STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF HERBOXIDIENE (GEX 1A) AND PYRENOPHOROL

A THESIS

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by

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DECLARATION

I hereby declare that the research work embodied in this thesis is the result of investigations carried out by me at Indian Institute of Chemical Technology, Hyderabad, under the supervision of **Dr. J. S Yadav**, Bhatnagar Fellow, Indian Institute of Chemical Technology, Hyderabad. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other university.

(G. MADHUSUDHAN REDDY)

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G. MADHUSUDHAN REDDY

GENERAL REMARKS

- Boiling points and melting points are uncorrected. Melting points were recorded on Buchi R-535 apparatus.
- Infrared spectra were recorded on Thermo Nicolet Nexus 670 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}.
- Mass measurements were carried out on CEC-21-110B double focusing mass spectrometer operating at 70 eV using direct inlet systems and are given in mass units (*m*/*z*).
- Proton magnetic resonance spectra were recorded on Varian Gemini-200, Avance 300, Varian Unity-400, Inova-500 and Bruker 600MHz. Most of the samples were made in CCl_4/chloroform-d (1:1) using tetramethylsilane (Me_4Si) as the internal standard and are given in the δ scale. The standard abbreviations s, d, t, q, p, m, dd, dt, brs, refer to singlet, doublet, triplet, quartet, quintet, multiplet, double doublet, doublet triplet, broad singlet respectively.
- The optical rotations were measure on JASCO DIP-360 Digital polarimeter.
- All reactions involving air-sensitive compounds were conducted in oven-dried glassware at 90-110 ^{0}C for 6-12 h. Solutions were transferred with syringes or cannulas (double-ended needles) *via* nitrogen pressure.
- Analytical thin-layer chromatography (TLC) were performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light or by spraying sulphuric-β-naphthol or phosphomolybdic acid-sulphuric acid or sulphuric acid-anisaldehyde and heating the plates at 120 ^{0}C.
- All the reactions were monitored by employing TLC techniques using appropriate solvent systems for development. Anhydrous DMF, THF, diethyl ether, hexane and toluene were obtained from an Innovative Technologies solvent purification system. *n*-Pentane, petroleum-ether (boiling range 35 ^{0}C to 60 ^{0}C) were distilled over P_2O_5 and stored over pressed sodium wire; dry ether, dry benzene and dry THF were made by distilling them from sodium-benzophenone ketyl. All chlorinated solvents, pyridine, DMF and TEA were

distilled over CaH_2 and stored over 4 A^o molecular sieves. Acetone was distilled over potassium permanganate and potassium carbonate.

- All solvent extracts were concentrated at reduced pressure on Buchi-RE-121 rotary evaporator below 50 ^{0}C. Yields reported are isolated yields of material judged homogenous by TLC and NMR spectroscopy.
- All solvents used for silica gel column chromatography were distilled prior to use. Silica gel used was either 60-120 or 100-200 mesh.

ABBREVIATIONS

Ac	:	acetyl
Ar	:	aryl
Bn	:	benzyl
Bz	:	benzoyl
$BF_3.Et_2O$	:	boron trifluoride diethyl ether
n-BuLi	:	*n*-Butyllithium
t-BuOH	:	*tert*- butanol
t-BuOK	:	potassium *tert*-butoxide
CSA	:	camphor sulphonic acid
DCM	:	dichloromethane
DEAD	:	diethyl azodicarboxylate
DET	:	diethyl tartrate
DHP	:	dihydropyran
DIBAL	:	Diisobutylaluminium hydride
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMAP	:	4-dimethylaminopyridine
DME	:	dimethoxy ethane
DMS	:	dimethyl sulphide
DMSO	:	dimethylsulfoxide
DMF	:	*N*,*N*-dimethylformamide
DTBP	:	Di-*tert* butyl peroxide
EE	:	Ethoxy ethyl
ESI	:	Electro Spray Ionization
Et	:	ethyl
EtOH	:	ethanol
FAB	:	Fast Atom Bombardment
Hz	:	Hertz
IR	:	infra red
LAH	:	lithium aluminium hydride
Me	:	methyl
MeOH	:	methanol
MOM	:	methoxy methyl

MW	:	microwave
NMR	:	nuclear magnetic resonance
NaH	:	sodium hydride
NaHMDS	:	*N*-sodiumhexamethyldisilazane
NaH_2PO_4	:	sodium hydrogen phosphate
NBS	:	*N*-bromosuccinimide
PCB	:	*p*-chlorobenzoyl
PCC	:	pyridinium chlorochromate
Ph	:	phenyl
PMB-Br	:	*para*-methoxy benzyl bromide
PMR or ^{1}H NMR	:	proton magnetic resonance
PPTS	:	pyridinium *para*-toluene sulphonate
PTSA	:	*p*-toluenesulphonic acid
Py	:	pyridine
Piv	:	pivaloyl
r.t.	:	room temperature
Red-Al	:	sodium *bis*(methoxyethoxy)aluminiumhydride
$Sc(OTf)_3$	:	scandium trifluoromethanesulfonate
TBAF	:	tetra-*n*-butylammonium fluoride
TEA	:	triethyl amine
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
THP	:	tetrahydropyran
Ts	:	*p*-toluene sulphonyl
TPP	:	triphenyl phosphine
TBDMS or TBS	:	*tert*-butyl dimethylsilyl
TBDPS	:	*tert*-butyl diphenylsilyl

CONTENTS

Title of the thesis	**:**	Studies directed towards the total synthesis of Herboxidiene (GEX 1A) and (-)-Pyrenophorol
Name of the student	**:**	G. MADHUSUDHAN REDDY
Research supervisor	**:**	Dr. J. S. Yadav

The thesis entitled **"Studies directed towards the total synthesis of Herboxidiene (GEX 1A) and (-)-Pyrenophorol"** is divided into three chapters.

CHAPTER I : This chapter is divided into two sections.

Section A : It deals with the introduction of Herboxidiene and its previous synthetic approaches.

Section B : It deals with the current synthesis of tetrahydropyran core of Herboxidiene.

CHAPTER II: This chapter deals with the stereoselective synthesis of the highly functionalized side chain of Herboxidiene and its coupling with the tetrahydropyran core.

CHAPTER III: This chapter is divided into two sections.

Section A : It deals with the introduction of (-)-Pyrenophorol and its previous synthetic approaches.

Section B : It deals with the current synthesis of (-)-Pyrenophorol.

CHAPTER I

Section A : **Introduction of Herboxidiene and its previous synthetic approaches.**

Herboxidiene is a polyketide metabolite that was first isolated in 1992 by Barbara *et. al.* from the culture broth of *Streptomyces chromofuscus* A7847 cluster.

Figure 1 : Herboxidiene/GEX 1A

Herboxidiene (**1**) displays a wide range of useful biological activities such as herbicidal activity, lowering of plasma cholesterol, cytotoxic and anti-tumor activity in numerous cell lines.

It shows herbicidal activity against the broadleaf annual weeds oilseed rape (***Brassica napus),*** wild buckwheat ***(Polygonum convolvulus***), morning glory ***(Ipomoea*** *sp.*), and hemp sesbania ***(Sesbania exaltata)***.

Herboxidiene also activates the gene transcription of Low-density lipoprotein (LDL) receptors which bind to the cholesterol-rich lipoproteins in plasma and transport them into cells thereby decreasing the cholesterol level in plasma.

Herboxidiene also exhibits cytotoxicity *in vitro* against human tumor cell lines, epidermoid carcinoma A431 cells, human lung carcinoma A549 cells and human colon carcinoma DLD-1 cells, with IC_{50} values in the range of 0.0037-0.99 μM.

These alluring structural features and biological properties of Herboxidiene have compelled several synthetic chemists to attempt its total synthesis.

The first total synthesis of Herboxidiene (**1**) was accomplished by the kocienski group in 1999. Their synthetic approach was based on the union of the key fragments using the modified Julia olefination.

In 2007, Panek *et al* published a convergent synthesis of Herboxidiene making use of organosilane-based bond construction methodology.

Recently in 2011, Pedro Romea *et al* described an efficient synthesis of Herboxidiene based on highly stereoselective substrate-controlled reactions from two chiral lactate-derived ketones.

Section B : **Synthesis of tetrahydropyran core of Herboxidiene**.

Herboxidiene possesses several synthetically challenging structural features, including the trisubstituted tetrahydropyran core, the conjugated diene moiety, and the polyoxygenated side chain. These features challenged us to develop a flexible synthetic approach to this unique natural product.

The present work describes the convergent synthesis of Herboxidiene (**1**) exploiting the use of highly enantioselective crotylation, Prins cyclization reaction, a chiral starting material, AD-mix dihydroxylation, Shi epoxidation and Evans' alkylation to establish all the nine chiral centers contained in the target molecule. The retrosynthetic approach is outlined in scheme **1**.

The first disconnection at C9-C10 led to the functionalized tetrahydropyran core (**2**) and an oxygenated side chain (**3**). Olefin cross metathesis reaction could be explored to construct the diene from these fragments.

We anticipated using our Prins cyclization methodology to build the pyran core (**2**). Eventually, disconnection of the pyran ring revealed the homoallylic alcohol (**4**) and the aldehyde (**5**). Homoallylic alcohol (**4**) could be easily obtained by a highly enantioselective crotylation of aldehyde (**6**).

On the other hand, the oxygenated side chain (**3**) could be acquired *via* the Evans alkylation of the allylic alcohol (**7**) which could in turn be obtained by oxidation and a 3-carbon Wittig reaction of the alcohol (**8**). Further, alcohol (**8**) could be constructed by the asymmetric dihydroxylation of **9** that could be derived from the readily available (*S*)-Roche ester, (**10**).

This chapter deals with the synthesis of the tetrahydropyran core (**2**), while the construction of the highly functionalized side chain (**3**) is described in chapter II.

Scheme 1 : Retrosynthetic analysis of 1

Accordingly, the synthesis of the tetrahydronpyran core (**2**) started with the highly enantioselective crotylation of aldehyde (**6**) using the crotyl donor (**11**) in presence of *p*-TSA.H_2O in CH_2Cl_2 to furnish the homoallylic alcohol (**12**) in 86% yield and >99% ee. The benzyl ether in (**12**) was then removed under the Birch conditions to furnish the homoallylic alcohol (**4**) in 98% yield, which was now ready for the crucial Prins cyclization reaction.

Scheme 2 : Reagents and conditions:

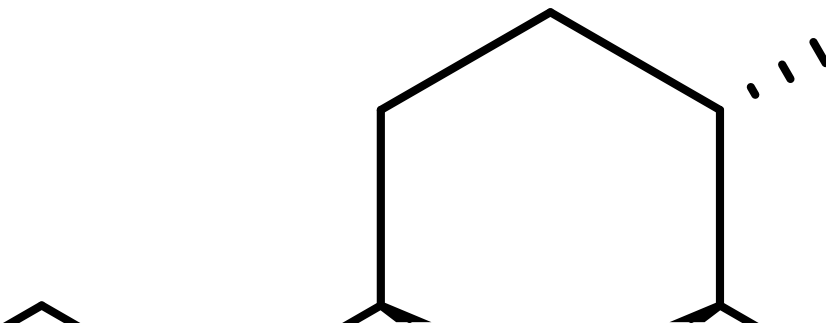
A. *p*-TSA.H_2O, CH_2Cl_2, 22 h, 86%; B. $NaNH_2/NH_3$, THF, 3 min, 98%

The homoallylic alcohol (**4**) was then subjected to Prins cyclization with aldehyde (**5**) in presence of $CeCl_3.7H_2O$ and LiI in refluxing DCE to obtain the tetrahydropyran product (**13**) in 68% yield. The resultant mixture of diastereomers was subjected to reductive deiodination with tributyltin hydride and AIBN in toluene at 110 °C to furnish **14** as a single diastereomer in 90% yield.

Scheme 3 : Reagents and conditions:

A. $CeCl_3.7H_2O$, LiI, DCE, 80 °C, 5 h, 68%; B. Bu_3SnH, AIBN, toluene, 110 °C, 30 min, 90%.

Treatment of **15** with TEMPO and BAIB in CH_2Cl_2/water oxidized the free hydroxyl group to carboxylic acid which was then esterified with CH_2N_2 that was generated *in situ* by treating NMU salt with aqueous KOH to obtain **16** in 98% yield.



Scheme 4 : Reagents and conditions:

A. TEMPO, BAIB, CH_2Cl_2:H_2O (2:1), 0 °C to rt, 2 h, 82%; B. CH_2N_2, Et_2O, 0 °C, 5 min, 98%; C. K_2CO_3, MeOH, 0 °C to rt, 2 h, 88%; D. (i) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 30 min, 85%; (ii) Ph_3PCH_3Br, *n*-BuLi, THF, 1 h, 75%

The pivalate ester in **16** was then hydrolyzed in presence of K_2CO_3 in MeOH to furnish the free alcohol (**17**) in 88% yield without affecting the methyl ester. Alcohol (**17**) was later oxidized with Dess-Martin periodinane and further subjected to one carbon Wittig olefination to furnish the key fragment (**2**) in 75% yield.

CHAPTER II

This chapter deals with the construction of the Herboxidiene side chain **3** and its coupling with the tetrahydopyran core (**2**).

The synthesis of the side chain (**3**) commenced with the masking of the hydroxyl group in (*S*)-Roche ester (**10**) as its benzyl ether using benzyl imidate in presence of catalytic amount of CF_3SO_2H that resulted in **18** in 88% yield. Controlled reduction of **18** with DIBAL-H in CH_2Cl_2 at -78 °C afforded the corresponding aldehyde which was immediately subjected to Wittig reaction with $Ph_3PCHCOOEt$ in benzene under reflux conditions to yield the *cis:trans* (5:95) mixture of unsaturated ester (**9**) in 92% yield, which could be separated by column chromatography.

Scheme 1 : Reagents and conditions:

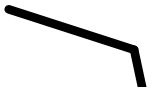
A. Benzyl 2,2,2-trichloroacetimidate, CF_3SO_2H, CH_2Cl_2:cyclohexane (2:1), 0 °C to rt, 1 h, 88%; B. (i) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 85%; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 92%; C. AD-mix β, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0 °C, 6 h, 88%;

Now the unsaturated ester (**9**) was subjected to Sharpless asymmetric dihydroxylation using AD-mix β in presence of $MeSO_2NH_2$ in *t*-BuOH:H_2O (1:1) at 0 °C to furnish an inseparable 93:7 diastereomeric mixture of diol (**19**) as observed in the ^1H NMR spectrum. The diastereomers could be separated by column chromatography after protecting the diol as its acetonide using 2,2-DMP in presence of *p*-TSA in CH_2Cl_2 to furnish the required diastereomer (**20**) in 85% yield.

Scheme 2 : Reagents and conditions:

A. 2,2-DMP, *p*-TSA, CH_2Cl_2, rt, 12 h, 85%; B. DIBAL-H, CH_2Cl_2, 0 °C to rt, 1 h, 82%; C. TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 90%.

Then the diastereomerically pure compound (**20**) was subjected to DIBAL-H reduction in CH_2Cl_2 to provide the alcohol (**21**) in 82% yield. The free hydroxyl group in **21** was then protected with tosyl chloride and Et_3N in CH_2Cl_2 to culminate in the tosylated product (**22**) in 90% yield.



Scheme 3 : Reagents and conditions:

A. *p*-TSA, MeOH, rt, 12 h, 85%; B. K_2CO_3, MeOH, 0 °C to rt, 1 h, 86%; C. NaH, MeI, THF, 0 °C, 1 h, 88%;

The acetonide group in **22** was then cleaved using *p*-TSA in MeOH to furnish the diol (**23**) in 85% yield. Treatment of **23** with K_2CO_3 in MeOH resulted in the epoxide (**24**) in 86% yield. Protection of the hydroxyl group in **24** as its methyl ether using NaH and MeI in THF resulted in the methylated compound **25** in 88% yield. Care was taken at this stage to prevent the competing Payne rearrangement reaction by maintaining the reaction mixture constantly at 0 $^{\circ}$C and by slow addition of MeI.

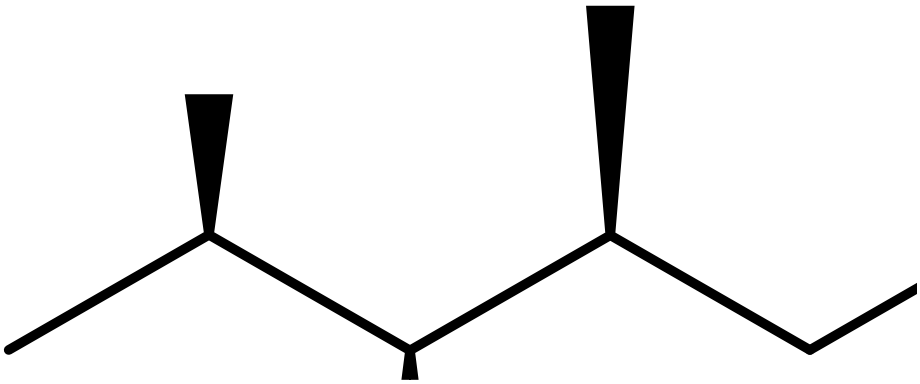
Scheme 4 : Reagents and conditions:

A. $LiAlH_4$, THF, 0 °C, 30 min, 92%; B. TBSCl, Imidazole, CH_2Cl_2, 0 °C to rt, 6 h, 90%; C. H_2, Pd/C, EtOAc, 2 h, 95%.

Compound **25** was then treated with $LiAlH_4$ in THF at 0 °C that resulted in the epoxide opening from the least hindered side to exclusively give the hydroxyl product (**26**) in 92% yield. The use of a bulkier hydride source is important for this selective opening of the epoxide.

The newly obtained hydroxyl group in **26** was then masked at its silyl ether using TBSCl and imidazole in CH_2Cl_2 to furnish the protected product (**27**) in 90% yield. Now the benzyl protection in **27** was removed under H_2 atmosphere in presence of Pd/C in EtOAc to obtain the hydroxyl product (**8**) in 95% yield.

Oxidation of **8** with IBX and DMSO in CH_2Cl_2 afforded the corresponding aldehyde which was then subjected to the 3-carbon Wittig reaction with $Ph_3PCH(CH_3)COOEt$ in benzene under reflux conditions to yield the *cis:trans* (8:92) mixture of unsaturated ester (**28**) in 82% yield, which could be separated by column chromatography. Reduction of the ester (**28**) using DIBAL-H in CH_2Cl_2 at 0 °C afforded the allylic alcohol (**7**) in 78% yield.



Scheme 5 : Reagents and conditions:

A.(i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 86%; (ii) $Ph_3PCH(CH_3)COOEt$, benzene, reflux, 1 h, 82%; B. DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 78%; C. I_2, TPP, Imidazole, THF, 0 °C, 86%. D. NaHMDS, -78 °C, 30 min, then **29**, 3 h, 92%;

Alcohol (**7**) was then converted into its iodide (**29**) in 86% yield by treating with TPP, imidazole and iodine in THF at 0 °C for 5 min. Evans' alkylation of iodide (**29**) was then carried out by reacting it with the enolate of **30** which was obtained by treatment with NaHMDS at -78 °C for 30 min to culminate in the product (**31**) in 92% yield as a single diastereomer.

Scheme 6 : Reagents and conditions:

A. $LiBH_4$, MeOH, 1 h, 80%; B.(i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 1 h, 75%; (ii) Ph_3PCH_3Br, *n*-BuLi, THF, -78 °C to rt, 1 h, 72%.

The reductive cleavage of the chiral auxiliary in **30** with $LiBH_4$ in MeOH at room temperature for 1 h furnished the alcohol (**32**) in 80% yield. IBX oxidation of this alcohol furnished the corresponding aldehyde which was then transformed into the terminal alkene (**3**) by a one carbon Wittig olefination.

Now with both the key fragments **2** and **3** in hand, the stage was set for their coupling utilizing the olefin cross-Metathesis reaction. Accordingly, condensation of olefins **2** and **3** in presence of Hoveyda-Grubbs II catalyst resulted in the target backbone (**33**) with 76% yield and an *E/Z* selectivity of >15:1.

Scheme 7: Reagents and conditions:

A. Hoveyda Grubbs II catalyst, CH_2Cl_2, 48 h, 76%;

The completion of synthesis of Herboxidiene from **33** is reported earlier and can be achieved in 3 steps involving TBS deprotection, regio and stereo selective epoxidation and hydrolysis of ester to furnish the target molecule (**1**).

Scheme 8: Completion of total synthesis

In conclusion, we have developed an efficient and concise route for the synthesis of GEX 1A/Herboxidiene in which the longest linear sequence includes 22 steps.

CHAPTER III

Natural products bearing medium and large size lactone rings have attracted considerable attention from synthetic chemists due to their interesting biological properties. Though many macrolides have complex structures with high substitution, simple macrolides also possess important biological properties which make them worth exploring**.**

Figure 1 : (-)-Pyrenophorol

Pyrenophorol (**1**) is one such macrolide that was first isolated in 1969 by Sigg *et al* from the plant pathogenic fungus *Byssachlamys nivea*. Shortly later, in 1971, this macrolide was re-isolated from the culture filtrates of *Stemphylium radicinum* by Grove *et. al.* Pyrenophorol is an inhibitor of prolyl endopeptidase and may improve human memory by blocking the metabolism of endogenous neuropeptides and has possible potential as antiamnesiac, memory enhancing drug.

Pyrenophorol also showed *in vivo* anthelminthic activity against the infective stages of the abomasums nematode, *Haemunchus cortortus*, which is one of the most common pathogenic parasites. Pyrenophorol was moderately active against the fungus *Microbotryum violaceum*, which is an obligate parasite on most of the plants of Carylophyllaceae family. It is also active against the alga *Chlorella fusca*, and the bacteria *Escherichia coli* and *Bacillus megaterium.*

The promising biological properties and structural features of Pyrenophorol (**1**) have prompted us to develop a new and efficient synthetic route for the total synthesis of this macrolide.

The retrosynthetic route is outlined in scheme **1**.

Scheme 1 : Retrosynthetic analysis of Pyrenophorol (1)

(-)-Pyrenophorol (**1**) could be envisioned to be obtained by intermolecular Mitsunobu cyclization of *seco* acid (**2**), which in turn could be obtained by olefin metathesis of allylic alcohol (**3**). The allylic alcohol (**3**) could be derived by the Wittig olefenation and sharpless asymmetric epoxidation of the TBDPS ester (**4**) of commercially available lactate ester.

Scheme 2 : Reagents and conditions:

A. (i) DIBAL-H, CH_2Cl_2, -78 °C, 15 min; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 92% (2 steps); B. $NaBH_4$, $NiCl_2.6H_2O$, MeOH, 0 °C, 1 h, 90%; C. (i) DIBAL-H, CH_2Cl_2, -78 °C, 15 min; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 94% (2 steps).

The synthesis commences with the DIBAL-H reduction of the silyl ether (**4**) in dry CH_2Cl_2 at -78 °C to give the corresponding aldehyde which was immediately subjected to 2-carbon Wittig olefination with $Ph_3PCHCOOEt$ in benzene under reflux conditions to give the unsaturated ester (**5**) in 92% yield. Reduction of the double bond using $NiCl_2$ and $NaBH_4$ gave the saturated ester (**6**) in 90% yield. Further reduction of alcohol (**6**) to the corresponding aldehyde under DIBAL-H conditions and subsequent 2-carbon Wittig olefination gave the ester (**7**) in 94% yield.

Scheme 3 : Reagents and conditions:

A. DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 92%; B. (+)-DIPT, Ti(O*i*Pr)$_4$, Molecular sieves, TBHP, CH_2Cl_2, -20 °C, 7 h, 78%; C. (i) TPP, Imidazole, I_2, THF:CH_3CN (4:1), 30 min; (ii) Zn dust, MeOH, reflux, 12 h, 82% (2 steps).

Reduction of ester (**7**) using DIBAL-H in dry CH_2Cl_2 provided the allylic alcohol (**8**) in 92% yield which was then subjected to Sharpless asymmetric epoxidation to give the epoxy alcohol (**9**) in 78% yield. Iodination of **9** followed by epoxide opening using zinc in refluxing MeOH gave the key intermediate (**3**) in 82% yield.

Scheme 4 : Reagents and conditions:

A. Methyl acrylate, Grubbs IInd generation catalyst, CH_2Cl_2, reflux, 24 h, 78%; B. (i) 3,4-dihydropyran, CSA, CH_2Cl_2, rt, 1 h, 88%; (ii) 20% aq. NaOH, MeOH, rt, 30 min, 85%; C. Bu_4NF, THF, 60 °C,2 h, 90%.

Subsequent cross metathesis of **3** with methyl acrylate gave the enoate (**10**) in 78% yield. Protection of the free hydroxy group of enoate as its tetrahydropyranyl ether, followed by hydrolysis under basic aqueous conditions yielded compound (**11**) in 85% yield. Desilylation of **11** gave the *seco* acid 2 which was now ready for the intermolecular Mitsunobu cyclization.

Scheme 5 : Reagents and conditions:

A. Ph_3P, DEAD, toluene:THF (10:1), -25 °C, 24 h, 60%; B. *p*-TSA, MeOH, rt, 30 min, 96%.

Mitsunobu cyclisation of **2** was carried out by Gerlach's procedure which resulted in macrolactonisation with complete inversion of configuration at C-4 to give the lactone **(12**). Finally, removal of the THP group furnished the target macrolide (**1**) in 96% yield as a white solid.

In summary, we have developed an efficient new route for the synthesis of (-)-Pyrenophorol (**1**) featuring Sharpless asymmetric epoxidation, olefin cross metathesis and intermolecular Mitsunobu cyclization starting from the readily available lactate ester.

TOTAL SYNTHESIS AND ITS ESSENCE:

Synthetic organic chemistry is perhaps the most expressive branch of chemistry in view of its creative power and unlimited scope. To appreciate its impact on modern humanity, one has to recognize that this science is a pillar behind pharmaceuticals, high-tech materials, polymers, fertilizers, pesticides, cosmetics, and clothing.[1]

Natural products can be harvested from their natural source - a process which can be tedious, time consuming and expensive. Furthermore, the number of structural analogues that can be obtained from harvesting is severely limited. To avoid these difficulties chemists developed ways to synthesize natural products in laboratory *via* a known set of reactions and using commercially available precursors: a process called total synthesis.

There could be various motives to perform total synthesis.

- To check the correctness of the structure of a natural product.
- To improve the knowledge related to the chemical properties of the molecule.
- To acquire a compound that could be less expensive or more easily accessible than the natural product.
- To modify some details in the molecular structure to enhance the activity of the product.

The birth of total synthesis occurred in the nineteenth century. The first conscious total synthesis of a natural product was that of urea in 1828 by Wöhler.[2] Significantly, this event also marks the beginning of organic synthesis and the first instance in which an inorganic substance (ammonium cyanate) was converted into an organic substance.

Figure 1:

The synthesis of acetic acid from elemental carbon by Kolbe[3] in 1845 is the second major achievement in the history of total synthesis. It is historically significant

that, in his 1845 publication, Kolbe used the word 'synthesis' for the first time to describe the process of assembling a chemical compound from other substances.

But perhaps, after urea, the most spectacular total synthesis of the nineteenth century was that of (+)-glucose by Fischer.[4] This total synthesis is remarkable due to the complexity of the target and the considerable stereochemical control that accompanied it. Subsequently, Fischer was awarded the second Nobel Prize for chemistry in 1902.

The "father" of modern organic synthesis is regarded as Robert Burns Woodward, who received the 1965 Nobel Prize for Chemistry for several brilliant examples of total synthesis such as his 1954 synthesis of strychnine[5].

Some modern classical examples of total synthesis include the synthesis of Taxol by Holton[6], Nicolaou[7] and Danishefsky[8] groups independently.

Figure 2:

It is the almost unlimited variation in structure and the constant discovery of new molecular constructs that keep the field of natural products synthesis very attractive and vibrant. The dazzling biological properties exhibited by many natural products and the attendant opportunities these molecules offer for probing biological questions also serve as major attractions in this field of investigation.

As synthetic chemists overcome horrifically challenging and devious problems, they enlarge everybody else's chemical toolkit. The new methods they find to perform reactions are often directly applicable to industrial chemistry, and thus indirectly total synthesis can be said to have contributed to many of the developments in chemistry, biology and medicine of the past century.

Most of the biologically active natural products are the secondary metabolites isolated from terrestrial plants, marine organisms or microbial fermentation broths.

INTRODUCTION TO HERBOXIDIENE / GEX1A

ISOLATION:

In 1992, screening of microbial fermentation broths for herbicidal activity by Barbara et al. led to the discovery of a novel polyketide, herboxidiene, **1** from an actinomycete member of the Streptomyces *chromofuscus* A7847 cluster.[9]

Further in 2002, while screening for new antitumor antibiotics, Herboxidiene was isolated along with five structurally related antibiotics named GEX1 compounds from the culture broth of Streptomyces sp.[11] The major compound of the active components was named GEX1A, and was identified to be herboxidiene, a potent herbicide and also as an anti-tumor agent, TAN-1609. The other active components were named GEX1Q1-Q5 for the order of the elution from ODS HPLC column.

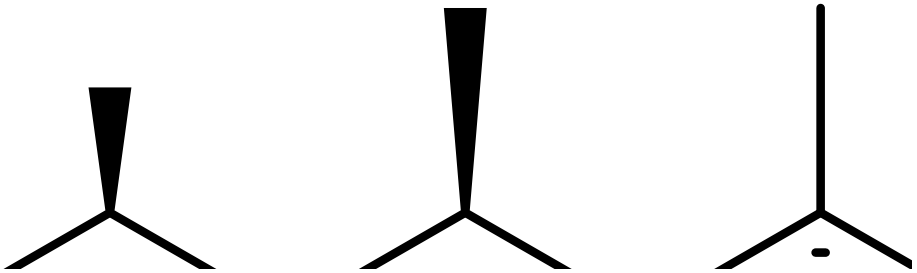


Figure 3 : GEX 1 compounds

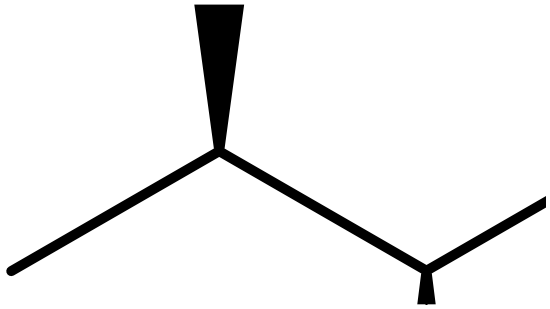
STRUCTURAL ELUCIDATION:

Based a combination of 1H NMR, 13C NMR, HMBC and HMQC spectroscopic studies, the Barbara group[9] assigned the polyketide structure **1** to Herboxidiene although uncertainty remained regarding the relative stereochemistry at C-7, C-12, C-16, C-17 and C-18.

Later in 1997, Edmunds et. al. re-isolated Herboxidiene and, by means of X-ray crystallographic analysis, degradation studies and partial synthesis, have unambiguously established its structure as **1**.[10]

The identical spectral data and, more significantly, the optical rotation values of the synthetic materials when compared with those of the fragments obtained from

degradation of natural herboxidiene, clearly showed the absolute configuration of the natural product to be as depicted in Figure **4**.



$[\alpha]_D = +29.2^o$ (from synthesis) $[\alpha]_D = -94.1^o$ (from synthesis)

$[\alpha]_D = +29.9^o$ (from degradation) $[\alpha]_D = -92.5^o$ (from degradation)

Figure 4 : Absolute configuration of GEX 1A/Herboxidiene

PHYSICO-CHEMICAL PROPERTIES:

Herboxidiene is a colorless solid that is soluble in water, methanol, *n*-butanol, acetone and ethyl acetate, but insoluble in hexane.

Molecular formula : $C_{25}H_{42}O_6$

Molecular weight : 438

HRFAB-MS *m/z* : 439.3085 $(M+H)^+$

$[\alpha]_D^{25}$: $+5.4^o$ (MeOH, *c* = 0.70)

UV (MeOH) λ_{max} : 238 nm (ε 21060)

BIOLOGICAL ACTIVITY:

Herboxidiene displays a wide range of useful biological activities such as herbicidal activity[9], lowering of plasma cholesterol[12], cytotoxic and anti-tumor activity in numerous cell lines.[11]

(i) Herbicidal activity:

The herbicidal activity of herboxidiene is comparable with current commercial herbicides for many of the monocotyledonous and dicotyledonous species tested. Of particular significance is the selective activity of this compound against the broadleaf annual weeds oilseed rape (***Brassica napus),*** wild buckwheat ***(Polygonum convolvulus***), morning glory ***(Ipomoea*** sp.), and hemp sesbania ***(Sesbania exaltata)*** when co-planted with wheat ***(Triticum aestivum)***, rice and soyabean which remained unaffected at a rate of 35g/acre.[9]

An examination of the structures of previously identified microbial polyketides which possess phytotoxic properties reveals that the majority of these compounds are macrocyclic. In contrast, herboxidiene represents an uncommon example of essentially linear phytotoxic polyketide. Structural alterations of herboxidiene did not significantly increase herbicidal activity.

Each of the herboxidiene analogs was tested for post-emergence herbicidal activity on ***T. aestivum*** and key weed species. Reduction of the acid group in Herboxidiene to its alcohol retained a significant level of activity indicating that the carboxylic acid functionality was not critical for biological activity. In contrast, the integrity of the polyoxygenated side chain of Herboxidiene proved to be essential for maintenance of activity. A minor modification such **as** oxidizing the free alcohol to the corresponding ketone, resulted in a marked decrease in activity. The loss of activity on opening the epoxide indicated that the intact epoxide ring was required for herbicidal activity.[9a]

(ii) Lowering Plasma cholesterol:

An abnormally elevated level of plasma cholesterol is one of the risk factors for the development of coronary heart disease. Herboxidiene activates the gene transcription of Low-density lipoprotein (LDL) receptors which bind to the cholesterol-rich lipoproteins in plasma and transport them into cells to clear the elevated level of plasma cholesterol.

The studies conducted indicated that Herboxidiene activated the synthesis of LDL receptor by 31%, thereby decreasing the cholesterol level in plasma.[12]

(iii) Anti-tumor activity:

All GEX1 compounds exhibited cytotoxicity *in vitro* against human tumor cell lines, epidermoid carcinoma A431 cells, human lung carcinoma A549 cells and human colon carcinoma DLD-1 cells, with IC50 values in the range of 0.0037-0.99 μM. The order of the strength of the cytotoxicity is as follows: GEX1A >GEX1Q5>GEX1Q3> GEX1Q2>GEX1Q1>GEX1Q4.[11]

GEX1A/herboxidiene also showed significant *in vivo* anti-tumor activity against the SVT2 murine fibrosarcoma.

GEX1A exerts cytotoxicity by affecting the cell cycle progression. A human normal fibroblast cell line, WI-38, when treated with GEX1 compounds markedly decreased the S-phase cells and arrested the cells in G1 and/or G2/M-phase, thereby preventing the cell proliferation.[10b]

Compound	***IC_{50} (μM)***			
	A431	**A549**	**DLD-1**	**WI-38**
GEX1A	0.0037	0.021	0.051	0.0076
GEX1Q1	0.93	---	---	2.8
GEX1Q2	0.51	---	---	1.8
GEX1Q3	0.033	0.26	0.70	0.11
GEX1Q4	0.99	---	---	5.4
GEX1Q5	0.013	0.080	0.13	0.028

Table 1: **Cytotoxicities of GEX1 compounds**

Currently, studies are in progress to increase the selective cytotoxicity to tumor cells for development of these compounds as clinical drugs for cancer therapy.

EARLIER SYNTHETIC APPROACHES

The alluring structural features and biological properties of Herboxidiene have compelled several synthetic chemists to attempt its total synthesis.

Herein, a brief account on the work carried out on total synthesis of Herboxidiene by some groups is documented.

Kocienski et al approach

The first total synthesis of Herboxidiene **1** was accomplished by the kocienski group[13] in 1999. Their synthetic approach was based on the union of the benzothiazolyl sulfone **3** and the aldehyde **2** (Scheme **1**) using the modified Julia olefination.

The synthesis of the C_1-C_{10} aldehyde fragment began with the α-methylation of the hex-5-enoyl bornane-10,2-sultam **4**, which when subjected to ozonolysis and subsequent treatment with 2,2-dimethylpropane 1,3-diol yielded the crystalline acetal **5**. Reductive removal of the chiral auxiliary, followed by oxidation gave the corresponding aldehyde **6**.

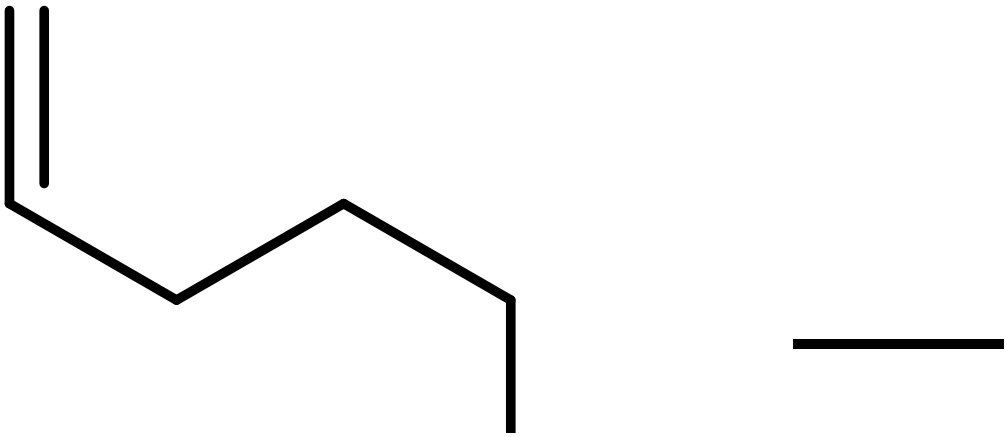
Scheme 1 : Retrosynthetic analysis

The 2-carbon chain extention in **6** was carried out by employing Julia olefination with sulfone **7** that resulted in 93% yield of the alkene **8** with a good stereo selectivity (E:Z = 93:7). Then, a highly stereoselective Sharpless asymmetric dihydroxylation gave the diol **9** in 83% yield.

Slow methanolysis of the acetal **9** at room temperature in presence of *p*-TSA gave an inseparable mixture of two major anomeric acetals **10** (α:β=3:1) in 73% yield. After protecting the free hydroxyl group as its *p*-methoxybenzyl ether **11**, the acetals were hydrolysed with aqueous acetic acid to a mixture of anomeric lactols **12**.

A further 2-carbon chain extension was accomplished using a Horner–Wadsworth–Emmons reaction with allyl diethylphosphonoacetate in the presence of caesium carbonate whereupon the intermediate unsaturated ester underwent ring closure to a mixture of two isomeric oxaneacetic esters (dr = 2 : 3) in which the desired isomer **13** was the minor component. On treatment with potassium *tert*-butoxide at -65 °C, the mixture isomerised rapidly and efficiently to give the desired isomer **13** as the exclusive product in 73% overall yield.

Oxidative cleavage of the *p*-methoxybenzyl ether in **13** with DDQ, oxidation with PCC and subsequent chain extension using sodium derivative of tert-butyl diethylphosphonoacetate gave the unsaturated ester **14** in 81% yield with an E:Z selectivity of 15:1.

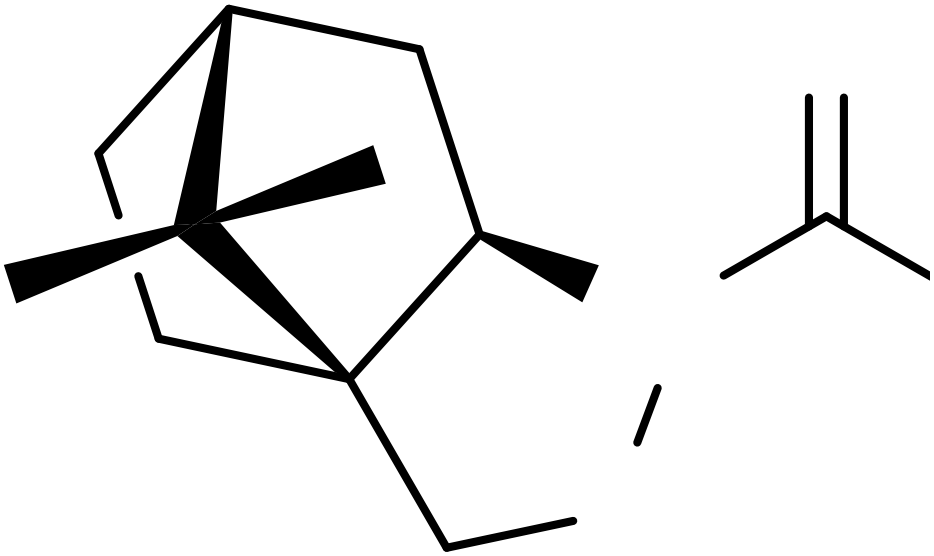


Scheme 2: Reagents and conditions:

A. (i) BuLi, THF, -78 °C, 2h; (ii) MeI, DMPU, -78 °C to rt, 12h, 80% (2 steps); B. (i) O_3, MeOH-CH_2Cl_2 (1:3), -78 °C, 2h; (ii) Me_2S, -78 °C to rt, 12h; (iii) 2,2-dimethylpropane-1,3-diol, *p*-TsOH, PHMe, reflux, 12h, 72% (3 steps); C. $LiAlH_4$, Et_2O, rt, 12h, 93%; D. Pyr.SO_3, Et_3N, DMSO, rt, 30 min, 96%; E. sulfone **7**, KHMDS, DME, -60 °C, 45 min, 93%; F. AD-mix α, $MeSO_2NH_2$, *t*-BuOH-H_2O (2:3), 0 °C, 18h, 83%; G. *p*-TsOH, MeOH, rt, 3d, α:β = 3:1, 73%; H. (i) KHMDS, THF, 0 °C, 20 min; (ii) PMBCl, TBAI, 0 °C to rt, 24h, 93% (2 steps); I. AcOH-THF-H_2O (3:2:2), 65 °C, 2h, α:β = 3:2, 74%; J. allyl diethylphosphonoacetate, Cs_2CO_3, THF, reflux, 18h, 82%; K. *t*-BuOK, THF, -65 °C, 10 min, 89%; L. DDQ, H_2O-CH_2Cl_2 (1:15), rt, 30 min, 95%; M. PCC, CH_2Cl_2, rt, 89%; N.

$(EtO)_2P(=O)CH_2CO_2Bu^t$, NaH, THF, 0 °C to rt, 81%; O. TFA, PhSMe, CH_2Cl_2, 96%; P. (i) $[Me_2N=CHCl]Cl$/THF-MeCN; (ii)$LiAlH(OBu^t)_3$

Construction of the C_{11}-C_{19} sulfone fragment **3** began with a highly stereoselective boron mediated aldol reaction between the propionyl sultam **16** and the (*S*)-aldehyde **17** (Scheme **3**) which gave the adduct **18** in 75% yield. Methylation of **18** was carried out by using methyl triflate and the proton sponge [1,8-bis(dimethylamino)naphthalene] to get the methylated adduct **19** in 90% yield with no trace of retroaldolisation.



Scheme 3: Reagents and conditions:

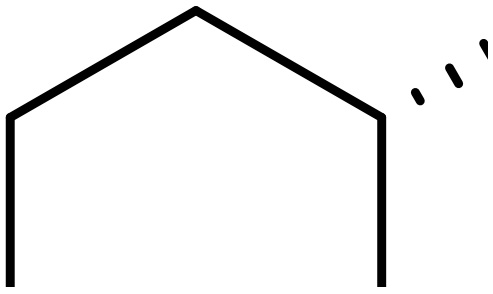
A. (i) Et_2BOTf, CH_2Cl_2, -5 °C; (ii) *i*-Pr_2NEt, 30 min; (iii) **19**, -78 °C, 3 h, 75% (3 steps); B. MeOTf, proton sponge, PhMe, 80 °C, 24 h, 90%; C. $LiAlH_4$, Et_2O, 0 °C, 15 min, 99%; D. Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h, 91%; E. (i) CH_2=C(Me)MgBr.Et_2O, 0 °C, 1 h; (ii) DMP, CH_2Cl_2, rt, 4 h, 80% (2 steps); F. $LiAlH_4$, LiI, Et_2O, -100 °C, 1 h, 75%; G. $(EtCO)_2O$, DMAP, pyridine, rt, 16 h, 97%; H. (i) LDA, THF, -78 °C, 30 min; (ii) TBSCl, DMPU; (iii) -78 °C to reflux, 1 h; (iv) aq.HCl, 68% ; I. $LiAlH_4$, Et_2O, 0 °C, 10 min, 90%; J. BTSH, Ph_3P, DIAD, THF, 0 °C to rt, 2h, 99%; K. TBAF.$3H_2O$, THF, rt, 32 h, 98%, L. Mo(VI), H_2O_2, H_2O-EtOH, rt, 24 h, 88%; M. $VO(acac)_2$, TBHP, CH_2Cl_2, -8 °C, 72 h, 69%; N. (i) Ph_3P, DMAD, THF, 0 °C; (ii) PCBOH, 0 °C to rt, 3 h, 74% (2 steps).

Reductive removal of the chiral auxiliary and subsequent oxidation gave the aldehyde **20**. Addition of isopropenylmagnesium bromide to aldehyde **20** gave a

mixture of allylic alcohols (*syn : anti* = 57 : 43) which was immediately oxidised to enone **21** in 80% overall yield. Reduction of enone **21** at -100 °C with lithium aluminium hydride in the presence of lithium iodide afforded **22** as a mixture of diastereoisomers (dr = 85 : 15) which could be separated by careful chromatography resulting in a 75% yield of enantiopure **22**. Finally, esterification of the pure alcohol afforded the propionate ester **23** in 97% yield.

The lithium enolate of propionate ester **23** was treated with TBSCl followed by DMPU to give (*E*)-silyl ketene acetal **24.** Rearrangement of **24** followed by acid hydrolysis of the intermediate silyl esters lead to the formation of a diastereoisomeric mixture of carboxylic acids **25** in 68% yield (dr = 86 : 14). After reduction to the corresponding alcohols, the diastereoisomers could be separated by flash chromatography. The major isomer **26** was subjected to a Mitsunobu reaction with 2-mercaptobenzothiazole to give the thioether **27**, which on TBS deprotection and oxidation gave the sulfone **28**.

Directed epoxidation of **28** with $VO(acac)_2$ and TBHP gave the oxirane **29** in 69% yield. The stereogenic center at C_{18} was then inverted under mitsunobu conditions using dimethyl azoicarboxylate, triphenyl phosphine and *p*-chlorobenzoic acid to afford the fragment **3** in 74% yield.



Scheme 4 : Reagents and conditions:

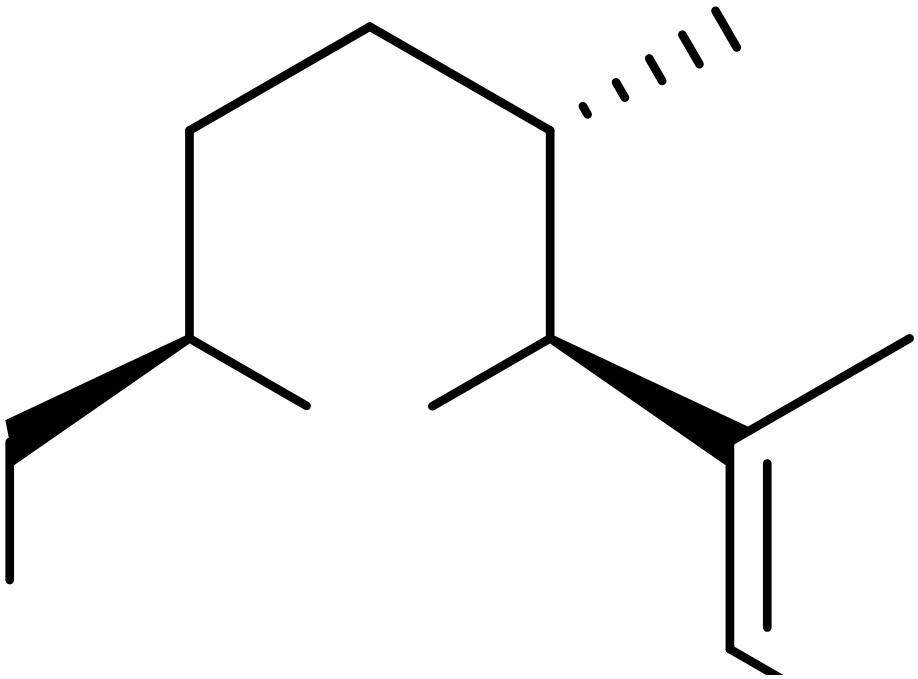
A. (i) LDA, THF, -78 °C, 15 min; (ii) **3**, -78 °C to -20 °C, 1.5 h, 81%; B. (i) K_2CO_3, MeOH, reflux, 2h, 72%; (ii) K_2CO_3, H_2O-MeOH (1:4), reflux, 1h, 84%.

The union of the sulfone **3** and aldehyde **2** was brought about via a one-pot Julia olefination to give the protected Herboxidiene derivative **30** in 81% yield and good

selectivity (E:Z = 91:9), which on hydrolysis gave Herboxidiene **1** in 84% yield (Scheme **4**).

Panek et al approach

In 2007, Panek et al published a convergent synthesis of Herboxidiene making use of organosilane-based bond construction methodology in three crucial ways[14] (Scheme **5**). The first disconnection at C9-C10 led a functionalized pyran core **31** and an oxygenated side chain **32** which could be united using a silicon-assisted sp2-sp2 cross coupling. Dihydropyran **31** could be obtained from *syn*-silane reagent **33** and the silyl-substituted methacrolein **34** utilizing stereoselective [4 + 2] annulation strategy. Further, the side chain **32** could be constructed from silane reagent (*S*)-**36** and *R*-silyloxy acetal (*S*)-**37**.



Scheme 5: **Retrosynthetic analysis**

Synthesis of C10-C19 fragment started with crotylation between (*S*)-**36** and (*S*)-**37** promoted by TMSOTf resulting in the *syn* homoallylic ether **38** in 62% yield and diastereoselectivity of >30:1. Arndt-Eistert conditions then converted **38** into diazoketone **39** in 97% yield over 2 steps. Rearrangement of **39** followed by trapping of the ketene with (+)-pseudoephedrine gave the homologated amide **40** in 80% yield which on Myers alkylation afforded **41** in 96% yield. Reductive removal of the

auxiliary, oxidation and subsequent Takai iodoolefination gave the (*E*)-vinyl iodide **32** in 75% yield (*E*/*Z* > 20:1).

Scheme 6: Reagents and Conditions

A. (*S*)-**36**, TMSOTf, CH_2Cl_2, -50 °C, 62%; B. (i) LiOH, THF-MeOH-H_2O, rt; (ii) $(COCl)_2$, DMF, CH_2Cl_2, rt, then CH_2N_2, Et_2O, 0 °C, 97% (2 steps); C. (*S*,*S*)-(+)-pseudoephedrine, $PhCO_2Ag$, CH_2Cl_2, rt, 80%; D. LDA, LiCl, THF, -78 °C to 0 °C, then MeI, 0 °C, 96%; E. LAH, THF, 0 °C to rt, 85%; F. (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C; (ii) $CrCl_2$, CHI_3, dioxane:THF (6:1), rt, 75% (2 steps).

Synthesis of the tetrahydropyran core was initiated by a TMSOTf-promoted [4 +2] annulation between *syn*-crotylsilane **33** and (*E*)-vinylsilyl aldehyde **34** resulting in the 2,6-dihydropyran **42** in 65% yield and high diastereoselectivity of >30:1. Reduction of **42**, followed by a hydroxyl-directed chemoselective hydrogenation using Wilkinson's catalyst afforded the tetrahydropyran product **43** in 87% yield over two steps. Alcohol **43** was then converted to a tosylate followed by displacement with sodium cyanide to give the desired nitrile **44**.

Scheme 7 : Reagents and conditions:

A. TMSOTf, DTBP, CH_2Cl_2:MeCN (3:1), -20 °C, 65%; B. (i) $LiAlH_4$, Et_2O, 0 °C; (ii) $RhCl(PPh_3)_3$, H_2, rt, 87% (2 steps); C. (i) TsCl, DMAP, Pyridine, CH_2Cl_2, rt; (ii) NaCN, DMF, reflux, 80% (2 steps).

Preactivation of vinylsilane **44** with TBAF followed by addition of $[AllylPdCl]_2$ and vinyl iodide **32** gave the desired product **45** exclusively as the (*E*,*E*)- diene isomer. Partial reduction of nitrile **45** to aldehyde, Pinnick oxidation followed by methylation with TMS-stabilized diazomethane provided methyl ester **46** in 59% yield over 3 steps. Removal of the TBDPS group followed by a directed epoxidation of the resulting

bishomoallylic alcohol using $VO(acac)_2$ gave a single diastereomer of **47** in 48% yield. Inversion of the C18 hydroxyl under modified Mitsunobu conditions and saponification of the resulting diester completed the total synthesis of herboxidiene **1** (66% yield in 2 steps).

Scheme 8 : Reagents and conditions:

A. TBAF, THF, 0 °C, then **32**, $[AllylPdCl]_2$, rt, 6 h, 50%; B. (i) DIBAL-H, CH_2Cl_2, -78 °C to 0 °C; (ii) $NaClO_2$-NaH_2PO_4-H_2O, 2-methyl-2-butene, *t*-BuOH, rt; (iii)$TMSCHN_2$, MeOH-benzene, rt, 59% (3 steps); C. TBAF, THF, rt, 81%; D. *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 0 °C, 48%; E. (i) 2-chlorobenzoic acid, PPh_3, DIAD, benzene, rt; (ii) K_2CO_3, MeOH-$H_2$0, 40 °C, 66% (2 steps).

Pedro Romea et al approach

Recently in 2011, Pedro Romea et al described an efficient synthesis of Herboxidiene based on highly stereoselective substrate-controlled reactions from two chiral lactate-derived ketones.[15]

In their retrosynthetic analysis, strategic disconnection at the C9-C10 bond provided an iodoalkene **48** and an alkyne **49** which could be assembled through a palladium-catalyzed Suzuki cross-coupling. Further fragment **48** could be obtained by an oxa-Michael cyclization of conjugated ester **50**, and a substrate-controlled aldol reaction from chiral ketone **52**, followed by reduction of the resulting aldol product to furnish diol **51**. Alkyne **49** could be obtained from an Ireland_Claisen rearrangement of ester **53**, which could be prepared by selective functionalization of diol **54**. This, in turn, would arise through a stereoselective one-pot aldol_reduction transformation from chiral ketone **55**.

Scheme 9 : Retrosynthetic analysis

The synthesis of fragment **48** began with a titanium-mediated aldol addition of lactate-derived ethyl ketone **52** to 3-butenal resulting in the aldol product **56** in 84% yield and a diastereomeric ratio of >97:3. Product **56** was stereoselectively converted to diol **51** through an internal hydride delivery using $(Me_4N)HB(OAc)_3$. Later, Hoveyda-Grubbs II catalyzed cross-metathesis of diol **51** with ethyl acrylate furnished conjugated ester **50** in 90% yield (E/Z > 97:3).

Scheme 10 : Reagents and conditions:

A. (i) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 78 °C, 30 min; (ii) 3-butenal, -78 °C, 30 min, 84% (2 steps); B. $(Me_4N)HB(OAc)_3$, AcOH/CH_3CN, -35 °C to 0 °C, 15 h, 96%; C. Ethyl acrylate, Hoveyda-Grubbs II, CH_2Cl_2, rt, 24 h, 90%; D. DBU, toluene, 100 °C, 5 h, 80%; E. (i) PhOCSCl, pyridine, CH_2Cl_2, 0 °C to

rt, 15 h; (ii) $(TMS)_3SiH$, AIBN, toluene, 100 °C, 2 h, 64% (2 steps); *t*-BuOK, THF, rt, 24 h, 61%; G. (i) H_2, Pd/C, EtOAc, rt; (ii) swern oxidation; (iii) $CrCl_2$, CHI_3, THF, rt, 2.5 h, 50% (3 steps).

The *oxa*-Michael cyclization of **50** using DBU afforded an inseparable 1.8:1 (cis:trans) mixture of diastereomers of **57** in 80% yield. Removal of the C5-hydroxy group under tin-free conditions, followed by chromatographic purification of the reaction mixture, furnished the desired ester containing the cis pyran ring (**58c**) in 54% yield. Importantly, treatment of the minor diastereomer **58t** with t-BuOK rendered **58c** as a single diastereomer in 61% yield.

Finally, hydrogenolysis of the benzyl ether and Swern oxidation of the resultant alcohol afforded the ketone, which was submitted to Takai conditions to deliver the C1-C9 fragment **48** as an E/Z 90:10 mixture in 50% yield.

Synthesis of C10-C19 fragment started with a sequential transformation consisting of a highly stereo-selective titanium-mediated aldol addition of chiral ketone **55** to methacrolein followed by reduction of the resultant aldolate with $LiBH_4$ which afforded all *syn* diol **54** (dr >97:3) in 81% yield. Then, selective monoacylation of the less sterically hindered hydroxyl group of 8 using Clarke's conditions and methylation of the resulting hydroxy ester with $(Me_3O)BF_4$/proton sponge furnished key intermediate **53** in 66% yield.

Scheme 11 : Reagents and conditions:

A. (i) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, -78 °C, 30 min; (ii) Methacrolein, , -78 °C, 30 min; (iii) $LiBH_4$, -78 °C, 1 h, 81% (3 steps); B. $(EtCO)_2O$, $CeCl_3.7H_2O$, CH_2Cl_2, rt, 48 h; (ii) $(Me_3O)BF_4$, proton sponge, CH_2Cl_2, rt, 2 h, 66% (2 steps); C. (i) LiHMDS, TBSCl, THF:DMPU (4:1), -78 °C, 45 min; (ii) $LiAlH_4$, Et_2O, 0 °C to rt, 30 min, 90% (2 steps); D. (i) Swern oxidation conditions; (ii) Ohira-Bestmann Reagent, MeONa, MeOH, THF, -78 °C to -40 °C, 1 h, 90% (2 steps).

Treatment of **53** with LiHMDS in 4:1 THF/DMPU at -78 °C then produced a lithium enolate that was trapped with TBSCl. The resulting ketene silyl acetal underwent a clean [3,3] sigmatropic rearrangement to furnish a silyl ester, which was reduced with $LiAlH_4$ to afford alcohol **59** as a single diastereomer (dr >97:3) in 81%

yield. Oxidation of **59** and further treatment under modified Ohira-bestmann conditions delivered **49** as a single diastereomer in 90% yield.

Scheme 12 : Reagents and conditions:

A. (i) Catecholborane, Cy_2BH, THF, 90 min, then NaOH; (ii) **48**, Tl_2CO_3, $Pd(PPh_3)_4$, THF:H_2O (3:1), rt, 15 h, 91% (2 steps); B. (i) HCl, EtOH, rt, 5 h; (ii) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, -25 °C, 24 h, 53% (2 steps); C. TMSOK, THF, rt, 2.5 h, 93%.

Hydroboration of **49** with catecholborane, followed by hydrolysis of the resultant boronate gave the corresponding boronic acid, **60**. Suzuki coupling of this boronic acid and iodoalkene **48** provided diene **61** in 91% yield. Removal of the silyl ether, epoxidation of the resulting bis-homoallylic alcohol and saponification of the ethyl ester furnished Herboxidiene (**1**) in 93% yield.

The appealing biological activity and enticing structural features of Herboxidiene have attracted much attention of the synthetic chemists during the recent past.

Herboxidiene possesses several synthetically challenging structural features, including the trisubstituted tetrahydropyran core, the conjugated diene moiety, and the polyoxygenated side chain. These features compelled us to develop a flexible synthetic approach to this unique natural product.

The present work describes the convergent synthesis of Herboxidiene **1**, which exploits the highly enantioselective crotylation, Prins cyclization reaction, a chiral starting material, admix dihydroxylation and Evans' alkylation to establish all the nine chiral centers contained in the target molecule.

The retrosynthetic approach is outlined in scheme **13**.

The first disconnection at C9-C10 led to the functionalized tetrahydropyran core **62** and an oxygenated side chain **63**. Olefin metathesis reaction could be explored to construct the diene from these fragments. We anticipated using our Prins cyclization methodology to build the pyran core **62**. Eventually, disconnection of the pyran ring revealed the homoallylic alcohol **64** and the aldehyde **65**. Homoallylic alcohol **64** could be easily obtained by a highly enantioselective crotylation of aldehyde **66**.

On the other hand, the oxygenated side chain **63** could be acquired *via* the Evans alkylation and Mitsunobu reaction of the allylic alcohol **67** which could in turn be obtained by the Wittig reaction of **68**. Further, alcohol **68** could be constructed by the asymmetric dihydroxylation of **69** that could be derived from the readily available (*S*)-Roche ester, **70**.

Scheme 13 : Retrosynthetic analysis of 1

Accordingly, the synthesis of **1** started with the highly enantioselective crotylation of aldehyde **66** using the crotyl donor **71** in presence *p*-TSA.H_2O in CH_2Cl_2 to furnish the homoallylic alcohol **72** in 86% yield and >99%.[16] The formation of compound **72** was confirmed by its ^{1}H NMR spectrum which showed a multiplet in 5.35-5.55 ppm region integrating for the two olefinic protons and a doublet at 1.67 ppm

corresponding to the terminal methyl group. Further, the ESI-MS spectrum displayed the $(M+H)^+$ peak at 221.

Scheme 14 : Reagents and conditions:

A. *p*-TSA.H_2O, CH_2Cl_2, 22 h, 86%; B. $NaNH_2/NH_3$, THF, 3 min, 98%

Then the benzyl ether in **72** was cleaved under Birch conditions[17] to furnish diol **64** in 98% yield. Disappearance of the signals corresponding to the benzylic group in the ^1H and ^{13}C NMR spectra and an $(M+Na)^+$ peak at 153 in the ESI-MS spectrum confirmed the product **64**.

Now the stage was set for the construction of tetrahydropyran ring utilizing the key Prins cyclization strategy that was developed by our group.[17] Accordingly, diol **64** was coupled with aldehyde **65** in presence of $CeCl_3.7H_2O$/LiI in DCE under reflux conditions to form the hemiacetal which smoothly cyclized to furnish a diastereomeric mixture of 4-iodotetrahydropyran **73** in 68% yield. The diastereomers did not need any separation at this stage as they afforded a single product on reductive dehalogenation in the next step.

Scheme 15 : Reagents and conditions:

A. $CeCl_3.7H_2O$, LiI, DCE, 80 °C, 5 h, 68%; B. Bu_3SnH, AIBN, toluene, 110 °C, 30 min, 90%.

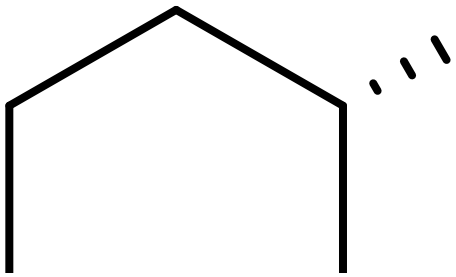
The product was confirmed by the analysis of ^1H, ^{13}C and mass spectra. ^1H NMR displayed the characteristic signals of the C-3, C-5 and C-7 protons corresponding to the tetrahydropyran ring resonating at 3.49, 3.90 and 3.33 ppm respectively. The *trans* methyl protons resonated as a doublet at 0.94 with a coupling constant of 6.8 Hz. The ^{13}C NMR spectrum displayed the resonances of C-3 and C-7 at

78.3 and 88.5 ppm respectively, while the C-5 resonance was observed at 35.5 ppm. The ESI-MS spectrum of **73** also showed the $(M+Na)^+$ peak at 447 thereby confirming the product.

The advantage of using the $CeCl_3.7H_2O/LiI$ reagent system instead of TFA or $BF_3.Et_2O$ as in the classical Prins cyclization that yields 4-hydroxytetrahydropyrans is that the reaction proceeds smoothly under neutral conditions even in presence of the highly labile protecting groups in good yields. Further, the reductive elimination of the iodide group is more facile than that of the hydroxyl group.

Reductive dehalogenation of **73** was carried out in presence of Bu_3SnH and AIBN in toluene at 110 °C to furnish the product **74** in 90% yield. The upfield shifting of the signals corresponding to the C-5 protons in the ^1H NMR spectrum confirmed the product. The ESI-MS spectrum of the product showed the $(M+Na)^+$ peak at 321.

Compound **74** was then oxidized under TEMPO-BAIB conditions to furnish the carboxylic acid **75** in 82% yield. This conversion was confirmed by the appearance of a signal at 174.6 ppm corresponding to the acid group in the ^{13}C NMR spectrum. The appearance of an additional C=O stretch in the FTIR spectrum at 1715 cm^{-1} also confirmed this.



Scheme 16 : Reagents and conditions:

A. TEMPO, BAIB, CH_2Cl_2:H_2O (2:1), 0 °C to rt, 2 h, 82%; B. CH_2N_2, Et_2O, 0 °C, 5 min, 98%; C. K_2CO_3, MeOH, 0 °C to rt, 2 h, 88%; D. (i) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 30 min, 85%; (ii) Ph_3PCH_3Br, *n*-BuLi, THF, 1 h, 75%

Esterification of **75** by the freshly generated CH_2N_2 from *N*-nitroso-*N*-methylurea furnished the ester **76** in 98% yield. Formation of the product was

confirmed by the appearance of a singlet at 3.66 ppm corresponding to the three methyl ester protonsin the ^{1}H NMR spectrum. ^{13}C NMR spectrum too showed an additional peak at 51.6 ppm while the ESI-MS spectrum displayed the $(M+Na)^{+}$ peak at 349.

The pivalate ester in compound **76** was then hydrolyzed in presence of K_2CO_3 in MeOH to provide the alcohol **77** in 88 % yield. During this reaction, the methyl ester too hydrolyzed. So the use of MeOH as solvent was significant in this step to restore the methyl ester functionality by trans-esterification. The disappearance of the signals corresponding to the pivalyl group at 1.18 ppm in the ^{1}H NMR spectrum and at 178.4, 38.7 and 27.2 ppm in the ^{13}C NMR spectrum confirmed the product. The ESI-MS spectrum too displayed the peak corresponding to $(M+Na)^{+}$ at 265.

The free hydroxyl group thus formed in **77** was oxidized using Dess-Martin periodinane[18] in CH_2Cl_2 to furnish the corresponding aldehyde which was further subjected to Wittig olefination with Ph_3PCH_3Br using *n*-BuLi in THF to afford the target fragment **62** in 75% yield. Formation of **62** was ascertained from the ^{1}H NMR spectrum by the disappearance of the triplet at 4.21 ppm corresponding to the $–CH_2OH$ protons and appearance of signals at 6.58 and 5.05 ppm corresponding to the olefenic protons. ^{13}C NMR spectrum of the product also showed the additional signals corresponding to the olefenic carbons at 116.9 and 132.7 ppm, while the ESI-MS spectrum displayed the peak corresponding to $(M+Na)^{+}$ at 261. The FTIR spectrum too lacked a strong –OH stretching frequency thereby confirming the product.

(-)-(1*R*, 2*S*, 4*R*, 1'*R*)-1-(1-Methylallyl)menthol (71)

A solution of crotyl chloride (2.57 g, 28.4 mmol) in dry THF (28 ml) was added dropwise to magnesium turnings (690 mg, 28.4 mmol) in dry THF (58 ml) at room temperature under a nitrogen atmosphere. When the bubbling had stopped the solution was allowed to cool to room temperature and was then cooled to 0 °C. A solution of (+)-menthone (2.58 g, 16.7 mmol) in dry THF (16.7 ml) was added slowly and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution (100 ml). Water (50 ml) was added and the biphasic mixture was filtered. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow oil (3.63 g), which was purified by column chromatography on silica gel to give homoallylic alcohol **71** as a colorless oil (2.37 g, 67%).

$[\alpha]_D^{25}$: −25.2 (*c* 2.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3573, 3077, 2952, 2874, 2845, 1635, 1457, 1377, 1161, 1010, 919.

^1H NMR (400 MHz, $CDCl_3$) : δ 5.75-5.89 (m, 1H), 5.13 (s, 1H), 5.07-5.11 (m, 1H), 2.57 (p, *J* = 7.3 Hz, 1H), 2.01-2.12 (m, 1H), 1.69-1.81 (m, 2H), 1.45-1.52 (m, 2H), 1.18-1.34 (m, 4H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 6H), 0.85 (d, *J* = 6.2 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$) : δ 140.8, 116.6, 76.2, 45.9, 45.2, 41.5, 35.2, 27.5, 25.0, 23.4, 22.6, 20.6, 17.9, 14.7.

ESI-MS $(M+Na)^+$: 233.

(3*R*,5*E*)-1-(benzyloxy)hept-5-en-3-ol (72)

PTSA·H_2O (455 mg, 2.39 mmol) was added to a solution of 3-benzyloxypropanal (4.020 g, 24.48 mmol) and alcohol **71** (10.060 g, 47.82 mmol) in dry CH_2Cl_2 (250 ml) at room temperature. The mixture was stirred for 22 h and then triethylamine (1 ml) and saturated aqueous sodium hydrogen carbonate solution (250 ml) were added and the mixture was stirred vigorously for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and brine (200 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil (15.64 g) which was purified by column chromatography on silica gel to give homoallylic alcohol **72** as a yellow oil (4.658 g, 86%).

$[\alpha]_D^{25}$: −4.2 (*c* 0.4, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3421, 3063, 3028, 2919, 2828, 1718, 1492, 1450, 1363, 1276, 1207, 1097, 1025, 969, 739, 698.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.20-7.37 (m, 5H), 5.35-5.55 (m, 2H), 4.50 (s, 2H), 3.56-3.81 (m, 3H), 2.60 (brs, 1H), 2.13 (t, *J* = 6.0 Hz, 2H), 1.69-1.75 (m, 2H), 1.68 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 138.5, 128.8, 128.7, 128.1, 128.0, 127.6, 73.7, 70.9, 69.3, 41.1, 36.3, 18.4.

ESI-MS $(M+H)^+$: 221.

(3*R*,5*E*)-hept-5-ene-1,3-diol (64)

To a solution of sodium (2.00 g, 86.9 mmol) in liquid NH_3 (60 mL) was added compound **72** (2.376 g, 10.8 mmol) in dry THF (10 mL). The mixture was stirred for 3 min and quenched with solid NH_4Cl (4.650 g). NH_3 was allowed to evaporate and the

residual mixture was taken in ethylacetate (50 mL) and washed with water (20mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and chromatography of the crude afforded pure diol **64** (1.376 g, 98% yield) as a pale yellow liquid.

$[\alpha]_D^{25}$: −4.4 (*c* 3.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3354, 3023, 2935, 1438, 1378, 1052, 969, 651.

^1H NMR (300 MHz, $CDCl_3$) : δ 5.33-5.61 (m, 2H), 3.73-3.87 (m, 3H), 2.57 (brs, 2H), 2.07-2.22 (m, 2H), 1.61-1.73 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 129.0, 126.6, 71.2, 61.4, 41.0, 37.7, 18.0

HRMS (+ESI) : *m/z* calcd. for $C_7H_{14}O_2Na$ $[M+Na]^+$: 153.0886, found: 153.0884.

(E)-3-((2R,3R,4R,6R)-6-(2-hydroxyethyl)-4-iodo-3-methyl-tetrahydro-2H-pyran-2-yl)but-2-enyl pivalate (73)

To a mixture of homoallylic alcohol **64** (1.250 g, 9.6 mmol) and aldehyde **65** (2.120 g, 11.5 mmol) in dichloroethane (30 mL) was added $CeCl_3.7H_2O$ (3.552 g, 9.6 mmol) and LiI (1.930 g, 14.4 mmol) and the reaction mixture was refluxed at 80 °C for 5h. After the completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the crude product was purified by silica gel column chromatography to afford 4-iodotetrahydropyran **73** (2.772 g, 68% yield) as a pale yellow oil.

$[\alpha]_D^{20}$: -73.7 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3447, 2965, 2872, 1725, 1478, 1456, 1371, 1281, 1149, 1092, 1058, 1029, 978, 771, 548.

^1H NMR (300 MHz, $CDCl_3$) : δ 5.52 (t, *J* = 6.8 Hz, 1H), 4.50-4.68 (m, 2H), 3.97-4.05 (m, 1H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.56-3.65 (m, 1H), 3.45 (d, *J* = 9.8 Hz, 1H), 2.38-2.46 (m, 2H), 2.25 (q, *J* = 12.8 Hz, 1H), 1.82-1.94 (m, 1H), 1.64-1.79 (m, 1H), 1.68 (s, 3H), 1.18 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 178.3, 138.9, 124.0, 88.4, 78.4, 60.6, 60.3, 46.5, 42.6, 38.7, 37.1, 35.5, 27.1, 19.1, 11.8.

HRMS (+ESI) : *m/z* calcd. for $C_{17}H_{29}O_4INa$ $[M+Na]^+$: 447.1002, found: 447.1003

(*E*)-3-((2*R*,3*S*,6*S*)-6-(2-hydroxyethyl)-3-methyl-tetrahydro-2H-pyran-2-yl)but-2-enyl pivalate (74)

A solution of **73** (2.550 g, 6.0 mmol), Bu_3SnH (3.2 mL, 12 mmol), and AIBN (0.197 mg, 1.2 mmol) in dry benzene (30 mL) was heated at 110 °C under N_2 atmosphere for 30 min. After the completion of reaction, the reaction mixture was cooled to room temperature, and diluted with Et_2O (30 mL) and saturated KF (50 mL). The organic layer was washed with saturated KF (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated i*n vacuo* to give the crude product which was then purified by silica gel column chromatography to afford pure tetrahydropyran **74** (1.613 g, 90% yield) as a colorless oil.

$[\alpha]_D^{20}$: −3.0 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3442, 2957, 2928, 2873, 1728, 1479, 1457, 1372, 1283, 1154, 1069, 1032, 956, 771.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.50 (t, *J* = 6.6 Hz, 1H), 4.51-4.67 (m, 2H), 3.75 (t, *J* = 5.1 Hz, 2H), 3.55-3.62 (m, 1H), 3.35 (d, *J* = 9.8 Hz, 1H), 1.80-1.86 (m, 1H), 1.69-1.77 (m, 2H), 1.67 (s, 3H), 1.35-1.60 (m, 3H), 1.19-1.26 (m, 1H), 1.17 (s, 9H), 0.68 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 178.4, 139.6, 122.9, 89.8, 78.7, 61.8, 60.5, 38.7, 37.7, 32.2, 32.1, 31.8, 27.1, 17.5, 11.9.

HRMS (+ESI) : *m/z* calcd. for $C_{17}H_{30}O_4Na$ $[M+Na]^+$: 321.2036, found:321.2035.

2-((2S,5S,6R)-5-methyl-6-((E)-4-(pivaloyloxy)but-2-en-2-yl)-tetrahydro-2H-pyran-2-yl)acetic acid (75)

Bis-acetoxyiodobenzene (2.350 g, 7.3 mmol) and TEMPO (0.156 g, 1.0 mmol) were added sequentially to the stirred solution of alcohol **74** (1.460 g, 4.9 mmol) in CH_2Cl_2 (50 mL) and water (25 mL) at 0 °C and allowed to warm to room temperature. After completion of the reaction, saturated aqueous $Na_2S_2O_3$ (50 mL) and Et_2O (100 mL) were added. The separated organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product which was purified by silica gel column chromatography to afford the pure acid **75** (1.253 g, 82% yield) as a colorless liquid.

$[\alpha]_D^{20}$: −2.1 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3446, 2957, 2924, 2851, 1730, 1715, 1459, 1377, 1283, 1154, 1071, 1031, 970, 771.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.56 (t, *J* = 6.7 Hz, 1H), 4.54-4.71 (m, 2H), 3.75-3.84 (m, 1H), 3.46 (d, *J* = 10.5 Hz, 1H), 2.59 (d, *J* = 1.5 Hz,

1H), 2.57 (s, 1H), 1.85-1.94 (m, 1H), 1.71 (s, 3H), 1.66-1.75 (m, 2H), 1.51-1.65 (m, 2H), 1.19 (s, 9H), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 178.3, 174.7, 139.1, 123.5, 90.4, 73.6, 60.6, 40.9, 38.7, 31.9, 31.8, 31.4, 29.7, 27.1, 17.4, 11.9.

HRMS (+ESI) : *m/z* calcd. for $C_{17}H_{28}O_5Na$ $[M+Na]^+$: 335.1829, found:335.1822.

(E)-3-((2R,3S,6S)-6-(2-methoxy-2-oxoethyl)-3-methyl-tetrahydro-2H-pyran-2-yl)but-2-enyl pivalate (76)

An ice-cold solution of 50% aqueous KOH (5 mL) and diethyl ether (10 mL) were taken in a separating funnel at to this was slowly added *N*-nitroso-*N*-methylurea (1.143 g, 11.1 mmol) with careful shaking (without placing the stopper). Then the organic layer was separated, dried over anhydrous KOH pellets and transferred into a solution of **75** (1.155 g, 3.7 mmol) in diethyl ether at 0 °C with slow stirring. Then the solvent was removed under vacuum and the crude product was purified by silica gel column chromatography to furnish pure ester **76** (1.182 g, 98% yield) as a colorless liquid.

$[\alpha]_D^{20}$: +5.6 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2956, 2924, 2853, 1734, 1459, 1374, 1282, 1154, 1071, 1052, 771.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.50 (t, *J* = 6.8 Hz, 1H), 4.54-4.68 (m, 2H), 3.74-3.81 (m, 1H), 3.66 (s, 3H), 3.35 (d, *J* = 9.8 Hz, 1H), 2.38-2.63 (m, 2H), 1.81-1.88 (m, 1H), 1.69-1.72 (m, 1H), 1.68 (s,

3H), 1.45-1.57 (m, 1H), 1.22-1.40 (m, 2H), 1.18 (s, 9H), 0.69 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 178.4, 171.8, 139.6, 122.7, 89.8, 73.8, 60.7, 51.6, 41.2, 38.7, 32.2, 32.0, 31.6, 27.2, 17.5, 12.0.

HRMS (+ESI) : *m/z* calcd. for $C_{18}H_{30}O_5Na$ $[M+Na]^+$: 349.1985, found:349.1982.

methyl 2-((2S,5S,6R)-6-((E)-4-hydroxybut-2-en-2-yl)-5-methyl-tetrahydro-2H-pyran-2-yl)acetate (77)

To a solution of pivalate ester **76** (0.456 g, 1.4 mmol) in methanol (10 ml) was added potassium carbonate (0.966 g, 7.0 mmol) at 0 °C and allowed to warm to room temperature over a period of 3 h. Methanol was then removed under reduced pressure and water (10 ml) was added. The mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography of the crude mixture afforded pure alcohol **77** (0.298 g, 88% yield) as a colorless oil.

$[\alpha]_D^{20}$: +19.2 (*c* 0.25, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3425, 2925, 2853, 1738, 1637, 1439, 1377, 1343, 1286, 1200, 1157, 1068, 1014, 766, 542.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.58 (t, *J* = 6.4 Hz, 1H), 4.21 (t, *J* = 6.4 Hz, 1H), 3.73-3.82 (m ,1H), 3.67 (s, 3H), 3.35 (d, *J* = 9.8 Hz, 1H), 2.37-2.64 (m ,2H), 1.81-1.88 (m, 1H), 1.47-1.73 (m, 2H), 1.65 (s, 3H), 1.16-1.43 (m, 2H), 0.72 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.7, 137.2, 127.5, 90.0, 74.0, 59.0, 51.5, 41.2, 32.2, 32.0, 31.6, 17.8, 11.9.

HRMS (+ESI) : *m/z* calcd. for $C_{13}H_{22}O_4Na$ $[M+Na]^+$: 265.1410, found: 265.1408.

methyl 2-((2S,5S,6R)-5-methyl-6-((E)-penta-2,4-dien-2-yl)tetrahydro-2H-pyran-2-yl)acetate (62)

To a solution of Dess-Martin Periodinane (0.579 g, 1.4 mmol) in CH_2Cl_2 (10 mL) was added H_2O (30 μl). To the resulting cloudy suspension was added a solution of the alcohol **77** (0.220 g, 0.91 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred until starting material disappeared (ca 0.5 h). Saturated solution of $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL, 1 M) was added to the mixture and stirred vigorously until the organic layer turned clear. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4 and then concentrated *in vacuo* to obtain the crude aldehyde (0.185 g, 85% yield) which was directly subjected to Wittig olefination. To a suspension of Ph_3PCH_3Br (1.372 g, 3.8 mmol) in THF (5.0 mL) at 0 °C, was added n-BuLi (1.4 mL, 2.5 M in THF, 3.4 mmol) dropwise through a syringe. The resulting solution was warmed to room temperature and then cooled back to –78 °C over a period of 30 min. To this solution was slowly added aldehyde (0.185 g, 0.77 mmol) in 3 mL THF through a cannula and the reaction mixture was warmed to room temperature and stirred for 1 h. Then the reaction was quenched with saturated NH_4Cl solution (10 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was chromatographed to afford the olefin **62** (0.137 g, 75% yield) as a colorless oil which solidified upon cooling.

$[\alpha]_D^{20}$: +50.8 (*c* 0.25, $CHCl_3$)

IR (Neat) ν_{max}/cm^{-1} : 2953, 2926, 2852, 1742, 1651, 1601, 1437, 1380, 1340, 1293, 1253, 1198, 1160, 1068, 1020, 990, 902, 764, 662.

1H NMR (300 MHz, CDCl3) : δ 6.58 (dt, *J* = 10.6, 16.6 Hz, 1H), 5.97 (d, *J* = 10.6 Hz, 1H), 5.05-5.21(m, 2H), 3.72-3.82 (m, 1H), 3.66 (s, 3H), 3.35 (d, *J* = 9.8 Hz, 1H), 2.60 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.40 (dd, *J* = 8.3, 6.8 Hz, 1H), 1.80-1.88 (m, 1H), 1.73 (d, *J* = 1.5 Hz, 3H), 1.46-1.71 (m, 2H), 1.15-1.41 (m, 2H), 0.70 (d, J = 6.0 Hz, 3H).

13C NMR (125 MHz, CDCl3) : δ 171.8, 137.3, 132.7, 128.6, 116.9, 90.2, 73.8, 51.5, 41.3, 32.3, 32.2, 31.6, 17.6, 12.2.

HRMS (+ESI) : *m/z* calcd. for $C_{14}H_{22}O_3Na$ $[M+Na]^+$: 261.1461, found: 261.1455.

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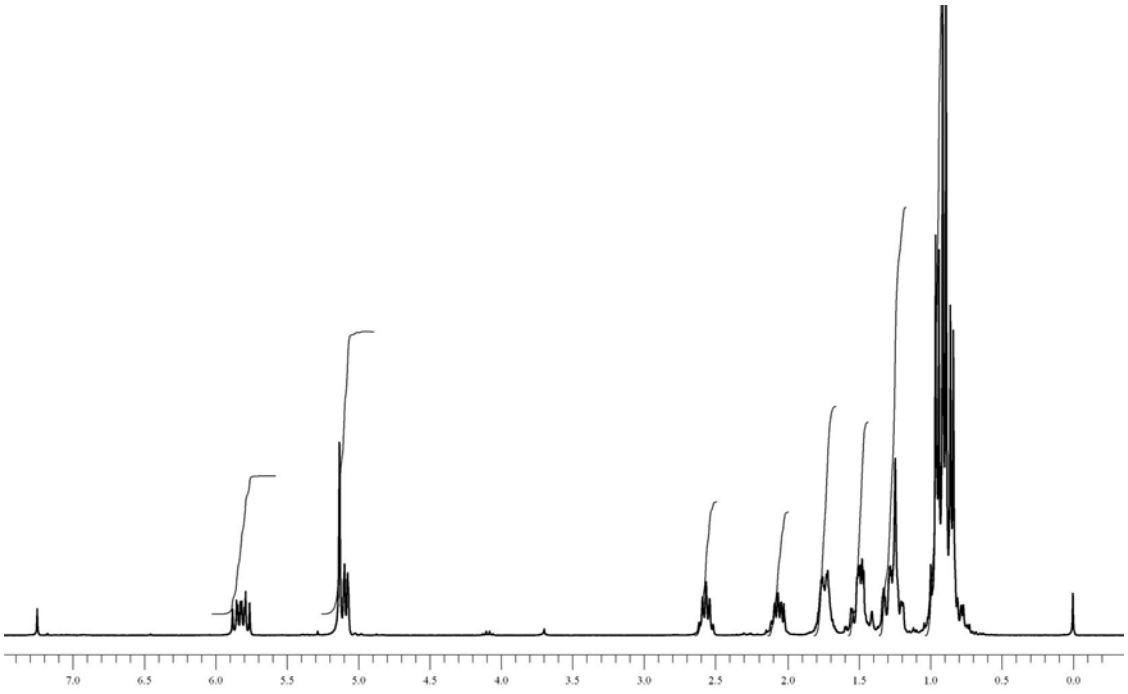
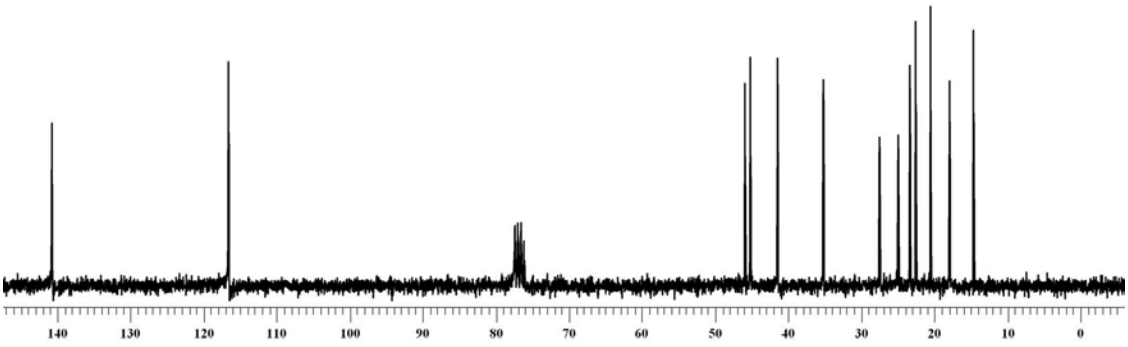


^{1}H NMR SPECTRUM OF COMPOUND **71**



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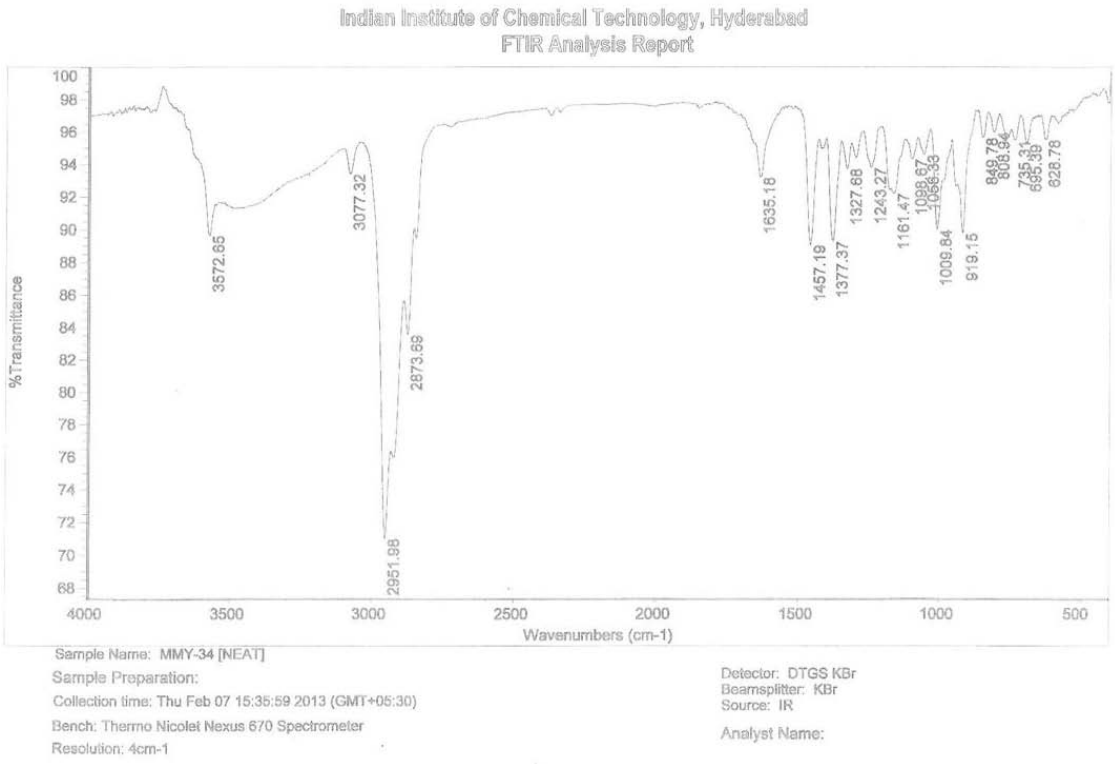
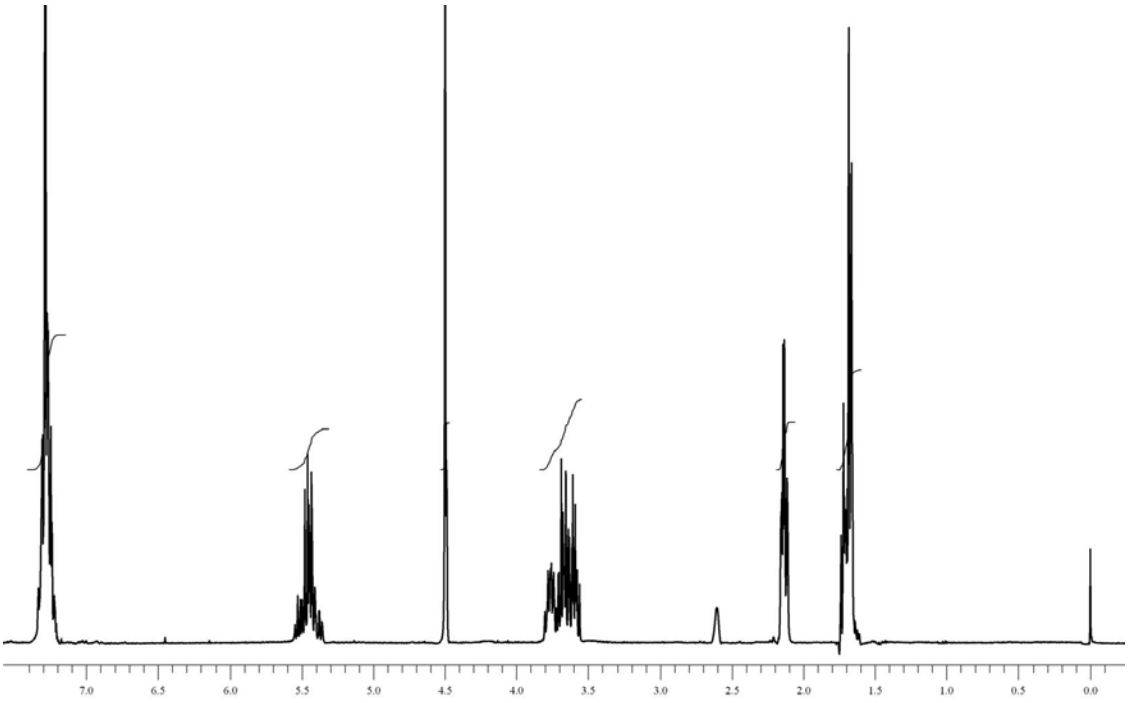


IR SPECTRUM OF COMPOUND 71



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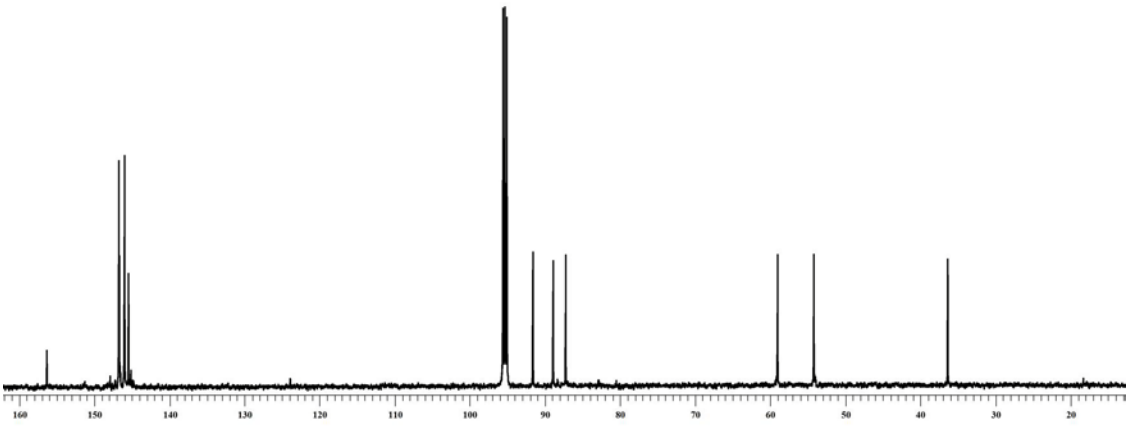

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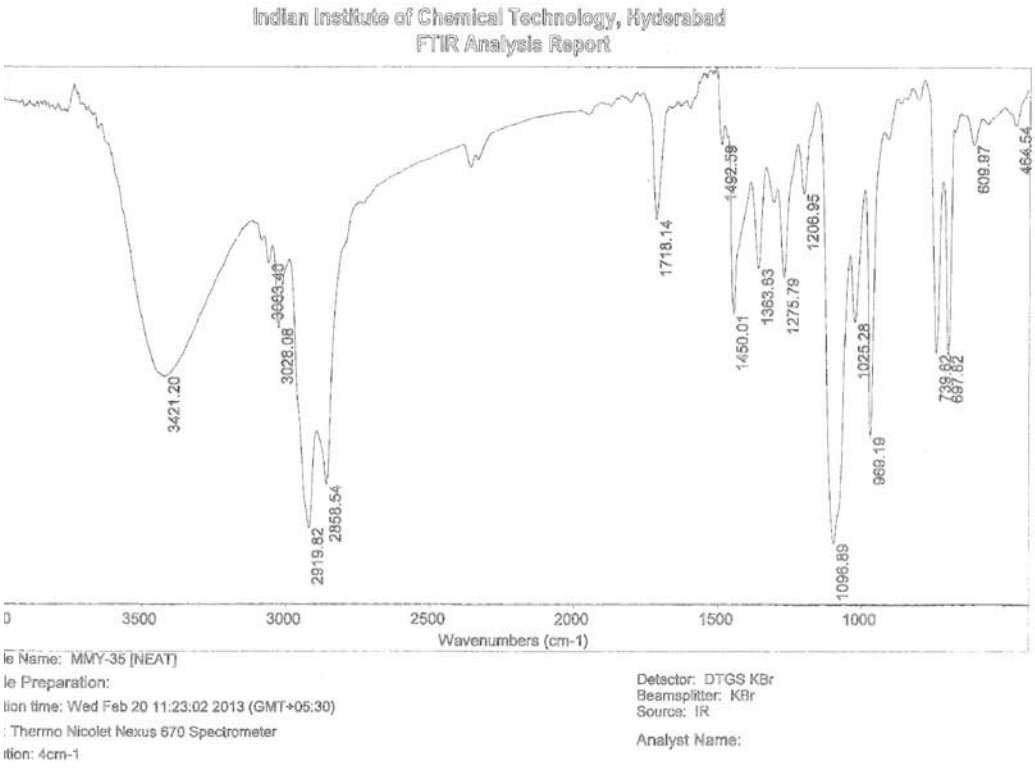

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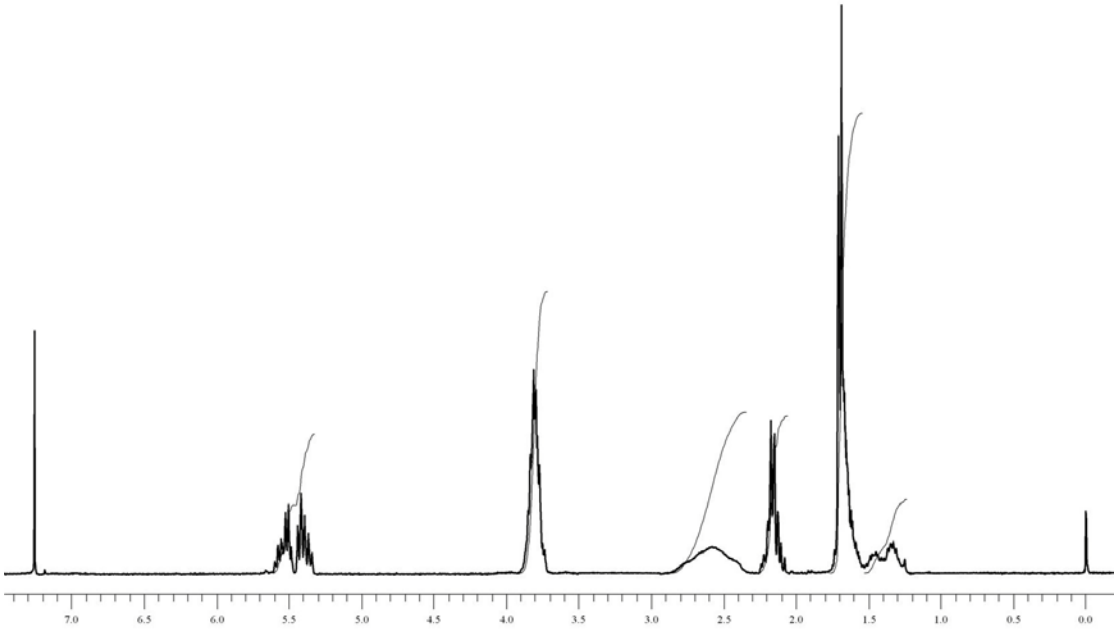
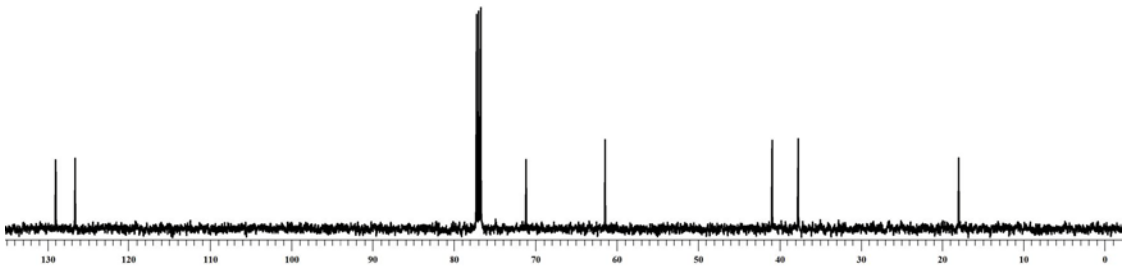


^{1}H NMR SPECTRUM OF COMPOUND **64**



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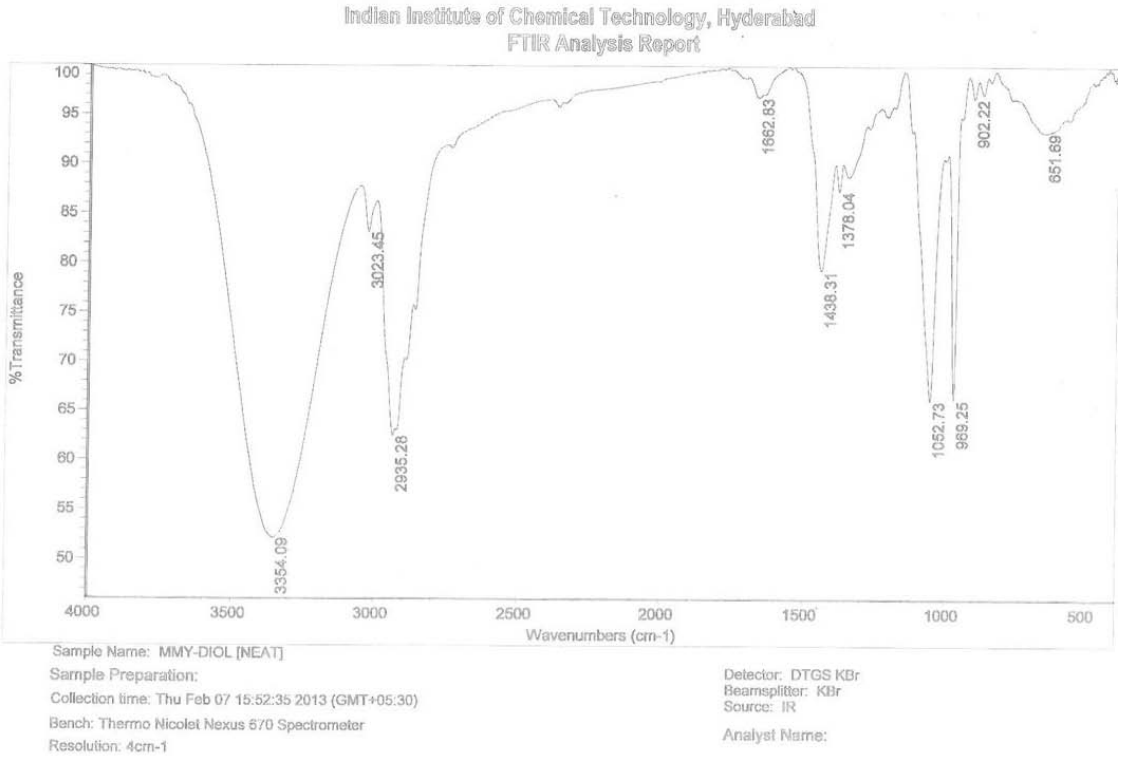

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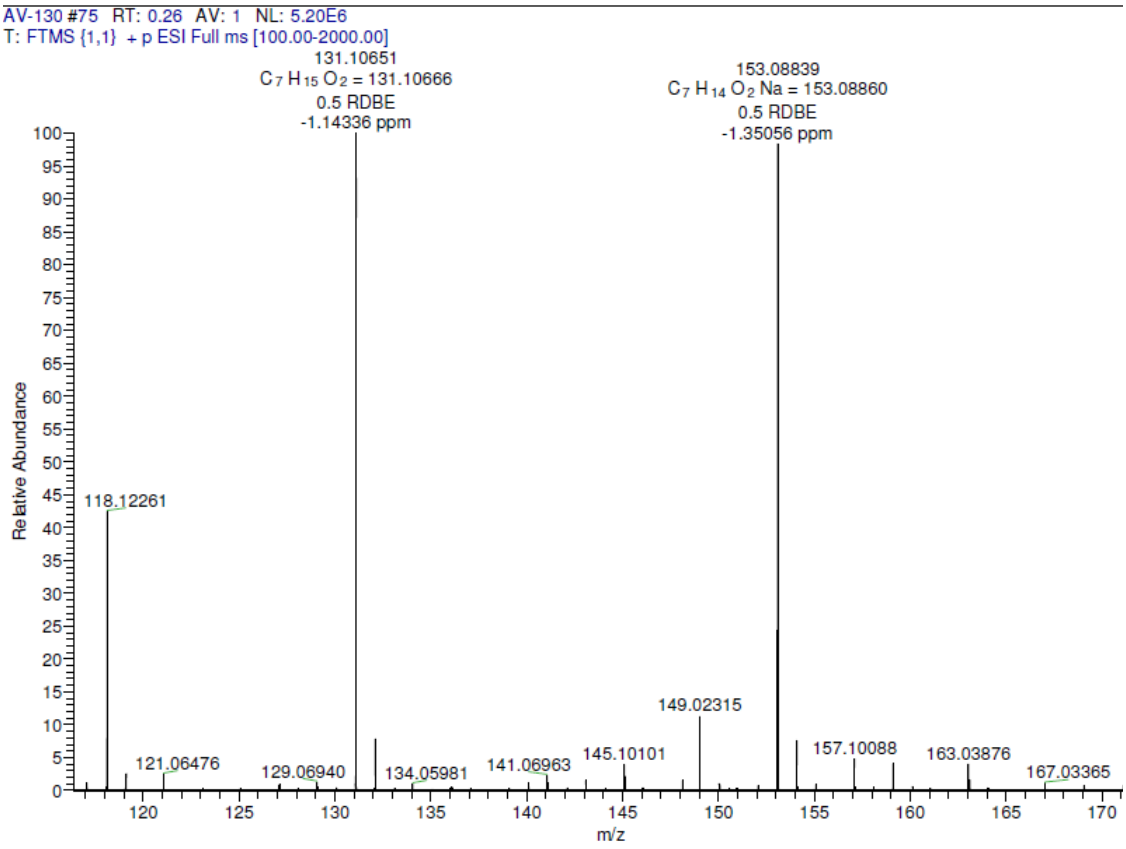
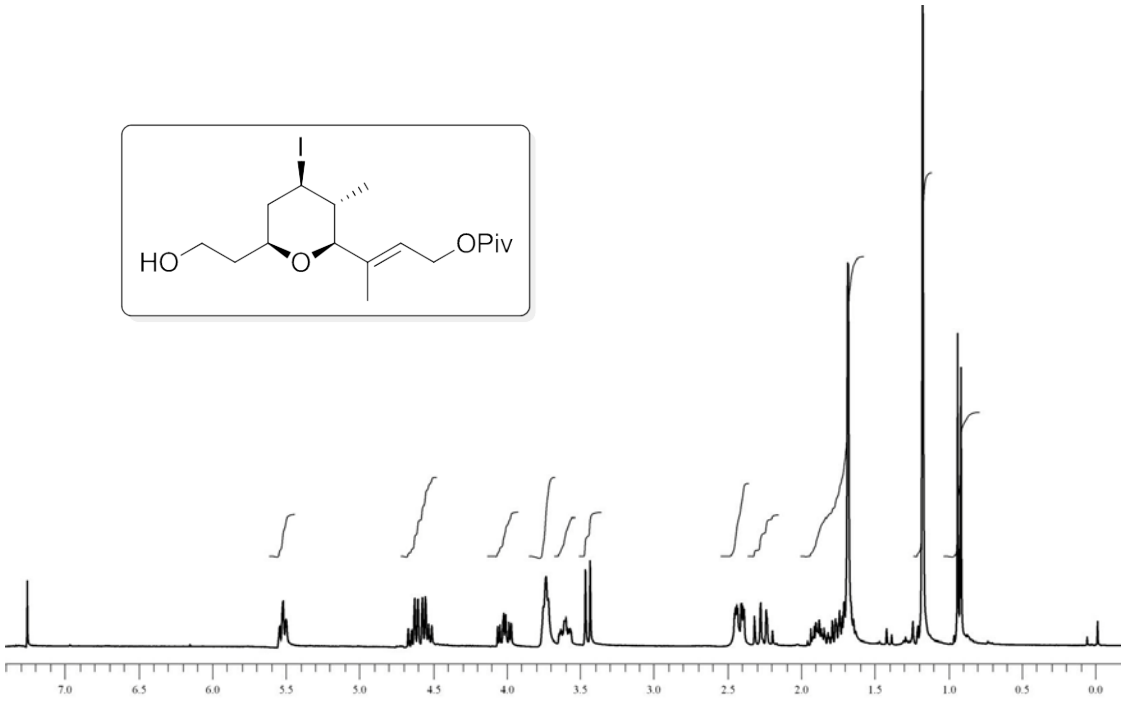


HRMS SPECTRUM OF COMPOUND **64**



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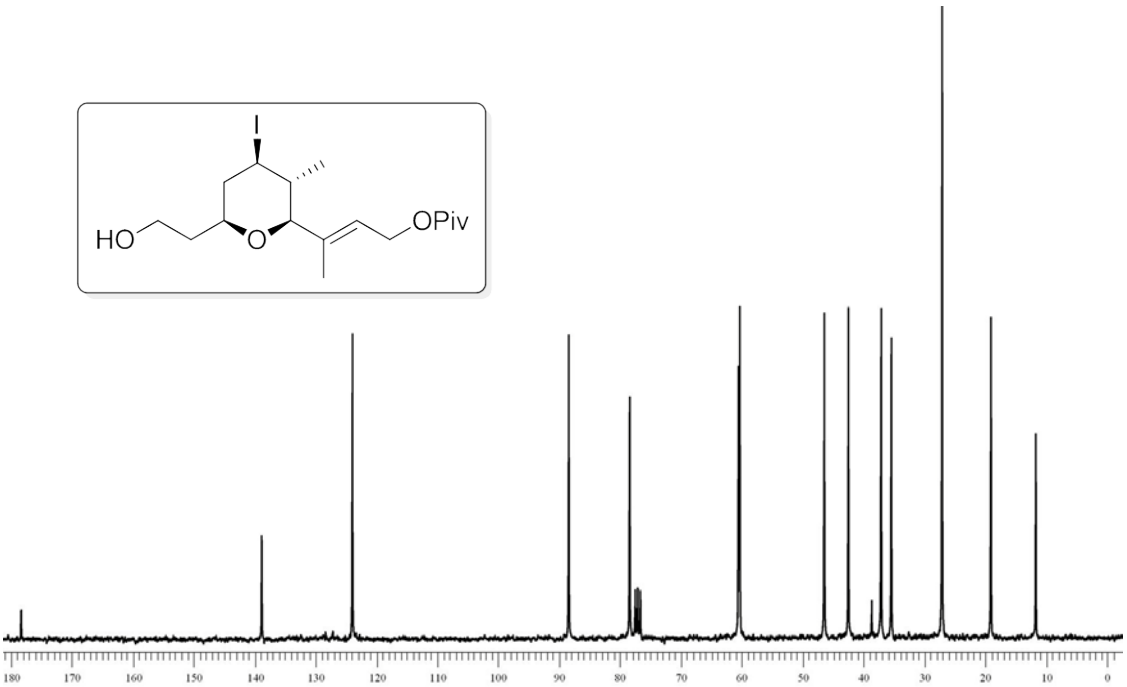
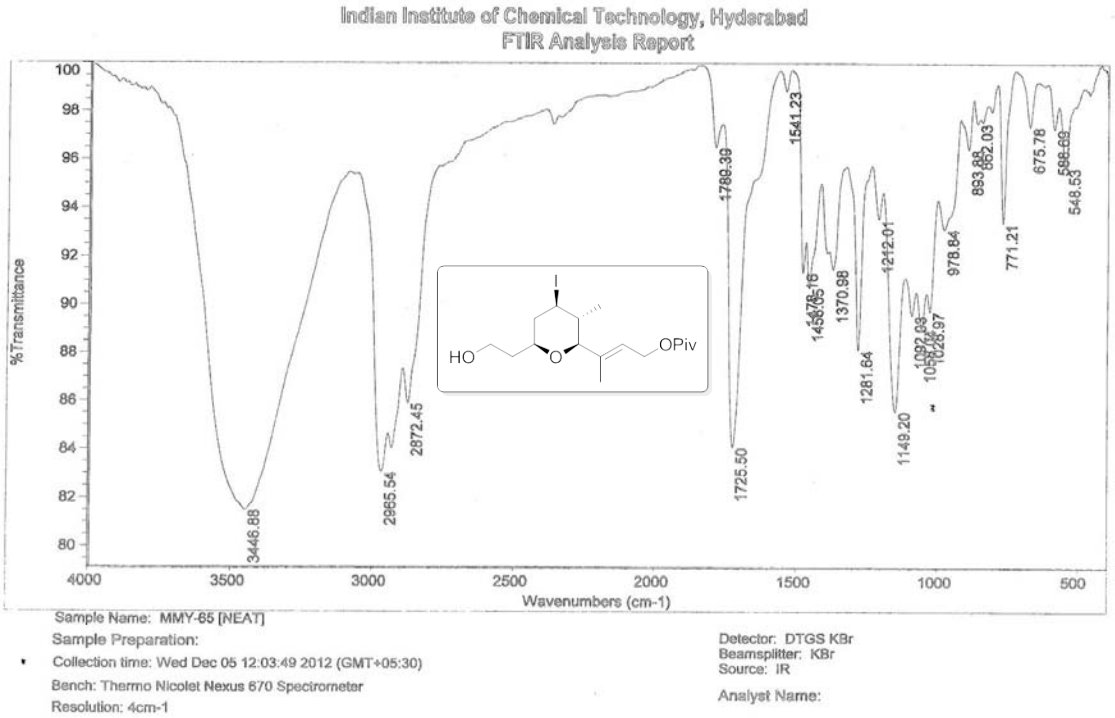


^{13}C NMR SPECTRUM OF COMPOUND **73**



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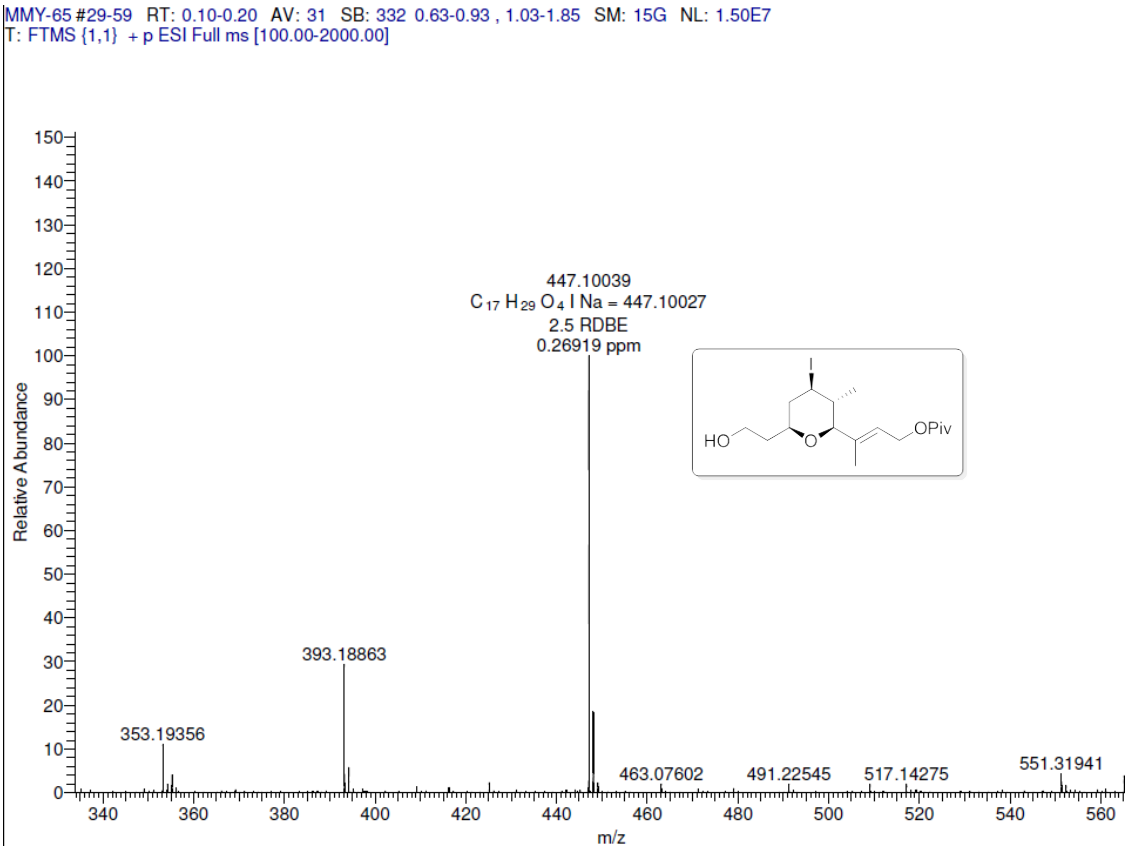

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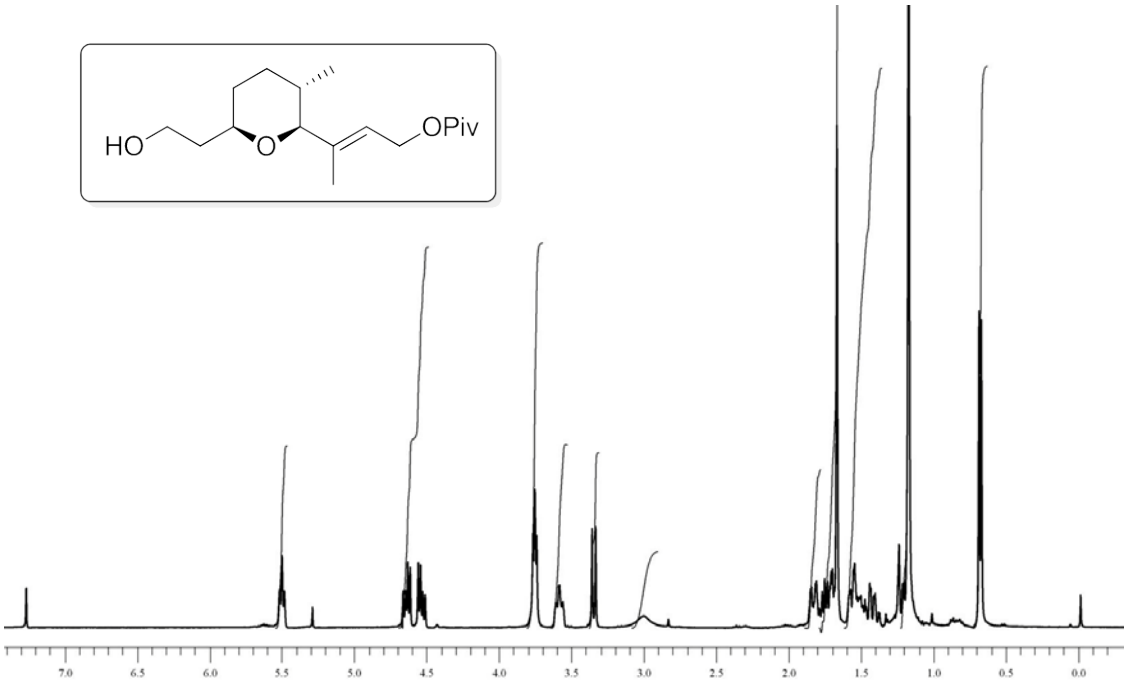

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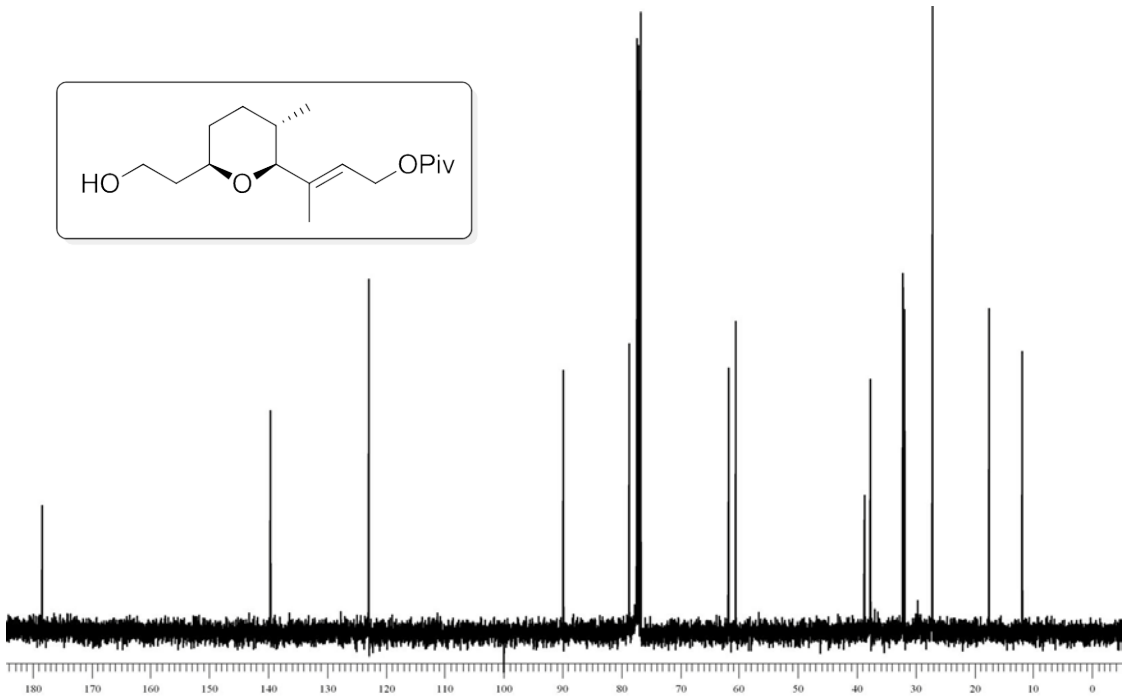

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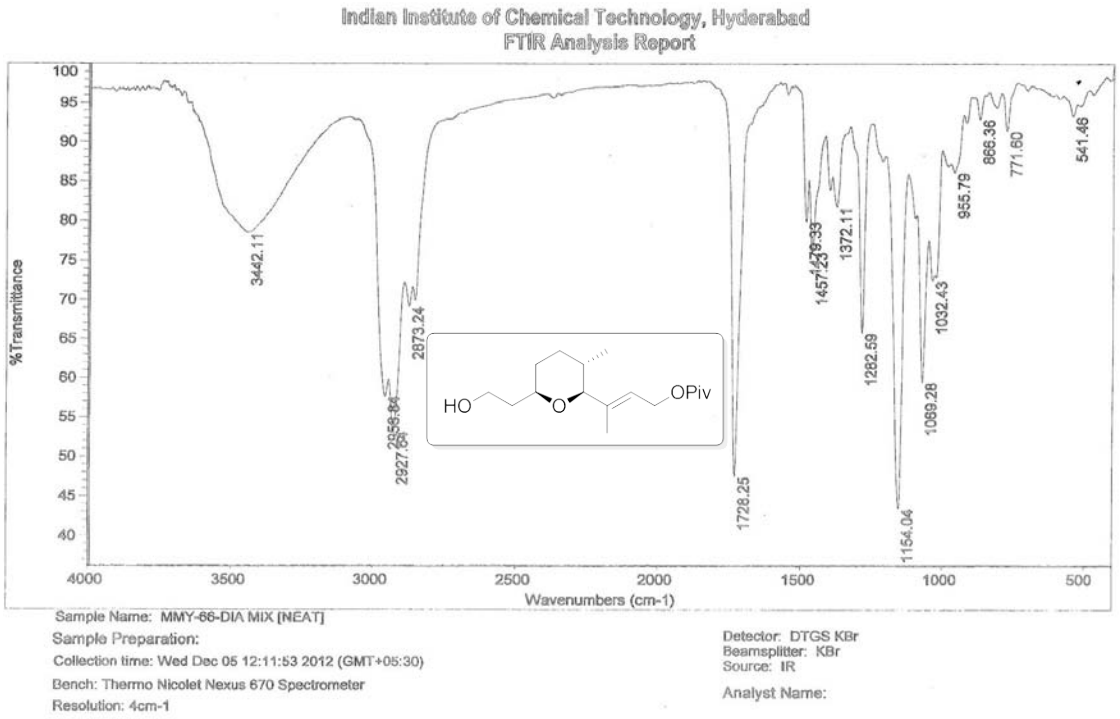

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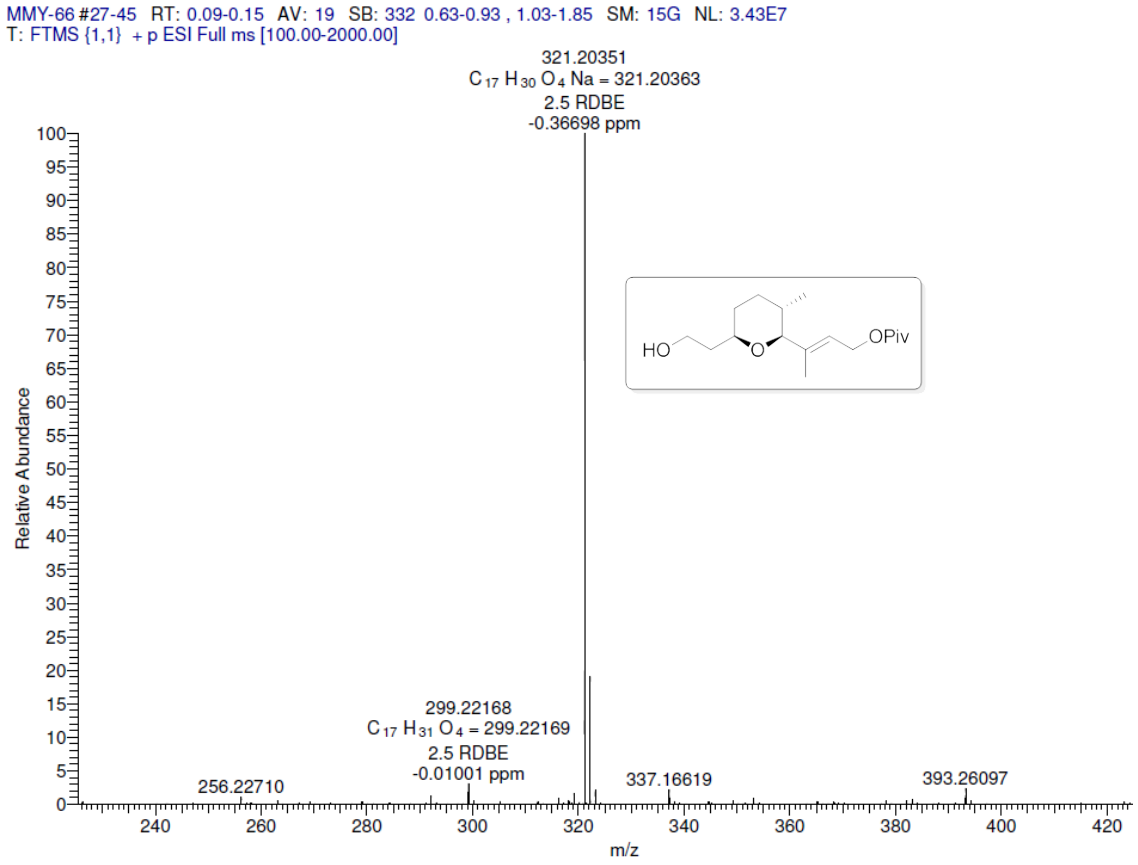

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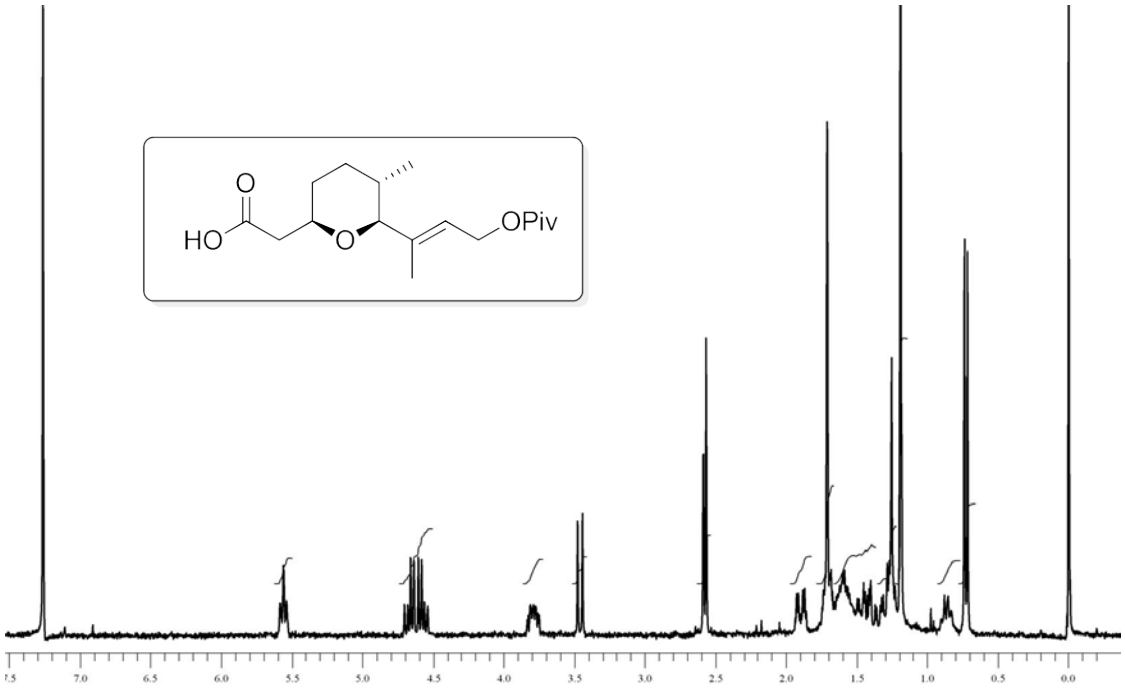

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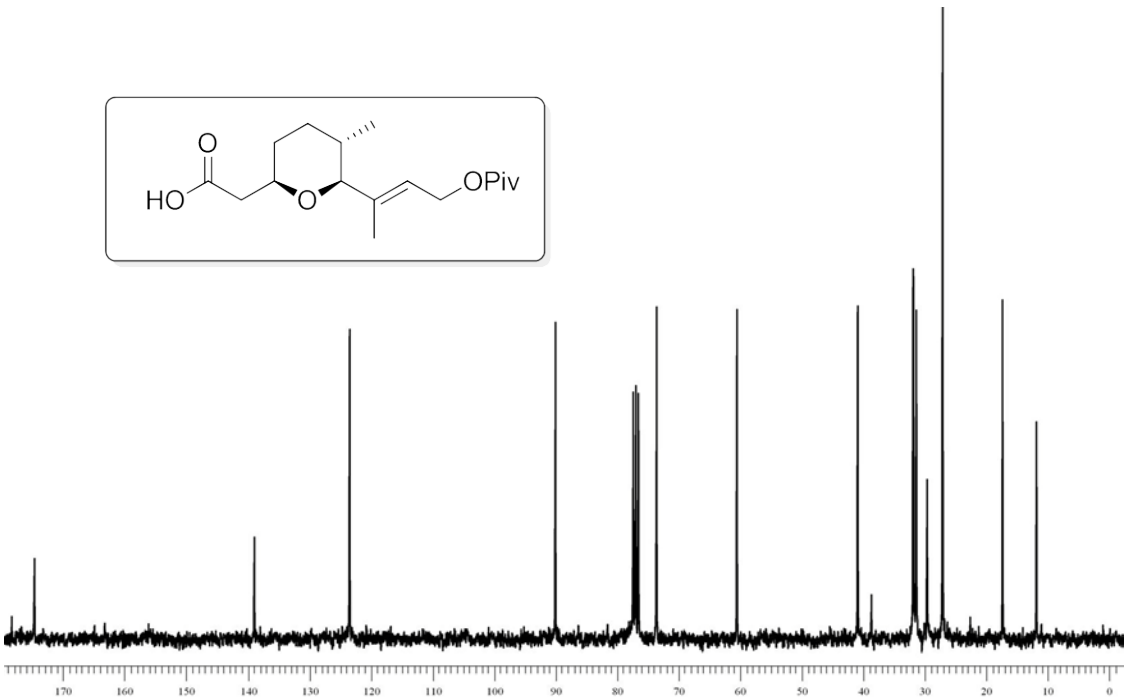

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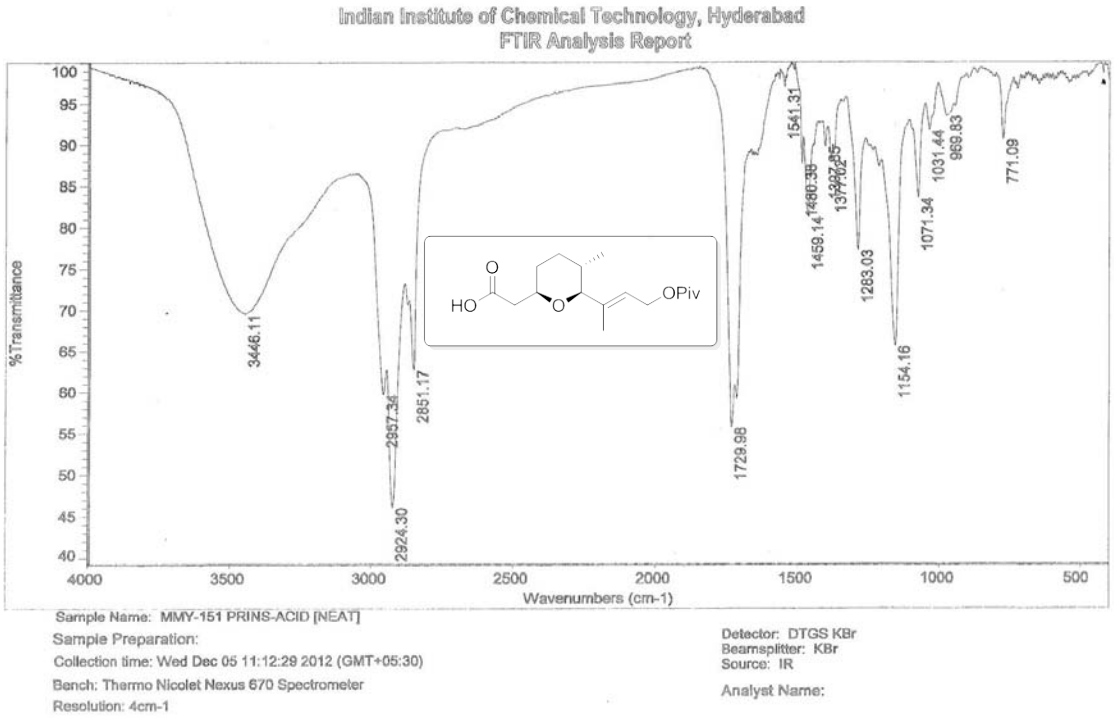

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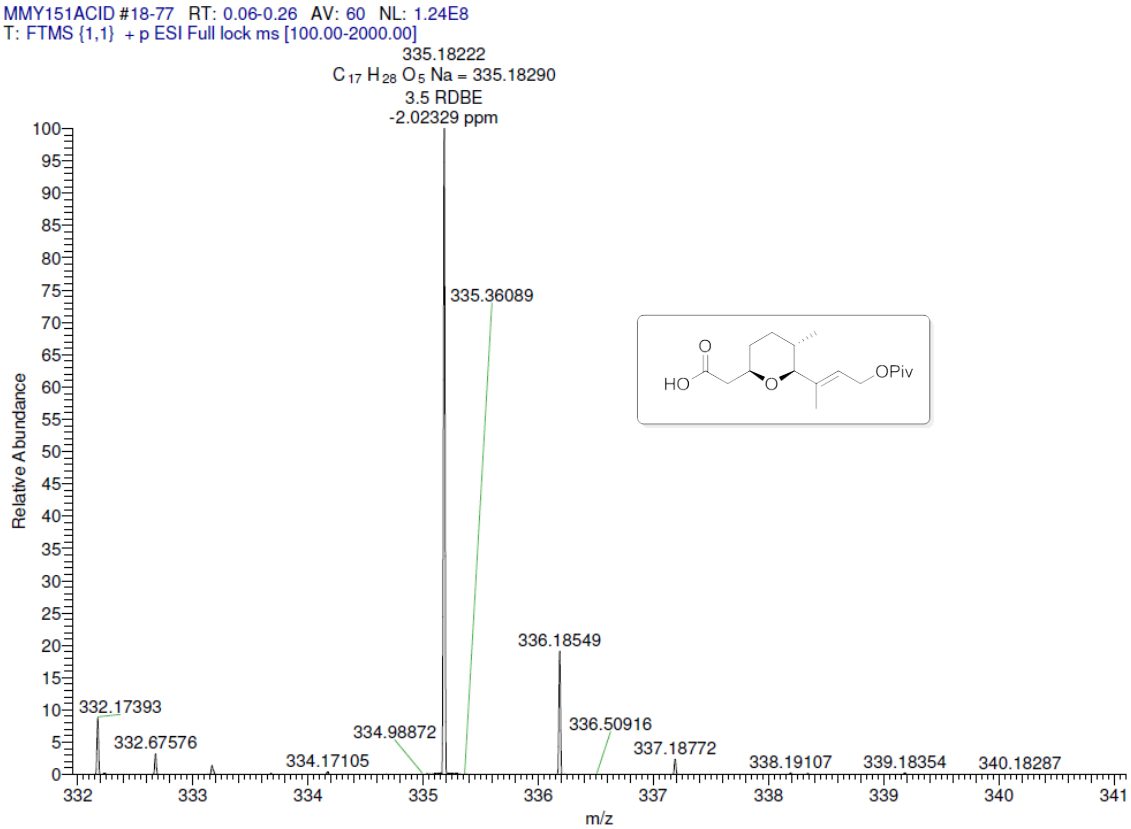

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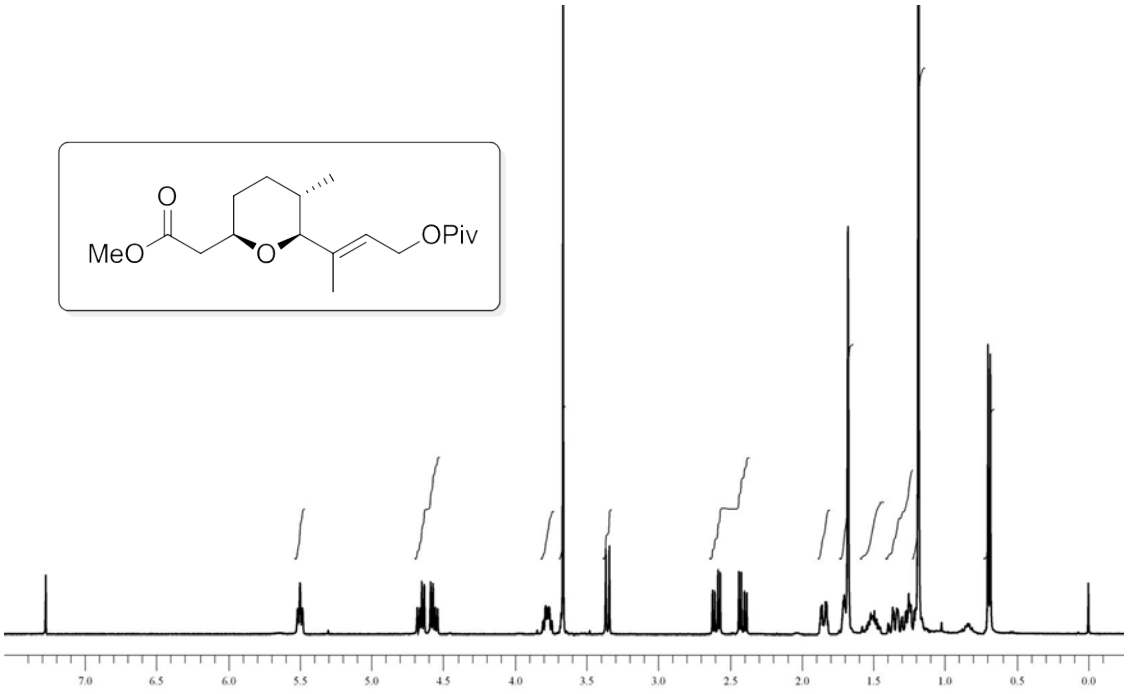

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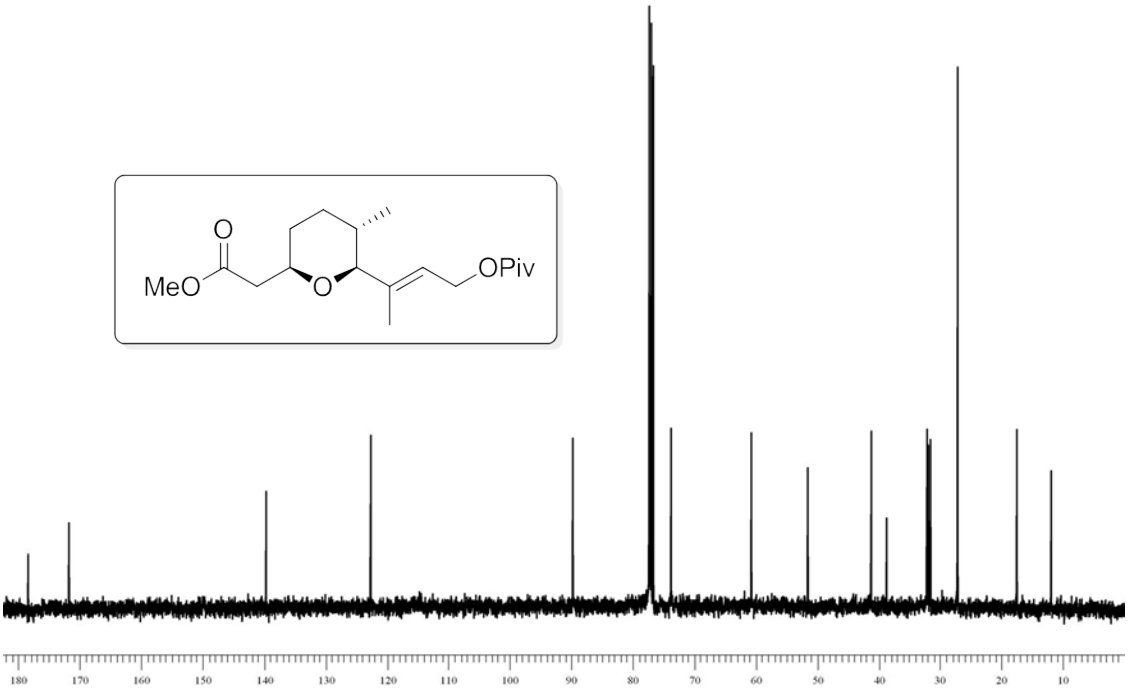

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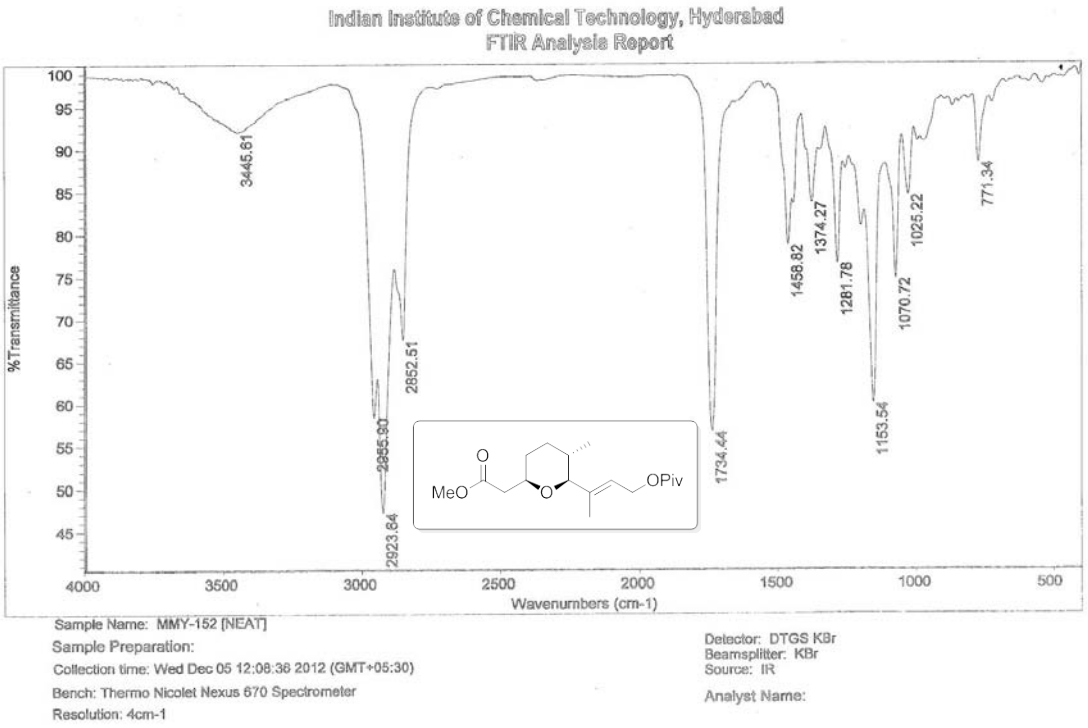

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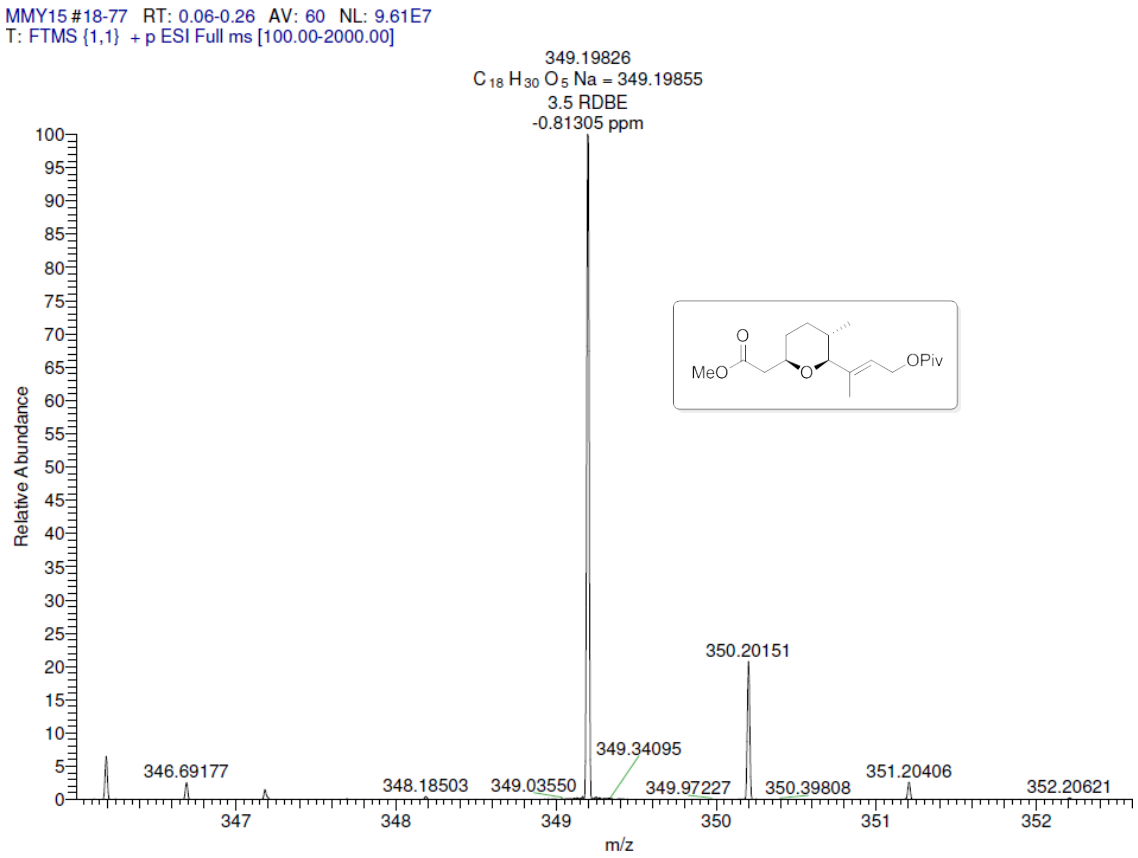

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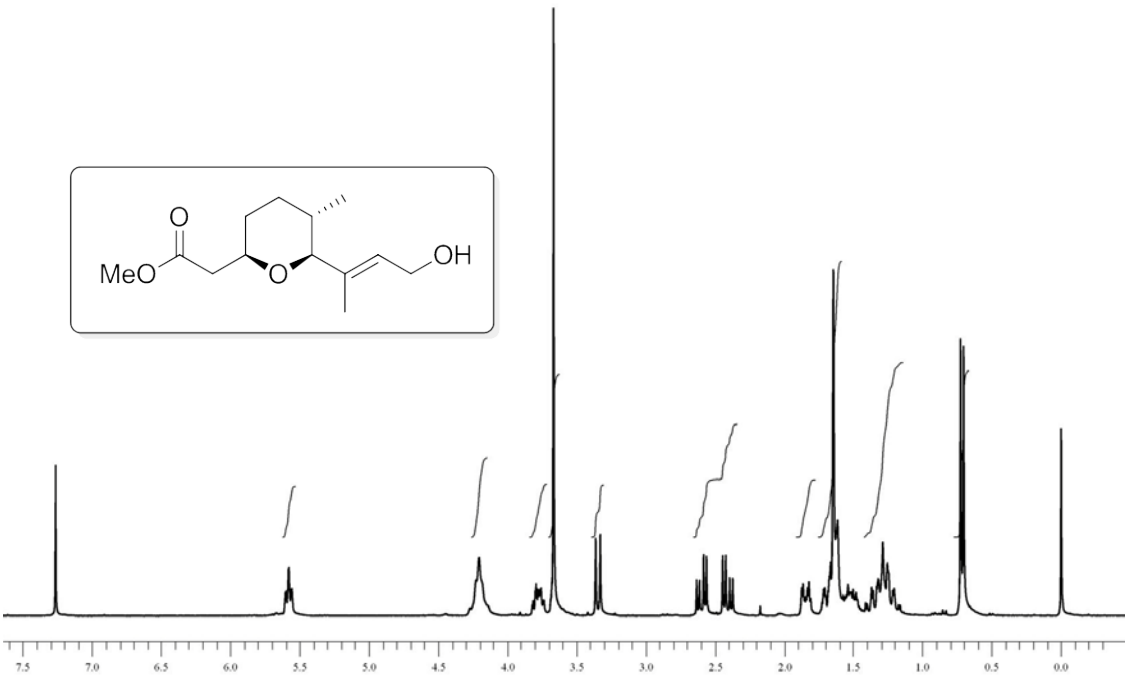

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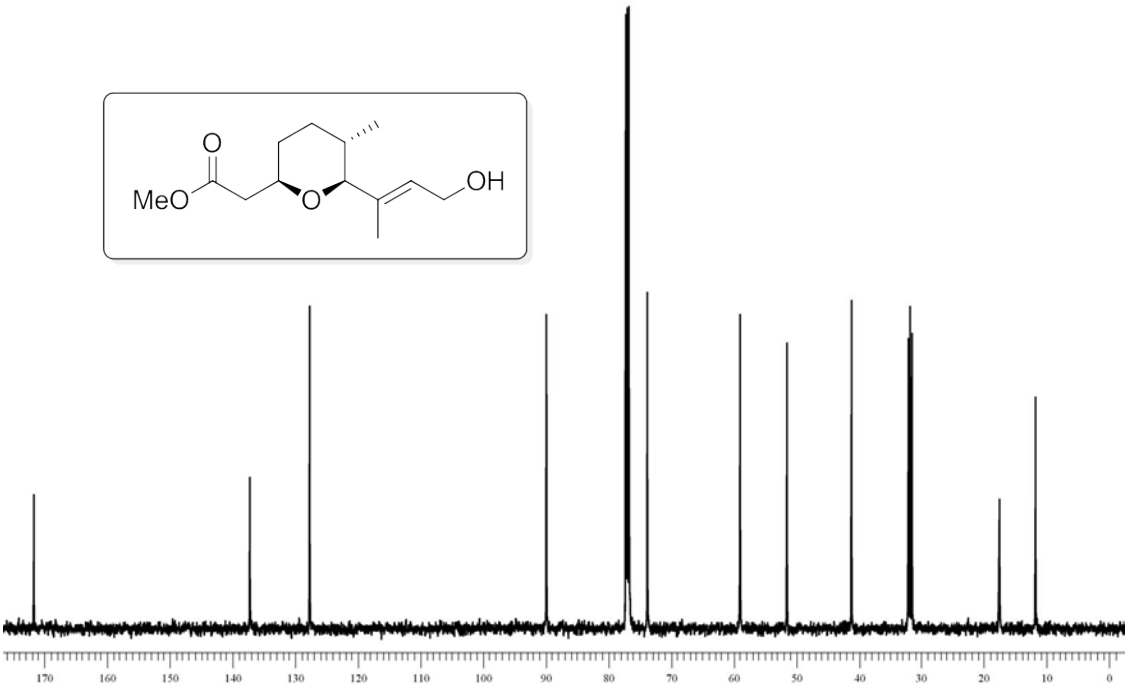

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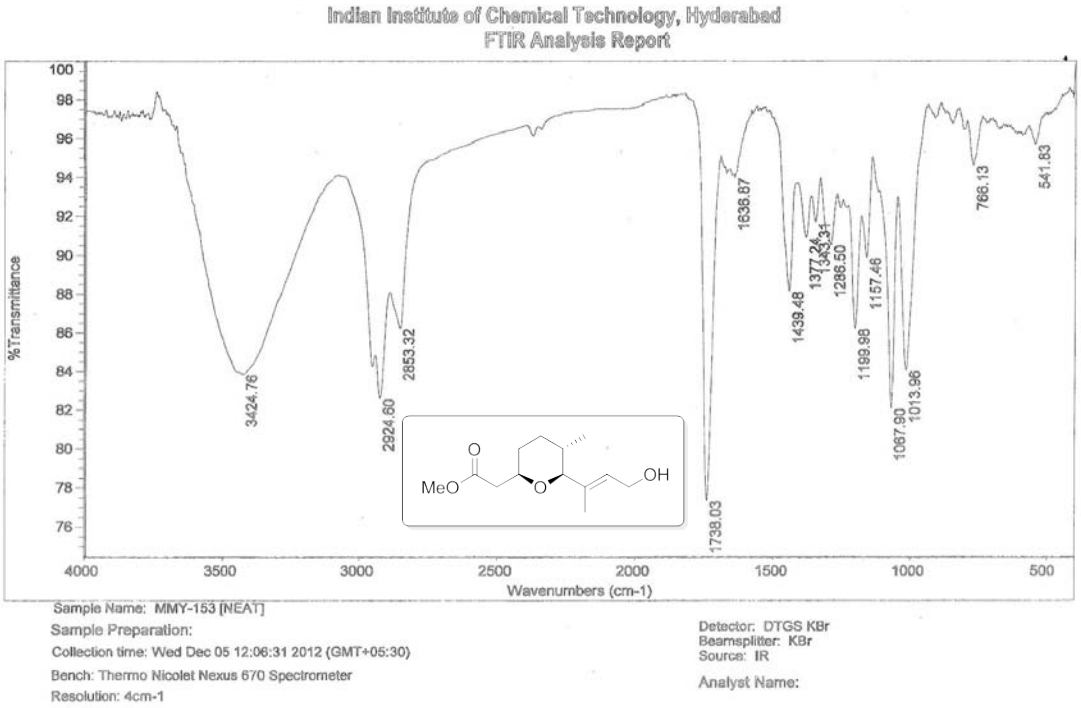

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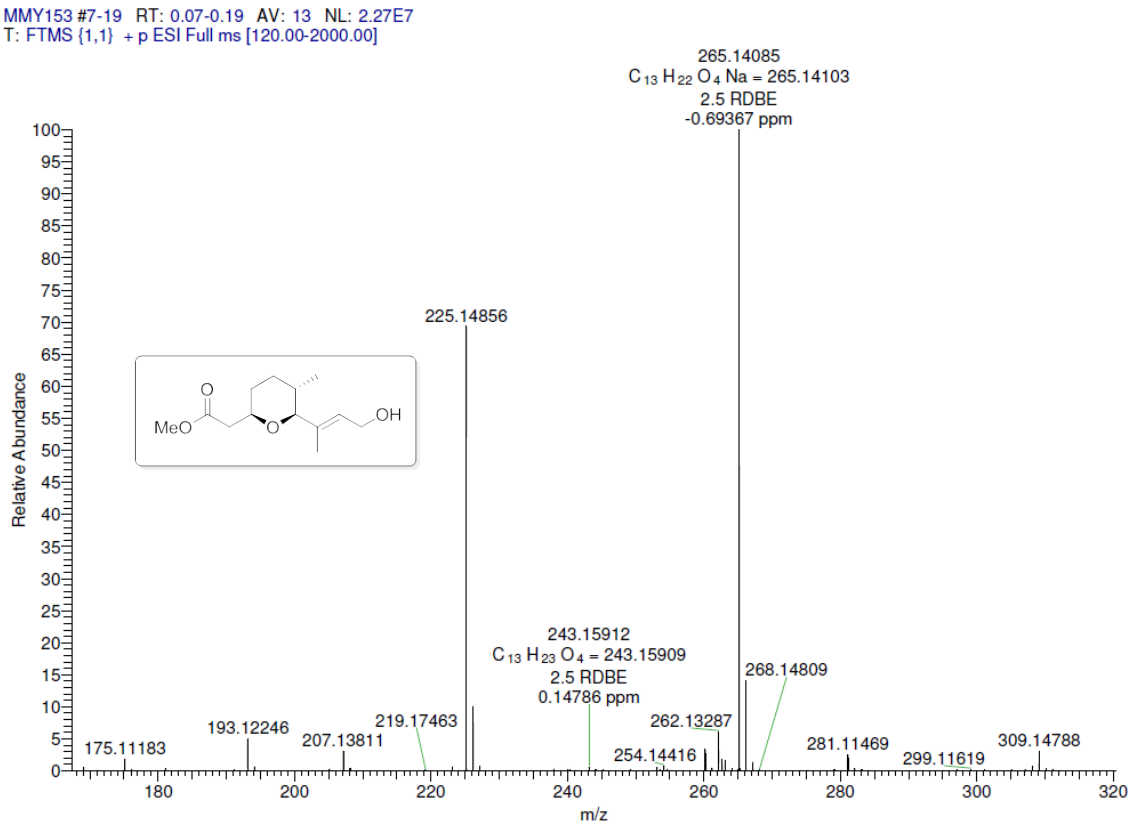

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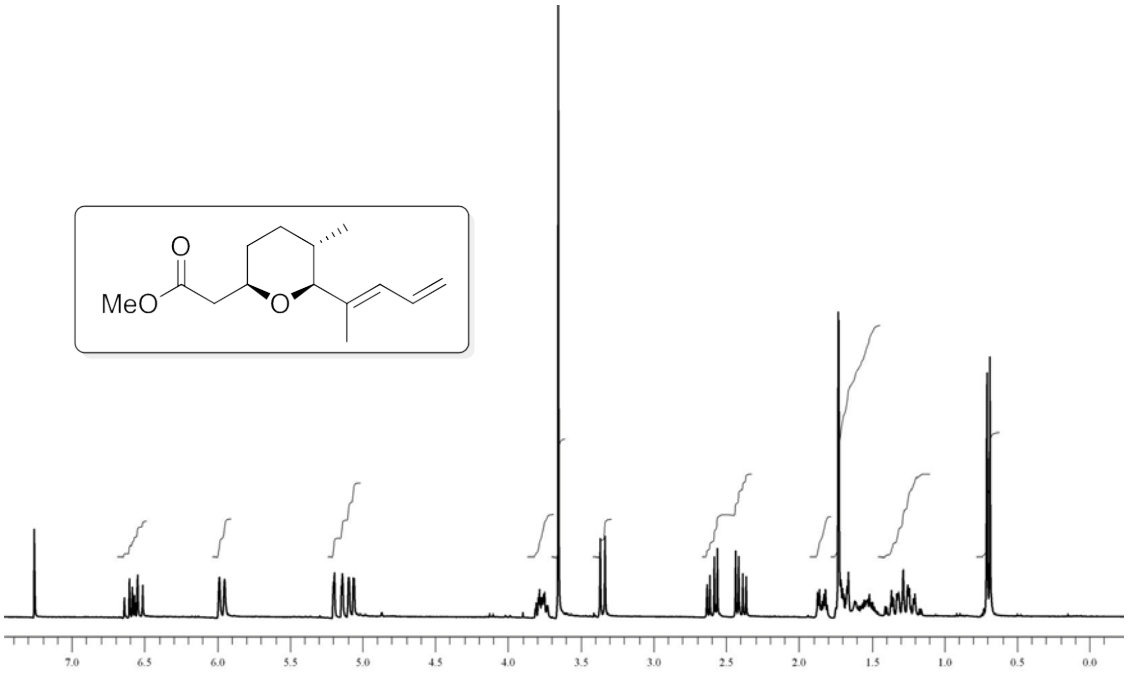
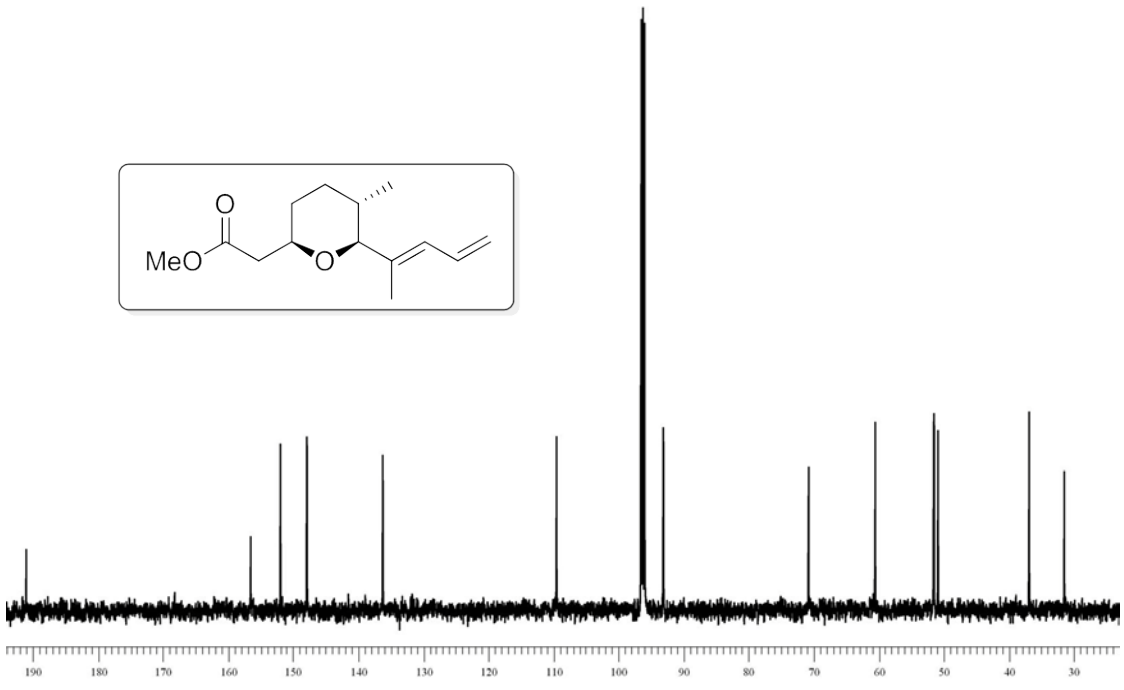
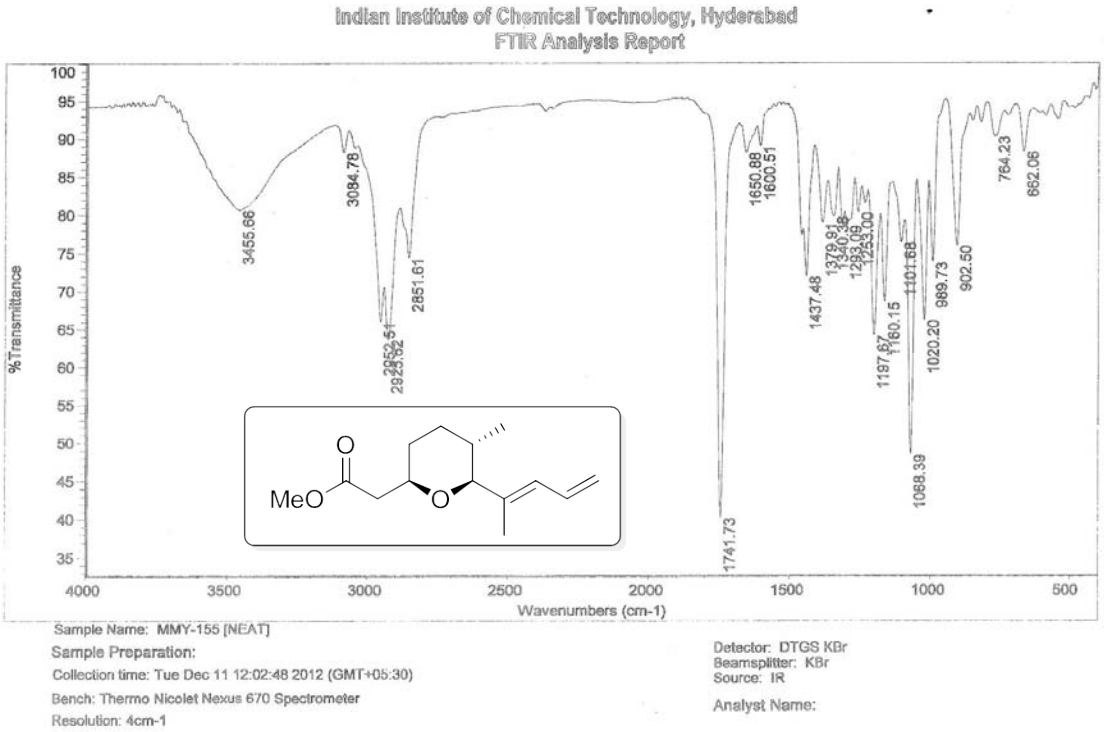


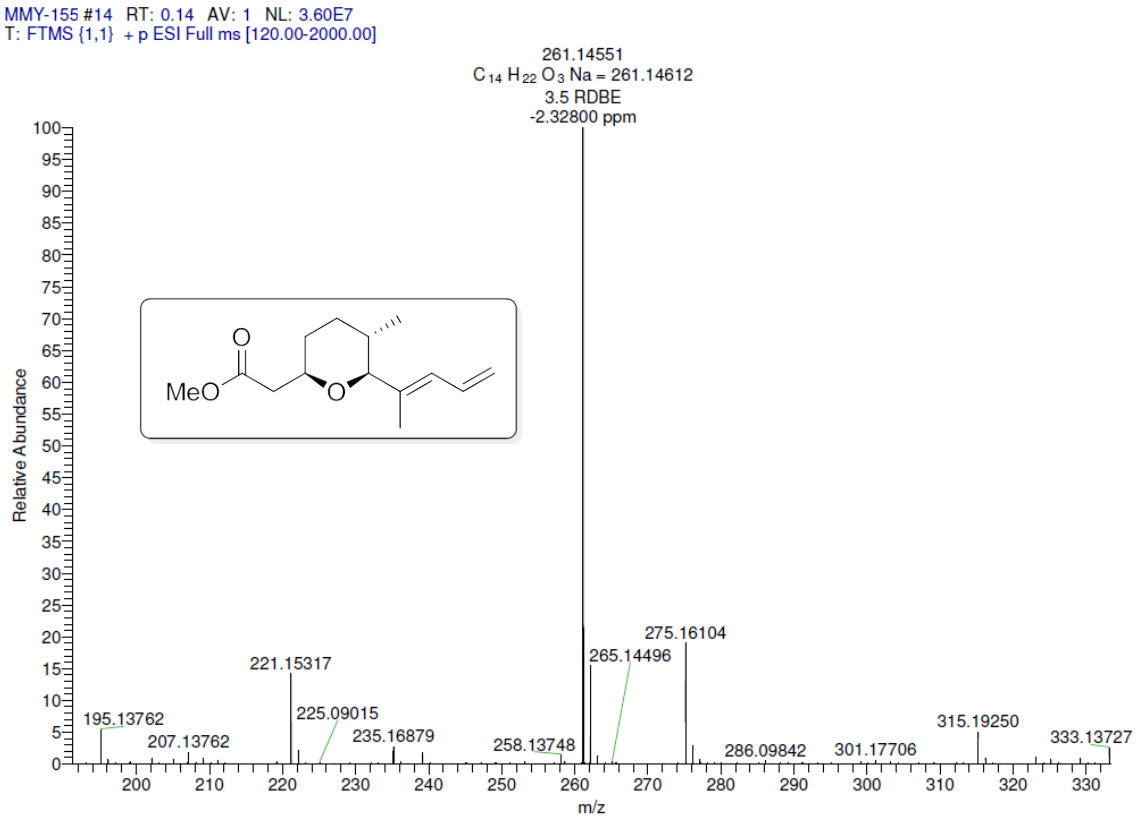
^{1}H NMR SPECTRUM OF COMPOUND **62**



^{13}C NMR SPECTRUM OF COMPOUND **62**



FTIR SPECTRUM OF COMPOUND **62**



HRMS SPECTRUM OF COMPOUND **62**

SYNTHESIS OF THE SIDE CHAIN:

With the tetrahydropyran fragment **62** in hand, the focus now shifted towards the synthesis of side chain **63**.

Scheme 17 : Reagents and conditions:

A. Benzyl 2,2,2-trichloroacetimidate, CF_3SO_2H, CH_2Cl_2:cyclohexane (2:1), 0 °C to rt, 1 h, 88%; B. (i) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 85%; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1h, 92%;

The synthesis commenced with the masking of the hydroxyl group in (*S*)-Roche ester, **70** as its benzyl ether using benzyl imidate in presence of catalytic amount of CF_3SO_2H that resulted in **78** in 88% yield.[1] Formation of **78** was confirmed by the ^1H and ^{13}C NMR spectra that displayed the signals corresponding to the benzyl group. ESI-MS too displayed the peak matching with $(M+Na)^+$ at 231.

Controlled reduction[2] of **78** with DIBAL-H in CH_2Cl_2 at -78 °C afforded the corresponding aldehyde which was subjected to Wittig reaction with $Ph_3PCHCOOEt$ in benzene under reflux conditions to yield the *cis:trans* (5:95) mixture of unsaturated ester **69** in 92% yield, which could be separated by column chromatography.

Scheme 18 : Reagents and conditions:

A. AD-mix β, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 0 °C, 6 h, 88%; B. 2,2-DMP, *p*-TSA, CH_2Cl_2, rt, 12 h, 85%; C. DIBAL-H, CH_2Cl_2, 0 °C to rt, 1 h, 82%; D. TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 90%;

The structure of **69** was ascertained by ^{1}H NMR spectrum which displayed the signals corresponding to olefinic protons as a dd and doublet at 6.89 and 5.81 ppm respectively, integrating for one proton each and the signals corresponding to the ethyl ester group at 4.17 and 1.29 ppm integrating for two and three protons respectively. The ^{13}C NMR spectrum too displayed the resonance corresponding to the olefinic carbons at 120.9 and 151.0 ppm, while the ESI-MS spectrum displayed the peak matching with $(M+H)^+$ at 249.

Now the unsaturated ester **69** was subjected to Sharpless asymmetric dihydroxylation[3] using AD-mix β in presence of $MeSO_2NH_2$ in *t*-BuOH:H_2O (1:1) at 0 °C to furnish an inseparable 93:7 diastereomeric mixture of diol **79** as observed in the ^{1}H NMR spectrum. The ^{1}H NMR and ^{13}C NMR spectra showed the disappearance of signals corresponding to olefin while the IR spectrum showed the appearance of strong absorption related to –OH stretching at 3424 cm^{-1}. The ESI-MS spectrum displayed a peak at 305 corresponding to $(M+Na)^+$.

The diastereomers could be separated by column chromatography after protecting the diol as its acetonide using 2,2-DMP in presence of *p*-TSA in CH_2Cl_2 to furnish the required diastereomer **80** in 85% yield. Formation of the product was confirmed by the appearance of signals corresponding to the acetonide functionality at 110.4, 26.9 and 25.6 ppm in the ^{13}C NMR spectrum. The strong absorption of –OH stretching at 3424 cm^{-1} disappeared in FTIR spectrum while the ESI-MS spectrum showed the $(M+Na)^+$ peak at 345.

Then the diastereomerically pure compound **80** was subjected to DIBAL-H reduction in CH_2Cl_2 to provide the alcohol **81** in 82 % yield. The ^{1}H and ^{13}C NMR spectra revealed the disappearance of the signals corresponding to the ethyl ester group and appearance of signals corresponding to $–CH_2OH$ at 3.58, 3.73 ppm in ^{1}H and 73.0 ppm in ^{13}C NMR respectively. Further, the FTIR spectrum too lacked the C=O stretching frequency at 1746 cm^{-1} while it displayed a strong –OH absorption at 3451 cm^{-1} and the ESI-MS spectrum showed the $(M+Na)^+$ peak at 303, thereby confirming the product **81**.

The free hydroxyl group in **81** was then protected with tosyl chloride and Et_3N in CH_2Cl_2 to culminate in the tosyl protected product **82** in 90% yield. This protection was ascertained by the appearance of the signals corresponding to the tosyl group at 7.77, 7.30 and 2.43 ppm in the ^1H NMR and at 127.5, 128.0 and 21.6 ppm in the ^{13}C NMR spectra. ESI-MS spectrum too showed the $(M+Na)^+$ peak at 457.

Scheme 19 : Reagents and conditions:

A. *p*-TSA, MeOH, rt, 12 h, 85%; B. K_2CO_3, MeOH, 0 °C to rt, 1 h, 86%; C. NaH, MeI, THF, 0 °C, 1 h, 88%.

The acetonide group in **82** was then cleaved using *p*-TSA in MeOH to furnish the diol **83** in 85% yield. The disappearance of the two singlets at 1.30 and 1.34 ppm in the ^1H NMR and at 26.7 and 27.0 ppm in the ^{13}C NMR spectrum corresponding to the acetonide group confirmed the product. The ESI-MS spectrum showed a peak at 417 that corresponds to $(M+Na)^+$. The FTIR spectrum too displayed two strong absorptions at 3423 and 3324 cm^{-1} corresponding to the two hydroxyl groups.

Treatment of **83** with K_2CO_3 in MeOH resulted in the epoxide **84** in 86% yield. This transformation was confirmed primarily by the disappearance of the signals corresponding to the tosyl group in the ^1H and ^{13}C NMR spectra. Further, the ESI-MS spectrum displayed the $(M+Na)^+$ peak at 245.

Protection of the hydroxyl group in **84** as its methyl ether using NaH and MeI in THF resulted in the compound **85** in 88% yield. Care was taken at this stage to prevent the competing Payne rearrangement reaction by maintaining the reaction mixture constantly at 0 °C and slow addition of MeI. The product was confirmed by the ^1H and ^{13}C NMR spectra which displayed the resonance of newly introduced methoxy group at 3.47 and 53.7 ppm respectively. The IR spectrum The ESI-MS spectrum too showed the peak at 259 that corresponds to $(M+Na)^+$.

Scheme 20 : Reagents and conditions:

A. $LiAlH_4$, THF, 0 °C, 30 min, 92%; B. TBSCl, Imidazole, CH_2Cl_2, 0 °C to rt, 6 h, 90%; C. H_2, Pd/C, EtOAc, 2 h, 95%;

Compound **85** was treated with $LiAlH_4$ in THF at 0 °C that resulted in the epoxide opening from the less hindered side to exclusively give the hydroxyl product **86** in 92% yield. The use of a bulkier hydride source is important for this selective opening of the epoxide. The ^{1}H NMR spectrum revealed a proton resonating at 3.79 ppm as a quintet (J = 6.0 Hz) and three protons at 1.19 ppm as a doublet (J = 6.0 Hz) corresponding to the terminal methyl group thereby confirming the product. The ^{13}C spectrum too showed the signals corresponding to the carbon attached to the hydroxyl group at 67.8 ppm and that of terminal methyl group at 19.4 ppm. The ESI-MS spectrum displayed the $(M+H)^+$ peak at 239.

The newly formed hydroxyl group in **86** was then masked at its silyl ether using TBSCl and imidazole in CH_2Cl_2 to furnish the protected product **87** in 90% yield. The product was confirmed by the appearance of new peaks corresponding to the TBS group in ^{1}H NMR spectrum as singlets at 0.07 and 0.69 ppm and at 25.9, 18.0 and -4.7 ppm in the ^{13}C NMR spectrum. The ESI-MS spectrum displayed the $(M+Na)^+$ peak at 375.

Now the benzyl protection in **87** was removed under H_2 atmosphere in presence of Pd/C in EtOAc to obtain the hydroxyl product **68** in 95% yield. The ^{1}H and ^{13}C NMR spectra of the product did not display any peaks corresponding to the benzyl group thereby confirming the cleavage. The ESI-MS spectrum showed a peak at 285 corresponding to $(M+Na)^+$.

Oxidation of **68** with IBX and DMSO in CH_2Cl_2 afforded the corresponding aldehyde which was then subjected to Wittig reaction with $Ph_3PCH(CH_3)COOEt$ in benzene under reflux conditions to yield the *cis:trans* (8:92) mixture of unsaturated ester **88** in 82% yield, which could be separated by column chromatography. The structure of **88** was ascertained by ^{1}H NMR spectrum which displayed the signals

corresponding to olefinic proton as a doublet at 6.73 ppm and the signals corresponding to the ethyl ester group at 4.13 and 1.29 ppm integrating for two and three protons respectively. The ESI-MS spectrum displayed a peak matching with $(M+Na)^+$ at 367. The FTIR spectrum too displayed a strong absorption at 1712 cm^{-1} corresponding to the carbonyl group.

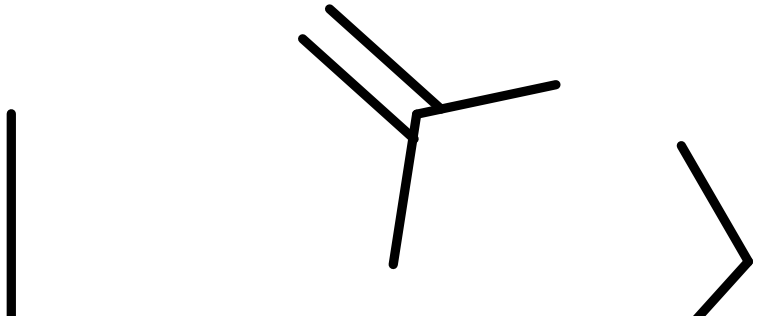
Scheme 21 : Reagents and conditions:

A. (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 86%; (ii) $Ph_3PCH(CH_3)COOEt$, benzene, reflux, 1h, 82%; B. DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 78%; C. I_2, TPP, Imidazole, THF, 0 °C, 5 min, 86%.

Reduction of the ester **88** using DIBAL-H in CH_2Cl_2 at 0 °C afforded the allylic alcohol **67** in 78% yield. The reaction was carefully monitored and the temperature of the reaction mixture was maintained uniformly at 0 °C to prevent the cleavage of TBS ether. Formation of alcohol **7** was ascertained by the disappearance of the signals corresponding to the ester group in ^1H and ^{13}C NMR spectra. ^1H NMR spectrum also showed the appearance of a singlet at 3.99 ppm corresponding to $–CH_2OH$, while it resonated at 69.7 ppm in the ^{13}C NMR spectrum. The ESI-MS spectrum displayed a peak at 325 corresponding to $(M+Na)^+$. The FTIR spectrum too did not reveal any peaks corresponding to the carbonyl group thereby confirming the transformation.

Alcohol **67** was then converted into its iodide **89** in 86% yield by treating it with TPP, imidazole and iodine in THF at 0 °C for 5 min[4]. Evans' alkylation[5] of this allylic iodide **89** was then carried out by treating it with the enolate of **90** obtained by treatment with NaHMDS at -78 °C for 30 min to culminate in the product **91** in 92% yield as a single diastereomer. Formation of the product was confirmed primarily by the presence of $(M+Na)^+$ peak at 540 in its ESI-MS spectrum. Further, the ^1H NMR spectrum of the product displayed the resonances corresponding to the auxiliary at 7.34-7.20, 4.64 – 4.72, 4.11 – 4.22 and 2.50 ppm, while the ^{13}C NMR spectrum displayed the resonances corresponding to the two carbonyls carbons at 177.1 and 153.1 ppm and the aromatic carbons at 135.4, 130.4, 129.5, 128.9 and 127.3 ppm. The

FTIR spectrum too displayed two strong absorptions at 1783 and 1701 cm^{-1} corresponding to the two carbonyl stretching frequencies.



Scheme 22 : Reagents and conditions:

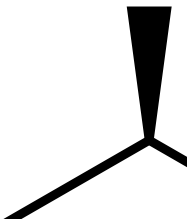
A. NaHMDS, -78 °C, 30 min, then **89**, 3 h, 92%; B. $LiBH_4$, MeOH, 1 h, 80%; C. IBX, DMSO, CH_2Cl_2, 0 °C to rt, 1h, 75%; D. Ph_3PCH_3Br, *n*-BuLi, THF, -78 °C to rt, 1h, 72%.

The next step was the reductive cleavage of the chiral auxiliary in **91** by treating it with $LiBH_4$ in MeOH at room temperature for 1 h to yield the alcohol **92** in 80% yield. This cleavage was confirmed by the disappearance of the signals corresponding to the auxiliary in ^1H, ^{13}C NMR and FTIR spectra. The ESI-MS spectrum displayed a peak at 367 corresponding to $(M+Na)^+$.

The free hydroxyl group thus formed in **92** was oxidized using IBX in DMSO and CH_2Cl_2 to furnish the corresponding aldehyde which was immediately subjected to Wittig olefination with Ph_3PCH_3Br using *n*-BuLi in THF to afford the target fragment **62** in 72% yield. Formation of **63** was ascertained from the ^1H NMR spectrum by the disappearance of the multiplet at 3.39-3.53 ppm corresponding to the $–CH_2OH$ protons and appearance of signals at 5.77–5.65 and 4.98–4.83 ppm corresponding to the olefenic protons. ^{13}C NMR spectrum of the product also showed the additional signals corresponding to the olefenic carbons at 144.7 and 111.9 ppm, while the ESI-MS spectrum displayed the peak corresponding to $(M+Na)^+$ at 363.

With both the fragments **62** and **63** in hand, stage was now set for their coupling utilizing the cross-Metathesis reaction. Accordingly, condensation of olefins **62** and **63** in CH_2Cl_2 in presence of Hoveyda-Grubbs II catalyst resulted in the target backbone

(**61**) with 76% yield and an *E/Z* selectivity of >15:1. Formation of the product was confirmed by the presence of $(M+Na)^+$ peak at 573 in its ESI-MS spectrum. The ^1H and ^{13}C NMR spectra displayed all the resonances at their respective chemical shifts and were in good agreement with the data reported in the literature.



Scheme 23 : Reagents and conditions:

A. Hoveyda-Grubbs II catalyst, CH_2Cl_2, 48 h, 76%.

The completion of synthesis of Herboxidiene from **61** is reported earlier[6] and can be achieved in 3 steps involving TBS deprotection, regio and stereo selective epoxidation and hydrolysis of ester to furnish the target molecule (**1**).

Scheme 24: Completion of total synthesis (Reported earlier in literature)

In conclusion, we have developed an efficient and concise route for the synthesis of GEX 1A/Herboxidiene in which the longest linear sequence includes 22 steps.

(S)-methyl 3-(benzyloxy)-2-methylpropanoate (78)

Benzyl 2,2,2-trichloroacetimidate (2.23 mL, 12.0 mmol, 1.2 equiv.) was added dropwise to a stirred solution of (S)-3-hydroxy-2-methylpropionic acid methyl ester (1.11 mL, 10.0 mmol) in cyclohexane:dicholoromethane (2:1, 15 mL) at 0 °C. Trifluoromethanesulfonic acid (53 µL, 1 mmol, 0.1 equiv.) was then added dropwise and the reaction mixture was slowly allowed to warm to rt. After stirring for 1 h, the reaction mixture was filtered and washed with dicholoromethane (2 × 15 mL). The filtrate was then sequentially washed with saturated aqueous sodium bicarbonate solution (20 mL) and brine solution (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford **78** (1.83 g, 88% yield) as a clear oil.

$[\alpha]_D^{20}$: +12.0 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3030, 2979, 2943, 2861, 1737, 1516, 1455, 1365, 1250, 1199, 1096, 1027, 824, 740, 698.

^1H NMR (400 MHz, $CDCl_3$) : δ 7.25-7.39 (m, 5H), 4.47-4.59 (m, 2H), 3.70 (s, 3H), 3.64-3.70 (m, 1H), 3.48-3.52 (m, 1H), 2.75-2.84 (m, 1H), 1.19 (d, *J* = 7.1Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 175.3, 138.0, 129.0, 128.2, 127.4, 73.1, 71.8, 51.5, 40.1, 13.9

ESI-MS $(M+Na)^+$: 231

(R,E)-ethyl 5-(benzyloxy)-4-methylpent-2-enoate (69)

DIBAL-H (7.9 mL, 12.7 mmol, 1.6 M solution in toluene) was added dropwise to a solution of ester **78** (2.205 g, 10.6 mmol) in CH_2Cl_2 (35 mL) at -78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (20 mL) followed by vigorous

stirring for 1h. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude aldehyde (1.604 g, 9.0 mmol) thus obtained was dissolved in benzene (30 mL), $Ph_3PCHCOOEt$ (3.758 g, 9.9 mmol) was added and the reaction mixture was refluxed at 80 °C for 1h. Then the reaction was quenched by adding H_2O (15 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, solvent removed *in vacuo* and the residue was purified by SiO_2 gel flash chromatography to give **69** (2.056 g, 92% yield) as a colorless oil.

$[\alpha]_D^{20}$: +13.2 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2978, 2873, 1718, 1653, 1454, 1368, 1307, 1271, 1187, 1155, 1096, 1033, 985, 743, 699.

^1H NMR (500 MHz, $CDCl_3$) : δ 7.22-7.31 (m, 5H), 6.89 (dd, *J* = 15.5, 7.3, 1H), 5.81 (d, *J* = 15.5, 1H), 4.49 (s, 2H), 4.17 (q, *J* = 7.3, 2H), 3.32-3.41 (m, 2H), 2.63 (p, *J* = 7.3, 1H), 1.29 (t, *J* = 7.3, 3H), 1.11 (d, *J* = 7.3, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5, 151.0, 138.1, 128.3, 128.2, 127.5, 127.5, 120.9, 73.8, 72.9, 60.1, 36.7, 15.9, 14.2

HRMS (+ESI) : *m/z* calcd. for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1489, found: 249.1490.

(2S,3R,4S)-ethyl 5-(benzyloxy)-2,3-dihydroxy-4-methylpentanoate (79)

A mixture of unsaturated ester **69** (5.704 g, 23.0 mmol), *t*-BuOH (45 mL), H_2O (45 mL), methanesulfonamide (2.628 g, 27.6 mmol), and enriched AD-mix-β (35 g, $K_3Fe(CN)_6$, 23.85 g; K_2CO_3, 10.02 g; $(DHQD)_2PHAL$, 0.94 g, $K_2OsO_2(OH)_4$, 185

mg) was stirred at 0 °C for 6 h. EtOAc (200 mL) and anhydrous Na_2SO_3 (28 g) were added, and the mixture was stirred at 20 °C for 45 min. The precipitate was filtered off and the solution diluted with H_2O (100 mL) and extracted with EtOAc. The combined organic extracts were washed with 1M aqueous HCl, then with brine, and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded the crude diol which was purified by silica gel column chromatography to furnish an inseparable 4:1 mixture of diols **79a** and **79c** as pale yellow oil (5.707 g, 88% yield).

$[\alpha]_D^{25}$: +4.9 (*c* 2.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3424, 2978, 2934, 1735, 1639, 1454, 1369, 1271, 1211, 1139, 1096, 1047, 862, 741, 700.

^1H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.38 (m, 5H), 4.52 (dd, *J* = 12.2, 14.7, 2H), 4.23-4.31 (m, 3H), 3.90 (dd, *J* = 6.4,2.2, 1H), 3.49-3.57 (m, 2H), 3.39 (brs, 1H), 2.07-2.17 (m, 1H), 1.31 (t, *J* = 7.1, 3H), 1.06 (d, *J* = 7.1, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 173.5, 137.8, 128.3, 127.7, 127.6, 74.7, 73.2, 73.0, 71.7, 61.8, 36.8, 14.1, 13.2,

HRMS (+ESI) : *m/z* calcd. for $C_{15}H_{22}O_5Na$ $[M+Na]^+$: 305.1359, found:305.1357.

(4S,5R)-ethyl-5-((S)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (80)

To a stirred solution of diastereomeric diols **79a** and **79b** (5.550 g, 19.68 mmol) in acetone (40 mL) was added 2,2-dimethoxy propane (7.25 mL, 59.06 mmol) and PTSA (145 mg). The mixture was stirred at ambient temperature for 12 h. The reaction

mixture was then quenched with solid sodium bicarbonate and filtered. Solvent was evaporated under vacuum to obtain a mixture of diastereomers which were separated by silica gel chromatography to obtain the pure diastereomer **80** (5.386 g, 85% yield) as a colorless liquid.

$[\alpha]_D^{20}$: +25.0 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2986, 2932, 1746, 1633, 1456, 1375, 1261, 1203, 1101, 868, 811, 742, 698.

^1H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.37 (m, 5H), 4.48 (s, 2H), 4.36 (d, *J* = 7.3, 1H), 4.12-4.31 (m, 3H), 3.41-3.48 (m, 2H), 2.10-2.19 (m, 1H), 1.44 (d, *J* = 9.5, 6H)1.24 (t, *J* = 6.8, 3H), 1.03 (d, *J* = 6.8, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.1, 138.3, 128.3, 127.5, 127.4, 127.3, 110.4, 80.1, 77.1, 72.9, 72.7, 61.3, 36.1, 26.9, 25.6, 14.0, 11.9.

HRMS (+ESI) : *m/z* calcd. for $C_{20}H_{25}O_5Na$ $[M+Na]^+$: 345.1701, found:345.1699.

((4R,5R)-5-((S)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (81)

To a solution of ester **80** (4.250 g, 13.20 mmol) in dry CH_2Cl_2 (70 mL) was added DIBAL-H (20.6 mL, 33.0 mmol, 1.6 M solution in toluene) dropwise at 0 °C. After warming the reaction mixture to r.t over a period of 1 h, the reaction was quenched with saturated aqueous solution of sodium potassium tartarate (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were washed

with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography to afford alcohol **81** (3.030 g, 82% yield) as colorless oil.

$[\alpha]_D^{25}$: +19.1 (*c* 2.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3451, 2985, 2932, 2875, 1636, 1456, 1374, 1247, 1216, 1168, 1103, 1053, 902, 854, 743, 699, 611, 512.

^1H NMR (400 MHz, $CDCl_3$) : δ 7.27-7.38 (m, 5H), 4.50 (s, 2H), 3.98-4.03 (m, 1H), 3.91 (dd, *J* = 6.3, 8.3, 1H), 3.73-3.79 (m, 1H), 3.58-3.65 (m, 1H), 3.43 (d, *J* = 6.3, 2H), 1.93-2.06 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.04 (d, *J* = 6.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 138.3, 128.4, 127.7, 127.6, 108.5, 79.2, 78.5, 73.1, 73.0, 62.8, 36.1, 27.1, 12.6.

HRMS (+ESI) : *m/z* calcd. for $C_{16}H_{24}O_4Na$ $[M+Na]^+$: 303.1566, found:303.1567.

((4R,5R)-5-((S)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl-4-methylbenzenesulfonate (82)

To a stirred solution of alcohol **81** (2.950 g, 10.53 mmol), triethylamine (2.2 mL, 15.80 mmol) and DMAP (catalytic) in dry dichloromethane (50 mL) at 0 °C was added *p*-toluene sulphonyl chloride (2.403 g, 12.64 mmol) portion wise. After stirring for 1 h at r.t, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was extracted with dichloromethane (2 × 20 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and

purification by silica gel chromatography afforded **82** (4.115 g, 90%) as a viscous liquid.

$[\alpha]_D^{25}$: +25.8 (*c* 2.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2986, 2934, 2873, 1598, 1454, 1365, 1251, 1215, 1179, 1097, 1057, 981, 912, 820, 772, 699, 665, 554.

^1H NMR (500 MHz, $CDCl_3$) : δ 7.77 (d, *J* = 8.4, 2H), 7.30 (d, *J* = 8.4, 2H), 7.28-7.36 (m, 5H), 4.45 (s, 2H), 4.05-4.16 (m, 3H), 3.84 (t, *J* = 6.5, 1H), 3.34-3.40 (m, 2H), 2.43 (s, 3H), 1.91-1.97 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 0.98 (d, *J* = 6.5, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 144.8, 138.1, 132.7, 129.8, 128.3, 128.0, 127.6, 127.5, 109.1, 78.9, 76.4, 73.0, 69.9, 36.2, 36.2, 27.0, 26.7, 21.6, 12.6,

HRMS (+ESI) : *m/z* calcd. for $C_{23}H_{30}O_6NaS$ $[M+Na]^+$: 457.1655, found:457.1660.

(2R,3R,4S)-5-(benzyloxy)-2,3-dihydroxy-4-methylpentyl-4-methylbenzenesulfonate (83)

To a stirred solution of compound **82** (4.050 g, 9.3 mmol) in methanol (30 mL) was added PTSA (0.160 g, 0.93 mmol) and the reaction mixture was stirred for 12 h at room temperature. Sodium bicarbonate was added to the reaction mixture to neutralize PTSA and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography to afford the diol **83** (3.125 g, 85%) as a white solid.

$[\alpha]_D^{20}$: +1.1 (*c* 2.0, $CHCl_3$)

IR (KBr) ν_{max}/cm^{-1} : 3423, 3324, 3064, 3035, 2966, 2921, 2859, 2801, 1729, 1600, 1455, 1419, 1353, 1267, 1185, 1148, 1095, 1058, 984, 961, 914, 891, 833, 813, 748, 699, 663, 581, 554, 516.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.79 (d, *J* = 8.3, 2H), 7.33 (d, *J* = 8.3, 2H), 7.27-7.39 (m, 5H), 4.49 (s, 2H), 4.00-4.10 (m, 2H), 3.87-3.93 (m, 1H), 3.57 (dd, *J* = 3.0, 5.3, 1H), 3.53 (d, *J* = 3.7, 1H), 3.57 (dd, *J* = 6.8, 9.8, 1H), 2.44 (s, 3H), 1.90-1.99 (m, 1H), 0.99 (d, *J* = 7.5, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 144.5, 137.4, 132.5, 129.8, 128.4, 127.9, 127.8, 127.7, 73.4, 72.8, 72.7, 70.9, 69.1, 36.8, 21.5, 12.6.

HRMS (+ESI) : *m/z* calcd. for $C_{20}H_{26}O_6NaS$ $[M+Na]^+$: 417.1366, found: 417.1347.

(1R,2S)-3-(benzyloxy)-2-methyl-1-((R)-oxiran-2-yl)propan-1-ol (84)

To a solution of diol **83** (3.075 g, 7.8 mmol) in methanol (30 ml) was added potassium carbonate (1.30 g, 9.4 mmol) at 0 °C and allowed to warm to room temperature over a period of 1 h. Methanol was then removed under reduced pressure and water (15 ml) was added. The mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography of the crude mixture afforded the epoxy alcohol **84** (1.49 g, 86%) as a colorless oil.

$[\alpha]_D^{25}$: −12.0 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3449, 3031, 2969, 2867, 1637, 1455, 1367, 1256, 1210, 1098, 991, 914, 869, 742, 698.

^1H NMR (500 MHz, $CDCl_3$) : δ 7.25-7.39 (m, 5H), 4.52 (q, *J* = 12.1, 2H), 3.62-3.67 (m, 1H), 3.57 (t, *J* = 8.4, 1H), 3.50 (q, *J* = 4.6, 1H), 3.07 (q, *J* = 3.7, 1H), 2.75 (t, *J* = 4.6, 1H), 2.71 (q, *J* = 2.8, 1H), 2.47 (d, *J* = 7.4, 1H), 2.03-2.16 (m, 1H), 1.03 (d, *J* = 6.5, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 138.0, 128.3, 127.6, 73.3, 73.1, 72.3, 53.5, 44.0, 37.8, 11.9.

HRMS (+ESI) : *m/z* calcd. for $C_{13}H_{18}O_3Na$ $[M+Na]^+$: 245.1148, found : 245.1152.

(R)-2-((1R,2S)-3-(benzyloxy)-1-methoxy-2-methylpropyl)oxirane (85)

To a cooled (- 15 °C) solution of the epoxy alcohol **84** (2.980 g, 13.4 mmol) and MeI (8.3 ml, 134 mmol) in anhydrous THF (130 ml) was added portion-wise, NaH (60% dispersion in mineral oil; 0.804 g, 20.1 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0 °C for 1 h. Water (50 ml) and Et_20 (100 ml) were added, the organic phase was separated and the aqueous layer extracted with Et_2O (2 × 100 ml). The combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel afforded the epoxy ether **85** (2.788 g, 88%) as a colorless oil.

$[\alpha]_D^{20}$: +9.8 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3031, 2974, 2932, 1628, 1456, 1365, 1258, 1199, 1092, 949, 950, 871, 840, 741, 699.

^1H NMR (400 MHz, $CDCl_3$) : δ 7.26-7.37 (m, 5H), 4.49 (s, 2H), 3.44-3.49 (m, 1H), 3.47 (s, 3H), 3.36-3.41 (m, 1H), 3.02-3.06 (m, 1H), 2.92-2.96 (m, 1H), 2.73 (t, *J* = 4.8, 1H), 2.48(dd, *J* = 2.7, 5.0, 1H), 1.97-2.06 (m, 1H), 1.02 (d, *J* = 6.7, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 138.3, 128.2, 127.5, 127.4, 82.8, 73.0, 72.0, 58.4, 53.7, 42.7, 37.1, 12.2.

HRMS (+ESI) : *m/z* calcd. for $C_{14}H_{20}O_3Na$ $[M+Na]^+$: 259.1305, found : 259.1310.

(2R,3R,4S)-5-(benzyloxy)-3-methoxy-4-methylpentan-2-ol (86)

To a suspension of $LiAlH_4$ (0.640 g, 16.8 mmol) in THF (35 mL) at 0 °C was slowly added a solution of epoxide **85** (2.650 g, 11.2 mmol) in THF (20 mL) through a cannula and stirred for 30 min. After the completion of reaction, the reaction mixture was quenched by slow addition of saturated aqueous NH_4Cl (10 mL) and the precipitate formed was filtered through a sintered funnel and washed with EtOAc. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography to afford **86** as a colorless oil (2.458 g, 92% yield).

$[\alpha]_D^{20}$: +6.8 (*c* 2.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3450, 3063, 3030, 2972, 2932, 1637, 1455, 1368, 1256, 1202, 1090, 950, 905, 744, 699.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.24-7.38 (m, 5H), 4.46-4.56 (m, 2H), 3.79 (p, *J* = 6.0, 1H), 3.48 (s, 3H), 3.44 (t, *J* = 6.0, 2H), 3.07 (dd, J = 3.7, 6.0, 1H), 1.98-2.12 (m, 1H), 1.19 (d, J = 6.0, 3H), 0.92 (d, J = 6.0, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 138.1, 128.3, 127.6, 127.5, 86.4, 73.0, 72.3, 67.8, 61.0, 35.2, 19.4, 11.7.

HRMS (+ESI) : *m/z* calcd. for $C_{14}H_{23}O_3$ $[M+H]^+$: 239.1658, found: 239.1647.

((2R,3R,4S)-5-(benzyloxy)-3-methoxy-4-methylpentan-2-yloxy)(*tert*-butyl)dimethylsilane (87)

To an ice cooled solution of alcohol **86** (2.310 g, 9.7 mmol) and imidazole (1.448 g, 21.3 mmol) in dry dichloromethane (40 mL) was added TBDMS-Cl (1.605 g, 10.7 mmol). After stirring for 15 min. at 0 °C the reaction mixture was warmed to room temperature and the stirring was continued for another 6 h. Then the reaction mixture was quenched using saturated aqueous NH_4Cl solution and extracted with dichloromethane (2 × 30 mL). The combined extracts was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford the silyl ether **87** (3.075 g, 90% yield) as a viscous liquid.

$[\alpha]_D^{20}$: +11.0 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3031, 2956, 2931, 2888, 2857, 1633, 1458, 1380, 1254, 1158, 1098, 989, 927, 834, 775, 751, 698.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.27-7.37 (m, 5H), 4.50 (s, 2H), 3.85 (p, *J* = 6.6, 1H), 3.46-3.52 (m, 1H), 3.43 (s, 3H), 3.30 (dd, *J* = 6.2, 8.8,

1H), 3.10 (dd, *J* = 3.9, 7.1, 1H),1.94-2.06 (m, 1H), 1.09 (d, *J* = 6.4, 3H), 0.86 (d, *J* = 6.6, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 138.5, 128.3, 127.6, 127.4, 85.5, 73.2, 72.9, 70.4, 60.9, 34.8, 25.9, 20.1, 18.0, 10.9, -4.7.

HRMS (+ESI) : *m/z* calcd. for $C_{20}H_{36}O_3NaSi$ $[M+Na]^+$: 375.2331, found:375.2324.

(2S,3R,4R)-4-(*tert*-butyldimethylsilyloxy)-3-methoxy-2-methylpentan-1-ol (68)

To a solution of benzyl ether **87** (2.950 g, 8.4 mmol) in ethylacetate (15 mL), under an atmosphere of nitrogen, was added palladium on activated carbon (10%, 90 mg). The flask was flushed with nitrogen followed by hydrogen, and the solution was stirred under hydrogen atmosphere for 2 h. The reaction mixture was diluted with ether (60 mL) and filtered through a pad of Celite and concentrated *in vacuo* to yield alcohol **68** (2.086 g, 95% yield) as colorless oil.

$[\alpha]_D^{20}$: +12.4 (*c* 0.50, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3444, 2956, 2931, 2858, 1638, 1467, 1381, 1254, 1157, 1096, 1034, 988, 928, 835, 776, 667.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.02 (p, *J* = 6.6 Hz, 1H), 3.59 (dd, *J* = 3.7, 11.5, 1H), 3.49 (dd, *J* = 7.1, 11.5, 1H), 3.43 (s, 3H), 2.89 (dd, *J* = 5.1, 7.7, 1H), 1.84-1.93 (m, 1H), 1.18 (d, *J* = 6.2, 3H), 0.91 (s, 9H), 0.89 (d, *J* = 3.4, 3H), 0.13 (s, 3H), 0.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 88.1, 69.2, 66.4, 59.9, 36.8, 25.7, 18.3, 17.9, 13.1, -4.8, -4.9.

HRMS (+ESI) : *m/z* calcd. for $C_{13}H_{30}O_3NaSi$ $[M+Na]^+$: 285.1861, found:285.1869.

(4S,5R,6R,E)-ethyl 6-(*tert*-butyldimethylsilyloxy)-5-methoxy-2,4-dimethylhept-2-enoate (88)

IBX (2.490 mg, 8.9 mmol) was dissolved in DMSO: CH_2Cl_2 (1:1, 20 mL) at 0 °C. To this was added a solution of alcohol **68** (1.950 g, 7.4 mmol) in CH_2Cl_2 (10 mL) at the same temperature and stirred for 2 h at room temperature. Then the reaction mixture was diluted with diethyl ether and filtered through a small pad of celite. To this filtrate was added saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the corresponding aldehyde (1.664 g, 86% yield) as colorless oil. The crude aldehyde thus obtained was dissolved in benzene (20 mL), $Ph_3PCH(CH_3)COOEt$ (3.485 g, 9.6 mmol) was added and the reaction mixture was refluxed for 1h. Then the reaction was quenched by adding H_2O (15 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, solvent removed *in vacuo* and the residue was purified by silica gel flash chromatography to afford the ester **88** (1.805 g, 82% yield) as a colorless oil.

$[\alpha]_D^{20}$: −3.2 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2957, 2932, 2893, 2858, 1712, 1648, 1465, 1369, 1250, 1147, 1096, 1002, 934, 834, 774, 667.

^{1}H NMR (500 MHz, $CDCl_3$) : δ 6.73 (d, *J*= 10.0, 1H), 4.13-4.22 (m, 2H), 3.90 (p, *J* = 5.0, 1H), 3.44 (t, *J* = 6.0, 3H), 2.87 (t, *J* = 5.0, 1H), 2.66-

2.72 (m, 1H), 1.84 (s, 3H), 1.29 (t, *J* = 7.0, 3H), 1.10 (d, *J* = 6.0, 3H), 1.02 (d, *J* = 6.0, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 168.5, 145.2, 125.4, 88.4, 69.7, 69.1, 60.3, 34.6, 25.8, 19.3, 18.0, 15.1, 14.2, 12.4, -4.6, -4.7.

HRMS (+ESI) : *m/z* calcd. for $C_{18}H_{36}O_4NaSi$ $[M+Na]^+$: 367.2275, found:367.2278.

(4S,5R,6R,E)-6-(*tert*-butyldimethylsilyloxy)-5-methoxy-2,4-dimethylhept-2-en-1-ol (67)

To a solution of ester **88** (1.680 g, 4.9 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAL-H (7.6 mL, 12.2 mmol, 1.6 M solution in toluene) dropwise at 0 °C and stirred at the same temperature for 1 h. Then the reaction was quenched with saturated aqueous solution of potassium-sodium tartarate (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography to afford alcohol **67** (1.150 g, 78% yield) as a colorless oil.

$[\alpha]_D^{20}$: +3.1 (*c* 1.0, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3423, 2957, 2931, 2858, 1633, 1459, 1379, 1253, 1149, 1093, 1005, 928, 834, 774, 670.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.41 (d, *J* = 9.0, 1H), 3.99 (s, 2H), 3.86 (p, *J* = 6.0, 1H), 3.44 (s, 3H), 2.80 (t, *J* = 5.3, 1H), 2.54-2.65 (m,

1H), 1.68 (s, 3H), 1.11 (d, J = 6.0, 3H), 0.95 (d, J = 6.0, 3H),0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 132.8, 130.3, 89.2, 69.7, 69.0, 60.6, 33.4, 25.8, 19.8, 18.0, 15.5, 13.8, -4.6, -4.7.

HRMS (+ESI) : *m/z* calcd. for $C_{16}H_{34}O_3NaSi$ $[M+Na]^+$: 325.2174, found: 325.2173.

(S)-4-benzyl-3-((2R,6S,7R,8R,E)-8-(*tert*-butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-enoyl)oxazolidin-2-one (91)

To a vigorously stirred solution of alcohol **7** (1.060 g, 3.5 mmol) in dry THF (30 mL) at 0 °C was added imidazole (0.476 g, 7.0 mmol), Ph_3P (1.834 g, 7.0 mmol) and I_2 (1.321 g, 5.2 mmol) in successive single portions. Stirring was continued at 0 °C for 5 min whereupon Et_2O (10 mL) was added to precipitate out Ph_3P=O. The solids were filtered off through a short pad of SiO_2 and the filtrate was concentrated *in vacuo* to obtain the crude allylic iodide **89** (1.244 g, 86% yield).

To a solution of NaHMDS (4.2 mL, 4.2 mmol, 1.0 M in THF) in THF (5.0 mL) at –78 °C was slowly added Evans' auxiliary **90** (0.985 g, 4.2 mmol) in THF (4.0 mL) through a cannula. The solution was stirred for 30 min and then to it was added the allylic iodide **89** (1.244 g, 3.0 mmol) in THF (5 mL). The solution was stirred at –78 °C for 2.5 h and then at –40 °C for 30 min and quenched with saturated aqueous NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography to give **91** (0.99 g, 64% yield, 92% brsm) as a viscous liquid.

$[\alpha]_D^{20}$: −23.1(*c* 1.30, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2958, 2928, 2856, 1783, 1701, 1457, 1384, 1245, 1211, 1096, 835, 774, 701.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.19-7.36 (m, 5H), 5.26 (d, *J* = 9.0 Hz, 1H), 4.64-4.72 (m, 1H), 4.11-4.22 (m, 2H), 3.93-4.01 (m, 1H), 3.82 (p, *J* = 6.0 Hz, 1H), 3.44 (s, 3H), 3.29 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.79 (t, *J* = 5.0 Hz, 1H), 2.69 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.52-2.60 (m, 2H), 2.00 (dd, *J* = 13.0, 9.0 Hz, 1H), 1.69 (s, 3H), 1.14-1.07 (m, 6H), 0.83–0.96 (m, 12H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 177.1, 153.1, 135.4, 132.3, 130.4, 129.5, 129.4, 128.9, 127.3, 89.7, 70.1, 66.0, 60.9, 55.3, 44.0, 38.1, 35.7, 33.8, 25.9, 20.1, 18.1, 16.3, 15.6, 15.2, -4.6

HRMS (+ESI) : *m/z* calcd. for $C_{29}H_{47}O_5NNaSi$ $[M+Na]^+$: 540.3116, found: 540.3120.

(2R,6S,7R,8R,E)-8-(*tert*-butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-en-1-ol (92)

To a solution of **91** (0.805 g, 1.5 mmol) in Et_2O (5 mL) at 0 °C was added MeOH (80 μL, 1.8 mmol) and $LiBH_4$ (1.8 mL, 1.8 mmol, 1.0 M in THF). The solution was stirred at r.t for 1 h and then quenched with NaOH (5.7 M, 1.1 mL) and stirred vigorously at room temperature for 10 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated under vacuum. The crude product was purified by silica gel column chromatography to give alcohol **92** (0.428 g, 80% yield) as a colorless oil.

$[\alpha]_D^{20}$: +7.8 (*c* 0.5, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 3479, 2931, 2858, 1750, 1463, 1379, 1255, 1230, 1183, 1098, 1050, 991, 930, 873, 835, 779.

^1H NMR (400 MHz, $CDCl_3$) : δ 5.20 (d, *J* = 8.3 Hz, 1H), 3.84 (p, *J* = 6.1 Hz, 1H), 3.40-3.53 (m, 2H), 3.45 (s, 3H), 2.80 (t, *J* = 5.6 Hz, 1H), 2.52-2.61 (m, 1H), 2.07 (dd, *J* = 12.2, 6.6 Hz, 1H), 1.78-1.90 (m, 2H), 1.62 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 132.1, 130.9, 89.8, 70.1, 68.5, 60.8, 44.4, 33.7,29.7, 25.9, 20.1, 18.1, 16.8, 16.1, 15.4, -4.5, -4.6.

HRMS (+ESI) : *m/z* calcd. for $C_{19}H_{40}O_3NaSi$ $[M+Na]^+$: 367.2639, found: 367.2623.

tert-butyl((2R,3R,4S,8R,E)-3-methoxy-4,6,8-trimethyldeca-5,9-dien-2-yloxy)dimethyl silane (63)

IBX (0.061 g, 0.22 mmol) was dissolved in DMSO:CH_2Cl_2 (1:1, 3.0 mL) at 0 °C and to this was added a solution of alcohol **92** (0.050 g, 0.14 mmol) in CH_2Cl_2 (2.0 mL) at the same temperature and stirred at r.t for 1 h. Then the reaction mixture was diluted with diethyl ether and filtered through a small pad of celite. To this filtrate was added saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether (2 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the corresponding aldehyde (0.037 g, 75% yield) as colorless oil which was then subjected to Wittig olefination.

To a suspension of Ph_3PCH_3Br (0.178 g, 0.5 mmol) in THF (2.0 mL) at 0 °C, was added n-BuLi (0.2 mL, 2.5 M in THF, 0.49 mmol) dropwise through a syringe. The resulting solution was warmed to room temperature and then cooled back to –78 °C

over a period of 30 min. To this solution was slowly added aldehyde (0.037 g, 0.11 mmol) in THF (1.0 mL) through a cannula and the reaction mixture was warmed to room temperature and stirred for 1 h. Then the reaction was quenched with saturated NH_4Cl solution (3 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuum. The crude product was chromatographed to afford the olefin **63** as colorless oil (0.026 g, 72% yield).

$[\alpha]_D^{20}$:+9.2 (*c* 0.25, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2957, 2927, 2856, 1736, 1460, 1378, 1253, 1096, 834, 772.

^1H NMR (400 MHz, $CDCl_3$) : δ 5.65-5.78 (m, 1H), 5.13 (d, *J* = 9.0 Hz, 1H), 4.85-5.01 (m, 2H), 3.83 (p, 1H), 3.44 (s, 3H), 2.77 (q, *J* = 5.8 Hz, 1H), 2.48-2.61 (m, 1H), 2.32 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.01 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.88 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 144.6, 131.6, 130.8, 111.9, 89.8, 70.1, 60.9, 47.2, 35.6, 33.7, 25.9, 20.2, 19.5, 18.1, 16.1, 15.4, -4.6.

HRMS (+ESI) : *m/z* calcd. for $C_{20}H_{40}O_2NaSi$ $[M+Na]^+$: 363.2689, found: 363.2693.

methyl 2-((2R,5S,6S)-6-((2E,4E,6S,8E,10S,11R,12R)-12-(*tert*-butyldimethylsilyloxy)-11-methoxy-6,8,10-trimethyltrideca-2,4,8-trien-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)acetate (61)

To a solution of alkenes **62** (0.021 g, 0.09 mmol) and **63** (0.010 g, 0.03 mmol) in dry CH_2Cl_2 (1.0 mL) was added Hoveyda-Grubbs 2nd gen. catalyst (3 mg). The reaction mixture was then stirred at room temperature for 48 h. The reaction mixture was then concentrated *in vacuo* and then directly chromatographed to afford **61** (0.012 g, 76% yield) as a colorless oil.

$[\alpha]_D^{20}$: +9.1 (*c* 0.30, $CHCl_3$)

IR (neat) ν_{max}/cm^{-1} : 2955, 2927, 2857, 1742, 1455, 1375, 1225, 1156, 1098, 1066, 834, 772.

^1H NMR (500 MHz, $CDCl_3$) : δ 6.17 (dd, *J* = 10.9, 14.8 Hz, 1H), 5.90 (d, *J* = 10.9 Hz, 1H), 5.54 (dd, *J* = 14.8, 7.9 Hz, 1H), 5.17 (dt, *J* = 34.6, 9.9 Hz, 1H), 3.86–3.79 (m, 1H), 3.79–3.72 (m, 1H), 3.66 (s, 3H), 3.43 (s, 3H), 3.32 (d, *J* = 9.9 Hz, 1H), 2.74-2.80 (m, 1H), 2.60 (dd, *J* = 14.8, 5.9 Hz, 1H), 2.56–2.50 (m, 1H), 2.41 (d, *J* = 5.9 Hz, 1H), 2.34-2.38 (m, 1H), 2.00 (dd, *J* = 12.8, 6.9 Hz, 1H), 1.90 (dd, *J* = 6.9, 13.8 Hz, 1H), 1.81–1.87 (m, 1H), 1.70 (d, *J* = 3 Hz, 3H), 1.64–1.68 (m, 1H), 1.58 (d, *J* = 1.0 Hz, 3H), 1.50–1.57 (m, 1H), 1.17–1.38 (m, 2H), 1.12 (d, *J* = 5.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.69 (d, *J* = 6.9 Hz, 3H), 0.06 (d, *J* = 2.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.9, 140.6, 134.5, 131.5, 130.9, 128.5, 123.9, 90.6, 89.8, 73.8, 70.1, 61.1, 51.6, 47.6, 41.3, 35.3,

33.7, 32.3, 32.2, 31.7, 25.9, 20.2, 20.1, 18.2, 17.7, 16.3, 15.9, 12.3, -4.2.

HRMS (+ESI) : *m/z* calcd. for CHO $[M+Na]^+$: 573.3946, found: 573.3941.

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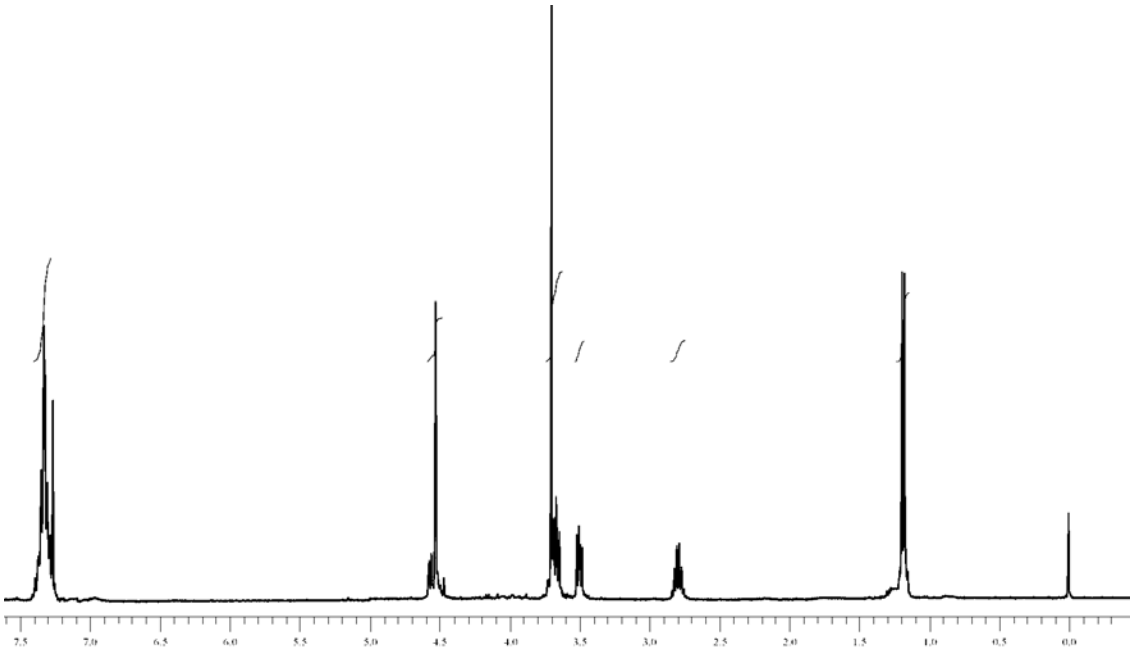
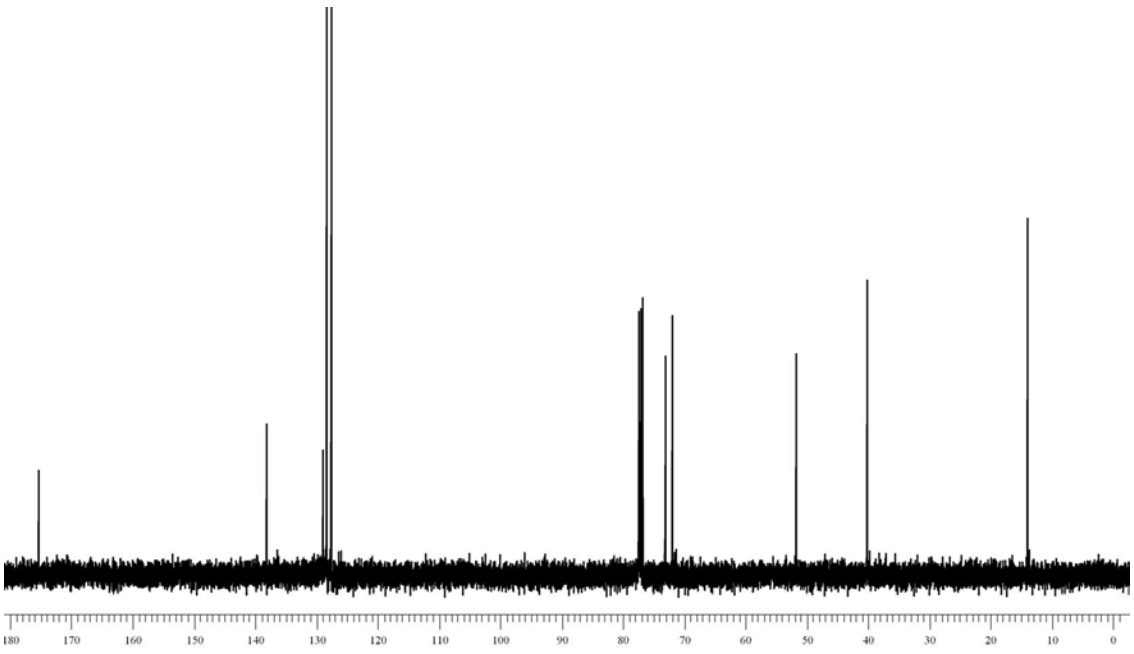


^{1}H NMR SPECTRUM OF COMPOUND **78**



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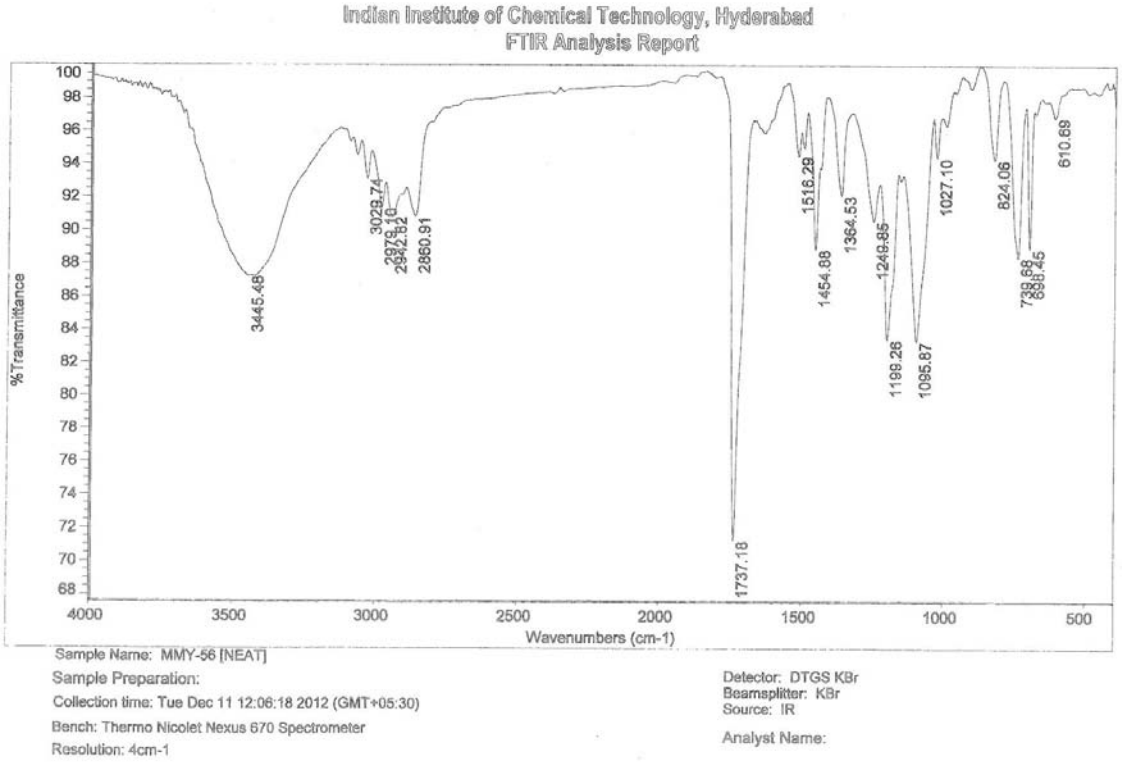

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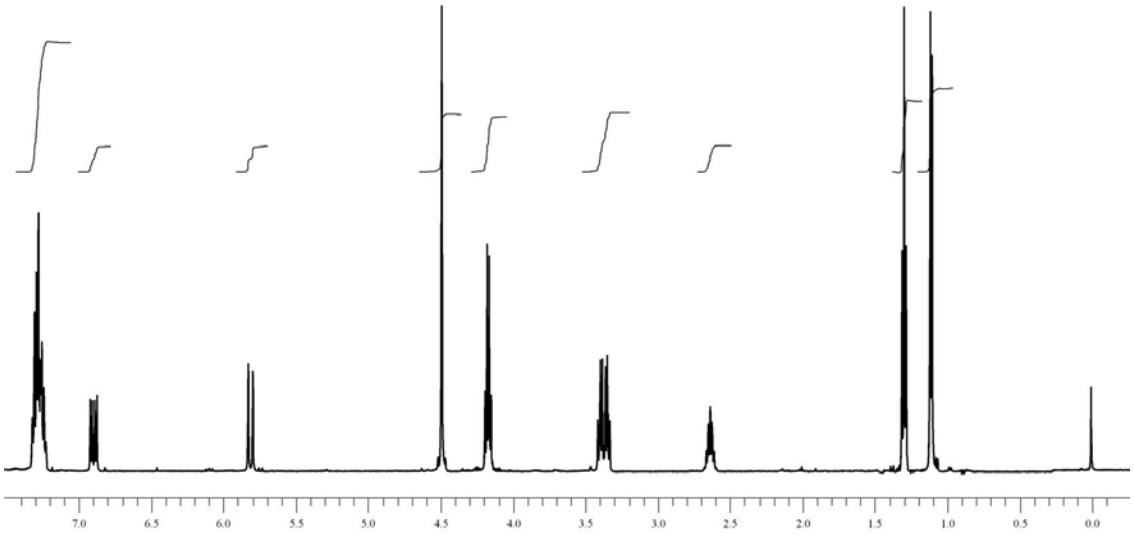
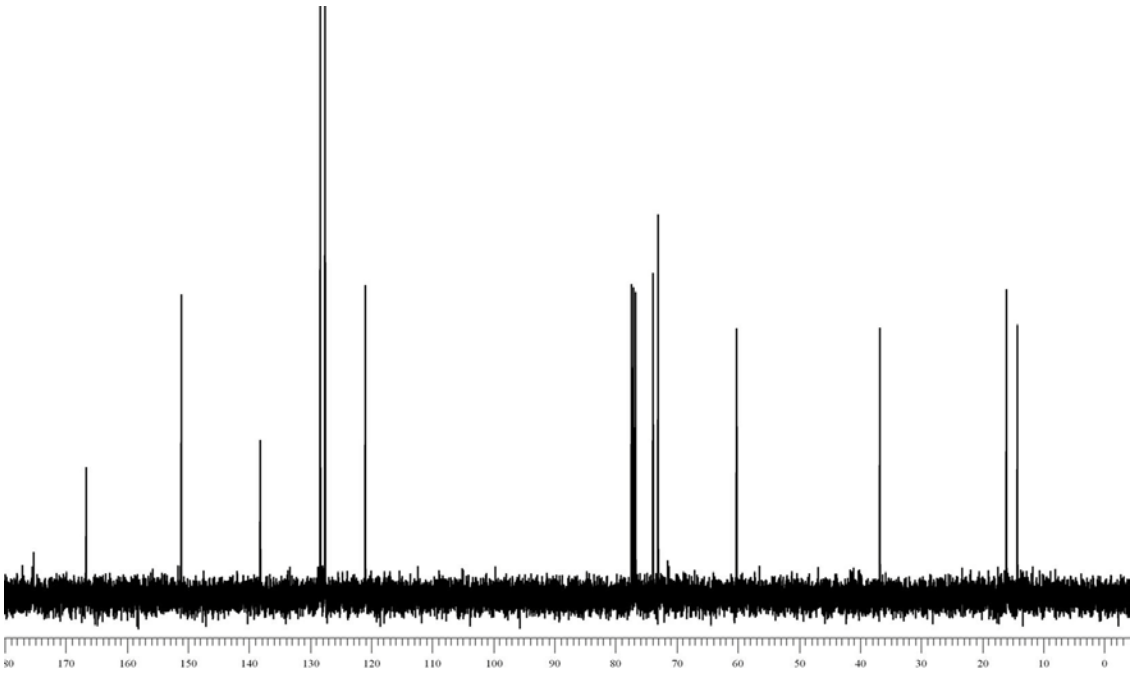
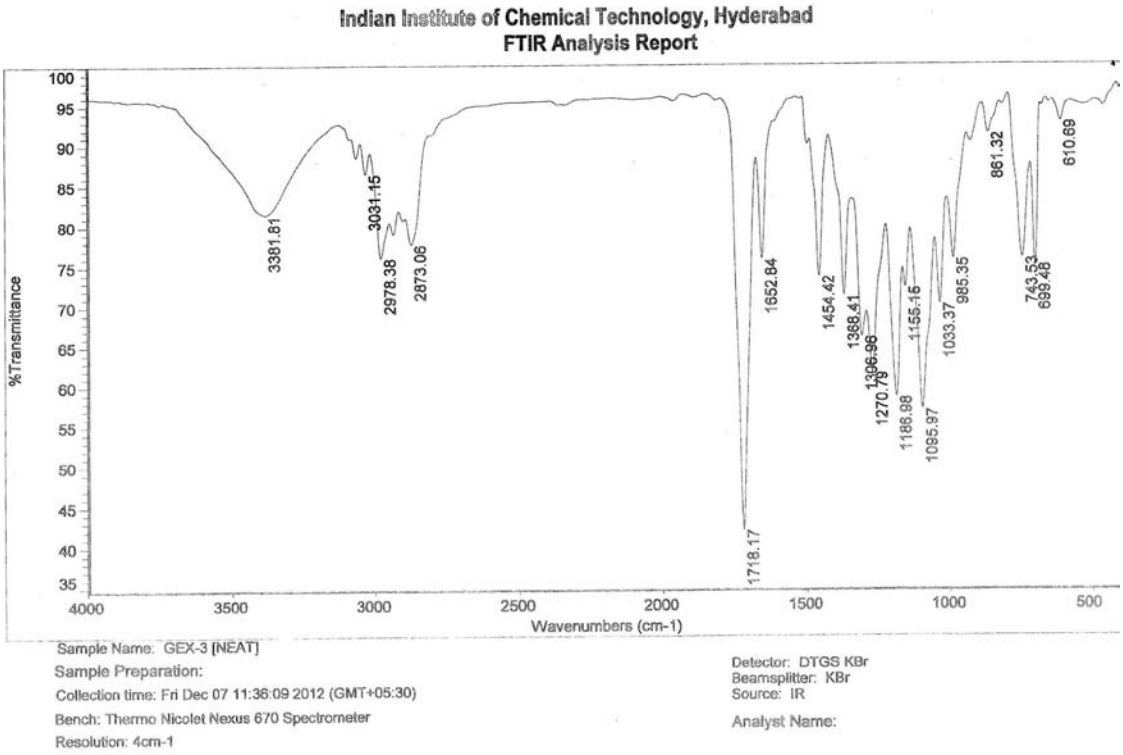


^{1}H NMR SPECTRUM OF COMPOUND **69**



^{13}C NMR SPECTRUM OF COMPOUND **69**



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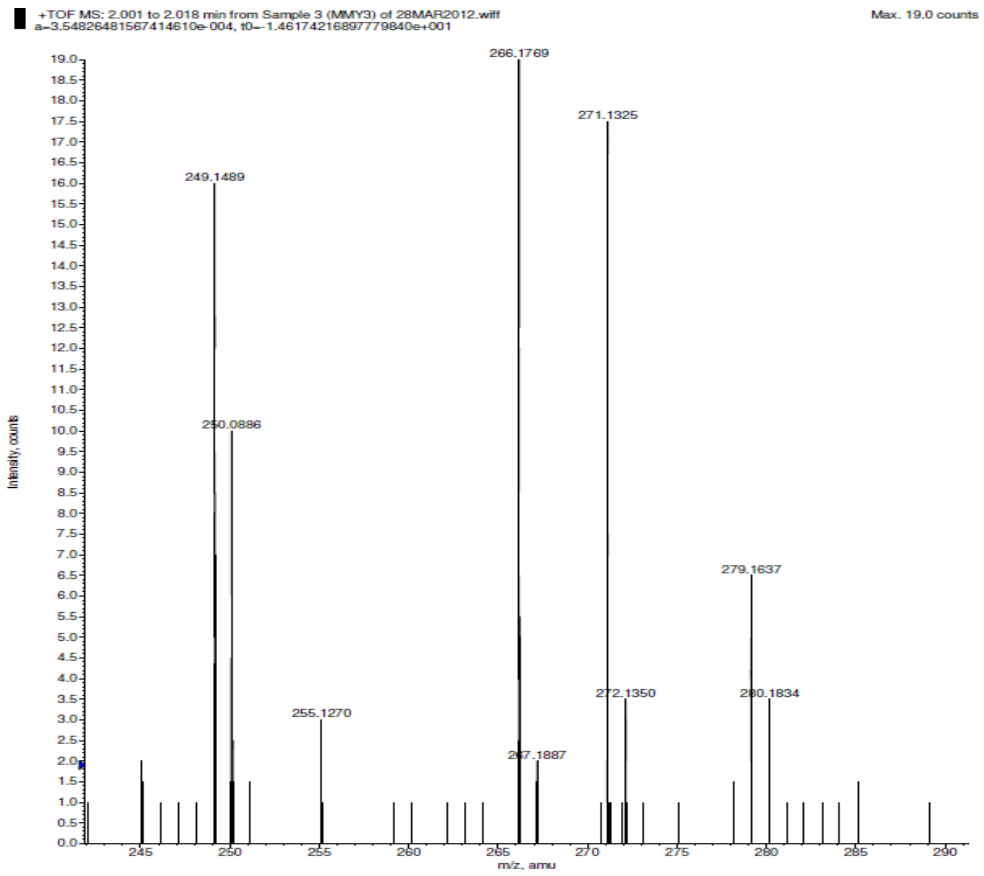

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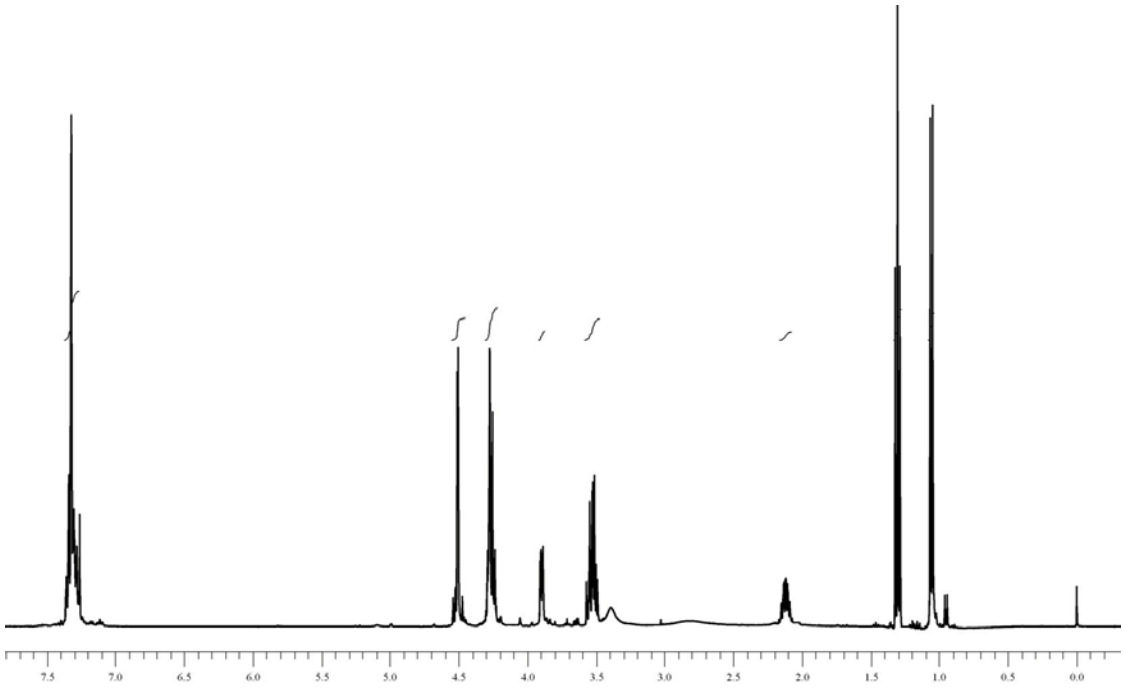
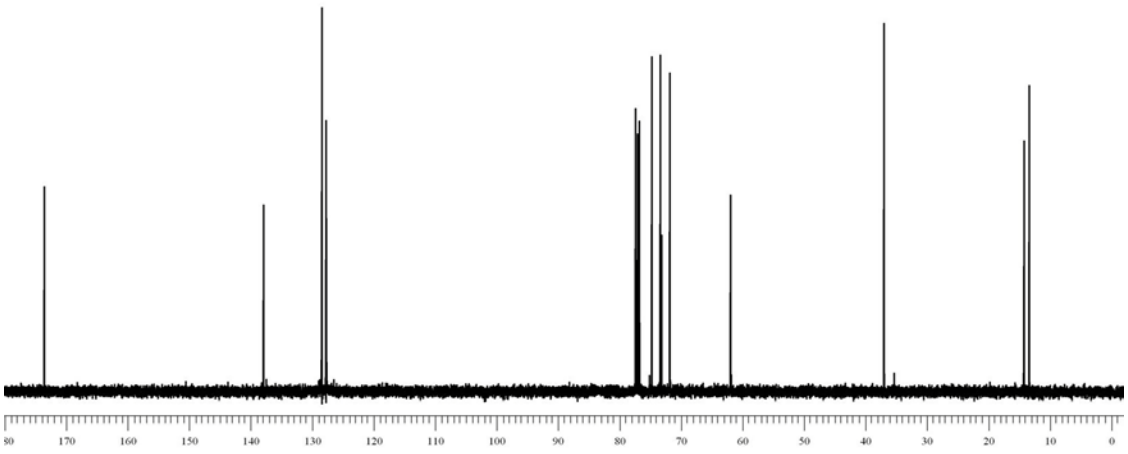
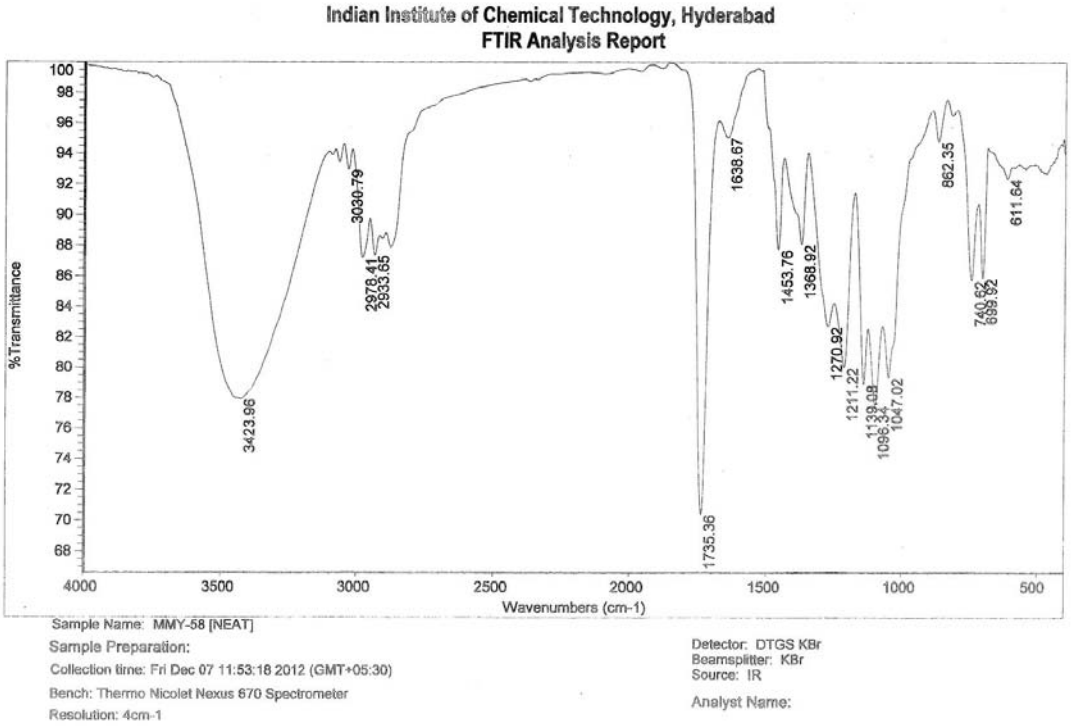


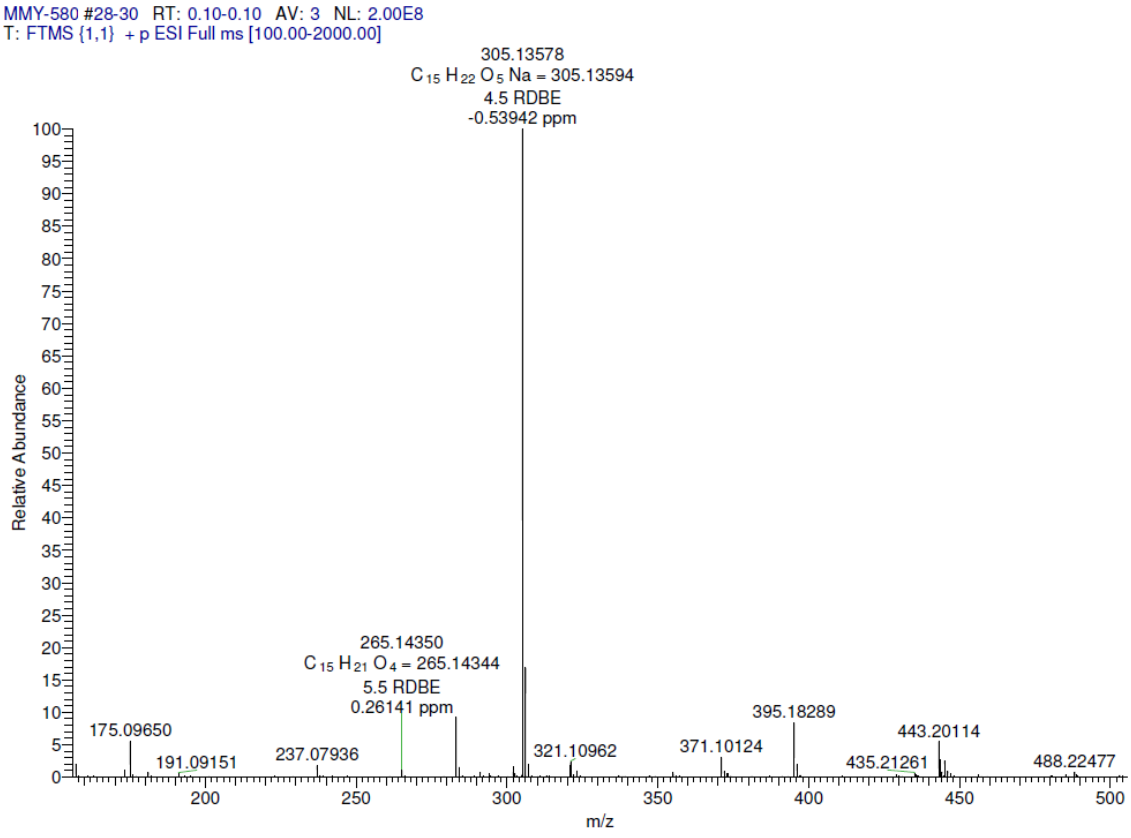
^{1}H NMR SPECTRUM OF COMPOUND **79**



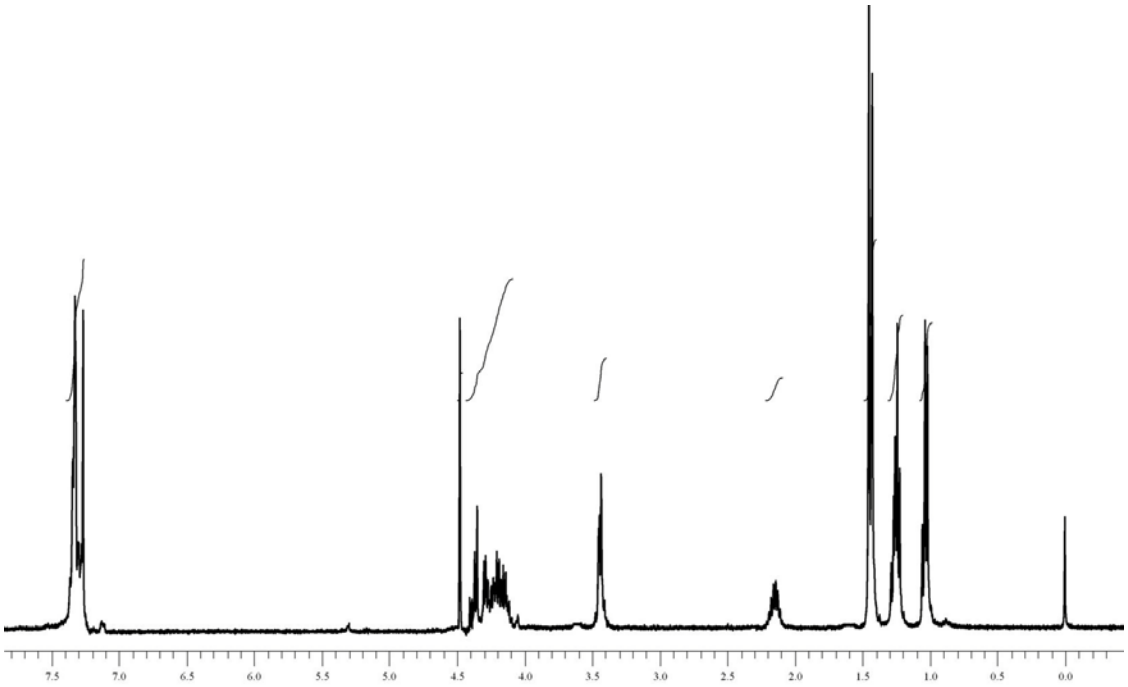
^{13}C NMR SPECTRUM OF COMPOUND **79**



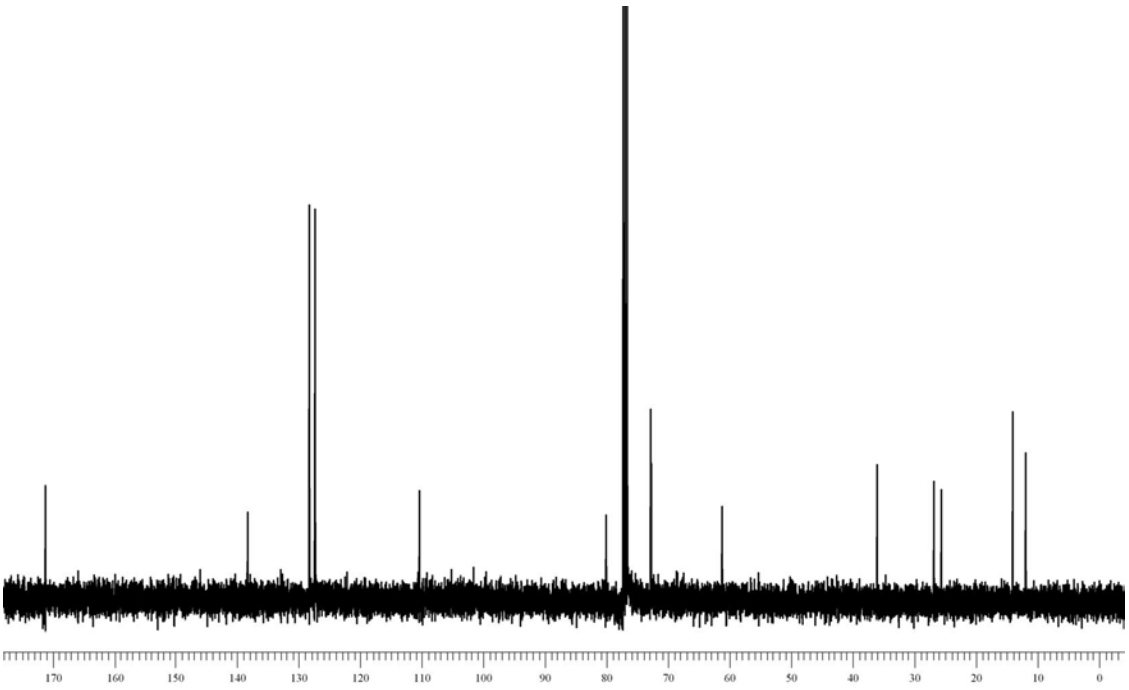
FTIR SPECTRUM OF COMPOUND **79**



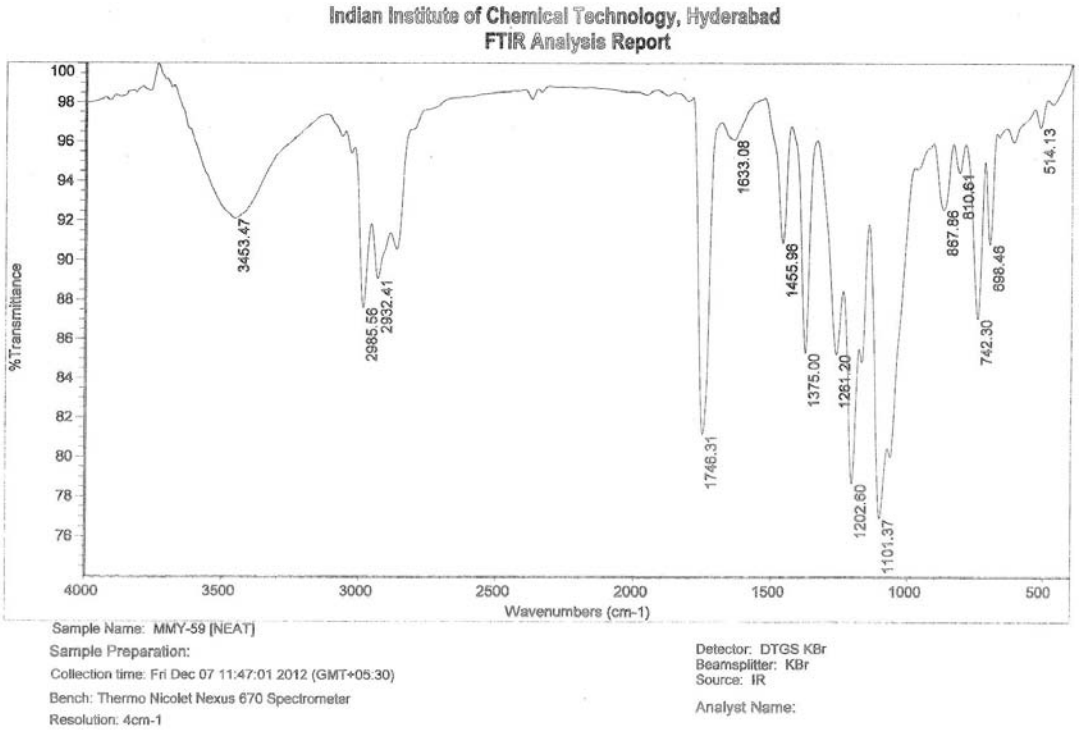
HRMS SPECTRUM OF COMPOUND **79**



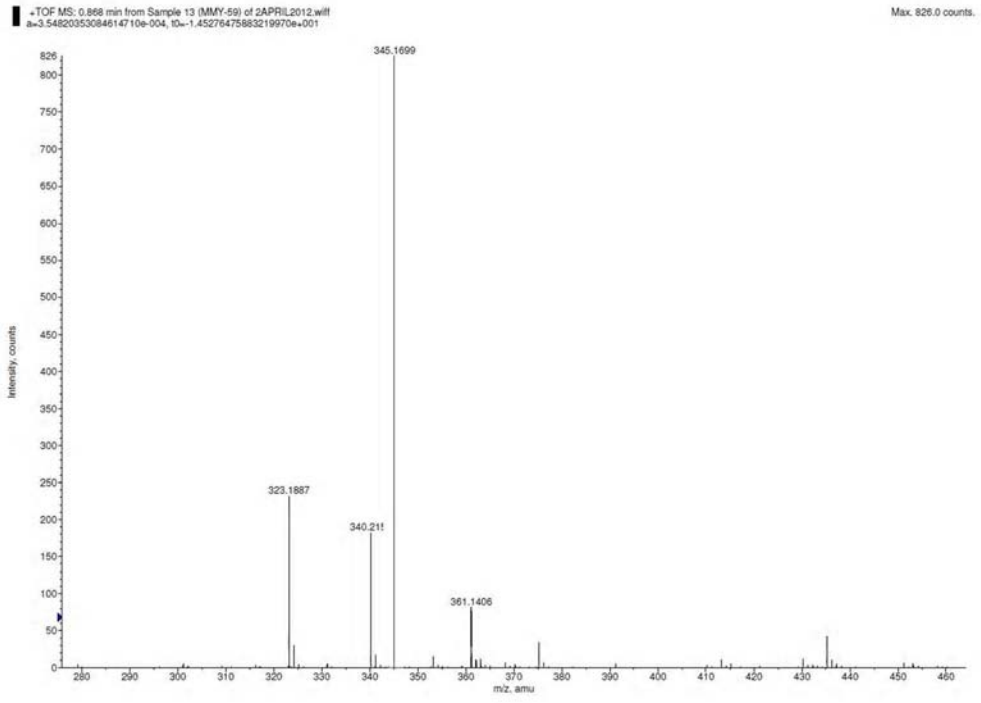
^{1}H NMR SPECTRUM OF COMPOUND **80**



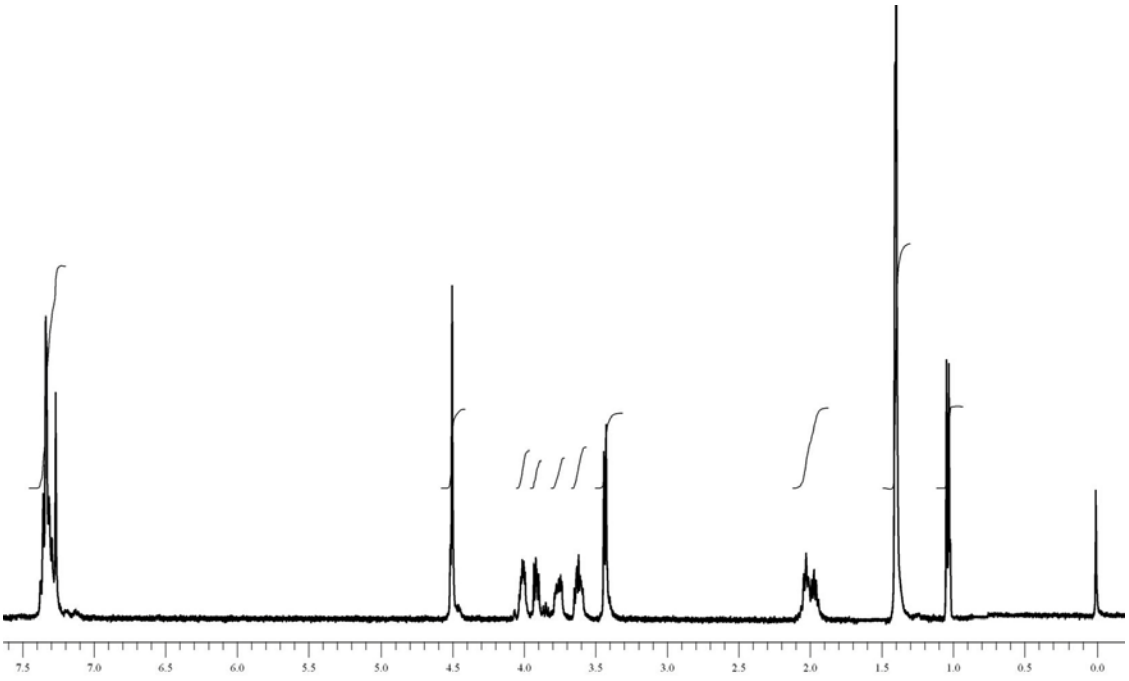
^{13}C NMR SPECTRUM OF COMPOUND **80**



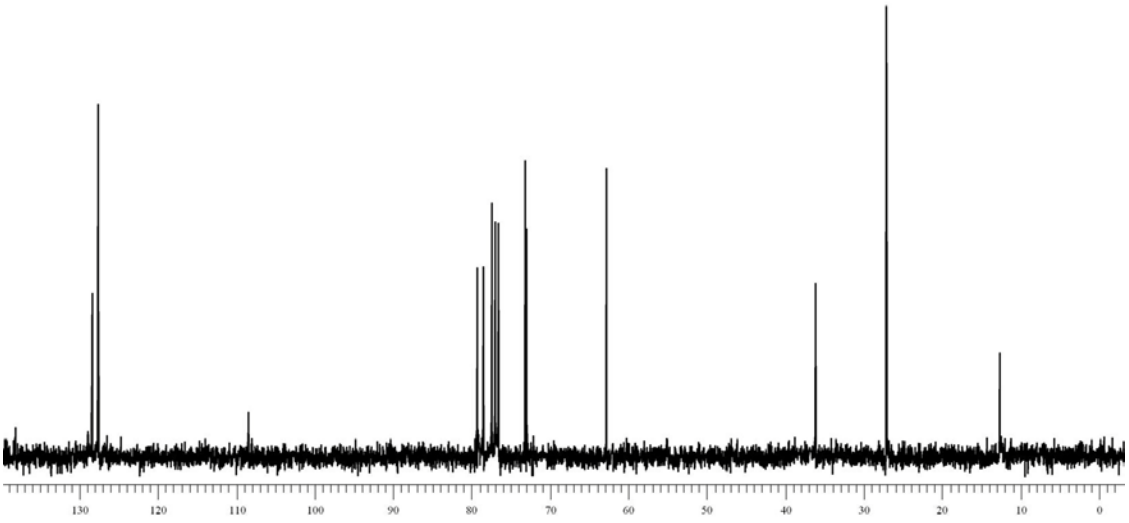
FTIR SPECTRUM OF COMPOUND **80**



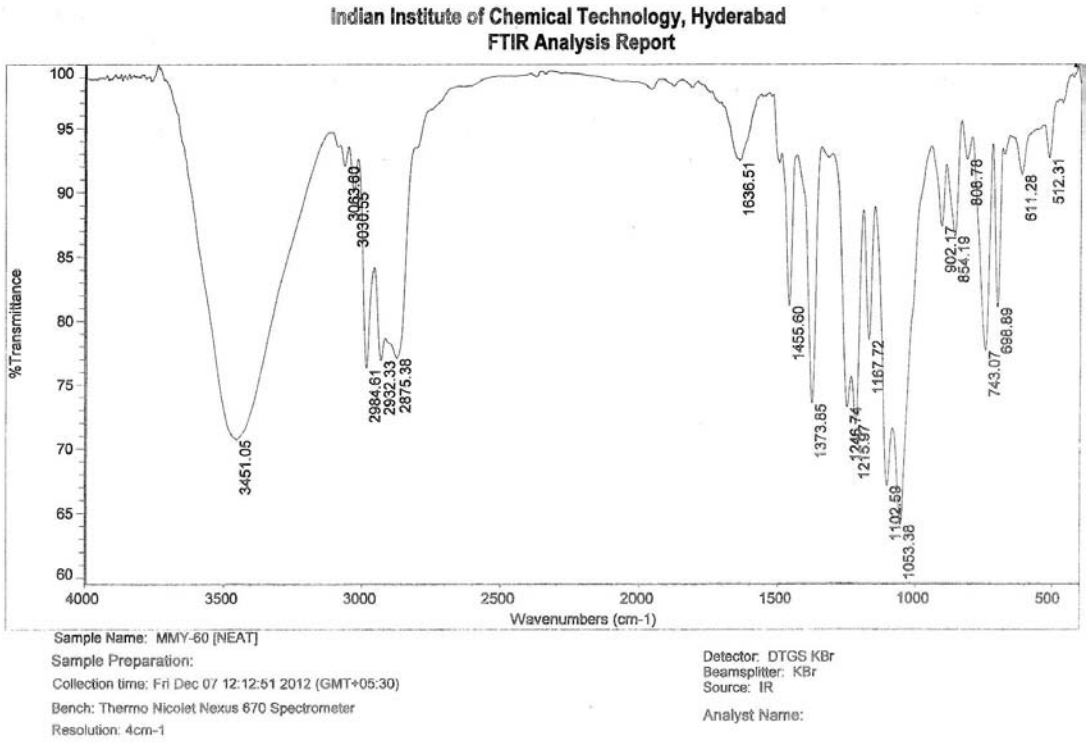
HRMS SPECTRUM OF COMPOUND **80**



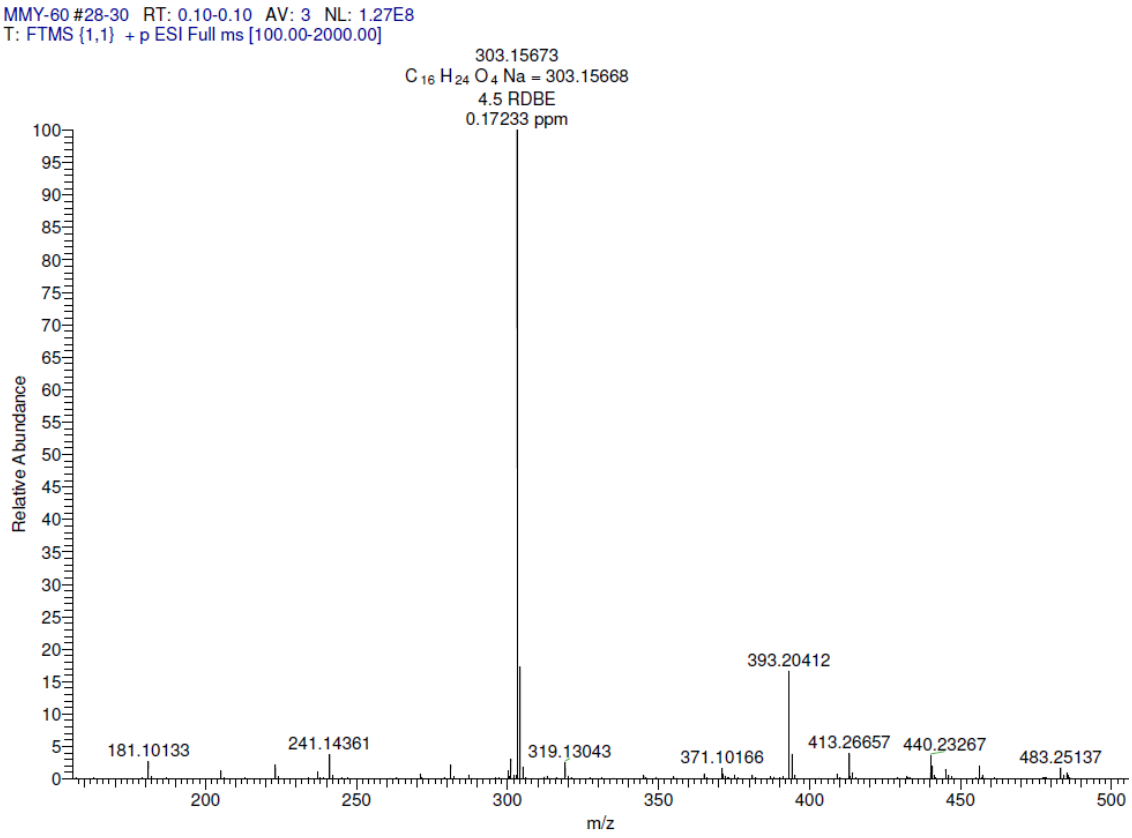
^{1}H NMR SPECTRUM OF COMPOUND **81**



^{13}C NMR SPECTRUM OF COMPOUND **81**



FTIR SPECTRUM OF COMPOUND **81**



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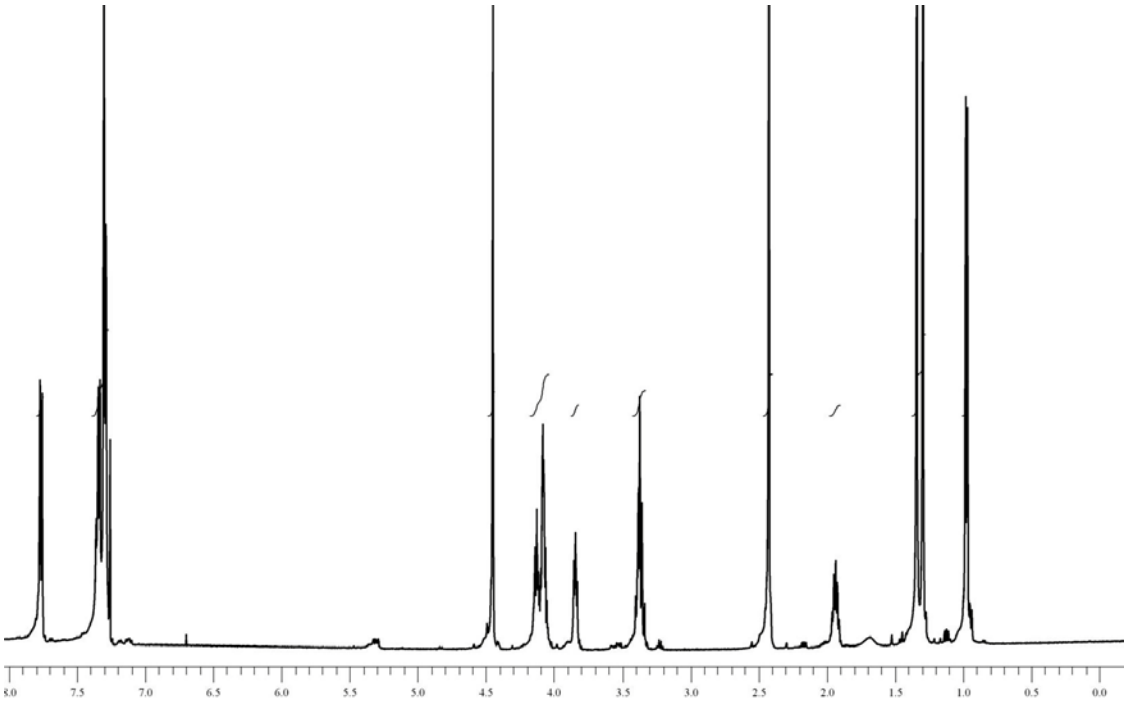
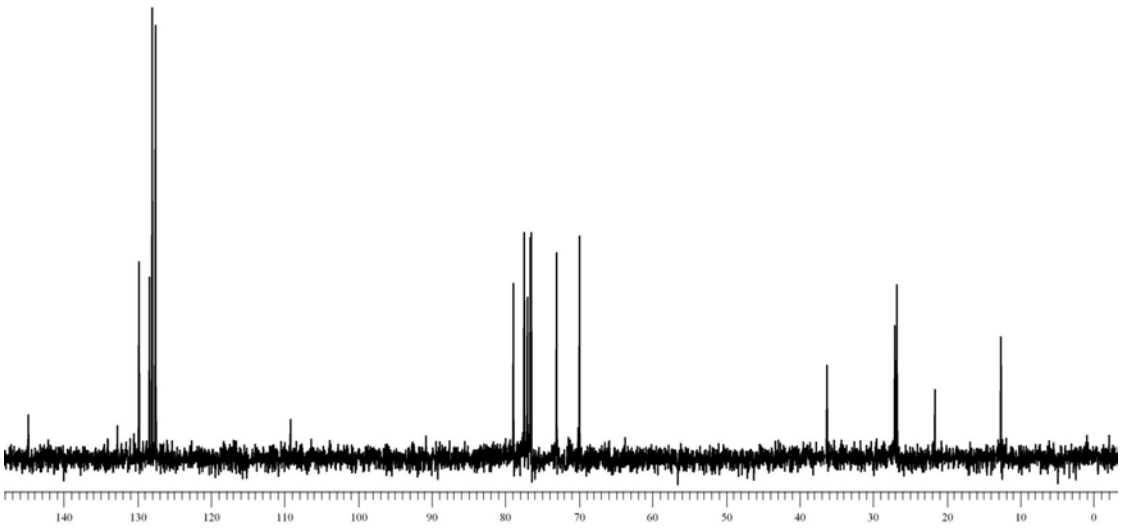
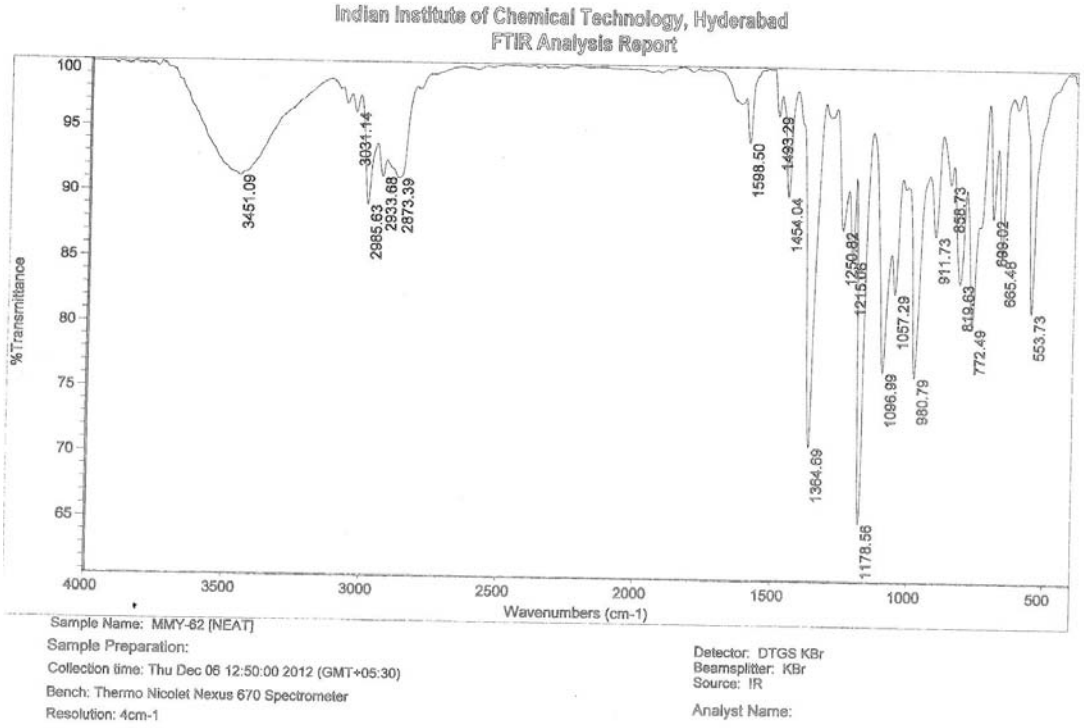


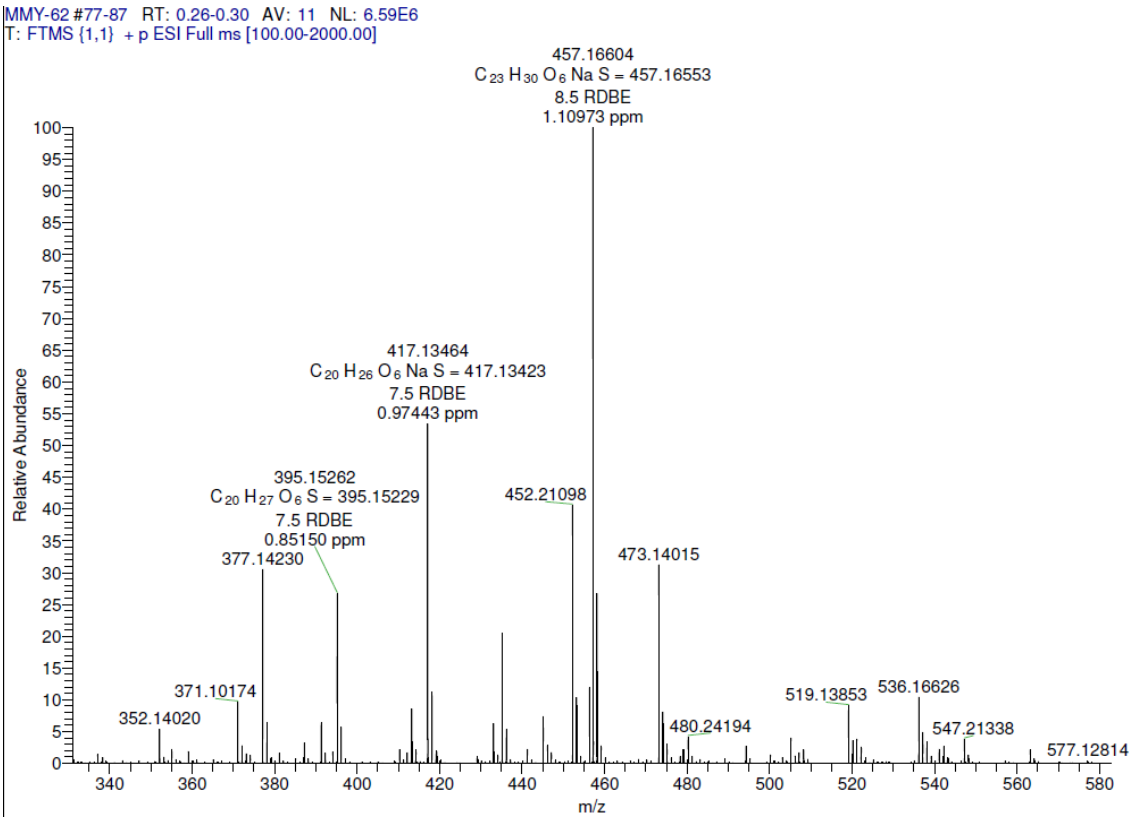
^{1}H NMR SPECTRUM OF COMPOUND **82**



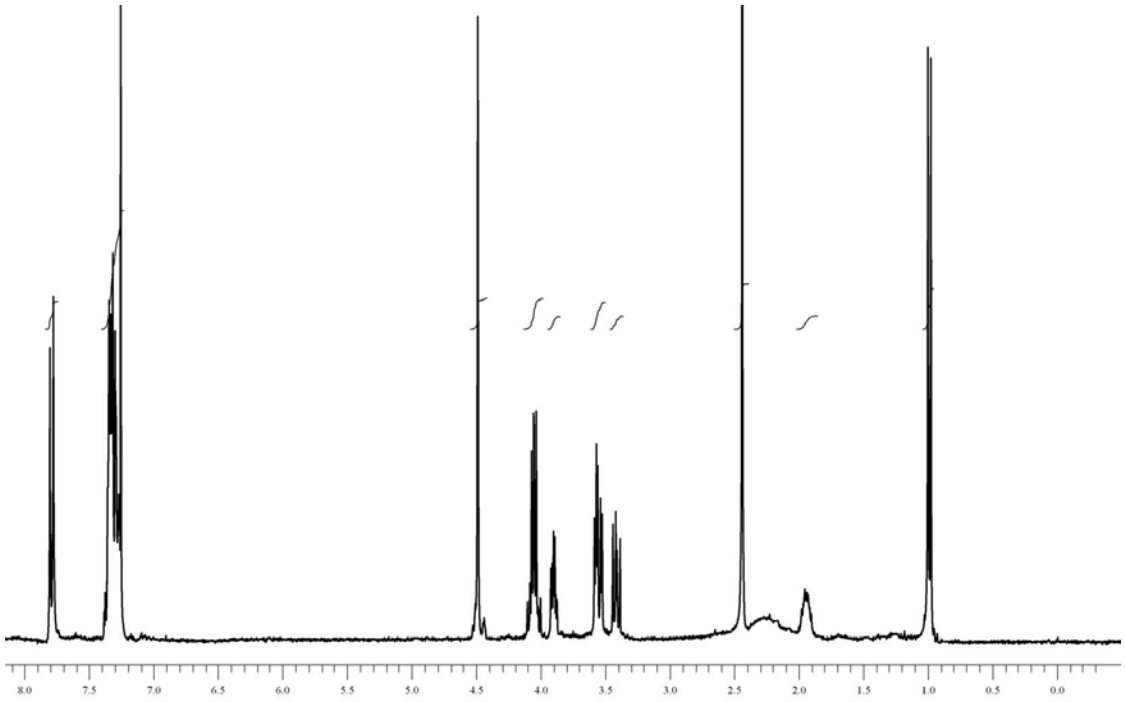
^{13}C NMR SPECTRUM OF COMPOUND **82**



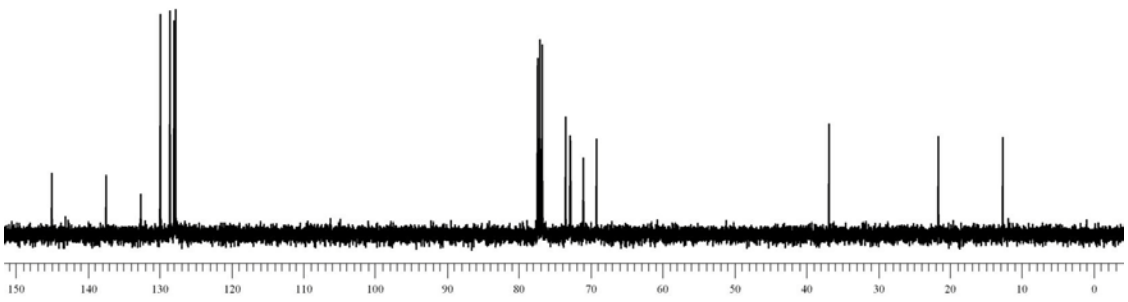
FTIR SPECTRUM OF COMPOUND **82**



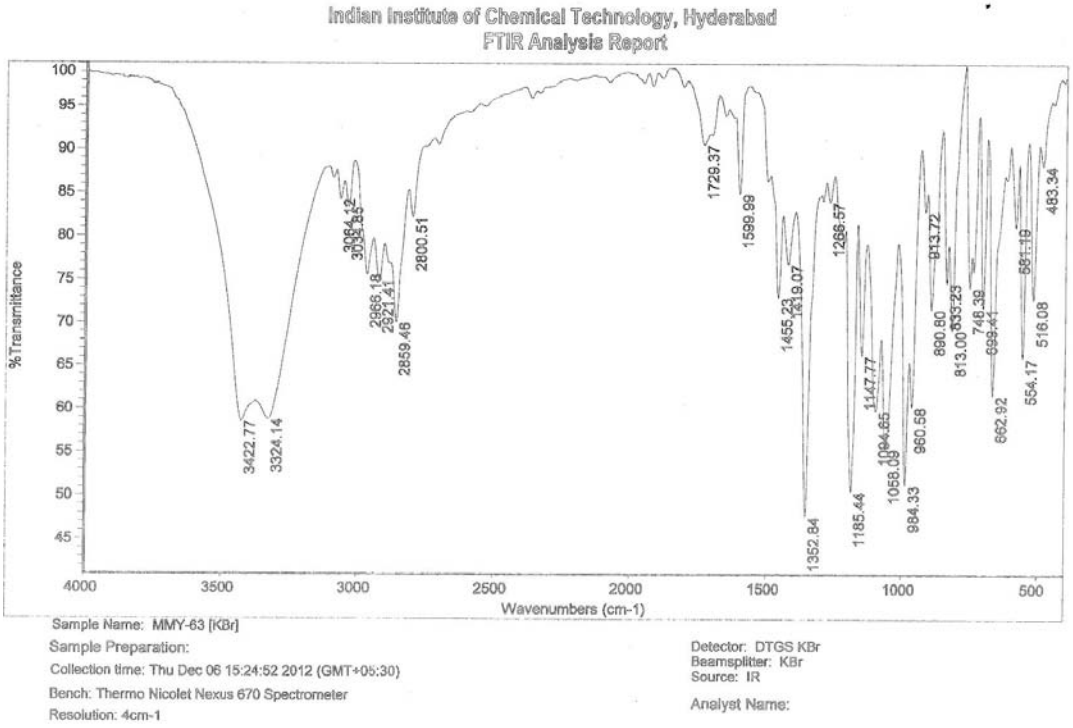
HRMS SPECTRUM OF COMPOUND **82**



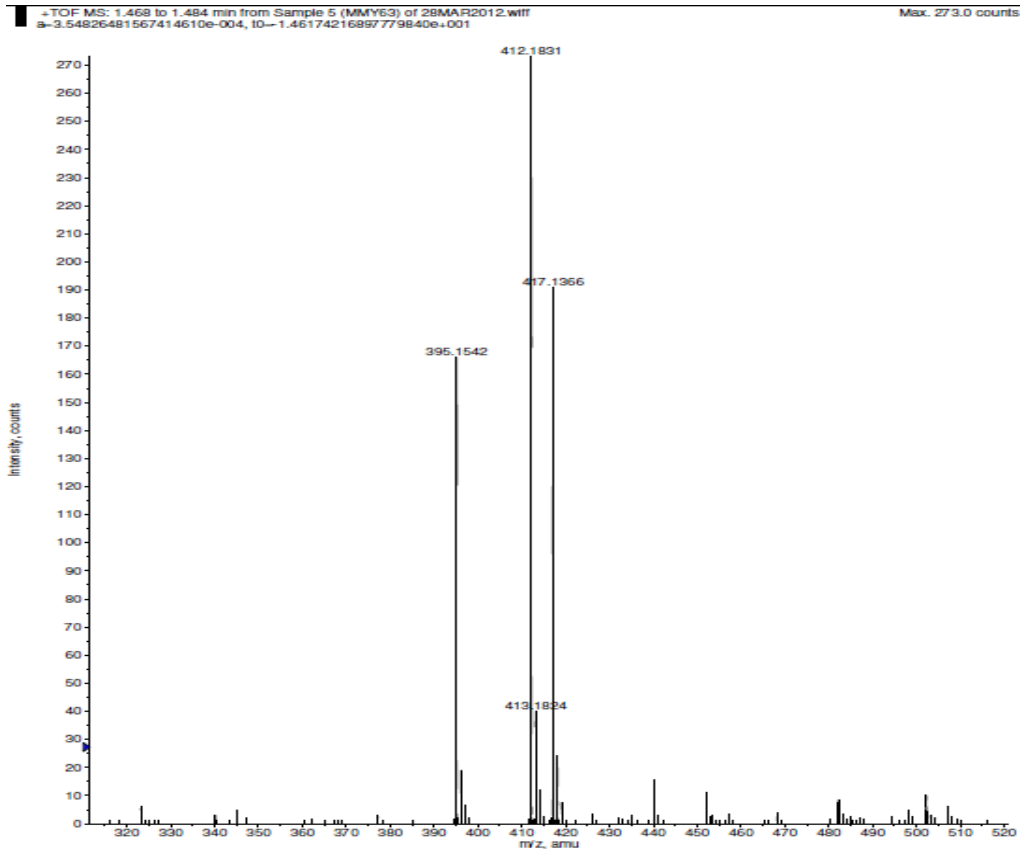
^{1}H NMR SPECTRUM OF COMPOUND **83**



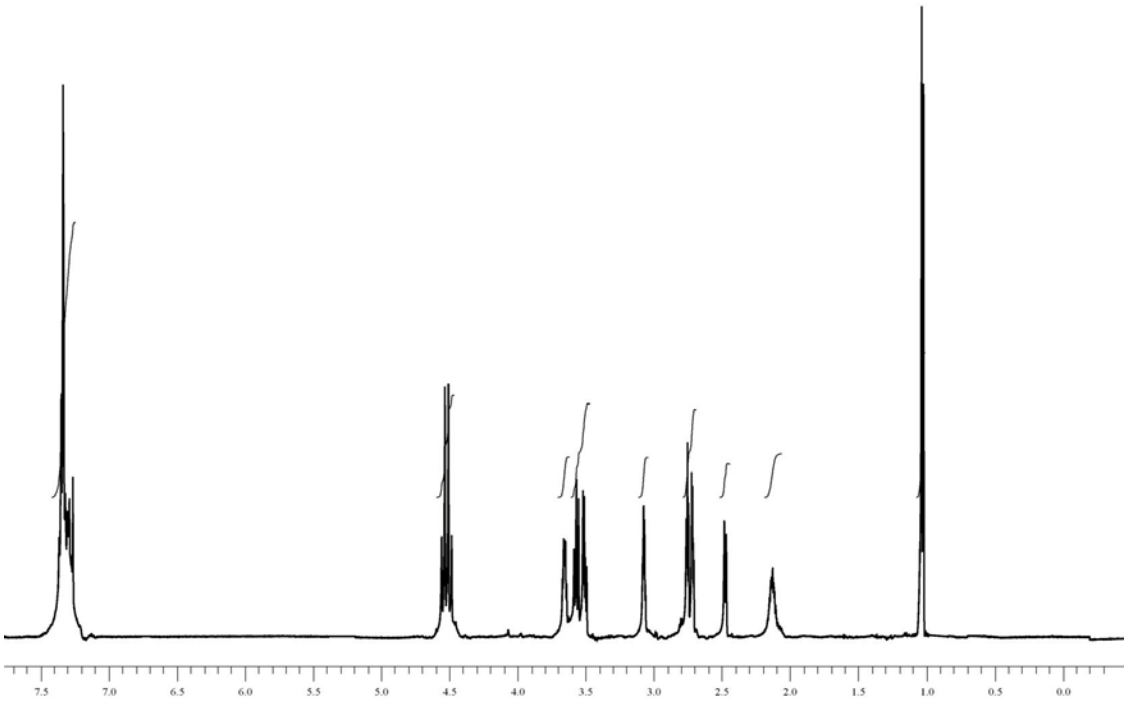
^{13}C NMR SPECTRUM OF COMPOUND **83**



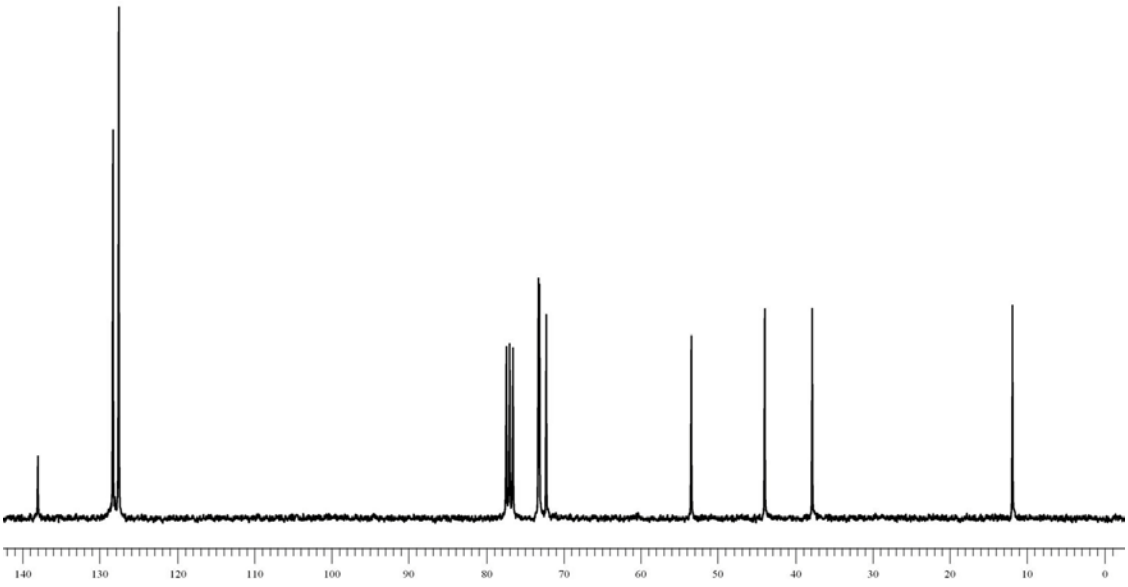
FTIR SPECTRUM OF COMPOUND **83**



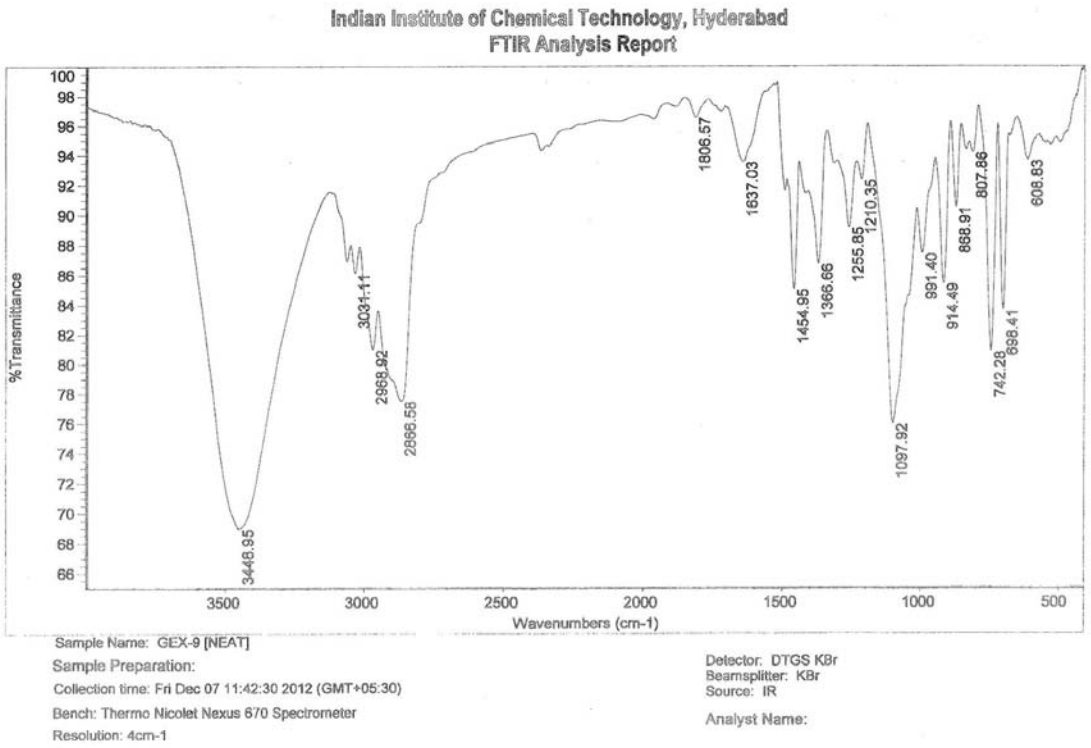
HRMS SPECTRUM OF COMPOUND **83**



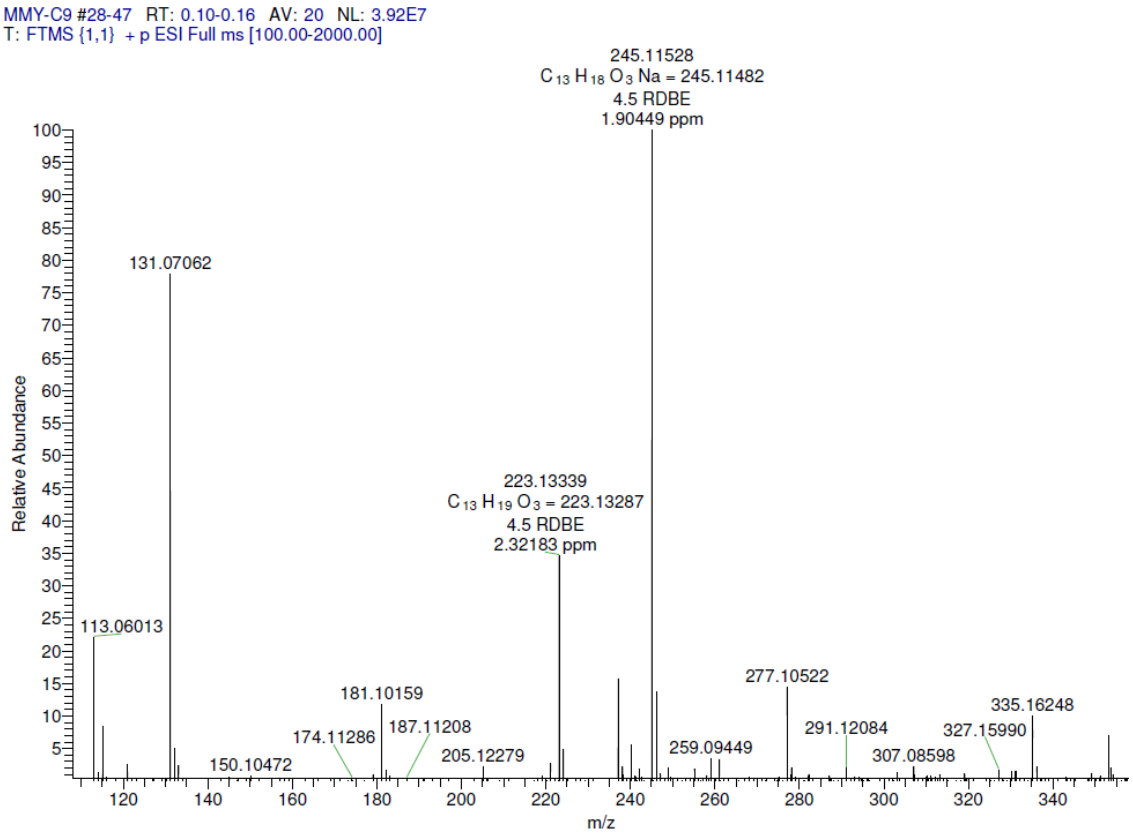
^{1}H NMR SPECTRUM OF COMPOUND **84**



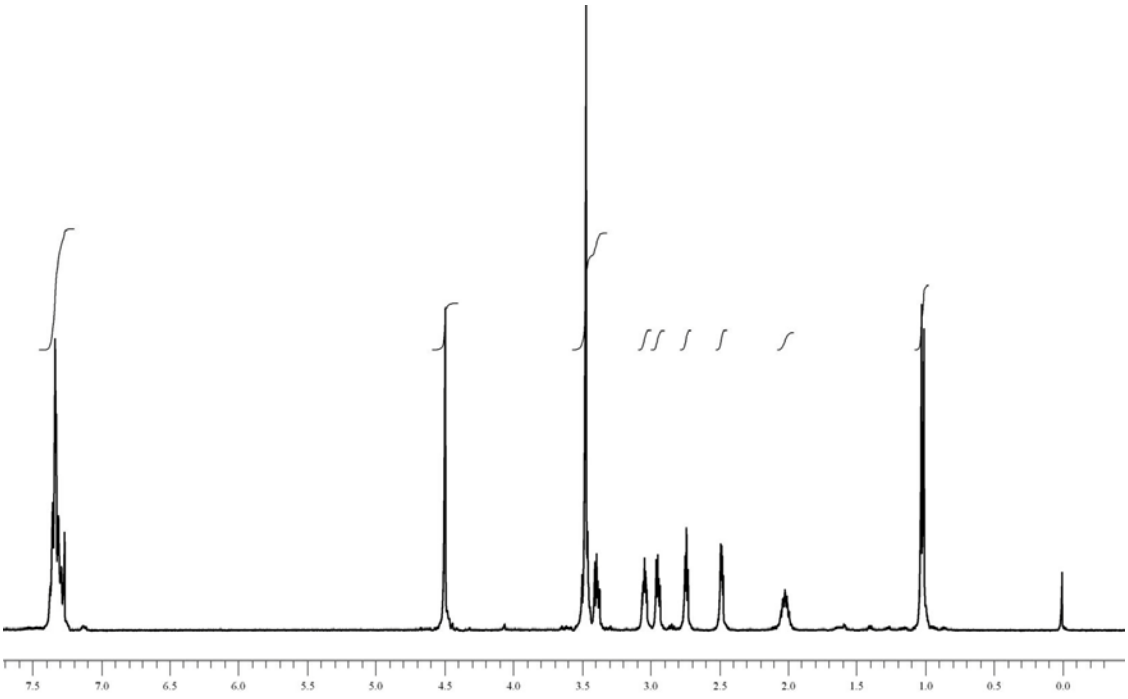
^{13}C NMR SPECTRUM OF COMPOUND **84**



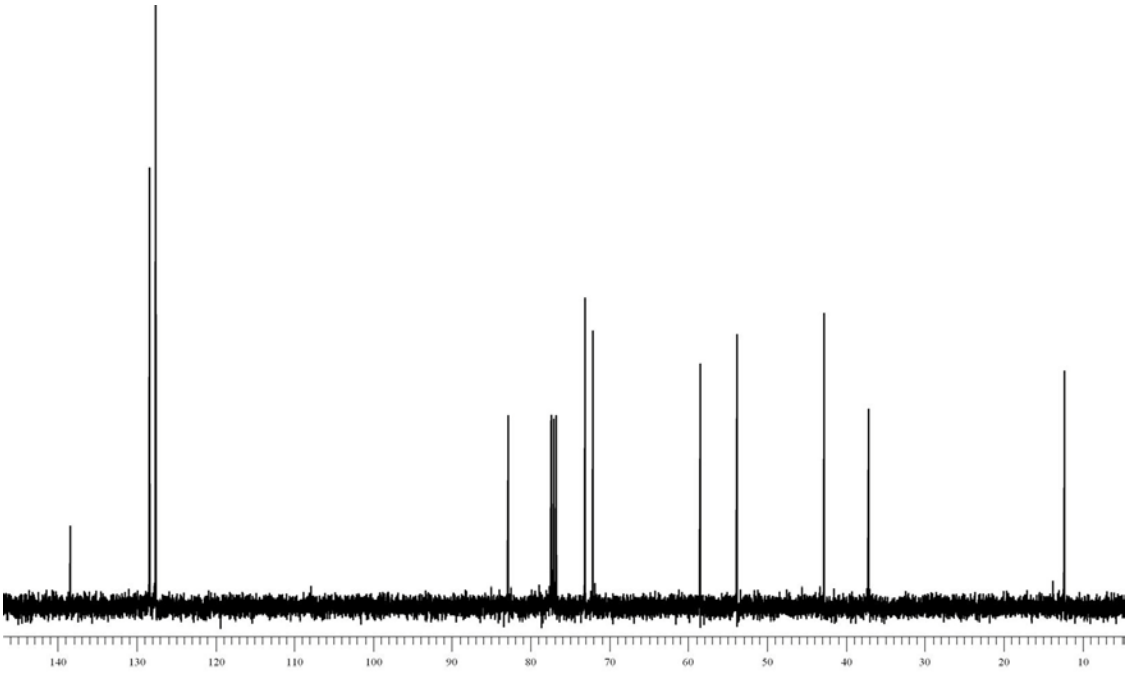
FTIR SPECTRUM OF COMPOUND **84**



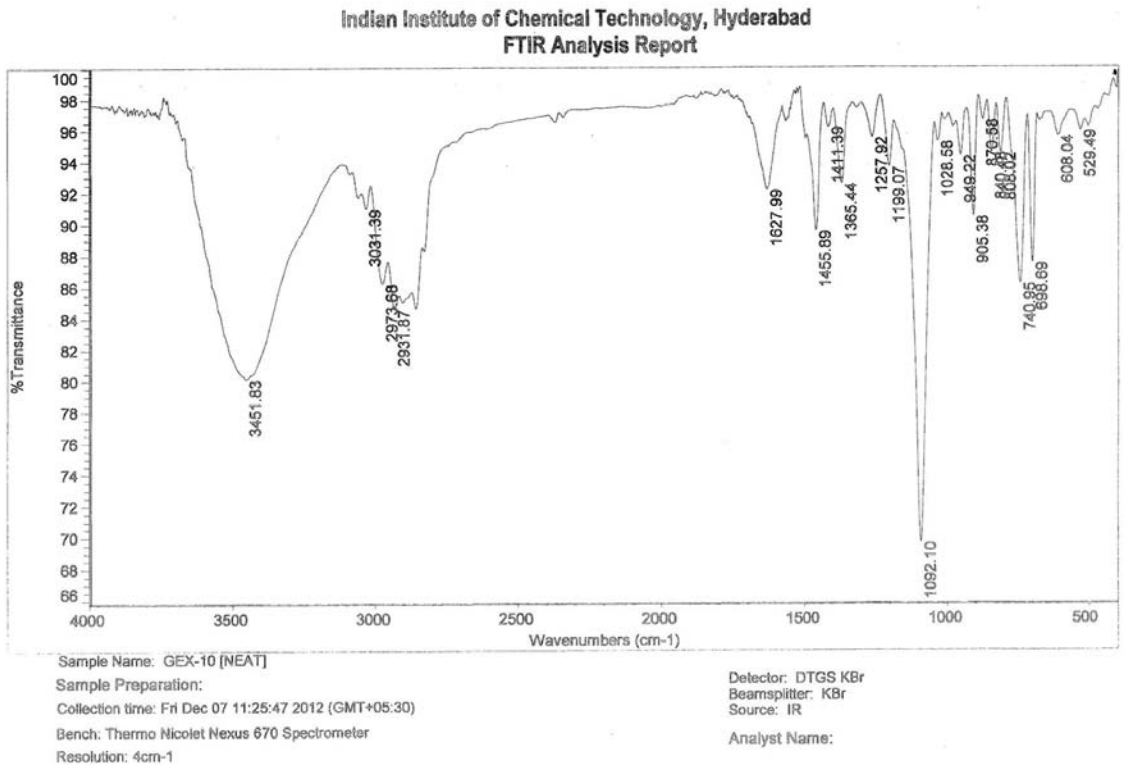
HRMS SPECTRUM OF COMPOUND **84**



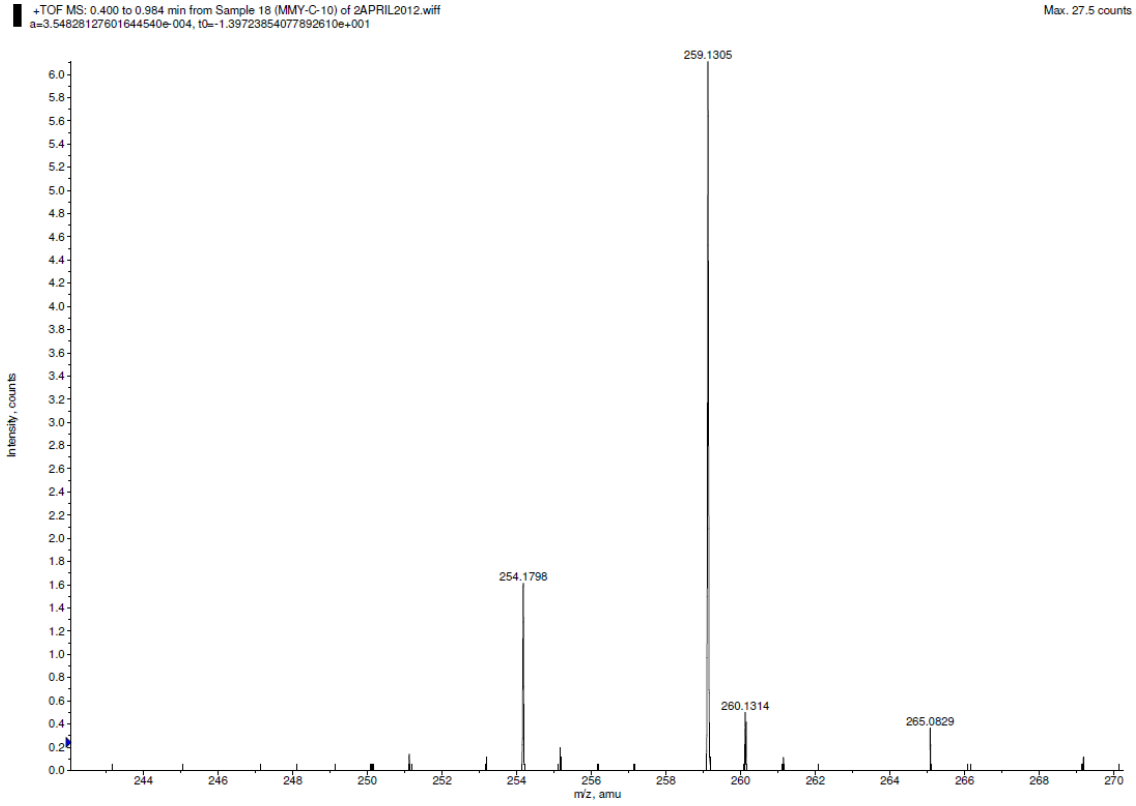
^{1}H NMR SPECTRUM OF COMPOUND **85**



^{13}C NMR SPECTRUM OF COMPOUND **85**



FTIR SPECTRUM OF COMPOUND **85**



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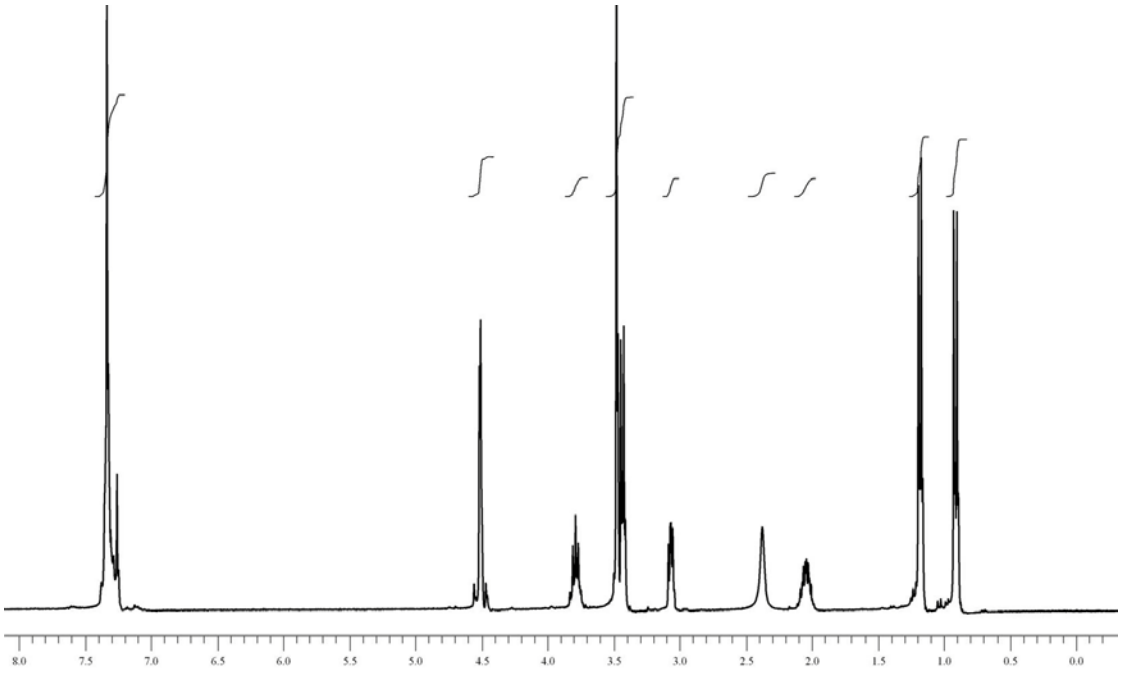
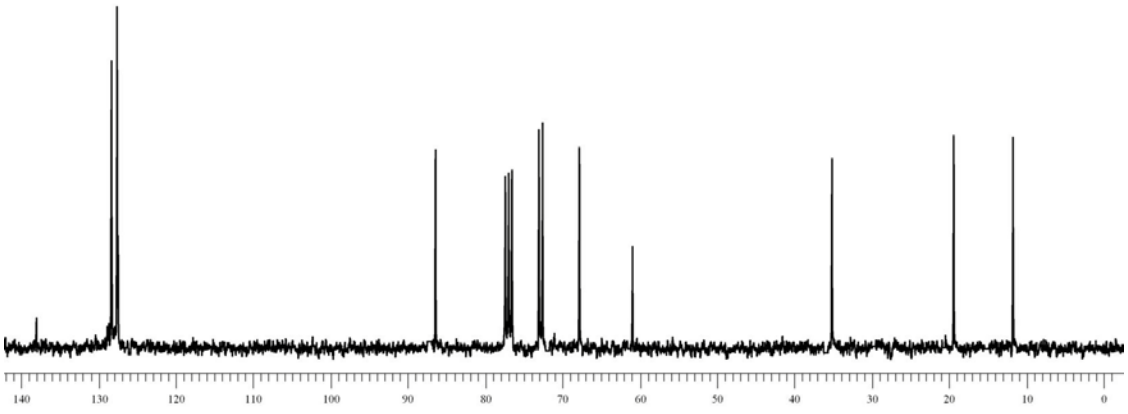
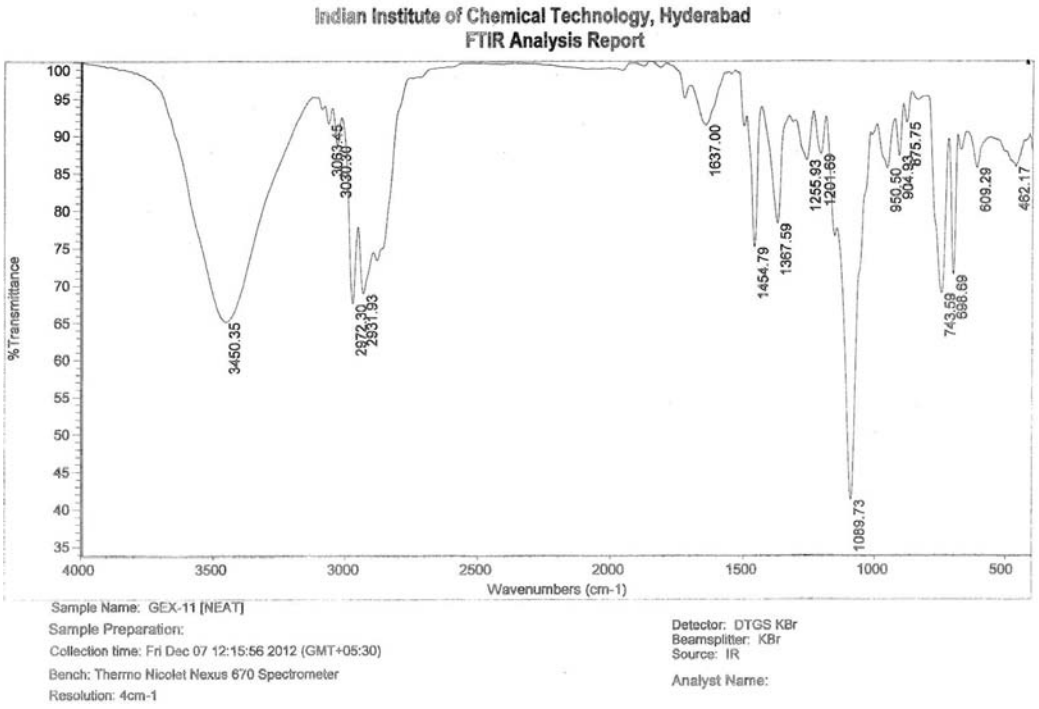


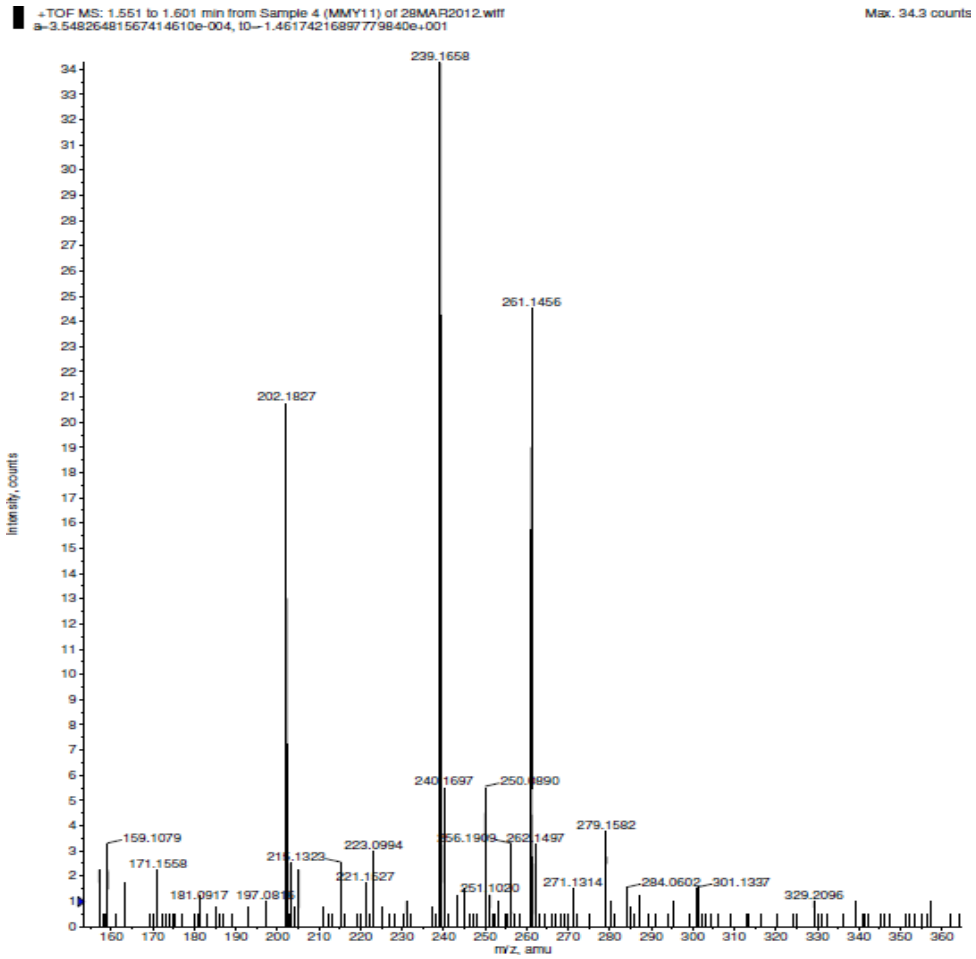
^{1}H NMR SPECTRUM OF COMPOUND **86**



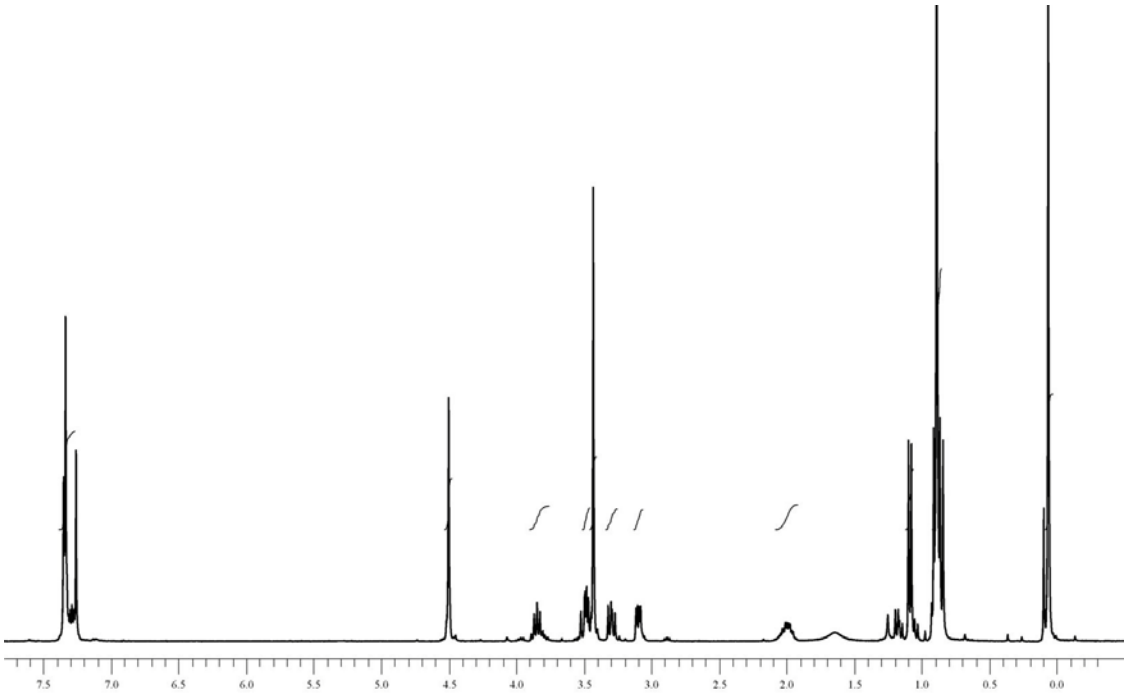
^{13}C NMR SPECTRUM OF COMPOUND **86**



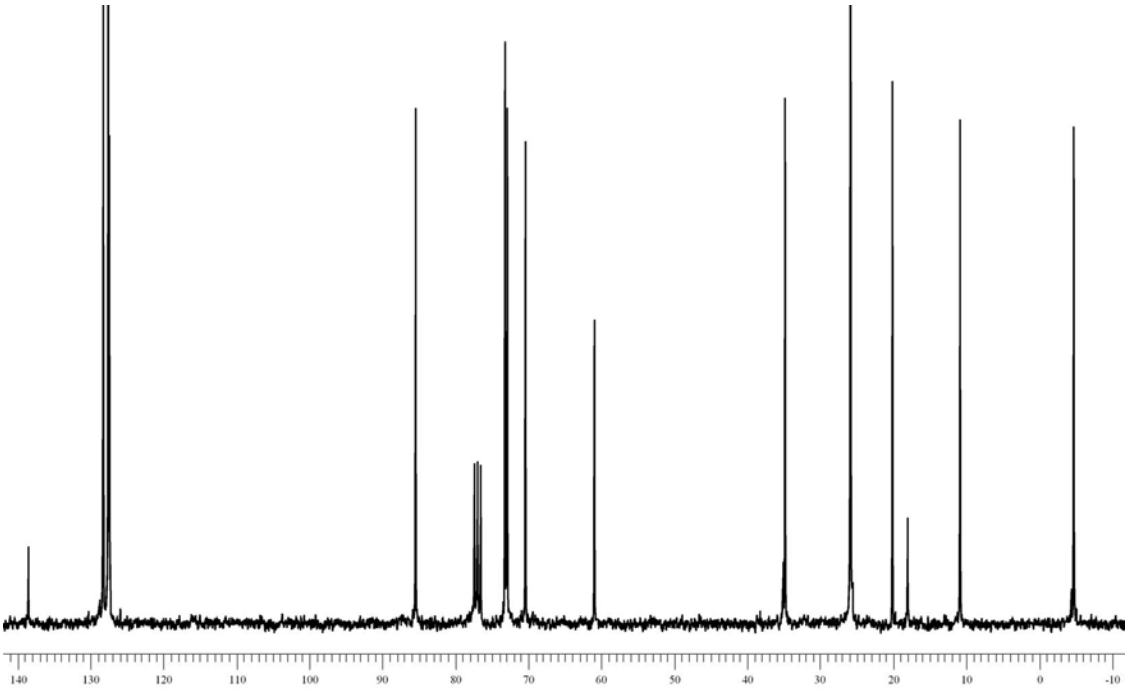
FTIR SPECTRUM OF COMPOUND **86**



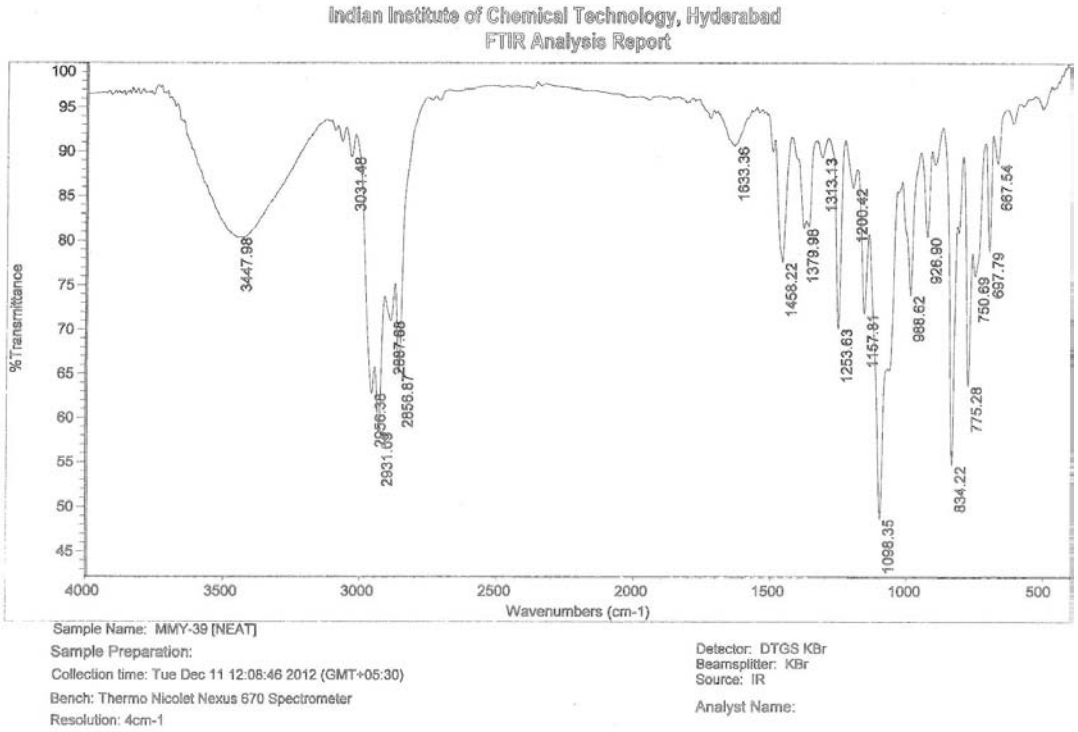
HRMS SPECTRUM OF COMPOUND **86**



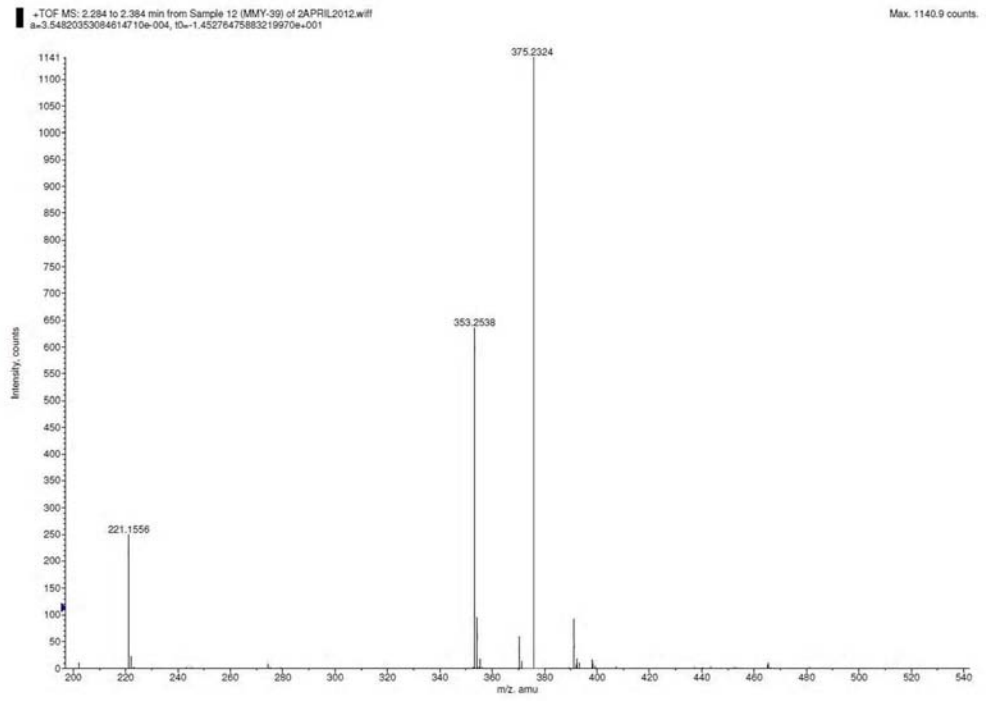
^{1}H NMR SPECTRUM OF COMPOUND **87**



^{13}C NMR SPECTRUM OF COMPOUND **87**



FTIR SPECTRUM OF COMPOUND **87**



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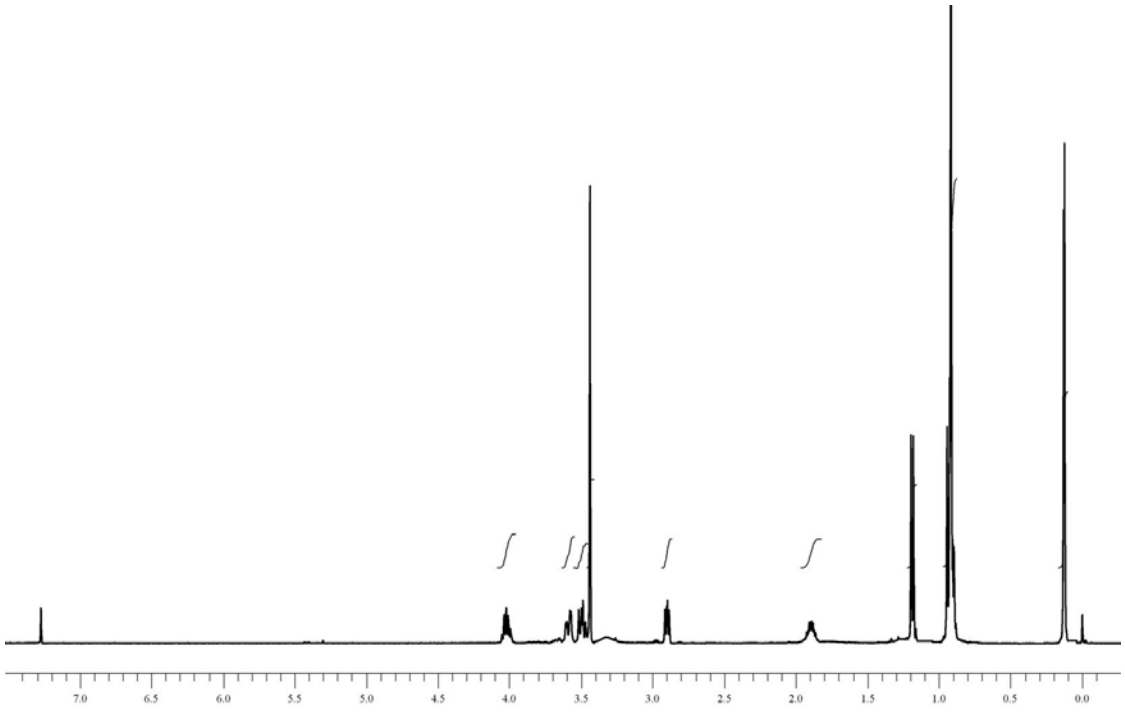
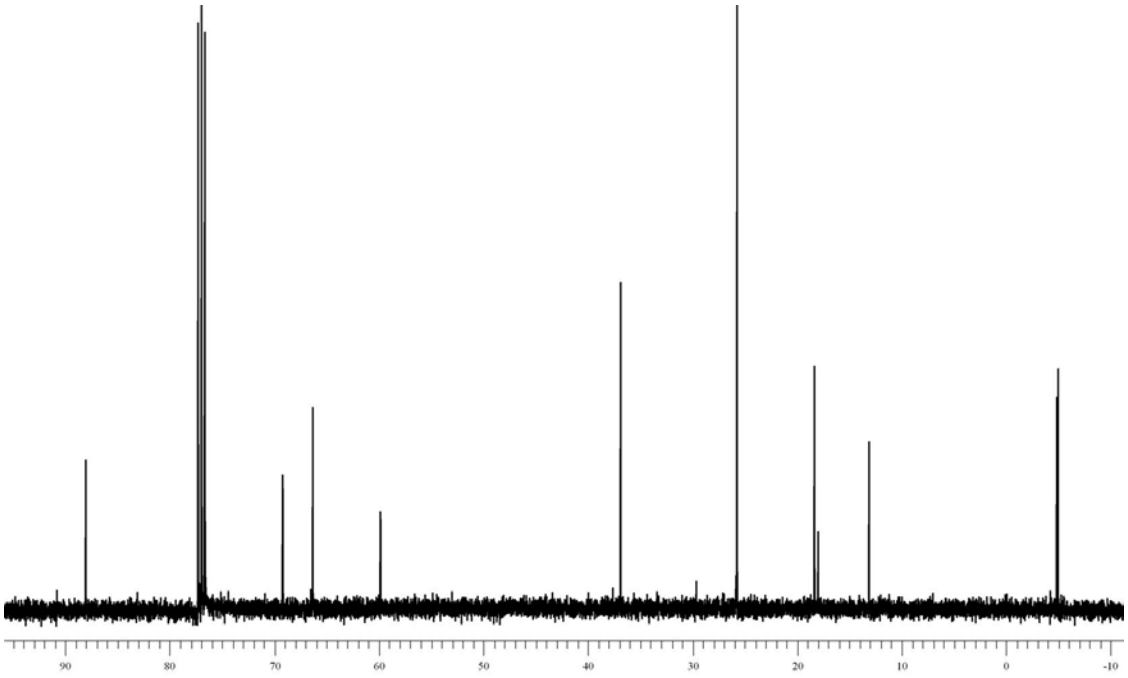
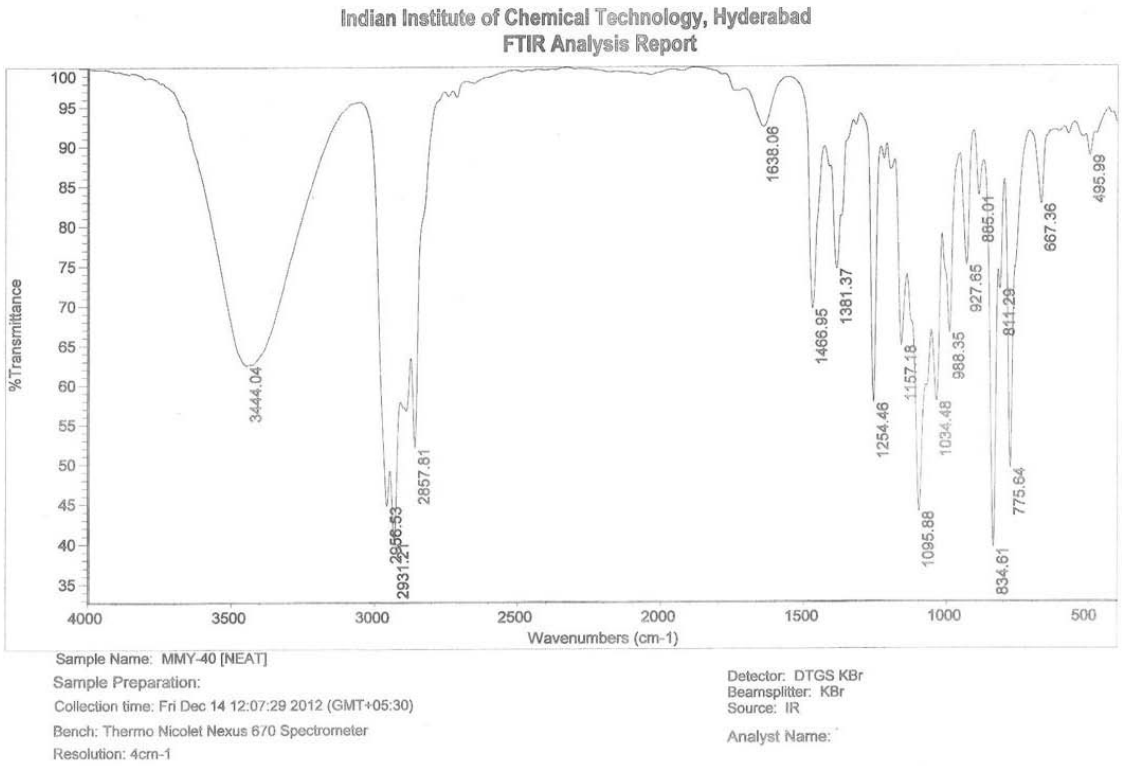


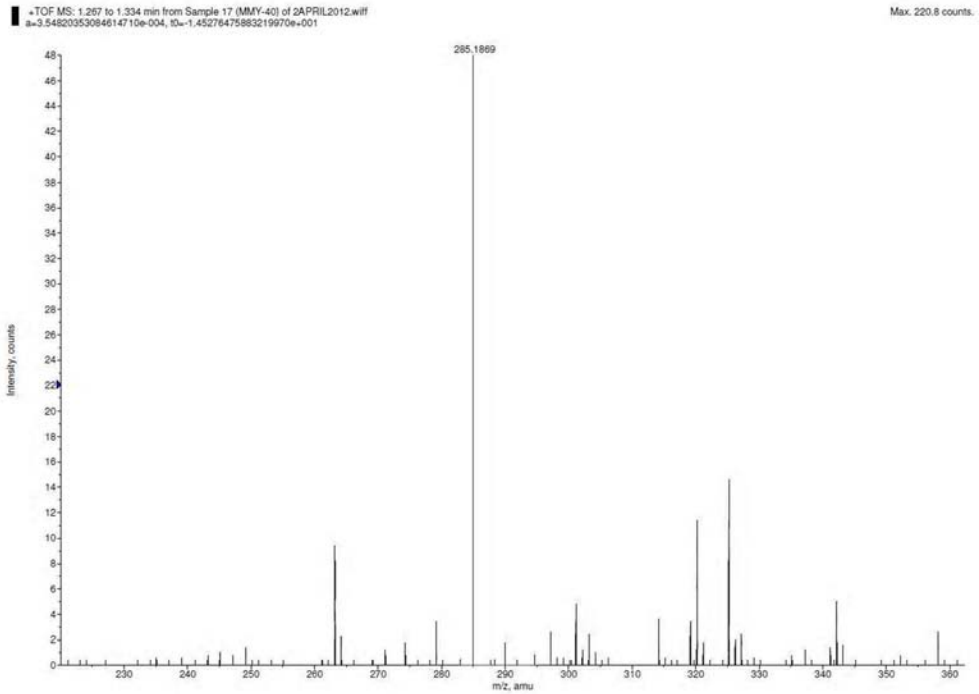
^{1}H NMR SPECTRUM OF COMPOUND **68**



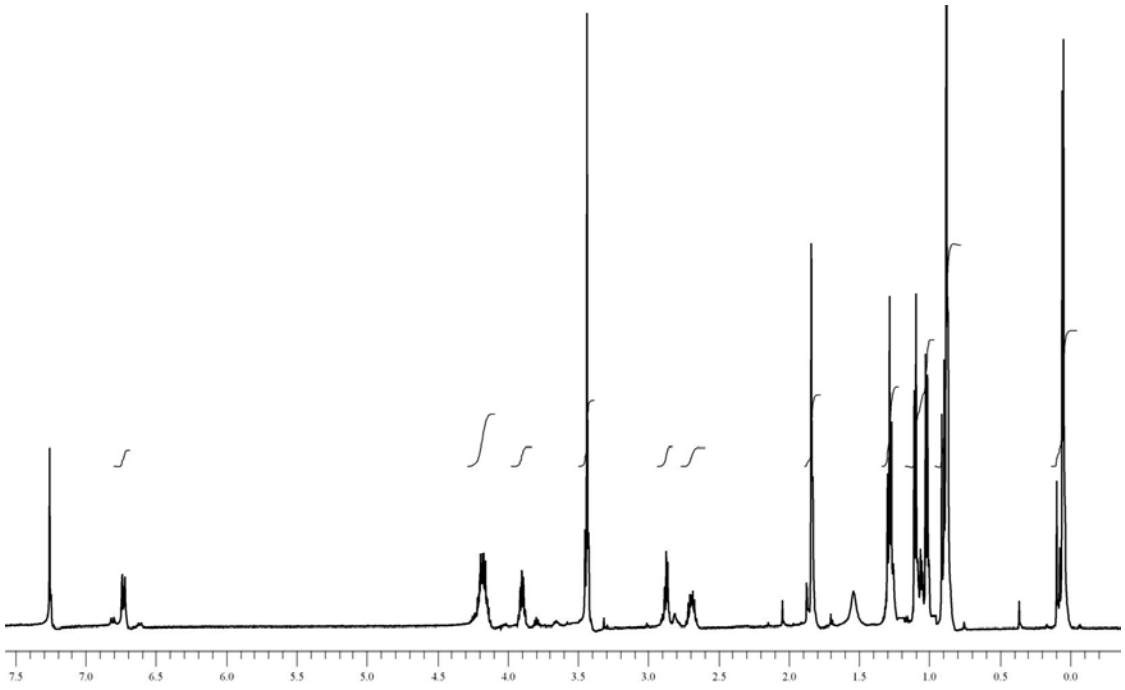
^{13}C NMR SPECTRUM OF COMPOUND **68**



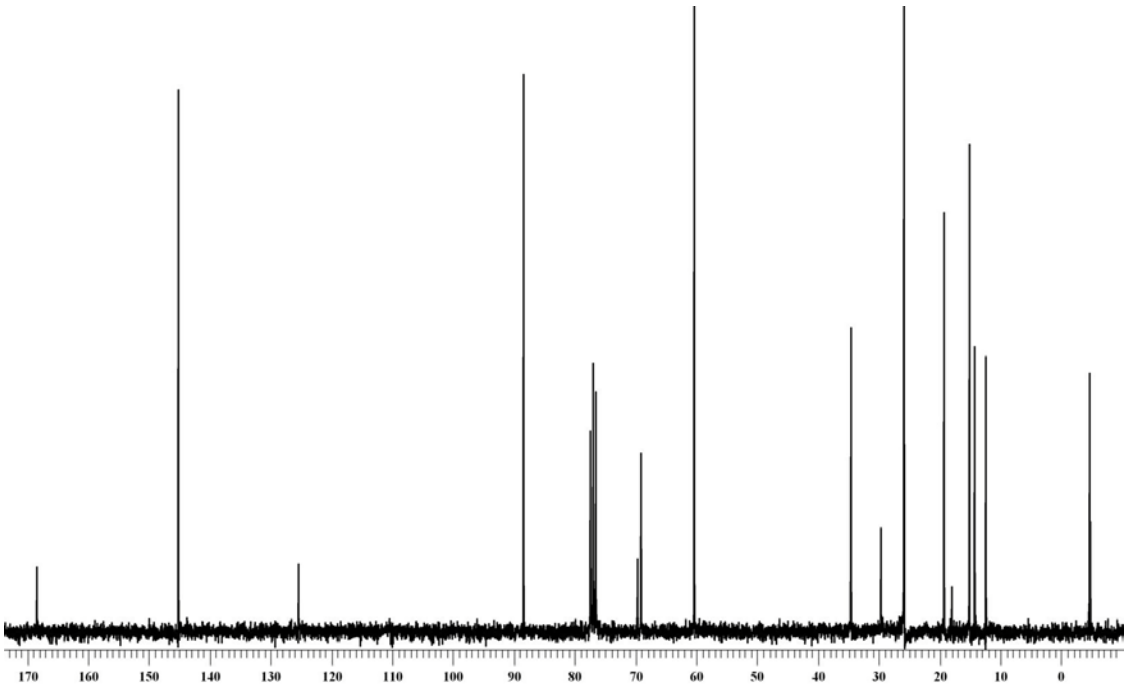
FTIR SPECTRUM OF COMPOUND **68**



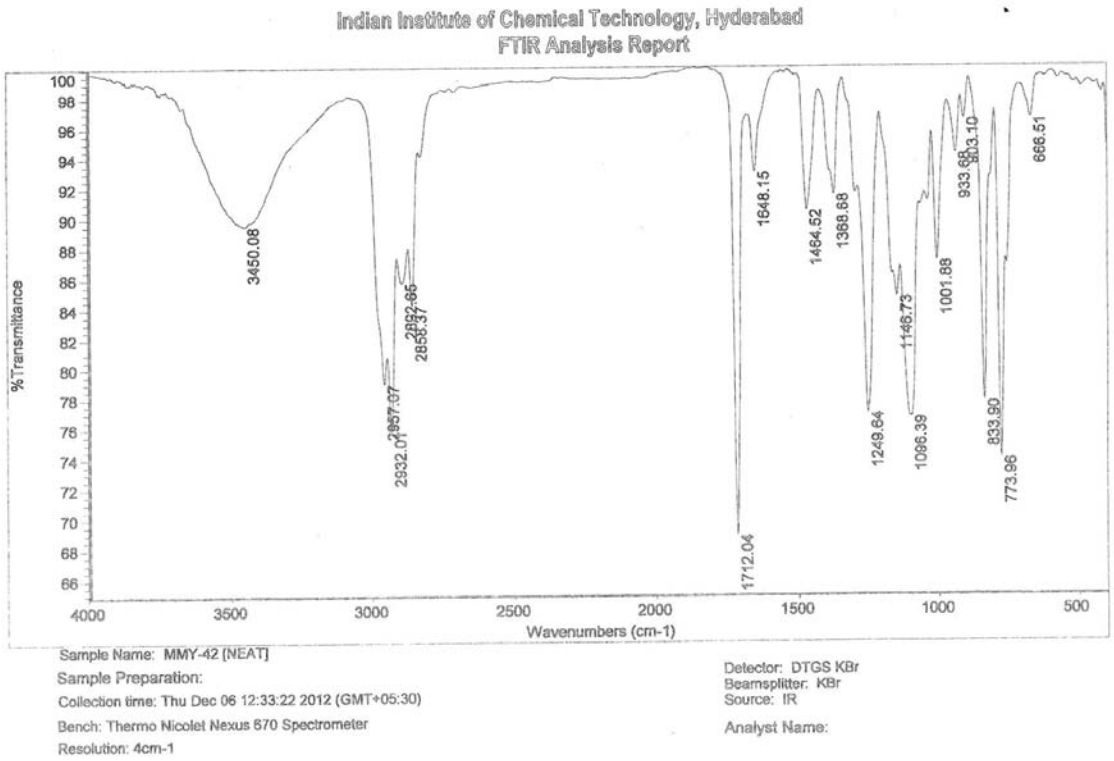
HRMS SPECTRUM OF COMPOUND **68**



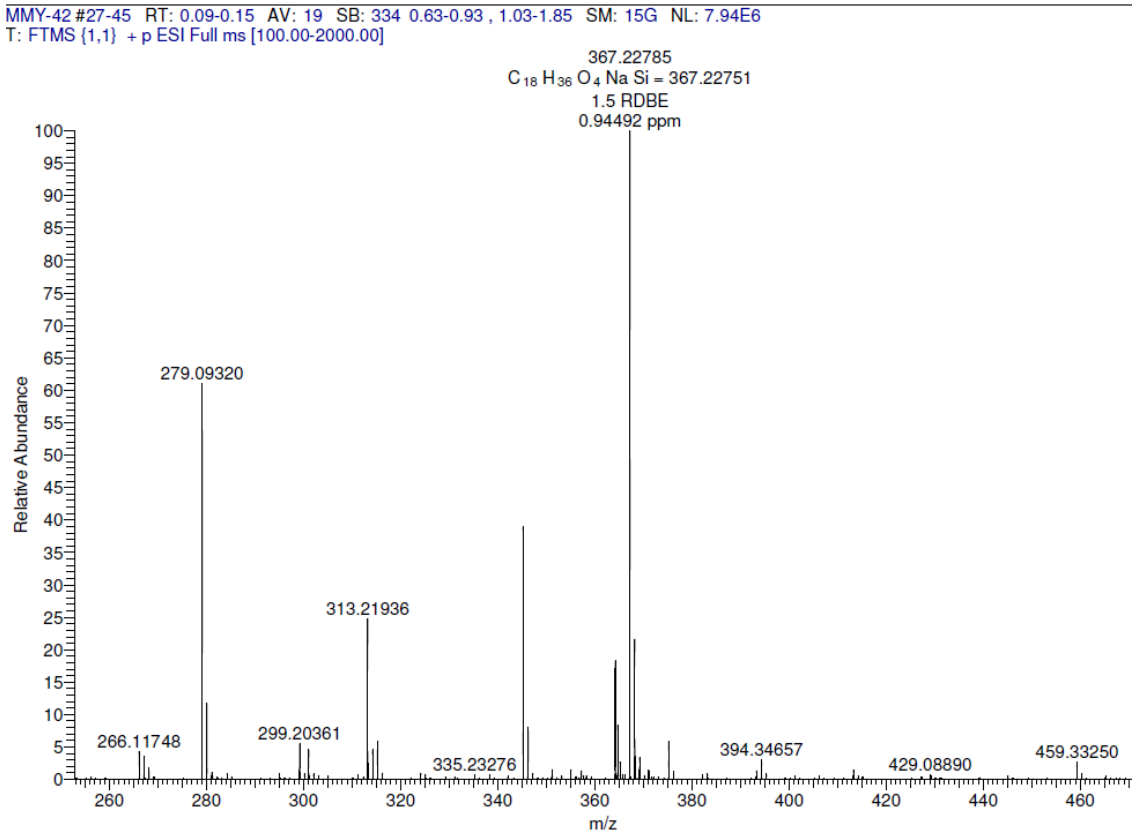
^{1}H NMR SPECTRUM OF COMPOUND **88**



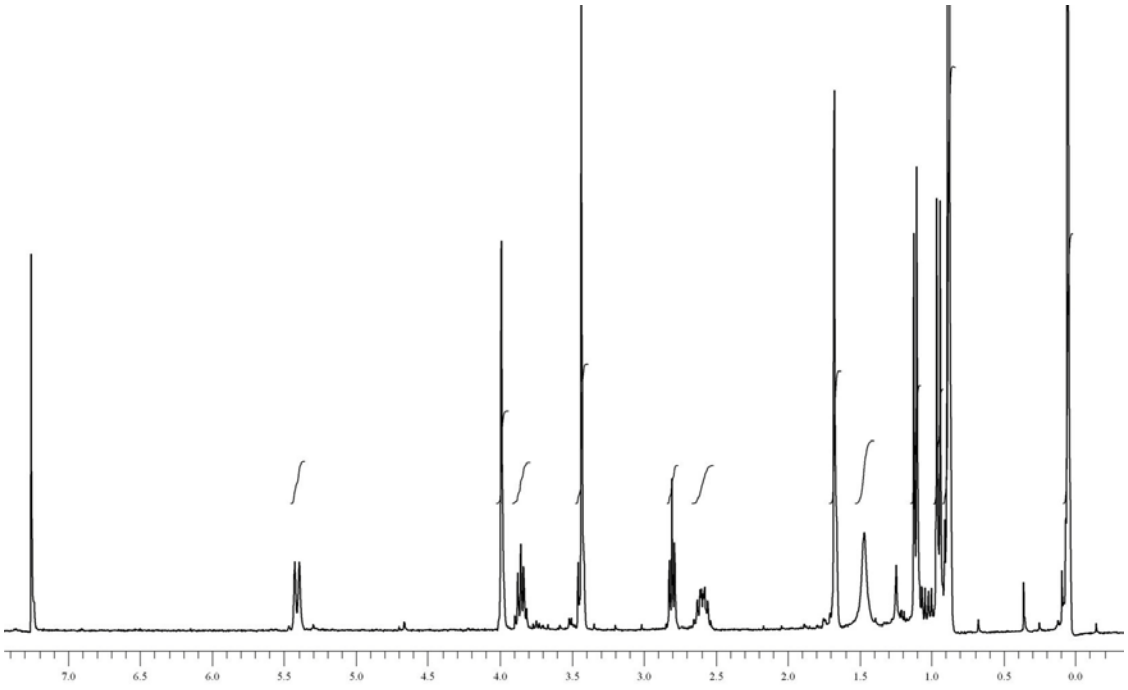
^{13}C NMR SPECTRUM OF COMPOUND **88**



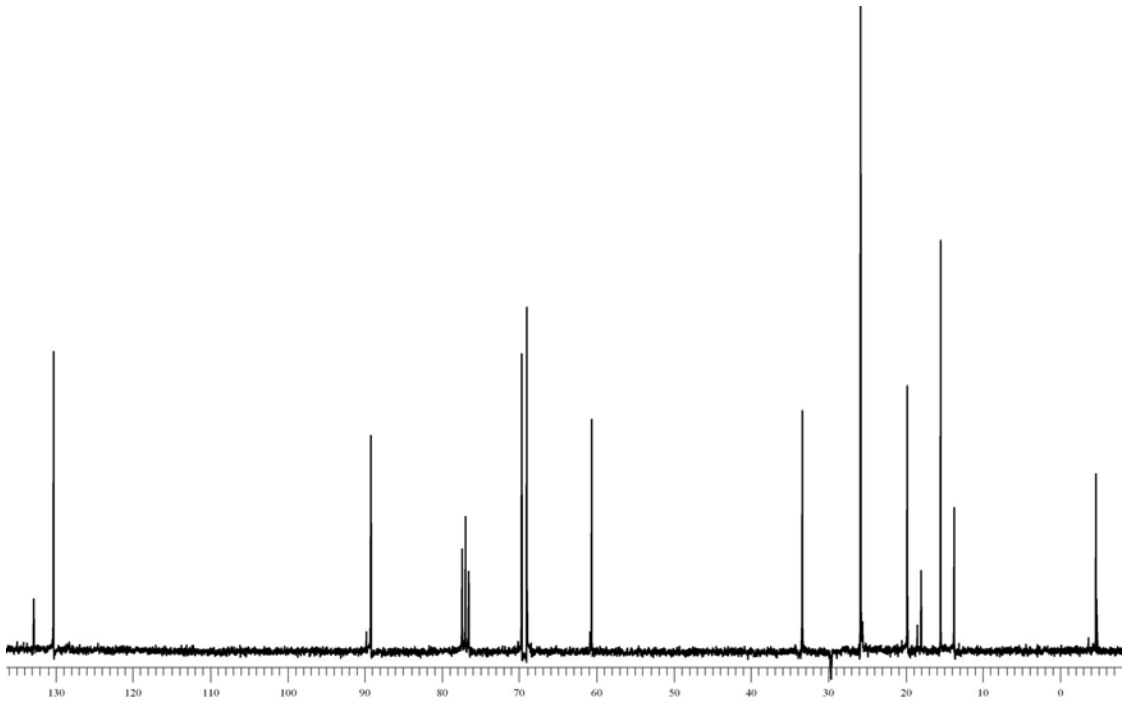
FTIR SPECTRUM OF COMPOUND **88**



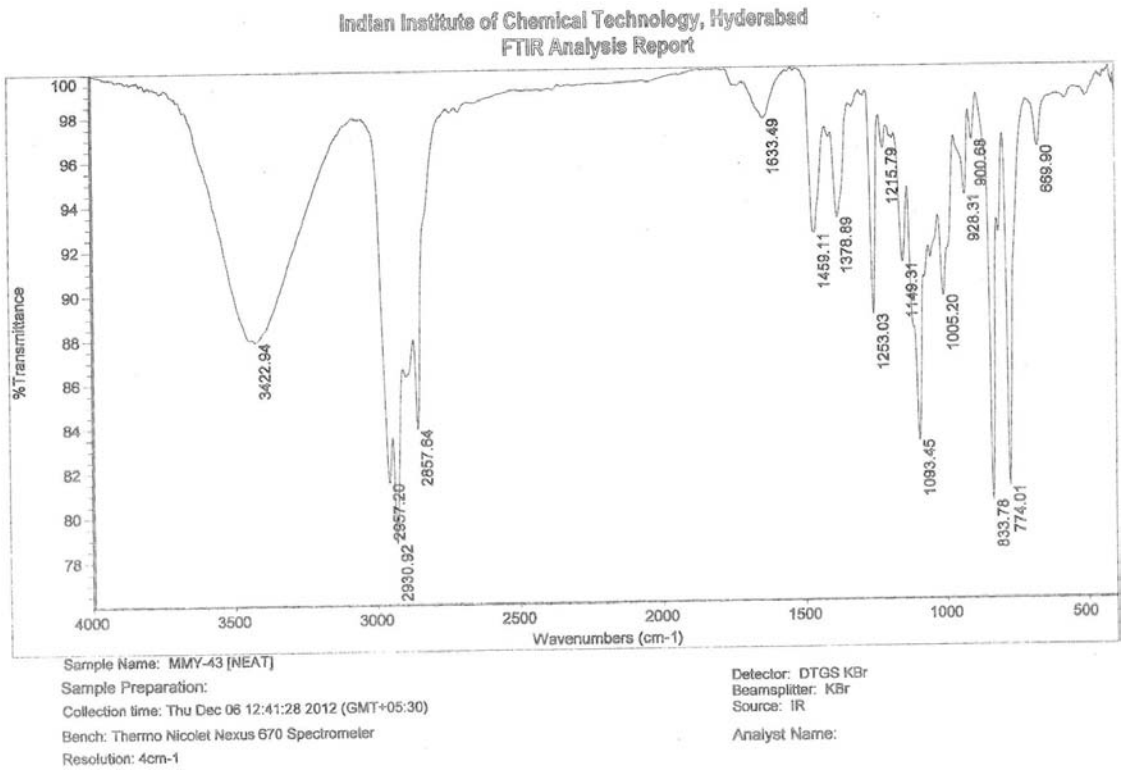
HRMS SPECTRUM OF COMPOUND **88**



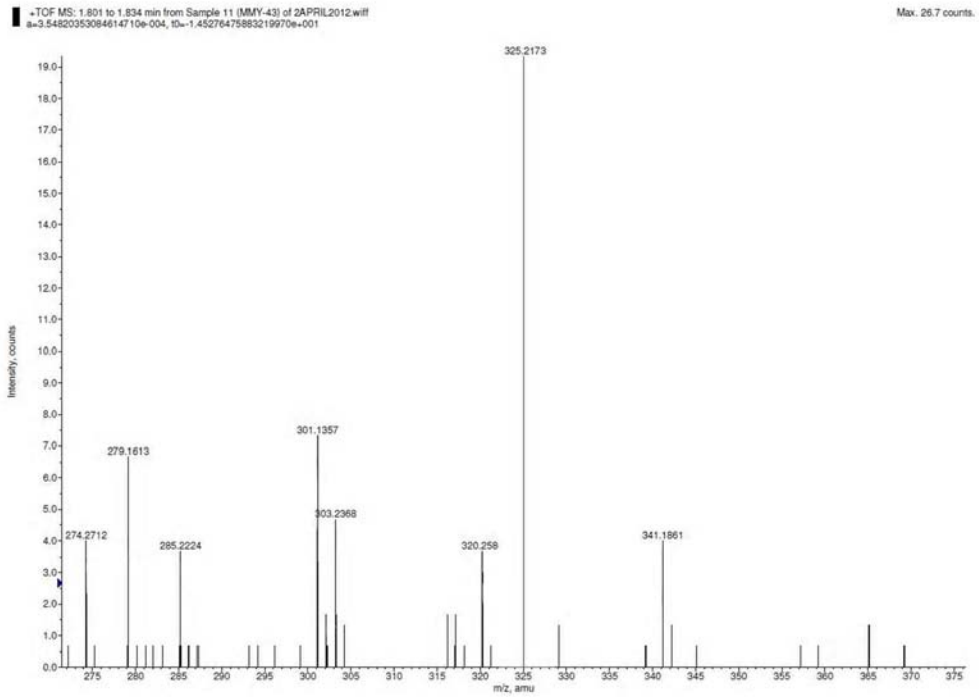
^{1}H NMR SPECTRUM OF COMPOUND **67**



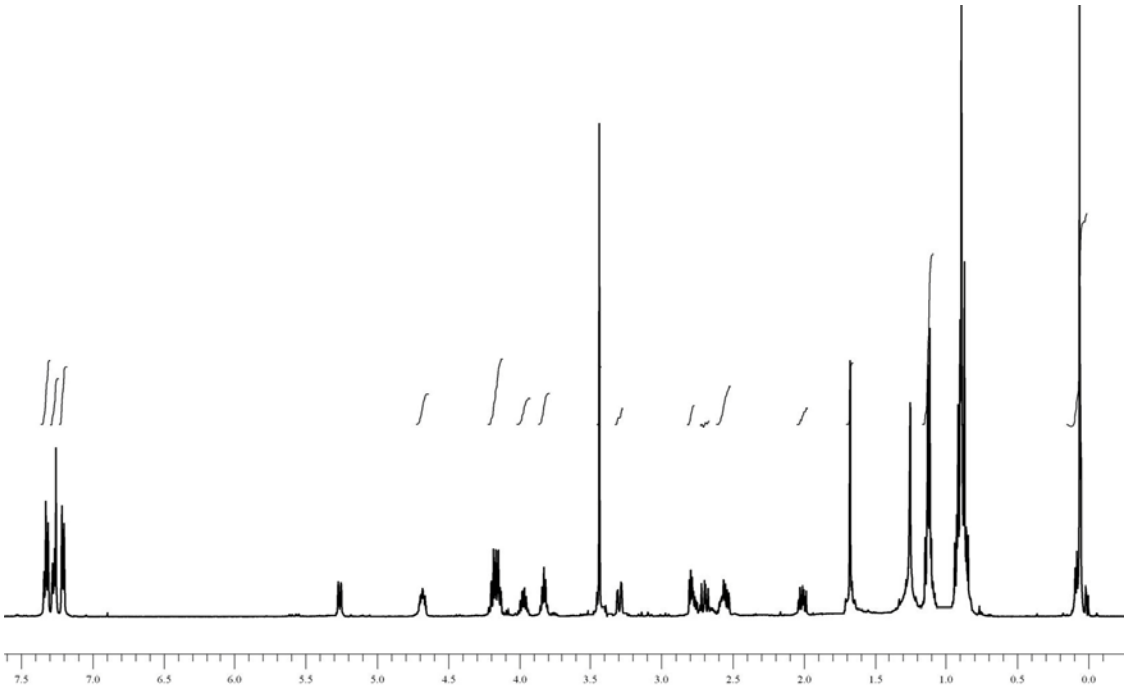
^{13}C NMR SPECTRUM OF COMPOUND **67**



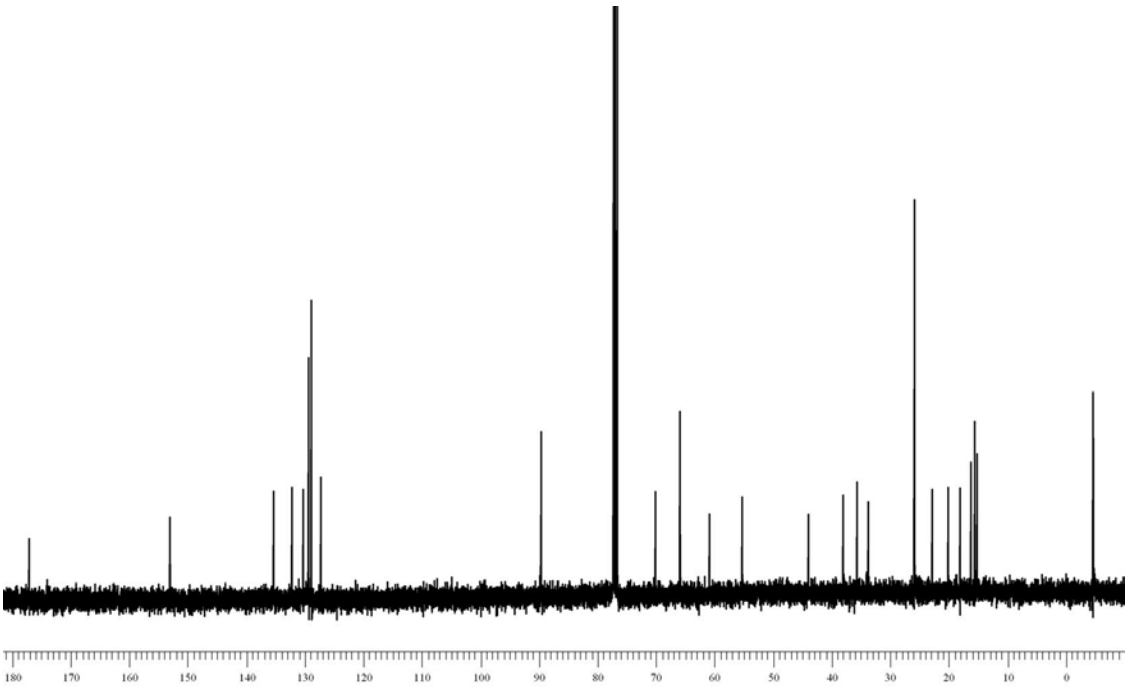
FTIR SPECTRUM OF COMPOUND **67**



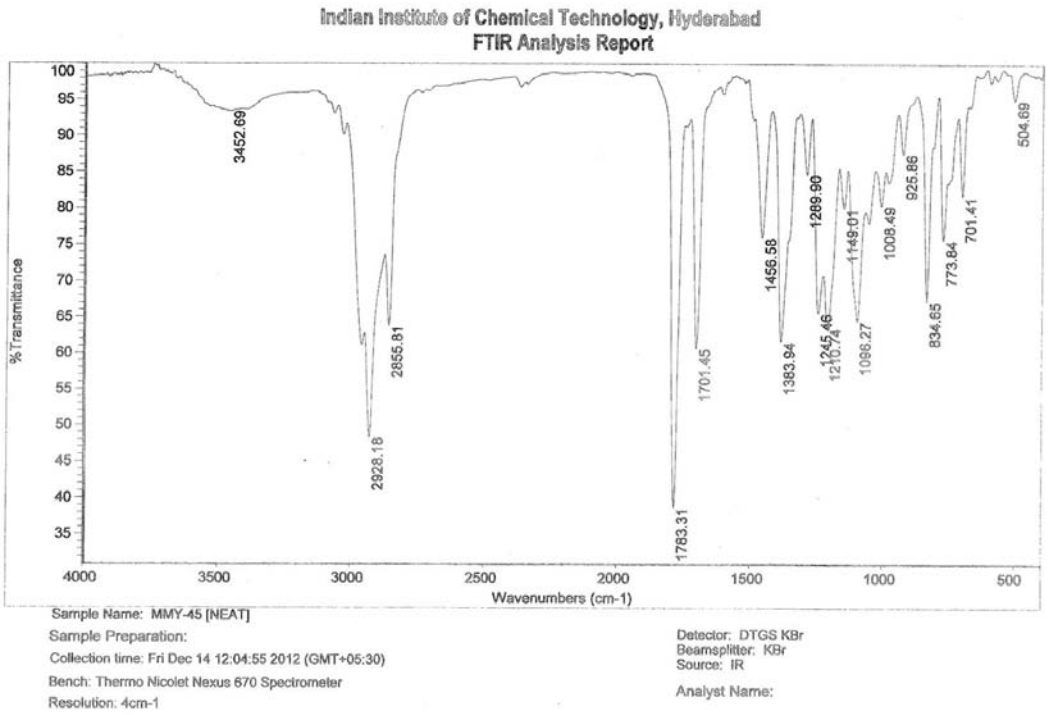
HRMS SPECTRUM OF COMPOUND **67**



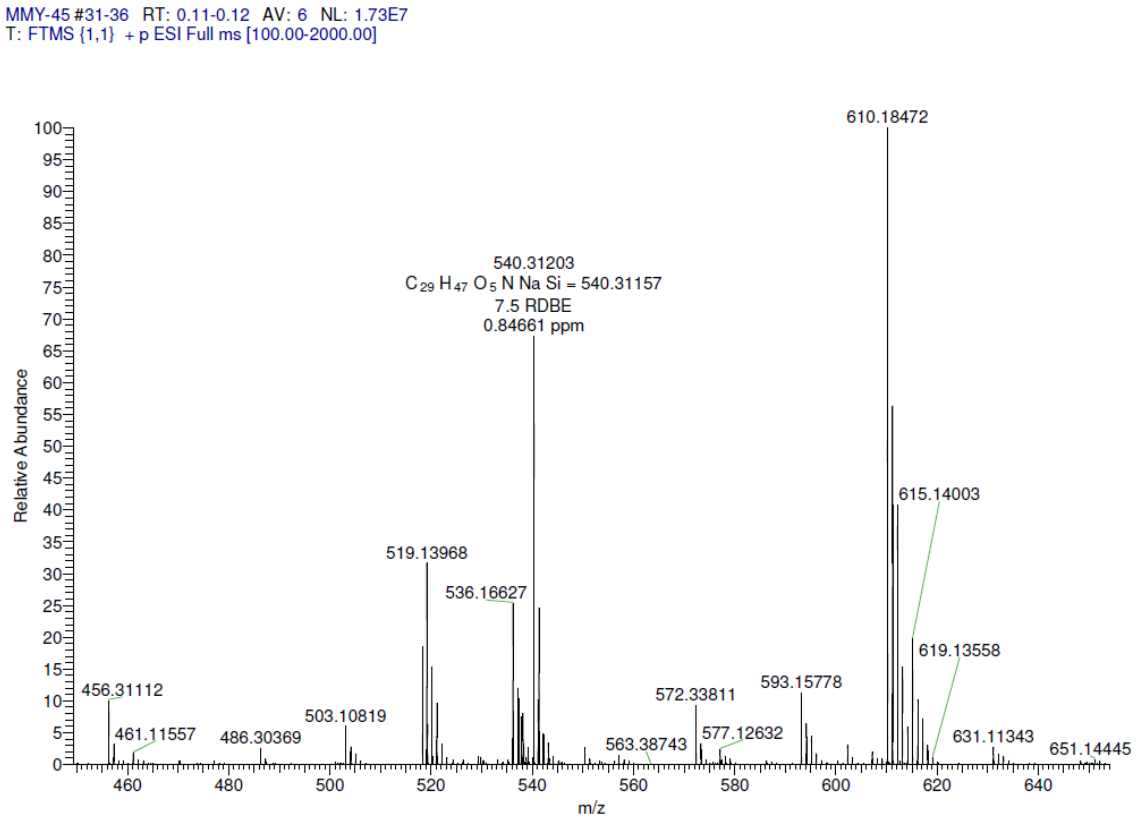
^{1}H NMR SPECTRUM OF COMPOUND **91**



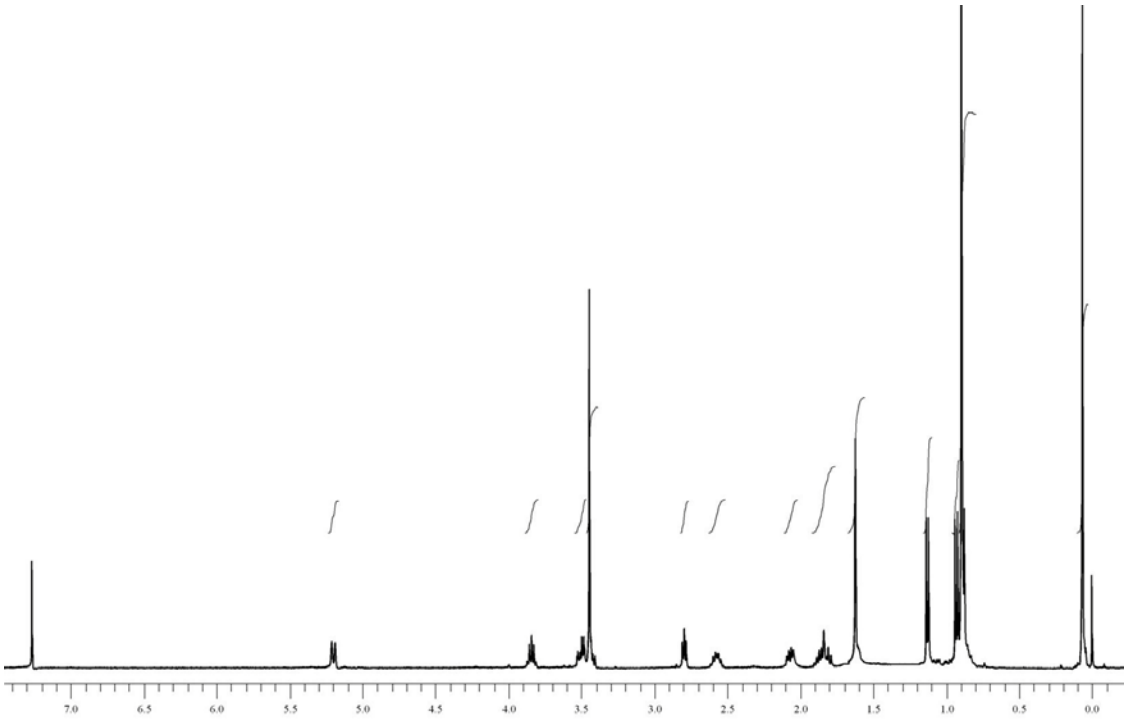
^{13}C NMR SPECTRUM OF COMPOUND **91**



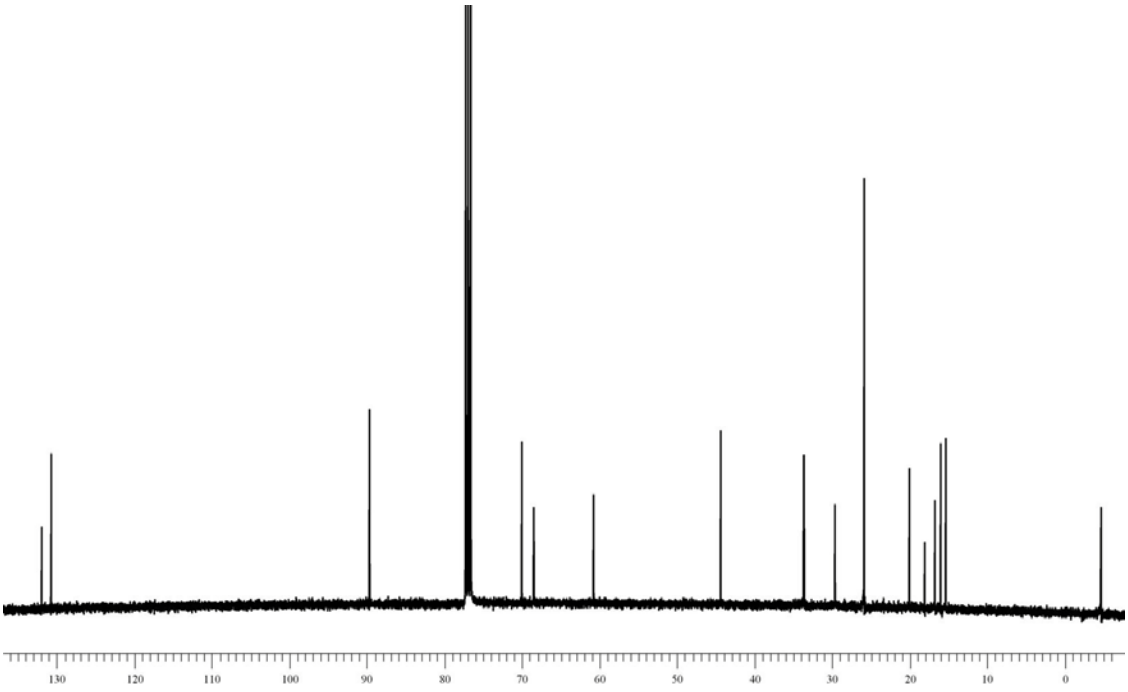
FTIR SPECTRUM OF COMPOUND **91**



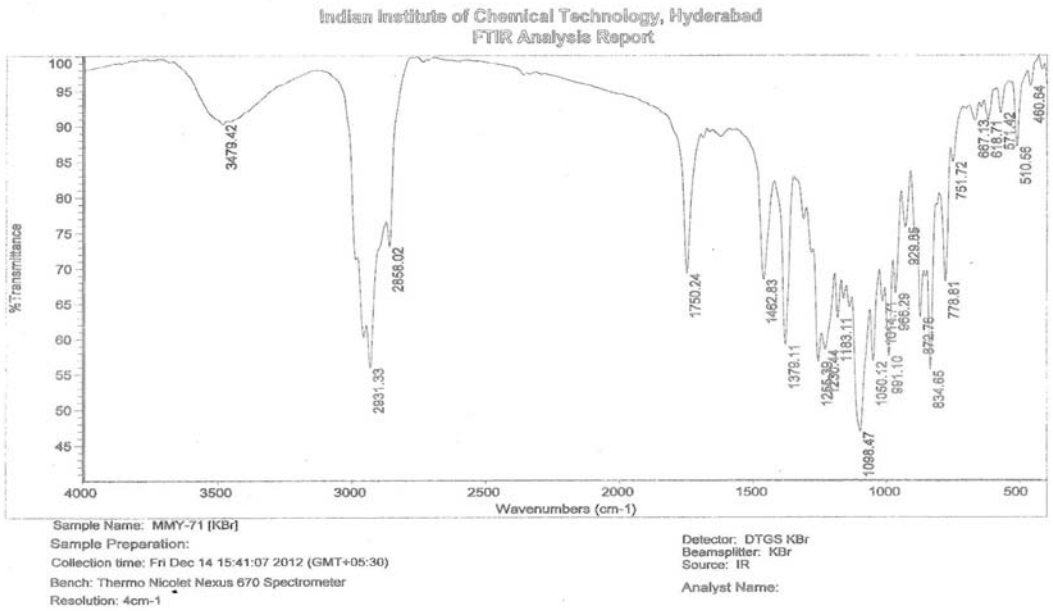
HRMS SPECTRUM OF COMPOUND **91**



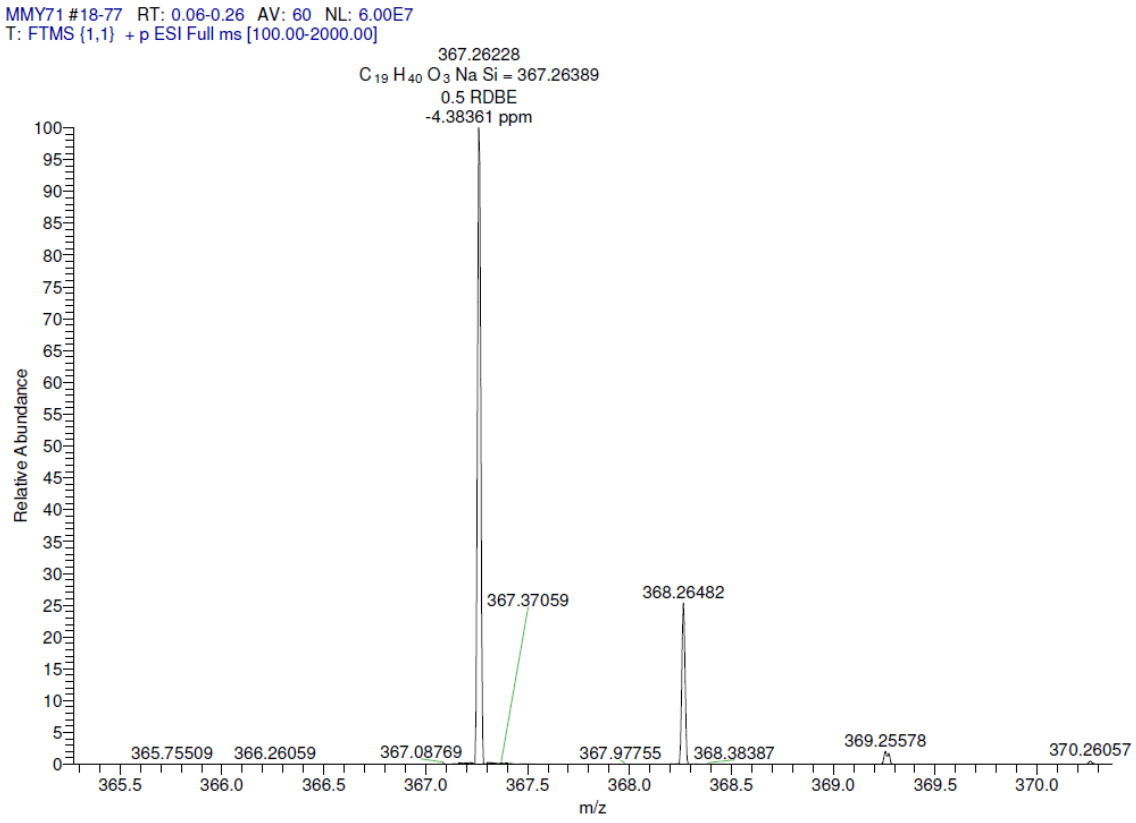
^{1}H NMR SPECTRUM OF COMPOUND **92**



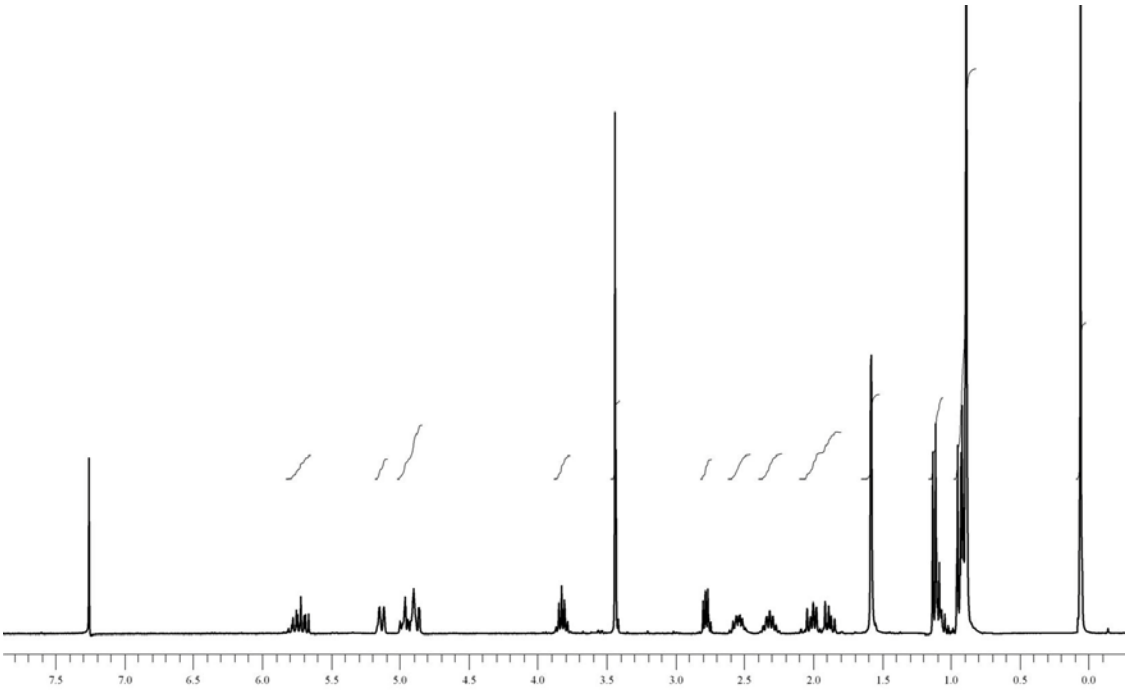
^{13}C NMR SPECTRUM OF COMPOUND **92**



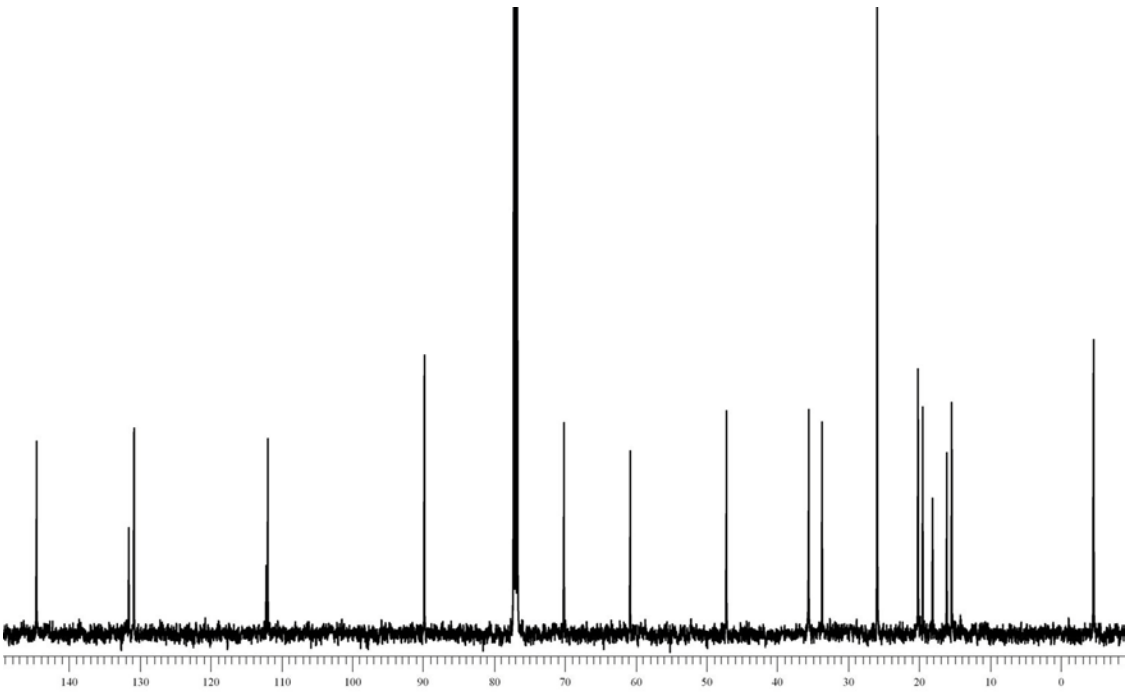
FTIR SPECTRUM OF COMPOUND **92**



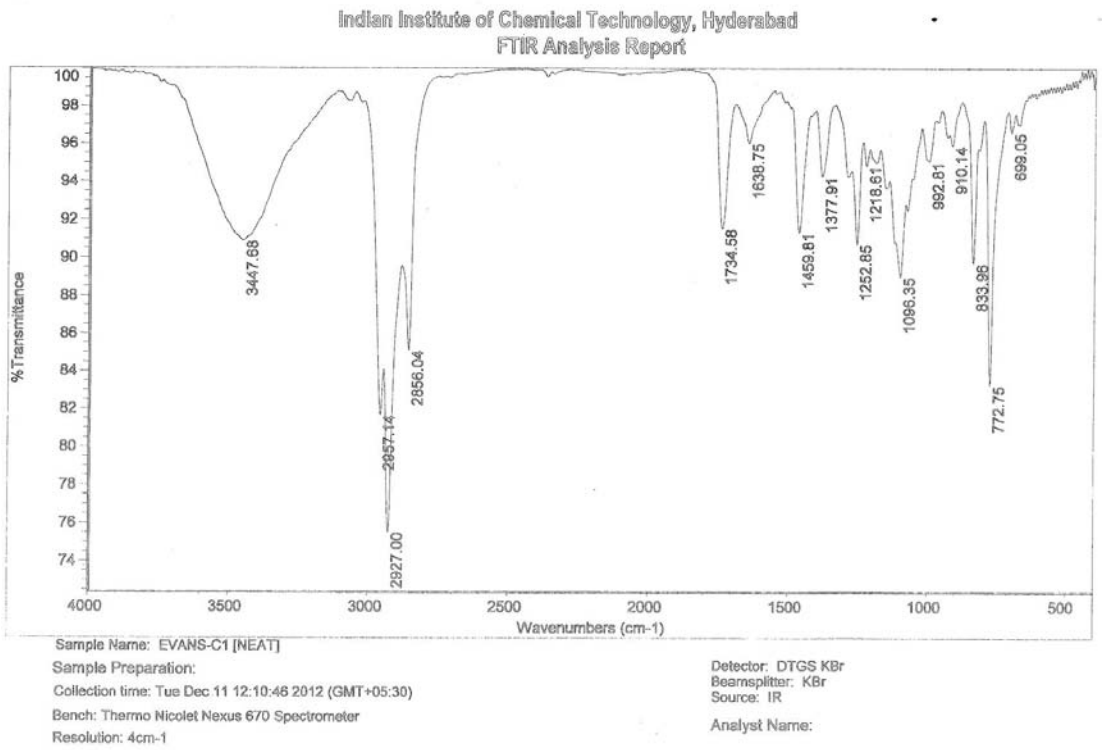
HRMS SPECTRUM OF COMPOUND **92**



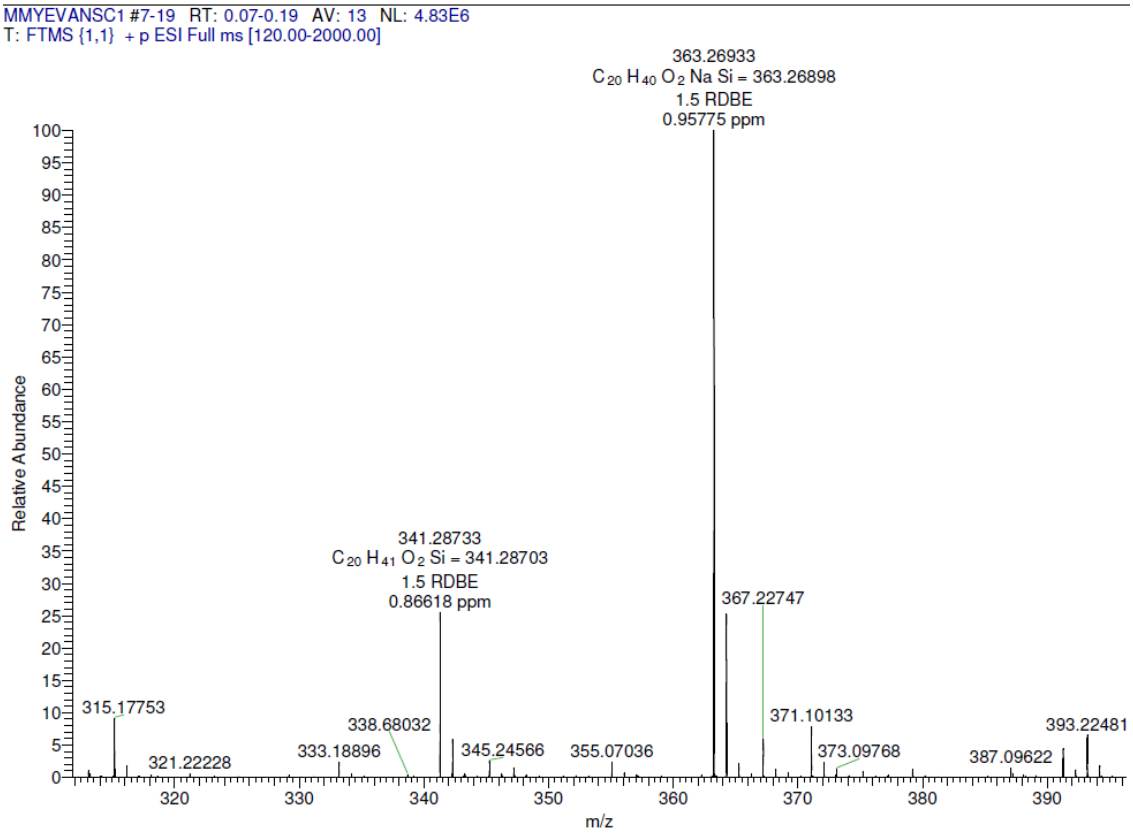
^{1}H NMR SPECTRUM OF COMPOUND **63**



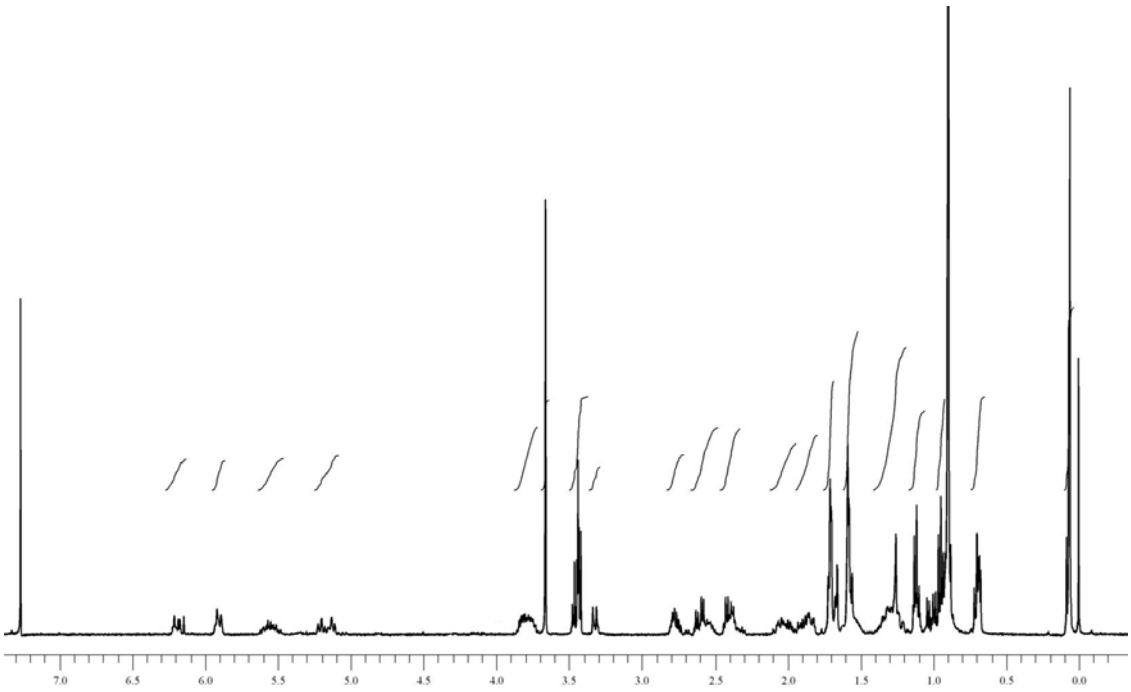
^{13}C NMR SPECTRUM OF COMPOUND **63**



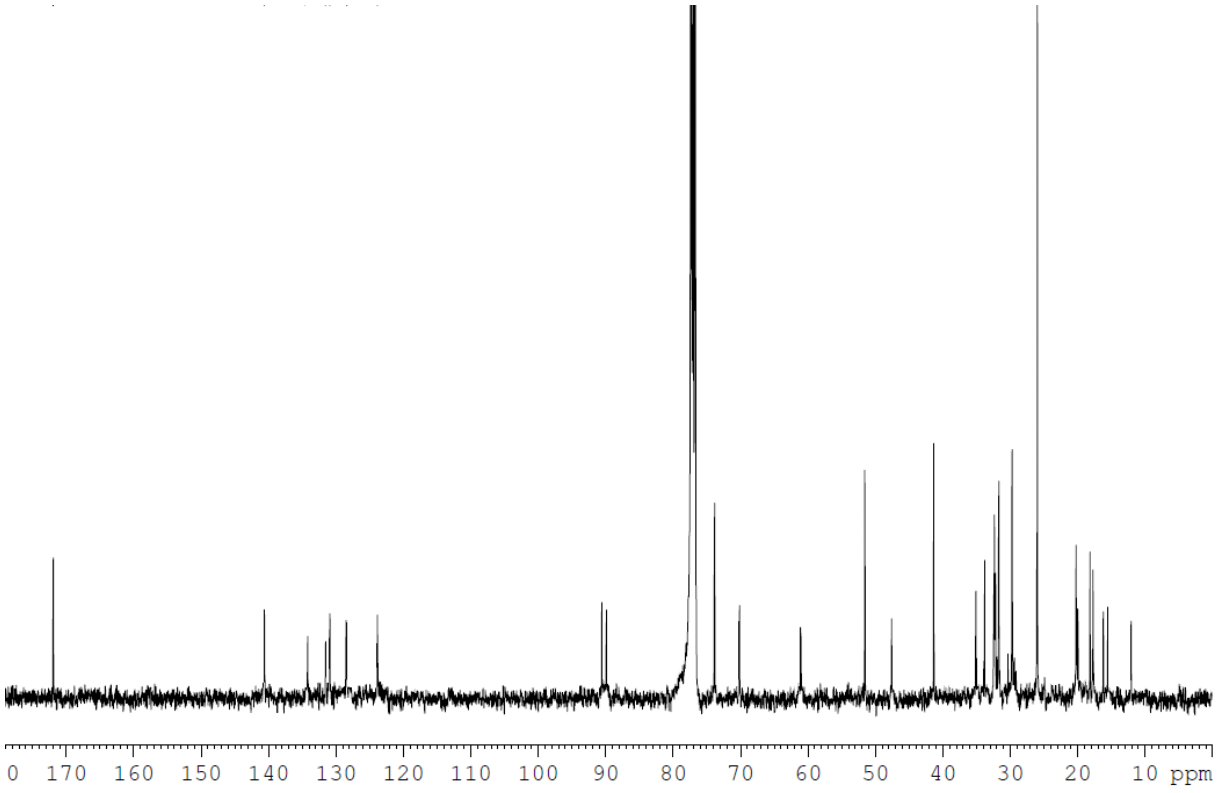
FTIR SPECTRUM OF COMPOUND **63**



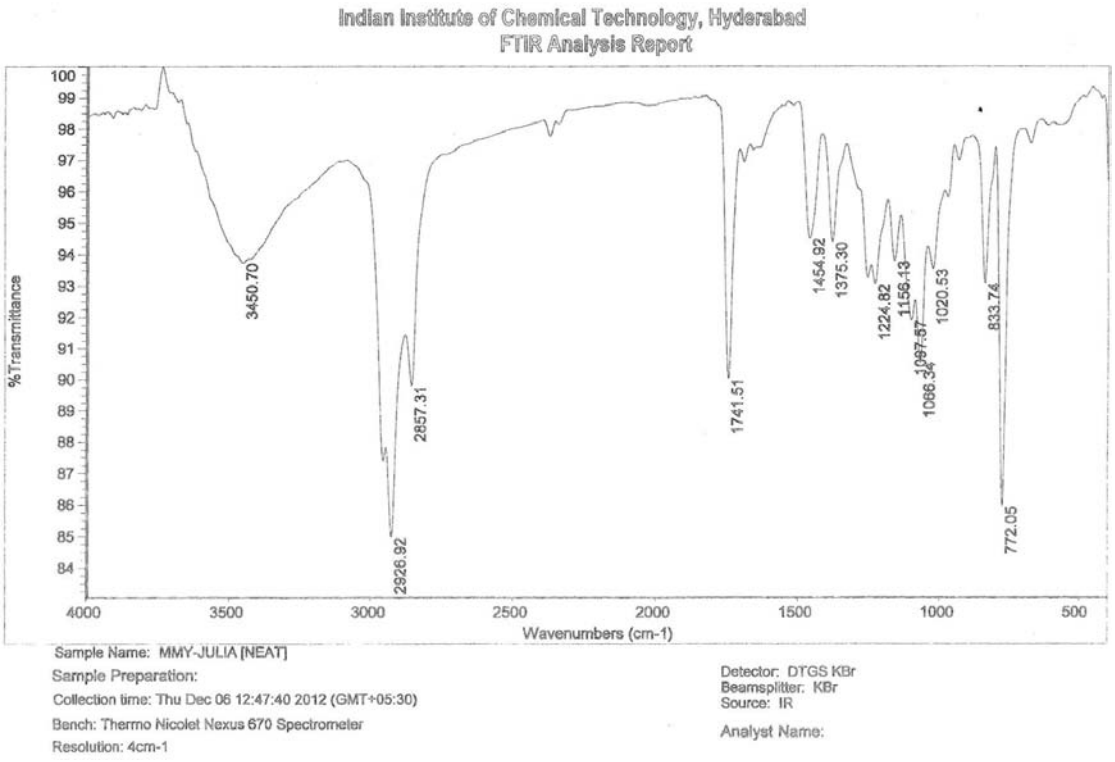
HRMS SPECTRUM OF COMPOUND **63**



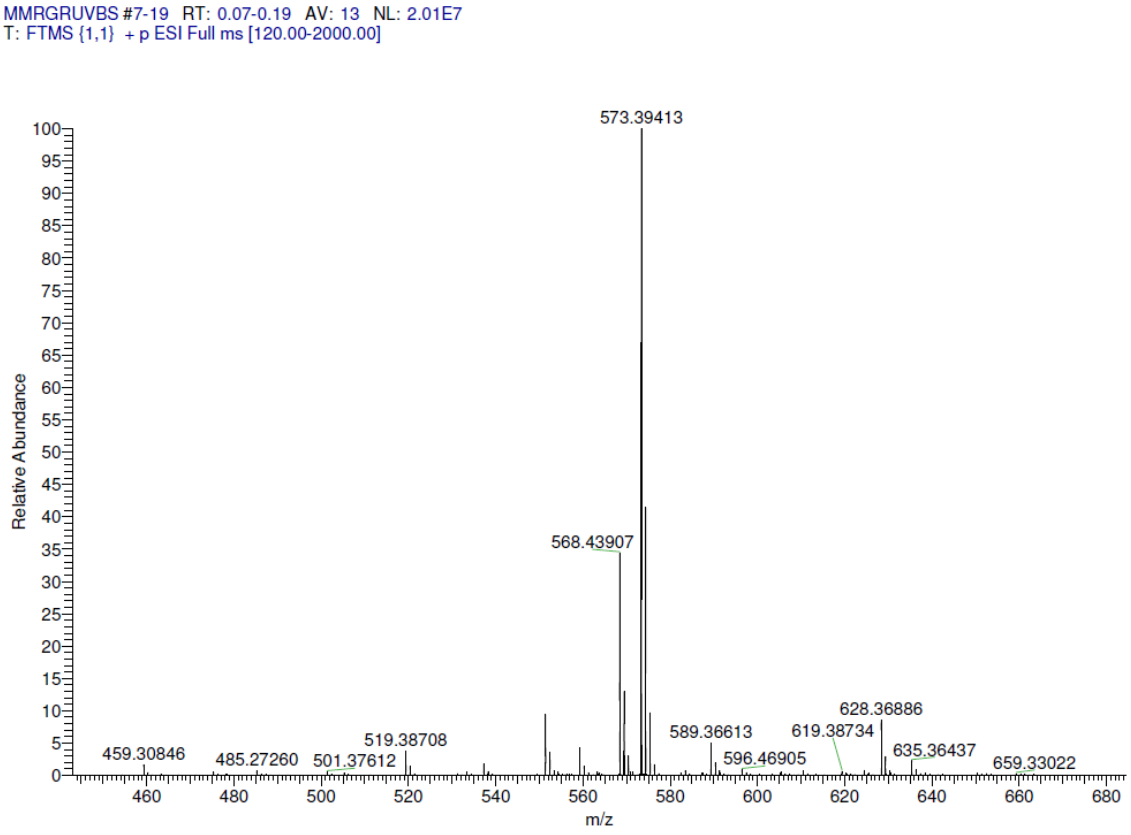
^{1}H NMR SPECTRUM OF COMPOUND **61**



^{13}C NMR SPECTRUM OF COMPOUND **61**



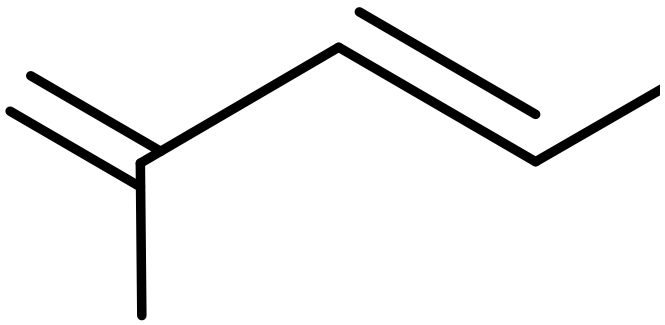
FTIR SPECTRUM OF COMPOUND **61**



HRMS SPECTRUM OF COMPOUND **61**

In the recent times, molecules bearing medium and large size lactone rings have attracted considerable attention from synthetic chemists due to their increasing range of biological properties. Though many macrolides have complex structures with high substitution, simple macrolides also possess important biological properties which make them worth exploring.[1] Most of these macrolides are isolated form fungi and marine sponges.

Naturally occurring macrodiolides are primarily divided into two groups: compounds having a C2 symmetry and a 16-membered ring derived by a head-to-tail dimerization of two identical C_8 hydroxy acid subunits such as Pyrenophorol (**1**),[2] Pyrenophorin(**2**),[3] tetrahydropyrenophorol (**3**),[4] Vermiculin (**4**)[5] etc and those having an unsymmetrical heterodimeric 14-membered ring like Colletallol (**5**)[6] and Grahamimycin A_1(**6**).[7]



Scheme 1 : Few common macrodiolides.

ISOLATION OF PYRENOPHOROL

Pyrenophorol (**1**) was first isolated in 1969 by Sigg *et al* from the plant pathogenic fungus *Byssachlamys nivea*[2a]. Shortly later, in 1971, this macrolide was re-isolated from the culture filtrates of *Stemphylium radicinum*[2b] by Grove et al. In 1996, Kind et al isolated pyrenophorol from the imperfect fungus *Alternaria alternata* and named it as helmidiol on the basis of its pronounced anthelmintic properties.[8] Most

recently in 2007, pyrenophorol was isolated from the ethyl acetate culture extract of an endophytic *Phoma* sp.[9]

The structure and absolute configuration of (–)-pyrenophorol was established by Zwanenberg group by means of total synthesis.[10] Later the relative stereochemistry of pyrenophorol was confirmed by X-ray diffraction analysis.[11]

Biological activity:

Pyrenophorol and its related macrolides exhibited a significant inhibitory effect on prolyl peptidase (PEP) enzyme with an IC_{50} value of 66 µM.[12]

Prolyl endopeptidase (PEP) is an enzyme that plays an important role in maturation and degradation of neuropeptides. Currently, new drugs are required that can improve memory by delaying the neurodegenerative process in conditions such as Alzheimer's disease.

Pyrenophorol, an inhibitor of prolyl endopeptidase, may improve memory by blocking the metabolism of endogenous neuropeptides and has possible potential as antiamnesiac, memory enhancing drug.

Pyrenophorol also showed *in vivo* anthelmintic activity against the infective stages of the abomasums nematode, *Haemunchus cortortus*, which is one of the most common pathogenic parasites.[8]

Pyrenophorol was moderately active against the fungus *Microbotryum violaceum*,[4] which is an obligate parasite on most of the plants of Carylophyllaceae family. It is also active against the alga *Chlorella fusca*, and the bacteria *Escherichia coli* and *Bacillus megaterium*.[13]

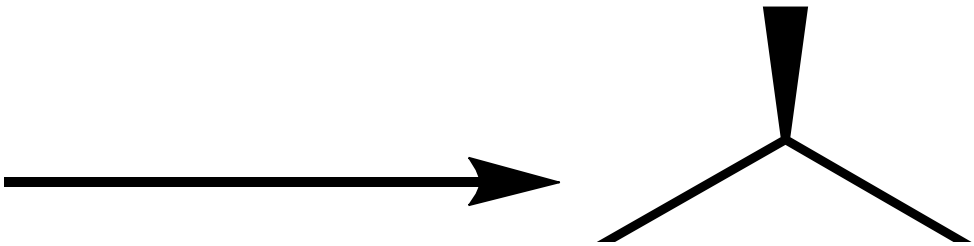
PREVIOUS SYNTHETIC APPROACHES

Herein, a brief account of the previous works carried out on the total synthesis of Pyrenophorol by various groups has been documented.

Zwanenburg approach

Scheme 2 : Retrosynthetic approach of 1

Zwanenburg *et al*,[10] reported the first stereoselective synthesis of (–)-pyrenophorol (**1**) using the photo induced rearrangement of an α,β-epoxy diazomethyl ketone to 4-hydroxy-2-alkenoate as the key step. Their synthetic approach was based on the two successive lactonisation steps of acid **7**, which could be in turn obtained from the allylic alcohol **8**.



Scheme 3 : Reagents and conditions:

A. L-(+)-DET, *t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, 77%; B. RuO_4, $CH_3CN:CCl_4:H_2O$ = 2:2:3, ClCOO*i*-Bu, Et_3N, CH_2N_2, 63%; C. *hv*, MeOH, TBDMSCl, Imidazole, DMF, 60% ; D. K_2CO_3, Allyl alcohol, 66%; E. NaOMe, MeOH, 0 °C, 87%; F. ethyl vinyl ether, PPTS, CH_2Cl_2, 98%; G. LiOH, $THF:H_2O$=1:1, 97%.

The key intermediate **9** was obtained from **8** by a chirality inducing Sharpless epoxidation, subsequent oxidation to the acid and further conversion into the corresponding epoxydiazomethyl ketone. Then a photo-induced rearrangement of this ketone gave the alkenoate which was protected as it silyl ether **7**.

Allylic ester **10** was obtained by transesterification of **7**, while the ethoxy ethyl protected acid **11** was obtained from **7** by the deprotection of 4-hydroxyl group, subsequent protection as ethoxy ethyl group and further hydrolysis of the ester.

Scheme 4 : Reagents and conditions:

A. DCC, DMAP, CH_2Cl_2, 75%; B. $MgBr_2$, Et_2O, 94%; C. $Pd(PPh_3)_4$, morpholin, THF, 77%; D. 2,6-$Cl_2C_6H_3C(O)Cl$, Et_3N, DMAP, toluene, reflux, 79%; E. n-Bu_4NF, THF, 95%.

The half-lactone **12** was obtained by the DCC coupling of fragments **10** and **11**, which on removal of the ethoxy ethyl and allyl protecting functions gave the seco acid **13**. Macrolactonisation and desilylation of **13** gave the target compound **1**.

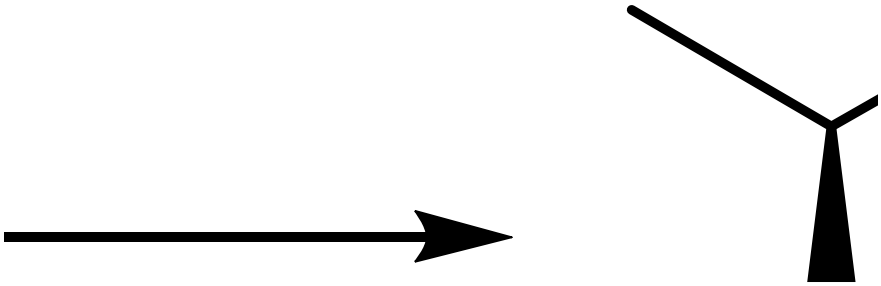
Kibayashi approach

Kibayashi and co-workers[14] reported the second enantioselective synthesis of (–)-pyrenophorol **1** by the macrolactonisation of the seco acid **14** under mitsunobu conditions. The seco acid **14** could be obtained from the enantiopure (R R)-diepoxide **15**.

Scheme 5 : Retrosynthetic approach of 1

Synthesis of the seco acid started with the addition of 1 eq of Vitride to the diepoxide **15** resulting in the corresponding epoxy alcohol which was protected as its silyl ether to furnish **16**. Then a further epoxide opening by Grignard reagent gave the unsaturated alcohol **17**.

O-mesylation of **17** followed by oxidation with RuO_4 gave the carboxylic acid which on treatment with $KHCO_3$ in aqueous methanol resulted in cyclisation to give the γ-lactone **18** as a single diastereomer. In this cyclization, the stereochemistry at C-4 was inverted due to SN_2 reaction.



Scheme 6 : Reagents and conditions:

A. Vitride (1 mol), THF, 0 °C to rt; B. TBDPSCl, DMAP, CH_2Cl_2, rt; C. Vinyl magnesiumchloride, CuI, THF, -15 °C; D. MsCl, Et_3N, CH_2Cl_2, 0 °C; E. RuO_4, CCl_4-CH_3CN-H_2O, rt; F. $KHCO_3$, MeOH-H_20, rt, 10 min; G. 1 M $LiN(SiMe_3)_2$ in THF, THF-HMPA, -78 °C, then PhSSPh, THF, -78 °C; H. 20% aq NaOH, MeOH, rt, then CH_2N_2, Et_2O 0 °C; I. *m*CPBA, -20 °C; J. Py (2 equiv), toluene, reflux; K. 2,3-dihydropyron, CSA. CH_2C1_2; L. 20% aq NaOH, MeOH, rt; M. *t*-Bu_4NF, THF, Reflux; N. Ph_3P. DEAD, Toluene-THF (10: 1). -25 °C, 10 h; O. TsOH-H_2O, MeOH, rt.

Treatment of the enolate of **18** with diphenyl disulfide followed by hydrolysis and esterification resulted in the α-phenylthio-γ-hydroxyester **19**. Oxidation of **19** to sulfoxide followed by pyrolysis gave the (E)-α, β-unsaturated hydroxy ester **20**. Tetrahydropyranyl protection and subsequent hydrolysis and desilylation furnished the seco acid **14**.

When the hydroxyl acid **14** was exposed to Mitsunobu conditions, macrolactonization took place with complete inversion of chirality at C-4 to give the dimerised product **21**, which on removal of O-protecting groups gave the target compound **1**.

The promising biological properties and structural features of Pyrenophorol **1** have prompted us to develop a new and efficient synthetic route for the total synthesis of this macrolide.

The retrosynthetic route is outlined in scheme **7**. (–)-Pyrenophorol (**1**) was foreseen to be synthesized by an intermolecular Mitsunobu cyclization of seco acid **22**, which in turn could be obtained by olefin metathesis of allylic alcohol **23** with methyl acrylate. The allylic alcohol **23** could be derived via the Wittig olefenation and Sharpless asymmetric epoxidation of the TBDPS ether **24** of the commercially available lactate ester.

Scheme 7 : Retrosynthetic approach of 1

The synthesis of pyrenophorol (**1**) began with the DIBAL-H reduction of the TBDPS ether **24** in dry CH_2Cl_2 at -78 °C that gave the corresponding aldehyde which was immediately subjected to 2-carbon Wittig olefination with $Ph_3PCHCOOEt$ in benzene under reflux conditions to give the unsaturated ester **25** in 92% yield over two steps. A 95:5 mixture of E:Z isomers were formed which could be separated by column chromatography. Formation of **25** was confirmed from its ^{1}H NMR spectrum which showed a dd at 6.92 and a doublet at 6.08 integrating for one proton each that correspond to the protons attached to the olefinic carbons. Their coupling constant of $J_{CH=CH}$ = 15.1 Hz ascertained the *trans* geometry of the olefin. ^{1}H NMR spectrum also showed the protons resonating at 4.09 as a quartet and at 1.25 as a triplet that correspond to the ester function. The ^{13}C spectrum also displayed the peaks corresponding to olefinic carbons at 151.0 and 119.1. Formation of **25** was further confirmed by ESI-MS which showed the $(M+H)^+$ peak at 383.

Reduction of the olefin **25** using $NaBH_4$ in the presence of $NiCl_2$ gave the saturated ester **26** in 90% yield. Formation of **26** was ascertained by the disappearance of signals at δ 6.92 and 6.08 in its ^{1}H NMR spectrum, and at 151.0 and 119.1 in its ^{13}C

NMR that correspond to the unsaturation. ESI-MS spectrum also showed the $(M+H)^+$ peak at 385, thereby confirming the reduction of **26**.

Scheme 8 : Reagents and conditions:

A. (i) DIBAL-H, CH_2Cl_2, -78 °C, 15 min; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 92% (2 steps); B. $NaBH_4$, $NiCl_2.6H_2O$, MeOH, 0 °C, 1 h, 90%; C. (i) DIBAL-H, CH_2Cl_2, -78 °C, 15 min; (ii) $Ph_3PCHCOOEt$, benzene, reflux, 1 h, 94% (2 steps).

Partial reduction of ester **26** with DIBAL-H in CH_2Cl_2 at -78 °C followed by another 2-carbon Wittig olefination of the resulting aldehyde with $Ph_3PCHCOOEt$ in benzene gave the unsaturated ester **27** in 94% yield (E:Z=95:5). Formation of **27** was confirmed by its ^1H NMR spectrum which displayed a multiplet in 6.81-6.92 region and a doublet at 5.73 corresponding to the protons attached to the olefinic carbons. ^{13}C spectrum too revealed the peaks at 149.1 and 121.1 corresponding to these olefinic carbons. The FTIR spectrum showed the carbonyl absorption frequency at 1721 cm^{-1} and the ESI-MS spectrum displayed the $(M+H)^+$ peak at 411 to confirm the product.

Scheme 9 : Reagents and conditions:

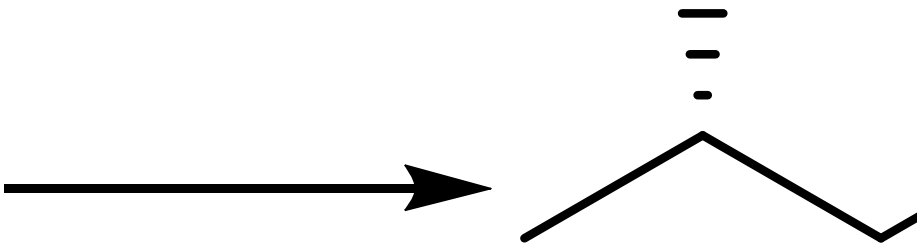
A. DIBAL-H, CH_2Cl_2, 0 °C, 1 h, 92%; B. (+)-DIPT, Ti(O*i*Pr)$_4$, Molecular sieves, TBHP, CH_2Cl_2, -20 °C, 7 h, 78%; C. (i) TPP, Imidazole, I_2, THF:CH_3CN (4:1), 30 min; (ii) Zn dust, MeOH, reflux, 12 h, 82% (2 steps).

DIBAL-H reduction of the unsaturated ester **27** in CH_2Cl_2 at 0 °C furnished the allylic alcohol **28** in 92% yield. Formation of **28** was confirmed by the disappearance of the peaks at 4.17 and 1.28 in its ^1H NMR spectrum and of absorption at 1721 cm^{-1} in its FTIR spectrum corresponding to the ester function. ESI-MS spectrum also confirmed this by displaying the $(M+H)^+$ peak at 369.

Allylic alcohol **28** was then subjected to Sharpless asymmetric epoxidation using (+)-DIPT, Ti(O*i*Pr)$_4$ and TBHP in anhydrous CH_2Cl_2 at -20 ^oC to get the epoxy alcohol **29** in 78% yield. Epoxidation was confirmed by the upfield shifting of the

multiplet in the ^{1}H NMR spectrum from 5.50-5.56 region to the 2.79-2.87 region. ^{13}C NMR spectrum also displayed a shift in resonances from 133.1 and 128.8 to 68.7 and 58.4 respectively. Further, ESI-MS spectrum showed a peak at 407 that corresponds to $(M+Na)^{+}$.

Epoxy alcohol **29** was then treated with TPP, imidazole and iodine to get the iodo compound which was immediately subjected to epoxide opening with Zn dust in methanol under refluxing conditions to furnish the allylic alcohol **23** in 82% yield over 2 steps. The structure of **23** was confirmed on the basis of ^{1}H NMR which showed two multiplets in 5.72-5.87 region and 5.04-5.21 region that correspond to the protons of the terminal olefin. ^{13}C NMR spectrum too showed the presence of olefinic carbons as expected, while the ESI-MS spectrum displayed the $(M+H)^{+}$ peak at 369.



Scheme 10 : Reagents and conditions:

A. Methyl acrylate, Grubbs IInd generation catalyst, CH_2Cl_2, reflux, 24h, 78%; B. (i) 3,4-dihydropyran, CSA, CH_2Cl_2, rt, 1h, 88%; (ii) 20% aq. NaOH, MeOH, rt, 30 min, 85%; C. Bu_4NF, THF, 60 °C,2h, 90%.

Allylic alcohol **23** was subjected to olefin cross metathesis with methyl acrylate using Grubbs IInd generation catalyst in CH_2Cl_2 under reflux conditions to give the coupled enoate **30** in 78% yield. Use of Grubbs Ist generation catalyst at this stage increased the reaction time and also reduced the yield of the product considerably. So the IInd generation catalyst was preferred for the cross metathesis. A negligible amount of *cis* isomer was formed which could be separated by column chromatography. Formation of **30** was confirmed by the ESI-MS spectrum which showed the $(M+H)^{+}$ peak at 427, while the ^{1}H NMR spectrum displayed the signals corresponding to the

internal olefin at 6.90 and 6.02 and those of methyl ester at 3.75. The FTIR spectrum too displayed strong absorption corresponding to the carbonyl stretching at 1724 cm^{-1}.

The hydroxyl group in the enoate **30** was protected as its tetrahydropyranyl ether with CSA and then subjected to basic hydrolysis with 20% aq. NaOH in MeOH to furnish the acid **32** in 85% yield. The disappearance of the signal due to the methyl ester in ^{1}H NMR and the appearance of signals due to the THP group confirmed the product. The ^{13}C NMR too showed the signals corresponding to the THP group, while the ESI-MS spectrum displayed the $(M-H)^{+}$ peak at 495.

Then the desilylation of **32** was carried out with Bu_4NF in THF to afford the seco acid 22 in 90% yield which was now ready for the key Mitsunobu cyslization. The ^{1}H and ^{13}C NMR spectra showed the absence of signals corresponding to the TBDPS group, while the ESI-MS spectrum displayed the $(M+Na)^{+}$ peak at 281, thereby confirming the desilylation.

Scheme 11 : Reagents and conditions:

A. Ph_3P, DEAD, toluene:THF (10:1), -25 °C, 24 h, 60%; B. PTSA, MeOH, rt, 30 min, 96%.

The stage was now set for the intermolecular Mitsunobu cyclisation of **22** which was carried out by Gerlach's procedure[15] using TPP and DEAD in toluene:THF (10:1) resulting in macrolactonisation with complete inversion of configuration at C-4 to give **33**. Formation of the cyclized product **33** was confirmed by the ESI-MS and ESI-HRMS spectra which showed the $(M+Na)^{+}$ peak at 503.2601 as compared to the calculated mass of 503.2620. The FTIR spectrum too was devoid of any strong absorption due to free OH groups, thereby confirming the macrolactonisation.

Finally, removal of the THP group in **33** with PTSA in methanol furnished the target macrolide **1** as a white solid in **96**% yield. The final product **33** was confirmed by the studying its ^{1}H NMR spectrum, which showed the absence of protons corresponding to THP protection and a strong absorption at 3382 cm^{-1} in FTIR spectrum proved the presence of free hydroxyl

groups. The spectral data and optical rotation of (-)-Pyrenophorol (**1)** were also compared with the literature values and were found to be identical in all respects.

CONCLUSION

In conclusion, we have developed an efficient new route for the synthesis of (-)-Pyrenophorol (**1**) featuring Sharpless asymmetric epoxidation, olefin cross metathesis and intermolecular Mitsunobu cyclization starting from the readily available lactate ester, following a simple an efficient route ensuring no compromise in the yield of the target molecule at any stage.

(S,E)-ethyl 4-(*tert*-butyldiphenylsilyloxy)pent-2-enoate (25):

DIBAL-H (11.6 mL, 11.6 mmol, 1.0M solution in toluene) was added dropwise to a solution of ester **24** (3.60 g, 10.51 mmol) in CH_2Cl_2 (45 mL) at -78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (20 mL) followed by vigorous stirring for 1h. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude aldehyde thus obtained was dissolved in benzene (50 mL) and $Ph_3PCHCOOEt$ (4.35g, 12.5 mmol) was added and the reaction mixture was refluxed for 1h. Then the reaction was quenched by adding H_2O (20 mL), and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, solvent removed *in vacuo* and the residue was purified by SiO_2 gel flash chromatography (1% EtOAc/hexane) to give **25** (3.66 g, 92% yield) as a colorless oil.

$[\alpha]_D^{25}$: −39.6 (*c* 2.0, $CHCl_3$);

IR (Neat) : υ_{max} 3071, 2965, 2931, 2860, 1736, 1473, 1427, 1376, 1267, 1177, 1135, 1110, 1029, 997, 822, 742, 701 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz,) : δ 7.66-7.73 (m, 4H), 7.33-7.44 (m, 6H), 6.92 (dd, *J* = 15.1, 4.7 Hz, 1H), 6.08 (d, *J* = 15.1 Hz, 1H), 4.40-4.44 (m, 1H), 4.09 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.04-1.08 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.4, 151.0, 135.6, 134.1, 129.8, 129.4, 127.5, 127.4, 119.1, 68.6, 60.2, 26.9, 23.2, 19.2, 14.2;

ESI-MS : *m/z*: 383 $(M+H)^+$;

(S)-ethyl 4-(*tert*-butyldiphenylsilyloxy)pentanoate (26):

To a solution of **25** (3.542 g, 9.27 mmol) in anhydrous MeOH (30 mL) at 0 °C was added $NiCl_2.6H_2O$ (0.66 g, 2.78 mmol) and $NaBH_4$ (0.70 g, 18.54 mmol) portion wise,

and was stirred at same temperature for 1h. Then the reaction mixture was filtered through celite, organic phase was concentrated and the residue was purified by SiO_2 gel flash chromatography (1% EtOAc/hexane) to give **26** 3.205 g, 90% yield) as a colorless oil.

$[\alpha]_D^{25}$: −6.2 (*c* 2.0, $CHCl_3$);

IR (Neat) : υ_{max} 3071, 2959, 2931, 2856, 1722, 1656, 1472, 1428, 1367, 1272, 1152, 1110, 1051, 980, 822, 740, 702 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.66-7.73 (m, 4H), 7.33-7.44 (m, 6H), 4.10 (q, *J* = 7.5 Hz, 2H), 3.92-3.94 (m, 1H), 2.38 (t, *J* = 7.5 Hz, 1H), 2.37 (t, *J* = 7.5 Hz, 1H), 1.78 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.03-1.08 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 173.6, 136.2, 134.0, 129.6, 129.4, 127.5, 127.4, 68.4, 60.0, 34.5, 30.0, 27.2, 23.0, 19.2, 14.1;

ESI-MS : *m/z*: 385 $(M+H)^+$;

(*S*,*E*)-ethyl 6-(*tert*-butyldiphenylsilyloxy)hept-2-enoate (27):

DIBAL-H (9.5 mL, 9.5 mmol, 1.0M solution in toluene) was added dropwise to a solution of ester **26** (3.083 g, 8.03 mmol) in CH_2Cl_2 (35 mL) at -78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (20 mL) followed by vigorous stirring for 1h. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude aldehyde thus obtained was dissolved in benzene (30 mL) and $Ph_3PCHCOOEt$ (3.436 g, 9.875 mmol) was added and the reaction mixture was refluxed for 1h. Then the reaction was quenched by adding H_2O (15 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, solvent removed *in vacuo* and the residue was purified

by SiO_2 gel flash chromatography (1% EtOAc/hexane) to give **27** (2.53 g, 94% yield) as a colorless oil.

$[\alpha]_D^{25}$: −19.4 (*c* 2.75, $CHCl_3$);

IR (Neat) : υ_{max} 2953, 2859, 1721, 1269, 1172, 1109, 1045, 738, 703, 618 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.64-7.69 (m, 4H), 7.33-7.46 (m, 6H), 6.81-6.92 (m, 1H), 5.73 (d, *J*= 15.6 Hz, 1H), 4.17 (q, *J*= 14.3, 7.1 Hz, 2H), 3.82-3.91 (m, 1H), 2.16-2.26 (m, 2H), 1.50-1.66 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H), 1.03-1.08 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 149.1, 149.0, 135.8, 129.6, 129.4, 127.5, 127.4, 121.1, 68.7, 60.3, 37.4, 27.8, 27.0, 23.1, 14.2;

ESI-MS : *m/z*: 411 $(M+H)^+$;

(*S*,*E*)-6-(*tert*-butyldiphenylsilyloxy)hept-2-en-1-ol (28):

A solution of compound **27** (2.30 g, 5.609 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and DIBAL-H (1M solution in toluene, 14.0 mL, 14.0 mmol) was slowly added over 10 min under N_2 atmosphere. After addition was complete, stirring was continued for 1h at 0 °C. The reaction mixture was then carefully quenched with saturated aqueous solution of potassium sodium tartrate solution (25 mL) and the mixture was stirred vigorously for 1h. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, the solvent removed *in vacuo* and the crude product was subjected to SiO_2 gel flash chromatography (10% EtOAc/hexane) to give the alcohol **28** (1.899 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$: −11.4 (*c* 2.5, $CHCl_3$);

IR (Neat) : υ_{max} 3380, 3069, 2930, 2857, 1665, 1464, 1427, 1375, 1188, 1107, 1050, 1003, 972, 821, 739, 703, 611, 507 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.63-7.70 (m, 4H), 7.34-7.45 (m, 6H), 5.50-5.56 (m, 2H), 3.98-4.03 (m, 2H), 3.79-3.89 (m, 1H), 1.99-2.09 (m, 2H), 1.40-1.63 (m, 2H), 1.00-1.11 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 135.9, 133.1, 129.4, 128.8, 127.5, 127.4, 68.9, 63.7, 38.7, 27.9, 27.0, 23.1, 19.2;

ESI-MS : *m/z*: 369 $(M+H)^+$;

((2S,3R)-3-((S)-3-(*tert*-butyldiphenylsilyloxy)butyl)oxiran-2-yl)methanol (29):

To a stirred suspension of 4Å molecular sieves (10 g) in dry CH_2Cl_2 (250 mL) under N_2 was added L-(+)- diisopropyl tartrate (0.127 mL, 0.606 mmol, 0.12 equiv) in one portion. The mixture was cooled to -20 °C and $Ti(O^iPr)_4$ (0.148 mL, 0.502 mmol, 0.1 equiv) was added in one portion. After 10 min, *t*-BuO_2H (8.69 M solution in CH_2Cl_2, 1.16 mL, 10.04 mmol, 2 equiv) was added dropwise over 5 min. The mixture was stirred at -20 °C for 30 min whereafter a solution of allylic alcohol **28** (1.858 g, 5.05 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over 30 min. The reactants were stirred at -20 °C for 7h and then quenched with H_2O (10 mL). EtOAc (100 mL) was added and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and washed with H_2O (50 mL), dried over anhydrous $MgSO_4$, and filtered. Following evaporation of the solvent *in vacuo*, the residue was purified by SiO_2 flash chromatography (15% EtOAc/hexane) to give **29** (1.51 g, 78%) as a colorless oil.

$[\alpha]_D^{25}$: −6.0 (*c* 1.0, $CHCl_3$)

IR (Neat) : υ_{max} 3424, 3069, 2927, 2856, 1740, 1463, 1427, 1376, 1262, 1107, 1047, 1002, 877, 821, 739, 703, 611 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.64-7.71 (m, 4H), 7.32-7.47 (m, 6H), 3.80-3.95 (m, 2H), 3.51-3.59 (m, 1H), 2.79-2.87 (m, 2H), 1.49-1.66 (m, 2H), 1.30-1.33 (m, 2H), 1.01-1.10 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 135.8, 129.6, 129.5, 127.5, 127.4, 69.0, 68.7, 61.6, 58.4, 35.2, 29.7, 27.0, 23.1, 19.2;

ESI-MS : *m/z*: 385 $(M+H)^+$;

(3S,6S)-6-(*tert*-butyldiphenylsilyloxy)hept-1-en-3-ol (23):

To a vigorously stirred solution of epoxy alcohol **29** (1.5 g, 3.90 mmol) in dry THF:CH_3CN (4:1, 30 mL) was added imidazole (1.59 g, 23.4 mmol), Ph_3P (2.93 g, 11.2 mmol) and I_2 (2.84 g, 11.2 mmol) in successive single portions. Stirring was continued at rt for 30 min whereupon Et_2O (20 mL) was added to precipitate out Ph_3P=O. The solids were filtered through a short pad of SiO_2 and the filtrate was concentrated *in vacuo* to obtain the crude iodo epoxide. To a vigorously stirred solution of this iodo epoxide in MeOH (25 mL) was added Zn dust (2.61 g, 40 mmol) and the reaction mixture was refluxed for 12h. After cooling to rt, it was filtered through a short pad of celite, washed well with MeOH and the filtrated was concentrated *in vacuo*. Purification of the residue by SiO_2 gel flash chromatography (10% EtOAc/hexane) furnished allylic alcohol **23** (1.08 g, 82%) as a colorless oil.

$[\alpha]_D^{25}$: −5.8 (*c* 1.0, $CHCl_3$);

IR (neat) : υ_{max} 3420, 3067, 2926, 2859, 1108, 871, 844, 819, 737, 704, 665, 610 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.63-7.72 (m, 4H), 7.34-7.45 (m, 6H), 5.72-5.87 (m, 1H), 5.04-5.21 (m, 2H), 4.16-4.23 (m, 1H), 3.46-3.56 (m, 1H), 1.46-1.81(m, 7H), 1.05 (s, 9H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 139.1, 135.6, 129.4, 127.5, 127.3, 115.7, 73.5, 71.2, 33.1, 31.4, 28.6, 26.9, 21.2;

ESI-MS : *m/z*: 369 $(M+H)^+$;

(4S,7S,E)-methyl 7-(*tert*-butyldiphenylsilyloxy)-4-hydroxyoct-2-enoate (30):

To a solution of **23 (**0.505 g, 1.372 mmol) in CH_2Cl_2 (50 mL), Grubbs II^{nd} generation catalyst (0.058 g, 0.067 mmol) was added and the reaction mixture was refluxed for 24 h under N_2 atmosphere. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2h under open air in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by SiO_2 flash chromatography (15% EtOAc/hexane) to give **30** as colorless syrup (0.456 g, 78% yield).

$[\alpha]_D^{25}$: −15.5 (*c* 0.35, $CHCl_3$);

IR (Neat) : υ_{max} 3447, 2925, 2855, 1724, 1657, 1461, 1432, 1376, 1272, 1168, 1108, 1045, 820, 738, 703, 611, 506 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.65-7.70 (m, 4H), 7.34-7.44 (m, 6H), 6.90 (ddd, *J*=1.5, 15.8 Hz, 1H), 6.02 (dt, *J*=1.5, 15.8 Hz, 1H), 4.18-4.26 (m, 1H), 3.91 (q, *J*=12.0, 6.0 Hz, 1H), 3.75 (s, 3H), 1.52-1.64 (m, 4H), 1.2 (d, *J*= 6.2Hz, 3H), 1.05 (s, 9H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 150.4, 150.3, 135.8, 129.6, 127.6, 127.4, 119.7, 71.1, 69.1, 51.6, 34.2, 31.6, 29.7, 27.0, 22.3;

ESI-MS : *m/z*: 427 $(M+H)^+$;

(4S,7S,E)-7-(*tert*-butyldiphenylsilyloxy)-4-(tetrahydro-2H-pyran-2-yloxy)oct-2-enoic acid (32)

3,4-Dihydropyran (0.414 g, 4.93 mmol) was added to a solution of **30** (0.42 g, 0.98 mmol) in CH_2Cl_2 (10 mL) followed by CSA (0.023 g, 0.1mmol) and the reaction mixture was stirred at rt for 1h. The solvent and excess dihydropyran were removed *in vacuo* and the crude product was purified by SiO_2 flash chromatography (5%

EtOAc/hexane) to give the protected alcohol, **31** as colorless syrup. This was then dissolved in MeOH (10 mL) and treated with 20% aqueous NaOH (2 mL) for 30 min. Then the reaction mixture was neutralized by the addition of dil HCl, MeOH was evaporated *in vacuo* and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was then subjected to SiO_2 gel flash chromatography (40% EtOAc/hexane) to give acid **32** (0.363 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$: −10 (*c* 0.65, $CHCl_3$);

IR (neat) : υ_{max} 3424, 2923, 2854, 1703, 1655, 1460, 1376, 1265, 1122, 1108, 1072, 1044, 1026, 980, 811, 771, 738, 705, 609 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.60-7.67 (m, 4H), 7.29-7.41 (m, 6H), 6.75-6.83 (m, 1H), 5.85 (d, *J* = 15.8 Hz, 1H), 4.49-4.61 (m, 1H), 4.14-4.20 m, 1H), 3.69-3.89 (m, 2H), 3.36-3.47 (m, 1H), 1.38-1.86 (m, 10H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.04 (s, 9H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.5, 150.4, 135.8, 129.5, 129.4, 129.3, 127.3, 127.2, 121.6, 95.9, 74.6, 74.3, 74.1, 69.1, 62.2, 62.1, 34.6, 30.9, 30.7, 30.5, 30.4, 29.6, 29.0, 27.0, 25.4, 25.3, 23.0, 19.2;

ESI-MS : *m/z*: 495 $(M-H)^+$;

(4S,7S,E)-7-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)oct-2-enoic acid (22):

To a solution of **32** (0.350 g, 0.709 mmol) in dry THF (40 mL) was added Bu_4NF (1.0 M in THF, 0.85 mL, 0.85 mmol) at 0 °C, and then the mixture was stirred for 2h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and

concentrated *in vacuo*. The crude product was purified by SiO_2 gel flash chromatography (70% EtOAc/hexane) to afford **22** (0.164 g, 90% yield) as a yellow liquid.

$[\alpha]_D^{25}$: +4.0 (*c* 0.5, $CHCl_3$);

IR (Neat) : υ_{max} 3424, 2923, 2852, 1702, 1656, 1459, 1378, 1266, 1122, 1072, 1026, 982, 810, 771 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 6.79-7.07 (m, 1H), 5.94-6.13 (m, 1H), 4.73-4.77 (m, 1H), 4.55-4.59 (m, 1H), 4.33-4.44 (m, 1H), 3.39 (t, *J*=7.36 Hz, 2H), 1.97-2.11 (m, 2H), 1.46-1.88 (m, 8H), 1.2 (d, *J*= 6.2Hz, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.5, 150.8, 120.1, 97.3, 74.8, 67.9, 60.3, 33.9, 30.6, 29.9, 25.2, 23.4, 19.2;

ESI-MS : *m/z*: 281 $(M+Na)^+$;

(3E,5S,8R,11E,13S,16R)-8,16-dimethyl-5,13-bis(tetrahydro-2H-pyran-2-yloxy)-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (33):

To a solution of **22** (0.130 g, 0.503 mmol) in dry toluene:THF (20:1, 80 mL), was added triphenylphosphine (0.660 g, 2.515 mmol) at -40 ^oC under argon atmosphere. To this mixture was added DEAD (0.437 g, 2.515 mmol) at same temperature and the reaction mixture was stirred at -25 °C for 24h. Then the solvent was removed *in vacuo* and the residue was subjected to SiO_2 gel flash chromatography (25% EtOAc/hexane) to afford **33** (0.072 g, 60%) as a yellow liquid.

$[\alpha]_D^{25}$: +7.5 (*c* 0.75, $CHCl_3$);

IR (neat) : υ_{max} 2924, 2854, 1749, 1718, 1647, 1459, 1373, 1271, 1073, 1271, 1073, 1026, 987, 868, 764 cm^{-1};

^1H NMR ($CDCl_3$, 300 MHz) : δ 6.54-6.81 (m, 2H), 5.78-5.88 (m, 2H), 4.99-5.09 (m, 2H), 4.65-4.70 (m, 1H), 4.45-4.49 (m, 1H), 3.99-4.18 (m, 4H), 3.69-3.85 (m, 1H), 3.36-3.47 (m, 1H), 1.72-1.84 (m, 4H), 1.41-1.56 (m, 4H), 1.12-1.32 (m, 18H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 165.0, 146.3, 122.8, 96.5, 73.9, 69.5, 64.0, 30.7, 29.7, 28.8, 25.3, 19.2, 18.4, 14.3, 14.1;

ESI-MS : *m/z*: 503 $(M+Na)^+$;

HRMS : calcd for $C_{26}H_{40}O_8Na$: 503.2620, found : 503.2601;

(3E,5S,8R,11E,13S,16R)-5,13-dihydroxy-8,16-dimethyl-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (1):

To a stirred suspension of **15** (0.026 g, 0.054 mmol) in CH_3OH (1.5 mL) was added PTSA (0.001 g, 0.005 mmol) and the reaction mixture was stirred at room temperature for 30 min. Then the solvent was evaporated *in vacuo* and the crude product was purified by SiO_2 gel flash chromatography (40% EtOAc/hexane) to afford **1** (0.015 g, 96% yield) as a white solid.

Mp : 136-138 ^oC;

$[\alpha]^{25}_D$: −3.2 (*c* 0.25, Acetone);

IR (KBr) : υ_{max} 3382, 2924, 2854, 1713, 1647, 1274, 1173, 1119 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 6.83 (dd, *J* =15.6 Hz, 2H), 5.89 (dd, *J* = 15.6 Hz, 2H), 5.01-5.10 (m, 2H), 4.16-4.24 (m, 2H), 2.48-2.69 (m, 2H), 1.53-2.01 (m, 8H), 1.20 (dd, *J* = 6.8 Hz, 6H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 165.0, 149.3, 122.0, 70.3, 69.7, 30.4, 28.8, 18.2;

ESI- MS : m/z : 335 $(M+Na)^+$;

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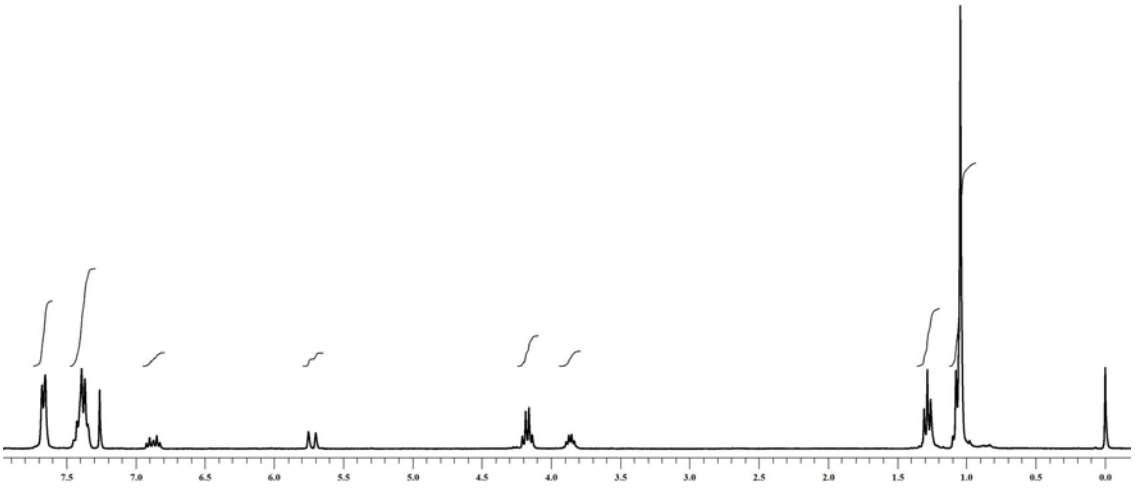

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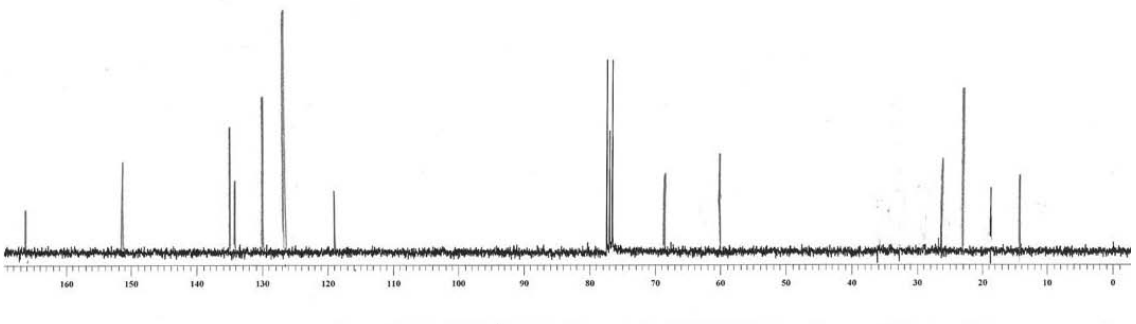

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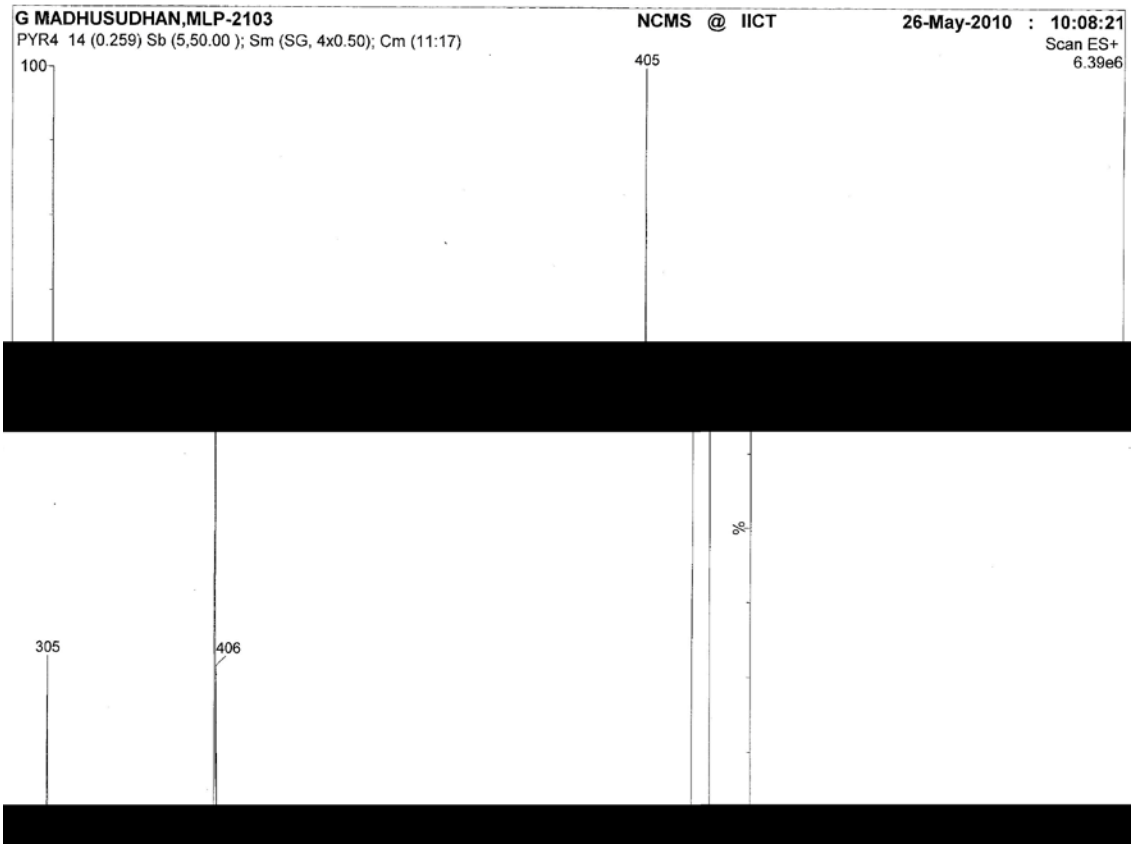

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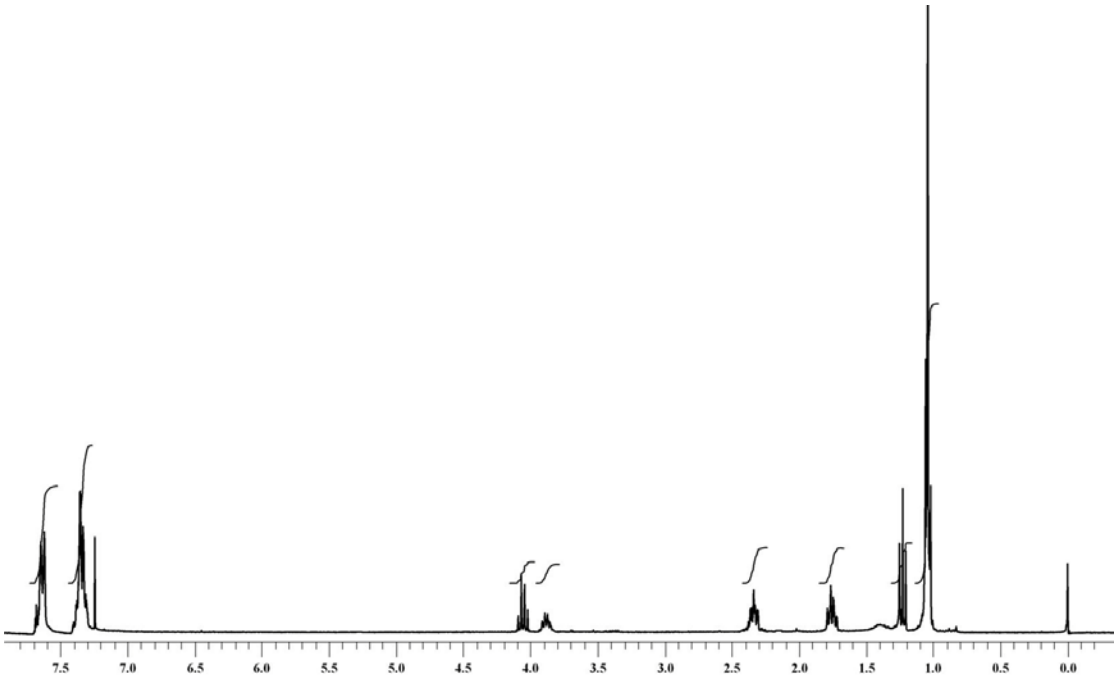

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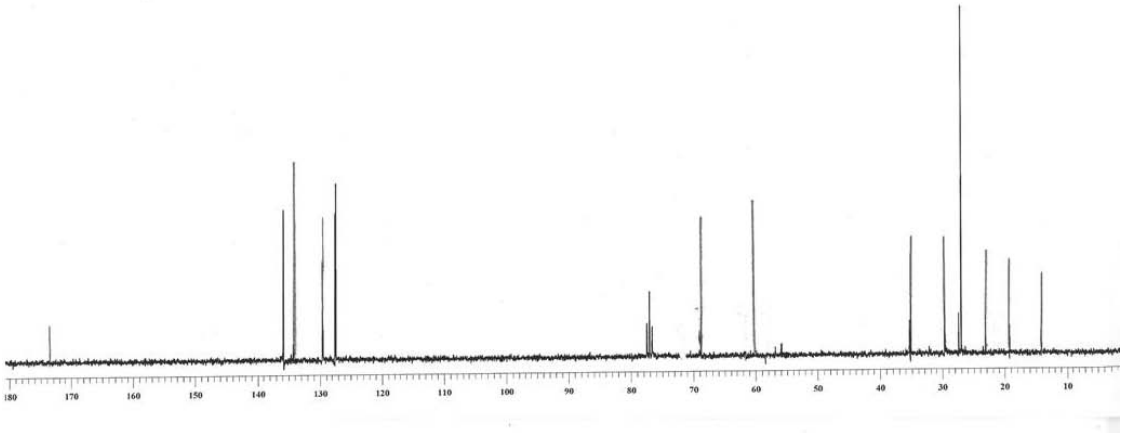

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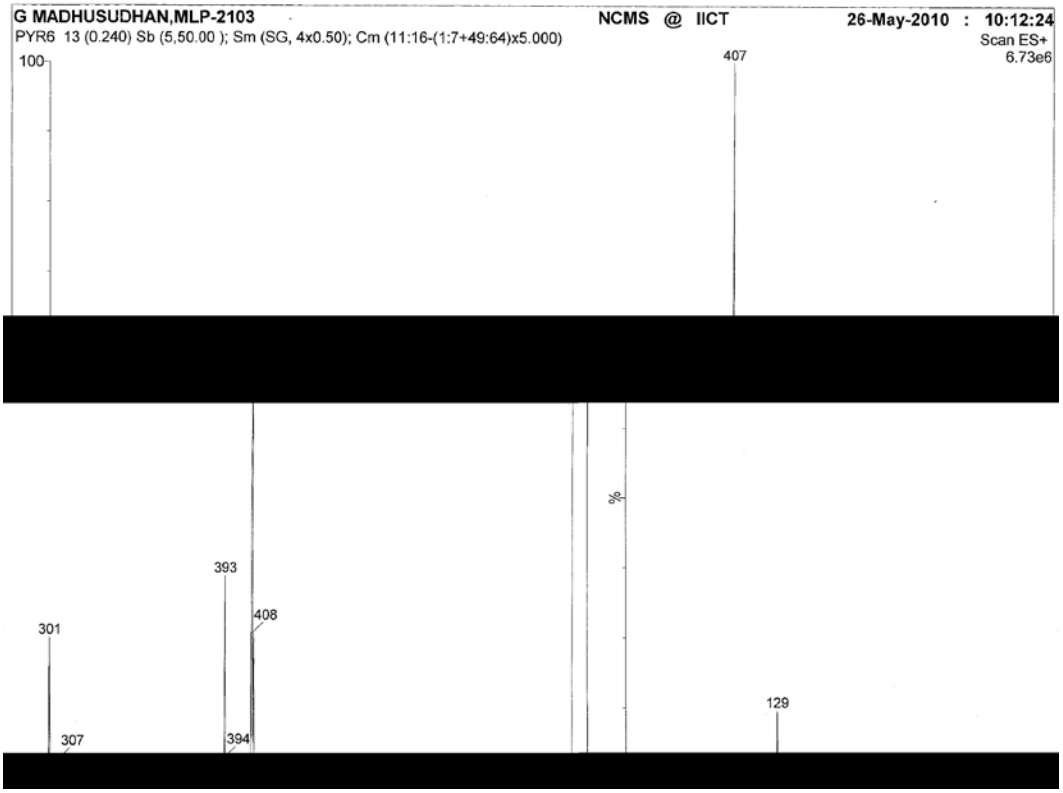

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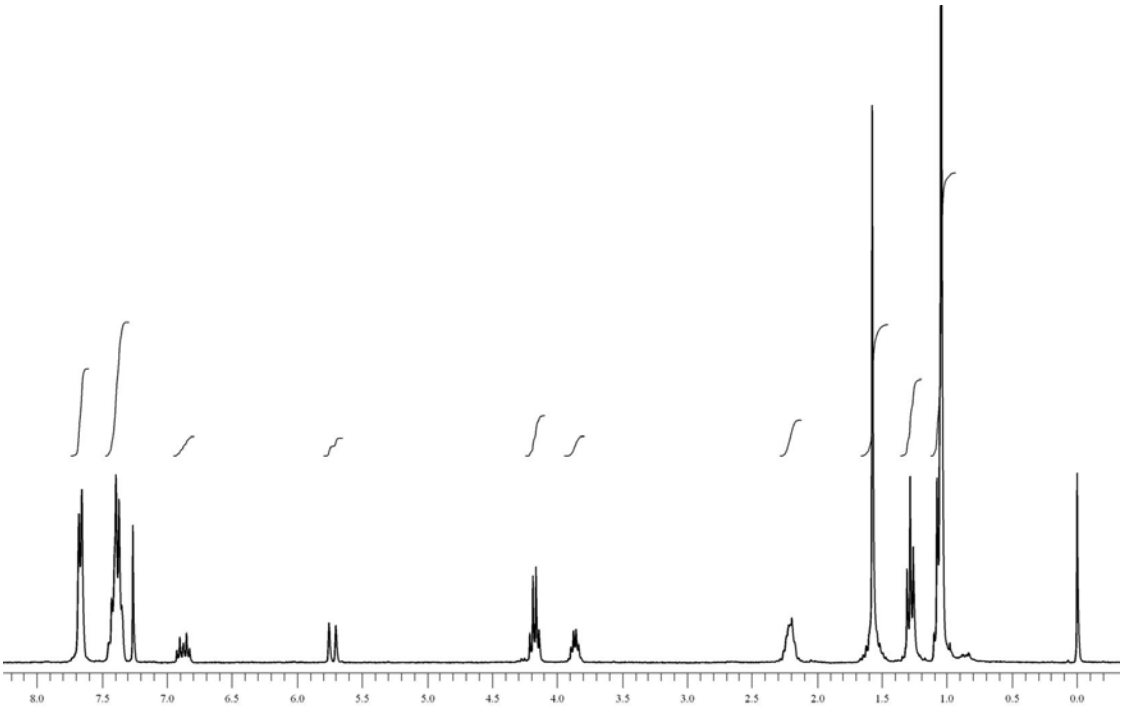

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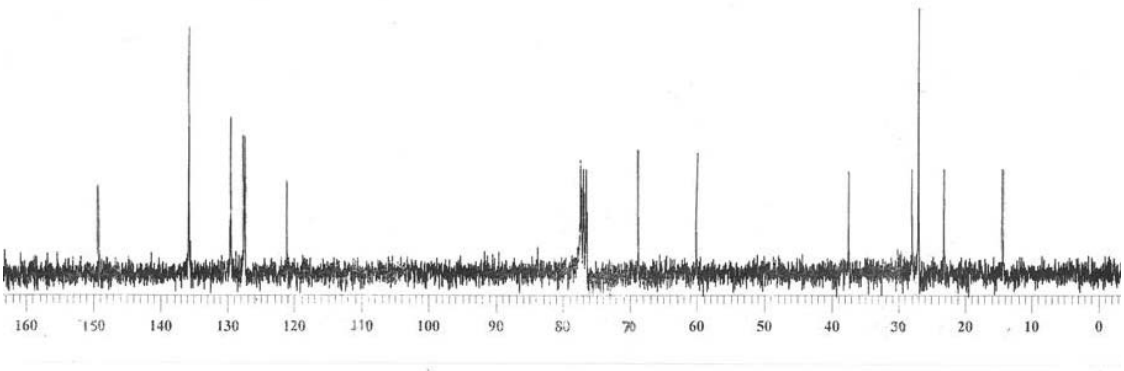

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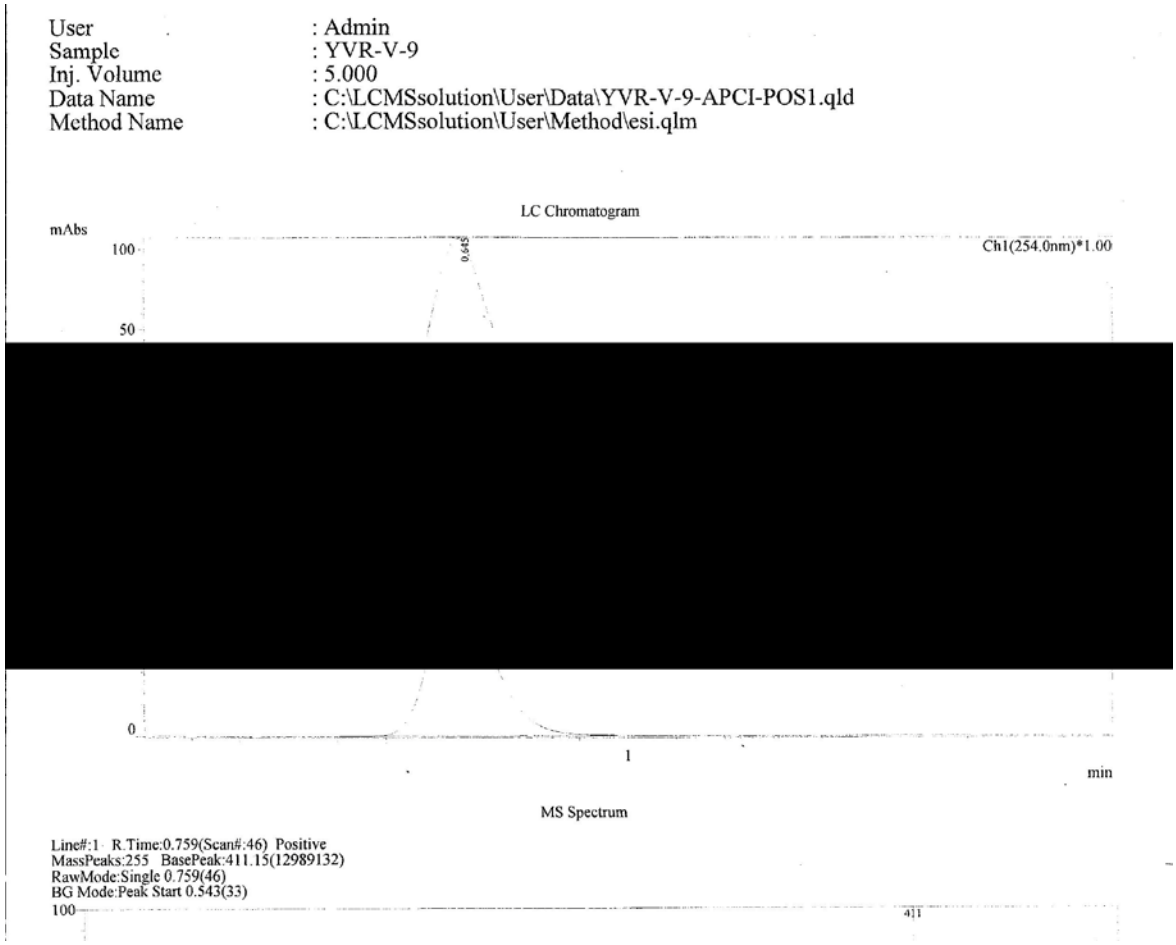

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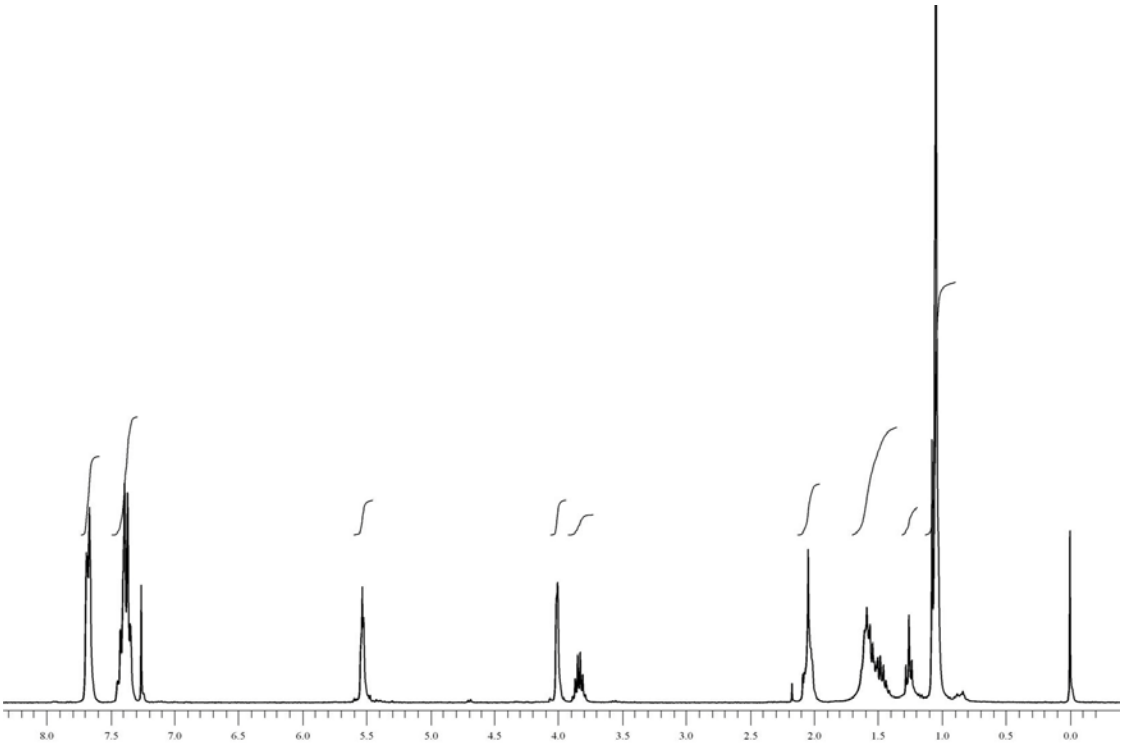

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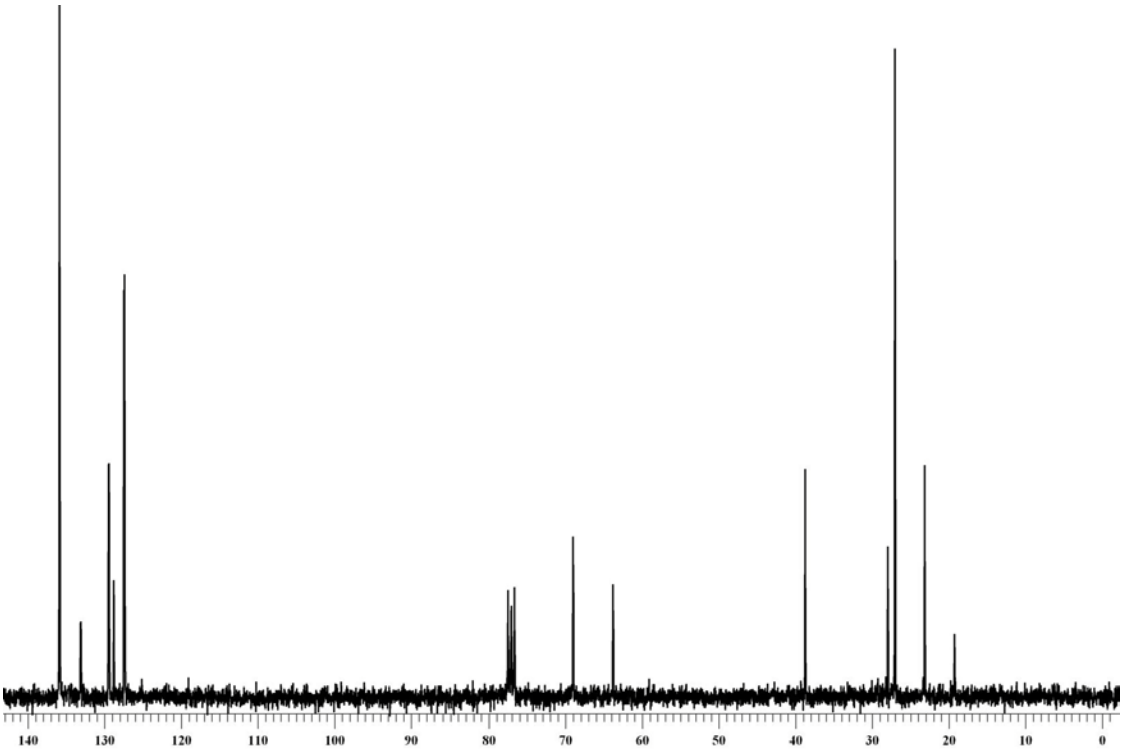

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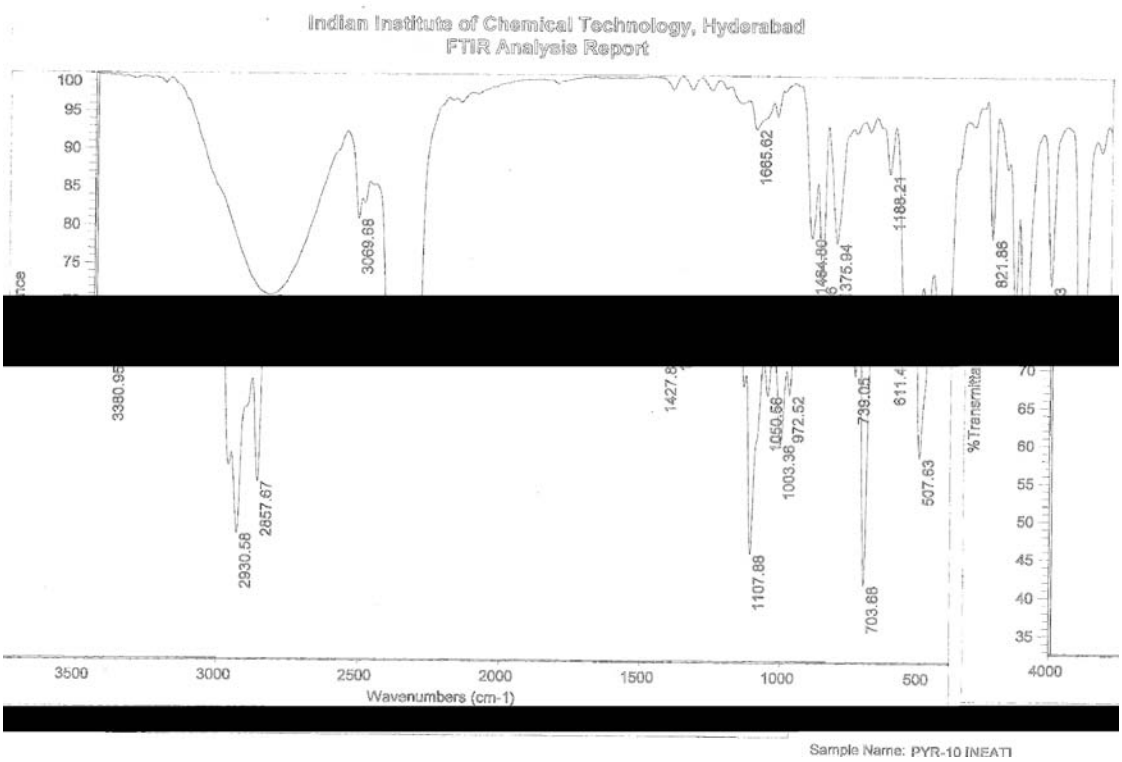

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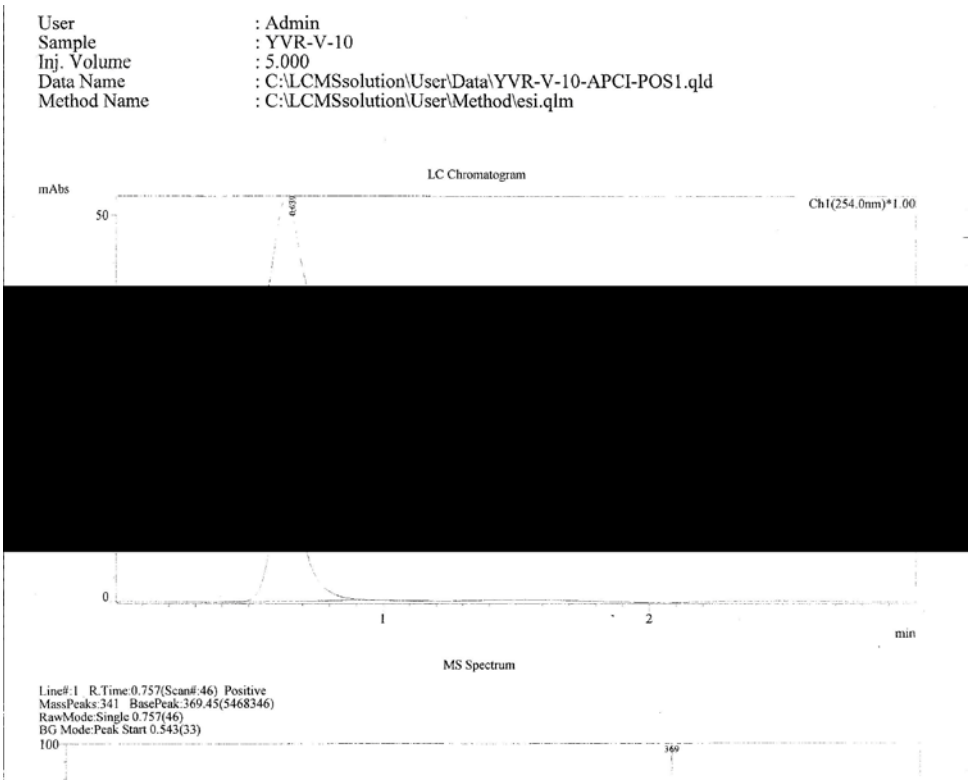

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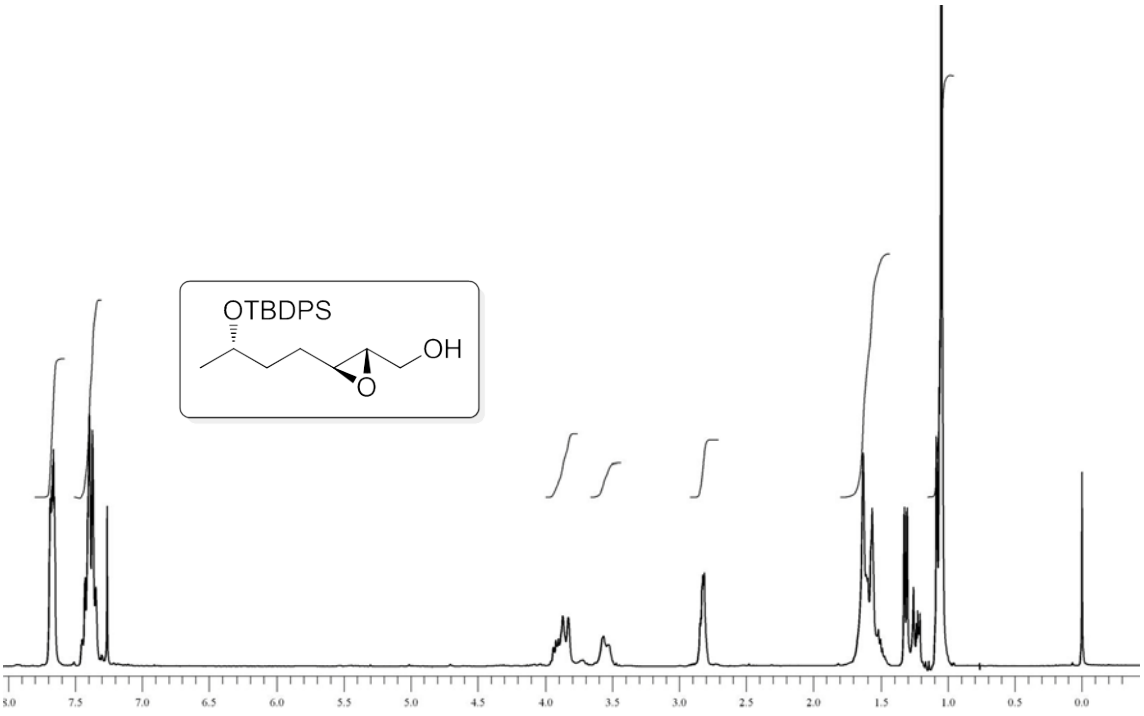

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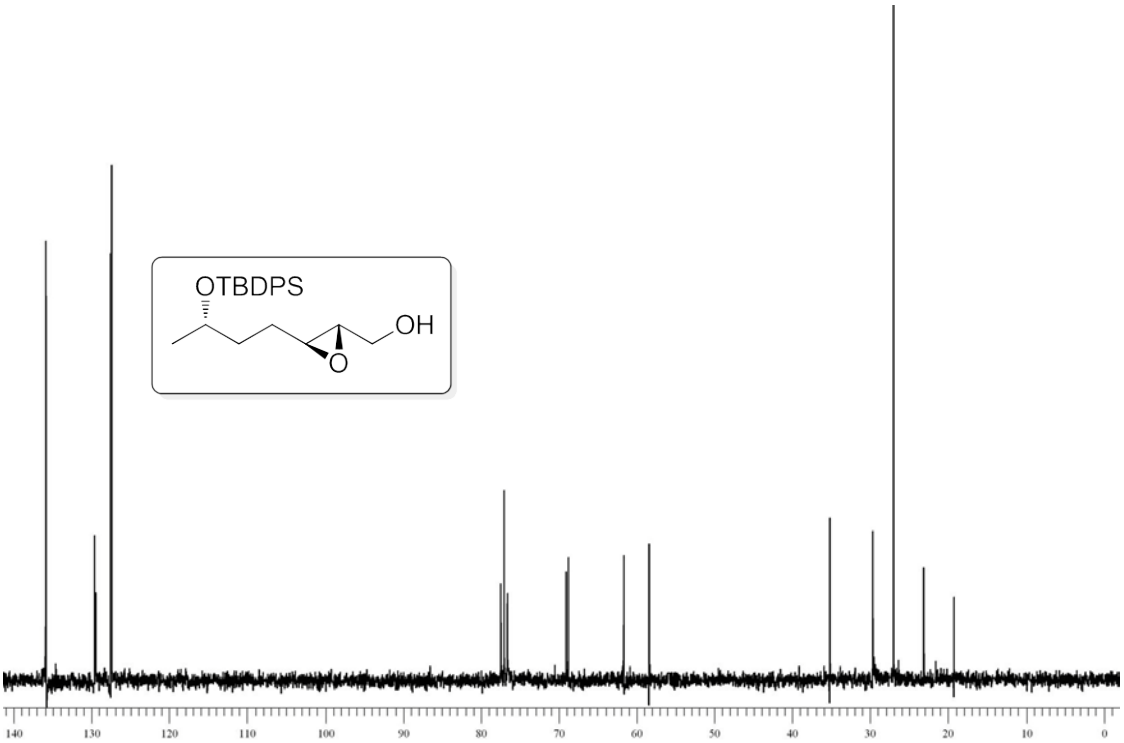
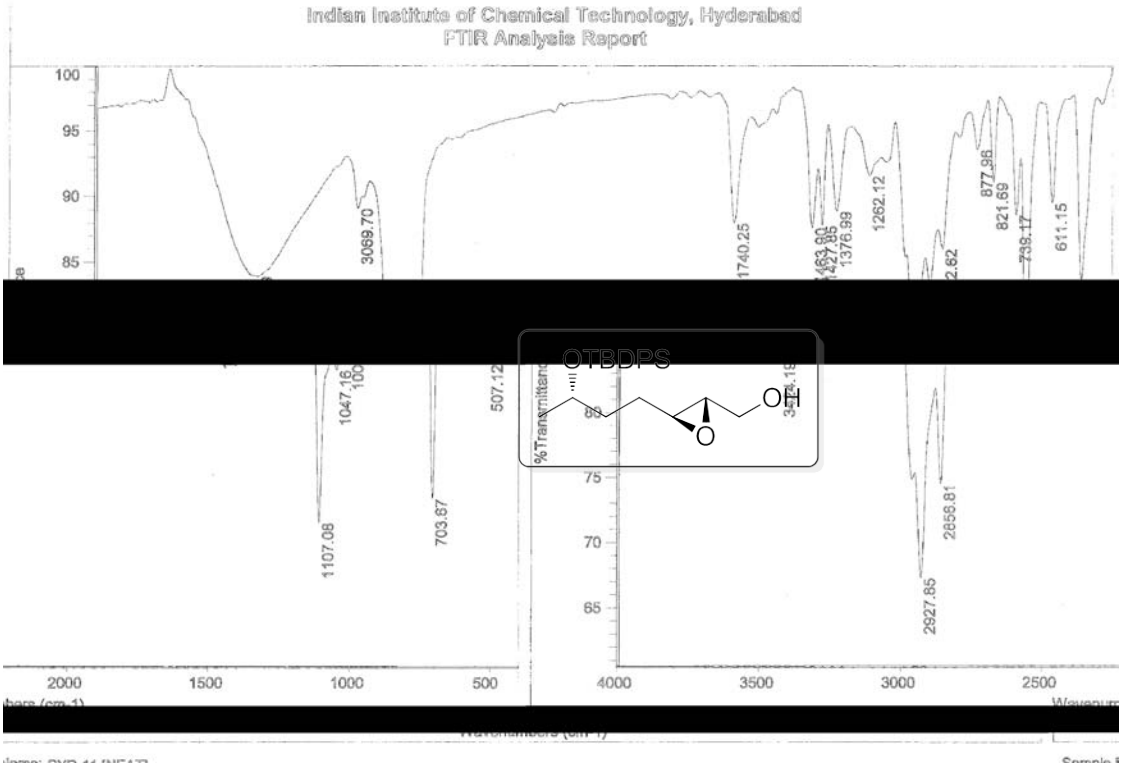
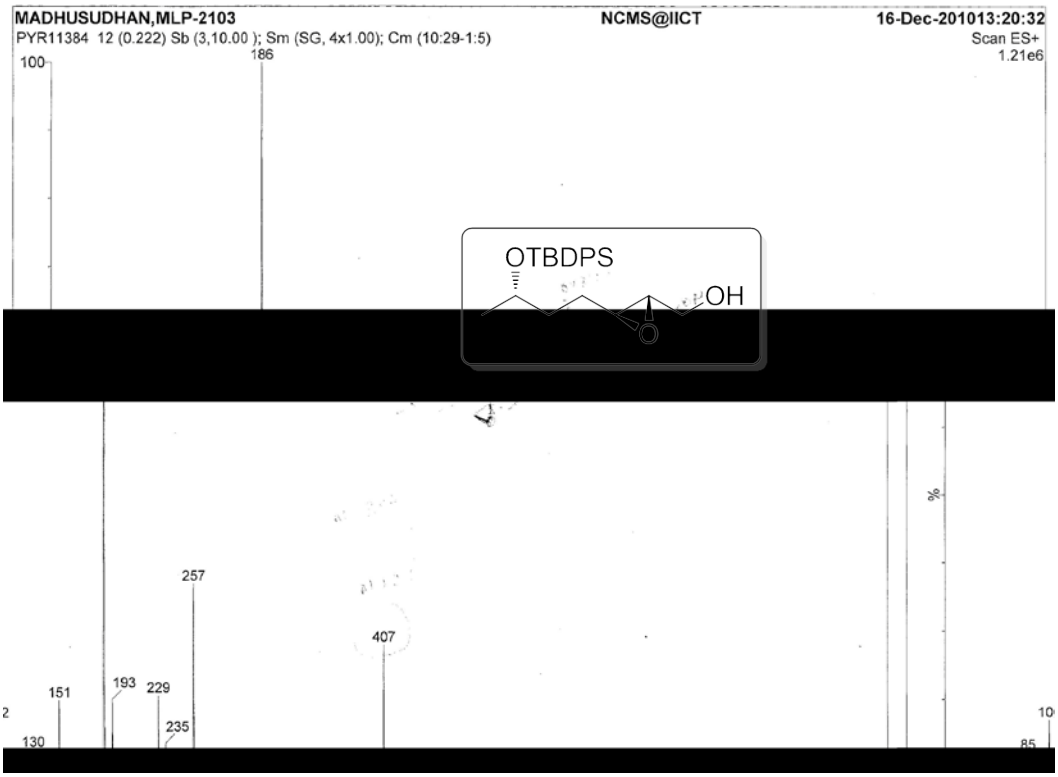


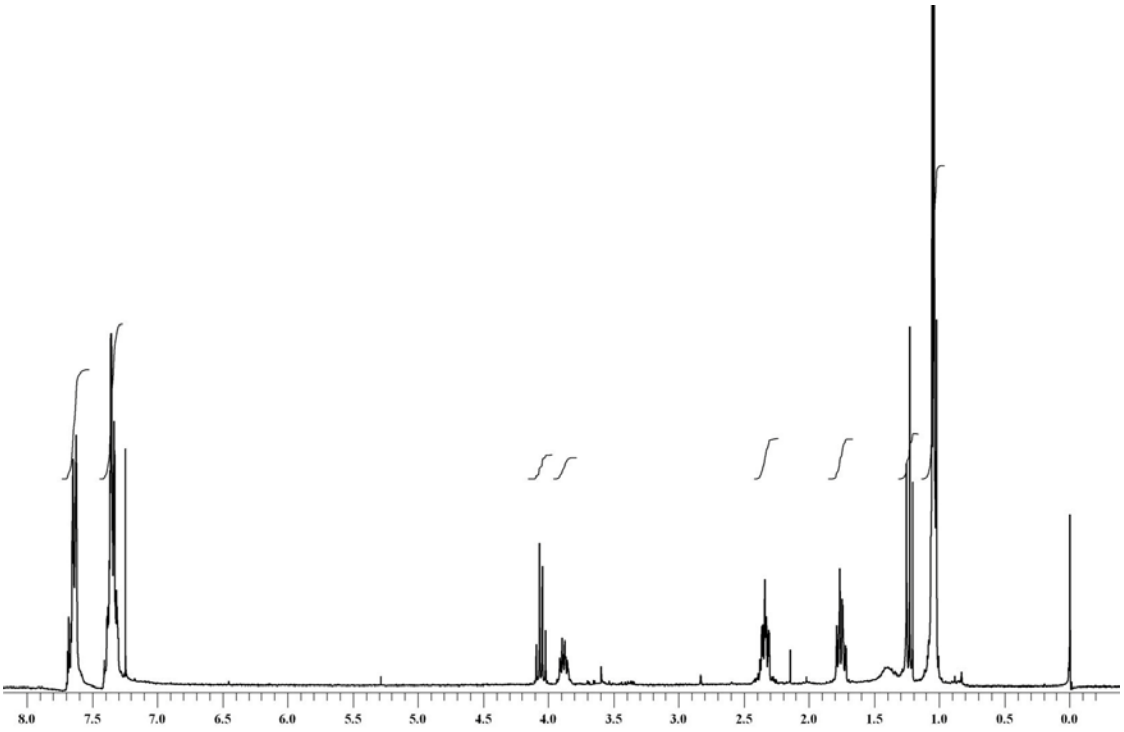
^{13}C NMR SPECTRUM OF COMPOUND **29**



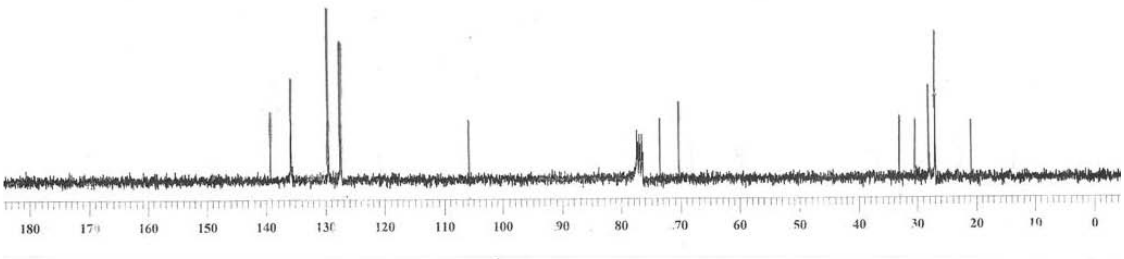
FTIR SPECTRUM OF COMPOUND **29**



ESI-MS SPECTRUM OF COMPOUND **29**

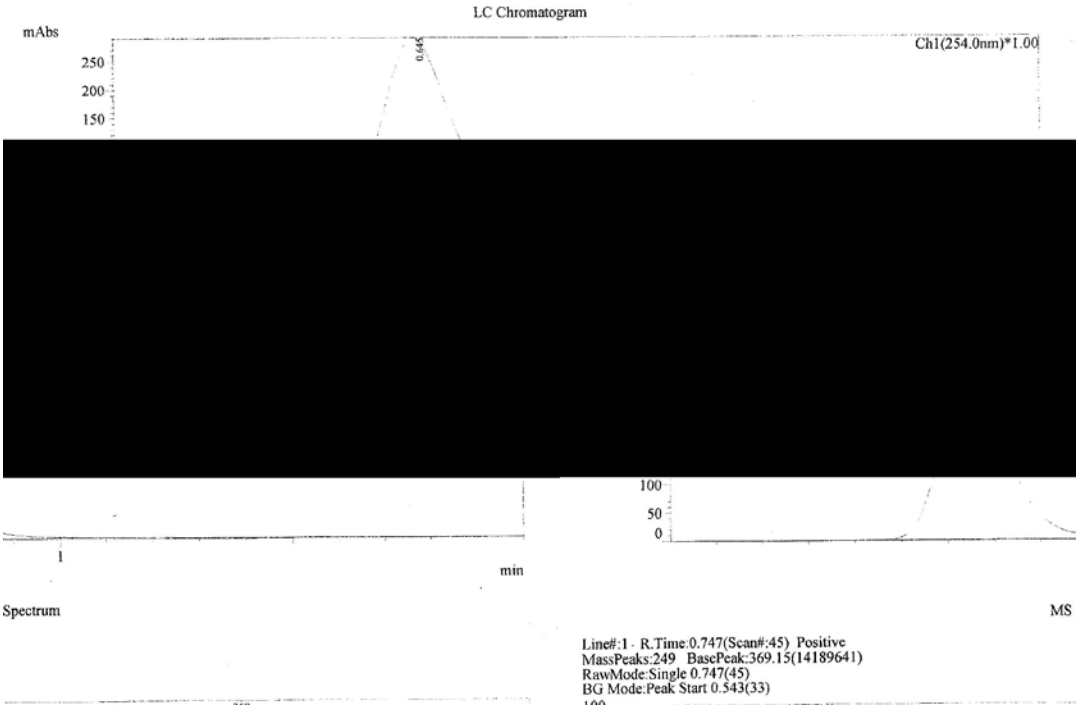


^{1}H NMR SPECTRUM OF COMPOUND **23**

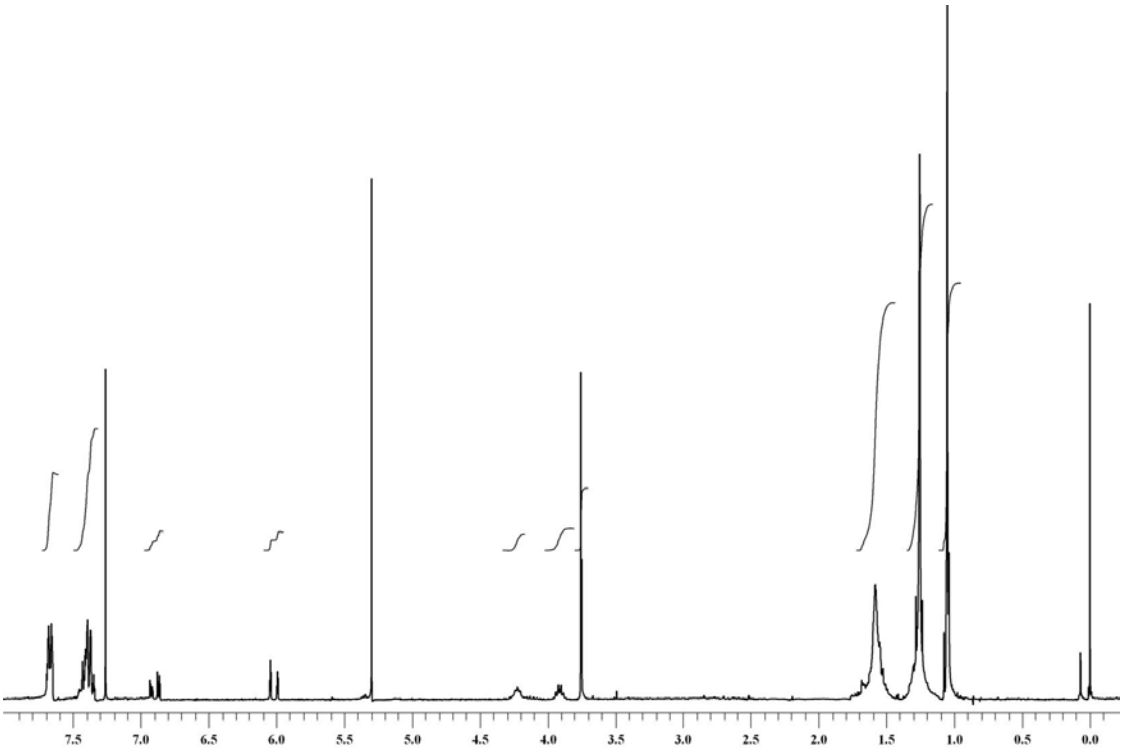


^{13}C NMR SPECTRUM OF COMPOUND **23**

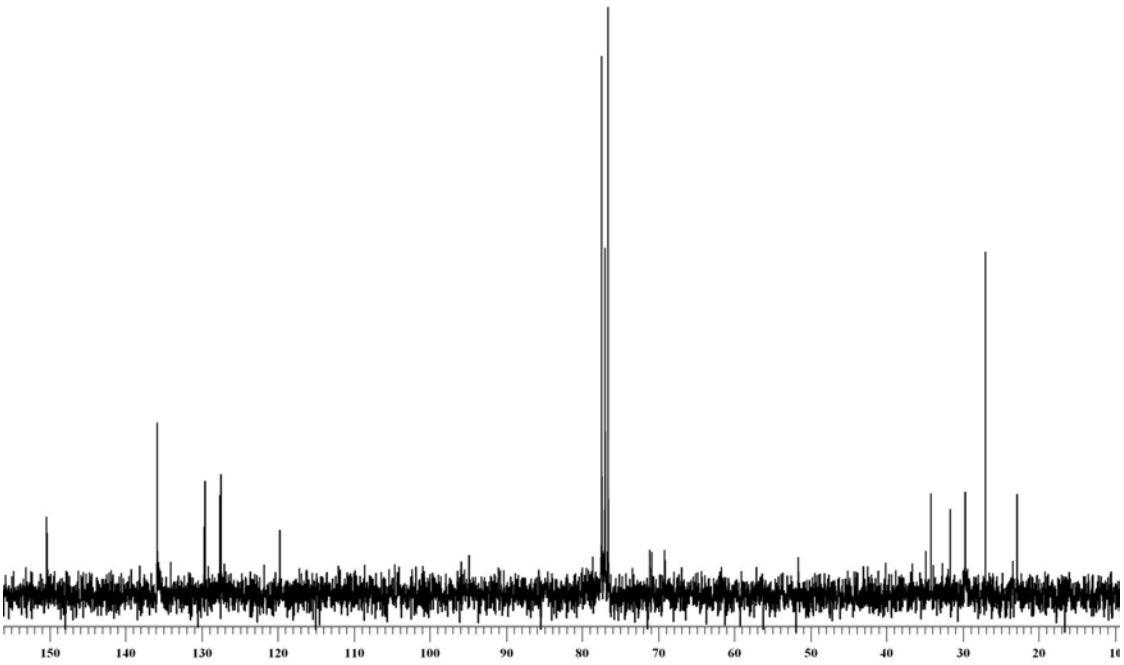
User : Admin
Sample : YVR13-2
Inj. Volume : 5.000
Data Name : C:\LCMSsolution\User\Data\YVR13-2-APCI-POS1.qld
Method Name : C:\LCMSsolution\User\Method\esi.qlm



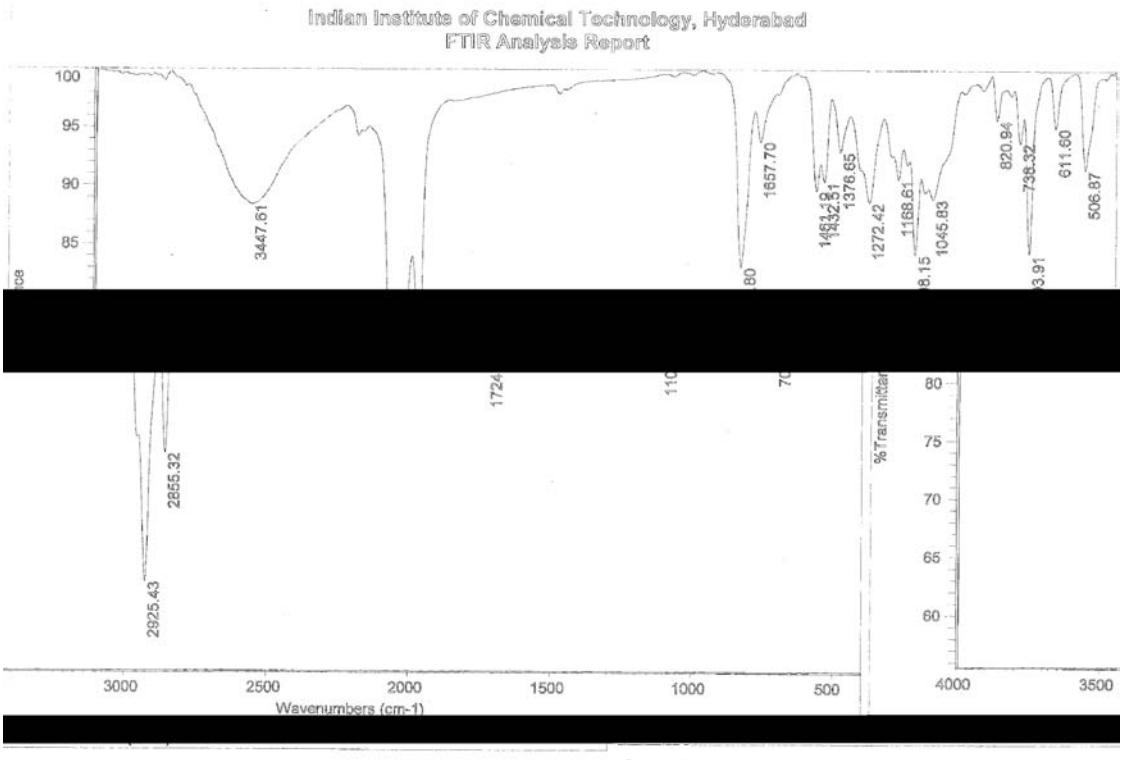
LC-MS SPECTRUM OF COMPOUND **23**



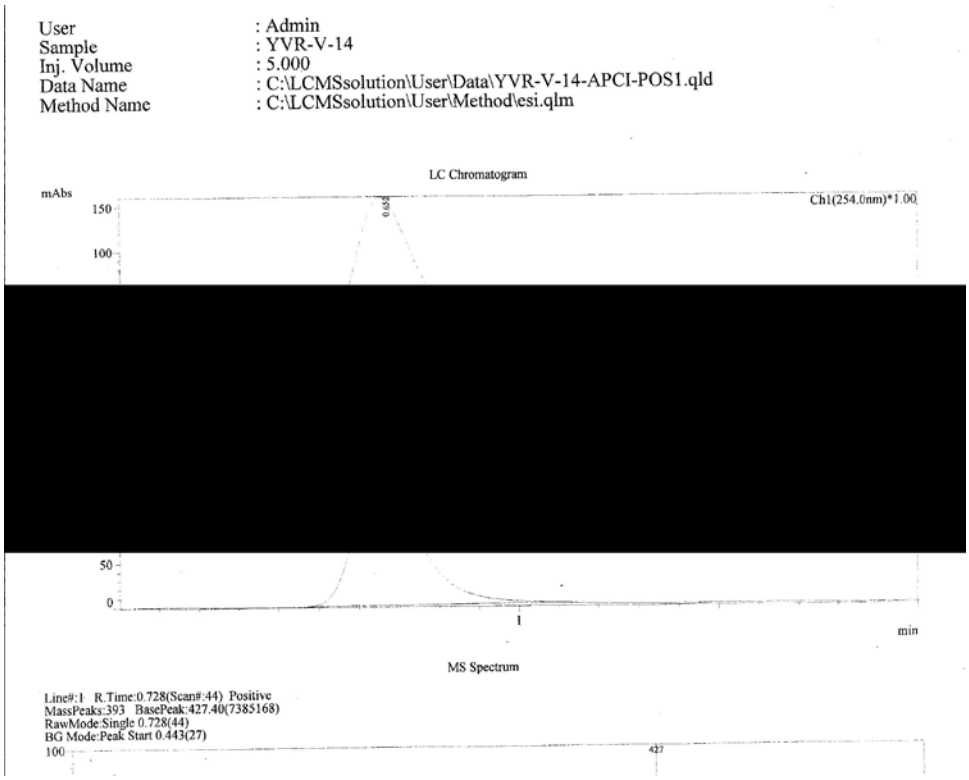
^{1}H NMR SPECTRUM OF COMPOUND **30**



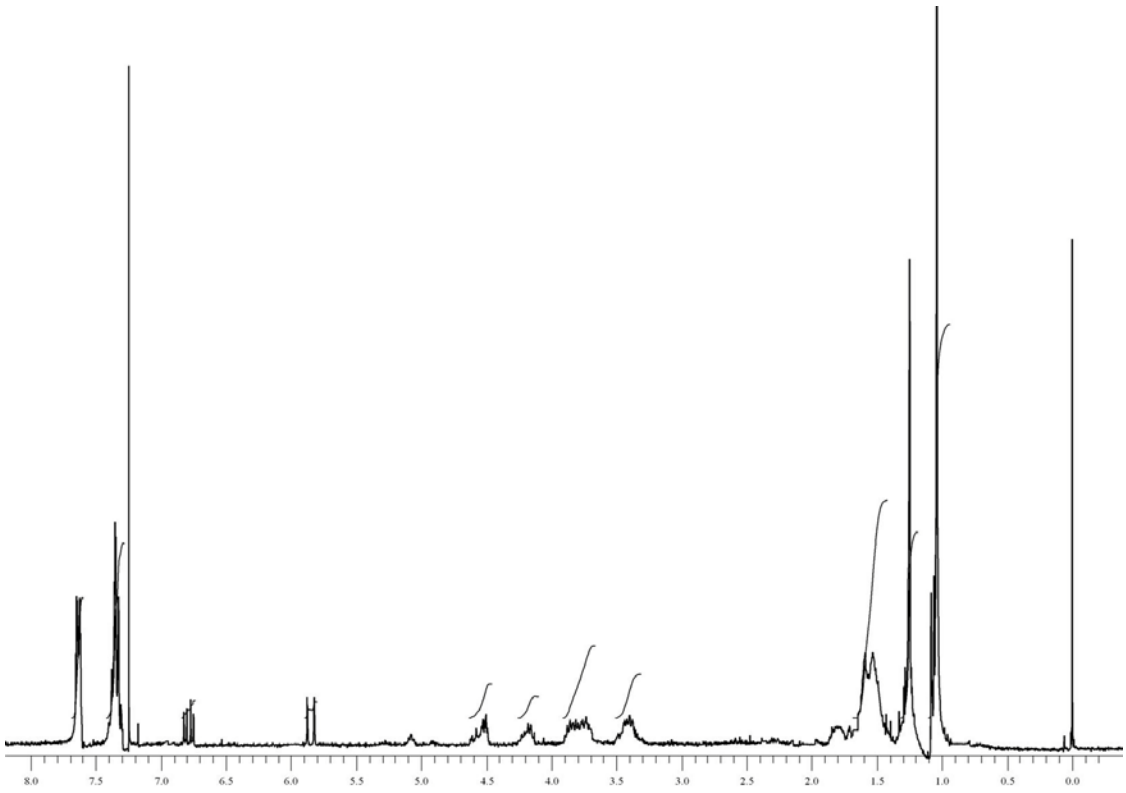
^{13}C NMR SPECTRUM OF COMPOUND **30**



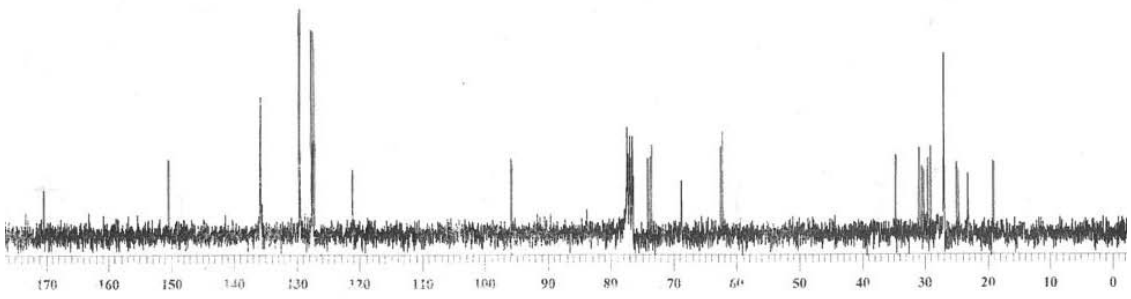
FTIR SPECTRUM OF COMPOUND **30**



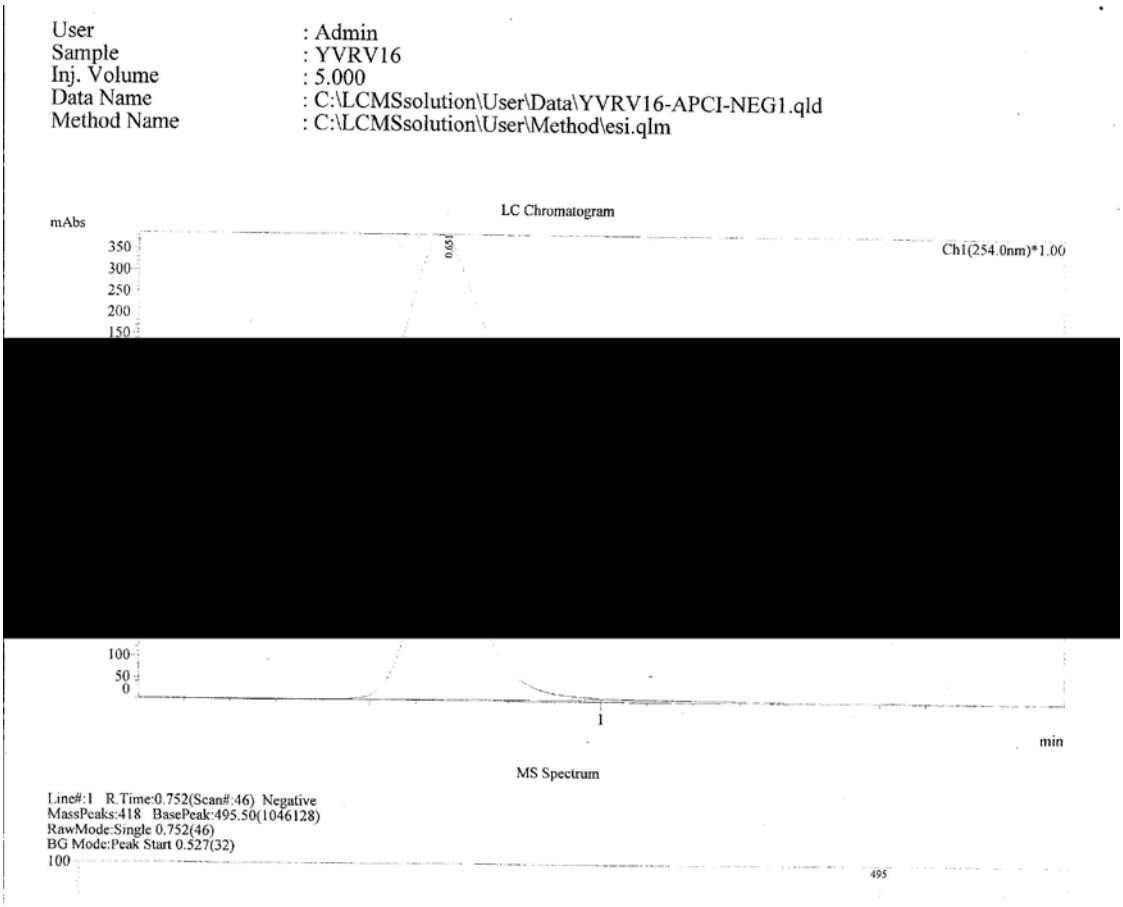
LCMS SPECTRUM OF COMPOUND **30**



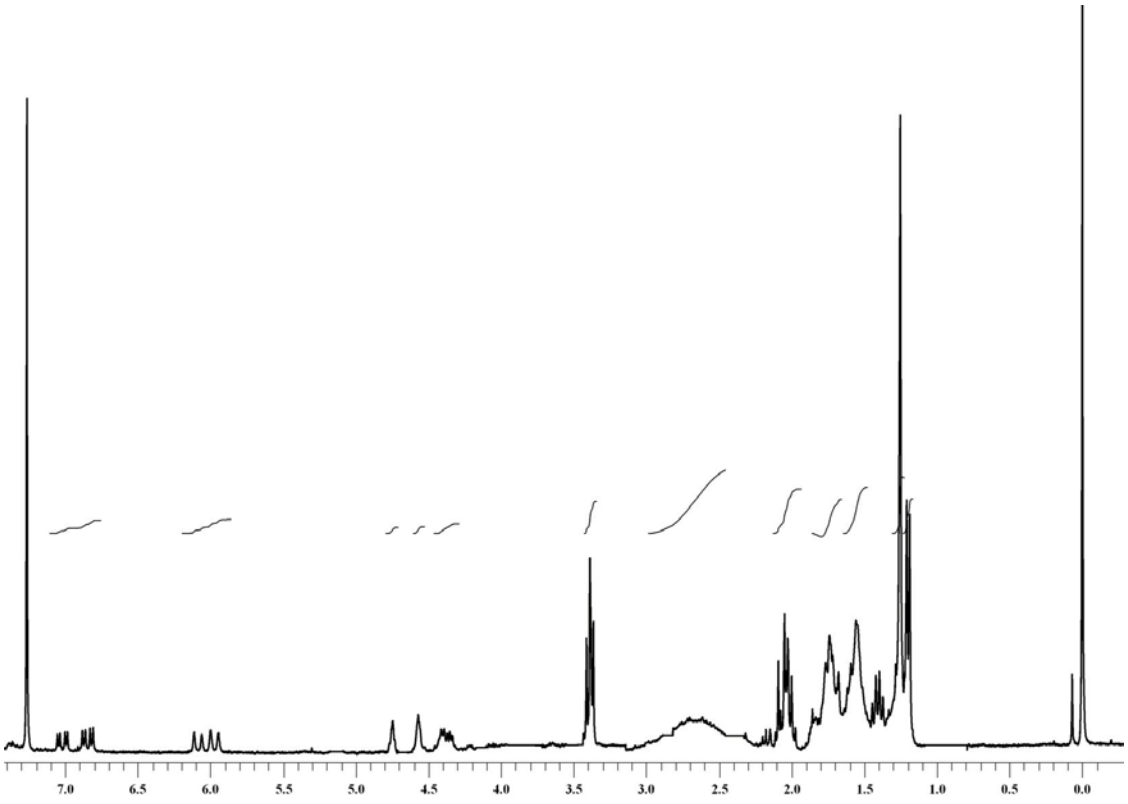
^{1}H NMR SPECTRUM OF COMPOUND **32**



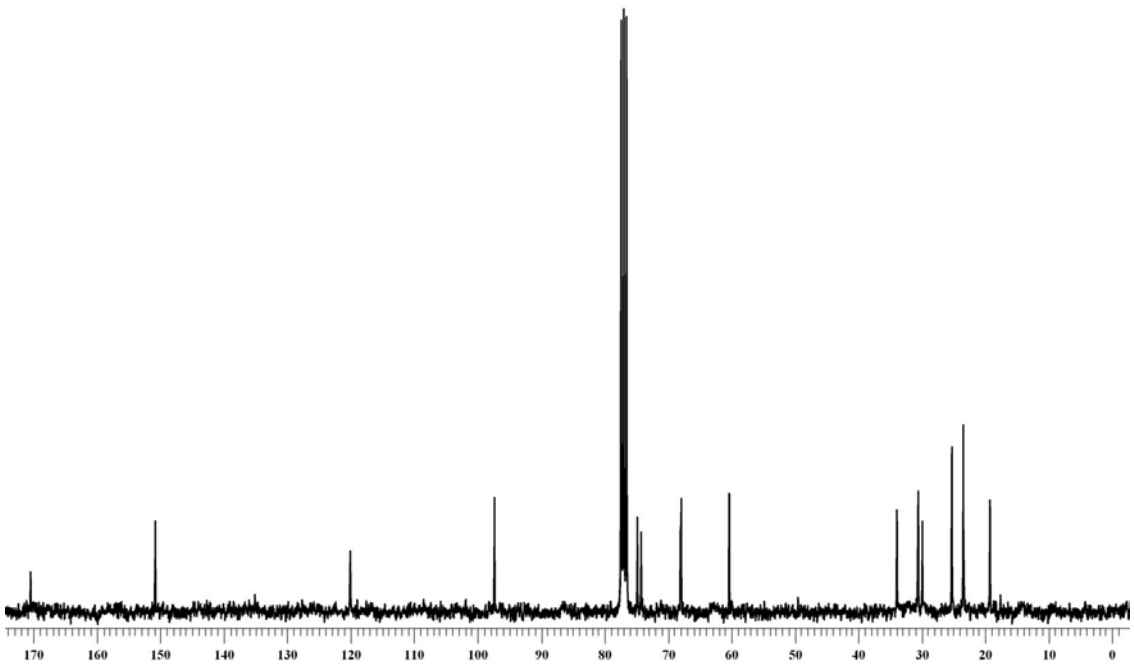
^{13}C NMR SPECTRUM OF COMPOUND **32**



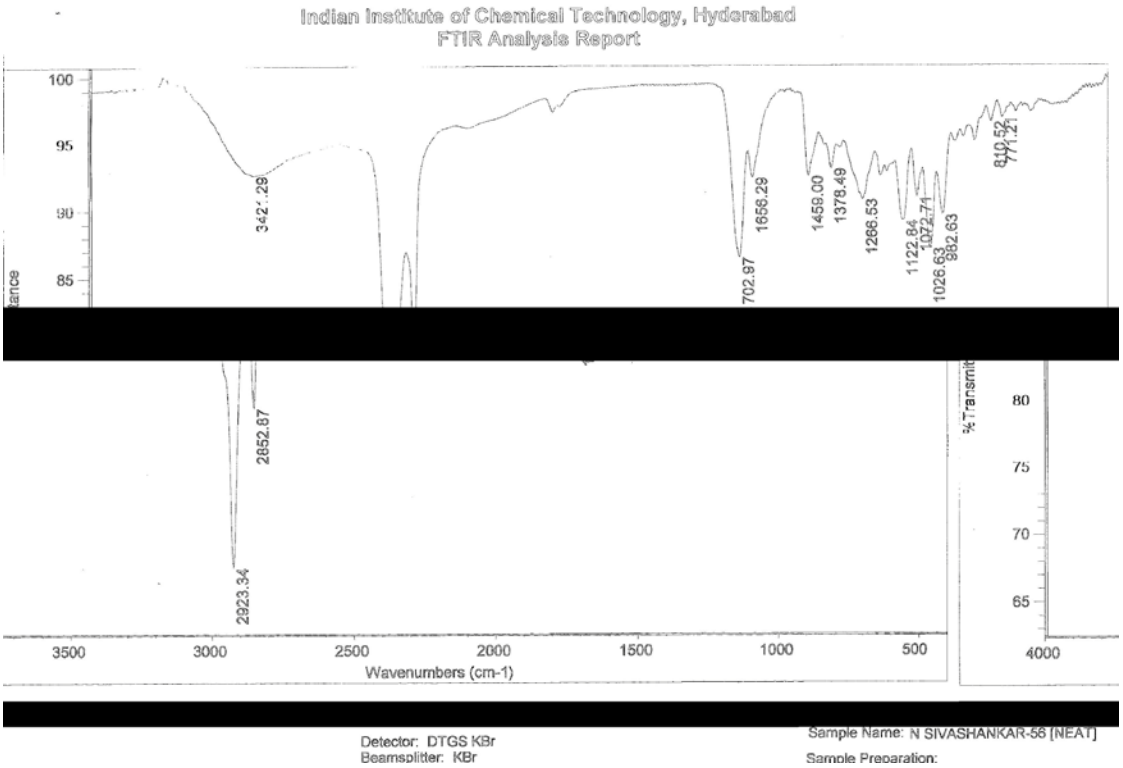
LCMS SPECTRUM OF COMPOUND **32**



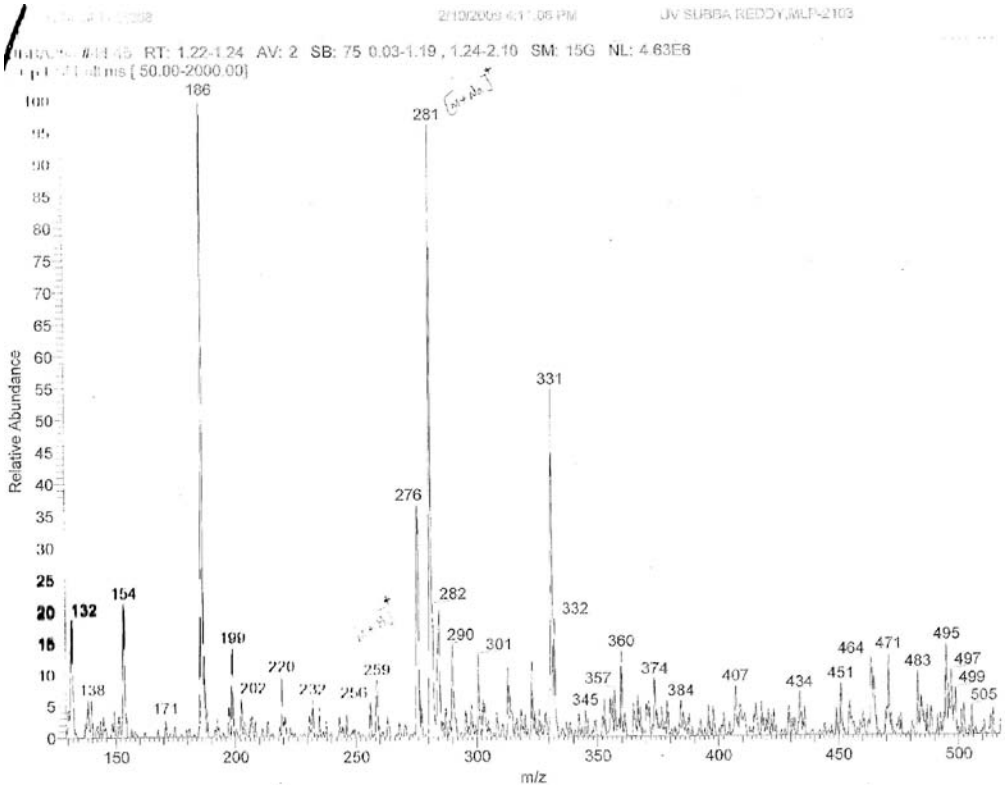
^{1}H NMR SPECTRUM OF COMPOUND **22**



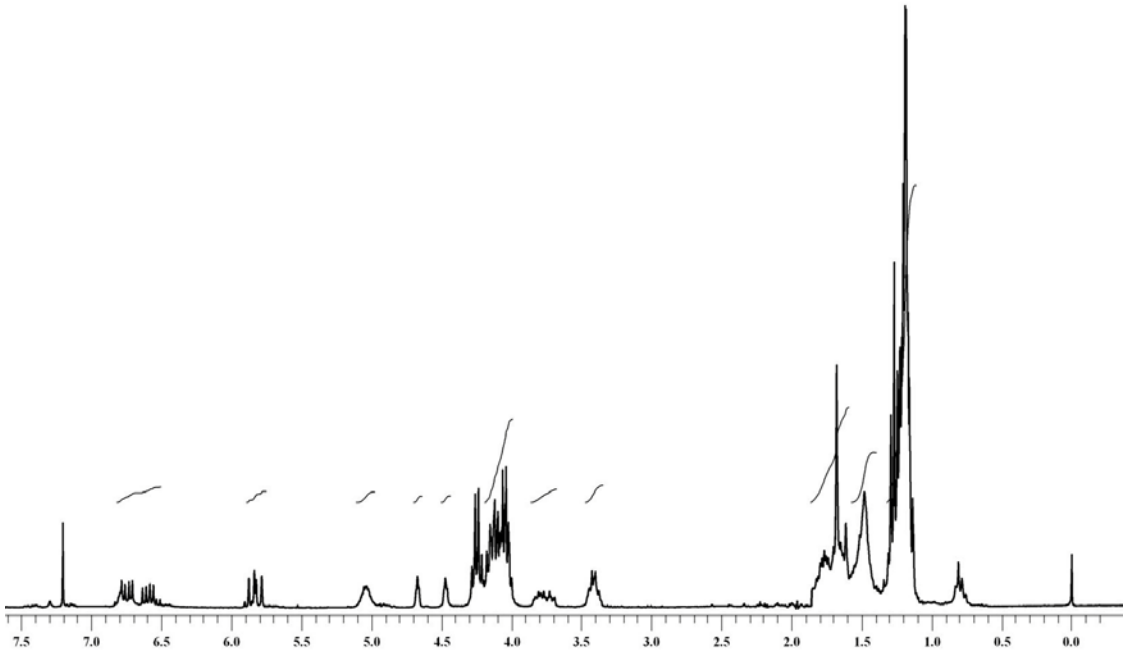
^{13}C NMR SPECTRUM OF COMPOUND **22**



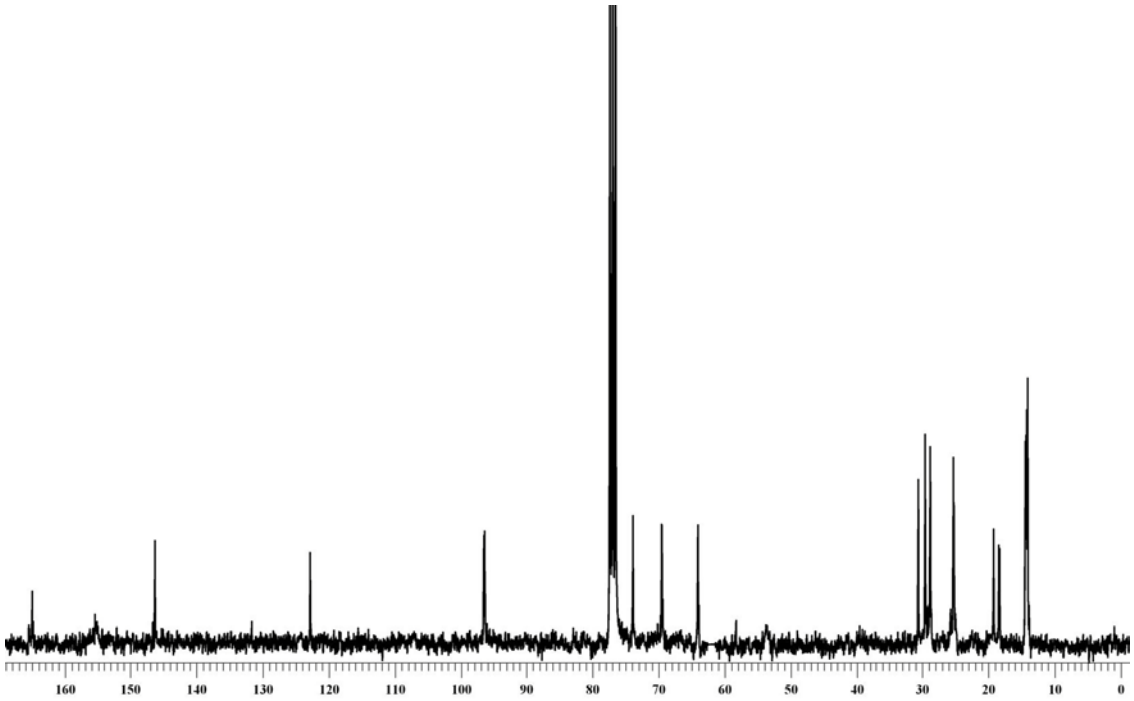
FTIR SPECTRUM OF COMPOUND **22**



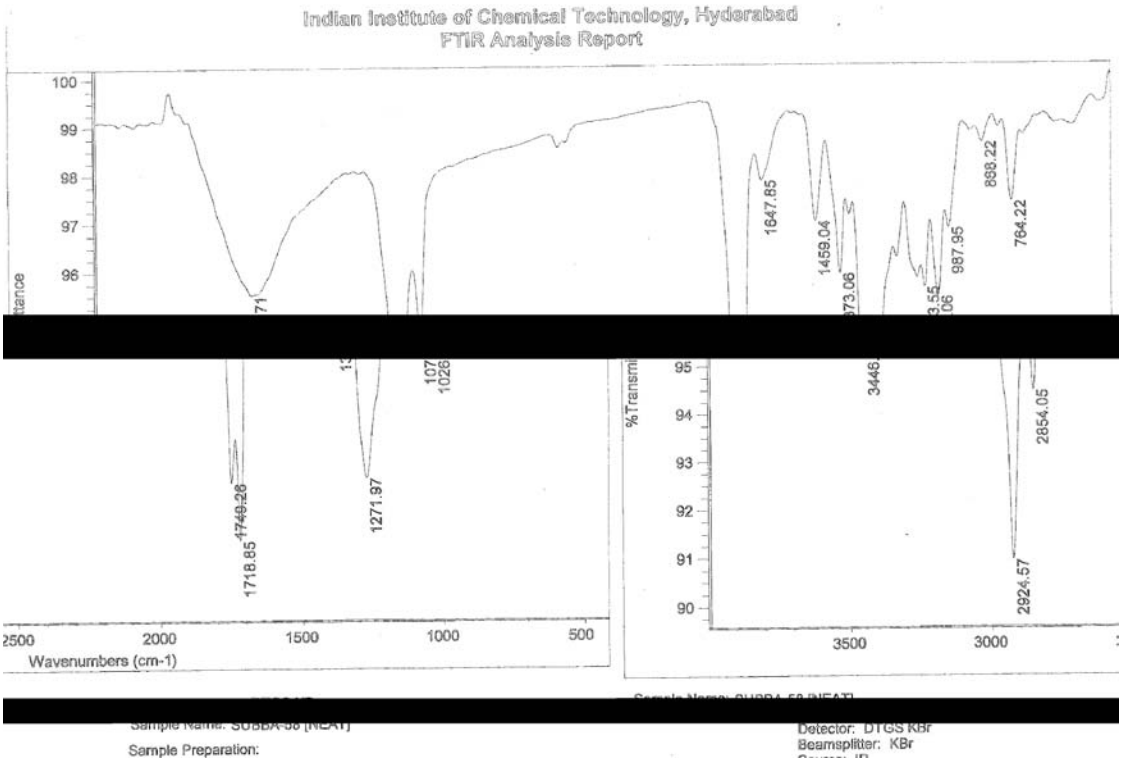
ESI-MS SPECTRUM OF COMPOUND **22**



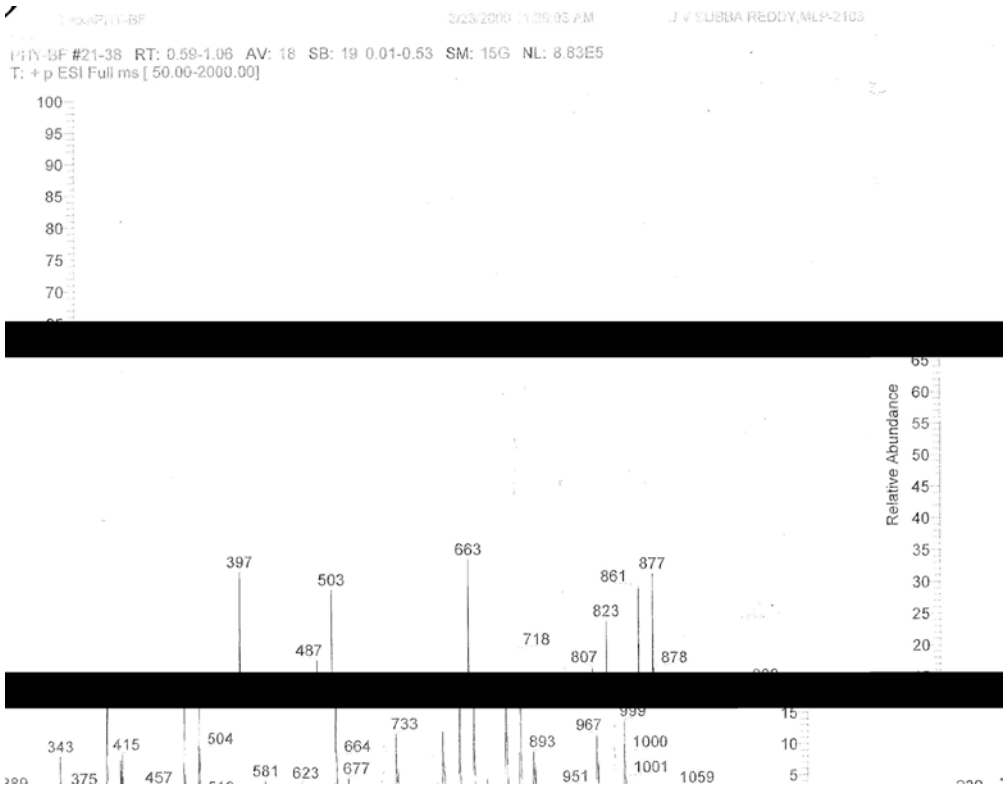
^{1}H NMR SPECTRUM OF COMPOUND **33**



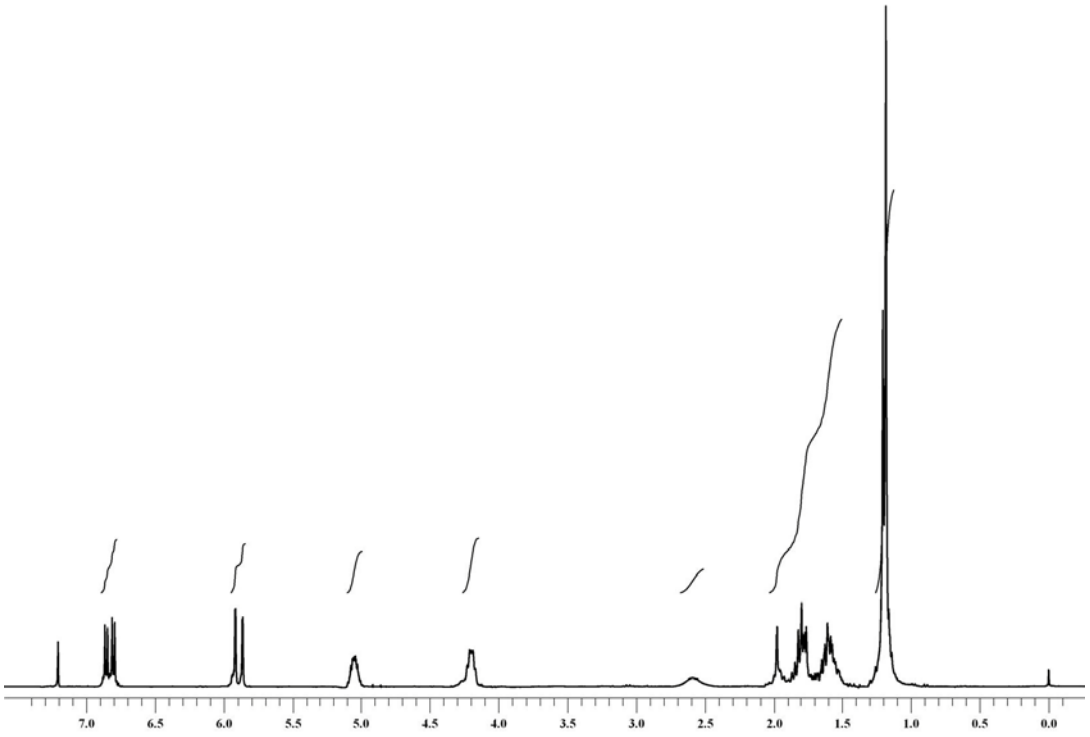
^{13}C NMR SPECTRUM OF COMPOUND **33**



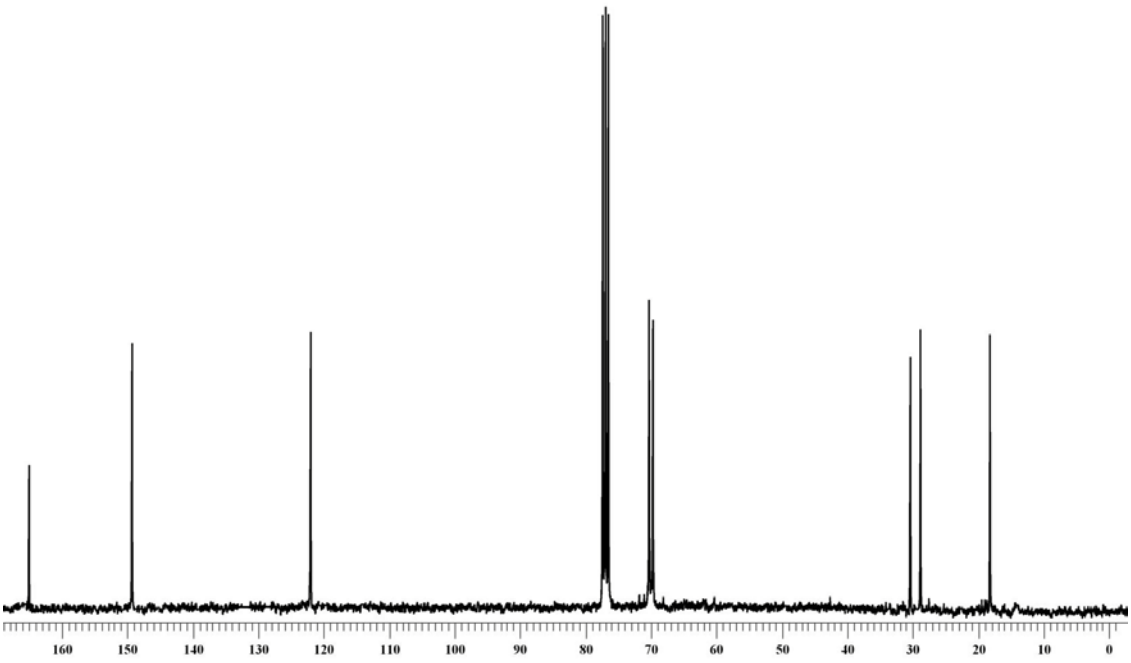
FTIR SPECTRUM OF COMPOUND **33**



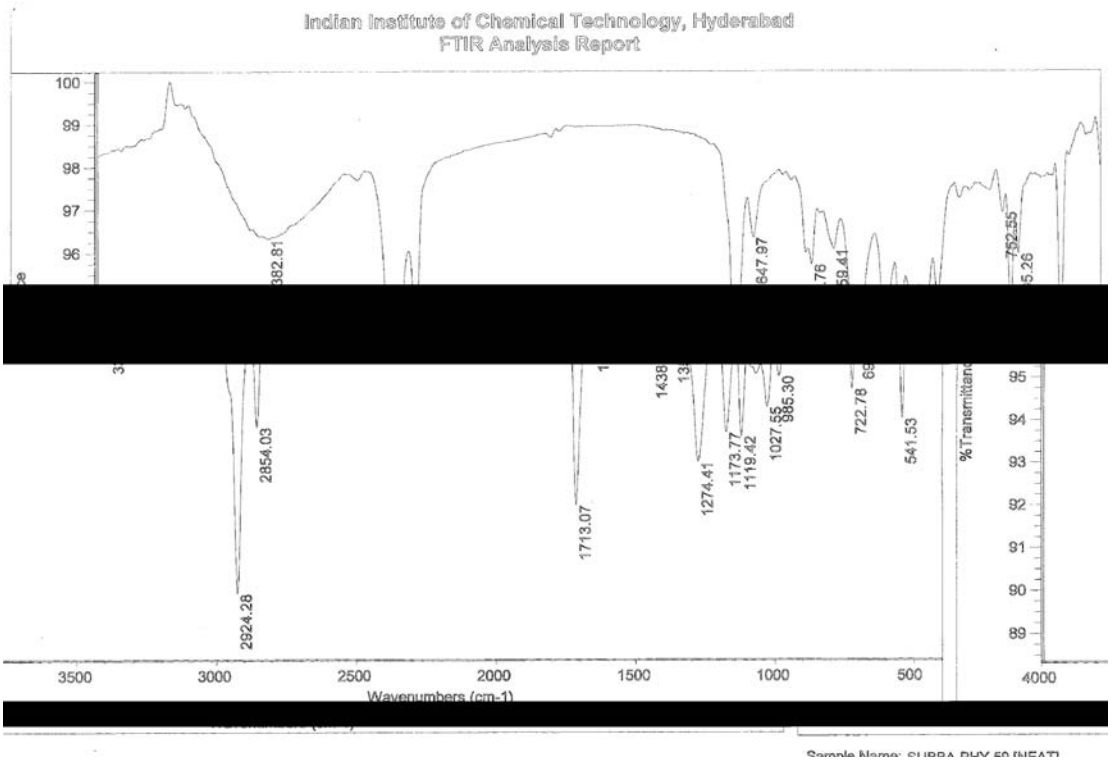
ESI-MS SPECTRUM OF COMPOUND **33**



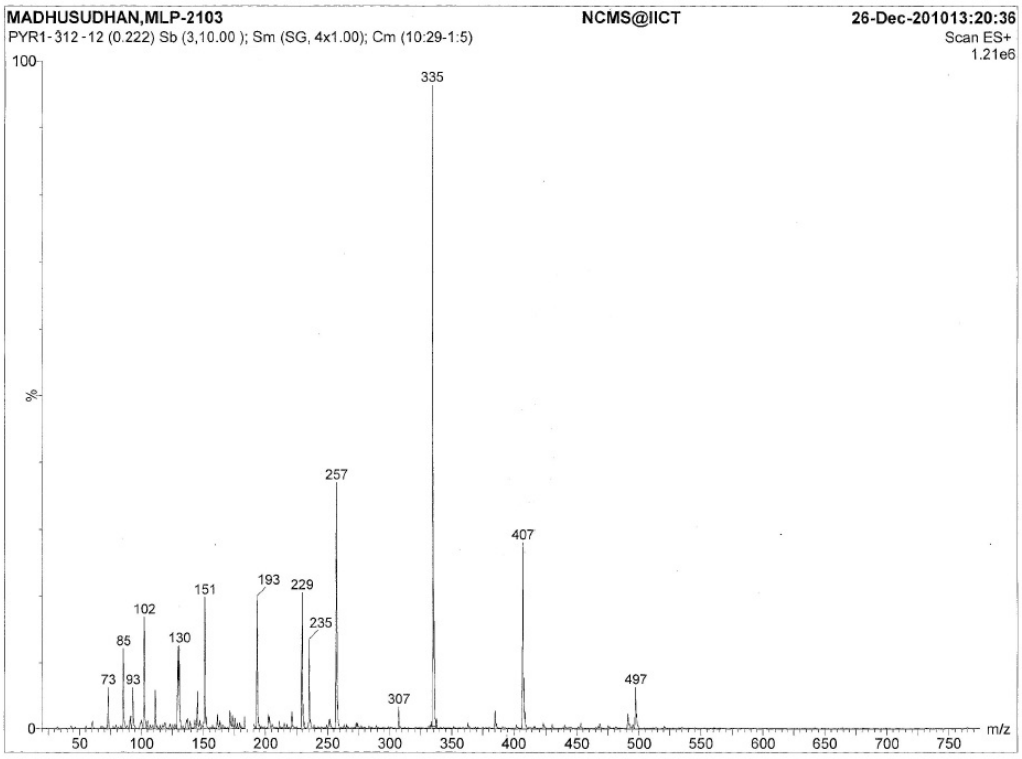
^{1}H NMR SPECTRUM OF COMPOUND **1**



^{13}C NMR SPECTRUM OF COMPOUND **1**



FTIR SPECTRUM OF COMPOUND **1**



ESI-MS SPECTRUM OF COMPOUND **1**

1) **Formal synthesis of Herboxidiene/GEX 1A**
   To be communicated

2) **Total synthesis of Pyrenophorol**
   J. S. Yadav, **G. Madhusudhan Reddy**, T. Srinivasa Rao and B. V. Subba Reddy

   Synthesis **2012**, *5*, 783-787

3) **A novel tandem ene/Prins cyclization for the synthesis of octahydropyrano[2,3-c]pyrrole derivatives**
   B. V. Subba Reddy, S. Rehana Anjum, **G. Madhusudhan Reddy**, J. S. Yadav

   Tetrahedron Letters **2011**, *53*, 1790-1793.

4) **$BF_3.OEt_2$- catalysed unusual formation of *cis* 2,3-disubstituted tetrahydrofuran scaffolds**
   B. V. Subba Reddy, S. Rehana Anjum, **G. Madhusudhan Reddy**, T. P. Rao

   Synlett **2011**, *20*, 2951-2954.

5) **$Cu(OTf)_2$/Cu(0)-catalyzed four-component reaction: a facile synthesis of triazoles via Click Chemistry**
   J. S. Yadav, B. V. Subba Reddy, **G. Madhusudhan Reddy**, Rehana Anjum.

   Tetrahedron Letters **2009**, *50*, 6029-6031.

6) **Iodine-Catalyzed Three-Component Reaction: A Rapid Synthesis of α-Alkoxy Azides and Homoallyl Ethers**
   J. S. Yadav, B. V. Subba Reddy, **G. Madhusudhan Reddy**, Ravirala Narender

   Synthesis **2009**, *6*, 963-968.

7) **Three component, regioselective, one-pot synthesis of β-hydroxytriazoles from epoxides via 'Click Reactions'**
   J. S. Yadav, B. V. Subba Reddy, **G. Madhusudhan Reddy**, D. Narasimha Chary

   Tetrahedron Letters **2007**, *48*, 8773–8776.

8) **$CeCl_3.7H_2O$/AcCl-catalyzed Prins–Ritter reaction sequence: a novel synthesis of 4-amido tetrahydropyran derivatives**
   J. S. Yadav, B. V. Subba Reddy, G. G. K. S. N. Kumar, **G. Madhusudhan Reddy**

   Tetrahedron Letters **2007**, *48*, 4903–4906.

9) **$CeCl_3$.$7H_2O$/LiI: A Novel Reagent System for the Synthesis of 4-Iodo tetrahydropyrans via Prins Cyclization**

   J. S. Yadav, B. V. Subba Reddy, G. G. K. S. N. Kumar, **G. Madhusudhan Reddy**

   Chemistry Letters **2007**, *36*, 426-427.