

**TOWARDS THE TOTAL SYNTHESIS OF  
MULTIPLOLIDE A, FEIGRISOLIDE B &  
PANDANGOLIDE 1 USING CHIRON APPROACH  
AND EXPLORATION OF CLICK REACTION IN  
CRYSTAL ENGINEERING**

A Thesis  
Submitted by  
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To  
**Jadavpur University**

For  
**The degree of Doctor of Philosophy**  
(in Chemistry)

Organic Chemistry Division  
National Chemical Laboratory  
Pune - 411 008  
INDIA  
April 2008

*Dedicated to My  
Beloved Parents*

## **DECLARATION**

The research work embodied in this thesis submitted for Ph.D. degree to Jadavpur University has been carried out at National Chemical Laboratory, Pune and Jadavpur University, Kolkata under the supervisions of **Dr. Mukund K. Gurjar**, Ex-Deputy Director and Head, Organic Chemistry: Technology, National Chemical Laboratory, Pune – 411 008 and **Prof. S. R. RayChaudhury**, Ex-Head, Department of Chemistry, Jadavpur University, Kolkata – 700 032. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

Date:

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## CERTIFICATE

This is to certify that the thesis entitled “*Towards the Total Synthesis of Multiplolide A, Feigrisolide B & Pandangolide 1 using Chiron Approach and Exploration of Click Reaction in Crystal Engineering*” submitted by Mr. Soumitra Chatterjee, who got his name registered on 25.06.2004 for the award of Ph.D. (science) degree of Jadavpur University, is absolutely based upon his own work under our supervisions and that neither this thesis nor any part of its has been submitted for any degree/diploma or any other academic award anywhere before.

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Jadavpur, Kolkata

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**Prof. S. R. Raychaudhuri**

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## General Remarks

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- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in  $\text{cm}^{-1}$ .
- $^1\text{H}$  Nuclear Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini), AC-200 MHz, MSL-300 MHz, AV-400 MHz and Bruker-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- $^{13}\text{C}$  Nuclear Magnetic Resonance spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz and Bruker-125 MHz spectrometers.
- Mass spectra were recorded on a CEC-21-110B, AP-1 QSTAR PULSAR, Finnigan Mat 1210 or MICRO MASS 7070 spectrometers at 70 eV using a direct inlet system.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV,  $\text{I}_2$  and anisaldehyde reagent in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

## Abbreviations

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Ac	-	Acetyl
AcOH	-	Acetic acid
Ac <sub>2</sub> O	-	Acetic anhydride
AIBN	-	Azoisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
BH <sub>3</sub> .DMS	-	Borane dimethyl sulfide complex
<i>n</i> -BuLi	-	<i>n</i> -butyl lithium
CCl <sub>4</sub>	-	Carbontetrachloride
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DIPEA	-	<i>N, N'</i> -Diisopropylethylamine
DMAP	-	4- <i>N, N'</i> -Dimethylaminopyridine
DMF	-	<i>N, N'</i> -Dimethylformamide
DMSO	-	Dimethyl sulfoxide
2,2-DMP	-	2,2-Dimethoxy propane
Et	-	Ethyl
EtOAc	-	Ethyl acetate
Et <sub>2</sub> O	-	Diethylether
EtOH	-	Ethanol
HgCl <sub>2</sub>	-	Mercuric chloride
HgO	-	Mercuric oxide
IBX	-	Iodoxy benzoic acid
Im	-	Imidazole
LAH	-	Lithium aluminium hydride
MeOH	-	Methanol
MeI	-	Methyl iodide
MsCl	-	Methanesulfonyl chloride



NaH	-	Sodium hydride
NEt <sub>3</sub>	-	Triethyl amine
Pd/C	-	Palladium on carbon
PDC	-	Pyridiniumdichromate
Pd(OH) <sub>2</sub>	-	Palladium hydroxide
Piv	-	Pivaloyl
PMB	-	<i>para</i> -Methoxybenzyl
<i>p</i> TSA	-	<i>para</i> -Toluenesulfonic acid
Py	-	Pyridine
TBAF	-	Tetrabutylammonium fluoride
TBDPS (TPS)	-	<i>tert</i> -Butyldiphenylsilyl
TBS	-	<i>tert</i> -Butyldimethylsilyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TMS	-	Trimethylsilyl
TPP	-	Triphenylphosphine

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## ABSTRACT

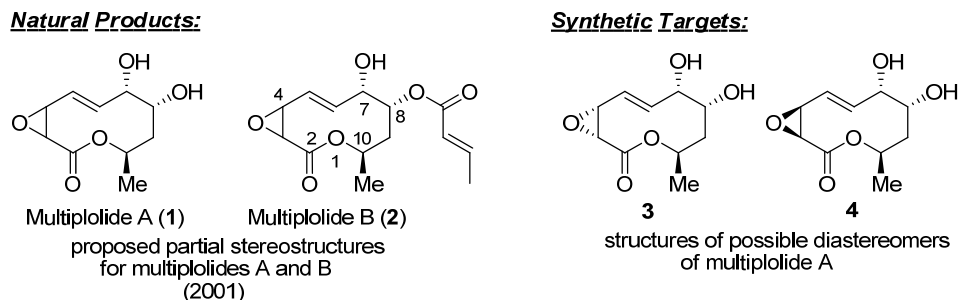
### *Towards the Total Synthesis of Multiplolide A, Feigrisolide B & Pandangolide 1 using Chiron Approach and Exploration of Click Reaction in Crystal Engineering*

#### Chapter 1: Towards the Total Synthesis of Multiplolide A

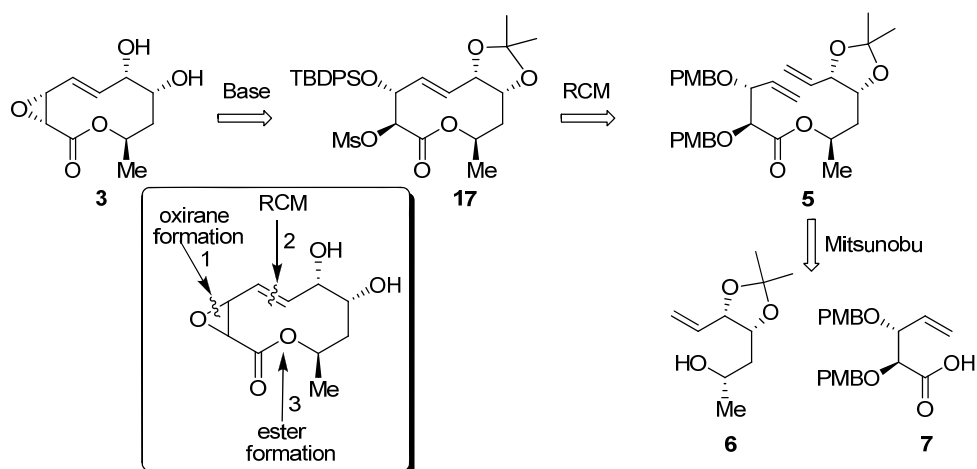
In 2001, Kittakoop and co-workers reported the isolation of two new antifungal 10-membered lactones, multiplolides A (**1**) and B (**2**), from the crude ethyl acetate extract of the culture broth of *Xylaria Multiplex*. Multiplolides A (**1**) and B (**2**) exhibited antifungal activity against *Candida albicans* with IC<sub>50</sub> values of 7 and 2 µg/mL, respectively. Multiplolides belong to the nonenolide group and are characterized by an epoxide functionality positioned in between the lactone carbonyl and ring olefin. The absolute configuration at C-7 of **2** was determined as *S* by the application of the Mosher method which indirectly established the absolute configurations of both C-8 and C-10 centers as *R, R*. By taking into account the positive optical rotation shown by both **1** and **2**, similar absolute configurations of C-7, C-8 and C-10 were proposed for multiplolide A (**1**).

As the complete stereochemical characterization is hampered by the lack of any spacial coupling between the hydrogens around the internal olefin in the NMR experiments, a total synthesis was deemed necessary to determine both the relative and absolute configuration of multiplolides.

**Figure 1:** Chemical structures of multiplolide A, B and both possible diastereomers of multiplolide A



**Figure 2:** Retrosynthetic strategy

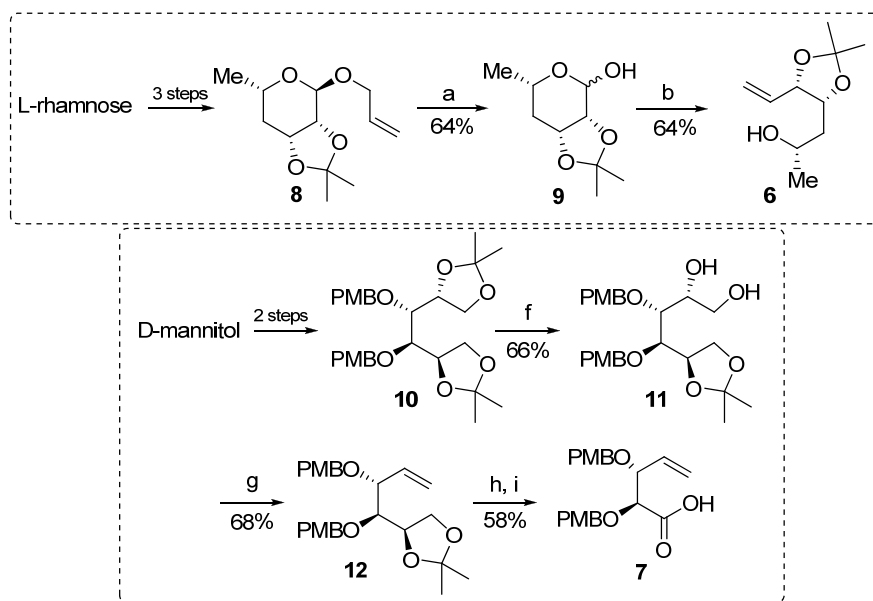


A retrosynthetic strategy for the synthesis of multiplolide A is depicted above. The basic premise is to utilize ring closing metathesis (RCM) reaction on the diene to install the macrocyclic framework. In addition, the vicinal diol unit situated between carbonyl and olefin not only forms the surrogate for the epoxide but more importantly depending upon the regiochemistry of the leaving group, the required stereochemistry of the epoxide can be ensured. After stereochemical comparisons, the requisite coupling partners were planned from easily available derivatives of L-rhamnose and D-mannitol, respectively.

The synthesis of alcohol **6** started with the known allyl 4-deoxy-2,3-*O*-isopropylidene-L-rhamnopyranoside (Scheme 1). The removal of the allyl group at the anomeric oxygen was effected first by isomerization of the double bond with potassium *t*-butoxide-DMSO followed by treatment with  $\text{Hg}^{2+}$  salts to give delallylated product **9**. One carbon homologation of **9** with  $\text{Ph}_3\text{C}=\text{CH}_2$  completed the synthesis of the alcohol **6**.

Synthesis of another key intermediate (Scheme 1) **7** was initiated from the known di-*O*-isopropylidene-D-mannitol derivative. The controlled hydrolysis of C2-symmetric derivative was efficiently dealt by employing PPTS in methanol. In order to derive the olefin from the resulting diol, it was first mesylated and then the resulting dimesylate compound was treated with NaI, Zn, in DMF at 150 °C to yield the olefin **12**. The acid catalyzed hydrolysis of that **12** with PPTS in methanol followed by sodium periodate cleavage and oxidation of the resulting aldehyde with sodium chlorite afforded acid **7**.

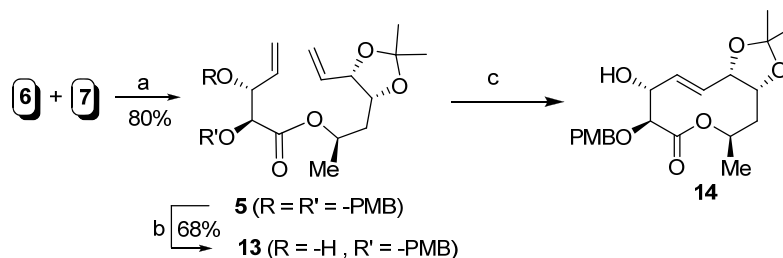
### Scheme 1: Synthesis of coupling partners **6** & **7**



*Reagents and conditions:* a) *i.* KO<sup>t</sup>Bu, DMSO, 100 °C, 1 h; *ii.* HgO, HgCl<sub>2</sub>, Acetone-H<sub>2</sub>O rt, 8 h, 64%; b) Ph<sub>3</sub>=CH<sub>2</sub>, THF, DMSO, rt, 24 h, 64%; c) PPTS, MeOH, 0 °C- rt, 12 h, 66%; d) *i.* MsCl, Et<sub>3</sub>N, 0 °C-rt, 1 h; *ii.* NaI, Zn, DMF, 150 °C, 2 h, 70%; e) PPTS, MeOH, rt, 36 h, 79%; f) *i.* NaIO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; *ii.* NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>, rt, 1 h, 73%.

The Mitsunobu reaction between alcohol **6** and acid **7** proceeded smoothly to afford the diene-ester **5** (Scheme 2). However, attempts for ring closure with compound **5** under various reaction conditions resulted in failures. Attributing this failure to the crowding around the reaction centers because of protecting groups, the deprotection of -OPMB ethers was attempted. Treatment of **5** with DDQ at pH 7 under buffer conditions, afforded **13**. The RCM reaction of **13** was successfully conducted at the reflux temperature of benzene using Grubbs' 2<sup>nd</sup> generation catalyst.

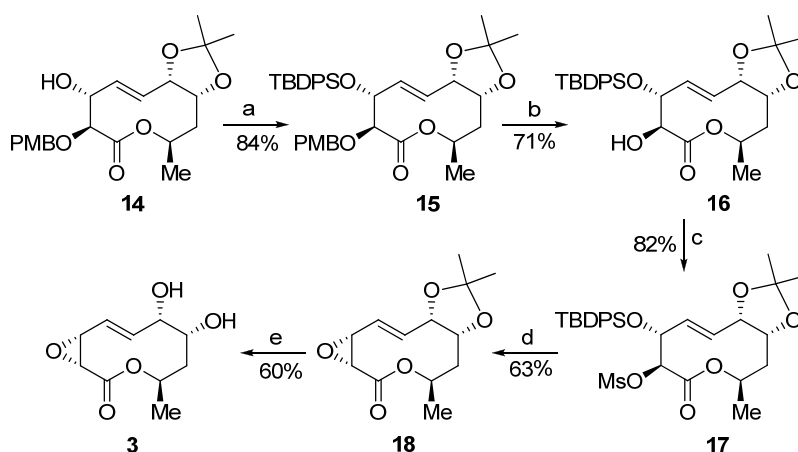
### Scheme 2: Coupling, PMB deprotection and RCM



*Reagent and conditions:* a) PPh<sub>3</sub>, DEAD, THF, 0 °C-rt, 3 h; b) DDQ, CH<sub>2</sub>Cl<sub>2</sub>, buffer, 0 °C-rt, 4 h; c) Grubbs' 2<sup>nd</sup> gen catalyst, benzene, reflux, 6 h.

To set the oxirane ring formation as required in isomer **3**, the free allylic-OH in **14** was protected as its TBDPS ether using *tert*-butyldiphenylsilyl chloride and imidazole. Then the remaining PMB was deprotected using DDQ in DCM-water solvent mixture and transformed to the corresponding mesylate **17**. TBDPS ether was cleaved using TBAF solution in THF. Under this highly basic condition oxirane ring was formed. Finally acetonide was cleaved using TFA in dry DCM condition to afford the one of multiplolide A isomer **3**. As the spectral and analytical data of **3** was not in agreement with the natural multiplolide A, we concluded that isomer **4** represents the absolute structure of multiplolide A and this has been confirmed by its synthesis from our group.

**Scheme 3: Total synthesis of Multiplolide A isomer 3**



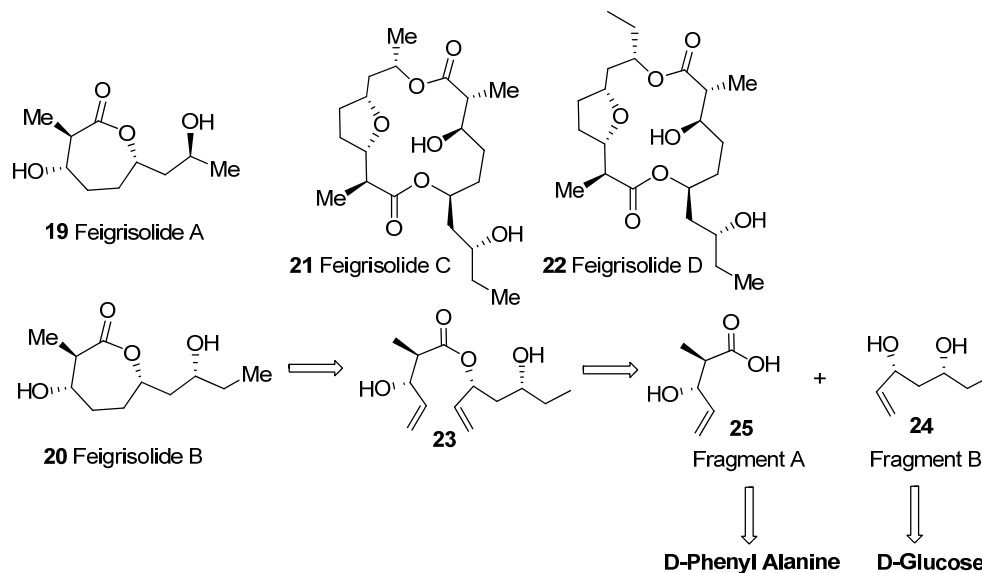
*Reagents and conditions:* a) TBDPS-Cl, Imidazole, DCM, reflux, 10 h, 84%; b) DDQ, CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (18:1), rt, 3 h, 71%; c) MsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt, 2 h, 82%; d) 1 M TBAF in THF, THF, 0 °C-rt, 8 h, 63%; e) TFA, DCM, 0 °C-rt, 4 h, 60%.

**Chapter 2: Section 1: Towards the total synthesis of feigrisolide B**

Recently Thiericke and co-workers isolated feigrisolides A-D (**19** – **22**, Figure 3) from the fermentation brothes *Streptomyces Griseus* (Strain GT 051922) and showed that these compounds possess strong antibacterial, as well as medium cytotoxic and antiviral activities. After extensive structural investigations, the constitution and relative configuration of Feigrisolides A and B was determined as indicated in figure 3. In light of their promising biological activity we initiated our total synthesis program choosing feigrisolide B as the appropriate target and RCM as the key reaction. As outlined in the figure 3, considering RCM as the key reaction, the

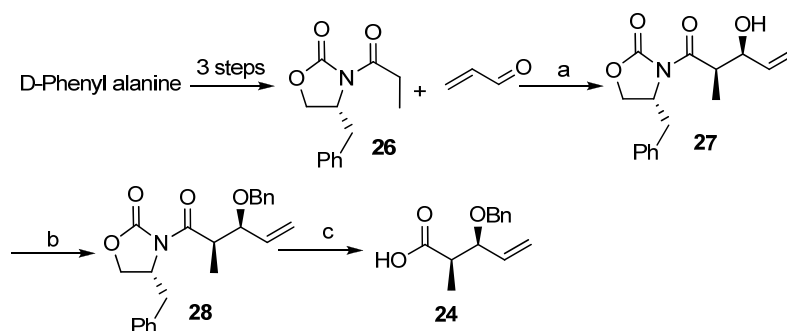
retrosynthetic disconnection has led to identify two key coupling fragments **24** and **25** and are planned to synthesize from D-glucose and D-phenyl alanine respectively.

**Figure 3:** Structures of Feigrisolides A – D (**19** – **22**) and retrosynthetic strategy



Synthesis of fragment A was started with the preparation of D-Phenyl alanine derived Evans' oxazolidinone. Reduction of D-phenyl alanine with sodium borohydride/iodine followed by treatment of resulting amino alcohol with dimethyl carbonate gave the oxazolidinone. This was treated with propionic anhydride in presence of triethyl amine and lithium chloride to obtain the key intermediate **26**.

**Scheme 4:** Synthesis of fragment A

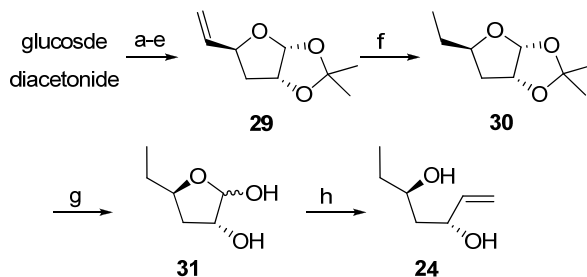


*Reagents and conditions:* a)  $\text{TiCl}_4$ ,  $i\text{Pr}_2\text{EtN}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h, 73%; b)  $\text{BnBr}$ ,  $\text{Ag}_2\text{O}$ ,  $\text{PhCH}_3$ , rt, 10 h, 64%; c)  $\text{LiOH}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{THF}-\text{H}_2\text{O}(4:1)$ , rt, 4 h, 58%.

Evans' aldolization of **26** with acrolein was carried out with  $\text{TiCl}_4$  and resulting aldol product **27** was benzylated by using silver oxide and benzyl bromide to

afford the benzyl ether **28**. Chiral auxiliary was removed by using LiOH, hydrogen peroxide in THF-H<sub>2</sub>O to furnish fragment A.

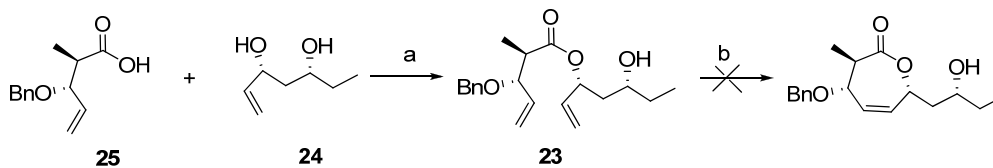
**Scheme 5:** Synthesis of fragment B



*Reagents and conditions:* a) NaH, CS<sub>2</sub>, MeI, 0 °C-rt, 1 h, 89%; b) TBTH, AIBN, PhCH<sub>3</sub>, reflux, 6 h, 68%; c) 0.8% H<sub>2</sub>SO<sub>4</sub>, MeOH, rt, 12 h, 60%; d) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 0.5 h, 90%; e) NaI, Zn, DMF, 150 °C, 2 h, 72%; f) 10% Pd-C, H<sub>2</sub>, EtOAc, rt, 8 h, 67%; g) 30% AcOH, H<sub>2</sub>SO<sub>4</sub>, 60 °C, 4 h, 55%; h) Ph<sub>3</sub>P=CH<sub>2</sub>, THF, rt, 6 h, 65%.

Synthesis of fragment B started with glucose diacetone acetonide (GDA). Deoxygenation followed by selective 5,6-acetonide deprotection, dimesylation and double elimination gave the olefin intermediate which on hydrogenation followed by hydrolysis and one carbon Wittig homologation provided the required coupling partner B.

**Scheme 6:** Coupling of two fragments and attempted RCM



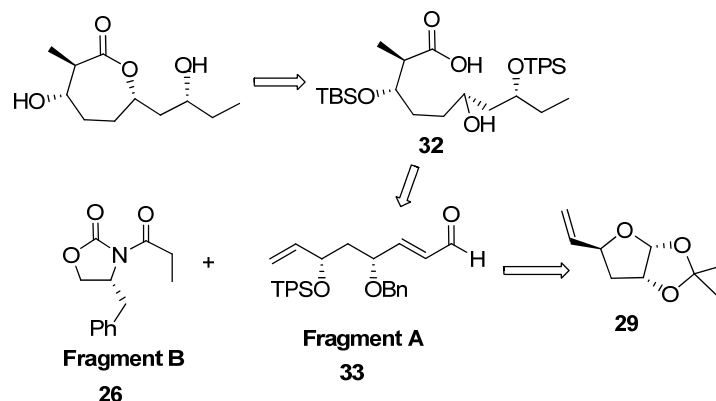
*Reagents and conditions:* a) DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 12 h, 60%; b) *i.* CH<sub>2</sub>Cl<sub>2</sub>, rt-reflux, *ii.* C<sub>6</sub>H<sub>6</sub>, rt-reflux, *iii.* PhCH<sub>3</sub>, rt-reflux, Grubbs' 1<sup>st</sup> or 2<sup>nd</sup> gen. Catalyst.

The coupling of two fragments **24** and **25** was facile by using DCC and the key RCM reaction was attempted with the available 1<sup>st</sup> and 2<sup>nd</sup> generation Grubbs' catalysts in different solvents and at different temperatures. However, in all the cases the reaction led to either complex mixture or the recovery of starting diene. As the key RCM reaction was found to be unsuccessful, we have revised our strategy by identifying the macrolactonization as the key reaction. The revised strategy is linear in



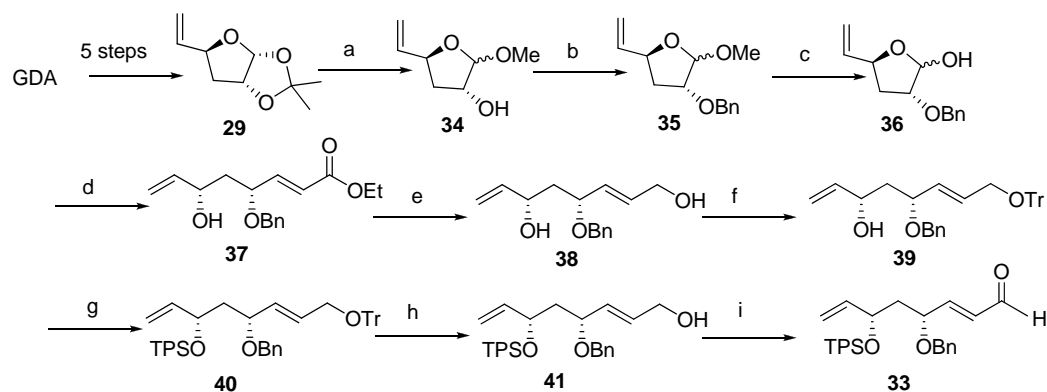
nature and employs Evans' aldol reaction of the advanced aldehyde **33** to address the induction of the key stereogenic centers of lactone ring.

**Figure 4:** Revised retrosynthetic strategy for Feigrisolide B



As outlined in Scheme 7, synthesis of the key aldehyde **33** was started with the methanolysis of known acetonide **29** followed by benzylation to afford the methyl furanosides **34**. Hydrolysis of the anomeric methyl ether followed two carbon Wittig homologation gave the diene ester **37** exclusive as *E*- isomer. Treatment of **37** with DIBAL-H followed by selective 1°-OH tritylation and protection of 2°-OH as its TBDPS ether gave **40**. Compound **40** was advanced to the key aldehyde intermediate **33** by a sequence of trityl deprotection and controlled oxidation reactions.

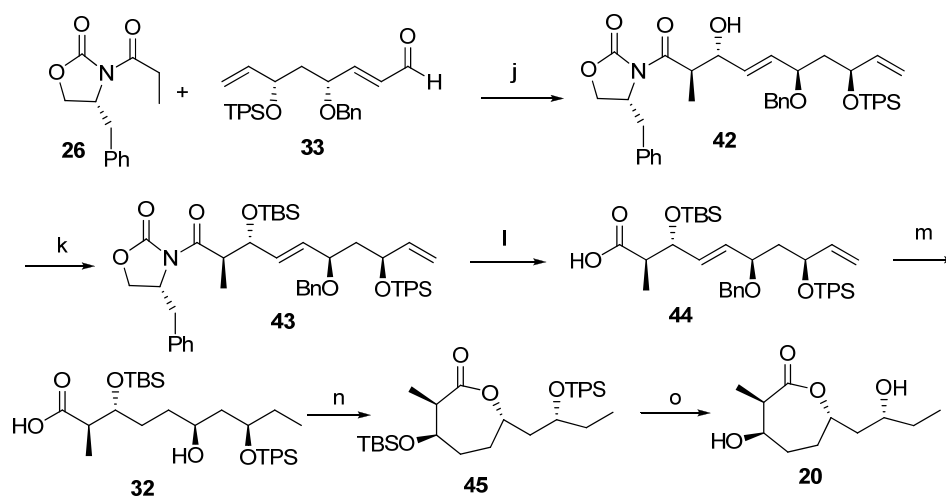
**Scheme 7:** Synthesis of fragment **33**



*Reagents and conditions:* a) H<sub>2</sub>SO<sub>4</sub>, MeOH, 60 °C, 12 h, 60%; b) BnBr, NaH, THF, rt, 6 h, 78%; c) aq. AcOH, H<sub>2</sub>SO<sub>4</sub>, 60 °C, 12 h, 55%; d) Ph<sub>3</sub>P=CHCO<sub>2</sub>Et, C<sub>6</sub>H<sub>6</sub>, 80 °C, 1 h, 74%; e) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 68%; f) TrCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h, 72%; g) TBDPS-Cl, Imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h, 87%; h) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 65%; i) PDC, Ac<sub>2</sub>O, 4ÅMS, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt, 4 h, 60%.

After having an easy access to the aldehyde **33**, it was subjected for the key Evans' aldol reaction by employing oxazolidinone **26** and  $\text{TiCl}_4$  as Lewis acid. The resulting aldol **42** [the unwanted *anti*-configuration of the aldol product **42** was confirmed at the end of the synthesis] was converted to the TBS ether **43** and the oxazolidinone auxiliary was removed by employing  $\text{LiOH}$  and  $\text{H}_2\text{O}_2$  to afford the acid **44**. Hydrogenolysis of acid **44** followed by lactonization using EDCI agent gave the protected feigrisolide B **45**. The global deprotection of **45** completed the synthesis of putative structure of 3-*epi* feigrisolide B.

**Scheme 8:** Total synthesis of putative structure of Feigrisolide B

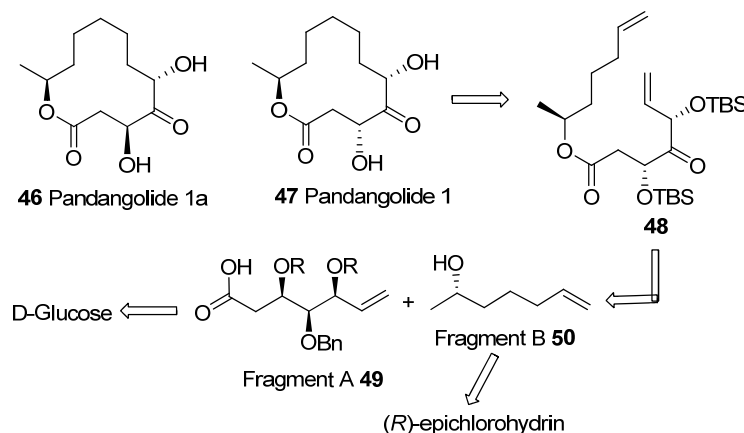


*Reagents and conditions:* j)  $\text{TiCl}_4$ ,  $^i\text{Pr}_2\text{EtN}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 0.5 h, 63%; k) TBDMS-OTf, 2,6-Lutidine,  $\text{CH}_2\text{Cl}_2$ , rt, 0.5 h, 80%; l)  $\text{LiOH}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{THF-H}_2\text{O}$ ,  $0\text{ }^\circ\text{C}$ -rt, 4 h, 55%; m)  $\text{Pd}(\text{OH})_2$ ,  $\text{EtOAc}$ , rt, 6 h, 62%; n) EDCI, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 12 h, 67%; o) HF-Pyridine complex, Pyridine, THF, 48 h, 45%.

## Chapter 2: Section 2: Towards the Total Synthesis of Pandangolide 1

A new hexaketide lactone, pandangolide 1a (**46**) and known pandangolide 1 (**47**) were isolated recently from the ethyl acetate crude extract of a *Cladosporium* sp. that was isolated from the Red Sea sponge *Niphates rowi*.

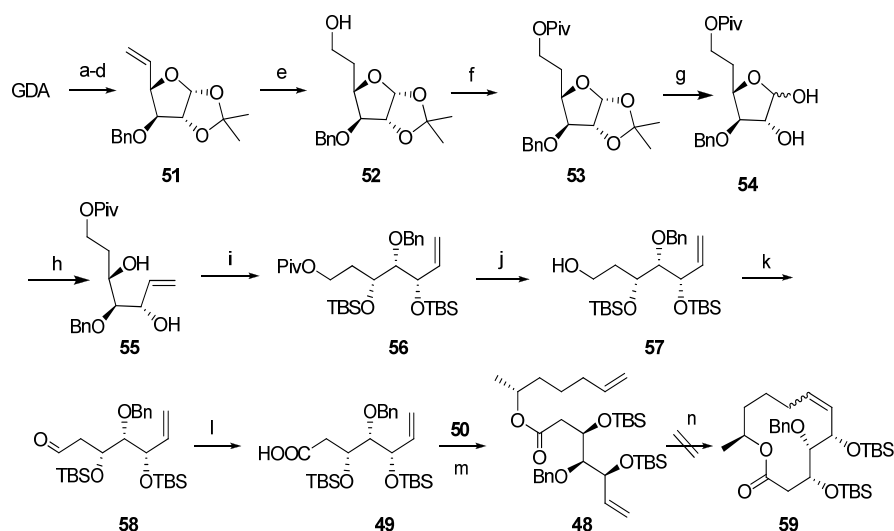
**Figure 5:** Structures of Pandangolides 1 & 1a, and the intended RCM approach



The absolute configuration of these compounds is proposed on the basis of chemical, spectroscopic, and biosynthetic arguments. In continuation of our constant interest in the area of total synthesis of macrolactones, pandangolide 1 was selected as a particular target. As outlined in Figure employing RCM as the key reaction, the olefins **49** and **50** were identified as the key fragments.

Synthesis of fragment A was started with the regioselective hydroboration/oxidation of the known olefin **51**. The resulting alcohol **52** was protected as its pivaloyl ester **53** and subjected for the acetonide hydrolysis to afford lactol **54**. One carbon Wittig homologation of **54** followed by TBS protection of resulting diol **55** gave **56**. Deprotection of pivaloyl ester in **56** was carried out using LiOH in ethanol-water. Subsequent two stage oxidation of alcohol **57** via aldehyde **58** afforded the acid fragment **49** and this was coupled with the alcohol **50** (prepared according to the literature procedure from *R*-epichlorohydrin) under Yamaguchi conditions. Once again, the RCM of the diene-ester **48** to form 12-membered lactone **59** employing both Grubbs' 1<sup>st</sup> gen and 2<sup>nd</sup> gen. catalysts in different solvents and at different temperatures was found to be futile.

### Scheme 8: Attempted synthesis of Pandangolide 1



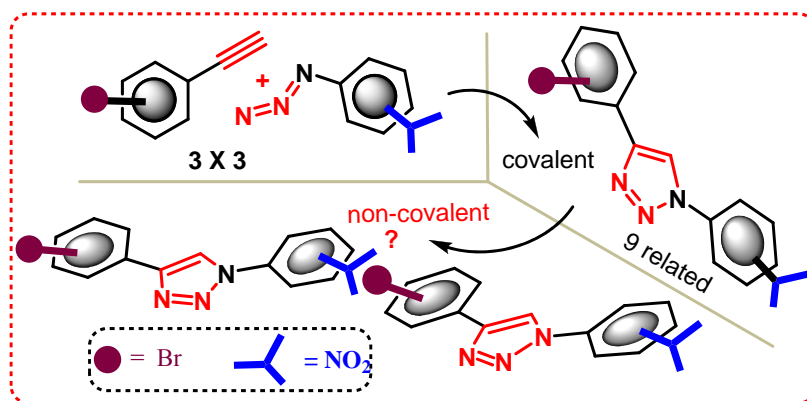
*Reagents and condition:* a) BnBr, NaH, THF, 0 °C, 1 h, 70%; b) 0.8% H<sub>2</sub>SO<sub>4</sub>, MeOH, rt, 12 h, 60% c) MsCl, Et<sub>3</sub>N, 0 °C, 0.5 h, 75%; d) Zn, NaI, DMF, 150 °C, 2 h, 65% e) BH<sub>3</sub>.DMS, THF, 0 °C, 3 h then 30% NaOH, H<sub>2</sub>O<sub>2</sub>, 60%; f) Piv-Cl, Et<sub>3</sub>N, DCM, 0 °C-rt, 4 h, 68%; g) 60% AcOH, H<sub>2</sub>SO<sub>4</sub>, 60 °C, 7 h, 55%; h) Ph<sub>3</sub>P=CH<sub>2</sub>, THF, 0 °C- rt, 2 h, 58%; i) TBS-Cl, Imidazole, DMF, rt, 12 h, 84%; j) LiOH, EtOH-H<sub>2</sub>O, 40 °C, 2h, 65% (with respect to starting material recovered); k) IBX, DMSO, 6 h, rt, 65%; l) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, DMSO-H<sub>2</sub>O, rt, 6 h, 55%; m) Yamaguchi reagent, 7-C chiral alcohol, Et<sub>3</sub>N, 0 °C-rt, 12 h, 67%; n) Grubbs' 1<sup>st</sup> Gen & 2<sup>nd</sup> Gen catalyst, DCM, PhCH<sub>3</sub>, reflux, 6 h.

### Chapter 3: Exploration of Click Reaction in Crystal Engineering

Unlike in organic synthesis, the connectivity in supramolecular synthesis extends over a larger range and encompasses a wide variety of intermolecular weak interactions. Considering its similarity in action to *synthon*, the phrase ‘supramolecular synthon’ has been coined by Desiraju to describe a set of noncovalent interactions that form and modulate recognition patterns in the solid state. Understanding how these supramolecular synthons operate/exist across a set of related molecules that yield a set of related crystal structures is a critical exercise to ensure three-dimensional structure control in molecular design for crystal engineering. However, reports documenting such a structural investigation of a group of isomers are very few because of the complexity involved in synthesizing the systems with architectural control and flexibility in the incorporation of functional groups and a deliberate suspicion about the crystallinity of the all isomers. In this context, developing simple and efficient protocols for generation of isomeric compound libraries (devoid of polar functional units) with sufficient flexibility in placing

complementary functional groups will be instrumental for crystal engineers to understand these weak non-covalent interactions, the topological constraints for intermolecular connectivity and to examine the predictability of corresponding weak synthons.

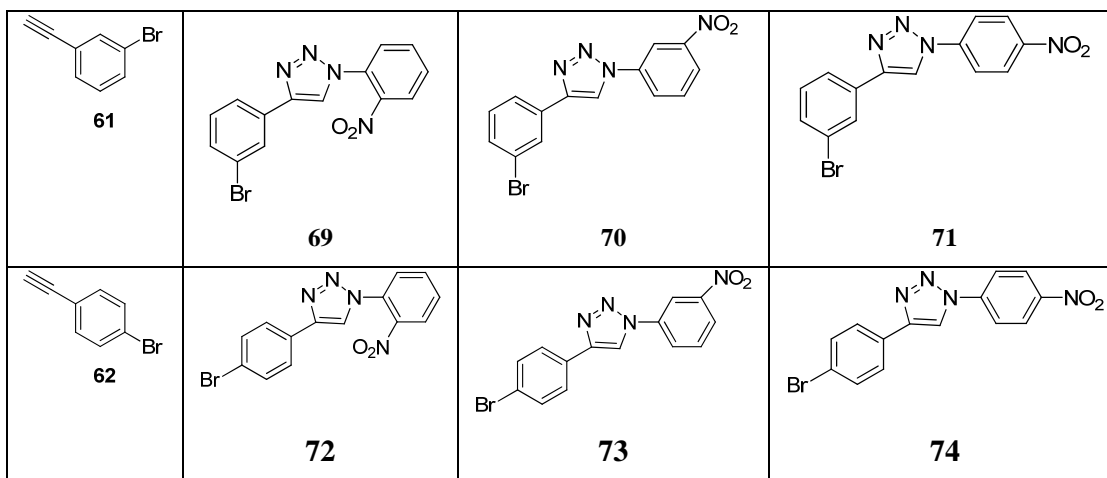
**Figure 6:** Click chemistry approach for synthesis of isomers for examining the predictability of a projected synthon



Herein, we document a simple protocol employing azide-alkyne “Click Reaction” for the synthesis of a collection of isomeric compounds (**66 – 74**) with modular positioning of Br and NO<sub>2</sub> on a flexible tricyclic template and examination of the occurrence of bifurcated Br...NO<sub>2</sub> synthon with respect to their relative disposition. Apart from the projected Br...NO<sub>2</sub> and competing Br...Br interactions, absence of any other stronger interactions in this system provided the necessary criteria for existence of weak interactions like C–H...O, C–H...N, C–H...Br and their influence on the overall packing of the crystal.

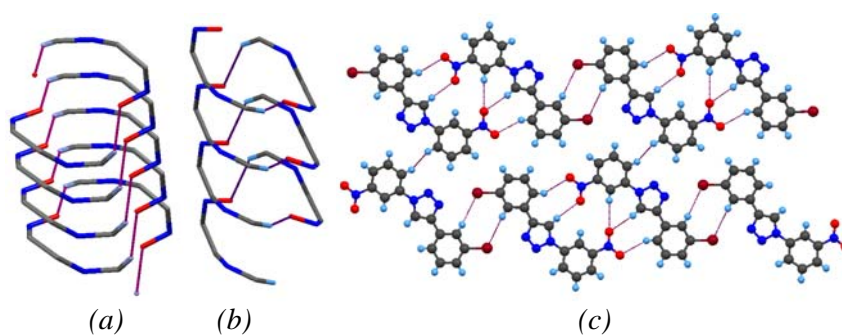
**Table 1:** Huisgen [3+2] cycloaddition reaction between alkynes **60 – 62** and azide precursors **63 – 65**, product distribution and compound identification number

	<p><b>63</b></p>	<p><b>64</b></p>	<p><b>65</b></p>
<p><b>60</b></p>	<p><b>66</b></p>	<p><b>67</b></p>	<p><b>68</b></p>



All of the above **9** compounds were isolated as crystalline solids and were characterized with the single crystal X-ray structural studies (Table 1). It was quite interesting to notice that none of the isomers have displayed the bifurcated Br...O<sub>2</sub>N synthon in their solid structures, though the experimental and *ab initio* calculations reveal that this three-center interactions in the bromine-containing systems are relatively stronger and can be regarded as a ‘discriminator synthon’ even in the presence of strong N–H/O hydrogen bonds. Triazoles bearing 2-nitrophenyl ring (**66** and **67**) formed helical assembly of molecules through C–H...O interactions, and the self-complimentary patterns noticed in the crystal structures of 3-nitrophenyl substituted triazole derivatives.

**Figure 7:** C–H...O mediated helical assembly in compounds a) **63** b) **64** and c) self complimentary patterns noticed in compound **70**



# INTRODUCTION



## ***INTRODUCTION***

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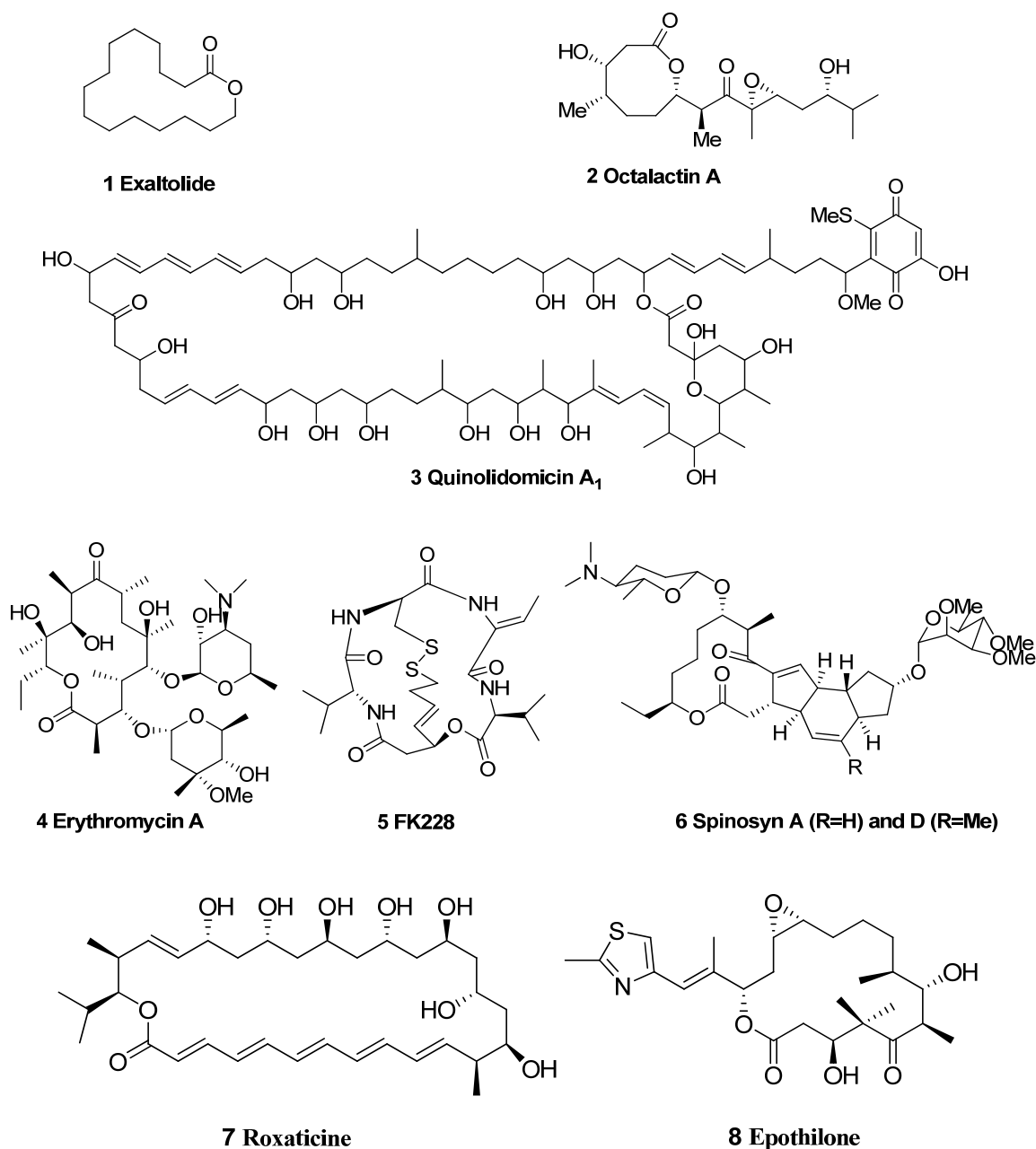
Natural products remain an important source of lead compounds for drug development.<sup>1</sup> However, while these compounds often exhibit great potency when tested against specific targets, other properties of these compounds, such as solubility, bioavailability, exposure, stability, and metabolism can require improvement. The application of synthetic chemistry to modify natural product drug leads has long been used to generate compounds with improved pharmacological properties. With the origin and development of modern science our understanding about the constitution of any given material has improved immensely, natural products not being an exception. With the advancements in the area of natural product isolation and characterization, it has become possible to isolate and identify the active compound responsible for the observed biological activity. As they are contained in very small quantities, often it is not practicable to isolate these natural products from their original resources for the commercial purposes. The solution for this problem is to synthesize them in laboratory by means of chemical synthesis. Accurate knowledge of the structure of the natural product is a prerequisite for its synthesis. It is common for natural product scientists to claim that natural products form the basis for many of the drugs currently in commercial use or in development, little comprehensive data have been presented to support such claims since Farnsworth and Morris reported their analysis of National Prescription Audit data for the 15-year period 1959-1973.<sup>2</sup> The role of natural products from all sources in drug discovery has been reviewed recently.<sup>3</sup> Further evidence of the importance of natural products is provided by the fact that close to half of the best selling pharmaceuticals in 1991 were either natural products or their derivatives.<sup>4</sup> Over the past 10 years, there has been a resurgence of interest in the investigation of natural materials as a source of potential, new chemotherapeutic agents.

Marine organisms, particularly sponge invertebrates and associated bacteria, are enormously rich sources of structurally diverse secondary metabolites with unique molecular architectures.<sup>5</sup> These marine natural products often possess unusual and sometimes unexpected biological activities, making them valuable molecular probes for the investigation of biochemical pathways. Among these fascinating and eye-catching



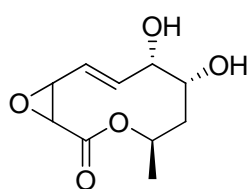
structures, a prominent class is the marine macrolides, which are highly oxygenated and stereochemically elaborated polyketides having a macrocyclic lactone as a conformational constraint.<sup>6</sup> Many marine macrolides demonstrate potent cell growth antiproliferative properties and offer considerable promise as lead structures for the development of new anti-cancer chemotherapeutic agents, provided the supply issue can be resolved. Ever since the first isolation of Exaltolide **1** in 1927 by Kerschbaum,<sup>7</sup> interest in macrocyclic lactones, defined as lactones with more than 8 atoms in the ring, has been increasing. Indeed, natural macrocyclic lactones present a large spectrum of interesting properties from perfumery, to phytotoxicity, to pheromone or insecticide activity, to medicinal (antibiotic, cytotoxic, antiangiogenesis) properties and a wide range of structures from 8-membered ones such as octalactins<sup>8</sup> **2** to the 60-membered quinolidomicins **3**. From their first isolation in the 50s, macrolide antibiotics, such as erythromycin **4**,<sup>9</sup> were widely used to treat bacterial infections, and because of their safety and efficacy, they are still the preferred therapeutic agents for treatment of respiratory infections. Another important class of macrolactones with a wide range of biological activities is the cyclodepsipeptides<sup>10</sup> such as, for example, FK228 (**5**), which is currently in phase II clinical trials as an anticancer drug and which acts as a prodrug that undergoes disulfide reduction within the cell to release a zinc-binding thiol. The biopesticide Spinosad, a mixture of Spinosyn A and D (**6**), is currently marketed for use against a wide variety of insects. Of the more than 200 polyene macrolactones known, some, such as roxaticine **7**, is currently used in the treatment of systemic fungal infections.<sup>11</sup> Epothilones **8**, with a mode of action similar to that of taxol and the potential to overcome known mechanisms of drug resistance, are considered to be promising anticancer drugs.<sup>12</sup> Even though many other efficient macrocyclization methods such as the intramolecular cross-coupling, Noxaki-Hiyama-Kishi, and HWE methods and lactonization of seco acids have been developed over the years, but the bond formation through ring-closing metathesis (RCM) method has found to be the most dramatic invention for the preparation of macrolactones. This approach appears to be one of the more frequently used approaches to obtain macrocyclic lactones in recent years.

Figure 1

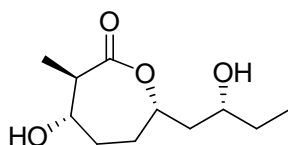


As part of long standing program in our group, three newly isolated natural products having medium sized lactones namely, multiplolide A, feigrisolide B and pandangolide 1 were selected as the targets for our total synthesis program. The basic premise of our synthesis is to use RCM as the key reaction and adopting a chiral pool approach for the key intermediates.

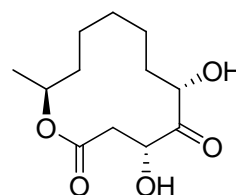
Figure 2



9 Multiplolide A



10 Feigrisolide B



11 Pandangolide 1

Considering the common feature of our intended synthesis of **9** – **11**, *i.e.* RCM for key macrolactone construction, some of the recent developments in the area of RCM based macrolactone synthesis will be discussed here in brief.

### **A brief overview of factors affecting the stereochemical outcome of RCM in case of medium size rings:**

Ever since the birth of the art of organic synthesis, as marked by Wöhler's synthesis of urea in 1828, progress in this field has, to a large degree, been dependent on our ability to construct carbon frameworks through carbon–carbon bond forming reactions. The Grignard,<sup>13</sup> Diels–Alder,<sup>14</sup> and Wittig reactions<sup>15</sup> are three of the most prominent such processes that played decisive roles in shaping the science of chemical synthesis as we know it today. During the last quarter of the previous century, two more such reactions emerged as rivals to the aforementioned carbon–carbon bond forming processes: the palladium-catalyzed cross-coupling reactions and those collectively known as metathesis reactions. As the most stringent test, total synthesis often serves as a measure of the power of a given reaction. Surveys of relevant applications of enabling reactions are, therefore, of importance in that they not only help to underscore the scope and generality of such processes in chemical synthesis, but they also serve to place into perspective that particular reaction within the field, and to inspire future improvements and new applications. The fact that the Nobel Prize for the year 2005 was awarded to Grubbs', Chauvin and Schrock for their contributions in the area of metathesis, explains by itself the utility of the transformation and hence its wide applicability towards the synthesis of materials which are used in different walks of life. The awesome impact of this transformation in the area of total synthesis of natural products is clearly evident from the literature. This

transformation offers various merits such as tolerance to various functional and protecting groups, easy and non-hazardous experimental procedures and reproducibility, which are of the particular interest to synthetic organic chemist. The development of new catalysts, which make previously impossible transformations possible and in some cases complement each other in stereochemical outcome, has made this tool even more effective and attractive.

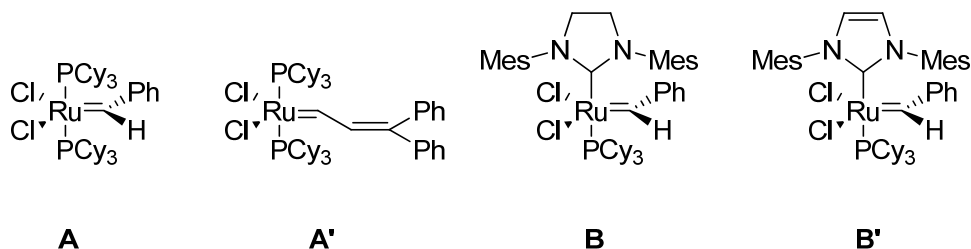
Coupled with all these advantages this transformation still possesses considerable challenges, still holds areas to be conquered and that are what fascinates synthetic chemists to employ it in their synthetic endeavors. One of such areas is synthesis of medium sized rings (6 – 12-membered) using RCM and the prediction of the stereochemical outcome for the same. Strain predisposes cycloalkenes of 6- to 12-membered ring atoms for the reverse process, that is, for ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP). Therefore, the number of successful applications of RCM to this series is still rather limited.

One approach to circumvent this problem is to incorporate control elements that force the cyclization precursors to adopt conformations suitable for ring closure.<sup>16</sup> Hydroxyl protecting groups are sometimes employed spanning hydroxyl groups in vicinity of the olefin with the anticipation that they should exert this function by aligning the olefinic side chains in a cyclization-friendly conformation. The extent of bias, if any, conferred by such a group on the stereochemistry of the newly formed double bond is much less understandable and cannot be predicted with certainty. In general, RCM reactions in the macrocyclic series tend to give mixtures of the (*E*) and (*Z*)-configured cyclic olefins, and a reliable and general method of controlling the geometry of the newly formed double bond has yet to be found.<sup>17,18</sup>

The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. It was thus in 1992 that Grubbs and Fu published two seminal papers<sup>19,20</sup> describing the application of ring-closing metathesis to the synthesis of simple five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst that had been first prepared by Schrock.<sup>21</sup> Progress in the development of the metathesis reaction has been directly correlated to improvements in the

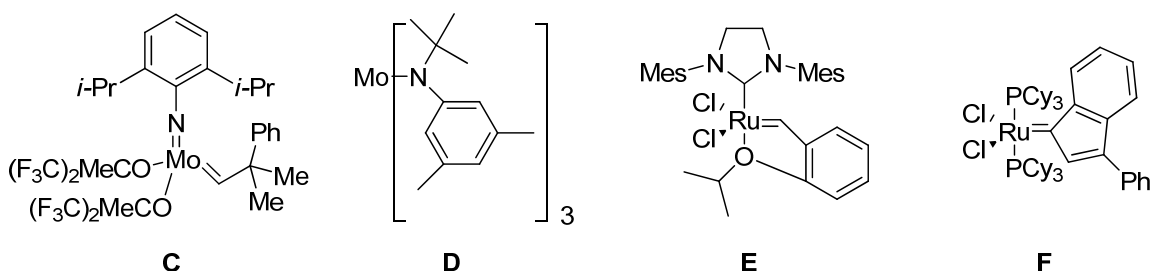
functional group compatibility and the reactivity of the catalysts. There are two main types of catalysts in use today. The first group contains ruthenium-complexes such as **A**, **A'**, **B**, and **B'** and related catalysts such as **E** and **F**, whereas the second group is comprised of molybdenum complexes such as **C** and **D**.

**Figure 3**



The catalysts **A**, **B**, and **C** are most commonly used for the RCM reactions. Those designated with a prime are closely related in structure to their parent complexes and show a similar reactivity pattern. The functional group tolerance of the ruthenium and the molybdenum catalysts can vary somewhat, but the Mo-based complexes suffer the potential disadvantage of being more air and moisture sensitive. The high selectivity and reactivity of **A-F** for carbon-carbon  $\sigma$ -bonds minimizes protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes.

**Figure 4**

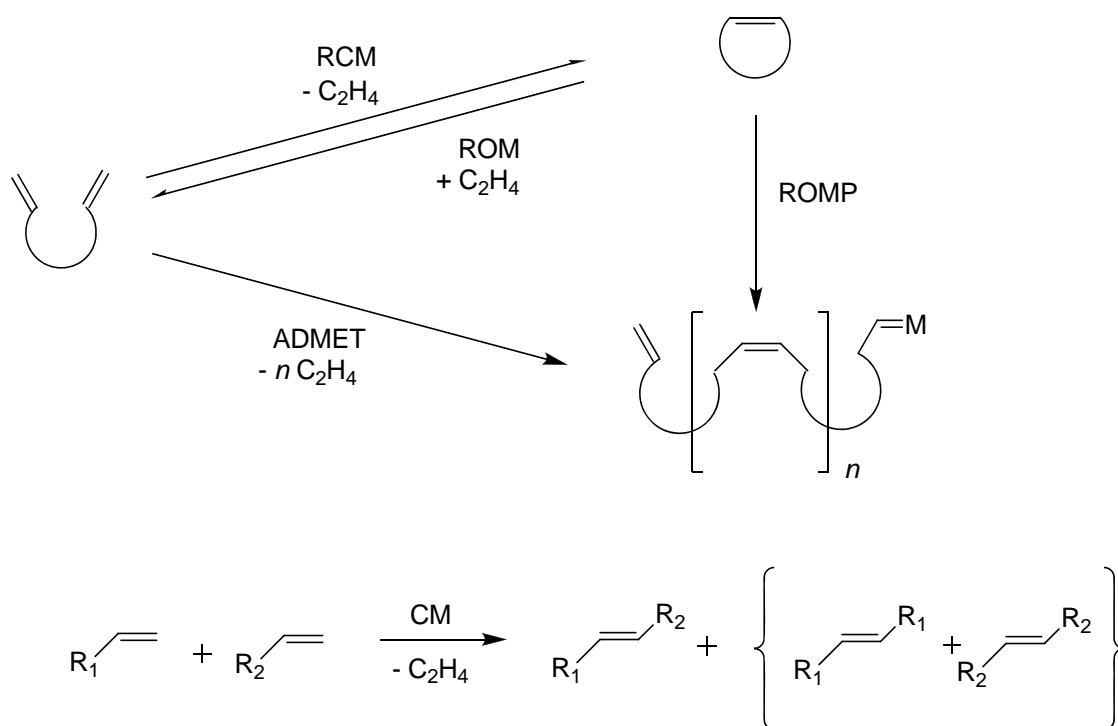


### General mechanism:

The generally accepted mechanism of RCM reactions (“Chauvin’s mechanism”)<sup>22</sup> consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkene, metal carbenes and metallacyclobutane intermediates. Since all individual steps of the catalytic cycle are reversible, an equilibrium mixture of olefins is obtained. Therefore it is

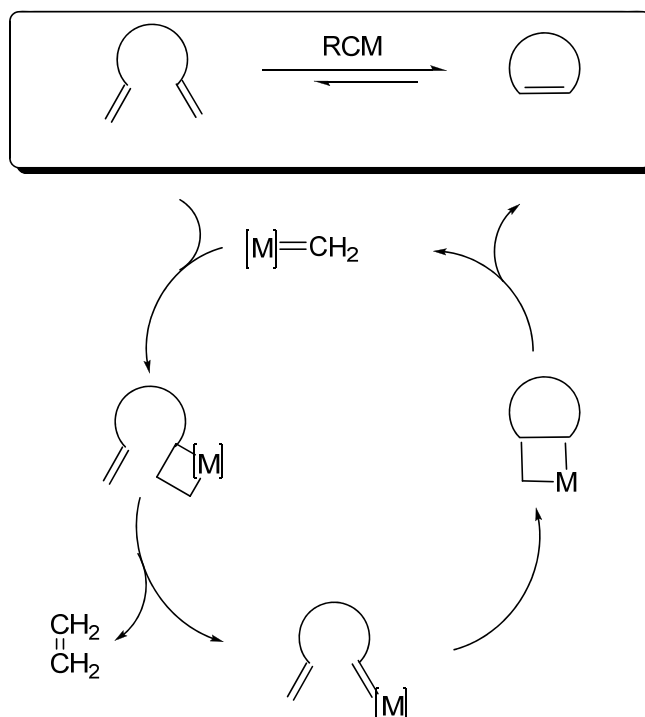
necessary to shift this equilibrium in one direction in order to make metathesis productive in preparative terms. The major ways to do this are depicted in scheme 1 and the mechanism of one such application, the ring closing metathesis (RCM) of a diene is shown in scheme 2. In this particular case, the forward process is entropically driven because the RCM cuts one substrate molecule into two products. If one of them is volatile (ethene, propene etc.) the desired cycloalkene will accumulate into the reaction mixture.

### Scheme 1



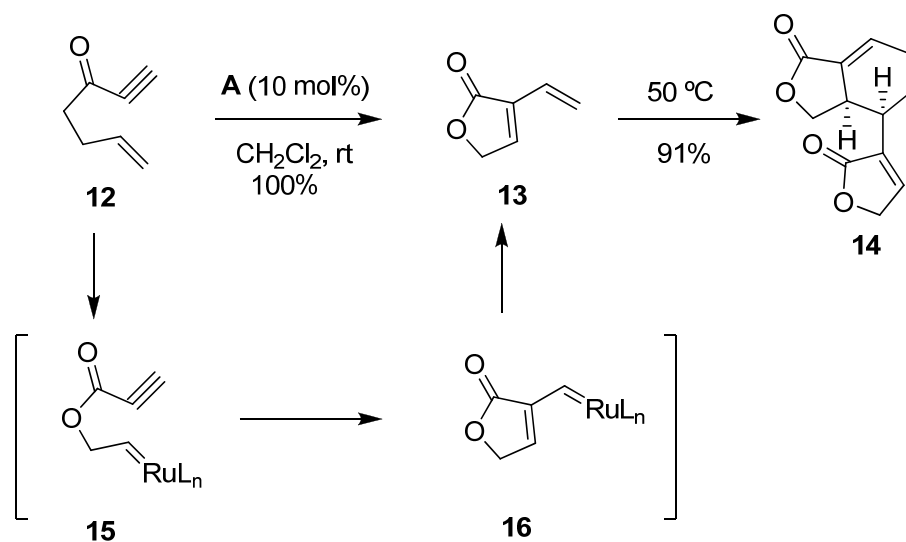
Another important factor for productive RCM is the sensitivity of the most metathesis catalysts to the substitution pattern of the olefin as this constitutes a kinetic obstacle for the retro-reaction. This argument, however, does not apply to strained cycloalkenes because the release of the ring strain provides the formidable driving force for ring opening metathesis (ROM) or ring opening metathesis polymerization (ROMP). Finally it should be mentioned that the intrinsic competition between RCM and acyclic diene metathesis polymerization (ADMET) can be controlled to some extent by adjusting the dilution of the reaction mixture and is also strongly influenced by preexisting conformational constraints in the substrate.

## Scheme 2

**Different sizes of lactones formed using RCM reaction:***Five and six membered lactones:*

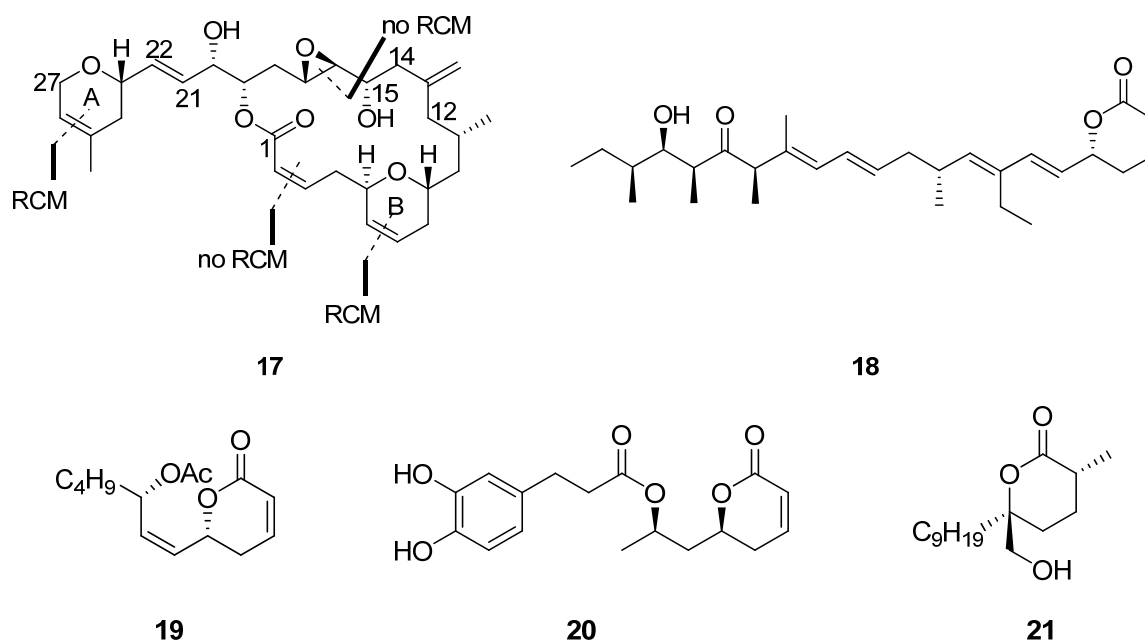
In contrast to the numerous applications of RCM to the synthesis of dihydrofurans and dihydropyrans, there are fewer reports of forming five- and six membered lactones via RCM reactions. Hoyer reported a nice example of a tandem enyne metathesis/Diels-Alder reaction as the key step in the synthesis of the butenolide natural product differolide **14**.<sup>23</sup> When the Grubbs' catalyst **A** was added slowly to allyl propynoate **12**, enyne metathesis ensued to generate the diene **13**, which underwent spontaneous dimerization via a [4 + 2]-cycloaddition to give differolide **14** (Scheme 3). The Diels-Alder reaction proceeded with complete stereoselectivity and 9:1 regioselectivity. Investigation of the enyne RCM reaction by <sup>1</sup>H NMR suggested that the benzylidene carbene **A** initially reacted with the double bond in **12** to give **15** that then underwent RCM to give **16**. This "ene-then-yne" mechanism was supported by the finding that a high substrate concentration was necessary to achieve high conversion rates.

Scheme 3

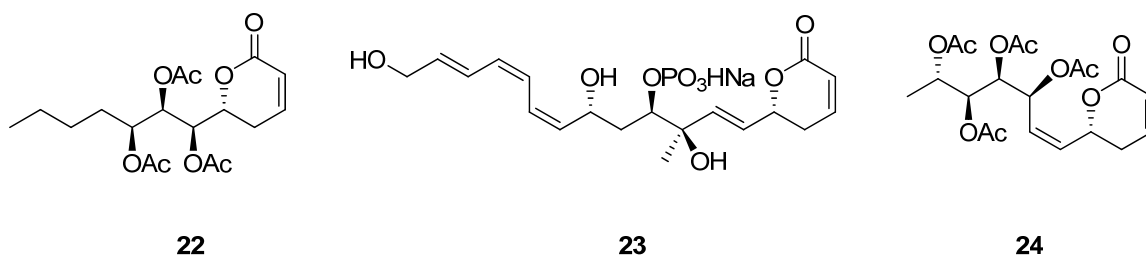


Six-membered lactone rings constitute a structural feature common to numerous biologically active natural products,<sup>24</sup> many of which exhibit antitumor properties. Members of this class of compounds that have been synthesized using RCM include laulimalide (**17**),<sup>25</sup> callystatin A (**18**),<sup>26</sup> umuravumbolide (**19**),<sup>27</sup> tarchonanthuslactone (**20**),<sup>28</sup> malyngolide (**21**),<sup>29</sup> boronolide (**22**),<sup>30</sup> fostriecin (**23**),<sup>31,32</sup> and spicigerolide (**24**).<sup>33</sup>

Figure 5

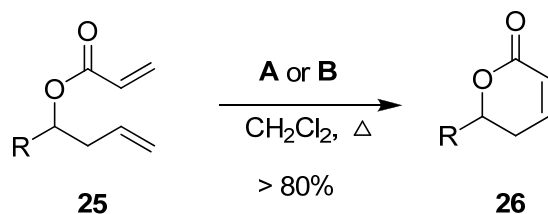






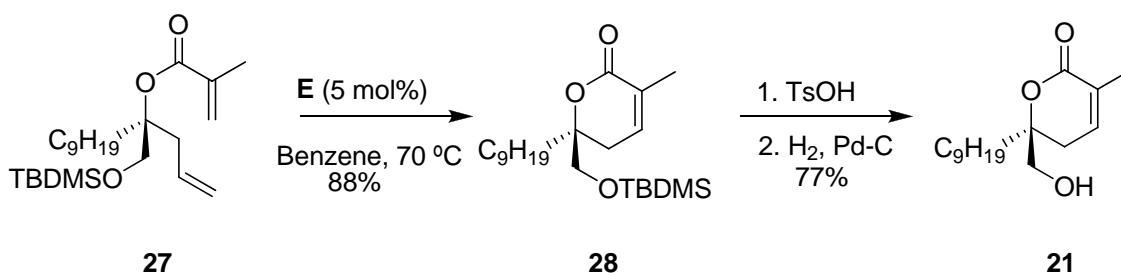
The strategies that were developed for preparing all of these natural products featured RCM reactions wherein allyl acrylates **25** were treated with either Grubbs' catalyst **A** or **B**, sometimes in the presence of a Lewis acid such as titanium tetrakisopropoxide, to yield **26** (Scheme 4). Hydroxyl groups have typically been protected during the RCM step, although this tactic was more frequently a consequence of the synthetic pathway rather than because of problems with the ruthenium catalysts.

#### Scheme 4



An illustrative example of using a RCM in the synthesis of valerolactone-derived natural products is found in Honda's synthesis of malyngolide **21** (Scheme 5).<sup>29</sup> The RCM substrate **27** was first prepared by a sequence that featured a Sharpless epoxidation to generate the first stereocenter. When **27** was treated with Grubbs' catalyst **A**, the lactone **28** was obtained in low yield. However, use of 5 mol% of the more reactive and recyclable Hoveyda catalyst **E**<sup>34</sup> afforded **28** in very good yield, and the synthesis of **21** was then completed in two steps.

## Scheme 5

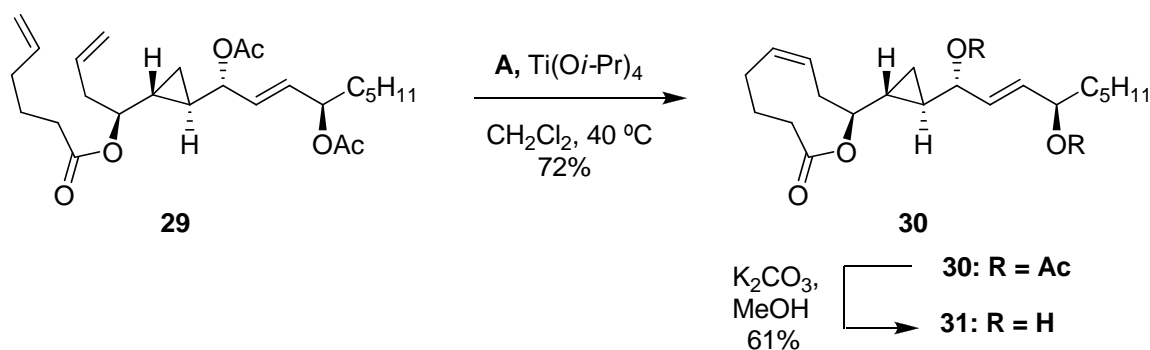


Although seven and eight-membered cyclic ethers can be constructed through RCM reaction but reports for the preparation of seven and eight-membered lactones using RCM method have hardly been found in the literature.

*Nine and ten membered lactones:*

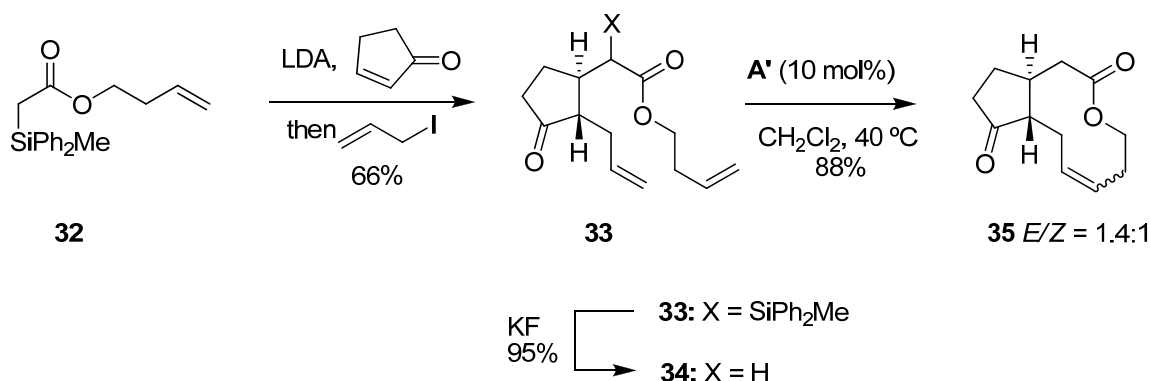
The formation of medium-sized lactones by RCM constitutes a considerable challenge, since the inherent ring strain predisposes cycloalkenes containing 8-11 atoms toward ring-opening metathesis or ring opening metathesis polymerization. A rare example of preparing the nine-membered lactone moiety of a natural product by RCM was reported by Takemoto in a synthesis of halicholactone **31** (Scheme 6). After considerable experimentation, it was discovered that **29** at high dilution underwent efficient RCM using the binary catalyst system of **A** and  $\text{Ti}(\text{O}i\text{-Pr})_4$ , which was first reported by Fürstner,<sup>35</sup> to give the desired *Z*-isomer **30** as the major product together with 11% of the corresponding dimer. The synthesis of **31** was completed by methanolysis of the two acetyl groups. When these hydroxy groups were protected as their corresponding SEM or MOM ethers, the yield of the RCM reaction was only 19%; 45% of the starting material was recovered as was 8% of a dimer.

## Scheme 6



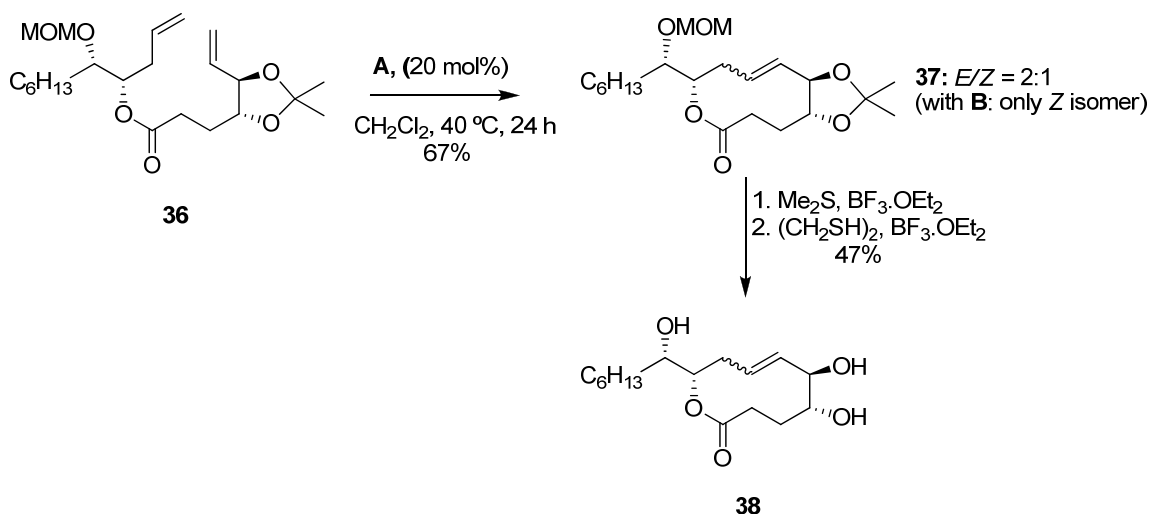
The first construction of a 10-membered lactone using a RCM was reported by Fürstner and Müller in 1997 in their synthesis of the jasmine ketolactone (*Z*)-**35**, a minor component of the essential oil of jasmine.<sup>35</sup> The first step in the diastereoselective synthesis of the RCM substrate **32** involved an efficient three-component reaction with the lithium enolate derived from **33**, cyclopentenone, and allyl iodide (Scheme 7). The methyl-diphenylsilyl group, which was required for the selective 1,4-addition of the enolate to cyclopentenone, was removed by reacting **33** with KF in aqueous methanol to give **34**. Heating a dilute solution of **34** in the presence of **A'** then furnished **35** as a mixture (1.4:1) of *E/Z* isomers in 88% combined yield. The natural product (*Z*)-**35** was separated by chromatography.

### Scheme 7



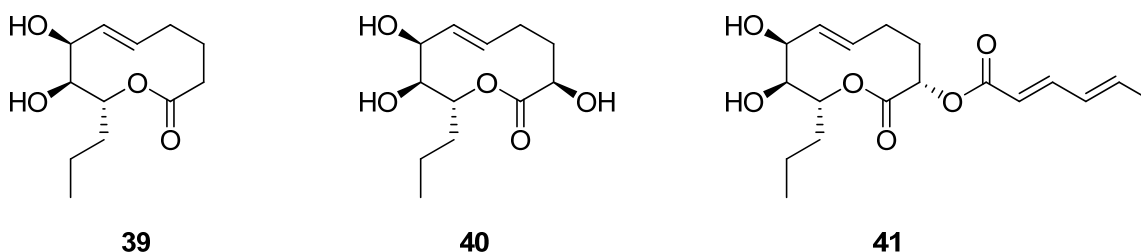
Marco recently reported a total synthesis of microcarpalide **38**, a naturally occurring nonenolide with cytotoxic and antimicrofilament activity,<sup>36</sup> by an approach that featured the RCM of **36**, which was prepared from (*S,S*)-tartaric acid and (*R*)-glycidol. When the RCM was catalyzed by **A**, a mixture (*E/Z* = 2:1) of macrocyclic lactones **37** was obtained from which the *E*-isomer was isolated by chromatography (Scheme 8). Alternatively, treatment of **36** with the 2<sup>nd</sup> generation catalyst **B** furnished almost exclusively the thermodynamically more stable (*Z*)-**37**. This observation is in agreement with those of Grubbs, who found that the *E/Z*-ratio in ring-closures using **B** is not kinetically controlled but is rather the result of an equilibration of the products (Scheme 8).<sup>37</sup> The synthesis of **38** was then completed by global deprotection of **37** in two steps.

## Scheme 8



Fürstner reported the first total syntheses of the phytotoxic agents herbarumin I **39** and II **40** and of the closely related pinolidoxine **41**.<sup>38</sup> All possible stereoisomers of **41** were prepared, and the spectra and analytical data of each were compared with those reported for the natural product, thereby unambiguously establishing the structure of this promising herbicidal agent and correcting a previous assignment. The nonenolides **39-41** each contain a carbon-carbon double bond, so RCM clearly emerged as an attractive reaction that could provide a convergent approach to these targets.

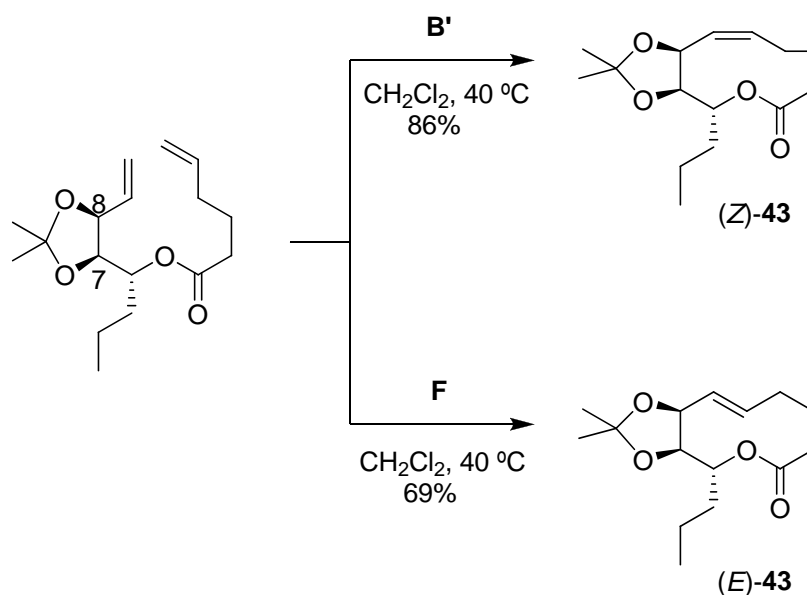
Figure 6



The salient features of using RCM in these syntheses are illustrated in the steps leading to herbarumin I **39** (Scheme 9). The diene **42** was prepared from D-ribose in a few steps by standard methods. The isopropylidene protecting group spanning the oxygen atoms at C-7 and C-8 was expected to stabilize a conformation of **42** that would be predisposed toward ring closure. Semiempirical calculations for **43** revealed that the Z-

isomer is about  $3.5 \text{ kcal mol}^{-1}$  more stable than the *E*-isomer. Hence, conducting the RCM of **42** and related dienes under conditions of thermodynamic control would be expected to be counterproductive for obtaining the *E*-alkenes found in **39-41**.

### Scheme 9

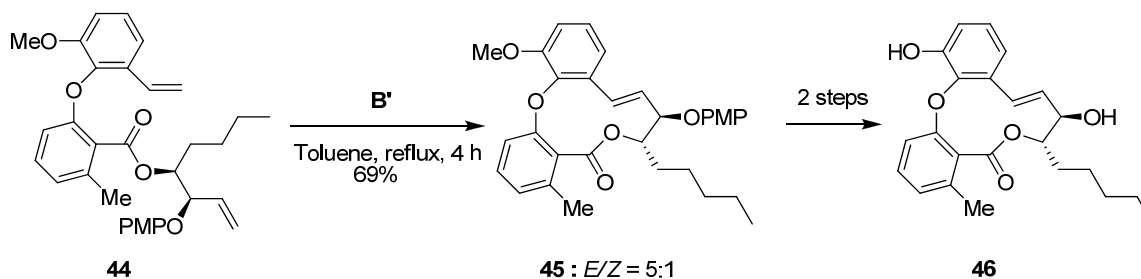


This prediction then suggested that RCM catalysts known to equilibrate the initial products should not be employed,<sup>37</sup> and it is gratifying that the results obtained using two different RCM catalysts were fully consistent with this hypothesis. Namely, cyclization of **42** with the 2<sup>nd</sup> generation catalyst **B'**, which was known to provide mixtures enriched with the thermodynamically favored product, led to the selective formation of (*Z*)-**43**. In contrast, exposure of the diene **42** to catalytic amounts of the ruthenium indenylidene complex **F**, which has properties very similar to those of **A**, afforded the desired lactone (*E*)-**43** as the major product, but the *Z*-isomer (9% yield) was also isolated. The *E/Z*-ratio in this reaction did not evolve over time, suggesting that product formation occurs under kinetic control. Hydrolysis of the acetal moiety in (*E*)-**43** then afforded natural **39**.

#### *Eleven and Twelve membered ring lactones:*

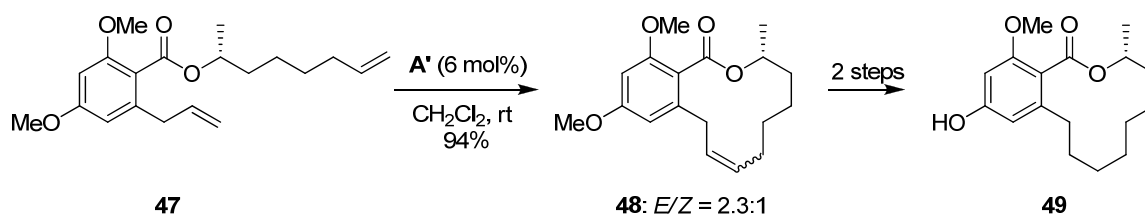
Recently Fürstner *et al.* have synthesized eleven-membered lactone aspercyclide **C** **46** using kinetic controlled RCM method.<sup>39</sup>

## Scheme 10



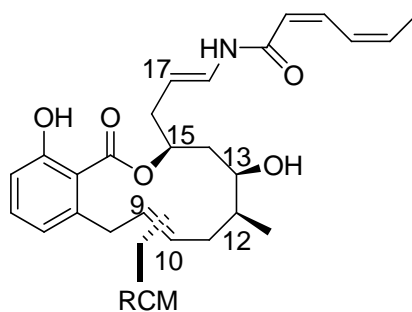
Fürstner's synthesis of (+)-lasiodiopodin **49** represents one of the early applications of RCM to the preparation of 12-membered macrolide natural products.<sup>40</sup> Cyclization of **47** using **A'** as the catalyst gave **48** as a mixture of double bond isomers ( $E/Z = 2.3:1$ ) in excellent yield (Scheme 11). Hydrogenation of this mixture and cleavage of one phenolic methyl ether then completed the synthesis of (+)-**49**. Because the double bond formed by the RCM was reduced, the purist may question this approach to saturated, naturally occurring macrocycles based upon its inefficient use of functionality.

## Scheme 11



Salicyliallamides **A** and **B** (**50** and **51**) comprise a novel class of secondary metabolites isolated from the marine sponge *Haliclona* by Boyd in 1997.<sup>41</sup> Salicyliallamide **A** **50**, which displays potent cytotoxicity in the NCI 60-cell line human tumor assay and appears to have a novel mechanism of action, possesses a 12-membered salicylate macrolide and a novel dienyl enamide side chain.

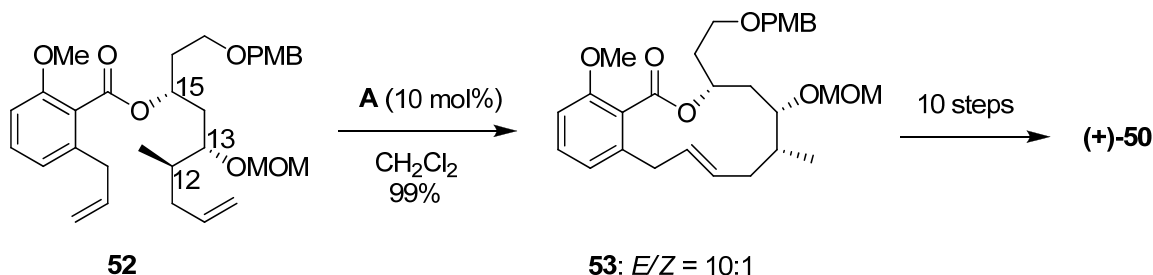
Figure 7



**50:** 17*E*  
**51:** 17*Z*

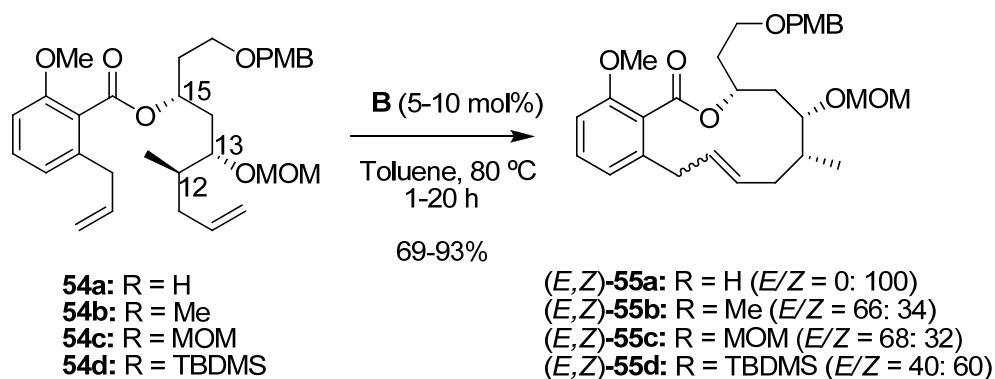
The correct absolute stereochemistry of salicylilhalamide A was established by De Brabander, who first synthesized both (+)-**50** and (-)-**50**.<sup>42</sup> In all of the total syntheses of salicylilhalamide A reported to date, the C9-C10 *E*-double bond, and hence the macrocycle, was generated by a RCM reaction. The stereogenic centers in **52**, which was the RCM substrate in De Brabander's synthesis,<sup>42</sup> were constructed by an asymmetric Brown allylation (C15) and an asymmetric aldol reaction employing Oppolzer's sultam (C-12 and C-13) (Scheme 12). Exposure of **52** to Grubbs' catalyst **A** produced **53** with good *E/Z*-selectivity. The synthesis of (+)-**50** was then completed in 10 steps, wherein the 17*E* enamide moiety was established by addition of a vinyl lithium reagent to an isocyanate.

Scheme 12



Shortly after De Brabander's initial account was published, Fürstner reported a very similar approach to the macrolide core of **50** (Scheme 13).<sup>43</sup> The stereocenter at C-12 in the RCM substrates **54a-d** was generated by an Evans asymmetric alkylation, while the centers at C-13 and C-15 were formed by an enantioselective hydrogenation.

## Scheme 13

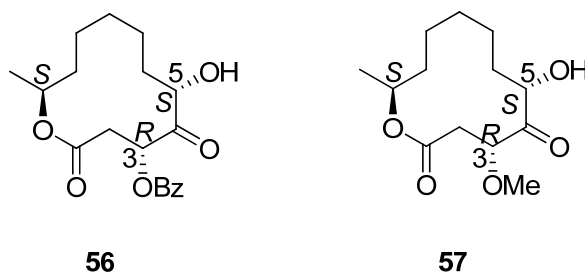


Because one of the double bonds in **54a-d** was trisubstituted, the 1<sup>st</sup> generation Grubbs' catalyst **A**, which is known to be sensitive to double bond substitution, was ineffective, and the more reactive Grubbs' catalyst **B** had to be employed. The stereochemical course of the RCM of **54a-d** was found to be highly dependent upon whether the phenolic hydroxy group was free or protected. Thus, the diene **54a** (R = H) was cleanly converted into (*Z*)-**55a** upon treatment with catalytic amounts of **B**. That the *Z*-double bond was formed exclusively was unexpected, because **B** had been shown to favor formation of the more stable *E*-configured products *via* isomerization.<sup>37</sup> Fürstner speculated that conformational factors, such as a constraining hydrogen bond between the phenolic hydroxyl and the carbonyl group in **54a**, were responsible for the stereochemical outcome of the RCM cyclization. Fürstner's findings together with those of De Brabander<sup>42</sup> illustrate that the stereochemistry of the double bond formed upon the RCM of even very closely related substrates is not always predictable, even when a 2<sup>nd</sup> generation Ru-catalyst is employed. The findings of De Brabander and Fürstner have been mirrored in subsequent syntheses of (-)-salicylilalamide **A** **47**. For example, Snider cyclized dienes very similar to **54a** and **54d** using **A** as the catalyst to obtain primarily a *Z*-olefin when the phenolic hydroxyl group was free and a mixture (4: 1) of *E/Z*-isomers when it was protected as a TBDMS ether.<sup>44</sup> In Smith's synthesis of (-)-**50**,<sup>45</sup> a diene closely related to **52** was cyclized with **A** (10 mol%) to give a mixture (10:1) of *E*- and *Z*-lactones, a result identical to that of De Brabander. Porco recently reported the total synthesis of oximidine II, another salicylate enamide macrolide closely related to **50**, by a strategy in which a macrocyclic conjugated triene was formed by RCM.



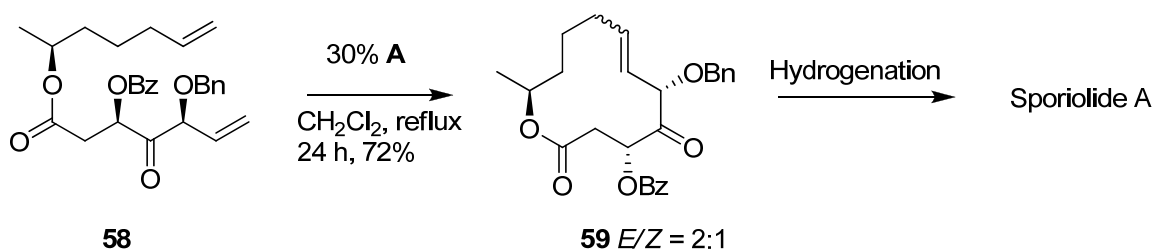
Sporiolide A **56** and Sporiolide B **57** are the macrolides from marine-derived fungus *cladosporides* species.

**Figure 8**

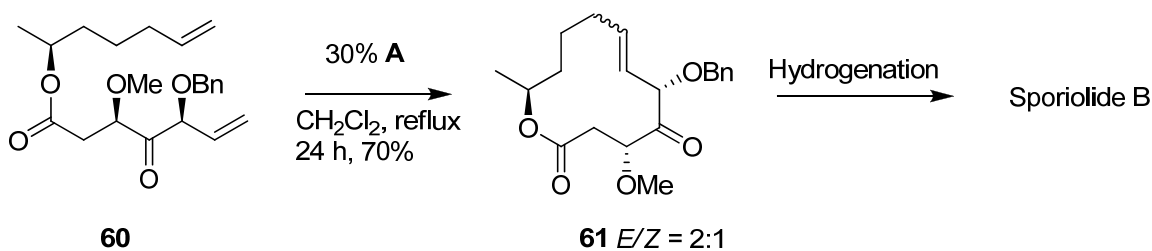


Recently Du *et al.*, have synthesized both sporiolide A<sup>46</sup> and sporiolide B<sup>47</sup> respectively using RCM as key reaction with Grubbs' 1<sup>st</sup> generation catalyst.

**Scheme 14**



**Scheme 15**



In view of interesting results obtained for different sized lactone ring formation we have planned to synthesize molecules of different ring-size using RCM as the key reaction. Our first two chapters deal with few molecules which are medium-sized ring lactones as well as stereochemically promising. All these compounds are biologically active too. So we will concentrate on the synthesis of these molecules using chiron approach and keeping RCM as a mandatory tool for all molecules.

# **CHAPTER 1**

Towards the Total Synthesis of Multiplolide A

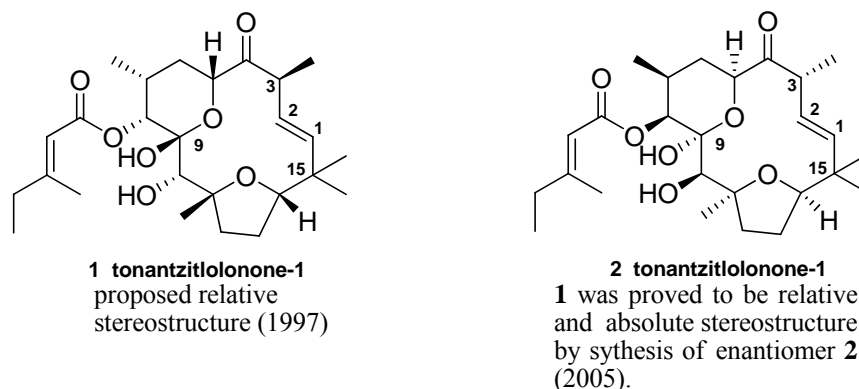
## **PRESENT WORK**

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## PRESENT WORK

Though the modern day analytical techniques have bestowed the isolation chemists with deeper insights to understand the structures of natural products isolated, the opportunities for synthetic chemists to contribute in the area of natural product structure elucidation are not totally exhausted.<sup>48</sup> Nature sometime tests even teases the awesome influence of the analytical techniques by presenting simple looking structures out of its bag. Those compounds, after isolation, can be identified structurally using spectroscopic analysis. Relative as well as absolute stereochemistry can also be determined through spectroscopy as well as different chemical studies. Few compounds are there in nature where stereochemistry cannot be determined through spectroscopic analysis as well as chemical analysis. So for the determination of relative as well as absolute stereochemistry, syntheses of different diastereomers are very necessary. Similar was the case with tonantzitlolone (Figure 1), which was isolated in 1997 and the relative stereochemistry was proposed as represented by structure **1**. However, the absolute stereostructure could not be determined at that time. This was achieved by the synthesis of the enantiomer **2** in the year 2005. All the spectral and analytical data for **2** was in excellent agreement with natural product, except for optical rotation (authentic natural product,  $[\alpha]_D^{20} = +134^\circ$  ( $c$  0.25,  $\text{CHCl}_3$ ); found,  $[\alpha]_D^{20} = -119^\circ$  ( $c$  0.06,  $\text{CHCl}_3$ )). This clearly established **1** as the correct absolute stereostructure for tonantzitlolone.<sup>49</sup>

**Figure 1:** Partial and total stereostructure for tonantzitlolone-1

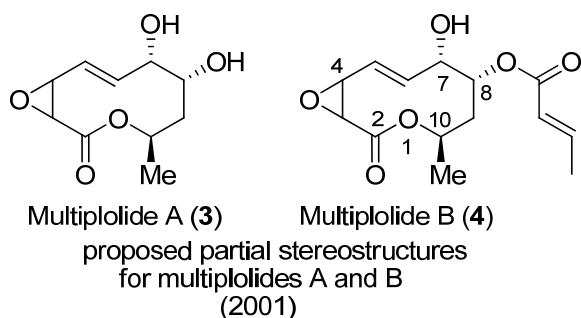


The case of multiplolides A **3** and B **4** was another story of partial structure elucidation.<sup>50</sup> The most striking feature of multiplolides from structural elucidation point

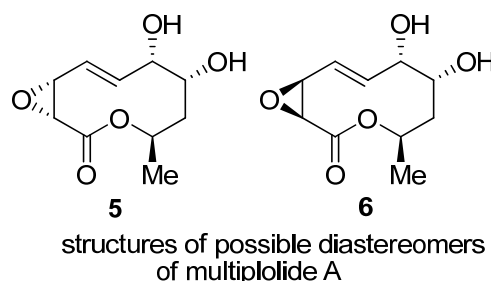
of view is the epoxide functionality set in between lactone carbonyl and olefin, and the epoxide protons are spatially isolated from the protons on other chiral centers resulting in partial structural elucidation, leaving the two possible diastereomeric structures **5** & **6** for the central core of multiplolides.

**Figure 2:** Chemical structures of multiplolide A, B and both possible diastereomers of multiplolide A

**Natural Products:**



**Synthetic Targets:**

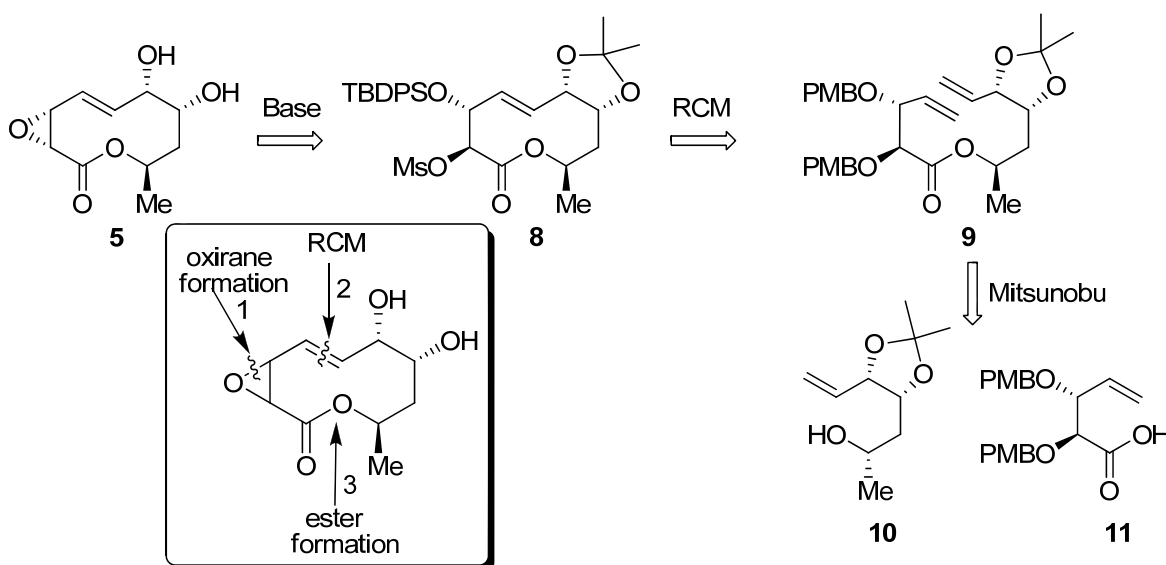


As is the case with every natural product, the structures of multiplolides A and B were elucidated on the basis of their spectral data. The ESI-TOF mass spectrum of multiplolide A **3** gave an accurate mass of  $m/z$  215.0923  $[(M + H)^+, \Delta +0.5 \text{ mmu}]$ , establishing the molecular formula of **3** as  $C_{10}H_{14}O_5$ . The IR spectrum of multiplolide A **3** exhibited an absorption peak at  $1721 \text{ cm}^{-1}$ , characteristic of an ester carbonyl.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of multiplolide A **3** showed a methyl doublet at  $\delta$  1.30, a nonequivalent methylene (at  $\delta$  1.21 and 2.21), five oxy protons (at  $\delta$  3.60, 3.75, 3.95, 4.50, and 5.25), and two olefinic protons (at  $\delta$  5.72 and 5.88). The  $J_{\text{H-5,H-6}}$  value of 15.0 Hz revealed a *trans*-configuration of the olefinic protons in **3**. The  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) of multiplolide A **3** showed 10 signals, attributable to one methyl, one methylene, seven methine, and one quaternary carbon, as determined by DEPT experiments. The  $^1\text{H}$ - $^1\text{H}$  COSY spectrum of multiplolide A **3** conclusively demonstrated the connectivity from H-3 to H-11. The epoxide moiety at carbons 3 and 4 in **3** was evident from the HMBC spectrum, in which the  $^{13}\text{C}$ - $^1\text{H}$  one-bond coupling constant ( $^1J_{\text{C-H}}$ ) of 167 Hz (for C-3 and C-4) was observed. The HMBC spectrum also showed the correlation of both H-3 and H-10 to the carbonyl carbon (C-2), H-4 to C-6, H-5 to C-7, and H-9 to both C-7 and C-11. The NOESY spectrum of **3** revealed correlations of the methyl group to H-9<sub>ax</sub>, and H-9<sub>ax</sub> to both H-8



ambiguity it was decided to synthesize both the possible diastereomers of multiplolide A [3-*R*, 4-*R* **5** and 3-*S*, 4-*S* **6**]. Comparison of the analytical data for both the isomers with that of natural product would enable us to determine the stereochemistry at C-3 and C-4 for multiplolide A. Success in synthesizing multiplolide A would leave synthesis of multiplolide B as a matter of few straight forward protection-deprotections. Retrosynthetic strategy of making  $\alpha$ -oxirane ring of multiplolide A is depicted below.

**Scheme 1:** Retrosynthetic strategy



Three major disconnections were visualized; one at the oxirane ring, other at ring olefin and the final one at the ester linkage. Since the oxirane functionality is positioned  $\alpha$  to carbonyl it would be wise to install it in the end, therefore priority was given to the disconnection at the oxirane ring. It would require a leaving group on one of the carbons and the free hydroxyl on the other to install the oxirane. The leaving group was envisaged at homoallylic position. As the epoxide is *alpha* so attack of free hydroxyl group should come from *alpha* side. The knowledge of the position of leaving group (C-4) and the absolute stereochemistry at that center would enable us to state the absolute stereochemistry of the oxirane ring beyond any ambiguity and hence fix the missing link in its structure elucidation.

In line with the practice of our group to use the RCM reaction for the synthesis of various natural products and synthetically important intermediates,<sup>52,53</sup> the construction of the ring olefin of multiplolide A and consequently the macrocycle formation was planned

by employing the RCM reaction on a suitable diene-ester. It is observed that the outcome of the RCM reaction is highly dependent on substrate and reaction conditions. The situation becomes complex and the prediction difficult when the olefins involved in the ring closure reaction are surrounded by multiple chiral centers. Oxygen functions on these centers, their stereochemistry and nature of the protections all contribute towards the stereochemical outcome of reaction leaving behind very less space for prediction. Keeping this in mind the path was chosen so as to offer enough flexibility with the substrates for RCM.

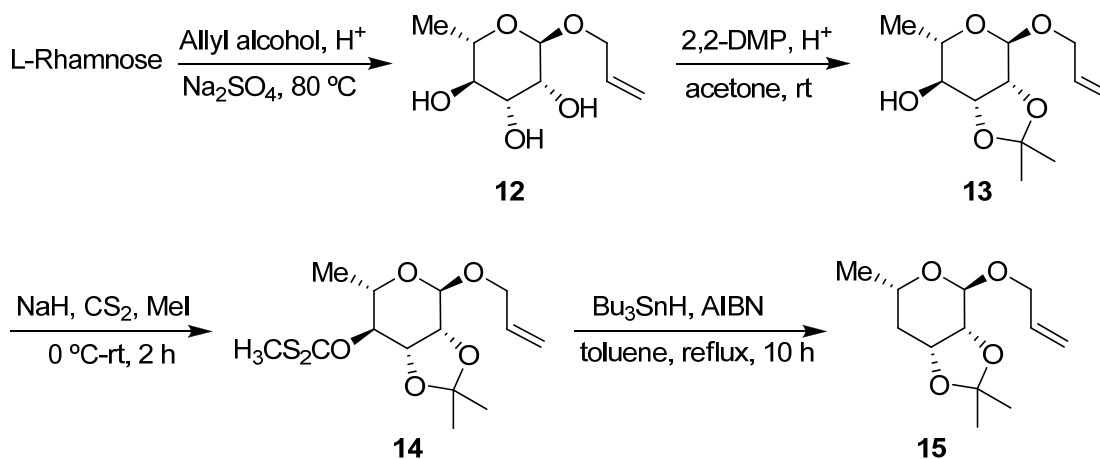
In view of the chances of epimerization at C-3 under the reaction conditions where base needs to be employed for ester formation (eg. DCC or Yamaguchi), the di-PMB ester **9** was visualized from the Mitsunobu reaction between the alcohol **10** and acid **11**. Remaining pertinent to the practice of using cheaply available sugars for total synthesis, D-mannitol and L-rhamnose were chosen as precursors for acid **11** and alcohol **10** respectively after careful stereochemical investigations for the synthesis of both the diastereomers of multiplolide A.

### **Synthesis of fragment 10**

Synthesis of the alcohol **10** (Scheme 2) began with the preparation of the known<sup>54</sup> deoxy derivative **15** from L-rhamnose in four steps. L-Rhamnose was converted into its allyl glycoside **12** by treatment with allyl alcohol in presence of acid and sodium sulfate at 80 °C. The crude glycoside was then converted into the 2,3-*O*-isopropylidene derivative **13** using 2,2-dimethoxypropane in acetone and in the presence of catalytic acid. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **13** revealed the presence of only one anomer. The anomeric proton appeared as a singlet at 4.99 ppm in the <sup>1</sup>H NMR spectrum whereas the C-1 resonated at δ 96.1 in the <sup>13</sup>C NMR spectrum indicating α-configuration. Two singlets at δ 1.35 and 1.52 in the <sup>1</sup>H NMR spectrum integrating for three protons each were assigned to methyl groups of isopropylidene protection, which was further supported by presence of a peak for quaternary carbon at 109.3 ppm in the <sup>13</sup>C NMR spectrum. Results from mass spectrum, IR, and elemental analysis were in accordance with the structure **13**.

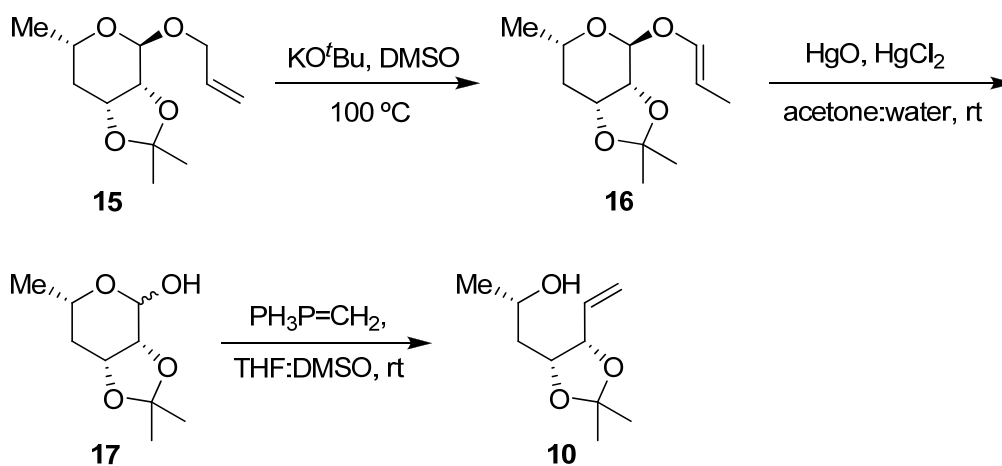


## Scheme 2



The free hydroxyl at C-4 was deoxygenated using the Barton's protocol.<sup>54c</sup> The xanthate derivative **14** was prepared by treating **13** with NaH, CS<sub>2</sub> and MeI. Subsequently the xanthate derivative **14** was treated with *n*-Bu<sub>3</sub>SnH and catalytic AIBN in refluxing toluene to obtain the deoxy derivative **15**. The structure **15** was well supported by <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectrum and elemental analysis. In the <sup>1</sup>H NMR spectrum of **15**, two signals for C-4 methylene protons were located in the upfield region (1.35-1.42 ppm as a multiplet and at  $\delta$  1.80 ppm as a doublet of a double doublet). In the partially decoupled <sup>13</sup>C NMR spectrum C-4 resonated at  $\delta$  36.1 as a triplet confirming the presence of methylene group.

## Scheme 3



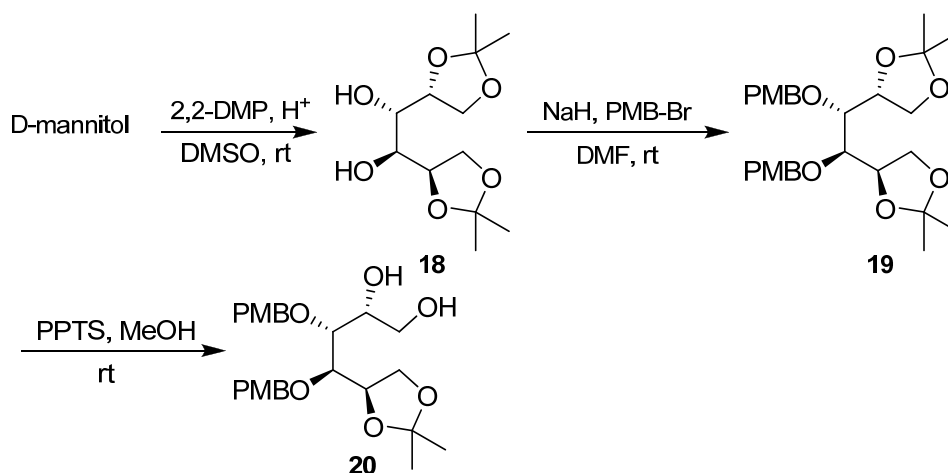
Deallylation of **15** was carried out in a two step sequence (Scheme 3),<sup>55</sup> first step being the isomerisation to the vinyl ether **16** by treatment with KO<sup>t</sup>Bu in DMSO at 100 °C. The crude vinyl ether **16** was treated with HgO to afford the lactol **17** as an inseparable anomeric mixture. Signals for the anomeric protons of the two anomers appeared at  $\delta$  4.89 and 5.42 ppm in the <sup>1</sup>H NMR spectrum whereas the anomeric carbons resonated at  $\delta$  92.5 and 93.0 ppm in the <sup>13</sup>C NMR spectrum. One carbon Wittig homologation of **17** by treatment with methyltriphenylphosphorane in THF:DMSO mixture furnished the required alcohol fragment **10**. The three signals for the olefinic protons integrating for one proton each, appeared at  $\delta$  5.23, 5.30, 5.78 ppm in the <sup>1</sup>H NMR spectrum. The presence of two olefinic carbons at  $\delta$  117.9 (triplet) and  $\delta$  134.2 (doublet) in the DEPT spectrum along with other analytical data such as mass spectrum, elemental analysis and IR spectrum supported the proposed structure **10**.

### Synthesis of fragment 11

The preparation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **18** was carried out employing literature procedure (Scheme 4).<sup>56</sup> The free hydroxyl functions at C-3 and C-4 in the isopropylidene derivative **18** were protected as PMB-ethers by treatment with NaH and PMB-Br<sup>57</sup> in DMF to afford the di-PMB derivative **19**. The isopropylidene groups of **19** resonated at  $\delta$  1.33 and 1.41 in the <sup>1</sup>H NMR spectrum. The benzylic methylene groups appeared as a singlet at  $\delta$  4.60 and the aromatic protons at  $\delta$  6.83 and 7.22. In the <sup>13</sup>C NMR spectrum and the DEPT spectrum the benzylic methylenes were observed at  $\delta$  66.7 and 74.0 ppm. The highest peak at  $m/z$  525 [M+Na]<sup>+</sup> in the mass spectrum and the elemental analysis supported the structure **19**. The next job was to remove one of the isopropylidene groups of *C*<sub>2</sub>-symmetric **19** keeping the other one intact. This was achieved employing PPTS<sup>58</sup> in MeOH at room temperature. After running the reaction for various time intervals it was noted that 12 h was the optimum reaction time. At this time even though some starting material remained unreacted, the yield of the required diol **20** was maximum. The starting material could be easily separated on a silica gel column and recycled. The loss of one of the isopropylidene groups was evident from the <sup>1</sup>H NMR spectrum where signals due to isopropylidene group at  $\delta$  1.34 and 1.43 integrated for three protons each as compared to the signals due to benzylic protons at  $\delta$

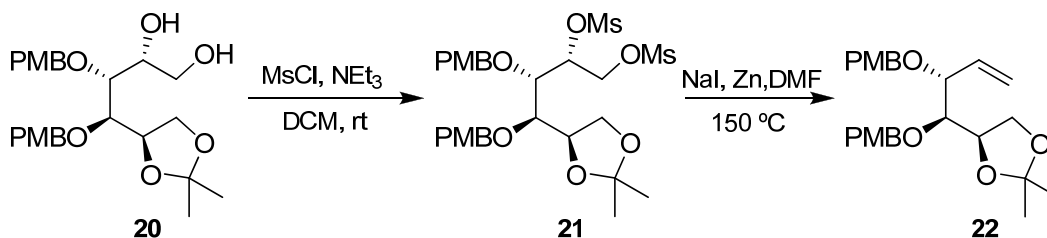
4.50, 4.57, 4.60, and 4.67 which integrated for four protons. In the mass spectrum the peak was seen at  $m/z$  485  $[M+Na]^+$  confirming proposed structure. The  $^{13}C$  NMR spectrum and elemental analysis were also found to match the proposed structure **20**.

#### Scheme 4



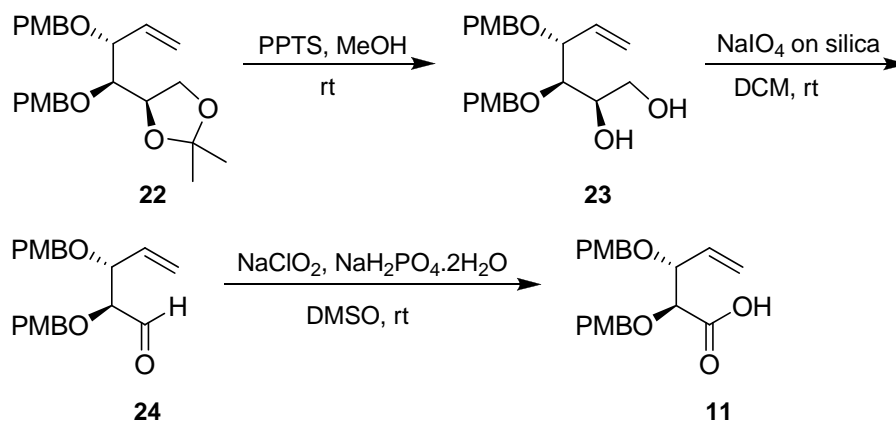
Conversion of the vicinal diol unit in **20** into the terminal olefin **22** was effected using a two step procedure (Scheme 5).<sup>59</sup> In the first step the diol **20** was converted to its dimesyl derivative **21** by treatment with MsCl in presence of triethylamine in DCM. The crude dimesylate was treated with NaI, Zn in DMF at 150 °C to procure the olefin **22**. The terminal olefinic protons were seen between  $\delta$  5.13-5.38 as a multiplet and the internal proton as a doublet of a double doublet at  $\delta$  5.85 in the  $^1H$  NMR spectrum. A triplet in the partially decoupled  $^{13}C$  NMR spectrum at  $\delta$  118.1 ppm confirmed the presence of  $SP^2$  methylene in the compound. Other analytical data was found in accordance with the structure.

#### Scheme 5



The isopropylidene protection in **22** was cleaved using PPTS in methanol to furnish the diol **23**. The absence of peaks due to isopropylidene group in the  $^1\text{H}$  and the  $^{13}\text{C}$  NMR spectra was evident for the successful removal of the protecting group. The structure was further supported by the IR spectrum with absorption corresponding to free hydroxyl at  $3436\text{ cm}^{-1}$  and elemental analysis (Scheme 6).

### Scheme 6



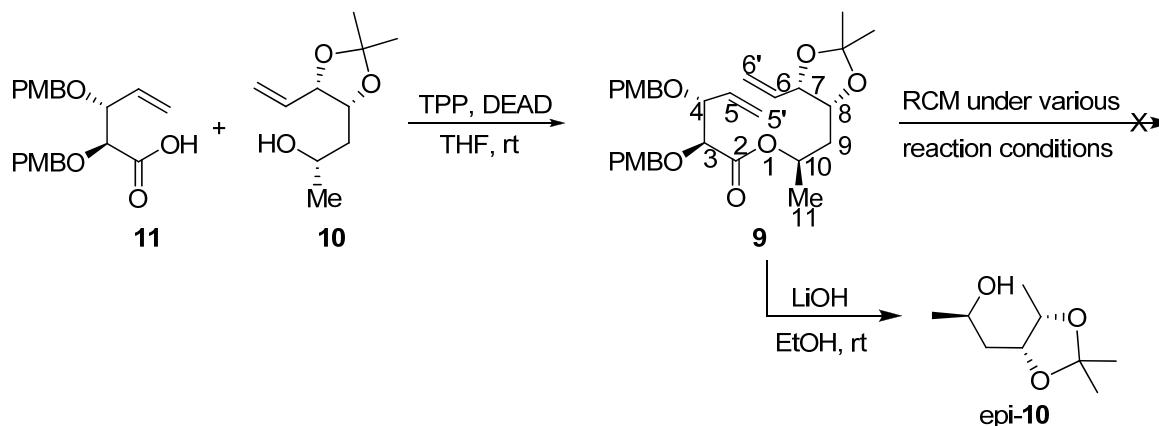
The diol **23** was cleaved by using sodium metaperiodate adsorbed on silica gel<sup>60</sup> to afford the aldehyde **24**, which was oxidized to the acid **11** on treatment with NaClO<sub>2</sub> and NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O in the presence of 2-methyl-2-butene.<sup>61</sup> In the IR spectrum the O-H stretching was observed at  $3394\text{ cm}^{-1}$  and the C=O stretching at  $1724\text{ cm}^{-1}$ . The carbonyl carbon was observed at  $\delta$  173.4 ppm in the  $^{13}\text{C}$  NMR spectrum. Other analytical data such as the  $^1\text{H}$  NMR spectrum, mass spectrum, and elemental analysis of **11** were in accordance with the proposed structure.

Thus the alcohol **10** was synthesized from L-rhamnose and the acid **11** was synthesized from D-mannitol. Having successfully prepared the requisite coupling partners for the synthesis of multiplolide A isomer, the next step was to proceed further sequence of reactions as per the retrosynthetic plan. The fact that there was no clue whatsoever to speculate which of the isomers of multiplolide A (**5** or **6**) was more plausible to be a natural product, had made the choice entirely capricious. The literature survey revealed that the prediction of the stereochemical outcome of the RCM reaction, particularly for the medium (8 – 12 membered) ring size was far from straight forward.

Keeping this in mind, the strategy was designed in such a way to offer at least three diene substrates to suit the requirement of *E* configured olefin.

So after Mitsunobu coupling of alcohol **10** and acid **11**, our main aim was to construct the 10-member core through ring closing metathesis.

### Scheme 7



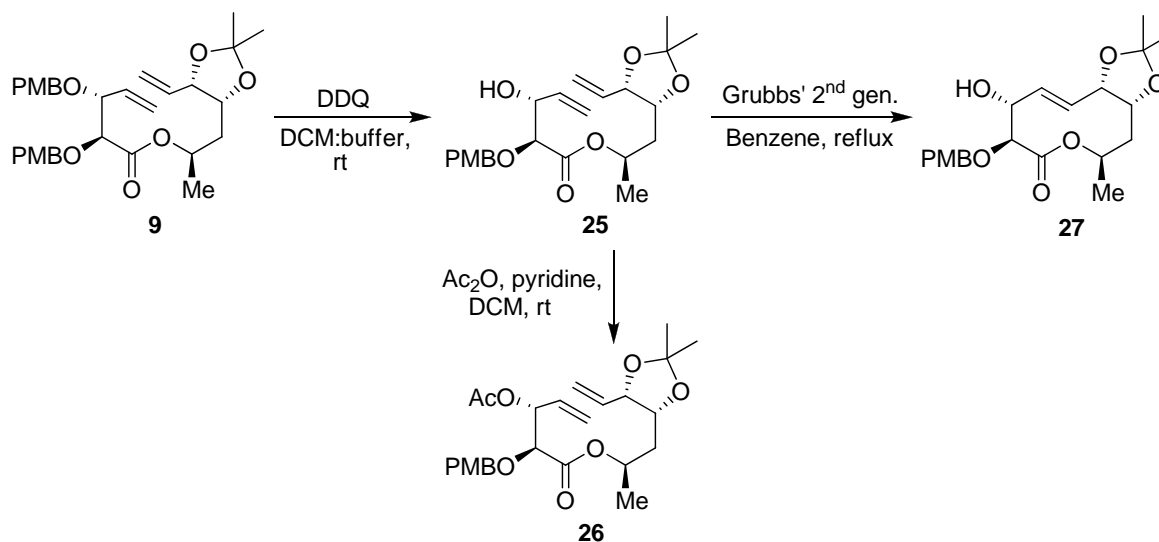
The Mitsunobu<sup>62</sup> reaction between alcohol **10** and acid **11** proceeded smoothly to procure the diene-ester **9** (Scheme 7). In the <sup>1</sup>H NMR spectrum the isopropylidene signals were observed at  $\delta$  1.32 and 1.47 as singlets whereas the signals due to PMB-methoxyl groups were observed at  $\delta$  3.77 and 3.78 as singlets, each integrating for three protons. The H-10 was observed at  $\delta$  5.10 as a quartet with  $J = 6.3$  Hz. The structure was further supported by IR spectrum, which revealed ester carbonyl at  $1736\text{ cm}^{-1}$ . The ester carbonyl appeared at  $\delta$  169.6 in the <sup>13</sup>C NMR spectrum. The highest mass peak  $m/z$  563  $[M+Na]^+$  and elemental analysis served as supporting evidences for structure **9**. The inversion of configuration at the alcohol center during the Mitsunobu reaction was confirmed by hydrolyzing the ester formed **9**. However attempts for ring closure with compound **9** under various reaction conditions resulted in failures. Attributing this failure to the crowding around the reaction centers because of protecting groups, therefore the deprotection of -OPMB ether was attempted.

Compound **9** on treatment with DDQ under pH 7 buffer condition, afforded compound **25** (Scheme 8). Cleavage of one of the PMB-ethers was evident from the <sup>1</sup>H and <sup>13</sup>C NMR spectra. In the <sup>1</sup>H NMR spectrum the presence of only one singlet at  $\delta$  3.79 integrating for three protons, two doublets at  $\delta$  4.39 and 4.69 integrating for two protons

and aromatic protons integrating for four protons clearly established that one of the PMB groups was cleaved. The presence of only one benzylic carbon at  $\delta$  72.5 and only one quaternary carbon at  $\delta$  159.6 in the  $^{13}\text{C}$  NMR spectrum further cemented the conclusion. All other analytical data was also found in accordance. Without entirely depending on precedence, the acetate **26** was prepared from compound **25**.

At this stage the RCM reaction of **25** was attempted in DCM with Grubbs' 2<sup>nd</sup> generation catalyst at reflux temperature but reaction was sluggish even after 36 h and the conversion rate also slow. So benzene was substituted as a solvent and the reaction was conducted at the reflux temperature of benzene using Grubbs' 2<sup>nd</sup> generation catalyst. This proved to be extremely rewarding and complete conversion into the product **27** was achieved within 6 h. Product was purified by column chromatography and to our delight the product showed the peak at 415  $[\text{M}+\text{Na}]^+$  in the mass spectrum corresponding to the ring closed product **27**.

### Scheme 8

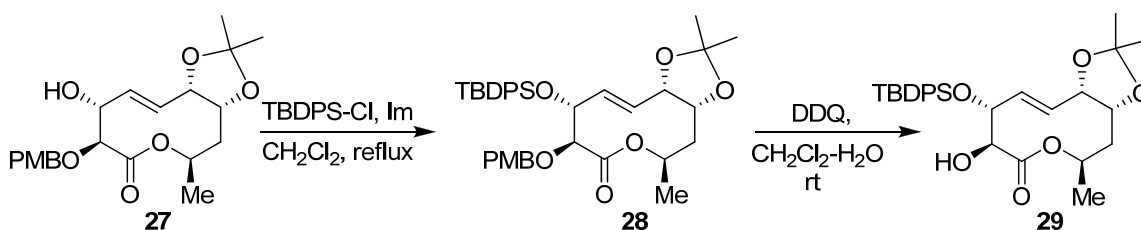


The geometry of the newly formed double bond was *trans* as established by the coupling constant 16.5 Hz. Structure of **27** was further supported by the absence of signals for olefinic methylenes in the  $^{13}\text{C}$  NMR spectrum.

As our target was to synthesize compound **5** so we focused our attention to tune the position of leaving group starting from the *E*-macrocyle **27**, in our hands. As outlined in Scheme 9, first the allylic free hydroxyl group was protected to its TBDPS ether **28**.

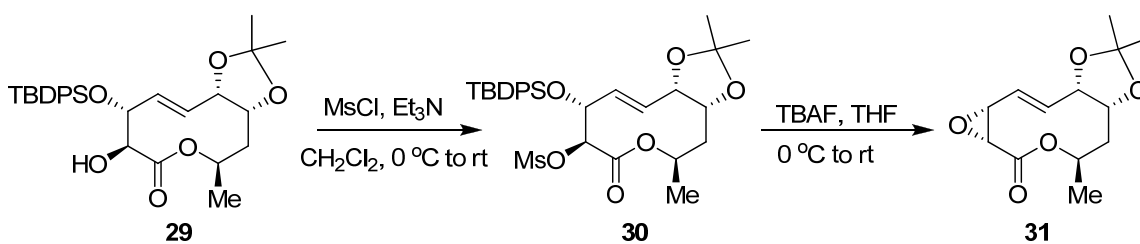
Presence of this compound was confirmed by  $^1\text{H}$  NMR where 9H singlet signal indicated the presence of  $^t$ Butyl group of TBDPS protection. Then the homoallylic PMB ether was deprotected using DDQ. Absence of methyl group of PMB in both  $^1\text{H}$  and  $^{13}\text{C}$  spectra indicated that the deprotection reaction was successfully done.

### Scheme 9



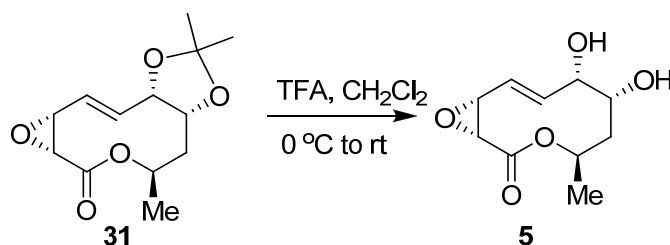
Free hydroxyl group in scheme 10, was subsequently transformed to a good leaving group  $-\text{OMs}$  (**30**). After the mesylation reaction, H-3 that resonated at  $\delta$  3.97 in the starting material was changed to  $\delta$  4.55 in  $^1\text{H}$  spectra. Presence of methyl group at  $\delta$  2.51 also indicated the presence of mesyl group in the product. TBDPS deprotection followed by epoxide (**31**) formation was achieved in the same pot using TBAF solution. Absence of both mesyl group and TBDPS group indicated the formation of epoxide. Presence of two protons at  $\delta$  3.75 and  $\delta$  3.78 respectively supported that the epoxide was formed. This was further confirmed by mass spectroscopy.

### Scheme 10



Final acetonide deprotection using TFA gave the compound **5**. Interestingly, compound **5** was found to exist as an equilibrating mixture of conformational isomers (3:1, at 25 °C) in solution.

## Scheme 11



The major:minor ratio was observed to be temperature dependent to some extent. Maximum separation in the signals due to each isomers was observed when the  $^1\text{H}$  NMR was recorded at 0 °C in  $\text{CDCl}_3$ . Whereas a substantial increment in the ratio of major isomer was noticed when the NMR was recorded at high temperatures in  $\text{DMSO-D}_6$ . When the NMR was recorded at 80 °C the peaks due to major and minor isomer merged into each other at the expense of the multiplicity of the peaks. From the comparison of the data from natural product and **6** with the  $\mathbf{5}_{\text{major}}$  and  $\mathbf{5}_{\text{minor}}$  it is evident that both the components represent the same constitution and configuration and presumably are conformational isomers.

**Table 1:**  $^1\text{H}$  NMR in  $\text{CDCl}_3$  at 0 °C (400 MHz)

H		Major Conformer $\delta$ (J = Hz)		Minor Conformer $\delta$ (J = Hz)
<b>11</b>	d	1.37 (6.8)	d	1.41 (6.9)
<b>9</b>	dd	1.51 (6.0, 16.2)	merged	1.37-1.42
<b>9'</b>	ddd	2.31 (2.3, 7.8, 16.2)	ddd	2.51 (2.3, 7.8, 16.1)
<b>4</b>	ddd	3.74 (0.8, 1.9, 4.0)	m	3.93-3.95
<b>3</b>	d	3.76 (4.0)	d	3.79 (4.5)
<b>8</b>	dd	3.87 (2.8, 7.3)	dd	3.98 (2.9, 8.2)
<b>7</b>	dd	4.24 (2.8, 8.4)	m	4.49-4.51
<b>10</b>	m	5.20-5.24	merged	5.18-5.25
<b>6</b>	dd	5.58 (8.4, 16.2)	merged	5.80-5.84
<b>5</b>	ddd	5.82 (0.8, 1.9, 16.2)	dt	5.71 (2.0, 16.8)

**Table 2:**  $^{13}\text{C}$  NMR in  $\text{CDCl}_3$  at 25 °C (100 MHz)

<b>Major</b>	19.7 (q)	35.7 (t)	53.0 (d)	58.0 (d)	69.7 (d)	72.1 (d)	75.6 (d)	125.9 (d)	129.3 (d)	166.7 (s)
<b>Minor</b>	17.9 (q)	34.9 (t)	53.03 (d)	55.2 (d)	68.9 (d)	70.3 (d)	72.5 (d)	121.3 (d)	137.4 (d)	167.6 (s)

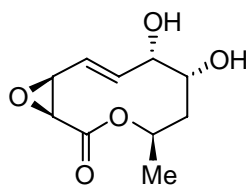


**Table 3:** Comparitive  $^1\text{H}$  and  $^{13}\text{C}$  NMR of compounds **5** and **6** with data reported for natural multiplolide A **3** in  $\text{CDCl}_3$  at  $25\text{ }^\circ\text{C}$  (400 MHz)

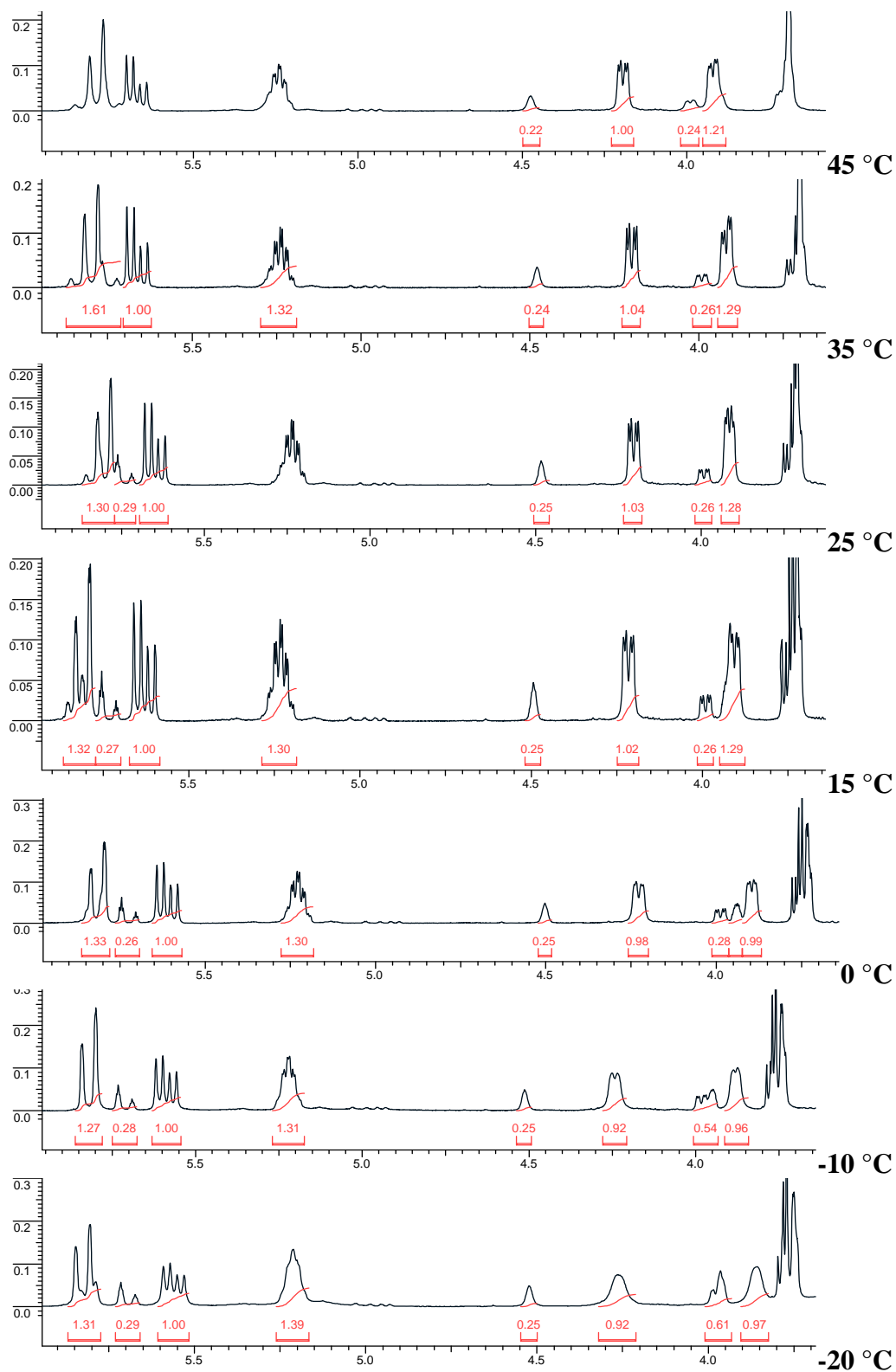
$^1\text{H}$ NMR					$^{13}\text{C}$ NMR				
<b>3</b> $\delta$ (Hz)	(m)	<b>4</b> $\delta$ (Hz)	(m)	<b>H</b>	Nat. $\delta$ (Hz)	<b>3</b>	<b>4</b>	Nat.	<b>C</b>
1.28 (4.0, 16.0)	dd	1.53 (6.3, 16.1)	dd	<b>9<sub>eq</sub></b>	1.21 (3.7, 16.0)	19.7	17.8	17.6	<b>11</b>
1.36 (6.7)	d	1.38 (6.7)	d	<b>11</b>	1.30 (6.8)	35.7	35.4	35.2	<b>9</b>
2.24 (3.4, 8.5, 16.0)	ddd	2.28 (2.3, 7.7, 16.1)	ddd	<b>9<sub>ax</sub></b>	2.21 (3.4, 8.3, 16.0)	52.9	54.5	54.5	<b>4</b>
3.65 (4.6)	d	3.68 – 3.73	m	<b>3</b>	3.60 (4.5)	58.0	55.1	54.9	<b>3</b>
3.80	m	3.79–3.81	m	<b>4</b>	3.75	69.6	67.9	68.1	<b>8</b>
4.05 (3.0, 8.4)	dd	3.90 (3.1, 7.4)	dd	<b>8</b>	3.95 (2.7, 8.2)	72.0	68.3	68.2	<b>10</b>
4.55	m	4.19 (3.1, 8.3)	dd	<b>7</b>	4.50	75.6	72.4	72.2	<b>7</b>
5.30	m	5.18-5.25	m	<b>10</b>	5.25	125.9	117.7	117.2	<b>5</b>
5.76 (1.4, 2.1, 15.6)	ddd	5.64 (8.3, 16.1)	dd	<b>5</b>	5.72 (1.2, 1.2, 15.4)	129.1	133.3	133.6	<b>6</b>
5.93 (1.1, 2.5, 15.6)	ddd	5.80 (2.2, 16.1)	dd	<b>6</b>	5.88 (0.9, 2.2, 15.4)	166.6	167.2	167.2	<b>2</b>

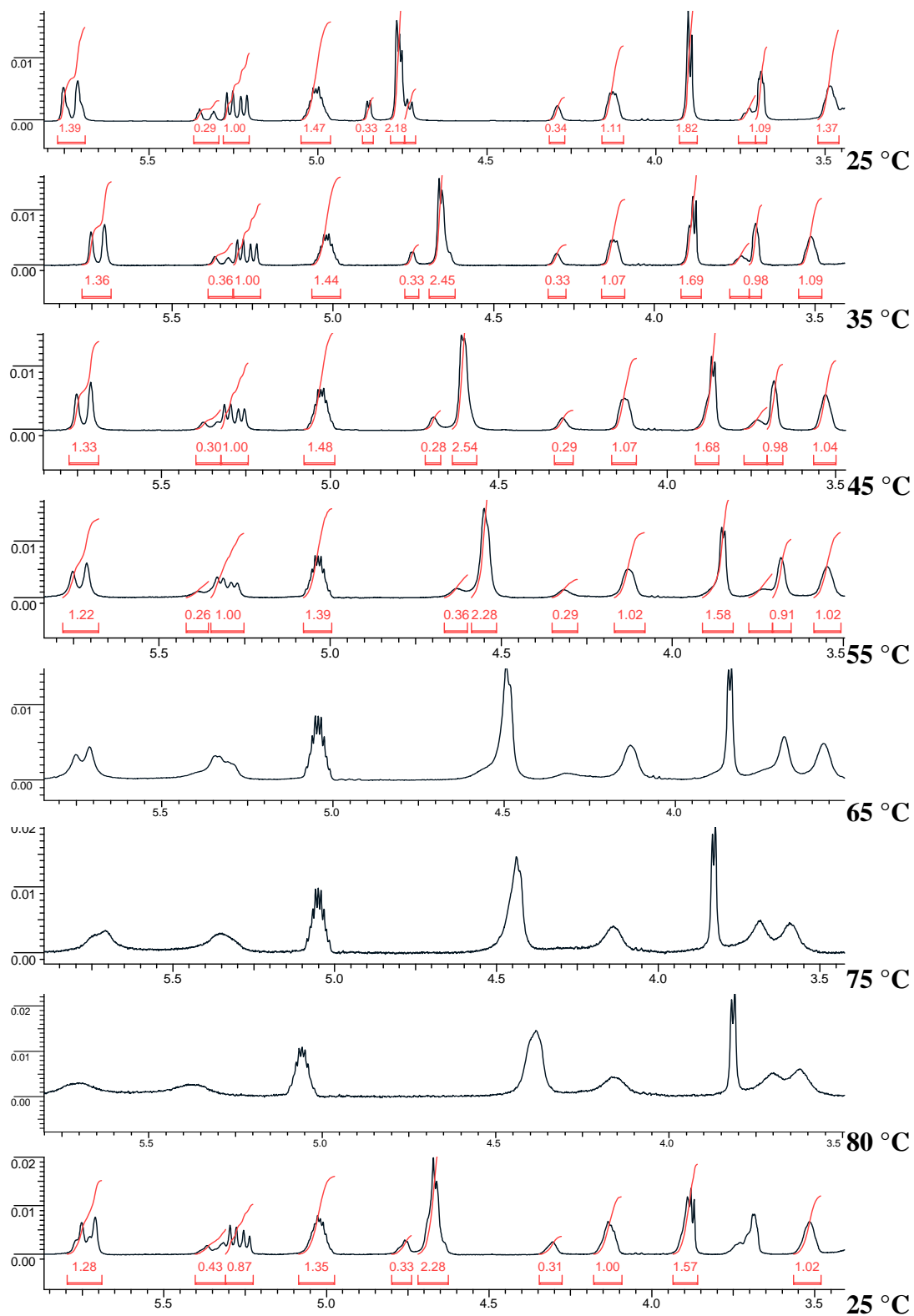
The fact that the natural product did not exist as the mixture of conformational isomers and no correlation of the data of any of the conformers of **5** with natural multiplolide A unequivocally designated **6** as the natural product and compound **5** was the diastereomer of the natural product. Absolute stereochemistries of both the diastereomers were confirmed. Natural product stereochemistry was  $3S, 4S, 7S, 8R$ , and  $10R$  and diastereomeric compound was having stereochemistry  $3R, 4R, 7S, 8R$ , and  $10R$ .

In conclusion, after synthesizing both the diastereomers and examining all the data obtained from both the isomers, it was found that the orientation of the oxirane ring in the natural product is  $\beta$  and the actual structure of Multiplolide A is given below.



Multiplolide A

Low Temperature  $^1\text{H}$  NMR of Compound 5 in  $\text{CDCl}_3$ 

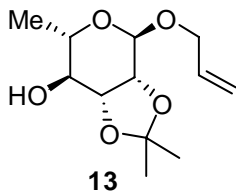
High Temperature  $^1\text{H}$  NMR of Compound 5 in  $\text{DMSO-}D_6$ 

## **EXPERIMENTAL**

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## **EXPERIMENTAL**

### **Allyl 6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -L-mannopyranoside (13)**



A mixture of L (-) rhamnose (10.0 g, 60.97 mmol), anhydrous sodium sulfate (20.0 g, 140.84 mmol), freshly distilled allyl alcohol (100 mL) and concentrated sulfuric acid (1 mL) was heated at 80 °C for 20 h. The reaction mixture was filtered through *Celite*, the filtrate passed through a bed of IR-400 resin and concentrated to afford the allyl pyranoside (11.2 g, 90%) as a viscous oil (used for next step without further purification). The above product (11.2 g, 54.9 mmol), acetone (110 mL), 2,2-dimethoxypropane (22 mL, 179.38 mmol) and *p*-TSA (150 mg) were stirred at rt for 10 h, and triethylamine (4 mL) was introduced followed by concentration. The crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:5) to give **13** as colorless oil.

**Yield** : 12.48 g, 84% over two steps

**Mol. Formula** : C<sub>12</sub>H<sub>20</sub>O<sub>5</sub>

**Mol. Weight** : 244

**ESI-MS *m/z*** : 267 [M+Na]<sup>+</sup>

**Elemental Analysis** : Calcd: C, 59.01; H, 8.20 %

Found: C, 59.24; H, 8.05%

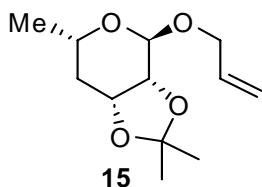
**[ $\alpha$ ]<sub>D</sub><sup>25</sup>** : -34.2 (*c* 1.3, CHCl<sub>3</sub>); literature [ $\alpha$ ]<sub>D</sub> = -32

**IR (CHCl<sub>3</sub>)  $\tilde{\nu}$**  : 3453, 2936, 1520, 1384, 1140, 1079, 1051 cm<sup>-1</sup>

**<sup>1</sup>H NMR** (200 MHz, :  $\delta$  1.29 (d,  $J$  = 6.3 Hz, 3H), 1.35 (s, 3H), 1.52 (s, 3H), 3.38 (dd,  $J$  = 6.8, 9.2 Hz, 1H), 3.68 (dq,  $J$  = 6.2, 9.2 Hz, 1H), 4.0 (ddt,  $J$  = 1.4, 6.2, 12.8 Hz, 1H), 4.07 (br.d,  $J$  = 6.2 Hz, 1H), 4.14 (br. t,  $J$  = 5.6 Hz, 1H), 4.19 (ddt,  $J$  = 1.4, 5.2, 12.8 Hz, 1H), 4.99 (s, 1H), 5.21 (ddd,  $J$  = 1.4, 3.0, 10.3 Hz, 1H), 5.30 (ddd,  $J$  = 1.4, 3.0, 17.2 Hz, 1H), 5.90 (dddd,  $J$  = 5.2, 6.2, 10.3, 17.2 Hz, 1H)

**<sup>13</sup>C NMR** (50 MHz, : 17.3 (q), 26.1 (q), 27.9 (q), 65.7 (d), 67.8 (t), 74.3 (d), 75.8 (d), 78.5 (d), 96.1 (d), 109.3 (s), 117.6 (t), 133.6 (d) ppm

**Allyl 4,6-dideoxy-2,3-*O*-isopropylidene- $\alpha$ -L-lyxo-hexo-pyranoside (15)**



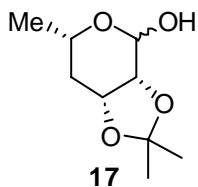
To a solution of **13** (5.0 g, 20.49 mmol) in dry THF (50 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.0 g, 25.0 mmol) followed by carbon disulfide (1.9 mL, 31.65 mmol) after 30 min. The stirring continued for 30 min and then methyl iodide (2.0 mL, 32.08 mmol) was introduced. After 2 h, reaction mixture was quenched by the addition of ice-water and repeatedly extracted with ethyl acetate. The combined organic extract was washed with water, dried over sodium sulfate and concentrated. The crude xanthate **14** (6.5 g, 19.46 mmol) was dissolved in toluene (75 mL), degassed with Argon, AIBN (50 mg) and tri-*n*-butyltinhydride (7.7 mL, 29.05 mmol) were added. The contents were heated under reflux for 10 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **15** as colorless oil.

**Yield** : 3.8 g, 81%, over two steps

**Mol. Formula** : C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>

<b>Mol. Weight</b>	:	228
<b>ESI-MS <math>m/z</math></b>	:	251 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 63.16; H, 8.77% Found: C, 62.92; H, 8.49%
<b><math>[\alpha]_D^{25}</math></b>	:	-56.2 ( <i>c</i> 1.2, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3083, 2934, 1647, 1457, 1382, 1373, 1244, 1146, 1082 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	:	$\delta$ 1.16 (d, <i>J</i> = 6.3 Hz, 3H), 1.28 (s, 3H), 1.35-1.42 (m, 1H), 1.46 (s, 3H), 1.80 (ddd, <i>J</i> = 2.3, 6.8, 13.1 Hz, 1H), 3.66- 3.82 (m, 1H), 3.88 (br.d, <i>J</i> = 5.3 Hz, 1H), 3.94 (ddt, <i>J</i> = 1.4, 6.2, 12.9 Hz, 1H), 4.13 (ddt, <i>J</i> = 1.4, 5.2, 12.9 Hz, 1H), 4.25 (ddd, <i>J</i> = 5.5, 6.7, 12.2 Hz, 1H), 4.99 (s, 1H), 5.14 (ddd, <i>J</i> = 1.4, 3.0, 10.3 Hz, 1H), 5.23 (ddd, <i>J</i> = 1.6, 3.0, 17.2 Hz, 1H), 5.85 (dddd, <i>J</i> = 5.3, 6.2, 10.3, 17.2 Hz, 1H)
<b><sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)</b>	:	21.2 (q), 26.3 (q), 28.2 (q), 36.1 (t), 62.1 (d), 67.8 (t), 70.9 (d), 72.7 (d), 96.8 (d), 108.6 (s), 117.3 (t), 134.0 (d) ppm

#### 4,6-Dideoxy-2,3-*O*-isopropylidene- $\alpha,\beta$ -L-lyxo-hexo-pyranose (**17**)

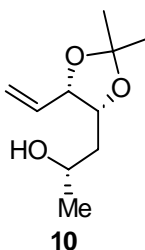


A mixture of **15** (2.5 g, 10.96 mmol), potassium *tert*-butoxide (1.6 g, 14.29 mmol) and DMSO (40 mL) was heated at 100 °C for 1 h, diluted with brine and repeatedly extracted with diethyl ether. The combined ether layer was washed with water, dried over sodium sulfate and concentrated. The residue **16** (2.42 g, 10.61 mmol) was taken in acetone:water (9:1) mixture (50 mL) at 0 °C, yellow mercuric oxide (3.0 g, 13.89 mmol)

and mercuric chloride (3.0 g, 11.07 mmol) were added over a period of 30 minutes. The stirring was continued for 8 h at room temperature, filtered through *Celite* and the filtrate was concentrated. The residue was partitioned between water and ethyl acetate and the organic layer was washed with saturated potassium iodide solution, brine, dried over sodium sulfate, filtered and concentrated. Purification of the crude on silica gel by eluting with ethyl acetate-light petroleum (1:6) furnished **17**.

<b>Yield</b>	:	1.32 g, 64% over two steps
<b>Mol. Formula</b>	:	C <sub>9</sub> H <sub>16</sub> O <sub>4</sub>
<b>Mol. Weight</b>	:	188
<b>ESI-MS <i>m/z</i></b>	:	211 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 57.45; H, 8.51% Found: C, 57.74; H, 8.37%
<b>[<math>\alpha</math>]<sub>D</sub><sup>25</sup></b>	:	+0.46 ( <i>c</i> 1.1, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3413, 2985, 2935, 1456, 1383, 1373, 1243, 1137, 1052 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	:	$\delta$ 1.21 (d, <i>J</i> = 6.3 Hz, 2.25H), 1.27 (d, <i>J</i> = 6.2 Hz, 0.75H), 1.35 (s, 2.25H), 1.37 (s, 0.75H), 1.42-1.50 (m, 1H), 1.52 (s, 2.25H), 1.54 (s, 0.75H), 1.82-1.93 (m, 1H), 3.44-3.60 (m, 0.25H), 3.74 (d, <i>J</i> = 3.4 Hz, 0.75H), 3.94-4.10 (m, 2H), 4.27-4.41 (m, 1H), 4.89 (dd, <i>J</i> = 2.3, 10.6 Hz, 0.25H), 5.42 (d, <i>J</i> = 3.2 Hz, 0.75H)
<b><sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)</b>	:	21.2 (q), 21.5 (q), 26.3 (q), 26.4 (q), 28.0 (q), 28.2 (q), 35.7 (t), 36.1 (t), 62.4 (d), 67.5 (d), 70.7 (d), 72.8 (d), 72.9 (d), 73.0 (d), 92.5 (d), 93.0 (d), 108.7 (s), 109.7 (s) ppm



**(2S,4R,5S)-4,5-O-Isopropylidene-hept-6-ene-2-ol (10)**

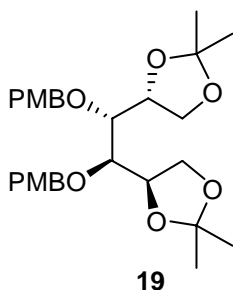
To a solution of **17** (1.0 g, 5.32 mmol) in THF: DMSO (4:1, 15 mL) at 0 °C was added methyltriphenylphosphorane ylide [generated by the action of *n*-butyllithium (8.49 mL, 20.21 mmol) with Ph<sub>3</sub>P<sup>+</sup>CH<sub>3</sub>I<sup>-</sup> (8.60 g, 21.29 mmol) in anhydrous THF (40 mL) at 0 °C]. The reaction mixture was stirred at rt for 24 h, quenched with saturated ammonium chloride and filtered. The organic layer was separated and aqueous layer extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to furnish **10**.

<b>Yield</b>	: 0.63 g, 64%
<b>Mol. Formula</b>	: C <sub>10</sub> H <sub>18</sub> O <sub>3</sub>
<b>Mol. Weight</b>	: 186
<b>ESI-MS <i>m/z</i></b>	: 209 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	: Calcd: C, 64.52; H, 9.68% Found: C, 64.64; H, 9.82%
<b>[α]<sub>D</sub><sup>25</sup></b>	: +17.7 ( <i>c</i> 0.8, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	: 3436, 2988, 2935, 1645, 1456, 1381, 1372, 1166, 1040, 667 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	: δ 1.23 (d, <i>J</i> = 6.3 Hz, 3H), 1.38 (s, 3H), 1.42 (ddd, <i>J</i> = 3.0, 8.6, 14.3 Hz, 1H), 1.49 (s, 3H), 1.62 (ddd, <i>J</i> = 3.3, 9.8,

14.3 Hz, 1H), 2.08 (br. s, 1H), 3.93-4.12 (m, 1H), 4.43 (ddd,  $J = 3.3, 6.4, 9.8$  Hz, 1H), 4.51-4.58 (m, 1H), 5.23 (ddd,  $J = 0.8, 1.7, 10.3$  Hz, 1H), 5.30 (ddd,  $J = 1.0, 1.7, 17.2$  Hz, 1H), 5.78 (ddd,  $J = 7.3, 10.3, 17.2$  Hz, 1H)

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ) : 23.9 (q), 25.5 (q), 28.0 (q), 39.1 (t), 64.6 (d), 74.8 (d), 79.4 (d), 108.1 (s), 117.9 (t), 134.2 (d) ppm

### 1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-(4-methoxybenzyl)-*D*-mannitol (**19**)



To a solution of 1,2:5,6-Di-*O*-isopropylidene-*D*-mannitol **18** (15.0 g, 57.25 mmol) in DMF (150 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 6.87 g, 171.75 mmol). After 1 h, 4-methoxybenzyl bromide (19.9 mL, 137.21 mmol) was added and stirring was continued for 36 h at room temperature. The reaction mixture was decomposed with ice-water and repeatedly extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to a syrup, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to furnish **19**.

**Yield** : 25.3 g, 88%

**Mol. Formula** :  $\text{C}_{28}\text{H}_{38}\text{O}_8$

**Mol. Weight** : 502

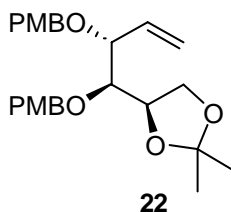
**ESI-MS  $m/z$**  : 525  $[\text{M}+\text{Na}]^+$

**Elemental Analysis** : Calcd: C, 66.93; H, 7.57 %



<b>Elemental Analysis</b>	: Calcd: C, 64.93; H, 7.35%
	Found: C, 64.63; H, 7.05%
<b><math>[\alpha]_D^{25}</math></b>	: +9.2 ( <i>c</i> 1, CHCl <sub>3</sub> )
<b>IR (Neat) <math>\tilde{\nu}</math></b>	: 3449, 2986, 2935, 1613, 1514, 1463, 1422, 1381, 1371, 1302, 1250, 921, 851, 823 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	: $\delta$ 1.34 (s, 3H), 1.43 (s, 3H), 3.55-3.75 (m, 4H), 3.78 (s, 6H), 3.80-3.92 (m, 2H), 4.02 (dd, <i>J</i> = 6.2, 8.3 Hz, 1H), 4.21-4.30 (m, 1H), 4.50, 4.57 (2d, <i>J</i> = 11.3 Hz, 2H), 4.60, 4.67 (2d, <i>J</i> = 11.4 Hz, 2H), 6.84, 6.85, 7.22, 7.23 (4d, <i>J</i> = 8.6 Hz, 8H)
<b><sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)</b>	: 25.0 (q), 26.5 (q), 55.0 (q), 63.4 (t), 66.4 (t), 71.0 (d), 73.4 (t), 73.9 (t), 75.8 (d), 78.2 (d), 78.7 (d), 108.3 (s), 113.7 (d), 129.7 (d), 129.9 (s), 130.0 (s), 159.2 (s), 159.3 (s) ppm

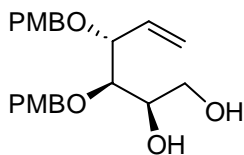
**(3*R*,4*S*,5*R*)-2,3-bis(4-Methoxybenzyloxy)-5,6-*O*-isopropylidene-hex-1-ene (22)**



To a solution of **20** (5.0 g, 10.82 mmol) in DCM (50 mL) at 0 °C was added Et<sub>3</sub>N (4.5 mL, 32.34 mmol) followed by methanesulfonyl chloride (2.1 mL, 27.20 mmol). After 1 h at room temperature, the reaction mixture was partitioned between water and DCM. The organic layer was dried over sodium sulfate and concentrated. The crude dimesylate **21** (5.81 g, 9.40 mmol), Zn (2.98 g, 47 mmol) and NaI (14.10 g, 94.0 mmol) were heated at 150 °C in DMF. After 2 h, the solvent was removed by washing the reaction mixture with water for several times and extracted with ethyl acetate. The organic layer was washed with saturated sodium thiosulfate, water, dried over sodium

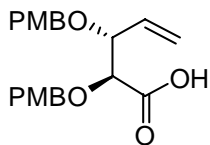
sulphate, evaporated and the residue purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **22**.

<b>Yield</b>	: 3.15 g, 68%, over two steps
<b>Mol. Formula</b>	: C <sub>25</sub> H <sub>32</sub> O <sub>6</sub>
<b>Mol. Weight</b>	: 428
<b>ESI-MS <i>m/z</i></b>	: 451 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	: Calcd: C, 70.09; H, 7.48% Found: C, 70.31; H, 7.20%
<b>[α]<sub>D</sub><sup>25</sup></b>	: +7.7 ( <i>c</i> 1.3, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	: 2987, 2935, 1612, 1586, 1464, 1442, 1380, 1370, 1302, 1218, 1173, 1036, 848, 823 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	: δ 1.32 (s, 3H), 1.40 (s, 3H), 3.69-3.73 (m, 1H), 3.79 (2s, 6H), 3.80-3.93 (m, 3H), 4.18 (ddd, <i>J</i> = 3.8, 6.3, 7.5 Hz, 1H), 4.27 (d, <i>J</i> = 11.5 Hz, 1H), 4.44-4.69 (m, 3H), 5.13-5.38 (m, 2H), 5.85 (ddd, <i>J</i> = 7.2, 9.9, 17.7 Hz, 1H), 6.83 (d, <i>J</i> = 8.6 Hz, 4H), 7.20, 7.23 (2d, <i>J</i> = 8.6 Hz, 4H)
<b><sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)</b>	: 25.3 (q), 26.5 (q), 55.1 (q), 65.4 (t), 70.2 (t), 74.5 (t), 76.4 (d), 80.1 (d), 80.8 (d), 108.0 (s), 113.5 (d), 113.6 (d), 118.1 (t), 129.4 (d), 129.5 (d), 130.2 (s), 130.6 (s), 135.7 (d), 159.09 (s), 159.13 (s) ppm

**(2*R*,3*R*,4*R*)-3,4-bis(4-Methoxybenzyloxy)hex-5-ene-1,2-diol (23)****23**

Compound **22** (3.5 g, 8.18 mmol), PPTS (0.2 g) and methanol (35 mL) were stirred for 36 h at room temperature and worked up as described above (see preparation of compound **20**) to give **23**.

<b>Yield</b>	: 2.52 g, 79%
<b>Mol. Formula</b>	: C <sub>22</sub> H <sub>28</sub> O <sub>6</sub>
<b>Mol. Weight</b>	: 388
<b>Elemental Analysis</b>	: Calcd: C, 68.04; H, 7.22% Found: C, 67.77; H, 7.40%
<b>[α]<sub>D</sub><sup>25</sup></b>	: +9.5 (c 0.7, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	: 3436, 3007, 2932, 1612, 1586, 1514, 1464, 1302, 1248, 1174, 1035, 823 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	: δ 3.57-3.79 (m, 5H), 3.80 (s, 3H), 3.81 (s, 3H), 3.97-4.17 (m, 2H), 4.30, 4.59 (2d, <i>J</i> = 11.5 Hz, 2H), 4.50, 4.60 (2d, <i>J</i> = 11.1 Hz, 2H), 5.30-5.45 (m, 2H), 5.93 (ddd, <i>J</i> = 7.1, 10.9, 16.8 Hz, 1H), 6.84, 6.86, 7.20, 7.21 (4d, <i>J</i> = 8.7 Hz, 8H)
<b><sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)</b>	: 55.0 (q), 63.1 (t), 70.3 (t), 71.1 (d), 73.4 (t), 79.6 (d), 79.8 (d), 113.6 (d), 113.7 (d), 118.8 (t), 129.4 (d), 129.6 (d), 129.9 (s), 134.5 (d), 159.2 (s) ppm

**(2*S*,3*R*)-2,3-bis(4-Methoxybenzyloxy)pent-4-enoic acid (11)****11**

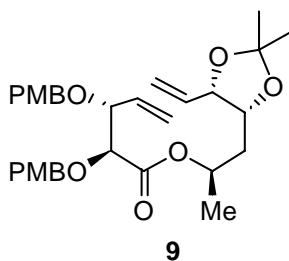
A solution of **23** (1.4 g, 3.61 mmol), sodium metaperiodate adsorbed on silica gel (12 g containing 2.45 g of NaIO<sub>4</sub>) in DCM (25 mL) was stirred at rt for 1 h, filtered and concentrated to afford aldehyde **24** (1.21 g, 3.4 mmol), which was dissolved in <sup>t</sup>BuOH:H<sub>2</sub>O (3:1, 30 mL). To this solution were successively added NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O (1.59 g, 10.19 mmol), 2-methy-2-butene (7 mL) and sodium chlorite (918 mg, 10.2 mmol). The reaction was stirred for 1 h at rt and was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined extract was dried over sodium sulfate and concentrated to afford a crude product, which was purified on silica gel by eluting with ethyl acetate-light petroleum (1:1.5) to afford **11** as colorless oil.

<b>Yield</b>	:	974 mg, 73%, over two steps
<b>Mol. Formula</b>	:	C <sub>21</sub> H <sub>24</sub> O <sub>6</sub>
<b>Mol. Weight</b>	:	372
<b>ESI-MS <i>m/z</i></b>	:	395 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 67.74; H, 6.45% Found: C, 67.89; H, 6.51%
<b>[α]<sub>D</sub><sup>25</sup></b>	:	-46.8 ( <i>c</i> 0.9, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3394, 1724, 1612, 1514, 1249, 1174, 1036, 668 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	:	δ 3.78 (s, 3H), 3.80 (s, 3H), 3.97 (d, <i>J</i> = 3.4 Hz, 1H), 4.11-4.16 (m, 1H), 4.30, 4.56 (2d, <i>J</i> = 11.5 Hz, 2H), 4.49, 4.67

(2d,  $J = 11.6$  Hz, 2H), 5.29-5.38 (m, 2H), 5.79-5.96 (m, 1H), 6.82, 6.85, 7.17, 7.23 (4d,  $J = 8.7$  Hz, 8H)

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ) : 55.11 (q), 55.14 (q), 70.5 (t), 73.2 (t), 79.7 (d), 80.1 (d), 113.7 (d), 113.8 (d), 119.8 (t), 128.7 (s), 129.4 (s), 129.5 (d), 129.9 (d), 134.0 (d), 159.3 (s), 159.6 (s), 173.4 (s) ppm

**(2*S*,3*R*)-((*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-yl) 2,3-bis(4-methoxybenzyloxy)pent-4-enoate (**9**)**



To a solution of **10** (200 mg, 1.07 mmol), **11** (500 mg, 1.34 mmol) and TPP (563 mg, 2.15 mmol) in THF (8 mL) at 0 °C was added DEAD (0.34 mL, 2.16 mmol). Stirring was continued at 0 °C for 1 h and then at room temperature for next 2 h at which time it was concentrated and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **9**.

**Yield** : 467 mg, 80%

**Mol. Formula** :  $\text{C}_{31}\text{H}_{40}\text{O}_8$

**Mol. Weight** : 540

**ESI-MS  $m/z$**  : 563  $[\text{M}+\text{Na}]^+$

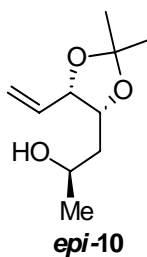
**Elemental Analysis** : Calcd: C, 68.89; H, 7.41%  
Found: C, 69.02; H, 7.54%

$[\alpha]_D^{25}$  :  $-38.9$  ( $c$  1.0,  $\text{CHCl}_3$ )



- IR** (CHCl<sub>3</sub>)  $\tilde{\nu}$  : 2934, 1736, 1612, 1513, 1464, 1381, 1249, 1173, 1037, 667 cm<sup>-1</sup>
- <sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) :  $\delta$  1.20 (d,  $J$  = 6.3 Hz, 3H), 1.32 (s, 3H), 1.47 (s, 3H), 1.54 (ddd,  $J$  = 4.9, 6.6, 14.0 Hz, 1H), 1.86 (ddd,  $J$  = 6.6, 9.1, 14.0 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.92 (d,  $J$  = 4.7 Hz, 1H), 4.09 (br. dd,  $J$  = 4.7, 7.9 Hz, 1H), 4.17 (ddd,  $J$  = 5.0, 6.0, 9.1 Hz, 1H), 4.31, 4.40, 4.54, 4.69 (4d,  $J$  = 11.7 Hz, 4H), 4.48 (br. dd,  $J$  = 6.3, 7.7 Hz, 1H), 5.10 (q,  $J$  = 6.3 Hz, 1H), 5.20-5.36 (m, 4H), 5.66-5.96 (m, 2H), 6.81, 6.83, 7.19, 7.24 (4d,  $J$  = 8.7 Hz, 8H)
- <sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) : 19.7 (q), 25.7 (q), 28.3 (q), 36.5 (t), 55.2 (q), 69.5 (d), 70.4 (t), 72.6 (t), 74.9 (d), 79.6 (d), 80.5 (d), 80.8 (d), 108.5 (s), 113.6 (d), 113.7 (d), 118.7 (t), 119.4 (t), 129.4 (d), 129.5 (s), 129.7 (d), 130.1 (s), 134.0 (d), 134.6 (d), 159.1 (s), 159.4 (s), 169.6 (s) ppm

**(2*R*,4*R*,5*S*)-4,5-*O*-Isopropylidene-hept-6-ene-2-ol (*epi*-10)**

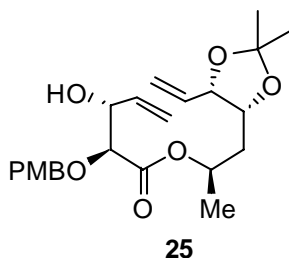


To a solution of **9** (50 mg, 0.092 mmol) in moist EtOH (2 mL) was added LiOH.H<sub>2</sub>O (7 mg, 0.17 mmol) and the reaction mixture was stirred at room temperature for 0.5 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate- light petroleum (1:6) to furnish ***epi*-10** as colorless oil.

**Yield** : 18 mg, 81%

<b>Mol. Formula</b>	: C <sub>10</sub> H <sub>18</sub> O <sub>3</sub>
<b>Mol. Weight</b>	: 186
<b>ESI-MS <i>m/z</i></b>	: 209 [M+Na] <sup>+</sup>
<b>[α]<sub>D</sub><sup>25</sup></b>	: +8.0 ( <i>c</i> 0.6, CHCl <sub>3</sub> )
<b><sup>1</sup>H NMR</b> (200 MHz, CDCl <sub>3</sub> )	: δ 1.20 (d, <i>J</i> = 6.2 Hz, 3H), 1.38 (s, 3H), 1.42-1.51 (m, 1H), 1.52 (s, 3H), 1.56-1.64 (m, 1H), 3.93-4.09 (m, 1H), 4.36 (ddd, <i>J</i> = 3.6, 6.3, 10.0 Hz, 1H), 4.56 (dd, <i>J</i> = 6.5, 7.5 Hz, 1H), 5.24-5.37 (m, 2H), 5.80 (ddd, <i>J</i> = 7.5, 10.0, 17.4 Hz, 1H)
<b><sup>13</sup>C NMR</b> (50 MHz, CDCl <sub>3</sub> )	: 23.4 (q), 25.6 (q), 28.0 (q), 39.0 (t), 67.6 (d), 78.4 (d), 79.8 (d), 109.0 (s), 118.7 (t), 133.9 (d) ppm

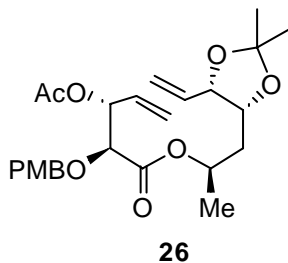
**(2*S*,3*R*)-((*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-yl) 3-hydroxy-2-(4-methoxybenzyloxy)pent-4-enoate (25)**



To a solution of **9** (400 mg, 0.74 mmol) in DCM (35 mL) at 0 °C was added aqueous NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub> (pH 7) buffer (15 mL) and DDQ (800 mg, 3.52 mmol). The reaction was allowed to warm to room temperature. After 4 h at rt, it was filtered through *Celite* and layers separated. The aqueous layer was extracted with DCM and the combined organic layer was dried over sodium sulphate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:6) to afford unreacted **9** (94 mg) and **25**.

<b>Yield</b>	:	162 mg, 68%, based on recovered starting material
<b>Mol. Formula</b>	:	C <sub>23</sub> H <sub>32</sub> O <sub>7</sub>
<b>Mol. Weight</b>	:	420
<b>ESI-MS <i>m/z</i></b>	:	443 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 65.71; H, 7.62% Found: C, 65.95; H, 7.80%
<b>[α]<sub>D</sub><sup>25</sup></b>	:	+4.3 (c 1.2, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3436, 2925, 2854, 1744, 1615, 1518, 1459, 1379, 1250, 1171, 1097, 1037 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)</b>	:	δ 1.27 (d, <i>J</i> = 6.3 Hz, 3H), 1.33 (s, 3H), 1.48 (s, 3H), 1.58 (ddd, <i>J</i> = 4.6, 5.8, 14.2 Hz, 1H), 1.88 (ddd, <i>J</i> = 7.2, 9.0, 14.2 Hz, 1H), 2.68 (br. s, 1H), 3.79 (s, 3H), 3.87 (d, <i>J</i> = 4.8 Hz, 1H), 4.22 (ddd, <i>J</i> = 4.6, 6.0, 9.0 Hz, 1H), 4.32-4.36 (m, 1H), 4.39 (d, <i>J</i> = 11.2 Hz, 1H), 4.50 (br. dd, <i>J</i> = 6.2, 7.6 Hz, 1H), 4.69 (d, <i>J</i> = 11.2 Hz, 1H), 5.12-5.39 (m, 5H), 5.69-5.94 (m, 2H), 6.86, 7.25 (2d, <i>J</i> = 8.7 Hz, 4H)
<b><sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)</b>	:	20.0 (q), 25.6 (q), 28.2 (q), 36.6 (t), 55.2 (q), 70.0 (d), 72.5 (t), 73.4 (d), 75.1 (d), 79.7 (d), 80.7 (d), 108.6 (s), 113.9 (d), 117.2 (t), 118.7 (t), 128.9 (s), 129.9 (d), 134.0 (d), 136.0 (d), 159.6 (s), 169.9 (s) ppm

**(2*S*,3*R*)-((*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-yl) 3-acetoxy-2-(4-methoxybenzyloxy)pent-4-enoate (**26**)**



To a solution of **25** (20 mg, 47.6  $\mu\text{mol}$ ) and pyridine (15.4  $\mu\text{L}$ , 0.19 mmol) in dry DCM (2 mL) was added acetic anhydride (6.7  $\mu\text{L}$ , 71.4  $\mu\text{mol}$ ) at 0  $^{\circ}\text{C}$  and then the reaction mixture was stirred at room temperature for 3 h. Water was added to the reaction mixture and aqueous layer was extracted with DCM. Combined organic layer was thoroughly washed with water, dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to furnish the acetate derivative **26**.

**Yield** : 19 mg, 86%

**Mol. Formula** :  $\text{C}_{25}\text{H}_{34}\text{O}_8$

**Mol. Weight** : 462

**Elemental Analysis** : Calcd: C, 64.92; H, 7.41%  
Found: C, 64.59; H, 7.14%

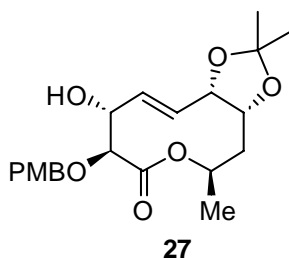
$[\alpha]_{\text{D}}^{25}$  :  $-14.47$  ( $c$  1.3,  $\text{CHCl}_3$ )

**$^1\text{H}$  NMR** (200 MHz,  $\text{CDCl}_3$ ) :  $\delta$  1.25 (d,  $J = 6.1$  Hz, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.58 (ddd,  $J = 4.8, 6.6, 14.0$  Hz, 1H), 1.81 (ddd,  $J = 6.7, 9.1, 14.0$  Hz, 1H), 2.07 (s, 3H), 3.81 (s, 3H), 4.01 (d,  $J = 4.2$  Hz, 1H), 4.19 (ddd,  $J = 4.6, 6.1, 9.1$  Hz, 1H), 4.42 (d,  $J = 11.8$  Hz, 1H), 4.53 (dd,  $J = 6.2, 7.6$  Hz, 1H), 4.76 (d,  $J = 11.8$  Hz, 1H), 5.06- 5.19 (m, 1H), 5.24-5.30 (m, 3H), 5.37-

5.39 (m, 1H), 5.58-5.63 (m, 1H), 5.79 (ddd,  $J = 7.7, 10.2, 17.1$  Hz, 1H) 5.87 (ddd,  $J = 6.6, 10.4, 17.2$  Hz, 1H), 6.87, 7.26 (2d,  $J = 8.7$  Hz, 4H)

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) : 19.6 (q), 20.9 (q), 25.7 (q), 28.2 (q), 36.5 (t), 55.2 (q), 70.0 (d), 72.5 (t), 74.3 (d), 74.9 (d), 78.4 (d), 79.6 (d), 108.6 (s), 113.8 (d), 118.8 (t), 119.1 (t), 128.9 (s), 129.8 (d), 132.1 (d), 133.9 (d), 159.5 (s), 168.8 (s), 169.7 (s) ppm;

**(3a*R*,5*R*,8*S*,9*R*,11a*S*,*E*)-9-Hydroxy-8-(4-methoxybenzyloxy)-2,2,5-trimethyl-4,5,8,9-tetrahydro-3aH-[1,3]dioxolo[4,5-d]oxecin-7(11aH)-one (27)**



A degassed solution of **25** (124 mg, 0.3 mmol) and Grubbs' 2<sup>nd</sup> Generation catalyst (7 mg, 8  $\mu\text{mol}$ ) in dry benzene (150 mL) was heated to reflux under argon atmosphere for 6 h and then concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:4) to furnish compound **27**.

**Yield** : 74 mg, 64%

**Mol. Formula** :  $\text{C}_{21}\text{H}_{28}\text{O}_7$

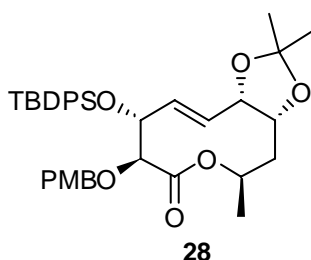
**Mol. Weight** : 392

**ESI-MS  $m/z$**  : 415  $[\text{M}+\text{Na}]^+$

**Elemental Analysis** : Calcd: C, 64.29; H, 7.14%  
Found: C, 64.44; H, 7.07%

- $[\alpha]_D^{25}$  : +36.4 (*c* 1.1, CHCl<sub>3</sub>)
- IR (CHCl<sub>3</sub>)  $\tilde{\nu}$  : 3448, 2983, 2934, 1719, 1607, 1514, 1458, 1381, 1253, 1170, 1103 cm<sup>-1</sup>
- <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  1.35 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 3H), 1.49-1.51 (m, 1H), 2.31 (br. s, 1H), 2.52 (ddd, *J* = 4.3, 9.8, 15.8 Hz, 1H), 3.80 (s, 3H), 4.09 (d, *J* = 3.9 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.43 (dd, *J* = 6.4, 9.8 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.50-4.55 (m, overlapped, 1H), 4.78 (dd, *J* = 6.6, 8.1 Hz, 1H), 5.05-5.19 (m, 1H), 5.72 (ddd, *J* = 1.2, 8.0, 16.5 Hz, 1H), 5.98 (dd, *J* = 3.0, 16.5 Hz, 1H), 6.86, 7.22 (2d, *J* = 8.7 Hz, 4H)
- <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) : 18.2 (q), 25.2 (q), 28.0 (q), 35.2 (t), 55.2 (q), 69.3 (d), 70.0 (d), 72.4 (t), 75.3 (d), 78.5 (d), 83.2 (d), 108.5 (s), 114.0 (d), 126.1 (d), 128.8 (s), 129.8 (d), 133.3 (d), 159.7 (s), 170.7 (s) ppm

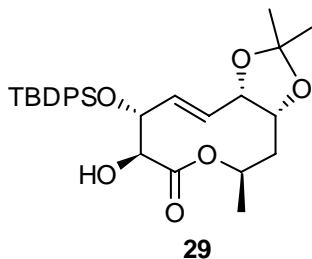
**(3a*R*,5*R*,8*S*,9*R*,11a*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-8-(4-methoxybenzyloxy)-2,2,5-trimethyl-4,5,8,9-tetrahydro-3aH-[1,3]dioxolo[4,5-*d*]oxecin-7(11aH)-one (28)**



To a solution of **27** (150 mg, 0.38 mmol) in dry DCM (10 mL) and imidazole (39 mg, 0.57 mmol) was added *tert*-butyldiphenylchloro silane (126  $\mu$ L, 0.49 mmol) and the reaction mixture was refluxed for 10 h and then concentrated. The residue was purified on silica gel column by eluting with ethyl acetate-light petroleum (1:9) to afford **28**.

<b>Yield</b>	:	203 mg, 84%
<b>Mol. Formula</b>	:	C <sub>37</sub> H <sub>46</sub> O <sub>7</sub> Si
<b>Mol. Weight</b>	:	630
<b>ESI-MS <i>m/z</i></b>	:	653 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 70.48; H, 7.30 Found: C, 70.73; H, 7.17%
<b>[α]<sub>D</sub><sup>25</sup></b>	:	+2.9 ( <i>c</i> 3.3, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3018, 2929, 2856, 2742, 1725, 1701, 1685, 1601, 1578, 1501 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)</b>	:	δ 1.11 (s, 9H), 1.34 (d, <i>J</i> = 6.9 Hz, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 1.44-1.52 (m, overlapped, 1H), 2.50 (ddd, <i>J</i> = 3.9, 9.9, 15.2 Hz, 1H), 3.66 (d, <i>J</i> = 3.8 Hz, 1H), 3.78 (s, 3H), 3.93, 4.11 (2d, <i>J</i> = 11.1 Hz, 2H), 4.44–4.51 (m, 2H), 4.83 (dd, <i>J</i> = 6.5, 7.4 Hz, 1H), 5.13–5.21 (m, 1H), 5.93 (dd, <i>J</i> = 2.4, 16.0 Hz, 1H), 6.06 (dd, <i>J</i> = 7.0, 16.0 Hz, 1H), 6.76, 6.96 (2d, <i>J</i> = 8.6 Hz, 4H), 7.32–7.44 (m, 6H), 7.57–7.61 (m, 2H), 7.76–7.81 (m, 2H)
<b><sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)</b>	:	18.2 (q), 19.3 (s), 25.3 (q), 26.9 (q), 28.0 (q), 35.3 (t), 55.2 (q), 67.8 (d), 71.1 (d), 72.1 (t), 75.5 (d), 78.9 (d), 83.6 (d), 108.3 (s), 113.7 (d), 127.1 (d), 127.68 (d), 127.73 (d), 129.0 (d), 129.6 (d), 129.8 (d), 129.9 (s), 132.9 (s), 133.3 (d), 133.6 (d), 134.8 (d), 135.7 (d), 136.1 (d), 159.4 (s), 168.7 (s) ppm

**(3a*R*,5*R*,8*S*,9*R*,11a*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-8-hydroxy-2,2,5-trimethyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecin-7(11a*H*)-one (29)**



At room temperature, a solution of **28** (190 mg, 0.30 mmol) DDQ (170 mg, 0.75 mmol) in DCM-Water (6 mL, 18:1), was stirred for 3 h. To this aqueous sodiumbicarbonate solution was added and the contents were partitioned between water and DCM. The aqueous layer was extracted with DCM and the combined organic layer was dried over sodium sulphate and concentrated. The residue was purified on silica gel column by eluting with ethyl acetate-light petroleum (1:6) gave **29**.

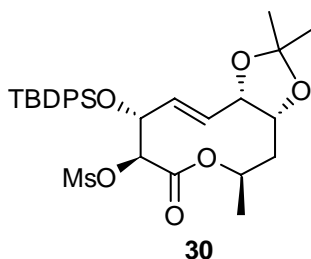
<b>Yield</b>	: 110 mg, 71%
<b>Mol. Formula</b>	: C <sub>29</sub> H <sub>38</sub> O <sub>6</sub> Si
<b>Mol. Weight</b>	: 510
<b>ESI-MS <i>m/z</i></b>	: 533 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	: Calcd: C, 68.23; H, 7.45 Found: C, 68.38; H, 7.67
<b>[α]<sub>D</sub><sup>25</sup></b>	: +1.43 ( <i>c</i> 2.6, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	: 3448, 3072, 3015, 2984, 2931, 2858, 1735, 1680, 1599, 1578, 1511 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)</b>	: δ 1.12 (s, 9H), 1.35 (d, <i>J</i> = 6.9 Hz, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 1.57 (br. dd, <i>J</i> = 5.2, 7.1 2H), 2.56 (ddd, <i>J</i> = 4.2, 9.9, 15.8 Hz, 1H), 3.97 (t, <i>J</i> = 4.8 Hz, 1H), 4.37–4.45 (m, 2H), 4.80 (dd, <i>J</i> = 6.4, 8.1 Hz, 1H), 5.12–5.26 (m, 1H), 5.95 (dd, <i>J</i> = 3.0, 16.1 Hz, 1H), 6.14 (ddd, <i>J</i> = 1.0, 8.1,



16.1 Hz), 7.37–7.43 (m, 6H), 7.60–7.65 (m, 2H), 7.79–7.84 (m, 2H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) : 18.2 (q), 19.3 (s), 25.3 (q), 26.9 (q), 28.0 (q), 35.2 (t), 68.7 (d), 71.8 (d), 75.4 (d), 76.9 (d), 78.8 (d), 108.5 (s), 127.7 (d), 127.8 (d), 128.8 (d), 129.8 (d), 130.0 (d), 132.0 (d), 132.8 (s), 133.4 (s), 135.7 (d), 136.0 (d), 167.7 (s) ppm

**(3a*R*,5*R*,8*S*,9*R*,11*α**S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-2,2,5-trimethyl-7-oxo-4,5,7,8,9,11a-hexahydro-3aH-[1,3]dioxolo[4,5-d]oxecin-8-yl methanesulfonate (30)**



At 0 °C, a solution of **29** (100 mg, 0.19 mmol), triethylamine (66 μL, 0.475 mmol), DMAP (catalytic) was treated with methanesulfonyl chloride (34 μL, 0.437 mmol) and the reaction mixture was warmed to rt and stirred for 2 h. The reaction was portioned between water and DCM and the aqueous layer was extracted with DCM. Combined organic layer was dried over sodium sulphate and concentrated. Purification of the resulting crude product by column chromatography (1:6 ethyl acetate- light petroleum) afforded **30** (95 mg, 82 %) as a sticky white solid.

**Yield** : 95 mg, 82 %

**Mol. Formula** : C<sub>30</sub>H<sub>40</sub>O<sub>8</sub>SSi

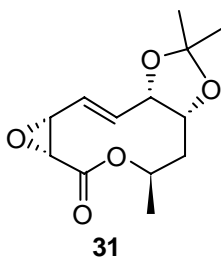
**Mol. Weight** : 588

**ESI-MS *m/z*** : 611 [M+Na]<sup>+</sup>

**Elemental Analysis** : Calcd: C, 61.22; H, 6.80  
Found: C, 61.48; H, 6.73%

$[\alpha]_D^{25}$	:	+2.0 ( <i>c</i> 1.4, CHCl <sub>3</sub> )
IR (CHCl <sub>3</sub> ) $\tilde{\nu}$	:	3018, 2986, 2932, 2859, 1741, 1589 cm <sup>-1</sup>
<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> )	:	$\delta$ 1.14 (s, 9H), 1.35 (d, <i>J</i> = 6.8 Hz, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 1.53 (br. m, 1H), 2.49–2.56 (m, 1H), 2.51 (s, 3H), 4.37 (d, <i>J</i> = 3.8 Hz, 1H), 4.47 (dd, <i>J</i> = 6.5, 9.5 Hz, 1H), 4.55 (dt, <i>J</i> = 1.3, 3.7 Hz, 1H), 4.84 (dd, <i>J</i> = 7.0, 8.0 Hz, 1H), 5.20–5.23 (m, 1H), 5.88 (dd, <i>J</i> = 3.0, 16.1 Hz, 1H), 6.16 (ddd, <i>J</i> = 1.0, 8.5, 16.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.60–7.62 (m, 2H), 7.83–7.85 (m, 2H)
<sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> )	:	17.9 (q), 19.3 (s), 25.3 (q), 26.8 (q), 27.9 (q), 35.2 (t), 37.4 (q), 69.2 (d), 70.1 (d), 75.4 (d), 78.6 (d), 80.2 (d), 108.6 (s), 127.9 (d), 128.1 (d), 129.4 (d), 130.1 (d), 130.4 (d), 130.8 (d), 132.1 (s), 133.0 (s), 135.7 (d), 136.1 (d), 164.5 (s) ppm

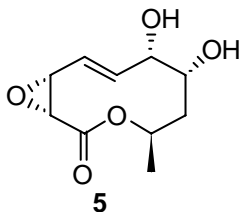
**(1a*R*,4*R*,5a*R*,8a*S*,10a*R*,*E*)-4,7,7-Trimethyl-5,5a,8a,10a-tetrahydro-1aH-[1,3]dioxolo[4,5-*g*]oxireno[2,3-*c*]oxecin-2(4H)-one (31)**



To a solution of **30** (90 mg, 0.15 mmol) in dry THF (2 mL), 1M solution of TBAF in THF (0.36 mL, 0.36 mmol) was added at 0 °C and the contents were stirred at rt for 8 h. To this was added satd. ammonium chloride and the aqueous layer was extracted with ethyl acetate and the combined organic layer was dried with sodium sulphate and concentrated. The residue was purified on silica gel column by eluting with ethyl acetate-light petroleum (1: 9) to afford **31**.

<b>Yield</b>	: 24 mg, 63%
<b>Mol. Formula</b>	: C <sub>13</sub> H <sub>18</sub> O <sub>5</sub>
<b>Mol. Weight</b>	: 254
<b>ESI-MS <i>m/z</i></b>	: 277 [M+Na] <sup>+</sup>
<b>Elemental Analysis</b>	: Calcd: C, 61.42; H, 7.09 Found: C, 61.63; H, 7.26
<b>[α]<sub>D</sub><sup>25</sup></b>	: +3.62 ( <i>c</i> 1.7, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	: 2986, 2927, 2855, 1737, 1456, 1371, 1221, 1167, 1080 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (400 MHz, Acetone d<sub>6</sub>)</b>	: δ 1.31 (s, 3H), 1.40 (d, <i>J</i> = 6.9 Hz, 3H), 1.40 (s, 3H), 1.65–1.71 (m, 1H), 2.25 (ddd, <i>J</i> = 1.7, 9.8, 15.9 Hz, 1H), 3.75 (ddd, <i>J</i> = 0.7, 2.2, 3.9 Hz, 1H), 3.78 (d, <i>J</i> = 4.1 Hz, 1H), 4.39 (dd, <i>J</i> = 6.2, 9.6 Hz, 1H), 4.73 (dd, <i>J</i> = 7.1, 8.3 Hz, 1H), 4.93–4.99 (m, 1H), 5.58 (dd, <i>J</i> = 9.0, 16.2 Hz, 1H), 5.95 (d, <i>J</i> = 16.2 Hz, 1H)
<b><sup>13</sup>C NMR (100 MHz, Acetone d<sub>6</sub>)</b>	: 24.6 (q), 27.4 (q), 29.4 (t), 52.7 (d), 57.3 (d), 69.8 (d), 75.4 (d), 77.9 (d), 107.9 (s), 127.4 (d), 128.0 (d), 166.3 (s) ppm

**(1*R*,4*R*,6*R*,7*S*,10*R*,*E*)-6,7-Dihydroxy-4-methyl-3,11-dioxabicyclo[8.1.0]undec-8-en-2-one (5)**

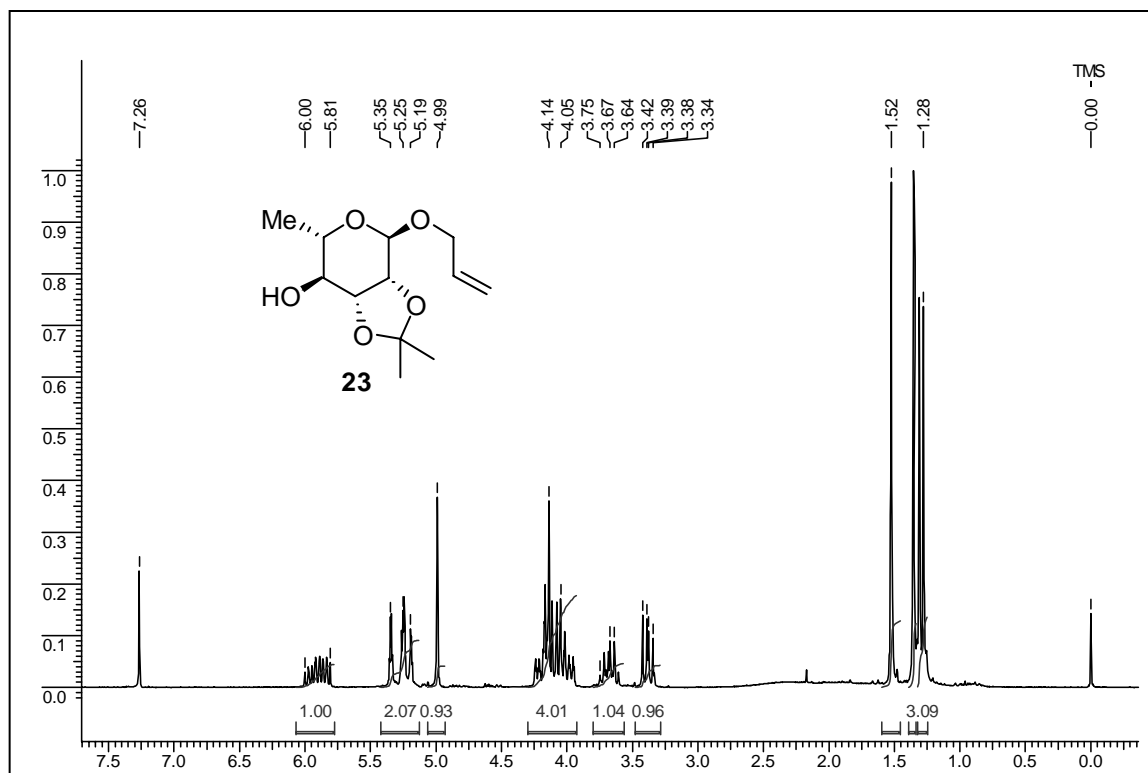
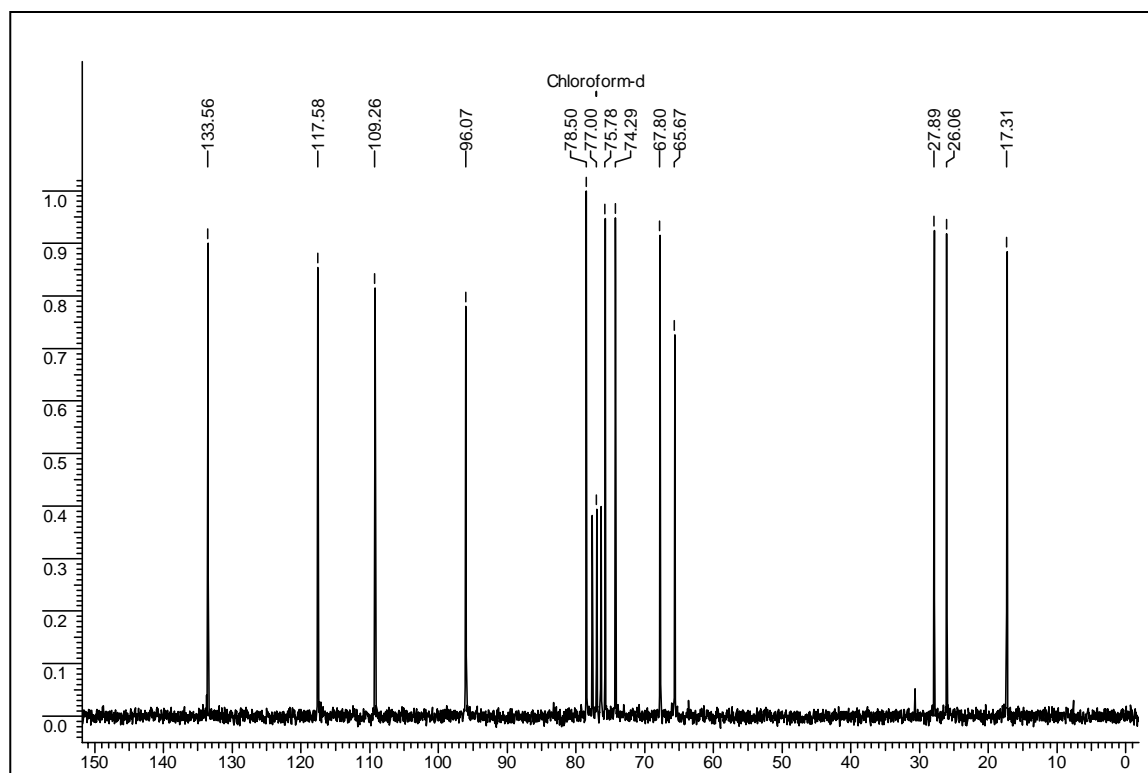


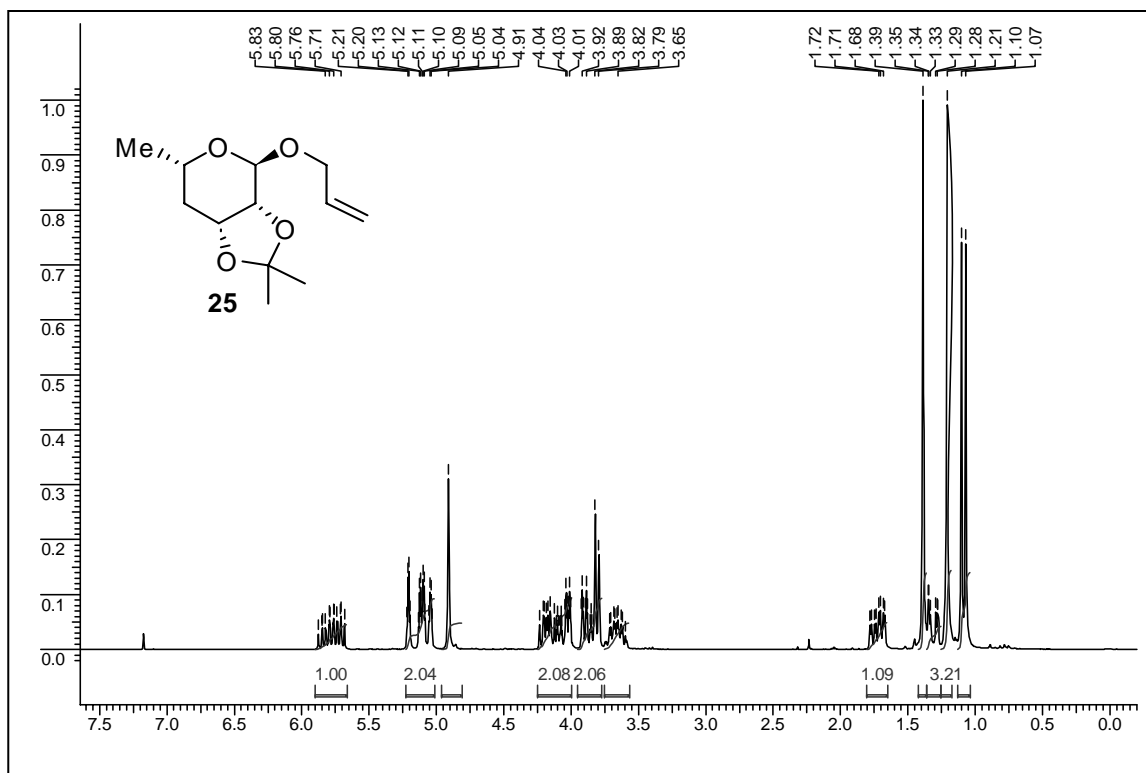
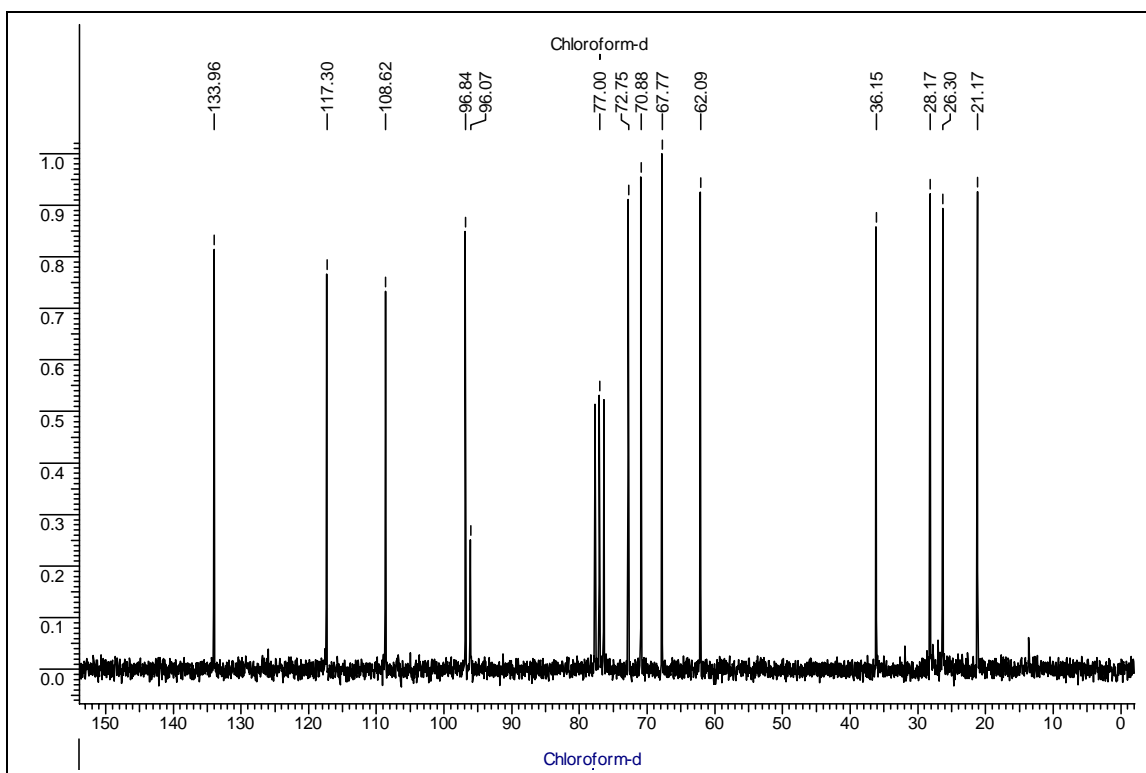
At 0 °C, a solution of **31** (20 mg, 78.7 μmol) in dry DCM (1 mL) was treated with TFA (10 μl) and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified on silica gel column by eluting with ethyl acetate- light petroleum (1: 1) to furnish **5**.

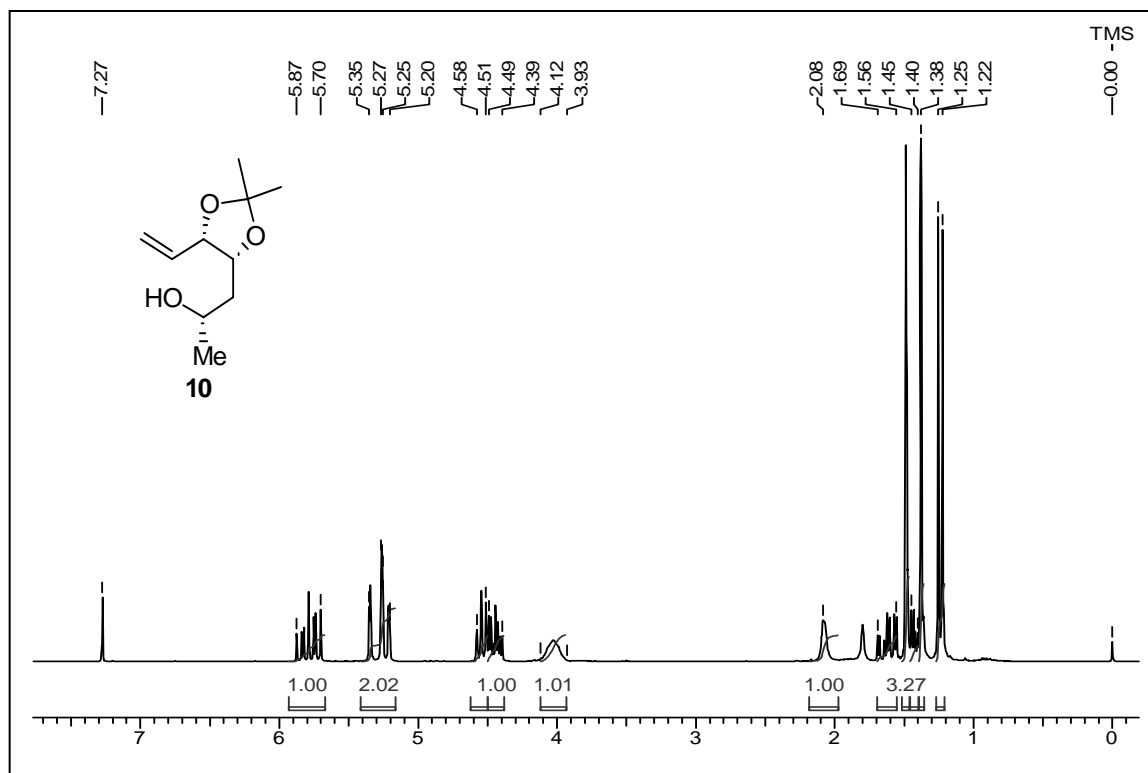
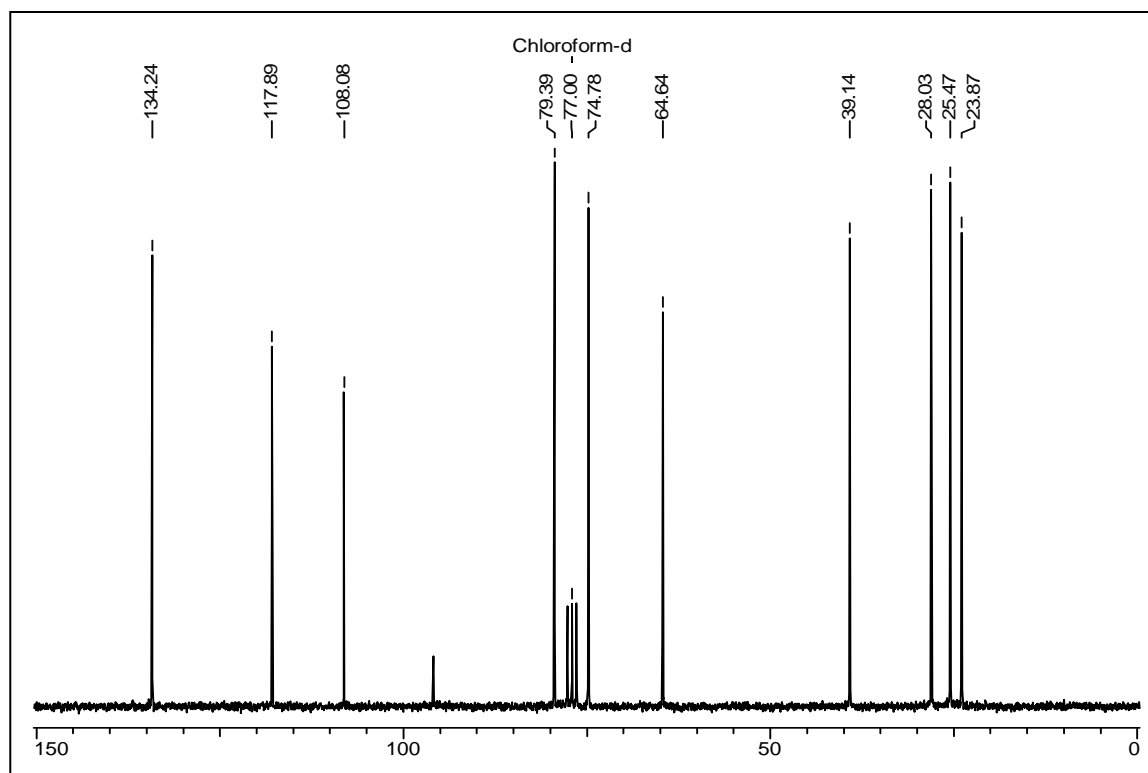
<b>Yield</b>	:	10mg, 60%
<b>Mol. Formula</b>	:	C <sub>10</sub> H <sub>14</sub> O <sub>5</sub>
<b>Mol. Weight</b>	:	214
<b>ESI-MS <i>m/z</i></b>	:	237 [M+Na] <sup>+</sup> , 254 [M+H+K] <sup>+</sup>
<b>Elemental Analysis</b>	:	Calcd: C, 56.07; H, 6.54 Found: C, 55.79; H, 6.27
<b>[α]<sub>D</sub><sup>25</sup></b>	:	-11.78 ( <i>c</i> 0.5, CHCl <sub>3</sub> )
<b>IR (CHCl<sub>3</sub>) <math>\tilde{\nu}</math></b>	:	3401, 2926, 2854, 1731, 1648, 1460, 1369, 1221, 1103, 1065 cm <sup>-1</sup>
<b><sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)</b>	:	δ 1.38 (d, <i>J</i> = 6.7 Hz, 3H), 1.53 (dd, <i>J</i> = 6.3, 16.1 Hz, 1H), 2.28 (ddd, <i>J</i> = 2.3, 7.7, 16.1 Hz, 1H), 3.68–3.73 (m, 2H), 3.90 (dd, <i>J</i> = 3.1, 7.4 Hz, 1H), 4.19 (dd, <i>J</i> = 3.1, 8.3 Hz, 1H), 5.18–5.25 (m, 1H), 5.64 (dd, <i>J</i> = 8.3, 16.1 Hz, 1H), 5.80 (dd, <i>J</i> = 1.8, 16.1 Hz, 1H)
<b><sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)</b>	:	19.7 (q), 35.7 (t), 53.0 (d), 58.0 (d), 69.7 (d), 72.1 (d), 75.6 (d), 125.9 (d), 129.3 (d), 166.7 (s) ppm.

## SPECTROSCOPIC DATA

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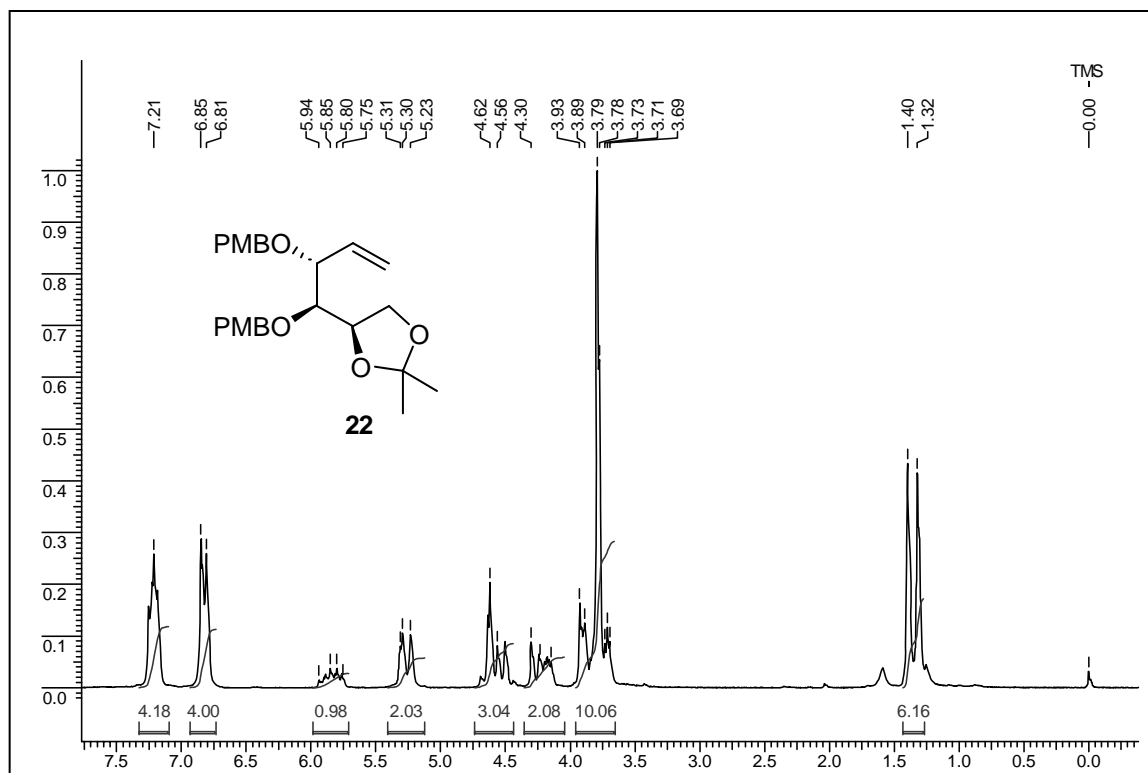
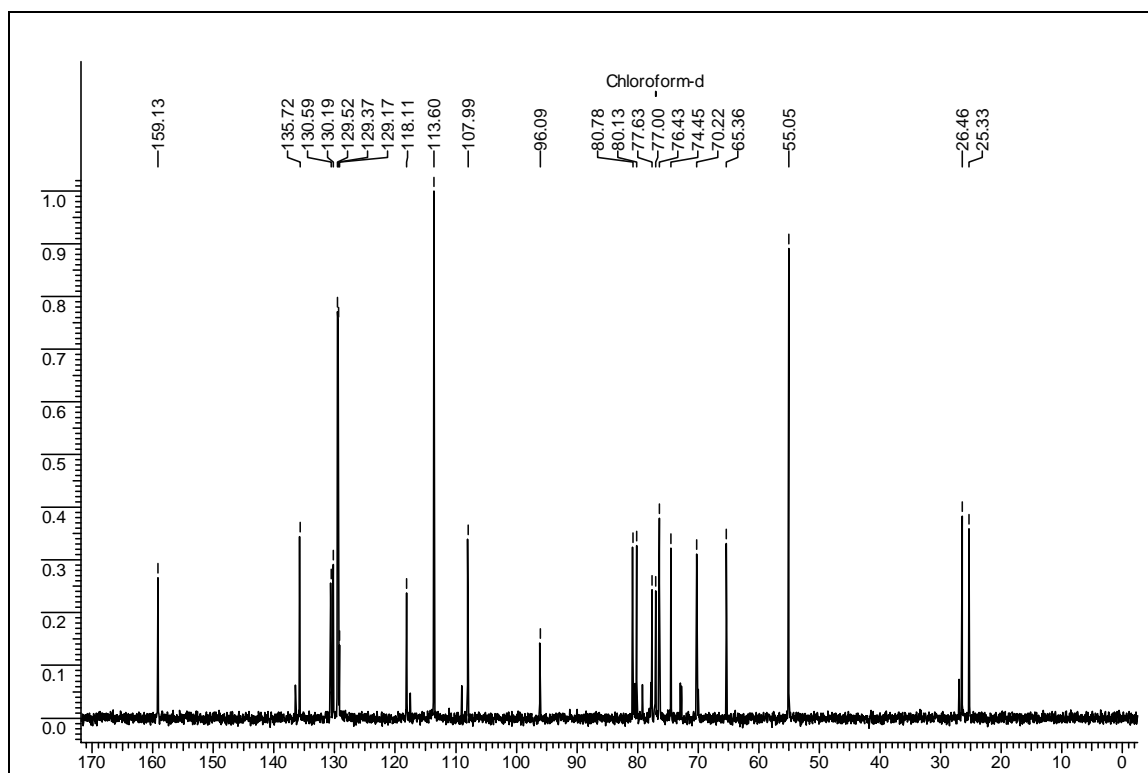
**$^1\text{H}$  NMR spectra of compound 23** **$^{13}\text{C}$  NMR spectra of compound 23**

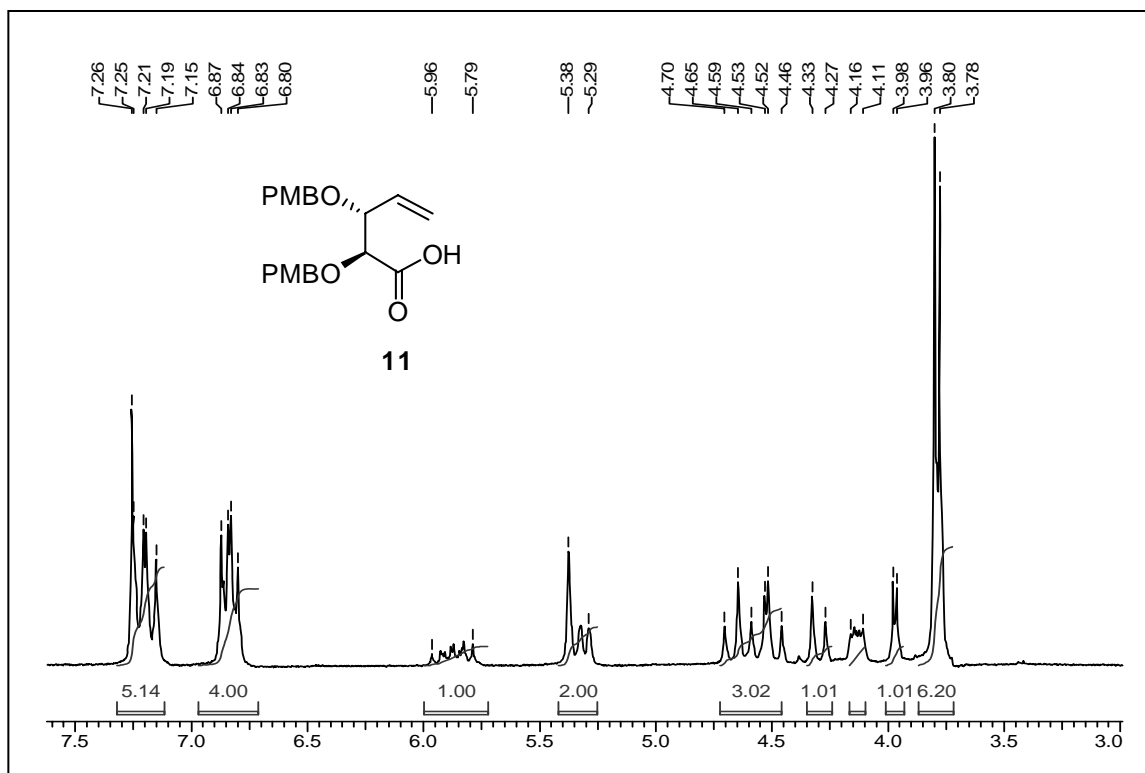
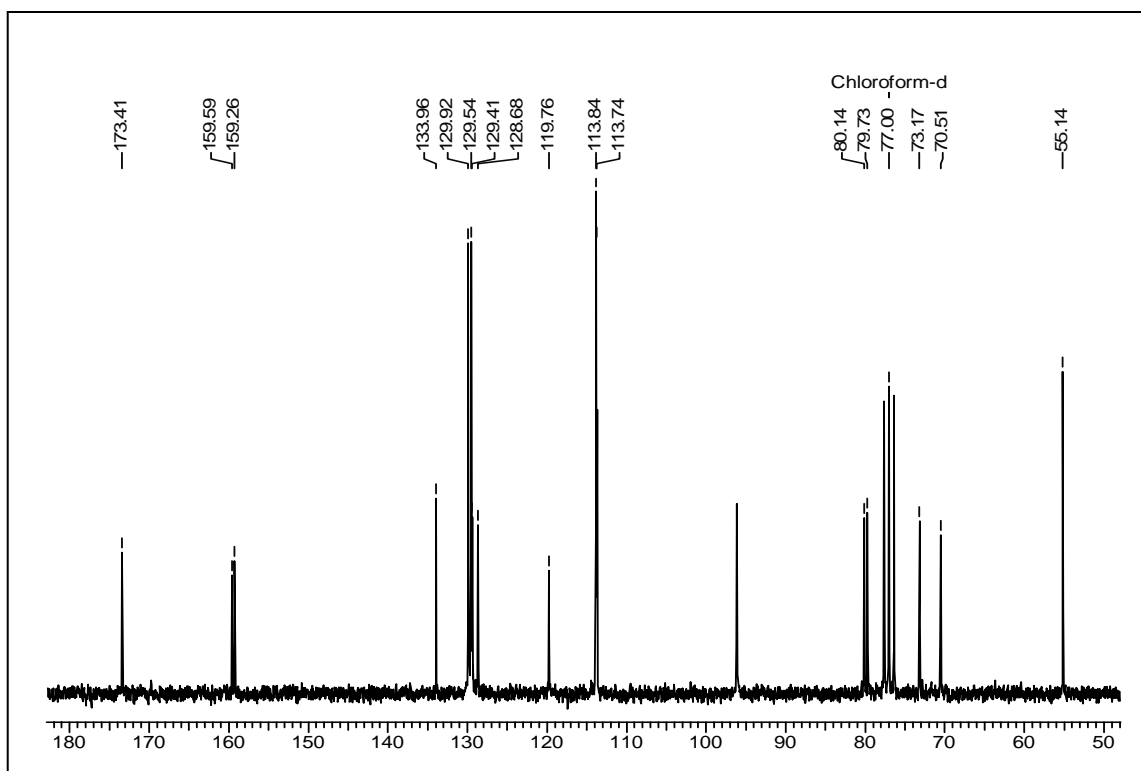
**$^1\text{H}$  NMR spectra of compound 25** **$^{13}\text{C}$  NMR spectra of compound 25**

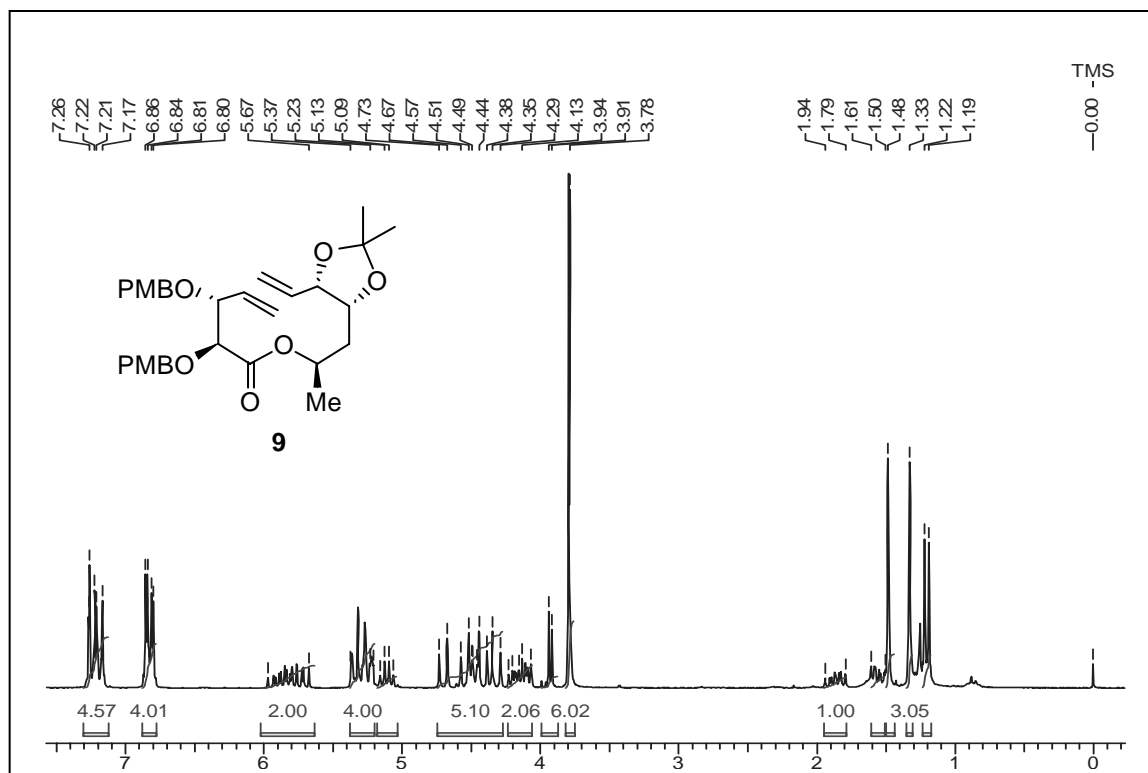
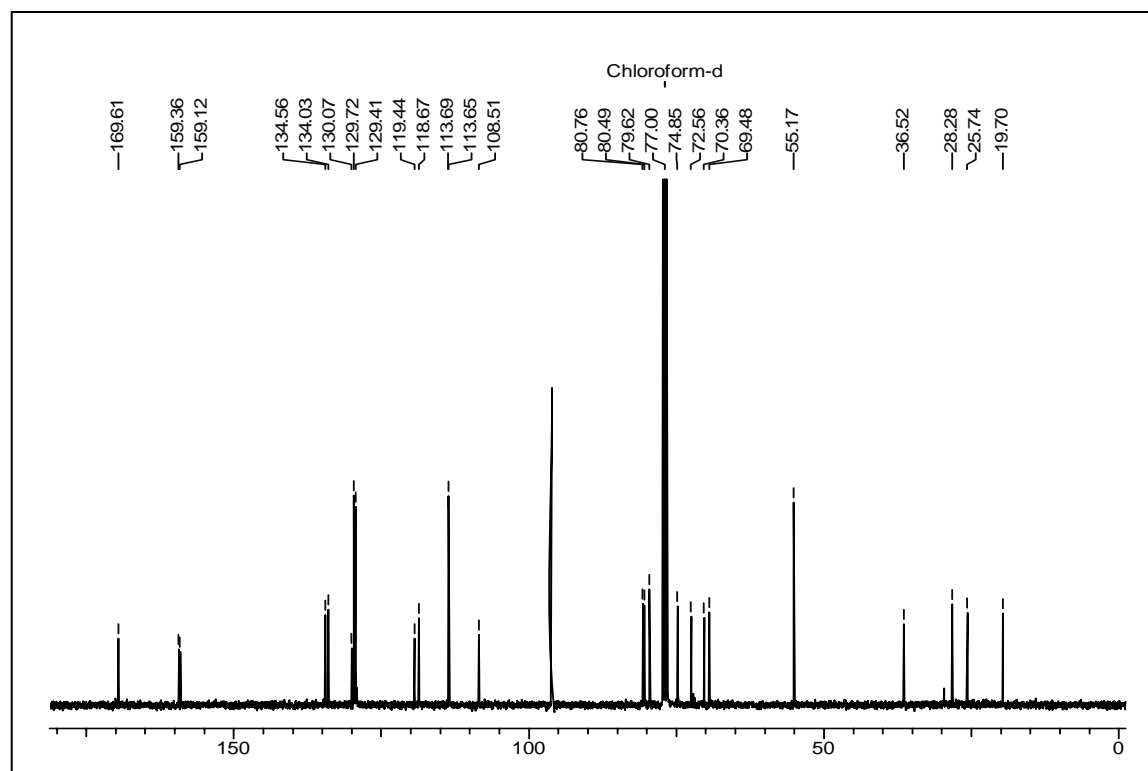
**$^1\text{H}$  NMR spectra of compound 10** **$^{13}\text{C}$  NMR spectra of compound 10**

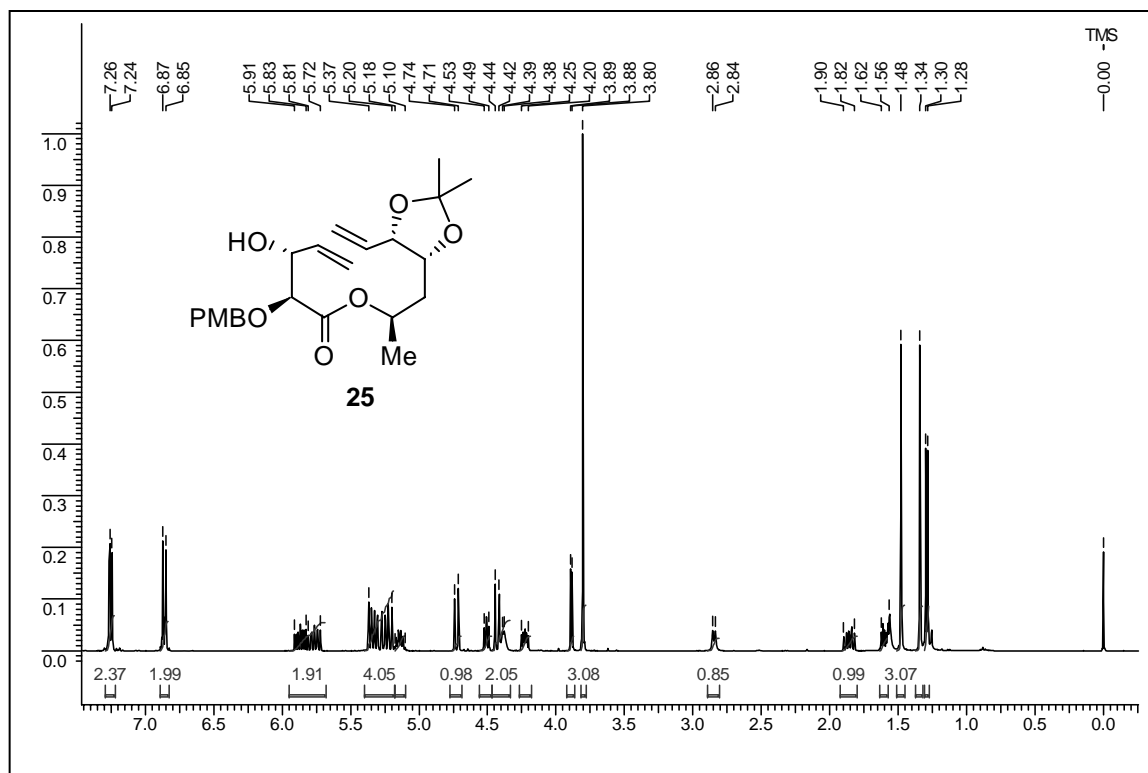
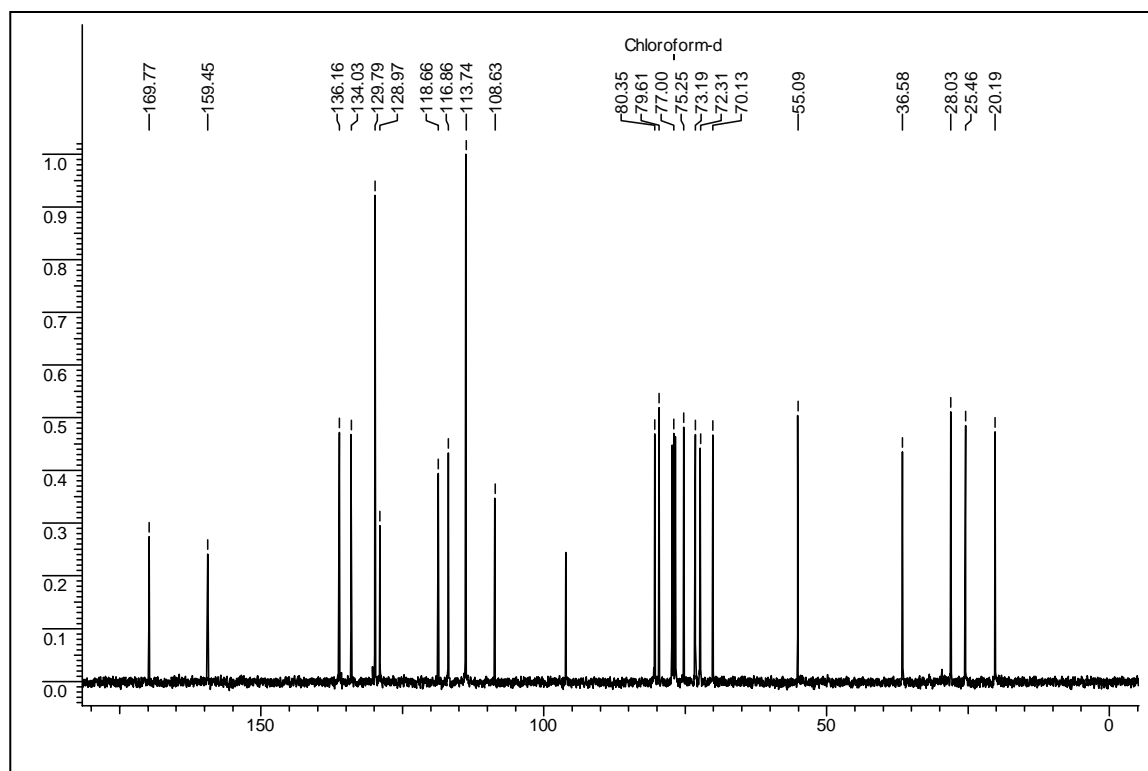


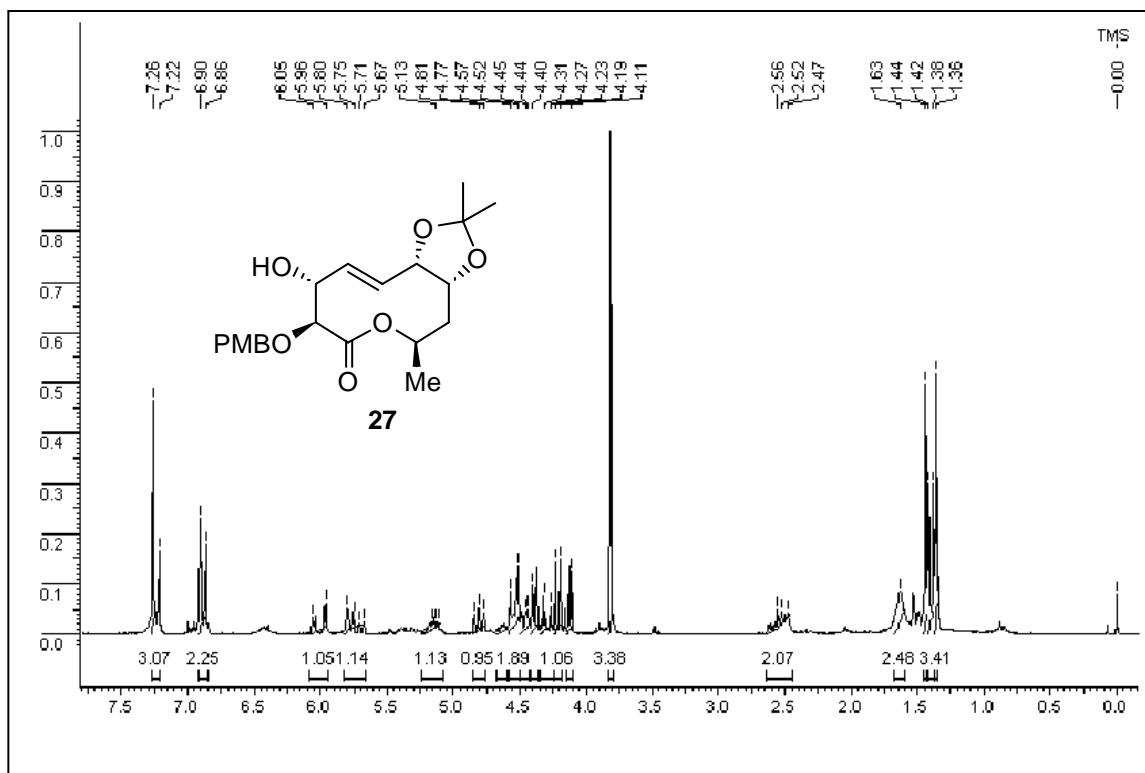
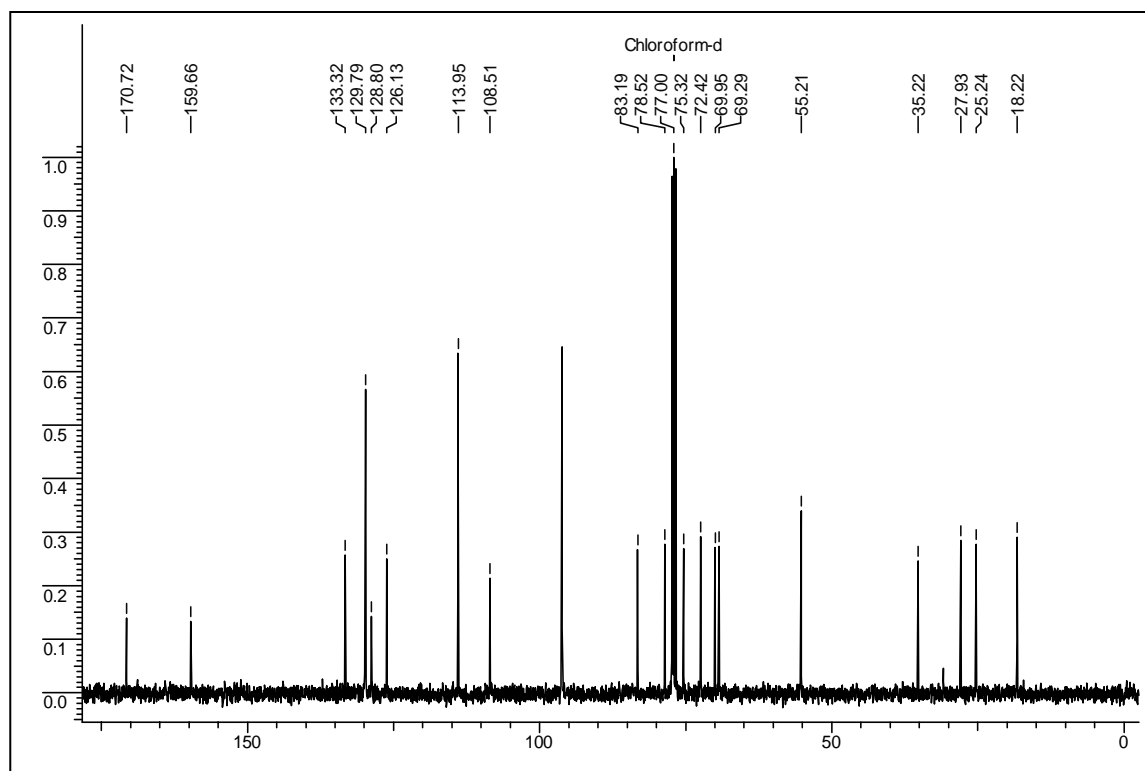


**$^1\text{H}$  NMR spectra of compound 22** **$^{13}\text{C}$  NMR spectra of compound 22**

**$^1\text{H}$  NMR spectra of compound 11** **$^{13}\text{C}$  NMR spectra of compound 11**

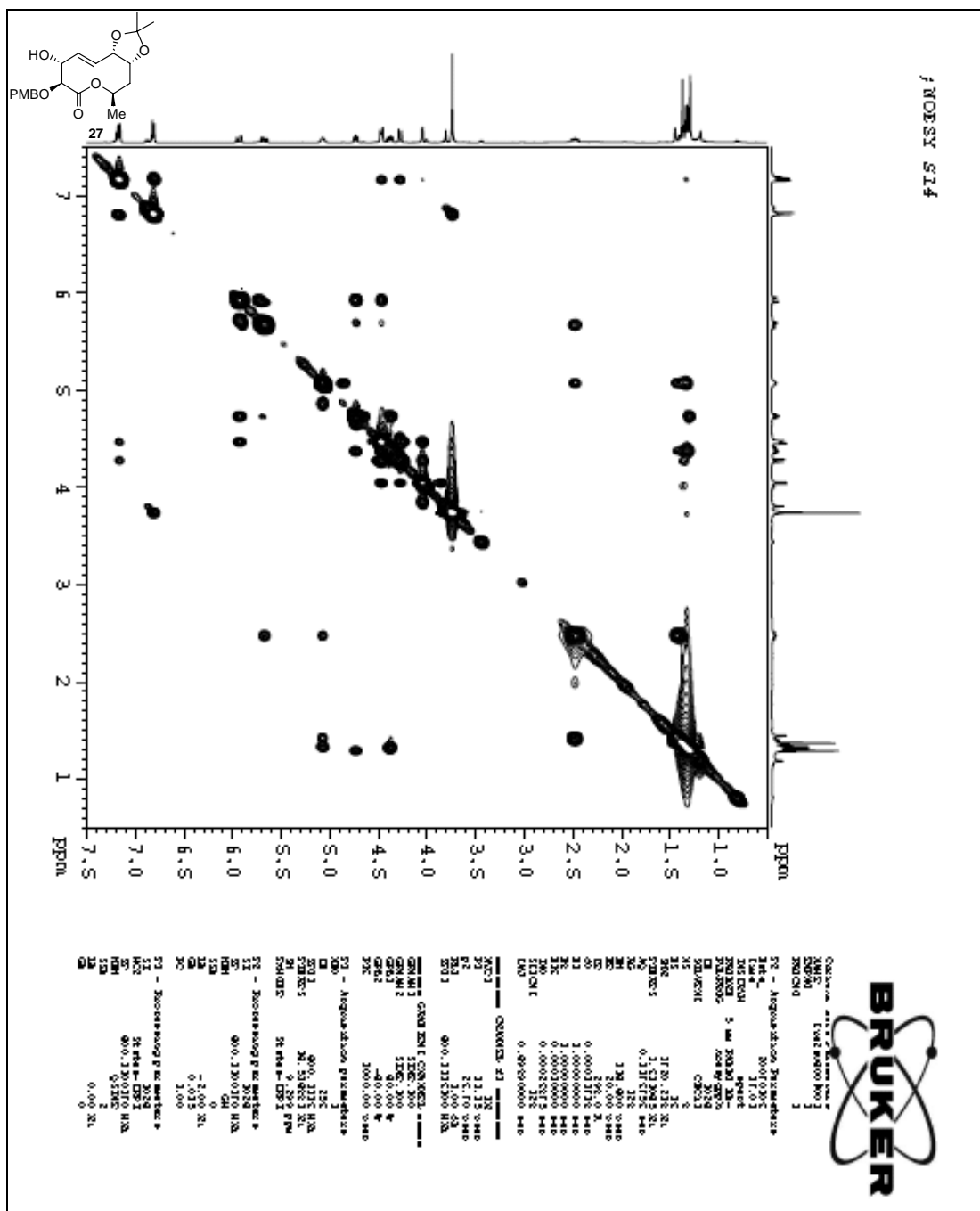
**$^1\text{H}$  NMR spectra of compound 9** **$^{13}\text{C}$  NMR spectra of compound 9**

**$^1\text{H}$  NMR spectra of compound 25** **$^{13}\text{C}$  NMR spectra of compound 25**

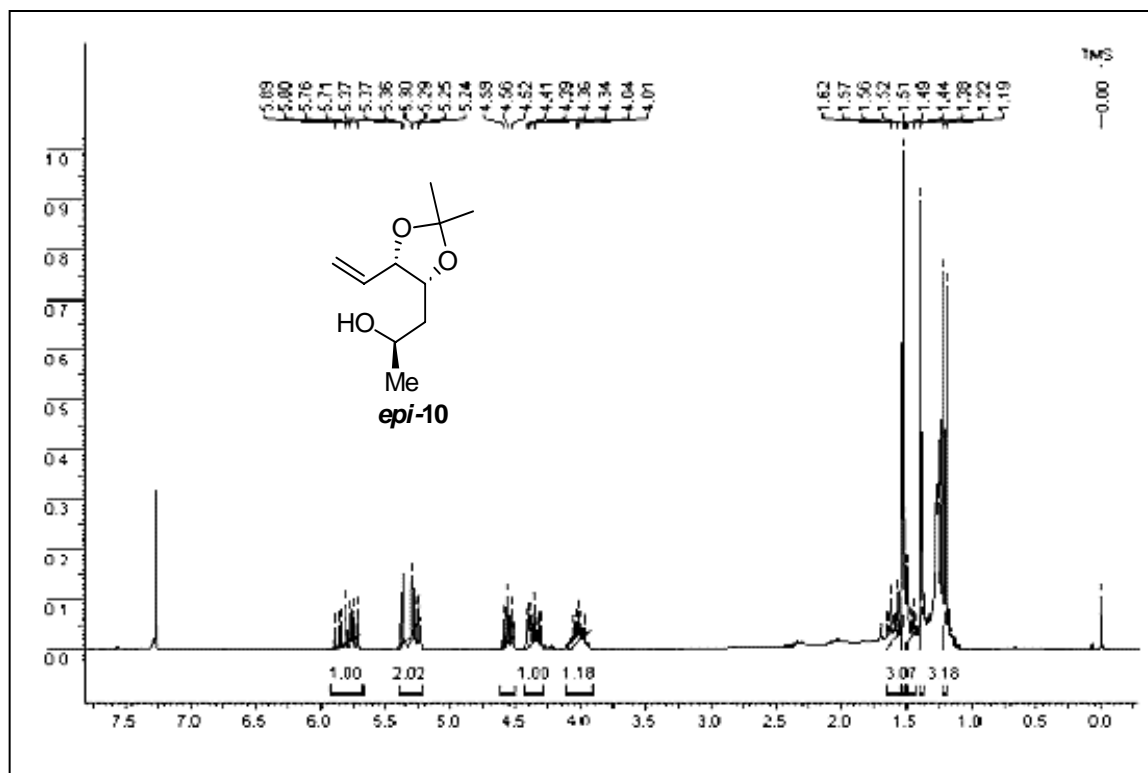
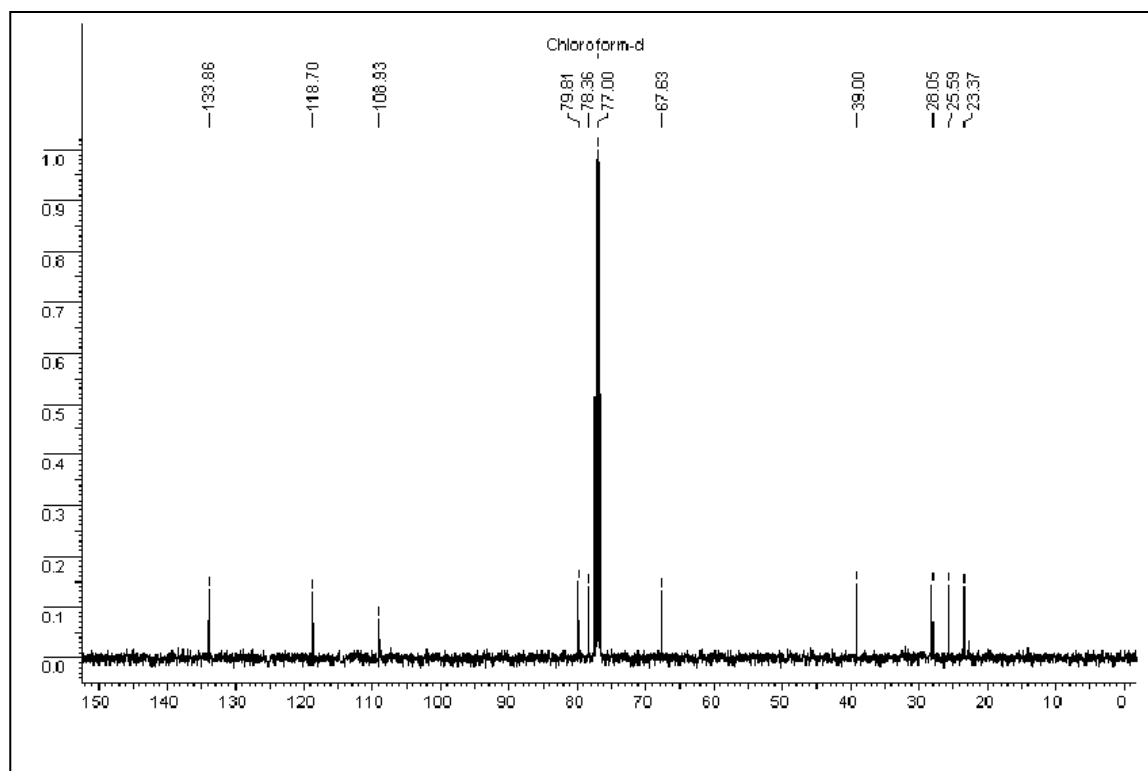
**$^1\text{H}$  NMR spectra of compound 27** **$^{13}\text{C}$  NMR spectra of compound 27**

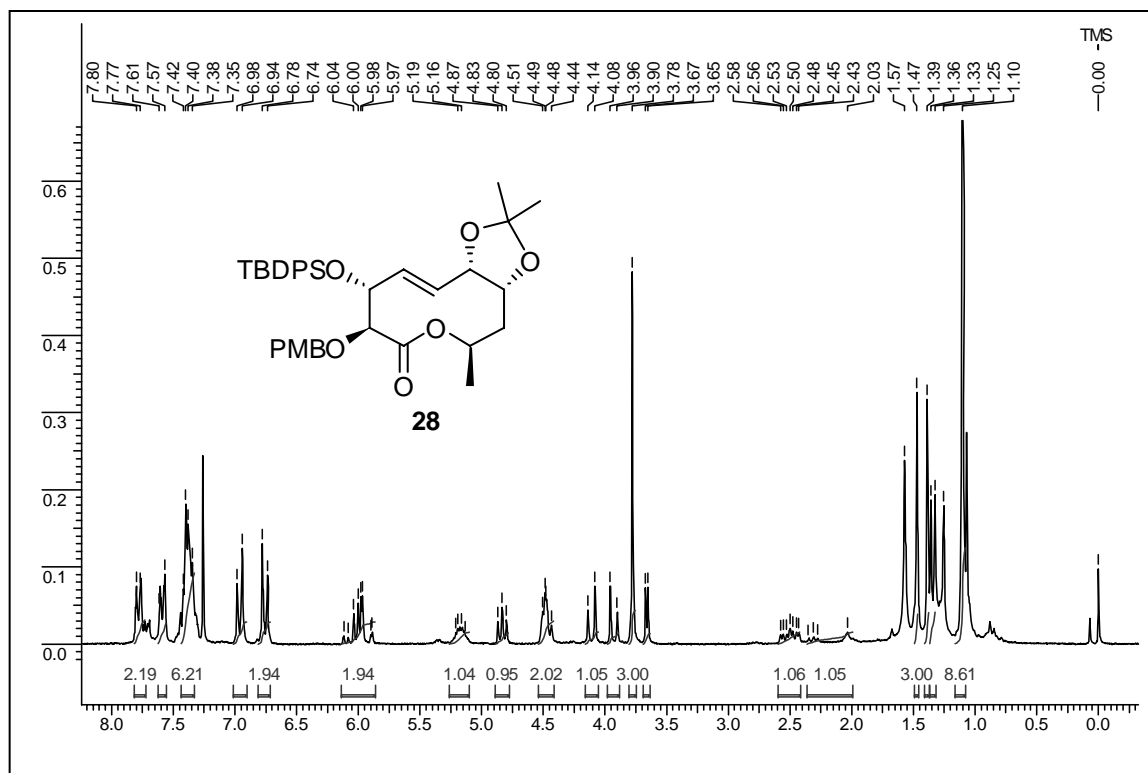
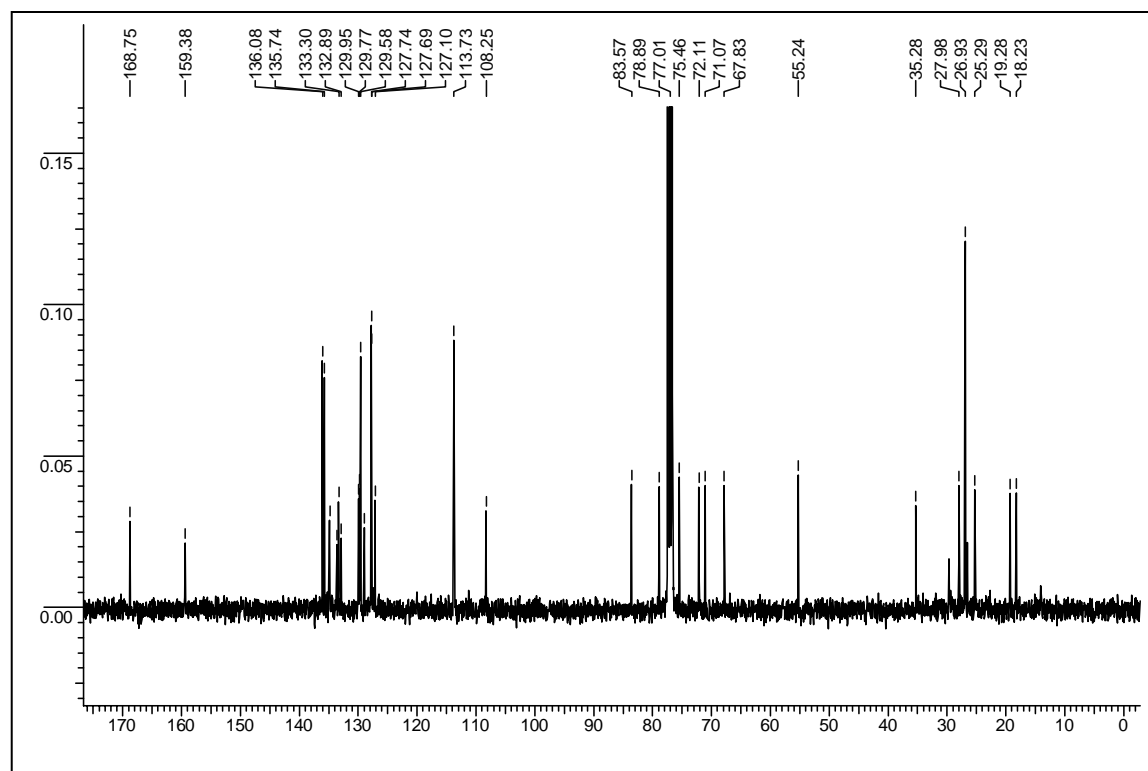


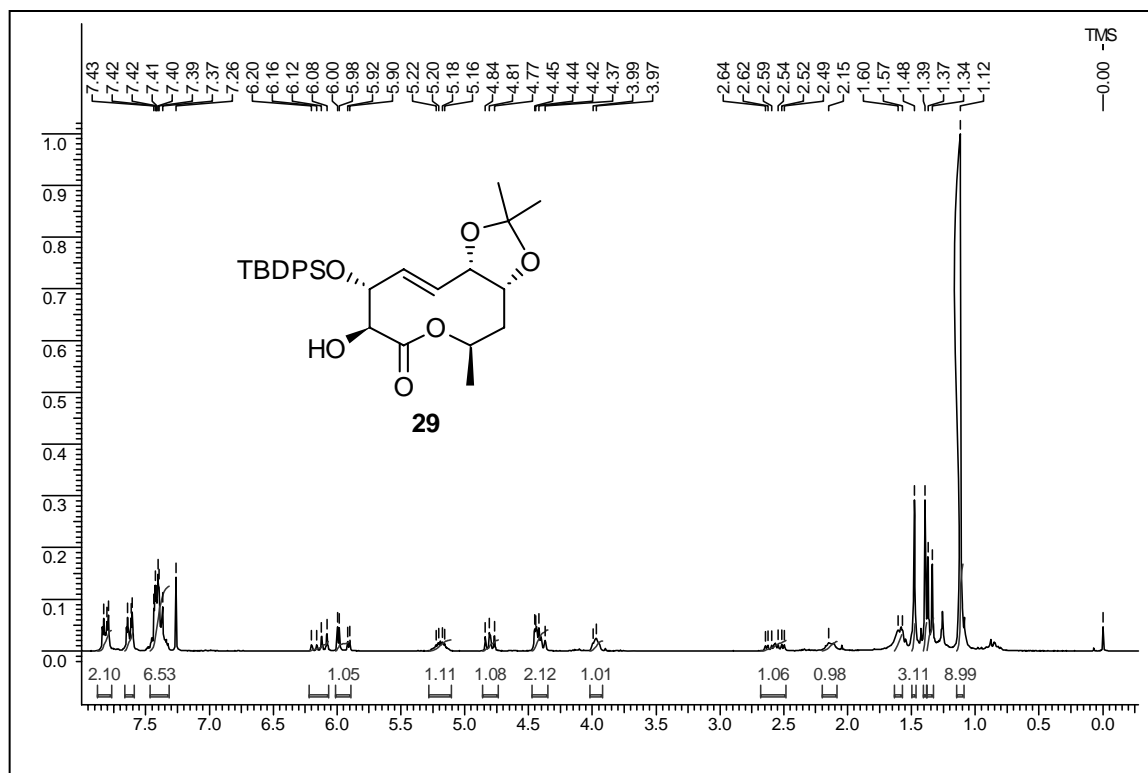
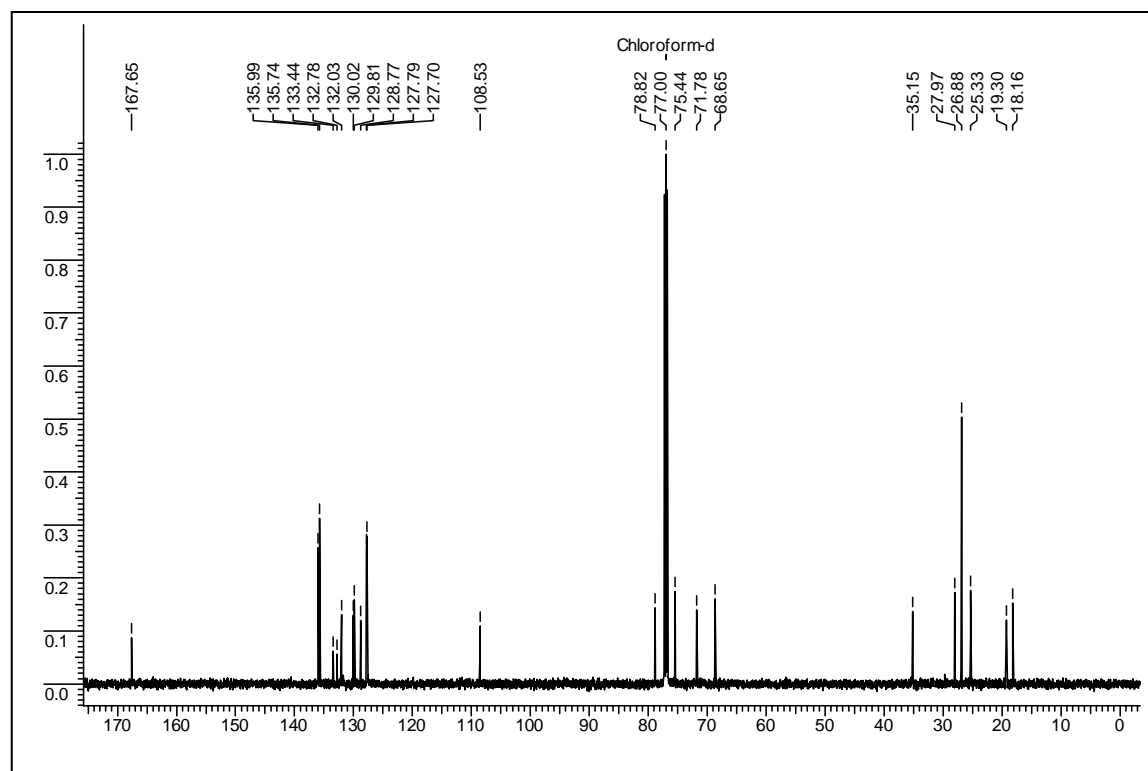
<sup>1</sup>H NOESY spectra of compound 27

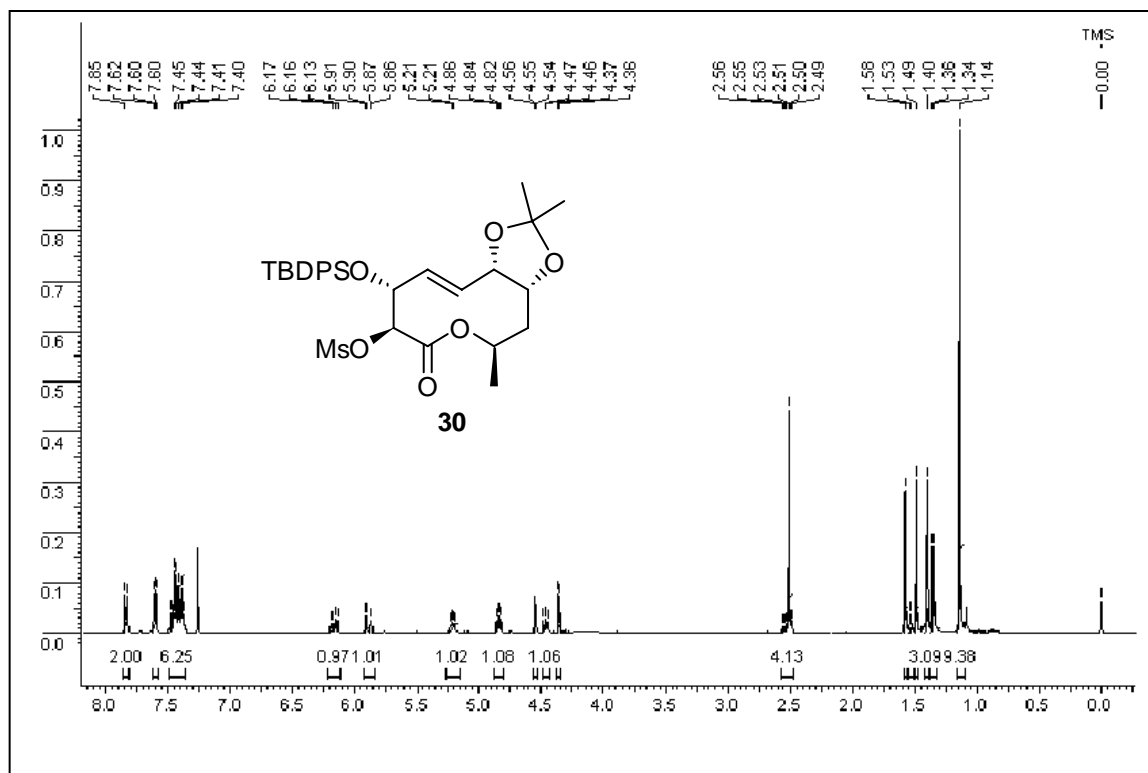
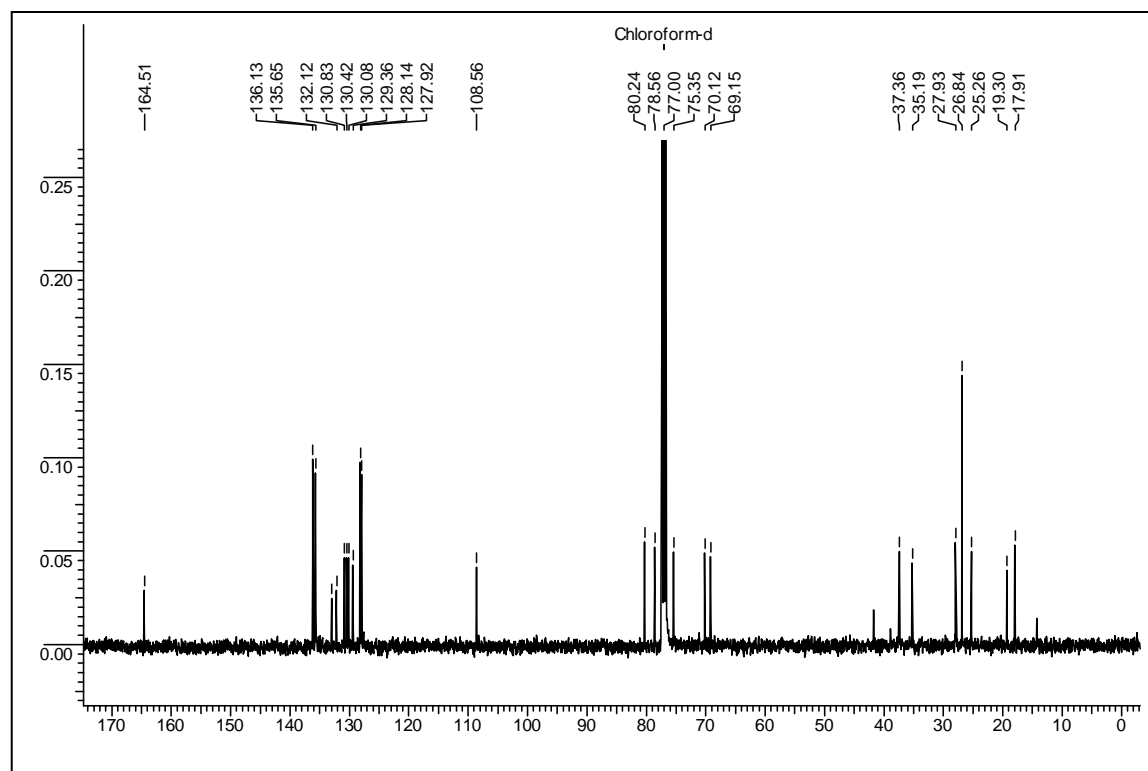


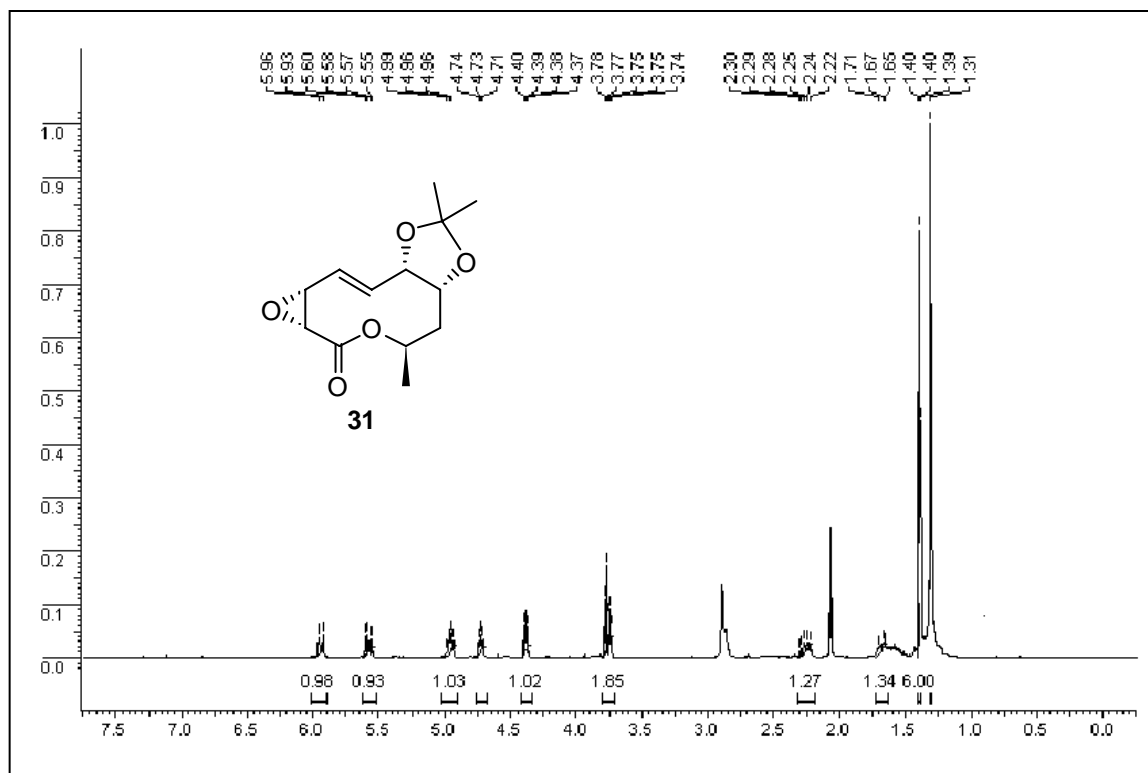
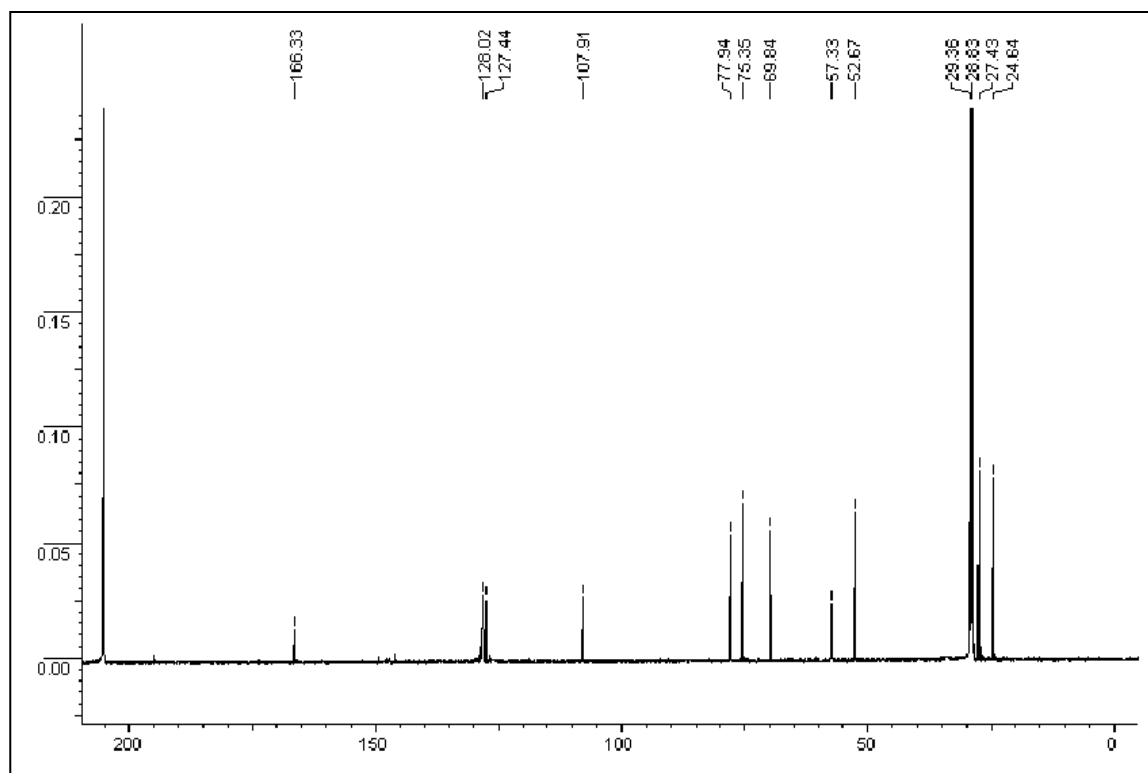


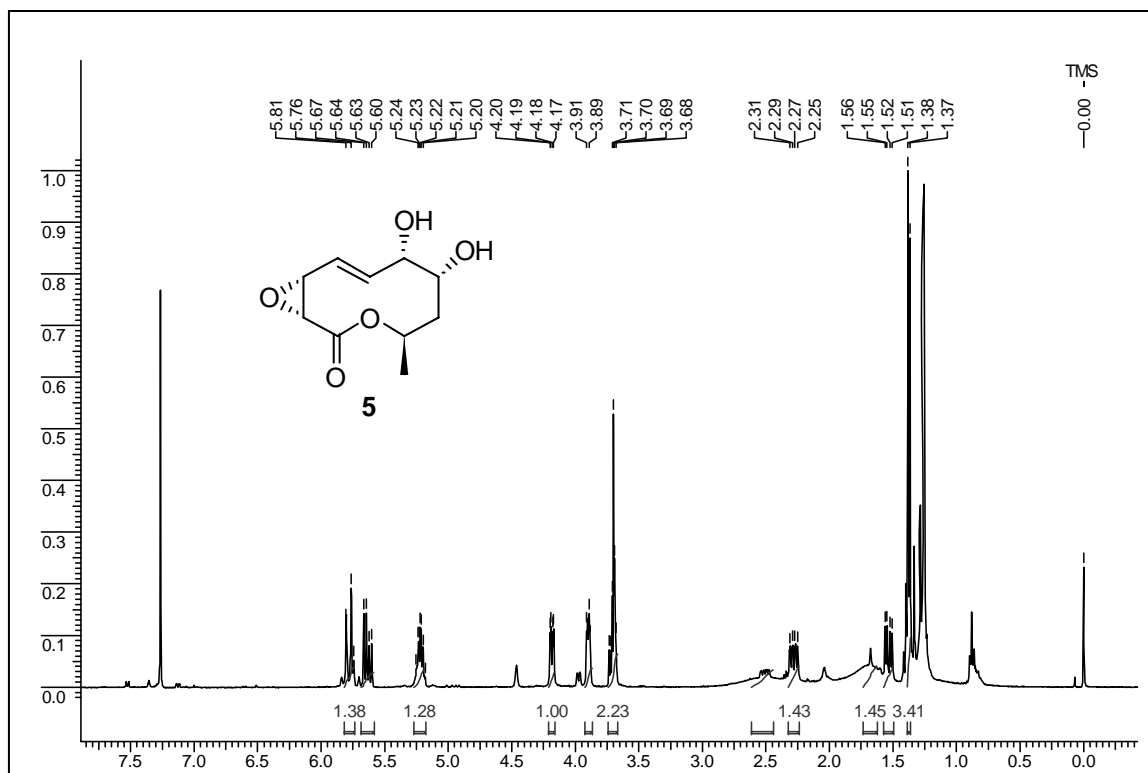
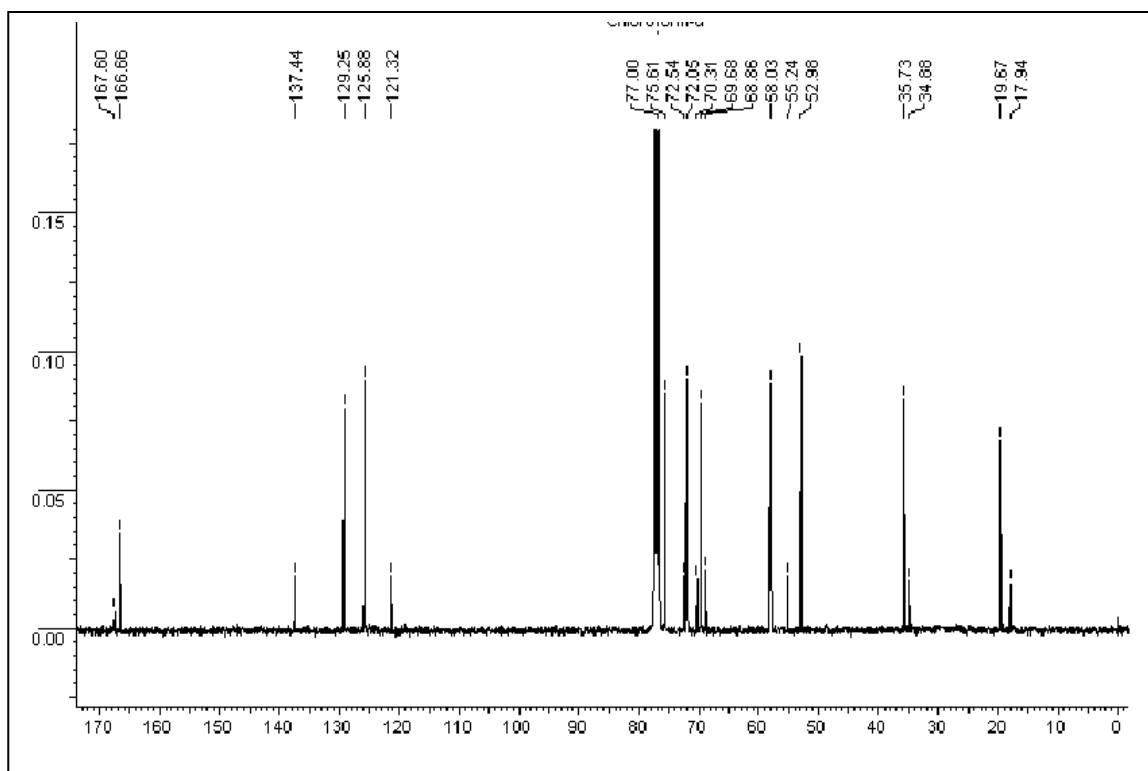
**$^1\text{H}$  NMR spectra of compound *epi-10*** **$^{13}\text{C}$  NMR spectra of compound *epi-10***

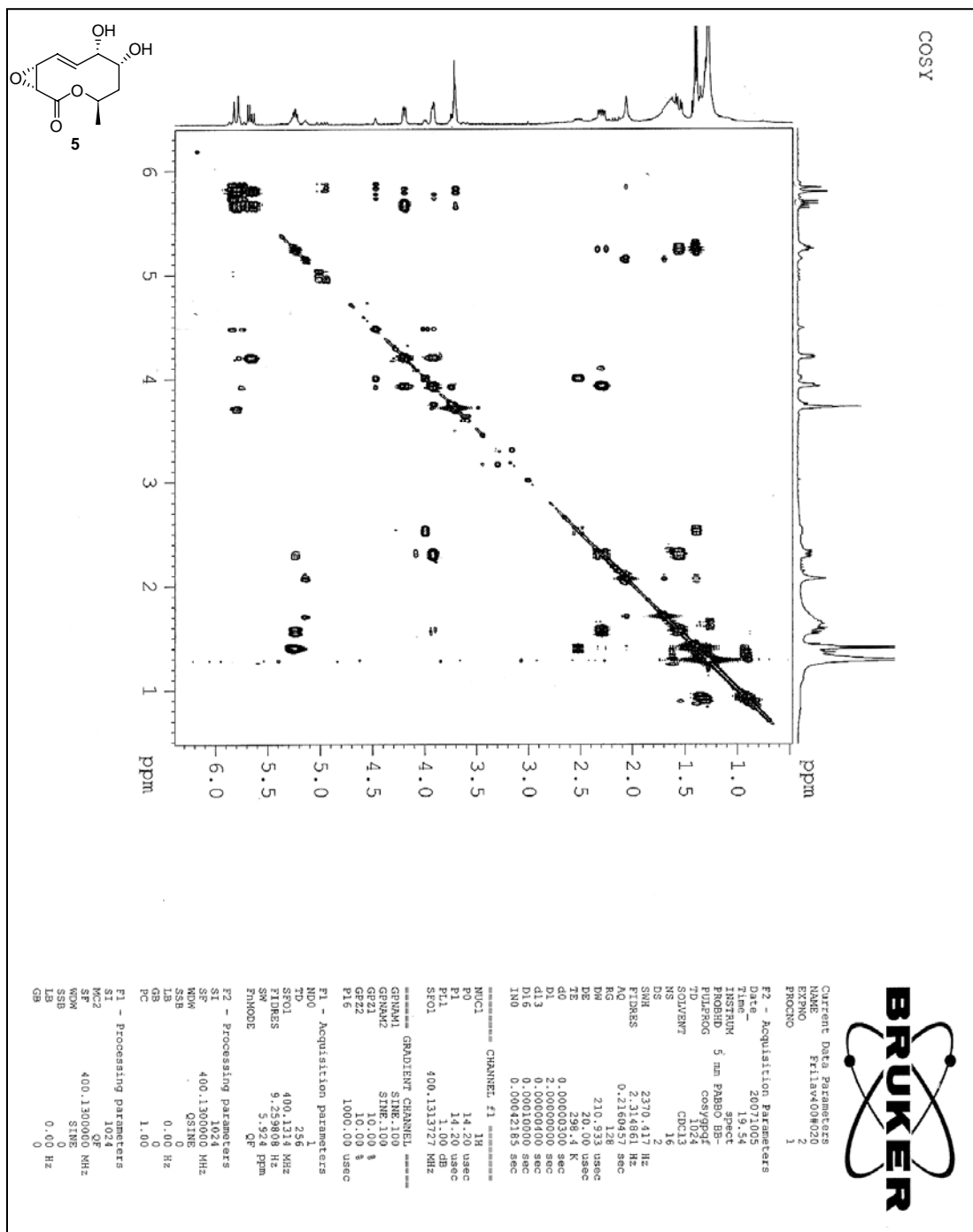
**$^1\text{H}$  NMR spectra of compound 28** **$^{13}\text{C}$  NMR spectra of compound 28**

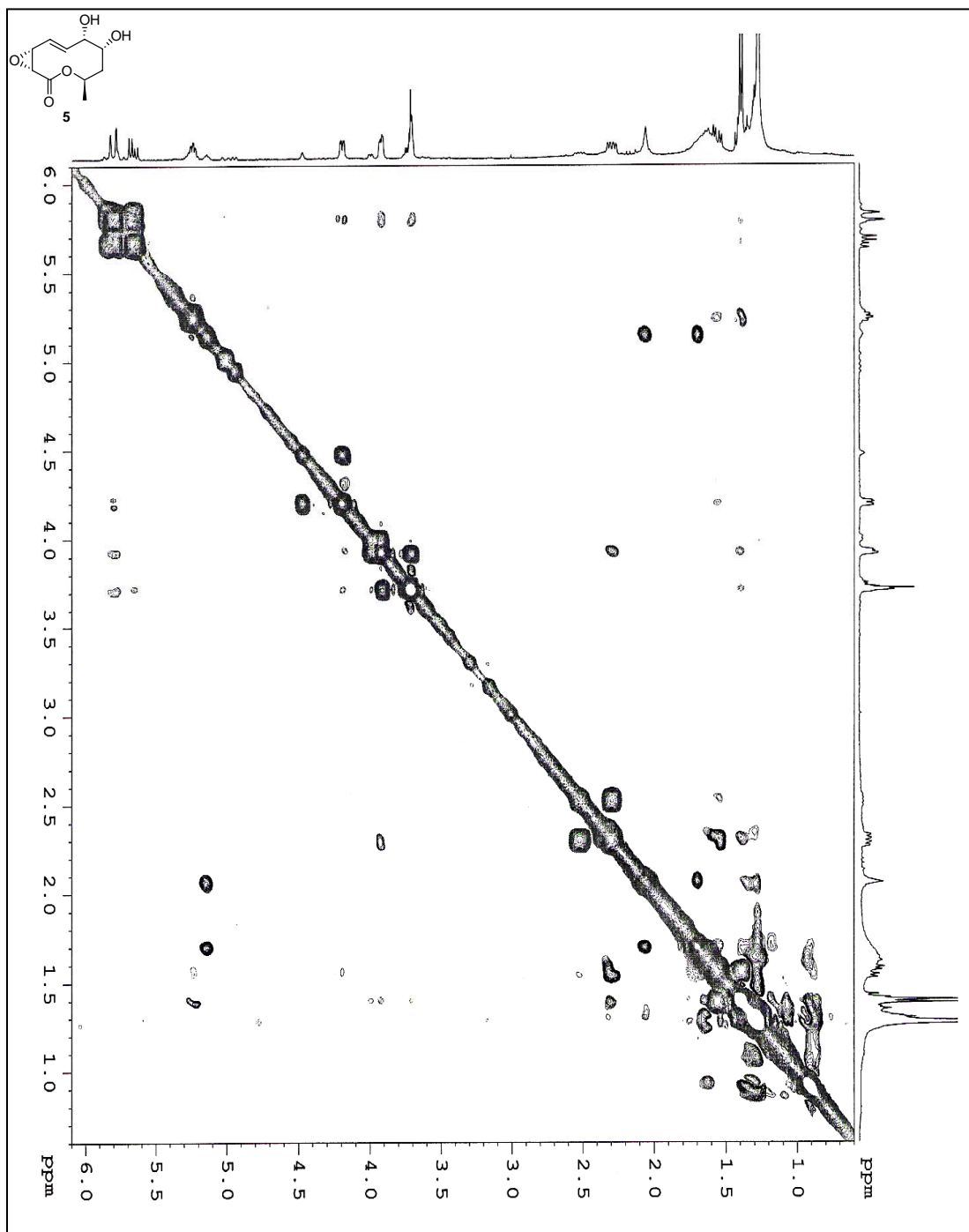
**$^1\text{H}$  NMR spectra of compound 29** **$^{13}\text{C}$  NMR spectra of compound 29**

**$^1\text{H}$  NMR spectra of compound 30** **$^{13}\text{C}$  NMR spectra of compound 30**

**$^1\text{H}$  NMR spectra of compound 31** **$^{13}\text{C}$  NMR spectra of compound 31**

**$^1\text{H}$  NMR spectra of compound 5** **$^{13}\text{C}$  NMR spectra of compound 5**

$^1\text{H}$  COSY spectra of compound 5

$^1\text{H}$  NOESY spectra of compound 5



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## **CHAPTER 2: Section 1**

Towards the Total Synthesis of Feigrisolide B

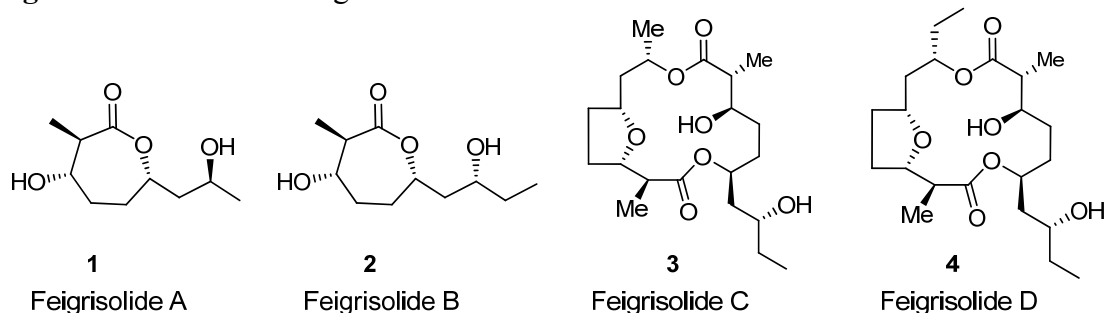
## **PRESENT WORK**

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## PRESENT WORK

Two groups of medium diolides have been isolated from fungi *Streptomyces*: unsymmetrical 14-membered macrolides such as grahamimycin A<sub>1</sub><sup>1</sup> and colletodiol,<sup>2</sup> and C<sub>2</sub>-symmetric 16-membered lactones, like pyrenophorin,<sup>3</sup> vermiculine,<sup>4</sup> conglobatin,<sup>5</sup> and elaiophylin.<sup>6</sup> A number of these secondary metabolites and their analogues showed promising antibiotic activity.<sup>7</sup> Recently Thiericke and co-workers isolated four new secondary metabolites named as feigrisolides A-D (Figure 1) from the fermentation brothes *Strptomyces Griseus* (Strain GT 051922) and revealed that these compounds possess strong antibacterial, as well as medium cycotoxic and antiviral activities. It has been found that feigrisolides A (**1**) and B (**2**) belong to hepta-lactones, and the other two compounds, feigrisolide C (**3**) and D (**4**) belong to 16-membered non symmetric macrolides.<sup>8</sup>

**Figure 1:** Structures of feigrisolides A-D



After extensive NMR studies for the determination of their constitution and the comparison NMR data of feigrisolides A and B, it is clearly seen that one extra methylene group is present in feigrisolide B compared to feigrisolide A. IR and UV studies are almost same for the two compounds. The HRFAB-MS ( $m/z = 217.1469$   $[M + H]^+$ , C<sub>11</sub>H<sub>21</sub>O<sub>4</sub>) for feigrisolide B and HRFAB-MS ( $m/z = 203.1314$   $[M + H]^+$ , C<sub>10</sub>H<sub>19</sub>O<sub>4</sub>) for feigrisolide A clearly supported the presence of an extra methylene group in feigrisolide B.



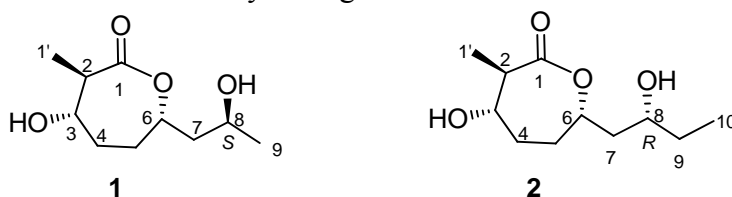
**Table 1:** NMR comparison data of feigrisolides A and B

Position	Feigrisolide A ( <b>1</b> )		Feigrisolide B ( <b>2</b> )	
	$\delta$ $^1\text{H}$ (multi. J = Hz)	$\delta$ $^{13}\text{C}$	$\delta$ $^1\text{H}$ (multi. J = Hz)	$\delta$ $^{13}\text{C}$
1		177.5(s)		177.6 (s)
2	2.50 (dq, 8.3, 7.2)	45.3 (d)	2.50 (dq, 8.3, 7.0)	45.3 (d)
3	3.98 (q, 8.3)	81.1 (d)	3.98 (bq, 8.3)	81.0 (d)
4	2.03 ( $\alpha$ , m)	29.1 (t)	2.03 ( $\alpha$ , m)	29.1 (t)
	1.67 ( $\beta$ , m)		1.68 ( $\beta$ , m)	
5	1.66 ( $\alpha$ , m)	35.3 (t)	1.65 ( $\alpha$ , m)	30.6 (t)
	2.01 ( $\beta$ , m)		2.01 ( $\beta$ , m)	
6	4.19 (m)	77.1 (d)	4.21 (m)	77.3 (d)
7	1.68 (m)	42.9 (t)	1.70 (m)	40.7 (t)
8	4.08 (m)	65.2 (d)	3.78 (m)	70.4 (d)
9	1.21 (d, 6.3)	23.1 (q)	1.51 (m)	29.9 (q)
10	-	-	0.92 (t, 7.5)	10.0 (q)
1'	1.16 (d, 7.2)	13.7 (q)	1.16 (d, 7.2)	13.7 (q)
OH x 2	4.35 (2H, br. s)		4.75 (2H, br. s)	

From the  $^1\text{H}$  and  $^{13}\text{C}$  NMR comparison studies it is clear that feigrisolide A and B are having common structural features. For the determination of the 8-OH stereochemistry of feigrisolide A, Helmchen's method of esterification was applied.<sup>9</sup> Where the compound was reacted with each one of the enantiomers of 2-phenylbutyric acid resulted in the (2*R*)-2-phenylbutyrate derivative and (2*S*)-2-phenylbutyrate derivative, respectively and from that *S*-configuration of C-8 was found for feigrisolide A. From the NMR comparison it is evident that methyl group at C-8 in feigrisolide A is replaced by an ethyl group in feigrisolide B. Acylation of feigrisolide B with acetic anhydride and pyridine also yields a mono-acetate derivative. A comparison of the  $^1\text{H}$  spectra of parent compound and derivative indicates that acylation of the hydroxyl group at C-8 is due to the downfield shift of the signals for H-8 ( $\Delta\delta=1.14$  ppm). The relative stereochemistry of feigrisolide B seems to be identical to feigrisolide A based on both,

identical coupling constants in the  $^1\text{H}$  NMR spectra, and NOESY NMR experiments. Determining the absolute stereochemistry of the C-8 center of feigrisolide B, the same method was applied here. From the comparison study of the (2*R*)-ester derivative and (2*S*)-ester derivative, a significant low-field shift for 10-H signal ( $\Delta\delta=0.22$ ) and significant high-field shifts for 3-H ( $\Delta\delta=0.04$ ), 6-H ( $\Delta\delta=0.14$ ), and 2-H ( $\Delta\delta=0.10$ ) signals of (2*R*)-derivative with regard to those of (2*S*)-derivative clearly indicate the *R*-configuration of C-8. Also in the case of feigrisolide B, the absolute stereochemistry at C-8 did not allow to predict the absolute stereochemistry of the ring. Therefore, feigrisolide B was (2*R*, 3*S*, 6*S*, 2'*R*)-3-hydroxy-6-(2-hydroxybutylmethyl-hepta-lactone).

**Figure 2:** Relative stereochemistry of feigrisolides A and B

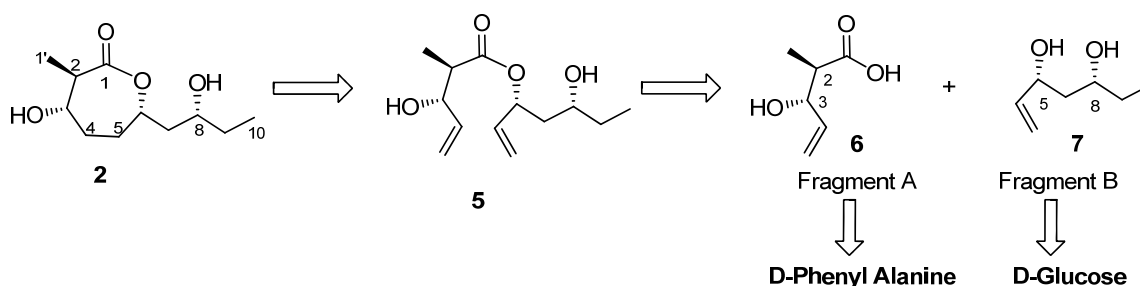


Out of all these four compounds feigrisolide B (**2**) was found to be the most promising compound in terms of biological activity. In the light of inherent interest generated by the promising biological activity, and with necessity of determining the absolute stereochemistry, feigrisolide B has been identified as the appropriate target for total synthesis.

The basic disconnection of the feigrisolide B skeleton between C(4)-C(5) identifies ring closing metathesis as the key transformation and the acid and **6** alcohol **7** as appropriate synthons. As the complete information about the stereochemistry of all the centers is not available, in pursuit of confirming its relative and absolute stereochemistry, we have opted for a combination of catalytic asymmetric transformation and selection of appropriate chiral pool intermediates. We anticipated that this approach would add the flexibility to our strategy that can address the synthesis of possible diastereomers if required. For acquiring possible epimers at C(5) center, two different approaches for coupling **6** and **7** were selected: (a) coupling under classical acid activation conditions and (b) coupling with net C(5) inversion under Mitsunobu conditions. In order to address the stereochemical diversity at C(2) and C(3) centers of the acid **6**, Evans' aldol reaction

of acrolein with D/L-phenyl alanine derived oxazolidinones was selected as an appropriate stereochemical transformation as it can address the synthesis of either of the syn/anti-aldol products by changing the reaction conditions appropriately. A representative retrosynthetic disconnections and the corresponding intermediate has been given in Scheme 1 by selecting the stereochemical information that was given for the feigrosolide B.

**Scheme 1: Retrosynthetic strategy**



**Synthesis of Fragment A:**

From the retrosynthetic strategy of fragment A, it is clear that Evans' aldol reaction is the key reaction for the synthesis of this fragment. Therefore a brief account on Evans' aldol reaction is discussed below.

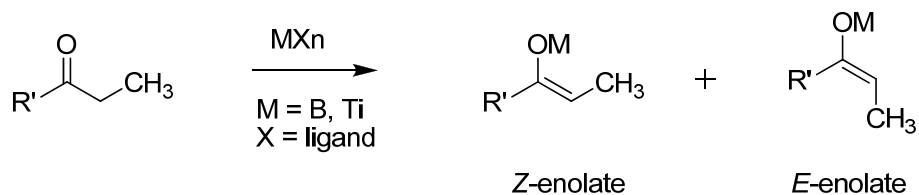
**A short account on Crimmins' modified Evans' asymmetric aldol reaction:**

Over the last decade, the stereochemical attributes of the asymmetric aldol reaction have been improved through the introduction of architecturally refined enolate metal centers and is one of the most important and general methods for asymmetric carbon-carbon bond formation. The utility of the asymmetric aldol addition has been amply demonstrated through a multitude of synthetic applications.<sup>10</sup> Dibutylboron enolates of *N*-acyl oxazolidinones, pioneered by Evans, are the most commonly utilized enolates and are<sup>11</sup> highly effective for the preparation of Evans' syn products in asymmetric aldol additions.<sup>12</sup> The recently developed titanium (IV)<sup>13,14,15</sup> enolates of *N*-acyloxazolidinones and oxazolidinethiones, tin (IV) enolates of *N*-acyl sultams, and tin (II) enolates<sup>16</sup> of thiazolidinethiones have also been shown to be effective in creating well ordered transition states for aldol reactions. Considerable efforts has been employed to develop stereoregulated variants of this methodology by Evans and Heathcock.<sup>12,17</sup> It has

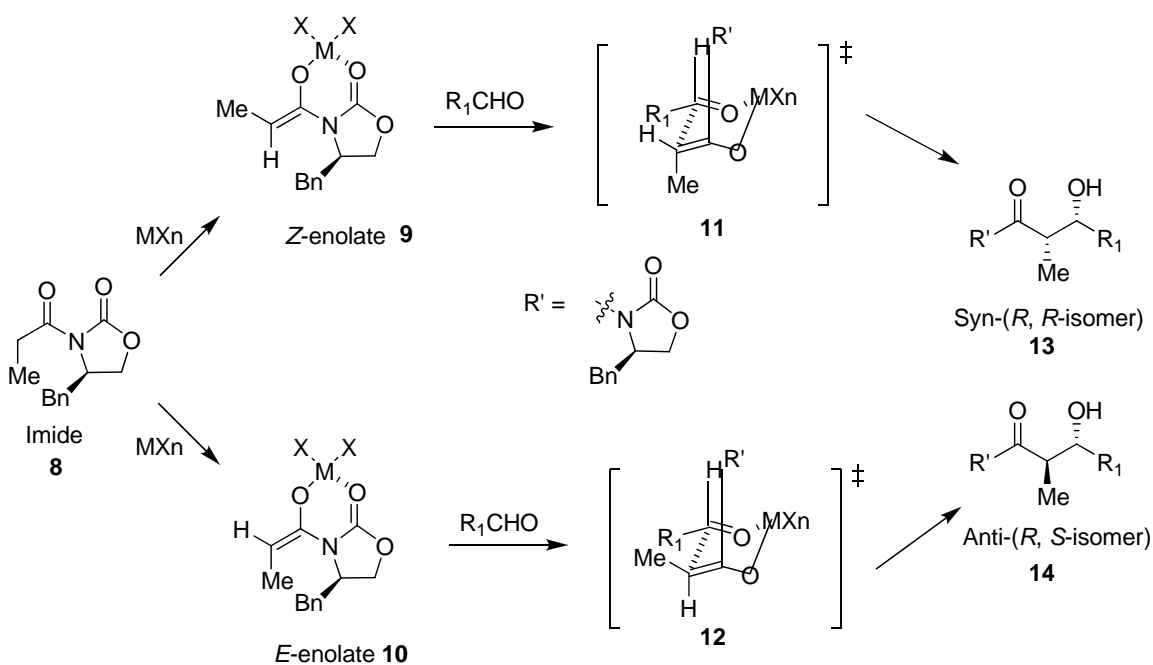
been well appreciated that kinetic aldol stereoselection is in part, defined by enolate geometry where two stereocenters are generated. According to the postulate put forward by Evans *et. al*, most boron mediated aldol reactions are pericyclic in nature and proceed through a chair like transition state proposed by Zimmerman and Traxler,<sup>18</sup> where (Z)-boron enolate (**9**) gives syn-aldol products and (E)-boron enolate (**10**) afford anti-aldol products (Figure 1).<sup>19</sup> Exhaustive studies<sup>20</sup> on this titanium mediated aldol reaction has done by Crimmins' *et. al*. This method is operationally simple, and the cost is lower than aldol additions with dibutylboron triflate. The use of 1.05 equiv of titanium tetrachloride, 2.5 equiv of (-)- sparteine or N-ethyl-diisopropylamine also proved highly efficient and syn-selective as with the N-acyloxazolidinethiones and N-acyloxazolidinones. The advantage of the use of TiCl<sub>4</sub> (-)-sparteine or N-ethyl-diisopropylamine for the enolization of N-acyloxazolidinones is that the reagents can be used as purchased, the reaction proceeds well even at 0 °C, and no oxidative workup is required. The relative cost is approximately 35-40% less relative to the dibutylborontriflate procedure. The Crimmins' aldol methodology is logistically easier for the formation of titanium enolates. One particularly attractive attribute is the flexibility imparted by Crimmins' chelated and nonchelated models, which is dependent on the amount of TiCl<sub>4</sub> and N-ethyl-diisopropylamine. Modification provided the access to both the Evans' syn product via the nonchelated model (**11**) and the non-Evans' syn adduct via the chelated model (**12**) (Figure 2). To proceed via the chelated transition states **11**, one of the ligand on titanium (typically chloride) must be displaced by the carbonyl group of oxazolidinone. Although these groups are not sufficiently nucleophilic to completely displace this ligand on their own, the ligand can be easily abstracted with a second equivalent of titanium. A consequence of this is that these substrates will occasionally give mixtures of products resulting from incomplete conversion of **11** to **12**. Also addition of chelating ligands, extra equivalents of amine bases (sparteine, Hunig's base etc), or even some solvent molecules tend to disfavor the transition state **15**, because of their preferential chelation to the titanium enolate. So when the reaction proceeds through the<sup>21</sup> non-chelated transition state (**11**) the Evans' syn adduct (**13**) and when the chelated transition state (**12**) non Evans' syn adduct (**14**) forms. The level of syn/anti selectivity is high (normally > 20:1) and comparable to traditional boron-mediated aldol reactions for both the chelated and

nonchelated titanium-mediated conditions. It should be pointed out that Crimmins has shown that the chirality of (-)-sparteine does not influence the stereochemical outcome of the transformation.

**Figure 3**

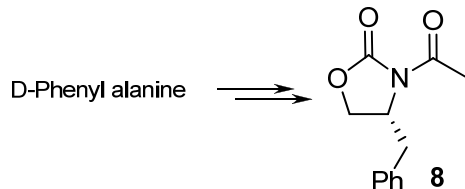


**Figure 4:** Zimmermann-Taxler transition state



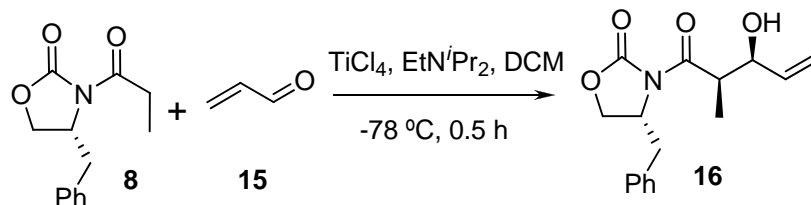
Synthesis of fragment A was started with the preparation of D-Phenyl alanine derived Evans' oxazolidinone. Reduction of D-phenyl alanine with sodium borohydride/iodine followed by treatment of resulting amino alcohol with dimethyl carbonate gave the key oxazolidinone,<sup>22</sup> which was treated with propionic anhydride in presence of triethyl amine and lithium chloride to obtain the known key intermediate **8**.

## Scheme 2



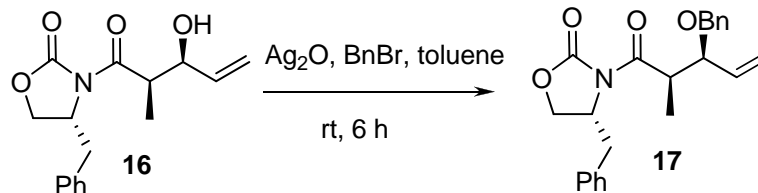
Initial Evans' aldolisation<sup>23</sup> of **8** with acrolein was carried out with  $\text{TiCl}_4$  and diisopropylethyl amine. From the previously described aldol reaction, in Zimmerman-Taxler transition state it was clearly evident that minimum energy conformer is the *Z*-enolate transition state. So when the reaction was carried out then both the newly generated center would be of opposite stereochemistry with the stereochemistry of the benzyl group of chiral auxiliary. Presence of br. s at  $\delta$  3.12 and two terminal olefinic proton at  $\delta$  5.20,  $\delta$  5.33 and one internal olefinic proton at  $\delta$  5.85, respectively in  $^1\text{H}$  NMR clearly indicated the presence of newly generated hydroxyl group and incorporation of olefin from acrolein.

## Scheme 3

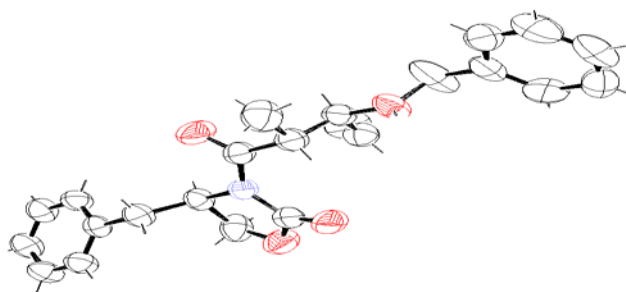


Benylation of **16** was accomplished by using silver oxide and benzyl bromide in dry toluene to obtain the benzyl ether **17**. As it was known that use of strong bases can cause the hydrolysis of chiral auxiliary, we opted for silver oxide as mild base. Conversion of free hydroxyl to its benzyl ether was confirmed by the absence of br. s peak present in the alcohol **16**, as well as the chemical shift change of the C-H attached to hydroxyl group which was at  $\delta$  4.69 in **16** and shifted to  $\delta$  3.95 after benzylation. The structure as well as the stereochemistry of the newly generated centers in aldol reaction was further confirmed by the X-ray analysis of this compound. From the single crystal data, the stereochemistry of the  $-\text{OH}$  group and  $-\text{Me}$  group was *syn*.

## Scheme 4

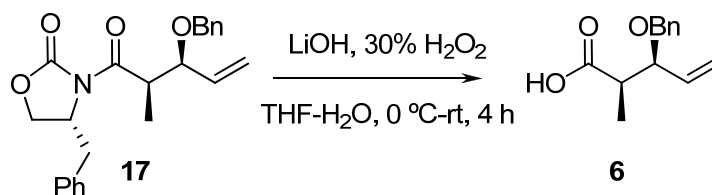


**Figure 5:** ORTEP diagram of benzyl protected compound (**17**) (*displacement ellipsoids are drawn at the 50% probability level*)



Removal of the chiral auxiliary in **17** was affected by using lithium hydroxide and 30% hydrogen peroxide to afford the acid fragment **6**. The characteristic broad singlet of acid -H at  $\delta$  9.9 ppm and the absence of aromatic protons in the  $^1\text{H}$  NMR spectrum of **6** confirmed the removal of chiral auxiliary. In the  $^{13}\text{C}$  NMR spectrum of **6**, acid carbonyl resonated at  $\delta$  177 where in earlier imides carbonyl signals resonated below  $\delta$  175. IR spectra of acid compound showed stretching frequency at  $1710\text{ cm}^{-1}$  which was a characteristic peak for acid.

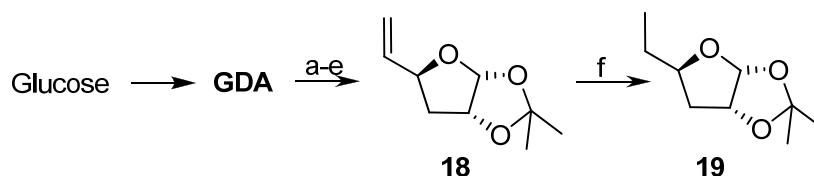
## Scheme 5



Synthesis of fragment B started with D-glucose. D-Glucose was converted into glucose diacetonide (GDA) and deoxygenation of free hydroxyl group present at 3-position of GDA was affected by employing the Barton-McCombie protocol to procure

3-deoxy compound. Selective 5,6 acetonide deprotection of resulting deoxycompound using 0.8%  $\text{H}_2\text{SO}_4$  in methanol gave the diol. Conversion of the diol to the corresponding dimesylate, followed by Zn-NaI mediate double elimination provided the 5,6-olefin **18**. The spectral and analytical data of **18** were found to be in agreement with the data reported earlier.<sup>24</sup> Hydrogenation of **18** lead to the formation of saturated compound **19** which was confirmed by the  $^1\text{H}$  NMR spectra where the olefinic protons were missing instead of that methyl triplet was observed.

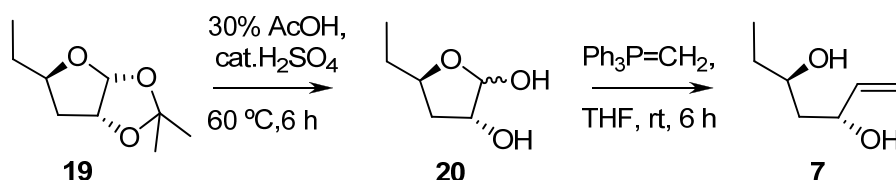
### Scheme 6



**Reagents and conditions:** a) NaH,  $\text{CS}_2$ , MeI, THF,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 1 h. b) TBTH, AIBN (cat), toluene, reflux, 6 h. c) 0.8%  $\text{H}_2\text{SO}_4$ , MeOH, 12 h. d) MsCl,  $\text{Et}_3\text{N}$ , DCM,  $0\text{ }^\circ\text{C}$ , 0.5 h. e) Zn, NaI, DMF,  $150\text{ }^\circ\text{C}$ , 2 h. f) 10% Pd-C,  $\text{H}_2$ , EtOAc, rt, 8 h.

Acid-mediated deprotection of the acetonide group in **19** and one carbon homologation of the resulting lactol **20** gave the alcohol **7**. The structure of **7** was confirmed by the presence of two terminal olefinic protons resonating at  $\delta$  5.05-5.27 and the internal olefin at  $\delta$  5.85. This structure was devoid of any anomeric proton or carbon in both  $^1\text{H}$  and  $^{13}\text{C}$  NMR was the further indication of the completion of the reaction.

### Scheme 7

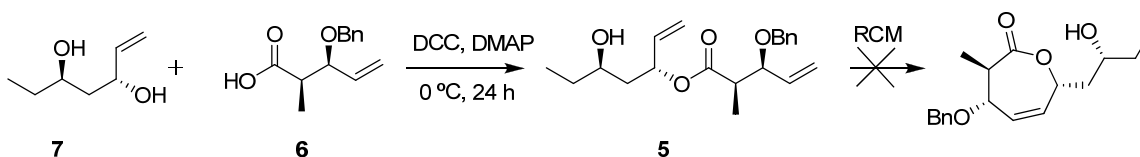


After having an easy access for both the fragments, the stage was now set for their coupling and subsequent ring closing metathesis. The coupling reaction of **6** and **7** was carried out at  $0\text{ }^\circ\text{C}$  to get the selective esterification of allylic hydroxyl group. After

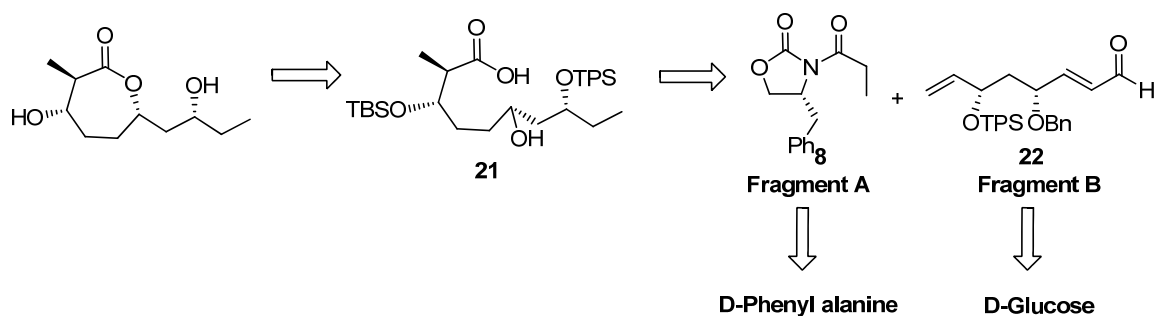


completion of the reaction, formation of desired product **5** was confirmed by NMR spectrum. In the  $^{13}\text{C}$  NMR spectra, carbonyl peak was shifted from  $\delta$  177.6 (**6**) to  $\delta$  173.2 (**5**) which clearly indicated the formation of ester. But our major concern was which free hydroxyl group was coupled with acid. From the reactivity point of view, allylic hydroxyl should be more reactive than the other free secondary hydroxyl groups. In the  $^1\text{H}$  NMR spectrum of **7**, two hydroxyl groups containing C-H were resonated at  $\delta$  3.73-3.85 (H-7) and  $\delta$  4.30-4.42 (H-5). In the coupling product **5**, one of these protons was shifted downfield almost 1.0 ppm and the other shifted little upfield (0.2 ppm). These results provided the sufficient proof for the formation of the desired product. Moreover, the single product in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR confirmed the absence of another possibility of coupling.

### Scheme 8

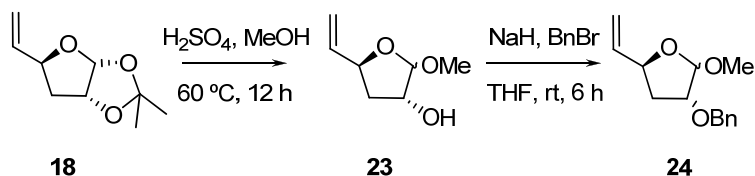


After successful coupling reaction, RCM reaction was carried out in different solvents (DCM, benzene, toluene) using both 1<sup>st</sup> and 2<sup>nd</sup> generation Grubbs' catalyst from room temperature to reflux conditions. But unfortunately in all the cases this reaction failed and starting material was recovered. Though, RCM reaction has been used extensively for the construction of medium size lactones, however, an exhaustive search of the available data in this regard has revealed a striking point that there was no single report where the RCM has been used for the 7-membered lactone construction. Attributing the failure of the proposed RCM based strategy for feigrisolide B to our ignorance at this stage, we have revised our strategy by considering the macro lactonization as the key transformation and identifying some of the intermediates of the previous strategy as starting point. As depicted below, the modified strategy is linear in nature and uses the Evans' aldol reaction as one of the key coupling reaction and an intramolecular lactonization at the advanced stage.

**Scheme 9: Modified Retrosynthetic Strategy**

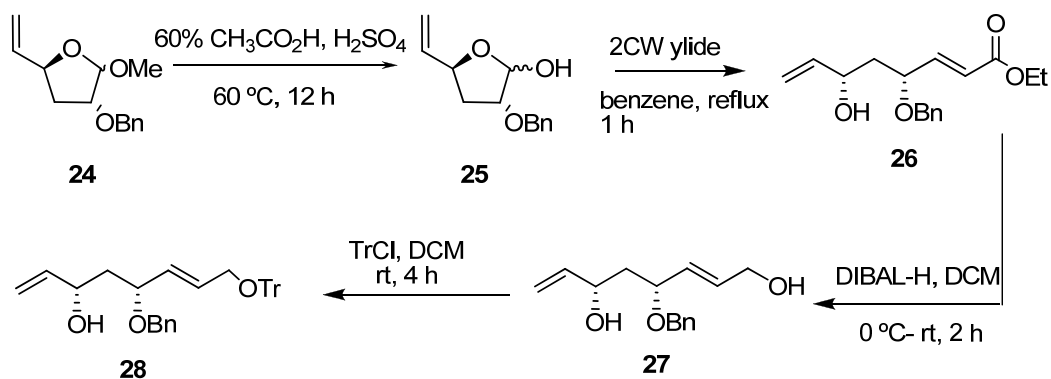
As indicated in the Scheme 1, Fragment A is one of the intermediate that has been used in the previous approach and synthesis of fragment B was planned from **18** prepared earlier. To minimize the number of steps, the hydrogenation of the intermediate alkene functional group was planned at a later stage.

Thus the synthesis of feigrisolide B was started from available intermediate **18**.<sup>24</sup> Subjecting compound **18** for the 1,2-acetonide deprotection using catalytic amount of sulfuric acid in methanol afforded the methylfuranoside **23**. Protection of the C(2)-OH in **23** as its benzyl ether **24** followed by hydrolysis of the anomeric –OMe using acetic acid-sulfuric acid combination gave lactol **25**.

**Scheme 10**

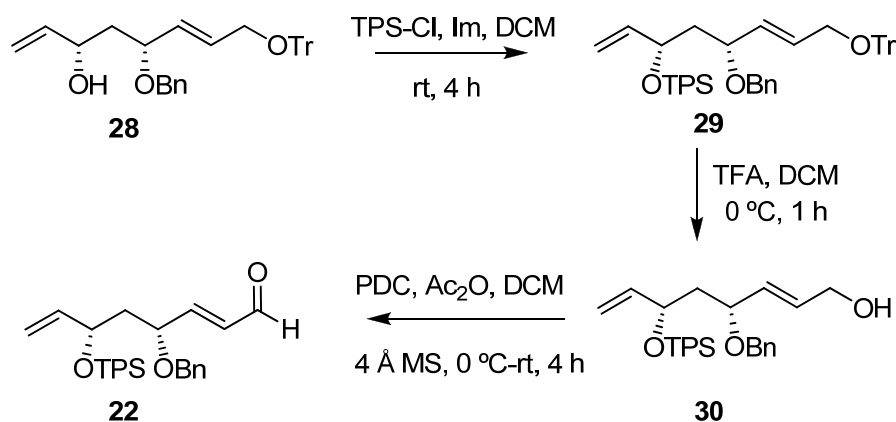
Lactol **25** was subjected to two-carbon Wittig homologation reaction. Presence of olefin proton at  $\delta$  6.9 clearly indicated the presence of  $\beta$ -proton of  $\alpha,\beta$ -unsaturated ester **26**. Value of coupling constant for olefinic proton, 16 Hz, indicated the *trans*-geometry of the newly formed internal olefin. Subsequently ester **26** was reduced by DIBAL-H to corresponding alcohol **27** followed by the selective protection of primary -OH group to its trityl ether **28**. Reduction of ester to alcohol was confirmed by the absence of the triplet and quartet signals seen in ester  $^1\text{H}$  NMR. This was further confirmed by the absence of ester carbonyl at  $\delta$  166.2 in  $^{13}\text{C}$  NMR spectrum.

## Scheme 11



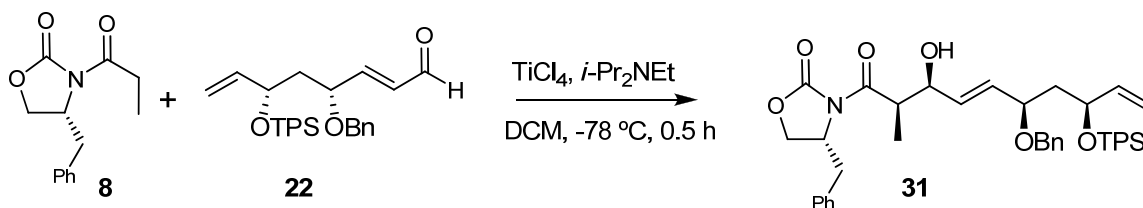
Protection of the free secondary hydroxyl group in **28** as its TBDPS (TPS) ether **29** by using TBDPS-Cl and imidazole followed by trityl group removal (TFA at 0 °C) of resulting **29** gave **30**. Controlled oxidation of the primary hydroxyl group in **30** was affected by using PDC in presence of acetic anhydride to complete the synthesis of the key aldehyde fragment **22**.

## Scheme 12



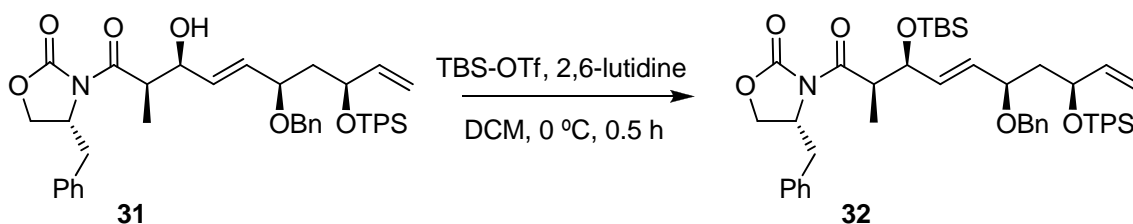
Fragment A (**8**) and fragment B (**22**) were subjected to the Evans' *syn*-aldol<sup>26</sup> reaction and from the NMR study it was seen that aldehyde proton of the starting material was absent in the product **31** and the methyl center generated after the reaction was showing a clear doublet which was a triplet earlier. From the NMR spectra it was clearly evident that only single diastereomer was formed.

## Scheme 13



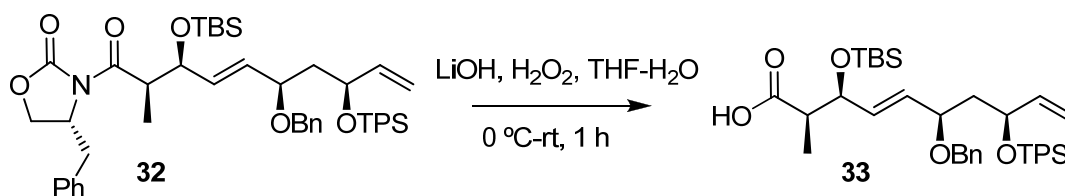
Newly generated hydroxyl group in the aldol reaction was protected as its TBDMS (TBS) ether **32** using TBS-OTf. Presence of TBS group was confirmed by the two methyl singlet signals around  $\delta$  0 in  $^1\text{H}$  NMR and two carbon signals at  $-4.0$ , and  $-3.5$ , respectively in  $^{13}\text{C}$  NMR spectra.

## Scheme 14



After the formation of basic structural core, required acid and alcohol functionality have to be demasked. For getting the free acid functionality, chiral auxiliary was removed and the hydrolysis was done such a way that directly acid could be obtained. Lithium hydroxide and 30% hydrogen peroxide method was found to be the best method for the preparation of acid **33**. Presence of acid was confirmed by IR spectroscopy, where stretching frequency at  $1709\text{ cm}^{-1}$  was the characteristic peak of acid carbonyl. Two imide carbonyl peaks at  $\delta$  153 and 174 were absent in  $^{13}\text{C}$  NMR of acid, instead,  $\delta$  178 peak was appeared for acid carbonyl.

## Scheme 15

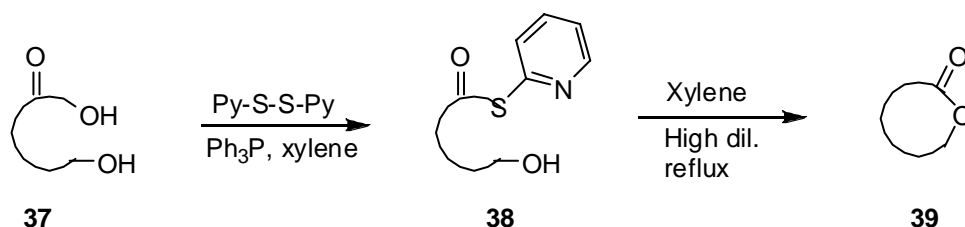




The lactonization of  $\omega$ -bromoalkanoic acids by the activation of either of the two or both the interacting centers are well reviewed.<sup>32</sup> A number of methods are reported in literature, some of them are discussed below:

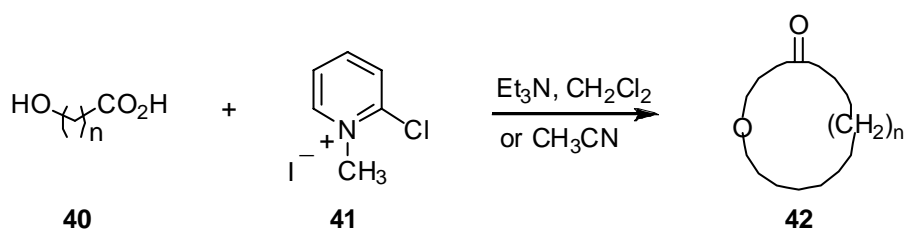
Corey-Nicolaou method (double activation method): Corey and Nicolaou have discovered a highly efficient method for the synthesis of macrolactones.<sup>33</sup> Dipyridyl disulphide was treated with hydroxyalkanoic acid (**37**) to form 2-pyridinethioester (**38**), which on refluxing in xylene under high dilution condition led to macrolactone (**39**).

### Scheme 17



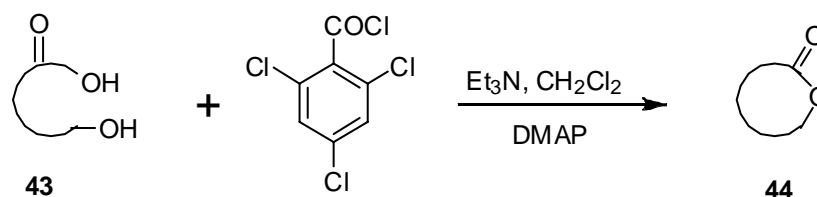
Mukaiyama method: Mukaiyama *et al.*,<sup>34</sup> introduced a new reagent 1-methyl 2-chloropyridinium iodide (**41**) for effective cyclization. This method is closely related to “double activation” method for the synthesis of macrolactones. A series of hydroxyalkanoic acids (**40**;  $n = 5, 6, 7, 10, 11$  and  $14$ ) were cyclized by slow addition to the reagent **41** in the presence of  $\text{Et}_3\text{N}$  in refluxing  $\text{CH}_2\text{Cl}_2$  or  $\text{CH}_3\text{CN}$ .

### Scheme 18



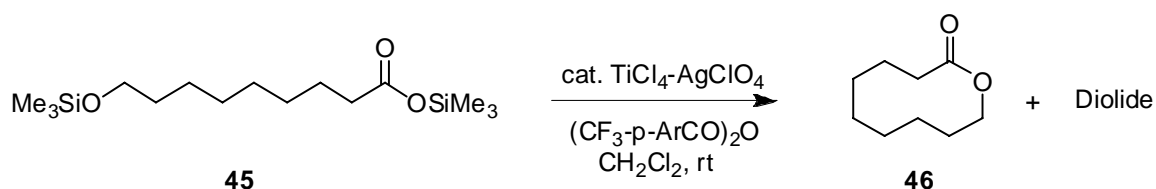
Yamaguchi method: This method<sup>35</sup> is the most popular and commonly used method in recent times for the synthesis of macrolactones even for esterification reaction. This reaction involves lactonization of mixed anhydride formed by the treatment of  $\omega$ -hydroxy acid (**43**) and 2, 4,6-trichlorobenzoyl chloride in the presence of  $\text{Et}_3\text{N}$ .

## Scheme 19



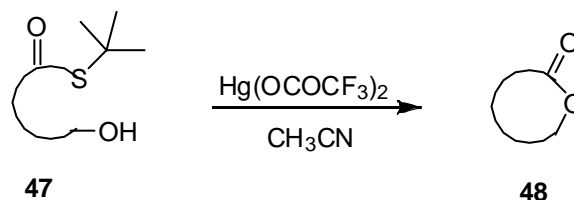
Recently, Mukaiyama and coworkers<sup>36</sup> have reported a new activation method for lactonization. Silyl  $\omega$ -siloxyalkanoate (**45**) was subjected to lactonization using *p*-trifluoromethylbenzoic anhydride and a catalytic amount of a mixture of  $\text{TiCl}_4$  and  $\text{AgClO}_4$ . For 8- and 9-membered ring lactones yields were 0% and for decanolide, yield was 33%. Only in case of undecanolide yield is high (70%).

## Scheme 20



Some other methods are reported for the macrolactonization, in which Masamone method<sup>37</sup> involves cyclization of *S*-*t*-butyl thioesters of hydroxy acids (**137**) using mercuric trifluoroacetate as an activating agent. The lactonization proceeds rapidly in dilute acetonitrile at room temperature. Good results were observed using the method observed by Gerlach<sup>38</sup> (50% yield).

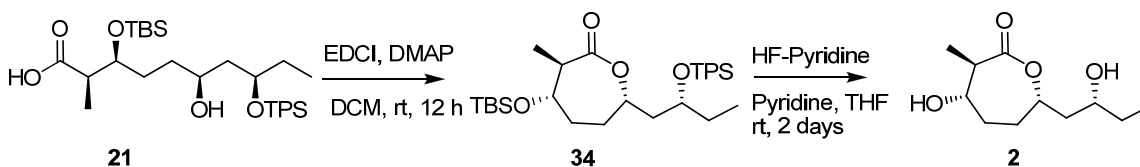
## Scheme 21



Now stage was all set for the cyclization reaction. After considering all the above coupling reagents, we decided to choose the reaction to try in simple coupling reagent DCC, DMAP condition which was used in the previous scheme for coupling, but in that condition a complex reaction mixture was resulted. Then we opted for EDCI agent,

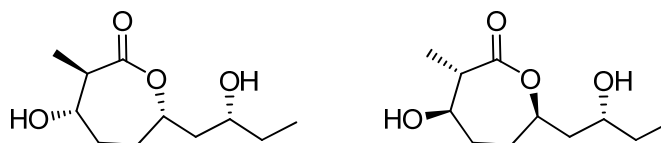
which is another simple as well as good coupling reagent used mainly in peptide synthesis. Under high dilution conditions, desired coupling product **34** was obtained in good yields. Proton adjacent to carbonyl group was shifted downfield from  $\delta$  2.58 to  $\delta$  3.04 indicated the formation of cyclic system. The  $\delta$ -shift of free hydroxyl containing C-H from  $\delta$  4.0 to  $\delta$  4.5 in  $^1\text{H}$  NMR was the strong evidence for the formation of lactone ring. After the formation of seven-membered lactone ring, protecting groups were removed and thus completed the synthesis of our target molecule **2**.

### Scheme 22



After synthesizing this molecule, the data of this compound was not matching with the natural product. During the course of our synthesis, a similar approach for synthesis of feigrisolide B was published.<sup>39</sup> Though, the discrepancy in the spectral data of synthetic and natural feigrisolide B was indicated, surprisingly the data of our final compound **2** was not matched with the data of putative feigrisolide B reported. In addition to this another possible diastereomer of feigrisolide B was disclosed very recently and once again its data was also different from the data we obtained.

**Figure 6:** Structures of recently synthesized products

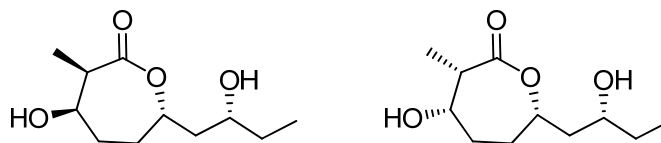




**Table 2:** Comparison data for natural and synthetic compounds

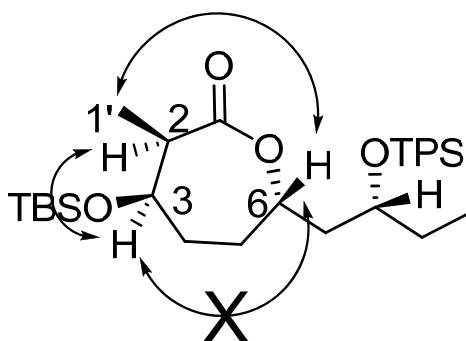
Position	<sup>1</sup> H Natural	<sup>1</sup> H GVM Sharma	<sup>1</sup> H Ours	<sup>13</sup> C Natural	<sup>13</sup> C GVM Sharma	<sup>13</sup> C Ours
1				177.6	176.6	174.6
2	2.50 (dq, 7.0, 8.3)	3.22 (dq, 5.22, 7.55)	2.92 (dq, 6.7, 8.2)	45.3	46.3	44.9
3	3.98 (br q, 8.3)	3.905 (m)	3.59-3.76 (m, 2H)	81.0	77.9	77.0
4	1.68, 2.03 (m)	1.86, 2.08 (m)	1.45-2.08 (m)	29.1	29.8	29.7
5	1.65, 2.01 (m)	1.70, 1.98 (m)	1.45-2.08 (m)	30.6	31.8	34.9
6	4.21 (m)	4.65 (m)	4.69 (m)	77.3	72.2	70.9
7	1.70 (m)	1.98 (m)	1.45-2.08 (m)	40.7	44.4	42.9
8	3.78 (m)	3.72 (m)	3.59-3.76 (m, 2H)	70.4	70.9	70.8
9	1.51 (m)	1.52 (m)	1.45-2.08 (m)	29.9	31.0	30.0
10	0.92 (t, 7.5)	0.96 (t, 7.5)	0.96 (t, 7.3)	10.0	11.1	9.7
1'	1.16 (d, 7.0)	1.38 (d, 7.8)	1.29 (d, 6.7)	13.7	14.5	14.2

The structure of two synthesized compounds by Sharma and co-workers were fully resolved with the help of NOE studies. In order to resolve structural ambiguity of our compound we have carried out the COSY and NOESY studies of the cyclized lactone **2**. After examining these data, we concluded that the product obtained has *cis*-stereochemistry between lactone substituents at C-2 and C-3. This could be attributed unanticipated stereochemical outcome in Evans' aldol step. Instead of getting the *syn*-geometry of the two newly generated centers *anti*-product was obtained as an exclusive product at this stage. In that case there were two possible products those could be formed.

**Figure 7:** Structure of two possible products

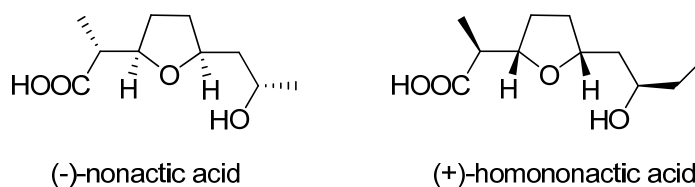
From NOE studies of our synthesized compound, we have noticed through space connectivity between C-1' methyl and C-6 (H) as well as C-2 (H) and C-3 (H) and there was no correlation between C-3 (H) and C-6 (H). From the previous analysis it was clear that C-2 (H) and C-3 (H) are in the same side and C-1 methyl was in the same side with C-6 (H). C-3 (H) and C-6 (H) were placed in different sides. As the stereochemistry of C-6 (H) was carried forward from sugar moiety and there was no chance of epimerization of this center, we concluded that the stereochemistry of the synthesized molecule was (2*R*, 3*R*, 6*S*, 8*R*)-3-hydroxy-6-(2-hydroxybutylmethyl-hepta-lactone).

**Figure 8:** NOE studies for compound **34**



After the completion of our synthesis another report was published where the synthesis of feigrisolide A was performed.<sup>40</sup> In that case also the data of synthesized compound and the data of natural product were not comparable. After the extensive studies, they concluded that the proposed structures of feigrisolide A and feigrisolide B were wrong, and the data of the natural feigrisolide A (?) was fully matched with the data of (-)-nonactic acid.<sup>41</sup> They also proposed that the structure of feigrisolide B was not the seven-membered lactone, instead, it was (+)-homononactic acid.<sup>42</sup> These nonactic acid and homononactic acid were not seven-membered lactones. The basic skeleton of these compounds are tetrahydrofuran ring. This report clearly indicated that our synthesized product was not related to any natural product isolated.

**Figure 9**

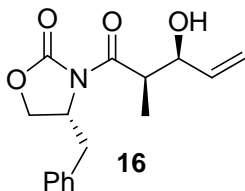


## **EXPERIMENTAL**

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## **EXPERIMENTAL**

### **(R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one (16)**



Compound **8** (2.5 g, 0.011 mol) was taken in dry DCM (50 mL) and at 0 °C freshly distilled TiCl<sub>4</sub> (1.3 mL, 0.012 mol) was added and stirred for 15 mins. The reaction mixture became turbid yellow. To this solution dry DIPEA (4.8 mL, 0.028 mol) was added and the reaction mixture became blood red. Temperature was maintained 0 °C and stirred it again for 15 mins. Then the reaction mixture was cooled to – 78 °C and freshly distilled acrolein (0.8 mL, 0.012 mol) solution in dry DCM (12 mL) was added to the reaction mixture and stirred for 0.5 h. Reaction mixture was quenched with saturated solution of NH<sub>4</sub>Cl and aqueous layer was washed with DCM and combined organic layer was dried over sodium sulphate and concentrated. The crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:6) to obtain white solid **16**.

<b>Yield</b>	: 2.26 g, 73%
<b>Mol Formula</b>	: C <sub>16</sub> H <sub>19</sub> NO <sub>4</sub>
<b>Mol Weight</b>	: 289
<b>Optical rotation</b> [α] <sub>D</sub> <sup>25</sup>	: –39.1 (c 1.35, CHCl <sub>3</sub> )
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.26 (d, <i>J</i> = 7.0 Hz, 3H), 2.78 (dd, <i>J</i> = 9.4, 13.3 Hz, 1H), 3.12 (br. s, 1H), 3.24 (dd, <i>J</i> = 3.3, 13.3 Hz, 1H), 3.87 (ddd, <i>J</i> = 3.9, 7.0, 10.8 Hz, 1H), 4.19 (m, 2H), 4.45-4.51 (m, 1H), 4.63-4.75 (m, 1H), 5.19 (dt, <i>J</i> = 1.6, 10.6 Hz, 1H), 5.33 (dt, <i>J</i> = 1.6, 17.2 Hz, 1H), 5.85 (ddd,

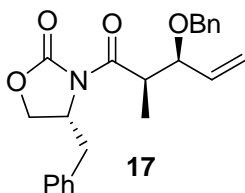
$J = 5.5, 10.6, 17.2$  Hz, 1H), 7.18-7.33 (m, 5H)

$^{13}\text{C}$  : 11.0 (q), 37.7 (t), 42.4 (d), 55.1 (d), 66.1 (t), 72.5 (d),  
( $\text{CDCl}_3$ , 50 MHz) 116.1 (t), 127.3 (d), 128.9 (d), 129.3 (d), 135.0 (d),  
137.4 (d), 153.0 (s), 176.4 (s) ppm

**Elemental analysis Cald.** : C, 66.42; H, 6.42%

**Found** : C, 66.63; H, 6.49%

**(R)-4-Benzyl-3-((2R,3S)-3-(benzyloxy)-2-methylpent-4-enyl)oxazolidin-2-one (17)**



Compound **16** (2 g, 0.007 mol) was taken in dry toluene (5 mL) and freshly prepared solid silver oxide (2.42 g, 0.011 mol) was added to it followed by benzyl bromide (1.6 mL, 0.014 mol). Then the reaction mixture was stirred at room temperature for 6 h and the reaction mixture was filtered over *Celite* bed. Filtrate was concentrated and purified over column chromatography using ethyl acetate in light petroleum to obtained 680 mg of starting material (**16**) back and white crystalline solid **17**.

**Yield** : 1.24 g, 64% with respect to recovered starting material

**Mol Formula** :  $\text{C}_{22}\text{H}_{24}\text{NO}_4$

**Mol Weight** : 366

**Optical rotation**  $[\alpha]_{\text{D}}^{25}$  :  $-25.7$  ( $c$  2,  $\text{CHCl}_3$ )

$^1\text{H}$  :  $\delta$  1.26 (d,  $J = 6.6$  Hz, 3H), 2.71 (dd,  $J = 9.6, 13.6$  Hz,  
( $\text{CDCl}_3$ , 200 MHz) 1H), 3.26 (dd,  $J = 3.3, 13.6$  Hz, 1H), 3.91 (t,  $J = 8.3$  Hz,  
1H), 3.98 (t,  $J = 6.8$  Hz, 1H), 4.05 (dd,  $J = 1.9, 8.3$  Hz,

1H), 4.11 (t,  $J = 6.8$  Hz, 1H), 4.31 (d,  $J = 11.7$  Hz, 1H),  
 4.49 (m, 1H), 4.61 (d,  $J = 11.7$  Hz, 1H), 5.28 (br. d,  $J =$   
 $7.7$  Hz, 1H), 5.33 (br. s, 1H), 5.89 (ddd,  $J = 7.3, 10.6,$   
 $16.9$  Hz, 1H); 7.18-7.34 (m, 10H)

$^{13}\text{C}$  : 12.5 (q), 37.8 (t), 42.2 (d), 55.4 (d), 65.8 (t), 70.2 (t),  
 (CDCl<sub>3</sub>, 50 MHz) 80.9 (d), 118.7 (t), 127.2 (d), 127.4 (d), 127.8 (d), 128.2  
 (d), 128.8 (d), 129.3 (d), 135.4 (s), 136.1 (d), 138.4 (s),  
 153.0 (s), 174.1 (s) ppm

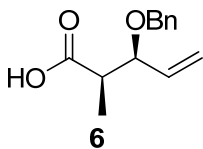
**Elemental analysis Cald.** : C, 72.11; H, 6.60%

**Found** : C, 72.17; H, 6.59%

Crystal data	<b>107</b>
Formula	C <sub>22</sub> H <sub>24</sub> NO <sub>4</sub>
M <sub>r</sub>	366
Temp. (K)	297(2)
Crystal system	monoclinic
space group	P 21
A [Å]	11.553(4)
B [Å]	7.502(2)
C [Å]	12.142(4)
$\alpha$ [°]	90
$\beta$ [°]	98.138(5)
$\gamma$ [°]	90
V [Å <sup>3</sup> ]	1041.76
Z	4

N1	N	1.05978(14)	H1	H	1.4267	0.3933	C3	C	0.90128(18)
		0.3518(3)			0.17890(14)	0.2828			0.3409(4)
									0.30070(19)
O1	O	0.88460(14)	C2	C	1.18436(17)	H3	H	0.8526	0.3728
		0.3500(3)			0.05615(14)			0.3483(3)	0.16351(18)
									0.2307
C1	C	1.44751(19)	H2	H	1.2292	0.2726	O4	O	0.75452(13)
		0.4484(4)			0.2199(2)	0.2199			0.1391(3)
									0.32982(16)

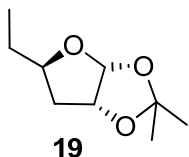
H4	H	0.7045	0.2301	0.3012	C14	C	1.23592(18)	0.5355(4)	0.1667(2)	C22	C	0.9135(2)	0.0147(4)	0.2478(2)			
C5	C	1.36254(17)	0.5320(3)	0.14620(18)	H14A	H	1.1905	0.6084	0.1104	H22	H	0.8726	0.0155	0.1761			
C6	C	0.5074(3)	-	0.0589(4)	0.2897(2)	H14B	H	1.2313	0.5888	0.2387	C23	C	0.5386(3)	0.0723(4)	0.4679(3)		
H6	H	0.5349	-0.1079	0.2280	C15	C	0.5848(2)	0.0007(4)	0.3786(3)	H23	H	0.5891	0.1142	0.5288			
C7	C	1.02865(19)	0.3578(4)	0.28548(19)	O2	O	1.05570(16)	0.2918(3)	0.00030(15)	C24	C	0.8744(3)	0.4676(6)	0.3910(3)			
C8	C	1.3964(2)	0.6109(4)	0.0531(2)	C17	C	0.3480(3)	0.0245(5)	0.3824(4)	H24A	H	0.9340	0.4576	0.4543			
H8	H	1.3405	0.6666	0.0018	H17	H	0.2678	0.0318	0.3839	H24B	H	0.7999	0.4377	0.4125			
C9	C	1.5629(2)	0.4450(4)	0.2017(2)	C18	C	1.5943(2)	0.5253(4)	0.1086(2)	H24C	H	0.8722	0.5876	0.3634			
H9	H	1.6191	0.3887	0.2523	H18	H	1.6717	0.5228	0.0958	C25	C	1.1742(2)	0.2611(5)	0.0500(2)			
O3	O	1.10577(15)	0.3709(4)	0.36280(14)	C19	C	0.4222(4)	0.0828(5)	0.4688(3)	H25A	H	1.2285	0.3145	0.0057			
C11	C	1.5112(2)	0.6090(4)	0.0346(2)	H19	H	0.3936	0.1311	0.5302	H25B	H	1.1903	0.1344	0.0571			
H11	H	1.5324	0.6645	-	0.0280	C20	C	0.3886(3)	-	0.0457(4)	0.2922(3)	C26	C	0.9982(3)	-	0.1006(6)	0.2692(3)
C12	C	0.9880(2)	0.3333(4)	0.07736(19)	H20	H	0.3362	-0.0851	0.2319	H26A	H	1.0413	-0.1057	0.3399			
C13	C	0.87711(19)	0.1449(4)	0.3285(2)	C21	C	0.7144(3)	-	0.0185(6)	0.3790(4)	H26B	H	1.0155	-0.1777	0.2138		
H13	H	0.9174	0.1171	0.4030	H21	H	0.7601	-0.1152	0.4062								

**(2R,3S)-3-(Benzyloxy)-2-methylpent-4-enoic acid (6)**

Benzyl protected compound **17** (1 g, 0.003 mol) was taken in 15 mL THF-H<sub>2</sub>O (4:1) mixture at 0 °C and LiOH (100 mg, 0.005 mmol) was added to it followed by 30% H<sub>2</sub>O<sub>2</sub> solution (1.2 mL). Then the reaction mixture was stirred for 4 h and bulk of THF was removed under vacuum and resulting mixture was extracted with DCM (3 x 50 mL). Combined organic layer was dried over sodium sulfate and concentrated. Crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:9) to procure white solid **6**.

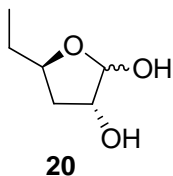
<b>Yield</b>	: 338 mg, 58%
<b>Mol Formula</b>	: C <sub>13</sub> H <sub>16</sub> O <sub>3</sub>
<b>Mol Weight</b>	: 220
<b>Optical rotation</b> [α] <sub>D</sub> <sup>25</sup>	: -21.6 (c 1, CHCl <sub>3</sub> )
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.16 (d, <i>J</i> = 7.0 Hz, 3H), 2.60 (qu, <i>J</i> = 6.7, 13.4 Hz, 1H), 3.97 (t, <i>J</i> = 6.8 Hz, 1H), 4.29 (d, <i>J</i> = 11.8 Hz, 1H), 4.54 (d, <i>J</i> = 11.8 Hz, 1H), 5.20 (br.d, <i>J</i> = 7.4 Hz, 1H), 5.27 (br. s, 1H), 5.73 (ddd, <i>J</i> = 7.8, 11.3, 16.3 Hz, 1H), 7.22 (br. s, 5H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 12.1 (q), 44.6 (d), 70.7 (t), 81.1 (d), 119.7 (t), 127.8 (d), 128.4 (d), 135.3 (d), 177.6 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 70.89; H, 7.32%
<b>Found</b>	: C, 70.72; H, 7.51%



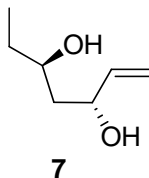
**(3aR,5R,6aR)-5-Ethyl-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxole (19)**

Compound **18** (5 g, 0.03 mol) was taken in HPLC grade ethyl acetate (50 mL) and 10% Pd-C was added to the reaction mixture in catalytic amount under hydrogen atmosphere. Hydrogen balloon pressure was applied to the reaction medium for 8 h at room temperature and the complete reaction mixture was filtered through *Celite* pad and washed thoroughly with ethyl acetate. Filtrate was concentrated under vacuum and residue was purified by column chromatography using ethyl acetate in light petroleum (1:9) to obtain colorless liquid **19**.

<b>Yield</b>	: 4.14 g, 82%
<b>Mol Formula</b>	: C <sub>9</sub> H <sub>16</sub> O <sub>3</sub>
<b>Mol Weight</b>	: 162
<b>Optical rotation</b> $[\alpha]_D^{25}$	: -18.7 ( <i>c</i> 2.5 CHCl <sub>3</sub> )
<b><sup>1</sup>H</b>	: $\delta$ 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 1.30 (s, 3H), 1.39-1.45 (m, (CDCl <sub>3</sub> , 200 MHz) 2H), 1.47 (s, 3H) 1.87-2.05 (m, 2H), 3.96 (m, 1H), 4.63 (dt, <i>J</i> = 3.9, 7.2 Hz, 1H), 5.88 (d, <i>J</i> = 3.9 Hz, 1H)
<b><sup>13</sup>C</b>	: 9.3 (q), 24.3 (q), 28.5 (q), 30.5 (t), 40.2 (t), 76.9 (d), (CDCl <sub>3</sub> , 50 MHz) 80.6 (d), 104.3 (d), 110.7 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 58.32; H, 8.39%
<b>Found</b>	: C, 58.11; H, 8.16%

**(3R,5R)-5-Ethyltetrahydrofuran-2,3-diol (20)**

Compound **19** (4 g, 0.024 mol) was taken in 30% acetic acid solution (40 mL) in water and few drops of concentrated sulfuric acid was added to it. The reaction mixture was heated at 60 °C for 4 h and then the reaction mixture was cooled to room temperature. The reaction mixture was neutralized with solid NaHCO<sub>3</sub> until the effervescence ceased. Then the whole solution was diluted with water and extracted with ethyl acetate for several times (3 x 50 mL). Combined organic layer was dried over sodium sulphate and concentrated under vacuum to get colorless liquid **20** (1.69 g, 55%), which was not purified and directly used for the next reaction.

**(3R,5R)-Hept-1-ene-3,5-diol (7)**

To a solution THF solution (10 mL) of compound **20** (1 g, 0.008 mol), one carbon Wittig ylide in THF solution (generated by treatment of 16.16 g of triphenylphosphonium methyl iodide salt with *n*-BuLi (1.6 M, 17.6 mL) at 0 °C for 1 h) was added at 0 °C and then after 0.5 h the reaction mixture was warmed to room temperature and again stirred for 1 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution and extracted with ethyl acetate. Combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. Residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:3) to obtain colorless oil **7**.

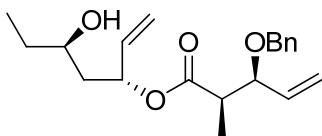
**Yield** : 640 mg, 65%

**Mol Formula** : C<sub>7</sub>H<sub>14</sub>O<sub>2</sub>

**Mol Weight** : 130

<b>Optical rotation</b> $[\alpha]_D^{25}$	:	-18.6 ( <i>c</i> 1.9, MeOH)
<b><math>^1\text{H}</math></b> (CDCl <sub>3</sub> , 200 MHz)	:	$\delta$ 0.92 (t, <i>J</i> = 7.5 Hz, 3H), 1.42- 1.72 (m, 4H), 3.58 (br s, 2H), 3.73-3.85 (m, 1H), 4.30-4.42 (m, 1H), 5.05-5.27 (br. m, 2H), 5.85 (ddd, <i>J</i> = 5.9, 10.3, 16.7 Hz, 1H)
<b><math>^{13}\text{C}</math></b> (CDCl <sub>3</sub> , 50 MHz)	:	9.6 (q), 30.7 (t), 42.5 (t), 73.5 (d), 114.2 (t), 140.9 (d) ppm
<b>Elemental analysis Cald.</b>	:	C, 64.58; H, 10.84%
<b>Found</b>	:	C, 64.42; H, 10.93%

**(2*R*,3*S*)-((3*R*,5*R*)-5-Hydroxyhept-1-en-3-yl) 3-(benzyloxy)-2-methylpent-4-enoate (5)**



**5**

Acid compound **6** (338 mg, 1.54 mmol) was taken in dry DCM (10 mL) and DCC (349.5 mg, 1.69 mmol) was added to it at 0 °C and stirred for 2 h, then the mixture of alcohol **7** (200 mg, 1.54 mmol) and catalytic amount of DMAP in dry DCM (10 mL) was added to the previous solution mixture and again stirred for 24 h at 0 °C. Then the reaction mixture was washed thoroughly with water and dried over sodium sulphate and concentrated. Crude residue was purified on column chromatography over silica gel using ethyl acetate in light petroleum (1:19) to obtain colorless liquid **5**.

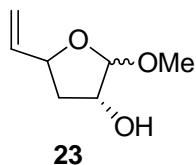
<b>Yield</b>	:	306 mg, 60%
<b>Mol Formula</b>	:	C <sub>21</sub> H <sub>31</sub> O <sub>4</sub>
<b>Mol Weight</b>	:	347
<b>Optical rotation</b> $[\alpha]_D^{25}$	:	+ 9.0 ( <i>c</i> 4.0, CHCl <sub>3</sub> )

$^1\text{H}$ ( $\text{CDCl}_3$ , 200 MHz)	: $\delta$ 0.91 (t, $J = 7.4$ Hz, 3H), 1.24 (d, $J = 7.1$ Hz, 3H), 1.42-1.50 (m, 2H), 1.75 (dt, $J = 1.4, 6.9$ Hz, 2H), 2.66 (t, $J = 6.9$ Hz, 1H), 3.58 (m, 1H), 4.02 (dd, $J = 1.2, 6.7$ Hz, 1H), 4.37 (d, $J = 11.8$ Hz, 1H), 4.61 (d, $J = 11.8$ Hz, 1H), 5.15 (ddd, $J = 1.2, 2.4, 10.2$ Hz, 1H), 5.28 (ddd, $J = 1.2, 2.4, 16.8$ Hz, 1H), 5.32-5.49 (m, 3H), 5.69-6.90 (m, 2H), 7.22-7.32 (m, 5H)
$^{13}\text{C}$ ( $\text{CDCl}_3$ , 50 MHz)	: 9.7 (q), 12.4 (q), 30.4 (t), 41.2 (t), 45.2 (d), 70.3 (d), 70.5 (t), 73.4 (d), 81.4 (d), 117.1 (t), 119.0 (t), 127.5 (s), 127.7 (d), 128.2 (d), 136.1 (d), 136.2 (d), 173.2 (s) ppm

**Elemental analysis Cald.** : C, 72.59; H, 8.99%

**Found** : C, 72.73; H, 8.81%

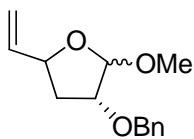
**(3R)-2-Methoxy-5-vinyl-tetrahydrofuran-3-ol (23)**



Compound **18** (12 g, 0.07 mol) was taken in 100 mL MeOH and catalytic amount of sulfuric acid was added to it and the reaction mixture was stirred for 12 h at 60 °C. Then the reaction mixture was cooled to room temperature and solid  $\text{NaHCO}_3$  was added to neutralize the excess acid. MeOH was almost evaporated under vacuum and residue was partitioned between ethyl acetate and water. Ethyl acetate layer was dried over sodium sulphate, concentrated and purified by column chromatography using ethyl acetate in light petroleum (1:3) to procure colorless oil **23**.

<b>Yield</b>	: 6.1 g, 60%
<b>Mol Formula</b>	: C <sub>7</sub> H <sub>12</sub> O <sub>3</sub>
<b>Mol Weight</b>	: 144
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.92-2.03 (m, 2H), 3.34 (s, 3H), 4.22 (dd, <i>J</i> = 1.0, 4.2 Hz, 1H), 4.72 (dt, <i>J</i> = 7.3, 8.4 Hz, 1H), 4.78 (s, 1H), 5.09 (m, 1H), 5.22 (m, 1H), 5.74 (ddd, <i>J</i> = 7.4, 10.1, 17.3 Hz, 1H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 38.4 (t), 54.4 (q), 76.1 (d), 80.6 (d), 109.1 (d), 116.0 (t), 139.9 (d) ppm
<b>Elemental analysis Cald.</b>	: C, 58.32; H, 8.39%
<b>Found</b>	: C, 58.58; H, 8.47%

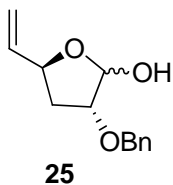
**(3*R*)-3-(Benzyloxy)-2-methoxy-5-vinyl-tetrahydrofuran (24)**



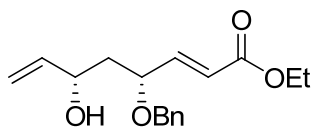
**24**

Compound **23** (6 g, 0.042 mol) was taken in 60 mL of dry THF and cooled to 0 °C. At that temperature NaH (2 g, 0.05 mol, 60% dispersed in oil) was added and stirred for 0.5 h. Then at 0 °C, BnBr (6 mL, 0.055 mol) was added dropwise and the reaction mixture was warmed to room temperature and stirred for 6 h. Then the reaction mixture was quenched with ice cold water and the water layer was extracted with ethyl acetate. Combined organic layer was dried over sodium sulphate and concentrated under vacuum. Residue was purified by column chromatography using ethyl acetate in light petroleum (1:6) to obtain colorless oil **24**.

<b>Yield</b>	: 7.61 g, 78%
<b>Mol Formula</b>	: C <sub>14</sub> H <sub>18</sub> O <sub>3</sub>
<b>Mol Weight</b>	: 234
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.80-1.94 (m, 1H), 2.16 (dd, <i>J</i> = 6.4, 13.4 Hz, 1H), 3.35 (s, 3H), 3.99 (d, <i>J</i> = 4.9 Hz, 1H), 4.55 (s, 2H), 4.73 (dt, <i>J</i> = 7.3, 8.5 Hz, 1H), 4.94 (s, 1H), 5.10 (ddd, <i>J</i> = 1.5, 2.4, 10.1 Hz, 1H), 5.24 (ddd, <i>J</i> = 1.5, 2.6, 17.2 Hz, 1H), 5.82 (ddd, <i>J</i> = 7.4, 10.1, 17.2 Hz, 1H), 7.32 (m, 5H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 36.0 (t), 54.4 (q), 71.2 (t), 80.9 (d), 83.2 (d), 106.9 (d), 115.9 (t), 127.6 (d), 127.7 (s), 128.4 (d), 137.8 (s), 139.9 (d) ppm
<b>Elemental analysis Cald.</b>	: C, 71.77; H, 7.74%
<b>Found</b>	: C, 72.00; H, 7.71%

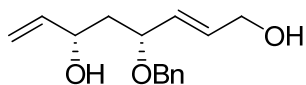
**(3*R*,5*S*)-3-(Benzyloxy)-5-vinyltetrahydrofuran-2-ol (25)**

Benzyl protected compound **24** (7.5 g, 0.032 mol) was taken in 75 mL of acetic acid in water and catalytic amount of sulfuric acid was added to it. The reaction mixture was heated at 60 °C for 12 h and then cooled to room temperature. Reaction was neutralized with solid NaHCO<sub>3</sub>, extracted with ethyl acetate for several times and the combined organic layer was dried over sodium sulphate, concentrated. The crude lactol residue **25** (3.88 g) was subjected to the next reaction without purification.

**(4*R*,6*S*,*E*)-Ethyl 4-(benzyloxy)-6-hydroxyocta-2,7-dienoate (26)****26**

Crude compound **25** (3.8 g, 0.017 mol) was taken in 80 mL of benzene and 2-carbon Wittig ylide (7.1 g, 0.02 mol) was added to it. Reaction mixture was heated to reflux for 1 h, then cooled it to room temperature and concentrated under vacuum. Residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:4) to obtain colorless oil **26**.

<b>Yield</b>	: 3.71 g, 74%
<b>Mol Formula</b>	: C <sub>17</sub> H <sub>22</sub> O <sub>4</sub>
<b>Mol Weight</b>	: 290
<b>Optical rotation</b> $[\alpha]_D^{25}$	: -2.6 ( <i>c</i> 1.1 CHCl <sub>3</sub> )
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: $\delta$ 1.29 (t, <i>J</i> = 7.1 Hz, 3H), 1.73 (ddd, <i>J</i> = 4.8, 7.3, 14.0 Hz, 1H), 1.87 (ddd, <i>J</i> = 4.8, 8.3, 14.0 Hz, 1H), 3.73 (br. s, 1H), 4.18 (q, <i>J</i> = 7.1 Hz, 2H), 4.20-4.33 (m, 1H), 4.42, 4.55 (2d, <i>J</i> = 11.9 Hz, 2H), 4.52-4.65 (m, 1H), 5.07 (br. d, <i>J</i> = 10.5 Hz, 1H), 5.16-5.30 (m, 1H), 5.77-6.25 (m, 2H), 6.86 (dd, <i>J</i> = 6.8, 15.8 Hz, 1H), 7.25-7.32 (m, 5H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 14.1 (q), 41.8 (t), 60.6 (t), 70.6 (d), 71.5 (t), 74.6 (d), 114.2 (t), 121.8 (d), 127.9 (d), 128.4 (d), 140.2 (s), 147.0 (d), 150.0 (d), 166.2 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 70.32; H, 7.64%
<b>Found</b>	: C, 70.09; H, 7.37%

**(4*R*,6*S*,*E*)-4-(Benzyloxy)octa-2,7-diene-1,6-diol (27)****27**

Compound **26** (3.5 g, 0.012 mol) was taken in dry DCM (35 mL) and cooled to 0 °C, then 2.36 (M) DIBAL-H solution in toluene (16 mL, 0.037 mol) was added to the reaction mixture dropwise and stirred at that temperature for 2 h. Then the mixture was quenched with saturated solution of sodium-potassium tartarate and the aqueous solution was washed several times with DCM (3 x 30 mL) and the combined organic layer was dried over sodium sulphate. After concentration of organic layer, crude residue was purified over silica gel using ethyl acetate in light petroleum (1:1.5) to procure colorless liquid **27**.

**Yield** : 2.04 g, 68%

**Mol Formula** : C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>

**Mol Weight** : 248

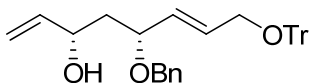
**Optical rotation**  $[\alpha]_D^{25}$  : +51.0 (*c* 1.35, CHCl<sub>3</sub>)

**<sup>1</sup>H** : δ 1.66 (ddd, *J* = 3.5, 4.1, 14.5 Hz, 1H), 1.86 (dt, *J* = 9.1, 14.5 Hz, 1H), 4.09 (ddd, *J* = 4.2, 7.7, 9.3 Hz, 1H), 4.18 (d, *J* = 1.3 Hz, 1H), 4.2 (d, *J* = 1.3 Hz, 1H), 4.26-4.33 (m, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 5.07 (ddd, *J* = 1.5, 3.0, 10.4 Hz, 1H), 5.22 (ddd, *J* = 1.5, 3.0, 17.2 Hz, 1H), 5.64 (ddt, *J* = 1.5, 7.8, 15.7 Hz, 1H), 5.74-5.93 (m, 2H), 7.26-7.32 (m, 5H)

**<sup>13</sup>C** : 42.6 (t), 62.5 (t), 70.3 (t), 71.7 (d), 79.3 (d), 114.4 (t), 127.8 (d), 127.9 (d), 128.5 (d), 130.8 (d), 132.8 (d),



137.8 (s), 140.3 (d) ppm

**Elemental analysis Cald.** : C, 72.55; H, 8.12%**Found** : C, 72.32; H, 8.05%**ESI-MS (*m/z*)** : 249 [M+H]<sup>+</sup>**(3*S*,5*R*,*E*)-5-(Benzyloxy)-8-(trityloxy)octa-1,6-dien-3-ol (28)****28**

Reduced alcohol **27** (2 g, 0.008 mol) was taken in dry DCM (20 mL) and dry Et<sub>3</sub>N (3.9 mL, 0.028 mol) was added to it and stirred for 10 mins and solid Ph<sub>3</sub>C-Cl (4.26 g, 0.015 mol) was added to the reaction mixture and stirred for 4 h. Reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:7) to obtain thick yellowish liquid **28**.

**Yield** : 3.44 g, 87%**Mol Formula** : C<sub>34</sub>H<sub>34</sub>O<sub>3</sub>**Mol Weight** : 490**Optical rotation** [α]<sub>D</sub><sup>25</sup> : +29.50 (*c* 1.2, CHCl<sub>3</sub>)

**<sup>1</sup>H** : δ 1.63-1.74 (dt, *J* = 3.7, 14.5 Hz, 1H), 1.80-1.96 (dt, *J* = 9.3, 14.5 Hz, 1H), 3.40 (s, 1H), 3.67 (d, *J* = 3.0 Hz, 1H), 4.03-4.13 (m, 1H), 4.31 (m, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 5.06 (ddd, *J* = 1.5, 3.0, 10.4 Hz, 1H), 5.23 (ddd, *J* = 1.5, 3.0, 17.2 Hz, 1H), 5.75-5.91 (m, 3H), 7.18-7.48 (m, 20H)

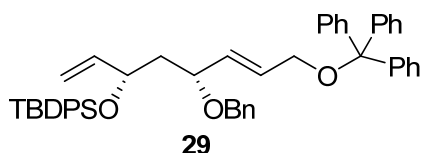
$^{13}\text{C}$  : 42.8 (t), 63.9 (t), 70.2 (t), 72.0 (d), 79.8 (d), 87.0 (s),  
 (CDCl<sub>3</sub>, 50 MHz) 114.2 (t), 127.1 (d), 127.8 (d), 128.0 (d), 128.5 (d),  
 128.6 (d), 130.6 (d), 130.9 (d), 137.8 (s), 140.5 (d),  
 144.1 (s) ppm

**Elemental analysis Cald.** : C, 83.23; H, 6.98%

**Found** : C, 83.31; H, 7.19%

**ESI-MS (*m/z*)** : 513 [M+Na]<sup>+</sup>

**((*3S,5R,E*)-5-(Benzyloxy)-8-(trityloxy)octa-1,6-dien-3-yloxy)(*tert*-butyl)diphenylsilane (**29**)**



Trityl protected compound **28** (3.4 g, 0.007 mol) was taken in dry DCM (40 mL) and imidazole (0.7 g, 0.011 mol) followed by TBDPS-Cl (2.5 mL, 0.009 mol) were added to the reaction mixture and stirred for 4 h. Then the mixture was washed several times with water and the water layer was extracted with DCM. Combined organic layer was dried over sodium sulphate and concentrated. Crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:19) to get colorless liquid **29**.

**Yield** : 3.44 g, 87%

**Mol Formula** : C<sub>50</sub>H<sub>52</sub>O<sub>3</sub>Si

**Mol Weight** : 728

**Optical rotation** [ $\alpha$ ]<sub>D</sub><sup>25</sup> : +24.5 (*c* 3.7, CHCl<sub>3</sub>)

$^1\text{H}$  :  $\delta$  1.03 (s, 9H), 1.63 (ddd, *J* = 4.8, 7.5, 12.5 Hz, 1H),  
 (CDCl<sub>3</sub>, 200 MHz) 2.03 (ddd, *J* = 5.3, 8.2, 13.4 Hz, 1H), 3.49 (d, *J* = 13.4

Hz, 1H), 3.56 (d,  $J = 3.0$  Hz, 1H), 3.78-3.85 (m, 1H), 4.20 (d,  $J = 11.9$  Hz, 1H), 4.31 (dd,  $J = 5.6, 7.1$  Hz, 1H), 4.47 (d,  $J = 11.9$  Hz, 1H), 4.70-4.89 (m, 2H), 5.6 (m, 2H), 5.77 (ddd,  $J = 7.2, 10.4, 17.2$  Hz, 1H), 7.15-7.46 (m, 25H), 7.60-7.71 (m, 5H)

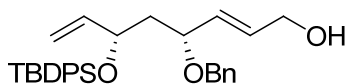
$^{13}\text{C}$  : 19.4 (s), 27.1 (q), 44.1 (t), 64.2 (t), 69.8 (t), 72.4 (d), (CDCl<sub>3</sub>, 50 MHz) 76.4 (d), 86.9 (s), 114.9 (t), 127.0 (d), 127.3 (d), 127.3 (d), 127.5 (d), 127.67 (d), 127.7 (d), 127.73 (d), 127.8 (d), 127.9 (d), 128.2 (s), 128.6 (d), 129.4 (d), 129.5 (d), 129.6 (s), 129.9 (d), 131.5 (d), 134.2 (s), 134.8 (d), 135.5 (d), 135.9 (d), 136.0 (d), 138.8 (s), 140.6 (d), 144.2 (s) ppm

**Elemental analysis Cald.** : C, 82.37; H, 7.19%

**Found** : C, 82.59; H, 7.40%

**ESI-MS ( $m/z$ )** : 751 [M+Na]<sup>+</sup>

**(4*R*,6*S*,*E*)-4-(Benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)octa-2,7-dien-1-ol (30)**

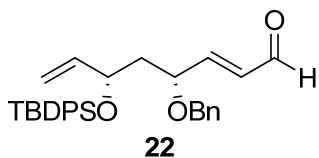


**30**

Compound **29** (4.3 g, 0.006 mol) was dissolved in 50 mL of dry DCM and the reaction mixture was cooled to 0 °C and at that temperature neat TFA (0.53 mL, 0.007 mol) was added dropwise to it. Temperature was maintained 0 °C for 0.5 h, then the reaction mixture was concentrated and the crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:4) to obtained yellowish oil **30**.

<b>Yield</b>	: 1.81 g, 63%
<b>Mol Formula</b>	: C <sub>31</sub> H <sub>38</sub> O <sub>3</sub> Si
<b>Mol Weight</b>	: 486
<b>Optical rotation</b> $[\alpha]_D^{25}$	: +34.9 ( <i>c</i> , 0.7, CHCl <sub>3</sub> )
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: $\delta$ 1.03 (s, 9H), 1.59 (ddd, <i>J</i> = 5.1, 7.3, 13.6 Hz, 1H), 2.01 (ddd, <i>J</i> = 5.4, 8.2, 13.6 Hz, 1H), 3.81 (ddd, <i>J</i> = 5.1, 7.5, 12.4 Hz, 1H), 4.07 (dd, <i>J</i> = 1.1, 5.4 Hz, 2H), 4.2, 4.43 (2d, <i>J</i> = 11.9 Hz, 2H), 4.30 (dd, <i>J</i> = 5.4, 10.9 Hz, 1H), 4.77 (ddd, <i>J</i> = 1.0, 1.6, 17.1 Hz, 1H), 4.88 (ddd, <i>J</i> = 1.0, 1.6, 10.4 Hz, 1H), 5.41-5.86 (m, 3H), 7.13-7.41 (m, 11H), 7.60-7.68 (m, 4H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 19.4 (s), 27.1 (q), 44.0 (t), 62.9 (t), 69.9 (t), 72.3 (d), 76.0 (d), 114.9 (t), 127.3 (d), 127.4 (d), 127.5 (d), 127.6 (d), 128.2 (d), 129.5 (d), 129.6 (d), 131.7 (d), 131.8 (d), 134.2 (s), 135.97 (d), 136.04 (d), 138.7 (s), 140.6 (d) ppm
<b>Elemental analysis Cald.</b>	: C, 76.50; H, 7.87%
<b>Found</b>	: C, 76.32; H, 8.11%
<b>ESI-MS (<i>m/z</i>)</b>	: 509 [M+Na] <sup>+</sup>

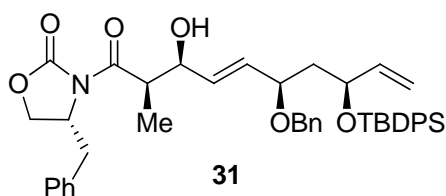
**(4*R*,6*S*,*E*)-4-(Benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)octa-2,7-dienal (22)**



A mixture of alcohol **30** (1.7 g, 0.003 mol) and 4 Å molecular sieves (1.7 g) was taken in 40 mL of dry DCM and the mixture was cooled to 0 °C. At that temperature PDC (6.57 g, 0.015 mol) and catalytic amount of acetic anhydride were added to the reaction suspension. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 3.5 h, then concentrated. The solid residue was scratched thoroughly and filtered over *Celite* pad and washed with ethyl acetate for several times. Combined organic layer was concentrated under vacuum and the crude aldehyde was immediately subjected to the next reaction.

<b>Yield</b>	: 1 g, 60%
<b>Mol Formula</b>	: C <sub>31</sub> H <sub>36</sub> O <sub>3</sub> Si
<b>Mol Weight</b>	: 484
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.05 (s, 9H), 1.64 (ddd, <i>J</i> = 5.1, 7.2, 12.4 Hz, 1H), 1.98 (ddd, <i>J</i> = 4.9, 7.8, 13.1 Hz, 1H), 4.03-4.12 (m, 1H), 4.24, 4.42 (2d, <i>J</i> = 11.6 Hz, 2H), 4.31 (dd, <i>J</i> = 6.9, 12.4 Hz, 1H), 4.84 (dt, <i>J</i> = 1.4, 17.1 Hz, 1H), 4.94 (dt, <i>J</i> = 1.4, 10.3 Hz, 1H), 5.76 (ddd, <i>J</i> = 6.7, 10.3, 17.1 Hz, 1H), 6.11 (ddd, <i>J</i> = 1.0, 7.7, 15.8 Hz, 1H), 6.51 (dd, <i>J</i> = 5.8, 15.8 Hz, 1H), 7.12-7.42 (m, 11H), 7.59-7.67 (m, 4H), 9.45 (d, <i>J</i> = 7.8 Hz, 1H)

**(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*,8*S*,*E*)-6-(benzyloxy)-8-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-2-methyldeca-4,9-dienoyl)oxazolidin-2-one (**31**)**



Compound **8** (0.48 g, 0.002 mol) was taken in dry DCM (12 mL) and at 0 °C freshly distilled TiCl<sub>4</sub> (0.24 mL, 0.002 mol) was added and stirred for 15 mins. The reaction mixture became turbid yellow. To this solution dry DIPEA (0.9 mL, 0.005 mol) was added and the reaction mixture became blood red. Temperature was maintained 0 °C and stirred it again for 15 mins. Then the reaction mixture was cooled to – 78 °C and aldehyde **22** (1 g, 0.002 mol) solution in dry DCM (2 mL) was added to the reaction mixture and stirred for 0.5 h. Reaction mixture was quenched with saturated solution of NH<sub>4</sub>Cl and aqueous layer was washed with DCM and combined organic layer was dried over sodium sulphate and concentrated. The crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:6) to obtain white sticky gel **31**.

<b>Yield</b>	: 931 mg, 63%
<b>Mol Formula</b>	: C <sub>44</sub> H <sub>51</sub> NO <sub>6</sub> Si
<b>Mol Weight</b>	: 717
<b>Optical rotation</b> [α] <sub>D</sub> <sup>25</sup>	: +10.6 ( <i>c</i> 2.8, CHCl <sub>3</sub> )
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 1.03 (s, 9H), 1.21 (d, <i>J</i> = 7.1 Hz, 3H), 1.61 (ddd, <i>J</i> = 4.3, 7.9, 13.5 Hz, 1H), 2.00 (ddd, <i>J</i> = 5.2, 8.7, 13.5 Hz, 1H), 2.77 (dd, <i>J</i> = 9.4, 13.5 Hz, 2H), 3.25 (dd, <i>J</i> = 3.3, 13.5 Hz, 1H), 3.75-3.89 (m, 2H), 4.17, 4.44 (2d, <i>J</i> = 11.7 Hz, 2H), 4.14-4.19 (m, 1H), 4.26-4.34 (m, 1H), 4.37-4.45 (m, 1H), 4.59-4.68 (m, 1H), 4.75 (ddd, <i>J</i> = 1.3, 2.7, 17.0 Hz, 1H), 4.87 (ddd, <i>J</i> = 1.3, 2.7, 10.5 Hz, 1H), 5.43-5.84 (m, 3H), 7.13-7.40 (m, 16H), 7.61-7.68 (m, 4H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: 11.1 (q), 19.3 (s), 27.1 (q), 37.8 (t), 44.2 (t), 55.2 (d), 55.6 (d), 66.2 (t), 69.9 (t), 72.1 (d), 72.4 (d), 76.0 (d),

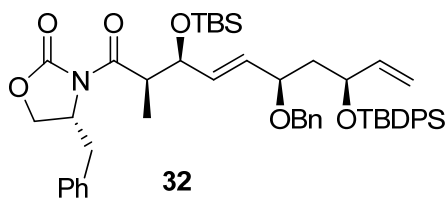
115.0 (t), 127.4 (d), 127.49 (d), 127.54 (d), 128.2 (d),  
 129.0 (d), 129.41 (s), 129.44 (s), 129.5 (s), 132.5 (d),  
 135.2 (s), 135.9 (d), 136.0 (d), 140.5 (d), 153.5 (s),  
 176.1 (s) ppm

**Elemental analysis Calcd.** : C, 76.61 H, 7.16%

**Found** : C, 76.42 H, 7.41%

**ESI-MS (*m/z*)** : 740 [M+Na]<sup>+</sup>

**(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*,8*S*,*E*)-6-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxy)-2-methyldeca-4,9-dienoyl)oxazolidin-2-one (**32**)**



Compound **31** (900 mg, 1.26 mmol) was taken in dry DCM (25 mL) and dry 2,6-lutidine (0.22 mL, 1.89 mmol) was added to it followed by freshly prepared TBDMS-OTf (0.35 mL, 1.51 mmol) and the reaction mixture was stirred for 0.5 h. Then the reaction mixture was concentrated and crude product was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:9) to procure colorless oil **32**.

**Yield** : 836 mg, 80%

**Mol Formula** : C<sub>43</sub>H<sub>56</sub>NO<sub>6</sub>Si<sub>2</sub>

**Mol Weight** : 947

**Optical rotation** [ $\alpha$ ]<sub>D</sub><sup>25</sup> : +19.8 (*c* 1.3, CHCl<sub>3</sub>)

**<sup>1</sup>H** :  $\delta$  -0.03 (s, 3H), 0.01 (s, 3H), 0.88 (s, 9H), 1.02 (s, 9H),  
 (CDCl<sub>3</sub>, 200 MHz) 1.19 (d, *J* = 6.8 Hz, 3H), 1.51 (ddd, *J* = 4.1, 8.5, 13.8

Hz, 1H), 2.0 (ddd,  $J = 5.2, 9.0, 13.8$  Hz, 1H), 2.76 (dd,  $J = 9.5, 13.3$  Hz, 1H), 3.27 (dd,  $J = 3.0, 13.3$  Hz, 1H), 3.71-3.81 (m, 1H), 3.96-4.10 (m, 3H), 4.14, 4.44 (2d,  $J = 11.8$  Hz, 2H), 4.25-4.34 (m, 2H), 4.48-4.58 (m, 1H), 4.73 (ddd,  $J = 0.9, 1.9, 17.3$  Hz, 1H), 4.86 (ddd,  $J = 0.9, 1.9, 10.3$  Hz, 1H), 5.47 (dd,  $J = 6.8, 15.7$  Hz, 1H), 5.60 (dd,  $J = 5.3, 15.7$  Hz, 1H), 5.74 (ddd,  $J = 7.3, 10.3, 17.3$  Hz, 1H), 7.11-7.40 (m, 16H), 7.60-7.67 (m, 4H)

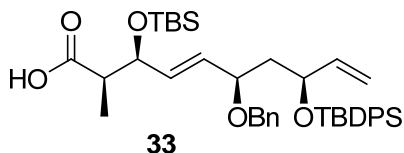
$^{13}\text{C}$  : -4.0 (q), -3.5 (q), 13.0 (q), 18.2 (s), 19.3 (s), 25.9 (q), (CDCl<sub>3</sub>, 50 MHz) 27.1 (q), 38.5 (t), 44.5 (t), 55.03 (d), 55.7 (d), 65.9 (t), 72.2 (d), 72.5 (d), 74.2 (d), 75.9 (d), 115.1 (t), 127.2 (d), 127.3 (d), 127.47 (d), 127.52 (d), 127.6 (d), 128.16 (d), 128.22 (d), 128.95 (d), 129.01 (d), 129.3 (s), 129.4 (s), 129.5 (s), 135.9 (d), 136.0 (d), 140.5 (d), 153.0 (s), 174.8 (s) ppm

**Elemental analysis Cald.** : C, 69.22; H, 8.51%

**Found** : C, 68.97; H, 8.42%

**ESI-MS ( $m/z$ )** : 970 [M+Na]<sup>+</sup>

**(2*R*,3*S*,6*R*,8*S*,*E*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxy)-2-methyldeca-4,9-dienoic acid (33)**





Compound **32** (800 mg, 0.96 mmol) was taken in 12 mL THF-H<sub>2</sub>O (4:1) mixture at 0 °C and LiOH.H<sub>2</sub>O (65 mg, 1.54 mmol) was added to it followed by 30% H<sub>2</sub>O<sub>2</sub> solution (2.1 mL). Then the reaction mixture was stirred for 4 h and bulk of THF was removed under vacuum and resulting mixture was extracted with DCM. DCM layer was washed with 3 (N) HCl (3 x 15 mL) and organic layer was dried over sodium sulfate and concentrated. Crude residue was purified by column chromatography using 25% ethyl acetate in light petroleum to get colorless oil **33**.

<b>Yield</b>	: 356 mg, 55%
<b>Mol Formula</b>	: C <sub>40</sub> H <sub>56</sub> O <sub>5</sub> Si <sub>2</sub>
<b>Mol Weight</b>	: 672
<b>Optical rotation</b> $[\alpha]_D^{25}$	: +33.2 ( <i>c</i> 1.1, CHCl <sub>3</sub> )
<b>IR</b> $\nu_{\sim}$	: 1253, 1362, 1427, 1462, 1495, 1709, 2856, 2927, 3072 cm <sup>-1</sup>
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: $\delta$ 0.01 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.03 (s, 9H), 1.10 (d, <i>J</i> = 7.0 Hz, 3H), 1.51 (ddd, <i>J</i> = 2.7, 7.4, 13.8 Hz, 1H), 1.99 (ddd, <i>J</i> = 5.4, 8.5, 13.8 Hz, 1H), 2.55 (dd, <i>J</i> = 4.8, 7.1 Hz, 1H), 3.72-3.81 (m, 1H), 4.13, 4.41 (2d, <i>J</i> = 11.9 Hz, 2H), 4.22-4.35 (m, 2H), 4.73 (ddd, <i>J</i> = 0.9, 1.8, 17.1 Hz, 1H), 4.85 (ddd, <i>J</i> = 0.9, 1.8, 10.4 Hz, 1H), 5.44-5.48 (m, 2H), 5.75 (ddd, <i>J</i> = 7.2, 10.4, 17.1 Hz, 1H), 7.10-7.41 (m, 11H), 7.60-7.67 (m, 4H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	: -5.2 (q), -4.2 (q), 11.2 (q), 18.1 (s), 19.3 (s), 25.7 (q), 27.0 (q), 44.2 (t), 46.2 (d), 69.9 (t), 72.3 (d), 73.7 (d), 75.7 (d), 114.9 (t), 127.3 (d), 127.5 (d), 127.6 (d), 128.2

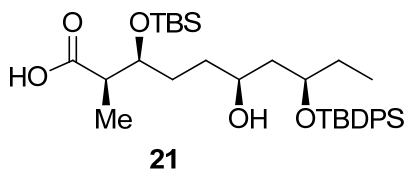
(d), 129.4 (d), 129.5 (d), 132.4 (d), 132.7 (d), 134.1 (s),  
135.9 (d), 136.0 (d), 138.4 (s), 140.5 (d), 178.4 (s) ppm

**Elemental analysis Cald.** : C, 71.38; H, 8.39%

**Found** : C, 71.51; H, 8.40%

**ESI-MS (*m/z*)** : 695 [M+Na]<sup>+</sup>

**(2*R*,3*S*,6*S*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxy)-6-hydroxy-2-methyldecanoic acid (21)**



Acid compound **33** (300 mg, 0.44 mmol) was dissolved in 30 mL of HPLC grade ethyl acetate and Pd(OH)<sub>2</sub> (60 mg) was added to it. Hydrogen balloon pressure was applied on reaction mixture for 6 h. Then the mixture was filtered on *Celite* pad and washed thoroughly with ethyl acetate and filtrate was concentrated and purified on column chromatography using 30% ethyl acetate in light petroleum to get colorless oil **21**.

**Yield** : 162 mg, 62%

**Mol Formula** : C<sub>33</sub>H<sub>54</sub>O<sub>5</sub>Si<sub>2</sub>

**Mol Weight** : 586

**Optical rotation** [α]<sub>D</sub><sup>25</sup> : -5.9 (*c* 0.8, CHCl<sub>3</sub>)

**<sup>1</sup>H** : δ 0.07 (s, 6H), 0.65 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H),  
(CDCl<sub>3</sub>, 200 MHz) 1.04 (s, 9H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.33-1.40 (m,  
4H), 1.52-1.59 (m, 4H), 2.58 (dd, *J* = 4.7, 7.1 Hz, 1H),  
3.67-3.78 (m, 1H), 3.83-3.99 (m, 2H), 7.36-7.43 (m,

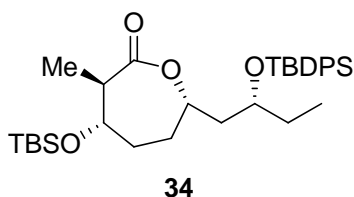
6H), 7.66-7.73 (m, 4H)  
 $^{13}\text{C}$  : -4.7 (q), -4.3 (q), 9.2 (q), 11.4 (q), 18.0 (s), 19.3 (s),  
 (CDCl<sub>3</sub>, 50 MHz) 25.8 (q), 27.0 (q), 44.4 (t), 70.5 (d), 73.8 (d), 75.3 (d),  
 127.5 (d), 127.7 (d), 129.7 (d), 129.9 (s), 135.9 (d),  
 178.4 (s) ppm

**Elemental analysis Cald.** : C, 67.53; H, 9.27%

**Found** : C, 67.62; H, 9.48%

**ESI-MS (*m/z*)** : 609 [M+Na]<sup>+</sup>

**(3*R*,4*S*,7*S*)-4-(*tert*-Butyldimethylsilyloxy)-7-((*R*)-2-(*tert*-butyldiphenylsilyloxy)butyl)-3-methyloxepan-2-one (34)**



Seco acid compound **21** (150 mg, 0.26 mmol) was taken in dry DCM (100 mL). EDCI (75 mg, 0.39 mmol), HOBt (53 mg, 0.39 mmol) and DMAP (48 mg, 0.39 mmol) were added to it at 0 °C and the reaction mixture was warmed to room temperature and stirred for 12 h. Then the solution was washed with water and organic layer was dried over sodium sulfate and concentrated. Crude residue was purified by column chromatography using ethyl acetate in light petroleum (1:4) to obtain colorless oil **34**.

**Yield** : 97 mg, 67%

**Mol Formula** : C<sub>33</sub>H<sub>52</sub>O<sub>4</sub>Si<sub>2</sub>

**Mol Weight** : 568

**Optical rotation** [ $\alpha$ ]<sub>D</sub><sup>25</sup> : +33.2 (*c* 1.8, CHCl<sub>3</sub>)

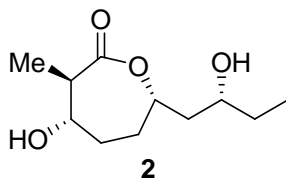
$^1\text{H}$	:	$\delta$ 0.00 (s, 3H), 0.04 (s, 3H), 0.80 (t, $J = 7.3$ Hz, 3H),
( $\text{CDCl}_3$ , 200 MHz)		0.85 (s, 9H), 1.04 (s, 9H), 1.10 (d, $J = 7.8$ Hz, 3H), 1.28-1.38 (m, 2H), 1.51-1.63 (m, 6H), 3.04 (dq, $J = 5.7, 7.8$ Hz, 1H), 3.65-3.81 (m, 2H), 4.45-4.56 (m, 1H), 7.31-7.42 (m, 6H), 7.62-7.69 (m, 4H)
$^{13}\text{C}$	:	-5.0 (q), -4.9 (q), 9.2 (q), 12.8 (q), 18.0 (s), 19.5 (s),
( $\text{CDCl}_3$ , 50 MHz)		25.7 (q), 27.1 (q), 28.0 (t), 30.0 (t), 30.4 (t), 42.4 (t), 50.2 (d), 70.1 (d), 71.6 (d), 76.0 (d), 127.6 (d), 127.7 (d), 129.7 (d), 134.1 (s), 134.1 (s), 135.8 (d), 135.9 (d), 174.2 (s) ppm

**Elemental analysis Cald.** : C, 69.67; H, 9.21%

**Found** : C, 69.82; H, 8.96%

**ESI-MS ( $m/z$ )** : 591  $[\text{M}+\text{Na}]^+$

**(3*R*,4*S*,7*S*)-4-Hydroxy-7-((*R*)-2-hydroxybutyl)-3-methyloxepan-2-one (2)**



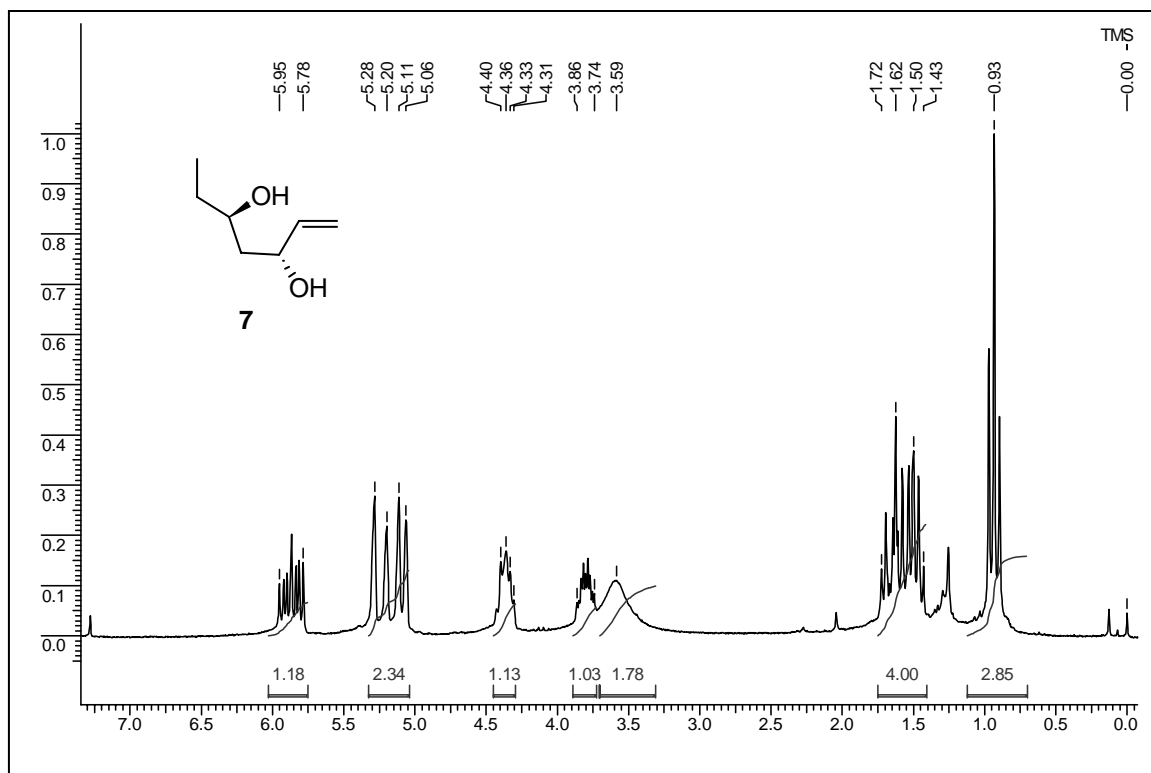
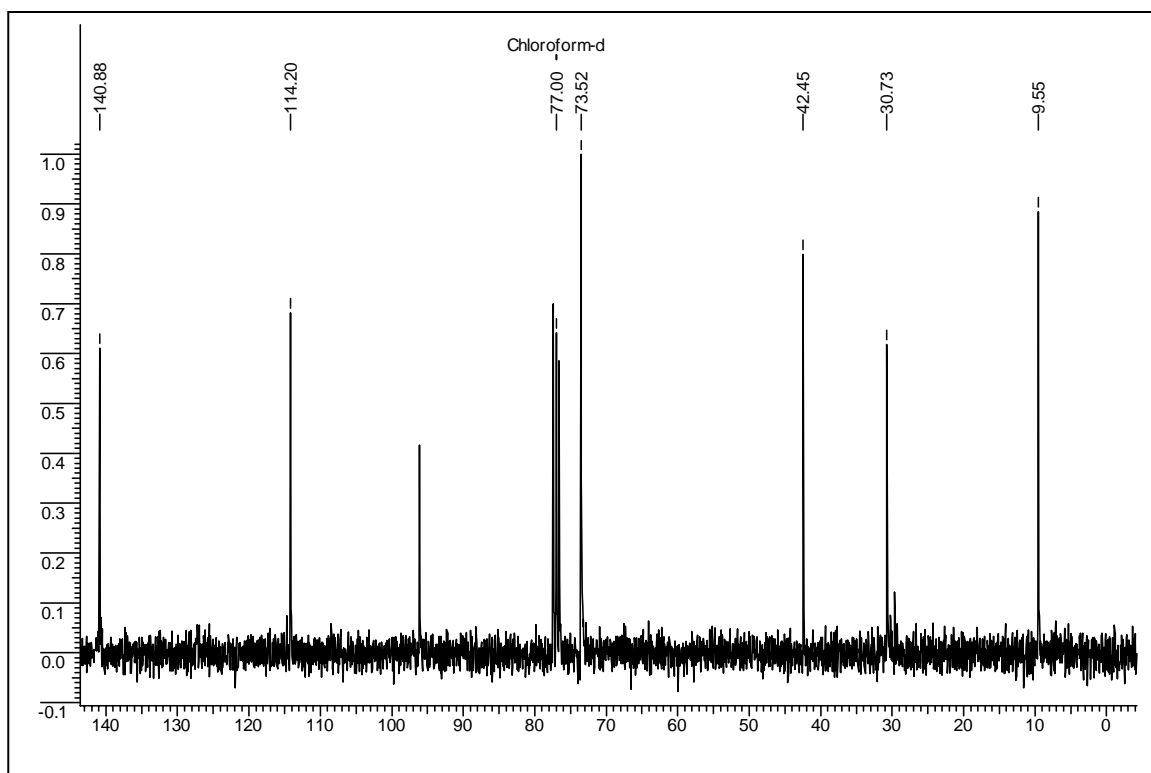
7-membered lactone compound **34** (90 mg, 0.16 mmol) was taken in THF (2 mL) and HF-pyridine solution in pyridine (0.5 mL) was added and every 6 h reaction was monitored by TLC and 0.5 mL of HF-pyridine solution in pyridine was added to it until the reaction was complete. After 48 h the reaction mixture was quenched with water and THF was evaporated under vacuum and the rest was diluted with ethyl acetate and the organic layer was thoroughly washed with water. Then the organic layer was dried over sodium sulfate and concentrated under reduced pressure and crude residue was purified

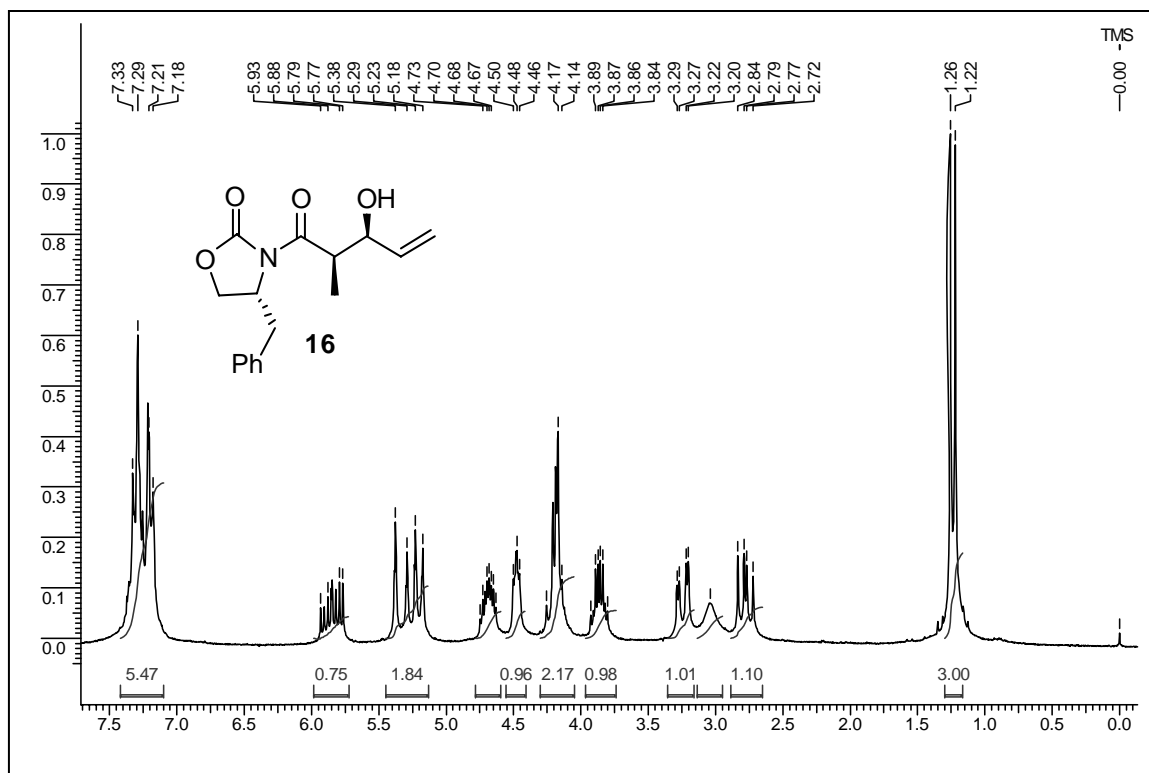
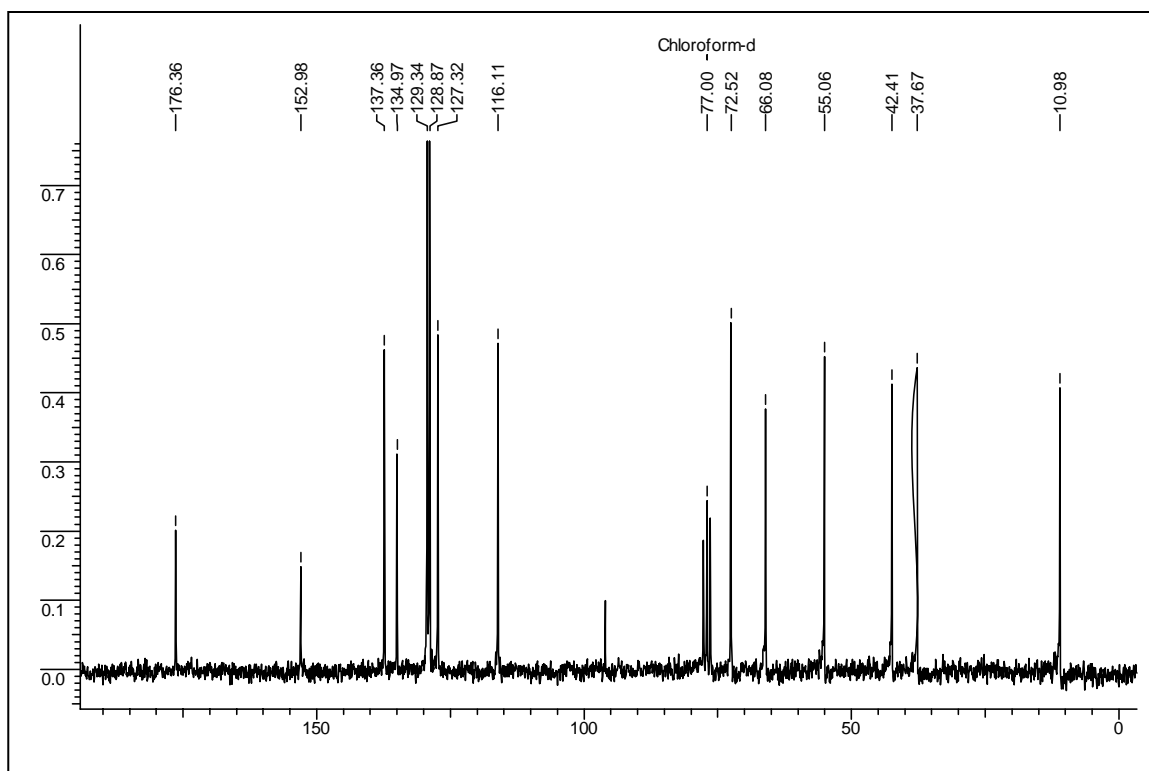
by flash column chromatography using 80% ethyl acetate in light petroleum to obtain colorless liquid **2**.

<b>Yield</b>	: 15 mg, 45%
<b>Mol Formula</b>	: C <sub>11</sub> H <sub>20</sub> O <sub>4</sub>
<b>Mol Weight</b>	: 216
<b>Optical rotation</b> $[\alpha]_D^{25}$	: -6.9 ( <i>c</i> 0.7, CHCl <sub>3</sub> )
<b>IR</b> $\nu_{\sim}$	: 1216, 1384, 1459, 1725, 2401, 2856, 2928, 3020, 3412 cm <sup>-1</sup>
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 500 MHz)	: $\delta$ 0.96 (t, <i>J</i> = 7.3 Hz, 3H), 1.29 (d, <i>J</i> = 6.7 Hz, 3H), 1.45- 2.08 (m, 8H), 2.92 (dq, <i>J</i> = 6.7, 8.2 Hz, 1H), 3.59-3.76 (m, 2H), 4.63-4.74 (m, 1H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 125 MHz)	: 9.7 (q), 14.2 (q), 29.7 (t), 30.0 (t), 34.9 (t), 42.9 (t), 44.9 (d), 70.8 (d), 70.9 (d), 77.0 (d), 174.6 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 61.09; H, 9.32%
<b>Found</b>	: C, 60.82; H, 9.17%
<b>ESI-MS</b> ( <i>m/z</i> )	: 239 [M+Na] <sup>+</sup>

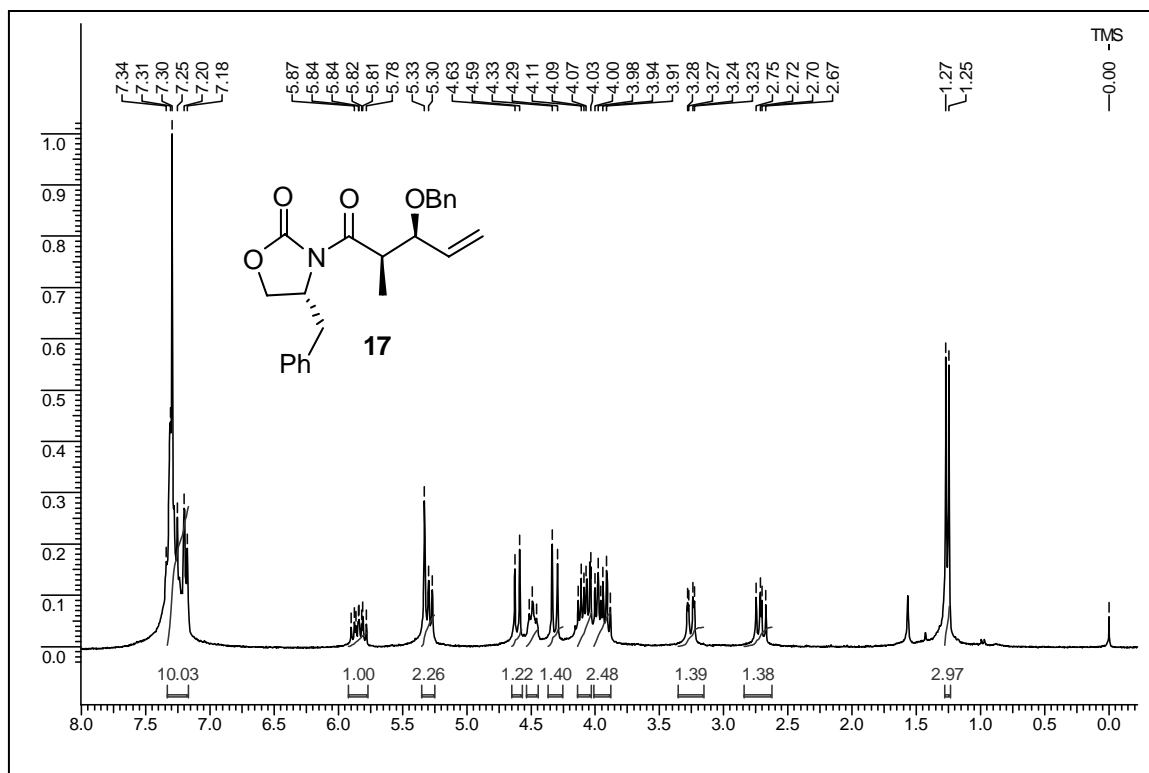
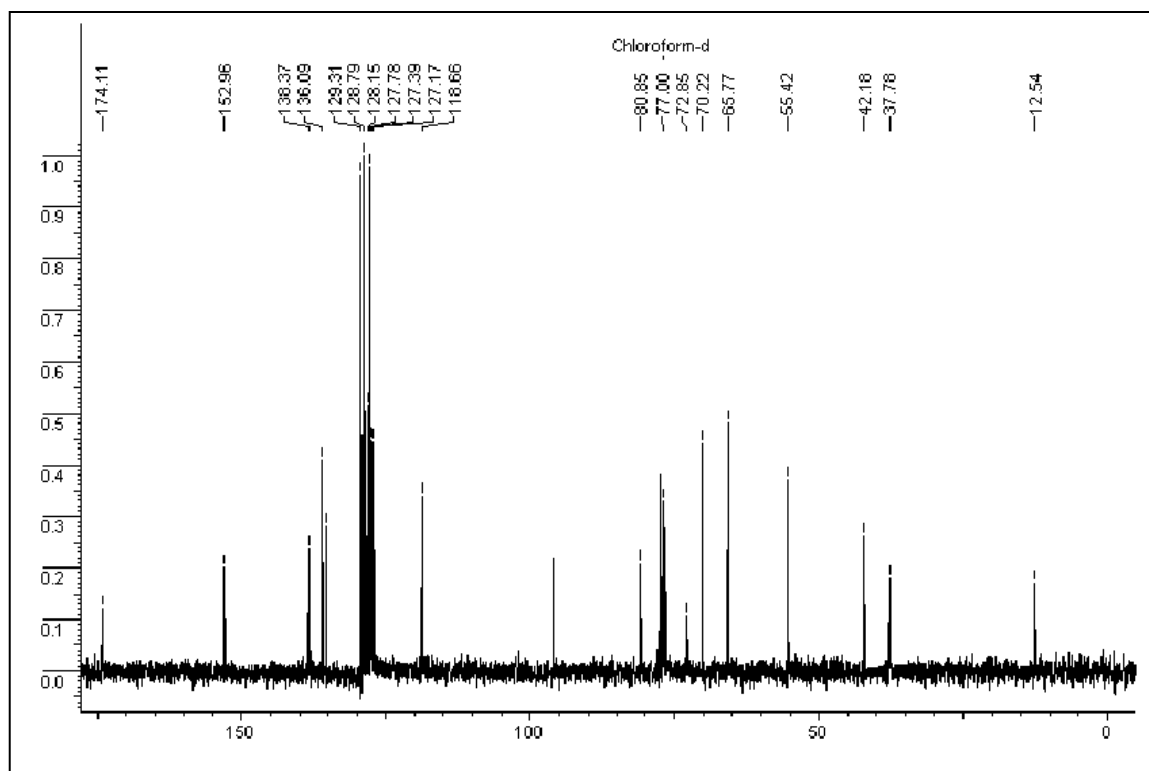
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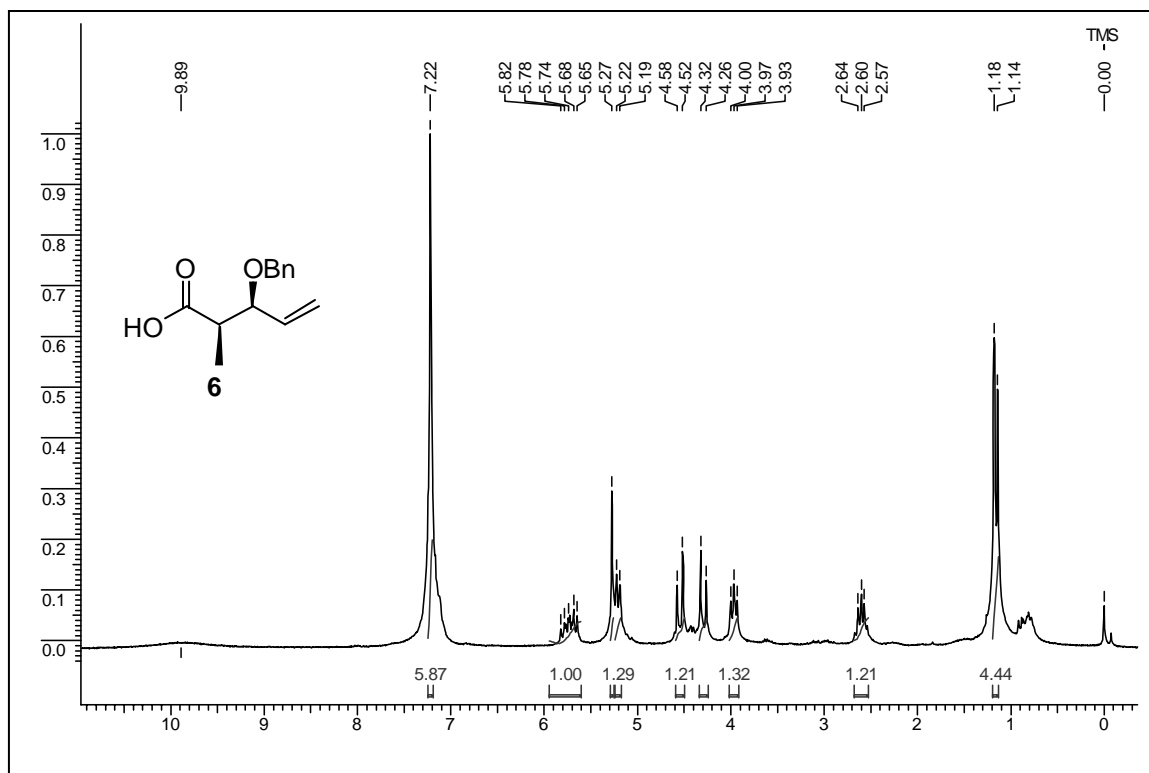
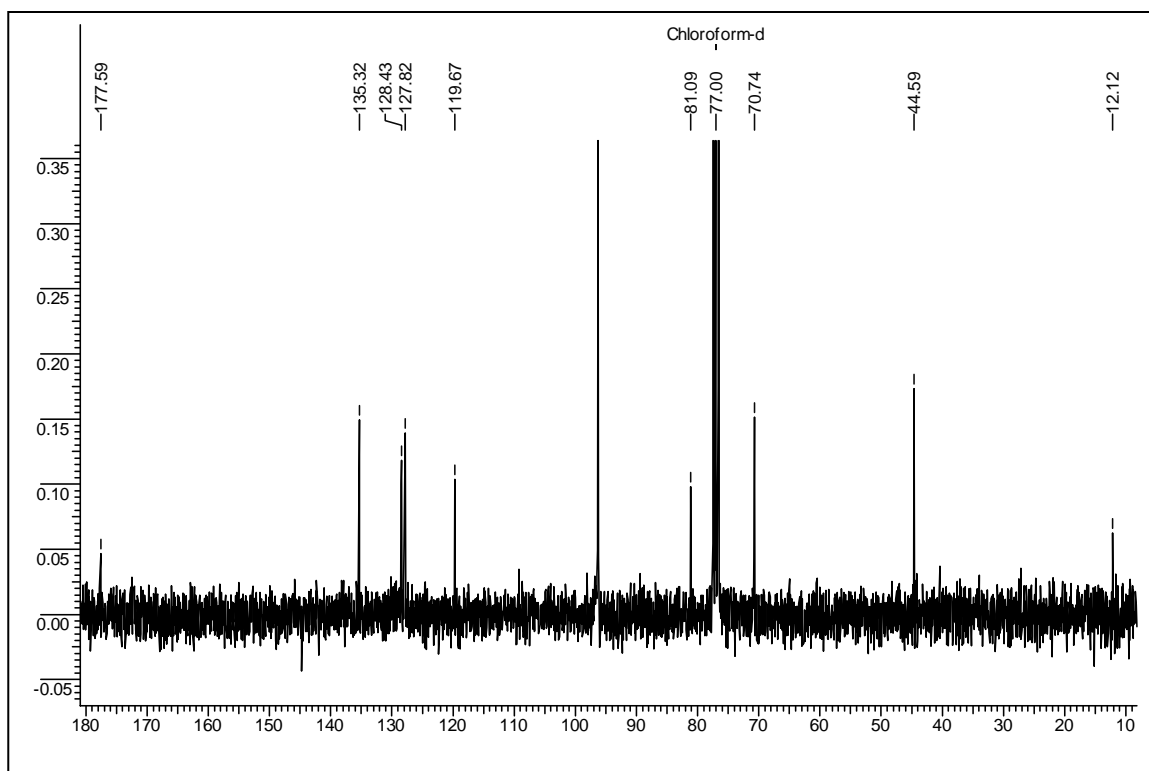
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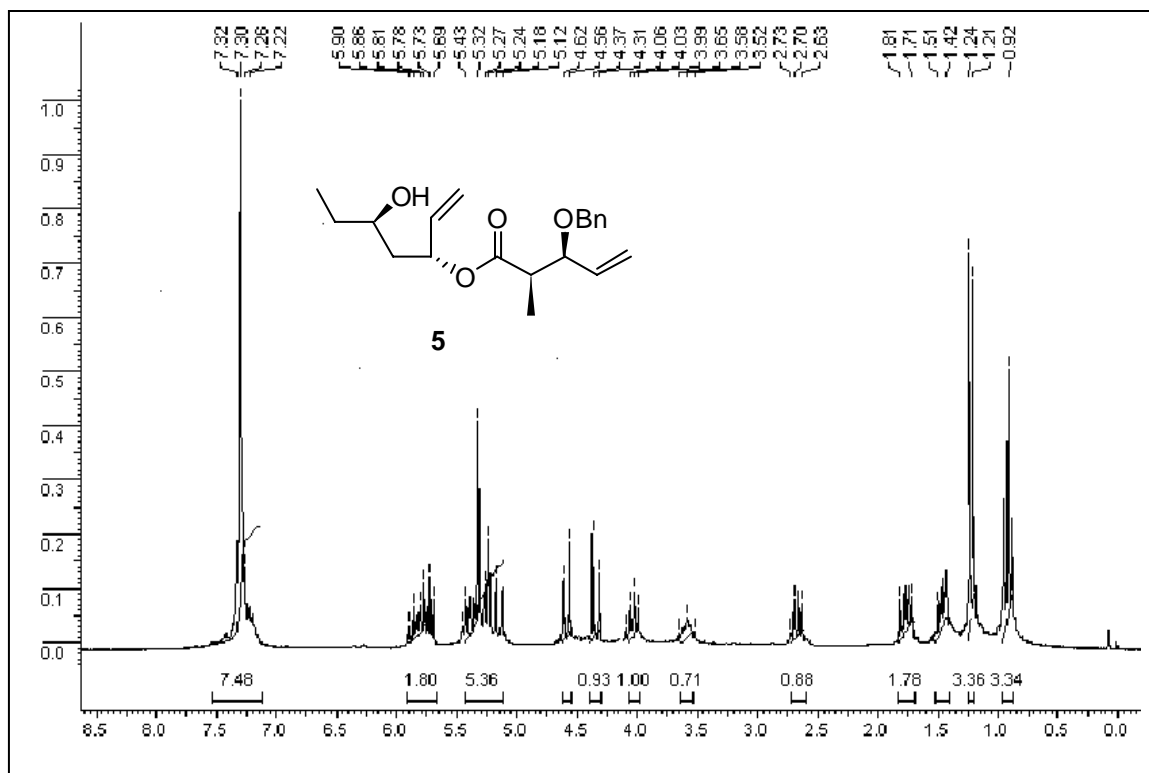
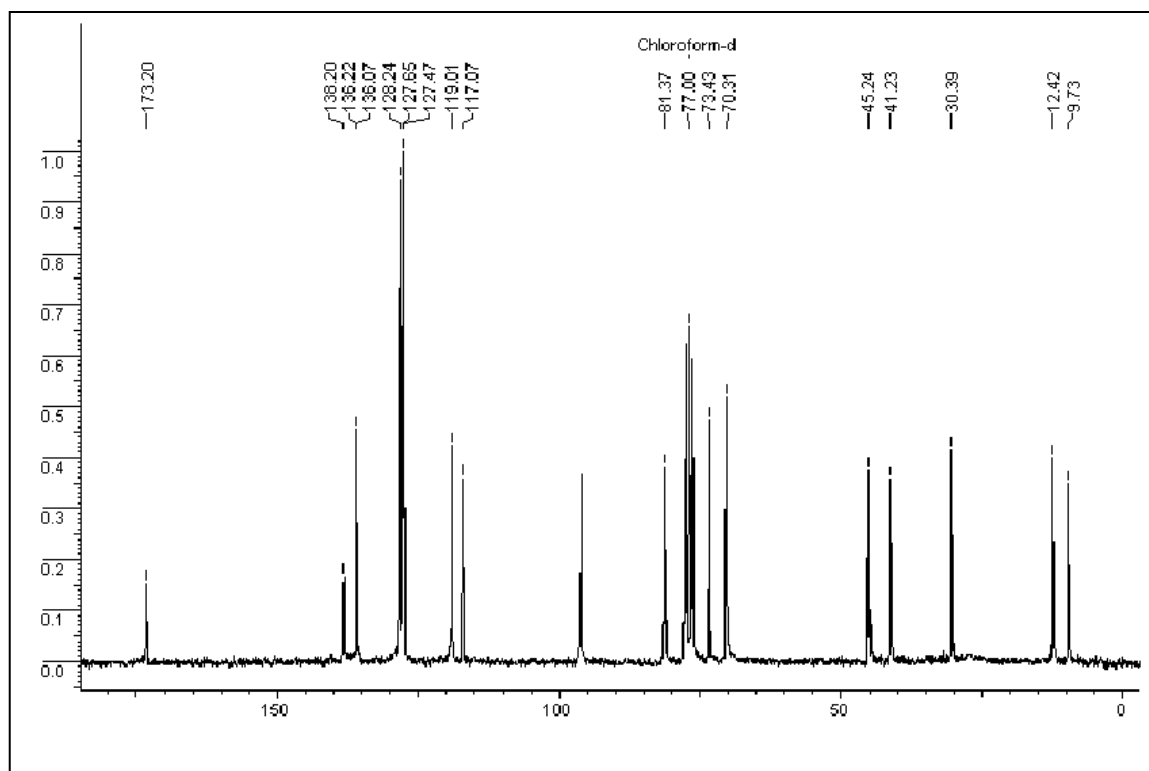
**$^1\text{H}$  NMR spectra of compound 7** **$^{13}\text{C}$  NMR spectra of compound 7**

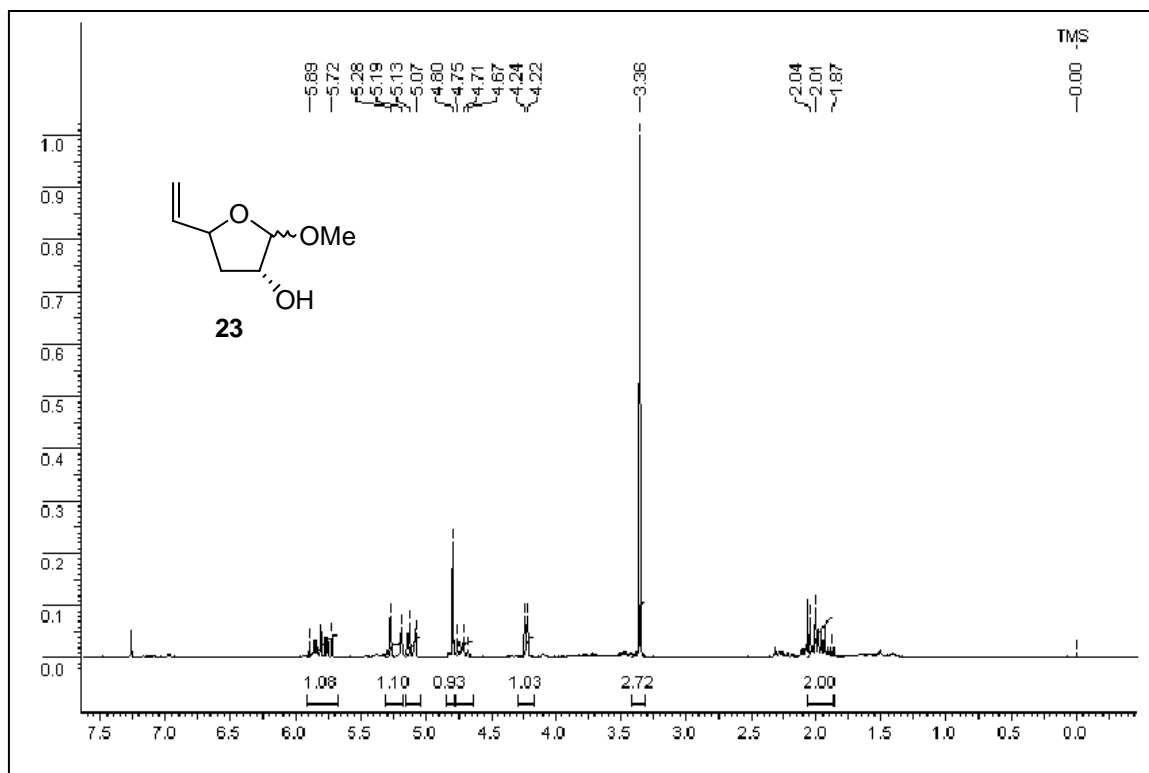
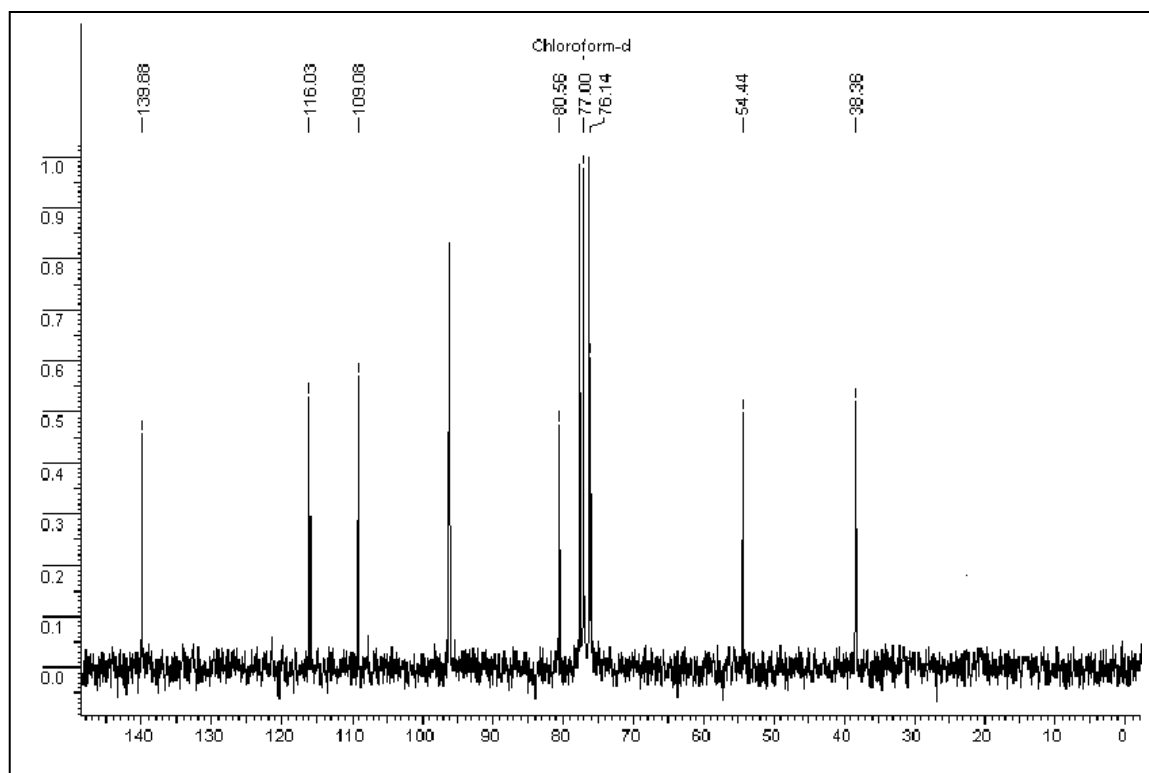
**$^1\text{H}$  NMR spectra of compound 16** **$^{13}\text{C}$  NMR spectra of compound 16**

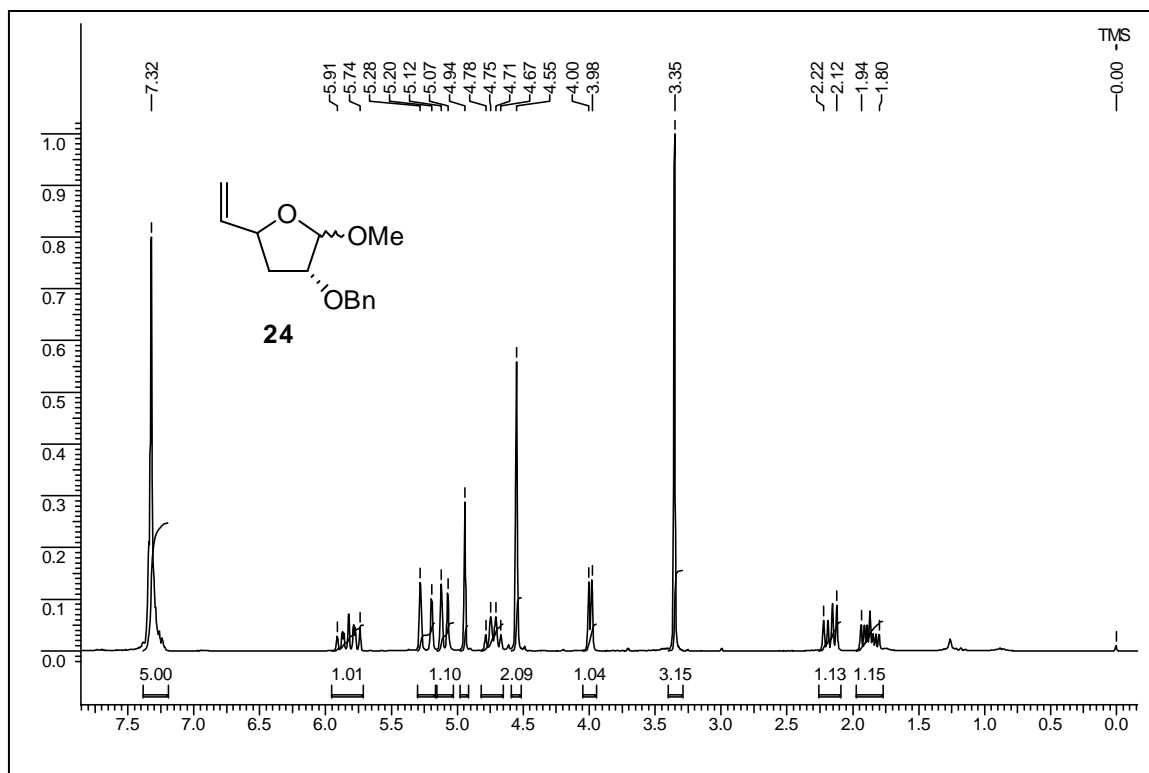
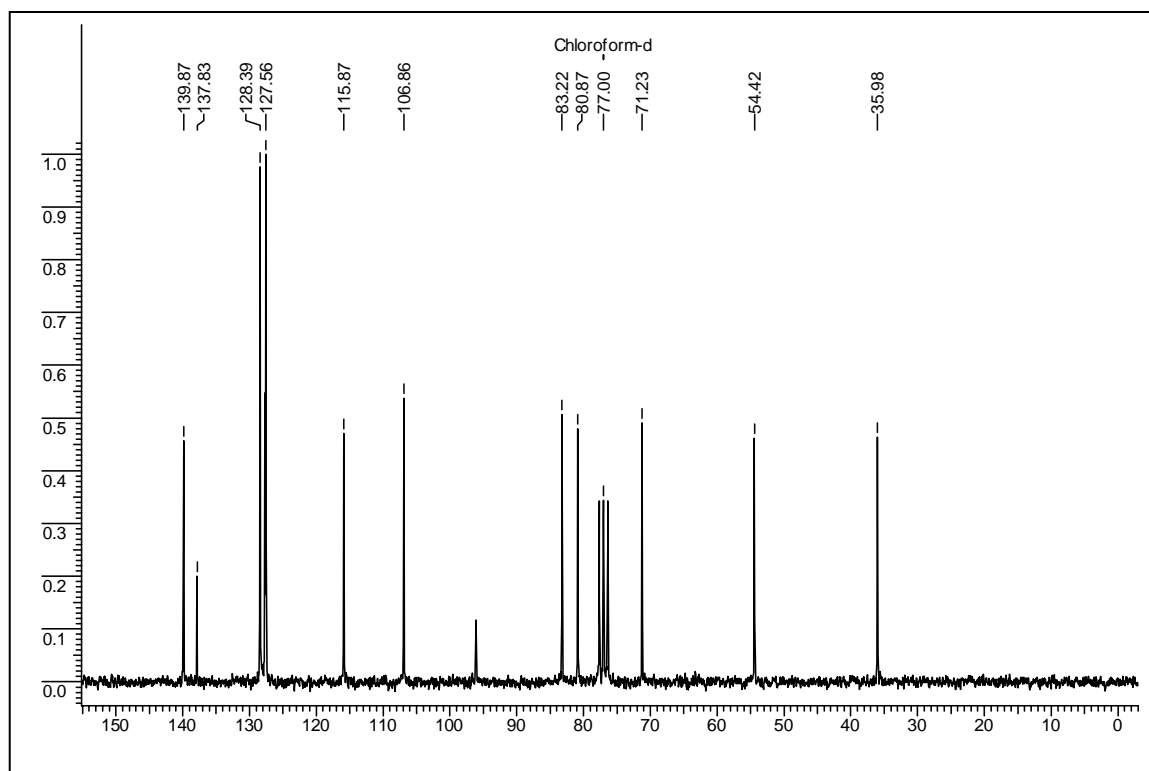


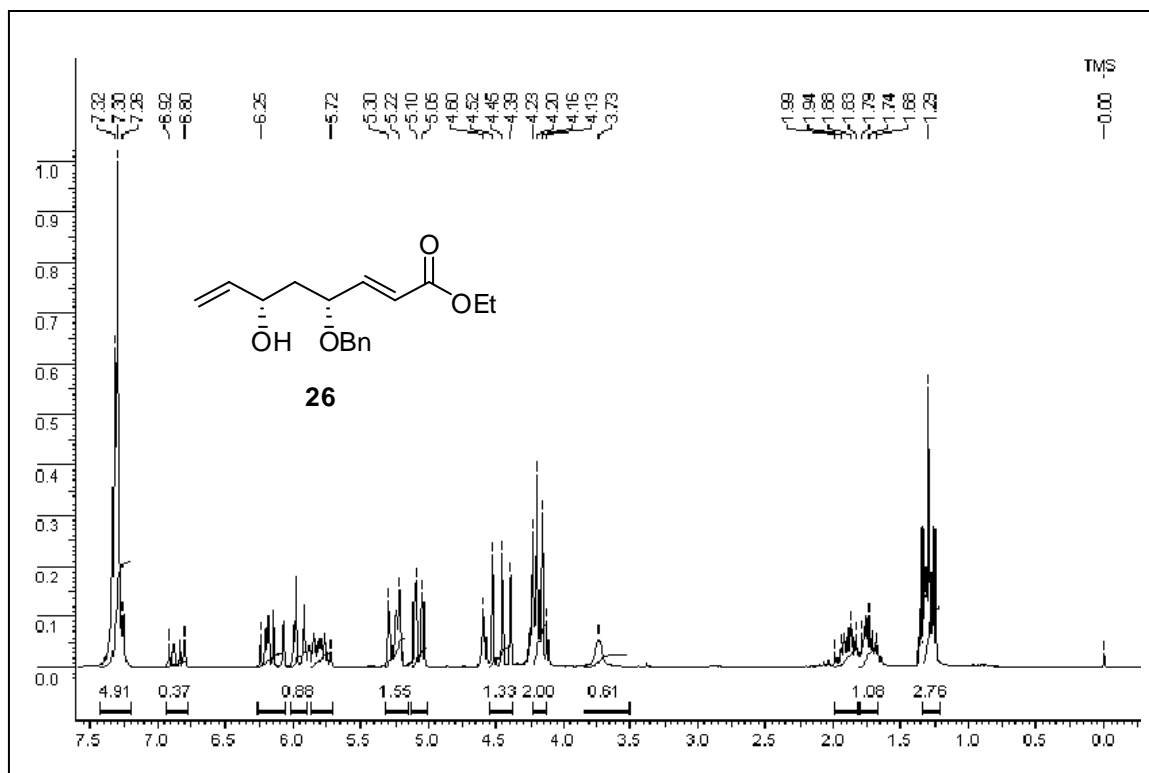
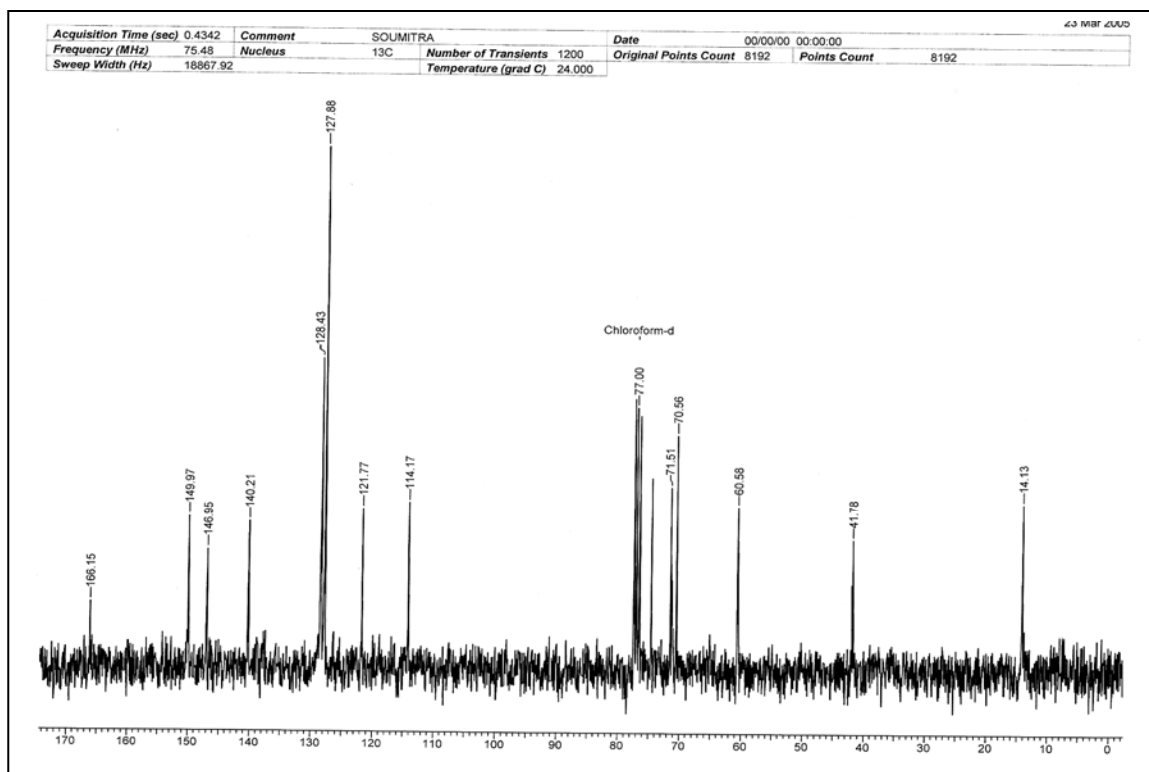
**$^1\text{H}$  NMR spectra of compound 17** **$^{13}\text{C}$  NMR spectra of compound 17**

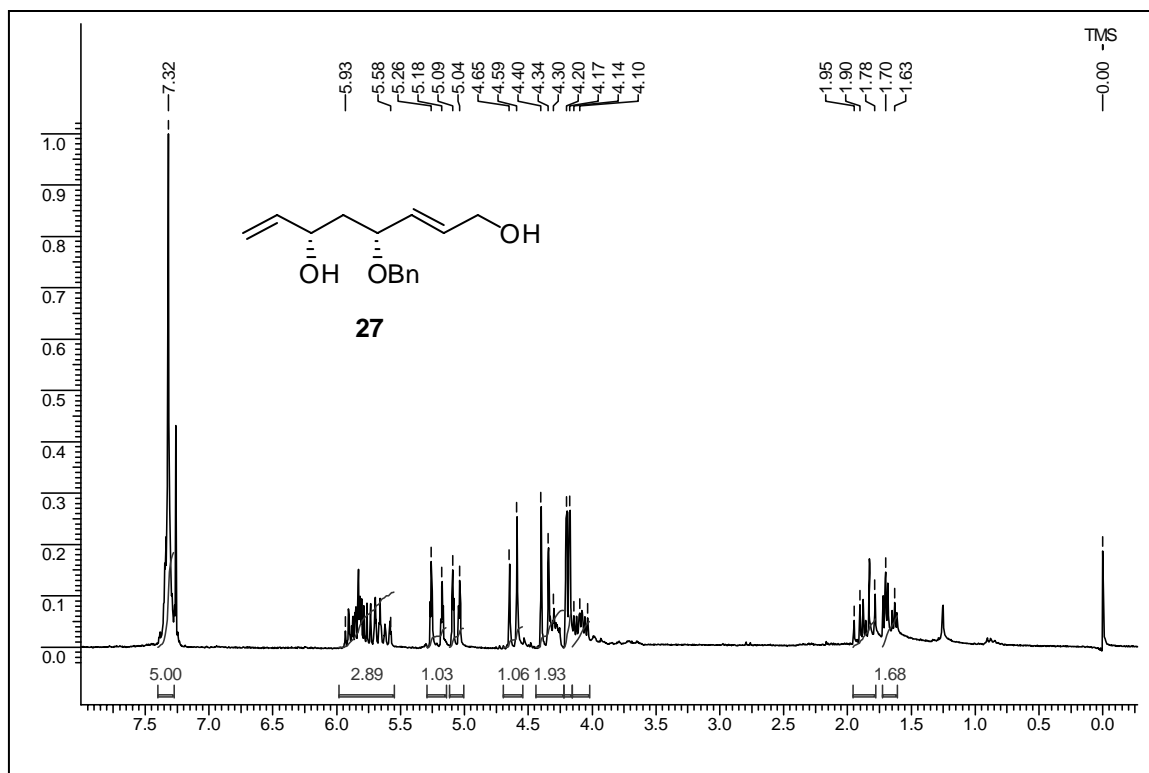
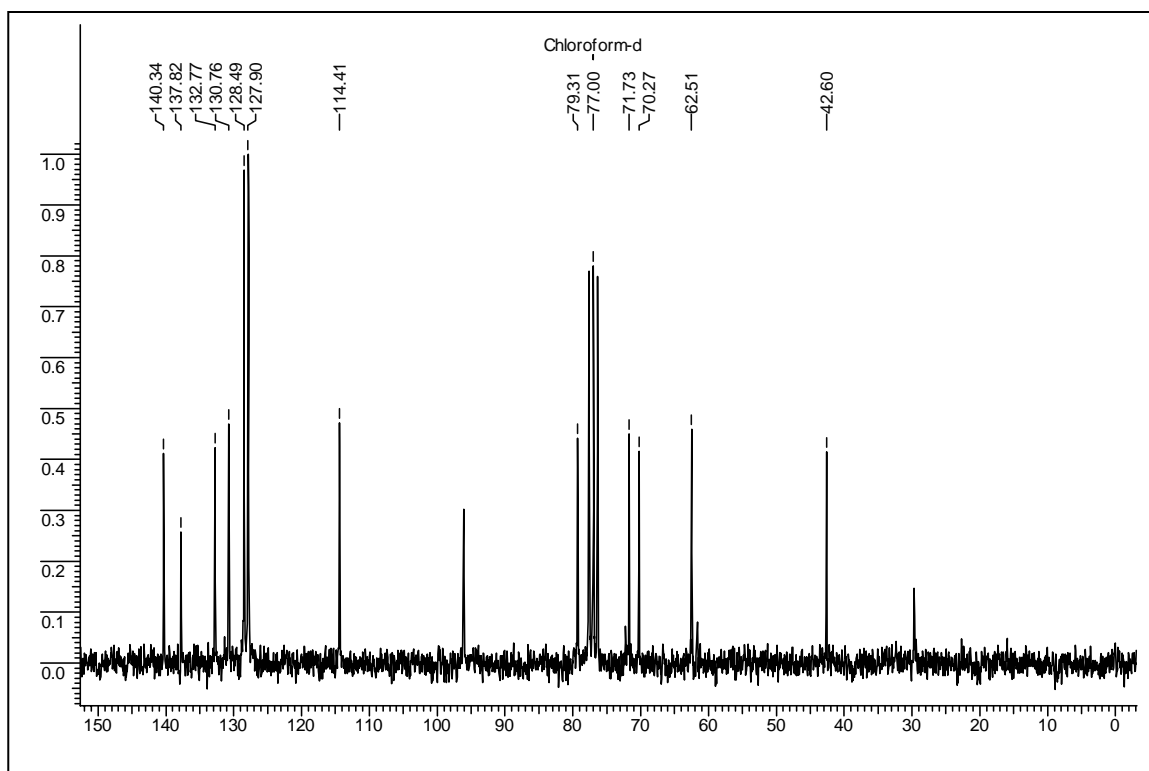
$^1\text{H}$  NMR spectra of compound 6 $^{13}\text{C}$  NMR spectra of compound 6

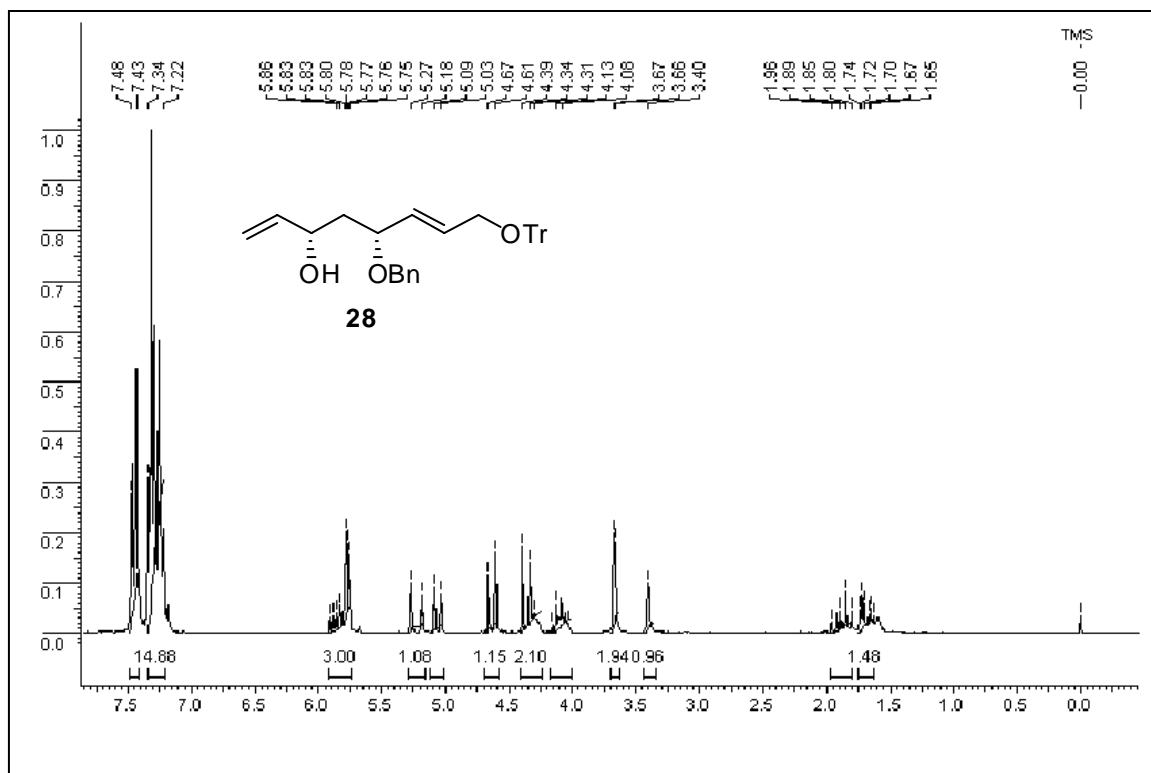
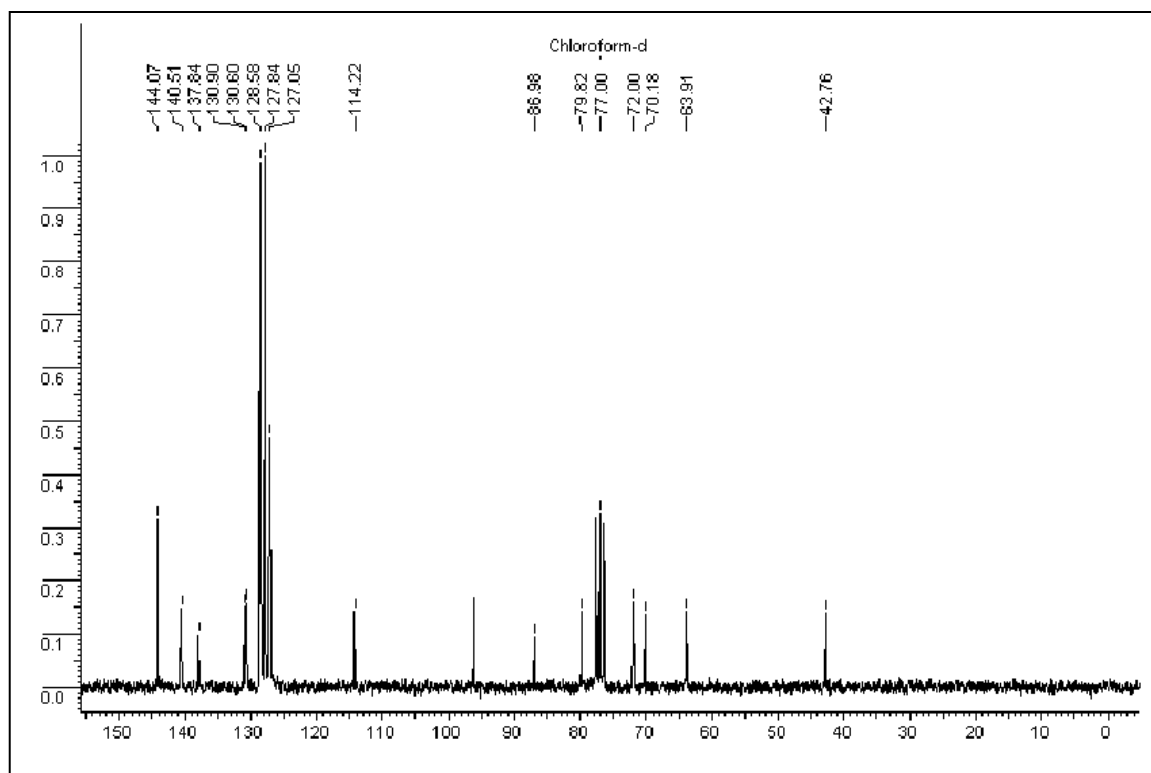
**$^1\text{H}$  NMR spectra of compound 5** **$^{13}\text{C}$  NMR spectra of compound 5**

**$^1\text{H}$  NMR spectra of compound 23** **$^{13}\text{C}$  NMR spectra of compound 23**

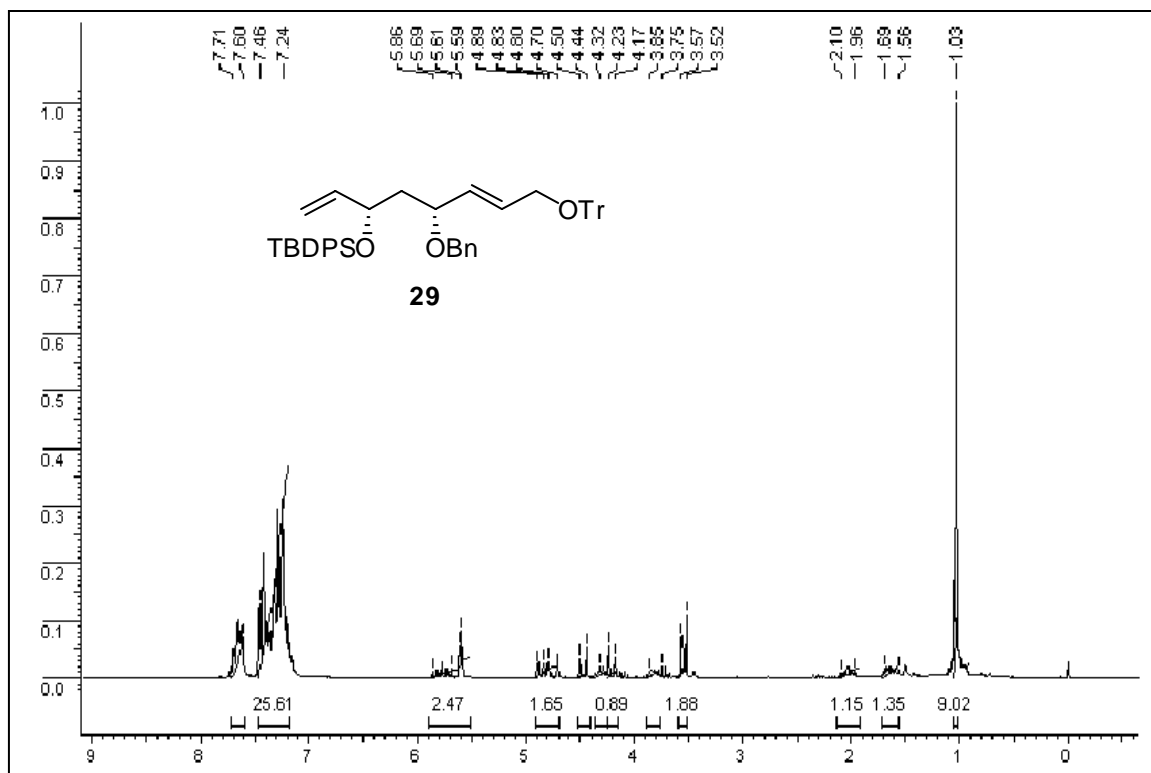
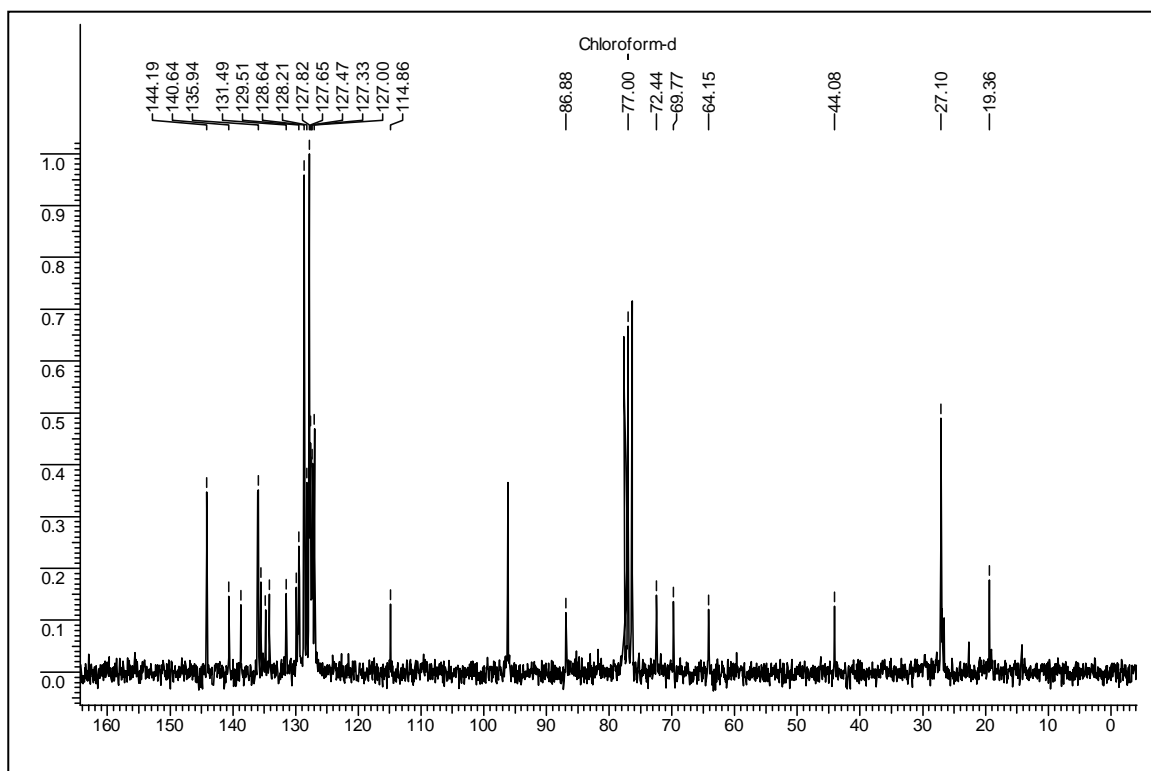
**$^1\text{H}$  NMR spectra of compound 24** **$^{13}\text{C}$  NMR spectra of compound 24**

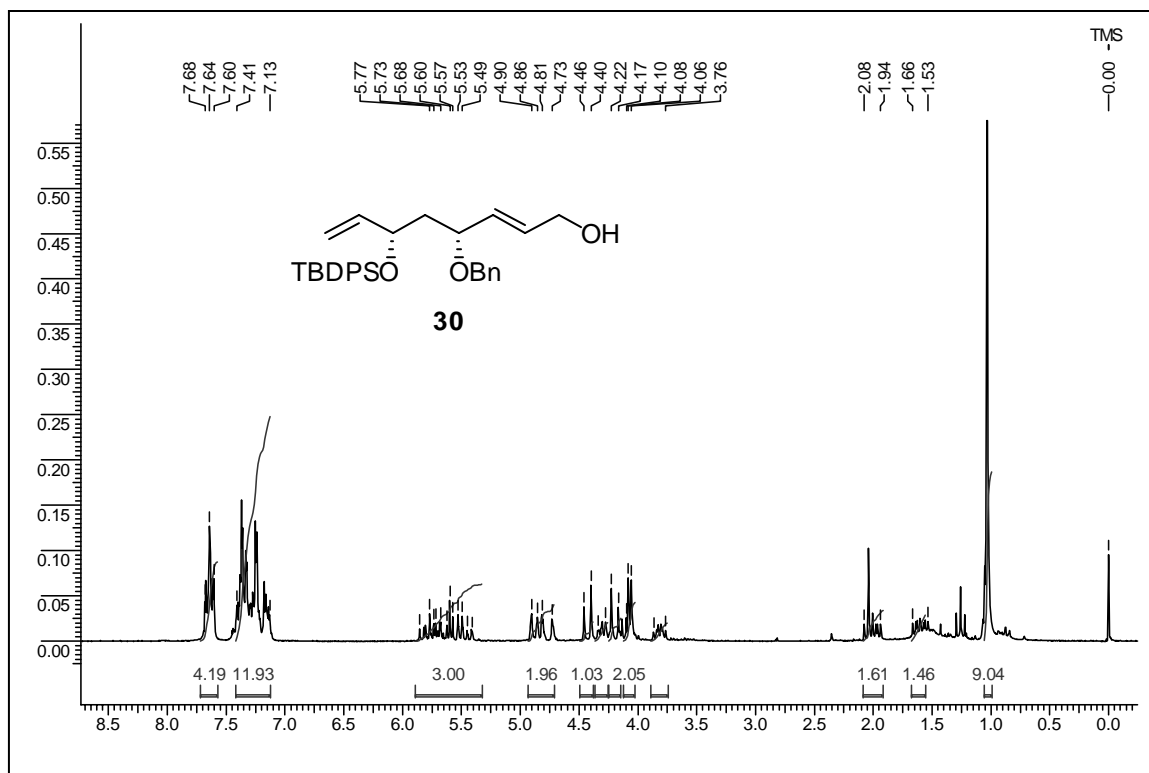
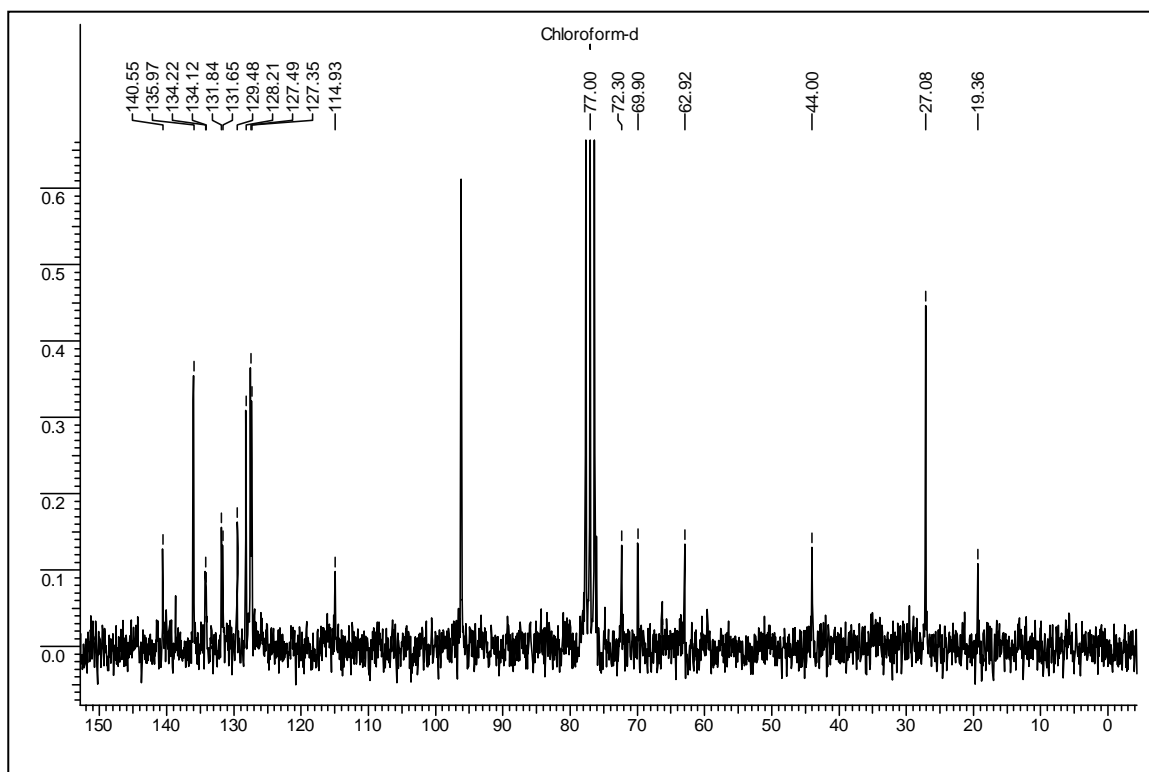
**<sup>1</sup>H NMR spectra of compound 26****<sup>13</sup>C NMR spectra of compound 26**

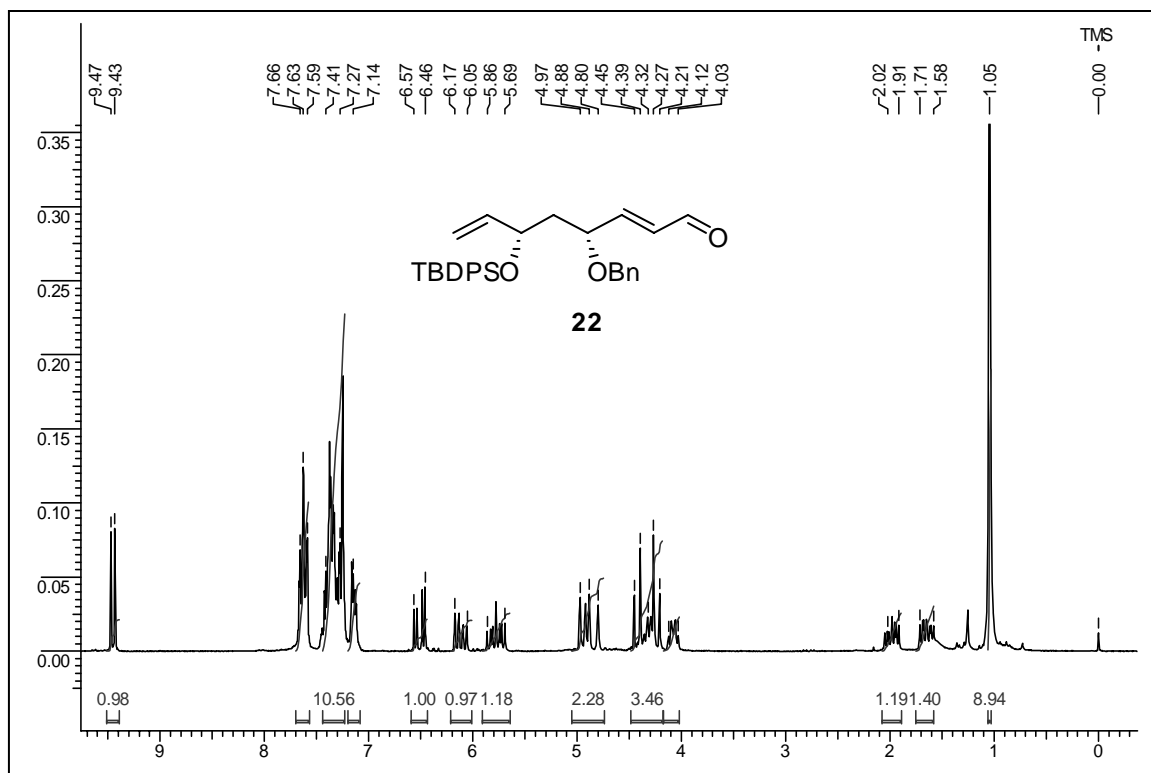
**$^1\text{H}$  NMR spectra of compound 27** **$^{13}\text{C}$  NMR spectra of compound 27**

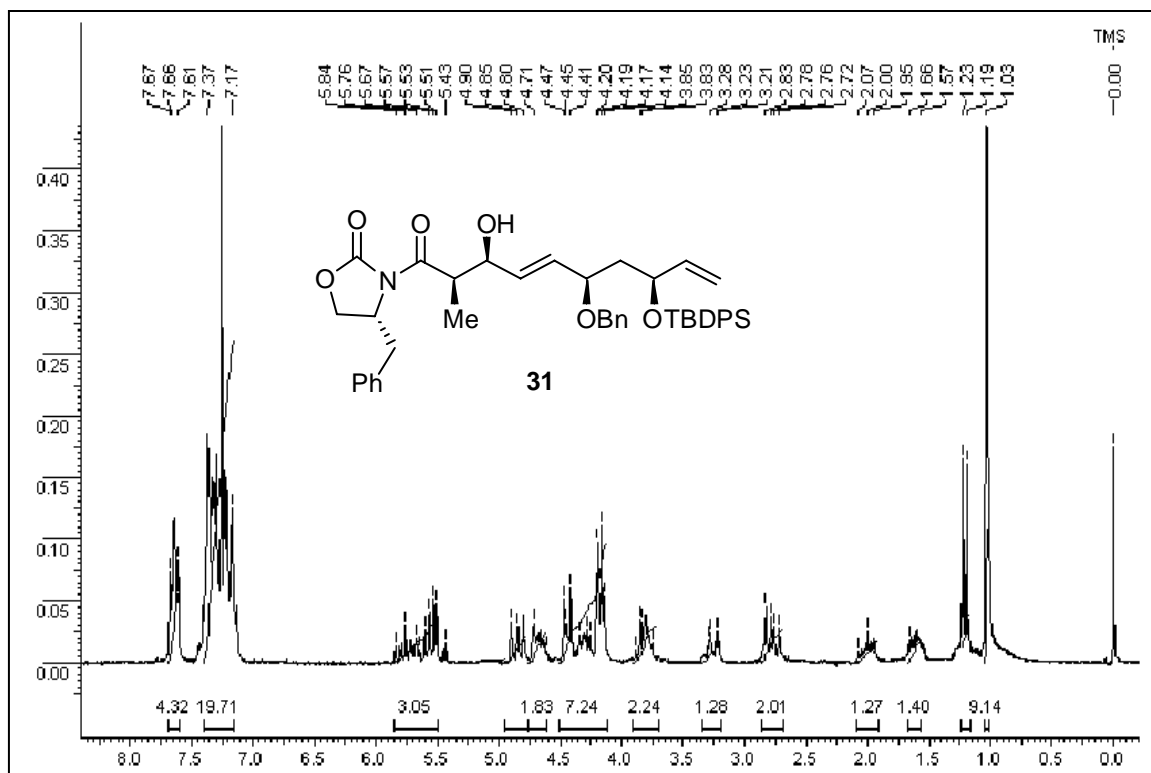
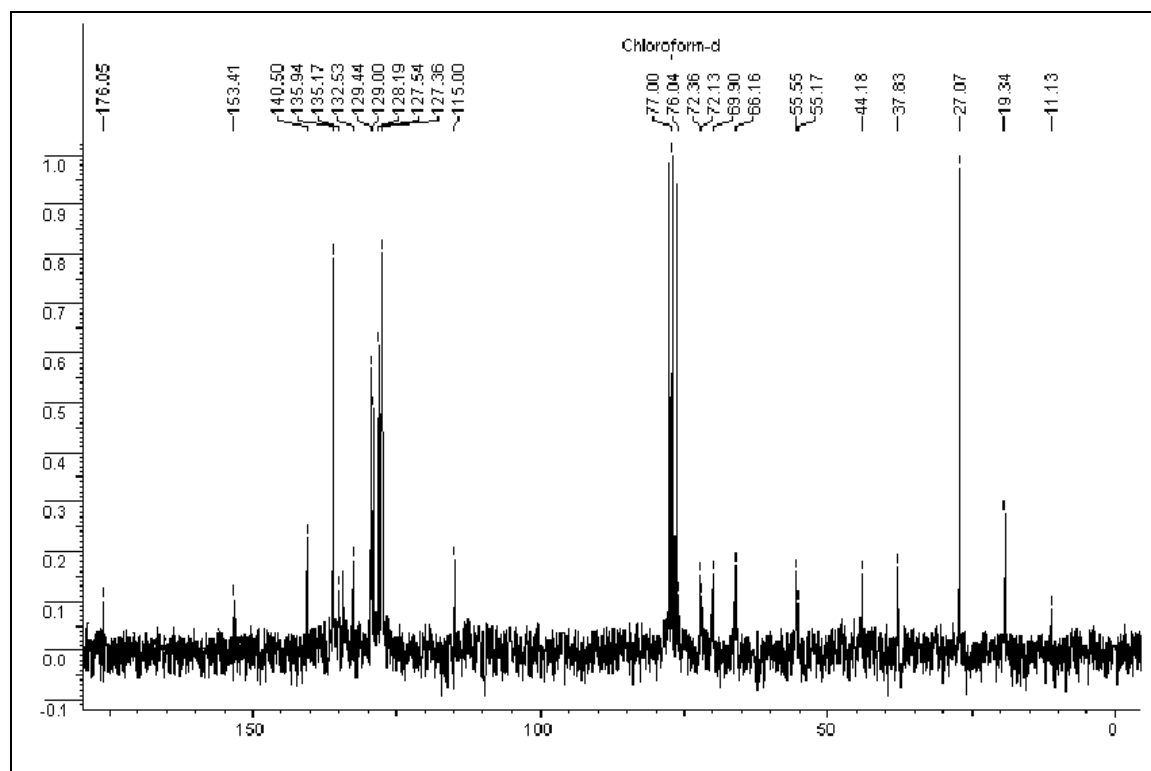
**$^1\text{H}$  NMR spectra of compound 28** **$^{13}\text{C}$  NMR spectra of compound 28**

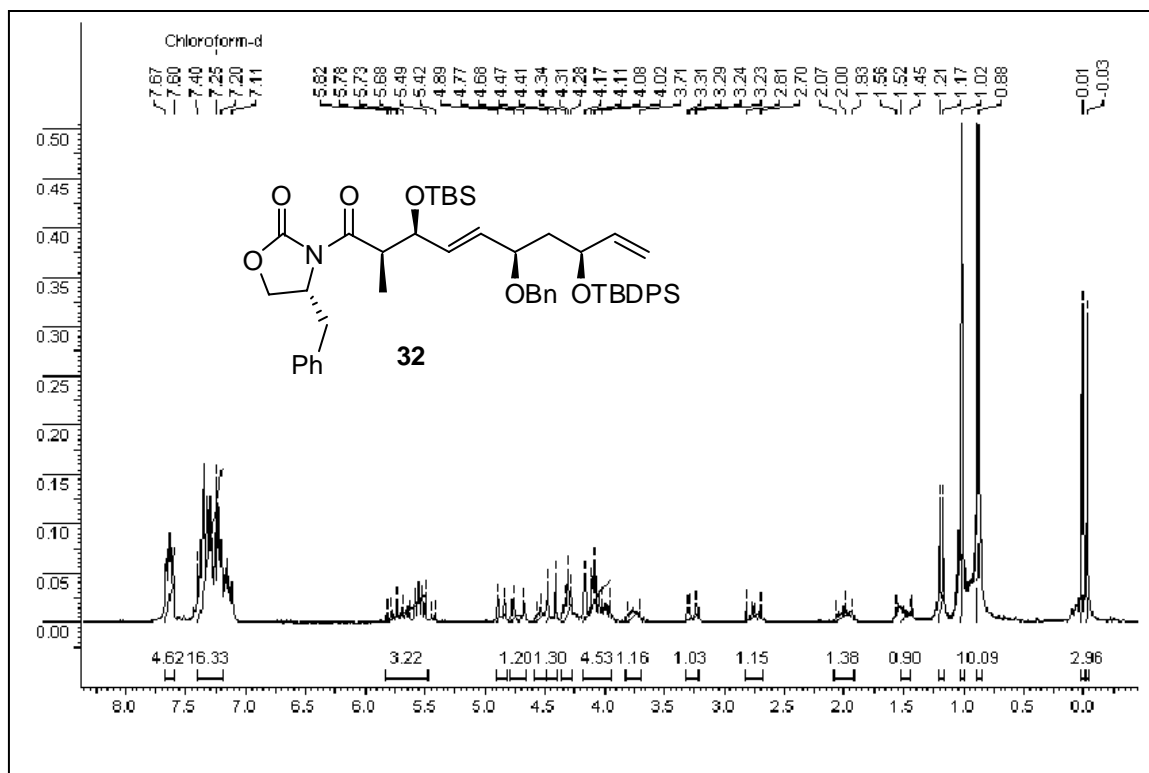
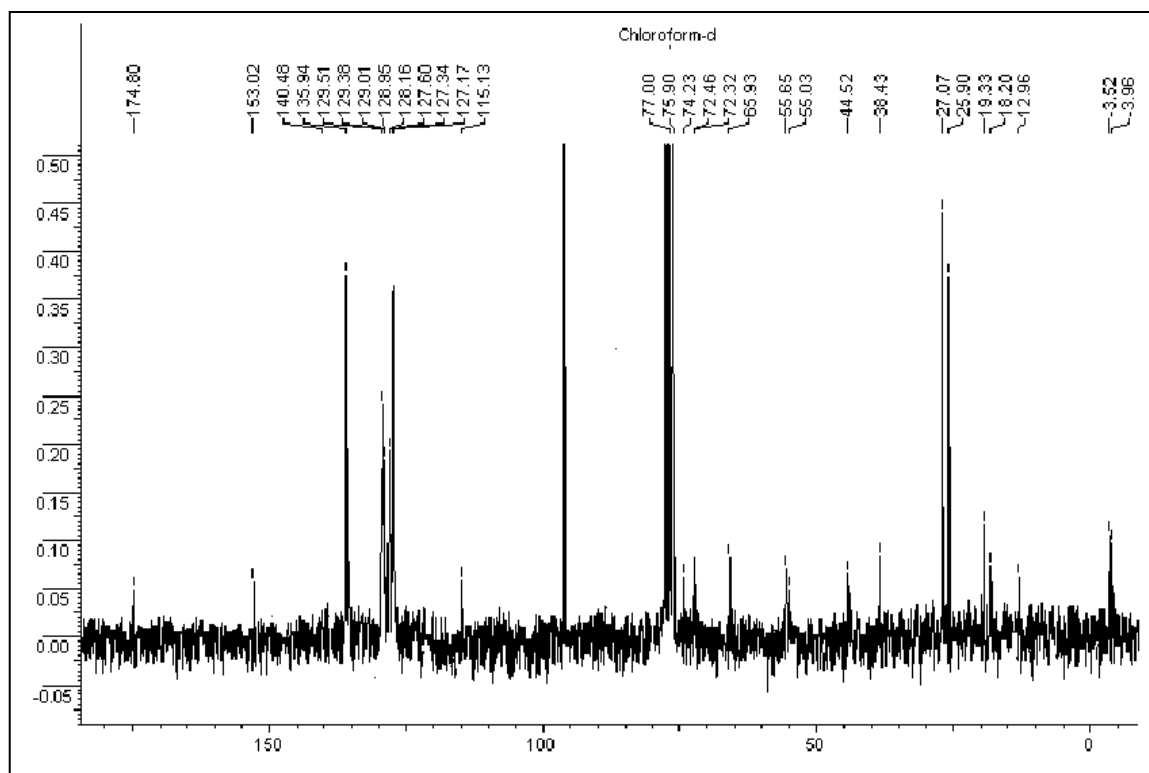


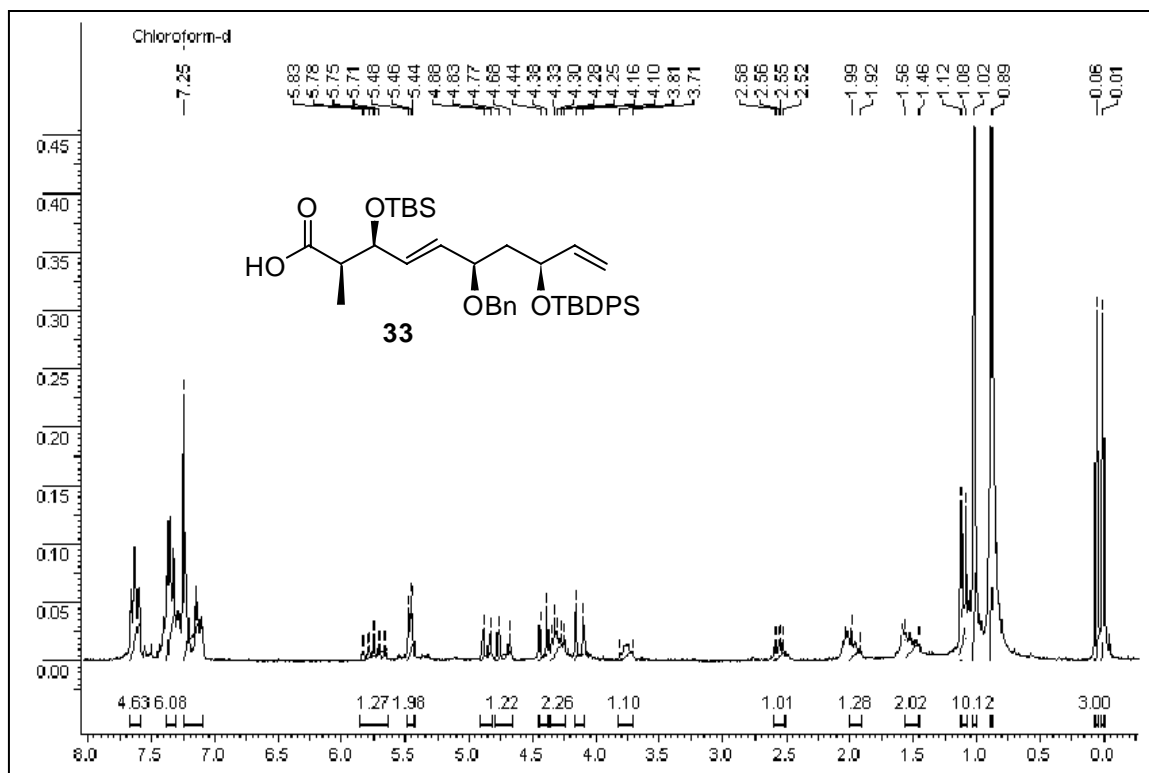
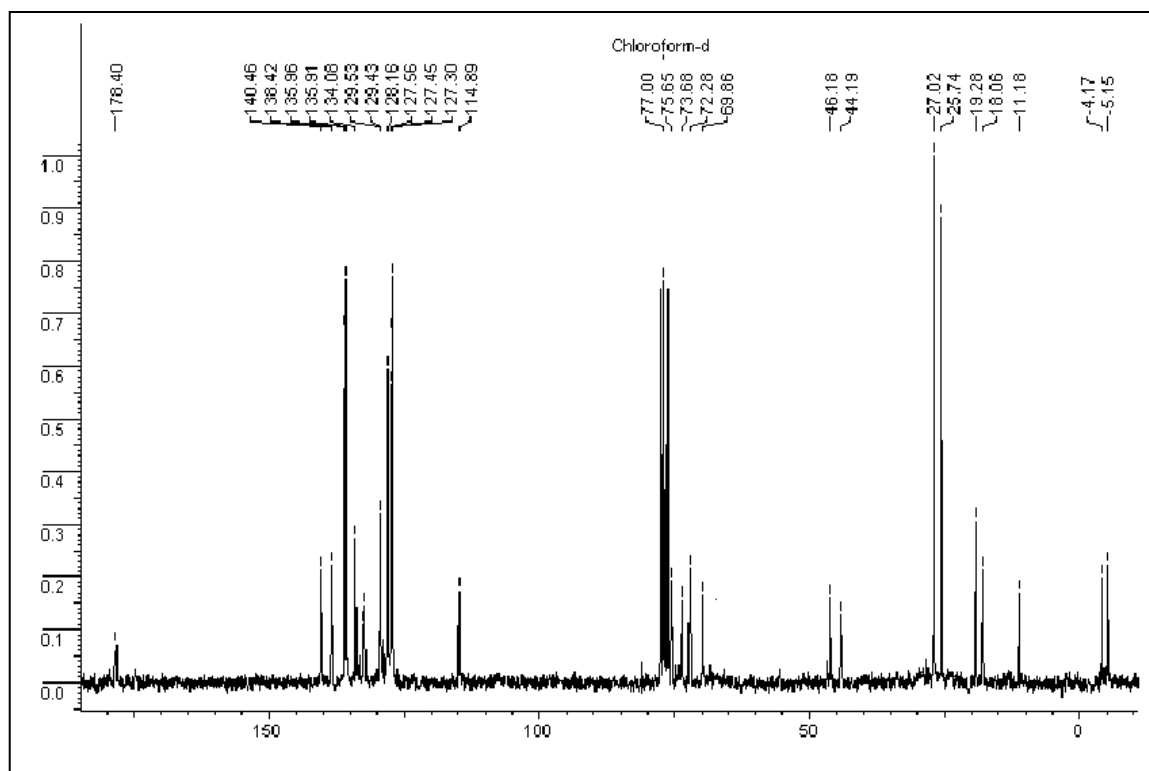
**$^1\text{H}$  NMR spectra of compound 29** **$^{13}\text{C}$  NMR spectra of compound 29**

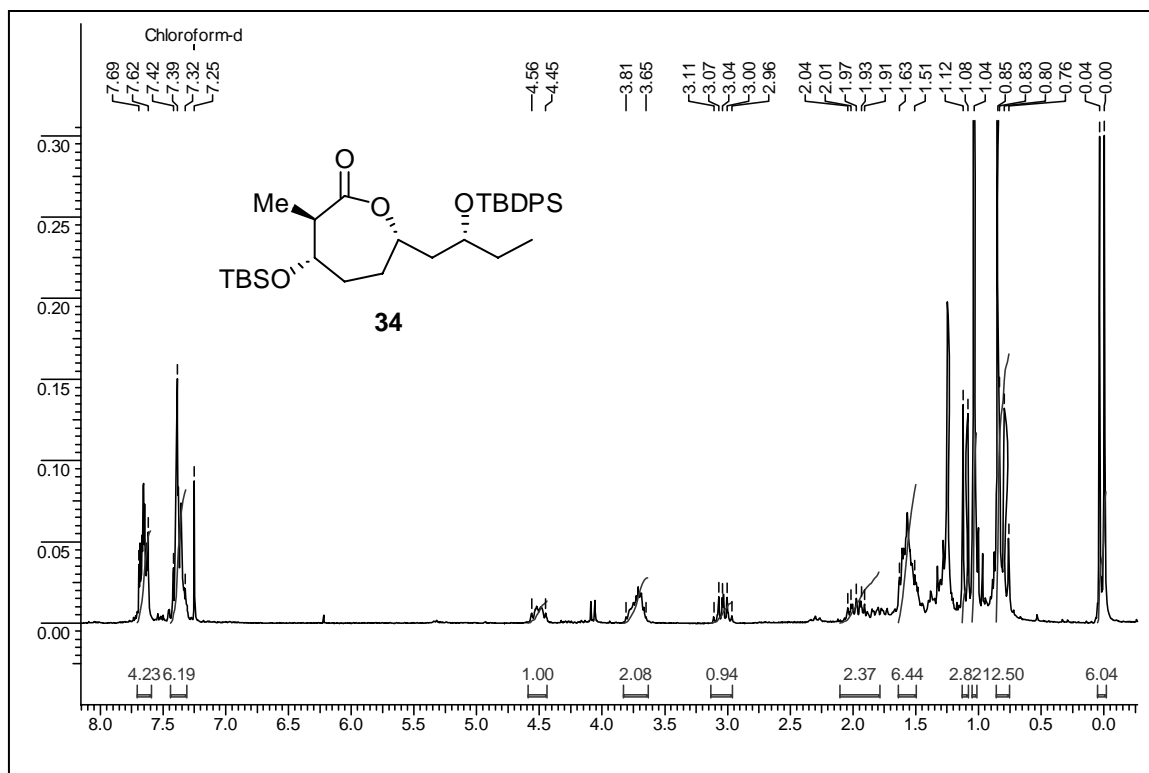
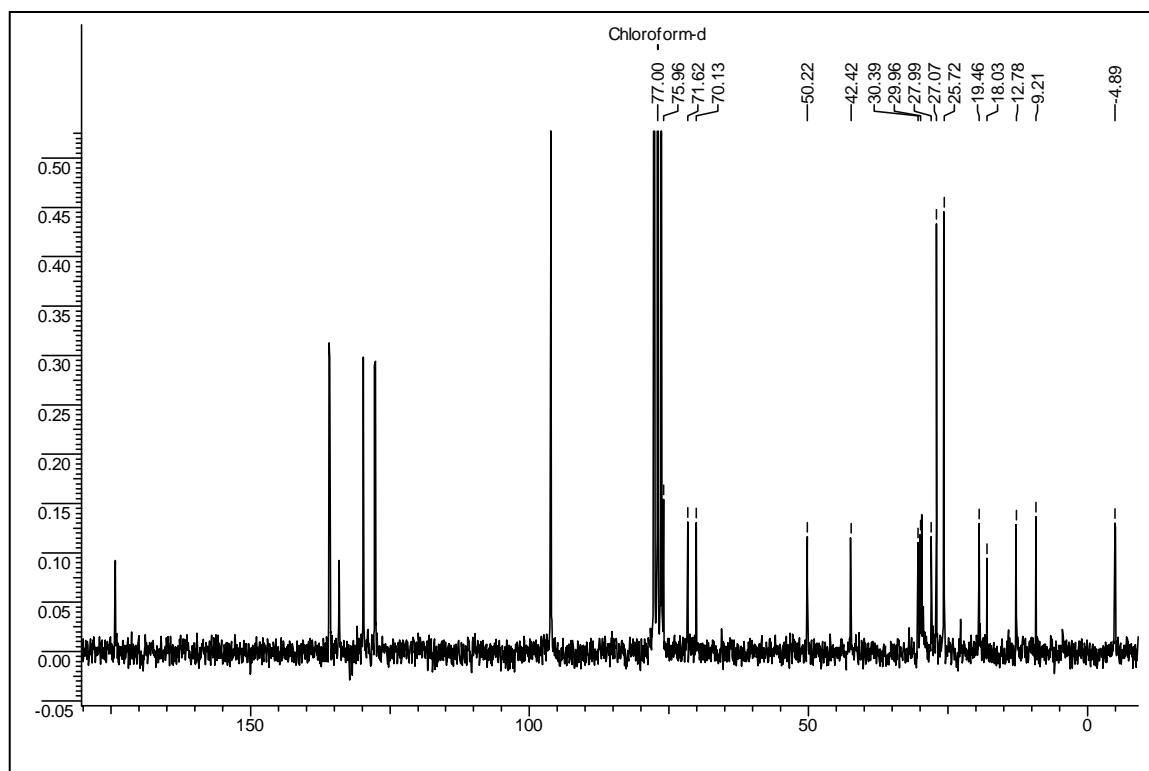
**$^1\text{H}$  NMR spectra of compound 30** **$^{13}\text{C}$  NMR spectra of compound 30**

$^1\text{H}$  NMR spectra of compound **22**

**<sup>1</sup>H NMR spectra of compound 31****<sup>13</sup>C NMR spectra of compound 31**

**<sup>1</sup>H NMR spectra of compound 32****<sup>13</sup>C NMR spectra of compound 32**

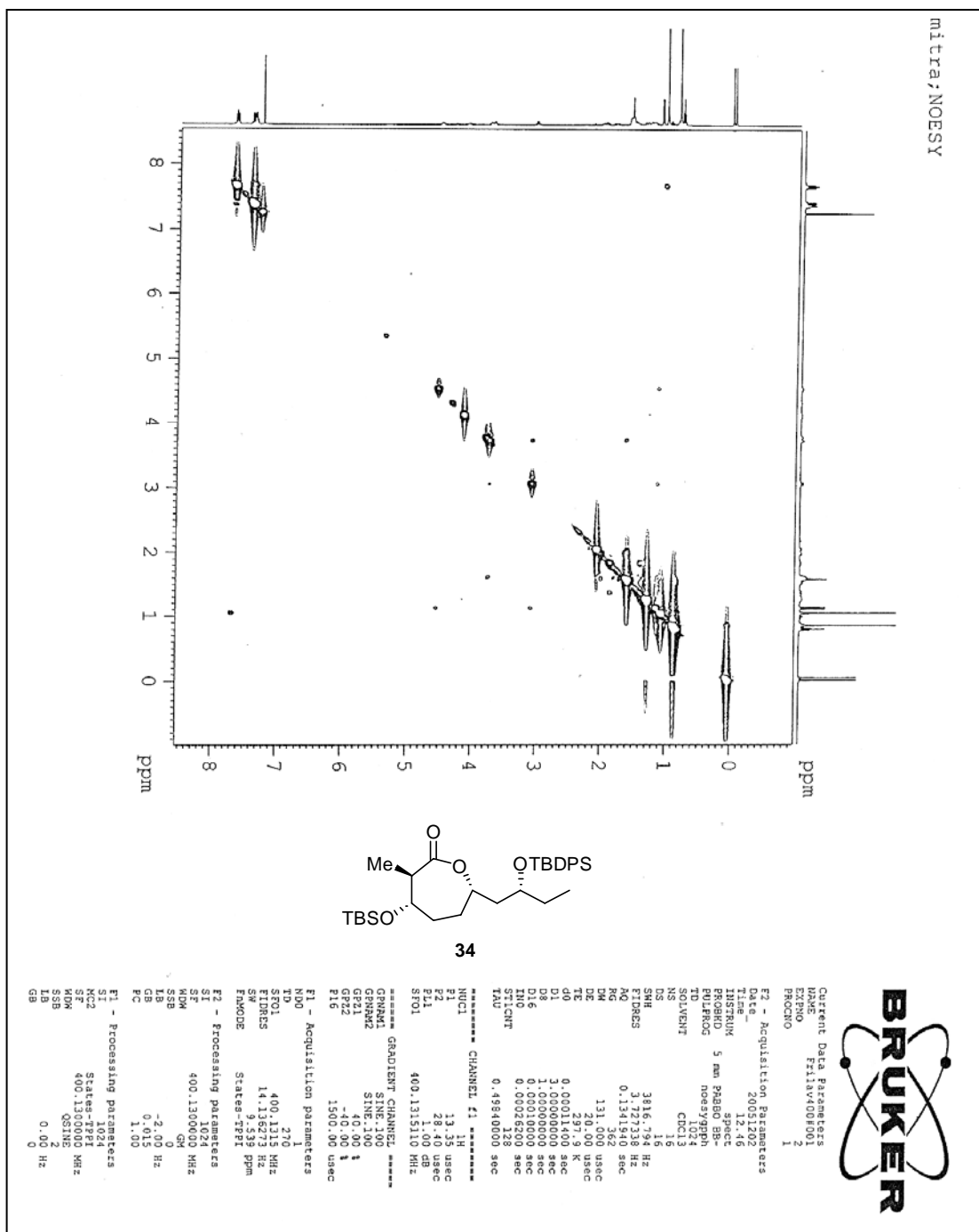
**$^1\text{H}$  NMR spectra of compound 33** **$^{13}\text{C}$  NMR spectra of compound 33**

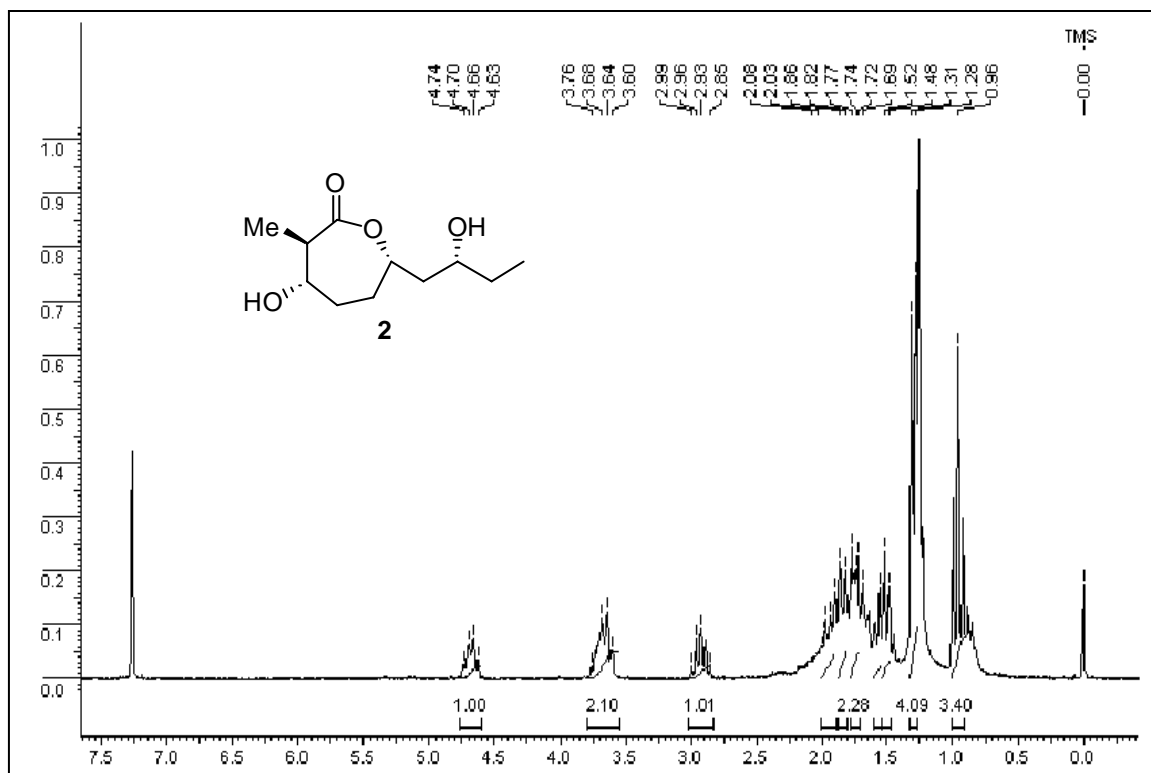
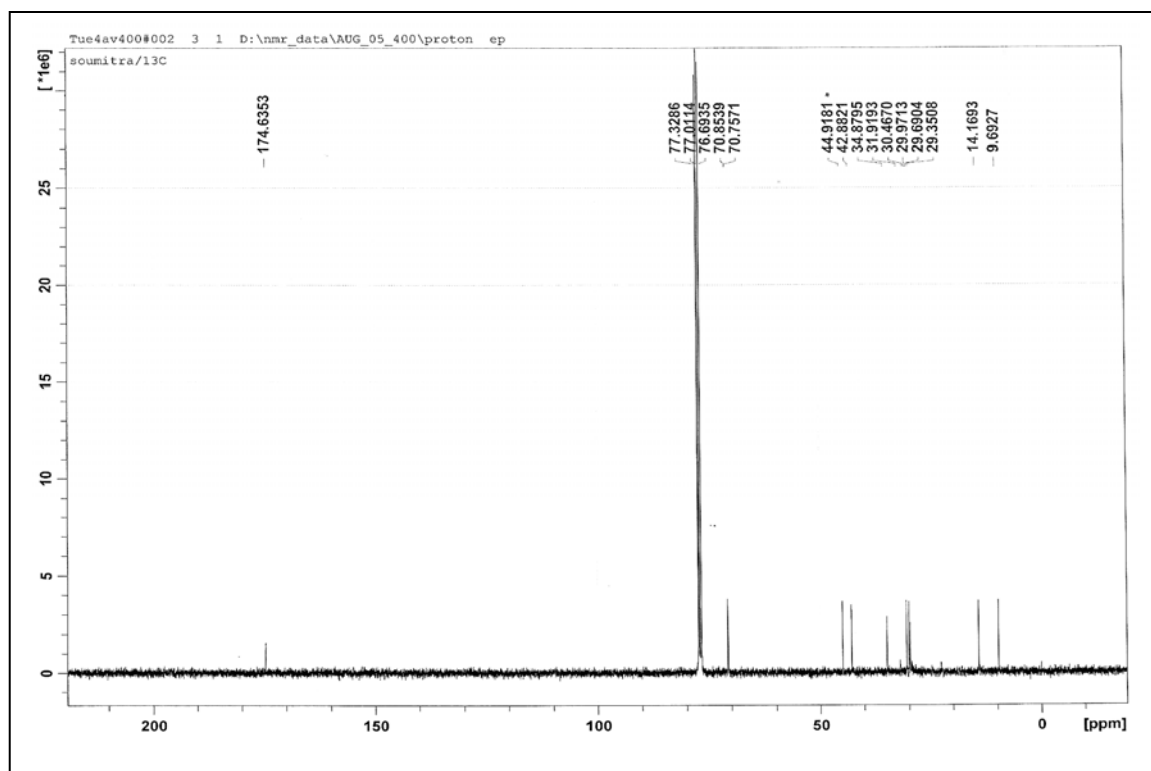
**$^1\text{H}$  NMR spectra of compound 34** **$^{13}\text{C}$  NMR spectra of compound 34**





## NOESY spectra of compound 34



**$^1\text{H}$  NMR spectra of compound 2** **$^{13}\text{C}$  NMR spectra of compound 2**

## **CHAPTER 2: Section 2**

Towards the Total Synthesis of Pandangolide 1

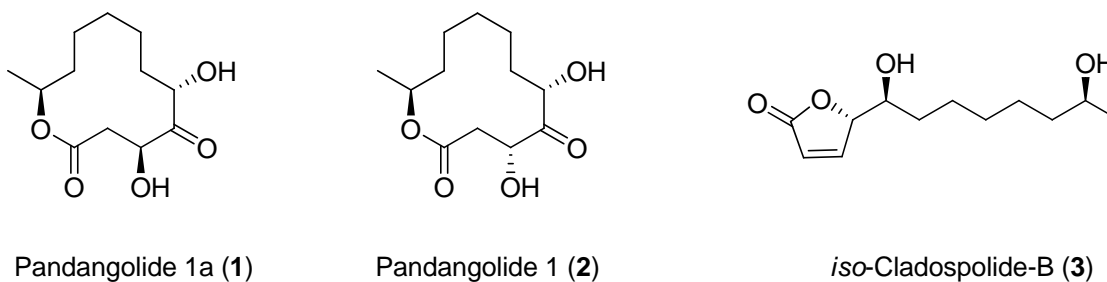
## **PRESENT WORK**

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## PRESENT WORK

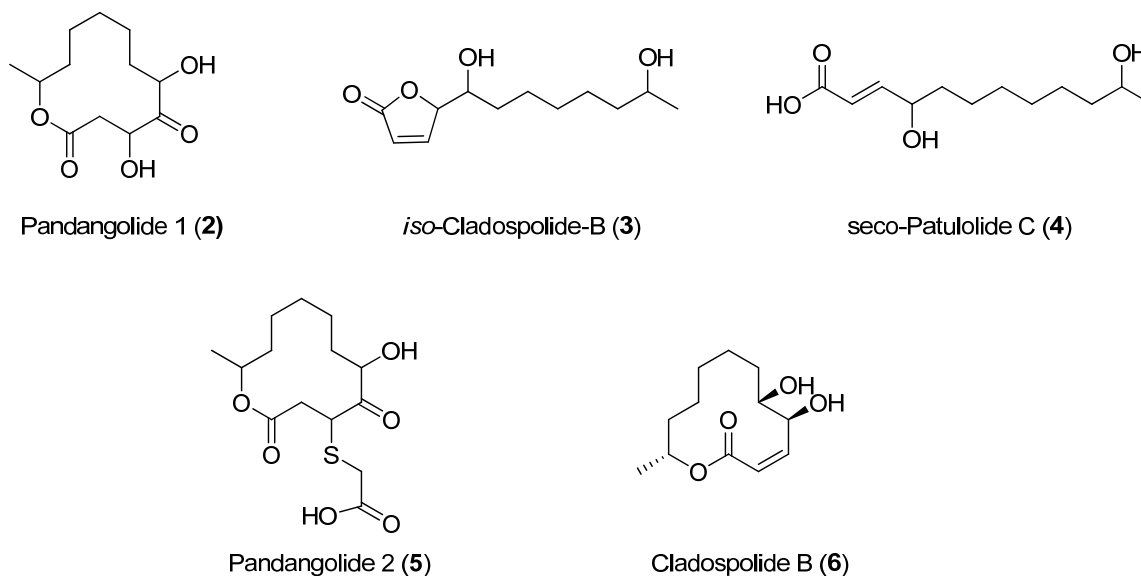
Marine fungi are attracting increasing attention as a potential source of new pharmaceuticals and pharmaceutical leads.<sup>43,44</sup> Isolates belonging to cosmopolitan genera, such as *Aspergillus*, *Penicillium*, *Alternaria*, and *Cladosporium*, are a significant source of new secondary metabolites from marine-derived fungi.<sup>45</sup> Species belonging to these genera are routinely isolated from the surfaces, inner tissues, and internal spaces of marine algae,<sup>46,47</sup> sponges,<sup>48</sup> ascidians,<sup>47</sup> and other marine invertebrates.<sup>49</sup> To date, more than 75 metabolites from 25 sponge-derived fungal strains have been described.<sup>48,50,51</sup> Some of these reported metabolites exhibit bioactive properties and are structurally unique, while many others are structurally related to metabolites produced by fungi isolated from terrestrial habitats.<sup>52</sup> Recently Carmeli *et al.* have isolated a new hexaketide lactone, pandangolide 1a (**1**, 2.4 mg, 1.6% of crude extract), along with its known diastereoisomer pandangolide 1 (**2**, 3.4 mg, 2.3% of crude extract) and the known *iso*-cladospolide B (**3**, 25.7 mg, 17.6% of crude extract), from the ethyl acetate extract of a *Cladosporium* sp. that was isolated from the Red Sea sponge *Niphates rowi*.<sup>53</sup>

**Figure 1**



Ireland and co-workers isolated pandangolide 1<sup>54</sup> (**2**) along with three other compounds of the same class from the fermentation of a marine fungal species obtained from a tissue sample of a marine sponge collected in Indonesia in October 1996, named *iso*-cladospolide B (**3**), *seco*-patulolide C (**4**), and pandangolide 2 (**5**), and the known terrestrial fungal metabolite, cladospolide B (**5**).

Figure 2

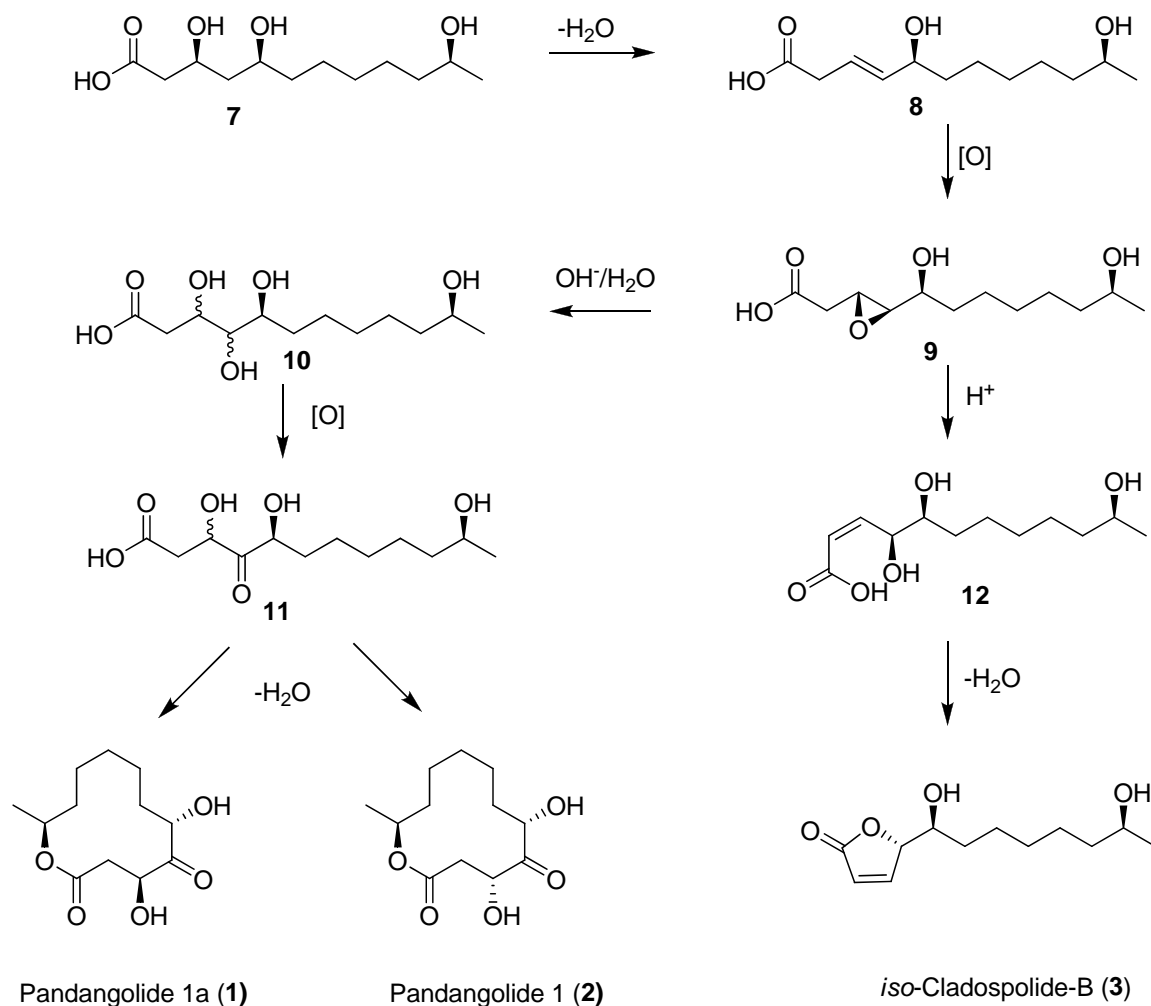


Pandangolide 1 was isolated as an oil that showed a protonated molecular ion in the positive ion FAB MS spectrum at  $m/z$  245 ( $M+H$ )<sup>+</sup> corresponding to the molecular formula  $C_{12}H_{21}O_5$ .  $^{13}C$  NMR spectrum also contained 12 signals. Again, a signal at  $\delta$  175.27 indicated the presence of ester functionality plus another signal at  $\delta$  213.09 arising from keto-carbonyl functionality. The absorbances at 1732 and 1716  $cm^{-1}$  noticed in IR spectrum of **1** supported the presence of ester and keto-carbonyl groups. A broad absorbance centered at 3444  $cm^{-1}$  indicated the presence of hydroxyl group(s). The  $^1H$  NMR spectrum contained three methine signals at  $\delta$  4.83, 4.40, and 4.09, indicating three oxygenated carbons. Also present were two signals at  $\delta$  3.30 and 3.15 that coupled to one another with a magnitude of 19.2 Hz and, on analysis of an HMQC experiment, were shown to be attached to the same carbon at  $\delta$  43.87. Inspection of a gradient multiple quantum COSY experiment showed the presence of two spin systems. One contained the two geminally coupled signals and the signal at  $\delta$  4.40; the second encompassed all the remaining protons. The data also allowed the assignment of a terminal methyl functionality ( $\delta$  1.19) adjacent to an oxygen-bearing methine ( $\delta$  4.83). This methine could also be assigned as part of a lactone functionality by virtue of its proton and carbon chemical shifts. The observance of a number of key HMBC correlations from H2, H3, H5, and H6

with the keto group (C4) allowed the assignment of its position between the two spin systems. The rest of the carbons were again assigned to a long methylene chain to complete the macrolide. The HMQC experiment showed that nearly all of the methylene protons had different chemical shifts from their geminal partner, providing further evidence for a macrocycle. This is in contrast to the straight-chain compounds which did not show diastereotopic methylene protons. Further analysis of the COSY and HMBC allowed assignment of structure **1**. All these assignments and structural elucidation determined the core structure of the molecule but the absolute configuration of hydroxyl group(s) and the methyl center was unknown till 2005. In 2005 Carmeli group first proposed the absolute configuration on the basis of chemical, spectroscopic, and biosynthetic arguments. Comparison of the NMR data of pure pandangolide **1** and pandangolide **1a** suggested that they differed only in the configuration of C-3 since the carbon chemical shift differences peaked for C-3 (3.0 ppm) and declined to both sides of C-11 (0.1 ppm) and C-6 (0.4 ppm). Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data and optical rotations of both compounds (**1** and **2**) with the NMR data in  $\text{CD}_3\text{OD}$  and optical rotations in MeOH of pandangolide **1** revealed that compound **1** was identical in all respects to pandangolide **1**.<sup>54</sup>

The absolute stereochemistry of compounds **1** and **2** was determined using Riguera's method for the determination of the absolute stereochemistry of secondary alcohols<sup>56</sup> which suggest that the C-3 stereochemistry in **1** and **2**, is reversed and fixed the stereogenic center at position 5 to be *S*.

On the basis of biosynthetic considerations, shown in Scheme 1, a common trihydroxydodecanoic acid-polyketide precursor is suggested for compounds **1**, **2**, **3**. We suggest that the stereochemistry of C-11 in pandangolides **1a** (**1**) and **1** (**2**) is *S*, similar to that of *iso*-cladospolide B (**3**), considering the function of type I modular PKS in generating a polyketide chain.<sup>57</sup>

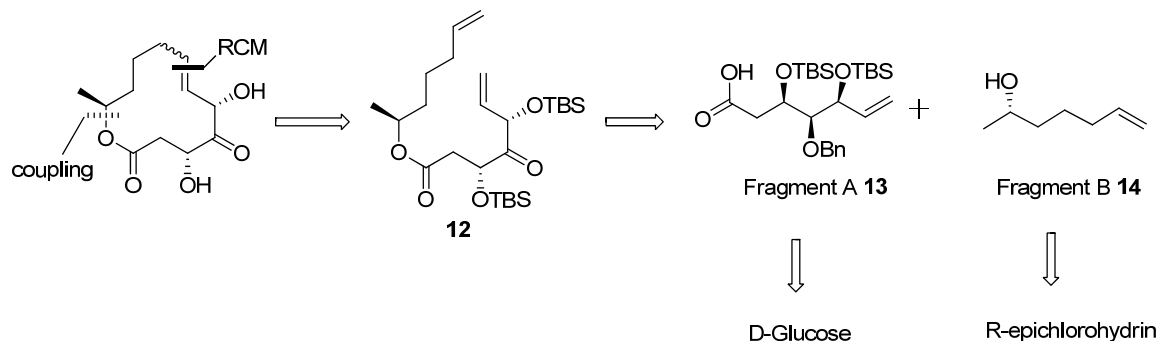
**Scheme 1: Biosynthesis of compound 1, 2, 3**

Considering the structural similarity of pandangolide 1 and pandangolide 1a, as there was no total synthesis confirming the relative and absolute configurations proposed, pandangolide 1 was selected as the initial synthetic target. The key retrosynthetic disconnections planned for the total synthesis of **2** were given in Scheme 2. The central issue in our retrosynthetic strategy is the formation of macrolactone ring where the RCM has been opted as the key reaction. Keeping the RCM as the key transformation, the central skeleton of **2** has been divided into two fragments; (i) acid fragment **13** and (ii) long chain chiral alcohol **14**. D-glucose has been identified as a suitable chiral precursor for the synthesis of fragment **13**, after comparing the absolute configuration of the stereogenic centers present. The synthesis of alcohol **14** was planned from easily available *R*-



epichlorohydrin by treating it with suitable alkenyl Grignard reagent and subsequent two step protocol for the terminal deoxygenations via an oxirane intermediate.

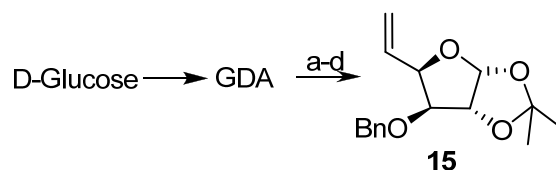
### Scheme 2: Retrosynthetic strategy



#### Preparation of fragment A:

As intended our exercise towards the total synthesis of padangolide **1** started with the synthesis of fragment A from easily available D-glucose. The known benzyl ether **15** was made from D-glucose by following the established procedures. Thus protection of D-glucose as its diacetonide (acetone in anhydrous  $\text{CuSO}_4$ ) followed by benzylation of free 3-OH using benzyl bromide gave benzyl ether in 56% overall yield. The 5,6-acetonide group was selectively cleaved using 0.8%  $\text{H}_2\text{SO}_4$  in MeOH. Following the established double elimination procedure in our group, diol was converted to the known olefin **15**.<sup>58</sup>

### Scheme 3



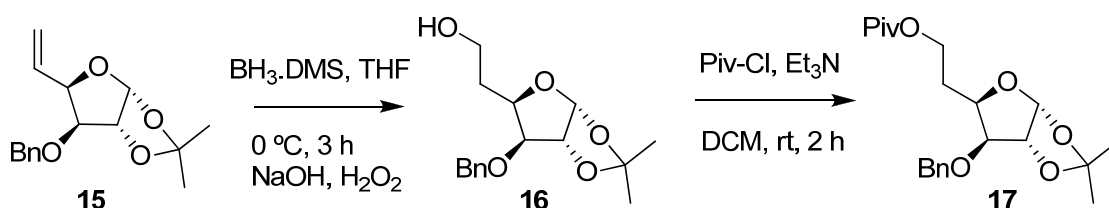
**Reagents and conditions:** a)  $\text{NaH}$ ,  $\text{BnBr}$ , THF,  $0\text{ }^\circ\text{C} \rightarrow \text{rt}$ , 1 h. b) 0.8%  $\text{H}_2\text{SO}_4$ , MeOH, 12 h. c)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ , DCM,  $0\text{ }^\circ\text{C}$ , 0.5 h. e)  $\text{Zn}$ ,  $\text{NaI}$ , DMF,  $150\text{ }^\circ\text{C}$ , 2 h.

Hydroboration/oxidation of compound **15** by using borane-dimethyl sulfide complex followed by treatment with  $\text{NaOH}/\text{H}_2\text{O}_2$  provided the alcohol **16** with complete regioselectivity. The structural identity of alcohol **16** was confirmed with the help of NMR spectroscopy. For example, in the  $^1\text{H}$  NMR of compound **16**, there was no terminal methyl group present in the upfield region. A triplet at  $\delta$  60.3 ppm in the  $^{13}\text{C}$  NMR confirmed the

placement of the newly introduced -OH group at the terminal carbon of the olefin. The other methylene group resonated at  $\delta$  30.9 ppm in the  $^{13}\text{C}$ NMR supported the assigned regiochemistry.

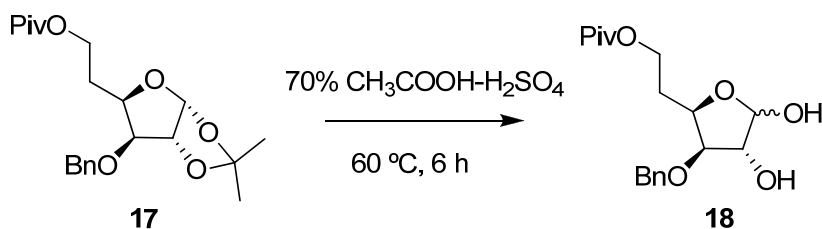
After fixing the regiochemical outcome of the hydroboration reaction, we continued the synthetic sequence with the alcohol **16**. The free hydroxyl group was protected as its pivaloyl ester **17** by treating with pivaloyl chloride and triethyl amine.

#### Scheme 4



Treatment of compound **17** with cat.  $\text{H}_2\text{SO}_4$  in acetic acid at 60 °C brought the 1,2-acetonide deprotection to afford the lactol **18**.<sup>25</sup> The absence of the two methyl singlet signals of acetonide group and the upfield shift of anomeric proton from  $\delta$  5.91 to  $\delta$  5.46 in  $^1\text{H}$  NMR spectrum of **18** evidenced the 1,2-acetonide deprotection.

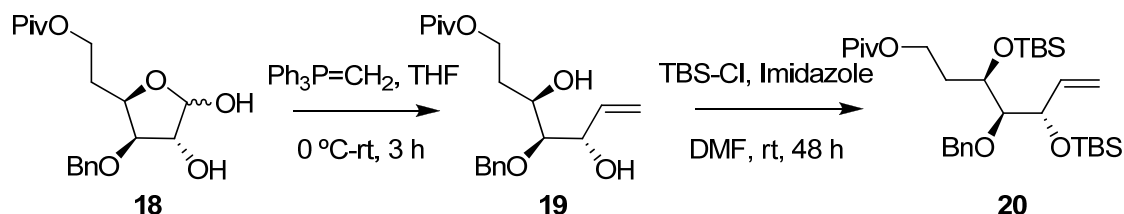
#### Scheme 5



One-carbon Wittig homologation of lactol **18** by employing  $\text{H}_2\text{C}=\text{PPh}_3$  (generated in situ using triphenyl phosphonium iodide and *n*-butyl lithium) afforded the olefin **19** in good yield. In the  $^1\text{H}$  NMR spectrum of **19**, absence of a peak corresponding to anomeric-H and the presence of three new H's in the downfield region (1H at  $\delta$  5.94 and 2H at  $\delta$  5.23 and 5.37), confirmed the assigned structure. This functional group transformation was further confirmed by  $^{13}\text{C}$  NMR spectroscopy where  $\delta$  116.6 and 138.0 peaks respectively were the two characteristic signals of terminal and internal olefinic carbons. The two free -OH groups present in **19** were protected as their TBDMS ethers by using

TBDMS-Cl and imidazole as base. Purification of the di-TBS product **20** was complicated by its close polarity with the unreacted TBS-Cl. Considering this difficulty, we have proceeded further with the crude TBS protected product for the deprotection of terminal pivaloyl group.

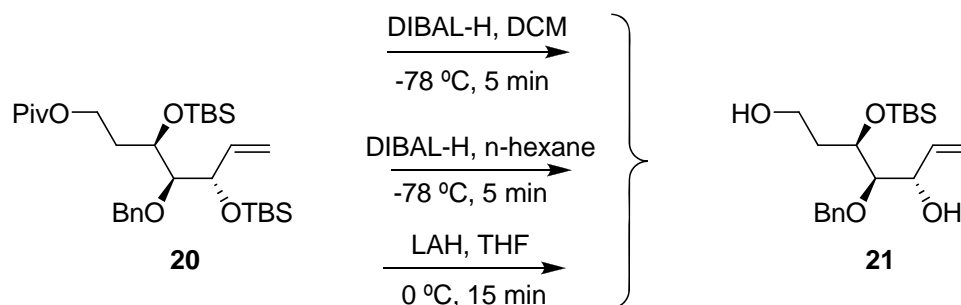
### Scheme 6



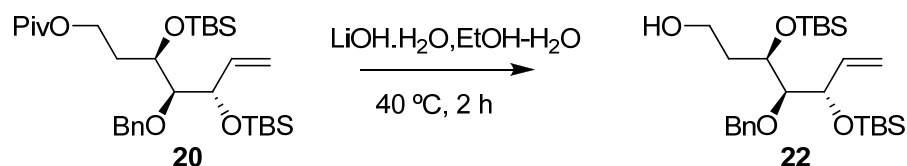
The pivaloyl deprotection of **20** was carried out with DIBAL-H in DCM at  $-78\text{ }^\circ\text{C}$ .<sup>59</sup> Complete disappearance of starting compound was noticed within 5 min. However, after chromatographic purification, we noticed that the major product isolated **21**, has only one TBS group and the desired product was obtained only in 5% yield. Even in aprotic solvent like *n*-hexane, the DIBAL-H reduction resulted with the same result. When LAH was employed as the reducing agent, unrequired product **21** was isolated exclusively. This product formation was indicated from mass spectroscopy where  $m/z$  value was observed  $390\text{ [M+Na]}^+$ ,  $406\text{ [M+K]}^+$  in ESI-MS. From  $^1\text{H}$  NMR study absence of one TBS group also confirmed the obtained result.

Considering the unanticipated TBS deprotection in the hydride reduction, we next opted for base mediated saponification of the pivaloyl group. Our initial experiments by using lithium hydroxide in moist ethanol method at  $40\text{ }^\circ\text{C}$ , once again afforded the formation of compound **21** in major proportion, however, the proportion of the desired product was increased to certain extent. Encouraged by this, several parameters of this reaction were varied and come up with optimized conditions where the reaction was stopped once the unrequired product started forming.

## Scheme 7

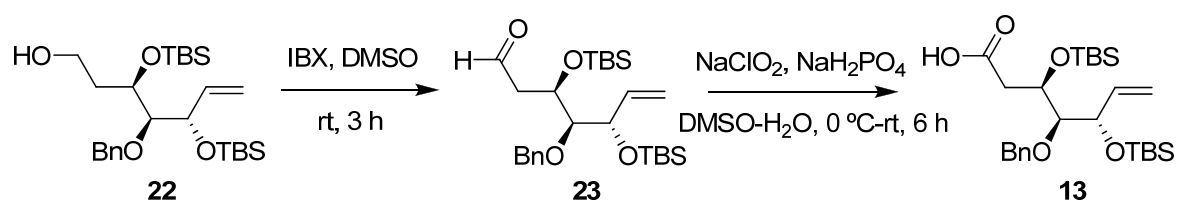


## Scheme 8



After successful deprotection of pivaloyl group now target was to make the key acid fragment **13**. The oxidation of the primary alcohol **22** to the acid **13** was carried out by employing two step protocols. Thus the primary hydroxyl group was first oxidized to an aldehyde **23** under IBX-DMSO conditions and further oxidation of the resulting aldehyde to corresponding acid by using sodium chlorite in sodiumdihydrogen phosphate buffer. Considering its decomposition on storage, only  $^1\text{H}$  NMR of the intermediate aldehyde was taken. The aldehyde-H was appeared at  $\delta$  9.74 as a triplet, and the methylene protons adjacent to aldehyde functionality were also deshielded from  $\delta$  1.77 and  $\delta$  1.96 to  $\delta$  2.60 and  $\delta$  2.77 respectively in the  $^1\text{H}$  NMR spectrum of compound **23**. Absence of this aldehyde peak in  $^1\text{H}$  NMR spectrum of **13** and appearance of a quaternary carbon singlet at  $\delta$  175.5 in the  $^{13}\text{C}$  NMR of **13** confirmed the further oxidation of aldehyde unit to acid. Mass spectroscopy and elemental analysis were also in accordance with the formation of the acid product.

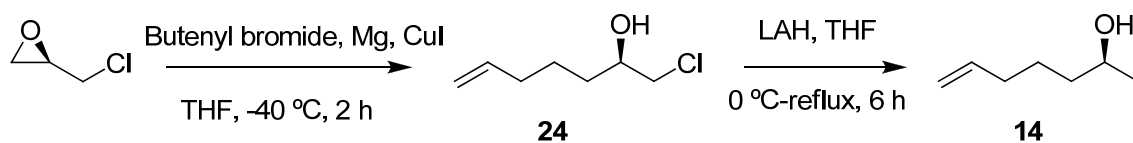
## Scheme 9



### Synthesis of fragment B:

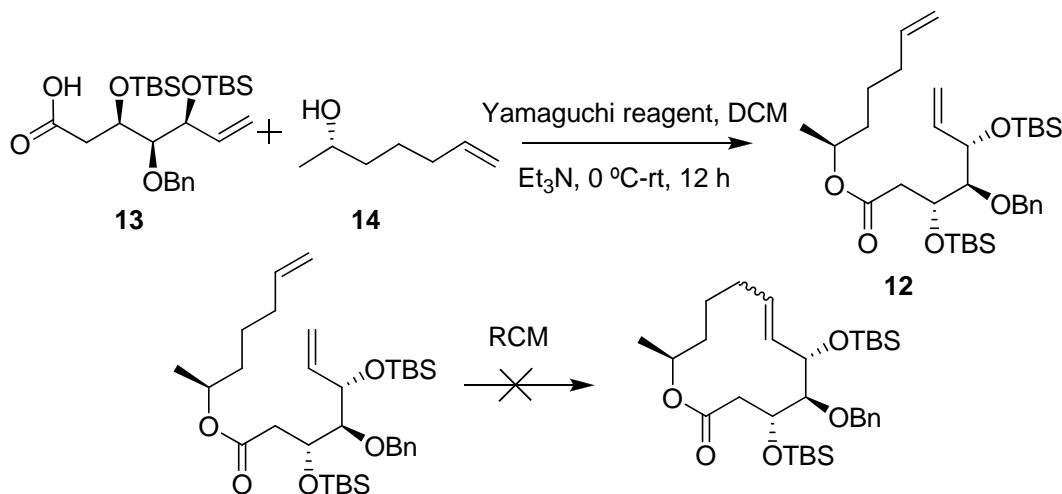
Synthesis of fragment B was straight forward. Thus the treatment of *R*-epichlorohydrin with 3-butenyl magnesium bromide gave the chlorohydrin **24** in 78% yield.<sup>60</sup> The resulting chlorohydrin **24** was subjected to reductive dehalogenation by employing LAH to procure the key alcohol **14**. The spectral and analytical data of **14** was fully in accordance with the reported data.<sup>61</sup>

#### Scheme 10



After successful preparation of both the fragments, coupling of these two fragments was done by using Yamaguchi reagent. Formation of coupling product **12** was confirmed by <sup>1</sup>H NMR where proton at  $\delta$  3.70-  $\delta$  3.77 was deshielded to  $\delta$  4.80-  $\delta$  4.87. This coupling product was subjected to the RCM reaction, but unfortunately in both 1<sup>st</sup> generation and 2<sup>nd</sup> generation Grubbs' catalyst reaction was failed in DCM, benzene, and toluene solvents.

#### Scheme 11



In conclusion, we attempted to synthesize the 12-membered lactone, pandangolide 1 by using RCM as the key reaction. Although synthesis of 12-membered ring lactones by RCM protocol are known. However, it was not successful in our case. As we noticed in

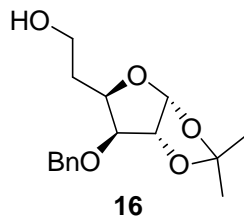
chapter 1, by varying the protecting groups, fate of RCM reaction can be changed. So work in this direction is progressing in our group.

## **EXPERIMENTAL**

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## **EXPERIMENTAL**

### **2-((3*aR*,5*R*,6*S*,6*aR*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethanol (16)**



Olefin compound **15** (4.5 g, 0.016 mol) was taken in 30 mL dry THF and  $\text{BH}_3\cdot\text{DMS}$  (2 mL, 0.021 mol) diluted with 15 mL of dry THF was added to it dropwise for 1 h period at 0 °C. The reaction mixture was stirred at same temperature for 2 h more. Then the reaction mixture was quenched with 2 mL of water at 0 °C and stirred for 5 mins. Then 3(N) NaOH solution (16 mL) followed by 30%  $\text{H}_2\text{O}_2$  solution (16 mL) were added to the reaction mixture and stirred for 3 h at room temperature. Then the whole mixture was extracted with ethyl acetate for several times (3 x 50 mL). Combined organic layer was dried over sodium sulphate and concentrated under vacuum. The crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:2) to obtain yellowish thick liquid **16**.

<b>Yield</b>	: 2.88 g, 60%
<b>Mol Formula</b>	: $\text{C}_{16}\text{H}_{22}\text{O}_5$
<b>Mol Weight</b>	: 294
<b>Optical rotation</b> $[\alpha]_D^{25}$	: $-16.8$ ( $c$ 0.75, $\text{CHCl}_3$ )
<b><math>^1\text{H}</math></b>	: $\delta$ 1.32 (s, 3H), 1.49 (s, 3H), 1.80-2.04 (m, 2H), 2.97 (br. s, 1H), 3.72-4.74 (m, 7H), 5.91 (d, $J = 3.8$ Hz, 1H), 7.32 (br. s, 5H)
<b><math>^{13}\text{C}</math></b>	: 26.2 (q), 26.7 (q), 30.9 (t), 60.3 (t), 71.7 (t), 78.5 (d), 82.2



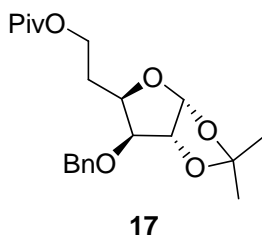
(CDCl<sub>3</sub>, 50 MHz) (d), 82.6 (d), 104.7 (d), 111.3 (s), 127.7 (d), 128.0 (d),  
128.5 (d), 137.4 (s) ppm

**Elemental analysis Calcd.** : C, 65.29; H, 7.53; O, 27.18%

**Found** : C, 65.42; H, 7.61%

**ESI-MS (*m/z*)** : 317 [M+Na]<sup>+</sup>

**2-((3*aR*,5*R*,6*S*,6*aR*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethyl pivalate (17)**



Compound **16** (2.8 g, 0.01 mol) was taken in 30 mL of dry DCM and dry triethylamine (7.5 mL, 0.05 mol) was added to it. Freshly distilled pivaloyl chloride (2.5 mL, 0.02 mol) was added to the reaction mixture at room temperature and stirred for 2h. Then the reaction mixture was quenched with water and the water layer was extracted with DCM (2 x 40 mL). Combined organic layer was dried over sodium sulphate and concentrated. Crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:9) to obtain colorless oil **17**.

**Yield** : 2.45 g, 68%

**Mol Formula** : C<sub>21</sub>H<sub>30</sub>O<sub>6</sub>

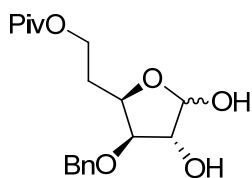
**Mol Weight** : 378

**Optical rotation** [ $\alpha$ ]<sub>D</sub><sup>25</sup> : -19.3 (*c* 4.65, CHCl<sub>3</sub>)

**<sup>1</sup>H** :  $\delta$  1.19 (s, 9H), 1.32 (s, 3H), 1.46 (s, 3H), 1.94 (ddd, *J* =  
(CDCl<sub>3</sub>, 200 MHz) 6.1, 12.2, 14.2 Hz, 1H), 2.11 (ddd, *J* = 6.1, 8.3, 14.2 Hz,

	1H), 3.80 (d, $J = 3.1$ , Hz, 1H), 4.09-4.17 (m, 2H), 4.22-4.31 (m, 1H), 4.5, 4.71 (2d, $J = 12.1$ Hz, 2H), 4.62 (d, $J = 3.8$ Hz, 1H), 5.90 (d, $J = 3.8$ Hz, 1H)
$^{13}\text{C}$ ( $\text{CDCl}_3$ , 50 MHz)	: 26.3 (q), 26.7 (q), 27.3 (q), 38.7 (s), 61.5 (t), 71.8 (t), 76.8 (d), 82.2 (d), 82.2 (d), 104.7 (d), 111.4 (s), 127.7 (d), 128.0 (d), 128.5 (d), 137.4 (s), 178.2 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 66.65; H, 7.99; O, 25.37%
<b>Found</b>	: C, 66.72; H, 8.23%
<b>ESI-MS (<math>m/z</math>)</b>	: 401 $[\text{M}+\text{Na}]^+$

**2-((2R,3R,4R)-3-(Benzyloxy)-4,5-dihydroxytetrahydrofuran-2-yl)ethyl pivalate (18)**



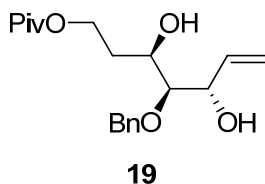
**18**

Pivaloyl protected compound **155** (2.45 g, 0.006 mol) was taken in 25 mL of 70% acetic acid solution and catalytic amount of concentrated sulfuric acid was added to it. The reaction mixture was heated at 60 °C for 6 h. Then the reaction mixture was cooled to room temperature and solid  $\text{NaHCO}_3$  was added to it portion wise until the effervescence ceased. Then the aqueous layer was extracted with ethyl acetate (3 x 75 mL) and the combined organic layer was dried over sodium sulphate and concentrated. Crude residue **156** was not purified and directly used for the next reaction.

<b>Yield</b>	: (1.2 g, 55%)
<b>Mol Formula</b>	: $\text{C}_{18}\text{H}_{26}\text{O}_6$
<b>Mol Weight</b>	: 338

$^1\text{H}$  :  $\delta$  1.18 (s, 9H), 1.94-2.03 (m, 2H), 3.85-3.88 (m, 1H),  
 (CDCl<sub>3</sub>, 200 MHz) 4.11-4.38 (m, 5H), 4.52, 4.72 (2d,  $J = 12.1$  Hz, 2H), 5.46  
 (d,  $J = 3.8$  Hz, 1H), 7.31 (br. s, 5H)

**(3R,4S,5S)-4-(Benzyloxy)-3,5-dihydroxyhept-6-enyl pivalate (19)**



Lactol **18** (1.2 g, 0.004 mol) was taken in 15 mL of dry THF and 1-carbon Wittig ylide [generated by using triphenylphosphonium iodide (14.5 g) and 1.6 (M) BuLi solution in *n*-hexane (9.7 mL) in 50 mL dry THF for 0.5 h] was added to it at 0 °C. Then the reaction mixture was stirred at 0 °C for 1 h and then warmed at room temperature and stirring was continued for further 2 h. Again the reaction mixture was cooled to 0 °C and saturated NH<sub>4</sub>Cl solution was added dropwise to quench the reaction. Aqueous layer was extracted with ethyl acetate and the combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:3) to procure colorless oil **19**.

**Yield** : 0.692 gm, 58%

**Mol Formula** : C<sub>19</sub>H<sub>28</sub>O<sub>5</sub>

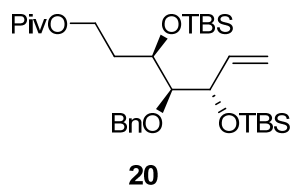
**Mol Weight** : 336

**Optical rotation**  $[\alpha]_{\text{D}}^{25}$  : +2.6 (*c* 1.45, CHCl<sub>3</sub>)

$^1\text{H}$  :  $\delta$  1.19 (s, 9H), 1.77, 1.83 (2br. d,  $J = 6.3$  Hz, 2H), 3.80  
 (CDCl<sub>3</sub>, 200 MHz) (dd,  $J = 3.8, 4.6$  Hz, 1H), 3.82 (ddd,  $J = 3.8, 6.4, 10.3$  Hz,  
 1H), 4.10-4.24 (m, 2H), 4.30-4.36 (m, 1H), 4.64, 4.78 (2d,

	$J = 11.1$ Hz, 2H), 5.23 (dt, $J = 1.5, 10.3$ Hz, 1H), 5.37 (dt, $J = 1.5, 17.2$ Hz, 1H), 5.94 (ddd, $J = 5.8, 10.3, 17.2$ Hz, 1H)
$^{13}\text{C}$ ( $\text{CDCl}_3$ , 50 MHz)	: 27.3 (q), 33.4 (t), 38.8 (s), 61.2 (t), 68.7 (d), 73.3 (d), 75.4 (t), 84.0 (d), 116.6 (t), 128.2 (d), 128.6 (d), 137.7 (s), 138.0 (d), 178.5 (s) ppm
<b>Elemental analysis Cald.</b>	: C, 67.83; H, 8.39; O, 23.78%
<b>Found</b>	: C, 67.92; H, 8.61%
<b>ESI-MS (<math>m/z</math>)</b>	: 359 $[\text{M}+\text{Na}]^+$

**(3*R*,4*S*,5*S*)-4-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)hept-6-enyl pivalate (**20**)**

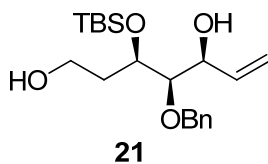


Wittig product **19** (0.69 g, 0.002 mol) was taken in 10 mL of dry DMF and imidazole (0.68 g, 0.01 mol) was added to it followed by TBDMS-Cl (1 g, 0.007 mol) was added and the reaction mixture was stirred for 48 h. After the formation of the di-TBS ether the reaction mixture was diluted with diethyl ether and organic layer was washed with water for several times to remove as much as DMF used in the reaction. Ether layer was dried over sodium sulphate and concentrated. Crude reaction mixture was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:19) to procure colorless oil **20** (1.53 gm). If the yield was 100% also then product should be obtained 1.16 g. From NMR spectra it was clear that sufficient amount of TBDMS-Cl was present in the system along with product and the product and TBDMS-Cl ratio is almost 1:1 so we proceeded further for the next reaction. Meanwhile, the presence of the product was further confirmed by mass spectroscopy.

**Molecular formula:** C<sub>31</sub>H<sub>56</sub>O<sub>5</sub>Si<sub>2</sub>

**ESI-MS (m/z):** 588 [M+Na]<sup>+</sup>

**(3R,4R,5S)-4-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)hept-6-ene-1,5-diol (21)**



Di-TBS protected compound **20** (50 mg, 0.089 mmol) was taken in 5 mL of dry DCM and reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and 1.679 (M) DIBAL-H solution (0.32 mL) in toluene was added to the reaction mixture dropwise. After 5 mins the reaction mixture was quenched with few drops of MeOH and then the reaction mixture was warmed to  $0\text{ }^{\circ}\text{C}$  and saturated solution of Na-K tartarate was added and stirred for 1 h. Then the reaction mixture was extracted with DCM (2 x 25 mL) and the combined organic layer was dried over sodium sulphate and concentrated. Crude residue was chromatographed over silica gel using ethyl acetate in light petroleum (1:9) and (1:6) two products respectively to obtain 20 mg, 60% of pivaloyl and mono-TBS deprotected product **21** and 2 mg, 5% of only pivaloyl deprotected product **22**.

Same di-TBS protected compound **20** (50 mg, 0.089 mmol) was taken in 5 mL of dry THF and LAH (2 mg, 0.053 mmol) was added to it at  $0\text{ }^{\circ}\text{C}$ . After 15 mins the reaction was quenched with saturated solution of sodium sulphate and stirred for 2 h. Then the solid residue was filtered off and the filtrate was dried over sodium sulphate and concentrated. Crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:6) to obtain colorless liquid 17 mg, 52% of pivaloyl and mono-TBS deprotected compound **21** exclusively.

**Yield** : 20 mg, 60% in DIBAL-H reaction, 17 mg, 52% in LAH reaction

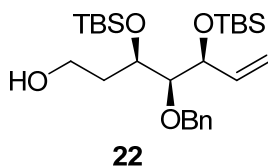
**Mol Formula** : C<sub>20</sub>H<sub>34</sub>O<sub>4</sub>Si

**Mol Weight** : 367

**<sup>1</sup>H** :  $\delta$  0.02 (s, 3H), 0.03 (s, 3H), 0.89 (s, 9H), 1.63-1.87 (m, (CDCl<sub>3</sub>, 200 MHz) 2H), 3.24 (t,  $J$  = 4.9 Hz, 1H), 3.76 (t,  $J$  = 5.5 Hz, 2H), 3.91 (q,  $J$  = 4.4, 8.8 Hz, 1H), 4.38 (tt,  $J$  = 1.5, 5.4 Hz, 1H), 4.61, 4.81 (2d,  $J$  = 11.5 Hz, 2H), 5.18 (dt,  $J$  = 1.7, 10.5 Hz, 1H), 5.29 (dt,  $J$  = 1.7, 17.2 Hz, 1H), 5.99 (ddd,  $J$  = 5.3, 10.5, 17.2 Hz, 1H), 7.29-7.36 (br. m, 5H)

**ESI-MS ( $m/z$ )** : 390 [M+Na]<sup>+</sup>, 406 [M+K]<sup>+</sup>

**(3*R*,4*S*,5*S*)-4-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)hept-6-en-1-ol (**20**)**



Di-TBS protected compound **20** (700 mg, 1.24 mmol) was taken in moist EtOH (10 mL) and LiOH.H<sub>2</sub>O (156 mg, 0.006 mol) was added to it. Then the reaction mixture was heated at 40 °C for 2 h and cooled to room temperature. Then the EtOH was removed as much as possible in rota vapour and the residue was diluted with water and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and concentrated. Crude residue was purified by column chromatography over silica gel using ethyl acetate in light petroleum (1:9) to obtain colorless oil **22** and 136 mg of starting material **20** was recovered.

**Yield** : 312 mg, 65% (with respect to starting materials recovered)

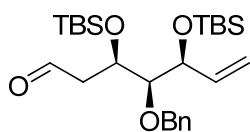
**Mol Formula** : C<sub>26</sub>H<sub>48</sub>O<sub>4</sub>Si<sub>2</sub>

**Mol Weight** : 481

**Optical rotation** [ $\alpha$ ]<sub>D</sub><sup>25</sup> : -5.9 ( $c$  .65, CHCl<sub>3</sub>)

$^1\text{H}$	:	$\delta$ -0.06 (s, 3H), -0.01 (s, 3H), 0.00 (2s, 6H), 0.86 (s, 9H),
(CDCl <sub>3</sub> , 200 MHz)		0.89 (s, 9H), 1.77 (ddd, $J$ = 5.1, 9.5, 14.3 Hz, 1H), 1.96 (ddd, $J$ = 5.2, 9.5, 14.3 Hz, 1H), 3.34 (d, $J$ = 5.8 Hz, 1H), 3.66-3.71 (m, 1H), 3.74-3.80 (m, 1H), 3.89 (dd, $J$ = 5.5, 11.6 Hz, 1H), 4.11 (dd, $J$ = 7.0, 14.3 Hz, 1H), 4.34 (t, $J$ = 5.3 Hz, 1H), 4.66, 4.70 (2d, $J$ = 12.0 Hz, 2H), 5.09 (dt, $J$ = 1.7, 10.3 Hz, 1H), 5.23 (dt, $J$ = 1.7, 17.2 Hz, 1H), 5.99 (ddd, $J$ = 5.3, 10.3, 17.2 Hz, 1H), 7.26-7.34 (m, 5H)
$^{13}\text{C}$	:	-4.9 (q), -4.8 (q), -4.6 (q), -4.4 (q), 18.0 (s), 18.2 (s),
(CDCl <sub>3</sub> , 50 MHz)		25.89 (q), 25.92 (q), 35.0 (t), 60.4 (t), 72.1 (d), 73.7 (d), 74.2 (t), 84.3 (d), 114.8 (t), 127.5 (d), 127.7 (d), 128.3 (d), 137.9 (d), 138.7 (s) ppm
<b>Elemental analysis Cald.</b>	:	C, 64.95; H, 10.06; O, 13.31; Si, 11.68%
<b>Found</b>	:	C, 64.89; H, 9.83%
<b>ESI-MS (<math>m/z</math>)</b>	:	504 [M+Na] <sup>+</sup>

**(3*R*,4*S*,5*S*)-4-(Benzyloxy)-3,5-bis(tert-butyldimethylsilyloxy)hept-6-enal (23)**



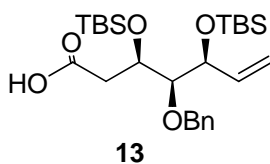
**23**

Alcohol compound **22** (300 mg, 0.624 mmol) was taken in 6 mL dry DMSO and IBX (436 mg, 1.87 mmol) was added to it, then the reaction was stirred at room temperature for 3 h and then saturated solution of NaHCO<sub>3</sub> was added to the reaction mixture. Reaction mixture was filtered off and filtrate was extracted with diethyl ether. Ether layer was washed with water for several times and organic layer was dried over

sodium sulphate and concentrated. Crude residue **23** was directly used for the next reaction.

<b>Yield</b>	: 194 mg, 65%
<b>Mol Formula</b>	: C <sub>26</sub> H <sub>46</sub> O <sub>4</sub> Si <sub>2</sub>
<b>Mol Weight</b>	: 479
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ 0.00, 0.01 (2s, 12H), 0.86 (s, 9H), 0.89 (s, 9H), 2.60 (ddd, <i>J</i> = 2.6, 6.0, 16.4 Hz, 1H), 2.77 (ddd, <i>J</i> = 2.1, 4.9, 16.4 Hz, 1H), 3.35 (dd, <i>J</i> = 4.9, 6.2 Hz, 1H), 4.20 (dd, <i>J</i> = 6.0, 11.1 Hz, 1H), 4.39 (t, <i>J</i> = 4.9 Hz, 1H), 4.65, 4.72 (2d, <i>J</i> = 12.0 Hz, 2H), 5.16 (dt, <i>J</i> = 1.6, 10.5 Hz, 1H), 5.27 (dt, <i>J</i> = 1.6, 17.2 Hz, 1H), 6.03 (ddd, <i>J</i> = 5.2, 10.5, 17.2 Hz, 1H), 7.34 (br. s, 5H), 9.74 (t, <i>J</i> = 2.2 Hz, 1H)
<b>ESI-MS (<i>m/z</i>)</b>	: 502 [M+Na] <sup>+</sup>

**(3*R*,4*S*,5*S*)-4-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)hept-6-enoic acid (**13**)**

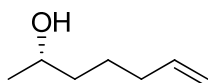


Crude aldehyde **23** (194 mg, 0.41 mmol) was taken in 10 mL of 1:1 DMSO-H<sub>2</sub>O mixture solvent, and NaH<sub>2</sub>PO<sub>4</sub> (10 mg, 0.08 mmol) was added to it. 80% NaClO<sub>2</sub> (39 mg, 0.53 mmol) was dissolved in 5 mL of water and that solution was added to the reaction mixture dropwise at 0 °C. After 0.5 h of stirring, the reaction mixture was warmed to room temperature and again stirred for 6 h, and then the reaction mixture was extracted with DCM. Water layer was acidified with very dilute HCl and again extracted with DCM thoroughly (3 x 50 mL). The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude residue was purified by column



chromatography over silica gel using ethyl acetate in light petroleum (1:9) to obtain colorless oil **13**.

<b>Yield</b>	:	110 mg, 55%
<b>Mol Formula</b>	:	C <sub>26</sub> H <sub>46</sub> O <sub>5</sub> Si <sub>2</sub>
<b>Mol Weight</b>	:	497
<b>Optical rotation</b> $[\alpha]_D^{25}$	:	-12.2 (c 0.6, (CHCl <sub>3</sub> ))
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	:	$\delta$ -0.02, 0.00, 0.01, 0.02 (4s, 12H), 0.85 (s, 9H), 0.88 (s, 9H), 2.57 (dd, $J = 6.1, 15.9$ Hz, 1H), 2.80 (dd, $J = 4.6, 15.9$ Hz, 1H), 3.31 (dd, $J = 4.6, 6.5$ Hz, 1H), 4.15 (dd, $J = 6.3, 11.1$ Hz, 1H), 4.36 (t, $J = 5.0$ Hz, 1H), 4.67 (s, 2H), 5.13 (dt, $J = 1.6, 10.5$ Hz, 1H), 5.25 (dt, $J = 1.6, 17.2$ Hz, 1H), 5.99 (ddd, $J = 5.3, 10.5, 17.2$ Hz, 1H), 7.26-7.33 (m, 5H)
<b><sup>13</sup>C</b> (CDCl <sub>3</sub> , 50 MHz)	:	-5.00 (q), -4.8 (q), -4.6 (q), -4.4 (q), 18.0 (s), 18.2 (s), 25.8 (q), 25.9 (q), 38.3 (t), 69.6 (d), 73.2 (d), 73.9 (t), 83.9 (d), 115.4 (t), 127.6 (d), 127.7 (d), 128.3 (d), 137.7 (d), 138.4 (s), 175.5 (s) ppm
<b>Elemental analysis Cald.</b>	:	C, 63.11; H, 9.37; O, 16.17; Si, 11.35%
<b>Found</b>	:	C, 62.89; H, 9.42%
<b>ESI-MS (<math>m/z</math>)</b>	:	518 [M+Na] <sup>+</sup>

**(S)-Hept-6-en-2-ol (14)****14**

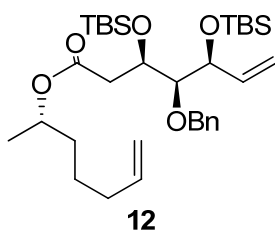
At 0 °C butenyl bromide (5.5 mL, 0.055 mol) was added to a suspension of Mg (1.31 g, 0.055 mol) in 5 mL dry THF dropwise. Then the reaction mixture was warmed to room temperature slowly and kept with stirring for 1 h. In another RB flask a suspension of CuI (0.63 gm, 30 mol%) in THF (5 mL) was taken and the previously generated Grignard reagent was added to it at –40 °C and stirred for 0.5 h. Then *R*-epichlorohydrin (1 g, 0.011 mol) was added slowly to the organocuprate reagent generated *in situ*. The complete reaction mixture was stirred for 2 h at –40 °C and then quenched with saturated solution of NH<sub>4</sub>Cl. Then the solid mass was filtered off and the filtrate was extracted with ethyl acetate and dried over sodium sulphate. Dried organic layer was concentrated under vacuum and the crude chlorohydrin compound **24** (1.03 g, 64%) was directly used for the next reaction.

Crude chlorohydrin product **24** (1.03 g, 0.007 mol) was taken in 10 mL of dry THF and at 0 °C LAH (1.064 g, 0.028 mol) was added to the reaction mixture portionwise. Then the reaction mixture was warmed to room temperature and then refluxed for 6 h. After completion of the reaction, reaction mixture was cooled to room temperature and quenched with saturated solution of sodium sulphate. Solid mass was filtered off and the filtrate was dried over sodium sulphate and concentrated under reduced pressure at low temperature and the crude residue was purified over silica gel using ethyl acetate in light petroleum (1:1) to obtain reddish yellow liquid **14**.

<b>Yield</b>	:	451 mg, 57%
<b>Mol Formula</b>	:	C <sub>7</sub> H <sub>14</sub> O
<b>Mol Weight</b>	:	114
<b>Optical rotation</b> $[\alpha]_D^{25}$	:	Calculated: +10.07 ( <i>c</i> 2, MeOH); Reported: +10.4 ( <i>c</i> 0.79, CHCl <sub>3</sub> )

<b>IR</b> $\nu_{\sim}$	:	3351, 2966, 2931, 2868, 1641, 1455, 1376, 1320, 1123
<b><math>^1\text{H}</math></b> ( $\text{CDCl}_3$ , 200 MHz)	:	$\delta$ 1.11 (d, $J = 6.2$ Hz, 3H), 1.31-1.45 (m, 4H), 1.68 (br. s, 1H), 1.95-2.05 (m, 2H), 3.68-3.77 (m, 1H), 4.84-4.99 (2 merged dt, 2H), 5.72 (ddd, $J = 6.7, 10.2, 17.1$ Hz, 1H)
<b><math>^{13}\text{C}</math></b> ( $\text{CDCl}_3$ , 50 MHz)	:	23.6 (q), 25.0 (t), 33.7 (t), 38.8 (t), 67.9 (d), 114.7 (t), 138.6 (d) ppm
<b>Elemental analysis Cald.</b>	:	C, 73.63; H, 12.36; O, 14.01%
<b>Found</b>	:	C, 73.51; H, 12.42%
<b>ESI-MS</b> ( $m/z$ )	:	115 $[\text{M}+\text{H}]^+$ , 137 $[\text{M}+\text{Na}]^+$

**(3R,4S,5S)-((S)-Hept-6-en-2-yl)4-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)hept-6-enoate (**12**)**

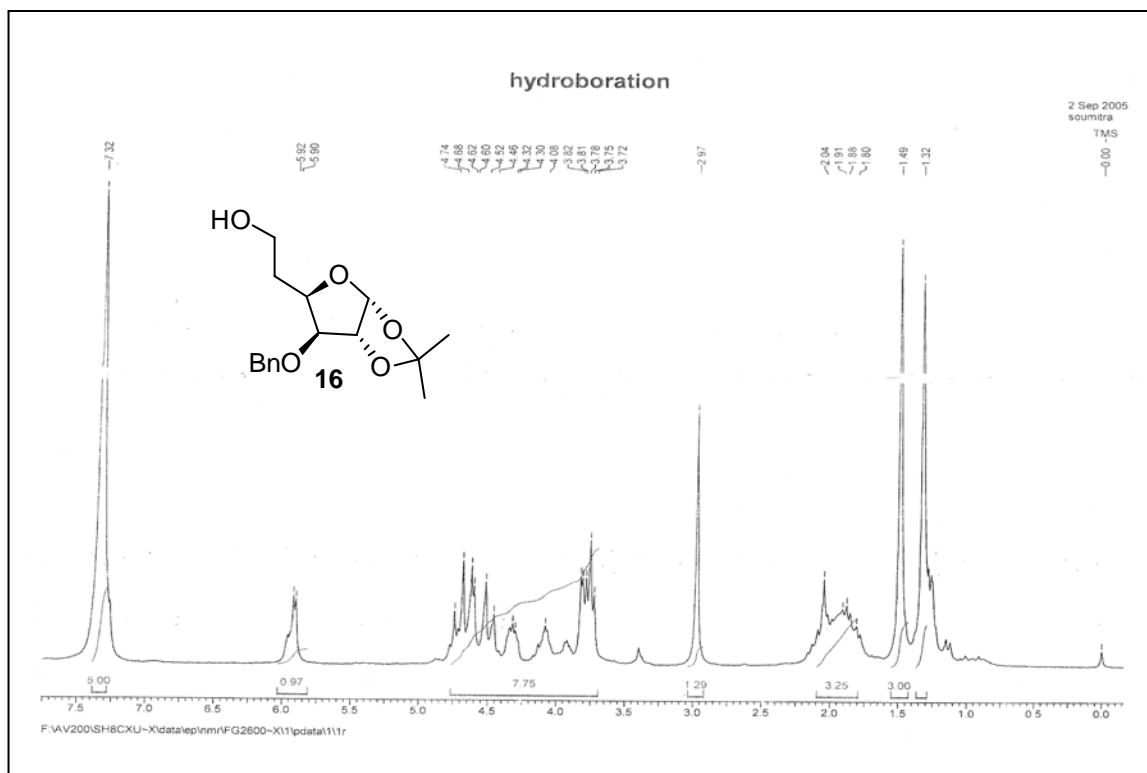
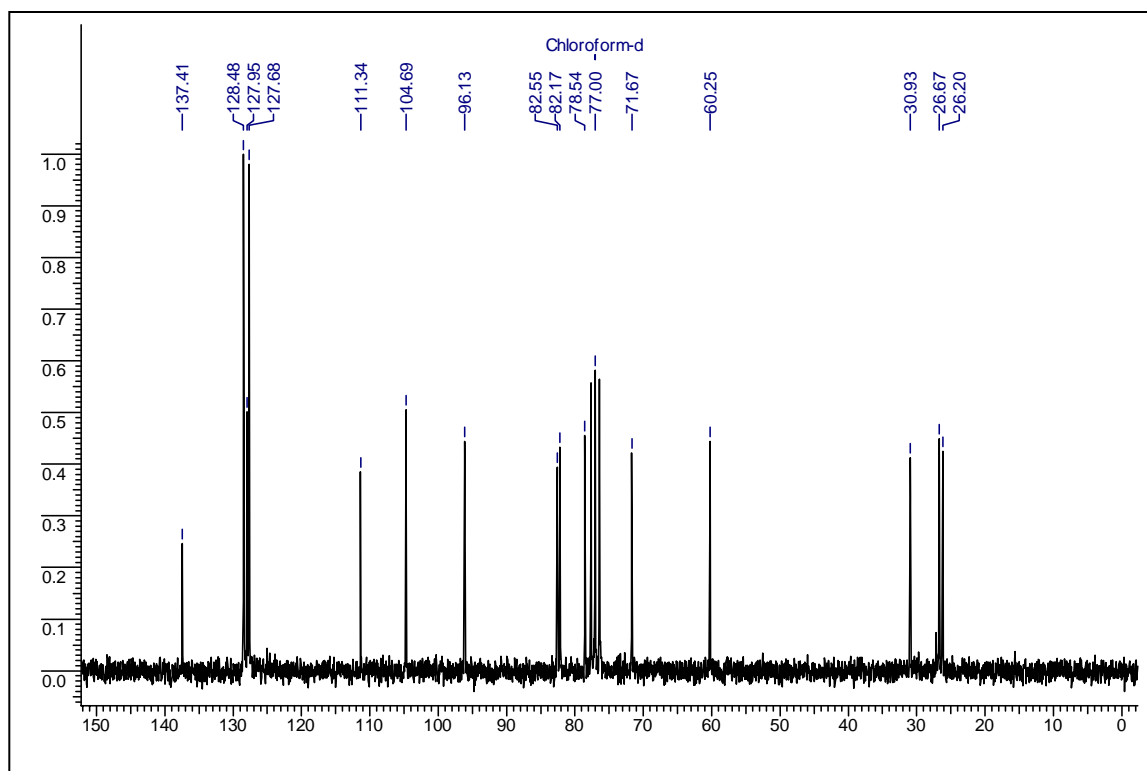


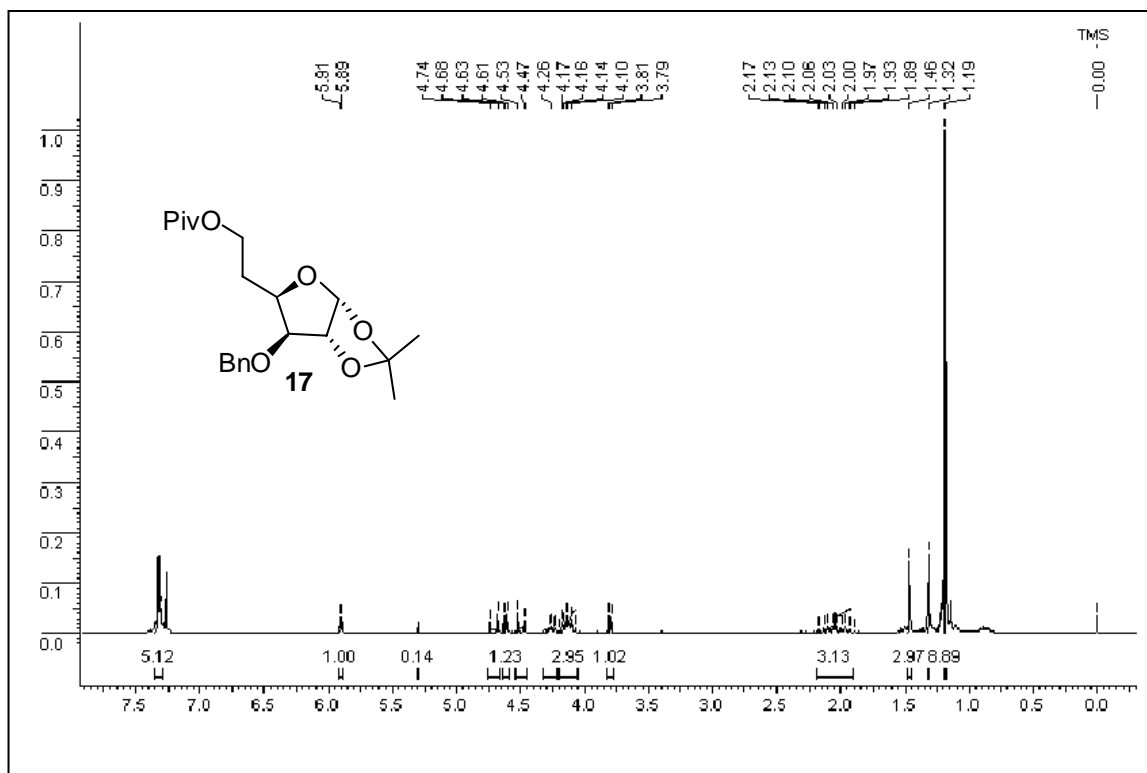
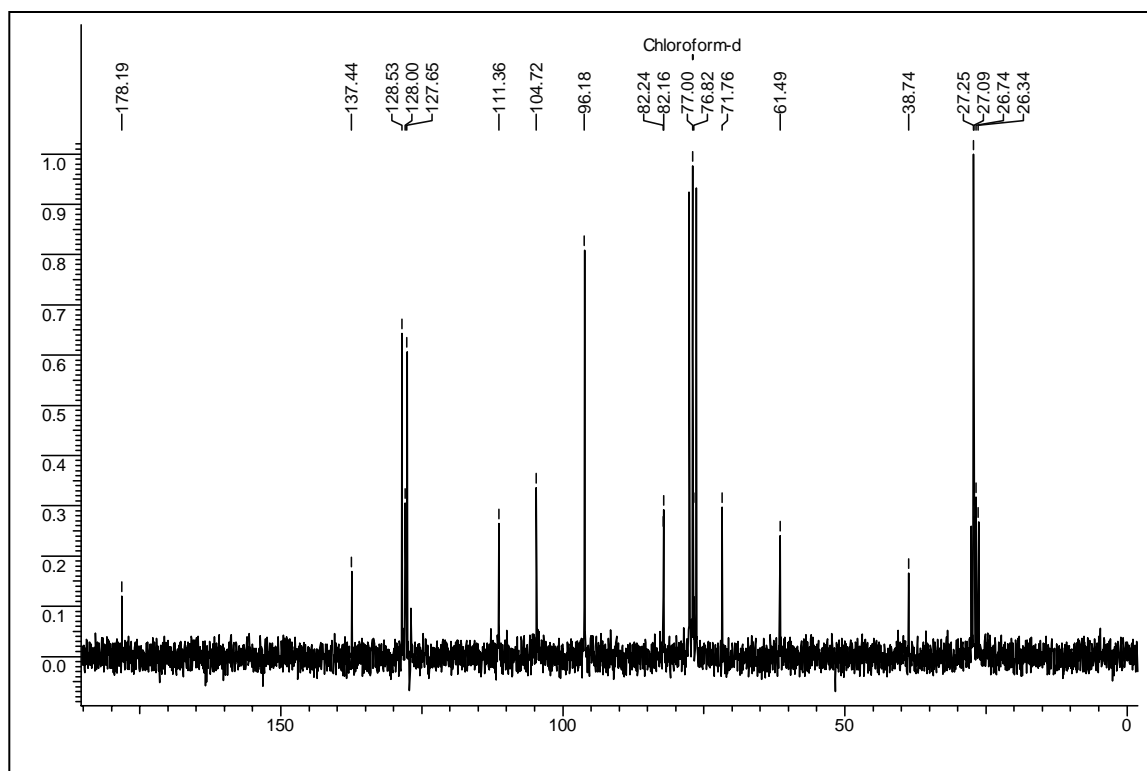
Acid **13** (100 mg, 0.202 mmol) was taken in dry DCM (2 mL) and triethylamine (0.04 mL, 0.263 mmol) was added to it followed by Yamaguchi reagent (0.04 mL, 0.222 mmol) and stirred for 2 h at room temperature. Then a mixture of alcohol **14** (23 mg, 0.202 mmol) and catalytic amount of DMAP in 0.5 mL dry DCM solution was added to the mixed acid anhydride and stirred again at room temperature for 12 h. The complete reaction mixture was diluted with DCM and quenched with saturated solution of  $\text{NaHCO}_3$ . Organic layer was separated and the aqueous layer was extracted with DCM and combined organic layer was dried over sodium sulphate and concentrated. Crude residue was purified by flash column chromatography over silica gel using ethyl acetate in light petroleum (1:19) to obtain colorless oil **12**.

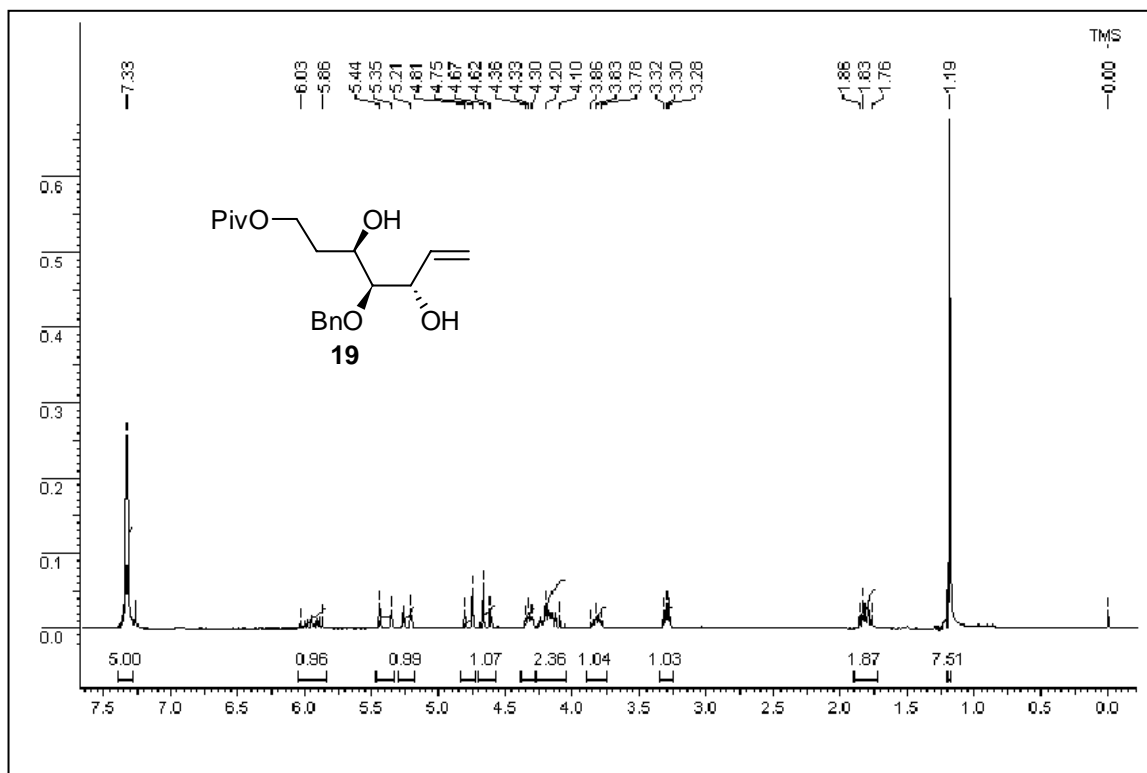
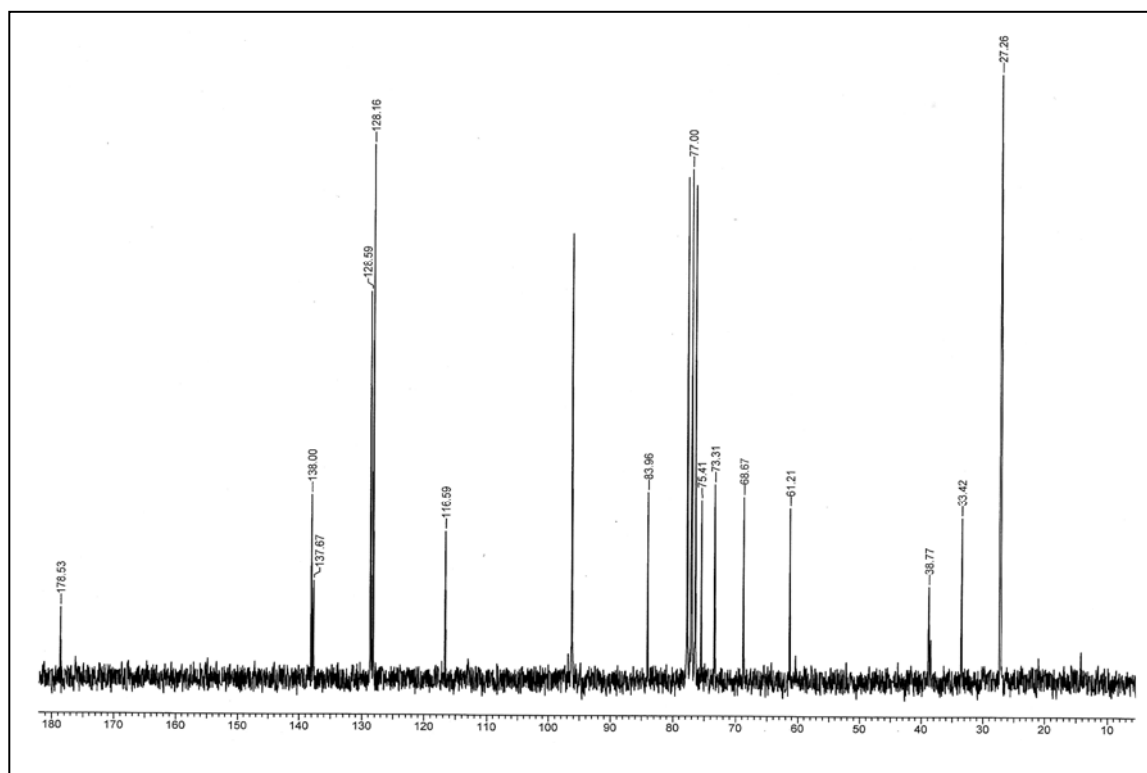
<b>Yield</b>	: 81 mg, 67%
<b>Mol Formula</b>	: C <sub>33</sub> H <sub>58</sub> O <sub>5</sub> Si <sub>2</sub>
<b>Mol Weight</b>	: 591
<b><sup>1</sup>H</b> (CDCl <sub>3</sub> , 200 MHz)	: δ -0.04, -0.02, 0.00, 0.01 (4s, 12H), 0.83 (s, 9H), 0.89 (s, 9H), 1.18 (d, <i>J</i> = 6.3 Hz, 3H), 1.40-1.56 (m, 4H), 2.0-2.08 (m, 2H), 2.46 (dd, <i>J</i> = 7.1, 15.8 Hz, 1H), 2.76 (dd, <i>J</i> = 4.4, 15.8 Hz, 1H), 3.30 (t, <i>J</i> = 5.4 Hz, 1H), 4.19-4.25 (m, 1H), 4.34 (t, <i>J</i> = 5.4 Hz, 1H), 4.61, 4.70 (2d, <i>J</i> = 12.0 Hz, 2H), 4.80-4.87 (m, 1H), 4.87-5.04 (2dt merged, 2H), 5.09 (dt, <i>J</i> = 1.6, 10.5 Hz, 1H), 5.22 (dt, <i>J</i> = 1.6, 17.2 Hz, 1H), 5.75 (ddd, <i>J</i> = 6.8, 10.3, 17.1 Hz, 1H), 5.98 (ddd, <i>J</i> = 5.8, 10.5, 17.2 Hz, 1H), 7.28-7.33 (m, 5H)
<b>ESI-MS (<i>m/z</i>)</b>	: 614 [M+Na] <sup>+</sup>

## SPECTROSCOPIC DATA

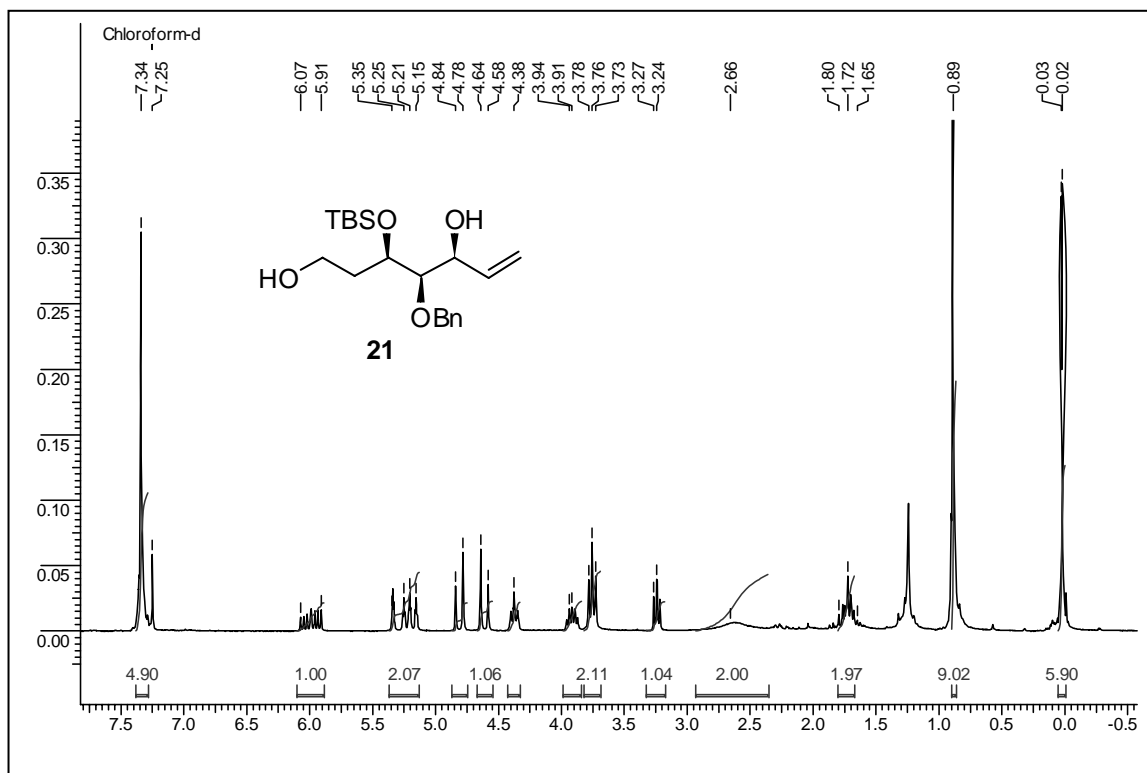
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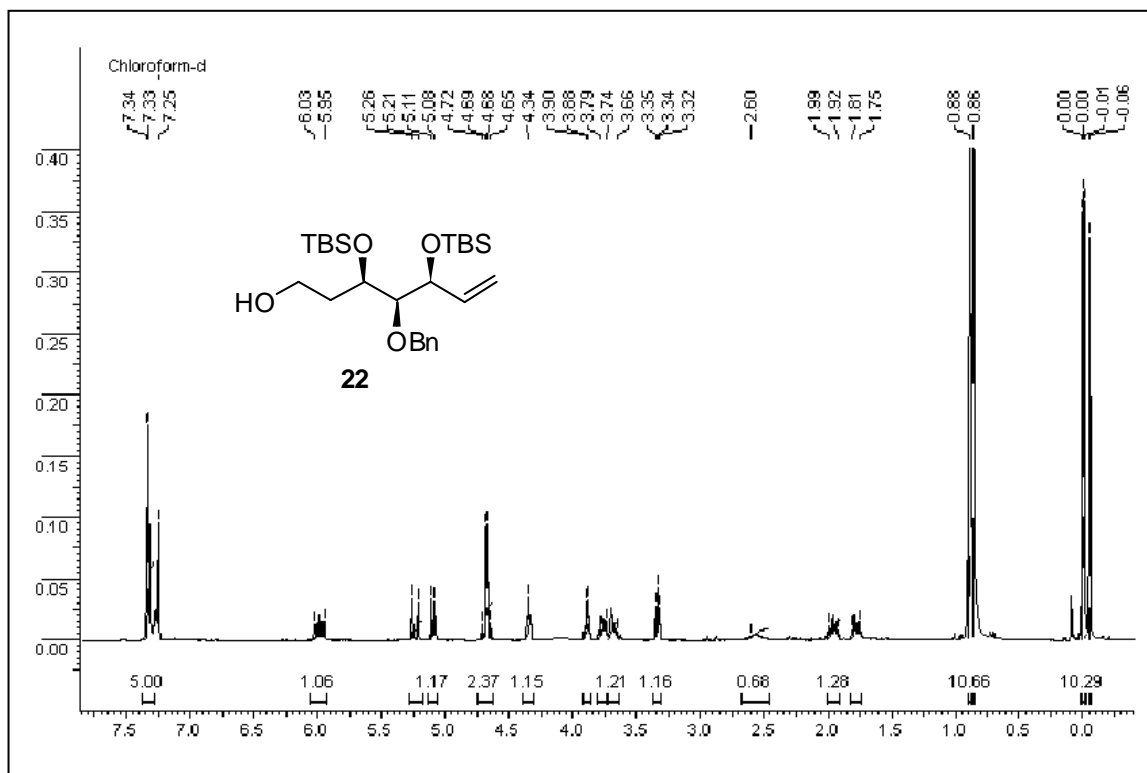
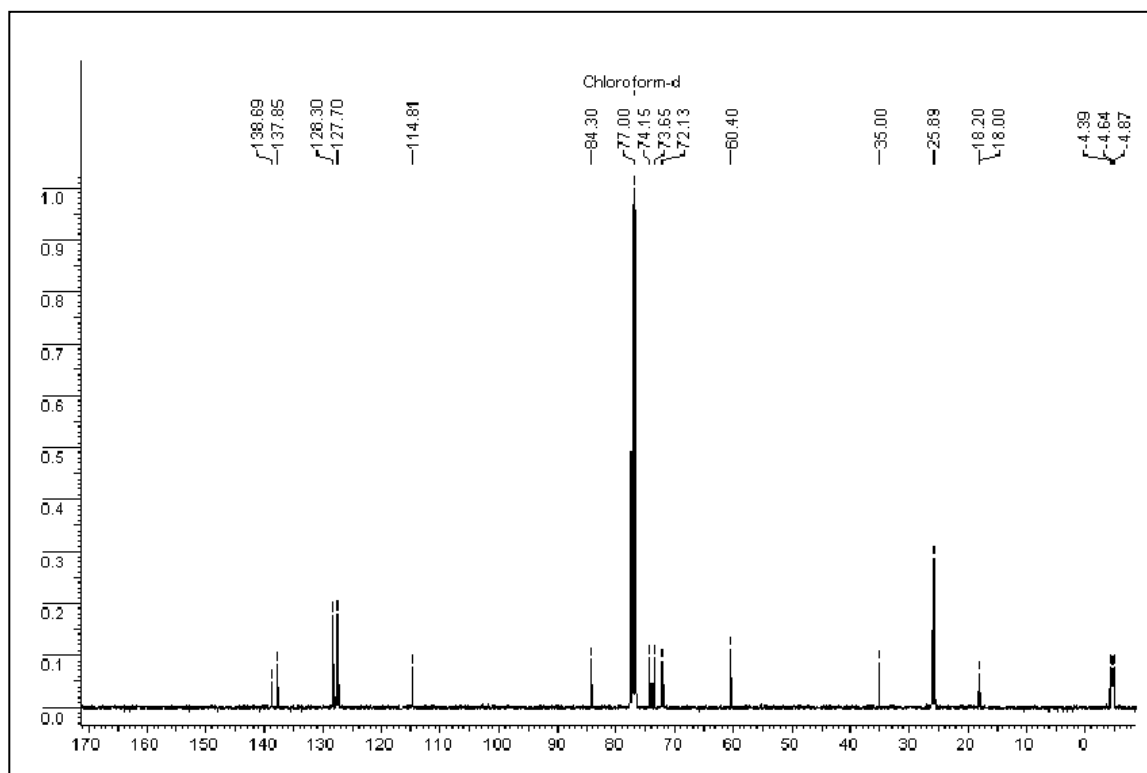
**$^1\text{H}$  NMR spectra of compound 16** **$^{13}\text{C}$  NMR spectra of compound 16**

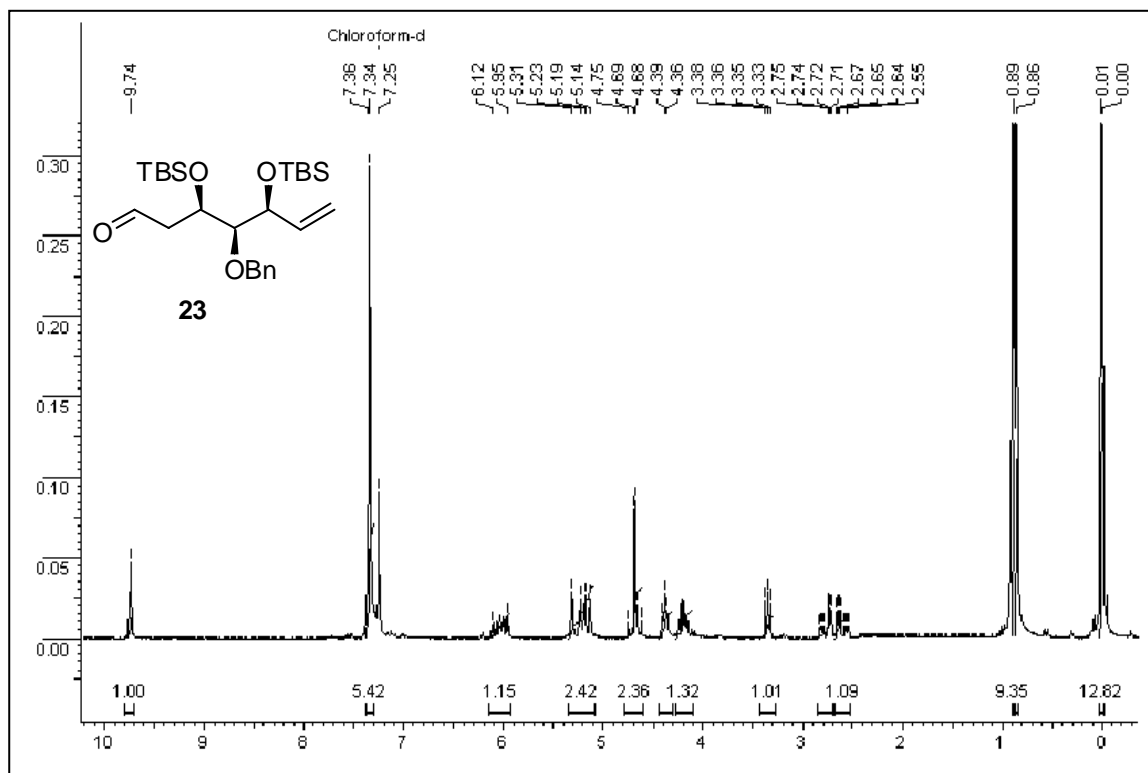
**$^1\text{H}$  NMR spectra of compound 17** **$^{13}\text{C}$  NMR spectra of compound 17**

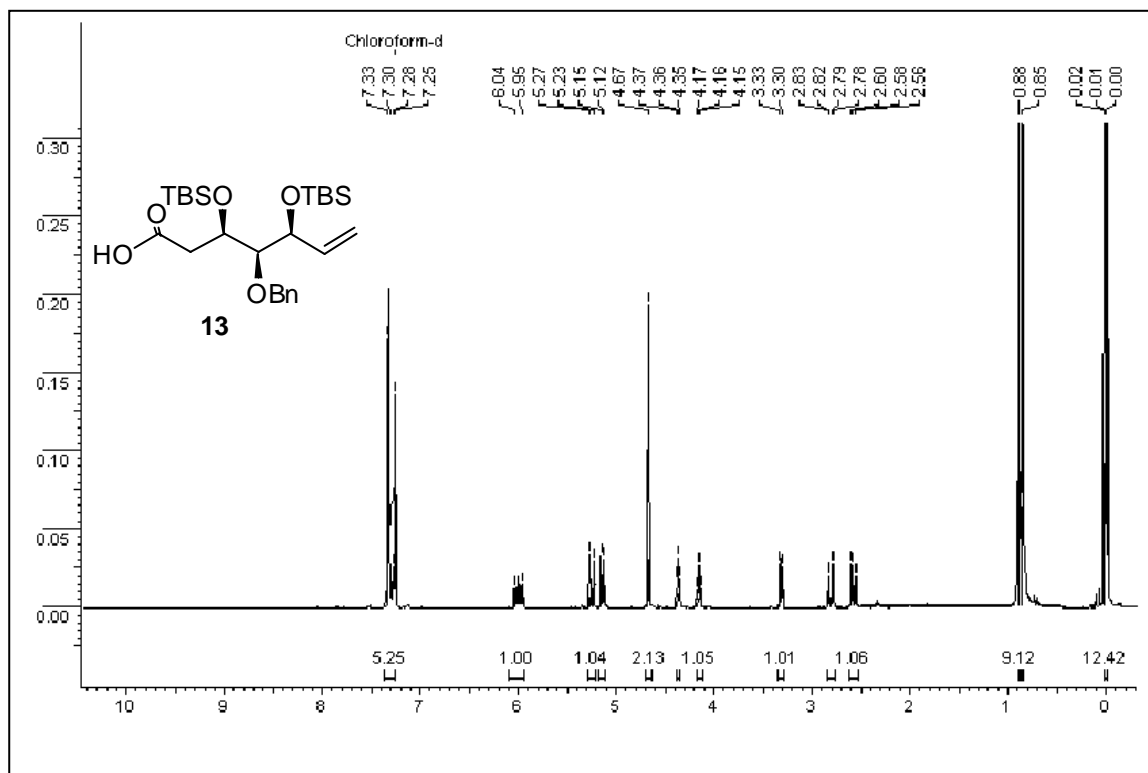
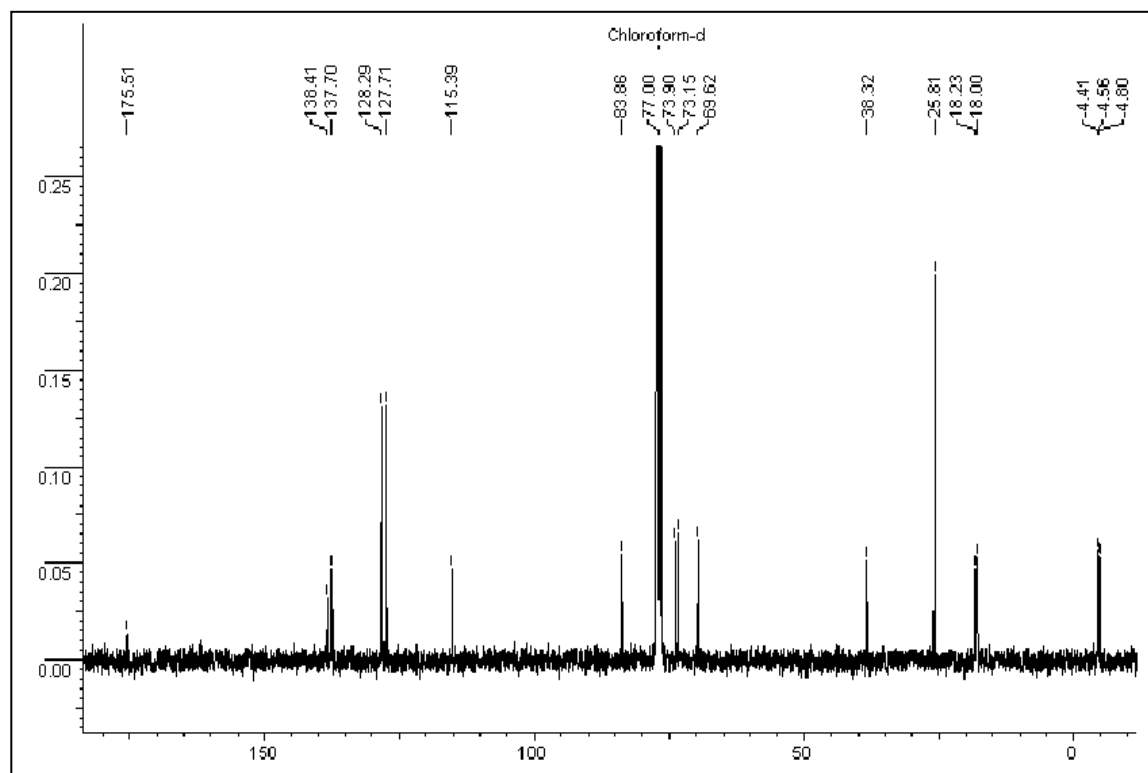
$^1\text{H}$  NMR spectra of compound 19 $^{13}\text{C}$  NMR spectra of compound 19

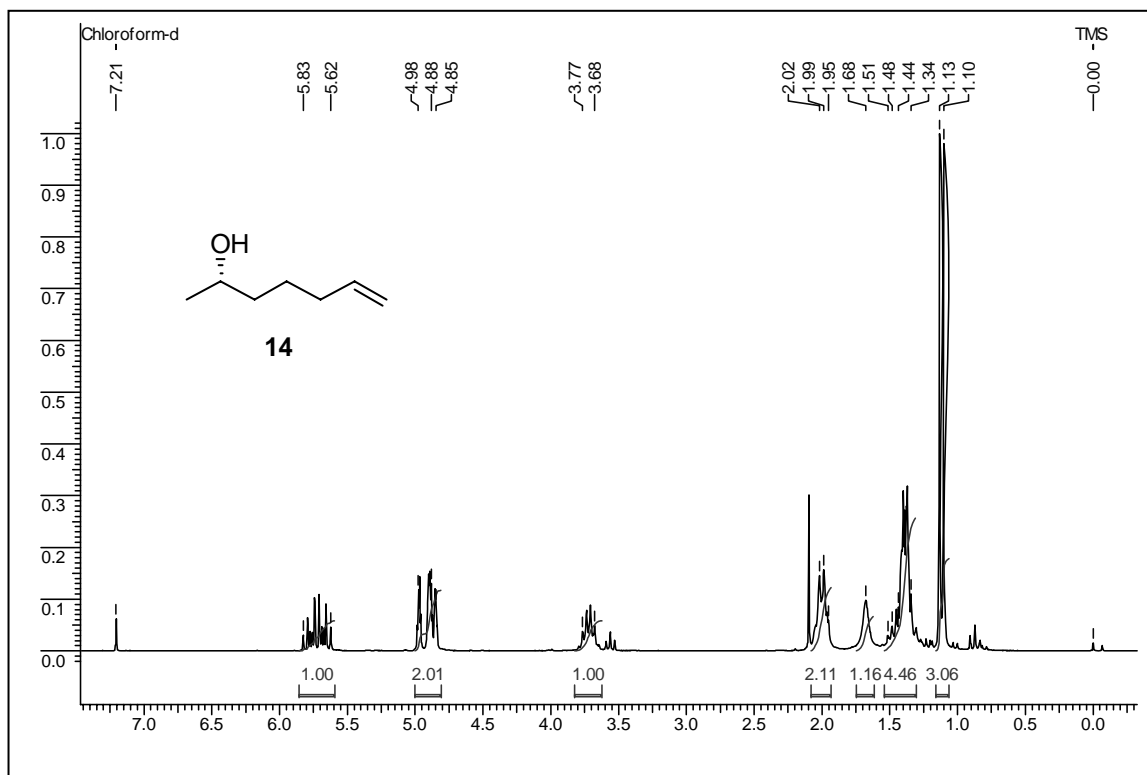
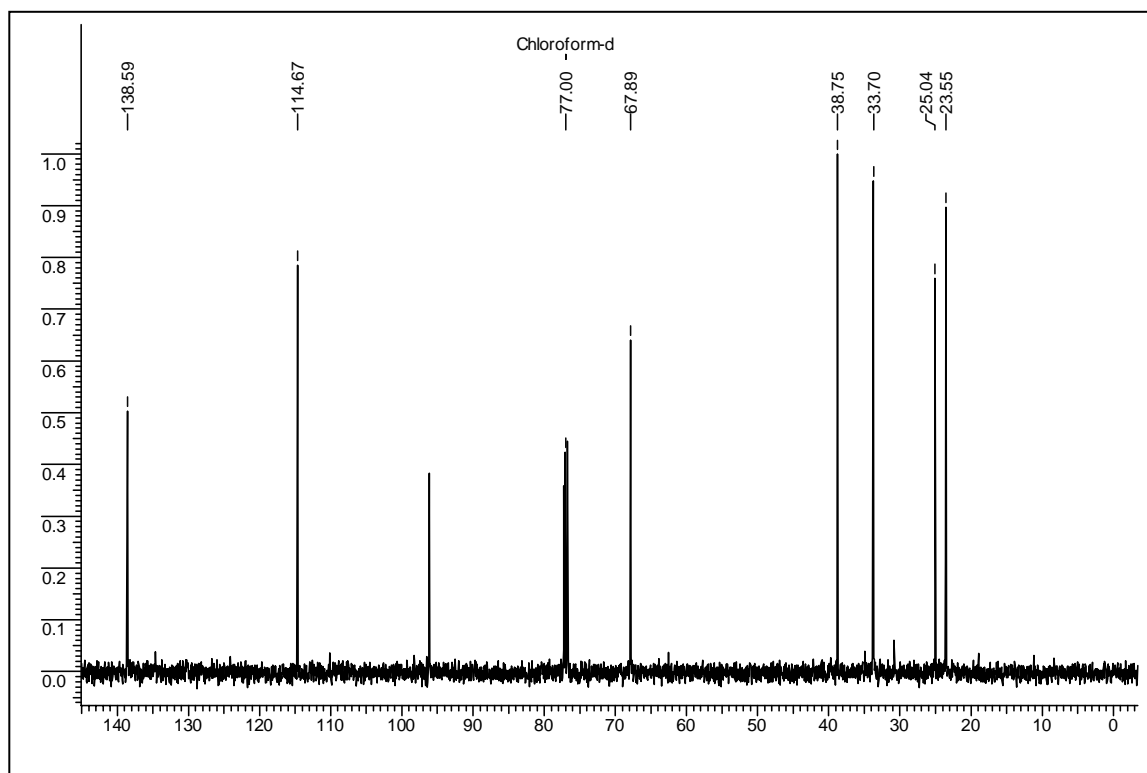


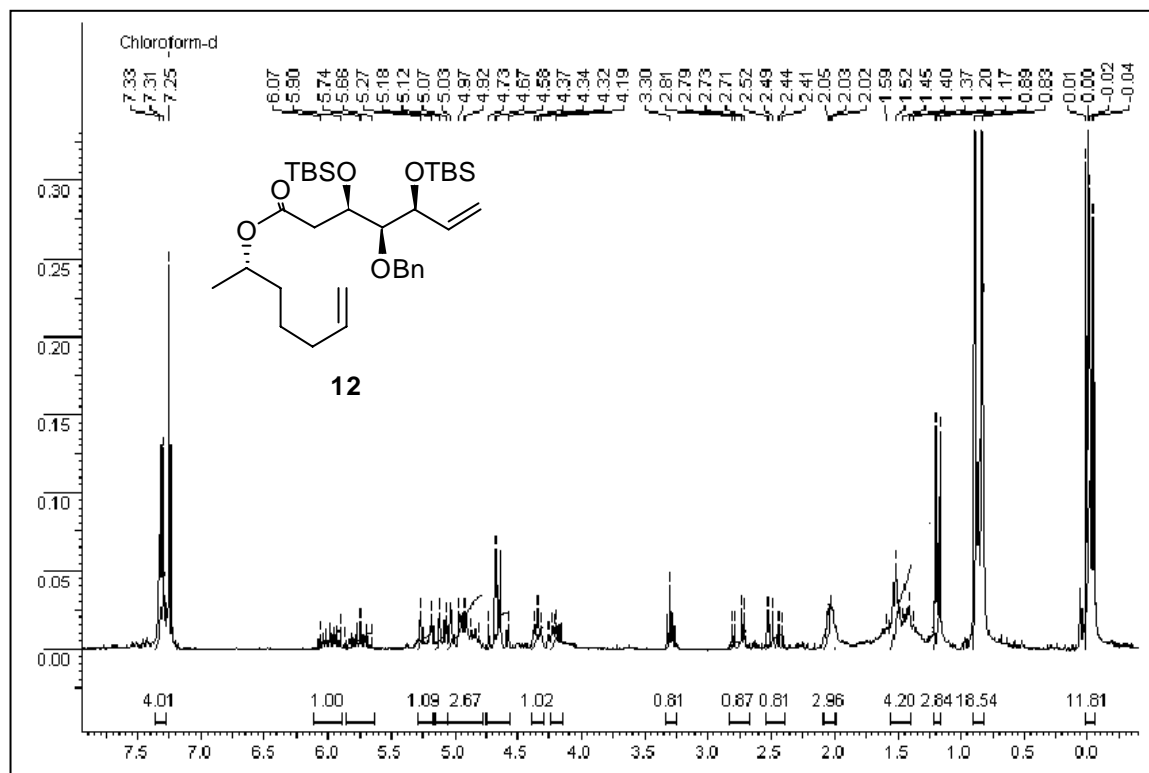
**$^1\text{H}$  NMR spectra of compound 21**

$^1\text{H}$  NMR spectra of compound 22 $^{13}\text{C}$  NMR spectra of compound 22

**$^1\text{H}$  NMR spectra of compound 23**

$^1\text{H}$  NMR spectra of 13 $^{13}\text{C}$  NMR spectra of compound 13

**$^1\text{H}$  NMR spectra of compound 14** **$^{13}\text{C}$  NMR spectra of compound 14**

**<sup>1</sup>H NMR spectra of compound 12**

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## **CHAPTER 3**

Exploration of Click Chemistry in Crystal  
Engineering

# INTRODUCTION

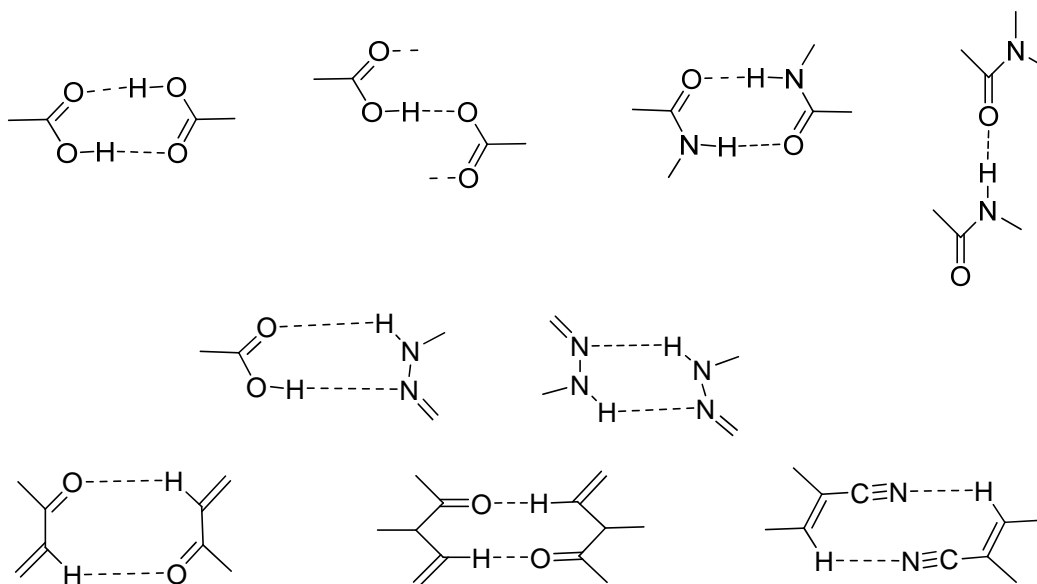


## INTRODUCTION

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The term crystal engineering can be explained as the understanding of intermolecular interactions in the context of crystal packing and in utilization of such understanding in the design of new solids with desired physical and chemical properties.<sup>1</sup> The importance of crystal engineering lies in the fact that the physical properties of a solid are dictated by the crystal packing of the compound, that is, how the modular components of a compound are oriented with respect to each other in three dimensions. To generate a stable, three-dimensional, predictable architecture, control of the assembly process is crucial and will only be realized by careful choice of suitable intermolecular ‘connectors’, as intermolecular interactions constitute the supramolecular ‘glue’.

While applying crystal engineering into organic synthesis, different strategies will come into consideration where the molecules aggregate to form an assembly. In this aggregation some intermolecular linkers play a major role. In crystal engineering studies these linkers are named as *supramolecular synthons*. The term *synthon* has been used in organic chemistry for many years. Corey’s original definition of a *synthon* is “structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operation.”<sup>2</sup> The concept of *synthon* revolutionized organic synthesis as it is the basis of retrosynthetic analysis whereby some target molecule is broken down into successively simpler fragments until suitable starting materials are found. The *synthon* defines the connectivity between two fragments. Desiraju has applied this ‘disconnection approach’ to supramolecular chemistry.<sup>3</sup> Any supramolecular network can be broken into nodes (molecules) and node connectors (*synthons*). If molecules are built by connecting atoms together with covalent bonds, then supramolecular assemblies (crystals) are built by connecting molecules together with intermolecular forces.

**Figure 1:** Some supramolecular synthons used to generate infinite networks

Schmidt was the first person to coin the term ‘crystal engineering’ in a study of photochemical reactions of cinnamic acid derivatives in 1964.<sup>4</sup> Since then the field has greatly expanded to include areas as diverse as coordination polymers,<sup>5</sup> shape selective catalysis,<sup>6</sup> chemical sensors,<sup>7</sup> and non-linear optics.<sup>8</sup>

Although the main concern of crystal engineering is the bond connectivity but the nature of that connection especially in organic chemistry is very important. Organic chemistry is defined in terms of covalent bonding between atoms. Supramolecular chemistry on the other hand is a relatively new scientific discipline and as such can not rely on a similar function. Like organic synthesis, supramolecular chemistry is concerned with connectivity. This connectivity, however, extended over a larger range and encompasses intermolecular forces rather than intramolecular bonds. In supramolecular chemistry, intermolecular forces link molecules together to form three-dimensional solids. Intermolecular forces comprise a number of different interactions including hydrogen bonds, van der waals forces, dipole-dipole interactions and hydrophobic forces.

The fundamental objective of crystal engineering is to design organic solids that can find applications in material chemistry.<sup>9</sup> This needs to integrate our understanding about the interactions of various types and strengths that glue the molecules in the crystal structures, recognition events of complimentary functional groups, geometrical and topological constraints for intermolecular connectivity.<sup>10</sup> In this context identifying the



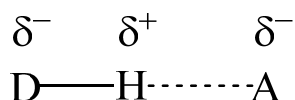
interaction patterns<sup>11</sup> of supramolecular synthons<sup>12</sup> and understanding how these operate/exist across a set of related molecules that yield a set of related crystal structures are critical exercises to ensure three-dimensional structure control in molecular design for crystal engineering. Molecular design by employing conventional hydrogen bonding has been extensively practiced.<sup>13</sup> However, a number of weaker and softer interactions and respective synthons have been identified. The nature of these weak interactions in crystal structures can vary from passive to supportive (structure stabilization) to one that is actually intrusive (structure destabilization).<sup>14</sup> Attempts to understand how these weak/soft interactions operate/exist across a set of related molecules has been limited to simple aromatic systems or to flexible biaryl systems containing stronger interactions too and this in general resulted with no similarities in the crystal structures of isomeric compounds.<sup>15</sup> For example, Glidewell and co-workers have examined the occurrence of I...NO<sub>2</sub> synthon employing diaryl compounds connected through a variety of polar functional groups and varying the I and NO<sub>2</sub> groups positions systematically. However, it led to the conclusion that the aggregation pattern for any one compound is not readily predictable from knowledge of the patterns in the other isomers. Apart from this, there are very few investigations that address predictability of weak synthons in isomeric compounds especially in absence of any strong non-covalent interactions.<sup>16</sup> Partly, this is because of the complexity involved in synthesizing the systems with architectural control and flexibility in the incorporation of functional groups and a deliberate suspicion about the crystallinity of the all isomers. In this context, developing simple and efficient protocols for generation of isomeric compound libraries (devoid of polar functional units) with sufficient flexibility in placing complimentary functional groups will be instrumental for crystal engineers to understand these weak non-covalent interactions, the topological constraints for intermolecular connectivity and to examine the predictability of corresponding weak synthons. To know about crystal engineering in details, all the major interactions associated with the crystal structures are to be discussed. Major interactions those affect/guide the crystal structures are divided into mainly two parts, 1) primary strong interactions 2) secondary weak interactions. It is observed that in major cases the stronger interactions guide the crystal orientation/packing but in absence of stronger interactions crystal structures are mainly guided by weaker interactions. Most interestingly, sometimes

it is also seen that in presence of stronger interactions also structural orientations are governed by the weaker interactions. So the role of all major interactions (stronger/weaker) are discussed here in brief.

### Hydrogen Bonding:

Amongst the various non-covalent interactions, hydrogen bonding is of major interest in crystal engineering. A formal definition of a hydrogen bond is difficult to express succinctly in words. For many years, hydrogen bonds were thought to obey the definition of Atkins<sup>17</sup> “a link formed by a hydrogen atom lying between two strongly electrostatic atoms such as oxygen, nitrogen, fluorine”. However, it is now widely accepted that a hydrogen atom attached to less electronegative atoms *e.g.* carbon, sulfur *etc.*, can form a hydrogen bond with a variety of less electronegative acceptors *e.g.* S, Se, Cl, Br, I,  $\pi$ . It is primarily electrostatic in nature whereby a small finite positive charge is associated with hydrogen atom. The donor and acceptor atoms have a slightly negative charge associated with them, (at least relative to the hydrogen atom).

**Figure 2:** Partial charges shown for donor and acceptor atoms in a hydrogen bond.



From the previous description of a hydrogen bond, it is evident that a great variety of donor and acceptor atoms of differing electronegativity can participate in a hydrogen bond. Therefore the strength of any one hydrogen bond can also vary greatly.

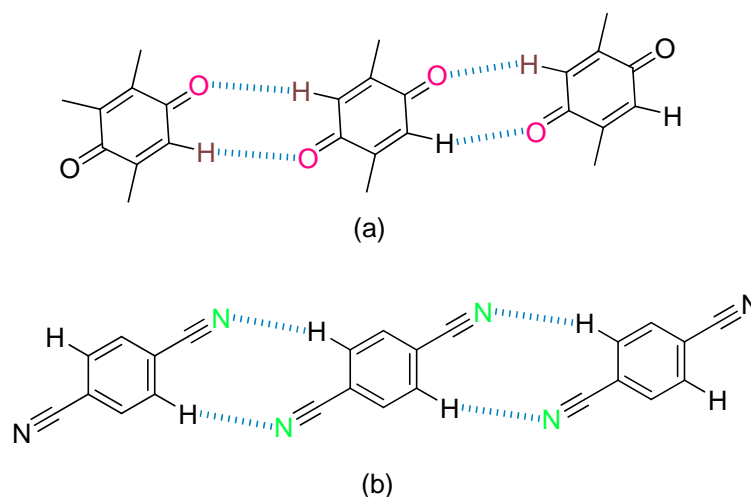
### C-H...O/N interactions:

In recent years, the weaker hydrogen bonds C-H....O, X, N (where X= F, Cl, Br, I) have been recognized as viable intermolecular forces for constructing functional solids.<sup>3</sup> Even though inherently weaker than conventional D-H....A, (where D, A= O, N, F) weaker interactions used in sufficient numbers can generate predictable architectures. In particular, C-H....O interaction has received significant attention both in terms of understanding their nature and as a directional force in crystal engineering.<sup>18</sup> Very often C-H....O interactions occur in structures where stronger hydrogen bonds also exist.

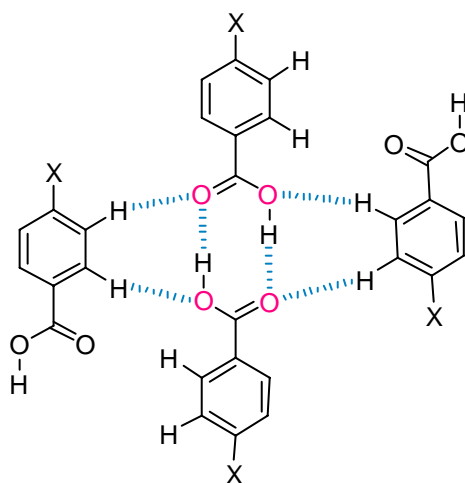
Obviously, stronger hydrogen bonds donors will compete more effectively for oxygen acceptor sites, relegating C-H...O interactions to a subservient role in architecture formation. However, there are many examples in the literature, where C-H...O interactions are primary structure forming agents.<sup>19</sup> In these cases stronger hydrogen bonds interactions are absent.

Desiraju<sup>20</sup> has recently published a comparative study of C-H...O, C-H...N, interactions involving similar hydrogen bonding patterns in the structures of 1,4-benzoquinone,<sup>21</sup> and 1,4-dicyanobenzene.<sup>22</sup> In all the structures the same one dimensional chain architectures are formed.

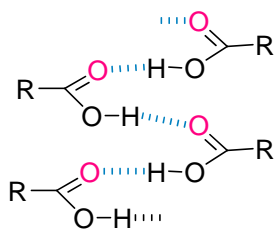
**Figure 3:** Similar hydrogen bonded patterns are formed in (a) *via* C-H...O interactions and (b) *via* C-H...N interactions.



While discussing C-H...O interactions, it must be mentioned that in carboxylic acid structures two distinct motifs are displayed. First, the common acid-acid dimer motif in which each acid group links *via* hydrogen bonds through the carboxylic acid hydrogen to the carbonyl acceptor of the adjacent acid group. Frequently when the acid has a substituent in the *para* position, the dimers link together using C-H...O interactions to generate two-dimensional sheets.<sup>23</sup>

**Figure 4:** C-H...O hydrogen bonding in *para* substituted aromatic compounds

A much less common motif is the hydrogen-bonded catamer pattern. This produces a one-dimensional chain in which each carboxylic acid unit links to two others.

**Figure 5:** Hydrogen-bonded pattern of a catamer motif

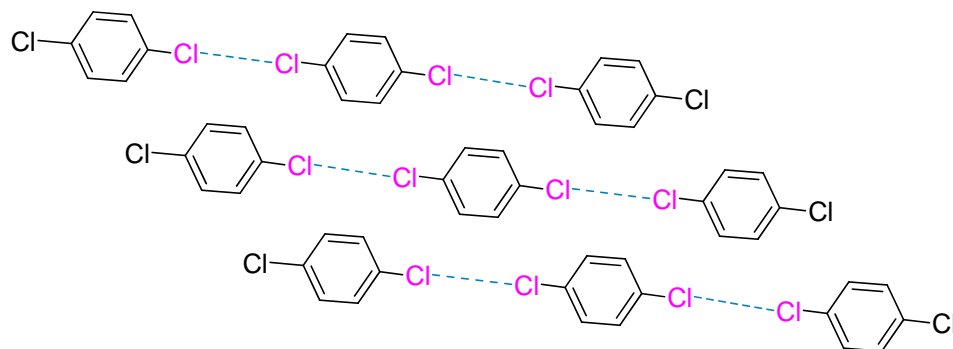
The study shows that weaker hydrogen bond interactions (C-H.....O/N) possess directionality and robustness and hence can be used as structure-directing agents. Intermolecular interactions of the type C-H...X where X=F, have also received attention in the literature<sup>24</sup> as viable forces for crystal engineering, although for, X= Cl, Br, I, some questions remain as to whether they are robust enough.

### Halogen - Halogen interactions:

Speculation and debate has surrounded X...X interactions for many years. Their strength, nature, directionality are still poorly understood with little literature being published. Research was subdivided into two areas: (a) influence of X...X on molecular hydrogen-bonded crystals and (b) influence of X...X forces on ionic hydrogen-bonded networks. Supramolecular synthon must be robust enough to form in the presence of other

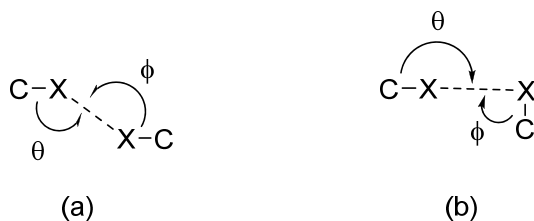
intermolecular interactions such as C-H...O, C-H...X,  $\pi$ - $\pi$ , hydrophobic forces, *etc.*, if they are to be a structural tool in crystal engineering. The nature of halogen-halogen interactions are still under controversy. Many halogen-containing molecular crystals exhibit X...X contacts (where X = Cl, Br, I) that are significantly shorter than the sum of the van der Waals radii,<sup>1</sup> ( $r_{Cl}$ =1.75 Å,  $r_{Br}$ =1.85 Å,  $r_I$ = 2.05 Å).<sup>25</sup>

**Figure 6:** Short Cl...Cl contacts seen in the structure of 1,4-dichlorobenzene



These short distances are associated with certain angular geometric preferences defined by the angles  $\theta$  and  $\phi$ .

**Figure 7:** (a) Type I contacts where  $\theta = \phi$  and (b) Type II contacts where  $\theta = 180^\circ$  and  $\phi = 90^\circ$



This observation is not new, but explanations of the nature of these contacts have only been postulated in recent years, with two different hypotheses being proposed. Using the crystallographic structure database (CSD), Desiraju *et al.*, have analyzed 794 crystal structures for short X...X contacts and found that as polarizability of the halogen atom increases, type II contacts become more significant than type I contacts.<sup>26</sup> They concluded that they are weak, attractive interactions due to induced polarization of the valence electron cloud of each atom.

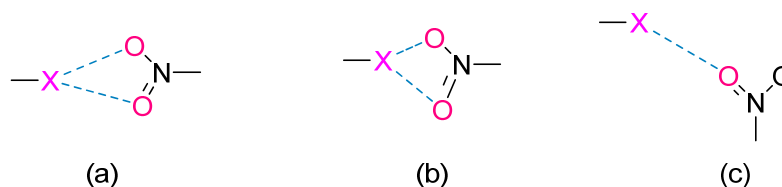
Stone *et al.*, have proposed a different model where the inherent anisotropy of halogen atoms causes them to pack together in a least repulsive manner resulting in short

X...X distances.<sup>27</sup> The debate has still not been resolved and indeed it has been noted that it is inherently difficult to distinguish between specific attractive forces *i.e.*, increased attraction and nonspherical atoms packing closely together *i.e.*, decreased repulsion.<sup>28</sup>

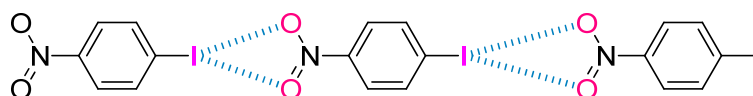
However, there is convincing evidence that short F...F contacts are unfavourable.<sup>29</sup> Theocharis *et al.*, concluded that the small van der Waals radius for fluorine (1.47 Å) coupled with its high electronegativity, has a repulsive effect and causes adjacent molecules to pack in a manner so as to maximize non-bonded F...F distances.

### **Bifurcated halogen interactions:**

This interaction is the extension of halogen-halogen interaction, the only difference here is another interacting atom which is other than halogen (mainly oxygen of nitro group). Bifurcated halogen bonds have attracted a great deal of interest in recent years because these weak three-center interactions play a crucial structural role in crystal architecture. Desiraju and co-workers first described the identification of the I...O mediated, iodo...nitro supramolecular synthon and its use in retrosynthetically guided supramolecular synthesis as well as in the design of organic crystals with the property of second harmonic generation (SHG).<sup>3,30</sup> Allen *et al.*, examined the geometrical preferences of X(Cl, Br, I)...O(nitro) synthons and concluded that the C-X...O angles prone to linearity as the X...O shortens.<sup>31</sup> More recently Nangia and co-workers have reported that these soft and weak three-center interactions can be regarded as a 'discriminator synthon' even in the presence of strong N-H...O hydrogen bonds.<sup>32</sup> These X...O<sub>2</sub>N contacts are of three types: a bifurcated contact where both the distances are equal ( $D_1 \approx D_2$ ), a more unsymmetrical contact where  $D_1 > D_2$  and finally a contact where only one of the two nitro group O-atoms makes a contact with atom X. Generally the proportion of the first case decreases as one proceeds from Cl→Br→I. These trends have been generally noted in subsequent studies.

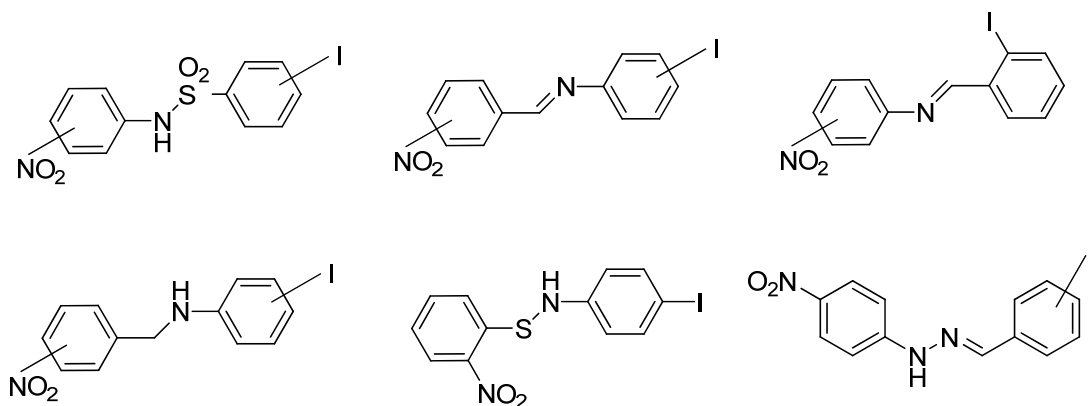
**Figure 8:** Three types of halo...nitro interactions

Out of many other types of chain patterns, infinite ribbons are formed using the I...O<sub>2</sub>N synthon when 4-iodonitrobenzene crystallizes.

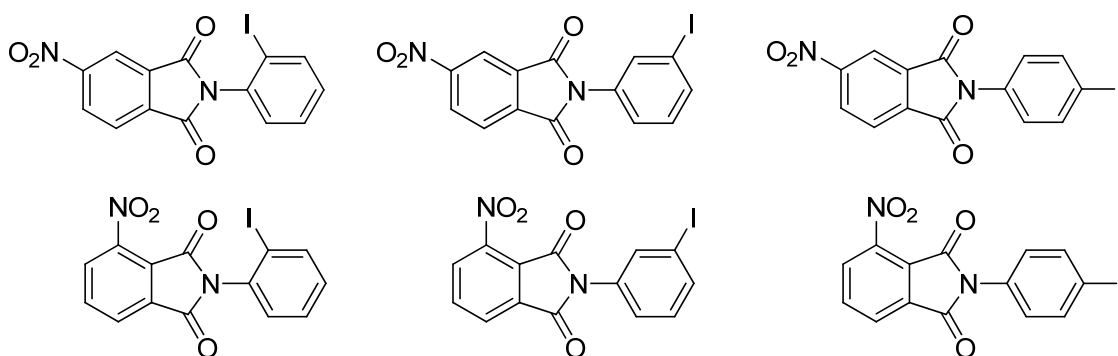
**Figure 9:** Infinite chains of 4-iodonitrobenzene

The bifurcated halo...nitro synthon, especially the iodo...nitro interaction has been a topic of extensive research in the recent years. Several groups have designated it as a robust synthon and as a predictable interaction that can be extended in the crystal engineering. However, on several occasions, the predictability correlate the interaction patterns intermolecularly between a series of compounds where the nitro-substituted aromatic ring is connected with a halo substituted aromatic ring through a suitable linker. But serious problems often arise in that no correspondence in molecular and crystal structure is easily perceived. This happens for several reasons, out of that the most difficult issue is the presence of polar connectors having stronger interactions, which suppress the weaker interactions present in the molecules. Moreover, a little change in position or functionality in the system may cause a huge change in the intermolecular interactions.

Glidewell and co-workers<sup>33</sup> have tried with different linkers to find out the correlation but all the linkers were polar enough to dominate within the system.

**Figure 10:** Series of isomeric compounds with different polar linkers

It is very important to note that, within each series of isomers, no two compounds manifest the same selection of direction-specific intermolecular interactions and, again within each series, no one structure is readily predictable from a knowledge of all the others. With the results obtained in mind they extended their studies towards more rigid isomeric systems N-(iodophenyl)nitrophthalimides) where polar linkers are excluded so that the hard hydrogen bonding interactions can be eliminated and the molecular frameworks have only a single degree of torsional freedom, about the N-aryl bond, so restraining somewhat the range of possible intermolecular interactions.<sup>34</sup>

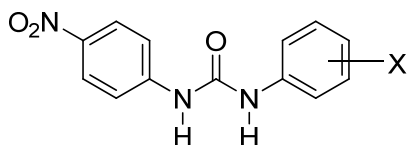
**Figure 11:** Isomeric compounds of somewhat rigid conformation

Although, here the polar linkers were removed and slight rigidity was brought into the system but still from thorough investigation of the different crystallographic data obtained from these isomeric compounds it is noteworthy to mention that, again it is difficult to discern any pattern in the intermolecular interactions which can provide a convincing interpretation of the conformational characteristics.



Recently Nangia and co-workers<sup>35</sup> also tried to find correlation between isomeric compounds with suitable disposition of nitro and halo group in unsymmetrical urea derivatives but the pattern similarity between the isomeric compounds was still not clearly understood.

**Figure 12:** Chemical structures of unsymmetrical diaryl urea derivatives



From the examples provided above that deal with the structural analyses of a group of isomeric compounds, it is evident that there is a need for a suitable soft linker without any functional unit that can form the strong non-covalent interactions without any substantial conformational flexibility. One of the fundamental requirements here is the flexibility and practicality in the incorporation of this linker. In this context, we have selected the currently coroneted “triazole-linker” in a variety of applications ranging from medicine, biology, to materials, as a soft linker and intended to introduce it in the area of crystal engineering.

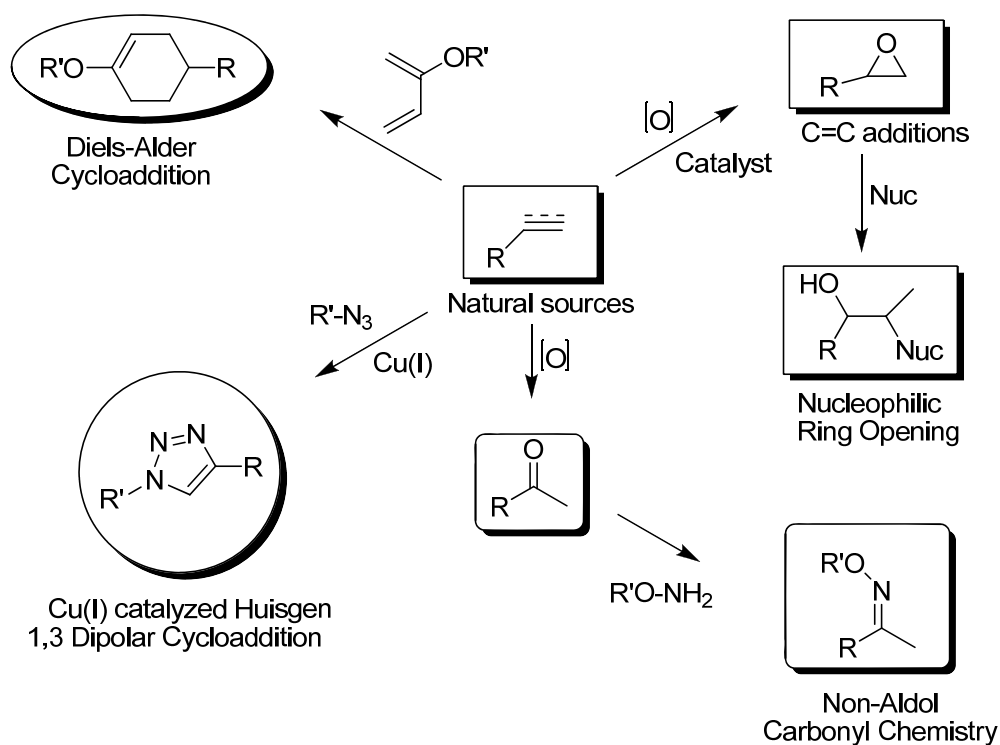
### “Click Chemistry” and the Triazole Linker

Following nature’s lead, Sharpless and coworkers<sup>36</sup> endeavor to generate substances by joining small units together with heteroatom links (C-X-C). The goal is to develop an expanding set of powerful, selective, and modular “blocks” that work reliably in both small and large-scale applications. They have termed the foundation of this approach as “Click Chemistry”, and have defined a set of stringent criteria that a process must meet to be useful in this context. Carbon-heteroatom bond forming reactions comprise the most common examples, including the following classes of chemical transformations.

- Cycloadditions of unsaturated species, especially 1,3 dipolar cycloaddition reactions, but also Diels-Alder family of transformations;

- Nucleophilic substitution chemistry, particularly ring opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, and episulfonium ions;
- Carbonyl chemistry of the “non-aldol” type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides; and
- Additions to carbon-carbon multiple bonds, especially oxidative cases such as epoxidation, dihydroxylation, aziridination, and sulfonylhalide addition, but also Michael additions to Nu-H reactants.

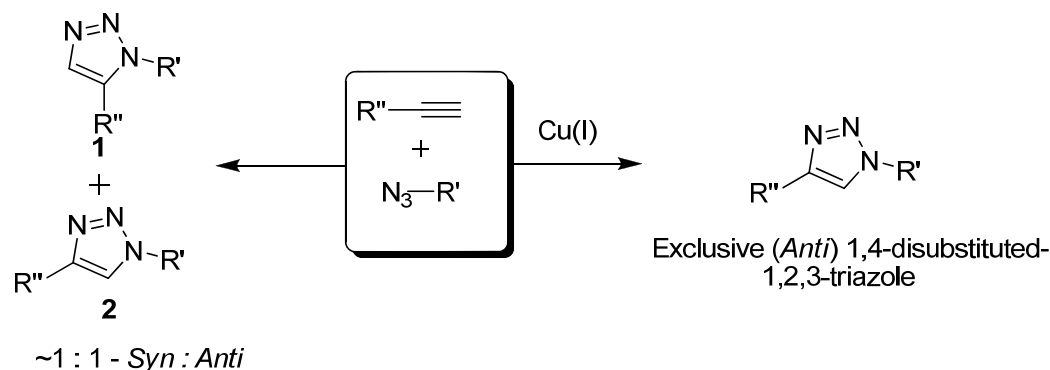
Figure 13



Of all the reactions which achieve “click status” the Huisgen 1,3 dipolar cycloaddition<sup>37</sup> of alkynes and azides to yield 1,2,3 triazoles is undoubtedly the premier example of a click reaction. The ease of synthesis of alkyne and azide functionalities, coupled with their kinetic stability and tolerance to a wide variety of functional groups and reaction conditions, make these complementary coupling partners particularly attractive. However, it was the recent discovery of the dramatic rate acceleration of the azide-alkyne coupling event,<sup>38,39</sup> under copper(I) catalysis and the beneficial effects of water that have

placed this reaction at the ‘center-stage’ of click chemistry. This new reaction process requires no protecting groups, and proceeds with almost complete conversion and selectivity for the 1,4-disubstituted 1,2,3-triazole (*anti*-1,2,3-triazole). No purification is generally required. This ‘near perfect’ reaction has become synonymous with click chemistry, and is often referred as ‘The Click Reaction’.<sup>40</sup>

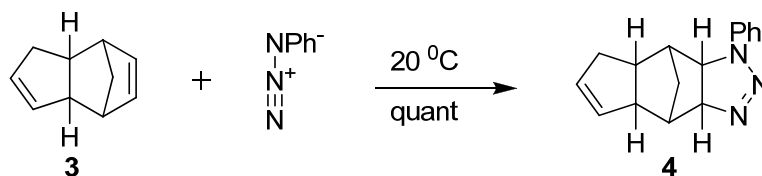
**Figure 14**



### A brief review on 1,3 dipolar cycloaddition:

Around 110 years ago, O. Dimoth discovered the formation of triazoles by addition of organic azides to acetylenes. Of greater mechanistic interest is the closely related reaction of phenyl azide with bicyclo-[2,2,1]hept-2-ene and its derivatives, described by Alder and Stein in 1931.<sup>41</sup>

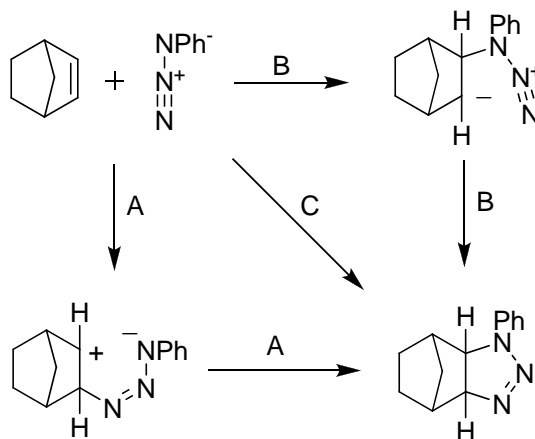
**Scheme 1**



Huisgen<sup>42</sup> in early 60's described the plausible mechanism involved in the reaction between azides and carbon-carbon double bond. Phenyl azide has two mesomeric structures with electron octets on all atoms, and both are dipolar in character. Three more canonical forms each having one electron sextet contribute to somewhat less extent. On the basis of all octet structures phenyl azide is a linear tripole: the middle nitrogen holds the formal positive charge while the negative charges shared between the end nitrogen atoms.

In addition of phenyl azide to double bond, three mechanisms are conceivable. (A) The positive end of the dipole may initiate the attack and the negative pole complete the addition; or (B) the negative center may be attached first, and then the positive end; (C) both the charge centers may add at the same time.

**Figure 15**



Doubts concerning mechanisms A and B are immediately raised because the sluggish organic azide displays neither strong electrophilic nor nucleophilic character. The concerted process C is immune to such objections. Here a synchronous shift of electrons result in the formation of two new s-bonds and allow all three nitrogen atoms to achieve stable octets without having to bear a formal charge.

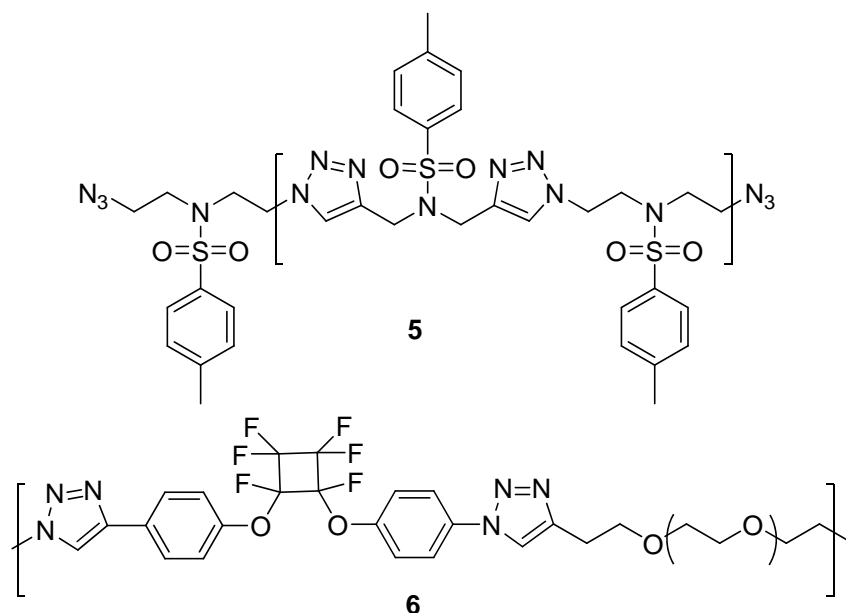
Azides are essentially inert to most biological and organic conditions, including highly functionalized biological molecules, molecular oxygen, water and majority of common reaction conditions in organic synthesis.<sup>39,43</sup> For the formation of 1,2,3-triazole using Cu(I) as catalyst where azides can react with acetylene  $10^7$  times faster than the previously described methods. Till date this is probably the most powerful discovery of click reaction.

Despite the thermodynamic favorability of azide decomposition, kinetic factors allow aliphatic azides to remain nearly invisible until presented with a good dipolarophile. This kinetic stability of alkynes and azides is directly responsible for their slow cycloaddition, which generally requires elevated temperatures and long reaction times.<sup>44,45</sup> Good regioselectivity in the uncatalyzed Huisgen type cycloaddition is observed for

coupling reactions involving highly electron-deficient terminal alkynes,<sup>46</sup> but reactions with other terminal alkynes usually afford mixtures of 1,4- and 1,5-regioisomers.<sup>47</sup>

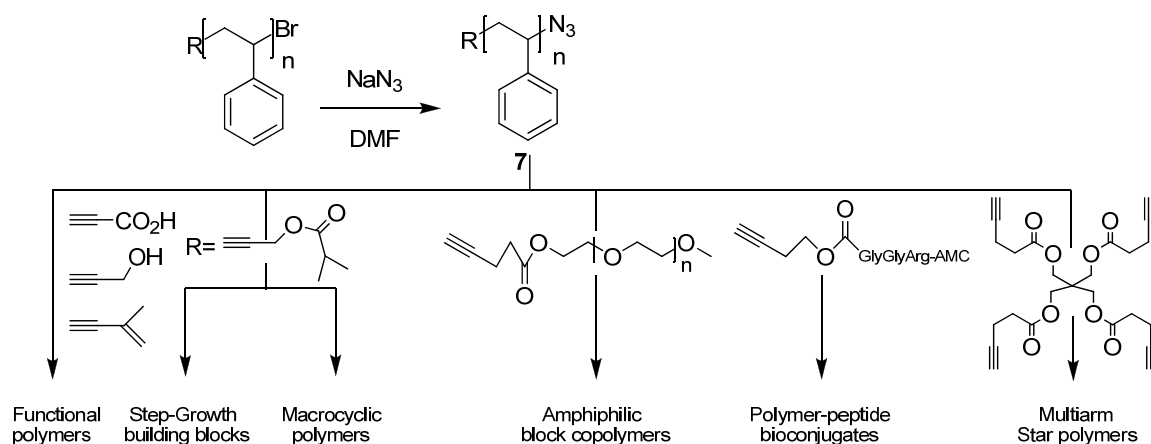
Thus only following the recent discovery of the advantages of Cu(I) catalyzed azide-alkyne coupling, did the main benefits to this cycloaddition, become clear. Cu(I) catalysis dramatically improves the regioselectivity to afford the 1,4-regioisomer exclusively and increases the reaction rate up to  $10^7$  times,<sup>48</sup> eliminating the need for elevated temperatures. This high yielding reaction tolerates a variety of functional groups and affords the 1,2,3-triazole product with minimal work up and purification, as an ideal click reaction.

Click chemistry was postulated initially as a specific organic reaction but by time it became a very important tool in different fields of chemistry. The major improvement was seen in materials chemistry.<sup>49</sup> In 2004, Hawker, Fokin, Sharpless, and co-workers have reported the first illustration on this field. Afterwards, the popularity of click chemistry within the materials science grew considerably by the influential works of Hawker, Fréchet, and Finn. Hawker, Fokin, Sharpless, and co-workers explored first the CuAAC of various molecular building blocks for the convergent synthesis of dendrimers. Overall, this method was found to be a straightforward strategy for the large-scale synthesis of triazole-based dendrimers. Shortly after, Finn and co-workers studied the click cycloaddition of azide- and alkyne-functionalized monomers for the preparation of either linear polymer chains or three-dimensional polymer networks. The latter was investigated as novel adhesives for copper surfaces, as triazole rings have a strong ability to coordinate transition metals.

**Figure 16:** Examples of linear polymer structures

The first important application of CuAAC in polymer chemistry is undeniably the synthesis of functionalized polymers (either end-functionalized or side-functionalized). The post-functionalization of synthetic polymers is an important feature of macromolecular engineering, as many polymerization mechanisms are rather sensitive to bulky or functional groups.

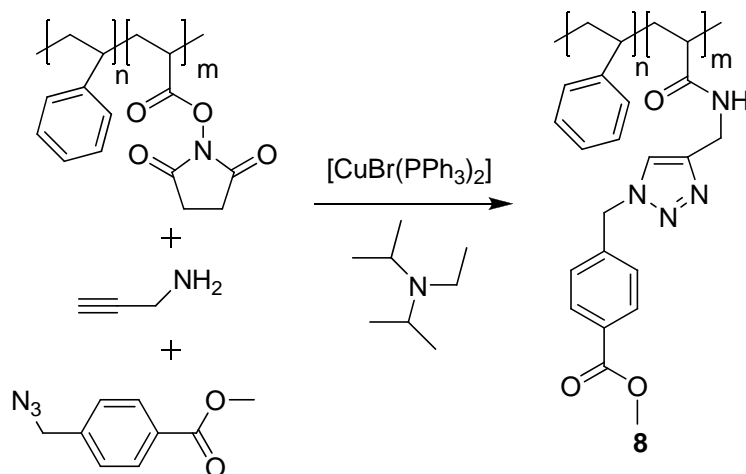
**Scheme 2:** Variations of simple theme: Examples of macromolecular architectures obtained by Click reaction



Polymers with multiple functional side chains have been prepared by CuAAC using precursors built with alkynefunctionalized monomers. For example, Fréchet and co-workers constructed dendronized polymers (i.e. linear polymer chains with bulky side

dendrons) through cycloaddition of the side chains. Hawker and co-workers explored this concept even further and reported some very elegant examples of cascade side-chain functionalization of macromolecules.

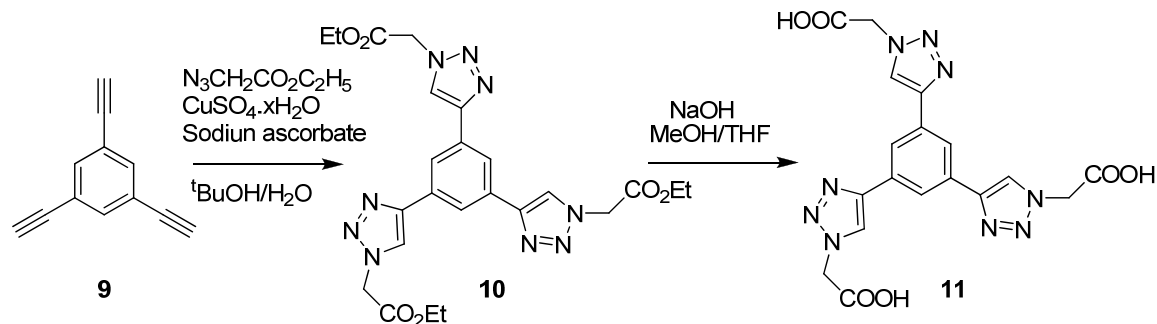
**Scheme 3:** Examples of cascade functionalization of synthetic macromolecules



Along with that, click reaction with CuAAC was investigated for modifying biological polymers such as nucleic acids or polysaccharides. Moreover, this is very useful for preparing polymer bioconjugates also. Several reports indicated that sequence-defined oligopeptides can be linked to synthetic macromolecules using click ligation. More complex biological entities such as proteins, enzymes, viruses, bacteria, and cells may also be transformed using azide-alkyne chemistry.

The search for very large pores in metal organic frameworks (MOFs) is currently topical, due to the unprecedented properties they generate in adsorption and now in drug delivery. Keeping constant the inorganic part, the size of the pores by acting on the length of the rigid linker can be tuned. Devic and co-workers<sup>50</sup> recently prepared a porous MOF (denoted MIL-103, MIL = Materials Institut Lavoisier) based on an extended tritopic linker (1,3,5-benzenetrisbenzoate) and lanthanide chains. To investigate the effect of the addition of nitrogen lone pairs and small flexible endings at the periphery of the rigid core they prepared a new trigonal nitrogen-rich linker including 1,2,3-triazole rings [named MIL-112, formulated  $\text{La}(\mathbf{L})(\text{H}_2\text{O})_2 \cdot 6\text{H}_2\text{O}$  from X-ray, and chemical analysis] using click chemistry as the synthetic tool.

**Scheme 4:** {4-[3,5-Bis-(1-carbonylmethyl-1*H*-[1,2,3]triazol-4-yl)-phenyl]-[1,2,3]triazol-1-yl}acetic acid (later denoted **LH<sub>3</sub>**) synthesis

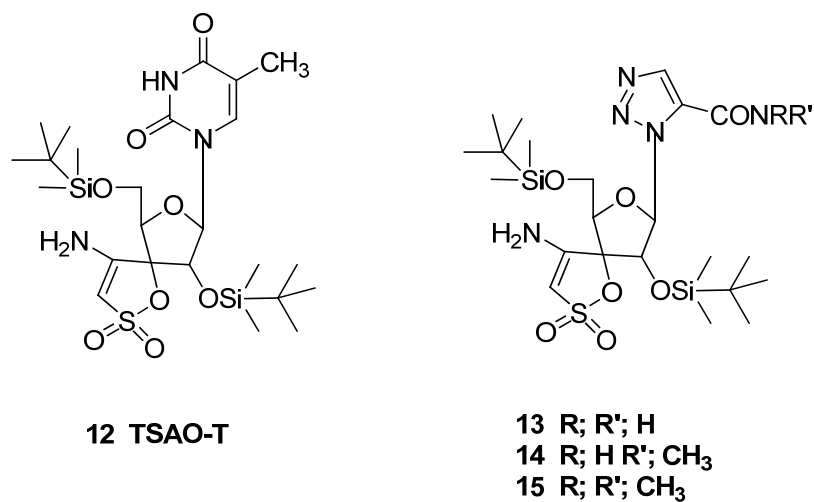


A wide range of applications made the click reaction one of the frontier reaction in the all fields of chemistry. Further interest in this reaction stems from the interesting biological activity of 1,2,3-triazoles. These heterocycles function as rigid linking units that can mimic the atom placement and electronic properties of a peptide bond without the same susceptibility to hydrolytic cleavage. Due to their ability to mimic certain aspects of a peptide bond, many known 1,2,3-triazoles possess varied biological activity, including *anti*-HIV activity,<sup>51</sup> selective  $\beta_3$  adrenergic receptor inhibitor,<sup>52</sup> *anti*-bacterial activity,<sup>53</sup> *anti*-tuberculosis activity<sup>54</sup> and more.<sup>55</sup>

[2',5'-bis-*O*- (*tert*-butyldimethylsilyl)- $\beta$ -D-ribofuranosyl]-3'-spiro-5''- (4''-amino-1'',2''-oxathiole-2'',2''-dioxide) nucleosides (TSAO) was discovered by Velazquez *et al.* The prototype compound of this family is the thymine derivative, designated as TSAO-T (**12**). Structure–activity relationship (SAR) studies with the TSAO class of compounds have revealed that stringent requirements exist with regard to the structural determinants for optimum *anti*-HIV activity in cell culture. Several members of this class of compounds showed potent *anti*-HIV-1 activity comparable to that of the TSAO prototype derivative. Among these derivatives of TSAO, 1,2,3-triazoles **13**, **14** and **15** (Figure 15) were endowed with potent *anti*-HIV-1 activity. In particular, compound **15** emerged as the most active triazole TSAO derivative and can be considered as a novel lead compound to develop further TSAO derivatives with potent *anti*-HIV-1 activity.

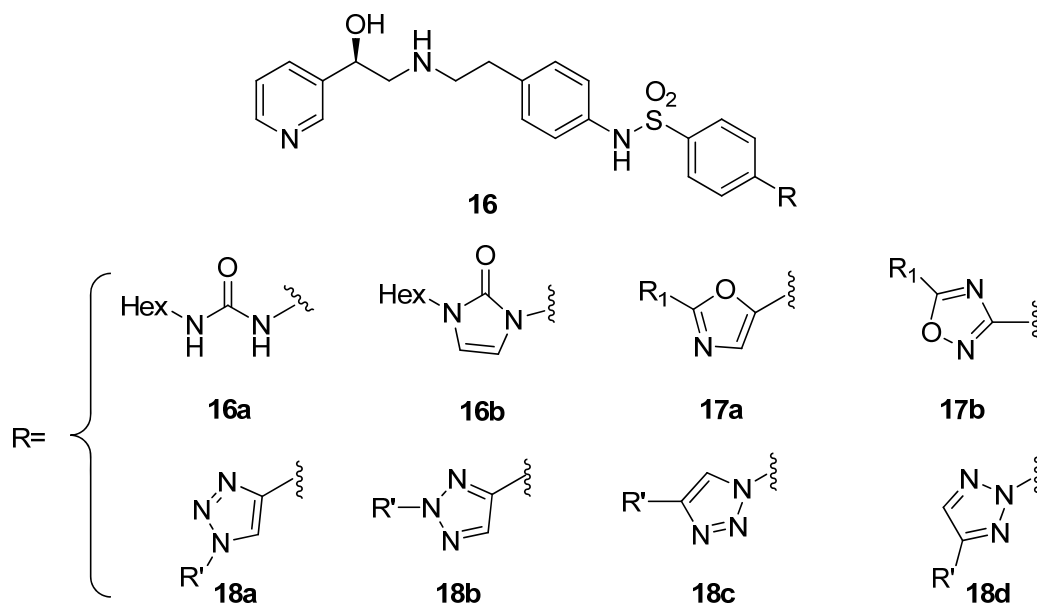


Figure 17



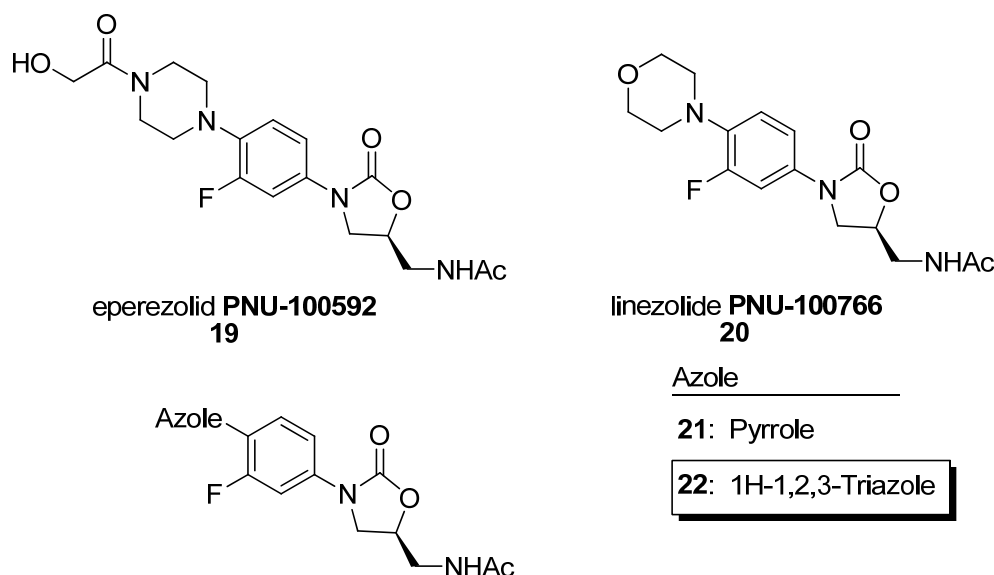
Earlier it was found that that while aryl sulfonamides such as urea **16a** and imidazolone **16b** are potent and selective  $\beta_3$ -AR agonists ( $\beta_3$  EC<sub>50</sub>=6.3 and 14 nM, respectively), both compounds suffer from poor oral bioavailability in the dog (%F= <1 and 7, respectively). Recent publications from Merck describe the successful substitution of oxazole and oxadiazole functionalities for the urea moiety, resulting in compounds of general structure **17a** and **17b**. These series of compounds were found to be  $\beta_3$ -AR agonists with improved pharmacokinetic profiles.

Figure 18



The totally synthetic oxazolidinones typified by eperezolid (**19**) and linezolid (**20**) are one such class of antibacterial agents with potent activity against Gram-positive organisms. The (azolyphenyl) oxazolidinone subclass has been discovered wherein the morpholine ring of linezolid (**20**) has been replaced with various five-membered nitrogen-containing heterocycles (azoles). Some of these analogues have interesting levels of antibacterial activity. In particular, the pyrrole **21** and the 1*H*-1,2,3-triazole **22** analogues have excellent Gram-positive activity (MICs < 0.5-1  $\mu$ g/mL), *vide infra*.

**Figure 19**



It is apparent from the above discussion that “Click Reaction” in general and the triazole unit in particular has a great impact on several areas of research in the recent years. Encouraged by the simplicity of this “Click Reaction” and as described in the earlier part that detail the importance of soft linkers in addressing the predictability of a particular weak synthon like halo...nitro, we have initiated a program to employ this simple azide-alkyne “Click Reaction” for the synthesis of a collection of isomeric compounds with modular positioning of halo and NO<sub>2</sub> on a flexible tricyclic template and examination of the occurrence of the bifurcate X...NO<sub>2</sub> synthon with respect to their relative disposition. Apart from the projected X...NO<sub>2</sub> and competing X...X interactions, absence of any other stronger interactions in this system could provide the necessary criteria for existence of weak interactions like C–H...O, C–H...N, C–H...Br and their influence on the overall packing of the crystal.

## **PRESENT WORK**

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## ***PRESENT WORK***

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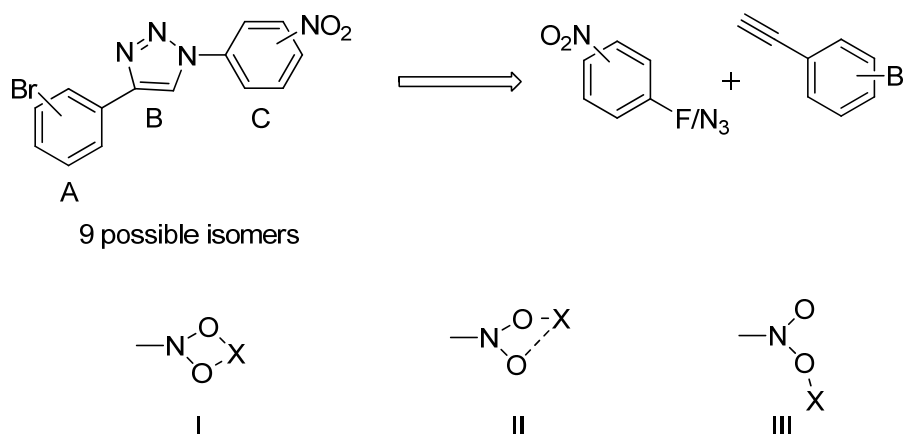
The current resurgence of classical Huisgen [3+2] cycloaddition by Sharpless-Finn-Kolb's "click reaction" has ascertained the triazole ring as an important heterocyclic pharmacophore in general and the overall process for affixation of ligands on to biopolymers by post modification processes in particular. Herein, we describe the potential of azide-alkyne "click reaction" in crystal engineering to synthesize a collection of isomeric compounds with modular positioning of Br and NO<sub>2</sub> on a flexible tricyclic template and reveal the occurrence and nature of bromo-nitro synthon with respect to their relative disposition.

As it expressed by Dunitz "the crystal is a supramolecule par excellence" that present how intermolecular links operate together. A detailed knowledge of intermolecular interactions and identifying respective molecular functionalities that form defined network structures will help to design the crystals for material applications. In this context, considering its similarity in action to *synthon*, the phrase 'supramolecular synthon' has been coined by Desiraju to describe a set of noncovalent interactions that form and modulate recognition patterns in the solid state. Various synthons comprising strong conventional hydrogen bonding to weak or unconventional (C-H ...O, C-H ...N, C-H ...X and C-H ... $\pi$ ) hydrogen bonding interactions have been identified. Homosynthons comprising conventional hydrogen bonding (COOH...COOH, OH...OH, CONH<sub>2</sub>...CONH<sub>2</sub>, X...X) were more reliably employed in crystal engineering because of their directionality and robustness. A recent trend in this regard is investigation of a set of isomeric compounds where the complimentary functional groups that control association are varied systematically on flexible templates, which indeed has provided valuable insight in crystal engineering. In this context, developing a simple synthetic tool that can deliver the medium size crystalline molecular systems with predictable architectural control and flexibility in the incorporation of functional group is warranted.

Inspired with the broad spectrum application of Cu(I)-catalyzed 1,3-cycloaddition between an azide and an alkyne in the discovery of drugs and materials, we have initiated a program to explore its potential in molecular design for crystal engineering. Our initial attempts in this regard are focused on well-established NO<sub>2</sub>-Br heterosynthon and to

evaluate the occurrence of this synthon in a group of isomeric compounds where they are well separated through a flexible template. As shown in figure 20, the tricyclic template comprising the 1,2,3-triazole unit as a linker (ring B) was designed with modular positioning of  $-\text{Br}$  and  $-\text{NO}_2$  groups on ring A and ring C, respectively. Apart from the projected  $\text{NO}_2\dots\text{Br}$  and competing  $\text{Br}\dots\text{Br}$  interactions, absence of any other stronger interactions in this system should provide the necessary criteria for existence of weak interactions like  $\text{C-H}\dots\text{O}$ ,  $\text{C-H}\dots\text{N}$ ,  $\text{C-H}\dots\text{Br}$  and their interplay to influence the overall packing of the crystal.

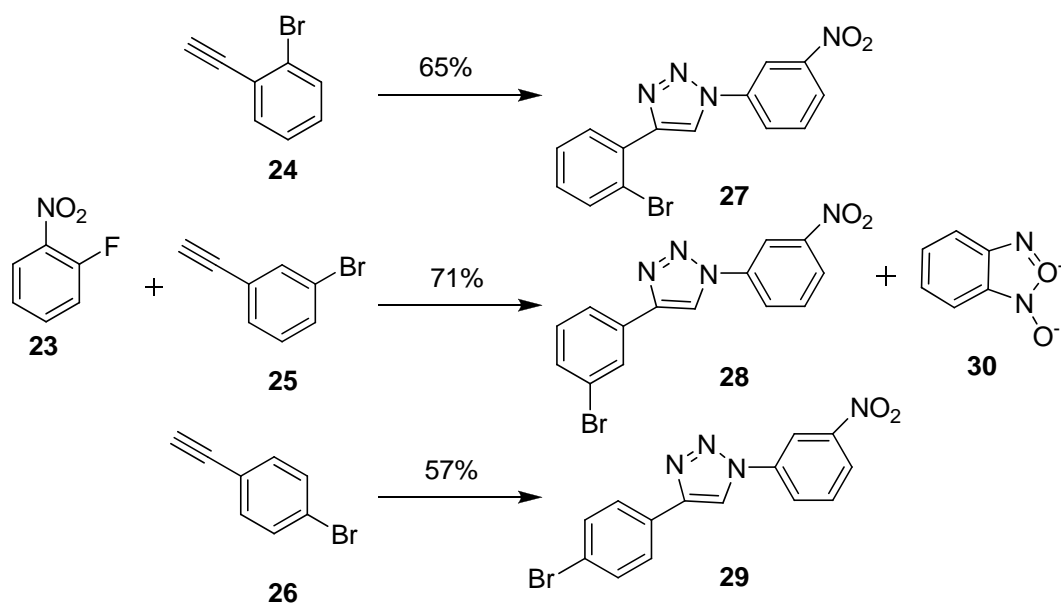
**Figure 20:** Key “Click chemistry” protocol, designed isomers and possible N-O...Br synthon geometries



Considering the competitive formation of the regiomer products in one hand and the known conversion of the  $\alpha$ -azido nitrobenzene to benzofuroxan under the thermal Huisgen [3+2]-azidoalkyne cycloadditions conditions on the other hand, we opted for a  $\text{S}_{\text{N}}\text{Ar}$  reaction of fluoronitrobenzenes with sodium azide as a potential alternative in this regard.<sup>56</sup> The feasibility of  $\text{S}_{\text{N}}\text{Ar}$  click reaction was examined with simple phenyl acetylene employing three regiomer fluoronitrobenzenes adopting the conditions developed in general for copper mediated azide cycloadditions earlier. In general, the reactions with 2-fluoronitrobenzene (**23**) are facile, with 4-isomer (**36**), prolonged heating is required. As the reactions with 3-fluoronitrobenzene (**31**) resulted only in the cycloaddition product of  $\text{NaN}_3$  with phenyl acetylene, 3-azidonitrobenzene (**32**) was employed under similar condition to prepare the 3- $\text{NO}_2$  isomer. Considering the competitive formation of the regioisomeric products in Huisgen [3+2] cycloaddition condition by using different

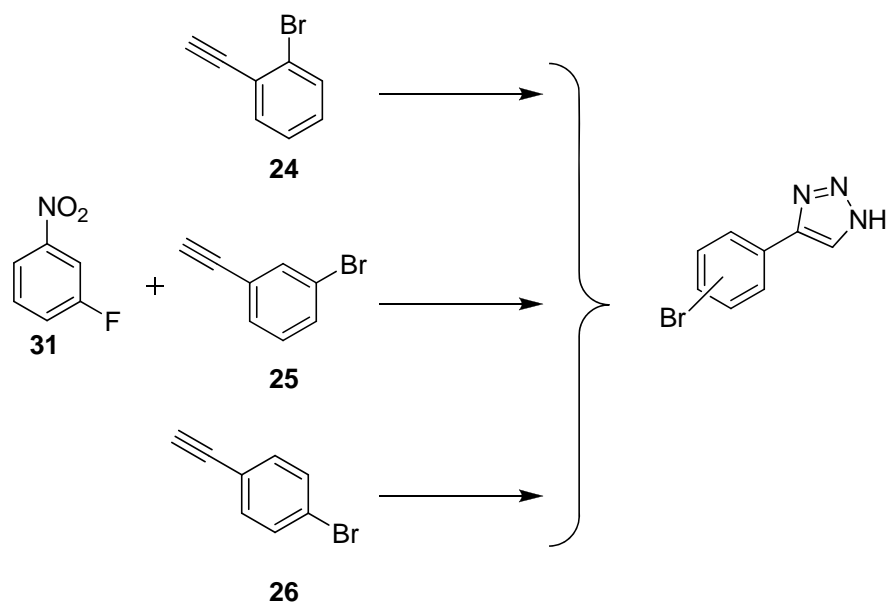
organic solvents,<sup>57</sup> we opted for a recently developed method of this reaction under aqueous condition. In case of 2-azidofluorobenzene intramolecular cyclized product (**30**) of nitroazidobenzene was obtained as side product. Formation of this side product clearly suggests that fluoro group was replaced by azide group first and then the cycloaddition reaction proceeded mechanistically. These compounds were also characterized by <sup>1</sup>H and <sup>13</sup>C NMR's as well as X-ray crystallography.

### Scheme 5



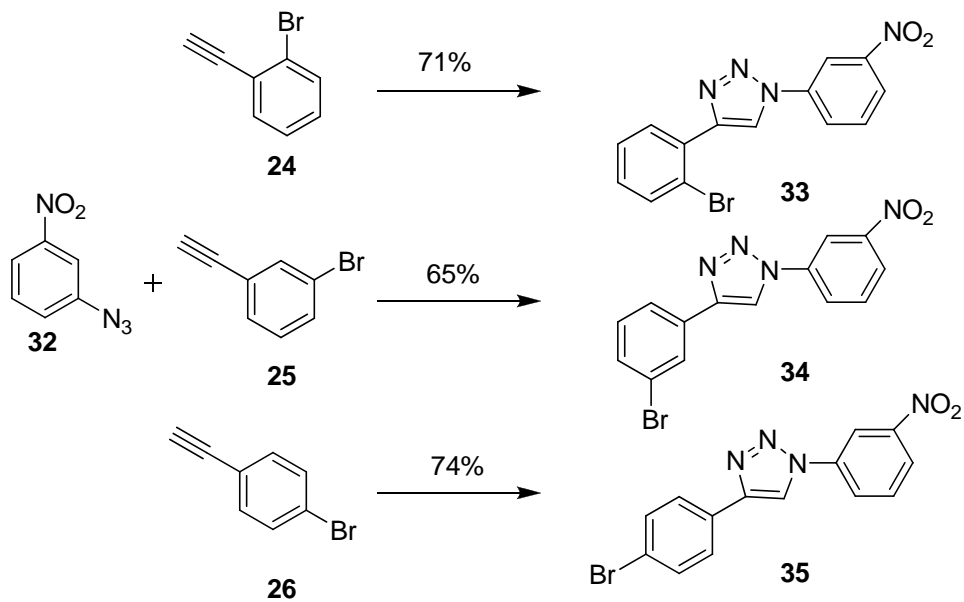
*Reagents and conditions:* L-proline, Na<sub>2</sub>CO<sub>3</sub>, NaN<sub>3</sub>, sodium ascorbate, CuSO<sub>4</sub>·5H<sub>2</sub>O, DMSO- H<sub>2</sub>O (9:1), 70 °C, 24 h.

## Scheme 6



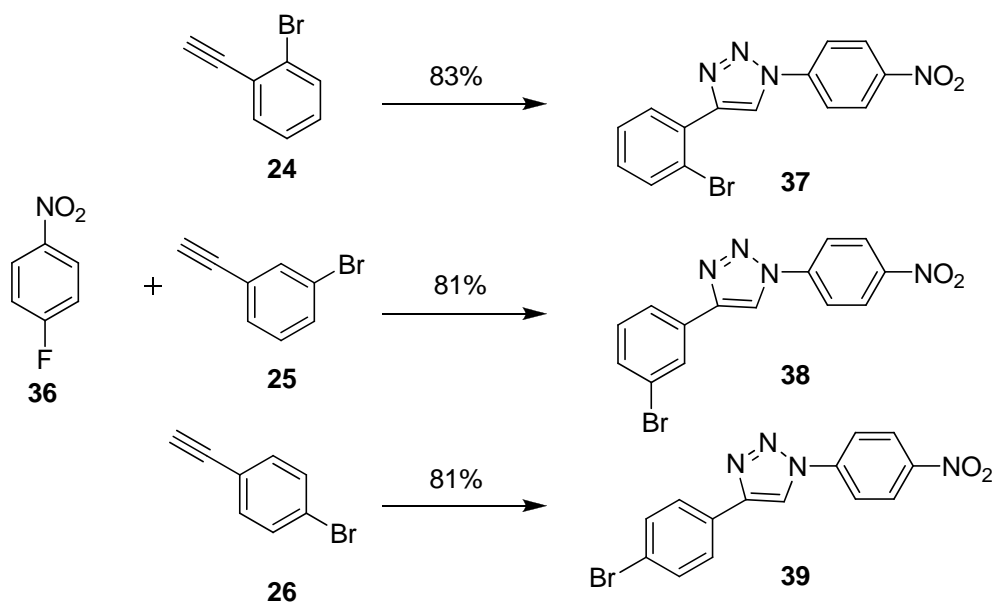
*Reagents and conditions:* L-proline,  $\text{Na}_2\text{CO}_3$ ,  $\text{NaN}_3$ , sodium ascorbate,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ , DMSO-  $\text{H}_2\text{O}$  (9:1), 70 °C, 48 h.

## Scheme 7



*Reagents and conditions:* L-proline,  $\text{Na}_2\text{CO}_3$ , sodium ascorbate,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ , DMSO-  $\text{H}_2\text{O}$  (9:1), 70 °C, 24 h

## Scheme 8



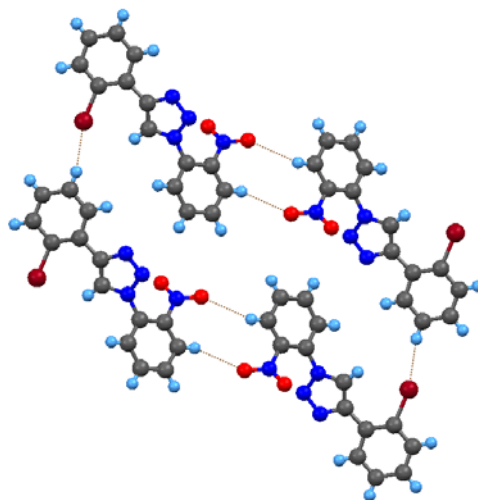
*Reagents and conditions:* L-proline,  $\text{Na}_2\text{CO}_3$ ,  $\text{NaN}_3$ , sodium ascorbate,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ , DMSO-  $\text{H}_2\text{O}$  (9:1), 70 °C, 48 h.

From the NMR studies, it has been found that for 1,4 disubstituted 1,2,3-triazole, the only proton present in triazole ring comes as most deshielded proton at above  $\delta$  8.5 in all the cases. These structures have further been confirmed by the X-ray studies. Detailed X-Ray crystallographic studies of available 9 compounds have been done and all the inherent structural features present in those 9 compounds are described below.

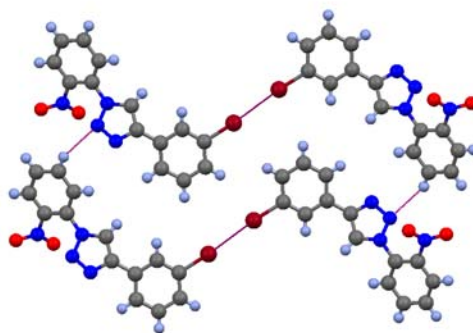
**P2NPT series:**

The molecular assembly **28** in its crystal structure was mainly dominated by weak C-H...O interaction. There are two C-H...O interactions present in the assembly, one is aromatic carbon containing hydrogen with one oxygen of nitro group having a bond distance of 2.675 Å and the another one is triazole ring containing hydrogen with another oxygen of nitro group where the bond distance is 2.648 Å.



**Figure 21:** Extended structure of 2BP2PNT (**27**)

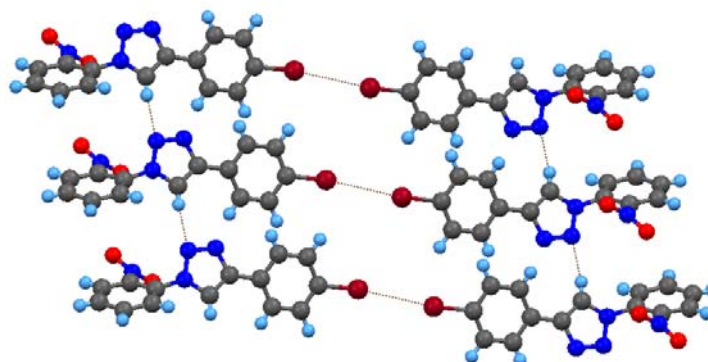
From the structural investigation of compound **28** it has been observed that the main interaction here is Br...Br interaction with a bond length of 3.696 Å which is in very close proximity with the van der Waals radii between two Br atoms. 2D picture of this compound reveals that it is a kind of dimer of two molecules where the chain propagates through Br...Br interaction. Along with that interaction, another major interaction which governs the structural assembly is the C-H...N interaction where the bond distance is 2.540 Å. This is also well fitted in the range of van der Waals radii. So this is also an example of compound where molecular assembly is dictated by weak interactions.

**Figure 22:** Expanded structure of 3BP2NPT (**28**)

The main structural feature of the assembly of compound **29** is the zig-zag orientation. The chain propagates through the Br...Br interaction. This Br...Br interaction is 3.473 Å which is also within the range of van der Waals radii of two Br atoms. Another

important feature of this structure is that, although the two molecules are arranged in anti parallel fashion to propagate the chain but the chains which are propagating are parallel. This interesting observation was not found in the earlier two examples.

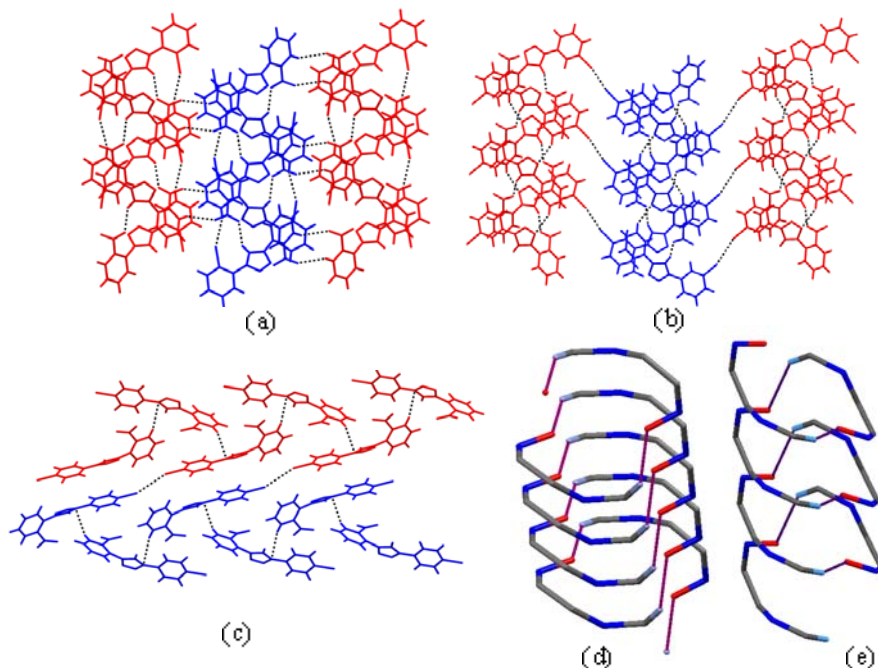
**Figure 23:** Expanded structure of 4BP2NPT (29)



#### **Comparative structural analysis of 27 – 29:**

The crystal structures of the above three compounds contain one molecule for asymmetric unit. In all the three structures, none of the aromatic ring is coplanar with the triazole ring. The crystal structures of the three compounds in general are dominated by the C-H...O and/or C-H...N, C-H...Br and Br...Br interactions and do not pack in their crystals *via* NO<sub>2</sub>...Br synthon. Molecules in first two structures form isostructural helical assemblies along crystallographic 2<sub>1</sub>-screw axis linked *via* C-H...O interaction involving C1-H1 group of triazole ring and oxygen O1 of nitro group. The helical assembly also brings the unit translated molecules close together *via* C-H...N interaction along with additional C-H...Br contact in the first structure. The neighboring helices are bridged *via* centrosymmetric C-H...O interaction engaging nitro group phenyl ring in the first one whereas in the second they are linked *via* centrosymmetric Br...Br short contact.

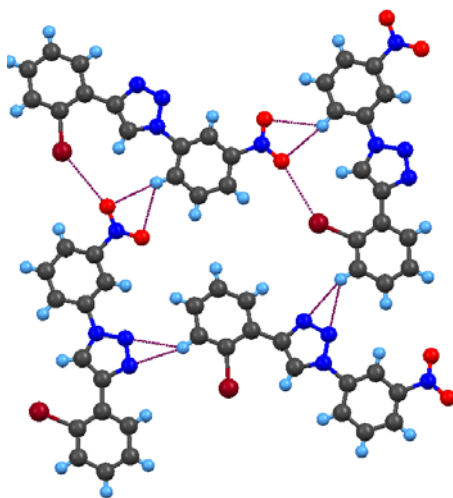
**Figure 24:** Secondary structures of **27-29** and helical assemblies in the crystal structure of (d) **27** and (e) **28**



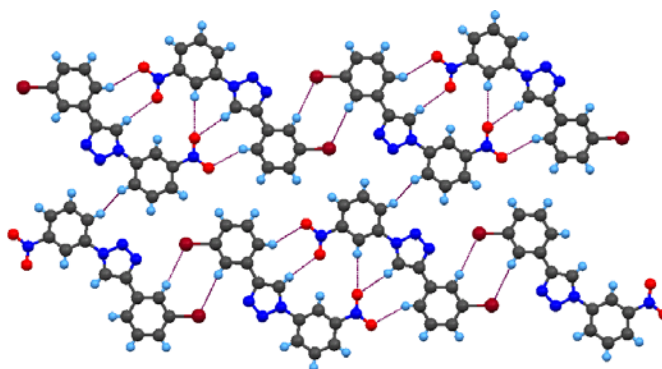
In the last structure *c*-glide related molecules are linked *via* weak C-H... $\pi$  interaction between C-H group of phenyl ring bearing nitro group and triazole ring forming a layer. This layer links with another layer in anti-parallel fashion along *b*-axis *via* centrosymmetric Br...Br short contact.

### **P3NPT series:**

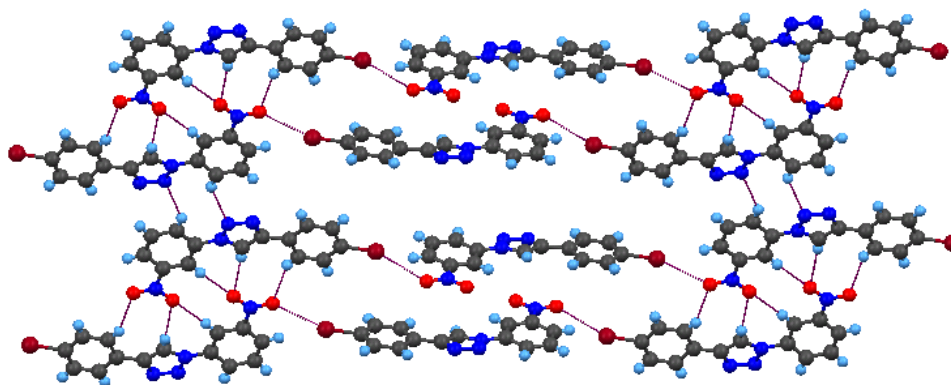
In the structure of **33**, the basic feature is the one dimensional infinite sheet. Unlike in 2-Nitro series, all three rings in the compound **33** are almost coplanar. Although two kind of C-H...O interactions are present here with a bond length 2.666 Å and 2.717 Å, respectively along with two C-H...N interactions with bond lengths of 2.713 Å and 2.727 Å, respectively, although these interactions are present in the system but the structure is mainly governed by strong Br...NO<sub>2</sub> interaction. This interaction is having a bond length of 3.318 Å. No Br...Br short contacts are visible in this structure.

**Figure 25:** Expanded structure of 2BP3NPT (33)

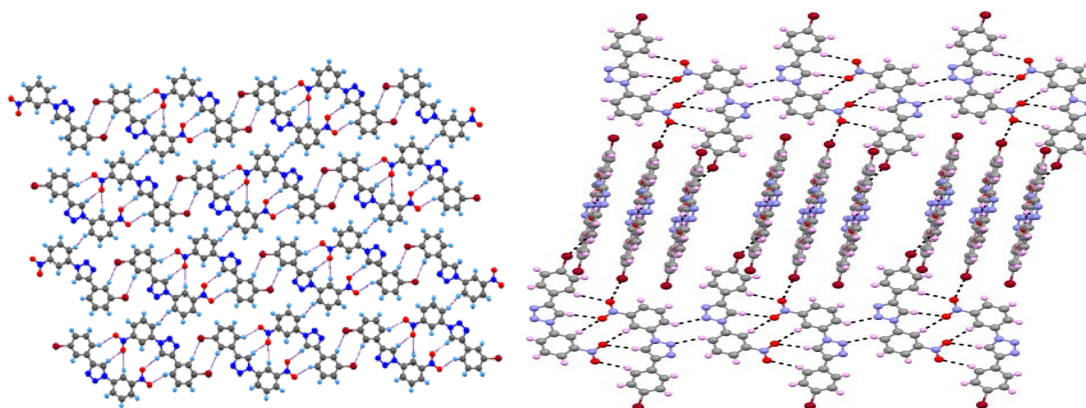
In 3BP3NPT, two parallel infinite sheets are organized between themselves. Several C-H...O bondings are seen in the molecule within the range of their van der Waals radii. Total five different C-H...O interactions are present in the molecule having bond lengths of 2.438 Å, 2.471 Å, 2.547 Å, 2.658 Å and 2.671 Å respectively. Two different C-H...Br interactions are also found in this structure with the bond length of 2.985 and 3.035 Å respectively.

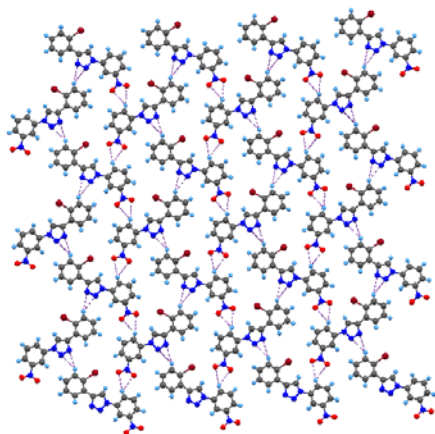
**Figure 26:** Expanded structure of 3BP3NPT (34)

The most interesting nature of this structure is that, in spite of having these many bonds in the molecular assembly there is no connectivity between two parallel sheets. Here in this structure also the triazole ring is almost coplanar with the other two aromatic rings attached to it.

**Figure 27:** Expanded structures of 4BP3NPT (35)

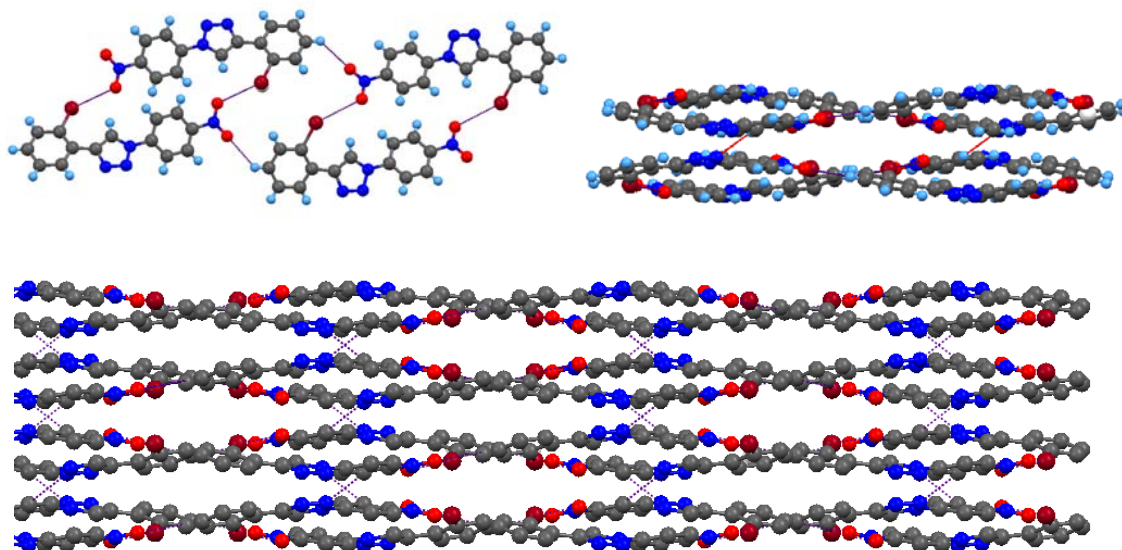
Infinite number of horizontal and vertical ribbons formed *via* C-H...O and C-H...N interactions are organized between themselves. While considering the two-dimensional picture of this structure it is observed that there has been a crossing between horizontal and vertical sheets but if the three-dimensional picture is observed thoroughly then it has easily been found that there has not been any crossing between horizontal sheets and vertical sheets, instead of that every two horizontal sheet is linked by one vertical sheet and vice versa. Three different C-H...O interactions are observed in the structure with bond lengths of 2.488 Å, 2.558 Å and 2.700 Å, respectively but the most interesting feature of this compound is the interaction between Br...NO<sub>2</sub> which is having a bond length of 3.169 Å. This is the major connector between the horizontal and vertical sheets.

**Figure 28:** Structures for comparisons

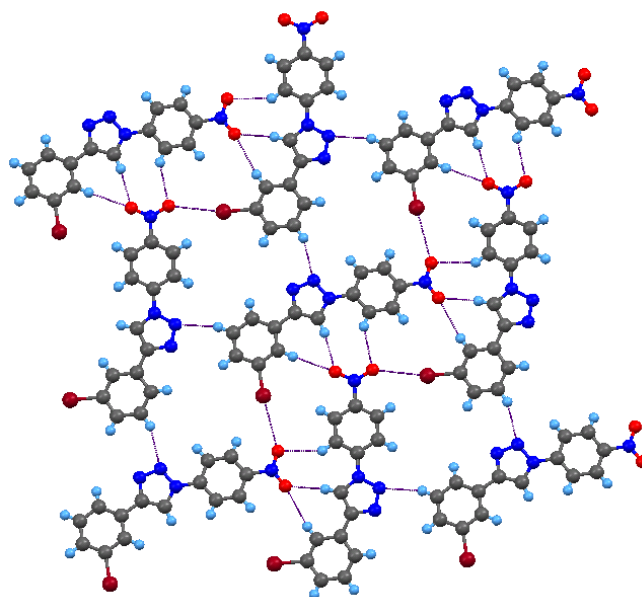


After individual studies of each compound if all the results are summarized together then several similarities as well as differences can be observed. Crystal structures of this series are solely dominated by C-H...O and halogen bonding (Br...O) interactions. In all three structures, both aromatic rings are nearly coplanar with the triazole ring. Molecules in **34** and **35** form a zero dimensional face-to-face centrosymmetric dimeric assembly *via* C-H...O interactions except in **33** due to presence of bromine atom at ortho position which prevents face-to-face alliance. The molecular packing in **35** is isostructural. The face-to-face dimers are connected *via* centrosymmetric C-H...N interaction forming a planar sheet diagonal to *ab* plane. These successive sheets along the *c*-axis are perpendicularly stitched through Br...O contact in **35** forming a square grid type network. In **34**, the face-to-face dimers are formed between the two symmetry independent molecules in the asymmetric unit *via* C-H...O interactions. These dimers are extended in two dimensions forming a sheet pattern through C-H...Br contact. Along the third dimension these sheets are stacked one over the other with interplanar spacing  $\sim 3.5$  Å. In **33**, the nitro group carrying phenyl ring has adapted almost opposite orientation with the respective phenyl ring in **34** and **35**. Due to this change at the single molecular level inhibits the formation of face-to-face dimeric assembly. Instead, the molecular assemblies are 'zig-zag' chains bridged *via* bifurcated C-H...O and Br...O contact that resemble flat helical ribbons. These flat ribbons stitched together *via* bifurcated C-H...N interaction forming a planar sheet. Here also the flat ribbons have  $\sim 3.5$  Å spacing along the third dimension.



**P4NPT series:****Figure 29:** Expanded structure of 2BP4NPT (37)

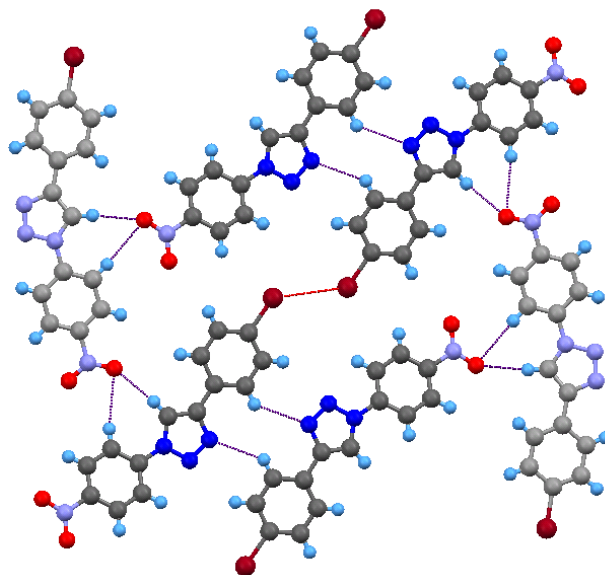
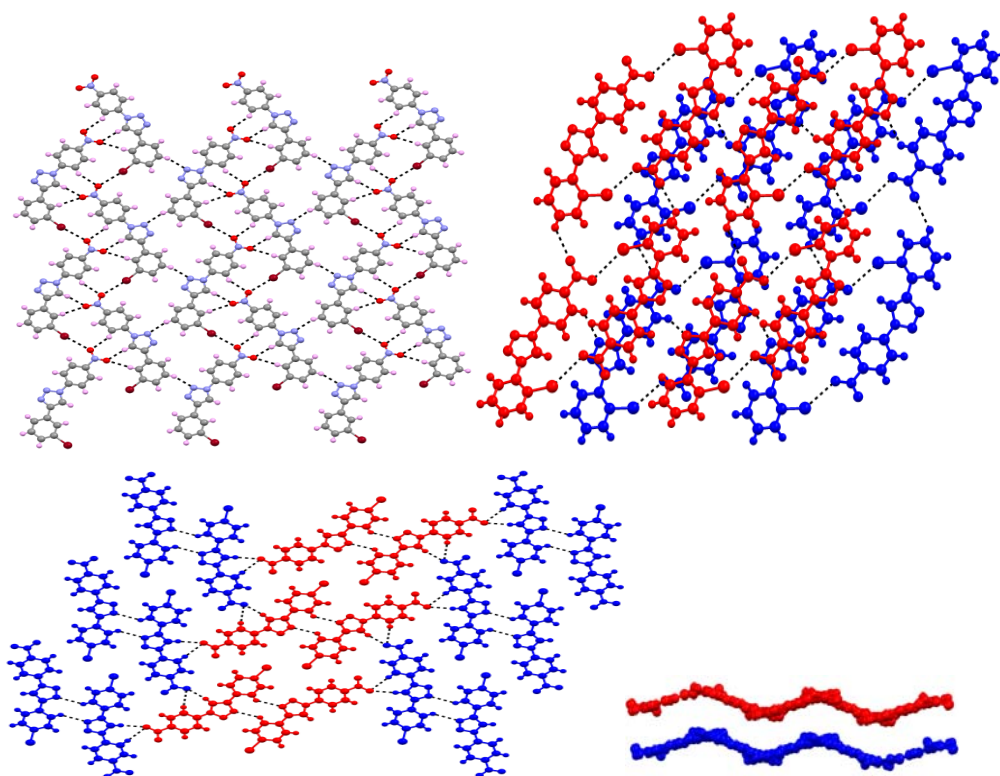
In this structure the major feature is that the two molecules are packed together with Br...NO<sub>2</sub> interaction with bond length of 3.268 Å. The structure looks like a dimeric unit of which two monomeric units are attached through Br...NO<sub>2</sub> interaction. In this structure the triazole ring is coplanar with one of the aromatic ring but the nitro group containing aromatic ring is out of plane with the other two rings, although the deviation is less. In this structural assembly one C-H...O and one C-H...N interaction is present having a bond length of 2.623 Å and 2.560 Å, respectively. Two C-H...Br interactions are also present in the system with bond length of 2.620 Å and 2.987 Å. Due to the orientation of one aromatic ring which is noncoplanar with the other two rings, the total assembly is apparently showing zig-zag kind of structure.

**Figure 30:** Expanded structure of 3BP4NPT (**38**)

Secondary structure of **38** is characterized by the one-dimensional infinite sheet having Br...NO<sub>2</sub> interaction (3.292 Å) for chain propagation. This structure is very similar to the structure of compound 2BP3NPT. Other than this, three different C-H...O interactions are present with the bond length of 2.329 Å, 2.561 Å and 2.663 Å, respectively and a C-H...N interaction with the bond length of 2.524 Å is also present in the system.

The structural assembly of compound **39** shows infinite number of parallel sheets. Here also all three rings are almost coplanar like the previous structure. Here in this structure two C-H...O interactions are present with the bond length of 2.314 Å and 2.714 Å respectively, one C-H...N interaction is also present having a bond length of 2.598 Å but unlike the previous structure there is no such Br...NO<sub>2</sub> interaction present in the system.



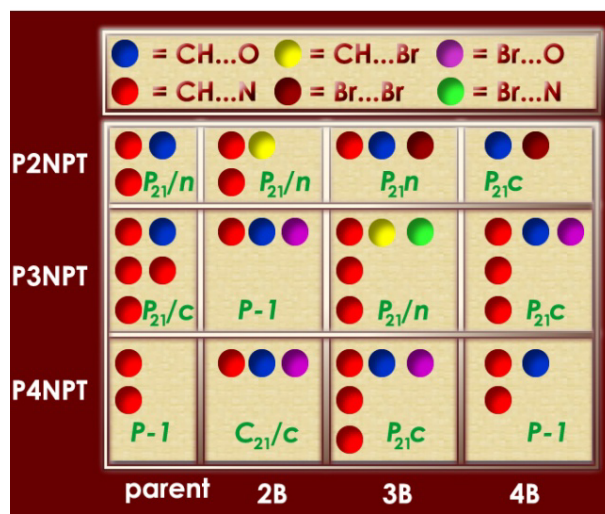
**Figure 31:** Expanded structure of 4BP4NPT (**39**)**Figure 32:** Comparative structural analysis of compounds **38** - **40**

In this series of three structures, both aromatic rings are nearly coplanar with the central triazole ring. In **39**, there are two independent molecules in the asymmetric unit that

differ by small dihedral angle difference between the triazole and bromophenyl ring. Crystal structures of compound **38**, and **39** forms a 2D-sheet and that of compound **37** displayed a corrugated strand structure. The spacing between the parallel sheets is about 3.9 Å. In compound **37**, molecules form centrosymmetric dimers *via* halogen bonding contacts (Br...O). The halogen bonded dimeric unit is linked *via* centrosymmetric C-H...O interaction with the neighboring dimeric unit along a-axis whereas along c-axis they are associated *via* C-H...N contact having c-glide relation forming corrugated network. The structure of **38** revealed flat helical self-assembly around the crystallographic two-fold screw axis through C-H...O and Br...O contacts. These flat helices are bridged along the c-axis *via* C-H...N interaction forming 2D sheet. In compound **39** also molecules form 2D sheet network through C-H...N and bifurcated C-H...O contacts. Both symmetry independent molecules form centrosymmetric dimers *via* C-H...N contact with their respective pair. These different dimers are bridged through C-H...O contact forming flat sheet pattern. It is interesting to note here that molecules do not associate *via* Br...Br contacts in any of the above three cases.

As indicated in the introduction, the prime objective of this investigation is to develop a simple protocol for the synthesis of a group of isomeric compounds having the orthogonal functional groups that form the weaker intermolecular interactions. The copper (I) catalyzed Huisgen azide-alkyne cycloaddition (CuAAC) has been proven as highly relevant because of selectivity and its operational simplicity. The second objective is to examine the occurrence and geometrical preference of an identified Br...NO<sub>2</sub> weak interaction. Apart from the projected Br...NO<sub>2</sub> interaction, the absence of any strong and direction-specific intermolecular interactions in the present template gave an equal opportunity for the other weaker intermolecular interactions such as C-H...O, C-H...N, C-H...Br, and Br...Br short contacts to play their role in molecular aggregation. A comprehensive compilation of various weaker interactions observed in crystal structures of all compounds revealed that out of nine compounds, molecules in four compounds have Br...NO<sub>2</sub> association (Type III geometry), in two compounds Br...Br short contact and in one compound C-H...Br electrostatic interaction were present. It was quite interesting to notice that none of the isomers have the Type I geometry which has been identified as a

robust synthon. A close look at the secondary structures of a set of isomeric compounds reveal substantial similarity in the patterns of supramolecular aggregation and the nature of the interactions involved. This is quite striking when compared with the earlier reports where it has been observed that projected synthon appears to behave predictably only for specific isomeric forms, but normally to be absent for the remaining isomeric forms and also complexity involved in extrapolating the aggregation patterns from one isomer to others, even in simple isomers. The observed similarities in the 3 different groups of the present investigation is highly remarkable and demonstrates that it is not the weaker interactions that altered the intramolecular association, however, it is the relatively strong interactions which disturb the predictable weaker complimentary interaction patterns. It also indicates that structural analysis of weaker interactions in isolation and then examining the influence of strong interaction over them will give more valuable informations that can be used as the starting premise for crystal structure predictions in general and molecular design for material applications in particular.



**Figure 33:** (a) Space group, various weak interactions noticed in the crystal structures of all 9 compounds and no. of such interactions in each crystal structure. (b) Relative orientation of nitrophenyl and bromophenyl rings with respect to the aligned triazole in each series.

In conclusion, the potential of Cu(I) catalysed azide-alkyne “click reaction” as a simple synthetic tool for crystal engineering to build a collection of isomeric compounds

with modular positioning of complimentary functional groups was demonstrated. The elegance of this approach is that all the 9 compounds prepared through the [3+2]-azidoalkyne cycloaddition are crystalline. The investigation comprising the crystal structural analyses of closely related molecules demonstrate how weaker interactions like C-H $\cdots$ O and C-H $\cdots$ N could form self-complimentary motifs that are sufficiently strong enough to direct the crystal packing in general and also to block are fine tune the relatively stronger interactions like Br $\cdots$ NO<sub>2</sub> and Br $\cdots$ Br. The helical assembly of molecules through C-H $\cdots$ O interactions in P2NPT series, and the self complimentary patterns displayed in the crystal structures of P3NPT series shows that one can design materials that require a reversible alternative for covalent bond by employing exclusively weak hydrogen bonding interactions like C-H $\cdots$ O/N to form either 2D sheets or 3D-helical networks and work in this direction is progressing in our lab.

## **EXPERIMENTAL**

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## EXPERIMENTAL

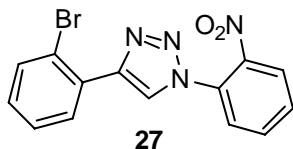
### General experimental procedure for S<sub>N</sub>Ar reaction:

Fluoronitrobenzene (100 mg, 0.71 mmol) was mixed with bromophenylacetylene (128 mg, 0.71 mmol) in 9:1 DMSO:H<sub>2</sub>O (10 mL). To the mixture were added L-proline (16 mg, 0.142 mmol), Na<sub>2</sub>CO<sub>3</sub> (15 mg, 0.142 mmol), NaN<sub>3</sub> (55 mg, 0.852 mmol), sodium ascorbate (14 mg, 0.071 mmol), and CuSO<sub>4</sub>·5H<sub>2</sub>O (9 mg, 0.036 mmol). The mixture was stirred for 24-48 h at 70 °C and then the mixture was poured into 30 mL of ice-cold water. The solid residue was filtered and crystallized in different solvent systems to procure white to yellow crystalline solid in 57-83% yield.

### General procedure for cycloaddition reactions with 3-azidobenzene (32):

A mixture of 3-Azidonitrobenzene (116 mg, 0.71 mmol), bromophenylacetylene (128 mg, 0.71 mmol) was taken in 9:1 DMSO:H<sub>2</sub>O (10 mL) in a round bottom flask and L-proline (16 mg, 0.142 mmol), Na<sub>2</sub>CO<sub>3</sub> (15 mg, 0.142 mmol), sodium ascorbate (14 mg, 0.071 mmol), and CuSO<sub>4</sub>·5H<sub>2</sub>O (9 mg, 0.036 mmol) were added to that mixture and the complete reaction mixture was heated at 70 °C (bath temperature) for 24 h with stirring. The reaction mixture was cooled to room temperature and diluted with 30 mL of water and combined water layer was thoroughly extracted with ethyl acetate (3 x 50 mL). Organic layer was dried over sodium sulphate and concentrated under vacuum. The crude solid was purified by column chromatography over 230-400 silica using ethyl acetate/light petroleum (1:4) to obtain white to yellow solids (65-74%). This solid was crystallized with different solvent systems.

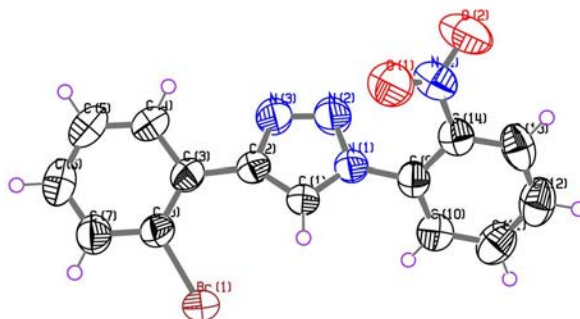
### 4-(2-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (2BP2NPT, 27)



Yield: 169 mg (65%). MP: 125 °C. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) δ 7.24 (dt, *J* = 1.7, 7.8 Hz, 1H), 7.46 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.68 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.73 (br. s, 1H), 7.75 (br. s, 1H), 7.83 (dt, *J* = 1.6, 8.1 Hz, 1H), 8.12 (dd, *J* = 1.5, 8.2 Hz, 1H), 8.24 (dd, *J* = 1.8, 7.8 Hz,

1H), 8.56 (s, 1H).  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 121.3 (s), 124.3 (d), 125.7 (d), 127.4 (s), 127.8 (d), 128.1 (s), 129.7 (d), 130.7 (d), 130.9 (d), 133.7 (d), 142.0 (s), 145.9 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$  : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.98; H, 2.39; Br, 23.19; N, 16.51%.

**Figure 34:** The molecular structure of compound 27 (displacement ellipsoids are drawn at the 50% probability level)

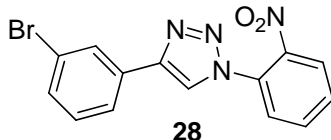


**Bond length and bond angle in Å and °**

Br1...C8	1.896(4)	O1...N4	1.209(4)	C3 C8 Br1	121.6(3)
N1...N2	1.335(5)	C4...C5	1.359(6)	C1 C2 N3	107.1(3)
N1...C1	1.348(5)	O2...N4	1.212(4)	C1 C2 C3	134.9(4)
N1...C9	1.406(5)	C10...C11	1.377(6)	N3 C2 C3	118.0(3)
C1...C2	1.346(5)	C13...C12	1.388(7)	N2 N3 C2	109.6(3)
C3...C8	1.388(5)	C12...C11	1.362(7)	N3 N2 N1	107.0(3)
C3...C4	1.391(5)			C10 C9 C14	118.3(4)
C3...C2	1.467(5)			C10 C9 N1	120.2(4)
C8...C7	1.380(5)	N2 N1 C1	110.0(3)	C14 C9 N1	121.4(4)
C2...N3	1.363(5)	N2 N1 C9	120.1(3)	C7 C6 C5	119.7(4)
N3...N2	1.308(5)	C1 N1 C9	129.8(3)	C13 C14 C9	121.2(4)
C9...C10	1.377(6)	N1 C1 C2	106.3(3)	C13 C14 N4	118.3(4)
C9...C14	1.400(6)	C8 C3 C4	115.7(4)	C9 C14 N4	120.4(4)
C6...C7	1.358(6)	C8 C3 C2	125.3(3)	C5 C4 C3	122.8(4)
C6...C5	1.381(7)	C4 C3 C2	119.0(4)	O1 N4 O2	124.2(4)
C14...C13	1.365(6)	C7 C8 C3	122.1(4)	O1 N4 C14	118.4(4)
C14...N4	1.463(6)	C7 C8 Br1	116.3(3)	O2 N4 C14	117.2(4)

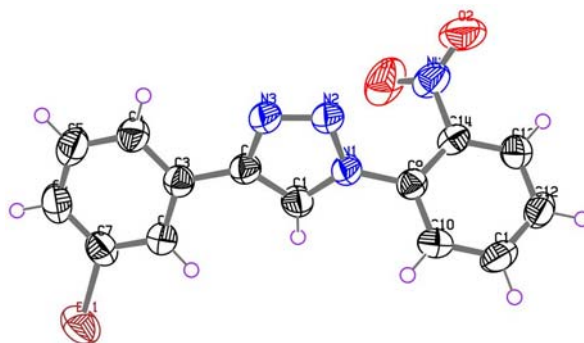
C4 C5 C6	119.7(5)	C9 C10 C11	120.7(4)	C11 C12 C13	120.8(5)
C6 C7 C8	120.0(4)	C14 C13 C12	118.9(4)	C12 C11 C10	120.0(5)

#### 4-(3-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (3BP2NPT, 28)



Yield: 174 mg (71%). MP: 101 °C. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) δ 7.02-7.44 (m, 3H), 7.58-7.82 (m, 4H), 7.94-8.04 (m, 2H). <sup>13</sup>C (100 MHz, CDCl<sub>3</sub>) 121.4 (d), 123.1 (s), 124.5 (d), 125.7 (d), 126.9 (d), 127.90 (d), 129.0 (d), 130.5 (d), 130.8 (d), 131.5 (d), 131.8 (s), 133.8 (d), 144.4 (s), 146.9 (s) ppm. Anal. Calcd for C<sub>14</sub>H<sub>9</sub>BrN<sub>4</sub>O<sub>2</sub> : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.76; H, 2.52; Br, 23.42; N, 16.11%.

**Figure 35:** The molecular structure of compound 28 (displacement ellipsoids are drawn at the 50% probability level)



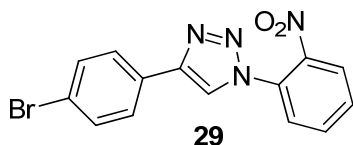
#### Bond length and bond angle in Å and °

Br1...C3	1.893(3)	C3...C7	1.381(4)	C10...N1	1.465(4)
N2...C2	1.335(4)	C4...C9	1.378(4)	C11...C12	1.374(4)
N2...N3	1.354(3)	C4...C10	1.389(4)	C12...C13	1.380(5)
N2...C4	1.427(3)	C5...C14	1.389(4)	N1...O2	1.213(4)
N3...N4	1.306(3)	C5...C6	1.393(4)	N1...O1	1.213(4)
C1...N4	1.360(3)	C7...C8	1.372(5)		
C1...C2	1.366(4)	C8...C14	1.386(4)		
C1...C5	1.467(4)	C9...C13	1.376(4)		
C3...C6	1.380(4)	C10...C11	1.368(4)	C2 N2 N3	110.8(2)



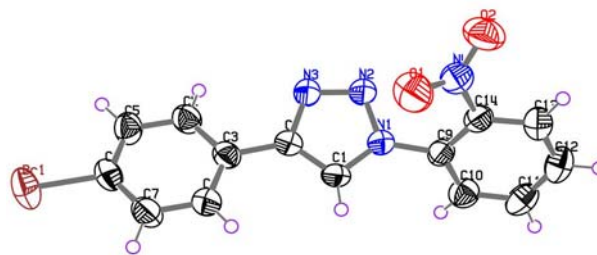
C2 N2 C4	128.7(2)	C9 C4 N2	120.2(3)	C11 C10 N1	117.6(3)
N3 N2 C4	120.5(2)	C10 C4 N2	121.6(2)	C4 C10 N1	120.8(3)
N4 N3 N2	106.6(2)	N3 N4 C1	109.6(2)	C10 C11 C12	119.7(3)
N4 C1 C2	107.6(2)	C14 C5 C6	119.1(3)	C11 C12 C13	119.6(3)
N4 C1 C5	122.9(2)	C14 C5 C1	121.2(3)	O2 N1 O1	124.1(3)
C2 C1 C5	129.5(3)	C6 C5 C1	119.7(3)	O2 N1 C10	118.4(3)
N2 C2 C1	105.4(2)	C3 C6 C5	119.7(3)	O1 N1 C10	117.3(3)
C6 C3 C7	121.3(3)	C8 C7 C3	118.9(3)	C9 C13 C12	120.5(3)
C6 C3 Br1	119.3(2)	C7 C8 C14	121.0(3)	C8 C14 C5	120.0(3)
C7 C3 Br1	119.4(2)	C13 C9 C4	120.5(3)		
C9 C4 C10	118.2(3)	C11 C10 C4	121.5(3)		

#### 4-(4-Bromophenyl)-1-(2-nitrophenyl)-1H-1,2,3-triazole (4BP2NPT, 29)



Yield: 140 mg (57%). MP: 136-137 °C. <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.50 (m, 1H), 7.57 (dt, *J* = 2.2, 8.7 Hz, 1H), 7.65-7.88 (m, 5H), 8.06 (s, 1H), 8.06-8.22 (m, 1H). <sup>13</sup>C (100 MHz, CDCl<sub>3</sub>) 121.0 (d), 122.7 (s), 125.6 (d), 127.5 (d), 127.9 (d), 129.8 (d), 130.8 (d), 132.2 (d), 132.4 (d), 133.8 (d), 144.4 (s), 147.4 (s) ppm. Anal. Calcd for C<sub>14</sub>H<sub>9</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27; Found: C, 48.44; H, 2.40; Br, 23.11; N, 16.41.

**Figure 36:** The molecular structure of compound **29** (displacement ellipsoids are drawn at the 50% probability level)



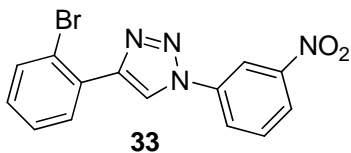
**Bond length and bond angle in Å and °**

Br1...C1	1.903(3)	C9...C10	1.369(5)	C14 C5 C4	118.6(3)
C1...C2	1.375(5)	C10...C13	1.366(5)	C14 C5 N3	120.6(3)
C1...C8	1.376(5)	C13...C14	1.381(5)	C4 C5 N3	120.7(2)
N3...C6	1.344(4)			N1 C11 C6	107.5(3)
N3...N2	1.352(3)			N1 C11 C3	121.3(2)
N3...C5	1.423(4)			C6 C11 C3	131.1(3)
C2...C7	1.387(4)	C2 C1 C8	121.5(3)	N2 N1 C11	109.8(2)
C3...C7	1.384(4)	C2 C1 Br1	118.8(2)	C3 C7 C2	121.0(3)
C3...C12	1.388(4)	C8 C1 Br1	119.7(2)	O2 N4 O1	123.9(3)
C3...C11	1.472(4)	C6 N3 N2	110.4(2)	O2 N4 C4	118.7(3)
C6...C11	1.363(4)	C6 N3 C5	130.8(3)	O1 N4 C4	117.3(3)
C4...C9	1.376(4)	N2 N3 C5	118.6(2)	C1 C8 C12	119.0(3)
C4...C5	1.388(4)	C1 C2 C7	118.8(3)	C10 C9 C4	119.4(3)
C4...N4	1.469(4)	C7 C3 C12	118.6(3)	C9 C10 C13	120.2(3)
C5...C14	1.383(4)	C7 C3 C11	119.8(3)	N1 N2 N3	106.7(2)
C11...N1	1.359(4)	C12 C3 C11	121.6(3)	C8 C12 C3	121.1(3)
N1...N2	1.305(3)	N3 C6 C11	105.5(3)	C10 C13 C14	120.9(3)
N4...O2	1.214(4)	C9 C4 C5	121.0(3)	C13 C14 C5	119.6(3)
N4...O1	1.220(3)	C9 C4 N4	117.4(3)		
C8...C12	1.378(5)	C5 C4 N4	121.4(3)		

Table 1

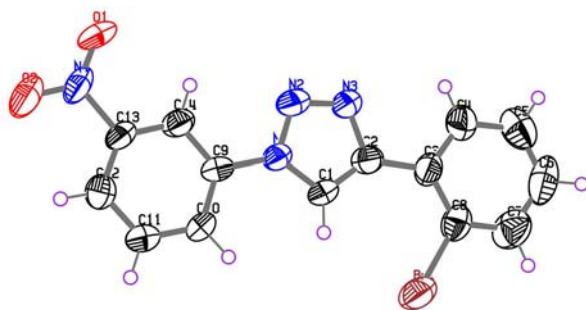
Crystal data	27	28	29
Formula	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>
M <sub>r</sub>	345.16	345.16	345.16
Crystal size, mm	0.77x0.68x0.54	0.51x0.23x0.13	0.68x0.25x0.20
Temp. (K)	297(2)	297(2)	297(2)
Crystal system	monoclinic	monoclinic	monoclinic
space group	P2 <sub>1</sub> /n	P2 <sub>1</sub> /n	P2 <sub>1</sub> /c
A [Å]	12.388(13)	9.2835(11)	5.4468(9)
B [Å]	8.051(9)	7.2943(9)	20.778(3)
C [Å]	14.256(15)	20.794(2)	12.482(2)
β [°]	103.305(18)	97.444(2)	102.427(3)
V [Å <sup>3</sup> ]	1384(2)	1396.2(3)	1379.6(4)
Z	4	4	4
F(000)	688	688	688
D calc [g cm <sup>-3</sup> ]	1.657	1.642	1.662
μ [mm <sup>-1</sup> ]	2.981	2.954	2.989
Absorp.correction	multi-scan	multi-scan	multi-scan
T <sub>min</sub>	0.2074	0.3142	0.2357
T <sub>max</sub>	0.2959	0.7001	0.5862
reflns. collected	6344	8147	6843
Unique reflns.	2419	2448	2427
Observed reflns.	1685	1881	1896
h, k, l (min, max)	(-12, 14), (-7, 9), (-16, 16)	(-11, 10), (-8, 8), (-24, 24)	(-6, 6), (-22, 24), (-9, 14)
R <sub>int</sub>	0.0517	0.0238	0.0221
No. of parameters	190	190	226
R <sub>1</sub> [I>2σ(I)]	0.0466	0.0369	0.0361
wR <sub>2</sub> [I>2σ(I)]	0.1245	0.0876	0.0823
R <sub>1</sub> (all data)	0.0699	0.0518	0.0503
WR <sub>2</sub> (all data)	0.1376	0.0942	0.0889
goodness-of-fit	0.960	1.030	1.045
Δρ <sub>max</sub> , Δρ <sub>min</sub> (eÅ <sup>-3</sup> )	0.923, -0.280	0.568, -0.389	0.657, -0.506

## 4-(2-Bromophenyl)-1-(3-nitrophenyl)-1H-1,2,3-triazole (2BP3NPT, 33)



Yield: 173 mg (71%). MP: 131-132 °C.  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (ddd,  $J = 1.8, 7.4, 9.2$  Hz, 1H), 7.46 (dt,  $J = 1.3, 7.8$  Hz, 1H), 7.69 (dd,  $J = 1.1, 8.1$  Hz, 1H), 7.78 (t,  $J = 8.2$  Hz, 1H), 8.20 (dd,  $J = 1.8, 7.8$  Hz, 1H), 8.27 (ddd,  $J = 1.0, 2.1, 8.2$  Hz, 1H), 8.33 (ddd,  $J = 1.0, 2.1, 8.2$  Hz, 1H), 8.66 (t,  $J = 2.1$  Hz, 1H), 8.79 (s, 1H).  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 115.3 (d), 120.6 (d), 121.3 (s), 123.2 (d), 126.0 (d), 127.9 (d), 129.9(d), 130.4 (s), 130.8 (d), 131.0 (d), 133.7 (d), 137.8 (s), 146.6 (s), 149.1 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$  : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 49.00; H, 2.81; Br, 23.42; N, 16.11%.

**Figure 37:** The molecular structure of compound **33**(displacement ellipsoids are drawn at the 50% probability level)

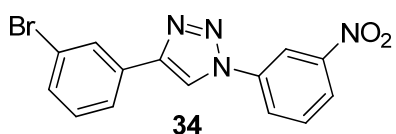


**Bond length and bond angle in Å and °**

O1...N4	1.20(2)	C5...C7	1.38(2)	N2 N1 C9	108.8(12)
Br1...C10	1.914(18)	N2...N3	1.29(2)	N2 N1 C3	119.7(11)
N1...N2	1.342(18)	C6...C9	1.33(2)	C9 N1 C3	131.5(12)
N1...C9	1.343(18)	C6...N3	1.380(19)	C8 C1 C3	117.5(15)
N1...C3	1.442(19)	N4...O2	1.210(19)	C12 C2 C10	115.5(15)
C1...C8	1.37(2)	N4...C8	1.492(18)	C12 C2 C6	119.0(14)
C1...C3	1.37(2)	C10...C11	1.35(3)	C10 C2 C6	125.5(15)
C2...C12	1.38(2)	C11...C14	1.41(3)	C1 C3 C5	122.1(15)
C2...C10	1.41(2)	C12...C13	1.41(3)	C1 C3 N1	119.0(13)
C2...C6	1.49(2)	C13...C14	1.34(3)	C5 C3 N1	118.9(13)
C3...C5	1.39(2)			C8 C4 C7	117.0(15)
C4...C8	1.36(2)			C7 C5 C3	118.6(14)
C4...C7	1.42(2)			N3 N2 N1	107.8(12)

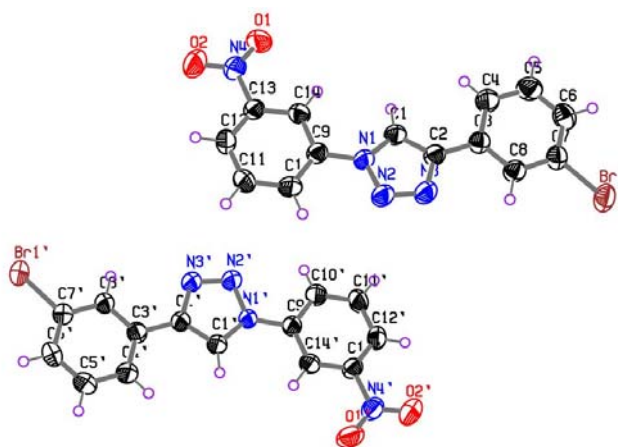
C9 C6 N3	106.6(14)	N2 N3 C6	109.1(14)	C2 C10 Br1	121.4(12)
C9 C6 C2	136.4(14)	C4 C8 C1	124.0(13)	C10 C11 C14	119.1(19)
N3 C6 C2	117.0(14)	C4 C8 N4	119.1(14)	C2 C12 C13	121.9(18)
O1 N4 O2	123.7(14)	C1 C8 N4	116.9(14)	C14 C13 C12	120(2)
O1 N4 C8	117.1(16)	C6 C9 N1	107.7(13)	C13 C14 C11	119.8(19)
O2 N4 C8	119.1(14)	C11 C10 C2	123.6(18)		
C5 C7 C4	120.9(15)	C11 C10 Br1	115.0(14)		

#### 4-(3-Bromophenyl)-1-(3-nitrophenyl)-1H-1,2,3-triazole (3BP3NPT, 34)



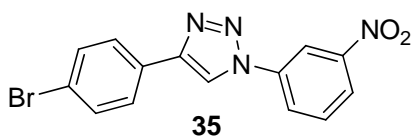
Yield: 159 mg (65%). MP: 195-196 °C.  $^1\text{H}$  (400 MHz, DMSO- $\text{D}_6$ )  $\delta$  7.37-7.54 (m, 2H), 7.84-7.99 (m, 2H), 8.14 (t,  $J$  = 1.6 Hz, 1H), 8.32 (dd,  $J$  = 1.6, 8.3 Hz, 1H), 8.46 (dd,  $J$  = 1.6, 8.3 Hz, 1H), 8.86 (t,  $J$  = 2.0 Hz, 1H), 9.58 (s, 1H).  $^{13}\text{C}$  (100 MHz, DMSO- $\text{D}_6$ ) 112.7 (d), 118.5 (d), 120.7 (s), 121.1 (d), 122.4 (d), 123.8 (d), 126.4 (d), 129.1 (d), 129.2 (d), 129.6 (d), 130.6 (s), 135.6 (s), 144.8 (s), 146.9 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$ : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.91; H, 2.83; Br, 23.09; N, 16.06%.

**Figure 38:** The molecular structure of compound 34 (displacement ellipsoids are drawn at the 50% probability level)



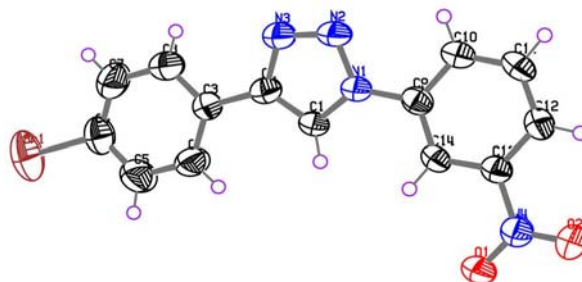
**Bond length and bond angle in Å and °**

Br1...C2	1.908(3)	C7 C2 C4	121.8(3)
C1...N4	1.483(4)	C7 C2 Br1	118.4(2)
C2...C7	1.377(4)	C4 C2 Br1	119.7(2)
C2...C4	1.380(5)	N2 N3 C13	109.3(3)
N3...N2	1.309(4)	C7 C6 C5	120.6(3)
N3...C13	1.368(4)	C2 C7 C6	119.8(3)
C5...C6	1.464(4)	C12 N1 N2	110.4(2)
C6...C7	1.381(4)	C12 N1 C10	129.7(3)
N1...C12	1.341(4)	N2 N1 C10	119.9(3)
N1...N2	1.353(3)	C9 C10 N1	119.4(3)
N1...C10	1.429(4)	O1 C11 O2	123.0(3)
C9...C10	1.376(4)	N1 C12 C13	105.8(3)
C11...O1	1.200(4)	C12 C13 N3	107.5(3)
C11...O2	1.208(4)	C12 C13 C14	130.1(3)
C12...C13	1.362(4)	N3 C13 C14	122.4(3)
N4...O3	1.225(4)	N3 N2 N1	106.9(2)
C13...C14	1.469(4)		

**4-(4-Bromophenyl)-1-(3-nitrophenyl)-1H-1,2,3-triazole (4BP3NPT, 35)**

Yield: 181 mg (74%). MP: 230-231 °C. <sup>1</sup>H (400 MHz, DMSO-D<sub>6</sub>) δ 7.46 (br. s, 1H), 7.50 (br. s, 1H), 7.71-7.78 (m, 3H), 8.18 (dd, *J* = 2.1, 8.1 Hz, 1H), 8.30 (dd, *J* = 2.5, 8.2 Hz, 1H), 8.68 (t, *J* = 2.1 Hz, 1H), 9.35 (s, 1H). <sup>13</sup>C (100 MHz, DMSO-D<sub>6</sub>) 112.8 (d), 118.2 (d), 120.0 (s), 121.2 (d), 123.9 (d), 125.1 (d), 125.6 (d), 127.5 (s), 127.7 (d), 129.7 (d), 130.1 (d), 135.7 (s), 145.3 (s), 146.9 (s) ppm. Anal. Calcd for C<sub>14</sub>H<sub>9</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.75; H, 2.81; Br, 23.23; N, 16.30%.

**Figure 39:** The molecular structure of compound **35** (displacement ellipsoids are drawn at the 50% probability level)



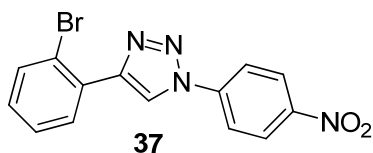
**Bond length and bond angle in Å and °**

Br1...C1	1.896(4)	C7...C9	1.353(5)	C7 N3 C2	130.7(3)
N4...O1	1.214(4)	C10...C13	1.376(6)	N2 N3 C2	119.6(3)
N4...O2	1.224(4)	C12...C14	1.374(6)	C6 C4 C8	117.5(4)
N4...C8	1.465(4)			N1 N2 N3	107.2(3)
C1...C10	1.353(6)			C2 C5 C8	117.8(3)
C1...C12	1.363(6)			C4 C6 C11	121.3(4)
N1...N2	1.307(4)	O1 N4 O2	123.5(3)	N3 C7 C9	106.1(3)
N1...C9	1.362(4)	O1 N4 C8	118.4(3)	C5 C8 C4	123.1(3)
C2...C5	1.379(5)	O2 N4 C8	118.1(3)	C5 C8 N4	117.8(3)
C2...C11	1.389(5)	C10 C1 C12	119.9(4)	C4 C8 N4	119.0(3)
C2...N3	1.425(4)	C10 C1 Br1	119.6(3)	C7 C9 N1	107.9(3)
C3...C13	1.369(5)	C12 C1 Br1	120.5(3)	C7 C9 C3	129.8(3)
C3...C14	1.373(5)	N2 N1 C9	109.1(3)	N1 C9 C3	122.3(3)
C3...C9	1.478(5)	C5 C2 C11	120.7(3)	C1 C10 C13	120.2(4)
N3...C7	1.342(4)	C5 C2 N3	119.4(3)	C6 C11 C2	119.5(4)
N3...N2	1.356(4)	C11 C2 N3	119.9(3)	C1 C12 C14	119.9(4)
C4...C6	1.374(5)	C13 C3 C14	117.8(4)	C3 C13 C10	121.1(4)
C4...C8	1.382(5)	C13 C3 C9	120.8(3)	C3 C14 C12	121.2(4)
C5...C8	1.379(5)	C14 C3 C9	121.4(3)		
C6...C11	1.380(5)	C7 N3 N2	109.7(3)		

Table 2

Crystal data	33	34	35
Formula	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>
M <sub>r</sub>	345.16	266.26	345.16
Crystal size, mm	0.76x0.07x0.0	0.33x0.26x0.0	0.37x0.32x0.0
	6	9	3
Temp. (K)	297(2)	297(2)	297(2)
Crystal system	monoclinic	triclinic	monoclinic
space group	P2 <sub>1</sub> /n	P-1	P2 <sub>1</sub> /n
A [Å]	7.228(7)	7.4402(6)	8.667(3)
B [Å]	13.308(13)	12.4535(10)	5.2323(18)
C [Å]	14.521(15)	14.6016(12)	30.304(11)
α [°]	90	91.2720(10)	90
β [°]	93.675(19)	98.9940(10)	96.248(6)
γ [°]	90	96.3090(10)	90
V [Å <sup>3</sup> ]	1394(2)	1327.14(19)	1366.0(8)
Z	4	4	4
F(000)	688	688	688
D calc [g cm <sup>-3</sup> ]	1.645	1.727	1.678
μ [mm <sup>-1</sup> ]	2.959	3.107	3.019
Absorp.correction	multi-scan	multi-scan	multi-scan
T <sub>min</sub>	0.2120	0.4270	0.4013
T <sub>max</sub>	0.8518	0.7673	0.9149
reflns. collected	9670	12926	6524
Unique reflns.	2455	4654	2403
Observed reflns.	1522	3565	1718
h, k, l (min, max)	(-8, 8), (-15, 13), (-17, 17)	(-8, 8), (-14, 14), (-17, 17)	(-9, 10), (-6, 5), (-36, 27)
R <sub>int</sub>	0.0571	0.0269	0.0289
No. of parameters	190	379	226
R <sub>1</sub> [I > 2σ(I)]	0.1357	0.0342	0.0459
wR <sub>2</sub> [I > 2σ(I)]	0.3958	0.0785	0.1064
R <sub>1</sub> (all data)	0.1755	0.0492	0.0675
WR <sub>2</sub> (all data)	0.4175	0.0847	0.1186
goodness-of-fit	1.141	1.023	1.034
Δρ <sub>max</sub> , Δρ <sub>min</sub> (eÅ <sup>-3</sup> )	2.445, -0.631	0.436, -0.291	0.645, -0.540

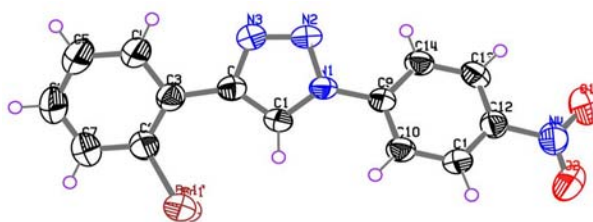
## 4-(2-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (2BP4NPT, 37)





Yield: 203 mg (83%). MP: 170-171 °C.  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (ddd,  $J = 1.8, 7.4, 9.2$  Hz, 1H), 7.47 (dt,  $J = 1.2, 7.8$  Hz, 1H), 7.69 (dd,  $J = 1.2, 7.9$  Hz, 1H), 8.04 (t,  $J = 2.6$  Hz, 1H), 8.09 (t,  $J = 2.6$  Hz, 1H), 8.2 (dd,  $J = 1.6, 7.8$  Hz, 1H), 8.42 (t,  $J = 2.6$  Hz, 1H), 8.47 (t,  $J = 2.6$  Hz, 1H), 8.79 (s, 1H).  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 120.5 (d), 121.3 (s), 124.1 (d), 124.9 (d), 125.6 (d), 127.9 (d), 130.0 (d), 130.2 (d), 130.8 (d), 131.9 (s), 133.8 (d), 141.1 (s), 146.7 (s), 147.3 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$ : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.57; H, 2.90; Br, 22.89; N, 16.12%.

**Figure 40:** The molecular structure of compound 37 (displacement ellipsoids are drawn at the 50% probability level)

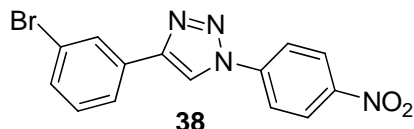


**Bond length and bond angle in Å and °**

Br1...C10	1.897(6)	N4...O2	1.218(7)	C6 C2 C3	121.1(5)
N3...N2	1.343(5)	C6...C7	1.374(7)	C6 C2 N3	119.7(4)
N3...C1	1.364(6)	C9...C13	1.382(8)	C3 C2 N3	119.2(4)
N3...C2	1.414(6)	C9...C10	1.391(8)	C8 C3 C2	119.6(5)
C1...C4	1.367(7)	C10...C11	1.387(9)	C1 C4 N1	106.7(4)
C2...C6	1.383(6)	C11...C12	1.368(10)	C1 C4 C9	134.6(5)
C2...C3	1.389(7)	C12...C14	1.373(11)	N1 C4 C9	118.6(4)
C3...C8	1.377(8)	C13...C14	1.376(10)	N1 N2 N3	107.4(4)
C4...N1	1.369(6)			C8 C5 C7	122.2(5)
C4...C9	1.466(7)			C8 C5 N4	119.7(5)
N2...N1	1.303(6)			C7 C5 N4	118.1(5)
C5...C8	1.379(7)	N2 N3 C1	109.8(4)	N2 N1 C4	110.3(4)
C5...C7	1.379(7)	N2 N3 C2	120.4(4)	O1 N4 O2	123.6(5)
C5...N4	1.469(7)	C1 N3 C2	129.8(4)	O1 N4 C5	118.3(5)
N4...O1	1.210(7)	N3 C1 C4	105.8(4)	O2 N4 C5	118.1(5)

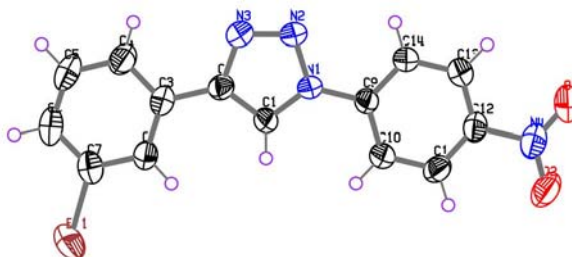
C7 C6 C2	119.4(5)	C10 C9 C4	126.3(5)	C11 C12 C14	120.0(7)
C6 C7 C5	119.1(5)	C11 C10 C9	122.2(6)	C14 C13 C9	122.6(6)
C3 C8 C5	118.6(5)	C11 C10 Br1	115.7(5)	C12 C14 C13	119.7(7)
C13 C9 C10	116.1(5)	C9 C10 Br1	122.0(4)		
C13 C9 C4	117.7(5)	C12 C11 C10	119.4(7)		

#### 4-(3-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (3BP4NPT, 38)



Yield: 198 mg (81%). MP: 217-218 °C.  $^1\text{H}$  (400 MHz, DMSO- $\text{D}_6$ )  $\delta$  7.36-7.54 (m, 2H), 7.96 (dt,  $J = 1.8, 7.6$  Hz, 1H), 8.14 (t,  $J = 1.6$  Hz, 1H), 8.26, 8.31, 8.45, 8.51 (4br. m, 4H), 9.47 (s, 1H).  $^{13}\text{C}$  (100 MHz, DMSO- $\text{D}_6$ ) 118.6 (d), 120.8 (d), 122.6 (s), 123.8 (d), 124.1 (d), 126.5 (d), 127.4 (d), 129.1 (d), 129.4 (d), 130.5 (s), 139.3 (s), 145.0 (s), 145.1 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$ : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.63; H, 2.88; Br, 23.29; N, 16.48%.

**Figure 41:** The molecular structure of compound 38 (displacement ellipsoids are drawn at the 50% probability level)

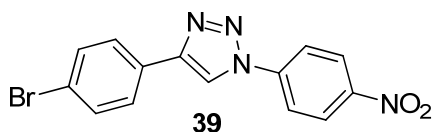


#### Bond length and bond angle in Å and °

Br1...C10	1.897(3)	N1...N2	1.303(3)	C3...C6	1.388(4)
N3...C1	1.346(3)	N1...C7	1.368(4)	N4...O2	1.218(4)
N3...N2	1.353(3)	C2...C10	1.381(4)	N4...C5	1.467(4)
N3...C3	1.418(3)	C2...C8	1.386(4)	C4...C6	1.366(4)
O1...N4	1.220(3)	C3...C9	1.384(4)	C4...C5	1.378(4)

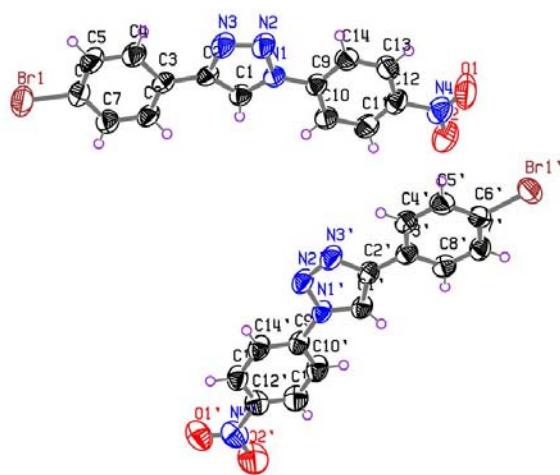
C5...C12	1.372(4)	C10 C2 C8	119.9(3)	C1 C7 C8	130.0(2)
C1...C7	1.357(4)	N1 N2 N3	107.3(2)	N1 C7 C8	122.5(2)
C7...C8	1.470(4)	C9 C3 C6	120.5(2)	C2 C8 C11	118.8(3)
C8...C11	1.391(4)	C9 C3 N3	119.8(2)	C2 C8 C7	120.4(2)
C9...C12	1.381(4)	C6 C3 N3	119.8(2)	C11 C8 C7	120.8(3)
C10...C14	1.382(4)	O2 N4 O1	123.6(3)	C12 C9 C3	119.7(3)
C11...C13	1.382(5)	O2 N4 C5	118.3(3)	C2 C10 C14	121.5(3)
C13...C14	1.372(5)	O1 N4 C5	118.1(3)	C2 C10 Br1	118.7(2)
		C6 C4 C5	118.9(3)	C14 C10 Br1	119.8(2)
		C12 C5 C4	122.3(3)	C13 C11 C8	120.2(3)
		C12 C5 N4	118.7(3)	C5 C12 C9	118.7(3)
C1 N3 N2	109.9(2)	C4 C5 N4	119.0(3)	C14 C13 C11	121.3(3)
C1 N3 C3	129.3(2)	C4 C6 C3	119.9(3)	C13 C14 C10	118.3(3)
N2 N3 C3	120.7(2)	N3 C1 C7	105.9(2)		
N2 N1 C7	109.4(2)	C1 C7 N1	107.5(2)		

#### 4-(4-Bromophenyl)-1-(4-nitrophenyl)-1H-1,2,3-triazole (4BP4NPT, 39)



Yield: 198 mg (81%). MP: 149-150 °C.  $^1\text{H}$  (400 MHz, DMSO- $\text{D}_6$ )  $\delta$  7.59 (t,  $J=2.2$  Hz, 1H), 7.64 (t,  $J=2.2$  Hz, 1H), 7.77 (t,  $J=2.2$  Hz, 1H), 7.82 (t,  $J=2.2$  Hz, 1H), 8.01 (t,  $J=2.2$  Hz, 1H), 8.06 (t,  $J=2.2$  Hz, 1H), 8.28 (t,  $J=2.2$  Hz, 1H), 8.44 (t,  $J=2.2$  Hz, 1H), 8.48 (t,  $J=2.2$  Hz, 1H).  $^{13}\text{C}$  (100 MHz, DMSO- $\text{D}_6$ ) 118.2 (d), 118.5 (d), 119.9 (s), 123.7 (d), 125.5 (d), 127.3 (s), 130.1 (d), 139.1 (s), 144.9 (s), 145.2 (s) ppm. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{BrN}_4\text{O}_2$ : C, 48.72; H, 2.63; Br, 23.15; N, 16.23; O, 9.27%; Found: C, 48.70; H, 2.40; Br, 23.43; N, 16.01%.

**Figure 42:** The molecular structure of compound **39** (displacement ellipsoids are drawn at the 50% probability level)



**Bond length and bond angle in Å and °**

Br1...C14	1.899(4)	C8 N1 N2	110.4(3)
N1...C8	1.341(4)	C8 N1 C4	129.6(3)
N1...N2	1.363(4)	N2 N1 C4	119.8(3)
N1...C4	1.414(5)	N2 N3 C10	109.9(3)
C1...N4	1.380(6)	N1 C8 C10	105.9(3)
N3...N2	1.303(5)	C8 C10 N3	107.0(3)
N3...C10	1.376(5)	C12 C14 Br1	118.6(3)
C8...C10	1.370(5)	N3 N2 N1	106.7(3)
C12...C14	1.376(6)		

Table 3

Crystal data	37	38	39
Formula	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>9</sub> BrN <sub>4</sub> O <sub>2</sub>
M <sub>r</sub>	345.16	266.26	345.16
Crystal size, mm	0.68x0.25x0.20	0.88x0.13x0.08	0.82x0.43x0.12
Temp. (K)	297(2)	297(2)	297(2)
Crystal system	monoclinic	monoclinic	triclinic
space group	C2/c	P2 <sub>1</sub> /c	P-1
A [Å]	29.52(2)	7.5222(8)	9.6141(15)
B [Å]	7.057(5)	14.1697(15)	12.0915(19)
C [Å]	13.022(9)	13.0479(14)	12.900(2)
α [°]	90	90	87.535(2)
β [°]	97.405(12)	90.391(2)	71.407(2)
γ [°]	90	90	76.183(2)
V [Å <sup>3</sup> ]	2690(3)	1390.7(3)	1379.3(4)
Z	8	4	4
F(000)	1376	688	688
D calc [g cm <sup>-3</sup> ]	1.705	1.649	1.662
μ [mm <sup>-1</sup> ]	3.066	2.965	2.990
Absorp.correction	multi-scan	multi-scan	multi-scan
T <sub>min</sub>	0.2296	0.1800	0.1930
T <sub>max</sub>	0.5791	0.7888	0.7155
reflns. collected	6468	7835	13109
Unique reflns.	2377	2434	4834
Observed reflns.	1764	1859	3401
<i>h, k, l</i> (min, max)	(-34, 28), (-5, 8), (-15, 15)	(-8, 8), (-16, 14), (-15, 15)	(-11, 11), (-14, 14), (-15, 15)
R <sub>int</sub>	0.0378	0.0258	0.0356
No. of parameters	199	190	379
R <sub>1</sub> [I > 2σ(I)]	0.0385	0.0387	0.0429
wR <sub>2</sub> [I > 2σ(I)]	0.0953	0.0958	0.1159
R <sub>1</sub> (all data)	0.0556	0.0547	0.0674
WR <sub>2</sub> (all data)	0.1037	0.1033	0.1284
goodness-of-fit	1.010	1.041	1.019
Δρ <sub>max</sub> , Δρ <sub>min</sub> (eÅ <sup>-3</sup> )	0.314, -0.234	0.489, -0.444	0.856, -0.469

**Table 4: Selected torsion angles:**

$\tau_1$  is C<sub>14</sub>-C<sub>9</sub>-N<sub>1</sub>-N<sub>2</sub>,  $\tau_2$  is N<sub>3</sub>-C<sub>2</sub>-C<sub>3</sub>-C<sub>4</sub>,  $\tau_1'$  is C<sub>1</sub>-N<sub>1</sub>-C<sub>9</sub>-C<sub>10</sub>,  $\tau_2'$  is C<sub>1</sub>-C<sub>2</sub>-C<sub>3</sub>-C<sub>8</sub>,  $\tau_3$  is O<sub>1</sub>-N-C-C,  $\tau_3'$  is O<sub>2</sub>-N-C-C,  $\tau$  is the torsion angle between Br-C-C-N<sub>4</sub>.

Compound	$\tau_1$	$\tau_2$	$\tau_3$	$\tau_3'$	$\tau_1'$	$\tau_2'$	$\tau$
<b>27</b>	54.17	-19.43	38.29	37.70	55.06	-23.21	-147.42
<b>28</b>	-51.33	15.97	-41.08	-40.67	-52.40	14.72	138.01
<b>29</b>	50.46	16.75	35.26	35.86	58.57	15.31	-50.72
<b>33</b>	-1.78	2.80	-7.63	-9.79	-1.80	2.13	-179.51
<b>34</b>	-5.59	1.03	2.47	3.70	-3.65	0.43	-179.32
<b>35</b>	-12.91	8.32	1.33	0.48	-12.55	7.61	4.17
<b>37</b>	-24.08	-4.37	-1.20	0.53	-23.78	-2.54	5.01
<b>38</b>	-5.93	6.60	-1.96	-1.22	-4.53	6.61	1.53
<b>39</b>	-13.05	8.96	10.54	7.85	-16.22	10.97	9.46

**Table 5: Geometric parameters of intermolecular interactions**

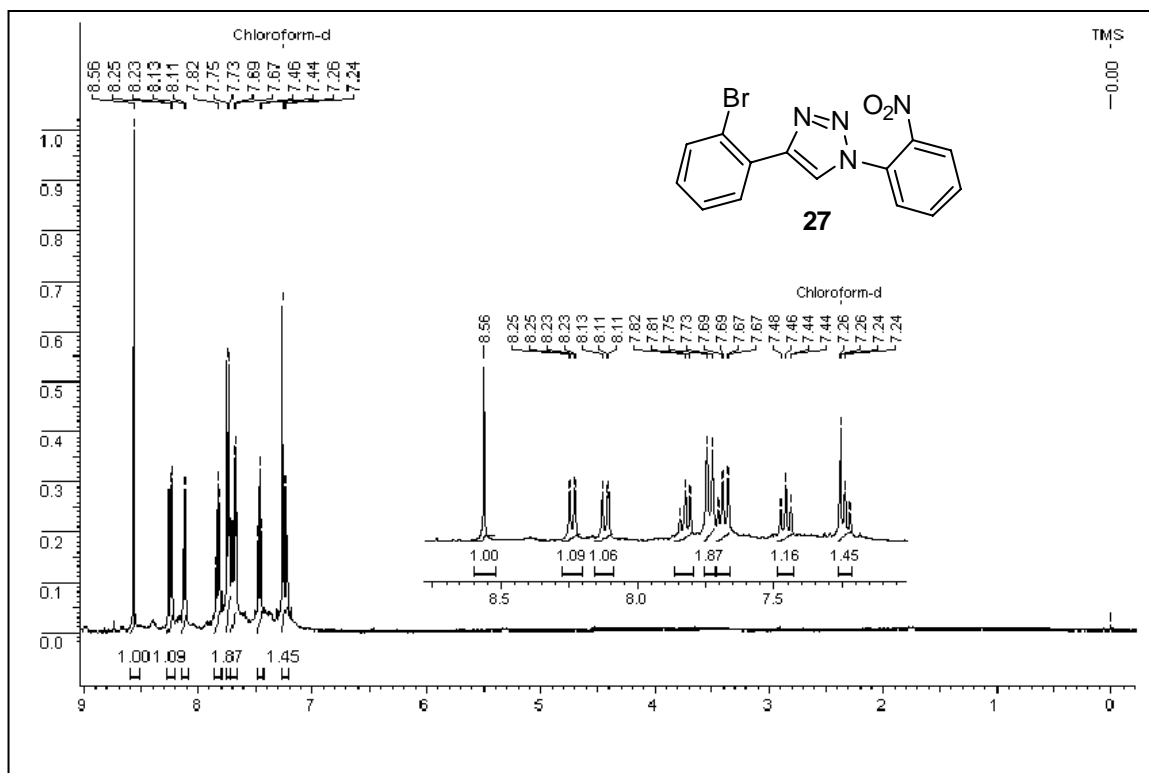
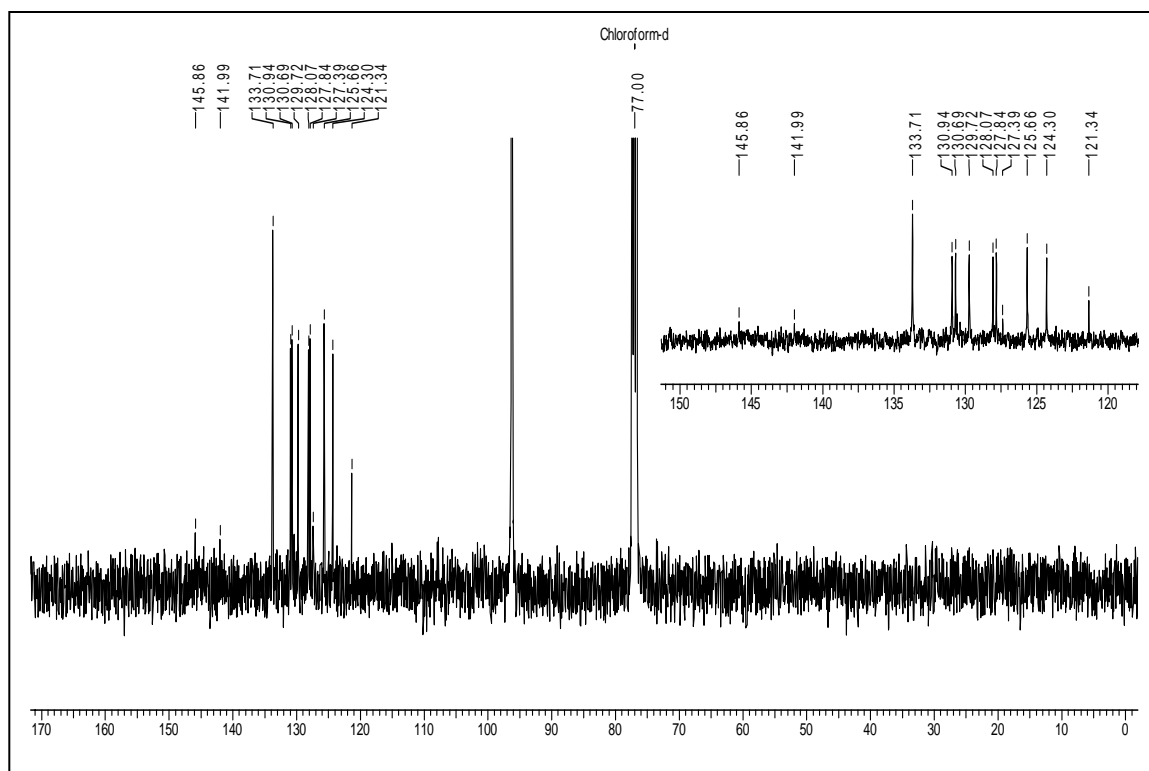
	D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A (°)
<b>27</b>	C(1)-H(1)...O(1)	0.93	2.65	3.451(6)	141
	C(13)-H(13)...O(2)	0.93	2.68	3.482(6)	145
	C(5)-H(5)...Br(1)	0.93	2.92	3.690(6)	145
<b>28</b>	C(1)-H(1)...O(1)	0.93	2.32	3.153(4)	150
	C(11)-H(11)...N(2)	0.93	2.54	3.360(4)	147
	C(7)-Br(1)...Br(1)	1.893(3)	3.696(1)		140.5(3)
<b>29</b>	C(12)-H(12)...O(2)	0.95(4)	2.82(4)	3.715(4)	158(3)
	C(12)-H(12)...O(1)	0.95(4)	2.76(4)	3.308(4)	117(3)
	C(1)-H(1)...N(2)	0.86(3)	2.66(3)	3.447(4)	152(2)
	C(1)-H(1)...N(3)	0.86(3)	2.82(3)	3.530(4)	141(2)
	C(6)-Br(1)...Br(1)	1.903(3)	3.473(1)		155.5(2)
<b>33</b>	C(10)-H(10)...O(2)	0.93	2.67	3.57(2)	165
	C(10)-H(10)...O(1)	0.93	2.72	3.336(19)	125

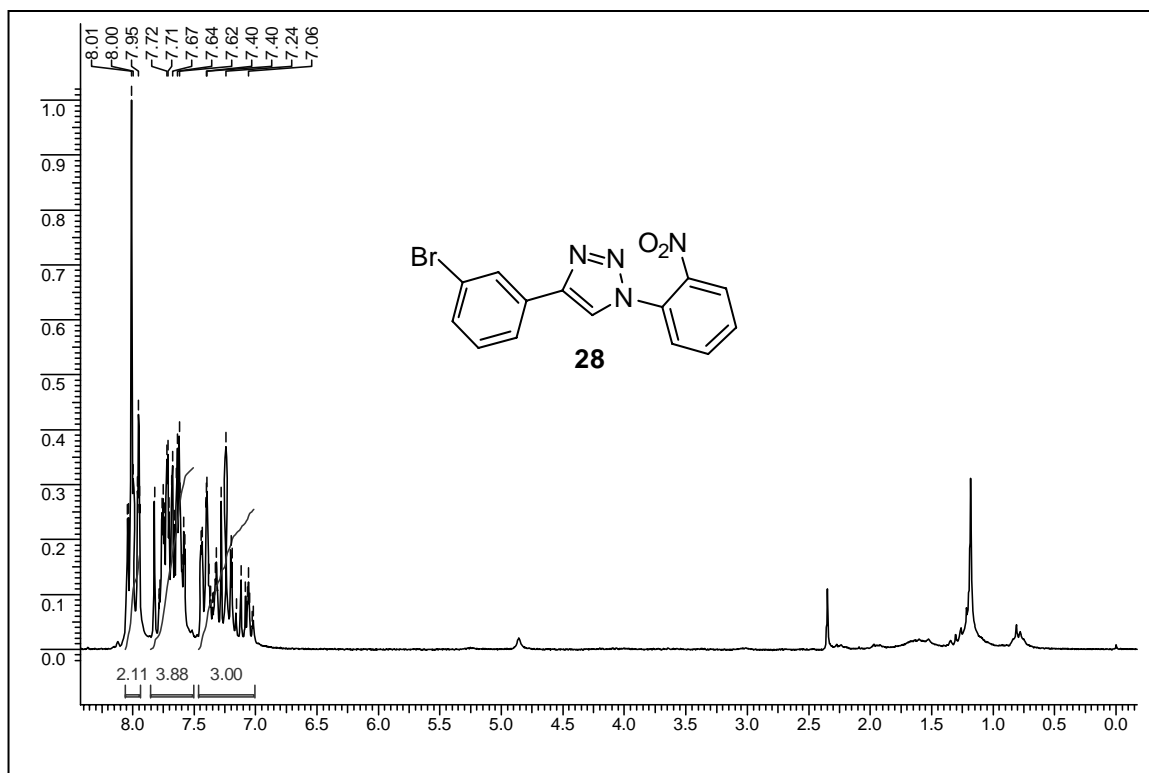
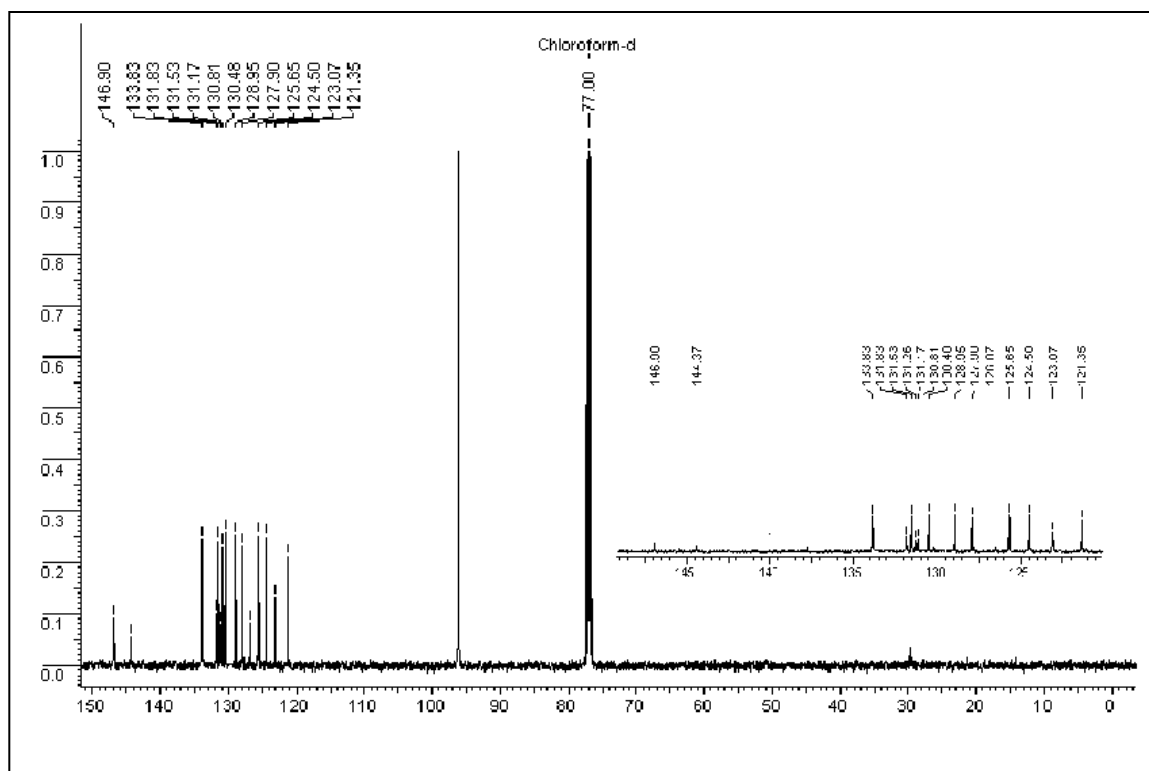
	C(11)-H(11)···O(1)	0.93	2.76	3.365(19)	124
	C(7)-H(7)···N(2)	0.93	2.73	3.45(2)	135
	C(7)-H(7)···N(3)	0.93	2.71	3.61(2)	161
	C(8)-Br(1)···O(2)	1.913(2)	3.317(17)		144.28(3)
<b>34</b>	C(1)-H(1)···O(1')	0.93	2.47	3.395(3)	173
	C(4)-H(4)···O(2')	0.93	2.67	3.478(4)	146
	C(14)-H(14)···O(1')	0.93	2.72	3.635(4)	166
	C(8)-H(8)···Br(1')	0.93	3.04	3.926(3)	161
	C(1')-H(1')···O(1)	0.93	2.44	3.351(4)	167
	C(4')-H(4')···O(2)	0.93	2.55	3.391(4)	151
	C(14')-H(14')···O(1)	0.93	2.66	3.584(4)	173
	C(8')-H(8')···Br(1)	0.93	2.98	3.908(3)	172
<b>35</b>	C(1)-H(1)···O(1)	0.89(3)	2.56(3)	3.413(5)	161(3)
	C(4)-H(4)···O(2)	0.86(4)	2.70(4)	3.482(5)	153(3)
	C(14)-H(14)···O(1)	0.92(3)	2.49(3)	3.404(4)	177(3)
	C(10)-H(10)···N(2)	0.93(4)	2.56(4)	3.342(5)	142(3)
	C(6)-Br(1)···O(2)	1.896(4)	3.169(3)		158.1(4)
<b>37</b>	C(6)-H(6)···O(1)	0.93	2.62	3.321(5)	132
	C(11)-H(11)···N(2)	0.93	2.56	3.231(4)	130
	C(8)-Br(1)···O(2)	1.914(4)	3.268(4)		145.2(3)
<b>38</b>	C(1)-H(1)···O(2)	0.93	2.93	3.247(3)	169
	C(8)-H(8)···O(2)	0.93	2.66	3.556(4)	161
	C(10)-H(10)···O(1)	0.93	2.56	3.387(4)	148
	C(5)-H(5)···N(2)	0.93	2.52	3.387(4)	155
	C(7)-Br(1)···O(1)	1.897(3)	3.292(3)		160.1(3)
<b>39</b>	C(1)-H(1)···O(2')	0.93	2.36	3.279(5)	171
	C(10)-H(10)···O(2')	0.93	2.60	3.523(5)	174
	C(10)-H(10)···O(1')	0.93	2.80	3.538(5)	137
	C(1')-H(1')···O(2)	0.93	2.31	3.230(5)	168
	C(10')-H(10')···O(2)	0.93	2.71	3.620(5)	165
	C(10')-H(10')···O(1)	0.93	2.80	3.594(5)	144
	C(4)-H(4)···N(3)	0.93	2.65	3.401(5)	139
	C(4')-H(4')···N(3')	0.93	2.60	3.334(5)	137
	C(13')-H(13')···Br(1')	0.93	3.10	3.812(4)	135

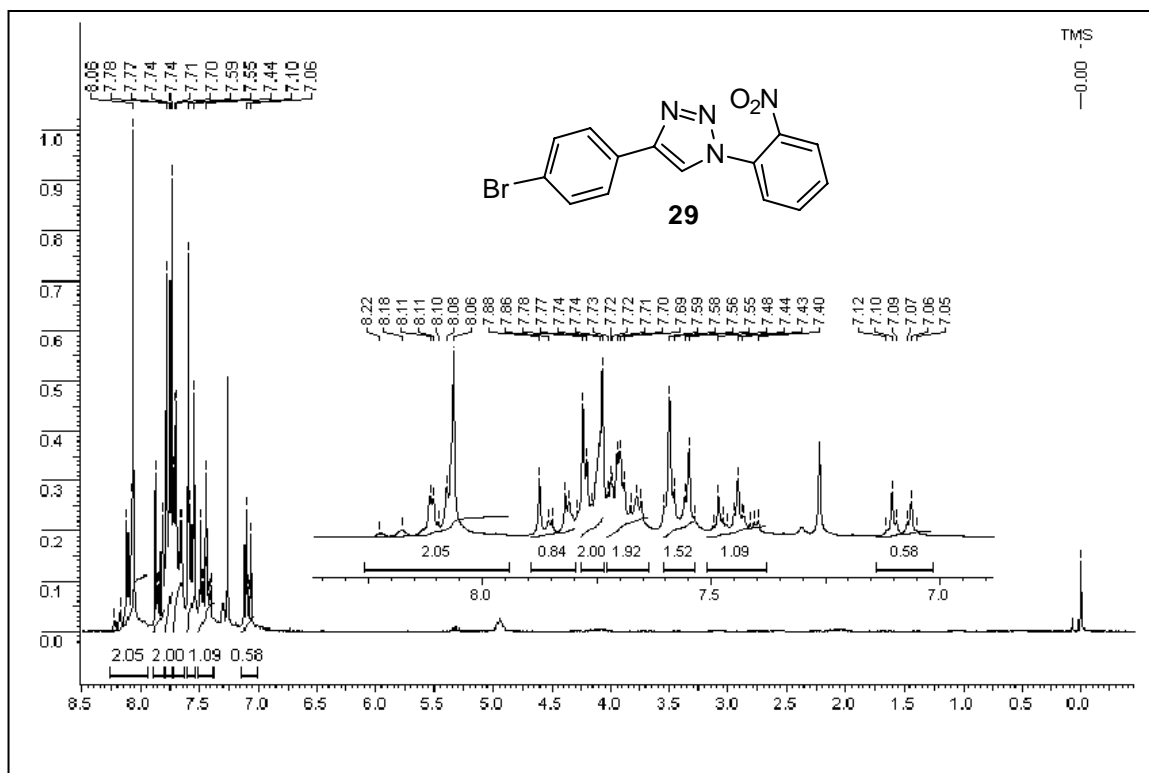
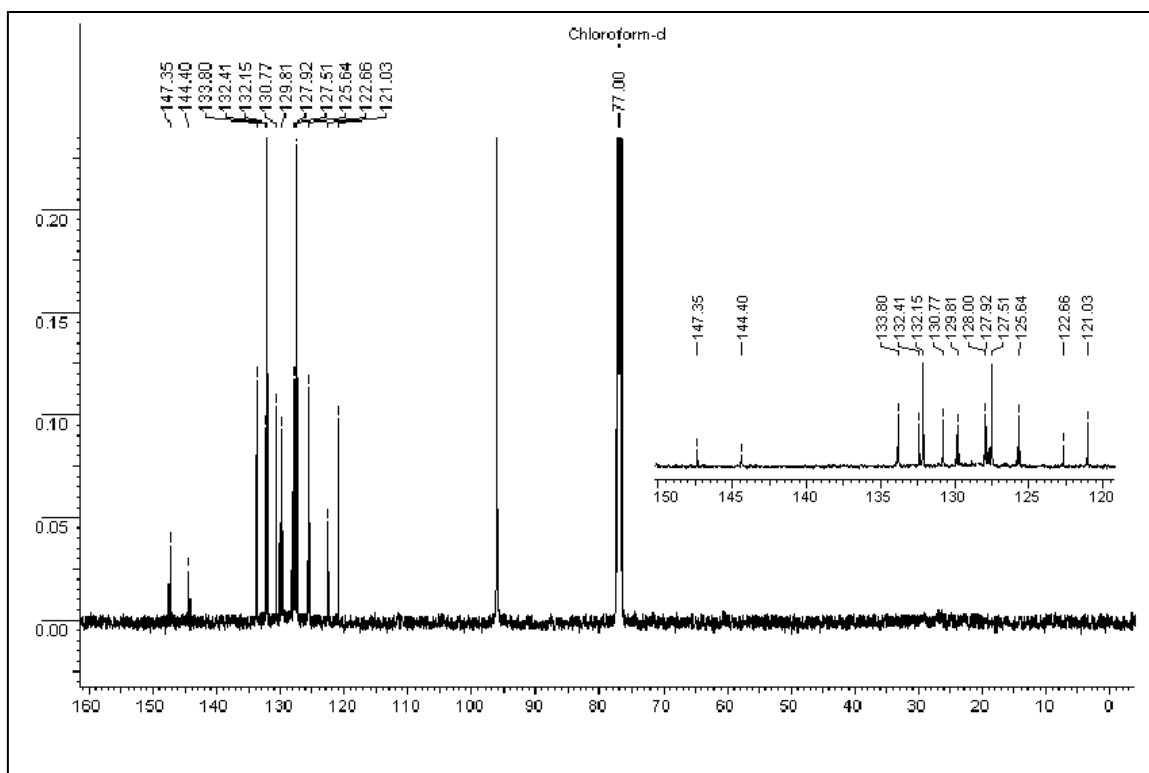
## SPECTROSCOPIC DATA

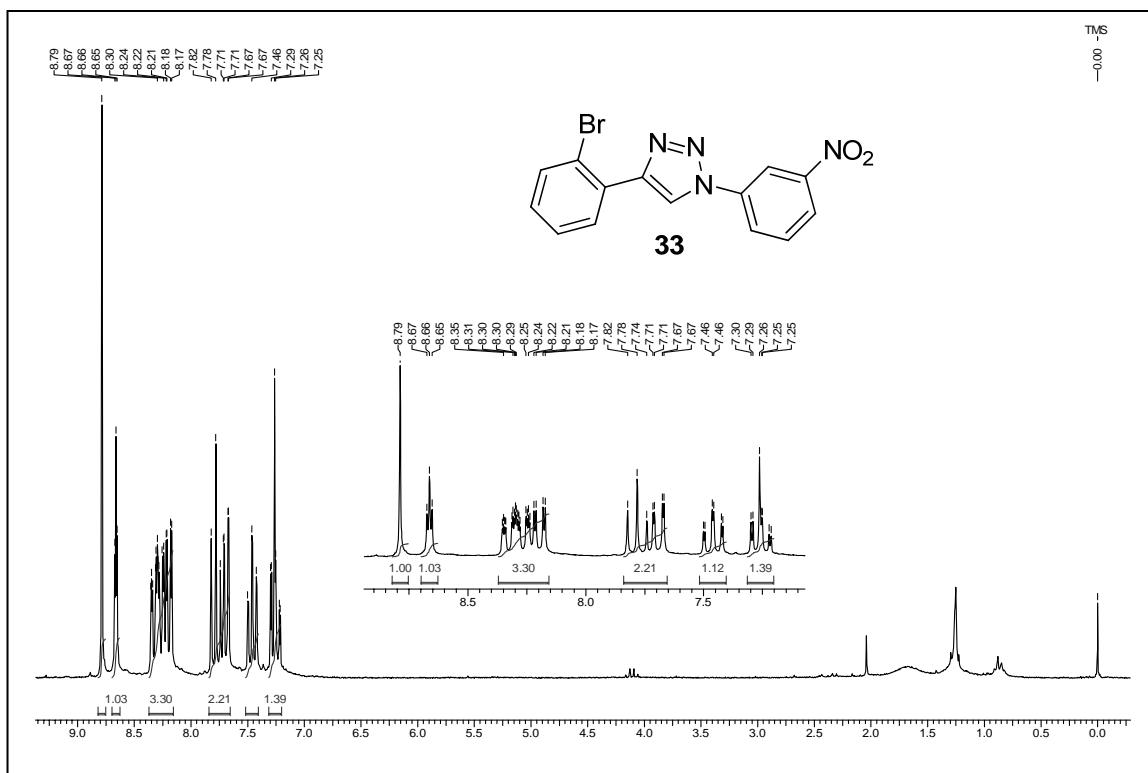
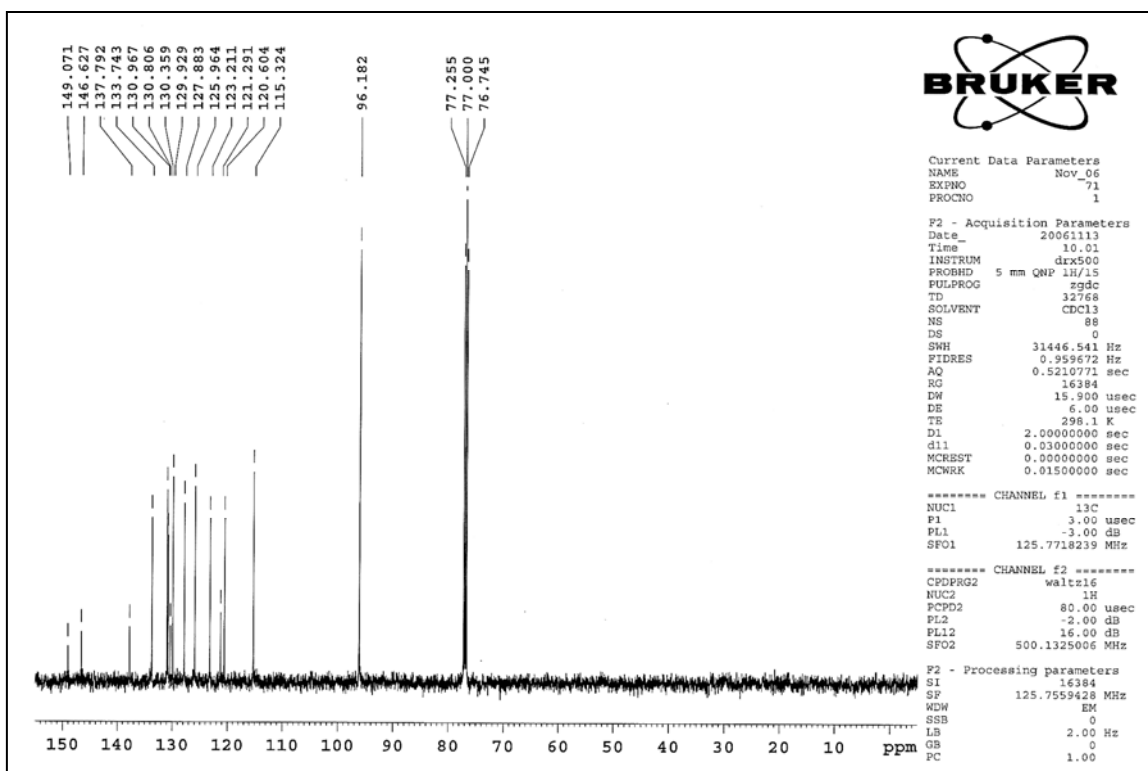
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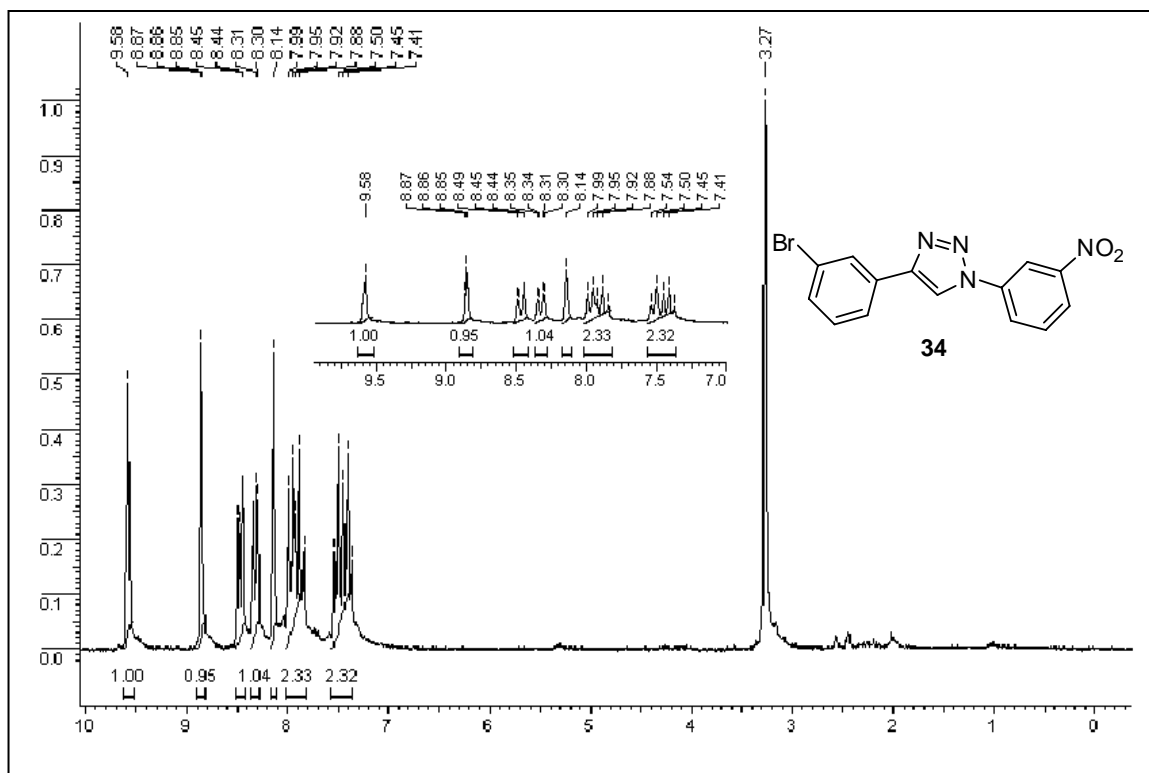
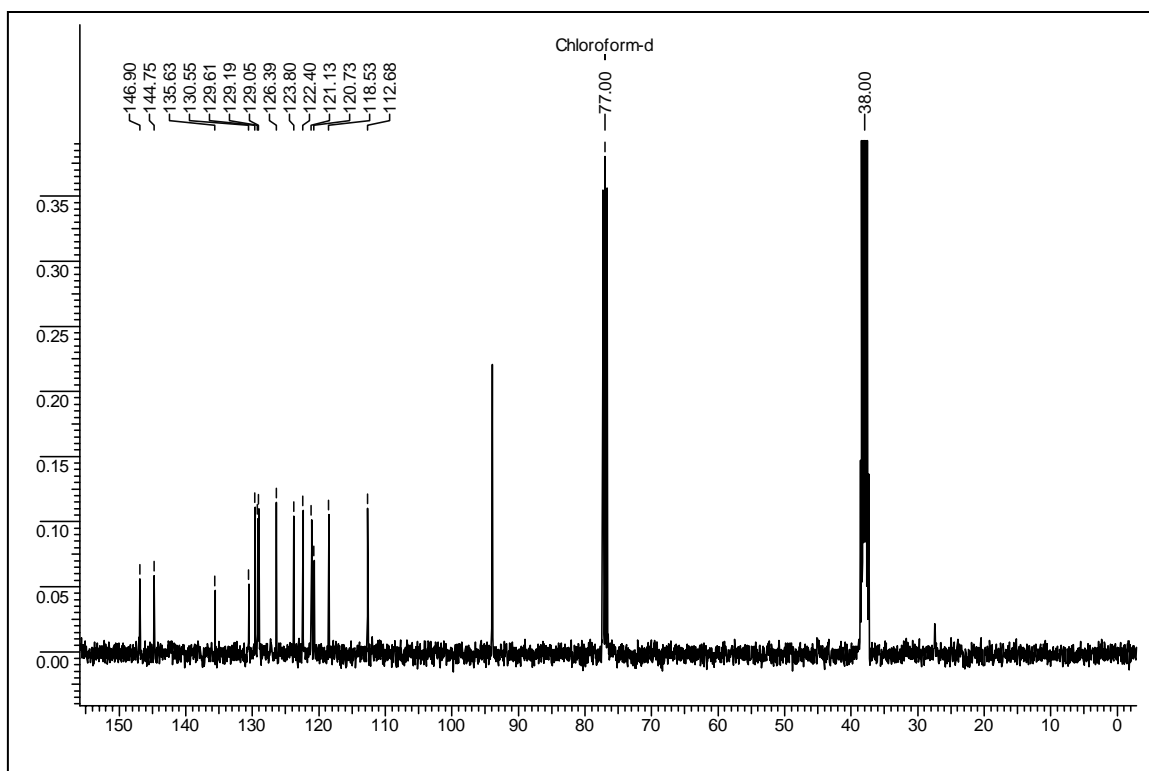


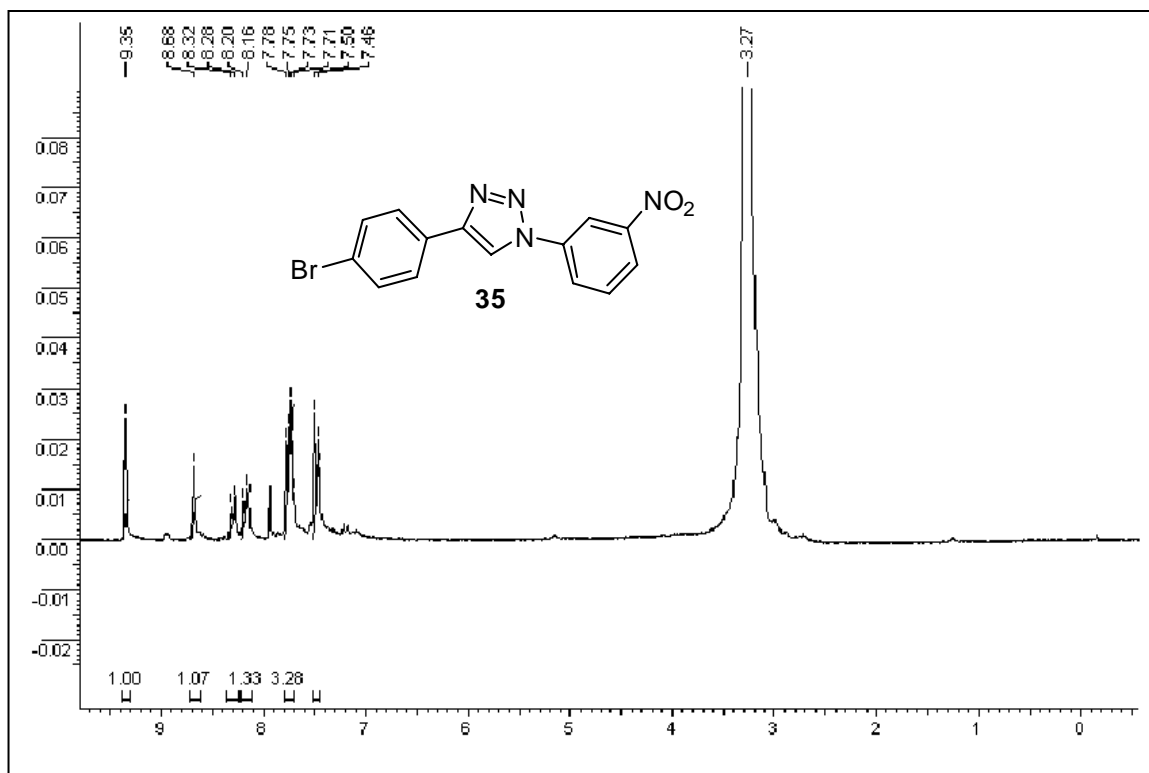
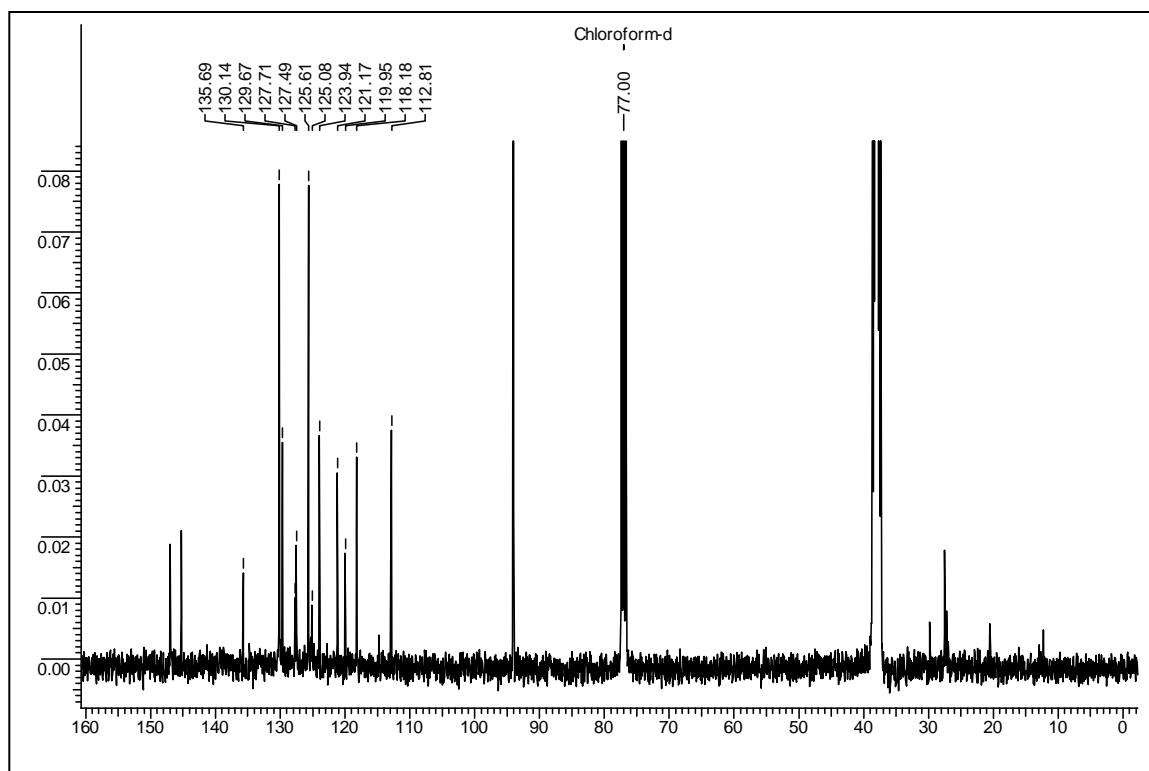
$^1\text{H}$  NMR spectra of compound 27 $^{13}\text{C}$  NMR spectra of compound 27

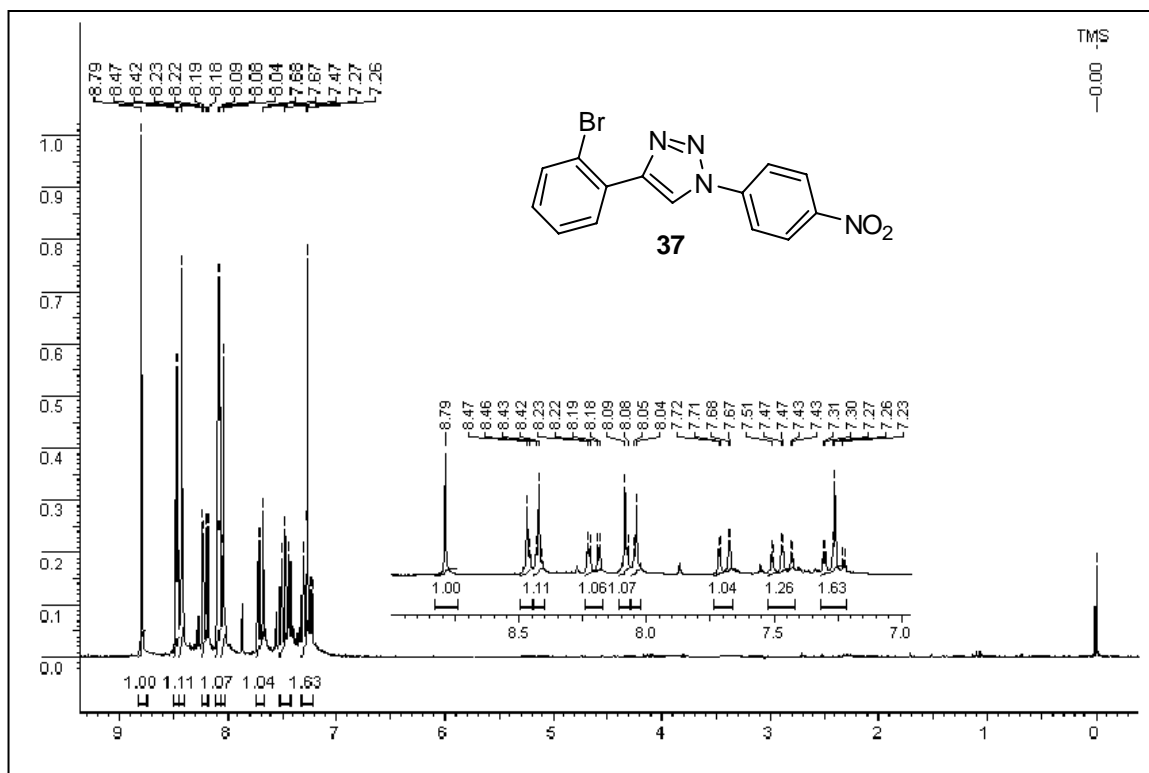
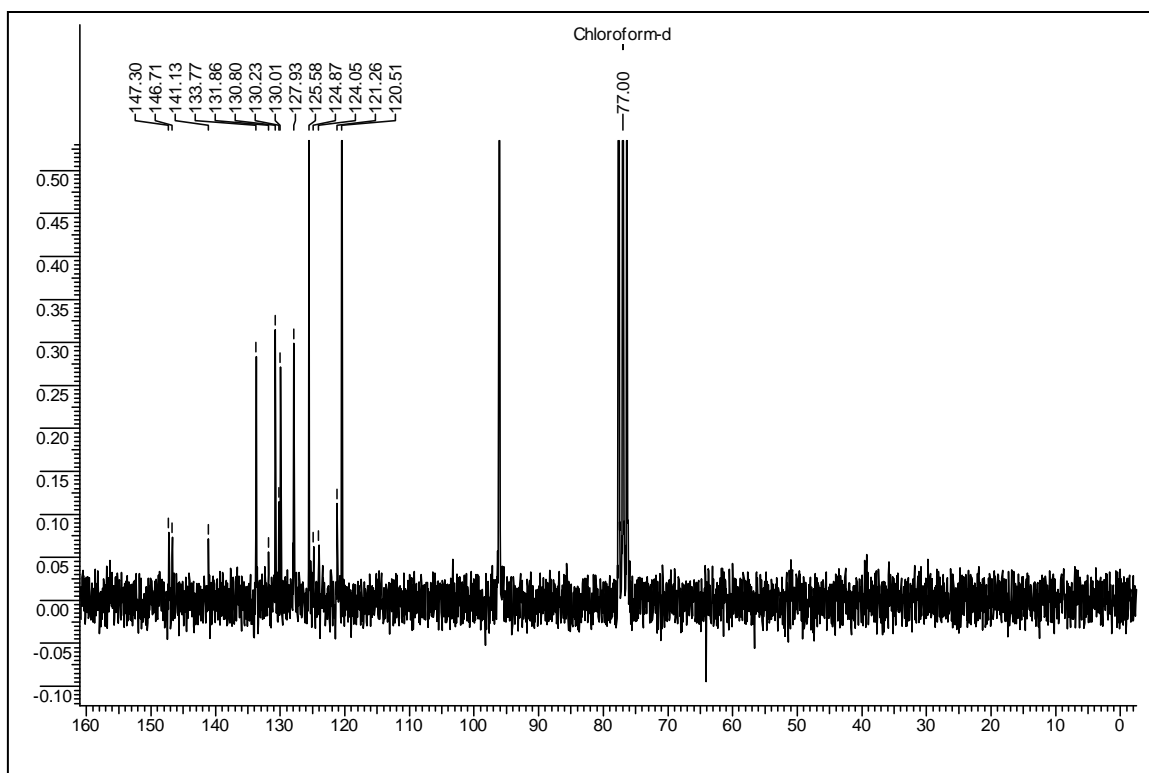
**$^1\text{H}$  NMR spectra of compound 28** **$^{13}\text{C}$  NMR spectra of compound 28**

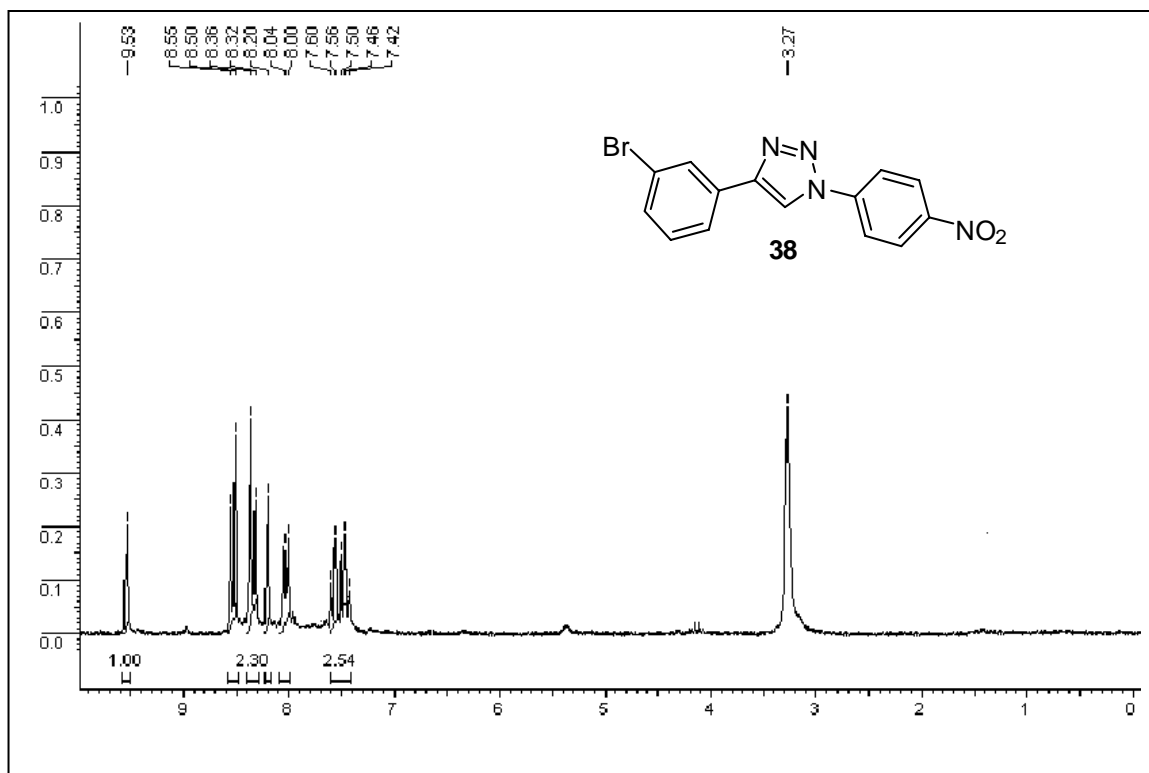
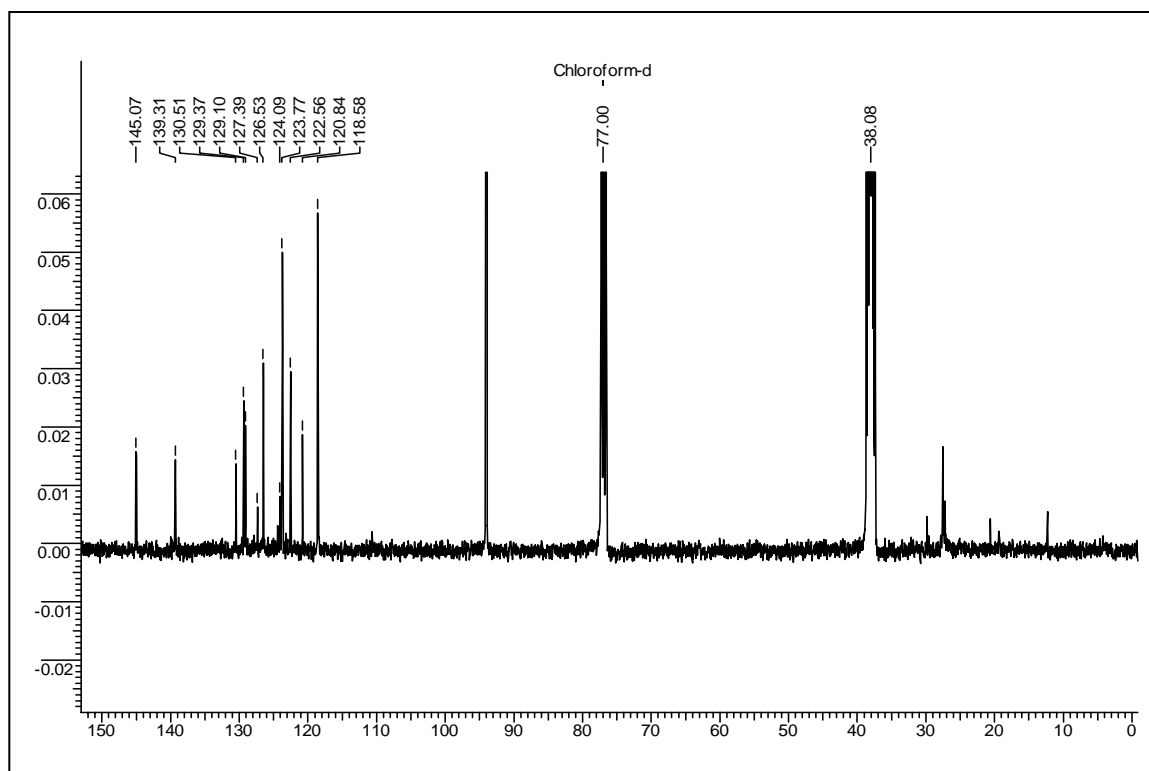
<sup>1</sup>H NMR spectra of compound 29<sup>13</sup>C NMR spectra of compound 29

<sup>1</sup>H NMR spectra of compound 33<sup>13</sup>C NMR spectra of compound 33

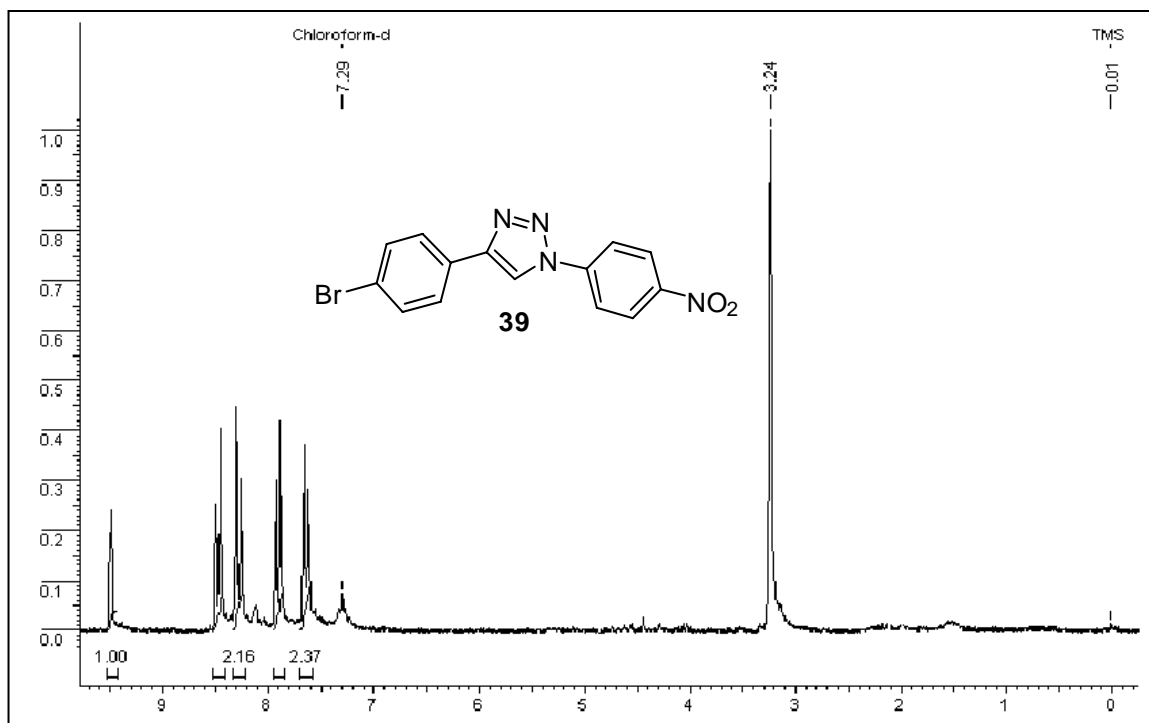
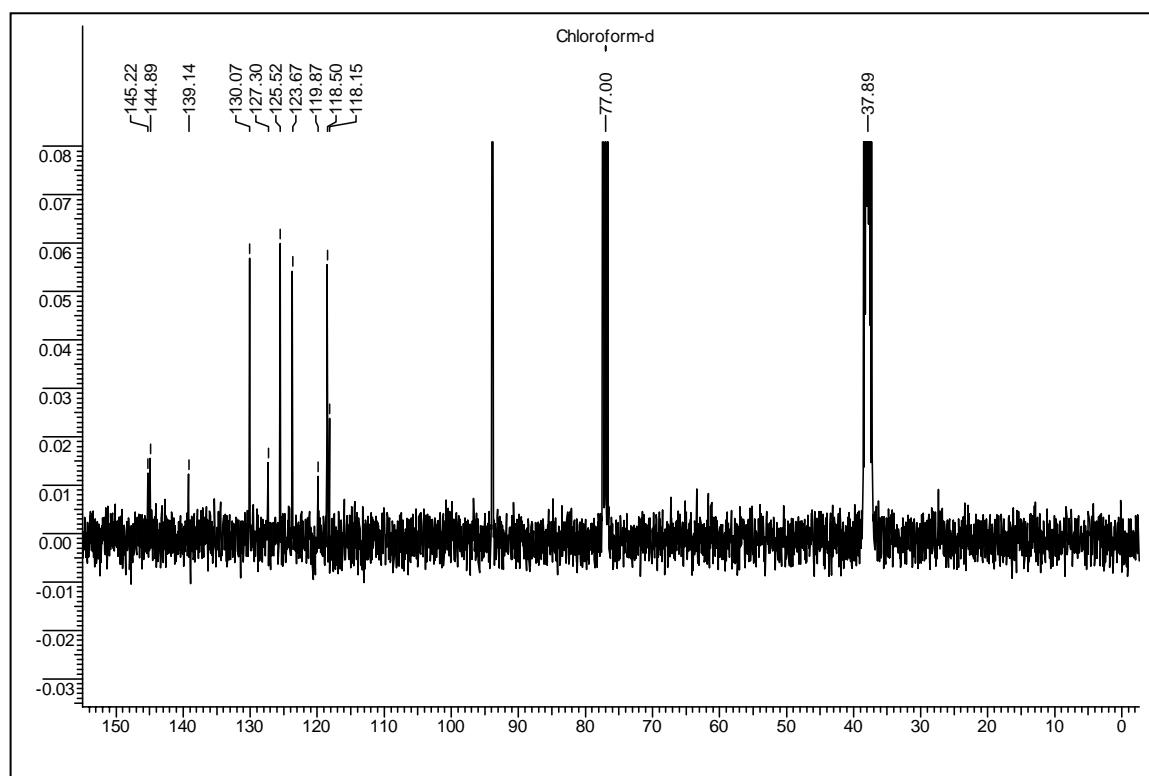
**$^1\text{H}$  NMR spectra of compound 34** **$^{13}\text{C}$  NMR spectra of compound 34**

**$^1\text{H}$  NMR spectra of compound 35** **$^{13}\text{C}$  NMR spectra of compound 35**

$^1\text{H}$  NMR spectra of compound 37 $^{13}\text{C}$  NMR spectra of compound 37

**$^1\text{H}$  NMR spectra of compound 38** **$^{13}\text{C}$  NMR spectra of compound 38**



**$^1\text{H}$  NMR spectra of compound 39** **$^{13}\text{C}$  NMR spectra of compound 39**

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## *List of Publications*

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1. “*Total Synthesis and Determination of Relative and Absolute Configuration of Multiplolide A*” C. V. Ramana, Tushar. P. Khaladkar, Soumitra Chatterjee and Mukund K. Gurjar, *J. Org. Chem.* (ASAP article)
2. “*Copper Catalyzed Azide-Alkyne Cycloaddition*” Approach for Molecular Library Synthesis to Evaluate a Synthon Robustness: A Case Study with Br···NO<sub>2</sub> Synthon” C. V. Ramana, Soumitra Chatterjee, Kulbhushan A. Durugkar and Rajesh G. Gonnade, Manuscript communicated for publication.