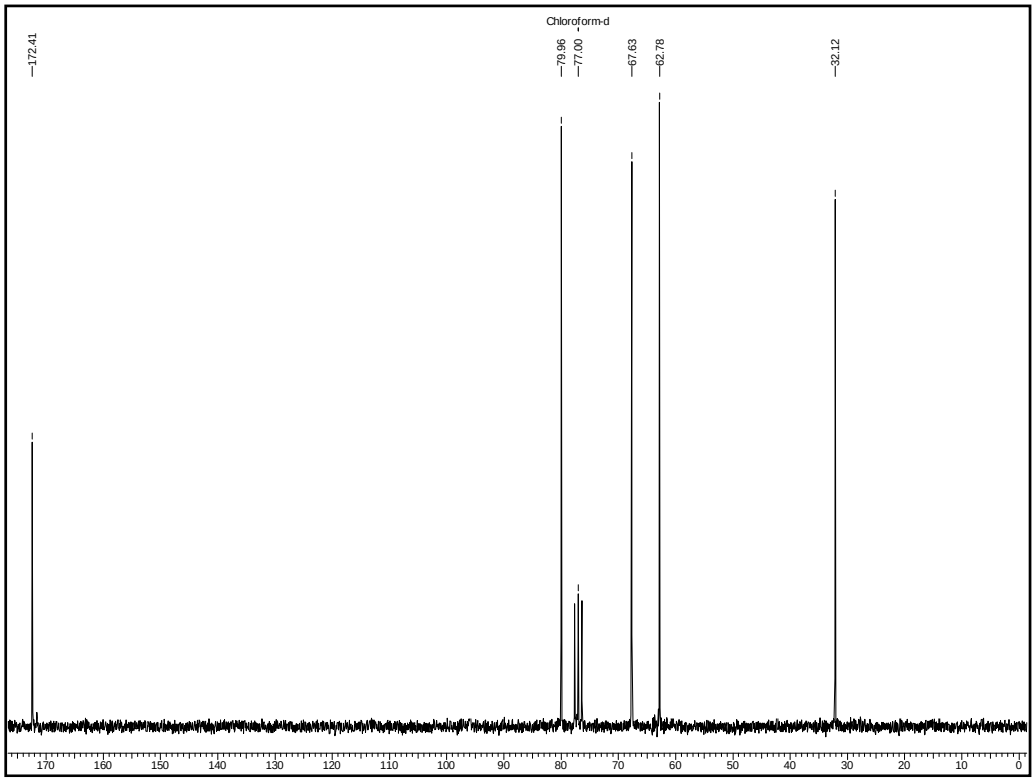
^{1}H NMR Spectrum of 90 in $CDCl_3$



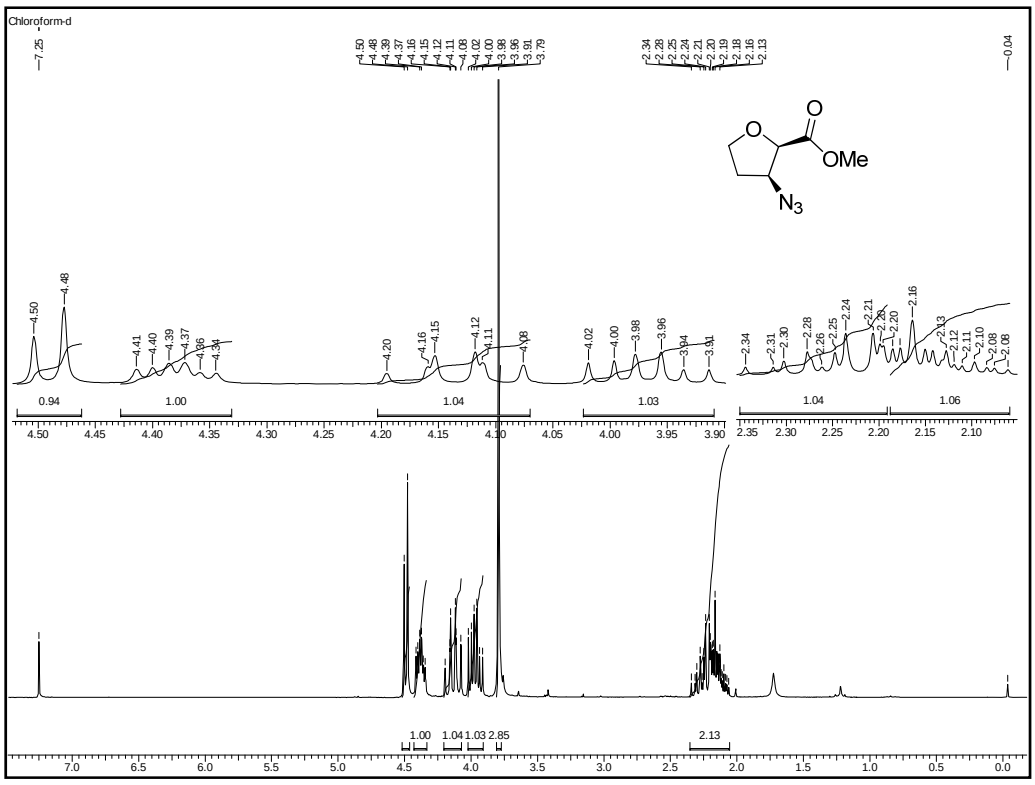
^{13}C NMR Spectrum of 90 in $CDCl_3$



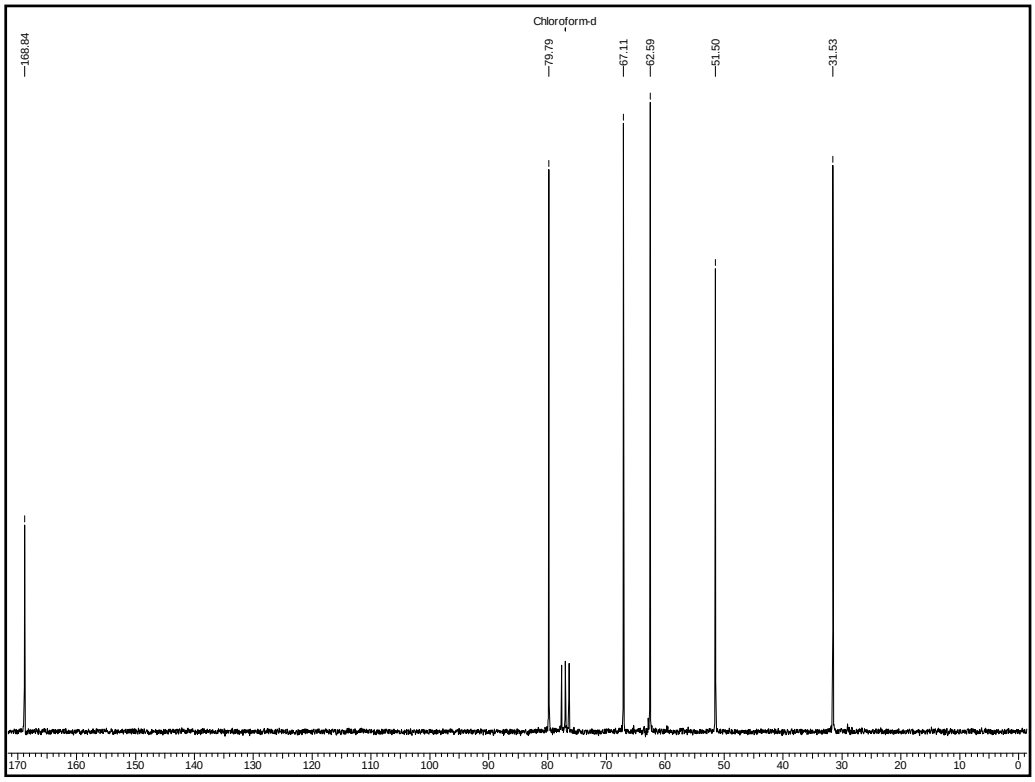
^{1}H NMR Spectrum of 91 in $CDCl_3$



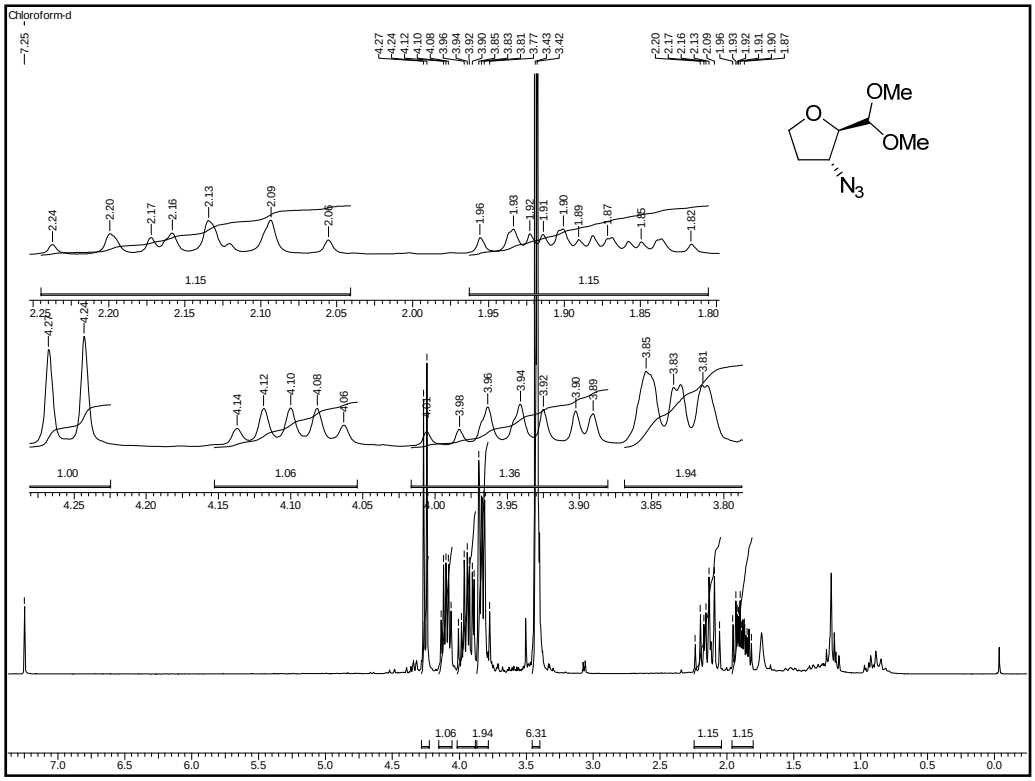
^{13}C NMR Spectrum of 91 in $CDCl_3$



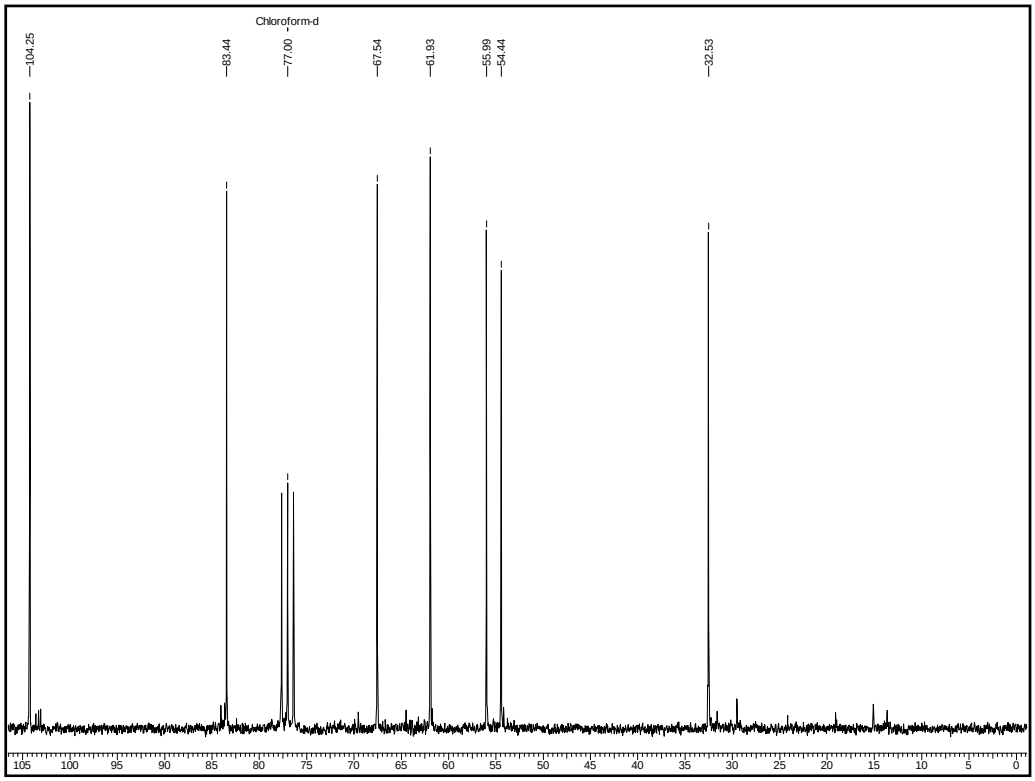
^{1}H NMR Spectrum of 92 in $CDCl_3$



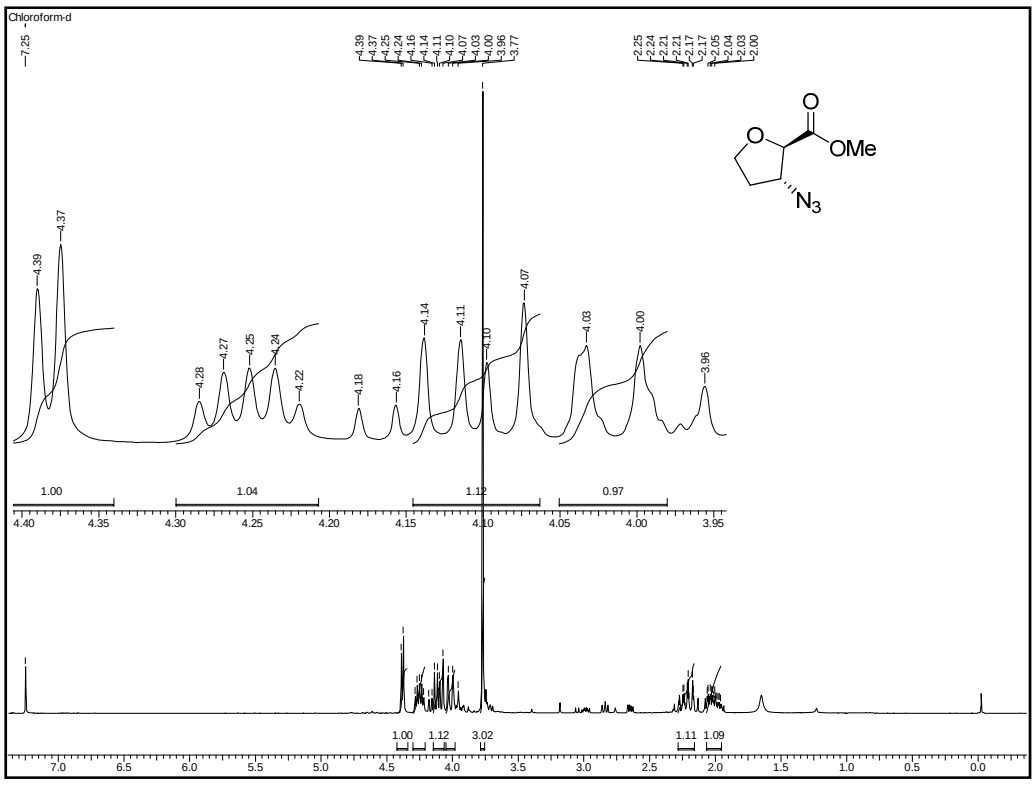
^{13}C NMR Spectrum of 92 in $CDCl_3$



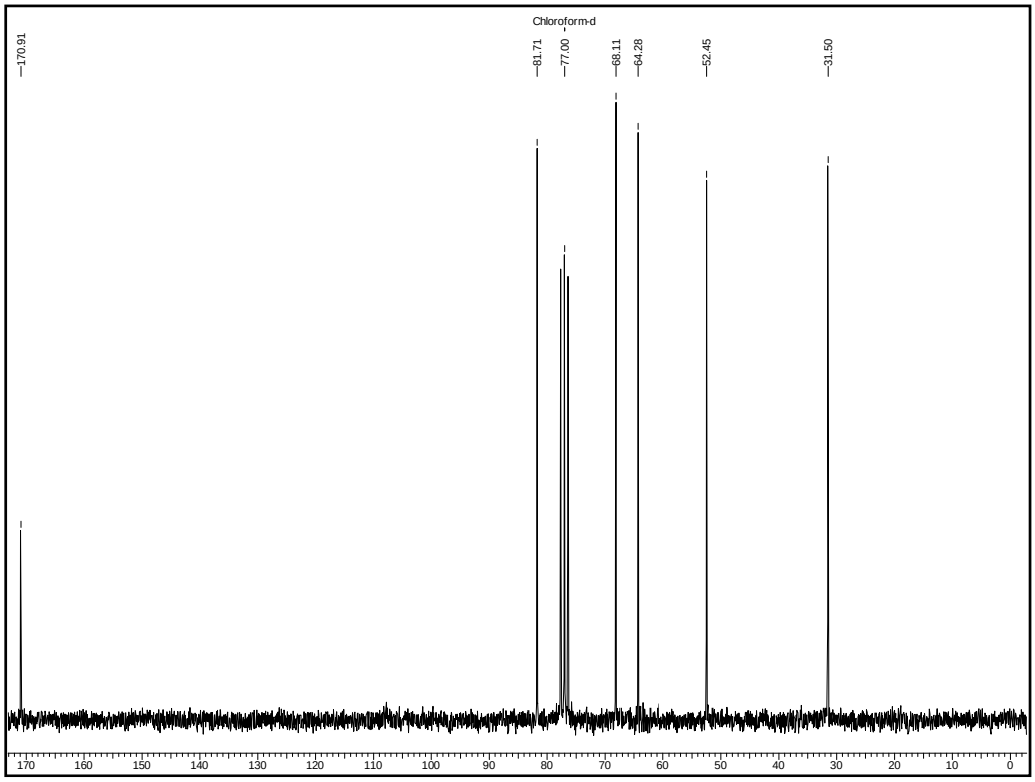
^{1}H NMR Spectrum of 95 in $CDCl_3$



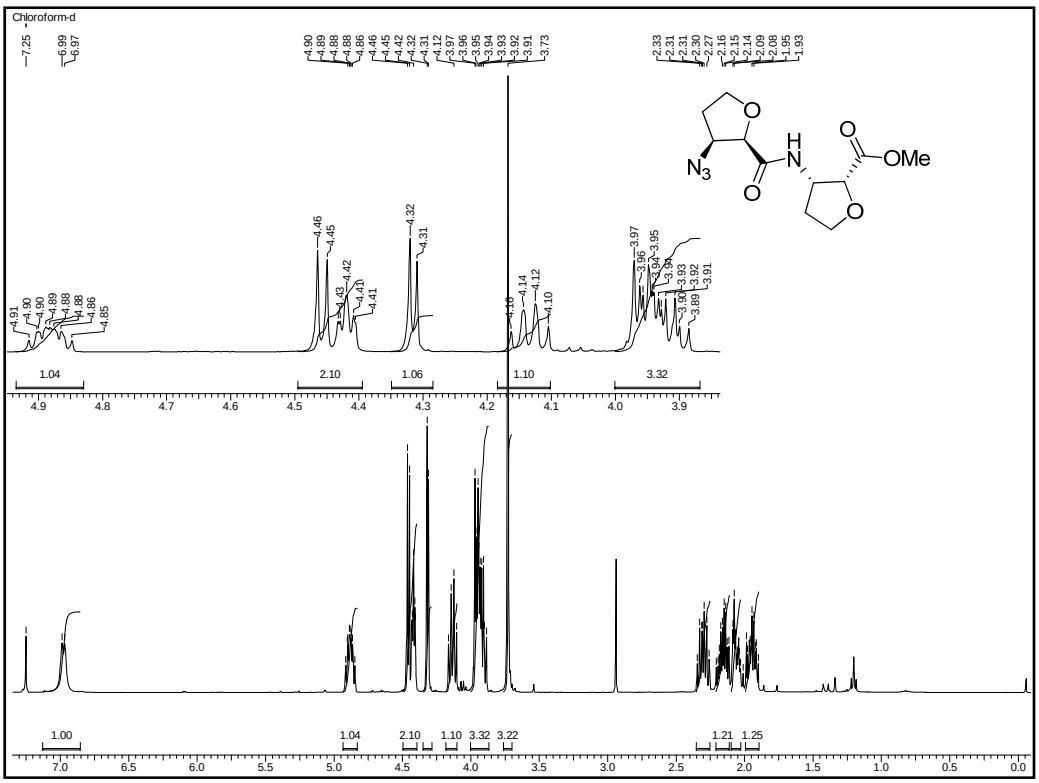
^{1}H NMR Spectrum of 95 in $CDCl_3$



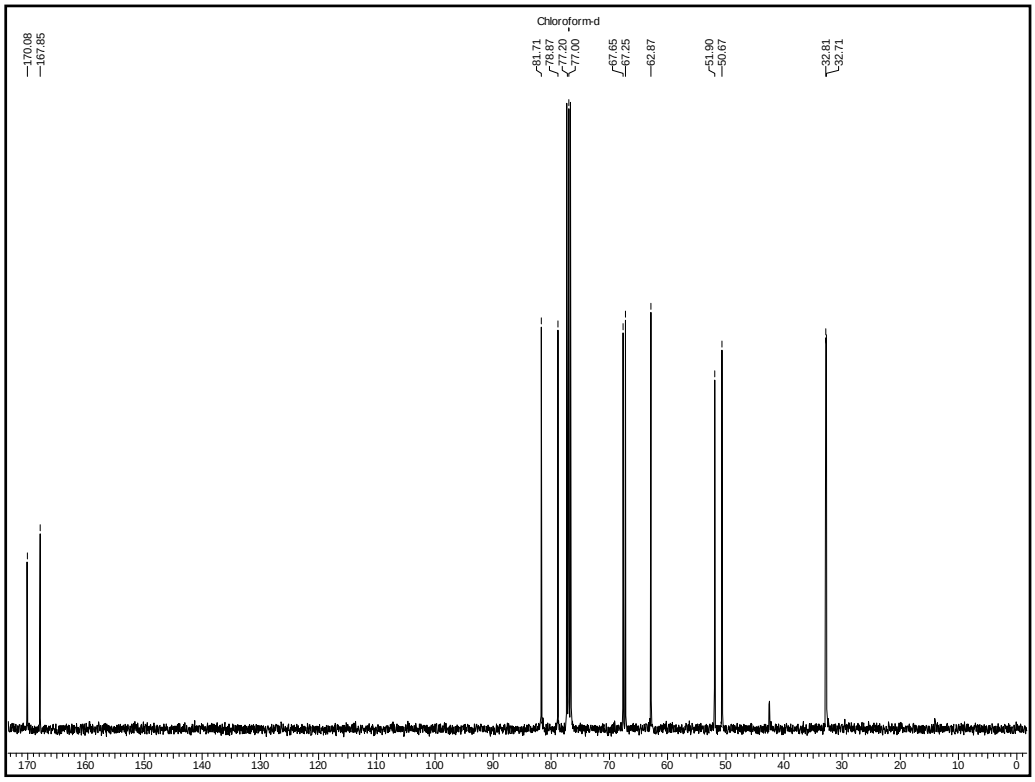
^{1}H NMR Spectrum of 97 in $CDCl_3$



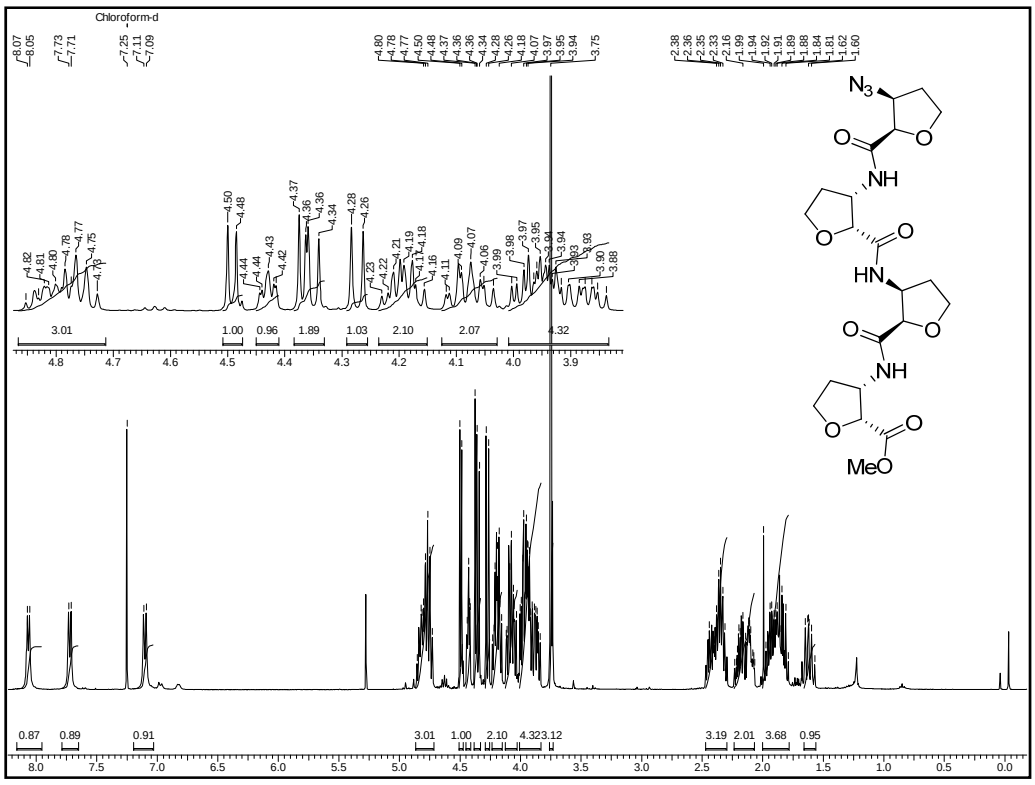
^{1}H NMR Spectrum of 97 in $CDCl_3$



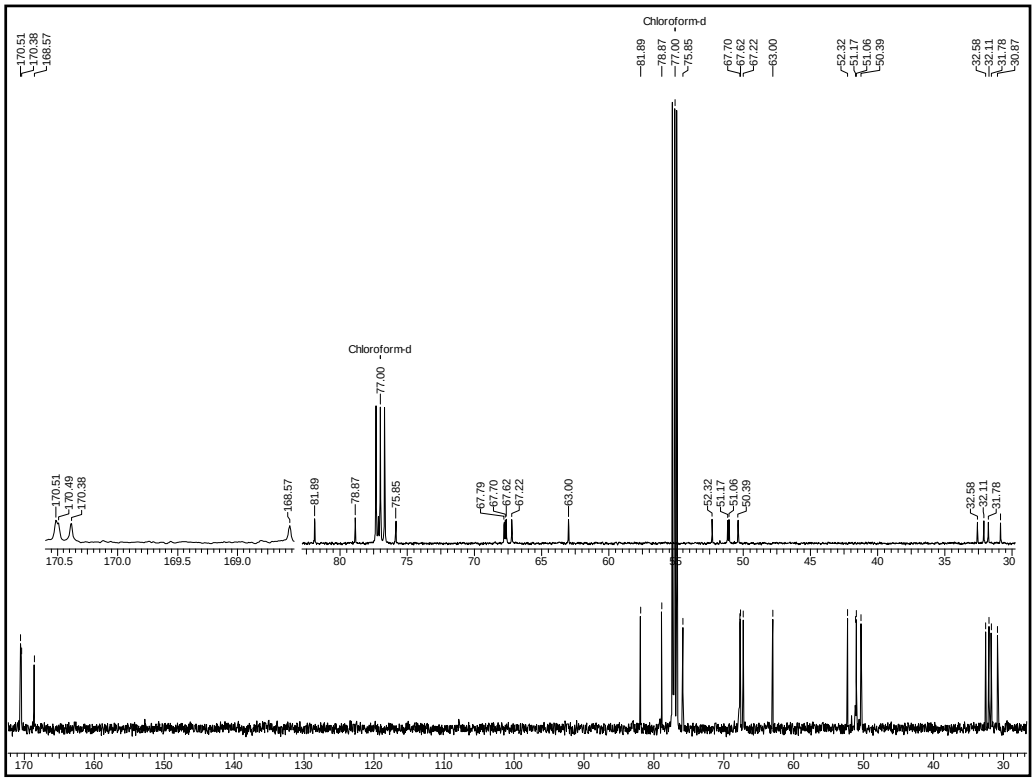
^{1}H NMR Spectrum of 98 in $CDCl_3$



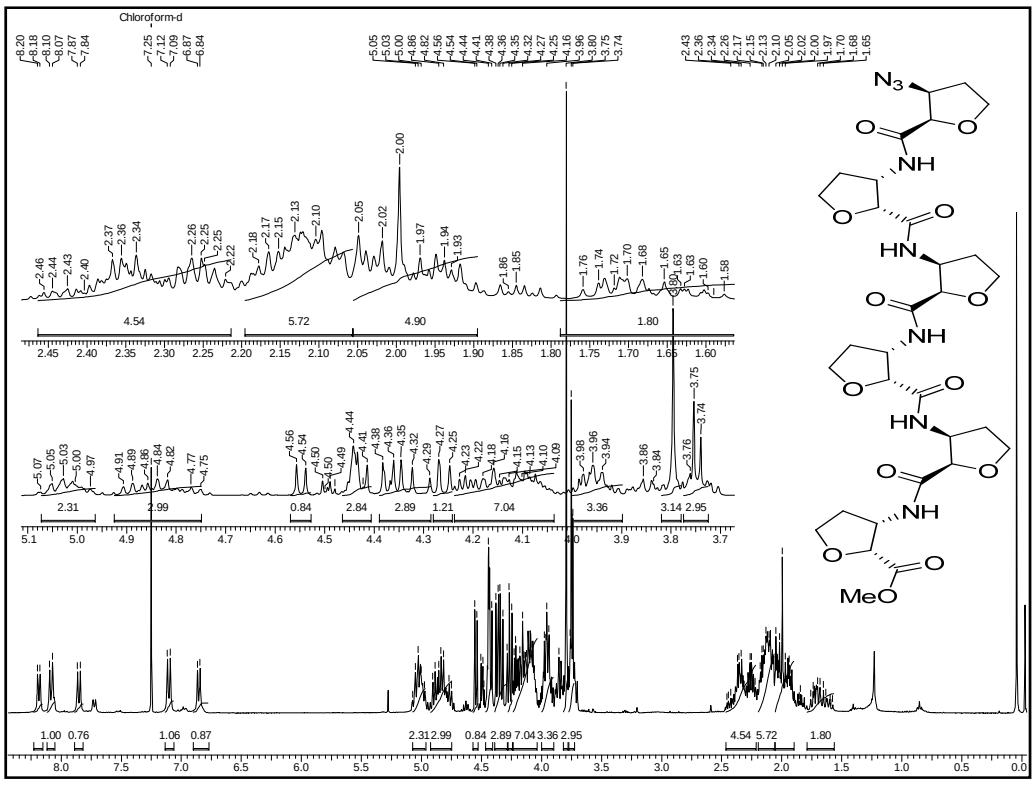
^{13}C NMR Spectrum of 98 in $CDCl_3$



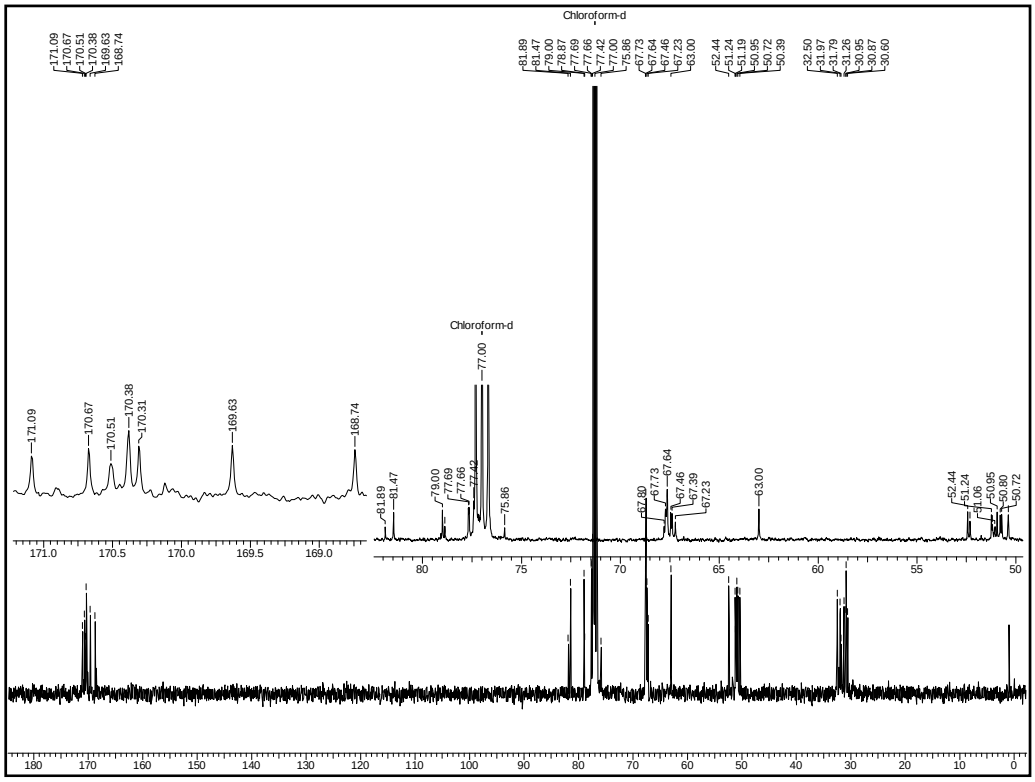
^{1}H NMR Spectrum of 99 in $CDCl_3$



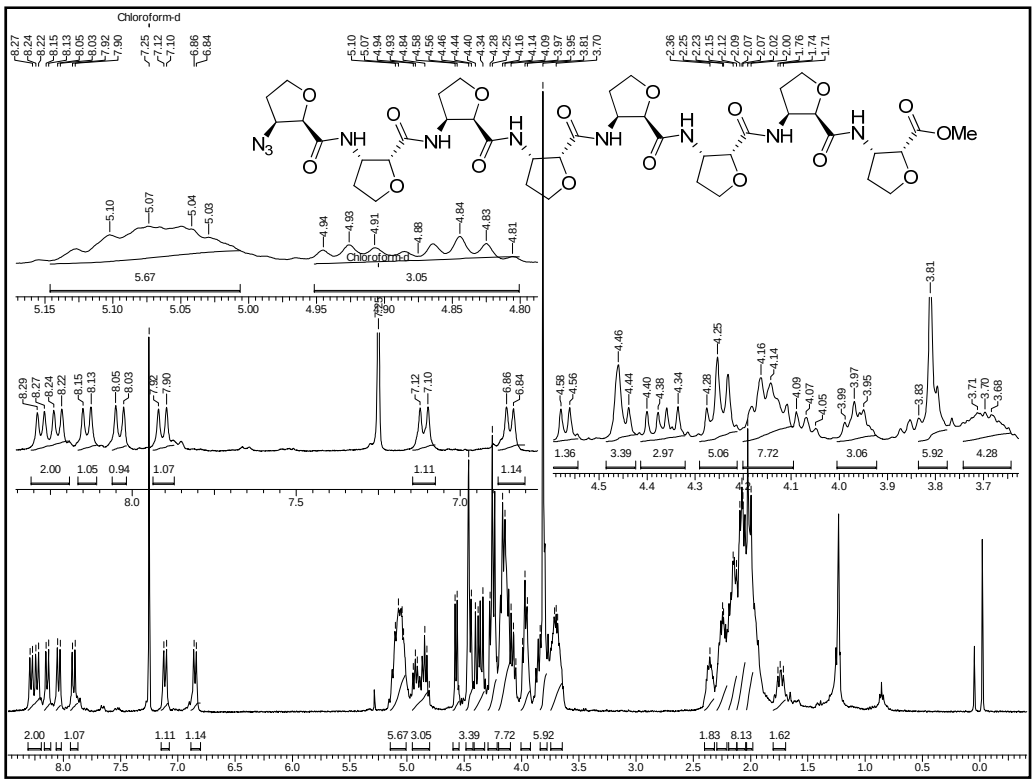
^{13}C NMR Spectrum of 99 in $CDCl_3$



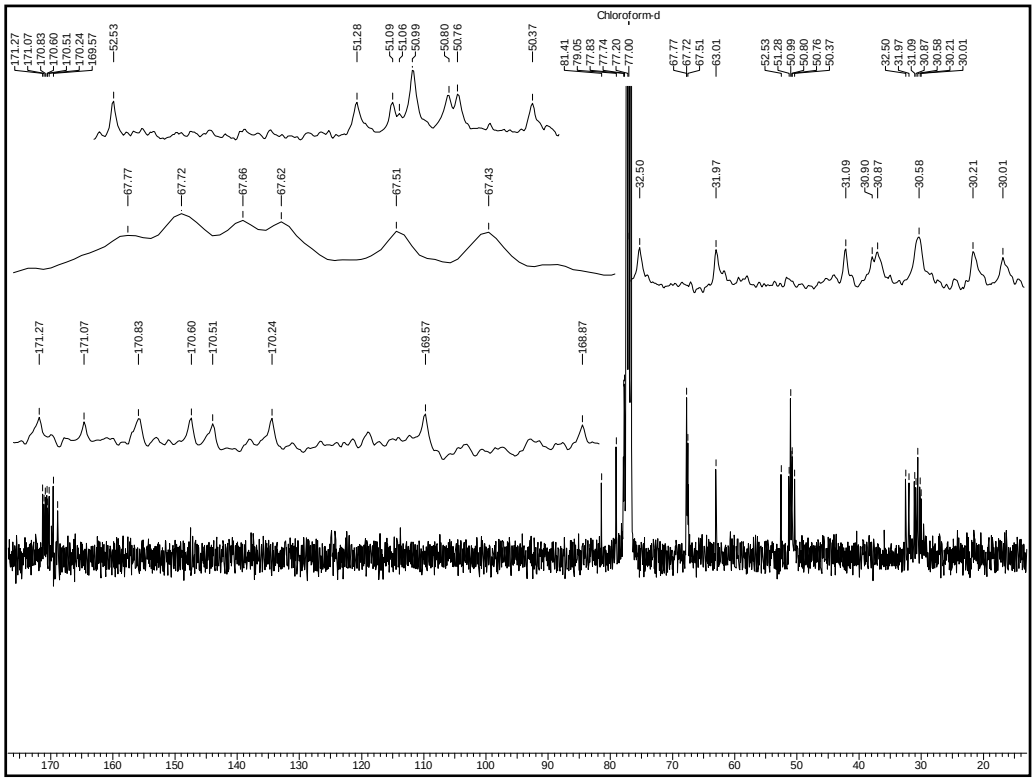
^{1}H NMR Spectrum of 100 in $CDCl_3$



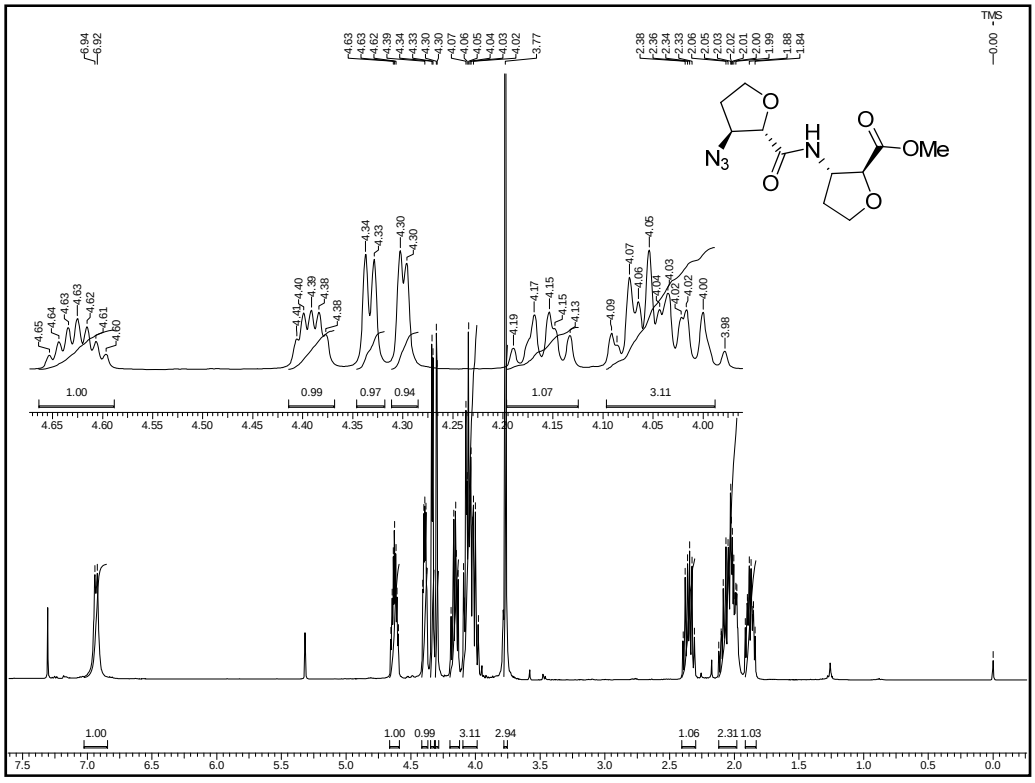
^{13}C NMR Spectrum of 100 in $CDCl_3$



^{1}H NMR Spectrum of 101 in $CDCl_3$



^{13}C NMR Spectrum of 101 in $CDCl_3$



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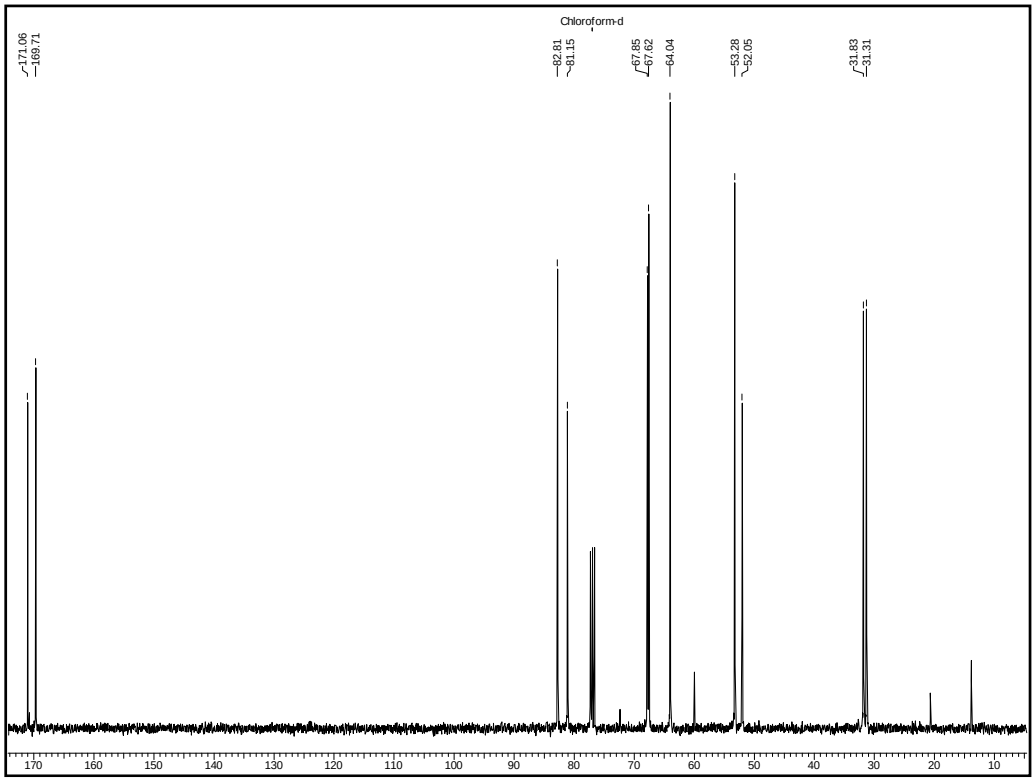

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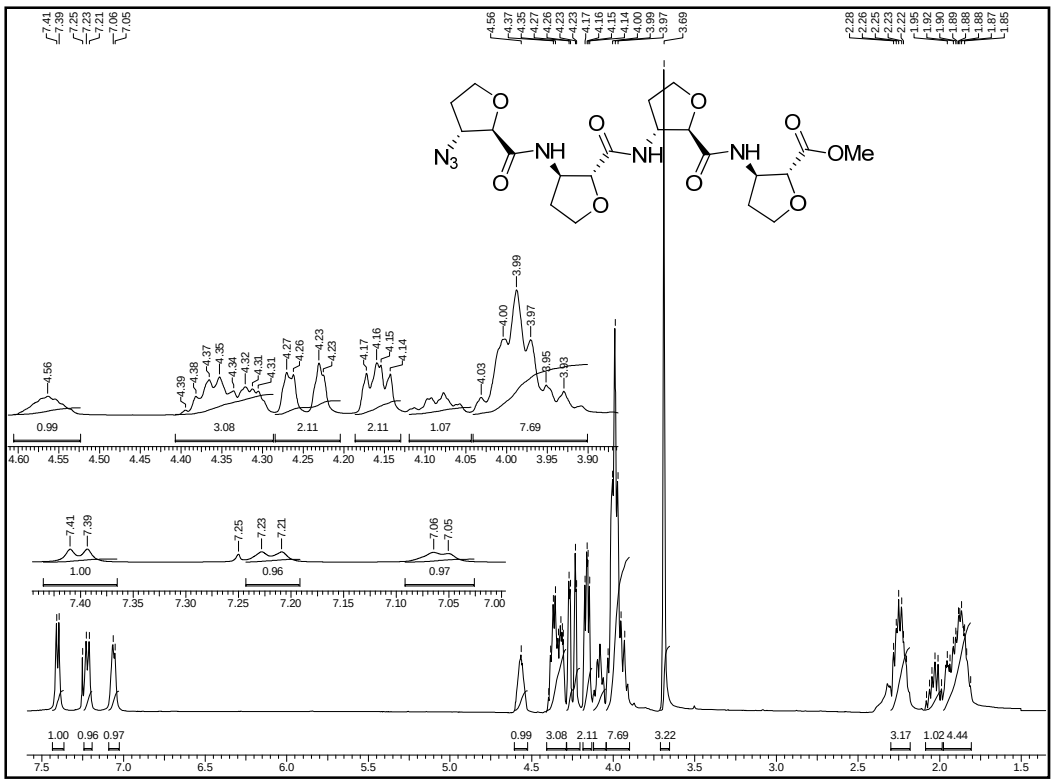
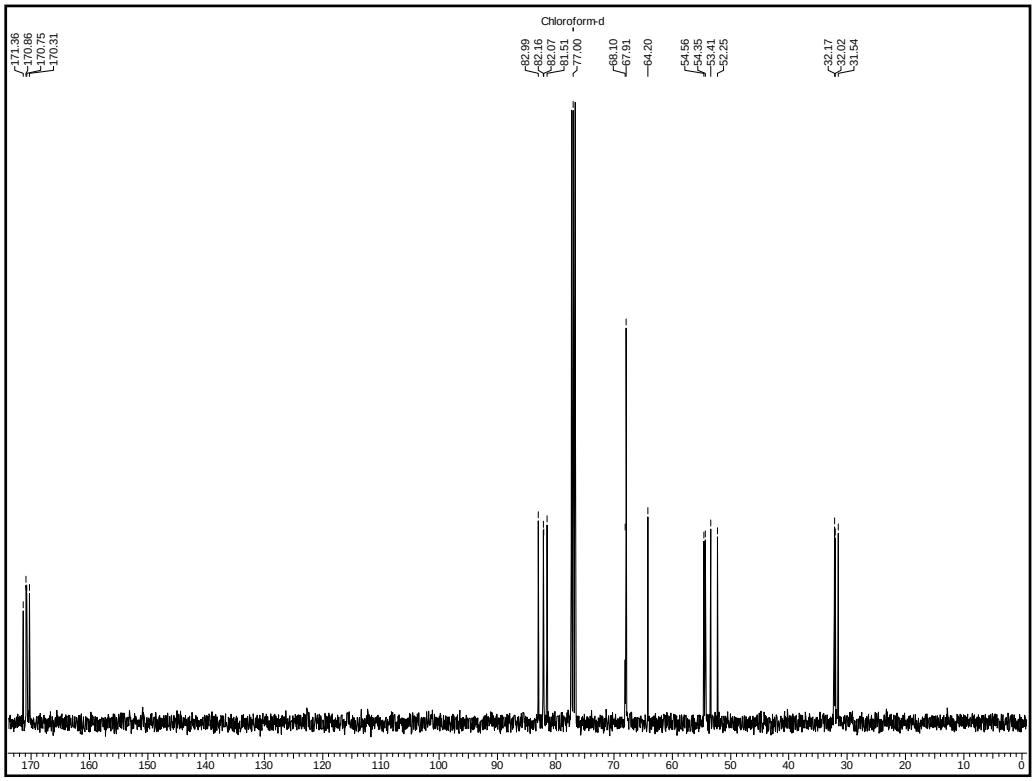
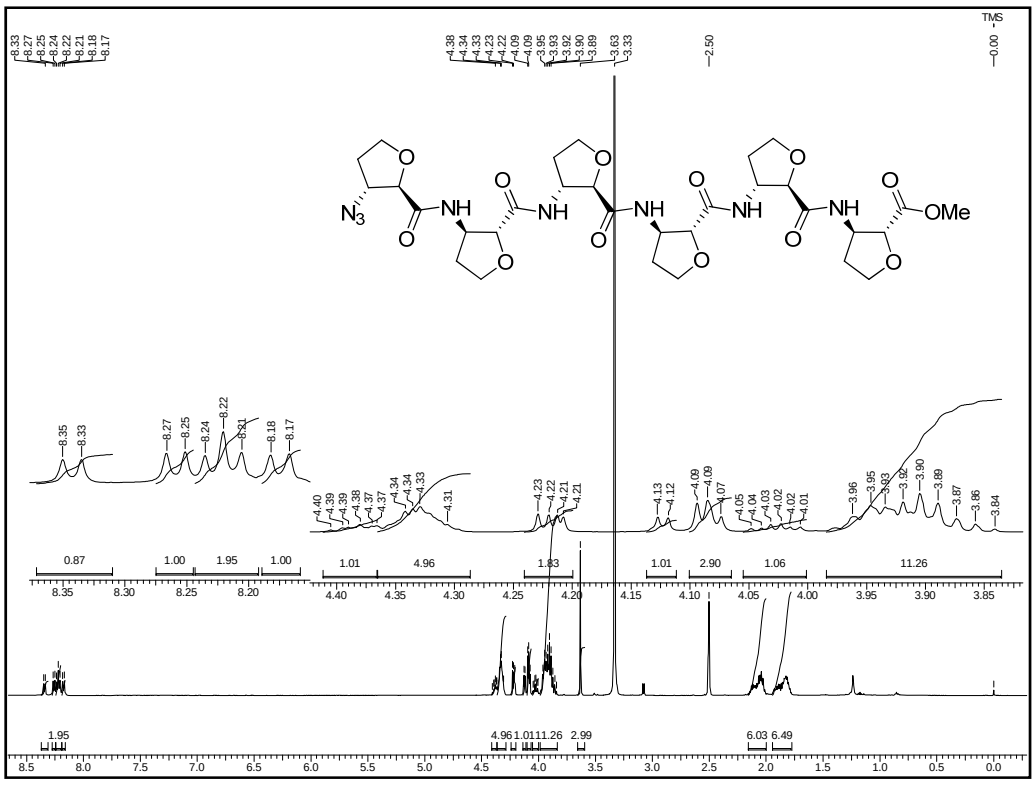


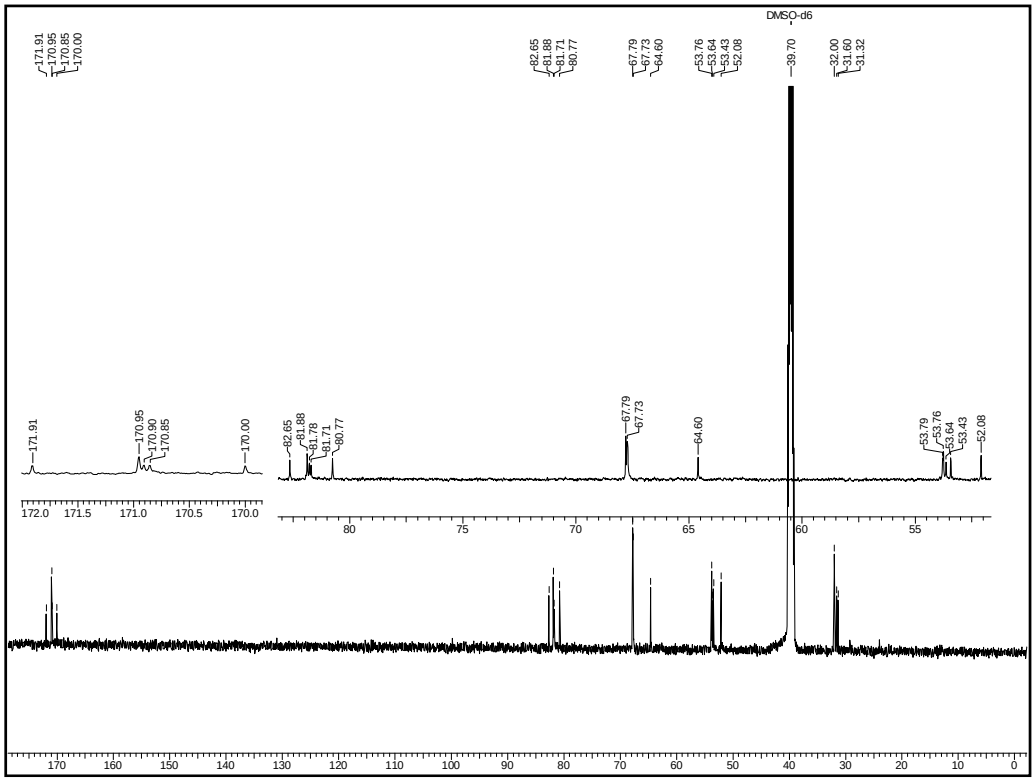
^{1}H NMR Spectrum of 103 in $CDCl_3$



^{13}C NMR Spectrum of 103 in $CDCl_3$



^{1}H NMR Spectrum of 104 in DMSO-d_6



^{13}C NMR Spectrum of 104 in DMSO-d_6

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LIST OF PUBLICATION

1. A modular total synthesis of aculeatins A, B, E, F and 6-*epi*-aculeatins E, F- *Tetrahedron* **2010,** *66,* 390-399.
2. Total Synthesis of Sacidumligana-D (communicated)