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SYNTHETIC STUDIES TOWARDS D(+)-BIOTIN AND DEVELOPMENT OF OTHER USEFUL SYNTHETIC METHODOLOGIES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

BY

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NOVEMBER 2005

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CERTIFICATE

Certified that the work incorporated in the thesis entitled ***"Synthetic Studies Towards D(+)-biotin and Development of Other Useful Synthetic Methodologies"*** submitted by **Guduru Ramakrishna** was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

November, 2005
National Chemical laboratory,
Pune-411008

Dr. Subhash P. Chavan
Research Supervisor

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DECLARATION

I hereby declare that the thesis entitled ***"Synthetic Studies Towards D(+)-biotin and Development of Other Useful Synthetic Methodologies"*** submitted for Ph.D degree to the university of pune has been carried out at Organic Chemistry: Technology division, National Chemical Laboratory, Pune, under the supervision of Dr. Subhash P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

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Dedicated To My Parents

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Lots of people have touched my life both in happy and trying times and made it better over last 5 years, But there are four people who did that for last 28 years and to whom I owe every thing I am today and everything I might become tomorrow. I thank my parents, bother, Venkat and uncle (LVSR), who shaped me as an Individual I am today. This thesis is a form to pay respect to their attributes.

Finally I thank CSIR, New Delhi, for financial support.

NCL, Pune *G. Ramakrishna*

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General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each section refers to that particular section only.
3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80^{o}C.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz) or **Bruker DRX-500** (125 MHz). Figures in parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Optical rotations were recorded at ambient temperature on **JASCO Dip – 181** digital polarimeter using sodium vapor lamp.
10. Mass spectra were recorded at an ionization energy 70eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), sovent medium, a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
11. Starting materials were obtained from commercial sources or prepared using known procedures.
12. Microanalytical data were obtained using a **Carlo-Erba CHNS-O EA 1108** Elemental analyzer within the limits of accuracy (± 0.4%)

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Ac	Acetyl
acac	acetoacetate
AIBN	2,2-Azobis(isobutyronitrile)
Ar	Aryl
BMS	Boron dimethyl sulfide
Bu	Butyl
^{t}Bu	*tert*-Butyl
CAN	Ceric ammonium nitrate
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminium hydride
DMAP	*N*,*N*-Dimethyl amino pyridine
DMF	*N*,*N*-Dimethyl formamide
DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
EDC	Ethylene dichloride
Et	Ethyl
HMDS	Hexamethyldisilazane
LDA	Lithium diisopropyl amide
mCPBA	m-Chloroperbenzoic acid
Me	Methyl
Ms	Methane sulfonyl
NCS	*N*-Chlorosuccinamide
NMO	*N*-Methyl morpholine N-oxide
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
Pd/C	Palladized carbon
PPTS	Pyridinium p-toluene sulfonate
Ph	Phenyl
PPh_3	Triphenyl phosphine
p TSA	*p*-Toluene sulfonic acid

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^{i}Pr	Isopropyl
Py	Pyridine
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TBDMSCl	*tert*-Butyldimethylsilyl chloride
Ts	Tosyl
TBHP	*tert*-butyl hydrogen peroxide
TBTH	tri-n-butyltin hydride
TMSOTf	Trimethylsilyl triflate
TBSOTf	t-Butyldimethylsilyl triflate

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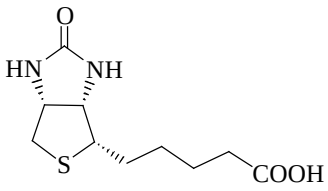
Abstract

The thesis entitled **"Synthetic Studies Towards D(+)Biotin and Development of Other Useful Synthetic Methodologies"** is devided in to two chapters.

Chapter 1: Deals with general introduction, recent reports of (+)-biotin and attempted methods toward (+)-biotin which culminated in the synthesis of (+)-biotin and is devided in to two sections.

Chapter 2: Constitutes the general introduction, attempted methods toward synthesis of Salacinol and its analogues, and development of a methodology for Iodocyclisations of β,γ- unsaturated acids and alcohols using Ceric ammonium nitrate/NaI and its application to the synthesis of (-)-wine lactone.

Chapter 1: Synthetic Studies Towards D(+)-Biotin



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(+)-Biotin 1 is one of the water-soluble B-complex vitamins. It plays an important role as a coenzyme in carboxylation reactions related to biochemical processes such as gluconeogenesis and fatty acid biosynthesis. It is widely used in poultry feeds for the rapid growth of chicks and healthy hatching of eggs. The main sources of biotin are liver, kidney, pancreas, yeast, milk and egg yolk. Biotin deficiency in poultry and swine causes series of severe symptoms. These deficiencies are corrected by using biotin as a feed additive. Hence it is a commercially important molecule.

Section-1 Total synthesis of D(+)-biotin: a review

This section presents a general introduction to D(+)-biotin along with brief account about its isolation, biosynthesis and its application in medicine. This section also presents

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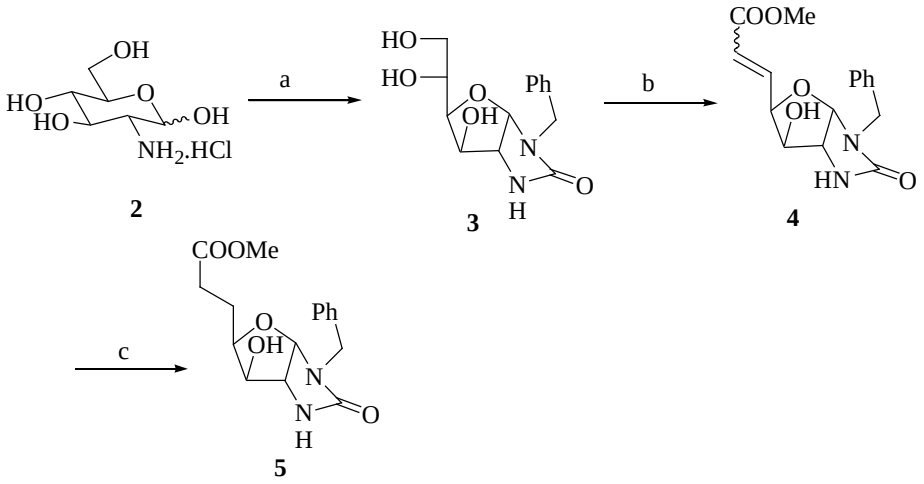
the brief account of some of the important and the recent synthetic approaches toward the synthesis of biotin.

Section-2: Total synthesis of D(+)-biotin using *N*-acyliminium ion chemistry

Use of *N*-acyliminium ions for carbon-carbon bond formation is very well known in the synthesis of biotin. This has led to the development of elegant syntheses of (+)-biotin *via* an intramolecular cyclization by Speckamp and our group to generate the *cis* biotin skeleton with excellent stereocontrol. We have previously shown the intermolecular carbon-carbon bond formation *via* *N*-acyliminium ion on hydroxy imidazolidin-2-ones (monocyclic hemiaminal) and alkoxy imidazolidin-2-one (monocyclic hemiaminalethers)



Scheme 1. Reagents and conditions: a) i) **BnNCO, aq $NaHCO_3$;** ii) **pyridine(cat.), H_2O, 55 °C 82%;** b) i) **$NaIO_4$, acetone: H_2O (9:1), rt, 30 min;** ii) **Ph_3P=CHCOOMe, dichloromethane, rt.;** c) **Pd/C (10%), methanol, rt.**

Our interest in acyliminium ion chemistry led us to explore the reactivity of bicylic hemiaminalethers for carbon-carbon bond formation *via* *N*-acyliminium ion formation. Accordingly we chose glucosamine hydrochloride as a readily available starting material from which the required bicyclic hemiaminalether **3** was prepared in single step by treating glucosamine hydrochloride with BnNCO in the presence of aqueous sodium bicarbonate solution followed by heating the reaction mixture in water in the presence of catalytic amount of Pyridine, in good yield. The diol of bicyclic intermediate **3** was cleaved using sodium metaperiodate followed by two carbon homologation with Wittig ylide furnished

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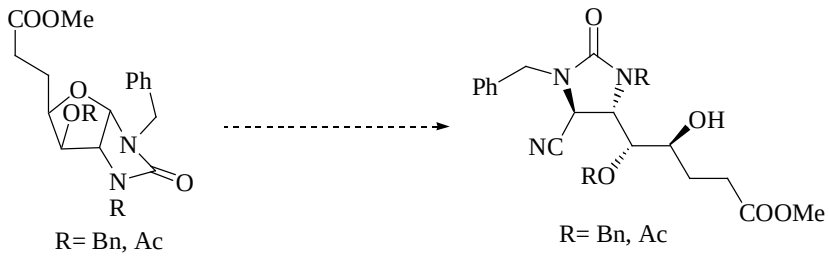
the olefin **4** as a mixture of isomers which on hydrogenation of olefin gave alkylated bicyclic imidazolidin-2-one **5** (Scheme1).

We believed that intermediate **5** is an ideal substrate to compare the reactivity of the monocyclic hemiaminal ethers with acyclic hemiaminals and alkylation leading to intermediate 6 would provide an easy access to biotin skeleton in less number of steps. We envisaged that the hemiaminal oxygen attached to the carbon of the imidazolidin-2-one ring next to nitrogen should have similar reactivity like monocyclic hemiaminal (hydroxyimidazolidin-2-one) thereby facilitating the carbon-carbon bond formation. Unfortunately various attempts of carbon-carbon bond formation using TMSCN on intermediate 5 and derivatives of intermediate 5 under a variety of Lewis acid mediated conditions *viz.* $BF_3.Et_2O$, $TiCl_4$, TMSOTf, $SnCl_4$, etc. proved to be ineffective (scheme 2).

The above sequence of reactions demonstrated the unusual stability of bicyclic hemiaminalether even to the strong Lewis acid conditions, unlike acyclic hemiaminals.

The unusual stability of bicyclic hemiaminalether **5** prompted us to look in to other options available to weaken the carbon-oxygen bond of imidazolidin-2-one ring. We envisaged that this could be achieved in two ways. One way is to convert the oxygen attached to the imidazolidin-2-one as an integral part of the lactone ring which would facilitate the cleavage of the C-O bond of hemiaminalether. The other way is to convert it to enol so that the oxygen attached to imidazolidin-2-one could be in enolic form. This would drive the reaction to ring opening as it is likely to favour the formation of ketone .



Scheme 2.

Accordingly the terminal diol of **3** was protected as the acetonide using acetone and cat. *p*-TSA at room temperature. The product obtained was subsequently protected with benzyl bromide and NaH in DMF to furnish the protected bicyclic intermediate **7** in excellent yields (86%). The acetonide of **7** was unmasked with cat. p-TSA in refluxing

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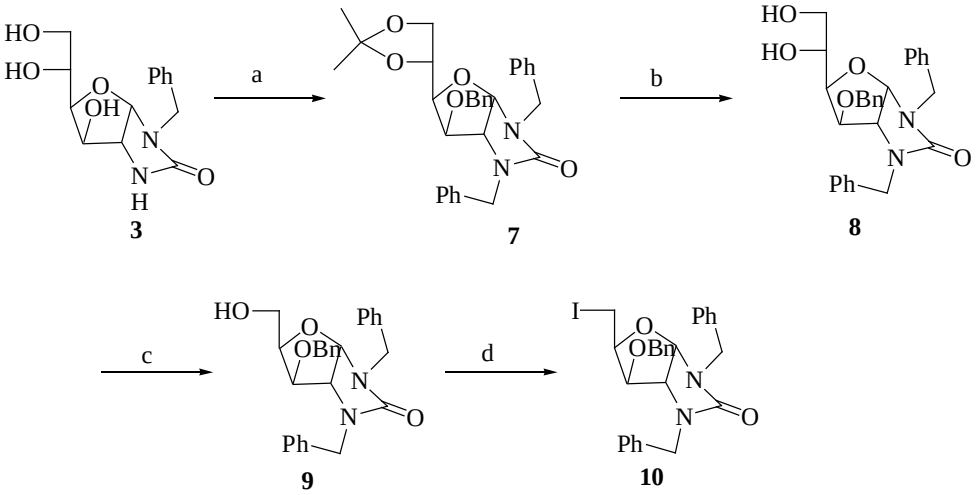
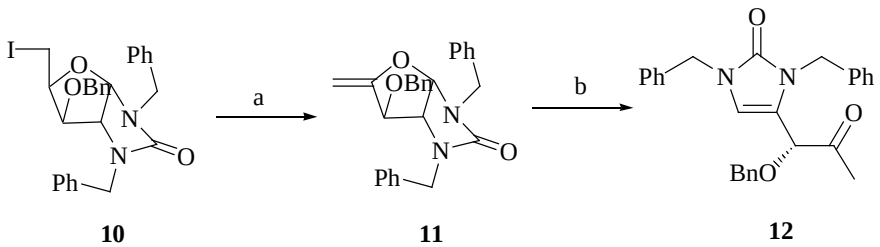
tetrahydrofuran:water (9:1) to furnish the diol **8** in excellent yield (98%). Diol **8** was then cleaved to the aldehyde using sodium metaperiodate in acetone/water (9:1). and was subsequently reduced with sodium borohydride in methanol at room temperature to furnish the alcohol **9** in high yield. (94%). The desired halo compound was obtained by treatment of alcohol **9** under standard conditions TPP-NaI in reluxing toluene in 92% yield.



Scheme 3. Reagents and conditions: a) **i**) p-TSA (cat), acetone, rt; **ii**). NaH, BnBr, DMF, 0 ^{o}C- rt, 6 h, 86% over two steps.; **b**). p-TSA(cat.), THF:H_2O (9:1), reflux, 6 h, 98%.; **c**) **i**) $NaIO_4$, acetone: H_2O (9:1), rt, 30 min; **ii**)$NaBH_4$, methanol rt. 94%.; **d**)Ph_3P,I_2, toluene, reflux. 92% .

The halo compound **10** was then subjected to dehydrohalogenatuion by base catalysed deprotonation using DBU in refluxing toluene to furnish enol ether **11** in 80% yield. As per the planned synthetic route the enol ether was subjected to the Lewis acid mediated ring opening in the presence of nucleophile TMSCN expecting the carbon-carbon bond formation on imidazolidin-2-one ring. Unfortunately various attempts to realize carbon-carbon bond formation resulted only in the eliminated product 12 (Scheme 4).



Scheme 4. Reagents and conditions: a) DBU, toluene, reflux, 80%; **b**) trimethylsilylcyanide, BF_3Et_2O, DCM, -78ºC- rt.

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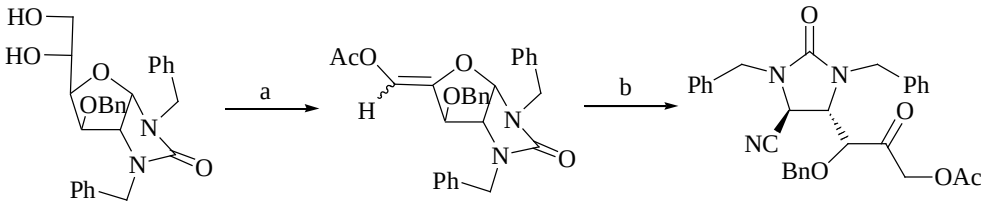
Even though we could not obtain the expected alkylated product, encouraged by the ring opening, and formation of acyliminium ion, we turned our attention to check the feasibility of alkylation on enolacetate **14** which could be obtained in less number of steps as compared to enolether **11.** Thus the aldehyde obtained by cleavage of diol was treated with acetic anhydride, triehtylamine and catalytic DMAP in refluxing ethylenedichloride to furnish the exocyclic enolacetate 1**3** in good yield (83%) over two steps.

Gratifyingly, carbon-carbon bond formation *via* an acyliminium ion was affected by treating the enolacetate **13** with $BF_3.Et_2O$ in the presence of trimethylsilyl cyanide in dichloromethane at -78 ºC to room temperature for 15 min to furnish the cyano substituted imidazolidin-2-one **14** in good yield (62%) as a single diastereomer (scheme 5).



8 **13** **14**

Scheme 5. Reagents and conditions: a) i) $NaIO_4$, acetone: water (9:1), 30 min, **ii**) Ac_2O, Et_3N, DMAP (cat.), EDC, reflux, 4 h, 82%. **b**) TMSCN, $BF_3.Et_2O$, DCM, -78 ^{0}C, rt. 15 min., 62%.

Having attained the key carbon-carbon bond formation, the stage was now set to invert the C-5 proton of imidazolidin-2-one **14** to arrive at requisite stereochemistry of target molecule.The cyano imidazolidin-2-one **14** on reduction with sodium borohydride followed by treatment with trimethylsilychloride in methanol gave the required methyl ester **15** in excellent yield (93% over two steps) as a 1:1 distereomeric mixture. The stereochemistry at C 4 carbon in imidazolidin-2-one **15** that appears as C-2 of the target molecule is to be inverted at certain stage to arrive at requisite stereochemistry of target molecule. Accordingly the diol of **15** was cleaved by using $NaIO_4$ in acetone:water (9:1) to furnish an aldehyde which on subsequent treatment with ethylene glycol and *p*- TSA gave the dioxalane derivative **16** in good yield.(65% over two steps). Selective *O*-debenzylation of **16** was accomplished using Pd-$CaCO_3$ in methanol in excellent yield (93%).Correction of stereochemistry at C-4 of **17** was achieved by epimerization with cat. DBU in refluxing toluene, which on concomitant cyclisation resulted in the formation of lactone. Directly reducing the lactone obtained with sodium borohydride in refluxing methanol furnished the diol **18** in good yield. (86%) over two steps (scheme 6).

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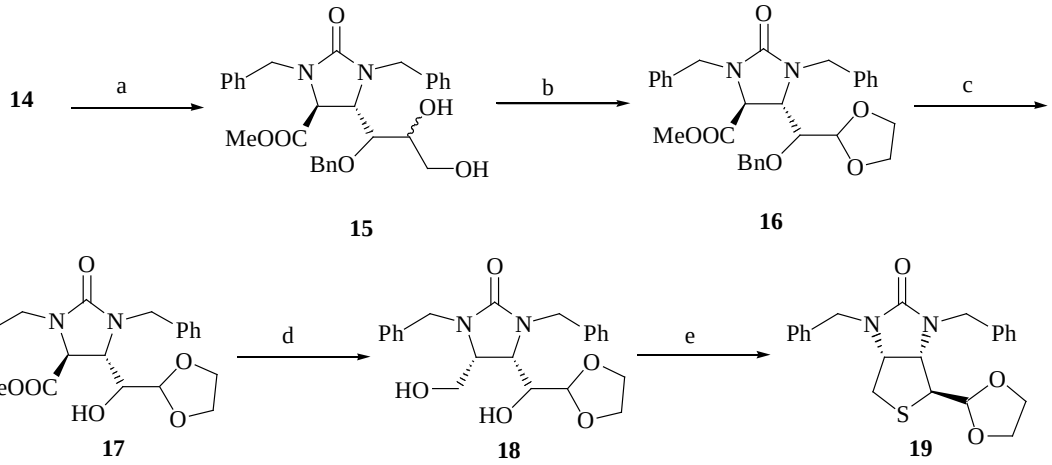
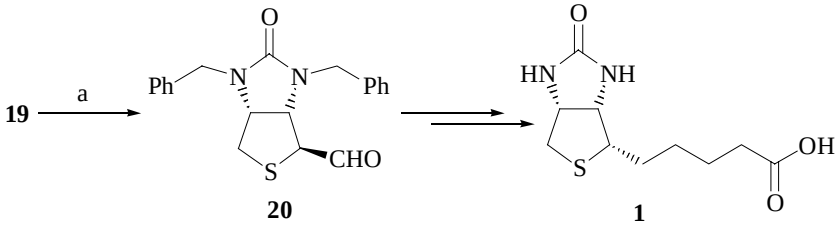


Scheme 6. Reagents and conditions: a) $NaBH_4$, MeOH, 0 ^{0}C to rt, 4 h.; **b**) TMSCl, MeOH, 40 ^{0}C, 4 h, 93% over two steps; **c**) **i**) $NaIO_4$, acetone: water (9:1), rt, 30 min; **ii**) ethylene glycol, p-TSA, C_6H_6, reflux, 6 h, 65% over two steps.; **d**) Pd-$CaCO_3$, MeOH, rt, 24 h, 95%.; **e**) DBU (cat), toluene, reflux, 24 h.; **f**) $NaBH_4$, EtOH, reflux, 2 h, 86% over two steps.; g) **i**) MsCl, Et_3N, DMAP(cat.), 0 ^{0}C to rt, 4 h, 74%.; **ii**) Na_2S, DMF, 100 ^{0}C, 2 h, 78%.

Sullfur was introduced in to the system by sulfonylating both the primary and secondary hydroxyl groups of **18** with mesyl chloride in the presence of triethylamine and subsequent treatment with sodium sulfide in DMF to give the tetrahydro-thienoimidazolidin-2-one **19** in good yield (73%).



Scheme 7. Reagents and conditions: a) 6N HCl, CH_3COOH, rt, 24 h, 82%

The dioxalane of the tetrahydro-thienoimidazolidin-2-one **19** was unmasked using 6N HCl in acetic acid at room temperature for 24h to furnish the aldehyde **20** in good yield (80%). The aldehyde **20** was readily converted to biotin (scheme 7).

Chapter 2: Studies Toward Synthesis of Salacinol and Devolepment of Useful Synthetic Methodologies.

Section 1: Studies Toward Synthesis of Salacinol

This section gives the brief account of isolation, its biological importance and the literature reports on the synthesis of salacinol and formal total synthesis of salacinol.

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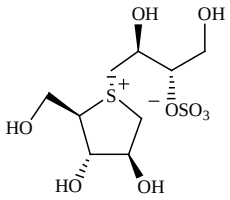
About 40 years have passed since the classical glycosidase inhibitor, nojirimycin was discovered from the cultured broth of the *Streptomyces* species. Since then, over one hundred glycosidase inhibitors have been isolated from plants and micro-organisms. Glycosidases are involved in the biosynthesis of the oligosaccharide chains and quality control mechanisms in the endoplasmic reticulum (ER) of the *N*-linked glycoproteins. Inhibition of these glycosidases can have profound effects on quality control, maturation, transport, and secretion of glycoproteins and can alter cell-cell or cell-virus recognition processes. This principle is the basis for the potential use of glycosidase inhibitors for viral infection, cancer, and genetic disorders.



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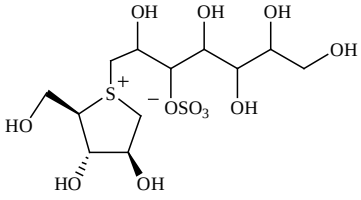

22

Salacinol **21** and kotalanol **22** are α-glucosidase inhibitors isolated from the Hippocrateaceae plant Salacia reticulata. WIGHT, is a large woody climbing plant widespread in SriLanka and South India. Extracts of this plant have been traditionally used in the Ayurvedic system of Indian medicine as a treatment for non-insulin-dependent diabetes. In view of both its very high glycosidase inhibitory activity and its novel structure, chemists have conducted much research on the total synthesis of **21** and its analogues. As the absolute configurations of the kotalanol **22** side chain have not yet been established, all the work has focused on salacinol.

Synthesis of Salacinol.

The thioarabinitol fragment was synthesized by simple alkylation of mono aldehyde **27** with metal alkyls. Thus D-threitol derivative **34** was prepared from D-diethyl tartrate **23** by methoxymethylation [MOMC1, ***(****i*-Pr)$_2$NEt, CHC1$_3$] followed by LiAlH$_4$ reduction to give **24** in 94% overall yield. Mono TBS protection of **24** was effected by treatment with 1 equiv of TBDMSCl in the presence of a sodium hydride in THF to furnish **26** in 94% yield, which was then subjected to Swern oxidation [(COCl)$_2$, Me$_2$SO, Et$_3$N] to give aldehyde **27** in 95% yield(scheme8).

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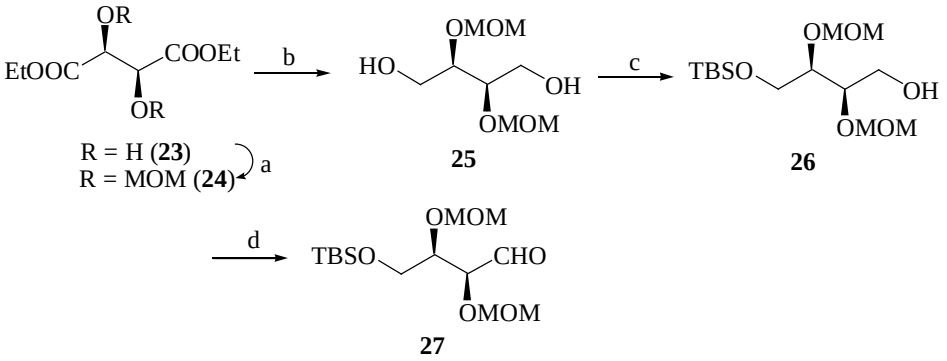
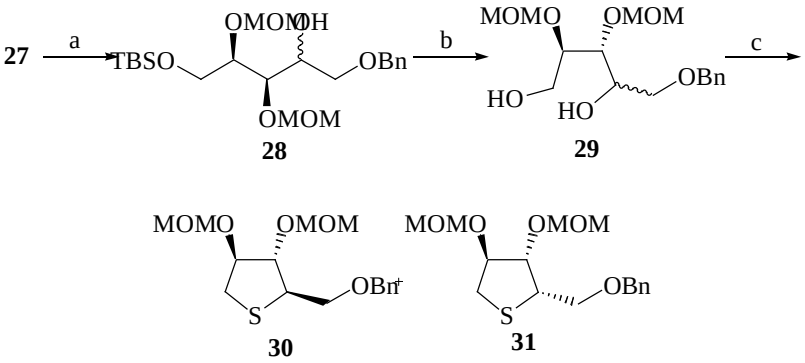


Scheme 8. Reagents and conditions: a) MOMC1, **(i**-Pr)$_2$NEt, CHC1$_3$, 60 ºC, 36h, **b**) LiAlH$_4$, THF, rt., 12h, 94%; **c**) NaH, TBSCl, THF, rt. 1h, 74%; **d**) (COCl)$_2$, Me$_2$SO, Et$_3$N, CH$_2$Cl$_2$, -78 ºC, 95%.

Treatment of the aldehyde **27** with (Benzyloxymethyl)tributyl stannane in the presence of BuLi to yield the alkylated pentitol **28** in 65% yield as an inseperable mixture of diastreoisomers (scheme 9). Deprotection of TBS ether of **28** was effected with *tetra n*-butylammoniumfluoride in THF in 90% yield. The unmasked diol **29** was protected as dimesylate derivative with methane sulfonyl chloride in the presence of triethylamine which on subsequent treatment with sodium sulfide in DMF at 100 °C gave the protected thioarabinitol **30** and **31** in 86% yield over two steps (Scheme 9). The mixture of isomers were separated using flash column chromatography to obtain **30** in 42% yield as first fraction from column chromatography, which was used for the synthesis of salacinol **22**.



Scheme 9. Reagents and conditions: a) BnOCH$_2$SnBu$_3$, BuLi, THF, -78 ºC 15min.; **b**) TBAF, THF, rt., 1h, 92%. **c**) **i**) MsCl, Et$_3$N, CH$_2$Cl$_2$, 1h. **ii**) Na$_2$S, DMF, 100 ºC 2h, 86% over two steps.

The methoxymethyl ethers and Benzyloxy ether was deprotected in one pot by treating thioarabinitol **39** with BCl$_3$ in DCM at -78 ºC to furnish the tiol **42** in 37% yield. (scheme 10).

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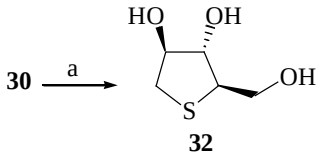
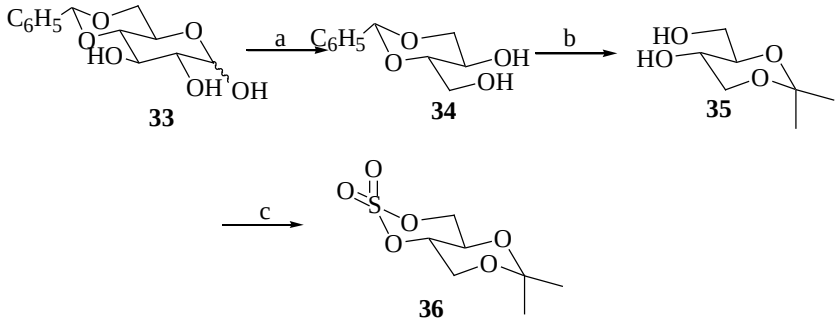


Scheme 10. Reagents and conditions: a) BCl_3; DCM; -78 ºC; 37%

We synthesized the protected D-erythritol cyclic sulfate from 4,6-O-benzylidene-D-glucose by a modified procedure. 4,6-O-benzylidene-D-glucose **33** was oxidized with sodium metaperiodidate followed by reduction with $NaBH_4$ in one pot to furnish the diol **34** in very high yield (92%). The diol **34** was protected as acetonide and then subjected to hydrogenolysis over Pd/C to furnish the diol **35** in 84% yield from **34.** The diol **35** was treated thionyl chloride in the presence of triethylamine followed by oxidation with Sodium metaperiodate in the presence of Ruthenium trichloride to furnish cyclic sulfate **36** in 80% yield (scheme11).



Scheme 11. Reagents and conditions: a) $NaIO_4$, $NaHCO_3$, H_2O, rt then $NaBH_4$, H_2O/EtOH, rt; **b**) **i**) $CH_3(OCH_3)C]CH_2$, TsOH, DMF, 0 ºC; **ii**) H_2, Pd/C, EtOH, rt. **c**) $SOCl_2$, anh. NEt_3, CH_2Cl_2, 0 ºC then $RuCl_3$, $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$, rt.

Coupling of both the fragments **32** and **36** can be achieved by warming both the fragments in DMF at 45 ºC to furnish **37** which on treatment with 0.01% HCl would give salacinol (scheme12).thus constituiting the formal total synthesis of salacinol.

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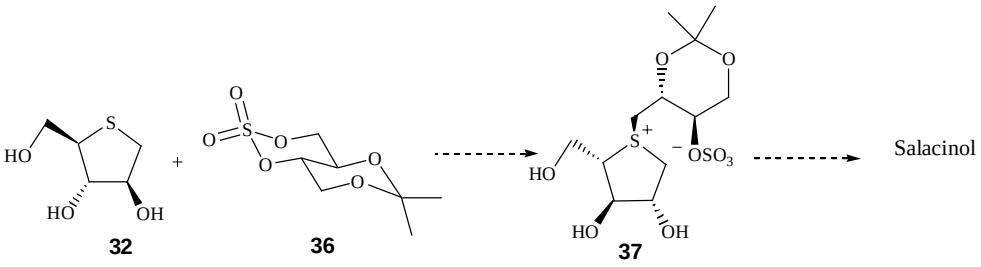
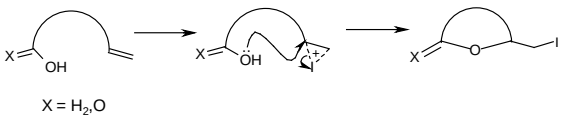


Scheme 12.

Section-4: $(NH_4)_2Ce(NO_3)_6$ (CAN) / NaI as an Efficient Reagent in Iodocyclisations: Synthesis of (-)-Wine lactone.

Part I: $(NH_4)_2Ce(NO_3)_6$ (CAN) / NaI as an Efficient Reagent in Iodocyclisations

Scheme 13



The simple addition of electrophilic reagents to double bonds is one of the conceptually important and synthetically useful processes in organic chemistry resulting in the development of many novel reaction protocols. Reactions performed using Iodine as an electrophile has been known for long time. Different reagents and conditions have been adopted for the efficient conversion of β, γ or γ, δ-unsaturated acid/ alcohol to the corresponding lactones/ethers (scheme 13). Quest for mild conditions to effect these transformations led us to explore the utility of Ceric ammonium nitrate (CAN) as an oxidizing agent The generality and the ease of reaction is demonstrated in this section.

Part II: Synthesis of (-)-Wine lactone.

This part describes the diastereoselective and short (4 steps) synthesis of (-)-wine lactone involving a novel iodolactonization protocol, starting with (+)-Isolimonene, which is abundantly available in nature. isolimonene has the requisite number of carbon atoms as that of wine lactone with the isopropenyl group strategically placed in the desired

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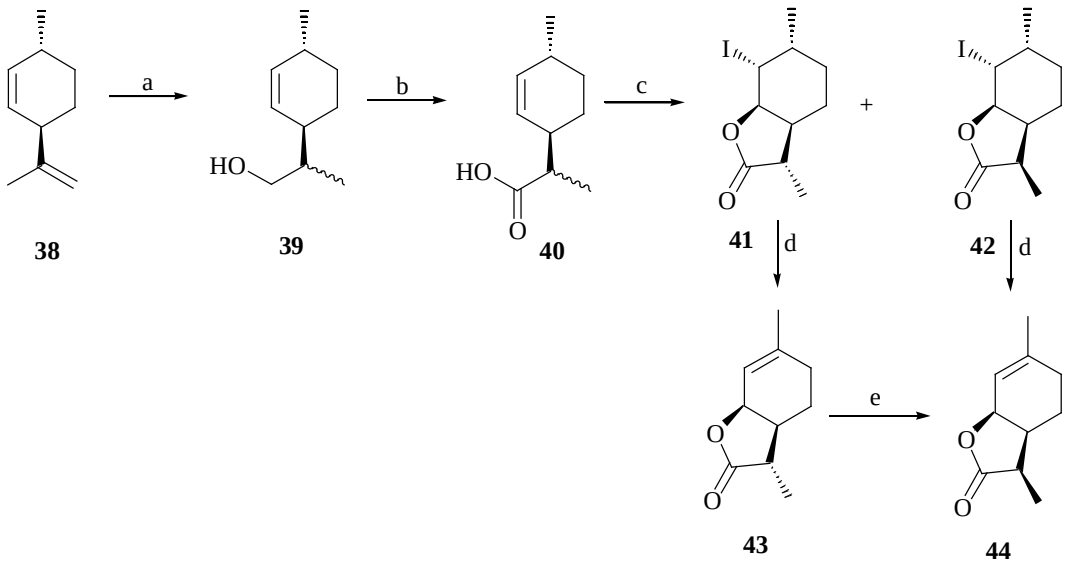
stereochemical disposition. To accomplish epimeric iodolactones **41** and **42,** (+)-isolimonene **38** was hydroborated regioselectively. Thus (+)-isolimonene was selectively hydroborated at the terminal double bond with 9-borabicyclo[3.3.1]-nonane (9-BBN) and subsequent oxidative hydrolysis with alkaline H_2O_2 to furnish alcohol **39** in 76% yield. The alcohol **39** thus obtained was oxidized with Jone's reagent at 0 ºC to furnish γ,δ-unsaturated acid 40 in 78% yield. Acid **40** thus obtained was subjected to the iodolactonization using $(NH_4)_2Ce(NO_3)_6$ (CAN) / NaI at room temperature to furnish a mixture of iodolactones **41** and **42** in 47% yield (scheme 14). The structures of both the iodolactones **41** and **42** were confirmed by subjecting the respective iodolactones to dehydrohalogenation with DBU at room temperature in tetrahydrofuran. Thus iodolactone **41** on dehydrohalogenation with DBU furnished the natural wine lactone (-)-**43**.



Scheme 14. Reagents and conditions: a) 9-BBN, THF, H_2O_2, NaOH 76%; **b**) Jones reagent, acetone, rt. 78% **c**) $(NH_4)_2Ce(NO_3)_6$ (CAN), NaI, acetonitrile, rt.47%; **d**)DBU, toluene, reflux 81%.

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CHAPTER-I

Synthetic studies towards D(+)-biotin

SECTION- I

Total synthesis of D(+)-biotin: A review

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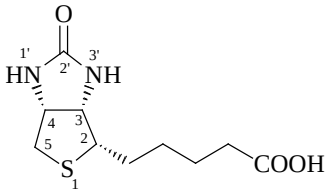
1.1.1 Introduction

The Chemistry of Biotin dates back to 1936 when it was isolated by Kogl[1] from egg yolk. A few years later it was also isolated from beef liver[2] and from milk concentrate.[3] It is also known as anti-egg white injury factor, bios IIB, vitamin H *etc*. Chemically biotin is (+)-*cis*-hexahydro-2-oxo-1*H*-thieno[3,4-d]-imidazole-4-valeric acid.



D-(+)-Biotin

Biotin is one of the water-soluble B-complex group of vitamins. In bound form it is distributed widely as a cell constituent of animal and human tissues. The main sources of biotin are liver, kidney, pancreas, egg yolk, yeast and milk. A high content of biotin in cow's milk occurs in early lactation. It is also present in different plant materials, especially in seeds, pollen, molasses, rice, mushroom, fresh vegetables and in some fruits. Moist fish contain biotin in small amounts.

Biochemically, biotin functions as a cofactor for enzymes principal to carboxylation reactions. These reactions are involved in important biochemical processes *e.g.*, gluconeogenesis and fatty acid synthesis.

1.1.1a Structure determination:

The empirical formula for biotin $C_{10}H_{16}N_2O_3S$ was established in 1941 and the full structure in 1942 by du Vigneaud.[4,5] The structure was confirmed by the first total synthesis of biotin in Merck Laboratories by Harris and coworkers in 1945.[6] The absolute configuration was established more than 20 years later by X-ray crystallographic analysis.[7]

Biotin has three contiguous chiral carbon atoms and therefore, four diastereomeric racemic forms are possible, of which only (+)-biotin **1** is biologically active, while, *epi*, *allo* and *epi-allo*-biotin **I**, **II**, and **III** respectively and their enantiomers are biologically inactive. Of the four diastereomeric racemic forms, only D(+)-biotin occurs in nature whereas other isomers are of synthetic origin.

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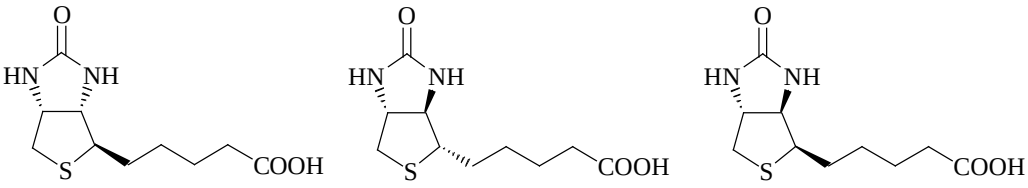
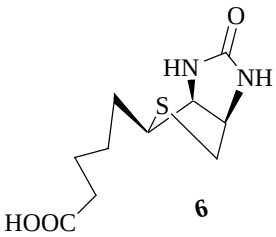


epi-Biotin **I** *allo*-Biotin **II** *epiallo*-Biotin **III**

In 1976 two groups redetermined the crystal structure of biotin and results reported were in agreement with the previous ones, but more accurate.[8] According to these data, ureido ring is planar while the thiophane ring has an envelope conformation **IV**. The valeric acid side chain is not fully extended but twisted and there is a strong interaction between C_6 and $N_{3'}$, a feature of importance in determining the biochemical reactivity of biotin. This envelope conformation **IV** of thiophane ring is also found in solution as shown by Glassel and Marquet.[9]



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1.1.1b Biosynthesis:

A number of fungi and bacteria synthesize biotin from pimelic acid by a metabolic pathway, whose last step involves the conversion of dethiobiotin to biotin. This pathway has been thoroughly investigated.[10-13] All the intermediates from pimelic acid to dethiobiotin are formed by classical biochemical reactions. Recently Marquet and coworkers solved the elucidation of the mechanism for the transformation of dethiobiotin to biotin. Evidence has been presented that the biosynthesis of biotin *Aspergillus niger* and *E. Coli* proceeds by the introduction of sulfur at C_1 and C_4 of dethiobiotin without apparent involvement of C_2 and C_3.[14,15] A more recent study clearly demonstrates that sulfur is introduced at C_4 of dethiobiotin with loss of the 4 pro *S* hydrogen atom. Since the configuration of biotin at C_3 is *S*, it follows that sulfur is introduced with retention of configuration at C_4, prochiral center of dethiobiotin.

1.1.1c Biotin Deficiency:

Because of biosynthesis by intestinal flora, a deficiency of biotin seldom occurs in humans. In rare cases, biotin deficiency when inducted, results in dermatitis, a loss of appetite,

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nausea, vomiting, depigmentation, alopecia, weight loss, anemia, elevated blood cholesterol and depression.[16] These symptoms can be reversed by giving biotin at the level of adult requirement, 150-300 µg/dose. Recently a rare life threatening genetic defect in biotin metabolism, that is biotin-dependent-carboxylase deficiency, has been determined in a small number of young children. Johnson *et al*[17] reported: "A diet which is marginally deficient in the vitamin biotin may cause sudden unexpected death of young broiler chickens when they are exposed to stress. Chickens affected with this disorder have low levels of biotin in their livers. In condition of biotin insufficiency, we postulate that a similar disorder, triggered by mild stress may occur in the human infants". They used radiochemical technique to measure the biotin content of 204 livers obtained from infants at autopsy. The levels of biotin in the livers of infants who had died of sudden infant death syndrome (SIDS; cot death) were significantly lower than those in livers of infants of similar age, who had died of explicable causes. These findings support an association of biotin with SIDS.

In poultry, biotin is an essential vitamin for normal growth, feed conversion, and reproduction as well as healthy skin, feathers and bones. Biotin deficiency in poultry causes reduced growth rate, impaired feed conversion, reduced feed intake, perosis and other deformities causing leg-weakness, poor feathering and food dermatitis. In broilers, a biotin deficiency causes breast blisters, fatty liver and kidney syndrome, parrot beak and death. Biotin deficiency also causes dramatic symptoms in swine, *e.g*. Reduced growth rate, dermatitis, excessive hair loss, furry tongue, food tensions, stiff-legged gait, squatness, and hind-leg spasms. These deficiencies are corrected by using biotin as a feed additive for poultry and swine.

1.1.1dUses:

It is used in pharmaceutical preparation of ointments, tonics, *etc*. It is also used in poultry for rapid growth of chicks and healthy hatching of eggs.

In recent years a utilization of strong biotin avidin complex has emerged in biochemistry as an important and versatile method for isolation, localization, immunoassay and drug delivery.[18a] It has been recently recognized that biotin finds use in cosmetic[18b] and it administered orally for brittle nails and hair loss.

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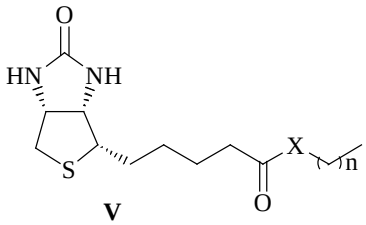
Avidin-Biotin system in immunochemistry:[19]

One of the most useful interactions in immunochemistry involves the specific binding of water-soluble vitamin: biotin, to the egg white protein avidin. Avidin is a tetramer containing four identical subunits of molecular weight 15,000. Each subunit contains a high affinity binding site for biotin with a dissociation constant of approximately 10-15 M. The binding is undisturbed by extremes of pH buffer salts or even chaotropic agents, such as guanidine hydrochloride (up to 3 M). The strength of the avidin biotin interaction has provided the researcher with a unique tool for use in immunoassays, receptor studies, immunocytochemical staining and protein isolation.

The avidin biotin system is particularly well suited for use as a bridging or sandwich system in association with antibody-antigen interactions. The biotin molecule can easily be activated and coupled to either antigens or antibodies, usually with complete retention of activity. Subsequently avidin can be conjugated with enzymes, fluorochromes, ferritin or colloidal markers and used as high affinity secondary reagents, which can greatly increase the sensitivity of an assay. In addition, since only one conjugate preparation is required for many different assays, the biotin-avidin system can be very attractive for use in immunological procedures. The following are some of the biotin derivatives in use.

a). Biotin derivatives as gelators of organic solvents: [20]



V

X = NH, n = 15, 11, 10, 7, 5, 2

The recovery of spilled solvents, disposal of used cooking oil and novel drug delivery systems have been suggested as possible applications for gelling compound. Several of these compounds are capable of forming stable gels with a variety of organic solvents.

Several bis-*N*-alkylated (+)-biotin derivatives were synthesized and evaluated for activities against HIV-1 protease. The most potent inhibitor, **VI** has K_i of 0.50 mM and antiviral IC_{90} of 7mM. The (+)-biotin analogues in general have good translations from enzymic K_i to antiviral cell assay IC_{90}. Other derivatives of biotin also like *N*-hydroxysuccinimidobiotin, sulfosuccinimidobiotin, *N*-iodoacetyl-*N*-biotinylhexylenediamine, biotinhydrazide,

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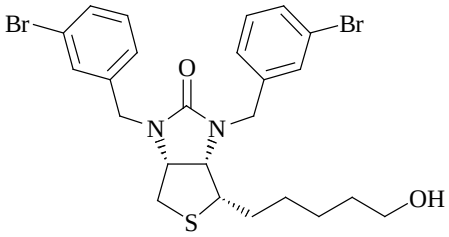
immobilized biotin, biotincellulose of biotin are commonly used derivatives in different applications.

b). Biotin derivatives as anti HIV protease inhibitors:[21]



VI

Biotin possesses a deceptively simple-looking structure. Its skeleton consists of a bi-heterocyclic core, to which is attached a carboxybutyl side chain. The heterocyclic system comprises a cyclic urea and a tetrahydrothiophene ring (which will subsequently be called thiophane). It further possesses three contiguous stereocenters on the thiophane ring in the all-*cis* configuration. Because of the fundamental and commercial importance, biotin has, ever since it was discovered, attracted the attention of both academic and industrial synthetic chemists.

A continuous endeavor over a period of more than 50 years has now resulted in more than 40 original contributions on the total synthesis of biotin. Many of earlier syntheses known were lengthy involving a number of steps, without any stereochemical control. Then there was a drought of published information for 20 years when no significant progress in biotin synthesis was made. However, the recent recognition of the importance of biotin in poultry, biochemistry and pharmaceutical formulations, revived the interest in this molecule, and this is evident by a boom in a number of international patents (around 50) between 1970-2000. The above figure excludes the applications of biotin in biochemistry and related subjects.

Some of the recent syntheses are discussed briefly since the syntheses of biotin up to 1992 were already reviewed by R. B. Tejwani of this laboratory,[22] as well as is reviewed by De Clercq in 1997[23] the current section is mostly restricted to syntheses reported after 1992.

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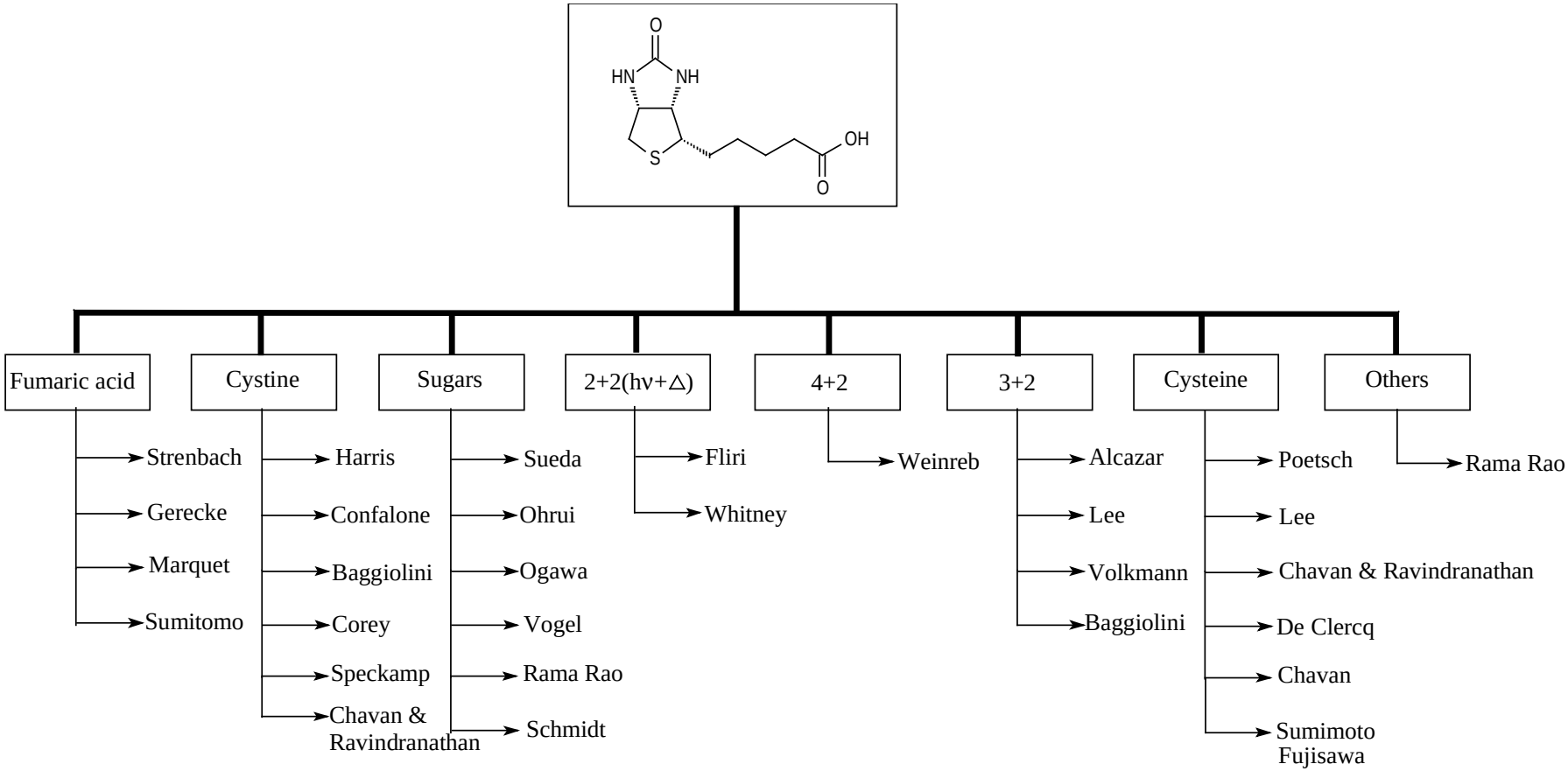
1.1.2 Earlier Approaches

Chart 1 shows Up to date approaches for biotin synthesis starting from different starting materials.

Chart 1:[23]



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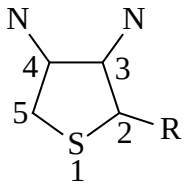
However the classical Hoffmann La Roche synthesis that till date is the commercially practiced technology with modifications is described.

Schemes constitute the vehicle of the synthetic chemist. They are conceived so that the chemist can grasp the important stages in each shown sequence. Relevant experimental conditions are listed, including yields when they have been clearly reported in the original literature. The following stereochemical designations are used in the schemes: an unprefixed Arabic numeral is used for achiral molecules and for chiral molecules which possesses the correct enantiomeric configuration for eventual conversion into (+)-biotin; the opposite enantiomeric configuration is indicated by prefix *ent* and racemic mixtures by the prefix *rac*. Throughout the section/thesis, the atom numbering along the thiophane nucleus shown below will be used:



Hoffmann-La Roche's Lactone-Thiolactone approach:

Goldberg, Sternbach's Approach 1: [24-26] (Pat. 2,489232, Nov. 22, 1949; Chem. Abstr. **1951**, 45, 184.)

In 1946 Goldberg, Sternbach[24-26] described the total synthesis of (+)-biotin starting from cheaply available fumaric acid (see Scheme 1).

Fumaric acid is converted into the cyclic anhydride **4** *via* a four step sequence involving bromination of fumaric acid to yield *meso*-dibromo succinic acid, double substitution of the latter with benzyl amine, formation of the cyclic ureide **3** with phosgene, followed by formation of anhydride **4** upon treatment of **3** with acetic anhydride. At this stage *cis* relation of the vicinal amino groups at C_3 and C_4 centers are fixed. In the second stage, the thiophane nucleus is formed by conversion of *meso*-**4** into thiolactone **6**. This involves reduction of anhydride **4** with zinc in acetic acid, treatment of the resultant acetoxy lactone **5** with hydrogen sulfide, and its further reduction with zinc to yield thiolactone **6** in racemic

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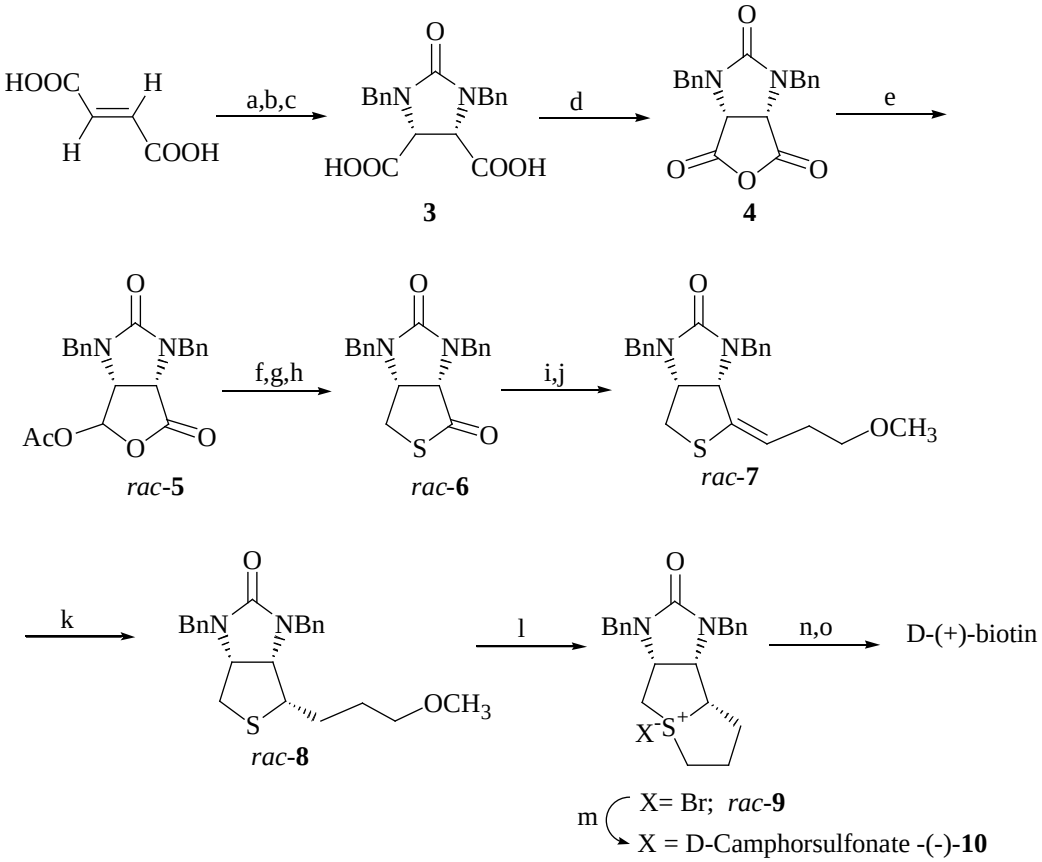
form. In the third stage, part of the carboxy butyl chain of biotin is introduced *via* Grignard reaction with subsequent dehydration to from the exocyclic olefin **7** with undefined double-bond stereochemistry. Catalytic hydrogenation of the latter yields **8** with the desired all *cis* relative configuration, at centers C_2, C_3 and C_4. In the fourth stage ether **8** is converted into the thiophanium salt **9** by treatment with hydrobromic acid (HBr).



Scheme 1: Reagents and conditions: **a**) Br_2; **b**) $PhCH_2NH_2$, EtOH; **c**) $COCl_2$, KOH; **d**) Ac_2O; **e**) Zn, Ac_2O, HOAc; **f**) H_2S, HCl; **g**) KSH, EtOH; **h**) Zn, HOAc; **i**) $ClMg(CH_2)_3OCH_3$; (j) HOAc; **k**) H_2, cat.; **l**) HBr; **m**) silver *d*-camphorsulfonate, followed by fractional crystallization;**n**) $NaCH(COOEt)_2$; **o**) 48% HBr.

At this point, resolution is effected by conversion of bromide **9** into the diastereomeric sulfonate salt **10** which are readily separated in excellent yield by simple fractional crystallization. In the final stage of the synthesis the side chain is accomplished by reaction of diastereomer (-)-**10** with sodium diethyl malonate. In this important step, selective attack is observed at the least hindered primary center of the trimethylene thiophanium

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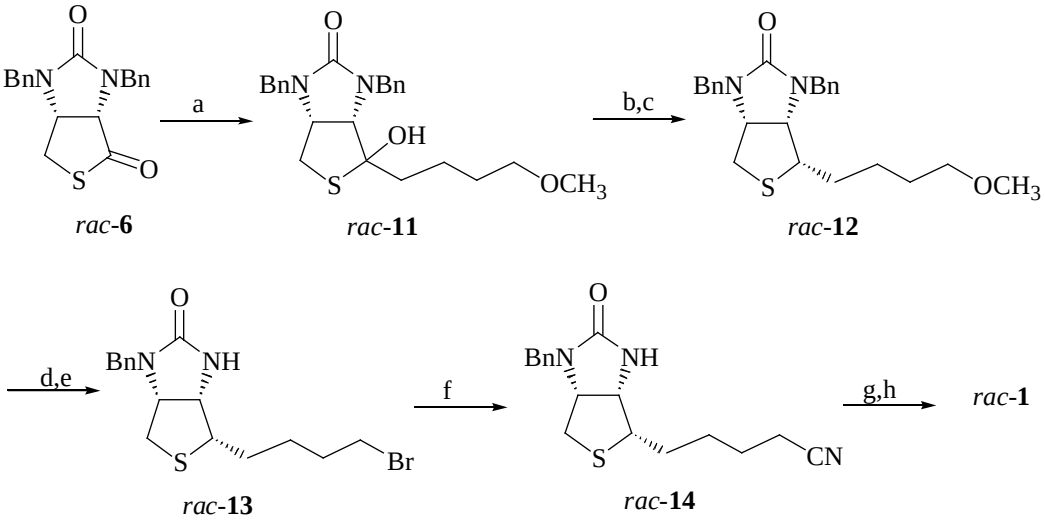
moiety. Finally heating with conc. hydrobromic acid effected hydrolysis, subsequent decarboxylation, and debenzylation all in one operation furnished biotin.

Several intermediates in the above scheme, and in particular, thiolactone **6** has been obtained later in racemic or homochiral form by other groups thus constituting new formal synthesis of *rac*-biotin or (+)-biotin respectively.

Several other groups have also used the establishment of stereocenter 2 *via* catalytic hydrogenation of an exocyclic olefin subsequently. The use of benzyl groups as protective groups in the imidazolidothiophane and related intermediates has been commonly utilized in almost all-later synthesis.

Goldberg, Sternbach's Approach II: [25] (US Pat. 2,489235, Nov. 22, 1949; Chem. Abstr. **1951**, 45, 186a.)

Another approach by Goldberg[25] described a route in which the thiophanium salt were not involved. The conversion of thiolactone **6** into *rac*-biotin involved a sequence of eight steps (Scheme 2).



Scheme 2: Reagents and conditions: a) $CH_3O(CH_2)_4Br$, Mg, ether; PhH; **b**. HOAc, reflux; **c**) H_2, Pd/C, MeOH; **d**) Na, liq.NH_3; **e**) HBr, HOAc, 90 ^oC; **f**) KCN, H_2O; **g**) NaOH, H_2O/MeOH; **h**) Na, liq. NH_3

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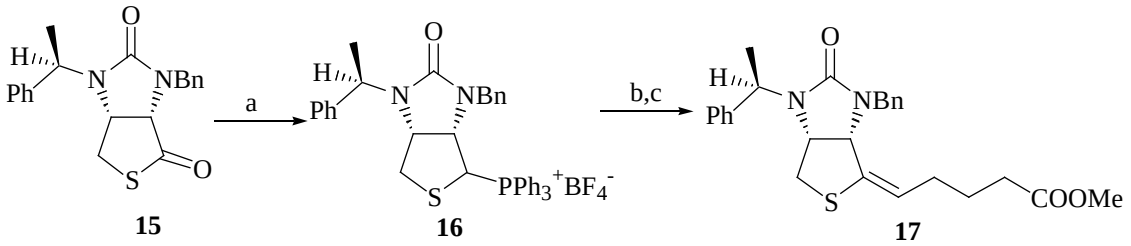
Thus Grignard reaction of **6** with 4-methoxybutyl bromide furnished the alcohol **11**. Dehydration of **11** followed by catalytic hydrogenation yielded **12**. Removal of one benzyl group with sodium in liquid ammonia and conversion of the terminal methoxy alkyl group into the corresponding bromide **13** and its one carbon homologation with potassium cyanide furnished **14**, whose basic hydrolysis resulted in the formation of the corresponding carboxylic acid. Subsequent debenzylation with sodium in liq. ammonia furnished (±)-biotin.

Eyers Approach: Wittig Olefination: [27] (Eur. Pat. Appl. EP 0 387 747, 19 Sept. 1990; Chem. Abstr. **1991**, 114, 81435t)

More recently Eyer *et al* [27] have developed an alternative Wittig sequence starting from thiolactone **15**. The sequence of reactions involves reduction with diisobutyl aluminium hydride (DIBAL-H) to the corresponding hydroxy derivative, which is directly converted to phosphonium salt **16** with triphenylphosphine hydrogen tetrafluoroborate. Condensation of the corresponding ylide with methyl 5-oxopentanoate gave **17** in fair yield (Scheme 3).



15 **16** **17**

Scheme 3:Reagents and conditions: a) $(Me_2CHCH_2)_2AlH$, $PhCH_3$, -70 ^oC; **b**) Ph_3P-HBF_4, CH_3CN, reflux, 97%; **c**) KO^tBu, THF, $OHC(CH_2)_3CO_2Me$, THF, 65%.

Senuma's approach: Auxillary based resolution: [28] (*Chem.Pharm.Bull.* **1990**, *38*, 882.)

Senuma and co workers reported[28] an alternative method for the industrial resolution of hydroxyl lactone **18** in 1990. (Scheme 4). It involves the direct resolution of the hydroxy lactone *rac*-**18** (*trans*-epimer) with optically active amines. Thus the reaction of *rac*-**18** with cinchonidine readily gave the cinchonidine salt of **19a** in 45% yield with an optical purity evaluated at more than 98%. Upon acidification, the salt readily underwent cyclization to give a 42% overall yield of **18**. Evaporation of the mother liquor of the salt afforded after acidification *ent*-**18** in 36% yield. The undesired enantiomer is readily converted to *meso*-

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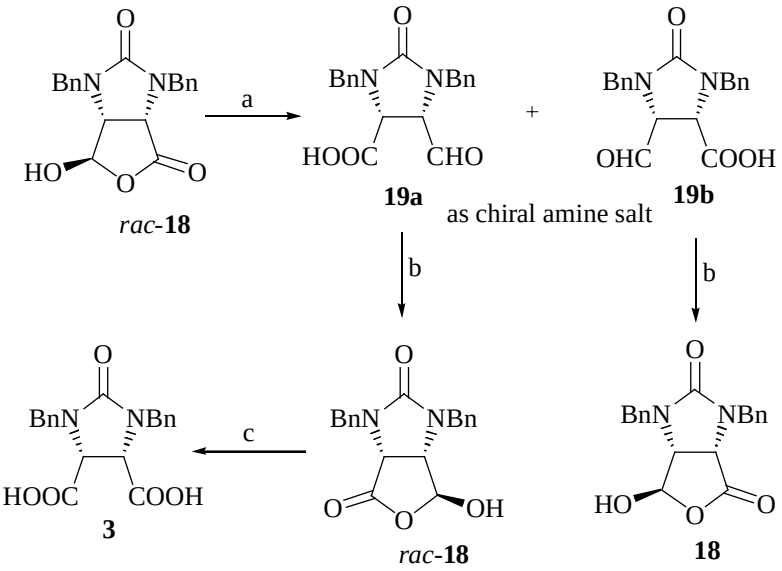
diacid **3** by facile oxidation with sodium chlorite. To find a more practical and inexpensive resolving agent applicable for industrial use, the authors also examined the optical resolution of *rac*-**18** with various *N*-alkyl-*D*-glucamines



Scheme 4: Reagents and Conditions: a) Cinchonidine:45% of precipitated salt or *N*-*n*-butyl-*D*-glucosamine derivative: 46% of precipitated salt; **b**) HCl; **c**). $NaClO_2$, 87%.

Matsuki's approach: [29] (*Tetrahedron Lett.* **1993**, *34*, 1167.)

The further development of efficient asymmetric strategies in the context of the original Hoffmann-La Roche scheme culminated in 1993 by Matsuki and co-workers report on the highly enantioselective reduction of *meso*-1,2-dicarboxylic anhydride to yield optically active lactones using Noyori's lithium aluminium hydride-ethanol-1,1'-bis-2-naphthol complex (BINAL-*H*).[29] When applied to *meso*-**4**, the desired lactone **20** was directly obtained in 76% yield with 90% *ee*, which was enriched to 95% *ee* by recrystallization from benzene/cyclohexane (Scheme 5).[30]

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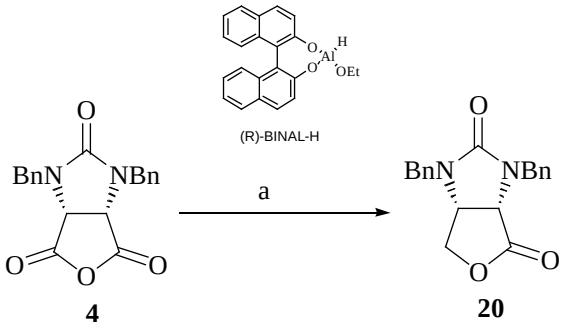

90% ee; 95% ee (after crystallisation)

Scheme 5: Reagents and Conditions: a) (*R*)-BINAL-H, -78 °C to rt., THF, 76%.

Although the chiral recognition mechanism is not clear, the general mechanism proposed by Noyori can be applied[30] to explain outcome of the reaction.

Lonza's approach: [31] (Eur. Pat. Appl. EP 0 270 076, 8 June, 1988; Chem. Abstr. **1988**, *109*, 128718b.)

Another interesting asymmetric approach has been developed by chemists at Lonza that center about the hydrogenation of furoimidazole derivative **24** (Scheme 6).[31] The synthesis of this intermediate **24** involves a straightforward four-step sequence starting from tetronic acid. Treatment of the latter with the diazonium salt derived from aniline leads to diazo compound **22** which is converted into **24** *via* reaction with a primary amine such as (*S*)-1-phenylethyl amine followed by reduction to **23** and subsequent imidazolone ring formation with ethyl chloroformate.[32] It is interesting to note that both **24** and *ent*-**24** can lead to the diastereomer with the desired (3*S*, 4*R*)-configuration depending on the hydrogenation conditions:

1. Rhodium on alumina in DMF for **24** (54% yield of crystalline **25**) and
2. Palladium on carbon in acetic acid for *ent*-**24**(54% yield).[33]

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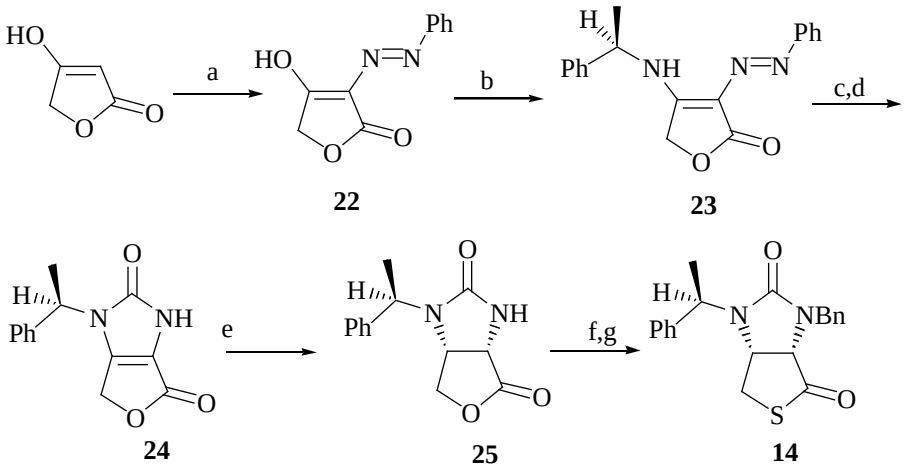
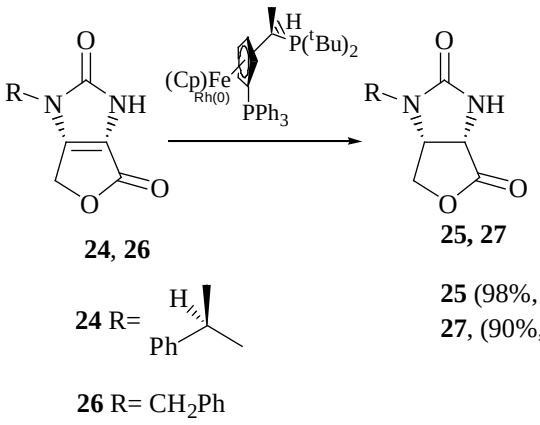


Scheme 6: Reagents and Conditions: a) $PhNH_2$, $NaNO_2$, HCl, 92%; **b**) (R)-$PhCH(NH_2)CH_3$, $B(OEt)_3$, $PhCH_3$, 80 ^oC; **c**) H_2, Pt/C, EtOAc, 40 bar, 84%; **d**) ClCOOEt, Et_3N, THF, Et_3N, CH_3CN, reflux, 66%; **e**) H_2, Rh/Al_2O_3, DMF, 40 bar, 54%; **f**) NaH, DME, $PhCH_2Br$; **g**). CH_3COSK, $CH_3CON(CH_3)_2$, 150 ^oC, 69%.

McGarity's approach: Asymmetric hydrogenation: [33, 34] (Eur. Pat. Appl. EP 624 587 17th Nov. 1994; Chem. Abstr. **1995**, *122*, 81369q.)

A further dramatic improvement has been claimed very recently when the hydrogenation was performed in the presence of a rhodium complex and a chiral ferrocenylphosphine ligand (Scheme 7).[33, 34] The reduction of achiral **26** into **27** (95% yield; 90% *ee*) constitutes a second example in which the chirality is introduced involving a catalytic pathway.



Scheme 7: Reagents and Conditions: a) Rh(0)= $[Rh(norbornadiene)Cl]_2$, chiral ligand, $PhCH_3$, 70 ^oC, H_2, 50 bar, 95%.

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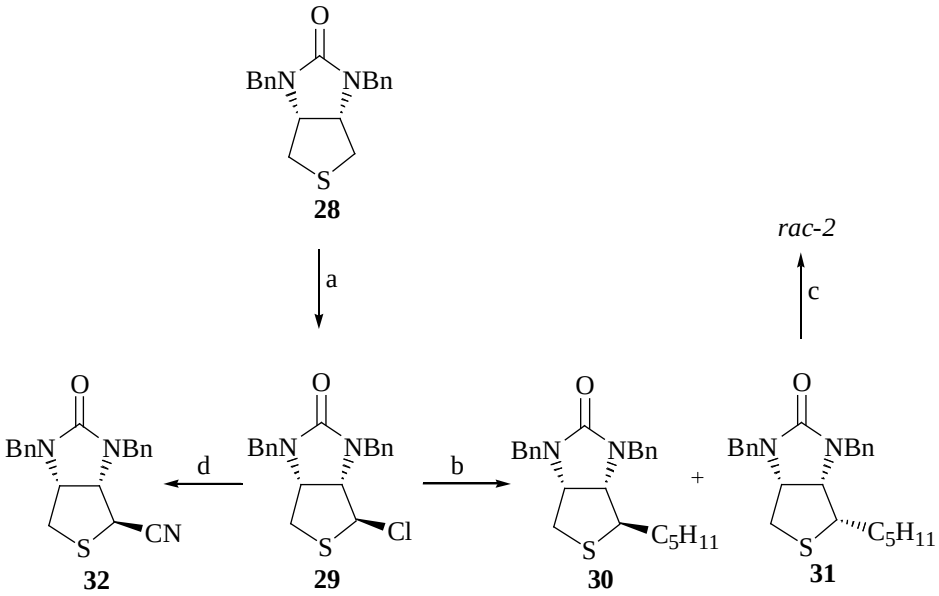
Kinoshita's approach: α-chlorination of thioophane: [35] (*J. Org. Chem.* **1986**, *51*, 3447)

In 1983 Kinoshita group[35] described a six-step synthesis of **28**. In 1986 Bates and Rosenblum described[36] the chlorination of **28** with *N*-chlorosuccinamide stereoselectively and further converted it to deoxybiotin **2** in racemic form (Scheme 8).



Scheme 8: Reagents and Conditions: a) NCS, PhH, 100%; **b**) n-pentyl(Me)CuLi (mol of LiCl/mol of R_2CuLi=1), -60 ^oC, ether, 53%; **c**) Na, liq. NH_3 or HBr (48%); **d**) NaCN.

Bihovsky's approach: α-chlorination, diastereomer separation: [37] (*Tetrahedron* **1990**, *46*, 7667.)

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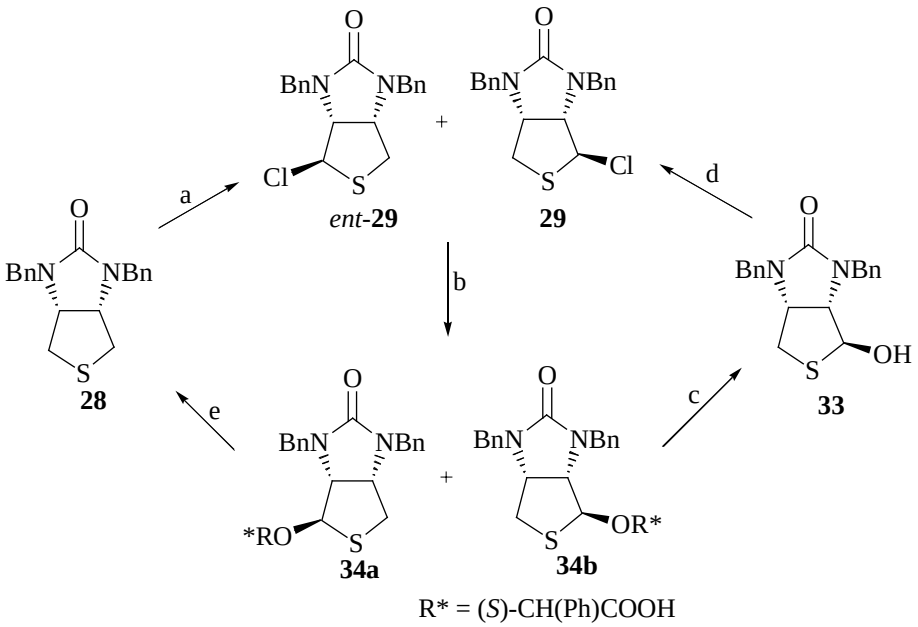

Scheme 9: Reagents and Conditions: **a**) NCS; **b**) R*-OH = (*S*)-(+)-mandelic acid, 75%; diastereomer separation by crystallization; CCl_4, reflux, 33% isolated with R* = -CH(Ph)COOH; **c**) H_2SO_4/dioxane; **d**) HCl, $CHCl_3$; **e**) Et_3SiH, CF_3COOH.

Bihovsky and Bodepudi[37] succeeded in resolving **33** as shown in Scheme 9. The resolution was accomplished by separation of the diastereomeric alkoxy derivative **34a** and **34b** that were obtained by reaction of *rac*-**29** with optically active secondary alcohols. The most efficient alcohol was (*S*)(+)-mandelic acid, since the diastereomers could be readily separated by crystallization. Acid hydrolysis of **34b** led to (+)-**33** and hence to (+)-**6**, *via* oxidation or to **29** *via* treatment with HCl.

Yamano's approach: Enzymatic resolution: [38] (*Bull. Chem. Soc. Jpn.* **1993**, *66*, 1456.)

Successful enzyme catalyzed kinetic resolutions were reported by Yamano *et al.* (Scheme 10).[38] A variety of commercially available enzymes and microorganisms were investigated in order to effect the enantioselective hydrolysis of the ester **35**, which was obtained by conventional acylations of *rac*-**33**.

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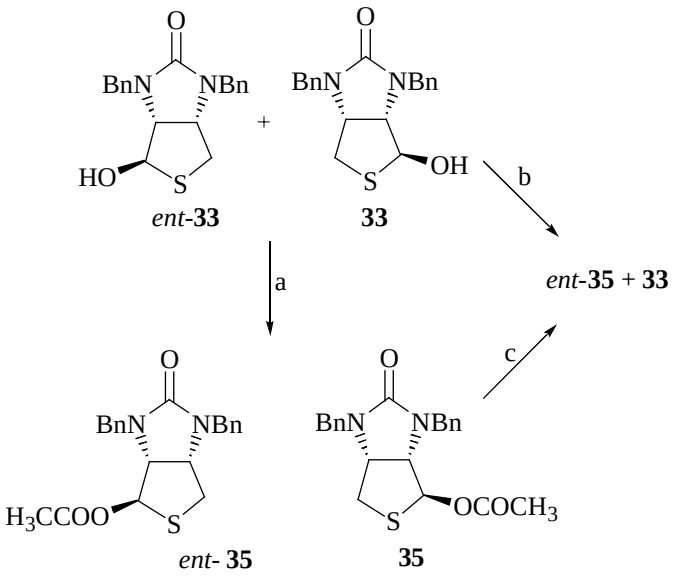

Scheme 10: Reagents and Conditions: a) Ac_2O, pyridine, 98%; **b**) *Streptomyces rochei* var. volubilis; 27% conversion; 92 and 94% ee after crystallization; **c**) LIP (*P.aeruginosa* TE3285; TOYOBO immobilized lipase), 0.3% H_2O, 4A^o molecular sieves (MS), $PhCH_3$, vinyl acetate; 56% conversion; 99 and 99.8% ee after crystallization of alcohol.

In a second approach, the same group found that direct resolution of alcohol **33** was accomplished *via* acylation with the lipoprotein from *Pseudomonas aeruginosa* TE 3285 in toluene.[39] Curiously, addition of molecular sieves (MS) 4Aº to the reaction mixture improved the reactivity, while at the same time as addition of a small amount of water was found to be beneficial for the reaction.

Synthesis *via N*-acyliminium ion chemistry:

Approaches involving the carbon-carbon bond formation using *N*-acyliminium ions are discussed briefly as follows.

Speckamp, Poetsch and Casutt's approach: [40a, b] (*Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391.)

In a joint effort, Speckamp and co workers and Poetsch and Casutt have used the intramolecular version of the condensation of silyl enol ether with *N*-acyliminium intermediate

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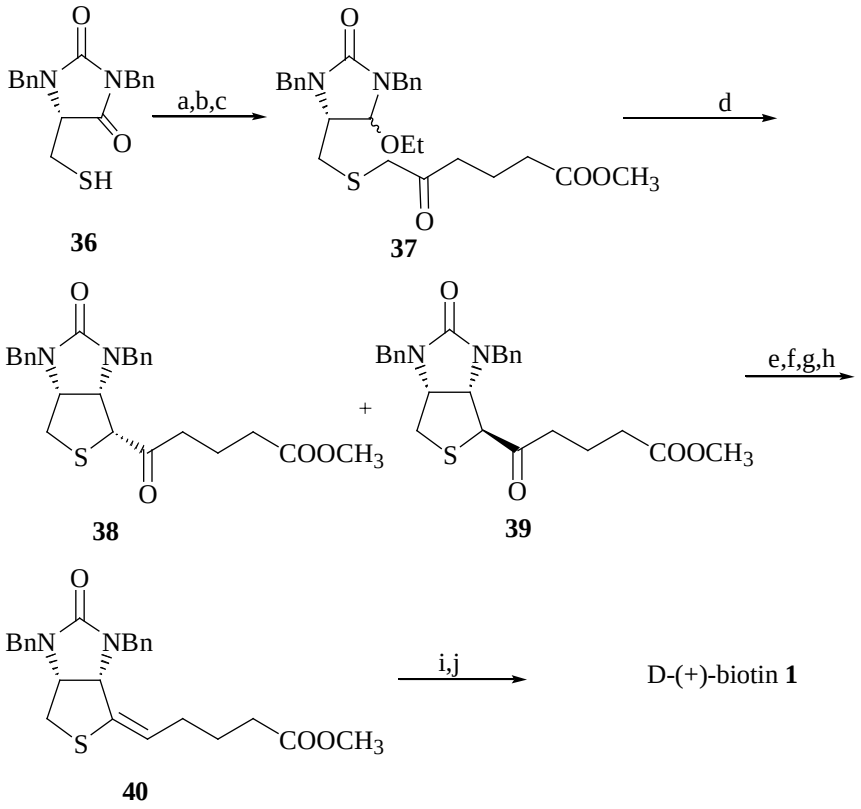
to effect the ring closure of thio ether **37** to the thiophane nucleus (Scheme 11)[40a, b] from the known intermediate **36**. The intermediate **36** is readily available from L-cysteine. Reduction with DIBAL-H led to the formation of corresponding hydroxy imidazolidinone (10:1) ratio of *cis*:*trans* diastereomers. Coupling with appropriate α-chloro ketone furnished the thioether, which was converted into the ethoxy derivative **37**. The crucial cyclization step involved the use of ethyl(trimethylsilyl)acetate/tetra-*n*-butylammonium fluoride for the *in situ* enol ether formation and addition of trimethylsilyl triflate (TMSOTf) to induce the cyclization. This led to a 78% yield of the two diastereomers **38** and **39** (3:2 ratio). The probable mechanism for the cyclization may be attributed to chair like transition state to yield **38** possessing the required all *cis* configuration whereas the formation of a diastereomer **39** by boat like confirmation can be explained.



Scheme 11: Reagents and Conditions: **a**) DIBAL-H, THF, -70°C, 1h; **b**) $MeO_2C(CH_2)_3C(O)CH_2Cl$, Et_3N, 4h; **c**) H_2SO_4/EtOH, methyl orange, pH=3.1, 0 °C, 2h, 72%. **d**) 2.1 eq. of $(TMS)CH_2CO_2Et$, 0.03 eq. of TBAF, THF, -78°C to 25°C, 18h, then 1.5eq. of TMSOTf, DCM, -78 °C, 1h, 78%; **e**) $NaBH_4$, MeOH, 25°C; **f**). $MeSO_2Cl$, Et_3N, DCM; **g**) DBU, 60 °C, 2h; **h**) KOH/MeOH, 2h, 87%; **i**) H_2 (10 bar), 10% Pd/C, 2-propanol, 50°C, 18h; **j**) 48% HBr, 100 °C, 2h, 85%.

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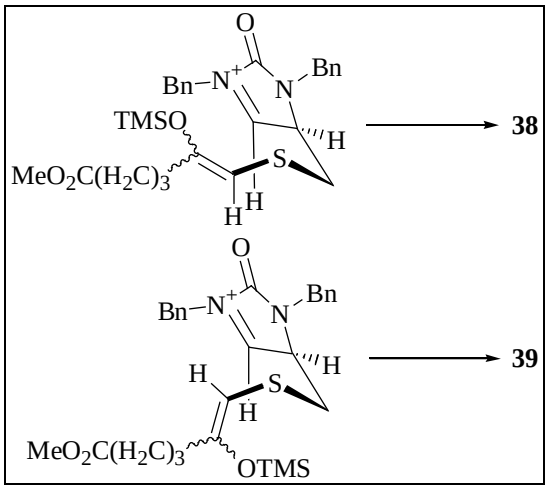
The loss of stereochemical control does not influence however, the further conversion of **38** and **39** into biotin. In deed, the mixture is converted to the same exocyclic olefin **40** *via* sodium borohydride reduction, mesylation, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) elimination and saponification. Final conversion of **40** to biotin proceeds in the usual way.

Independently, our group has reported two syntheses of biotin on similar lines of *N*-acyliminium cyclisation shown in Scheme 12.[41a,b]



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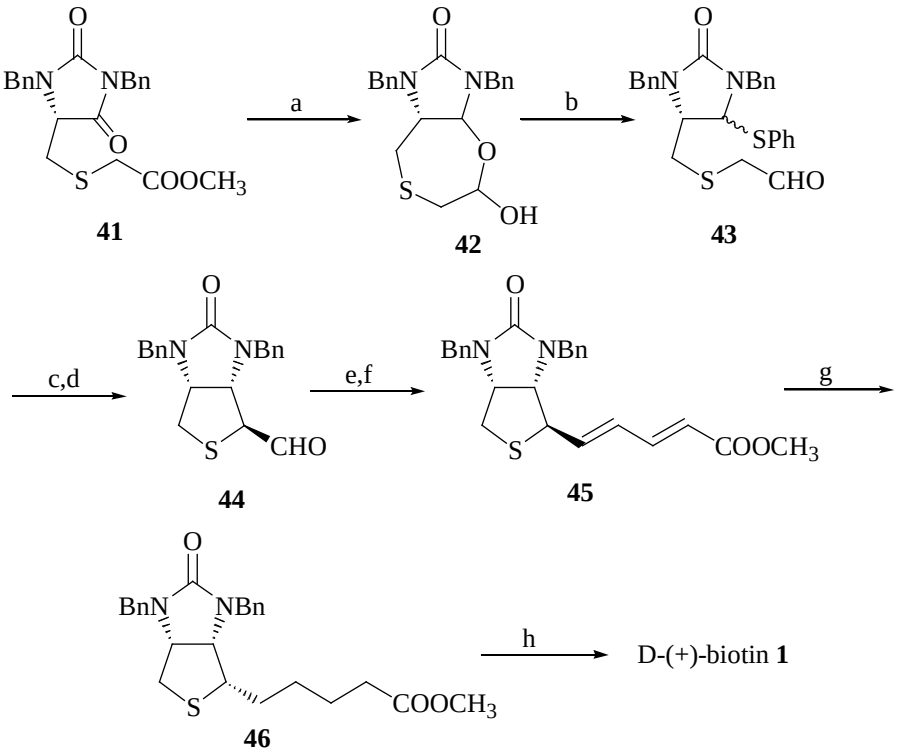

Scheme 12: Reagents and conditions: **a**) DIBAL-H, $PhCH_3$, 72%; **b**) p-TsOH, PhSH, 70%; **c**) $^tBuMe_2SiCl$, DBU, DCM; **d**) $^tBuMe_2SiOTf$ (cat.), p-NO_2PhCHO, DCM, 87%; **e**) Ph_3P=CH-CH=CH-CO_2Me, DCM; **f**) DBU, DCM, 86%; **g**) H_2 (3 bar), Pd/C, MeOH 92%; **h**) 48% HBr.
Chavan's approach: [41a] (US patent 5,274,107; Chem. Abstr. **1994**, *120*, 217097t; *J. Org. Chem*. **2001**, *66*, 6197-6201)

The hydantoin **41** could be readily synthesized from cystine/cysteine. DIBAL(H) reduction of carbonyl and ester of **41** furnished lactol **42**. Treatment of lactol **42** with thiophenol resulted in the formation of thioaminal aldehyde. Conversion of thioaldehyde **43** to the corresponding silyl enol ether followed by trialkyl triflate mediated cyclization in the presence of *p*-nitrobenzaldehyde as the thiophenol scavenger leads to the thermodynamically more stable thiophane aldehyde **44**.

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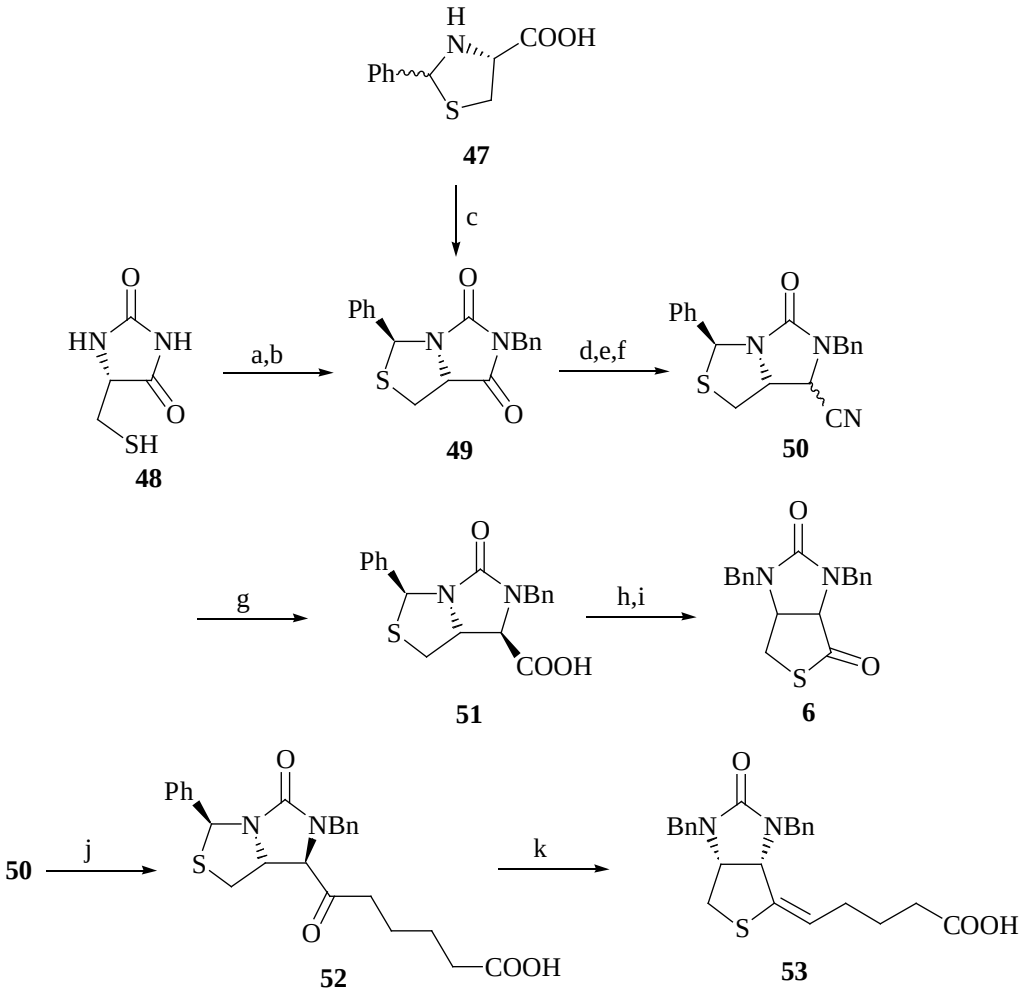

Scheme 13:Reagents and conditions: **a**) $PhCHO$, $POCl_3$, $PhCH_3$; **b**) $PhCH_2Cl$, K_2CO_3, DMF, 79%; **c**) $PhCH_2NCO$, acetone, HCl, DCM, 85%; **d**) $NaBH_4$, THF/H_2O; **e**) 1,1'-carbonyldiimidazole, THF; **f**) CH_3I, DMF; KCN, DMF, 78%; **g**) KOH, EtOH, H_2O, 91%; **h**) Zn, AcOH; **i**) N,N'-dicyclohexylcarbodiimide, C_5H_5N, p-TsOH; 70%; **j**) $Br(CH_2)_4Br$, Mg, THF, CO_2, HCl, 65%; **k**) Zn, AcOH; piperidine, AcOH, 70%.

The transformation of **44** into biotin involved first Wittig reaction with the 4-carbon ylide, followed by deconjugation with base to yield the exocyclic olefin **45**. Further catalytic hydrogenation led to dibenzyl biotin methyl ester **46**, which on treatment with 48% HBr furnished D(+)-biotin.[41a]

Poetsch and Casutt 's approach: [42] (*Chimia* **1987**, *41*, 148.)

In 1987 Poetsch and Casutt reported[42] shortest enantiospecific sequence to (+)-biotin (Scheme 26). The crucial intermediate in the synthesis is nitrile **50**. This is obtained from the

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bicyclic thiazolidine hydantoin **49** *via* selective reduction and cyanide introduction on the activated 1-(alkoxycarbonyl) imidazole derivative. The starting material **49** is obtained either from the readily available hydantoin **48**[43] or from the known thiazolidine carboxylic acid **47**.[44] Two different routes were developed that allow the conversion **50** into biotin. The direct Grignard reaction on **50** led to **52** followed by reductive opening of the thiazolidine which leads to an intermediate thiol that is cyclized using piperidine acetate/acetic acid to yield the biotin precursor **53**. Alternatively nitrile **50** is converted to the thermodynamically more stable acid which after reductive cleavage furnished the corresponding thiol acid, which was further cyclized to thiolactone **6**.

Chavan's approach II: Intermolecular trapping of acyliminium ion: [45] (*J. Org. Chem.* **2005**; 70(5); 1901.)

The amidoalkylation was performed on hydroxy hydantoin **54**[45] with a variety of nucleophiles like enol ethers, aromatic compounds, allyltrimethylsilane, tin acetylides and ketene silyl acetal.(Scheme 14). The reaction proceeds with a very high degree of diastereoselectivity to furnish the corresponding 7-substituted imidazothiazolone. Reaction of **54** with 1,2-bis TMS furnished **57** in excellent yields. The α-hydroxy ketone **57** was subjected to Baeyer-Villiger oxidation with *tert*-butylhydroperoxide in alkaline methanol to furnish the keto acid in 70% yield. This keto acid on esterification with diazomethane furnished the keto ester **58** in quantitative yield. The intermediate **58** being epimeric at C-7 with respect to (+)-biotin, was epimerized by reductive cleavage of carbon-sulfur bond with Zn/AcOH. Further cyclization of thiol thus obtained with the carbonyl function was performed in the presence of piperidine and acetic acid followed by dehydration to afford the olefin **40.**

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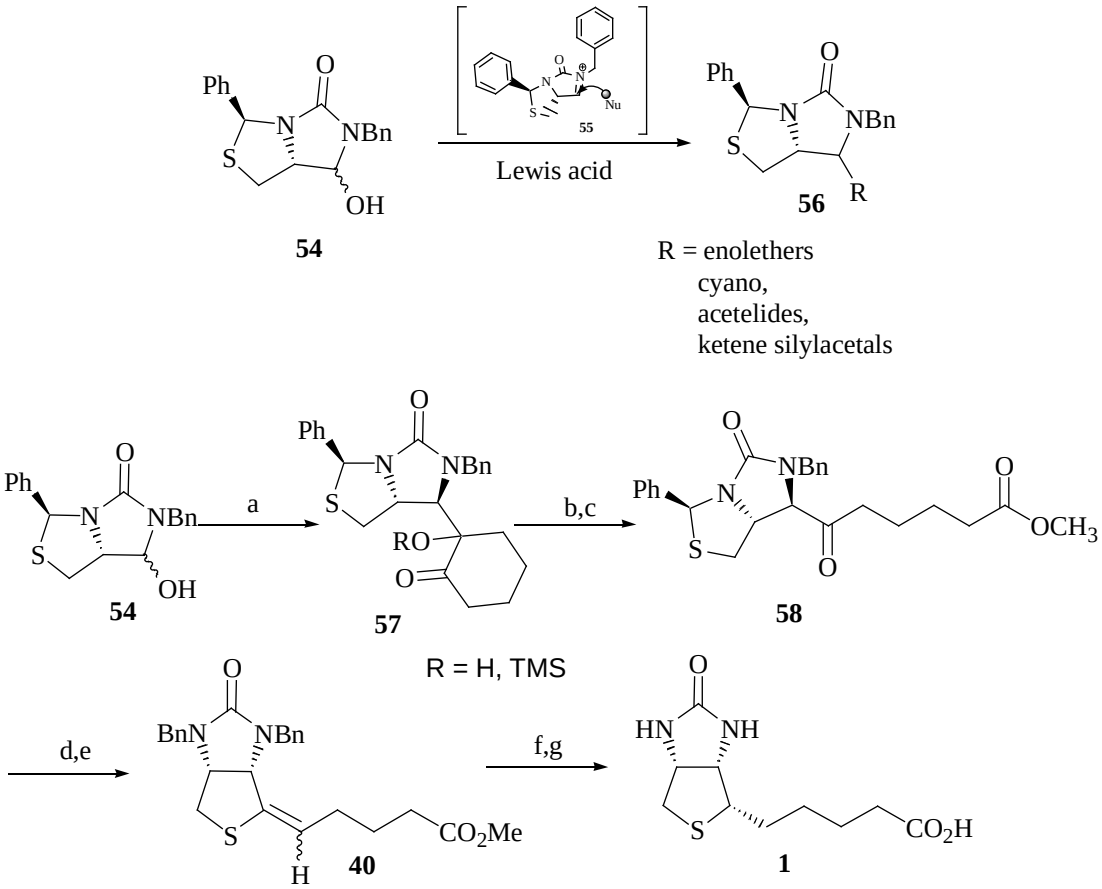

Scheme 14: Reagents and conditions: a) 1,2-bis-trimethylsilyloxy-cyclohexene (1.5 equiv), $BF_3.OEt_2$, DCM, 98%; **b**) 70% TBHP, KOH-MeOH, 15 min.; **c**) CH_2N_2, 10 min, 70%; **d**) Zn/AcOH, 80°C, 5h; **e**) AcOH/ piperidine, 100°C, 90 min, 70%; **f**) H_2/Pd-C, MeOH, 200 psi, 100%; **g**) 47% HBr, 5h, 78%.

Stereospecific hydrogenation was carried out in the presence of 10% palladium on carbon to furnish *N*,*N*'-dibenzyl biotin methyl ester in quantitative yield. Removal of *N*-benzyl groups was achieved with aq. HBr (47%) at reflux temperature to afford (+)-biotin.

Approaches involving sugars as chirons:

Syntheses of biotin utilizing monosaccharides as chiral synthons are described briefly as follows.

The monosaccharides that have been used as chiral starting materials for further multistep conversion to (+)-biotin are further shown in a way that immediately allows analysis of the sequences that will be necessary for their conversion to biotin. Four different hexoses

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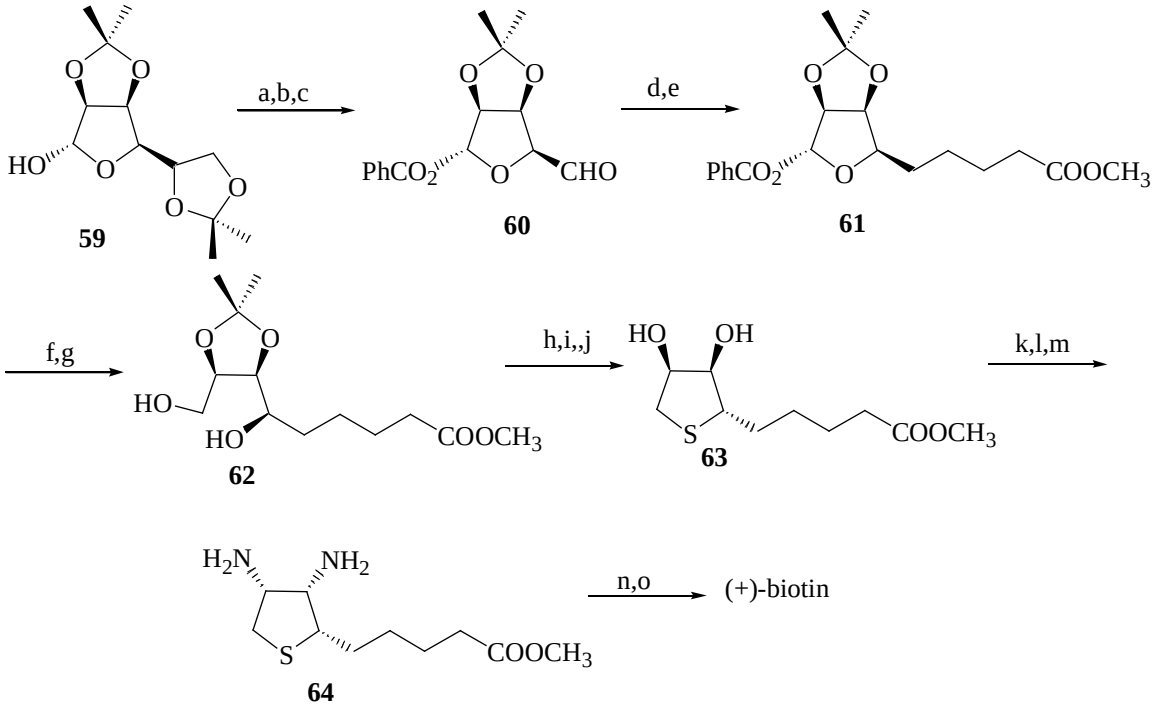
and one pentose, D-arabinose, have been used as starting materials. Crucial in the design of all syntheses in this area is the obtention of the thiophane nucleus *via* double SN^2 displacement of a dimesylate obtained from a diol. In view of the configuration at C-2 in biotin and the inversion that occurs at this center during the final thiophane closure step, the absolute configuration at this specific center is crucial. It corresponds to the (*R*)-configuration at C-4 in the hexoses that have been used and to the (*S*)-configuration at C-2 in the pentose D-arabinose.



Scheme 15: Reagents and conditions: **a**) $PhCOCl$, C_5H_5N; **b**) $HOAc$, H_2O; **c**) $NaIO_4$, CH_3COCH_3/H_2O; **d**) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; **e**) H_2, Pd/C, CH_3OH; **f**) $NaOCH_3$, CH_3OH; **g**) $NaBH_4$; **h**) CH_3SO_2Cl; **i**) Na_2S, HMPA, 100 °C; **j**) 90% HCOOH, 20 °C; **k**) CH_3SO_2Cl; **l**) NaN_3, HMPA, 80 °C; **m**) PtO_2, $MeOH/Ac_2O$; **n**) $Ba(OH)_2$, H_2O, 140 °C; **o**) $COCl_2$.

All syntheses additionally have in common that the biotin carboxyalkyl side chain is introduced *via* Wittig condensation using 3-(methoxycarbonyl)-2-propenylidene triphenylphosphorane followed by catalytic hydrogenation. In all cases, the amino groups will also be introduced *via* sequences involving SN^2 substitution of a leaving group by azide followed by reduction of the azide.

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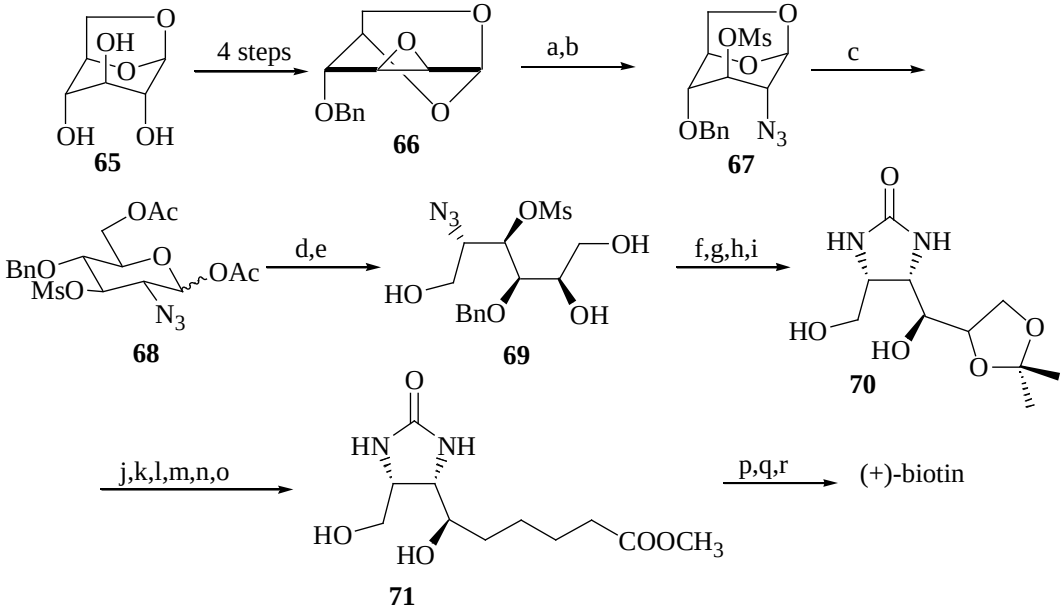
Ohrui's approach: Mannofuranose: [46] (*Tetrahedron Lett.* **1975**, 2765.)

Ohrui and Emoto began the series in 1975 (Scheme 15).[46] In their approach the di-*O*-isopropylideneprotected *R*-D-mannofuranose **59** is converted to diol **62**. The sequence involves formation of the benzoate of the anomeric alcohol, selective hydrolysis of the 5,6-isopropylidene group, and oxidative cleavage of the vicinal diol to yield aldehyde **60**. Subsequent Wittig treatment and catalytic hydrogenation afforded **61**. Base treatment of the latter generated the hemiacetal that was reduced to diol **62**. After thiophane formation and hydrolysis the obtained diol **63** is converted to the diamine **64** via inversion. Final obtention of (+)-biotin occurs after saponification and phosgene treatment.



Scheme 16: Reagents and conditions: a) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH/H_2O$, 120 °C 85%; **b**) MsCl,; **c**) $BF_3.Et_2O$, Ac_2O 95% (over two steps); **d**) HCl, CH_3OH; **e**) $NaBH_4$, $B(OH)_3$, EtOH 45% (over two steps); **f**) $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH; **g**) LiN_3, DMF, 80 °C; **h**) H_2, Lindlar, EtOH; **i**) $COCl_2$, 45% (over 4 steps);; **j**) Ac_2O, C_5H_5N **k**) $AcOH/H_2O$, 70 °C; **l**) $NaIO_4$, $EtOH/H_2O$; **m**) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; **n**) H_2, Pd/C, CH_3OH; **o**) CH_3ONa, CH_3OH 40% (over 6 steps); **p**) CH_3SO_2Cl, C_5H_5N, -10 °C; **q**) Na_2S, DMF, 100 °C; **r**) NaOH.

Ogawa's approach: Glucose: [47] (*Carbohydr. Res.* **1977**, *57*, C31.)

Ogawa and co-workers have used D-glucose as starting material (Scheme 16).[47] Its conversion to diol **70**, which upon thiophane formation leads to biotin, requires no less than 18

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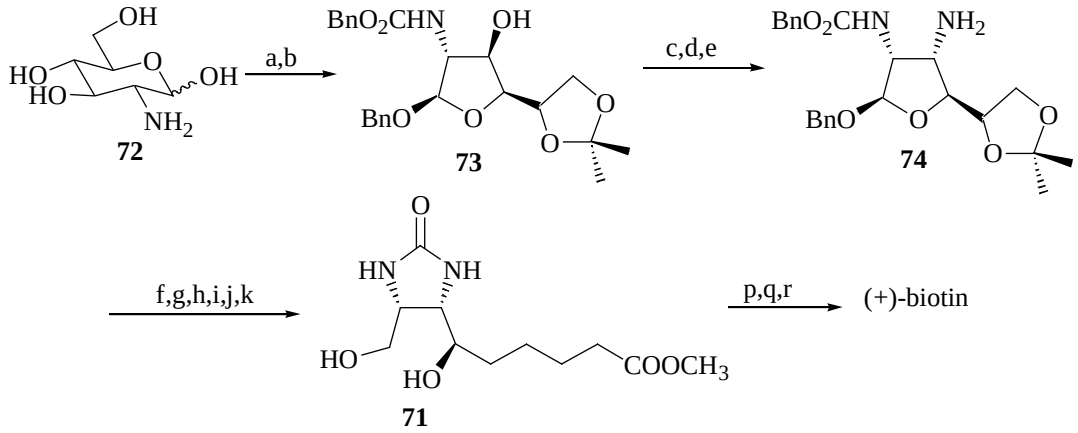
steps when starting from **65**. It is of interest to note that within the scheme the introduction of the second amine required the displacement of a mesylate in the bridged intermediate **66**. Since this would demand a sterically very hindered displacement, it was decided to convert the congested cyclic acetal **66** into the linear mesylate **67** which was found to be an adequate substrate for substitution.



Scheme 17: Reagents and conditions: a) $PhCH_2OC(O)Cl$, $NaHCO_3$; **b**) $(CH_3)_2C$-$(OCH_2Ph)_2$, p-TsOH, DMF, 120 °C; **c**) p-TsCl, C_5H_5N; **d**) NaN_3, DMF; **e**) H_2, RaNi; **f**) NaH, DMF; **g**) $HOAc/H_2O$; **h**) $NaIO_4$; **i**) $Ph_3P{=}CHCH{=}CHCOOCH_3$; **j**) H_2, Pd/C; **k**) $NaBH_4$, CH_3OH.

Ohrui's approach: Glucosamine: [48] (*Agric. Biol. Chem.* **1978**, *42*, 865.)

Ohrui group developed a shorter sequence to the same diol **71** that took advantage of the correct absolute configuration of the amino group in D-glucosamine that will eventually appear at C-4 in (+)-biotin (Scheme 17).[48] Worthy of note here is the use of a benzyloxycarbonyl group as reactive amine protecting group to form the imidazolidinone ring upon treatment of **74** with sodium hydride.

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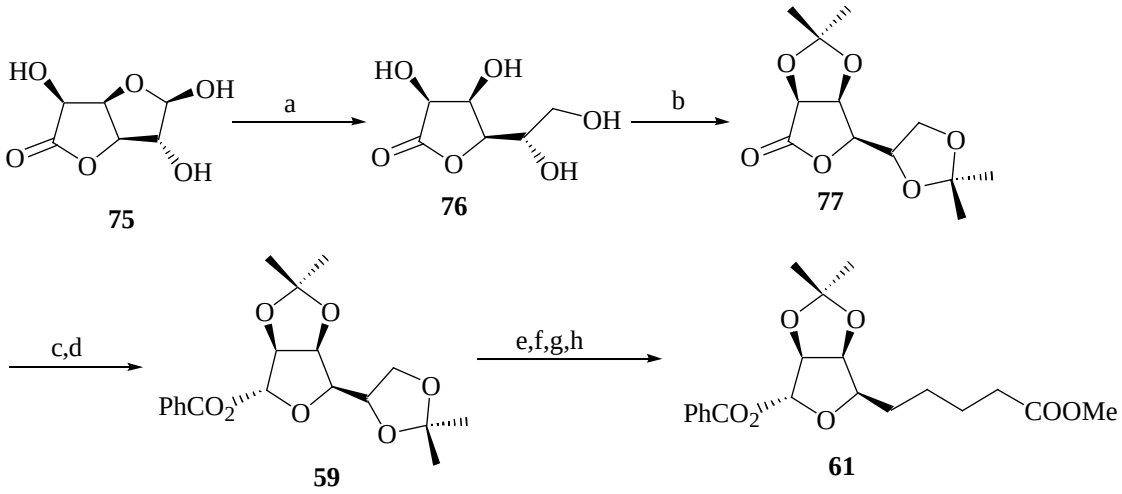
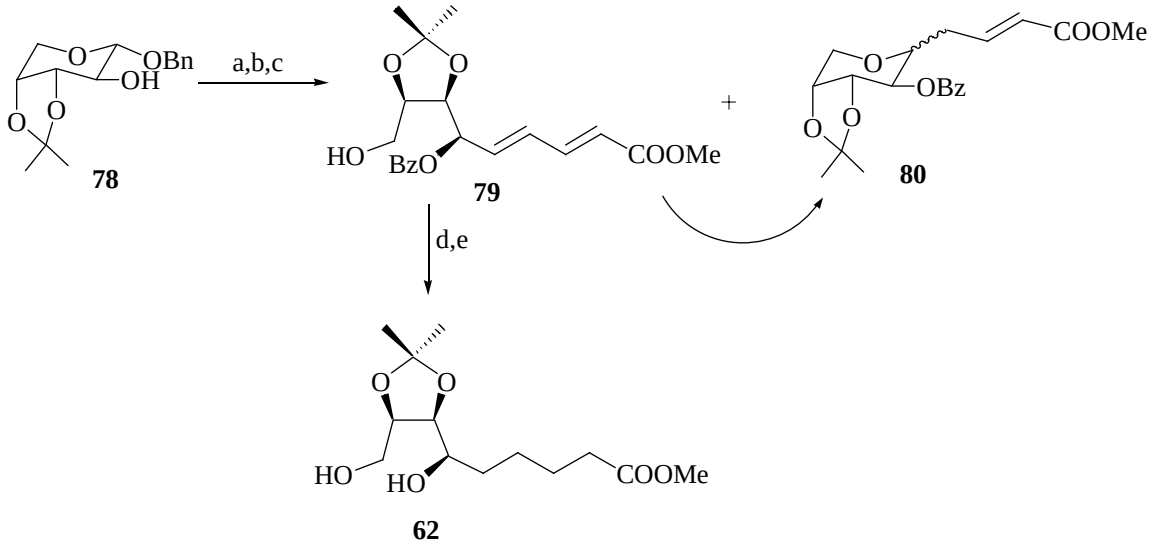


75 **76** **77** **59** **61**

Scheme 18: Reagents and conditions: **a**) H_2, RaNi; **b**) $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH; **c**) $NaBH_4$, CH_3OH, 0 °C; **d**) PhCOCl, CH_5N 96% (over two steps); **e**) CH_3OH, HCl; **f**) $NaIO_4$, acetone/H_2O, 0 °C; **g**) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; **h**) H_2, Pd($NaBH_4$) 79% (over 4 steps).

Ravindranathan's approach: Glucose: [49] (*Carbohydr. Res.* **1984**, *134*, 332.)

A modified synthesis of (+)-biotin from D-glucose was reported by Ravindranathan and co-workers in 1984.[49] The synthesis which is outlined in Scheme 18 leads to the Ohrui intermediate **59**. The starting substance is D-glucurono-6,3-lactone **75** which is first reduced to L-gulono-1,4-lactone **76**. The remaining steps are essentially similar to the Ohrui sequence (Scheme 18).



78 **79** **80** **62**

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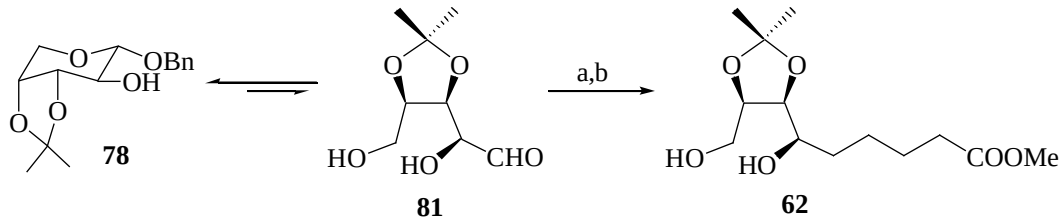
Scheme 19: Reagents and conditions: **a**) PhCOCl, C_5H_5N; **b**) H_2, Pd/C, dioxane; **c**) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; **d**) H_2, Pd/C; **e**) $NaOCH_3$, CH_3OH (65% yield).

Vogel's approach: D-Arabinose: [50] (*Liebigs Ann. Chem.* **1980**, 1972.)

In the context of the use of carbohydrates as starting material for (+)-biotin, D-arabinose is the most logical choice. Vogel and co-workers of BASF reported on this approach in 1980 (Scheme 19).[50] Starting from **78** the corresponding hemiacetal was subjected to Wittig treatment, reduction, and benzoateremoval to yield the known diol **62**. This sequence suffered, however, from a low yield in the Wittig reaction. This was partly due to the formation of the tetrahydropyran **80** intermediate through intramolecular Michael addition of the free hydroxy group to the unsaturated system of **79**.



Scheme 20: Reagents and conditions: **a**) $Ph_3P{=}CHCH{=}CHCOOCH_3$, PhCOOH; **b**) H_2, Pd/C.

Schmidt's approach: D-Arabinose: Wittig modification: [51] (*Synthesis* **1982**, 747.)

This major shortcoming was solved by Schmidt and Maier in 1982 (Scheme 20).[51] D-Arabinose is first converted to the 3,4-*O*-isopropylidene derivative **78**. The latter reacted under the dihydroxy aldehyde form with the usual Wittig reagent, in the presence of benzoic acid, to yield after subsequent catalytic hydrogenation diol **62** in 39% yield. The same Wittig transformation in the presence of an acid ion exchange resin has been claimed to proceed in 53% yield. In 1988, Schmidt and Maier claimed an 82% yield of Wittig product upon simple heating in toluene. The same sequence as shown in Scheme 20 has also been reported but starting from 3,4-cyclohexylidene-D-arabinose.

Amongst the other approaches towards D(+)-biotin some of them are briefly described as follows:

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Chavan's approach III: Radical cyclisation: [52] (*Tetrahedron* **2005**, 61, 9273.)

The key steps involve the unusual stereochemical outcome of radical cyclization[52] of compound **84** to prepare 5,5-fused system **85**. (Scheme 21). Compound **54** on reductive cleavage of carbon-sulphur bond after methoxylation of OH group, with Bu_3SnH in the presence of catalytic amounts of AIBN in benzene at elevated temperatures furnished the corresponding tin thiolate, which without isolation was alkylated with ethyl chloroacetate under anhydrous conditions in acetone using K_2CO_3, furnished **82**. **82** was converted to its thiophenyl derivative **83** with excess of thiophenol in dichloromethane and catalytic amount of *p*-TSA. The ester moiety in the compound **83** was then reduced to aldehyde **43** with DIBAL-H in toluene at –78 ^oC, the crude aldehyde **43** was then converted to its TBS enol ether **84** (*trans:cis* = 3:1) by using TBDMSCl, and DBU in dichloromethane at reflux for 30 min. The crucial step of synthesis, radical cyclisation of silyl enolether **84** was refluxed with Bu_3SnH and catalytic amount of AIBN under argon atmosphere, a single cyclized product **85** was obtained in 53% yield, which was eventually shown to be the undesired 5,5-fused system **85** with incorrect stereocenter at C-5 position. In the next step TBS group was deprotected and oxidized to the corresponding aldehyde under Swern oxidative conditions to furnish bicyclic aldehyde **44.**

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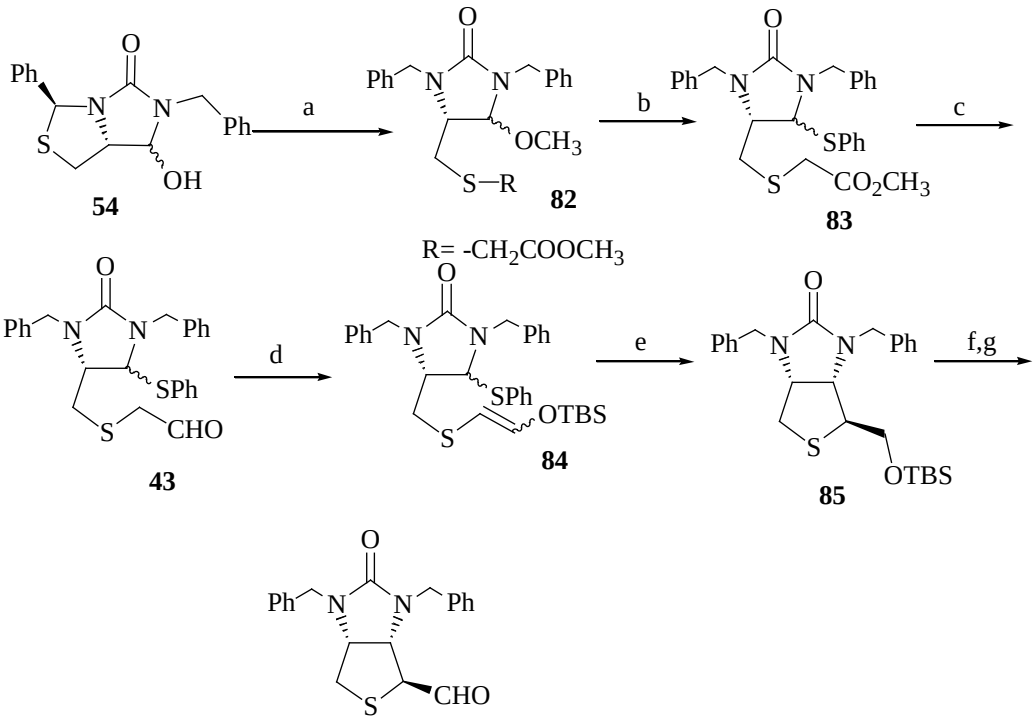
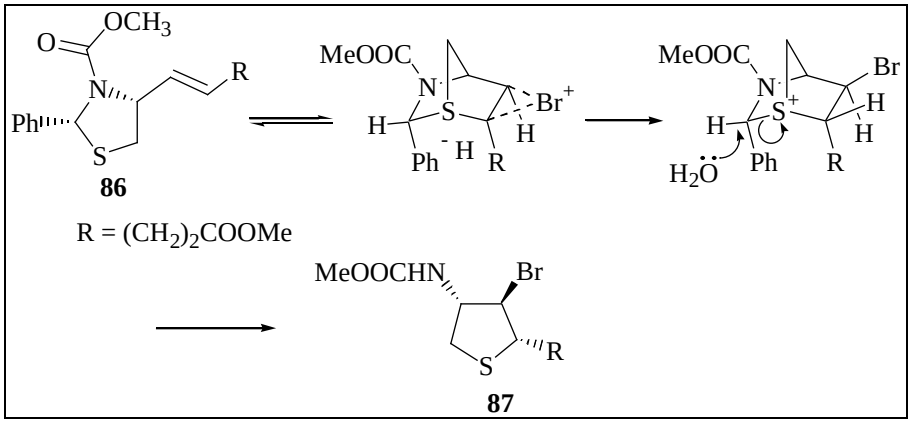


54 **82** **83** **43** **84** **85** **44**

Scheme 21:Reagents and conditions: **a**) **i**) MeOH, pTSA (catalytic), 15 min, 98%; **ii**) Bu_3SnH, iii) $ClCH_2COOMe$, 80% **b**) PhSH, *p*-TSA (cat.), DCM 10 min., 93%; **c**) DIBAL-H, toluene, -78^o C, 2h, 78%; **d**) TBSCl, DCM, DBU, reflux, 30 min., 80% **e**) Bu_3SnH, AIBN, benzene, reflux, 4h, 53%. **f**) $BF_3.Et_2O$, $CHCl_3$, rt. 2 h, 75%; **g**) $(COCl)_2$, DMSO, DCM, Et_3N, -78 ºC to room temp. 2.5 h, 61%.



86 **87**

Scheme 22:

Confalone's approach: [53] (*J. Am. Chem. Soc.* **1975**, *97*, 5936.)

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In 1975, Confalone and co-workers reported an interesting approach in which bromination of olefin **86** resulted in a spectacular and stereospecific rearrangement to **87**. (Scheme 22).[53] It is interesting to note here that the rearrangement occurring upon bromination of **86** is stereospecific.

De Clercq's approach:[43] (*Tetrahedron Lett.* **1993**, *34*, 4365.)

In 1993 and 1994 De Clercq[43] described two different approaches of biotin based on a thermal intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide to an alkene. The approach described in Scheme 23, takes full advantage of the stereochemical outcome of the above mentioned rearrangement (Scheme 22).[53] Indeed, when the methyl ester **89** was brominated in the presence of water, bromide **90** was obtained as the sole isomer. The amino group in **90** was further converted into the benzylated carbamoyl azide **92** *via* cleavage of the urethane to yield **91**, followed by *N*-benzylation by reductive amination, and introduction of the acyl azide group.

When bromide **92** was treated with DBU, the expected E2 elimination product **93** was obtained in excellent yield.

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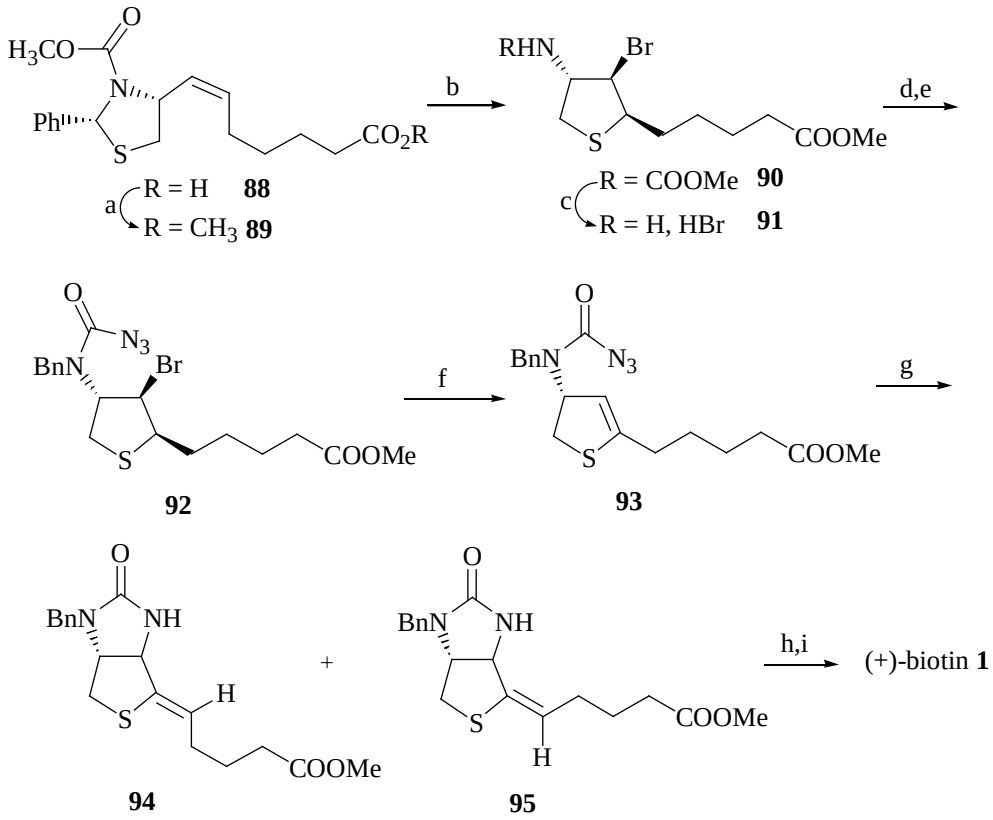

Scheme 23: Reagents and conditions: **a**) CH_2N_2, Et_2O, 0 °C, 99%; **b**) Br_2, $CHCl_3$, H_2O, rt, 65%; **c**) HBr, HOAc, 85%; **d**) PhCHO, $NaCNBH_3$, THF, H_2O, rt; **e**) $COCl_2$, DBU, DCM, 0 °C, NaN_3, acetone/H_2O, rt, 54%; **f**) DBU, THF, reflux, 95%; **g**) autoclave, DCM, 150 °C, 3h, 78%; **h**) H_2 (4 bar), $Pd(OH)_2/C$, EtOAc, rt; **i**) HBr (48%), reflux, 78%.

The crucial intramolecular 1,3-dipolar cycloaddition was effected by treatment of **93** at high temperature in an autoclave. This led to a mixture of (*E*)- and (*Z*)- exocyclic olefins **94** and **95** that were further converted into biotin in the usual way (Scheme-23).

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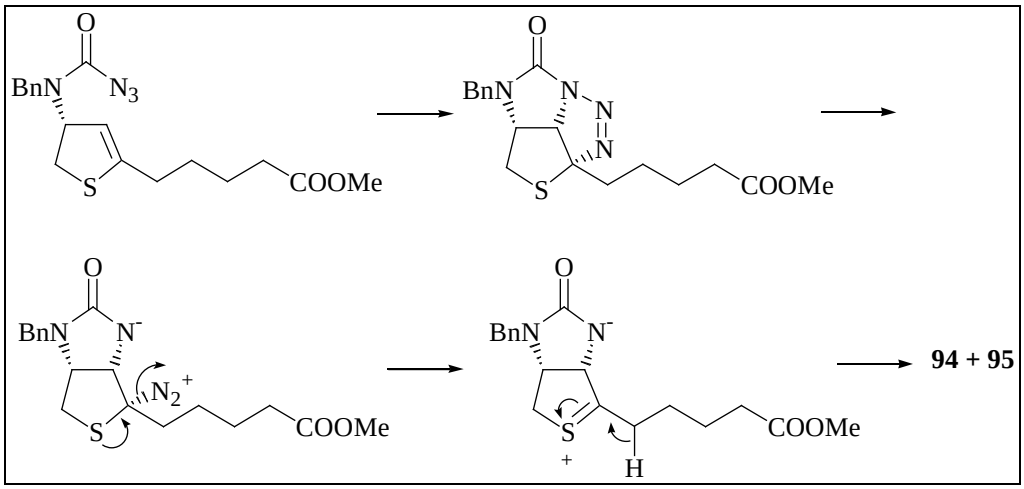

De Clercq's approach II: (*Tetrahedron Lett.* **1994**, *35*, 2615.)

The second approach involved the intramolecular cycloaddition of the benzylated carbamoyl azide **100** (Scheme 24).[55, 56] When this reaction was effected in water as solvent at 145 ^{o}C (autoclave), a mixture of the two monobenzylated forms of biotin **101** and **102** was directly obtained. According to De Clercq the mechanism of this transformation would involve formation of a triazoline, subsequent formation to yield a betaine, nitrogen expulsion with assistance of the proximal sulfur with the concomitant formation of tricyclic sulfonium intermediate, and final nucleophilic attack of water to form the carboxylic side chain of biotin.

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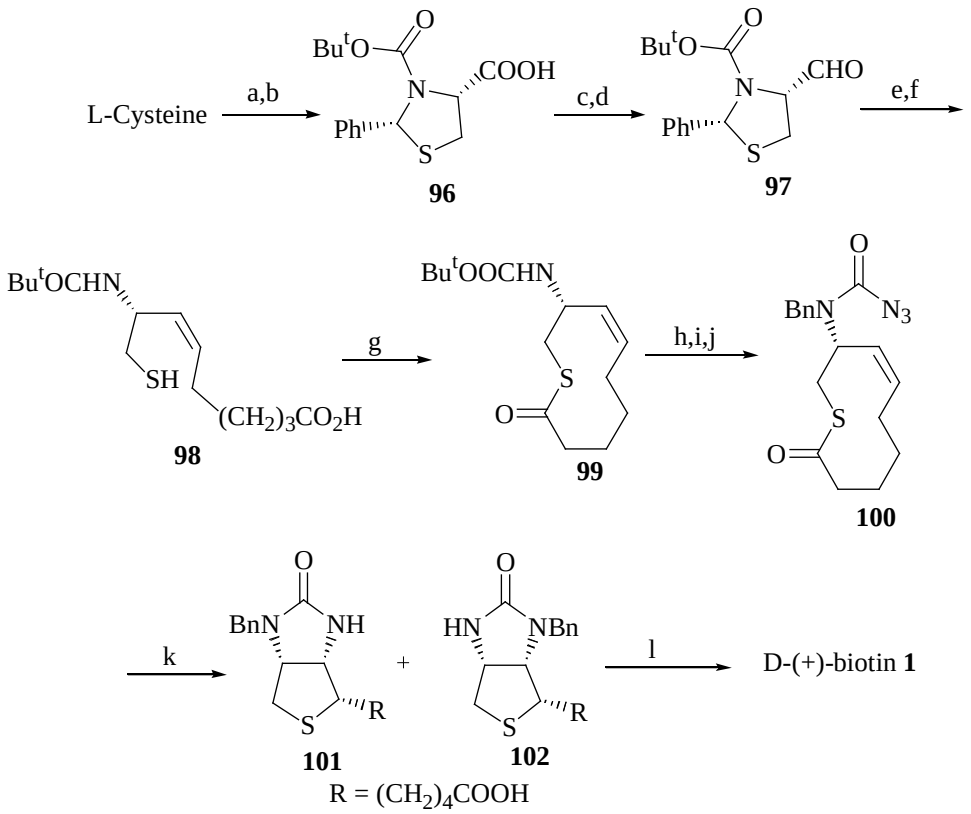
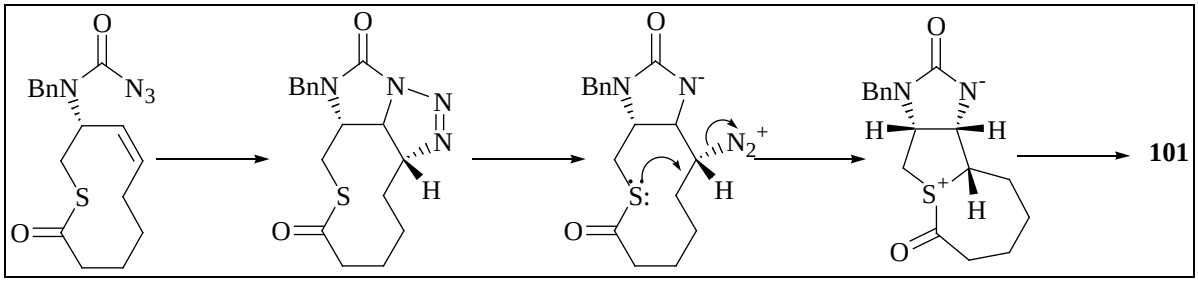


Scheme 24:Reagents and conditions: **a**) PhCHO, KOAc, H_2O, EtOH, rt; **b**) $(Boc)_2O$, NaOH, H_2O, dioxane, 80%; **c**) Me_2S/BH_3, THF; **d**) $(COCl)_2$, DMSO, -60 °C, Et_3N, 66%; **e**) $[Ph_3P(CH_2)_5COOH]Br$, 2eq. of LDA, THF, rt, 1h; **f**) Na liq.NH_3, H_3O^+, 78%; **g**) $PhOP(O)Cl_2$/DMF, DCM, rt, 24%; **h**) HCl, Et_2O, 0 °C; **i**) PhCHO, $NaCNBH_3$, THF/H_2O (pH=4), 0 °C; **j**) $COCl_2$, DBU, NaN_3, acetone/H_2O, rt; 40%; **k**) H_2O, autoclave, 145 °C, 2h, 42%; **l**) HBr (48%), reflux, 2h, 85%.



Fujisawa's approach: [57] (*J. Org. Chem.* **1994**, *59*, 5865)

In 1994 Fujisawa and coworkers reported an interesting approach to (+)-deoxybiotin from L-cysteine (Scheme 25).[57]

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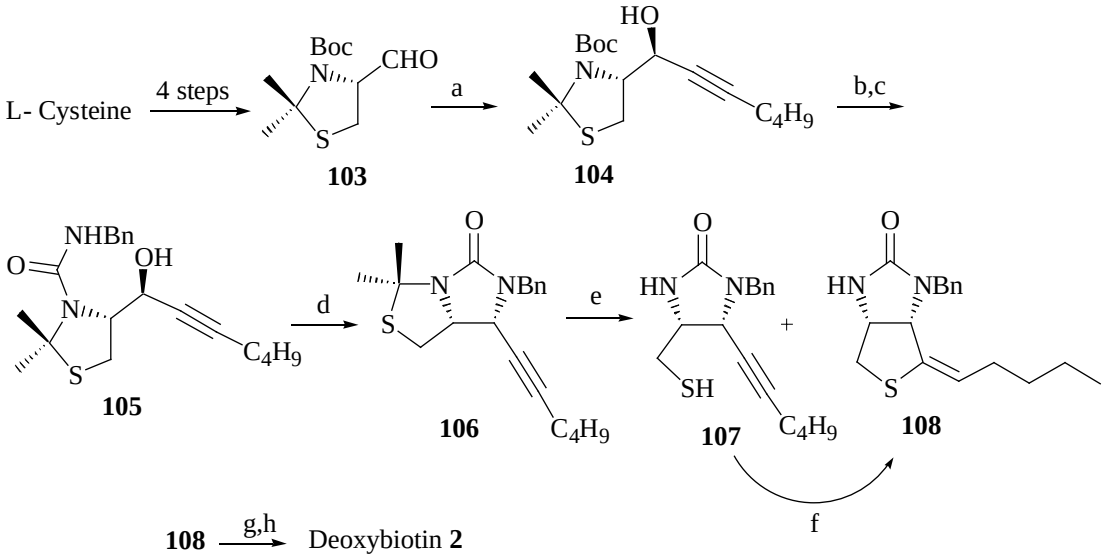
The synthesis involves the diastereoface discrimination in the addition of an acetylide to chiral aldehyde **103**. The compound **103** is obtained from L-cysteine *via* a known four-step sequence involving thiazolidine formation, *N*-urethane protection, esterification and reduction with DIBAL-H.[58] When the chlorozinc acetylide derived from 1-hexyne was condensed with aldehyde **103**, the propargylic alcohol **104** was obtained as the sole isomer in very good yield. The high selectivity is rationalized in terms of chelation-control model in which the metal is chelated by the aldehyde and carbamate oxygens. Introduction of the amino group at C_3 in the required configuration resulted from an internal SN^2 displacement *via* potassium hydride treatment of the tosylated alcohol **105**. The latter was obtained from **104** after hydrolysis and formation of the mixed urea. Deprotection of the acetonide in **106** with 1 eq. of p-toluenesulphonic acid (*p*-TsOH) led to the cyclized thiophane **108** (23% yield !) along with thiol **107** in 65% yield.

Further cyclization of **107** presented a regiochemical problem, since an undesired six membered isomer was formed in addition to desired **108**. The final conversion of **108** into (+)-deoxybiotin **2** further involved catalytic hydrogenation and debenzylation.



Scheme 25: Reagents and conditions: a) $C_4H_9C{\equiv}C\text{-}ZnCl$, Et_2O, 10h, 86%; **b**) p-TsOH, MeOH, 35 °C, 11h; **c**) $PhCH_2NCO$, C_5H_5N, 0 °C, 70%; **d**) KH, (5eq), p-TsCl, HMPA (30 eq), THF, 86%; **e**) p-TsOH,

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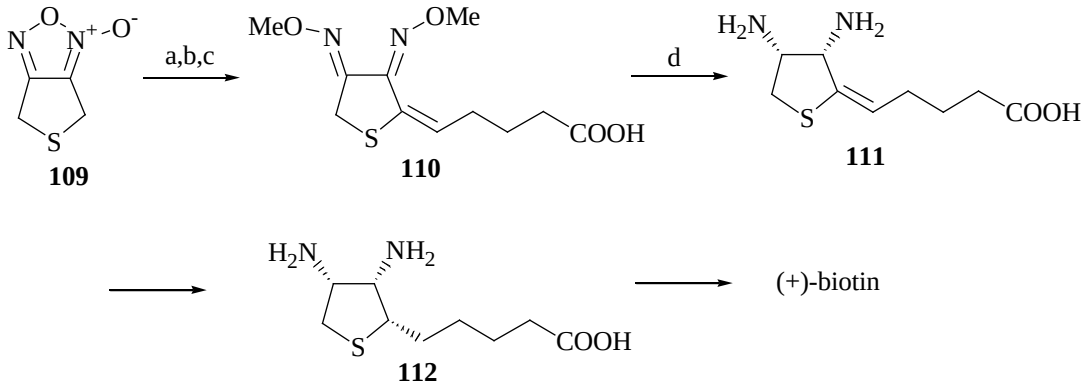
MeOH/H_2O, 40 °C, 15h (O_2 free!!) **107** (65%), **108** (23%); **f**) CsOH, H_2O/THF (10:1), 40 °C, 50%; **g**) H_2 (10 bar), Pd/C, 2-propanol/H_2O (6:1), 40°C; **h**) HBr (47%), reflux, 73%.

Kurimoto's approach: [59] (JP 06 263 752, Sept 20, 1994; Chem. Abstr. **1995**, *122*, 81011s.) An interesting short and enantioselective synthesis of (+)-biotin has been claimed by Kurimoto *et al.*[59] Starting from **109**, the carboxybutyl chain is introduced *via* condensation with 5-oxopentanoic acid (Scheme 26).

After reduction of the furoxan ring with hydrazobenzene and methylation, acid **111** is obtained. When the latter is reduced with borane-THF complex in the presence of norephedrine the *cis*-3,4-diamino derivative **112** is formed. The diamine **112**, *via* a known precursor, is converted to (+)-biotin.



Scheme 26: Reagents and conditions: a) LDA, $OHC(CH_2)_3CO_2H$; **b**) PhNHNHPh; **c**) methylation; **d**) BH_3/THF, norephedrine.

Chen's approach: [60] (*Synthesis*, **2000**, 2004.)

In 2000 Chen and co workers reported[60] an efficient and enantioselective synthesis of D-(+)-biotin using BINAL-*H* reduction of *meso*thioanhydride **117** (Scheme 27).

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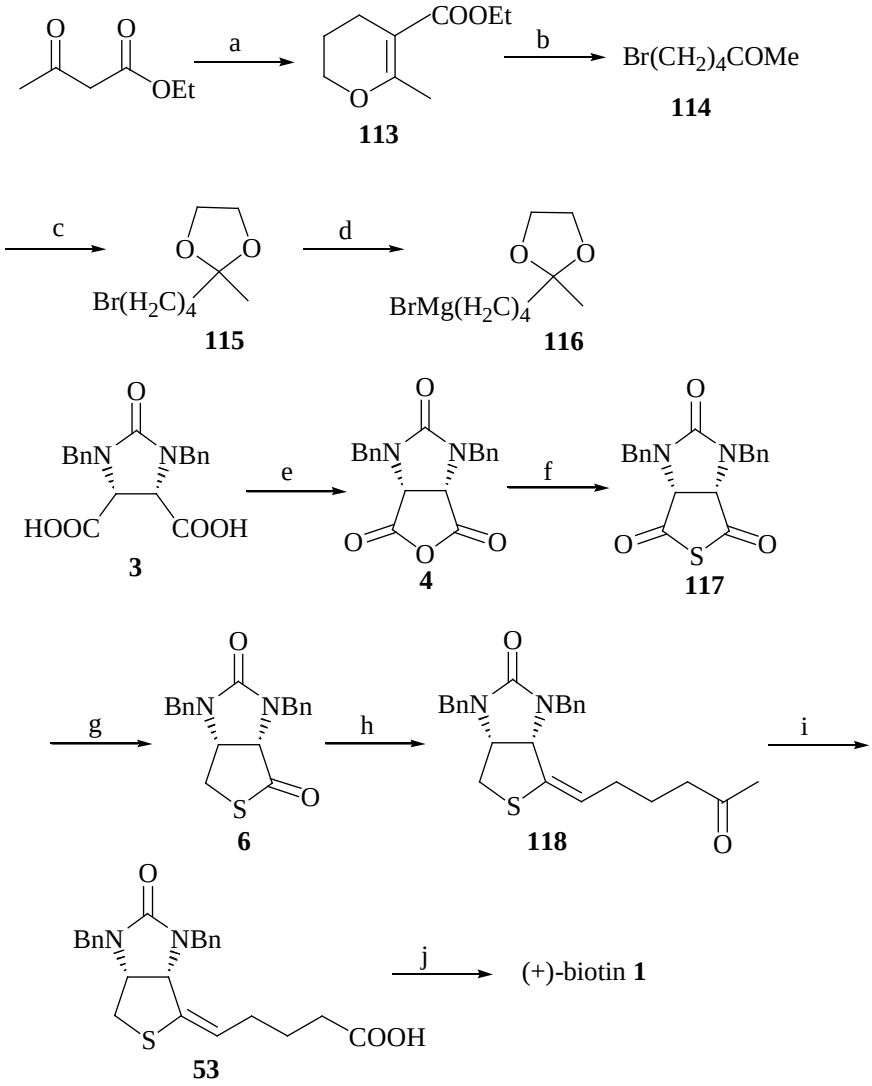
The synthesis starts with *cis*-1,3-dibenzyl-2-imidazolidine-4,5-dicarboxylic acid **3**. The key steps are the enantioselective reduction of meso-1,2-dicarboxylicthioanhydride **117** to prepare the (3a*S*, 6a*R*)-thiolactone **6**, and the introduction of the C_6 side chain at C_2 in **6** *via* a modified Grignard reaction. This novel synthesis proceeded in six steps starting from **3** to afford **1** with 21% overall yield.



Scheme 27: Reagents and conditions: **a**) 1-Bromo-3-chloropropane, K_2CO_3, toluene, 80 ^oC, 94%; **b**) 47% HBr, NaBr, H_2SO_4, 50 ^oC, 86%; **c**) $(CHOH)_2$, TsOH, toluene, reflux, 92%; **d**) Mg, THF, rt; **e**). Ac_2O, 83% H_3PO_4 (cat.) ,reflux, 98%; **f**) $Na_2S.9H_2O$, THF, H_2O, rt, 49%; **g**) (R)-BINAL-H, THF, -78 ^oC to rt, 83%; **h**) **95**, THF, reflux, then 30% H_2SO_4, 60 ^oC, 82%; **i**) I_2, KI, 10% NaOH, dioxane, 60 ^oC, 75%; **j**) 75% HCOOH, CH_3SO_3H, 10% pd/c, reflux, 85%.

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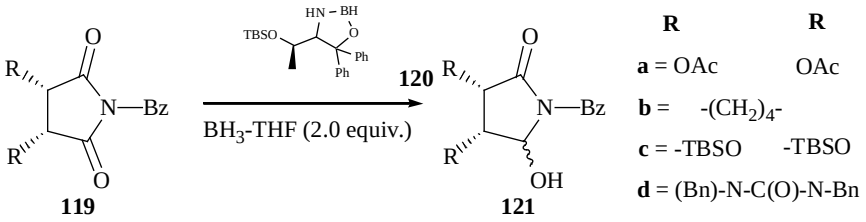
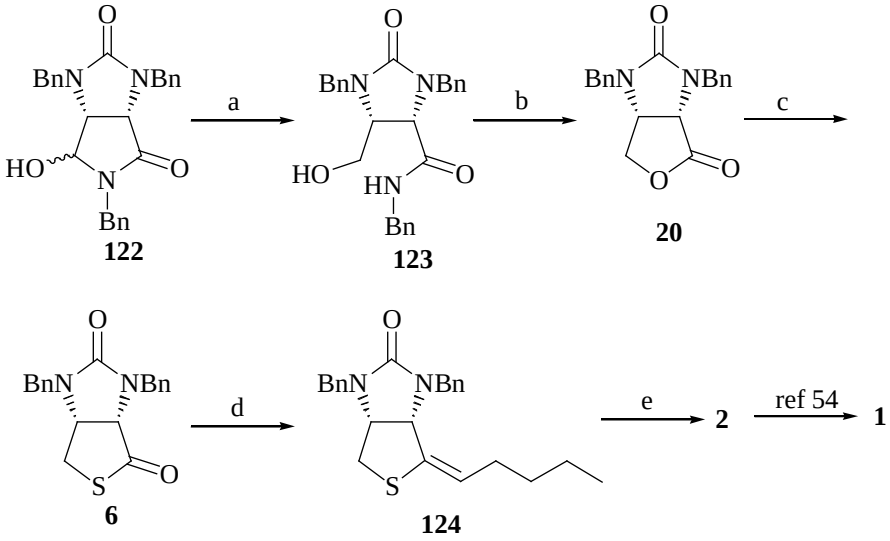
Shimazu's approach: Asymmetric reduction: [61] (*Tetrahedron Lett.* **1999**, *40*, 8873.)

In 1999 Shimazu and coworkers[61] reported stereocontrolled reduction of *meso*-imides using oxazaborolidine.



The known *meso*-imide **119** was reduced using oxazaborolidine derived from L-threonine and borane-THF complex **120** to give lactams **121a-d** in high enantiomeric purity. This methodology was successfully applied to the synthesis of (+)-deoxybiotin in an enantio controlled manner in good overall yield.



Scheme 28: Reagents and conditions: a) $NaBH_4$ (4.0 eq), THF-H_2O (10:1), 71%; **b**) 2N H_2SO_4-1,4-dioxane (8:1), 0 ^oC, 92%; **c**) CH_3COSK, DMF, 150 ^oC, 87%; **d**) n-$C_5H_{11}MgBr$, THF, AcOH, reflux, 82%; **e**) **i**) Pd black, H_2, 40 ^oC, ^{i}PrOH-H_2O(6:1), 90%; **ii**) Na liq. NH_3, THF, 62%.

The hydroxy lactam **122** was reduced with $NaBH_4$ to give hydroxy amide **123** in 71% yield and the subsequent treatment with sulfuric acid gave the lactone **20** in 92% yield. Thiolactone **6** formation was carried out as described in the literature[62] in 87% yield. The side chain was

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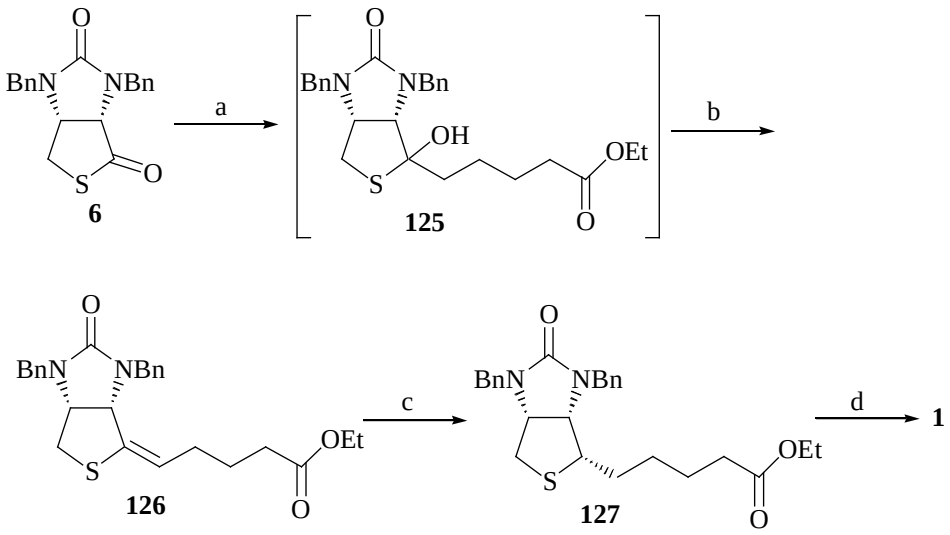
introduced by the addition of a Grignard reagent followed by treatment with acetic acid gave **124** in 82% yield. Stereospecific hydrogenation of double bond and further *N*-debenzylation with Na in liq. NH_3 gave (+)-deoxybiotin **2** in 62% yield.

Seki's approach I: [63,64] (*Tetrahedron Lett.* **2000**, *41*, 5099.)

Very recently Seki *et al* reported[63] a facile synthesis of D(+)-biotin by using Fukuyama coupling[64] of carbonyl compounds.



Scheme 29: Reagents and conditions: a) $IZn(CH_2)_4CO_2Et$ **103** (3 eq), $PdCl_2(PPh_3)_2$ (10 mol%), THF, toluene, DMF, 20 ^oC, 35h; **b**) pTSA, toluene, 20 ^oC, 18h, 86%; **c**) H_2, (70 atms), Pd/C, EtOH, 100 ^oC, 3h, 91%; **d**) **i**) 48% aq. HBr, reflux, 48h; **ii**) ClCOOEt, NaOH; **iii**) HCl, 80%.

The known thiolactone **6** with zinc reagent **103** in presence of $PdCl_2(PPh_3)_2$ in mixed solvent at 20 ^oC for 35 h gave alcohol **125** which without purification was allowed to react with *p*-TSA in toluene at 20^oC to furnish the known olefin **126** in 86% yield. The final conversion of **126** into (+)-biotin **1** further involved catalytic hydrogenation and debenzylation.(Scheme 29).

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Mioskowski's approach: [65] (*Eur. J. Org. Chem.* **2000**, 3575.)

Mioskowski and co workers[65] reported the synthesis of the diastereomers of dethiobiotin using the conjugate addition of 4-phenyloxazolidin-2-one to a nitroalkene (Scheme 30).

Nitroalkene **130** was prepared according to the sequence described in scheme 30. Commercially available 7-bromoheptanenitrile was converted in three efficient steps into known methyl 7-nitroheptanoate **129**. Henry reaction of **129** with acetaldehyde followed by elimination of hydroxy group by converting it into its acetate with Ac_2O followed by basic alumina treatment yielded nitroalkene **131** as a 90:10 (*E*) and (*Z*) isomers. Conjugate addition of the potassium salt generated from either (*R*)-**132** or (*S*)-**132** by treatment with potassium *tert*-butoxide in THF in the presence of 0.1 eq of 18-crown-6, with nitroalkene **131** furnished two diastereomeric adducts (85:15) which were separated by column chromatography.

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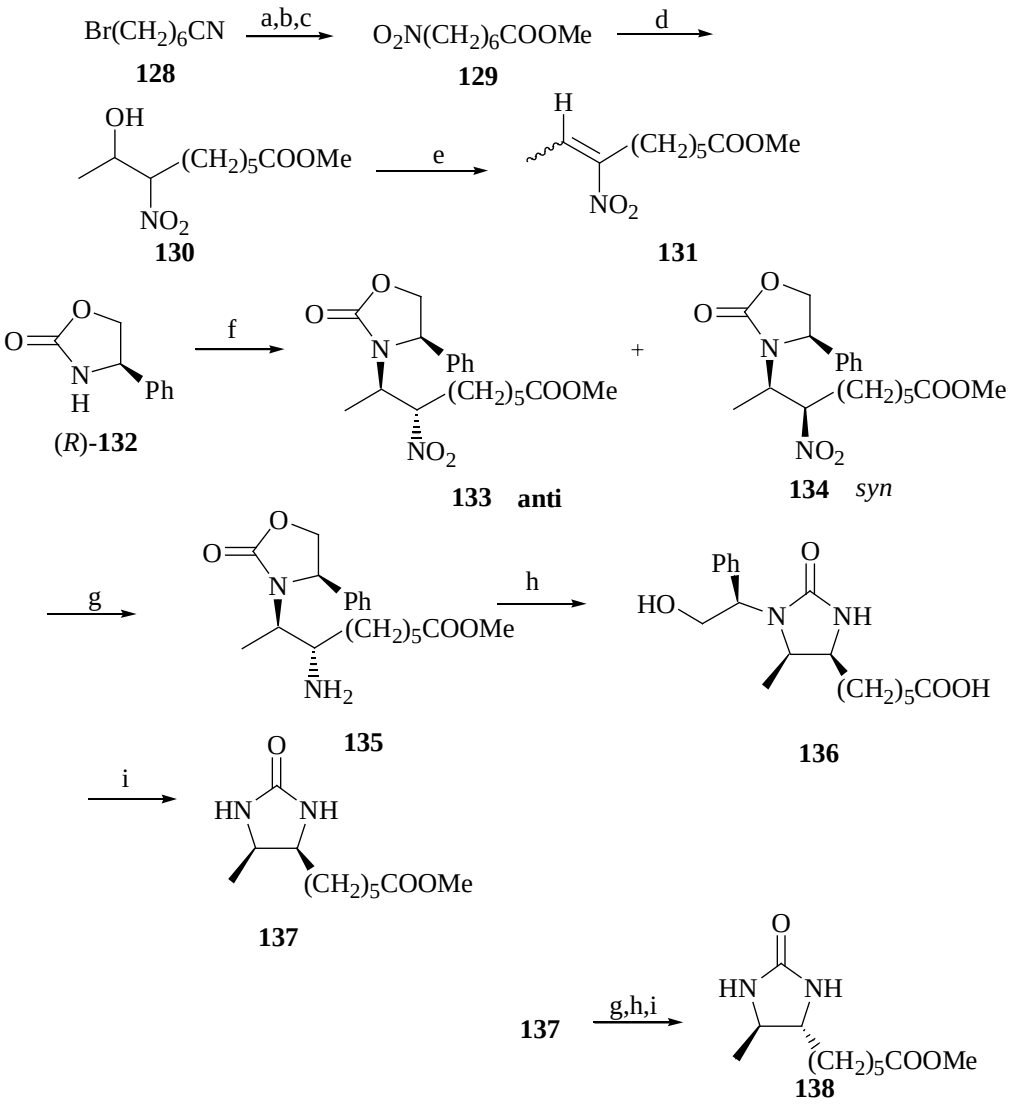

Scheme 30: Reagents and conditions: a) H_2SO_4, MeOH, 40h, reflux, 66%; **b**) NaI, acetone, 30h, reflux, 94%; **c**). $AgNO_2$, ether, 3 days, rt, 80%; **d**) CH_3CHO, KOH, MeOH, 19h, 0 °C, 84%; **e**) **i**) DMAP, Ac_2O, ether, 16h, rt; **ii**) DMAP, basic alumina, 4h, reflux, 63%; **f**) **i**) ^tBuOK, 18-crown-6 (cat.), THF, 0 °C, 20 min, **ii**) **73**, -78 °C, 45 min; **iii**) AcOH, 74%. **g**). HCO_2NH_4, Pd/C, MeOH, 3 days, 72%; **h**) KOH, MeOH, 16h, reflux, 89%; **i**) H_2, $Pd(OH)_2$/C, MeOH, H_2SO_4(cat), 2 days 63%.

The adducts **133** and **134** and their enantiomers *ent*-**133** and *ent*-**134** obtained from (*S*)-4-phenyloxazoldin-2-one were then all converted into the dethiobiotin methyl ester or into its stereoisomers. Treatment of **133** with ammonium formate in the presence of palladium on carbon in methanol afforded the corresponding amine **135**. Heating this compound at reflux with potassium hydroxide in methanol led to the more stable imidazolidinone **136**. And finally

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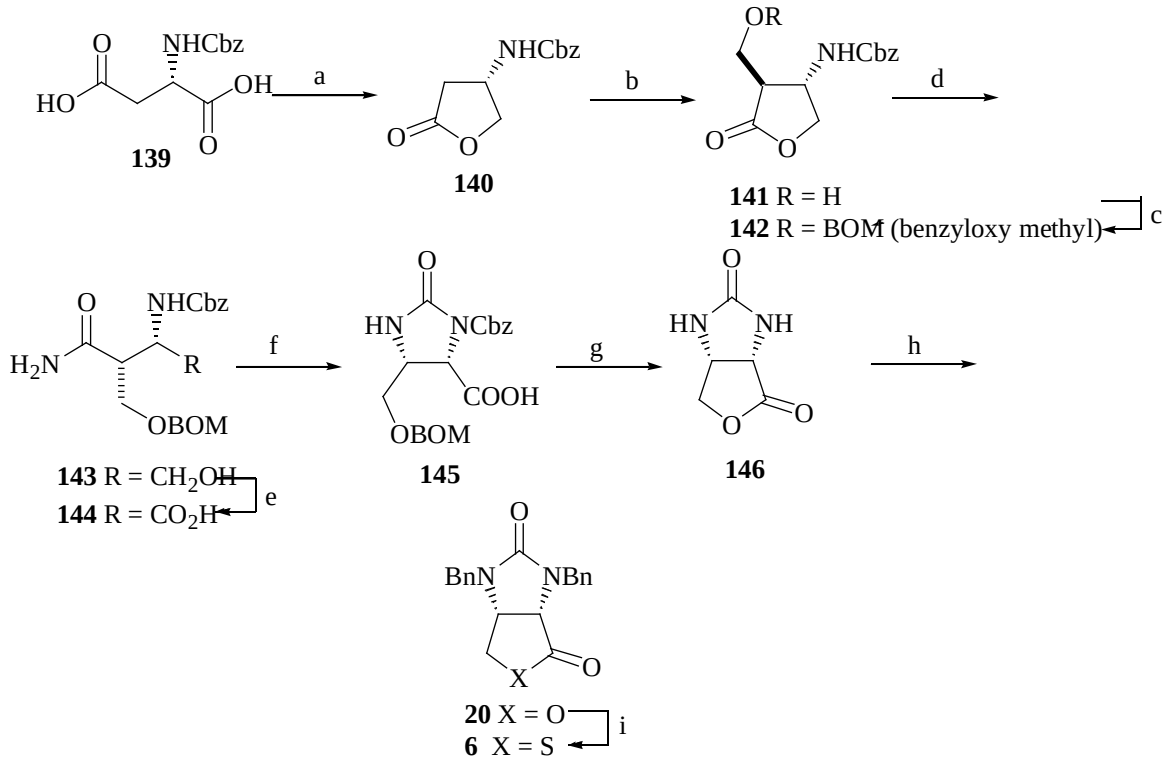
the imidazolidinone **136** was subjected to hydrogenolysis to get imidazolidinone **137**. The same sequence was carried out for nitro compound **134** as summarized in the above scheme, 30.



Scheme 31: Reagents and conditions: a) **i**). Ac_2O, **ii**). $NaBH_4$, THF, **iii**). HCl, 95%; **b**). **i**). LDA, THF, **ii**). HCHO, –78 °C, 62%, *trans*/*cis* = 12:1; **c**). BOMCl, *i*-Pr_2NEt, THF, quant.; **d**). NH_4OH, MeOH, 58%; **e**). Jones' reagent, acetone, 76%; **f**). NaOCl, NaOH, H_2O, 70%; **g**). H_2, $Pd(OH)_2/C$, MeOH, 80%; **h**). BnBr, NaH, DMF, 84%; **i**) AcSK, DMF,92%

Sekis's approach II: [66] **Aspartic acid:** (*Synthesis* **2002,** *3*, 361-364.)

In 2002 Seki et. al. reported the synthesis of biotin starting from L-aspartic acid as chiral synthon.(scheme 31)[66]

The aldol reaction of an *N*-Cbz-3-amino-4-butanolide **140**, derived from L-aspartic acid, with formaldehyde gave the *trans*-disubstituted 3-amino-4-butanolide **141** stereoselectively. Following protection of the hydroxyl group of **141**, amidation and oxidation provided the substituted L-asparagine derivative **144**. The Hofmann rearrangement of **144** with sodium hypochlorite in the presence of sodium hydroxide and subsequent hydrogenation gave the

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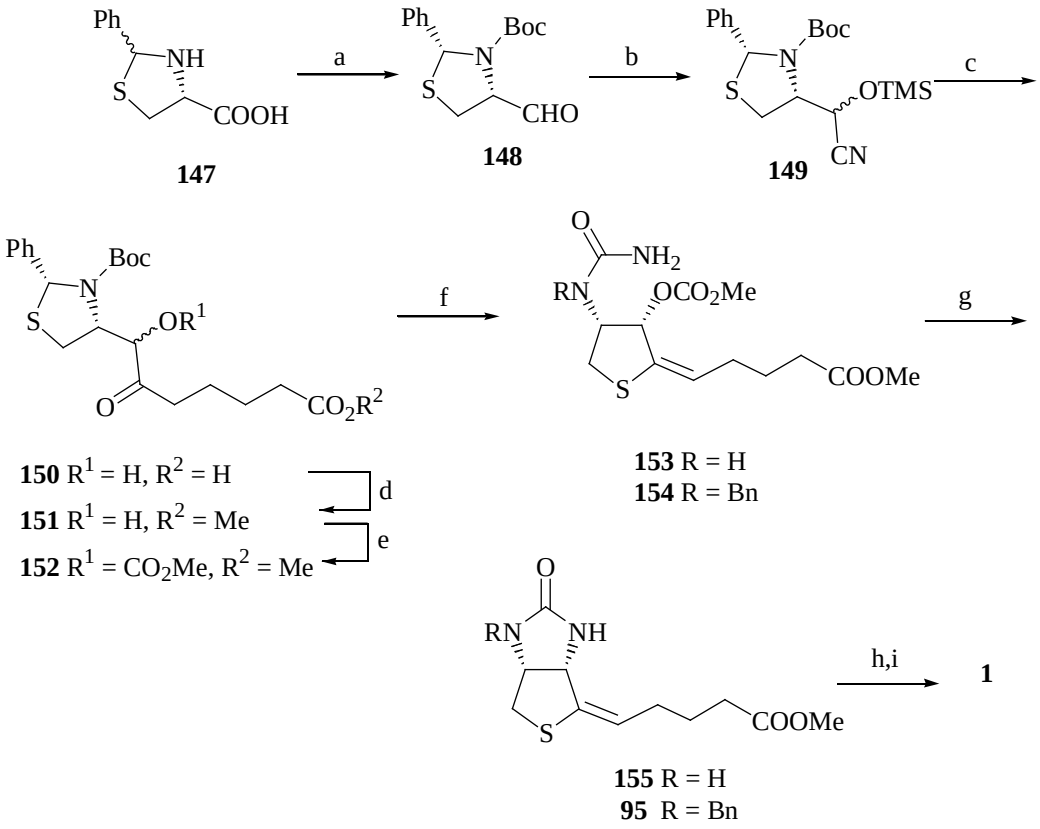
bicyclic lactone **146**, which upon dibenzylation and thionation, gave the thiolactone **6**, a key intermediate for the synthesis of (+)-biotin.



Scheme 32: Reagents and conditions: a). **i**) PhCHO, AcOK, EtOH, H_2O, 96%; **ii**) $SOCl_2$, EtOH **ii**) $Ca(BH_4)_2$, EtOH, quant; **iii**) $(Boc)_2O$, Na_2CO_3, THF, H_2O, 88%. **iv**) SO_3-Py, Et_3N, DMSO 10 ºC, quant. **b**) TMSCN, *n*-Bu_3P, −10°C, CH_2Cl_2, **c**) **i**) $BrMg(CH_2)_4MgBr$, *n*-Bu_2O, toluene, −3 to −25°C, **ii**) CO_2, **iii**) aq. citric acid, 79%; **d**) Me_2SO_4, K_2CO_3, 25°C, DMF, 73%; **e**) $ClCO_2Me$, Et_3N, DMAP, 0°C, THF, quant.; **f**) for **5a**: **i**) AcCl, MeOH, toluene, 0°C, **ii**) KOCN, H_2O, 25°C, 86%; for **5b**: i) AcCl, MeOH, toluene 0°C, (ii) PhCHO, $NaBH_3CN$, THF, H_2O, 5°C, **iii**) KOCN, H_2O, 25°C, 82%; **g**) for **6a**: $Pd(OAc)_2$, $NaHCO_3$, $P(OEt)_3$, THF, H_2O, 38 °C, 30%; for **6b**: $Pd(OAc)_2$, $NaHCO_3$, $P(OEt)_3$, DMF, *n*-Bu_4NCl, 100°C, 77%; **h**) H_2, $Pd(OH)_2$/C, 25°C, AcOEt; **i**) aq. HBr, reflux, 85% (two steps).

Seki's approach III: (*Tetrahedron Letters* **2002,** *43*, 3269; *J. Org. Chem.* **2002**, *67*, 5527.)

In the same year 2002 Seki et. al. reported yet another synthesis of biotin starting from thiazolidine carboxylic acid **147**. (Scheme 32)[67]

The synthesis of *cis*-fused bicyclic ring skeleton of biotin is based on the palladium-catalysed intramolecular allylic amination with the retention of configuration. The aldehye **148** prepared

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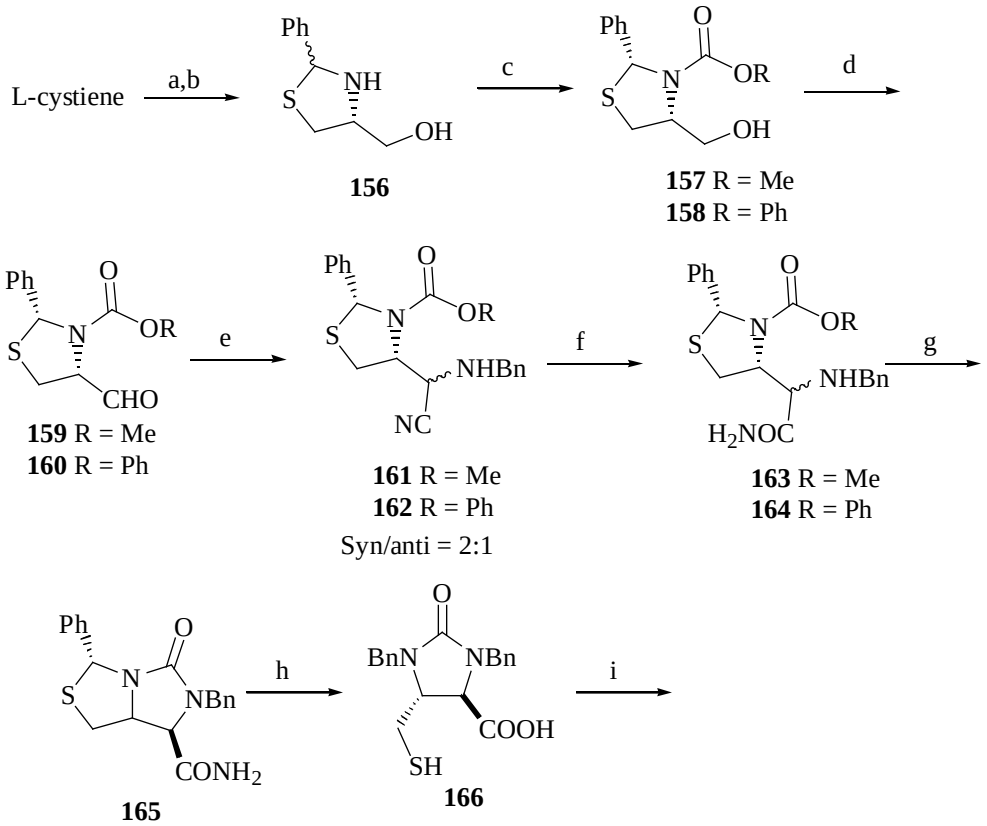
from L-cystiene in 4-steps followed by oxidation of primary alcohol with sulfur trioxide/pyridine as an oxidant. The aldehyde **148** was subjected to Lewis base catalysed cyanosilylation with TMSCN in the presence of n-Bu_3P at –10 ºC to obtain cyano silylated compound **149** with excellent diastereoselectivity (anti/syn = 92:8) in high yield. The carboxybutyl chain of **1** was installed by the reaction of the *in situ.* generated *O*-TMS-cyanohydrin **149** with di-Grignard reagent derived from 1,4-dibromobutane and subsequent treatment with carbon dioxide. The ketoacid **150** thus obtained was esterified and purified by crystallization to give enantiomerically and diastereomerically pure ketoester **151** in 73% yield. The hydroxyl group of **151** was then protected as a methyl carbonate, which, in a later step, functioned as an activating group for the ring closure. Treatment of **152** with acetyl chloride in the presence of methanol effected the successive transformations involving removal of the Boc and benzylidene groups, cyclization to the tetrahydrothiophene ring and dehydration. (Scheme 32)



Scheme 33: Reagents and conditions: a). PhCHO, H_2O, EtOH, 96%; **b**). **i**). $SOCl_2$, EtOH; **ii**). $Ca(BH_4)_2$, EtOH, quant.; **c**). $ClCO_2R$, Na_2CO_3, THF, H_2O, **157** 88%, **158** 86%; **d**). SO_3–py, Et_3N, DMSO, **159** 91%, **160** 92%; **e**). **i**). $BnNH_2$, CH_2Cl_2, MS (4 Å) **ii**) TMSCN, **161** 84%, **162** quant. **f**). H_2O_2, K_2CO_3, DMSO, **163**

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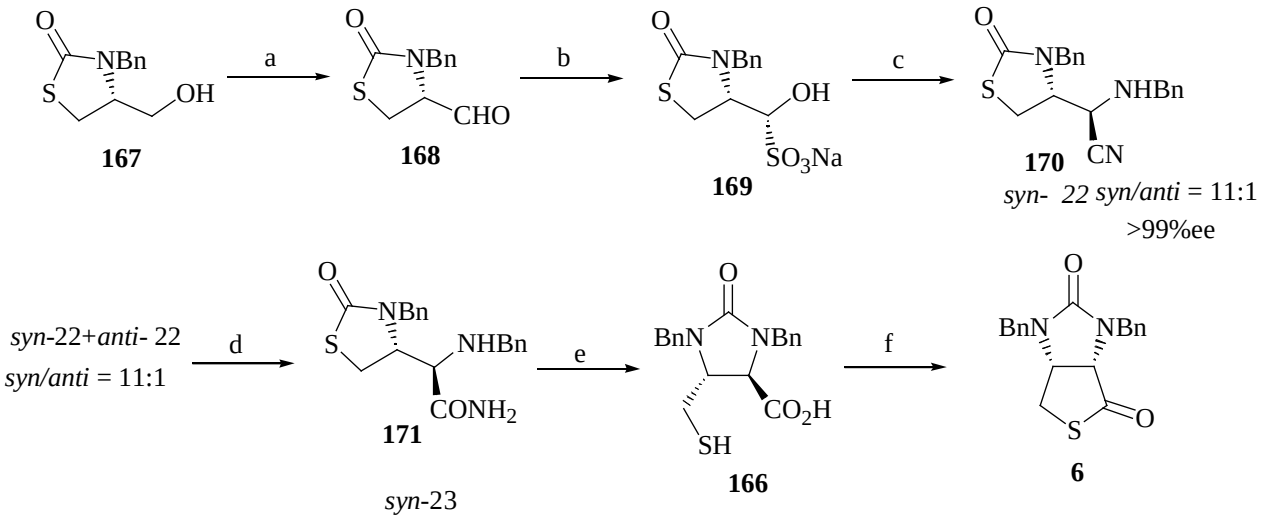
65%, **164** 60%; **g**). DMF, 100 °C, 2 h, 60%; **h**). i). Zn, AcOH, 100 °C **ii**). HCl, H_2O, AcOH, 110 °C, 87%; **i**). DCC, *p*-TsOH, pyridine, toluene, 75%.

The resulting crude amine hydrochloride was treated with potassium cyanate to furnish a *cis*- allylic carbonate **153** in 86% yield based on **152**. Treatment of **153** with $Pd(OAc)_2$ in the presence of $P(OEt)_3$ and $NaHCO_3$ in aqueous THF afforded the desired cyclized product **155** albeit in a poor yield (30%). conditions as those for the cyclization of **154**, expectedly affording **95** in good yield (60%). Following the reported procedure, the compound **95** was converted to (+)- biotin (**1**) in 85% yield through hydrogenation and subsequent deprotection with aqueous HBr, thus providing access to biotin in 11 steps.

Seki's approach IV: [68] (*Synthesis* **2003,** 15, 2311.)

The same group Seki et. al. reported another synthesis of biotin from L-cysteine utilizing Strecker reaction as key sep.(Scheme 33). [68]

The Strecker reaction of (2*R*,4*R*)-2-phenyl-3-phenoxycarbonylthiazolidine- 4-carbaldehyde **159/160** which was readily prepared from L-cysteine, with benzylamine and trimethylsilyl cyanide provided amino nitrile **161/162** stereoselectively (*syn–anti*, 2:1). Amidation of **161/162** and subsequent cyclization gave bicyclic compound **165**, which, upon reduction with zinc dust, hydrolysis and subsequent cyclization, furnished thiolactone **166**, a key intermediate for (+)-biotin **1**.



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Scheme 34: Reagents and conditions: **a**) DCC, TFA, pyridine, DMSO, AcOEt, 50˚C, 3h; **b**) $NaHSO_3$, AcOEt, H_2O, 20 ˚C, 18h; **c**) **i**) $BnNH_2$ (1.7 equiv), CH_2Cl_2, 20 ˚C, 2h, **ii**) NaCN (1.2 equiv), 8–20 ˚C 20h, **iii**) $NaHSO_3$ (0.3 equiv), NaCN (0.3 equiv), 20 ˚C, 1.5 h. **d**) **i**) H_2O_2, K_2CO_3, DMSO/CH_2Cl_2, 20 ˚C, 2.5 h, **ii**) H_2O, filtration, **iii**) for the filtrate: HCl; **e**) (i) DMF, 90 ˚C, 1h, **ii**) HCl; **f**) DCC, TFA, pyridine, $CHCl_3$, 5˚C reflux, 5h; **g**) 120 ˚C, 5h DMF.

Seki's approach V: (*Tetrahedron Letters* **2004,** *45*, 6579.;*Chemistry- A European journal* **2004**, *10*, 6102.)

In another synthesis of biotin from same group a *syn*-selective Strecker reaction of α-amino aldehyde **168** to β-amino-α-amino nitrile *syn* **172** was obtained to allow an access to thiolactone **6**, a key intermediate for **1**. (Scheme 34) Overcoming the problems of earlier synthesis like using TMSCN for cyanosilylation. Amino alcohol **167** was allowed to the Moffatt oxidation employing DCC in the presence of TFA and pyridine to effect a clean conversion to α-amino aldehyde **168** (90% yield) The resulting solution of **168** in AcOEt was treated with sodium bisulfite (1.1 equiv) in water to provide the bisulfite adduct **169** in excellent yields (99% conversion). The aqueous solution of **169** (vide supra) was treated with benzylamine in a biphasic system involving CH_2Cl_2 and water at 20 ºC for 2 h. The resulting mixture involving an imine and a bisulfite adduct of the imine was treated with NaCN (1.2equiv) at 8 ºC and the whole was stirred at ambient temperature for 20h to provide α-amino nitrile **170** as a solution of CH_2Cl_2 with high diastereoselectivity and in high yield (syn/anti = 11:1, 95% assay yield). The resulting CH_2Cl_2 solution of **170** was directly allowed to amidation employing H_2O_2, K_2CO_3 and DMSO. The reaction smoothly proceeded even in a mixed solvent of DMSO and CH_2Cl_2 to afford the corresponding amide **171** in quantitative yield. *Syn* **171** was allowed to undergo the ring transformation from 2-thiazolidinone to 2-imidazolidinone through *S,N*-carbonyl migration and subsequent hydrolysis to give thiol carboxylic acid **166** in 95% yield. The compound **166** obtained was cyclized and isomerized to thiolactone **6** in 93% yield. In contrast, the antiisomer *anti* **171** was directly converted to **6** in 91% yield with heating at a higher temperature (120 ºC) through the *S,N*-carbonyl migration followed by spontaneous cyclization.

Chen's approaches: (*Synthesis* **2003**, *14*, 2155.; *Chem. Pharm. Bull.* **2005**, *53*,743.)

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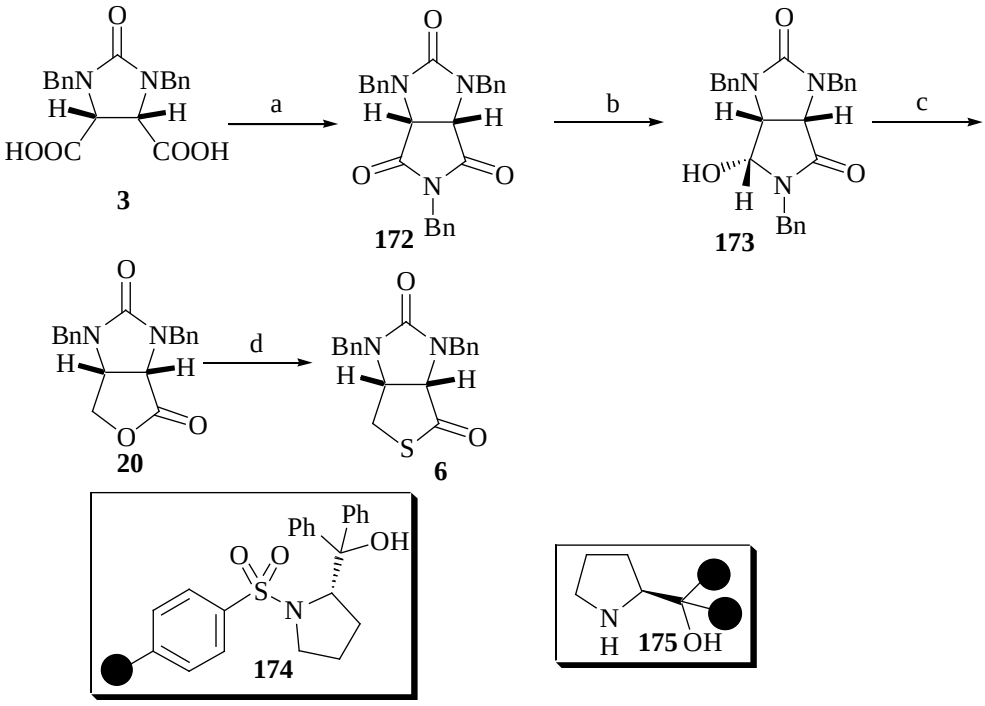
The essential steps in the two syntheses involve the enantioselective reduction of *meso*-cyclic imide **172** catalyzed by a polymer-supported chiral oxazaborolidine derived from (*S*)-diphenylprolinol and polymer-bound sulfonyl chloride **174**, or chiral polymer supported oxaborolidine **175** derived form polymer supported ligand. (Scheme 35)[70] The reduction using -80% NaH, $BF_3.Et_2O$, **175**, THF, reflux, was claimed to be advantageous over **174**, $BH_3{\cdot}SMe_2$, THF, reflux in avoiding the use of BH_3.DMS and easy for large scale production which was replaced by NaH, and $BF_3.Et_2O$.



Scheme 35: Reagents and conditions: a). $PhCH_2NH_2$, 4Å MS, xylene, reflux, 12 h 95%; **b**) **174**, $BH_3{\cdot}SMe_2$, THF, reflux, 6 h 91%/ 80% NaH, $BF_3.Et_2O$, **175**, THF, reflux, 5.5 h., 82 %; **c**) KBH_4, LiCl, THF, r.t., 6 h, then 1 N aq. HCl, 55 °C, 30 min, 90% (two steps); **d**) EtSC(S)SK, DMF, 125 °C, 3 h, 93%;

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SECTION- II

Total synthesis of D(+)-biotin using N-acyliminium ion chemistry

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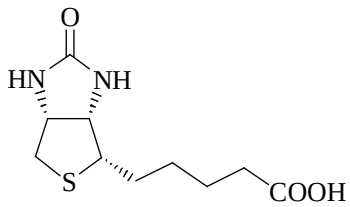
1.2.1 Introduction:

D-(+)-Biotin (Vitamin H),[1a] **1** is a biocatalyst of reversible metabolic reactions involving carbon dioxide transport in organisms. As one of the B-complex group of vitamins, it is significant for human nutrition and animal health. In the pharmaceutical context it is used as an additive and as an avidin complex in the area of drug delivery, immunoassay, isolation and localization. The egg white protein and its bacterial counterpart, streptavidin are standard reagents for diverse detection schemes. Simply such methods entail applying a biotinylated probe to the sample and then detecting the bound probe with a labeled avidin or streptavidin. These techniques are commonly used to localize antigens in cells and tissues and to detect biomolecules in immunoasays and DNA hybridization techniques. In some applications, immobilized avidins are used to capture and release of biotinylated targets.



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Lack of efficient fermentation methods have drawn the attention of organic chemists towards the synthesis of biotin. Many synthetic approaches,[1,2,3,4] such as diastereoisomeric or enzymatic resolutions,[1f,1g] chiral pool methods involving carbohydrates,[2] cysteine,[3] L-aspartic acid,[4] as well as asymmetric syntheses have been described. Yet there is no efficient chiral synthetic route for synthesis of biotin that serves the industrial purpose. Increasing demand for biotin in the field of medicine and nutrition along with lack of efficient chiral synthetic route has prompted many synthetic chemists to pursue research towards the synthesis of biotin as is evidenced by the number of publications in this area over last few years leading to the innovation of new synthetic strategies. Towards this end we have taken up the synthesis of biotin, and from our group we have already contributed to the area of *N*-acyliminium ion[3e,3f] chemistry by accomplishing three elegant syntheses of biotin,[1h,3e,3f] one of which is the short synthesis[3f] capable of making it to industrial scale.

To the best of our knowledge only one synthesis of D-(+)-biotin from glucosamine[2d] has been reported and all the syntheses from carbohydrates, including glucosamine, feature the construction of the ureido ring during the final stages of the synthesis. It has been reported[5] that reaction of 2-amino-2-deoxy pyranoses with arylisocyanates in aqueous $NaHCO_3$-dioxane at room temperature, gives 2-arylureido-2-deoxy sugars which on subjecting to basic pH result in the formation of hydroxy imidazolidinones. Subsequent treatment with acid furnishes the *cis*-fused furanoid bicycles in high yields. Our ongoing interest in *N*-acyliminium chemistry[3e,3f] led us to devise a strategy for cationic carbon-carbon bond formation in order to construct the ureido ring.

1.2.2 Chemistry of *N*-acyliminium Ions: An Introduction[10]

Iminium ions are important, reactive species in Organic synthesis for the construction of carbon-carbon and carbon-heteroatom bonds. The well known Mannich and Pictet-Spengler reactions which played a major role in Organic synthesis belong to this class of reactions using electrophilic iminium ions. These reactions are α–amidoalkylation reactions with the iminium ions serving as a defining reactive species.

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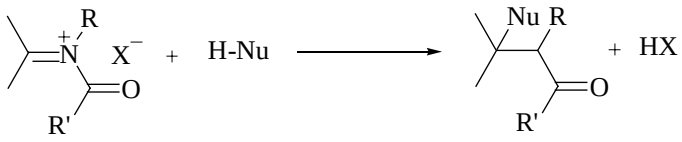
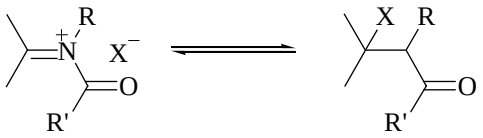
A further classification of iminium ion-based chemistry entails iminium species in which nitrogen is acylated. Due to the electron withdrawing nature of the carbonyl on nitrogen, the iminium carbon is more electron deficient, which imparts more electrophilicity to *N*-acyliminium ions and hence greater reactivity. This favourable situation is exploited a great deal into a versatile electrophilic chemistry known as α–amidoalkylation reactions. These reactions are expressed generically as shown in eq.-1



eq.-1

In synthetic transformations, these reactive species (*N*-acyliminiumion) are almost exclusively produced *in situ*. during the course of reaction. An *N*-acyliminium ion is most likely not generated stoichiometrically in the course of reaction, as it can exist in equilibrium with a covalent adduct. (eq-2). The proportion of ionic and covalent form varies significantly depending on the nature of the anion and experimental conditions.



eq.-2

In the reaction of α-alkoxy carbamates with Lewis acids, Yamamoto et. al. not only identified intermediate *N*-acyliminium ions in solution but also established this type of equilibrium.

The sub type involving cyclisation, i.e. intramolecular reaction of *N*-acyliminium ions, have received considerable attention in organic synthesis, particularly with respect to the synthesis of alkaloid natural products. But these reactions are sparsely used in their carbohydrate counterparts. Our group is actively involved in utilizing the *N*-acyliminum ion species for intermolecular carbon-carbon bond formation for the synthesis of biotin. The present section delineates various efforts towards the synthesis of biotin utilizing both inter

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and intramolecular carbon-carbon bond formation reaction using sugar scaffolds as chiral synthons.

1.2.3 Retrosynthesis:

Our synthesis of **1** is based on initial retrosynthetic analysis as depicted in Scheme **1**. The crucial step for the construction of *cis*-fused bicyclic ring skeleton of **1** is based on the carbon-carbon bond formation on *N*-acyliminium ion species formed by ring opening of cyclic hemiaminal ether **4** which could provide cyano intermediate **3**.

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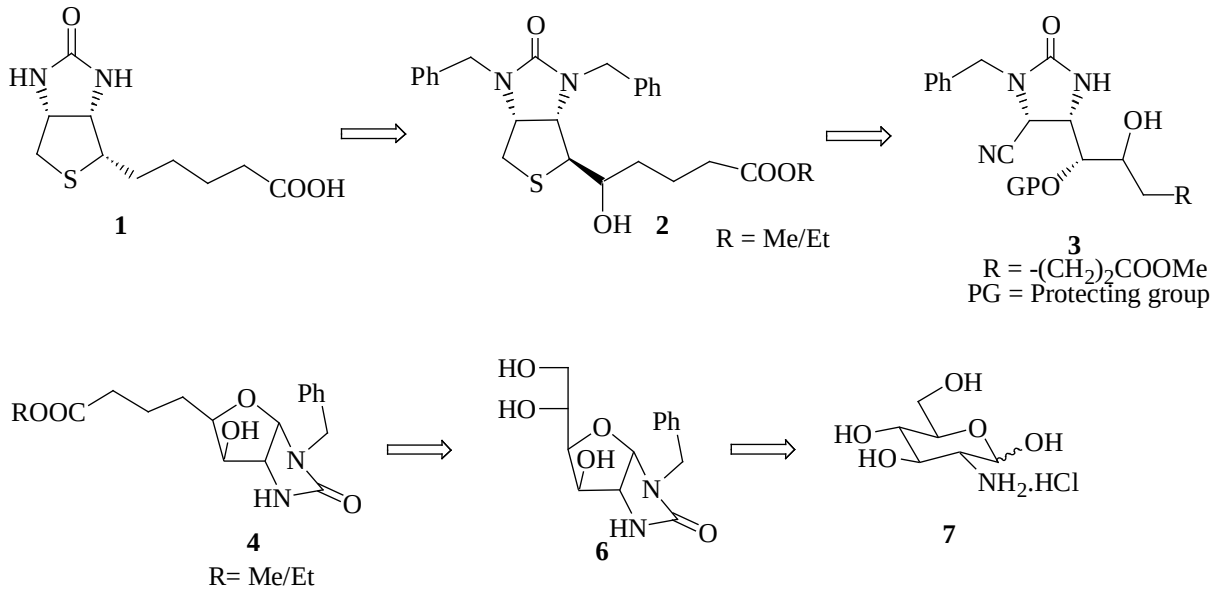

Scheme 1:

It was realised that intermediate **3** would provide an easy access to biotin skeleton, which inturn would be easily accessed from imidazolidin-2-one **4.** The imidazolidin-2-one **4** was envisaged to be obtained from **6** by cleavage of 5,6 diol followed by subsequent Wittig olefination and subsequent hydrogenation which would serve as side chain of the target molecule. This in turn was anticipated to be obtained from glucosamine hydrochloride, the readily available and cheap starting material, by treatment with benzyl isocyanate followed by intramolecular attack of oxygen on acyliminium ion. It was our surmise that synthesis following this retrosynthesis would provide biotin in minimum number of steps.

1.2.4 Present Work: Results and discussion:

Following literature procedure treatment of Glucosamine hydrochloride **7** with benzyl isocyanate in aqueous sodium bicarbonate–dioxane at room temperature gave the desired benzylureido-2-deoxysugar **7a**, which in the presence of a catalytic amount of pyridine in water at 55 ºC furnished *cis*- furanoid bicycle **6** in 82% yield (scheme 2) in contrast to hydroxyimidazolidinone described in the literature.[5] IR spectrum of compound **6** displayed

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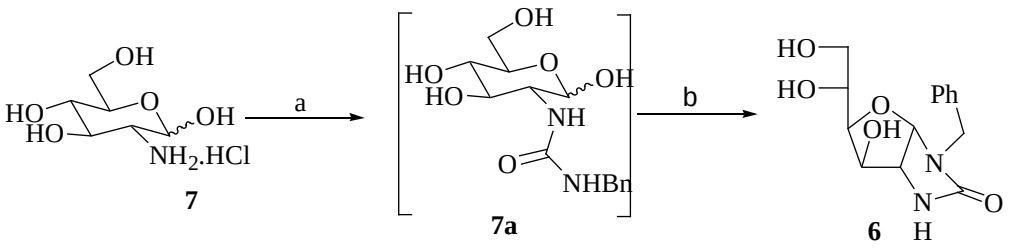
strong absorption band at 1692 cm^{-1}characteristic of ureido carbonyl of imidazolidinone ring and a strong, broad absorption band due to hydroxyl groups at 3358 cm^{-1}. ^{1}H NMR spectrum displayed a signal at δ 5.29 (*J* = 6.35 Hz) as a doublet which was assigned to the proton on the carbon bonded to oxygen and nitrogen (hemiaminal carbon). The coupling constants indicate the *syn*-orientation of two ring junction protons. ^{13}C-NMR spectum displayed a signal at δ 160.38 characteristic of ureido carbonyl of imidazolidinone ring. The signal at δ 89.73 as doublet was assigned to ring junction proton on hemiaminal carbon. While the other signals at δ 74.90, 75.06, 69.11, 64.55, 61.64 represent the carbons of tetrahydrofuran system, the signal at δ 44.88 which appeared as a triplet was assigned to -*N*-$\underline{C}H_2$Ph. M^+ 294 in mass spectrum ascertained the product as *cis*- furanoid imidazolin-2-one **6**. The elucidated structure was further confirmed by single crystal X-ray analysis.



Scheme-2: Reagents and conditions: a) BnNCO, aq $NaHCO_3$; **b**) pyridine (cat.), H_2O, 55 ^oC 82%;

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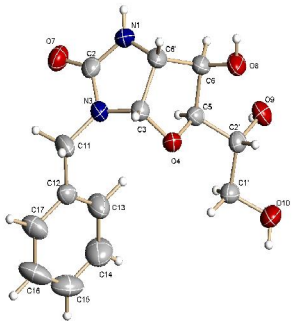


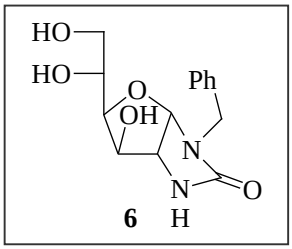
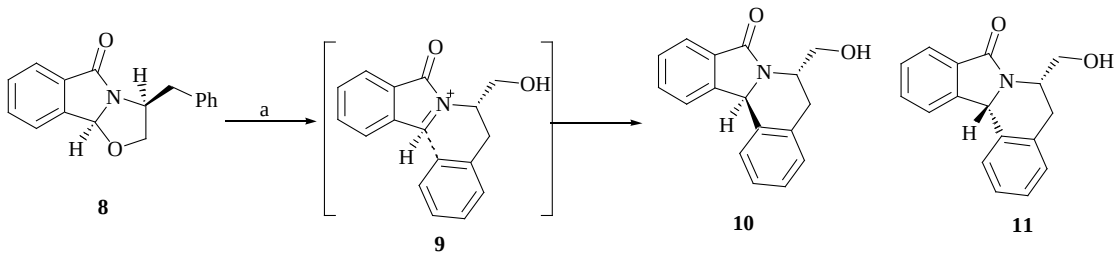


Fig. 1: ORTEP representation of **6**

It is very well documented in the literature that acyclic aminal ethers are very much susceptible to even mild acidic conditions resulting in the formation of *N*-acyliminiumion species which was exploited for carbon-carbon bond formation.[3e,f] We surmised that the hemiaminal oxygen attached to the carbon of the imidazolidin-2-one ring next to nitrogen should have similar reactivity like monocyclic hemiaminal (hydroxyimidazolidin-2-one) thereby facilitating the carbon-carbon bond formation.

Reviewing the literature provided support to our proposition wherein cyclic hemiaminal ethers served as precursors for *N*-acyliminium ion[6,7,8] by the activation of oxygen atom of fused bicyclic lactam as depicted in schemes **3, 4** and **5.**

Allin S. M ; Northfield C. J.; Page M. I.; Slawin A. M. Z.; (*Tetrahedron Lett.* **1998**, *39*, 4905-4908.)



Scheme 3: Reagents and conditions: ***a***) $SnCl_4/TiCl_4/BF_3.Et_2O/H_2SO_4$/TMSOTf; CH_2Cl_2; -10 ºC

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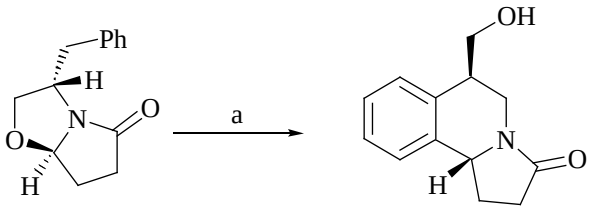
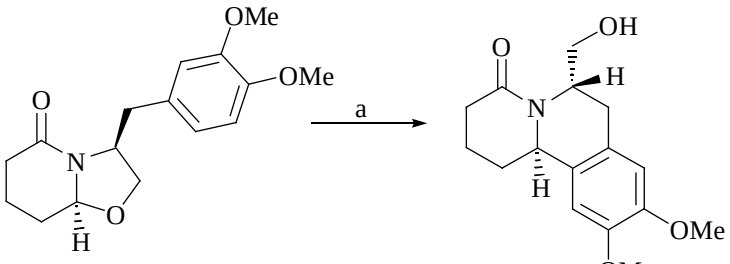
Allin S. M.; James S. L.; Martin W. P. Smith A. D. (*Tetrahedron Lett.* **2001**, *42*, 3943-3946.)



12 **13**

Scheme 4: Reagents and conditions: a) $TiCl_4$; CH_2Cl_2; -10 ºC; 20 h

Allin S. M.; Vaidya D. G.; James S. L.; Allard J. E.; Smith A. D.; McKee V.; Martin W. P. (*Tetrahedron Lett.* **2002**, *43*, 3661-3663.)



14 **15**

Scheme 5: Reagents and conditions: a) $SnCl_4$; CH_2Cl_2; -10 ºC; 20 h.

Having the required literature support for the key *N*-acyliminium amidoalkylation, we were all set for the synthesis of biotin. In accordance with the planned retrosynthesis, the terminal diol of *cis*-furanoimidazolidinone **6** was cleaved using sodium metaperiodate in acetone-water. Initially to see the feasibility of carbon-carbon bond formation *via* *N*-acyliminium ion species on intermediate **18,** the aldehyde **16** obtained was subjected to two carbon homologation with Wittig ylide to furnish the olefin **17** as a mixture of diastereomers. This olefin **17** on hydrogenation gave bicyclic imidazolin-2-one **18.** (scheme **6**)

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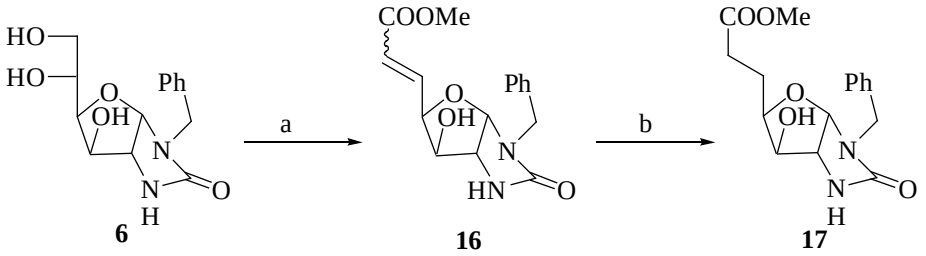
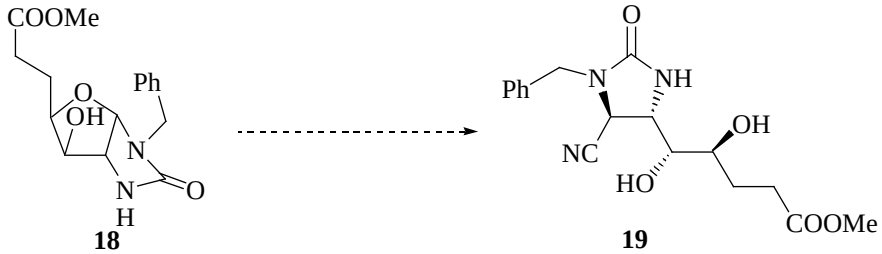


Scheme 6: Reagents and conditions: a) **i**) $NaIO_4$, acetone-H_2O (9:1), rt, 30 min; **ii**). $Ph_3P{=}CHCOOMe$, dichloromethane, rt.; **b**) Pd/C (10%), methanol, rt.

Unfortunately various attempts of carbon-carbon bond formation using TMSCN on intermediate 18 employing variety of Lewis acid mediated conditions *viz.* $BF_3.Et_2O$, $TiCl_4$, TMSOTf, $SnCl_4$, etc. as well as conventional acid conditions proved to be ineffective (scheme 7). Various conditions employed for carbon-carbon bond formation of 18 *via. N*-acyliminium ion species are depicted in table 1.



Scheme 7

Table 1

Sr. No	Nucleophile	Lewis acid/acid	Reaction conditions	Result
1.	TMSCN	$BF_3.Et_2O$ (3.0-6.0 equiv)	0 ºC-room temp. 24 h CH_2Cl_2/CH_3CN/THF	Starting material recovered

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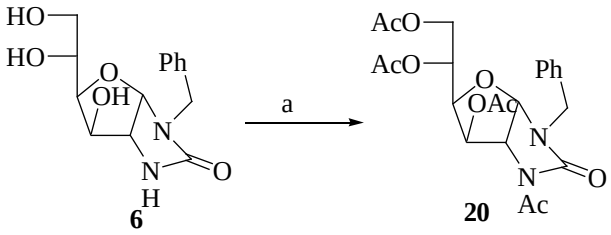
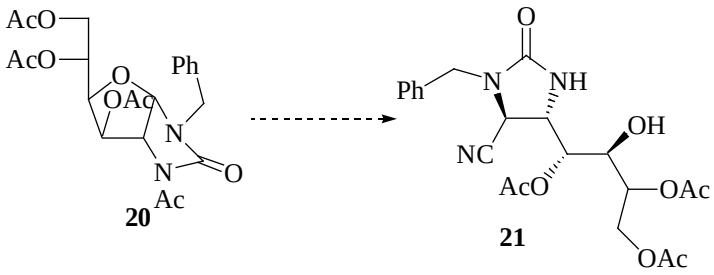
2.	TMSCN	$TiCl_4$ (3.0-6.0 equiv)	0 ºC-room temp. 24 h $CH_2Cl_2/CH_3CN/THF$	Starting material recovered
3.	TMSCN	$SnCl_4$ (3.0-6.0 equiv)	0 ºC-room temp. 24h $CH_2Cl_2/CH_3CN/THF$	Starting material recovered
4.	PhSH	*p*-TSA (0.3-5.0 equiv)	Room temp. PhSH	Starting material recovered

Further, treatment of **6** with acetic anhydride in the presence of $BF_3.Et_2O$ as the Lewis acid furnished the tetra acetate **20** in very good yield. (86%)



Scheme 8: Reagents and conditions: a) Ac_2O, $BF_3.Et_2O$, rt., 86%

Subjecting the tetra acetate **20** again to various Lewis acids as well as conventional acids for amidoalkylation of imidazolidinone ring met with failure and various efforts for ring opening of tetraacetate **20** are tabulated in table **2**.



Scheme 9

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Table 2.

Sr. No	Nucleophile	Lewis acid/acid	Reaction conditions	Result
1.	TMSCN	$BF_3.Et_2O$ (10.0 equiv)	0 ºC-room temp. CH_2Cl_2; 24 h	Starting material recovered
2.	TMSCN	$SnCl_4$ (10.0 equiv)	0 ºC-room temp. CH_2Cl_2; 24 h	Starting material recovered
3.	PhSH	p-TSA (0.3-5.0 equiv)	room temp/reflux. PhSH; 24 h	Starting material recovered

From the above set of conditions employed for the generation and intramolecular trapping of *N*-acyliminium ion species, it was imperative that, unlike the reported bicyclic lactams the current furo imidazolidin-2-one skeleton (**6**, **18** and **20**) is highly stable to the various Lewis acids and acidic conditions.

Faced with unforeseen problems for the key amidoalkylation *via N*-acyliminium ion it was inevitable for us to look at other options available to solve the problem of generating *N*-acyliminium from bicyclic hemiaminalether. We envisaged that this could be achieved in two ways.

1. By converting the oxygen attached to the imidazolidin-2-one as an integral part of the lactone ring there by rendering it labile which was expected to cleave the carbon-oxygen bond of hemiaminalether, forming *N*-acyliminium ion.
2. The other way is to convert it to enol so that the oxygen attached to imidazolidin-2-one could be in enolic form. It was our surmise that this would drive the reaction towards ring opening as it is likely to favour the formation of ketone.

Accordingly the terminal diol of **6** was protected as the acetonide using acetone and catalytic amount of *p*-TSA at room temperature. The product obtained was subsequently protected with benzyl bromide and NaH in DMF to furnish the protected bicyclic intermediate **22** in excellent yields (86%) over two steps.

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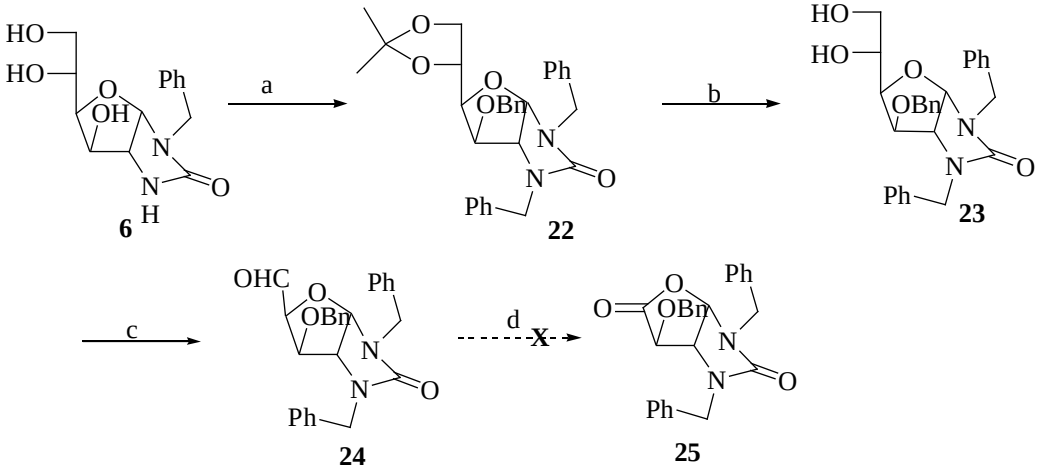

Scheme 10: Reagents and conditions: a) i) p-TSA (cat), acetone, rt; **ii)**. NaH, BnBr, DMF, 0 ^{o}C- rt, 6 h, 86% over two steps.; **b)**. p-TSA(cat.), THF:H_2O (9:1), reflux, 6 h, 98%.; **c)** i) $NaIO_4$, acetone: H_2O (9:1), rt, 30 min; **d)**PCC; DCM, rt./PDC, DCM, rt.

The ^{1}H NMR showed the signals at δ 1.35 Hz as singlet corresponding to six methyl hydrogens indicating the introduction of acetonide and four doublets at δ 5.38 Hz; (*J* = 15.63 Hz), 4.67 (1H, *J* = 14.65 Hz), 4.61(d, 1H, *J* = 15.63 Hz) and 4.41(d 1H, *J* = 14.65 Hz) for the four nonequivalent benzylic CH_2 protons and a signal at M^+ 514 in mass spectra confirmed the assigned structure of the product.

The acetonide of **22** was then unmasked with catalytic amount of *p*-TSA in refluxing tetrahydrofuran:water (9:1) to furnish the diol **23** in excellent yield. (98%) The disappearance of singlet at δ 1.35 Hz corresponding to dioxalane of starting material and appearance of two broad singlets (D_2O exchangeable) at δ 3.4 Hz and 2.8 Hz indicating the presence of two unprotected –O<u>H</u> groups ascertained the product.

Diol **23** was then cleaved to the aldehyde **24** using sodium metaperiodate in acetone/water (9:1). It was anticipated that treatment of aldehyde **24** with either PCC (pyridinium chlorochromate) or PDC (pyridinium dichromate) would furnish the lactone **25**. But neither of the reagents could furnish the desired lactone **25** but resulted only in the decomposition of starting material.

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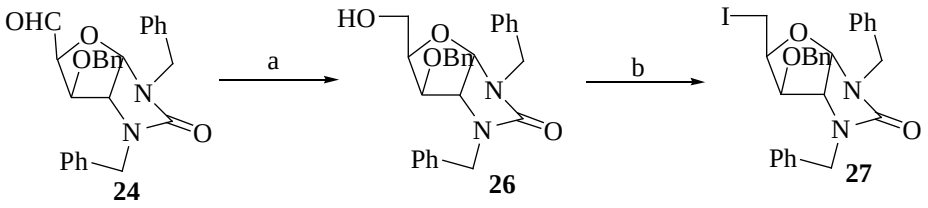

Scheme 11: Reagents and conditions: a) $NaBH_4$, methanol rt. 94%.; **b**)Ph_3P,I_2, toluene, reflux. 92%

Having failed to obtain the desired lactone, **25** we turned our attention towards utilizing enol ether for amido alkylation. The aldehyde **24** was thus reduced to alcohol **26** with sodiumborohydride in methanol at room temperature in high yield. (94%). The M+ value of 444 in mass spectrum confirmed the product. The desired halo compound **27** was then obtained smoothly by treatment of alcohol **26** under standard conditions TPP-I_2 in relfuxing toluene in 92% yield. (Scheme **11**)

The halo compound **27** was then subjected to dehydrohalogenation by base catalysed deprotonation using DBU in refluxing toluene to furnish enol ether **28** in 80% yield. The proton NMR showed a signal at δ 4.60 as a singlet integrating for two protons and was assigned to enolic =C$\underline{H}_2$. The ^{13}C NMR showed signals at δ 157.90 Hz corresponding to quaternary enolic carbon and δ 89.28 Hz corresponding to the =$\underline{C}H_2$ of enol and the M+ value of 426 in the mass spectrum confirmed the product. As per the planned synthetic route, the enolether was activated with Lewis acid (BF_3. Et_2O) in the presence of nucleophile (TMSCN) expecting the carbon-carbon bond formation *via* *N*-acyliminium ion species on imidazolidinone ring. Unfortunately various attempts of carbon-carbon bond formation on imidazolidinone ring resulted only in the isolation of eliminated product **30**. (Scheme **12**) ^{1}H NMR of the product **30** showed signals at δ 6.20 Hz as singlet was assigned to the olefin proton (=C$\underline{H}$) while the signal at δ 1.95 Hz was assigned to the α-methyl ketone (-COC$\underline{H}_3$). The assigned structure was confirmed by the signals at δ 111.18 Hz and 117.69 Hz. in ^{13}C NMR spectrum corresponding to olefinic carbons (=$\underline{C}$H and =$\underline{C}$-) of imidazolidinone confirmed the product.

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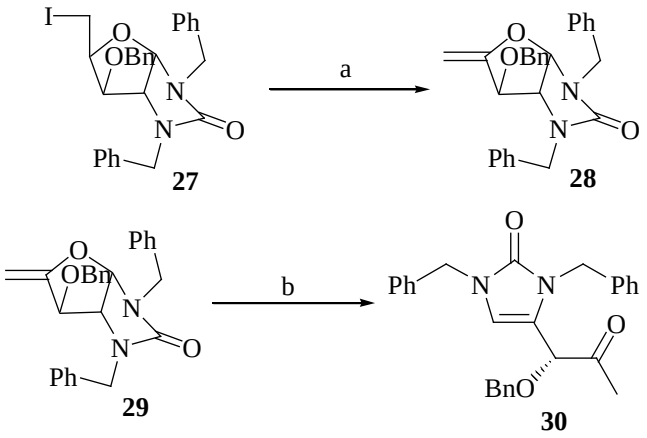

Scheme 12: Reagents and conditions: **a**) DBU, toluene, reflux, 80%; **b**) trimethylsilylcyanide, BF_3. Et_2O, DCM, -78 ºC- rt.

Eventhough we could not obtain the desired intermolecular carbon-carbon bond formation, encouraged by the formation of *N*-acyliminium ion species as indicated by the formation of eliminated product **30**, we turned our attention towards the carbon-carbon bond formation on enol acetate **31** which could be obtained in less number of steps compared to the enolether **29**. Thus the aldehyde **24** obtained by cleavage of diol **23** was treated with acetic anhydride in the presence of triethylamine and catalytic amount of DMAP in refluxing ethylenedichloride to furnish the exocyclic enolacetate **31** in good yield (83%) over two steps (scheme **13**). IR spectrum of **13** showed at 1755 cm^{-1} for ester carbonyl indicating the introduction of acetate moiety and a carbonyl at 1718 cm^{-1} for ureido carbonyl of imidazolidinone. The appearance of absorption band at 1210 cm^{-1} corresponding to -C-O stretching frequency of vinyl esters assures the formation of enol acetate. The ^1H NMR spectrum displayed signals at δ 6.60 as a singlet was assigned to (=C<u>H</u>-OAc) and a signal at δ 2.24 as a singlet integrating for three protons was assigned to (=CH-OCOC<u>H</u>$_3$). The assigned structure was ascertained by signals at δ 150.87 and 116.10 corresponding to quaternary enolic carbon and tertriary carbon respectively in ^{13}C -NMR. Further M^+ of 484.02 confirmed the proposed structure.

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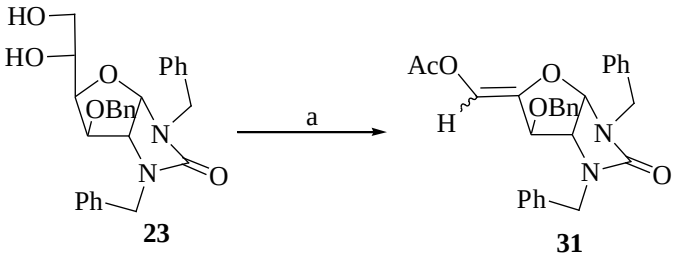
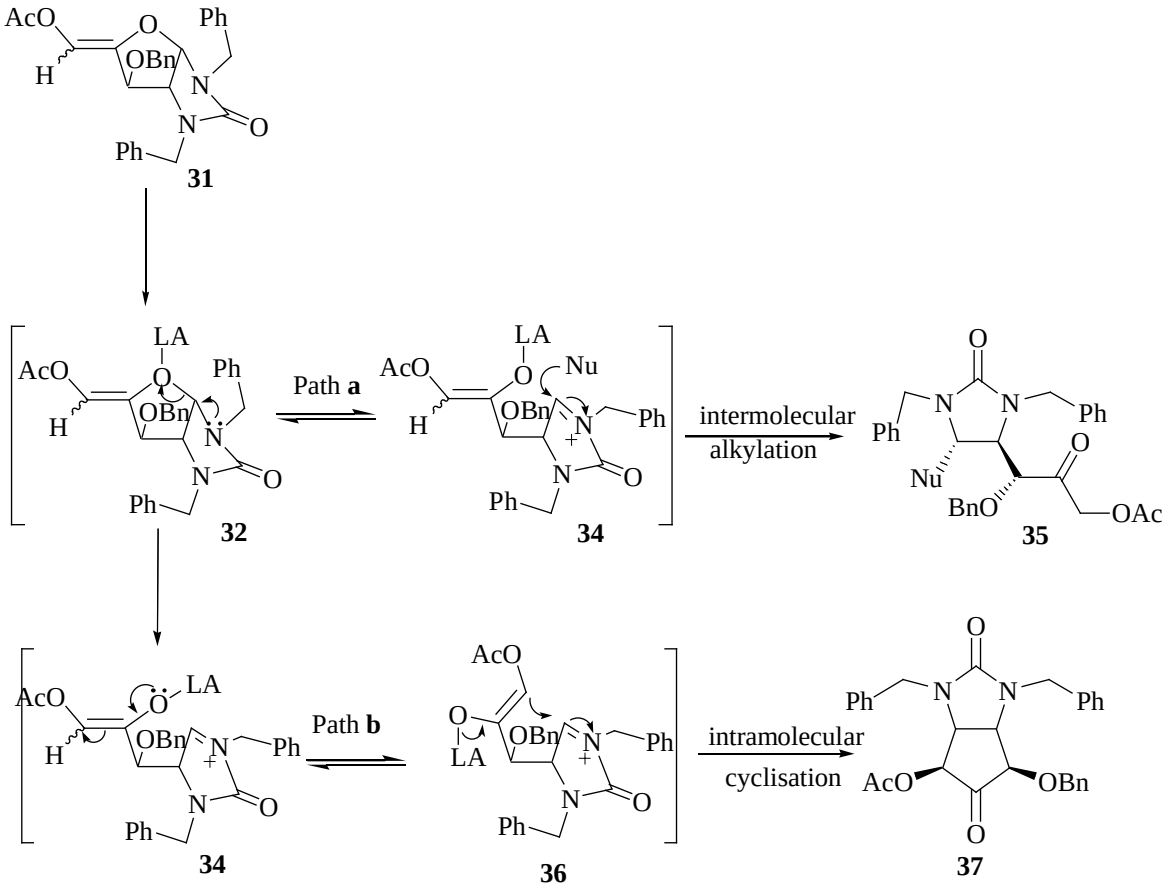


Scheme 13: Reagents and conditions: a) **i**) $NaIO_4$, acetone: water (9:1), 30 min, **ii**) Ac_2O, Et_3N, DMAP (cat.), EDC, reflux, 4 h, 82%.



Scheme 14

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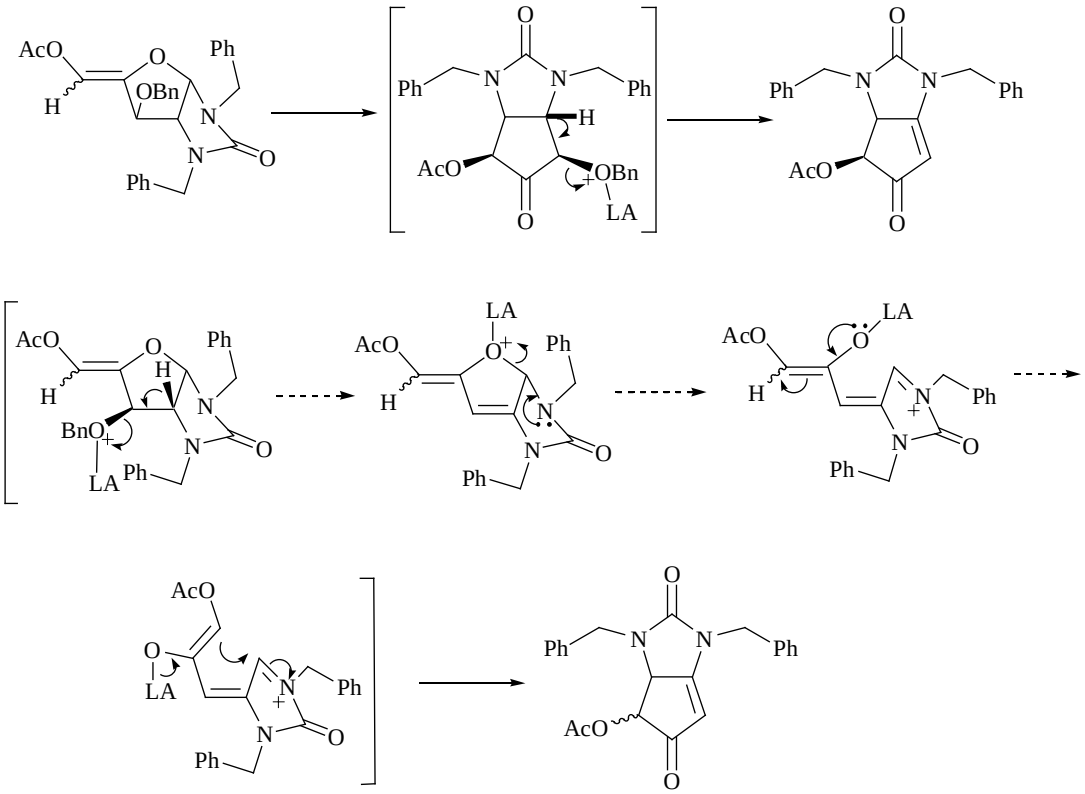

Scheme 15

Looking closely at enolacetate **31**, it was our premise that, generating an *N*-acyliminium ion species employing Lewis acid gives an opportunity for the intermediate **34** to take two different courses of reaction. (Scheme **14**)

1. In the presence of an external nucleophile, like cyanide ion as indicated by path a, the *N*-acyliminium ion formed **34** would be quenched by external nucleophile resulting in the formation of intermolecular carbon-carbon bond formation providing the intermediate **35** an useful intermediate for the synthesis of biotin.
2. On the otherhand, in the absence of an external nucleophile, activating enolacetate **31** with Lewis acid forms *N*-acyliminium ion species **34** and the activated oxygen being in equllibrium with its ketoform **36**, the carbanion formed adjacent to OAc (**36**) functionality should in turn act as proximate nucleophile leading to the intramolecular carbon-carbon bond formation, giving substituted cyclopentanone **37**. We envisaged this to be a potential intermediate for the synthesis of biotin.

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Accordingly attempting the intramolecular carbon-carbon bond formation employing Lewis acid does effect the cyclisation but unfortunately resulted in the exclusive formation of enamide **39** with the elimination of benzyloxy group of cyclopentanone. IR spectrum of **39** displayed absorption bands at 1747 cm^{-1} and 1624 cm^{-1} corresponding to α, β unsaturated ketone and ureido carbonyl respectively. The considerable shift in the absorption band to lower frequency was observed for ureido carbonyl. ^{1}H NMR spectrum of compound **39** displayed a signal at δ 2.09 as a singlet which was assigned to methyl ester of acetate, a signal at δ 4.47 as a doublet of doublet (J = 4.43, 2.14 Hz) was assigned to ring junction proton (-*N*-C<u>H</u>-) coupling with the adjacent acetate proton and a long range allylic coupling of 4.43 Hz with vinylic proton. While a signal at δ 5.18 as a doublet (J = 2.14 Hz) was assigned to proton on carbon flanked by acetate. The small coupling constant of 2.14 Hz with the adjacent ring junction proton confirms the *β*- orientation of –OAc functionality on cyclopentenone ring. The signal at δ 5.19 as doublet (J = 4.43 Hz) was assigned to vinylic proton involved in allylic coupling with ring junction proton. The proposed structure was confirmed by ^{13}C-NMR spectrum which displayed signal at δ 193.59 for ketone carbonyl, a signal at δ 167.87 as a quaternary singlet carbon was ascribed to ring junction enamide carbon, while the signal at δ 98.62 as tertiary doublet carbon was ascribed to the vinylic carbon of enamide adjacent to ketone of cyclopentenone. The assigned structure was confirmed undoubtedly by mass spectrum which indicated a (M+1) value of 377.12.

Attempts towards the intramolecular cyclisation of enolacetate **31** employing various Lewis and conventional acids are summarized in the table **3**.

Table 3

Sr.No	Lewis acid/acid	Solvent/Conditions	Product **39** (Yield %)
1.	$BF_3.Et_2O$ (1.0. equiv)	CH_2Cl_2; -78 ºC 30 min.	Complex mixture
2.	$BF_3.Et_2O$(1.0 equiv.)	THF; -78 ºC; 30 min	,,
3.	$SnCl_4$ (1.0. equiv)	CH_2Cl_2; -78 ºC 30 min	,,
4.	$TiCl_4$(1.0. equiv)	CH_2Cl_2; -78 ºC; 30 min	,,

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5.	Iodine (1.0. equiv)	CH_2Cl_2; 0 ºC; 2h	42
6.	Iodine (1.0. equiv)	THF; 0 ºC; 2h	45
7.	Iodine:Et_3N(1:0.1) (1.0 equiv)	CH_2Cl_2	No reaction
8.	$FeCl_3$ (1.0 equiv)	THF; rt. 12h	82
9.	$MgBr_2.Et_2O$ (2.0 equiv.)	CH_2Cl_2; rt. 24h	No reaction
10.	PPTS (1.0 equiv.)	CH_2Cl_2; rt. 24h	No reaction
11.	*p*-TSA (0.2 equiv)	CH_2Cl_2; 0 ºC; 24h	No reaction
12.	*p*-TSA (0.2 equiv)	CH_2Cl_2; rt; 2h	86
13.	TMSOTf (1.0 equiv.)	CH_2Cl_2; 0 ºC; 10 min	92
14.	Trifluoroacetic acid (0.1 equiv.)	CH_2Cl_2; rt; 15 min	76

Once we isolated the enamide formed we felt it was important to know at which stage of the reaction the elimination is taking place. As shown in scheme **15** we thought of two plausible mechanisms for the elimination of the benzyloxy group, forming an enamide.

1. The elimination may take place after the intramolecular carbon-carbon bond formation, in which case the enamide formed would be optically active.
2. Or it may take place before the cyclisation as shown in path b *i.e.* initial debenzyloxation forming conjugated double bond, which could further undergo the intramolecular cyclisation leading to the enamide in which case the product would be optically in active.

We felt that if elimination is taking place after the intramolecular cyclisation it could be suppressed. But the experimental fact that the enamide **39** is optically active provides the support that elimination of benzyloxy group takes place after the intramolecular cyclisation. Which on the otherhand if the debenzyloxylation has taken place according to path **b** the product formed should be optically inactive as all the stereocenters are destroyed during the course of reaction. The fact that the product formed is optically active provides support to the formation of enamide after the intramolecular cyclisation.

But unfortunately we could not supress the unwanted elimination of benzyloxy group inspite of employing various reaction conditions. Probably the rate of elimination of the

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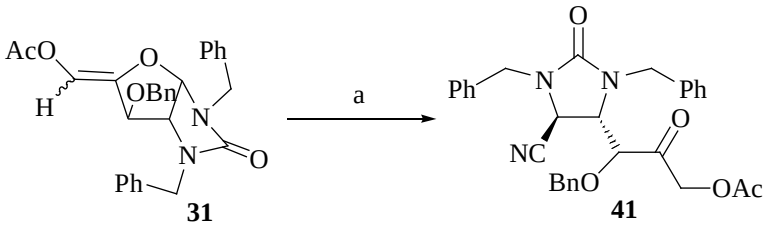
benzyloxy group is matching the rate of cyclisation as no other product was observed during the course of reaction in any of the reaction conditions employed. The transformation is clean and the substrate is unreactive to even excess of *p*-TSA at and below 0 ºC as revealed by the proton NMR after quenching the reaction at or below 0 ºC. While performing the reaction at room temperature shows instantaneous change in starting material even with catalytic amount of *p*-TSA directly resulting in the formation of enamide. The same is the case with other Lewis acids like TMSOTf and conventional acids as mentioned in table **3** which resulted in the excl;usive formation of enamide **39**.

Having failed to obtain the desired substituted cyclopentanone from the intramolecular cyclisation strategy, we turned our attention towards intermolecular carbon-carbon bond formation.



Scheme 16: Reagents and conditions: a) TMSCN, $BF_3.Et_2O$, DCM, -78 ^{0}C, rt. 15 min., 62%.;

Gratifyingly, carbon-carbon bond formation *via* an *N*-acyliminium ion was affected by activating enolacetate **31** with $BF_3.Et_2O$ in the presence of trimethylsilyl cyanide in dichloromethane at -78 of the benzyloxy group ºC to room temperature for 15 min. to furnish the cyano substituted imidazolidin-2-one **41** in good yield (62%) as a single diastereomer. IR spectrum of **31** displayed a weak abosorption band at 2401 cm^{-1} revealing the introduction of cyano functionality, while strong absorption bands at 1723 cm^{-1}, 1710 cm^{-1}, and 1699 cm^{-1} were assigned to the ester, keto and ureido carbonyls respectively. The disappearance of signal characteristic of enol (Ac-O-C<u>H</u>)at δ 6.60 in proton NMR assured the ring opening of tetrahydrofuran of bicyclic skeleton. The signal at δ 3.83 as a doublet of doublet (J = 5.48, 2.74 Hz) integrating for 1 proton was assigned to imidazolidine proton on carbon flanked by 2-oxo propyl ester. (–C<u>H</u>-CHOBn-$COCH_2$OAc) while the signal at δ 4.00 as doublet (J = 2.73 Hz) was assigned to imidazolidinone proton on carbon flanked by cyano moiety. (NC-C<u>H</u>-).

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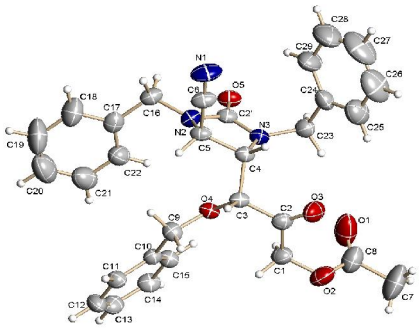
The small coupling constant of 2.73 Hz between the two protons of imidazolidinone ring indicated the *trans*-orientation of two appendages of imdizolidinone ring. ^{13}C-NMR spectrum showed the signal characteristic of quaternary carbon for cyano functionality at δ 115.63 confirming the akylation of imidazolidinone ring. A signal at δ 201.50 was assigned to carbonyl functionality, while signals at δ 169.85 and δ 158.05 were assigned to ester and ureido carbonyls respectively thus further providing proof to the proposed structure. Further the M^+ value of 511.04 confirmed the proposed structure. The relative stereochemistry of the alkylated product was further confirmed by single crystal X-ray analysis.



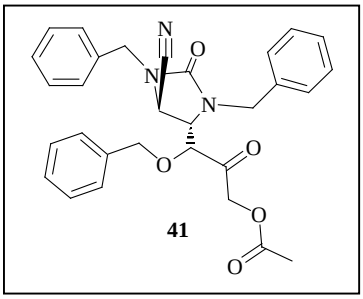


Fig 2: ORTEP representation of **41**

Having attained the key carbon-carbon bond formation, the stage was now set to invert the C-5 proton of imidazolidinone to arrive at requisite stereochemistry of target molecule.

The cyano imidazolidin-2-one **41** on reduction with sodium borohydride in methanol resulted in diol as a mixture of products, two diastereoisomers each of cyano imidzolidinone and methoxycarbonyl imidazolidinone, formed by reduction of keto functionality and partial hydrolysis of cyano to ester, in varied proportions. The partial hydrolysis of cyano to ester can be attributed to the base catalysed methanolysis by trace amounts of sodium hydroxide present in sodium borohydride. Attempts to completely convert the cyano to ester resulted in partial reduction of ester formed to the corresponding alcohol.

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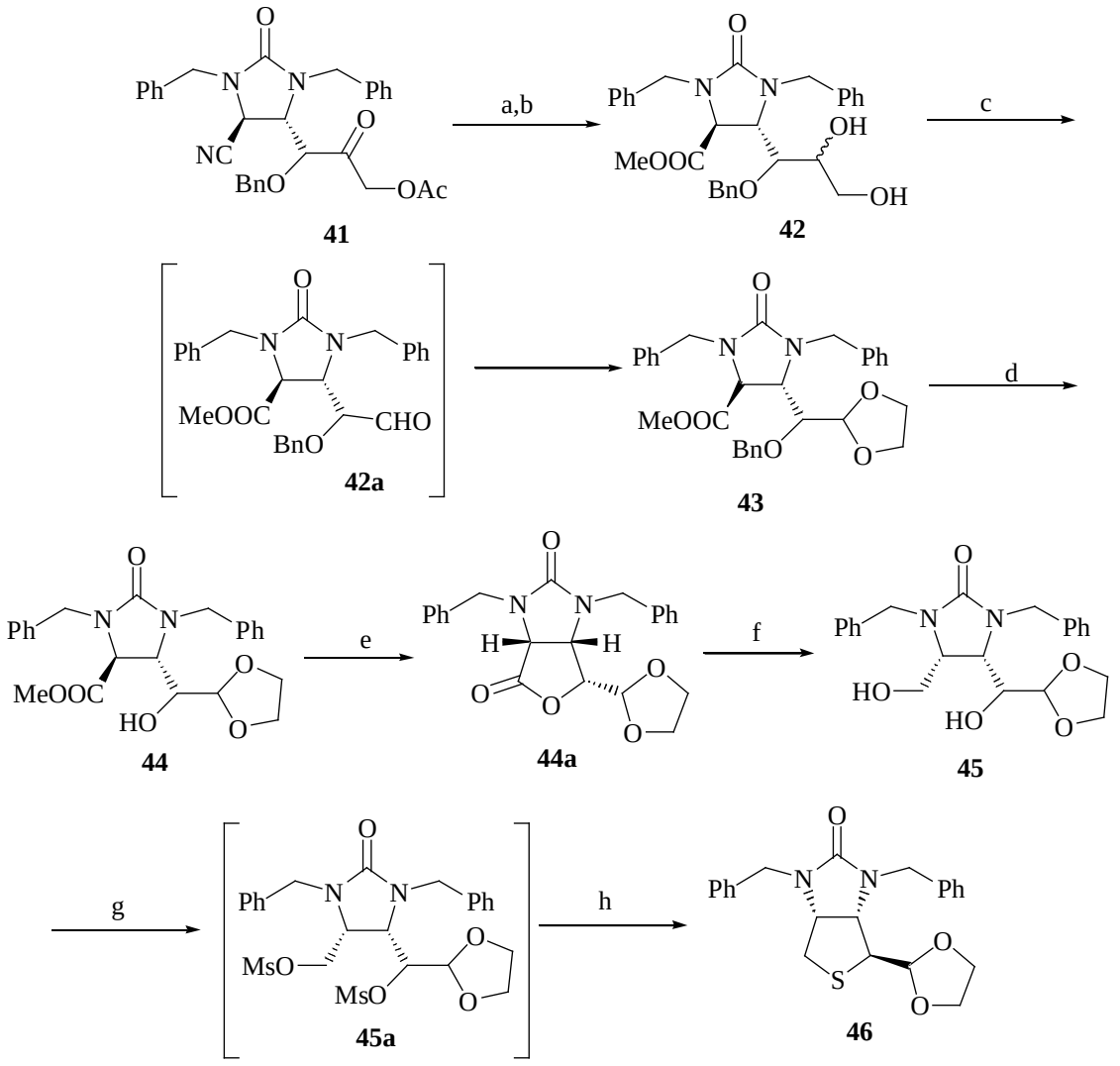

Scheme 17: Reagents and conditions: a) $NaBH_4$, MeOH, 0 ^{0}C to rt, 4 h.; **b**) TMSCl, MeOH, 40 ^{0}C, 4 h, 93% over two steps; **c**) **i**) $NaIO_4$, acetone: water (9:1), rt, 30 min; **ii**) ethylene glycol, p-TSA, C_6H_6, reflux, 6 h, 65% over two steps.; **d**) Pd-$CaCO_3$, MeOH, rt, 24 h, 95%.; **e**) DBU (cat), toluene, reflux, 24 h.; **f**) $NaBH_4$, EtOH, reflux, 2 h, 86% over two steps.; **g**) MsCl, Et_3N, DMAP(cat.), 0 ^{0}C to rt, 4 h; **h**) Na_2S, DMF, 100 ^{0}C, 2 h, 78%.

The problem of formation of multiple products was addressed by subjecting the crude reaction mixture obtained on reduction with sodium borohydride to trimethylsilyl chloride in methanol to furnish the required methyl ester **42** in excellent yield (93% over two steps) as a 1:1 distereomeric mixture. No selectivity was observed under the ordinary reduction conditions. ^{1}H NMR spectrum of **41** showed signal at δ 3.41 integrating for three protons which was assigned to methyl ester. The assigned structure was confirmed by ^{13}C NMR spectral

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analysis which showed the appearance of signal at δ 171.03 corresponding to carbonyl of ester functionality (O<u>C</u>OCH$_3$) and a signal at δ 52.00 corresponding to the methyl carbon of ester functionality (OCO<u>C</u>H$_3$). Further disappearance of signal at 115.63 in ^{13}C NMR which is the characteristic for cyano functionality assured the product formation.

The stereochemistry at C-4 carbon in imidazolidin-2-one **41** that appears as C-2 of the target molecule is to be inverted at certain stage to arrive at requisite stereochemistry of target molecule. So, as to invert the C-4 carbon in imidazolidin-2-one **41,** it is necessary to keep the aldehyde functionality intact towards the end of the synthesis. So instead of alkylating the aldehyde **42a** to obtain the side chain of target molecule it was decided to retain the aldehyde functionality. Bearing this in mind and the necessity to avoid the diastereoisomeric mixture, it was decided to cleave the diol and protect it as dioxalane derivative.

Accordingly the diol **42** was cleaved by using $NaIO_4$ in acetone:water (9:1) to furnish an aldehyde **42a** which on subsequent treatment with ethylene glycol and *p*- TSA gave the dioxalane derivative **43** in good yield.(65% over two steps). IR spectrum of compound **43** displayed strong absorption bands at 1746 cm^{-1} and 1690 cm^{-1} corresponding to ester and ureido carbonyls respectively. The multiple absorption bands at 1079 cm^{-1}, 1030 cm^{-1}, 989 cm^{-1}, 946 cm^{-1} along with weak CH_2 stretching frequency of acetal at 2892 cm^{-1} is indicative of the introduction of cyclic acetal functionality. The signal at δ 3.45 as doublet of doublet integrating for one proton (J = 1.46, 5.13 Hz) was assigned to the proton on carbon of imidazolidinone flanked benzyloxy-[1,3]dioxalan-2-ylmethyl group. (–C<u>H</u>-CHOBn-C) While a signal at δ 4.09 as doublet (J = 1.46 Hz) was assigned to proton on carbon of imidazolidine flanked by methyl ester (MeOOC-C<u>H</u>). The small coupling constant of 1.46 Hz is indicative of *trans*-orientation of the two substituents on imidazolidinone ring. Signals appearing at δ 3.71 and 3.81 as multiplets integrating for 4 protons were assigned to the methylene protons of the dioxolane while the signal at δ 4.80 as doublet with J = 3.66 Hz was assigned to the dioxolane proton. The assigned structure was further confirmed by the ^{13}C NMR spectral analysis which showed peaks at δ 64.94 and δ 65.17 corresponding to the methylene carbons of dioxolane and a signal at δ 103.03 corresponding to the dioxalane. The product was further confirmed by the HRMS spectral analysis which showed the mass of 539.217 requiring 539.215 for the assigned structure.

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Selective *O*-debenzylation of **43** was accomplished by hydrogenation of **43** at atmospheric pressure in the presence of catalytic amount of Pd-$CaCO_3$ in methanol in excellent yield (95%). The disappearance of protons for the benzylmethylene group and the number of protons in the aromatic region integrating for 10 protons confirmed the debenzylation. Further, the disappearance of methylene carbon in ^{13}C ascertained the product.

Correction of stereochemistry at C-4 of **44** was achieved by epimerization with catalytic amount of DBU in refluxing toluene, which on concomitant cyclisation resulted in the formation of lactone (**44a**). Attempts to purify the lactone **44a** by column chromatography resulted in the opening of the lactone on silica gel. Though the hydroxy acid obtained by eluting the column with ethylacetate cyclised on standing, we preffered to avoid the ring opening by directly reducing the lactone obtained with sodium borohydride in refluxing methanol to furnish the diol **45** in good yield. (86% over two steps.) The disappearance of ester carbonyl at 1746 cm^{-1} in the IR along with the appearance of broad peak at 3400 cm^{-1} indicated the reduction of lactone, which was further confirmed by ^{13}C NMR spectrum which showed the appearance of additional methylene carbon at δ 57.69 along with the disappearance of ester carbonyl at δ 171.70 in lactone.

Sulfur was introduced in to the system by sulfonylating both the primary and secondary hydroxyl groups with mesyl chloride in the presence of triethylamine gave dimesylate derivative **45a** which on subsequent treatment with sodium sulfide in DMF furnished the tetrahydro-thienoimidazolidinone **46** in good yield (78%). The ^{1}H NMR spectrum displayed signals as doublet at δ 2.76 (J = 12.3 Hz) and a signal as dd at δ 2.99 (J = 3.91 and 12.13 Hz) were assigned to methylene protons adjacent to sulfur. Along with this a signal at δ 3.39 as a doublet with small coupling constant of 2.34 Hz was assigned to the methine proton adjacent to sulfur, indicated the *trans*- disposition of C_2-C_3 substituents of tetrahydro-thieno system. The assigned structure was further confirmed by ^{13}C- NMR spectral analysis displaying signals at δ 36.20 for the methylene carbon of sulfide and at δ 54.58 for methine carbon of sulfide. The structure was further confirmed by HRMS which indicated the mass of 397.159 requiring 397.158. The dioxalane of the bicyclic skeleton was unmasked using 6N HCl in acetic acid at room temperature for 24h to furnish the aldehyde **47** in good yield (82%). IR absorbtion for aldehyde were observed at 1705 cm^{-1} and 1695 cm^{-1} for the aldehyde and ureido

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carbonyls respectively. ^{1}H NMR spectrum displayed singlet at δ 9.13 for –C<u>H</u>O, a singlet at δ 3.51 for C_2 proton while a doublet at δ 4.34 (J = 7.9 Hz) was assigned to C_3 proton. No coupling between C_2 and C_3 indicated the *anti*-orientation, doublet of doublet at δ 2.29 (13.15, 4.18 Hz) was assigned to C_5 H_β and showed a doublet at δ 2.68 (J = 13.15 Hz) was attributed to C_5 H_α. ^{13}C-NMR spectrum showed doublet at δ 189.80 for <u>C</u>HO. Mass spectrum (M^+, 352) and fragmentations confirmed the assigned structure.

Though the aldehyde has incorrect stereochemistry, as it was shown in our earlier syntheses it could be rectified in the later stages during the homologation of side chain.

The aldehyde **47** was treated with [3-carbomethoxypropene-2-ylidine-1]triphenylphosphorane in dichloromethane furnished *N*,*N*-dibenzyl, methylester of tetradehydrobiotin **48** in 89 % yield. IR spectrum of **48** confirmed the presence of unsaturated ester as the ester carbonyl absorption appeared at lower frequency. 1650 cm^{-1}. ^{1}H NMR spectrum in C_6D_6, displayed doublet at 5.76 (J = 15.2 Hz), doublet of doublet at 5.33 (J = 5.2, 10.78 Hz) and doublet of doublet at 5.27 (J= 15.2, 8.29 Hz) were assigned to three olefin protons. One of the olefinic protons centered at δ 7.2 merged with multiplet (aromatic protons). Two multiplets, centered at δ 3.5 and 3.4 were assigned to ring junction protons. Carbomethoxy protons appeared as a singlet at δ 3.42. Doublet of doublet at δ 3.27 was assigned to C_2 proton (J = 8.99, 3.86 Hz). Two doublet of doublets at δ 2.35 (J = 12.25, 4.3 Hz) and 2.22 (J = 12.25, 5.8 Hz) were assigned to $C_{5\alpha}$ and C $_{5\beta}$ protons respectively. ^{13}C NMR spectrum showed four olefinic carbons as doublets at δ 142.7, 136.6, 146.7, 121.68. M^+ at 434 confirmed the assigned structure. The Wittig product **48** was also epimeric at C_2 as was the aldehye **47**. The ester was hydrolysed with aqueous NaOH in methanol to furnish the deconjugated product **49**. ^{1}H NMR spectrum of acid obtained indicated deconjugation of olefin as all the olefinic protons exhibited multiplet centered at δ 6.0 and four proton multiplet centered at δ 3.0 was assigned to two methylenes. Hydrogenation of deconjugated acid **49** using 10% Pd/C in methanol furnished *N*,*N*-dibenzylbiotin.

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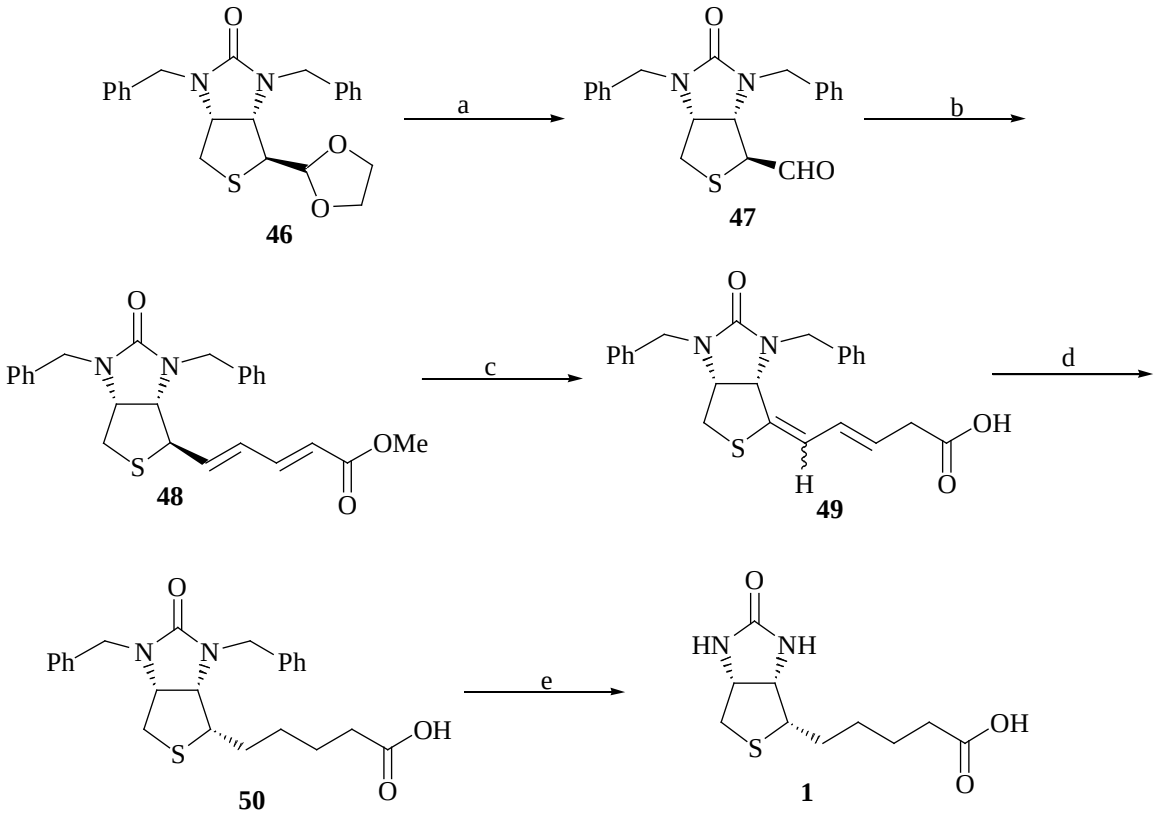

Scheme 18: Reagents and conditions: a). 6N HCl, CH_3COOH, rt, 24 h, 82% **b**). Ph_3P=CH-CH=CH-$COOCH_3$, DCM, rt, 12 h, 89%; **c**). 1M NaOH, MeOH, 0^oC, 12 h, 97%; **d**). 10%Pd-C/H_2 (3 atm), 8 h, 92%. **e**). 48% HBr, reflux, 2 h, 80%.

Removal of *N*-benzyl groups was achieved with aq. HBr (48%) at reflux temperature afforded (+) biotin, which was characterized as methyl ester (reflux for 2h in methanol in the presence of catalytic amount of conc. H_2SO_4 in 95% yield) had $[\alpha]_D$ = +78 (as compared to $[\alpha]_D$= +81 for an authentic sample).

In conclusion:

1. Intramolecular carbon-carbon bond formation was achieved on sugar scaffold. Though we could not achieve the desired cyclopentanone derivative through intramolecular cyclisation reaction, these type of cylisations could provide a lead to the synthesis of carbacyles from sugar scaffolds using intramolecular acyliminium cyclisations.
2. Intermolecular carbon-carbon bond formation was achieved on sugar scaffolds effectively utilizing *N*-acyliminium ions, leading to the elegant synthesis of biotin

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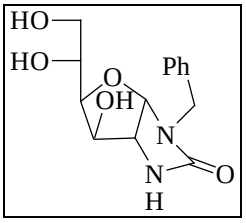
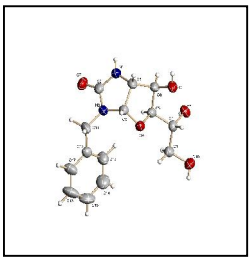
1.2.5 Experimental

1.3-Benzyl-5-(1,2-dihydroxy-ethyl)-6-hydroxy-hexahydro-furo[2,3-*d*]imidazol-2-one (6)





D-glucosamine hydrochloride (25.0 g, 116 mmol.) was dissolved in water (175 mL) and solid $NaHCO_3$ (9.7g, 116 mmol.) was added slowly. To this was added benzylisocyanate (16 mL, 127 mmol.) in dioxane (50 mL) slowly. The reaction mixture was allowed to stir for 30 min.which resulted in the precipitation of a white solid. The solid precipitated was filtered using Buchner funnel, washed with acetone and the resultant solid was suspended in water and was heated in the presence of catalytic pyridine 2 mL for 8h. The solid was filtered and the filtrate was concentrated to furnish the crude intermediate which was purified by crystallization from water to furnish **6.**

Yield	: 28.0 g, (82%)
Mol. Formula	: $C_{14}H_{18}N_2O_5$, white solid
Melting point	: 123 ^{0}C
Optical Rotation $[\alpha]_D$	: +51.52 (*c* 0.94, MeOH)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3358, 2921, 2856, 1692, 1463, 1376, 480.
^{1}**H** NMR ($CDCl_3$, 200MHz)	: 3.37 (bs, 1H), 3.54(d, *J* = 6.35 Hz, 1H), 3.91 (m, 9H), 4.38 (d, *J* = 15.14 Hz, 1H), 5.28 (d, *J* = 6.35 Hz, 1H), 7.10 (m, 5H).
^{13}**C NMR** (DMSO d_6, 50MHz)	: 44.88, 61.64, 64.55, 69.11, 75.06, 79.40, 89.73, 127.62, 44 128.10, 128.95, 138.84, 160.38.
MS (m/z)	: 294(M^+), 233, 187, 174, 106, 91(100), 77, 65.
Elemental Analysis	**Calcd.** : C 57.13; H 6.16; N 9.52
	Found : C 56.94; H 6.56; N 9.24

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Crystal data for compound 6: $C_{14}H_{18}N_2O_5$ M= 294.3; space group Monoclinic, P2(1), a = 7.6332(12) Å, b = 9.5764(15) Å, c = 9.5875(15) Å , beta = 100.092(2)°, alpha = 90° gamma = 90°, V = 689.99(19) Å3, Dc = 2, 1.417 Mg/m^3 (Mo-Kα) = 0.108 mm^{-1} T = 312 Crystal size= 0.52 x 0.47 x 0.16 mm Theta range for data collection = 2.16 to 26.99 °, Limiting indices = 9<=h<=9, -12<=k<=12, -12<=l<=12 Reflections collected / unique 7590 / 2993 [R(int) = 0.0209] Completeness to theta = 26.99 , 99.8 %, Absorption correction = semi-empirical from equivalents Max. and min. transmission = 0.9829 and 0.9458, Refinement method = Full-matrix least-squares on F2 Data / restraints / parameters 2993 / 1 / 245; Goodness-of-fit on F2 = 1.097, Final R indices [I>2sigma(I)]= R1 = 0.0362, wR2 = 0.0932, R indices (all data)= R1 = 0.0366, wR2 = 0.0936, Absolute structure parameter = -0.1(8), Largest diff. peak and hole = 0.185 and -0.257 e.$Å^{-3}$.

Bond lengths [Å] and angles [deg] for comp-3.		**Torsion angles [deg] for comp-3**	
C(2)-O(7)	1.2298(19)	O(4)-C(5)-C(6)-O(8)	80.55(14)
C(2)-N(1)	1.340(2)	C(2')-C(5)-C(6)-O(8)	-39.23(16)
C(2)-N(3)	1.367(2)	O(4)-C(5)-C(6)-C(6')	-38.38(13)
C(3)-O(4)	1.4166(18)	C(2')-C(5)-C(6)-C(6')	-158.16(12)
C(3)-N(3)	1.4483(19)	N(3)-C(11)-C(12)-C(17)	179.05(17)
C(3)-C(6')	1.549(2)	N(3)-C(11)-C(12)-C(13)	-0.7(3)
C(5)-O(4)	1.4400(16)	C(17)-C(12)-C(13)-C(14)	-2.5(3)
C(5)-C(2')	1.513(2)	C(11)-C(12)-C(13)-C(14)	177.2(2)
C(5)-C(6)	1.5258(19)	C(12)-C(13)-C(14)-C(15)	1.2(4)
C(6)-O(8)	1.4156(18)	C(13)-C(14)-C(15)-C(16)	0.7(4)
C(6)-C(6')	1.536(2)	C(14)-C(15)-C(16)-C(17)	-1.2(4)
C(11)-N(3)	1.4548(19)	C(13)-C(12)-C(17)-C(16)	2.1(3)
C(11)-C(12)	1.511(2)	C(11)-C(12)-C(17)-C(16)	-177.7(2)
C(12)-C(17)	1.372(2)	C(15)-C(16)-C(17)-C(12)	-0.2(4)
C(12)-C(13)	1.375(3)	O(4)-C(5)-C(2')-O(9)	-174.61(11)
C(13)-C(14)	1.391(3)	C(6)-C(5)-C(2')-O(9)	-58.07(15)
C(14)-C(15)	1.370(4)	O(4)-C(5)-C(2')-C(1')	60.94(15)
C(15)-C(16)	1.352(4)	C(6)-C(5)-C(2')-C(1')	177.48(12)
C(16)-C(17)	1.388(3)	O(10)-C(1')-C(2')-O(9)	62.71(16)
C(1')-O(10)	1.4200(19)	O(10)-C(1')-C(2')-C(5)	-174.33(12)
C(1')-C(2')	1.514(2)	O(8)-C(6)-C(6')-N(1)	154.42(12)
C(2')-O(9)	1.4187(17)	C(5)-C(6)-C(6')-N(1)	-87.76(14)
C(6')-N(1)	1.436(2)	O(8)-C(6)-C(6')-C(3)	-95.31(14)
O(7)-C(2)-N(1)	126.57(15)	C(5)-C(6)-C(6')-C(3)	22.51(14)
O(7)-C(2)-N(3)	124.94(14)	O(4)-C(3)-C(6')-N(1)	117.36(13)
N(1)-C(2)-N(3)	108.48(13)	N(3)-C(3)-C(6')-N(1)	-2.64(15)
O(4)-C(3)-N(3)	113.70(11)	O(4)-C(3)-C(6')-C(6)	0.70(15)
O(4)-C(3)-C(6')	106.51(11)	N(3)-C(3)-C(6')-C(6)	-119.30(12)
N(3)-C(3)-C(6')	103.17(12)	O(7)-C(2)-N(1)-C(6')	176.38(15)
O(4)-C(5)-C(2')	109.61(11)	N(3)-C(2)-N(1)-C(6')	-4.89(19)
O(4)-C(5)-C(6)	103.86(11)	C(6)-C(6')-N(1)-C(2)	115.98(15)
C(2')-C(5)-C(6)	115.01(11)	C(3)-C(6')-N(1)-C(2)	4.69(18)
O(8)-C(6)-C(5)	110.47(12)	O(7)-C(2)-N(3)-C(3)	-178.38(14)
O(8)-C(6)-C(6')	112.02(13)	N(1)-C(2)-N(3)-C(3)	2.86(17)
C(5)-C(6)-C(6')	101.43(11)	O(7)-C(2)-N(3)-C(11)	-20.2(2)
N(3)-C(11)-C(12)	116.41(13)	N(1)-C(2)-N(3)-C(11)	161.00(14)
C(17)-C(12)-C(13)	118.77(16)	O(4)-C(3)-N(3)-C(2)	-114.90(13)

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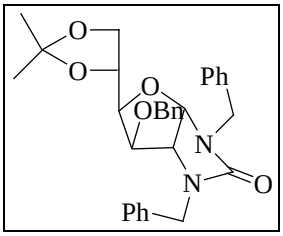
C(17)-C(12)-C(11)	117.18(15)	C(6')-C(3)-N(3)-C(2)	0.03(15)
C(13)-C(12)-C(11)	124.05(14)	O(4)-C(3)-N(3)-C(11)	87.10(16)
C(12)-C(13)-C(14)	119.80(18)	C(6')-C(3)-N(3)-C(11)	-157.96(13)
C(15)-C(14)-C(13)	120.7(2)	C(12)-C(11)-N(3)-C(2)	115.34(17)
C(16)-C(15)-C(14)	119.5(2)	C(12)-C(11)-N(3)-C(3)	-88.82(19)
C(15)-C(16)-C(17)	120.29(19)	N(3)-C(3)-O(4)-C(5)	87.16(13)
C(12)-C(17)-C(16)	120.9(2)	C(6')-C(3)-O(4)-C(5)	-25.78(14)
O(10)-C(1')-C(2')	108.76(12)	C(2')-C(5)-O(4)-C(3)	164.38(11)
O(9)-C(2')-C(5)	109.02(12)	**C(6)-C(5)-O(4)-C(3)**	**41.00(13)**
O(9)-C(2')-C(1')	111.71(12)		
C(5)-C(2')-C(1')	112.45(11)		
N(1)-C(6')-C(6)	111.68(14)		
N(1)-C(6')-C(3)	102.75(12)		
C(6)-C(6')-C(3)	104.33(12)		
C(2)-N(1)-C(6')	113.54(14)		
C(2)-N(3)-C(3)	111.84(12)		
C(2)-N(3)-C(11)	121.82(13)		
C(3)-N(3)-C(11)	122.40(14)		
C(3)-O(4)-C(5)	**107.09(10)**		

1,3-Dibenzyl-6-benzyloxy-5-(2,2-dimethyl-(1,3)dioxalan-4-yl)-hexahydro-furo[2,3-d]imidazol-2-one (22).



To a stirred solution of compound **6** (28.48 g, 98.6 mmol.) in dry acetone (250 mL) was added *p*-TSA (0.92 g, 4 mmol.) and was allowed to stir at room temprature for 1h. Acetone was removed under reduced pressure and the resultant residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution and then with brine. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to furnish the crude dioxalane derivative. The crude residue was used for further reaction without purification. To a stirred suspension of NaH (10.3 g, 430.0 mmol.) washed with dry pet ether and the residue (32.0 g, 95.8 mmol.) in dry DMF (100 mL) was added dropwise BnBr (28.0 mL, 238.0 mmol.) at 0 ^{0}C and was allowed to stir at room temperature for 6h. The reaction mixture was quenched with dil. HCl and diluted with water. The resulting suspension was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate and filtered. After evaporation of solvent

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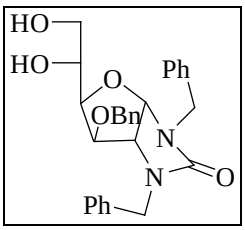
under reduced pressure the residue was purified by column chromatography on silica gel (eluting with ethyl acetate:petether (20:80)) to provide compound **4** as a pale yellow oil

Yield	: 42.0 g, (86%).
Mol. Formula	: $C_{31}H_{34}N_2O_5$, Viscous liquid.
Optical Rotation $[\alpha]_D$	: -4.16 (*c* 1.24, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3017, 2932, 1700, 1372, 1215, 759, 488, 462, 435.
^{1}**H NMR** ($CDCl_3$, 200MHz)	: 1.35(s, 6H), 3.61-3.74(m, 2H), 3.76-3.83(m, 3H), 4.01(d, *J*= 14.65 Hz, 1H), 4.04(d, *J*= 16.60 Hz, 1H), 4.26(m, 2H), 4.44(d, *J*= 16.60 Hz, 1H), 4.61(d, *J*= 15.63Hz, 1H), 4.67(d, *J*=14.65Hz, 1H), 5.38(d, *J*=6.84, 1H), 7.06-7.41(m, 15H).
^{13}**C** ($CDCl_3$, 50MHz)	: 25.24, 26.64, 45.20, 46.28, 62.85, 67.11, 71.89, 72.04, 79.24, 79.87, 87.18, 108.91, 127.25-128.61, 126.73, 137.36, 158.64.
MS (ESI) m/z	: 514.02
Elemental Analysis	**Calcd. :** C 70.87; H 6.37; N 5.90
	Found : C 70.76; H 6.68; N 5.63

1,3-Dibenzyl-6-benzyloxy-5-(1,2-dihydroxy-ethyl)-hexahydro-furo[2,3-d]imidazol-2-one(23).



To a stirred solution of the compound **22** (20g, 38.9 mmol.) in a mixture of THF and water (9:1) was added *p*-TSA (0.74 g, 3.8 mmol) and refluxed for 6 h. The reaction mixture was cooled to the room temperature, extracted with ethyl acetate, washed with saturated aqueous

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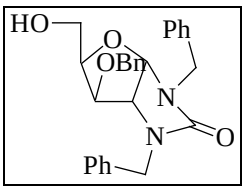
$NaHCO_3$ solution and then with brine. The organic layer was separated, dried on anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography (eluting with ethyl acetate:petether (60:40)) to furnish the compound **23**.

Yield	: 18.0 g, (98%)
Mol. Formula	: $C_{28}H_{30}N_2O_5$; White solid
Melting point	: 63 ^{0}C
Optical Rotation $[\alpha]_D$	: -10.02 (*c* 0.94; $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3406(b), 3029, 2929, 2874, 1690, 1452, 482, 445.
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.52 (m, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 3.8 (d, *J*= 6.36 Hz, 1H), 3.99 (m, 3H), 4.35 (d, *J*= 14.71 Hz, 1H), 4.39 (d, *J*= 11.92 Hz, 1H), 4.42 (d, *J*= 11.92 Hz, 1H), 4.45 (d, *J*= 12.31 Hz, 1H), 4.60 (d, *J*= 15.10Hz, 1H), 4.61 (d, *J*= 14.70 Hz, 1H), 4.80 (d, *J*= 15.11 Hz, 1H), 5.40 (d, *J*= 6.36 Hz, 1H), 7.28 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 45.20, 46.56, 61.93, 64.17, 68.62, 71.85, 78.69, 79.43, 87.15, 128.68-127.32, 137.17, 136.29, 158.79
MS (ESI) m/z	: 474.044
Elemental Analysis	**Calcd. :** C 72.953, H 6.35, N 6.30.
	Found : C 73.07, H 6.73, N 6.37.

1,3-Dibenzyl-6-benzyloxy-5-hydroxymethyl-hexahydro-furo[2,3-*d*]imidazol-2-one (26).



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To a stirred solution of compound **23** (1.267 g, 2.60 mmol.) in a mixture of acetone and water (9:1) was added solid $NaIO_4$ (1.957 g, 6.60 mmol.) in portions. The reaction mixture was allowed to stir at room temperature for 15 min. Acetone was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with water, brine and dried over anhydrous sodim sulfate and filtered. Organic solvent was removed under reduced pressure and the residue (1.184 g) was dissolved in methanol, cooled to 0 ºC and sodium borohydride (0.098 g, 26.0 mmol) was added in portions over a period of time. The reaction mixture was warmed to room temperature and allowed to stir for 1h. After the completion of the reaction (as per TLC), the solvent was removed *in vaccuo*, the crude reaction mixture was quenched with dil. HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and solvent was removed *in vaccuo* to furnish alcohol which on purification using column chromatography (eluting with ethyl acetate:petether (30:70)) gave alcohol **26.**

Yield	: 1.11g, (94%)
Mol. Formula	: $C_{27}H_{28}N_2O_4$; White solid
Melting point	: 94 ºC
Optical Rotation $[\alpha]_{Na}$	: +91.96 (*c* 0.58, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3441, 3016, 2927, 1696, 1463, 1452, 1235, 755, 416, 406
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.70-4.00 (m, 5H); 4.15 (d, *J* = 12.21 Hz, 1H); 4.21 (d, *J* = 11.72 Hz, 1H); 4.26 (d, *J* = 15.14 Hz, 1H) 4.38 (d, *J* = 12.21 Hz, 1H); 4.74 (d, *J* = 11.72 Hz, 1H); 5.47 (d, *J* = 6.35 Hz, 1H); 7.07-7.3 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 44.98, 46.97, 60.42, 62.52, 71.67, 78.98, 80.60, 86.78, 127.43, 128.06, 128.50, 128.83, 136.69, 137.03, 158.79
MS (ESI) m/z	: 444.03.
Elemental Analysis	**Calcd. :** C 72.953, H 6.35, N 6.30.
	Found : C 73.07, H 6.73, N 6.37.

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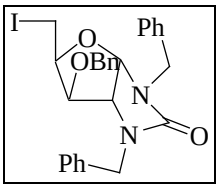
1,3-Dibenzyl-6-benzyloxy-5-iodomethyl-hexahydro-furo[2,3-*d*]imidazol-2-one (27).



A mixture of substrate **26** (1.0 g, 2.25 mmol.), TPP (1.18 g, 4.50 mmol.), and imidazole (0.15 g, 2.25 mmol.) in THF was heated to reflux in a two neck round bottomed flask. To this was added dropwise Iodine (0.57 g, 4.50 mmol.) in THF *via* syringe over a period of 15 min. and the reaction mixture was allowed to reflux for 12 h. After the completion of the reaction, the reaction mixture was cooled to room temperature partitioned between water and ethylacetate. The organic layer was separated, washed with dil. aqueous sodium thiosulfate solution followed by brine. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vaccuo* and the crude residue was purified by column chrormatography (eluting with ethyl acetate:petether (15:85)) to furnish the iodo imidazolidinone **27**.

Yield	: 1.22g, (98%)
Mol. Formula	: $C_{27}H_{27}IN_2O_3$; Colourless syrup
Optical Rotation $[\alpha]_D$	: -38.28 (*c* 0.84, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.28(d, *J* = 7.33 Hz, 2H); 3.80-3.95 (m, 2H); 4.15 (dd, 7.33, 2.93 Hz, 1H); 4.22 (d, *J* = 15.13 Hz, 1H); 4.28 (d, *J* = 11.24 Hz, 1H); 4.35 (s, 2H); 4.67 (d, *J* = 15.13 Hz, 1H); 4.85 (d, *J* = 14.67 Hz, 1H); 5.47 (d, *J* = 6.34 Hz, 1H); 7.15-7.50 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 1.40, 44.80, 46.90, 62.0, 72.15, 79.50, 79.76, 87.18, 127.36, 127.65, 127.95, 128.28, 128.76, 136.58, 136.77, 158.57

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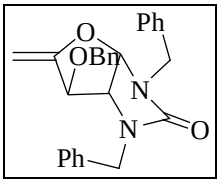
MS (ESI) m/z	: 554.02
Elemental Analysis	**Calcd. :** C 58.49, H 4.90, N 5.05.
	Found : C 58.45, H 4.61, N 5.19.

1,3-Dibenzyl-6-benzyloxy-5-methylene-hexahydro-furo[2,3-*d*]imidazol-2-one (28).



A mixture of iodoimidazolidinone (0.50 g, 0.90mmol) and DBU (0.02 g, 0.09 mmol.) was heated at 80 ºC for 4 h. and the reaction mixture was purified by column chromatography (eluting with ethyl acetate:petether (10:90)) to furnish the enolether **28**.

Yield	: 0.30 g; 80%
Mol. Formula	: $C_{27}H_{26}N_2O_3$; Colourless syrup
Optical Rotation $[\alpha]_D$	: -52.47 (*c* 0.84, $CHCl_3$)
IR (neat) $\tilde{\nu}$ (cm^{-1})**:**	: 3063, 3030, 2924, 1711, 1666, 1495, 1242, 1029, 751
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.83(d, *J* = 5.37 Hz, 1H); 4.03 (s, 1H); 4.18 (d, *J* = 14.65 Hz, 1H); 4.25 (d, *J* = 14.65 Hz, 1H); 4.27 (d, *J* = 14.65 Hz, 1H); 4.58 (d, *J* = 15.14 Hz, 1H); 4.61 (m, 2H); 4.64 (d, *J* = 15.14Hz, 1H); 4.91 (d, 15.14 Hz, 1H); 5.57 (d, *J* = 5.37 Hz, 1H); 7.15- 7.45 (m, aromatic, 15H)
^{13}C ($CDCl_3$, 50MHz)	: 45.35, 46.86, 62.37, 69.94, 78.43, 88.95, 89.28, 127.73, 128.09, 128.42, 128.57, 136.36, 136.51, 136.99, 157.90, 158.42
MS (ESI) m/z	: 426.03

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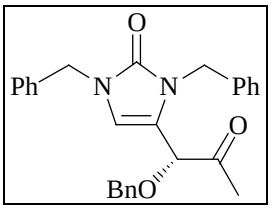
1,3-Dibenzyl-4-(1-benzyloxy-2-oxo-propyl)-1,3-dihydro-imidazol-2-one (30)



To a stirred solution of compound **6** (100 mg, 15.49 mmol.) taken in DCM (1 mL.) in a 2 neck round bottomed flask at –78 ^{0}C was added TMSCN (3.34 mL, 25.1 mmol.) and allowed to stir for 5 min. To this reaction mixture was added $BF_3.Et_2O$ (6.43 mL, 32.4 mmol.) and the reaction mixture was allowed to stir at this temperature for 10 min, brought to room temperature and allowed to stir for 15 min, quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layer was separated, washed with water, brine and dried over anhydrous sodium sulphate and filtered. The organic solvent was removed *in vaccuo* and the residue was purified by column chromatography on silica gel (eluting with ethyl acetate:petether (15:75)) to furnish the pure compound **30** as thick liquid.

Yield	: 0.072 g, (72%)
Mol. Formula	: $C_{27}H_{26}N_2O_3$
IR (neat) $\tilde{\nu}$ (cm^{-1})**:**	: 3063, 3030, 2924, 1711, 1666, 1495, 1242, 1029, 751
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.95 (s, 3H); 4.27 (d, *J* = 11.72 Hz, 1H); 4.36 (d, *J* = 11.72 Hz, 1H); 4.48 (s, 1H); 4.65-5.10 (m, 4H); 6.13 (s, 1H); 6.90-7.55 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 25.83, 45.13, 47.30, 70.97, 111.18, 117.69, 127.03, 127.39, 127.84, 128.46, 128.76, 136.40, 137.06, 153.90, 204.11

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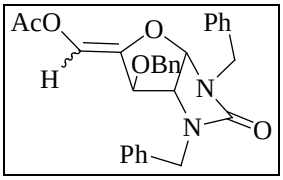
Acetic acid 1,3-dibenzyl-6-benzyloxy-2-oxo-hexahydro-furo[2,3-d]imidazol-5-ylidenemethyl ester (31).



To a stirred solution of compound **23** (12.67 g, 26.0 mmol.) in a mixture of acetone and water (9:1) was added solid $NaIO_4$ (19.57 g, 66.0 mmol.) in portions. The reaction mixture was allowed to stir at room temperature for 15 min. Acetone was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with water, brine and dried over anhydrous sodim sulfate. Organic solvent removed under reduced pressure and the residue (11.84 g) was dissolved in ethylene dichloride. To this crude reaction mixture in EDC was added acetic anhydride (5.03 mL, 53.0 mmol.), triethylamine (10.8 mL, 80.0 mmol.) and DMAP (0.652 g, 5.3 mmol.) and the reaction mixture was heated at reflux for 4h. The reaction mixture was cooled to room temparature and diluted with DCM. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silicagel (eluting with ethyl acetate:petether (25:75)) to furnish the compound **31**

Yield	: 10.3 g, (85%)
Mol. Formula	: $C_{29}H_{28}N_2O_5$, yellow solid.
Melting point	: 72-74 ^{0}C
Optical Rotation $[\alpha]_D$	: -5.72 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3029, 2926, 2868, 1755, 1718, 1451, 1363, 1227, 496, 442
^{1}H NMR ($CDCl_3$+CCl_4, 200MHz)	: 2.24 (s, 3H), 3.86 (d, *J* = 5.9 Hz, 1H), 4.0 (s, 1H), 4.39 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 8.8 Hz, 1H,), 4.58 (d, *J* =

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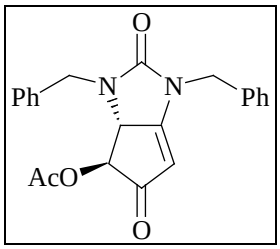
	15.1 Hz, 1H), 4.90 (d, *J* = 14.6 Hz, 1H), 5.64 (d, *J* = 5.9 Hz, 1H), 6.60 (s, 1H), 7.1-7.4 (m, 15 H)
^{13}C ($CDCl_3$, 50MHz)	: 20.71, 45.78, 47.21, 62.98, 70.08, 77.83, 90.59, 116.10, 127.0-129.0, 136.42, 136.97, 140.03, 158.55, 159.97, 167.56.
MS (ESI) m/z	: 484.02.
Elemental Analysis	**Calcd. :** C 71.89, H 5.83, N 5.78
	Found : C 71.50, H 6.07, N 5.68.

Acetic acid 1,3-dibenzyl-2,5-dioxo-1,2,3,3a,4,5-hexahydro-cyclopentamidazol-4-yl ester (39)



To enolactetate **31** (0.20 g, 0.41 mmol) in DCM 2mL taken in a round bottomed flask at room temperature was added catalytic triflouroacetic acid (0.004 g, 0.041 mmol.). The reaction mixture was allowed to stirr for 15 min. After the completion of reaction as per tlc the reaction mixture was neutralized with aquoues sodium bicarbonate solution (1mL) and extracted with DCM (2x5 mL). The combined organic layers was dried over anhydrous sodium sulfate, solvent removed under reduced pressure and the crude product obtained was purified by column chromatography on silica gel (eluting with ethyl acetate:petether (25:75)) to furnish **39**.

Yield	: 0.118 g,(76%)
Mol. Formula	: $C_{22}H_{20}N_2O_4$, White solid.
Melting point	: 64-66 ºC

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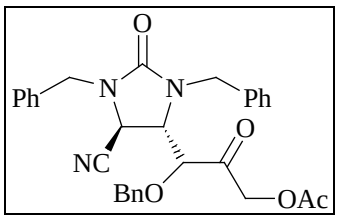
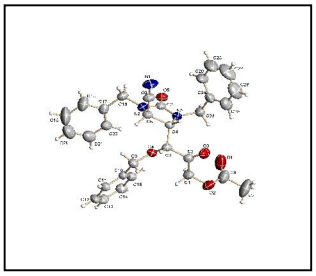
Optical Rotation $[\alpha]_D$	: -17.94 (*c* 1.55; $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 2926, 1747, 1624, 1384, 1229, 1126, 751, 701.
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.09 (s, 3H); 4.37 (dd, *J* = 4.43, 2.14 Hz, 1H); 4.43(d, *J* = 14.91 Hz, 1H); 4.64 (d, *J* = 14.90 Hz, 1H); 4.82 (d, *J* = 14.90 Hz); 4.90 (d, *J* = 14.91 Hz, 1H); 5.18 (d, *J* = 2.14 Hz, 1H); 5.19 (d, *J* = 4.43 Hz, 1H); 7.30 (m, 10 H)
^{13}C ($CDCl_3$, 50MHz)	: 20.55, 47.03, 47.70, 62.71, 78.21, 98.62, 128.03, 128.45, 129.00, 134.11, 134.83, 157.60, 167.87, 169.82, 193.59
MS (ESI) m/z	: [M+H] 377.12.
Elemental Analysis	**Calcd. :** C 70.20; H 5.36; N 7.44 **Found :** C 69.91; H 5.16; N 7.21

Acetic acid 3-benzyloxy-3-(1,3-dibenzyl-5-cyano-2-oxo-imidazolidin-4-yl)-2-oxo-propyl ester (41).





To a stirred solution of compound **31** (7.5 g, 15.49 mmol.) in DCM (35 mL.) in a 2 neck round bottomed flask at –78 ^{0}C was added TMSCN (3.34 mL, 25.1 mmol.) and allowed to stir for 5 min. To this was added $BF_3.Et_2O$ (6.43 mL, 32.4 mmol.) and the reaction mixture was allowed to stir at this temperature for 10 min, brought to room temperature and another 0.5 eq of TMSCN (1.0 mL, 7.74 mmol) was added. The reaction mixture was allowed to stir for another 15 min, quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM. The organic layer was separated, washed with water, brine and dried over anhydrous sodium sulphate and filtered. The organic solvent removed under reduced pressure

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and the residue was purified by column chromatography on silica gel(eluting with ethyl acetate:petether (35:65)) to furnish the pure compound **41.**

Yield	: 4.78 g, (61%)
Mol. Formula	: $C_{30}H_{29}N_3O_5$, white solid.
Melting point	: 58 ºC
Optical Rotation $[\alpha]_D$	: +18.69 (*c* 0.58, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3032, 2250, 1723, 1710, 1693, 1449, 1363, 1078.
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.12 (s, 3H), 3.83 (dd, *J* = 5.48, 2.74 Hz, 1H), 3.89 (d, *J* = 5.48 Hz, 1H), 4.00 (d, *J* = 2.73 Hz, 1H), 4.00 (d, *J* = 14.87 Hz, 1H), 4.08 (d, *J* = 15.26 Hz, 1H), 4.27 (d, *J* = 17.65 Hz, 1H), 4.39 (d, *J* = 11.74 Hz, 1H), 4.52 (d, *J* = 17.65 Hz, 1H), 4.56 (d, *J* = 11.74 Hz, 1H), 4.92 (d, *J* = 15.26 Hz, 1H), 4.97 (d, *J* = 14.87 Hz, 1H), 7.09-7.46 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 20.17, 46.08, 46.67, 47.00, 57.00, 66.96, 73.73, 79.42, 115.00, 126.17-129.05, 134.89, 135.44, 135.59, 158.05, 169.85, 201.50.
MS (ESI) m/z	: 511.5.
Elemental Analalysis	**Calcd. :** C 70.43, H 5.71, N 8.21.
	Found : C 70.70, H 5.59, N 8.17.

Crystal data of compound 41: $C_{30}H_{29}N_3O_5$; M= 511.56, space group = 0 Monoclinic, P2(1), a = 12.1575(18) Å, b = 7.5820(11) Å , c = 15.312(2) Å. alpha = 90°. beta = 92.297(2)°, gamma = 90°, V= 1410.3(4) $Å^3$, Dc = 2, 1.205 Mg/m^3, (Mo-Kα) = 0.083 mm^{-1}, F(000)= 540; Crystal = 0.75 x 0.28 x 0.16 mm; Theta range for data collection 1.68 to 26.00 °, Limiting = -14<=h<=14, -9<=k<=9, -17<=l<=18 ; Reflections collected / unique 11003 / 5391 [R(int) = 0.0231] ; Completeness to theta = 26.00, 99.6 %, Absorption correction Semi-empirical from equivalents; max. and min.= 0.9869 and 0.9405, Refinement method = Full-matrix least-squares on F2; Data / restraints / parameters 5391 / 1 / 344 ; Goodness-of-fit on

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F2 =1.078, Final R indices [I>2sigma(I)] R1 = 0.0493, wR2 = 0.1179 ; R indices (all data)= R1 = 0.0598, wR2 = 0.1242, Absolute structure parameter = -1.1(11), Largest diff. peak and hole= 0.137 and -0.110 e.Å^{-3}.

Bond lengths [Å] and angles [deg] for comp-**41**.

C(1)-O(2)	1.418(3)
C(1)-C(2)	1.504(3)
C(2)-O(3)	1.195(3)
C(2)-C(3)	1.514(3)
C(3)-O(4)	1.419(2)
C(3)-C(4)	1.533(3)
C(4)-N(3)	1.458(3)
C(4)-C(5)	1.540(3)
C(5)-N(2)	1.443(3)
C(5)-C(6)	1.483(3)
C(6)-N(1)	1.130(3)
C(7)-C(8)	1.520(5)
C(8)-O(1)	1.204(5)
C(8)-O(2)	1.321(5)
C(9)-O(4)	1.420(3)
C(9)-C(10)	1.493(3)
C(10)-C(15)	1.382(3)
C(10)-C(11)	1.385(3)
C(11)-C(12)	1.380(3)
C(12)-C(13)	1.366(4)
C(13)-C(14)	1.371(4)
C(14)-C(15)	1.375(3)
C(16)-N(2)	1.449(3)
C(16)-C(17)	1.504(4)
C(17)-C(22)	1.368(4)
C(17)-C(18)	1.372(4)
C(18)-C(19)	1.415(7)
C(19)-C(20)	1.350(8)
C(20)-C(21)	1.337(7)
C(21)-C(22)	1.374(4)
C(23)-N(3)	1.468(3)
C(23)-C(24)	1.502(4)
C(24)-C(25)	1.365(4)
C(24)-C(29)	1.375(4)
C(25)-C(26)	1.376(7)
C(26)-C(27)	1.349(8)
C(27)-C(28)	1.363(8)
C(28)-C(29)	1.378(5)
C(2')-O(5)	1.223(3)
C(2')-N(3)	1.355(3)
C(2')-N(2)	1.362(3)
O(2)-C(1)-C(2)	111.3(2)
O(3)-C(2)-C(1)	122.7(2)
O(3)-C(2)-C(3)	121.0(2)
C(1)-C(2)-C(3)	116.27(19)
O(4)-C(3)-C(2)	110.81(16)
O(4)-C(3)-C(4)	110.23(16)
C(2)-C(3)-C(4)	112.41(17)
N(3)-C(4)-C(3)	113.71(15)
N(3)-C(4)-C(5)	102.04(15)
C(3)-C(4)-C(5)	111.04(16)
N(2)-C(5)-C(6)	109.51(17)
N(2)-C(5)-C(4)	102.82(16)
C(6)-C(5)-C(4)	112.31(18)
N(1)-C(6)-C(5)	176.1(3)
O(1)-C(8)-O(2)	123.1(3)
O(1)-C(8)-C(7)	126.2(5)
O(2)-C(8)-C(7)	110.7(5)
O(4)-C(9)-C(10)	111.83(17)
C(15)-C(10)-C(11)	118.50(19)

Torsion angles [deg] for comp-**41**.

O(2)-C(1)-C(2)-O(3)	4.0(4)
O(2)-C(1)-C(2)-C(3)	-173.9(2)
O(3)-C(2)-C(3)-O(4)	168.2(2)
C(1)-C(2)-C(3)-O(4)	-13.9(3)
O(3)-C(2)-C(3)-C(4)	44.3(3)
C(1)-C(2)-C(3)-C(4)	-137.8(2)
O(4)-C(3)-C(4)-N(3)	-58.2(2)
C(2)-C(3)-C(4)-N(3)	66.0(2)
O(4)-C(3)-C(4)-C(5)	56.2(2)
C(2)-C(3)-C(4)-C(5)	-179.62(16)
N(3)-C(4)-C(5)-N(2)	17.64(18)
C(3)-C(4)-C(5)-N(2)	-103.87(17)
N(3)-C(4)-C(5)-C(6)	-99.98(18)
C(3)-C(4)-C(5)-C(6)	138.51(18)
N(2)-C(5)-C(6)-N(1)	-17(4)
C(4)-C(5)-C(6)-N(1)	97(4)
O(4)-C(9)-C(10)-C(15)	-0.2(3)
O(4)-C(9)-C(10)-C(11)	179.04(19)
C(15)-C(10)-C(11)-C(12)	-0.7(3)
C(9)-C(10)-C(11)-C(12)	180.0(2)
C(10)-C(11)-C(12)-C(13)	0.1(4)
C(11)-C(12)-C(13)-C(14)	1.0(4)
C(12)-C(13)-C(14)-C(15)	-1.5(4)
C(13)-C(14)-C(15)-C(10)	0.8(4)
C(11)-C(10)-C(15)-C(14)	0.3(3)
C(9)-C(10)-C(15)-C(14)	179.5(2)
N(2)-C(16)-C(17)-C(22)	-37.8(3)
N(2)-C(16)-C(17)-C(18)	144.9(3)
C(22)-C(17)-C(18)-C(19)	1.3(6)
C(16)-C(17)-C(18)-C(19)	178.7(4)
C(17)-C(18)-C(19)-C(20)	-3.5(9)
C(18)-C(19)-C(20)-C(21)	3.0(10)
C(19)-C(20)-C(21)-C(22)	-0.3(8)
C(18)-C(17)-C(22)-C(21)	1.4(5)
C(16)-C(17)-C(22)-C(21)	-176.0(3)
C(20)-C(21)-C(22)-C(17)	-2.0(6)
N(3)-C(23)-C(24)-C(25)	114.8(3)
N(3)-C(23)-C(24)-C(29)	-64.5(4)
C(29)-C(24)-C(25)-C(26)	-1.2(5)
C(23)-C(24)-C(25)-C(26)	179.5(4)
C(24)-C(25)-C(26)-C(27)	2.5(8)
C(25)-C(26)-C(27)-C(28)	-2.4(10)
C(26)-C(27)-C(28)-C(29)	1.0(9)
C(25)-C(24)-C(29)-C(28)	-0.2(6)
C(23)-C(24)-C(29)-C(28)	179.1(4)
C(27)-C(28)-C(29)-C(24)	0.3(7)
O(5)-C(2')-N(2)-C(5)	-168.27(18)
N(3)-C(2')-N(2)-C(5)	13.4(2)
O(5)-C(2')-N(2)-C(16)	-7.3(3)
N(3)-C(2')-N(2)-C(16)	174.31(18)
C(6)-C(5)-N(2)-C(2')	100.0(2)
C(4)-C(5)-N(2)-C(2')	-19.6(2)
C(6)-C(5)-N(2)-C(16)	-61.0(3)
C(4)-C(5)-N(2)-C(16)	179.39(18)
C(17)-C(16)-N(2)-C(2')	112.6(2)
C(17)-C(16)-N(2)-C(5)	-88.7(2)
O(5)-C(2')-N(3)-C(4)	-178.86(19)
N(2)-C(2')-N(3)-C(4)	-0.5(2)
O(5)-C(2')-N(3)-C(23)	24.6(3)
N(2)-C(2')-N(3)-C(23)	-157.11(17)
C(3)-C(4)-N(3)-C(2')	108.48(18)

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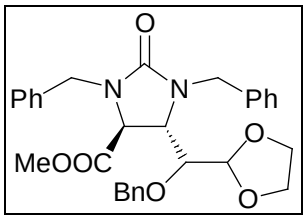
C(15)-C(10)-C(9)	123.43(18)	C(5)-C(4)-N(3)-C(2')	-11.2(2)
C(11)-C(10)-C(9)	118.06(18)	C(3)-C(4)-N(3)-C(23)	-95.4(2)
C(12)-C(11)-C(10)	120.7(2)	C(5)-C(4)-N(3)-C(23)	144.92(19)
C(13)-C(12)-C(11)	120.0(2)	C(24)-C(23)-N(3)-C(2')	95.2(2)
C(12)-C(13)-C(14)	119.9(2)	C(24)-C(23)-N(3)-C(4)	-58.8(3)
C(13)-C(14)-C(15)	120.4(2)	O(1)-C(8)-O(2)-C(1)	-0.6(6)
C(14)-C(15)-C(10)	120.5(2)	C(7)-C(8)-O(2)-C(1)	177.5(3)
N(2)-C(16)-C(17)	114.24(19)	C(2)-C(1)-O(2)-C(8)	-83.2(3)
C(22)-C(17)-C(18)	117.9(3)	C(2)-C(3)-O(4)-C(9)	115.2(2)
C(22)-C(17)-C(16)	121.9(2)	C(4)-C(3)-O(4)-C(9)	-119.75(19)
C(18)-C(17)-C(16)	120.1(3)	C(10)-C(9)-O(4)-C(3)	-155.41(18)
C(17)-C(18)-C(19)	119.0(4)		
C(20)-C(19)-C(18)	120.5(4)		
C(21)-C(20)-C(19)	120.7(4)		
C(20)-C(21)-C(22)	119.3(4)		
C(17)-C(22)-C(21)	122.5(3)		
N(3)-C(23)-C(24)	112.30(19)		
C(25)-C(24)-C(29)	118.7(3)		
C(25)-C(24)-C(23)	120.8(3)		
C(29)-C(24)-C(23)	120.6(3)		
C(24)-C(25)-C(26)	120.4(4)		
C(27)-C(26)-C(25)	120.5(5)		
C(26)-C(27)-C(28)	120.3(5)		
C(27)-C(28)-C(29)	119.5(5)		
C(24)-C(29)-C(28)	120.7(4)		
O(5)-C(2')-N(3)	126.2(2)		
O(5)-C(2')-N(2)	125.1(2)		
N(3)-C(2')-N(2)	108.69(17)		
C(2')-N(2)-C(5)	110.85(17)		
C(2')-N(2)-C(16)	123.27(18)		
C(5)-N(2)-C(16)	122.90(17)		
C(2')-N(3)-C(4)	111.75(16)		
C(2')-N(3)-C(23)	120.90(18)		
C(4)-N(3)-C(23)	122.75(17)		
C(8)-O(2)-C(1)	114.5(3)		
C(3)-O(4)-C(9)	114.84(15)		

1,3-Dibenzyl-5-(benzyloxy-[1,3]dioxolan-2-yl-methyl)-2-oxo-imidazolidine-4-carboxylic acid methyl ester (43).



To a stirred solution of diol **41 (**4.04g, 8.72 mmol.) in a 9:1 mixture of acetone and water, was added sodium metaperiodate (5.12g, 17.44 mmol.) in portions. The reaction mixture was allowed to stir at room temperature for 30 min. Acetone was removed under reduced pressure

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and the residue partitioned between ethyl acetate and water. The organic layer was separated washed with water, brine, dried over anhydrous sodium sulfate and filtered. The organic layer was concentrated under reduced pressure to furnish the crude aldehyde (4.12 g) which was subjected to the further reaction. To a stirred solution of an aldehyde in benzene in a round bottomed flask fitted with Dean-Stark apparatus were added ethylene glycol (0.972 mL, 17.44 mmol.), *p*-TSA (0.828 g, 4.36 mmol.) and refluxed for 6h. The reaction mixture was cooled to room temperature and the organic solvent was removed under reduced pressure. The resultant residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with water followed by brine, dried over anhydrous sodium sulfate and filtered. The organic solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (eluting with ethyl acetate:petether (15:85)) to furnish the dioxalane derivative **9** as a colourless syrupy liquid.

Yield	: 3.2g, (65% over 2 steps).
Mol. Formula	: $C_{30}H_{32}N_2O_6$, viscous liquid.
Optical Rotation $[\alpha]_D$	: + 1.68 (*c* 0.84, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3386, 2952, 2892, 1746, 1690, 1451, 1359, 1219, 1151, 1079, 754, 702.
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.45 (dd, *J* = 1.46, 5.13 Hz, 1H), 3.50 (s, 3H), 3.71 (m, 3H), 3.81 (m, 2H), 4.09 (s, 1H), 4.08 (d, *J* = 15.39 Hz, 1H), 4.50 (d, *J* = 11.72 Hz, 1H), 4.70 (d, *J* = 11.72 Hz, 1H), 4.80 (d, *J* = 3.66, 1H), 4.86 (d, *J* = 14.66 Hz, 1H), 4.94 (d, *J* = 15.39Hz, 1H); 7.18-7.31 (m, 15H).
^{13}C ($CDCl_3$, 50MHz)	: 46.97, 47.37, 51.93, 55.83, 57.04, 64.83, 65.02, 73.66, 103.06, 127.39-128.68, 137.01, 137.65, 159.78, 171.03.
HRMS(M+Na)	: Found 539.2179. requires 539.2158
Elemental Analysis	**Calcd. :** C 69.75, H 6.24, N 5.42.
	Found : C 69.92, H 6.51, N 5.40.

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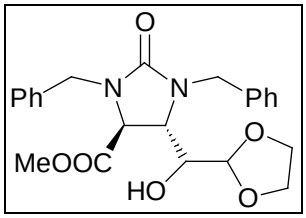
1,3-Dibenzyl-5-([1,3]dioxolan-2-yl-methyl)-2-oxo-imidazolidine-4-carboxylic acid methyl ester (44)



To the substrate **43** (2.468 g, 4.76 mmol) dissolved in methanol (10 mL) was added catalytic amount of Pd-$CaCO_3$ and stirred under hydrogen atmosphere (1atm.) for 24h at room temperature. The reaction mixture was filtered through a small pad of celite and the celite washed with methanol (1x10mL). The combined organic layers were evaporated under reduced pressure and the residue thus obtained was purified by column chromatography on silica gel (eluting with ethyl acetate:petether (40:60)) to furnish the hydroxyester **44.**

Yield	: 1.89 g, (95%)
Mol. Formula	: $C_{23}H_{26}N_2O_6$, viscous liquid.
Optical Rotation $[\alpha]_D$	: -15.59 (*c* 0.80, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3444, 3011, 2953, 2891, 1746, 1697, 1451, 1359, 1217, 1079, 700.
^{1}H NMR ($CDCl_3$, 500MHz)	: 3.55 (s, 3H), 3.64 (s, 2H), 3.71 (s, 1H) 3.77-3.95 (m, 4H), 4.12 (d, *J*= 15.1 Hz, 1H), 4.18 (d, *J*= 15.5 Hz, 1H), 4.71 (s, 1H), 4.92 (d, *J*= 15.1 Hz, 1H), 4.98 (d, *J*= 15.5 Hz, 1H), 7.25- 7.34 (m, 10H)
^{13}C ($CDCl_3$, 125 MHz)	: 46.60, 47.09, 51.82, 56.55, 64.76, 64.89, 71.93, 102.18, 127.14-128.12, 136.42, 136.91, 159.68, 170.70.
HRMS: (M+Na)	: Found 427.1873. $C_{23}H_{27}N_2O_6Na$ requires 427.1869.
Elemental Analysis	**Calcd. :** C 64.78, H 6.15, N 6.57.

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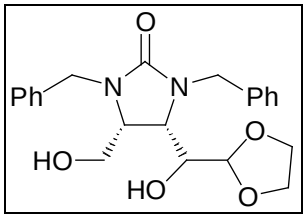
Found : C 64.64, H 6.12, N 6.40.

1, 3- Dibenzyl-4- ([1,3]dioxolan-2-yl-hydroxy-methyl)-5-hydroxymethyl-imidazolidine-2-one (45).



To a stirred solution of hydroxy ester **44 (**1.662 g, 2.604 mmol.) in toluene (10 mL) was added DBU .0.17 mL, 1.416 mmol.) and refluxed for 24h. Toluene was removed under reduced pressure and the residue was partitioned between ethyl acetate and dil. HCl. The organic layer was separated, washed with water, brine, dried over anhydrous sodium sulfate and filtered. The organic solvent was removed under reduced pressure and the crude lactone **44a** (1.502 g) was used for further reduction without purification. The lactone was dissolved in ethanol (5 mL) and to it was added $NaBH_4$ (2.828 g, 76.46 mmol) portionwise and allowed to stir at room temperature for 30 min and at reflux for 2h. The reaction mixture was cooled and ethanol was removed under reduced pressure. The residue was quenched with dil. HCl and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and filtered. The organic solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (eluting with ethyl acetate:petether (50:25)) to furnish the diol **45.**

Yield	: 1.28 g, (86% over two steps).
Mol. Formula	: $C_{20}H_{26}N_2O_5$, solid.
Melting point	: 119 ^oC
Optical Rotation $[\alpha]_D$	: -11.06 (*c*, 0.46, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3386, 2952, 2892, 1746, 1690, 1451, 1359, 1219, 1151, 1079, 754, 702.

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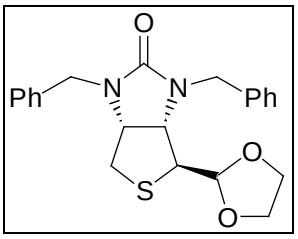
^{1}H NMR ($CDCl_3$, 500 MHz)	: 3.45 (dd, *J* = 2.38, 9.14 Hz, 1H), 3.80 (m, 4H), 3.94 (m, 4H), 4.10 (d, *J* = 15.50 Hz, 1H), 4.21 (d, *J*, 15.50 Hz, 1H), 4.93 (d, *J* = 5.16 Hz, 1H), 4.99 (d, *J* = 15.50 Hz, 1H), 5.04 (d, *J* = 15.90, 1H), 7.25-7.34 (m, 10H)
^{13}C ($CDCl_3$, 125 MHz)	: 45.53, 47.33, 55.25, 56.93, 57.69, 65.05, 65.26, 71.28, 103.53, 127.20-128.66, 136.94, 137.66, 162.40.
Elemental Analysis	**Calcd. :** C 65.61, H 6.29, N 7.29.
	Found : C 66.01, H 6.04, N 6.91.

1,3-Dibenzyl-6-[[1,3]dioxolan-2-yl-tetrahydro-thieno]-[3,4-d]-imidazol-2-one (46)



To a stirred solution diol **45** (1.20 g 3.12 mmol.) in DCM (5 mL) at 0 ^{0}C under nitrogen was added triethylamine (1.50 mL, 10.92 mmol.) MsCl (0.6 mL, 17.81 mmol.) and DMAP (0.060 mg, 0.312 mmol.). The reaction mixture was stirred at room temperature for 2h, diluted with DCM, washed with dil. HCl, brine, dried over anhydrous sodium sulfate and filtered. The organic solvent removed under reduced pressure to furnish the dimesylate derivative. The resultant dimesylate derivative was dissolved in DMF (10 mL) and to it was added Na_2S (58%) (0.324 g, 3.80 mmol.) and heated at 90 ^{0}C for 3h. DMF was removed under reduced pressure, dil HCl was added and extracted with ethyl acetate. The organic layer was washed with dil HCl, brine, dried over anhydrous sodium sulfate and filtered. The organic solvent removed under reduced pressue and purified by column chromatography (eluting with ethyl acetate:petether (25:75)) to furnish the dioxalane derivative **46** as a white solid.

Yield : 0.64 g, (78%).

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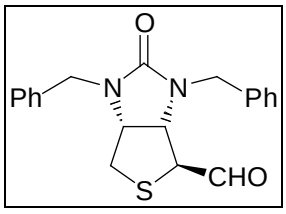
Mol. Formula	: $C_{22}H_{24}N_2O_3S$, solid.
Melting point	: 94 °C
Optical Rotation $[\alpha]_D$	: + 62.87(*c* 0.56, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:**	: 3443, 3007, 2924, 2890, 1691, 1464, 1239, 1130, 1039,736.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 2.76 (d, *J* = 12.13 Hz, 1H), 2.99 (dd, *J* = 3.9, 12.13 Hz, 1H), 3.39 (d, *J* = 2.34 Hz, 1H), 3.78 (m, 4H), 4.01 (m, 2H), 4.08 (d, *J* = 5.87 Hz, 1H), 4.16 (d, *J* = 5.87 Hz, 1H), 4.83 (m, 3H), 7.3 (m, 10H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: 36.18, 46.29, 54.56, 61.80, 62.50, 65.00, 65.59, 105.77, 127.45-128.63, 137.16, 137.42, 159.43.
HRMS (M+H)	: Found 397.1597. $C_{22}H_{25}N_2O_3S$ requires 397.1586.
Elemental Analysis	**Calcd. :** C 66.64, H 6.10, N 6.90, S 8.09.
	Found : C 66.36, H 6.38, N 6.90, S 8.00

1,3-Dibenzyl-4-formyl-1H-tetrahydrothieno-[3,4-d]-imidazol-2(3H)-one (47):



The dioxalane derivative **46** (0.64 g, 0.24 mmol.) was dissolved in a mixture of acetic acid and 6N HCl and stirred at room temperature for 24h. Acetic acid was removed under reduced pressure and the crude reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to furnish the crude aldehyde which was purified by column chromatography (eluting with ethyl acetate:petether (30:70)) to furnish the aldehyde **47**.

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Yield : 0.46 g, (82%)

Mol. Formula : $C_{20}H_{20}N_2O_2S$, solid

Melting point : 140-141 ^oC

Optical Rotation $[\alpha]_D$: -62.4 (*c* 0.75, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})**:** : 3120, 2940, 1705, 1695, 1605, 1595, 1500, 1450, 1250

^{1}H NMR ($CDCl_3$, 200MHz) : 2.29 (dd, *J* = 4.7, 13.15 Hz, 1H); 2.68 (dd, *J* = 4.7, 13.15 Hz, 1H); 3.59 (s, 1H); 4.11 (dd, *J* = 4.7, 7.78 Hz, 1H); 4.16 (d, *J* = 15.4 Hz, 1H); 4.34 (d, *J* = 7.9 Hz, 1H); 4.36 (d, *J* = 15.4 Hz, 1H); 4.47 (d, *J* = 15.4 Hz, 1H); 4.68 (d, *J* = 15.4 Hz 1H); 7.25 (m, 10H); 9.13 (s, 1H).

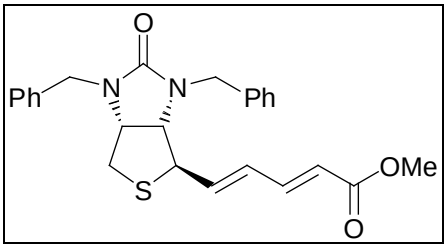
^{13}C NMR ($CDCl_3$, 50MHz) : 34.71, 46.42, 47.16, 59.30, 60.63, 61.96, 127.59, 127.68, 127.78, 128.65, 128.71, 136.77, 137.02, 159.75, 189.90.

MS (m/z) : 352(M^+, 5), 323(5), 277(93), 264(6), 91(100), 65(6).

Elemental Analysis **Calcd. :** C, 68.16; H, 5.72; N, 7.95; S, 9.1

Found : C, 67.95; H, 5.70; N, 7.84; S, 9.5.

1,3-Dibenzyl-4-[1-(1E,3E)-4-methoxycarbonyl-1,3-butadienyl]1H-tetrahydro-thieno[3,4d]imidazol-2(3H)-one (48):



A mixture of aldehyde **47** (0.450 g, 1.278 mmol.) and 3-methoxy carbonyl-2-propenylidine triphenyl phosphorane (0.55 g, 1.533 mmol) in dichloromethane (5 mL) was stirred for 12h, and then concentrated under reduced pressure at room temperature. The residue was purified by column chromatography (eluting with ethyl acetate:petether (15:85)) to give ester **48**.

Yield : 0.49 g, (89%)

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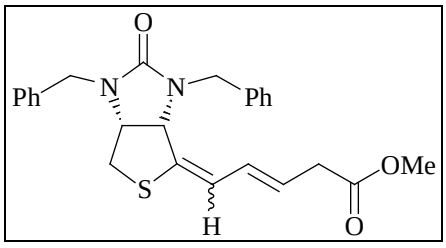
Mol. Formula	: $C_{25}H_{26}N_2O_3S$, viscous liquid.
Optical Rotation $[\alpha]_D$	: +62.13 (c 1.24, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3020, 2920, 1700, 1650, 1600, 1510, 1450, 1370, 1260, 1150, 1020
^{1}**H NMR** ($CDCl_3$, 200MHz)	: 2.22 (dd, *J* = 12.25, 5.8 Hz, 1H). 2.35 (dd, *J* = 12.25, 4.3 Hz, 1H), 3.27 (dd, *J* = 8.89, 3.86 Hz, 1H), 3.42 (s, 3H), 4.67 (t, *J* = 15.2 Hz, 2H), 4.7 (d, *J* = 15.2 Hz, 2H), 5.27 (dd, *J* = 15.2, 8.29 Hz, 1H), 5.53 (dd, *J* = 15.2, 10.78 Hz, 1H), 5.76 (d, *J* = 15.2Hz, 1H), 7.25 (m, 11H)
^{13}**C NMR** ($CDCl_3$, 50MHz)	: 36.67, 36.98, 46.25, 46.48, 51.30, 55.12, 61.51, 65.91, 121.68, 127.45, 127.93, 128.49, 129.59, 136.7, 136.77, 138.6, 142.70, 158.88, 166.6
MS (m/z)	: 434(M^+, 43), 402(7), 277(100), 264(13), 187(15), 155(9), 91(76)
Elemental Analysis	**Calcd.:** C 69.09; H 6.03; N 6.45; S 7.38; **Found:** C 69.40; H 5.85; N 6.1; S 7.40

Pentanoic acid, 5-[hexahydro-2-oxo-1,3-dibenzyl-4H-thieno(3,4-d)imidazol-3,5-dienyl] methyl ester (49a):



To a solution of ester **14** (0.43 g, 1 mmol.) in methanol (5 mL) was added 1M NaOH (5 mL) and reaction mixture was stirred for 3h and left at 0^{o}C for 12h. Methanol was removed by rotary evaporation under reduced pressure and the residue was diluted with dichloromethane (20 mL) and water (5 mL). The pH of the solution was adjusted to pH 2 with 1N hydrochloric

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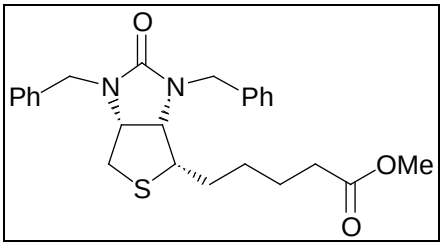
acid and stirred for 5 min. Organic layer was washed with water, brine, dried and evaporated in *vacuo* to give acid **49** as viscous liquid, and it was treated with diazomethane to furnish its ester and was characterized as its methyl ester **49a**.

Yield	: 0.31 g, (97%).
Mol. Formula	: $C_{25}H_{26}N_2O_3S$, viscous liquid.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}):	: 3040, 2940, 17440, 1700, 1610, 1600, 1510, 1460, 1380, 1260, 1190
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.0-2.6 (m, 3H). 3.1 (d, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 4.3-3.7 (m, 3H), 5.1-4.6 (m, 3H), 6.2-5.5 (m, 3H), 7.30 (m, 10H).
^{13}C NMR ($CDCl_3$, 50MHz)	: 37.43. 37.87, 44.93, 46.66, 51.70, 58.95, 64.80, 125.95, 124.08, 126.35, 127.16, 127.38, 127.56, 127.99, 127.68, 128.08, 128.26, 128.60, 130.90, 135.60, 136.93, 137.14, 138.47, 158.72, 171.30.
MS (m/z)	: 434(M^+, 6), 343(3), 277(7), 238(3), 136(5), 106(29), 91(100), 65(10).
Elemental Analysis	**Calcd.:** C, 69.09; H, 6.03; N, 6.45; S, 7.40. **Found:** C, 69.26; H, 5.96; N, 6.51; S, 7.44.

1H-Thieno(3,4-d)-imidazol-4-pentanoic acid hexahydro-2-oxo-1,3-dibenzyl methyl ester (16):



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A mixture of unsaturated ester **49a** (434 mg, 1 mmol) and 10% palladium on charcoal (150 mg) in methanol (10 mL) was hydrogenated (3 atm) for 8h. Filtration of the catalyst and the removal of the solvent under reduced pressure furnished a residue which was purified by column chromatography (1:5 ethyl acetate/n-hexane) to furnish ester of biotin ester as a white solid.

Yield	: 0.295g, 99%.
Mol. Formula	: $C_{25}H_{30}N_2O_3S$
Melting point	: 78-80 ^oC
Optical Rotation $[\alpha]_D$	: - 42.13^o (*c* 1.05, $CHCl_3$)
IR (Nujol+$CHCl_3$)	: 2970, 2840, 1740, 1690, 1600, 1500, 1460, 1250
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.75-1.25 (m, 6H). 2.34 (t, *J* =7.0 Hz, 2H); 2,68 (dd, *J* = 12.6, 5.8 Hz, 1H), 2.80 (dd, *J* = 12.6, 4.0 Hz, 1H), 3.70 (s, 3H,), 3.2 (m, 1H), 3.97 (d, *J* = 15.2 Hz, 1H), 4.0-3.84 (m, 1H), 4.17 (d, *J* = 15.2 Hz, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 5.15 (d, *J* = 15.2 Hz, 1H), 7.25 (m, 10H)
^{13}C NMR($CDCl_3$, 50MHz)	: 24.85, 28.00, 28.70, 34.07, 46.85, 48.20, 51.68, 54.44, 61.44, 62.90, 127.83, 128.47, 128,90, 137.01, 137.25, 161.24, 178.09
MS (m/z)	: MS: 438(M^+, 6), 347(15), 277(29), 265(14), 240(9), 187(17), 91(100), 85(6), 65(9).
Elemental Analysis	**Calcd.:** C 68.46; H 6.89; N 6.38; S, 7.31 **Found:** C 68.52; H 7.0; N 6.52; S 7.62.

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Spectra

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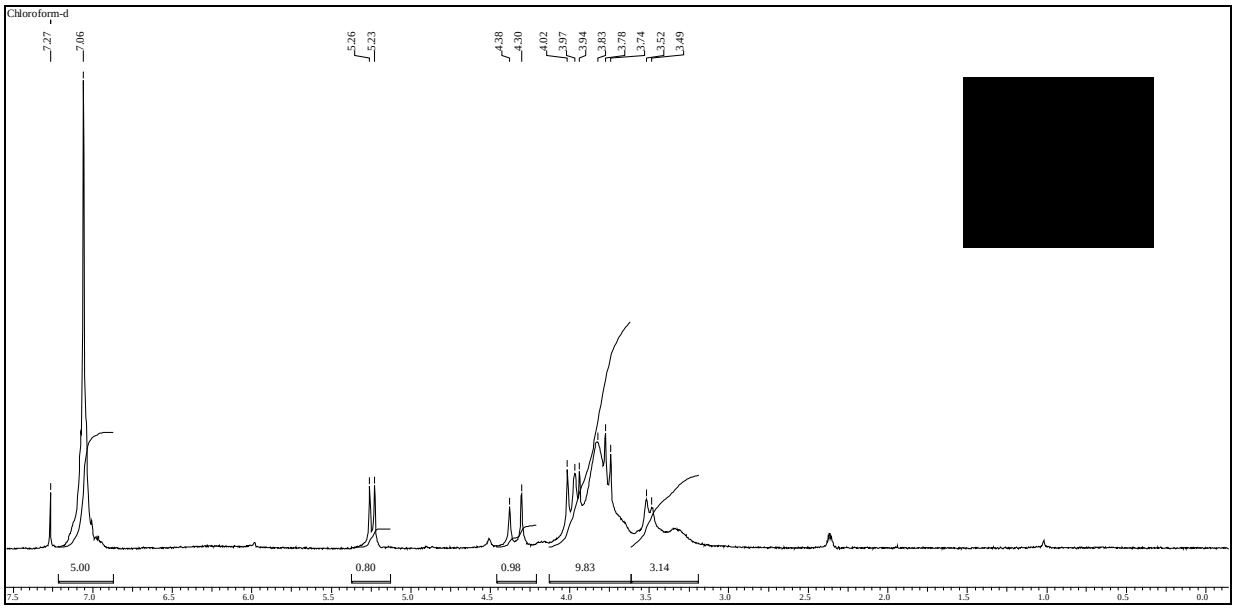
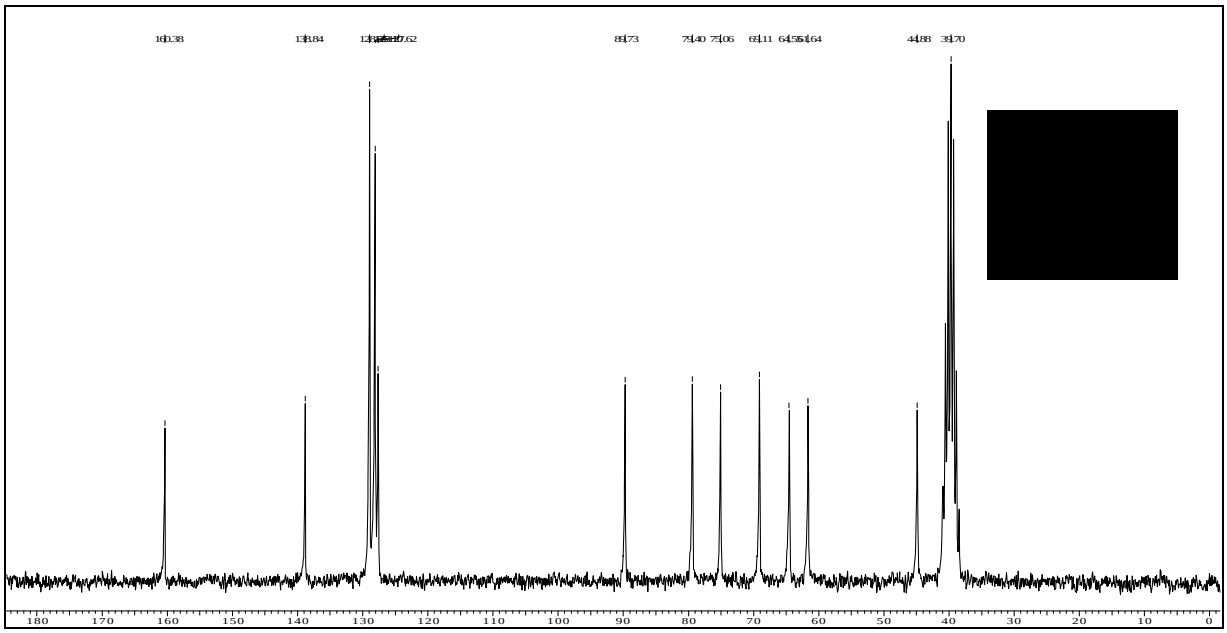


^{1}H NMR spectrum of compound **6** ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound **6** (DMSO d_6, 200 MHz)

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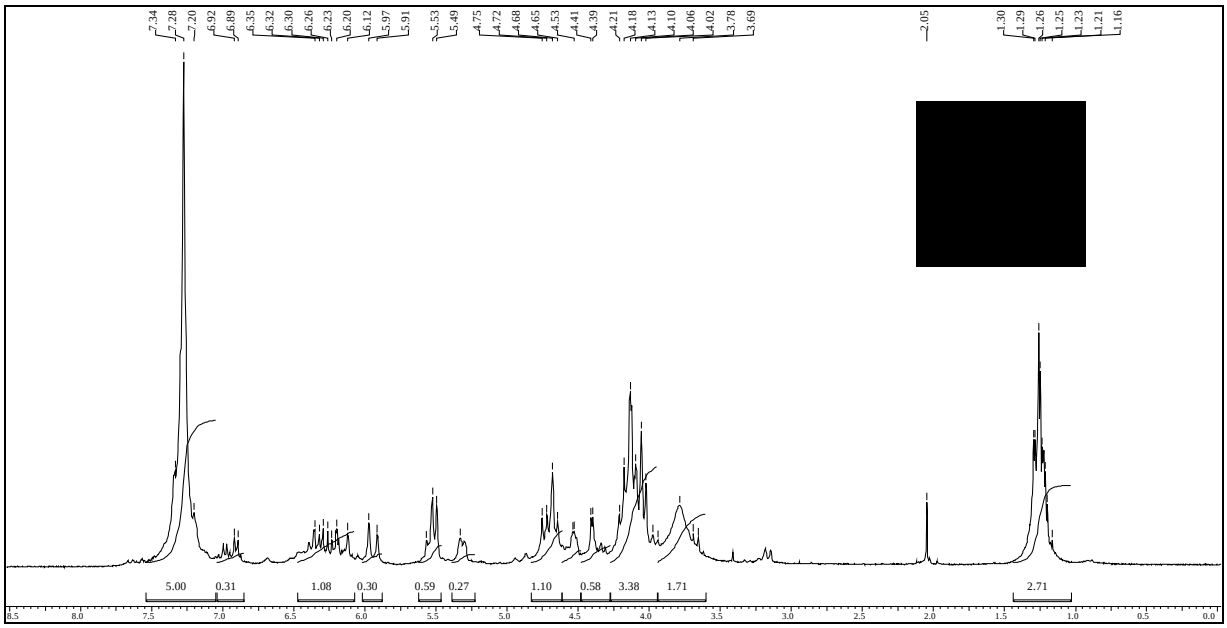
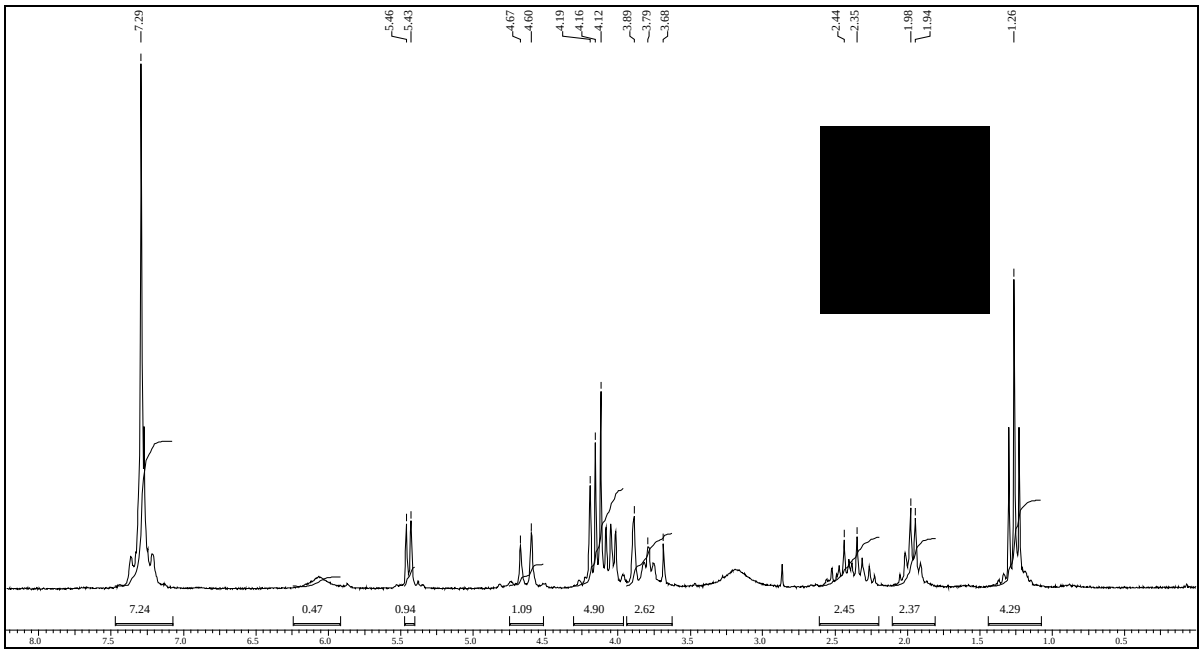


^{1}H NMR spectrum of compound **17** ($CDCl_3$, 200 MHz)



^{1}H NMR spectrum of compound **18** ($CDCl_3$, 200 MHz)

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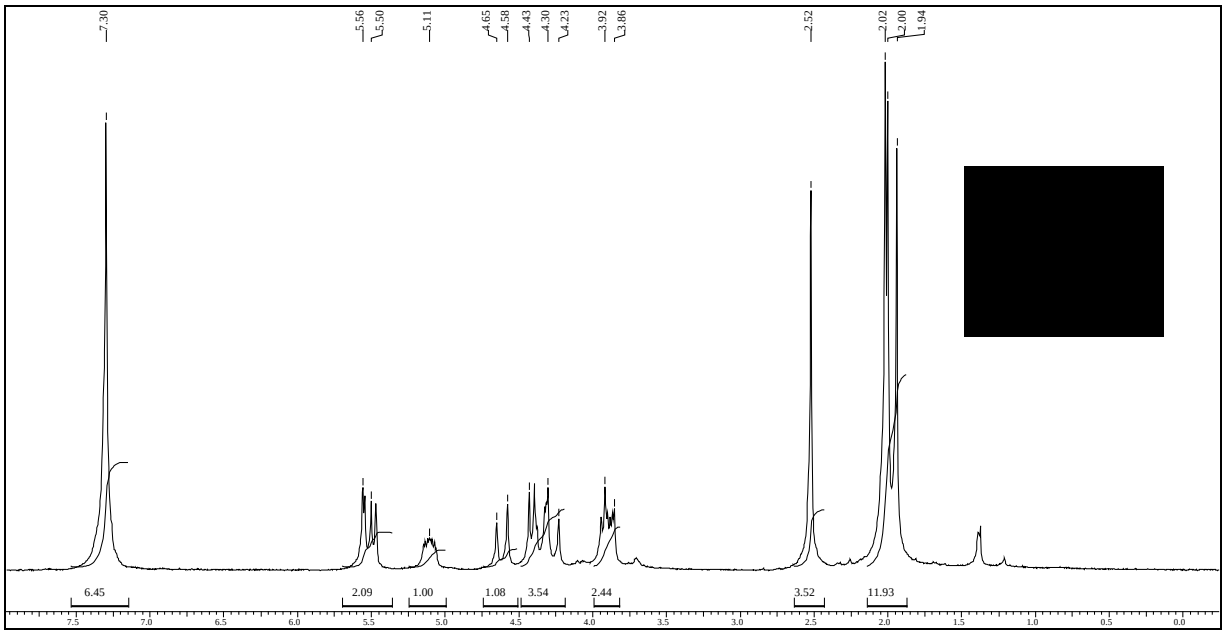
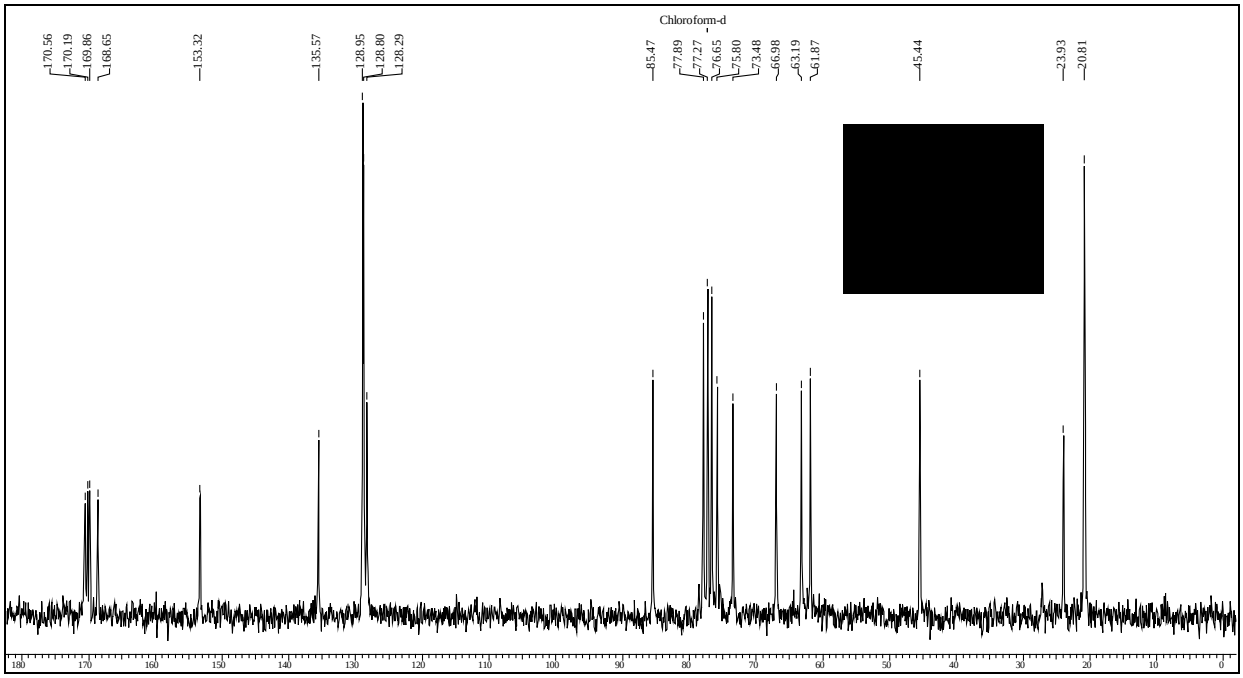


^{1}H NMR spectrum of compound **21** ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound **21** ($CDCl_3$, 50 MHz)

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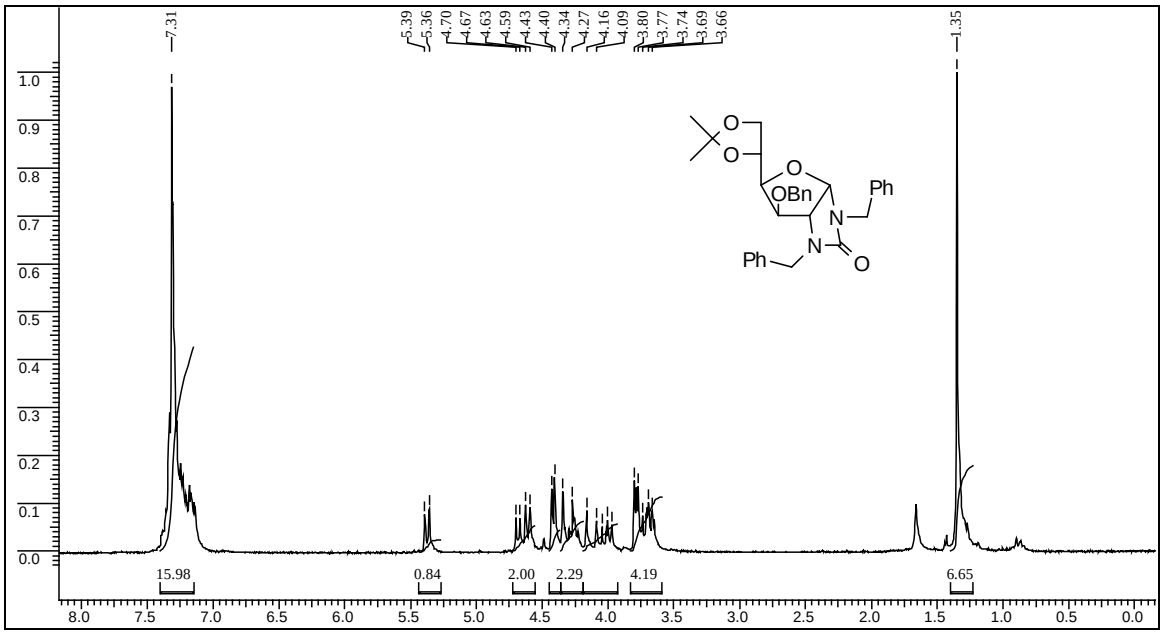
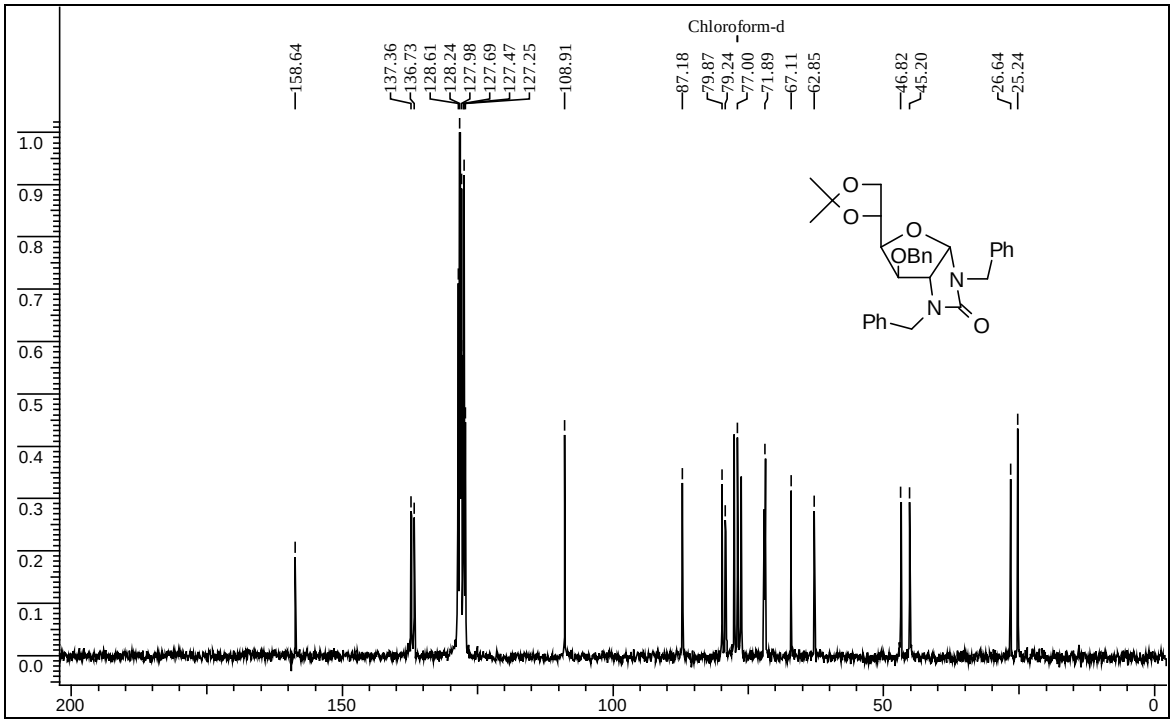


^{1}H NMR spectrum of compound **22** ($CDCl_3$, 500 MHz)



^{13}C NMR spectrum of compound **22** ($CDCl_3$, 500 MHz)

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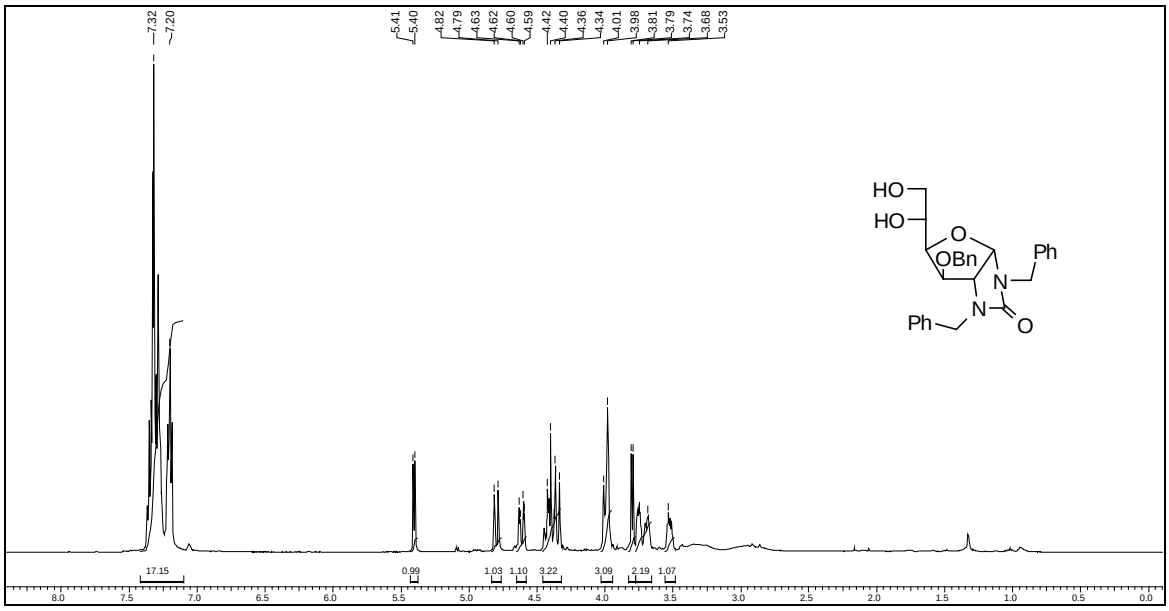
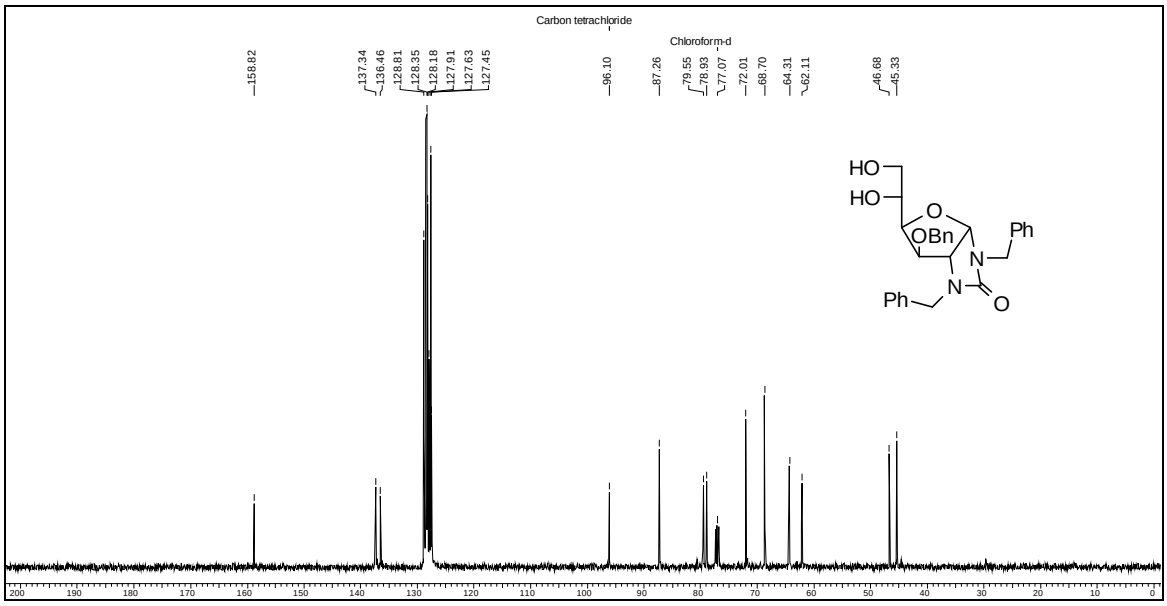


^{1}H NMR spectrum of compound **23** ($CDCl_3$, 500 MHz)



^{13}C NMR spectra of compound **23** ($CDCl_3$+CCl_4, 125 MHz)

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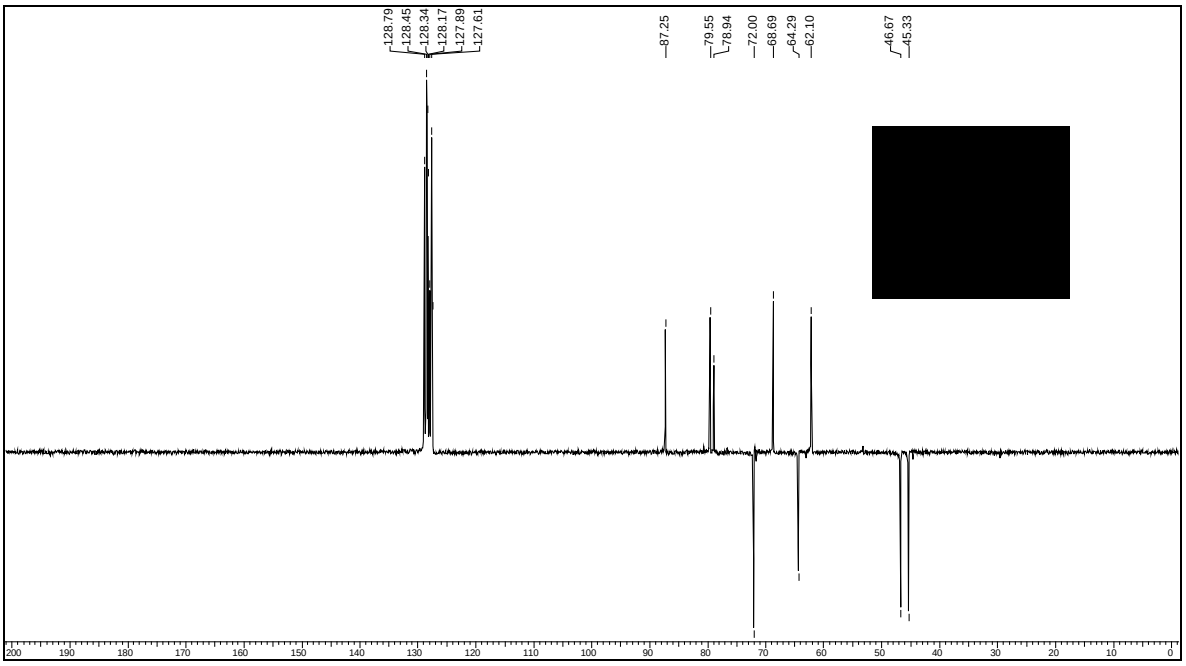
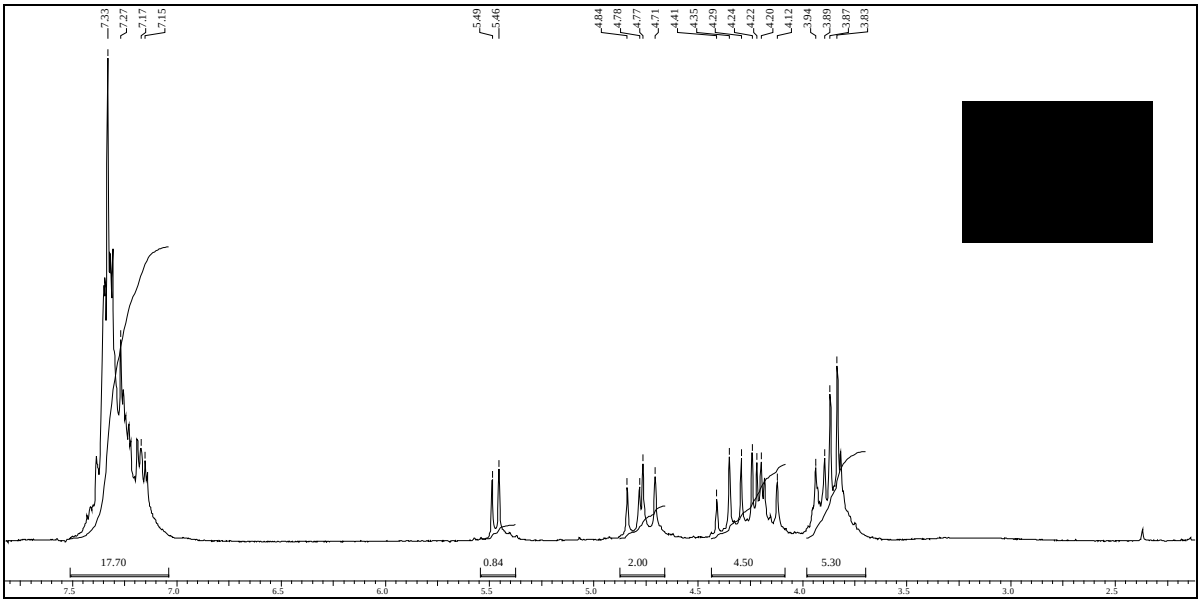


DEPT NMR spectra of compound **23** ($CDCl_3$+CCl_4, 125 MHz)



^{1}H NMR spectrum of compound **26** ($CDCl_3$+CCL_4, 200 MHz)

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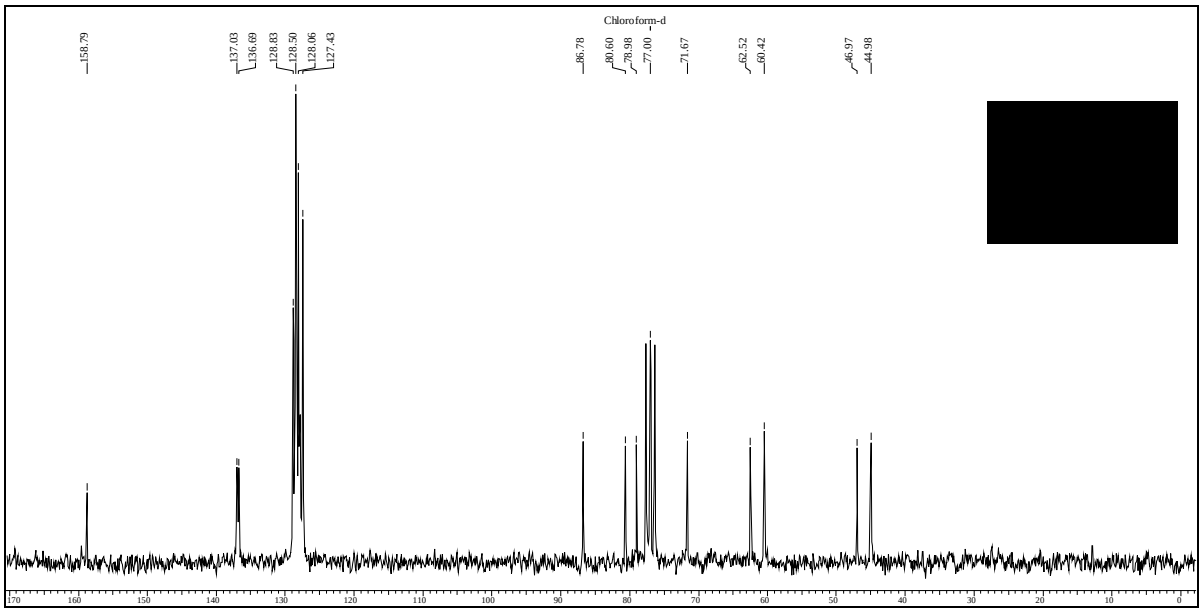
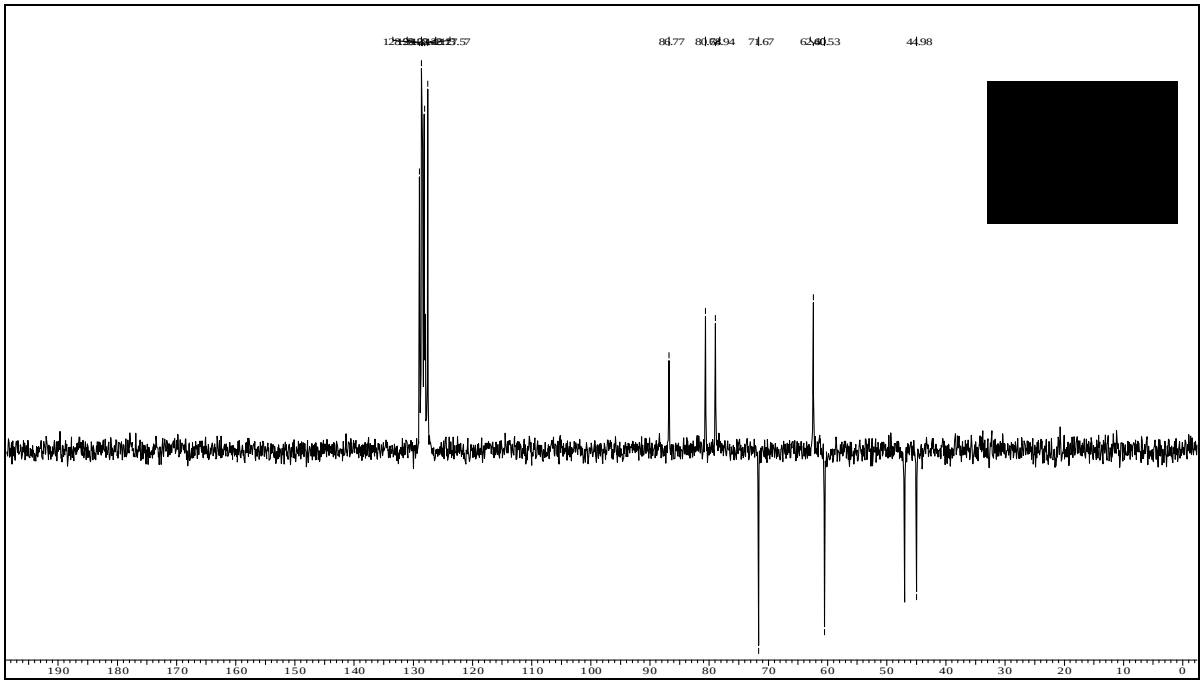


^{13}C NMR spectrum of compound **26** ($CDCl_3$, 200 MHz)



DEPT NMR spectrum of compound **26** ($CDCl_3$, 200 MHz)

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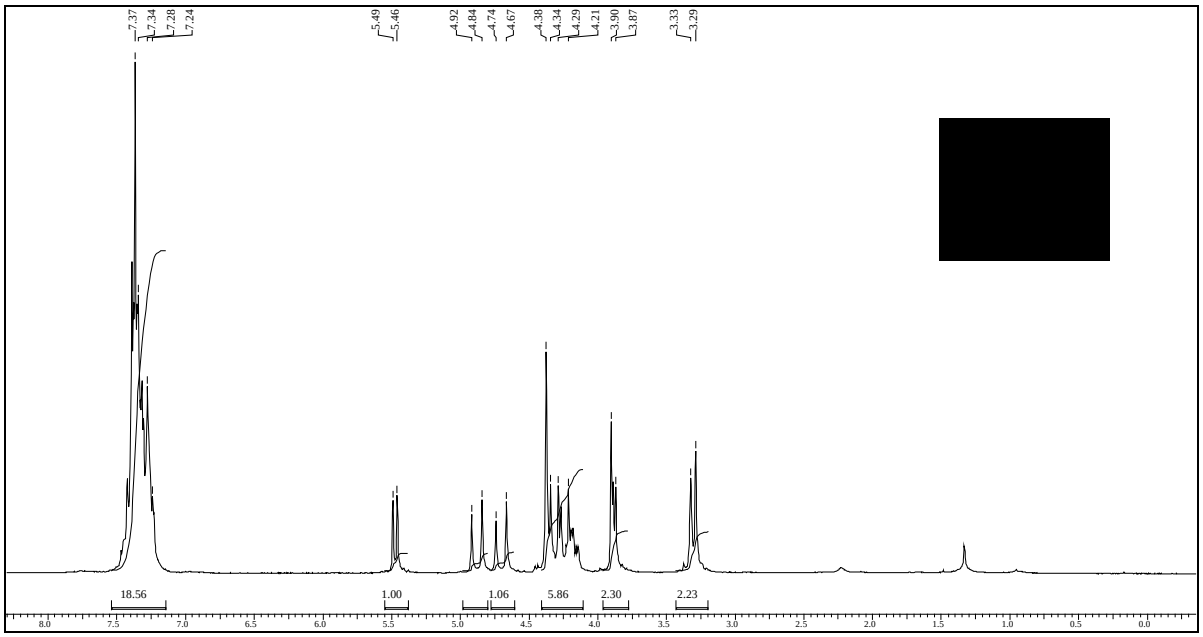
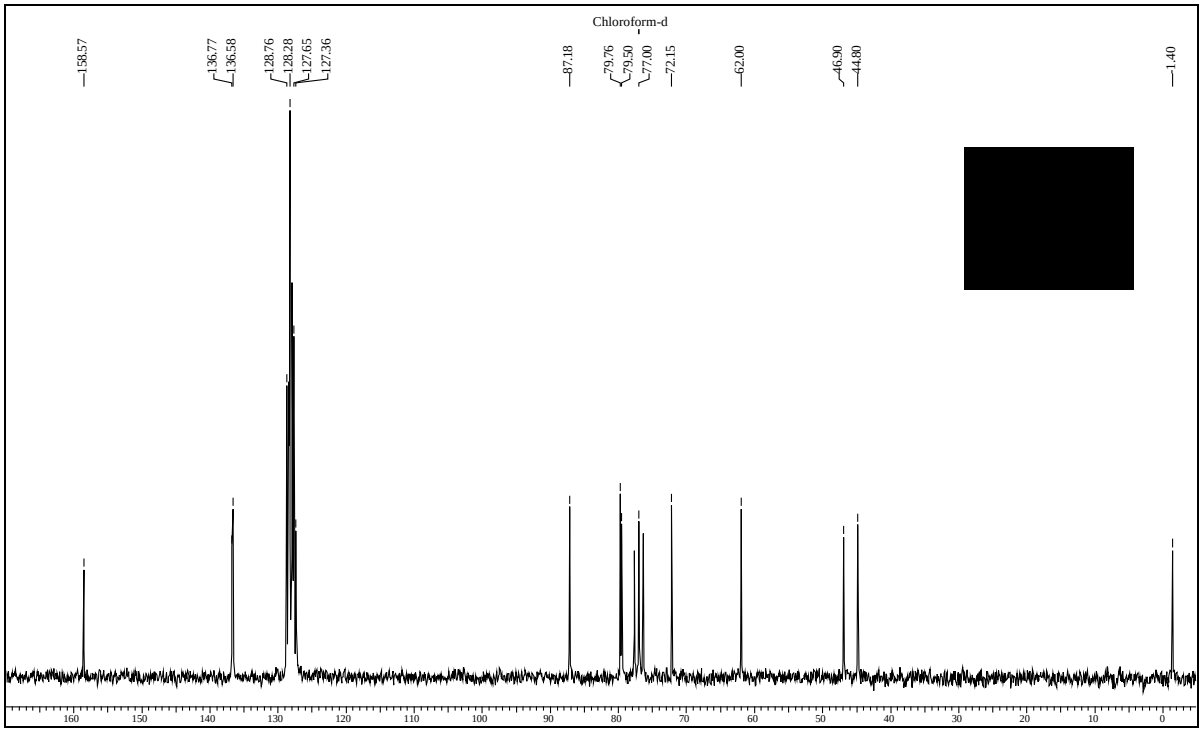


^{1}H NMR spectrum of compound **27** ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound **27** ($CDCl_3$, 50 MHz)

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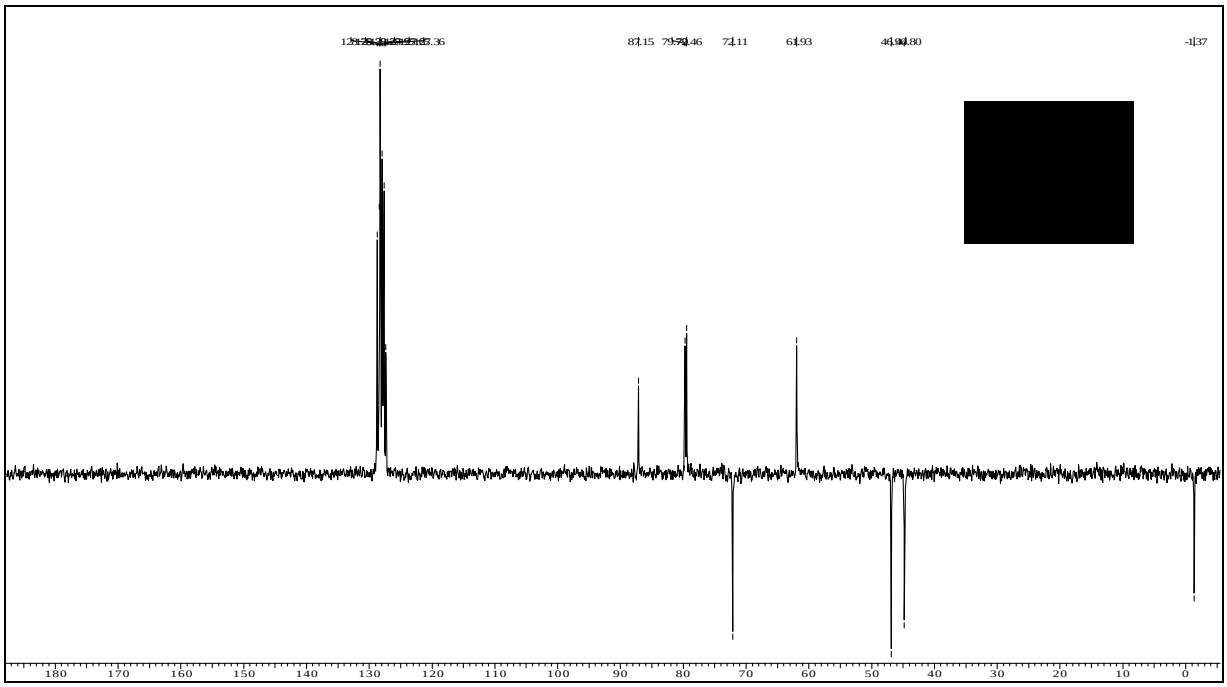
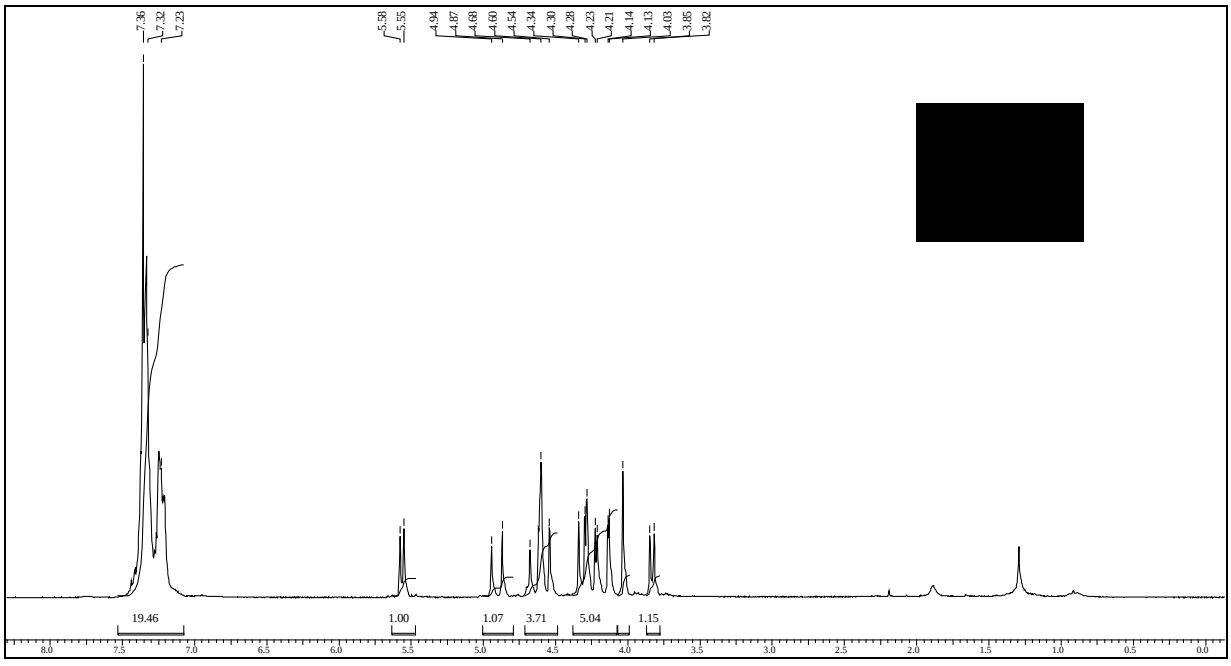


DEPT NMR spectrum of compound **27** ($CDCl_3$, 50 MHz)



^1H NMR spectrum of compound **28** ($CDCl_3$, 200 MHz)

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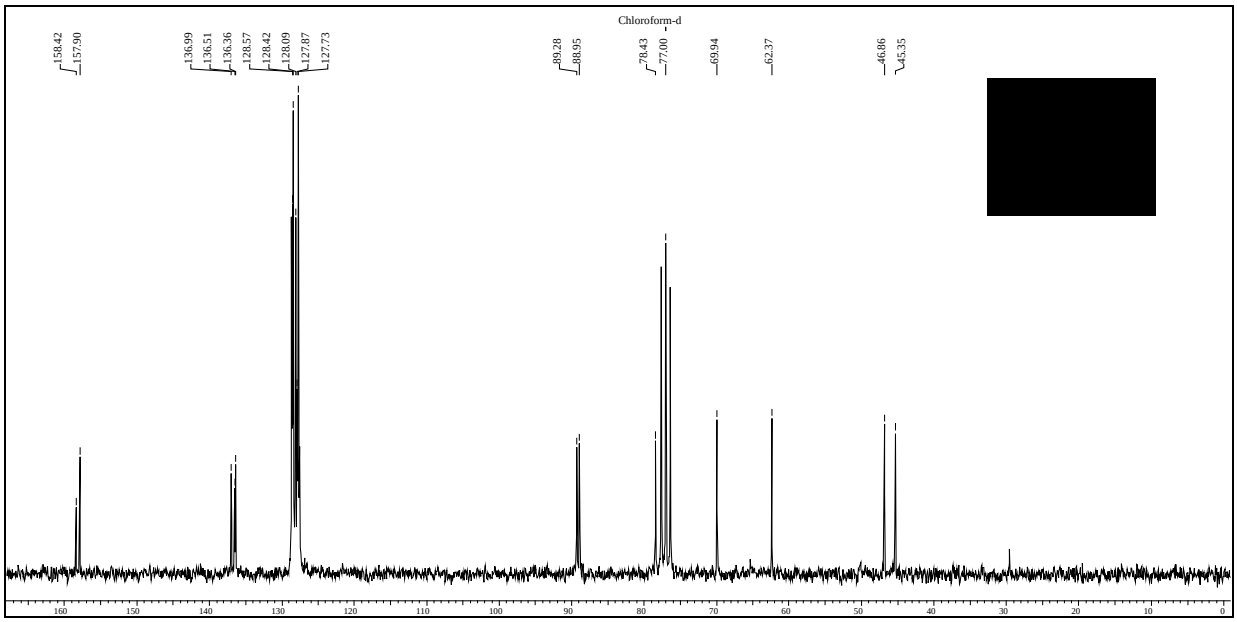
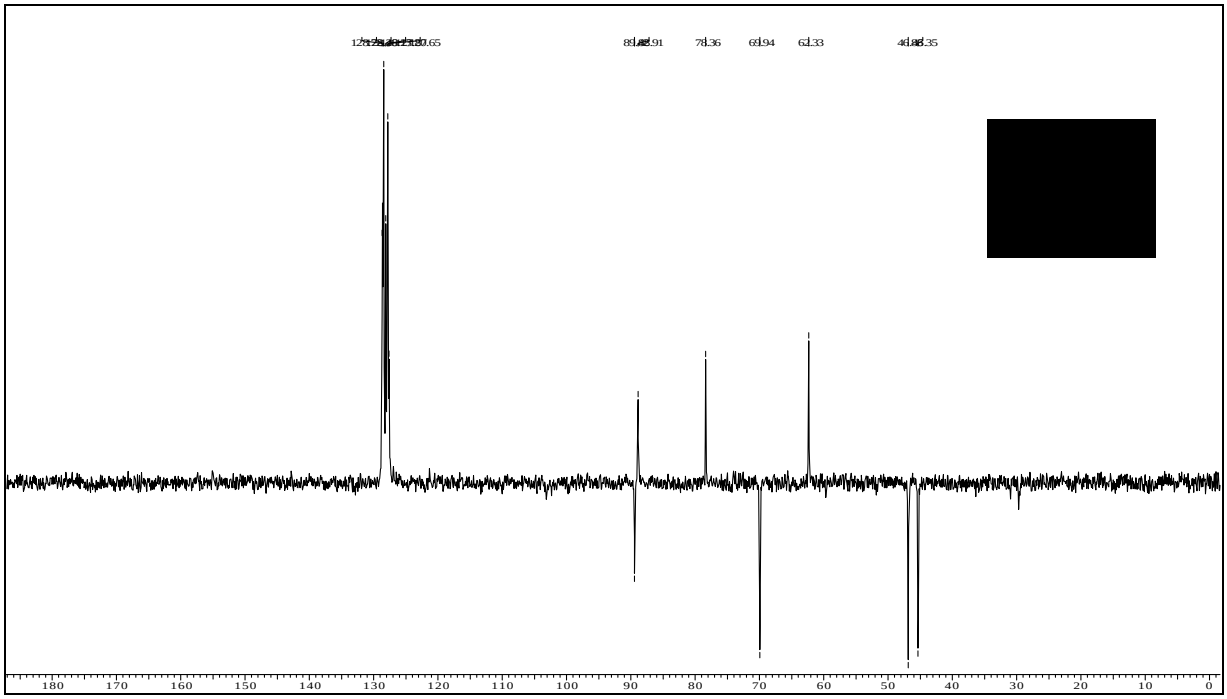


^{13}C NMR spectrum of compound **28** ($CDCl_3$, 50 MHz)



DEPT NMR spectrum of compound **28** ($CDCl_3$, 50 MHz)

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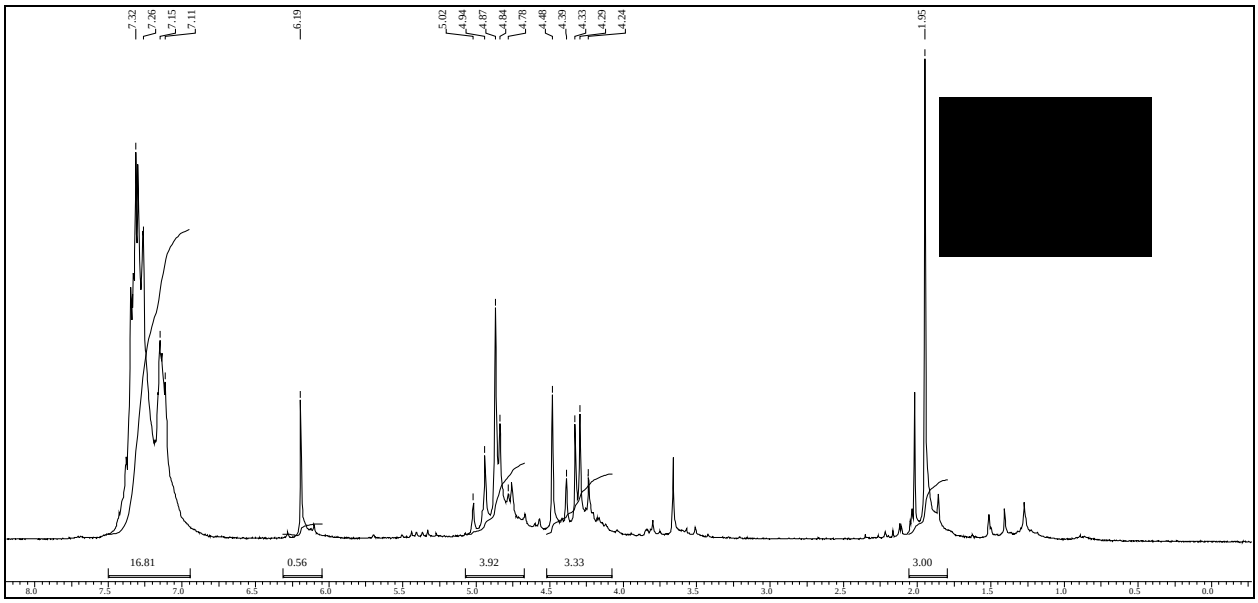
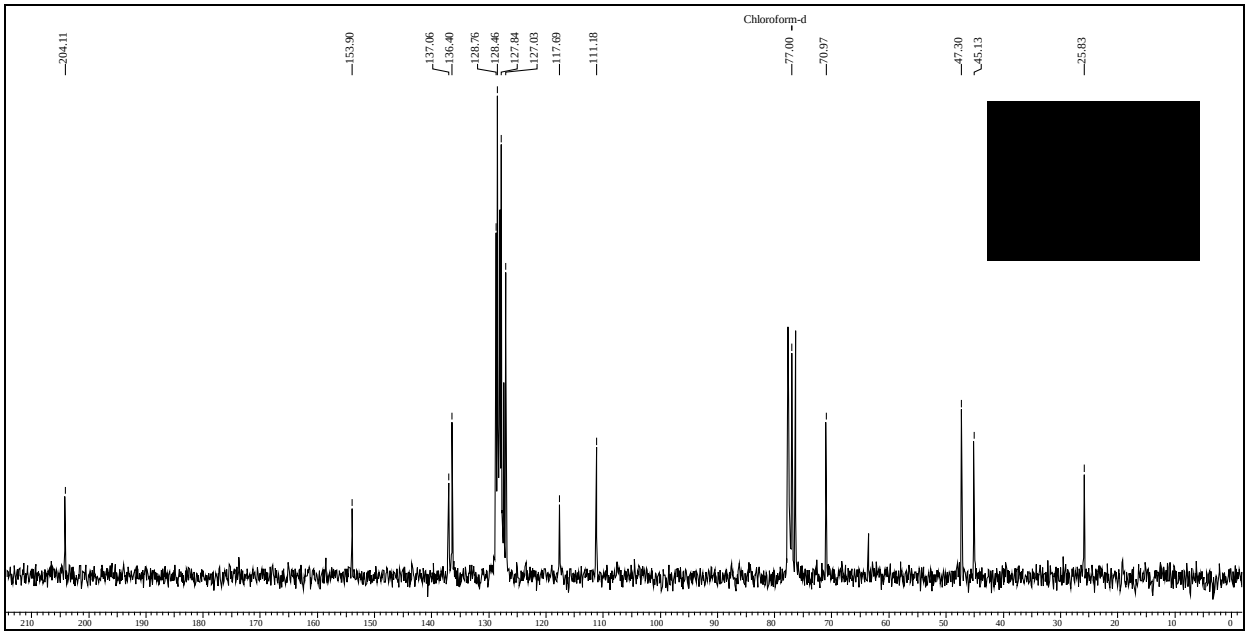


^{1}H NMR spectrum of compound **30** ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound **30** ($CDCl_3$, 50 MHz)

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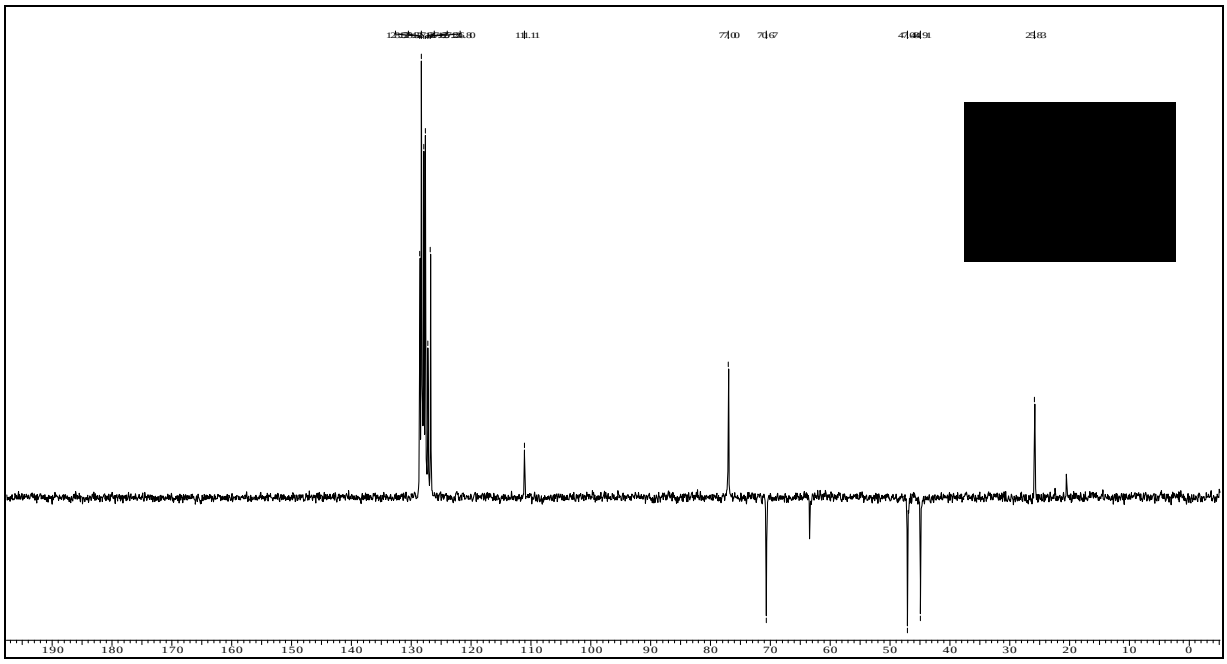
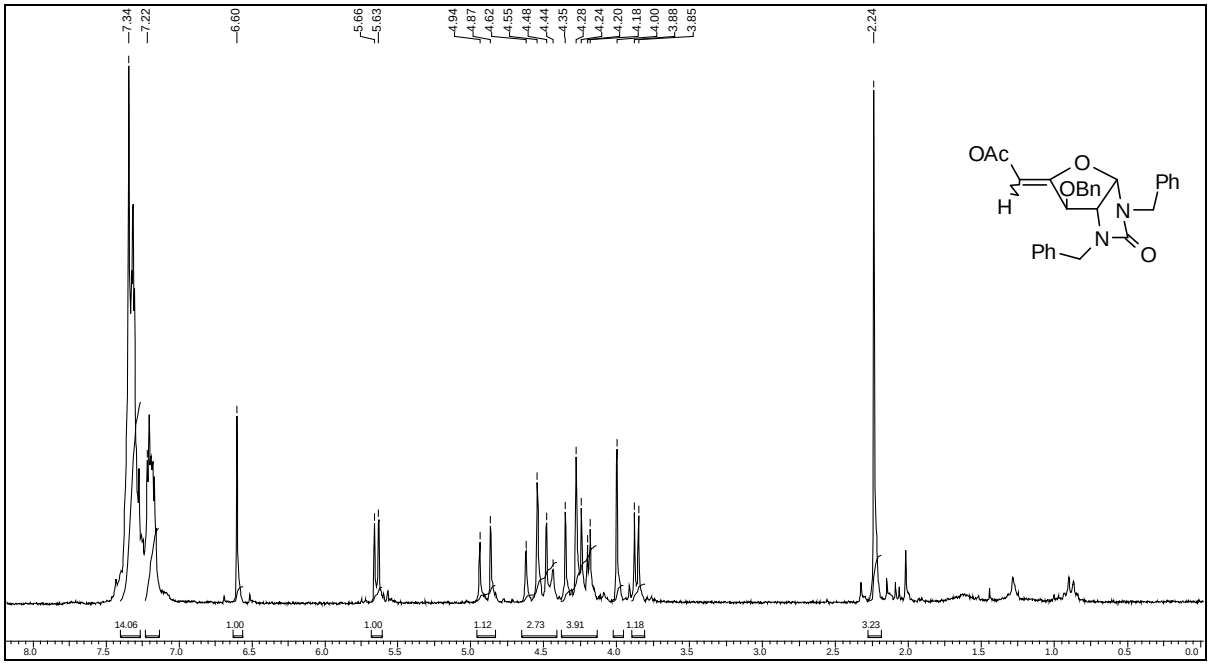


DEPT NMR spectrum of compound **31** ($CDCl_3$, 50 MHz)



^1H NMR spectrum of compound **31** ($CDCl_3$+CCl_4, 200 MHz)

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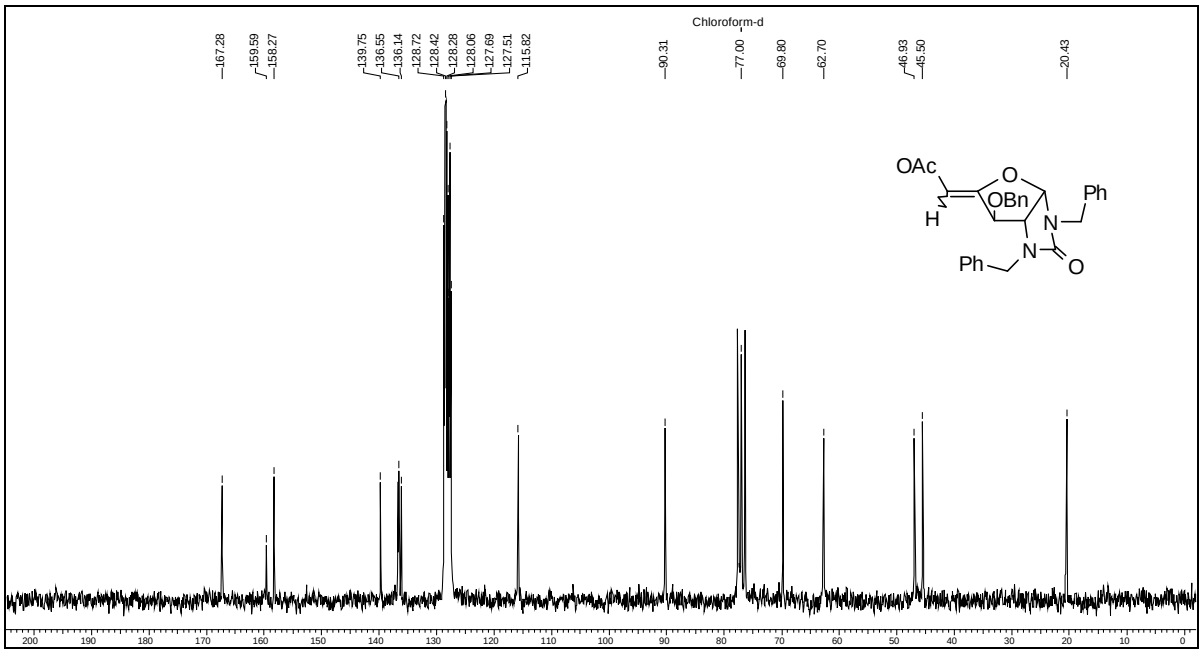
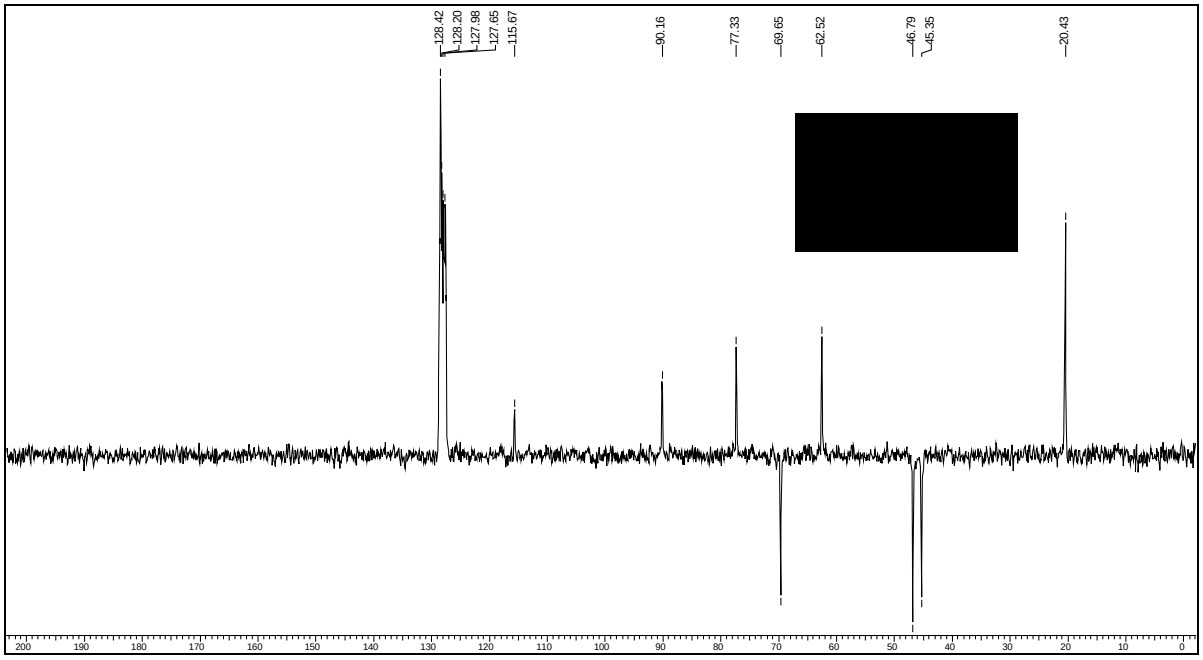


^{13}C NMR spectrum of compound **31** ($CDCl_3$, 50 MHz)



DEPT NMR spectrum of compound **31** ($CDCl_3$, 50 MHz)

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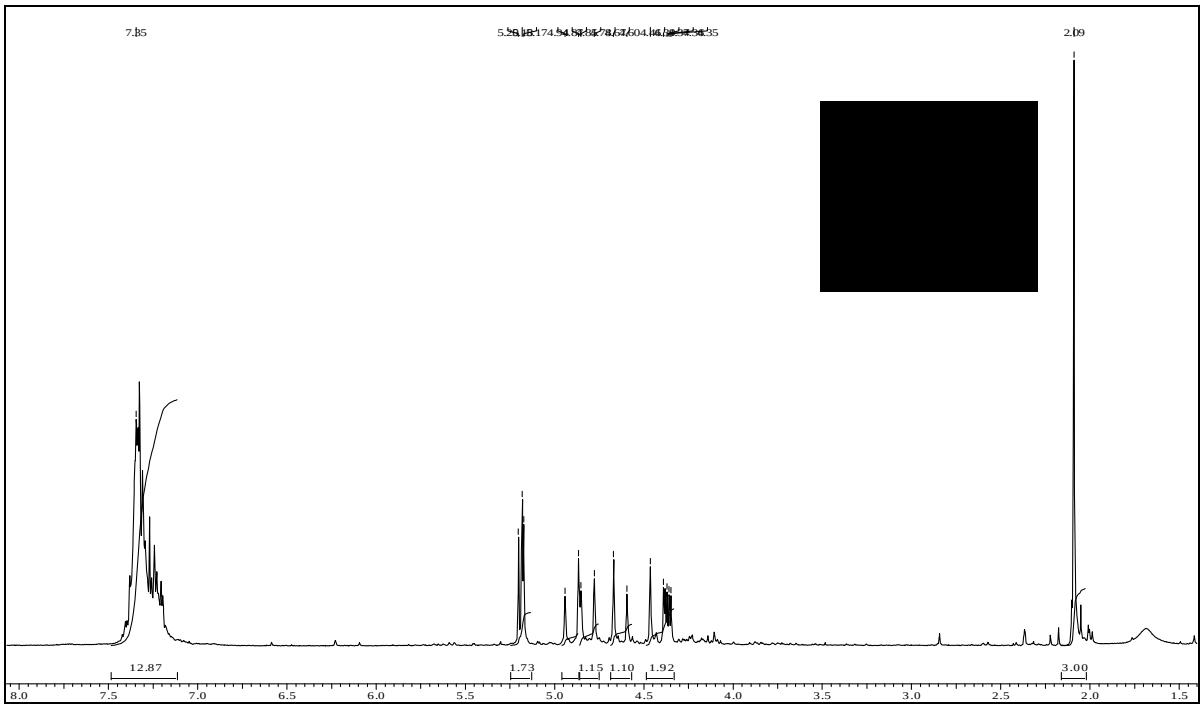

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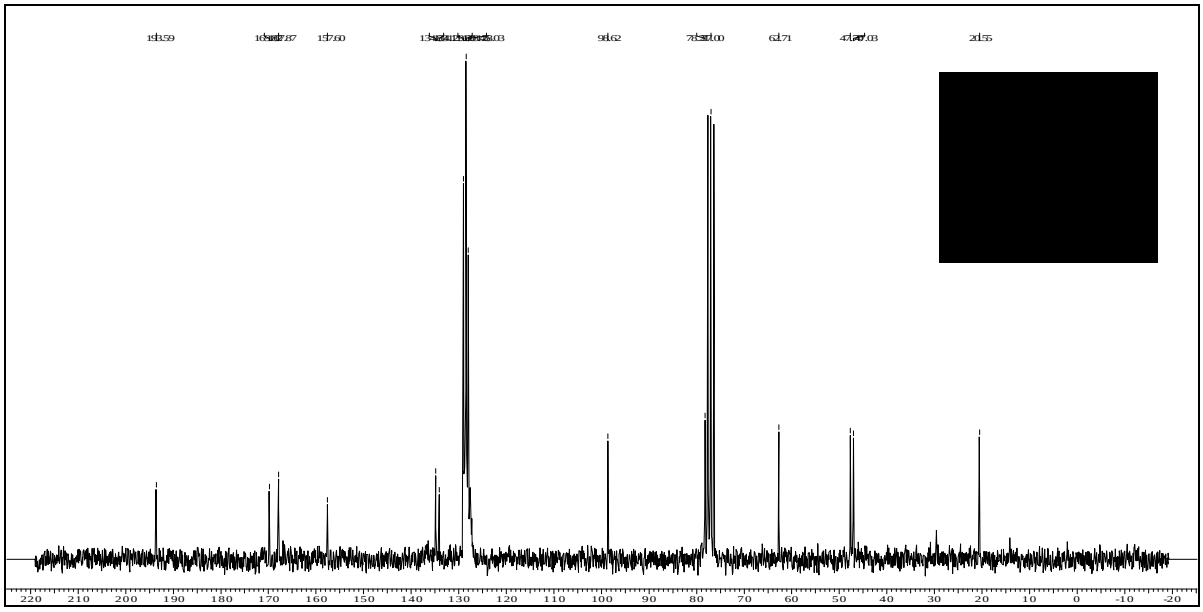

^{13}C NMR spectrum of compound **31** ($CDCl_3$+CCl_4, 200 MHz)

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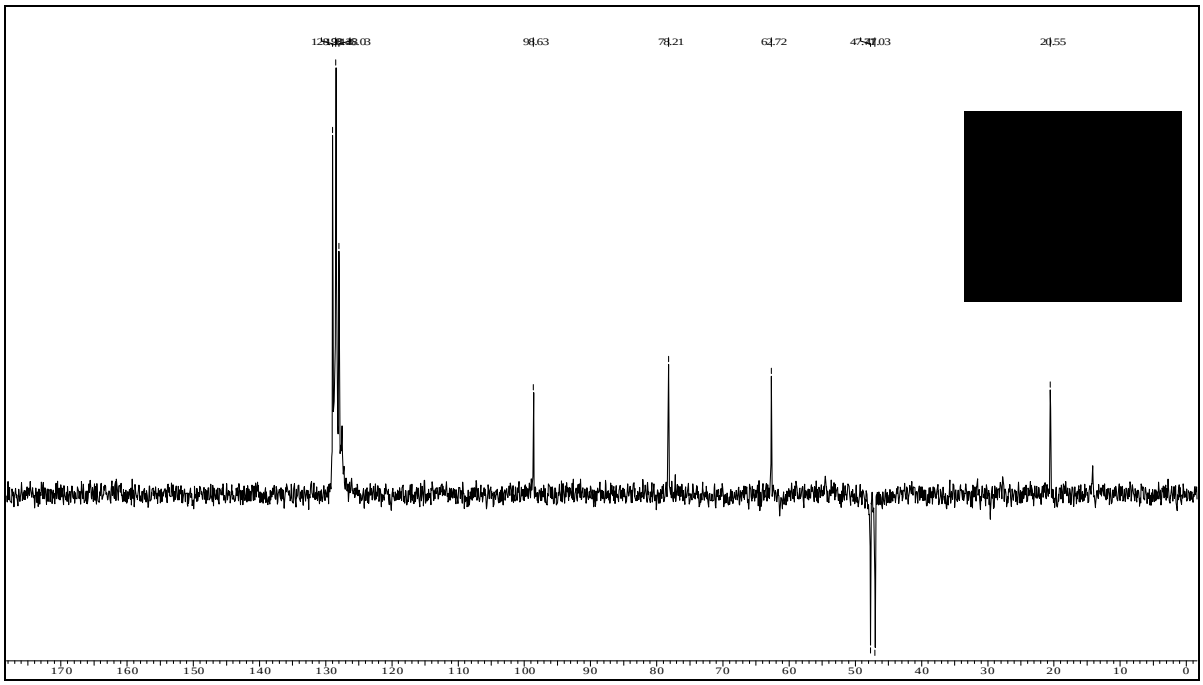
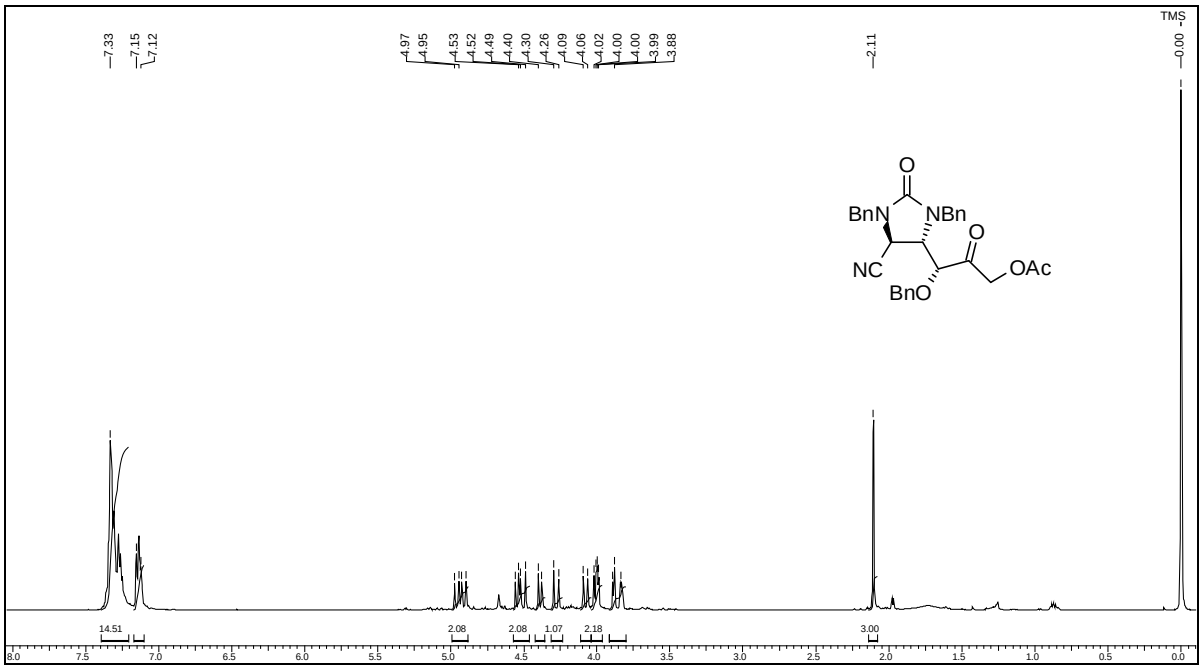


DEPT NMR spectrum of compound **31** ($CDCl_3$+CCl_4, 200 MHz)



^{1}H NMR spectrum of compound **41** ($CDCl_3$, 125 MHz)

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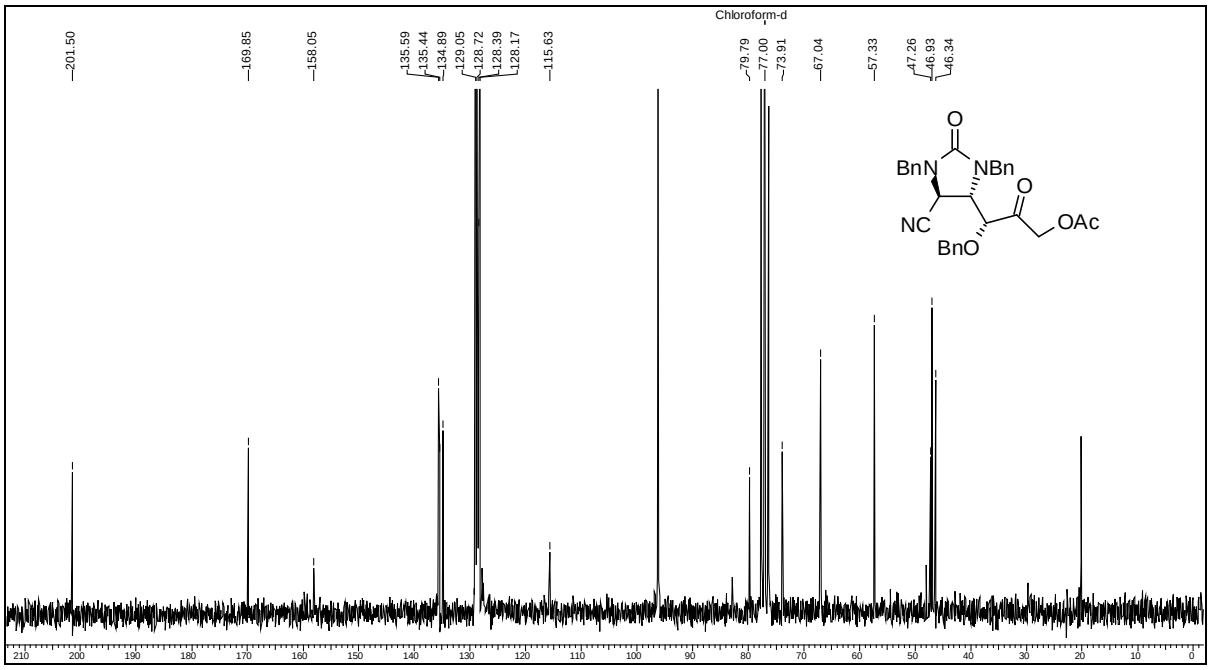
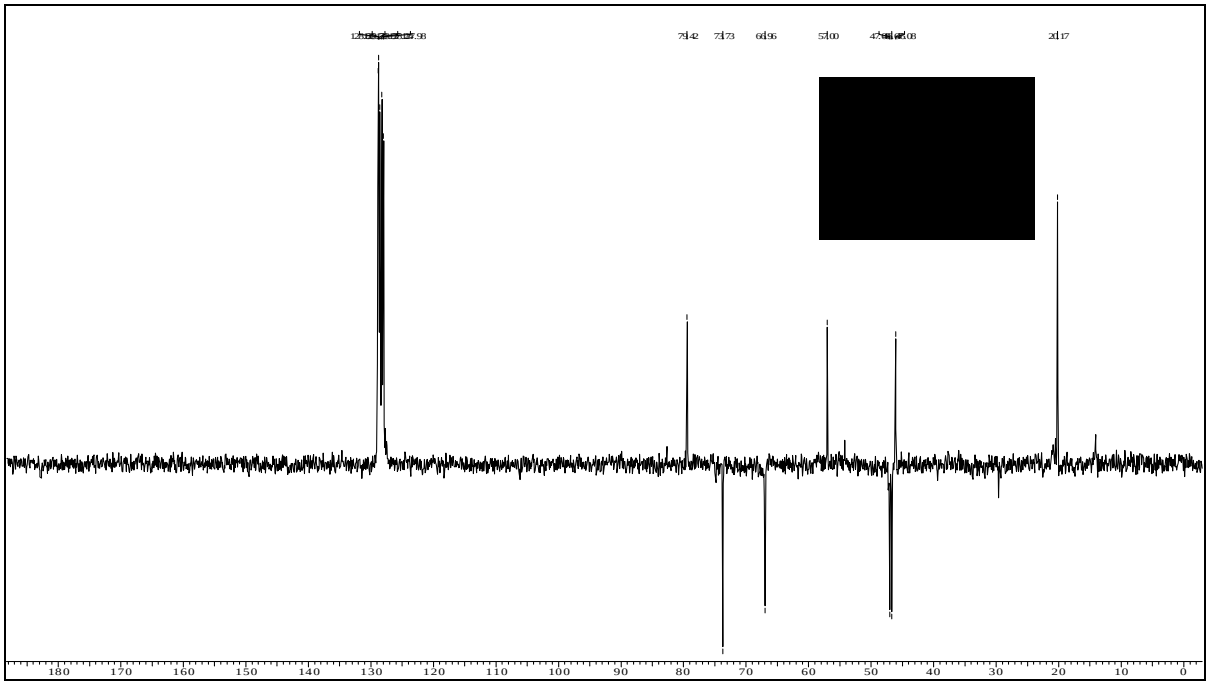


^{13}C NMR spectrum of compound **41** ($CDCl_3$, 125 MHz)



DEPT NMR spectrum of compound **41** ($CDCl_3$, 125 MHz)

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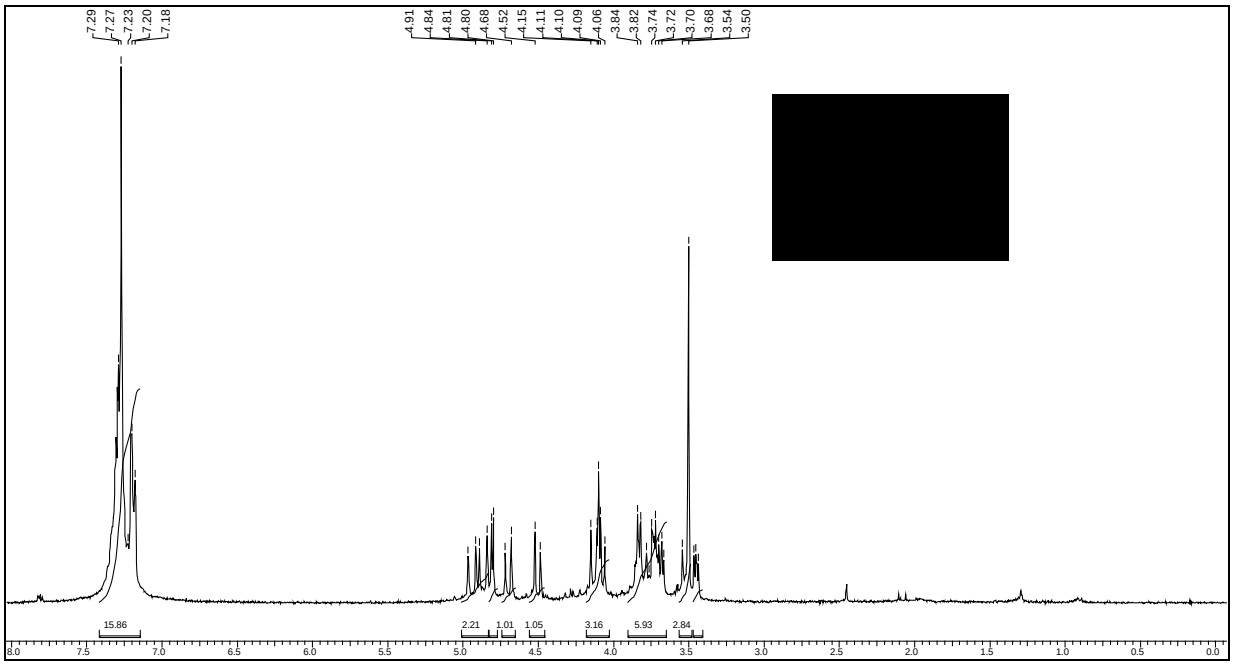
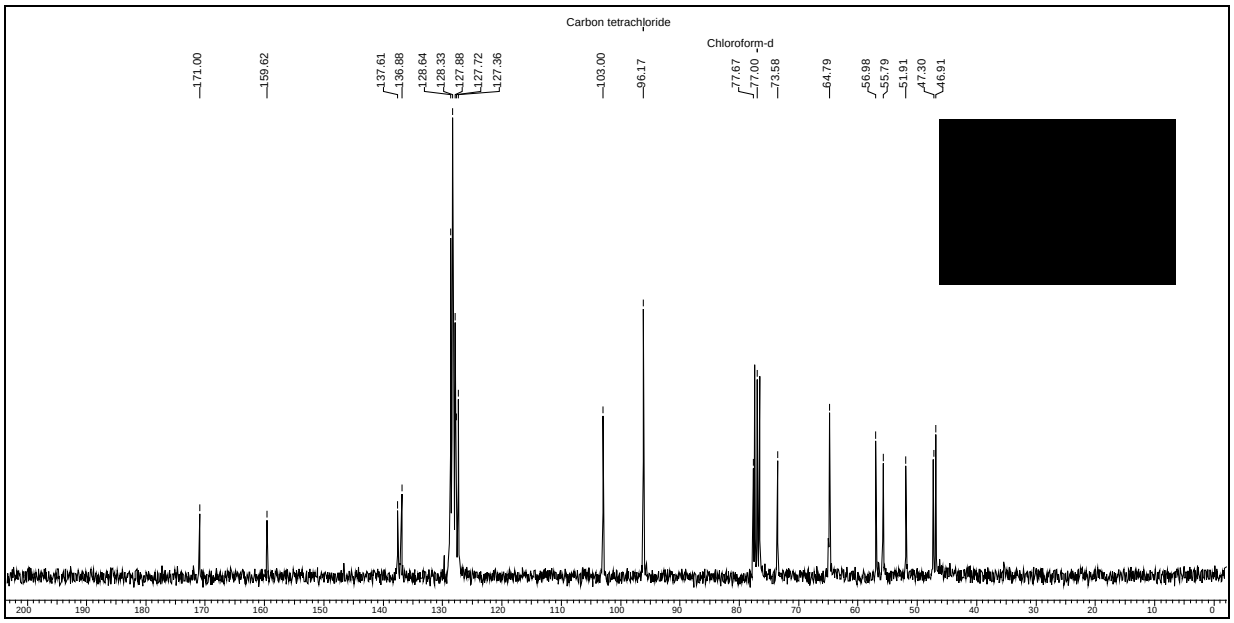


^{1}H NMR spectrum of compound **43** ($CDCl_3$+CCl_4, 300 MHz)



^{13}C NMR spectrum of compound **43** ($CDCl_3$+CCl_4, 50 MHz)

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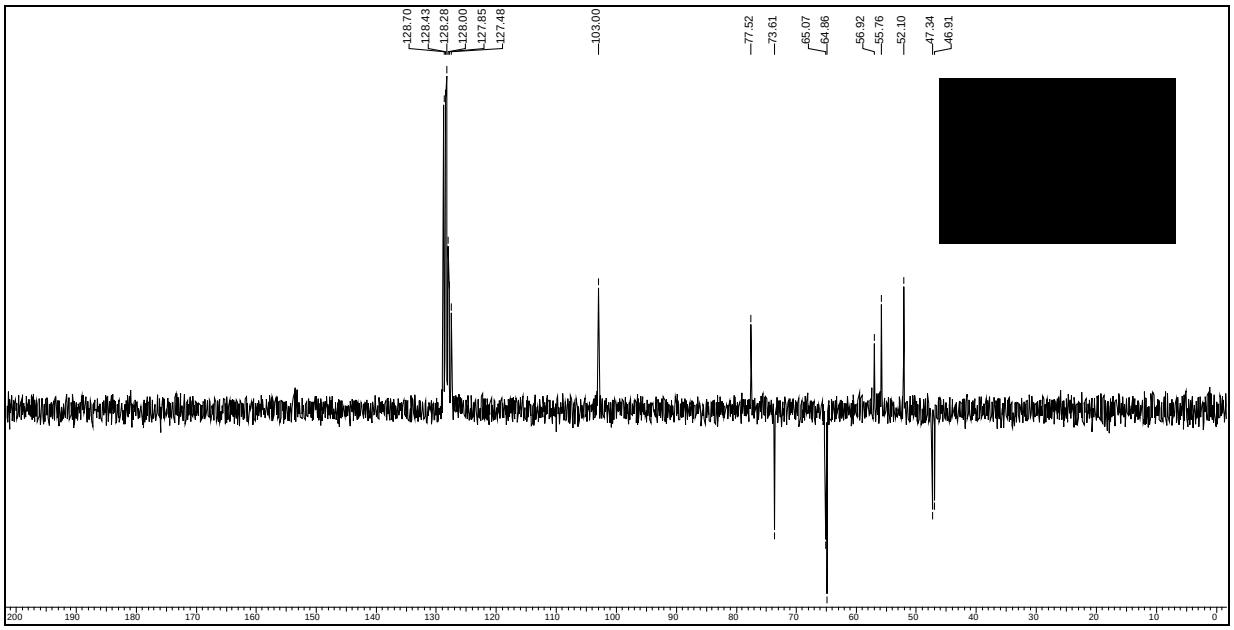

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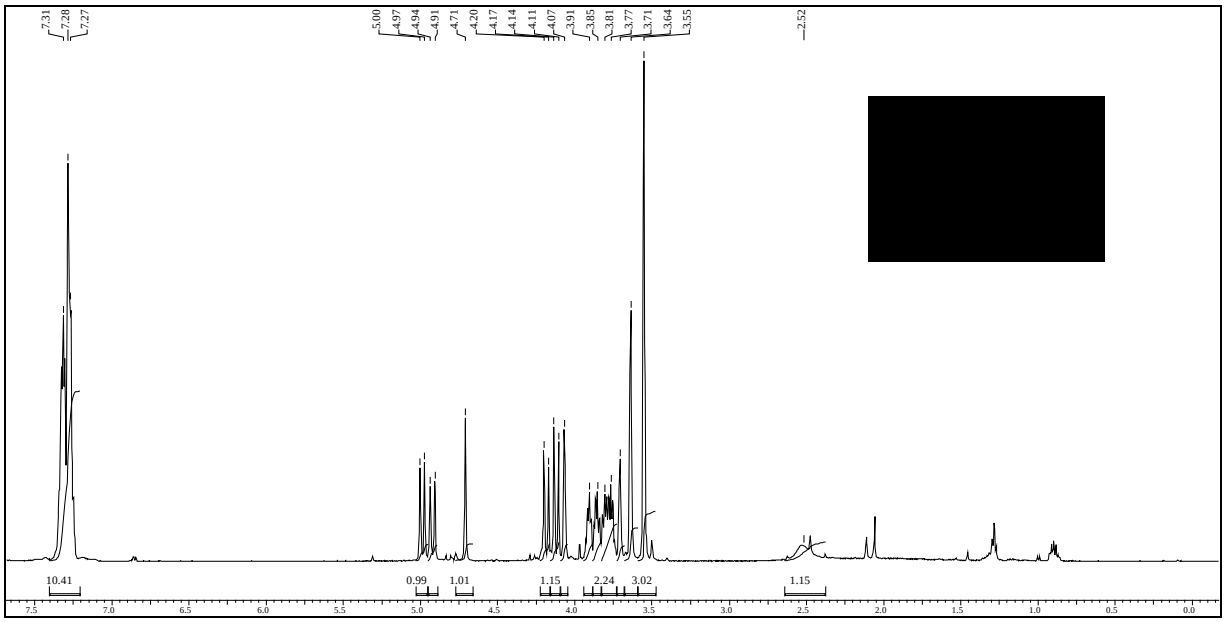

^{13}C NMR spectrum of compound **44** ($CDCl_3$+CCl_4, 500 MHz)

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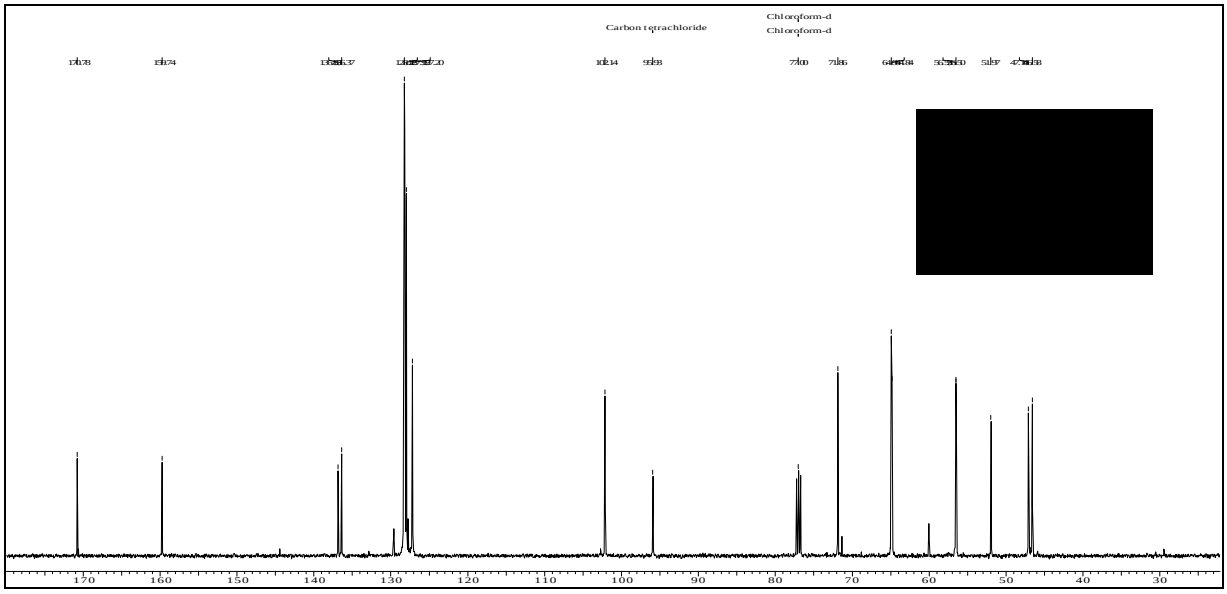
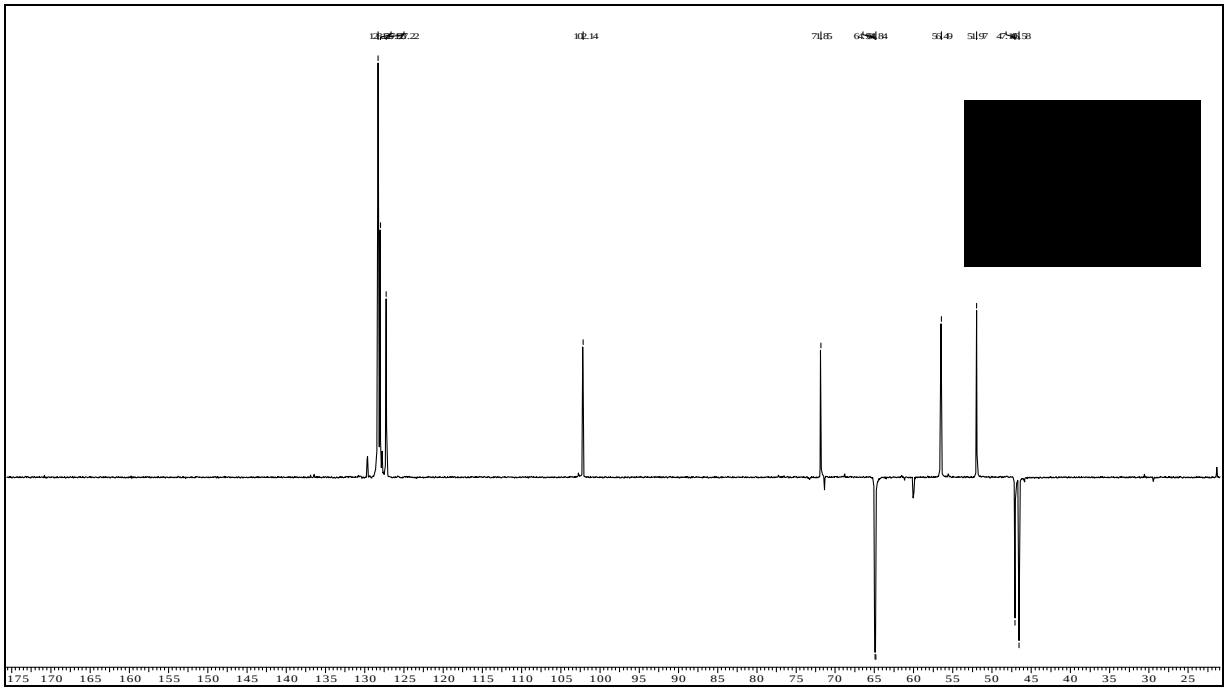


^{13}C NMR spectrum of compound **44** ($CDCl_3$+CCl_4, 125 MHz)



DEPT NMR spectrum of compound **44** ($CDCl_3$+CCl_4, 125 MHz)

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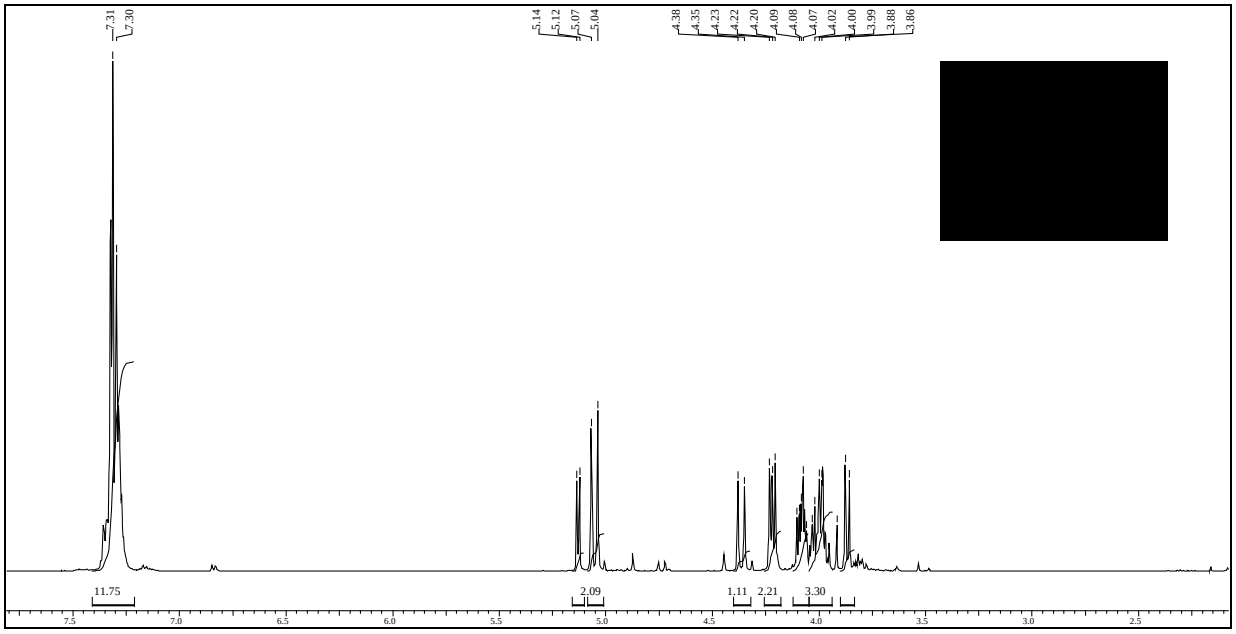
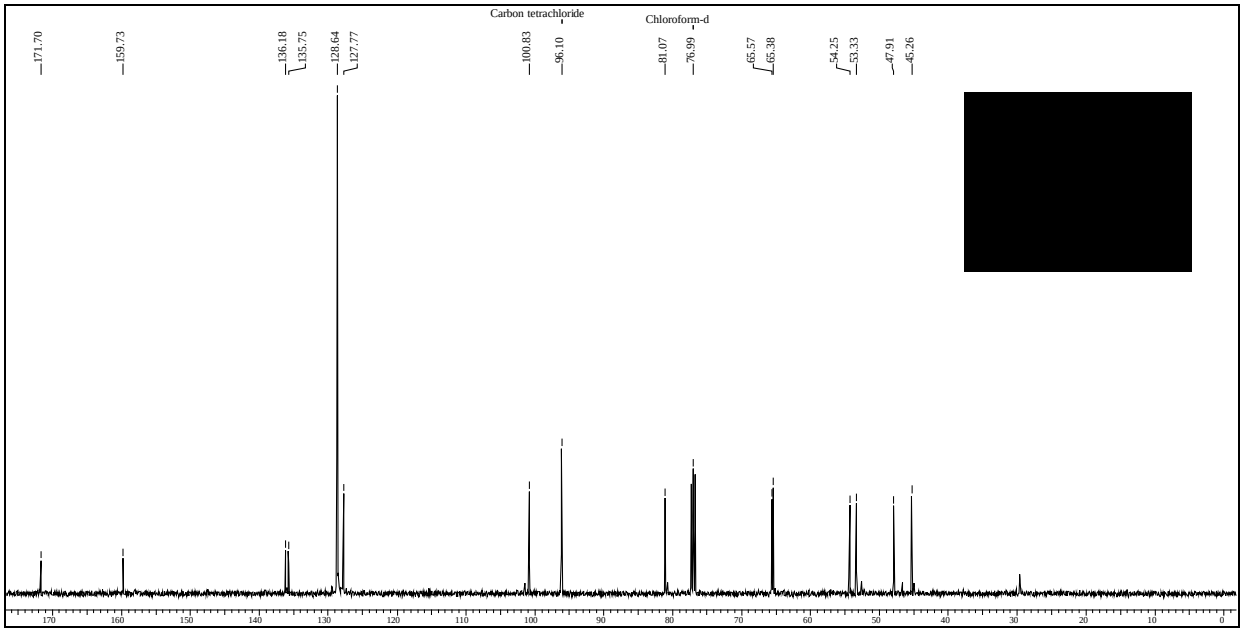


^{1}H NMR spectrum of compound **44a** ($CDCl_3$+CCl_4, 500MHz)



^{13}C NMR spectrum of compound **44a** ($CDCl_3$+CCl_4, 125 MHz)

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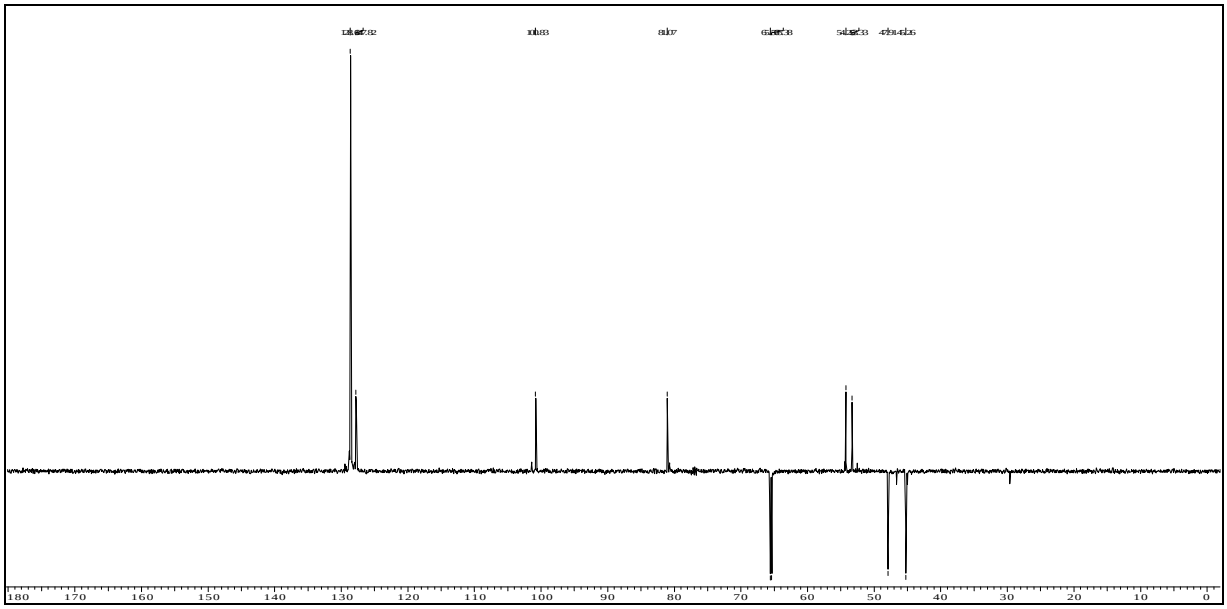
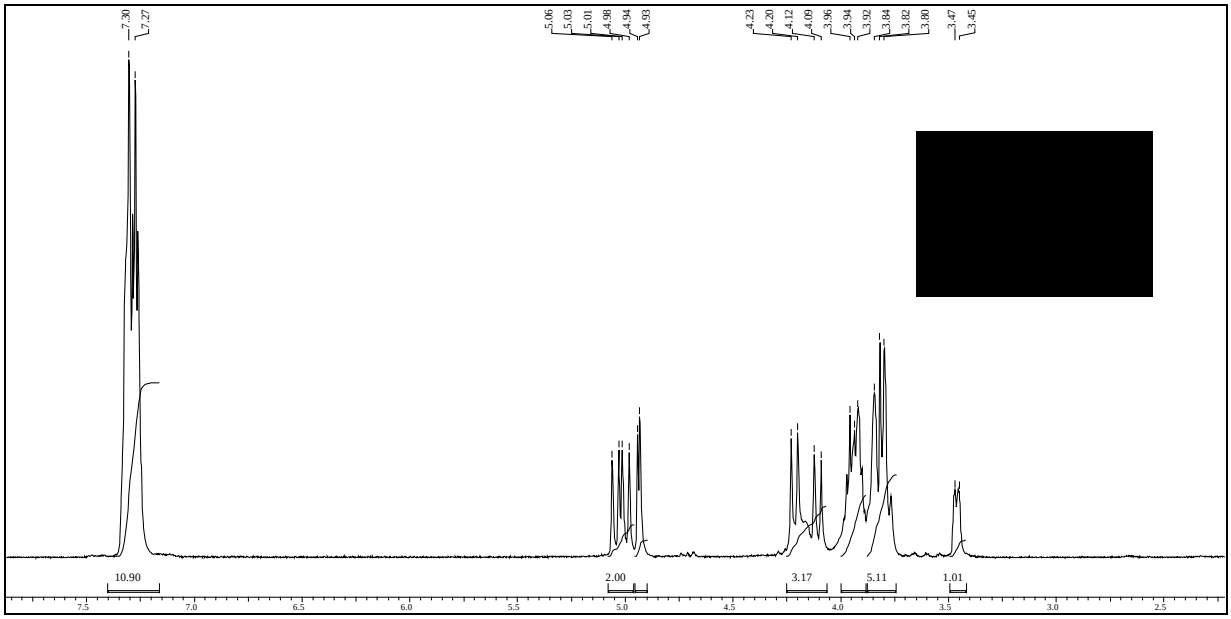


DEPT NMR spectrum of compound **44a** ($CDCl_3$+CCl_4, 125 MHz)



^{1}H NMR spectrum of compound **45** ($CDCl_3$+CCl_4, 500MHz)

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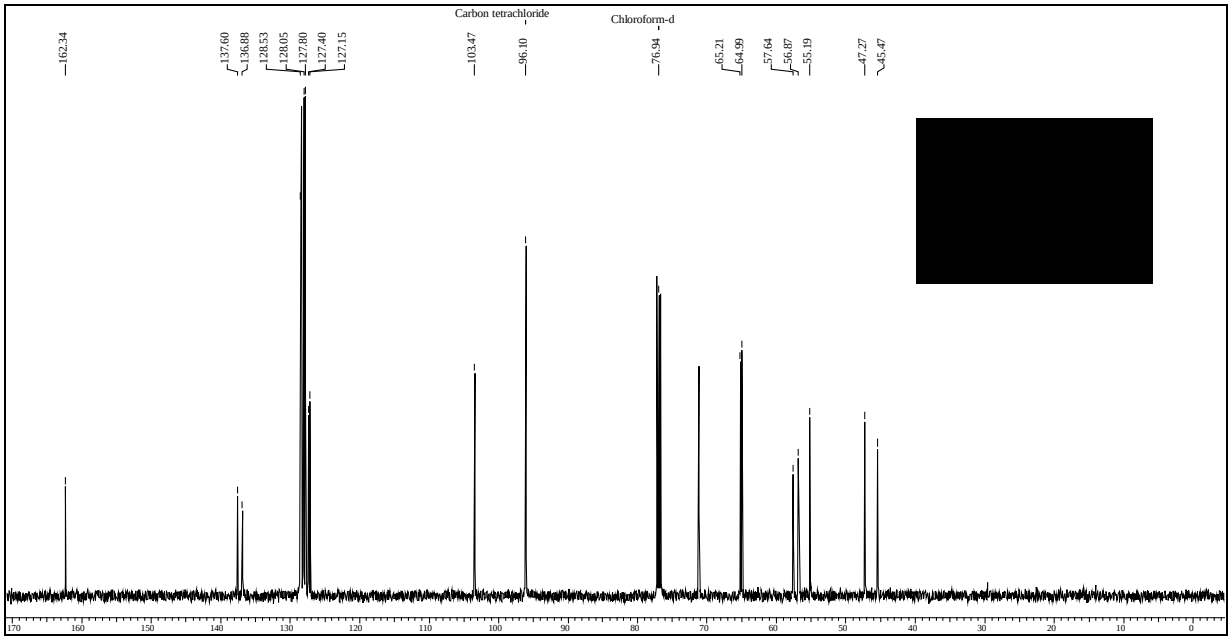
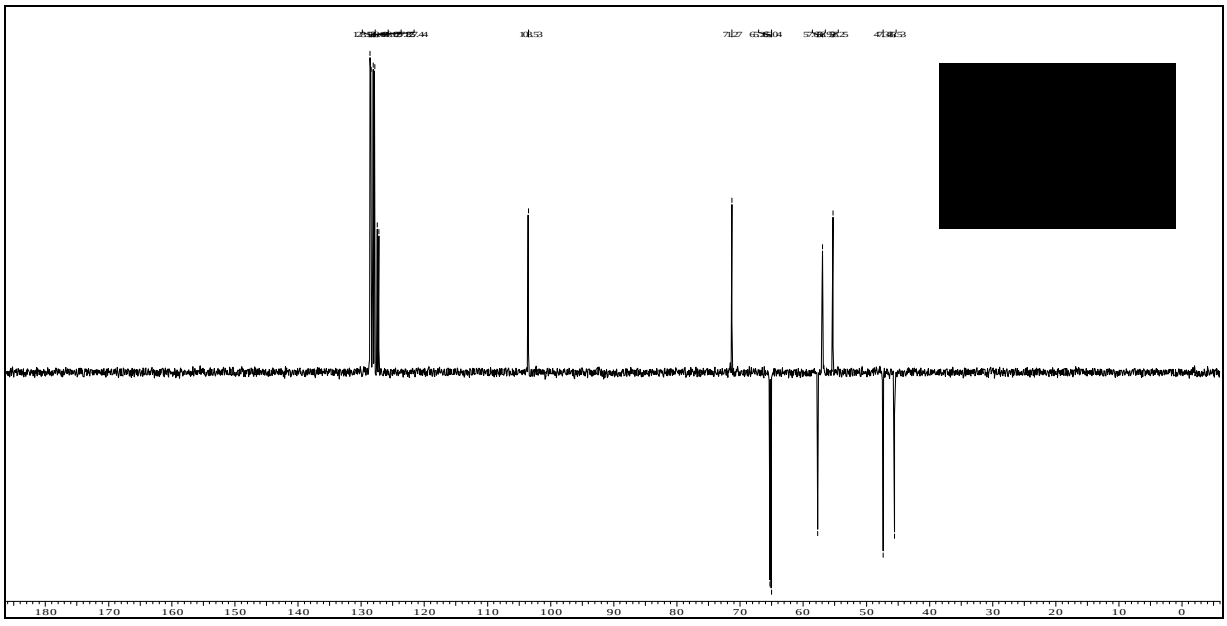


^{13}C NMR spectrum of compound **45** ($CDCl_3$+CCl_4, 125 MHz)



DEPT NMR spectrum of compound **45** ($CDCl_3$+CCl_4, 125 MHz)

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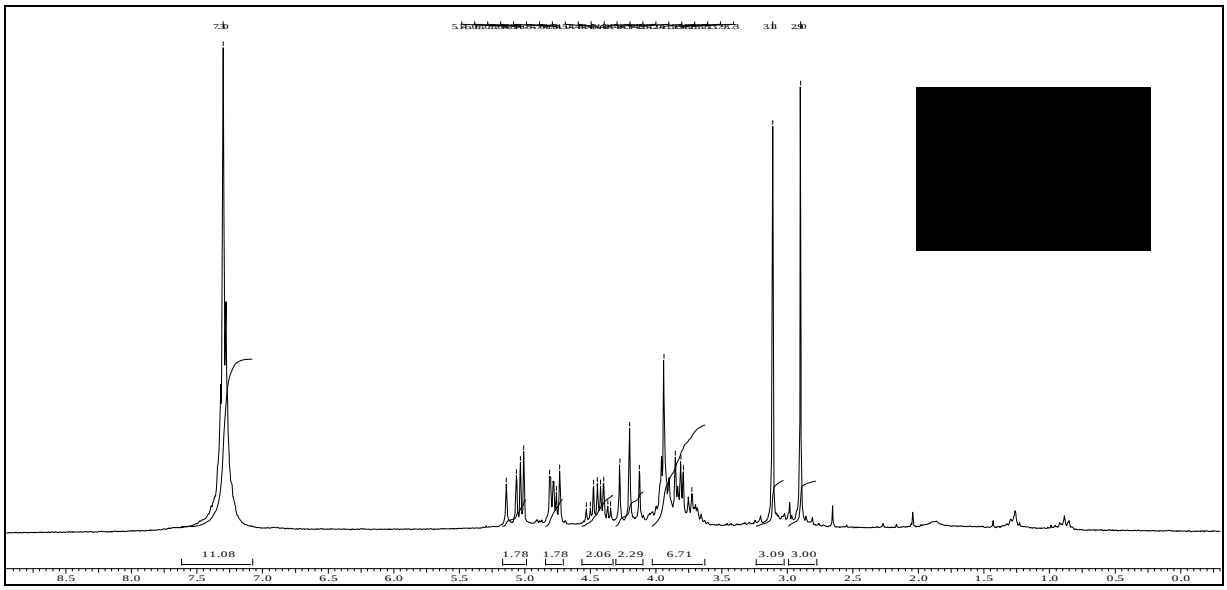
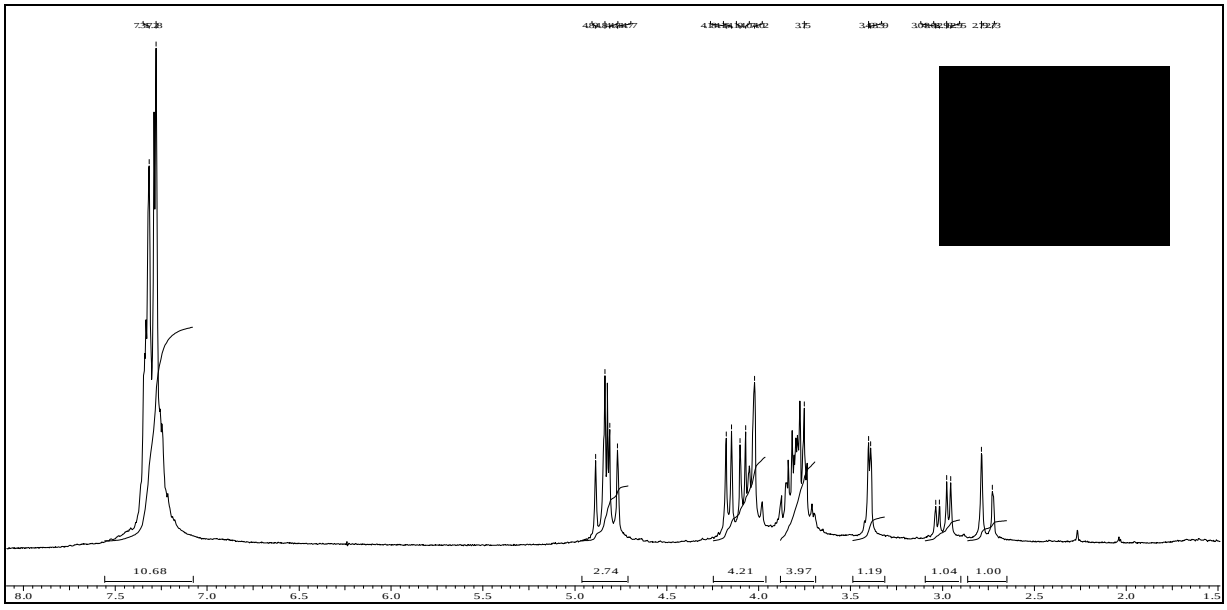


^{1}H NMR spectrum of compound **45a** ($CDCl_3$+CCl_4, 500MHz)



^{1}H NMR spectrum of compound **46** ($CDCl_3$+CCl_4, 200MHz)

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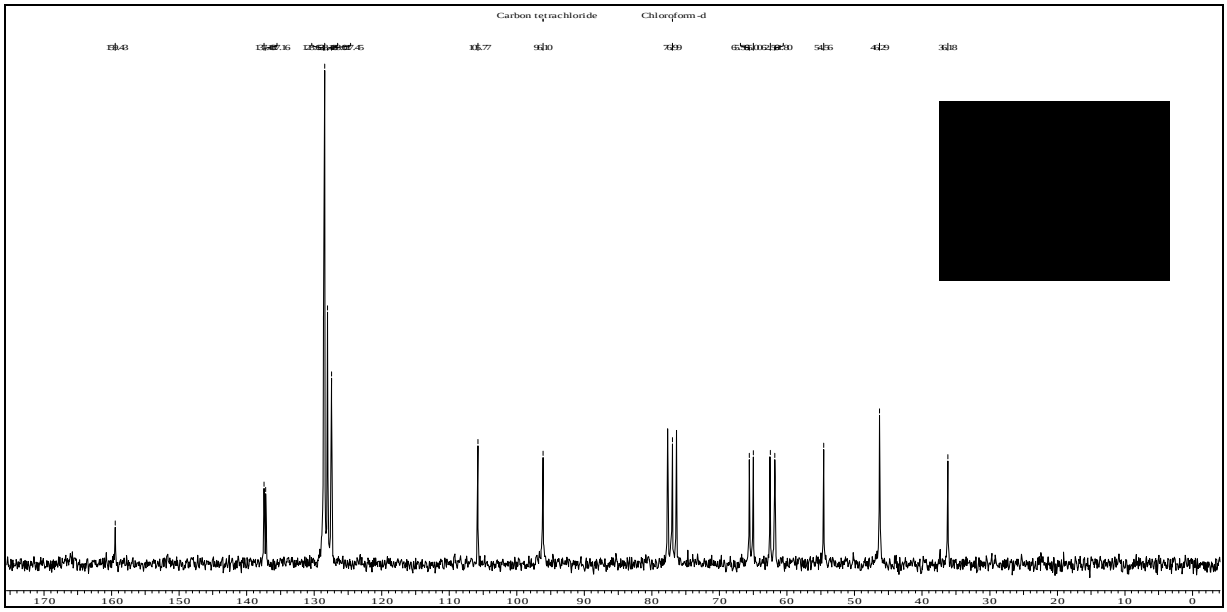
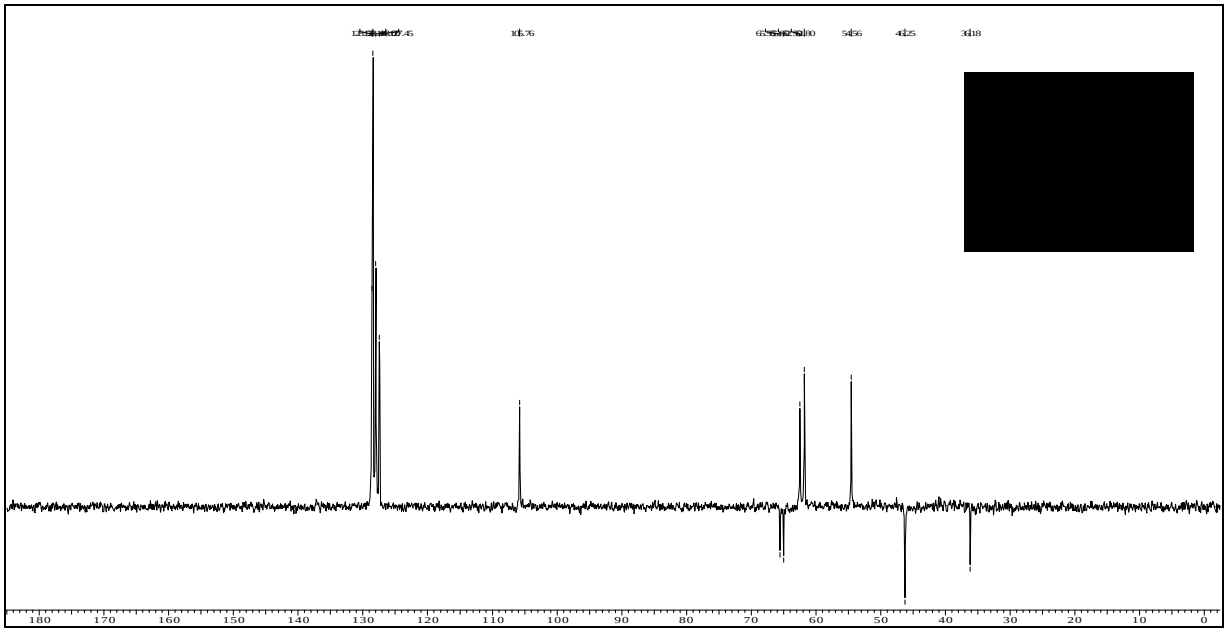


^{13}C NMR spectrum of compound **46** ($CDCl_3$+CCl_4, 50 MHz)



DEPT NMR spectrum of compound **46** ($CDCl_3$+CCl_4, 50 MHz)

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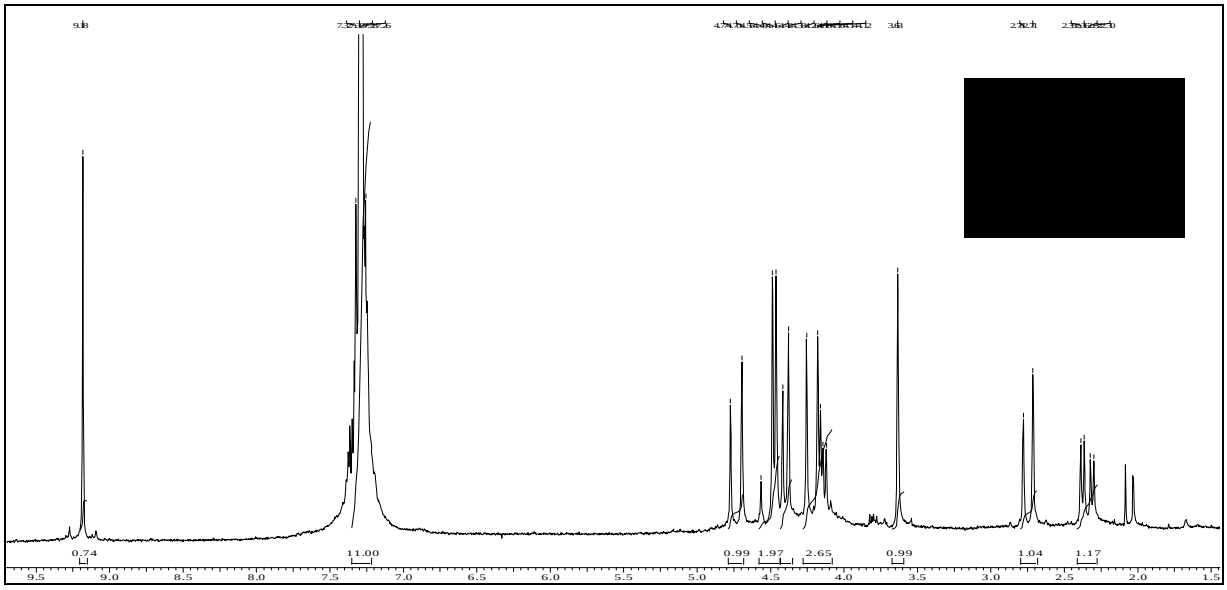
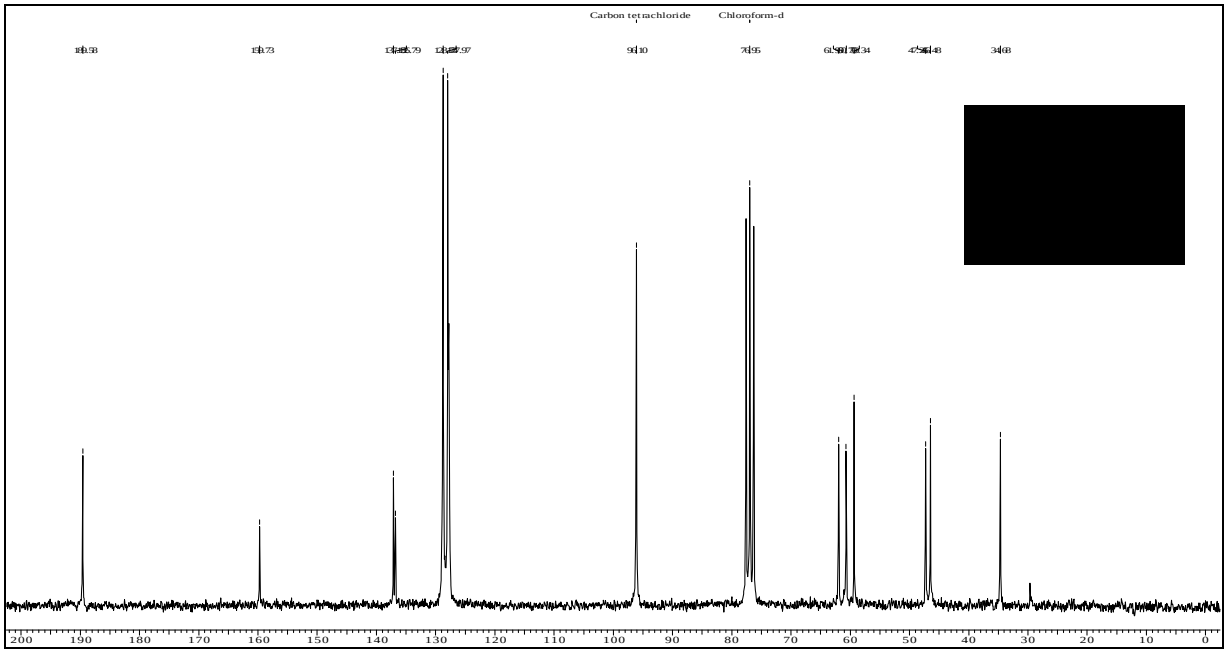


^{1}H NMR spectrum of compound **47** ($CDCl_3$+CCl_4, 200MHz)



^{13}C NMR spectrum of compound **47** ($CDCl_3$+CCl_4, 200MHz)

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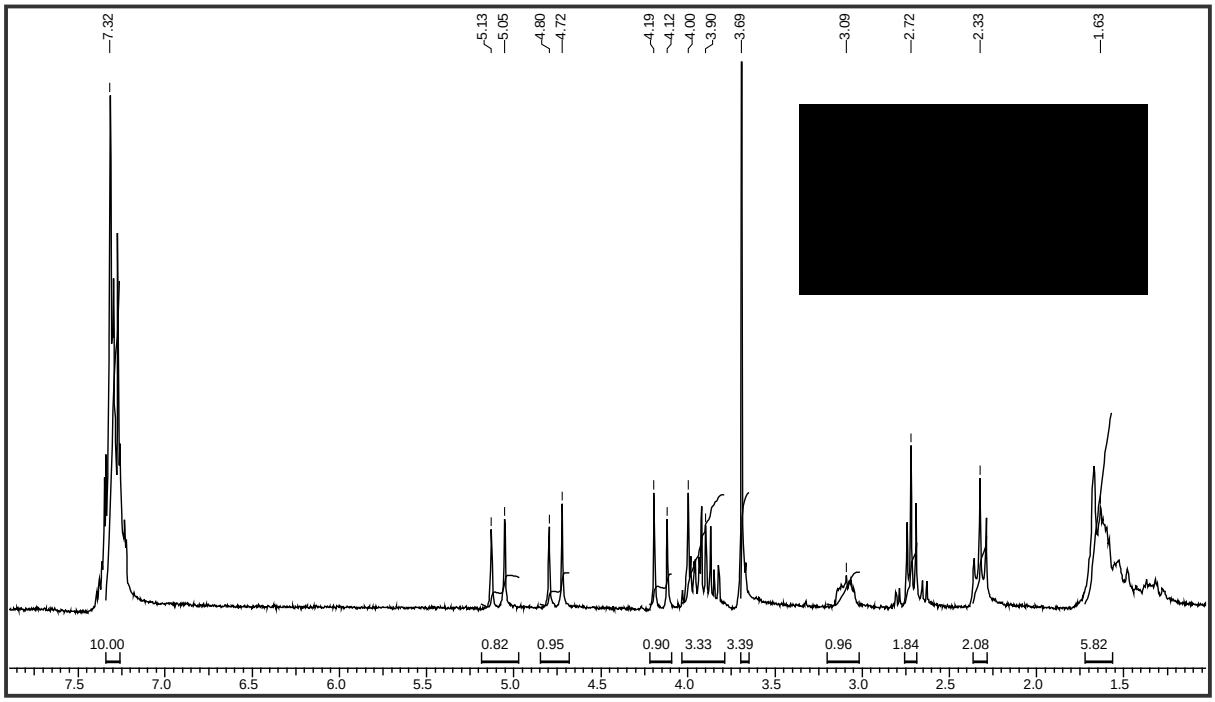
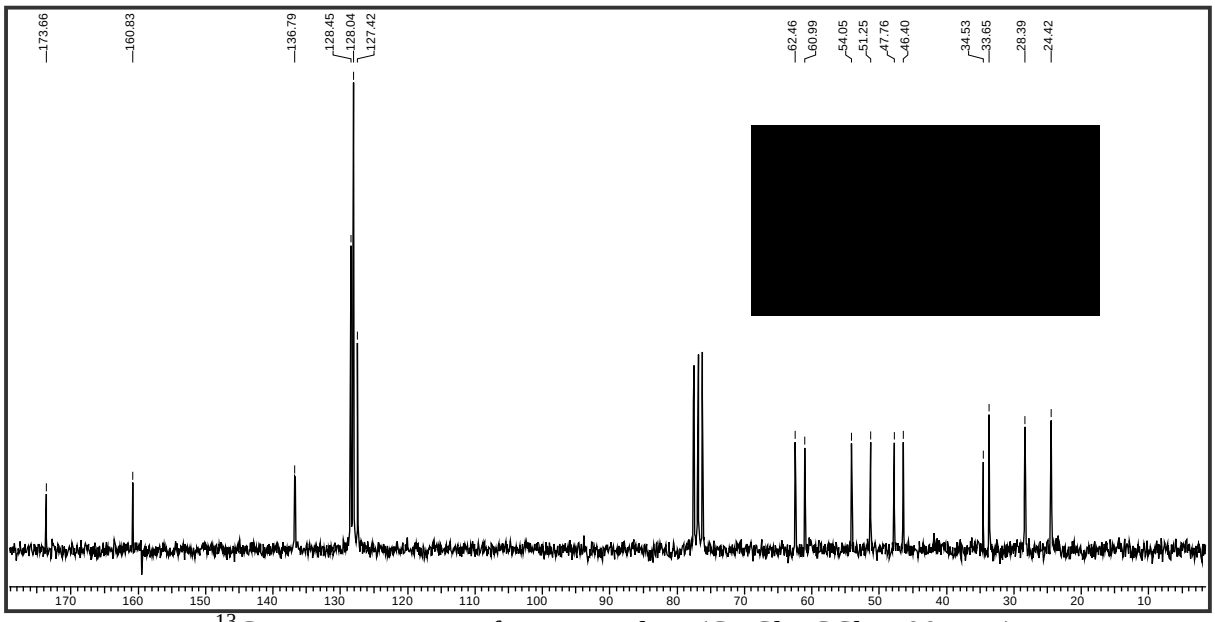


^{1}H NMR spectrum of compound **47** ($CDCl_3$+CCl_4, 200MHz)



^{13}C NMR spectrum of compound **47** ($CDCl_3$+CCl_4, 200MHz)

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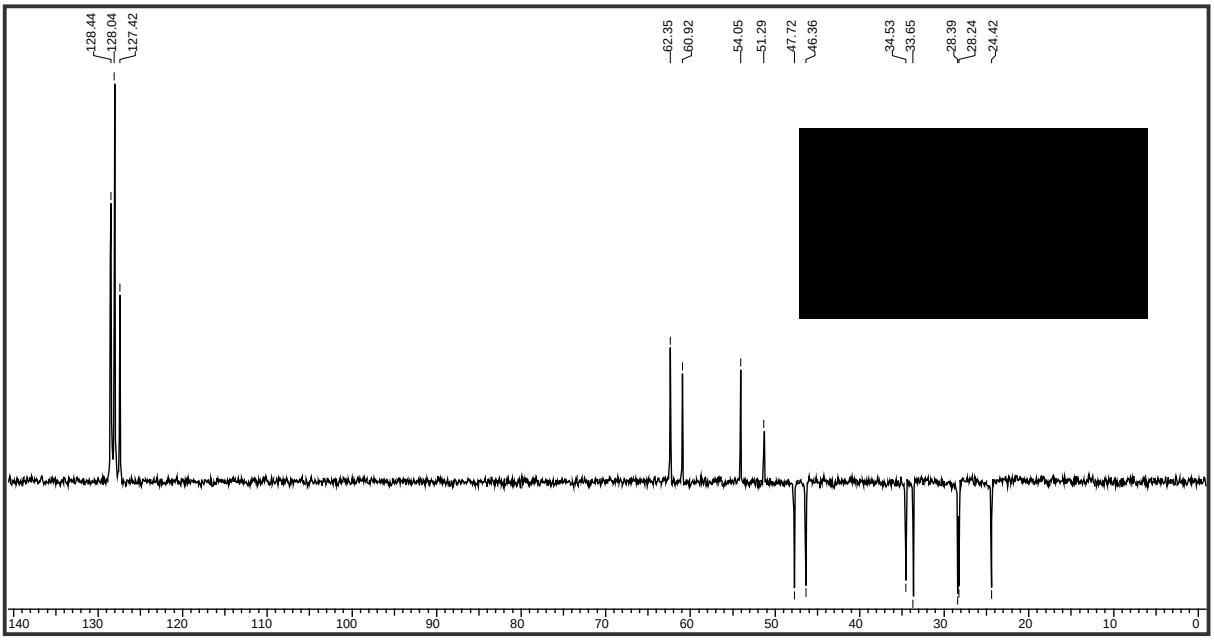

DEPT NMR spectrum of compound **47** ($CDCl_3$+CCl_4, 200MHz)

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CHAPTER-II

SECTION- I

Studies Toward Synthesis Of Salacinol

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2.1.1 Introduction

About 40 years have passed since the classical glycosidase inhibitor, nojirimycin was discovered from the cultured broth of the *Streptomyces* species. Since then, over one hundred glycosidase inhibitors have been isolated from plants and micro-organisms. Intestinal α-glucosidase inhibitors were postulated to be powerful therapeutic agents in carbohydrate metabolic disorders, especially diabetes mellitus. Postprandial hyperglycemia and hyperinsulinemia are expected to be diminished by inhibition of poly- and oligosaccharide digestion in the intestinal tract. Practically a few α-glucosidase inhibitors of microbial origin, i.e., acarbose, are clinically used for the treatment of diabetes mellitus. Modifying or blocking biological processes by specific glycosidase inhibitors has revealed the vital functions of glycosidases in living systems. Since enzyme-catalyzed carbohydrate hydrolysis is a biologically widespread process, glycosidase inhibitors have many potential applications as agrochemicals and therapeutic agents. Glycosidases are involved in the biosynthesis of the oligosaccharide chains and quality control mechanisms in the endoplasmic reticulum (ER) of the *N*-linked glycoproteins. Inhibition of these glycosidases can have profound effects on quality control, maturation, transport, and secretion of glycoproteins and can alter cell-cell or cell-virus recognition processes. This principle is the basis for the potential use of glycosidase inhibitors for viral infection, cancer, and genetic disorders.

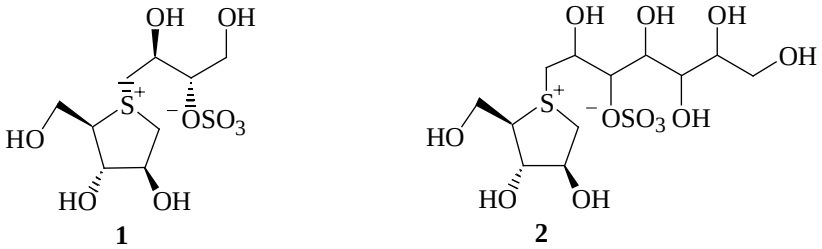

Fig-1.

Salacinol **1** and kotalanol **2** are α-glucosidase inhibitors isolated from the *Hippocrateaceae* plant *Salacia reticulata*. WIGHT, a large woody climbing plant widespread in SriLanka and South India (Fig.1). Extracts of this plant have been traditionally used in the Ayurvedic system of Indian medicine as a treatment for non-insulin-dependent diabetes.[1] The

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methanol extract from the roots and stems of *S. reticulata* is reported to show inhibitory activity against the increase in serum glucose levels after the administration of sucrose or maltose in rats.[1b] It was demonstrated that **1** and **2** were responsible for this inhibitory activity.[1a,c] Salacinol **1** is obtained as a colourless prisms,[1b] [α_D^{28}] +4.9 (c = 0.35, MeOH) structurally consists of a sulfate group as was confirmed by rhodizonate test, and its IR spectrum showed absorption bands due to hydroxyl (3417, 1073, 1019 cm^{-1}) and sulfate (1262, 1238, 801 cm^{-1}). The molecular formula of 1 has been shown as $C_9H_{18}O_9S_2$ by high resolution FAB-MS and SIMS analyses. From the spectral evidences the following structure was assigned to salacinol **1.** The molecule constitutes two fragments 1) 1-deoxy-4-thiopentafuranose (1-5-C) and 1-deoxyhexitol-3-sulfate moieties (1'-4' C). The connections of sulfonium moiety was confirmed by HMBC experiment. The assigned structure **1** was clarified by X-ray crystallographic analysis.[1b]

These novel glycosidase inhibitors have unique zwitterionic structures in which the sulfonium cation is stabilized by the sulfate anion. It was assumed that the sulfonium center permanently mimics the incremental positive charge that forms at both the ring oxygen and the anomeric carbon of the glycoside during hydrolysis in the active site of a glycosidase thus blocking the glycosidase from acting on the glycoside. In view of both its very high glycosidase inhibitory activity and its novel structure, chemists have conducted much research on the total synthesis of **1** and its analogues. As the absolute configurations of the kotalanol **2** side chain have not yet been established, all the work has focused on salacinol.[3–7] Nitrogen and selenium analogues have also been described.[3,6,8–10]

2.1.2 Inhibitory activity of Salacinol:

Salacinol **1** showed the competitive inhibition[1a] for the intestinal α-glucosidase *in vitro*; IC50 values were 3.2 µg/ml to sucrase, and 0.59 µg/ml to isomaltase (substrate : isomaltase 3.7 mM). The inhibitory activities of **1** against maltase and sucrase were nearly equal to those of acarbose while the inhibitory activity against isomaltase was much more potent than that of acarbose. (table-1). Further more this compound (1: 1.3-10 mg/kg,p.o.) more strongly inhibited the increase of serum glucose levels in sucrose loaded rats than

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acarbose. Therefore it was concluded that salacinol **1** is a more potent α-glucosidase inhibitor isolated from natural medicine and is responsible constituent of antidiabetic Ayurvedic traditional medicine "*Kotala himbutu*", the roots of S. *reticulata*.

Table 1: Comparision of inhibitory activity of salacinol 1 and acarbose.

Substrate	Km (M)	Ki (μg/ml)	
		Salacinol (**1**)	Acarbose
Maltose	$2.7x10^{-3}$	0.31	0.12
Sucrose	$2.0x10^{-2}$	0.32	0.37
Isomaltose	$4.5x10^{-3}$	0.47	75

Rat small intestine brush border membrane vesicles were used as the preparation of small intestinal α-glucosidase such as maltase, sucrase and isomaltase. The substrate (maltose : 3-37mM, sucrose : 3-37 mM, isomaltose: 0.46-3.7 mM), test compound and enzyme in 0.1 M maleate buffer (pH 6.0) were incubated together for 30 min at 37 ºC. The glucose concentration was determined by the glucose oxidase method.

2.1.3 Earlier approaches

All the strategies described in the literature to obtain the zwitterionic moiety are based on the nucleophilic attack of the heteroatom of a protected or unprotected polyhydroxylated heterocycle (thioarabinitol fragment) at the least hindered carbon atom of an L- protected erythritol cyclic sulfate. L-protected erythritol provides the side chain of salacinol.

Yuasa's approach[1d] (*Tetrahedron Lett.* **1994,** 44, 8243-8246.)

Much before salacinol **1** was isolated, Yuasa and coworkers synthesized a thiacyclopentane[1d] derivative with the sulfur atom being in trivalent state as a new class of glucosidase inhibitor. This class of compounds was first created as the sulfimide derivatives, (**3** and **4**) which has shown a weak inhibitory effect toward β-glucosidase.

The synthesis of thiaarabinitol fragment was achieved in 10 steps starting from D-xylose which was first transformed first in 6 steps to methyl 3,5-di-*O*-benzyl-5-thio-α and β-D-xylofuranoside (**5** and **6**). Both **5** and **6** was then subjected to an intramolecular cyclisation between 5-S and C-2 under the condition of iodination, using iodine, triphenylphosphine and imidazole, to give exclusively compound **7**, with α-configuration at anomeric carbon. The

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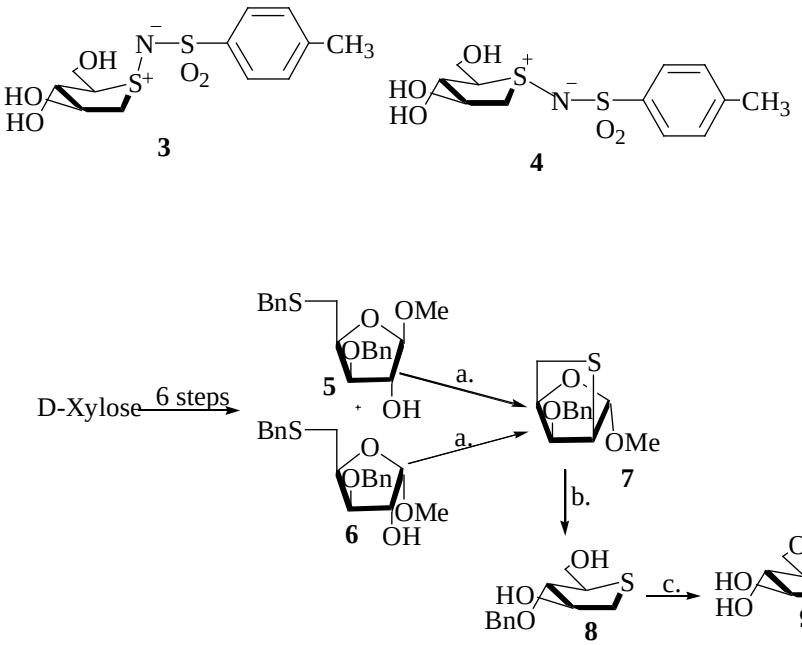
simultaneous hydrolysis and *in situ* reduction of **7** with sodium cyanoborohydride in aqueous acetic acid afforded **8** which was deprotected by Birch reduction to give compound **9**.



Scheme1. Reagents and conditions: a) Ph_3P, I_2, imid, 110 ºC; **b**) $Na(CN)BH_3$, 90% AcOH, 40 ºC; **c**) Na/ liq. NH_3

In 2000, Yuasa *et al.* were the first to present the synthesis of salacinol **1** and its diastereoisomer[4] (Scheme 2 and 3). Later, Ghavami *et al.* reported their own synthesis of **1**, its enantiomer of salacinol and its diastereoisomers (Fig. 2).[5–7] More recently the same group extended this method to prepare other sulfonium analogues with two different six membered rings,[3] one of them obtained from alditols using the procedure described by Benazza *et al.*[11] All these literature reports utilize D-xylose and D-Glucose as chiral synthons for the synthesis of the thioarabinitol fragment of salacinol and its enantiomer respectively.

Yuasa's approach[4] (*Tetrahedron Lett.* **2000,** *41*, 6615)

The synthesis reported is a semisynthesis[4] wherein the thiocyclopentane fragment of salacinol was prepared according to the reported synthesis by the same group earlier for the synthesis of sulfimide derivatives long before salacinol **1** was isolated. The tethering arm of salacinol **1** is a derivative of erythritol and the cyclic precursor was derived from D or L

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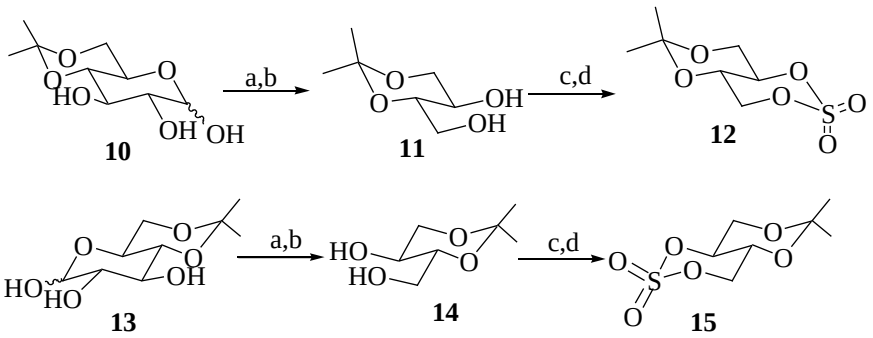
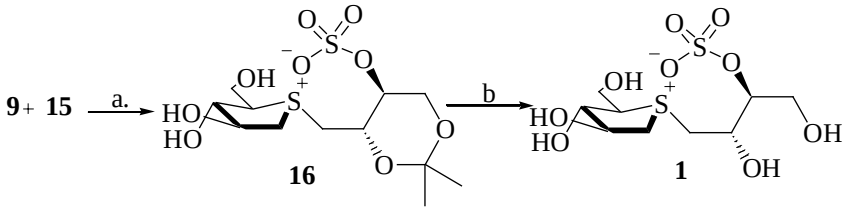
glucose depending on the protecting groups. Periodate oxidation of 4,6-*O*-isopropylidene-D or L-glucose **10, 13** respectively followed by reduction of the resulting aldehyde gave the 2,4 or 1,3-*O*-isopropylidine erythritol **11** or **14** respectively. Formaion of the cyclic sulfate at the remaining diol was carried out by the conventional method including treatment of diol with thionyl chloride in the presence of triethyamine followed by oxidation with catalytic ruthenium trichloride in the presence of sodium metaperiodate to furnish the cyclic sulfates **12** and **15** respectively.



Scheme 2. **a**) $NaIO_4$ (2 equiv.), $NaHCO_3$, H_2O, bromocresol green, 5 h; **b**) $NaBH_4$, CH_3OH, 10 min; **c**) $SOCl_2$ (1.2equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, 0 ºC 10 min; **d**) $RuCl_3$ (cat.), $NaIO_4$ (2 equiv.), CH_3CN, CCl_4, H_2O, 30 min;



Scheme 3. **a**) DMF, 45 ºC, 13 h; **b**) 0.01% HCl, 40 ºC, 4 h

The coupling reaction between both fragments thiocyclopentane and cyclic sulfate was achieved by heating the mixture of both fragments in DMF at 45 ºC for 13 h to furnish **16** and its diastereoisomer in 61% and 64 % yield which on subsequent deisopropylination with 0.01% HCl gave salacinol and its diastereomer in 75% and 74% respectively.

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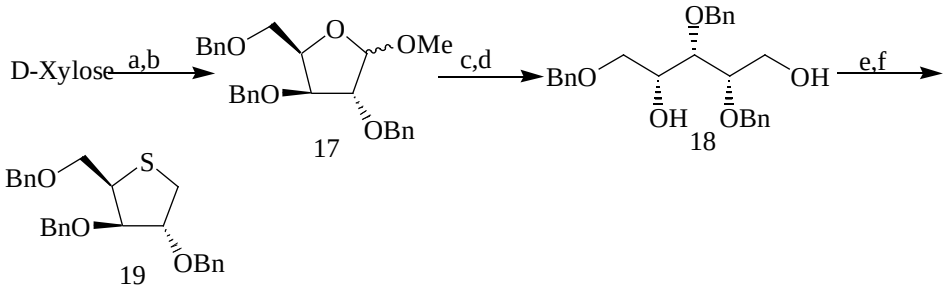
2) Ghavami's approach:[5a] (*J. Org. Chem.* **2001,** 66, 2312.)

The thio-arabinitols **19** and **24** were synthesized from D-xylose and D-glucose respectively as shown in schemes **4** and **5**.

a) Yoshimura and coworkers:[5b] *Bioorganic and Med. Chem. Lett.* **1998**, *8*, 989-992.

Methyl 2,3,5-tri -*O*- benzyl-D-xylofuranoside **17** obtained from D-xylose in 2 steps, was hydrolysed under acidic conditions and reduced by $LiBH_4$ in THF to give xylitol **7** which was converted to its dimesylate, which in turn was treated with sodiumsulfide in DMF at 100 ºC for 3h to give 1,4-anhydro-4-thio-L-arabitol **19**.[5b]



Scheme 4. Reagents and conditions: a) H^+/ MeOH; b) BnCl, NaOH 59% **c**) 6M HCl/ THF; **d**) $LiBH_4$, 66%; **e**) MsCl, Et_3N,CH_2Cl_2 rt; **f**) $Na_2S.9H_2O$, 84%.

Yoshimura's approach:[5c] *J. Org. Chem.* **1997,** *62*, 3143.

Diisopropylidene glucose was converted to 3-*O*-benzylxylose **21** using reported protocols. 3-*O*-benzylxylose was then subjected to acidic methanolysis to produce anomeric mixture of 3-*O*-benzylxyloside in high yield.[5c] The separated anomers of **22** were mesylated and then treated with sodium sulfide in DMF to yield bicyclic compound **23** as a mixture of anomers. Hydrolysis of the mixture of anomers followed by borohydride reduction gave 1,4-anhydro-4-thioarabinitol in 90% yield. The primary alcohol was protected with *tert*-butyldiphenyl silyl (TBDPS) group to give intermediate **24** in 87% yield.(scheme 5)

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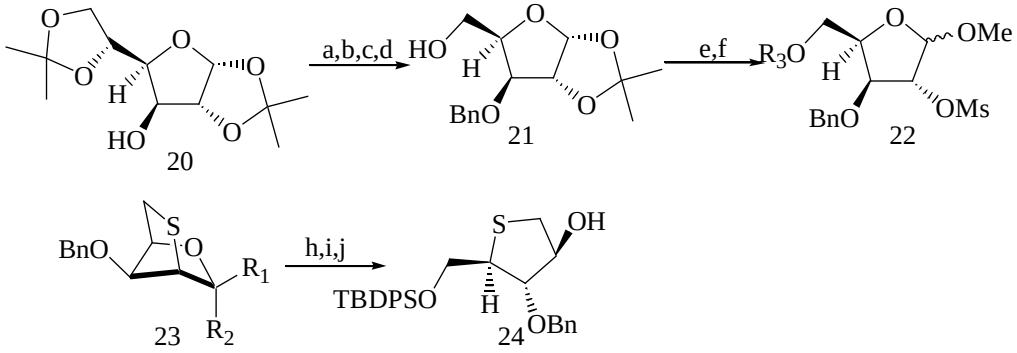
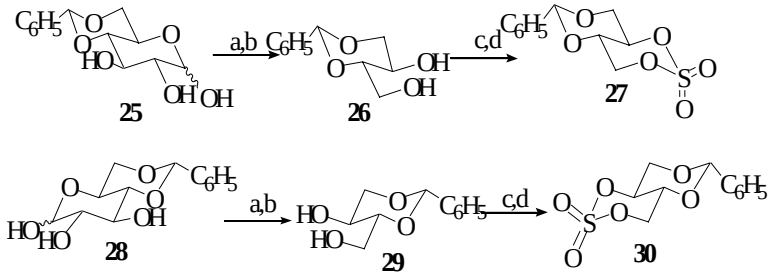


Scheme5. Reagents and conditions: **a**) BnBr, NaH, DMF, THF; **b**) 2 M HCl, THF; **c**) $NaIO_4$, H_2O, MeOH; **d**) $NaBH_4$, MeOH, 84% from **17**; **e**) 5% HCl/MeOH, 91%; **f**) MsCl, pyridine; **g**) Na_2S, DMF, 100 °C, 78% (*R*-anomer) from **22**; **h**) 4 M HCl, THF; **i**) $NaBH_4$, MeOH, 90% from **23**; **j**) TBDPSCl, imidazole, DMF, 87%.

The 2,4-*O*-benzylidene- L- (**27**) and D- (**30**) erythritol-1, 3-cyclic sulfates[5a] were synthesized from L- and D-glucose, respectively (Scheme **6**).



Scheme 6. Reagents and conditions: **a**) $NaIO_4$, $NaHCO_3$, H_2O, rt **b**) $NaBH_4$, H_2O/EtOH, rt., 92%; **c**) $SOCl_2$, and. NEt_3, CH_2Cl_2, 0 ºC **d**) $RuCl_3$, $NaIO_4$, CH_2Cl_2/CH_3CN/H_2O, rt, 80%

Coupling of both the fragments was achieved by stirring the mixture of fragments followed by deprotection of benzylidine protecting group under hydrogenolytic conditions to furnish salacinol and its isomer.

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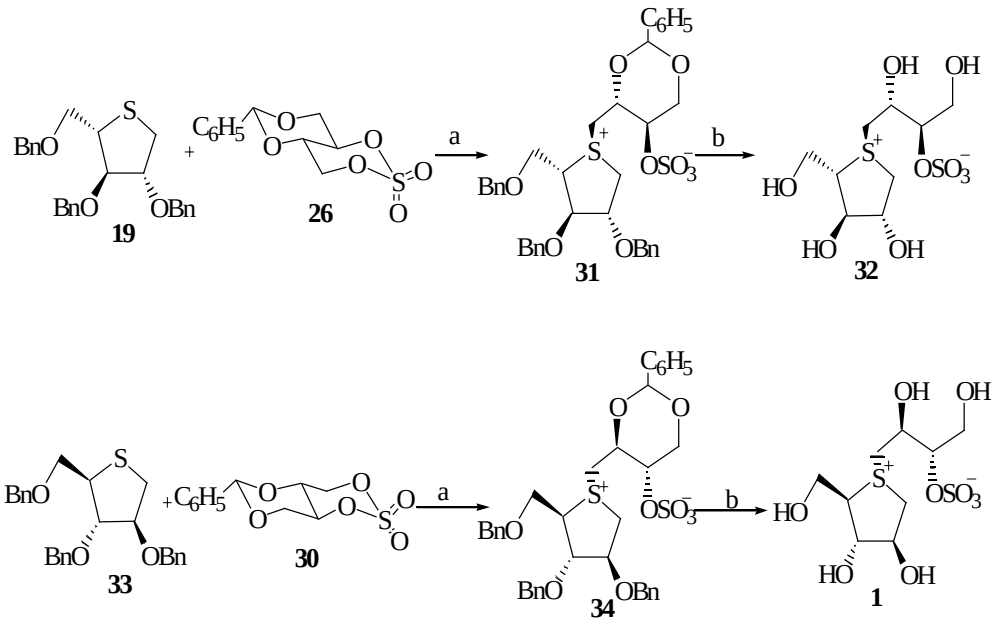

Scheme7. Reagents and conditions: a) K_2CO_3, acetone rt.; **b**) Pd/C, H_2, AcOH

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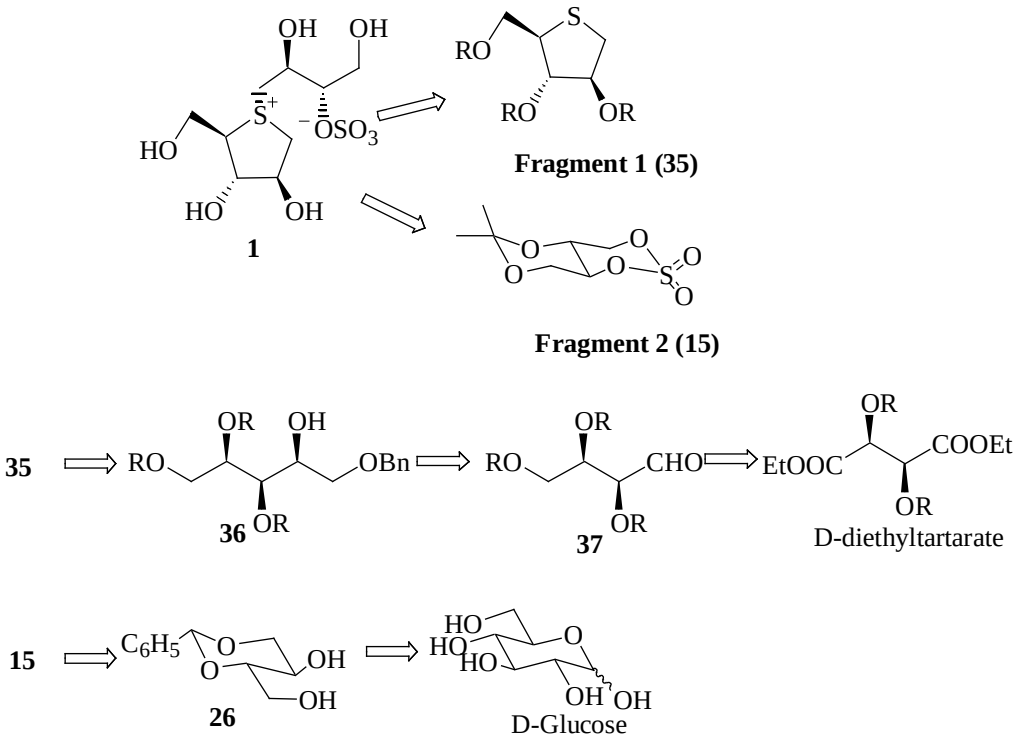
2.1.4 Retrosynthesis:

Retrosynthesis reveals that salacinol could be synthesized by nucleophilic ring opening of cyclic sulfate 15 with thioarabinitol 35. we decided to prepare the cyclic sulfate according to the modified literature procedure[12] as the erythro fragment required for the synthesis of salacinol could be easily derived from D-Glucose. We envisaged that the thioarabinitol fragment could be easily obtained from pentitol 36, which in turn could be obtained from aldehyde 37 by alkylation with metal alkyls. Further aldehyde 37 could be easily prepared from D- diethyl tartarate. The alkylation of aldehyde 37 gives the flexibility of preparing various substituted analogues of salacinol.



Scheme 8.

2.1.5 Present Work: Results and discussion:

All the reported syntheses of salacinol **1** utilize naturally occurring chiral pool starting matrerials (sugar scaffolds), for the synthesis of thioarabinitol fragment of salacinol and its

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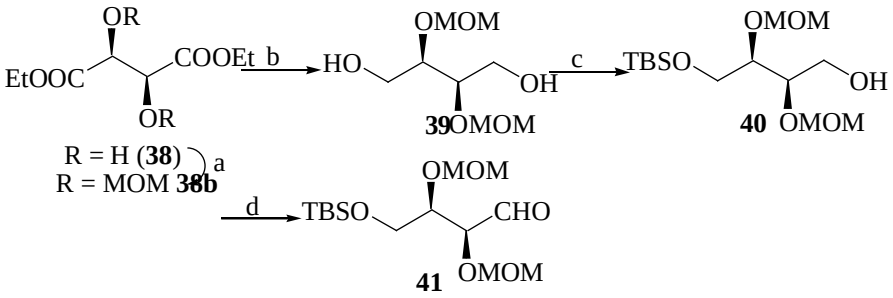
enantiomer these syntheses lack the generality to access various substituted analogues of salacinol, so there is a necessity to develop a general synthetic sequence using a relatively inexpensive starting materials. We envisaged that tartaric acid could serve as an excellent starting material for this purpose as both the isomers are readily available and an added advantage is various analogues of salacinol could be easily synthesized by simple alkylation of mono aldehyde **37** with metal alkyls, (benzyloxymethyl)tributyl stannane.[13] It was decided to prepare the monoaldehyde **37** from diethyl tartarate.

Synthesis of Fragment 1

The D-threitol derivative **39** was prepared from D-diethyl tartrate[14] **35** by methoxymethylation (MOMC1, **(***i*-Pr)$_2$NEt, CHC1$_3$,) to give **38b.** The proton NMR showed signals at δ 3.34 integrating for 6 protons along with a signal at δ 4.64 and 4.78 each integrating for 2 protons which were assigned to methyl and methylene protons of methoxy methyl protecting group. The introduction of methoxymethyl groups was further confirmed by ^{13}C NMR spectrum which showed signals at δ 96.38 as triplet ($\underline{CH_2}OCH_3$) and a signal at δ 75.63 as a quartet ($CH_2O\underline{CH_3}$) representing methoxymethyl group. The protected diester **38b** was reduced with $LiAlH_4$ using THF as the solvent to furnish the diol **39** in 94% yield.



Scheme 9.Reagents and conditions: a) MOMC1, ***(i*-Pr)$_2$NEt, CHC1$_3$, 60 ºC, 36h, **b**) $LiAlH_4$, THF, rt., 12h, 94% **c**) NaH, TBSCl, THF, rt. 1h, 74%; **d**) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, -78 ºC, 95%.

The ^{1}H NMR spectrum of **39** indicated the disappearance of protons corresponding to ethyl ester, while a signal at δ 3.71 as a multiplet integrating for 4 protons was assigned to protons on newly formed methylene group. The structure of the product formed was further confirmed by analysis of ^{13}C NMR spectrum which showed a signal at δ 79.48 as a triplet

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carbon, a representative of primary hydroxymethyl group while disappearance of singlet carbon at δ 168.59 in starting material provides proof for the reduction product. Mono TBS protection[15] of **39** was effected by treatment with 1 equiv. of TBDMSCl in the presence of a sodium hydride in THF to furnish **40** in 94% yield, ^{1}H NMR spectrum of product **40** showed two singlets at δ 0.00 integrating for 6 protons and a signal at δ 0.83 integrating for 9 protons were assigned to proton of TBDMS group and it was further confirmed by M+1 of 325.20 in mass spectra. The mono alcohol **40** was then subjected to Swern oxidation $(COCl)_2$, Me_2SO, Et_3N) to give **41** in 95% yield. The proton NMR spectrum showed a signal corresponding to aldehyde at δ 9.69 undoubtedly confirmed the product formation. Treatment of the aldehyde **41** with (Benzyloxymethyl)tributyl stannane[13] in the presence of BuLi yielded the alkylated pentitol **42** in 65% yield as an inseperable mixture of diastreoisomers. The HPLC of column purified sample indicated the presence of both the diastereoisomers in (1:1) ratio. The product that is faster moving on the tlc is ascertained as the required isomer based on the result, that conversion of the faster moving spot to its corresponding cyclic sulfide **44** and further deprotection of **44** furnished **46** with all the spectral data matching. The proton NMR showed signals at δ 4.65 corresponding to two protons and multiplet at δ 7.24 along with a multiplet at δ 3.71 indicated the introduction of benzyloxy methyl group. This was further confirmed by ^{13}C NMR which showed signals at δ 62.60, 62.23 corresponding to -$\underline{CH_2}OCH_2Ph$ for the two diastereoisomers, while the signals at δ 73.30 and 71.00 for -$CH_2O\underline{CH_2}Ph$ and signals at δ 127.56, 127.73, 128.26 and 138.09 corresponding to phenyl carbons established the expected structure. Further confirmation of assigned structure was obtained from mass spectrum showing M+1 value of 445.26.

Since no diastereoselectivity was observed during the alkylation using metal (Benzyloxymethyl)tributyl stannane it was decided to oxidize the newly formed hydroxyl group and selectively reduce it to alcohol (*syn* reduction) to arrive at the required isomer. But unfortunately we failed to obtain the *syn* selectivity under various reduction conditions and the results are summarized in table 1.

Reduction of ketone with sodium borohydride and K-selectride at -78 ºC gave almost 1:1 mixture of diastereomers, while reduction under Luche conditions and using $Li(Et)_3BH$

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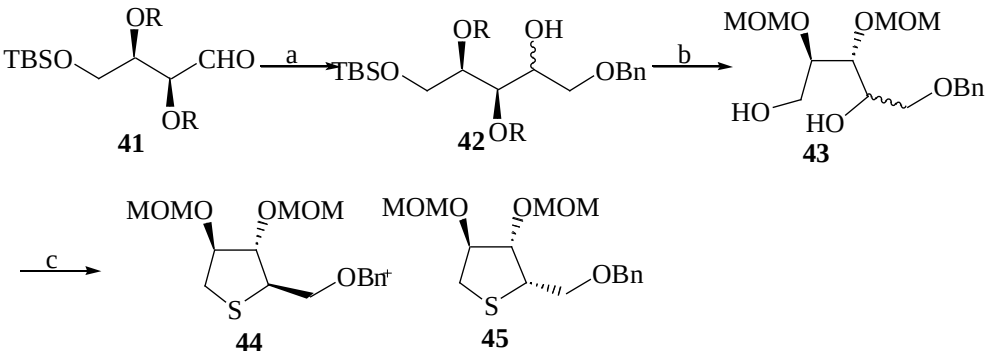
furnished only the undesired isomer in major amounts. The product ratios obtained were determined by HPLC.

Table 1.

Sr. No	Reaction conditions	Yield %	Diastereomeric ratio syn/anti(HPLC)
1.	$NaBH_4$; Methanol, rt.	78	1:1
2.	K-selectride, THF; -78 ºC; 1h.	68	4.8:5.2
3.	$CeCl_3$; $NaBH_4$; Methanol; -78 ºC to rt. 12h	74	1.3:8.7
4.	$Li(Et)_3BH$; THF; -78 ˚C; 1h.	82	2:8

Having failed to obtain the desired *syn*- selectivity, it was decided to go ahead with a mixture of isomers.



Scheme 10. Reagents and conditions: a) $BnOCH_2SnBu_3$, BuLi, THF, -78 ºC 15 min.; **b**) TBAF, THF, rt., 1h, 92%. **c**) **i**) MsCl, Et_3N, CH_2Cl_2, 1h. **ii**) Na_2S, DMF, 100 ºC 2h, 86% over two steps.

Thus deprotection of TBS ether of **42** was effected with *tetra* n-butylammoniumfluoride in THF in 90% yield. The proton NMR spectrum of **42** showed the disappearance of signals corresponding to TBS group while the appearance of a broad singlet (D_2O exchangeable) integrating for two protons from δ 2.55 to δ 2.8 affirmed the presence of two free hydroxyl groups. Similarly ^{13}C NMR spectrum indicated the disappearance of signals

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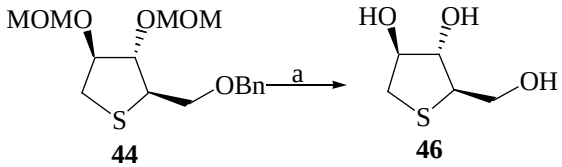
corresponding to *t*-butyl and methyl carbons of TBS group providing proof for the deprotection of primary hydroxyl functionality. The assigned structure of **43** was further confirmed by the presence of peak at M+Na value of 353.13 in ESR mass spectra. Having obtained the desired pentane diol **43** the next task in hand was the formation of cyclic sulfide. The unmasked diol **43** was protected as its dimesylate with methane sulfonyl chloride in the presence of triethylamine which on subsequent treatment with sodium sulfide in DMF at 100 °C gave the protected thioarabinitol **44** and **45** in 86% yield over two steps (Scheme 10) as a mixture of diastereoisomers. The mixture of isomers were separated using flash column chromatography to furnish **44** eluting as first fraction form column chromatography in 42% yield. The steochemistry of the product was confirmed by deprotection of the methoxy methylene and benzyloxy ethers to furnish the required triol **46**, IR spectrum of **44** indicated the disappearance of strong band characteristic of free hydorxy groups while the absorption bands at 1151 cm^{-1} and 1098 cm^{-1} were assigned to the stretching of carbon-sulfur bond of sulfide. ^{1}H NMR spectrum revealed two doublet of doublets, one at δ 2.93 with J = 4.80 and 11.36 Hz integrating for one proton and the other resonating at δ 3.15 with J = 5.05 and 11.36 Hz representing nonequivalent methylene protons of cyclic sulfide. An apparent multiplet at δ 3.54 integrating for two protons was assigned to protons on methylene carbon attached to tetrahydrothiophane ring, while a signal at δ 3.79 again as apparent multiplet integrating for one proton was conferred to methine proton adjacent to sulfur of tetrahydrothiophane ring. The signals at δ 2.93 and at δ 3.15 as doublet of doublets were indicative of the formation of cyclic sufide. Further ^{13}C NMR spectral analysis indicated an upfield signal at δ 29.67 as a doublet, was assigned to the methylene carbon of cyclic sulfide, while a signal at δ 49.42 was assigned to methine carbon of cyclic sulfide supporting the formation of cyclised product. Further the assigned structure was confirmed by the presence of a signal at $[M+Na]^{+}$ 351.21 in ESR mass spectrum.



44 **46**

Scheme 11.Reagents and conditions: a) BCl_3, DCM, -78 ºC, 1h, 37%

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Having obtained the necessary cyclised product the deprotection of **44** to arrive at the thioarabinitol fragment of salacinol was achieved by demethoxymethylation of two secondary hyrdoxy functionalities of ring and debenzylation of primary hydroxyl group in one pot by treating **44** with BCl_3 at -78 ºC to furnish **9** in 37% yield.The ^1H, ^{13}C NMR and optical rotation of thioarabinitol fragement thus obtained by deprotection of methoxymethyl ethers and *O*-benzyl group were in good agreement with the reported values.

Synthesis of Fragment 2:

The protected L-Erythritol cyclic sulfate was prepared from 4,6-*O*-benzylidene-D-Glucose as per the literature precedents.(scheme 12) The 4,6-*O*-benzylidene-D-Glucose was subjected to cleavage with sodium metaperiodate oxidation followed by $NaBH_4$ reduction in one pot to obtain the diol **11** in 92% yield. ^1H NMR spectrum of diol **11** showed a multiplet at δ 3.67 to 3.55 integrating for 3 protons and were assigned to the three axial protons on the six membered ring. Two signals at δ 3.74 and 3.92 as doublet of doublets with J = 5.7 and 12.1 Hz and J = 1.7 an 12.1 Hz respectively integrating for 1 proton each were assigned to protons on carbon of hydorxymethyl group attached to six membered ring. While a signal at δ 4.20 as a multiplet was assigned to the equatorial proton of the six membered ring. The most down field aliphatic signal at δ 5.53 as singlet represents the benzylidene proton. The assigned structure was confirmed by ^{13}C NMR spectral analysis which showed signals at δ 62.59, 62.76, 72.21 and 84.22 for carbons attached to oxygen while a signal at δ 102.36 was assigned to benzylidine carbon. The structure of the diol **11** formed was further confirmed by ESI Mass spectra which showed the signal at 211 for [M+H] and 233 for [M+Na].

The diol **11** thus obtained was then protected as acetonide using 2-methoxy propene in the presence of catalytic *p*-TSA in DMF to furnish **12** in 96% as a white solid. The ^1H NMR showed the signals corresponding to acetonide as two singlets at δ 1.43 and 1.57 each integrating for three protons. This was confirmed by ^{13}C NMR spectral analysis which showed signals corresponding to methyl carbons of acetonide at δ 19.3 and 29.1, while a signal at δ 100.0 for quaternary carbon confirmed the formation five membered acetonide. The structure formed was further confirmed by a peak at 273.11 for [M+Na] mass spectroscopy. Having obtained the differentially protected erythritol the desired L-erythritol was obtained by the

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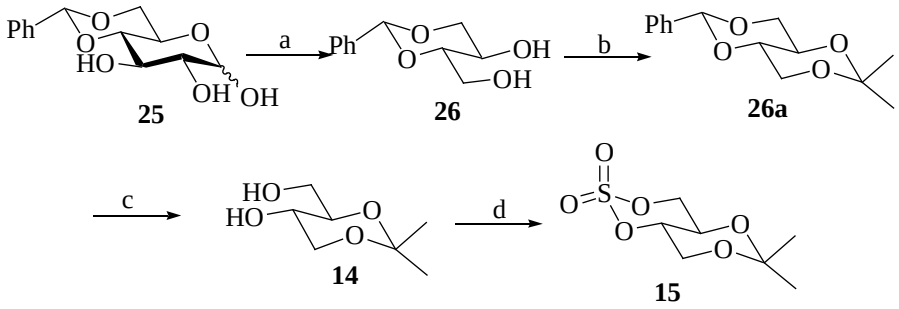
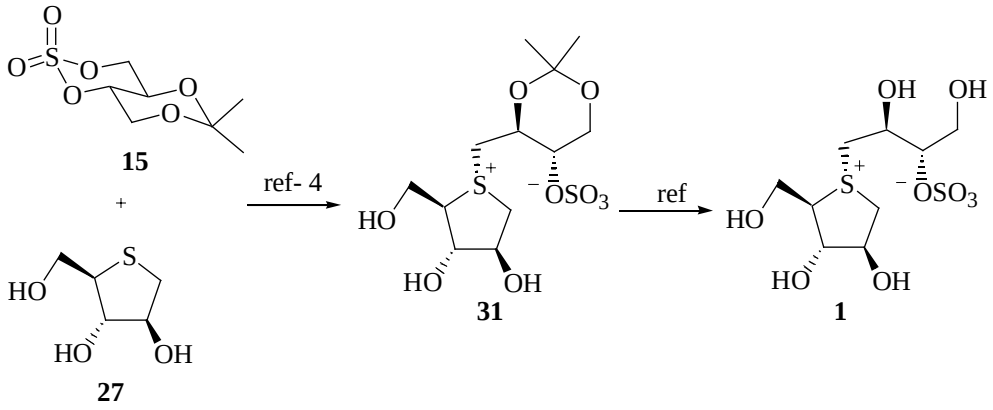
hydrogenolysis of **12** over Pd/C to furnish the desired diol **14** in 84% yield. ^{1}H NMR spectrum of diol **14** showed the disappearance of aromatic protons and benzylidine proton indicating the unmasking the diol, while the signals at δ 1.47 and 1.53 as singlets each integrating for 3 protons confirmed the presence of 1,3 acetonide. The assigned structure was further confirmed by ^{13}C NMR spectrum.

The diol thus obtained was convered to cyclic sulfate **15** by treating **14** with thionyl chloride in the presence of anhydrous triethylamine in DCM which was concentrated to dryness on completion of the reaction to furnish crude cyclic sulfite. The crude cyclic sulfite was oxidized *in situ* with catalytic $RuCl_3$ in the presence of sodium metaperiodate to furnish **15** in one pot .



Scheme 12.Reagents and conditions: **a**) $NaIO_4$, $NaHCO_3$, H_2O, rt then $NaBH_4$, H_2O/EtOH, rt; **b**) $CH_3(OCH_3)C]CH_2$, TsOH, DMF, 0 ºC; **c**) $SOCl_2$, anh. NEt_3, CH_2Cl_2, 0 ºC then $RuCl_3$, $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$, rt; **d**) 11, H_2, Pd/C, EtOH, rt.



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Having the two required fragments for the synthesis of salacinol **1** the desired coupling of two fragments could be achieved by heating the mixture of two fragments in DMF at 45 ºC for 13h. followed by deprotection of acetonide with 0.01% HCl as per the literature procedure.

2.1.6 Conclusions:

In conclusion thioarabinitol fragment of salacinol **1** was prepared by novel synthetic route starting from D-diethyl tartarate. Although the desired stereocontrol during the key alkylation of monoaldehyde was not very high, the synthetic sequence could well, serve as a potential route for the synthesis of various substituted thioarabinitol fragments thereby furnish various analogues of salacinol.

Thus formal total synthesis of salacinol was accomplished. This synthethic sequence can provide a lead for the synthesis of salacinol and its analogues, substituted α-to sulfur in thioarabinitol skeleton.

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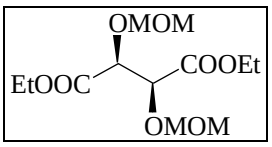
2.1.7 Experimental:

Diethyl 2*S*,3*S* -*O*-Bis(methoxymethylene)-tartrate[14] (38b)



To a stirred, cooled (0 ºC) mixture of diethyl D-tartrate (50.0 g) and *N*,*N*-diisopropylethylamine (103.0 ml) in $CHC1_3$ (400 ml) was added a solution of chloromethyl methyl ether (40.85 ml) in $CHC1_3$ (360 ml). The mixture was heated at 60 ºC with stirring. After 36 h, ethyl acetate (500 mL) was added to the cooled (to room temperature) reaction mixture and the reaction mixture was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified by column chromatography on silica gel (eluting with ethyl acetate:petether.(25:75) to furnish **38b**.

Yield	: 80.64g, (94%)
Mol. Formula	: $C_{12}H_{22}O_8$; Pale yellow oil
$[\alpha]_D$	: -142.7 (*c* 1.57, MeOH)
IR (neat) $\tilde{\nu}$ (cm^{-1}):	: 1760,1735
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.31 (t, *J* = 7 Hz, 6H), 3.34 (s, 6 H), 4.24 (q, *J* = 7.0 Hz, 4 H), 4.64 (1/2 AB q, *J* = 7.5 Hz, 2H), 4.68 (s, 2 H), 4.78 (1/2 AB q, *J* = 7.5 Hz, 2H).
^{13}C NMR($CDCl_3$, 50MHz)	: 13.98, 55.94, 61.07, 75.63, 96.38, 168.59
Mass *m/z*	: 263 (M+ - 31, 1.2), 217 (54), 192 (45), 117 (100).
Elemental Analysis	: **Calcd.** : C 48.97; H 7.53. **Found** : C 48.72; H 7.37.

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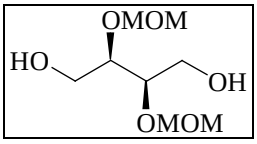
2*R*,3*R*-*O*-Bis(methoxymethylene)threitol[14] (39).



To a stirred, cooled (0 ºC) suspension of $LiAlH_4$ (1.94 g, 26.2 mmol) in THF (8.0 mL) was added dropwise a solution of **38b** (6.53 g, 52.5 mmol) in THF (50 mL). The mixture was stirred at room temperature for 14 h and quenched by addition of 4N KOH (6 mL) and then water under ice cooling. The mixture was filtered through a Celite pad and washed with ethylacetate and after drying (Na_2SO_4) and filtering. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2) (eluting with ethyl acetate:petether.(50:50)to obtain the product as white solid.

Yield	: (4.24 g); 92%
Mol. Formula	: $C_8H_{18}O_6$; White solid.
Melting Point	: 62-63 ºC;
Optical Rotation[α]$_D$	: +7.7 (*c* 3.37, MeOH)
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.93 (br t, 2H), 3.41 (s, 6H), 3.71 (br s, 4H), 3.74 (s, 2H), 4.66 (d, *J* = 7.5 Hz, 2H), 4.74 (d, J = 7.5 Hz, 2H);
^{13}C NMR($CDCl_3$, 50MHz)	: 55.74, 61.49, 79.48, 97.17,
Mass (m/z)	: 191 (M+ 1 – H_2O, 0.8), 189 (0.81, 179 (1.2), 147 (44), 117 (74), 105 (51), 103 (47), 88 (l00), 73 (82).
Elemental Analysis	: **Calcd.** : C 45.71; H 8.63.
	Found : C 45.43; H 8.57.

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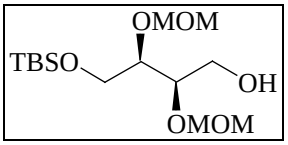
4-(*tert*-Butyl-dimethyl-silanyloxy)-2*R*,3*R*-bis-methoxymethylene-butan-1-ol[15] (40)



Sodium hydride (0.376 g) was suspended in THF (8.0 ml) after being washed with hexane. The diol **39** (1.98 g, 9.42mmol) was added to this mixture at room temperature and stirred for 45 min. at which time a large amount of an opaque white precipitate had formed. The *tert*-butyldimethylsilyl chloride (1.414 g, 9.42 mmol) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ethyl acetate, washed with 10% aqueous K_2CO_3 and brine, dried, filtered and concentrated *in vaccuo*. The resulting oil was purified by column chromatography using ethyl acetate/hexane (30/70) mixture as an eluent.

Yield	: 2.89 g, (94%)
Mol. Formula	: $C_{14}H_{32}O_6Si$; Colourless liqid.
Optical Rotation $[\alpha]_D$	: - 0.39 (*c* 1.04, $CHCl_3$)
IR $\tilde{\nu}$ **(cm^{-1})** (neat)	: 3481, 2953, 1472, 1464, 1255, 1034, 838.
^{1}H NMR ($CDCl_3$, 200MHz)	: 0.00 (s, 6H); 0.83 (s, 9H); 3.25 (bs, 1H); 3.33 (s, 3H); 3.36 (s, 3H); 3.67 (m, 4H); 4.63 (m, 4H).
^{13}C ($CDCl_3$, 50MHz)	: 5.46, 25.84, 55.73, 62.15, 62.41, 78.35, 80.33, 97.18, 97.58
MS (ESI) m/z	[M+Na] 347.18
Elemental Analysis	**Calcd**. : C 51.82; H 9.94.
	Found : C 51.94; H 10.17

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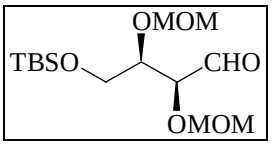
4-(*tert*-Butyl-dimethyl-silanyloxy)-2*R*,3*S*-bis-methoxymethylene-butaraldehyde (41)



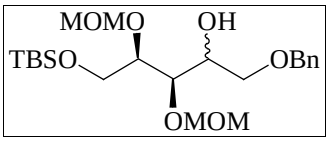
To a stirred and cooled (-78 ºC) solution of oxalyl chloride (0.54 mL) in CH_2C1_2 (4.0 mL) was added a solution of Me_2SO (0.87 mL) in CH_2C1_2 (4.0 mL) over a period of 5 min. After stirring for 15 min at -78 ºC, a solution of **40** (1.0 g) in CH_2C1_2 (4 mL) was added to the mixture over a period of 5 min. After 1 h of stirring at -78 ºC, triethylamine (2.50 mL) was added to the reaction mixture over a period of **5** min, and the mixture was stirred for further 5 min. The reaction was allowed to warm to ambient temperature and water (10 mL) was added to the mixture. The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 and the combined extracts were washed with water and dried (Na_2SO_4,) and filtered. Evaporation of the solvent under reduced pressure left an oil which was used as such for further alkylation.

Yield : 0.87 g, **(**87%)

Mol. Formula : $C_{14}H_{30}O_6Si$; Colourless liqid.

^{1}H NMR ($CDCl_3$, 200MHz) : 0.00 (s,1H); 0.82 (s, 9H); 3.27 (s, 3H); 3.38 (s, 3H); 3.69 (m, 2H); 3.97 (m, 1H); 4.11 (d, 1H, J = 3.16 Hz); 4.64 (m, 4H); 9.69 (s, 1H).

1-Benzyloxy-5-(*tert*-butyl-dimethyl-silanyloxy)-3*R*,4*R*,-bis-methoxymethylene-pentan-2-ol (42)



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A solution of the α-benzyloxy organostannane (0.718 g) in 5 mL of anhydrous tetrahydrofuran was cooled to -78 ºC under nitrogen. The solution was stirred while n-butyllithium (1.45 mL) was added. Within 5 min, the exchange was complete (change of colourless solution to dark green colour) and the substrate **41** (0.50 g) in anhydrous THF was added to the reaction mixture. After 10 min, the cold reaction mixture was partitioned between water and ethyl acetate and the organic phase was dried (sodium sulfate), filtered and the solvent was evaporated *in vaccuo* to give the crude product which was purified by flash chromatography using ethyl acetate/petether (30/70) as eluent to give the desired pentan-2-ol **42** as a mixture of diastereoisomers in 1:1 ratio.

Yield	: 0.45 g (65%)
Mol. Formula	: $C_{22}H_{40}O_7Si$; Colourless liqid.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3450, 2954, 1673, 1453, 151, 1100.
^{1}H NMR ($CDCl_3$, 200MHz)	: 0.00 (s, 6H); 0.80 (s, 9H); 3.26 (s, 3H); 2.33 (s, 3H); 3.51 (m, 2H); 3.69 (m, 4H); 3.89 (m, 2H); 4.5 (m, 2H); 4.57 (m, 1H); 4.67 (m, 2H); 7.24 (m, 5H). (As a 1:1 mixture of diastereoisomers)
^{13}C NMR ($CDCl_3$, 50MHz)	: -5.45, 18.8, 25.86, 29.67, 55.60, 55.76, 62.24, 62.61, 69.33, 69.83, 70.90, 71.01, 78.20, 78.44, 78.87, 96.89, 97.60, 98.19, 98.40, 127.56, 127.73, 128.27, 138.09 (23 resonances for 22 carbons)
MS (ESI) m/z	: $[M+Na]^+$ 467.24
Elemental Analysis	: **Calcd.** C 59.43; H 9.07. **Found**: C 59.65; H 9.21.

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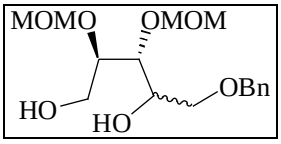
(2*R*,3*R*-5-(benzyloxy)-2,3-bis(methoxymethylene)pentane-1,4-diol (43)



To an ice cooled solution of **42** (0.40 g, 0.9 mmol) in THF was added TBAF (1M) in THF and stirred at room temperature for 1h. After the completion of the reaction the solvent was removed under reduced pressure and resultant crude mass was dissolved in ethyl acetate and washed with water. The organic layer was washed with brine, dried (Na_2SO_4), fitered and solvent evoparated under reduced pressure to furnish the crude diol which was purified by column chromatography(SiO_2) using ethyl acetate/petether (60/40) as eluent to furnish the diol **43** as a colourless oil.

Yield	: 0.260 g; (86%)
Mol. Formula	: $C_{16}H_{16}O_7$; Colourless liquid
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.96 (br s, 2H); 3.32 (s, 6H,), 3.31 (m, 1H); 3.45 (s, 1H); 3.48 (s,1H); 3.70 (m, 1H); 3.84 (m, 1h); 3.97 (m, 1H); 4.57 (m, 5H); 7.25 (m, 5H)
^{13}C ($CDCl_3$, 50MHz)	: 54.92, 54.98, 55.27, 55.46, 60.55, 61.17, 68.0, 68.71, 69.66, 70.08, 72.46, 72.52, 77.24, 77.78, 78.87, 79.0, 96.10, 96.83, 97.30, 126.88, 126.97, 127.50, 136.81, 136.89 (24 resonances for 17 carbons)
MS (ESI) m/z	: [M+Na] 353.13
Elemental Analysis	: **Calcd.** C 58.17; H 7.93 **Found** C 57.90; H 7.91

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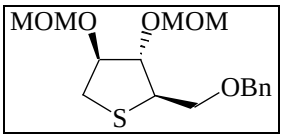
(2*R*,3*S*,4*S*)-2-((benzyloxy)methyl)-tetrahydro-3,4-bis(methoymethylene) thiophene (44)



To the diol **43**(0.26 g; 0.70 mmol) in DCM was added Et_3N and MsCl at 0 ºC and stirred for 1h at room temperature. The reaction mixture was diluted with DCM (5 mL), washed with water, brine, dried (Na_2SO_4), filtered and the solvent evoparated to give the crude dimesylate which was heated with Na_2S (0.082 g, 1.05 mmol) in DMF (2 mL) at 100 ºC for 3h. The solvent was evaporated under reduced pressure and extracted with ethylacetate (20 ml), dried on anhydrous sodium sulfate, filtered and concentrated under reduced pressure to furnish **44** and **45** as a mixture of isomers. The mixture of isomers were further separated by flash chromatography(SiO_2) using ethyl acetate/petether (15/85) as eluent, to furnish the required isomer **44** eluting first through column, while further elution with the same solvent ratio ethyl acetate/petether (15/85) as eluent furnished **45**.

Yield	: 0.108 g; (42%)
Mol. Formula	: $C_{16}H_{24}O_5S$; Colourless liquid
Optical Rotation $[\alpha]_D$	: +40.43 (*c* 1.1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500MHz)	: 2.93 (dd, *J* = 11.36, 4.80 Hz, 1H); 3.15 (dd, *J* = 11.36, 5.18 Hz,1H); 3.39 (s, 6H); 3.48-3.58 (app.m, 2H); 3.79 (app.m, 1H); 4.21 (t, 1H, *J* = 4.04 Hz); 4.32 (dd, 1H, *J* = 4.80, 4.04 Hz); 4.60 (d, *J* = 5.56 Hz, 2H); 4.65 (d, *J* = 10.62 Hz, 1H); 4.69 (d, *J* = 10.62 Hz, 1H); 4.75 (s, 2H) 7.26 (m,5H).
^{13}C ($CDCl_3$, 125MHz)	: 33.40, 49.32, 55.54, 72.26, 72.98, 83.08, 83.40, 95.88, 95.72, 127.63, 128.29, 138.12,
MS (ESI) m/z	: [M+Na] 351.12

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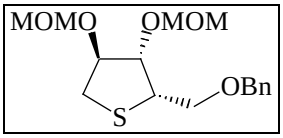
Elemental Analysis : **Calcd.** : C 59.97; H 6.71
Found : C 60.05; H 6.31

(2*R*,3*S*,4*S*)-2-((benzyloxy)methyl)-tetrahydro-3,4-bis(methoymethylene) thiophene (45)



Yield : 0.097 g; (38%)

Mol. Formula : $C_{16}H_{24}O_5S$; Colourless liquid

Optical Rotation $[\alpha]_D$: -54.48 (*c* 1.9, $CHCl_3$)

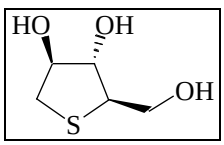
^{1}H NMR ($CDCl_3$, 200MHz) : 2.78 (d, *J* = 11.11, 1H); 3.08 (dd, *J* = 11.24, 3.54 Hz, 1H) 3.28 (s, 3H); 3.31 (s, 3H); 3.50 (dd, *J* = 12.51, 2.91 Hz, 1H); 3.73 (dd, *J* = 12.51, 4.55 Hz, 2H); 4.15 (t, *J* = 2.91 Hz, 1H); 4.28 (m, 1H); 4.46 (d, *J* = 2.02 Hz, 2H); 4.56 (d, J = 12.63 Hz, 1H); 4.60 (d, J = 12.63 Hz, 1H); 4.61 (2, 2H); 7.26 (m,5H).

^{13}C NMR ($CDCl_3$, 50MHz) : 33.73, 47.75, 55.44, 55.60, 68.77, 73.02, 81.70, 95.43, 96.57, 127.49, 128.18, 137.94,

MS (ESI) m/z : [M+Na] 351.12

Elemental Analysis : **Calcd.** : C 59.97; H 6.71
Found : C 60.05; H 6.31

(2S,3R,4R)-2-((Benzyloxy)methyl)-tetrahydrothiopene-3,4-diol:(46)



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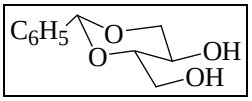
To a solution of **45** (0.108 g) in 2 mL of CH_2Cl_2, cooled to -78 C ,Borontrichloride (1M in DCM) (0.62 ml) was added dropwise and allowed to stir for 1h at -78 ºC. The reaction mixture was then quenched with aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate (2x5 mL) The organic layer was further washed twice with 2mL of water. The organic layer was discarded and the combined aqueous layer was concentrated under vaccum to dryness. The crude reaction mixture was suspended in dry methanol (10 mL), filtered over a pad of celite and the residue was washed with methanol (2x10 mL). The combined methanol layers was concentrated *in vaccuo* to furnish the crude triol. The crude triol was purified over silicagel using 1:9 MeOH: Chloroform(10/90) as eluent to furnish the pure triol **46.**

Yield	: 0.018 g; (37%)
Mol. Formula	: $C_5H_{10}O_3S$;
Optical Rotation $[\alpha]_D$	: +39.90 (*c* 1.25, MeOH); Lit. +40.2 (*c* 1.28, MeOH)
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.70 (dd, *J* = 6.16, 6.32 Hz, 1H); 2.99 (dd, *J* = 5.68, 10.73 Hz, 1H); 3.22 (q, *J* = 5.43 Hz, 1H); 3.59 (dd, *J* = 6.83, 6.69 Hz, 1H); 3.82 (dd, *J* = 5.43, 10.73 Hz, 1H), 3.85 (t, *J* = 5.56 Hz, 1H); 4.10 (q, *J* = 5.56 Hz, 1H)
^{13}C NMR ($CDCl_3$, 50MHz)	: 35.21, 54.53, 66.30, 80.07, 81.42
MS (ESI) m/z	: [M+Na] 173
Elemental Analysis	: **Calcd.** : C 39.98; H 6.71; S 21.35 **Found** : C 39.68; H 6.51; S 21.15

4-Hydroxymethyl-2-phenyl-[1,3]dioxin-5-ol: (26)



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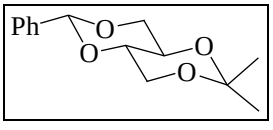
To a solution of 4,6-*O*-benzylidene-D-glucose **25** (10.0 g, 37.4 mmol) in 70 mL of water was added a solution of $NaIO_4$ (16.1 g, 75.4 mmol) and $NaHCO_3$ (3.17 g, 37.7 mmol) in 130 mL of water at 0 ºC. The pH was maintained to 6–7 by adding few drops of a saturated $NaHCO_3$ solution. The mixture was stirred at room temperature for 5 h. A solution of $NaBH_4$ (2.00 g, 52.9 mmol) in 20 mL of water was added dropwise at 0 ºC. The mixture was stirred at rt for 30 min, and neutralized with acetic acid. The precipitate formed was filtered, and rinsed with ethyl acetate. The filtrate was extracted with ethyl acetate (350 mL), the organic phases were washed with 1 N $Na_2S_2O_3$ (75 mL) and with brine (75 mL), dried over $MgSO_4$ and filtered. The diol **26** was concentrated under vacuum and purified by flash chromatography (petether/AcOEt: 3/7) as a white solid.

Yield	: 7.24 g; (92%)
Mol. Formula	: $C_{11}H_{14}O_4$
Melting point	: 138-139 °C, lit.135-136 °C
Optical Rotation $[\alpha]_D$	: -44° (*c* 1.0, MeOH) (lit.-43° (*c* 2.0, MeOH))
^{1}H NMR ($CDCl_3$, 200MHz)	: 3.67-3.55 (3H, m, H-3, H-2, H-4ax); 3.74 (1H, dd, *J*1b,2 5.7 Hz, H-1b), 3.92 (1H, dd, *J*1a,1b) 12.1, *J*1a,2) 1.7 Hz, H-1a), 4.20 (1H, m, H-4eq), 5.53 (1H, s, C*H*Ph), 7.53-7.28 (5H, m, Ar),
^{13}C NMR($CDCl_3$, 50MHz)	: 62.59, 62.76, 72.21, 84.22, 102.36, 127.49, 128.99, 129.77, 139.52.
Mass:(*m*/*z*)	: 211 [M+H], 233 [M+Na].
Elemental Analysis	**Calcd.** : C 62.85; H 6.71. **Found** : C 62.96; H 6.55.

1,3-*O*-Benzylidene-2,4-*O*-isopropylidene-L-erythritol (26a)



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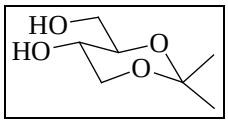
A solution of diol **26** (4.37 g, 20.8 mmol), distilled 2-methoxypropene (6.0 mL, 62.9 mmol) and TsOH (67.4 mg, 0.35 mmol) in non-anhydrous DMF was vigorously stirred at 0 ºC for 24 h. The mixture was neutralized with 1.03 g of Na_2CO_3. The precipitate was filtered, and washed with cyclohexane. To the filtrate was added 400 mL of water, and the aqueous phase was extracted with 200 mL of cyclohexane. The organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2) (cyclohexane/AcOEt: 9/1C0.1% NEt_3) to give **26a** in yield as a white solid.

Yield	: 4.99 g, (96%)
Melting Point	: 68-70 °C
Mol. Formula	: $C_{14}H_{18}O_4$; White solid.
Optical Rotation $[\alpha]_D$	: +2 (*c* = 1.2, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.43 (s, 3H); 1.57 (s, 3H); 3.80–3.73 (m, 2H,); 3.93–3.88 (m, 1H); 4.01–3.95 (m, 2H); 4.23 (dd, 1H, J = 4.0, 10.3 Hz); 5.62 (s, 1H); 7.38–7.35 (m, 3H, H arom); 7.80–7.47 (m, 2H, H arom.)
^{13}C NMR ($CDCl_3$, 50MHz)	: 19.3, 29.1, 62.3, 66.6, 69.6, 75.0, 100.0, 102.0, 129.2–128.3–126.1, 137.2
HRMS (ESIC)	: Calcd. for [M+Na] 273.1103. Found 273.1113.

2,4-*O*-Isopropylidene-L-erythritol (14)



To a solution of **26a** (4.86 g, 19.4 mmol) in 160 mL of ethanol, was added 2.46 g of 10% Pd/C. The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 days. The catalyst was filtered through a pad of celite and rinsed with methanol. The filtrate was concentrated under vacuum and ethanol (160 mL) and fresh catalyst (10% Pd/C (2.02 g)) was added. The mixture was stirred at rt. for 5 days under an atmosphere of H_2. The catalyst was

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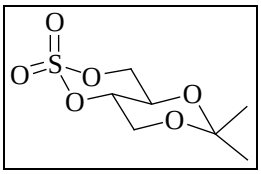
filtered on membrane and rinsed with methanol. The filtrate was concentrated under vacuum and the crude product was purified by flash chromatography (petether/AcOEt: 4/6).

Yield	: 2.78 g, (88%)
Mol. Formula	: $C_7H_{14}O_4$ Colourless oil.
Optical Rotation $[\alpha]_D$	: +45 (*c* 1.1, MeOH)
^{1}H NMR (CD3OD, 200MHz)	: 1.35 (s, 3H, CH_3); 1.48 (s, 3H, CH_3); 3.48 (td, H_2, *J* = 5.6, 9.2, 9.2 Hz, 1H); 3.69–3.57 (m, H_3, H_{1b} and H_{4b}, 3H); 3.82– 3.76 (m, H_{1a} and H_{4a}, 2H);
^{13}C (CD_3OD, 50MHz)	: 19.7, 28.9, 63.3, 64.0, 65.5, 76.5, 99.9
HRMS (ESIC)	: Calcd. for [M+Na] 185.0790. Found 185.0786.

2,4-*O*-Isopropylidene-1,3-*O*-sulfonyl-L-erythritol (15)



To a solution of diol **14** (1.08 g, 6.66 mmol) and anhydrous NEt_3 (2.8 mL, 20.1 mmol) in 28 mL of anhydrous DCM at 0 ºC under Ar, was added dropwise a solution of freshly distilled $SOCl_2$ (0.680 mL, 9.37 mmol) in 28 mL of anhydrous DCM. After complete addition (45 min), the mixture was concentrated under vacuum to give a brown solid. To a solution of this solid (6.6 mmol) in 50 mL of DCM/CH_3CN (5/5) containing $RuCl_3$ (33.5 mg, 0.16 mmol) was added a solution of $NaIO_4$ (4.64 g, 21.7 mmol) in 25 mL of water. The mixture was stirred for 24 h and then diluted with 100 mL of DCM and 100 mL of water. The aqueous phase was extracted twice with 100 mL of DCM. The organic phases were washed with brine (2x100 mL), dried over Na_2SO_4 and filtered. The sulfate **15** was concentrated under vacuum and purified by flash chromatography (pentane/ether 9/1). A white solid (1.03 g) was isolated in 69% yield. R_f 0.16 (pentane/ether 9/1).

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Yield	: (1.03 g); 69%
Mol. Formula	: $C_7H_{12}O_6S$
Optical Rotation [α]$_D$	: -4 (*c* 1.1. $CHCl_3$)
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.43 (s, 3H, CH_3); 1.55 (s, 3H, CH_3); 3.92 (dd, H_{1b}, *J* = 10.3, 10.3 Hz, 1H); 4.03 (dd, H_{1a}, *J* = 5.4, 10.3 Hz, 1H); 4.22 (td, H_3, *J* = 4.8, 10.3, 10.3 Hz, 1H); 4.46 (dd, H_{4b}, *J* = 4.8, 10.3 Hz, 1H); 4.61 (dd, H_{4a}, *J* = 10.3, 10.3 Hz, 1H); 4.66 (td, H_2, *J* = 5.4, 10.3, 10.3 Hz, 1H);
^{13}C NMR ($CDCl_3$, 50MHz)	: 18.9, 28.5, 60.8, 64.7, 73.3, 76.6, 101.1,
HRMS (ESIC)	: Calcd. for [M+Na] 247.0252. Found 247.0264.

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Spectra

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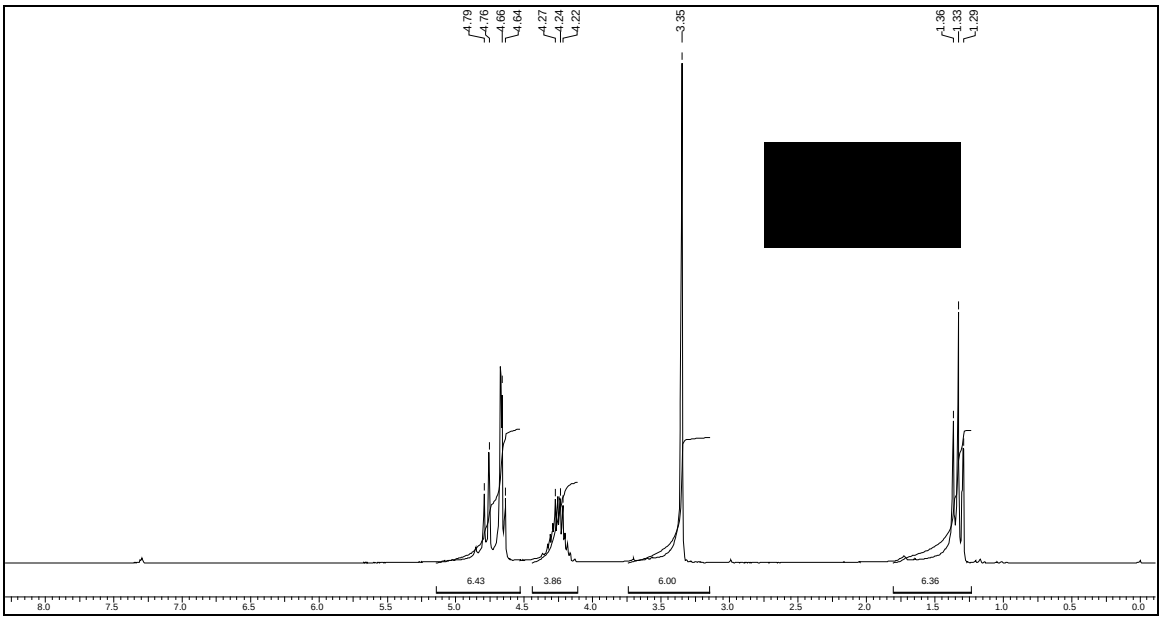
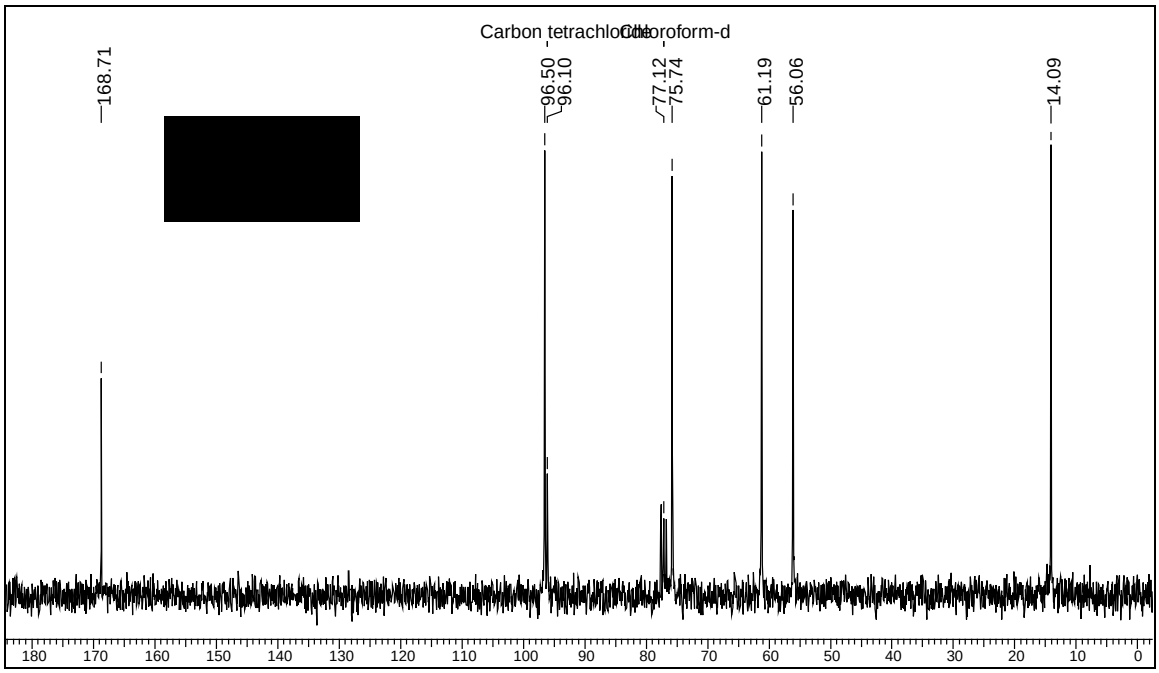


^{1}H NMR spectrum of compound **38b.** (200 mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **38b**. (50mHz, $CDCl_3$)

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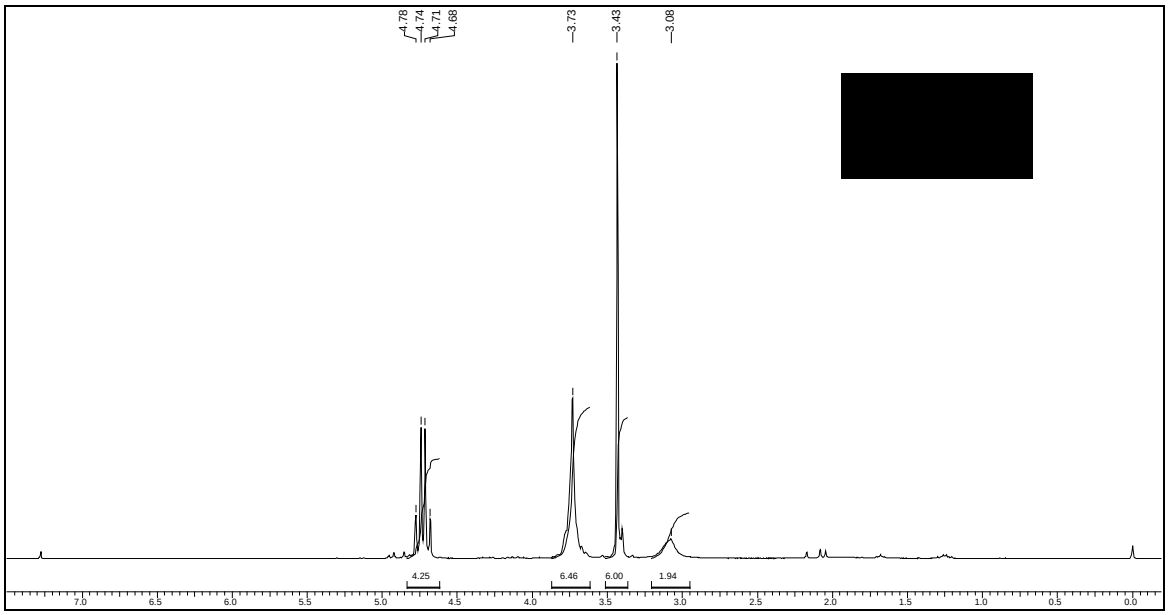
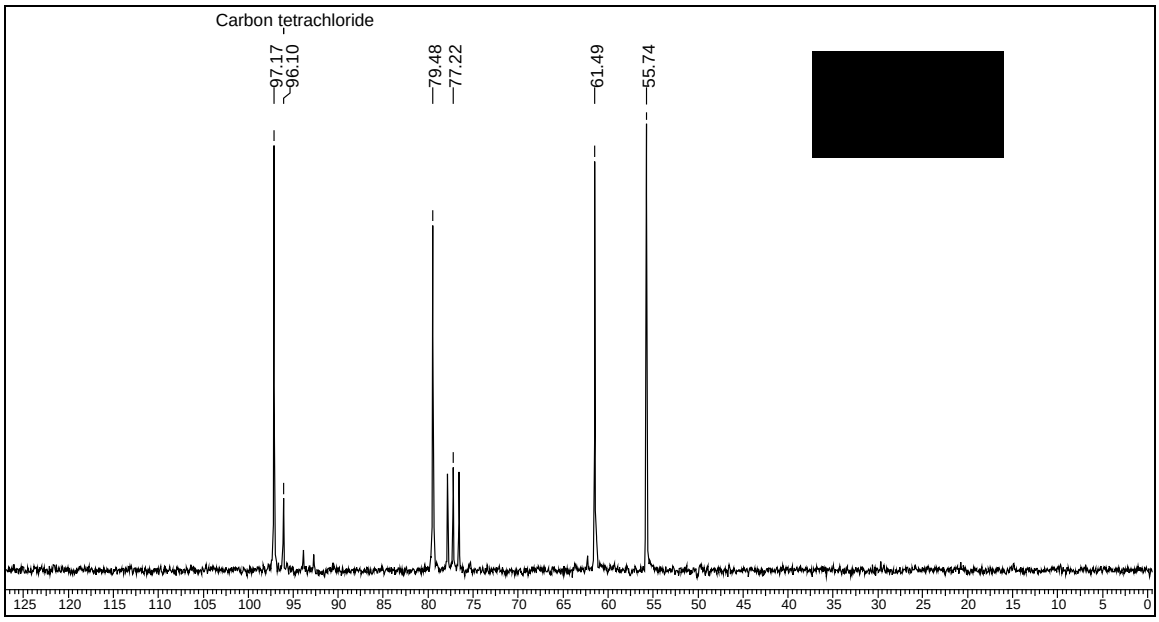


^{1}H NMR spectrum of compound **39** (200mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **39** (50mHz, $CDCl_3$)

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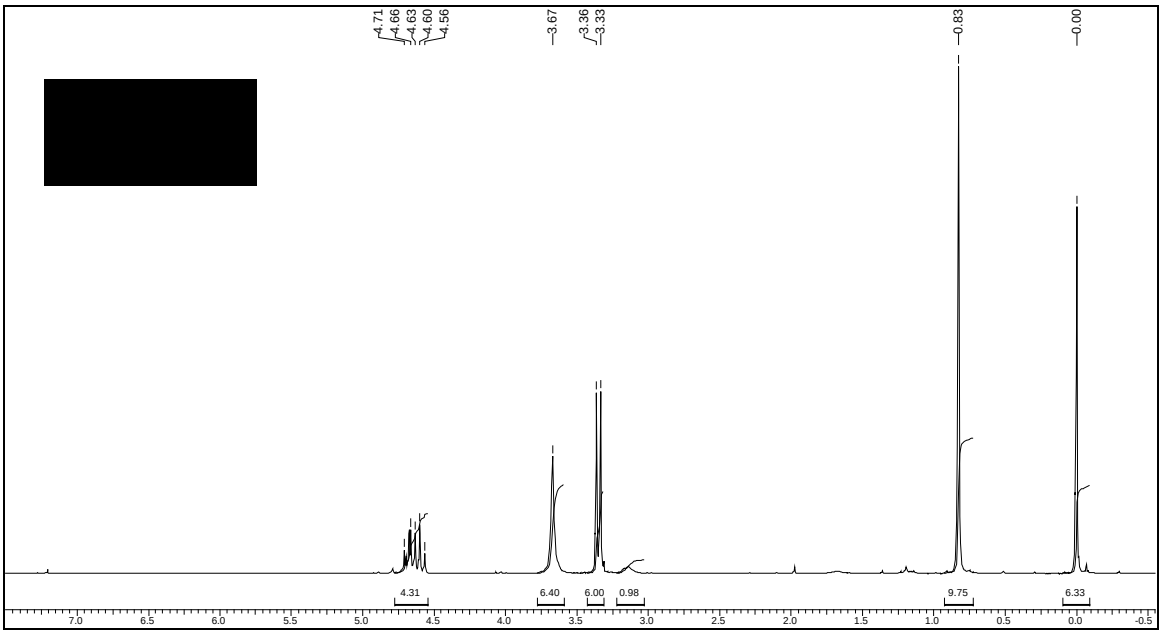
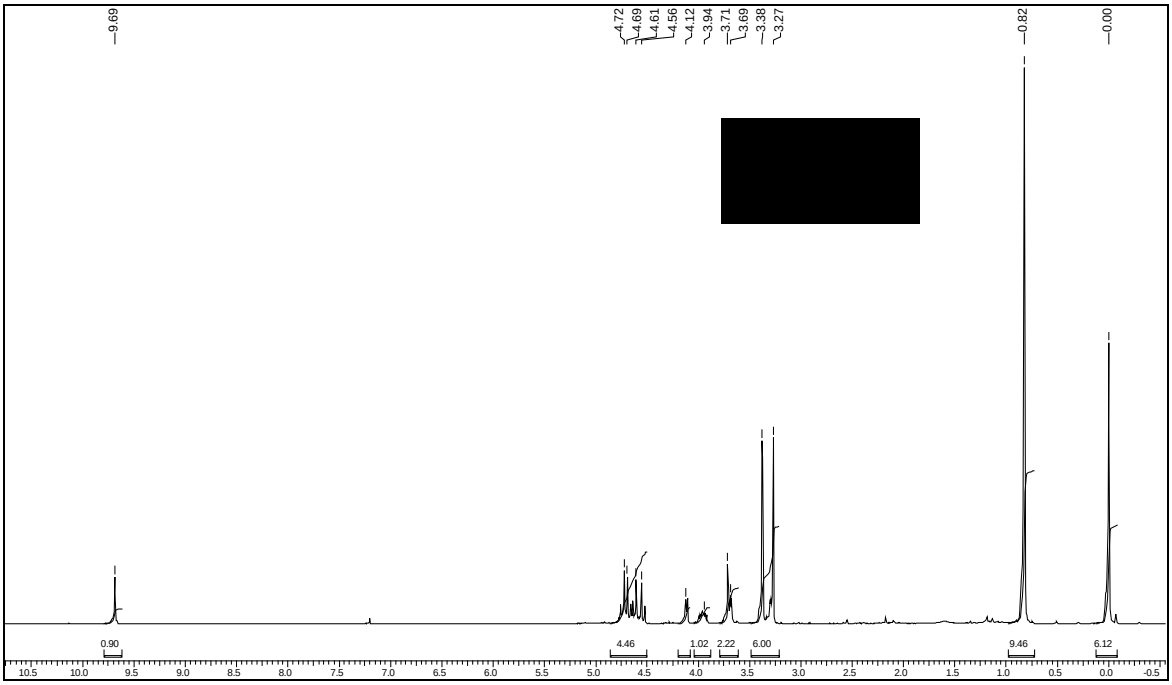


^{1}H NMR spectrum of compound **40** (200mHz, $CDCl_3$)



^{1}H NMR spectrum of compound **41** (200mHz, $CDCl_3$)

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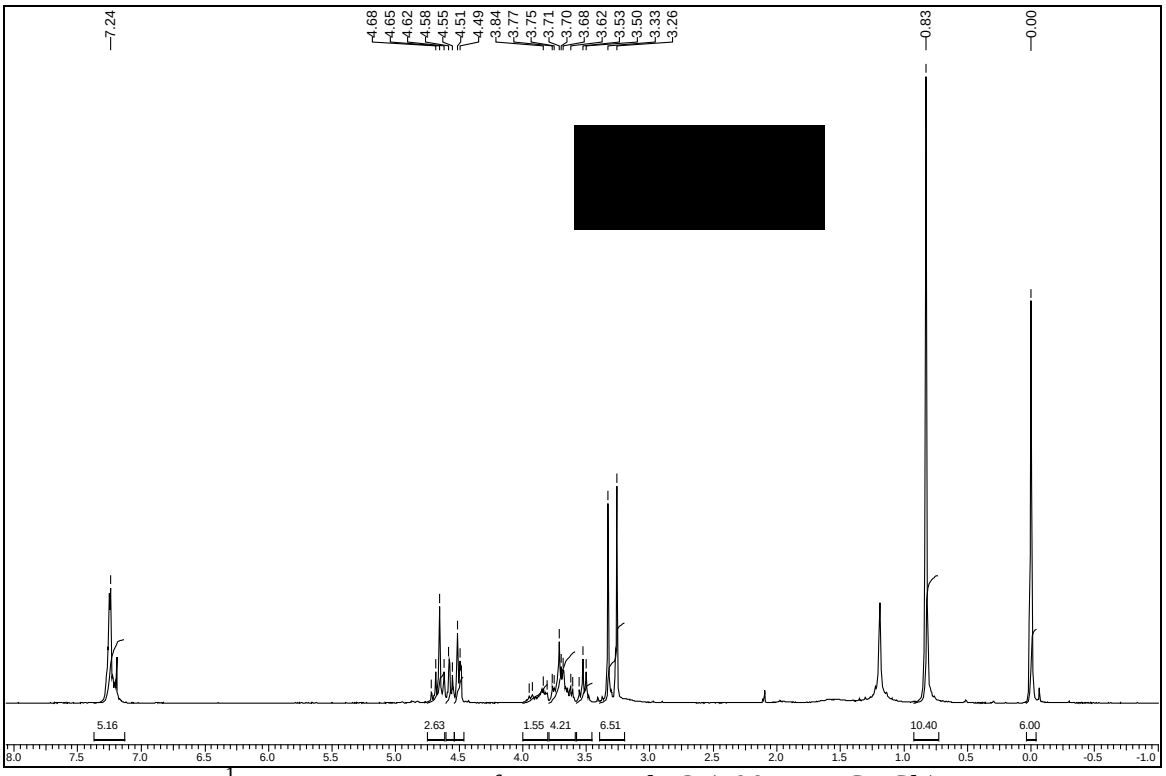
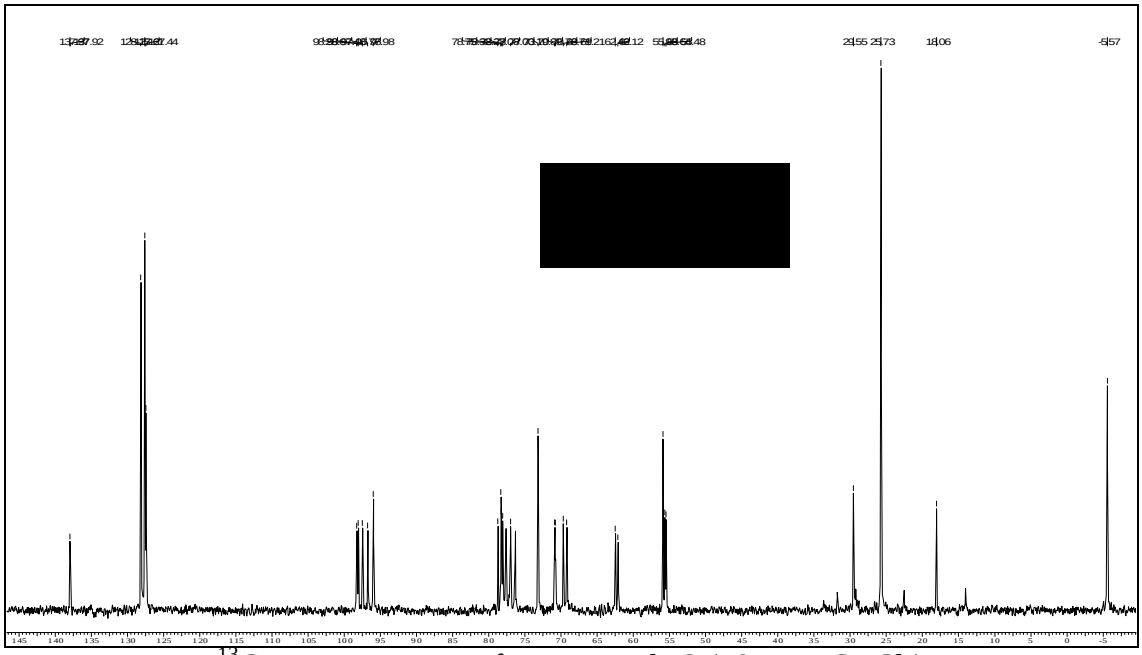


^{1}H NMR spectrum of compound **42** (200mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **42** (50mHz, $CDCl_3$)

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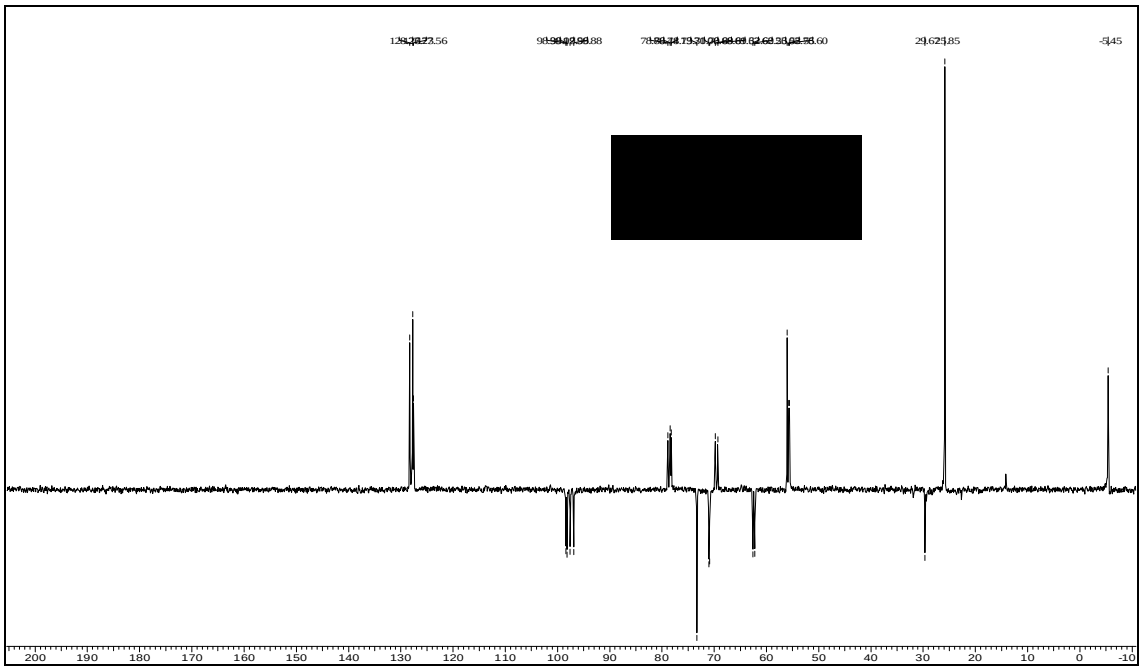
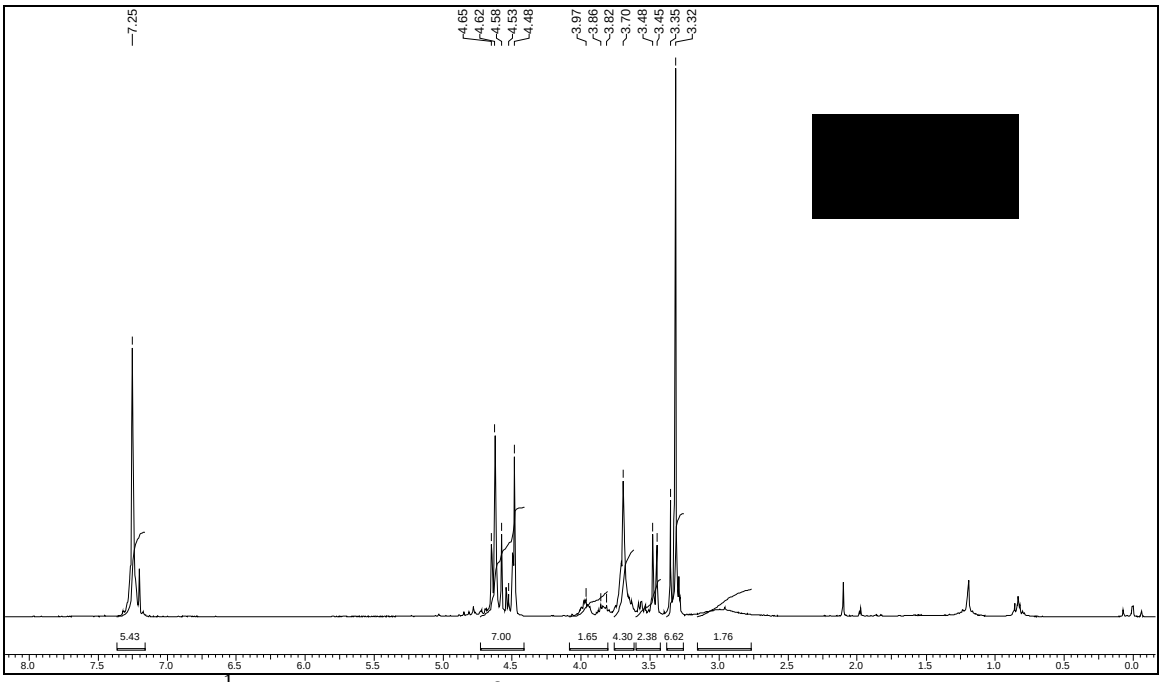


DEPT NMR spectrum of compound **42** (50mHz, $CDCl_3$)



^{1}H NMR spectrum of compound **43** (200mHz, $CDCl_3$)

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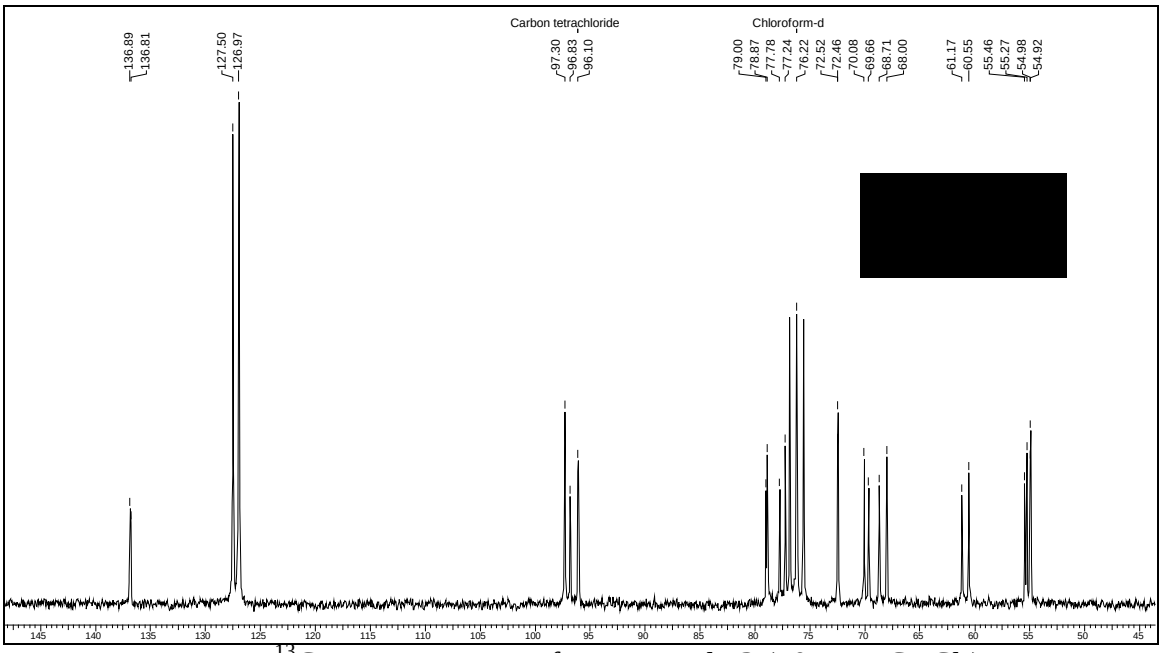
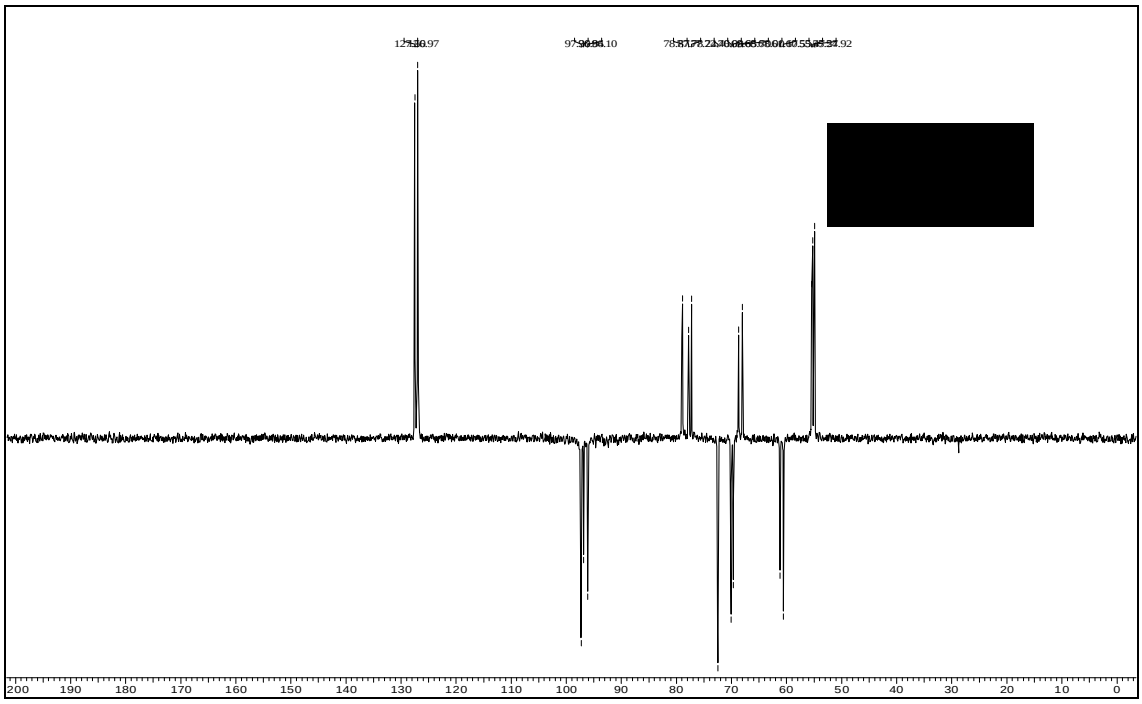


^{13}C NMR spectrum of compound **43** (50mHz, $CDCl_3$)



DEPT NMR spectrum of compound **43** (50mHz, $CDCl_3$)

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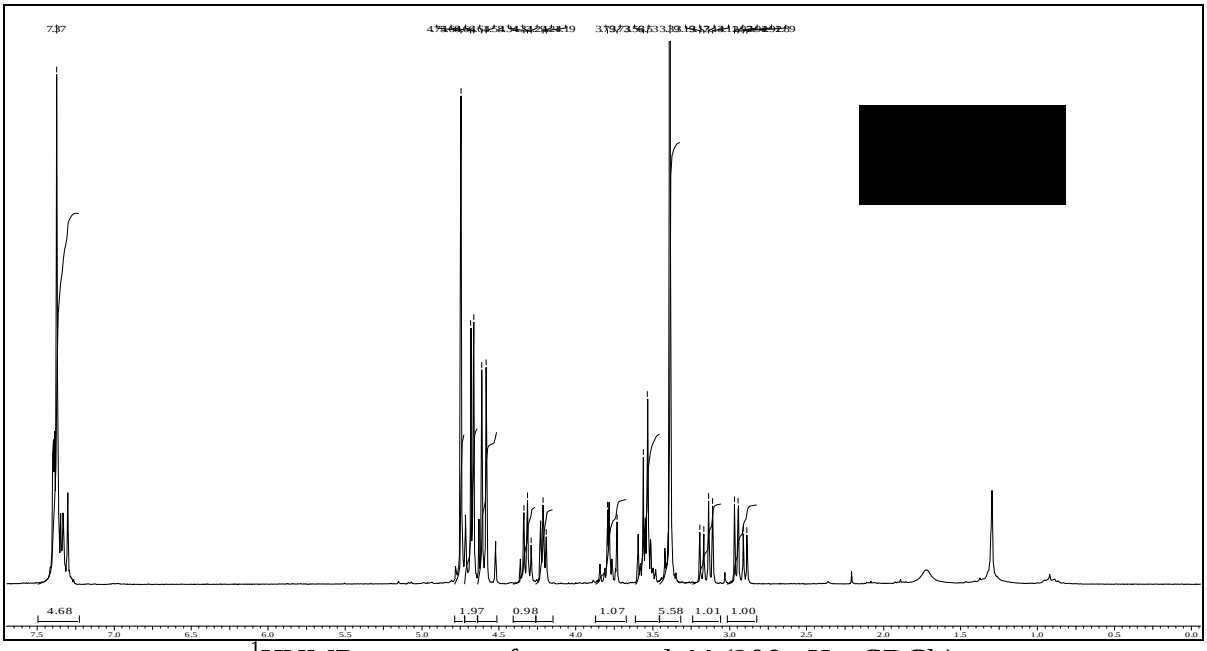
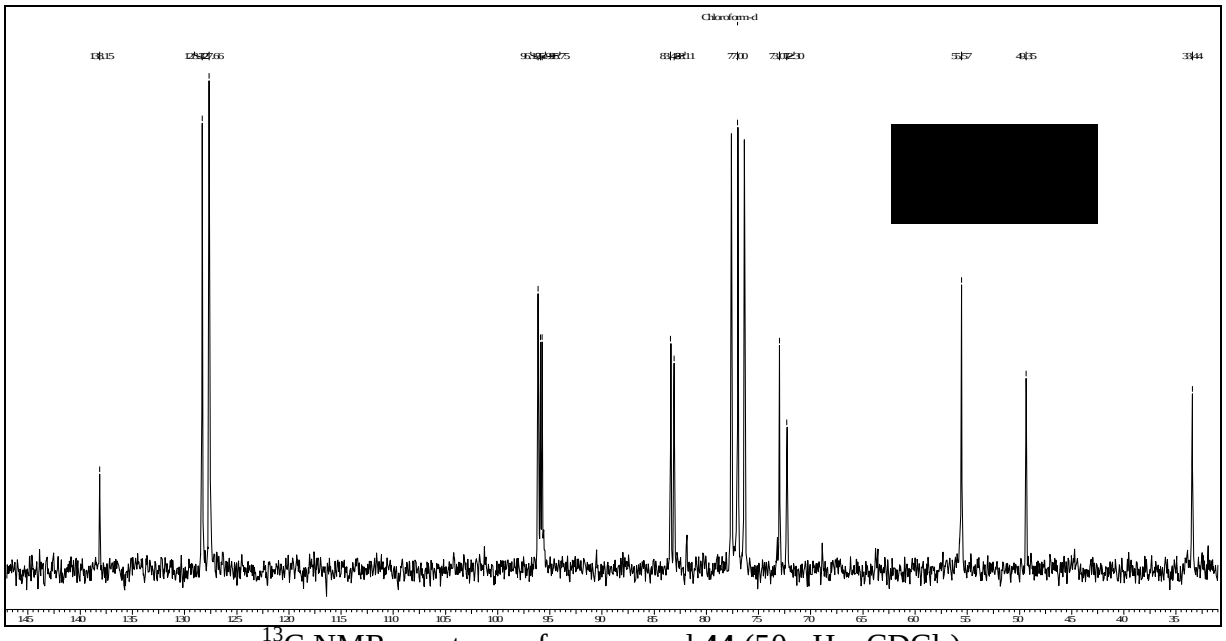


^{1}HNMR spectrum of compound **44** (200mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **44** (50mHz, $CDCl_3$)

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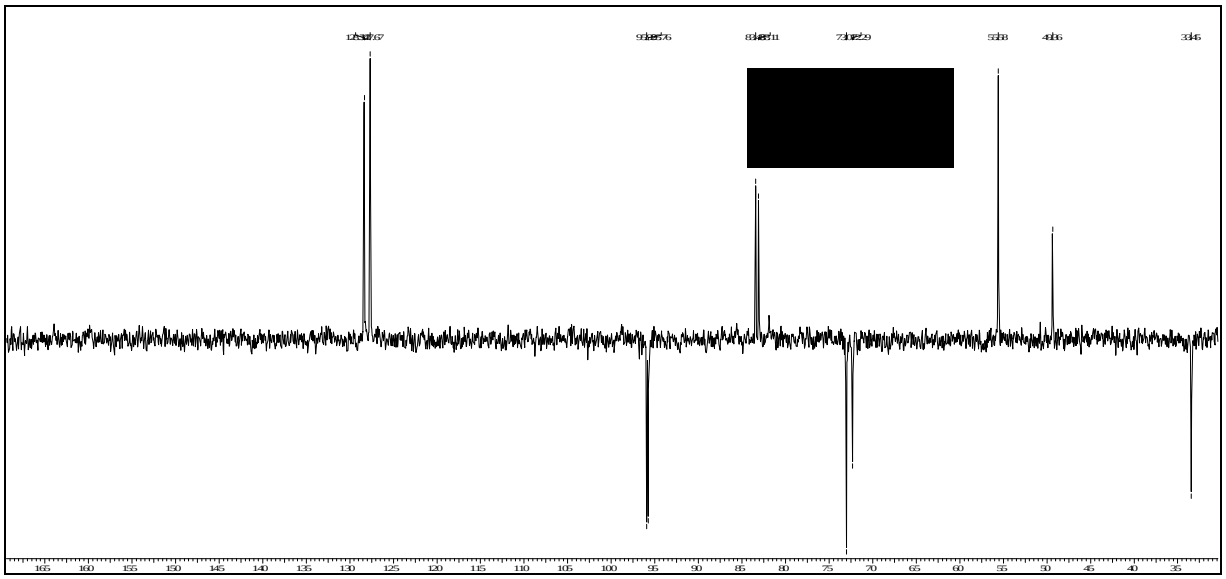
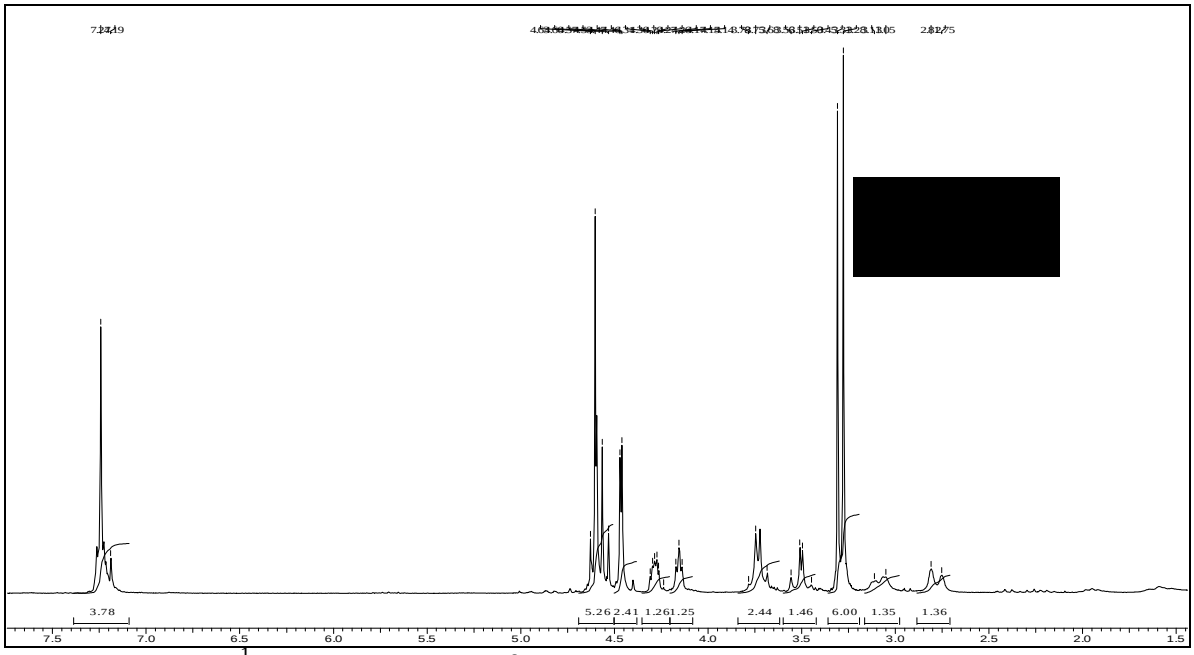


DEPT NMR spectrum of compound **44** (50 mHz, $CDCl_3$)



^{1}H NMR spectrum of compound **45** (200mHz, $CDCl_3$)

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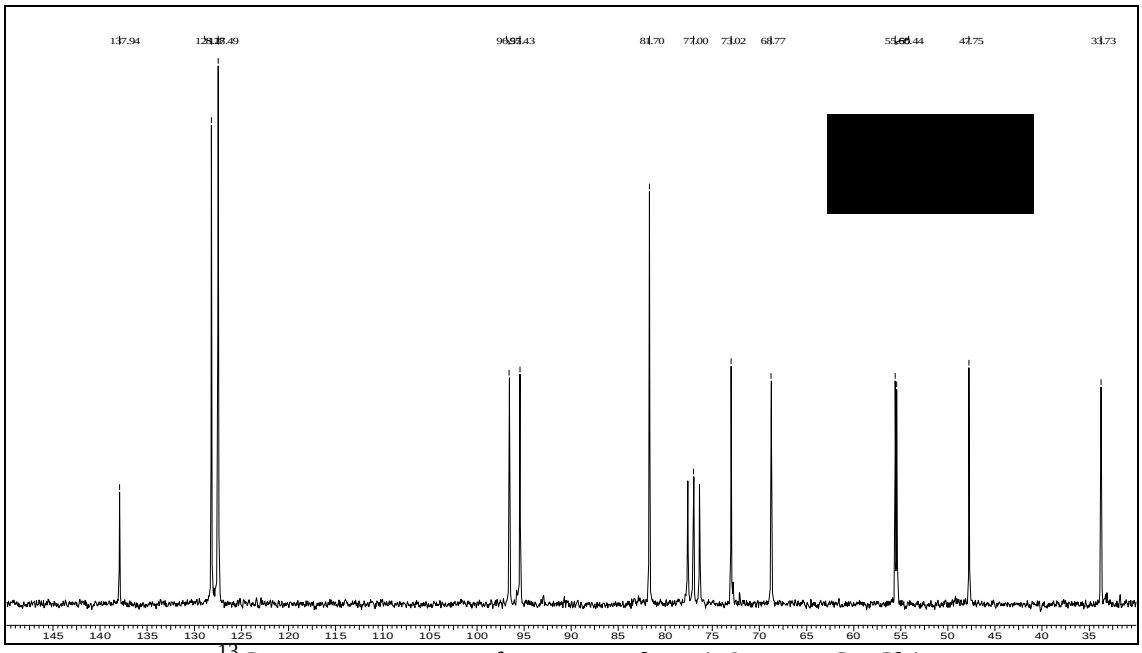
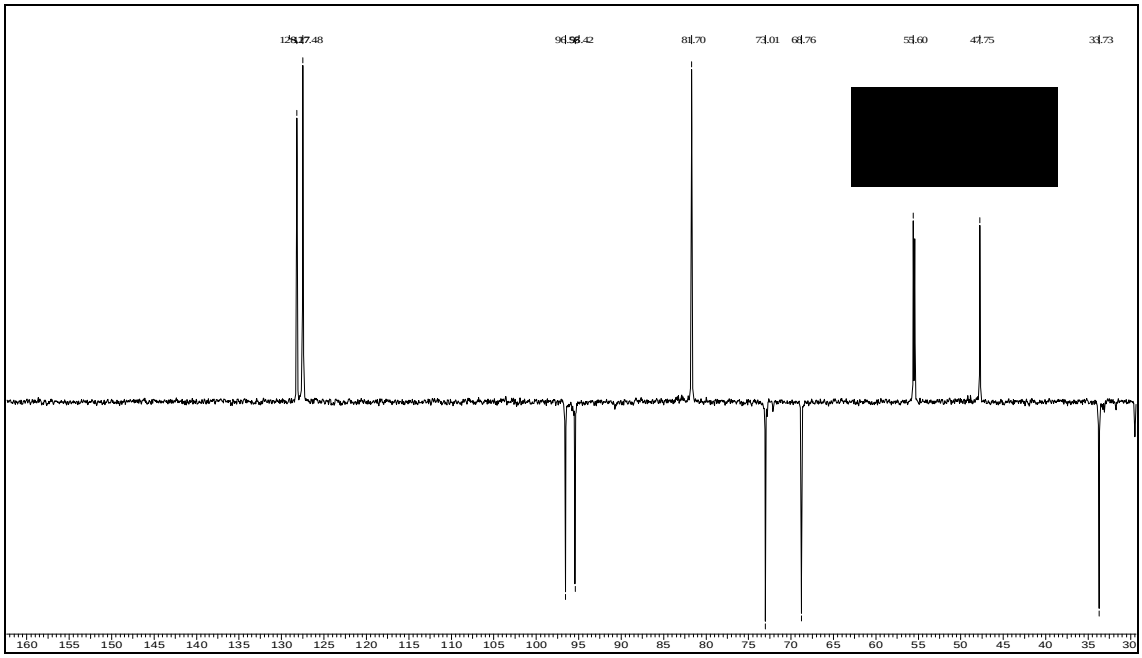


^{13}C NMR spectrum of compound **45** (50 mHz, $CDCl_3$)



DEPT NMR spectrum of compound **45** (50 mHz, $CDCl_3$)

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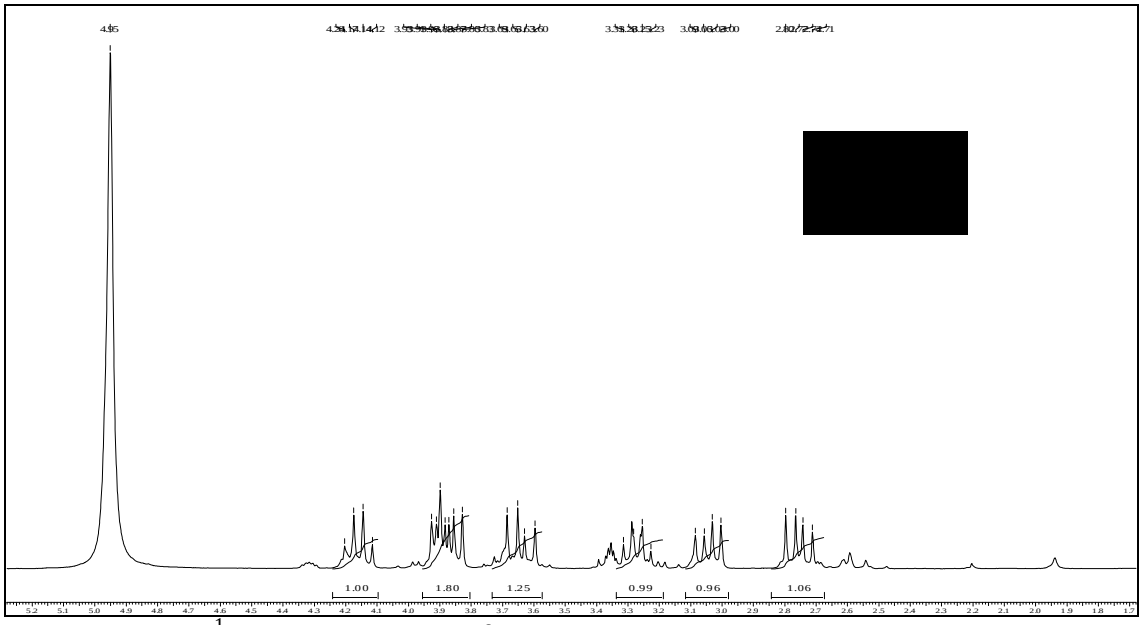
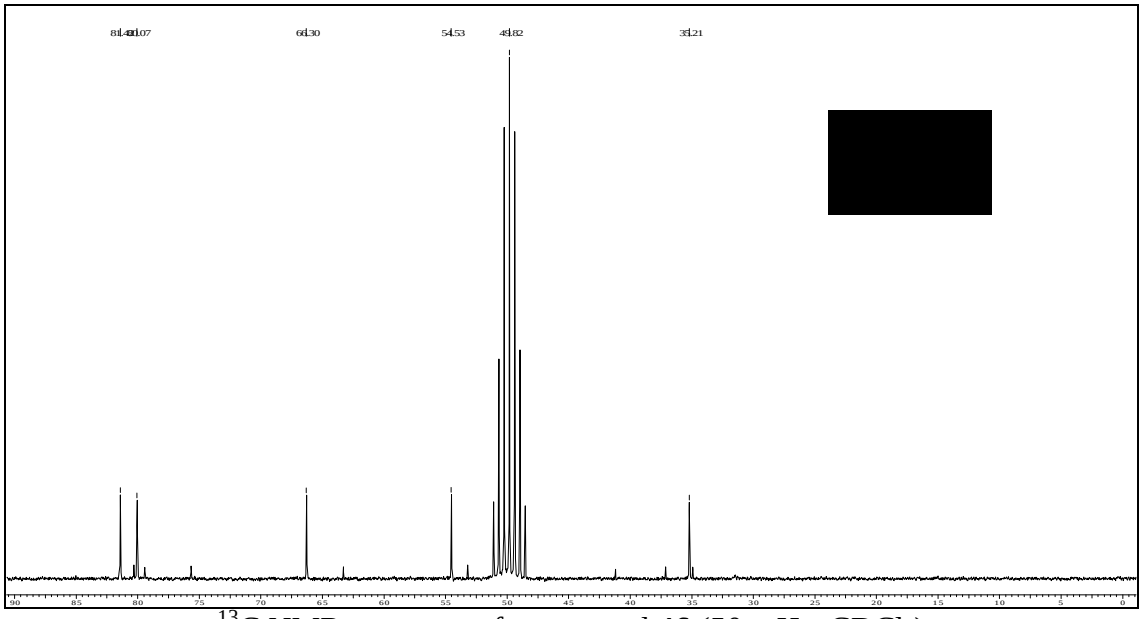


^{1}H NMR spectrum of compound **46** (200mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **46** (50 mHz, $CDCl_3$)

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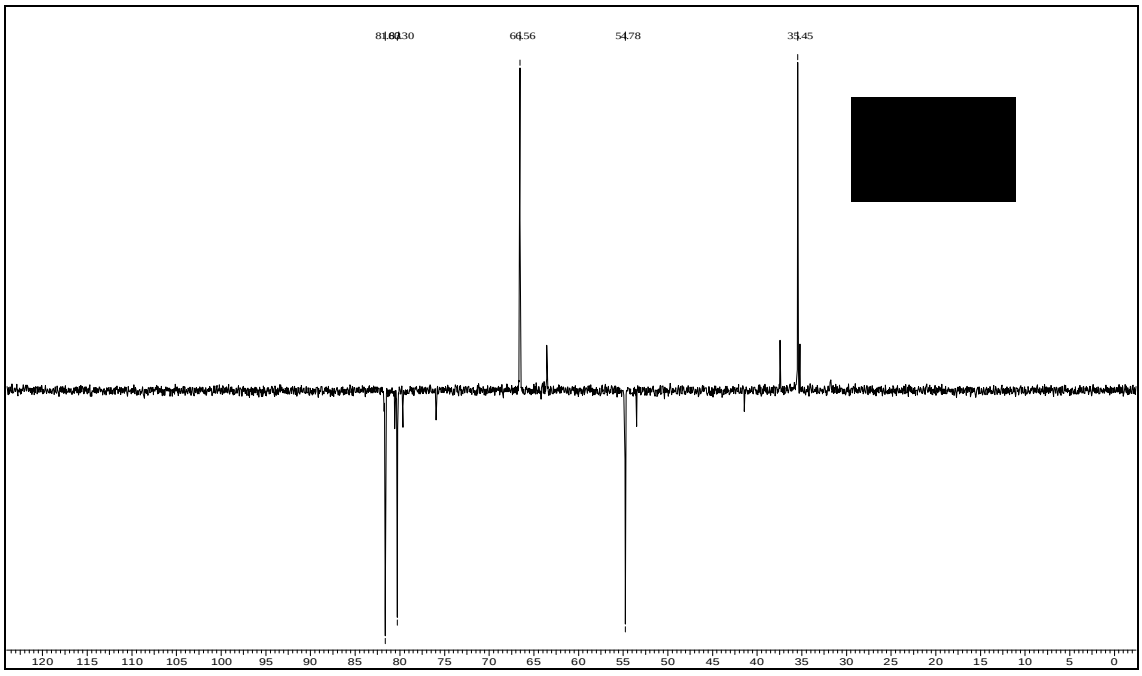
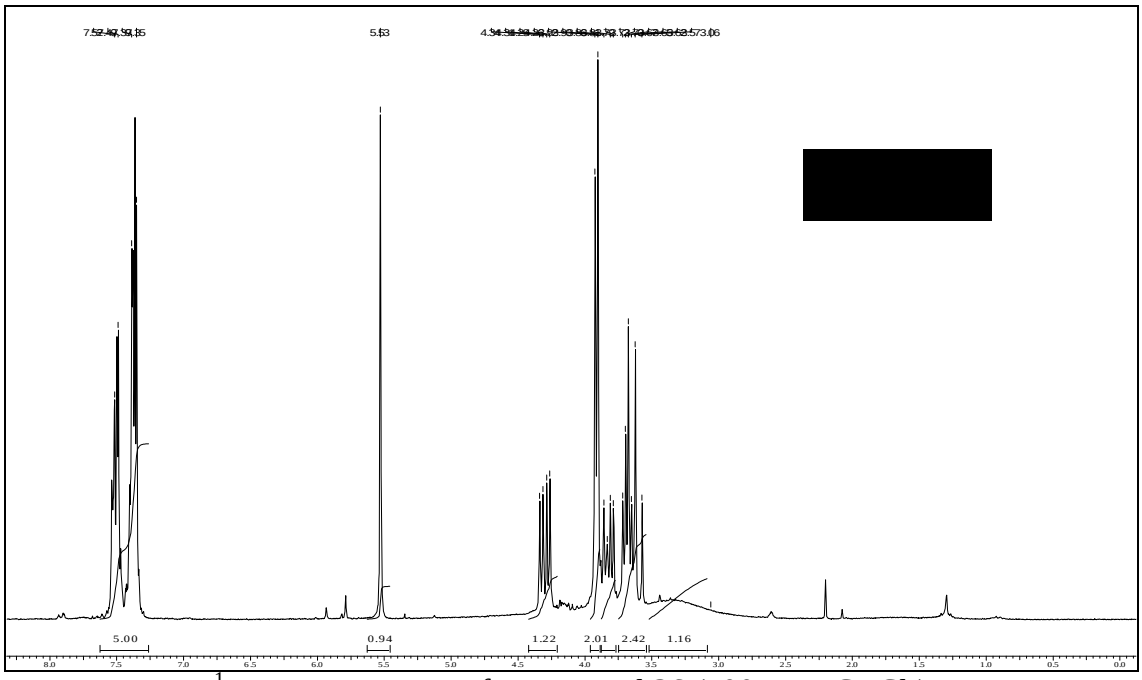


DEPT NMR spectrum of compound **46** (50 mHz, $CDCl_3$)



^{1}H NMR spectrum of compound **26** (200mHz, $CDCl_3$)

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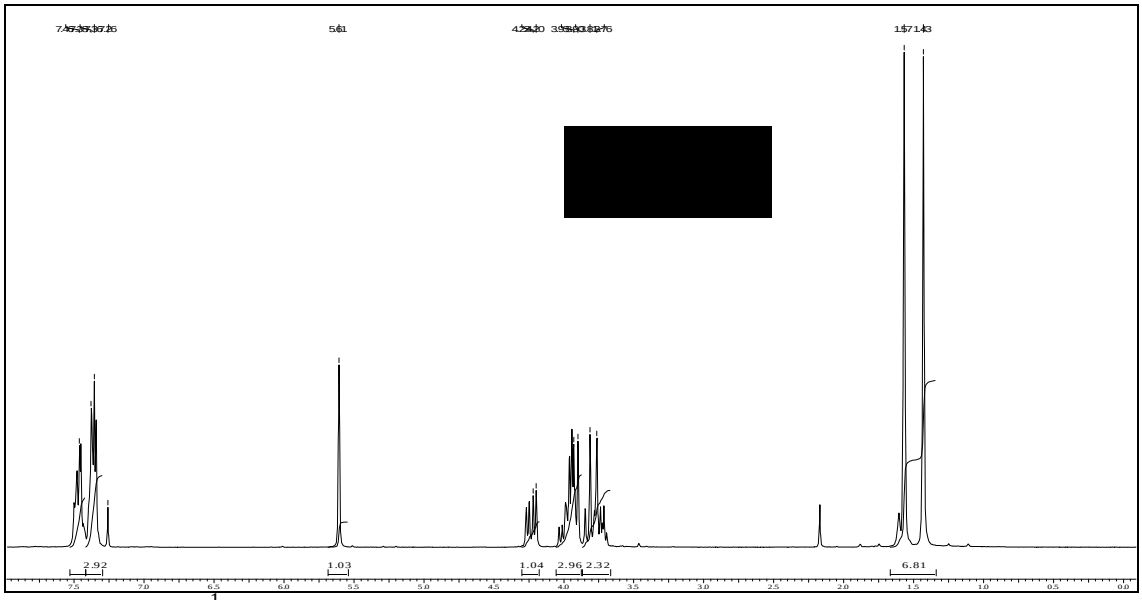
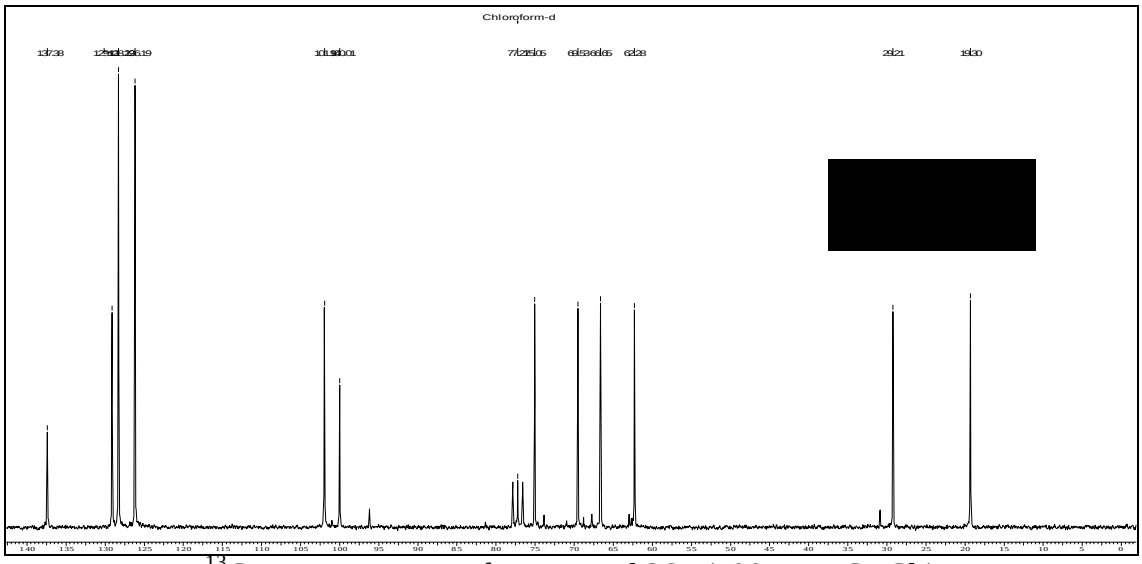


^{1}H NMR spectrum of compound **26a** (200mHz, $CDCl_3$)



^{13}C NMR spectrum of compound **26a** (200mHz, $CDCl_3$)

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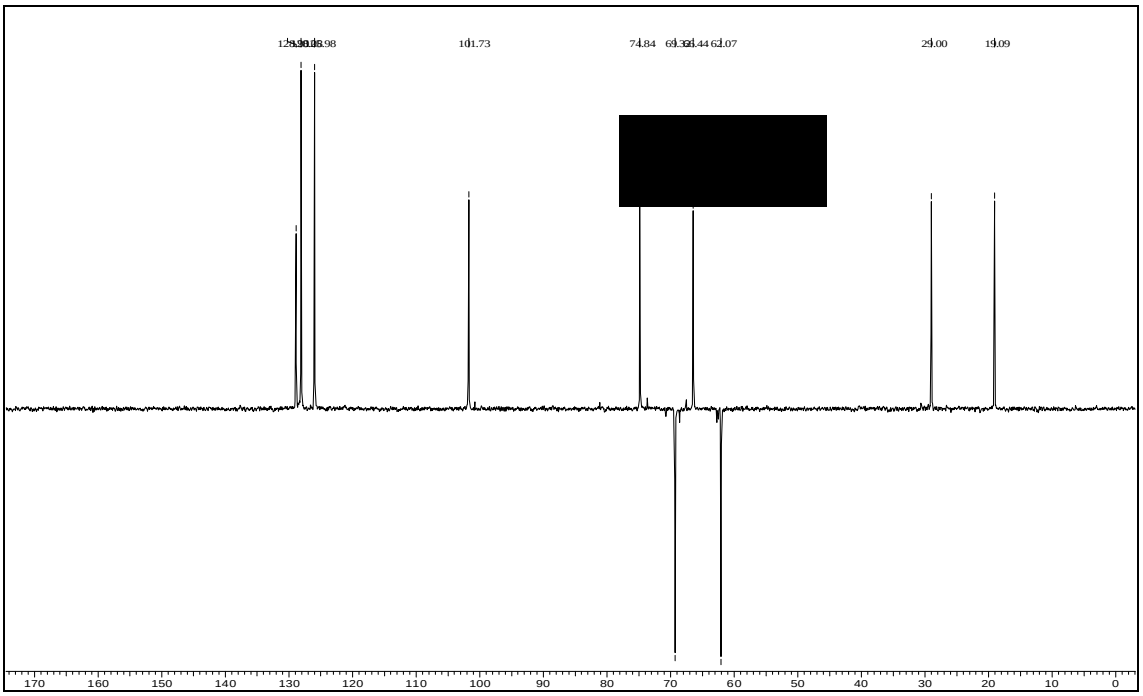

DEPT NMR spectrum of compound **26a** (200mHz, $CDCl_3$)

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2.1.9 References:

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CHAPTER-II

SECTION-II

$(NH_4)_2Ce(NO_3)_6$ (CAN) / NaI as an Efficient Reagent in Iodocyclisations: Synthesis of Wine lactone.

PART-I

$(NH_4)_2Ce(NO_3)_6$ (CAN) / NaI as an Efficient Reagent in Iodocyclisations.

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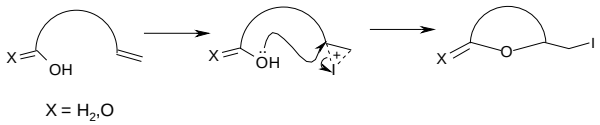
2.2.1.1 Introduction

Iodocyclisations are the reactions of great importance in organic synthesis as demonstrated in Corey's prostaglandin[1] synthesis as well as in the total synthesis of tumor inhibitors eg; Vernolepin and vernomenin[2], Vitamin D_2 and D_3[3] syntheses and the synthesis of prostacyclin.[4]

Different reagents and conditions have been adopted for the efficient conversion of β, γ or γ, δ unsaturated acid/ alcohol in to the corresponding lactones/ethers as shown by various methods, a few of them to mention are one by Bougault[5] a conventional protocol for iodolactonisations using I_2 which albeit easier to handle requires long reaction times and the other methods like cyanogen iodide,[6] iodosuccinimide,[7] N-I(collidine)2+ClO4-,[8] $Na_2S_2O_8$[9] , $FeCl_3$/NaI[10] etc. Most of these protocols use either substantial quantities of the reagents or require extended reaction times and high temperatures. A reaction accomplished with comparable efficiency and short reaction times is an advantage to the organic chemist. Ceric ammonium nitrate is well known for its oxidizing properties.[11a,b,c,d,e] It was decided to exploit the propensity of $(NH_4)_2Ce(NO_3)_6$ as an oxidant in combination with NaI to effect the iodoetherifications and iodolactonisations at room temperature as shown in scheme-1



Scheme-1:

2.2.1.2 Earlier Methods

The following section deals with the reported methods of iodolactonisation/iodoetherification.

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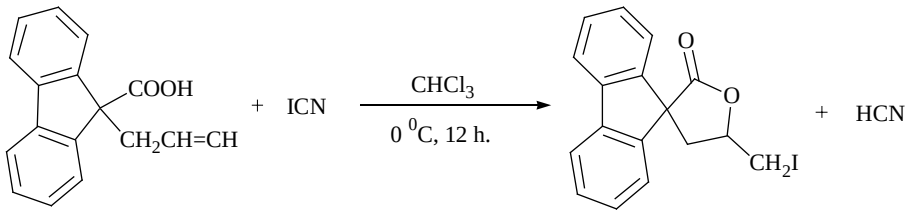
ICN in iodolactonisation :[6]

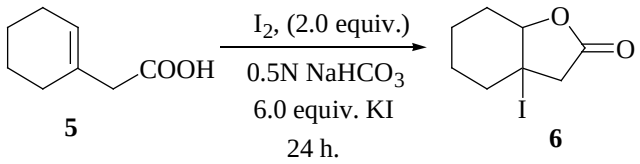
Richard, T. A; Kenneth L. (*J. Am. Chem. Soc.*, **1953**, 1048.)



Scheme 2:

Cyanogen iodide reacts with γ, δ-unsaturated acids (2, 2-diphenylpenten-4-oic acid, 9-allyl-9-fluorocarboxylic acid and penten-4-oic acid) to furnish corresponding δ-iodo-γ-pentanolactone.(scheme 2.)

I_2 and KI in the presence of $NaHCO_3$:[6b] **Tamelen V. and Shamma, M**. (*J. Am. Chem. Soc.*, **1954**, 2315.)



Scheme 3:

Tamelen *et. al.*[6b] in their study of iodolactonisation treated certain β, γ and γ, δ-unsaturated acids to yield five-membered iodolactone on treatment with iodine-potassium iodide in $NaHCO_3$ solution at room temperature. It is pertinent to note that both I_2 as well as KI are used in excess.(scheme 3.)

Iodoetherification using I_2 :[6c] **Norman, W**. (*Tetrahedron Letters*, **1977**, 2805.)

The author used I_2 for iodoeherification as the key step for the synthesis of prostaglandin (5, 6-didehydro-9-deoxy-6, 9 α-epoxy prostaglandin).(scheme 4.)

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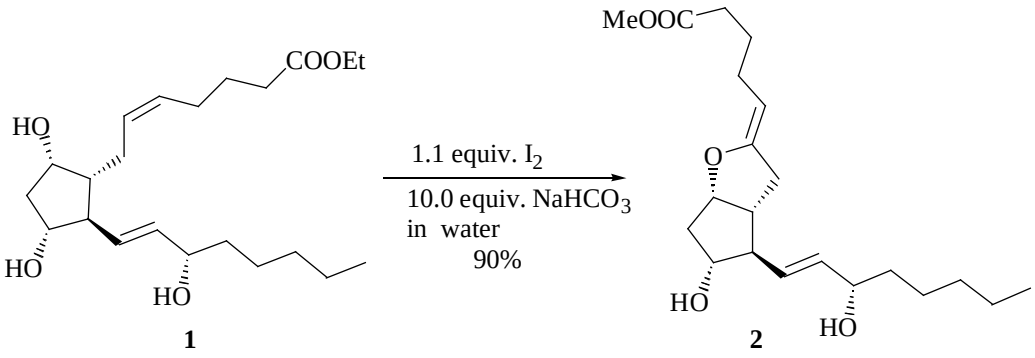
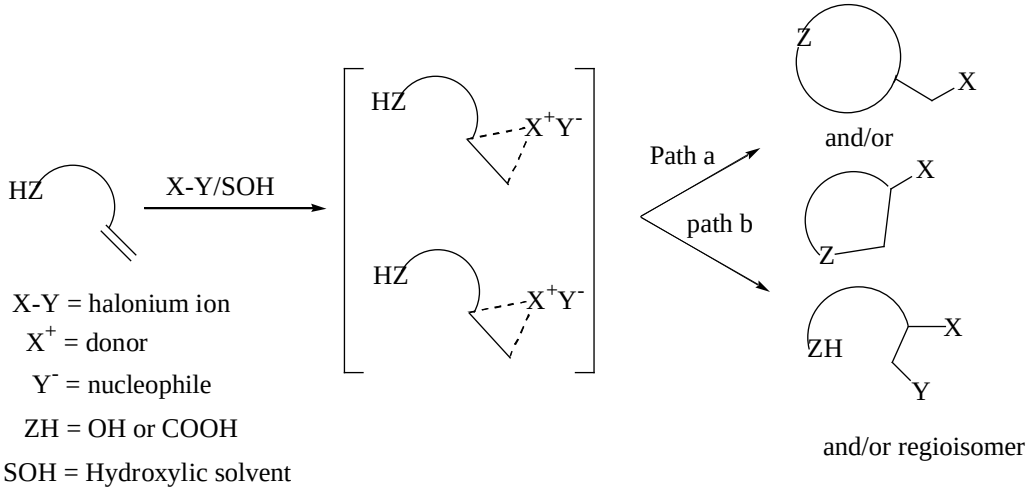


Scheme 4

I(Collidine)$_2^+$ClO$_4^-$:[8] Robert, D. E; Joseph, W. M; Herman, S.(*Synthesis*, **1988**, 862.)



Scheme 5

I(Collidine)$_2^+$ClO$_4$ was used to react with unsaturated alcohols and carboxylic acids in dichloromethane at ambient temperature to furnish three to seven-membered ring

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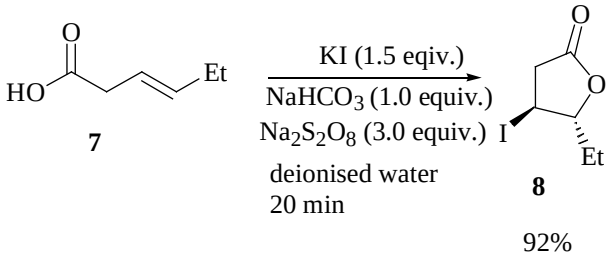
iodoether and four-to seven-membered-ring iodo lactones, respectively, in moderate yields generally with high regioselectivity.(scheme 5.)

$Na_2S_2O_8$ and KI :[9] **April, C. R; Robert, C. M. April; M. S**. *Synlett*, (**1993**, 899.)



Scheme 6

In this study it was shown that oxidation of KI with sodium persulphate in the presence of salts of β, γ-and γ, δ-unsaturated carboxylic acids affords γ-lactone in high yields at ambient temperature and with short reaction times.(scheme 6.)

2.2.1.3 Present Work: Results and Discussion

A reaction accomplished with comparable efficiency and short reaction times is an advantage to the organic chemist. Ceric ammonium nitrate is well known for its oxidizing properties.[11a,b,c,d,e] It was decided to exploit the propensity of $(NH_4)_2Ce(NO_3)_6$ as an oxidant in combination with NaI to effect the iodoetherifications and iodolactonisations at room temperature

Compound 1 (table-1) was taken as the substrate to test the hypothesis. Thus, to alcohol **1** (as a mixture of *endo:exo* isomers in the ratio of 3:1) (1.97 mmol, 1eq) in CH_3CN (4ml) was added the NaI (2eq) and $(NH_4)_2Ce(NO_3)_6$ (2eq) and stirred for 45 min. After the completion of the reaction as per tlc, ethylacetate was added to the reaction mixture and the reaction mixture was subsequently washed with water, saturated Na_2SO_3 solution and then with saturated $NaHCO_3$ solution. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the residue thus obtained was purified using column chromatography (SiO_2) to furnish the corrresponding iodoether exclusively from *endo* isomer whereas the *exo* isomer remained unreacted and the iodoether was obtained in excellent yield (based on *endo* isomer). Similarly, a mixture of the *endo* and

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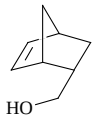
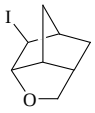
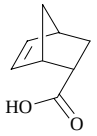
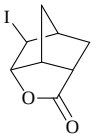
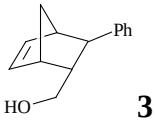
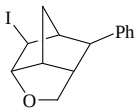
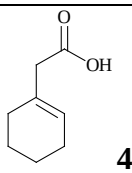
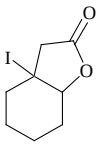
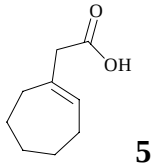
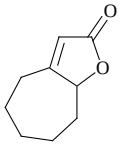
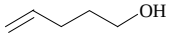
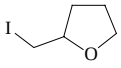
exo acids (entry-2) was also subjected and excellent yield of corresponding iodolactone was obtained.

A variety of olefinic alcohols and acids were subjected to the iodocyclisations and the corresponding iodoethers and iodolactones were obtained in moderate to excellent yields. The results of the present study are summarized in table-1. It is interesting to note that when olefin acid (entry-5) when subjected to the present protocol the corresponding iodolactone could not be isolated, instead butenolide **13** was obtained. Formation of butenolide may be attributed to the elimination of HI from the corresponding iodolactone under the reaction conditions.

entry	Substrate	Product	% Yield	Time (min)
1.	 **1**	 **9**	96	45
2.	 **2**	 **10**	89	15
3.	 **3**	 **11**	65	45
4.	 **4**	 **12**	73	30
5.	 **5**	 **13**	33	45
6.	 **6**	 **14**	35	30

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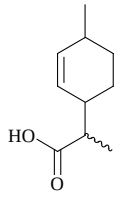
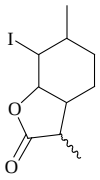
7.	 **8**	 **16**	47	30

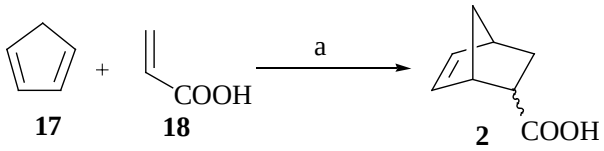
Having established the efficacy and genarality, we have demonstrated the utility of the present protocol by formal synthesis of wine lactone,[12] which is presented in next section. Thus the acid **8** (as a mixture of isomers) when subjected to iodolactonisation furnished iodolactones **16** as a mixture of diastereomers in 9:5 ratio.

2.2.1.4 Conclusion: In conclusion it has been demonstrated CAN/NaI as an efficient reagent to effect iodolactonisation as well as iodoetherification at room temperature requiring short reaction time. The mildness, efficiency, generality and operational simplicity of the present protocol would be a useful addition to the repertoire of synthetic chemists.

2.2.1.5 PREPARATION OF SUBSTRATES:

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2):

The compound 2 was prepared from a reaction of cyclopentadiene 1 and acrylic acid 2. The reaction mixture was refluxed for 4 hrs. in acetone to furnish bicyclo[2.2.1] hept-5-ene-2-carboxylic acid 3 in 85% yield, (*endo*:*exo*=3:1).



17 **18** **2**

Scheme 4. a) acetone, reflux, 4h, 85%

2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene (3):

2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene **3** was formed as a mixture of *endo* and *exo* isomer (3:1) from 3-phenyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **20** (a

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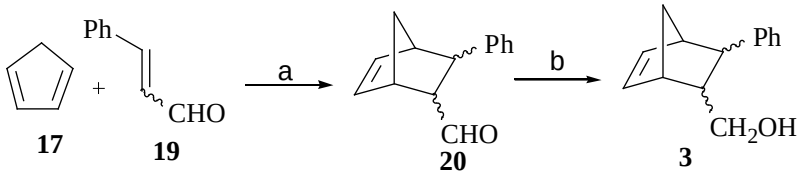
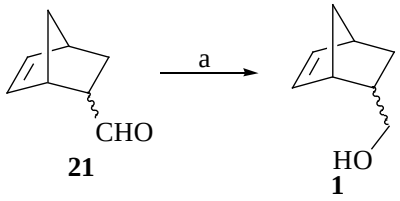
Diels-Alder adduct of cyclopentadiene **17** and cinnamaldehyde **19**) by reducing it with $NaBH_4$ in 87% yield.



Scheme 4. a) acetone, reflux, 4h b) NaBH4 Methanol, 87% over two steps

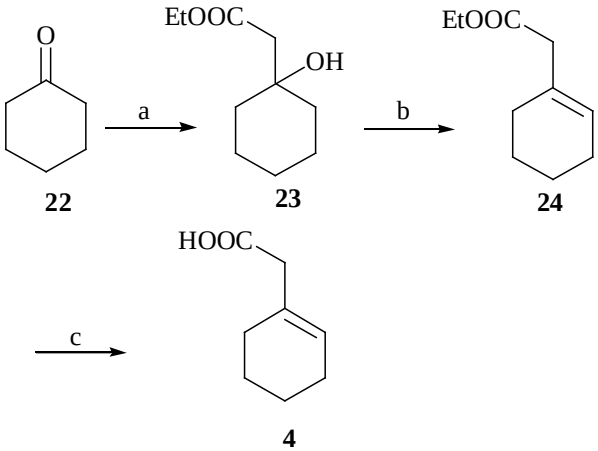
2-Hydroxy methyl bicyclo[2.2.1]hept-5-ene 1:

It was prepared as a mixture of *endo*:*exo* (3:1) from bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **21** (a condensation product of cyclopentadiene **17** and acrolein) by reducing it with $NaBH_4$ as shown in the following scheme 5.



Scheme 5. a) $NaBH_4$, AcOH; 5 min; rt. 93%

2-(1-cyclohexenyl) acetic acid 14:



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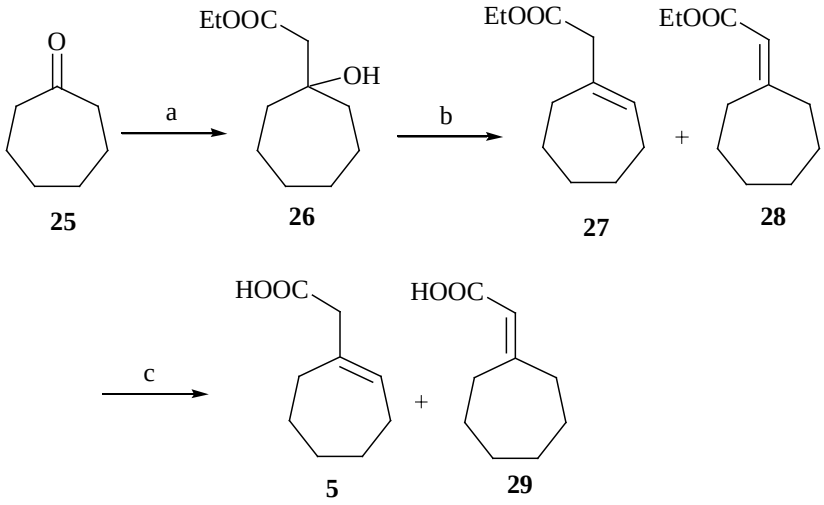
Scheme 6. Reagents and conditions: a) Zn; $BrCH_2COOEt$; benzene; reflux; 6h. 66% b) $SOCl_2$; Pyridine, 0 ºC 30 min.; 87%. c) KOH; MeOH:Water(3:1); 98%.

The β, γ-unsaturated acid **4** was prepared by the Reformatsky reaction of ethyl bromo acetate on cyclohexanone **22** by refluxing for 6 hrs. to furnish hydroxy compound **23** in 66% yield. The compound **23** on dehydration using thionyl chloride and pyridine as dehydrating agent furnished alkene **24** in 87% yield. The ester group of **24** was then hydrolysed using 3 eq. of KOH in $MeOH/H_2O$ system to furnish 2-(1-cyclohexenyl) acetic acid **4** in 100% yield.

2-(1-cycloheptenyl) acetic acid 18a:

Cycloheptanone 2**5** on Reformatasky reaction with ethyl bromo acetate and zinc provided hydroxy compound **26** in 60% yield. The compound **26** on dehydration using thionyl chloride and pyridine to furnished a mixture of α, β- **28** and β, γ-unsaturated esters **27** in 80% yield. The mixture of esters without separation was subjected to hydrolysis using 3 eq. of KOH in $MeOH/H_2O$ system to furnish a mixture of acids **5** and **29** (4:1) respectively.



Scheme 6. Reagents and conditions: a) Zn; $BrCH_2COOEt$; benzene; reflux; 6h. 60% b) $SOCl_2$; Pyridine, 0 ºC 30 min.; 80%. c) KOH; MeOH:Water(3:1); 88%.

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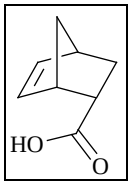
2.2.1.6 Experimental:

General Procedure for iodoetherification, iodolactonisation and butenolide formation: To a 2 mmol of β, γ-unsaturated alcohol or acid in 25 mL of acetonitrile was added 4 mmol. of NaI followed by 4 mmol. of Cericammonium nitrate in 10 ml of water. The reaction mixture was stirred for 15-120 min. Ethylacetate was added to the reaction mixture and the reaction mixture was subsequently washed with water, saturated Na_2SO_3 solution and then with saturated $NaHCO_3$ solution. The organic solvent was dried over anhydrous Na_2SO_4, filtered and was then removed on rotary evaporator under reduced pressure and the residue thus obtained was purified by column chromatography (SiO_2) to furnish the corresponding iodoether or iodolactone (or butenolide) respectively.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2):



To a 3.67g (55.56 mmol) of freshly cracked cyclopentadiene **17** in 25 ml. of acetone was added, 2g (27.78 mmol) of acrylic acid **18**. The solution was refluxed for 4 hrs. After completion of reaction the solution was concentrated, which on column purification furnished 3.26g of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **2** as mixture of *endo* and *exo* isomer (*endo* being the major one) in 85% yield.

Mol. Formula	: $C_8H_{10}O_2$;
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	2500-3700 (broad band), 1699, 1416, 1276.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.2-1.6 (m, 3H), 1.8-2.0 (m, 1H), 2.75-3.05 (m, 2H), 3.25 (br s, 1H). 6.0 (m, 1H olefinic), 6.2 (m, 1H olefinic).

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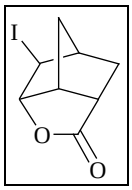
9-Iodo-5-oxa tricyclo[4.2.1.0^{3,7}]nonan-4-one (9):



To a 1g (7.25 mmol) of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **2** in 20 ml of acetonitrile, was added 2.17g (14.5 mmol) of NaI followed by was added 2.34g (14.5 mmol) of cericammonium nitrate in 10 mL of water. The reaction mixture was allowed to stirr for 15 min. After completion, ethyl acetate 50 mL was added to the reaction mixture. and the reaction mixture was subsequently washed with water 1x25 mL, saturated Na_2SO_3 solution (2x25 mL) and then with saturated $NaHCO_3$ solution (1x25 mL). The organic solvent was dried over anhydrous Na_2SO_4, filtered and the solvent was removed on rotary evaporator under reduced pressure and the residue thus obtained was purified by column chromatography (SiO_2) to furnish 1.64g of 9-iodo-5-oxa tricyclo[4.2.1.0^{3,7}]nonan-4-one 21 in 86% yield.

Yield	: 1.64 g, (86%)
Mol. Formula	: $C_8H_9IO_2$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	1735, 1160, 1060.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.6-1.95 (m, 2H), 1.95-2.2 (m, 1H), 2.35 (d, 1H J=16 Hz) 2.5 (dd, 1H J=16Hz, J=4Hz), 2.7 (br s, 1H), 3.17 (m, 1H), 3.9 (m, 1H), 5.17 (m, 1H).
^{13}C-NMR ($CDCl_3$, 50MHz):	: 30.2 (d), 34.09 (t), 36.85 (d), 37 (t), 46.41 (d), 46.42 (d), 88.38 (d), 178.7 (s).
Mass (m/z)	: 264, 167, 137, 127, 91, 79, 66.

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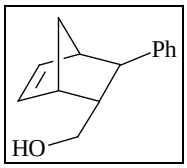
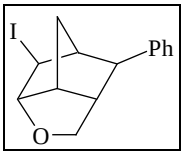
2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene (3):



To a 1.0g (5 mmol) ice cold solution of 3-phenyl bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **5** in 10 ml of acetic acid, was added 0.575g (15.0 mmol.) of $NaBH_4$ in small portions with continuous stirring. Reaction mixture was stirred for 10 min. After the completion of reaction (by tlc), the reaction mixture was neutralized by adding saturated solution of $NaHCO_3$. The organic compound was isolated using 3x25 ml portions of EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 0.88g of 2-hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene **3** in 87% yield.

Yield	: 0.88 g, (87%)
Mol. Formula	: $C_8H_9IO_2$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 3200, 3010, 1631, 1590, 1470.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.6 (m, 1H), 1.75-2.0 (m, 2H), 2.1 (m, 1H), 2.6 (m, 1H), 2.9 (br s, 1H), 3.06 (br s, 1H), 3.35 (m, 1H), 3.65 (m, 1H), 6.15 (m, 1H olefin), 6.35 (m, 1H olefin), 7.05-7.5 (m, 5H aromatic).

2-Iodo-9-phenyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane 22:



Yield	: 0.19 g, (65%)

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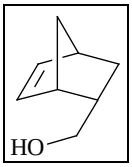
Mol. Formula	: $C_{14}H_{15}IO$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 3057, 2971, 2875, 1494, 1293, 1249, 1218, 1140, 1058.
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.15 (m, 2H), 2.55 (br s, 1H), 2.72 (m, 3H), 3.85 (m, 3H), 4.8 (m, 1H), 7.1-7.45 (m, 5H aromatic).
^{13}C-NMR ($CDCl_3$, 50MHz):	: 34.58 (t), 37.29 (d), 45.05 (d), 46.61 (d), 50.63 (d), 54.14(d), 73.86 (t), 89.00 (d) 126.08 (d), 126.81 (d), 128.27 (d), 143.01 (s).
Mass (m/z)	: 326, 234, 199, 169, 141, 115, 91, 77

2-Hydroxy methyl bicyclo[2.2.1]hept-5-ene (1):



To a stirred ice cold solution of 1.0g (8.2 mmol) of bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **21** in 10 ml of CH_3COOH was added, 0.93g (24.6 mmol) of $NaBH_4$ in small portions. The reaction mixture was stirred for 10 minutes at the same temperature. After completion of the reaction and usual work-up furnished 0.95g of 2-hydroxy methyl bicyclo[2.2.1]hept-5-ene **1** in 93% yield as a mixture of *endo* and *exo* isomers (3:1).

Yield	: 0.95 g, (93%)
Mol. Formula	: $C_8H_{12}O$;
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3341, 3046, 1717, 1410, 1248.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.25 (m, 2H), 1.47 (d, 1H J=8H), 1.8 (m, 1H), 2.25 (m, 2H), 2.5-3.0 (m, 2H), 3.1-3.5 (m, 1H), 3.5-4.0 (m, 1H), 5.95 (m, 1H olefinic), 6.1 (m, 1H olefinic).

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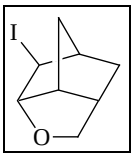
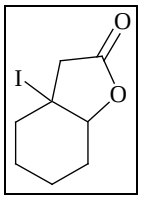
2-Iodo-4-oxa tricyclo[4.2.1.0^{3,7}]nonane 23:



Yield	: 0.23 g, (96%)
Mol. Formula	: $C_8H_{11}IO$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 2946, 1445 1060, 910.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.24 (d, 1H, *J* = 11.0 Hz), 1.75 (d, 1H, *J* = 11.0 Hz), 1.95-2.3 (m, 2H), 2.35 (m, 2H), 2.65 (br s, 1H), 3.5-3.9 (m, 3H), 4.7 (d, 1H, *J* = 6.0 Hz).
^{13}C NMR ($CDCl_3$, 50MHz):	: 36.68 (t), 36.97 (d), 37.41 (t), 37.49 (d), 43.81 (d), 46.49 (d), 73.73 (t), 89.17 (d).
Mass (m/z)	: 250, 167, 123, 93, 79.

3-Iodo perhydro cyclohexa[b] furan-2-one 25:



Yield	: 0.16 g, (73%)
Mol. Formula	: $C_8H_{11}IO_2$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 1786, 1237, 1200, 1156, 755.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.65 (m, 6H), 1.9-2.4 (m, 3H), 2.85-3.4 (m, 2H), 4.8 (m, 1H).
^{13}C NMR ($CDCl_3$, 50MHz):	: 19.35 (t), 22.22 (t), 24.50 (t), 37.18 (s), 39.53 (t), 50.23 (t), 86.29 (d), 174.29 (s).
Mass (m/z)	: 266.

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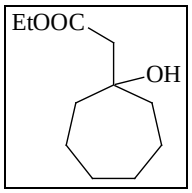
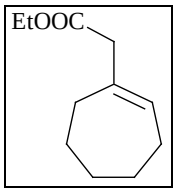
Ethyl-2-(1-hydroxy cycloheptyl) acetate 16:



To a refluxing solution of cycloheptanone **25** 2.0 g (17.85 mmol) in 25 ml benzene and Zn (1.16g (53.55 mmol), was added a solution of ethyl bromoacetate (3.72 g (22.3 mmol) in 25 ml benzene dropwise. The solution was then refluxed for 6 hrs. After completion of reaction, the reaction mixture was cooled and quenched with 25 mL of 10% HCl solution. The solution was then filtered and the organic layer was separated and aqueous layer was extracted with 3x25 ml portions of ethyl acetate. The combined organic layers was then dried over anhydrous Na_2SO_4, filtered and on concentration on rotary evaporator and column purification (SiO_2) furnished 2.20g of ethyl-2-(1-hydroxy cycloheptyl) acetate **26** in 62% yield.

Yield	: 2.20g, (62%)
Mol. Formula	: $C_{11}H_{20}O_3$;
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3523, 2925, 1716, 1201.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.25 (t, 3H –$COOCH_2\underline{CH_3}$), 1.3-1.95 (m, 12H), 2.47 (s, 2H-$\underline{CH_2}COOCH_2CH_3$), 3.3 (br s 1H –OH), 4.15 (q, 2H –$COO\underline{CH_2}CH_3$).

Ethyl 2-(1-cycloheptenyl) acetate 27:



To an ice cold solution of ethyl-2-(1-hydroxy cycloheptyl) acetate **27** 1.8g (5.56 mmol) and pyridine 0.9g (6.94 mmol) in 10 ml of dichloromethane was added, $SOCl_2$ 1.73g (6.94 mmol) dropwise. The mixture was stirred for 0.5 hrs. After completion of reaction, the

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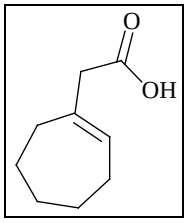
reaction is quenched with 25 ml of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with 3x15 ml portions of dichloromethane. The combined organic layers was dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 1.47g mixture of ethyl 2-(1-cycloheptenyl) acetate **27** and α, β-unsaturated ester in 90% yield.

Yield	: 1.47g (90%)
Mol. Formula	: $C_{11}H_{18}O_2$;
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 2925, 1737, 1716, 1635, 1446, 1147.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.25 (t, 3H), 1.35-1.9 (m, 6H), 2-2.25 (m, 2H), 2.35 (m, 1H), 2.85 (m, 1H), 2.95 (s, 2H), 4.15 (q, 2H), 5.7 (m, 1H olefinic).

2-(1-Cycloheptenyl) acetic acid (5):



To a 1.0 g (5.5 mmol) solution of the mixture of α, β-and β, γ-ester in 15 ml of MeOH/Water (3:1) system was added, powdered potassium hydroxide 0.92g (16.5 mmol). The reaction mixture was refluxed for 4 hrs. After completion of the reaction, the reaction mixture was cooled and 25 ml of saturated $NaHCO_3$ was added. The solution was then extracted with 3x25 ml portions of EtOAc. The aqueous layer was then neutralized with 15 ml. of dil. H_2SO_4 which was then extracted with 3x25 ml. portions of dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and was then concentrated on rotary evaporator under reduced pressure. The residue thus obtained on purification by column chromatography (SiO_2) furnished 0.78g of the acid as
a (1:4) mixture of α, β-and β, γ-acids in 92% yield.

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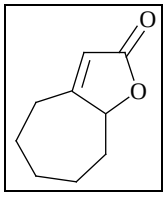
Yield	: 0.78g, (92%)
Mol. Formula	: $C_9H_{14}O_2$
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3500-2500 (broad band), 1686, 1627, 1417, 1256, 877.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.35-2.25 (m, 8H), 2.4 (m, 2H), 2.95 (m, 2H), 5.65 (m, 1H olefinic) 11.05 (br s, 1H -COOH).
Mass (m/z)	: 154, 137, 126, 94, 79, 67.

4,5,6,7,8,8a-Hexahrdro-cyclohepta[b]furan-2-one 26



Yield	: 0.14g, (33%)
Mol. Formula	: $C_8H_9IO_2$;
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 2937, 1751, 1626, 1446, 1452, 1355, 1190.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.1-1.65 (m, 4H), 1.65-2.00 (m, 3H), 2.25 (m, 1H), 2.7 (m, 2H), 4.95 (m, 1H), 5.75(s, 1H).
^{13}C NMR ($CDCl_3$, 50MHz):	: 25.49 (t), 26.03 (t), 28.62 (t), 29.57 (t), 33.32 (t), 84.52 (d), 115.5 (d), 172.93 (s), 174.54 (s).
Mass (m/z)	: 152, 123, 95, 81, 67.

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Spectra

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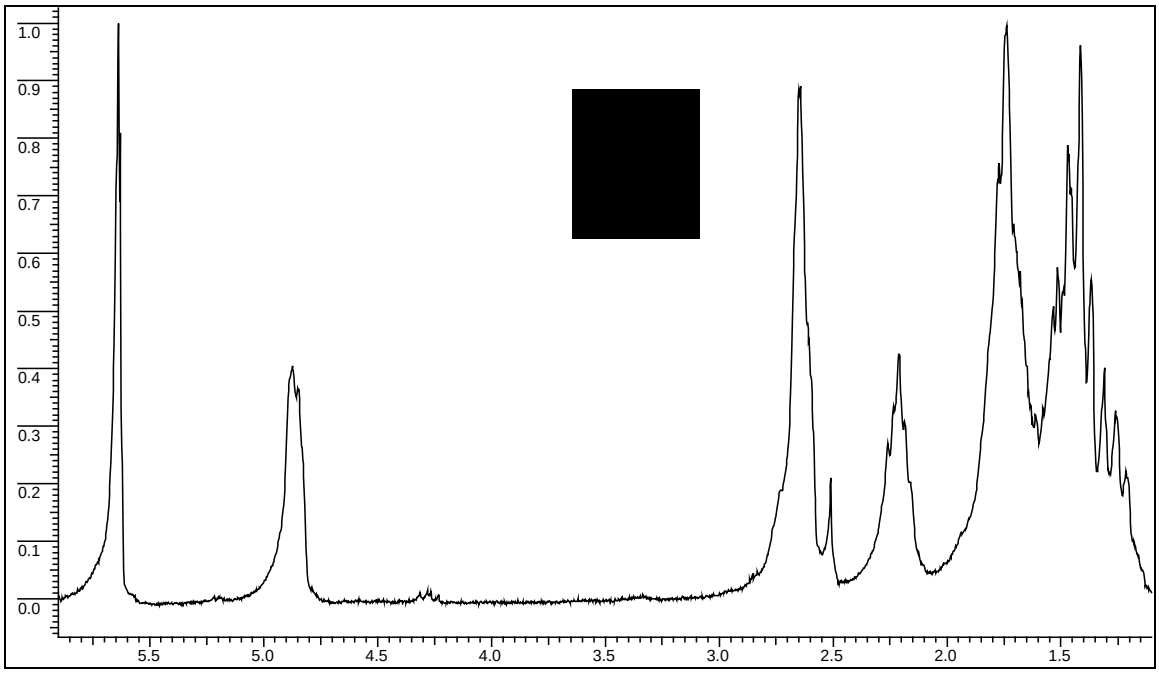
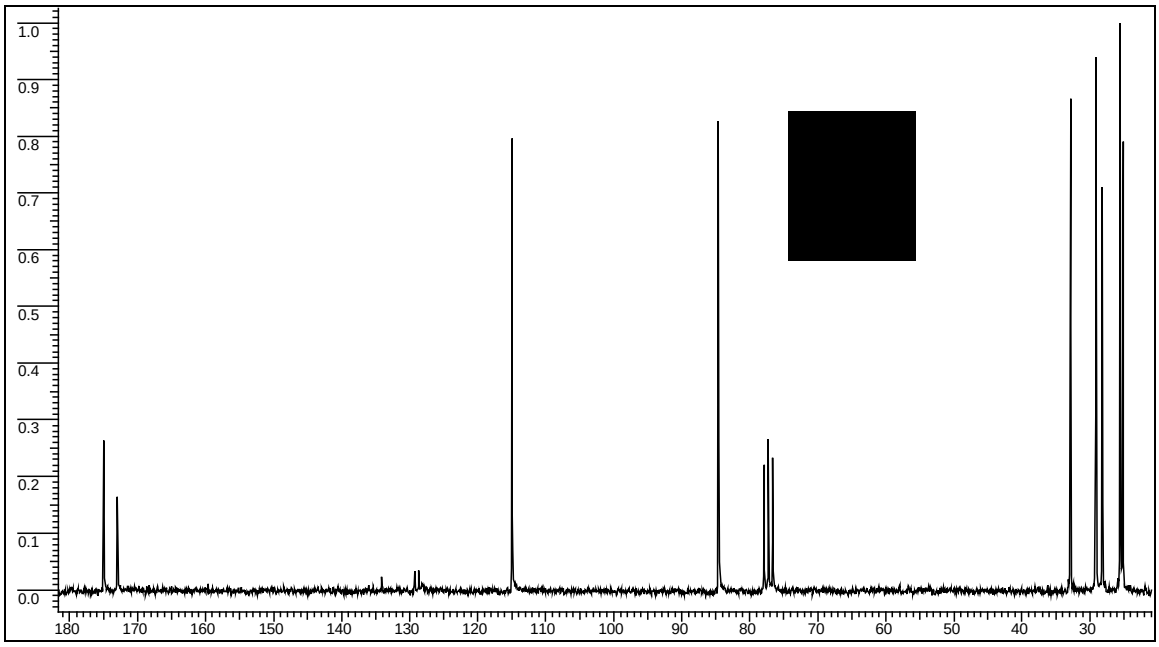


^{1}H NMR spectrum of compound **13** ($CDCl_3$ 200 MHz)



^{13}C NMR spectrum of compound **13** ($CDCl_3$ 200 MHz)

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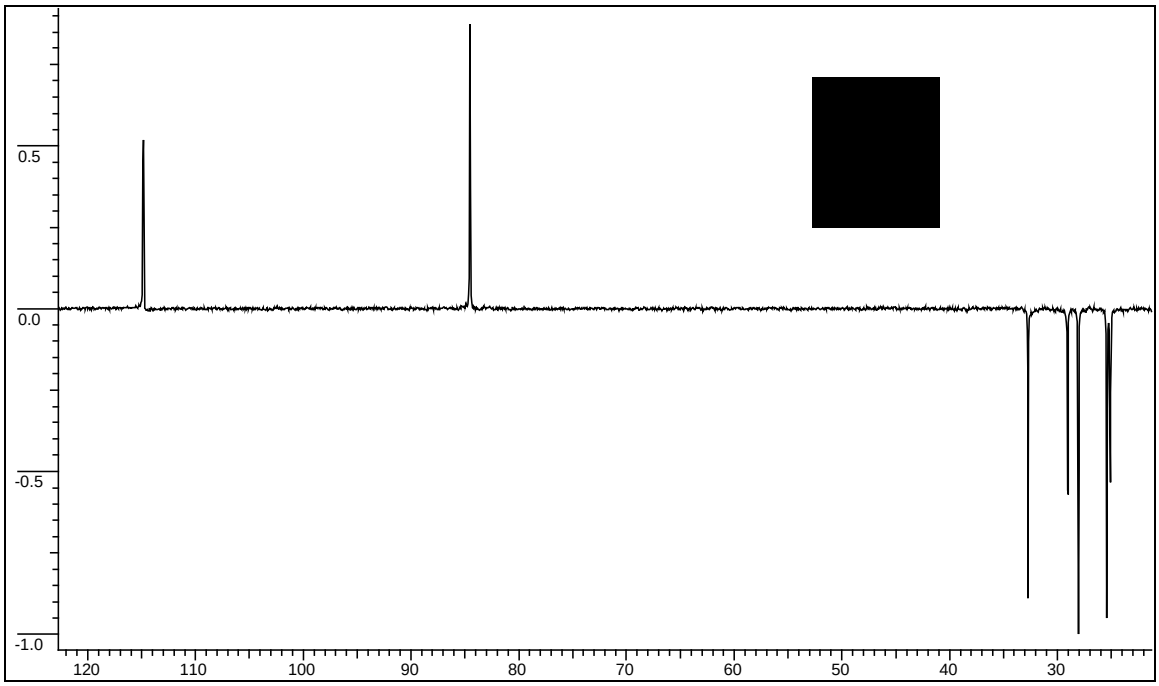
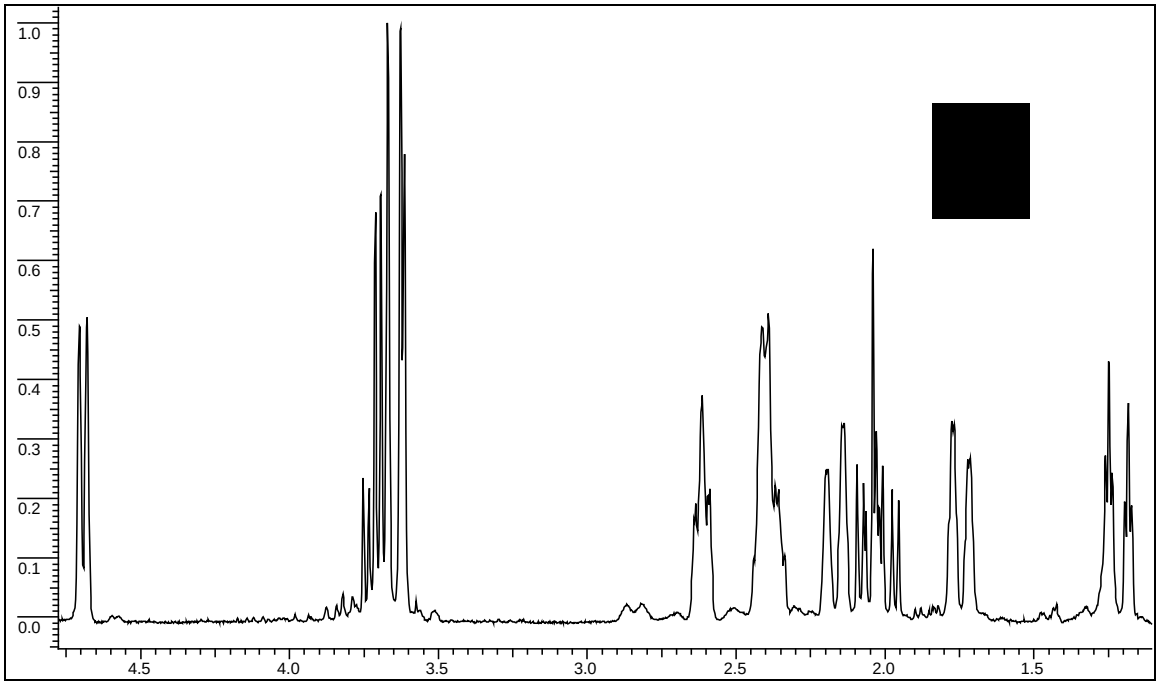


DEPT NMR spectrum of compound **13** ($CDCl_3$ 200 MHz)



^{1}H NMR spectrum of compound **9** ($CDCl_3$ 200 MHz)

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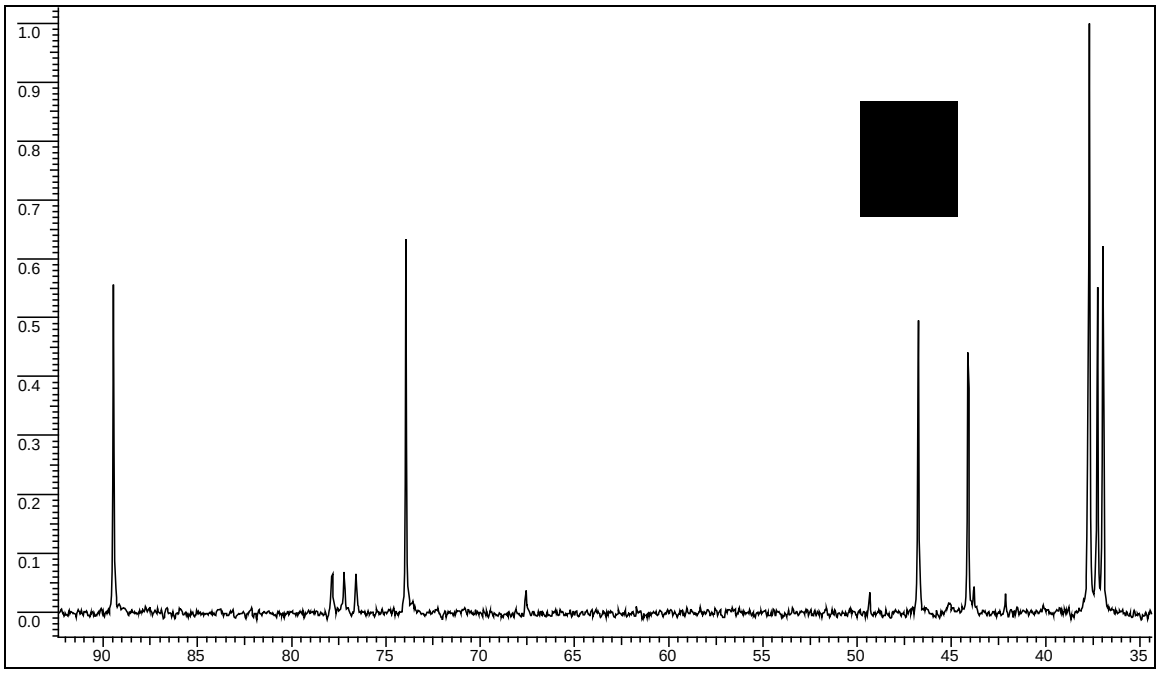
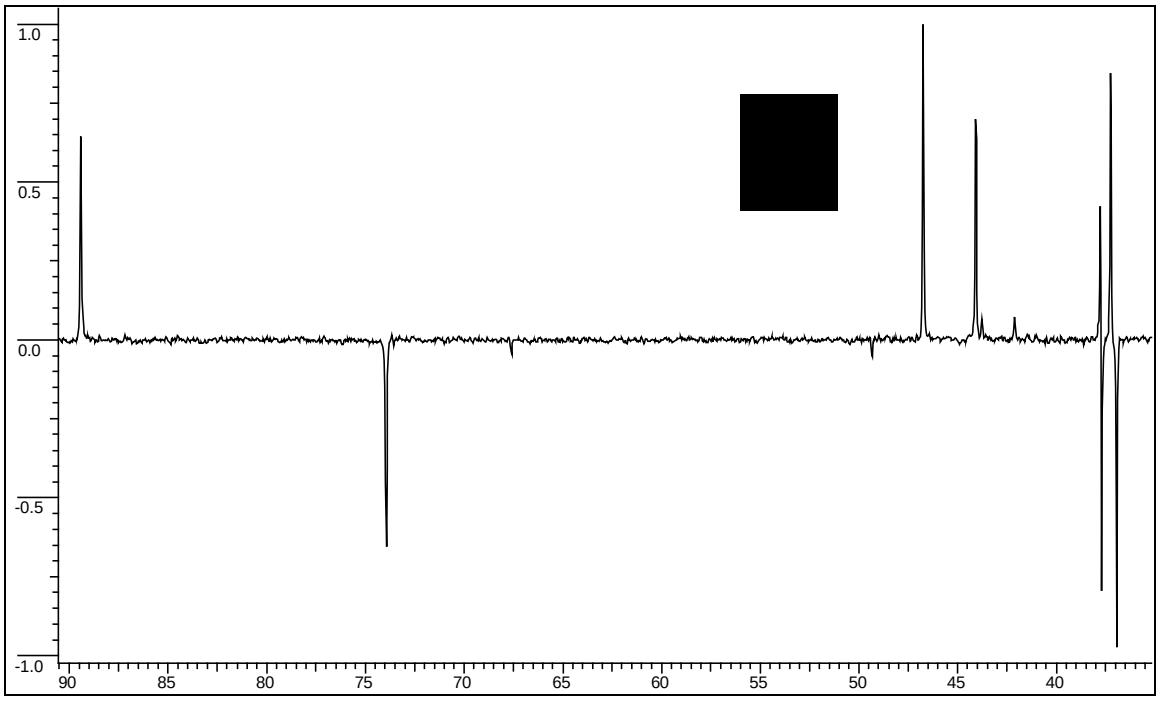


^{13}C NMR spectrum of compound **9** ($CDCl_3$ 200 MHz)



DEPT NMR spectrum of compound **13** ($CDCl_3$ 200 MHz)

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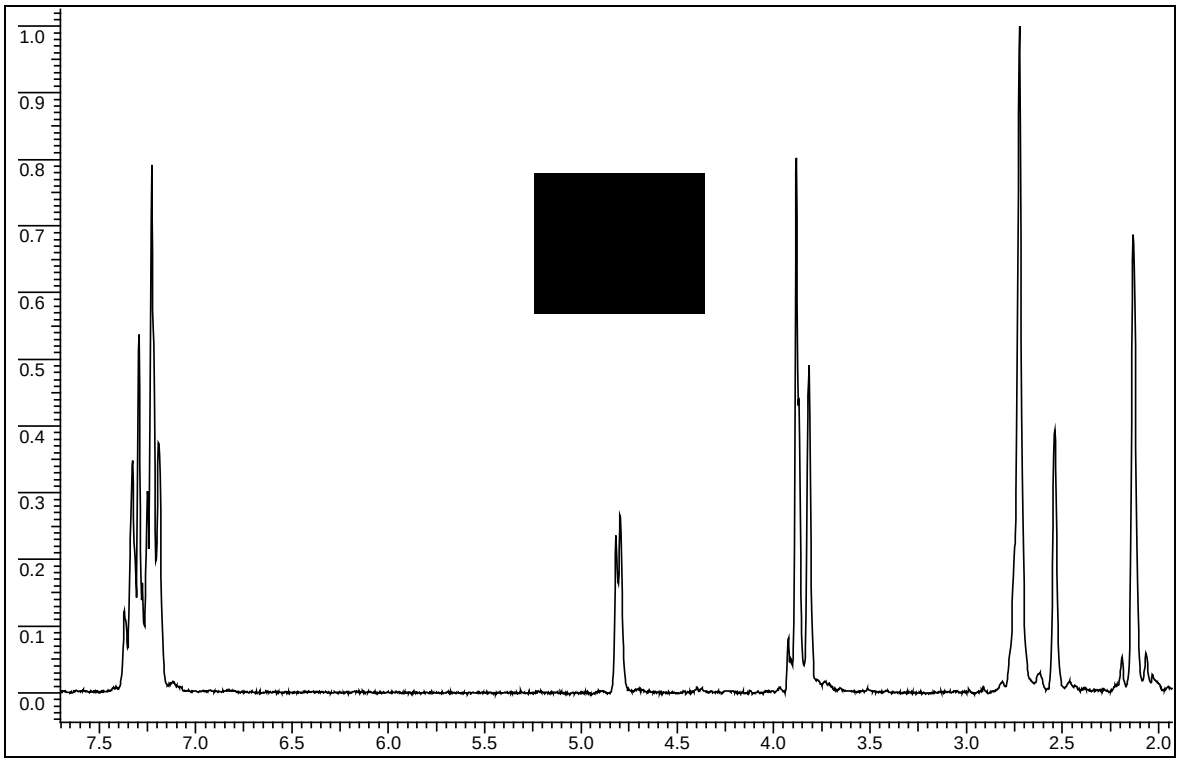
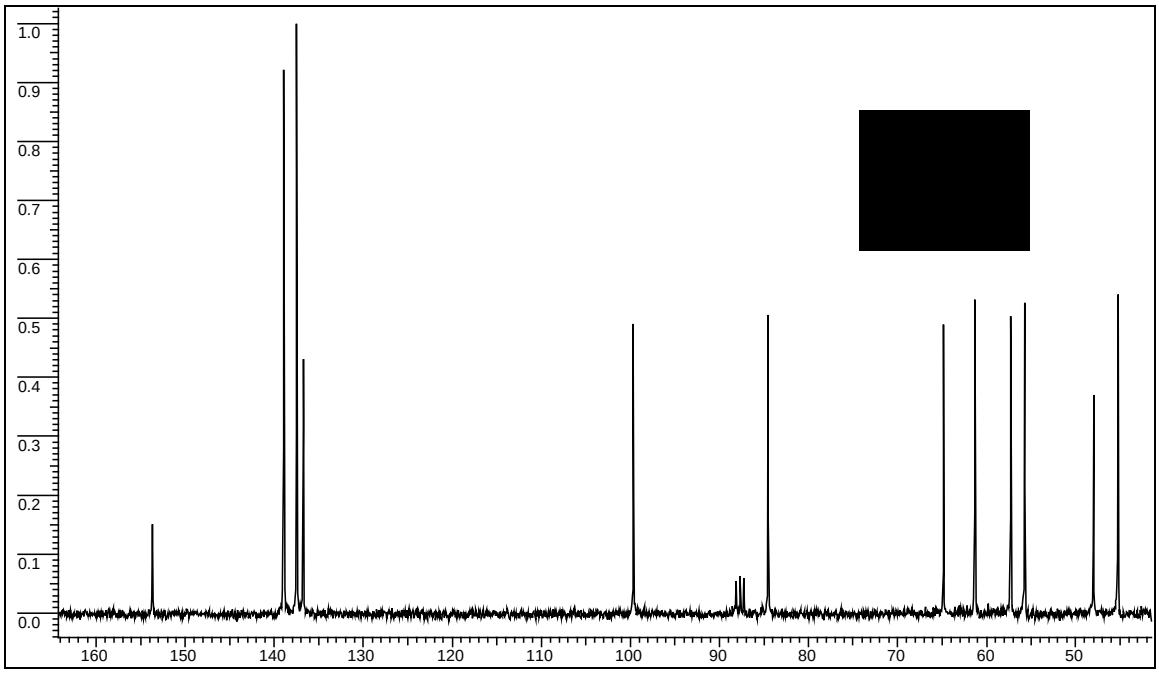


^{1}H NMR spectrum of compound **11** ($CDCl_3$ 200 MHz)



^{13}C NMR spectrum of compound **9** ($CDCl_3$ 200 MHz)

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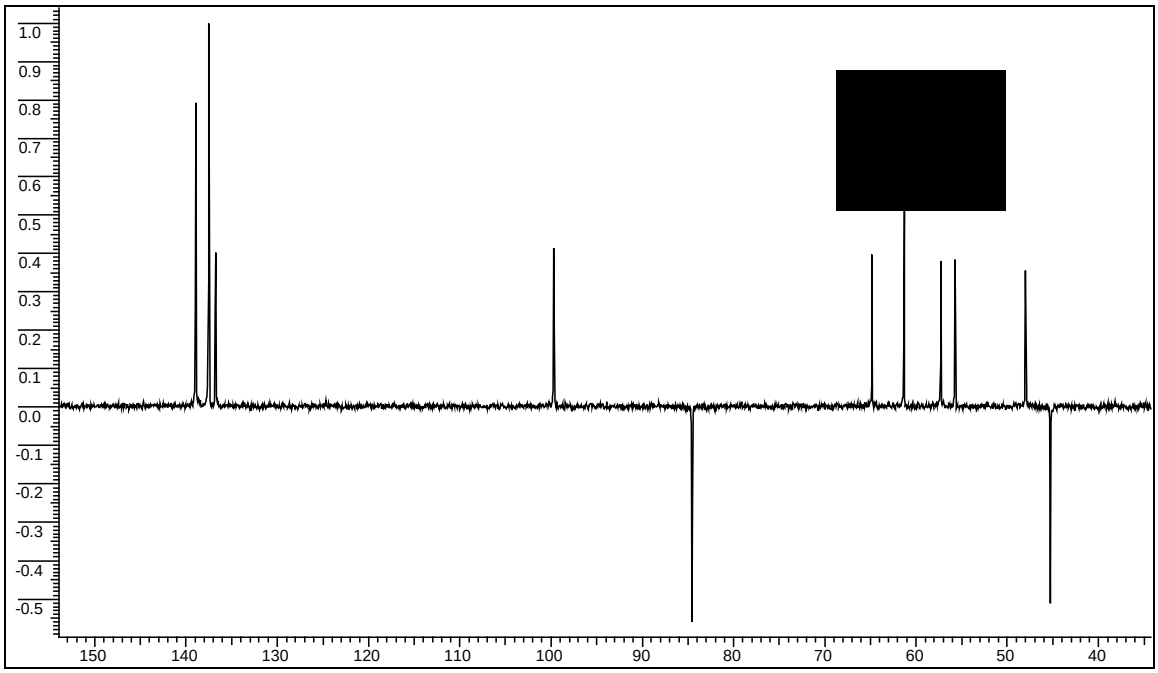
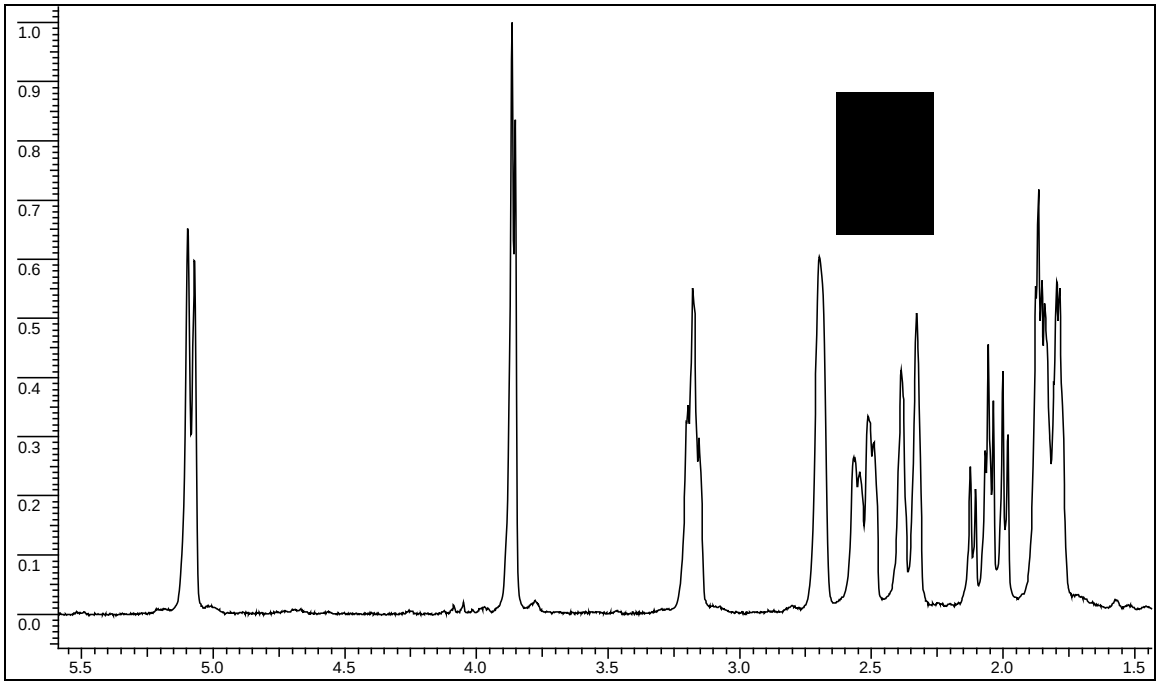


DEPT NMR spectrum of compound **11** ($CDCl_3$ 200 MHz)



^{1}H NMR spectrum of compound **10** ($CDCl_3$ 200 MHz)

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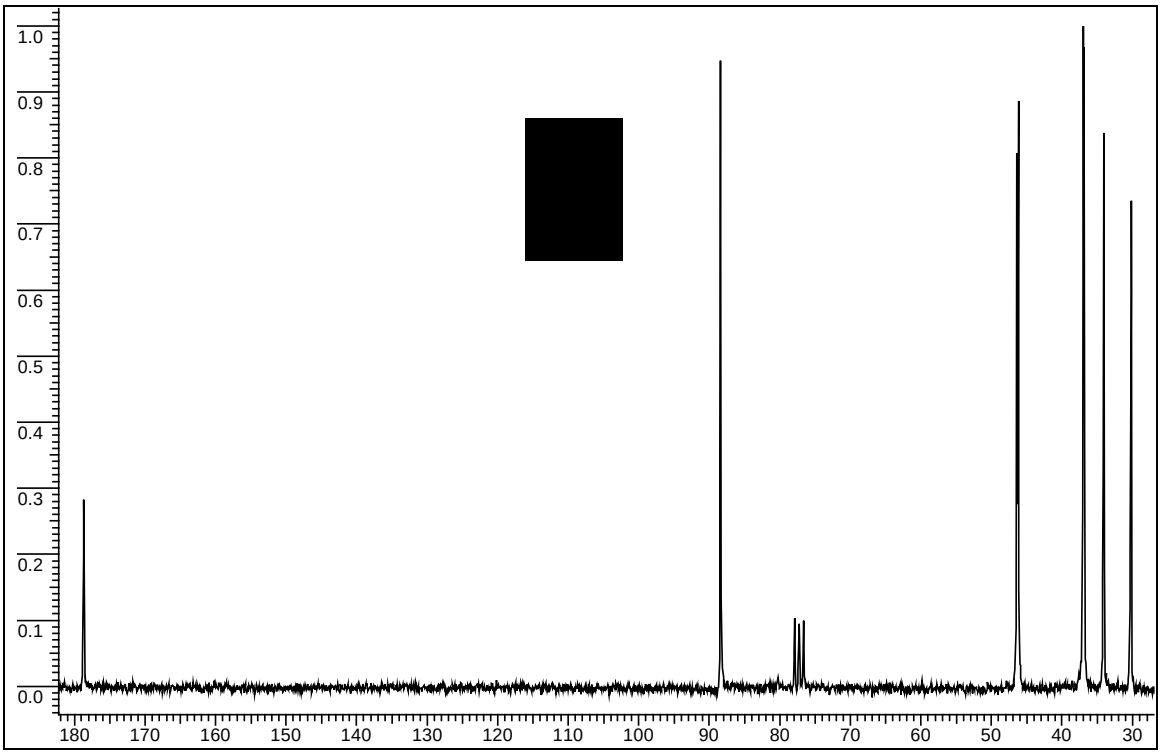
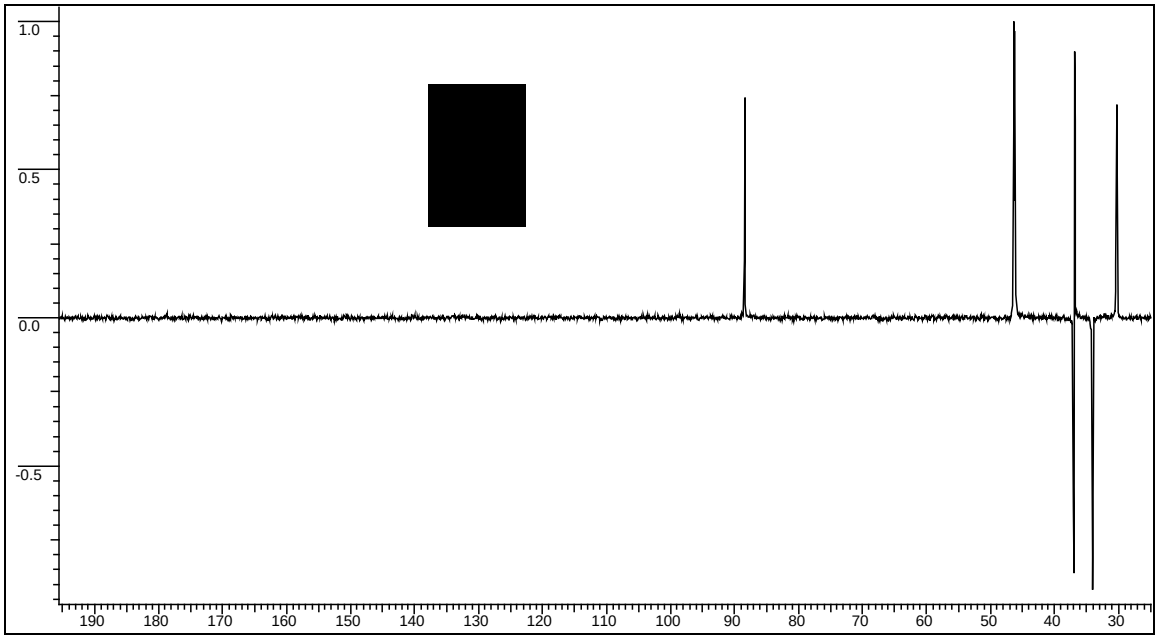


^{13}C NMR spectrum of compound **10** ($CDCl_3$ 200 MHz)



DEPT NMR spectrum of compound **10** ($CDCl_3$ 200 MHz)

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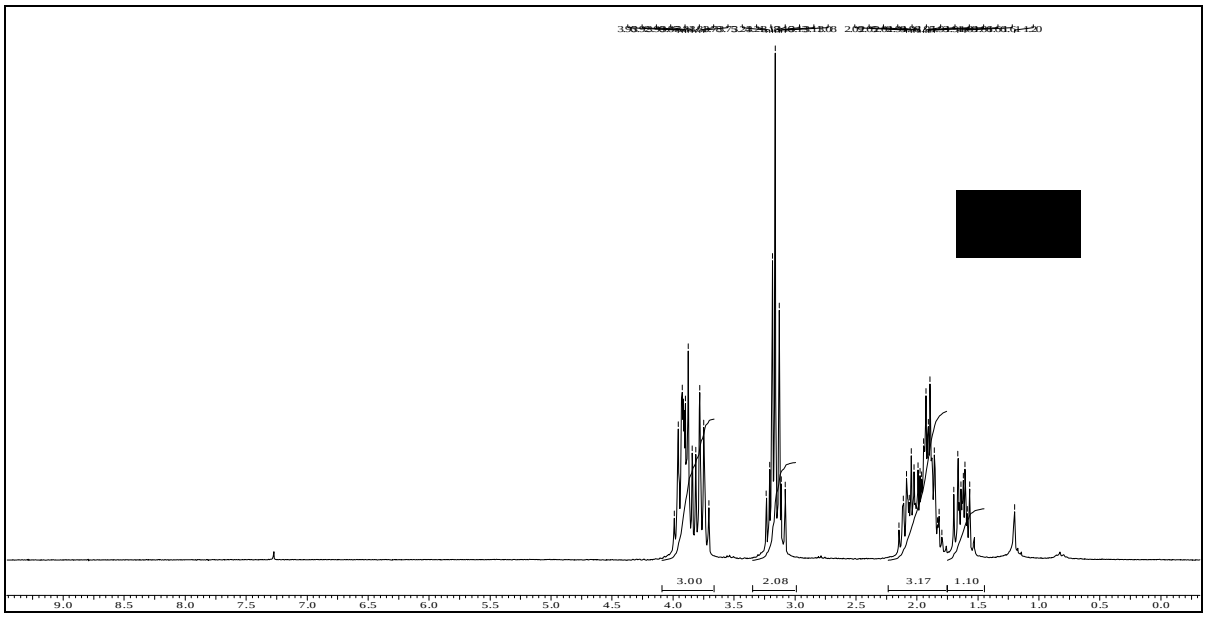
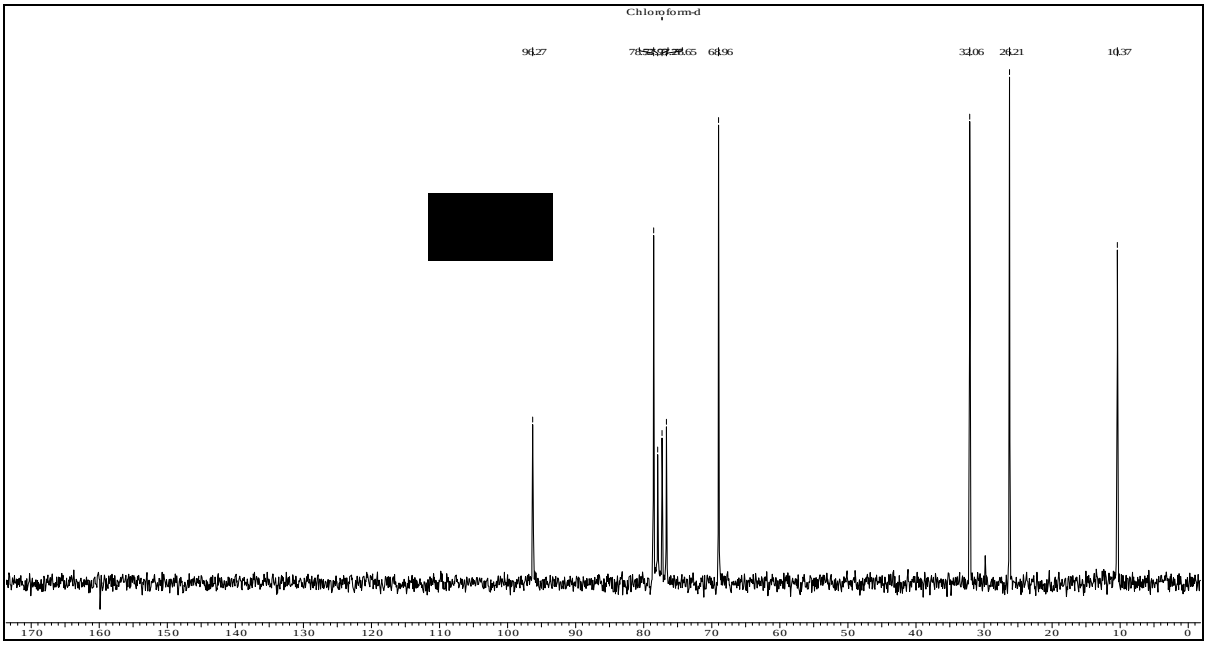


^{1}H NMR spectrum of compound **14** ($CDCl_3$ 200 MHz)



^{13}C NMR spectrum of compound **14** ($CDCl_3$ 200 MHz)

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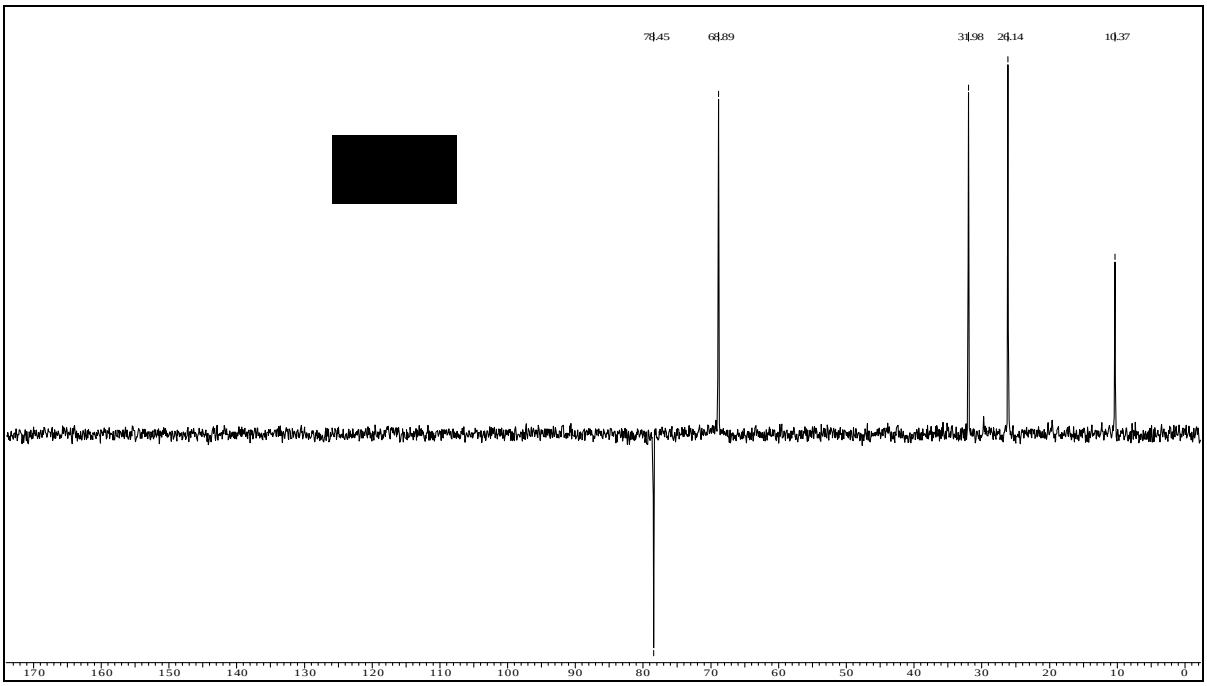

DEPT NMR spectrum of compound **14** ($CDCl_3$ 200 MHz)

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2.2.1.8 References:

Presented at the Fourth National Symposium in chemistry (Chemical Research Society of India). Feb 1-3,2002. National Chemical Laboratory, Pune – 411008- INDIA.

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SECTION-II

PART-II

Efficient and Simple Synthesis of (-)-Wine lactone

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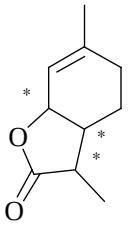
2.2.2.1 Introduction

(-)-Wine lactone, **(-)-1a** is a bicyclic terpenoid found in white wine, Gewurztraminer and Scheurebe as an important flavor component.[1] Recently, wine lactone was also found in orange juice and black pepper.[2] In 1975, Southwell identified a group of bicyclic terpenoid lactones[3] in the urine of koala animals after feeding of the leaf of *Eucalyptus punctata*. One of these lactones was assigned the constitution **1** [3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one].



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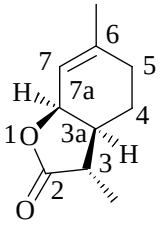

(-)-1a, Wine lactone
(-)-(3*S*, 3a*S*, 7a*R*)

Guth[4] identified one of the eight stereoisomers with constitution **1** in white wine types Gewurztraminer & Scheurebe as an important flavor component in 1997. Later Guth synthesized all the eight stereoisomers and compared their threshold values which differed considerably.[4] The compound with the highest odor activity is the lactone **(-)-1a**, which was found to be identical to the natural product and was named “wine lactone”. The odor of the wine lactone **(-)-1a** is described as woody and coconut-like with an odor threshold as low as 0.02 pg/L of the air; the odor activity of the enantiomer, **(+)- 1a** displaying a threshold value of > 1 µg/L of the air, is lower by a factor of > 10^8.

2.2.2.2 Earlier approaches:

In order to judge an adequate background and to appreciate the problem involved in the synthesis, a brief survey of the reported racemic and chiral syntheses of the wine lactone is presented.

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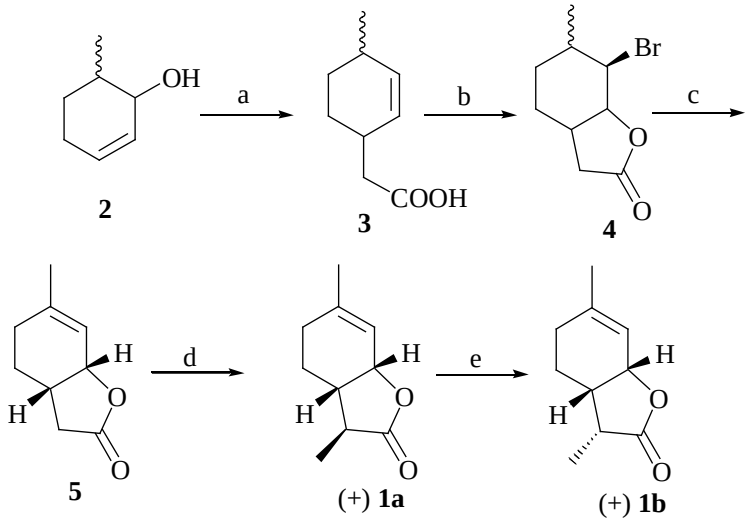
Bartlett's Approach:[5] (*J. Org. Chem.*, **1981**, 46, 3896.)

Prior to the discovery of the wine lactone, a diastereoselective route was developed in 1981 by Bartlett *et al*[5] who prepared racemic **1a** and its *endo* C-3-epimer **1b** by utilizing the

potential of Claisen rearrangement of 2-cyclohexenol derivative **(scheme 1)**. Orthoacetate Claisen rearrangement of a 3:1 mixture of *trans*- and *cis*-6-methyl-2-cyclohexenols **2** led to *trans*/*cis* mixture of methylcyclohexenylacetic acids **3** in 60% yield after ester hydrolysis. Bromolactonization of this material and DBU induced dehydrohalogenation convert both the isomers to the unsaturated lactone **5**. Alkylation of the lithium enolate of the lactone **5** with methyl iodide provided the *exo*-methyl isomer **1a** stereospecifically. The epimeric lactone **1b** was obtained on kinetically controlled protonation of the enolate of **1a**.



Scheme 1: Reagents & conditions: **a**) $Me(OEt)_3$, *o*-NO_2-PhOH, 150^0C, HO^-, MeOH, 60% **b**) NBS/$CHCl_3$, 99% **c**) DBU/Xylene, reflux, 59% **d**) LDA/THF, -78^0C, CH_3I, 90%, >30:1 **e**) LDA/THF, -78^0C, AcOH, 99%, 20:1

Guth's Approach:[5](*Helv. Chim. Acta*., **1996**, 79, 1559.)

Starting from (+)- and (-)-limonene,[5] Guth prepared the eight stereoisomers with constitution **1** as a mixture of diastereomers and separated them by preparative HPLC. Thus according to Guth's approach **(scheme 2)**, (+)-limonene **6** was hydroborated regioselectively with 9-BBN followed by oxidation to yield diastereomeric mixture of alcohols **7a** and **7b** which was oxidized to the corresponding acids **8a** and **8b**.

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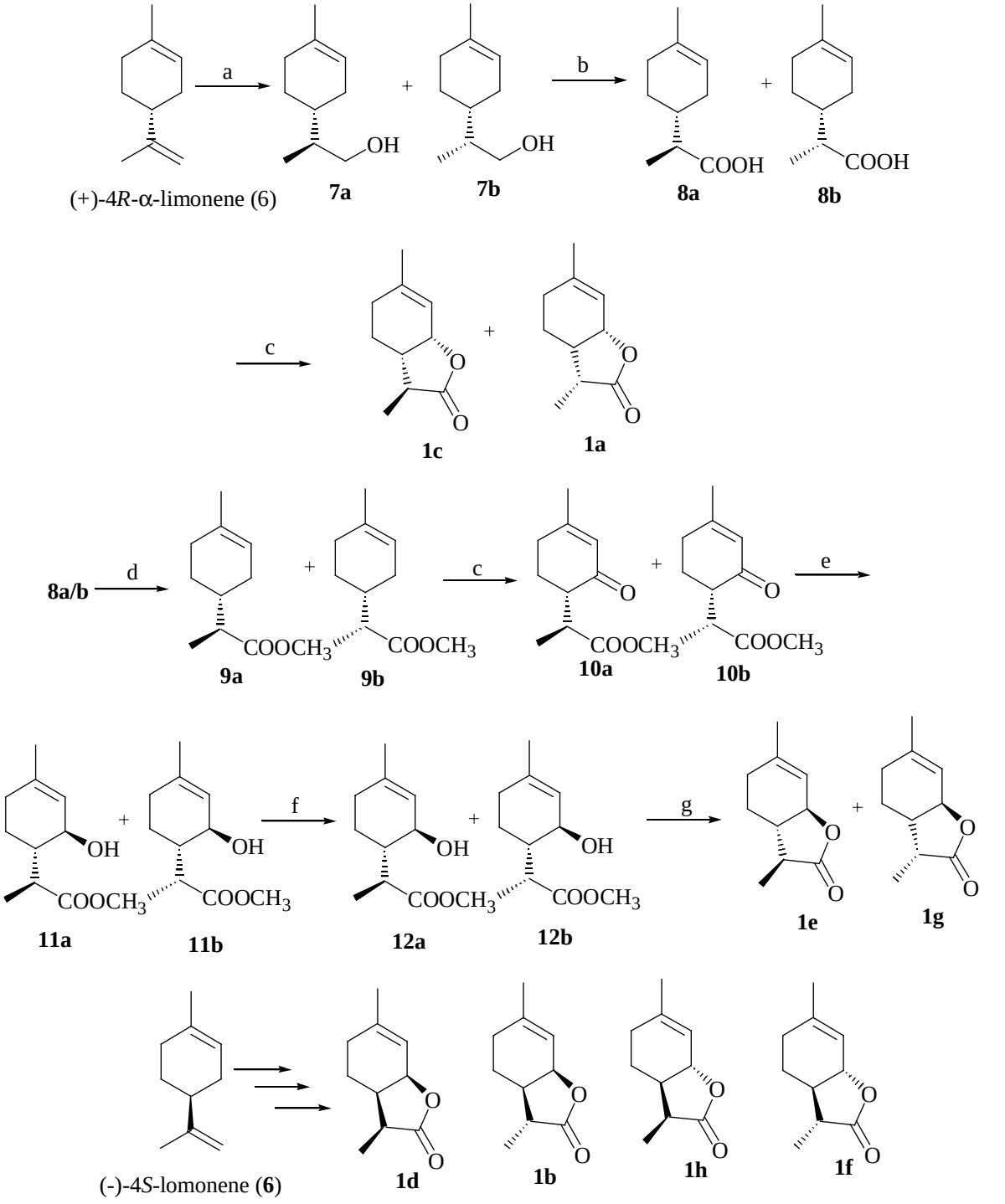

Scheme 2: Reagents & conditions: **a**) 9-BBN/THF **b**) PDC/DMF **c**) PDC/C_6H_6/*tert*-BuOOH **d**) MeOH/H_2SO_4 **e**) $NaBH_4$, $CaCl_2$, *iso*-PrOH **f**) NaOH/MeOH/H_2O **g**) DCC/C_6H_6

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Cyclization of the acids **8a** and **8b** with PDC/*tert*-BuOOH in benzene gave *cis*-lactones **1a** and **1c**. Analogously, lactones **1b** and **1d** were obtained in moderate yield 30% as 1:1 mixture starting from (-)-limonene. *trans*-lactones **1e** and **1g** were obtained from diastereoisomeric acids **8a** and **8b** by converting to methyl esters **9a** and **9b**. Allylic oxidation and hydride reduction furnished allylic alcohols **11a** and **11b** which were then saponified into *trans*-hydroxy acids **17a** and **17b,** on cyclization yielded **1e** and **1g**. Analogously, **1f** and **1h** were obtained from (-)-limonene.

Eventhough, this route is short and provides all the eight stereoisomers of wine lactone, it is not diastereoselective/enantioselective and involves tedious separation techniques such as HPLC.

Bergner's Approach:[6] (*Eur. J. Org. Chem.*, **2000**, 419.)

Bergner *et al*[6] reported the first chiral synthesis of enantiomerically pure (-)-wine lactone, **(-)-1a** and its C-3-epimer **(+)-1b**. while diastereoselectivity was provided by iodolactonization of **16** and enolate alkylation of **17**. Asymmetric allylic substitution on **13** was followed by Krapcho decarbomethoxylation[8] of **(+)-14** to **15** on saponification and iodolactonization of the corresponding acid **16** furnished **(-)-17**. Dehydrohalogenation of **17** with DBU yielded the unsaturated lactone **(+)-18**. Reaction of **(+)-18** with a reagent prepared from methyllithium and CuBr in diethyl ether at -20^0C gave a mixture of regioisomers **19a/19b:19c** = 55:45. Iodolactonization of **19a/19b** gave a 92:8 mixture of diastereomers **(-)-20a** and **20b**. Major diastereomer **(-)-20a** was obtained in pure form by recrystallization. Dehydrohalogenation with DBU gave lactone **(+)-21**. Finally alkylation of **(+)-21** with methyl iodide furnished **(-)-1a**. The epimeric lactone **(+)-1b** was prepared from **(-)-1a** by deprotonation and subsequent reprotonation.

Although this route is the first enantio- and in all steps the diastereoselective, it is too lengthy and involves use the of expensive Pd-complexes for the allylic substitution.

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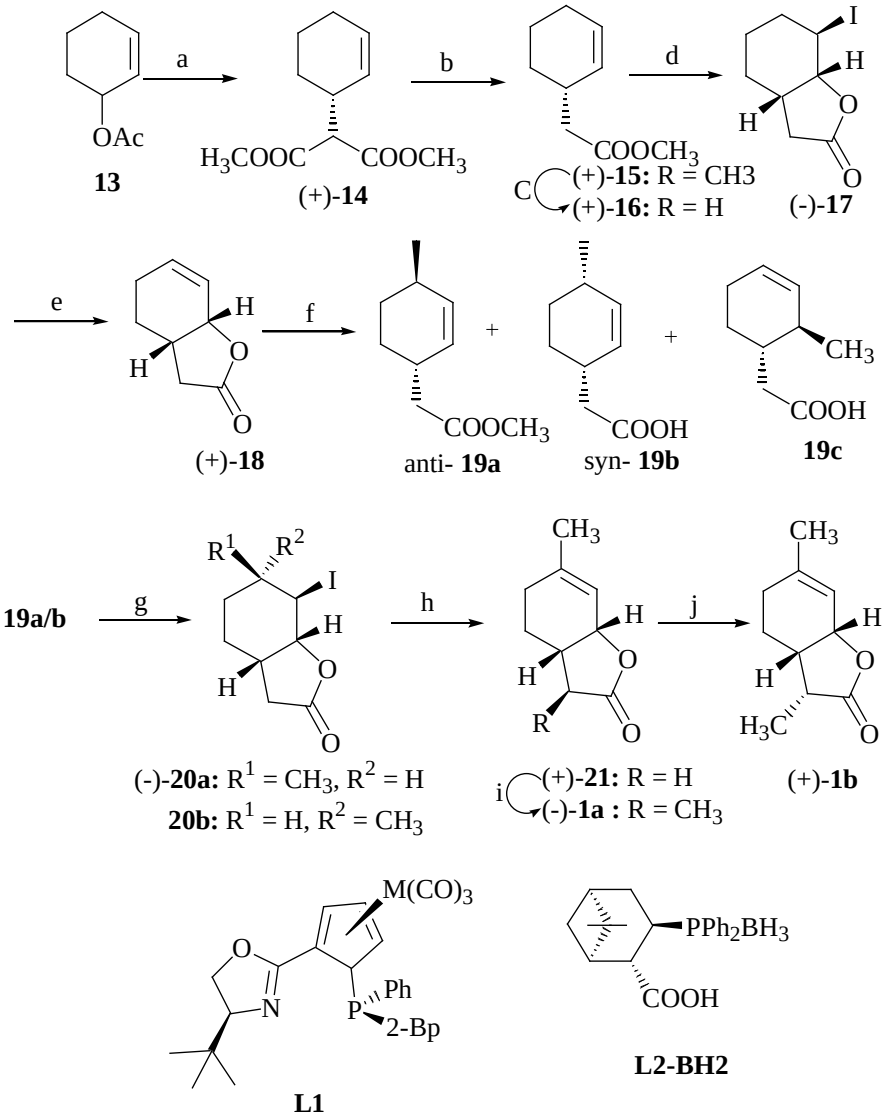

Scheme 3: Reagents & conditions: a) Procedure 1: 0.1 mol% of $[C_3H_5PdCl]_2$, 0.12 mol% of **L1**, THF, $NaCH(COOCH_3)_2$, 5 ^{0}C, 88%, 82% *ee* Procedure 2: 3.0 mol% of $[C_3H_5PdCl]_2$, 9 mol% of **L2**, THF, $LiCH(COOCH_3)_2$, room temp., 91%, 95% *ee* **b**) NaCl, H_2O, DMSO, 160^{0}C, 74% **c**) NaOH, 120^{0}C, 95% **d**) KI, I_2, $NaHCO_3$, H_2O, 82%, > 99.9% ee **e**) DBU, THF, reflux, 82-91% **f**) i. MeLi/CuI, Et_2O ii. MeMgCl/CuBr, Me_2S, THF/Me_2S, -20^{0}C-0^{0}C **g**) KI, I_2, $NaHCO_3$, H_2O, THF, room temp., 95%, dr=92:8 after recrystallization 60%, dr = 99:1 **h**) DBU/THF reflux, 92% **i**) LDA, MeI, THF, -78^{0}C, 79-90%. **j**) LDA, THF then $H_2C(COO$*t*$-Bu)_2$, -78^{0}C, 61-74%

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2.2.2.3 Present work

The present section primarily concerns with the diastereoselective synthesis of (-)-wine lactone **(-)-1a**, a bicyclic terpenoid, an important flavor component found in white wine,[1] orange juice and black pepper.[2] The literature survey (1.1) indicates that wine lactone is synthesized in both racemic[4] and optically pure form.[5,6] Prior to the discovery of wine lactone, Bartlett *et al*[4] synthesized various bicyclic terpenoids including racemic wine lactone and its *endo*-C-3-epimer using Claisen rearrangement. Guth[5] synthesized all the eight stereoisomers and separated them by chromatography in order to compare their threshold values. The earlier syntheses are non-stereoselective and lead to formation of other stereoisomers also whereas the recent synthesis by Helmchen *et al*[6] involves use of expensive Pd-complexes for asymmetric allylic substitution involving large number of steps (12 steps). Isolimonene has the requisite number of carbon atoms as that of wine lactone with the isopropenyl group strategically placed in the desired stereochemical disposition. It was thought worthwhile to attempt the synthesis of wine lactone through selective functionalization of the double bond. The present work describes the diastereoselective and short (4 steps) synthesis of (-)-wine lactone involving a novel iodolactonization protocol, starting with (+)-isolimonene, which is abundantly available in nature, thus making it an ideal candidate. The current sequence of synthesis was utilized earlier by our group for the synthesis of the same molecule utilizing Iodolactonisation of unsaturated ester using $FeCl_3$/NaI as key step. Herein we describe the same synthetic sequence utilizing much facile iodolactonisation reagent Ceric ammonium nitrate/ Sodium iodide for the key iodolactonisation.

2.2.2.4 Results and Discussions:

The retrosynthetic plan for (-)-wine lactone is outlined in the **scheme 4**. As briefed in **scheme 4**, the key intermediate, iodolactone **(-)-25a** could be obtained by the iodolactonization of the corresponding γ,δ-unsaturated acid **24**. In order to obtain γ,δ-unsaturated acid **24**, the ideal starting material was obviously (+)-isolimonene **22**, which is a natural product and available readily. To accomplish epimeric iodolactones **(-)-25a** & **(+)-25b**,

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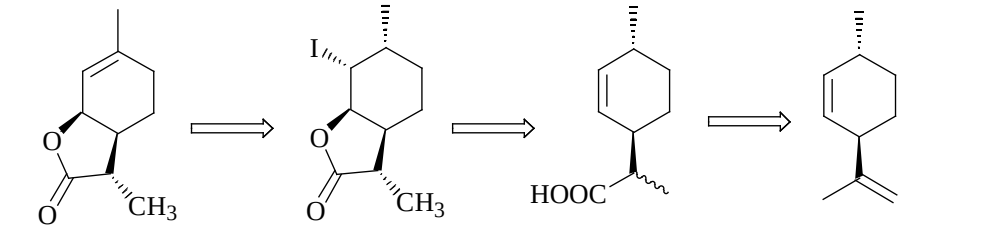
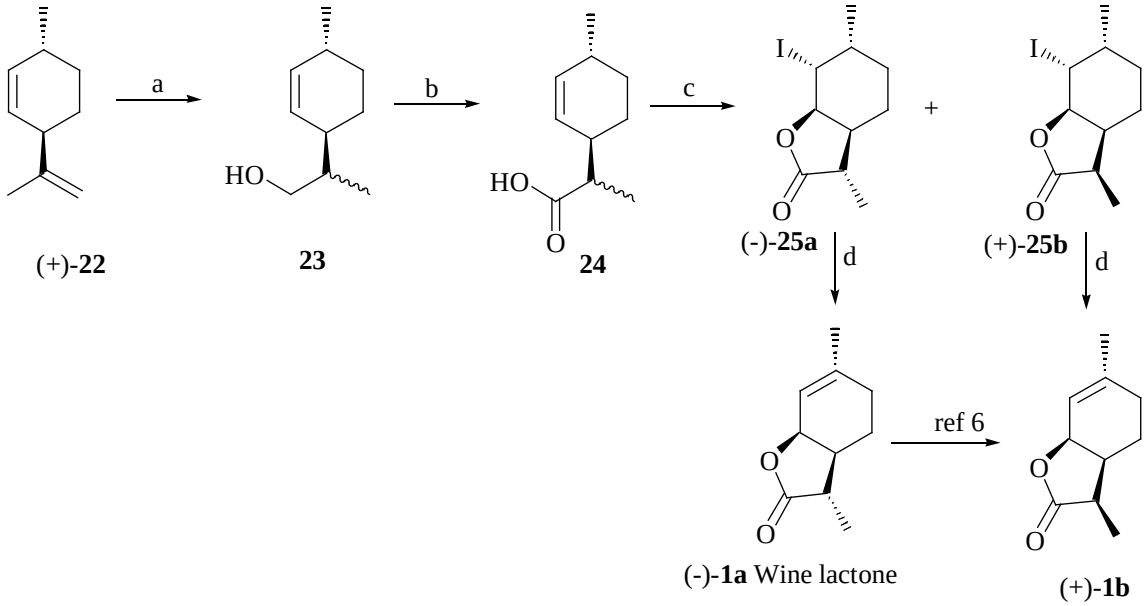
(+)-isolimonene **22** was hydroborated regioselectively. Thus (+)-isolimonene **22** was selectively hydroborated at the terminal double bond with 9-borabicyclo[3.3.1]-nonane (9-BBN)[9] and subsequent oxidative hydrolysis with alkaline H_2O_2 to furnish alcohol **23** in 76% yield.



(-)-**1a**, Wine lactone (-)-**25a** **24** **22**, (+)- isolimonene

Scheme 4



(+)-**22** **23** **24** (-)-**25a** (+)-**25b** (-)-**1a** Wine lactone (+)-**1b**

Scheme 5: Reagents and conditions: a) i) 9-BBN/THF, 0 ºC-room temp. 15 h ii. $NaOH/H_2O_2$, 0ºC-room temp., 1h, 76% b) Jone's reagent, 0 ºC- room temp., 2h, 78% c) CAN/NaI CH_3CN, rt, 35 min., 47% d) DBU/THF, room temp., 5h, 71-76%.

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The alcohol **23** thus obtained was oxidized with Jone's reagent[10] at 0 ºC to furnish γ,δ-unsaturated acid **24** in 78% yield. IR spectrum of the compound **24** showed broad absorption band at 3000 cm^{-1} for carboxylic group and a strong acid carbonyl at 1700 cm^{-1}. ^{1}H-NMR spectrum showed a doublet at δ 0.95 (*J* = 6.83 Hz) for the methyl group in the cyclohexene ring, two doublets at δ 1.15 (*J* = 6.84 Hz) for the methyl α-to carboxylic group, and a multiplet at δ 5.42-5.58 (2H) for olefinic protons.

Acid **24** thus obtained was subjected to the iodolactonization[11] using I_2 and saturated $NaHCO_3$ at 0^0C to furnish a mixture of iodolactones **25a** & **25b** in 52% yield. Ceric ammonium nitrate/ NaI mediated iodolactonization and iodoetherification protocol described in the earlier section was successfully used for the synthesis of wine lactone. The unique ability of Ceric ammonium nitrate to act both, as a Lewis acid and as oxidant was exploited. CAN oxidizes NaI to I_2 and in turn, further activates I_2 to undergo facile iodolactonization reaction. By using this protocol, CAN/NaI mediated iodolactonization of the acid **24** at room temperature in CH_3CN yielded a mixture of iodolactones **25a** & **25b** in 47% yield in just 35 min. This may be contrasted with the conventional protocol of iodolactonization which involves the use of I_2 and $NaHCO_3$ at 0 ^{0}C. Under these conditions 52% yield of the same iodolactone was observed. The mixture of iodolactones were separated by careful column chromatography (silica gel 60-120 mesh, eluent: ethyl acetate:pet ether 0.75:99.25). The probable structures of both the iodolactones were assigned by IR, ^{1}H & ^{13}C-NMR and mass spectral analysis. IR spectrum of the compound **25a** showed absorption at 1780 cm^{-1} for lactone carbonyl and the absence of broad absorption peak at 3300 cm^{-1} for hydroxyl group. ^{1}H-NMR spectrum of iodolactone **25a** showed doublet at δ 1.01 (3H) for -CHC*H*$_3$ with *J* = 6.34 Hz while the same methyl protons appeared at δ 0.94 (3H, -CHC*H*$_3$) with *J* = 5.37 Hz for its epimeric iodolactones **25b**. Another doublet appeared at δ 1.29 (3H) with *J* = 7.33 Hz for –COCHC*H*$_3$ for **25a**. The same methyl protons of the iodolactone **25b** appeared at the same δ value *i.e.* at δ 1.29 as doublet with *J* = 6.98 Hz. Even methylene (-CH_2) and methine (-C*H*) protons differ for both the iodolactones **25a** & **25b,** which is evident and presented in the experimental section. Multiplet at δ 1.39-1.47 (4H) for methylene group, multiplet at δ 1.81-1.93 for methine group (-COC*H*CH_3), multiplet at δ 2.35-2.51 for methylene group, a triplet at

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δ 4.66 with *J* =3.76 Hz for methine proton (-C*H*I), a dd at δ 4.93 with *J* = 3.92 Hz for methine proton (-C*H*O-) were the other distinguishing peaks in the ^{1}H NMR spectrum of the iodolactone **25a**. Similarly, multiplet at δ 1.21-1.43 (4H) for methylene group, a multiplet at δ 1.64-1.75 for methine protons, multiplet at δ 2.74-2.83 (2H) for methylene protons and another multiplet at δ 4.72-4.77 (2H) for methylene protons were the other distinguishing peaks in the ^{1}H-NMR spectrum of the epimeric iodolactone **25b**. ^{13}C-NMR spectrum of iodolactones **25a** & **25b** differ considerably. ^{13}C-NMR spectrum of the iodolactone **25a** revealed a quartet at δ 14.02 for –CH*C*H$_3$, the same methyl group appeared as quartet at δ 8.93 for iodolactone **25b**. Another quartet appeared at δ 22.26 for (-COCH*C*H$_3$) for **25a**, the same methyl group appeared as quartet at δ 23.71 for epimer *i.e.* **25b**. Triplet at δ 26.27 (-*C*H$_2$), triplet at δ 28.06 (-*C*H$_2$), doublet at δ 31.81 for methine carbon (-*C*HCH$_3$), doublet at δ 38.81 (-*C*H), doublet at δ 41.55 (-*C*HI), doublet at δ 43.39 (-CO*C*HCH$_3$), doublet at δ 81.73 (-*C*HO-) and a singlet at 179.07 for lactone carbonyl were the other distinguishing peaks in the ^{13}C-NMR spectrum of the iodolactone **25a**. A triplet at δ 23.28 (-*C*H$_2$), triplet at δ 27.85 (-*C*H$_2$), a doublet at δ 30.66 (-*C*HCH$_3$), doublet at δ 35.66 (-*C*H), doublet at δ 42.25 (-*C*HI), doublet at δ 42.59 (-CO*C*HCH3), a doublet at δ 82.23 (-*C*HO-) and a singlet at δ 179.07 for lactone carbonyl were the other distinguishing peaks in ^{13}C-NMR spectrum of the compound **25b**. The stereochemistry of the lactone methyl could be ascertained at this juncture by comparison of the ^{13}C values of the methyl α to lactone with wine lactone and *epi*-wine lactone. Thus the iodolactone whose ^{13}C NMR of CH$_3$ α to lactone which appeared at δ 13.44 matched well with ^{13}C of wine lactone which appeared at δ 13.62 was assigned the structure as **(-)-25a**. Similarly, the other isomeric iodolactone whose ^{13}C-NMR of CH$_3$ α to lactone which appeared at δ 8.93 compared well with the ^{13}C-NMR shift of *epi*-wine lactone which appeared at δ 9.13 was assigned structure as **(+)-25b**. Further confirmation of the stereochemistry was established after conversion of the iodolactone to wine lactone and its epimer as described below.

The structures of both the iodolactones **25a** and **25b** were confirmed by subjecting the respective iodolactones to dehydrohalogenation with DBU at room temperature in tetrahydrofuran. Thus iodolactone **25a** on dehydrohalogenation with DBU furnished the natural wine lactone **(-)-1a**. The physical and spectral properties of **(-)-1a** thus obtained were

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found to be identical in all respects with the data reported in the literature.[6] Since iodolactone **25a** furnished **(-)-1a**, the structure of the iodolactone was confirmed to be **(-)-25a.** On the similar line, when the iodolactone **25b** was dehydrohalogenated with DBU, it furnished C-3-epimer of **(-)-1a** *i.e.* **(+)-1b**. The spectral data and the physical properties of **(+)-1b** thus obtained were identical in all respects with the values reported in the literature.[6] Since the iodolactone **25b** furnished **(+)-1b** on dehydrohalogenation, the structure of the iodolactone was confirmed as **(+)-25b**. Additionally, mass spectrum showed M^+ at 294 for (+)-**25b**.

Enantiomeric purity of both the iodolactones **(-)-25a** & **(+)-25b** and wine lactone **(-)-1a** & its C-3-epimer **(+)-1b** were determined by chiral GC analysis on Chrompack β-CD (25m × 0.25 mm) at 180^0C. Iodolactone **(-)-25a** showed *ee* of 98.99% with retention time $\mathbf{t_R}$= 29.152 min while its epimer **(+)-25b** showed *ee* of 99.06% with retention time $\mathbf{t_R}$= 31.022 min. Thus both the iodolactones **(-)-25a** & **(+)-25b** were well separated on GC. The optical rotation observed was $[\alpha]_D^{20}$ = -37.26 (c=3, $CHCl_3$) for iodolactone **(-)-25a** and $[\alpha]_D^{20}$ = +21.63 (c=3, $CHCl_3$) for epimeric iodolactone **(+)-25b**.

Dehydrohalogenation of iodolactone **(-)-25a** with DBU in tetrahydrofuran at room temperature furnished the natural wine lactone **(-)-1a** in 75% yield. The synthetic wine lactone thus obtained was found to be in > 99% *ee*. ^{1}H-NMR spectrum of **(-)-1a** showed doublet at δ 1.25 (3H) with *J* = 7.39 Hz for methyl group (-CH*C*H_3). Doublet at δ 1.01 (3H) for methyl group in ^{1}H-NMR spectrum of **(-)-25a** collapsed to a singlet at δ 1.73 (3H) (-CH=C*C*H_3) indicating downfield shift after dehydrohalogenation. Triplet at δ 4.66 (1H, -*CH*I) observed in ^{1}H-NMR spectrum of **(-)-25a** disappeared and appearance of multiplet at δ 5.51 (1H) confirmed the presence of olefinic proton. ^{13}C-NMR spectrum of the compound **(-)-1a** displayed 10 signals corresponding to 10 carbons in the molecule. Among these signals, doublet at δ 118.49 (H_3CC=*C*H) and a singlet at δ 140.84 (H_3C*C*=CH) were characteristics of the olefinic carbons. Mass spectrum showed M^+ peak at 166 (32). The optical rotation observed was $[\alpha]_D^{20}$= -13.48 (*c* 3.0, $CHCl_3$), literature[6] $[\alpha]_D^{20}$ = -13.1 (*c* 3.0, $CHCl_3$).

On the similar lines, epimeric iodolactone **(+)-25b** was also dehydrohalogenated with DBU in tetrahydrofuran at room temperature to furnish unnatural isomer of the wine lactone *i.e.* **(+)-1b** in 71% yield.

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^{1}H-NMR spectrum of the compound **(+)-1b** showed multiplet at δ 1.12-1.16 (1H), a doublet at δ 1.19 (3H) for methyl group (-CH*CH*$_3$) with J= 7.35 Hz, multiplet at δ 1.66-1.70 (1H), a singlet at δ 1.79 for methyl group attached to the olefinic carbon (-CH=C*CH*$_3$), a multiplet at δ 1.95-2.03 (2H) for methylene group, a multiplet at δ 2.23-2.31 (1H) for methine proton (-*CH*CHCH$_3$), a dq at δ 2.89 (1H) with *J* = 7.52 Hz & *J* = 7.33 Hz for methine proton (-*CH*CH$_3$), a multiplet at δ 5.65-5.68 (1H) confirmed the presence of olefin. ^{13}C-NMR spectrum of the compound **(+)-1b** displayed 10 signals corresponding to 10 carbons in the molecule. Among these signals, doublet at δ 116.80 (H$_3$CC=*CH*-) and a singlet at δ 143.93 (CH$_3$*C*=CH-) were the characteristics peaks for olefinic carbons. The optical rotation observed $[\alpha]_D^{20}$ = +112.15 (c=3, $CHCl_3$), literature[6] $[\alpha]_D^{20}$ = +112 (c=3, $CHCl_3$). Enantiomeric purity was determined by chiral GC to be 99.86% (retention time $\mathbf{t_R}$=13.271 min). Mass spectrum showed M^+ peak at 166(22).

2.2.2.5 Conclusions

1. A diastereoselective route, simple synthesis of natural wine lactone **(-)-1a** and its C-3-epimer in 26% overall yield has been achieved.

2. CAN/NaI mediated iodolactonization, a novel protocol developed by us has been utilized as the key step to accomplish epimeric iodolactones **(-)-25a** & **(+)-25b**.

3. The starting material (+)-isolimonene is a natural product and available readily.

4. The reagents used and the reaction conditions employed are easy and thereby making the sequence efficient and attractive.

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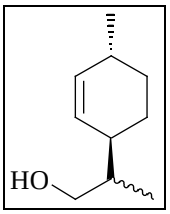
2.2.2.6 Experimental

2-[(*1R, 4R*)-Methyl-cyclohex-2-enyl]-propan-1-ol[9], [23]



A solution of (+)-isolimonene **22** (6.138 g, 0.045 mol) in tetrahydrofuran (35 mL) was introduced into a three necked 250 mL round bottomed flask under argon atmosphere. The 9-borabicyclo[3.3.1]nonane (9-BBN, 0.5 M solution in THF, 110 mL, 6.71 g, 0.055 mol) was added slowly at 0^0C over a period of 1h with stirring. The reaction mixture was stirred at 0^0C for 2h, brought to room temperature and stirred for 5 hr. Then 3N NaOH (25 mL) was added in a single portion at 0^0C and H_2O_2 (50%, 14.4 mL) was added dropwise at such a rate that the temperature of the reaction should not rise above 10^0C. The reaction was stirred at room temperature for 2h. The aqueous phase was saturated with NH_4Cl and extracted with diethyl ether. The combined organic extracts were washed with water (30 mL), brine (30 mL) was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude alcohol **44**. The alcohol was purified by column chromatography (silica gel 60-120 mesh, eluent ethyl acetate:pet. ether 5:95).

Yield	: 5.283 g (76%).
Molecular Formula	: $C_{10}H_{18}O$; Colourless liqid.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3500-3350 (broad absorption), 3015, 2940, 1281.
^{1}H NMR ($CDCl_3$, 200MHz)	: 0.8-1 (m, 6H), 1.2-2.00 (m, 5H), 2.35-2.51 (m, 2H), 3.45-3.87 (m, 2H), 5.5 (d, 2H).
Mass (m/z)	154 (M+, 23), 121 (20), 107 (37), 94 (100), 79 (42), 67 (27).

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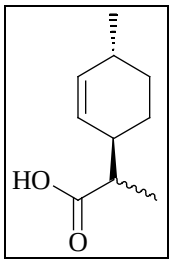
2-[(*1R, 4R*)-Methyl-cyclohex-2-enyl]-propionic acid[10], [24]



The alcohol **23** (2.4 g, 15.6mmol) was dissolved in acetone (25 mL) and cooled to 0^0C. Jones' reagent was added dropwise till the dark orange brown colour persisted. The reaction mixture was brought to room temperature and stirred for 2 h. Diethyl ether (45mL) was added to precipitate out the chromous salts. The reaction mixture was filtered through short bed of celite and the residue was washed with diethyl ether (2 × 20mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to furnish crude acid. The acid was purified by column chromatography (silica gel 60-120 mesh, eluent:ethyl acetate:pet. ether 12:88).

Yield	: 2.07 g (78%).
Molecular Formula	: $C_{10}H_{15}O_2$.; Colourless liqid.
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	: 3000-2500, 1690, 1280.
^{1}H NMR ($CDCl_3$, 200MHz)	: 0.00 (s, 6H); 0.83 (s, 9H); 3.25 (bs, 1H); 3.33 (s, 3H); 3.36 (s, 3H); 3.67 (m, 4H); 4.63 (m, 4H).
^{13}C NMR ($CDCl_3$, 50MHz)	: 0.95 (d, 3H, *J* = 6.93 Hz), 1.15 (dd, 3H, *J* = 6.84 Hz), 1.25-1.5 (m, 2H), 1.7-1.95 (m, 2H), 2.1-2.25 (m, 1H), 2.3-2.55 (m, 2H), 5.45 (d, 1H, *J* = 10 Hz), 5.59 (d, 1H, *J* = 10 Hz).
Mass (ESI) m/z	167 (M^+-1, 9), 94 (100), 79 (32).

Iodolactones[12] (-)25a & (+)-25b

To a solution of isolimonene acid **24** (1.5 g, 8.93 mmol) in acetonitrile (12 mL) was added NaI (2.68 g, 17.86 mmol) and Cericammonium nitrate (2.901 g, 17.86 mmol) in 5 mL of water was added dropwise. The solution was allowed to stirr at room temperature for 35

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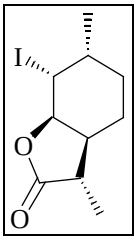
min.. The reaction mixture was quenched with water (8 mL) and extracted successively with dichloromethane (4 × 30 mL). The organic layer was washed with saturated $Na_2S_2O_3$ (25 mL), water (25 mL), and finally with brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to furnish crude epimeric mixture of iodolactones **(-)-25a** & **(+)-25b**. Both the iodolactones were separated by careful column chromatography (60-120 mesh, eluent: ethyl acetate:pet ether 0.75:99.25).

Iodolactones **(-)-25a** & **(+)-25b** were also obtained as mixture by conventional method using saturated $NaHCO_3/I_2$ in diethyl ether at 0^0C in 52% yield.[11]

Yield: 1.55 g (59%).

[(*3S, 3aS, 6R, 7R, 7aR*)-(*3a*, 4, 5, 6, 7, *7a*)-Hexahydro-3,6-dimethylbenzofuran-2(3H)-one, Iodolactone [(-)-25a]



Molecular Formula : $C_{10}H_{15}IO_2$; solid.

Ee: 98.99% $\mathbf{t_R}$ [(-)-8a]: 29.152 min

Melting Point. 75-76 ºC

Optical Rotation $[\alpha]_D$: -37.26, (*c* 3.0, $CHCl_3$)

IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$) : 2965, 2873, 1780, 1455, 1385.

^{1}H NMR ($CDCl_3$, 200MHz) : 1.01 (d, 3H, *J* = 6.34 Hz), 1.29 (d, 3H, *J* = 7.33 Hz,), 1.39-1.47 (m, 4H), 1.81-1.93 (m, 1H), 2.35-2.51 (m, 2H), 4.66 (t, 1H, *J* = 3.76 Hz), 4.92 (dd, 1H, J = 3.92 Hz,).

^{13}C NMR($CDCl_3$, 50MHz) : 14.02 (q), 22.26 (q), 26.37 (t), 28.06 (t), 31.81 (d),

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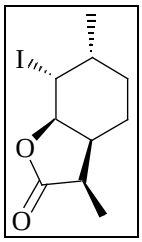
	38.81 (d), 41.55 (d), 43.39 (d), 81.73 (d), 179.07 (s).
Mass (m/z)	294 (M^+, 8), 167 (76), 149 (18), 121 (48), 93 (100), 81 (32), 67 (11).
Elemental Analysis	**Calcd.** : C 40.83; H 5.14; I 43.14
	Found : C 40.90; H 5.20; I 42.71

[(*3R, 3aS, 6R, 7R, 7aR*)-(*3a*, 4, 5, 6, 7, *7a*)-Hexahydro-3,6-dimethylbenzofuran-2(3H)-one, Iodolactone [(+)-25b]



Molecular Formula	: $C_{10}H_{15}IO_2$; solid.
Ee:	: 99.06% $\mathbf{t_R}$ [(+)-8b]: 31.022 min.
Melting Point.	: 72-73^{0}C.
Optical Rotation $[\alpha]_D$	: +21.63, (*c* 3.0, $CHCl_3$).
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 2965, 2934, 2875, 1781, 1455, 1385, 1328.
^{1}H NMR ($CDCl_3$, 200MHz)	: 0.94 (d, 3H, *J* = 5.37 Hz), 1.29 (d, 3H, *J* = 6.98 Hz), 1.21-1.43 (m, 4H), 1.64-1.75 (m, 1H), 2.74-2.83 (m, 2H), 4.72-4.77 (m, 2H).
^{13}C NMR($CDCl_3$, 50MHz)	: 8.93 (q), 23.28 (t), 23.70 (q), 27.85 (t), 30.66 (d), 35.66 (d), 42.25 (d), 42.59 (d), 82.23 (d), 179.07 (s).
Mass (m/z)	294 (M^+, 7), 167 (94), 149 (18), 121 (54), 93 (100), 77 (12), 67 (8).
Elemental Analysis	**Calcd.** : C 40.83; H 5.14; I 43.14
	Found : C 40.95; H 5.02; I 42.83

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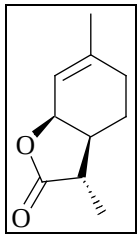
(-)-(*3S,3aS,7aR*)-*3a*,4,5,*7a*-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one: Wine lactone [(-)-1a]



A solution of **(-)-25a** (0.250 g, 0.85mmol) & DBU (0.166 g, 1.09mmol) in dry tetrahydrofuran (10mL) was stirred at room temperature for 5h. 6N HCl (15mL) was added and the mixture was extracted with diethyl ether (4×20mL). The combined organic layer was washed with water (5mL), brine (5mL) and dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone **(-)-1a**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet.ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane.

Yield	: 0.107 g, (76%).
Molecular Formula	: $C_{10}H_{14}O_2$; solid.
Ee:	: 99.58% $\mathbf{t_R}$ [(-)-1a]: 10.939 min.
Melting Point.	: 49-50 ºC (48-50 ºC)[6].
Optical Rotation $[\alpha]_D$	: -13.48, (*c* 3.0, $CHCl_3$), ((-13.1, (*c* 3.0, $CHCl_3$).
IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$)	: 3020, 2981, 2935, 1761, 1216.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.25 (d, 3H, *J* = 7.39 Hz), 1.73 (s, 3H), 1.77-2.02 (m, 4H), 2.19-2.32 (m, 1H), 2.34-2.45 (m, 1H), 4.85-4.90 (m, 1H), 5.51 (m, 1H).
^{13}C NMR($CDCl_3$, 50MHz)	: 13.62 (q), 21.85 (t), 23.29 (q), 25.53 (t), 37.11 (d), 39.90 (d), 74.89 (d), 118.49 (d), 140.84 (s), 179.51 (s).
Mass (m/z)	166 (M^+, 22), 151 (37), 138 (12), 123 (14), 107 (40), 93 (100), 79 (87), 67 (52), 55 (88).

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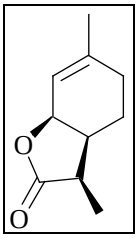
Elemental Analysis **Calcd**. : C 72.26 H 8.49

Found : C 72.37 H 8.46

(+)-(*3R,3aS,7aR*)-*3a*,4,5,*7a*-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one: [(+)-1b]



A solution of **(-)-25b** (0.250 g, 0.85mmol) & DBU (0.166 g, 1.09mmol) in dry tetrahydrofuran (10mL) was stirred at room temperature for 5h. 6N. HCl (15mL) was added and the mixture was extracted with diethyl ether (4×20mL). The combined organic layer was washed with water (5mL), brine (5mL) and dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone **(-)-1b**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet. ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane.

Yield : 0.1 g, (71%).

Molecular Formula : $C_{10}H_{14}O_2$; solid.

Ee: : 99.86% $\mathbf{t_R}$ [(+)-1b]: 13.271 min.

Melting Point. : 58-60^{0}C (57-59^{0}C)[6].

Optical Rotation [α]$_D$: +112.15, (*c* 3.0, $CHCl_3$), [+112, (*c* 3.0, $CHCl_3$).

IR $\tilde{\nu}$ (cm^{-1}) ($CHCl_3$) : 3020, 2981, 2935, 1761, 1216.

^{1}H NMR ($CDCl_3$, 200MHz) : 1.12-1.16 (m, 1H), 1.19 (d, 3H, *J* = 7.35 Hz), 1.66-1.70 (m, 1H), 1.79 (s, 3H), 1.95-2.03 (m, 2H), 2.23-2.31 (m, 1H), 2.89 (dq, 1H, *J* = 7.52 Hz, *J* = 7.33 Hz), 4.60-4.64 (m, 1H), 5.65-5.68 (m, 1H).

^{13}C NMR($CDCl_3$, 50MHz) : 9.13 (q), 19.51 (t), 23.62 (q), 28.73 (t), 37.62 (d), 40.05 (d), 74.56 (d), 116.80 (s), 143.92 (s178.33 (s).

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Mass (m/z)	166 (M^+, 32), 151 (57), 138 (12), 123 (19), 93 (100), 79 (65), 55 (39).
Elemental Analysis	**Calcd.** : C 72.26 H 8.49
	Found : C 72.40 H 8.52

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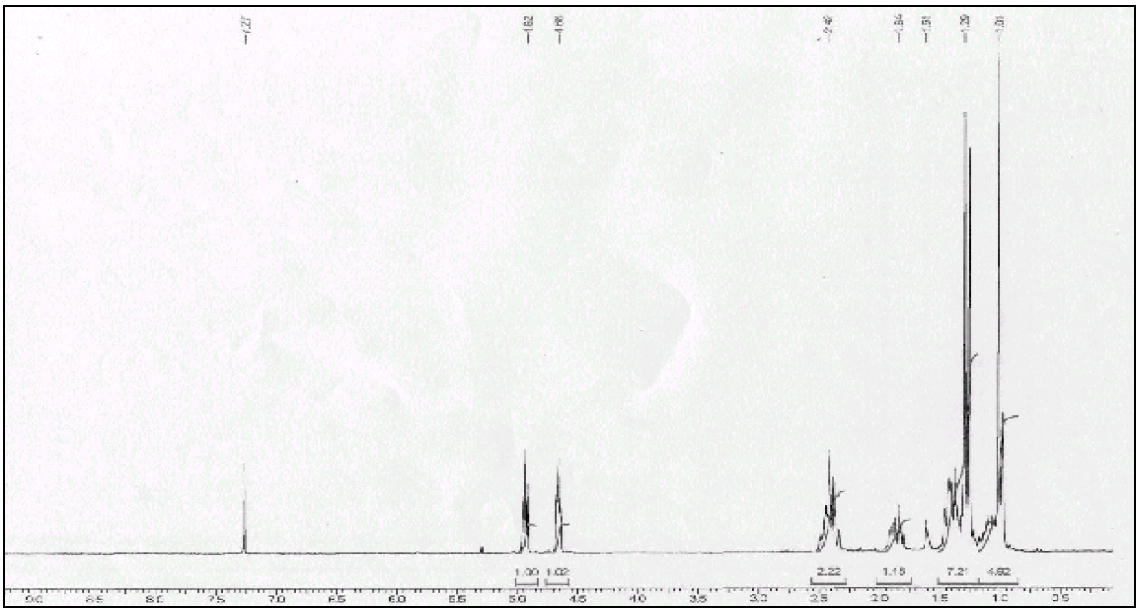
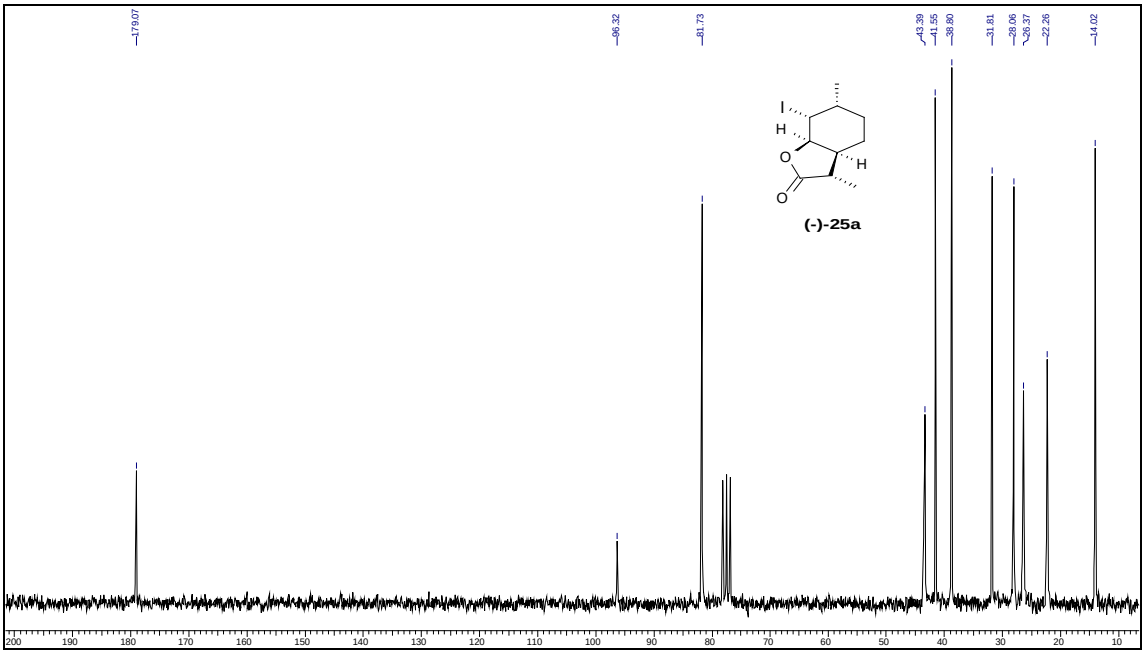


^{1}H-NMR spectrum of Compound **(-)-25a** ($CDCl_3$, 200 MHz)



^{13}C-NMR of compound **(-)-25a** ($CDCl_3$+CCl_4, 50 MHz)

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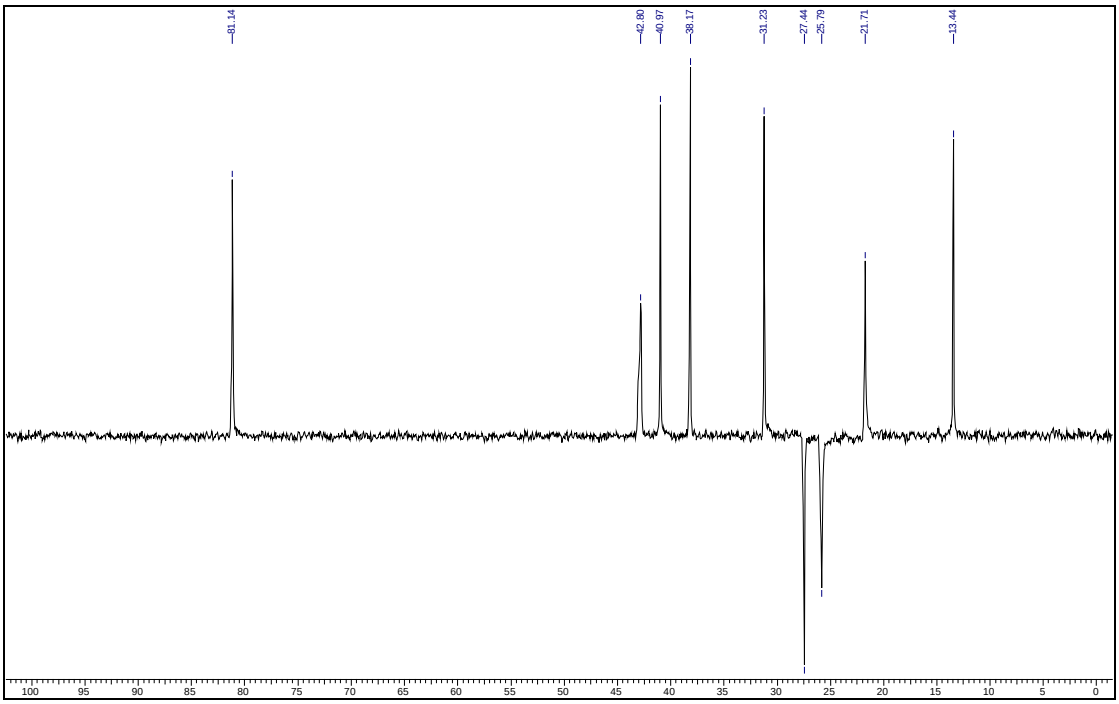
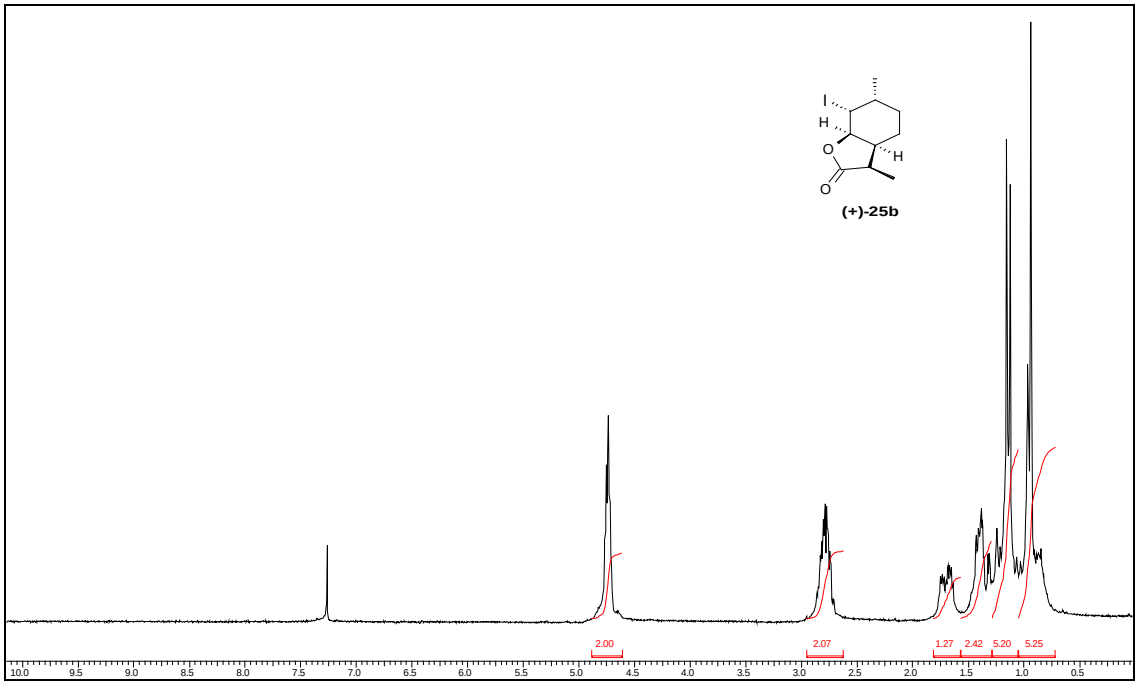


DEPT of compound **(-)-25a** ($CDCl_3$+CCl_4, 50 MHz)



^{1}H-NMR spectrum of Compound **(+)-25b** ($CDCl_3$, 200 MHz)

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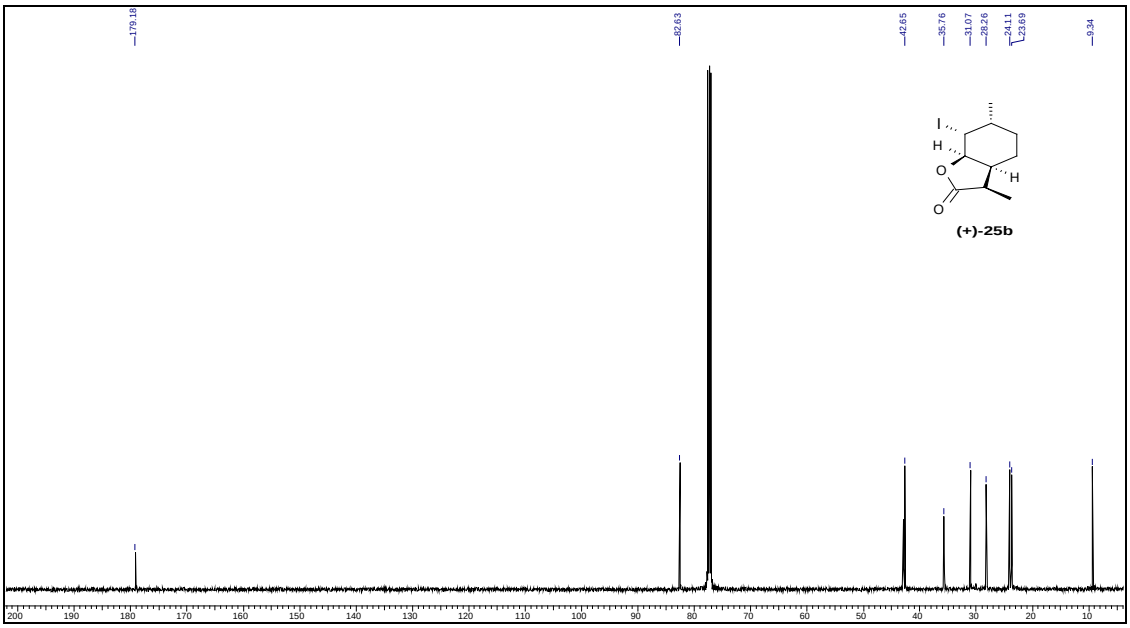
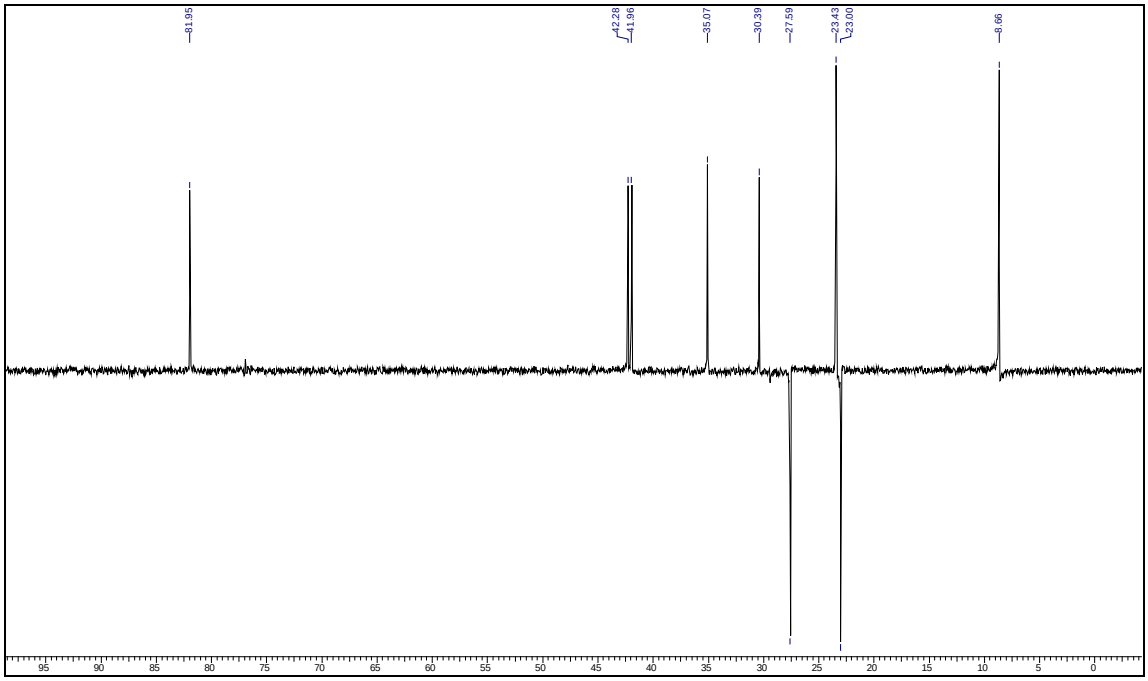


^{13}C-NMR of compound **(-)-25b** ($CDCl_3$+CCl_4, 50 MHz)



DEPT of compound **(-)-25b** ($CDCl_3$+CCl_4, 50 MHz)

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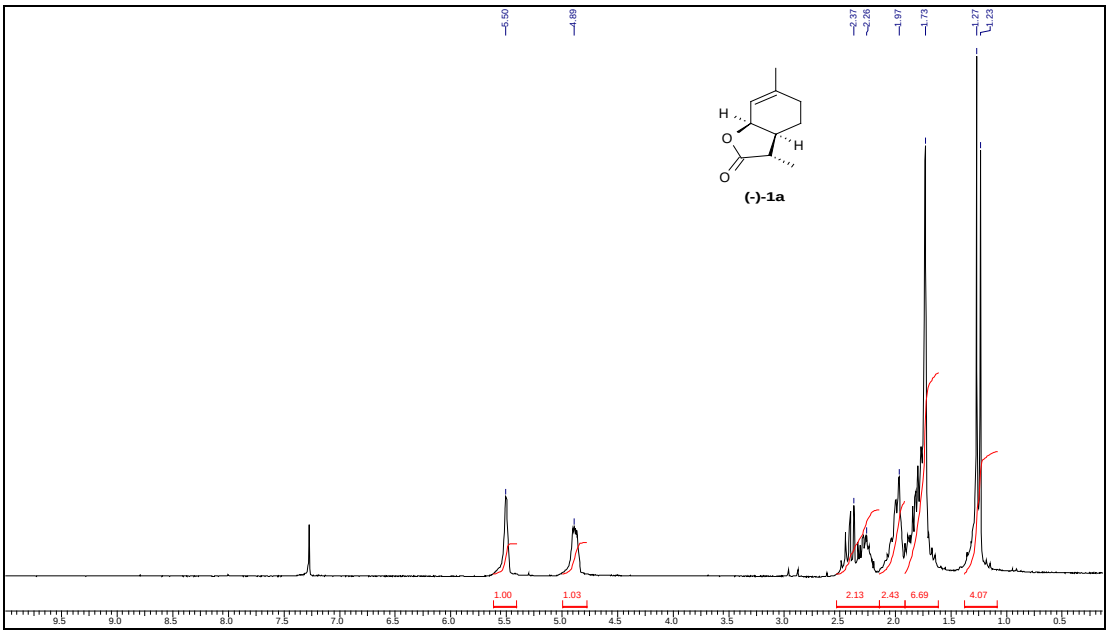
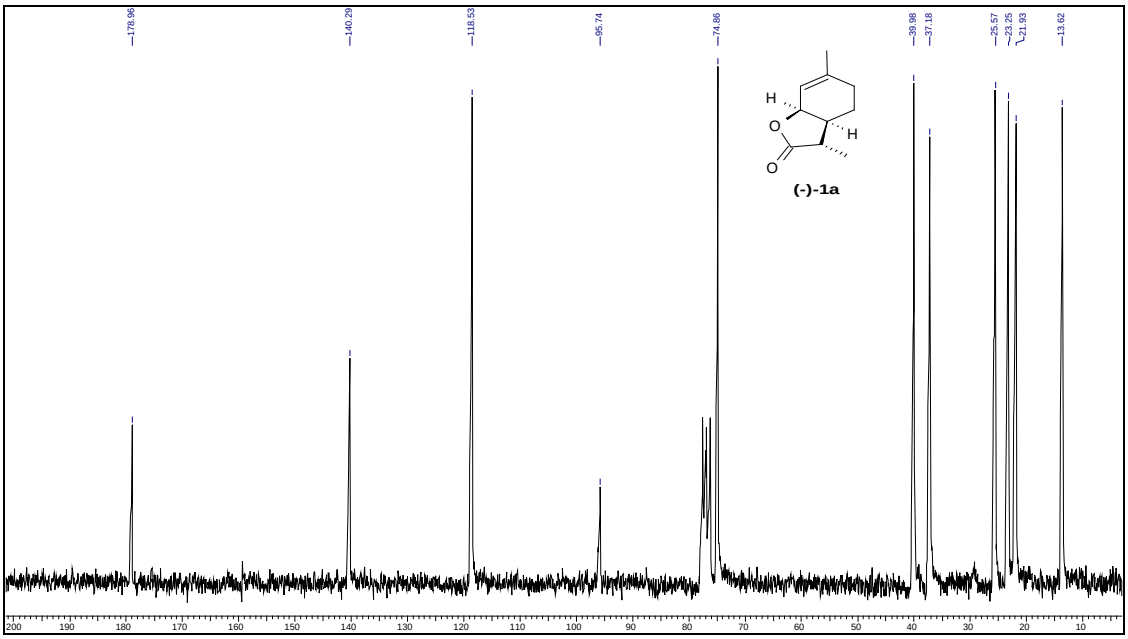


^{1}H-NMR spectrum of compound **(-)-1a**, Wine lactone ($CDCl_3$, 200 MHz)



^{13}C NMR of compound **(-)-1a**, Wine lactone ($CDCl_3$+CCl_4, 50 MHz)

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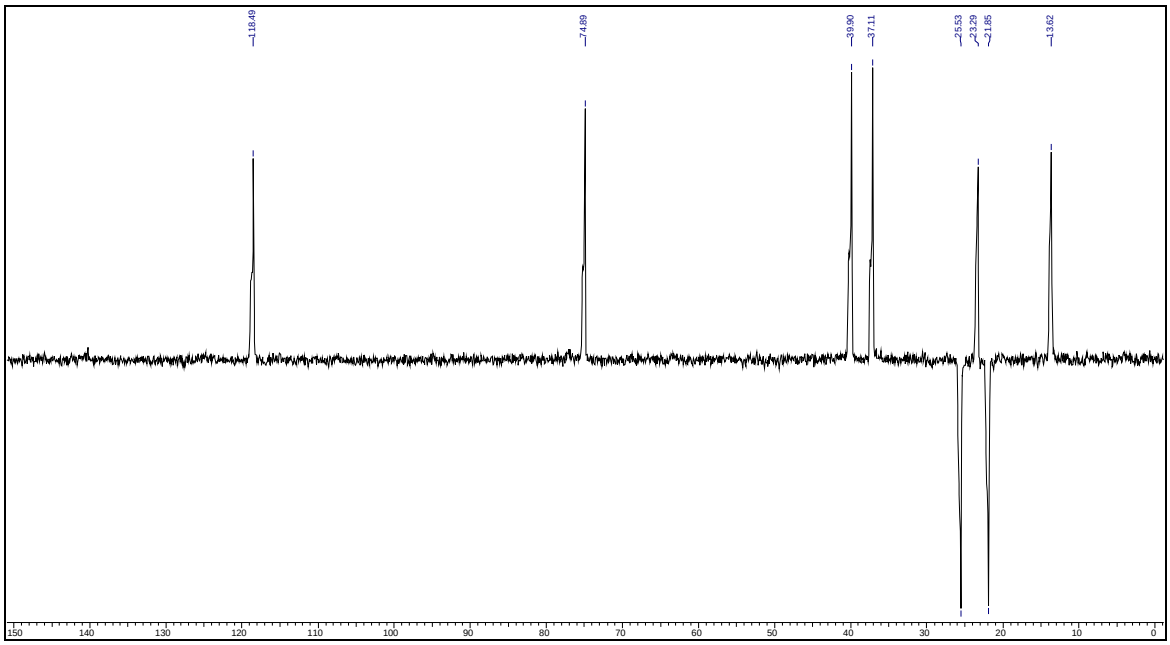
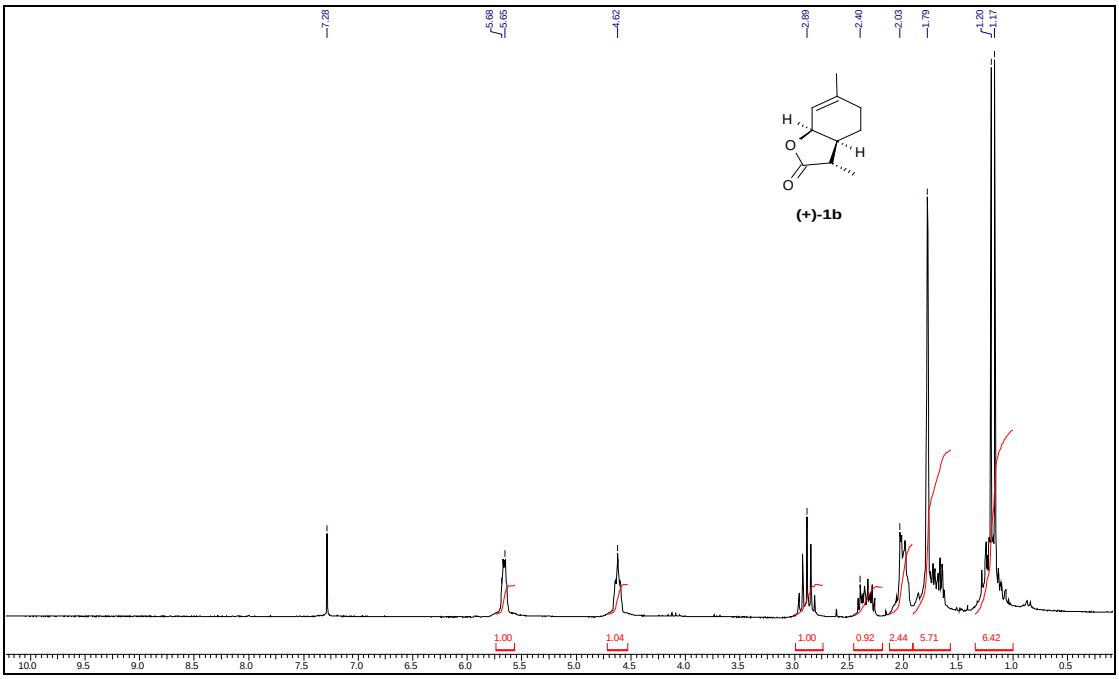


DEPT of compound **(-)-1a**, Wine lactone ($CDCl_3$+CCl_4, 50 MHz)



^{1}H NMR spectrum of compound **(+)-1b** ($CDCl_3$, 200 MHz)

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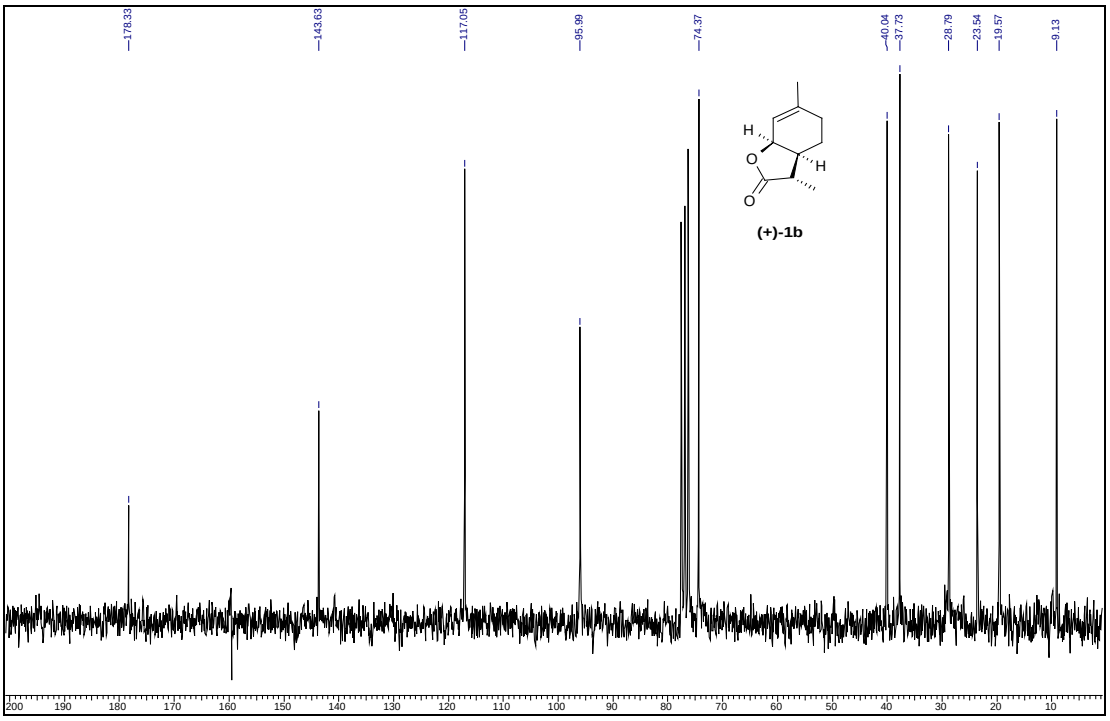
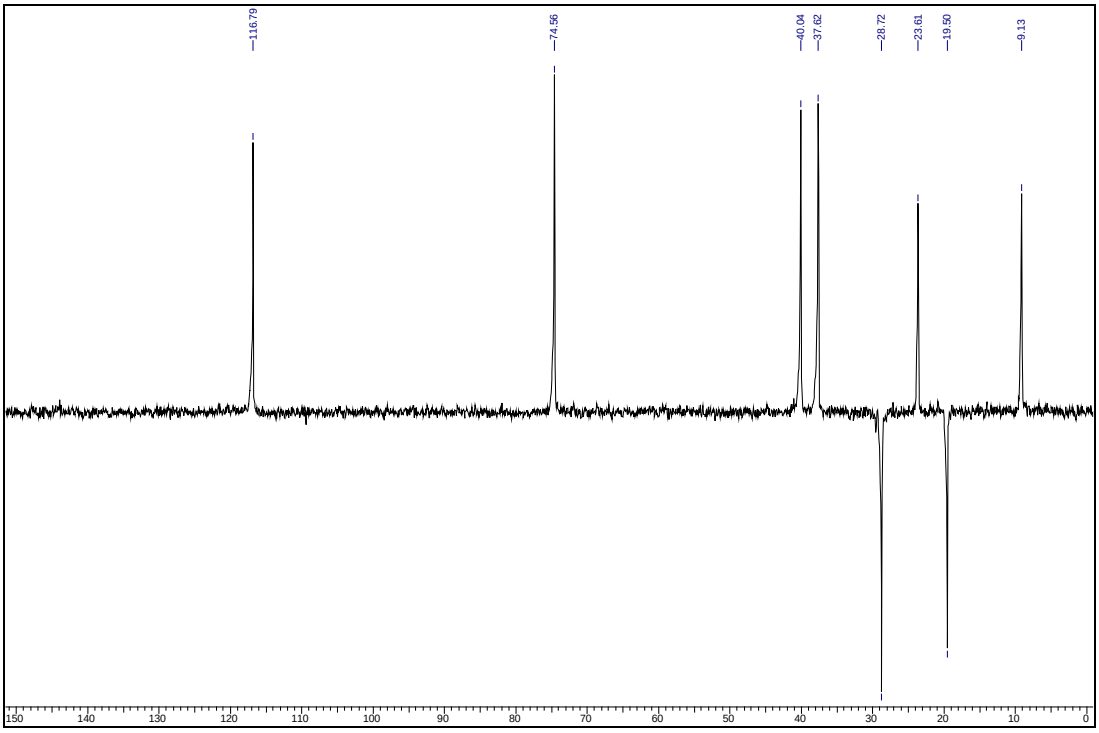


^{13}C NMR of compound **(+)-1b** ($CDCl_3$+CCl_4, 50 MHz)



DEPT of compound **(+)-1b** ($CDCl_3$+CCl_4, 50 MHz)

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2.2.2.7 References

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