SYNTHETIC STUDIES TOWARDS STEROID INTERMEDIATE, LIPOIC ACID AND OTHER BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS SUBMITTED TO THE

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IN

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"Synthetic Studies towards Steroid Intermediate, Lipoic Acid and other biologically active compounds"** submitted by **Abhijeet N. Purude** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. This work is original and has not been submitted partially or fully, for any degree or diploma of this or any other University.

(Dr. Uttam R. Kalkote)
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Abhijeet N. Purude

Dedicated To
My Family

DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies towards Steroid Intermediate, Lipoic Acid and other biologically active compounds"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune. This work was carried out at National Chemical Laboratory, Pune, India. This work is original and has not been submitted partially or full, for any degree or diploma of this or any other University.

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CONTENTS

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Ar	-	Aryl
Aq	-	Aqueous
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
*t*Bu	-	*tertiary* butyl
BuLi	-	Butyl lithium
Cat.	-	Catalytic
Cbz	-	Carbobenzyloxy
$CDCl_3$	-	Deuterated chloroform
DBAD	-	Dibenyl azodicarboxylate
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-l)phthalazine
DDQ	-	2, 3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	-	Diisopropyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DMAC	-	*N, N*-Dimethylacetamide
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N*-Dimethylformamide
DMAP	-	*N,N*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
Ee	-	Enantiomeric excess
eq.	-	Equivalents
Et	-	Ethyl
EtOH	-	Ethanol
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine

gm	-	gram
hr	-	hour
$HBSia_2$	-	di-siamylborane
Hz	-	Hertz
HPLC	-	High pressure liquid chromatography
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
IR	-	Infrared
LDA	-	Lithium diisopropyl amide
LiHMDS	-	Lithium hexamethyl disilazide
m-CPBA	-	*m*-Chloroperbenzoic acid
Me	-	Methyl
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
M. p.	-	Melting point
Ms	-	Methanesulfonyl
MeI	-	Methyl iodide
Mes	-	2,4,6-trimethylbenzoate
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*p*-Methoxy benzyl
p-TSA	-	*p*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
rt	-	Room temperature
Et_3N	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBDMSCl	-	*tert*-Butyldimethyl silyl chloride
TBDPSCl	-	*tert*-Butyldiphenyl silyl chloride
TFA	-	Trifluoroacetic acid
Tf	-	Trifluoromethanesulfonate

THF	-	Tetrahydrofuran
TMS	-	Tetramethylsilane
TLC	-	Thin layer chromatography
Ts	-	*p*-Toluenesulphonyl (Tosyl)
VA	-	Vinyl Acetate

General remarks

- ^{1}H NMR spectra were recorded on AV-200 MHz, MSL-300 MHz, AV-400 MHz and AV-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV-50 MHz, MSL-75 MHz, AV-100 MHz and AV-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- HPLC analysis were carried out on Shimatzu instrument
- All reactions are monitored by Thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (230–400 mesh) used for flash column chromatography was purchased from Spectrochem Pvt. Ltd., Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

Abstract

The thesis entitled **"Synthetic Studies towards Steroid Intermediate, Lipoic acid and other biologically active compounds"** is divided into three chapters

Thesis Introduction:

The importance of obtaining optically pure materials hardly requires restatement. Manufacture of chemical products applied either for the promotion of human health or to combat pests that otherwise adversely impact on the human food supply is now increasingly concerned with the enantiopurity. A large proportion of such products contain at least one chiral center. Hence tremendous efforts have been made to for the preparation of enantiomerically pure compounds the pharmaceutical industries. The desirable reasons for producing optically pure materials include the following: (i) biological activity often associated with only one enantiomer (ii) enantiomers may exhibit different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable. All conceivable methods for the production of optically pure materials are summarized (Figure 1).

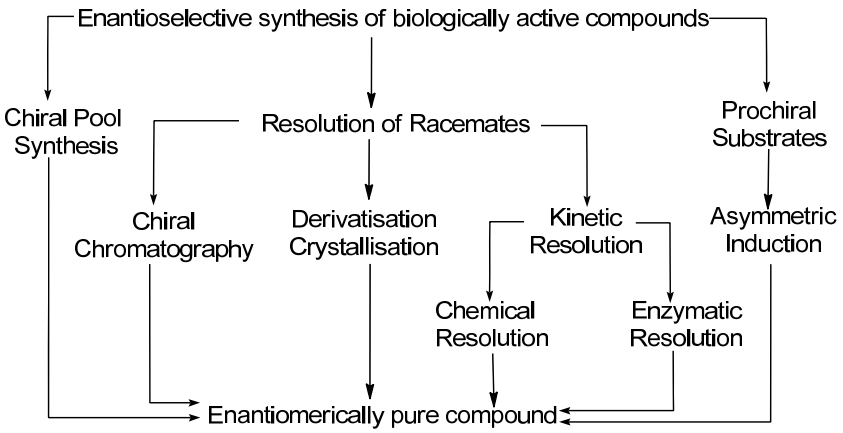


Figure 1

Among these methods enzymatic resolution is widely used since

(1) Enzymes are chemoselctive, regioselective, stereoselective, and ecofriendly

(2) Enzymatic reactions are affected to a lesser extent by side reactions (**3)** Enzymes can operate in both aqueous and non-aqueous media accepting a broad range of substrates. **(4)** Immobilization techniques increase stability of enzymes.Range of enzymes is commercially available for resolution of racemates. Among which lipases

accept a broad range of substrates with excellent stereoselectivity. Lipases are the most studied and found in most of the organisms. Methods in which lipase catalyzed resolution have been widely used are (Figure 2).

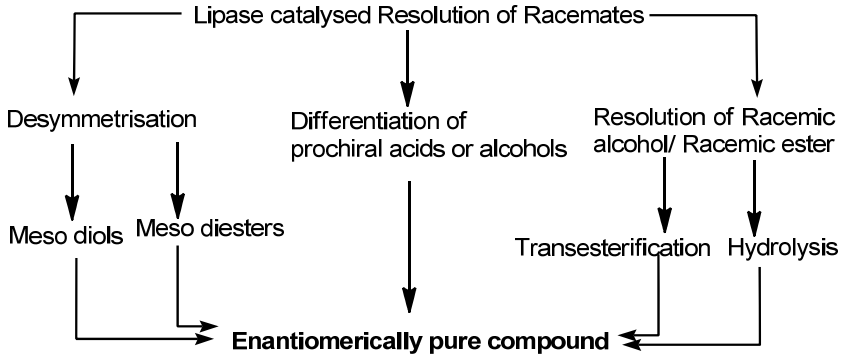


Figure 2

Thus, in the presence of a suitable enzyme as well as the appropriate solvent, one enantiomer of the racemic mixture is either selectively transesterified or selectively hydrolyzed to the corresponding alcohol, leaving the second unreacted enantiomer in pure form; this describes key role of enzymes (Figure 3).

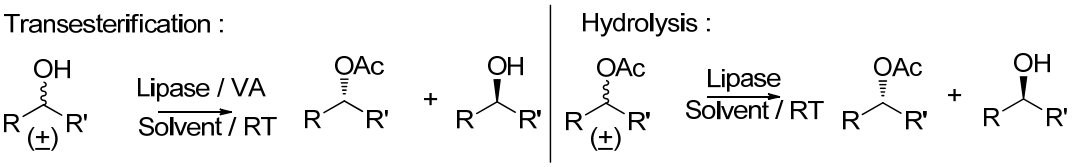


Figure 3

The versatility and high intigirity of lipases is attributed to their **1)** High catalytic efficiency on a broad range of substrates. **2)** High regioselectivity and chiral recognition. **3)** High stability **4)** the reversibility of their mode of action into ester synthesis. **5)** Non-toxic and environmentally friendly nature, and **6)** Low cost. Taking in to consideration these significances of enzymes (Lipase) as biocatalyst, and in continuation of our early research work we synthesized following compounds by chemoenzymatic methods. (Figure 4)

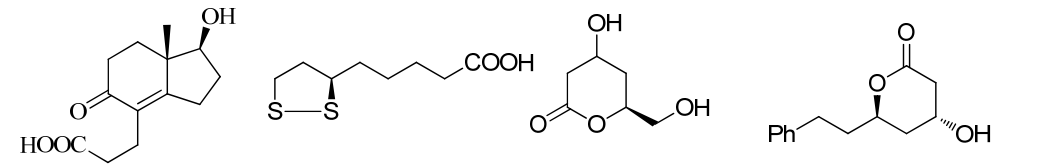


Figure 4

Chapter 1: Chemoenzymatic method for synthesis of Steroid Intermediate.

This chapter is divided in two sections.

Section 1: Introduction and literature review of Steroids

Steroids are a class of organic compounds with a chemical structure that contains the core of Gonane (**5**) or a skeleton derived there from. Usually, methyl groups are present at the carbons C_{10} and C_{13}. At carbon C_{17} an alkyl side chain may also be present. Sterols are special forms of steroids, with a hydroxyl group at position C-3 and a skeleton derived from cholestane.[1] Gonane is the simplest possible steroid and is composed of seventeen carbon atoms, bonded together to form four fused rings. Three cyclohexane rings A, B, and C and cyclopentane ring D form the Gonane (**5**).

During the synthesis of steroid, **C-D** ring preparation is the prime object and hence intermediate **1** has dragged attention of chemists and various methods have been reported for its synthesis. Thus intermediate (1S, 7aS)-1-hydroxy-5-oxo- 4-(2'-carboxyethyl)-7a-methyl tetrahydroindane (**1)** is the significant key intermediate of several steroids (Figure 5)[1, 2]

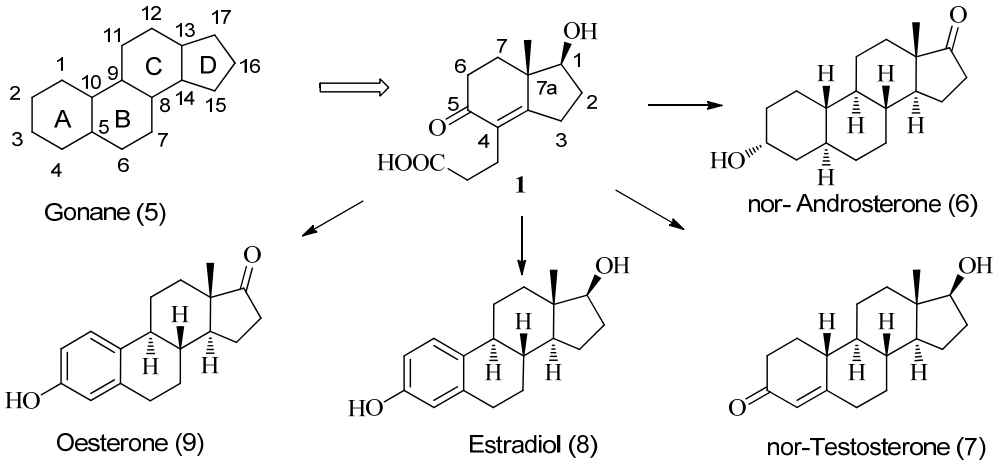
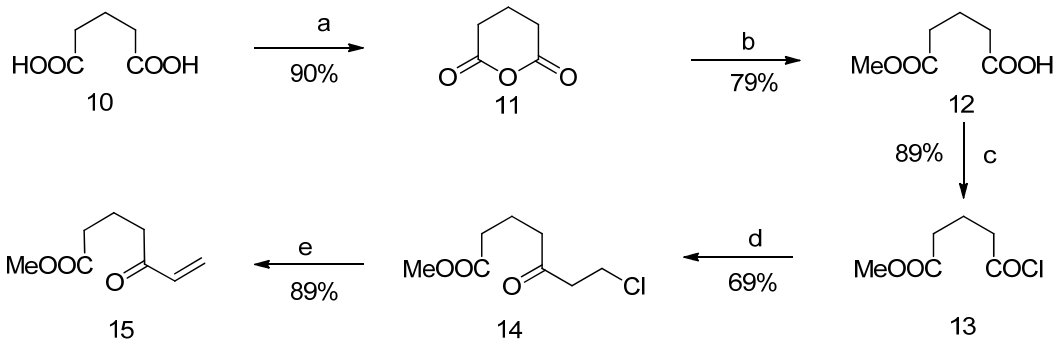


Figure 5

Various approaches have been used for syntheses of (1*S*, 7a*S*)-1-Hydroxy-5-oxo- 4-(2'-carboxyethyl)-7a-methyl tetrahydr-indane (**1**) and its enantiomer[1, 2] *viz* asymmetric Robinson Annulation, chemical resolution, microbial reduction and stereoselective reduction. Since all of the above methods involve use of narcotic drugs or cacogenic chemicals or lengthy reaction sequence, hence we planned chemoenzymatic route[3, 4] to prepare optically pure (1*S*, 7a*S*)-1-hydroxy-5-oxo-4-(2'-carboxyethyl)-7a-methyl tetrahydro-indane **(1)** from commercially available glutaric acid (**10**).

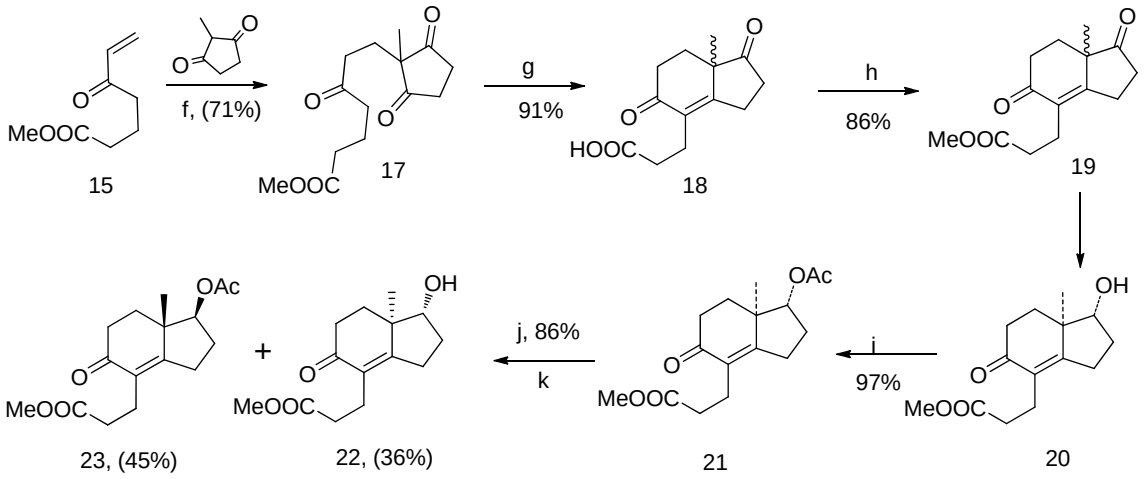
Chapter 1: Section II: Chemoenzymatic Synthesis of Steroid Intermediate

In this section we explored chemoenzymatic[5, 6] route to prepare optically pure (1*S*, 7a*S*)-1-hydroxy-5-oxo-4-(2'-carboxyethyl)-7a-methyl tetrahydro-indane **(1)** from commercially available glutaric acid (**10**). As illustrated in scheme 1, Glutaric acid (**10**) on dehydration furnished glutaric anhydride **(11)** which on refluxing with methanol gave methyl glutarate **(12).** Intermediate **(12)** on treatment with thionyl chloride gave methyl 5-chloro-5-oxopentanoate **(13).** Ethylene was reacted with above intermediate (**13**) in presence of aluminium chloride to afford methyl 7-chloro-5-oxoheptanoate (**14**). This intermediate **14** on treatment with triethylamine undergoes β-elimination to furnish methyl 5-oxohept-6-enoate (**15**).



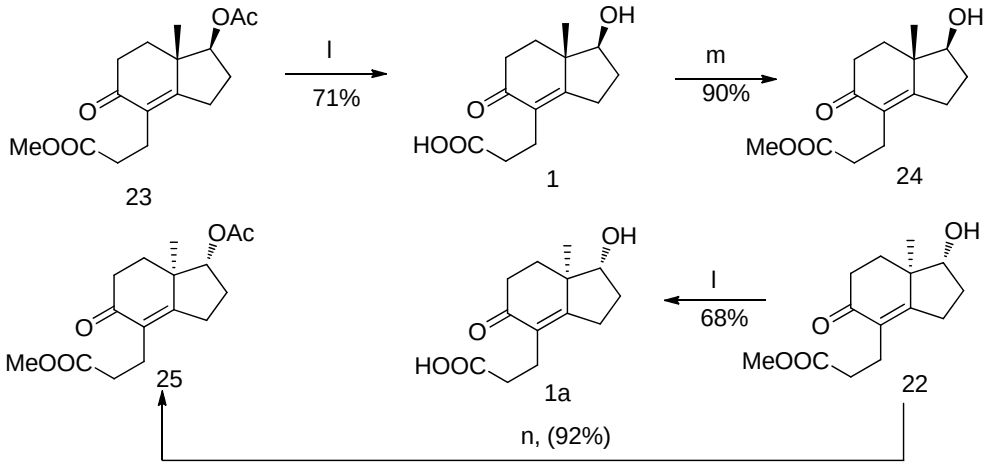
Scheme 1. *Reagents and conditions:* (a) Ac_2O/-H_2O; (b) MeOH/ H^+/ reflux; (c) $SOCl_2$ /reflux; (d) Ethylene/ $AlCl_3$/ EDC; (e) DCM/ TEA.

After preparation of methyl 5-oxohept-6-enoate (**15**) it was subjected to Michael addition (Scheme 2) by simply treatment with 2-methylcyclopentane-1, 3-dione (**16**) in presence of pyridine to furnish methyl 7-(1-methyl-2, 5-di-oxocyclopentyl)-5-oxoheptanoate (**17**). Subsequently intermediate **17** on treatment with 5 N HCl underwent aldol condensation reaction to generate 1, 5-dioxo-4-(2'-carboxyethyl)-7a-methyl tetrahydroindane (**18**). This bis-keto **18** acid was esterified in presence of catalytic amount of H_2SO_4 and methanol under refluxing condition to furnish intermediate 1, 5-dioxo-4-(2'-carbomethoxy ethyl)-7a-methyl tetra-hydro-indane (**19**). The reduction of ester (**19**) by $NaBH_4$ gave (±) (*cis)*-1-hydroxy-5-oxo-4-(2'-carbomethoxy-ethyl)-7a-methyltetra-hydro-indane (**20)**. The compound **20** on acylation gave acetyl derivative **21** which was subjected to enzymatic resolution.



Scheem 2. *Reagents and conditions:* (f) Py/ PhMe, reflux; (g) C_6H_6/ H^+; (h) MeOH/ H^+, reflux; (i) $NaBH_4$/ MeOH; (k) AcCl/ TEA; (k) PPL/ phosphate buffer + EtOH.

During enzymatic screening, (±) (*cis)*-1-Acetoxy-5-oxo-4-(2'-carbomethoxyethyl)-7a-methyl tetrahydroindane (**21**) was treated with different enzymes in phosphate buffer (pH 7) with 10% ethanol as a co-solvent to carry out the hydrolytic resolution [7-11, 13]. In case of PPL enzyme, (±) **21** was effectively hydrolyzed to (1*R*, 7a*R*) alcohol **22** and the (1*R*, 7a*R*) acetate **23** remained unreacted. Acetoxy derivative **23** converted in to **1** by acid hydrolysis and subsequent esterification afforded the hydroxyester **24**.The optical purity[12] of **22** and **24** (>95% e.e.) was determined by chiral HPLC using Chiralcel OD [4.6 mm Id x 25 cm] column (λ 254 nm, flow rate: 1 ml/min; mobile phase: Hexane: Isopropanol 95:05).



Scheme 3. *Reagents and conditions:* (l) HCl/ H_2O; (m) CH_2N_2, ether; (n) Ac_2O, Et_3N, DCM

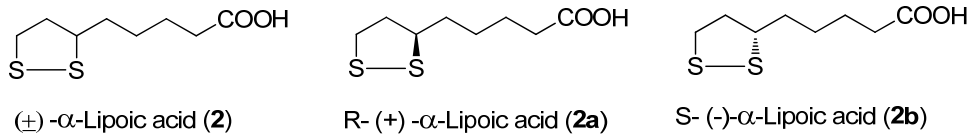
In order to know absolute configuration of **22** and **23,** these were hydrolysed with 6.5N HCl to obtain the products **1**and **1a** respectively**.** X-Ray structure of **1a** and **23** shown syn configuration. Specific rotation of **1** was found identical with reported for (1*S*, 7aS)-1-hydroxy-5-oxo-4-(2'-carboxyehtyl)-7a-methyltetrahydro-indane (**1**)[1]. Further, (1*R*, 7aR)-1-hydroxy-5-oxo-4-(2'-carbomethoxyehtyl)-7a-methyltetrahydro-indane **(22)** on treatment with acetyl chloride in presence of triethyl amine furnished (1*R*, 7aR) 1-acetoxy-5-oxo-4-(2'-carbo-methoxyethyl)-7a-methyltetrahydro-indane (**25**). This is nothing but opposite enantiomer of the (1*S*, 7aS) 1-acetoxy-5-oxo-4-(2'-carbo-methoxyethyl)-7a-methyltetrahydro-indane (**23**).

Chapter 2: Studies towards synthesis of Lipoic Acid

This chapter is divided into four sections

Section I: Introduction and literature review

Lipoic acid (**1**) was first isolated in 1950 by Reed and co-workers at the University of Texas in Austin[14, 15]. The first purified sample of lipoic acid was 30 mg of yellow crystals that were extracted from 100 kg of liver residue. (Figure 7)



(±) -α-Lipoic acid (**2**) R- (+) -α-Lipoic acid (**2a**) S- (-)-α-Lipoic acid (**2b**)

Figure 6

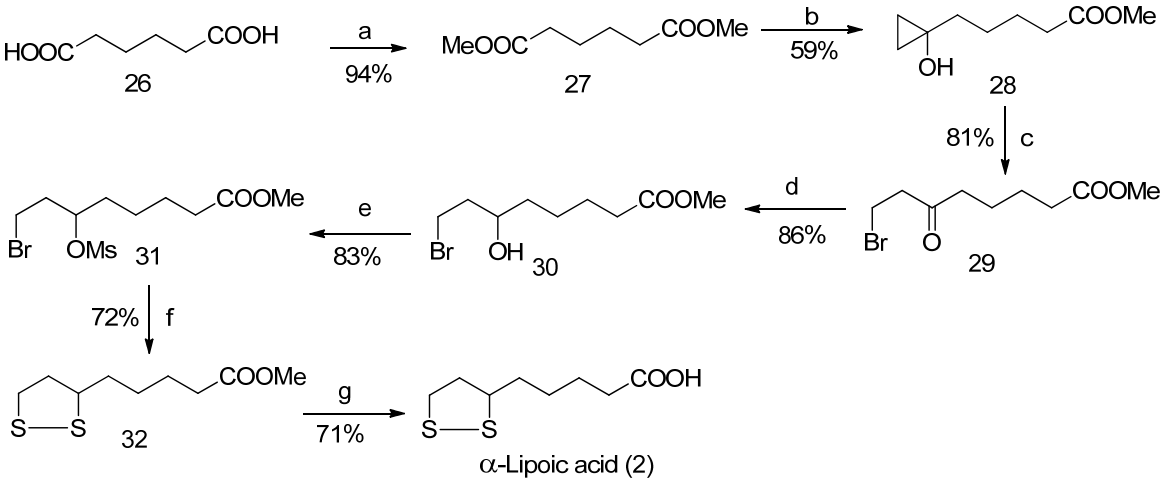
Biological Importance of α-Lipoic acid

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms. The absolute configuration of the natural α-(+)-lipoic acid was confirmed as R by the synthesis of its unnatural (-)-antipode from S-malic acid by Golding. **1)** α-lipoic acid functions as a universal antioxidant and free radical scavenger. 2) α-lipoic acid is a co-enzyme associated with a-keto acid dehydrogenation. 3) Recycles both Fat and Water-soluble antioxidant vitamins. 4) Improves sugar metabolism and energy production. (i.e. controls diabetes). 5) α-lipoic acid has been used as a therapeutic agent in a number of conditions related to liver. 6) α-lipoic acid appears to have the potential to slow the process of aging. 7) α-lipoic acid significantly reduces inflammation and it also acts as an antitumour agent. 8) α-lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication. The R-(+) enantiomer is 100 times more effective

than the S-(-)-enantiomer[16, 17] at enhancing insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism[18-20]. Hence α-lipoic acid became readily apparent through synthetic point of view. The literature review reveals formal and total synthesis of α-lipoic acid[20-22]. Among which some of these involves bio-catalytic resolution[23-25], and some of which includes organo-catalysis as key step, remaining are comprised of chiral pool synthesis[26-29]. We have successfully accomplished the synthesis of racemic α-lipoic acid, (R)-(+)-α-lipoic acid and (S)-(-)-α-lipoic acid.

Chapter 2: Section II: Synthesis of (±)-α-Lipoic Acid: Kulinkovich Approach

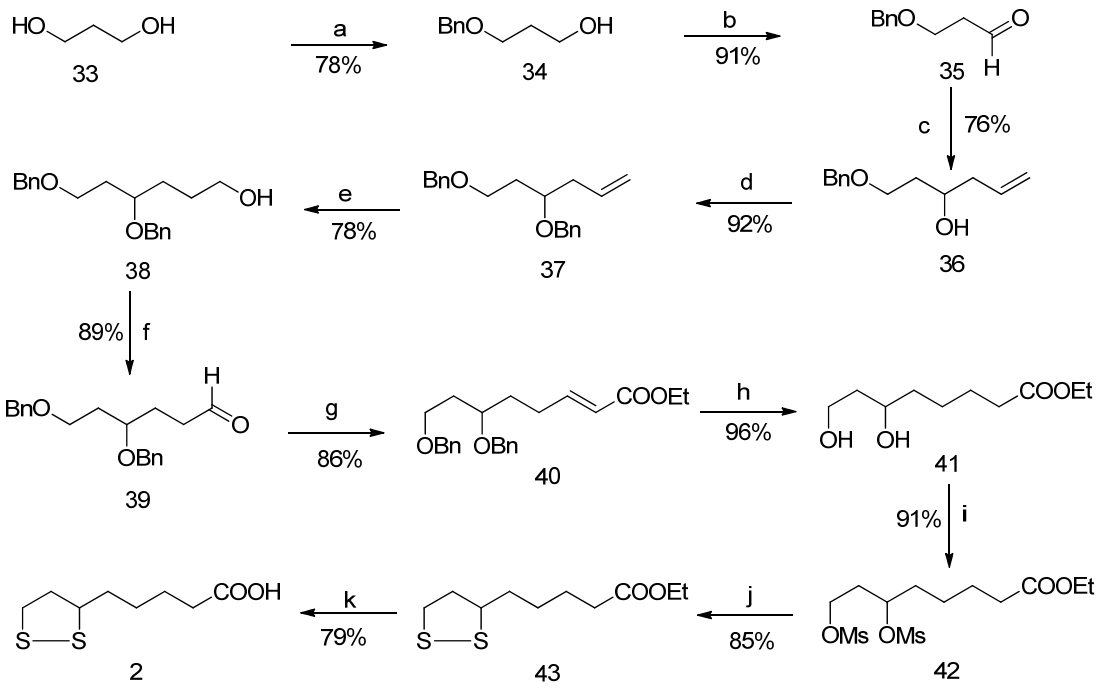
The efficient synthesis of naturally occurring molecules which are pharmaceutically important product is still a challenge in synthetic organic chemistry. Hence the key intermediate compounds with a defined carbon skeleton and defined stereo-genic property have to be generated. Therefore easy protocol which produces intermediate by short route must be implemented. In this section we synthesised (±)-α-lipoic acid (**2**) from inexpensive and commercially available adipic acid *via* Kulinkovich cyclopropanation.[30-33](Scheme 4). Accordingly, adipic acid **(26)** was converted to dimethyl adipate (**27**) which was subjected to Kulinkovich cyclopropanation to give the cyclopropanol (**28)**. Electrophilic bromination of cyclopropanol (**28)** afforded methyl 8-bromo-6-oxo-octanoate **(29)**. The reduction of (intermediate **29)** with $NaBH_4$ in dry MeOH at 0^oC- RT for 5 hr gave methyl 8-bromo-6-hydroxy octanoate **(30).** The bromoalcohol (**30)** is transformed into methyl lipoate (**32)** via mesylation followed by treatment with Na_2S/ S powder. Lipoic acid **(2)** obtained from methyl lipoate (**32**) by simple alcoholic KOH hydrolysis.



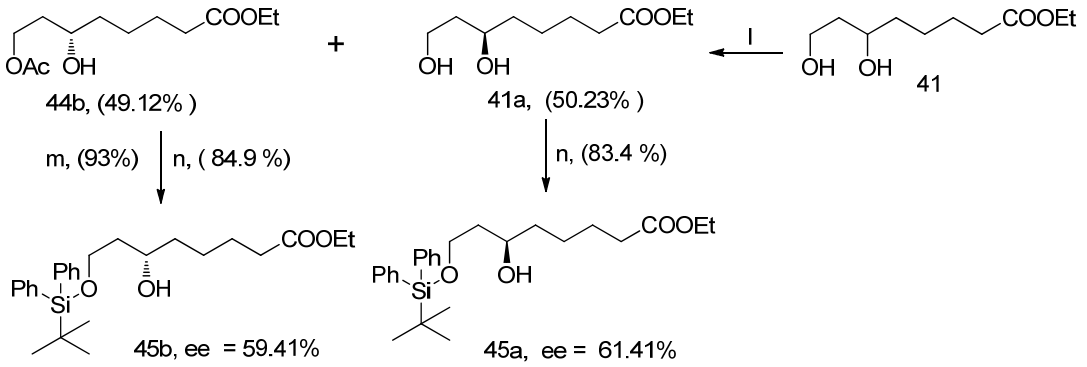
Scheme 4. *Reagents and conditions:* (a) MeOH, H^+, reflux; (b) (i) EtMgBr, THF; ii) $Ti(O^iPr)_4$, THF; iii) 5% aq H_2SO_4**;** (c) Br_2/ NBS, THF, reflux; (d) $NaBH_4$, MeOH**. ;**(e) MsCl, TEA, DCM, RT; (f) Na_2S, S_8, DMF, reflux; (g) KOH, MeOH.

Chapter 3: Section II: Chemoenzymatic Synthesis of (R)/ (S) -α-Lipoic Acid

In this section we synthesized of α-lipoic acid (**2**) from cheap and commercially available propane-1, 3-diol **(33)** using biocatalysis as a key step. As shown in scheme 5, propane-1, 3-diol **(33)** converted to bis benzyloxy intermediate **(39)**, via sequential protection, oxidation, barbier allylation, hydroboration and further protection. This bis benzyloxy intermediate **(39)** converted to dihydroxyl intermediate **(41)** via Wittig homologation and hydrogenation. Intermediate, ethyl 6, 8-dihydroxy octanoate (**41)** converted to ethyl lipoate (**43)** via mesylation followed by treatment with Na_2S/ S powder. Ethyl lipoate (**43)**, on hydrolysis by ethanolic potassium hydroxide under N_2 atmosphere produces (±)-α-lipoic acid **(2)**. After standardizing whole protocol for racemic part, we planned synthesis of chiral α-lipoic acid *via* enzymatic resolution of ethyl 6, 8-dihydroxy octanoate (**41) (**Scheme 5).



Scheme 5. *Reagents and conditions:* (a) NaH, BnBr, THF; (b) PCC, DCM, Celite; (c) Allyl-Br, Zn, THF, aq NH_4Cl; (d) NaH, BnBr, DMF; (e) $B_2H_6.Me_2S$, THF, H_2O_2, AcONa; (f) PCC, DCM; (g) Ph_3P=CHCOOEt, THF; (h) H_2, Pd-C, ethyl acetate; (i) TEA, MsCl, DCM, 0^oC-RT; (j) Na_2S, S_8, DMF, reflux; (k) KOH, EtOH, RT-12 hrs.



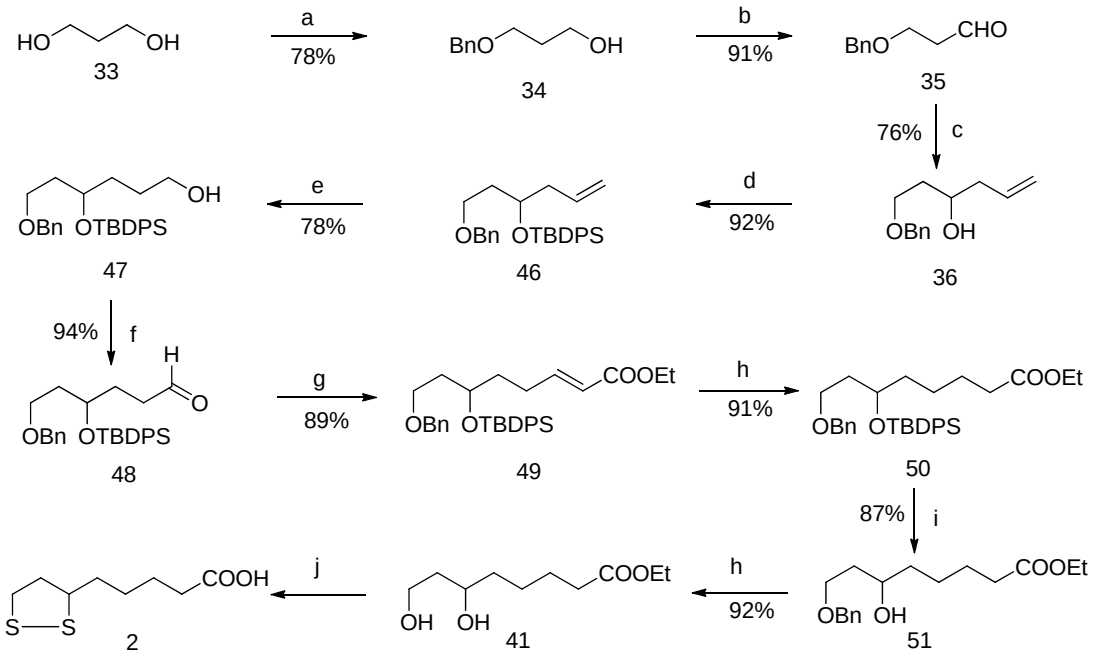
Scheme 6. *Reagents and conditions:* (l) CCL/ Vinyl Acetate, TBME; (m) K_2CO_3/ MeOH; (n) Imidazole, TBDPS-Cl, DCM

During the enzymatic transesterfication, enzyme acylated one enantiomer of diol **41** to yield **44b** whereas other enantiomer remained unreacted as diol **41a** (scheme 6). The enantio purity of these compounds was also determined by Chiral HPLC after converting to their corresponding TBDPS derivatives (**45a, 45b**). Chiral HPLC analysis confirmed the low selectivity (59-61 %) of enzymes used for the transesterification of diol **41**.

Chapter 2: Section IV: Synthesis of (*R*)-Lipoic Acid and (S)-Lipoic Acid

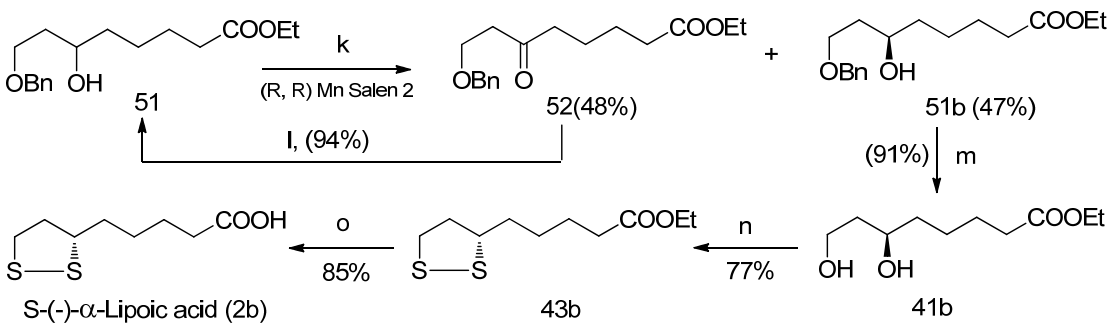
As seen in previous section (chapter 2, section III) new protocol for synthesis of (±)-α-lipoic acid successfully demonstrated but failed to synthesis chiral lipoic acid by chemoenzymatic route. This failure insisted us to replace enzyme by chiral metal complexes for use in advanced asymmetric catalysis.[29] The most widely used chiral chiral metal complexes for kinetic resolution are Co salen for hydrolytic resolution of epoxideand Mn salen for oxidative resolution of secondary alcohol. The significance of Mn salen catalyzed resolution prompted us to resolve hydroxy intermediate **51** in order to develop a feasible process for R and S (α)-lipoic acid (**2a-b**).

1,3-propane diol subjected to sequence of reactions (Chapter 2, Section III, Scheme 5) to furnish 1-(Benzyloxy)hex-5-en-3-ol (**36**). Intermediate (**36**) further sybjected to four steps, on protection, hydroboration, oxidaiton and wittig reaction gave α-β unsaturated intermediate **49** in 60.03% yield over four steps. This on hydrogenation and deprotection afforded ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**51**) in 79.17% over two steps (Scheme 7).



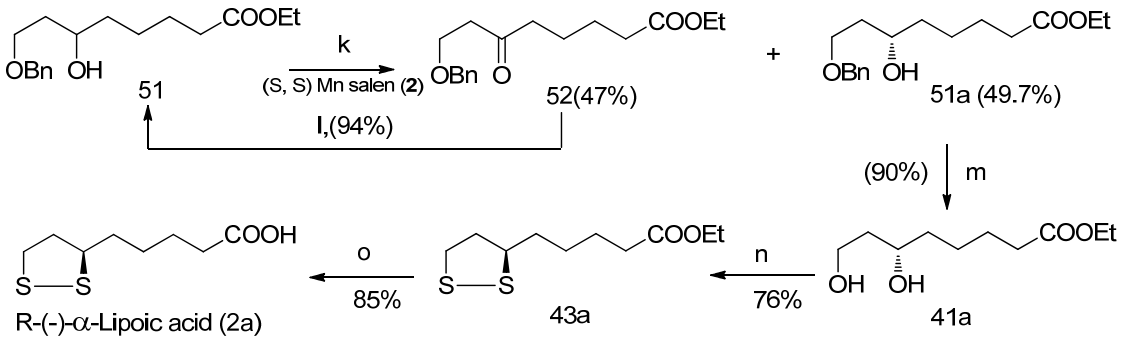
Scheme 7. *Reagents and conditions:* (a) NaH, BnBr, THF: DMF; (b) PCC, DCM, Celite, RT; (c) Allyl bromide, Zn, THF, aq NH_4Cl; (d) Imidazole, DCM, TBDPSCl; (e)$B_2H_6.Me_2S$, THF, H_2O_2, CH_3COONa; (f) PCC, DCM; (g) Ph_3P=CHCOOEt, THF; (h) H_2, Pd-C, EtOAc, RT; (i) TBAF, THF, RT; (j) (i) TEA, MsCl, DCM, 0^oC-RT; (ii) Na_2S, S powder, DMF, reflux; (iii) KOH, EtOH, RT.

Racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**51**) on treatment with (R, R) Mn salen (**2**) underwent oxidative resolution to afforded (R)-ethyl 8-(benzyloxy)-6-hydroxy-octanoate (**51b**) in high enantiomeric excess and yields (47%) and ethyl 8-(benzyloxy)-6-oxooctanoate **(52)** in 48% yield. (R)-Ethyl 8-(benzyloxy)-6-hydroxy-octanoate (**51b**) on hydrogenation, mesylation and refluxing with sodium sulphide and sulphur in DMF gave S-ethyl lipoate (**43b**) in 69.3% yield (Scheme 8).



Scheme 8. *Reagents and conditions:* (k) (R, R)-Mn salen (**2**) (2 mole %), $PhI(OAc)_2$, KBr , DCM + H_2O / RT; (l) $NaBH_4$, EtOH, RT; (m) H_2, Pd-C, EtOAc, RT; (n) (i) TEA, MsCl, DCM, 0^oC-RT; (ii) Na_2S, S powder, DMF, reflux; (o) KOH, EtOH, .

Similarly, R-ethyl lipoate (**43a**) was obtained in high enantiomeric excess from racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**51**) on treatment with Mn salen (S, S) (**2**) along with co-oxidant $PhI(OAc)_2$ and KBr in biphasic solvent (Scheme 9).



Scheme 9

R-ethyl lipoate (**43a**) and S-ethyl lipoate (**43b**) were hydrolyzed to corresponding R-lipoic acid (**2a**) and S-lipoic acid (**2b**) by treatment with KOH in ethanol, their spectral data and specific rotation were identical with the reported data in literature. Enantiomeric excess of **51a** and **51b** were determined by chiral HPLC (Column: chiralcel OD-H, mobile phase:IPA: pet ether(10:90), Wave length: 254 nm). Ethyl 8-(benzyloxy)-6-oxooctanoate obtained during Mn salene oxidation reaction was reduced with sodium borohydride to yield ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**52**) in 94% yield

Chapter 3: Studies towards synthesis of Compactin and Mevinolin Lactone

This chapter is divided into three sections

Section 1: Introduction and literature review of statin Intermediate

Introduction:

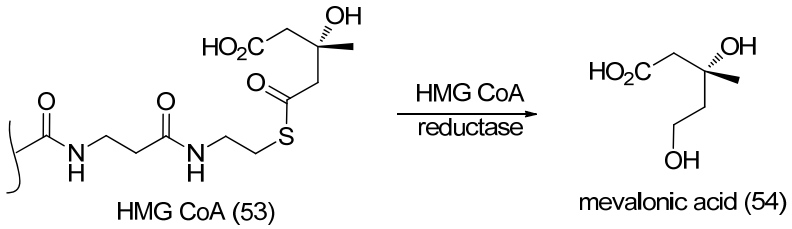


Figure 7.

In 1976, Endo et al, at the Sankyo Co. and Brown et al at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A

reductase (HMG CoA reductase) from the metabolites of *Penicillium citrinum* and *P. brevicompactum*, respectively. The new compound, shown to have structure **60** was named ML236B by the Japanese group and compactin by the British workers. In 1980, Alberts et al at Merck, Sharp & Dohme, reported the isolation of a relative of compactin **(60)** from *Aspergillus terrus*. This Merck compound was named as mevinolin and shown to have stereostructure **61**. The same fungal metabolite was isolated from Monascus rubber and named as monacolin K. In humans, more than one half of total body cholesterol is derived from *de novo* synthesis. The rate-limiting step of *de novo* synthesis is the reduction of HMG CoA (**53**) to mevalonic acid (**54**) by HMG CoA reductase (Figure 1). Because of their potent inhibitory activity on this key enzyme HMG CoA reductase; compactin and related compounds act as hypocholesterolemic agents. Various synthetic analogues of compactin are found to act as inhibitors of HMG CoA reductase. In all these analogues, a β-hydroxy-δ-lactone portion or its open chain form is present and it is essential for the activity.The literature review reveals various methods for synthesis of compactin lactone. Among which some of these involves bio-catalytic resolution, and some of which includes organo-catalysis as key step, remaining are comprised of chiral pool synthesis[34-37].

Chapter 3: Section II: Formal Synthesis of Compactin Lactone moiety

In the last three decades, many examples of asymmetric catalysis have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds such as epoxidaiton, oxidative cyclization, halohydrin formation, dihydroxylation and amino-hydroxylation.

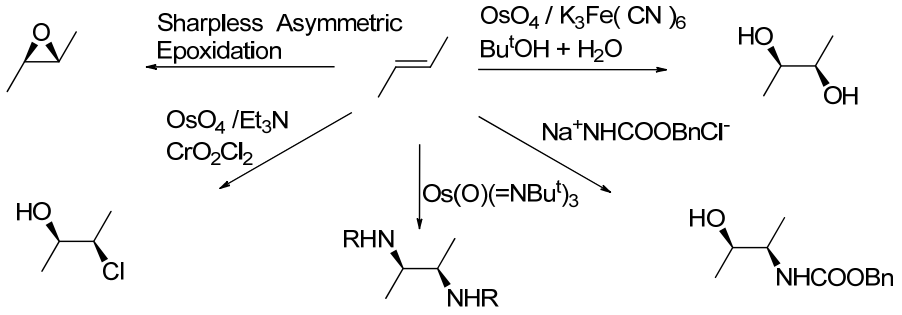
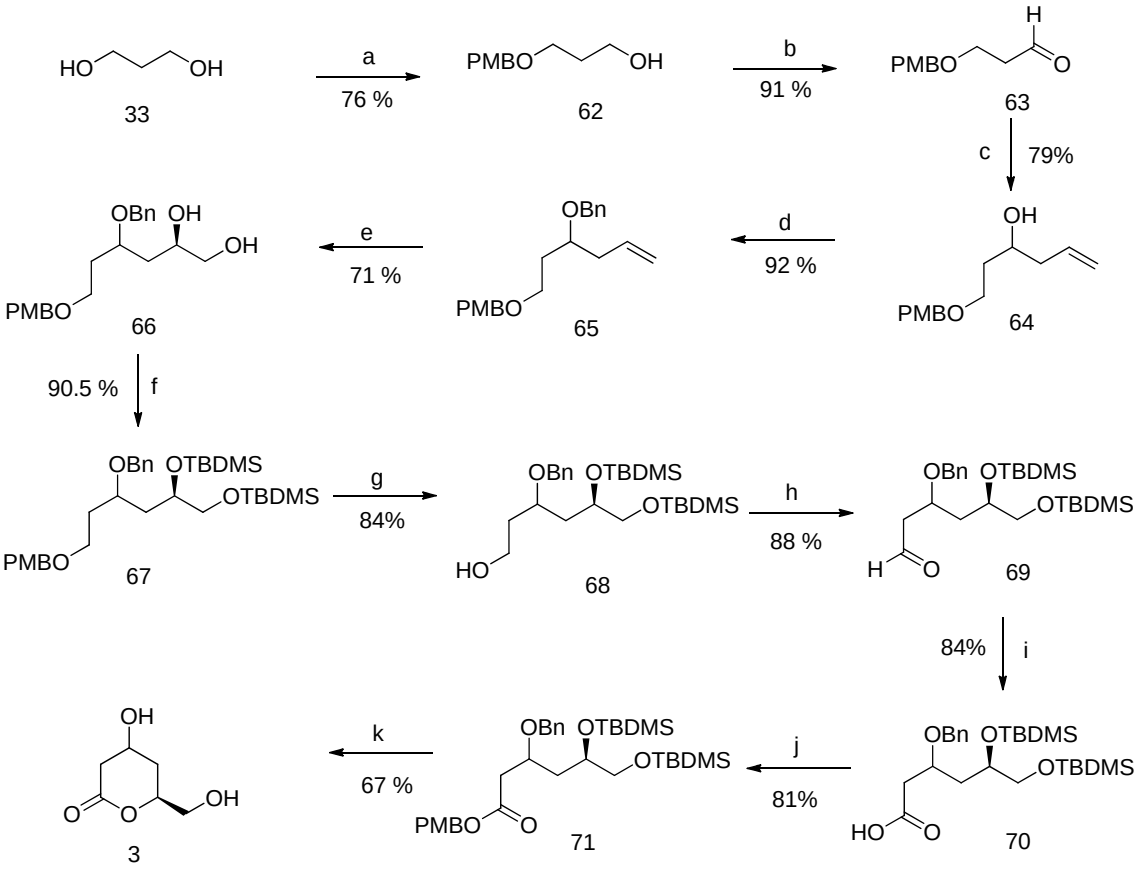


Figure 8: Transtion metal mediated 1, 2 di-functionalisation of olefins

A common feature of most of these reactions is the phenomenon of ligand acceleration, [7] wherein a metal catalyzed process turns over faster in the presence of a

co-ordinating ligand (Figure 2). The ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way. Hence, we implemented the OsO_4 catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and feasible and selective transformation in the synthesis of compactin lactone **(3)** (Scheme 8).



Scheme 8. *Reagents and conditions:* (a) NaH, PMB-Cl, DMF; (b) PCC, DCM, RT; (c) Allyl-Br, Zn, THF, aq NH_4Cl; (d) NaH, BnBr, TBAI DMF; (e) AD-mix β, ^{t}-BuOH + H_2O; (f) TBDMS-Cl, Imidazole, DCM; (g) DDQ, DCM:H_2O; (h) PCC, DCM, RT; (i) $NaClO_2$, NaH_2PO_4, DMSO, H_2O; (j) PMB-OH, EDCI, DMAP, DCM; (k) TBAF, THF-RT.

As depicted in Scheme 2, Monoprotection of propane-1, 3-diol **(33)** as 4-methoxy-benzyl ether was achieved to produce hydroxyl compound **62**, which on oxidation with PCC afforded aldehyde **63** in quantitative yield. Aldehyde **63** on treatment with allyl-zinc-bromide under Barbier conditions (aq NH_4Cl + Acetonitrile + Zn + allyl bromide), gave racemic 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol (**64**). This intermediate **64** on further treatment with sodium hydride and benzyl bromide furnished **65**. The olefin **65** on dihydroxylation with OsO_4 under conditions of

Sharpless asymmetric dihydroxylation afforded terminal diol **66;** which on treatment with TBDMS-Cl and imidazole in DMF undergoes masking of both OH groups to produce intermediate **67**. The compound **67** on treatment with DDQ gave **68**. The oxidation of **68** with PCC and $NaClO_4$, afforded acid **70.** The acid **70** further esterified with 4-methoxybenzyl alcohol to furnish ester **71** which cyclized to lactone **3** by using TBAF**.**

Chapter 3: Section III: Synthesis of Mevinic acid analogue[37]

Statins are a class of drug used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases, and statins are therefore used in the prevention of these diseases. All these statins resemble in structural features along with lactone ring (**4**). This lactone ring (**4**) or its open form is responsible for significant biological activity of statins. Further open chain form of this lactone ring resembles Mevalonate (**72**) or Mevalonic acid (**54**). Mevalonate (**72**) is a required building block for cholesterol biosynthesis and lovastatin (Mevinolin) (**61**) interferes with its production by acting as a reversible competitive inhibitor for HMG-CoA reductase which binds it.

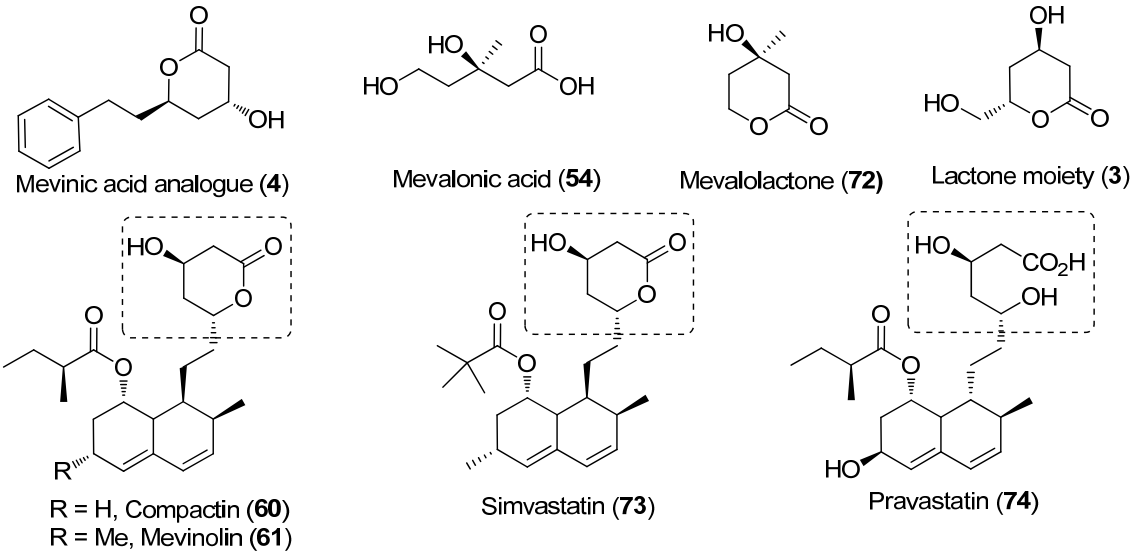
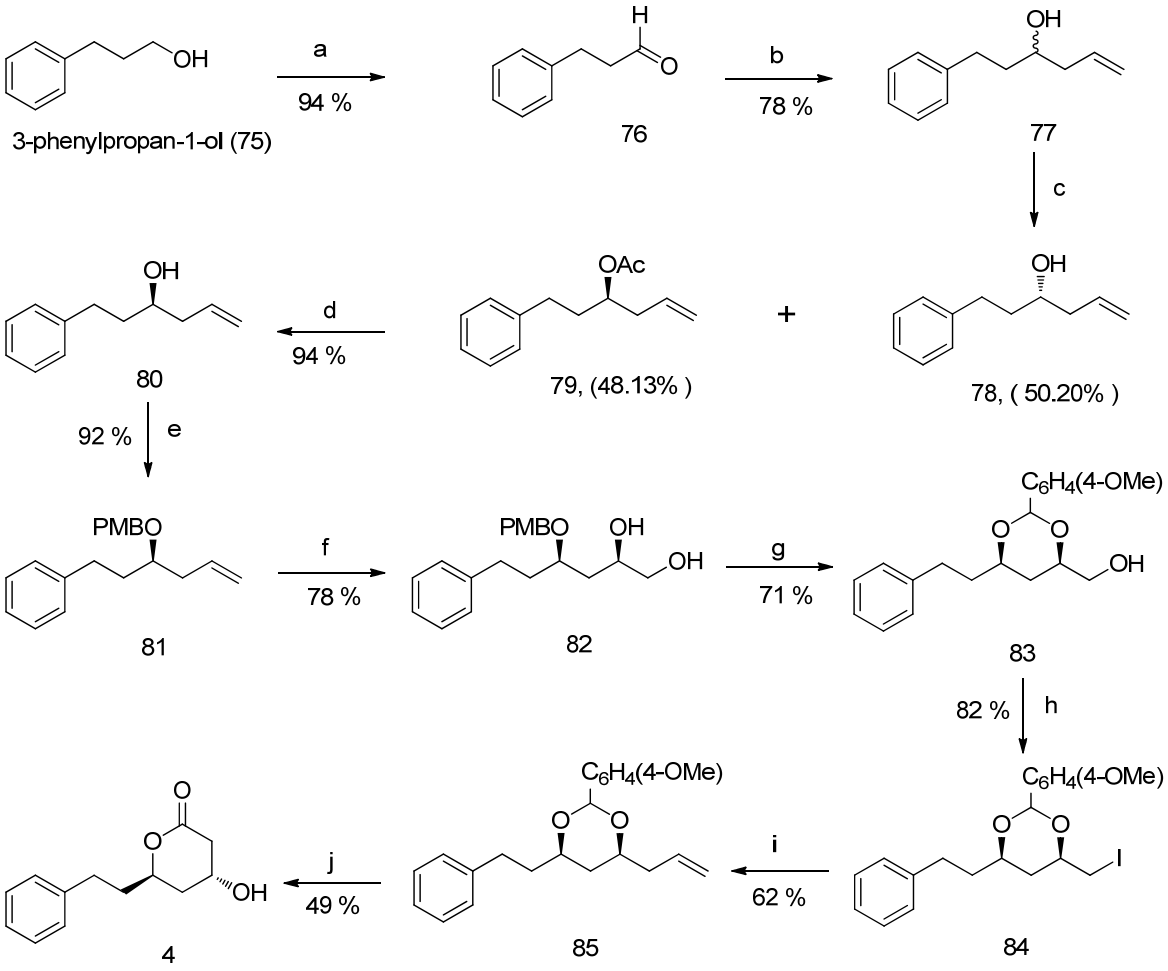


Figure 9

This significant role made statin lactone **4** or its analogue **3** as attractive targets to chemists to venture their total synthesis.Various methods have been reported over formal and total synthesis of enantiopure lactone moiety of statins (lovastatin), employing chiron approach, or kinetic resolution of racemate, all reported synthesis comprises of expensive starting material as well as lengthy route with low overall

yield as seen in previous methods. To overcome these factors here we provide simple, short, and selective route for synthesis of lovastatin lactone moiety (Mevinic acid analouge), via enzymatic resolution[4-6], dihydroxylation and acid catalyzed ring closure.



Scheme 11. *Reagents and conditions:* (a) PCC, DCM, RT; (b) Allyl-Br, Zn, THF, aq NH_4Cl; (c) CAL, VA, TBME; (d) K_2CO_3, MeOH; (e) NaH, PMB-Cl, DMF, RT (f) Bu^tOH+H_2O, DHQD, OsO_4/ $K_3Fe(CN)_6$; (g) DDQ, DCM; (h) I_2, TPP, Imidazole, THF dry; (i) Vinyl-Mg-Br, CuI, dry THF; (j) $RuCl_4$, $NaIO_4$, CCl_4, A, H_2O.

As outlined in the Scheme (2), 3-phenylpropan-1-ol **(75)**, on oxidation by using produced aldehyde **76** in quantitative yield which on treatment with Zn/ AllylBr under Barbier conditions furnished racemic intermediate 1-phenylhex-5-en-3-ol (**77**). This intermediate **77** implemented for enzymatic resolution via trans-esterification[7-9]. During this process, enzyme acylated half of racemic **77** to furnish enantiopure (R)-1-phenylhex-5-en-3-yl acetate (**79**) where as other part remains intact as enantiopure

(S)-1-phenylhex-5-en-3-ol (**78**). (R)-1-phenylhex-5-en-3-yl acetate (**79**) further hydrolyzed to (R)-1-phenylhex-5-en-3-ol (**80**), and both isomers **78** and **80** characterized by HPLC chromatography. Further intermediate **80** on protection and Sharpless asymmetric dihydroxylation furnished intermediate **82,** which on treatment with DDQ under anhydrous conditions underwent rearrangement[36] to produce hemiacetal intermediate **83.** Hemiacetal **83** on Iodination, vinylation and $RuCl_4$ catalysed cyclisation furnished target lactone **4.**

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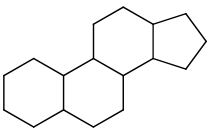
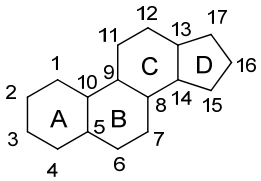
Chapter 1, Section I: Introduction and literature review of Steroids

1.1.1. Introduction

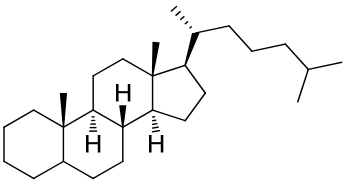
Steroids are a class of organic compounds with a chemical structure that contains the core of gonane or a skeleton derived there from. Usually, methyl groups are present at the carbons C-10 and C-13. At carbon C-17 an alkyl side chain may also be present. Sterols are special forms of steroids, with a hydroxyl group at position C-3 and a skeleton derived from cholestane.[1] Gonane is the simplest possible steroid and is composed of seventeen carbon atoms, bonded together to form four fused rings. The three cyclohexane rings (designated as rings A, B, and C in the figure to the right) form the skeleton of phenanthrene; ring D has a cyclopentane structure. Hence, together they are called cyclopentaphenanthrene.[2] commonly, steroids have a methyl group at the carbons C-10 and C-13 and an alkyl side chain at carbon C-17. Further, they very by the configuration of the side chain, the number of additional methyl groups and the functional groups attached to the rings.



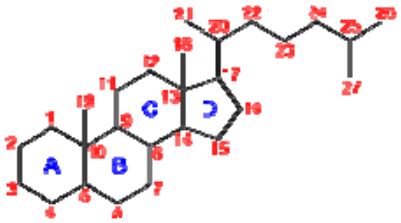
Gonane (**1**)



C atoms in gonane



Cholestane (2)



C atoms in cholestane

Figure 1

Hundreds of distinct steroids are found in plants, animals, and fungi. All steroids are made in cells either from the sterols lanosterol (animals and fungi) or from cycloartenol (plants). Both lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.[2,3]

Steroids are classified into following groups

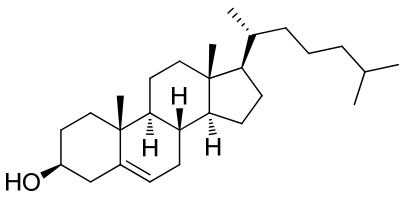
1) Animal steroids: (i) Insect steroids: Ecdysteroids such as ecdysterone

2) Vertebrate steroids: (i) Steroid hormones : Sex steroids are a subset of sex hormones that produce sex differences or support reproduction. They include androgens, estrogens, and progestagens. (ii) Corticosteroids: include glucocorticoids and mineralocorticoids. Glucocorticoids regulate many aspects of metabolism and immune function, whereas mineralocorticoids help maintain blood volume and control renal excretion of electrolytes. Most medical 'steroid' drugs are corticosteroids. (iii) Anabolic steroids are a class of steroids that interact with androgen receptors to increase muscle and bone synthesis. There are natural and synthetic anabolic steroids. In popular language, the word "steroids" usually refers to anabolic steroids. (iv) Cholesterol, which modulates the fluidity of cell membranes and is the principal constituent of the plaques implicated in atherosclerosis.

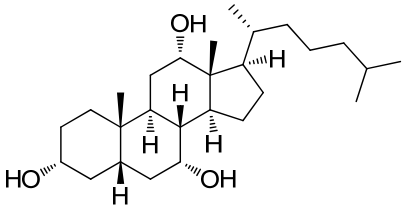
(3) Plant steroid: (i) Phytosterols, (ii) Brassinosteroids

(4)Fungus steroids: (i) Ergosterols

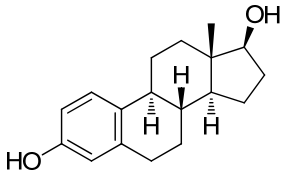
Here are the examples of some significant steroids.



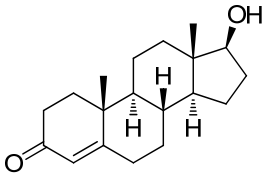
Cholesterol



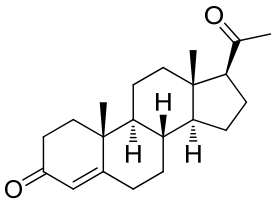
Cholic acid



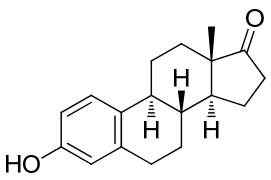
Esterdiol



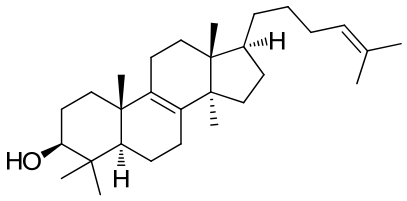
Testosterone



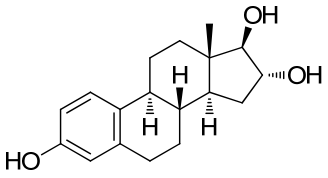
Progesterone



Estron e



Lanosterol



Estriol

Figure 2

After revelling all of the above structures, it is observed that, all the steroids have A, B, C, and D ring in sequential fusion. Further A-B ring fusion and C-D ring fusion have axial methyl groups respectively along with either hydroxyl group or other than hydroxyl group on C_1. Spatial orientation of methyl group on C_{10} or C_{13} and orientation of group on C_{17} , discriminates one steroid from the other.

In view of the importance of steoid it was thought to synthesized steroid skeleton, CD ring, by chemoenzymatic fashion. (Figure 3)

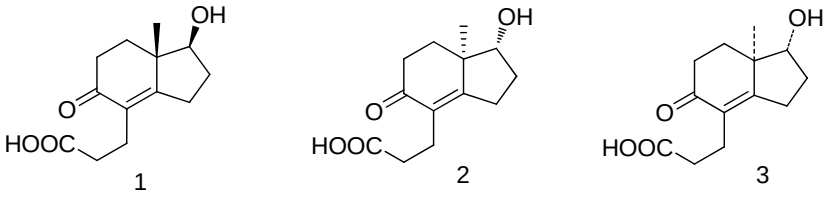


Figure 3

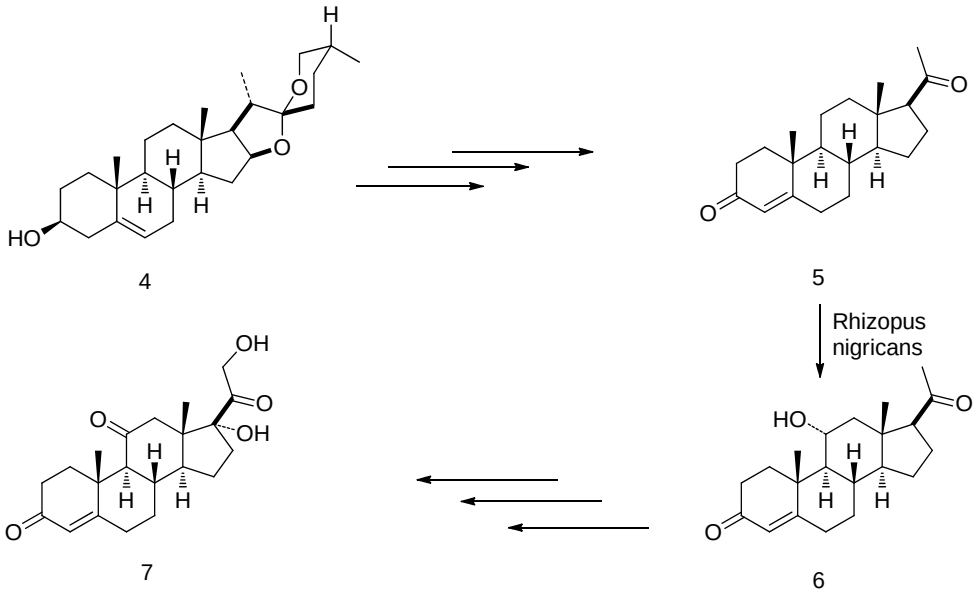
1.1.2. Literature review

The existence of steroids has been known for more than a century with the isolation of cholesterol from gall stones by Chevreul in 1815,[1] the elucidation of its chemical structure by Windaus in 1932,[2] and the first total synthesis of equilenin accomplished by Bachmann in 1939 taking advantage of Butenandt's ketone.[3] With their discovery probably dating from ancient times and their chemical characterization in the 1930s,[4] vitamins D have also largely contributed to the incontestable explosion of interest in steroid chemistry. For a long time, however, only few efficient asymmetric methods such as Diels–Alder or aldol cyclization, were available to control the formation of stereogenic centers**.** [5, 6]

1.1.2.1 Marker and peterson *et al.*

First hemi-synthesis of progesterone **5** reported in 1947 by Marker, from sapogenins **4** extracted from agaves of Mexico and the Southern United States, has revealed as a major breakthrough in modified steroid synthesis.[7]

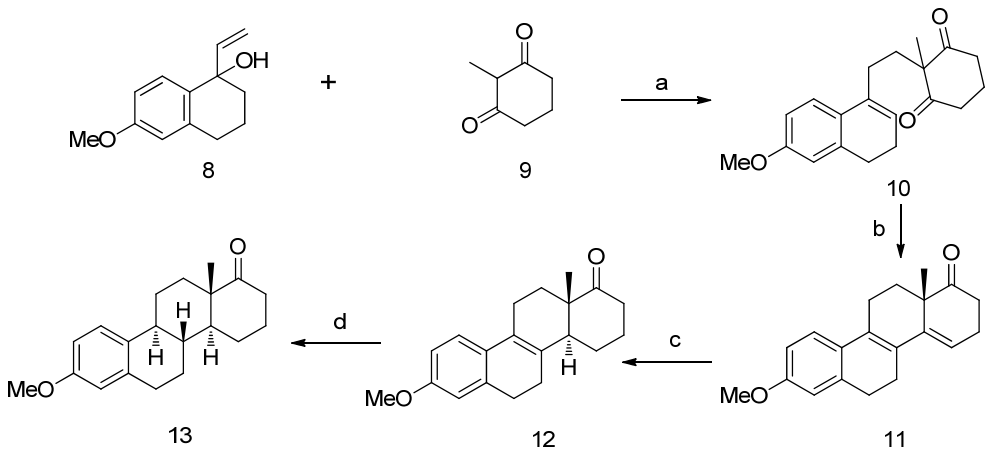
In 1952, Peterson[8] showed that microbiological hydroxylation of progesterone **5** by the mushroom, Rhizopus nigricans, occurred regio- and stereo-selectively at the C (11) position [9,10] opening up a route to the preparation of cortisone **7**.[11]



Scheme 1

1.1.2.2 Torgov *et al.*

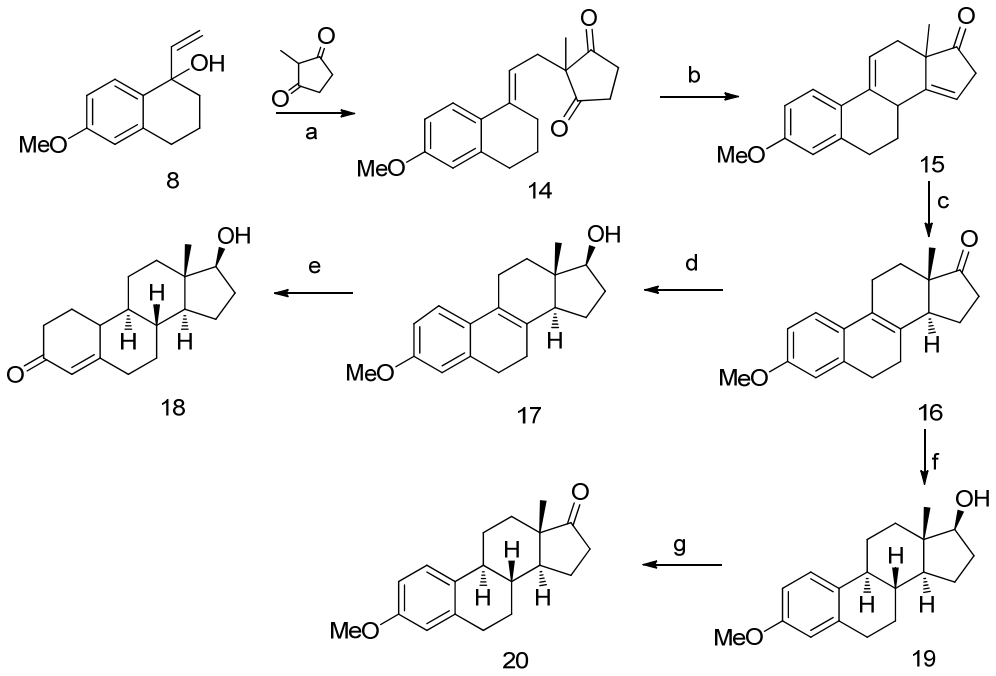
Torgov and coworkers synthesized steroidal core via condensation of 6-methoxy-1-vinyl-1, 2, 3, 4-tetrahydronaphthalen-1-ol- (**8**) with 2-methylcyclohexane-1,3-dione (**9)** in the presence of Triton B as a base to give a seco-C tricyclic intermediate **10** which on cyclization yielded Torgov diene **11** and was converted into D-homo-estrone (**13)**[12]



Scheme 2. *Reagents and conditions:* (a) Triton B; (b) P_2O_5; (c) H_2/ Pd; (d) K, liq NH_3.

1.1.2.3 Ananchenko and Torgov *et al.*

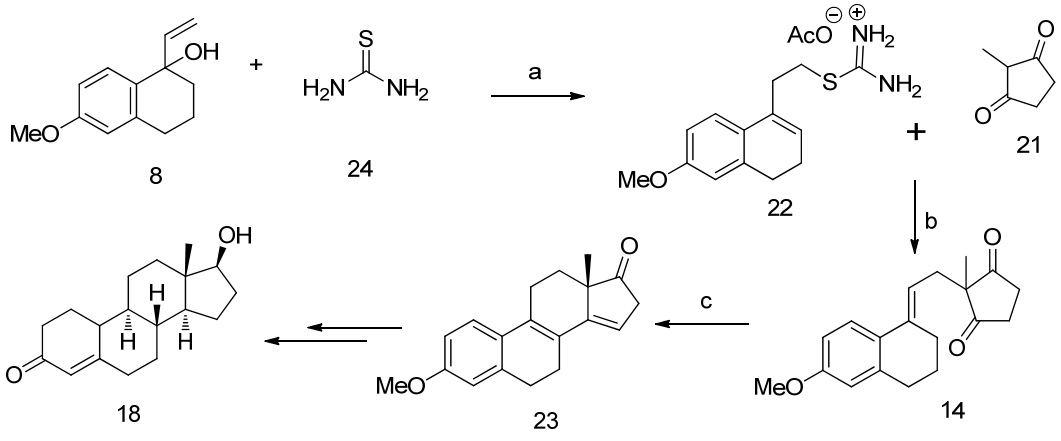
Ananchenko and Torgov extended above Scheme 2 protocol to the preparation of 19-nor-testosterone (**18)** and estrone (**20)** by using methylcyclopentanedione (**21)** as the D-ring precursor.[13] The thermodynamically disfavored trans-CD-ring junction was obtained by hydrogenation of the C_{14}–C_{15} double bond, while the anti-relation between the vicinal C_8 and C_9 atoms was established by a Birch-type reduction.[14]



Scheme 3. *Reagents and conditions:* (a) Triton B , MeOH; (b) TsOH, PhH; (c) H_2/ Pd, (d) $LiAlH_4$, THF; (e) (i) K, Li, EtOH, NH_3, (ii) HCl, $CHCl_3$, (f) K, NH_3; (g) PCC.

1.1.2.4 Windholz and Wendler *et al.*

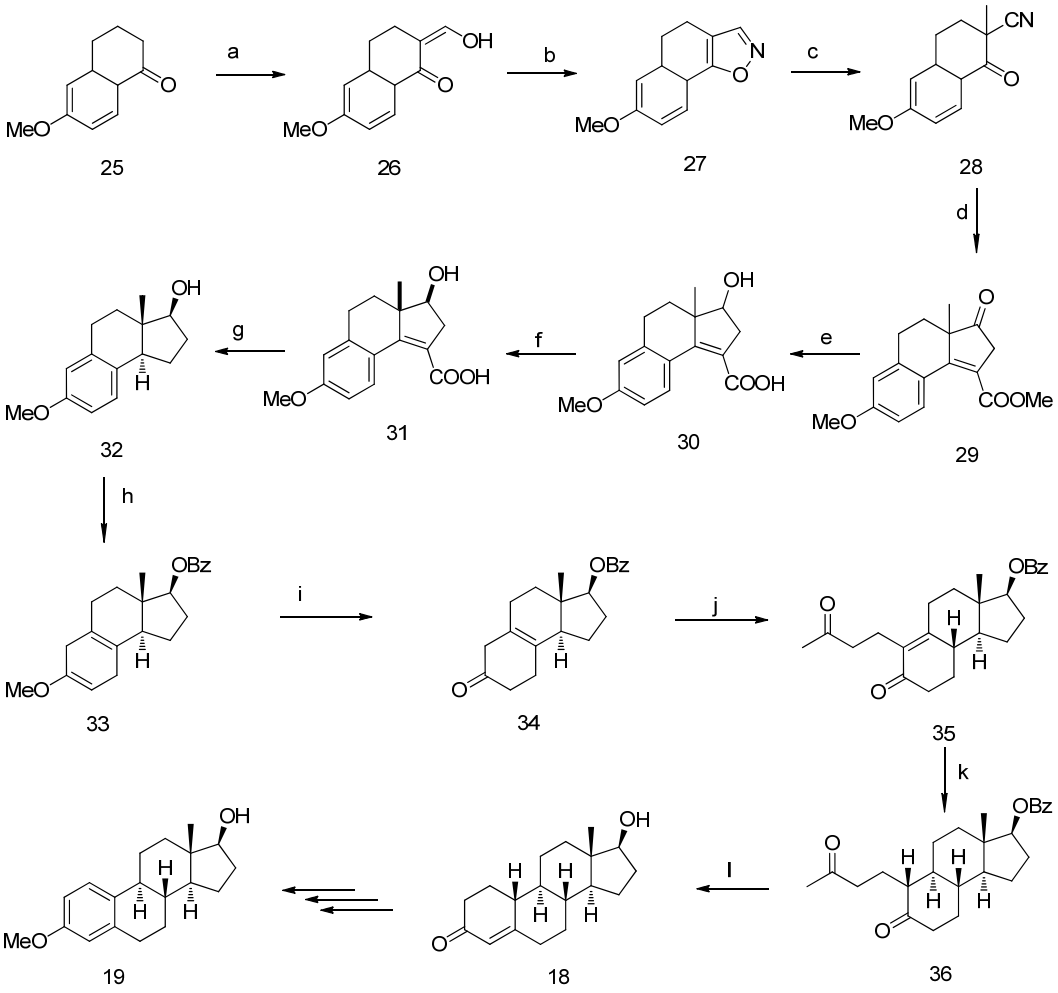
Windholz and Wendlersynthesised oral contraceptive nor testosterone (**18)** via condensation of methylcyclopentanedione and (**21)** thiouronium salt (**22)**.[15-17]



Scheme 4. *Reagents and conditions:* (a) AcOH, (b) (i) Py, PhMe, Δ; (c) TsOH, PhH;

1.1.2.5 Velluz *et al.*

In 1960 Velluz and co-workers from Roussel-Uclaf carried out the first enantioselective synthesis of (+)-nor-testosterone (**18)** on industrial scale.

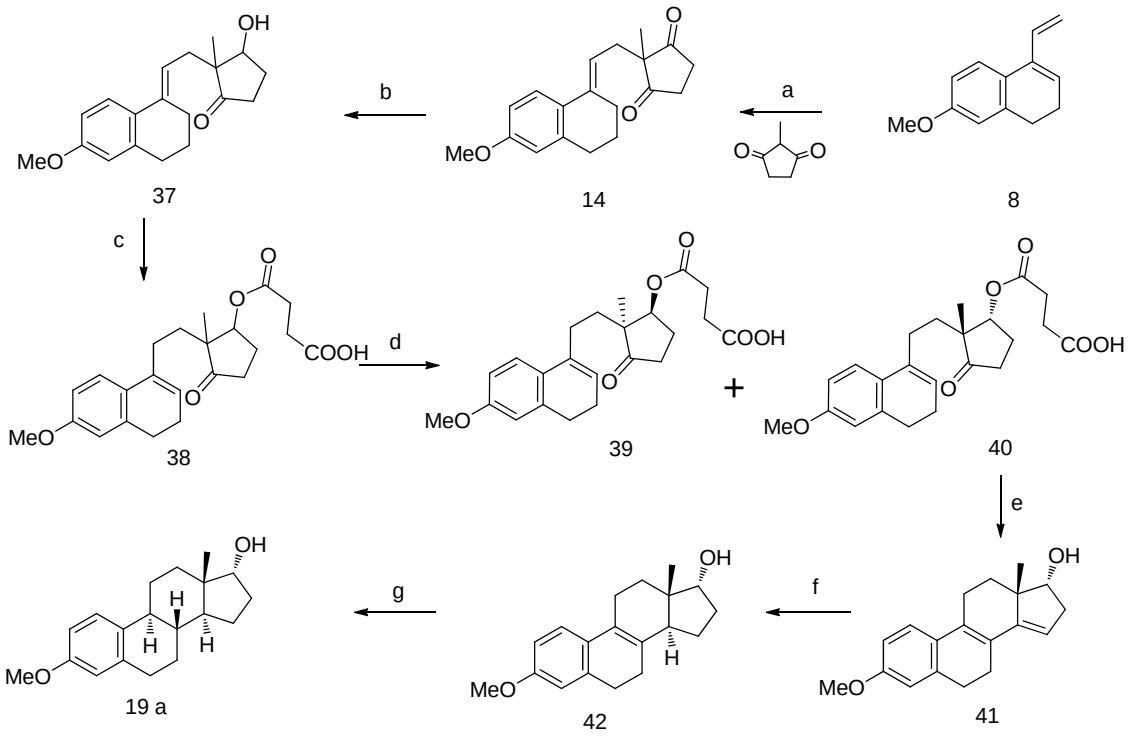


Scheme 5. *Reagents and conditions:* (a)HCOOEt, EtONa, PhH; (b) $H_2NOH.HCl$, AcOH; (c) (i) Bu^tOK, Bu^tOH, (ii) MeI; (d) $(CH_2COOH)_2$, Bu^tOH, Bu^tOK; (e) (i) $NaBH_4$/ EtOH; (ii) $Ba(OH)_2$, EtOH, H_2O; (f) (i) L-(+)-Threonin; (ii) Heat, (g) H_2/ Pd; (h) (i) PhCOCl, TEA (ii) Li/ NH_3; (i) $(COOH)_2$, EtOH + H_2O; (j) (E)-1,3-dichlorobut-2-ene; (k) (i) H_2/ Pd; (l)(i) HCl.

In this approach a tricyclic acid (**30**), was synthesised from **25**, which has been resolved by (+)-(1S, 2S)-1-p-nitrophenyl-2-aminopropane-1,3-diol. This is followed by sequential steps to furnish (+)-nor-testosterone (**18**) and (+)-β-estradiol (**19**).[18- 25]

1.1.2.6 Wendler *et al.*

An elegant strategy was elaborated for unnatural esterdiol (**19a**) by the Wendler and coworkers in Merck group in which secodione **14** obtained from the Torgov reaction, selectively reduced to a ketol and its hemisuccinate subjected to an optical resolution with quinine. The dextrorotatory enantiomer **39** was recycled via saponification and oxidation of the hydroxyl group at position C (17).[26, 27]

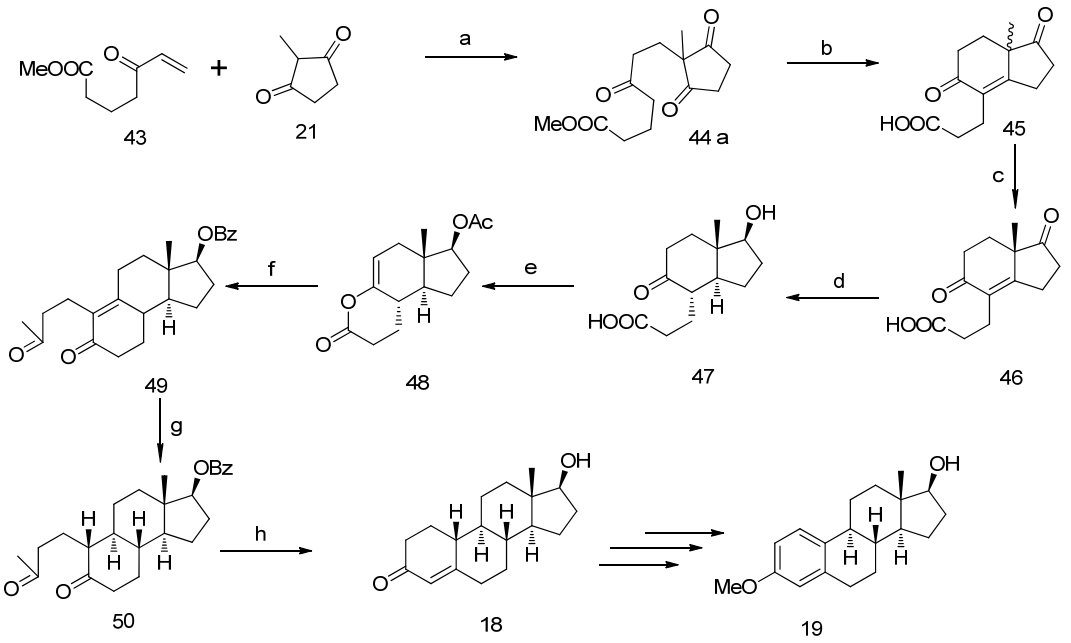


Scheme 6. *Reagents and conditions:* (a) Pyridine, PhH, Reflux; (b) $(^{t}BuO)_3AlLiH$, THF; (c) Pyridene, Succinic anhydride; (d) (i) quinine, acetone; (ii) crystalization, (iii) H_2SO_4, H_2O, PhH, EtOAc; (e) (i) p-TsOH/ PhH, (ii) KOH, MeOH; (f) H_2/ Pd, PhH (g) K , NH_3.

1.1.2.7 Velluz and Amiard *et al.*

Velluz and Amiard *et al***;** chemists from Roussel-Uclaf have prepared optically pure bicyclic acid **46** via a Robinson annulation and its resolution with (-)-ephedrine**.**[28] A significant result **47** was obtained with the diastereoselective reduction and hydrogenation of this acid that led to the CD--ring trans junction. Acid catalysed cyclisation of intermediate **47** leads to the formation of an intermediate- δ-lactone **48 .** Intermedaite **48** on treatment with the Grignard reagent of 2-(2-bromo-ethyl)-2-

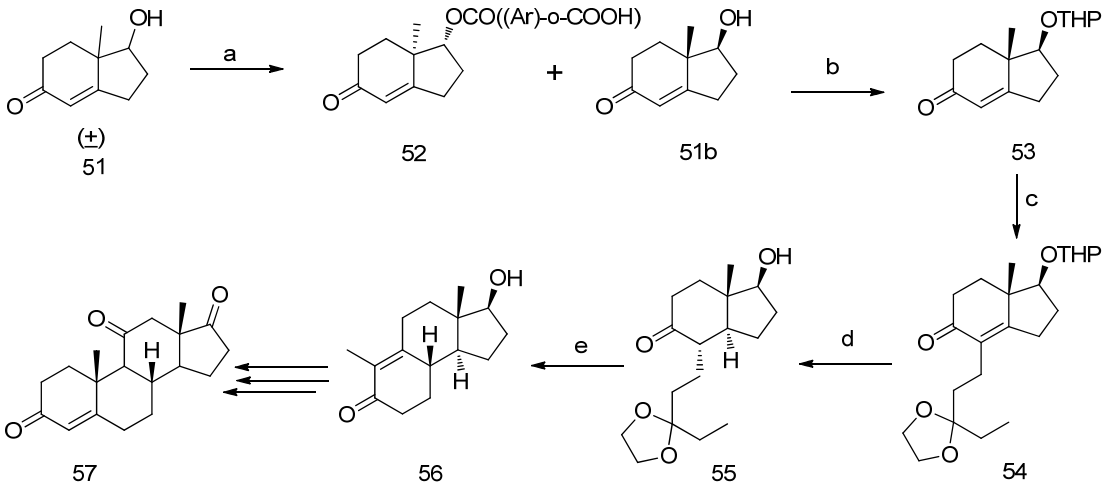
methyl-[1, 3] dioxolane, according to the Fujimoto–Belleau reaction, [29] allowed the construction of the B-ring **49**. A subsequent cyclization through aldol condensation and further sequence of reactions completed the synthesis of nor testerone **18** and esterdiol **19.** [30]



Scheme 7. *Reagents and conditions:* (a) Pyridine, PhH, Reflux; (b) 5N HCl; (c) (i) (-) Ephidrine/ PhH, (ii) $(COOH)_2$, acetne; (d) $NaBH_4$/ -NaOH; (i) H_2/ Pd, EtOH; (e) Ac_2O/ -AcONa; (f)) (i) (3-(2-methyl-1,3-dioxolan-2-yl)propyl)-MgBr, THF; (ii) AcOH, (iii) KOH, MeOH; (iv) PhCOCl, Pyridine, PhH; (g) (i) H_2-Pd; (ii) HCl, AcOH. (h) NaOMe.

1.1.2.8 Hajos and Parrish *et al.*

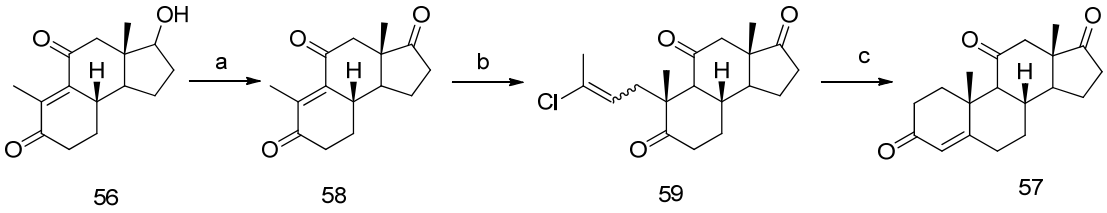
Hajos and Parrish reported the synthesis of the optically active (-)-17β-hydroxy-des-A-androst-9(10)-in-5-one (**56**), easily accessible from the indenol (**51)** via a Robinson annulation of methylcyclopentanedione with methyl vinylacetone followed by a selective carbonyl reduction. The corresponding hydroxyl group was converted to phthalate and resolved through diastereomeric salt formation with brucine.[31, 32]



Scheme 8. *Reagents and conditions:* (a) Phthalic anhydride, pyridine; (ii) Brucine, PhH; (iii) 0.16 N HCl, Acetone; (iv) 5 N NaOH; (b) DHP, H^+; (c) NaH, DMSO, 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane; (d) (i) H_2/ Pd EtOH; (ii) H^+, MeOH. (e) NaOMe, MeOH;

1.1.2.9 Stork *et al.*

Stork and coworkers reported adrenosterone **(57)** synthesis by reductive alkylation of the tricyclic enedione **56** with theWichterle reagent and cyclization [26]

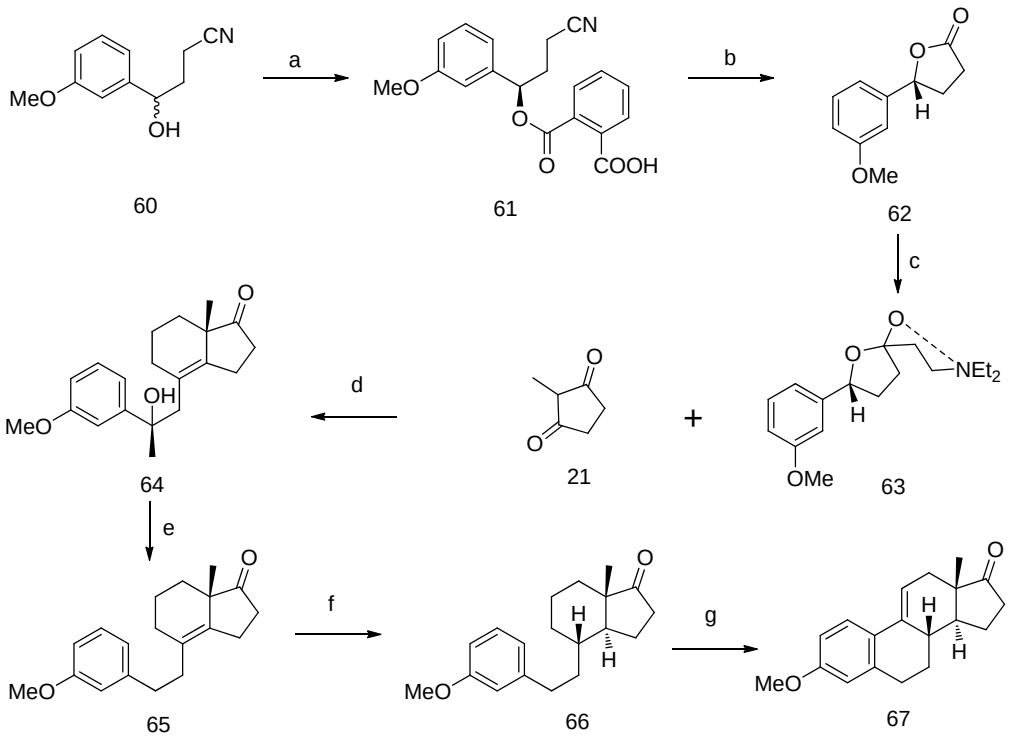


Scheme 9. *Reagents and conditions* (a) PCC; (b) 1, 3-dichlorobut-2-ene; (c) Wichterle

1.1.2.10 Smith *et al.*

Smith and co-workers implemented optical resolution step at an early stage on the acid phthalate derivative of a hydroxy nitrile (**60**) using (R)-(+)-α-methylbenzylamine.[33] The resulting optically active lactone was readily converted into the desired Mannich base from the corresponding vinyl ketone in a few steps. Its condensation with 2-methyl-1,3-cyclopentanedione in refluxing toluene/acetic acid

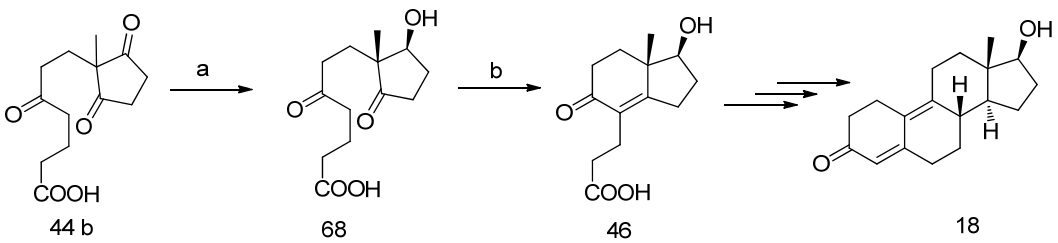
afforded predominantly the expected ketol epimer (**64**). The dehydroxylated enedione adduct transformed to (+)-3-methoxy-1, 3, 5(10), 9(11)-estratetraen-17-one (**67**) [34-35]



Scheme 10. *Reagents and conditions:* (a) Phthalic anhydride, pyridine; (ii) (+)-α-methylbenzylamine, PhH; (iii) 3 N HCl; (b) (i) 10 % NaOH (ii) 3 N HCl; (c) (i) DIBAL-H/ PhMe, (ii) Vinylmagnesium bromide, THF, (iii) MnO_2, Et_2NH; (d) (i) AcOH, reflux; (e) (i) TsOH, PhMe (ii) Pd (C)/ PhMe (f) (i) $NaBH_4$, EtOH, (ii) Pd(C), MeOH; (iii) Jones reagent; (g) 10 N HCl.

1.1.2.11 Bellet *et al.*

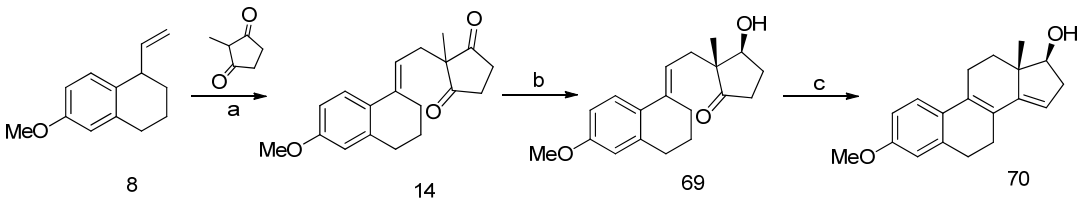
Bellet and Gibian *et al* proposed the use of Rhizopus arrhizus for the enantioselctive reduction of cyclopentane-1,3-Dione, which further converted by sequence of reactions to synthesise 19 nor testosterone. [36-37]



Scheme 11. *Reagents and conditions:* (a) Rhizopus arrhizus (b) 5 N HCl.

1.1.2.12 Gibian and Kieslich *et al.*

Gibian and Kieslich followed Torgov reaction for the synthesis Torgov secodione **14**. Enzymatic reduction of **14** with Saccharomyces uvarum[38] gave **69** which further on acid treatment converted to **70**.[37]

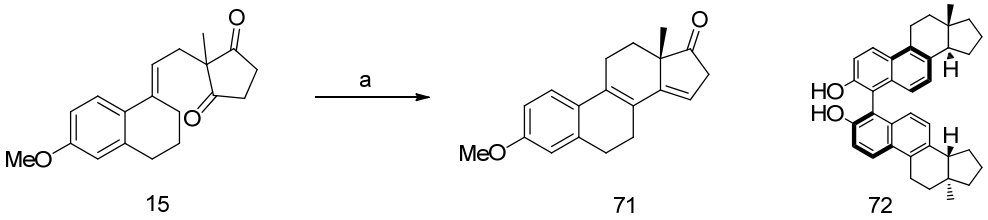


8 14 69 70

Scheme 12. *Reagetns and conditions:* (a) Triton B (b) Saccharmoyces uvarum; (c) H^+

1.1.2.13 Enev *et al.*

Enev and co-workers reported the first catalytic and enantioselective cyclization of the well-known methyl secodione (**15**) to estrone. This methodology involved an elegant asymmetric desymmetrization of the cyclopentanedione unit **15** promoted by a new sterically demanding bis-steroidal titanium complex, with excellent high intrigity.[39]



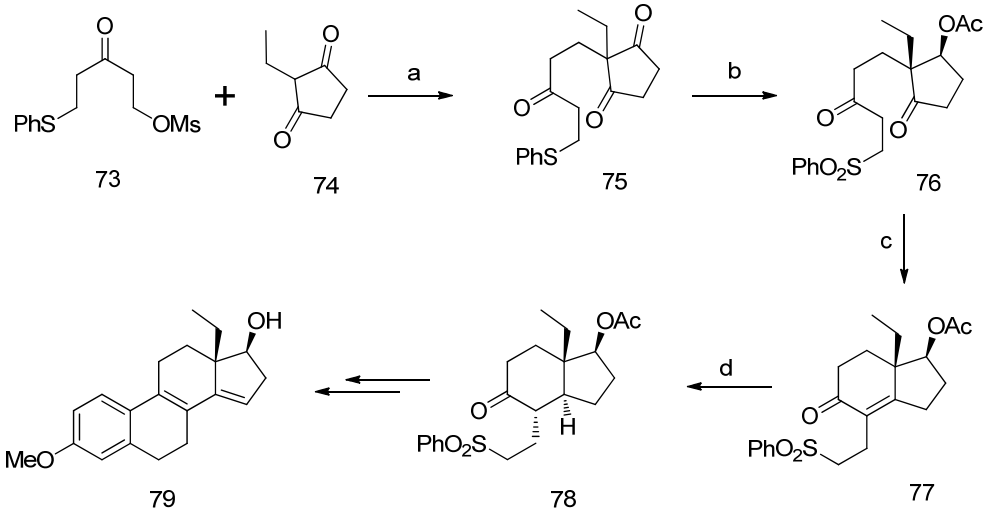
15 71 72

Scheme 13. *Reagents and conditions:* (a) L-(^{i}PrO)$_2$TiCl$_2$ (20%), AgBF$_4$, MS, PhMe.

1.1.2.14 Dai and Zhou *et al.*

Dai and Zhou *et al* prepared optically active steroid CD-ring synthon by microbial asymmetric reduction of a prochiral trione (**75**), This prochiral trione, obtained by alkylation of 2-ethylcyclopentane-1,3-dione (**74**) with 3-oxo-5-(phenylthio)-pentyl methane-sulfonate (**73**), was enzymatically reduced with Saccharomyces cerevisiae. After sulfur oxidation and acid-catalyzed cyclization

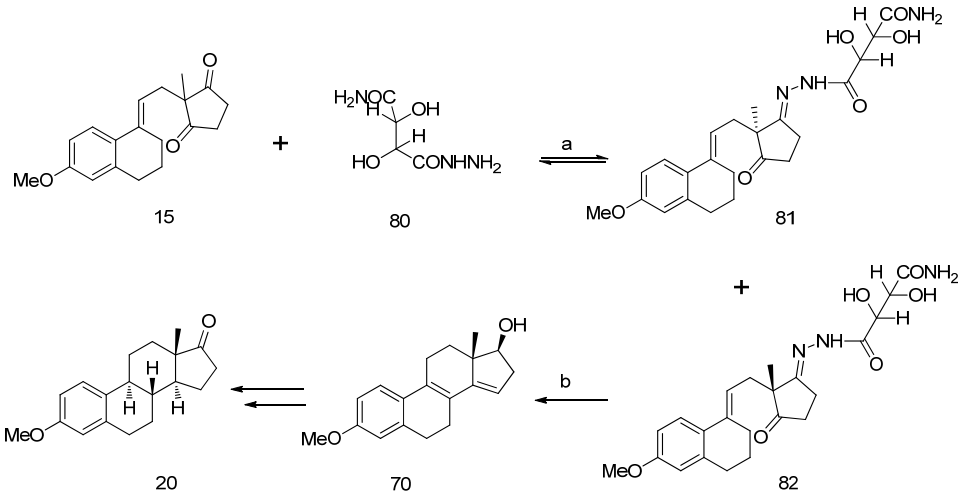
yielded unsaturated ketosulfone **77**. Selective catalytic hydrogenation of **77** the gave **78**[40] which was converted to target steroid **79.**



Scheme 14 *Reagents and conditions:* (a) TEA, THF; (b) (i) Saccharmoyces cerevisiae; (ii) Ac_2O, Py; (iii) $NaIO_4$, MeOH/ H_2O; (c) *p*-TsOH/ PhH; (d) (i) H_2/ Pd; (ii) H^+/ EtOH.

1.1.2.15 Bucourt and Narau *et al*

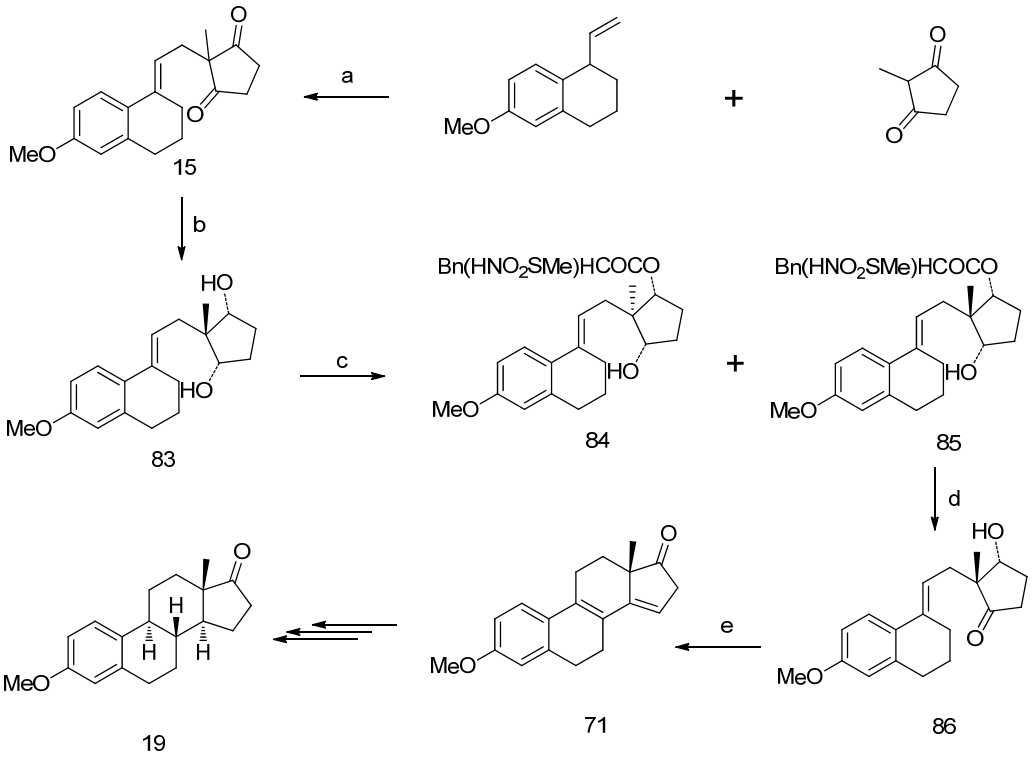
Roussel-Uclaf chemists used L-tartaric acid hydrazide to resolve Torgov secodione (**15**), a precursor of (+)-estrone (**20**).[41]



Scheme 15 *Reagents and conditions:* (a) AcOH, MeOH, H_2O; (b) HCl, dioxane, H_2O; (c) (i) K, Liq NH_3.

1.1.2.16 Bucourt and Narau *et al.*

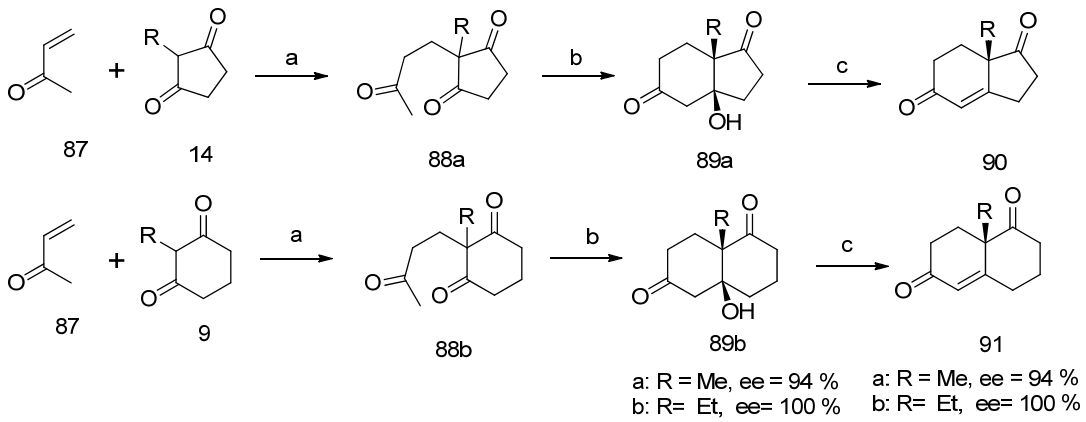
In another approach, Narau and co-workers reported the enantio-convergent synthesis of an optically pure steroid intermediate by considering first the stereoselective reduction of the Torgov secodione **15** into meso-diol **83** followed by its partial esterification with N-mesyl (S)-phenylalanyl chloride as a chiral reagent. The diastereoisomers were separated by chromatography and converted into a unique optically pure estrone precursor **71** via a sequence of protection–deprotection–oxidation and a final acid-promoted cyclization.[42]



Scheme 16. *Reagents and conditions:* (a) Triton B, PhH; (b) $(t\text{-BuO})_3AlHLi$, THF (c) N-mesyl (S)-phenylalanyl chloride, pyridine; (d) (i) Swern oxidation; (ii) KOH, MeOH.; (e) (i) HCl, MeOH, (ii) Swern oxidation.

1.1.2.17 Hajos–Parrish–Eder–Sauer–Wiechert reaction *et al.*

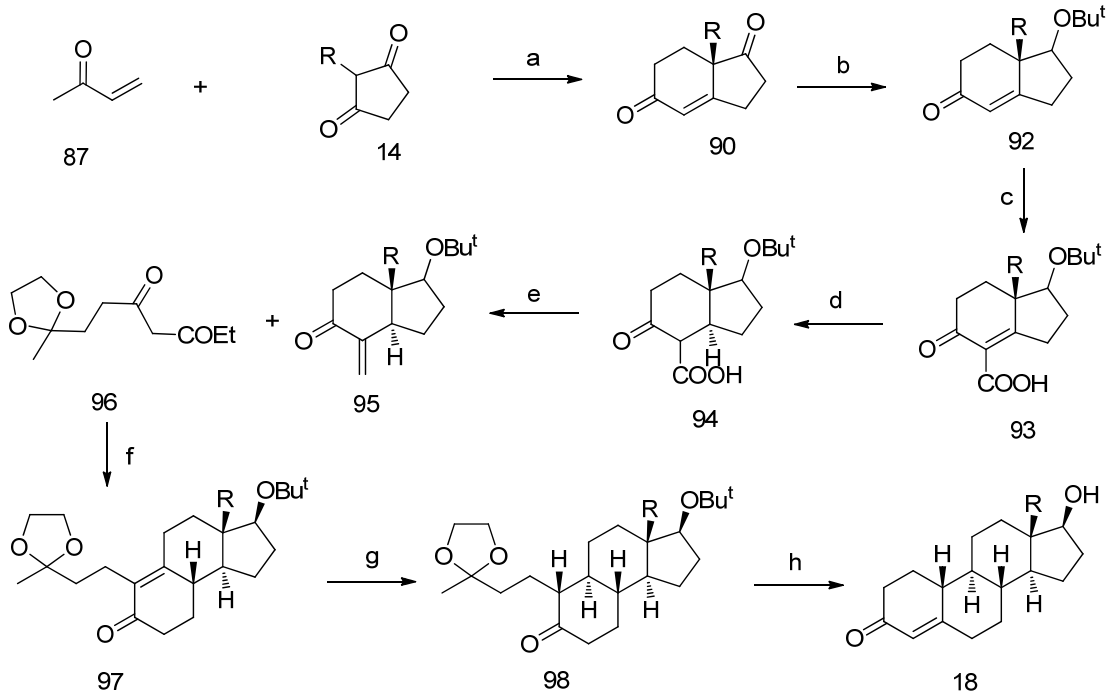
Hajos, Parrish[43] and Eder, Sauer, Wiechert[44] demonstrated the use of L-proline to obtain ketol (**89a,b**)**.** Aldol product **89a** formed undergoes acid catalysed de-hydration to form the indane-dione **90a** This methodology was also applied to the preparation of the Wieland–Miescher ketone (**91**).[45-47]



Scheme 17 *Reagents and conditions:* (a) AcOH, H_2O; (b) L Proline, DMF; (c) H^+/ PhH.

1.1.2.18. Hajos and Parrish *et al.*

Hajos and Parrish synthesised 19-nor-steroids by protocol as shown in scheme 18 on industrial scale.

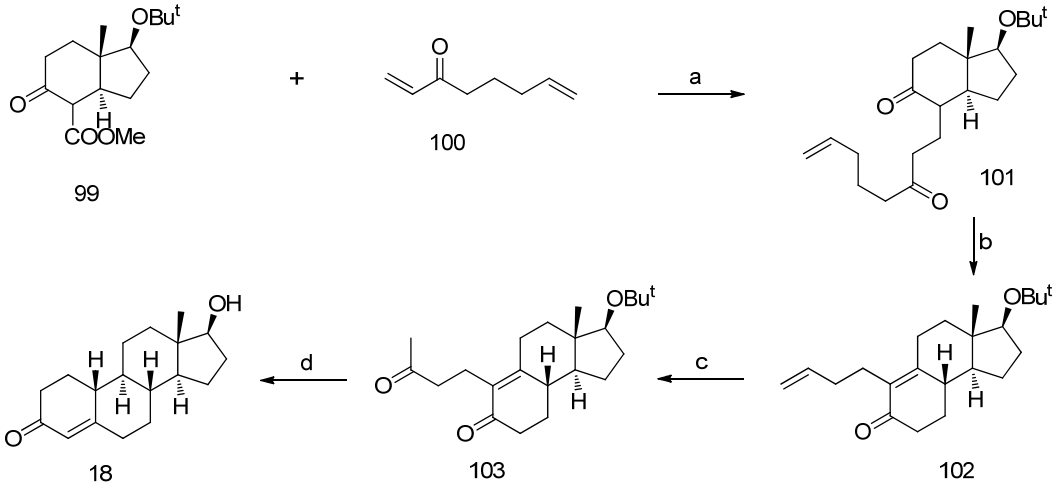


Scheme 18. *Reagents and conditions:* (a) (i) AcOH, H_2O; (ii) L Proline, DMF; (iii) H^+/ PhH; (b) (i) $NaBH_4$, EtOH; (ii) 2-methylprop-1-ene, (iii) H_3PO_4, $BF_3.OEt_2$; (c) MeOMgOCOOMe, DMF; (d) H_2, Pd-$BaSO_4$, MeOH; (e) HCHO, piperidine, DMSO, H_2; (f) (i) NaOMe, MeOH; (ii) H^+ (g) H_2, Pd, MeOH; (h) HCl, MeOH

2-Methyl cyclo-penatane-1,3-dione **14** on condensation with methyl vinyl ketone **87** gave triketone **90,** which on sequential reactions furnished keto acid **93** on hydrogenation gave rise to the unique trans-indanedione **94.** Michael addition of a substituted β-keto ester to the methylene ketone **95** followed by aldol condensation, ring annulation, saponification, hydrogenation, and acid catalysed aldol condenastion furnished the tricyclic compound **97**, which was converted into the required 19-nor-steroid **18**.[48-50]

1.1.2.19 Tsuji and co-workers *et al.*

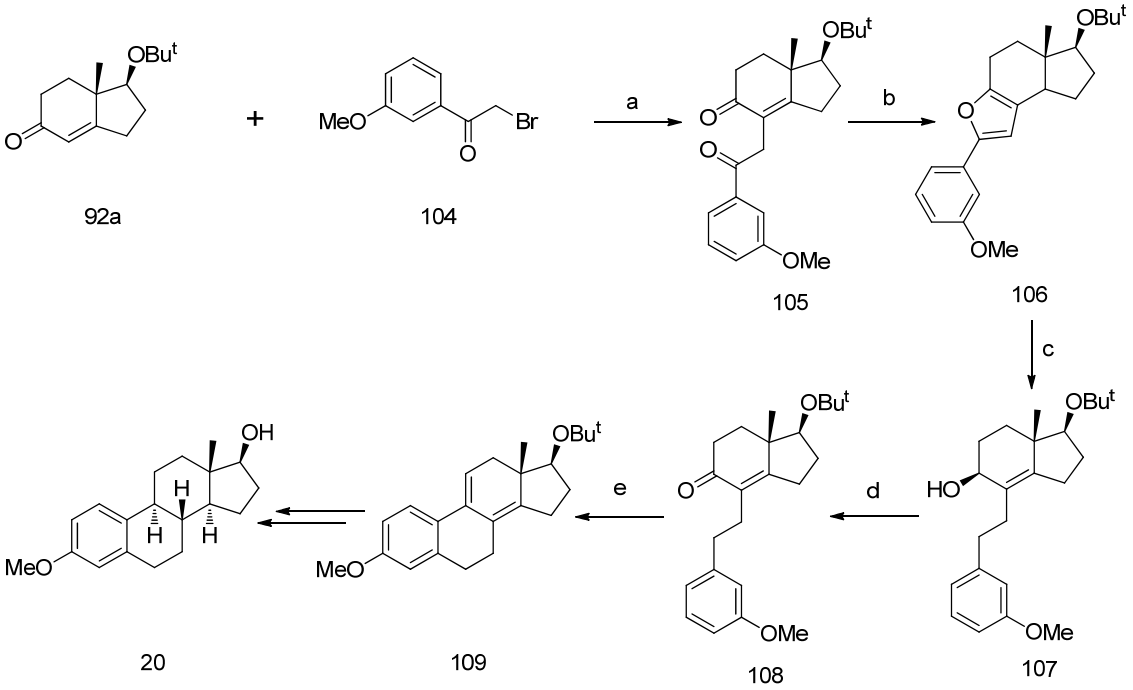
Michael addition of **100** with the bicyclic keto ester (**99**) gave 101,which further on annulation and stereo-controlled hydrogenation reactions afforded the target tetracyclic compound (**18**).[51-52]



Scheme 19. *Reagents and conditions:* (a) NaH, PhH; (ii) NaI, HMPA, H_2O; (b) EtONa, EtOH; (c) O_2, $PdCl_2$ - CuCl / DMF + H_2O; (d) (i) H_2, Pd, MeOH; (ii) HCl, MeOH

1.1.2.20 Eder and Sauer *et al.*

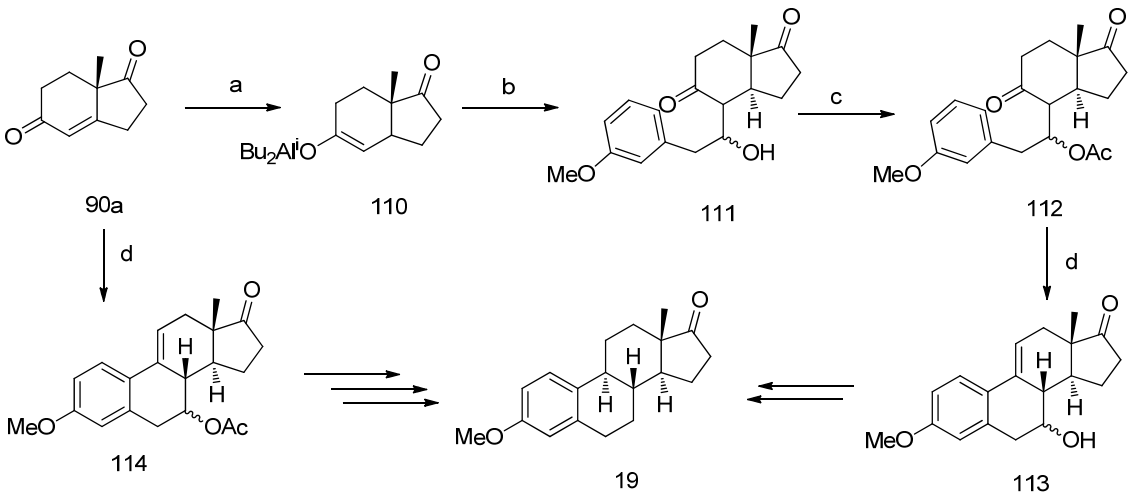
The conjugated enolate of the tert-butyl protected ketol obtained from (+)-indenedione could be alkylated at the C (8)-position by suitable alkyl chains in order to build up A- and B-rings of steroid backbones. Thus, Eder trapped the transient enolate with m-methoxyphenacyl bromide to prepare estradiol.[53-55]



Scheme 20. *Reagents and conditions:* (a) NaH, PhH; (b) (i) $HC(OMe)_3$, H^+, MeOH, (ii) TsOH, PhH; (c) H_2, Pd, MeOH; (d) (i) Jones reagent (ii) MeONa, MeOH; (e) (i) H^+ MeOH; (ii) H_2/ Pd, EtOAc.

1.1.2.21 Daniewski *et al.*

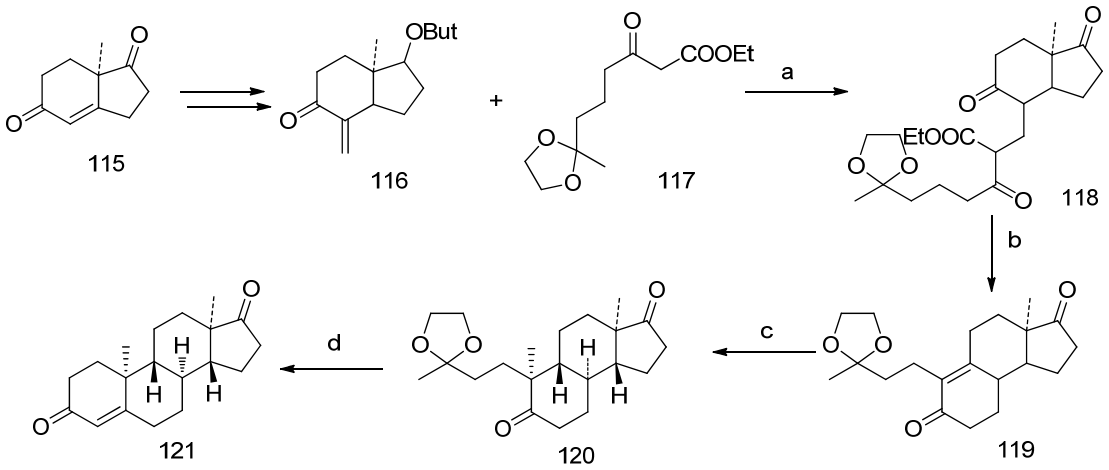
Daniewski reported a convenient access to a trans-hydrindanedione from the indenedione CD-building block involving a reductive addition of a tert-butylcopper / DIBAL-H complex. Condensation of the diisobutylaluminum enolate with m-methoxyphenylacetaldehyde gave a 9, 10-seco compound (**111**), which served as a precursor for the synthesis of estrone and 7-hydroxy-estrone. [56]



Scheme 21. *Reagents and conditions:* (a)(i) BuLi, Cu-I, DIBAL-H, THF, HMPA; (b) m-$OMeC_6H_4CH_2CHO$ (c) Ac_2O, Pyridine, (d) (i) Al_2O_3, PhMe; (ii) H_2, Pd, MeOH; $HClO_4$, AcOH.

1.1.2.22 Rychnovsky *et al.*

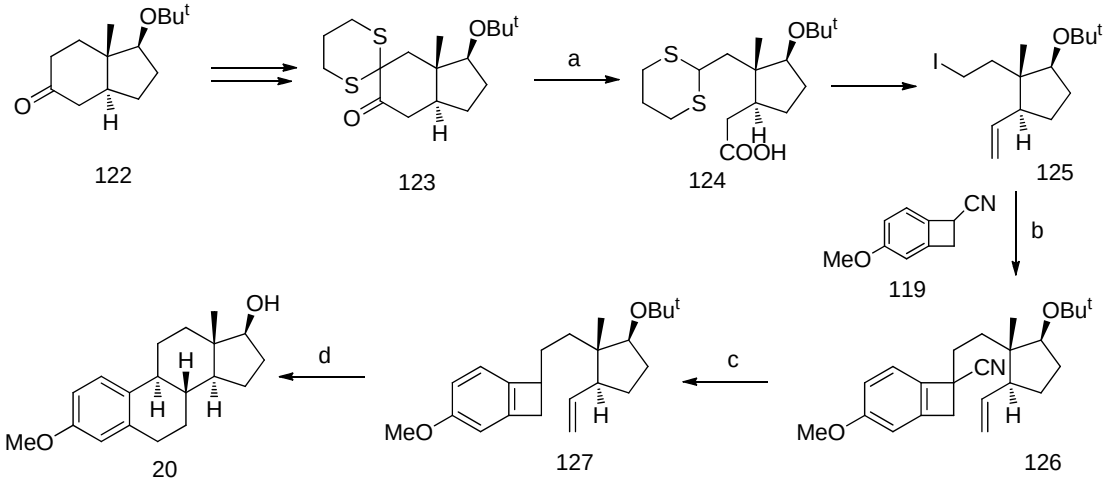
Rychnovsky synthesized ent-testosterone (**121**) from (-) - indane-di-one (**115**) utilizing Hajos and Parrish protocol.[61]



Scheme 22. *Reagents and conditions:* (a) MeONa / MeOH, HCOOH; (b) (i) NaOH (ii) HCl; (c) Li / NH_3, MeI; (d) MeOH, HCl

1.1.2.23 Kametani *et al.*

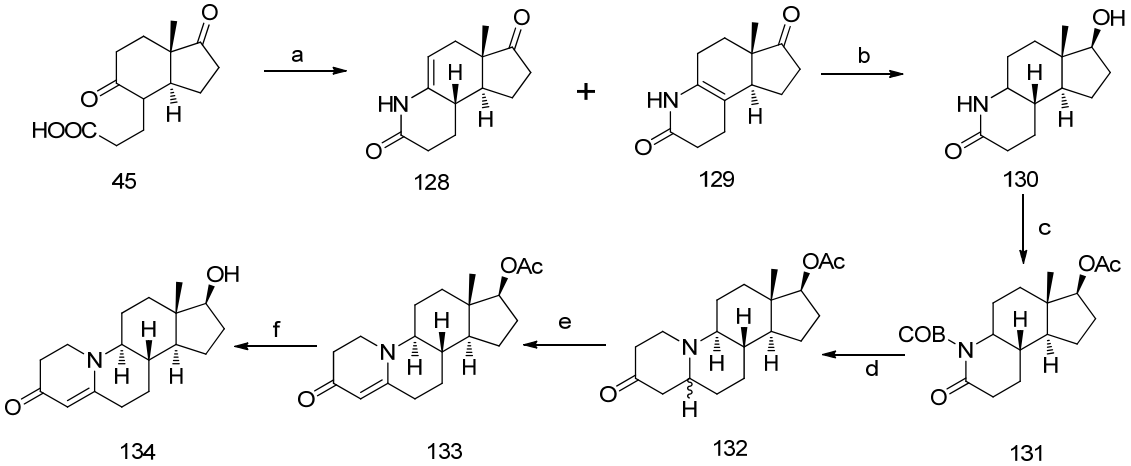
Kametani proposed a novel asymmetric approach to esteradiol by an intramolecular cycloaddition reaction of a benzocyclobutene derivative involving an o-quinodimethane intermediate. The construction of the precursor proceeded via C-ring cleavage of the Hajos–Parrish indanone, derivatization to the primary alkyl iodide, and condensation with 1-cyano-4-methoxybenzocyclobutene at the C(11)-position. Although the yields are generally moderate to good, this convergent synthesis is particularly the access to the optically pure cyclopentane derivative, and 10 steps from the indanone.[58]



Scheme 23. *Reagents and conditions:* (a) KOH, ^{t}-BuOH; (b) (i) NaH, DMF; (c) Na/ NH_3, EtOH, THF; (d) (i) 180^{o}C, *o*-dichlorobenzene, MeOH; (ii) HCl, H_2O, dioxane.

1.1.2.24 Guarna *et al.*

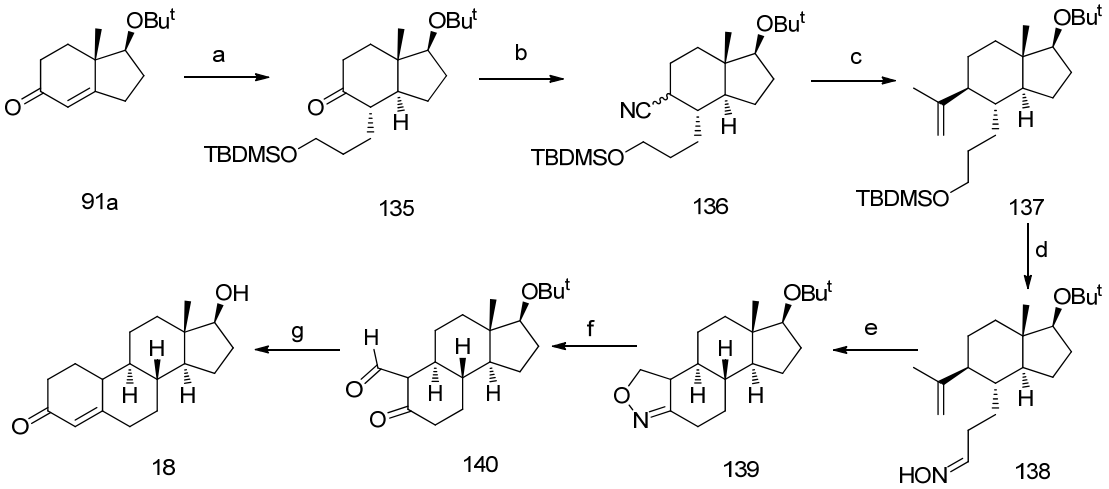
Guarna and coworkers synthesized 19-nor-10-azasteroids, class of substrates that inhibit the enzyme, steroid 5a-reductase. [59-60]



Scheme 24. *Reagents and conditions:* (a) NH_4HCO_3, HCOOH; (b) (i) $NaBH_3CN$, MeOH; (c) (i) Ac_2O, pyridine; (ii) Boc_2O, DMAP, Et_3N, DCM; (iii) $LiEt_3BH$/ THF; (d) (i) But-3-en-2-one, TMSOTf, Et_3N, DCM; (d) (i) $Hg(OAc)_2$, EDTA, AcOH; (ii) KOH, H_2O, MeOH.

1.1.2.25 Fukumoto *et al.*

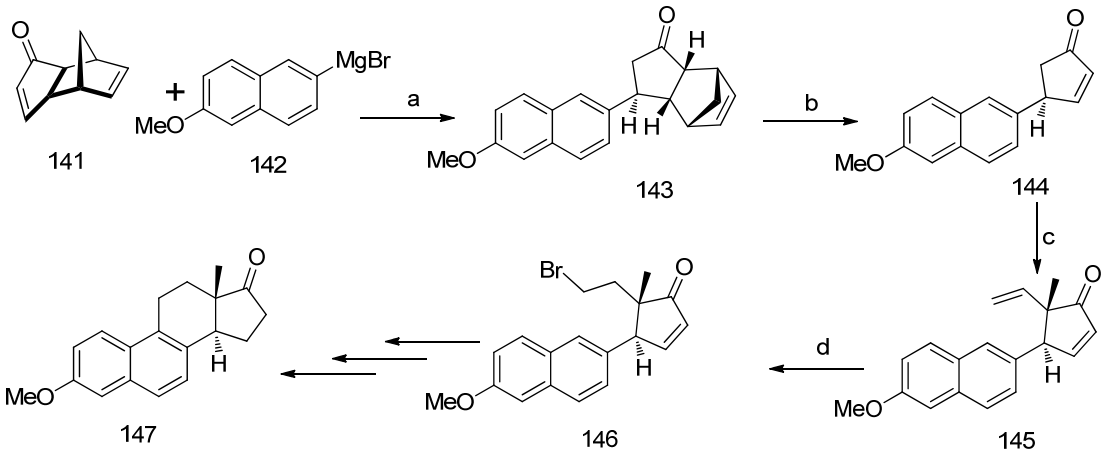
Fukumoto proposed a new synthetic methodology consisting of a 1, 3-dipolar cycloaddition of a nitrile oxide to build the B-ring and facilitate the elaboration of the cyclohexenone A-ring during the nor testerone synthesis.[61 - 64]



Scheme 25. *Reagents and conditions:* (a) (i) NaH, DMSO, TBDMSO-$(CH_2)_3$-I; (ii) $NaBH_4$, $COCl_2$; (b) $TsCH_2NC$, ^{t}-BuOK, ^{t}-BuOH; (c) (i) MeLi, hexane; (ii) Si-gel; (iii) MeLi, hexane; (iv) $POCl_3$ -pyridine; (d) (i) Bu_4NF, THF; (ii) SO_3•pyridine, DMSO; (iii) $HONH_2$; (e) (i) NaClO, H_2O; (ii) CH_2Cl_2; (f) (i) H_2, Ra-Ni, $B(OMe)_3$, MeOH, H_2O; (ii) SO_3-pyridine, DMSO; (g) (i) Ph_3P=CH-CO-CH_3, xylene; (ii) H_2, Pd; (h) (i) KOH, H_2O, MeOH; (ii) CF_3CO_2H .

1.1.2.26 Takano and Inomata *et al.*

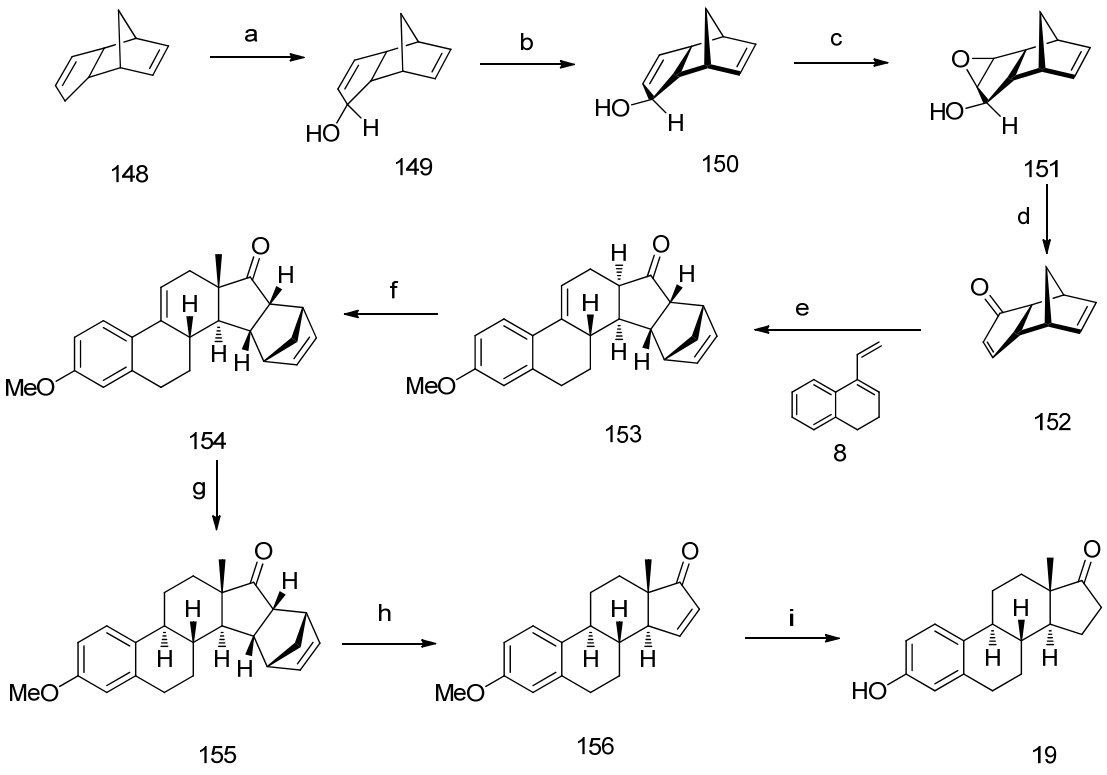
Takano's research group had exploited the reactivity of the chiral cyclopentadienone synthon for the elaboration of the estrogenic steroid, (+)-equilenin. The reaction sequence started with the 1,4-addition of a naphthalene derived Grignard reagent catalyzed by copper(I) iodide followed by metallo-enamine formation and two successive alkylations with vinyl bromide and methyl iodide, respectively. Upon thermolysis, the seco-C steroid was liberated and converted into (+)-equilenin via a Pummerer type cyclization as a key step.[65]



Scheme 26.*Reagents and conditions:* (a) (6-methoxynaphthalen-2-yl)MgBr, CuI, THF; (b) Ph-O-Ph, reflux, retero Dile'sAlder; (c) NaHMDS, THF, Vinyl-Br.

1.1.2.27 Takano and Moriya *et al.*

As reported by Takano, the optically active tricyclic dienone, accessible from racemic dicyclopentadiene via allylic oxidation and lipase-mediated kinetic hydrolysis of the corresponding acetate,[66] was revealed to be an excellent dienophile to react regio- and diastereoselectively with Dane's diene in the presence of diethylaluminum chloride. Methylation of the exo-adduct at C(13) occurred exclusively from the convex face of the enolate, leading to the transfused CD-ring junction of natural steroid skeletons. Hydrogenation of the C(9)–C(11) double bond by triethylsilane and trifluoroacetic acid gave rise to the trans-BC fused product, which underwent a retro Diels–alder reaction upon heating. A few transformations liberated the (+)-estrone.[67]

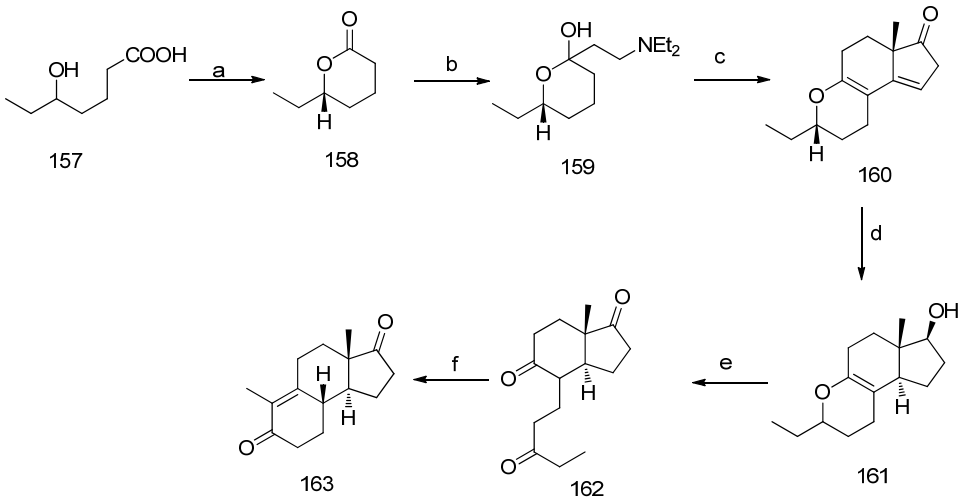


Scheme 27. *Reagents and conditions:* (a) SeO_2, Dioxane, H_2O; (b) (i) MeCOCl, pyridine, PhH; (ii) CCL lipase; (c) (i) PCC, (ii) H_2O_2/NaOH, MeOH, CH_2Cl_2; (d) (i) NH_2-NH_2- H_2O; (ii) PCC/ CH_2Cl_2; (e) Et_2AlCl/ CH_2Cl_2 ; (f) ^{t}-BuOK / DME, MeI ;

(g) Et_3SiH- CF_3CO_2H, CH_2Cl_2; (h) Ph-O-Ph, reflux; (i) H_2/ Pd, EtOH; (ii) BBr_3, CH_2Cl_2.

1.1.2.28. Rosenberger *et al.*

Rosenberger and co-workers achieved the construction of the optically pure (-)-17β-hydroxy-des-A-androst- 9-en-5-one, a BCD-tricyclic steroid precursor, starting from a chiral d-lactone readily obtained by selective enzymatic reduction of the prochiral 5-keto heptanoic acid with Margarinomyces bubaki. On sequential vinylmagnesium chloride addition, diethylamine trapping, and mild acid treatment, the crude oxime ether afforded a masked Mannich base, which was condensed with 2-methylcyclopentane- 1,3-dione to give predominantly the 13β-trans diene. Suitable manipulations of this key substrate, depicted in Scheme 27**,** led to the target tricyclic adduct.[68-69]

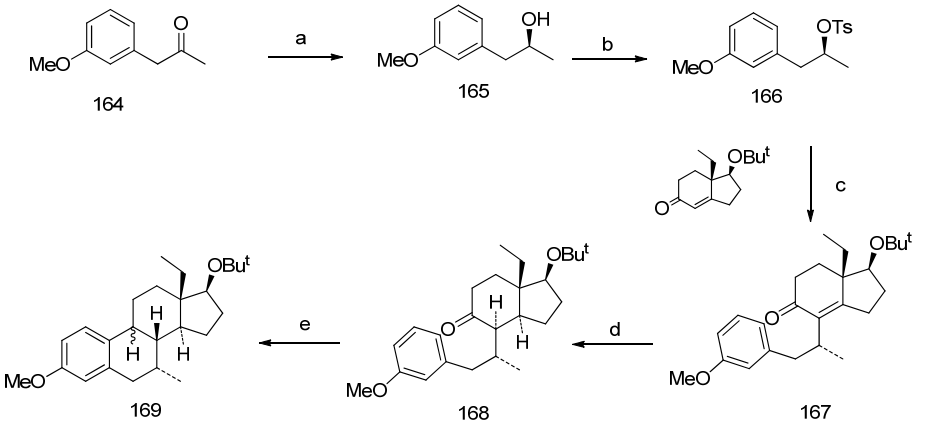


Scheme 28.*Reagents and conditions:*(a) *Cladosporium butyri*; (b) (i) Vinyl-MgBr, CuI, THF; (ii) Et_2NH; (c) 2-methyl cyclopentane-1,3-dione, AcOH, PhMe; (d) (i) $LiAlH_4$, THF; (ii) H_2 - Pd (e) (i) H_2SO_4, H_2O/ acetone (ii) Jones reagent; (f) TsOH/ PhH.

1.1.2.29 Cai and Sun *et al.*

A variety of 7-methyl-19-nor-steroids were synthesized by Cai and co-workers through alkylation of a CD-ring fragment indenone with a chiral tosylate derived from the product of asymmetric reduction of 1-(3-methoxy-phenyl)-2-propanone by Saccharomyces cerevisiae. Subsequent hydrogenation gave the trans-perhydroindane, which cyclized to produce the complete tetracyclic steroid skeleton. The natural trans-

anti-trans arrangement was established after a second hydrogenation and led to the 7a, 18-dimethyl estradiol (**169**).[70]



Scheme 29. *Reagents and conditions:*(a) Saccharomyces cerevisiae; Reduction;(b) (i) TsCl, Et_3N, DCM; (c) NaH/ DME; (d) H_2/ Pd, MeOH; (e) (i) PTSA (ii) H_2/ Pd, AcOEt

1.1.3. References

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Chapter 1, Section II: Chemoenzymatic Synthesis of Steroid Intermediate

1.2.1. Introduction

As seen in the previous literature survey over the last few years, several synthetic approaches for both steroids and vitamin D like structures have emerged in the area of steroid chemistry. All of these approaches have been drafted in sequential manner, such as the construction of the aliphatic side chain, the obtaining of the trans-hydroindane **C-D** ring, its elaboration through **B**-ring closure as a key step, followed by intra-molecular cyclo-additions or transition metal catalyzed reactions and finally, synthesis of ring **A.**[1] Among these steps formation of the **C-D** ring is the most significant, since axial methyl group as well as ring junction differentiate the one molecule from other (Figure 1).

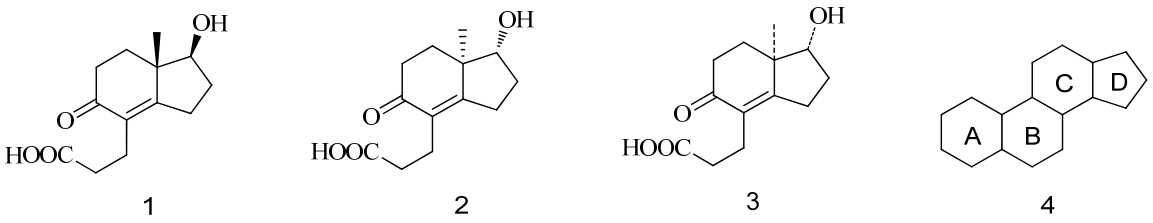


Figure 1

Hence synthesis of **C-D** ring intermediate has dragged attention of chemists and various methods have been reported for its synthesis. The compound (1S, 7aS)-1-hydroxy-5-oxo- 4-(2'-carboxyethyl)-7a-methyl tetrahydroindane (**1)** is the significant key intermediate of several steroids (Figure 2).[1]

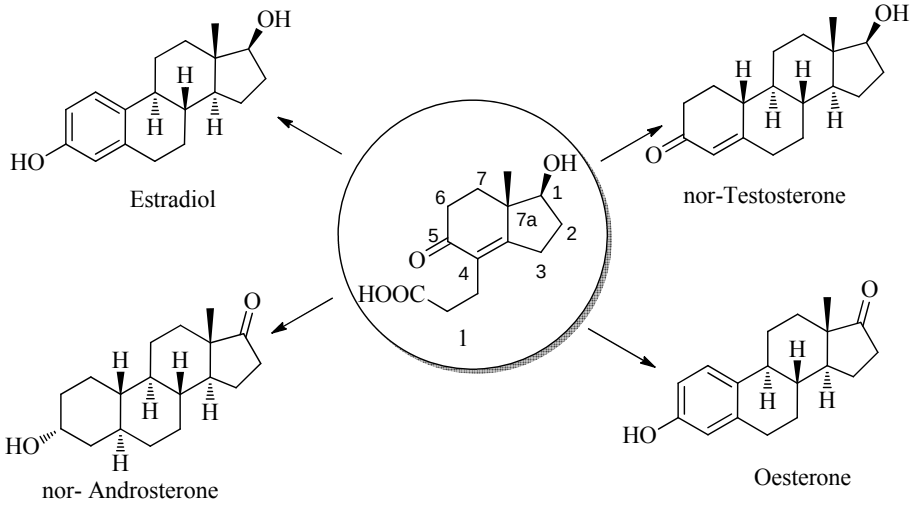


Figure 2

Different approaches are utilized for the synthesis of this optically active bicyclic fused **C-D** ring system as below:

1) Chemical resolution of diastereomers by recrystallization of respective salts or by chromatographic separation of diastereomers[1]

2) Desymmetrization of 2-substituted-1, 3-cyclopentanediones (**D** ring) either by a microbial reduction, or by formation of diastereoisomers, or by stereoselective reduction.[1a]

3) By amino acid ctalysed asymmetric Robinson annulation under Hajos–Parrish–Eder–Sauer–Wiechert reaction conditions.[2]

4) Use of chiral auxiliaries, as chiral metal–ligand complexes or chiral bases.[1, 3]

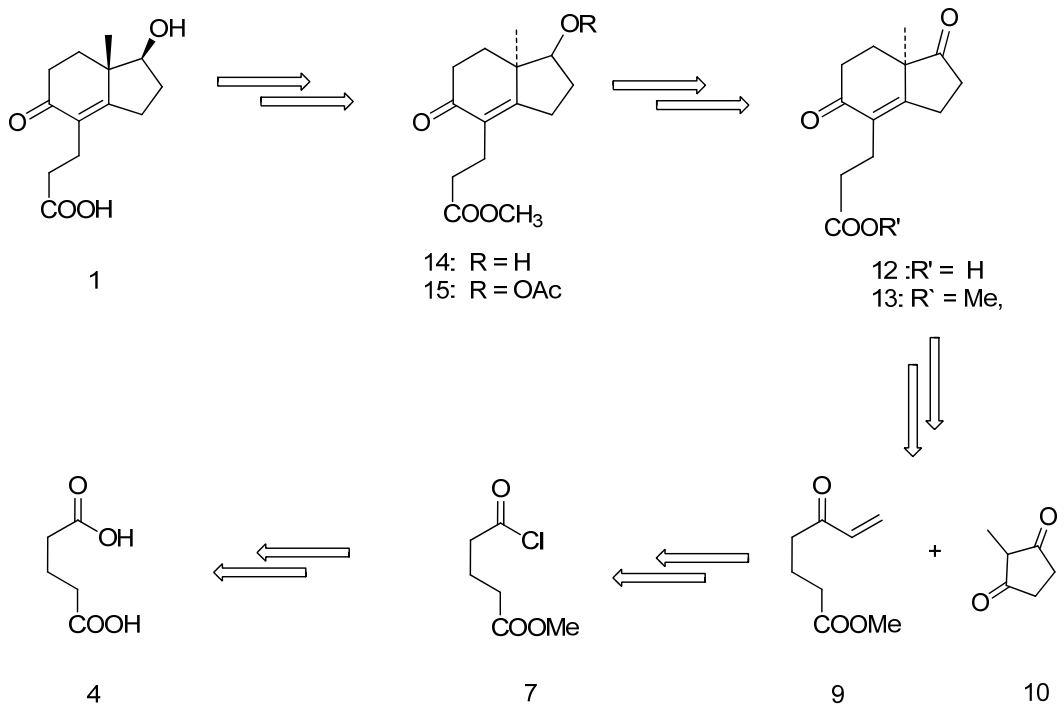
5) Chiral pool approach via utilisation of the naturally available substrates as starting material like quinic acid, malic acid, diethyl tartrate, mannitol, xylose, arabinose, glucose and camphor derivatives.[1]

But drawbacks of the above methods are the longer reaction time with low overall yields & lengthy reaction sequence with variable optical purity of the product. Further, above methods involve use of carcinogenic solvents and narcotic drugs. Whereas, enzymatic approaches such as microbial C-C bond formation and enzyme catalyzed resolution are not yet explored.

Owing to the significance of intermediate (1*S*, 7a*S*)-1-hydroxy-5-oxo-4-(2`-carboxyehtyl)-7a-methyl tetrahydroindane (**1**) and our research work in chemoenzymatic resolution of biologically active compounds, we planned to synthesize (1*S*,7a*S*)-1-hydroxy-5-oxo-4-(2`-carboxyehtyl)-7a-methyl tetrahydroindane (**1**) by enzymatic approach.[4, 5]

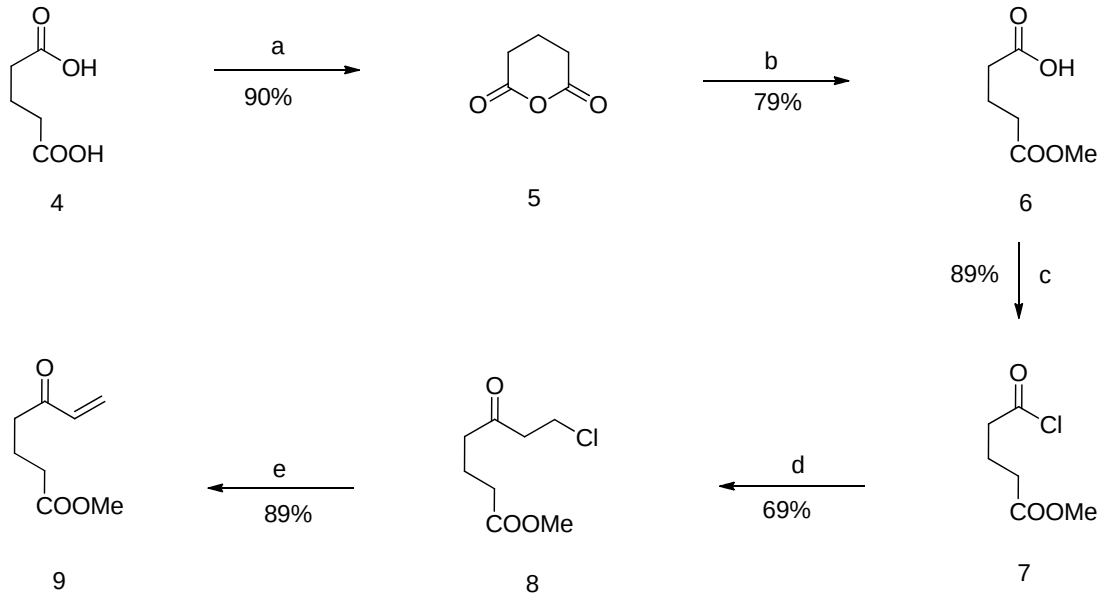
1.2.2. Present Work

From retrosynthesis (Scheme 1) it is clear that, steroid intermediate **1** can be produced *via* hydrolytic resolution of its corresponding racemic acetate intermediate **15** which in turn can be synthesised from the corresponding hydroxyl intermediate **14**. This hydroxyl intermediate **14** can be synthesised from bis-keto intermediate **12** via simple $NaBH_4$ reduction. This bis keto intermediate **12** in turn can be synthesised *via* Robinson annulation reaction between intermediate **9** and diketone **10**. The compound **9** can be prepared from commercially available glutaric acid (**4**).



Scheme 1

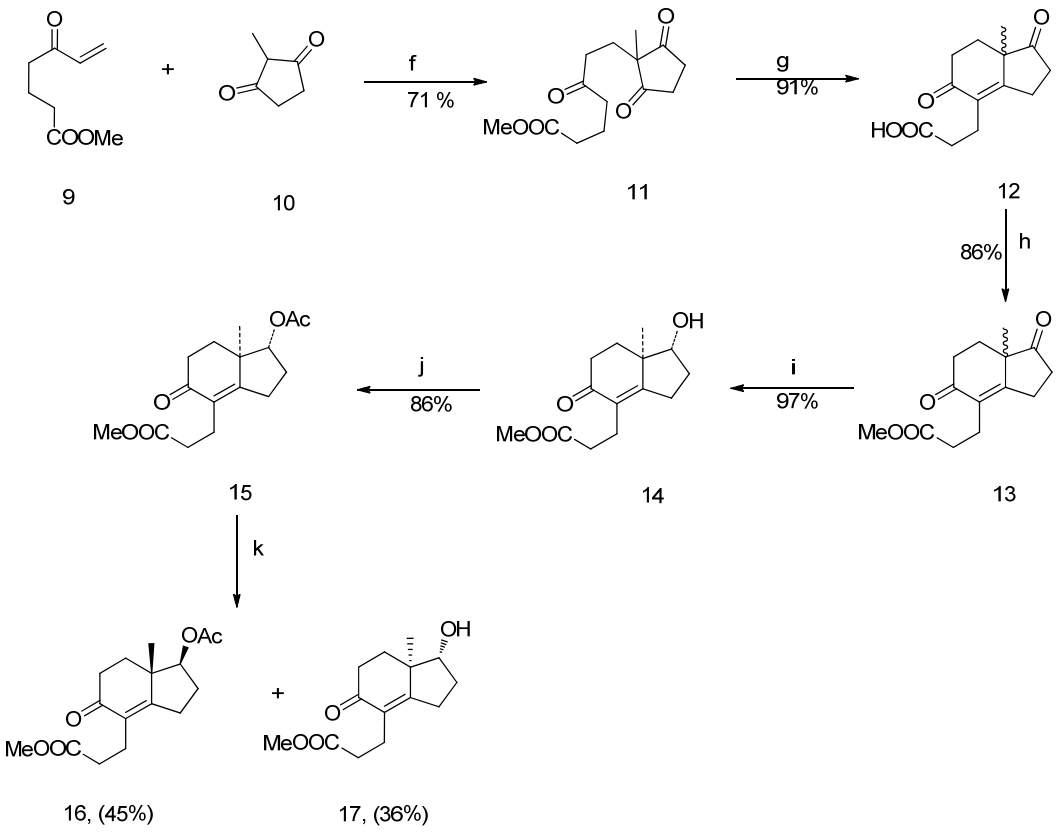
After evaluation of retrosynthetic studies we began our journey with glutaric acid (**4**) (Scheme 2). Glutaric acid (**4**) on treatment with acetic anhydride under refluxing condition underwent dehydration to furnish glutaric anhydride (**5)**. This glutaric anhydride (**5)** on refluxing with methanol underwent ring opening to give mono methyl glutarate (5-methoxy-5-oxopentanoic acid) (**6)** which was separated and purified by vacuum distillation. This intermediate **6** on treatment with thionyl chloride gave methyl 5-chloro-5-oxopentanoate (**7).** Ethylene was reacted with above intermediate (**7**) in presence of aluminium chloride to afford methyl 7-chloro-5-oxoheptanoate (**8**). This intermediate methyl 7-chloro-5-oxoheptanoate (**8**) on treatment with triethylamine underwent β-elimination to furnish methyl 5-oxohept-6-enoate (**9**). After having one fragment (**9**) in hand, our next process was 1, 4-Michael addition (Scheme 4). [6]



Scheme 3. *Reagents and conditions:* (a) Ac_2O/ -H_2O; (b) MeOH/ H^+/ reflux; (c) $SOCl_2$ /reflux; (d) Ethylene/ $AlCl_3$/ EDC; (e) DCM/ TEA

Michael addition (Scheme 4) was carried out simply by treatment of methyl 5-oxohept-6-enoate (**9**) with 2-methylcyclopentane-1, 3-dione (**10**) in presence of H_2SO_4 under refluxing condition in benzene as solvent to furnish methyl 7-(1-methyl-2, 5-di-oxocyclopentyl)-5-oxoheptanoate (**11**). Subsequently intermediate **11** on treatment with 5 N HCl underwent aldol condensation reaction to generate 1, 5-dioxo-4-(2'-carboxyethyl)-7a-methyl tetrahydroindane (**12**). This bis-keto acid was esterified in presence of catalytic amount of H_2SO_4 and methanol under refluxing condition to furnish intermediate 1, 5-dioxo-4-(2'-carbomethoxy ethyl)-7a-methyl tetra-hydro-indane (**13**). The reduction 1, 5-dioxo-4-(2'-carbomethoxy ethyl)-7a-methyl tetra-hydro-indane (**13**) with $NaBH_4$ gave (±) (*cis)*-1-hydroxy-5-oxo-4-(2'-carbomethoxy-ethyl)-7a-methyltetra-hydro-indane (**14)**. The compound **14** on acylation gave acetyl derivative **15**.

During last three decades many examples of the lipase catalyzed hydrolysis of ester and amide have been demonstrated[7-10]. Enzymatic hydrolysis of **15** with various enzymes in phosphate buffer (pH 7) was tried but even after 72 hrs, no hydrolysis was observed. This failure led us to investigate the medium engineering approach which involved the use of co-solvent.

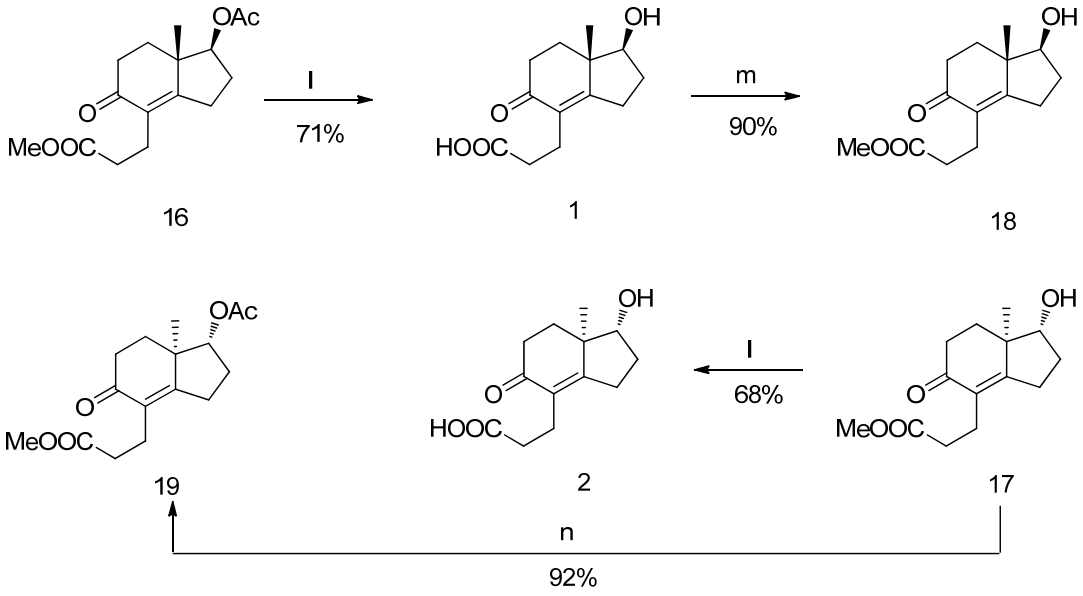


Scheem 4. *Reagents and conditions:* (f) Pyridine/ toluene, reflux; (g) Benzene / H^+, reflux; (h) MeOH / H^+, reflux; (i) $NaBH_4$ / MeOH; (k) AcCl / TEA; (k) PPL/ phosphate buffer + EtOH.

(±)(*cis)*-1-Acetoxy-5-oxo-4-(2'-carbomethoxyethyl)-7a-methyl tetrahydroindane(**15**) was treated with different enzymes in phosphate buffer (pH 7) with 10% ethanol as a co-solvent to carry out the hydrolytic resolution (Table 1). In case of PPL enzyme, (±) **15** was effectively hydrolyzed to (1*R*, 7a*R*) alcohol **17** and the acetate **16** remained unreacted. The optical purity >99% e.e. of **17** was determined by chiral HPLC using Chiracel OD [4.6 mm Id x 25 cm] column (λ =254 nm, flow rate: 1 ml/min; mobile phase: Hexane: Isopropanol 95:05). Further the acetoxy derivative **16** was converted in to **1** by acid hydrolysis and subsequent esterification afforded the hydroxyester **18**.

Table 1: Enzymatic hydrolysis of **15** in phosphate buffer (7 pH) and 10% ethanol

Enzyme	***Time (hr)***	***Product %***		***% ee***	
		1	***16***	***17***	***16***
Procine Pancreatic Lipase (PPL)	*24*	*36*	*45*	*95.2*	*95.5*
Pig Liver Esterase (PLE)	*24*	*95*	--	*0.0*	--
Trichosporium sp	*24*	*99*	--	*0.0*	
Chirazyme	*24*	*37*	*26*	*9.1*	*27.6*
Candida Cylindracea Lipase (CCL)	*24*	*22*	*38*	*25.2*	*79.1*
Candida Antarctica Lipase (CAL)	*24*	*33*	*36*	*18.7*	*4.1*

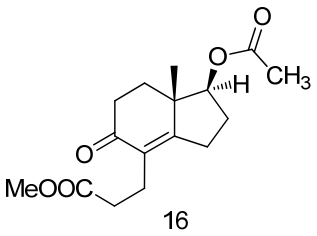


Scheme 4. *Reagents and conditions:* (l) HCl/ H_2O; (m) CH_2N_2, ether; (n) Ac_2O, Et_3N, DCM.

X-Ray structure of **2** and **16** showed cis configuration. In order to know absolute configuration of **16** and **17,** these were hydrolysed with 6.5 N HCl to obtain the products **1** and **2** respectively**.** Specific rotation of **1** was found identical with reported for (1*S*, 7aS)-1-hydroxy-5-oxo-4-(2'-carboxyehtyl)-7a-methyltetrahydro-indane (**1**)[1]. Further, (1*S*, 7aS)-1-hydroxy-5-oxo-4-(2'-carbomethoxyehtyl)-7a-methyltetrahydro-indane **(17)** on treat-ment with acetyl chloride in presence of triethyl amine furnished (1*R*, 7aR) 1-acetoxy-5-oxo-4-(2'-carbomethoxyethyl)-7a-

methyltetrahydro-indane (**19**). This is nothing but optical antipode of (1*S*, 7aS) 1-acetoxy-5-oxo-4-(2'-carbo-methoxyethyl)-7a-methyltetrahydro-indane (**16**).

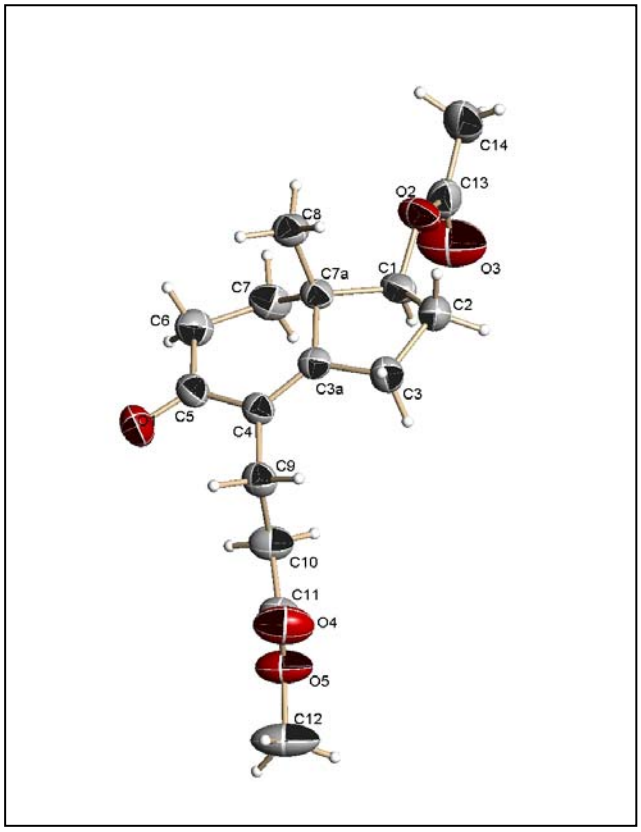
X-ray Crystal Structure Analysis for (1*S*, 7aS) 1-Acetoxy-5-oxo-4-(2'-carbo-methoxyethyl)-7a-methyltetrahydro-indane (16):



16

Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution in a solvent mixture of ethyl acetate and pet ether. Colourless crystal of approximate size 0.54 x 0.39 x 0.08 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, multiscan data acquisition. Total scans = 3, total frames = 1818, Oscillation / frame - 0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, α range = 1.89 to 23.33 º, completeness to β of 23.33 º is 99.7 %. SADABS correction applied, $C_{16}H_{22}O_5$, M = 294.34. Crystals belong to orthorhombic, space group $P2_12_12_1$, a = 7.1992(5), b = 10.1770(7), c = 21.534(2) Å, V = 1577.7(2) Å^3, Z = 4, D_c = 1.239 mg m^{-3}, μ (MoK) = 0.091 mm^{-1}, T = 295(2) K, 9479 reflections measured, 2259 unique [I>2σ(I)], R value 0.0436, wR2 = 0.1036. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in table 1. X-ray analysis revealed the conformation of the molecule and shows that -CH_3 and -OA_C are syn as well as β oriented. Caption to Fig 1. ORTEP diagram of the molecule. Ellipsoids are drawn at 40% probability.

Reference: G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997


C14
C13
O2
O3
C8
C7a
C1
C7
C2
C6
C3a
C3
C5
C4
C9
C10
C11
O4
O5
C12

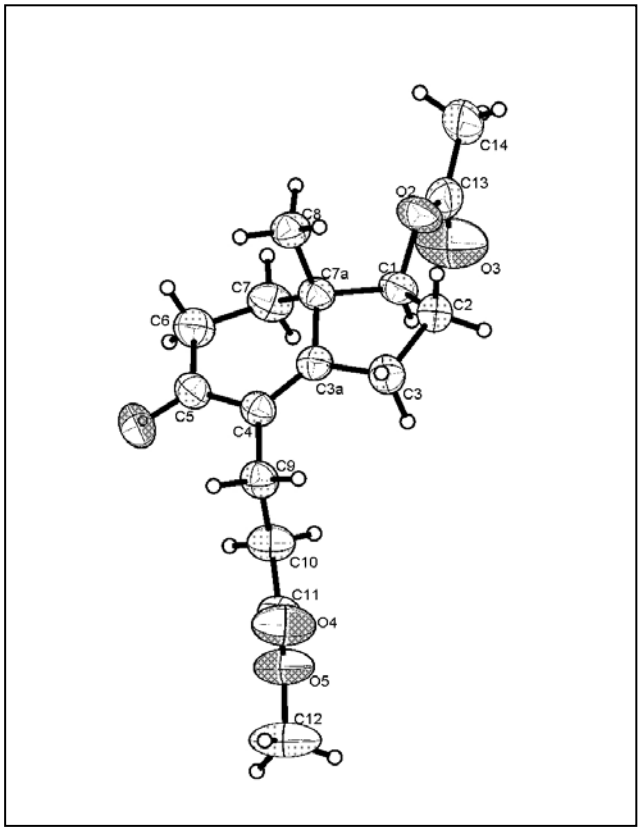
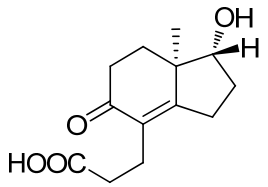

C14
C13
O2
O3
C8
C7a
C1
C7
C2
C6
C3a
C3
C5
C4
C9
C10
C11
O4
O5
C12

Table 1. Crystal data and structure refinement for $C_{16}H_{22}O_5$.

Empirical formula	$C_{16}H_{22}O_5$
Formula weight	294.34
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P_{21} P_{21} P_{21}
Unit cell dimensions	a = 7.1992(5) A,
	b = 10.1770(7) A,
	c =21.5341(15) A
Volume	1577.72(19) A^3
Z, Calculated density	4, 1.239 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	632
Crystal size	0.54 x 0.39 x 0.08 mm
θ range for collection	1.89 to 23.33 deg.
Limiting indices	-7<=h<=7, -11<=k<=11, -23<=l<=23
Reflections collected / unique	9479 / 2259 [R(int) = 0.0284]
Completeness to the ta =	23.33 99.7 %
Max. and min. transmission :	0.9929 and 0.9523
Refinement method :	Full-matrix least-squares on F^2
Data / restraints / parameters :	2259 / 0 / 193
Goodness-of-fit on F^2 ;	1.143
Final R indices [I>2sigma(I)]	R_1 = 0.0436, wR_2 = 0.1036
R indices (all data)	R_1 = 0.0507, wR_2 = 0.1069
Absolute structure parameter	0.2(17)
Largest diff. peak and hole	0.147 and -0.115 e.A^o

X-ray crystal structure analysis for (1*R*, 7*R*) 1-hydroxy-5-oxo-4-(2'-carbo-oxyethyl)-7a-methyltetrahydro-indane (2)

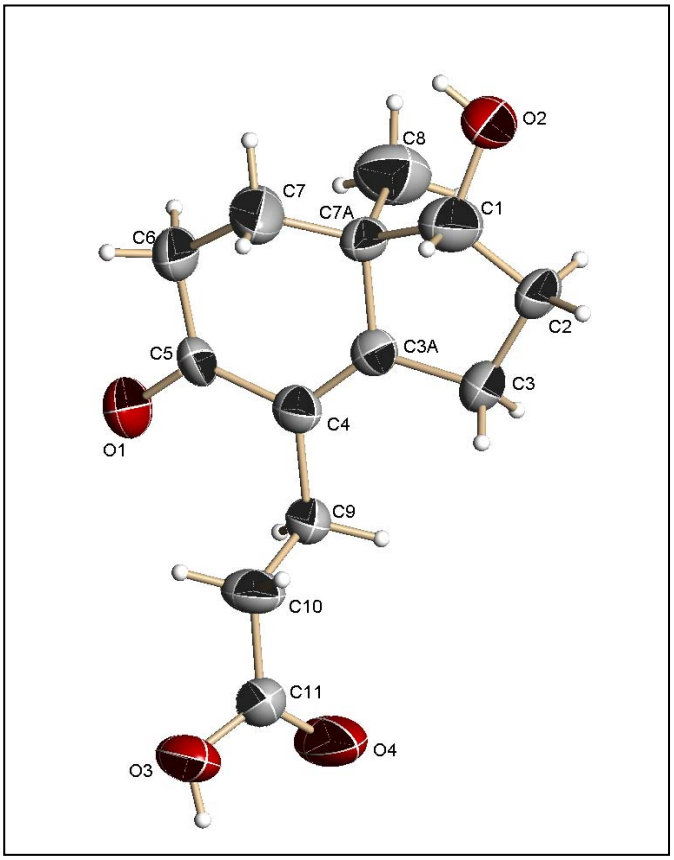


2

Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution in a solvent mixture of ethyl acetate and pet ether. Colourless crystal of approximate size 0.36 x 0.14 x 0.05 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, multiscan data acquisition. Total scans = 5, total frames = 3030, Oscillation / frame - 0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, α range = 2.48 to 23.46 º, completeness to θ of 23.46 º is 99.4 %. SADABS correction applied, C_{13} H_{18} O_4.H2O, M = 256.29. Crystals belong to monoclinic, space group $P2_1$, a = 9.6580(8), b = 13.4240(11), c = 10.3990(8) Å, V = 1348.06(19) $Å^3$, Z = 4, D_c = 1.263 g/cc, μ (MoK) = 0.096 mm^{-1}, T = 293(2) K, 13041 reflections measured, 3927 unique [I>2σ(I)], R value 0.0714, wR2 = 0.1677. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model however the hydrogens of solvent water molecules were refined. Data collection and refinement parameters are listed in Table 2. X-ray analysis revealed the conformation of the molecule and shows that -CH_3 and OH are syn as well as α oriented. Caption to Fig 1: ORTEP diagram of the molecule. Ellipsoids are drawn at 50% probability.

Reference

G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997


O2
C8
C7
C7A
C1
C6
C2
C5
C3A
C3
C4
O1
C9
C10
C11
O3
O4

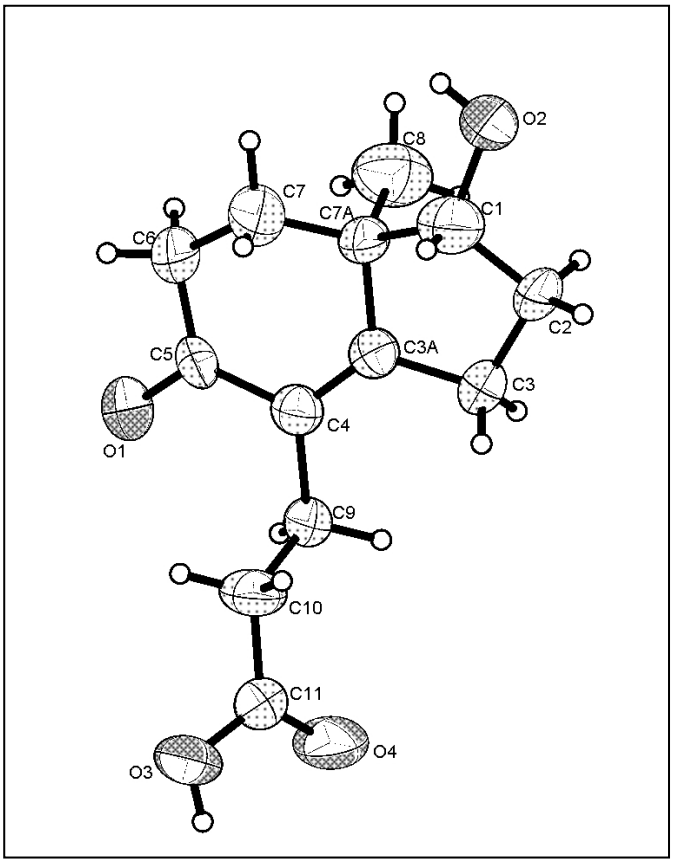

O2
C8
C7
C7A
C1
C6
C2
C5
C3A
C3
C4
O1
C9
C10
C11
O3
O4

Table 2. Crystal data and structure refinement for $C_{13}H_{18}O_4$

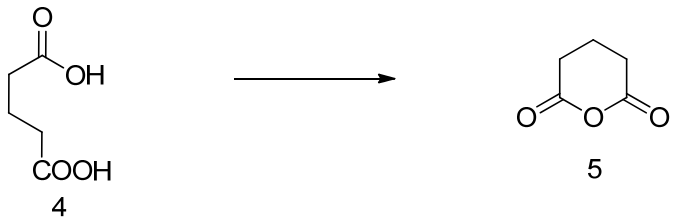
Empirical formula	C_{13} H_{18} O_4	
Formula weight	256.29	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P_{21}	
Unit cell dimensions	a = 9.6580(8) Å	α= 90°.
	b = 13.4240(11) Å	β= 90.894(2)°.
	c = 10.3990(8) Å	γ = 90°.
Volume	1348.06(19) $Å^3$	
Z	4	
Density (calculated)	1.263 gm/cc	
Absorption coefficient	0.096 mm^{-1}	
F(000)	552	
Crystal size	0.36 x 0.14 x 0.05 mm^3	
θ range for data collection	2.48 to 23.46°.	
Index ranges	-10<=h<=10, -14<=k<=14, -11<=l<=11	
Reflections collected	13041	
Independent reflections	3927 [R(int) = 0.0434]	
Completeness to theta = 23.46°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9954 and 0.9658	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3927 / 1 / 343	
Goodness-of-fit on F^2	1.104	
Final R indices [I>2sigma(I)]	R_1 = 0.0714, wR_2 = 0.1677	
R indices (all data)	R_1 = 0.0960, wR_2 = 0.1826	
Absolute structure parameter	3(2)	
Largest diff. peak and hole	0.385 and -0.179 e.$Å^{-3}$	

1.2.3 Conclusion

Efficient chemoenzymatic synthesis of (1*S*, 7a*S*)-1-hydroxy-5-oxo-4-(2'-carboxyethyl)-7a-methyltetrahydroindane (**1**) was achieved in high enantiomeric excess using glutaric acid as starting material and easily accessible enzyme (PPL) for resolution.

1.2.4. Experimental

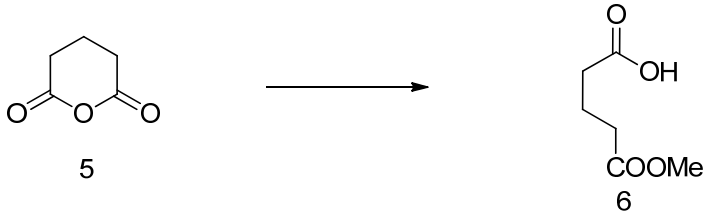
Preparation of glutaric anhydride (dihydro-2H-pyran-2, 6(3*H*)-dione) (5):



In a single neck flask, glutaric acid (58 gm) and acetic anhydride (46 mL) were taken and heated to reflux for 3 hr. After completion of the reaction, excess acetic anhydride and acetic acid formed during reaction were removed by distillation. The residue was distilled out under high vacuum at 145^{o}C to furnish 45 gm pure glutaric anhydride **5** (dihydro -2H-pyran-2, 6(3*H*) - dione).

Yield: 45.12 gm (90.13%); colorless solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78-1.91 (m, 2H), 2.57 (t, *J*= 6.65 Hz, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.95, 29.47, 166.91 ppm; Elemental Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.79; H, 5.41.

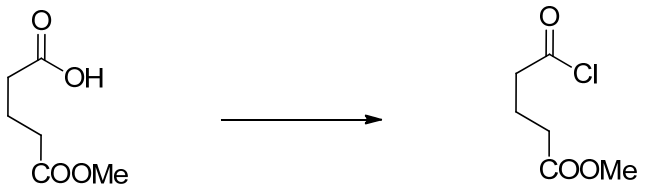
Preparation of monomethyl glutarate (5-methoxy-5-oxopentanoic acid) (6)



A mixture of glutaric anhydride (**6,** 45 gm) and methanol (260 mL) were refluxed for one hour. After completion of reaction, excess methanol was removed by distillation.

Isolation and purification of product from residue was carried out by high vacuum distillation to obtain monomethyl glutarate (5-methoxy-5-oxopentanoic acid) (**6**).
Yield: 45.52 gm (79.3 %); colorless viscous liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85-1.99 (m, 2H), 2.28-2.48 (m, 4H), 3.65 (s, 3H), 10.14 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.88, 31.68, 45.65, 51.31, 171.21, 171.31 ppm; Elemental Anal.Calcd for $C_6H_{10}O_4$: C, 49.31; H, 8.49. Found: C, 49.46; H, 8.55.

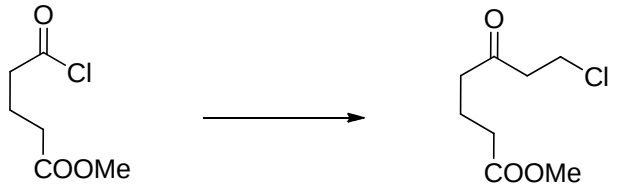
Preparation of methyl 5-chloro-5-oxopentanoate (7)



6 7

To the stirred solution of 5-methoxy-5-oxopentanoic acid (**6,** 45 gm, 0.3080 mol) in DCM, thionyl chloride (40 mL, 0.3387 mol, 1.1 eq) was added and refluxed for three hour. After completion of the reaction excess thionyl chloride was removed by distillation. The residue on distillation gave methyl 5-chloro-5-oxopentanoate (**7**).
Yield: 44.59 gm (88.1%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86-2.04 (m, 2H), 2.28-2.40 (m, 3H), 2.96 (t, *J*=7.04 Hz, 1H), 3.64 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.22, 32.23, 50.94, 172.1, 171.31 ppm.

Preparation of methyl 7-chloro-5-oxoheptanoate (8)



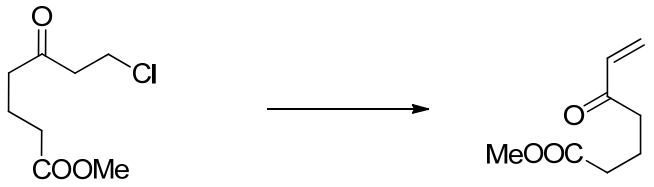
7 8

To the stirred solution of anhydrous $AlCl_3$ (32 gm, 0.2439 mol, 1.25 eq) in dry $CHCl_3$, a solution of methyl 5-chloro-5-oxopentanoate (**7**, 20 gm, 0.12 mol, 1 eq) in $CHCl_3$ (100 mL) was added slowly in 10 min. After stirring for ½ hr, N_2 balloon was replaced by ethylene balloon and the reaction mixture was stirred for 8 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction,

reaction mixture was quenched by ice cold water and extracted with chloroform (2 X 250 mL). The organic layer was separated and washed with brine, dried over Na_2SO_4 and concentrated over rotaevaporator under vacuum to get 7-chloro-5-oxoheptanoate (**8**).

Yield: 16.15 gm (69.2 %); viscous liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77-1.91 (m, 2H), 2.28 (t, *J*= 7.04 Hz, 2H), 2.47 (t, *J*= 7.05 Hz, 2H), 2.81 (t, *J*= 6.65 Hz, 2H), 3.60 (s, 3H), 3.67 (t, *J*= 6.65 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.13, 32.29, 37.87, 41.32, 44.34, 50.78, 172.68, 205.79 ppm; Elemental Anal. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80; Cl, 18.40. Found: C, 49.81; H, 6.65; Cl, 18.49.

Preparation of methyl 5-oxohept-6-enoate (9)

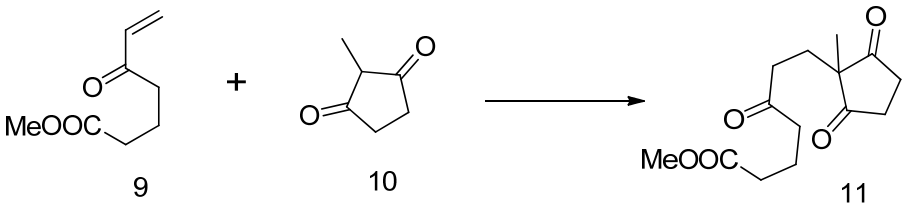


8 9

To the stirred solution of 7-chloro-5-oxoheptanoate (**8**, 10 gm, 0.051 mol, 1 eq) in chloroform (50 mL), triethyl amine (10.5 mL, 10.52 gm, 0.102 mol, 2 eq) was added under N_2 atmosphere and the reaction mixture was stirred at room temperature for 4 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched by ice cold water and extracted with chloroform (2 X 250 mL). The organic layer was separated and washed with brine, dried over Na_2SO_4 and concentrated over rotaevaporator under vacuum to get residue, which on silica gel column chromatography afforded **9**.

Yield: 7.21gm (89.1%); colourless viscous liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88-1.95 (m, 2H), 2.33 (t, *J*= 7.04 Hz, 2H), 2.62 (t, *J*= 7.05 Hz, 2H), 3.62 (s, 3H), 5.78-5.81 (d, *J*= 7.04 Hz, 1H), 6.15-6.35 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.63, 32.60, 37.96, 51.09, 127.80, 136.14, 173.09, 199.26 ppm; Elemental Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.59; H, 7.79.

Preparation of methyl 7-(1-methyl-2, 5-dioxo-cyclopentyl)-5-oxo-heptanoate (11)

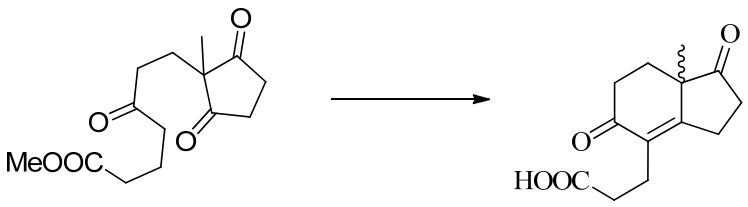


9 10 11

In one neck round bottom flask methyl-5-oxo-6-heptenoate (**9,** 5.4 gm, 0.0345 mol, 1 eq), 2-methylcyclopentane-1,3-dione (**10**, 4.25 gm, 0.037 mole, 1.25 eq), pyridine (0.2 eq) and toluene were placed. The reaction mixture was refluxed under nitrogen for 18 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with dil HCl and extracted with chloroform. The organic layer was separated and dried over anhydrous sodium sulphate, evaporated under vacuum to obtain crude residue, which was purified by silica gel column chromatography to afford methyl 7-(1-methyl-2, 5-dioxo-cyclopentyl)-5-oxo-heptanoate (**11)**

Yield: 6.51 gm, 71.41%; viscous liquid; IR ($CHCl_3$): ν_{max} 1721.3, 2953, 1106.87 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.74-1.86 (m, 4H), 2.25 (t, *J*= 7.05 Hz, 2H), 2.33-2.42 (m, 4H), 2.63-2.85 (m, 4H), 3.61 (s, 3H) ppm; ^{13}CNMR (125 MHz, $CDCl_3$): δ 18.19, 27.41, 32.34, 34.21, 36.02, 40.94, 50.90, 54.54, 172.86, 208.56, 215.28 ppm; Elemental Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.93; H, 7.56.

Preparation of 1, 5-dioxo-4-(2`-carboxyethyl)-7a-methyl tetrahydroindane (12)



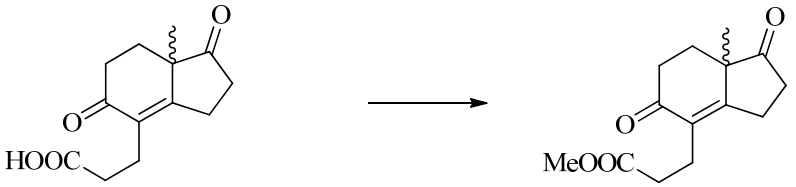
11 12

In one neck round bottom flask methyl 7-(1-methyl-2,5-dioxocyclopentyl)-5-oxoheptanoate (**11**, 4.5 gm, 0.016 mole) and HCl (5 N, 45 ml) were placed and heated at 50^{o}C for 6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, it was extracted with chloroform. Organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to

obtain 4.1 gm crude aldol condensation compound. The purification of the crude product was carried out by silica gel column chromatography to obtain pure 1,5-dioxo-4-(2`-carboxyethyl) 7a-methyl tetrahydro indane (**12)**.

Yield: 3.61 gm (91.09%); colourless solid, mp.126^{o}C; IR ($CHCl_3$): ν_{max} 1743.39, 1709.20, 1663.42, 1660, 1217.03 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.71-1.78 (m, 1H), 1.97-2.00 (m, 1H), 2.31-2.40 (m, 4H), 2.45-2.52 (m, 2H), 2.68-2.70 (m, 1H), 2.74-2.82 (m, 1H), 2.97-3.02 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.88, 21.14, 24.46, 28.52, 32.81, 35.55, 48.99, 131.96, 165.04, 178.56, 197.59, 217.36 ppm; Anal. calcd for $C_{13}H_{16}O_4$: C, 66.61; H, 6.77. Found: C, 66.54; H, 6.62. MS: 236.33 $(M)^+$, 237.12 $(M+1)^+$

Preparation of 1, 5-dioxo-4-(2'-carbomethoxyethyl)-7a-methyl tetrahydro indane (13)



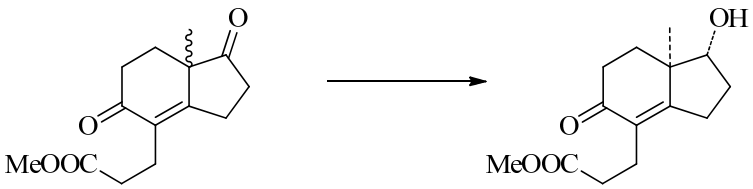
12 13

1,5-Dioxo-4-(2`-carboxyethyl) 7a-methyl tetrahydro indane (**12**, 3.5 gm) and dry methanol (50 mL) were placed in one neck round bottom flask and refluxed for 4 hrs under nitrogen in presence of catalytic H_2SO_4. The progress of the reaction was monitored by TLC. After completion, reaction mass was diluted with ice water and extracted with chloroform. The organic layer was separated, dried over sodium sulphate, and evaporated under vacuum to obtain crude residue. The purification of crude residue was carried out by silica gel column chromatography to obtain pure 1, 5-dioxo-4-(2'-carbomethoxyethyl)-7a-methyl tetrahydro indane (**13)**.

Yield: 3.2 gm (86.30%); colorless liquid; IR ($CHCl_3$): ν_{max} 1740.39, 1664.03, 1663, 2953.07, 1216.01 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.71-1.81 (m, 1H), 1.93-2.03 (m, 1H), 2.24- 2.54 (broad m, 7H), 2.65-2.79 (m, 2H), 2.93-2.99 (m, 1H), 3.54 (s, 3H) ppm, ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.79, 24.07, 28.30, 32.34,

32.52, 35.19, 48.56, 51.05, 131.79, 164.27, 172.99, 196.79, 216.83 ppm; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.28; H, 7.34.

Preparation of 1-hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (14)

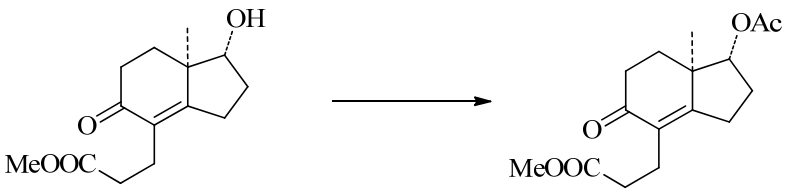


13 14

1,5-Dioxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**13**, 3.0 gm) and dry methanol were placed in one neck round bottom flask and heated to 50^{o}C under N_2 atmosphere and $NaBH_4$ (0.28 gm, 0.6 eq) was added to the stirred reaction mixture. The progress of the reaction was monitored by TLC, after 6 hrs when reaction was completed, methanol was evaporated under vacuum and crude reaction mass was extracted with chloroform, washed with brine, organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude residue. The purification of the crude residue was carried by silica gel column chromatography to obtain 1-hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydroindane (**14**).

Yield: 2.94 gm (97.3%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.64-1.96 (m, 2H), 1.99-2.05 (m, 2H), 2.26-2.55 (m, 8H), 3.56 (s, 3H), 3.72 (dd, *J* = 7.56, 11.35 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.25, 21.46, 25.10, 29.49, 32.47, 33.29, 33.83, 45.12, 51.23, 80.75, 131.68, 168.84, 173.39, 197.48; Anal calcd for $C_{14}H_{20}O_4$: C, 66.67; H, 7.93. Found: C, 66.42; H, 7.79; MS: 253 $(M+1)^+$.

Preparation of 1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (15)

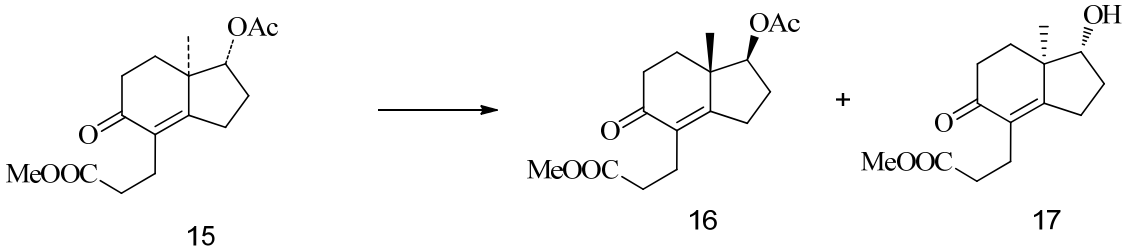


14 15

1-Hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**14**, 2.9 gm) was placed along with 10 ml pyridine in one neck RB, cooled to 0^{o}C, and to that 1.25 eq of acetic anhydride was added drop wise over half hour. The progress of the reaction was monitored by TLC. After completion of the reaction it was quenched with dilute HCl and extracted with chloroform, the organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude **15** (3 gm), purification of the crude mass carried was carried out by silica gel column chromatography to obtain 1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (1**5**).

Yield: 2.82 gm, (85.10%); colorless liquid;^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.83-1.99 (m, 2H), 2.09 (s, 3H), 2.33-2.66 (m, 10H), 3.64 (s, 3H), 4.79 (dd, *J* = 7.16, 11.06, Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.86, 20.05, 20.76, 24.49, 25.69, 31.61, 32.40, 33.07, 43.86, 50.53, 80.19, 131.89 166.59, 169.57, 172.55, 196.40 ppm; Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.36; H, 7.48; Found: C, 65.47; H, 7.61; MS: 295 $(M+1)^+$.

Enzymatic hydrolysis of 1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (15)



1-Acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**15**, 340 mg) was placed in 50 ml conical flask, phosphate buffer (27 ml, pH 7, 0.1M), ethanol (3 ml) and enzyme PPL (340 mg) were added to it and the reaction mixture was stirred at 30^{o}C. The progress of the reaction was monitored by TLC. After 24 hrs, the reaction mixture was filtered over celite bed and extracted with chloroform. Organic layer was separated and dried over sodium sulphate and evaporated under vacuum to obtain crude mass (300 mg). It was chromatgraphed to obtain fraction I (154 mg, 45.29%) and fraction II (105 mg, 36.03%)

Fraction I: 1-Acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydroindane (**16**): Yield: 154 mg, (45.29%); colorless solid $[\alpha]^{25}_{D}$= +32.03^{o}(c 1.0, $CHCl_3$); e.e. 95.56% (determined by chiral HPLC of **18,** prepared from **16**, column: Chiralcel OD [4..6 mm Id x 25 cm], λ =254 nm, flow rate: 1 ml/min; mobile phase: Hexane:IPA 95:05; retention time for 1**8** = 23.00, Retention time for racemic **14**: 20.56 and 22.20 (50.14 : 49.86 ratio). IR ($CHCl_3$): ν_{max} 2977.46, 1733.43, 1660.00,1659.00,1215.86 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.83-1.99 (m, 2H), 2.09 (s, 3H), 2.20-2.35 (m, 2H), 2.35-2.45 (m, 4H), 2.50-2.73 (m, 4H), 3.64 (s, 3H), 4.79 (dd, *J* = 7.71, 11.26 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.63, 20.80, 21.43, 25.18, 26.34, 32.29, 33.03, 33.70, 44.47, 51.27, 80.86, 131.70, 167.11, 170.24, 173.31, 197.17 ppm; Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. found: C, 65.36; H, 7.62.

Fraction II: 1-Hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**17**) Yield: 105 mg, (36.03) %; colourless liquid; $[\alpha]^{25}_{D}$ = -36.68^{o} (c 1.0, $CHCl_3$); e.e. 95.24 % (determined by chiral HPLC, column: Chiralcel OD [4.6 mm Id x 25 cm], λ =254 nm, flow rate: 1 ml/min; mobile phase: Hexane:isopropanol 95:05; retention time for **17** = 21.07, Retention time for racemic **14** : 20.56 and 22.20 (50.14 : 49.86 ratio); IR ($CHCl_3$): ν_{max} 3448.03, 2952.98, 1733.77, 1647.95, 1646.00, 1215.93 cm^{-1}; ^{1} H NMR (200 MHz, $CDCl_3$): δ 1.09 (s, 3H), 1.65-1.9 (m, 2H), 2.02-2.13 (m, 2H), 2.29-2.56 (m, 8H), 3.61 (s, 3 H), 3.78 (dd, *J* = 6.72, 11.36 Hz, 1H) ppm; ^{13} C NMR (125 MHz, $CDCl_3$): δ 15.37, 21.58, 25.21, 29.61, 32.58, 33.41,, 33.94, 45.24, 51.34, 80.86, 131.79, 168.96, 173.51, 197.59 ppm; Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.66; H, 7.93. found: C, 66.42; H, 7.81.

Preparation of (1S,7aS)-1-hydroxy-5-oxo-4-(2`-carboxyethyl)-7a-methyl tetra-hydro indane (1)

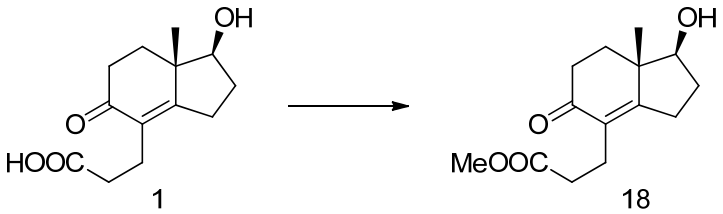
16 1

A mixture of 1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**16**, 112 mg) and HCl (6.5 N, 12 ml) was stirred at room temperature for 12 hrs. The

progress of the reaction was monitored by TLC. After completion of reaction, reaction mass was extracted with chloroform and organic layer was dried over sodium sulphate, and evaporated under vacuum to obtain crude mass; purification of the crude mass was carried out with silica gel column chromatography to obtain (1S, 7aS)-1-hydroxy-5-oxo-4-(2`-carboxyethyl)-7a-methyl tetrahydro indane (**1**, 64 mg).

Yield: 64 mg, (71.10%); colourless solid; mp 113^{o}C; $[\alpha]^{25}_{D}$= +31.5 ± 1 (c=1.0, acetone)[1]; observed $[\alpha]^{25}_{D}$ = + 30.9 (c=1.0, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (s, 3 H), 1.50-1.75 (m, 2H), 1.75-2.10 (m, 2H), 2.10-2.31 (m, 5H), 2.31-2.65 (m, 3H), 3.58 (dd, *J* = 7.84, 11.29 Hz, 1H) ppm; ^{13}CNMR (125 MHz, $CDCl_3$): δ 15.13 , 21.05, 24.78, 28.96, 32.53, 33.14, 33.63, 44.83, 130.74, 169.90, 173.99, 197.09 ppm; Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.54; H, 7.56. Found: C, 65.33; H, 7.44; MS: 239.14 $(M+1)^{+}$.

Preparation of (1S, 7aS) 1-hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetra-hydroindane (18)



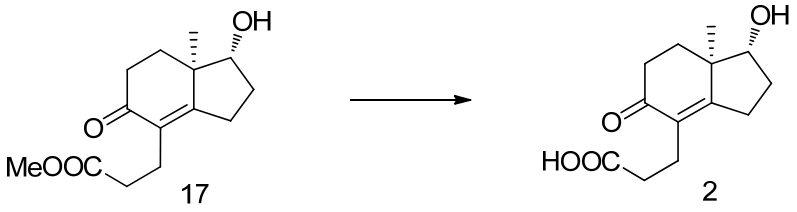
Diethyl ether (25 mL) and 50% KOH solution (25 mL) were placed in a flask cooled at ice-temperature with stirring, 33 mg N-nitroso methyl urea (5 eq. of the starting compound) was added and the stirring was continued. The compound **1** (15 mg, 0.063 mmole) was added and the reaction mixture stirred for 4 hours.

The progress of the reaction was monitored by T.L.C. After completion of the reaction, ether layer was separated and evaporated under vacuum to get pure (1*S*, 7a*S*)-1- hydroxy-5-oxo-4-(2`-carbmethoxyethyl)-7a-methyl tetra hydro indane (**18)**.

Yield: 14 mg (90.80) %; colorless liquid; $[\alpha]^{D}_{25}$ = +35.7^{o}(c=1.0, $CHCl_3$); e.e. 95.24 % (determined by chiral HPLC, column: Chiralcel OD [4.6 mm Id x 250 mm], λ=254 nm, flow rate: 1 ml/min; mobile phase: Hexane: isopropanol 95:05; retention time for **18** is 23.00, Retention time for racemic **14**: 20.56 and 22.20 (50.14:49.86 ratio); IR ($CHCl_3$): ν_{max} 1733.77, 1646.00, 1647.95, 3448.03, 2952.98, 1215.93 cm^{-1}; ^{1}H NMR

(200 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.65-1.9 (m, 2H), 2.02-2.13 (m, 2H), 2.29-2.56 (m, 8H), 3.61 (s, 3H), 3.58 (dd, *J* = 6.94, 11.782 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.37, 21.58, 25.21, 29.61, 32.58, 33.41, 33.94, 45.24, 51.34, 80.86, 131.79, 168.96, 173.51, 197.59 ppm.

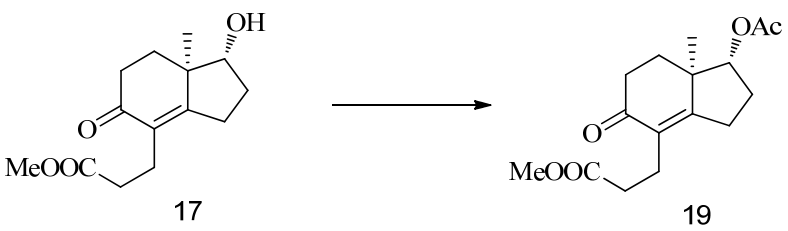
Preparation of (1R,7aR) 1-hydroxy-5-oxo-4-(2`-carboxyethyl)-7a-methyl tetra-hydro indane (2)



1-Hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**17**, 80 mg) and HCl (6.5 N, 8 ml) were stirred together at room temperature for 12 hrs. Progress of the reaction was monitored by TLC. After completion of the reaction, it was extracted with chloroform. The organic layer was separated and dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude residue. The crude residue was purified by silica gel column chromatography to get pure (1R, 7aR)1-hydroxy-5-oxo-4-(2'-carboxyethyl)-7a-methyl tetrahydroindane (**2**).

Yield: 52 mg, (68.78) %; colorless solid; mp 112°C, $[\alpha]^{25}_D$= -31.5 ± 1 (c 1.0, acetone)[1]; observed $[\alpha]^{25}_D$ = -30.8 (c 1.0, acetone); IR ($CHCl_3$): ν_{max} 3400, 3307.13, 1708.41, 1632.71 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (s, 3 H), 1.50-1.75 (m, 2H), 1.75-2.10 (m, 2H), 2.10-2.31 (m, 5H), 2.31-2.65 (m, 3H), 3.58 (dd, *J* = 7.84, 11.29 Hz, 1H) ppm; Anal. calcd for $C_{13}H_{18}O_4$: C, 66.66; H, 7.93; found: C, 66.52; H, 7.84.

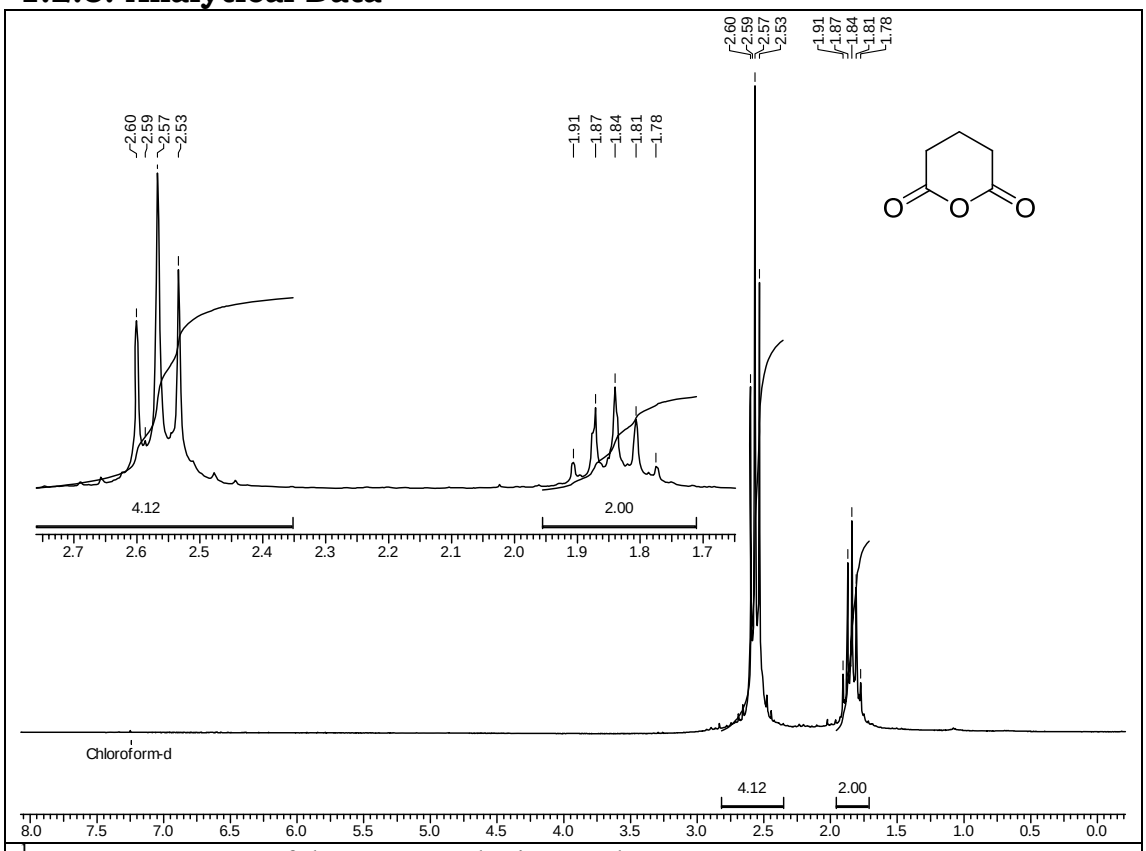
Preparation of (1R, 7aR)1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (19)



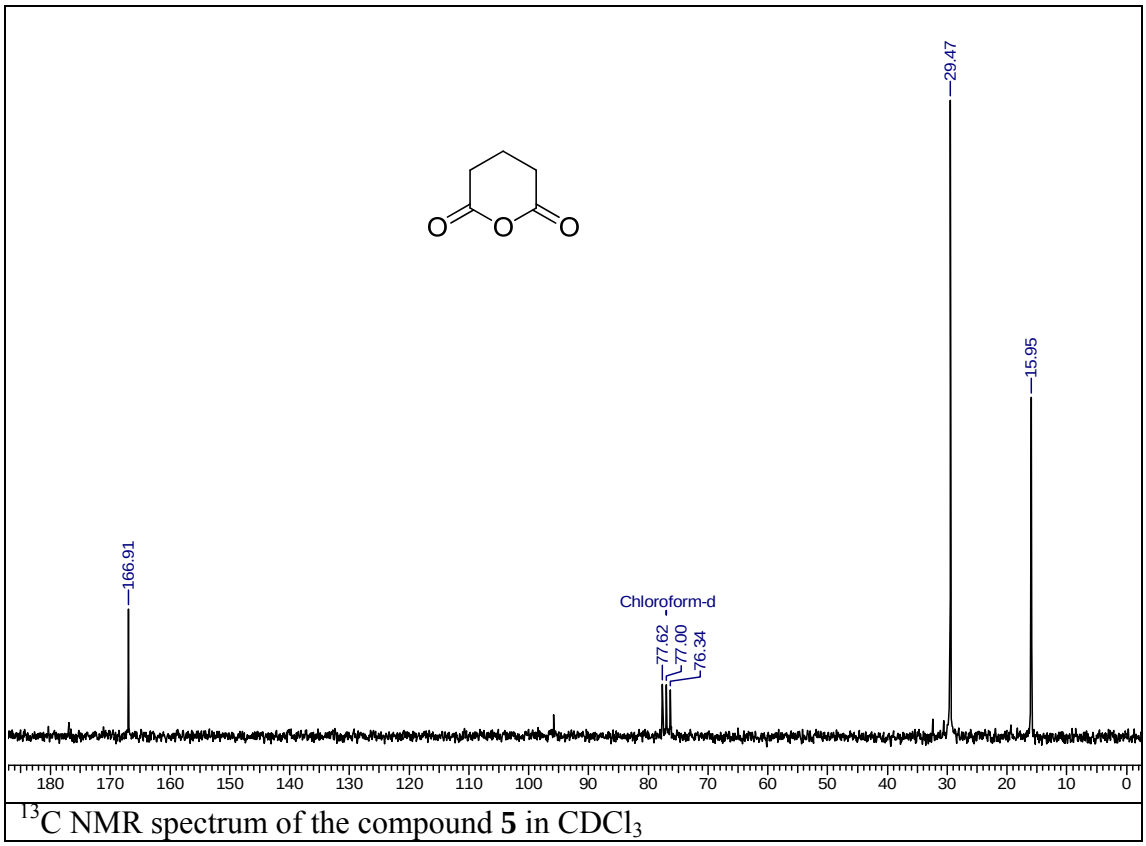
1-Hydroxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**17**, 0.2 gm) was placed along with triethyl amine (5 mL) and mixture was stirred in one neck RB, cooled to 0^{o}C, and to that acetic anhydride (0.1 mL, 1.25 eq) was added drop wise over half hour. Progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with dilute HCl and extracted with chloroform, the organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude residue, purification of crude residue was carried by silica gel column chromatography to obtain of 1-acetoxy-5-oxo-4-(2`-carbomethoxyethyl)-7a-methyl tetrahydro indane (**19**).

Yield: 0.21 gm (92.10%); colorless viscous liquid; $[\alpha]^{25}_{D}$= -34.03^{o}(c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7 (s, 3H), 1.84-1.91 (m, 2H), 1.96-2.03 (m, 2H), 2.09 (s, 3H), 2.35-2.76 (m, 8H), 3.64 (s, 3H), 4.80 (dd, *J* = 7.50, 11.28 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.63, 20.80, 21.43, 25.18, 26.34, 32.29, 33.03, 33.70, 44.47, 51.27, 80.86, 131.70, 167.11, 170.24, 173.31, 197.17 ppm; Anal. calcd for $C_{16}H_{22}O_5$: C, 65.30; H, 7.48; Found: C, 65.46; H, 7.61.

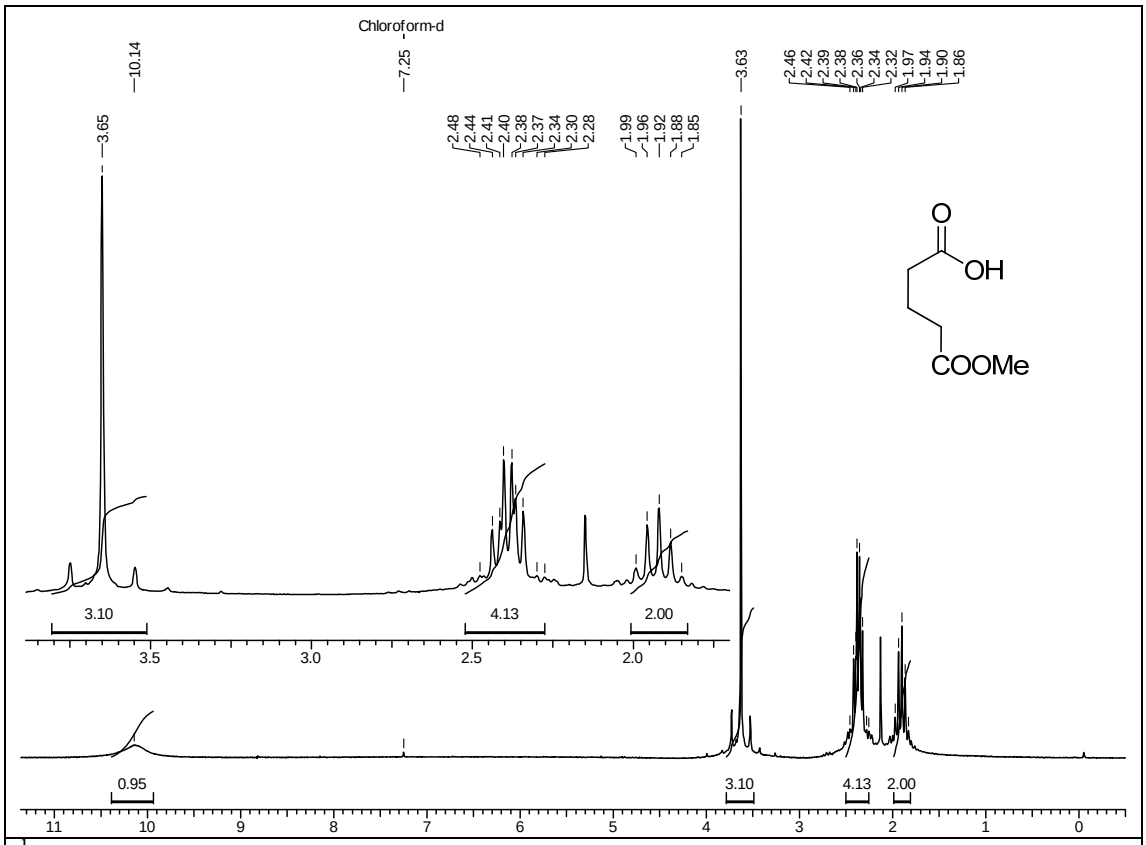
1.2.5. Analytical Data



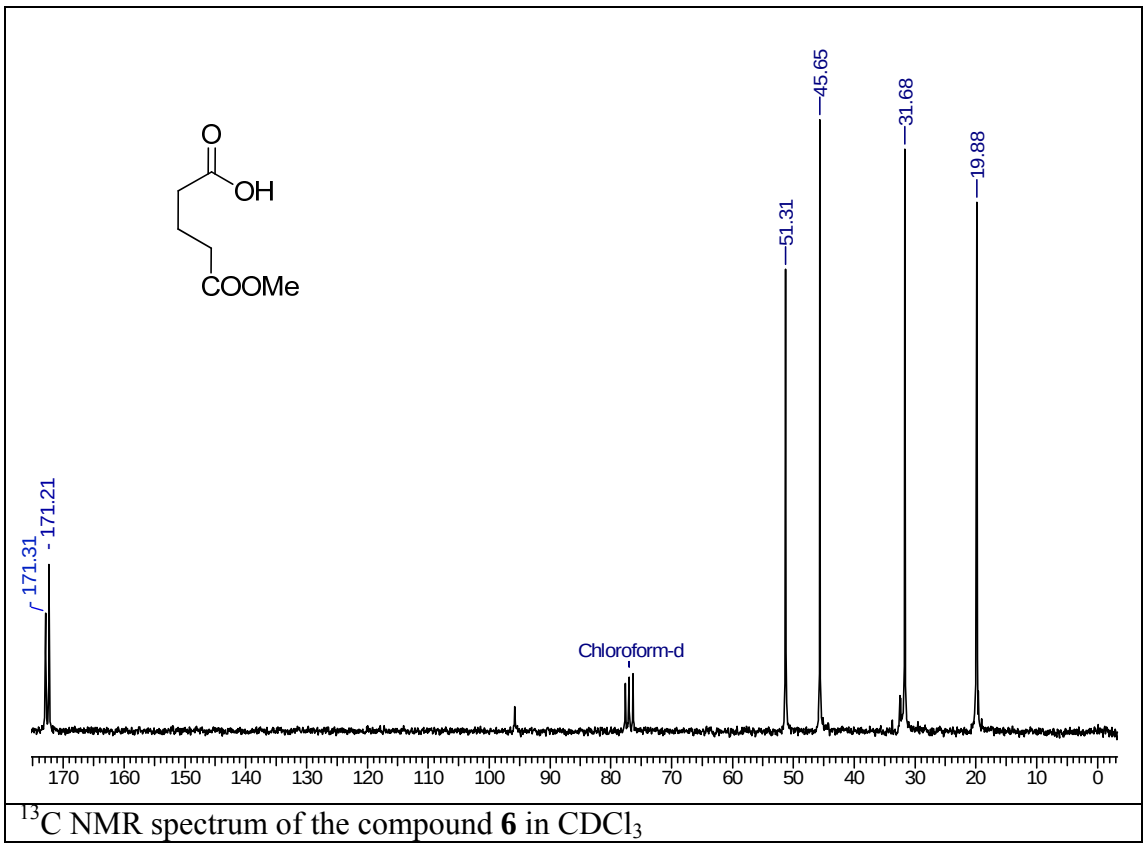
^{1}H NMR spectrum of the compound **5** in $CDCl_3$



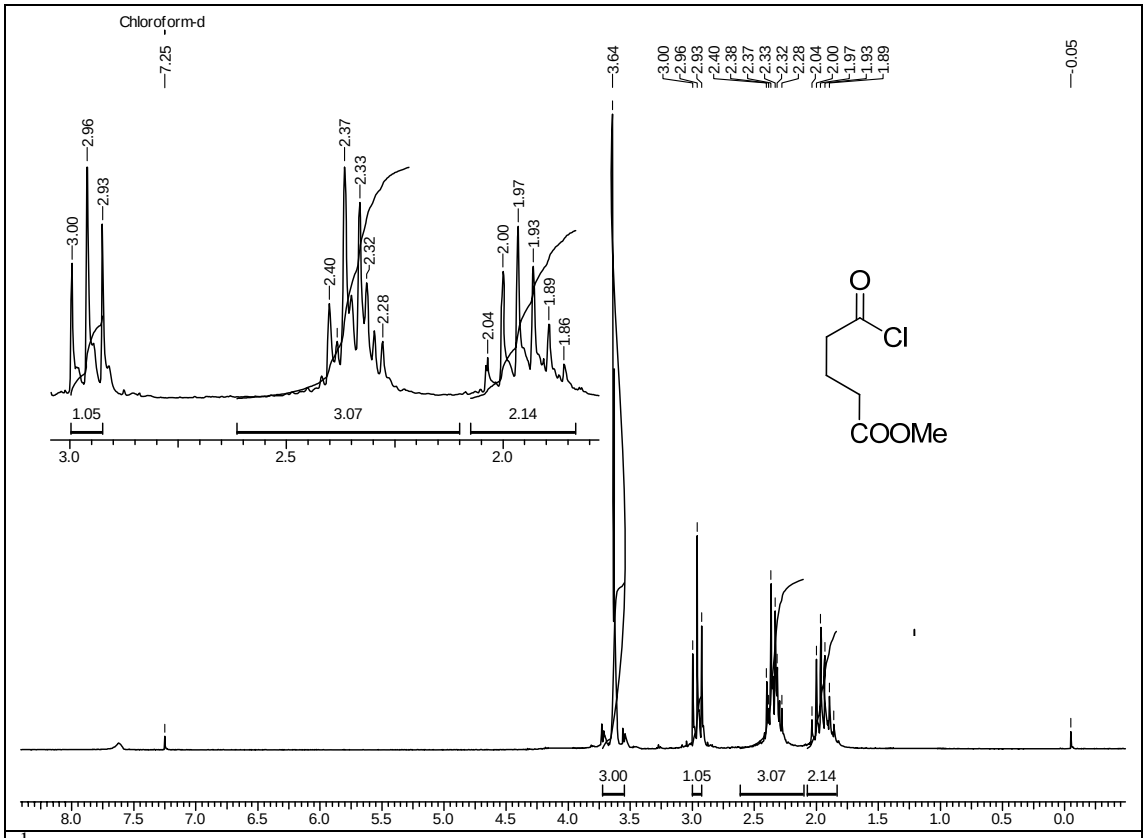
^{13}C NMR spectrum of the compound **5** in $CDCl_3$



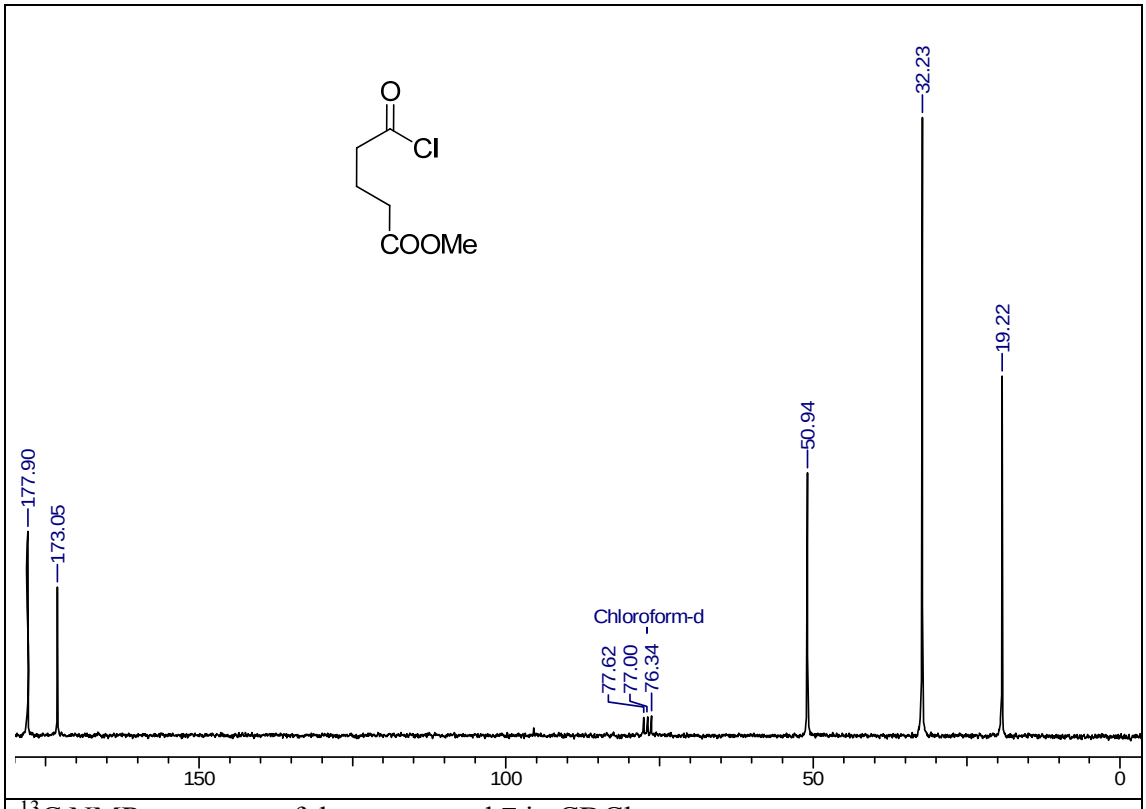
^{1}H NMR spectrum of the compound **6** in $CDCl_3$



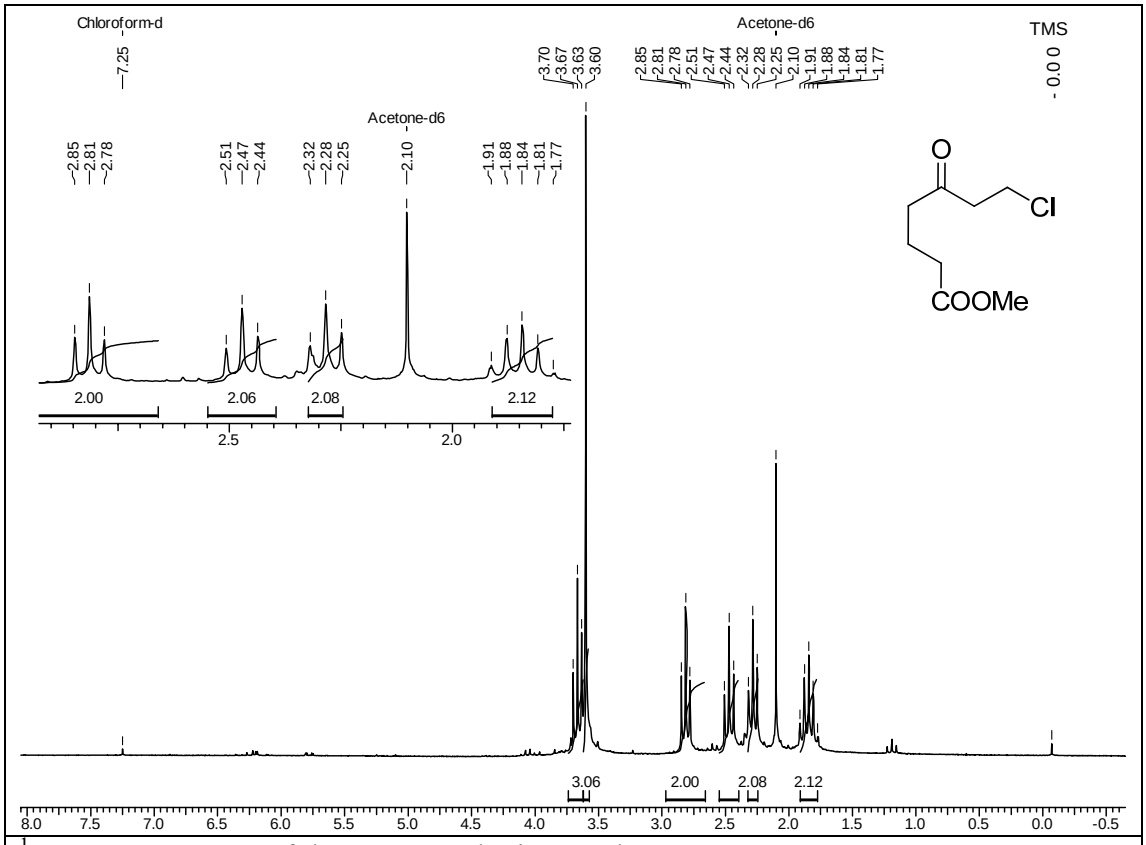
^{13}C NMR spectrum of the compound **6** in $CDCl_3$



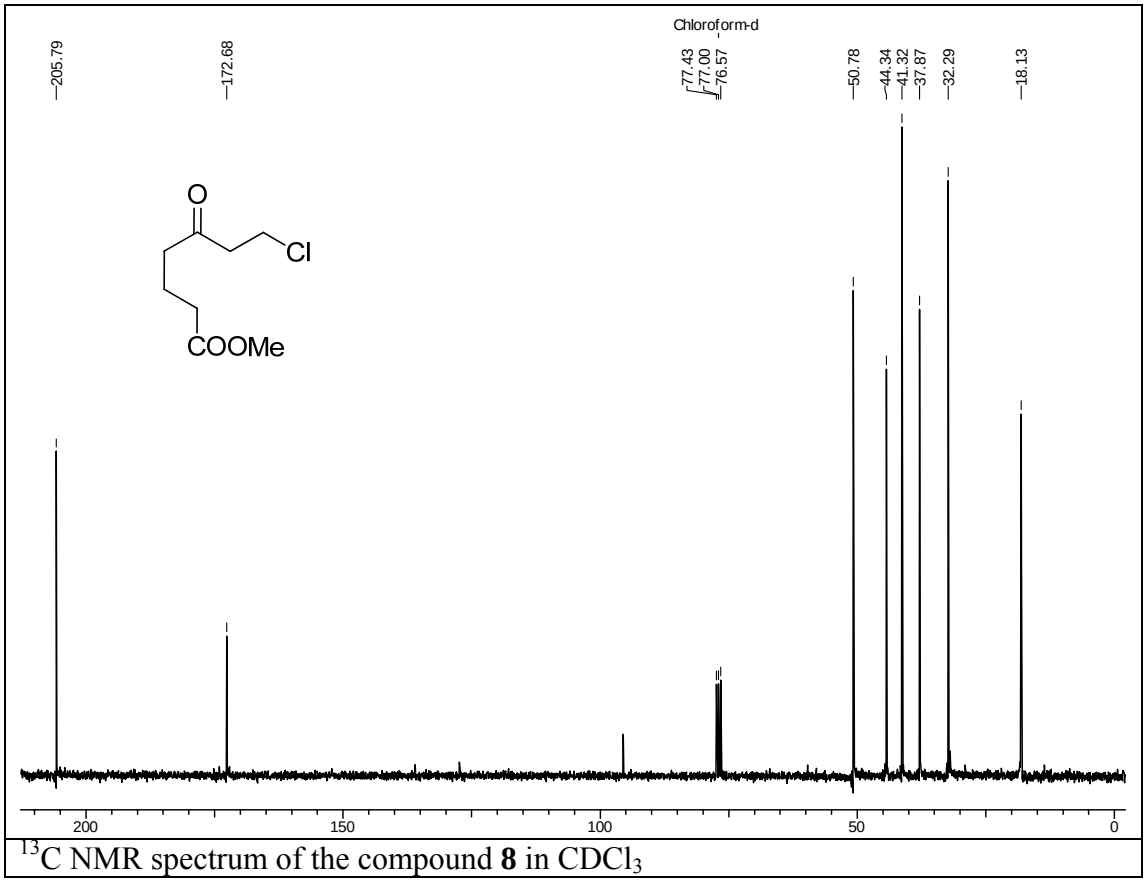
^{1}H NMR spectrum of the compound **7** in $CDCl_3$



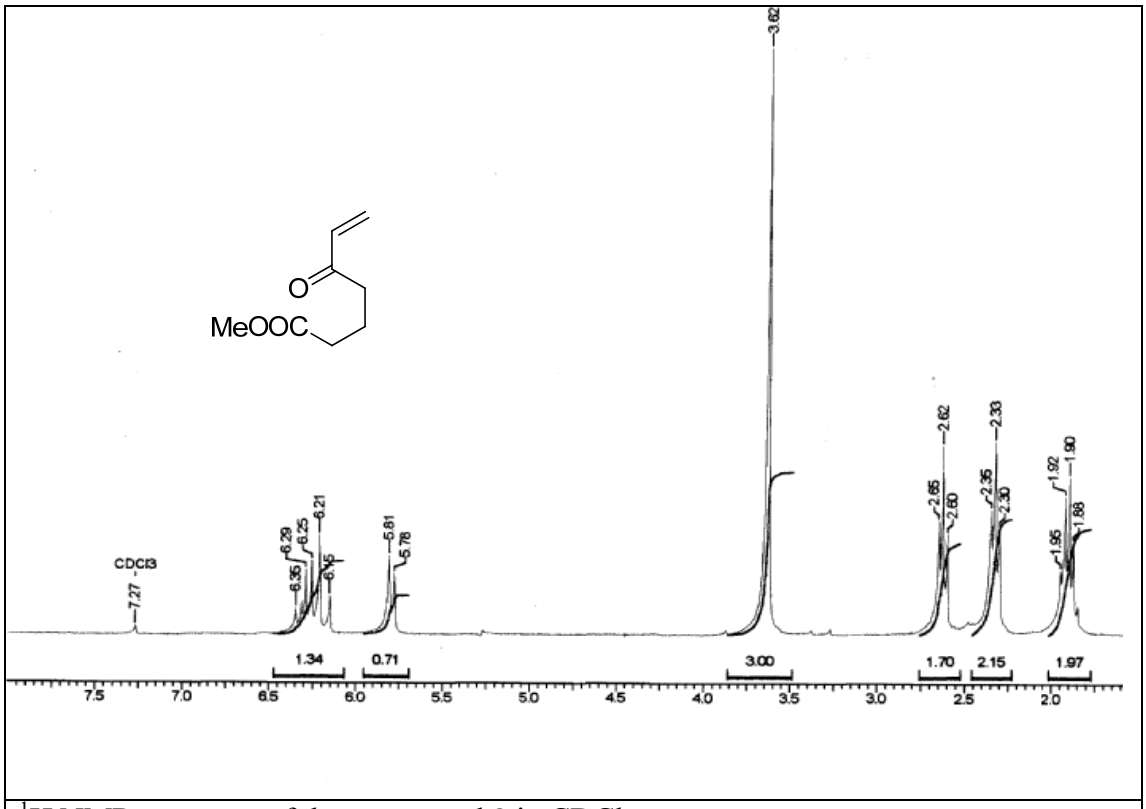
^{13}C NMR spectrum of the compound **7** in $CDCl_3$



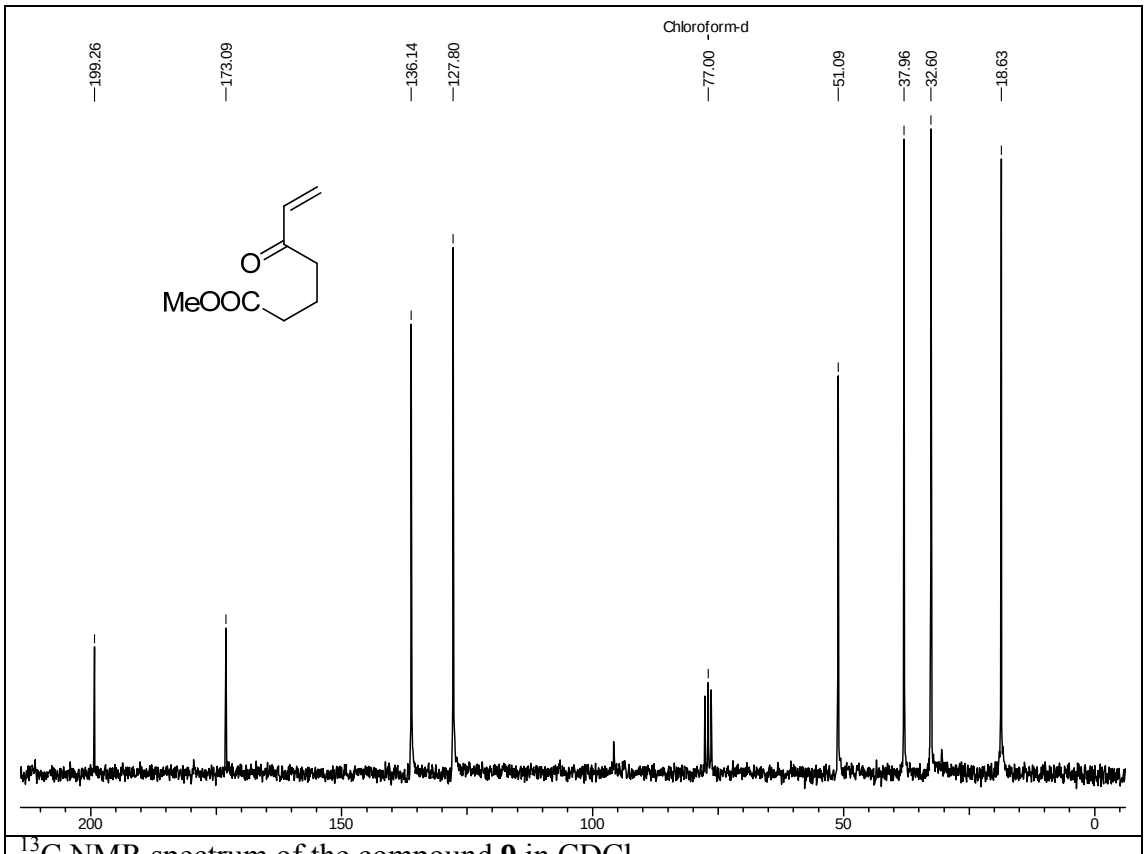
^{1}H NMR spectrum of the compound **8** in $CDCl_3$



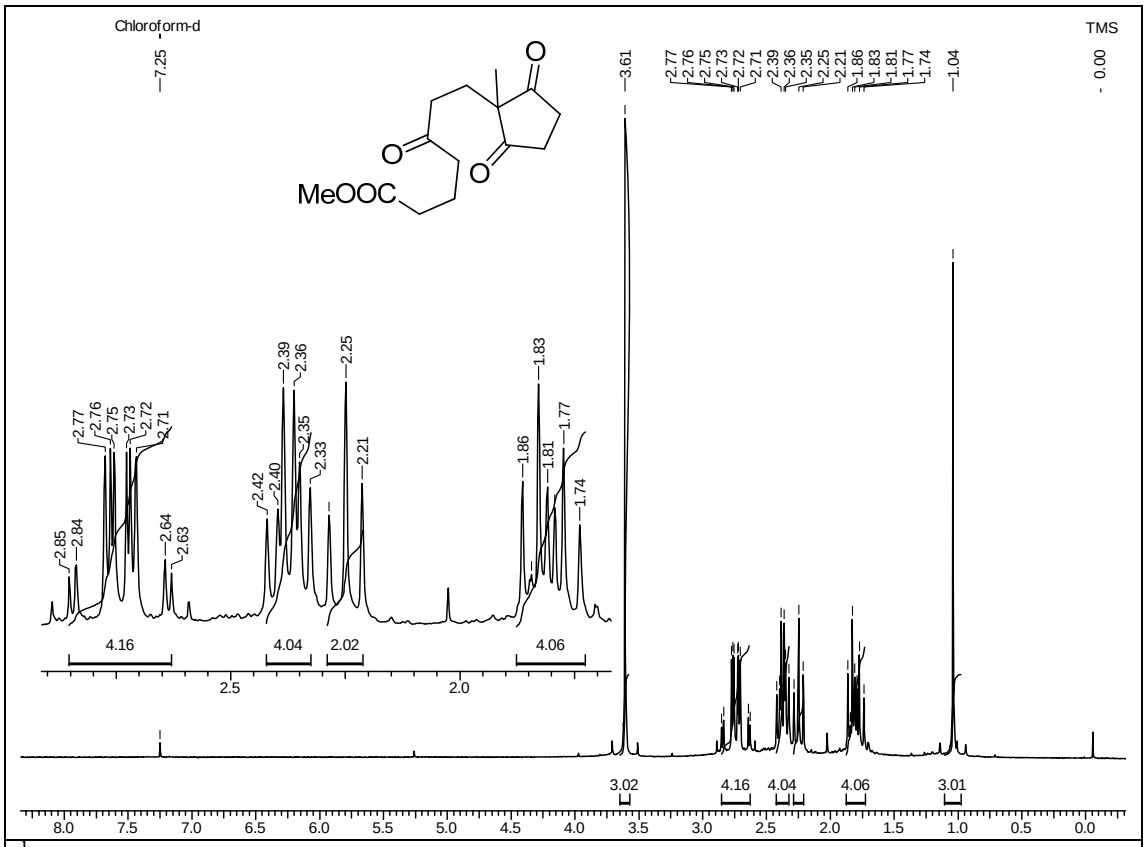
^{13}C NMR spectrum of the compound **8** in $CDCl_3$



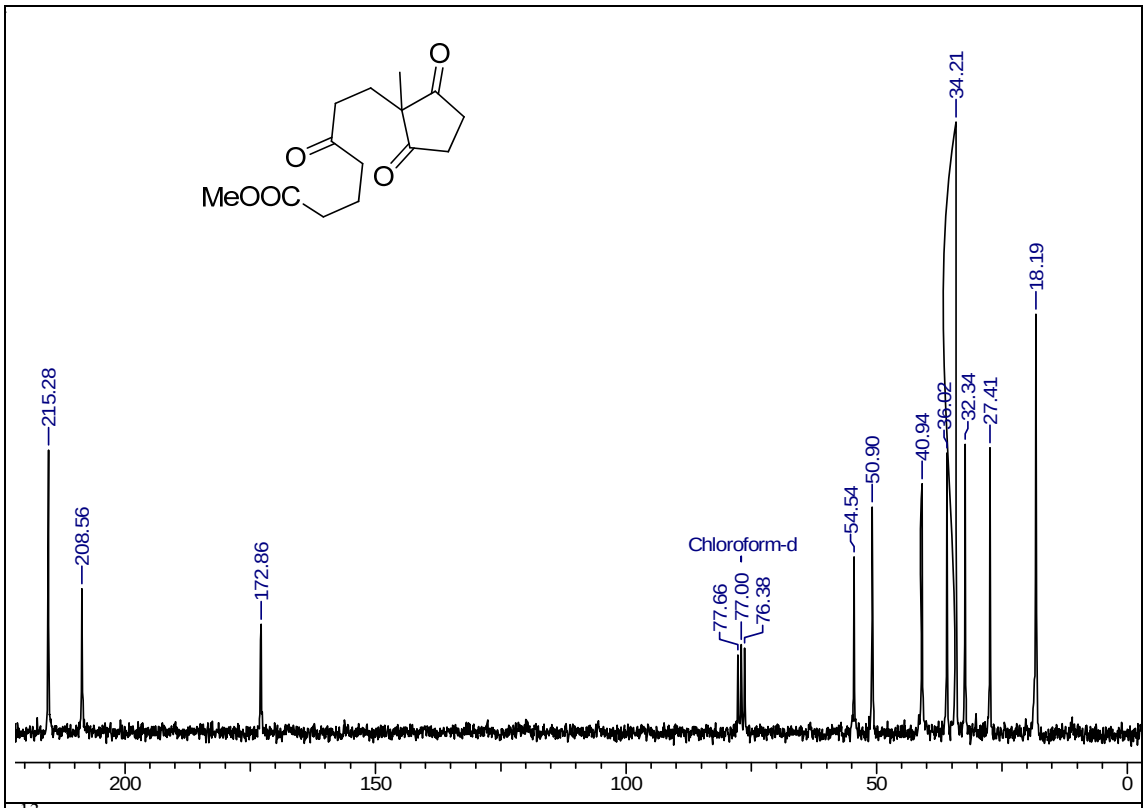
^{1}H NMR spectrum of the compound **9** in $CDCl_3$



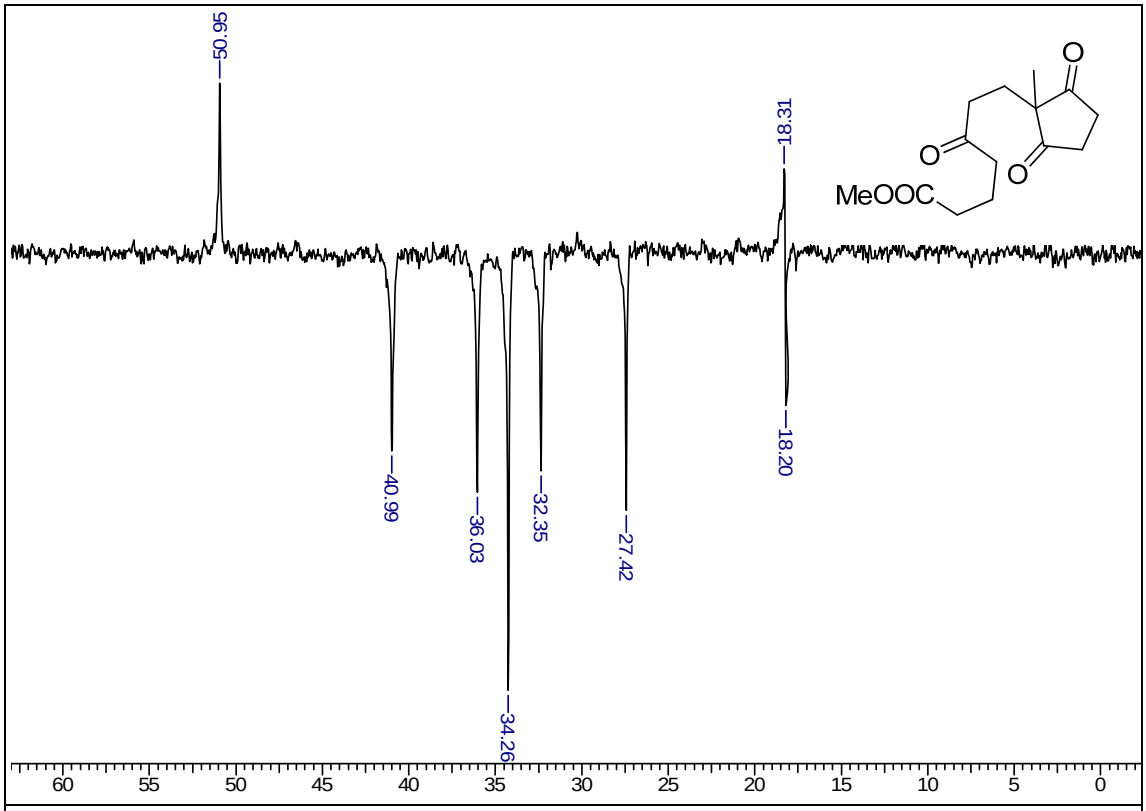
^{13}C NMR spectrum of the compound **9** in $CDCl_3$



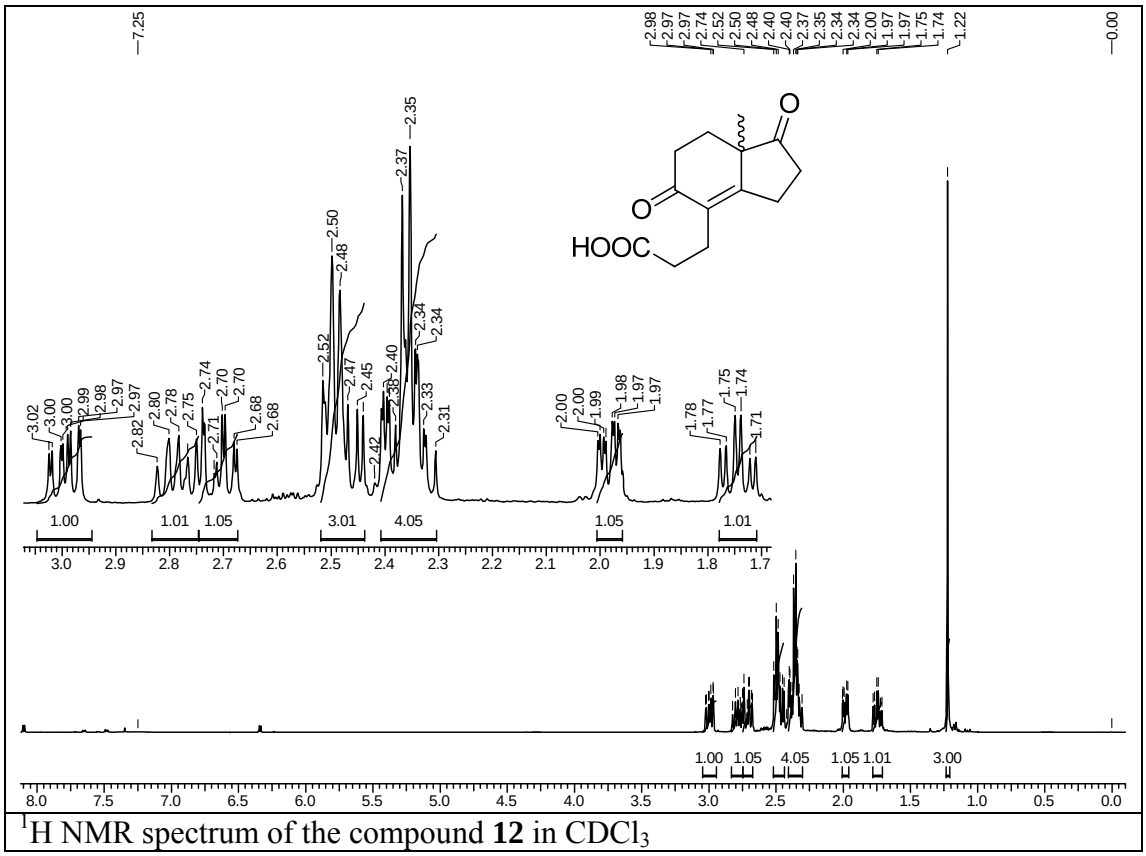
^{1}H NMR spectrum of the compound **11** in $CDCl_3$



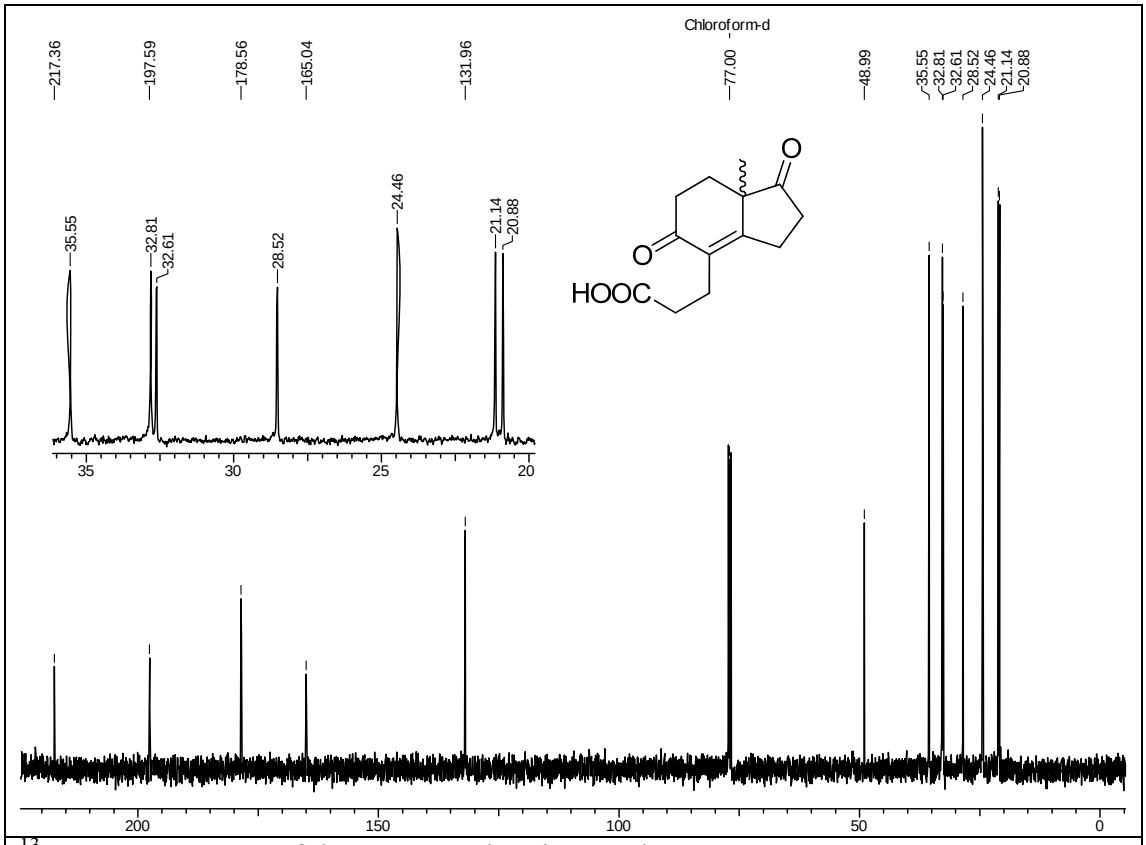
^{13}C NMR spectrum of the compound **11** in $CDCl_3$



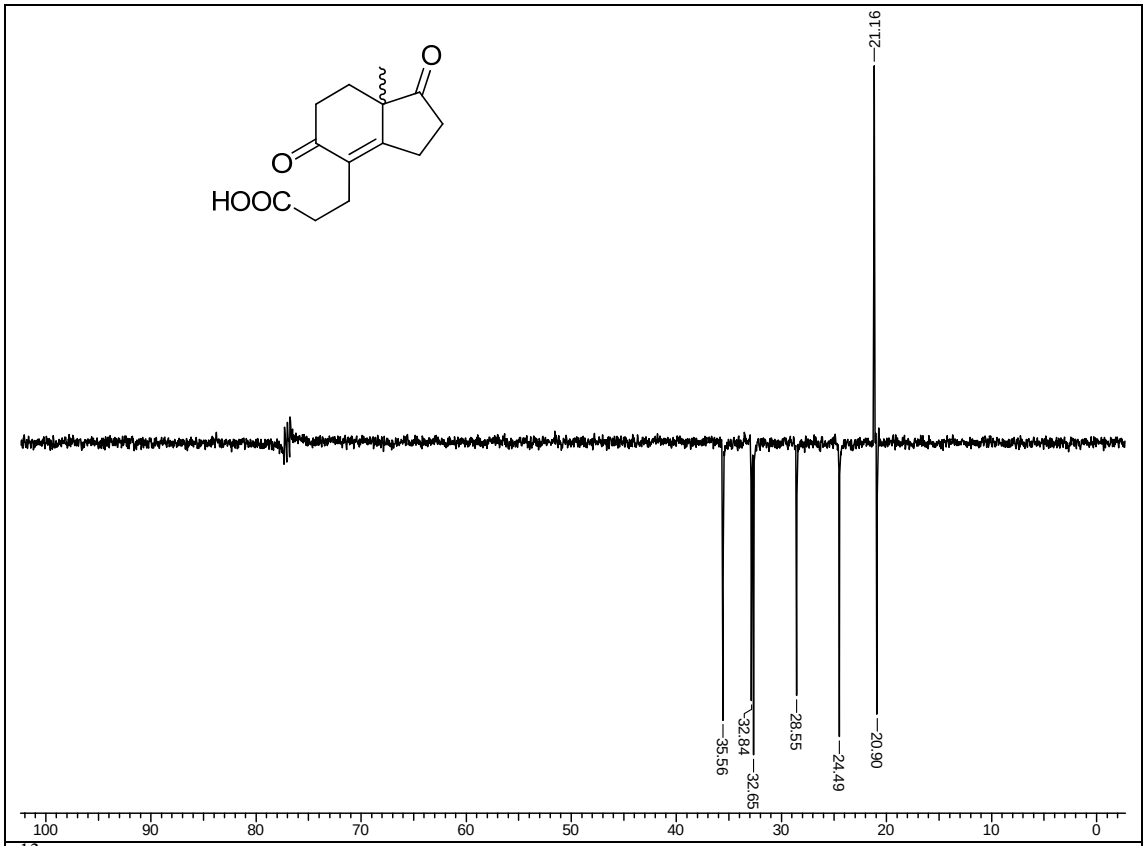
Dept NMR spectrum of the compound **11** in $CDCl_3$



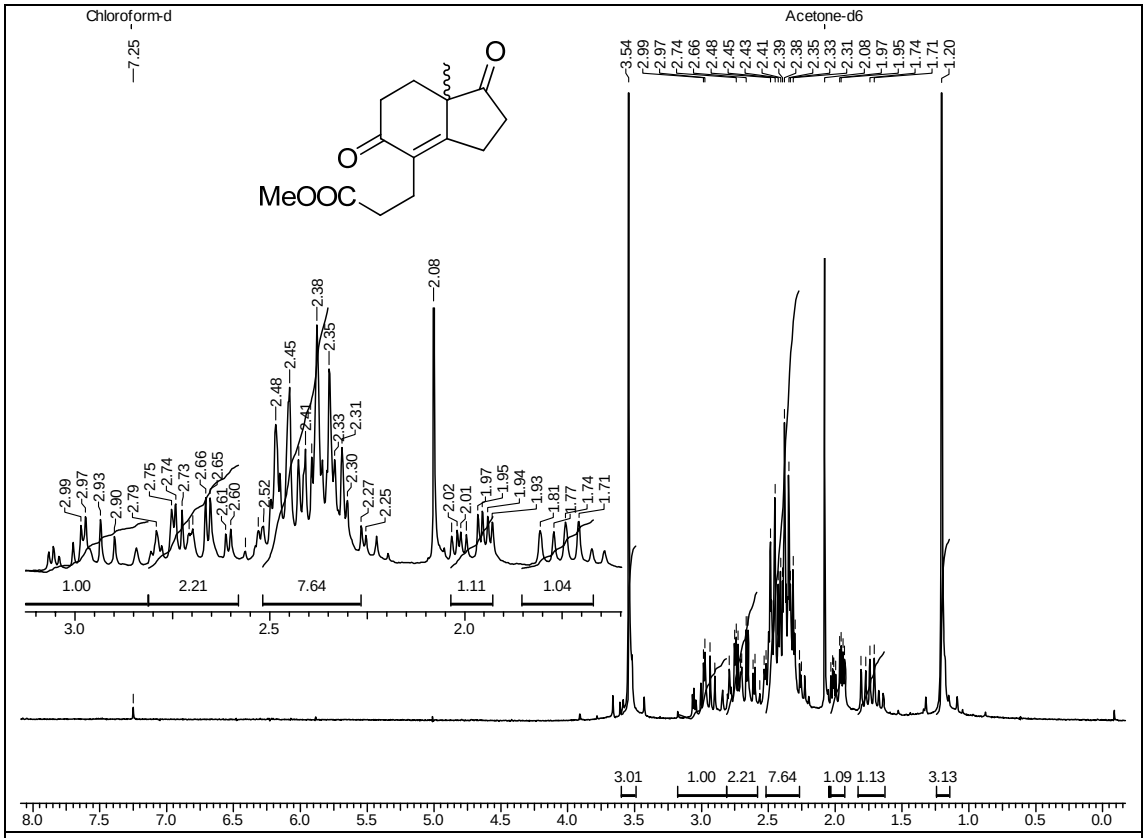
^{1}H NMR spectrum of the compound **12** in $CDCl_3$



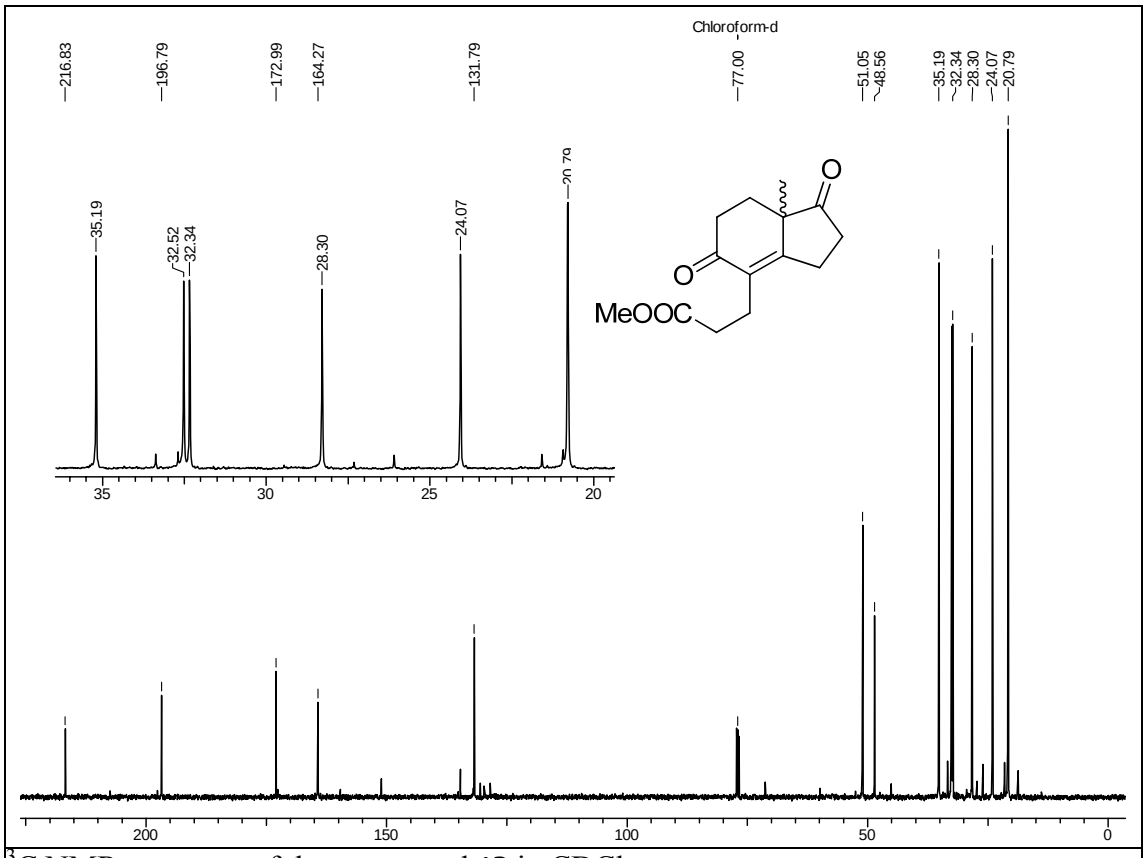
^{13}C NMR spectrum of the compound **12** in $CDCl_3$



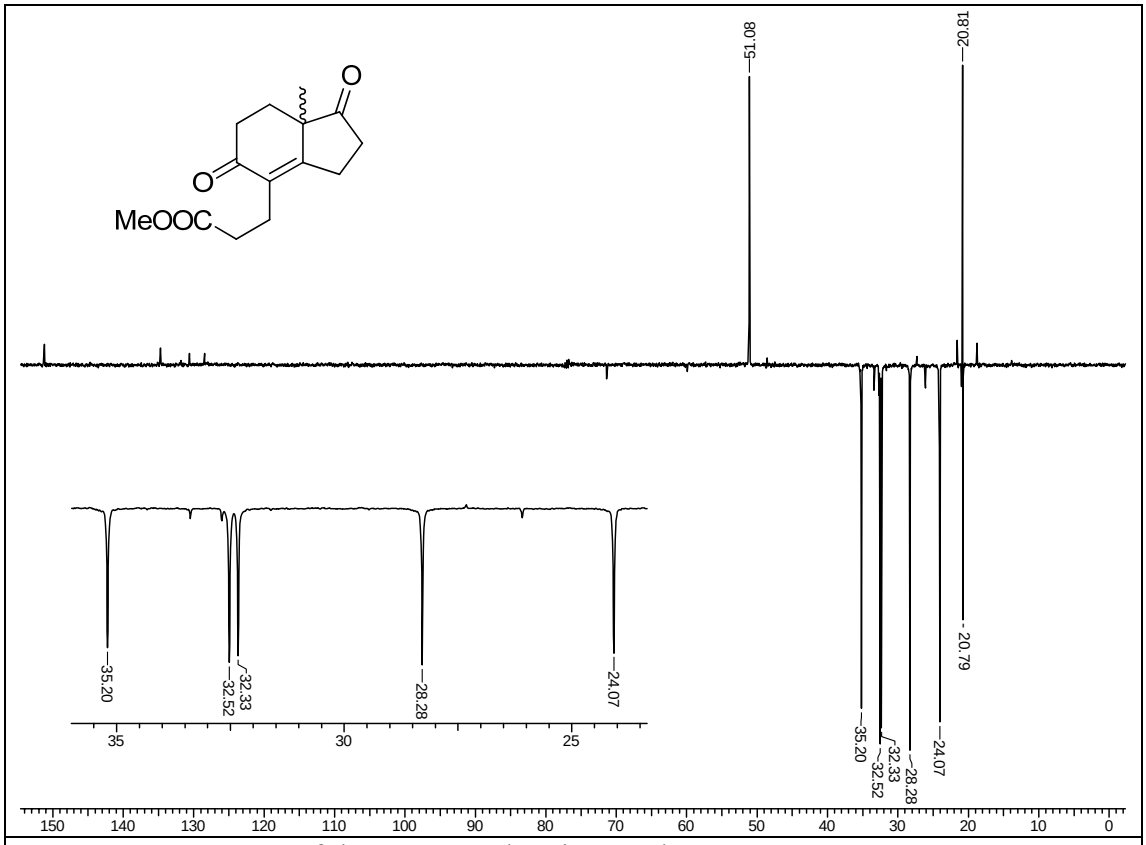
^{13}C NMR spectrum of the compound **12** in $CDCl_3$



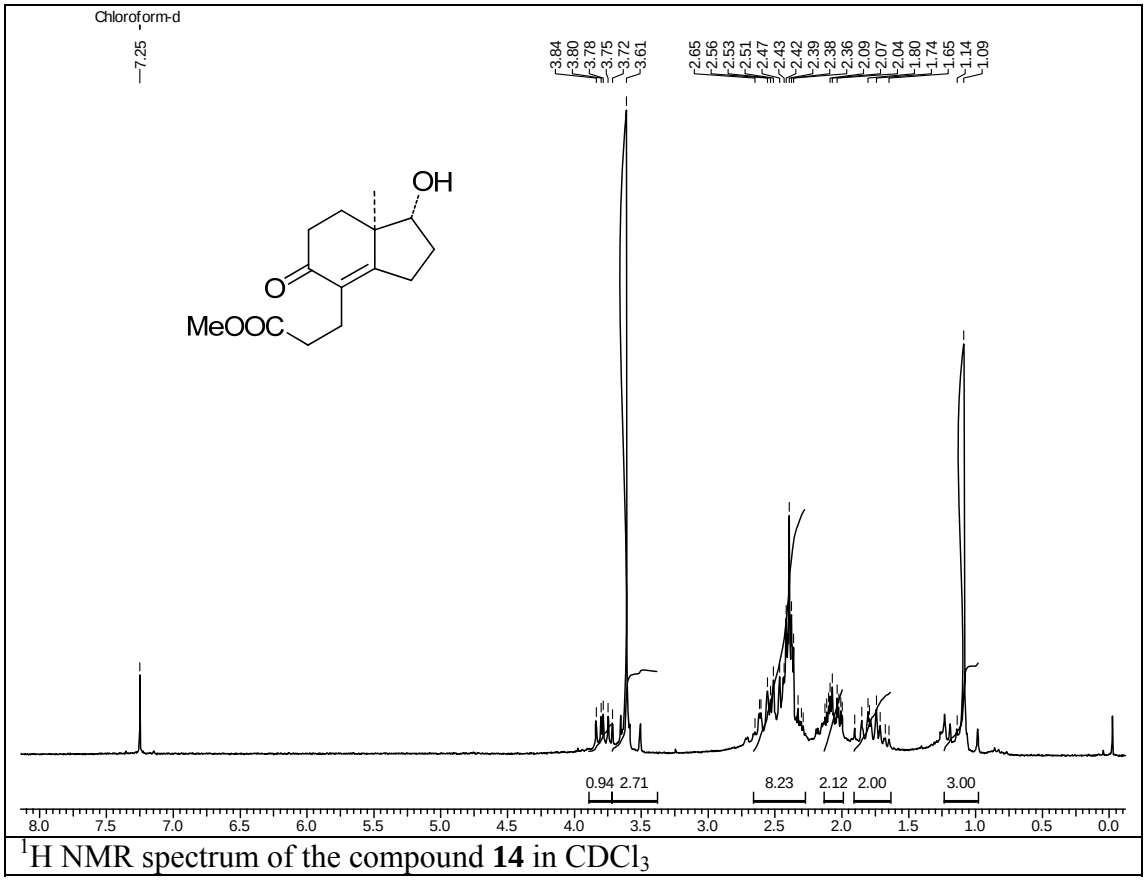
H NMR spectrum of the compound **13** in $CDCl_3$



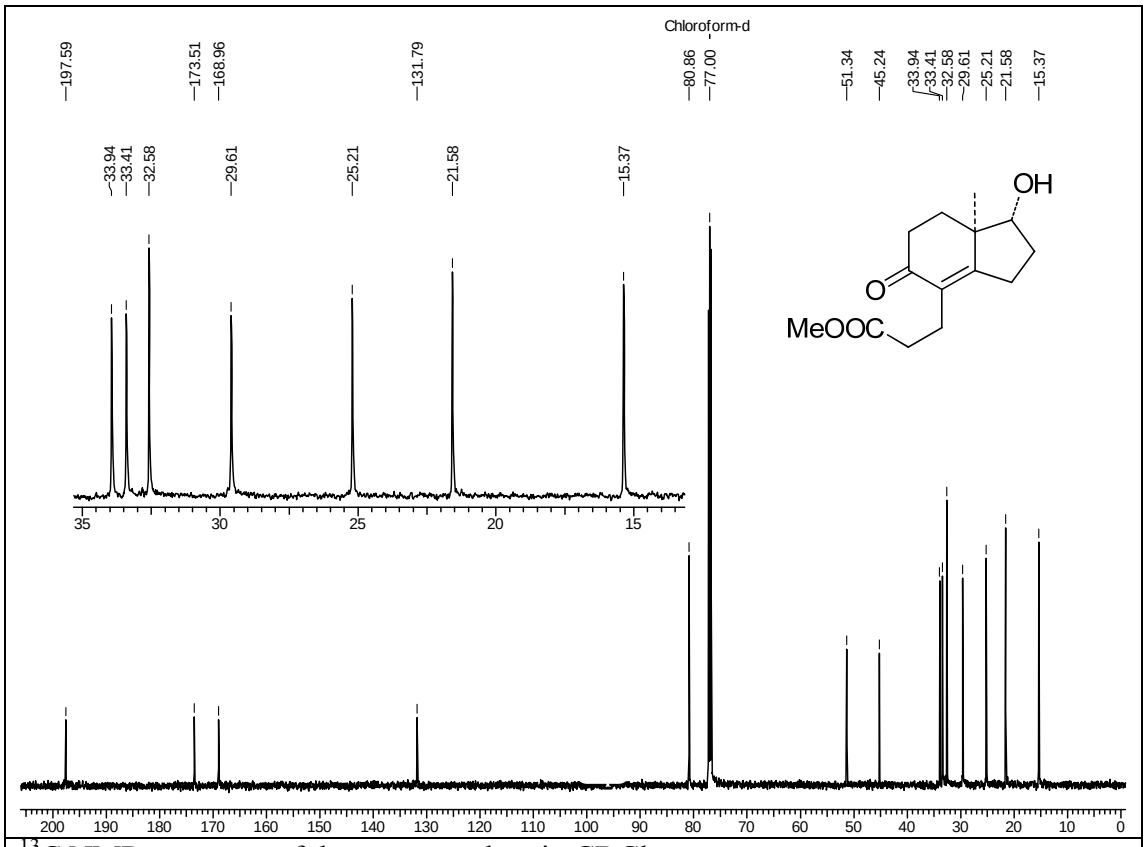
^{13}C NMR spectrum of the compound **13** in $CDCl_3$



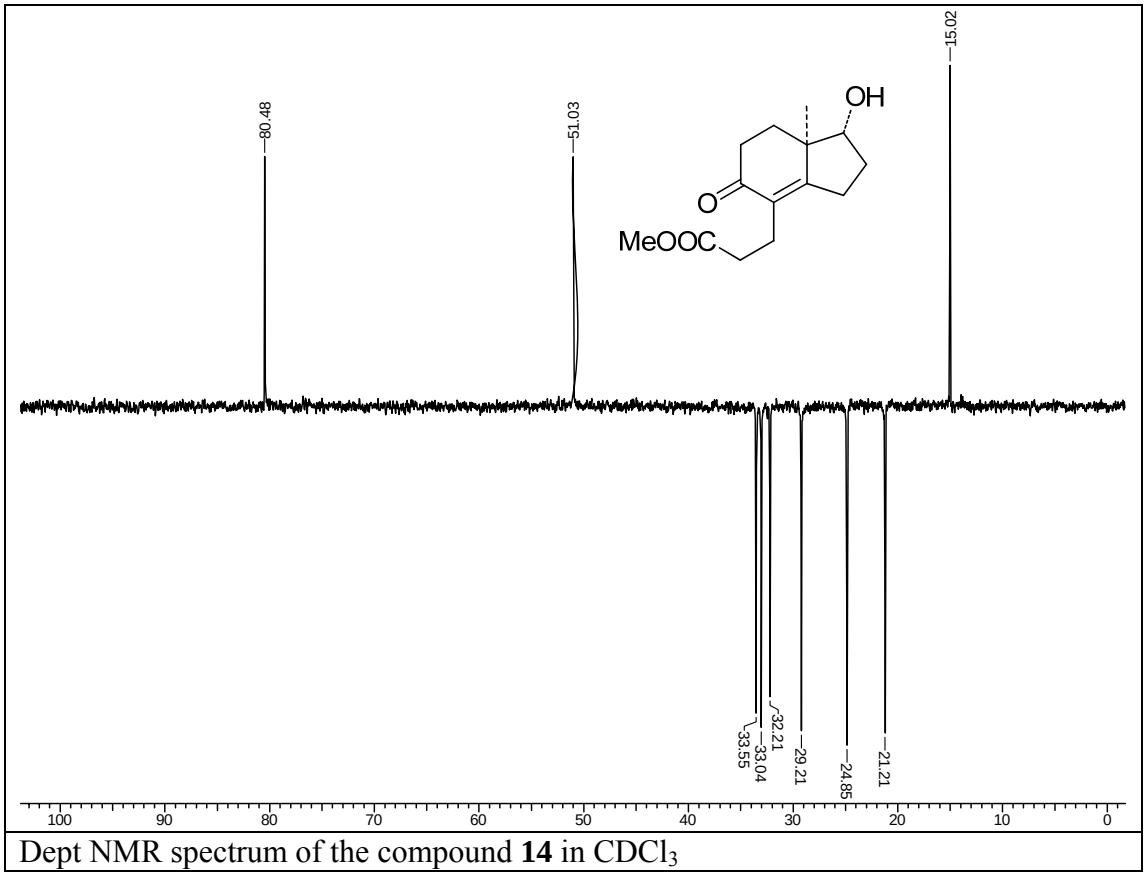
Dept NMR spectrum of the compound **13** in $CDCl_3$



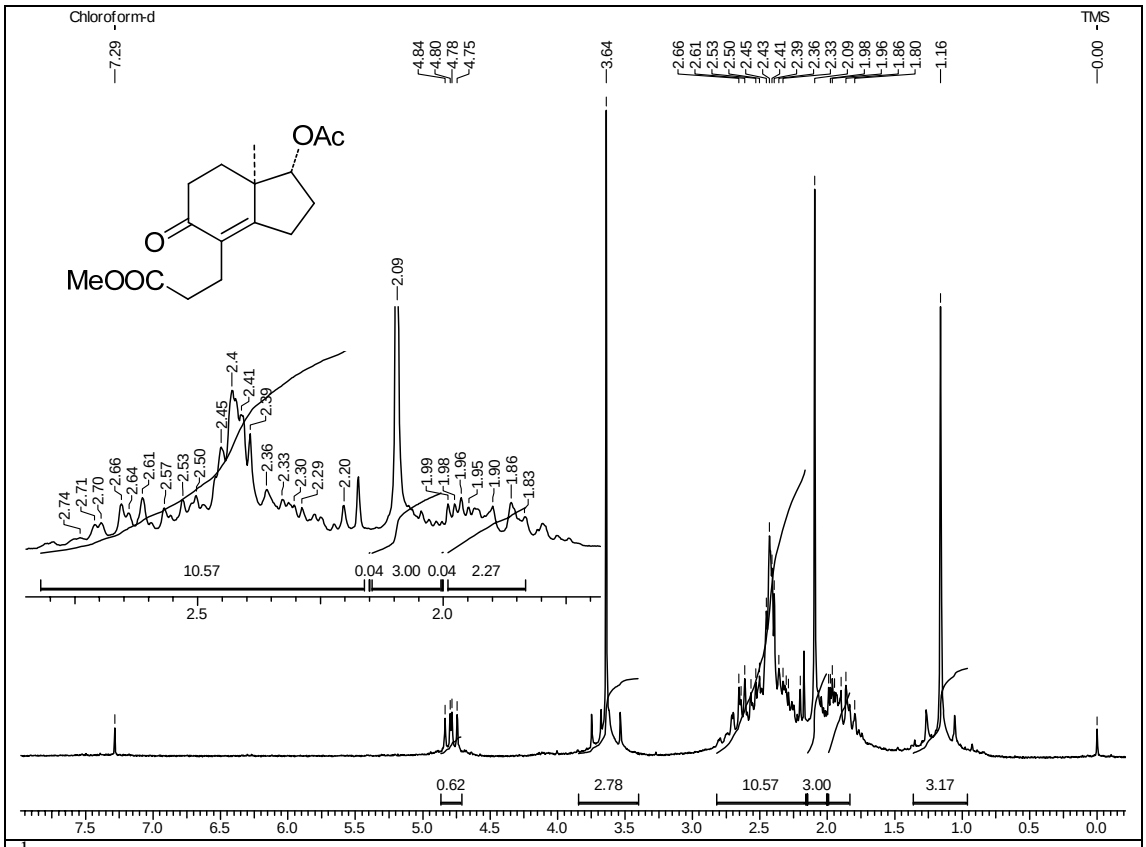
^{1}H NMR spectrum of the compound **14** in $CDCl_3$



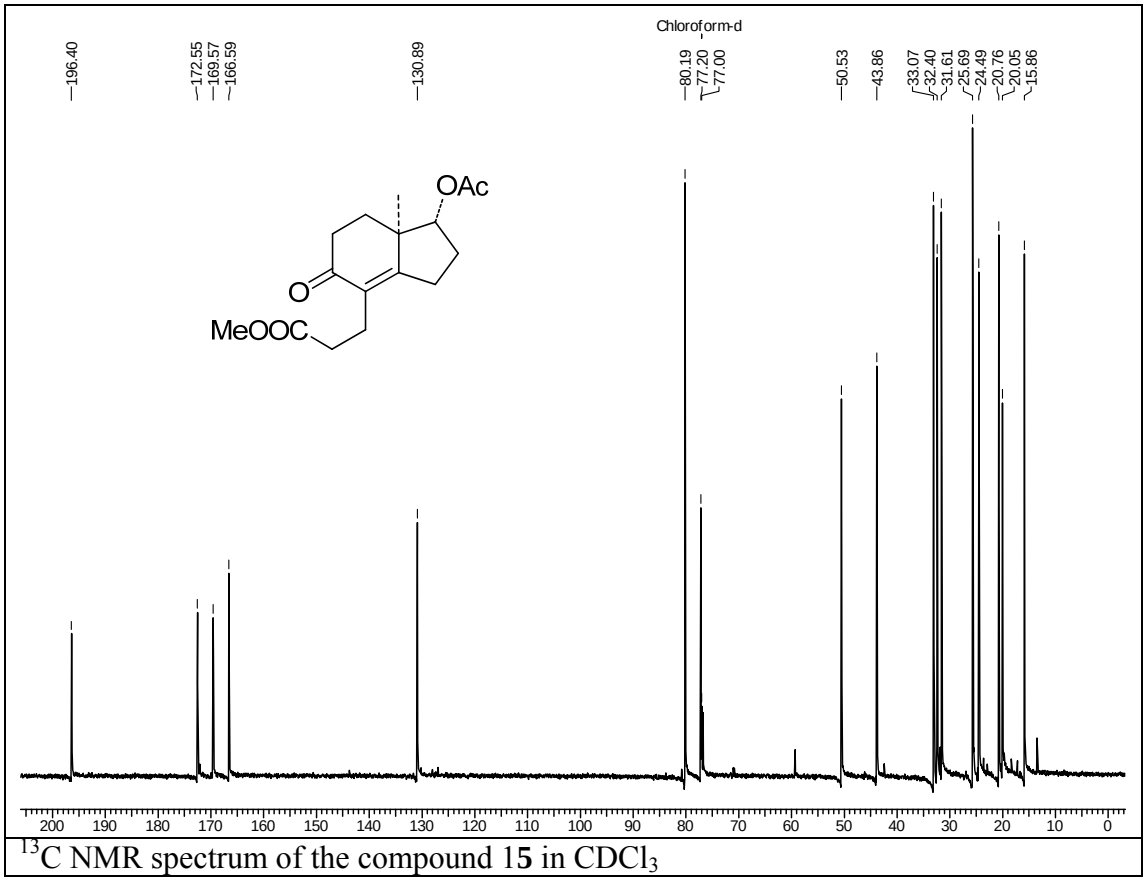
^{13}C NMR spectrum of the compound **14** in $CDCl_3$



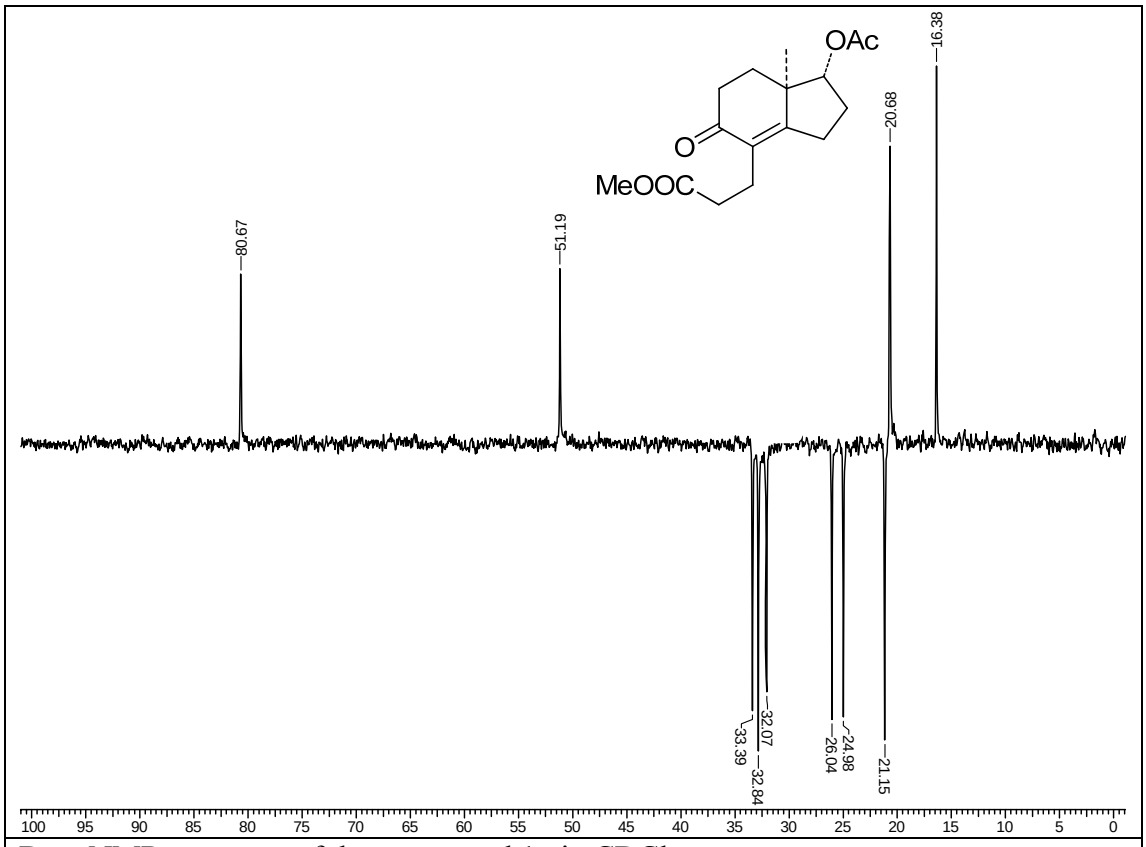
Dept NMR spectrum of the compound **14** in $CDCl_3$



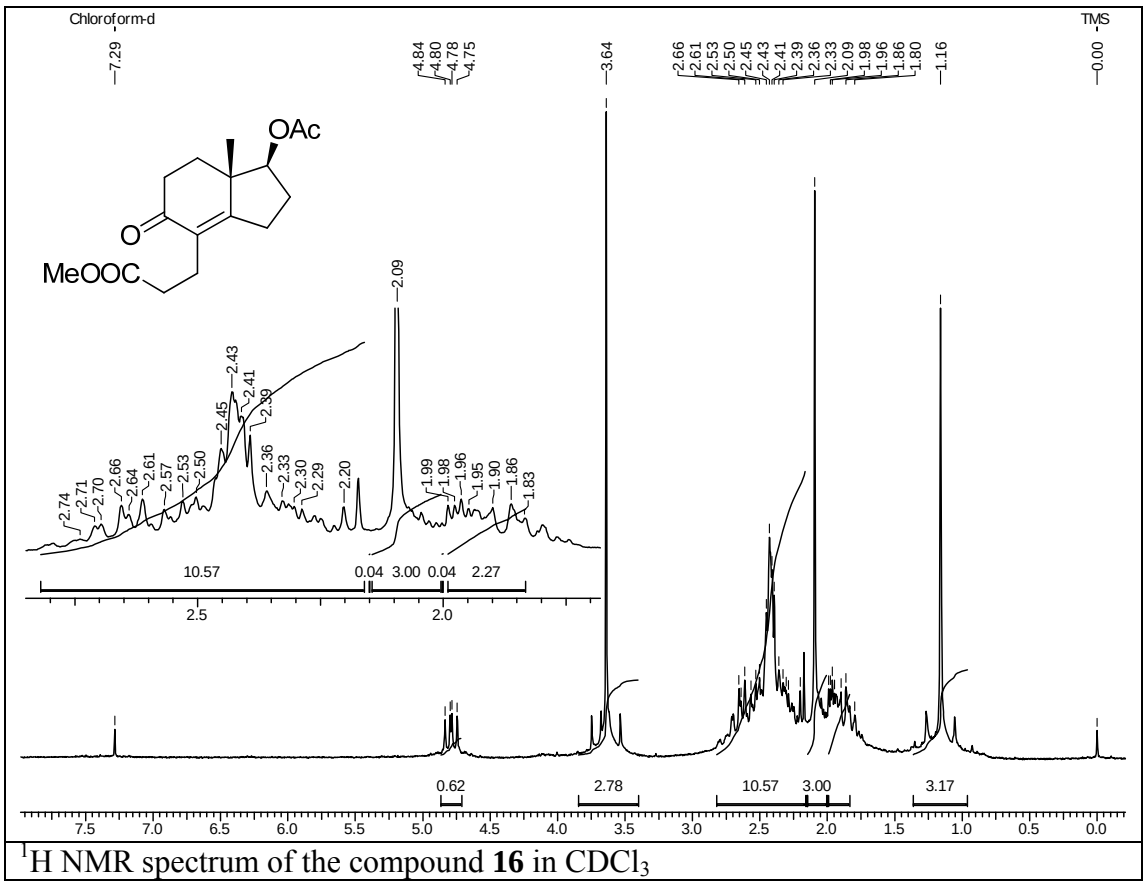
^{1}H NMR spectrum of the compound 1**5** in $CDCl_3$



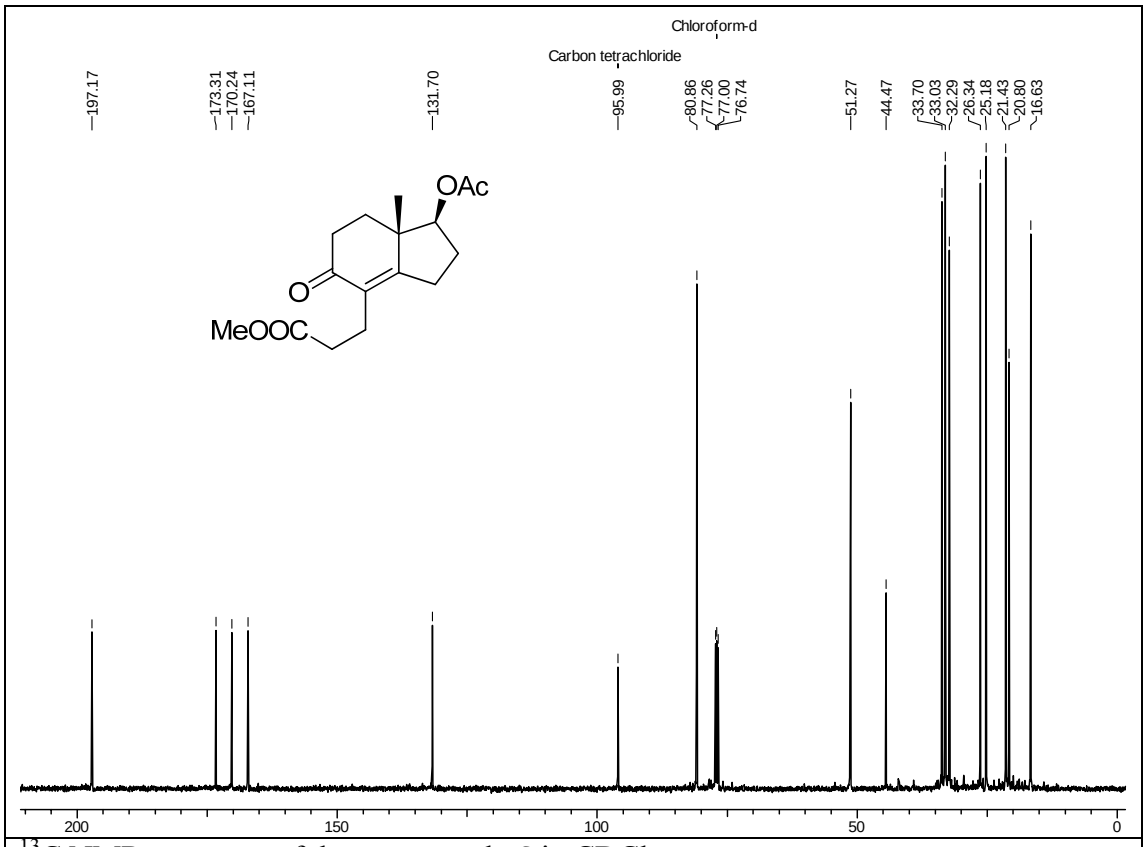
^{13}C NMR spectrum of the compound 1**5** in $CDCl_3$



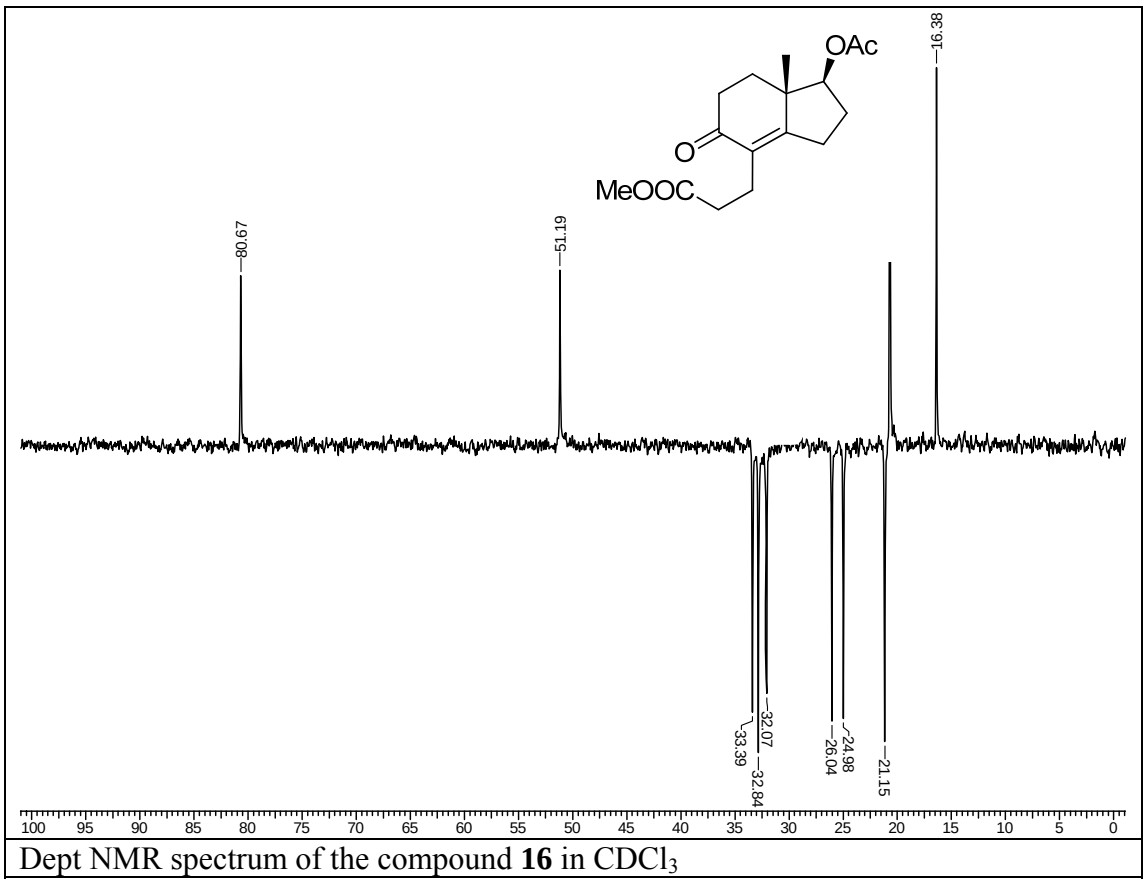
Dept NMR spectrum of the compound 1**5** in $CDCl_3$



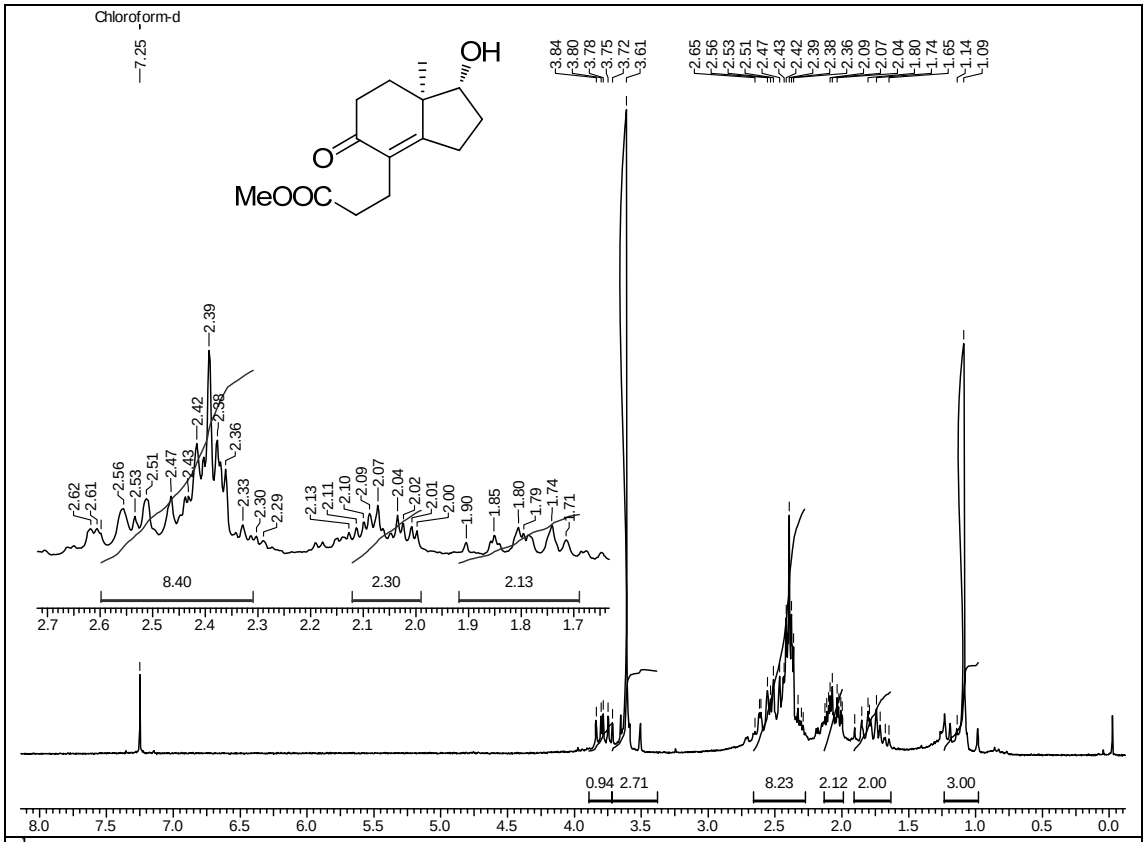
^{1}H NMR spectrum of the compound **16** in $CDCl_3$



^{13}C NMR spectrum of the compound **16** in $CDCl_3$



Dept NMR spectrum of the compound **16** in $CDCl_3$



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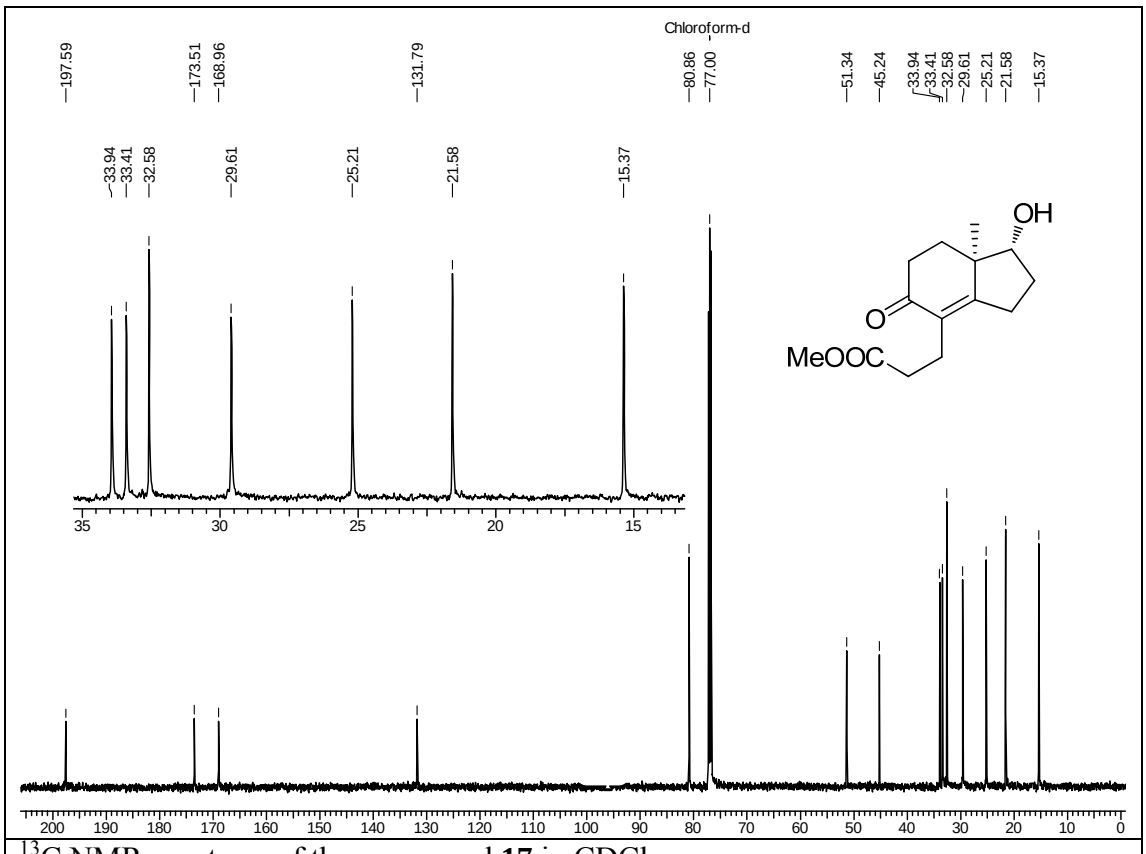

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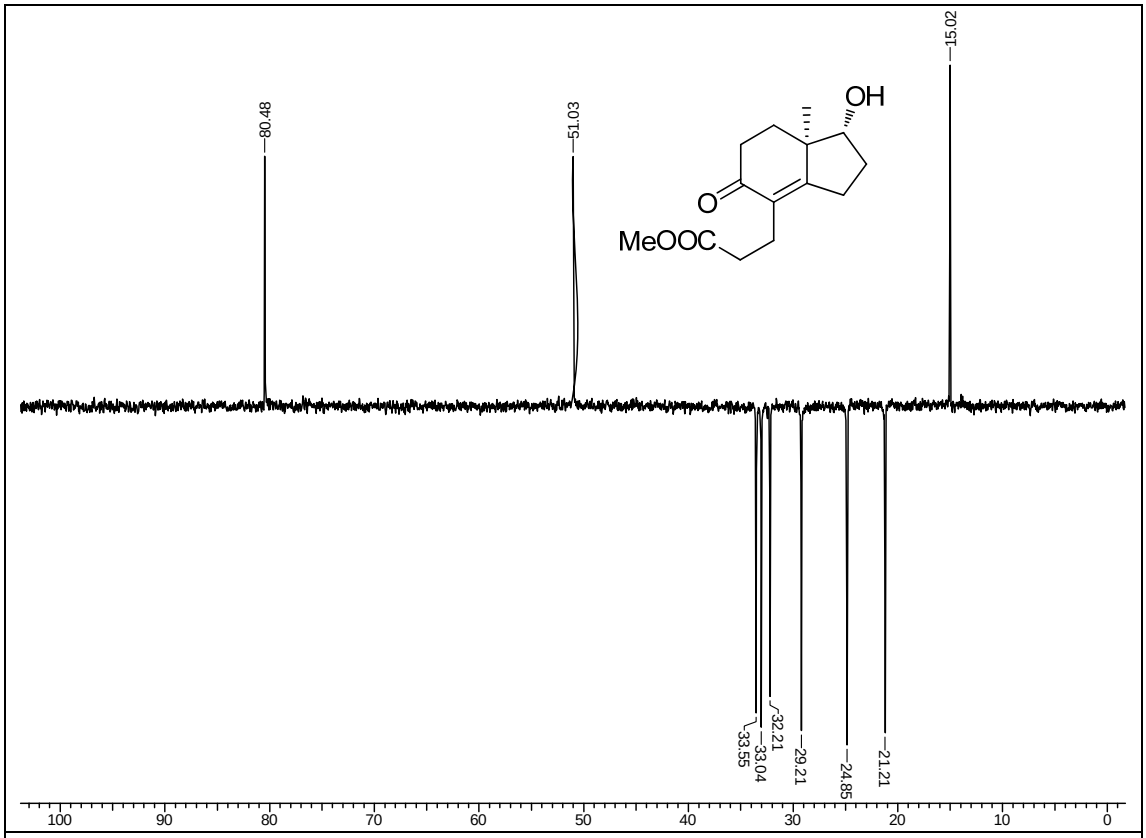

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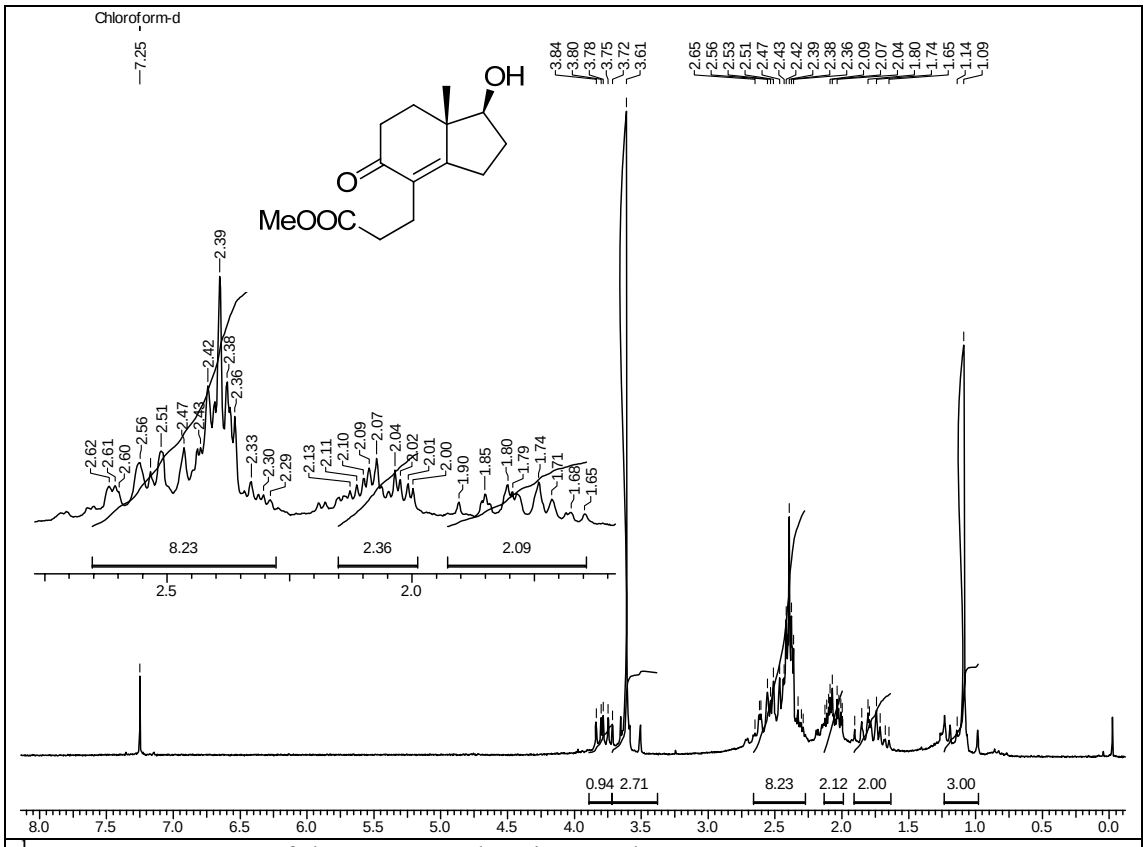

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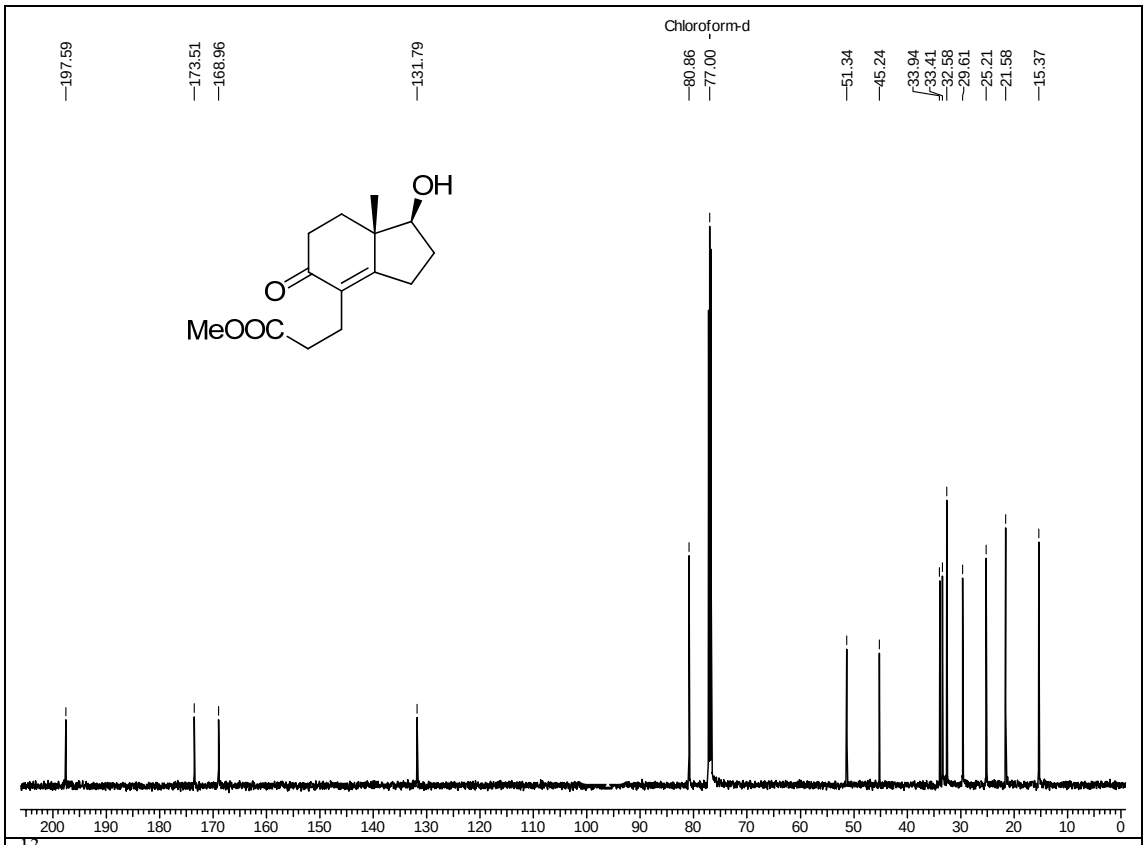
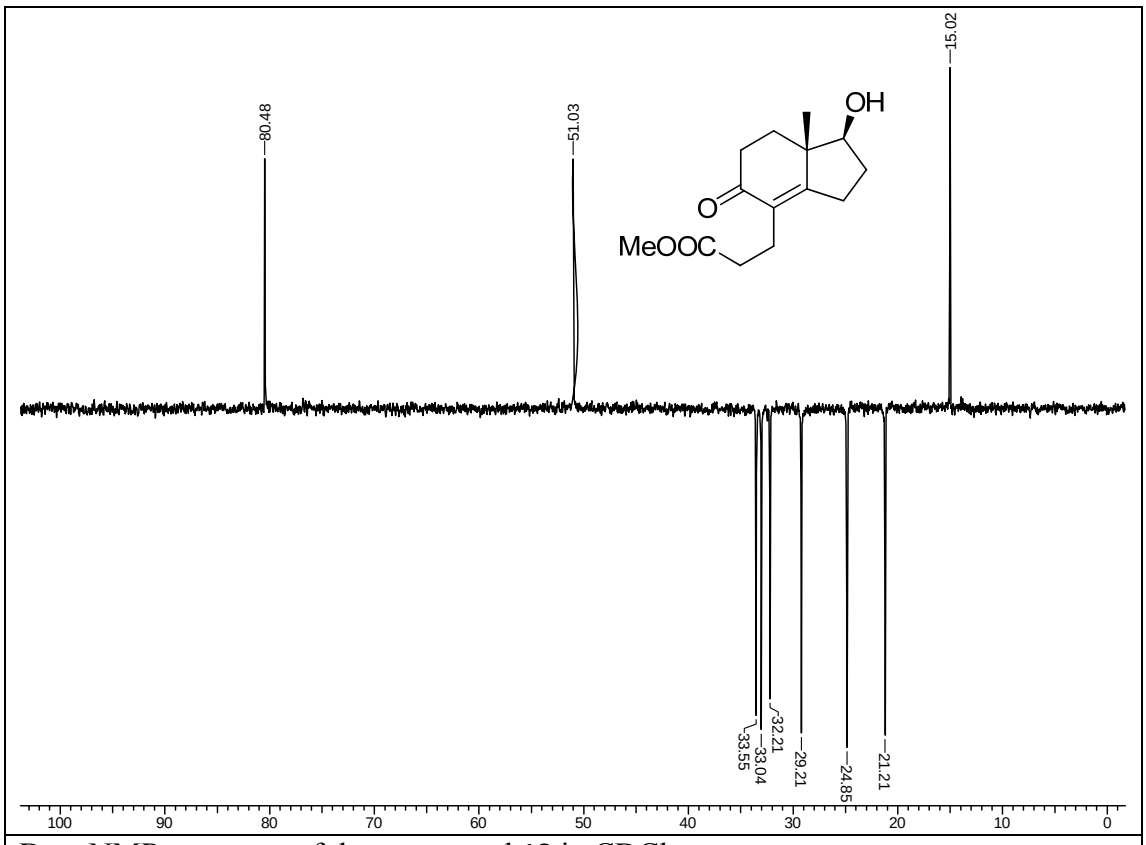


^{13}C NMR spectrum of the compound **18** in $CDCl_3$



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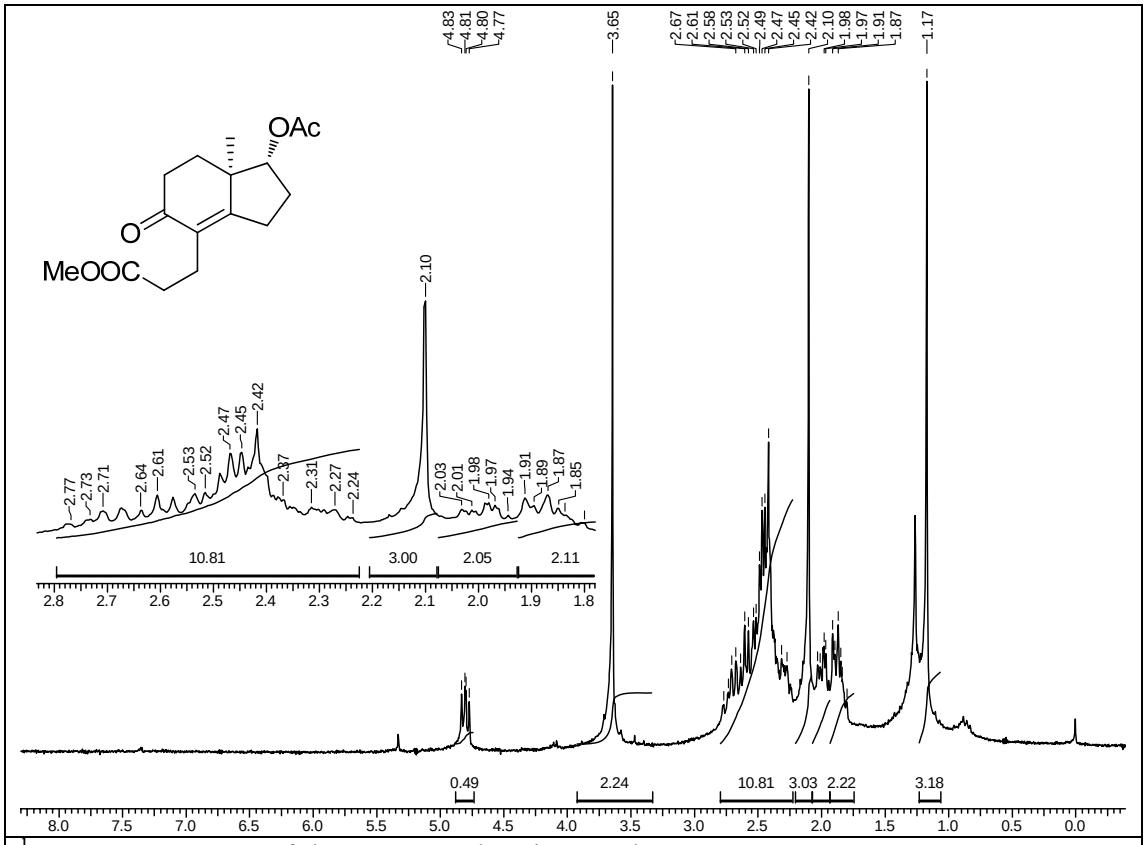
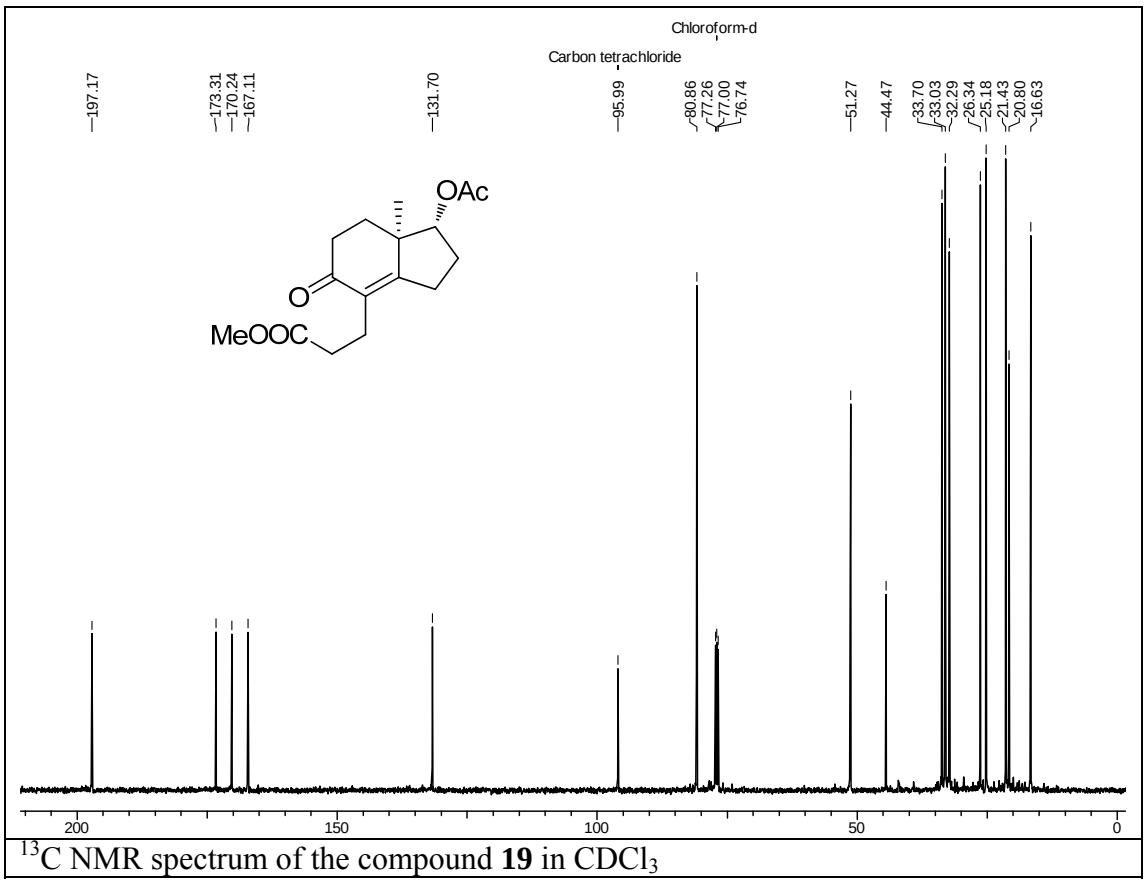
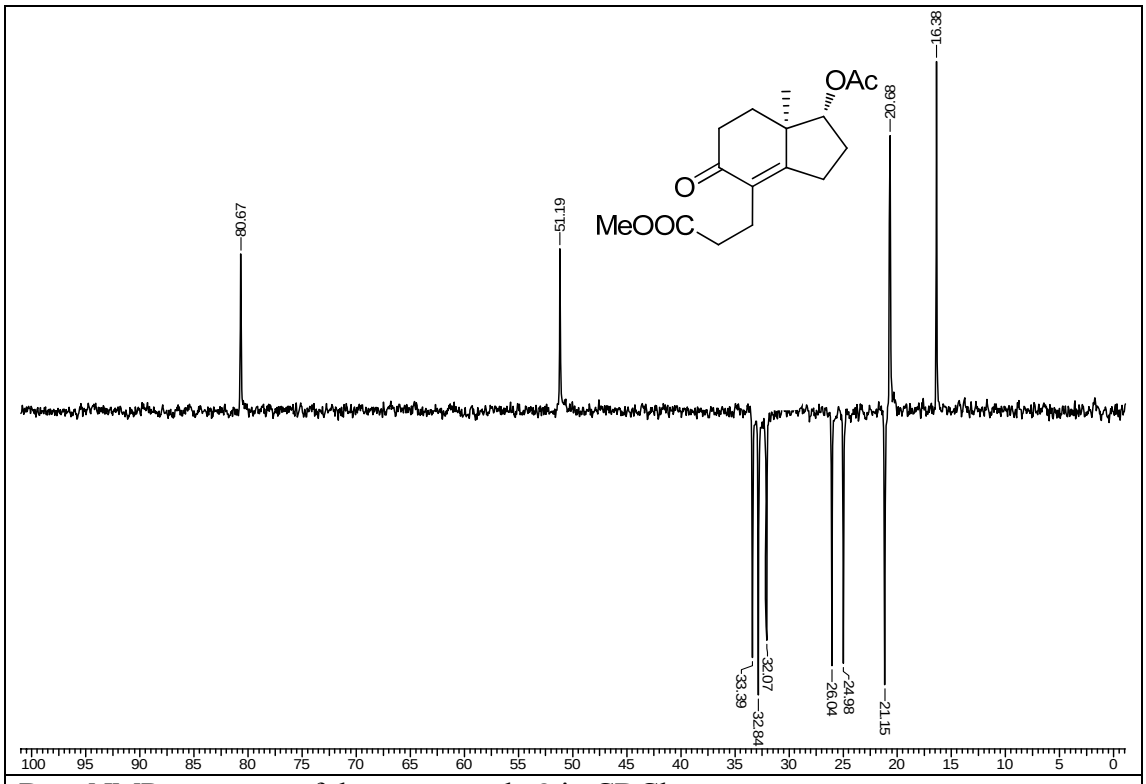


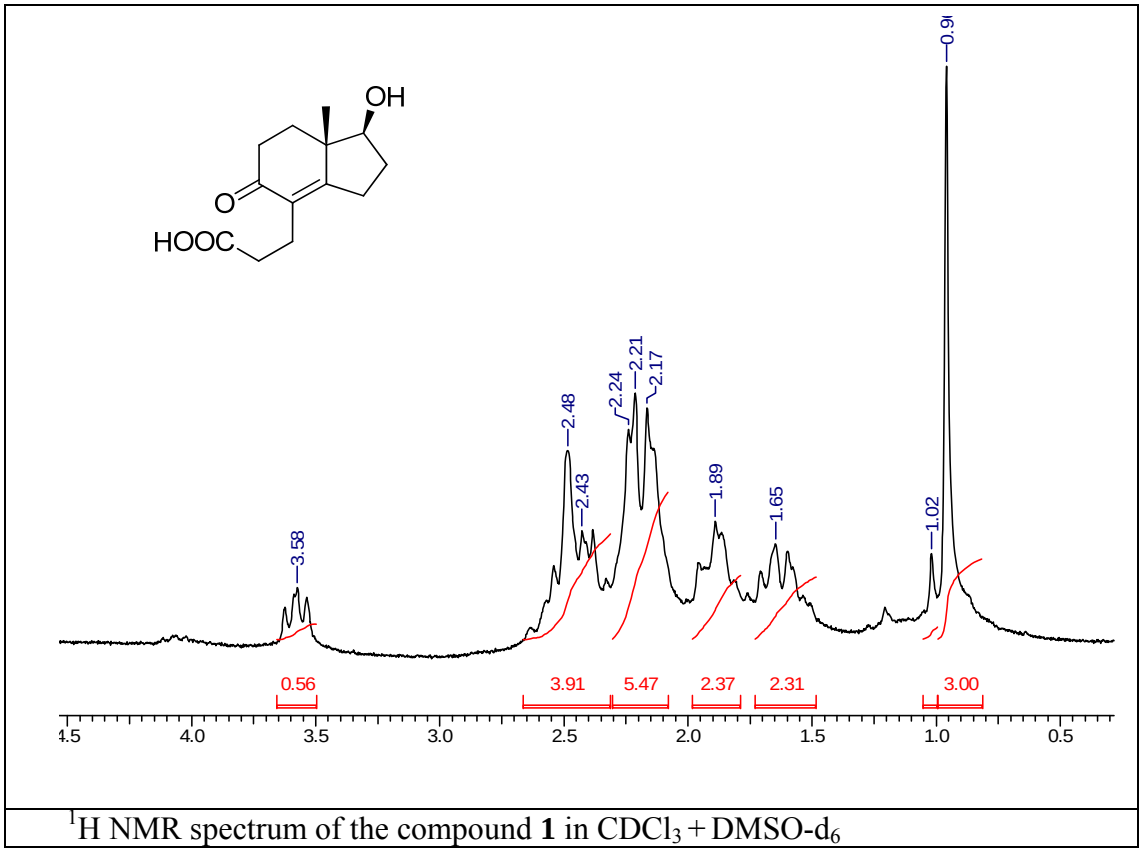
^{1}H NMR spectrum of the compound **19** in $CDCl_3$



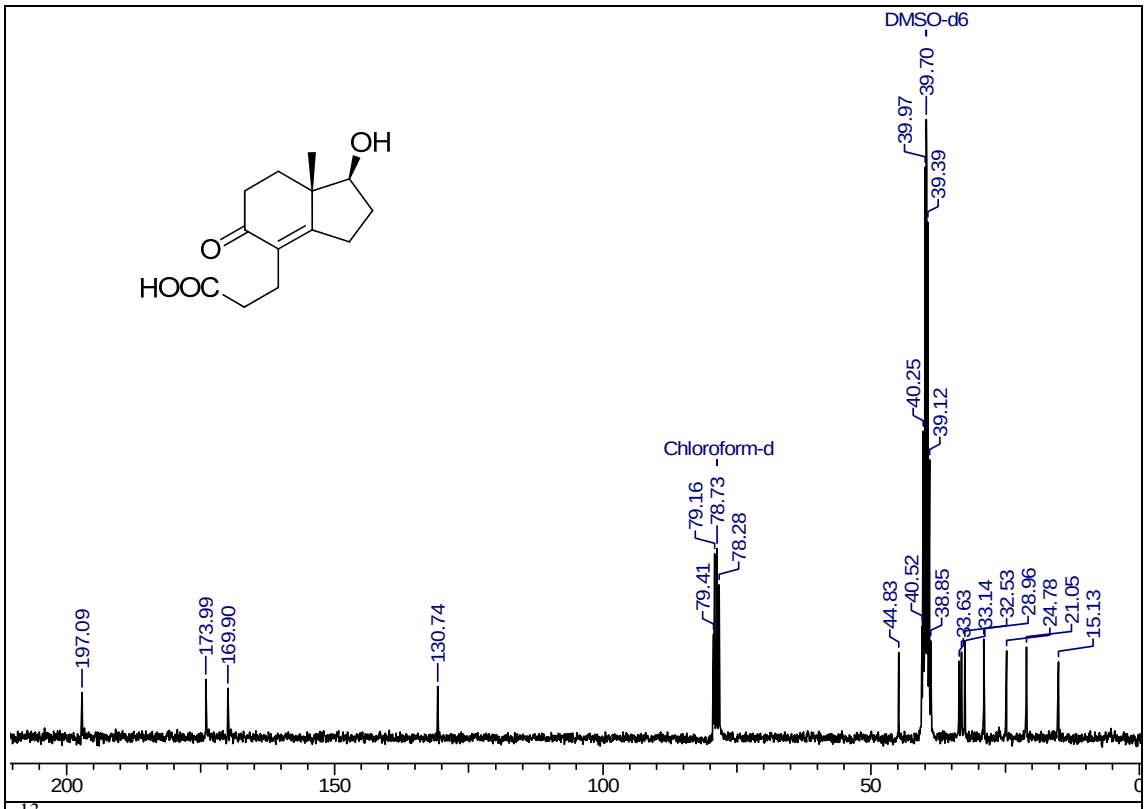
^{13}C NMR spectrum of the compound **19** in $CDCl_3$



Dept NMR spectrum of the compound **19** in $CDCl_3$

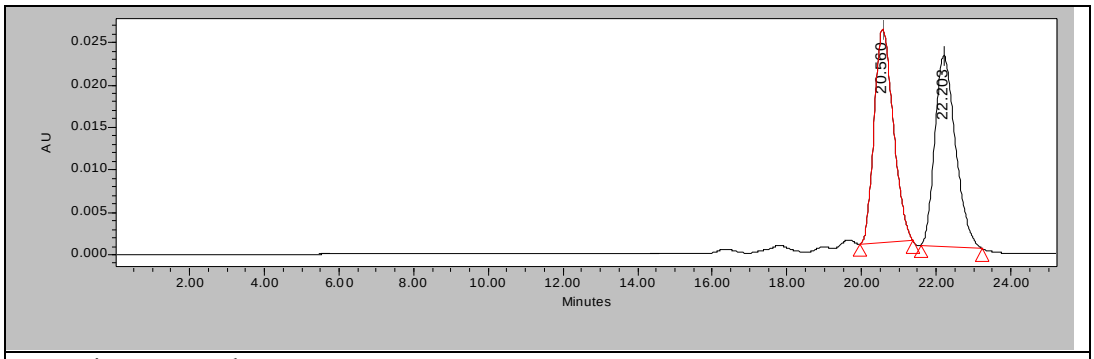


^{1}H NMR spectrum of the compound **1** in $CDCl_3$ + DMSO-d_6



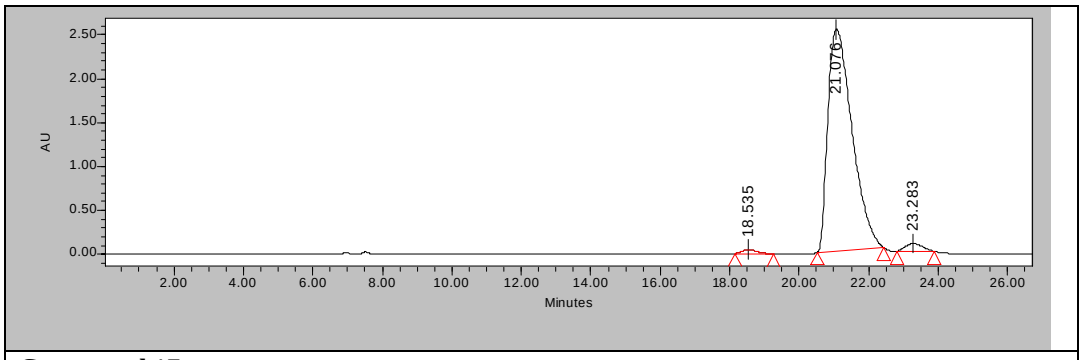
^{13}C NMR spectrum of the compound **1** in $CDCl_3$ + DMSO-d_6

Chiral HPLC Analysis of compound 14, 17 and 18:



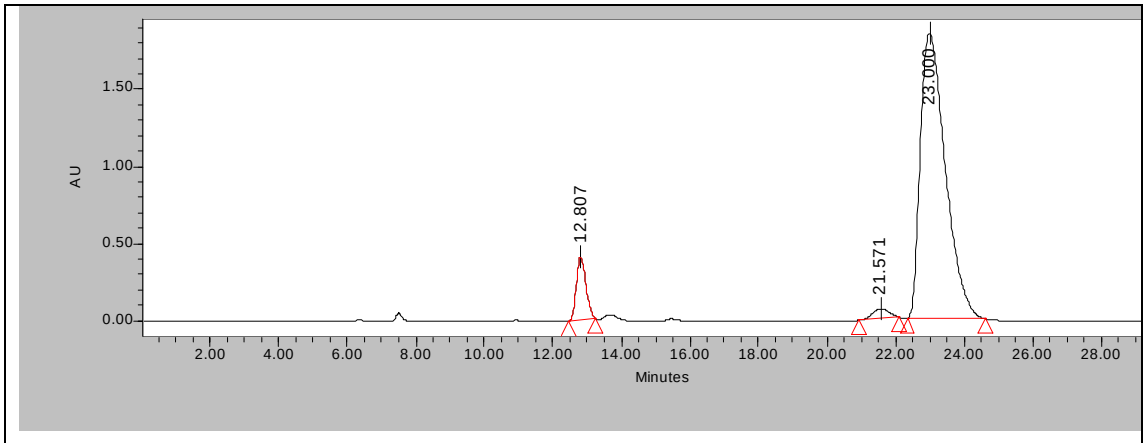
Racemic compound **14**

Pk #	Retention Time	Area	Area %	Height
1	20.560	893221	50.14	25066
2	22.203	888286	49.86	22572



Compound 17

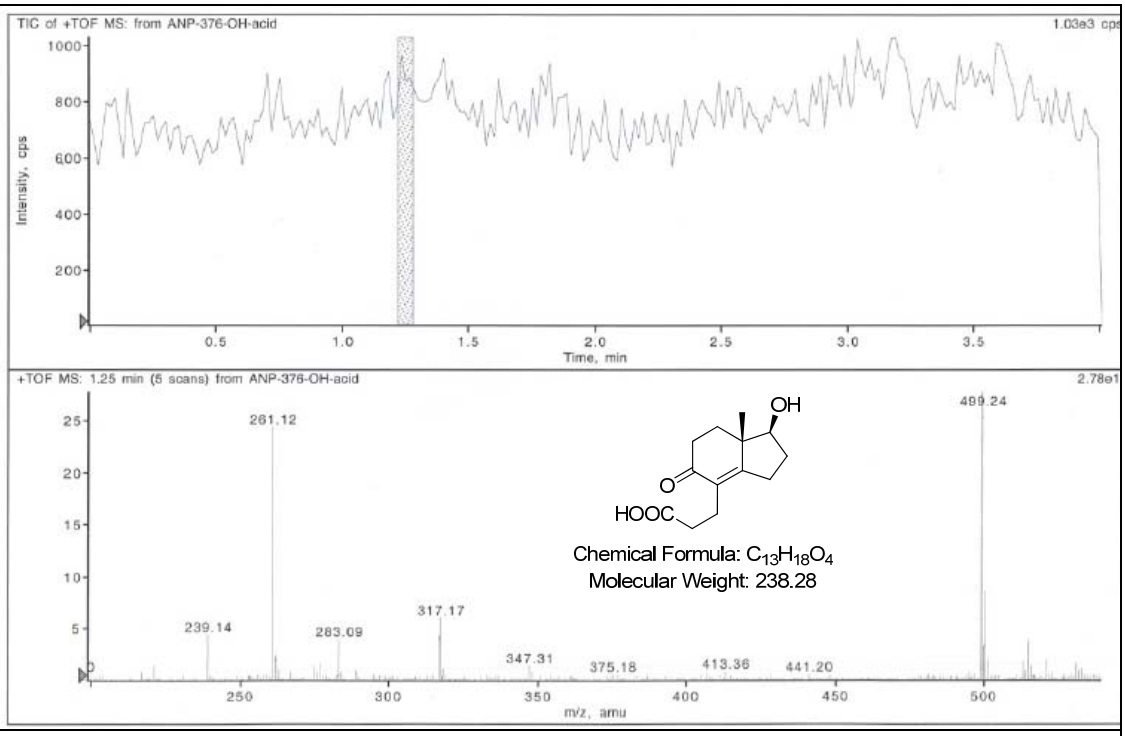
Pk #	Retention Time	Area	Area %	Height
1	18.535	1489691	1.18	48113
2	21.076	122214057	96.48	2524085
3	23.283	2973258	2.35	86789



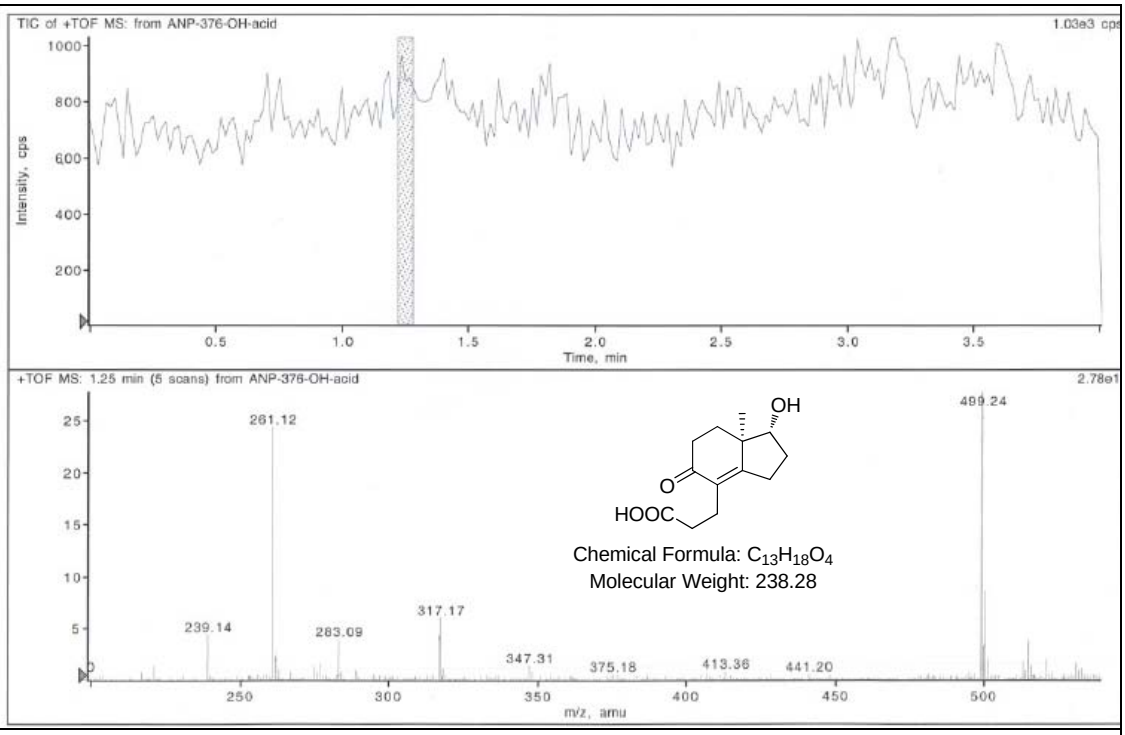
Compound 18

Pk #	Retention Time	Area	Area %	Height
1	12.807	7843784	7.57	406832
2	21.571	2122225	2.05	63707
3	23.000	93691376	90.39	1846626

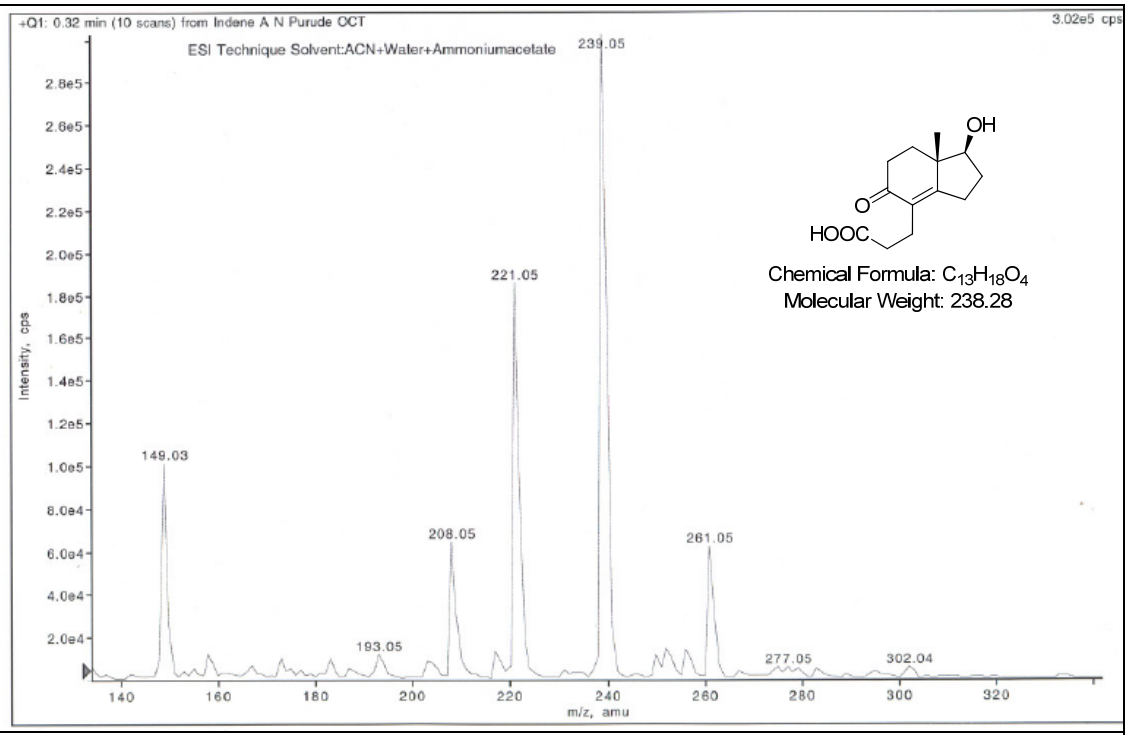
Column : Chiracel OD-H (250 x 4.6 mm)
Mobile phase : IPA + Hexane (5:95) Wavelenth : 254 nm
Flow : 1mL/min, Concentration : 1.00 mg/1.0 mL, mobile phase Injection vol.: 20 µL



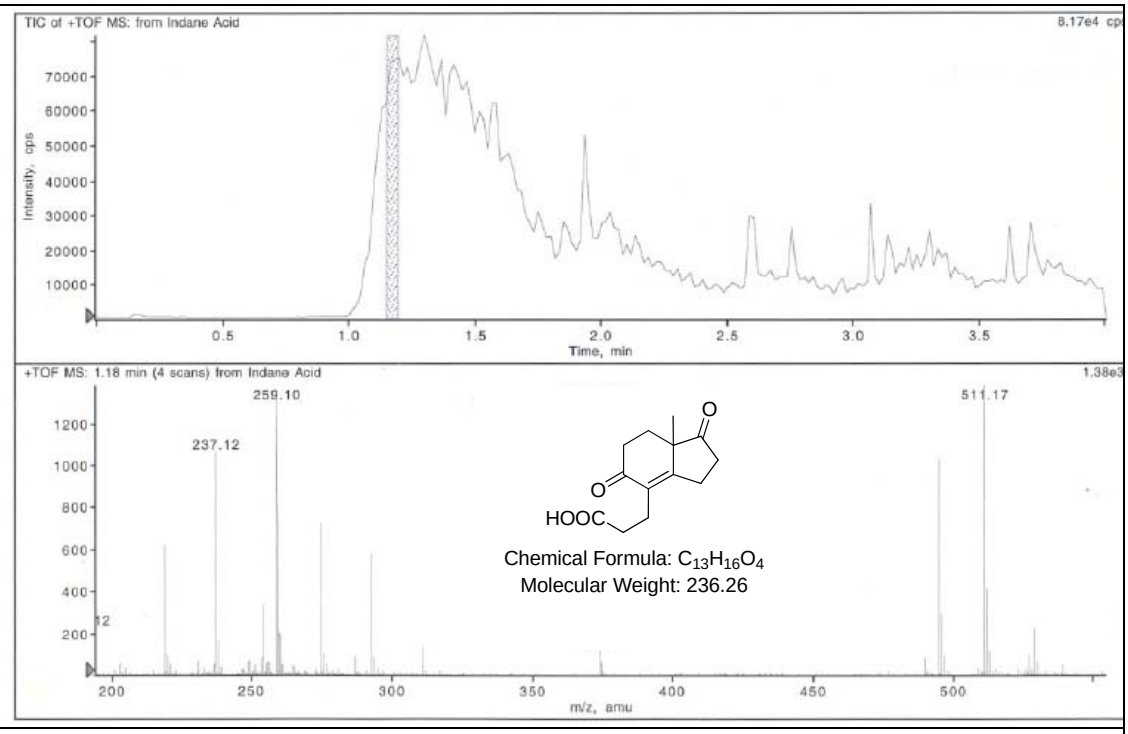
MS Chart of the compound 1 (M+ Na)



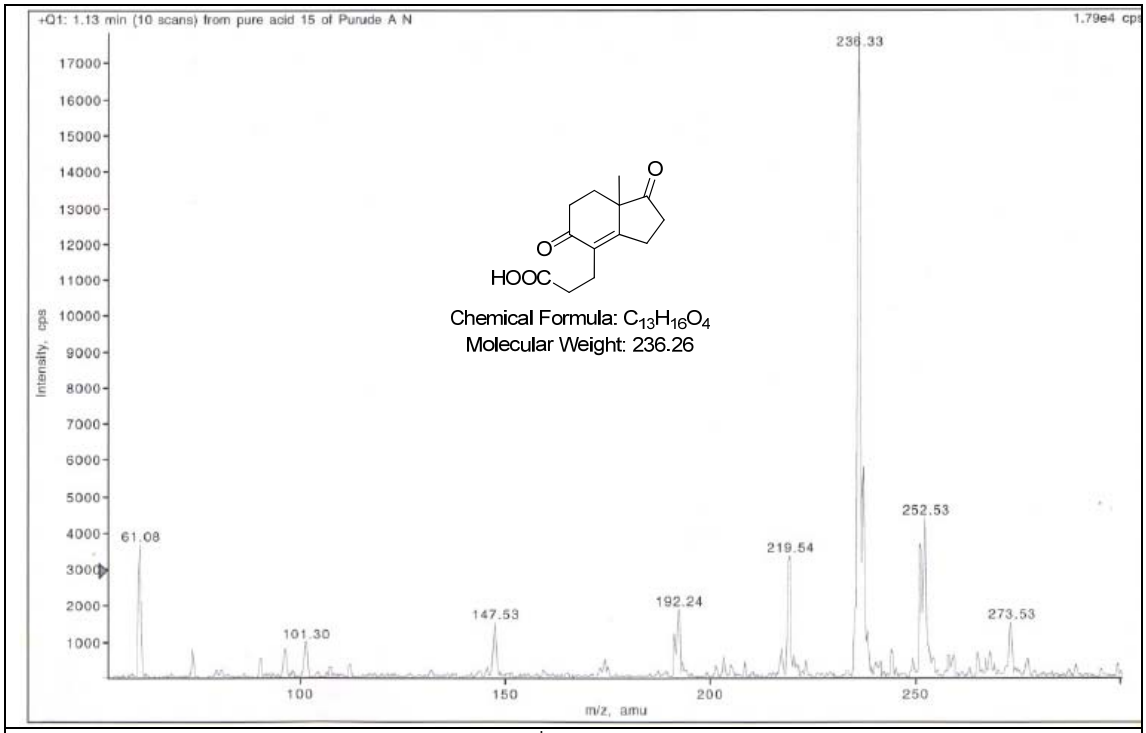
LCMS Chart of the compound 2 (M+ Na)



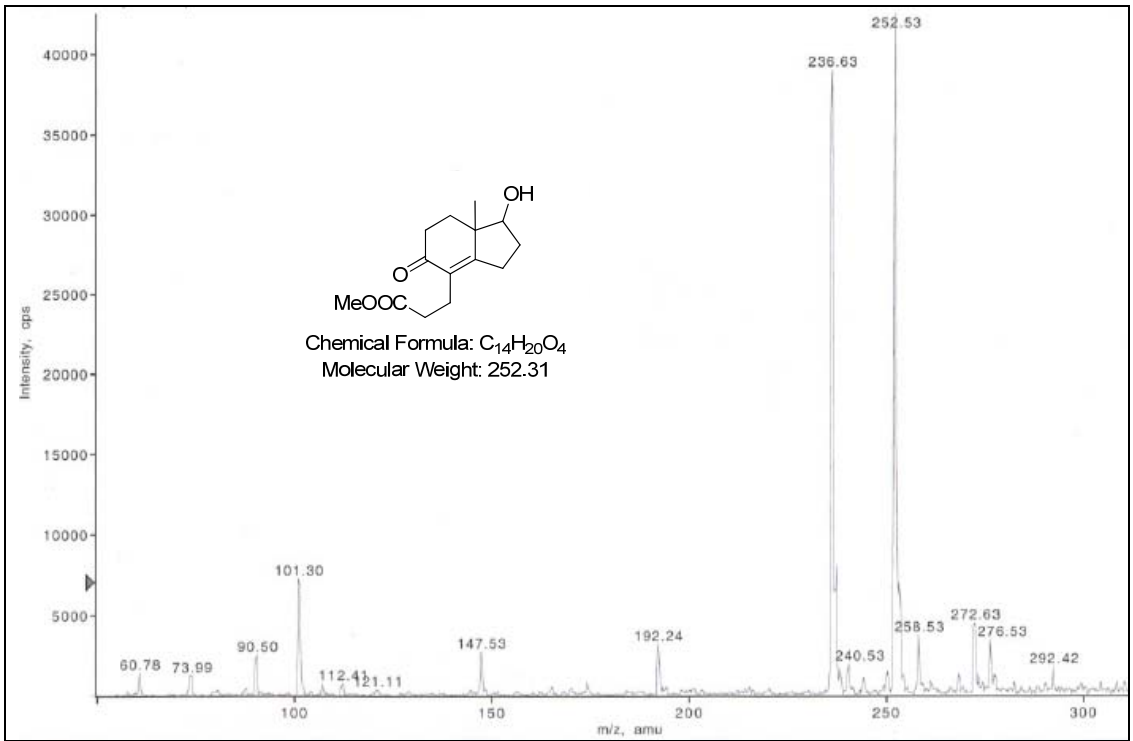
MS Chart of the compound 1 (M+1)



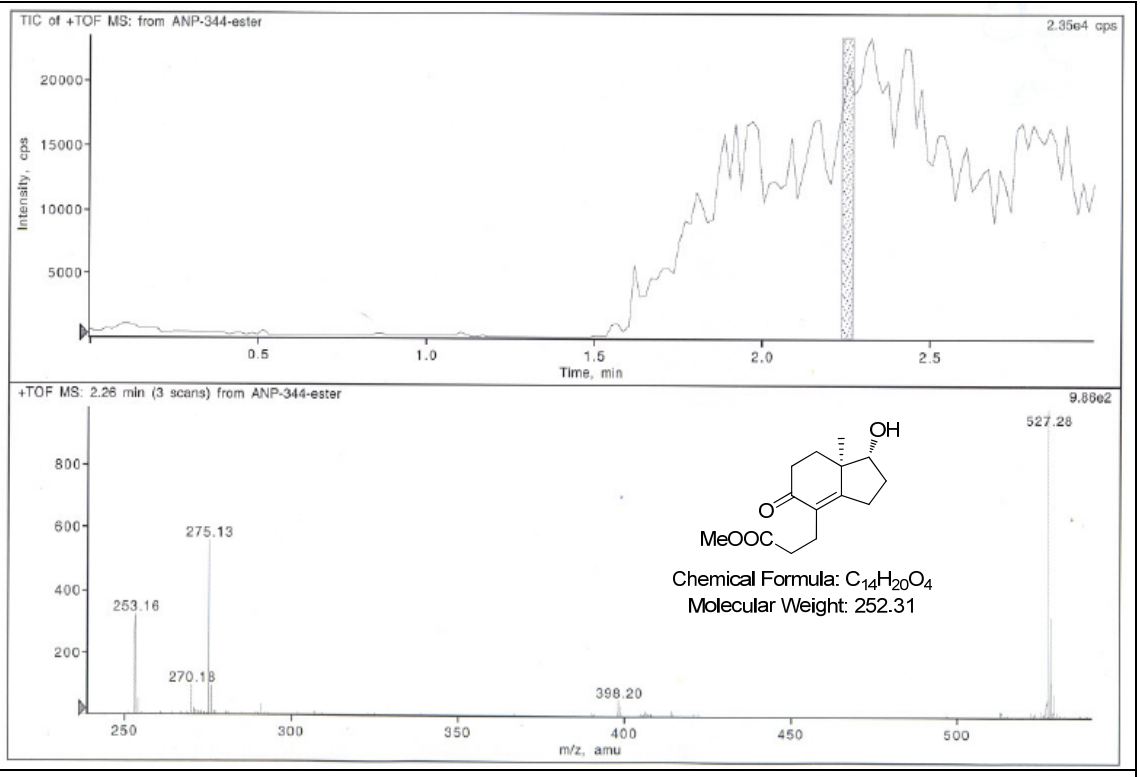
LCMS Chart of the compound 12 (M+1) and (M+H_2O)



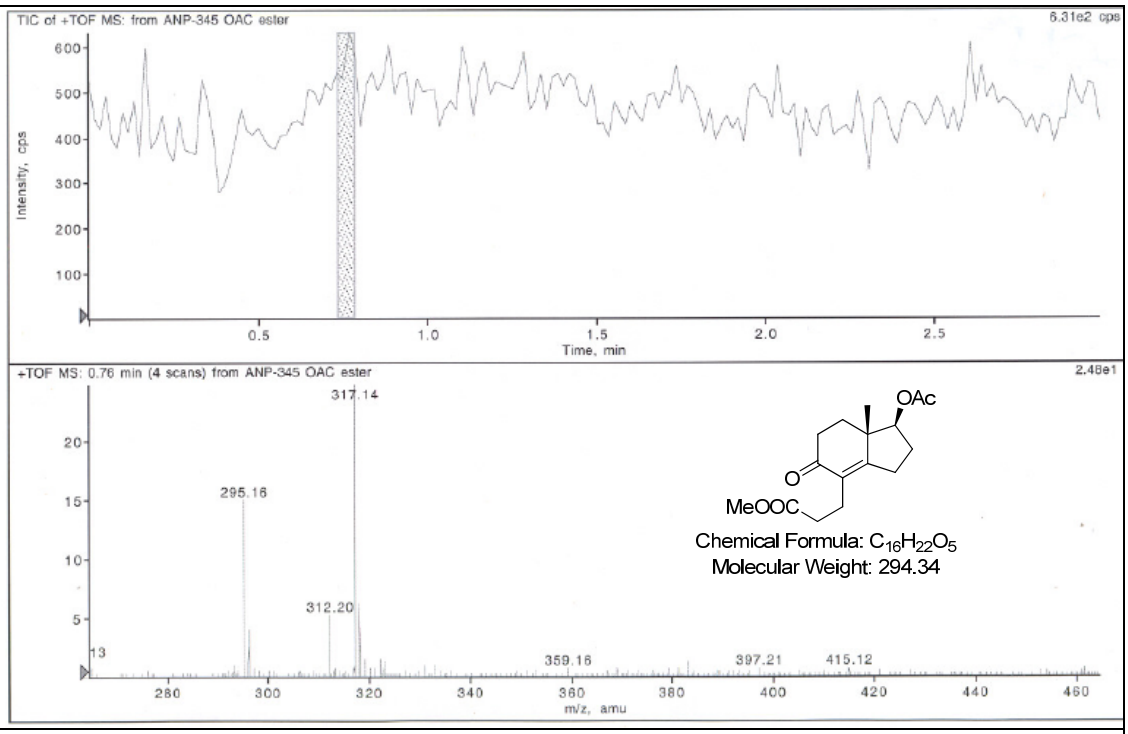
LCMS Chart of the compound 12 (M^+)



MS Chart of the compound 14 (M)



LCMS Chart of the compound 17 (M+1) and (M+Na)



LCMS Chart of the compound 16 (M+1) and (M+Na)

1.2.6. References

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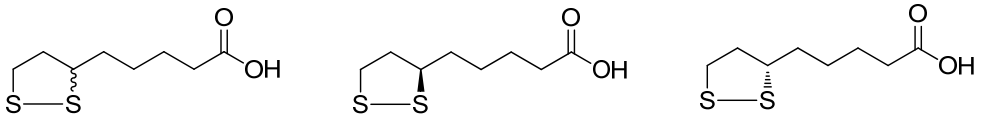
2.1.1 Introduction:

The synthesis of chiral molecules is of immense importance to the pharmaceutical industry. The main reason for this is that the biological properties of two enantiomers are in principle different. Given that one enantiomer may exhibit enhanced therapeutic properties over the other, and an understanding in vivo activity of both enantiomers is frequently a prerequisite for regulatory approval, the provision of a single enantiomer is often essential. Magnifying this fact we have decided to carry on synthesis of α-Lipoic-acid

α-Lipoic-acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues and in microorganisms.[1,2] It has been recognized as a vital cofactor for the multienzyme complexes which catalyze the oxidative decarboxylation of α-ketoacids such as pyruvate, α-ketoglutarate etc.[3] It is known to play a crucial role in photosynthesis and in tricarboxylic acid cycle.

Lipoic acid (**1**) was first isolated in 1951 by Reed and his co-workers [4] at the University of Texas in Austin. The first purified sample of lipoic acid was 30 mg of yellow crystals that were extracted from 100 kg of liver residue. The substance was known as α-lipoic acid (or) ALA. Some scientists believed the substance should be named thioctic acid because it contained two sulfur atoms (theion in Greek) and eight carbon atoms (octo in Greek). Ultimately, it was given the name lipoic acid because of its ability to dissolve in lipids. It is a molecule containing eight carbon atoms, one 1, 2-dithiolane ring and a carboxylic acid group. The chiral centre is embedded in the ring structure at the third position.

There are two forms of α-Lipoic-acid i.e., *R* and *S*: the natural isomer *R* is pharmacologically more active than that the *S*-isomer. Moreover, (±)-α-Lipoic acid can be important for pharmaceutical use without resolution, since the (*S*)-enantiomer does not negatively affect the activity of the (*R*)-enantiomer.



α- Lipoic acid (2) R- (+) -α- Lipoic acid (1) S- (-)- α- Lipoic acid (3)

Figure 1

α-Lipoic acid is not considered a vitamin because the humanbody can synthesize it in small amounts from essential fatty acids. α-Lipoic-acid is found in variety of foods, notably kidney, heart and liver meats as well as spinach, broccoli and potatoes. Lipoic acid works at the cellular level to help essential substances for metabolism to enter the mitochondria. Lipoic acid is an antioxidant. An increase in the amount of lipoic acid increases the amount of cellular fuel that is burned. This generates a greater energy reserve for the body that is available for growth, tissue repair and muscle development. Lipoic acid has been proposed as preventive against a variety of disease including aging, diabetes, cancer and cardiovascular disease.

α-Lipoic-acid does not accumulate in tissues and therefore does not have any toxicity in the amounts usually taken. Because it is distributed through the tissues, it is useful in a wide variety of conditions. It is particularly protective of the brain, which is the most sensitive of organs to free radical damage and the eye. However, animal experiments have shown that this protective effect is highly dependent upon the timing and the form of administration.

As part of the glycolytic pathway, α-Lipoic-acid stimulates insulin activity and reduces insulin resistance. It has been shown to enhance the burning of glucose. A-Lipoic-acid is a key part of the metabolic machinery that turns glucose (blood sugar) into energy for the body's need. One study of adult diabetic patients showed that α-Lipoic-acid increased the cellular uptake and oxidation of glucose by about 50%. This is important for athletes and for the overweight persons. The efficient burning of glucose is essential for the normal production of energy in the muscles, and impaired muscle metabolism have been found in the brain.

The reduction of α-Lipoic-acid (**1**) into dihydrolipoic acid (**4**) and the role of α-Lipoic-acid in the production of glutathione appear to be normal functions in the body. These functions are two of its several vitamins like physiologic functions. α-Lipoic- acid is unique in that, like vitamin C, it is effective as an antioxidant in water based tissues such as the blood, and yet as dihydro lipoic acid also is effective in protecting non-water based tissues like fatty tissues and membranes, a role it shares with vitamin E.

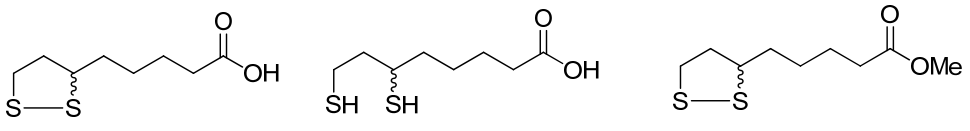


Figure 2

The α-Lipoic-acid and dihydrolipoic acid together function as a universal anti oxidants, i.e., quenches free radicals in both lipid and water-soluble positions of tissues and cells. α-Lipoic-acid and dihydrolipoic acids are extremely powerful quenchers of hydroxyl, singlet-oxygen, peroxy nitrite and other free radicals. We could also call α-Lipoic-acid a "broad spectrum" antioxidant because of its activity in aqueous and lipid phases.

Free radicals are associated with the development of artherosclerosis, lung disease and neurological disorders as well as being implicated in chronic inflammation, such as that found with rheumatoid arthritis and inflammatory bowel disease. Some and many other sources of environmental toxins either are themselves (or) lead to the creation of free radicals in the body.

A healthy body makes enough lipoic acid to supply its requirements; external sources are not necessary. However, several medical conditions appear to be accompanied by low level of lipoic acid injection, such as specific diabetes, liver cirrhosis and atherosclerosis.

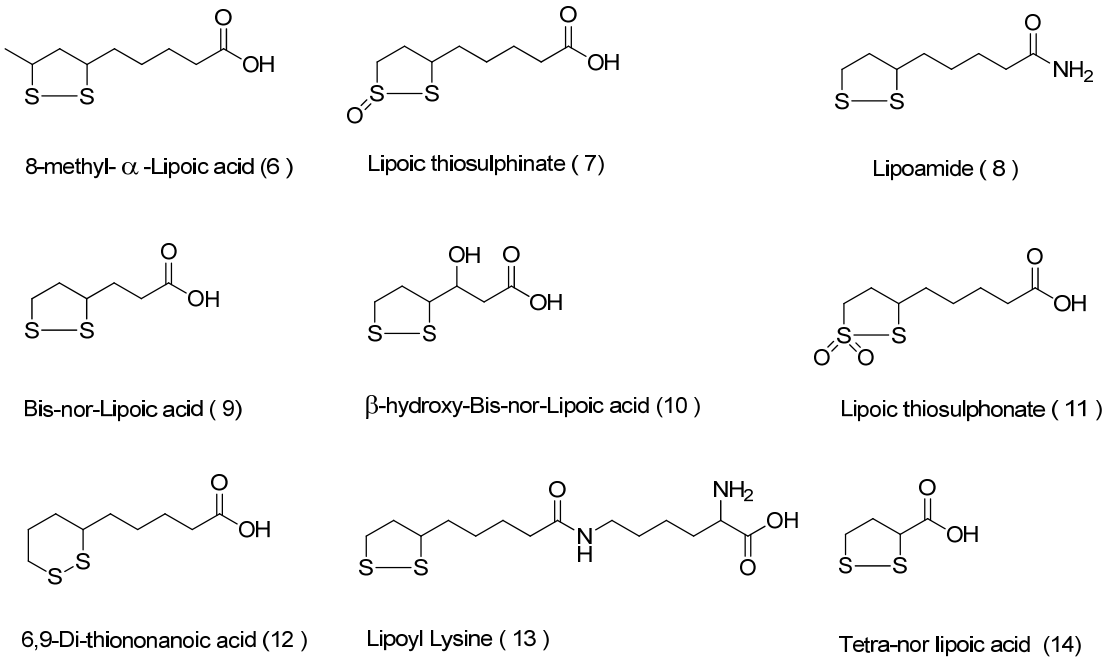


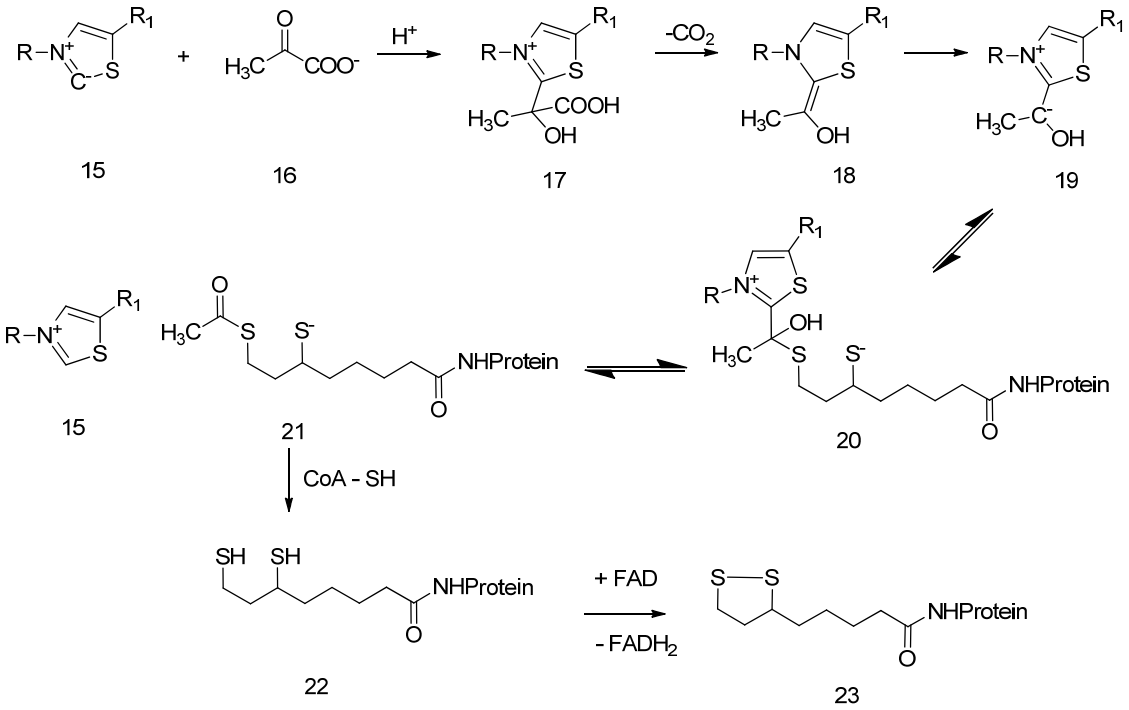
Figure 3 The structure of products related to α-Lipoic acid

As per the IUPAC nomenclature, α-Lipoic-acid is known as 1, 2-dithiolane-3-pentanoic acid. It has been known also known as 6, 8-thiooctic acid, 5-(1, 2-dithiolan-3-yl)-valeric acid (or) 5, 3-(1, 2-dithiolanyl)-pentatonic acid.

2.1.2 Biological Action of α-Lipoic Acid:

The complete oxidation of pyruvate during aerobic glycolysis takes place by tricarboxylic acid (TCA) cycle. Pyruvate undergoes oxidative decarboxylation before it enters TCA cycle.

The coenzymes required for the overall oxidative decarboxylation of pyruvate are thiamine pyrophosphate (TPP), nicotinamide adenine dinucleotide (NAD), α-lipoic acid, coenzyme A and flavin adenine dinucleotide (FAD). [5] The stages involved in this complex process are shown in scheme-1.



Scheme 1

Thiamine pyrophosphate interacts with lipoic acid to form an addition complex which subsequently gets cleaved to form acyl lipoic acid complex and TPP is regenerated. The acetyl group, now present as a thioester, is then transferred from acyl lipoic acid to coenzyme-A to form acyl-CoA by the acetyl-transfer enzyme system. Finally, the reduced lipoic acid moiety is reoxidised by the interaction with FAD and the cycle is completed. The acyl-CoA then enters the TCA cycle. FAD is regenerated by interaction with NAD+ in the electron transport system.

The hydrophobic interaction and the metal ion coordinating ability[6] of the molecule for the free passage of the compound in various tissues are the factors responsible for the high biological activity of α-Lipoic acid. α-Lipoic acid offers

metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards metal ions but a disulfide-metal ion interaction is still possible, and under stearically favoured conditions, may become very important. This could be true under enzymic conditions when the carbonyl group is no longer free but in the form of amide-linked to the protein. Further, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in the mixed ligand complexes due to the presence of valeric acid side chain.

2.1.3 Biological Importance of α-Lipoic acid:

- α-Lipoic acid functions as a universal antioxidant and free radical scavenger.[7]
- α-Lipoic acid is a co-enzyme associated with a-keto acid dehydrogenation. [8,9]
- Recycles both Fat and Water-soluble antioxidant vitamins.[10]
- Improves sugar metabolism and energy production. (i. e. controls diabetes).[11]
- α-Lipoic acid has been used as a therapeutic agent in a number of conditions related to liver.[12]
- α-Lipoic acid appears to have the potential to slow the process of aging.[13]
- α-Lipoic acid significantly reduces inflammation and it also acts as an antitumour agent.[14]
- α-Lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication.[15]
- α-Lipoic acid has been found beneficial against radiation injury, smoking, heavy metal poisoning and chagas disease.[16]
- α-Lipoic acid and/or products related to α-lipoic acid are used in dyes, pints, pigments and pestisides.

Apart from the pharmacological importance, α-Lipoic-acid also finds its use in cosmetic preparations. α-Lipoic acid and its derivatives are used in skin lotions, ointments and creams as skin-whitening cosmetics.[17].

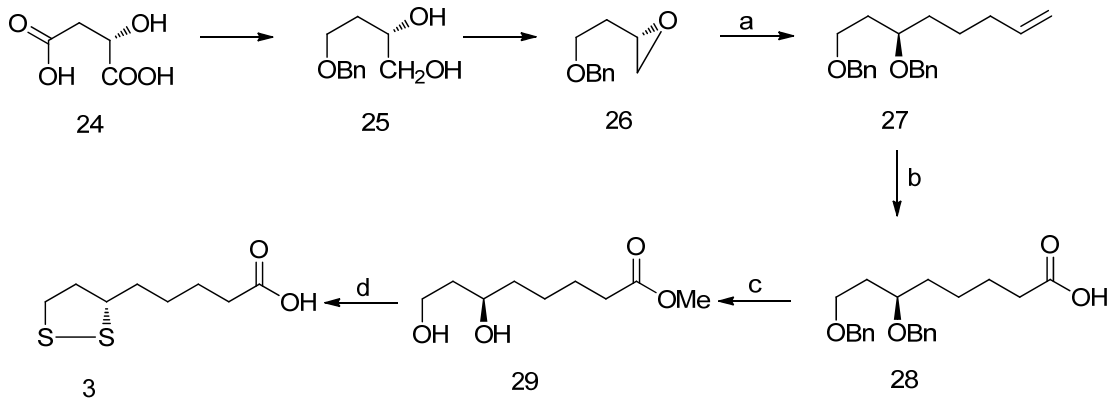
Finally, it is truly amazing how a relatively small and simple molecule like lipoic acid could have such a profound effect on so many diverse systems and functions in our body. It is thus becomes readily apparent that maintaining adequate α-Lipoic-acid status in our body is crucial for our long-term health and well being

2.1.4 Literature reviw of α-lipoic acid:

The chemical structure of α-Lipoic-acid was determined in the early 1950's and its absolute configuration was confirmed to be *R* in 1983, when Golding synthesized the complementary enantiomer from *S*-malic acid. It clearly indicates that scientists considered α-Lipoic-acid as small molecule and after knowing the pharmaceutical importance the scientific community was attracted by its synthesis as a result a number of synthses over (dl)-α-Lipoic acid and optically active R(+)-α-Lipoic acid have been documented in the literature.[18]

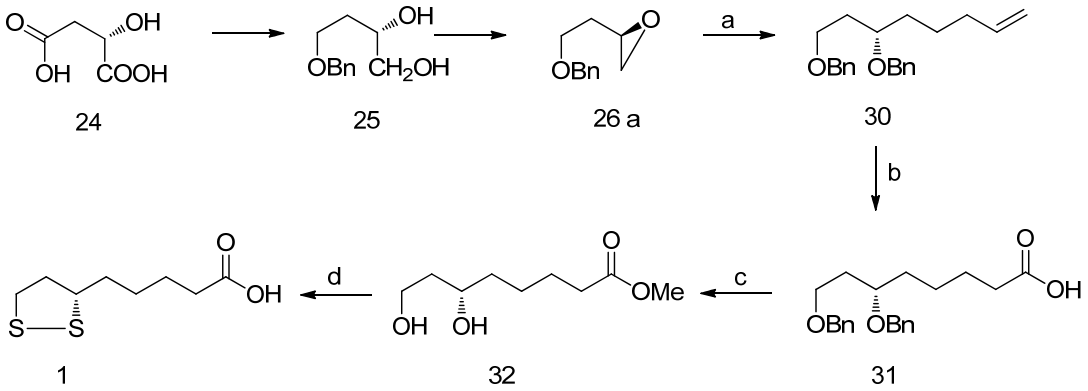
2.1.4.1 Golding *et al* [18, 19]

Golding and co-workers have utilized epoxide **26** as the chiral precursor, which was prepared by known procedure from (*S)* - malic acid **24**. Opening of epoxide with but-3-enyl magnesium chloride catalysed by lithium chloro cuprate furnished the compound **27**. The primary hydroxyl group was protected by benzylation, followed by hydroboration and oxidation to give the acid **28**. Esterification of acid **28** and deprotection of benzyl ether gave diol ester **29**, which was mesylated and converted to methyl lipoate by treatment with sulphur and Na_2S, in DMF and final hydrolysis of ester furnished the (*S*)-α-Lipoic aicd **3.**



Scheme 2. *Reagents and conditions:* (a) (i) CH_2=$CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; (ii) $PhCH_2Br$, NaH, THF; b) (i) $HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (c) (i) MeOH-HCl; (ii) Pd/C, H_2; (d) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH

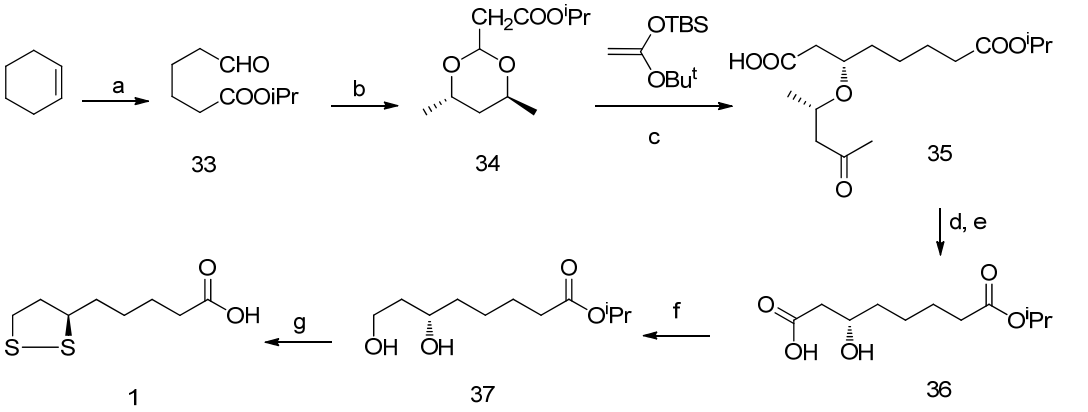
In another approach Golding and Brookes synthesized enantiomer of epoxide **26** for the synthesis of (*R)*- Lipoic acid. They used the same starting material i.e., (*S)*-malic acid **24** but inverted the configuration of hydroxyl group to prepare the epoxide **26a**. Epoxide **26a** was converted in to (R)-Lipoic acid **1** following the same sequence of reactions used in the earlier approach.



Scheme 3. *Reagents and conditions:* (a) (i) AcOK, Ac_2O; (ii) $MeSO_2Cl$, Et_3N; (iii) K_2CO_3, MeOH; (b) (i) CH_2=$CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; (ii) $PhCH_2Br$, NaH, THF; (c) (i) $HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (d) (i) MeOH-HCl; (ii) Pd/C, H_2; (e) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH.

2.1.4.2 Elliott *et al* [20]

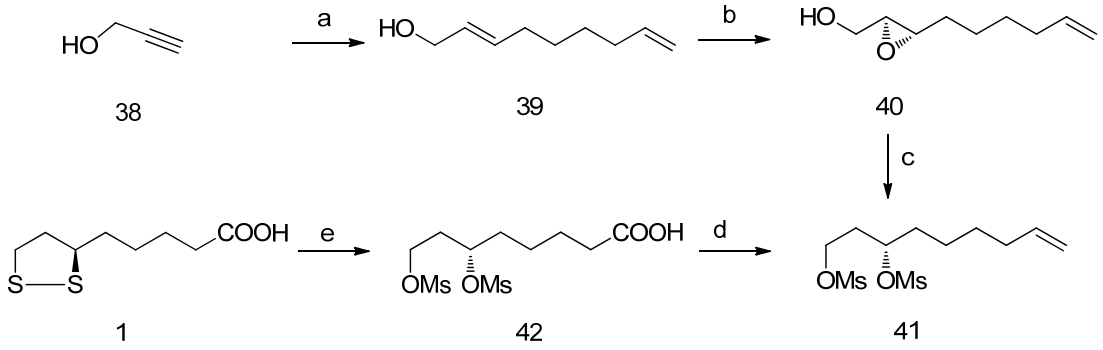
Elliott and co-workers have reported the synthesis of *R*-(+)-lipoic acid using highly diastereoselective $TiCl_4$ catalyzed aldol-type coupling of chiral acetal **34** with 1-*t*-butyldimethyl silyloxy ethane. The coupling product on hydrolysis followed by oxidation with Jones reagent gave acid **35**. Removal of the chiral auxiliary by β-elimination followed by hydroboration delivered the diol ester **37**. The diol ester **37** was converted to *R*-(+)-lipoic acid **1** by using Golding's Procedure.



Scheme 4. *Reagents and conditions:* (a) O_3, $^{i}PrOH$, -78 ^{o}C, Ac_2O, Et_3N; (b) (2*S*, 4*S*)-pentane-2, 4-diol, *p*-TSA, Benzene; (c) (i) $TiCl_4$, CH_2Cl_2, -78 ^{o}C; (ii) TFA, H_2O; (d) Piperidinium acetate, benzene, reflux, 97 %; (e) Jones oxidation; (f) BH_3.THF, 4 M aq. KOH, 82 %.; (g) (i) $MeSO_2Cl$, TEA, (ii) Na_2S, S, DMF, 60^{o}C, (iii) aq NaOH

2.1.4.3 Sutherland *et al*[21]

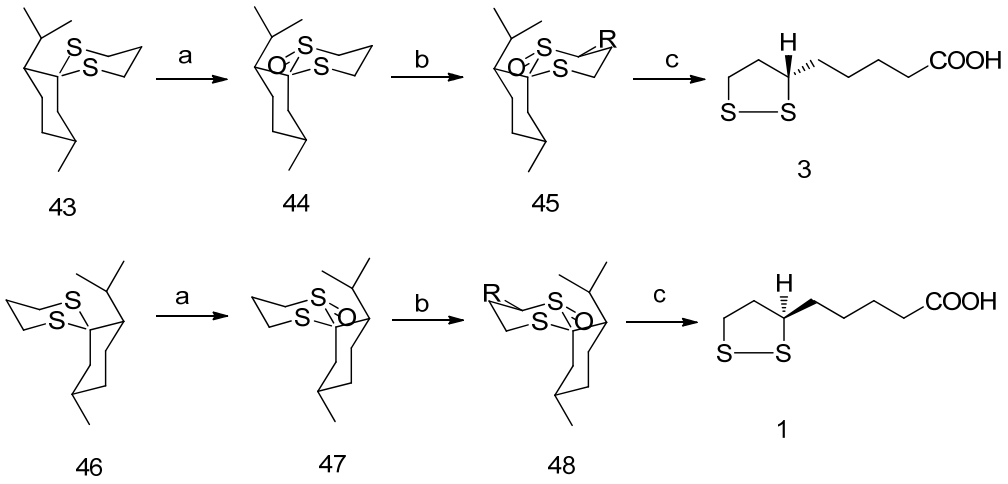
Sutherland and co-workers employed the alkylation of lithio dianion of propargyl alcohol **38** in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction to deliver the allyl alcohol **39**. Sharpless asymmetric epoxidation of allyl alcohol **39** gave the (2*S*, 3*S*)-epoxy alcohol **40**. Reduction of **40** with Red-Al and mesylation of the diol to give the dimesylate **41**. Ruthenium tetroxide oxidation of the terminal double bond gave acid **42** which is converted into *R*-(+)-Lipoic acid **1** by known sequence of reactions.



Scheme 5. *Reagents and conditions:* (a) Na, liq. NH_3, $Br(CH_2)_4CH{=}CH_2$; (b) L- (+)-diisopropyl tartarate, $Ti(OPr^{i})_4$, TBHP, CH_2Cl_2, -20 ^{o}C; (c) (i) Red-Al, THF; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (d) RuO_4; (e) (i) Na_2S, S, DMF, (ii) 4 M aq. KOH.

2.1.4.4 Ravindranathan *et al* [22]

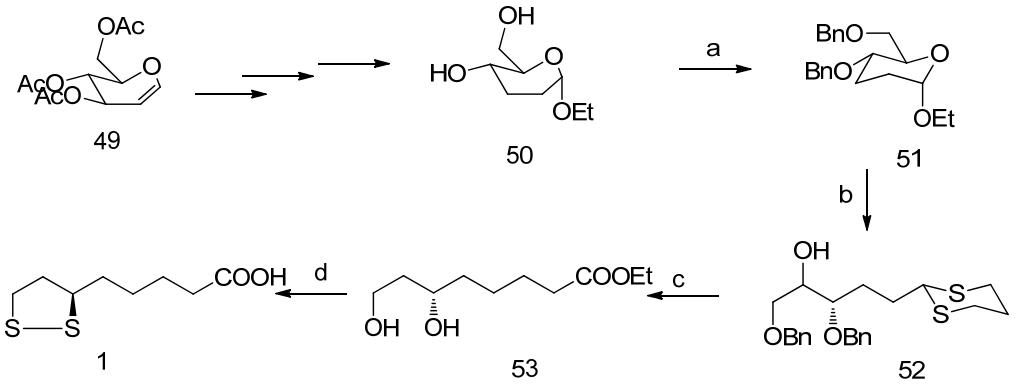
Ravindranathan's approach involves the formation of 1, 3-dithiane **43** from 1, 3-propane dithiol and L-menthone. Regioselective oxidation of dithiane **43** afforded sulfoxide **44**. Stereo selective alkylation of **44** to give **45** followed by hydrolytic cyclization afforded *R*-(+)-lipoic acid **1**. In the similar manner *S*-(-)-Lipoic acid prepared by using D-menthone. In their approach they recovered the starting L-menthone in almost quantitative yield. This is the shortest and probably the best synthesis for both the enantiomers of lipoic acid.



Scheme 6. *Reagents and conditions:* (a) $NaIO_4$, MeOH, 0 ^oC; (b) LDA, TMEDA, THF, Br-$(CH_2)_4CO_2Li$, -78 ^oC; (c) aq. HCl, benzene.

2.1.4.5 Rama Rao *et al* [23]

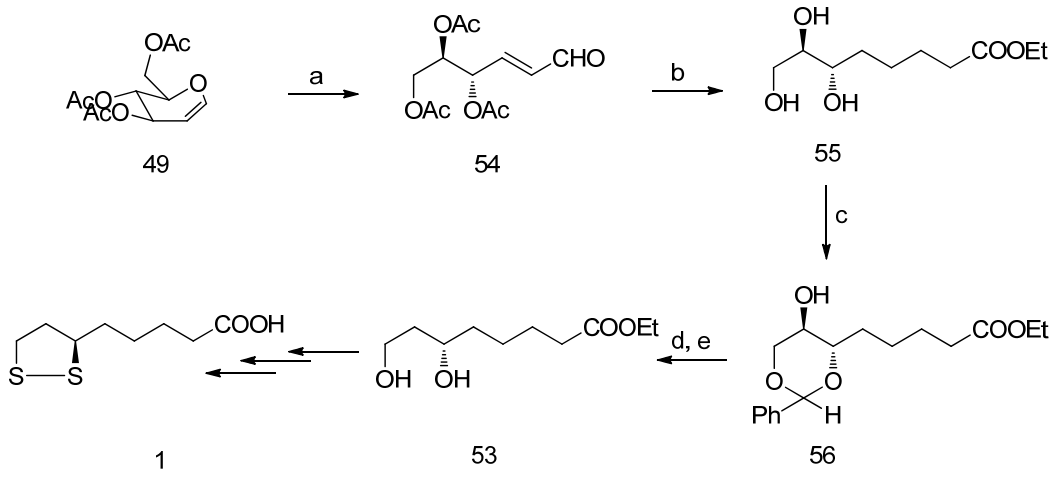
Rama Rao and co-workers have reported four different routes for the synthesis of lipoic acid. Rama Rao's first synthesized from D-glucose, which was converted to 4, 6-di-o-benzyl derivative **51** through 3, 4, 6-tri-o-acetyl-D-glucal **49** by known procedure. Treatment of **51** with propane dithiol followed by xanthate formation and tri-n-butyl tin hydride mediated reductive removal afforded dithiane derivative **52**. Sequential dithiane deprotection, two-carbon Wittig olefination, hydrogenation using Raney nickel delivered the diol **53**. The diol **53** was converted to *R*-(+)-lipoic acid **1** by the known procedure.



Scheme 7. *Reagents and conditions:* (a) NaH, BnBr; (b) (i) 1, 3-propane dithiol, $BF_3.Et_2O$, CH_2Cl_2; (ii) NaH, CS_2, MeI; (iii) n-Bu_3SnH, AIBN; (b) (i) HgO, $BF_3.OEt_2$;

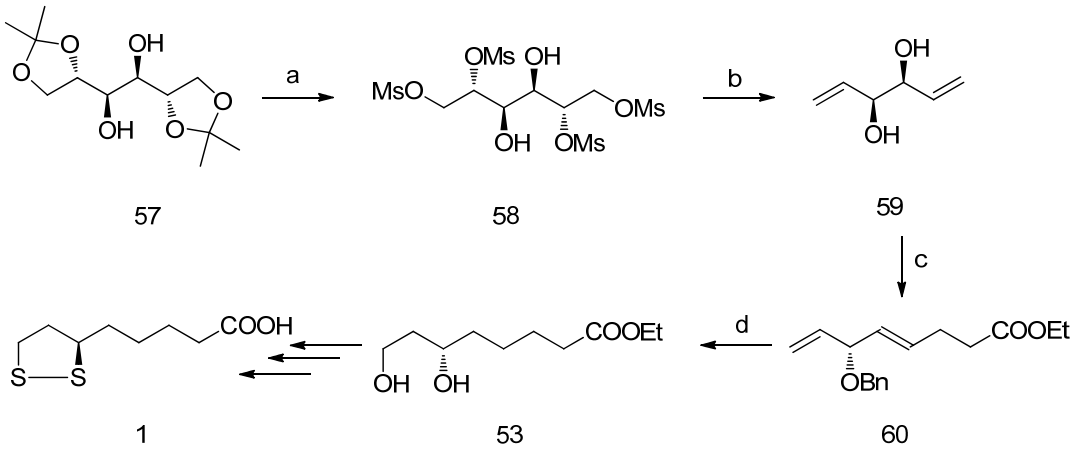
(ii) Ph_3P=CHCOOEt (c) H_2, Raney Ni.; (d) (i) $MeSO_2Cl$, TEA, (ii) Na_2S, S, DMF, 60^oC, (iii) aq NaOH

In Rama Rao's second approach: tri-o-acetyl-D-glucal **49** was converted to unsaturated aldehyde **54** using mercurous ion catalyzed ring opening. Sequential hydroxyl group protection, two carbon Wittig homologation and hydrogenation gave the tri-acetate **54**. Deacetylation and protection of 6, 8-hydroxyl groups with benzaldehyde dimethyl acetal gave the benzylidene protected compound **56**. Deoxygenation of the free hydroxyl group followed by removal of benzylidene protection gave the diol **53**, which was converted to *R*-(+)-Lipoic acid **1** (Scheme-8).



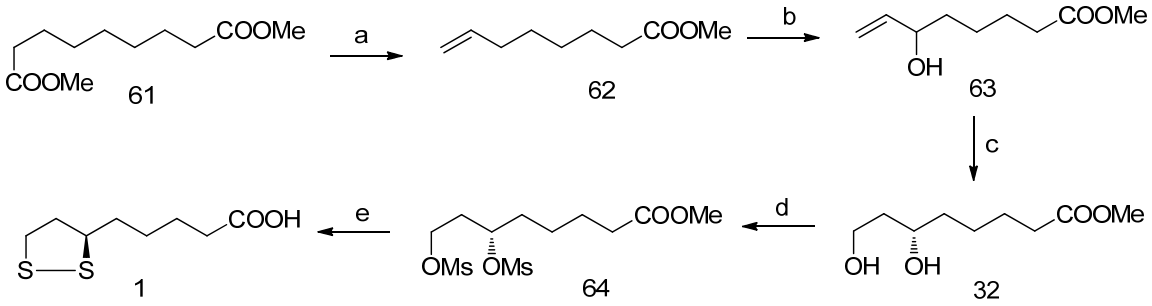
Scheme 8. *Reagents and conditions:* (a) (i) $HgSO_4$, H^+ Dioxane; (ii) Ac_2O, Pyridine; (b) (i) Ph_3P=CHCOOEt; (ii) H_2, Raney Ni; (iii) NaOEt, EtOH; (c) $PhCH(OMe)_2$, H^+; (d) (i) Thiocarbonyl diimidazole, THF; (ii) n-Bu_3SnH, AIBN; (e) H_2, Pd/C.

Third approach involves the utilization of mannitol diacetonide **57** as a chiral precursor. Benzoyl protection of the free hydroxyl groups followed by isopropylidene deprotection and mesylation gave the tetra mesylate **58**. Treatment of **58** with sodium Iodide and Zinc dust followed by debenzoylation gave (3*R*, 4*R*)-1, 2-divinyl glycol **59**. Selective protection of hydroxyl group and claisen-ester rearrangement of the resultant monoprotected benzyl ether delivered the compound **60**. Sequential hydroboration, oxidation and reduction of the double bond gave the known diol **53** which was converted in to *R*-(+)-lipoic acid **1** (Scheme 9).



Scheme 9. *Reagents and conditions:* (a) (i) PhCOCl, Pyridine; (ii) 50 % aq. AcOH (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (b) (i) NaI, Zn, DMF, Reflux; (ii) NaOMe; (c) (i) Bu_2SnO, Toluene, Reflux; (ii) 1.2 eq $PhCH_2Br$, DMF, 100^oC; (iii) $CH_3CH(OEt)_3$, Propionic acid (cat), 145^oC; (d) (i) 9-BBN, OH^- / H_2O_2; (ii) H_2, Pd/C.

Fourth approach, Rama Rao employed highly regioselective Sharpless allylic oxidation of the olefin **62** with TBHP and SeO_2 to deliver the compound **63** Hydroboration, oxidation of olefinic compound **63** delivered the known diol **64** which by a series of known reactions converted to (*R*)- α -lipoic acid **1** (Scheme-10).

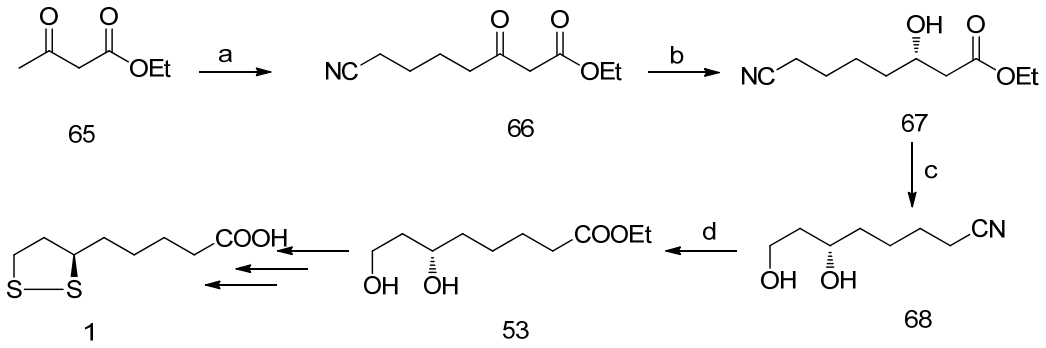


Scheme 10. *Reagents and conditions:* (a) $Pb(OAc)_4$, $CuSO_4$, Benzene; (b) TBHP, SeO_2, CH_2Cl_2; (c) B_2H_6-THF, NaOOH., (d) TEA, MsCl, DCM (e) Na_2S, S, DMF, Heat 60^{o}c

2.1.4.6 Gopalan and Jacobs [24]

Gopalan and Jacobs have utilized highly enantio-selective yeast reduction of α-keto ester **66** as the key step to deliver the compound **67**. Reduction of ester **67** with $LiBH_4$ in THF at room temperature gave the diol **68**. The diol **68** was converted in to

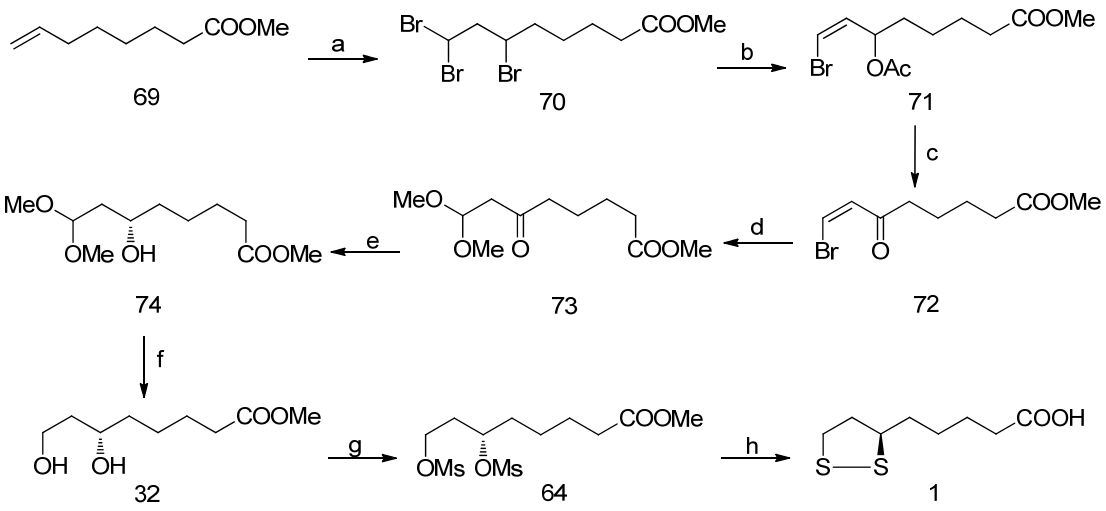
diol ester **53** by using ethanol in presence of acid. Diol ester **53** was converted to *R*-(+)-lipoic acid by a series of known reactions.



Scheme 11. *Reagents and conditions:* (a) (i) NaH, THF, HMPA, 0 ^{o}C; (ii) ^{n}BuLi, $I(CH_2)_3CN$; (b) Baker's Yeast (c) $LiBH_4$, THF, 0 ^{o}C; (d) EtOH, H^+, Reflux.

2.1.4.7 Bhalerao *et al* [25]

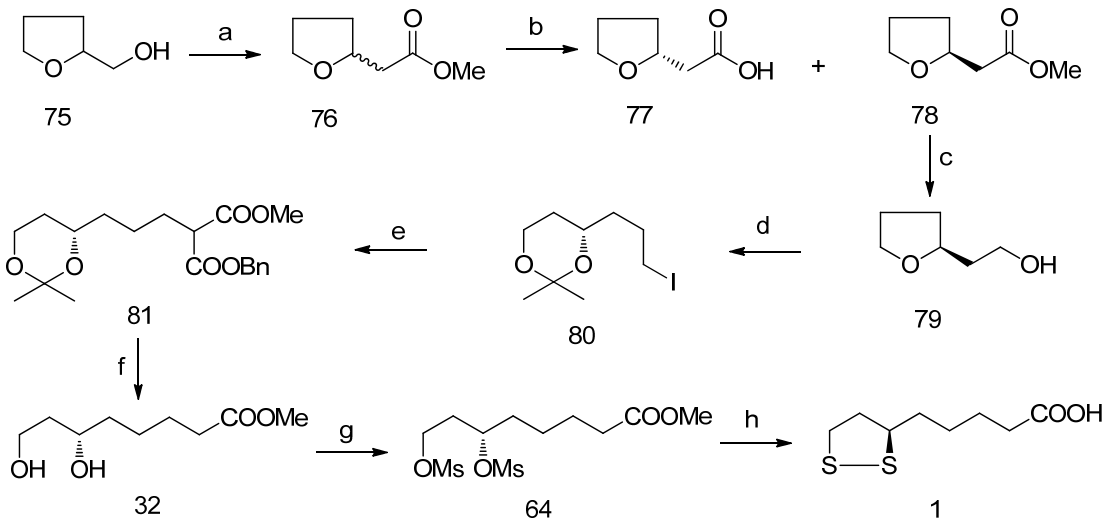
Bhalerao and co-workers have used copper catalyzed bromoform addition to alkene **69** to give methyl-6, 8, 8-tribromooctonoate **70**, which on treatment with potassium acetate and 18-crown-6 in DMF gave compound **71**. Hydrolysis, Oxidation and followed by treatment with triton-B gave the keto acetal **72**. The keto acetal **72** was reduced enantioselectively by baker's yeast to give compound **73**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **32**. The diol was converted to *R*-(+)-lipoic acid **1** in a similar fashion reported earlier.



Scheme 12. *Reagents and conditions:* (a) Cu, $CHBr_3$, 80 %; (b) AcOK, 18-crown-6, DMF; (c) K_2CO_3, MeOH then PCC, 68 %; (d) Triton B, MeOH; (e) Baker's Yeast, pH 4.5-5; (f) (i) H_3PO_4, Acetone; (ii) $NaBH_4$, MeOH; (g) $MeSO_2Cl$, TEA, (h) (i) Na_2S, S, DMF, 60^oC, (iii) aq NaOH

2.1.4.8 Iyengar's approach[26]

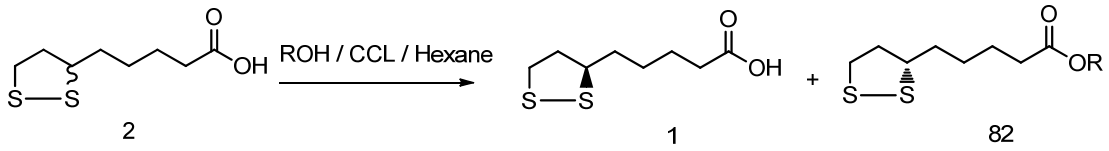
Iyengar and Laxmi have employed selective lipase hydrolysis of methyl 2-(tetrahydro-2- furyl) acetate **75** during which *R*-isomer undergoes hydrolysis but *S*-isomer remains intact. *S*-ester **78** was then reduced with $LiAlH_4$ to give the compound **79**. Regioselective opening of **79** with TMSCl, NaI in acetone gave iodo acetonide **80**. Alkylation of **80** followed by debenzylation and decarboxylation furnished the diol ester **32** which was converted to *R*-(+)-lipoic acid **1**.



Scheme 13. *Reagents and conditions:* (a) (i) TsCl, KOH, 93 %; (ii) KCN, 74 %; (iii) KOH, 93 %; (iv) MeOH, H^+; (b) Liphase/ Phosphate buffer (c) $LiAlH_4$, ether, 84 % (d) TMS-Cl, NaI, acetone; (e) Benzyl methyl malonate, NaH, THF, 25 %; (f) (i) Pd/C, H_2, 98 % (ii) MeOH, H^+, 98 %.; (g) TEA, MsCl, DCM (h) Na_2S, S, DMF, Heat 60^{o}c

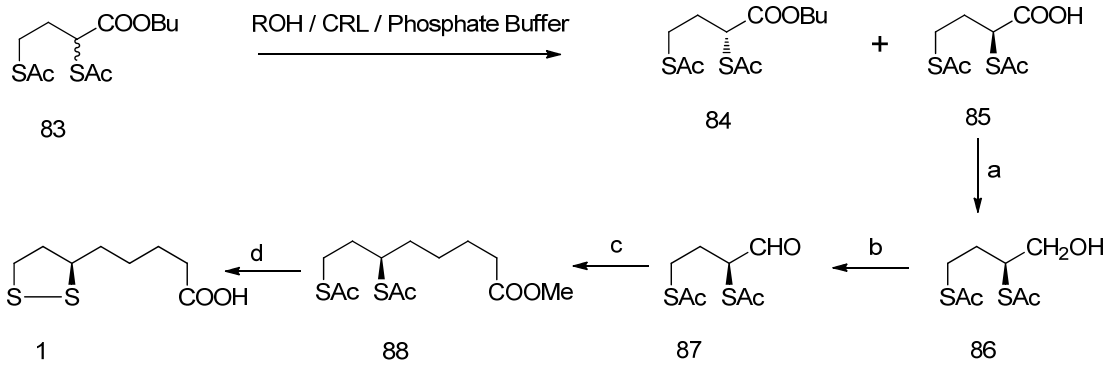
2.1.4.9 Fadnavis *et al* [27]

Fadnavis and Koteshwar have utilized lipase catalyzed enantioselective esterification of racemic α-Lipoic acid to deliver the *R*-(+)-lipoic acid **1**. In presence of lipase of candida rugosa *S*-isomer is converted to its corresponding ester **82**.



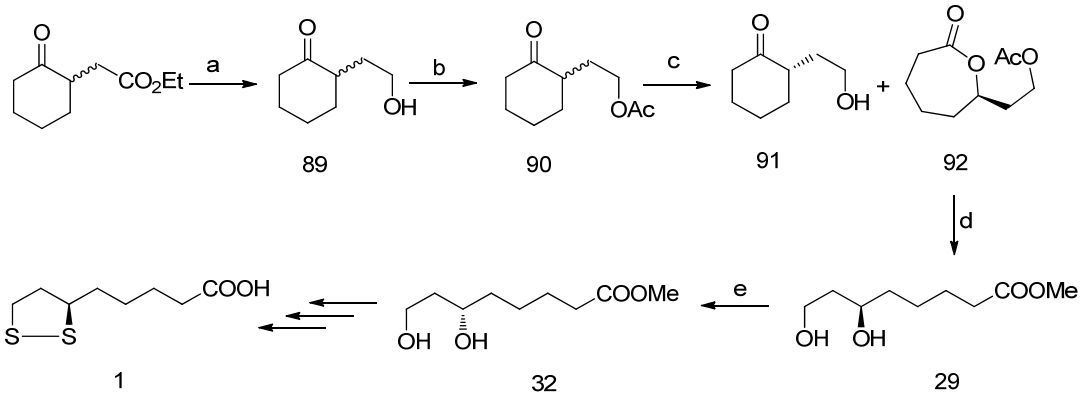
Scheme-14

In an another approach Fadnavis and co-workers have synthesized *R* and *S* isomers of lipoic acid using lipase catalyzed regio and stereospecific hydrolysis of *n*-butyl ester of 2, 4- dithioacetyl butanoic acid **83** to afford **84** and **85.** Hydroboration of **85** followed by PCC oxidation resulted in the formation of aldehyde **87**. Aldehyde **87** on four carbon Wittig homologation and subsequent hydrogenation with Wilkinson's catalyst gave the ethyl ester **88**. Hydrolysis of **88** with wheat germ lipase followed by treatment with oxidative enzyme mushroom tyrosinase gave *R*-(+)-lipoic acid **1**. Similarly *S*-(-)-lipoic acid was prepared from **84**.



Scheme- 15. *Reagents and conditions:*(a) (i) BH_3.DMS, 0 ^oC; (b) PCC (c) (i) Br^- $^+PPh_3$ $(CH_2)_3COOEt$, NaHMDS, -78 ^oC; (ii) $(PPh_3)_3RhCl$, H_2; (d) (i) Wheat germ Lipase, pH 7.0; (ii) Tyrosinase.

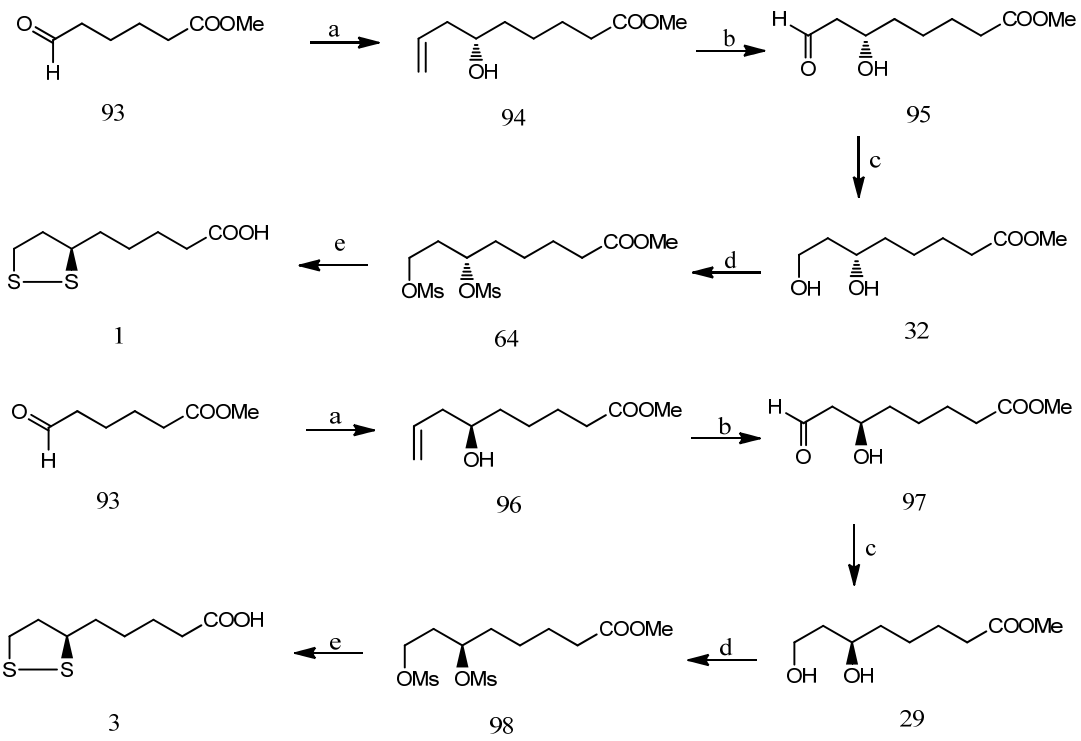
2.1.4.10 Adger *et al* [28] Adger and co-workers, regio and enantioselectively converted 2-(2-acetoxy ethyl) cyclohexanone **90** in to the lactone **92**, using monooxygenase enzyme. The lactone was converted to diol **29** using sodium methoxide in methanol. The stereochemistry at C-6 was inverted by using Mitsunobu reaction. Hydrolysis of benzoate ester delivered the known diol ester **32,** which was converted to *R*-(+)-lipoic acid **1** by a series of known reactions.



Scheme 16. *Reagents and conditions:* (a) (i) Ethylene glycol, *p*-TSA, Toluene; (ii) $LiAlH_4$, Ether, 0-25 ^oC; (b) Ac_2O, Pyridine, DMAP then HCl, MeOH; (c) 2-Oxo-3-4, 5, 5-trimethyl cyclopentenyl acetyl-CoA. Monooxegenase, NADPH, G-6-P, G-6-PDH; (d) NaOMe, MeOH; (e) (i) p-$NO_2C_6H_4COOH$, PPh_3, DEAD, THF; (ii) K_2CO_3, MeOH.

2.1.4.11 Zimmer *et al* [29]

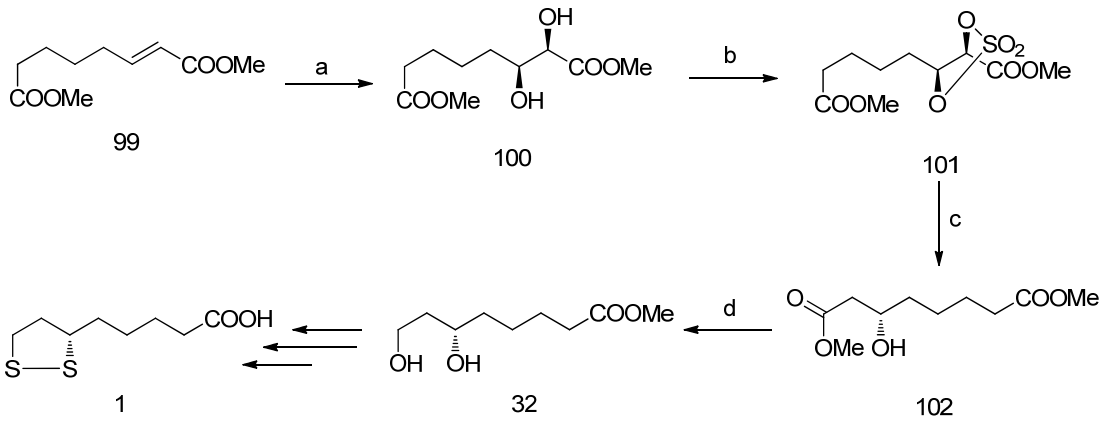
Zimmer and co-workers have employed catalytic asymmetric allyl stannation reaction as the key step to deliver the required stereochemistry. In the presence of 0.2 equivalents of (*S*)-BINOL, 0.2 eq. of $Ti(OiPr)_4$ and 4 A^o molecular sieves the aldehyde **93** and allyl tributyl stannane provided *R*-alcohol **94** with 98 % enantiomeric excess. This homoallylic alcohol converted to corresponding *R*-(+)-lipoic **1** by known sequence of reactions as shown below. Similarly Zimmer and co-workers has prepared *R*-(+)-lipoic **3** by same sequence of the reaction as shown below by using (*R*)-BINOL as catalyst for chiral induction.



Scheme 17. *Reagents and conditions:* (a) (*S*)-BINOL (0.2 eq), Ti (O^iPr) $_4$ (0.2 eq), CH_2Cl_2, 2 days, 75 %, 98 % ee. (b) O_3, MeOH ; (c) $NaBH_4$, MeOH, RT Stirring; d) TEA, MsCl, DCM (e) Na_2S, S, DMF, Heat 60^oC; (f) (*R*)-BINOL (0.2 eq), $Ti(OPr^i)_4$ (0.1 eq), CH_2Cl_2, 6 days, 89 %, 98% ee.

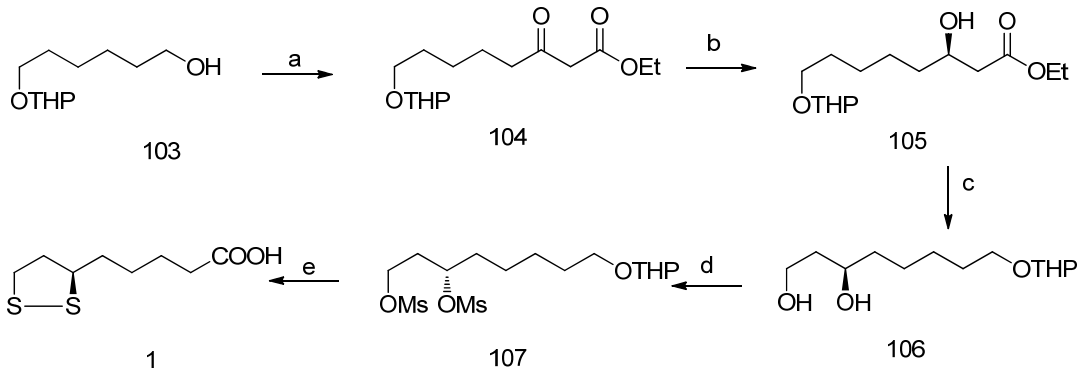
2.1.4.12 Sudalai *et al*[30]

Sudalai and co-workers employed Sharpless asymmetric dihydroxylation over **99** to afford intermediate **100** which on sulphone cyclisation and readuction with $NaBH_4$ undergoes sulphone ring opening to give deoxygenated product **102**. This intermediate **102** on reduction with borane.Me_2S furnishes intermediate **32**. This intermediate **32** converted into *R*-(+)-lipoic acid **1** by a series of known reactions.



Scheme 18. *Reagents and conditions:* (a) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, 0 ^oC, 95 %; (b) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 9 h; (ii) $RuCl_3$ (cat), $NaIO_4$, 85 %; (c) $NaBH_4$, DMAC, 20 % H_2SO_4, 63 %; (d) $NaBH_4$, Et_3N, MeOH:DMF (2:1), AcOH, 0 ^oC, 5h.

In another approach Ruthenium catalyzed asymmetric hydrogenation reactions had been implemented over keto intermediate **104** to get the β-hydroxy ester **105.** This β-hydroxy ester **105** on ester reduction followed by protection of alcohol, furnishes intermediate **106** respectively. This intermediate **106** converted into *R*-(+)-lipoic acid **1** by a series of known reactions as shown below.

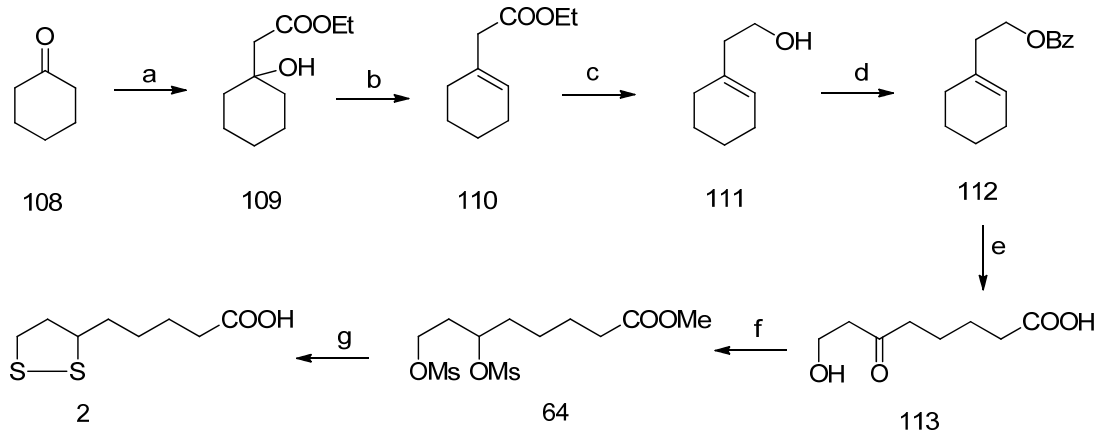


Scheme 19. *Reagents and conditions***:** (a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 75 %; (ii) N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1 h, 85 %; (or) Zn, $BrCH_2CO_2Et$, C_6H_6, PCC, CH_3CO_2Na, CH_2Cl_2, 4 h, 65 %; (b) H_2 (400 Psi), MeOH, (S)-BINAP-Ru; , 6hr, 90 %; (c) (i) $NaBH_4$, $CuSO_4$, EtOH, 7h, (ii) DHP, H^+; (d)(i) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 ^oC, 6 h; (ii) *p*-TSA, MeOH, 10 h; (iii) PCC, CH_2Cl_2, 3 h and then Ag_2O, NaOH, 1 h, 62 %; (e) $Na_2S.9H_2O$, DMF, HCl, 28 h, 45 %.

2.1.4.13 Chavan *et al.*[31, 32]

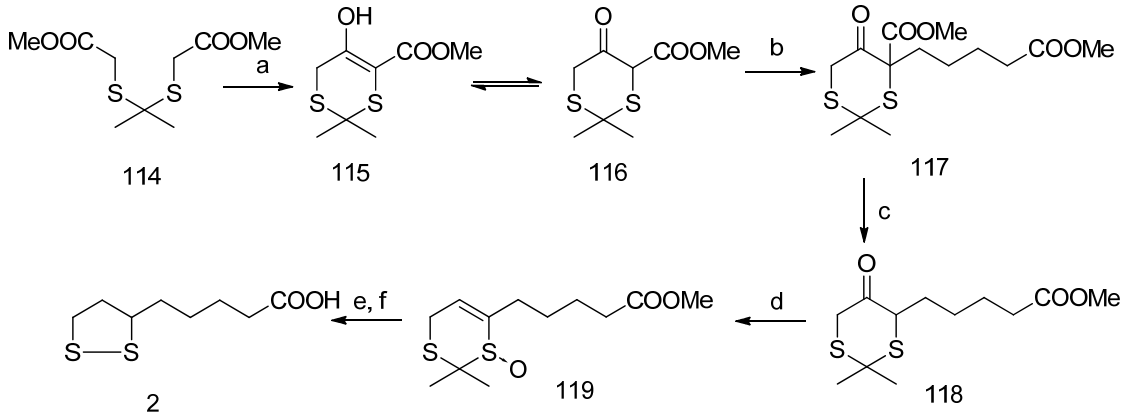
Chavan *et al* the synthesis of lipoic acid has been achieved by using modified Reformatsky reaction. In this protocol, β-elimination of the alcohol to furnish selectively the β, γ-unsaturated ester is another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone **108** to furnish alcohol ester **109**, which was then set for elimination using thionyl chloride and pyridine. The β, γ-ester **110** thus obtained was then reduced using DIBAL-H. The alcohol **111** formed, was then protected using benzoyl chloride to give benzoate ester **112**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **113**.

The reduction of ketoacid **113**, followed by esterification, furnished diol ester **64.** The diol ester **64** was then converted to racemic (α)-Lipoic acid **2** by known protocol as shown below (Scheme 20).



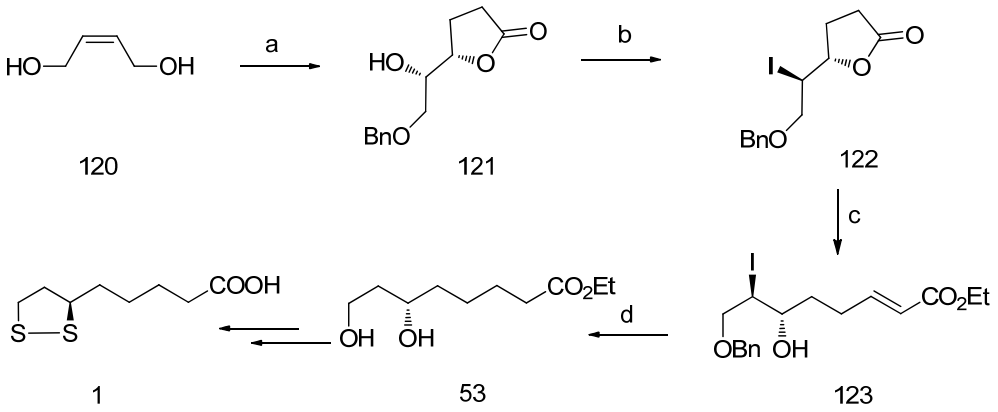
Scheme 20. *Reagents and conditions:* (a) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux, 65%; (b) $SOCl_2$, pyridine, DCM, 86 %; (c) DIBAL-H, DCM, -78 ^oC, 65 % ; (d) BzCl, Et_3N, DCM, 92%; (e) (i) O_3, DCM; (ii) Jones reagent, 85 %; (f) (i) $NaBH_4$, MeOH, 90 %; (ii) CH_2N_2, ether; 91 %; (iii) $MeSO_2Cl$, Et_3N, (g) Na_2S, S, DMF, 60 %

In another approach Chavan *et al* accomplished synthesis of racemic (α)-Lipoic acid **2** by using diester **114**, which was readily prepared in two steps from thioglycolic acid. Subjection of diester **114** to Dieckmann condensation delivered the α-keto ester **116** which exists in enolic form. Phase transfer catalyzed alkylation of **116** followed by decarboxylation gave the ester **117**. The keto ester **117** was converted into olefin acid **119** by treating with tosyl hydrazone followed by refluxing in presence of NaOH. Sequential reduction of double bond, oxidation to mono sulfoxide and final hydrolytic cyclization of **119** afforded racemic (α)-Lipoic acid **2** (Scheme 21).



Scheme 21. *Reagents and conditions:* (a) NaH, THF, 60 ^{o}C, 3 h, 86 %; (b) (i) K_2CO_3, $Br(CH_2)_4COOCH_3$, Bu_4NHSO_4, THF, rt; (c) DMSO, NaCl, H_2O, 140 ^{o}C; (d) (i) $TsNHNH_2$, MeOH, rt, 67 %; (ii) NaOH (2 equiv), iPrOH, Reflux, 84 %; (e) (i) Et_3SiH, TFA, 0 ^{o}C, rt, 73 %; (ii) $NaIO_4$, MeOH, 0 ^{o}C, 2 h, 68 %; (f) aq. HCl:Benzene (1:1), 50 ^{o}C, 7 h, 69 %

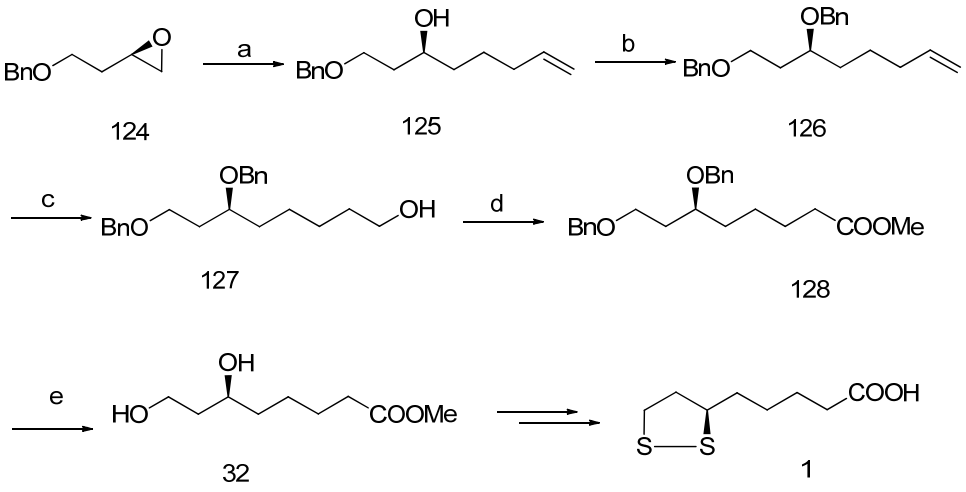
In third approach enantiomerically pure hydroxy lactone **121**, the versatile intermediate for synthesis, obtained in four steps from cis-2-butene-1,4-diol **120**, was treated with triphenylphosphine, iodine and imidazole to give the iodo lactone **122**. Reduction of the lactone using DIBAL-H at -78^{o}C followed by an in-situ two-carbon Wittig reaction gave the unsaturated ester **123**. Intermediate **123 was converted to** diol **53** by using W2 Raney nickel in the presence of hydrogen. The diol **(53)** a well known intermediate for the synthesis of (+)-lipoic acid.



Scheme 22. *Reagents and conditions:* (a) PPh_3, I_2, imidazole, 70 ^{o}C, 3 h, 94%; (b) DIBAL-H, DCM, 78 ^{o}C, 1 h, $Ph_3PCHCOOC_2H_5$, 24 h; rt, 96%; (c) W_2 Raney nickel, H_2, R.T., 24 hr, 84%.

2.1.4.14 Subhas Bose[33]

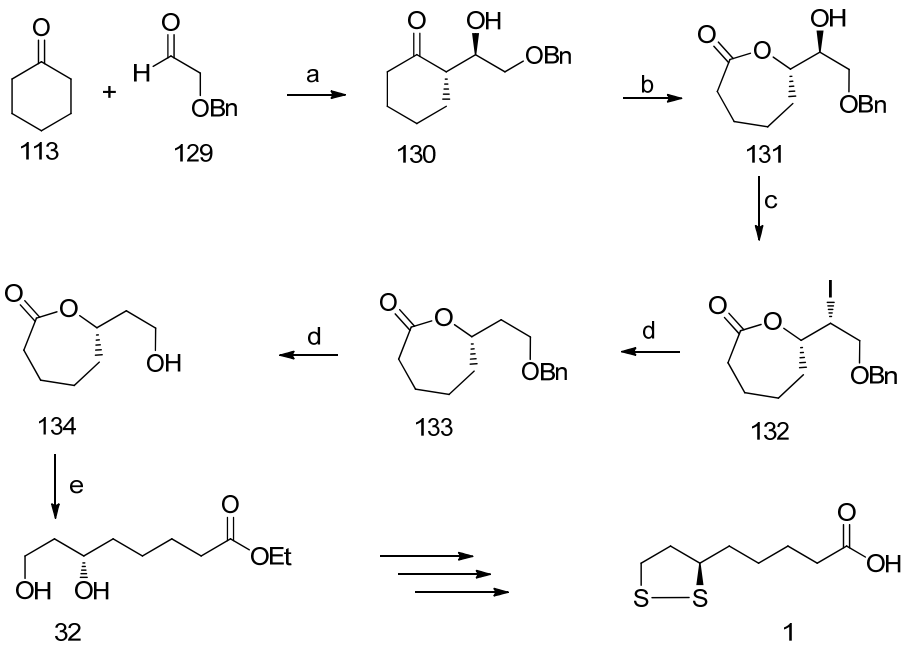
The regiospecific opening of epoxide (*R*)-**124** with but-3-enylmagnesium bromide (3 equiv)–78 °C furnished 1- enzyloxyoct-7-en-3-ol **125** in 90% yield. The hydroxy group in **125** was protected to yield **126** followed by elaboration of the terminal olefin into the corresponding acid function. This is immediately followed by esterification with diazomethane to afford the ester **128**. Removal of the benzyl group by hydrogenolysis gave the diol **32**, which was converted to (*R*)- α- lipoic acid **1**, by the standard sequence of reactions.



Scheme 23. *Reagents and conditions:* (a) CH_2=$CHCH_2CH_2$-MgBr, Li_2CuCl_4 (cat.), THF, –78 °C to R.T.; (b) NaH, BnBr, DBAI, DMF, 85%; (c) BH_3·DMS, $MeCO_2Na$, H_2O_2, THF, 88%; (d) (i) $NaClO_2$, TEMPO, NaOCl; (ii) CH_2N_2, Et_2O; (e) H_2, Pd/C, EtOH.

2.1.4.15 Duan *et al.*[34]

Duan and co-workers accomplished formal synthesis of *R*-(+)-lipoic acid using L-proline catalyzed diastereoselective cross-aldol reaction as key step. Cyclohexanone **113** on L-proline catalyzed aldol reaction with aldehyde **129** afforded hydroxy ketone **130**. Ketone **130** on Baeyer-Villiger oxidation followed by iodination and hydrogenation afforded lactone **134**. Lactone **134** on treatment with sodium methoxide afforded known diol **32** which converted to *R*-(+)-lipoic acid using known reaction sequence.



Scheme 24. *Reagents and conditions*: (a) L-proline, DMF, RT.; (b) *m*-CPBA, CH_2Cl_2, rt; (c) PPh_3, I_2, Im, toluene, reflux; (d) W_2 Raney Ni, H_2, MeOH, rt, (e) MeONa, MeOH, rt.

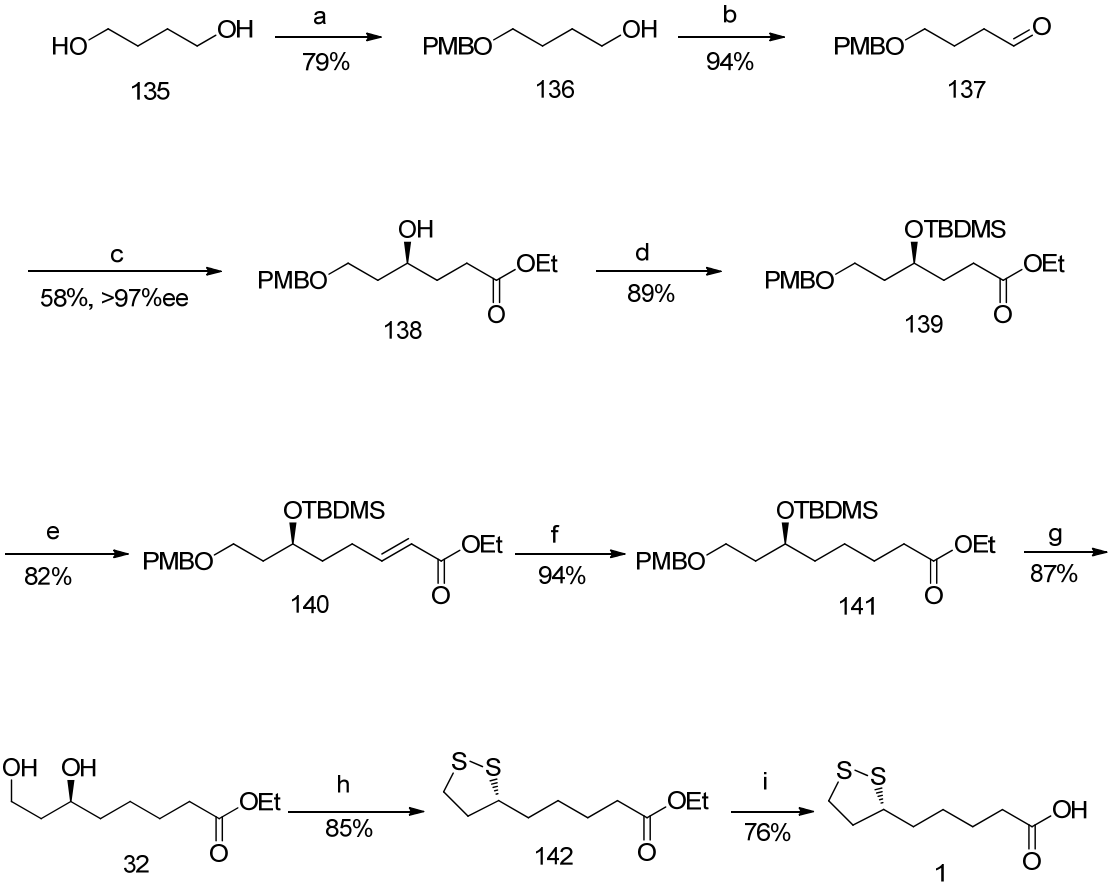
2.1.4.16 Kalkote *et al.*[35]

Again in an approach the synthesis of (*R*)-(+)-α-lipoic acid (1), starting from prochiral substrates using organo catalytic enantioselective aminoxylaiton has been achived. Organocatalyst utilised in this aspect is L-proline.

Thus the sequential synthesis starts from commercially available 1, 4-butanediol, which on mono-protection of 4-methoxy benzyl chloride followed by oxidation afforded aldehyde **137**. The aldehyde **137** then subjected to L-proline (20 mol%) catalyzed α-aminoxylation followed by wittig olefination at 0 ^oC. Thus formed γ-aminoxy α,β-unsaturated ester**,** was then subjected to Pd/C catalyzed hydrogenolysis to yield γ-hydroxy ester **138**. The γ-hydroxy ester **138** converted to its silyl ether **139** with TBDMSCl and imidazole in 89% yield.

This six carbon unit was extended to eight carbon unit by sequence of ester reduction to aldehyde, 2-carbon wittig homologation, reduction of α-β unsaturated double bond to yield **141.** In the next task ester **141** was treated with $TiCl_4$ to yield diol **32** which on tratment with MsCl in presence of Et_3N in anhydrous CH_2Cl_2 at 0 ^oC provided dimesylate. The dimesylate on treatment with Na_2S and sulfur in DMF at 80 ^oC for 24h afforded ethyl lipoate **142**. Finally hydrolysis of ethyl lipoate **142** with 0.1

M KOH aqueous solution in methanol at room temperature for 24h afforded *R*-(+)-lipoic acid **1.**

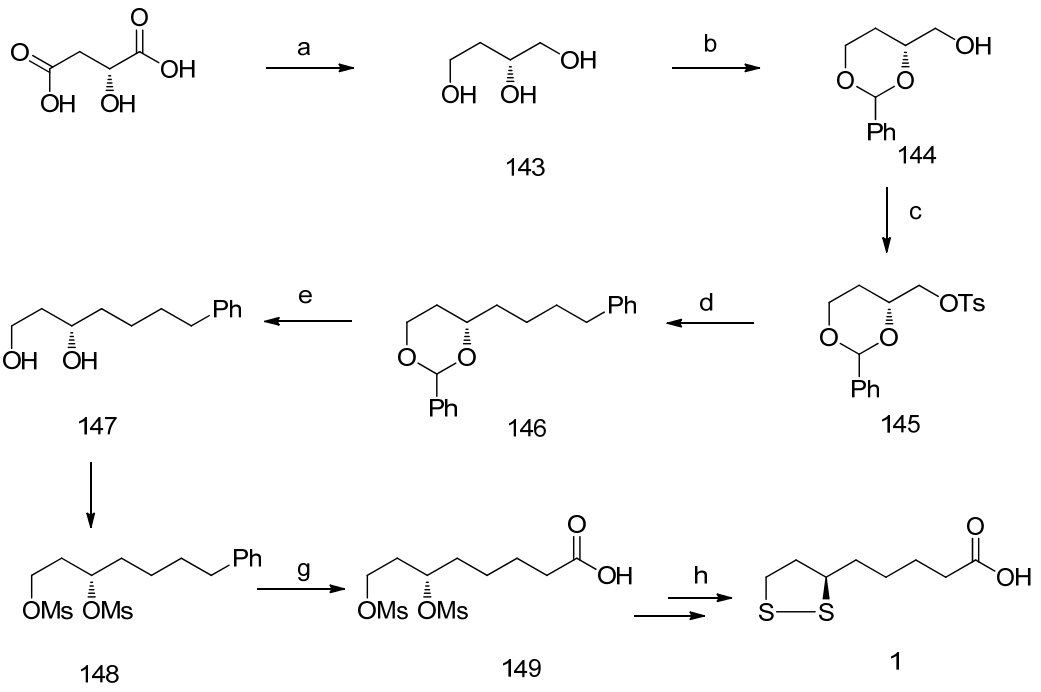


Scheme 25. *Reagents and reaction conditions*: (a) NaH, PMB-Cl, DMF (b) IBX, DMSO (c) (i) L-Proline, PhNO, DMSO, rt 15, (ii) $(EtO)_2P(O)CH_2COOEt$, LiCl, DBU, Acetinitrile, 0^oC; (iii) EtOAc, Pd/C, H_2 (d) TBDMS-Cl, Imidazole, DCM (e) DIBAL-H, DCM, -78^oC (f) (i) $(EtO)_2P(O)CH_2COOEt$, LiCl, DBU, Acetinitrile, 0^oC; (ii) EtOAc, Pd/C, H_2 (ii) (g) $TiCl_4$, DCM, RT (h) (i) TEA, MsCl, DCM (ii) Na_2S, S , DMF heat 80^oC (I) KOH, EtOH, RT, 24 hr.

2.1.4.17 Huang *et al.*[36]

Huang and co-workers recently reported asymmeric synthesis of *R*-(+)-lipoic acid starting from (*R*)-malic acid. (*R*)-malic acid convertd to triol **143** by literature method. Triol **143** on treatment with benzaldehyde under acidic conditions afforded acetal **144** which converted to its tosyl derivative **145**. Tosyl derivative **145** on treatment with Grignard reagent afforded **146**. Acetal **146** on iodine treatment gave diol **147** which

on mesylation get converted to **148**. Compound **148** on tratment with Ruthenium chloride and sodium periodate afforded acid **149** which converted to *R*-(+)-lipoic acid **1** by known reaction sequence.



Scheme 26. *Reagents and conditions*: (a) Ref. (b)PhCHO, TFA, CH_2Cl_2; (c)TsCl, Py, CH_2Cl_2 0 ^oC; (d) $Ph(CH_2)_3MgBr$, CuI, THF, -78 ^oC; (e) I_2, MeOH; (f) MsCl, Et_3N, CH_2Cl_2; (g) $RuCl_3.xH_2O$, $NaIO_4$, CH_3CN: EtOAc: H_2O, (2:2:3), rt.

2.1.5. References :

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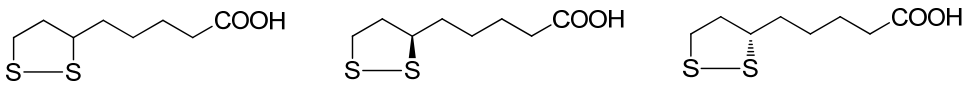
Chapter 2, Section II: Synthesis of (±)-α-Lipoic Acid: Kulinkovich Approach

2.2.1. Introduction:

The efficient synthesis of naturally occurring molecules which are pharmaceutically important product is still a challenge in synthetic organic chemistry. Primarily, during the synthesis, the key intermediate compounds with a defined carbon skeleton and defined stereo-genic property have to be generated. These intermediate compounds serving as precursor for desired targets have to be produced. Therefore easy protocol which produces intermediate by short route must be implemented. Hence in continuation of our studies on synthesis of biologically active compounds and development of novel synthetic methodologies, we planned a short and facile route for the synthesis of (±)-α-lipoic acid (**1**) *via* Kulinkovich cyclopropanation.[1]



(±) -α-Lipoic acid (**1**) R- (+) -α-Lipoic acid (**1a**) S- (-)-α-Lipoic acid (**1b**)

Figure 1

As seen in the literature review, various methods have been reported for formal and total synthesis of racemic or enantiopure lipoic acid, employing chiral-pool approach, kinetic resolution of racemate or enzymatic resolution. All reported syntheses include use of expensive starting materials as well as lengthy routes. To overcome these factors, we planned synthesis of (±)-α-lipoic acid (**1**) from inexpensive and commercially available adipic acid employing Kulinkovich cyclopropanation.

2.2.2. Mechanism of the Kulinkovich cyclopropanation: [2, 3]

The mechanistic cycle proposed for Kulinkovich cyclopropanation is depicted in Figure 2. As shown in Figure 2, first step involving is the ligand exchange reaction between titanium tetra-alkoxide and ethyl magnesium bromide provides the unstable

diethyl titanium intermediate **2a**, which furnishes titano-cyclopropane **2** *via* elimination of ethane. In the next step, a nucleophilic attack of **2** on the ester carbonyl furnishes the titanoxa-cyclopentane **3,** which undergoes rearrangement to furnish the intermediate **4.** Intermediate **4** further undergoes rearrangement to yield the titanium cyclopropane alkoxide **5.**

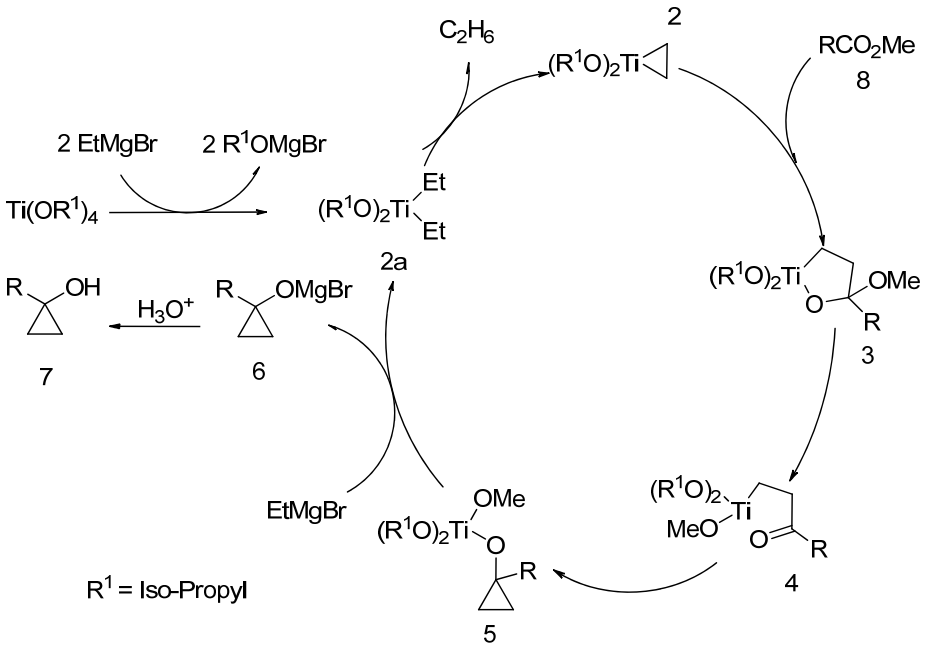


Figure 2

Titanium cyclopropane alkoxide **5** on metal exchange reaction with excess of Grignard reagent furnishes magnesium alkoxide **6** and regenerates the catalytically active species **2a**. Magnesium alkoxide on quenching by aqueous ammonium chloride yields cyclopropanol **7.** Cyclopropanes and their hydroxyl-substituted analogues are among the most reactive and versatile hydrocarbon frameworks. The implementation of cyclopropanols in asymmetric synthesis or synthetic methodology has increased due to the invention of Kulinkovich reaction, which was described for the first time in the late 1980s. In summary ethylmagnesium bromide on reaction with carboxylic ester **8**, in presence of catalytic amount of titanium tetraisopropoxide, furnished cyclopropanol **7** (Figure 3).

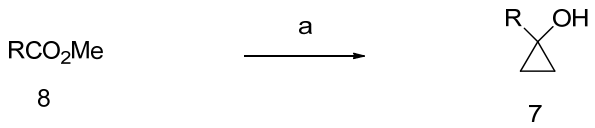


Figure 3. *Reagents and conditions:* (a) (i) EtMgBr, $Ti(O^iPr)_4$, THF, 20^oC; ii) 5% aq H_2SO_4 .

The ethyl group of the Grignard reagent in presence of titanium-tetra-isopropoxide serves as the synthetic equivalent of a di-carbanion **12** (Figure 4). The significance of this protocol is for the synthesis of cyclopropane derivatives as well as opening of cyclopropane derivatives so as to utilize resultant intermediate in total synthesis of bioactive molecules.[1]

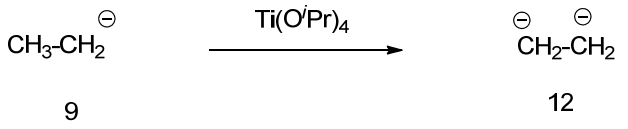
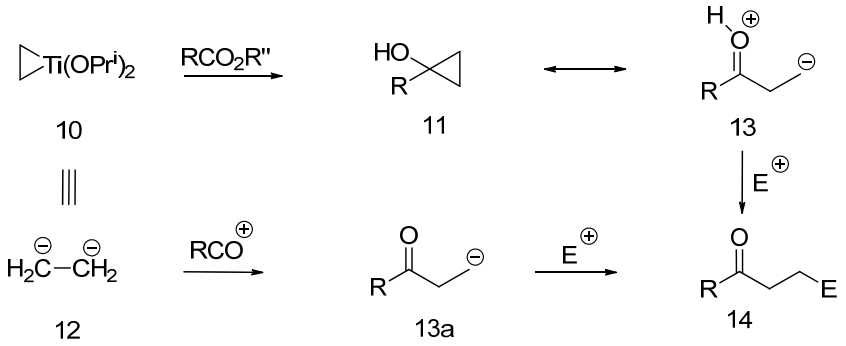


Figure 4

In this protocol heterolytic C_1-C_2 ring cleavage of substituted cyclopropanol is strongly facilitated by the Л-electron donor oxygen atom (Scheme 1). As a result, cyclopropanol **11** readily gives carbonyl zwitterion **13**, which further undergoes attack of electrophile to furnish ketone **14**. In these transformations, the carbonyl zwitterion **13** formally acts as synthetic equivalent of β-oxocarbanion **13a.**

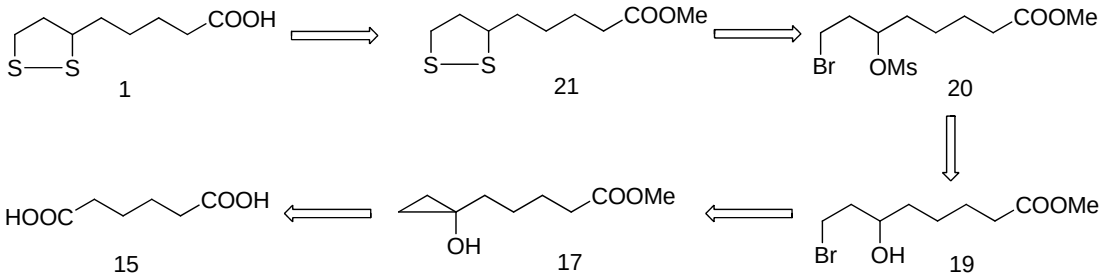


Scheme 1

As shown in the scheme 1, cyclopropane ring could be correlated to di-carbanion synthon **12** which undergoes attack of electrophile RCO^+ to furnish β-oxocarbanion **13a** which further undergoes attack of E^+ to furnish ketone **14**.

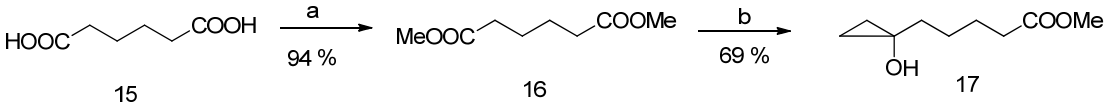
2.2.3. Present Work:

In order to develop a new approach for the synthesis of (±)-α-lipoic acid (**1**) involving Kulinkovich approach, a retrosynthesis of (α)-lipoic acid was designed as depicted in scheme 2 from readily available adipic acid. From retro-synthetic analysis it can be seen that methyl 8-bromo-6-hydroxyoctanoate (**19)** could serve as a key intermediate; which could be built up easily by employing Kulinkovich cyclopropanation reaction over inexpensive and readily available adipic acid.



Scheme 2

Accordingly, adipic acid was converted to dimethyl adipate (**16**) which was subjected to Kulinkovich cyclopropanation with ethylmagnesium bromide in presence of titanium tetraisopropoxide to give the cyclopropanol **17** (scheme 3). The structure of the product was confirmed by spectral analysis wherein cyclopropane ring methylene protons resonated as doublet of doublet at 0.40 ppm and another doublet of doublet at 0.71 ppm in ^{1}HNMR spectrum and at 13.5 ppm in ^{13}C NMR spectrum.



Scheme 3. *Reagents and conditions:* (a) MeOH, H^+, reflux; (b) (i) EtMgBr, THF; ii) $Ti(O^iPr)_4$, THF; iii) 5% aq H_2SO_4**.**

In the next step, the exocyclic oxygen atom favours ring-opening reaction. Such transformations are facilitated or initiated by I) Л-electron-donor effect of the oxygen which leads to stabilization of transition state. II) Removal of electron pair of oxygen atom with formation of unstable oxycyclopropyl cation radical. III) Heterolytic cleavage of the carbon-carbon covalent bond, either in presence of acid or base which promotes rearrangement of the cyclopropane ring. In the present protocol, case III is favorable (Figure 6) in which the hydroxyl group strongly activates the reaction and directs the heterolytic C_1-C_2 ring cleavage so that electron-deficient center oxygen atom is formed along with β carbanion center. This intermediate acts as homoenolate anion.

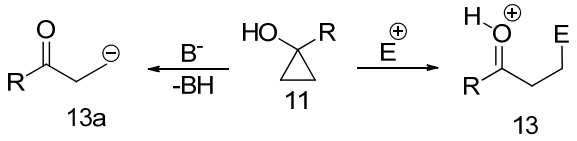
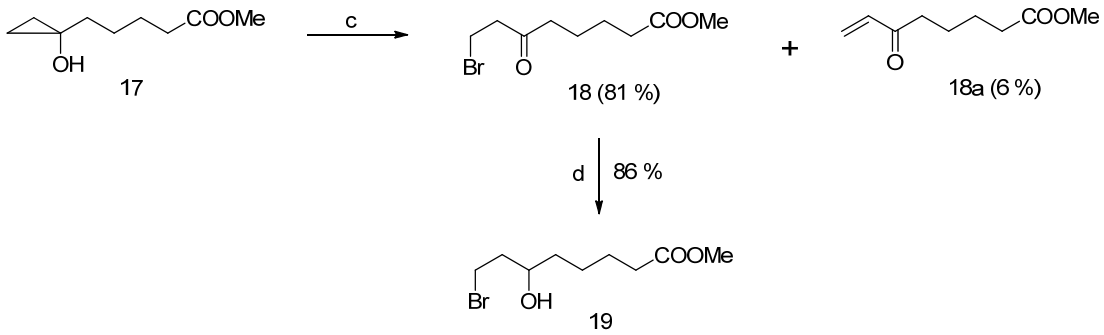


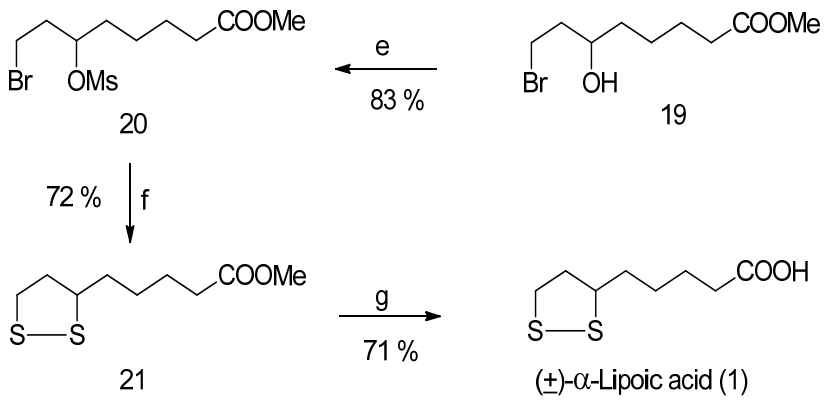
Figure 5

Electrophilic bromination[3] of cyclopropanol **17** afforded methyl 8-bromo-6-oxo-octanoate **(18)** and the elimination product **18a** (Scheme 4). Olefin protons of **18a** resonated in the region 5.79-6.28 ppm in ^{1}HNMR spectrum, whereas the triplet at 3.54 ppm in ^{1}HNMR spectrum of methyl 8-bromo-6-oxo-octanoate **(18)** confirmed the presence of methylene protons bonded to bromine atom. The reduction of **18** with $NaBH_4$ in dry MeOH at 0^{o}C- RT for 5 hr gave methyl 8-bromo-6-hydroxy octanoate **(19)** (Scheme 4). The presence of methine proton at 3.84 ppm in ^{1}HNMR confirmed the presence of hydroxyl group in the product **19**.



Scheme 4. *Reagents and conditions:* (c) Br_2 / NBS, THF, reflux; (d) $NaBH_4$, MeOH**.**

The bromoalcohol **19** is the key intermediate for the synthesis of (±)-α-lipoic acid (**1**). Treatment of **19** with methanesulfonyl chloride and triethylamine in dichloromethane gave the mesylate **20** in good yield (Scheme 5).



Scheme 5. *Reagents and conditions:* (e) MsCl, TEA, DCM, RT; (f) Na_2S, S_8, DMF, reflux; (g) KOH, MeOH.

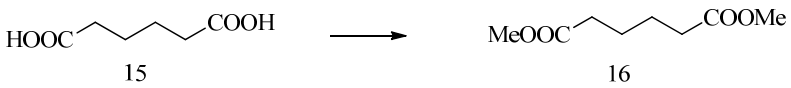
The ^{1}H NMR spectrum of **20** showed presence of a singlet at 3.06 ppm which supported presence of the mesyl group. The compound **20** on reaction with sodium sulfide and sulfur in *N, N*-dimethylformamide at 90^{o}C afforded methyl (±)-α-lipoate (**21).** It was confirmed by signals at 3.04-3.22 ppm (m, 2H) and 3.48-3.59 ppm (m, 1H) in ^{1}HNMR spectrum for H-8, 8' and H-6, respectively. The upfield shifts of the signals for these protons were expected because of the shielding effect of the sulfur atom. In the ^{13}C spectra, disappearance of mesyl group and only 9 carbon signals proved the formation of methyl lipoate. The hydrolysis of **21** with 0.1M potassium hydroxide in methanol at room temperature gave (±)-α-lipoic acid(**1).** The spectral data and elemental analysis were in good agreement with the reported data.

2.2.4. Conclusion:

We have successfully demonstrated the synthesis of (±)-α-lipoic acid by deploying Kulinkovich cyclopropanation approach on inexpensive and commercially available adipic acid.

2.2.5. Experimental

Preparation of dimethyl adipate (16)



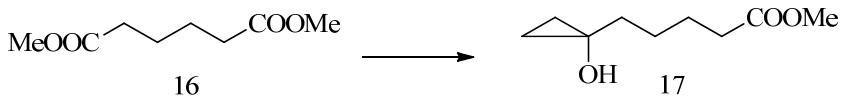
15 16

To the stirred solution of adipic acid **15** (50 gm, 0.3425 mol) in dry methanol (250 mL), catalytic amount of H_2SO_4 was added and the reaction mixture was heated to reflux under argon atmosphere. Progress of the reaction was monitored by TLC. After completion of reaction, work up of the reaction was carried out by evaporation of methanol by rotavapor; water (100 mL) was added to residue and extracted with ethyl acetate (2 x 250 mL). Organic layer was dried over anhydrous sodium sulphate and evaporated by rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (95:5) as eluent to afford dimethyl adipate **(16)**.

Yield: 54.00 gm (94%); colorless viscous liquid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.60-1.67 (m, 4H), 2.27-2.34 (m, 4H), 3.64 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ

24.11, 33.34, 51.20, 173.29 ppm; Elemental Anal. Calcd for $C_8H_{14}O_4$: C, 55.67; H, 8.15; Found: C, 55.69; H, 8.19.

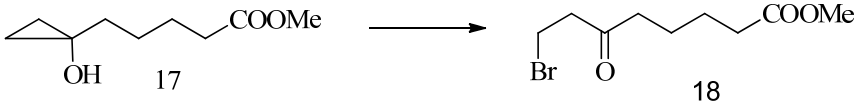
Preparation of methyl 5-(1-hydroxycyclopropyl)pentanoate (17)



To the stirred solution of **16** (1.74 gm, 10.0 mmol) in dry tetrahydrofuran (15 mL), was added tanium tetraisopropoxide (0.28 gm, 1.00 mmol) at 0°C in inert atmosphere, followed by addition of freshly prepared ethyl magnesium bromide (1 M, 20.0 mL, 20.0 mmol) in dry tetrahydrofuran. The reaction mixture was kept stirred to attain the room temperature (1/2 hr). Progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3 x 50 mL). The organic layer was combined, dried over anhydrous sodium sulphate and concentrated by rotavapour to get the crude reaction mass. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (75:25) as eluent to furnish methyl 5-(1-hydroxycyclopropyl)pentanoate **(17).**

Yield: 1.01 gm (59%); colorless viscous liquid; $C_9H_{16}O_3$; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.40 (dd, *J* = 5.06, 6.95 Hz, 2H), 0.71 (dd, *J* = 4.80, 6.95 Hz, 2H,), 1.51-1.60 (m, 4H), 1.63-1.74 (m, 2H), 2.13 (s, 1H), 2.32 (t, *J*= 7.20 Hz, 2H), 3.65 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.53, 24.67, 25.49, 33.98, 37.86, 51.48, 55.28, 174.19 ppm; Elemental Anal.Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36; Found: C, 62.72; H, 9.32.

Preparation of methyl-8-bromo-6-oxo-octanoate (18)

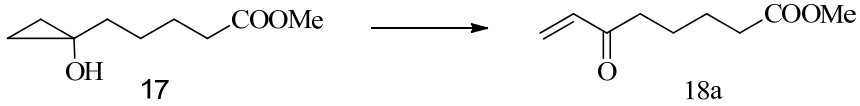


Bromine (0.384 gm, 2.4 mmol) in 2-propanol was added to a solution of **17** (0.345 gm, 2.0 mmol) in 2-propanol (10 mL) at 0°C, and stirred for 1 h. Progress of the reaction was monitored by TLC. After consumption of the starting material, reaction

was quenched with saturated solution of sodium thiosulphate (5 mL) and extracted with $CHCl_3$ (50 mL). The combined extract was washed with satd. solution of $NaHCO_3$, water, brine, dried over anhydrous sodium sulphate and concentrated by rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (95:5) as eluent to afford methyl 8-bromo-6-oxo-octanoate **(18)**.

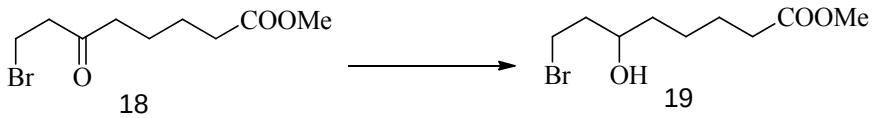
Yield: 0.406 gm (81%); colorless viscous liquid; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62-1.66 (m, 4H), 2.30-2.36 (m, 2H), 2.43-2.47 (m, 2H), 3.02 (t, *J* = 6.60 Hz, 2H), 3.55 (t, *J* = 6.60 Hz, 2H), 3.65 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.57, 24.96, 30.45, 33.78, 36.86, 39.91, 51.47, 174.06, 190.06 ppm. Elemental Anal. Calcd for $C_9H_{15}BrO_3$: C, 43.05; H, 6.02; Br, 31.82; O, 19.11; Found: C, 43.06; H, 6.02; Br, 31.92; O, 19.10.

Methyl 6-oxo-7-octenoate (18a)



Yield: 0.037 gm (6%); colorless viscous liquid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.59-1.66 (m, 4H), 2.31 (t, *J* = 7.10 Hz, 2H), 2.58 (t, *J* = 6.95 Hz, 2H), 3.63 (s, 3H), 5.78 (dd, *J* = 1.90, 9.70 Hz, 1H), 6.13 (dd, *J* = 2.02, 17.68 Hz, 1H,), 6.14-6.28 (dd, *J* = 9.7, 17.68 Hz, 1H) ppm; Elemental Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; Found: C, 65.29; H, 8.71.

Preparation of methyl 8-bromo-6-hydroxyoctanoate (19)

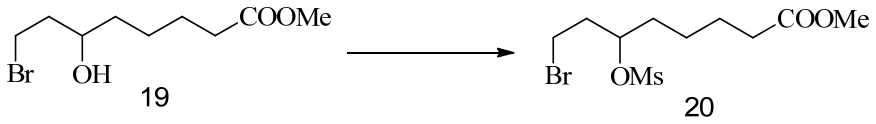


To the stirred solution of **18** (1.26 gm, 5.0 mmol) in methanol (15 mL) at 0^{o}C was added $NaBH_4$ (0.210 gm, 5.52 mmol) in argon atmosphere and stirred at the same temperature for 3 hr. Progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with dilute acetic acid and

extracted with ethyl acetate (2 x 25 mL), organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated by rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (85:15) as eluent to afford methyl 8-bromo-6-hydroxyoctanoate **(19).**

Yield: 1.088 gm (86%); colorless viscous liquid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.42-1.51 (m, 4H), 1.55-1.71 (m, 2H), 1.78 (br s, 1H), 1.90-2.00 (m, 2H), 2.34 (t, *J* = 7.20 Hz, 2H), 3.51-3.59 (m, 2H), 3.68 (s, 3H), 3.78-3.89 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.57, 24.96, 30.45, 33.78, 36.86, 39.91, 51.47, 69.09, 174.06 ppm; Elemental Anal. Calcd for $C_9H_{17}BrO_3$: C, 42.70; H, 6.77; Br, 31.57; Found: C, 42.65; H, 6.76; Br, 31.60.

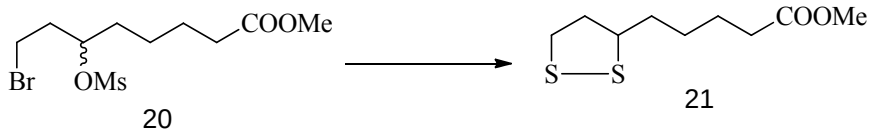
Preparation of methyl 8-bromo 6-(methylsulfonylloxy)-octanoate (20)



To the stirred solution of **19** (1.0 gm, 3.95 mmol) in dry CH_2Cl_2 (15 mL) were added Et_3N (0.479 gm, 4.74 mmol), DMAP (catalytic) and methanesulfonyl chloride (0.497 gm, 4.34 mmol) at 0^{o}C. The reaction mixture was stirred at same temperature for 1 hr and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), combined organic layer dried over anhydrous sodium sulphate and evaporated by rotavapor to get the crude residue. The crude residue was purified by neutral alumina gel column chromatography using petroleum ether/ ethyl acetate (95:05) as eluent to afford methyl 8-bromo-6-(methylsulfonyloxy)-octanoate **(20).**

Yield: 1.081 gm, (93%); colorless viscous liquid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40-1.52 (m, 2H), 1.64-184 (m, 4H), 2.06-2.26 (m, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 3.06 (s, 3H), 3.43-3.51 (m, 2H), 3.67 (s, 3H), 4.81-4.93 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.03, 24.35, 28.00, 33.48, 34.16, 37.21, 38.44, 51.37, 80.55, 173.47 ppm; Elemental Anal.Calcd for $C_{10}H_{19}BrO_5S$: C, 36.26; H, 5.78; Br, 24.12; S, 9.68; Found: C, 36.14; H, 5.62; Br, 24.16; S, 9.38.

Preparation of methyl 5-(1, 2-dithiolan-3-yl)pentanoate (Methyl lipoate) (21)



To the stirred solution of **20** (1.0 gm, 3.0 mmol) in dry DMF (15 mL) was added Na_2S (0.725 gm, 3.0 mmol) and sulphur powder (0.096 gm, 3.0 mmol) and refluxed at 90 ^oC for 24 hr. The reaction mixture was quenched by cold water and extracted with ethyl acetate (2 x 25 mL). Combined organic layer dried over anhydrous sodium sulphate and evaporated on rotavapor to get the crude reaction residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (80:20) as eluent to afford methyl 5-(1, 2-dithiolan-3-yl)pentanoate **(21).**

Yield: 0.475 gm (72%); colorless viscous liquid; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.45-1.53 (m, 2H), 1.59-175 (m, 4H), 1.82-1.99 (m, 1H), 2.33 (t, *J* = 7.10 Hz, 2H), 2.38-2.54 (m, 1H), 3.04-3.22 (m, 2H), 3.48-3.59 (m, 1H), 3.67 (s, 3H).; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.54, 28.65, 33.68, 34.50, 38.35, 40.08, 51.35, 56.15, 173.60 ppm.; Elemental Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.06; H, 7.32; S, 29.10; Found: C, 48.90; H, 7.05; S, 28.90.

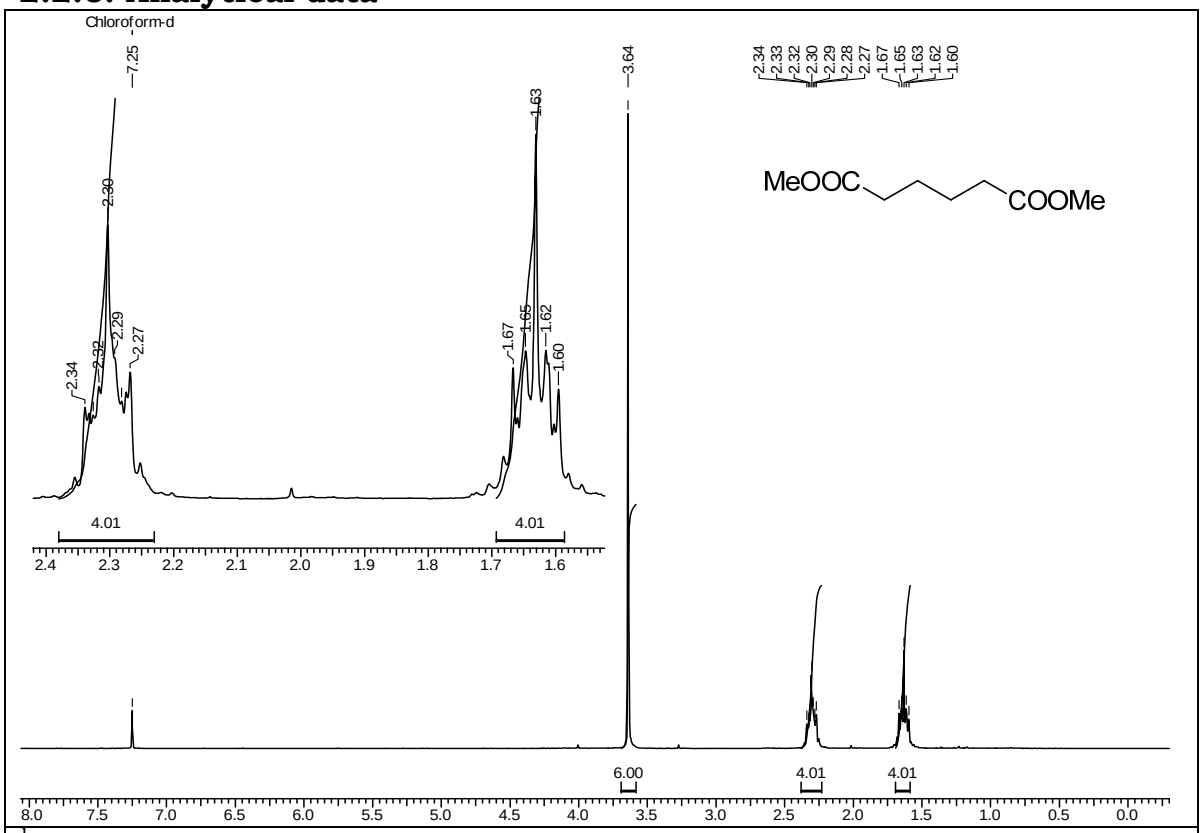
Preparation of 5-(1, 2-dithiolan-3-yl)-pentanoic acid (Lipoic acid) (1)

To the stirred solution of **21** (0.440 gm, 2.0 mol) in absolute methanol (10 mL) was added 0.1 M ethanolic KOH (8 mL) under nitrogen atmosphere. It was stirred for 12 hrs, ethanol was evaporated and the aqueous solution was washed with light petroleum to remove the impurities. The aqueous layer was acidified to pH 1 by the addition of 2 N HCl and then extracted with diethyl ether (3 x 25 mL). The combined organic fractions were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude reaction mass. The crude residue

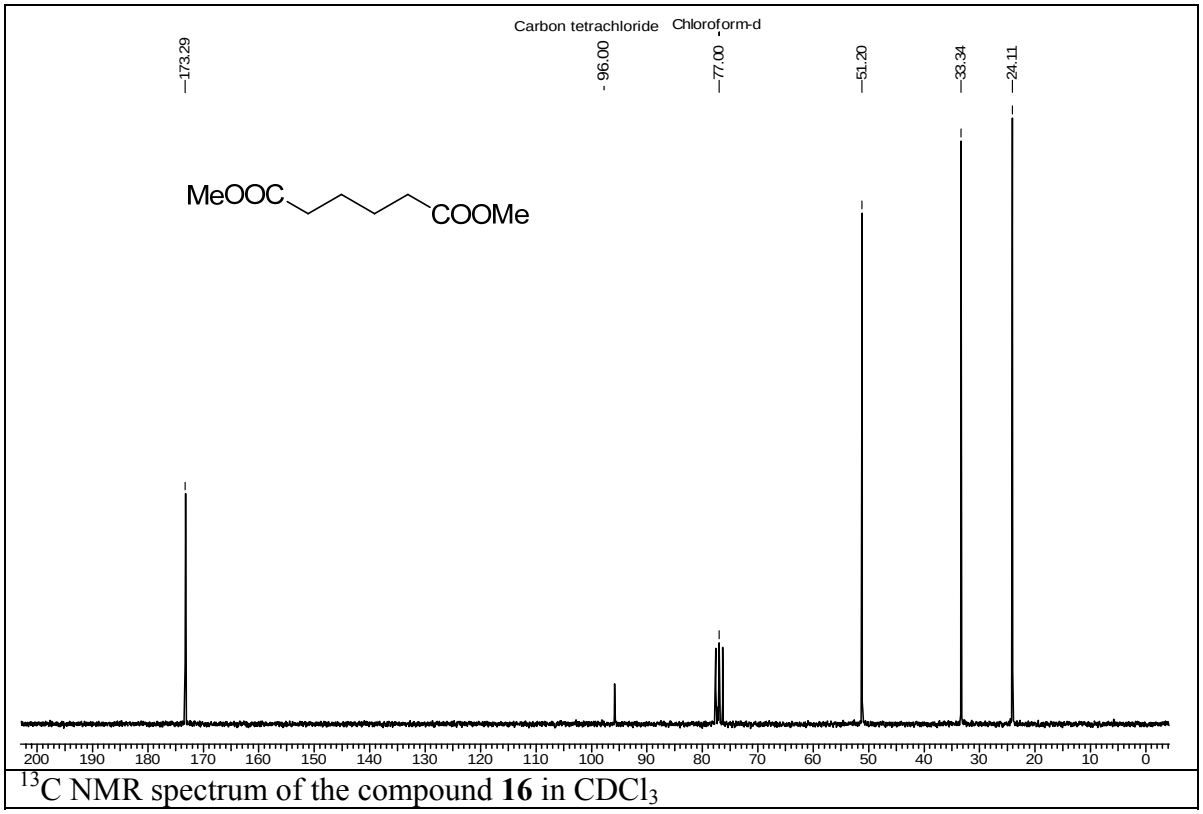
was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (70:30) as eluent to afford 5-(1, 2-dithiolan-3-yl)-pentanoic acid **(1)**.

Yield: 0.293 gm, (75%); Yellow solid; Melting point: 49^{o}C; IR ($CHCl_3$) cm^{-1}: 3018, 2934, 1701; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.41-1.51 (m, 2H), 1.55-1.74 (m, 4H), 1.81-1.98 (m, 1H), 2.36 (t, *J* = 7.20 Hz, 2H,), 2.44-2.53 (m, 1H), 3.03-3.24 (m, 2H), 3.49-3.63 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm.; Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.8; Found: C, 48.07; H, 6.74; S, 31. 91.

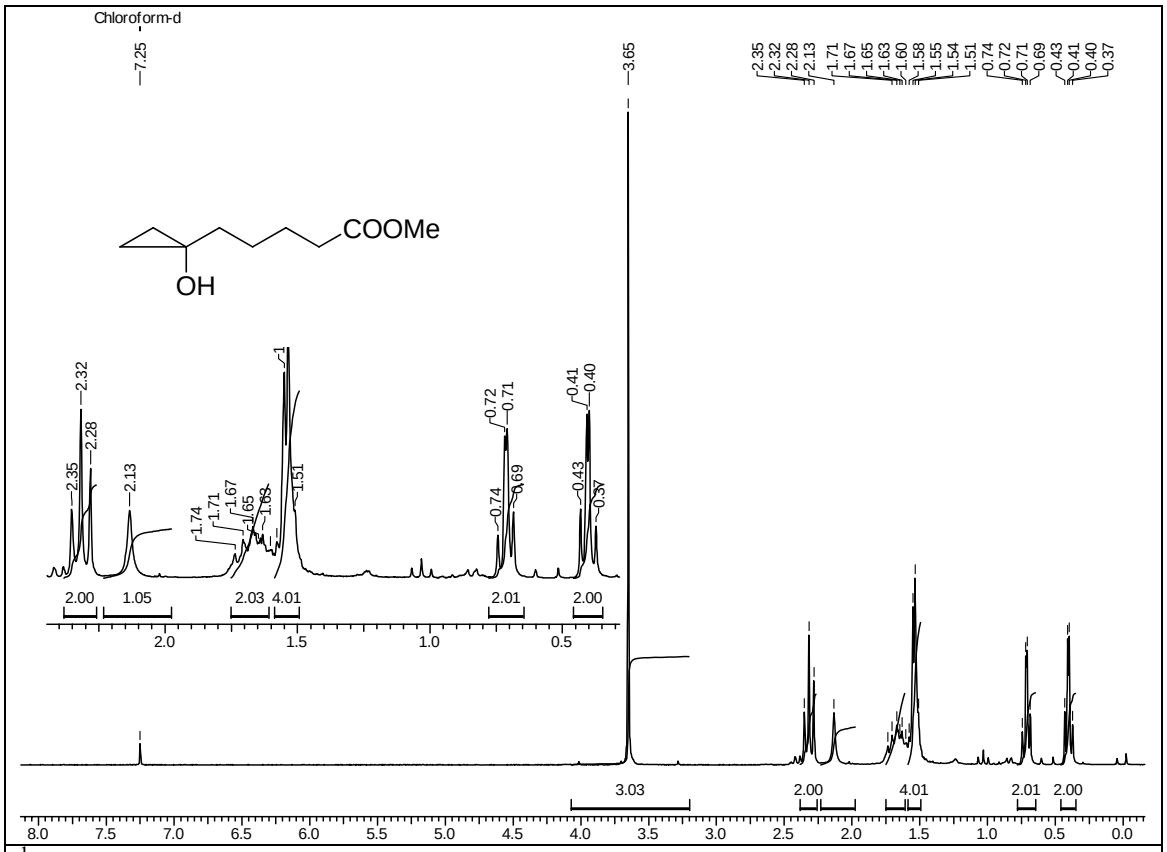
2.2.6. Analytical data



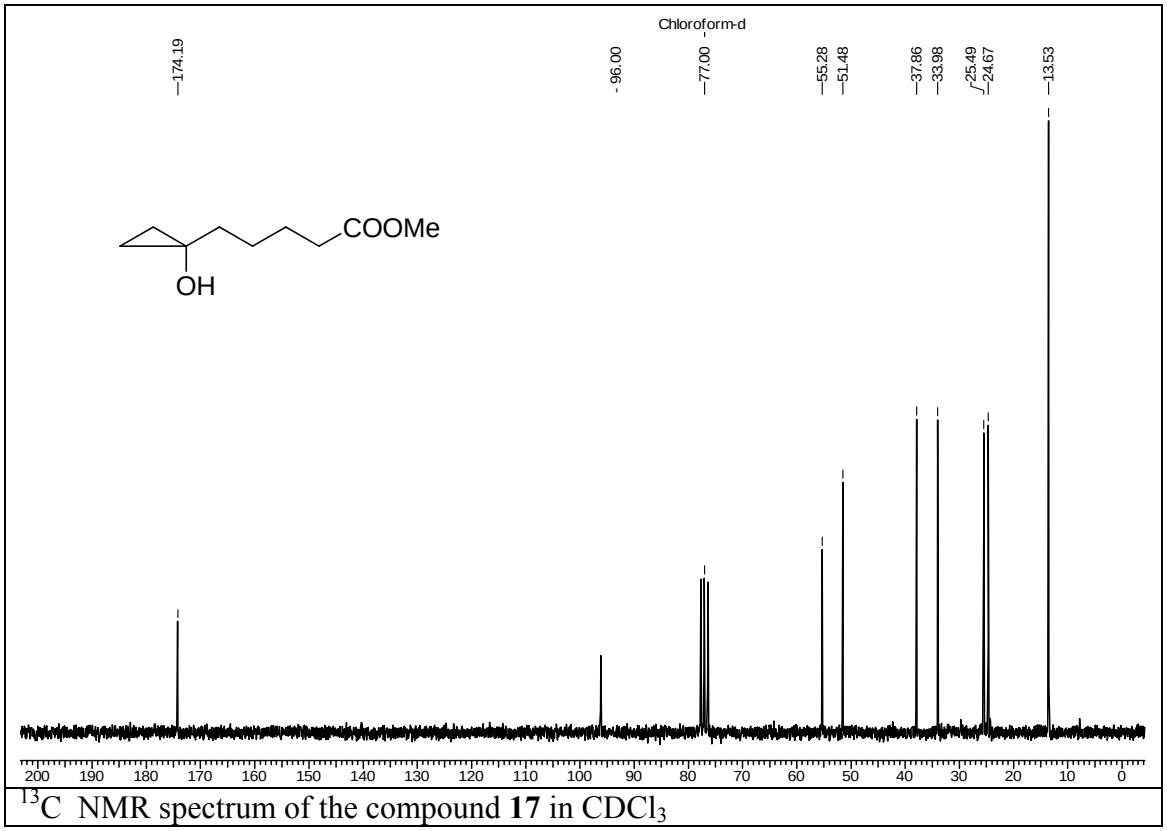
^{1}H NMR spectrum of the compound **16** in $CDCl_3$



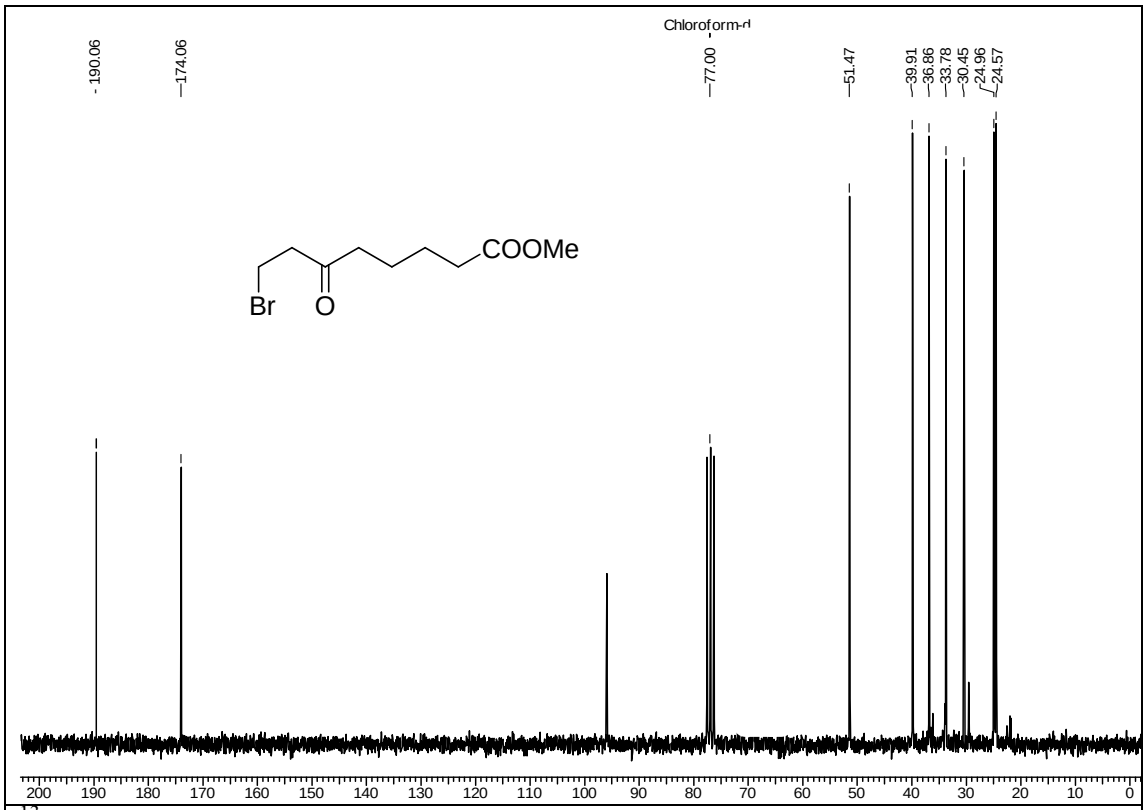
^{13}C NMR spectrum of the compound **16** in $CDCl_3$



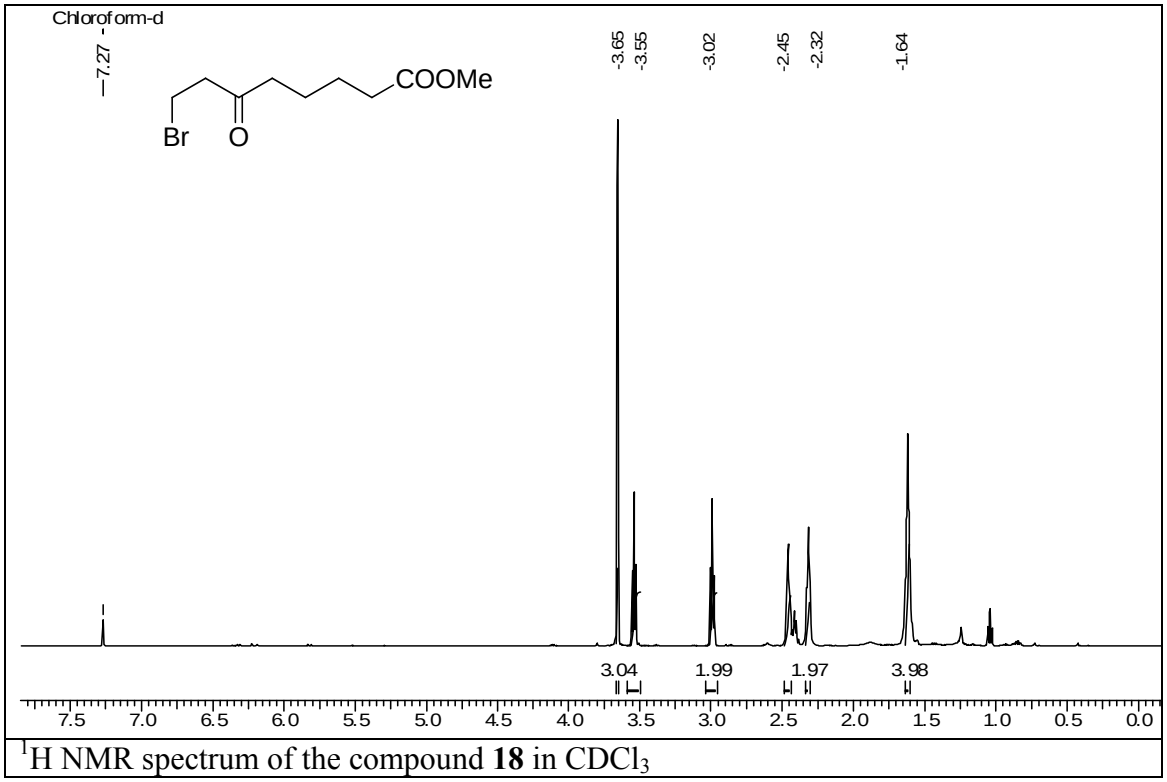
^{1}H NMR spectrum of the compound **17** in $CDCl_3$



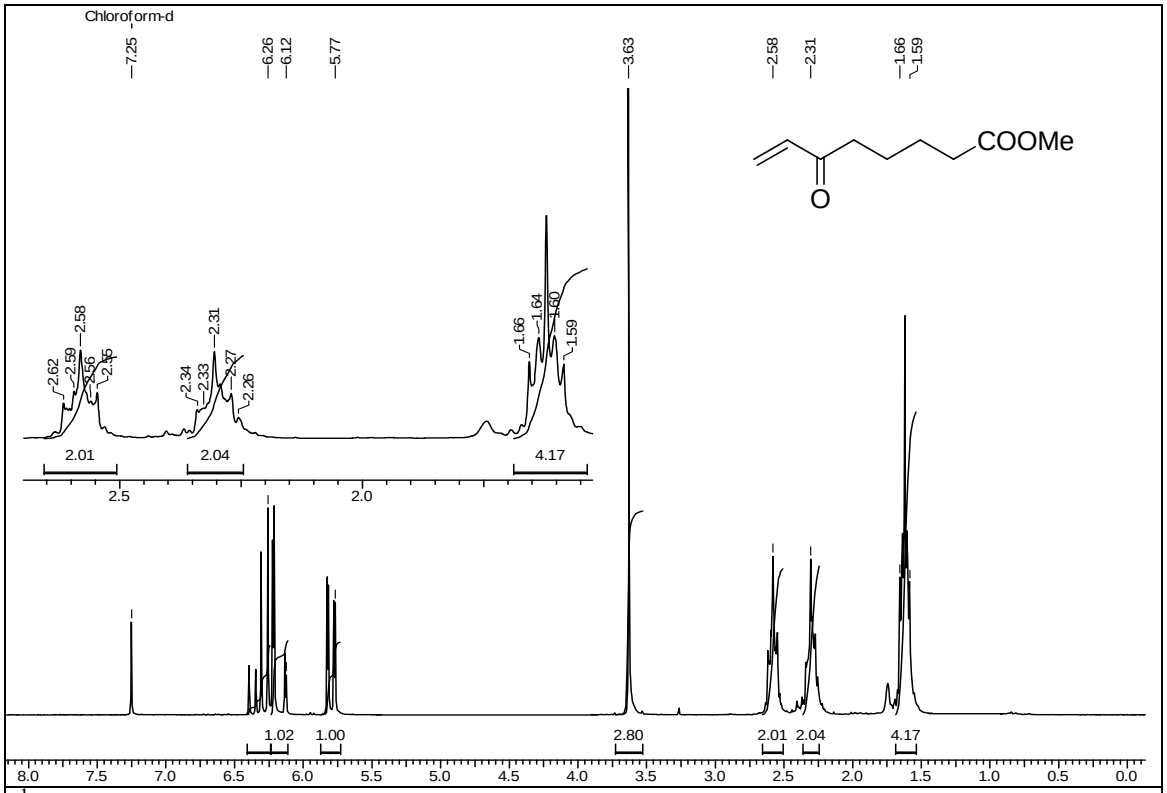
^{13}C NMR spectrum of the compound **17** in $CDCl_3$



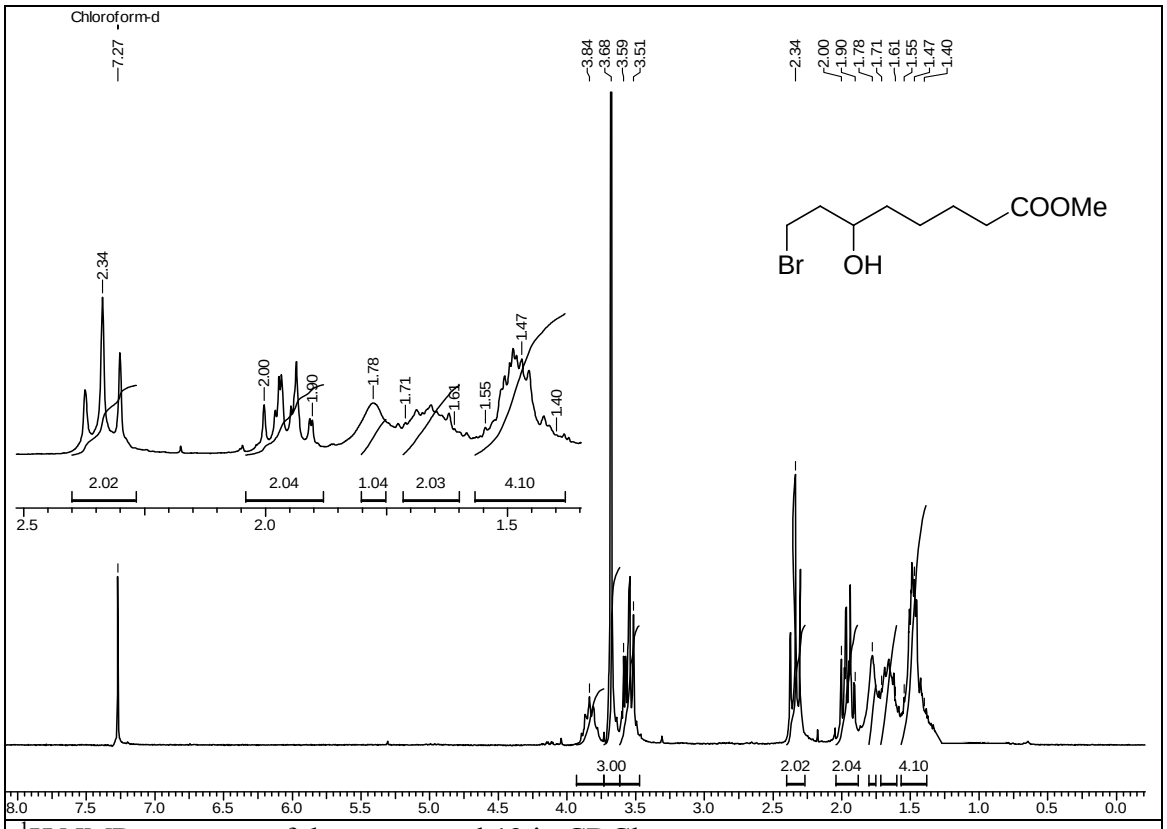
^{13}C NMR spectrum of the compound **18** in $CDCl_3$



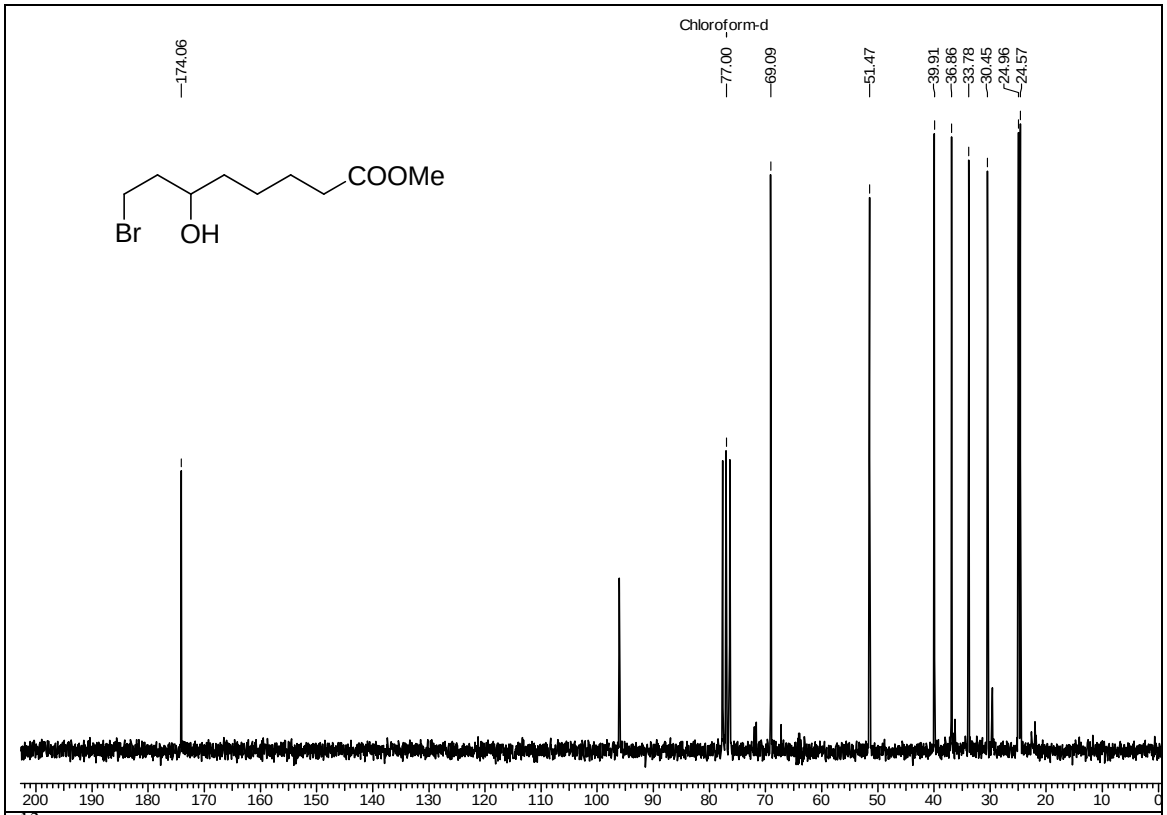
^{1}H NMR spectrum of the compound **18** in $CDCl_3$



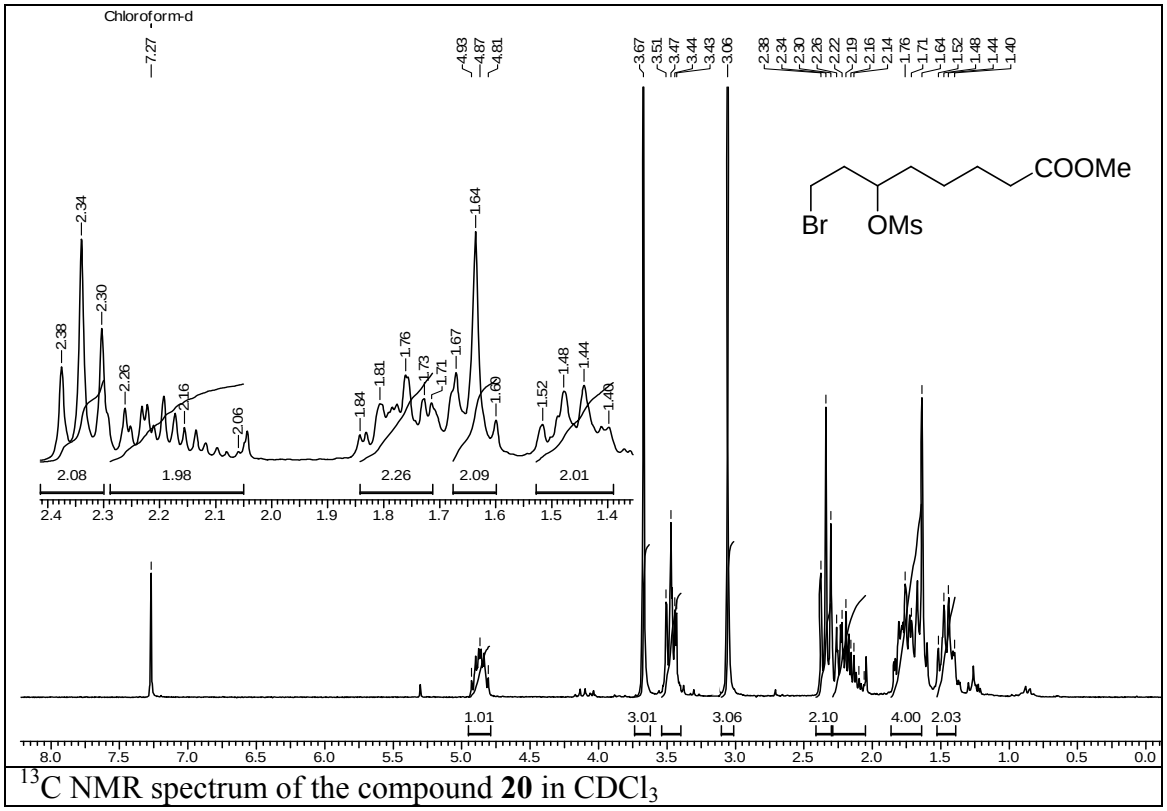
^{1}H NMR spectrum of the compound **18a** in $CDCl_3$



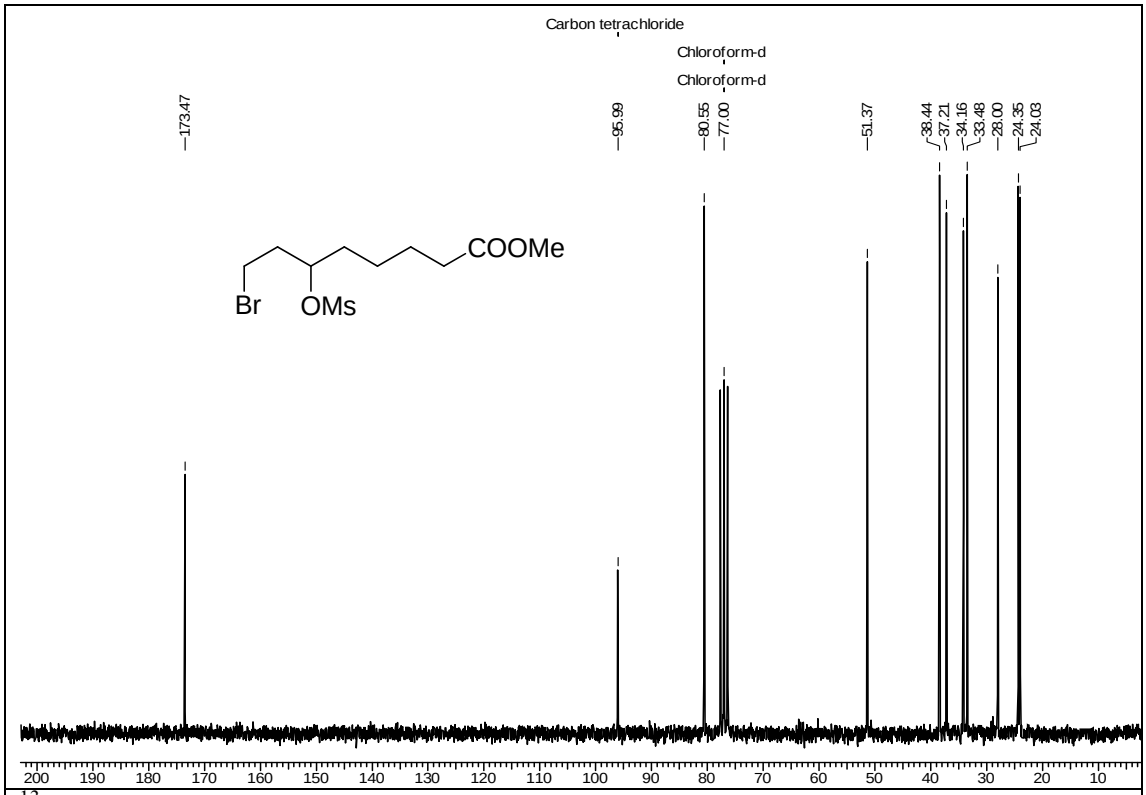
^{1}H NMR spectrum of the compound **19** in $CDCl_3$



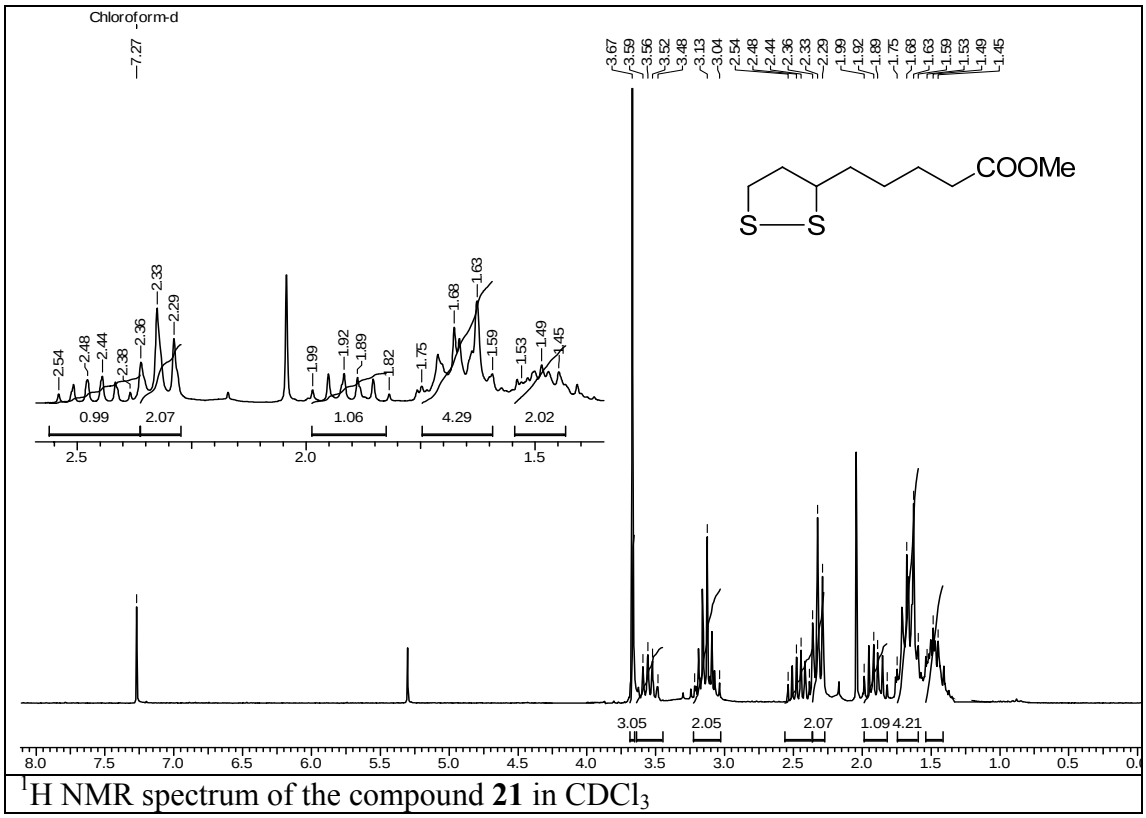
^{13}C NMR spectrum of the compound **19** in $CDCl_3$



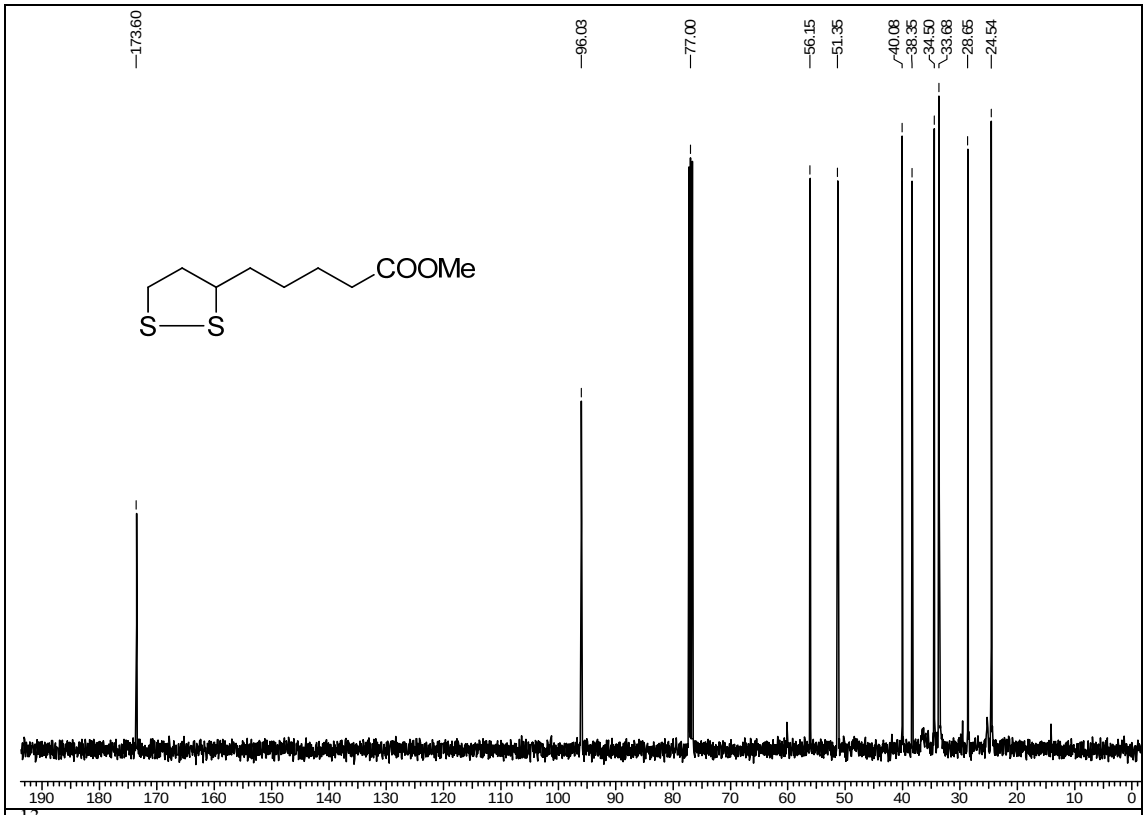
^{13}C NMR spectrum of the compound **20** in $CDCl_3$



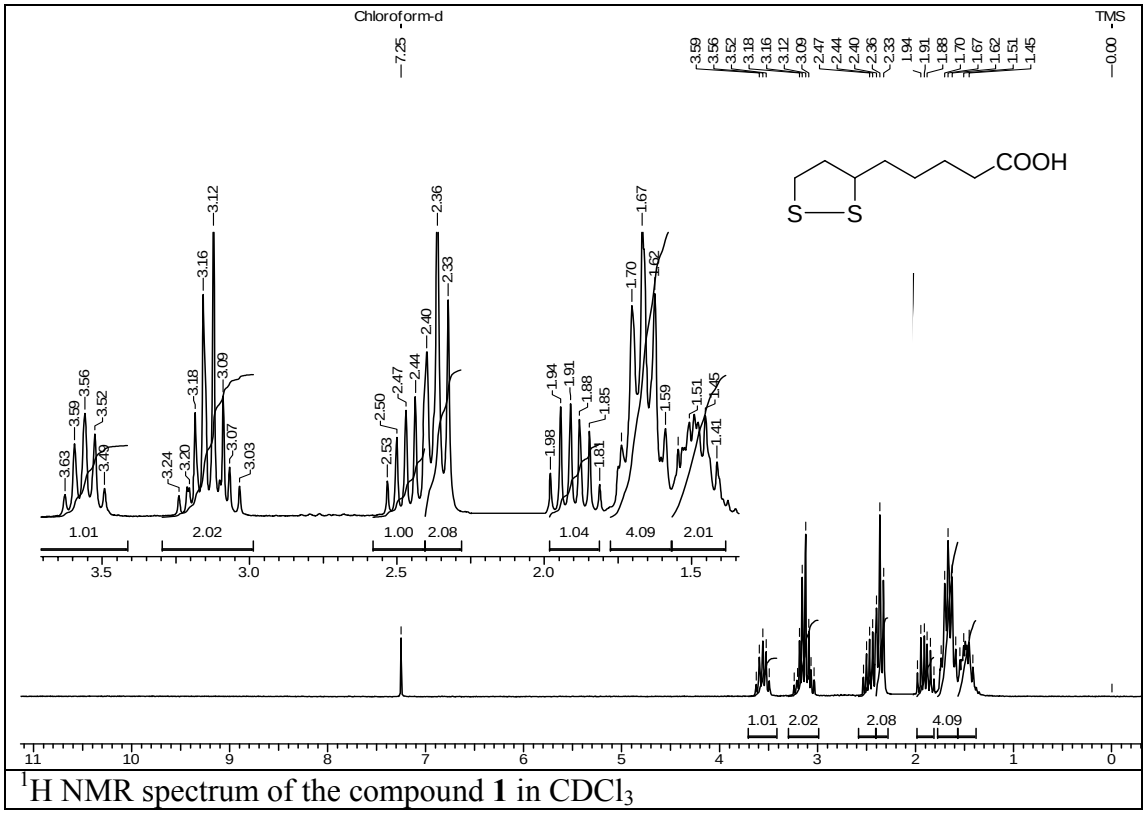
^{13}C NMR spectrum of the compound **20** in $CDCl_3$



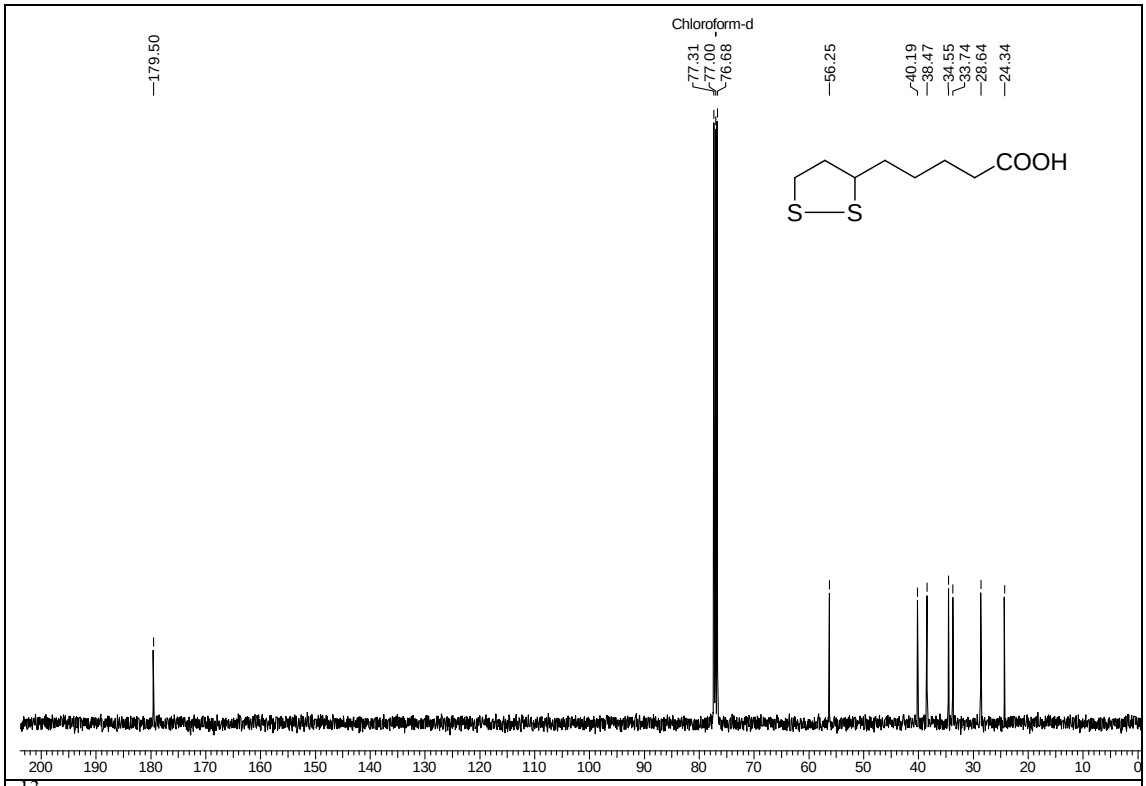
^{1}H NMR spectrum of the compound **21** in $CDCl_3$



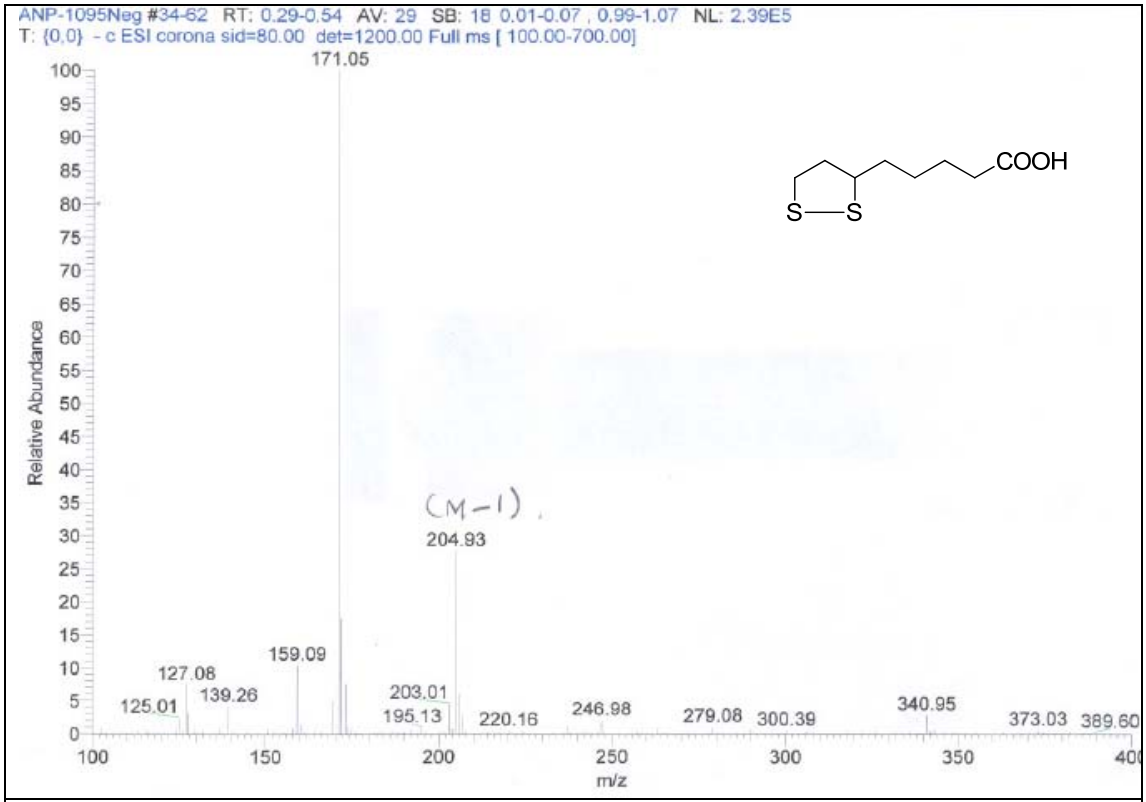
^{13}C NMR spectrum of the compound **21** in $CDCl_3$



^{1}H NMR spectrum of the compound **1** in $CDCl_3$



^{13}C NMR spectrum of the compound **1** in $CDCl_3$



LCMS chart of the compound **1** in $CDCl_3$

2.2.7. References:

1. (a) Kulinkovich, O. G.; Meijere, A. D.; *Chem. Rev.* **2000,** *100,* 2789-2834. (b) Kulinkovich, O. G. *Chem. Rev.* **2003,** *103,* 2597-2632. (c) Kulinkovich, O. G. *Eur. J. Org. Chem.* **2004,** 4517-4529. (d) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996,** *118,* 291-292.

2. (a) Kulinkovich, O. G.; Masalov, N. V.; Tyvorskii, V. I.; Kimpe, N. D.; Keppens, M.; *Tetrahedron Lett.* **1996**, *37*, 1095-1096. (b) Achmatowicz, B.; Jankowski, P.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 5589-5592. (c) Sviridov, S. V.; Vasilevskii, D. A.; Kulinkovich, O. G.; *Zh. Org. Khim.* **1991**, *27*, 1431-1433; *J. Org. Chem. USSR (Engl.Transl.)* **1991**, *27*, 1251-1253. (d) Kulinkovich, O. G.; Bagutskii, V. V. *Zh. Org. Khim. Russ.* **1997**, *33*, 898-901; *Russ. J. Org. Chem. (Engl. Transl.)* **1997**, *33*, 830- 836.

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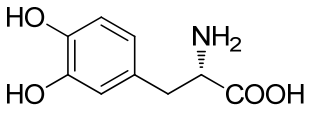
Chapter 2, Section III: Chemoenzymatic Synthesis of (R)/(S)-α-Lipoic Acid

2.3.1 Introduction:

In the recent past years, tremendous efforts have been made for the preparation of chiral compounds due to their importance in the pharmaceutical, agricultural, and food industries. Chirality is of prime significance, since most of the macromolecules in the living systems exist as single enantiomer. Since biologically active chiral drug interacts with receptor enzyme in a stereo-specific manner, and each enantiomer of the drug is discriminated by the receptor enzyme in appreciably different ways, it is very important to keep the idea of chiral discrimination or stereo-selective discrimination in mind during designing the syntheses of biologically active molecules.

As human enzymes and cell surface receptors are chiral, the two enantiomers of a drug may be absorbed, activated, or degraded in very different ways, both *in vivo* and in vitro. The two enantiomers may have unequal degree of freedom or different kind of activity. For example, one may be therapeutically effective, while the other may be ineffective or even toxic.

For example (L)-DOPA which is shown below is used in the treatment of Parkinson's disease.



L- DOPA

The active drug is the achiral compound dopamine formed from (l) - form *via* in vivo decarboxylation. As dopamine cannot cross the blood - brain barrier to reach the required site of action, the ``prodrug" (l)-form is administered. Enzyme-catalyse in vivo de-carboxylation and releases the drug in its active form (dopamine). The enzyme (l)-DOPA decarboxylase, however, discriminates both isomers and decarboxylates only the (l)-enantiomer. It is therefore essential to administrate DOPA in its pure (l)-form. Otherwise, the accumulation of (d)-DOPA, which cannot be metabolized by enzymes in the human body, may be dangerous. Hence the quest for single enantiomer is raised in past and solved in different cases such as,

(1) Only one enantiomer has the desired biological activity, and the other one does not show biological activity at all.

(2) Both the enantiomers have identical or nearly identical bioactivity.

(3) Both the enantiomers have different or opposite kinds of biological activity; and

(4) Only one enantiomer has the desired biological activity, and the other enantiomer neither shows biological activity and nor interferes in physiological action.

For example *R* enantiomer of the lipoic acid shows significant activity (100 times) in comparison with *S* enantiomer hence the enantiomer never interferes in physiological action of *R* enantiomer.[1,2] This Importance of chirality prompted us to synthesize chiral lipoic acid by chemoenzymatic route,[3] in continuation of our interest in biotransformation.

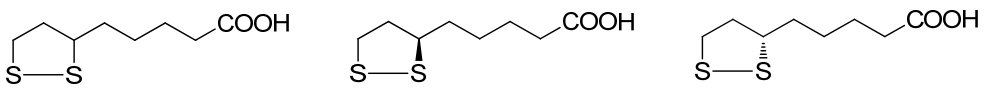
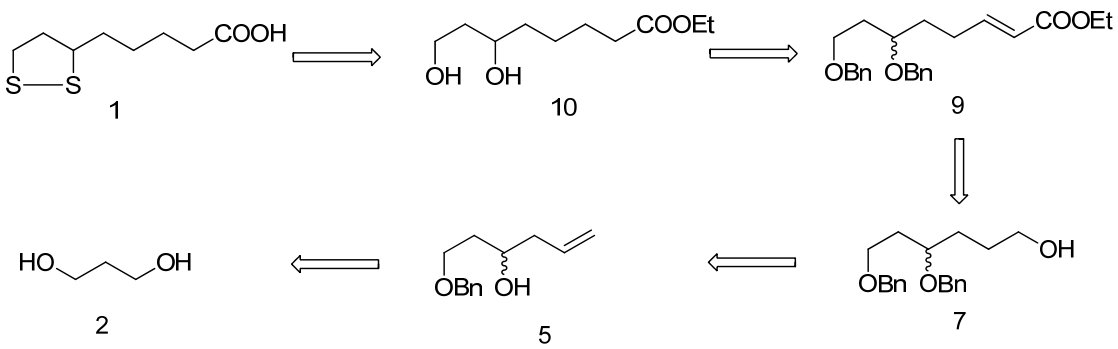


Figure 1

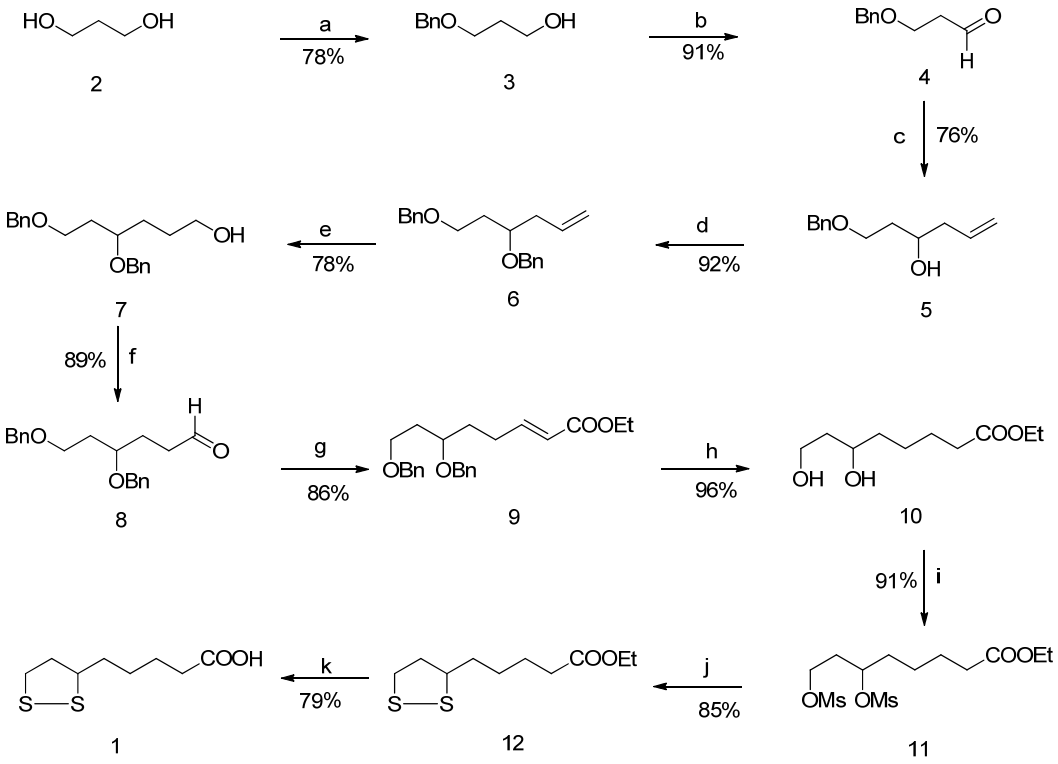
2.3.2 Present Work:

The literature review reveals formal and total syntheses of α-lipoic acid, among which some involve bio-catalytic resolution, some include organo-catalysis as key step while remaining are comprised of chiral pool synthesis. All the known methods are either of low overall yield or low feasibility of reaction or lengthy reaction sequence. Hence, we planned synthesis of α-lipoic acid from cheap and commercially available propane-1,3-diol using biocatalysis as a key step.



Scheme 1

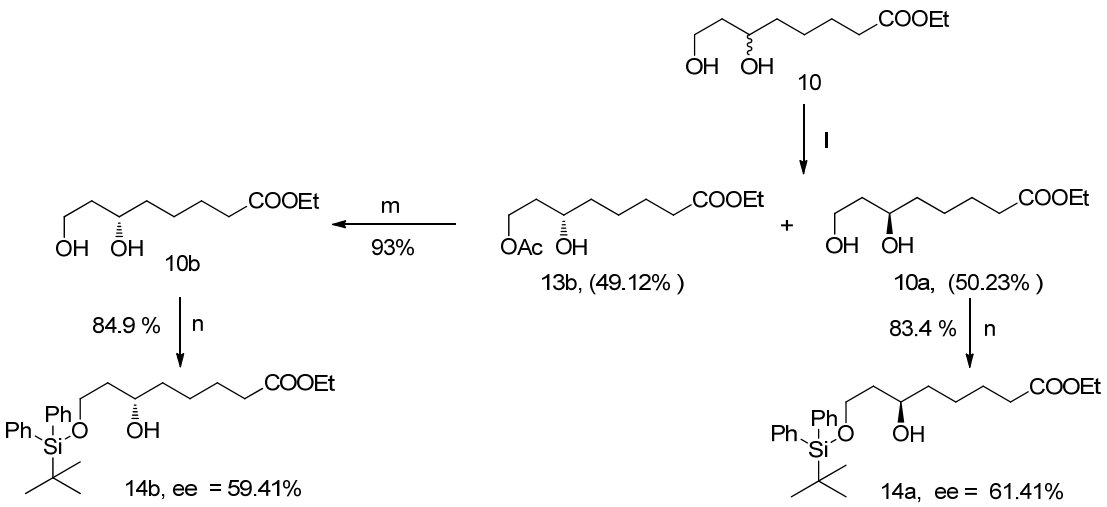
As per the retrosynthesis depicted in the scheme 1, ethyl 6,8-di hydroxyl-octanoate (**10**) is important synthon for the synthesis of α-lipoic acid which in turn can be easily synthesized from propane-1, 3-diol (**2).**



Scheme 2. *Reagents and conditions:* (a) NaH, BnBr, THF; (b) PCC, DCM, Celite; (c) Allyl-Br, Zn, THF, aq NH_4Cl; (d) NaH, BnBr, TBAI, DMF; (e) $B_2H_6.Me_2S$, THF, H_2O_2, AcONa; (f) PCC, DCM, Celite; (g) Ph_3P=CHCOOEt, THF; (h) H_2, Pd-C, ethyl acetate, RT; (i) TEA, MsCl, DCM, 0^oC-RT; (j) Na_2S, S_8, DMF, reflux; (k) KOH, EtOH, RT-12 hrs.

As shown in Scheme 2, propane-1,3-diol on treatment with sodium hydride and benzyl bromide in anhydrous THF under argon atmosphere gave intermediate **3** which on treatment with PCC afforded aldehyde **4**. Aldehyde **4** on treatment with allyl bromide and Zn in aq ammonuim chloride underwent barbier reaction and gave 1-(benzyloxy)-hex-5-en-3-ol (**5)**. This intermediate **5** on treatment with sodium hydride and benzyl bromide in anhydrous THF gave **6.** the bis benzyloxy intermediate **6** on hydroboration with $B_2H_6.Me_2S$ in dry THF produced alkyl borane, which on treatment with H_2O_2/ sodium acetate underwent rearrangement to yield 4, 6-(bis benzoloxy)-1-hexanol **(7).** This intermediate **7** on treatment with PCC afforded aldehyde **8**. Intermedaite aldehyde **8** on treatment with ethyl 2-

(triphenylphosphoranylidene)-acetate in anhydrous THF under N_2 atmosphere underwent two carbon homologation to furnish **9**, which on treatment with H_2 in anhydrous ethyl acetate, in presence of Pd as catalyst underwwent heterogeneous catalysis and give ethyl 6,8-dihydroxy octanoate (**10)**. This intermediate **10** on treatment with tri-ethyl amine and methane sulphonyl chloride in anhydrous DCM and under N_2 atmosphere give ethyl 6,8-dimesyloxy-octanoate **(11).** The intermediate **11** on treatment with sulphur powder in anhydrous DMF under anhydrous and refluxing condition furnished ethyl lipoate (**12)**, which on hydrolysis by ethanolic potassium hydroxide under N_2 atmosphere produced (±)-α-lipoic acid **(1)**. After standardizing whole protocol for (±)-α-lipoic acid **(1)**, we planned synthesis of chiral α-lipoic acid *via* enzymatic resolution of ethyl 6, 8-dihydroxy octanoate (**10) (**Scheme 3).



Scheme 3. *Reagents and conditions:* (l) CCL/ vinyl acetate, TBME; (m) K_2CO_3/ MeOH; (n) Imidazole, TBDPS-Cl, DCM

Various enzymes were employed for resolution of **10** *via* transesterifcation[3] by vinyl acetate in TBME solvent at RT. During the enzymatic transesterfication we observed that CCL enzyme acylated one enantiomer of diol **10** to yield **13b** whereas other enantiomer remained unreacted as diol **10a** (scheme 3). The intermediate **13b** was further treated with potassium carbonate and anhydrous methanol at RT to produce chiral **10b**. Optical purity of **10a** and **10b** were determined and compared with specific rotation values reported in literature and it was the the ee values were low. The enantiomeric purities of these compounds were also determined by Chiral

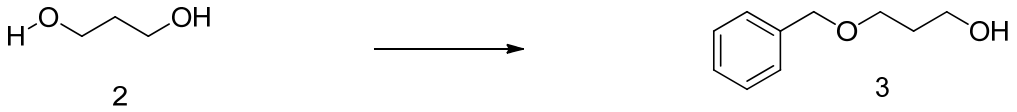
HPLC after converting them to their corresponding TBDPS derivatives (**14a, 14b**). Chiral HPLC analysis confirmed the low selectivity (59-61%) of enzyme used for the transesterification of diol **10**.

2.3.3. Conclusion

A new protocol for synthesis of (±)-α-Lipoic Acid was successfully demonstrated from propane-1,3-diol. Efforts towards the chemoenzymatic synthesis of chiral lipoic acid indicated that further work in in screening new enzymes could afford enantiomerically pure lipoic acid.

2.3.4. Experimental

Preparation of 3-(benzyloxy) propan-1-ol (3)

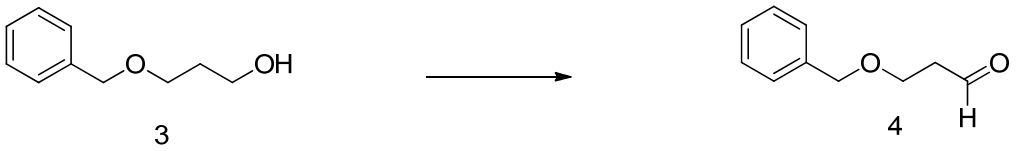


To the stirred solution of 1,3-propanediol (**2)** (25 gm, 0.329 mol) in THF (200 mL) sodium hydride (60 %, 16.45 gm, 0.411 mole, 1.25 eq) was added at 0°C and stirred at the same temperature. After ½ hour, benzyl bromide (70.32 gm, 0.411 mol, 1.25 eq.) and catalytic amount of TBAI were added and stirring continued at the same temperature for 6 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated on rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (8:2) as eluent to afford, 3-(benzyloxy)-propan-1-ol **(3).**

Yield: 42.62 gm (78%); colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 1H), 2.39-2.52 (m, 2H), 3.06 (m, 2H), 4.02 (t, *J*= 6.06 Hz, 2H), 5.00 (s, 2H), 7.83 (bs, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.02, 61.24, 68.87, 73.06, 127.53, 128.30, 137.97

ppm; Elemental Anal.Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.45.

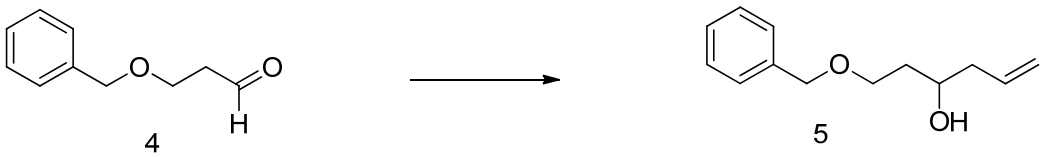
Preparation of 3-(benzyloxy)propanal (4)



To the stirred solution of 3-(benzyloxy)-propan-1-ol **(3)** (40 gm, 0.24 mol) in anhydrous DCM (500 mL), PCC (69.6 g, 0.3 mol, 1.25 eq) was added and kept for stirring at room temperature for ½ hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was stopped and the reaction mixture was filtered through celite bed. The celite bed was washed with DCM (50 mL), and combined organic layers was dried over anhydrous sodium sulphate and evaporated over rotaevaporator to afford crude residue. The residue was purified by alumina column chromatography using petroleum ether/ ethyl acetate (95: 5) as eluent to afford 3-(benzyloxy)-propanal **(4)**.

Yield: 35.97 gm (91%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77-1.90 (m, 2H), 3.39 (t, *J*= 6.98 Hz, 2H), 4.38 (s, 2H), 7.21 (s, 5H), 9.65 (t, *J*= 1.52 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.02, 68.87, 73.06, 127.53, 128.30, 137.97, 201.49 ppm.

Preparation of 1-(benzyloxy)-hex-5-en-3-ol (5)

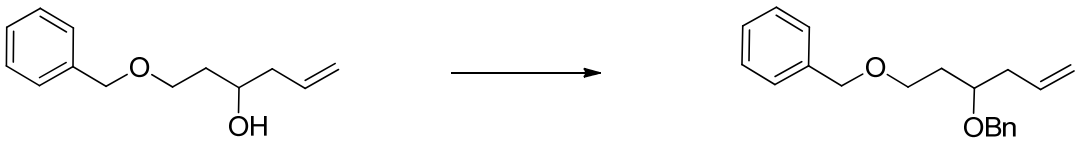


To the stirred solution of aldehyde **4** (30 gm, 0.183 mol) in dry THF, saturated solution of aq ammonium chloride (30 gm/ 100 ml) and Zn dust (23.42 gm, 0.366 mmol, 2 equi) were added. After ½ hr, allyl bromide (43.92 gm, 0.366 mol, 2 eq) was added slowly portion wise over 30 min at 30 °C and stirring was continued further for 6 hrs. The progress of the reaction was monitored by TLC.

After completion of the reaction, the reaction was mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated on rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (8:2) as eluent to furnish, 1-(benzyloxy)-hex-5-en-3-ol **(5):**

Yield: 28,63 gm (76%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.71 (m, 2H), 2.15 (t, *J*= 6.71 Hz, 2H), 2.88 (s, 1H), 3.51-3.63 (m, 2H), 3.74-3.80 (m, 1H), 4.43 (s, 2H), 4.97-5.07 (m, 2H), 5.64-5.85 (m, Hz, 1H), 7.21-7.25 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.82, 41.87, 68.70, 70.06, 73.17, 117.42, 127.54, 127.61, 128.33, 134.78, 137.88 ppm. Elemental Anal.Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.74; H, 8.84.

Preparation of 1, 3-(bis-benzyloxy)-hex-5-ene (6)

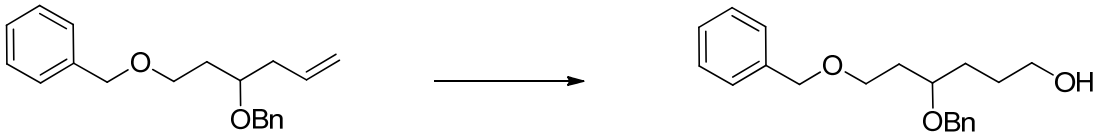


5 6

To the stirred solution of 1-(benzyloxy)hex-5-en-3-ol **(5)** (25 g, 0.12 mol) in dry THF (200 mL) was added sodium hydride (60%, 6 gm, 0.15 mol, 1.25 eq) at 0°C. After ½ hour, benzyl bromide (41.51gm, 0.24 mol, 2 eq) and catalytic amount of TBAI were added and stirring continued at the same temperature for 6 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated on rotavapor to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (95:5) as eluent to furnish 1, 3-(bis-benzyloxy)-hex-5-ene (**6**).

Yield: 33.04 gm (92%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69-1.78 (m, 2H), 2.25 (t, *J*= 6.41 Hz, 2H), 3.43-3.52 (m, 3H), 3.52-3.64 (m, 1H), 4.31-4.51 (m, 4H), 4.95-5.04 (m, 2H), 5.66-5.87 (m, 1H), 7.21-7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.28, 38.49, 66.75, 71.16, 72.89, 75.50, 117.13, 127.62, 127.71, 128.23, 128.27, 134.58, 138.44, 138.69 ppm. Elemental Anal.Calcd for $C_{13}H_{18}O_2$: C, 81.04; H, 8.16. Found: C, 81.09; H, 8.21.

Preparation of 1, 3-(bis-benzyloxy) hexan-1-ol (7)

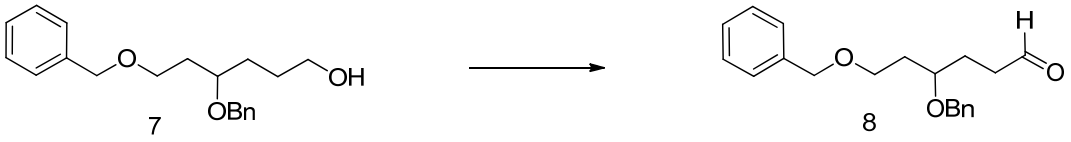


6 7

To the stirred solution of 1, 3-(bis-benzyloxy) hex-5-ene **(6)** (10 gm, 0.0338 mol) in dry THF (20 mL) at 0°C was added $B_2H_6.Me_2S$ (4.268 gm, 0.0423 mol, 1.25 equi, 2M in toluene, 24 mL). After stirring for 3 hr at 0°C, H_2O_2 (4.8 mL) was added and reaction mixture was allowed to attain the room temperature with stirring. Thereafter, aq solution of sodium acetate (10 ml) was added slowly portion-wise at 0 °C and further stirred for 1 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched slowly by addition of methanol at 0°C. The excess of methanol was evaporated under vacuum. This reaction mixture was then poured into water (50 mL) and extracted with ethyl acetate (2 × 250 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated on rotaevaporator to get the crude residue. The crude residue was purified by silica gel column chromatography to afford 1, 3-(bis-benzyloxy)-hexan-1-ol **(7).**

Yield: 8.274 g (78%); colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49-1.60 (m, 4H), 1.71-1.84 (m, 2H), 3.44-3.50 (m, 4H), 3.51-3.59 (m, 1H), 4.39-4.42 (m, 4H), 7.21-7.26 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.03, 30.24, 33.95, 62.38, 66.66, 70.92, 72.75, 75.79, 127.35, 127.49, 127.65, 127.82, 128.13, 138.17, 138.36 ppm. Elemental Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.4; H, 8.33. Found: C, 76.44; H, 8.38.

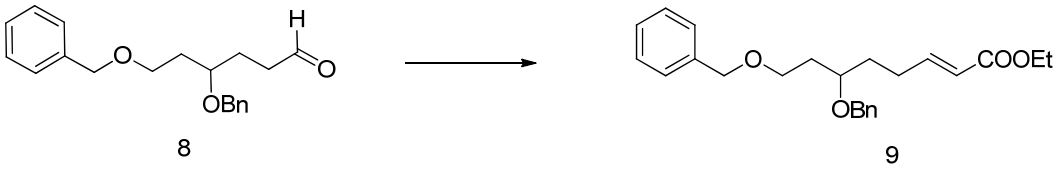
Preparation of 1, 3-(bis-benzyloxy)-hexanal (8)



To the stirred solution of 1, 3-(bis-benzyloxy)hexanol **(7)** (8 gm, 0.0255 mol) in anhydrous DCM (100 mL), PCC (7.38 gm, 0.031 mol, 1.25 eq)) and celite (8 gm) were added at room temperature and kept on stirring for ½ hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was was filtered through celite bed. The celite bed was washed with DCM (50 mL), and collected with filterate. Combined organic layers were concentrated on rotary evaporator to afford 1,3-(bis-benzyloxy)-hexanal **(8).** Since the comound **8** is unstable, we confirmed formation of compound **8** only by IR spectrometry and used it as such for further reaction.

Yield: 7.0743 gm (89%); yellow oil; IR ($CHCl_3$): ν_{max} 3069, 3007, 2949, 2839, 2356, 2045, 1719, 1577, 1513, 1251 and 742 cm^{-1}.

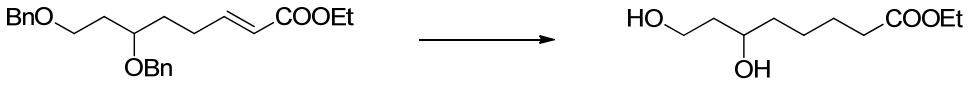
Preparation of (E)-ethyl-6, 8-bis-(benzyloxy)-oct -2-enoate (9)



Ethyl 2-(triphenylphosphoranylidene)-acetate (15.6 gm, 0.045 mol, 2eq.) was added to stirred solution of 1, 3-(bis-benzyloxy)-hexanal **(8)** (7 gm, 0.0225 mol) in THF under N_2 atmosphere and the reaction mixture was stirred for another 2 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through the celite bed and concentrated under vacuum to obtain crude product. The crude residue was purified by silica gel flash column chromatography to afford unsaturated ester (E)-ethyl 6,8-bis-(benzyloxy)-oct-2-enoate **(9).**

Yield: 7.37 gm (86%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J*= 7.15 Hz, 3H), 1.55-1.79 (m, 4H), 2.18-2.21 (m, 2H), 3.45-3.54 (m, 3H), 4.09 (q, *J*= 7.20 Hz, 2H), 4.39 (s, 4H), 5.71 (d, *J*= 15.66 Hz, 1H), 6.80-6.95 (m, 1H), 7.15-7.26 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.24, 19.36, 27.46, 34.94, 36.28, 60.04, 66.81, 70.16, 72.75, 121.14, 127.43, 127.53, 128.26, 129.60, 134.13, 135.83, 138.36, 148.90, 166.59 ppm; Elemental Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.41; H, 7.94.

Preparation of (E)-ethyl 6, 8-dihydroxyoctanoate (10)

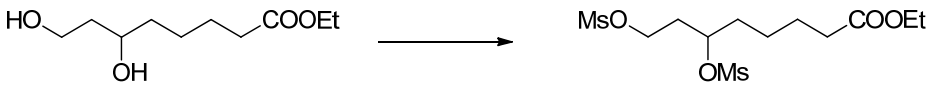


9 10

To the stirred solution of (E)-ethyl 6,8-bis-(benzyloxy)-oct-2-enoate **(9)** (7.00 gm, 0.0183 mol) in ethyl acetate (50 mL), was added 10% Pd/C (100 mg) and stirred under H_2 balloon pressure for 2 hrs. the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a bed of celite and concentrated under vacuum to obtain crude product. The crude residue was purified by flash column chromatography to afford ethyl 6, 8-dihydroxyoctanoate **(10).**

Yield: 3.58 gm (96%); yellow oil; IR ($CHCl_3$) ν_{max} 3020, 2400, 1731, 757 cm^{-1};
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.20 Hz, 3H), 1.36-1.43 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.30 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H) ppm. Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.84; H, 9.92.

Preparation of ethyl 6, 8-bis((methylsulphonyl)oxy) octanoate (11)



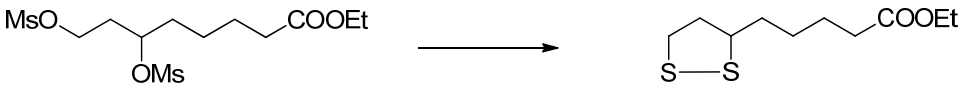
10 11

To the stirred solution of ethyl 6, 8-dihydroxyoctanoate **(10)** (0.500 gm, 0.0025 mol) in anhydrous CH_2Cl_2 (25 mL), was added Et_3N (1.01 gm, 0.01 mole, 4 eq) at 0°C and

$MeSO_2Cl$ (0.653 gm, 6 mL, 0.057 mol, 2.25 eq) dropwise. After addition, the reaction mixture was allowed to attain to attain room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude residue. This crude residue was purufued by silica gel column chromatography to afford Ethyl 6, 8 bis((methylsulphonyl)oxy)-octanoate **(11).**

Yield: 0.803 gm (91%); yellow viscouss oil**;** ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J*= 7.19 Hz, 3H), 1.49-1.74 (m, 4H), 2.01-2.06 (m, 2H), 2.25 (t, *J*= 7.30 Hz, 2H), 2.99-3.09 (m, 6H), 4.00-4.11 (m, 2H), 4.13-4.32 (m, 4H), 4.90- 4.98 (m, 1H) ppm. Elemental Anal. Calcd for $C_{12}H_{24}O_8S_2$: C, 39.99; H, 6.71; S, 17.79. Found: C, 39.94; H, 6.76; S, 17.81.

Preparation of ethyl 5-(1, 2-dithiolan-3-yl)-pentanoate (12)



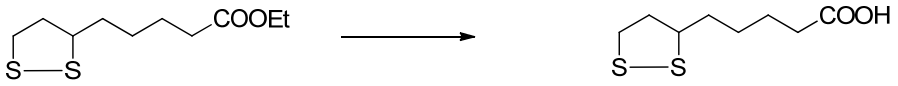
11 12

To the stirred solution of ethyl 6,8-bis((methylsulphonyl)oxy)-octanoate **(11)** (0.500 gm, 0.0014 mol) in anhyd DMF (10 mL), finely ground $Na_2S{\cdot}H_2O$ (0.218 gm, 0.0028 mol, 2 eq) and sulfur (90 mg, 0.00218 mol, 2 eq) were added in inert atmosphere and heated at 80 °C for 24 h and then stirred at room temperature for 1h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice-cold water (15 mL) and was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhyd Na_2SO_4, filtered and evaporated under reduced vacuum to furnish crude residue. This crude residue was purified by silica gel column chromatography to afford 276 mg (85%) of ethyl 5-(1, 2-dithiolan-3-yl)-pentanoate (ethyl lipoate) **(12)** as a yellow oil.

Yield: 0.276 gm (85%); yellow oil; IR ($CHCl_3$) νmax 3020, 2400, 1731, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J*= 7.19 Hz, 3H), 1.45-1.51 (m, 2H), 1.61-1.70 (m, 4H), 1.84-1.94 (m, 1H), 2.30 (t, *J*= 7.29 Hz, 2H), 2.36-2.53 (m, 1H), 3.03-3.20

(m, 2H), 3.49-3.62 (m, 1H), 4.06- 4.16 (q, *J*= 7.21 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 ppm. Elemental Anal. Calcd for $C_{10}H_{18}O_2S_2$: C, 51.24; H, 7.74; S, 27.36. Found: C, 51.30; H, 7.79; S, 27.41.

Preparation of 5-(1, 2-dithiolan-3-yl)-pentanoic acid or α-Lipoic acid (1)



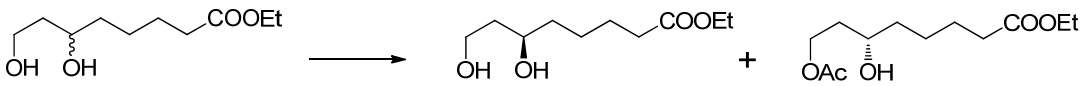
12 1

To the stirred solution of ethyl 5-(1, 2-dithiolan-3-yl)-pentanoate-(ethyl lipoate) **(12)** (200 mg, 0.0008547 mol) in MeOH (5 mL) was added aqueous KOH (0.1M, 5 mL) and stirred at room temperature for 24 h. the progress of the reaction was monitored by TLC. After completion of the reaction, the methanol was evaporated under reduced pressure and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2.

The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude lipoic acid. The resulting residue was purified by flash column chromatography (silica gel) using ethyl acetate-petroleum ether (15:85) as an eluent, to afford lipoic acid **1** as yellow solid.

Yield: 176 mg (79%); yellow solid; mp 48 °C; (Lit[1] 48°C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41- 1.55 (m, 2H), 1.59-1.75 (m, 4H), 1.81-1.98 (m, 1H), 2.36-2.53 (m, 3H), 3.03-3.24 (m, 2H), 3.49-3.63 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm. Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.08. Found: C, 46.59; H, 6.87; S, 31.17.

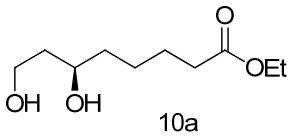
Enzymatic resolution of ethyl 6, 8-dihydroxyoctanoate (10)



10 (10a), 50.23 % (13b), 49.12 %

To the solution of ethyl 6, 8-dihydroxyoctanoate (**10**) (0.500 gm, 0.0025 mol) in TBME, was added vinyl acetate (0.4365 gm, 0.005 mol) and enzyme CCL and the reaction was stirred for 48 hrs. The progress of the reaction was monitored by TLC. After 50% trans acylation (50% consumption of starting material) the reaction was stopped and filtered over celite bed. Celite bed was washed with ethyl acetate and all washings along with filtrate collected together and concentrated under vacuum to get crude residue. Crude residue on flash column chromatography gave **10a** and **13b**.

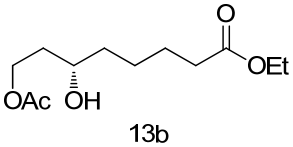
(R)-Ethyl-6, 8-dihydroxyoctanoate (**10a**)



10a

Yield: 251 mg (50.23%); yellow viscous oil; $[\alpha]_D$= +0.91 (c 2.00, Benzene){Lit[4] $[\alpha]_D$= +1.23 (c 1.62, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.29 Hz, 3H), 1.33-1.47 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.19 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 172.95 ppm.; Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.85; H, 9.91.

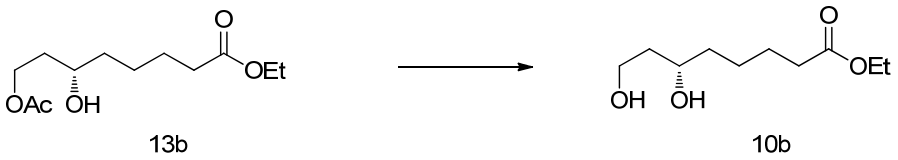
(R)-Ethyl-6-hydroxy8-acetoxy octanoate (**13b**)



13b

Yield: 296 mg (49.12%); yellow solid; mp 48°C; $[\alpha]_D$= +8.20 (c 1.00, $CHCl_3$){Lit.[5] $[\alpha]_D$= +12.80 (c 1.00 , $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J*= 7.16 Hz, 3H), 1.31-1.35 (m, 2H), 1.39-146 (m, 4H), 1.52-1.72 (m, 4H), 2.05 (s, 3H), 2.30 (t, *J*= 7.29 Hz, 2H), 3.65 (brs, 1H), 4.07-4.41 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.22, 20.98, 24.75, 25.12, 29.67, 34.19, 36.37, 37.01, 60.26, 61.72, 68.35, 171.49, 173.71 ppm. Elemental Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00; Found: C, 58.49; H, 9.04.

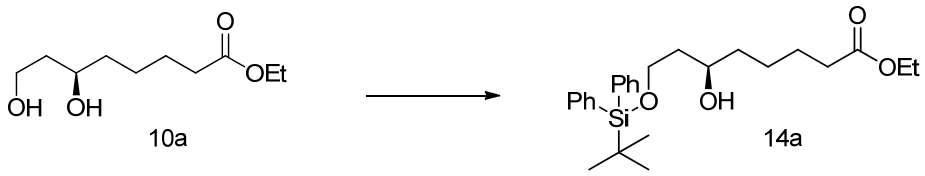
Preparation of (S) ethyl-6, 8-dihydroxyoctanoate (10b)



To the stirred solution of **13b** in methanol was added potassium carbonate (0.250 gm, 0.0011mole) and stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered over celite bed. Celite bed was washed with methanol and all washings along with filtrate were collected together and concentrated under vacuum to get crude residue. The resulting residue was purified by flash column chromatography (silica gel) using ethyl acetate-petroleum ether (25:85) as an eluent, to afford **10 b.**

Yield: 192 mg (93 %); yellow viscous liquid; $[\alpha]_D$= -0.9 (c 2.00, $CHCl_3$){Lit.[4] $[\alpha]_D$= -1.23 (c 1.62, $CHCl_3$)}; IR ($CHCl_3$) ν_{max} 3018, 2934, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.29 Hz, 3H), 1.33-1.47 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.19 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 76.36, 172.95 ppm. Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.85; H, 9.91.

Preparation of (R) ethyl 8-((tert-butyldiphenylsilyl)-oxy)-6-hydroxyoctanoate (14a)

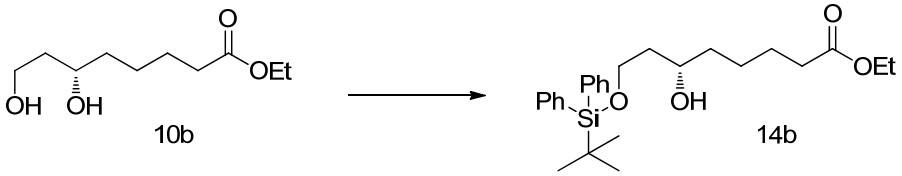


To the stirred solution of (R) ethyl-6, 8-dihydroxyoctanoate **(10a)** (200 mg, 0.009798 mol) in dry DCM (20 mL) was added imidazole (133 mg, 0.0195 mol, 2 eq) at 0°C. After stirring for 30 min, TBDPS-Cl (268 mg, 0.0097 mol, 0.27ml, 1 eq) was added portion wise with syringe and further stirring was continued for 12 hr at the same temperature. The progress of the reaction was monitored by TLC.

After completion of the reaction, the reaction mixture was quenched with cold water at 0 °C and extracted with DCM (2 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. The crude residual oil was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (75:25) as eluent to furnish (R)-ethyl 8-((tert-butyldiphenylsilyl)oxy)-6-hydroxyoctanoate **(14a).**

Yield: 360 mg (83.4 %); yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.18 (t, *J*= 7.15 Hz, 3H), 1.34-1.41 (m, 4H), 1.55-1.62 (m, 4H), 2.24 (t, *J*= 7.40 Hz, 2H), 3.29 (brs, 1H), 3.75-3.84 (m, 3H), 3.99-4.10 (q, *J*= 7.16 Hz, 2H), 7.25-7.37 (m, 5H), 7.58-7.62 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.22, 18.97, 24.95, 25.11, 26.76, 34.29, 37.09, 38.23, 60.18, 63.66, 71.68, 127.76, 129.83, 132.82, 132.92, 135.53, 173.77 ppm.

Preparation of (S)-ethyl 8-((tert-butyldiphenylsilyl)-oxy)-6-hydroxyoctanoate (14b)

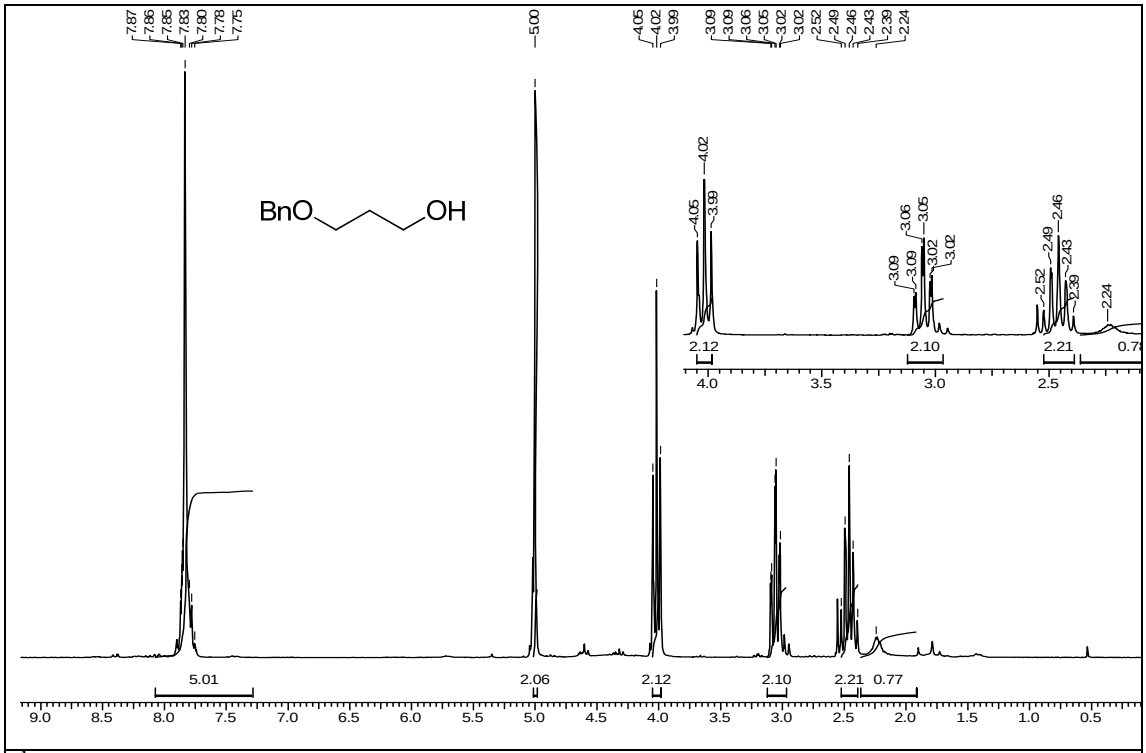


To the stirred solution of (S) ethyl-6, 8-dihydroxyoctanoate **10b** (192 mg, 0.009412 mol) in dry DCM (20 mL) was added imidazole (128 mg, 0.018824 mol, 2 eq) at 0 °C. After stirring for 30 min, TBDPS-Cl (258 mg, 0.009412 mmol, 0.25 ml, and 1eq) was added portion wise with syringe and stirred further for 12 hr at the same temperature. The progress of the reaction was monitored by TLC.

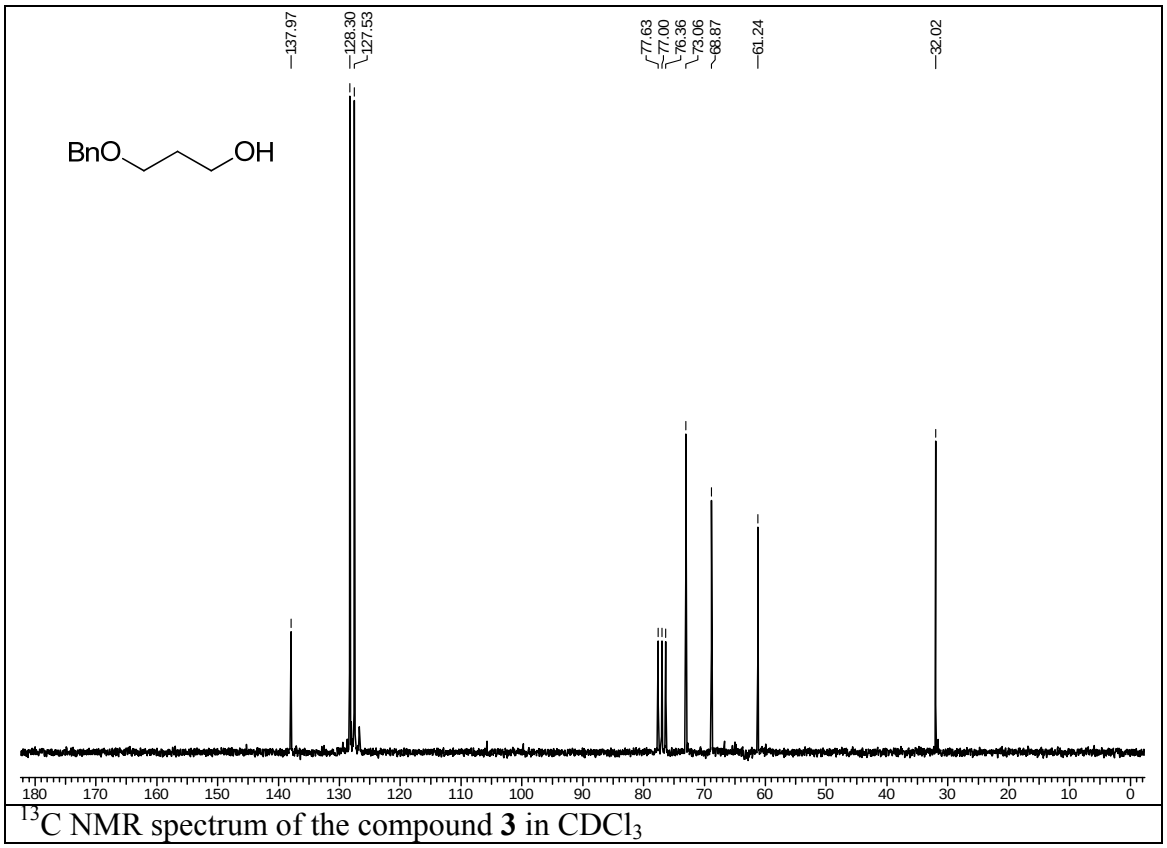
After completion of the reaction, the reaction mixture was quenched with cold water at 0 °C and extracted with DCM (2 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. The crude residual oil was purified by silica gel column chromatography using petroleum petrolium ether / ethyl acetate (75:25) as eluent to furnish (S) ethyl 8-((tert-butyldiphenylsilyl) oxy)-6-hydroxyoctanoate **14b.**

Yield: 349 mg (84.9 %); yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.18 (t, *J*= 7.15 Hz, 3H), 1.34-1.41 (m, 4H), 1.55-1.62 (m, 4H), 2.24 (t, *J*= 7.40 Hz, 2H), 3.29 (brs, 1H), 3.75-3.84 (m, 3H), 3.99-4.10 (q, *J*= 7.16 Hz, 2H), 7.25-7.37 (m, 5H); 7.58-7.62 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.22, 18.97, 24.95, 25.11, 26.76, 34.29, 37.09, 38.23, 60.18, 63.66, 71.68, 127.76, 129.83, 132.82, 132.92, 135.53, 173.77 ppm.

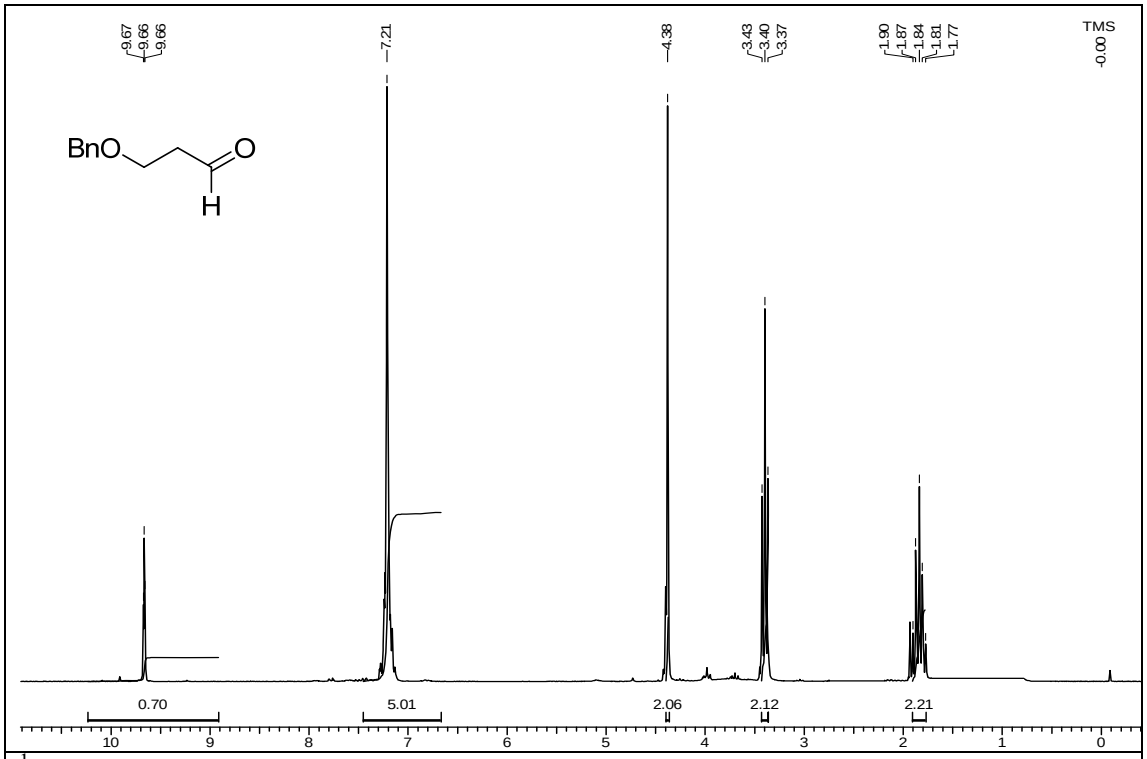
2.3.5. Analytical Data



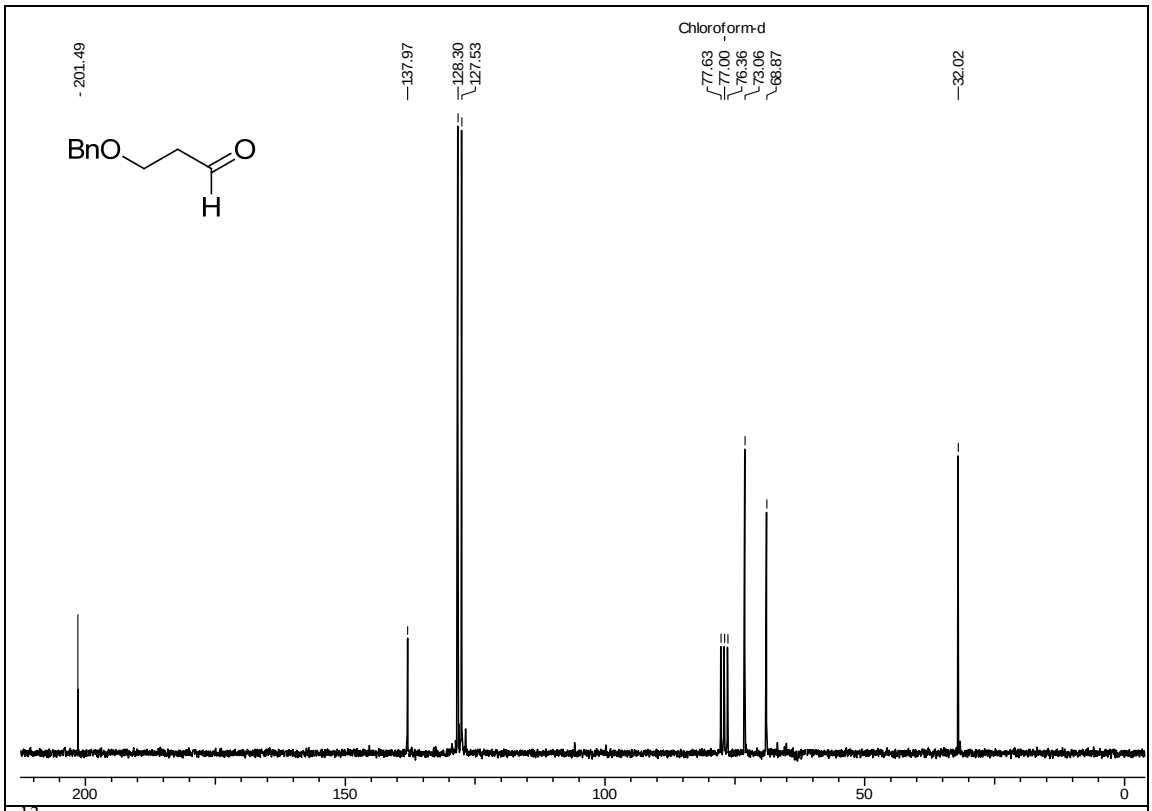
^{1}H NMR spectrum of the compound **3** in $CDCl_3$



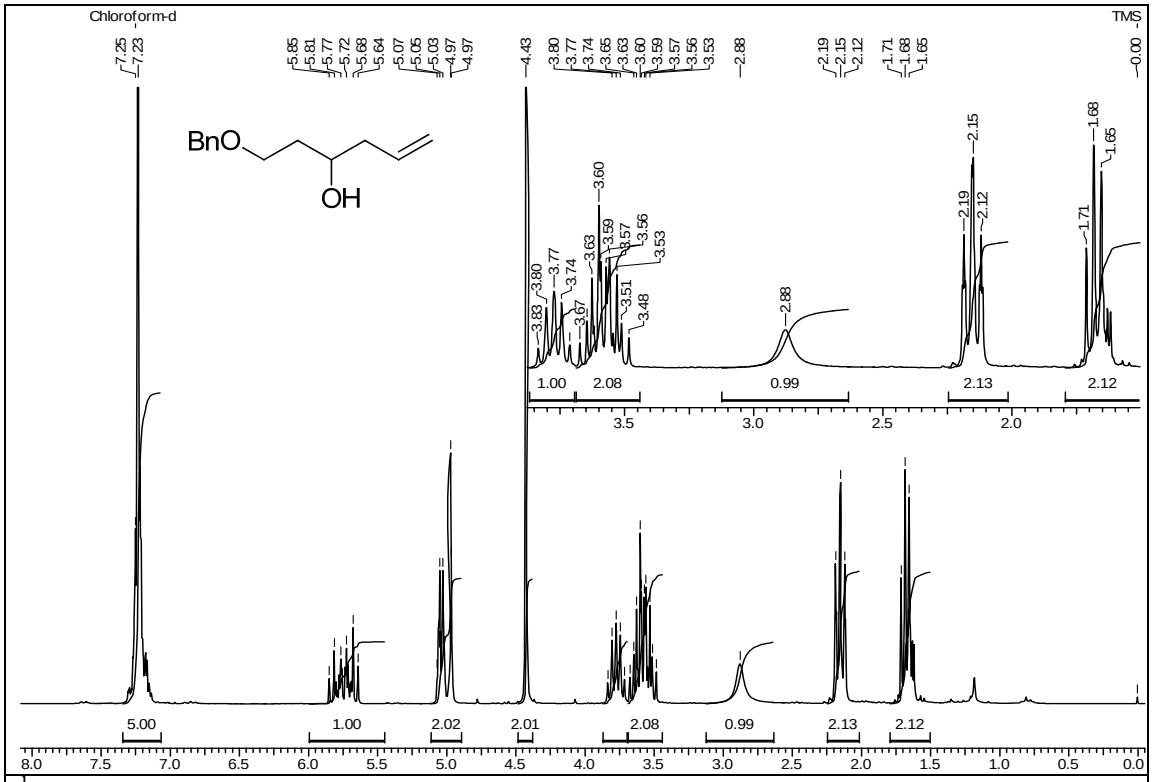
^{13}C NMR spectrum of the compound **3** in $CDCl_3$



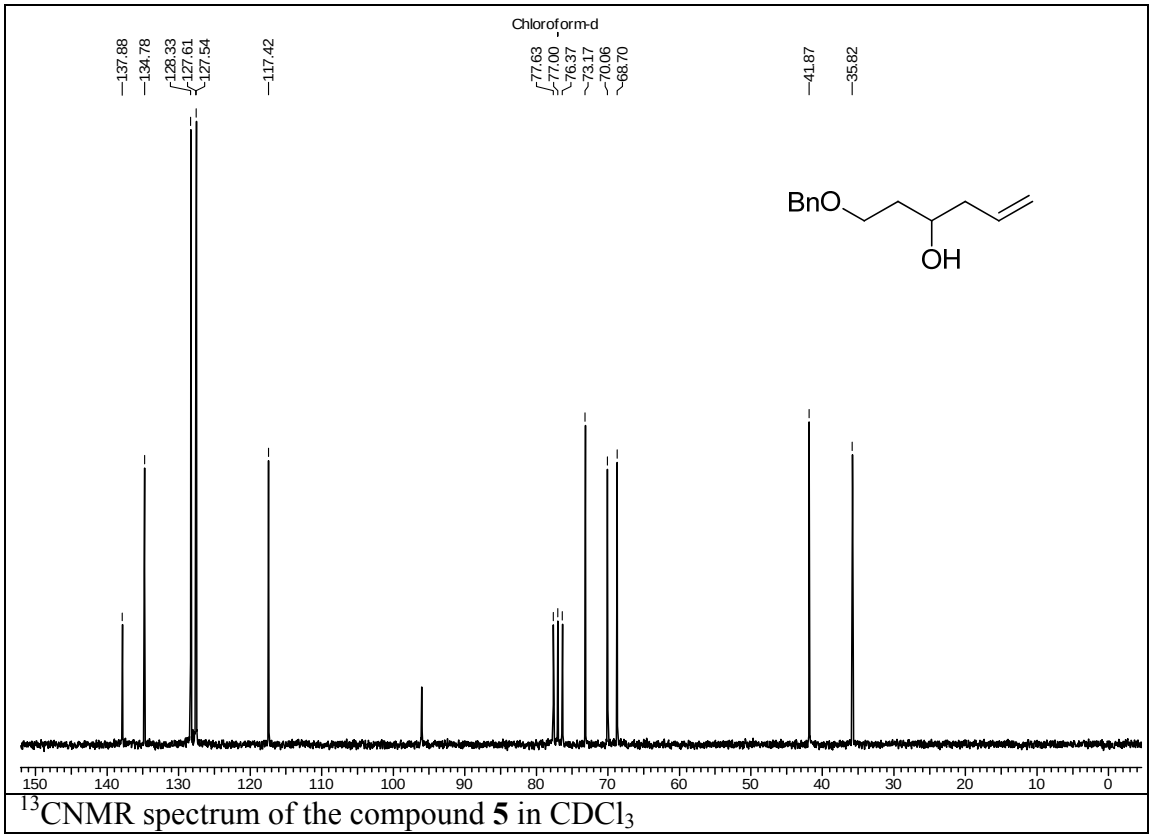
^{1}H NMR spectrum of the compound **4** in $CDCl_3$



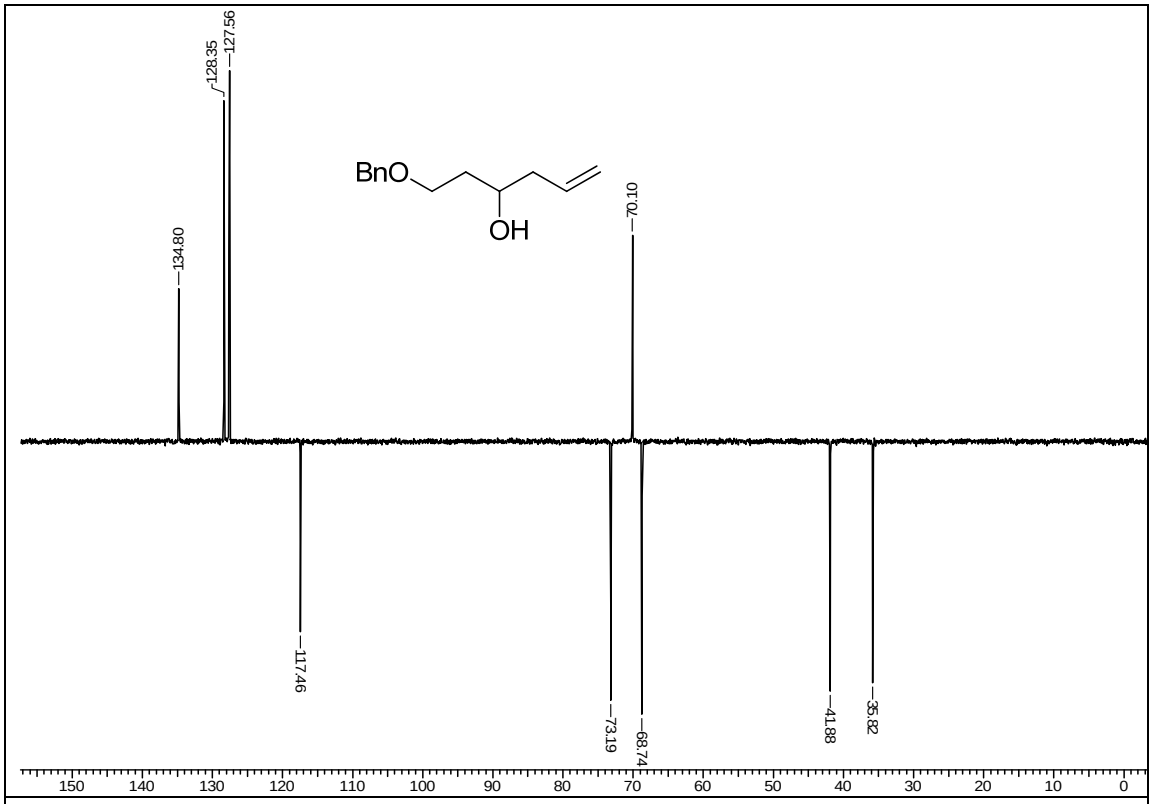
^{13}CNMR spectrum of the compound **4** in $CDCl_3$



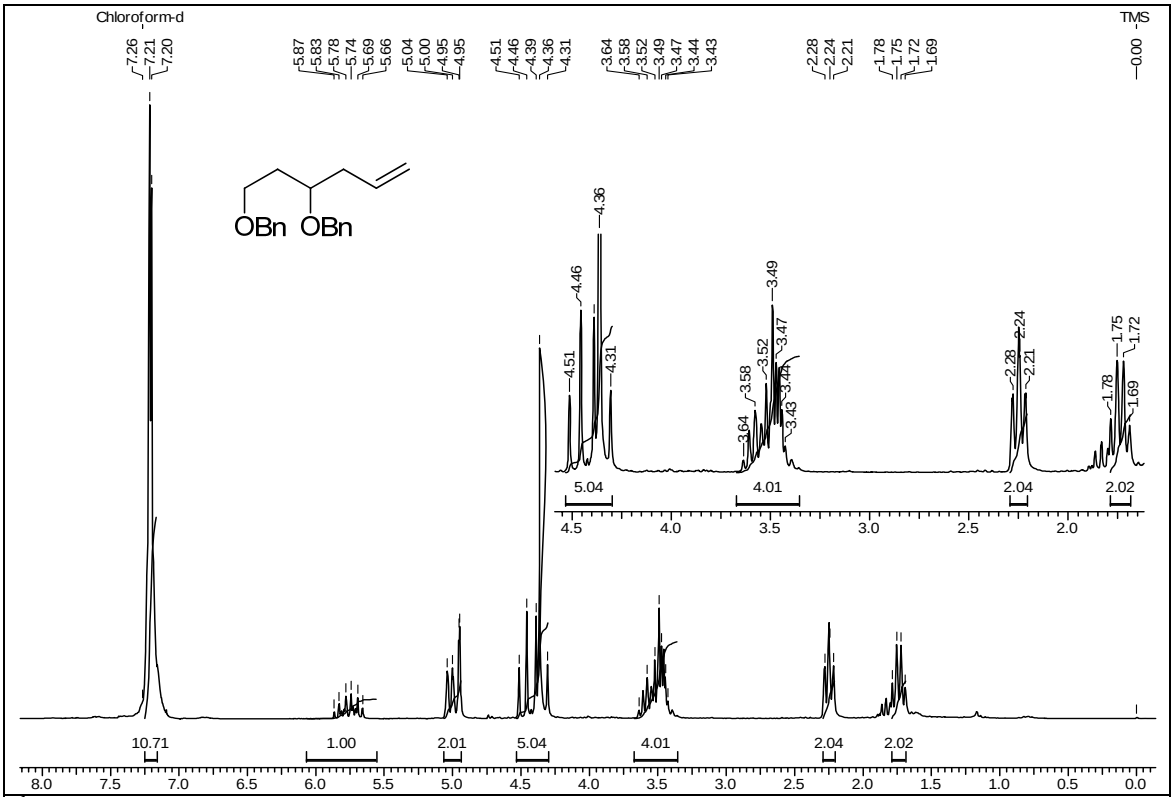
^{1}H NMR spectrum of the compound **5** in $CDCl_3$



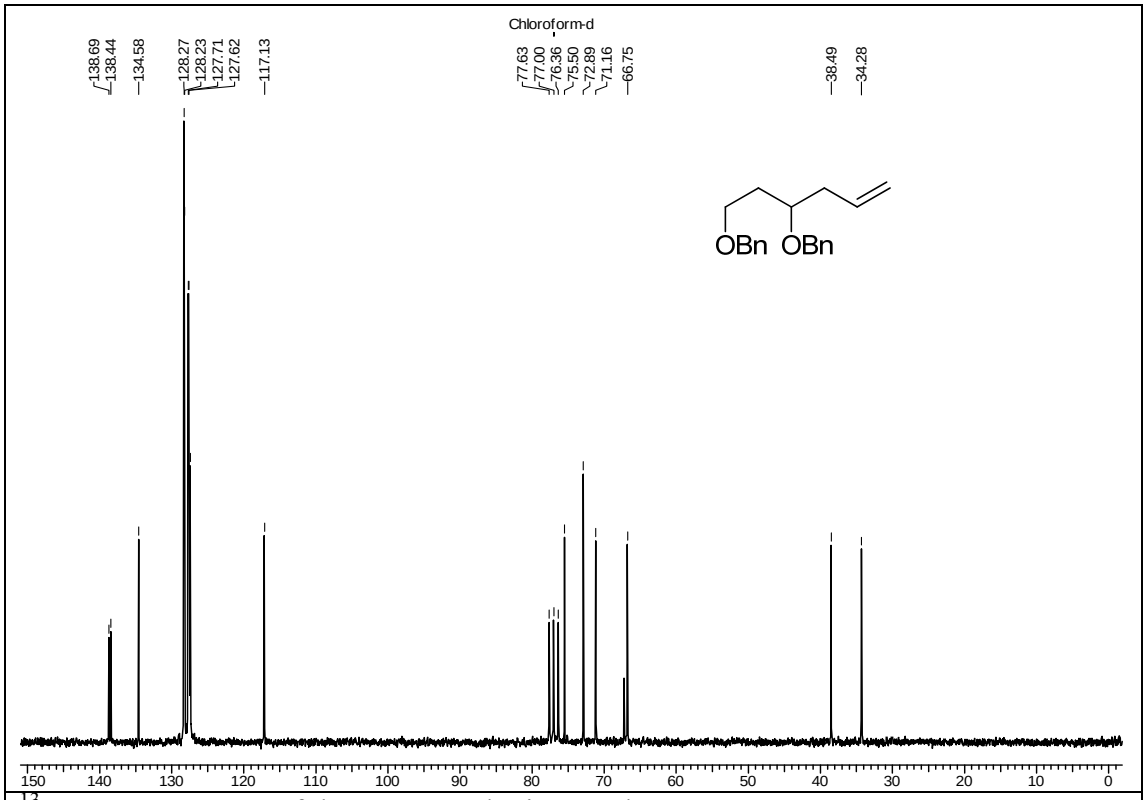
^{13}CNMR spectrum of the compound **5** in $CDCl_3$



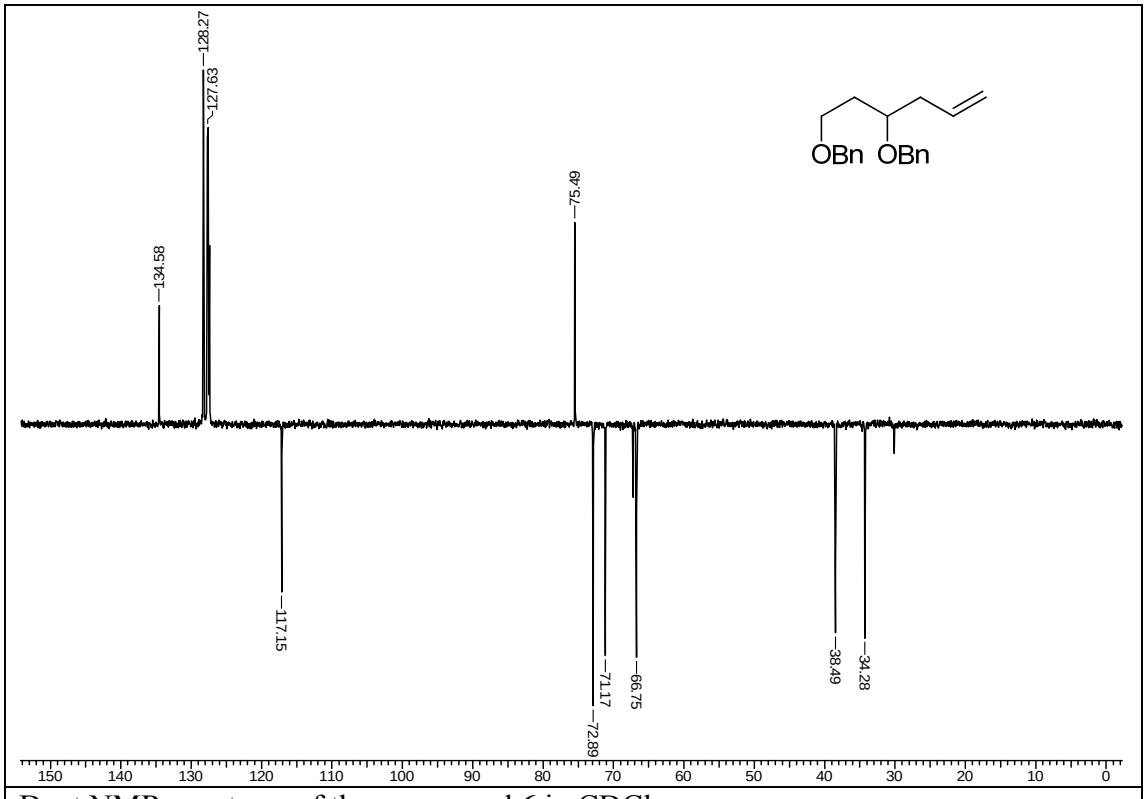
Dept NMR spectrum of the compound **5** in $CDCl_3$



^{1}H NMR spectrum of the compound **6** in $CDCl_3$



^{13}C NMR spectrum of the compound **6** in $CDCl_3$



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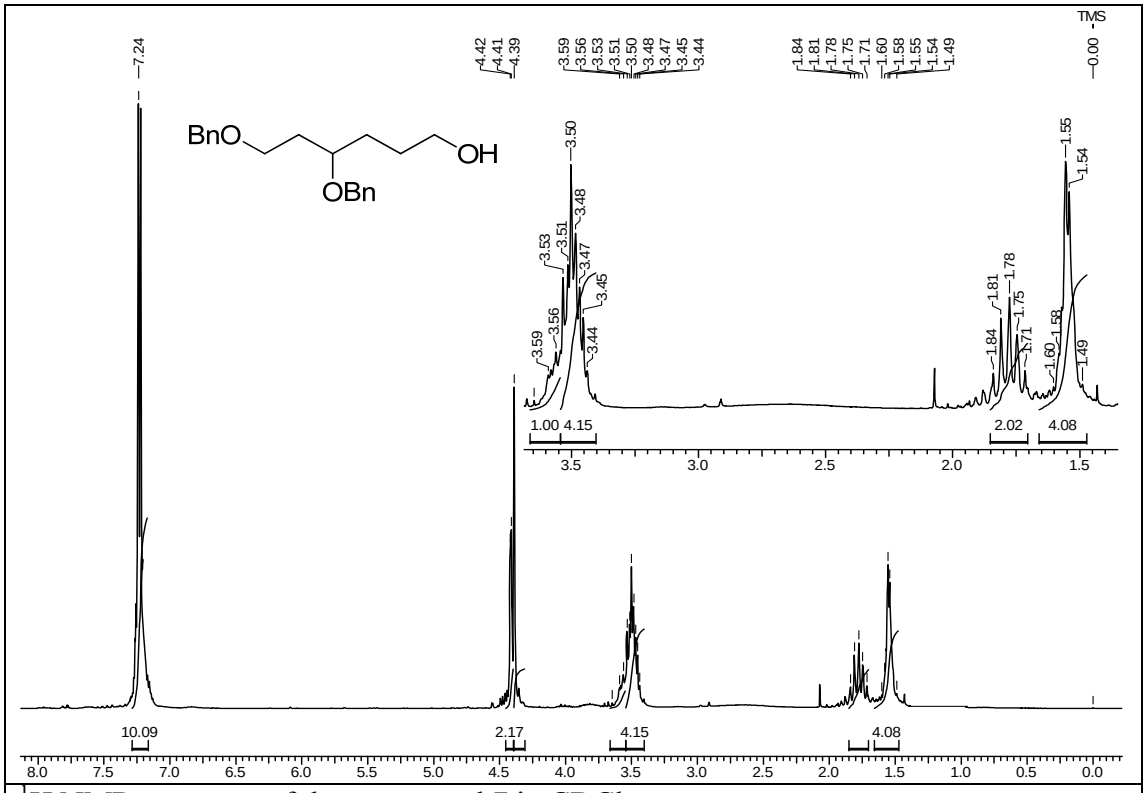

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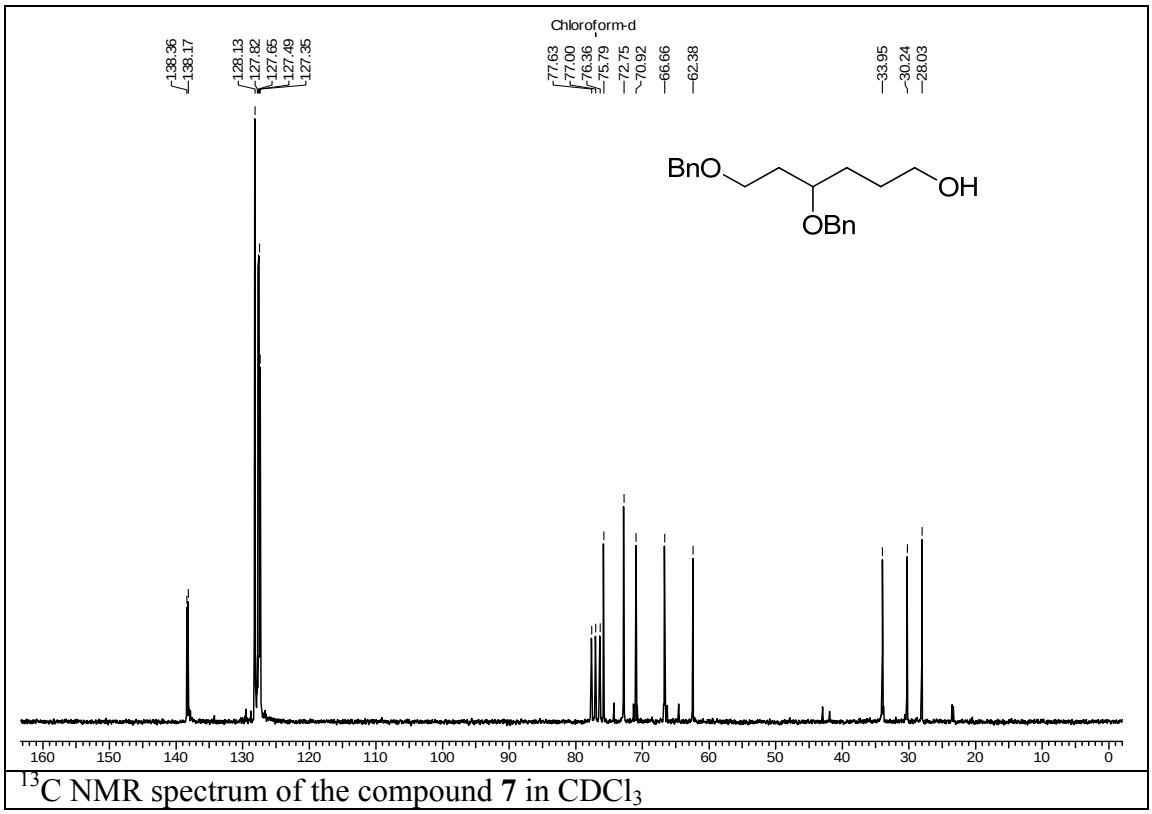

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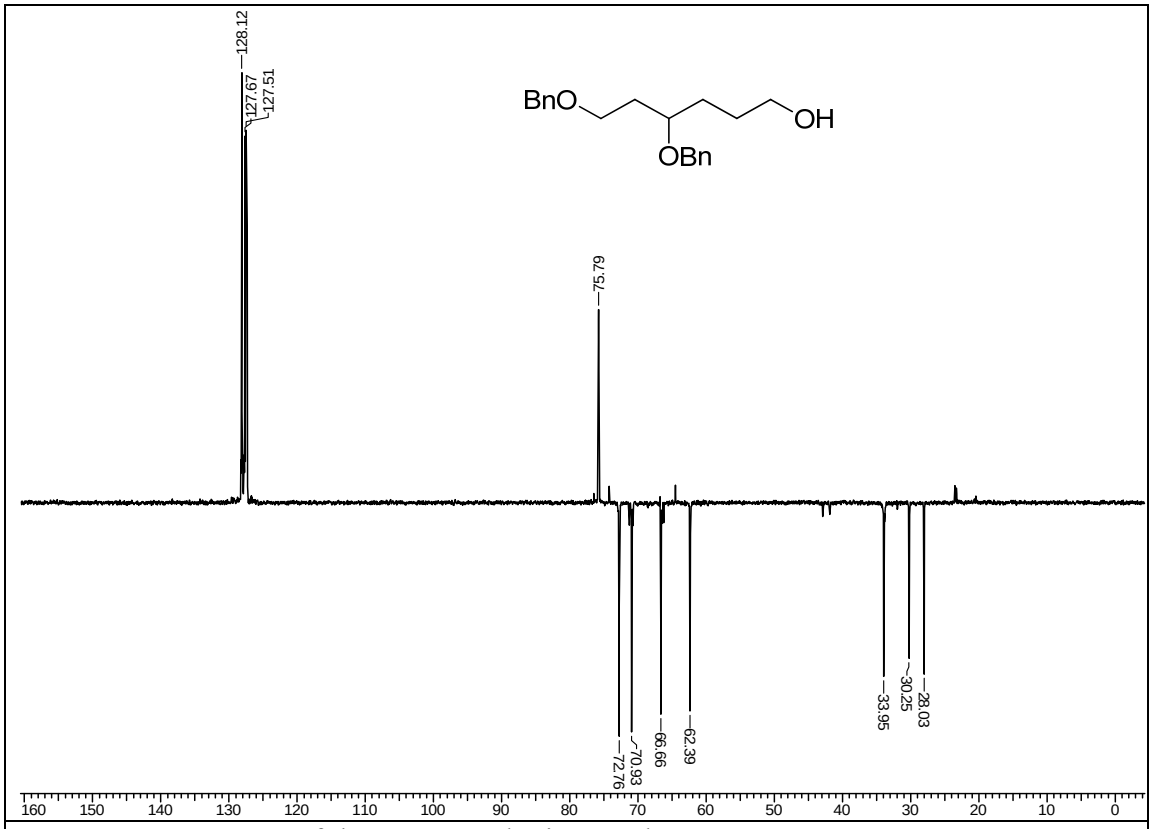

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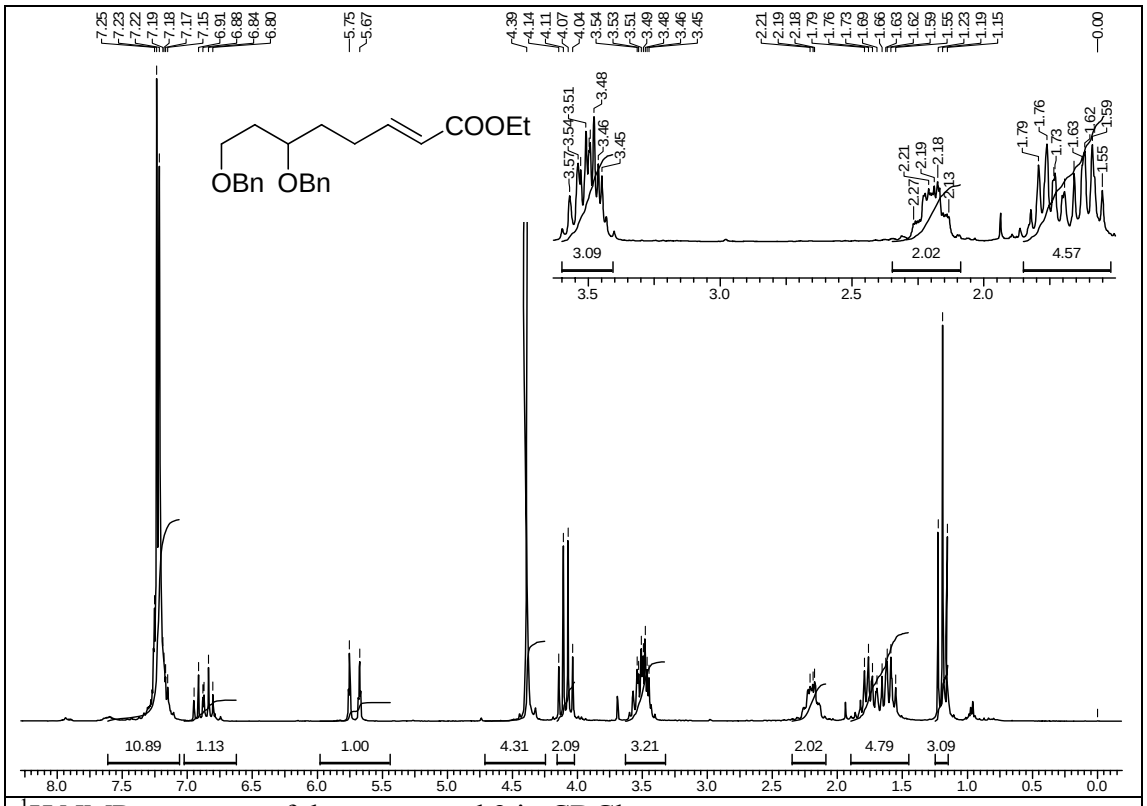

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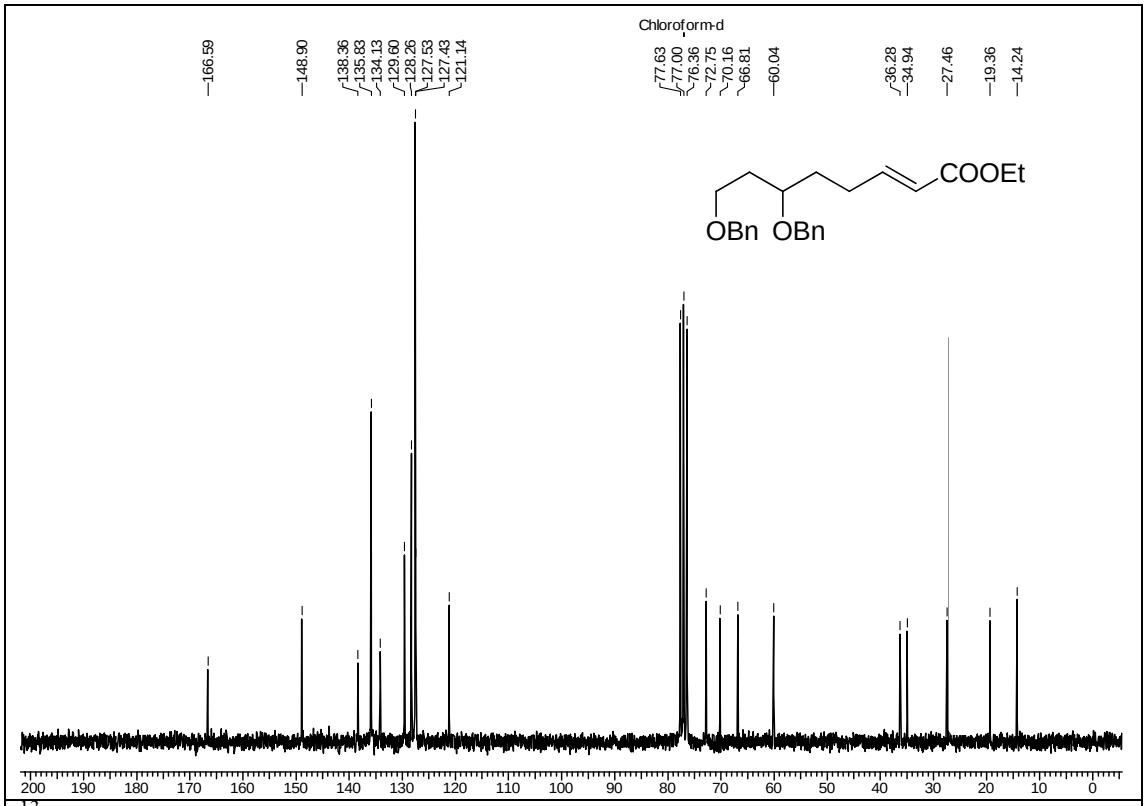

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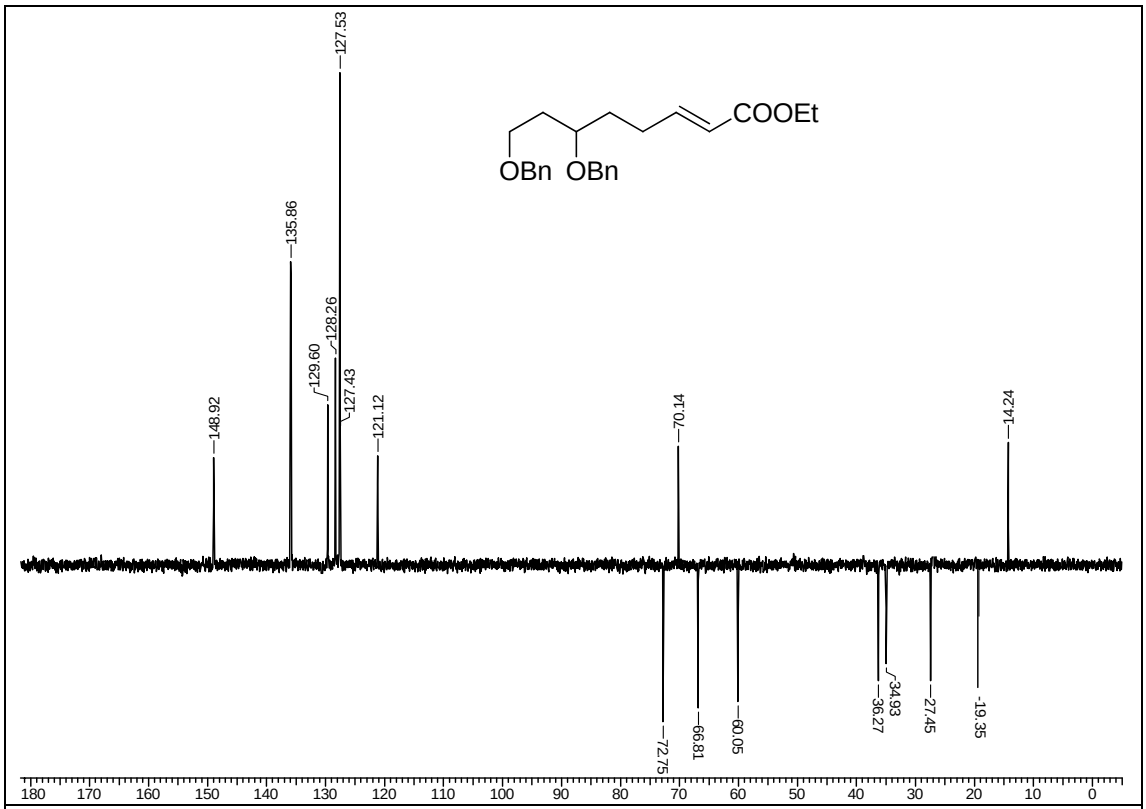

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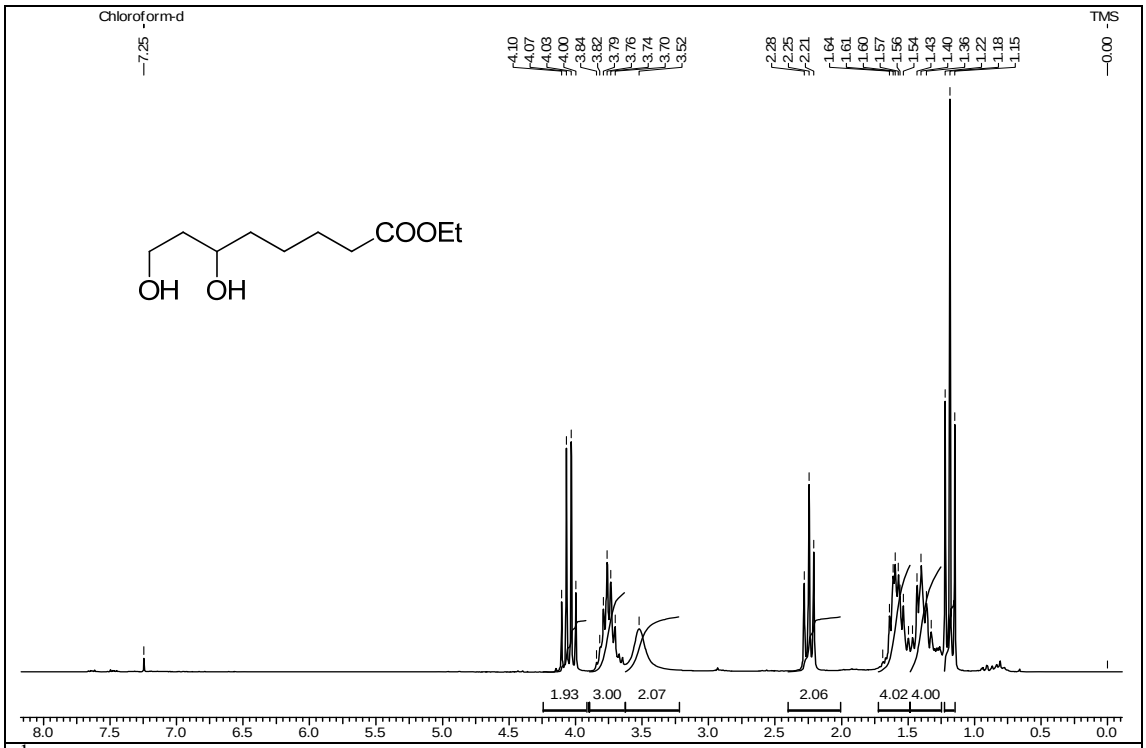

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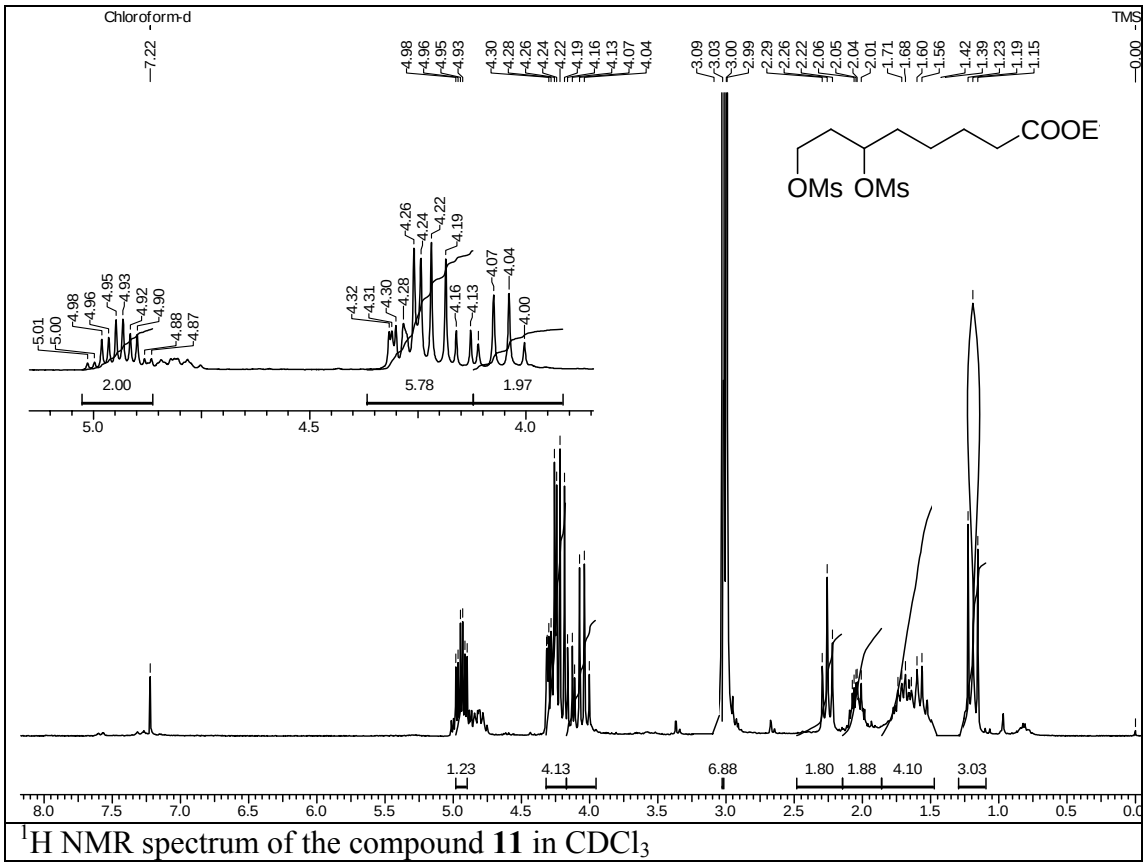

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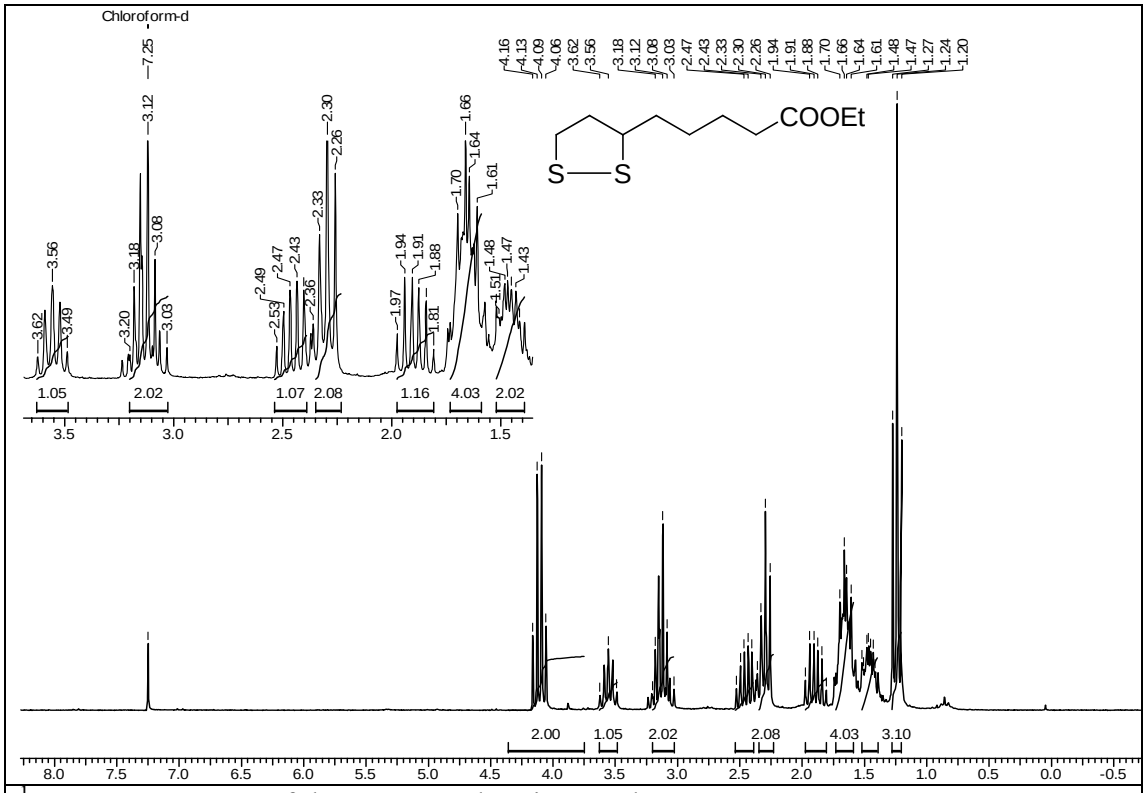

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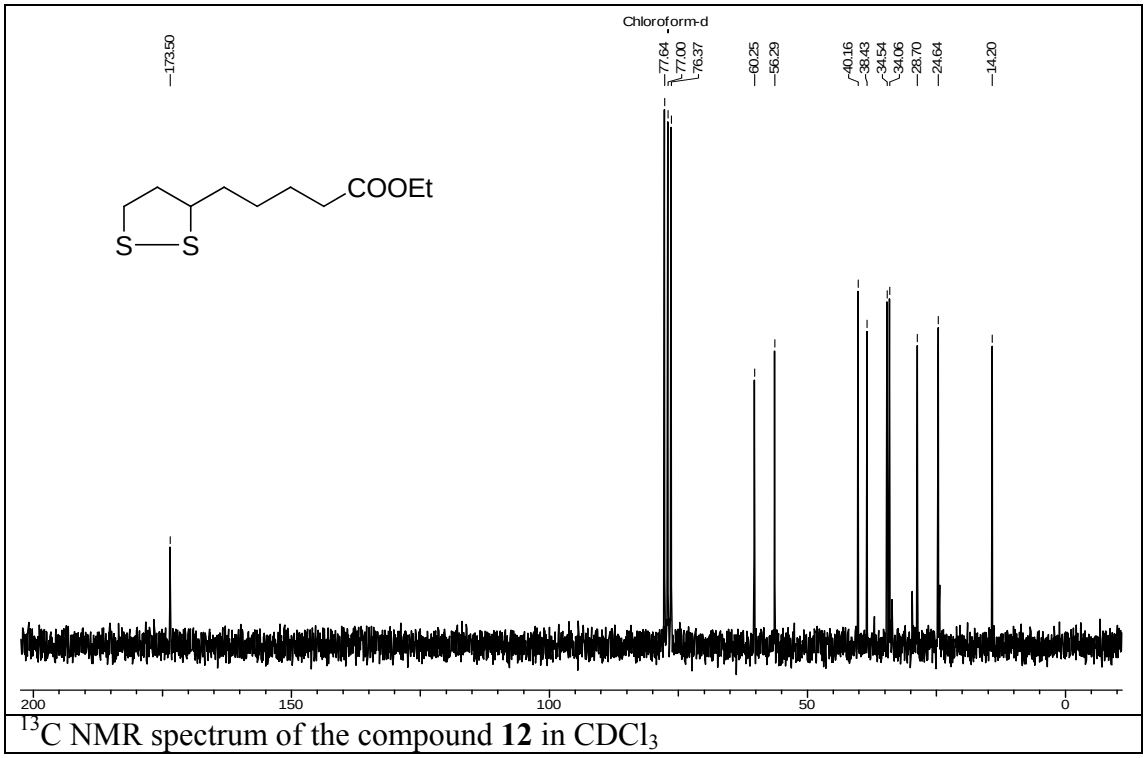

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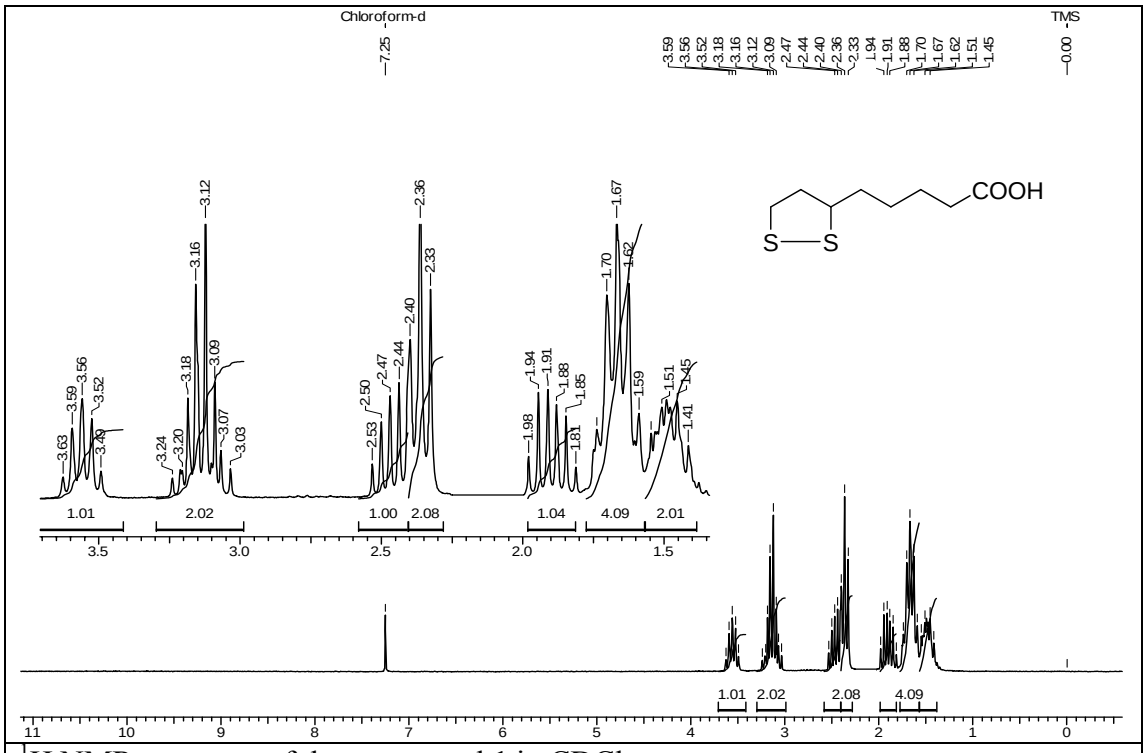

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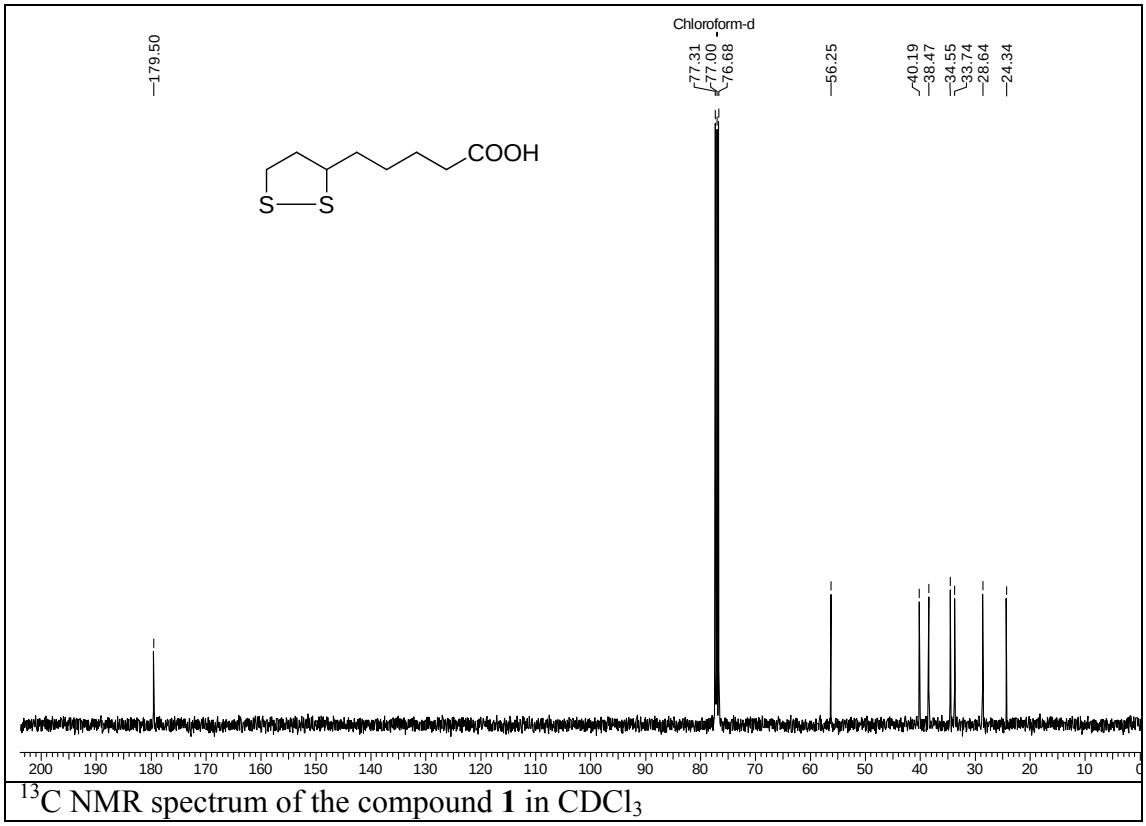

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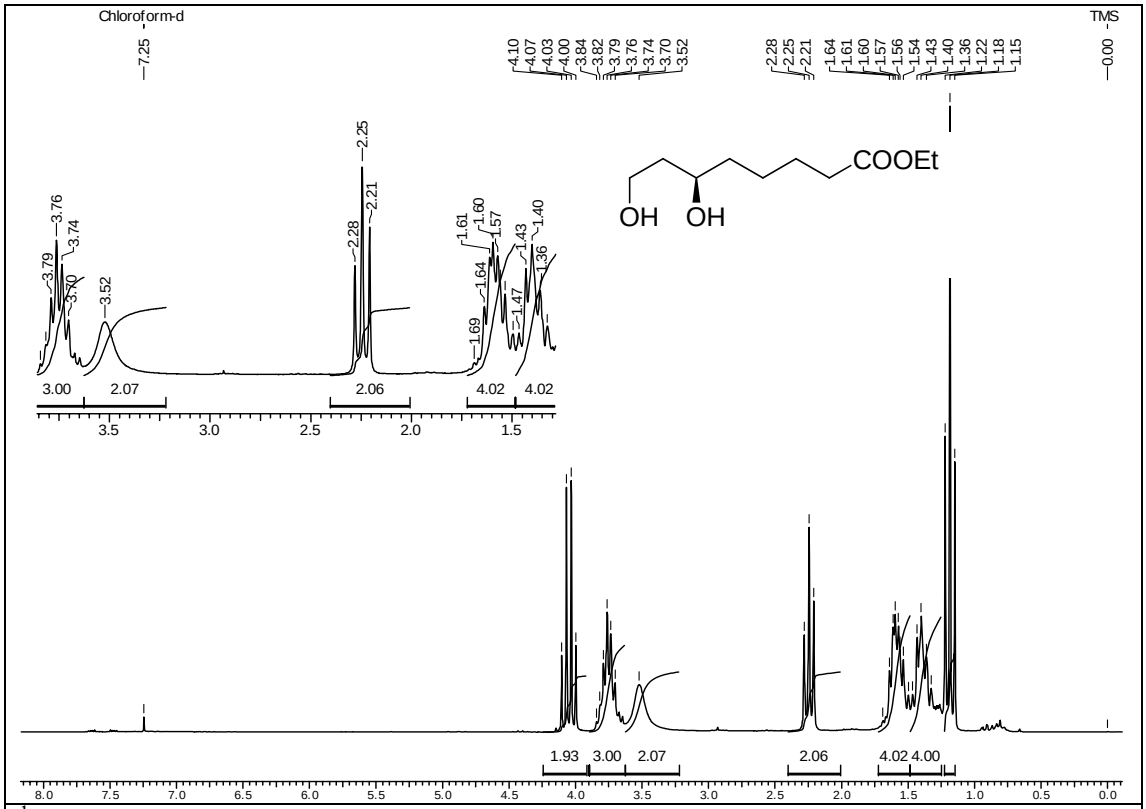
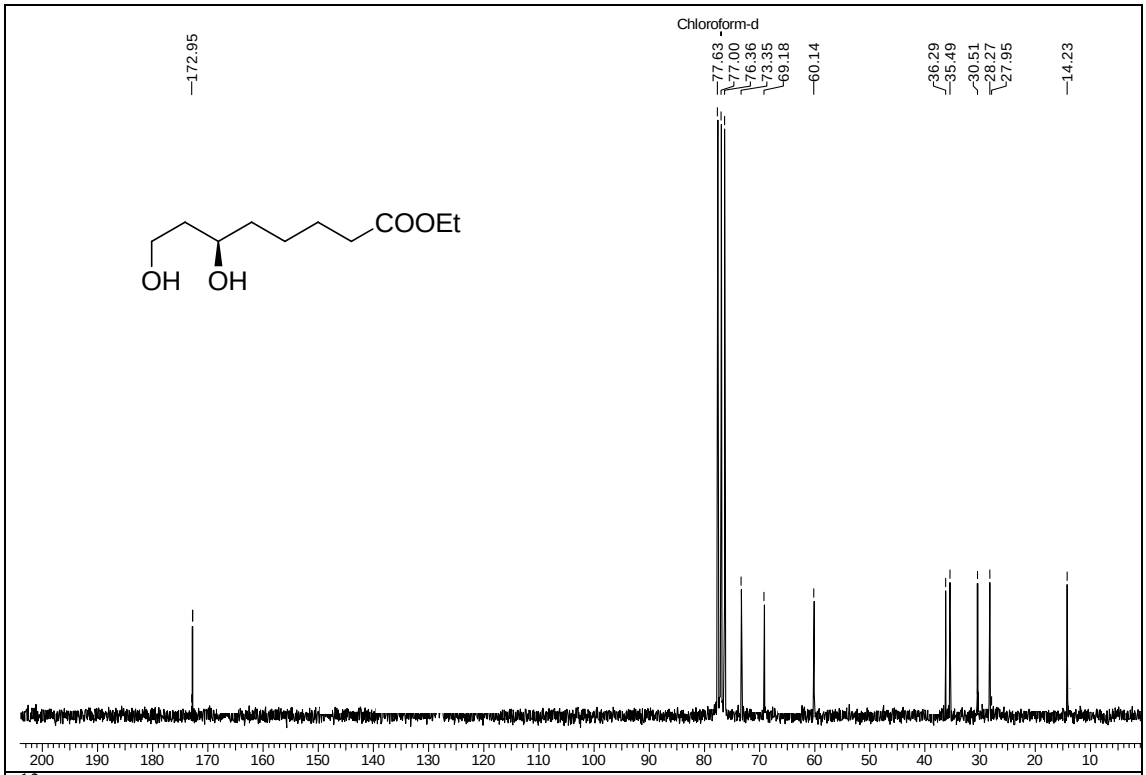
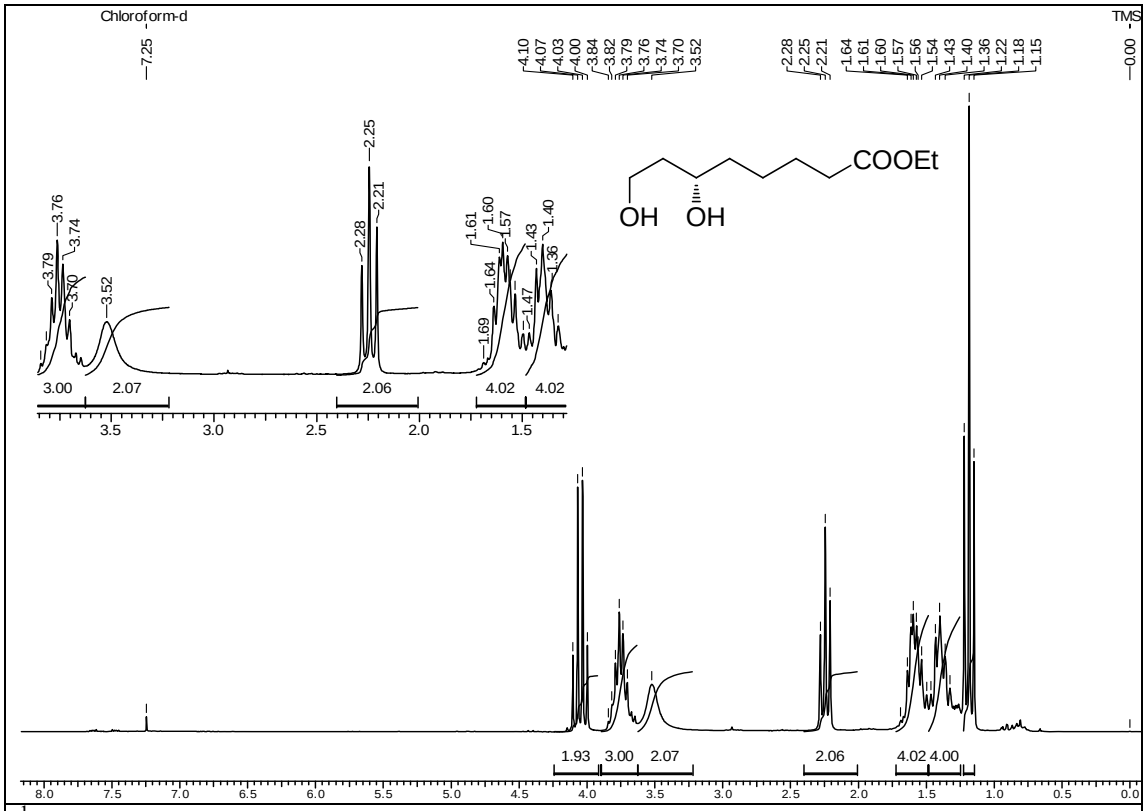


^{1}H NMR spectrum of the compound **10a** in $CDCl_3$



^{13}C NMR spectrum of the compound **10a** in $CDCl_3$



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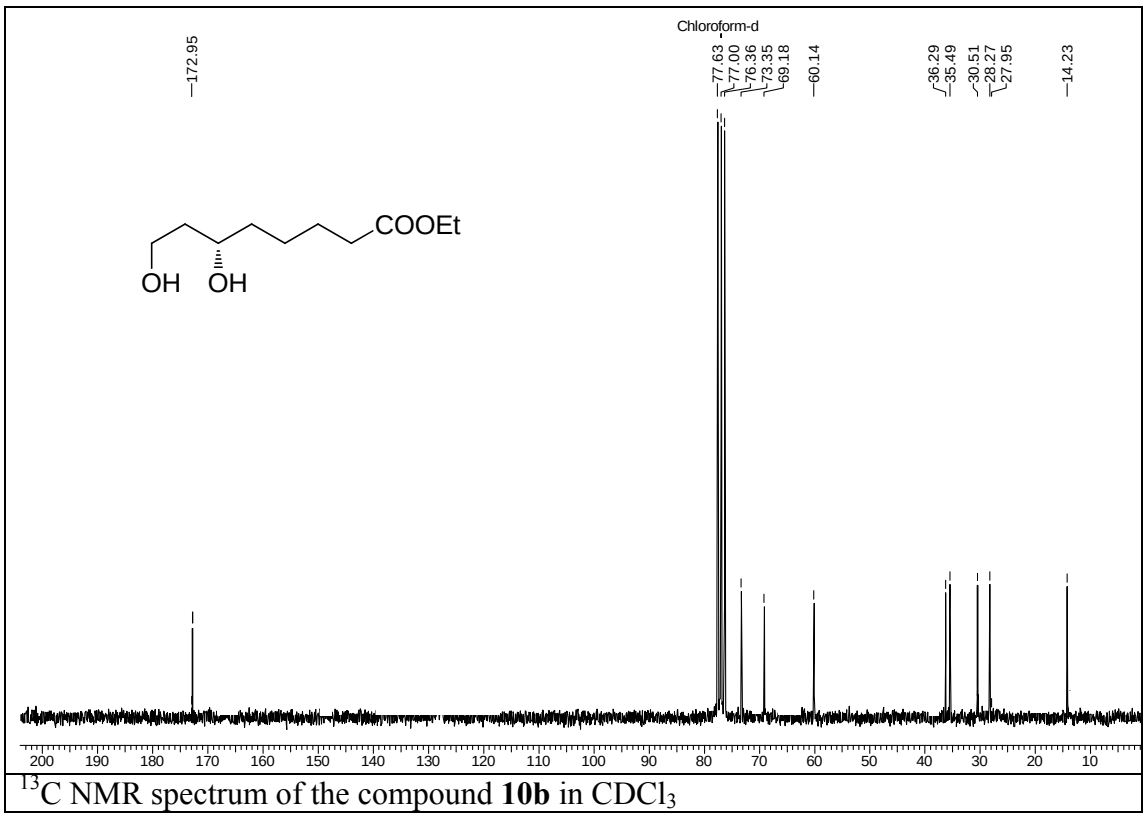
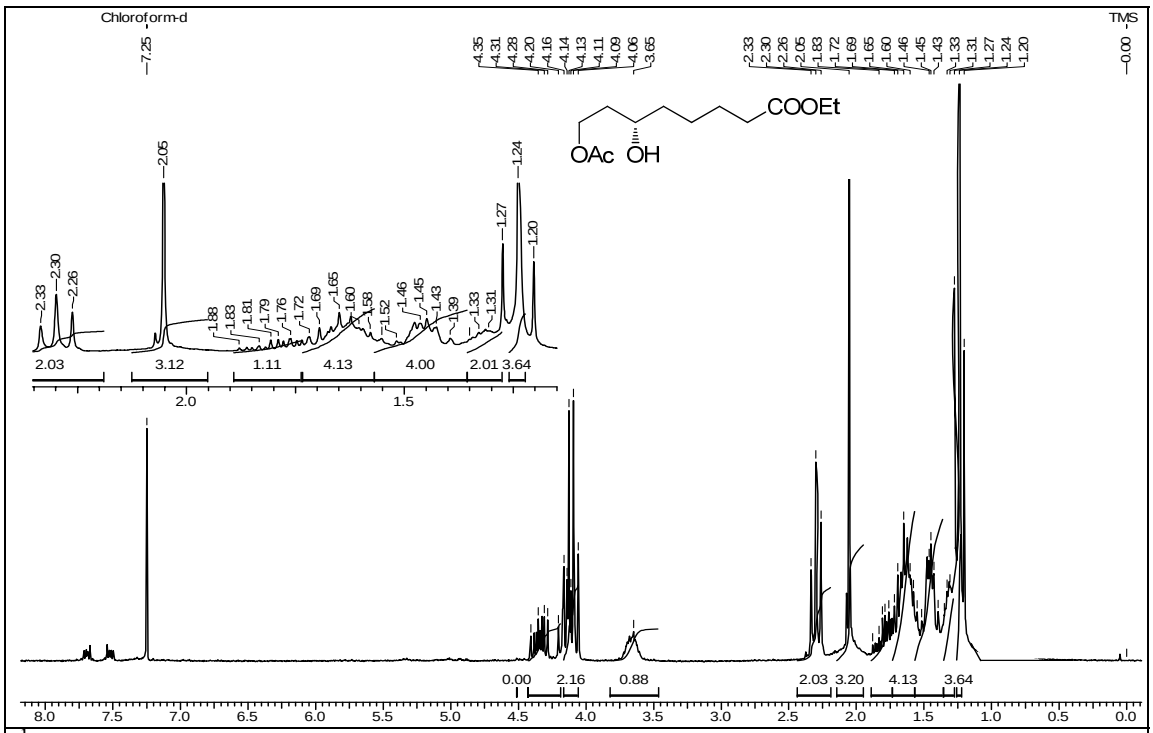


^{13}C NMR spectrum of the compound **10b** in $CDCl_3$



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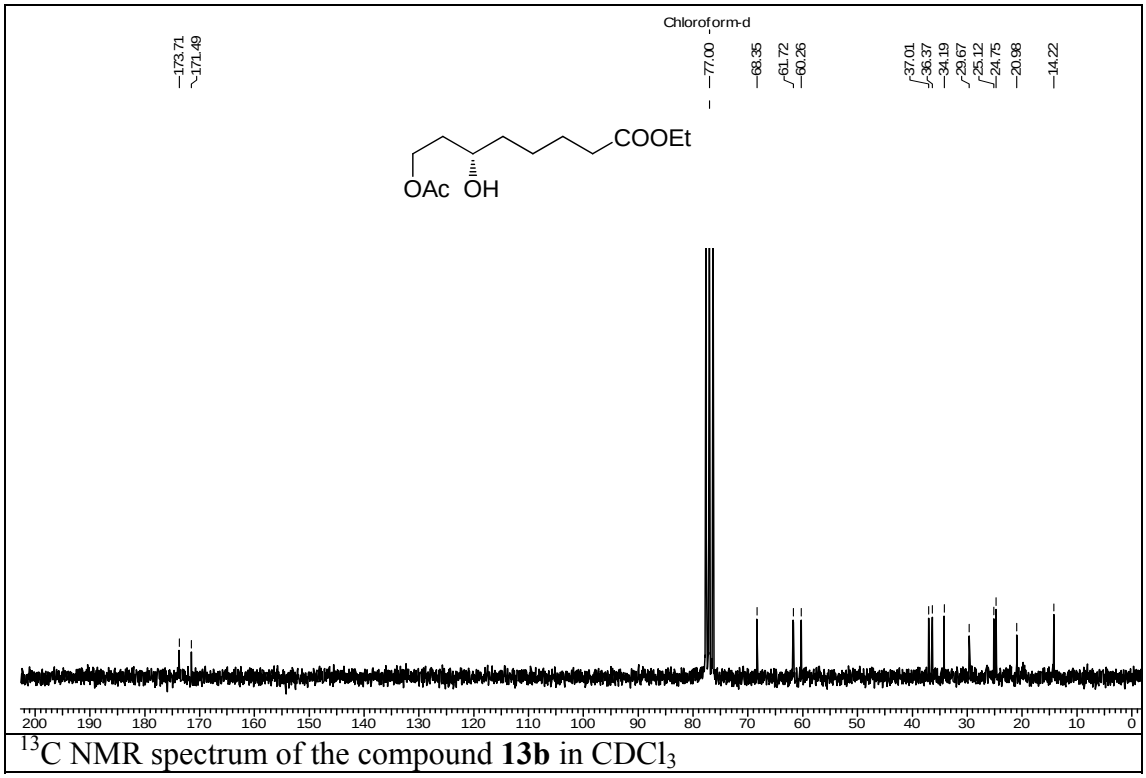
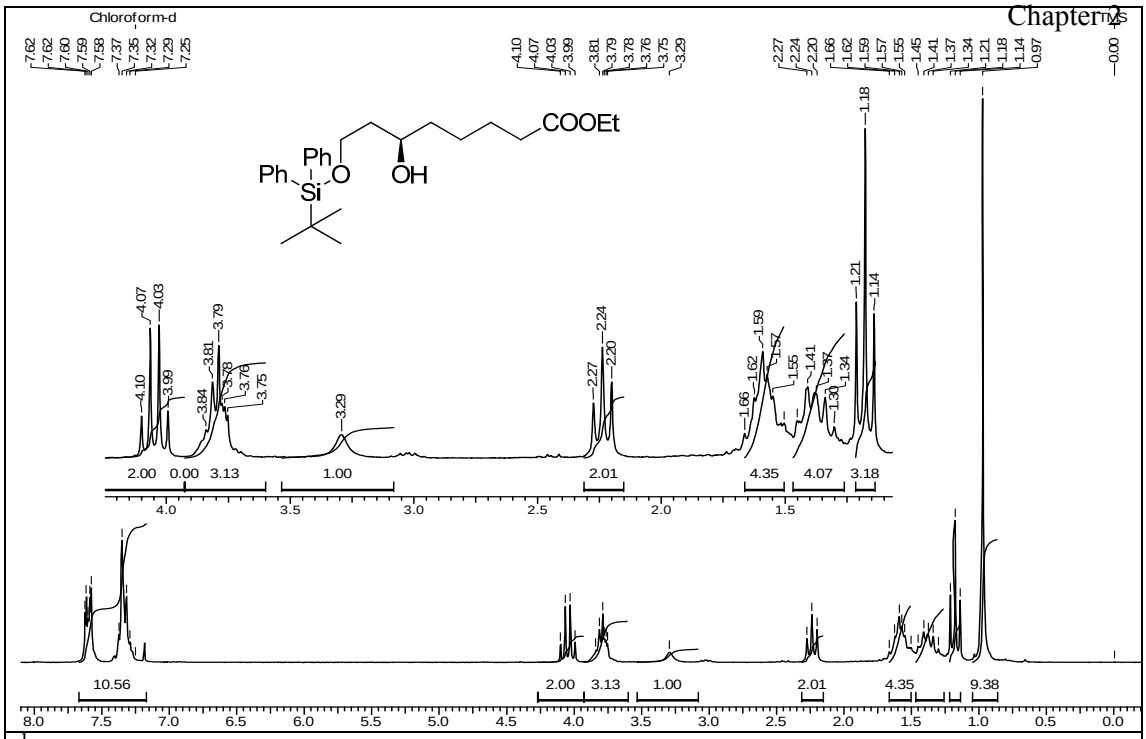
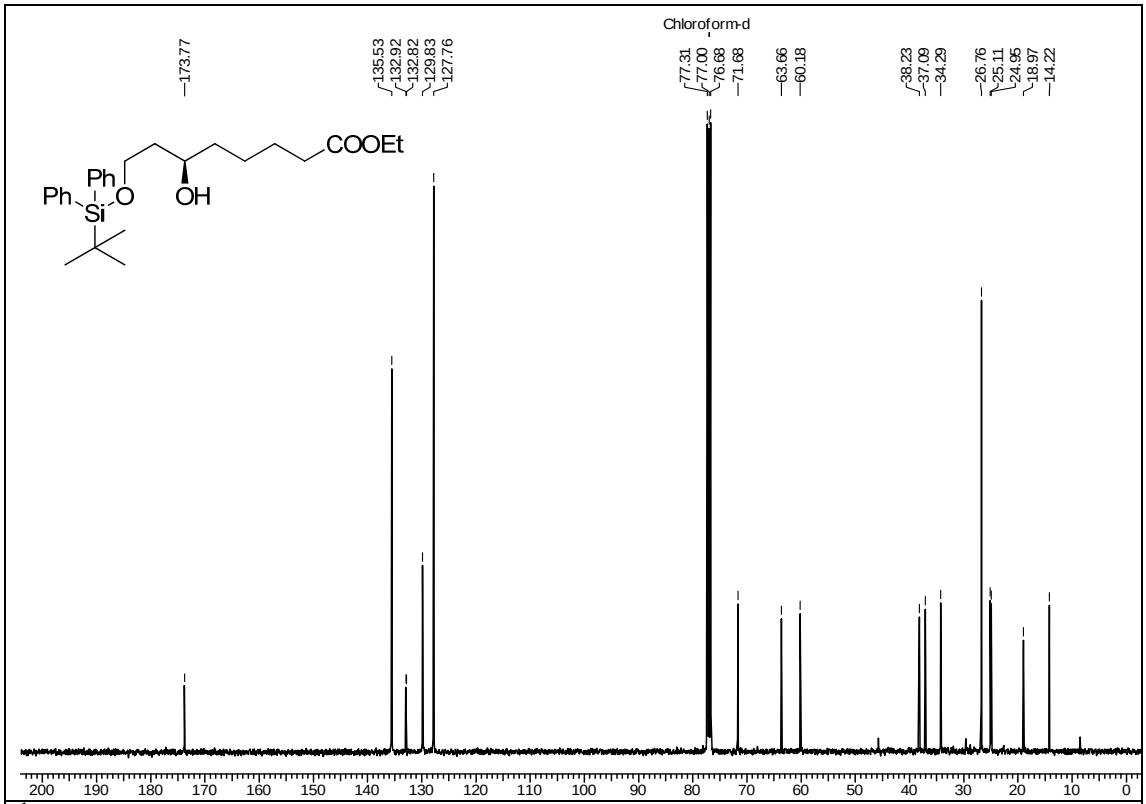


^{13}C NMR spectrum of the compound **13b** in $CDCl_3$



^{1}H NMR spectrum of the compound **14a** in $CDCl_3$



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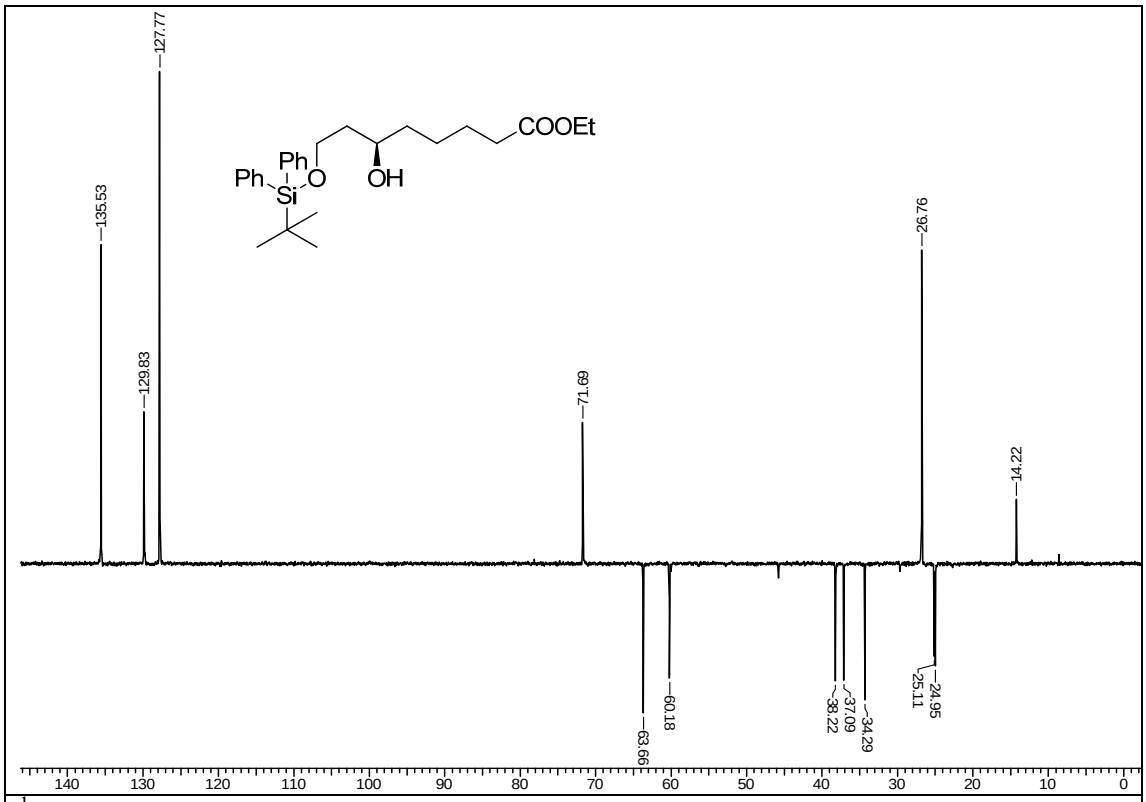

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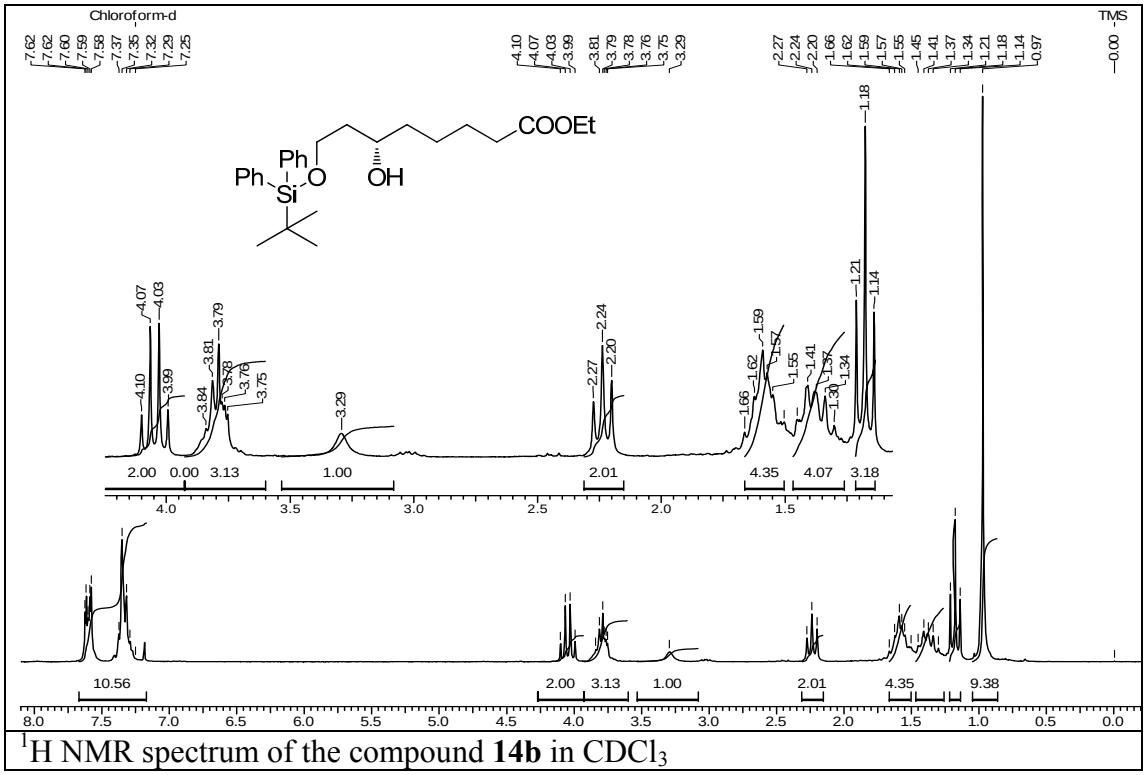
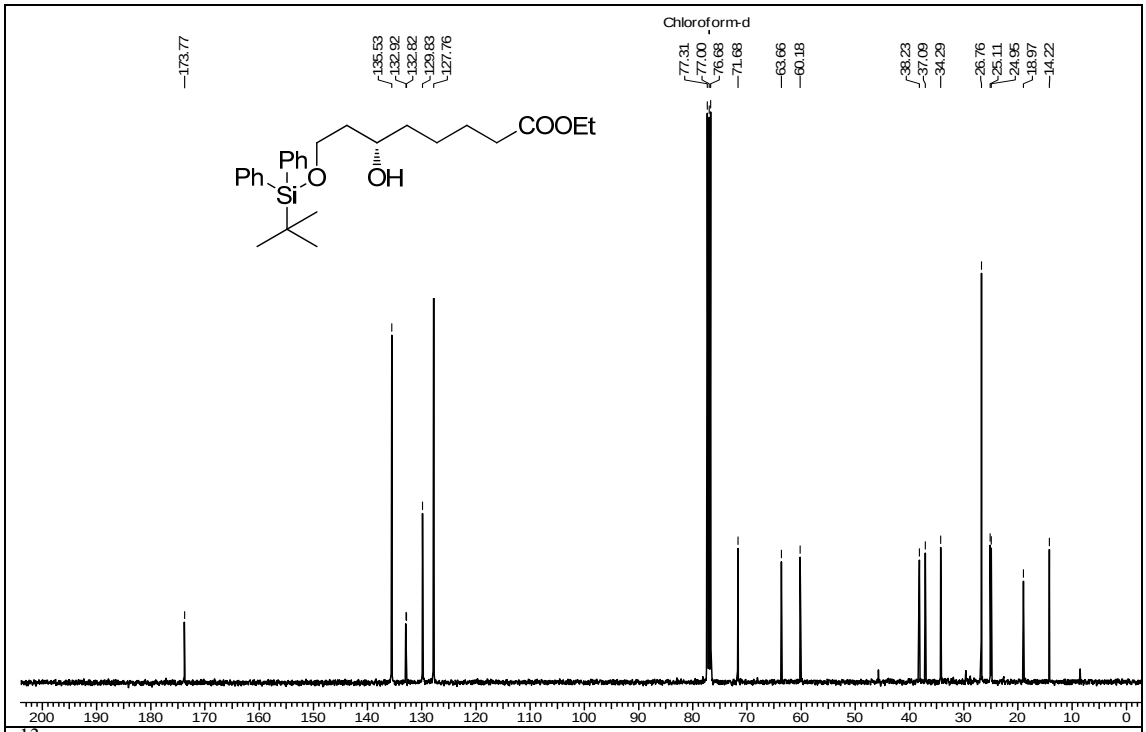


^{1}H NMR spectrum of the compound **14b** in $CDCl_3$



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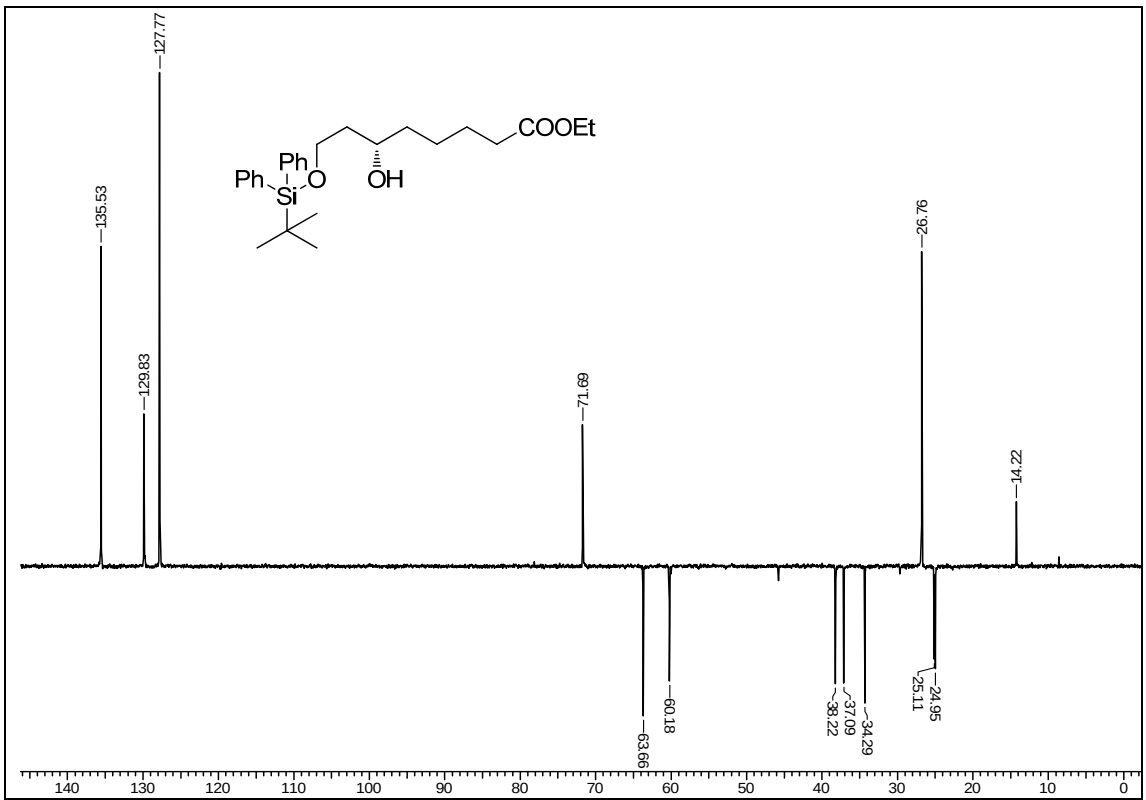
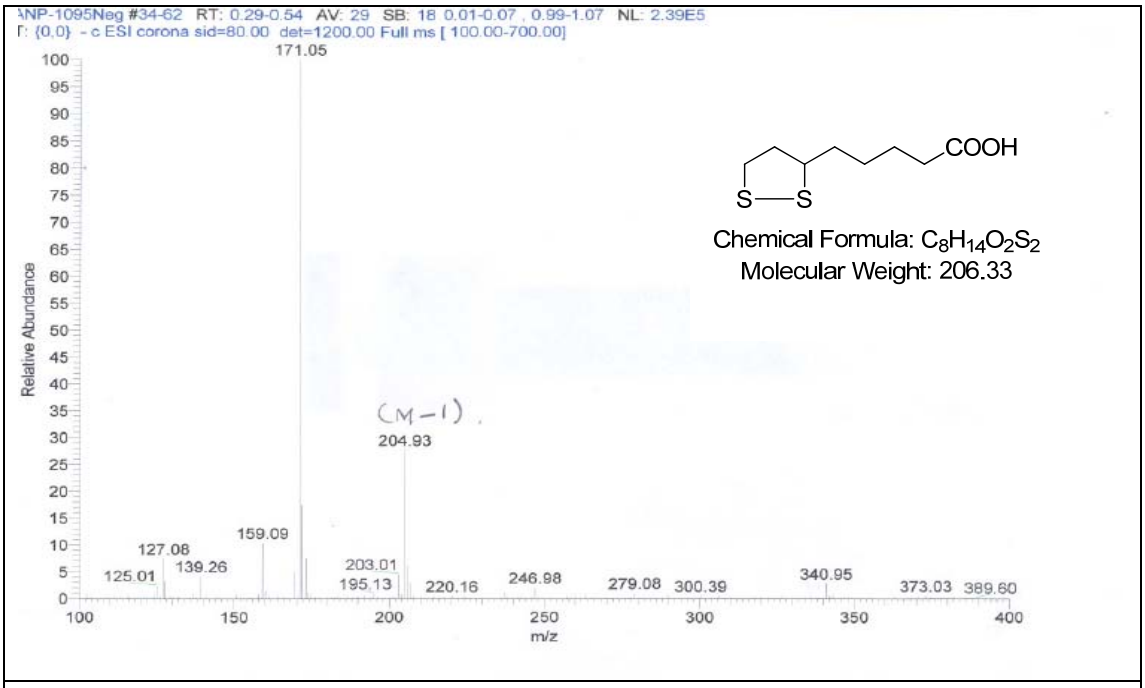
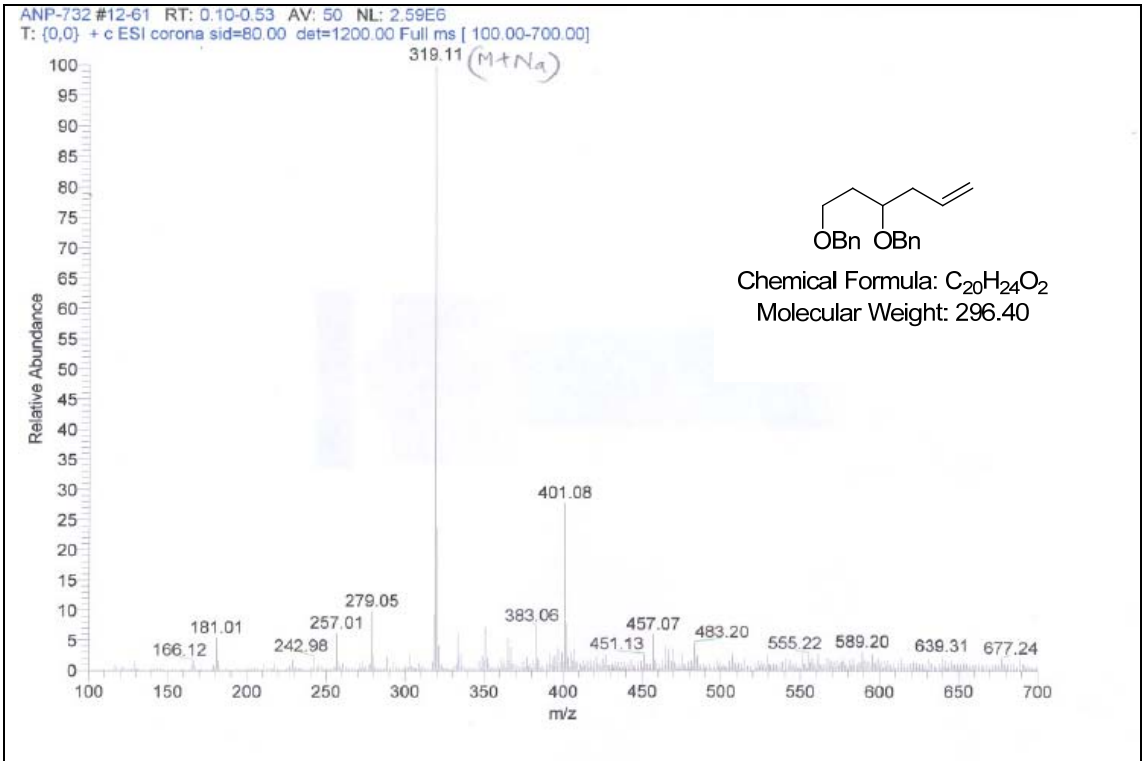


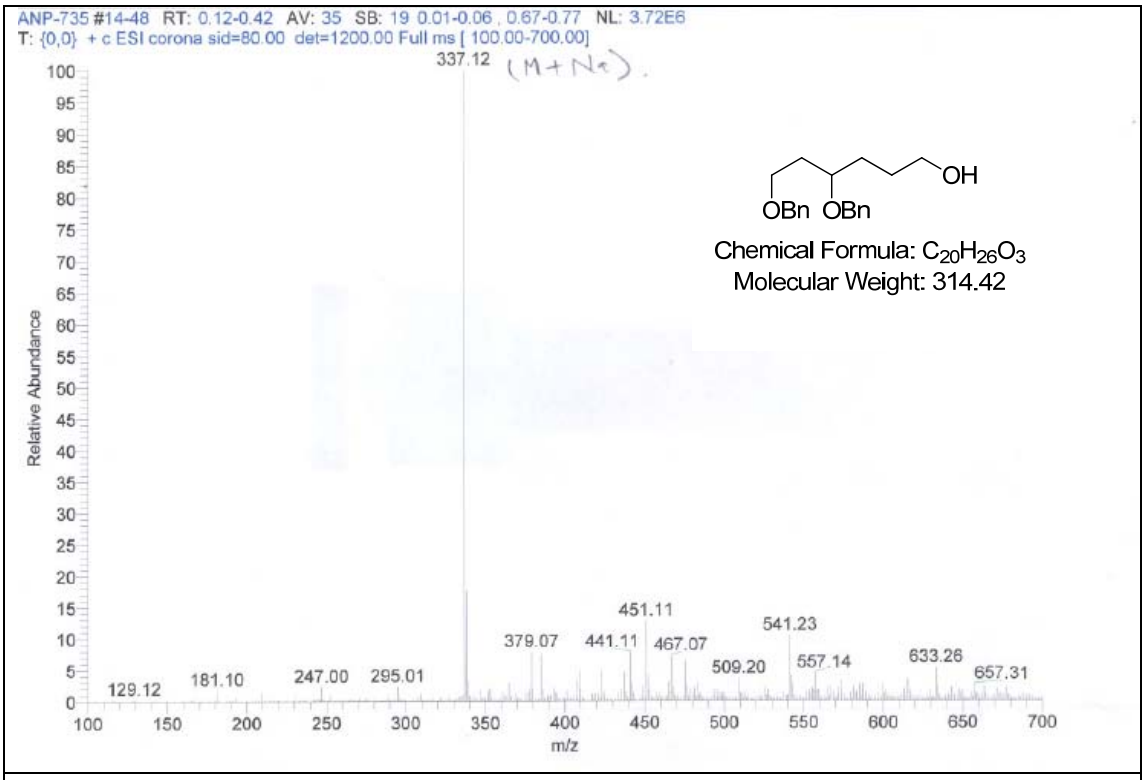
Dept NMR spectrum of the compound **14b** in $CDCl_3$



LCMS Chart of the compound 1



LCMS Chart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T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-700.00]
337.12
(M+Na).
OH
OBn OBn
Chemical Formula: C20H26O3
Molecular Weight: 314.42
Relative Abundance
m/z
129.12
181.10
247.00
295.01
379.07
441.11
451.11
467.07
509.20
541.23
557.14
633.26
657.31

LCMS Chart

2.3.6. References

1. (a) Reed, L. J.; DeBusk, B. G.; Gunsalus, I. C.; Hornberger, Jr. C. S. *Science*, **1951**, *114*, 93.

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Chapter 2, Section IV: Synthesis of (R)-Lipoic Acid and (S)-Lipoic Acid by Mn-salen catalysed Oxidative Resolution

2.4.1. Introduction

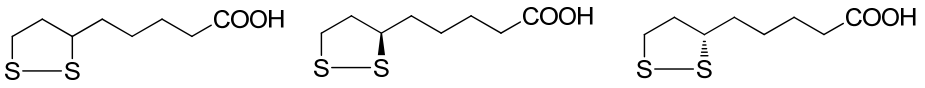
The importance of chiral molecules in both medicine and agricultural chemistry has been well recognized long back. For this purpose formation of carbon-carbon or carbon-hetero atom coupling has been always fascinating to the chemists since this leads to construction of carbon skeleton as well as it is useful in induction of the required functional group so as to architect desired chiral intermediate or molecule during asymmetric synthesis. To fulfill this thrust one must also need to develop efficient methods to generate enantiomerically pure synthons by resolution.

1) Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[1] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrates released from the resolving agent. This approach has proven to be especially useful if salt formation is straight-forward, as in the case of amines and carboxylic acids.[2]

2) Chiral chromatography generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out.

3) Kinetic resolution involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantio-enriched starting material and product, and the desired component is then isolated.[3]

Among all of above methods, kinetic resolution is the most widely used since it provides easy access of catalyst, separation and recovery of catalyst, and high enatiomeric excess and high practical feasibility.The most widely used chiral catalyst for kinetic resolution are Co salen for hydrolytic resolution of epoxide[4] and Mn salen for oxidative resolution of secondary alcohol.[5] The significance of Mn salen catalyzed resolution prompted us to resolve the (α)-lipoic acid intermediate in order to overcome our unsuccessful attempts with the use of biocatalyst (chapter 2, section III) and develop a feasible process for R and S (α)-lipoic acid (**1a-b**).

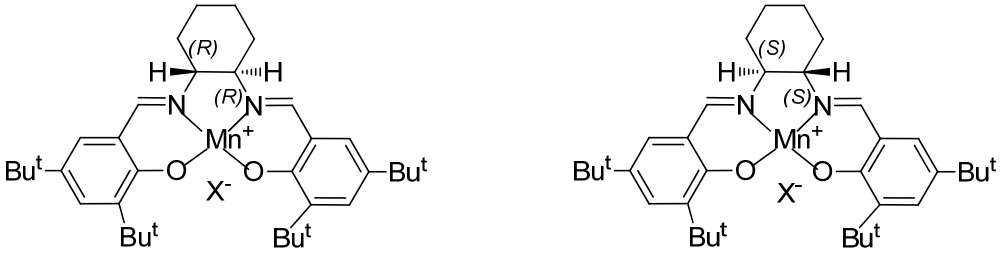


(±)-α-Lipoic acid (**1**) R-(+)-α-Lipoic acid (**1a**) S-(-)-α-Lipoic acid (**1b**)

Figure 1

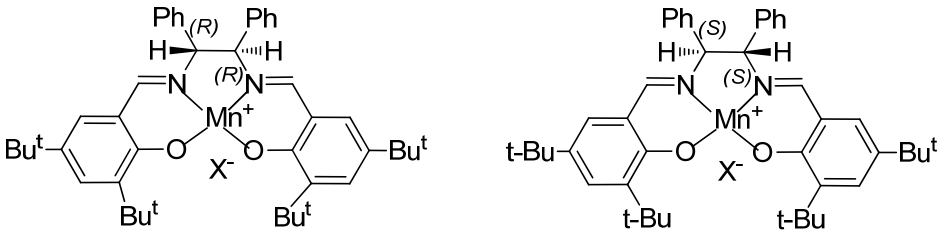
2.4.2. Short review on Mn salen catalysed oxidative resolution

The development of efficient catalytic asymmetric reactions is currently one of the most challenging and feasible tasks in synthetic organic chemistry. Many efforts have been devoted to the creation of chiral metal complexes for use in advanced asymmetric catalysis.[6]



(1R, 2R)- 2 (1S, 2S)- 2

(1,2- Cyclohexanediamino-N,N'- bis(3, 5- di-t-butylsalicylidene))manganese



(1R, 2R)- 2a (1S, 2S)- 2a

1,2-Diphenylethane-1,2-diamino-N,N'- bis(3, 5- di-t-butylsalicylidene))manganese-
X= Cl, Br, I, OAc, PF_6

Figure 2

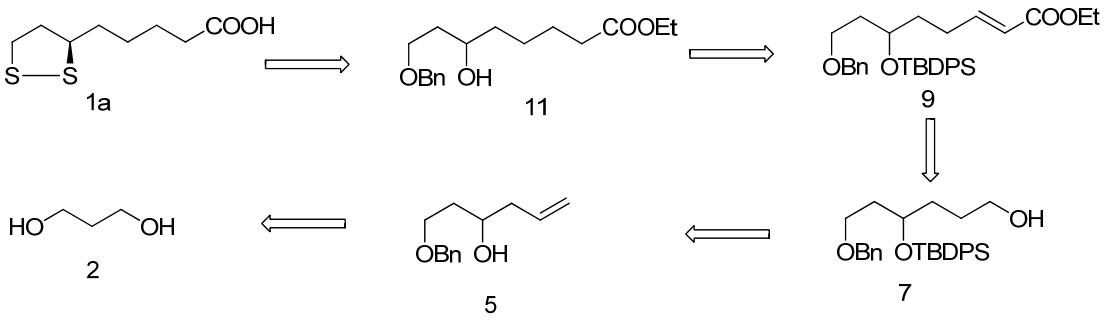
For this purpose Salen ligands are now recognized as efficient auxiliaries and many metallo-salen complexes have been found to serve as excellent catalysts for various asymmetric reactions such as epoxidation, aziridination, cyclopropanation, and Diels–Alder reactions, for kinetic resolution of racemic epoxides, and for asymmetric ring opening of

meso epoxides[7]. In particular, the pioneering studies of Jacobsen and co-workers and Katsuki and co-workers have led to the development of a variety of chiral Mn (salen) catalysts which epoxidize alkenes with high enantioselectivity[8] (Figure 2).

Recently, the study of Mn (salen) complexes is well documented for effective catalytic enantioselective oxidation of secondary alcohols to ketones in the presence of the co-oxidant diacetoxyiodobenzene[4]. Therefore, it was thought to extend this in asymmetric catalysis for the oxidative kinetic resolution of secondary alcohol, ethyl 8-(benzyloxy)-6-hydroxyoctanoate to S or R 8-(benzyloxy)-6-hydroxyoctanoate, important key intermediates of (R)-lipoic acid or (S)-lipoic acid.

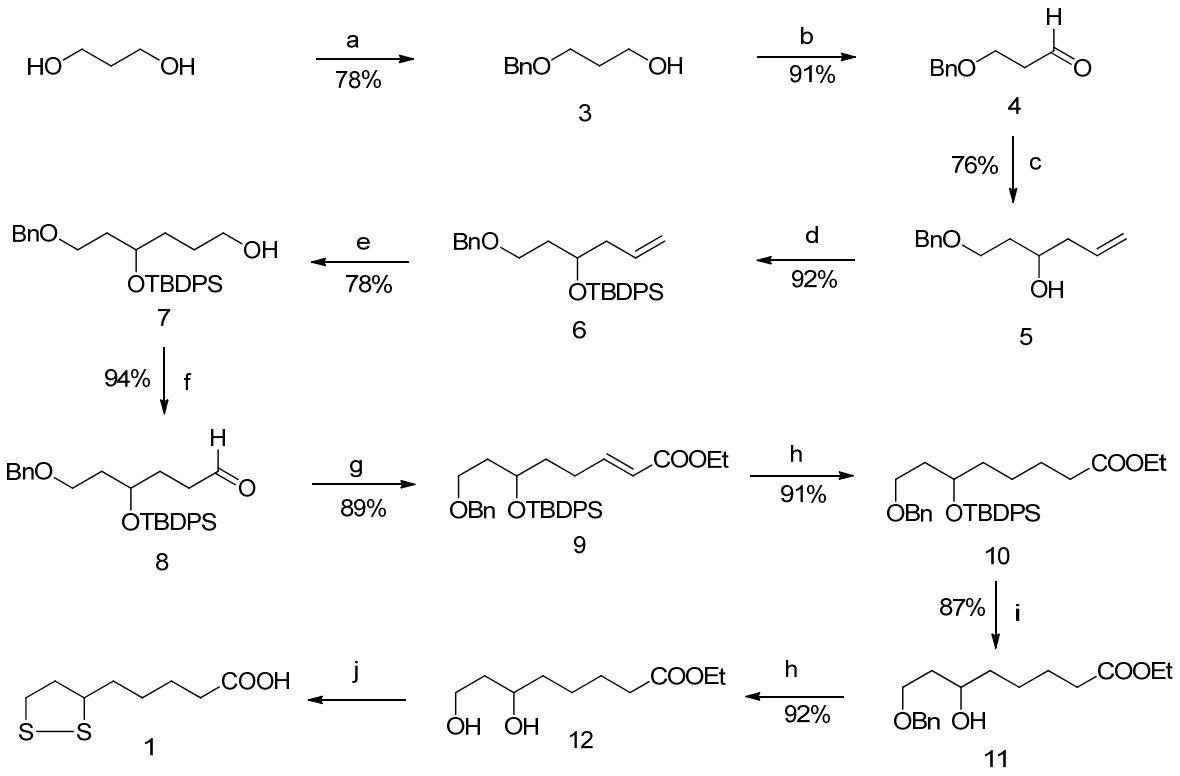
2.4.3. Present work

The significance of Mn salen catalyzed resolution and its application in asymmetric synthesis of R-(α)-lipoic acid and S-(α)-lipoic acid is shown scheme 1.



Scheme 1

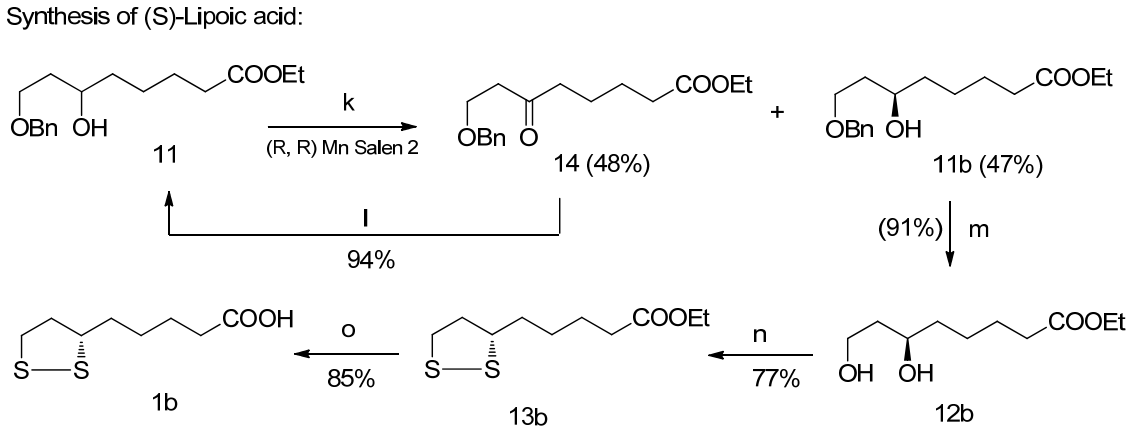
As depicted in retrosynthesis, it is easier to make desired key intermediate **11** which on resolution and functional group conversions could produce R or S lipoic acid (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) NaH, BnBr, THF: DMF; (b) PCC, DCM, Celite, RT; (c) Allyl bromide, Zn, THF, Aq NH_4Cl; (d) Imidazole, DCM, TBDPS-Cl, RT; (e) $B_2H_6.Me_2S$, THF, H_2O_2, CH_3COONa; (f) PCC, DCM, Celite; (g) Ph_3P=CHCOOEt, THF; (h) H_2, Pd-C, EtOAc, RT; (i) TBAF, THF, RT; (j) (i) TEA, MsCl, DCM, 0^oC-RT; (ii) Na_2S, S powder, DMF, reflux; (iii) KOH, EtOH, RT-12 hrs.

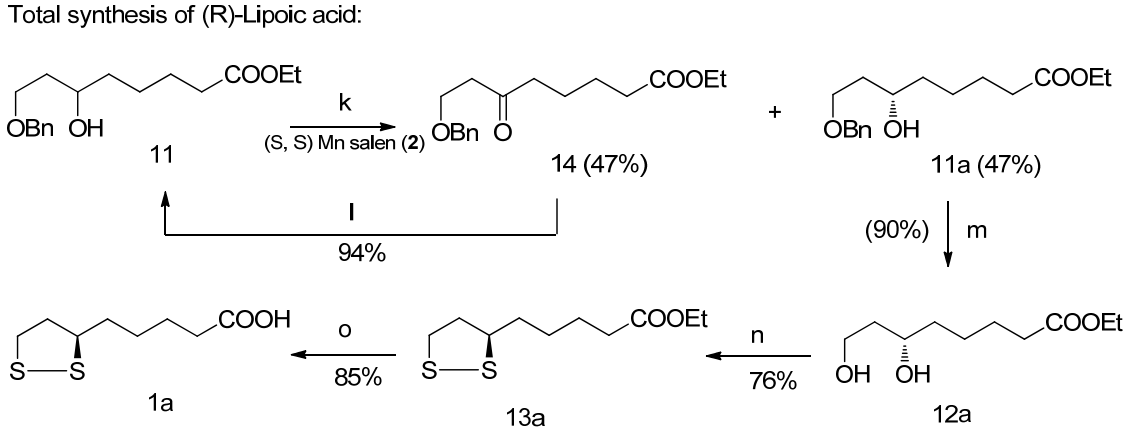
1-(Benzyloxy)hex-5-en-3-ol (**5**) which was prepared from 1,3-propane diol in three steps, on protection, hydroboration, oxidaiton and wittig reaction gave α-β unsaturated intermediate **9** in 60.03% yield over four steps. This on hydrogenation and deprotection afforded ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**11**) in 79.17% over two steps. Here, the hydrogenation was carried out simply by H_2/ Pd heterogenous catalysis and deprotection was carried out by treatment with TBAF. Ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**11**) is an important key intermediate for the synthesis of R/S lipoic acid. Racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**11**) on (R, R) Mn salen (**2**) catalyzed oxidative resolution of secondary hydroxyl group afforded (R)-ethyl 8-(benzyloxy)-6-hydroxy-octanoate (**11b**) in high enantiomeric excess and in excellent yields (47%) and ethyl 8-(benzyloxy)-6-oxooctanoate **(14)** in 48% yield. (R)-Ethyl 8-(benzyloxy)-6-hydroxy-octanoate (**11b**) on

hydrogenation, mesylation and refluxing with sodium sulphide and sulphur in DMF gave S-ethyl lipoate (**13b**) in 69.3% yield (Scheme 3).



Scheme 3. *Reagents and conditions:* (k) (R, R)-Mn salen (**2**) (2 mole %), $PhI(OAc)_2$, KBr , DCM + H_2O / RT; (l) $NaBH_4$, EtOH, RT; (m) H_2, Pd-C, EtOAc, RT; (n) (i) TEA, MsCl, DCM, 0^oC-RT; (ii) Na_2S, S powder, DMF, reflux; (o) KOH, EtOH, RT-12 hrs.

During the oxidative resolution process, racemic intermediate **(11)** was simply treated with (R, R) Mn salen (**2**) in combination with co-oxidant $PhI(OAc)_2$ and KBr in DCM and water.[9]



Scheme 4

Similarly, R-ethyl lipoate (**13a**) was obtained in high enantiomeric excess from racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**11a**) on treatment with Mn salen (S, S) (**2**) along with co-oxidant $PhI(OAc)_2$ and KBr in biphasic solvent (Scheme 4). Ethyl 8-(benzyloxy)-6-oxooctanoate **(14)** obtained during Mn salene oxidation reaction was

recycled by reducing with sodium borohydride to ethyl 8-(benzyloxy)-6-hydroxyoctanoate (**11a**) in 94% yield. R-ethyl lipoate (**13a**) and S-ethyl lipoate (**13b**) were hydrolyzed to corresponding R-lipoic acid (**1a**) and S-lipoic acid (**1b**) by treatment with KOH in ethanol, their spectral data and specific rotation were identical with the reported data in literature. Enantiomeric excess of **11 a** and **11b** were determined by chiral HPLC (Column: chiralcel OD-H, mobile phase: isopropanol:pet ether(10:90), Wave length: 254 nm).

Here, we propose mechanistic cycle for Mn catalysed oxidative resolution of secondary alcohol (Figure 3).

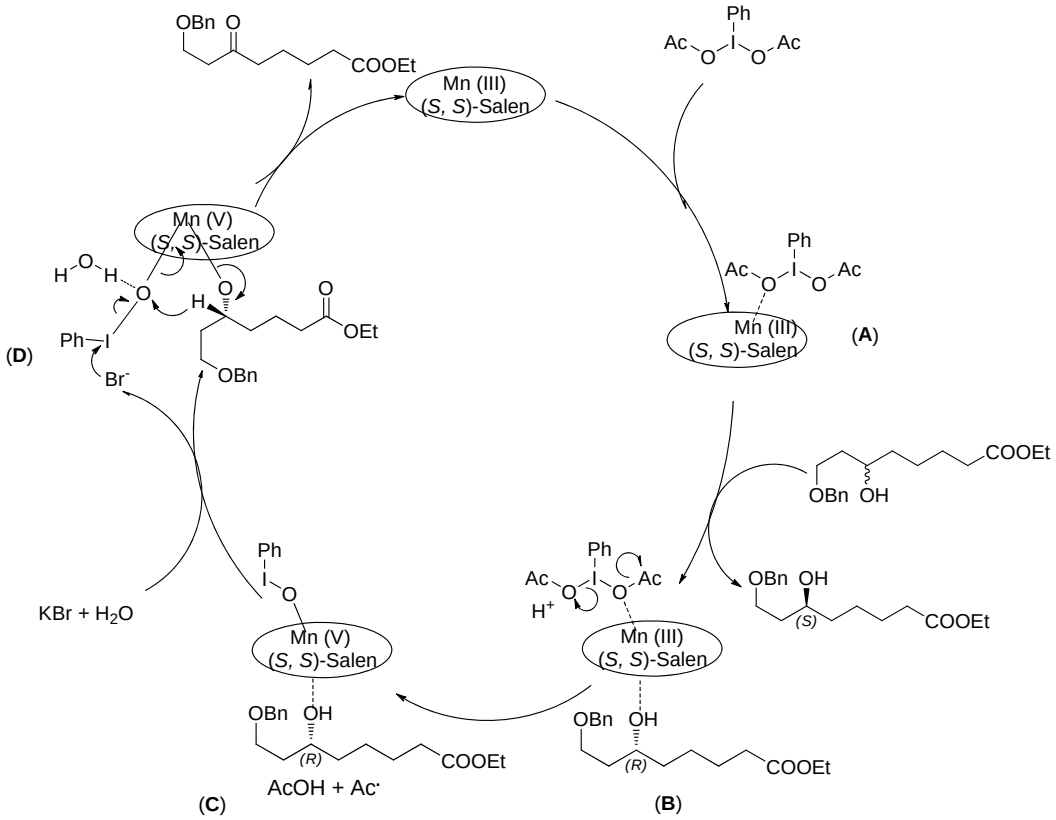


Figure 3: Proposed mechanistic cycle for Mn catalysed oxidative resolution

Above mechanistic cycle (Figure 3) represents a possible mechanism involving a ternary compound **A**, which was generated by addition of catalyst over $PhI(OAc)_2$. This adduct **A** coordinates with the substrate molecule to form the ternary compound **B**. Subsequent electronic reorganization, with elimination of the $CH_3(O)C^{\cdot}$ radical and an acetate group, generates the high-valent manganese adduct **C**. This adduct undergoes tandem attack of a PhIO-(iodosylbenzene) and water molecule to form adduct **D**. This adduct immediately undergoes Br^- induced reorganization of electrons and cleavage to produce keto compound and regeneration of the Mn salen complex. Therefore, it can be

concluded that the key step of this kinetic resolution reaction is the attack of the Br^- ion over the adduct **C** to form adduct **D**.

2.4.4. Conclusion

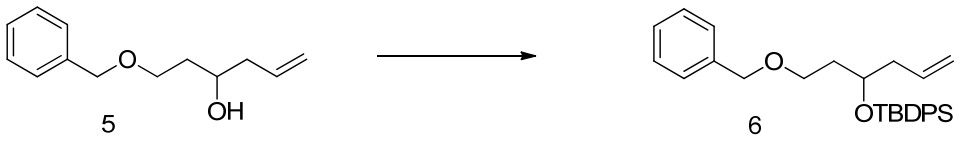
Syhtheses of (R)-α-lipoic acid and (S)-α-lipoic acid were achieved in high enatiomeric excess from easily available 1,3-propanediol in 12 steps in 15.2% overall yields, Mn salen (RR or SS) selective oxidation is a key step.

2.4.5. Experimental

Preparation of 1**-(benzyloxy)hex-5-en-3-ol (5)**

Preparation of **5** is described in earlier section (2.3.5.)

Preparation of ((1-(benzyloxy)hex-5-en-3-yl)oxy)-(tert-butyl)diphenylsilane (6)

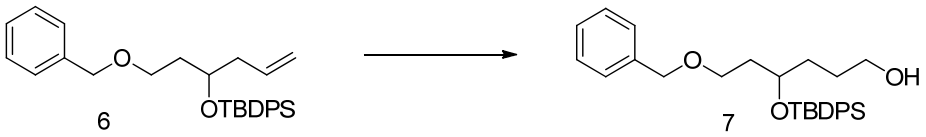


To the stirred solution of 1-(benzyloxy)hex-5-en-3-ol **(5)** (25 gm, 0.1213 mol) in dry DCM (1:1) (100 mL) imidazole (16.4 gm, 0.2426 mol, 2 eq) and TBDPS-Cl (41.69gm, 0.1517 mol, 1.25eq) were added at 0°C. The reaction mixture was stirred at room temperature for 12 hrs. The progress of the reaction was monitored by TLC. After completion, reaction was quenched with cold water at 0°C. The two phases were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over anhydrous Na_2SO_4 and evaporated on rotavapor to get the crude residue. The residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (95:05) as eluent to furnish the racemic ((1-(benzyloxy)hex-5-en-3-yl)oxy)-(tert-butyl)-diphenylsilane **(6)**.

Yield: 49.58 gm (92%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.66-1.75 (m, 2H), 2.04-2.18 (m, 2H), 3.36 (t, *J* = 6.68 Hz, 2H), 3.83-3.91 (m, 1H), 4.25 (s, 2H), 4.69-4.88 (m, 2H), 5.52-5.73 (m, 1H), 7.16-7.31 (m, 10H), 7.57-7.61 (m, 5H) ppm;

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.36, 26.83, 27.01, 36.05, 41.54, 66.86, 70.30, 72.67, 117.10, 127.36, 127.51, 127.68, 128.21, 129.51, 129.65, 134.18, 134.34, 134.50, 135.49, 135.89, 138.50 ppm; Elemental Anal. Calcd for $C_{29}H_{36}O_2Si$: C, 78.33; H, 8.16; Found: C, 78.23; H, 8.21; LCMS: 467.19 $(M+Na)^+$.

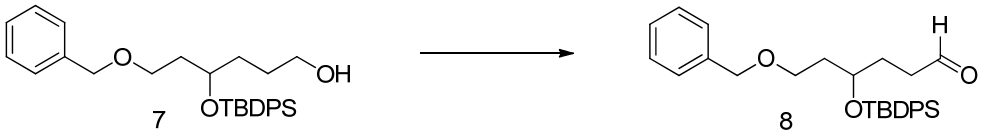
Preparation of 6-(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-hexan-1-ol (7)



To the stirred solution of ((1-(benzyloxy)hex-5-en-3-yl)oxy)-(tert-butyl)diphenylsilane **(6)**) (25 gm, 0.0563 mol) in dry tetrahydrofuran (20 mL) at 0°C, B_2H_6.DMS (2M in toluene, 28 mL, 4.272 gm, 0.0563 mol, 1 eq.) was added. After stirring for 3 hr at 0°C, H_2O_2 (4.3 mL) was added to the reaction mixture and stirring was continued at room temperature for 1 hr. After completion, reaction was quenched with aq solution of sodium acetate (10 mL) at 0°C. The resulting mixture was allowed to warm to room temperature over 1 h with constant stirring. Progress of the reaction was monitored by TLC. After completion, reaction was quenched by dropwise addition of methanol (25 mL) at 0°C. The excess of methanol and THF were evaporated on rotavapor. This reaction mixture then poured into water (50 mL) and was extracted with ethyl acetate (2×250 mL). The combined organic layers were washed with water, brine, dried over anuhydrous Na_2SO_4 and concentrated on rotavapor to give crude residue. The crude residue was purified by flash column chromatography to get 6-(benzyloxy)-4-((tert-butyl-diphenylsilyl)-oxy)-hexan-1-ol **(7).**

Yield: 20.29 gm (78%); colourless oil; IR ($CHCl_3$): ν_{max} 3401, 2936, 1613, 1248, 1083, 820, 729, 663 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.36-1.49 (m, 4H), 1.68-1.77 (m, 2H), 3.31-3.41 (m, 4H), 3.86-3.91 (m, 1H), 4.25 (s, 2H), 7.16-7.34 (m, 10H), 7.57-7.60 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.34, 27.01, 27.76, 32.84, 36.10, 62.83, 66.95, 70.47, 72.71, 127.49, 127.55, 128.25, 129.56, 134.29, 135.89, 138.40 ppm; Elemental Anal.Calcd for $C_{29}H_{38}O_3Si$: C, 75.28; H, 8.20;.Found: C, 75.39; H, 8.28,; LCMS: 485.22 $(M+ Na)^+$.

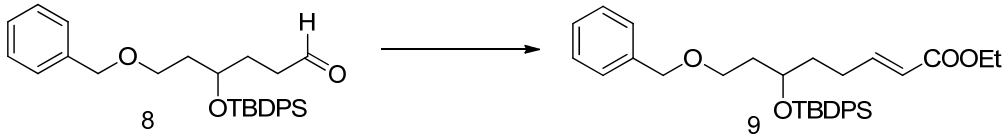
Preparation of 6-(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)hexanal(8)



To the stirred solution of 6-(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-hexan-1-ol **(7)** (20 gm, 0.0433 mol) in anhydrous $CHCl_3$ (200 mL) was added PCC (11.68 gm, 0.0542 mol, 1.25 eq) and stirred at room temperature for ½ hr. Progress of the reaction was monitored by TLC. After completion; stirring was stopped and the reaction mixture was filtered through celite bed. The celite bed was washed with $CHCl_3$ (50 mL). The combined organic layers were concentrated on rotavapor to afford, 6-(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)hexanal **(8)**.

Yield: 18.71 gm (94%); yellow oil; IR ($CHCl_3$): ν_{max} 2985, 1742, 1374, 1243, 1047, 759, 728, 608 cm^{-1}.

Preparation of (E)-ethyl 8-(benzyloxy)-6-((tert-butyldiphenylsilyl)oxy)oct-2-enoate (9)



To the stirred solution of 6-(benzyloxy)-4-((tert-butyl-diphenyl-silyl)oxy)hexanal **(8)** (18 gm, 0.039 mol) in dry THF, ethyl 2-(tri-phenyl-phosphoranylidene)-acetate (20.37 gm, 0.0585 mol, 2 eq) was added and stirred at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, reaction was filtered through a bed of celite and concentrated on rotavapor to obtain crude residue. The crude residue was purified by silica gel column chromatography to afford (E)-ethyl 8-(benzyloxy)-6-((tert-butyldiphenylsilyl)-oxy)-oct-2-enoate **(9).**

Yield: 0.661 gm (89%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.19 (t, *J* = 7.20 Hz, 3H), 1.42-1.54 (m, 2H), 1.65-1.77 (m, 2H), 2.01-2.12 (m, 2H), 3.38 (t, *J* = 6.60 Hz, 2H), 3.81-3.92 (m, 1H), 4.07 (q, *J* = 7.20 Hz, 2H), 4.26 (s, 2H), 5.52 (d, *J* = 15.67 Hz, 1H), 6.63-6.78 (m, *J* = 6.82 Hz, 15.67 Hz, 1H), 7.13-7.34 (m, 10H), 7.56-7.50 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.24, 19.36, 27.00, 27.46, 34.94, 36.28, 60.04,

66.81, 70.16, 72.75, 121.14, 127.43, 127.53, 128.26, 129.60, 134.13, 135.83, 138.36, 148.90, 166.59 ppm. Elemental Anal.Calcd for $C_{33}H_{42}O_4Si$: C, 74.68; H, 7.98;. Found: C, 74.54; H, 8.06.

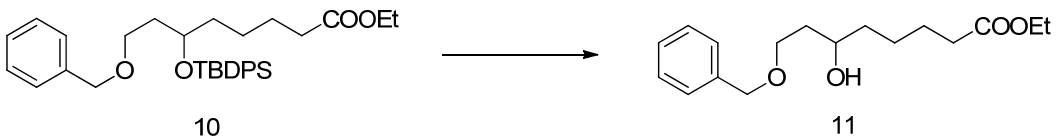
Preparation of ethyl 8-(benzyloxy)-6-((t-butyldiphenylsilyl)oxy)octanoate (10)

9 10

To the stirred solution of (E)-ethyl 8-(benzyloxy)-6-((tert-butyldiphenylsilyl)oxy)oct-2-enoate **(9)** (20 gm, 0.0377 mol) in ethyl acetate (50 mL) was added 10% Pd/C (100 mg) and stirred under H_2 balloon pressure for 2 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was filtered through celite bed, washed with ethyl acetate and concentrated on rotavapor to obtain crude residue. The residual oil was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (97:03) as eluent to afford ethyl 8-(benzyloxy)-6-((tert-butyldiphenylsilyl)-oxy)octanoate **(10).**

Yield: 18.26 gm (91%); yellow oil; IR ($CHCl_3$): ν_{max} 3020, 2930, 2859, 1726, 1374, 1216, 1081, 759, 703, 669 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$): δ 0.96 (s, 9H), 1.12-1.19, (t merged with m, *J* = 7.20 Hz, 5H), 1.30-1.37 (m, 4H), 1.65-1.75 (m, 2H), 2.02-2.10 (t, *J* = 7.55 Hz, 2H), 3.40 (t, *J* = 6.69 Hz, 2H), 3.76-3.88 (m, 1H), 4.01 (q, *J* = 7.20 Hz, 2H), 4.27 (s, 2H), 7.14-7.34 (m, 10H), 7.56-7.61 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.19, 19.35, 24.21, 24.47, 24.87, 27.00, 34.19, 36.27, 36.42, 60.07, 67.01, 70.54, 72.71, 127.42, 127.53, 128.22, 129.45, 129.69, 134.29, 134.43, 135.86, 138.47, 173.63 ppm; Elemental Anal. Calcd for $C_{33}H_{44}O_4Si$: C, 74.39; H, 8.32;. Found: C, 74.44; H, 8.26.

Preparation of ethyl 8-(benzyloxy)-6-hydroxyoctanoate (11)

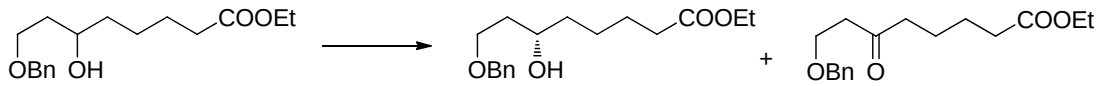


10 11

To the stirred solution of ethyl 8-(benzyloxy)-6-((tert-butyldiphenylsilyl)oxy)-octanoate **(10)** (18 gm, 0.0338 mol) in dry THF (50 mL) was added TBAF (8.837 gm, 0.0338 mole, 1 eq) in inert atmosphere and stirred for 6 hr. Progress of the reaction was monitored by TLC technique. After completion of the reaction, it was quenched with cold water at 0°C and extracted with ethyl acetate (3 x 100 mL). The organic layer was separated, washed with water (3 x 10 mL) followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. The residual oil was purified by silica gel column chromatography using petroleum ether/ethyl acetate (75:25) as eluent to afford ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11).**

Yield: 8.652 gm (87%); yellow oil; IR ($CHCl_3$): ν_{max} 3438, 3067, 2927, 1716, 1278, 1117, 1071, 714, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.20 Hz, 3H), 1.26-1.40 (m, 4H), 1.57-1.71 (m, 4H), 2.23 (t, *J* = 7.58 Hz, 2H), 2.96 (s, 1H), 3.51-3.63 (m, 2H), 3.67-3.74 (m, 1H), 4.04 (q, *J* = 7.20 Hz, 2H), 4.44 (s, 2H), 7.25 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.21, 19.36, 24.22, 24.88, 27.01, 34.21, 36.27, 36.43, 60.11, 67.02, 70.54, 72.72, 127.43, 128.24, 138.54, 173.67 ppm. Elemental Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.42; H, 8.94.

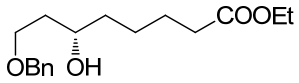
Preparation of (S)-ethyl 8-(benzyloxy)-6-hydroxyoctanoate (11a)



11 11a 14

To the stirred solution of racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11)** (700 mg, 2.377 mmol) in DCM (5 mL) was added water (1 mL), (S, S) Mn salen (**2**) (30 mg, 0.0476 mmol, 2 mole %), KBr (198 mg, 1.663 mmol, 0.7 eq) and stirred for ½ hr. Then $PhI(OAc)_2$ (535 mg, 1.663 mmol, 0.7 eq) was added and the reaction mixture was stirred further for 1 hr. The progress of the reaction was monitored by TLC. After completion, the reaction was diluted with DCM (20 mL) and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated on rotavapor to obtain crude residue. The residual oil was purified by column chromatography using petroleum ether/ ethyl acetate (8:2) as eluent to afford (S)-ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11a)** and ethyl 8-(benzyloxy)-6-oxooctanoate **(14).**

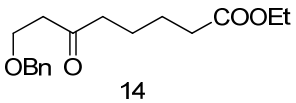
(S)-Ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11a)**



11a

Yield: 0.661 gm (49.7%); yellow oil; $[\alpha]_D^{25}$ = +7.81°(*c* 1, $CHCl_3$) { Lit.[10] $[\alpha]_D^{25}$ = +7.44 °(*c* 1.00, $CHCl_3$)}; ee >98%, [Chiral HPLC analysis: Chiralcel OD-H (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 10:90; flow rate: 0.5 mL/min., detector: 254 nm, t_R=17.35 min., t_S= 21.32 min.]; IR ($CHCl_3$): ν_{max} 3438, 3067, 2927, 1716, 1278, 1117, 1071, 714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.20 Hz, 3H), 1.36-1.57 (m, 4H), 1.62-1.71 (m, 4H), 2.23 (t, *J* = 7.58 Hz, 2H), 2.96 (s, 1H), 3.51-3.63 (m, 2H), 3.67-3.79 (m, 1H), 4.04 (q, *J* = 7.20 Hz, 2H), 4.44 (s, 2H), 7.25 (s, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.21, 19.36, 24.22, 24.88, 27.01, 34.21, 36.27, 36.43, 60.11, 67.02, 70.54, 72.72, 127.43, 128.24, 138.57, 173.67 ppm. Elemental Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.45; H, 8.82.

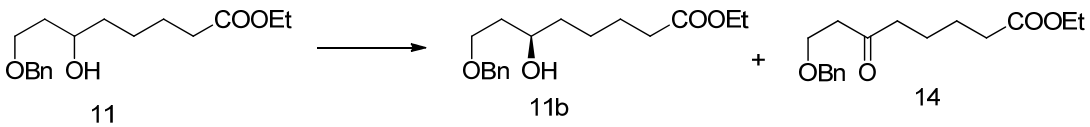
Ethyl 8-(benzyloxy)-6-oxooctanoate **(14)**



14

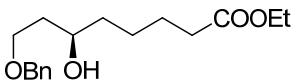
Yield: 0.661 gm (47.5%); yellow oil; IR ($CHCl_3$): ν_{max} 3437, 3021, 2924, 1745, 1604, 1215, 758, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.20 Hz, 3H), 1.50-1.57 (m, 4H), 2.19-2.23 (m, 2H), 2.40- 2.43 (m, 2H), 2.61 (t, (q, *J* = 6.31 Hz, 2H), 3.66 (t, *J* = 6.32 Hz, 2H), 4.00 (q, *J* = 7.20 Hz, 2H), 4.43 (s, 2H), 7.19-7.28 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.14, 22.81, 24.30, 33.98, 41.37, 42.77, 59.82, 60.20, 65.23, 73.14, 127.60, 128.30, 129.49, 132.96, 207.33, 208.80 ppm. Elemental Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.94; H, 8.32.

Preparation of (R)-ethyl 8-(benzyloxy)-6-hydroxyoctanoate (11b)



To the stirred solution of racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11)** (700 mg, 2.377 mmol) in DCM (5 mL) was added water (1 mL), (R, R) Mn salen (**2**) (30 mg, 0.0476 mmol, 2 mole %) and KBr (198 mg, 1.663 mmol, 0.7 eq) and stirred for ½ hr. Then $PhI(OAc)_2$ (535 mg, 1.663 mmol, 0.7 eq) was added and the reaction mixture was stirred for a further 1 hr . The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with DCM (20 mL), organic layer washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude residue. The residual oil was purified by column chromatography using petroleum ether/ ethyl acetate (8:2) as eluent to afford (R)-ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11b)** and ethyl 8-(benzyloxy)-6-oxooctanoate **(14).**

(R)-Ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11b)**



11b

Yield: 0.661 g (47%); yellow oil; $[\alpha]_D^{25}$ = -7.01° (*c* 1.00, $CHCl_3$) ee >98%, [Chiral HPLC analysis: Chiralcel OD-H (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 10:90; flow rate: 0.5 mL/min., detector: 254 nm, t_R= 17.39 min., t_S= 21.14 min.]; IR ($CHCl_3$): ν_{max} 3438, 3067, 2927, 1716, 1278, 1117, 714, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.20 Hz, 3H), 1.36-1.57 (m, 4H), 1.62-1.71 (m, 4H), 2.23 (t, *J* = 7.58 Hz, 2H), 2.96 (s, 1H), 3.51-3.63 (m, 2H), 3.67-3.79 (m, 1H), 4.04 (q, *J* = 7.20 Hz, 2H), 4.44 (s, 2H), 7.25 (s, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ14.21, 19.36, 24.22, 24.88, 27.01, 34.21, 36.27, 36.43, 60.11, 67.02, 70.54, 72.72, 127.43, 128.24, 139.57, 173.67 ppm; Elemental Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.46; H, 8.84.

Ethyl 8-(benzyloxy)-6-oxooctanoate **(14)**: Yield: 0.661 g (48.4%); yellow oil.

Preparation of (S)-ethyl6, 8 -dihydroxyoctanoate (12a)

11a 12a

To the stirred solution of **11a** (500 mg, 2.447 mmol) in ethyl acetate (10 mL) was added catalytic amount of 10% Pd (20 mg) and stirred under H_2 atmosphere at room temperature for 6 hrs. Progress of the reaction was monitored by TLC. After completion, reaction was stopped and filtered over celite bed, and celite bed washed with ethyl acetate. All the organic layers were combined and concentrated on rotavapor to get crude residue. Purification of the crude residue was carried out by silica gel column chromatography using petroleum ether: ethyl acetate, (40:60) to give **12a.**

Yield: 313 mg (90.3%); yellow oil; $[\alpha]_D^{25} = -1.84^o$ (*c* 2.00, $CHCl_3$) { Lit.[10] $[\alpha]_D^{23} = -1.23$ (*c* 1.62, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3438, 3020, 2400, 1731, 1216, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.20 Hz, 3H), 1.22-1.43 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.45 Hz, 2H), 3.52 (s, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 172.95 ppm. Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.84; H, 9.92.

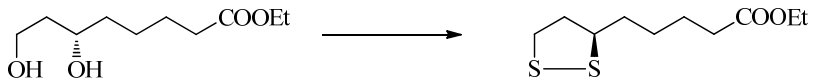
Preparation of (R)-ethyl 6, 8-dihydroxyoctanoate (12b)

11b 12b

To the stirred solution of **11b** (500 mg, 2.447 mmol) in ethyl acetate (10 mL) was added catalytic amount of 10% Pd (20 mg) and stirred under H_2 atmosphere at room temperature for 6 hrs. Progress of the reaction was monitored by TLC. After completion, the reaction was stopped and filtered over celite bed; celite bed was washed further with ethyl acetate. All The organic layers were combined and concentrated on rotavapor to get crude residue. Purification of the crude residue carried out by silica gel column chromatography using petroleum ether/ ethyl acetate (40:60) gave **12b.**

Yield: 315 mg (91.4%); yellow oil; $[\alpha]_D^{25} = +1.74^o$ (*c* 2.00, $CHCl_3$) { Lit.[10] $[\alpha]_D^{23} = +1.24^o$ (*c* 1.62, $CHCl_3$)}; IR ($CHCl_3$) ν_{max} 3438, 3020, 2400, 1731, 1216, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.20 Hz, 3H), 1.36-1.43 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.36 Hz 2H), 3.52 (s, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 172.95 ppm. Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.84; H, 9.92.

Preparation of (5*R*)-ethyl-5-(1, 2-dithiolan-3-yl)-pentanoate or (*R*)-ethyl lipoate (13a)

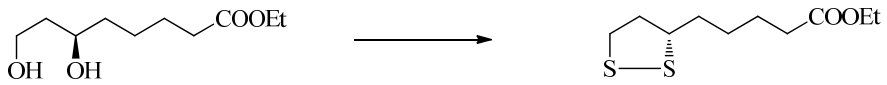


12a 13a

To the stirred solution of ethyl 6, 8-dihydroxyoctanoate **12a** (200 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0°C and $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotavapor to get crude compound. The crude compound was utilised directly in the next reaction. The solution of crude mysylate, finely ground $Na_2S{\cdot}H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhyd DMF (5 mL) was heated at 80 °C for 24 hr and then stirred at room temperature for 1hr. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated on rotavapor to furnish crude residue. The crude residue purified by silica gel column chromatrography using petroleum ether/ ethyl acetate (90:10) to furnish **13a** as yellow oil.

Yield: 173 mg (76.4%); yellow oil; $[\alpha]_D^{25}$ = +54.31°(*c* 1.00, $CHCl_3$) {Lit.[11] $[\alpha]_D$= +61° (*c* 1.00, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.22 Hz, 3H), 1.45-1.51 (m, 2H), 1.61-1.70 (m, 4H), 1.84-1.93 (m, 1H), 2.30 (t, *J* = 7.46 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.20 (m, 2H), 3.49-3.62 (m, 1H), 4.11 (q, *J* = 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 ppm.

Preparation of (5*S*)-ethyl-5-(1, 2-dithiolan-3yl)-pentanoate or (*S*)-ethyl lipoate (13b)



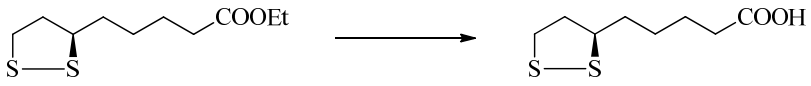
12b 13b

To the stirred solution of ethyl 6, 8-dihydroxyoctanoate **12b** (200 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0°C and $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (5 mL) and the organic layer was washed

with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotavapor to get crude compound. The crude compound was utilised directly in the next reaction. The solution of crude mysylate, finely ground $Na_2S{\cdot}H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhyd DMF (5 mL) was heated at 80 °C for 24 hr and then stirred at room temperature for 1hr. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated on rotavapor to furnish crude residue. The crude residue purified by silica gel column chromatrography using petroleum ether/ ethyl acetate (90:10) to furnish **13b** as yellow oil.

Yield: 174 mg (76.8%); yellow oil; $[\alpha]_D^{25}$ = -50.92° (*c* 1.00, $CHCl_3$) {Lit.[11] $[\alpha]_D$= -61° (*c* 1.00, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.22 Hz, 3H), 1.45-1.48 (m, 2H), 1.61-1.70 (m, 4H), 1.88-1.94 (m, 1H), 2.30 (t, *J* = 7.48 Hz, 2H), 2.43-2.49 (m, 1H), 3.08-3.20 (m, 2H), 3.49-3.62 (m, 1H), 4.11 (q, *J* = 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 ppm.

Preparation of (*R*)-5-(1, 2-dithiolan-3-yl)-pentanoic acid or (*R*)-α-lipoic acid (1a)



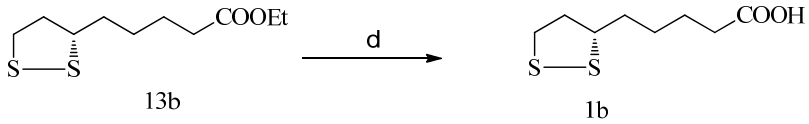
13a 1a

To the stirred solution of **13a** (110 mg, 0.4694 mmol) in EtOH (5 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at r. t. for 24 h. After completion of reaction EtOH was evaporated on rotavapor and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2. The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude residue. The resulting residue was purified by silica gel column chromatography using EtOAc-petroleum ether (15:85) as an eluent, to afford **1a** as yellow solid.

Yield: 82 mg (85%); yellow solid; mp 44°C, **(**Lit.[12] mp 44°C**)** ; $[\alpha]_D^{25}$ = +103.18° (*c* 0.88, Benzene){Lit.[12] $[\alpha]_D$= +102°(*c* 0.88, Benzene)}; IR ($CHCl_3$): ν_{max} 3021, 2928, 1709, 1409, 1216, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41-1.49 (m, 2H), 1.55-1.75 (m, 4H), 1.81-1.96 (m, 1H), 2.36 (t, *J* = 7.33 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.24 (m, 2H), 3.49-3.63

(m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm; Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.80. Found: C, 46.48; H, 6.90; S, 31.82; LCMS: 204.93 $(M-1)^+$.

Preparation of (*S*)-5-(1, 2-dithiolan-3-yl)-pentanoic acid or (*S*)-α-Lipoic acid (1b)

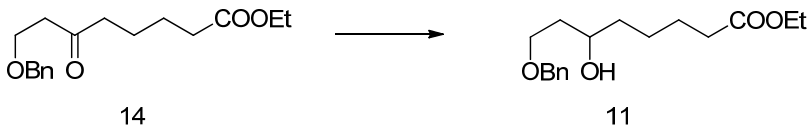


13b 1b

To the stirred solution of **13b** (100 mg, 0.4267 mmol) in EtOH (10 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at r. t. for 24 h. MeOH was evaporated on rotavapor and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2. The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotavapor to afford crude residue. The resulting residue was purified by flash column chromatography (silica gel) using petroleum ether/ ethylacetate (85:15) as an eluent, to afford **1b** as yellow solid.

Yield: 76 mg (86%); yellow solid; mp 44°C, (Lit.[12] mp 44°C); $[\alpha]_D^{25}$ = -101.4°(*c* 0.85, Benzene){Lit.[12] $[\alpha]_D$= -104.4° (*c* 0.85, Benzene)}; IR ($CHCl_3$): ν_{max} 3021, 2928, 1709, 1409, 1216, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.55 (m, 2H), 1.59-1.75 (m, 4H), 1.81-1.98 (m, 1H), 2.36 (t, *J* = 7.32 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.24 (m, 2H), 3.49-3.63 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm. Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.80. Found: C, 46.49; H, 6.89; S, 31.79; LCMS: 204.93$(M-1)^+$.

Ethyl 8-(benzyloxy)-6-hydroxyoctanoate (11)



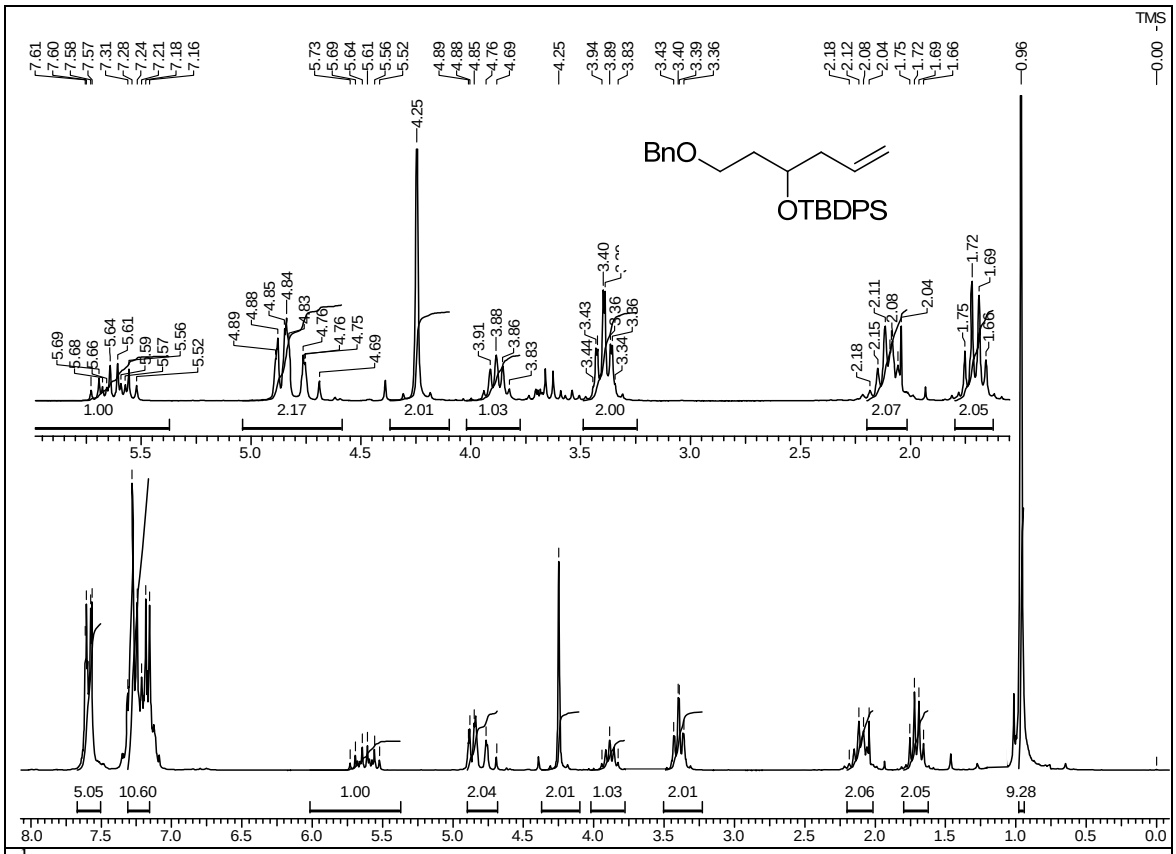
14 11

To the stirred solution of ethyl 8-(benzyloxy)-6-oxooctanoate **(14)** (700 mg, 2.4 mmol) in ethanol (20 mL) was added $NaBH_4$ (57 mg, 2.4 mmol, 1 eq) under N_2 atmosphere and reaction mixture was stirred for 3 hr. Progress of the reaction was monitored by TLC.

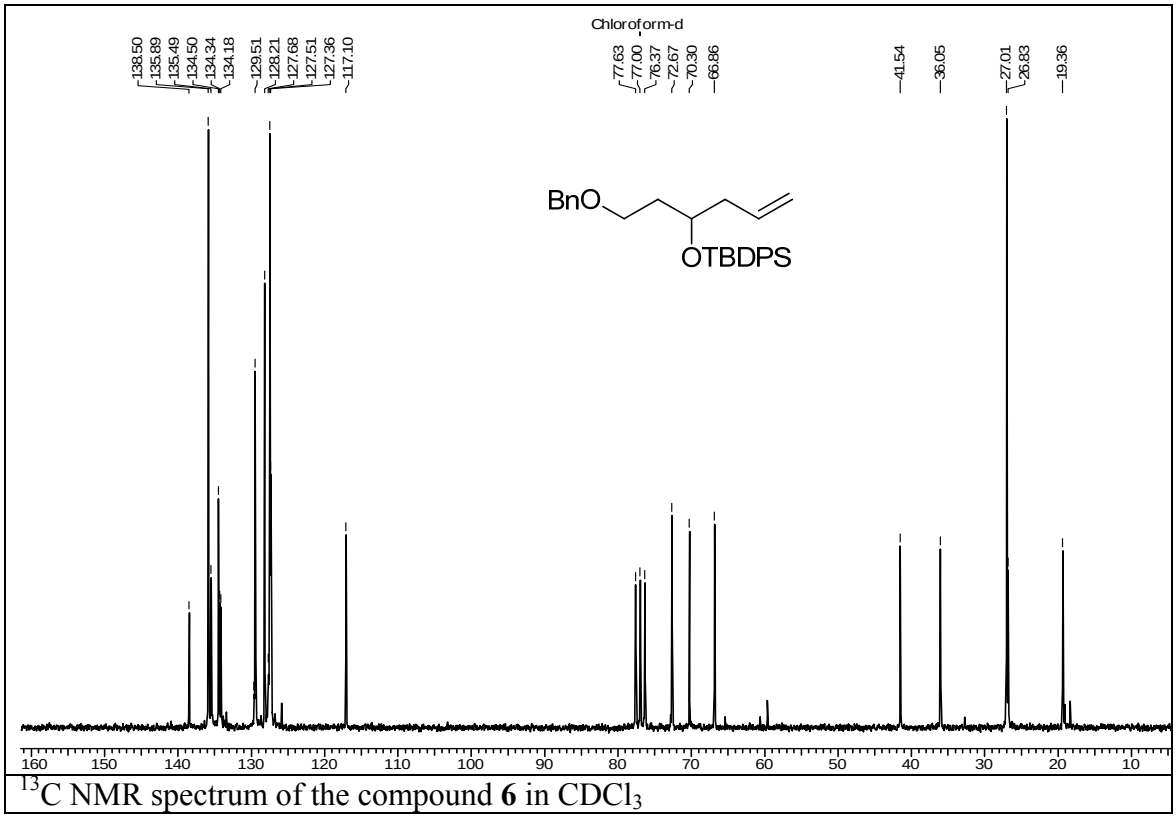
After completion of the reaction, the reaction was quenched with 1- 2-drops of acetic acid and excess of ethanol removed under vacuum. The crude reaction mass extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, (10 mL), dried over anhydrous Na_2SO_4 and concentrated on rotavapor to get the crude residue. The residual oil was purified by silica gel column chromatography using petroleum ether/ ethylacetate (75:25) as eluent to afford ethyl 8-(benzyloxy)-6-hydroxyoctanoate **(11).**

Yield: 662 mg, (94%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.20 Hz, 3H), 1.26-1.40 (m, 4H), 1.57-1.71 (m, 4H), 2.23 (t, *J* = 7.58 Hz, 2H), 2.96 (s, 1H), 3.51-3.63 (m, 2H), 3.67-3.74 (m, 1H), 4.04 (q, *J* = 7.20 Hz, 2H), 4.44 (s, 2H), 7.25 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.21, 19.36, 24.22, 24.88, 27.01, 34.21, 36.27, 36.43, 60.11, 67.02, 70.54, 72.72, 127.43, 128.24, 138.54, 173.67 ppm.

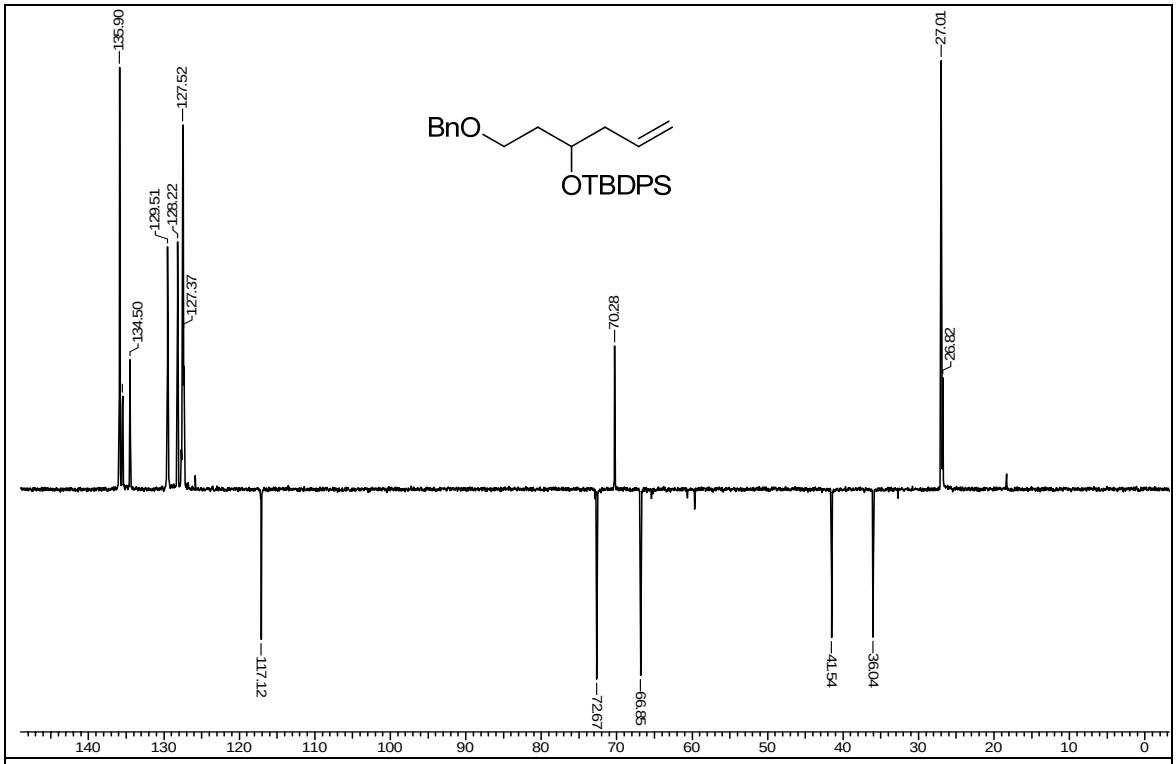
2.4.6. Analytical data



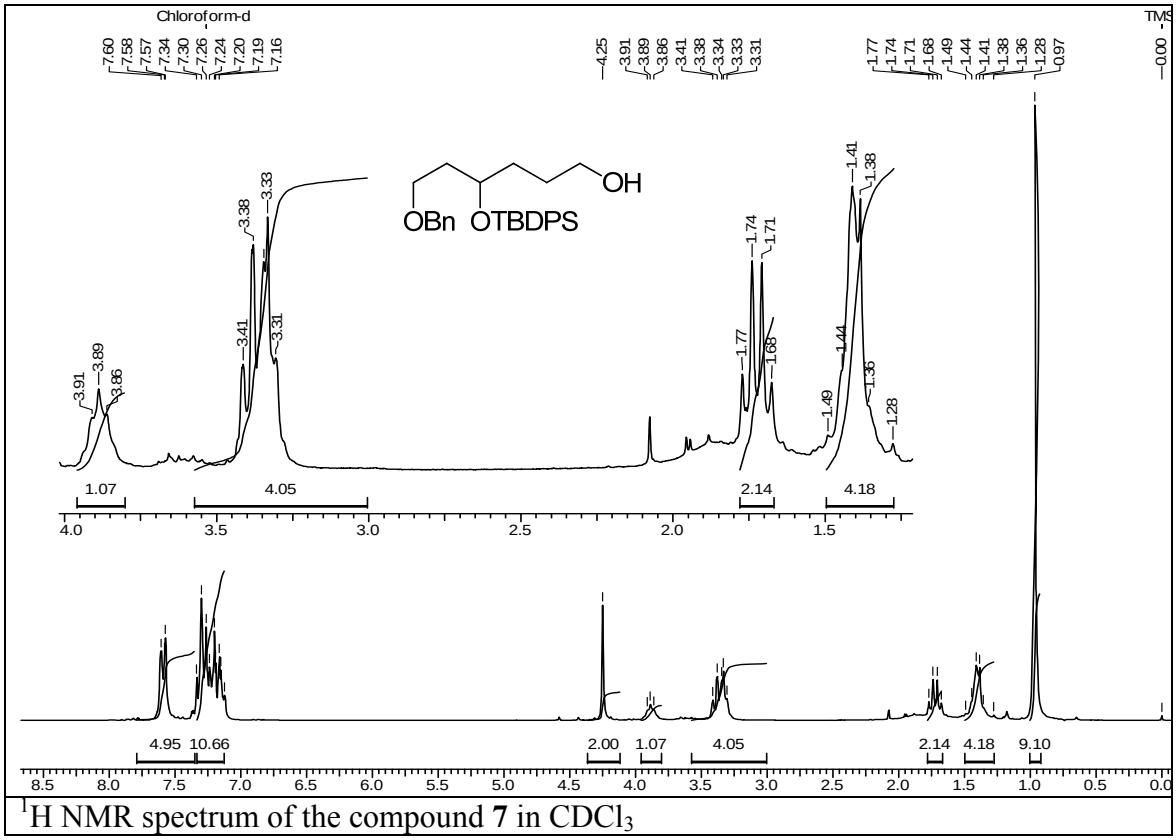
^{1}H NMR spectrum of the compound **6** in $CDCl_3$



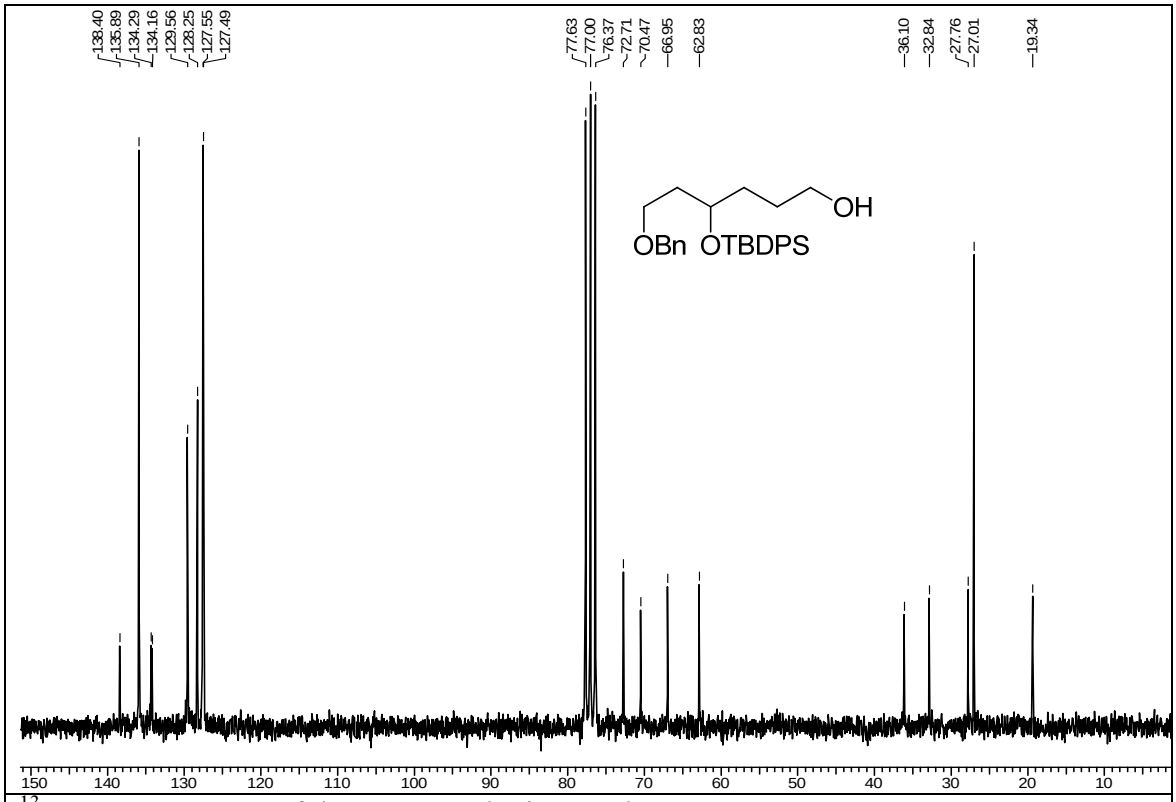
^{13}C NMR spectrum of the compound **6** in $CDCl_3$



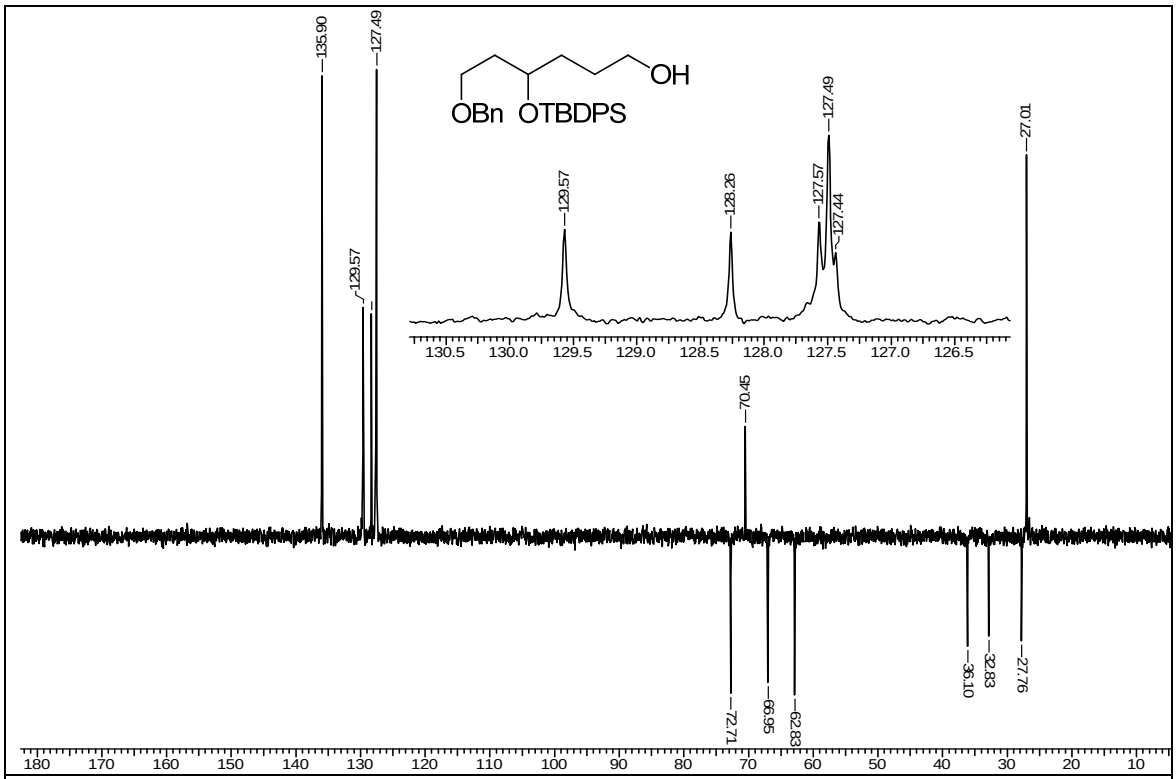
Dept NMR spectrum of the compound **6** in $CDCl_3$



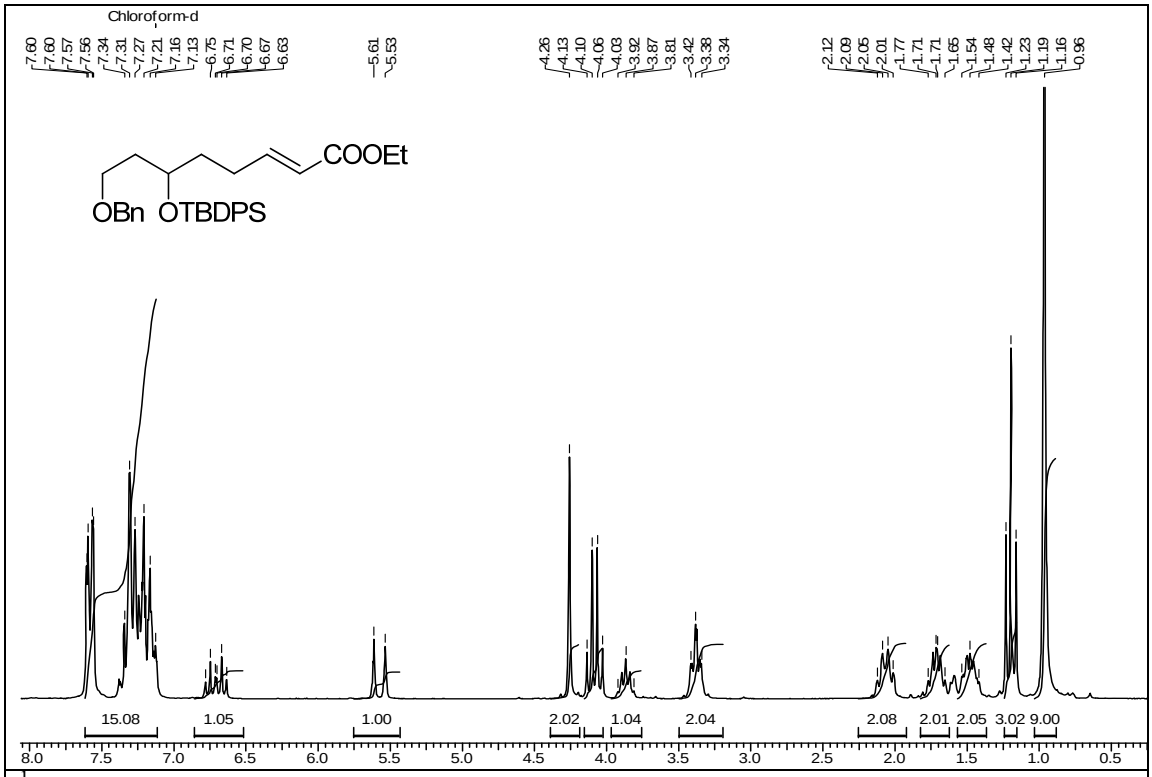
^{1}H NMR spectrum of the compound **7** in $CDCl_3$



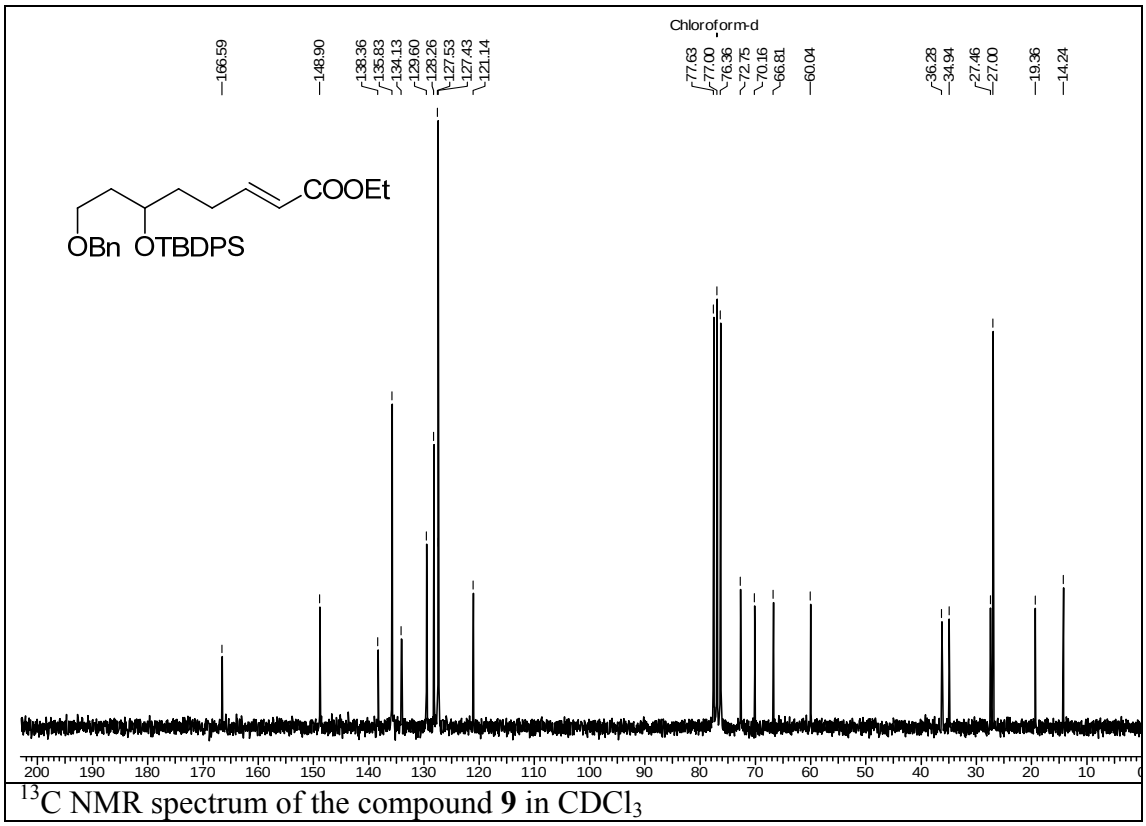
^{13}C NMR spectrum of the compound **7** in $CDCl_3$



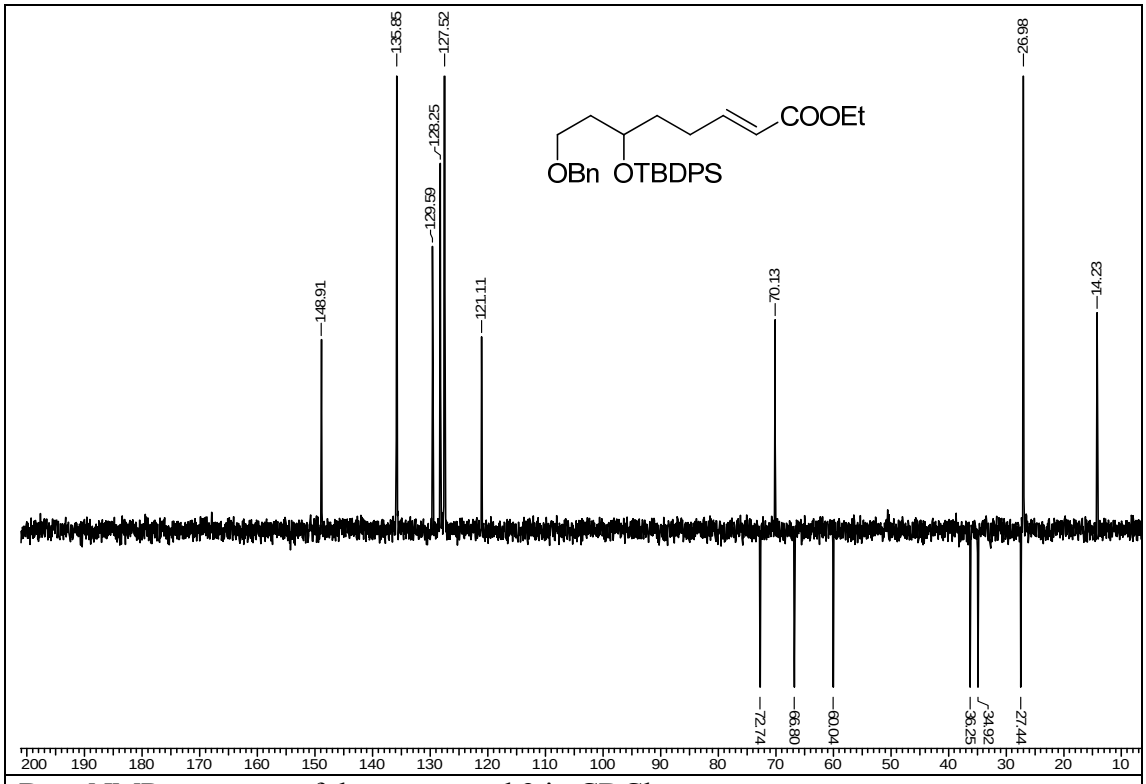
Dept NMR spectrum of the compound **7** in $CDCl_3$



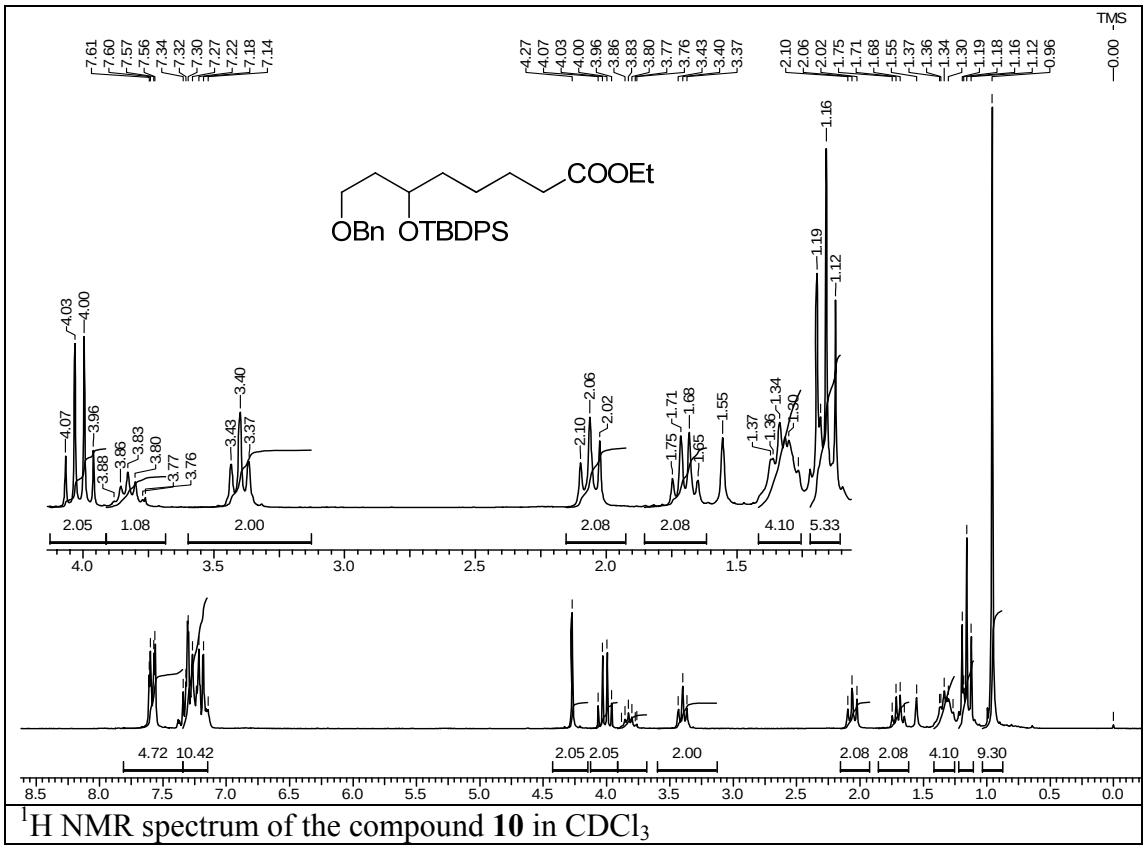
^{1}H NMR spectrum of the compound **9** in $CDCl_3$



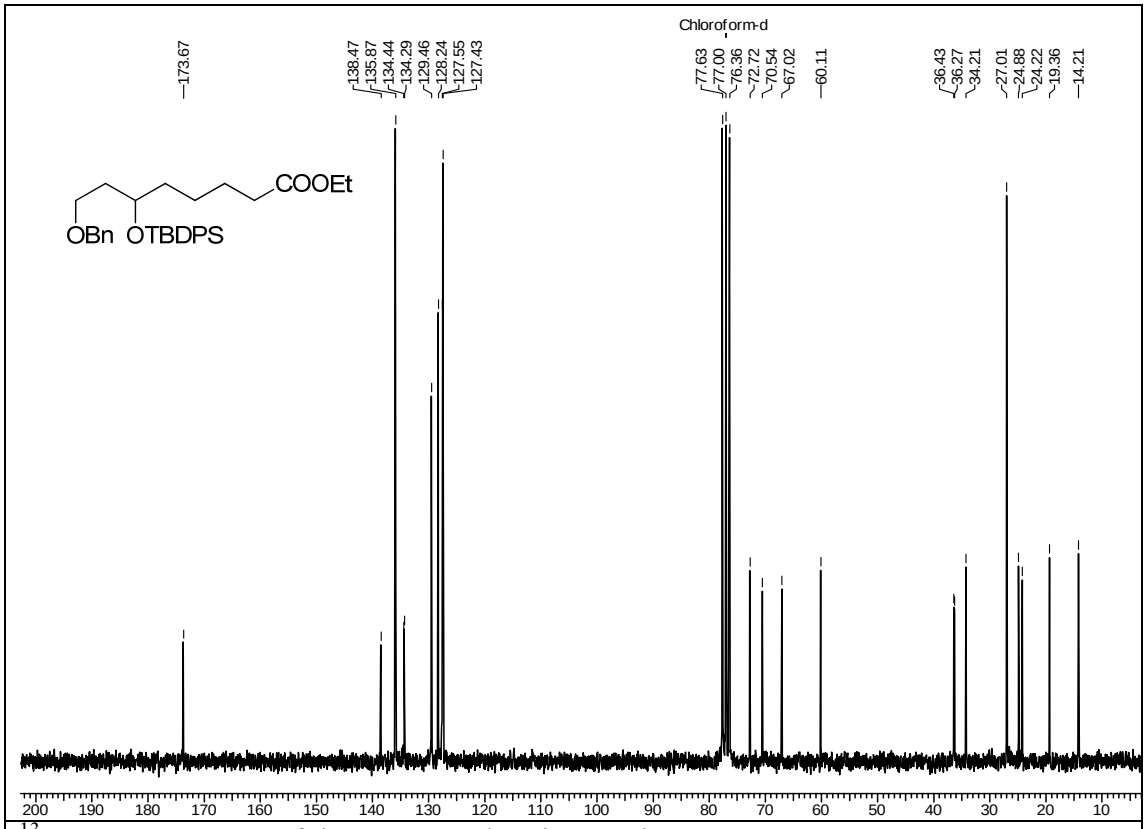
^{13}C NMR spectrum of the compound **9** in $CDCl_3$



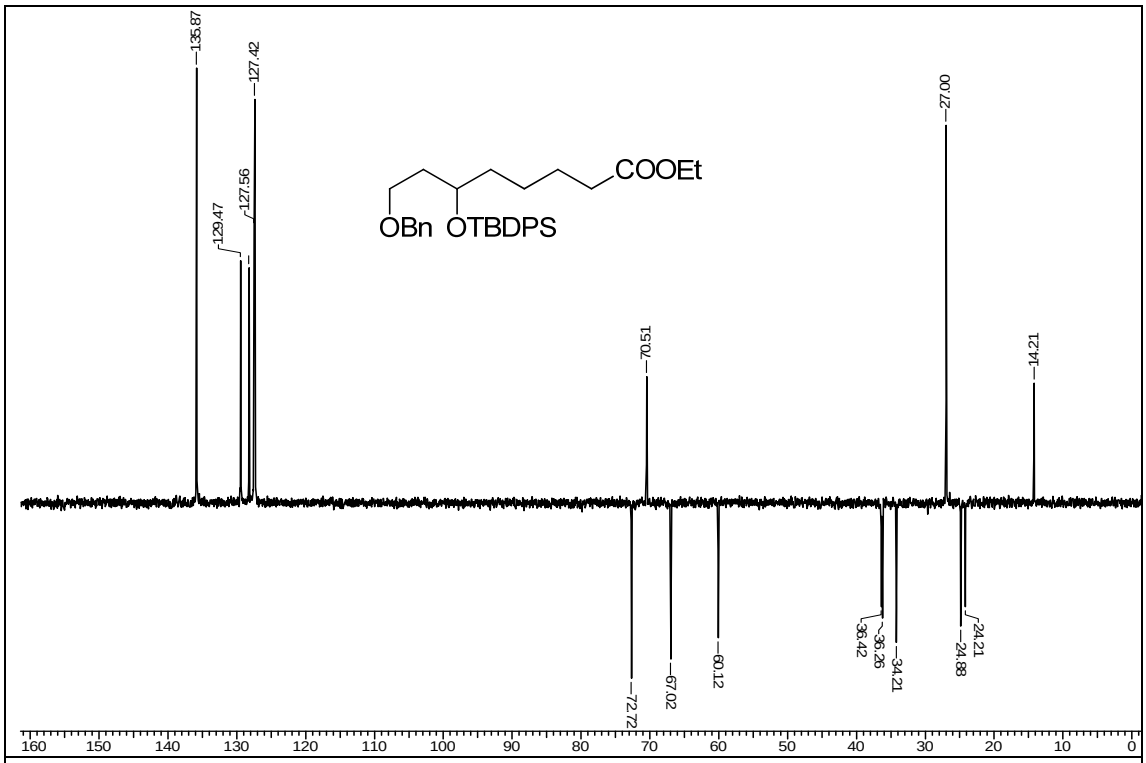
Dept NMR spectrum of the compound **9** in $CDCl_3$



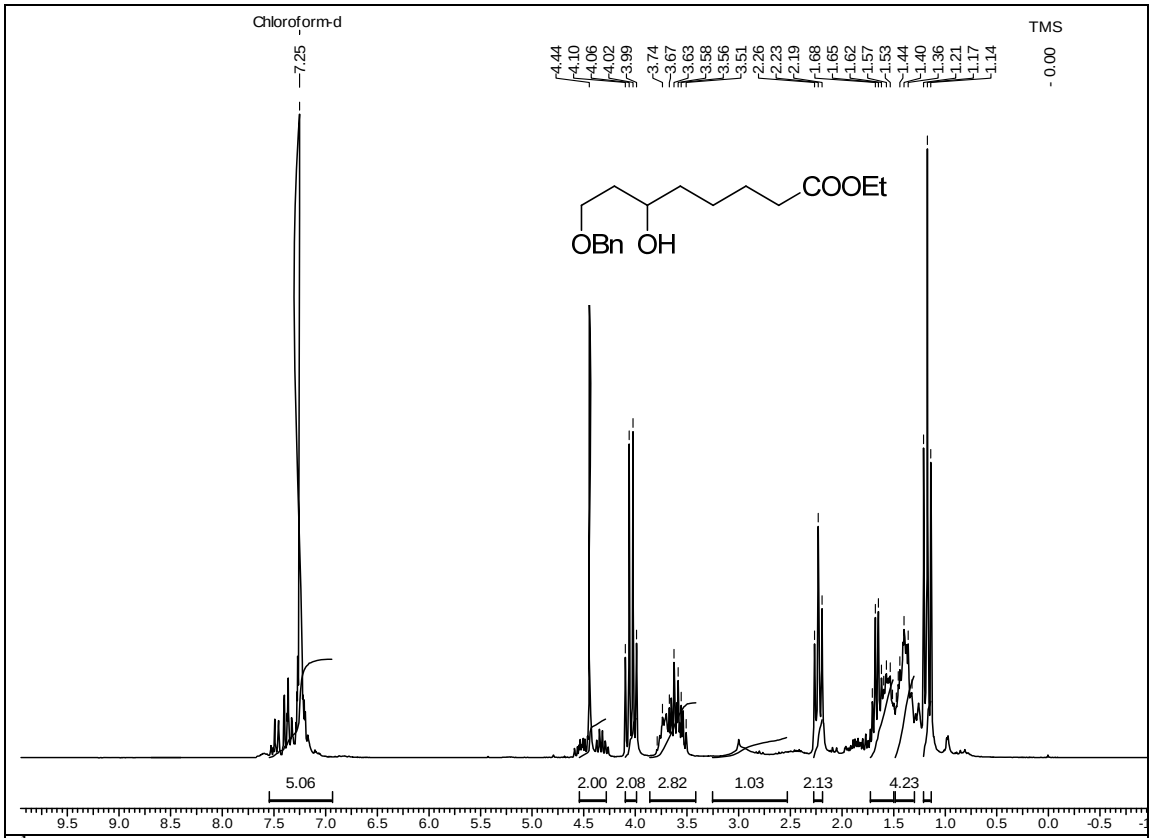
^{1}H NMR spectrum of the compound **10** in $CDCl_3$



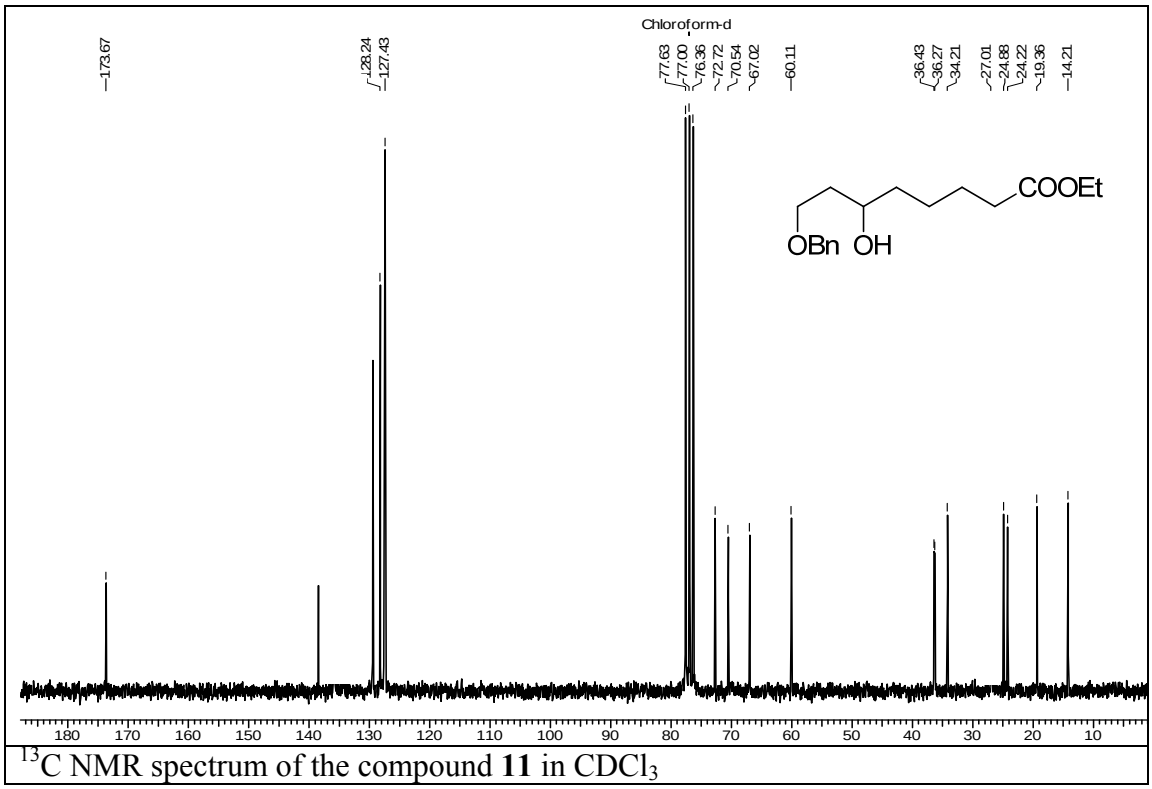
^{13}C NMR spectrum of the compound **10** in $CDCl_3$



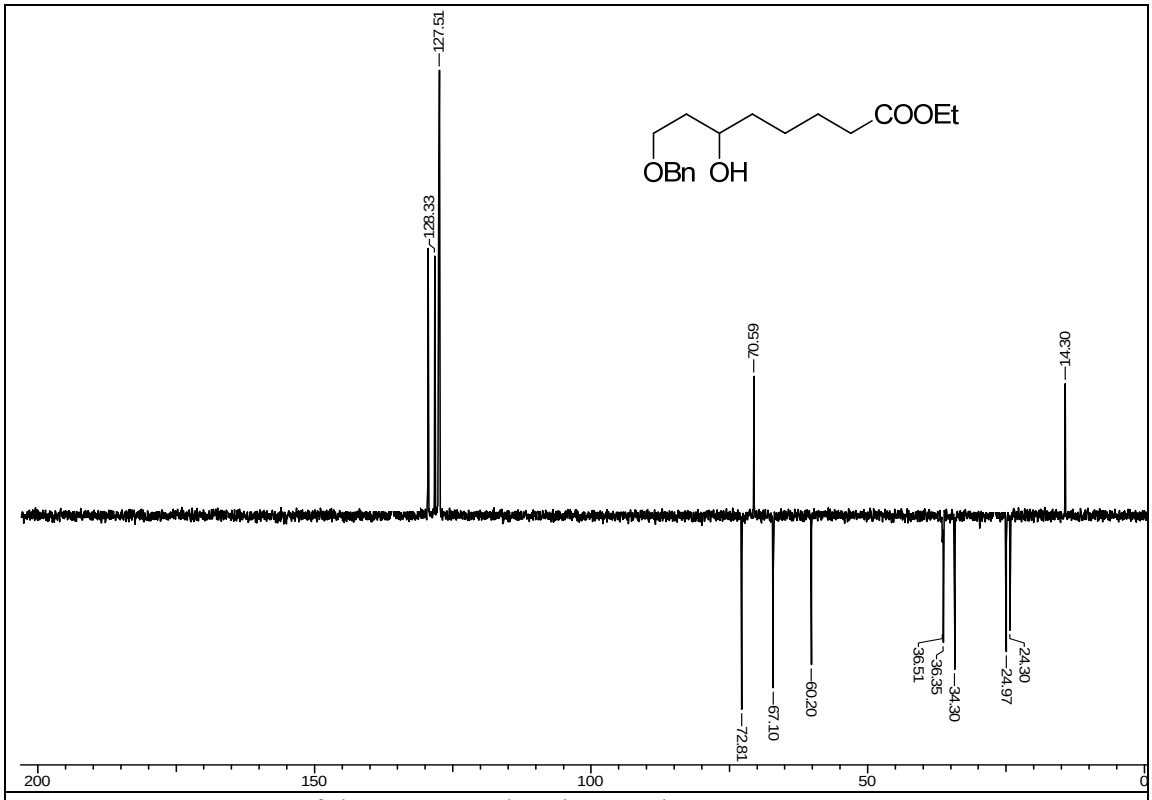
Dept NMR spectrum of the compound **10** in $CDCl_3$



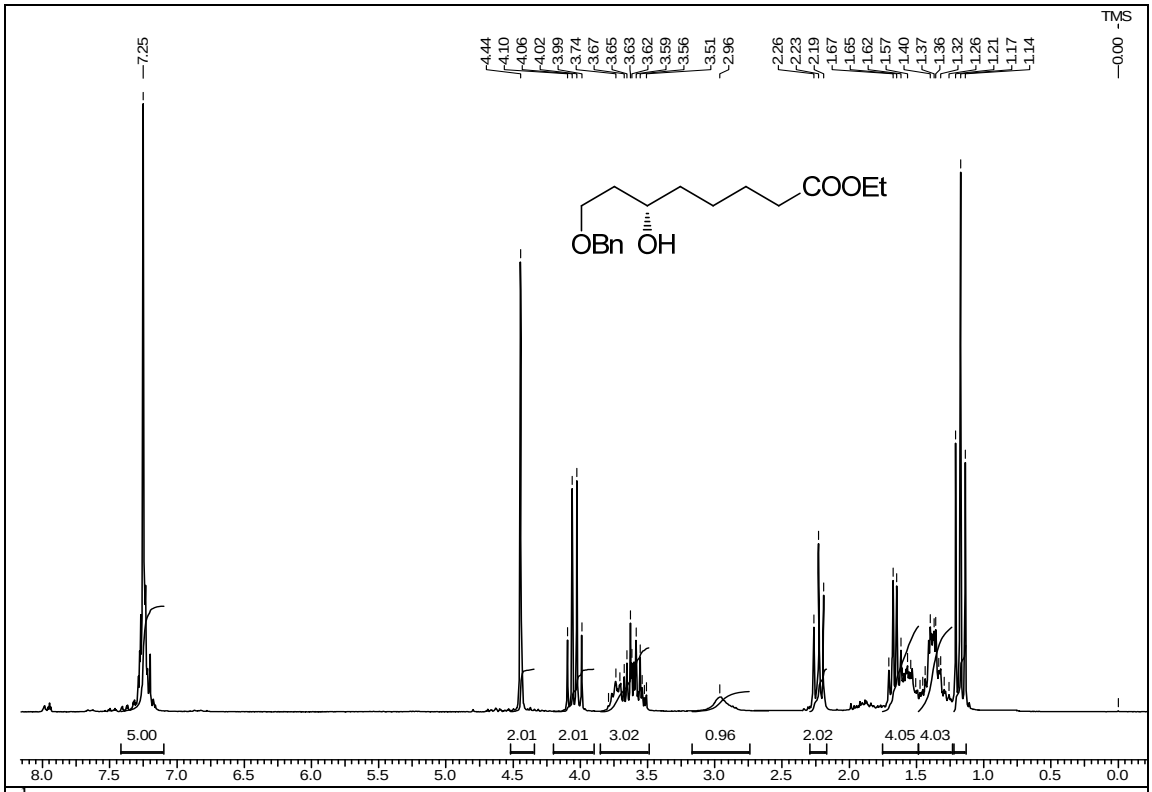
^{1}H NMR spectrum of the compound **11** in $CDCl_3$



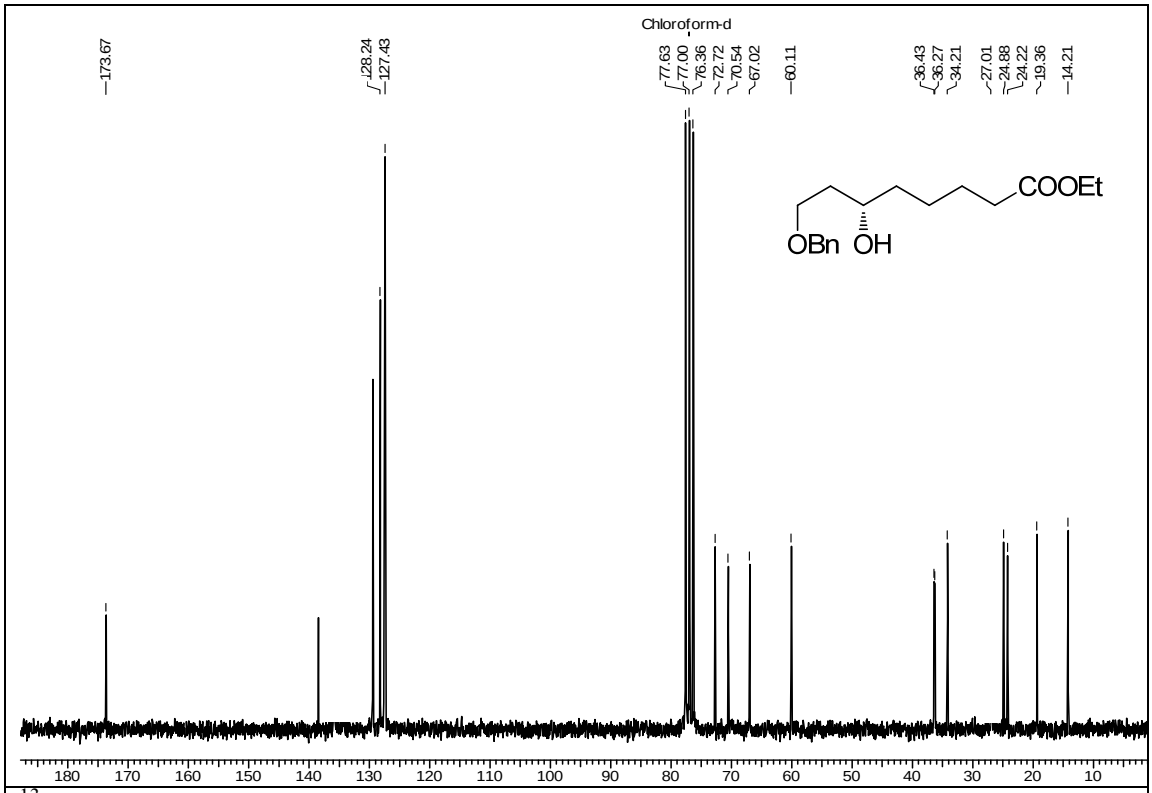
^{13}C NMR spectrum of the compound **11** in $CDCl_3$



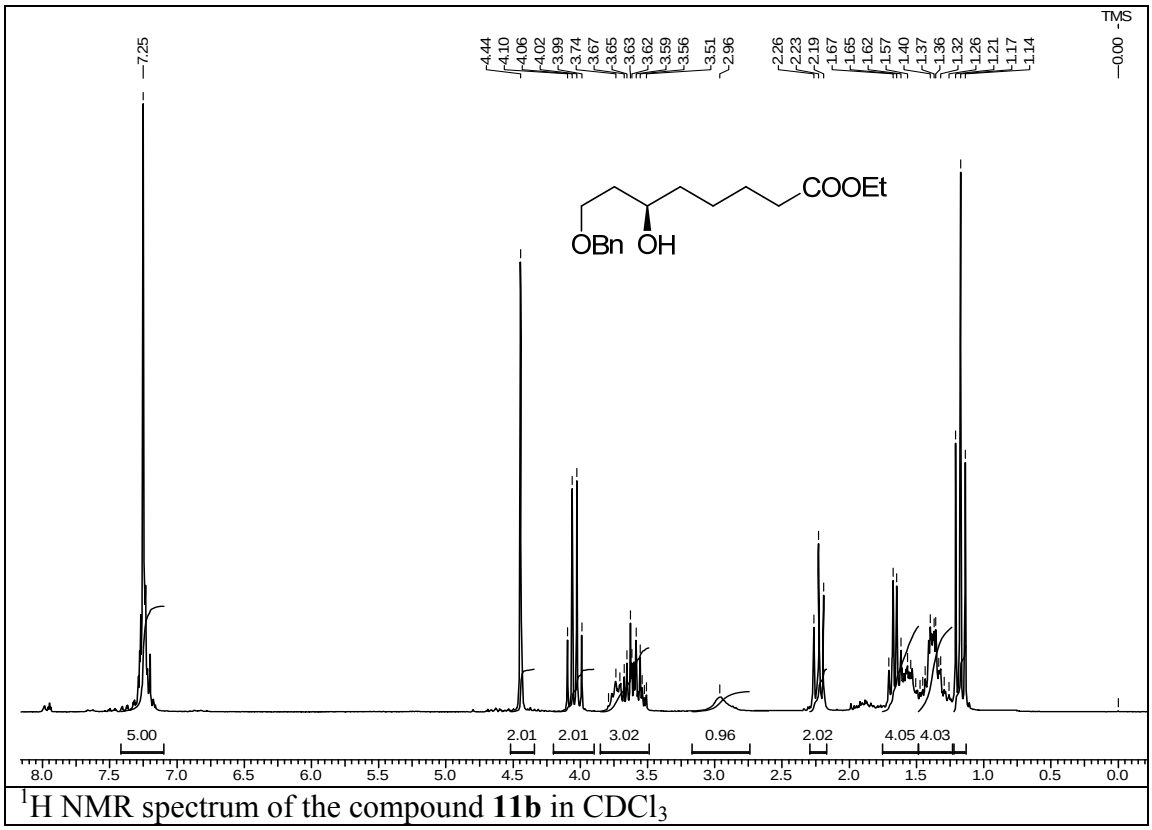
Dept NMR spectrum of the compound **11** in $CDCl_3$



^{1}H NMR spectrum of the compound **11a** in $CDCl_3$



^{13}C NMR spectrum of the compound **11a** in $CDCl_3$



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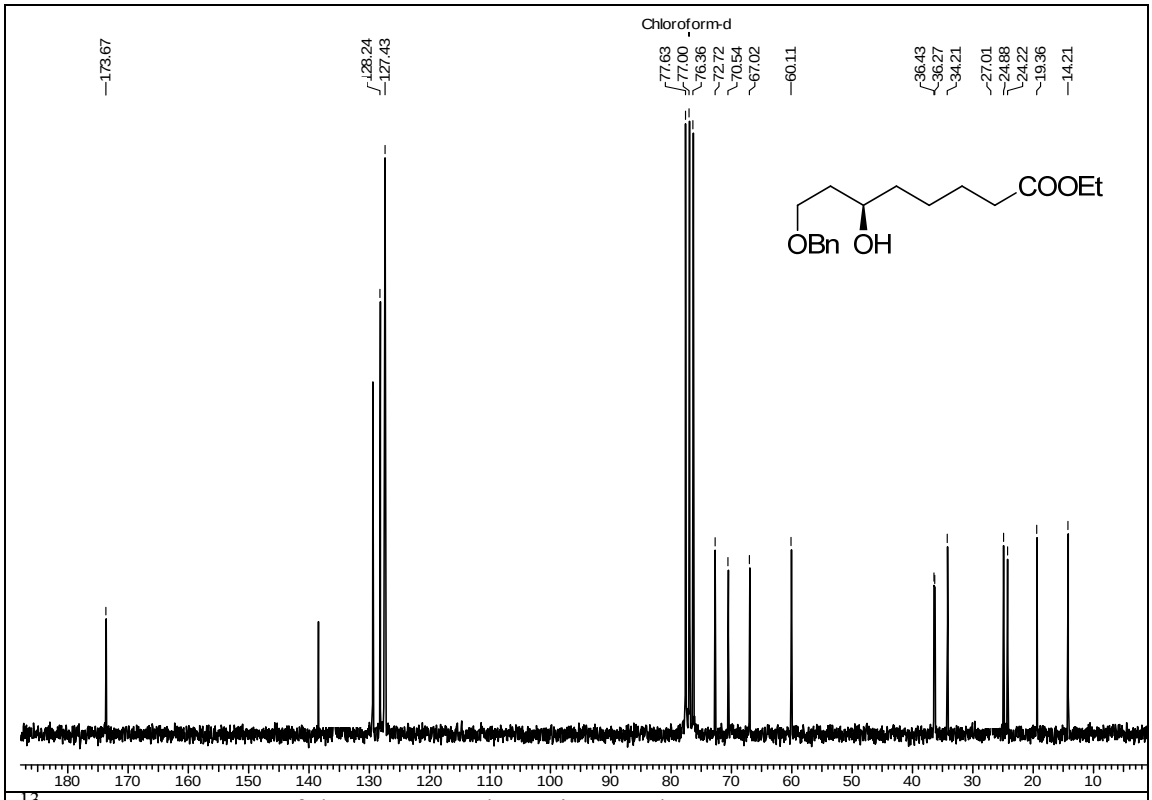

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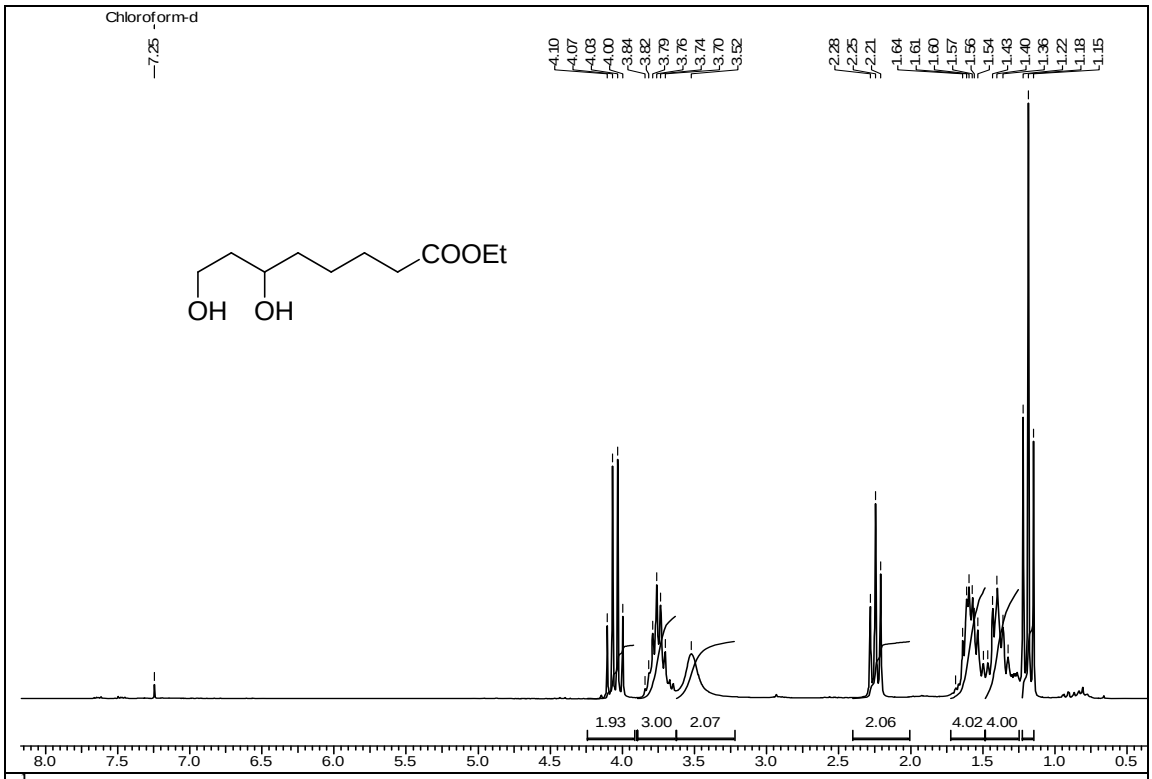

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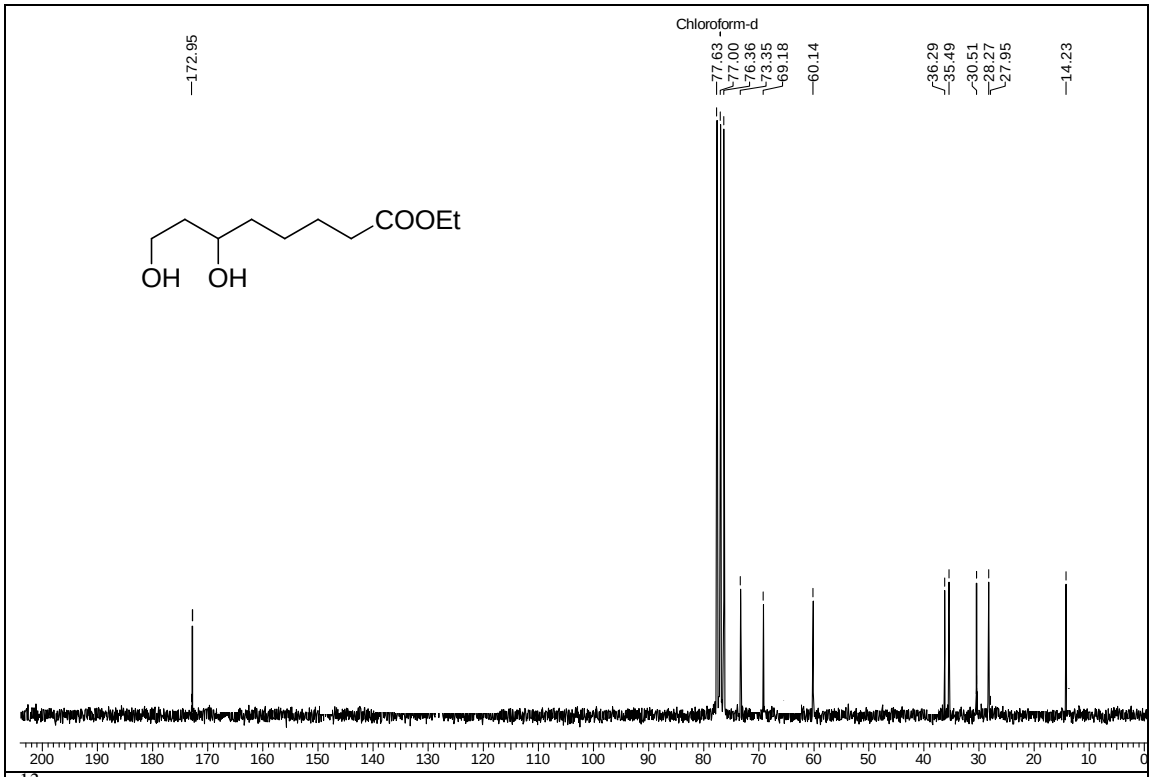
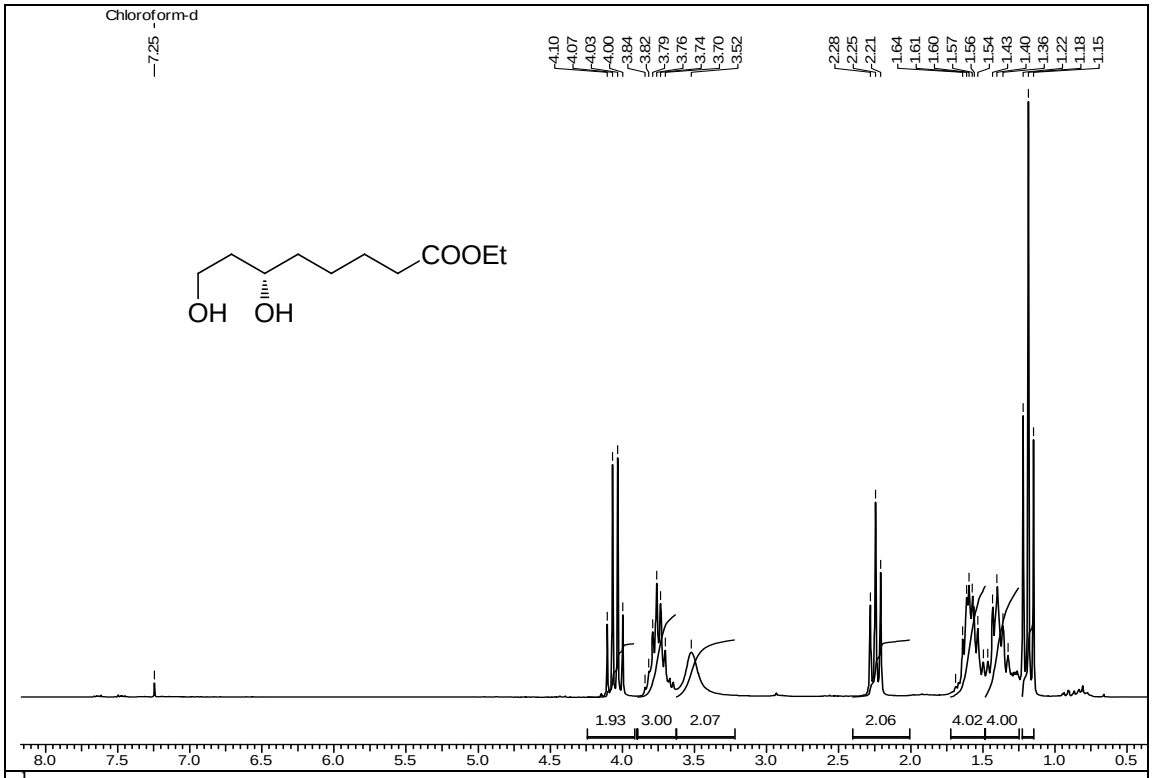
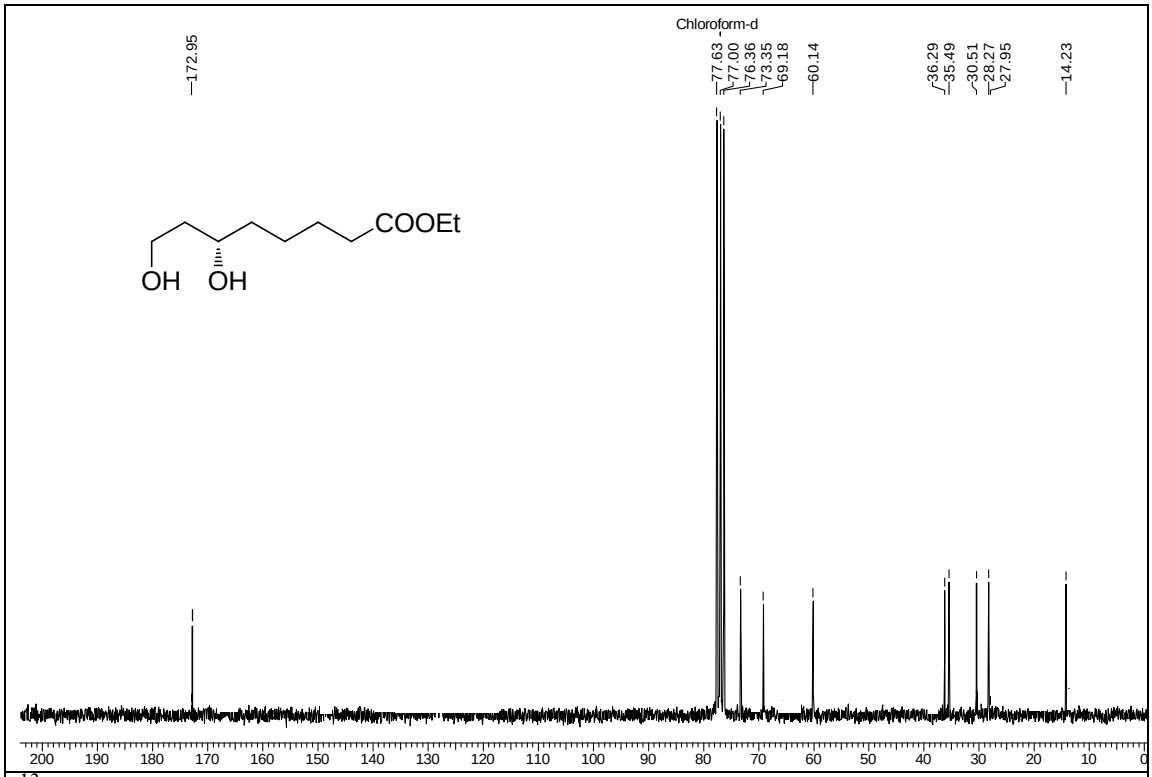


^{13}C NMR spectrum of the compound **12** in $CDCl_3$



^{1}H NMR spectrum of the compound **12a** in $CDCl_3$



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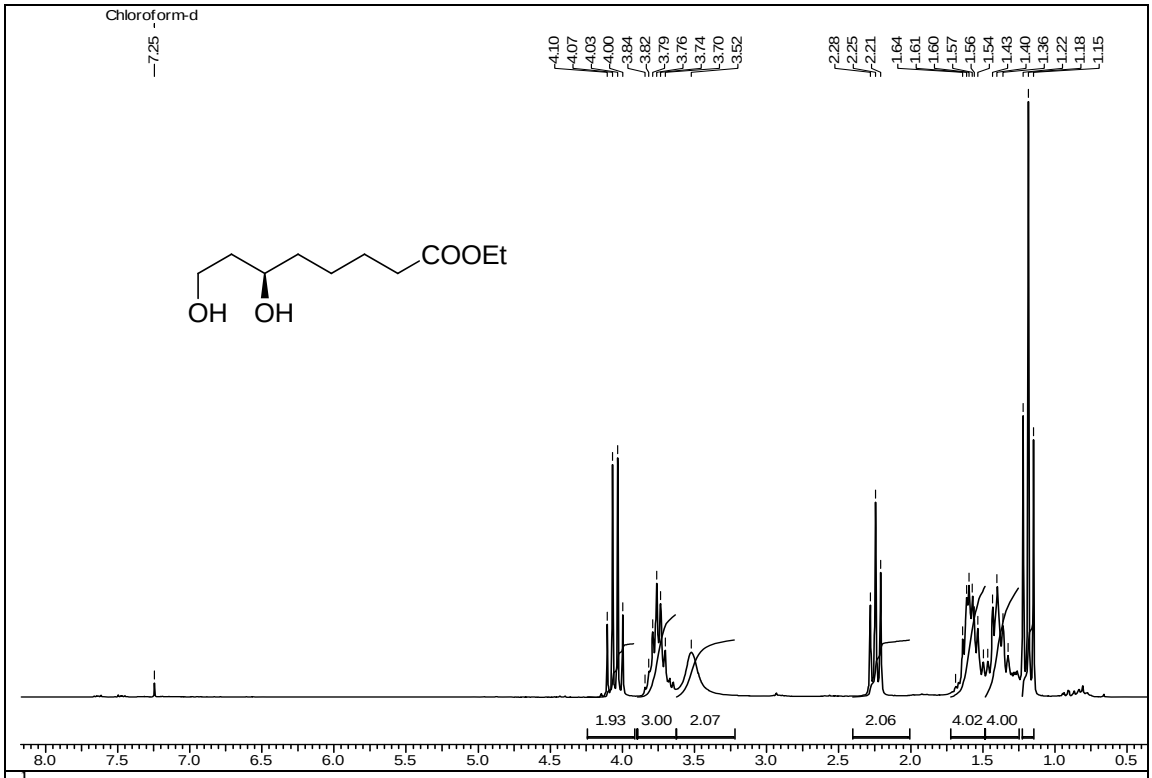
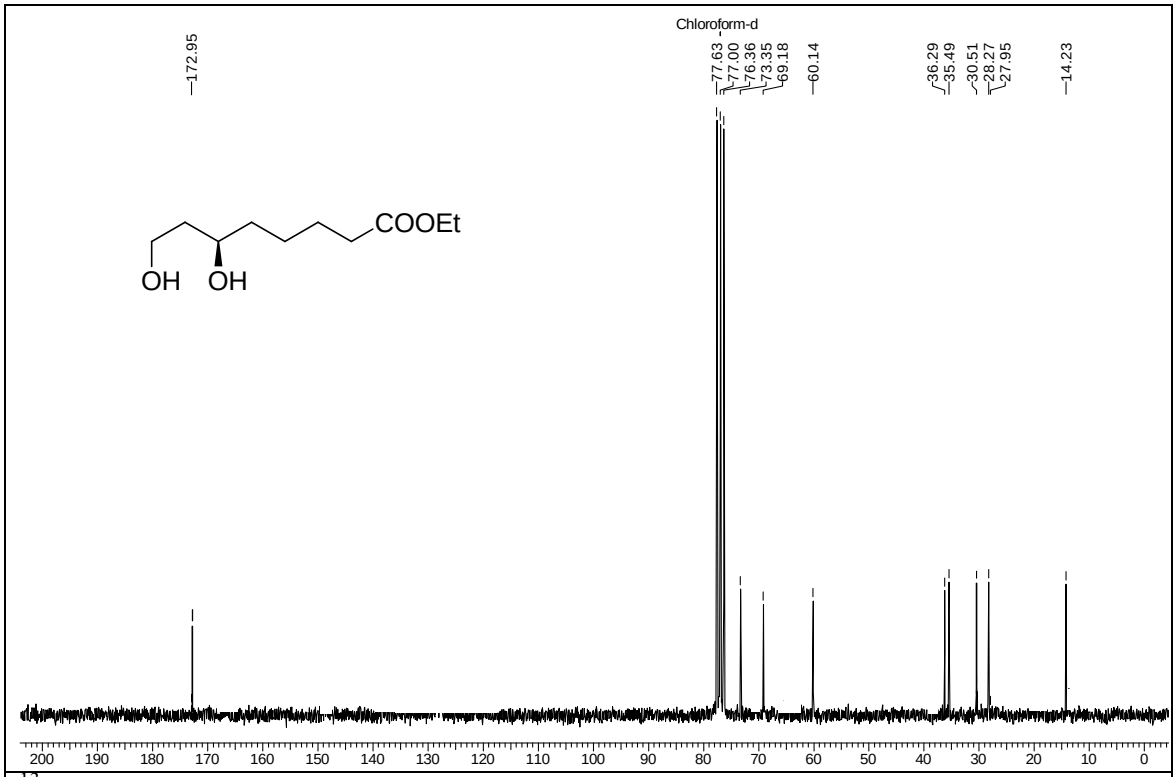


^{1}H NMR spectrum of the compound **12b** in $CDCl_3$



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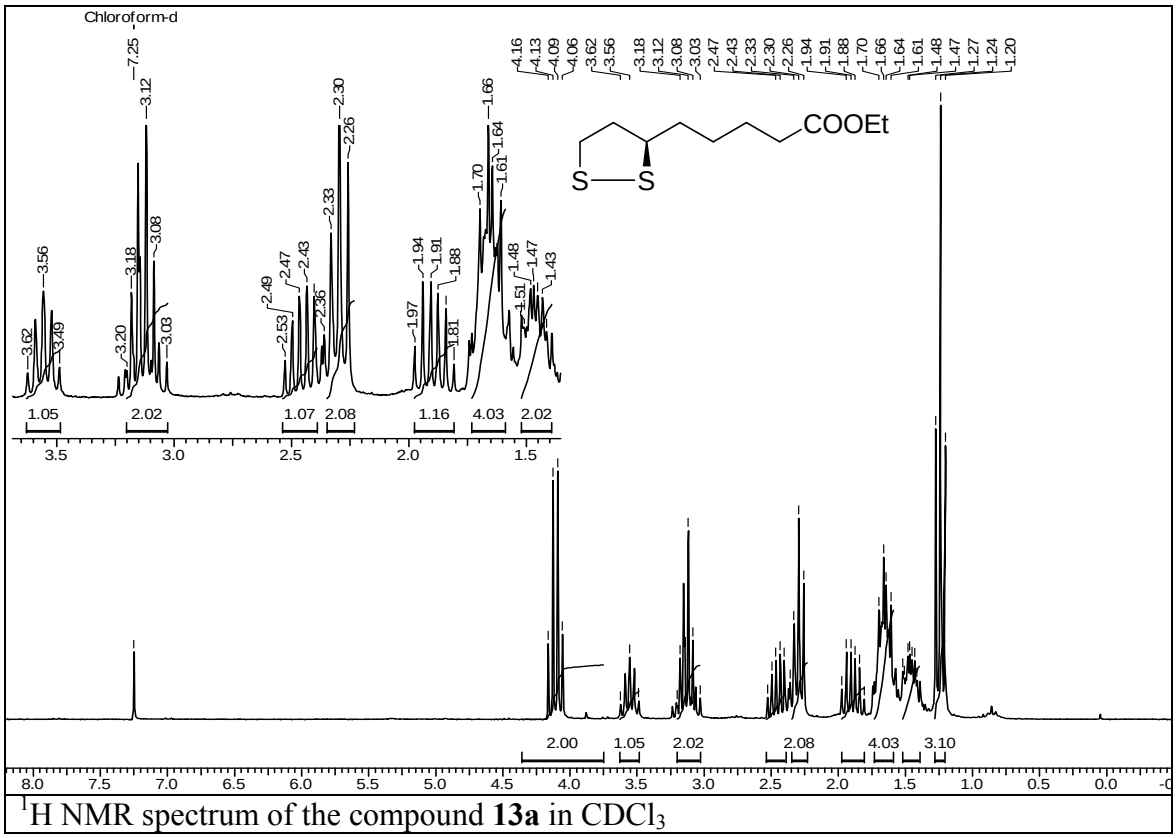
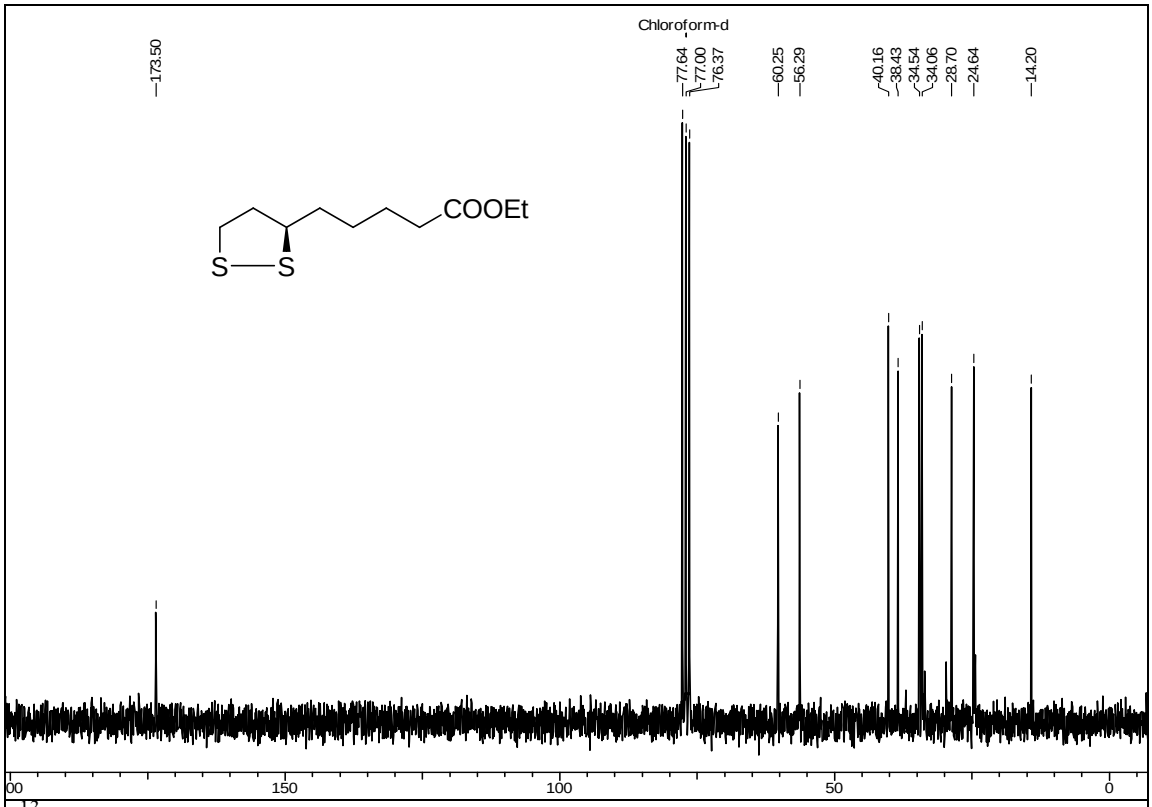


^{1}H NMR spectrum of the compound **13a** in $CDCl_3$



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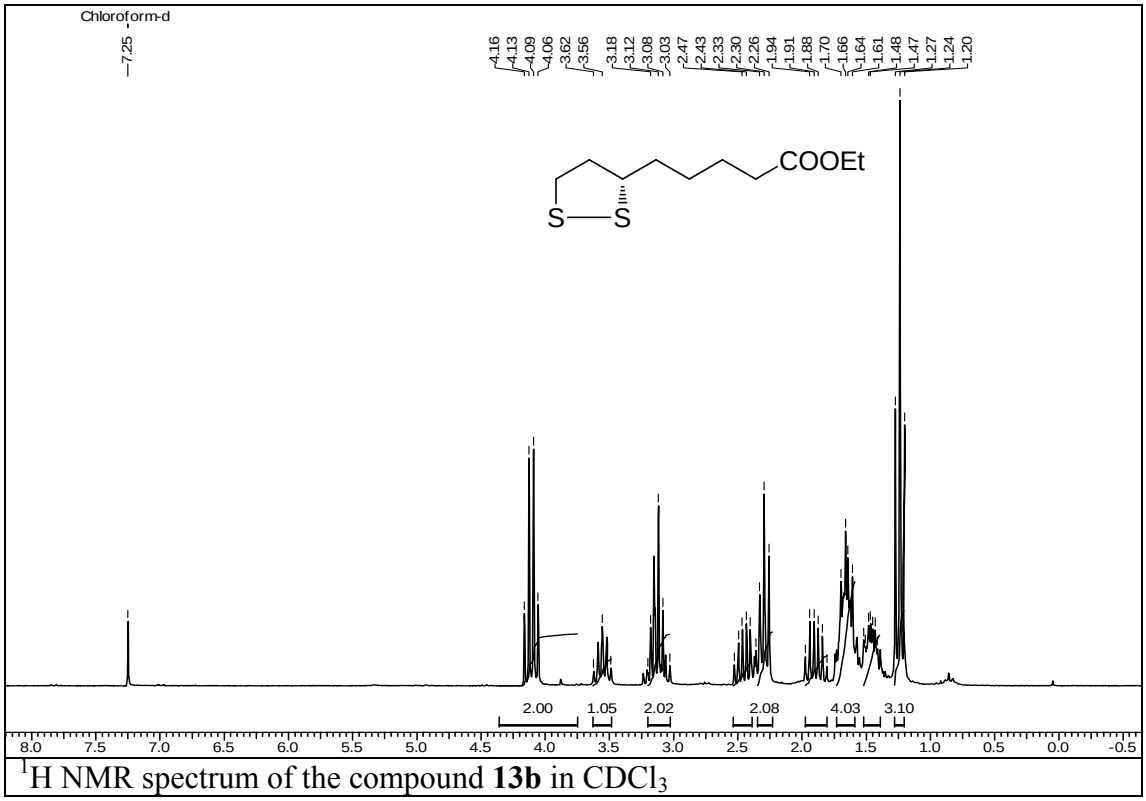

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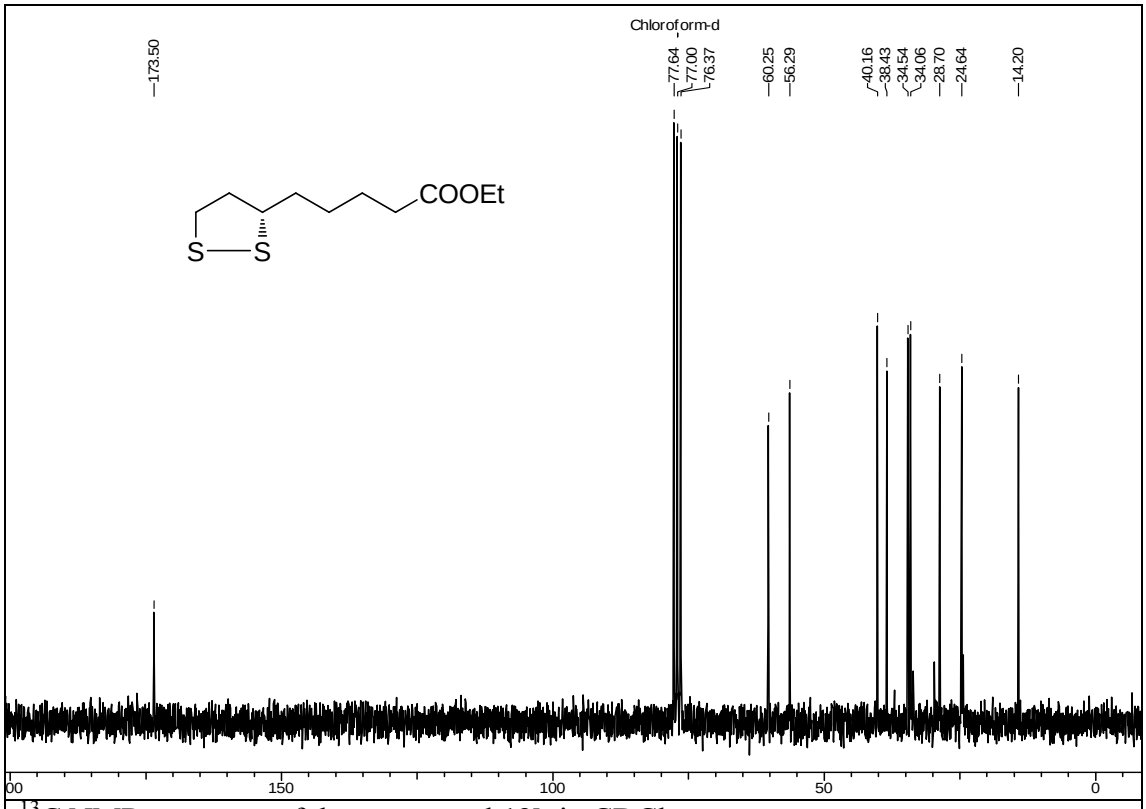

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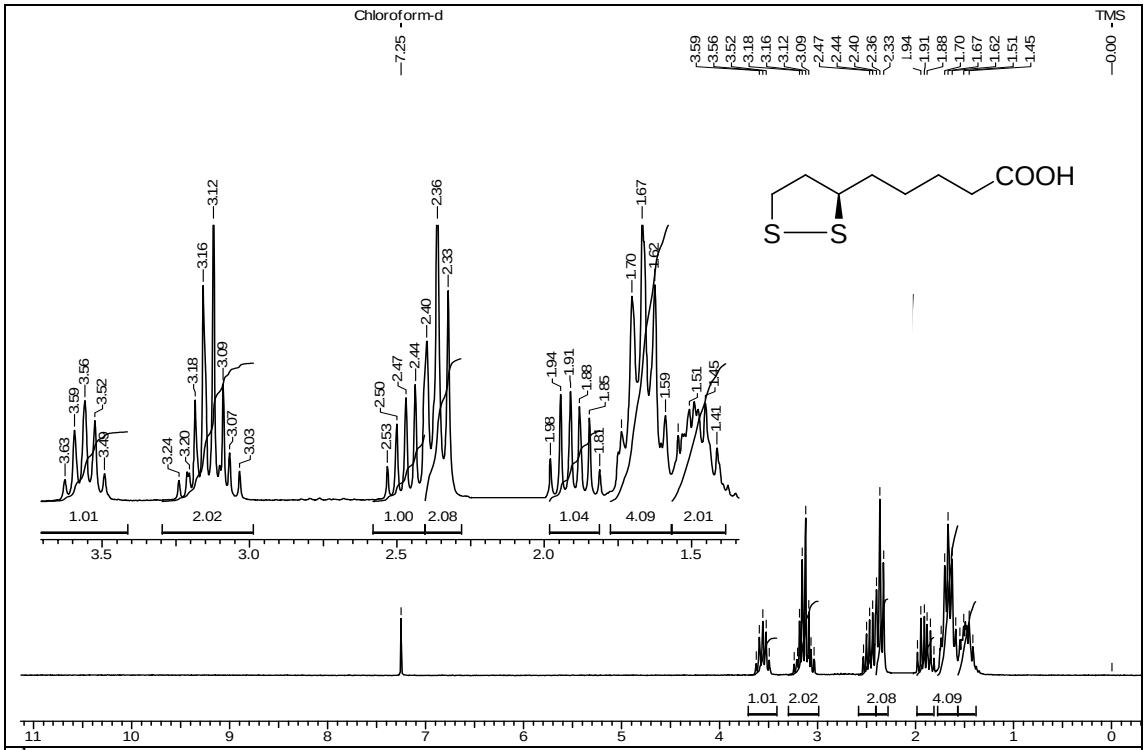
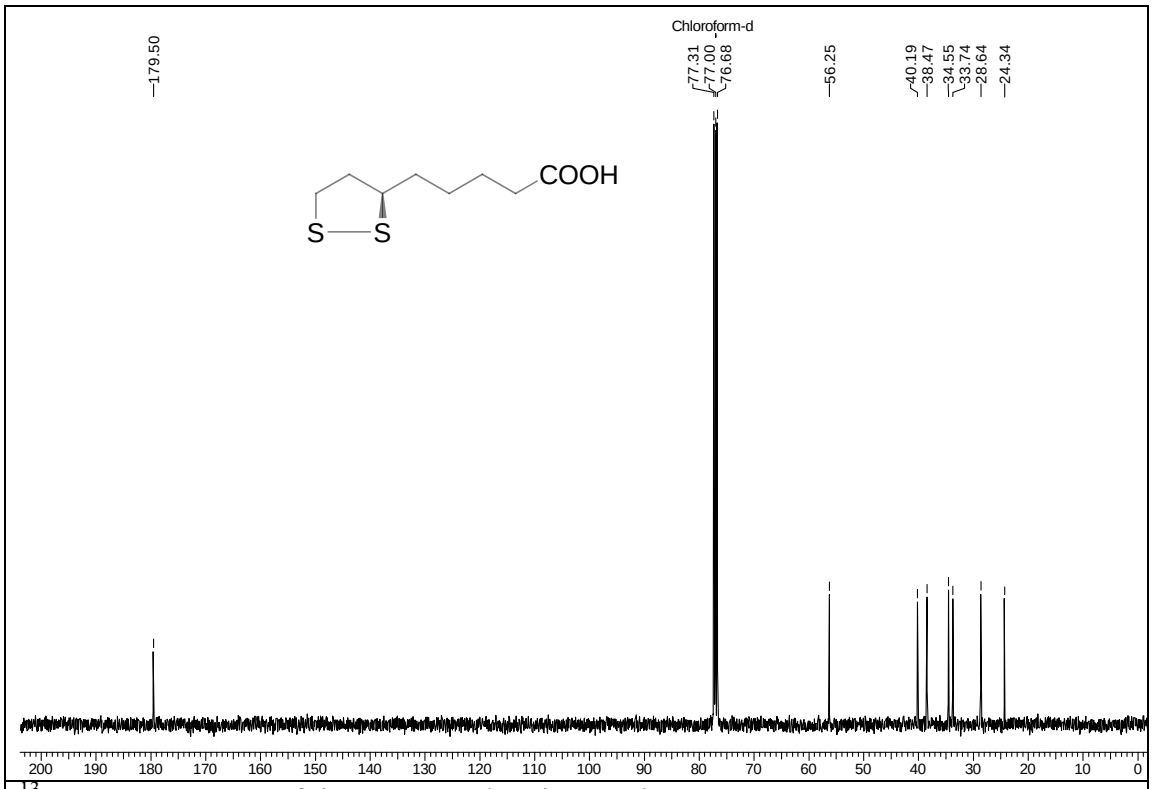


^{1}H NMR spectrum of the compound **1a** in $CDCl_3$



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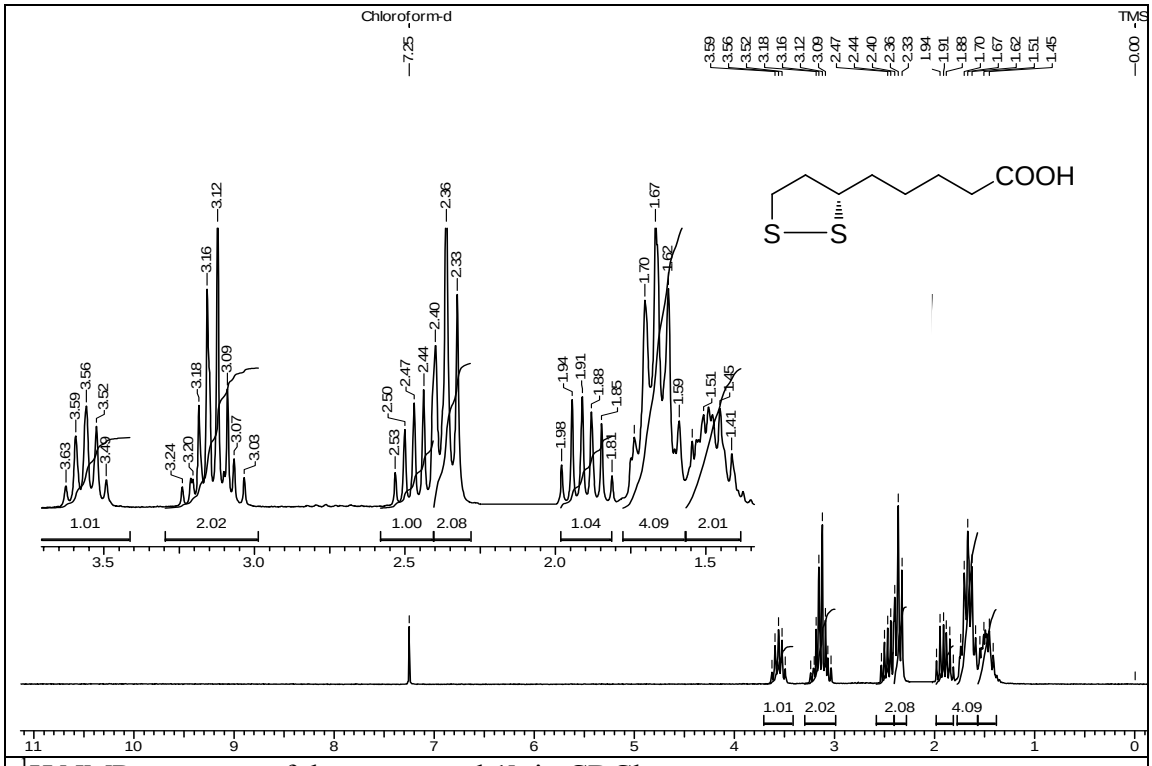
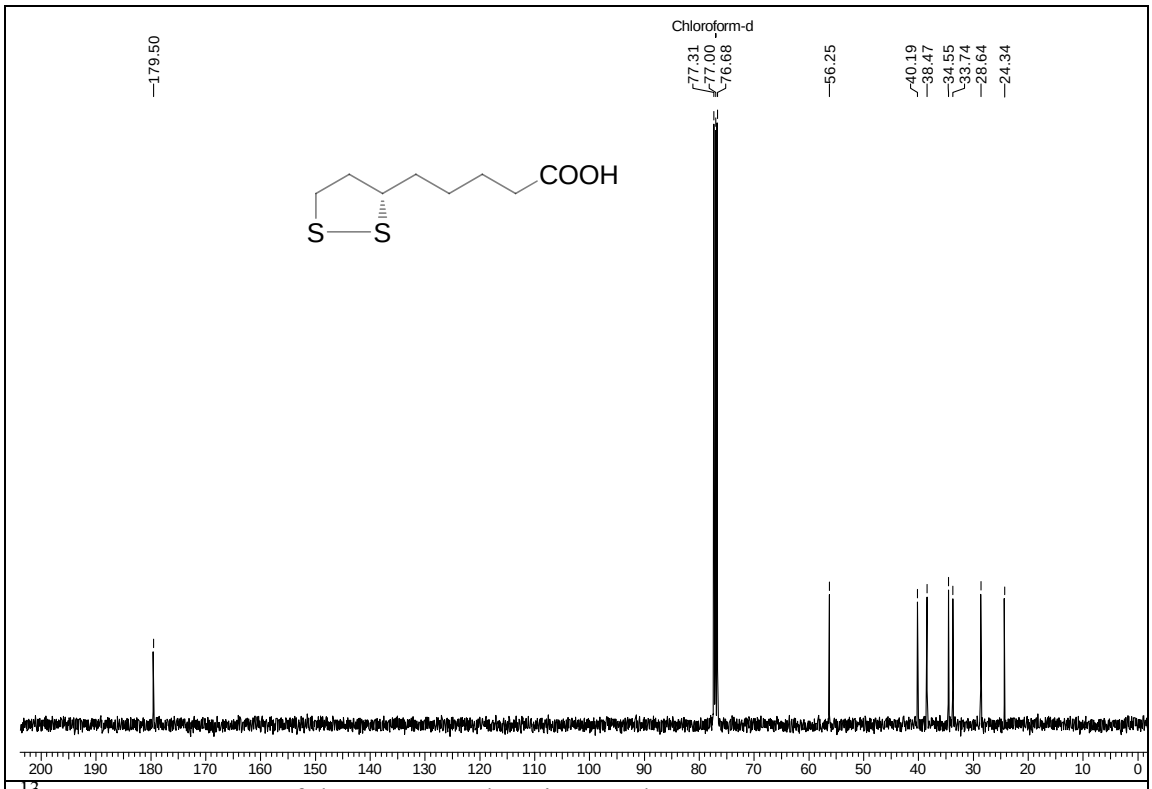
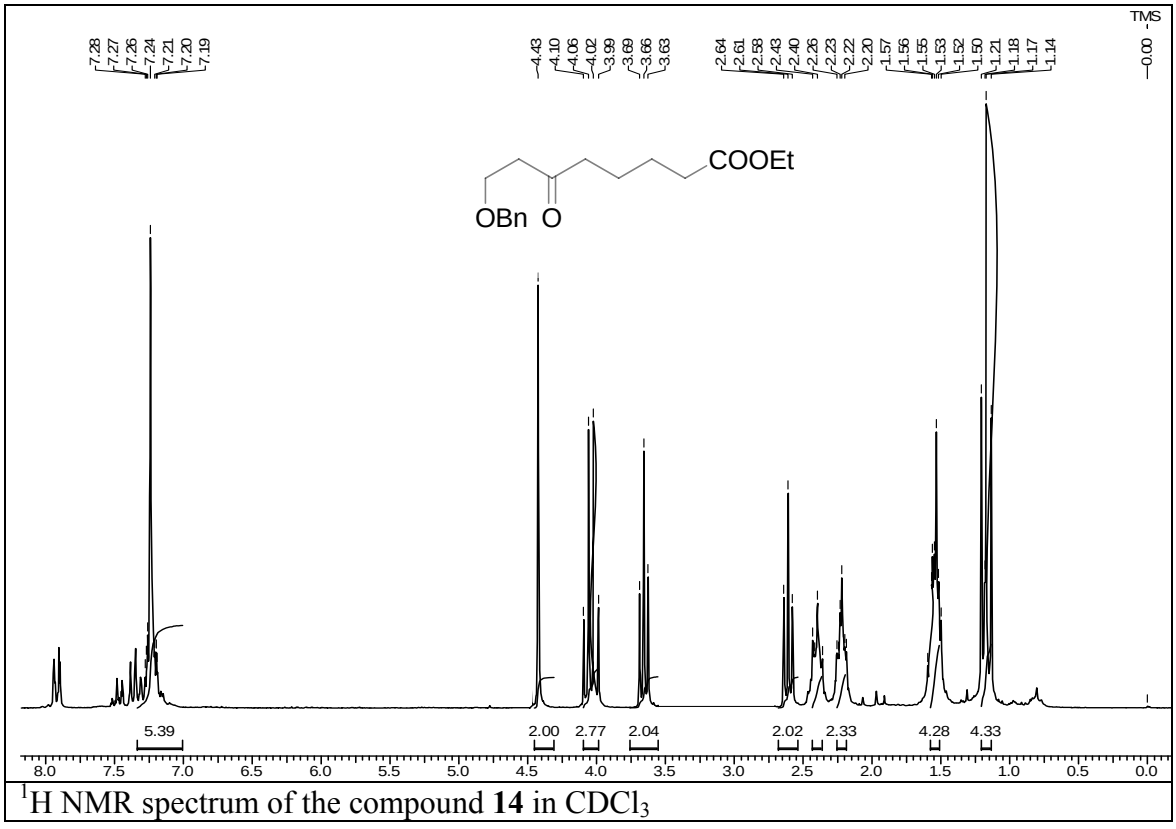


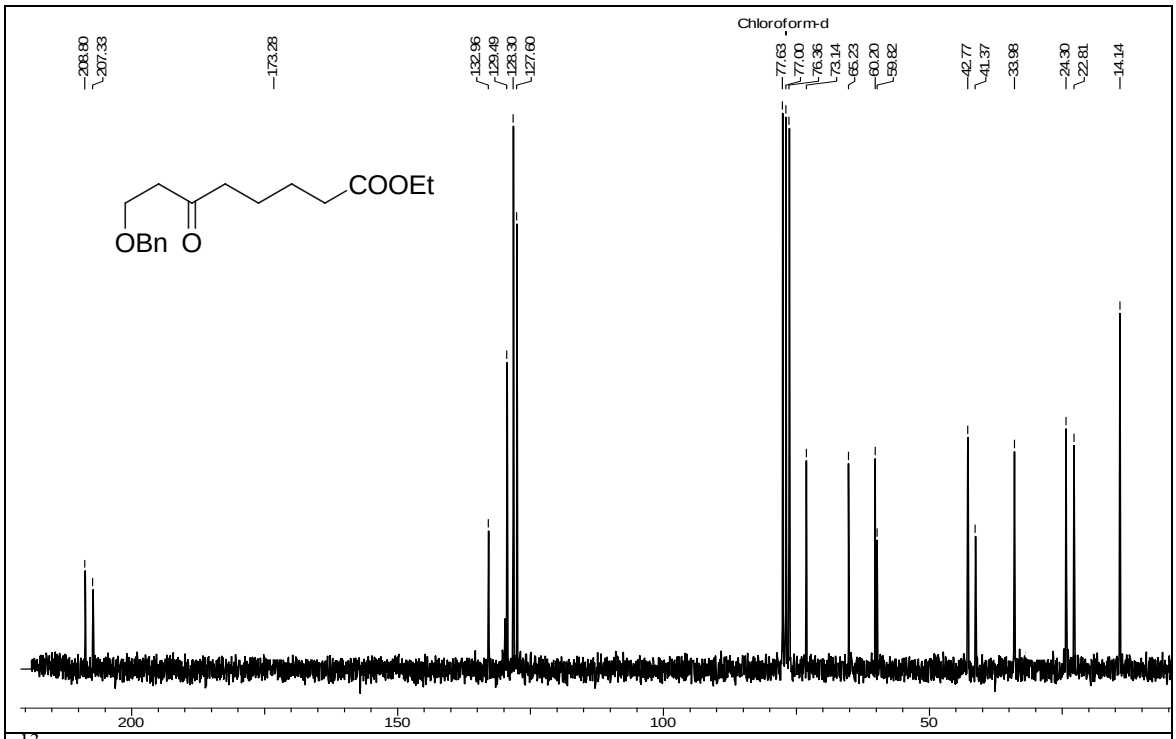
^{1}H NMR spectrum of the compound **1b** in $CDCl_3$



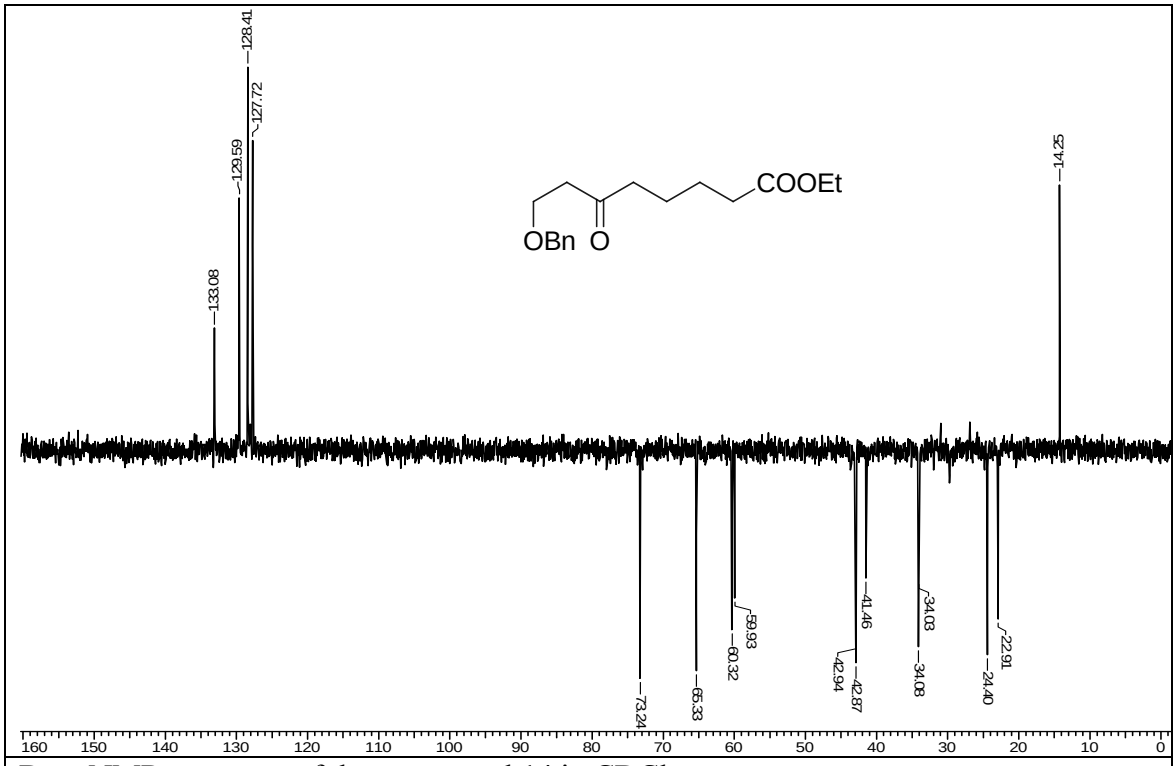
^{13}C NMR spectrum of the compound **1b** in $CDCl_3$



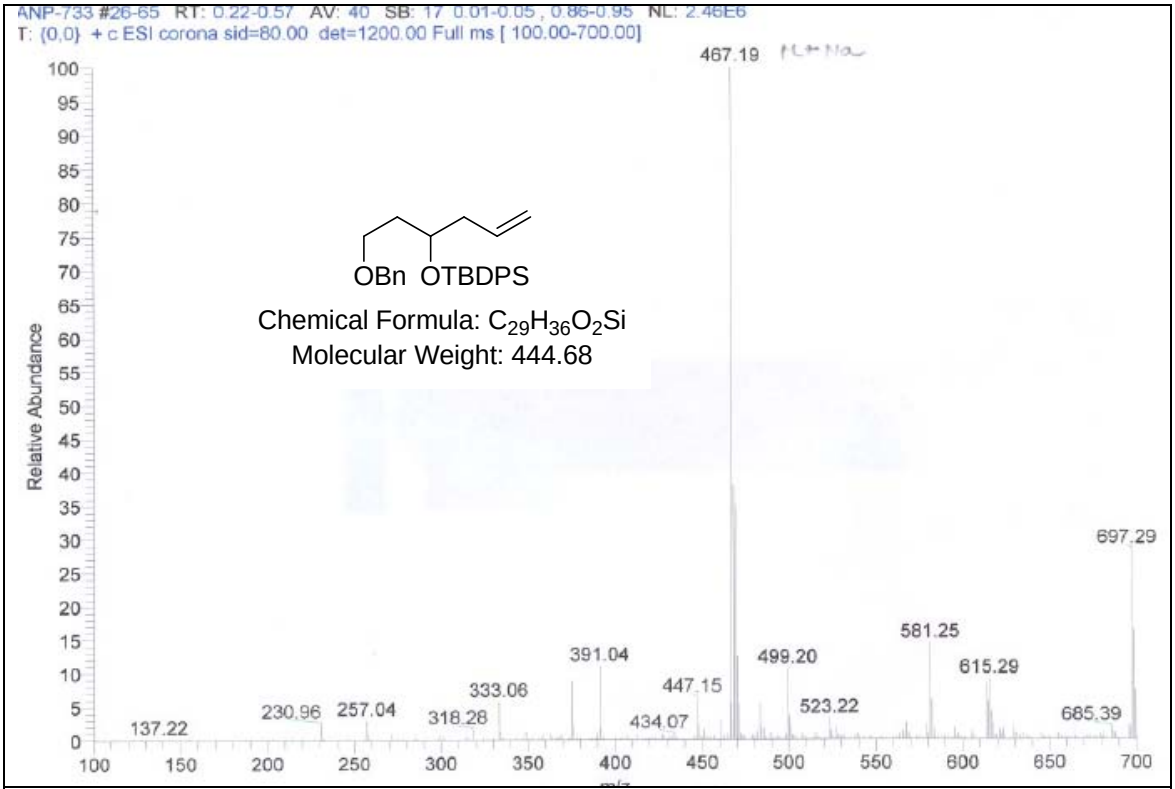
^{1}H NMR spectrum of the compound **14** in $CDCl_3$



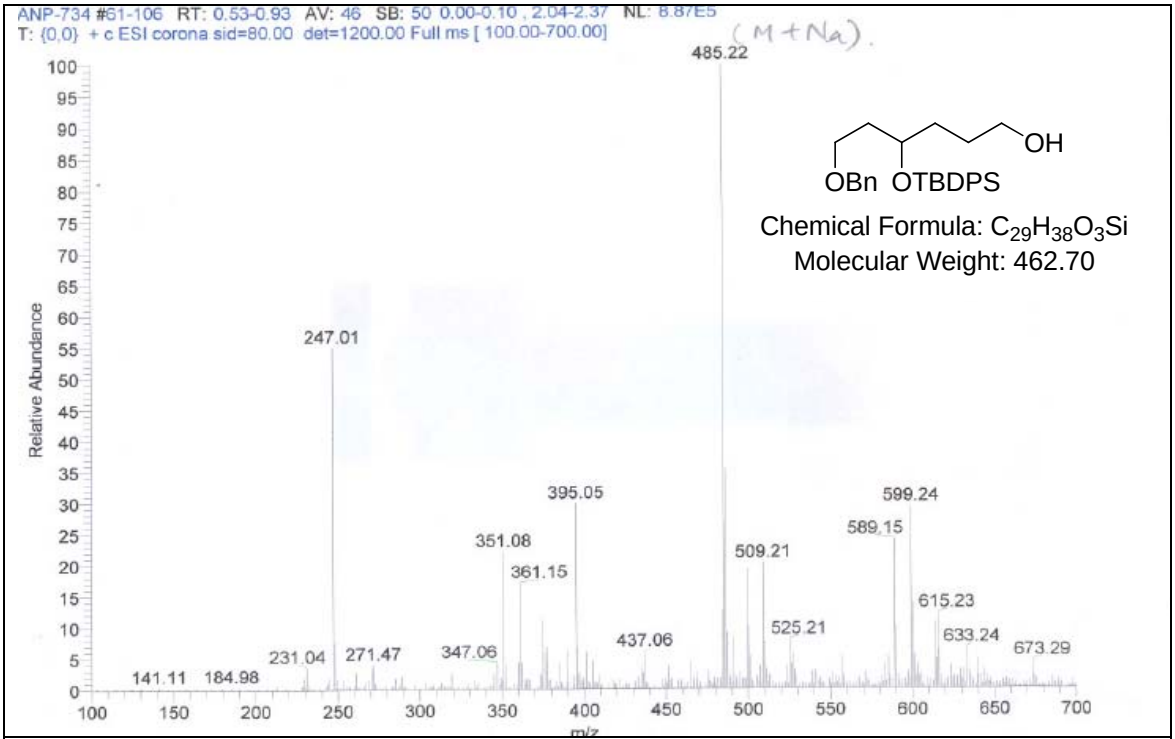
^{13}C NMR spectrum of the compound **14** in $CDCl_3$



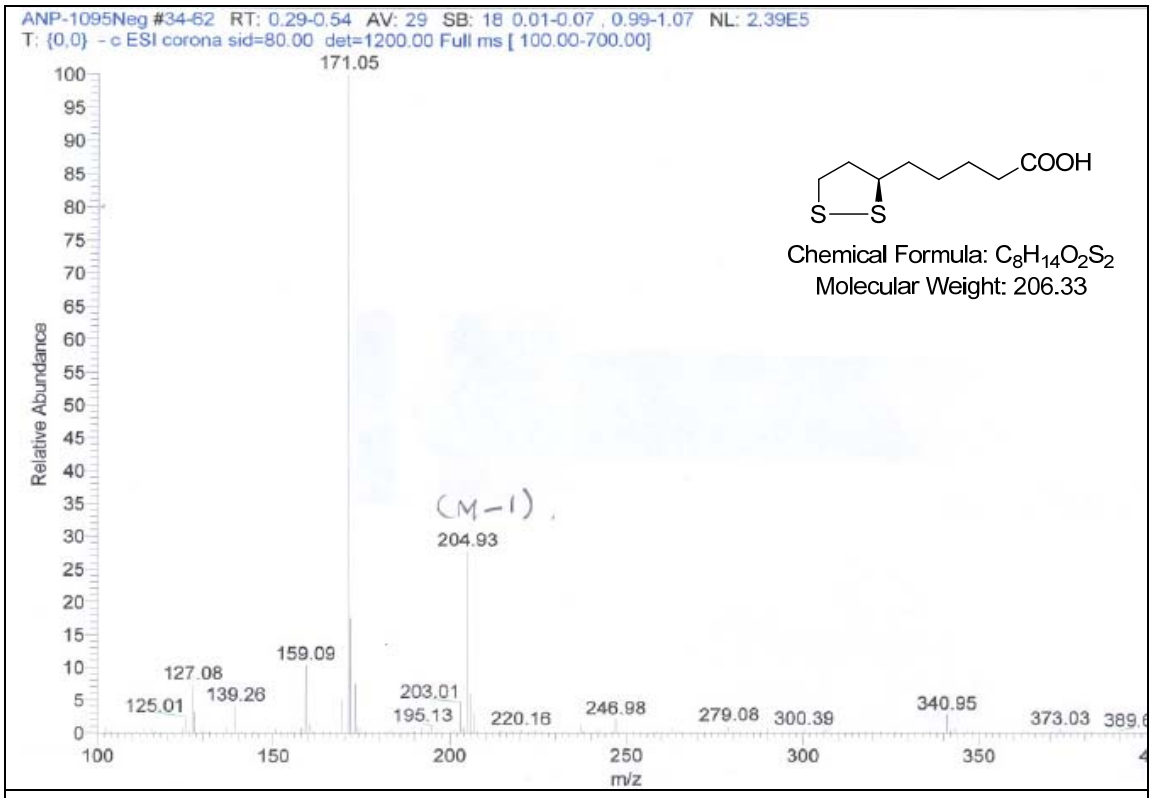
Dept NMR spectrum of the compound **14** in $CDCl_3$



LC MS spectrum of the compound **6**

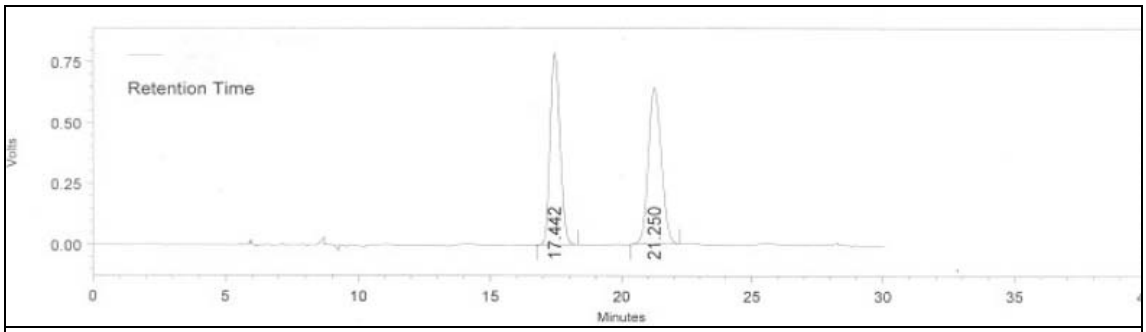


LC MS spectrum of the compound **7**



LCMS Chart of the compound 1a

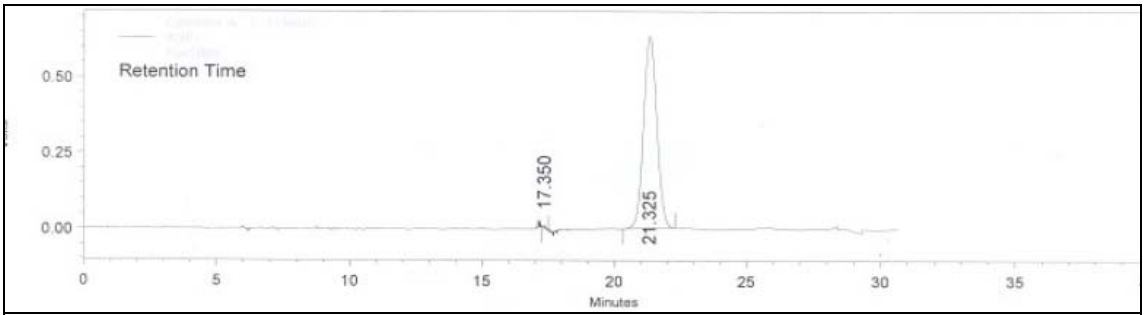
Chiral HPLC Analysis :



Racemic sample **10**

Pk #	Retention Time	Area	Area %
1	17.442	20707273	48.371
2	21.250	22101621	51.629

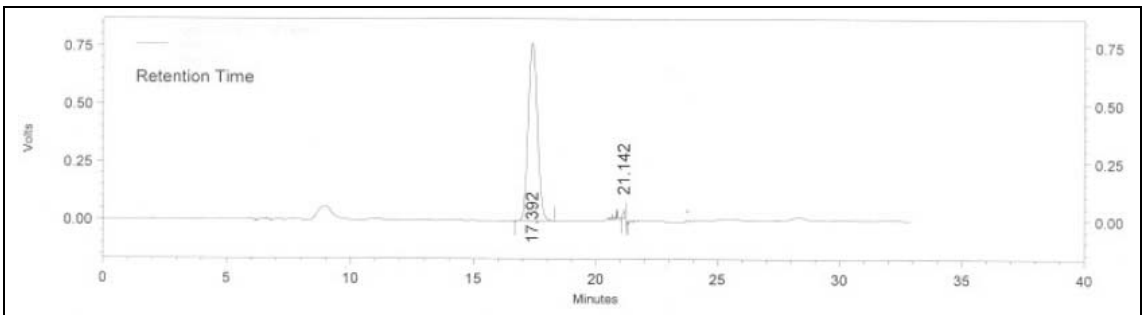
Column : Chiralcel OD-H (250 x 4.6 mm)
Mobile phase : IPA + Hexane (10:90)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 20 µL



Chiral sample **S Isomer (11a)**

Pk #	Retention Time	Area	Area %
1	17.350	55725	0.253
2	21.325	21953532	99.747

Column : Chiralcel OD-H (250 x 4.6 mm)
Mobile phase : IPA + Hexane (10:90)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 20 µL



Chiral sample **R Isomer (11b)**

Pk #	Retention Time	Area	Area %
1	17.392	20032744	99.027
2	21.325	196899	0.973

Column : Chiralcel OD-H (250 x 4.6 mm)
Mobile phase : IPA + Hexane (10:90)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 20 µL

2.4.7. References

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Chapter 3, Section I: Introduction and literature review of statin - Intermediate.

3.1.1. Introduction:

In 1976, Endo et al, at the Sankyo Co. and Brown et al at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase) from the metabolites of *Penicillium citrinum* and *P. brevicompactum*, respectively.[4, 5] The new compound, shown to have structure **1** was named ML236B by the Japanese group and compactin by the British workers. In 1980, Alberts et al at Merck, Sharp & Dohme, reported the isolation of a relative of compactin from *Aspergillus terrus*.[6] This Merck compound was named as mevinolin and shown to have stereostructure 3. The same fungal metabolite was isolated from Monascus rubber and named as monacolin K.[7]

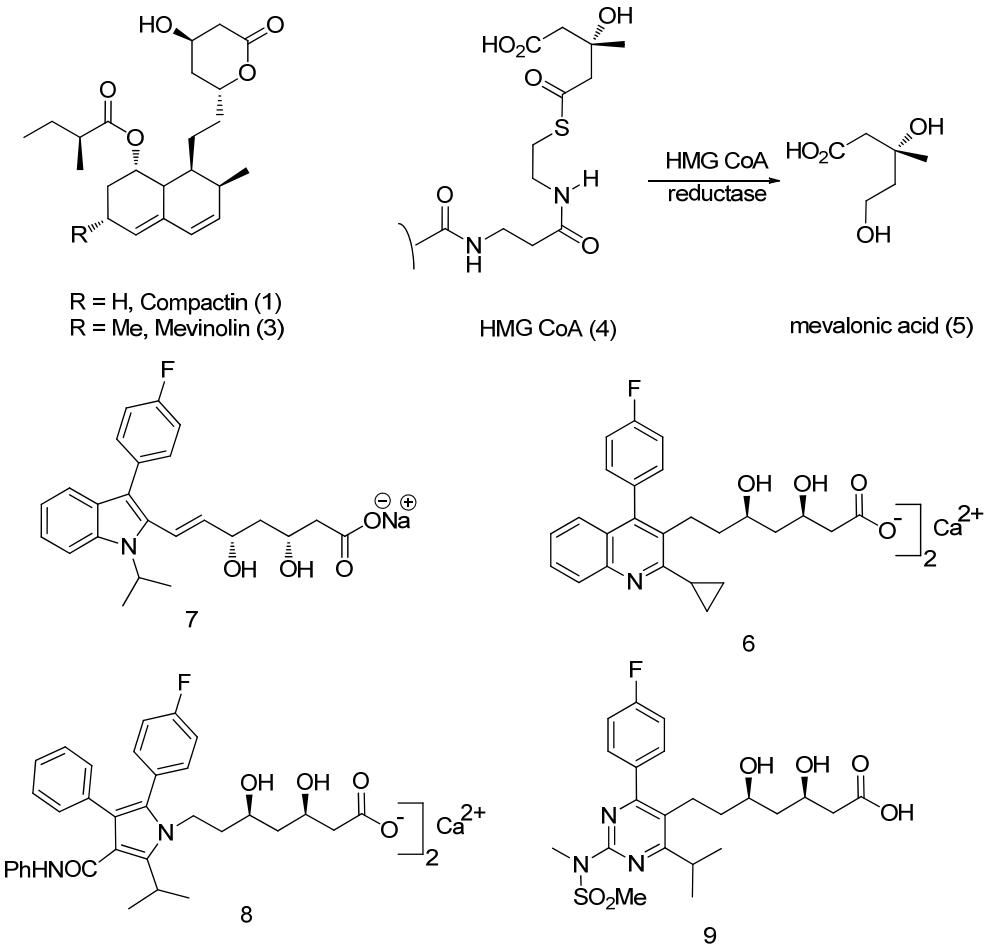
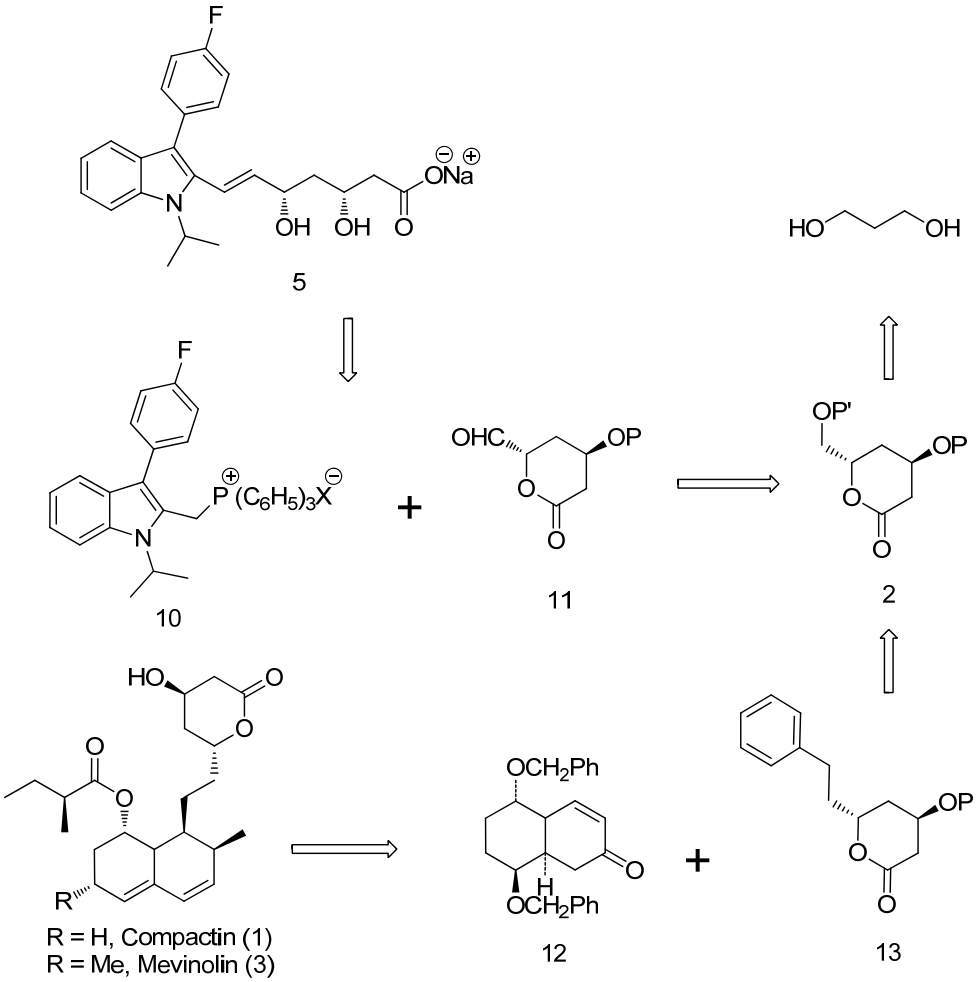


Figure 1.

In humans, more than one half of total body cholesterol is derived from *de novo* synthesis. The rate-limiting step of *de novo* synthesis is the reduction of HMG CoA (**4**) to mevalonic acid (**5**) by HMG CoA reductase (Figure 1).[8] Because of their potent inhibitory activity on this key enzyme HMG CoA reductase; compactin and related compounds act as hypocholesterolemic agents. Various synthetic analogues of compactin are found to act as inhibitors of HMG CoA reductase. Amongst these, pitavastatin **(6)** fluvastatin **(7)** and atorvastatin (**8**) rosuvastatin **(9)**[9, 10] have emerged as leading anti-hyperlipo-proteinemic agents and are used in treatment of arteriosclerosis and hyperlipoproteinemia.



Scheme 1.

In all these compounds, a β-hydroxy-δ-lactone (**2**) or its open chain form is essential for the activity. A retrosynthetic analysis for these compounds traces to a common lactone moiety **2** (P = or benzyl or TBDMS). We planned to develop a chemoenzymatic route for **2** utilizing propane-1, 3-diol.

3.1.2. Literature review of lactone 6-Hydroxymethyl-4-*tert*-butyldimethyl- silyloxy-(4*R*, 6*S*)-tetrahydro-2*H*-2-pyranone (2) and related lactones

Numerous reports on the synthesis of lactone 2 and related lactones are reported in literature.[11] these methods can be broadly divided into two types viz.

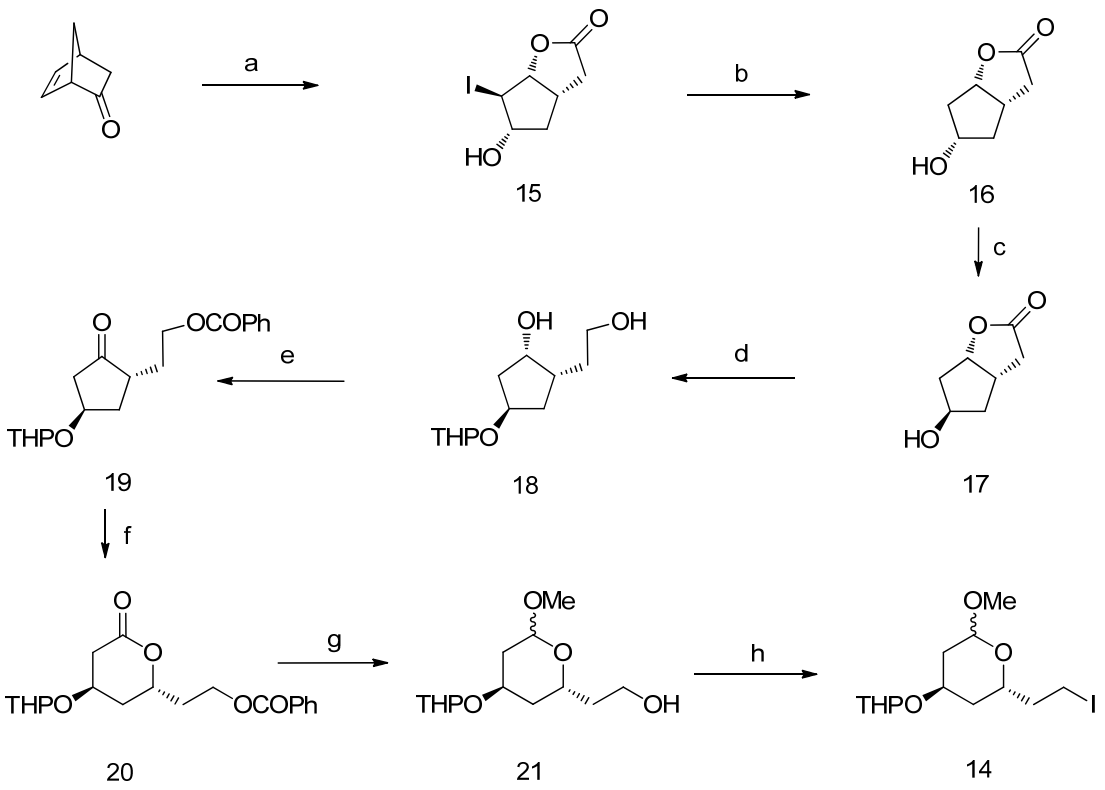
(I) Chemical methods

(II) Chemoenzymatic methods

(I) Chemical Methods

3.1.2.1. Sih and coworkers[12]

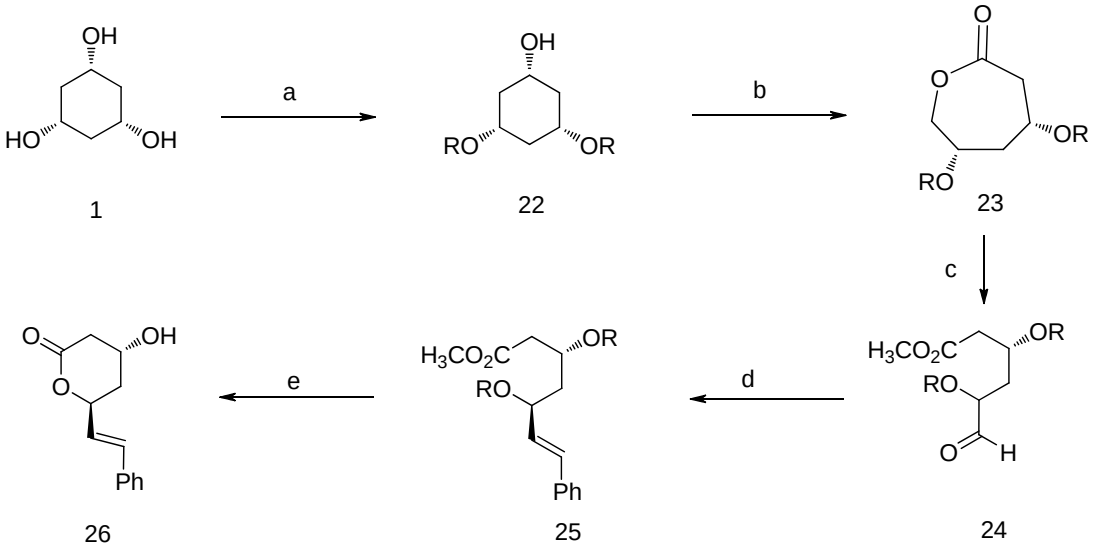
Sih and coworkers[12] reported the first total synthesis of compactin wherein racemic lactone **14** was synthesized as shown in Scheme 2. Conversion of 5-norbornen-2-one to iodolactone **15** and subsequent reductive deiodination with tributyltin hydride afforded lactone **16**. Mitsunobu inversion at hydroxy center followed by saponification, THP protection and borohydride reduction gave diol tetrahydropyranyl ether **18**. Selective benzoylation of primary alcohol and oxidation of the secondary hydroxyl group afforded ketone **19**, which was transformed to lactone **20** by Baeyer-Villiger oxidation. Further lactone **20** was transformed into lactone **14** by using sequence of reactions as shown below.



Scheme 2. *Reagents and conditions:* (a) (i) H_2O_2, OH; (ii) KI, I_2; (b) n-Bu_3SnH; (c) Ph_3P, DEAD, PhCOCl; (d) (i) NaOMe/ MeOH; (ii) DHP, PTSA; (iii) $NaBH_4$, MeOH (e) (i)PhCOCl, Imidazole; (ii) PCC, DCM; (f) DCM/ MCPBA; (g) (i) DIBALH, THF (ii). Ag_2O, CH_3I; (h) (i) TsCl, Pyridine; (ii) NaI/ PhI, reflux.

3.1.2.2. Prasad and Repic[13]

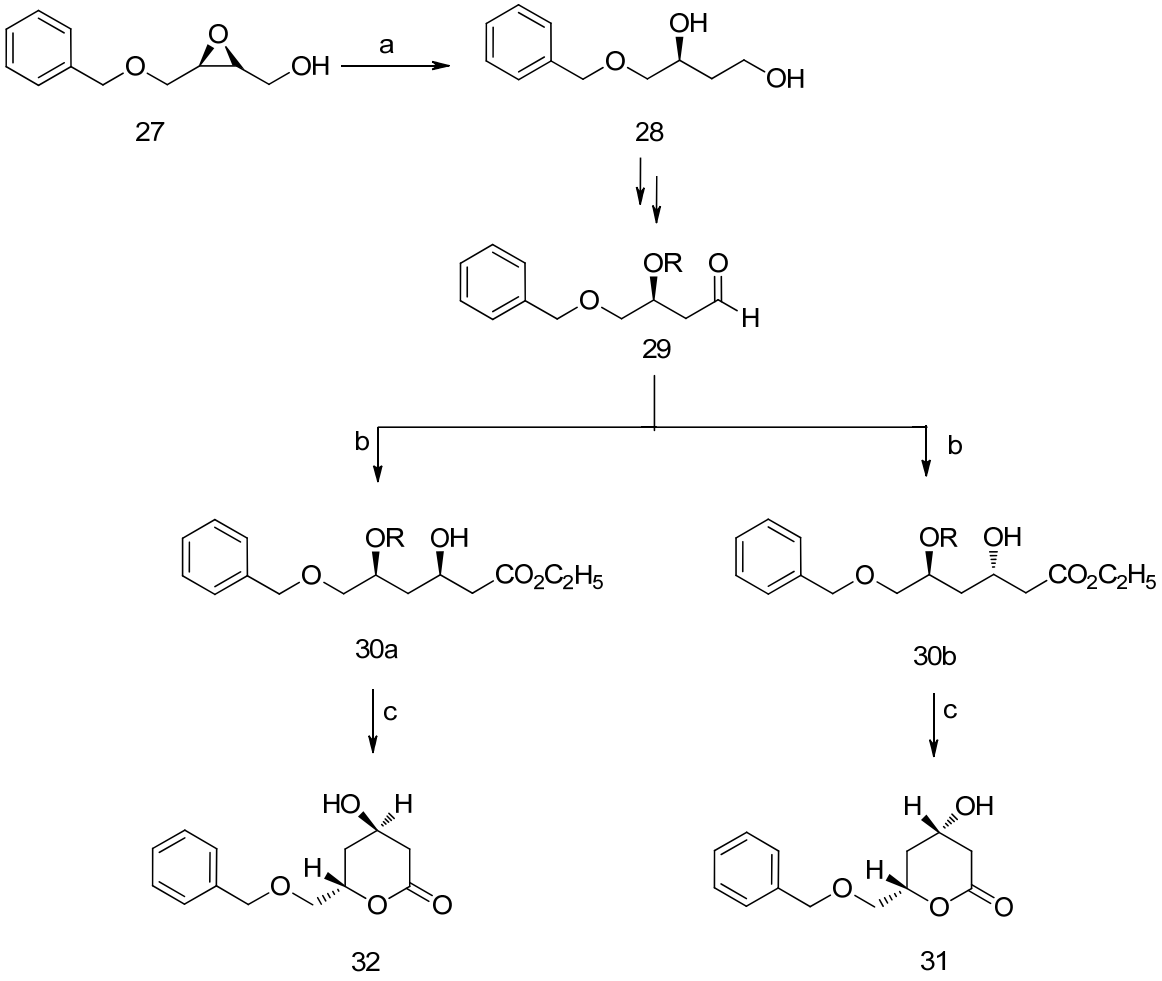
Prasad and Repic have published phlorogucinol based approach to the lactone



Scheme 3. *Reagents and conditions:* (a) (i) TBDPSCl, Imidazole, DMF; (b) (i) PCC, DCM; (ii) MCPBA, $NaHCO_3$; (c) (i) MeOH, CF_3COOH (ii) PCC, DCM; (d) (i) $PhCH_2$= PPh_3 , THF; (e) (i) TBAF, THF; (ii) AcOH, THF.

3.1.2.3. Kapa Prasad and coworkers[14]

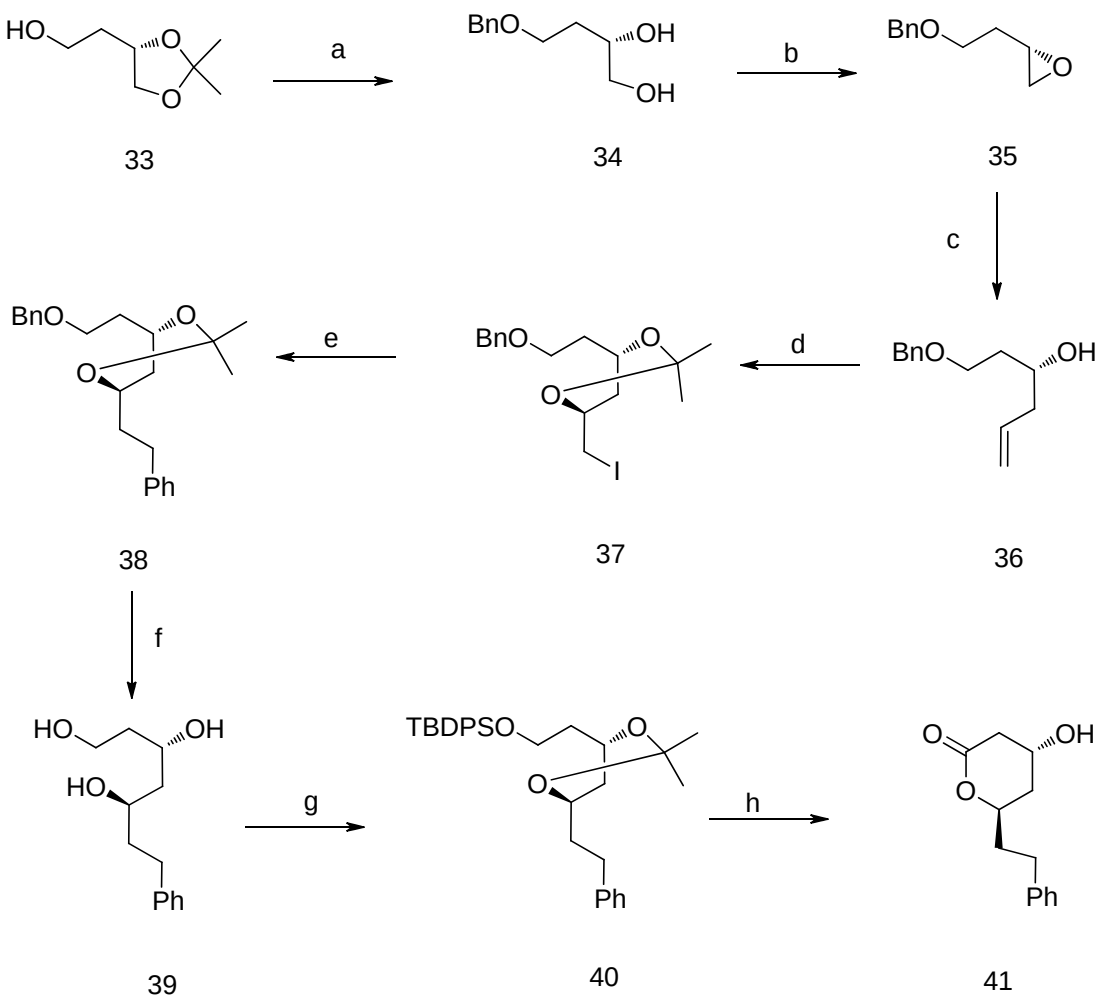
Kapa Prasad and coworkers reported the asymmetric synthesis of lactone **26** using optically active epoxide **27** Epoxide **27** was opened with Red-Al to give diol **28**. Diol **28** was further converted to chiral aldehyde **29**. Aldehyde **29** was converted to 1:1 diastereomeric mixture of aldol products **30a** and **30b** through modified Reformatsky condition. These diastereomers were separated by HPLC and were converted to lactones **31**and **31** through deprotection and cyclization.



Scheme 4. *Reagents and conditions:* (a) (i) Red-Al, THF; (b) (i) Zn, $(Et)_3AlCl$; (c) (i) TBAF, THF, -20^oC; (ii) 1N, NaOH, Dioaxane; (iii) Toluene, PTSA.

3.1.2.4. Clive and coworkers[15]

Clive and coworkers utilized L-malic acid and derivative **33** as a precursor to lactone **41.** Benzylation of **33** and hydrolysis of the acetonide afforded monoprotected triol **34** in 86% yield, which was converted to optically active epoxide **35**. The epoxide **35** was converted to **37** in two steps. Coupling of **37** via sulfone Wittig converted to **38** followed by deprotection to yield **39** (78% yield). Triol **39** through a muilti-step procedure was converted to the desired lactone **41** in 33% overall yield.

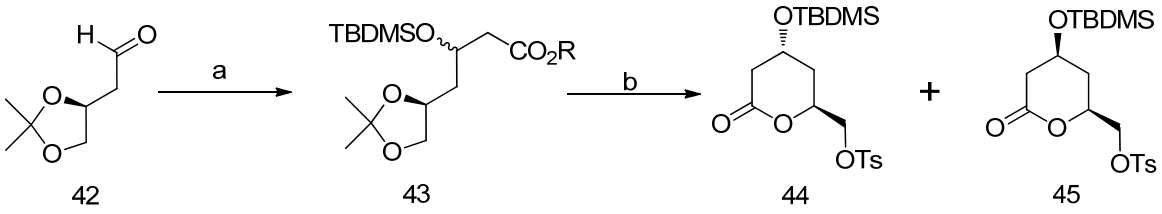


Scheme 5. *Reagents and conditions:* (a) (i) NaH, DMF, BnBr; (ii) AcOH, H_2O; (b) (i) MsCl, Pyridine; (ii) Triton- B; (c) Vinyl-Mg-Br, THF, -20^oC; (d) BuLi, CO_2, I_2; (e) Acetone, PTSA; (e) (i) $BnSO_2Ph$-CH_3/ DMF, KH, RT, 3hr; (ii) Na(Hg), MeOH; (f) TMS-I; (g) (i) TBDPSCl, Imidazole; (ii) Acetone, PTSA; (h) (i) TBAF, THF; (ii) Colins reagent; (iii) PDC, DMF (iv). HCl, DCM;

3.1.2.5. Heathcock and coworkers[16]

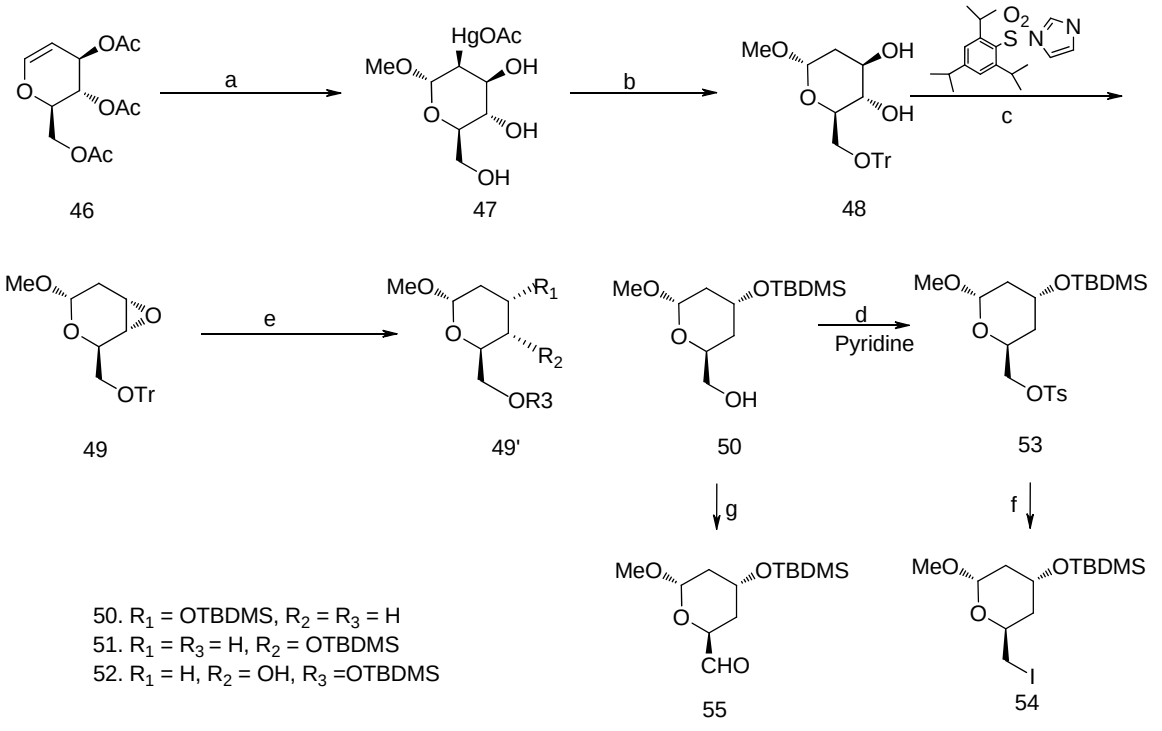
Heathcock and coworkers utilised aldehyde **42**, derived from L-malic acid for elaboration of the lactone synthon Addition of the lithium enolate of ethyl acetate to **42** and silylation of the resulting mixture of epimeric alcohols furnishes **43** in 88% yield.

Lactonization (60% yield) and subsequent tosylation provides **44** and **45**, which are separated by chromatography (91% combined yield).



Scheme 6. *Reagents and conditions:* (a) (i) BuLi, EtOAc, THF; (ii) TBDMS-Cl, Imidazole; (b) (i) AcOH, ; (ii) TsCl, Pyridine;

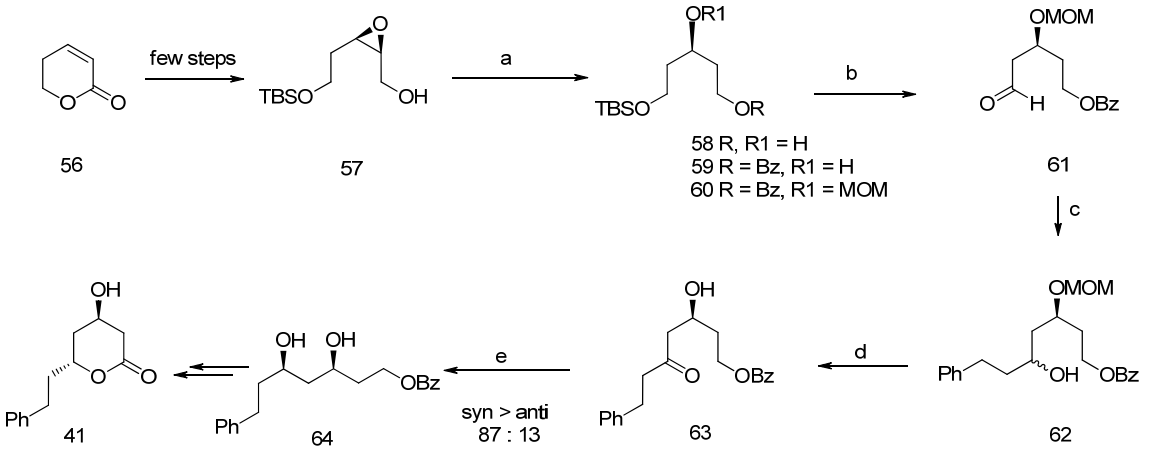
In an another approach Heathcock and coworkers utilised tri-O-acetyl-D-glucal (**46**) (Scheme 7).[16] Glucal **46** was converted to epoxide **49** through Corey's procedure.[17] Lithium aluminium hydride epoxide opening (90% axial selectivity), silyl protection followed by removal of trityl protection afforded alcohol **50** and an inseparable mixture of **51** and **52**. Alcohol **50** is converted **54** (95% yield) as shown below.



Scheme 7. *Reagents and conditions:* (a) (i) NaOMe, MeOH; (ii) $Hg(OAc)_2$, THF; (b) (i) $NaBH_4$, NaCl, MeOH; (ii) Tr-Cl, Pyridine; (c) NaH, Sulphone-Im, THF, -20°C; (d) LAH, THF, 0°C; (ii) TBDMSCl, Imidazole; (iii) Na, NH_3-EtO_2; (e)TsCl, Pyridine; (f) (i) NaI / MEK, 0°C; (g) Swern Oxidation .

3.1.2.6. C. Bonini and coworkers[18]

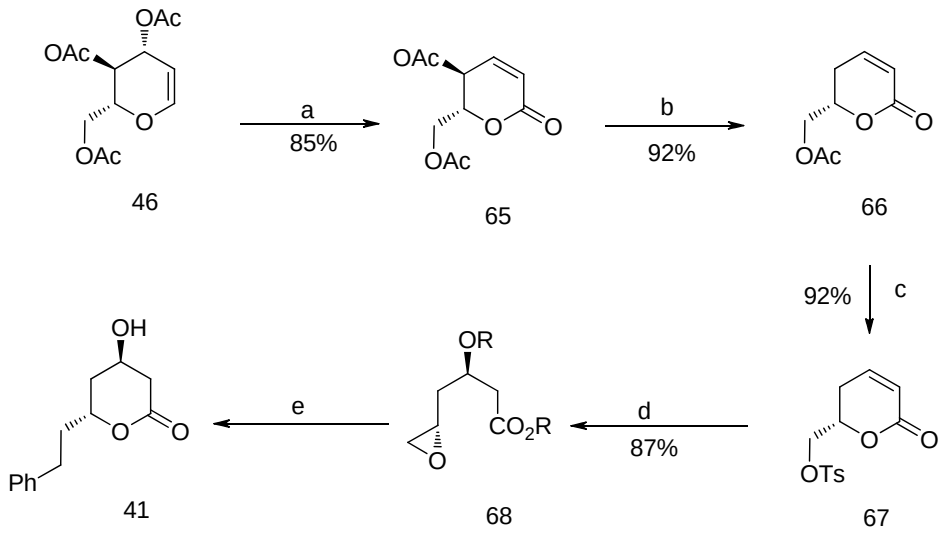
C. Bonini and coworkers developed the asymmetric synthesis of lactone **41** by asymmetric epoxidation of the appropriate allylic alcohol and subsequent introduction of the second chiral center via a $Ti(OiPr)_4$ mediated reduction of β–hydroxyketones The chiral epoxy alcohol **57** was prepared from the commercially available lactone **56**. Regioselective opening of **57** (Red/Al, 2hr, -20°C,) afforded exclusively diol **58**, which was transformed by standard procedure into compound **60**. Compound **60** was then desilylated and oxidized to aldehyde **61** (78% yield). Addition of Grignard reagent, ethylphenylmagnesium bromide on **61** afforded a diastereomeric mixture of alcohol, which was converted to β–hydroxyketone **63**. $Ti(OiPr)_4$ mediated $NaBH_4$ reduction of **63** affords required syn diol **64** (syn:anti > 87:13) which is further lactonized to lactone **41** in few steps.



Scheme 8. *Reagents and conditions:* (a) Red-Al, THF, -20°C; (b) (i) $TBAF_4$, THF; (ii) PCC, DCM; (c) $BnCH_2$-MgBr, THF, -20°C; (d) (i) PCC, DCM; (ii) Me_2BBr, THF; (e) (i) Ti-(isopropoxide)$_4$, THF; (ii) $NaBH_4$, THF, 80°C.

3.1.2.7. Roath and Roark[19]

Roath and Roark developed an asymmetric route for lactone **41** starting from commercially available tri-O-acetyl-D-glucal **46.** Treatment of **46** with PCC afforded unsaturated lactone **65** which is further converted to tosylate **67** in few steps. Tosylate **67** undergoes stereoselective Michael addition on treatment with sodium allyl alcoholate in allyl alcohol at low temperature (-43 to 0^{o}C) to afford a key chiral synthon **68**, which is easily converted to lactone **41** in two steps

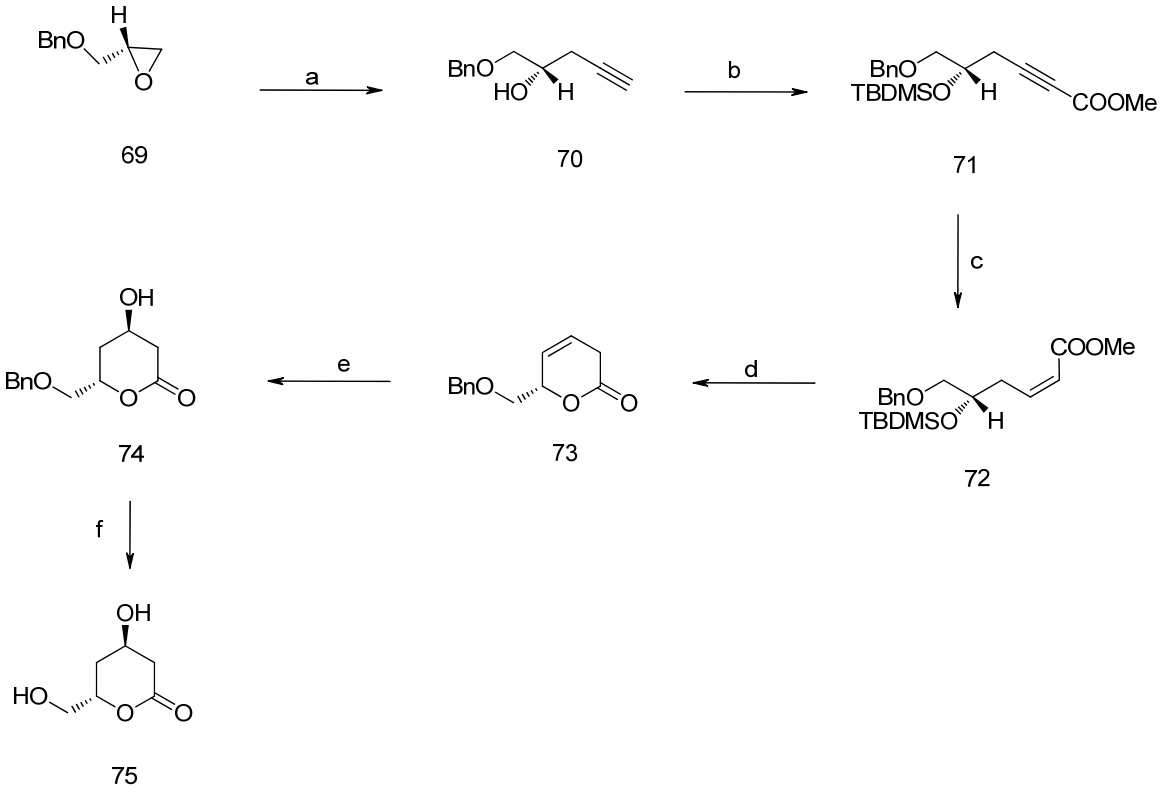


Scheme 9. *Reagents and conditions:* (a) (i) PCC, DCM, Celite; (b) (i) Zn, AcOH; (ii) TEA, RT stirring; (c) (i) 2N. HCl, (ii) TsCl, TEA; (d) (i) NaOMe/ MeOH; (e) Bn-MgCl, CuBr-Me_2S, THF; (iii) 10% Pd-C, Dioxane + Water.

3.1.2.8. S. Takano and coworkers[20]

S. Takano and coworkers developed a facile chiral synthesis for lactone moiety using (*R*)-O-benzylglycidol (**69**) as starting material. Treatment of sodium acetylide generated in situ with **69** affords the terminal acetylene **70**. Protection of free –OH as silyl ether and further methoxycarbonylation gives the ester **71** in 87% yield. Hydrogenation of **71** on Lindlar catalyst followed by brief exposure of the resulting

olefin **72** to acid furnishes the α,β–unsaturated δ–lactone **73** in 86% overall yield. Epoxidation of **73** using alkaline H_2O_2 followed by regioselective cleavage of epoxide using sodium phenylseleno(triisopropyloxy)borate affords β–ketol **74** in 87% yield. Finally, the benzyl group of **74** is removed by hydrogenolysis to afford the lactone **75** in 81% yield.

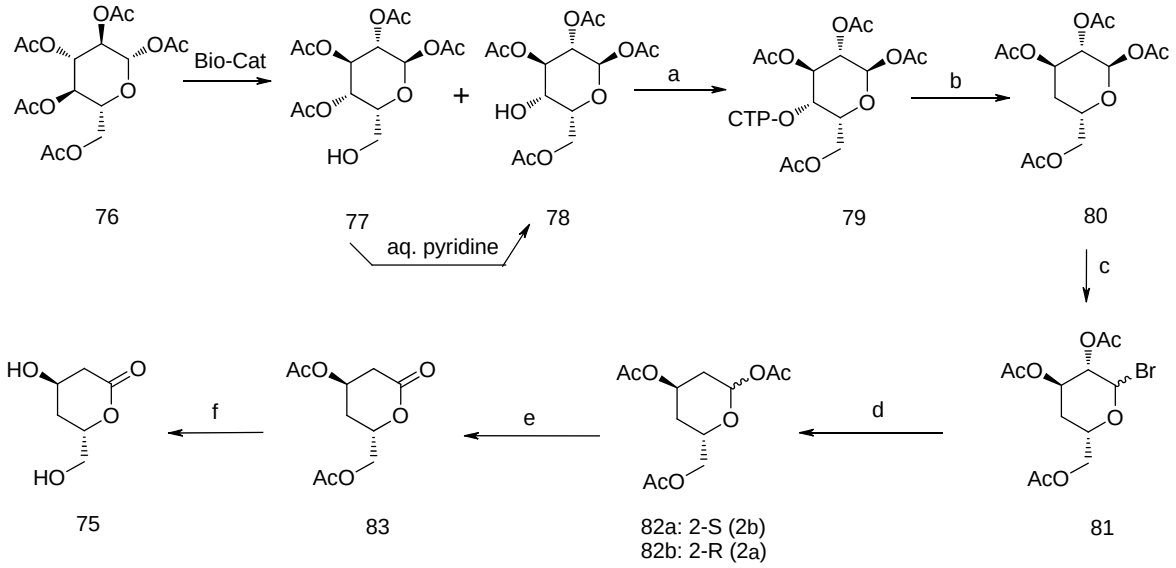


Scheme 10. *Reagents and conditions:* (a) (i) NaH, DMSO; (ii) Acetylene, THF; (b) (i) TBDMSCl, Imidazole, DMF; (ii) BuLi, THF, -78^oC; (iii) $ClCO_2Me$, -50^oC; (c) H_2/ Pd, quinoline, RT-1hr; (d) HCl, MeOH, RT; (e) (i) H_2O_2, NaOH, MeOH; (ii) $(PhSe)_2$, $NaBH_4$, AcOH, Iso-PrOH; (f) H_2/ $Pd(OH)_2$, $EtOAc_2$, RT-1hr

3.1.2.9. Y. Maki and coworkers[21]

Y. Maki and coworkers developed route to lactone **75** starting from glucose. Acetylated glucose **76** was rearranged to D-iodose derivative (**77** and **78**) by the modified Paulsen procedure ($SbCl_5$, NaOAc) followed by treatment of aqueous pyridine which

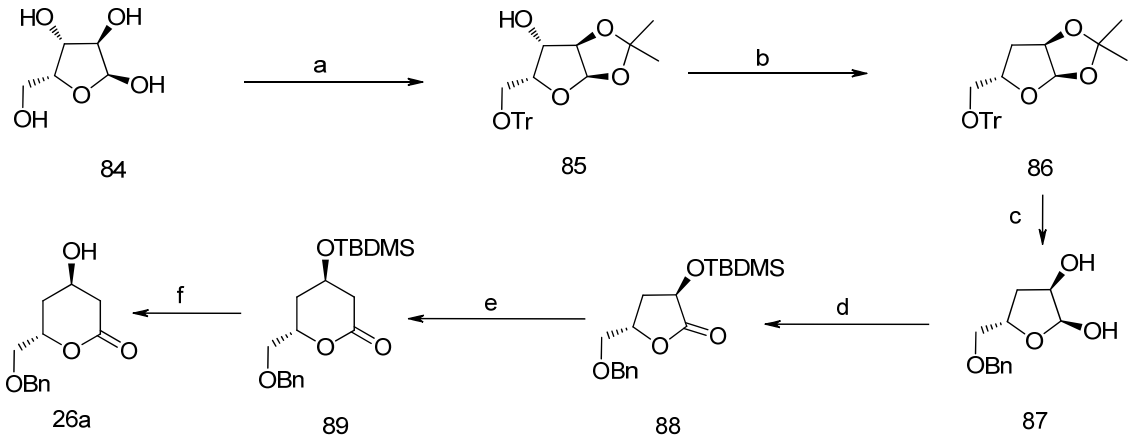
converted **77** to **78** by acyl migration. After conversion of **78** to the 4-O-phenoxythiocarbonyl derivative (**79**), the reaction with tributyltinhydride resulted in deoxygenation at C-4 of **78** to give the 4-deoxy derivative (**80**) which was treated with HBr to give 1-bromoderivative **81**. Radical rearrangement on **81** by heating at 80^{o}C with AIBN and tributyltinhydride afforded 1,3,6-tri-O-acetyl-2,4-dideoxy-β-D-iodopyranose (**82a**) which was hydrolyzed in aqueous dioxane and subsequently oxidized with bromine to give the lactone **83**. Deprotection of **83** to lactone **75** was achieved by dil. hydrochloric acid.



Scheme 11. *Reagents and conditions:* (a) (i) $SbCl_5$, DMSO; (ii) NaOAc, THF; (b) (i) PTC, Imidazole, DMF; Bu_3SnH, THF, RT-6 hr; (c) HBr, AcOH, RT; (d) (i) AIBN, Bu_3SnH, 80oC; (ii) (i) aq dioxane, (e) PCC, DCM; (f) dil-HCl, RT-12hr

3.1.2.10. M. Petrini and coworkers[22]

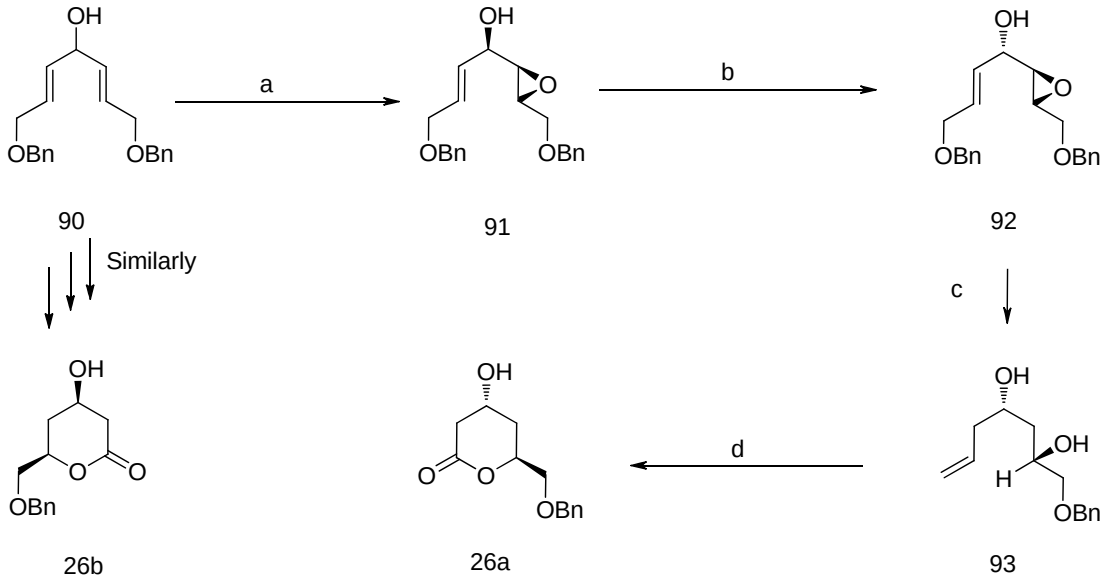
M. Petrini and coworkers developed a chiral route for lactone **32** using D-xylose (**84**) as starting material. Selective protection-deprotection of **85** afforded a diol which was selectively tritylated to give compound **85**. This was further deoxygenated by the to deoxy product **86**, which on acetonide deprotection afforded lactol **87**. The lactol **87** was to lactone **32** by sequence of reactions as shown below.



Scheme 12. Reagents and conditions: (a) (i) Acetone, $CuSO_4$ (anhy), (ii) AcOH, RT, 3. TrCl, Py; (b) (i) NaH, CS_2, MeI, THF, (ii) Bu_3SnH, AIBN, Benzene, reflux; (iii) H_2, Pd/C, EtOH; (c) (i) NaH, BnBr; (ii) 3.2 M HCl; dioxane (1:1); hr; (d) (i) Ag_2CO_3-celite; (ii) TBDMSCl, imidazole; (e) (i) $LiCHBr_2$, THF,-90^oC, HCl sat. in Et_2O; (f)TBAF, THF.

3.1.2.11. S. Takano and coworkers[23]

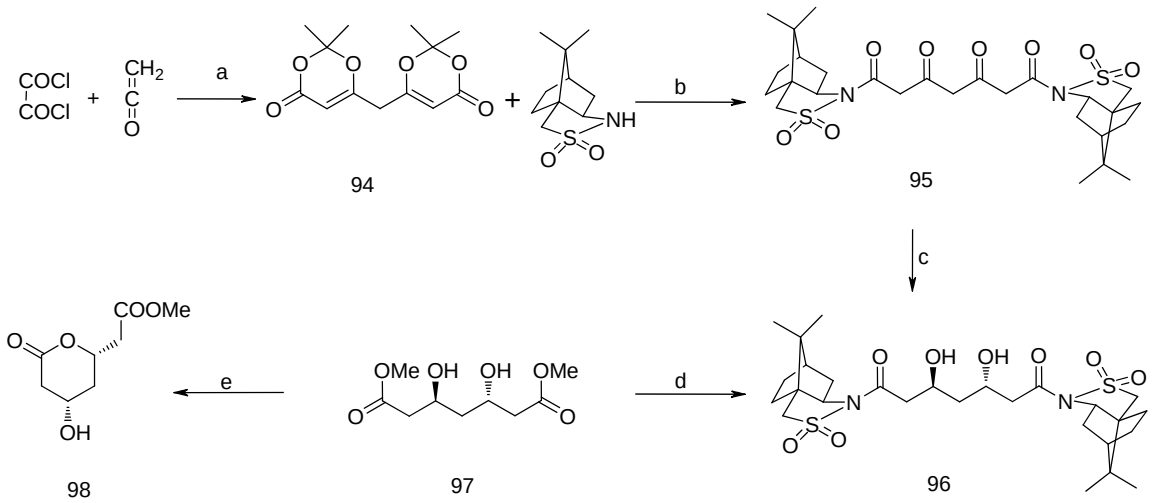
S. Takano and coworkers developed asymmetric synthesis for lactone **26a** based on Red-Al promoted intramolecular reductive cleavage of benzyl 4-hydroxy-2-butenyl ether structures. Thus, **92** which was obtained from **90** by Sharpless epoxidation and Mitsunobu inversion, on treatment with 3 eq. Red-Al afforded syn-diol **93**. It could be further converted into lactone **26a** in two steps



Scheme 13. *Reagents and conditions:* (a) (i) Diisopropyl-D-tartarate (9 mol %) (anhy), (ii) Ti-(O^iPr)$_4$ (7mol%), $^tBuO_3H$ (2 eq.) , 4 A^0 Mol.sieves; (b) i) 5 eq.DEAD, Ph_3P; p-(NO_2)-$C_6H_4CO_2H$, (ii) MeOH, NaOMe, (c) (i) 3 eq. Red-Al; (d) (i) OsO4 (2 mol %), $NaIO_4$ (2 eq.), THF; (ii) Ag_2CO_3-Celite

3.1.2.12. J. Kiegiel and coworkers[24]

J. Kiegiel and coworkers developed asymmetric route to δ–valerolactone **98** based on synthesis and asymmetric hydrogenation of 3, 5-dioxoheptanedionates. Bisdioxinonone **94** was obtained by the action of ketene on oxalyl chloride in acetone. Bisdioxinonone **94** and (1*S*)-bornane-10, 2-sultam were heated in toluene at 55^{o}C to obtain **95**. Compound **95** was hydrogenated by using (*S*)-Ru-BINAP as catalyst to afford anti-diol **96** in 96% de. Diol **96** was then transformed into enantiomerically pure dimethyl ester **97** by applying mild methanolysis in the presence of $NaHCO_3$, which on refluxing in benzene in the presence of pyridinium p-toluenesulfonate furnished enantiomerically pure lactone **98**.



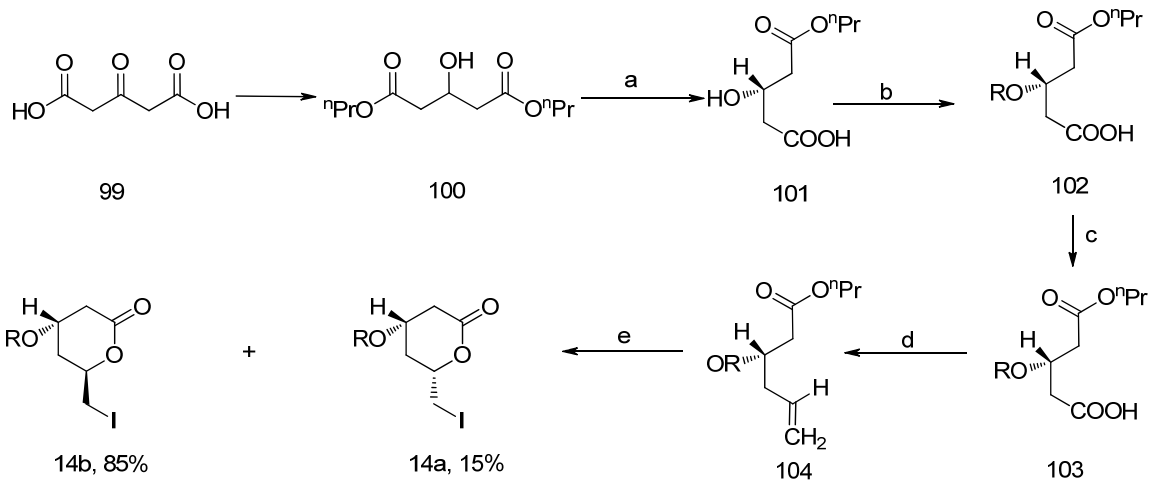
Scheme 14. *Reagents and conditions:* (a) Photochemical, EDC ; (b) Toluene, 55^{o}C ;(c) H_2/ (S)-Ru-BINAP; (d) MeOH, $NaHCO_3$; (e) PPTS, benzene

II) Chemoenzymatic Methods

Various chemoenzymatic methods are reported for the synthesis of chiral lactone synthon of compactin and mevinolin. In most of the reports, hydrolytic enzymes viz. lipases/esterases have been utilized to afford optically active intermediates and brief account of these methods is presented.

3.1.2.13. Badder et al.[25]

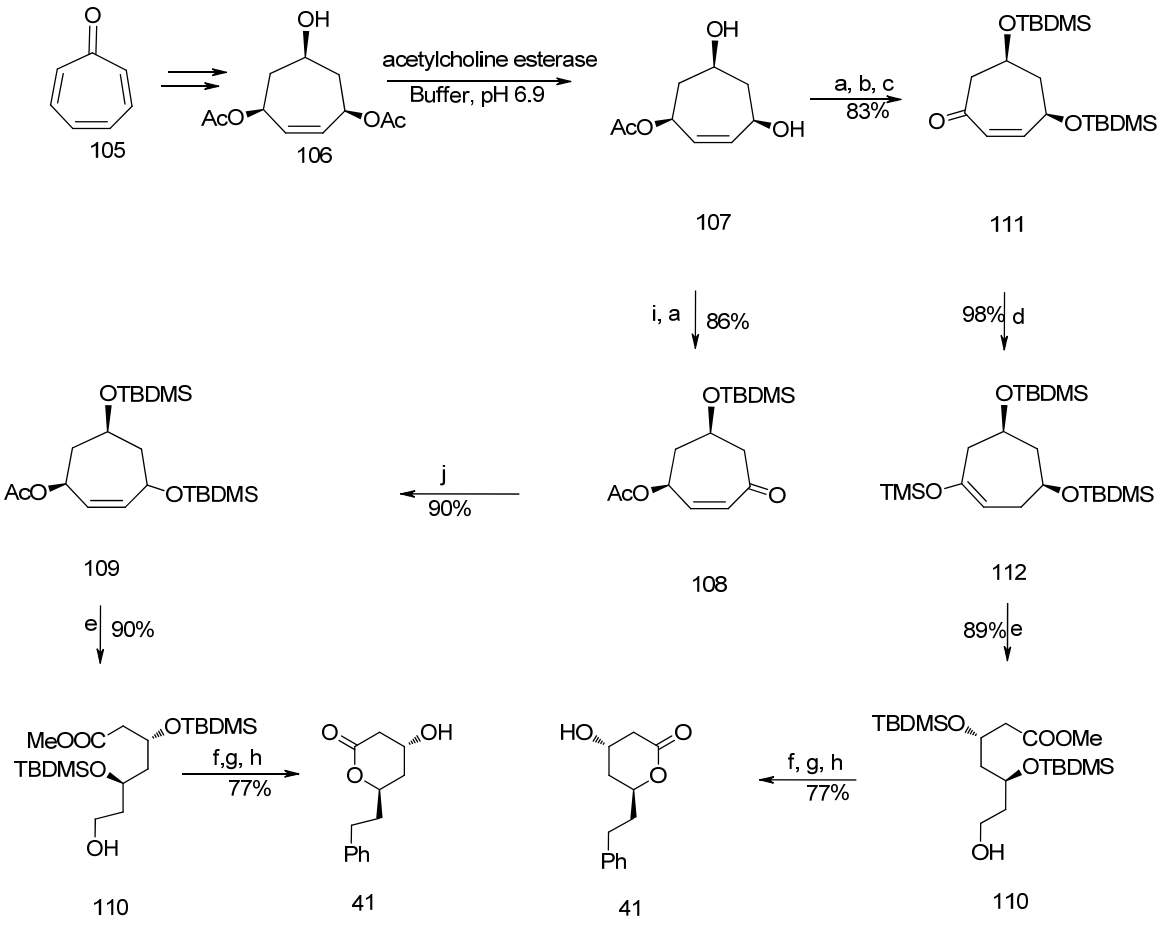
Badder et al developed a chemoenzymatic route for enantiomer of iodolactone **14** (R = TBDMS). Key step in this synthesis is enzyme PLE catalyzed saponification of prochiral di-n-propyl-3-hydroxyglutarate **100**.



Scheme 15. *Reagents and conditions:* (a) PLE, H_2O, Buffer (b) TBDMSCl, imidazole (c) (i) BH_3, THF -20 to 0^oC, (ii) PCC, CH_2Cl_2 (d) (i). CH_3PPh_3Br, toluene $KN(SiMe_3)_2$, -15 to 0^oC (ii) NaOH, EtOH, H_2O (e) Et2O, $NaHCO_3$, I_2 (5 eq.)

3.1.2.14. C. R. Johnson and coworkers[26]

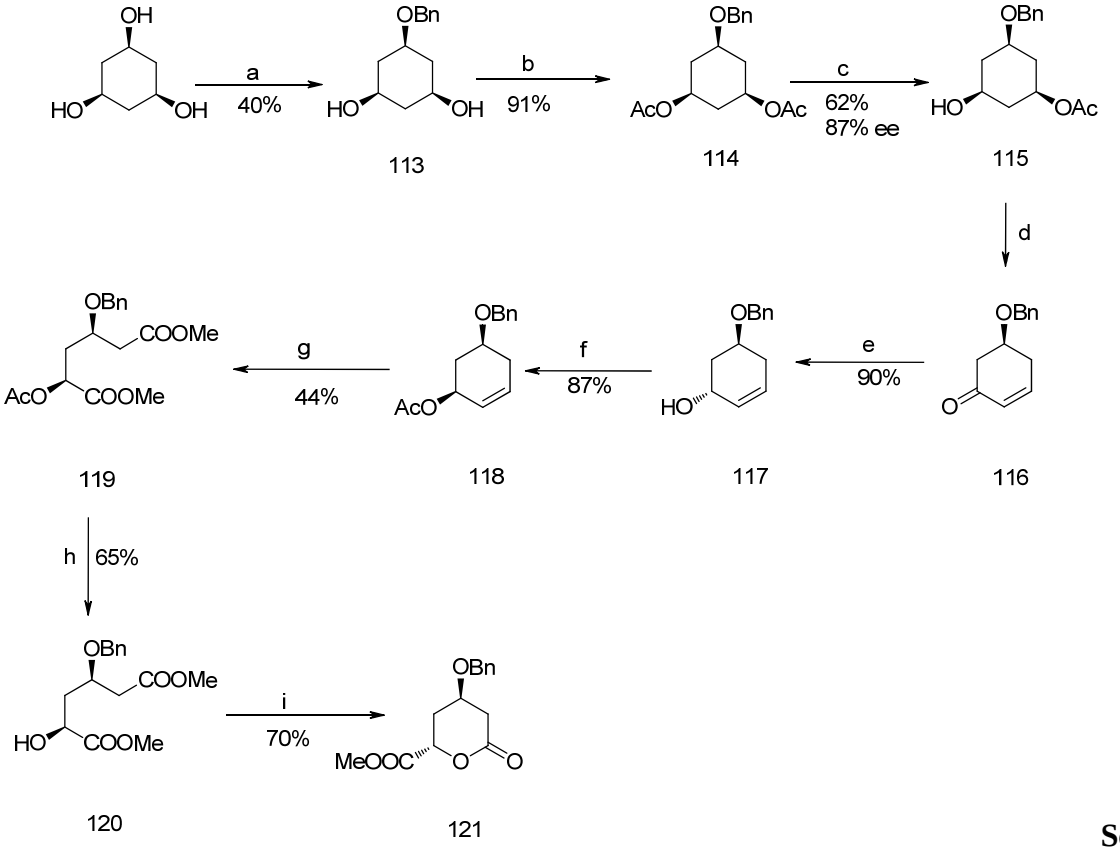
C. R. Johnson reported a chemoenzymatic route for both enantiomers of compactin analogue lactone **41.** Seven membered *meso*-diacetate **106**, that is obtained from troponone **105**, was desymmetrized by enzymatic hydrolysis catalyzed by electric eel acetylcholine esterase to afford chiral diol **107** in >95%. Compound **107** was further elaborated into both enantiomers of **41**. Main chemical steps involved protection-oxidation sequence to get pseudoenantiomeric enones **108**/**111** followed by MeCu catalyzed enolization of enone to form enol ether **109**/**112**. Ozonolysis of enol ethers followed $NaBH_4$ reduction and esterification afforded enantiomers of diprotected triol **110**, which could be converted to (+)-**41** or (-)-**41** in three steps.



Scheme 16. *Reagents and conditions:* (a)TBS-OTf, lutidine, CH_2Cl_2, 0°C (b) KOH, MeOH, 0°C; (c) PDC, CH_2Cl_2 (d) cat. MeCu, DIBALH- HMPA, -50°C, then at -78°C, MeLi, TMSCl; (e) O_3, MeOH, CH_2Cl_2, -78°C, then NaBH4 followed by CH_2N_2; (f) TsCl, Et_3N, DMAP; (g) Ph_2CuLi, Et_2O, 0°C (h) HF, CH_3CN; (i) MnO_2, CH_2Cl_2 (j) cat. MeCu, 2.5 eq. of DIBALH in HMPA/ THF, -50°C, then at -78°C, MeLi (2.5 equ.), TBSOTf (2.5 equv.)

3.1.2.15. K. Sakai and coworkers[3b]

K. Sakai and coworkers developed a chemoenzymatic synthesis for compactin lactone moiety utilizing phloroglucinol as starting material. *Meso*-diacetae **114**, prepared from phloroglucitol was desymmetrized by enzymatic hydrolysis catalyzed by PLE to afford optically active cyclohexanol **115** of 87% e.e. in 62% yield. Jones oxidation of **115** afforded the enone **116**, which on diastereloselective reduction using $NaBH_4$-$CeCl_3$ afforded 3,5-*trans* isomer **117**. Compound **117** was converted to the acetate **118** with desirable configuration by Mitsunobu method. The diester **119** was obtained from **118** via ozonolysis, Jones oxidation and subsequent esterification with CH_2N_2. After hydrolysis of acetate, lactonization of **120** in the presence of p-TsOH afforded the lactone moiety **121** of compactin. Thus, phloroglucinol was converted to lactone **121** in overall 1.73% yield.

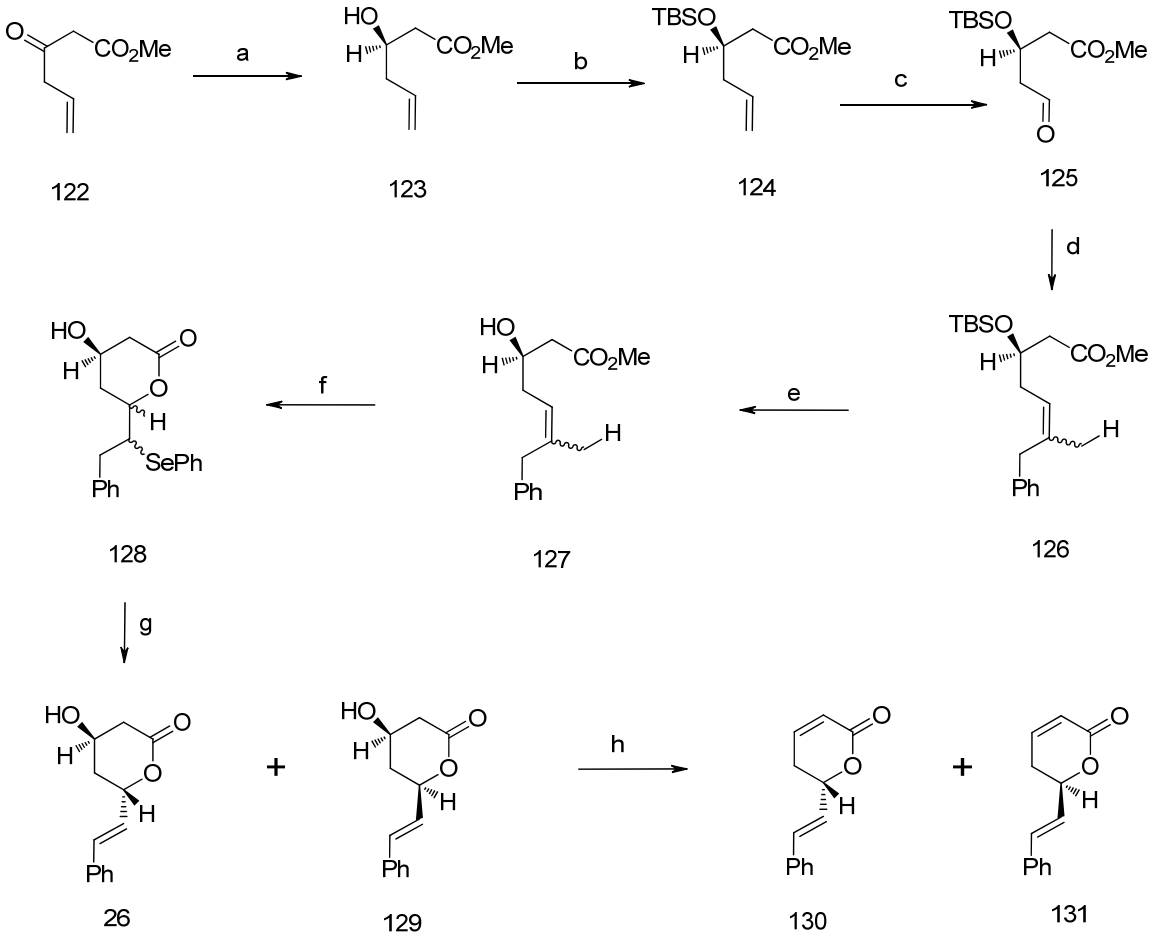


Scheme 17. *Reagents and conditions:* (a) NaH, BnCl, DMSO (b) Ac_2O, Pyridine (c) PLE,

pH =7 (d) Jones oxidn, 49%; (e)$NaBH_4$, $CeCl_3$ (f) PPh_3, DEAD, AcOH, $Lact^n$; (g) (i) O_3; (ii) Jones oxidn; (iii) CH_2N_2 (h) K_2CO_3/ MeOH; (i) PTSA, benzene.

3.1.2.16. D.W. Knight and coworker[27]

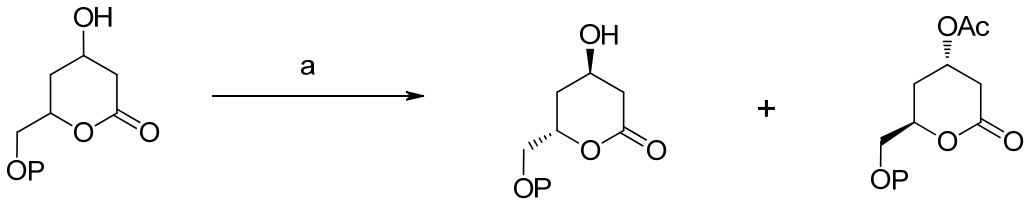
D.W. Knight and coworkers developed a chemoenzymatic route for optically active lactone **25** and its epimer, these were further converted to both enantiomers of the natural product goniothalamin **130** and **131**. Ozonolysis of the 3-silyloxyhexanoate **124**, derived from the yeast reduction product (3*R*)-(-)-3-hydroxyhex-5-enoate **123** (e.e. 78%), followed by Wittig homologation and selenolactonization leads to the lactones **26** and **129**. Subsequent dehydration gives **130** and **131**.



Scheme 18. *Reagents and conditions:* (a) B.Y.reduction; (b) NEt_3, TBDMSCl, DCM; (c) O_3, MeOH, AcOH; (d) PH_3P=BnBr, THF; (e) TBAF, THF, (f) PhSeH, THF, Lactn (g) TBHP, Heat; (h) TsCl, TEA, DCM, Heat, -H_20

3.1.2.17. Crobs and co-workers[28]

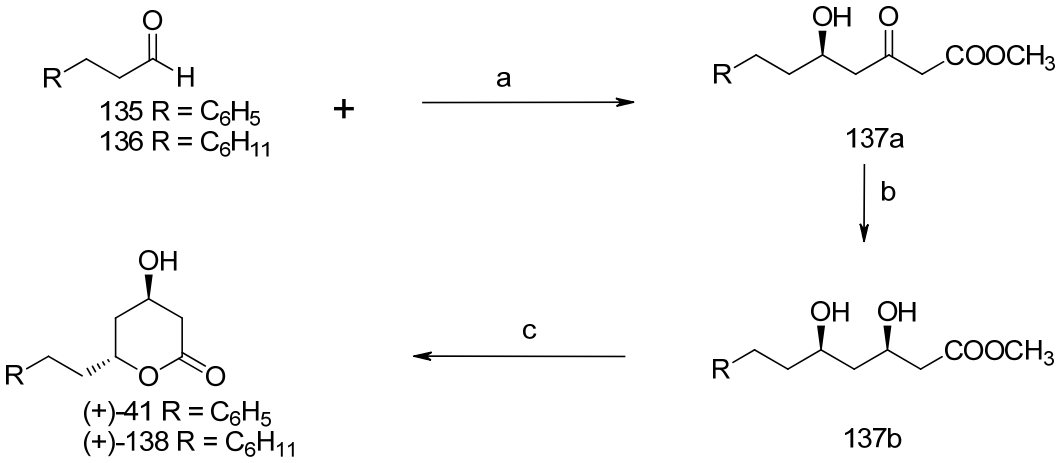
Crobs and co-workers have patented the enzymatic resolution of lactone **132.** Racemic lactones with formula **132** were resolved by enzymatic transesterification with vinyl acetate in THF using *Chromobacterium viscosum* lipase as catalyst at 40°C. Optically active lactone **133** with free secondary –OH was recovered with e.e. >95%.



Scheme 19. *Reagents and conditions:* (a) Vinyl acetate, TBME, *Chromobacterium Viscosum Lipase*.

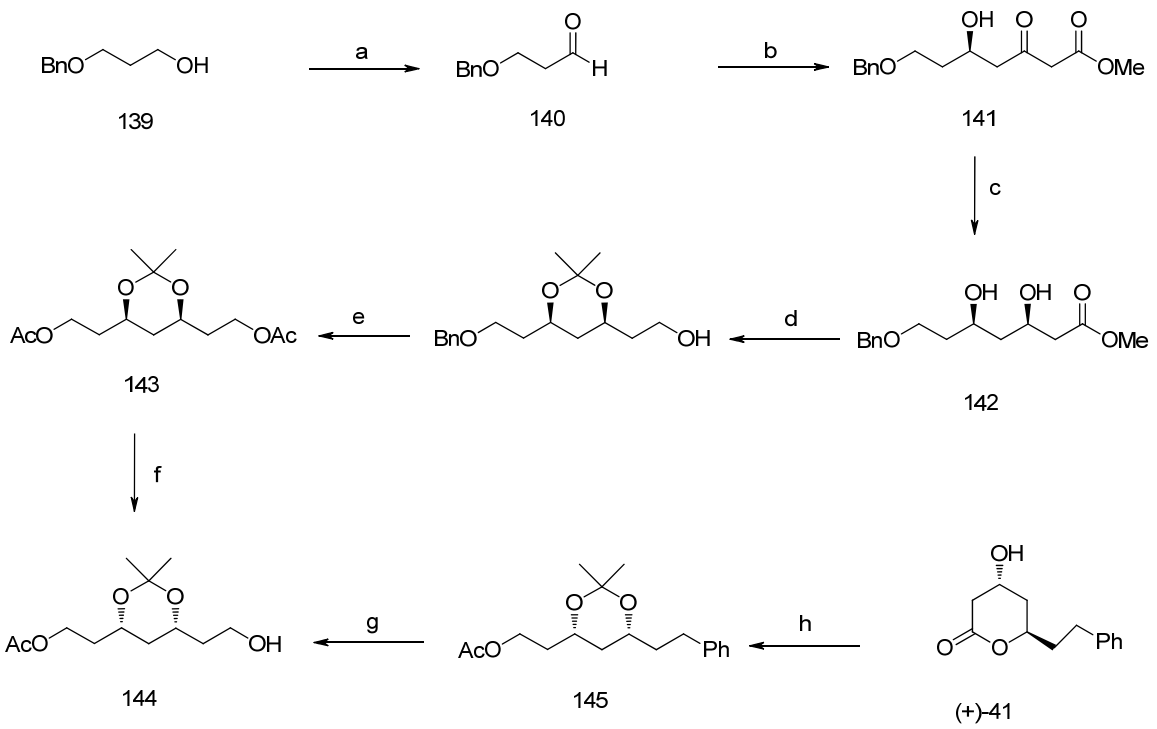
3.1.2.18. C. Bonini and coworkers[29, 30]

C. Bonini and coworkers reported a short synthesis of optically active mevinic acid analogues by biocatalytic lactonization of syn-3,5-dihydroxy esters. The starting syn-3,5-dihydroxyesters of type **137b** were prepared respectively from phenyl propionaldehyde **135** and cyclohexyl propionaldehyde **136** with the dianion of methyl acetoacetate followed by diastereoselective reduction of resulting aldols **137a**. Biocatalytic lactonization of these syn-dihydroxyesters was performed using PPL in ether solution. Corresponding lactones (+)-**41** and (+)-**138** of >98% e.e. were obtained in 35% yield.



Scheme 20. *Reagents and conditions:* (a) Methyl aceto-acetate, NaH, BuLi, HMPA, THF;
b) (i) Bu_3B, MeOH; (ii) $NaBH_4$; (c) PPL, ether.

In another chemoenzymatic route for lactone (+)-**41**, C. Bonini and coworkers obtained a new seven-carbon polyhydroxylated chiral synthon **144** as single enantiomer, in nearly quantitative yield by enzymatic desymmetrization of the *meso*-compound **143.** The compound **143** was prepared by the aldol condensation of aldehyde **140** with methylacetoacetate and subsequent diastereoselective reduction of the aldol **141** to syn 1,3-diol **142** followed by acetonoide protection, LAH reduction, debenzylation and acetylation to afford *meso*-diacetate **143**. *Meso*-diacetate **143** was desymmetrized to **144** with high degree of enantiotopic discrimination by *Pseudomonas fluorescens* lipase (PFL) catalyzed hydrolysis in phosphate buffer. Compound **144** could be further elaborated to lactone (+)-**41** in four chemical steps.

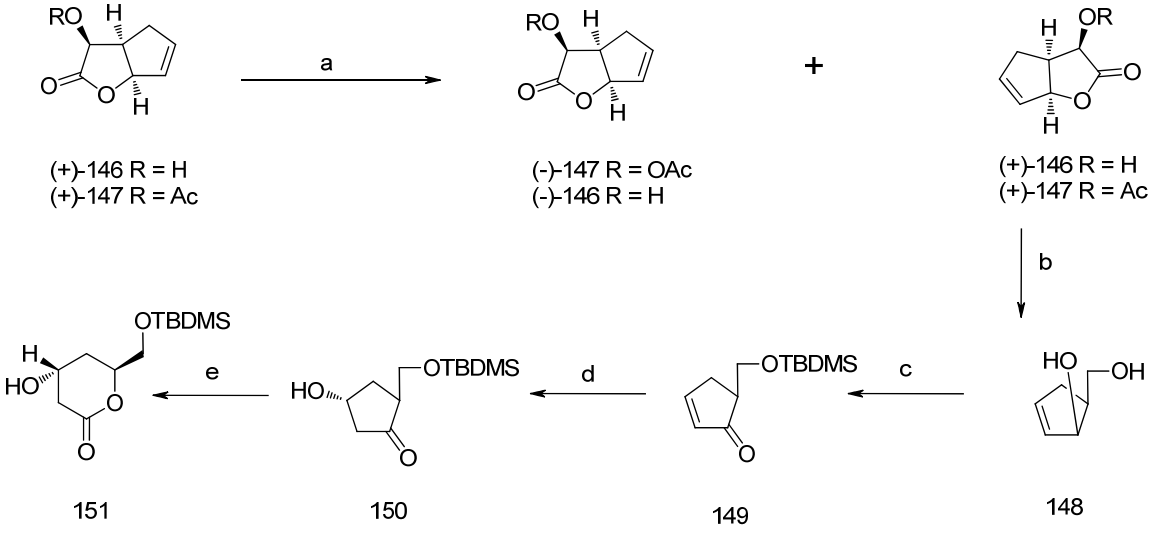


Scheme 21. *Reagents and conditions:* (a) PCC, DCM, Celite; (b) Methyl aceto-acetate, NaH, BuLi, HMPA, -78^{o}C THF, 38%; c) (i) Et_3B, MeOH; (ii) $NaBH_4$, THF, 66%; (d) (i) $(CH3)_2C(OCH_3)_2$, TsOH, 95%; (ii). $LiAlH_4$, THF, 95%; (e) (i) Pd/C, H_2, 85%; (ii) Ac_2O, Py, 98%.; (f) PFL, Buffer, pH 7, 98%, ee > 98%; (g) (i) TsCl, Py, 56%; (ii) Ph_2CuLi, Et_2O, 0^{o}C, 65%; (h)(i) MeOH, Na (Cat.), (98%); (ii) $RuCl_3.3H_2O$, CCl_4, CH_3CN, buffer then; (iii) PTSA (56%)

3.1.2.19. R. McCague et al.[31]

R. McCague et al reported a chemoenzymatic synthesis of mevinic acid lactone **151** starting from endohydroxylactone (+)-**146** or ester (+)-**147** which is obtained by enzymatic resolution of racemic endo-hydroxylactone **146** using *Pseudomonas flurorescens* lipase (PFL) either by esterification in an organic solvent, or by hydrolysis of the acetyl ester (±)-**147** in a buffer solution. Hydroxylactone (+)-**146** or ester (+)- **147** was reduced to diol **148** in three steps- $LiAlH_4$ reduction, sodium periodate diol clevage, and $NaBH_4$ reduction. Cyclopentenone **149** was obtained by selective monoprotection of diol **148** with TBDMSCl followed by PCC oxidation. Compound **148** was converted to

β–hydroxycyclopentanone by stereoselective epoxidation followed by epoxide opening using Kect's aluminium amalgam conditions. Baeyer-Villiger oxidation of cyclopentanone **150** provided the desired lactone **151** which posses the correct stereogenic center in the mevinic acids.

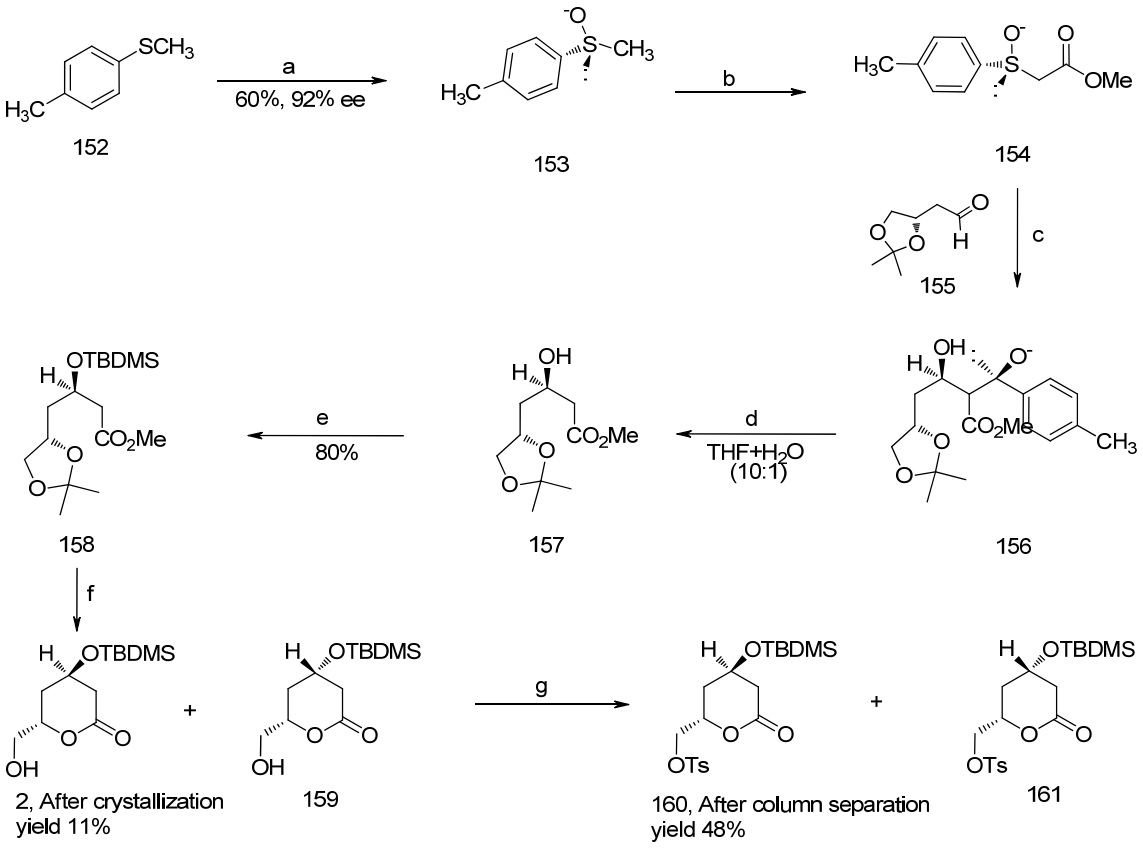


Scheme 22. *Reagents and conditions:* (a) PFL, vinyl acetate or PFL, buffer solution pH= 7; (b) (i) $LiAlH_4$, THF, (ii) $NaIO_4$, H_2O, (iii) $NaBH_4$; c) (i) TBDMSCl, Et_3N, DMAP; (ii) PDC, CH_2Cl_2; (d) (i) H_2O_2, NaOH, MeOH, 0^oC; (ii) Al(Hg), THF-H_2O; (e) DCM/ MCPBA.

3.1.2.20. S. M. Roberts and coworkers[32]

S. M. Roberts and coworkers developed an asymmetric synthesis of a α–silyloxy-δ-lactone (**2**, R = TBDMS) using (*R*)-methyl paratolylsulfoxide as a chiral auxillary. The chiral sulfoxide **153** was obtained via a straightforward biooxidation of methyl p-tolylsufide **152** using Baker's yeast (*Saccharomyces cerevisiae* NCYC 73) in 60% yield and 92% e.e.. The enolate ion of **153** was generated using LDA and reacted with methyl chloroformate to afford the α-sulfinylester **154**, which on treatment with *tert*-BuMgCl and aldehyde **155** underwent stereocontrolled aldol condensation to afford ester **156**. Desulphurization of **156** yielded C-3 epimers of **157** in ratio of 4:1, which were protected

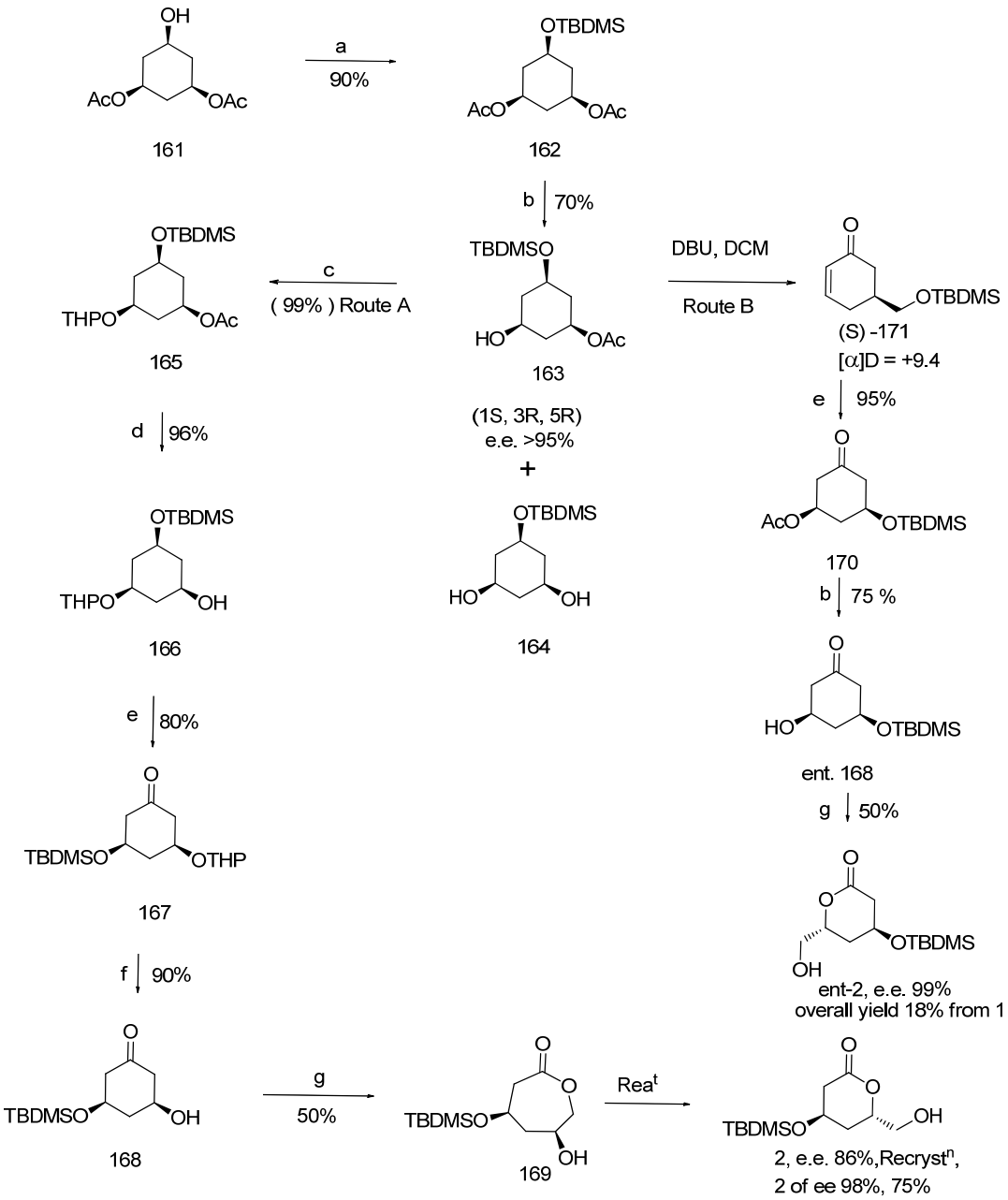
as TBDMS ethers **158**. Lactonization of **158** by heating to reflux in 80% acetic acid afforded the desired lactone **2** and **159**. Successive recrystallizations from hexane gave **2** in pure form. Alternatively, tosylation of a mixture of **2** and **159** afforded tosyl derivatives, **160** and **161**, which could be separated by flash chromatography. Thus pure lactone **2** was obtained from **152** in 2% overall yield.



Scheme 23. *Reagents and conditions:* (a)NCYC-73, (Saccharomyces cerevisiae) ,60%, 92% ee ; (b) (i) $ClCOOCH_3$, LDA, -78^oC; c) (i) ^tBuMgCl, THF; (d) Al/ Hg, 0^oC, MeOH, 0^oC, THF: H_2O; (e) TBDMSCl, DMF, imidazole, 50^oC, 80%; (e) 80% acetic acid, 100^oC, 1hr; (f) PTSCl, pyridine

3.1.2.20. Kalkote *et al.*[33]

Kalkote *et al* implemented chemoenzymatic synthesis for compactin lactone moiety utilizing phloroglucinol as starting material as shown in scheme 24.



Scheme 24. *Reagents and conditions:* (a)TBDMSCl, Et_3N, CH_2Cl_2, 0°C; (b) PLE, buffer pH 8, 70%; (c) DHP, PTSA, CH_2Cl_2, 0°C, 99%; (d) K_2CO_3, MeOH, 96% ; (e) PCC, DCM, 80%, $MgBr_2$, ether, 90%; (f) 3-chloroperbenzoic acid, DCM, $NaHCO_3$.

Free hydroxyl group in diacetate **161** was protected as TBDMS ether to afford meso-diacetate **162.** Meso-diacetate **162** was subjected to desymmetrization with PLE to afford optically active **163** in excellent yields. This was successfully converted in to Comapctin latone **2** and ent **2** by sequence of reactions as shown in Scheme 24.

3.1.3. References:

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Chapter 3, Section II: Formal Synthesis of Compactin lactone moiety

3.2.1. Introduction

Nature is an architect par excellence, produces hundreds of compounds through a variety of biogenetic pathways and quite a few of them have attracted the synthetic organic chemist's attention due to their remarkable structural features and/or the conferred specific bioactivity. Synthesis of bioactive molecules is in the forefront of synthetic organic chemistry, due to its varied applications in drug and pharmaceutical industries and biotechnologies. There are generally three routes to achieve enantio-selective synthesis.

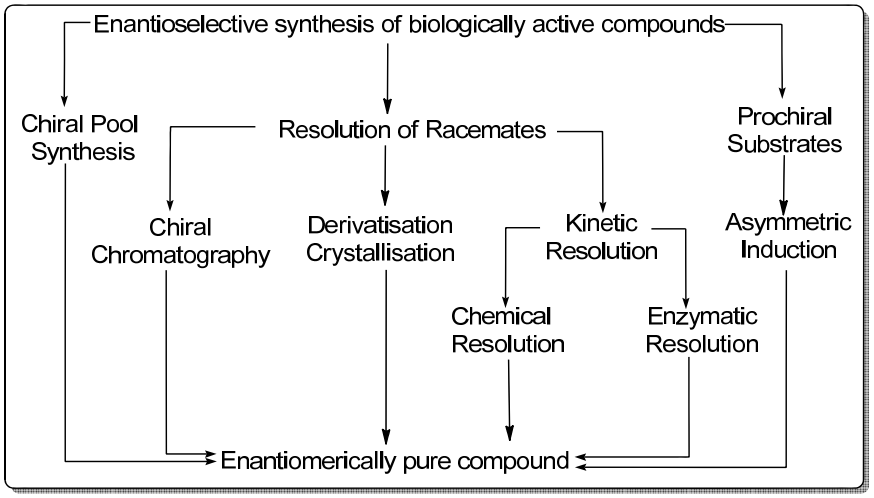


Figure 1: Enantioselective synthesis of biologically active compounds

Among these methods asymmetric induction over prochiral substrates leading to asymmetric synthesis is widely used since chiral induction can be carried out over any scale at normal and mild reaction conditions. Asymmetric catalysis provides, an especially practical entry into the chiral world due to economical use of asymmetric inducing agents.[1]

Among the asymmetric catalysis most useful is the carbon-heteroatom bond forming reaction; for example coupling of carbon and hetero atom via asymmetric dihydroxylation reaction which has been widely used. After the dihydroxylation, further modification can be made by coupling with acid as well as acid chlorides to afford beta hydroxy esters or lactones. This transformation could open an economically and ecologically benign avenue to a series of statin drugs. Hence, we planned the synthesis of lactone core of the compactin (statin) using dihydroxylation tool.

3.2.2. Introduction of Sharpless Asymmetric Dihydroxylation (SAD)

In the last three decades, many examples of asymmetric catalysis have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds such as epoxidaiton,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxy-lation[5] and amino-hydroxylation.[6]

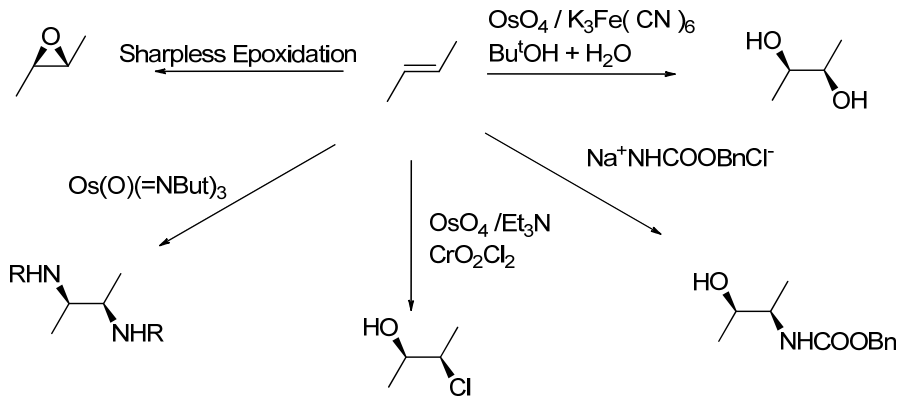


Figure 2: Transtion metal mediated 1, 2 di-functionalisation of olefins

A common feature of most of these reactions is the phenomenon of ligand acceleration,[7] wherein a metal catalyzed process turns over faster in the presence of a co-ordinating ligand (Figure 2). Since the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way, the OsO_4 catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and feasible and selective transformation in the organic chemistry.

3.2.3. Mechanism of Sharpless Asymmetric Dihydroxylation (SAD)

Two different mechanisms have been suggested for osmium-catalyzed dihydroxylation.

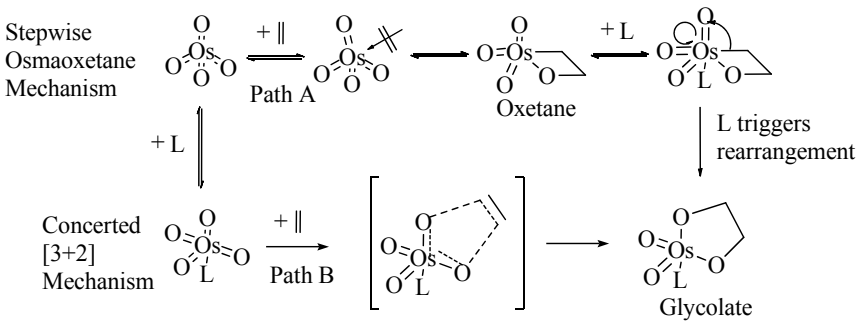


Figure 3: OsO_4 Mediated dihydroxylation of olefin, L: Ligand

Boseken and Criegee[8] originally proposed a concerted [3+2] pathway, (Figure 3, Path A) While Sharpless et al.[9a] and Jorgensen et al.[9b] suggested a stepwise [2+2] like addition of the olefin across an Os=O bond (Figure 3, Path B), followed by rearrangement of the resulting osmo-oxetane intermediate to the glycolate product.[5b] Sharpless et al. in his pioneering work, suggeted mechanism which employs inexpensive reagents for the oxidation of the osmium (VI) glycolate products with alkaline $^{t-}$BuOOH, or N-methylmorpholine N-oxide [10-11] to OsO_4 and enhance its synthetic utility[5b] (Figure 4).

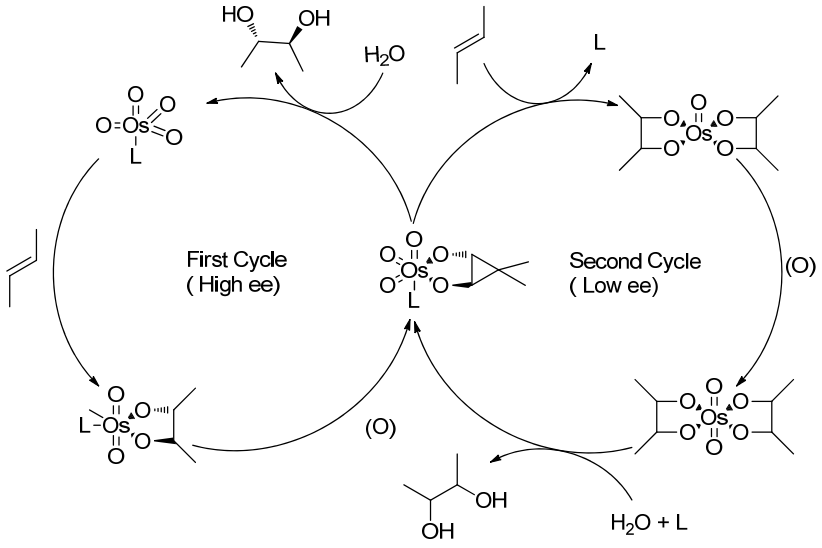


Figure 4: Osmium mediated 1, 2 - di-hydroxylation of olefins with NMO as co oxidants

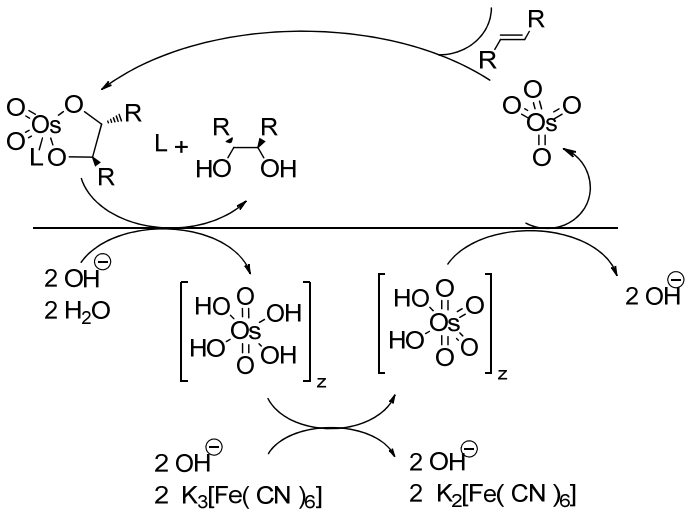


Figure 5: Osmium mediated 1, 2 di-hydroxylation of olefins with $K_3Fe(CN)_6$

Tsuji et al.[12] demonstrated that $K_3[Fe(CN)_6]$ and K_2CO_3 provides a powerful and economical system for the regeneration of osmium instead of NMO (Figure 5).

3.2.4. Empirical Rules for Predicting the Face Selectivity

Despite the mechanistic uncertainties, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (Figure 6).[13]

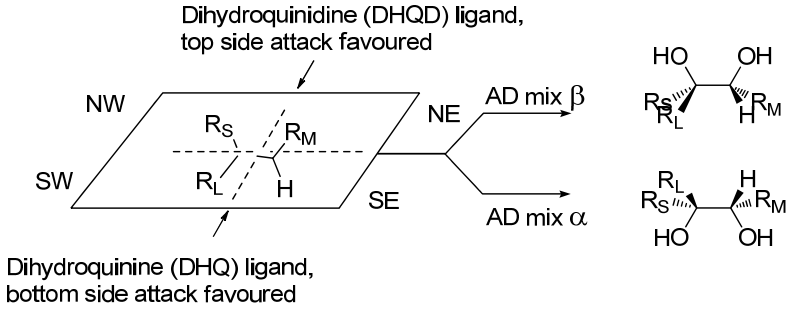


Figure 6: Mechanistic device for predicting selectivity of dihydroxylation

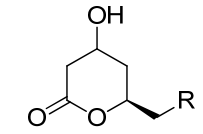
NE: North East, SE: South East, NW: North West, SW: South West

PHL Ligands : Aromatic groups prefered, PYR ligands : Aliphatic groups prefered

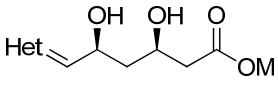
The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand-dependent. An olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the beta-face, in the case of DHQD derived ligands and from the bottom, i.e. from the alpha-face, in the case of DHQ derivatives.

3.2.5. Present Work

Statins are microbially as well as synthetically derived but the difference between them is that the microbially derived statins contain complex substituted chiral ring system, whereas synthetic statins possess simple heteroaromatic motif attached to 3,5-dihydroxy moiety.



Microbially derived statins



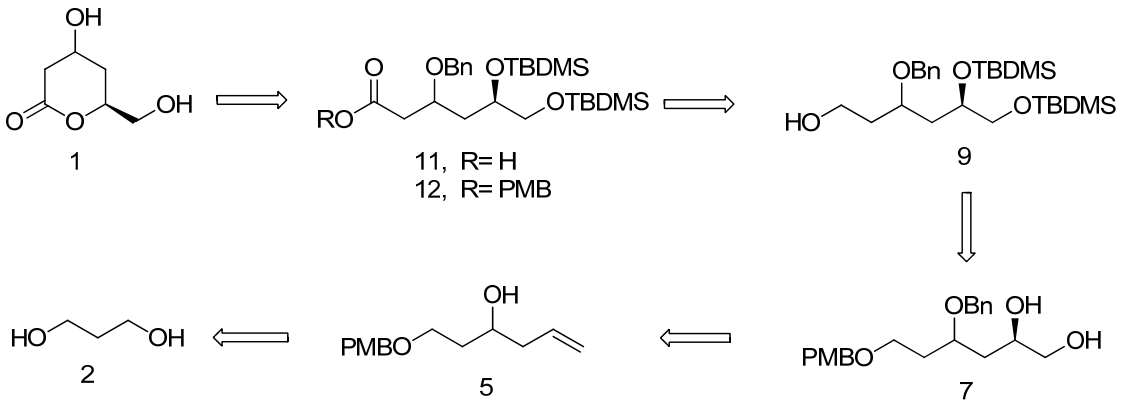
Synthetic Statins

Figure 7: General structure of fungal and synthetic statins.

Hence, the efficient synthesis of complex molecules, such as natural and pharmaceuticaly important products, is still a challenge in synthetic organic chemistry. During the synthesis key intermediate compound with a defined constitution and defined stereogenic properties has to be generated so that such intermediates serve as starting materials for further synthetic efforts to produce the desired targets. Hence, in continuation of our studies on synthesis of biologically active compounds and development of novel synthetic methodologies, we felt that 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol (**5**) is the valuable synthon for the construction of

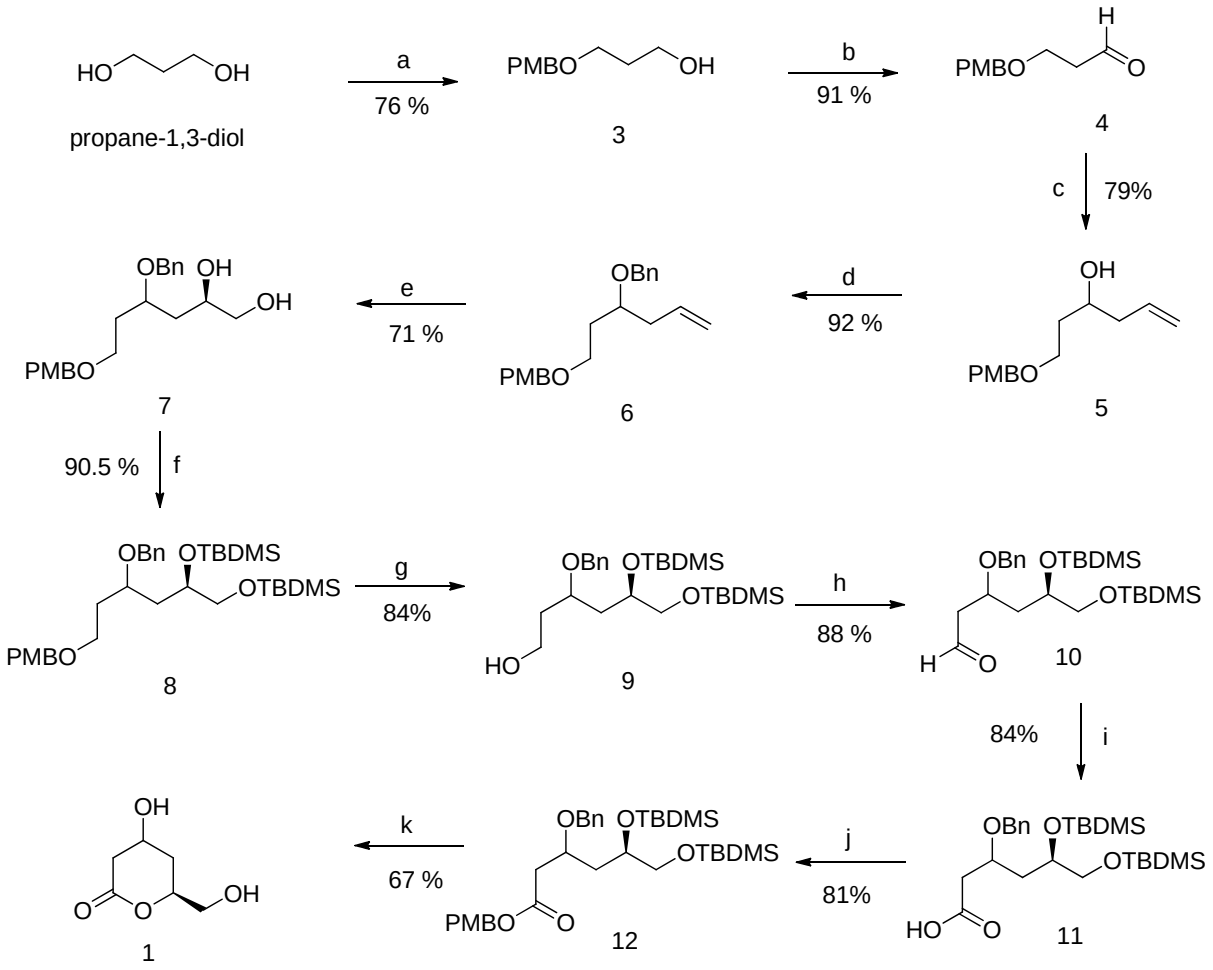
many challenging synthetic targets. Hence, we planned synthesis of lactone moiety of compactin and mevenolin via dihydroxylation and lactonization.

Various methods have been reported over formal and total synthesis of enantiopure δ-lactone moiety of statins (compactin and mevenolin), employing chiron approach, or kinetic resolution of racemate. All reported synthesis includes the use of expensive starting material as well as long route with low overall yield. To overcome this factor here, we provide two simple, short, selective, and economical schemes for synthesis compactin lactone moiety.



Scheme 1

As outlined in retrosynthesis (scheme 1) compactin lactone moiety can be synthesized from (5R)-3-(benzyloxy)-5,6-bis((tert-butyldimethylsilyl)oxy)hexanoic acid (**11)** or its corresponding ester (**12**), which in turn can be prepared from (2R)-4-(benzyloxy)-6-((4-methoxybenzyl)oxy)hexane-1,2-diol (**7**). This intermediate (**7**) can be synthesized from racemic 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol (**5**) which in turn can be synthesized from commercially available starting material propane-1,3-diol.



Scheme 2. *Reagents and conditions:* (a) NaH, PMB-Cl, DMF; (b) PCC, DCM, RT; (c) Allyl bromide, Zn, THF, aq NH_4Cl; (d) NaH, BnBr, TBAI, DMF; (e) AD-mix β ,^{t}-BuOH + H_2O; (f) TBDMS-Cl, imidazole, DCM; (g) DDQ, DCM:H_2O; (h) PCC, DCM, RT; (i) $NaClO_2$, NaH_2PO_4, DMSO, H_2O; (j) PMB-OH, EDCI, DMAP, DCM; (k) TBAF, THF-RT.

As depicted in Scheme 2, monoprotection of propane-1,3-diol as 4-methoxy-benzyl ether was achieved by using one equivalent of sodium hydride and 4-methoxy-benzyl chloride in anhydrous DMF and under nitrogen atmosphere to produce hydroxyl compound **3**, which on oxidation with PCC afforded aldehyde **4** in quantitative yield. Aldehyde **4** on treatment with allyl-zinc-bromide under Barbier conditions (aq NH_4Cl +

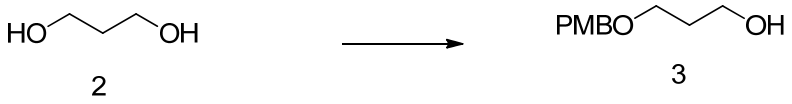
acetonitrile + Zn + allyl bromide), gave racemic 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol (**5**). This on further treatment with sodium hydride and benzyl bromide furnished 6. The olefin **6** on dihydroxylation with OsO_4 under conditions of Sharpless asymmetric dihydroxylation afforded terminal diol **7,** which on treatment with TBDMS-Cl and imidazole in DMF underwent masking of both OH groups to produce intermediate **8**. The compound **8** on treatment with DDQ gave **9**. The oxidation of **9** with PCC and $NaClO_4$, afforded **11.** The acid **11** was further esterified with 4-methoxybenzyl alcohol and cyclized to lactone **1** by using TBAF**.** Lactone **1** can be easily resolved enzymetically to chiral lactone **1a** by known procedure.[14]

3.2.6. Conclusion

Formal synthesis of Compactin lactone (**1a**) is achieved in 11 steps and 11% overall yields from easily available propan-1,3-diol, Sharpless asymmetric dihydroxylation and enzymatic resolution are the key steps.

3.2.7. Experimental

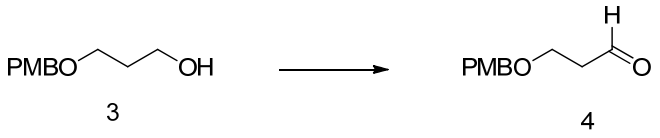
Preparation of 3-((4-methoxybenzyl) oxy) propan-1-ol (3)



To the stirred solution of propan-1,3-diol (25gm, 0.32 mole) in DMF sodium hydride (60 %, 16.45 gm, 0.411 mole, 1.25 eq) was added in argon atmosphere at ice cold temperature. After stirring for ½ hour 4-methoxy benzyl chloride (58 gm 0.411 moles, 1.25 eq) was added in argon atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with ice-cold water and extracted with DCM (250 mL x 2). Organic layer was separated and dried over anhydrous sodium sulphate and concentrated over rotaevaporator to get crude residue, which on silica gel column chromatography using ethyl Acetate: pet ether (25:75) as eluent afforded 3-((4-methoxybenzyl) oxy) propan-1-ol (**3**)

Yield: 52.80 gm, 76%; yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78-1.90 (m, 2H), 2.58 (s, 1H), 3.62 (t, *J*= 5.81 Hz, 2H), 3.75 (t, *J*= 5.87 Hz, 2H), 3.79 (s, 3H), 4.44 (s, 2H), 6.87 (d, *J*= 8.64 Hz, 2H), 7.25 (d, *J*= 8.65 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.97, 54.97, 60.88, 68.29, 72.56, 113.56, 129.05, 130.01, 158.96. Elemental Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; Found: C, 67.49; H, 8.34.

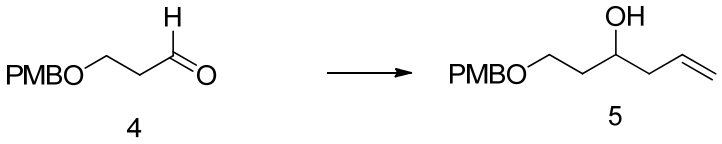
Preparation of 3-((4-methoxybenzyl)-oxy) propanal (4)



To the stirred solution of **3** (50 gm, 0.25 mole) in 500 mL $CHCl_3$, PCC (74.53 gm, 0.32 mole, 1.25 eq) was added in inert atmosphere slowly in portion, at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was filtered over celite and washed with $CHCl_3$. All organic washings were collected and concentrated over rotaevaporator get crude residue, which on alumina column chromatography using ethylacetate: pet ether (10: 90) as eluent afforded 3-((4-methoxybenzyl)-oxy) propanal (**4)**.

Yield: 46.5 gm, 94 %; yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.64-2.71 (m, 2H), 3.73- 3.79 (m, 2H), 3.80 (s, 3H), 4.45 (s, 2H), 6.87 (d, *J*= 8.74 Hz, 2H), 7.24 (d, *J*= 8.72 Hz, 2H), 9.77 (t, *J*= 1.83 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.71, 55.12, 63.37, 72.75, 113.71, 129.24, 129.80, 159.18, 201.21.

Preparation of 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol (5)



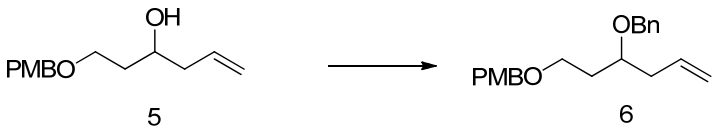
4 5

To the stirred solution of **4** (45 gm, 0.23 mole) in THF (300 mL) and aq NH_4Cl (saturated solution 200 mL), zinc (29.44 gm, 0.46 mole, 2 eq) was added slowly portion wise. After ½ hour of stirring, allyl bromide (55.44 gm, 0.46 moles, 2 eq) was added. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction was carried out by simply filtration over celite and extracted with DCM (2 X 250 mL). All organic washings were collected and concentrated over rotaevaporator to get crude residue which on silica gel column chromatography using ethyl Acetate: pet ether (15:85) as eluent afforded 1-((4-methoxybenzyl)oxy)hex-5-en-3-ol **(5).**

Yield: 43.2 g, 79 %; yellow viscous oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3451.7, 3018.57, 2936.37, 2862.78, 2838.19, 1612.80, 1513.35, 1245.79, 1216.36, 756.60, 668.21; ^{1}H NMR (200

MHz, $CDCl_3$): δ 1.64-1.72 (m, 2H), 2.17 (t, *J*= 6.70 Hz, *2*H), 2.88 (s, 1H), 3.49-3.63 (m, 2H), 3.73 (s, 3H), 3.76-3.82 (m, 1H), 4.38 (s, 2H), 4.98-5.08 (m, 2H), 5.69-5.90 (m, 1H), 6.78-6.84 (m, 2H), 7.16-7.25 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.08, 39.44, 55.15, 65.22, 72.65, 79.80, 113.71, 119.05, 129.38, 129.98, 132.20, 159.16; Elemental Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53, Found: C, 71.26; H, 8.64.

Preparation of 1-(((3-(benzyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene (6)

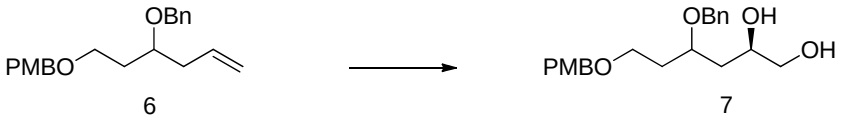


5 6

To the stirred solution of **5** (38 gm, 0.16 mole) in 200 mL DMF, sodium hydride (60 %, 8.04 gm, 0.20 mole, 1.25 eq) was added in inert atmosphere slowly portion wise, at ice cold temperature. After an hour, benzyl bromide (34 gm, 0.175 mole, 1.25 eq) was added followed by addition of catalytic amount of tetrabutyl ammonium iodide. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with ice-cold water and extracted with DCM. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated over rotaevaporator to get crude product which on silica gel column chromatography using, ethyl acetate: pet ether (3:97) as eluent afforded 1-(((3-(benzyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene **(6).**

Yield: 48.29 gm, 92 %; yellow viscous oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.74 (q, *J*= 6.20 Hz, 2H), 2.25 (t, *J*= 6.45 Hz, 2H), 3.43-3.49 (m, 2H), 3.51-3.64 (m, 1H), 3.70 (s, 3H), 4.31 (s, 2H), 4.37-4.53 (m, 2H), 4.96-5.05 (m, 2H), 5.67-5.87 (m, 1H), 6.79 (d, *J*= 8.59 Hz, 2H), 7.16 (d, *J*= 8.62 Hz, 2H), 7.20-7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.33, 38.56, 55.25, 66.48, 71.25, 72.62, 75.60, 111.61, 113.73, 117.20, 127.49, 127.79, 128.30, 129.34, 130.54, 134.65, 138.72; Elemental Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03, Found: C, 77.37; H, 8.11.

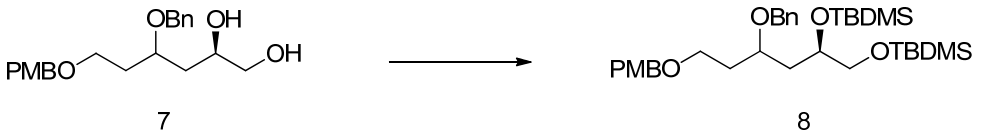
Preparation of (2R)-4-(benzyloxy)-6-((4-methoxybenzyl)oxy)hexane-1,2-diol (7)



A mixture of $K_3[Fe(CN)_6]$ (30.29 gm, 0.092 mol, 2 eq), K_2CO_3 (12.71 gm, 0.092 mole, 2 eq) and $(DHQD)_2$-PHAL (catalytic amount) in *t*-BuOH-H_2O (1:1, 100 mL) was cooled to 0^{o}C and osmium tetroxide (1 mL, 0.1M solution in toluene) was added. After stirring for 5 min at 0^{o}C, the olefin compound **6** (15 gm, 0.046 mole) was added in inert atmosphere in one portion. The reaction mixture was stirred at 0^{o}C for 24 hr. The progress of the reaction was monitored out by TLC. After completion of the reaction, the reaction was quenched with anhydrous sodium sulfite (10 gm). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc. The combined organic layers were separated and dried over anhydrous Na_2SO_4 and concentrated on rotaevaporator to afford the crude product which on silica gel column chromatography using ethyl acetate: pet ether (1:1) as eluent gave (2R)-4-(benzyloxy)-6-((4-methoxybenzyl)oxy)hexane-1,2-diol **(7)** .

Yield: 11.76 gm, 71 %; yellow viscous oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3418.04, 2936.30, 1612.24, 1513.36, 909.67, 733.97; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-1.76 (m, 2H), 1.83-2.07 (m, 2H), 3.45- 3.62 (m, 4H), 3.83 (s, 3H), 3.88-3.95 (m, 2H), 4.45 (s, 2H), 4.46-4.64 (m, 2H), 6.92 (d, *J*= 8.62 Hz, 2H), 7.29 (d, *J*= 8.68 Hz, 2H), 7.35-7.38 (m, 5H) . ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.05, 36.69, 55.06, 66.11, 66.74, 70.81, 71.47, 72.51, 73.95, 113.63, 127.58, 127.79, 128.27, 129.25, 130.13, 138.10, 159.03. Elemental Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83 Found: C, 69.93; H, 7.79.

1, 2-Bis-(t-butyldimethylsilyloxy)-4-benzyloxy-6-(4`-methoxy benzyloxy)-hexane (8)

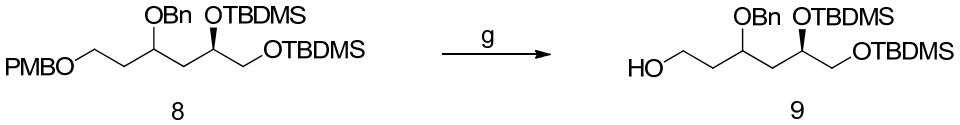


7 8

To the stirred solution of **7** (10 gm, 0.027 mole) in dry DMF, imidazole (4.76 gm, 0.070 mole, 2.5 eq) was added in inert atmosphere slowly portion wise, and cooled to 0^{o}C. After a ½ hour stirring, TBDMS-Cl (10.54 gm, 0.070 moles, 2.5 eq) was added and stirring was continued. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched ice-cold water and extracted with DCM. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated over rotaevaporator to get crude residue which on silica gel column chromatography using ethyl acetate: pet ether (5: 95) as eluent afforded 1, 2-bis-(t-butyl dimethyl silyloxy)-4-benzyloxy-6-(4`-methoxy benzyloxy) hexane **(8)**.

Yield: 14.7 gm, 90.05 % yellow viscous oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3029.29, 2929.43, 2857.24, 2253.66, 1513.80, 1471.23, 1250.60, 1098.73, 910.92, 735.66, 650.74; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.0 (s, 12H), 0.85 (s, 18H), 1.66-1.76 (m, 2H), 1.80-2.02 (m, 2H), 3.36-3.47 (m, 2H), 3.49-3.56 (m, 2H), 3.62-3.69 (m, 1H), 3.72 (s, 3H), 3.76-3.91 (m, 1H), 4.31-4.52 (m, 4H), 6.83 (d, *J*= 8.62 Hz, 2H), 7.21(d, *J*= 8.58 Hz, 2H), 7.25-7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.26, -4.70, -4.08, 18.14, 18.41, 26.05, 29.76, 34.75, 39.33, 55.27, 66.65, 67.66, 70.67, 70.88, 72.70, 73.46, 113.74, 128.32, 129.36, 130.73, 138.93. Elemental Anal. Calcd for $C_{33}H_{56}O_5Si_2$: C, 67.30; H, 9.58 Found: C, 67.36; H, 9.64.

Preparation of 3-benzyloxy-5, 6-bis-(t-butyldimethylsilyloxy)- hexanol (9)

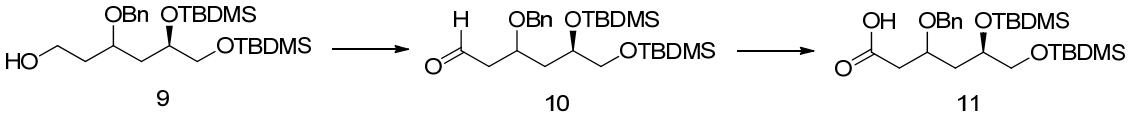


8 9

To the stirred solution of **8** (10 gm, 0.017 mole) in DCM:water (90 : 10), DDQ (4.8 gm, 0.021 mole, 1.25 eq) was added in inert atmosphere slowly in portion, at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with ice-cold water and extracted with DCM. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated over rotaevaporator to get crude product which on silica gel column chromatography using ethyl acetate: pet ether (25: 75) as eluent afforded 3-benzyloxy-5, 6-bis-(t-butyl dimethyl silyloxy)- hexanol **(9)**.

Yield: 6.69 gm, 84 %; IR ($CHCl_3$,): ν_{max} 3320.55, 3020.19, 2930.45, 1585.54, 1216.26, 909.35, 758.57, 666.19 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 12H), 0.86 (s, 9H), 0.88 (s, 9H), 1.70-2.10 (m, 4H), 3.37-3.59 (m, 2H), 3.67-3.90 (m, 4H), 4.42-4.69 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.37, -4.83, -4.16, 18.29, 25.92, 35.97, 38.16, 60.71, 67.40, 70.43, 70.59, 75.86, 127.63, 128.40, 138.23. Elemental Anal. Calcd for $C_{25}H_{48}O_4Si_2$: C, 64.05; H, 10.32. Found: C, 64.17; H, 10.41.

Preperation of (5R)-3-(benzyloxy)-5, 6-bis((t-butyldimethylsilyl)oxy)-hexanoic acid (11)

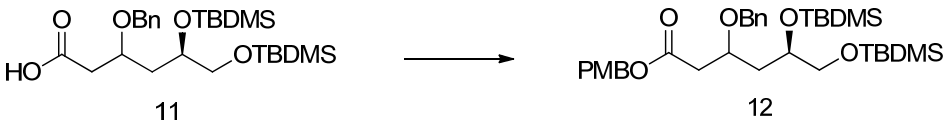


To the stirred solution of **9** (2 gm, 0.0086 mole) in DCM, PCC (3.9 gm, 0.017 mole, 2 eq) was added in inert atmosphere slowly portion wise, at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction was carried out by simply filtration and washing with DCM. All organic washings were collected and concentrated over rotaevaporator to get crude (5R)-3-(benzyloxy)-5,6-bis((tert-butyl-dimethylsilyl)oxy)hexanal (**10**); 1.83 gm (crude 92 % yield).

This crude **10** was further subjected for oxidation to acid, by stirring with $NaClO_2$ (2.82 gm, 0.038 mole, 2 eq) along with sodium di-hydrogen phosphate (4.55 gm, 0.038 mole, 2 eq), in DMSO (20 mL) as solvent. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction was carried out by extracting with diethyl ether, organic layers combined, dried over sodium sulphate and concentrated on rotaevaporator to get crude product which on silica gel column chromatography using ethyl acetate: pet ether (3:7) as eluent afforded 3-benzyloxy-5, 6-bis-(t-butyl dimethylsilyloxy) hexanoic acid (**11**).

Yield: 1.59 gm, 84 %, IR ($CHCl_3$, cm^{-1}): ν_{max} 3316.54, 3020.02, 2928.89, 1215.94, 837.33, 75.09, 668.50. ^1H NMR (200 MHz, $CDCl_3$):0.00 (s, 6H), 0.02 (s, 6H), 0.85 (s, 18H), 1.57-2.03 (m, 2H), 2.52-2.65 (m, 2H), 3.34- 3.56 (m, 2H), 3.70 - 3.86 (m, 1H), 3.99 - 4.10 (m, 1H), 4.46-4.61 (m, 2H), 7.25-7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.37, -4.86, -4.25, 18.03, 18.30, 25.93, 29.68, 39.91, 67.15, 70.31, 71.28, 72.90, 127.62, 127.81, 128.33, 138.08, 177.04. Elemental Anal. Calcd for $C_{25}H_{46}O_5Si_2$: C, 62.19; H, 9.60. Found: C, 62.31; H, 9.69.

Preparation of (5R)-4-methoxybenzyl 3-(benzyloxy)-5,6-bis((t-butyldimethylsilyl)-oxy)-hexanoate (12)

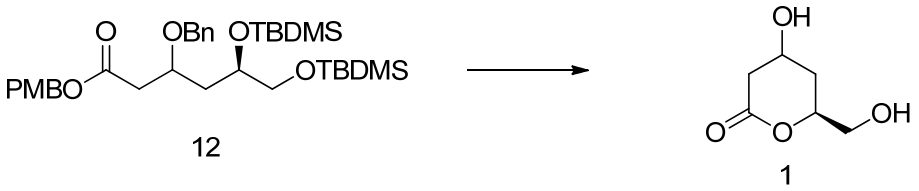


To the stirred solution of **11** (1 gm, 0.0021 mole) in anhydrous DCM, EDCI (0.61 gm, 0.0032 mole, 1.5 eq) was added in inert atmosphere and at room temperature. After a ½ hour stirring, 4-methoxybenzyl alcohol (0.44 gm, 0.0032 mole, 1.5 eq) was added and stirring was continued. The progress of the reaction was monitored by TLC.

After completion of the reaction, the reaction was quenched with ice-cold water and extracted with DCM. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated over rotaevaporator to get crude product which on silica gel column chromatography using ethyl acetate: pet ether. (5: 95) as eluent afforded (5R)-4-methoxybenzyl-3-(benzyloxy)-5,6-bis-((tert-butyldimethylsilyl)-oxy)hexanoate **(12)**

Yield: 1.02 gm, 81 %, yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (s, 12H), 0.85 (s, 18H), 1.68-1.98 (m, 2H), 2.46-2.71 (m, 2H), 3.33- 3.55 (m, 2H), 3.68 - 3.71 (m, 1H), 3.75 (s, 3H), 3.83-3.85 (m, 1H), 4.00-4.12 (m, 2H), 4.38-4.54 (m, 2H), 5.02 (s, 2H), 6.80 (d, *J*=8.59 Hz, 2H), 7.21-7.26 (m, 7H), ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.35, -4.79, -4.17, 18.04, 18.31, 25.95, 29.67, 35.91, 55.17, 66.56, 67.56, 70.58, 70.78, 73.36, 113.65, 127.76, 128.22, 129.26, 130.64, 138.83, 159.05. Elemental Anal. Calcd for $C_{33}H_{54}O_6Si_2$: C, 65.74; H, 9.03, Found: C, 65.89; H, 9.11.

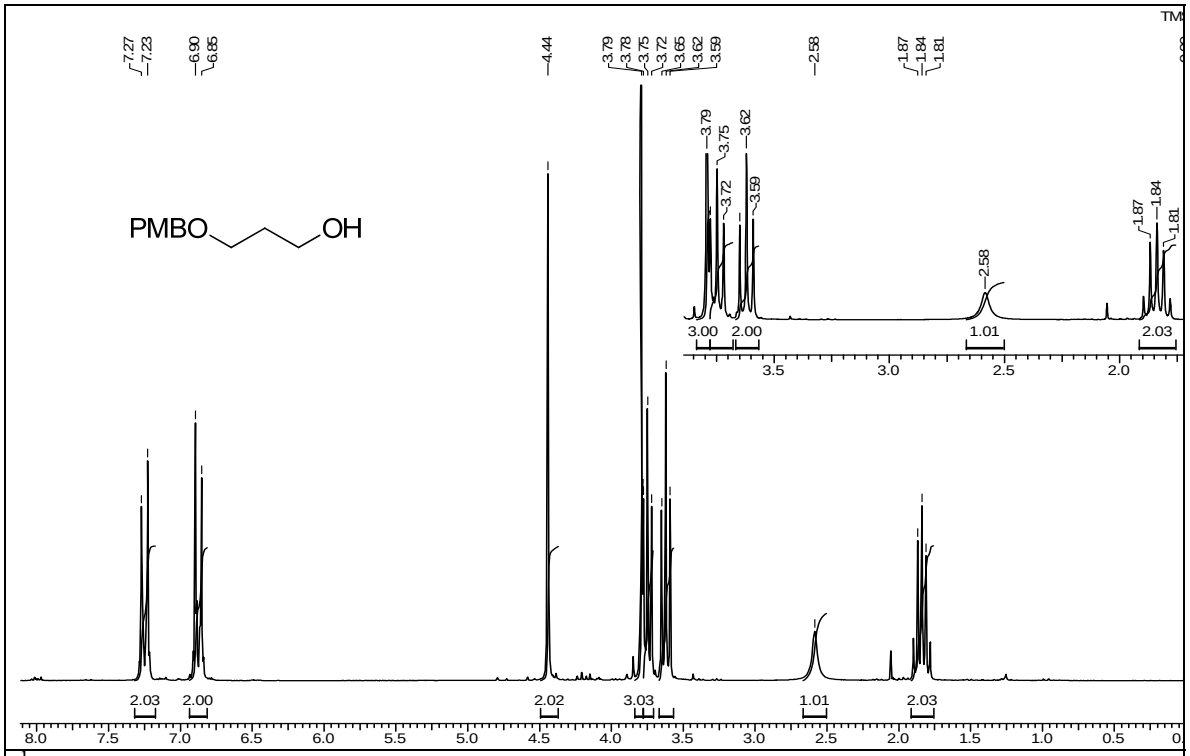
Preperation of (6S)-4-hydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-one (1)



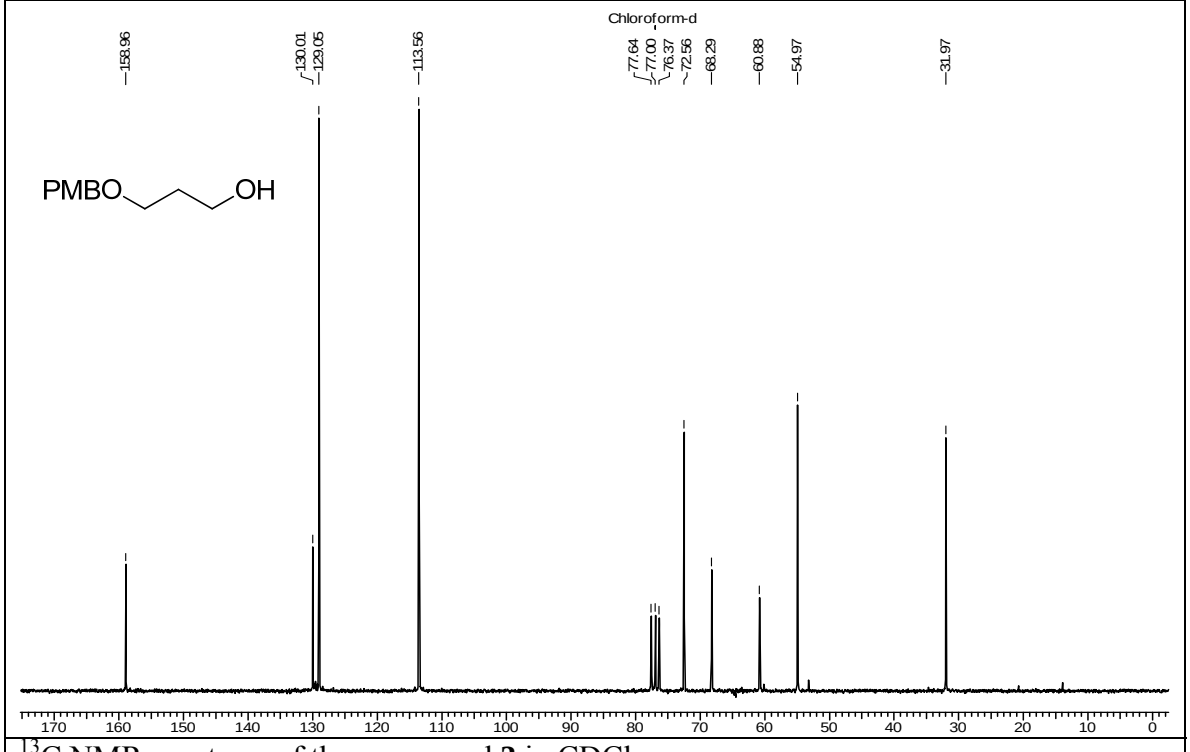
To the stirred solution of **12** (0.2 gm, 0.0004 mole) in THF, TBAF (0.20 gm, 0.0008 mole, 2 eq) was added in inert atmosphere slowly in portion at room temperature. The stirring was continued. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with ice-cold water and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulphate and concentrated on rotaevaporator to get crude residue which on silica gel column chromatography using ethyl acetate: pet ether (40: 60) as eluent afforded (6S)-4-hydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-one (**1**).

Yield: 32 mg, 67 %; yellow sticky viscous liquid IR ($CHCl_3$, cm^{-1}): ν_{max} 3320.55, 3020.19, 2930.45, 1585.54, 1216.26, 909.35, 758.57, 666.19; ^1H NMR (200 MHz, $CDCl_3$): δ 2.13-2.21 (m, 2H), 2.40 (t, *J*= 7.95 Hz, 2H), 3.92-3.97 (m, 1H), 4.26 (t, *J*= 7.03 Hz, 2H), 5.43-5.44 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.29, 32.99, 55.12, 64.53, 98.11, 177.95; Dept (50 MHz, $CDCl_3$): δ 23.29, 32.98, 55.12, 64.53, 98.12. Elemental Anal. .Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90.; Found: C, 49.41; H, 6.96.

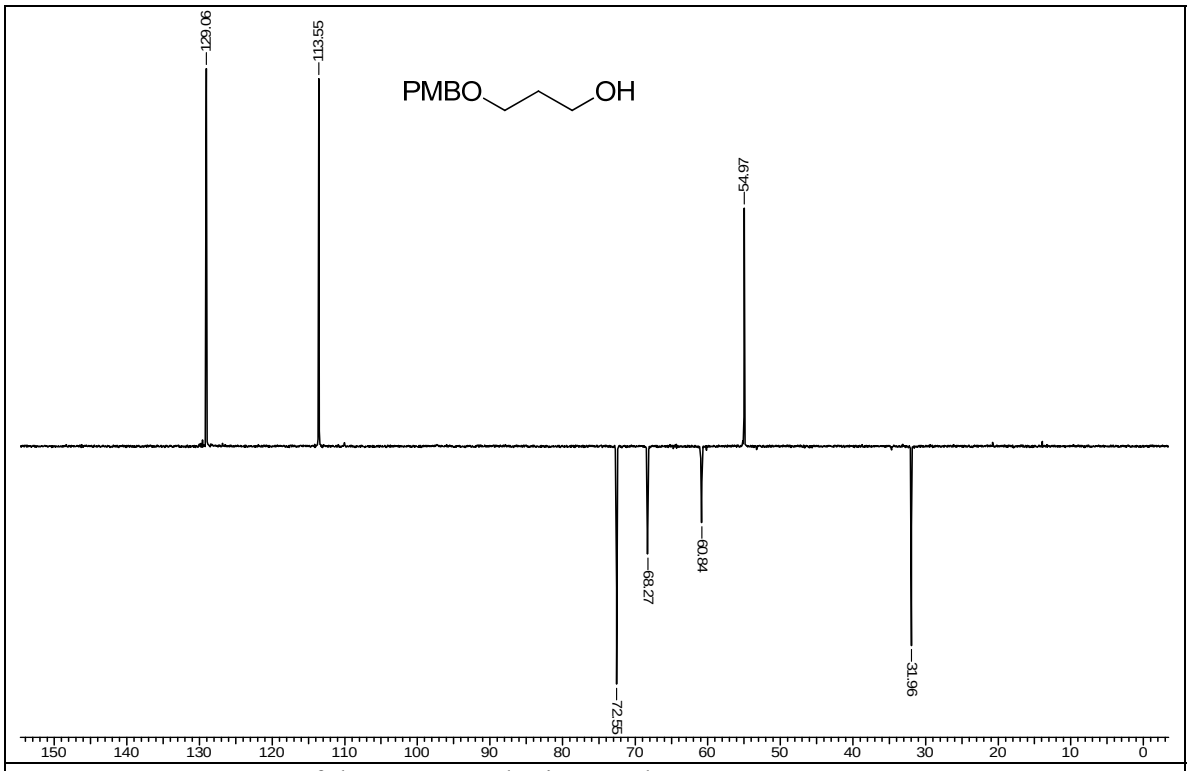
3.2.8. Analytical Data



^{1}H NMR spectrum of the compound **3** in $CDCl_3$



^{13}C NMR spectrum of the compound **3** in $CDCl_3$



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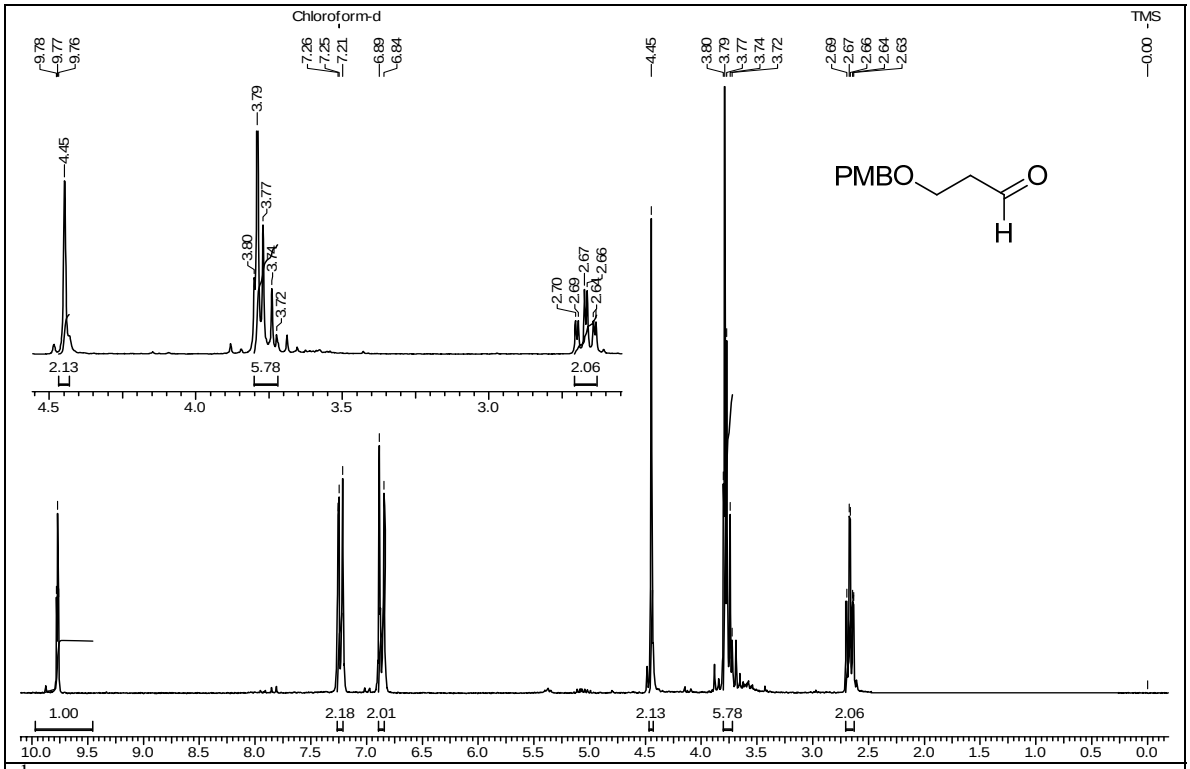
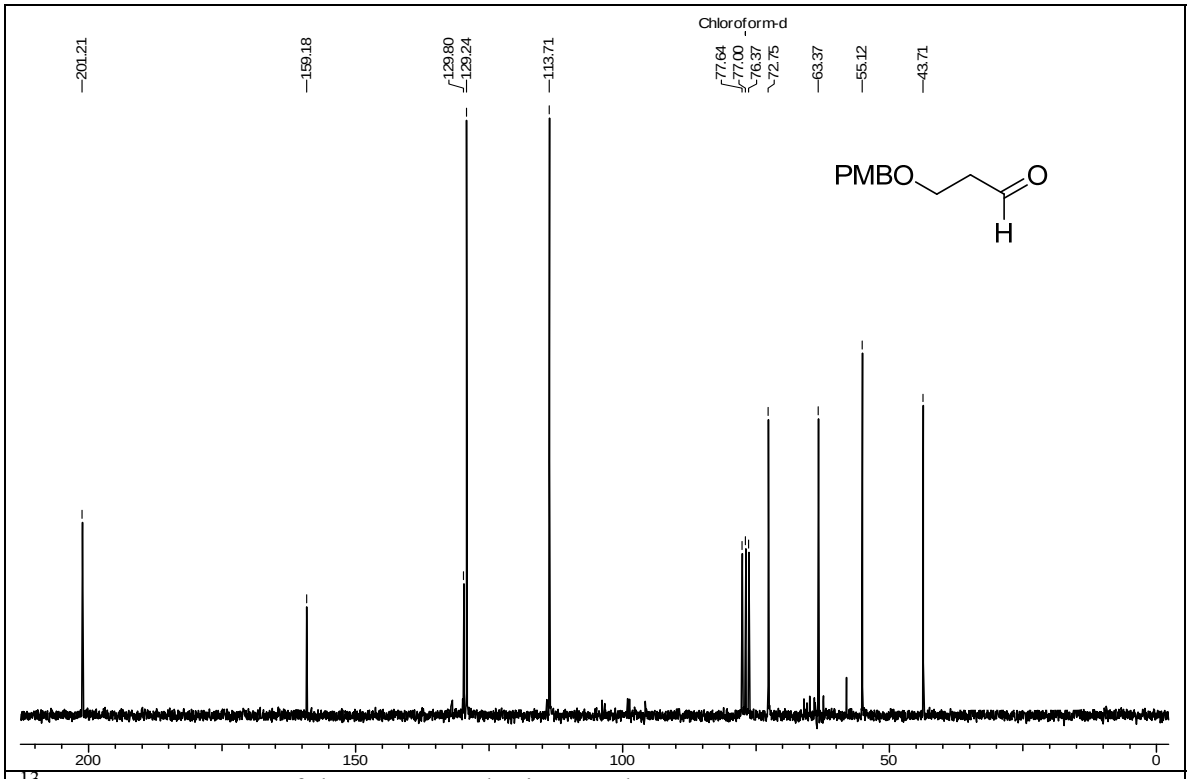


^{1}H NMR spectrum of the compound **4** in $CDCl_3$



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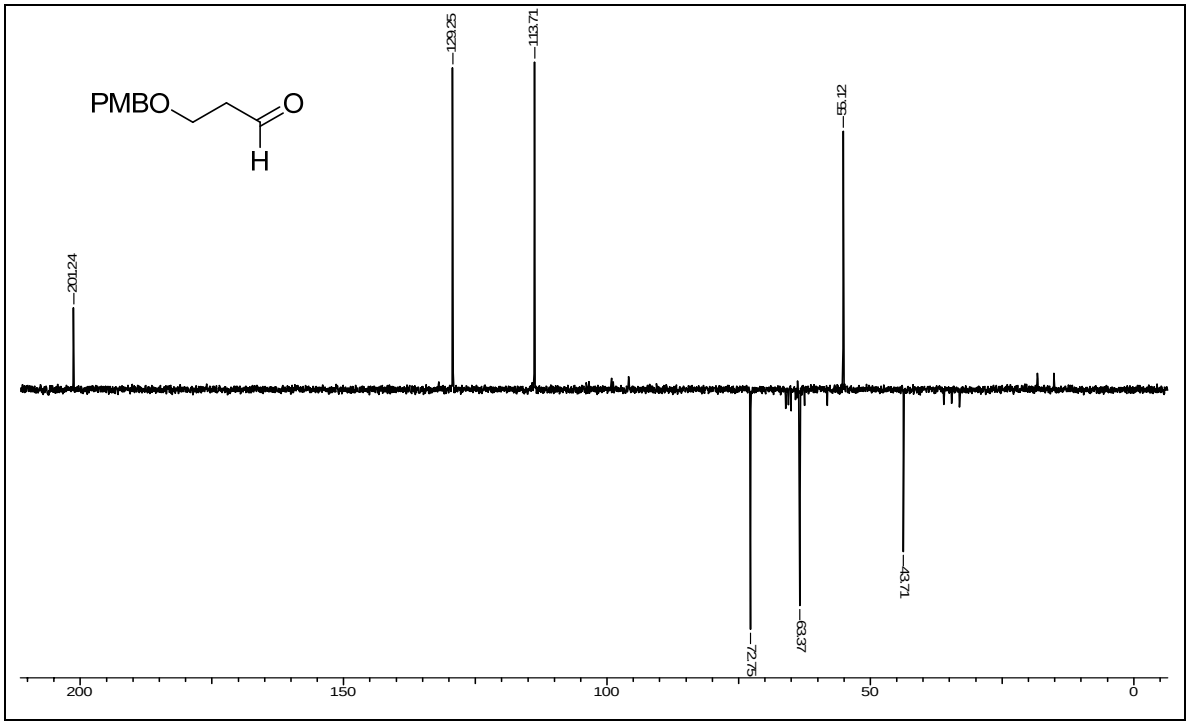

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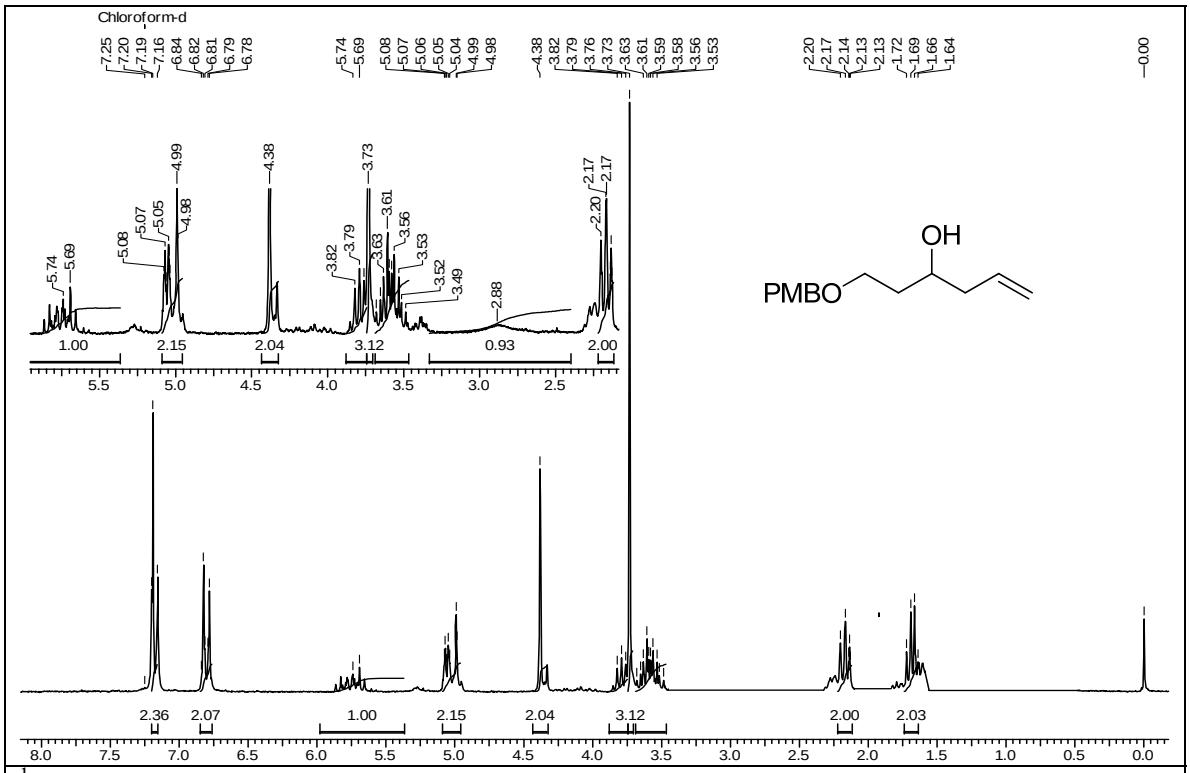
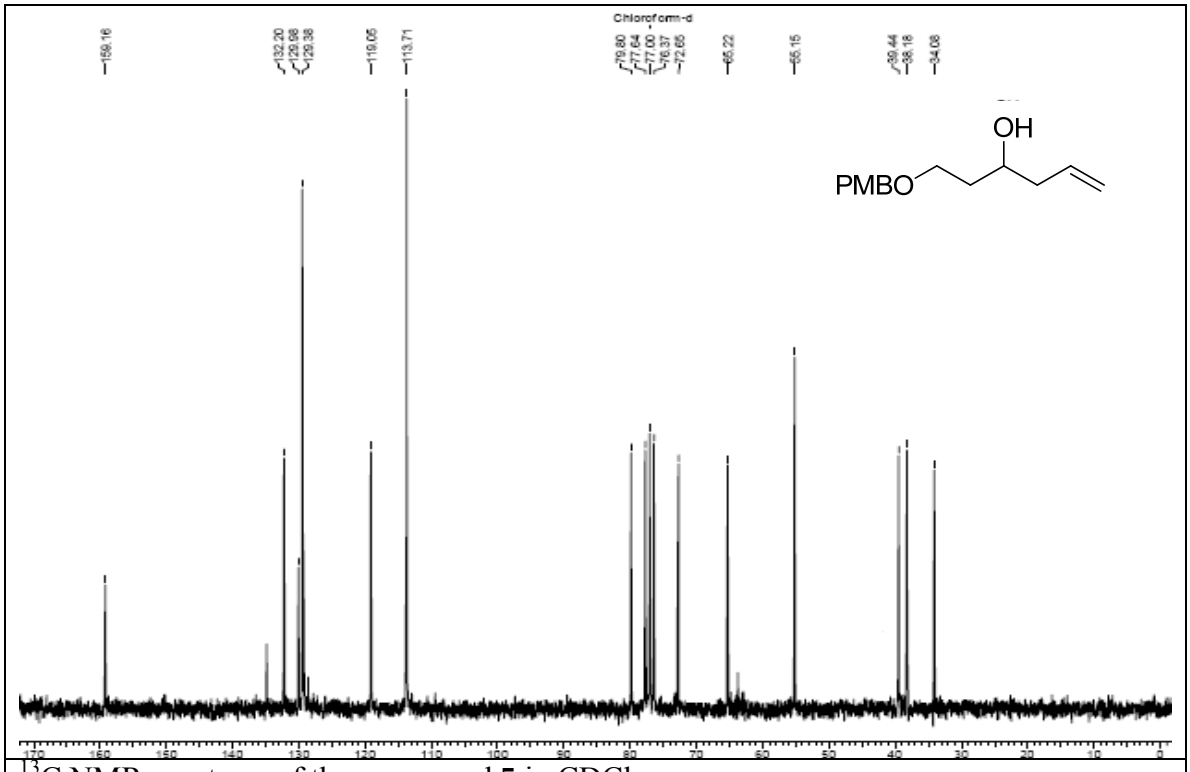
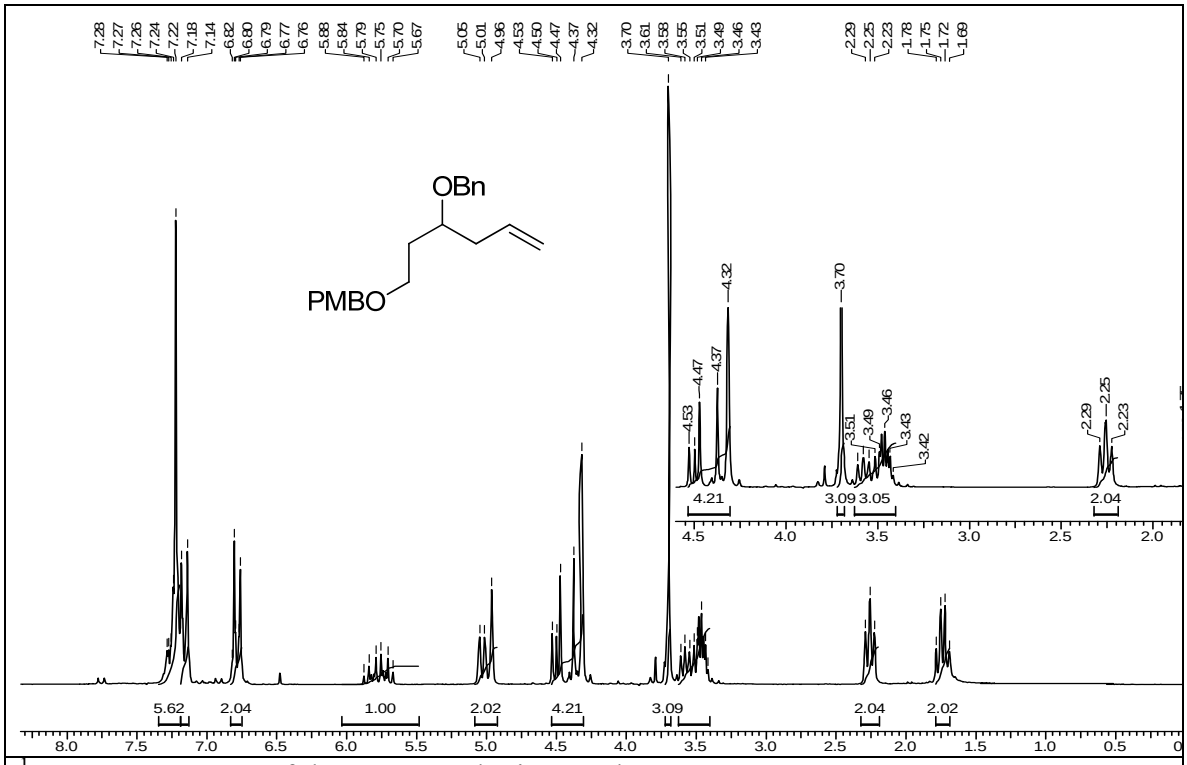


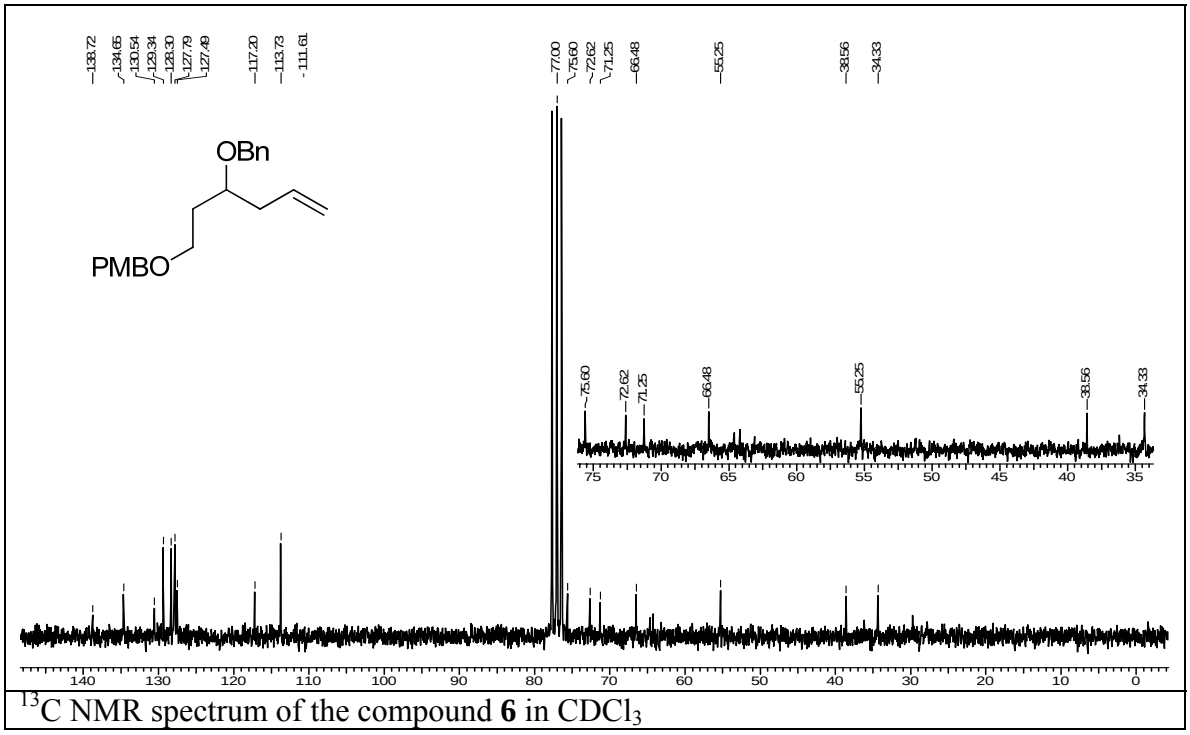
^{1}H NMR spectrum of the compound **5** in $CDCl_3$



^{13}C NMR spectrum of the compound **5** in $CDCl_3$



^{1}H NMR spectrum of the compound **6** in $CDCl_3$



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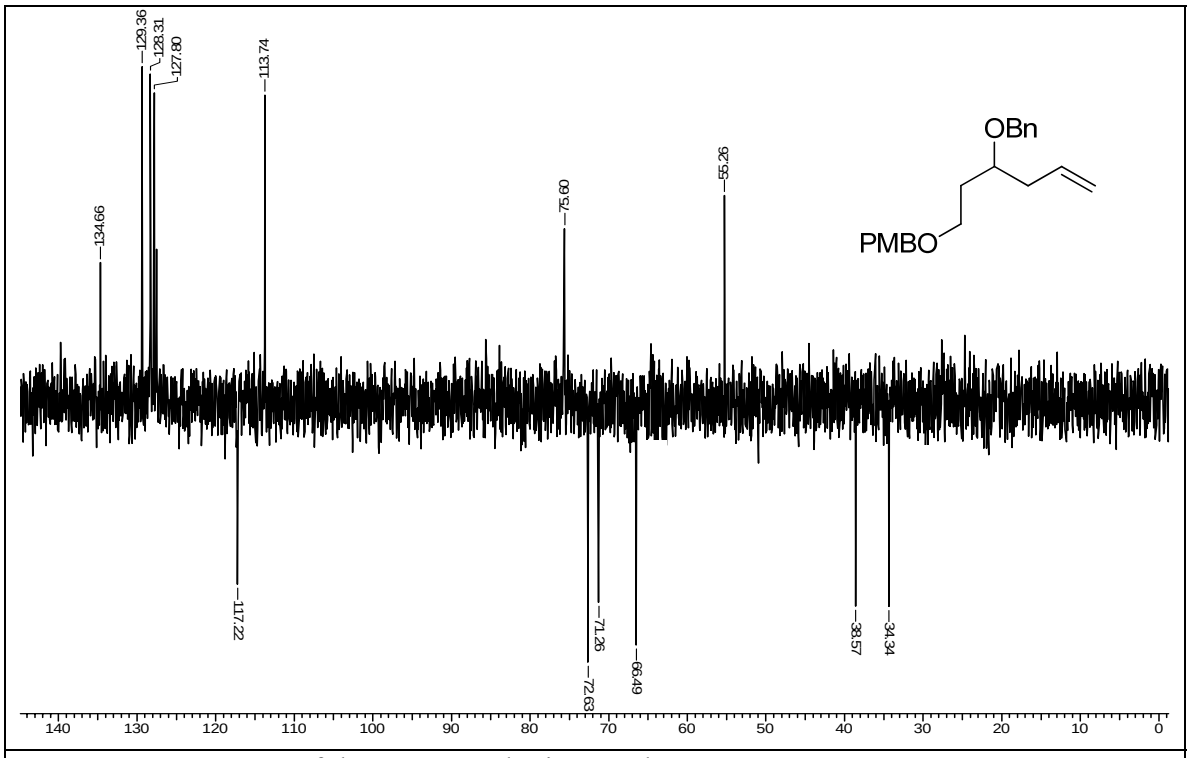

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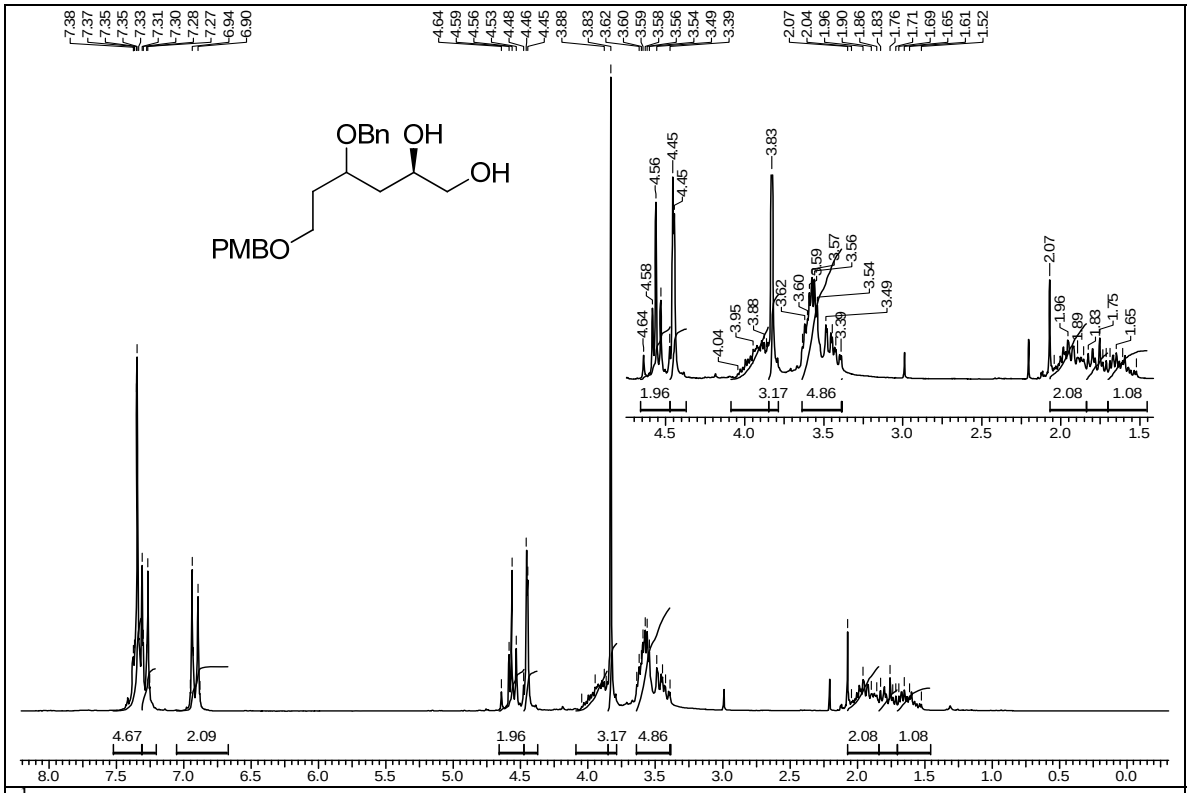

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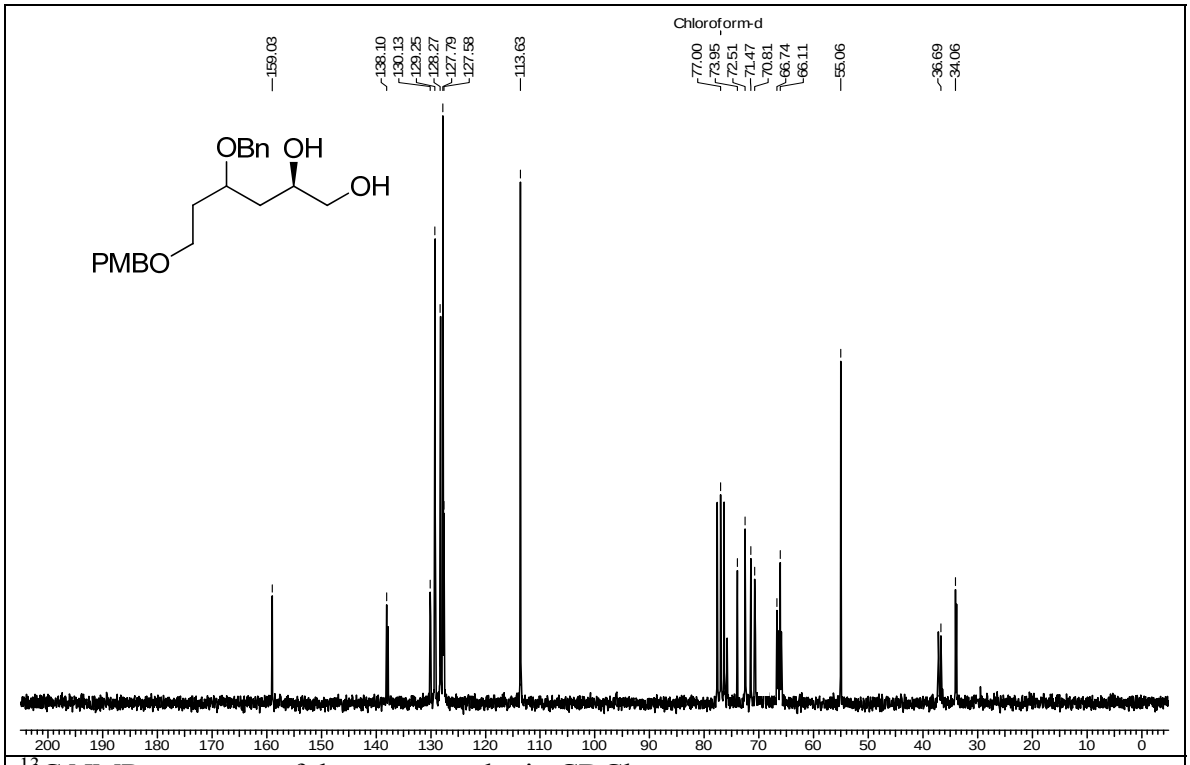

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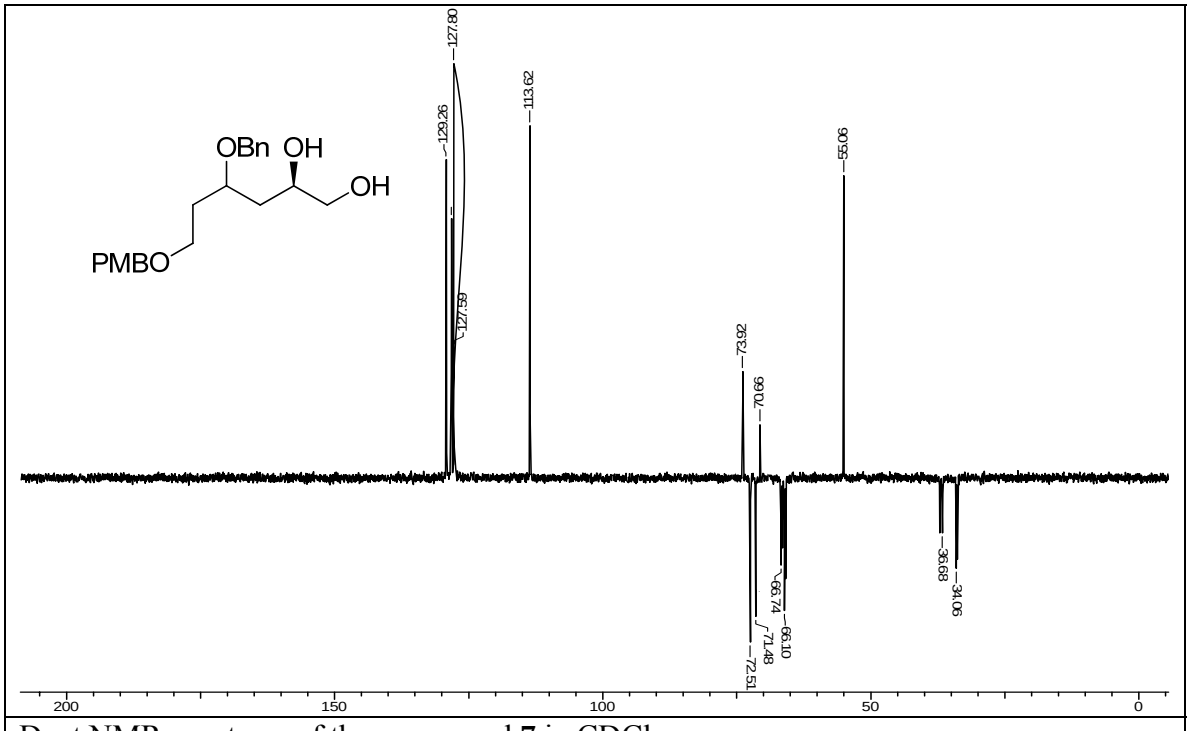

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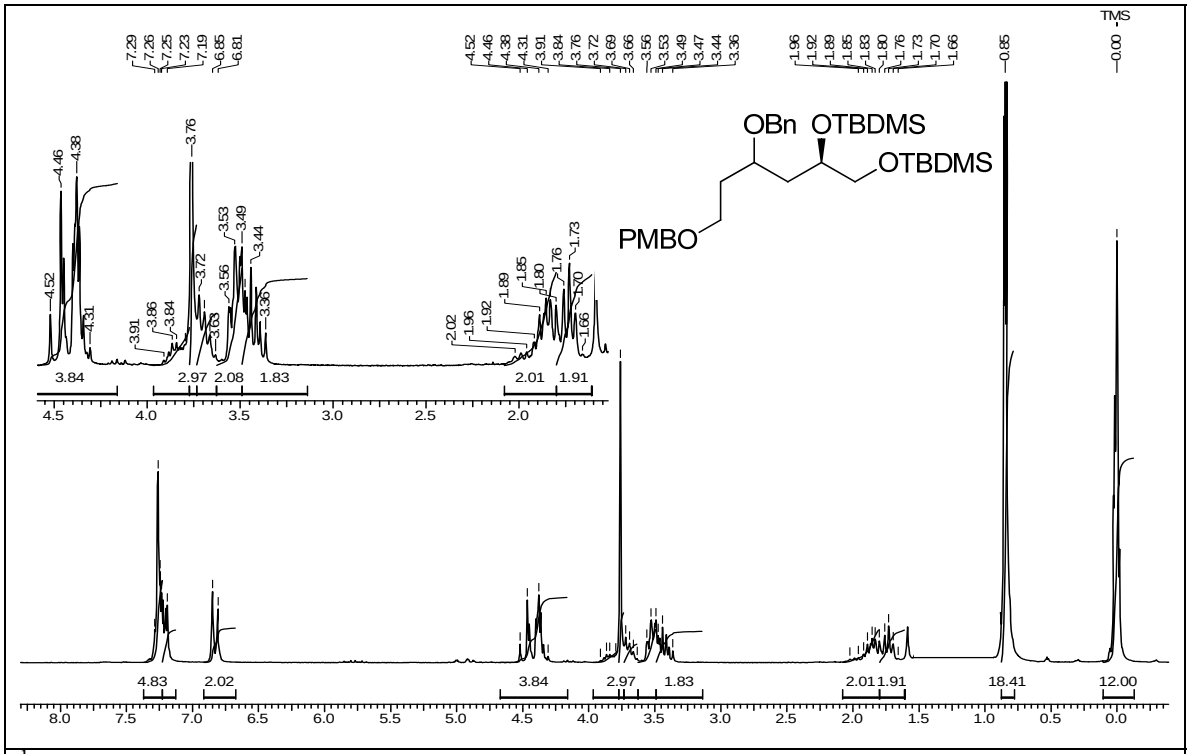
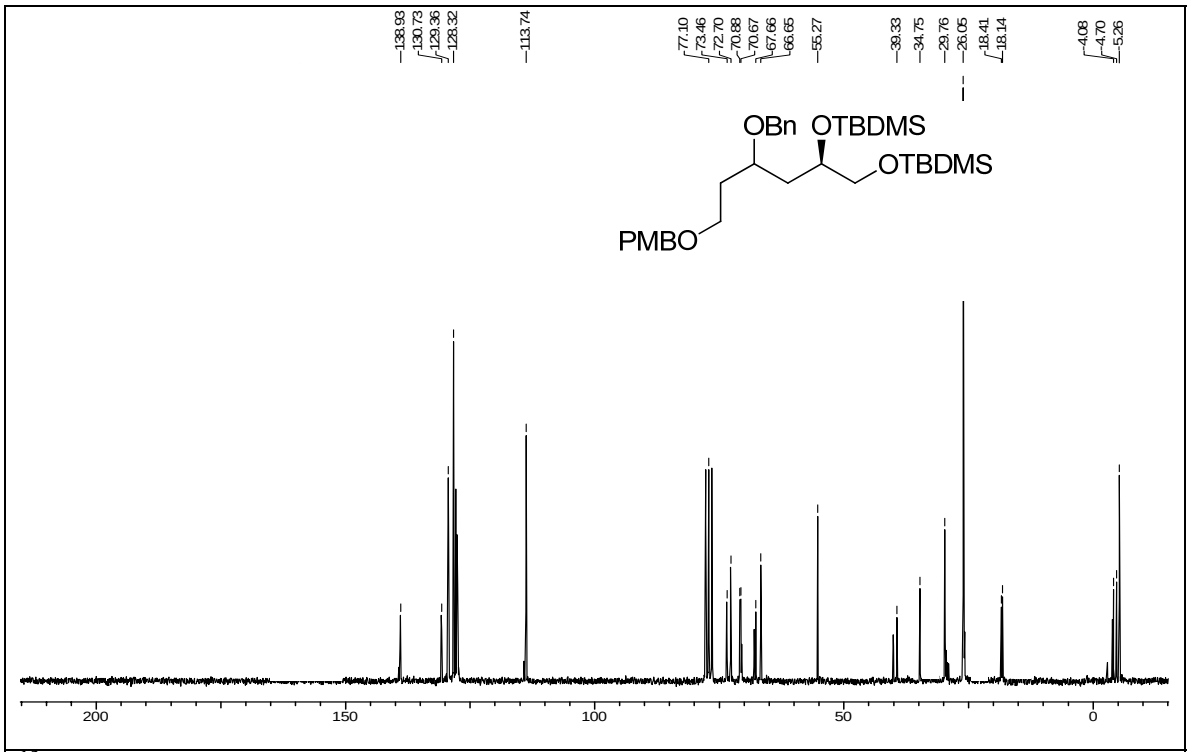


^{1}H NMR spectrum of the compound **8** in $CDCl_3$



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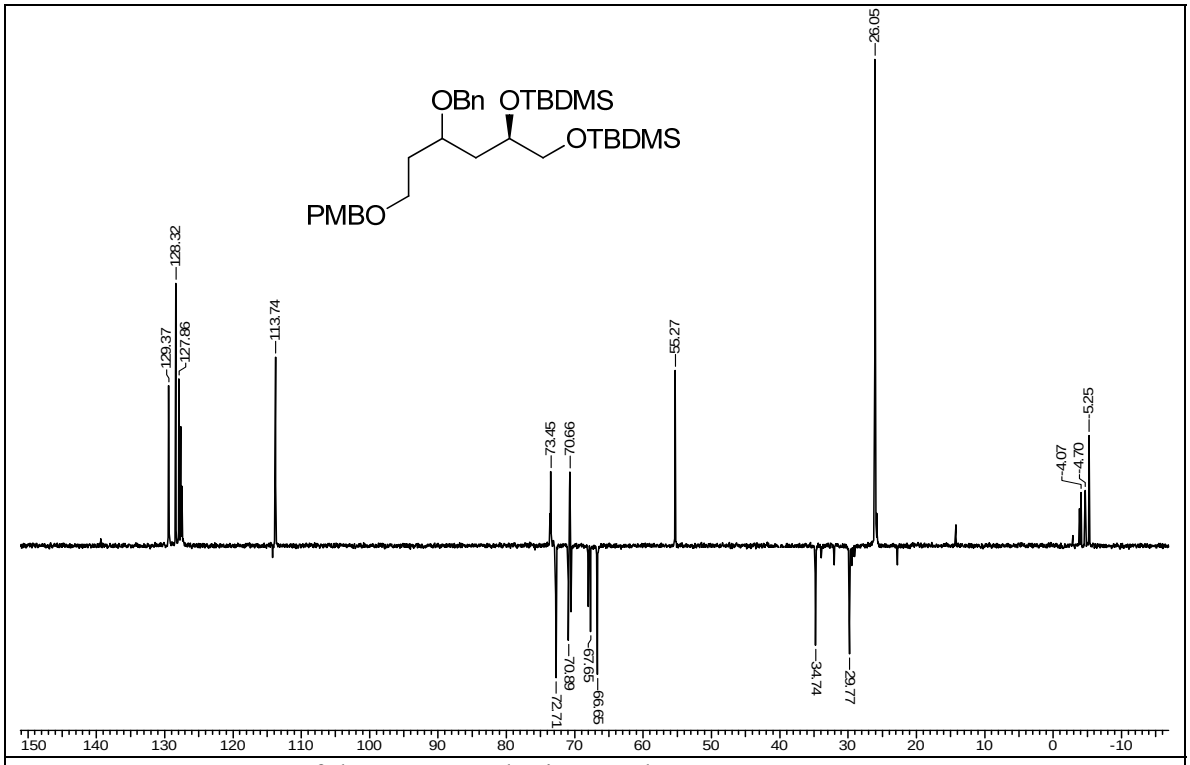

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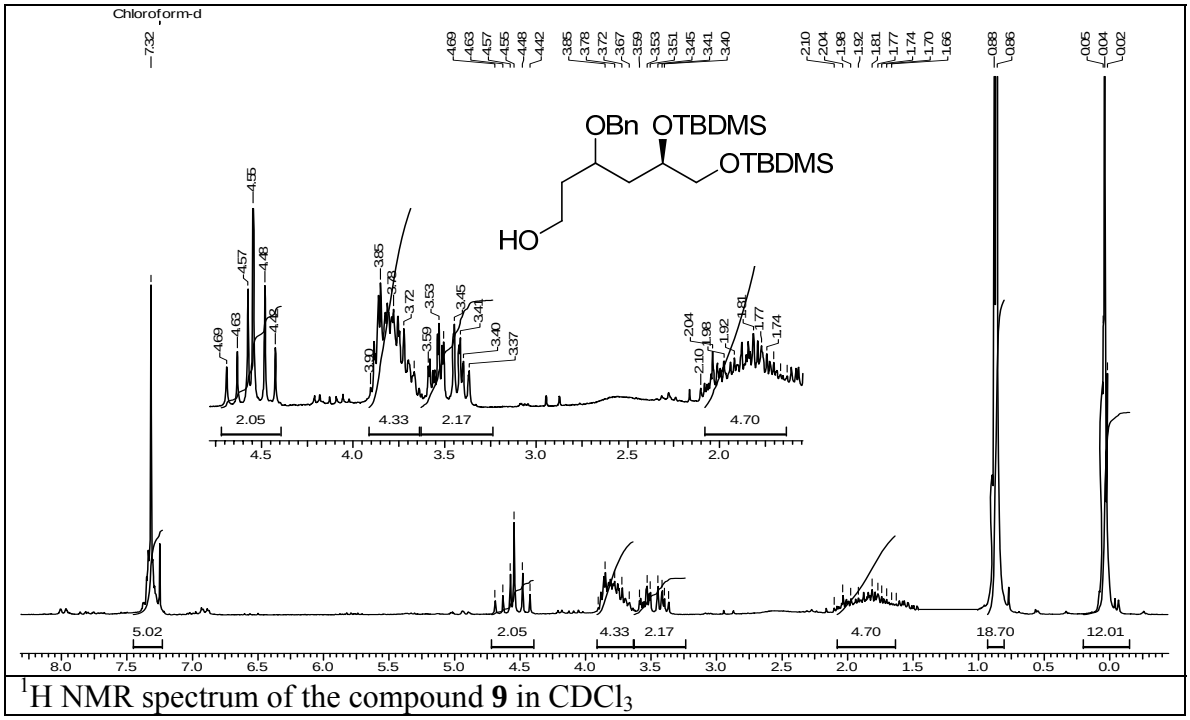
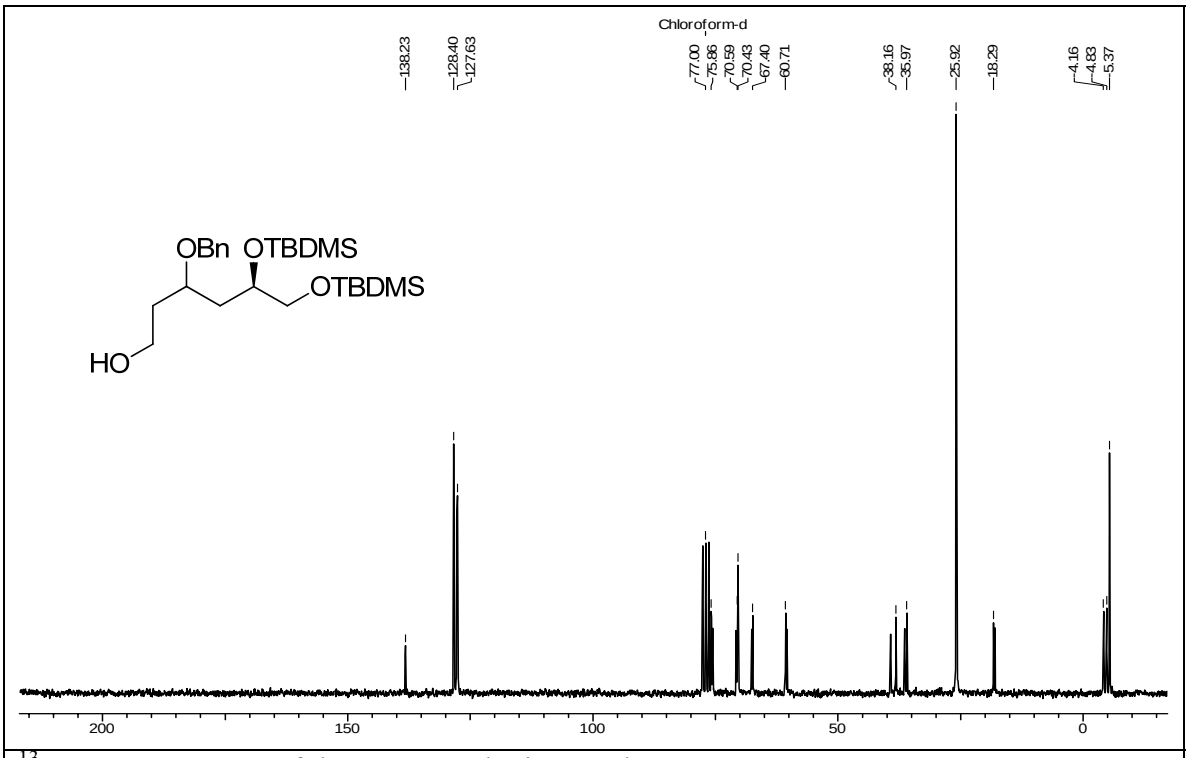


^{1}H NMR spectrum of the compound **9** in $CDCl_3$



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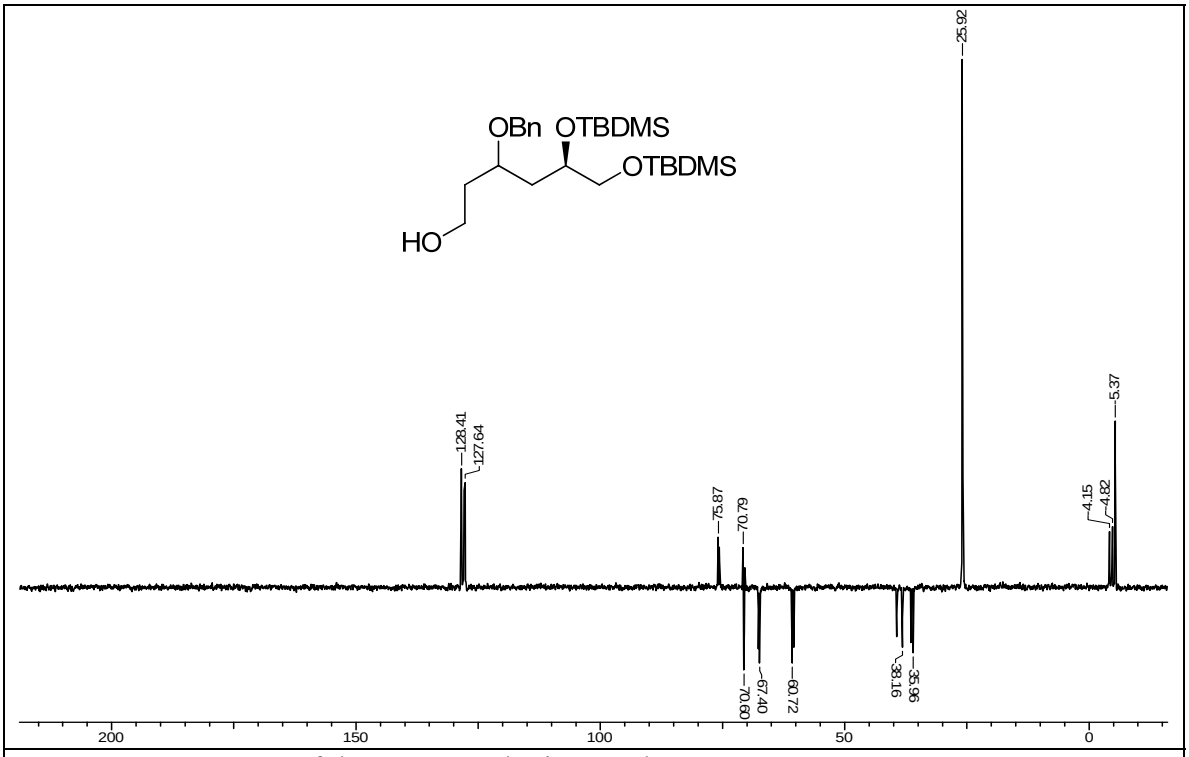

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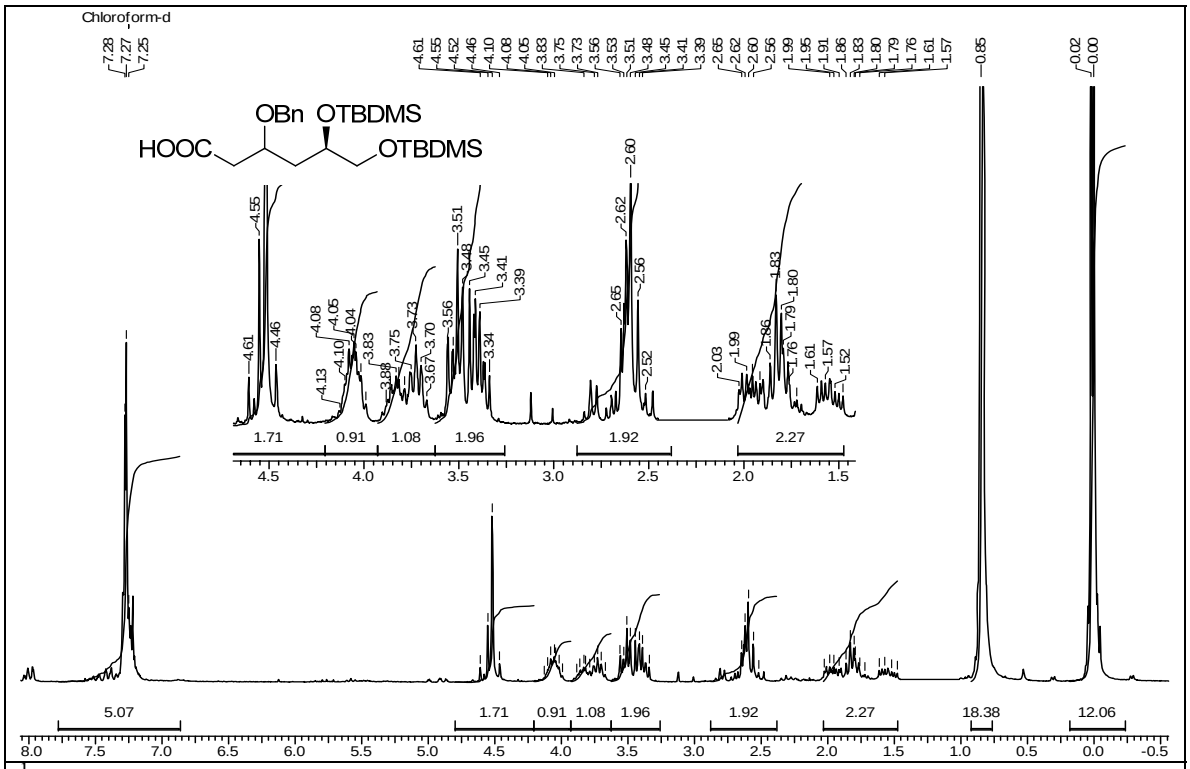
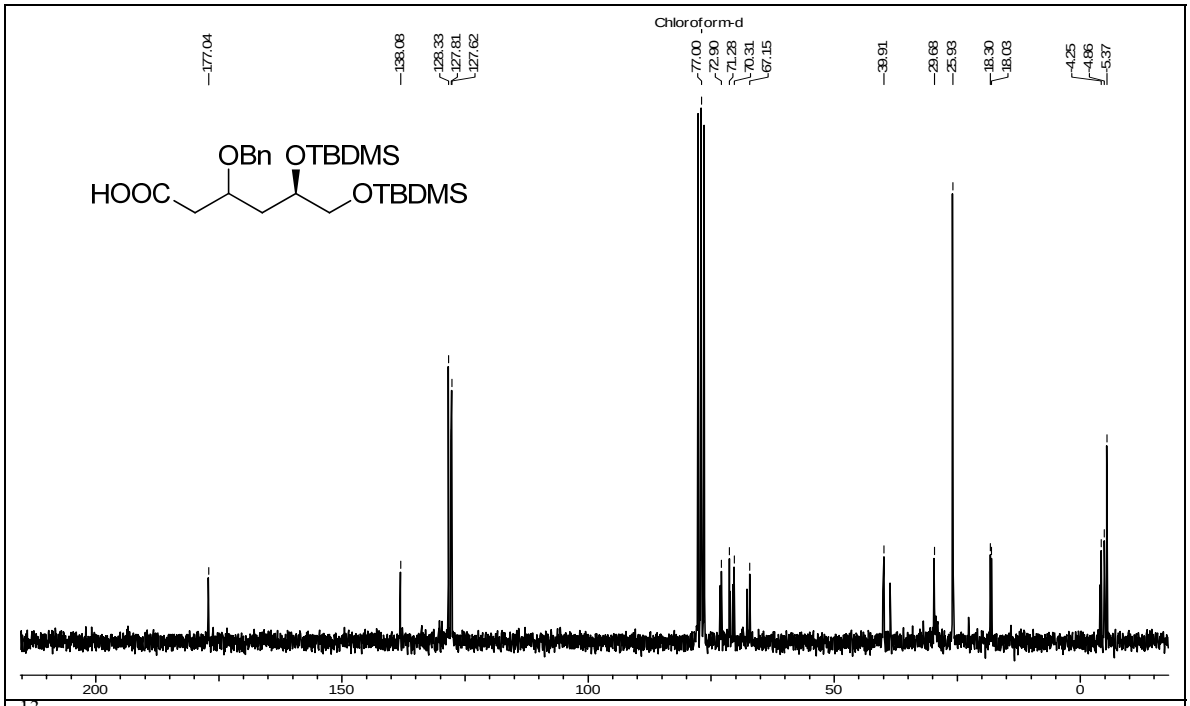
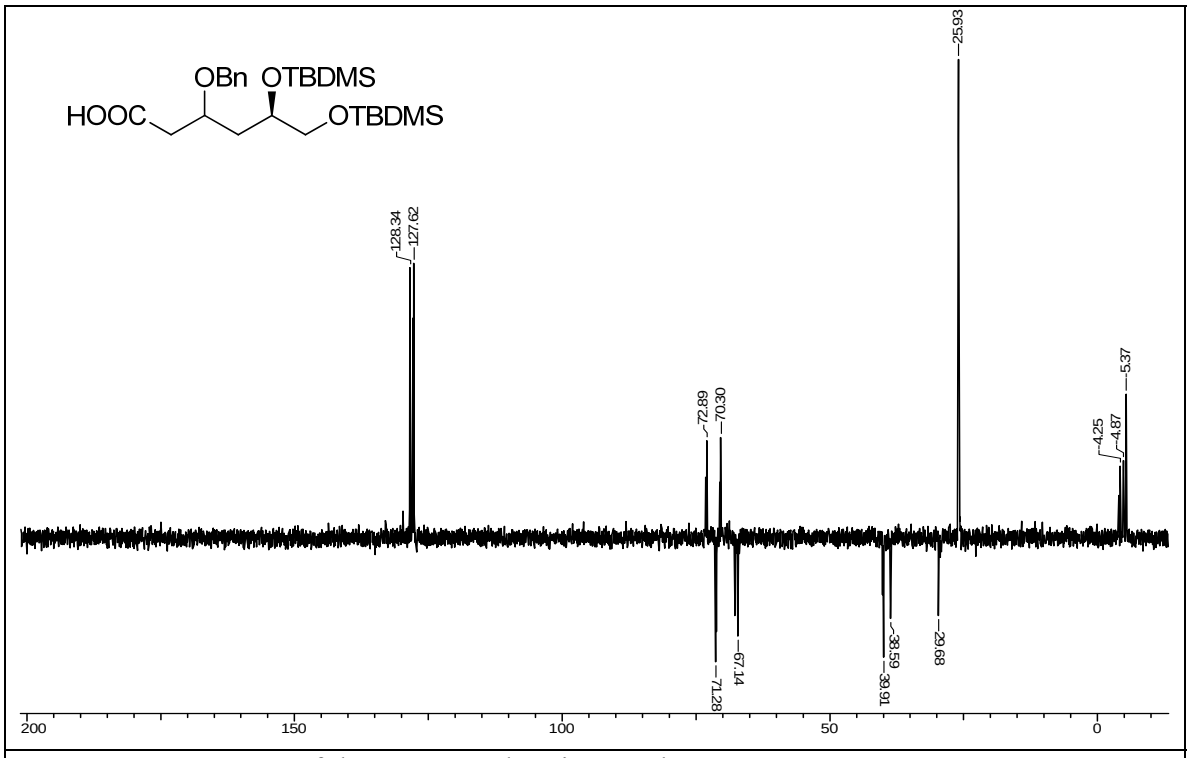


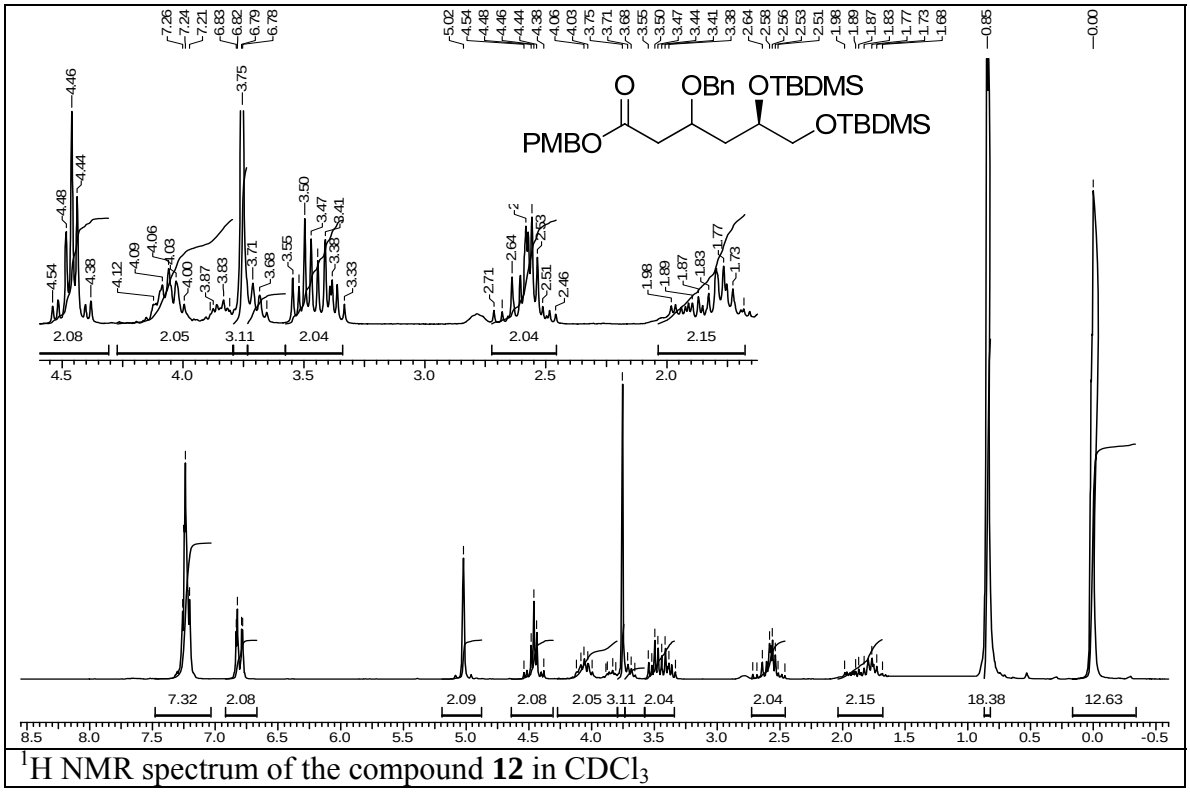
^{1}H NMR spectrum of the compound **11** in $CDCl_3$



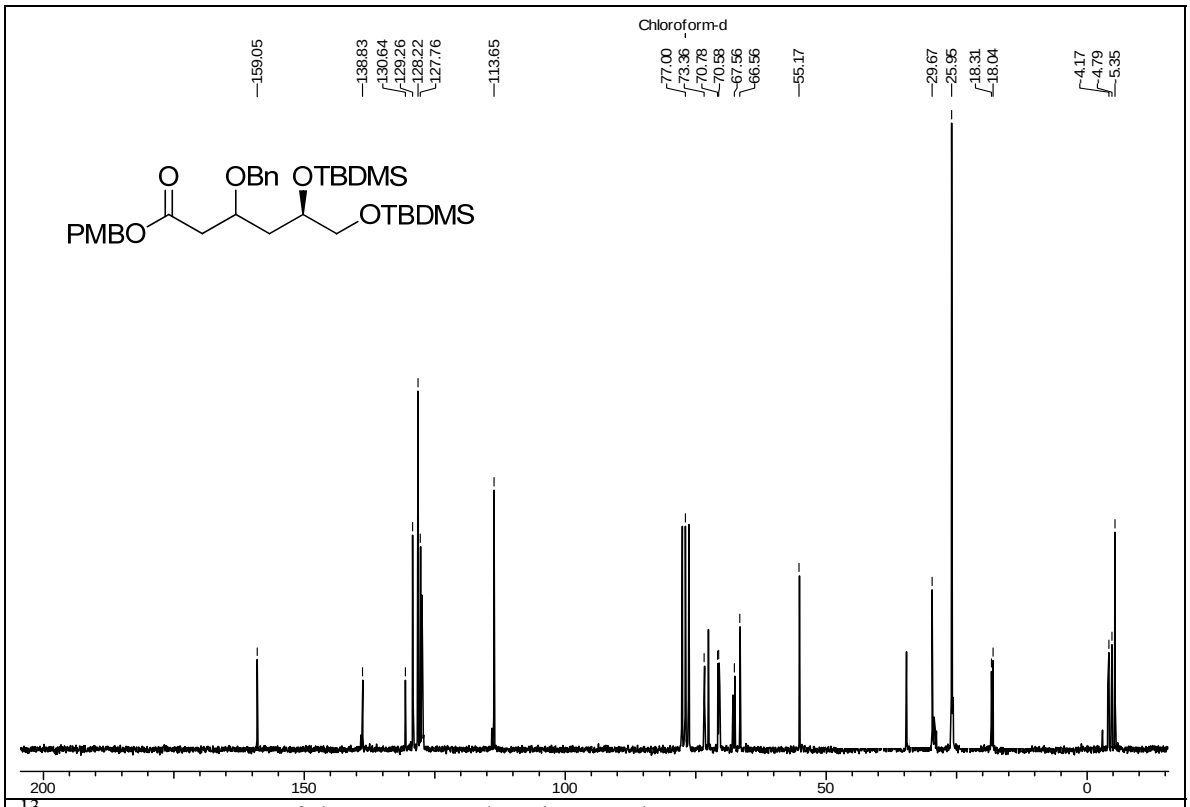
^{13}C NMR spectrum of the compound **11** in $CDCl_3$



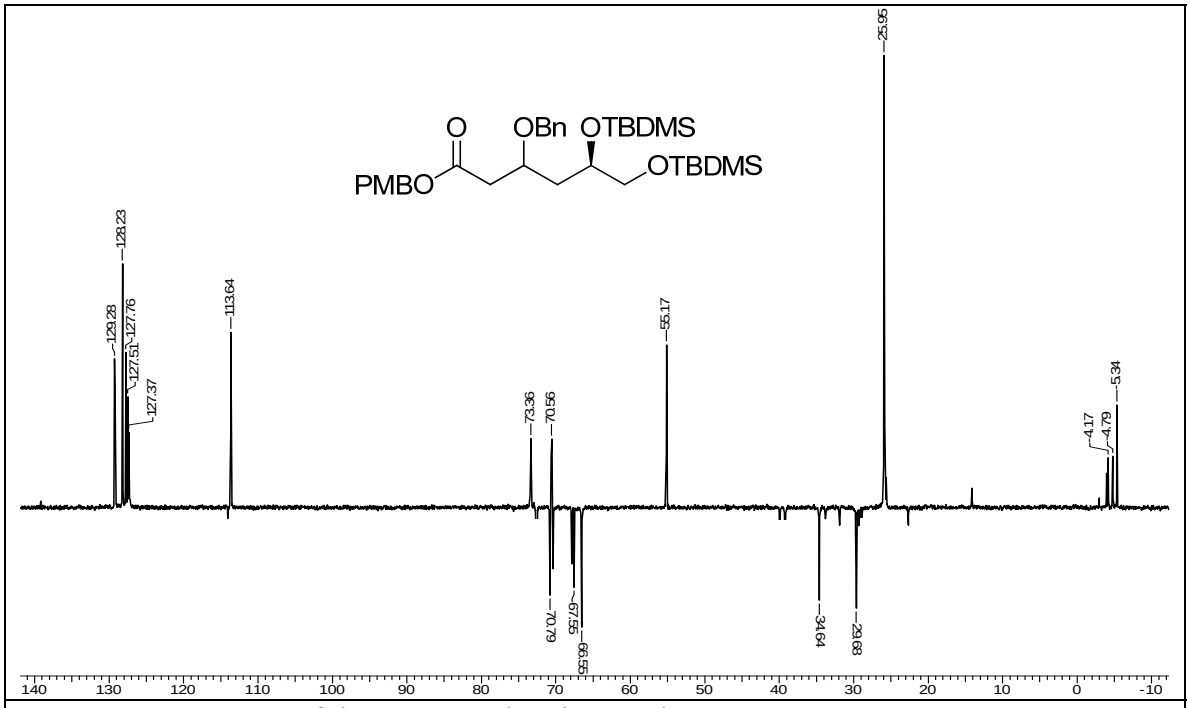
Dept NMR spectrum of the compound **11** in $CDCl_3$



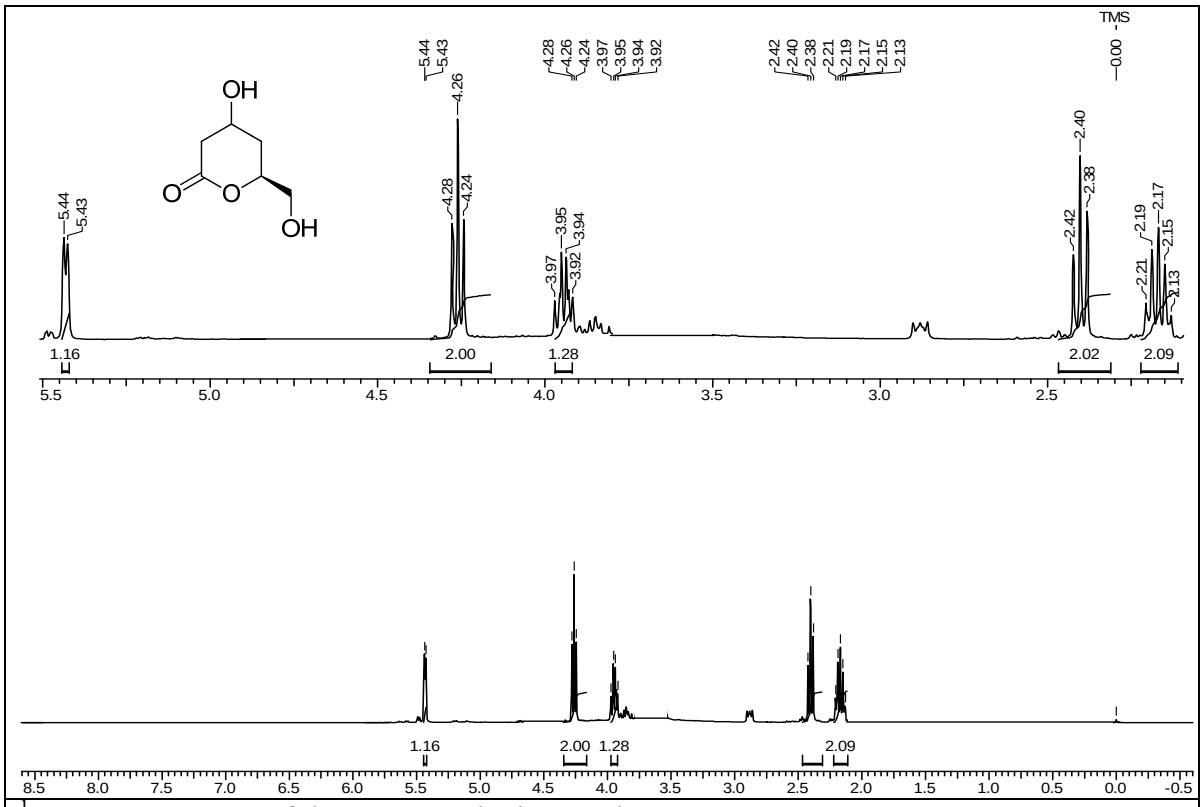
^{1}H NMR spectrum of the compound **12** in $CDCl_3$



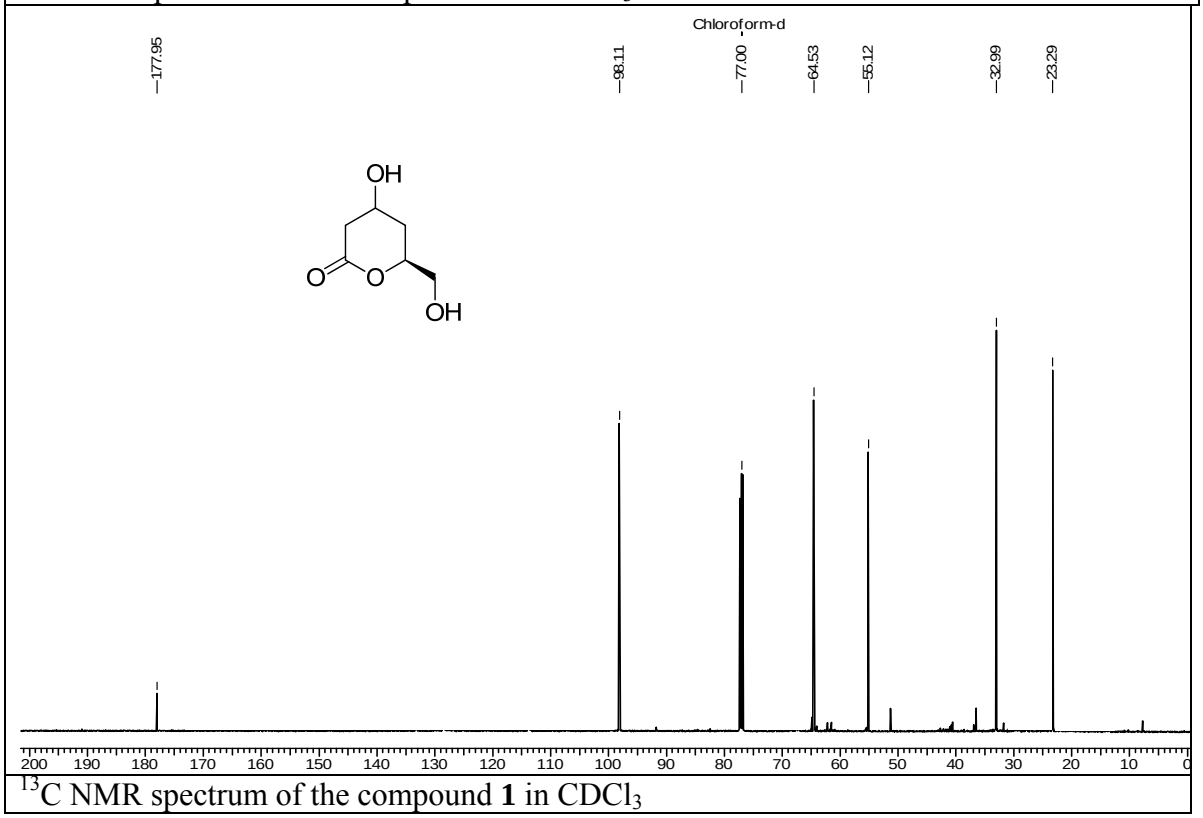
^{13}C NMR spectrum of the compound **12** in $CDCl_3$



Dept NMR spectrum of the compound **12** in $CDCl_3$



^{1}H NMR spectrum of the compound **1** in $CDCl_3$



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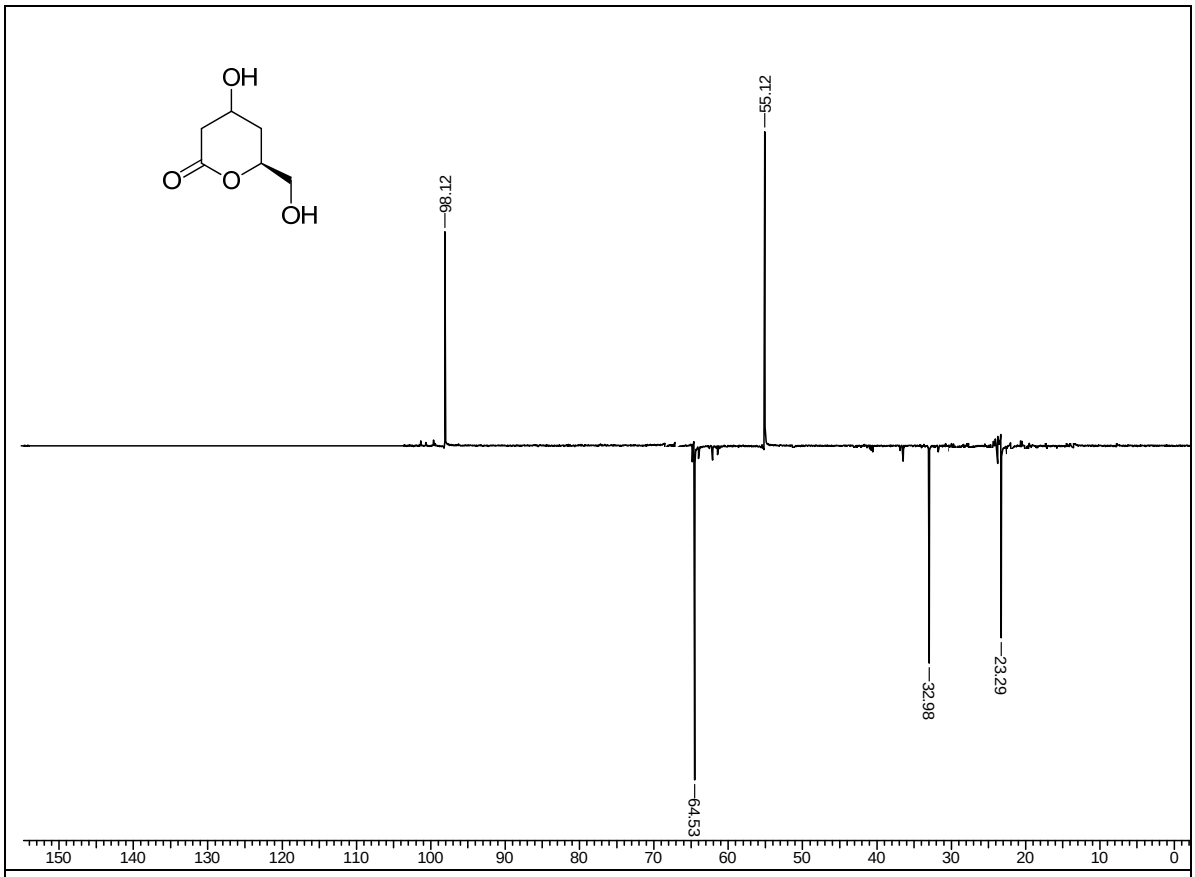

Dept NMR spectrum of the compound **1** in $CDCl_3$

3.2.9. References:

1. For recent reviews, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993.
2. (a) Katsuki, T.; Martin, V. S. *Org. React*. **1996**, *48*, 1. (b) Katsuki, T. *J. Mol. Catal. A: Chem*. **1996**, *113*, 87. For a recent review, see: Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 101-158.
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14. Blacker A.J.; John Crosby and Herbert A.L. United State Patent, 5,443,970 (**1995**)

Chapter 3, Section III: Synthesis of Mevinic Acid analogue

3.3.1. Introduction:

Statins are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases, and statins are therefore used in the prevention of these diseases.[1] Randomized controlled trials have shown that statins are also advocated to overcome diseases due to elevated cholesterol levels such as diabetes and high blood pressure. As of 2010, number of statins are in the market: Mevastatin (compactin, *ML-236B*) (**1**), lovastatin (Mevinolin, Mevacor, Altocor, Altoprev) (**2**), simvastatin (Zocor, Lipex) (**3**) and pravastatin (Pravachol, Selektine, Lipostat) (**4**). Several combination preparations of statin and other agents such as ezetimibe/ simvastatin, sold as Vytorin, are also available. Among these statins, Lovastatin (mevinolin) (**2**) is the first statin to be marketed and with high pharmaceutical integrity[2]. Lovastatin, being inactive in its lactone form, is active in hydrolysed β-hydroxy acid form. Lovastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), an enzyme which catalyzes the conversion of HMG-CoA to mevalonate.

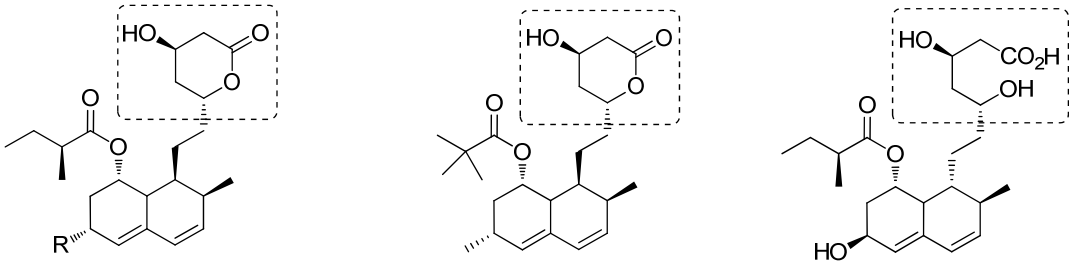


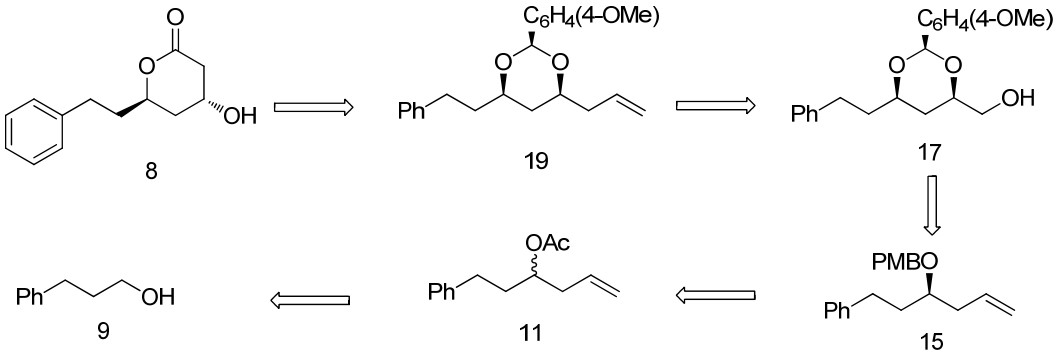
Figure 1

All these statins resemble in structural features with lactone ring **5**. The lactone ring **5** or its open form is responsible for significant biological activity of statins.[3] Further open chain form of this lactone ring resembles Mevalonolactone (**6**) or Mevalonic acid (**7**). Mevalonolactone (**6**) is a required building block for cholesterol biosynthesis and lovastatin (**2**) interferes with its production by acting as a reversible competitive inhibitor for HMG-CoA reductase.

Mevalonolactone (**6**) exists in equilibrium with Mevalonic acid (**7**) and is formed by internal condensation .. Mevalonic acid (**7**) is soluble in water and/ or polar organic solvents. Mevalonic acid (**7**) is a precursor in the biosynthetic pathway, known as the mevalonate pathway, which produces terpenes and steroids and cholesterol. Mevalonic acid is chiral and (3R) enantiomer is the only one that is biologically active. Drugs containing statin lactone (**5**) stops the production of mevalonocactone (**6**) by inhibiting HMG - CoA reductase. The significant role of statin lactone **5** or mevinic acid analogue **8** attracted chemist to venture their total synthesis,[4] hence the synthesis of mevinic acid analogue **8** was planned from phenyl propanol, an easily available starting material.

3.3.2. Present work:

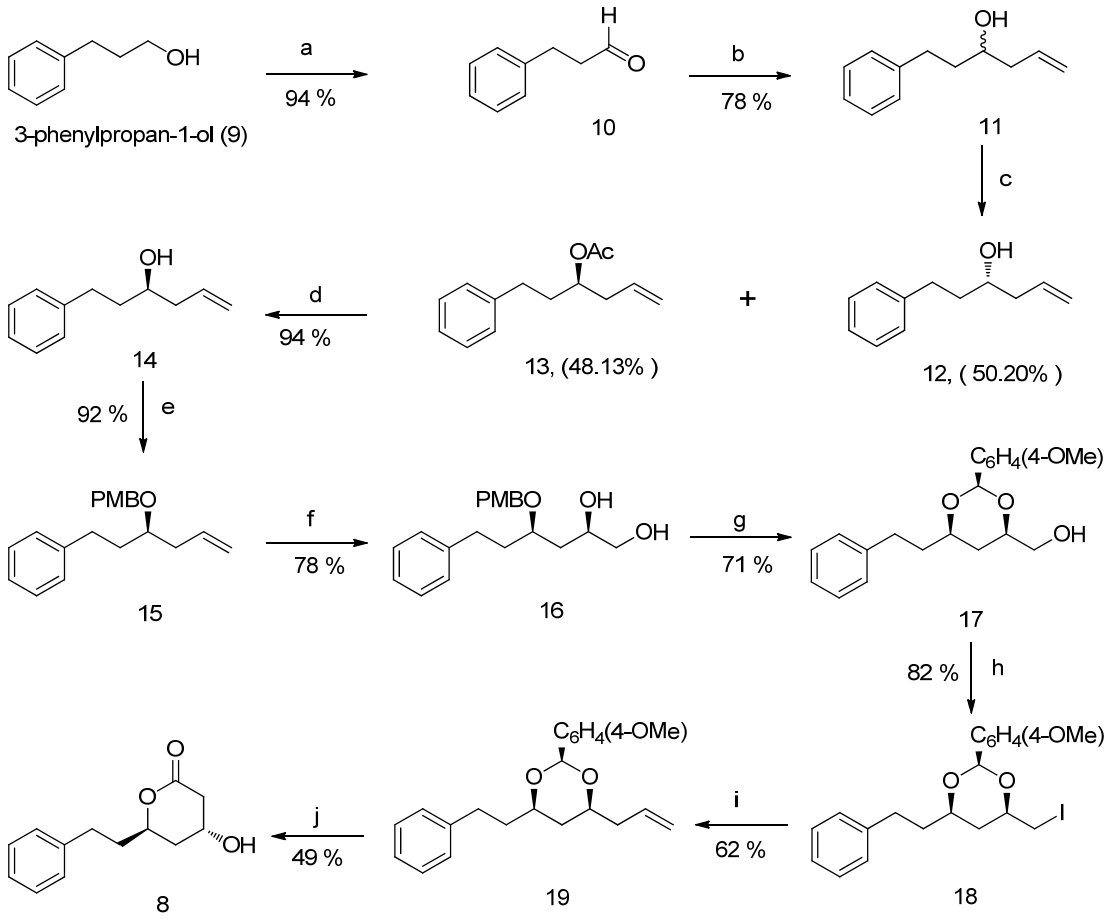
Various methods have been reported forformal and total synthesis of enantiopure lactone moiety of statins (lovastatin), employing chiron approach, or kinetic resolution of racemate. Most of the syntheses comprise of expensive starting materials and lengthy routes with low overall yields. To overcome these factors here we proposed simple, short and stereo-selective route for synthesis of mevinic acid analogue **8**, via dihydroxylation[5] and acid or base catalyzed ring closure.



Scheme 1

As outlined in retrosynthesis (Scheme **1)** it is clear that target lactone moiety can be cleaved to its open form analogue (**19**) which in turn can be obtained from intermediate (**17**). The intermediate **17** can be produced from **15**. The intermediate **15** can be obtained via resolution[6] from racemic synthon **11** which in turn can be synthesized from phenyl propanol.

As outlined in retrosynthesis and depicted in the Scheme 2, our journey began with 3-phenyl propan-1-ol, an inexpensive starting material. Primary step consisting of the oxidation of 3-phenylpropan-1-ol, by using 1.25 equivalents PCC in chloroform as solvent under inert atmosphere, produced aldehyde **10** in quantitative yield. The aldehyde **10** on treatment with allyl-zinc-bromide under Barbier conditions (aq NH_4Cl + acetonitrile +zinc + allyl bromide), afforded racemic 1-phenylhex-5-en-3-ol (**11**). The intermediate **11** was subjected to enzymatic resolution via transesterification. During this process racemic compound simply stirred with enzyme and transesterifying agent along with suitable solvent (Table 1). During this process half of the racemic part gets acylated to furnish enantiopure (R)-1-phenylhex-5-en-3-yl acetate (**13**) whereas other part remains as enantiopure (S)-1-phenylhex-5-en-3-ol (**12**). (R)-1-Phenylhex-5-en-3-yl acetate (**13**) further converted to (R)-1-phenylhex-5-en-3-ol (**14**) by treatment with K_2CO_3 / MeOH under anhydrous condition.



Scheme 2. *Reagents and conditions:* (a) PCC, DCM, RT; (b) Allyl bromide, Zn, THF, aq NH_4Cl; (c) CAL, vinyl acetate, TBME; (d) K_2CO_3, MeOH; (e) NaH, PMB-Cl, DMF, RT (f) Bu^tOH +H_2O, DHQD, OsO_4/ $K_3Fe(CN)_6$; (g) DDQ, dry DCM; (h) I_2, TPP, Imidazole, THF dry; (i) Vinyl Magnesium bromide, CuI, dry THF; (j) $RuCl_4$, $NaIO_4$, CCl_4, CH_3CN, H_2O.

Both enantiomer **12** and **14** were characterized by HPLC, optical rotation and spectral data. (R)-1-Phenylhex-5-en-3-ol (**14**) on treatment with sodium hydride and 4-methoxybezyl choride in presence of DMF under argon atmosphere furnished **15**. The olefin **15** on dihydroxylation with OsO_4 under conditions of Sharpless asymmetric dihydroxylation produced diol **16** which on treatment with DDQ under anhydrous conditions underwent rearrangement to produce hemiacetal **17**. The intermediate **17** was converted to iodide **18** which on treatment with vinyl magnesium bromide underwent C-

C coupling to furnish **19.** The intermediate **19** on treatment with $RuCl_3$ underwent tandem oxidation, deprotection and lactonisation to produce lactone **8.**

Table 1: Enzymatic transesterification of **11** by vinyl acetate as acylating agent

Enzyme	Time (hr)	% product		% ee	
		12	**14***	**12**	**14***
Candida antarctica Lipase (CAL)	24	50.20	45.24	99.55	98.49
Candida cylindracea Lipase (CCL)	24	50.16	45.30	99.55	95.36

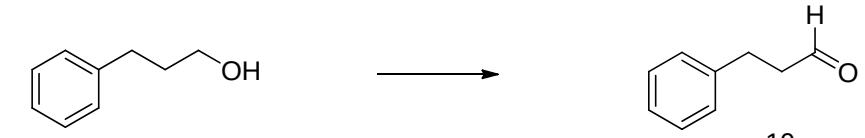
* Aceoxy intermediate **13** was converted to optical antipode **14** via chemical hydrolysis and overall yield is reported

3.3.3. Conclusion

Total synthesis of Mevinic acid analogue (**8**) is achieved in 10 steps and 8.9% overall yields with high enantiomeric purity, from easily available 3-phenylpropanol. Sharpless asymmetric dihydroxylation and enzymatic resolution are the key steps.

3.3.4. Experimental

Preparation of 3-phenylpropanal

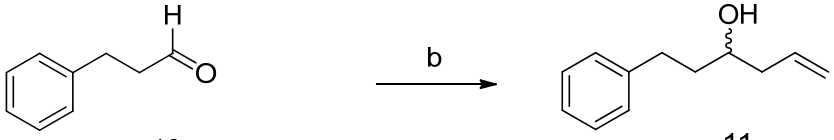


3-phenylpropan-1-ol (9) 10

To the stirred solution of 3-phenylpropanol (**9**, 25 gm, 0.18 mole) in $CHCl_3$ (250 mL), PCC (53.14 gm, 0.22 mole, 1.25 eq) was added slowly in portion at room temperature. The reaction was stirred for 1 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction was carried out by filtration over celite bed and washing with $CHCl_3$. All organic washings were combined and concentrated on rotaevaporator to get crude residue, purification by alumina column chromatography using ethyl acetate: pet ether (10: 90) as eluent, afforded (**10**)

Yield: 23.15 gm, 94 %; yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86-2.02 (m, 2H), 2.48- 2.56 (m, 2H), 7.30-7.33 (m, 5H), 9.76 (t, *J*=1.89 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 24.72, 30.90, 127.57, 128.33, 138.16, 179.69 ppm.

Preparation of 1-phenylhex-5-en-3-ol (11)



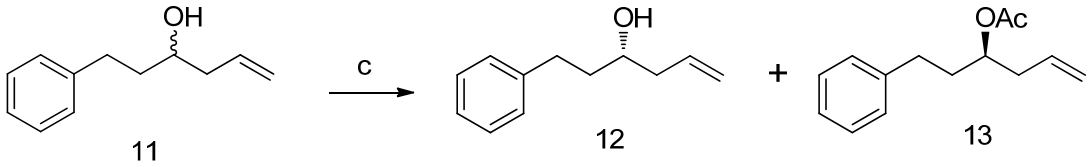
10 11

To the stirred solution of **10** (20 gm, 0.149 mole) in THF (200 mL) and aq NH_4Cl (saturated solution 100 mL), zinc (19.08 gm, 0.298 mole, 2 eq) was added slowly in portion. After ½ hour of stirring, allyl bromide (35.76 gm, 0.298 moles, 2 eq) was added dropwise. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction was carried out by filtration over celite and

extracted with DCM (2 X 250 mL). All organic washings were collected and concentrated on rotaevaporator to get crude residue, purification by silica gel column chromatography using ethyl acetate : pet ether (15:85) as eluent afforded 1-phenylhex-5-en-3-ol **(11)**

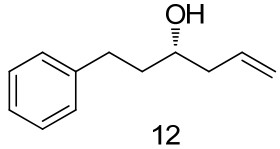
Yield: 21.01 gm, 78%; yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82-1.90 (m, 2H), 2.16-2.45 (m, 2H), 2.66-2.96 (m, 2H), 3.67-3.79 (m, 1H), 5.14-5.24 (m, 2H), 5.77-5.98(m, 1H), 7.24-7.35(m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 31.94, 38.34, 41.95, 69.85, 118.14, 125.73, 128.30, 134.56, 141.98 ppm.

Enzymatic resolution of 1-phenylhex-5-en-3-ol (11)



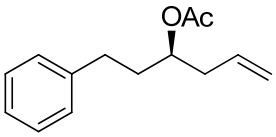
To the stirred solution of 1-phenylhex-5-en-3-ol (**11**, 1 gm, 0.0057 mol) in TBME, was added vinyl acetate (0.5 mL, 0.0057 mol) and enzyme CAL and the reaction was stirred for 96 hrs at 30^{o}C. The progress of the reaction was monitored by TLC. After 50% consumption of starting material, the reaction was stopped and filtered over celite bed. Celite bed was washed with ethyl acetate and all washings along with filtrate were collected together and concentrated on rotaevaporator to get crude residue. The resulting residue was purified by silica gel column chromatography using ethyl acetate-petroleum ether (15:85) as an eluent to afford **12** and **13** as yellow viscous liquid.

(S)-1-Phenylhex-5-en-3-ol (**12**)



Yield: 502 mg (50.20%); yellow viscous oil $[\alpha]_D$= -18.86 (c 2.00, $CHCl_3$){Lit.[8] $[\alpha]_D$= -19.48 (c 2.00, $CHCl_3$)}; ee >98%, [Chiral HPLC analysis: Chiralcel OD (250 x 4.6 mm) column; eluent: 2-propanol: petroleum ether 10:90; flow rate: 0.5 mL/min., detector: 220 nm, t_R= 26.11 min., t_S= 37.38 min.]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83-1.90 (m, 2H), 2.20-2.38 (m, 2H), 2.66-2.91 (m, 2H), 3.67-3.79 (m, 1H), 5.14-5.25 (m, 2H), 5.77-5.98 (m, 1H), 7.24-7.35 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 31.94, 38.34, 41.95, 69.85, 118.14, 125.73, 128.30, 134.56, 141.98 ppm. Elemental Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15; Found: C, 81.53; H, 9.26.

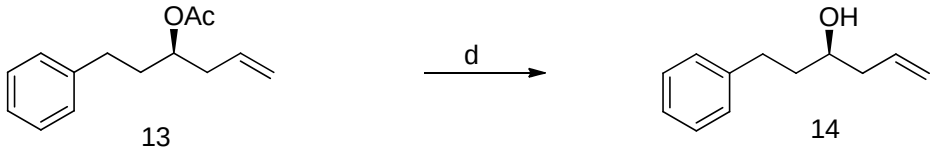
(R)-1-phenylhex-5-en-3-yl acetate (**13**)



13

Yield: 592 mg (48.13 %); yellow viscous oil, $[\alpha]_D$= +5.22 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.85 (m, 2H), 1.95 (s, 3H), 2.26 (t, J=6.77, 2H), 2.47-2.61 (m, 2H), 4.83-4.92 (m, 1H), 4.96-5.05 (m, 2H), 5.57-5.78 (m, 1H), 7.07-7.25 (m, 5H); ^{13}C NMR (100MHz, $CDCl_3$): δ 21.07, 31.68, 35.17, 38.61, 72.72, 117.75, 125.84, 128.22, 128.32, 133.40, 141.40, 170.64 ppm; Elemental Anal. Calcd for $C_{14}H_{20}O_2$: C, 77.03; H, 8.31; Found: C, 77.23; H, 8.51.

Preparation of (R)-1-phenylhex-5-en-3-ol (14)



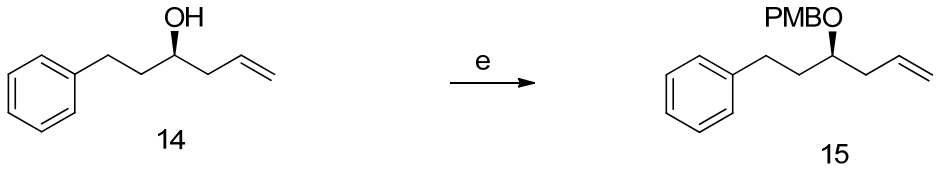
13 14

To the stirred solution of **13** (0.596 gm, 0.0028 moles) in methanol, potassium carbonate (0.77 gm, 0.0056 moles, 2 eq) was added and stirred at room temperature for three hours. The progress of the reaction was monitored by TLC. After completion, of the reaction, it

was quenched with dil HCl and methanol, evaporated solvent under vacuum and extracted residue with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated over rotaevaporator to get the crude product, purification by silica gel column chromatography using ethyl acetate: pet ether (15:85) as eluent gave (R)-1-phenylhex-5-en-3-ol **(14).**

Yield: 452 mg (94%); yellow viscous oil; $[\alpha]_D$= +19.28 (c 2.00, $CHCl_3$){Lit[8] $[\alpha]_D$= +19.48 (c 2.00, $CHCl_3$)}; ee >98%, [Chiral HPLC analysis: Chiralcel OD (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 10:90; flow rate: 0.5 mL/min., detector: 220 nm, t_R= 26.35 min., t_S= 35.06 min.]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82-1.90 (m, 2H), 2.16-2.45 (m, 2H), 2.66-2.95 (m, 2H), 3.67-3.79 (m, 1H), 5.14-5.24 (m, 2H), 5.77-5.98 (m, 1H), 7.24-7.35 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.94, 38.34, 41.95, 69.85, 118.14, 125.73, 128.30, 134.56, 141.98 ppm; Elemental Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 88.15; H, 9.31.

Preparation of (R)-1-phenyl-3-((4-methoxybenzyl)oxy)hex-5-en (15)



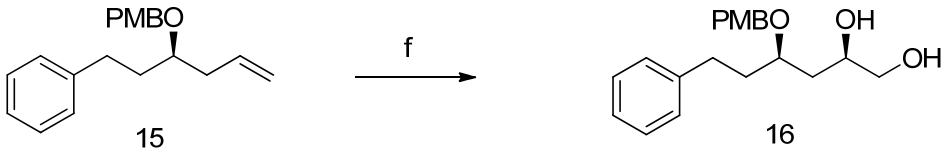
14 15

To the stirred solution of **14** (1.00 gm, 0.0057 mole) in 20 mL DMF, sodium-hydride (60 %, 0.288 gm, 0.0072 mole, 1.25 eq) was added in inert argon atmosphere slowly in portion, at ice cold temperature. After ½ hour of stirring, 4-methoxybenzyl chloride (1.11 gm, 0.0072 moles, 1.25 eq) and catalytic amount of tetrabutyl ammonium iodide was added in argon atmosphere. The progress of the reaction was monitored by TLC.

After completion of the reaction, work up of the reaction was carried out by quenching with ice-cold water and extracted with DCM. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated on rotaevaporator to

get crude **15**, purification by silica gel column chromatography using ethyl acetate: pet ether (5:95) as eluent afforded (R)-1-phenyl-3-((4-methoxybenzyl) oxy)hex-5-ene (**15**). Yield: 1.39 gm (92%); yellow viscous oil; $[\alpha]_D$= +28.4 (c 2.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79-1.87 (m, 2H), 2.20-2.35 (m, 2H), 2.67-2.92 (m, 2H), 3.68-3.83 (m, 5H), 4.49-4.59 (m, 1H), 5.14-5.20 (d, *J*=12.89 Hz, 2H), 5.82-6.03 (m, 1H), 6.82-7.00 (m, 2H) and 7.25-7.39 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.67, 35.68, 38.23, 55.26, 70.55, 113.77, 117.02, 125.68, 128.40, 129.34, 129.70, 130.90, 134.77, 142.36, 159.13 ppm.

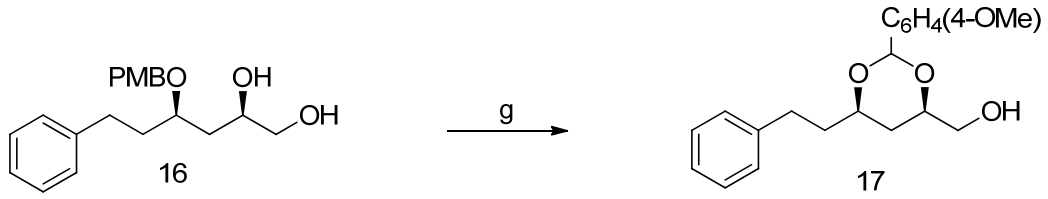
Preparation of (2R, 4R)-4-((4-methoxybenzyl)oxy)-6-phenylhexane-1,2-diol (16)



A mixture of $K_3[Fe(CN)_6]$ (6.5 g, 0.020 mol, 2 eq), K_2CO_3 (2.62 gm, 0.020 mole, 2 eq) and $(DHQD)_2$-PHAL (0.0002 mole, catalytic amount) in $^{t-}$BuOH-H_2O (1:1, 100 mL) was cooled to 0^{o}C and osmium tetroxide (100 mL, 0.1M solution in toluene) was added to the reaction mixture. After ½ hour of stirring at 0^{o}C, the olefin 6-[(4-methoxy) benzyloxy]-4-benzyloxy hexene (**15**, 1.5 gm, 0.0051 mol) was added in argon atmosphere in one portion. The reaction mixture was stirred at 0^{o}C for 24 hr. The progress of the reaction was carried out by TLC. After completion of the reaction, it was quenched with anhydrous sodium sulfite (1 gm), stirring was continued for an additional 45 min and then the solution was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated on rotaevaporator to get crude residue, purification by silica gel column chromatography using ethyl acetate: pet ether (1:1) as eluent, afforded (2R, 4R)-4-((4-methoxybenzyl)oxy)-6-phenylhexan-1,2-diol (**16**)

Yield: 1.30 gm (78%); yellow viscous oil; $[\alpha]_D$= + 51.08 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51-1.97 (m, 4H), 2.62-2.69 (m, 2H), 3.41- 3.61 (m, 2H), 3.68-3.72 (m, 1H), 3.77 (s, 3H), 3.81-4.05 (m, 2H), 4.33.-4.56 (m, 2H), 6.86 (d, *J*=8.59 Hz, 2H), 7.13-7.35 (m, 7H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ 29.57, 30.78, 31.36, 55.11, 69.20, 70.14, 70.79, 71.34, 113.76, 128.21, 128.30, 129.54, 129.71. 130.09, 141.75, 141.83 ppm; Dept NMR (50 MHz, $CDCl_3$): δ 29.58, 30.78, 31.36, 55.11, 69.20, 70.15, 70.79, 71.35, 113.76, 128.23, 128.31, 129.55, 129.72 ppm. Elemental Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.61; H, 7.81.

Preparation of ((4R, 6R)-2-(4-methoxyphenyl)-6-phenethyl-1, 3-dioxan-4-yl)methanol (17)

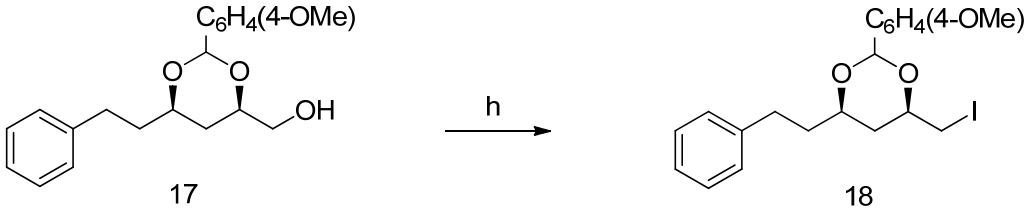


To the stirred solution of **16** (1.1 gm, 0.0034 mol) in dry dichloromethane (15 mL), dichloro dicyano quinone (0.77 g, 0.0034 mmol) was added slowly at 0°C and the mixture was stirred for 6 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with dichloromethane. After a few minutes, the layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on rotaevaporator to afford a residue, purification of the residue by silica gel column chromatography using ethyl acetate: pet ether (25:75) as eluent furnished ((4R, 6R)-2-(4-methoxyphenyl)-6-phenethyl-1, 3-dioxan-4-yl) methanol (**17**).

Yield: 0.77 gm (71 %); yellow oil; $[\alpha]_D$= +30.09 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.50-1.81 (m, 3H), 2.04-2.14 (m, 1H), 2.46-2.74 (m, 2H), 3.68-3.75 (m, 2H), 3.92-4.00 (m, 2H), 4.62 (s, 3H), 4.99-5.04 (m, 1H), 7.06-7.20 (m, 5H), 7.27 (d, **J**=8.28

Hz, 2H), 7.71 (d, **J**=8.34 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.57, 30.78, 31.36, 55.11, 69.20, 70.79, 71.34, 75.41, 113.76, 128.21, 128.30, 129.54, 129.71, 130.09, 141.75, 141.83 ppm. Elemental Anal. Calcd for $C_{20}H_{26}O_4$: C, 73.15; H, 7.37. Found: C, 73.34; H, 7.49.

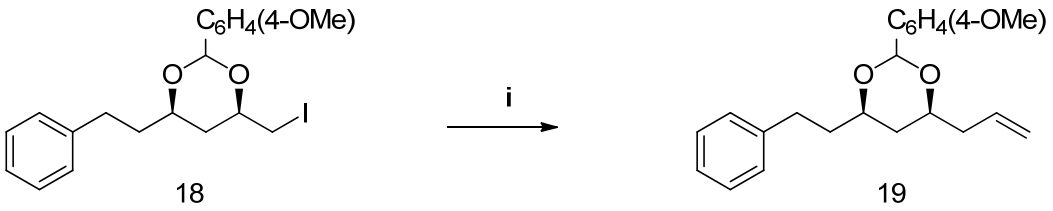
Preparation of (4R, 6R)-4-(iodomethyl)-2-(4-methoxyphenyl)-6-phenethyl-1, 3-dioxane (18)



To the stirred solution of **17** (0.5 gm, 0.0016 mole) in dry THF, imidazole (0.136 gm, 0.002 mole, 1.25 eq) and TPP (0.524 gm, 0.002 mole, 1.25 eq) were added. Iodine (0.506 gm, 0.002 mole, 1.25 eq) was added to the reaction mixture in portion at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, work up of the reaction carried out by simply quenching with ice-cold water and extraction with DCM. Combined organic layer was dried over anhydrous sodium sulphate and concentrated on rotaevaporator to get crude product, purification by silica gel column chromatography by using ethyl acetate: pet ether (5: 95) as eluent afforded (4R, 6R)-4-(iodomethyl)-2-(4-methoxyphenyl)-6-phenethyl-1,3-dioxane (**18**).

Yield: 0.547, gm 82%; $[\alpha]_D$= +25.6 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50-2.00 (m, 4H), 2.50-2.74 (m, 2H), 3.56-3.75 (m, 3H), 3.89-4.00 (m, 1H), 4.61 (s, 3H), 4.96-5.05 (m, 1H), 7.07-7.21 (m, 5H), 7.27 (d, 2 **J**=8.29 Hz, 2H), 7.71 (d, **J**=8.36 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.63, 30.63, 30.73, 34.89, 55.26, 70.48, 73.20, 73.92, 113.83, 125.92, 127.92, 128.28, 128.44, 129.46, 129.81, 132.30, 141.66 ppm; Elemental Anal. Calcd for $C_{20}H_{23}IO_3$: C, 54.81; H, 5.29; I, 28.95. Found: C, 54.96; H, 5.21; I, 28.84.

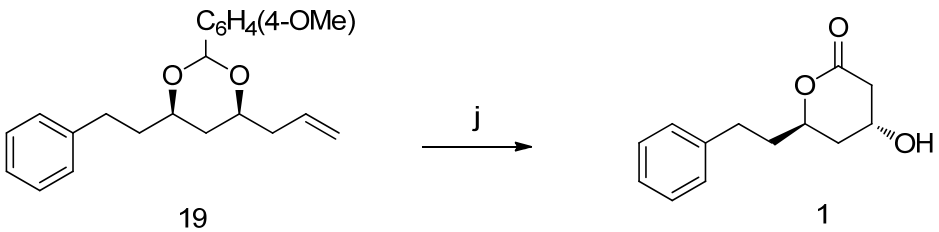
Preparation of (4S, 6R)-4-allyl-2-(4-methoxyphenyl)-6-phenethyl-1, 3-dioxane



To the stirred solution of **18** (0.5 gm, 0.0012 mole) in tetrahydrofuran, vinyl magnesium bromide solution (0.31 gm, 0.0024, 2 eq) and catalytic amount of CuI was added in argon atmosphere and the reaction was kept stirring for three hours. The progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with aq ammonium chloride and extracted with ethyl acetate (2 x 25 mL). Combined organic layers were dried over sodium sulphate and evaporated over rotaevaporator to get crude product **19**, purification by silica gel column chromatography by using ethyl acetate: pet ether (5: 95) as eluent, afforded **19**.

Yield: 0.239 gm 62%; colourless liquid; $[\alpha]_D$= +20.46 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.78 (m, 2H), 1.78-1.85 (m, 2H), 2.14-2.40 (m, 2H), 2.61-2.89 (m, 2H), 3.65-3.90 (m, 5H), 4.40-4.62 (m, 1H), 5.11-5.18 (m, 2H), 5.72-5.93 (m, 1H), 6.88 (d, **J**=8.21 Hz, 2H), 7.00-7.29 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.06, 35.38, 36.15, 36.61, 55.11, 69.20, 71.34, 75.41, 113.76, 115.91, 125.75, 128.21, 128.30, 129.54, 129.71, 130.09, 141.75, 141.83 ppm; Elemental Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.17; H, 7.69.

Preperation of (4R, 6R)-4-hydroxy-6-phenethyltetrahydro-2*H*-pyran-2-one (8)

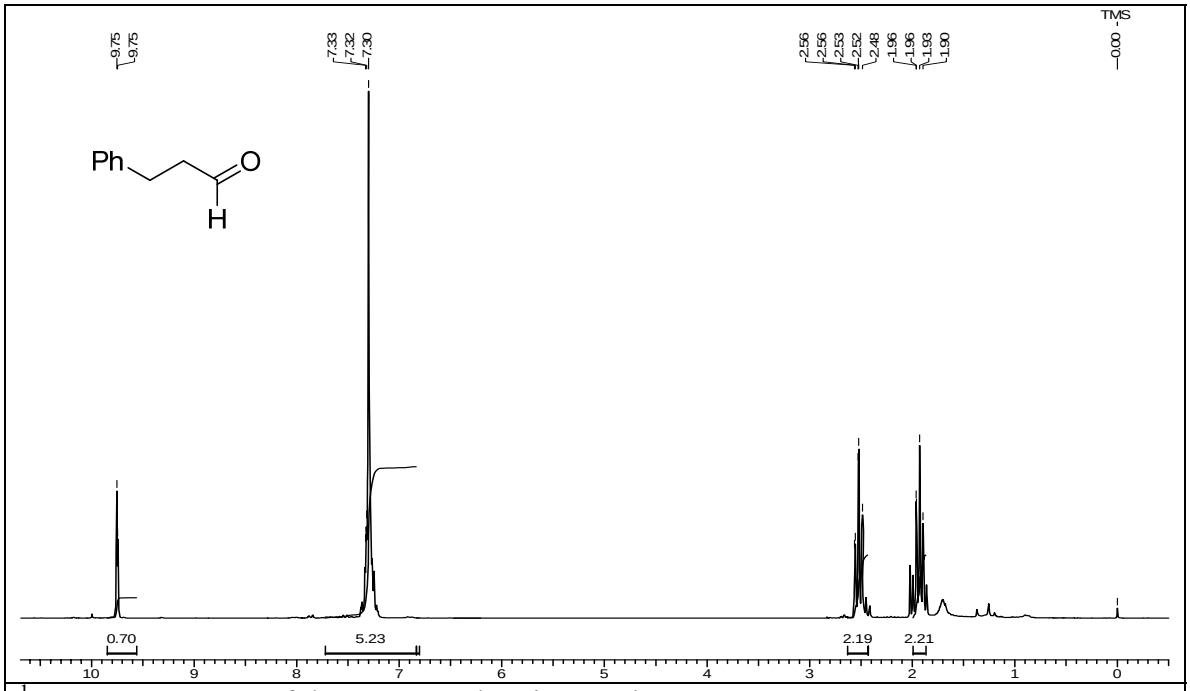


To the stirred solution of **19** (0.200 gm, 0.0006 mole) in carbontetrachloride: acetonitrile: water (1:1:2, 20 mL), $NaIO_4$ (0.256 gm, 0.0012 mole, 2 eq) and $RuCl_3$ (0.0484 gm, 0.0002 mole, 0.3 eq) were added at room temperature. The reaction mixture was stirred for 12hr. The progress of the reaction was monitored by TLC.

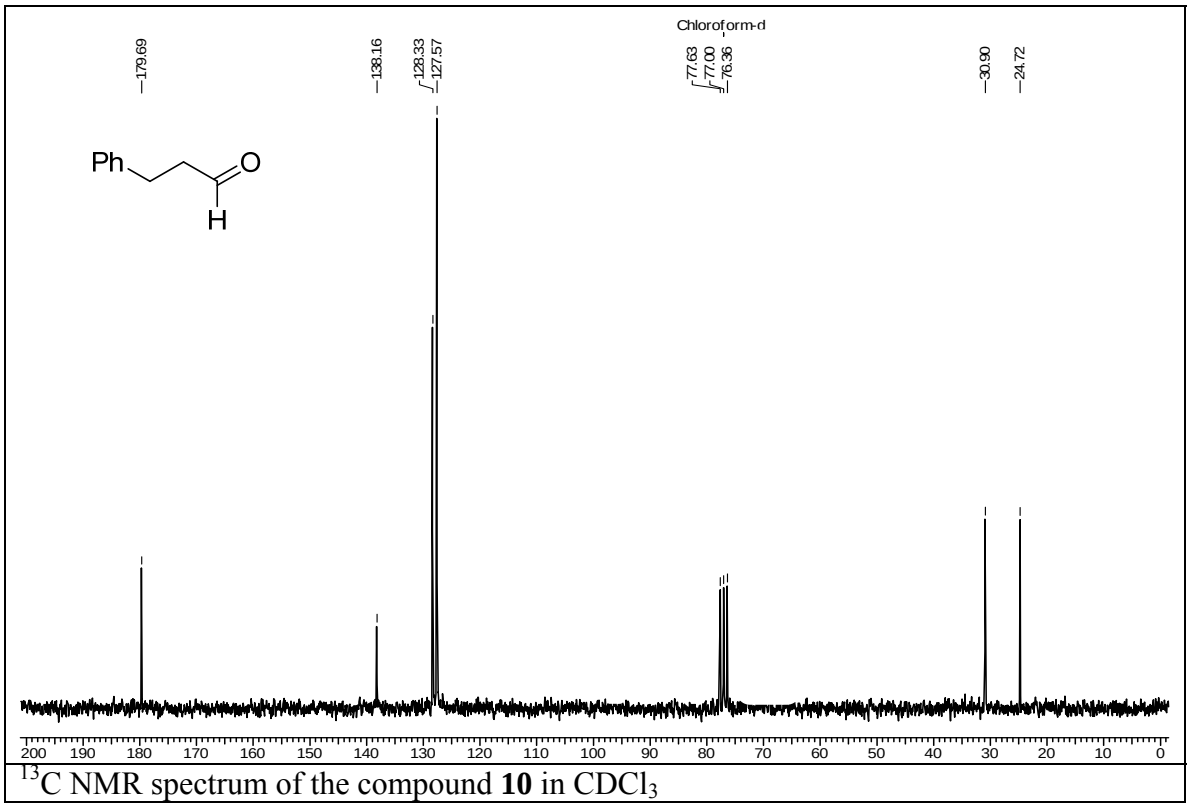
After completion of the reaction, it was quenched with ice-cold water and extracted with DCM (3 X 25 mL). Combined organic layers were dried over anhydrous sodium sulphate and evaporated on rotaevaporator to get crude product (0.149 gm, 71 %) of acid intermediate. The residue (0.149 gm) was dissolved in methanol (10 mL) and catalytic amount of HCl was added. This reaction mixture was stirred at room temperature for overnight. The progress of the reaction was monitored by TLC. After completion, reaction mixture was quenched with solid $NaHCO_3$, filtered and concentrated on rotaevaporator to get **8**, purification by silica gel column chromatography by using ethyl acetate: pet ether (35: 65) as eluent, affordded **8** (0.063 gm, 69 %) as a yellow sticky viscous liquid.

Yield: 0.063 gm (49%, overall yield for 2 steps); $[\alpha]_D$= +69.79 (c 2.00, $CHCl_3$) {Lit.[7] $[\alpha]_D$= +68.88 (c 2.29, $CHCl_3$)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74-2.09 (m, 4H), 2.53-2.89 (m, 4H), 4.31-4.39 (m, 1H), 4.65-4.70 (m, 1H), 7.09-7.26 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.84, 38.23, 39.33, 41.84, 63.36, 75.75, 126.84, 129.18, 141.70, 170.30. Elemental Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.71; H, 7.43.

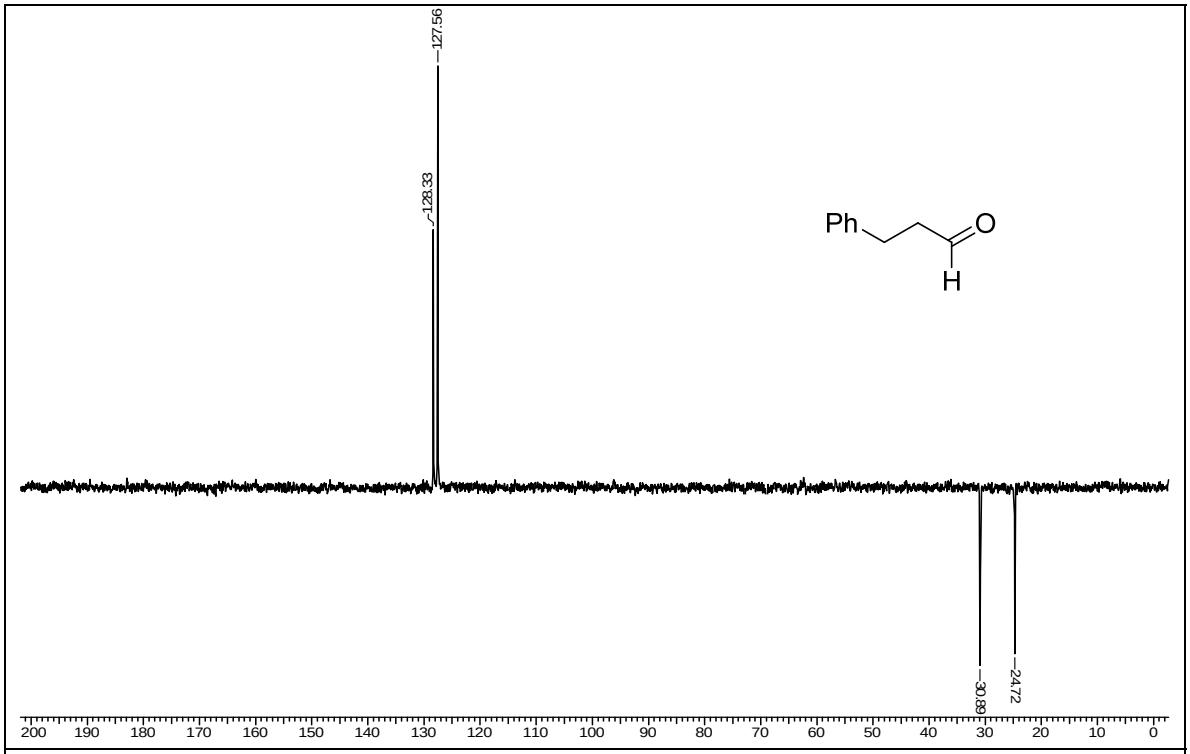
3.3.5. Analytical Data



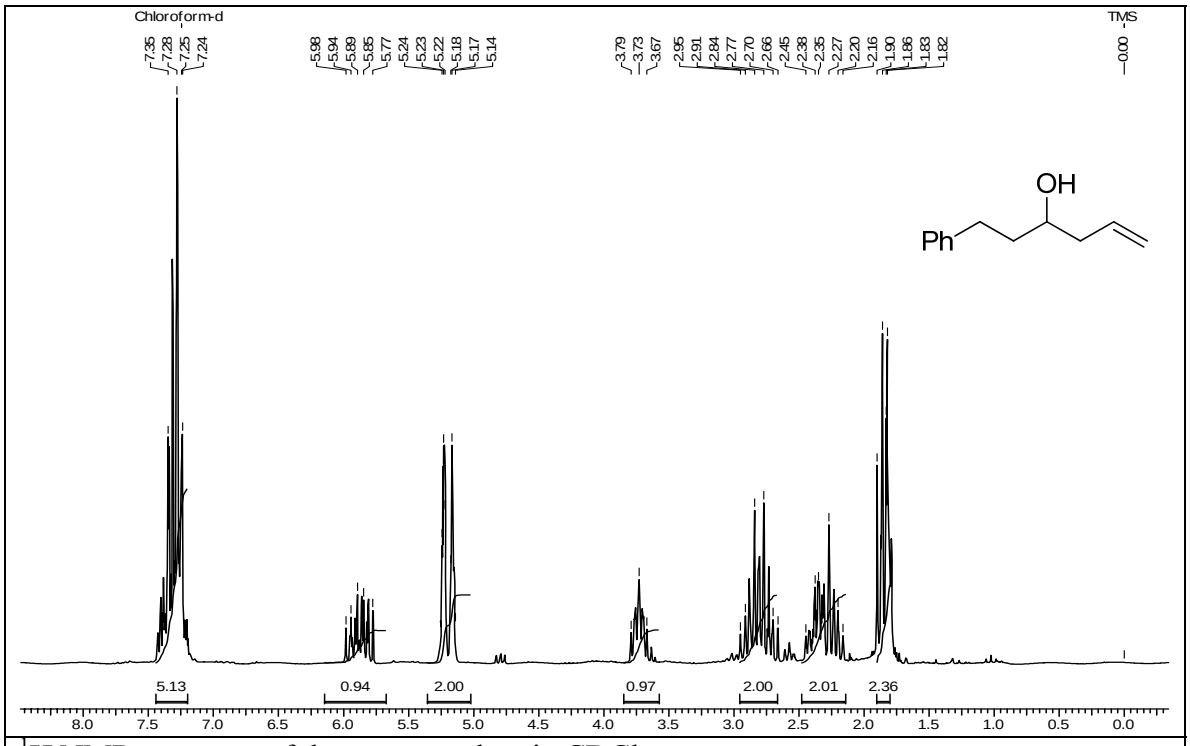
^{1}H NMR spectrum of the compound **10** in $CDCl_3$



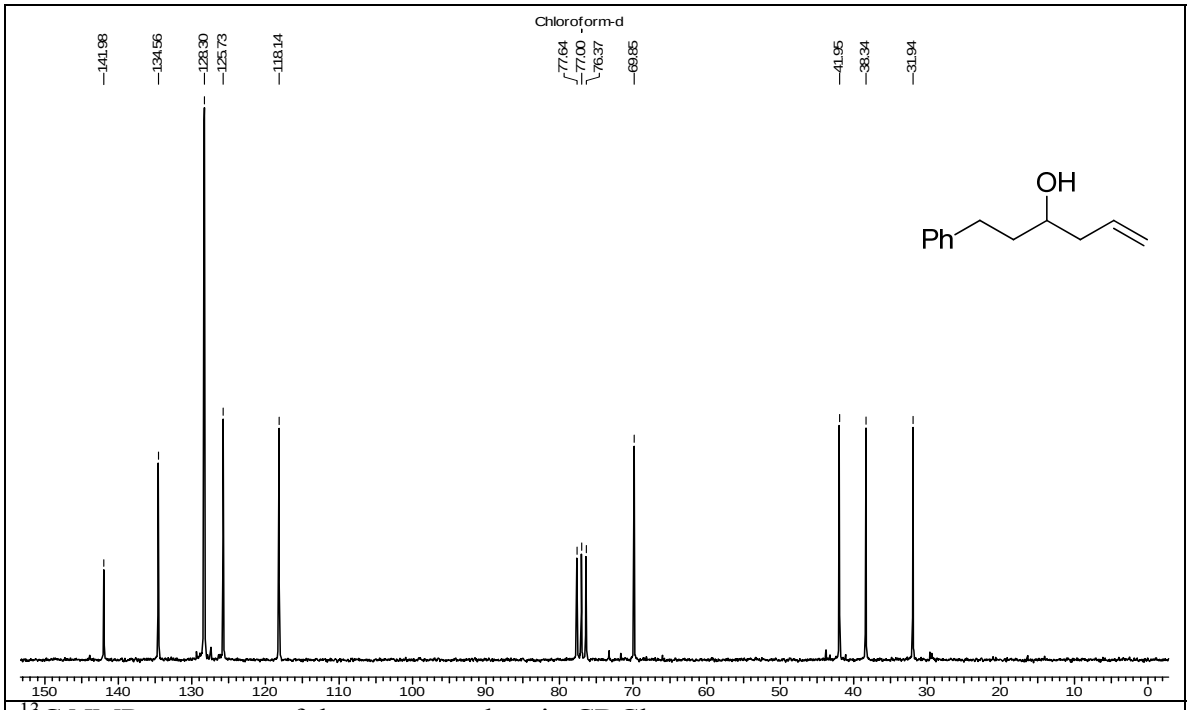
^{13}C NMR spectrum of the compound **10** in $CDCl_3$



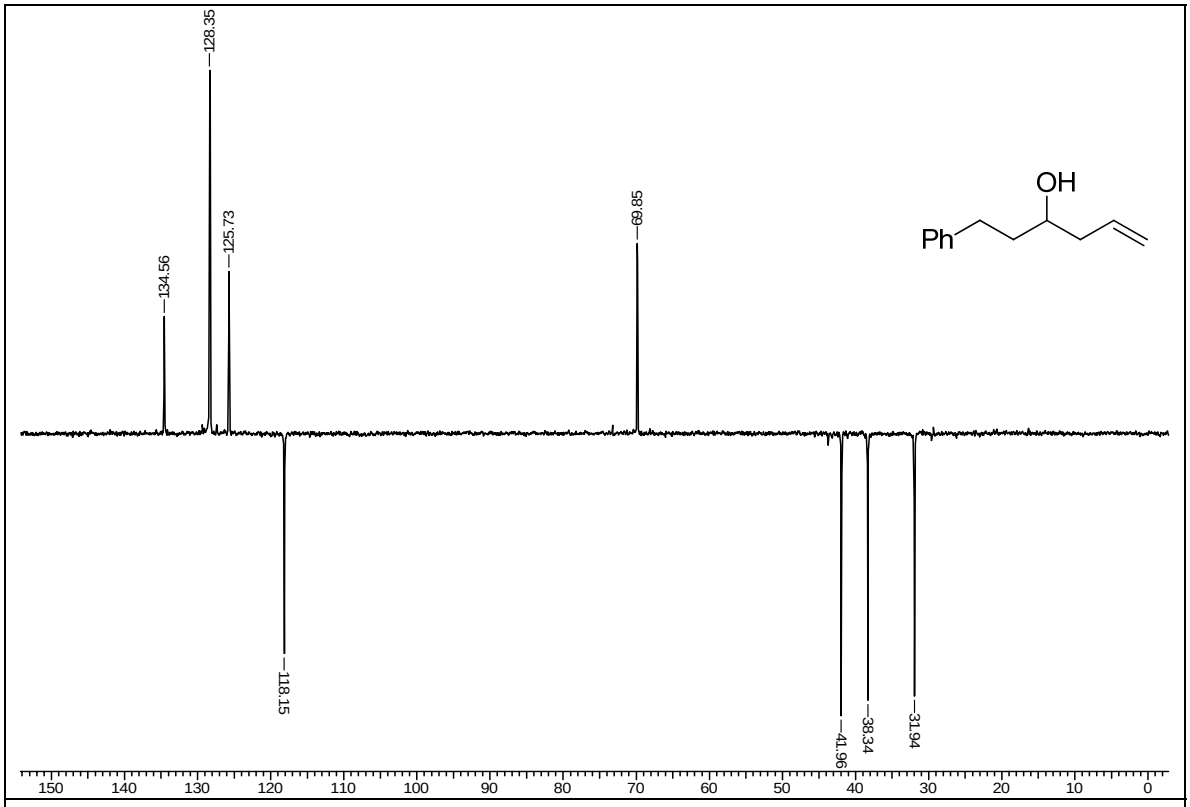
Dept NMR spectrum of the compound **10** in $CDCl_3$



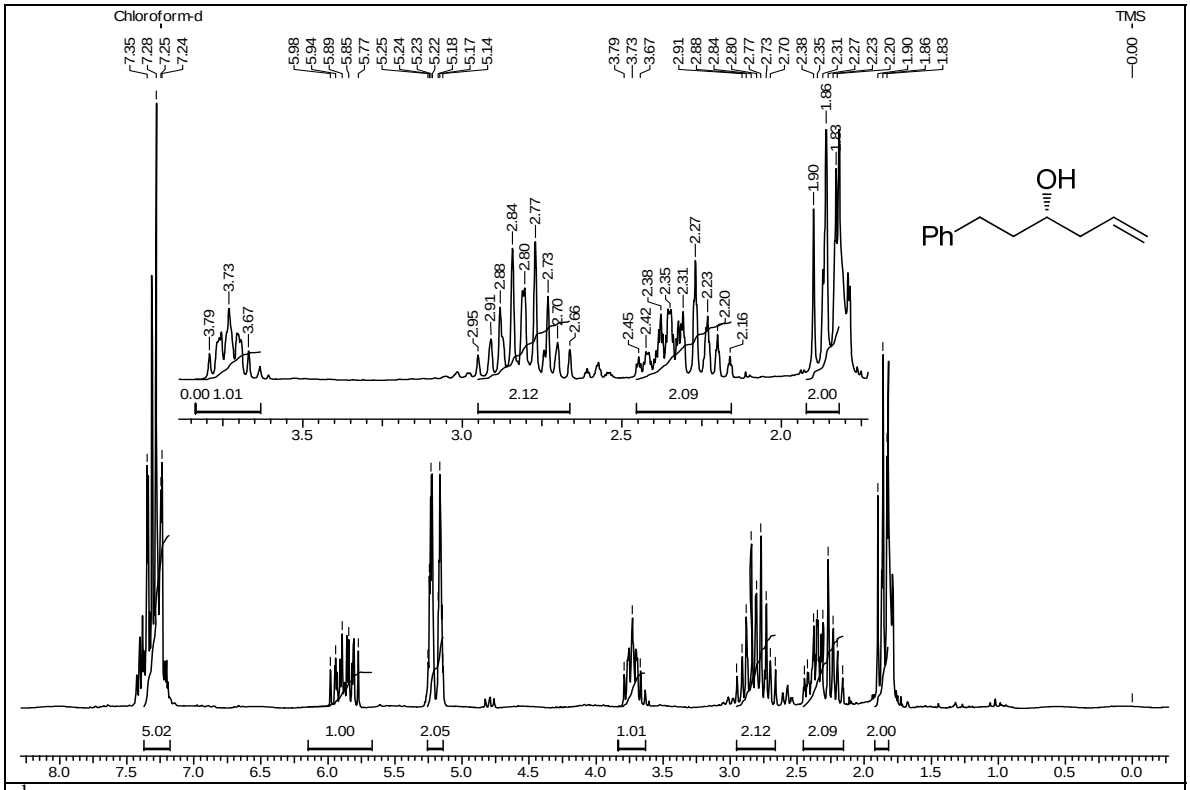
^{1}H NMR spectrum of the compound **11** in $CDCl_3$



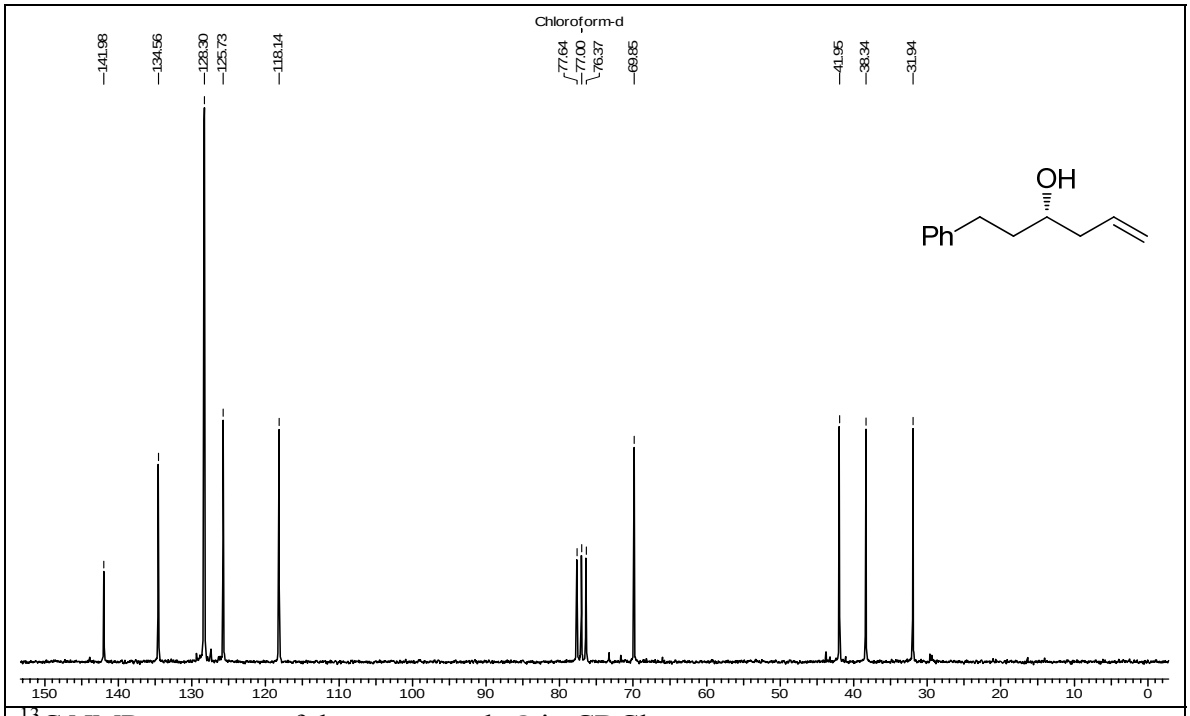
^{13}C NMR spectrum of the compound **11** in $CDCl_3$



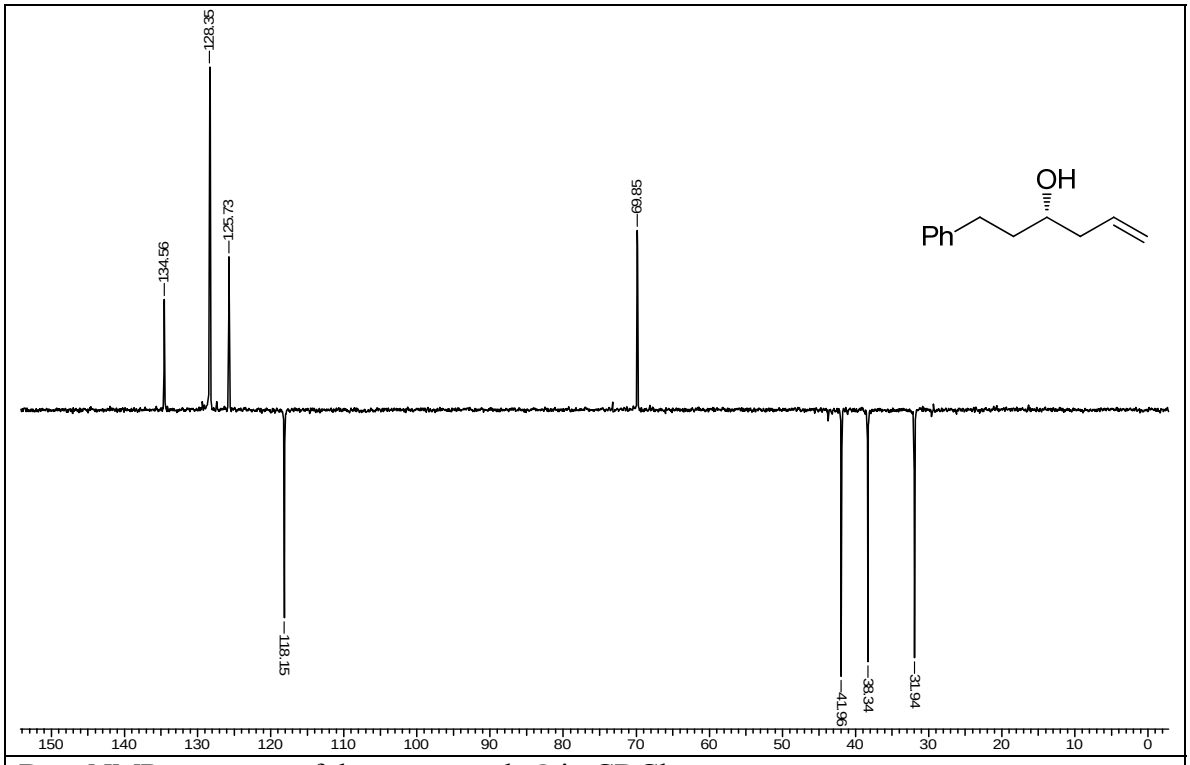
Dept NMR spectrum of the compound **11** in $CDCl_3$



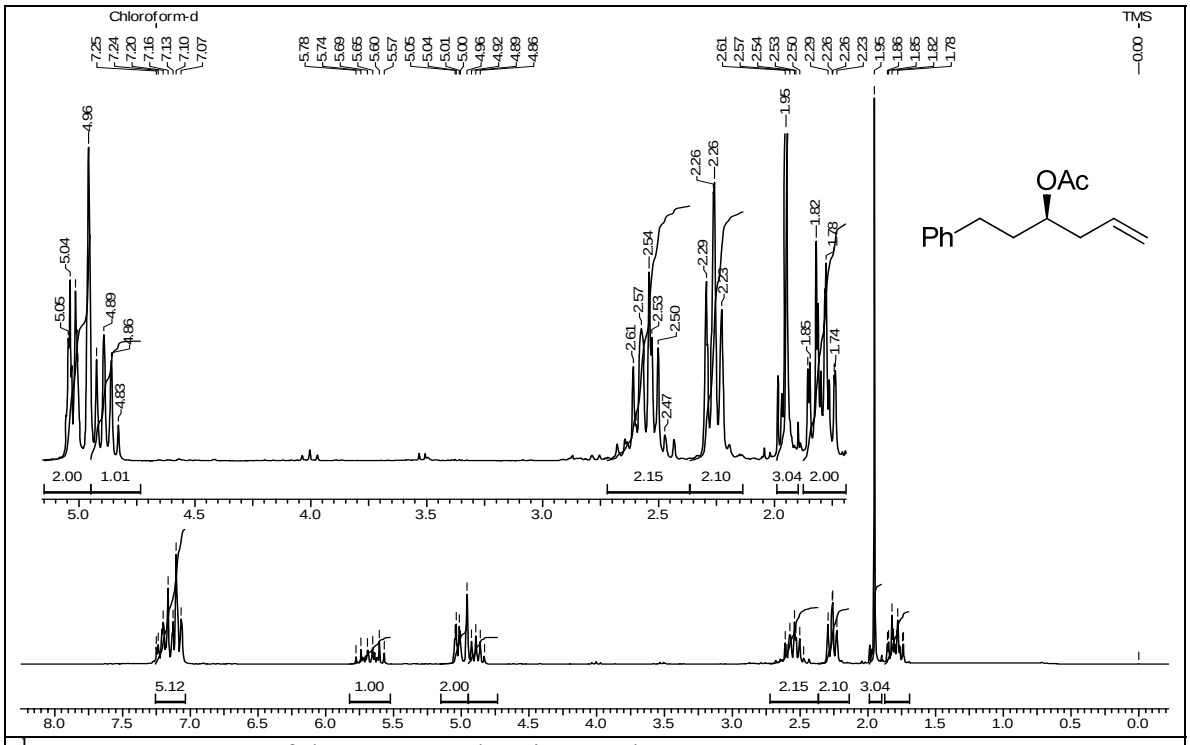
^{1}H NMR spectrum of the compound **12** in $CDCl_3$



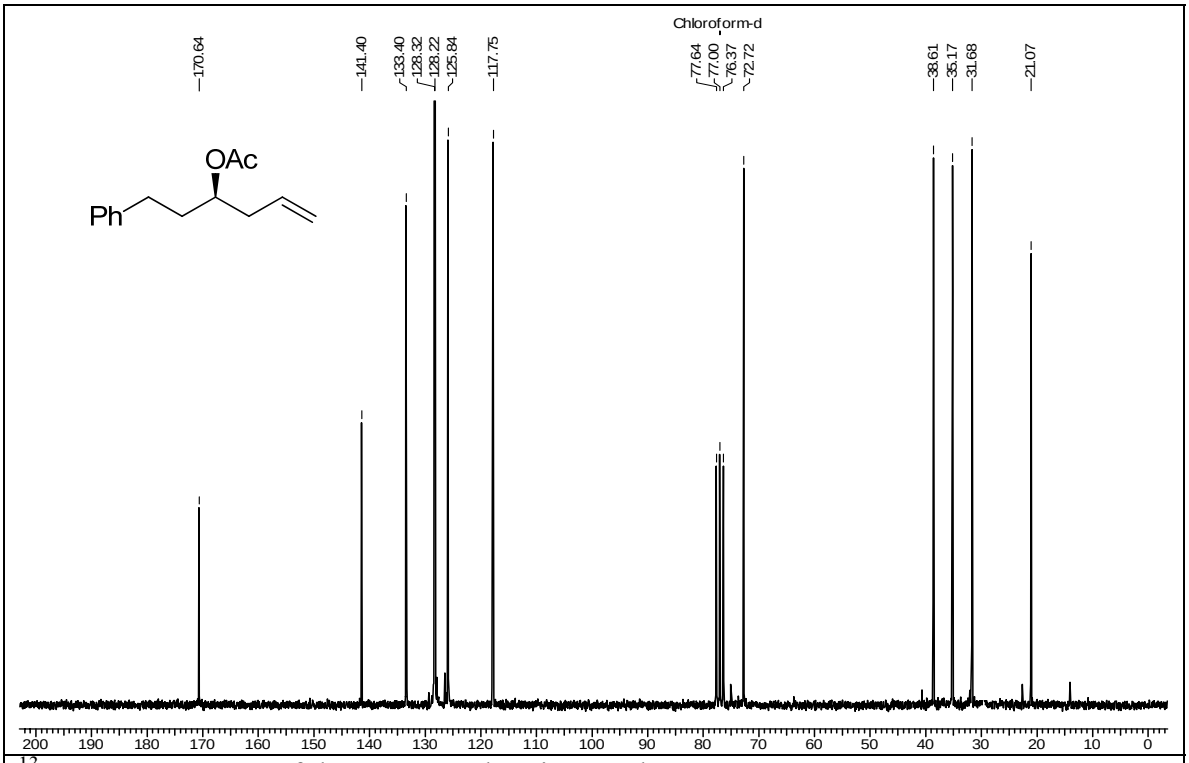
^{13}C NMR spectrum of the compound **12** in $CDCl_3$



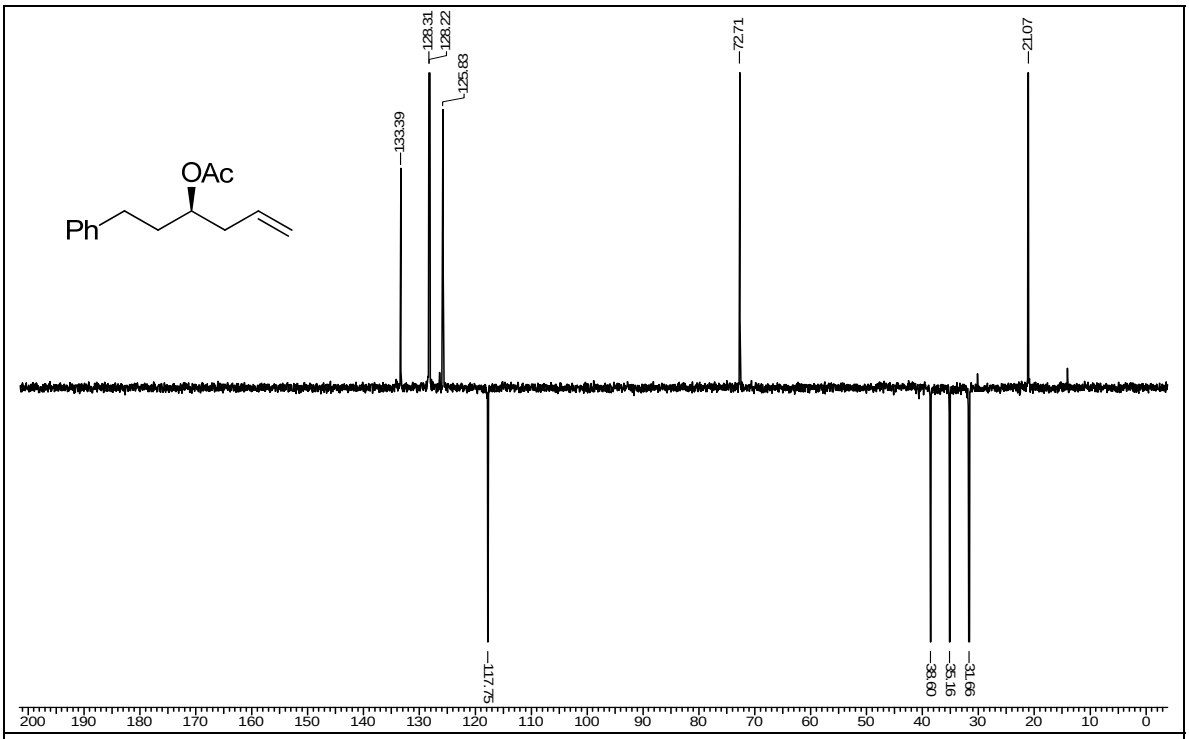
Dept NMR spectrum of the compound **12** in $CDCl_3$



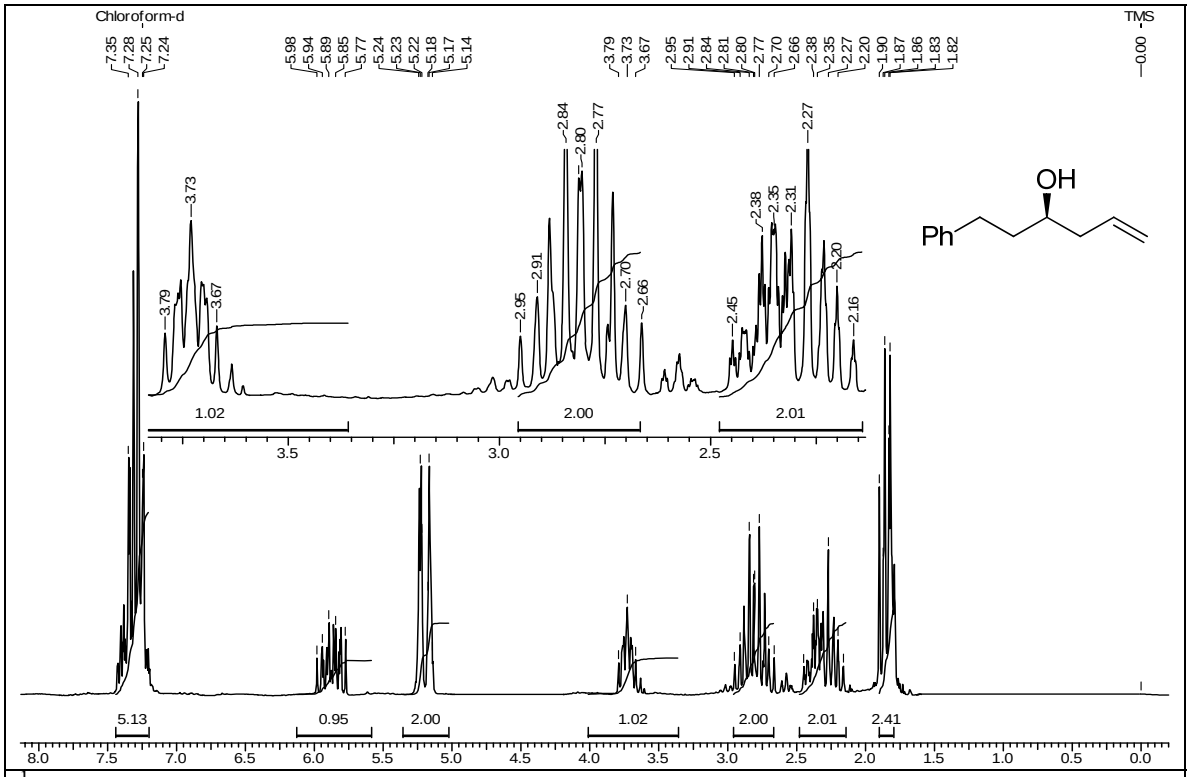
^{1}H NMR spectrum of the compound **13** in $CDCl_3$



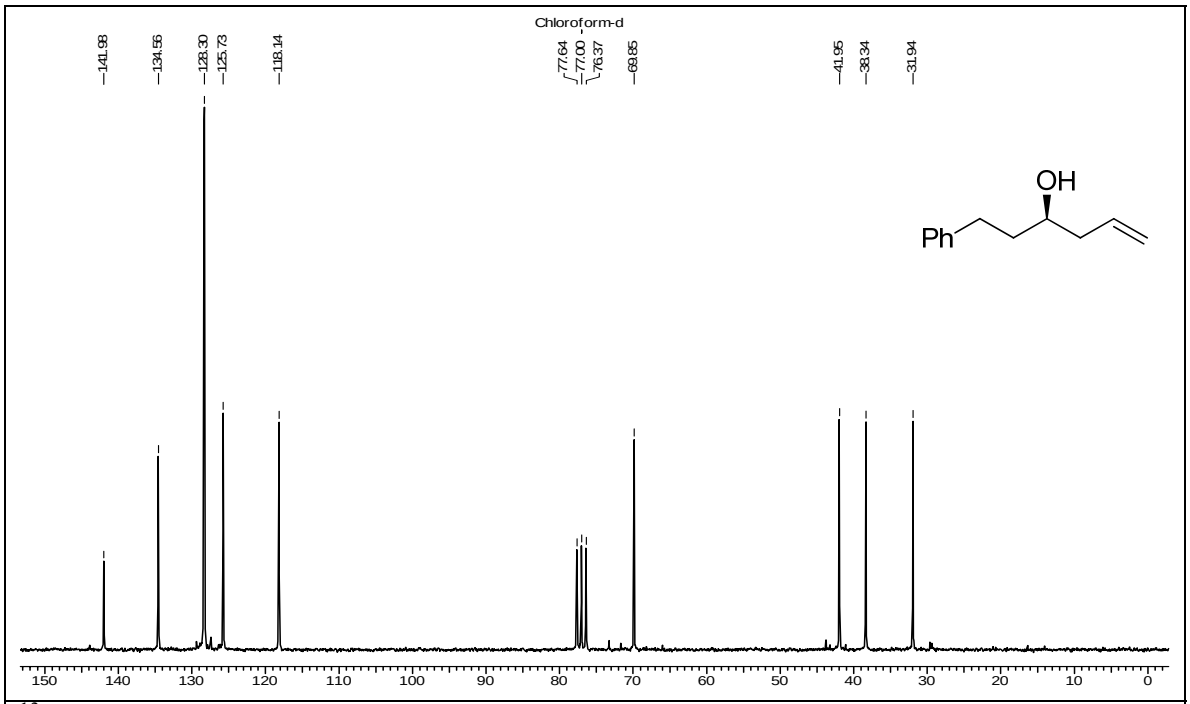
^{13}C NMR spectrum of the compound **13** in $CDCl_3$



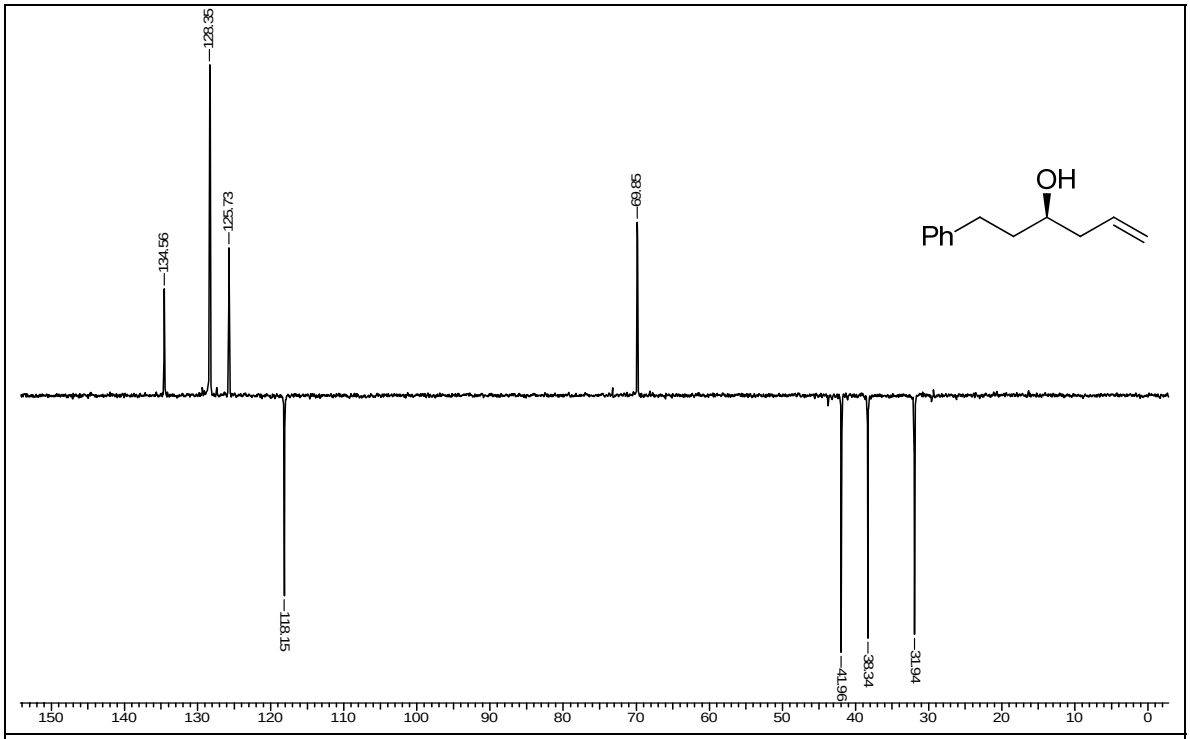
Dept NMR spectrum of the compound **13** in $CDCl_3$



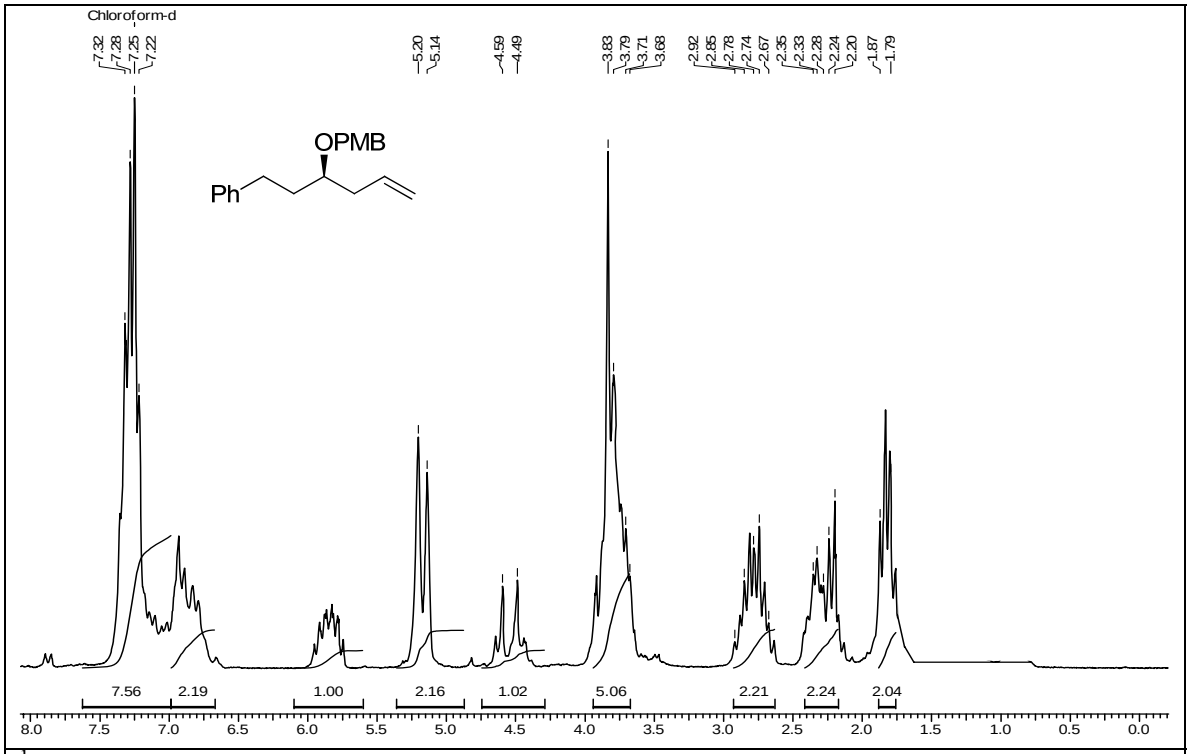
^{1}H NMR spectrum of the compound **14** in $CDCl_3$



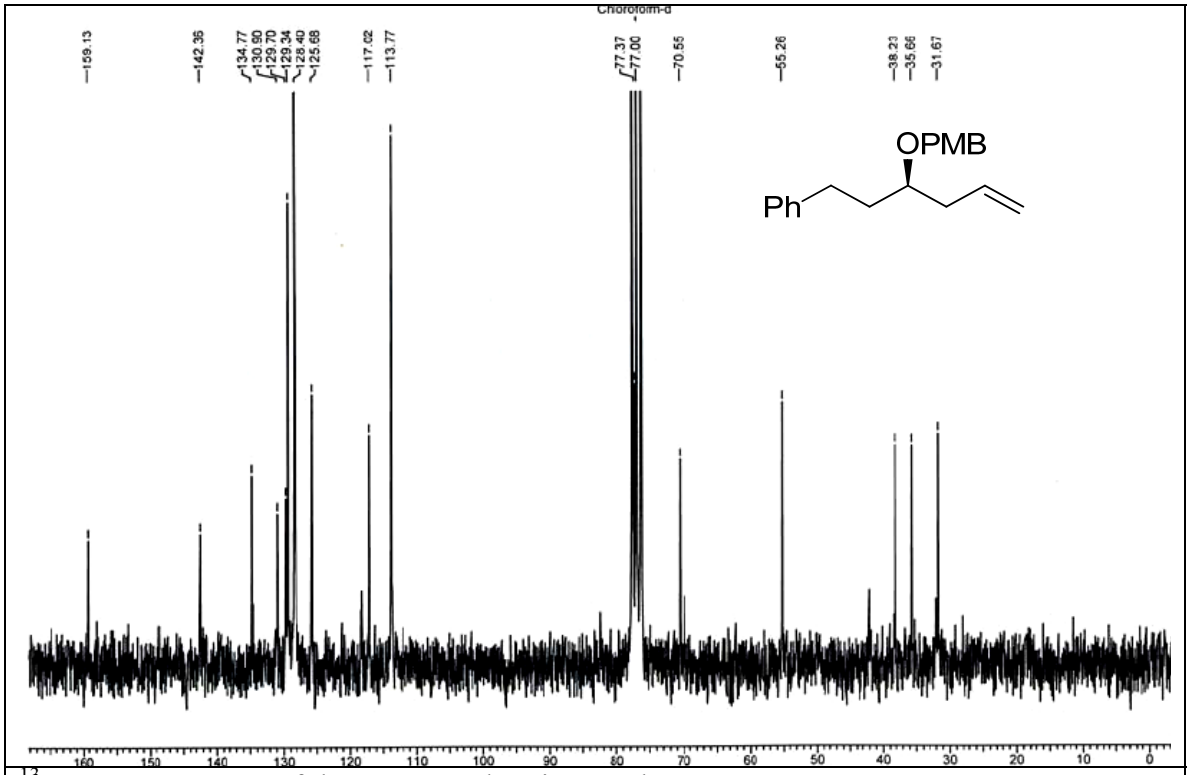
^{13}C NMR spectrum of the compound **14** in $CDCl_3$



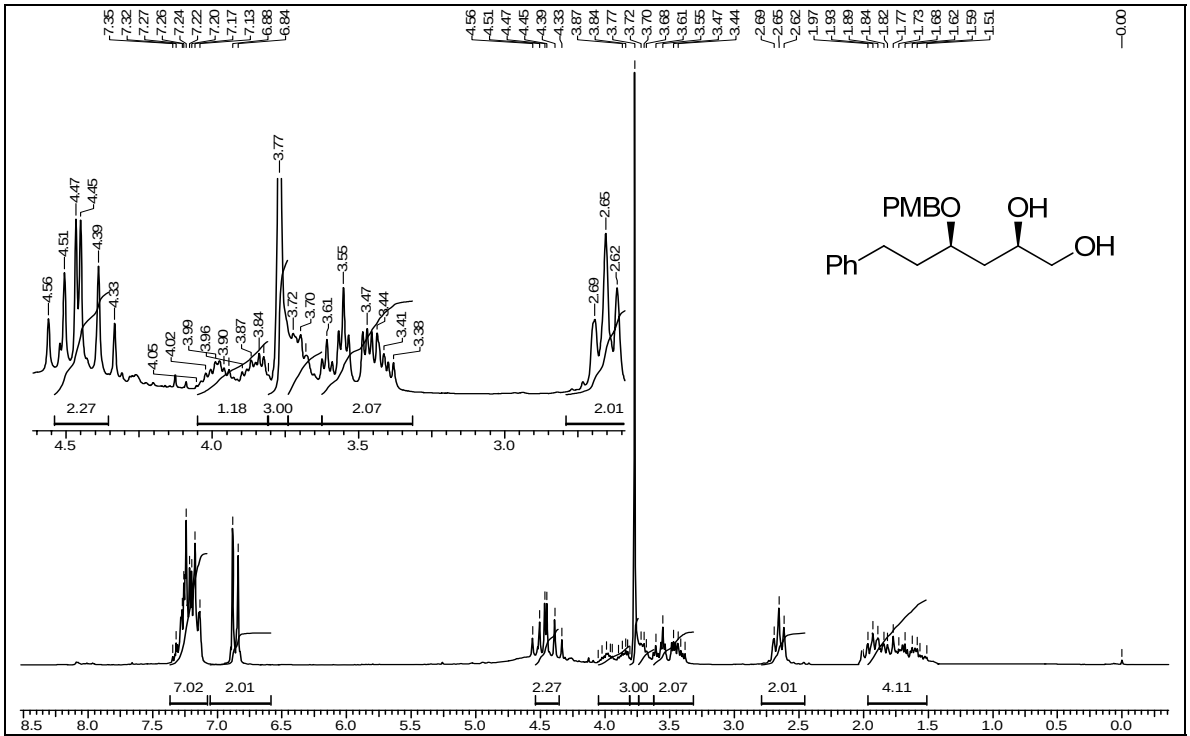
Dept NMR spectrum of the compound **14** in $CDCl_3$



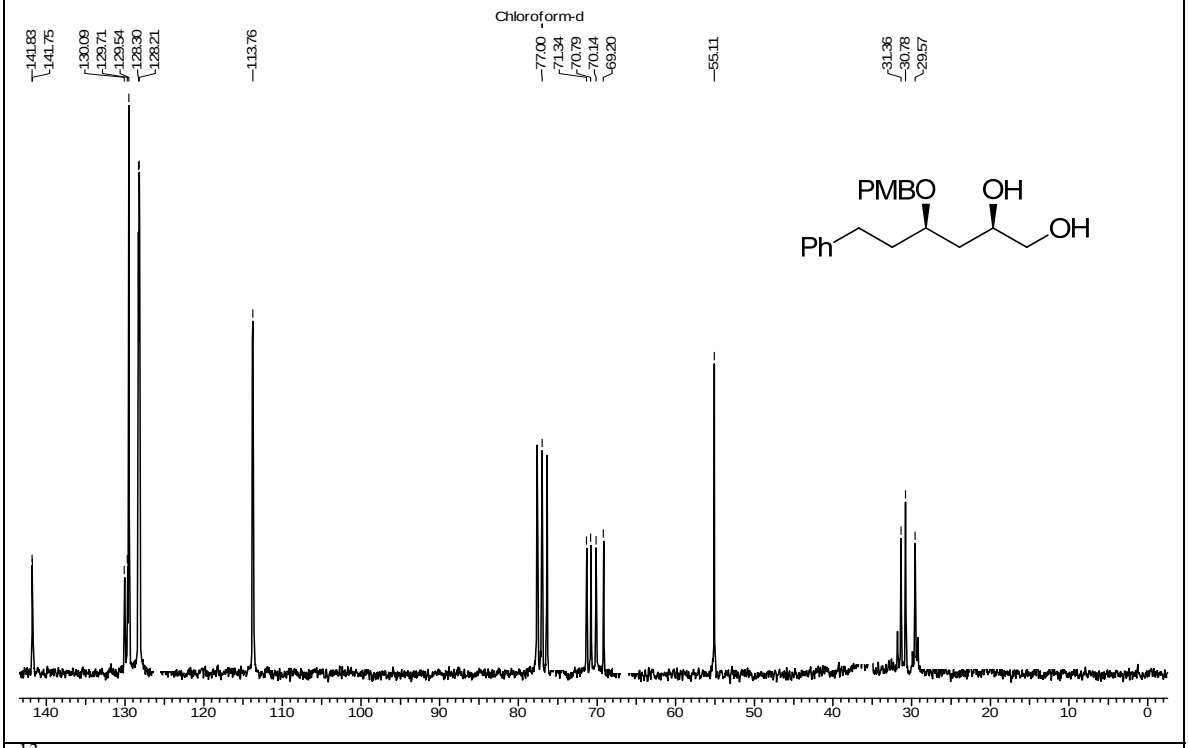
^{1}H NMR spectrum of the compound **15** in $CDCl_3$



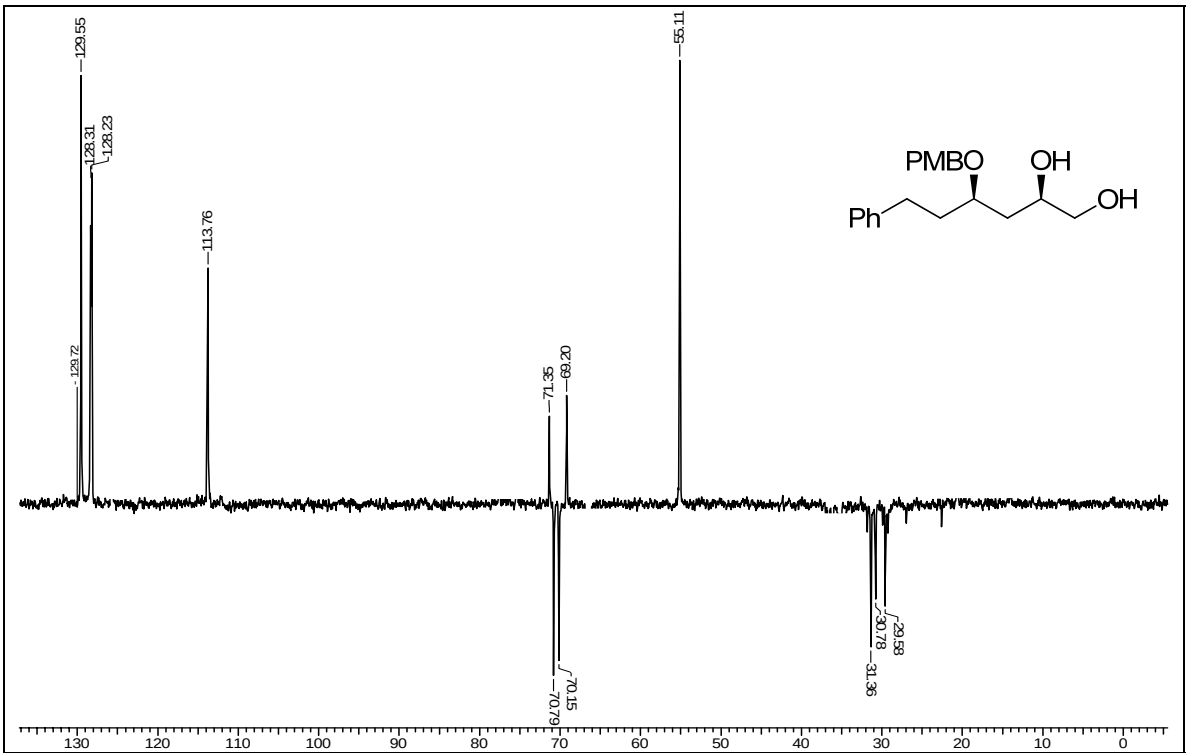
^{13}C NMR spectrum of the compound **15** in $CDCl_3$



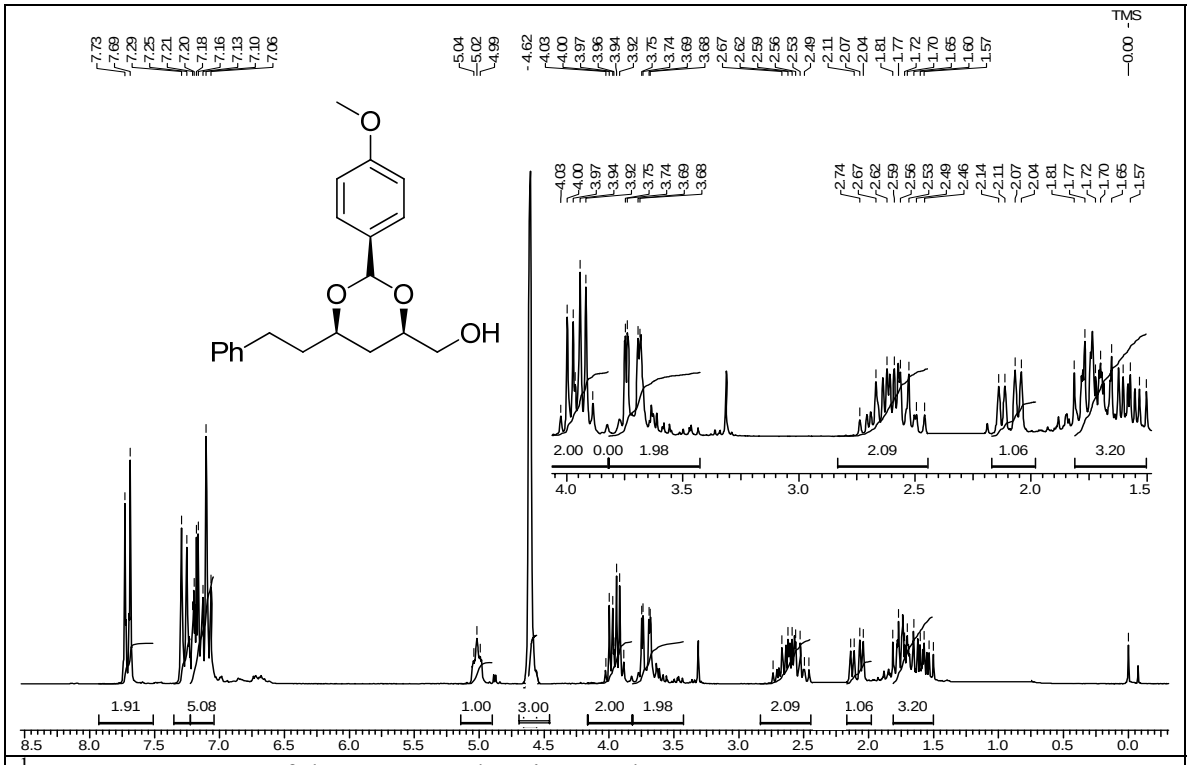
^{1}H NMR spectrum of the compound **16** in $CDCl_3$



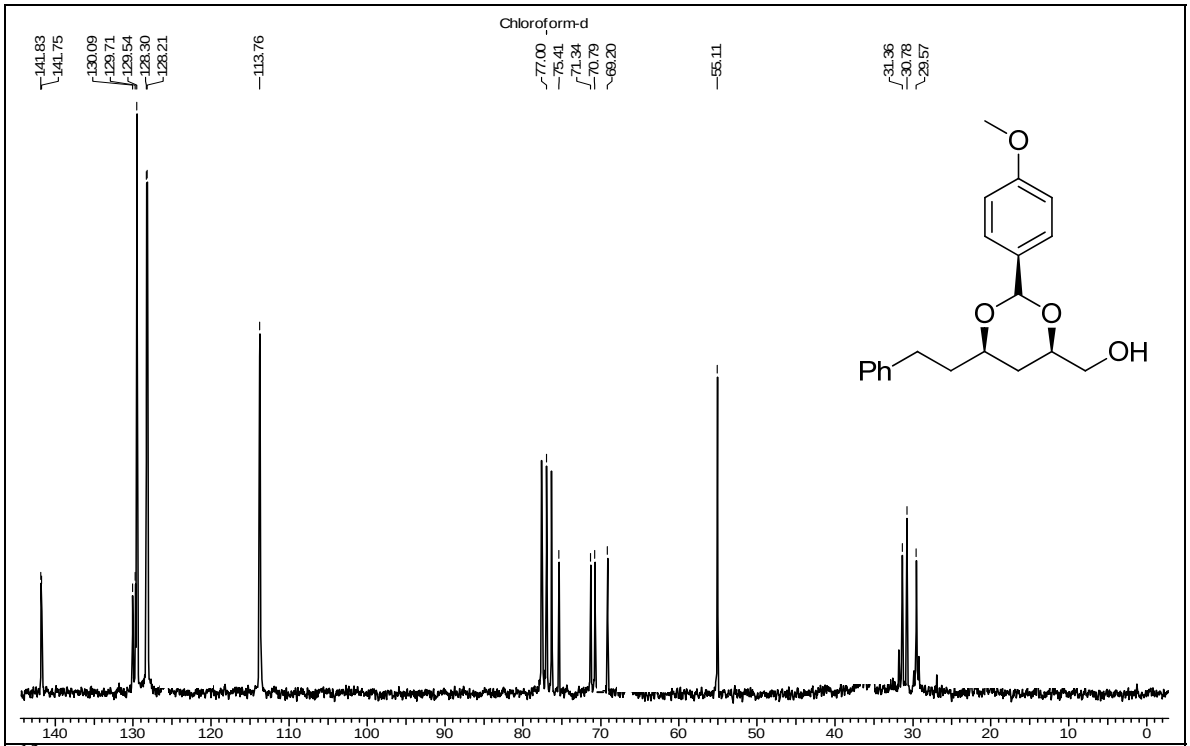
^{13}C NMR spectrum of the compound **16** in $CDCl_3$



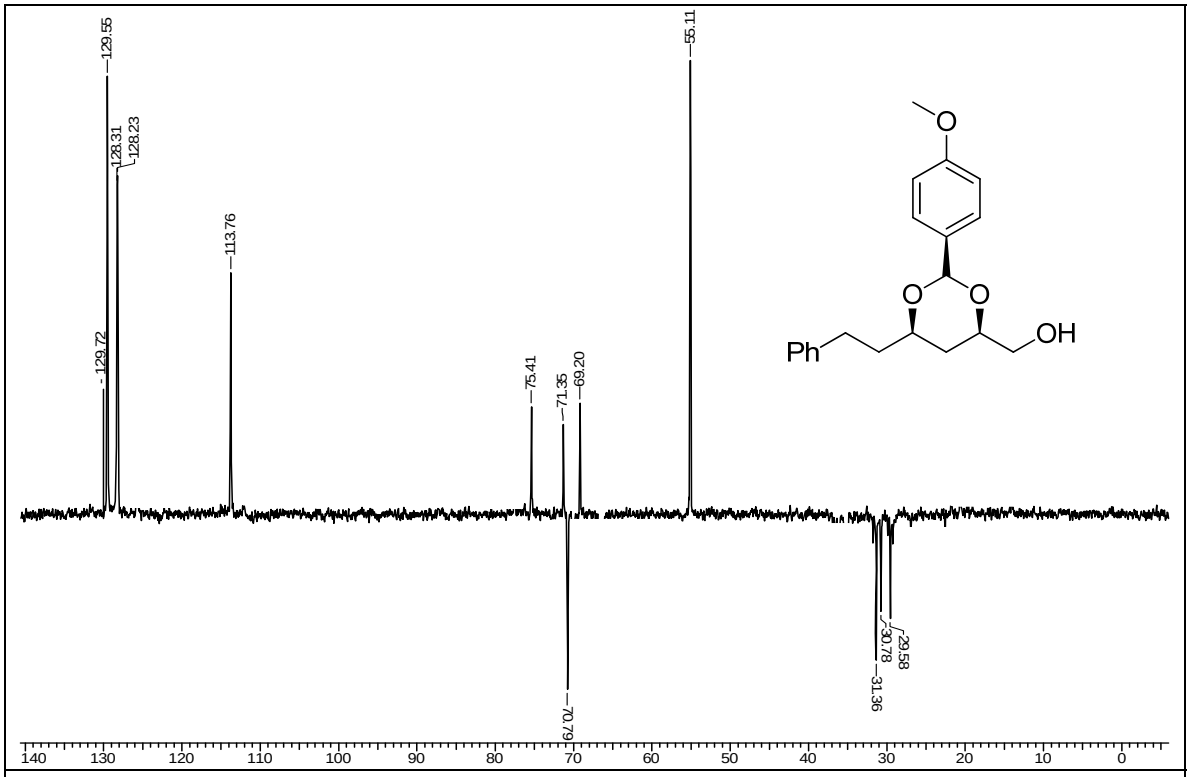
Dept NMR spectrum of the compound **16** in $CDCl_3$



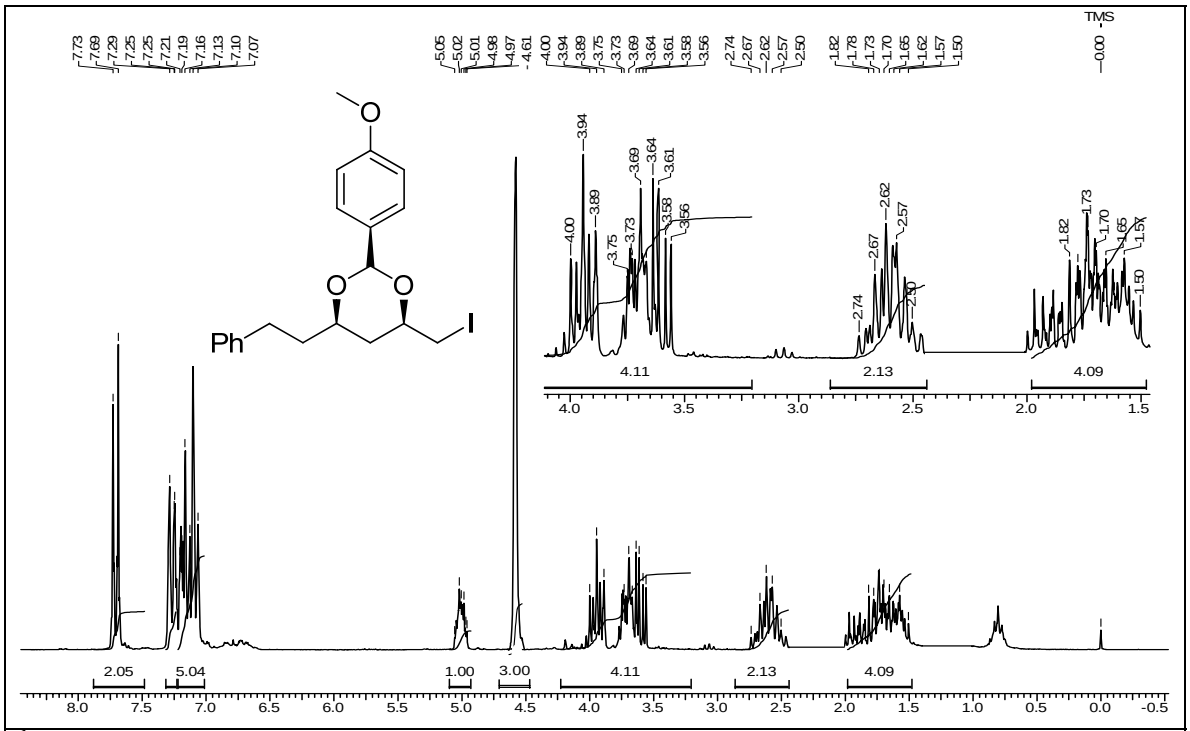
^{1}H NMR spectrum of the compound **17** in $CDCl_3$



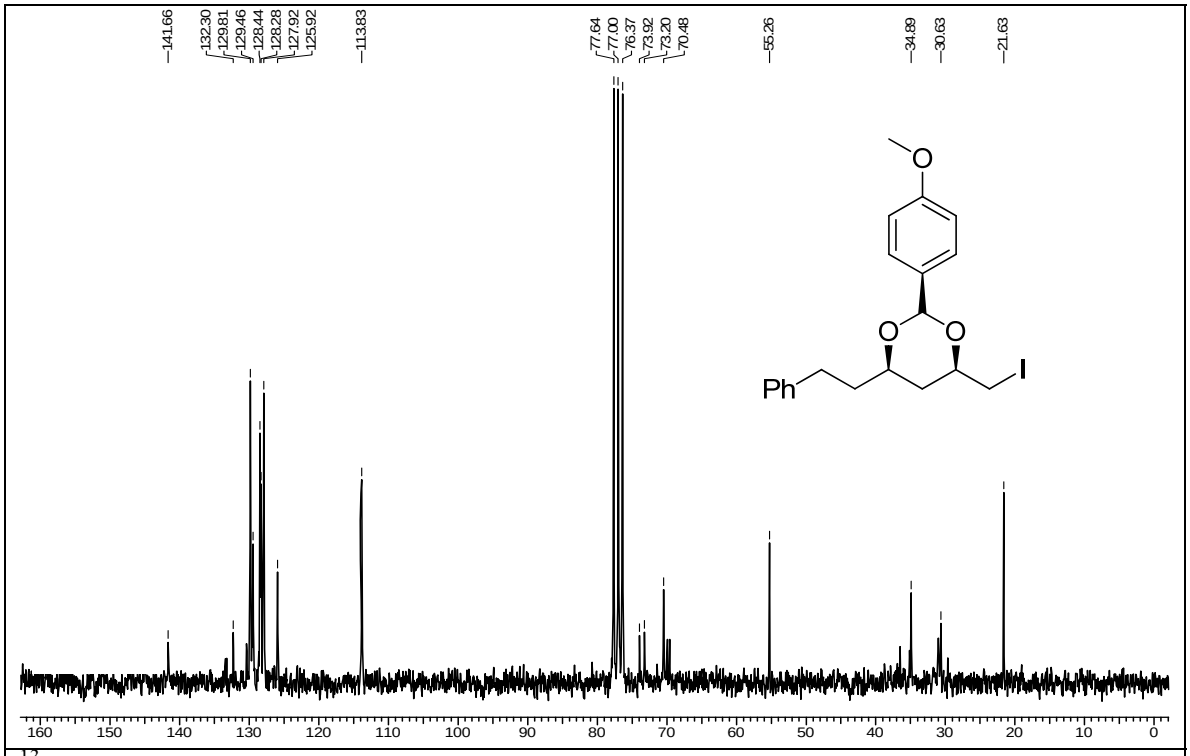
^{13}C NMR spectrum of the compound **17** in $CDCl_3$



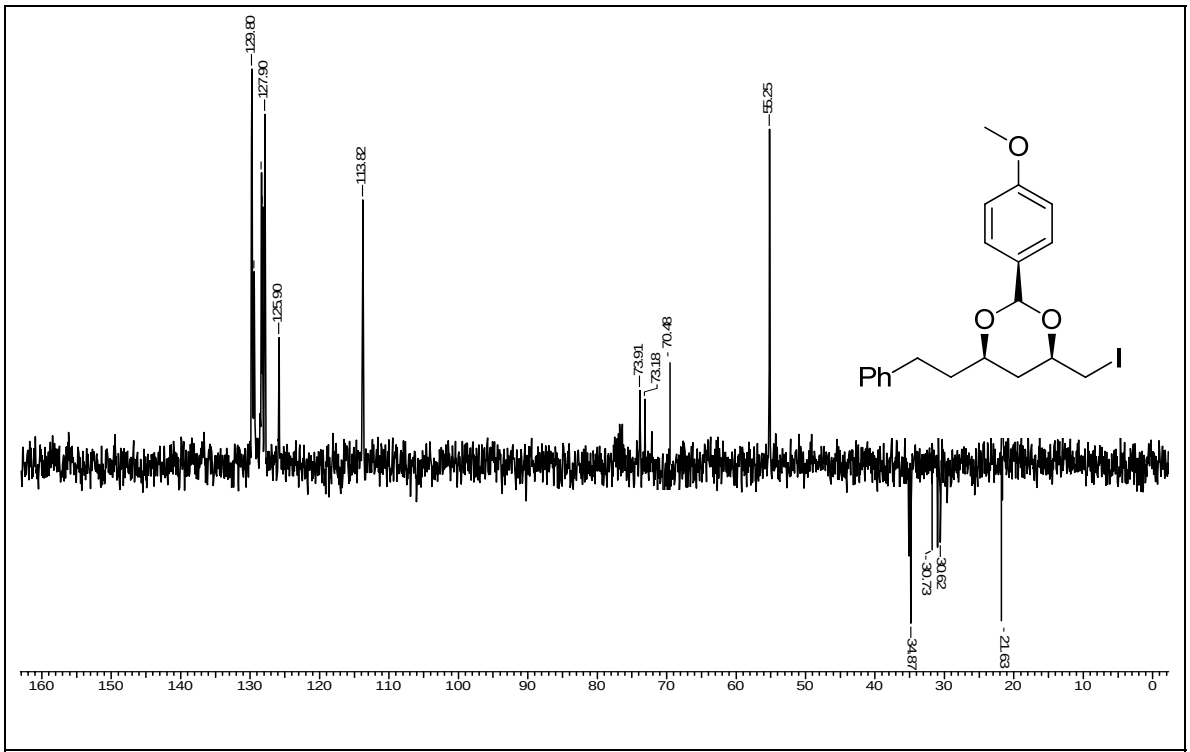
Dept NMR spectrum of the compound **17** in $CDCl_3$



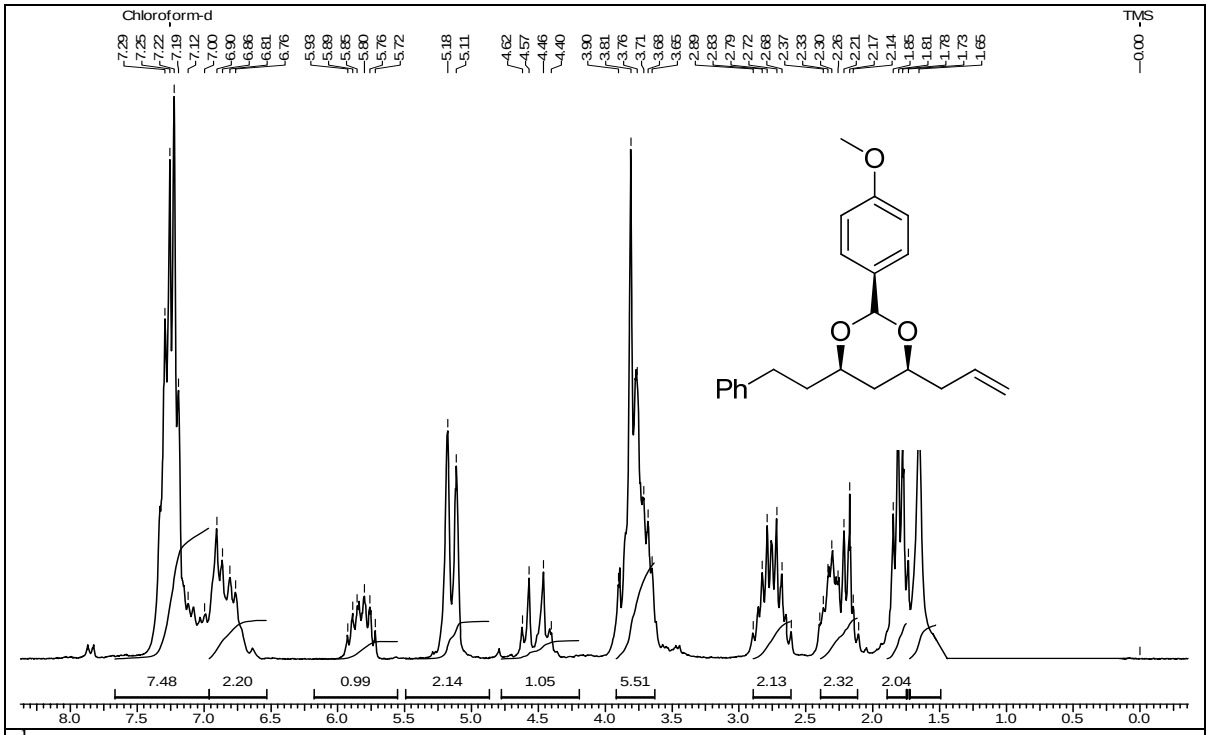
^{1}H NMR spectrum of the compound **18** in $CDCl_3$



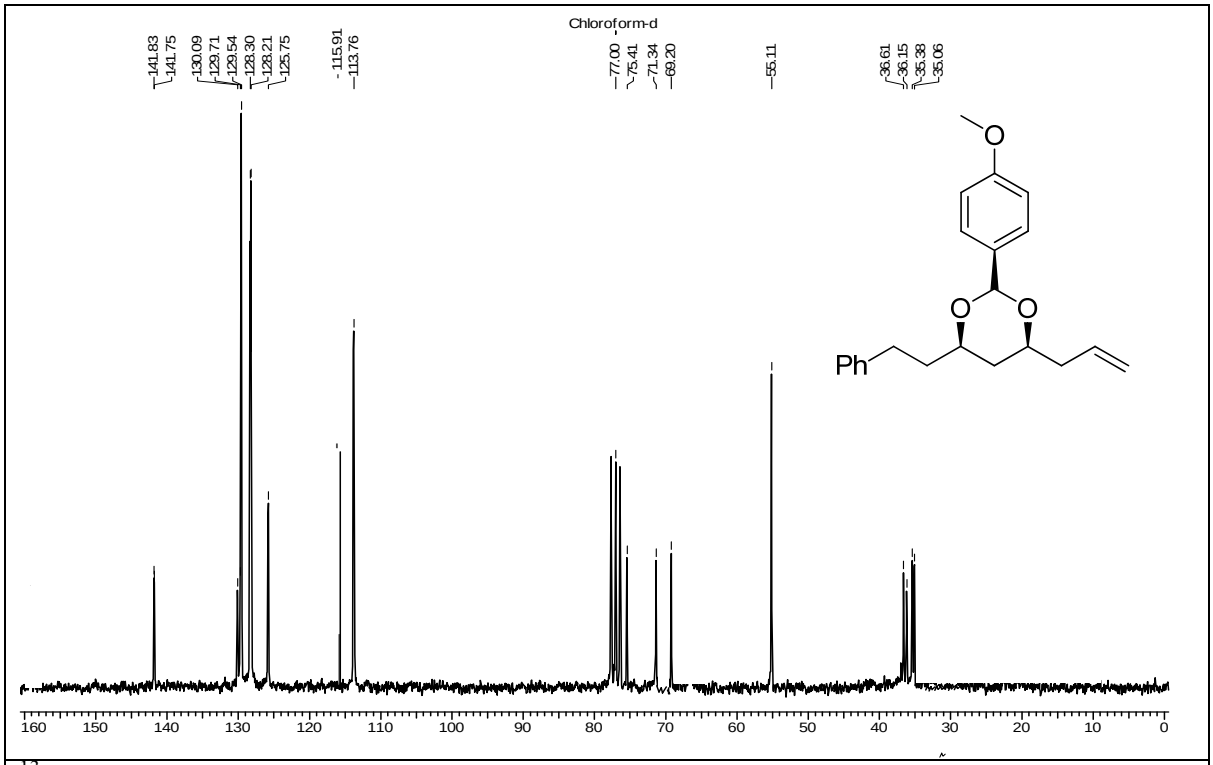
^{13}C NMR spectrum of the compound **18** in $CDCl_3$



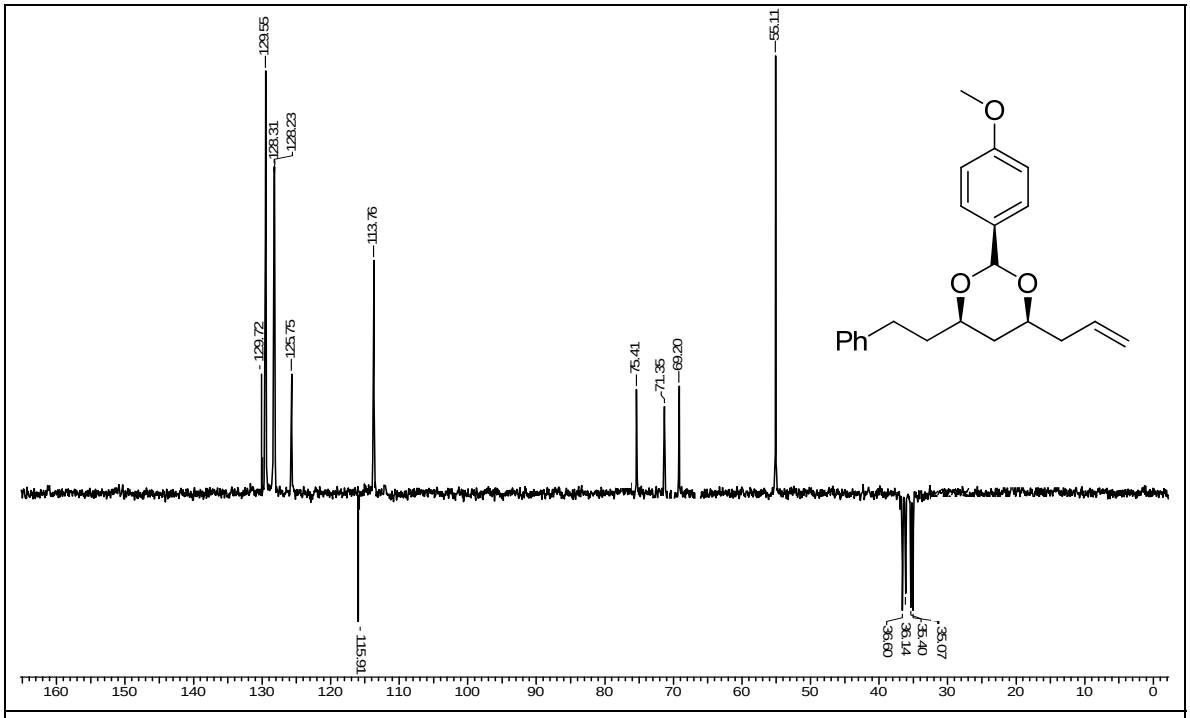
Dept NMR spectrum of the compound **18** in $CDCl_3$



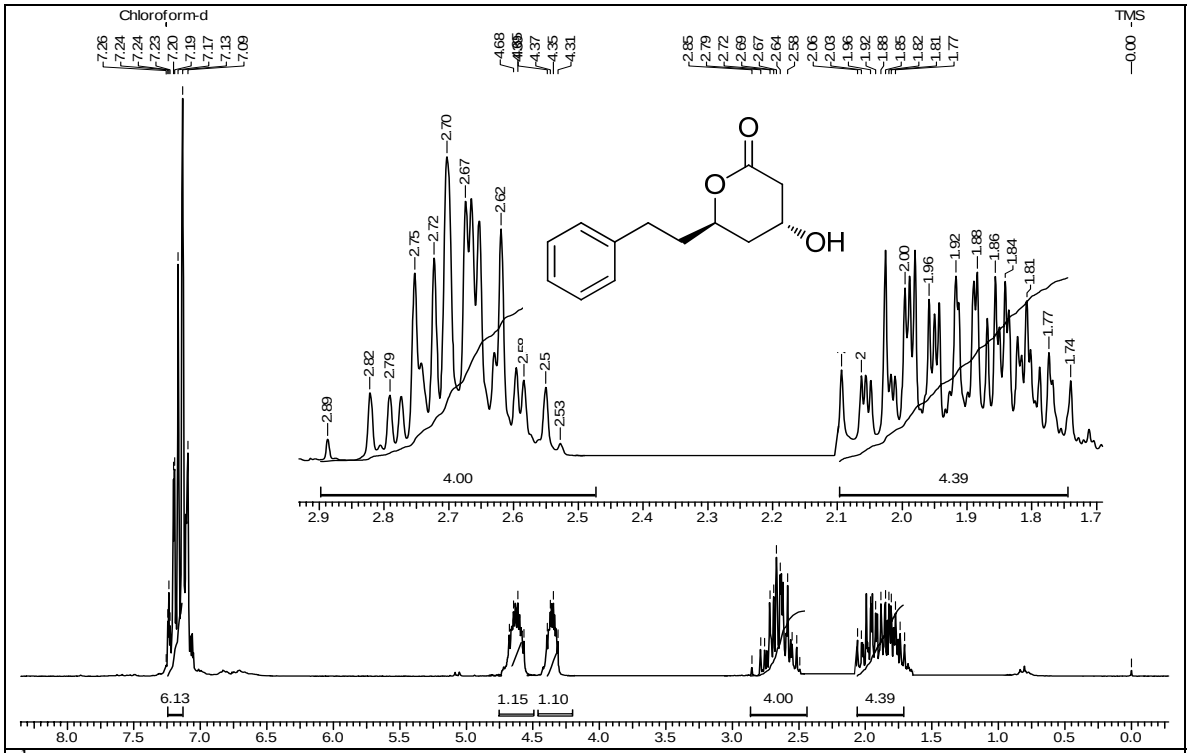
^{1}H NMR spectrum of the compound **19** in $CDCl_3$



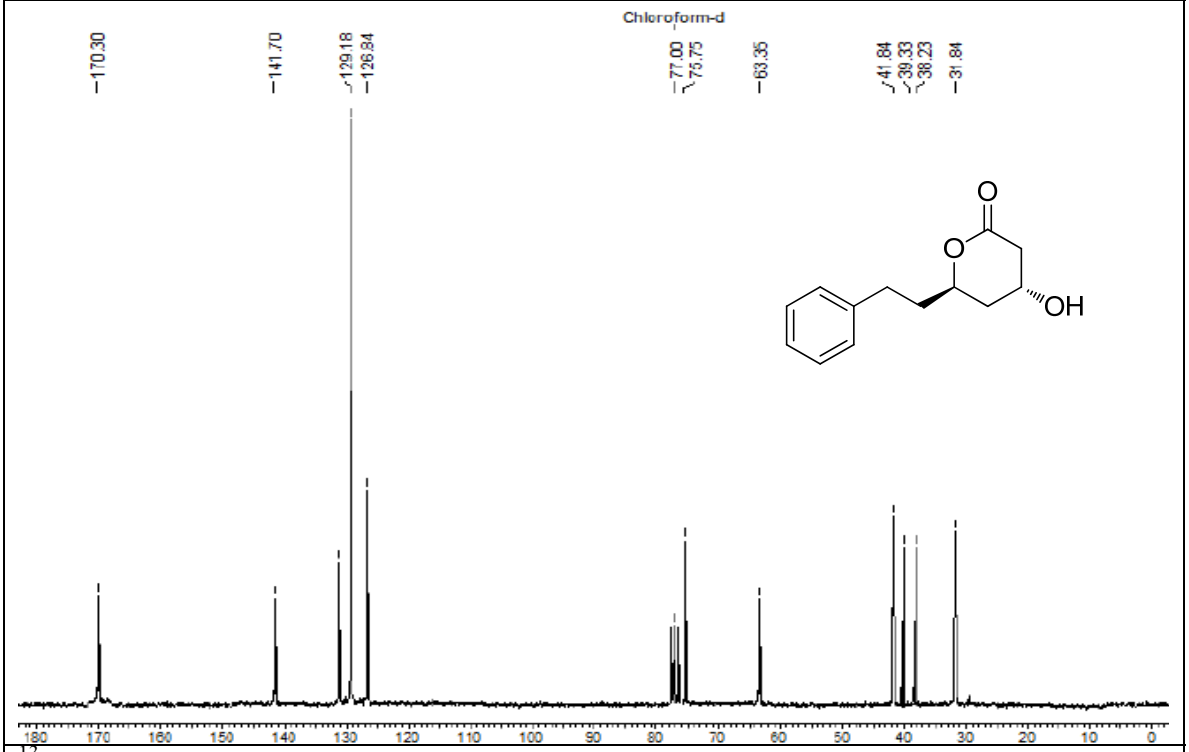
^{13}C NMR spectrum of the compound **19** in $CDCl_3$



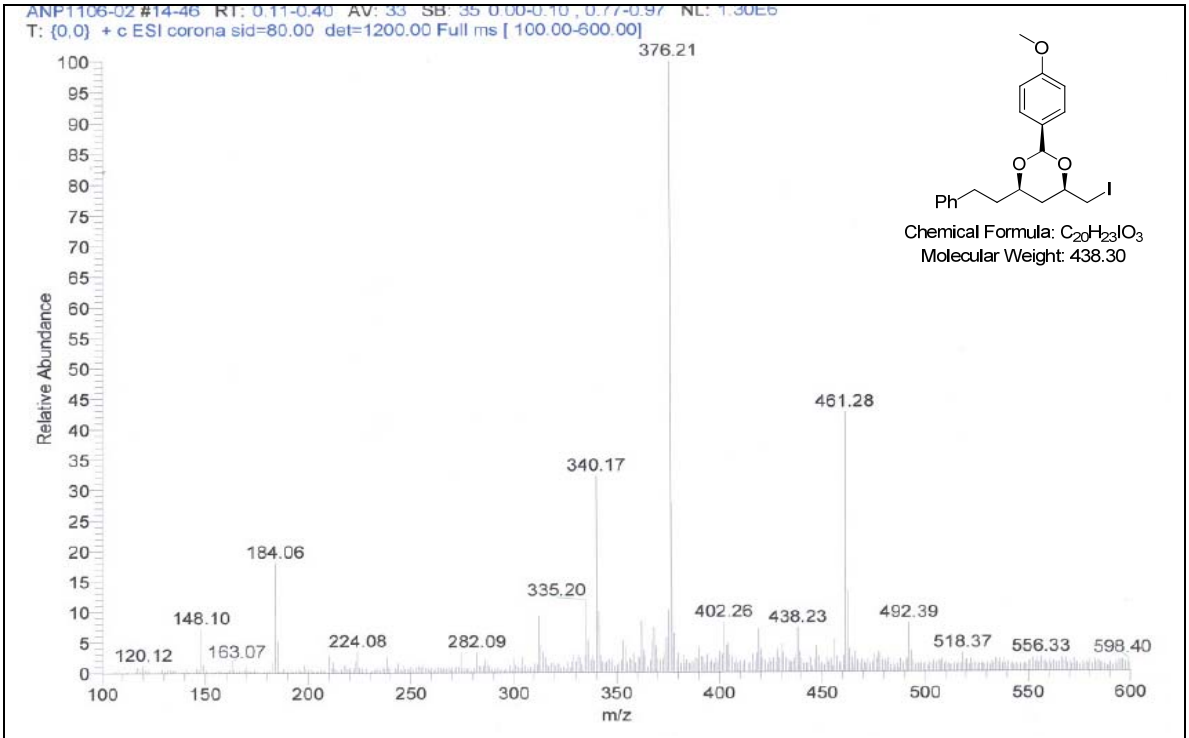
Dept NMR spectrum of the compound **19** in $CDCl_3$



^{1}H NMR spectrum of the compound **8** in $CDCl_3$

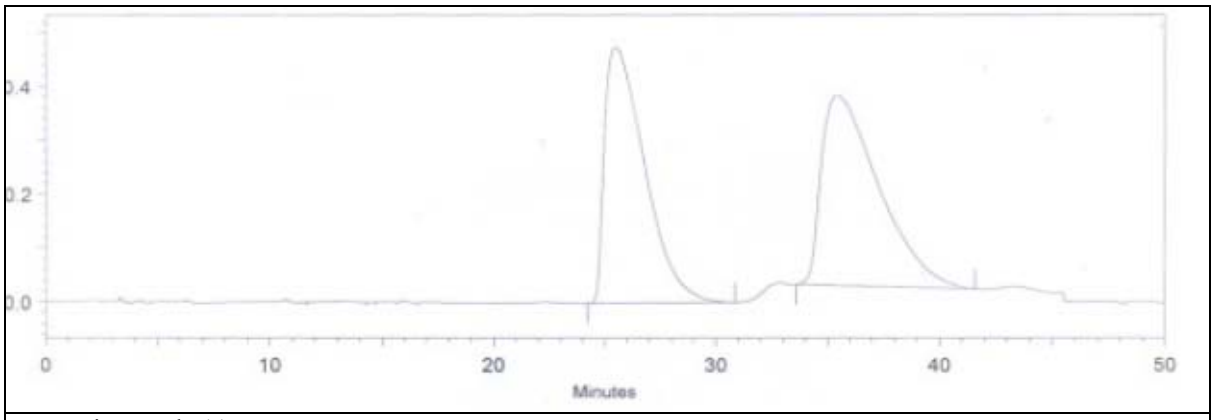


^{13}C NMR spectrum of the compound **8** in $CDCl_3$



LCMS Chartof the compound **18** (M+Na)

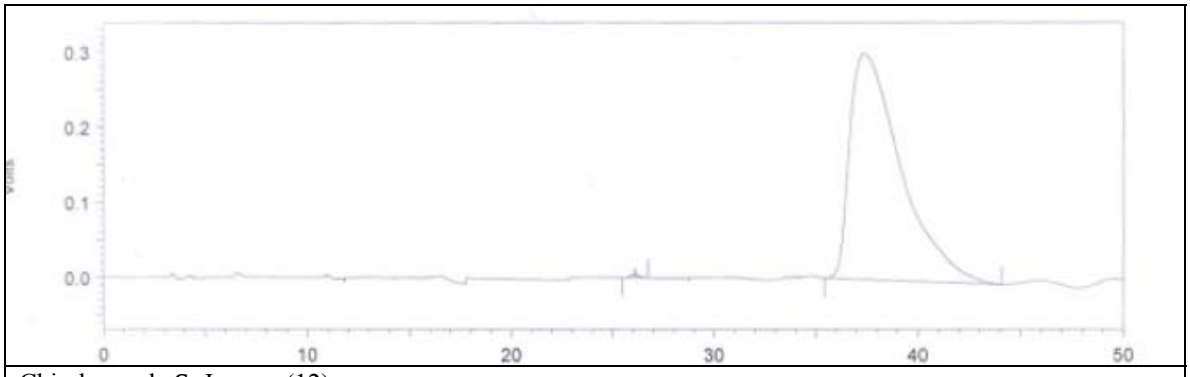
Chiral HPLC Analysis of compound 11, 12 and 14:



Racemic sample 11

Pk #	Retention Time	Area	Area %
1	25.492	59564560	48.59
2	35.417	63013806	51.40

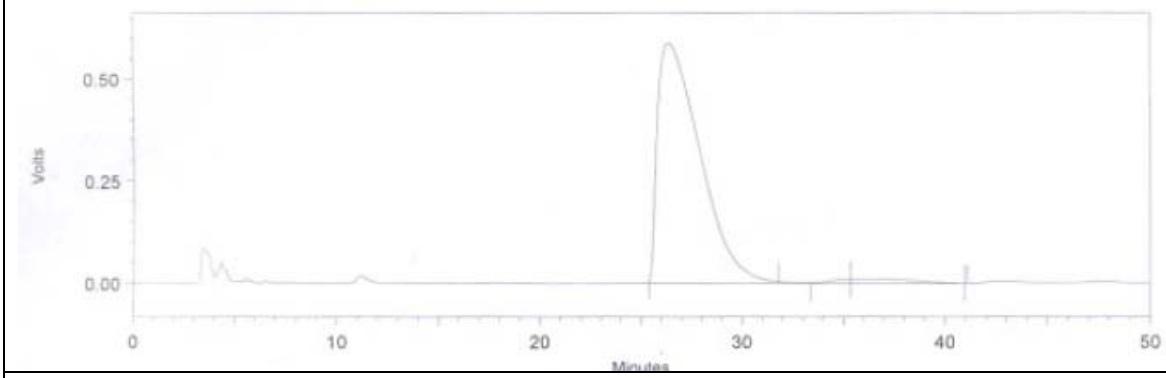
Column	: Chiracel OD (250 x 4.6 mm)
Mobile phase	: IPA + Hexane (10:90)
Wavelenth	: 220 nm
Flow	: 0.5 mL/min
Concentration	: 1.00 mg/1.0 mL mobile phase
Injection vol.	: 20 µL



Chiral sample **S-** Isomer (12)

Pk #	Retention Time	Area	Area %
1	26.117	116173	0.221
2	37.383	52347948	99.79

Column	: Chiracel OD (250 x 4.6 mm)
Mobile phase	: IPA + Hexane (10:90)
Wavelenth	: 220 nm
Flow	: 0.5 mL/min
Concentration	: 1.00 mg/1.0 mL mobile phase
Injection vol.	: 20 µL



Chiral sample **R-** Isomer (14)

Pk #	Retention Time	Area	Area %
1	26.358	85856046	96.976
2	35.067	656977	0.742

Column	**:** Chiracel OD (250 x 4.6 mm)
Mobile phase	**:** IPA + Hexane (10:90)
Wavelenth	**:** 220 nm
Flow	**:** 0.5 mL/min
Concentration	**:** 1.00 mg/1.0 mL mobile phase
Injection vol.	**:** 20 µL

3.3.6. References

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2. (a) Endo, A. J. Med. Chem. 1985, 28, 401- 405; (b) Vega, L.; Crundy, S. J. Am. Med. Assoc. 1987, 257, 33–38 and references cited therein.
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