SYNTHETIC STUDIES TOWARDS D-(+)-BIOTIN, OLOPATADINE, α-CUPARENONE AND DEVELOPMENT OF IMPORTANT SYNTHETIC METHODOLOGIES

A THESIS

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Under the supervision of

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards D-(+)-Biotin, Olopatadine, α-Cuparenone and Development of Important Synthetic Methodologies"** submitted by Mr. Pradeep B. Lasonkar was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies towards D-(+)-Biotin, Olopatadine, α-Cuparenone and Development of Important Synthetic Methodologies"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr. Subhash P. Chavan. This 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.

December, 2013

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Dedicated To

…….My parents

Acknowledgements

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Pradeep B. Lasonkar

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Contents

General Remarks

1. All the melting points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, Scheme numbers and reference numbers given in each section refer to that section only.
3. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC.
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/ninhydrine/PMA solutions.
6. In cases where chromatographic purification was done, silica gel (230-400 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 AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethylsilane/residual $CHCl_3$ was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent 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.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Abbreviations

Ac	Acetyl
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	*tert*-Butoxy carbonyl
Bu	Butyl
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
CSA	Camphorsulfonic acid
m-CPBA	*meta*-Chloroperbenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DET	Diethyl tartrate
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL	Diisobutylaluminium hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethylamino pyridine
DMP	2,2-Dimethoxypropane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-Dimethylformamide

DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Et	Ethyl
g	gram(s)
h	hour(s)
IBX	2-Iodoxybenzoic acid
Im	Imidazole
IR	Infra red
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
Hz	Hertz
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
Me	Methyl
min	minute(s)
mL	millilitres
mmol	millimole
MP	Melting point
Ms	Methanesulfonyl
MW	Molecular weight
NaHMDS	Sodium hexamethyl disilazide
NMO	*N*-Methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate
PDC	Pyridinium dichromate
PMA	Phosphomolybdic acid
PMB	*para*-Methoxybenzyl
PTC	Phase transfer catalysis

PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-Toluene sulfonic acid
Py	Pyridine
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBTH	Tributyltinhydride
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

Abstract

The thesis entitled, **"Synthetic Studies towards D-(+)-Biotin, Olopatadine, α-Cuparenone and Development of Important Synthetic Methodologies"** is divided into three chapters. Chapter one deals with the introduction and synthesis of D-(+)-biotin. The second chapter deals with the synthetic studies towards olopatadine and methodology for one-pot migration-formylation of benzyl aryl ethers. The synthetic studies towards α-cuparenone and a methodology for allylic oxidation of electron deficient cyclohexenes are described in chapter three.

Chapter 1: Synthetic studies towards D-(+)-biotin

Section 1: Introduction to biotin

The present section includes the details about biological action and comprehensive literature on synthesis of biotin. D-(+)-biotin (vitamin H)[1] is a water-soluble vitamin, involved in an essential part of the metabolic cycle causing catalytic fixation of carbon dioxide in the biosynthesis of fatty acids, sugars and α-amino acids. Kogl *et al*.[2] have firstly characterized it as a growth factor for yeast in 1936 in its methyl ester form, which was originally referred to as ''bios IIb'' and later as ''biotin." It is used as a feed additive especially in the poultry industry. In addition, recently it was found that biotin (**1**) enhances insulin secretion in animals, suggesting it to be a promising therapeutic candidate as an anti-diabetic drug.[3] Biotin has remarkably strong affinity towards avidin[4] and streptavidin[1b] so their complexes were extensively used in the area of drug delivery, immunoassay, isolation and localization. D-(+)-Biotin (Figure 1) finds usage clinically for the treatment of hair fall, brittle nails and in tonic formulations of children.[4b]

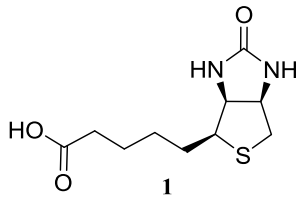

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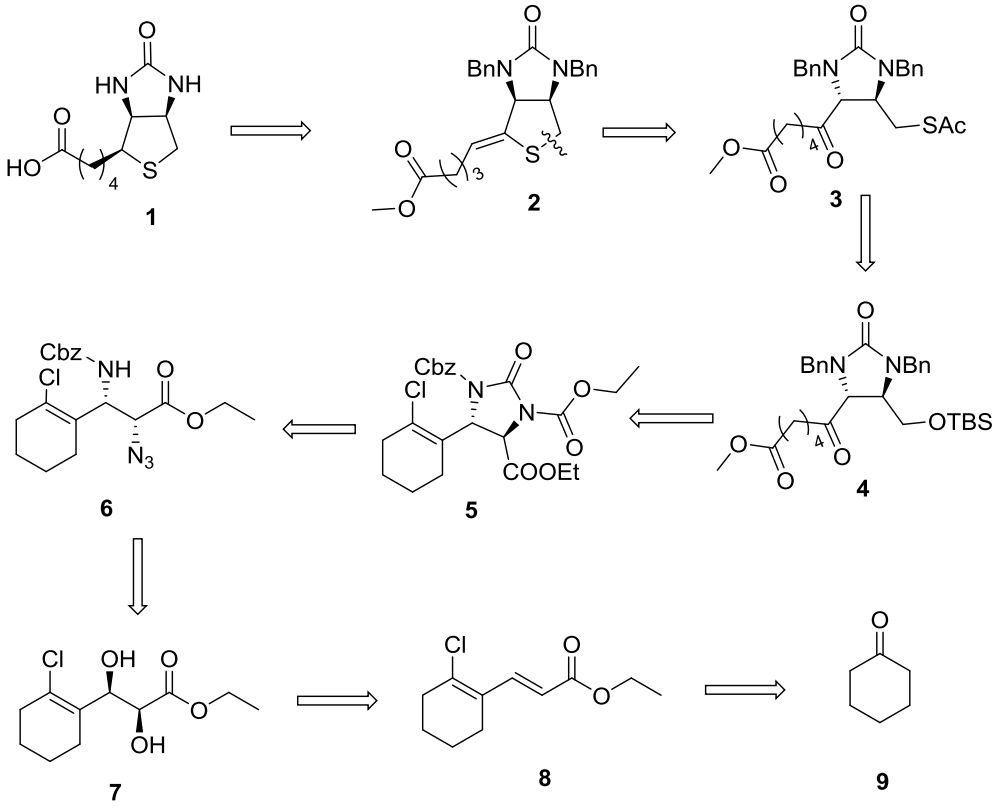
Figure 1. Structure of D-(+)-Biotin

Section 2: A novel and enantioselective synthesis of D-(+)-Biotin *via* Sharpless asymmetric dihydroxylation strategy

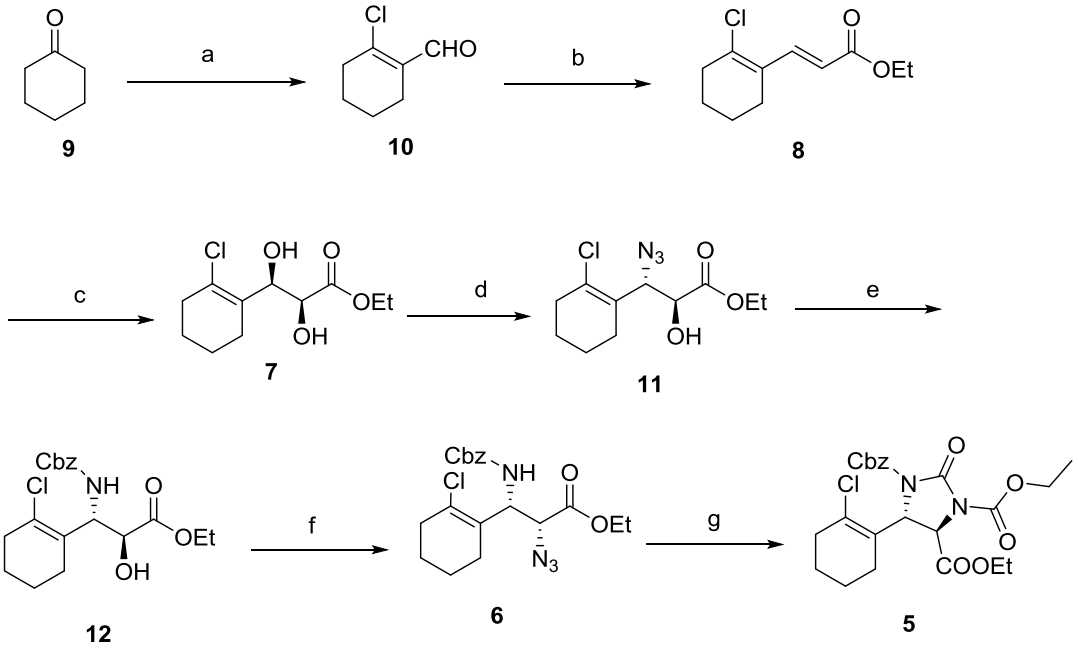
Lack of efficient fermentation methods for biotin have drawn the attention of organic chemists towards its synthesis. Over the past decades, many efforts have been made on the development of an efficient process for the total synthesis of D-(+)-biotin (**1**) and a number of new synthetic approaches involving different stratergies for the control of three adjacent stereogenic centers are reported in the literature. Very few syntheses of D-(+)-biotin involving intermolecular asymmetric induction are reported in the literature.[1a] Herein, synthetic efforts towards developing an asymmetric total synthesis of **1** starting from commercially available achiral starting material *viz.* cyclohexanone is described. The envisaged retrosynthetic strategy for biotin (**1**) is delineated in Scheme 1.



Scheme 1. Retrosynthetic plan

Accordingly, the synthesis of biotin (**1**) began from cyclohexanone (**9**) as a commercially available starting material (Scheme 2). Following a literature procedure,[5] cyclohexanone (**9**) was subjected to Vilsmeier-Haack reaction to furnish aldehyde **10**, which was homologated using Wittig reaction to afford unsaturated ester **8**. This prochiral unsaturated ester **8** was deemed to be a suitable substrate for the installation of the chiral centers. The compound **8** was subjected to Sharpless asymmetric dihydroxylation (SAD)

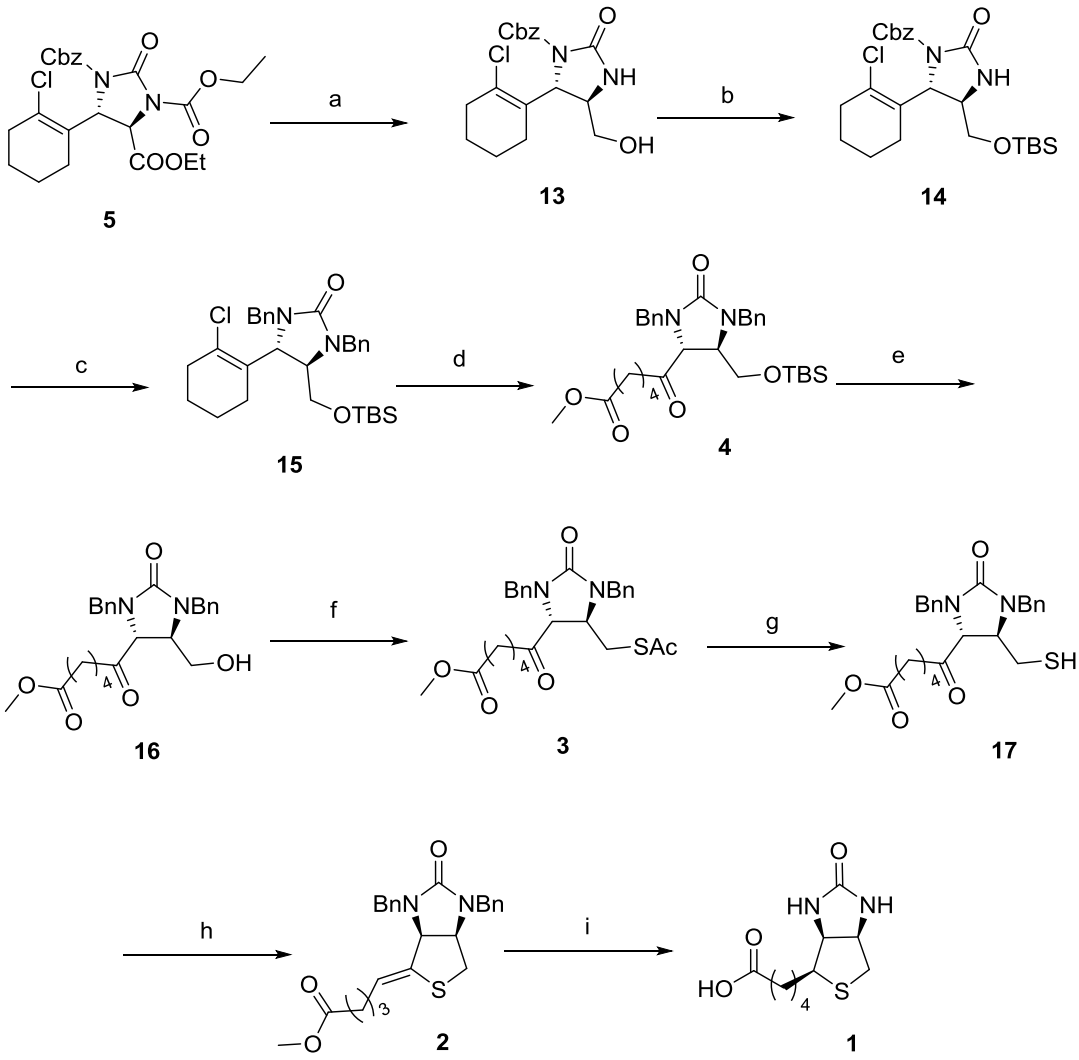
conditions with $(DHQD)_2PHAL$ as the chiral catalyst to yield chiral diol **7** in 84% yield with ≥99% *ee*. To install the azido functionality, diol **7** was converted into cyclic sulfite and by regioselective opening of this cyclic sulfite using NaN_3 get the β-azido ester **11**. Azide was reduced under Staudinger reaction condition followed by protection using CbzCl to furnish the carbamate **12**. The second amine was installed by converting hydroxyl group in **12** to its mesylate using mesyl chloride and triethylamine, which was displaced by azide using sodium azide in DMF to give azidoamine **6**.



Scheme 2. *<u>Reagents and conditions:</u> a) $POCl_3$, DMF, DCM, 0 °C-rt, 4 h, 95%; b) Ph_3PCHCO_2Et, DCM, rt, 4 h, 76%; c) $(DHQD)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^tBuOH:H_2O$ (1:1), 2 days, 84%, ≥99% ee; d) i) $SOCl_2$, Et_3N, DCM, 0 °C, 15 min; ii) NaN_3, DMF, rt, 4 h, 75% (over two steps); e) i) Ph_3P, Et_2O, rt, 2 h; ii) CbzCl, K_2CO_3, DCM, 0 °C, 80% (over two steps); f) i) MsCl, Et_3N, DCM, 0 °C, 30 min; ii) NaN_3, DMF, 50 °C, 12 h, 82% (over two steps); g) i) Ph_3P, Et_2O, rt, 2 h; ii) $ClCO_2Et$, Et_3N, DCM, 0 °C, 7 h, 86% (over two steps).*

The azide in **6** was further reduced by using Staudinger reaction condition to amine which on treatment with ethyl chloroformate in the presence of triethylamine, interestingly gave cyclic protected urea **5** (Scheme 2). After having compound **5** in hand, ester was reduced using $NaBH_4$ in methanol at 0 °C, to furnish hydroxyl compound **13**. Interestingly, here proximal carbamate was also selectively hydrolyzed during reduction. The protection of primary hydroxyl group in **13** with *tert*-butylchlorodimethylsilane in

the presence of imidazole in dichloromethane at room temperature gave TBS ether **14**. On treatment with sodium hydride and benzyl bromide, **14** was converted to its bisbenzyl imidazolidone **15**.



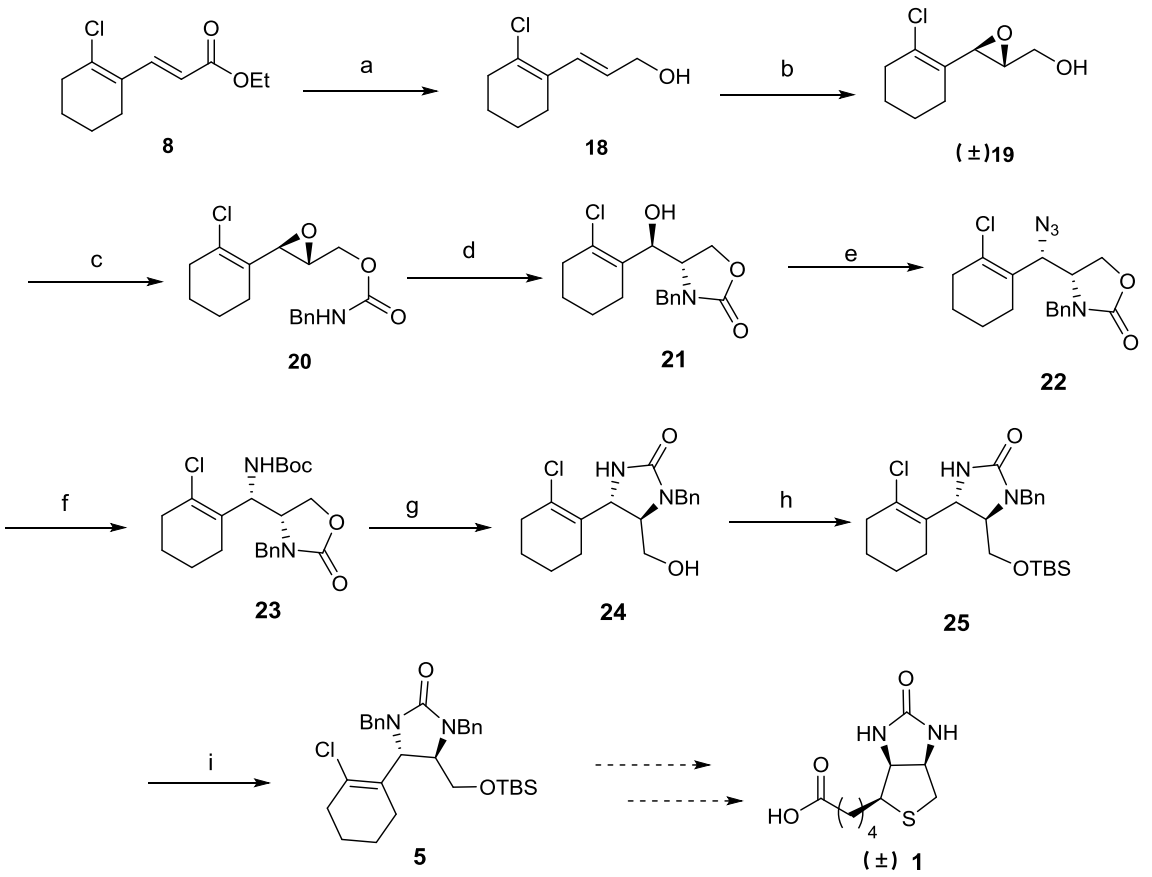
Scheme 3. *<u>Reagents and conditions:</u> a) $NaBH_4$, MeOH, 0 °C, 4 h, 79%, 30 min; b) TBSCl, imidazole, DMAP, DCM, 0 °C-rt, 24 h, 93%; c) NaH, BnBr, THF, 0 °C, 3 h, 95%; d) O_3, MeOH:DCM (1:5), $NaHCO_3$, -78 °C, 30 min, 92%; e) CSA, MeOH, rt, 30 h, 90%; f) i) TsCl, Et_3N, DMAP, DCM, 0 °C-rt, 24 h, 85%; ii) KSAc, DMF:THF, 80 °C, 2 h, 83 %; g) Lipase (Candida rugosa), phosphate buffer (pH 6.8), rt, 2 h, 80%; h) i) DBU, toluene, 100 °C, 3 h; ii) pTSA, toluene, rt, 4h, 82% (over two steps); i) ref. 6.*

On performing ozonolysis reaction in MeOH:DCM (1:5) solvent system, imidazolidone **15** was converted into ketoester **4**. Deprotection of TBS ether of **4** was carried out using camphorsulfonic acid in MeOH to afford the corresponding alcohol **16**. Introduction of

sulfur was done by converting the primary hydroxyl group into a good leaving group. Accordingly, the hydroxyl compound **16** was converted in to its tosylate derivative and it was in turn displaced by potassium thioacetate in DMF:THF (2:3) to furnish the thioacetate **3**. All the structural constituents for biotin were present and in place in compound **3**, the only thing remaining to complete the synthesis was acetate deprotection of **3** and the construction of thiophane ring. Efforts towards this seemingly simple deprotection of acetate **3** to thiol **17** failed under a variety of reaction conditions. Finally the hydrolysis under enzymatic condition using lipase (*Candida rugosa*) gave the requisite thiol **17** in good yields. Subsequent cyclization of thiol **17** by using catalytic amount of DBU furnished hydroxy thiophane and elimination of the hydroxy fuctionality using *p*TSA gave olefin **2** (Scheme 3). The olefin **2** thus obtained was identical with an authentic sample, with respect to IR, NMR, mass spectra, and specific rotation, prepared by a different route. Since the conversion of olefin **2** to (+)-biotin **1** has been reported by this group,[6] this constitutes a formal synthesis of D-(+)-biotin.

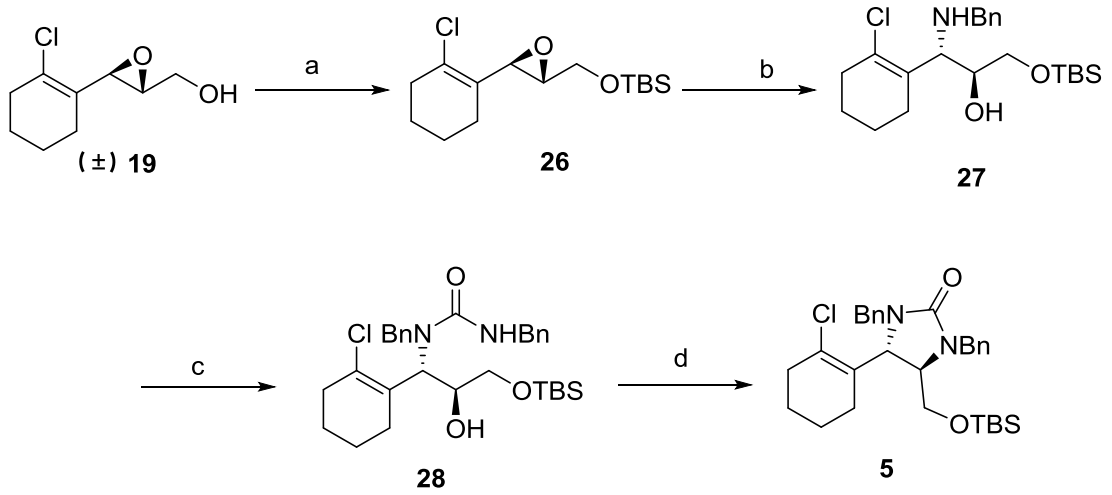
Section 3: Formal synthesis of biotin *via* epoxidation

This section describes the formal synthesis of biotin. The synthesis began from the unsaturated ester **8** (Scheme 4). Unsaturated ester **8** was reduced by using DIBAL-H to furnish allylic alcohol **18**, followed by epoxidation with *m*-CPBA and NaH_2PO_4 to get epoxy alcohol **19**. The crude epoxide **19** was treated with benzyl isocynate and pyridine in DCM to provide epoxy carbamate **20**. The subsequent intramolecular ring opening of **20** required extensive experimentation. Ultimately, the use of sodium hexamethyldisilazide in THF provided the desired oxazolidinone **21**.[7] The hydroxyl group of oxazolidinone **21** was activated as the methanesulfonate ester. Displacement with potassium phthalimide was attempted but it failed. Unwillingly, it was displaced by sodium azide as nitrogen containing nucleophile to provide azido oxazolidinone **22**. Azide was reduced under Staudinger reaction condition and amine was protected with $(Boc)_2O$ anhydride in THF: H_2O system (1:1), gave **23**. On treatment with NaH, **23** was converted into urea **24** liberating primary hydroxyl group. The primary hydroxyl group of **24** was protected as silyl ether by using TBSCl, imidazole and DMAP in DCM gave **25**. On treatment with sodium hydride, benzyl bromide **25** was converted to dibenzyl protected imidazolidone **5** (Scheme 3).



Scheme 4. *<u>Reagents and conditions:</u> a) DIBAL-H, DCM, -20 °C, 2 h; b) m-CPBA, NaH_2PO_4, DCM, 0 °C, 45 min; c) BnNCO, Py, DCM, rt, 12 h; d) NaHMDS, THF, 0 °C, 30 min, 63% (over four steps); e) i) MsCl, Et_3N, DCM, 0 ^oC, 30 min., ii) NaN_3, DMF, RT, Overnight, 80% (over two steps); f) i) Ph_3P, THF, RT, 2 h, ii) $(Boc)_2O$, THF:H_2O (1:1), 89% (over two steps) g) NaH, THF, 80 ^oC, 6 h. 92%; h) TBSCl, imdazole, DMAP, DCM, 24 h, 93%: i) NaH, BnBr, THF, 0 ^oC, 3 h, 95%.*

Fallowing this route, it was possible to access biotin in 22 steps and in 7.6% overall yield but this was not an azide free synthesis. As biotin has promising biological activity, an attempt was made to reduce the number of steps and avoid the use of sodium azide to make it a practical method (Scheme 5). Keeping these things in mind, synthetic strategy was modified. Accordingly, the primary hydroxyl group of epoxy alcohol **19** was protected as its silyl ether **26**.



***Scheme 5**: <u>Reagents and conditions</u>: a) TBSCl, imidazole, DMAP, DCM, 24 h, 93%; b) $BnNH_2$, $ZrCl_4$, 30 min, RT, 85%; c) BnNCO, DCM, RT, 12 h, 95%; d) KH, TsCl, HMPA, THF, 0 ^oC, 1 h, 81%.*

Epoxide **26** on ring opening aminolysis by using zirconium chloride with benzyl amine, afforded aminol **27**.[8] Aminol **27** on treatment with benzyl isocyanate gave acyclic urea **28**. Selective cyclization to the imidazolidone **5** was accomplished under carefully controlled conditions.

Chapter 2: Synthetic studies towards olopatadine and one-pot migration-formylation of benzyl aryl ethers under Duff reaction condition

Section 1: Introduction to olopatadine

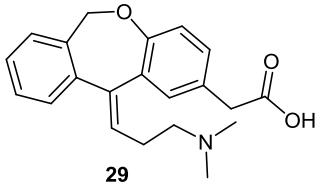
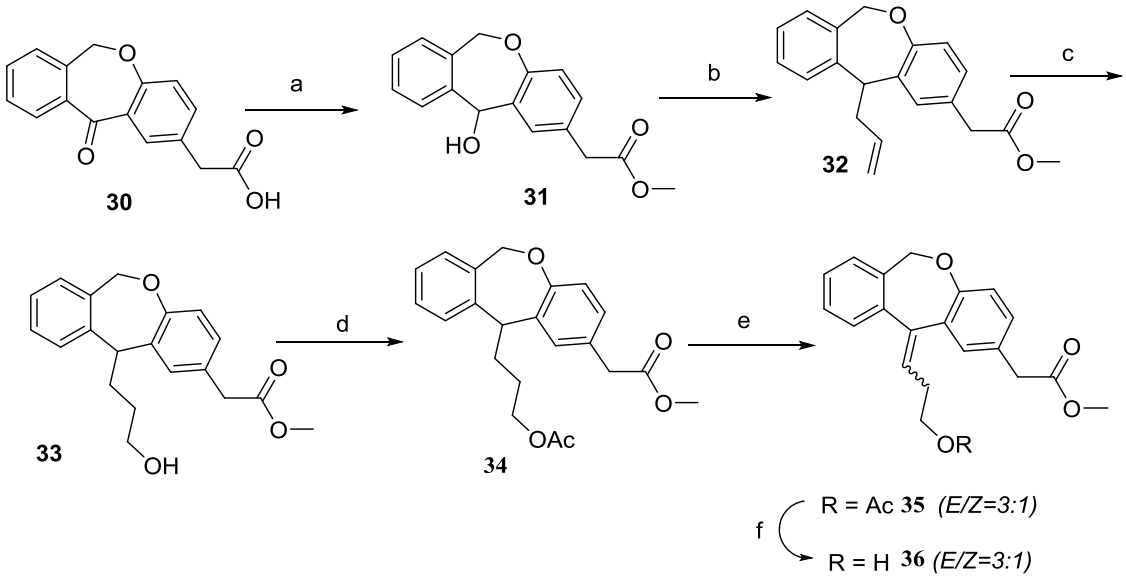


Figure 2. Structure of olopatadine

This section describes the biological activity and reported synthetic routes to olopatadine **29**. Olopatadine hydrochloride **29** is an antihistaminic drug ranked in 'Top 200 Brand Name Drugs by total US prescriptions in 2010'.[9] It is selective histamine H_1 receptor antagonist. It also shows mast cell stabilisation property. Olopatadine is used for the treatment of ocular symptoms of seasonal allergic conjunctivitis. The compound may be administered in a solid oral dosage form such as 'allelock®' tablets, as ophthalmic solution form 'pataday®', 'patanol®' and nasal spray 'patanase®'. Olopatadine was

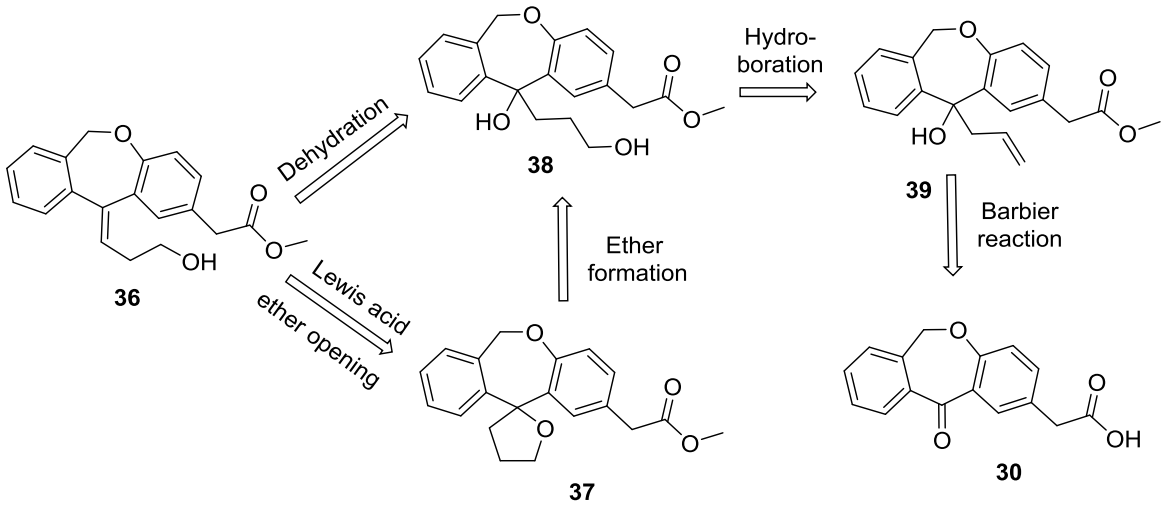
developed by Kyowa Hakko Kirin Co. Ltd. and is produced commercially by the synthetic route using Wittig reaction as the key step.[10]

Section 2: A simple synthesis of novel antihistaminic drug olopatadine



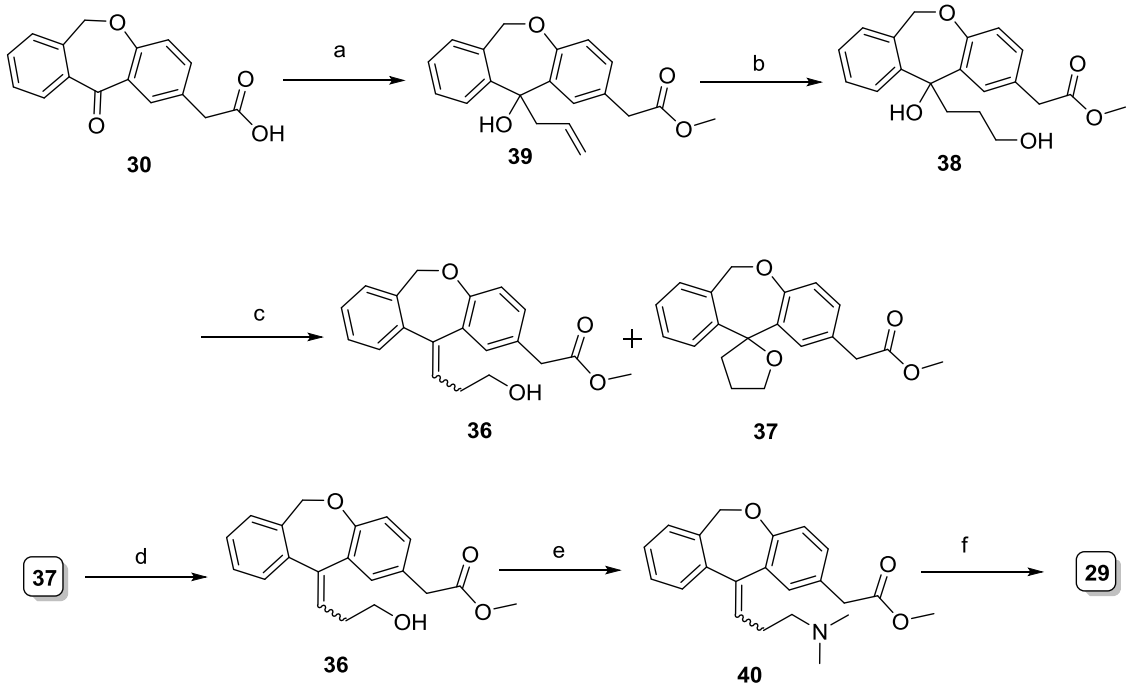
Scheme 6. *Reagents and conditions: a) i) $SOCl_2$, MeOH, 24 h, rt, quent; ii) $NaBH_4$, MeOH, 0 ºC, 2 h, 93%; iii) Allyl-TMS, $BF_3{\cdot}Et_2O$, 0 ºC-rt, DCM, 4 h, 83%; iv) $BH_3{\cdot}DMS$, NaOH, H_2O_2, THF, 0 ºC-rt, 12 h, 81%; a) Py, Ac_2O, 0 ºC-rt, DCM, 4 h, 96%; b) DDQ, Dioxane, Reflux, 12 h, 40%; c) K_2CO_3, MeOH, 30 min., 90 %.*

The synthesis (Scheme 6) of olopatadine (**29)** began from Isoxepac (**30**).[11] Isoxepac **30** on treatment with thionyl chloride in methanol gave the corresponding Isoxepac methyl ester. The keto group of Isoxepac methyl ester was reduced using sodium borohydride in methanol to furnish alcohol **31**. Alcohol **31** was converted into allyl compound **32**. Hydroboration was carried out on **32** to afford alcohol **33**. The primary hydroxyl group of **33** was protected as its acetate **34**. Next job was the introduction of key double bond. Accordingly, compound **34** was subjected to DDQ oxidation. Here desired compound **35** (*E/Z*=3/1) was obtained in low (40%) yield. Acetate deprotection smoothly worked in potassium carbonate, methanol and resulted in hydroxyl compound **36** (Scheme 6).



Scheme 7. Altered retrosynthetic analysis for olopatadine **1**

Having failed in yield improvement in the DDQ oxidation step, resulted in a changed strategy. According to the proposed plan (Scheme 7), synthesis of olopatadine (**29)** started from Isoxepac (**30**).



Scheme 8. *<u>Reagents and conditions:</u> a) i) $SOCl_2$, MeOH, 24 h, rt, quent; ii) Zn, Allyl bromide, DMF, 2 h, 0 ºC-rt, 91%; b) 9-BBN, NaOH, H_2O_2, THF, 24 h, 0 ºC-rt, 84%. c) Table 1; d) $AlCl_3$, DCM, 0 ºC-rt, 7 h, 95%; e) i) MsCl, Py, 2 h, 0 ºC-rt; ii) 50 % Me_2NH, MeOH, 3 h, 50 ºC 84% over two steps; f) ref. 10.*

Isoxepac **30** on treatment with thionyl chloride in methanol gave the corresponding Isoxepac methyl ester in quantitative yield. Barbier reaction on the methyl ester with allyl bromide in the presence of zinc powder in DMF as the solvent furnished the allylic alcohol **39**. Hydroboration of **39** afforded the diol **38**. In order to introduce the exocyclic double bond by acid mediated dehydration of diol **38** several different conditions were screened, as shown in table 1. Almost all the reaction conditions led to the predominant formation of the undesired *E*-olefin along with the generation of the spiro cylic ether **37** (Scheme 8). Whereas, **38** on treatment with Lewis acid ($BF_3{\cdot}Et_2O$) at room temparature led to the formation of cyclic ether **37** along with the formation of olefin **36** as the minor product (Table 1, entry 6). However, when the reaction was carried out at elevated temperature the olefin **36** was the only product formed (Table 1, entry 7). In both the cases the ratio of *E/Z* was 3:2, in the favor of the unwanted isomer.

Table 1 Acid mediated dehydration

Entry	Reagent[a]	Time (h)	Temperature	36 Yield (%)	37 Yield (%)	*E/Z*[b] of 2
1	HCl	24	RT	none	90	-----
2	H_2SO_4	24	RT	30	53	4/1
3	HCOOH	32	RT	45	32	4/1
4	PPTS[c]	14	80 °C	59	10	4/1
5	*p*TSA	1/4	RT	none	99	-----
6	$BF_3{\cdot}Et_2O$	6	0 °C	22	64	3/2
7	$BF_3{\cdot}Et_2O$	1/2	50 °C	95	none	3/2

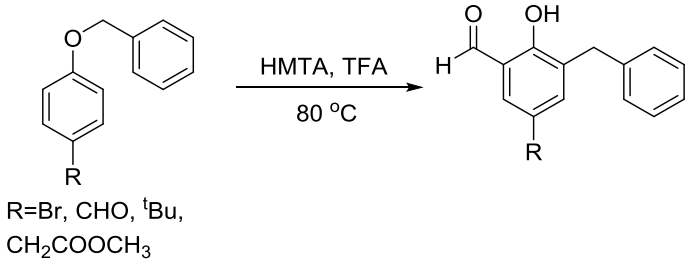
[a] DCM used as solvent. [b] *E/Z* ratio was confirmed by ^{1}H-NMR and HPLC. [c] EtOH used as solvent.

In order to improve the *Z* selectivity, different Lewis acids were screened along with their combination with base. Amongst various Lewis acids screened, it was observed that $AlCl_3$ gave the best result. Thus spiro ether **37** on treatment with 2.5 equivalents of $AlCl_3$ resulted in the formation of homoallyl alcohol **36** in 95% yield with *E/Z* in 2:3 ratio. The ratio of *E/Z* isomer could be improved to 1:9 after two crystallization. To complete the synthesis, the isomeric mixture (*E*/*Z* 4:6) of homoallyl alcohol **36** was subjected to mesylation and dimethylamination resulting in compound **40** (Scheme 8). Ohshima *et al.* have reported the saponification and *E/Z* isomer separation of the

corresponding acid. All the spectroscopic data of **40** was in good agreement with the reported one.[10]

Section 3: One-pot migration–formylation of benzyl aryl ethers under Duff reaction condition

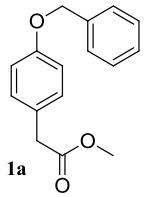
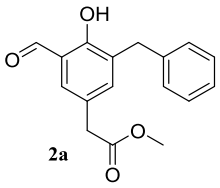
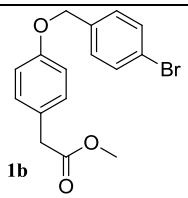
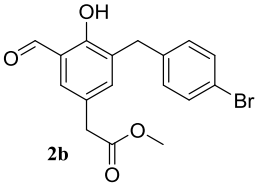
3,5-Disubstituted salicylaldehydes have been shown to possess interesting pharmacological properties and find usage in interesting environmental applications. This section describes a facile one-pot migration-formylation. The *ortho* rearrangement was mediated by TFA[12] followed by the formylation on the electronically rich phenolic ring. Literature search reveled that there is no report on *ortho* rearrangement and formylation in one pot.

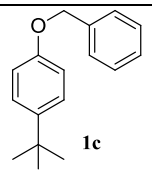
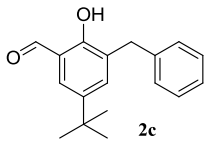
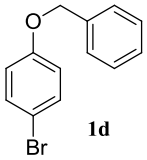
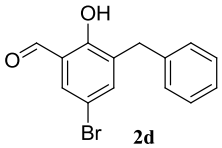
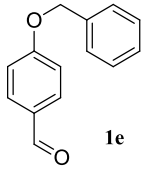
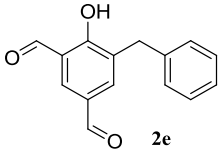
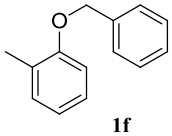
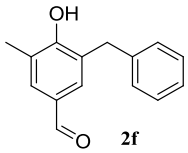
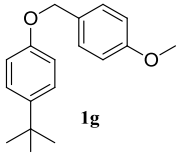
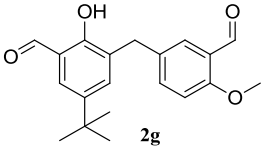
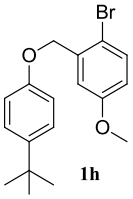
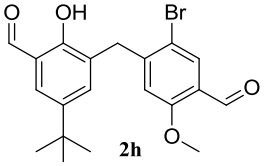


Scheme 9. One-pot migration-formylation of benzyl aryl ethers.

It was observed that benzyl aryl ethers undergo very facile *ortho* rearrangement and formylation in one pot. The results are presented in Table 2.

Table 2.

Entry	Substrate[a]	Time (h)	Product	Yield (%)[b]
1	 **1a**	**3**	 **2a**	**70**
2	 **1b**	**3.5**	 **2b**	**61**

3	 **1c**	**3**	 **2c**	**74**
4	 **1d**	**5**	 **2d**	**59**
5	 **1e**	**6**	 **2e**	**52**
6	 **1f**	**4**	 **2f**	**68**
7	 **1g**	**3.5**	 **2g**	**55**
8	 **1h**	**3**	 **2h**	**52**

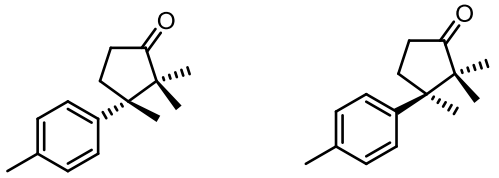
[a] Benzyl aryl ethers were prepared by treating corresponding phenols with the appropriate benzyl bromide in DMF under basic condition (K_2CO_3). [b] Isolated yield. [c] Debenzylated product observed, confirmed by ^{1}H-NMR.

Chapter 3: Synthetic studies towards α-cuparenone and unusual metal free auto-oxidation by air

Section 1: Introduction to α-cuparenone

α-Cuparenone **1** is a bicyclic sesquiterpene which exhibits itself in two isomeric forms. (+)-α-Cuparenone was isolated from the wood of the *Thuja orientallis* (mayurpankhi) by Sukh Dev[13a] and co-workers whereas (-)-α-cuparenone was isolated from the liverwort *Mannia fragrans* by Benesova and co-workers.[13b] This sesquiterpene is a synthetic challenge to organic chemists due to presence of two contiguous quaternary centers, one

of which is stereogenic in cyclopentane ring. Quaternary stereogenic center has been constructed in variety of ways.[14]

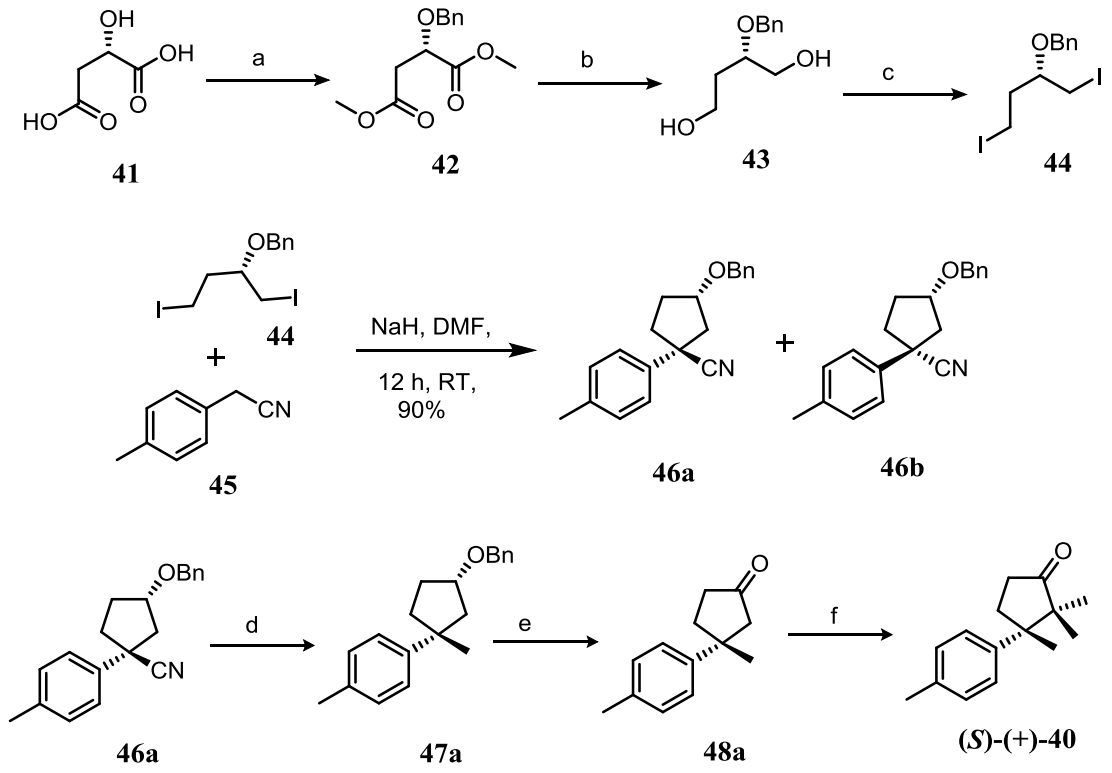


(+)-41 **(-)-41**

Figure 3. Structure of cuparenone

Section 2: A chiral pool based approach to antipodes of α-cuparenone

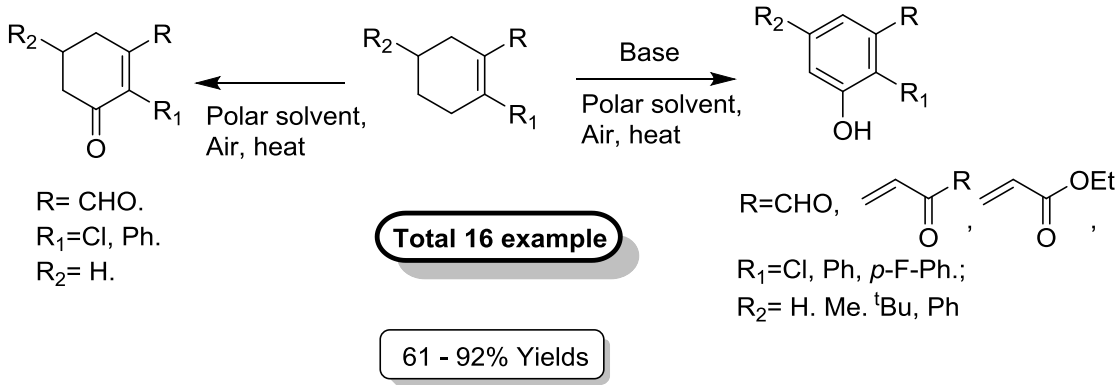
The synthesis started with the commercially available L-malic acid **41**. Malic acid **41** on treatment with thionyl chloride and methanol gave methyl ester. Secondary hydroxy group was protected using benzyl bromide, silver oxide in ethyl acetate as a solvent to furnish its *O*-benzyl ether **42**. The reduction of diester **42** was carried out using calcium borohydride to afford dihydroxy compound **43**. Both the hydroxy groups were converted to its mesylate derivative and mesylate was treated with sodium iodide to furnish the corresponding di-iodo compound **44**. Having di-iodo compound **44** in hand, next job was to construct cyclopentane ring. Thus 4-methyl benzyl cyanide **45** was treated with sodium hydride in DMF as a solvent at 0 ^{o}C followed by addition of **44**, afforded **46** as a diastereomeric mixture (50:50), which was separated by column chromatography using hexane/ethyl acetate (98:2) as eluent led to isolation of pure **46a** and **46b**. Next the functional group transformations were carried out separately on both diastereomers. Thus, cyanide **46a** was subjected to reduction using DIBAL-H to furnish aldehyde. The crude aldehyde was subjected to Huang-Minlon reaction conditions to give **47a**. Hydrogenolysis of **47a** was carried out using Pd/C as the catalyst to furnish hydroxyl compound. The hydroxy compound was oxidized by using IBX in dry DMSO as a solvent to furnish 3,3-disubstituted cyclopentanone **48a**. Finally, cyclopentanone **48a** was dimethylated using LiHMDS and methyliodide[14] to afford (+) α-cuparenone **40** (Scheme 10).



Scheme 10. *<u>Reagents & conditions</u> :- a) i) $SOCl_2$, MeOH, RT, 24 h; ii) Ag_2O, BnBr, EtOAc, RT, 6 h, 90%; b) $NaBH_4$, $CaCl_2$, EtOH, 2 h, 0 ^oC, 95%; c) i) Et_3N, MsCl, DCM, 0 ^oC, 6 h; ii) NaI, Acetone, Reflux, 4 h, 85% (over two steps); d) i) DIBAL-H, DCM, -78 ^oC, 1 h; ii) NaOH, NH_2NH_2, Ethylene Glycol, 180 ^oC, 24 h, 70%; e) i) Pd-C, H_2, 60 psi, 1 h, MeOH; ii) IBX, dry DMSO, 4 h, 95%; f) LiHMDS, MeI, DME, HMPA, 3 h,70%.*

Section 3: Unusual metal free auto-oxidation by air

Oxidation is one of the most fundamental transformations in organic chemistry. Direct oxygenation of allylalkane or alkylarenes to the corresponding carbonyl compounds is a highly important reaction because an oxygen atom can be introduced into organic substrates.



Conventionally for these transformations, a stoichiometric amount of an oxidant such as manganese dioxide, chromic acid, potassium dichromate, silver oxide, selenium dioxide, and periodic acid has been employed,[15,16] which produce environmentally unacceptable heavy metal wastes. From the perspective of atom efficiency and environmental concerns, however, the development of methods using molecular oxygen or air has attracted much attention. The present section describes unprecedented oxidation of electron deficient allylic carbon with molecular oxygen alone, with no requirement of transition metals or photo-activation, to afford the corresponding ketones as well as phenols in moderate to good yields. It was observed that using 2 equivalent of K_2CO_3, atmospheric oxygen (air) and DMF as solvent at 80 °C a variety of cyclohexenes undergo oxidation furnished the corresponding product.

Conclusion: The total syntheses of D-(+)-Biotin, Olopatadine, α-Cuparenone have been accomplished. Besides the total synthesis of biologically active molecules, methodologies like One-pot migration-formylation of benzyl aryl ethers and for allylic oxidation of electron deficient cyclohexenes have also been developed.

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Chapter 1. Synthetic Studies towards D-(+)-Biotin

Section 1

Introduction to biotin

1.1.1 Introduction

D-(+)-Biotin (vitamin H) is a water-soluble vitamin (Fig. 1). Isolation of **1** has been accomplished independently from three natural sources. Kogl *et al.*[1] have firstly characterized it as a growth factor for yeast in 1936 in its methyl ester form, which was originally referred to as ‘‘bios IIb’’ and later as ‘‘biotin.’’ The same compound was called ‘‘coenzyme R’’ by Nilsson *et al.*[2] and West *et al.*[3] in 1939, who isolated it from a root nodule bacteria, *Rhizobium trifolii*. Boas has noticed that uptake of excess amount of egg white in rats results in severe disorders, leading to death.[4] Because of dramatical improvement of the dysfunction by dietary **1**, the compound was named ‘‘protective factor X.’’ Gyorgy *et al.*[5] have finally assured the identity of the compound both with biotin and coenzyme R, and dubbed it ‘‘vitamin H.’’

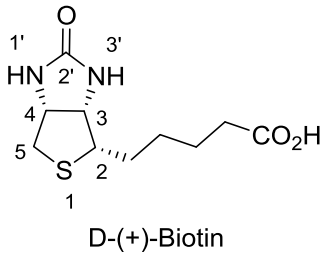


Figure 1. Structure of biotin (**1**)

The compound **1** is a cofactor of carboxylation enzymes and plays crucial roles in the metabolism of fatty acids, sugars, and α-amino acids. In addition to the increasing application to feed additives, recent reports have revealed that **1** enhances insulin secretion in animals, suggesting it for a promising therapeutic candidate for an anti-diabetic drug. The remarkably strong affinity of **1** with avidin and streptavidin has been extensively applied for such technologies as photoaffinity labeling.

1.1.1.1 Structure determination

Chemically biotin is (+)-*cis*-hexahydro-2-oxo-1*H*-thieno [3,4-*d*]-imidazole-4-valeric acid. 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.[6,7] The structure was confirmed by the first total synthesis of biotin in Merck Laboratories by Harris and co-workers in 1943.[8] X-ray crystallographic analyses of *bis* 4-bromoanilide of *N*-1-carboxybiotin in 1966 (Fig. 2)[9] and biotin itself in 1985,[10] have substantiated the structure of **1**, involving the absolute configuration.

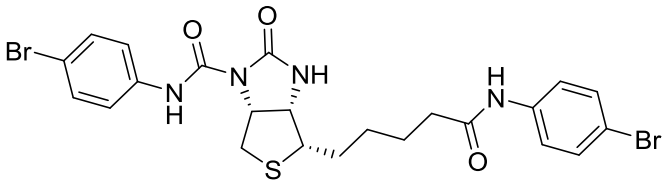


Figure 2. Structure of *bis* 4-bromoanilide of *N*-1-carboxybiotin

According to these data, ureido ring is planar while the thiophane ring has an envelope conformation (Fig. 3). 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.

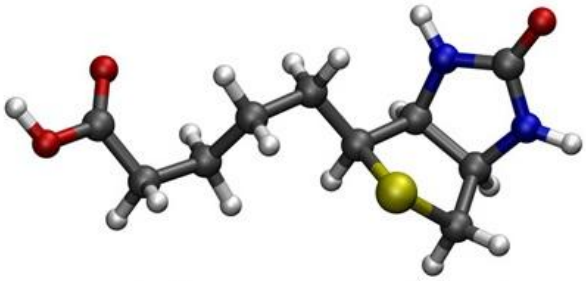
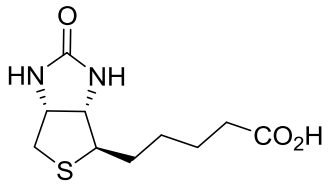
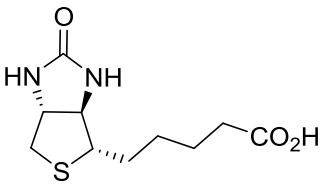


Figure 3. Crystal structure of biotin (**1**)

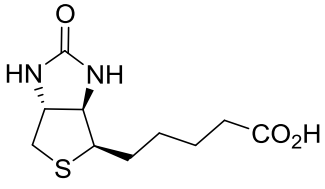
Biotin has three contiguous chiral carbon atoms and therefore, four diastereomeric racemic forms are possible, of which only (+)-biotin **1** is biologically active, while, *epi*, *allo* and *epi-allo*-biotin **I**, **II**, and **III** respectively and their enantiomers are biologically inactive. Of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



epi-Biotin **I**



allo-Biotin **II**



epiallo-Biotin **III**

1.1.1.2 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.[11-14] All the intermediates from pimelic acid to dethiobiotin are formed by classical biochemical reactions. Recently Marquet and co-workers solved the elucidation of the mechanism for the transformation of dethiobiotin to biotin. Evidence has been presented that the

biosynthesis of biotin in *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.[15,16] 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, the prochiral center of dethiobiotin.

1.1.1.3 Deficiency

Onset of biotin deficiency has first been recognized by Boas as early as in 1924, who demonstrated excess feeding of raw egg white to rats resulted in fatal loss of body weight as well as skin and hair abnormalities (*vide supra*).[4] Strong binding of biotin to avidin, present in the egg white, inhibits uptake of biotin through gastrointestinal tracts.

The biotin deficiency has been well investigated on poultries because of the economic significance. It is characterized by a series of clinical manifestations, such as locomotor[17] and skin lesion,[18] and rough and broken feathers. Hatchability[19] may be affected by the deficiency and the amount of biotin in eggs is known to decline in adult birds.[20] Broiler chickens of 3–4 weeks sometimes die suddenly after a few hours of recumbency. The disease is called ‘‘fatty liver and kidney syndrome (FLKS)’’[21] and characterized as considerable systemic lipids infiltration, especially in liver and kidney. Pigs, another important livestock, suffer from severe lameness[22] and inability in the reproductive performance upon biotin deficiency. The dangerous effects of chickens and pigs are cured by supplementation of biotin as a feed additive.[23–25]

Biotin-dependent multiple carboxylase defects in man are known to occur because of mutation of holocarboxylase[26] or biotinidase, which are much less common than in poultries.[27] Biotin deficiency may trigger teratogenesis. For instance, fetuses from dams given a biotin-deficient diet throughout gestation show some characteristics of intrauterine growth retardation including abnormal liver weight and a higher brain/liver ratio.[28]

1.1.1.4 Uses

Therapeutic efficacy of biotin, which provides a novel way to tackle diabetes, has been evaluated in patients with non-insulin-dependent diabetes mellitus. Biotin has been suggested to enhance glucose-induced insulin secretion in isolated perfused

pancreas islets of rats.[29–31] When the islets were stimulated with glucose and biotin, the ATP/ADP ratio and glucose oxidation, assessed by carbon dioxide production, elevated to ca. 160% and 200%, respectively, of those observed in the islets treated with glucose alone.[32] The data suggest that biotin enhances the degradation of glucose in the islets and, accordingly, accelerates the production of ATP, which results in the surge of the glucose-induced insulin secretion. Because of enhancement of the insulin secretion by biotin shortly following the stimulation, biotin is likely to induce the activities not by mediating *via* gene expression events but by direct participation in the process of glucose-induced insulin secretion.[32]

It is used in pharmaceuticals for the 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.[33] It has been recently recognized that biotin finds use in cosmetic[34] and it is administered orally for brittle nails and hair loss.

Avidin-biotin system in immunochemistry:[35]

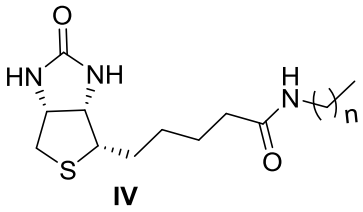
Biotin is known to display high affinity to avidin and its structural homolog, streptavidin. The binding ability is among the highest so far known for ligand–protein interactions. Avidin and streptavidin are isolated from *Streptomyces avidinii* and from hen egg white, respectively. Avidin is a tetramer 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.

Biotin derivatives in use:

The following are some of the biotin derivatives in use.

Biotin derivatives as gelators of organic solvents: [36]

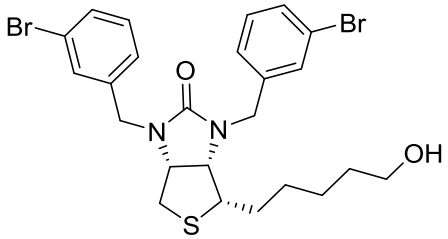


IV

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.

Biotin derivatives as anti HIV protease inhibitors: [37]



V

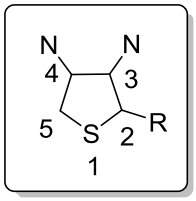
Several bis-*N*-alkylated (+)-biotin derivatives were synthesized and evaluated for activities against HIV-1 protease. The most potent inhibitor **V**, has K_i of 0.50 mM and antiviral IC_{90} of 7 mM. The (+)-biotin analogues in general have good translations from enzymic K_i to antiviral cell assay IC_{90}. Also, other derivatives of biotin like *N*-hydroxysuccinimidobiotin, sulfosuccinimidobiotin, *N*-iodoacetyl-*N*-biotinylhexylenediamine, biotinhydrazide, immo-bilized biotin, biotincellulose of biotin are commonly used in different applications.

Biotin possesses a deceptively simple-looking structure. Its skeleton consists of a biheterocyclic 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 60 years has now resulted in more than 50 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 60) between 1970-2010. The above figure excludes the applications of biotin in biochemistry and related subjects.

1.1.2 Synthesis of biotin: A literature survey

Asymmetric synthesis has acquired tremendous importance, especially in the pharmaceutical industry, since it is frequently the case that only a particular optically active isomer is therapeutically active. There is thus a continuing need for new methods of carrying out asymmetric syntheses and specific catalysts having a high degree of asymmetric induction for particular stereocenters *i.e.* the synthesis should lead to the desired isomer in high optical purity and in high chemical yield. Since review on synthesis of all categories up to 2005 has been covered by Amar Gopal,[38a] Priti Soni,[38b] Ramakrishna,[38c] from this group, as well as is reviewed by De Clercq in 1997[39] and by Seki in 2006,[40] syntheses of optically pure biotin reported after 2005 and representative syntheses of each strategy have been described in this present section. 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 possess 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:



Because of the biological activity of (+)-biotin (**1**) found in only the enantiomer shown in Figure 1, chiral synthesis leading to the single enantiomer is required. The compound **1** is featured by sulphur containing bicyclic ureido skeleton that supports 4-carboxybutyl chain at C-2. The first total synthesis of **1** has been accomplished by Harris *et al.*[8] in 1943. The synthesis involves 12 steps sequence starting from L-cystine. However, construction of the asymmetric centers is totally nonstereoselective, resulting in racemic mixtures of three diastereomers, *rac*-biotin, *rac-allo* biotin, and *rac-epiallo* biotin. The racemic biotin was finally resolved into **1** through optical resolution using L-arginine as the resolving agent. Although the method provided **1** in relatively less number of steps, *i.e.* 12 steps from L-cystine, it has drawbacks of unsatisfactory yields and poor stereoselectivities as well as need for optical resolution at the final step. To figure out the complicating issues, considerable efforts have been devoted both in industries and academia. From a practical point of view, the synthetic schemes of **1** are classified as the following three approaches that utilize proficiency:

(1) Resolution

(2) Desymmetrization

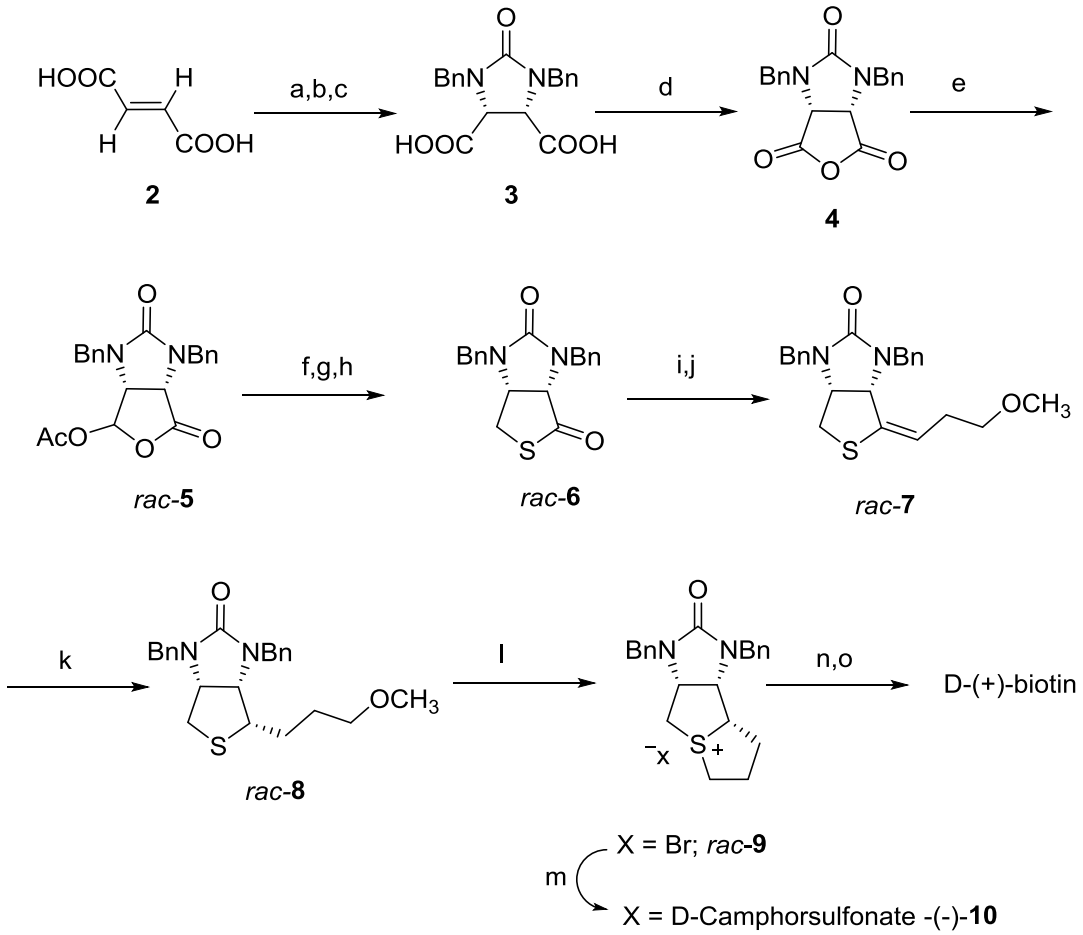
(3) Asymmetric induction.

1.1.2.1 Resolution-

Goldberg and Sternbach's approach: Late stage resolution (Pat. 2,489232, Nov. 22, 1949; Chem. Abstr. **1951**, 45, 184.)

In 1946 Goldberg and Sternbach[41-43] described the first economical synthesis of (+)-biotin starting from cheaply available fumaric acid (see Scheme 1).

Fumaric acid **2** 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 is fixed.



Scheme 1: Reagents and conditions*: a) Br_2, water, ; 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.*

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 form. In the third stage, part of the carboxybutyl chain of biotin is introduced *via* Grignard reaction with subsequent dehydration to from the exocyclic olefin **7** with undefined doublebond 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).

At this point, resolution is effected by conversion of bromide **9** into the diastereomeric sulfonate salts **10** which are readily separated in excellent yield by simple fractional crystallization. In the final stage of the synthesis, the side chain is established by

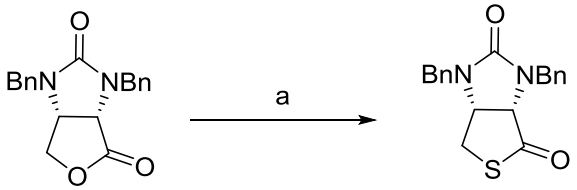
reaction of diastereomer (-)-**10** with sodium diethyl malonate. In this important step, selective attack is observed at the least hindered primary center of the trimethylene thiophanium moiety. Finally, heating with conc. hydrobromic acid effected hydrolysis, subsequent decarboxylation and debenzylation all in one operation, to furnish biotin.

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

The use of benzyl groups as protective groups in the imidazolidothiophane and related intermediates has been commonly utilized in almost all later syntheses.

Gerecke's approach: Auxillary based resolution (*Helv. Chim. Acta* **1970**, *53*, 991)

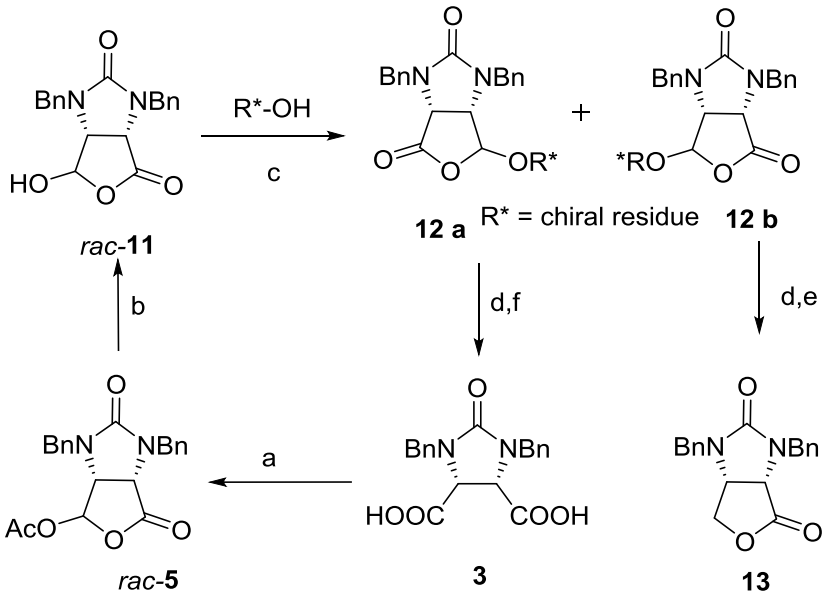
In 1970 Gerecke, Zimmerman and Aschwanden from Hoffmann-La Roche (Basel and Paris) reported on a further important development of the original Goldberg-Sternbach scheme that allows for the efficient production of the key thiolactone **6** in the required enantiomeric form starting from *meso*-acid **3**.[44] Crucial to this new development was the finding that lactone **13** could be converted in very high yield into the corresponding thiolactone **6** by treatment with potassium thioacetate in dimethylformamide at 150 °C (Scheme 2).



13 **6**

Scheme 2: Reagents and conditions: *a) CH_3COSK, DMF, 150 °C.*

Hence, any synthesis of *rac*- or (+)-**13** would constitute a new formal synthesis of *rac*- or (+)-biotin, respectively. The sequences that were originally used to convert the *meso*-compounds **3** into (+) - **13** are shown in Scheme 3.



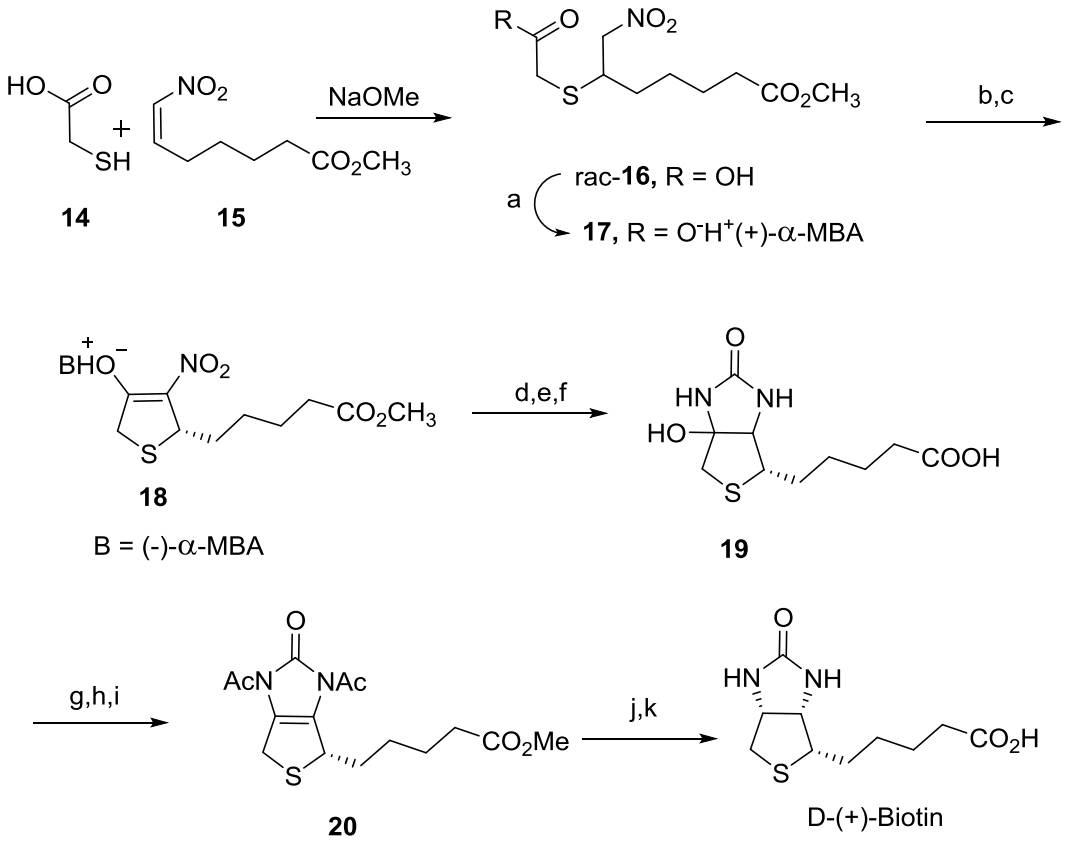
Scheme 3: Reagents and conditions: *a) Ac_2O, Zn/HOAc; b) NaOH, dioxane; c) R*-OH [(-)-menthol or (-)-borneol or (-)-4,4-dimethyl-3-hydroxydihydro-2(3H)-furanone], p-TsOH, $PhCH_3$; d) H_2SO_4, dioxane; e) $NaBH_4$, EtOH; f) CrO_3/H_2SO_4, dioxane.*

The method involves conversion of **3** into hydroxylactone **11** (undefined stereo-chemistry) *via* acetoxylactone **5** (Scheme 3). Treatment of **11** with an optically active alcohol leads to a diastereomeric mixture composed of **12a** and **12b** (both as epimeric mixtures). Selectivity in obtaining *cis*- or *trans* epimers could not be realized. Depending on the optically active alcohol used, i.e. (-)-menthol, (-)-borneol, or (-)-4,4-dimethyl-3-hydroxydihydro-2(3*H*)-furanone, the obtained diastereomers **12** crystallize in a different order and only two of the four possible diastereomers could be obtained in pure form. The required lactone (+)-**13** is further obtained from the **a**-series *via* acid hydrolysis followed by sodium borohydride reduction, while the unwanted stereoisomers of the **b**-series were recycled through acid hydrolysis followed by chromic oxidation to *meso*-**3**.

Field's approach: Early stage resolution (*J. Am. Chem. Soc.* **1978**, *100*, 7424)

The approach of Field and co-workers at Hoffmann-La Roche (1978) presents several interesting aspects (Scheme 4).[45] It involves the synthesis of the bicyclic dihydrothiophene derivative **20** in homochiral form, followed by catalytic hydrogenation. The enantioselectivity in the sequence is the result of an early

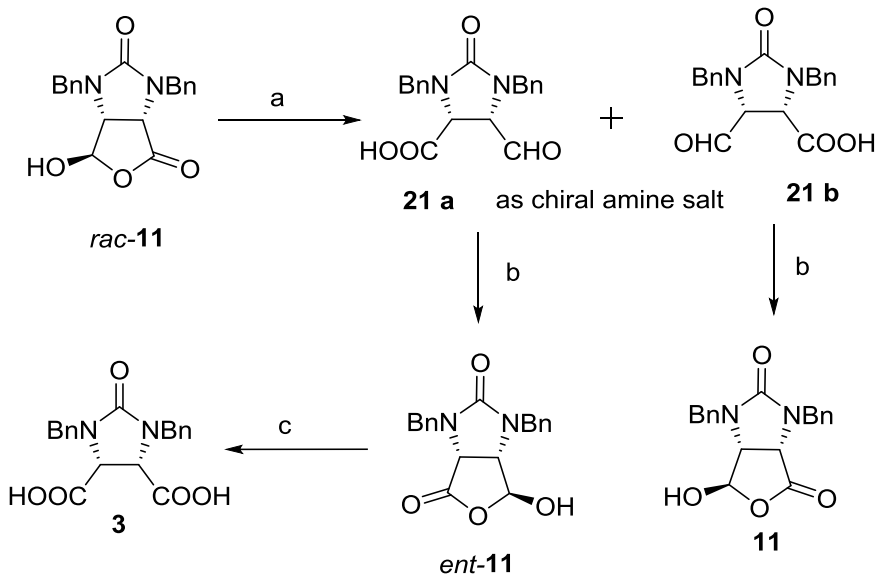
resolution of the acid **16**. In synthesis, the first step involves a conjugate addition of thioglycolic acid **14**, to the unsaturated nitro ester **15**. A salt of the (*S*)-enantiomer of **16** is obtained by treatment with (+)-*R*-methylbenzylamine (MBA). This salt is converted into the more stable dicyclohexylamine salt, which is converted to the phenol ester in 95% yield. When this ester is treated with (-)-*R*-methylbenzylamine in ethyl acetate, **18** is obtained as (-)-*R*-MBA salt. The construction of the imidazolone ring of **20** further involves a six-step sequence. After hydrogenation of the nitro group, the resulting amino ketone is treated with aqueous potassium cyanate and after acidification, alcohol **19** is obtained. Dehydration is effected in acetic acid. Finally, esterification and acetylation yields **20**.



Scheme 4: Reagents and conditions: *a) (+)-R-Methylbenzylamine ((+)-R-MBA), EtOAc; 30% yield, >97% ee after recrystallization; b) Dicyclohexylamine; c) PhOH, $SOCl_2$, pyridine (cat.); (-)-R-Methylbenzylamine, EtOAc; d) Pd/C (10%), HOAc/HCl; e) KNCO, H_2O; f) NaOH; g) HOAc, stripping at 55 °C; h) MeOH, H^+; i) Ac_2O, 110 °C; j) H_2 (550 psi), 5% Pd/C (10% loading), Ac_2O, 85 °C; k) NaOH, CH_3OH.*

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

Senuma and co-workers reported an alternative method for the industrial resolution of hydroxy lactone **11** in 1990 (Scheme 5).[46] It involves the direct resolution of the hydroxy lactone *rac*-**11** (*trans*-epimer) with optically active amines. Thus the reaction of *rac*-**11** with cinchonidine readily gave the cinchonidine salt of **21b** 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 **11**. Evaporation of the mother liquor of the salt afforded after acidification *ent*-**11** in 36% yield. The undesired enantiomer is readily converted to *meso*-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*-**11** with various *N*-alkyl-*D*-glucamines.

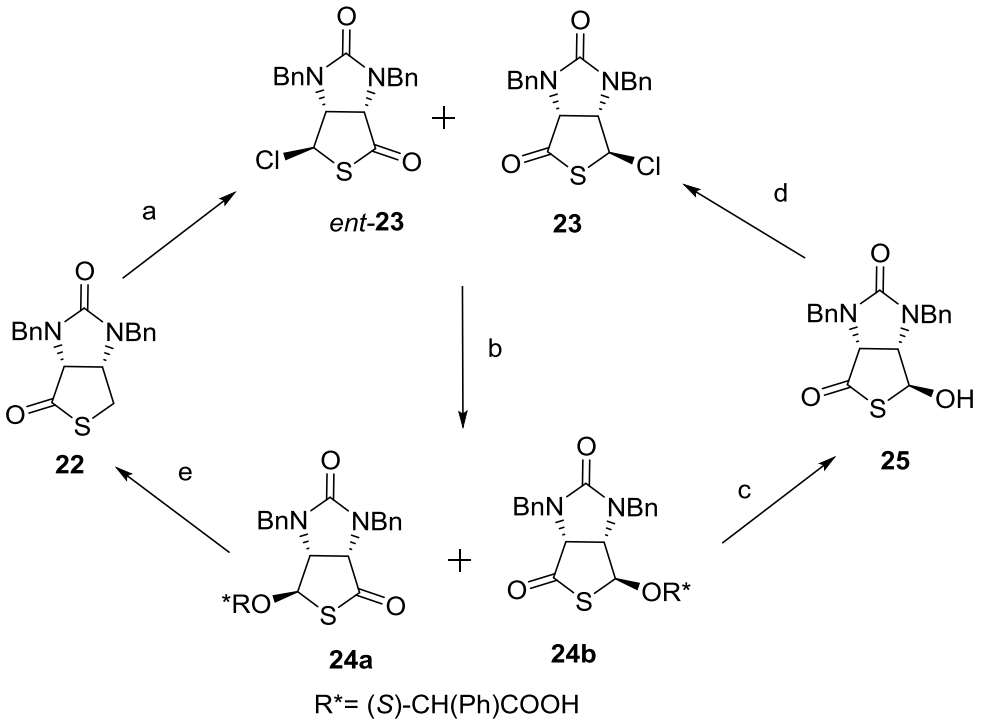


Scheme 5: Reagents and conditions: *a) Cinchonidine:45% of precipitated salt or N-n-butyl-D glucosamine derivative: 46% of precipitated salt; b) HCl; c) $NaClO_2$, 87%.*

Bihovsky's approach: α-Chlorination, diastereomer separation (*Tetrahedron* **1990**, *46*, 7667)

Bihovsky and Bodepudi[47] succeeded in resolving **25** as shown in Scheme 6. The resolution was accomplished by separation of the diastereomeric alkoxy derivative **24a** and **24b** that were obtained by reaction of *rac*-**23** with optically active secondary alcohols. The most efficient alcohol was (*S*)-(+)-mandelic acid, since the

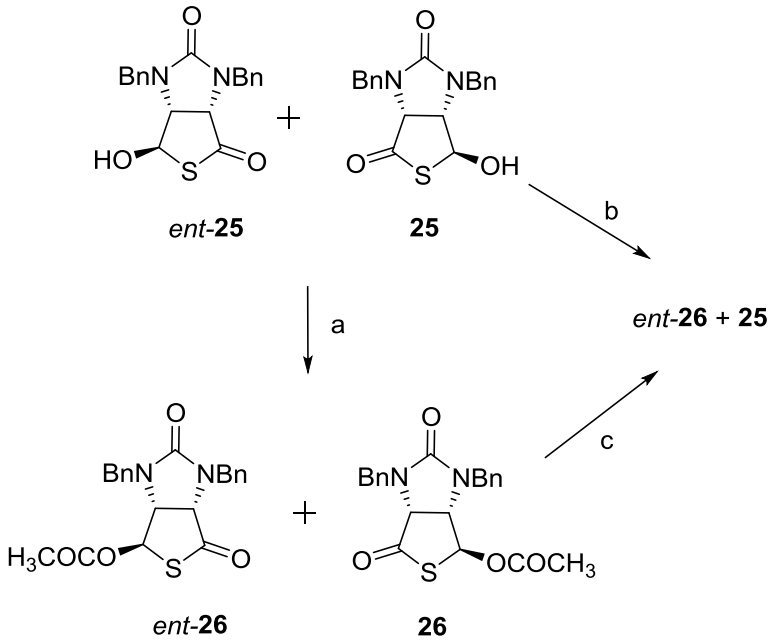
diastereomers could be readily separated by crystallization. Acid hydrolysis of **24b** led to (+)-**25** and hence to (+)-**6**, *via* oxidation or to **23** by treatment with HCl.



Scheme 6: Reagents and conditions: *a) NCS; b) R*-OH = (S)-(+)-Mandelic acid, 75%; diastereomer separation by crystallization; CCl_4, reflux, 33% isolated yield with R* = CH(Ph)COOH; c) H_2SO_4, dioxane; d) HCl, $CHCl_3$; e) Et_3SiH, CF_3COOH.*

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

Successful enzyme catalyzed kinetic resolutions were reported by Yamano *et al.* (Scheme 7).[48] A variety of commercially available enzymes and microorganisms were investigated in order to effect the enantioselective hydrolysis of the ester **26**, which was obtained by conventional acylations of *rac*-**25**. In a second approach, the same group found that direct resolution of alcohol **25** was accomplished *via* acylation with the lipoprotein from *Pseudomonas aeruginosa* TE 3285 in toluene.[49] Curiously, addition of molecular sieves (MS) 4 A^o 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.

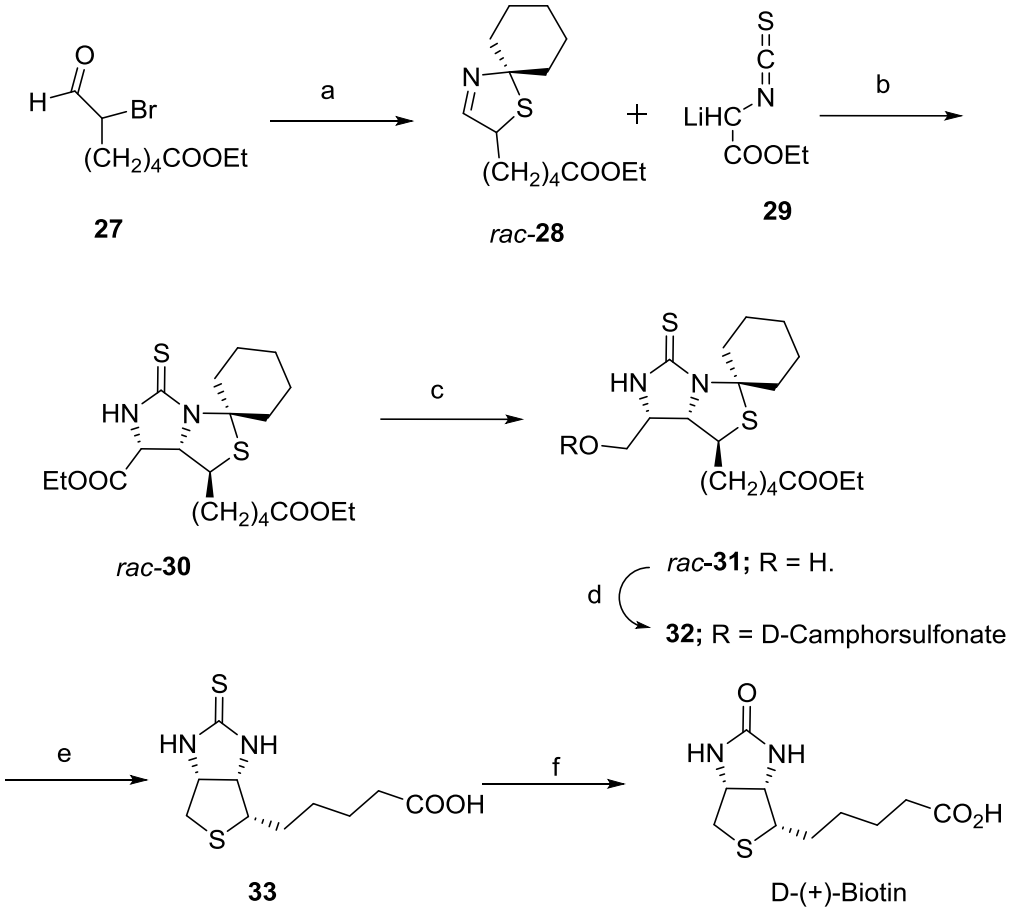


Scheme 7: Reagents and conditions: *a) Ac_2O, pyridine, 98%; b) Streptomyces rochei var. volubilis; 27% conversion; 92 and 94% ee after crystallization; c) LIP (P. aeruginosa TE3285; TOYOBO immobilized lipase), 0.3% H_2O, 4 A^o molecular sieves (MS), $PhCH_3$, vinyl acetate; 56% conversion; 99 and 99.8% ee after crystallization of alcohol.*

Volkmann's approach: Late stage resolution (*J. Am. Chem. Soc*. **1983**, *105*, 5946)

Volkmann and co-workers of Pfizer Central Research disclosed a very short approach to **1** (Scheme 8).[50] This approach is enantioselective through a resolution step at a late stage of the sequence. Central to the synthesis is the obtainment of thiazolidine **30** *via* a process which involves an ester enolate imine addition followed by an intramolecular amine/isothiocyanate condensation. The imine substrate **28** is obtained as the 3-thiazoline through reaction of brominated ethyl 7-oxoheptanoate **27** with sodium hydrogen sulfide, cyclohexanone, and ammonia. Crucial to the success of the addition of the lithium enolate of the isothiocyanato acetate ester **29** to thiazoline **28** is the prior activation of the imine through addition of an equivalent of boron trifluoride. In practice the diester **30** was obtained in 50% yield as the major product. Treatment of **30** with sodium borohydride resulted in the selective reduction of the α-amino ester to give alcohol **31**. This was converted to a mixture of *d*-camphorsulfonates, which were separated by silica gel chromatography. Isomer **32** was converted upon acid treatment to 2-thiobiotin **33** in 83% yield. The reaction

conditions affected thiazolidine ring hydrolysis, thiophane ring formation, and ester hydrolysis. The eventual thiourea/ urea transformation was realized by basic treatment with bromoethanol. In this procedure, the nucleophilic character of the thiourea sulfur atom was exploited in order to deliver, intramolecularly, the required oxygen atom *via* a labile alkoxyimidazoline.



Scheme 8: Reagents and conditions: *a) NaSH, cyclohexanone, NH_3, 90%; b) LDA, $SCNCH_2COOEt$, $BF_3.OEt_2$, THF, -78 °C, 50%; c) $NaBH_4$, CH_3OH, THF, 0 °C, 90%; d) Et_3N, d-camphorsulfonyl chloride, CH_2Cl_2; e) CF_3COOH, H_2O, 45 to 100 °C, 83%; f) $BrCH_2CH_2OH$, N-methylpyrrolidinone, 110 °C, Na_2CO_3, 64%.*

However, the classical Hoffmann La Roche synthesis with modifications is till date the commercially practiced technology. Although the method was initially impractical because of the use of optical resolution close to the final step, it was extended to an industrially viable approach by employing optically pure thiolactone **6** that was obtained by various methods involving optical resolution and Desymmetrization.

1.1.2.2 Desymmetrization-

Desymmetrization of *meso*-compounds is one of the most powerful transformations in asymmetric synthesis. Differentiation between two enantiotopic groups in such compounds leads to two or more stereocentres in only one step. Synthesis of **1**, hitherto developed by Desymmetrization (Chart 1), includes five approaches,

i) Desymmetrization of *meso*-cyclic anhydride by enantioselective reduction
ii) Desymmetrization of *meso*-thiocarboxylic anhydride by enantioselective reduction
iii) Desymmetrization of *meso*-cyclic imide by enantioselective reduction
iv) Desymmetrization of *meso*-diester by enzymatic asymmetric hydrolysis
v) Desymmetrization of *meso*-cyclic anhydride by asymmetric alcoholysis

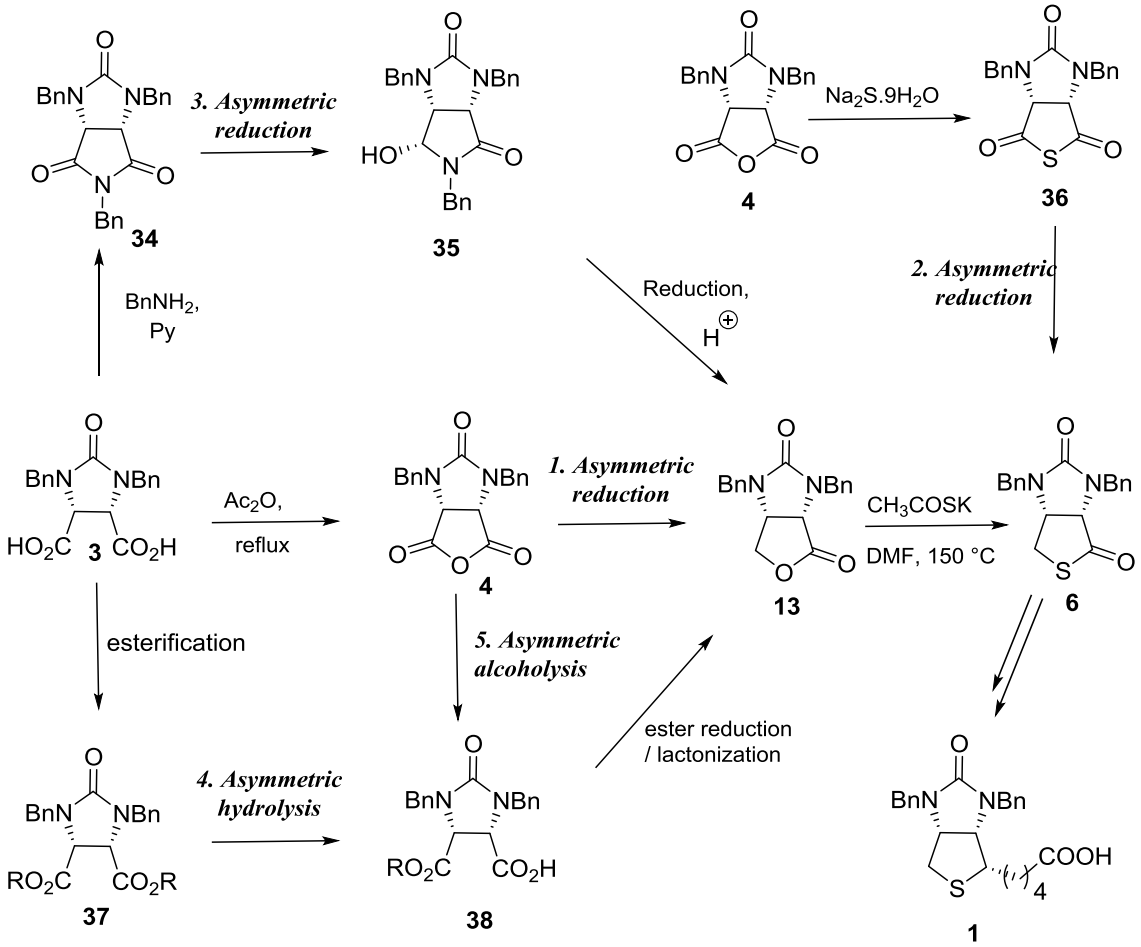
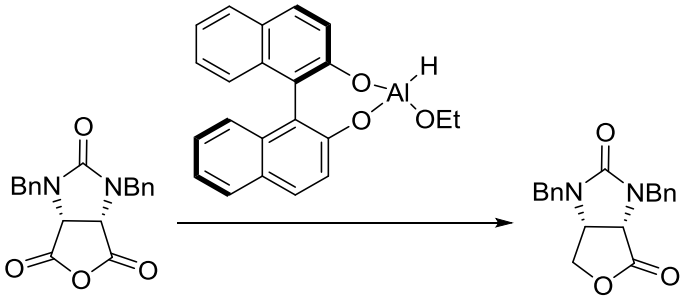


Chart 1. Earlier approaches for Desymmetrization.

i) Desymmetrization of meso-cyclic anhydride by enantioselective reduction-

If *meso*-cyclic anhydride/thiocarboxylic anhydride is treated with chiral reductant, it is possible to effect both desymmetrization and reduction to provide lactone/ thiolactone in a single step.

Matsuki approach (*Tetrahedron Letters* **1993,** 34, 1167)



4 **13**

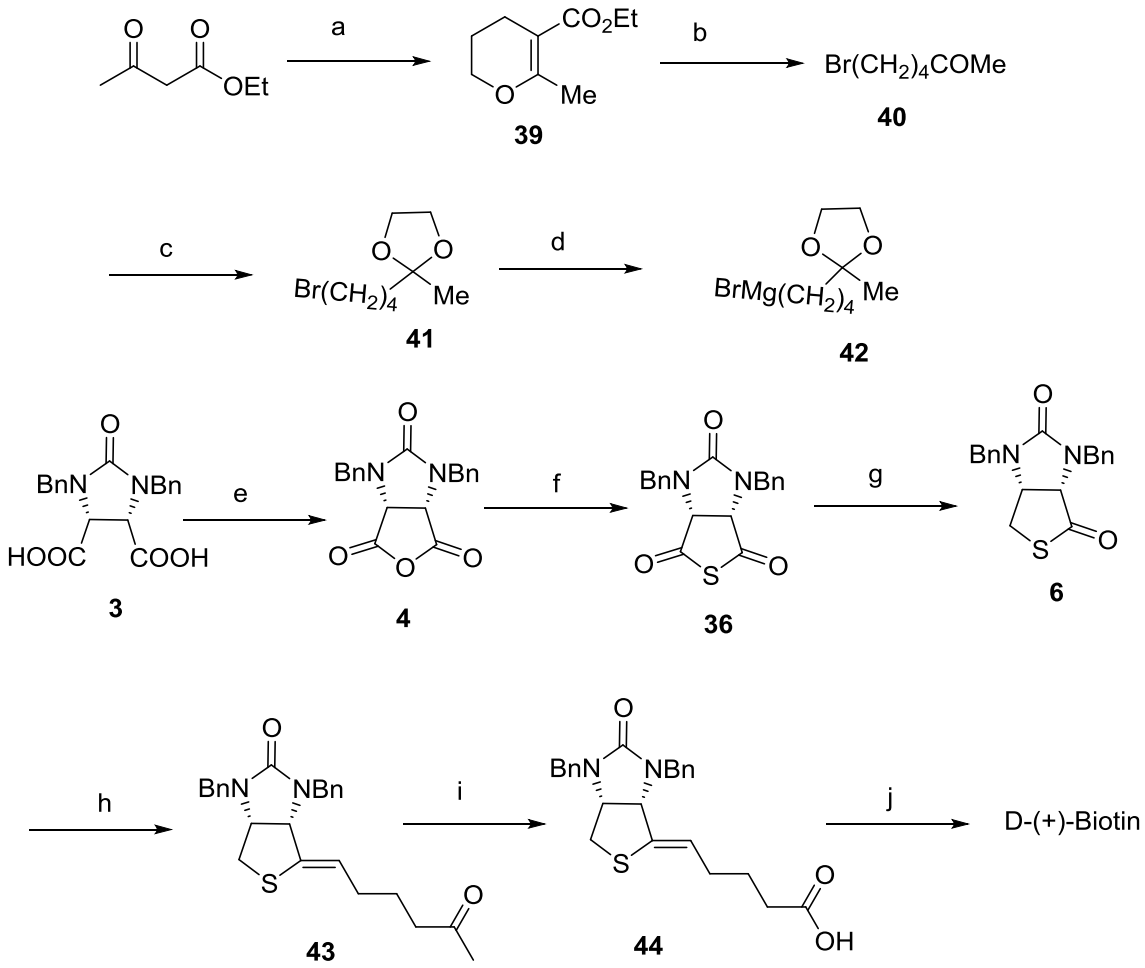
Scheme 9: Reagents and conditions: *a) (R)-BINAL-H, -78 °C to rt, THF, 76%.*

In 1993 Matsuki and co-workers reported a 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*).[51] When applied to *meso*-**4**, the desired lactone **13** was directly obtained in 76% yield with 90% *ee*, which was enriched to 95% *ee* by recrystallization from benzene/cyclohexane (Scheme 9).[52]

ii) Desymmetrization of meso thiocarboxylic anhydride by enantioselective reduction-

Chen's approach (*Synthesis* **2000**, 2004)

In 2000 Chen and co workers reported[53] an efficient and enantioselective synthesis of D-(+)-biotin using BINAL-*H* reduction of *meso*-thioanhydride **36** (Scheme 10). The synthesis started with *cis*-1,3-dibenzyl-2-imidazolidine-4,5-dicarboxylic acid **3**. The key steps were the enantioselective reduction of *meso*-1,2-dicarboxylicthioanhydride **36** to prepare the (3*S*, 4*R*)-thiolactone **6**, and the introduction of the 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 10: 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) $(CH_2OH)_2$, TsOH, toluene, reflux, 92%; d) Mg, THF, rt, 83%; e) Ac_2O, 83% H_3PO_4 (cat.), reflux, 98%; f) $Na_2S{\cdot}9H_2O$, THF, H_2O, rt, 49%; g) (R)-BINAL-H, THF, -78 ^oC to rt, 83%; h)* ***42****, 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%.*

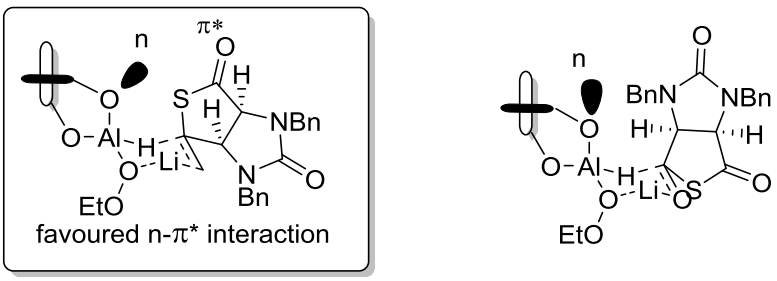
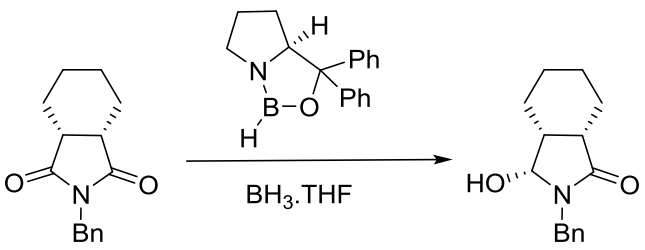


Figure 4. *A possible mechanism for asymmetric reduction of thiocarboxylic anhydride* ***36****.*

The reaction mechanism of the asymmetric reduction of **36** with (*R*)-BINAL-*H* is worth noticing (Fig. 4). As was the case with the reduction of aromatic, acetylenic, and olefinic ketones by (*R*)-BINAL-*H*, the stereochemical outcome of the reduction is ascribed in large part to the electronic nature of the substituents rather than their steric factor. The reductant approaches to the convex side of thiocarboxylic anhydride **36**. *Si*-face of the carbonyl group should be selectively reduced by means of a favorable n-π^* interaction between lone pair electrons of oxygen atom in the reductant and anti-bonding orbital in the thioanhydride carbonyl group.

iii) Desymmetrization of meso-cyclic imide by enantioselective reduction-

Stereoselective reduction of one of the carbonyls of *meso*-cyclic imide would lead to a product with three contiguous stereocentres. Speckamp *et al*.[54] reported desymmetrization of *meso*-cyclic imide using CBS-catalyst (Scheme 11). In case of the cyclic *meso*-imides, the nitrogen moiety is the large substituent (R_L), and the fused ring moiety is the small substituent (R_s). Because the enantioselectivity of the reduction is higher if the difference in size between R_L and R_s is larger, a decrease of the size of R_s should give a higher enantioselectivity (Fig. 5).



Scheme 11: Desymmetrization of meso-cyclic imide.

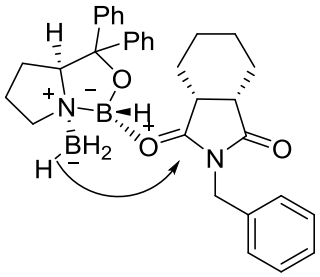
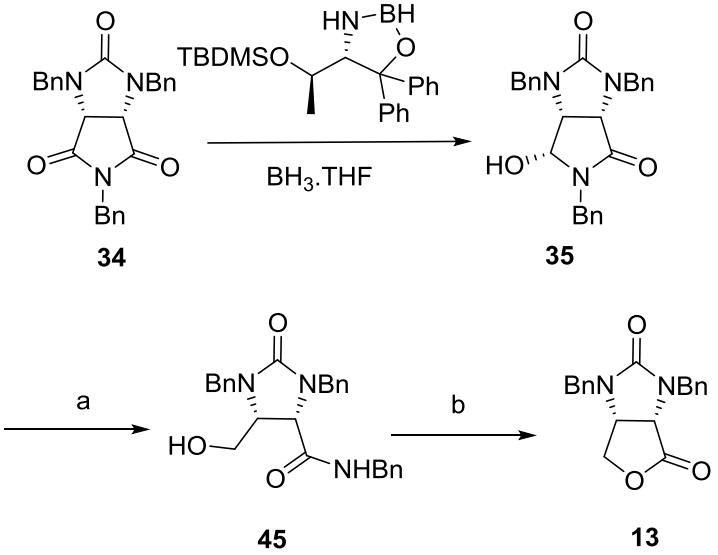


Fig.5. Possible mechanism

Shimizu's approach (*Tetrahedron Letters* **1999,** *40,* 8873)

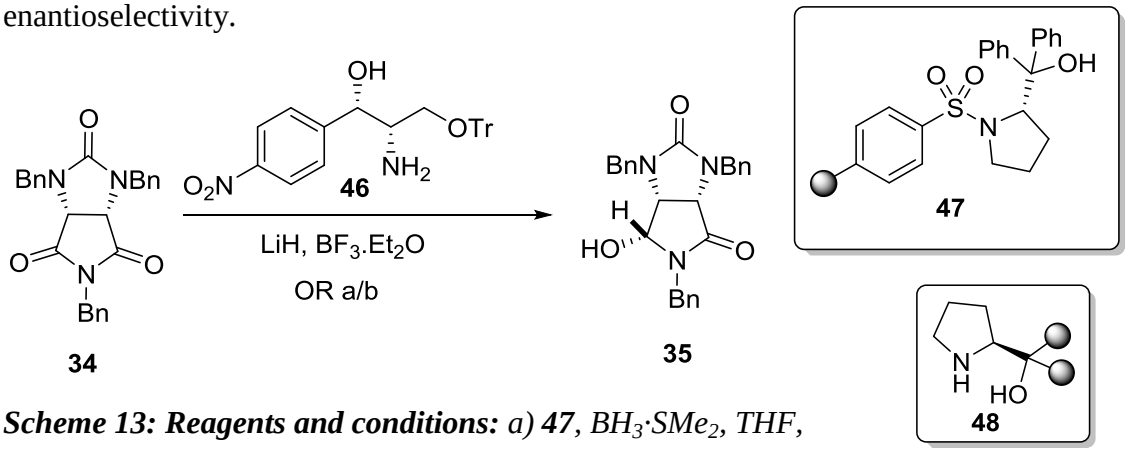
In 1999 Shimizu and coworkers[55] reported stereocontrolled reduction of *meso*-imides using oxazaborolidine (Scheme 12). The known *meso*-imide **34** was reduced using oxazaborolidine derived from L-threonine and borane-THF complex to give lactams **35** in high enantiomeric purity. This methodology was successfully applied to the synthesis of (+)-deoxybiotin in an enantio-controlled manner in good overall yield.



Scheme 12: Reagents and conditions: *a) $NaBH_4$ (4.0 eq), THF-H_2O (10:1); b) 2 N H_2SO_4-1,4-dioxane (8:1), 0 ^oC.*

Chen's approaches (*Tetrahedron Asymmetry* **2003**, *14*, 3667; *Synthesis*, **2003**, 2155; *Chem*. *Pharm. Bull*. **2005**, *53*, 743)

Catalytic asymmetric synthesis has been aimed at eliminating the use of stoichiometric amount of expensive chiral auxiliary. This was realized by the Chen group who developed catalytic version of the asymmetric synthesis of optically active lactone **13** through asymmetric reduction of imide **34** (Scheme 13).[56] The *meso*-cyclic imide **34** was subjected to enantioselective reduction upon treatment with LiH and $BF_3{\cdot}Et_2O$ in the presence of (1*S*,2*S*)-(+)-*threo*-1-(4- nitrophenyl)-2-amino-3-triphenylmethoxypropanol **46** under reflux in THF to give, after addition of sat. HCl/Et_2O and filtration, **35** in 85% yield and 98% enantiomeric excess. Sterically demanding chiral environment given by **46** is responsible for inducing the high enantioselectivity.



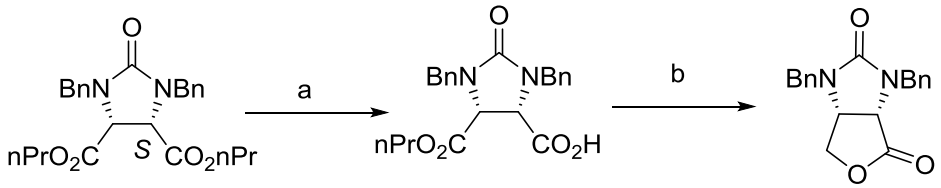
Scheme 13: Reagents and conditions: *a) **47**, $BH_3{\cdot}SMe_2$, THF, reflux; b) 80% NaH, $BF_3{\cdot}Et_2O$, **48**, THF, reflux.*

In situ generated oxazaborolidine catalyst using a water-soluble small molecule amino alcohol as ligand **46** gives good results. However, on large-scale the recovery and purification of the catalyst are problematic. Immobilization of chiral oxazaborolidine catalysts would offer a solution to the problem. Polymer supported oxazaborolidine catalysts have wide uses in asymmetric organic synthesis owing to the ease of isolation of product from polymeric chiral catalyst, the convenient work-up procedure. Accordingly, the enantioselective reduction of *meso*-cyclic imide **34** catalyzed by a polymer-supported chiral oxazaborolidine derived from (*S*)-diphenylprolinol and polymer-bound sulfonyl chloride **47**, or chiral polymer supported oxaborolidine **48** derived from polymer supported ligand was achieved (Scheme 13). The reduction using 80% NaH, $BF_3{\cdot}Et_2O$, **48**, THF, reflux was claimed to be advantageous over **47**, $BH_3{\cdot}SMe_2$, THF, reflux in avoiding the use of $BH_3{\cdot}$DMS and easy for large scale production which was replaced by NaH, and $BF_3{\cdot}Et_2O$.

iv) Desymmetrization of meso-diester by enzymatic asymmetric hydrolysis-

Iriuchijima's approach (*Agric. Biol. Chem.* **1982**, *46*, 1907)

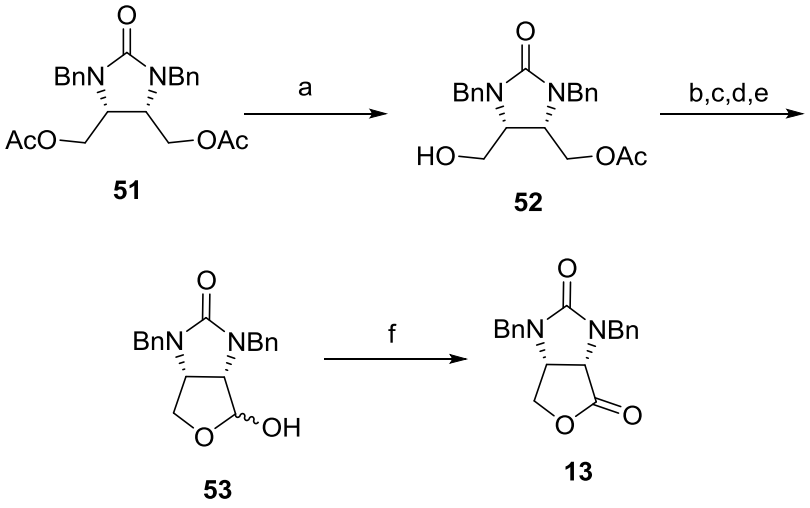
The application of enzymatic resolution procedures to obtain the chiral lactone (+)-1**3** has been reported (Scheme 14). In 1982, Iriuchijima and co-workers described the asymmetric hydrolysis of the prochiral diester **49** with pig liver esterase (PLE).[57] The *meso*-diester **49** has an interesting structure since it combines both a natural (*S*)-amino acid part and a unnatural (*R*)-amino acid part and enzymes are expected to preferentially hydrolyze the (*S*)-ester rather than the (*R*)-ester in **49**. Hydrolysis of the di-*n*-propyl ester with PLE gave **50** in 85% yield. Further reduction with lithium borohydride yielded (+)-**13** in 64% yield.



49 **50** **13**

Scheme 14: Reagents and conditions: *a) PLE, phosphate buffer; b) $LiBH_4$ (75% ee; 87% ee after recrystallization).*

Sih's approach (*Tetrahedron Lett.* **1984**, *25*, 4999)

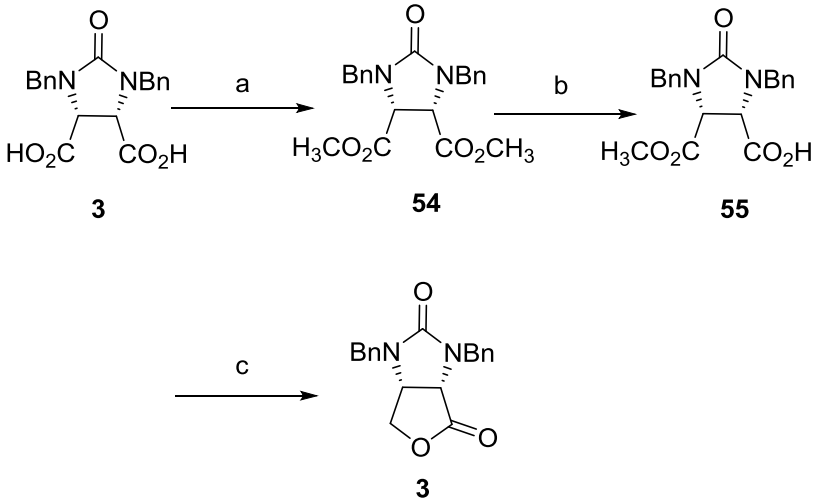


Scheme 15: Reagents and conditions: *a) PLE, phosphate buffer; b) CH_3OCH_2Cl, N,N-diisopropylethylamine, CH_2Cl_2; c) $LiAlH_4$, ether/THF; d) Collins oxidation; e) HCl, THF/H_2O; f) Collins oxidation (93% ee).*

The need to improve the enantioselectivity of the enzymic hydrolytic reaction prompted Sih in 1984 to use a different approach.[58] When the diacetate **51** was incubated with PLE, alcohol **52** was obtained (70% yield; 92% *ee*) indicating that the *pro-R* acetoxy group had been preferentially cleaved. Indeed, when **52** was subjected to a sequence involving Jones oxidation, basic hydrolysis, and lactonization, *ent*-**13** was obtained. Eventually **52** was converted into the desired enantiomer **13** *via* the uneventful sequence shown in Scheme 15.

Chen's approach (*Adv. Synth. Catal.* **2005**, *347*, 549)

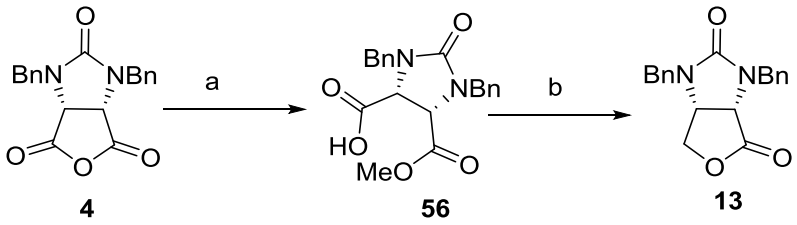
One of the serious drawbacks in enzymatic reaction comes from difficulty to separate the enzyme by filtration. Chen *et al.*[59] improved the workup to a great deal by the use of polymer supported pig liver esterase to achieve both high yield and high enantioselectivity (90% yield, 91% *ee*). The obtained half ester **55** was converted to lactone **13** by selective reduction of the ester group as described in Scheme 16.



Scheme 16. Reagents and conditions*: a) CH_3OH, H_2SO_4, benzene, reflux, 6 h, 95%; b) Polymer-supported PLE, 0.1 M aqueous phosphate, 0.1 M aqueous NaOH, pH 8, 45 h, 30 ºC, then 1 M aqueous HCl, 90%; c) $LiEt_3BH$, THF, 0 ºC to rt, 6 h, then 1 M aqueous HCl, 45 ºC, 1 h, 88%.*

v) Desymmetrization of meso-cyclic anhydride by asymmetric alcoholysis-

Deng's approach (*Synthesis* **2001**, 1737)

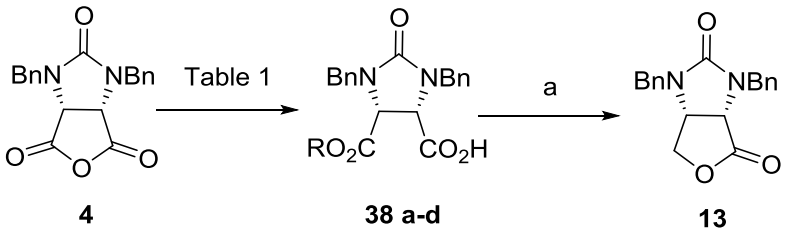


Scheme 17: Reagents and conditions: *a) DHQD-PHN, MeOH, Et_2O, -40 ºC; b) i) Cyanuric chloride, NMM, THF; ii) $NaBH_4$, H_2O; iii) aq. HCl.*

A different method for the desymmetrization of *meso*-acid anhydride **4** has been achieved by applying a modern technology that utilizes catalytic asymmetric esterification[60] wherein the use of a cinchona alkaloid derivative, DHQD-PHN (10 mol %) delivered an excellent *ee* (93% *ee*). Sodium borohydride used for the reduction of activated ester, which was *in situ* formed by the treatment with cyanuryl chloride, furnished the desired lactone **13** with the original asymmetric center virtually retained (Scheme 17).

Chen's approaches (*Tetrahedron Asymmetry* **2008,** *19***,** 1436; *Adv. Synth. Catal.*, **2009,** *351*, 547; *Tetrahedron Asymmetry*, **2010**, *21*, 665; *Chem. Pharm. Bull.* **2011,** *59*, 488).

In order to obtain a higher enantioselectivity, Chen's group developed this strategy (Scheme 18)[61] and the areas of improvements are: modification in the structure of cinchona catalyst and use of more rigid alcohol for alcoholysis. Firstly, they reported an inexpensive and easily available cinchona alkaloid-quinine-mediated desymmetrization of *meso*-cyclic anhydride **4** to prepare hemiester **38**, a direct precursor to lactone **13**. Using propargyl alcohol as nucleophile resulted hemiester **38a** in excellent yield but moderate enantioselectivity and required 1.1 equivalent catalyst **I**.[61a] Until quite recently, a remarkable breakthrough has been achieved by Connon *et al.* and Song *et al.*, who independently observed the highly stereoselective methanolysis of cyclic anhydrides catalyzed by Cinchona-derived amine-thiourea bifunctional organocatalyst **II** (Fig. 6) at room temperature, with 10 mol% catalyst loading. Similar conditions were studied for the conversion of cyclic anhydride **4** into lactone **13.** Due to the bulky size and the presence of multiple polar functionalities, a catalyst loading of 30 mol% was needed for desymmetrization of **4** with propargyl alcohol at room temperature, generating the hemiester **38b** in 96% yield and 82% *ee*. Chen group also used Song's protocol as being capable of facilitating the asymmetric methanolysis of various *meso*-cyclic anhydrides mediated by cinchona alkaloid-based sulfonamide **III**.[61c] However, under these conditions, the asymmetric desymmetrization of **4** using *trans* cinnamyl alcohol as the test nucleophile in MTBE with 0.5 equiv of Song's catalyst **III** at ambient temperature affords the desired hemiester **38c** with good enantioselectivity (92% *ee*).



Scheme 18: Reagents and conditions: *a) Borohydride anion exchange resin (BER, 3.3 mmol $BH4^-$/g), $CaCl_2$, EtOH, r.t., 24 h; then 5% HCl, 55 °C, 0.5 h, 95% (over two steps).*

Table 1

Catalyst	Catalyst loading	Nucleophile (R)	Yield	*ee*
I	1.1 equivalent	Propargyl alcohol	95	86
II	0.3 equivalent	Propargyl alcohol	96	82
III	0.5 equivalent	Trans Cinnamyl alcohol	98	92
IV	1.1 equivalent	MeOH	98	96

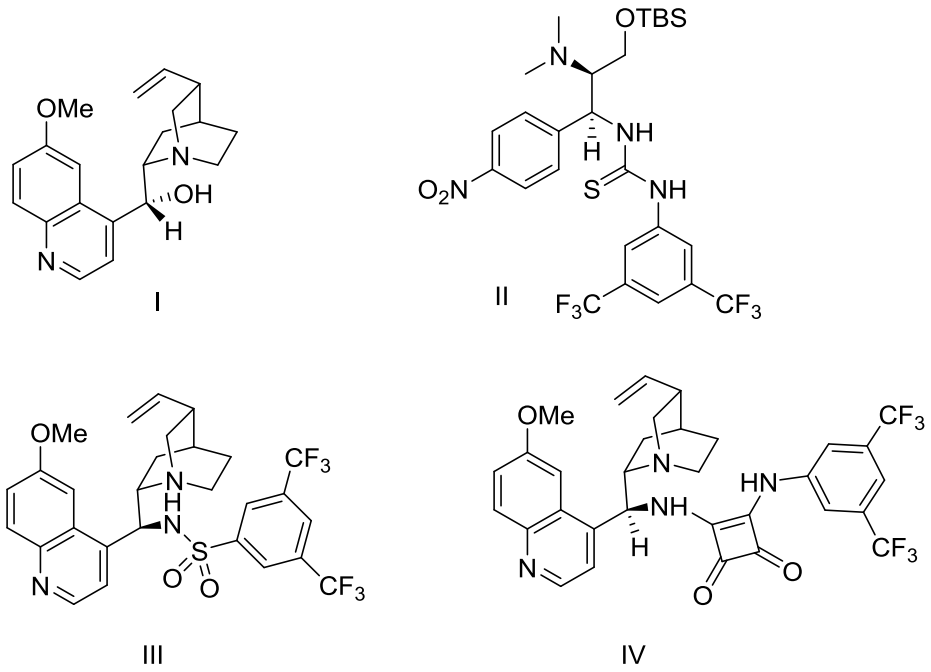


Figure 6. Structures of chiral amine organocatalysts

The efforts to develop asymmetric alcoholysis were concluded by the Chen group with utilizing newly developed bifunctional cinchona alkaloid-derived squaramide **IV**. The catalyst was developed by the same group. The asymmetric desymmetrization of **4** upon treatment with 3 eq of methanol in the presence of 5 mol% catalyst **IV** in methyl *tert*-butyl ether (MTBE) at room temperature resulted in hemiester **38d** in excellent yield with very low enantioselectivity (only 50% *ee*).[61d] It has been reported that the stoichiometric amount of organo-catalyst has found to constitute the key features for a highly efficient methanolytic desymmetrization of *meso*-cyclic anhydride in complex total synthesis due to the bulky size and the presence of multiple polar and basic functionalities of anhydrides. Then it was also

observed that anhydride **4** reacted very well leading to the corresponding product **38d** in 98% yield with 96% *ee* when the catalyst loading increased from 5 to 110 mol%. The resulting chiral hemiester **38d** was subjected to regioselective reduction with borohydride anion exchange resin (BER, 3.3 mmol $BH4^-$/g) in the presence of anhydrous $CaCl_2$ in EtOH for 18 h, subsequent acid-catalyzed lactonization with 5% HCl for 30 min at 55 °C furnished the desired lactone **13** in 95% overall yield with 98.5% enantiomeric excess.

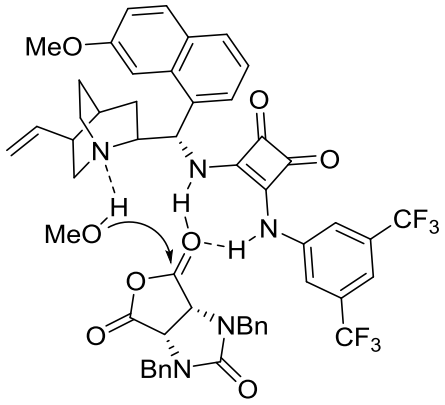


Figure 7. *The proposed transition-state model for the squaramide mediated enantioselective methanolysis reaction*

To account for the observed stereochemical outcome of this reaction, a transition state model was proposed and is depicted in Figure 7. The NH groups of the squaramide IV moiety are expected to form hydrogen-bonding interaction with the carbonyl group to activate the electrophile (anhydride **4**) and the quinuclidine group is believed to simultaneously act as a general base to activate the nucleophile (methanol).

1.1.2.3 Asymmetric induction-

Asymmetric induction[62] in stereochemistry describes the preferential formation in a chemical reaction of one enantiomer or diastereomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, catalyst or environment. Asymmetric induction is a key element in asymmetric synthesis. Asymmetric induction was introduced by Emil Fischer based on his work on carbohydrates. Several types of induction exist.

a) Internal asymmetric induction
b) Relayed asymmetric induction
c) External asymmetric induction

Internal asymmetric induction- Internal asymmetric induction makes use of a chiral center bound to the reactive center through a covalent bond and remains so during the reaction. The starting material is often derived from chiral pool synthesis. Chiral pool method for the synthesis of chiral compounds is efficient, when the carbon skeleton and functional groups as well as stereogenic centers of readily accessible natural product, that is chiral pool, are best suited for the synthesis of the target molecule.

Approaches involving L-cysteine/L-cystine as chirons:

L-Cysteine/L-cystine, carrying amino and thiol groups and chiral center with *S*-configuration, may serve as a proper starting material for (+)-biotin (**1**). Intrigued by the structural features of L-cysteine/L-cystine, some synthetic approaches using L-cysteine/L-cystine as the starting material have recently been developed. The synthetic approaches are classified as three categories according to the place of the bond to be assembled to the bicyclic skeleton of **1** (Fig. 8): (1) C-3-N-3' junction (De Clercq approach); (2) C-3-C-2 junction (Corey, Speckamp, and Chavan approaches); and (3) C-2-S-1 junction (Poetsch and Fujisawa approaches), are being discussed below in chronological order.

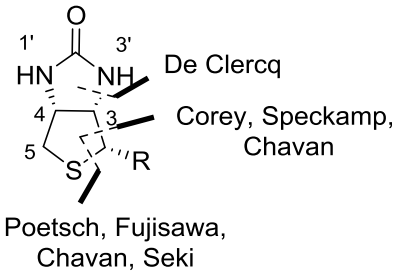
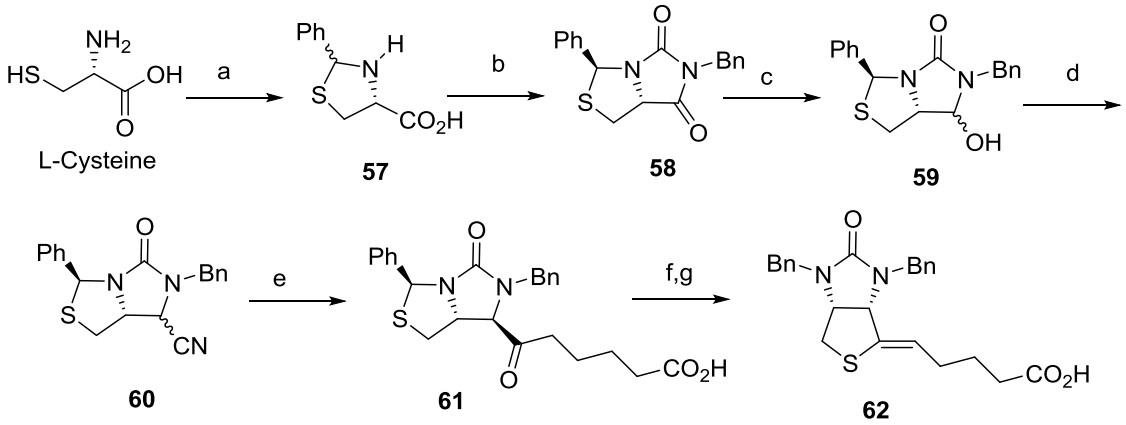


Figure 8. Synthesis of **1** from L-cysteine/L-cystine

Poetsch's approach (*Chimia* **1987**, *41*, 148)

Poetsch *et al.*[63] have reported an extremely concise synthesis of (+)-biotin (**1**) from L-cysteine (Scheme 19). L-Cysteine was first treated with benzaldehyde to simultaneously protect amino and thiol groups as a benzylidene acetal. The resulting thiazolidine derivative **57** was converted to bicyclic hydantoin **58** by the treatment with benzyl isocyanate and hydrochloric acid. Simple reduction of **58** with sodium borohydride furnished hydroxy derivative **59** that, upon activation by acetylation followed by treatment with trimethylsilyl cyanide (TMSCN) in the presence of titanium (IV) tetrachloride ($TiCl_4$), afforded cyano deriveative **60** in high yield. 4-

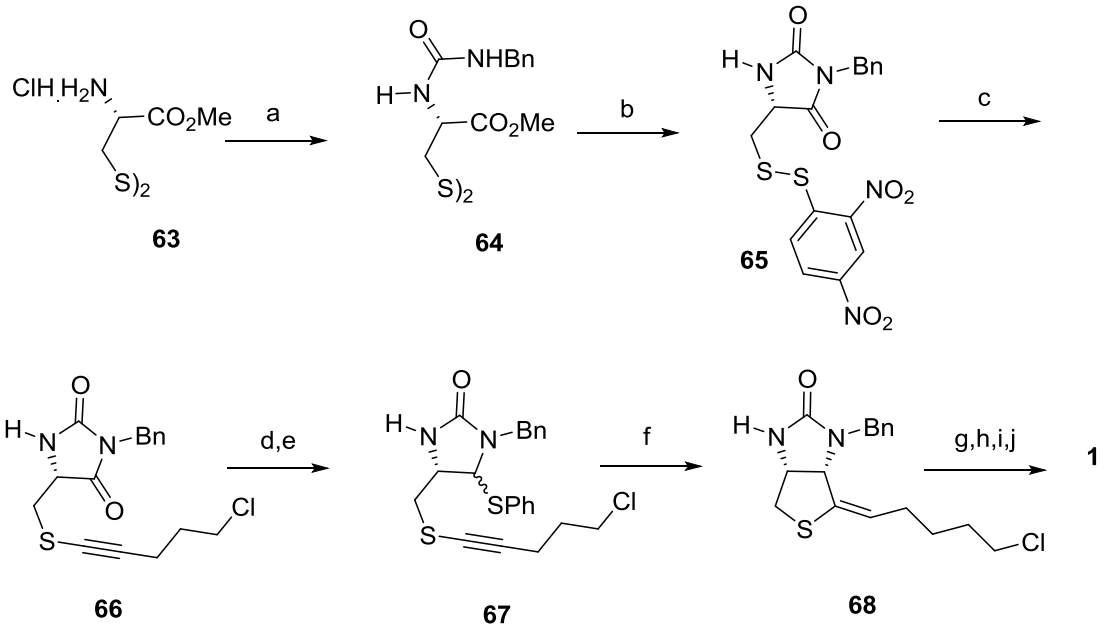
Carboxylbutyl chain was efficiently installed through the treatment of **60** with a di-Grignard reagent followed by quenching with carbon dioxide. Reductive cleavage of carbon-sulfur bond with zinc dust, and subsequent cyclization and dehydration provided vinyl sulfide **62**, a known precursor to **1**. The use of less costly reagents and high overall yield as well as the minimum steps (9 steps) makes the process one of the best among the practical approaches to **1**.



Scheme 19: Reagents and conditions: *a) PhCHO; b) (i) BnNCO, (ii) HCl; c) $NaBH_4$, THF, H_2O; d) (i) Ac_2O (ii) TMSCN, $TiCl_4$; e) (i) $BrMg(CH_2)_4MgBr$, (ii) CO_2, (iii) HCl; (f) Zn, AcOH; (g) Piperidine, AcOH.*

Corey's Approach (*Tetrahedron Lett.* **1988**, *29*, 57)

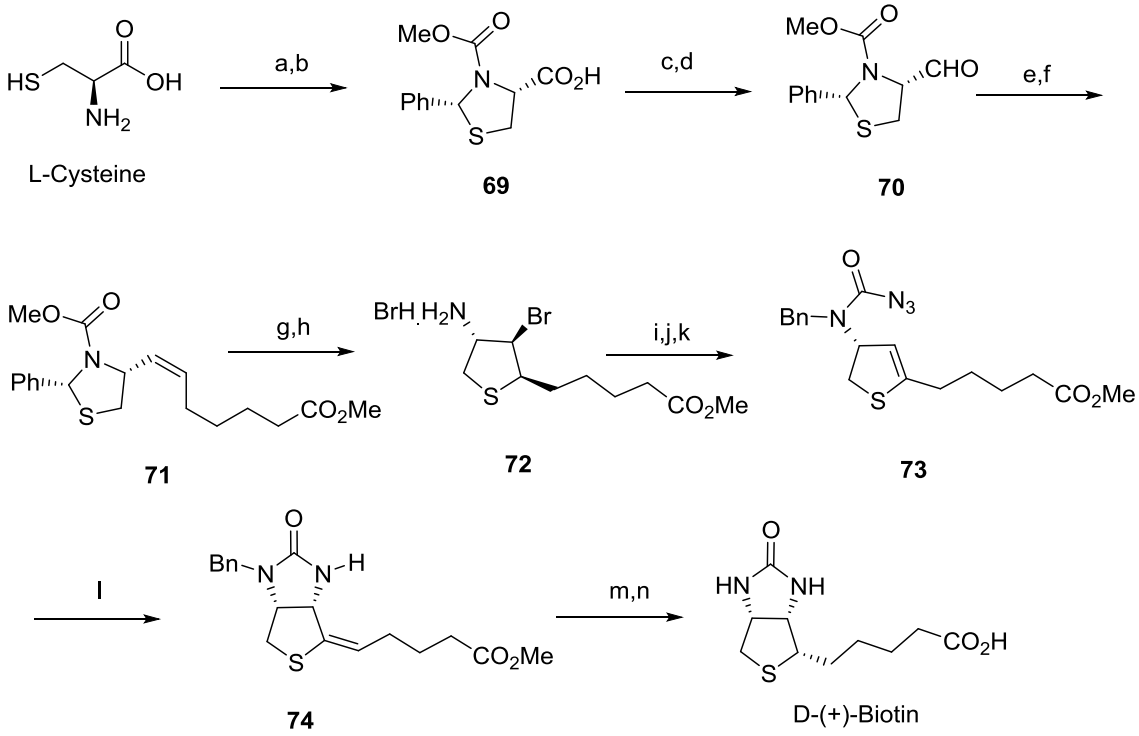
Corey *et al.*[64] have developed the synthesis of (+)-biotin (**1**) using radical cyclization of **67** as the key step (Scheme 20). 2,4-Dinitrophenyl sulfide **65** was first elaborated from L-cystine methyl ester hydrochloride **63**. Alkyne moiety in **66** was introduced by nucleophilic substitution of **65** with cerium 2-(3-chloropropyl)acetylide. Amidoalkylation of diphenyl disulfide with phosphine-activated alcohol derivative, which was prepared by reduction of **66**, afforded **67**. Treatment of **67** with tricyclohexyl tin hydride in the presence of azobisisobutyronitrile (AIBN) provided the desired cyclized product **68**, though in a moderate yield (40%). The resulting chloride **68** was then converted to **1** through substitution with sodium cyanide and hydrogenation, followed by hydrolysis and removal of the benzyl protective group.



Scheme 20: Reagents and conditions: *a) (i) $COCl_2$, (ii) $BnNH_2$; (b) (i) Ph_3P, DME, (ii) HCl, (iii) 2,4-Dinitrobenzenesulfinyl chloride; (c) $LiCC(CH_2)_3Cl,CeCl_3$, (d) DIBAL-H; (e) $(PhS)_2$, n-Bu_3P; (f) $(C_6H_{11})_3SnH$, AIBN; (g) NaCN; (h) H_2, Pd/C; (i) NaOH; (j) HBr.*

De Clercq's Approach (*Tetrahedron Lett.* **1993**, *34*, 4365)

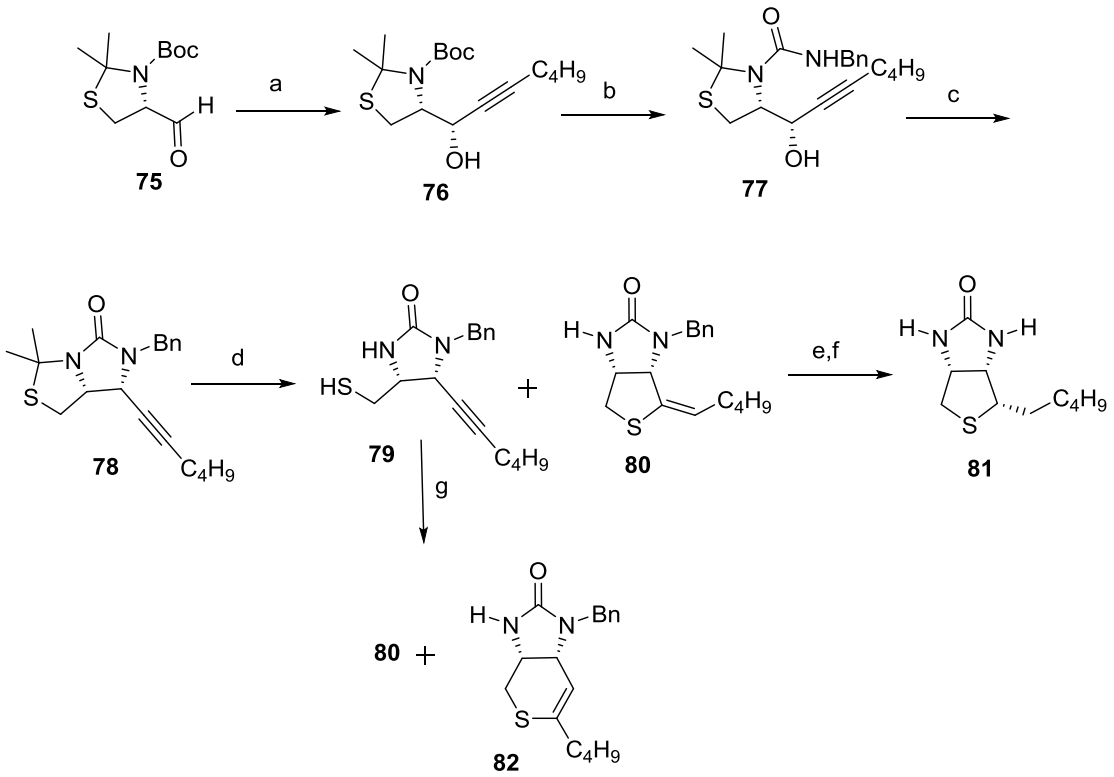
De Clercq *et al.*[65] have described a conceptually elegant synthesis of (+)-biotin (**1**) (Scheme 21). Ene-azide **73**, a substrate for ring formation, was obtained from L-cysteine. The Wittig reaction of aldehyde **70**, which was readily derived from L-cysteine, installed 4-carboxybutyl chain. Treatment of the resulting olefin **71** with bromine followed by hydrogen bromide allowed three consecutive reactions: cleavage of benzylidene acetal, installation of a new tetrahydrothiophene ring, and removal of the protective group. Benzylation of **72** and subsequent formation of acyl azide and final elimination of bromide anion with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) provided the required **73**. Intramolecular [2+3] cycloaddition of **73** followed by elimination of nitrogen gas gave an intermediate **74** carrying the required bicyclic skeleton in good yield.



Scheme 21: Reagents and conditions: *a) PhCHO, KOAc; b) $ClCO_2Me$, $NaHCO_3$; c) CH_2N_2; d) DIBAL-H; e) $[Ph_3P(CH_2)_5CO_2H]Br$, LDA; f) CH_2N_2; g) Br_2; h) HBr, AcOH; i) PhCHO, $NaBH_3CN$; j) $COCl_2$, DBU, NaN_3; k) DBU; l) Heat; m) H_2, $Pd(OH)_2/C$; n) HBr, reflux.*

Fujisawa's approach (*J. Org. Chem.* **1994**, *59*, 5865)

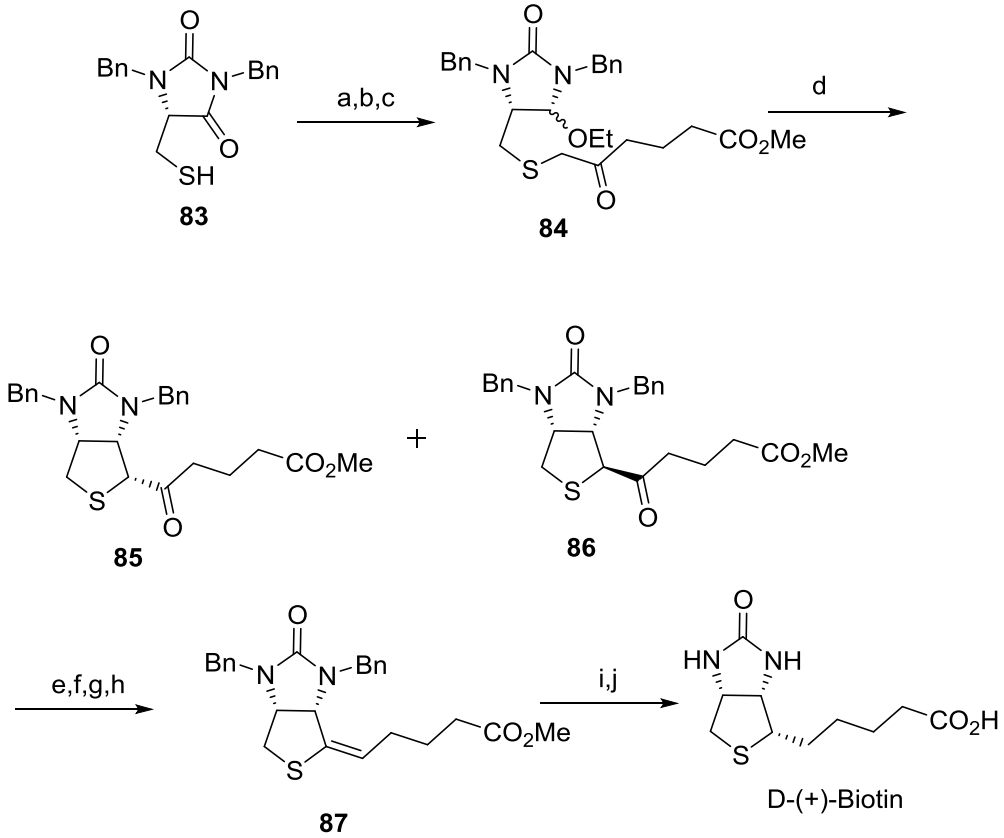
Fujisawa *et al.*[66] have developed the synthesis of (+)-biotin (**1**) using acid-catalyzed cyclization of yne thiol derivative **79** for the key step (Scheme 22). The compound **79** was synthesized from thiazolidine-4-carbaldehyde **75** that was readily derived from L-cysteine, through stereoselective addition of zinc salt of 2-butylacetylide. The alcohol **76** obtained was stereoselectively converted to **78** by a sequence involving removal of Boc group, ureide formation, and cyclization *via* S_N2 substitution. Simple treatment of **78** with *p*-toluenesulfonic acid led to cyclized product **80**. Non-cyclized compound **79** was converted to **80** by the treatment with cesium hydroxide in a moderate yield (50%), owing to the uncontrolled regioselectivity of the cyclization. The compound **80** was transformed to **1** through hydrogenation and deprotection to **81**, followed by subsequent microbial oxidation of the terminal methyl group. Practicability of the synthesis is, however lessened by the requirement of the bioprocess in the last step.



Scheme 22: Reagents and conditions: *a) (i) 1-Hexyne, n-BuLi, (ii) $ZnCl_2$; b) (i) p-TsOH, MeOH, (ii) BnNCO, pyridine; c) KH, p-TsCl, THF, HMPA; d) TsOH, H_2O, MeOH; e) H_2, Pd/C; f) HBr; g) CsOH, H_2O, THF.*

Speckamp, Poetsch and Casutt's approach (*Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391)

Speckamp and coworkers' approach involves highly convergent synthetic scheme wherein 4-carboxybutyl chain was installed by alkylation of a thiol group with methyl 6-chloro-5-oxohexanoate (Scheme 23).[67] Formation of the bicyclic skeleton of (+)-biotin (**1**) was carried out by intramolecular amidoalkylation of silyl enol ether, *in situ* generated from **84**. The resulting mixture of diastereomers **85** and **86** was converted to an intermediate **87** through reduction with sodium borohydride followed by elimination of hydroxyl group. The compound **87** was led to **1** through hydrogenation and subsequent cleavage of benzyl groups.



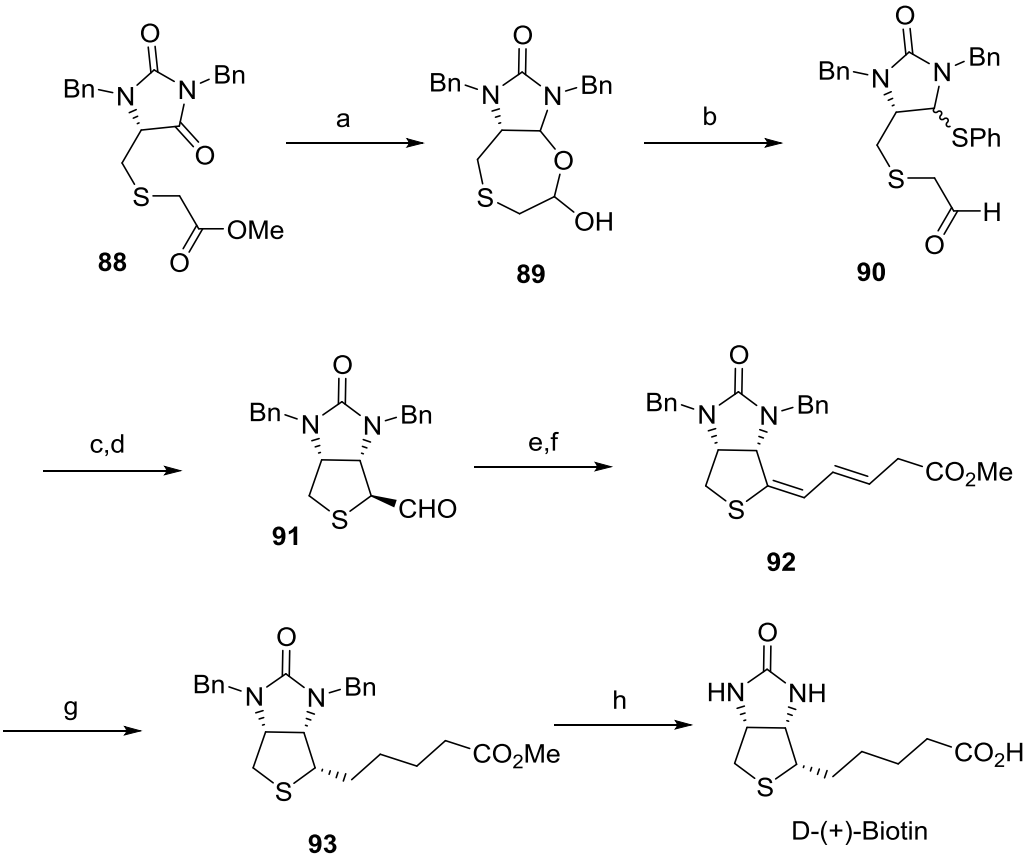
Scheme 23: Reagents and conditions: *a) DIBAL-H, THF, -70 ^{o}C, 1 h; b) $MeO_2C(CH_2)_3C(O)CH_2Cl$, Et_3N, 4 h; c) H_2SO_4/EtOH, methyl orange, pH=3.1, 0 ^{o}C, 2 h, 72%; d) 2.1 eq. of $(TMS)CH_2CO_2Et$, 0.03 eq. of TBAF, THF, -78 ^{o}C to 25 ^{o}C, 18 h, then 1.5 eq. of TMSOTf, DCM, -78 ^{o}C, 1 h, 78%; e) $NaBH_4$, MeOH, 25 ^{o}C; f) $MeSO_2Cl$, Et_3N, DCM; g) DBU, 60 ^{o}C, 2 h; h) KOH/MeOH, 2 h, 87%; i) H_2 (10 bar), 10% Pd/C, 2-propanol, 50 ^{o}C, 18 h; j) 48% HBr, 100 ^{o}C, 2 h, 85%.*

Independently, Chavan's group has reported two syntheses of biotin on similar lines of intramolecular *N* acyliminium cyclisation shown in Scheme 24 and Scheme 25.

Chavan's approaches (US patent 5,274,107; Chem. Abstr. **1994**, *120*, 217097t; *J. Org. Chem.* **2001**, *66*, 6197; *J. Org. Chem.* **2005**, *70*, 1901)[68]

Conversion of thioaldehyde **90** to the corresponding silyl enol ether followed by trialkyl silyl triflate mediated cyclization in the presence of *p*-nitrobenzaldehyde as thiophenol scavenger lead to the thermodynamically more stable thiophane aldehyde **91** (Scheme 24). The synthesis of aldehyde **90** involves reduction of hydantoin ester **88** to yield the cyclic hemiacetal **89**, which is further converted to **90** by treatment with thiophenol. The transformation of **91** into biotin involved first Wittig reaction

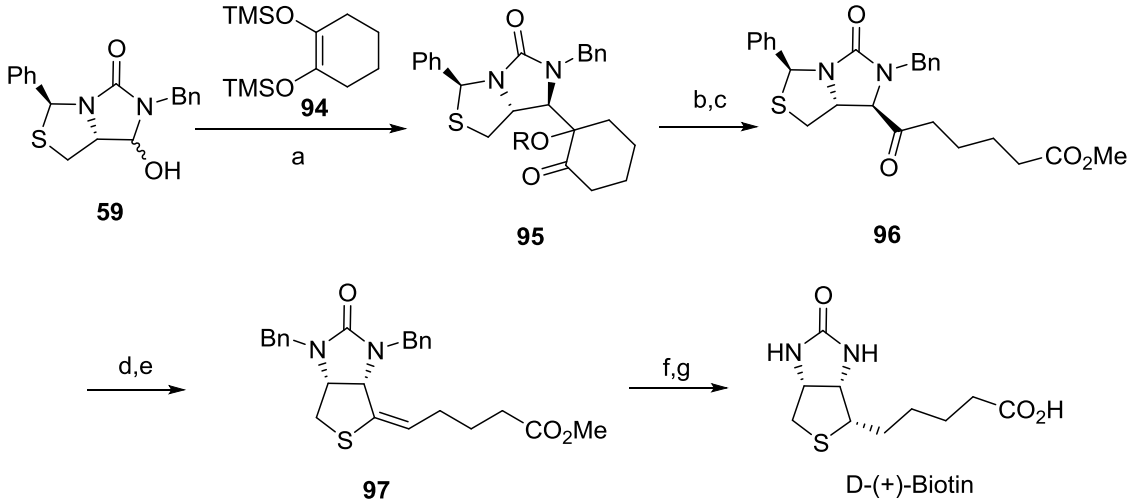
with the 4-carbon ylide, followed by deconjugation with base to yield the exocyclic olefin **92**. Further catalytic hydrogenation led to dibenzyl biotin methyl ester **93**, which on treatment with 48% HBr furnished D-(+)-biotin.



Scheme 24: 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.*

In the second approach (Scheme 25), the amidoalkylation was performed on hydroxy ureide **59**[68c] with 1,2-bis TMS **94** to furnish **95** in excellent yields. The ketone **95** 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 **96** in quantitative yield. The intermediate **96** 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 **97**. 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.

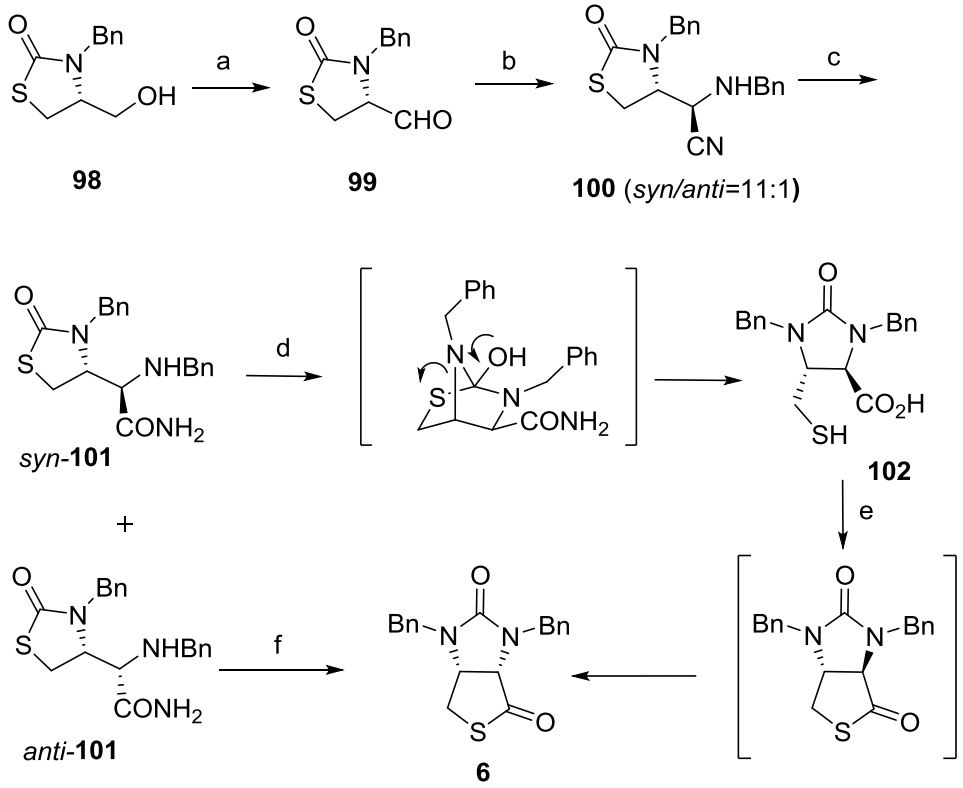


Scheme 25: Reagents and conditions: *a) $BF_3.OEt_2$, DCM, 98%; b) 70% TBHP, KOH-MeOH, 15 min; c) CH_2N_2, 10 min, 70%; d) Zn/AcOH, 80 ^oC, 5 h; e) AcOH/ piperidine, 100 ^oC, 90 min, 70%; f) H_2/Pd-C, MeOH, 200 psi, 100%; g) 47% HBr, 5 h, 78%.*

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

Seki *et al*. reported synthesis of biotin from L-cysteine utilizing Strecker reaction as key step.[69] A *syn*-selective Strecker reaction of α-amino aldehyde **99** to β-amino-α-amino nitrile *syn* **100** was achieved to allow an access to thiolactone **6**, a key intermediate for **1** (Scheme 26). Amino alcohol **98** was subjected to the Moffatt oxidation employing DCC in the presence of TFA and pyridine to effect a clean conversion to α-amino aldehyde **99** (90% yield). The resulting solution of **99** in ethyl acetate was treated with sodium bisulfite (1.1 equiv) in water to provide the bisulfite adduct in excellent yields (99% conversion). The aqueous solution of bisulfite adduct was treated with benzylamine in a biphasic system involving CH_2Cl_2 and water at 20 ^oC for 2 h. The resulting mixture containing an imine and a bisulfite adduct of the imine was treated with NaCN (1.2 equiv) at 8 ^oC and the whole was stirred at ambient temperature for 20 h to provide α-amino nitrile **100** 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 **100** was directly subjected 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 **101** in quantitative yield. *Syn* **101** 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 **102** in 95% yield. The compound **102** obtained was cyclised and isomerized to thiolactone **6** in 93% yield.



Scheme 26: Reagents and conditions: *a) DCC, TFA, pyridine, DMSO, EtOAc, 50 ^oC, 3 h; b) i) $NaHSO_3$, EtOAc, H_2O, 20 ^oC, 18 h; ii) $BnNH_2$ (1.7 equiv), CH_2Cl_2, 20 ^oC, 2 h, iii) NaCN (1.2 equiv), 8–20 ^oC 20 h, c) i) H_2O_2, K_2CO_3, DMSO/CH_2Cl_2, 20 ^oC, 2.5 h, ii) H_2O, filtration, iii) For the filtrate: HCl; d) (i) DMF, 90 ^oC, 1 h, ii) HCl; e) DCC, TFA, pyridine, $CHCl_3$, 5 ^oC-reflux, 5 h; f) 120 ^oC, 5 h DMF.*

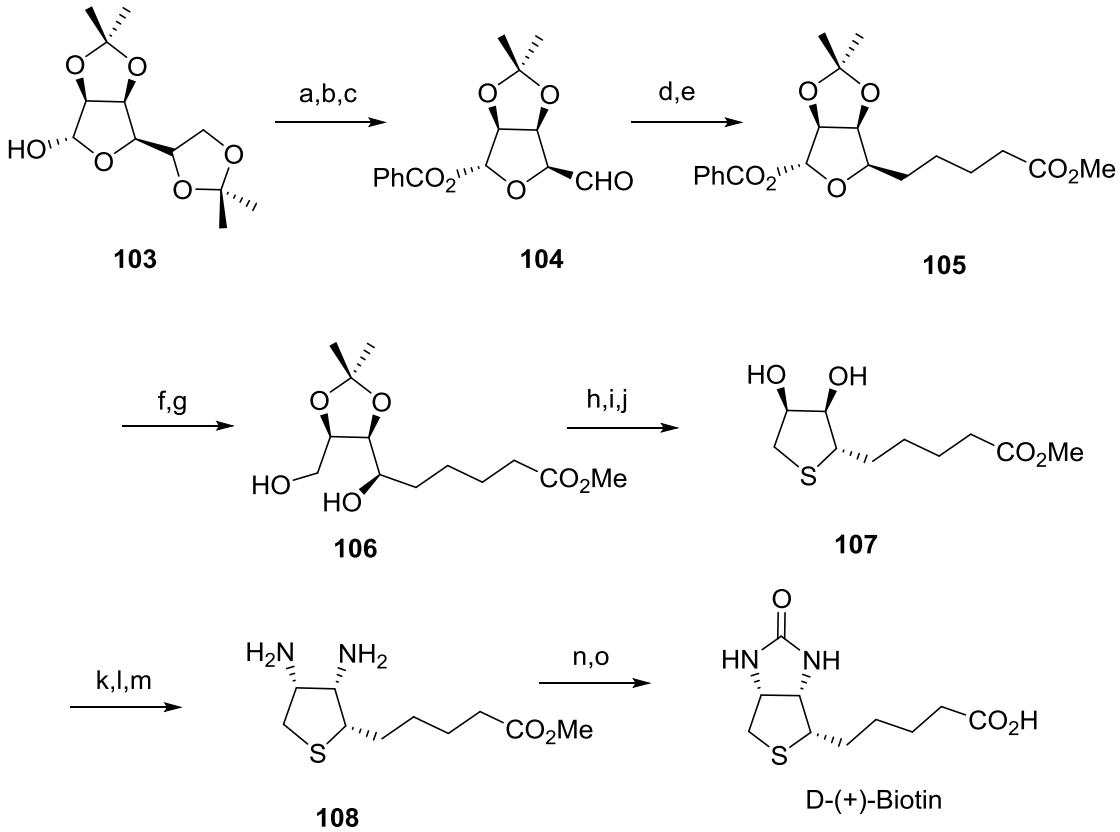
In contrast, the *anti* isomer *anti* **101** was directly converted to **6** in 91% yield with heating at a higher temperature (120 ºC) through the *S,N*-carbonyl migration followed by spontaneous cyclization.

Approaches involving sugars as chirons:

Syntheses of biotin utilizing monosaccharides as chiral synthons are described below briefly. 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. Crucial in the design of all syntheses in this area is the obtention of the thiophane nucleus *via* double S_N2 displacement of a dimesylate obtained from a diol. 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 were introduced *via* sequences involving S_N2 substitution of a leaving group by azide followed by reduction of the azide.

Ohrui's approach (*Tetrahedron Lett.* **1975**, 2765)



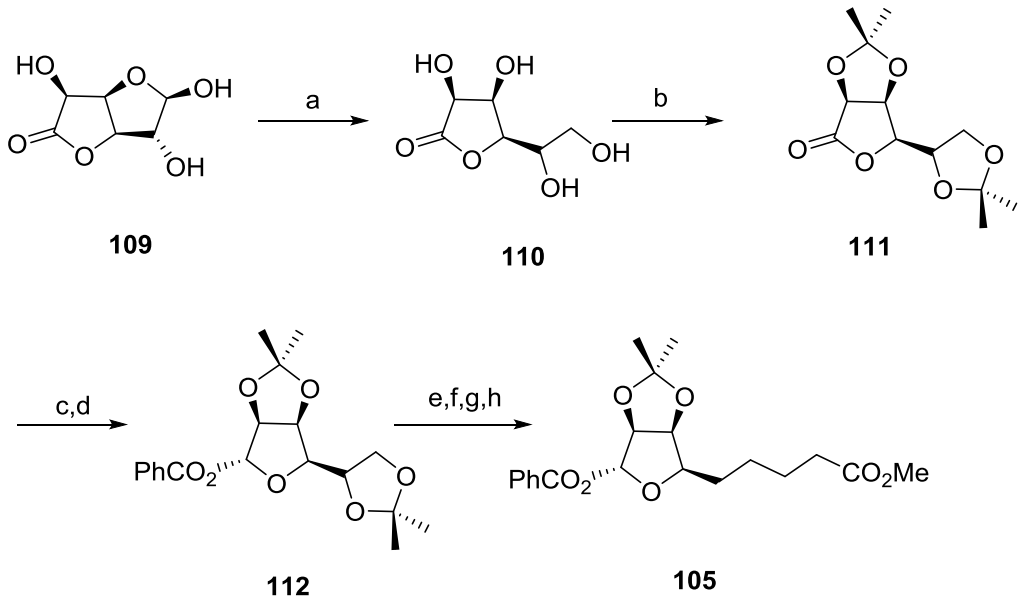
103 **104** **105** **106** **107** **108**

Scheme 27: 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) $COCl_2$.*

In 1975, Ohrui *et al.*[70] reported synthesis of biotin from mannofuranose as chiron (Scheme 27). In their approach the di-*O*-isopropylideneprotected *R*-D-mannofuranose **103** is converted to diol **106**. The sequence involved 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 **104**. Subsequent Wittig treatment and catalytic hydrogenation afforded **105**. Base treatment of the latter generated the hemiacetal that was reduced to diol **106**. After thiophane formation and hydrolysis the obtained diol **107** is converted to the diamine **108** *via* inversion. Final obtention of (+)-biotin occurs after saponification and phosgene treatment.

Ravindranathan's approach (*Carbohydr. Res.* **1984**, *134*, 332)

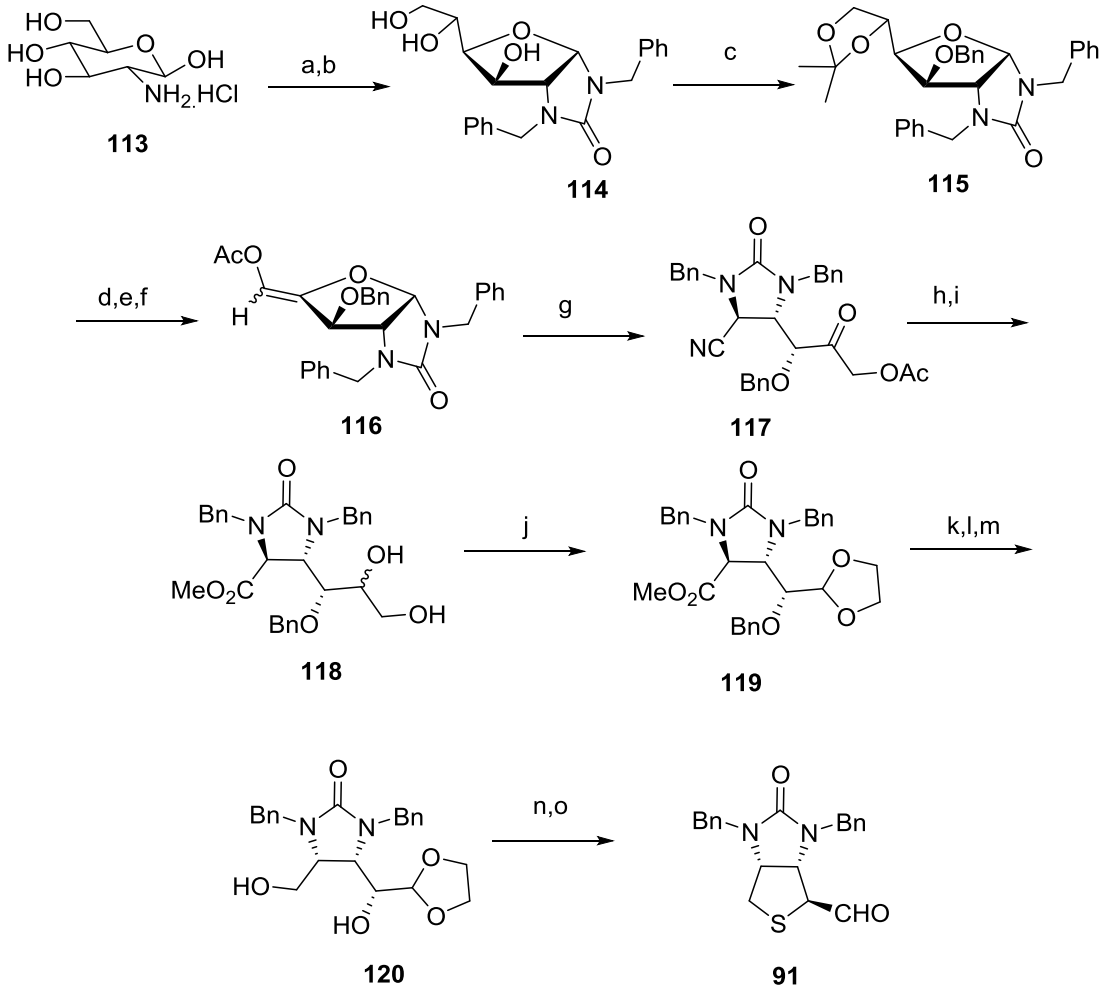
A modified synthesis of (+)-biotin from D-glucose was reported by Ravindranathan and co-workers in 1984.[71] The synthesis which is outlined in Scheme 28 leads to the Ohrui intermediate **105**. The starting substance is D-glucurono-6,3-lactone **109** which is first reduced to L-gulono-1,4-lactone **110**. The remaining steps are essentially similar to the Ohrui sequence (Scheme 27).



Scheme 28: Reagents and conditions: *a) H_2, Raney-Ni; b) $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH; c) $NaBH_4$, CH_3OH, 0 °C; d) PhCOCl, C_5H_5N; 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/C.*

Chavan's approach (*Tetrahedron Lett.* **2004**, *45*, 7307)

Chavan's group developed a sequence to the thiophane aldehyde **91** (Scheme 24) starting from D-glucosamine, by taking advantage of the correct absolute configuration of the amino group in D-glucosamine that will eventually appear at C-4 in (+)-biotin (Scheme 29).[72] By treating glucosamine hydrochloride with BnNCO in the presence of sodium bicarbonate followed by heating in the presence of catalytic amount of pyridine, furnished the *cis* furanoid bicycle **114**.



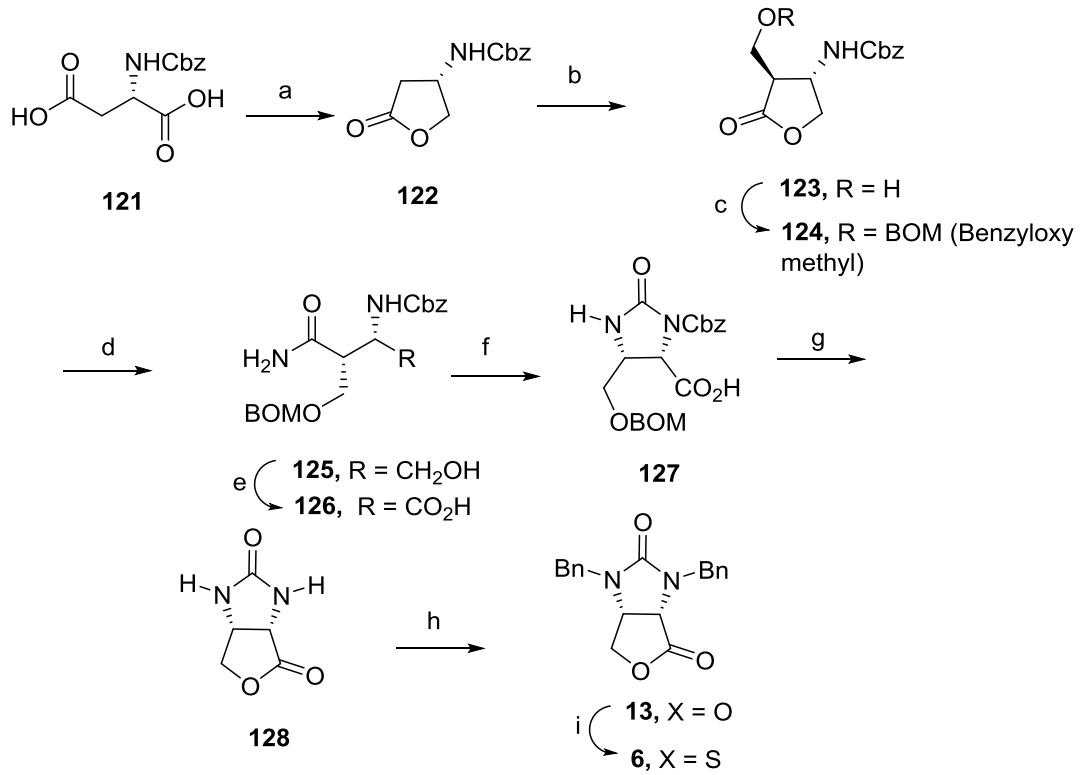
Scheme 29: Reagents and conditions: *a) (i) BnNCO, aq. $NaHCO_3$; (ii) Pyridine (cat.), H_2O; b) p-TSA (cat.), acetone, rt; c) NaH, BnBr, DMF; d) p-TSA (cat.), THF–H_2O (9:1), reflux; e) $NaIO_4$, acetone–H_2O (9:1), rt; f) Ac_2O, Et_3N, DMAP (cat.), DCM; g) TMSCN, $BF_3.Et_2O$, DCM, -78 ^oC to rt; h) $NaBH_4$, MeOH, 0 ^oC to rt; i) TMSCl, MeOH, 40 ^oC; j) (i) $NaIO_4$, acetone–water (9:1), rt; (ii) Ethylene glycol, p-TSA, C_6H_6, reflux; k) Pd–$CaCO_3$, MeOH, rt; l) DBU (cat.), toluene, reflux; m) $NaBH_4$, EtOH, reflux; n) (i) MsCl, Et_3N, DMAP (cat.), 0 ^oC to rt; (ii) Na_2S, DMF, 100 ^oC; o) 6 N HCl, CH_3COOH, rt.*

The diol **114** was protected as the acetonide and *N*-urea protected with benzyl bromide to furnish the protected bicyclic intermediate **115**. Demasking of acetonide resulted in diol, which was cleaved to the aldehyde which was subsequently treated with acetic anhydride to furnish the exocyclic enol acetate **116**. Intermolecular carbon–carbon bond formation *via* an acyliminium ion was effected by treating the enol acetate **116** with TMSCN and $BF_3.Et_2O$ to furnish the cyano substituted intermediate **117**. Compound **117** on reduction with $NaBH_4$ and further treatment with TMSCl in methanol resulted in methyl ester **118**. The diol **118** was cleaved to aldehyde and subsequently protected as the dioxalane derivative **119**. By following the sequence, selective *O*-debenzylation, epimerization and reduction dioxalane derivative **119** was converted into diol **120**. The thiophane nucleus was synthesised *via* double S_N2 displacement of a dimesylate obtained from the diol **120**. Treatment with acid furnished thiophane aldehyde **91.** The remaining steps are essentially similar to the previous approach (Scheme 24).

Approach involving L-aspartic acid as chiron:

Seki's approach (*Synthesis* **2002**, *3*, 361)

In 2002 Seki *et al.* reported the synthesis of biotin starting from L-aspartic acid as chiral synthon (Scheme 30).[73] The aldol reaction of an *N*-Cbz-3-amino-4-butanolide **122**, derived from L-aspartic acid, with formaldehyde gave the *trans*-disubstituted 3-amino-4-butanolide **123** stereoselectively. Protection of the hydroxyl group of **123**, amidation and oxidation provided the substituted L-asparagine derivative **126**. The Hofmann rearrangement of **126** with sodium hypochlorite in the presence of sodium hydroxide and subsequent hydrogenation gave the bicyclic lactone **128**, which upon dibenzylation and thionation, gave the thiolactone **6**, a key intermediate for the synthesis of (+)-biotin.



Scheme 30: Reagents and conditions: *a) i) Ac_2O; ii) $NaBH_4$, THF; iii) HCl; b) i) LDA, THF; ii) HCHO, –78 °C, trans/cis = 12:1; c) BOMCl, i-Pr_2NEt, THF, quant; d) NH_4OH, MeOH; e) Jones' reagent, acetone; f) NaOCl, NaOH, H_2O; g) H_2, $Pd(OH)_2/C$, MeOH; h) BnBr, NaH, DMF; i) AcSK, DMF.*

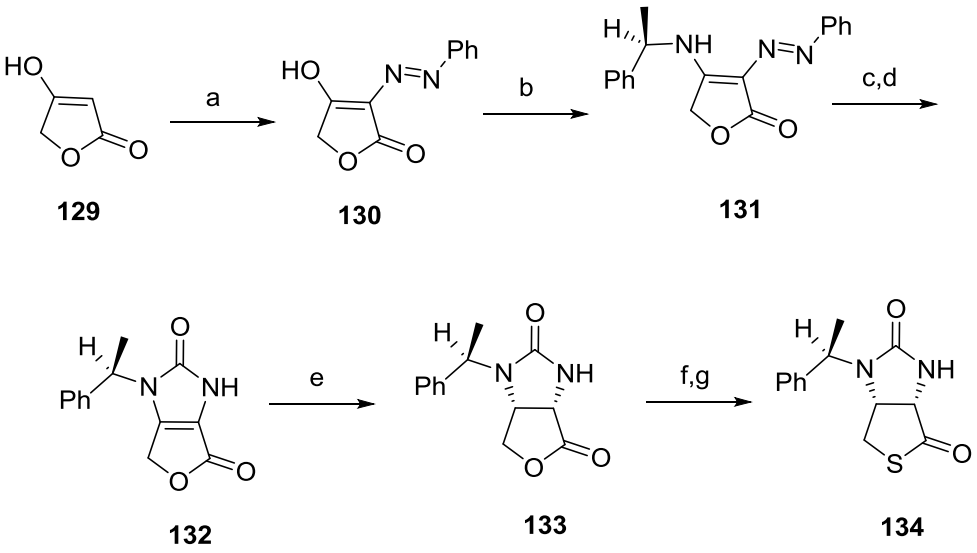
In **relayed asymmetric induction** the chiral information is introduced in a separate step and removed again in a separate chemical reaction. Special synthons are called chiral auxiliaries.

Garrity's approach (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 centers around the hydrogenation of furoimidazole derivative **132** (Scheme 31).[74a] The synthesis of this intermediate **132** involves a straightforward four-step sequence starting from tetronic acid **129**. Treatment of the latter with the diazonium salt derived from aniline leads to diazo compound **130** which is converted into **132** *via* reaction with a primary amine such as (*S*)-1- phenylethyl amine to afford **131** followed by reduction and subsequent imidazolone ring formation with ethyl chloroformate.[74b] It is interesting to note that both **132** and *ent*-**132** 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 **132** (54% yield of crystalline **133**).
2. Palladium on carbon in acetic acid for *ent*-**132** (54% yield).[74c]

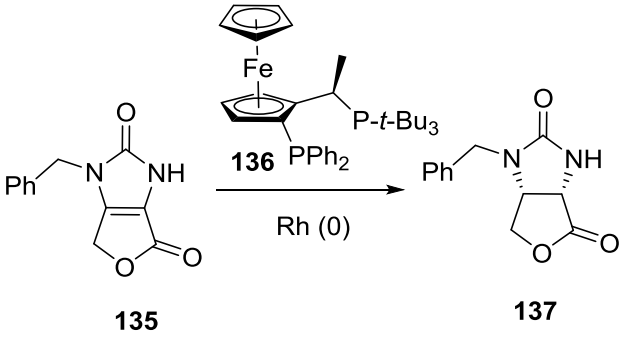


Scheme 31: Reagents and conditions: *a) $PhNH_2$, $NaNO_2$, HCl; b) (R)-$PhCH(NH_2)CH_3$, $B(OEt)_3$, $PhCH_3$, 80 ^oC; c) H_2, Pt/C, EtOAc, 40 bar; d) ClCOOEt, Et_3N, CH_3CN, reflux; e) H_2, Rh/Al_2O_3, DMF, 40 bar; f) NaH, DME, $PhCH_2Br$; g) CH_3COSK, $CH_3CON(CH_3)_2$, 150 ^oC.*

In **external asymmetric induction** chiral information is introduced in the transition state through a catalyst of chiral ligand. This method of asymmetric synthesis is economically most desirable.

Garrity's approach (Eur. Pat. Appl. EP 624 587 17th Nov. 1994; Chem. Abstr. **1995**, *122*, 81369q)[75]

The reduction of achiral **135** in the presence of a rhodium complex and a chiral ferrocenylphosphine ligand **136** into **137** (95% yield; 90% *ee*), constitutes a sole example where the chirality is introduced by a catalytic pathway (Scheme 32).



135 **137**

Scheme 32: Reagents and conditions: a) *Rh(0)= [Rh(norbornadiene)Cl]$_2$, PhCH$_3$, 70 ^{o}C, H$_2$, 50 bar.*

Up to date only one approach is reported by this strategy.

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Chapter 1. Synthetic Studies towards D-(+)-Biotin

Section 2

A novel and enantioselective synthesis of D-(+)-Biotin via Sharpless asymmetric dihydroxylation strategy

1.2.1 Summary

The present section deals with the enantioselective synthesis of D-(+)-biotin. The key steps in the sequence are the Sharpless asymmetric dihydroxylation of a (*E*)-ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate derivative to establish the stereocenters of D-(+)-biotin, establishment of the carboxyalkyl side chain by unmasking of cyclohexene by ozonolysis and enzymatic hydrolysis of a thioacetate.

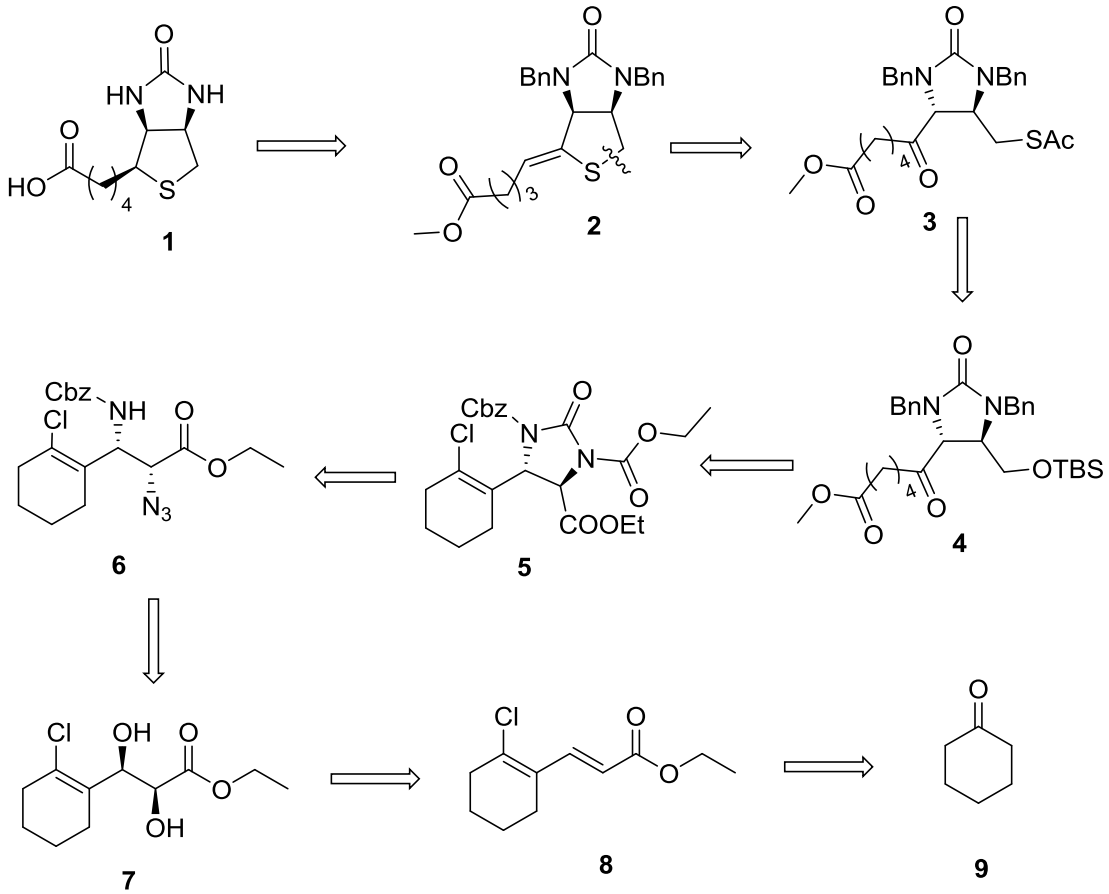
1.2.2 Introduction

Over the past decades, many efforts have been made on the development of an efficient process for the total synthesis of D-(+)-biotin (**1**) and a number of new synthetic approaches involving different stratergies for the control of three adjacent chiral centers are reported in the literature.[1] It may be emphasized that very few syntheses of D-(+)-biotin involving intermolecular asymmetric induction are reported in the literature.[1a] Many synthetic approaches, such as diastereoisomeric or enzymatic resolutions,[2] chiral pool methods involving carbohydrates,[3] cysteine[4] and L-aspartic acid[5] have been described. This research group has been actively involved in the stereoselective synthesis of D-(+)-biotin *via* chiral pool methods and has reported D-(+)-biotin syntheses starting from L- cysteine[6] and glucosamine.[7] Herein, contributions towards developing an asymmetric total synthesis of **1** starting from commercially available achiral starting material *viz.* cyclohexanone, is described.

1.2.3 Present work

The envisaged retrosynthetic strategy for biotin (**1**) is delineated in Scheme 1. A linear synthetic strategy was invoked wherein olefin **2** was conceived as the direct precursor to **1**. Olefin **2** would then in turn be accessed from thioacetate **3** upon hydrolysis and intramolecular cyclization. The carboxyalkyl side chain of biotin (**1**) could be unmasked by ozonolysis of cyclohexene **5**. The cyclohexene **5** could be readily obtained from azidoamine **6** by reduction and urea formation. The vicinal diamine group in **6** could be introduced *via* sequences involving opening of cyclic sulfite which could be prepared from diol **7** and S_N2 substitution of a leaving group by azide. Further analysis indicated that the diol compound **7** could be synthesized from the unsaturated ester compound **8** by using Sharpless asymmetric dihydroxylation

(SAD). The unsaturated ester **8** could be obtained from easily available, inexpensive starting material **9** *via* Vilsmeier-Haack reaction and Wittig reaction (Scheme 1).

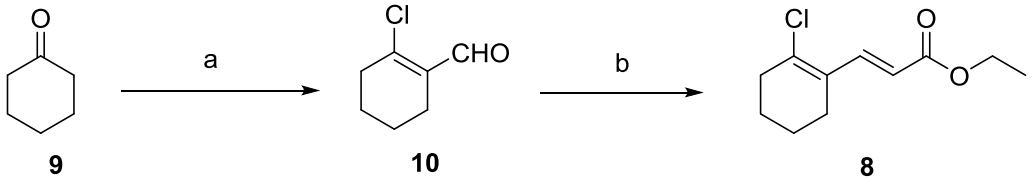


Scheme 1. *Retrosynthetic analysis for biotin **1**.*

1.2.4 Results and discussion

Accordingly, the synthesis of biotin (**1**) began from cyclohexanone (**9**) as a commercially available starting material. Following a literature procedure,[8] cyclohexanone (**9**) was subjected to Vilsmeier-Haack reaction to furnish aldehyde **10**, which was homologated using Wittig reaction to afford unsaturated ester **8** in 76% yield (Scheme 2). The IR spectrum of compound **8** showed strong bands at 1713 and 1622 cm^{-1} indicating the presence of ester and olefin functionalities. The ^{1}H NMR spectrum of compound **8** showed peaks at δ 5.85 and 7.91 as doublets corresponding to the protons of double bond of unsaturated ester compound **8**. The coupling constant of the two protons of the double bond was 15.9 Hz which revealed that the double bond had *trans* geometry. The ^{13}C NMR spectrum showed peak at δ 166.7

corresponding to the carbonyl carbon of ester functional group. Its DEPT NMR spectrum showed presence of five CH_2 groups, four for cyclohexene and one for ethyl ester. Finally, the structure of compound **8** was confirmed by HRMS analysis (Scheme 2).



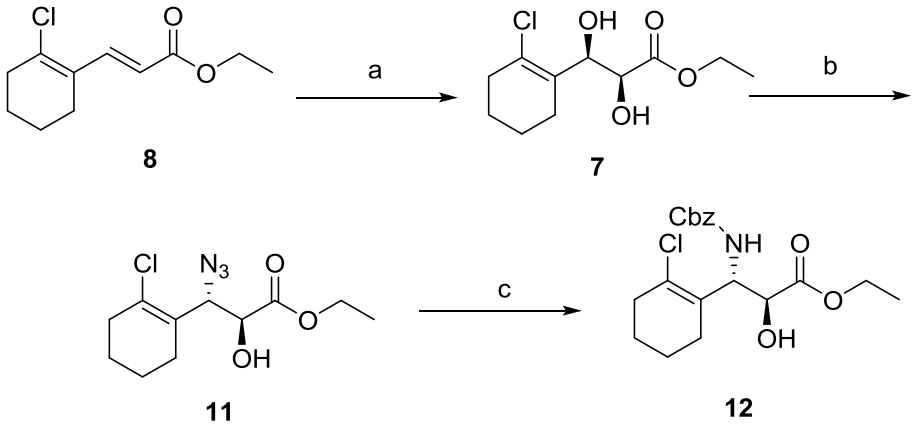
9 **10** **8**

Scheme 2. *Reagents and conditions: a) $POCl_3$, DMF, DCM, 0 °C-rt, 4 h, 95%; b) Ph_3PCHCO_2Et, DCM, rt, 4 h, 76%.*

This prochiral unsaturated ester **8** was deemed to be a suitable substrate for the installation of the chiral centers. The compound **8** was subjected to Sharpless asymmetric dihydroxylation (SAD)[9] conditions with $(DHQD)_2PHAL$ as the chiral catalyst to yield chiral diol **7** in 84% yield with ≥99% *ee*.[10] The IR spectrum of compound **7** showed strong bands at 3446 and 1736 cm^{-1} for free hydroxyl and ester functional groups respectively. In ^1H NMR spectrum of compound **7**, doublets at δ 5.85 and 7.91 were absent indicating the conversion of conjugated double bond into diol. ^{13}C NMR and DEPT NMR spectra of compound **7** showed the peaks at δ 72.1 and 73.2 for corresponding methine carbons [-CH(OH)-CH(OH)-]. Finally the structure of compound **7** was confirmed by HRMS analysis. The enantiomeric excess of diol **7** was determined by chiral HPLC analysis (Scheme 3).

To install the azido functionality, diol **7** was converted into cyclic sulfite/sulphate. Direct conversion of sulfite/sulphate to the corresponding diazide proved unsuccessful. Hence it was decided to convert sulfite to diamine in a stepwise fashion. This was done by regioselective opening of this cyclic sulfite using NaN_3 in DMF to get the β-azido ester **11** in 75% yield (over two steps).[11] The IR spectrum of azido ester **11** showed strong bands at 2104 and 1736 cm^{-1} indicating the presence of azide and ester functionalities respectively. Presence of broad band at 3448 cm^{-1} indicated the presence of hydroxyl group. Peak at δ 5.01 in its ^1H-NMR spectrum appeared as a doublet accounting for one proton adjacent to hydroxyl group. The proton adjacent to azide merged with the methylene protons of ester which appeared as multiplet at δ 4.19-4.36 integrating for three protons. Its ^{13}C-NMR spectrum

showed characteristic peak at δ 172.4 which was assigned to carbonyl carbon. Its DEPT spectrum showed presence two CH carbons that appeared at δ 65.1 and 71.6, while five CH_2 carbons appeared at chemical shifts in accordance with the structure of **11**. Finally the structure of compound **11** was confirmed by HRMS analysis.

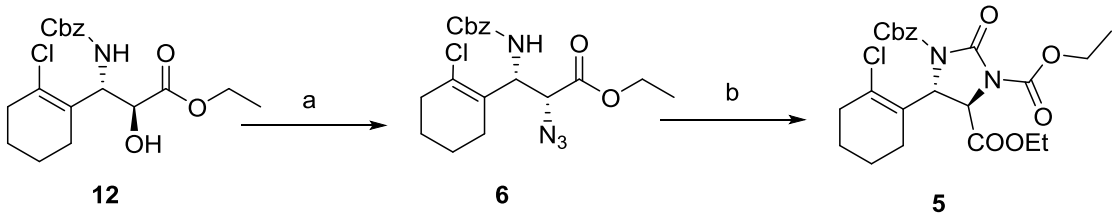


Scheme 3. *Reagents and conditions: a) $(DHQD)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^tBuOH:H_2O$ (1:1), 2 days, 84%, ≥99% ee; b) i) $SOCl_2$, Et_3N, DCM, 0 °C, 15 min; ii) NaN_3, DMF, rt, 4 h, 75% (over two steps); c) i) Ph_3P, Et_2O, rt, 2 h; ii) b) CbzCl, K_2CO_3, DCM, 0 °C, 80% (over two steps).*

Azide was reduced under Staudinger reaction condition[12] followed by protection using CbzCl to furnish the carbamate **12**. The IR spectrum of **12** displayed a strong absorption band at 1690 cm^{-1} indicating the presence of carbamate functionality while absence of absorption at 2104 cm^{-1} indicated azide reduction. ^1H NMR spectrum of compound **12** showed the presence of a new multiplet which appeared at δ 7.27-7.40 integrating for five protons which was attributed to Cbz group while multiplet appeared at δ 5.25-5.29 corresponding to proton of NH-CO-Bn. ^{13}C NMR spectrum showed the signals that appeared at δ 67.0 and 155.4 corresponding to carbons of Cbz group (NH-CO-CH_2-Ph and NH-CO-CH_2-Ph respectively). Additionally, DEPT experiment also showed the presence of six CH_2 and five CH carbons supporting the formation of **12**. Finally, the structure of compound **12** was confirmed by HRMS analysis (Scheme 3).

The second amine was installed by converting hydroxyl group in **12** to its mesylate using mesyl chloride and triethylamine, which was displaced by azide using sodium azide in DMF to give azidoamine **6** in 82% yield (over two steps). The IR

spectrum showed strong absorption bands at 2114 and 1742 cm^{-1} indicating the presence of azide and ester functionalities respectively. All the spectral data including HRMS analysis were also in good agreement with the assigned structure **6** (Scheme 4).



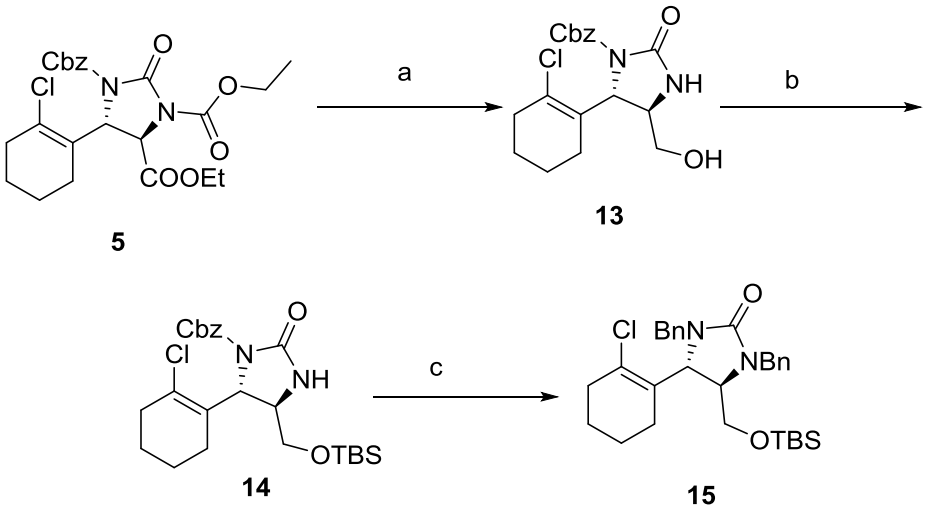
12 **6** **5**

Scheme 4. *Reagents and conditions: a) i) MsCl, Et_3N, DCM, 0 °C, 30 min; ii) NaN_3, DMF, 50 °C, 12 h, 82% (over two steps); b) i) Ph_3P, Et_2O, rt, 2 h;ii) $ClCO_2Et$, Et_3N, DCM, 0 °C, 7 h, 86% (over two steps).*

The azide in **6** was further reduced under Staudinger reaction condition to amine which on treatment with ethyl chloroformate in the presence of triethylamine, interestingly gave cyclic protected urea **5** (Scheme 4).[13] The IR spectrum of compound **5** showed strong bands at 1818, 1726, 1750 and 1694 cm^{-1} for carbonyl groups of ethyl carbamate, benzyl carbamate, ethyl ester and cyclic urea. The ^1H NMR spectrum of compound **5** showed multiplet at δ 1.25-1.38 for six protons corresponding to ethyl ester ($\underline{CH_3}CH_2OCO$-C) and ethyl carbamate ($\underline{CH_3}CH_2OCO$-N). ^{13}C NMR spectrum showed peaks at δ 147.4, 150.3, 151.0 and 168.6 for the carbonyl groups of carbamates, ester and urea. Finally, the structure of compound **5** was confirmed by HRMS analysis.

After having compound **5** in hand, ester was reduced using $NaBH_4$ in methanol at 0 °C, to furnish hydroxyl compound **13**. Interestingly, here proximal carbamate was also selectively hydrolyzed during reduction. The IR spectrum of compound **13** showed the absence of bands at 1818 and 1750 cm^{-1} for acyclic ethyl carbamate and ester indicating the hydrolysis during reduction of **5**. The ^1H NMR spectrum of compound **13** showed the absence of double doublet at δ 6.28 and a multiplet at δ 1.25-1.38 for six protons corresponding to acyclic ethyl carbamate and ester indicating the hydrolysis during reduction of **5**. ^{13}C NMR and DEPT NMR spectra were also in good agreement with the structure of compound **13**. Finally, the structure of compound **13** was confirmed by HRMS analysis (Scheme 5).

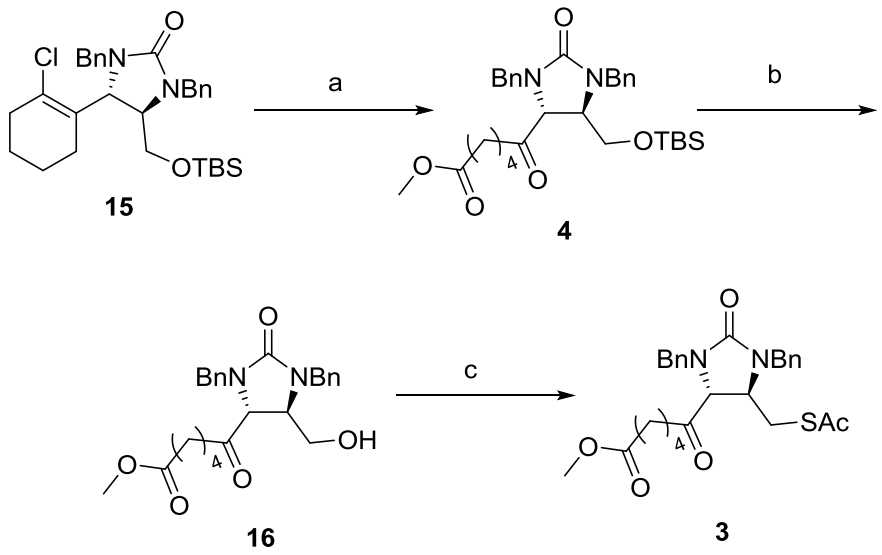
The protection of primary hydroxyl group in **13** with *tert*-butylchlorodimethylsilane in the presence of imidazole in dichloromethane gave TBS ether **14** in 93% yield. The IR spectrum of compound **14** showed the absence of broad band at 3370 cm^{-1} for hydroxyl group indicating the protection of hydroxyl group. Its ^{1}H-NMR spectrum showed peaks as singlets at δ 0.02 and 0.83 for six and nine protons respectively clearly showing the presence of TBS group. Peaks at δ -5.5, -5.4 and 25.7 in its ^{13}C-NMR spectrum corresponded to TBS group. Finally, the structure of compound **14** was confirmed by HRMS analysis.



Scheme 5. *Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C, 4 h, 79%, 30 min; b) TBSCl, imidazole, DMAP, DCM, 0 °C-rt, 24 h, 93%; c) NaH, BnBr, THF, 0 °C, 3 h, 95%.*

On treatment with sodium hydride and benzyl bromide, **14** was converted to its bisbenzyl imidazolidone **15** in 95% yield. An important and interesting feature of this transformation is the formation of bis *N*-benzyl derivative which involves deprotection of carbamate followed by alkylation in one pot. The IR spectrum of **15** displayed the strong absorption band at 1698 cm^{-1} indicating the presence of cyclic urea functionality while absence of absorption at 1775 cm^{-1} indicated carbamate hydrolysis. The ^{1}H NMR spectrum showed four upfield signals at δ 4.00, 4.08, 4.52 and 4.93 for four protons and multiplet at δ 7.24-7.32 for ten protons indicating that the presence of two benzyl groups. This was further confirmed by its ^{13}C NMR and DEPT NMR spectra, which showed a -CH_2- carbon singlets at δ 46.2 and 46.9 for the benzylic carbon. Finally, the structure of compound **15** was confirmed by HRMS analysis (Scheme 5).

On performing ozonolysis reaction in MeOH:DCM (1:5) solvent system, imidazolidone **15** was converted into ketoester **4** in 92% yield. The IR spectrum of ketoester **4** showed strong absorption bands at 1733, 1706 and 1690 cm^{-1} indicating the presence of ester, ketone and cyclic urea functionalities respectively. The ^{1}H NMR spectrum of compound **4** showed a singlet at δ 3.66 for three protons indicating the presence of methyl ester. The ^{13}C NMR spectrum showed peaks at δ 173.4 and 207.4 corresponding to ester and ketone functional groups respectively. Finally, the structure of compound **4** was confirmed by HRMS analysis.



Scheme 6. *Reagents and conditions: a) O_3, MeOH:DCM (1:5), $NaHCO_3$, -78 °C, 30 min, 92%; b) CSA, MeOH, rt, 30 h, 90%; c) i) TsCl, Et_3N, DMAP, DCM, 0 °C-rt, 24 h, 85%; ii) KSAc, DMF:THF, 80 °C, 2 h, 83 %.*

Deprotection of TBS ether of **4** was carried out using camphorsulfonic acid in MeOH to afford the corresponding alcohol **16** in 90% yield. The IR spectrum of **16** showed broad absorption band at 3409 cm^{-1} indicating the presence of hydroxyl group. The ^{1}H NMR spectrum of compound **4** showed absence of peaks at δ 0.02 and 0.83 for six and nine protons respectively clearly showing the absence of TBS group. This was further confirmed by its ^{13}C NMR and DEPT NMR spectra. Finally, the structure of compound **4** was confirmed by HRMS analysis.

After diamine installation only thing remaining was to construct tetrahydrothiophene ring. Introduction of sulfur was done by converting the primary hydroxyl group into a good leaving group. Accordingly, the hydroxyl compound **16**

was converted in to its tosylate derivative and it was in turn displaced by potassium thioacetate in DMF:THF (2:3) to furnish the thioacetate **3** in 83% yield (Scheme 6).[14] The IR spectrum of thioacetate **3** showed strong absorption band at 1710 cm^{-1} indicating the presence of acetate functionality. The ^{1}H NMR spectrum of compound **3** showed singlet at δ 2.24 for three protons indicating the presence of thioacetate ($\underline{CH_3}CO$-S-) group. ^{13}C NMR spectrum showed peaks at δ 159.0, 173.4, 194.2 and 206.6 for the corresponding carbonyl group of urea, ester, thiocetate and ketone. Finally, structure of compound **3** was confirmed by HRMS analysis (Scheme 6).

All the structural constituents for biotin were present and in place in compound **3**, the only thing remaining to complete synthesis was acetate deprotection of **3** and the construction of thiophane ring. Efforts towards this seemingly simple deprotection of acetate **3** to thiol **17** failed under a variety of reaction conditions (Table 1).[15]

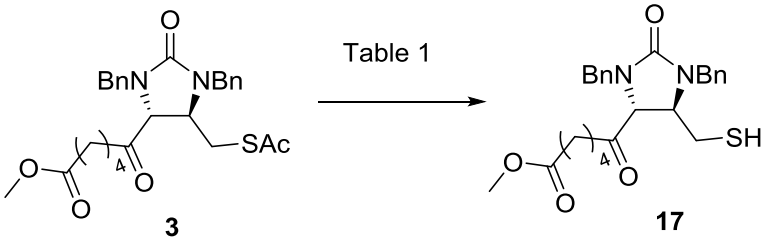


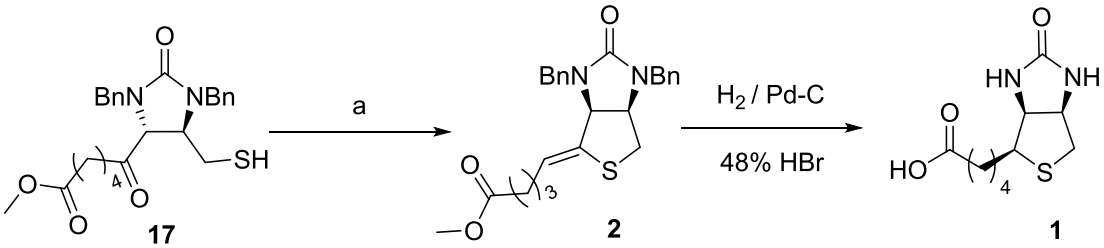
Table 1. Attempts towards acetate deprotection

Entry	Conditions	Results
1	Pyrrolidine, Et_3N, MeOH	Dimerization
2	K_2CO_3, MeOH	Dimerization
3	Acetyl chloride, MeOH	SM recovered[a]
4	DBU, toluene, RT	SM recovered[a]
5	DBU, toluene, 80 ^{o}C	Complex reaction mixture
6	$TiCl_4$, Zn, DCM	SM recovered[a]
7[b]	Lipase (*Candida cylindrica)*	SM recovered[a]
8[b]	Lipase (*Candida rugosa)*	**17** in 80%

[a] SM:starting material; [b]in phosphate buffer (pH 6.8).

Finally the hydrolysis under enzymatic condition using lipase (*Candida rugosa*)[16] gave the thiol **17** in 80% yield. The IR spectrum of thiol **17** showed absence of absorption band at 1710 cm^{-1} indicating the absence of acetate functionality. The ^{1}H NMR spectrum of compound **17** showed absence of singlet at δ 2.24 for three protons

indicating the absence of thioacetate, whereas it showed a double doublet at δ 1.11 for one proton characteristic of thiol (-CH_2-S<u>H</u>). ^{13}C NMR spectrum showed absence of peaks at δ 194.2 indicating hydrolysis of **3**. Finally, structure of compound **3** was confirmed by HRMS analysis.



Scheme 7. *Reagents and conditions: a) i) DBU, toluene, 100 °C, 3 h; ii) pTSA, toluene, rt, 4 h, 82% (over two steps).*

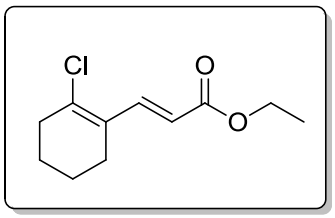
Correction of stereochemistry at C-3 of **17** was achieved by epimerization with catalytic amount of DBU in refluxing toluene, which on concomitant cyclisation and elimination using *p*TSA resulted in the formation of olefin **2** in 82% yield over two steps (Scheme 7). The ^{1}H NMR spectrum of compound **2** revealed a characteristic triplet at δ 5.54 integrating for one proton which was assigned to the olefinic proton. Finally, HRMS analysis confirmed the molecular formula (calculated for $C_{25}H_{28}O_3N_2NaS$ 459.1713, found 459.1707). The olefin **2** thus obtained was identical with an authentic sample, with respect to IR, NMR, mass spectra, and specific rotation,[6] prepared by a different route. Since the conversion of olefin **2** to (+)-biotin (**1)** has been reported by this group[6,7] and others,[1] this constitutes a formal synthesis of (+)-biotin.

1.2.5 Conclusion

In conclusion, an asymmetric synthesis of D-(+)-biotin has been achieved employing Sharpless asymmetric dihydroxylation as the single source of chirality. The enantioselectivity is introduced by intermolecular asymmetric induction, which is the first report of its kind utilized in the synthesis of biotin. The carboxyalkyl side chain of D-(+)-biotin is introduced by unmasking of cyclohexene by ozonolysis, which is also a novel strategy in synthesis.

1.2.6 Experimental

(*E*)-Ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate (8): A mixture of anhydrous



DCM (80 mL) and anhydrous DMF (15.7 mL, 204.08 mmol) was cooled to 0 ºC using ice, to that was added $POCl_3$ (15.1 mL, 163.26 mmol) dropwise and stirred further for 2 h at room temperature. Cyclohexanone **9** (10.0 g, 102.04 mmol) in DCM (20 mL) was added dropwise at 0 ºC and further stirred for 4 h at room temperature. Reaction mixture was quenched first by using ice followed by careful addition of sat. $NaHCO_3$ solution. Reaction mixture was allowed to separate in a separating funnel. The organic layer was separated and the aqueous layer was again extracted twice using DCM (50 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish chloro aldehyde **10** (14.0 g, 95%) as a crude product.

The crude aldehyde (14 g, 97.22 mmol) was dissolved in DCM (150 mL) and to that was added Ph_3PCHCO_2Et (50.7 g, 145.83 mmol). The reaction mixture was stirred further for 4 h. The solvent was removed under reduced pressure and the crude residue was directly adsorbed on simple silica gel and was purified using flash chromatography (SiO_2, 04:96 EtOAc: Pet. ether) to furnish the α,β-unsaturated ester **8** as a colorless liquid.

***R_f*:** 0.6 (Pet. ether-ethyl acetate, 9:1).

Yield: 25.7 g, 76%.

MF: $C_{11}H_{15}ClO_2$, **MW:** 214.68.

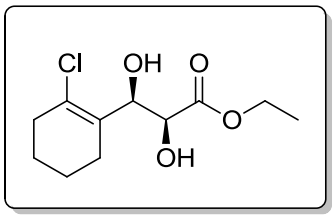
IR ($CHCl_3$, cm^{-1}): vmax 2938, 1713, 1622, 1292, 1175.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J*=7.1 Hz, 3 H), 1.62 - 1.76 (m, 4 H), 2.26 (brs, 2 H), 2.51 (brs, 2 H), 4.21 (q, *J*=7.1 Hz, 2 H), 5.85 (d, *J*=15.9 Hz, 1 H), 7.91 (d, *J*=15.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.2, 21.7, 23.3, 26.1, 35.1, 60.1, 118.1, 128.5, 139.0, 141.1, 166.7.

HRMS ESI $[M+H]^+$ calcd for $C_{11}H_{16}O_2Cl$ 215.0833, found 215.0832.

(2*S*,3*R*)-Ethyl 3-(2-chlorocyclohex-1-en-1-yl)-2,3-dihydroxypropanoate (7):



To a mixture of $K_3Fe(CN)_6$ (13.8 g, 42.03 mmol), K_2CO_3 (5.8 g, 42.03 mmol) and $(DHQD)_2PHAL$ (0.109 g, 0.14 mmol) in ^tBuOH-H_2O (1:1, 120 mL) cooled at 0 ^oC was added osmium tetroxide (1 mL of 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (1.32 g, 14.01 mmol). After stirring for 5 min at 0 ^oC, the olefin **8** (3 g, 14.01 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 2 days and then quenched with solid sodium sulfite (6 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3:7 EtOAc: Pet. ether) to provide the diol **7** as a white solid.

***R_f*:** 0.3 (Pet. ether-ethyl acetate, 8:2).

Yield: 2.92 g, 84%.

MF: $C_{11}H_{17}ClO_4$, **MW:** 248.70.

Melting Point: 65-67 °C.

$[\alpha]_D^{25}$ = +5.2 (*c* 1.92, $CHCl_3$).

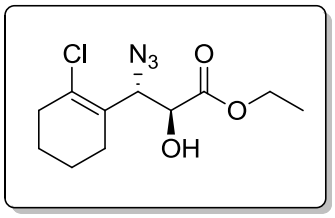
IR ($CHCl_3$, cm^{-1}): νmax 3446 (broad), 2937, 1736, 1105.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.31 (t, *J*=7.1 Hz, 3 H), 1.59 - 1.79 (m, 4 H), 2.12 - 2.43 (m, 4 H), 2.82 (brs, 1 H), 3.29 (brs, 1 H), 4.20 - 4.34 (m, 3 H), 4.95 (d, *J*=4.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.2, 22.0, 23.7, 25.5, 34.1, 62.1, 72.1, 73.2, 128.5, 132.6, 172.8.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{17}O_4ClNa$ 271.0708, found 271.0706.

(2*S*,3*S*)-Ethyl 3-azido-3-(2-chlorocyclohex-1-en-1-yl)-2-hydroxypropanoate (11):



To a cooled (0 °C) solution of diol **7** (2.5 g, 10.08 mmol) in DCM (25 mL) was added Et_3N (2.82 mL, 20.16 mmol) followed by thionyl chloride (1.02 mL, 12.09 mmol) in a dropwise manner. The resulting reaction mixture was stirred for two hours at rt and concentrated under reduced pressure to obtain the sulfite as a thick oil. The crude sulfite was dissolved in DMF (30 mL) and to this solution

was added sodium azide (1.3 g, 20 mmol) and stirred overnight. The reaction mixture was quenched using water (150 mL) and was extracted in ethyl acetate (2 × 20 mL). The combined organics were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* carefully. The crude product was purified on flash chromatography (SiO_2, 2:8 EtOAc: Pet. ether) to afford azidoalcohol **11** as a gummy liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 8:2).

Yield: 2.05 g, 75%.

MF: $C_{11}H_{16}ClN_3O_3$, **MW:** 273.71.

$[\alpha]_D^{25}$ = -40.9 (*c* 1.32, $CHCl_3$).

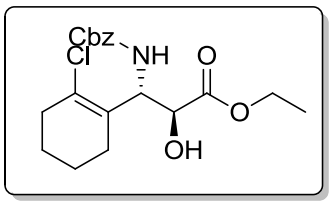
IR ($CHCl_3$, cm^{-1}): vmax 3448 (broad), 2938, 2104, 1736, 1603, 1267.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.34 (t, *J*=7.1 Hz, 3 H), 1.54 - 1.88 (m, 4 H), 2.19 (brs, 2 H), 2.40 (brs, 2 H), 2.92 (brs, 1 H), 4.19 - 4.36 (m, 3 H), 5.01 (d, *J*=5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 22.1, 23.6, 26.2, 34.2, 62.3, 65.1, 71.6, 128.6, 132.6, 172.4.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{16}O_3N_3ClNa$ 296.0772, found 296.0770.

(2*S*,3*S*)-Ethyl 3-(((benzyloxy)carbonyl)amino)-3-(2-chlorocyclohex-1-en-1-yl)-2-hydr-oxy pro panoate (12): To a solution of azidoalcohol **11** (2 g, 7.32 mmol) in diethyl ether (20 mL) was added PPh_3 (4.57 g, 18.31 mmol) and stirred until the evolution of nitrogen gas ceased (2 h). After completion of reaction, the solvent was evaporated under reduced pressure to obtain the amine as thick oil. The crude amine was dissolved in DCM (20 mL) and to this solution was added K_2CO_3 (2.51 g, 18.2 mmol) followed by CbzCl (1.49 mL, 8.74 mmol) and stirred overnight (12 h). The reaction mixture was filtered and filtrate was treated with water (30 mL) and was extracted with DCM (2 × 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified on flash chromatography using silica gel (2:8 EtOAc: Pet. ether) to afford carbamate **12** as a gummy liquid.



***R_f*:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 2.2 g, 85%.

MF: $C_{19}H_{24}ClNO_5$, **MW:** 381.85.

$[\alpha]_D^{25}$ = -17.94 (*c* 1.59, $CHCl_3$).

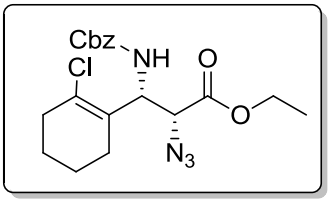
IR ($CHCl_3$, cm^{-1}): νmax 3393 (broad), 2932, 1732, 1690, 1511, 1218.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J*=7.2 Hz, 3 H), 1.57 - 1.69 (m, 4 H), 2.10 (brs, 2 H), 2.22 - 2.45 (m, 2 H), 2.96 (brs, 1 H), 4.07 - 4.19 (m, 1 H), 4.20 - 4.31 (m, 1 H), 4.39 (d, *J*=4.3 Hz, 1 H), 5.05 - 5.14 (m, 2 H), 5.25 - 5.29 (m, 1 H), 5.55 (d, *J*=8.2 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.0, 22.2, 23.6, 27.0, 34.3, 54.2, 62.3, 67.0, 72.4, 128.2, 128.3 (2C), 128.5 (2C), 129.4, 131.0, 136.4, 155.4, 172.5.

HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{25}O_5NCl$ 382.1416, found 382.1408.

(2*R*,3*S*)-Ethyl 2-azido-3-(((benzyloxy)carbonyl)amino)-3-(2-chlorocyclohex-1-en-1-yl) propanoate (6): To a stirred solution of carbamate **12** (2 g, 5.27 mmol) in dry



DCM (20 mL) was added Et_3N (2.21 mL, 15.81 mmol) at 0 °C, followed by dropwise addition of mesyl chloride (0.64 mL, 7.9 mmol) and the reaction mixture was stirred for 4 h under nitrogen atmosphere. The reaction mixture was diluted with DCM (20 mL) and washed with saturated solution of sodium bicarbonate (20 mL) and water (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *O*-mesyl compound.

To a solution of crude *O*-mesyl compound in anhydrous DMF (25 mL) was added sodium azide (0.68 g, 10.44 mmol) and the reaction mixture was stirred at 50 °C for 12 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (75 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 7:93 EtOAc: Pet. ether) to afford azide **6** as a gummy liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 9:1).

Yield: 2.12 g, 82%.

MF: $C_{19}H_{23}ClN_4O_4$, **MW:** 406.86.

$[\alpha]_D^{25}$ = +11.56 (*c* 1.73, $CHCl_3$).

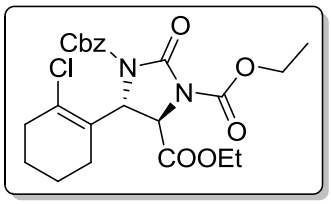
IR ($CHCl_3$, cm^{-1}): νmax 2930, 2114, 1742, 1505, 1216.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.26 (t, *J*=7.0 Hz, 3 H), 1.60 - 1.73 (m, 4 H), 1.98 - 2.19 (m, 2 H), 2.39 (brs, 2 H), 4.13 - 4.34 (m, 2 H), 4.48 (brs, 1 H), 4.99 - 5.15 (m, 2 H), 5.21 - 5.38 (m, 2 H), 7.27 - 7.44 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 22.1, 23.4, 27.0, 34.0, 53.4, 62.3, 64.8, 67.1, 128.1, 128.2 (2C), 128.5 (2C), 130.0, 130.6, 136.3, 155.2, 167.7.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{23}O_4N_4ClNa$ 429.1300, found 429.1295.

(4*R*,5*S*)-1-Benzyl 3,4-diethyl 5-(2-chlorocyclohex-1-en-1-yl)-2-oxoimidazolidine-1,3,4-tricarboxylate (5): To a solution of azide **6** (2.1 g, 5.17 mmol) in diethyl ether



(20 mL) was added PPh_3 (3.39 g, 12.92 mmol) and stirred until evolution of nitrogen gas ceased (2.5 h). After completion of reaction the solvent was evoporated under reduced pressure to obtain the amine as thick oil. The crude amine was dissolved in DCM (25 mL) and to this solution was added Et_3N (5.74 mL, 40.96 mmol) followed by ethyl chloroformate (3.88 mL, 40.96 mmol) at 0 ^oC and stirred (12 h). The reaction mixture was quenched with water (30 mL) and was extracted in DCM (2 × 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 8:2 EtOAc: Pet. ether) to afford urea **5** as a gummy liquid.

***R_f*:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 2.1 g, 86%.

MF: $C_{23}H_{27}ClN_2O_7$, **MW:** 478.92.

$[\alpha]_D^{25}$ = -8.12 (*c* 2.6, $CHCl_3$).

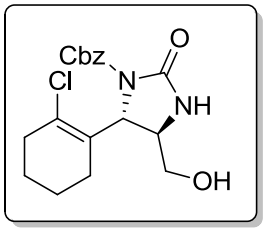
IR ($CHCl_3$, cm^{-1}): νmax 2929, 1818, 1750, 1726, 1694, 1437, 1250.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.25 - 1.38 (m, 6 H), 1.53 - 1.71 (m, 4 H), 1.89 (brs, 2 H), 2.18 - 2.45 (m, 2 H), 4.18 - 4.41 (m, 5 H), 5.15 (d, *J*=12.2 Hz, 1 H), 5.29 (d, *J*=2.9 Hz, 1 H), 5.38 (d, *J*=12.2 Hz, 1 H), 7.27 - 7.44 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.07, 14.14, 21.6, 23.2, 24.1, 33.9, 55.4, 58.0, 62.4, 63.7, 68.4, 128.3 (2C), 128.47, 128.53 (2C), 129.5, 131.7, 134.9, 147.4, 150.3, 151.0, 168.6.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{27}ClN_2O_7Na$ 501.1399, found 501.1400.

(4*R*,5*S*)-Benzyl 5-(2-chlorocyclohex-1-en-1-yl)-4-(hydroxymethyl)-2-oxoimidazolidine 1-carboxylate (13): To a solution of urea **5** (1.8 g, 3.76 mmol) in



methanol (15 mL) was added $NaBH_4$ (0.57 g, 15.04 mmol) at 0 ^oC portionwise. The reaction mixture was allowed to stir for 4 h at room temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The aq. solution of NH_4Cl was added to the semisolid mass and allowed to stir for 30 min and the reaction mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on flash chromatography (SiO_2, 9:1 EtOAc: Pet. ether) to afford alcohol **13** as a white solid.

***R_f*:** 0.3 (Ethyl acetate) long tail.

Yield: 0.9 g, 79%.

MF: $C_{18}H_{21}ClN_2O_4$, **MW:** 364.11.

Melting point: 165-167 °C.

$[\alpha]_D^{25}$ = -65.54 (*c* 2.0, $CHCl_3$).

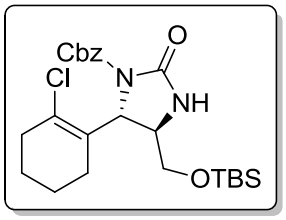
IR ($CHCl_3$, cm^{-1}): νmax 3370 (broad), 2931, 2860, 1773, 1389, 1337, 1288, 1117.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.35 - 1.55 (m, 3 H), 1.61 - 2.01 (m, 4 H), 2.13 - 2.37 (m, 3 H), 3.33 (brs, 1 H), 3.54 - 3.65 (m, 1 H), 3.73 - 3.76 (m, 1 H), 4.99 (d, *J*=12.1 Hz, 1 H), 5.19 (d, *J*=3.5 Hz, 1 H), 5.33 (d, *J*=12.1 Hz, 1 H), 7.26 - 7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 21.8, 23.4, 24.4, 33.9, 56.7, 57.9, 64.1, 67.5, 128.3 (3C), 128.4 (2C), 128.8, 131.6, 135.4, 151.1, 156.5.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{21}O_4N_2ClNa$ 387.1082, found 387.1080.

(4*R*,5*S*)-Benzyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-



en-1-yl)-2-oxoimidazolidine-1-carboxylate (14): To a solution of alcohol **13** (800 mg, 2.65 mmol) in anhydrous

DCM (10 mL) was added imidazole (360 mg, 5.3 mmol) followed by addition of TBSCl (600 mg, 3.97 mmol) and DMAP (cat.) at 0 ^{o}C under nitrogen atmosphere. The reaction was allowed to stir at room temperature for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 1:1 EtOAc: Pet. ether) to afford TBS ether **14** as a colorless liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 1:1).

Yield: 1.17 g, 93%.

MF: $C_{24}H_{35}ClN_2O_4Si$, **MW:** 479.08.

$[\alpha]_D^{25}$ = -47.5 (*c* 4.0, $CHCl_3$).

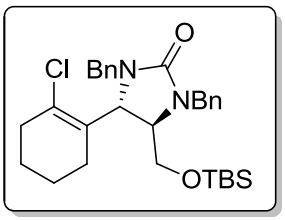
IR ($CHCl_3$, cm^{-1}): νmax 2923, 2857, 1775, 1390, 1333, 1108.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 0.02 (s, 6 H), 0.83 (s, 9 H), 1.48 - 1.63 (m, 4 H), 1.85 - 2.03 (m, 2 H), 2.18 - 2.26 (m, 2 H), 3.28 - 3.31 (m, 1 H), 3.63 (qd, *J*=10.4, 4.4 Hz, 2 H), 5.06 (d, *J*=12.3 Hz, 1 H), 5.17 (d, *J*=2.5 Hz, 1 H), 5.32 (d, *J*=12.3 Hz, 1 H), 6.70 (s, 1 H), 7.25 - 7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ -5.5, -5.4, 18.1, 21.7, 23.4, 24.4, 25.7 (3C), 33.8, 56.3, 57.8, 65.2, 67.4, 128.1, 128.27 (2C), 128.34 (2C), 128.8, 131.8, 135.6, 150.9, 155.9.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{35}O_4N_2ClNaSi$ 501.1947, found 501.1947.

(4*R*,5*S*)-1,3-Dibenzyl-4-(((tert-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl)imidazolidin-2-one (15): To the suspension of 60% NaH



(137 mg, 5.72 mmol) (washed with dry petroleum ether 2-3 times) in dry THF (10 mL) was added TBS ether **14** (1.1 g, 2.29 mmol) in anhydrous THF (5 mL) at 0 ^{o}C and stirred for 10 min. Then benzyl bromide (0.72 mL, 5.72 mmol) was added drop wise and reaction mixture was stirred for 3 h at room temperature. On completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (2 × 15 mL) and washed with water followed by brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by

flash chromatography (SiO_2, 1:9 EtOAc: Pet. ether) to afford benzyl protected cyclic urea **15** as a white solid.

***R_f*:** 0.6 (Pet. ether-ethyl acetate, 8:2).

Yield: 1.14 g, 95%.

MF: $C_{30}H_{41}ClN_2O_2Si$, **MW:** 525.19.

Melting Point: 87-89 °C.

$[\alpha]_D^{25}$ = -33.1 (*c* 2.9, $CHCl_3$).

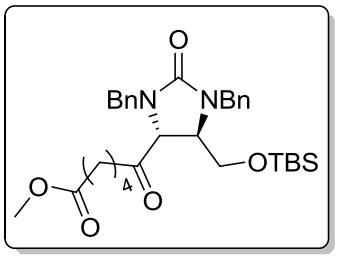
IR ($CHCl_3$, cm^{-1}): νmax 2930, 2857, 1698, 1448, 1252, 1119.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ -0.04 (s, 3 H), -0.02 (s, 3 H), 0.83 (s, 9 H), 1.08 - 1.65 (m, 6 H), 2.18 - 2.24 (m, 2 H), 3.09 (dt, *J*=6.1, 3.9 Hz, 1 H), 3.40 - 3.67 (m, 2 H), 4.00 (d, *J*=12.3 Hz, 1 H), 4.08 (d, *J*=12.3 Hz, 1 H), 4.52 (d, *J*=15.0 Hz, 1 H), 4.56 - 4.59 (m, 1 H), 4.93 (d, *J*=15.0 Hz, 1 H), 7.24 - 7.32 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ -5.6, -5.5, 18.3, 21.7 (2C), 23.6, 25.9 (3C), 34.3, 46.2, 46.9, 56.6, 57.8, 62.6, 127.3, 127.4, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 130.2, 131.1, 137.4, 137.4, 160.3.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{30}H_{41}O_2N_2ClNaSi$ 547.2518, found 547.2523.

Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate (4): To a cooled solution of benzyl protected cyclic urea **15** (1.1 g, 2.10 mmol) and sodium hydrogen carbonate (352 mg, 4.20 mmol) in dichloromethane (20 mL) and methanol (4 mL) at -78 °C, ozone was bubbled. Ozone introduction was stopped when solution turned blue (35 min) and dimethyl sulfide (1 mL, excess) was added at the same temperature. The solution was allowed to warm to room temperature. The solvent was evaporated under reduced pressure, washed with water (15 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 2:8 EtOAc: Pet. ether) to afford methyl ester **4** as white solid.



***R_f*:** 0.5 (Pet. ether-ethyl acetate, 7:3).

Yield: 1.07 g, 92%.

MF: $C_{31}H_{44}N_2O_5Si$, **MW:** 552.77.

Melting Point: 62-64 °C.

$[\alpha]_D^{25}$ = -12.18 (*c* 2.0, $CHCl_3$).

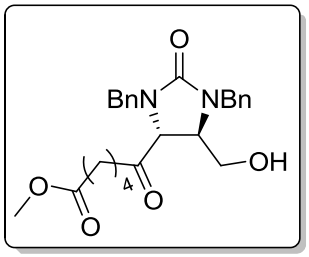
IR ($CHCl_3$, cm^{-1}): νmax 2924, 1733, 1706, 1690, 1463, 1252.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ -0.06 (s, 3 H), -0.05 (s, 3 H), 0.81 (s, 9 H), 1.32 - 1.39 (m, 4 H), 1.98 - 2.08 (m, 1 H), 2.11 - 2.23 (m, 3 H), 3.16 (q, *J*=4.3 Hz, 1 H), 3.39 - 3.55 (m, 2 H), 3.66 (s, 3 H), 3.70 (d, *J*=4.3 Hz, 1 H), 4.04 (d, *J*=14.8 Hz, 2 H), 4.89 (d, *J*=15.3 Hz, 1 H), 4.82 (d, *J*=14.8 Hz, 1 H), 7.19 - 7.33 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ -5.6, -5.5, 18.3, 22.5, 24.2, 25.9 (3 C), 33.7, 37.4, 46.3, 47.2, 51.5, 56.4, 62.7, 63.5, 127.69, 127.75, 128.1 (2 C), 128.74 (2 C), 128.77 (2 C), 128.8 (2 C), 136.5, 137.0, 159.6, 173.4, 207.4.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{31}H_{44}O_5N_2NaSi$ 575.2912, found 575.2915.

Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(hydroxymethyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate (16): To a solution of ester **4** (1 g, 1.81 mmol) in MeOH (10 mL) was



added camphorsulfonic acid (42 mg, 0.18 mmol) at 0 ^oC. The reaction was allowed to stir at room temperature for 30 h. After completion of reaction (monitored by TLC), the reaction mixture concentrated under reduced pressure. The aq. solution of sodium hydrogen carbonate was added to the semisolid mass and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 6:4 EtOAc: Pet. ether) to afford alcohol **16** as a white solid.

***R_f*:** 0.3 (Pet. ether-ethyl acetate, 6:4).

Yield: 713 mg, 90%.

MF: $C_{25}H_{30}N_2O_5$, **MW:** 438.51.

Melting Point: 84-86 °C.

$[\alpha]_D^{25}$ = -11.12 (*c* 2.0, $CHCl_3$).

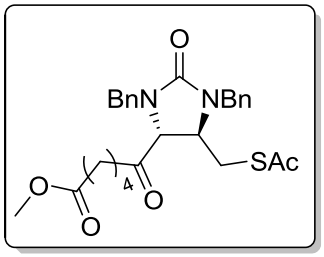
IR ($CHCl_3$, cm^{-1}): νmax 3409 (broad), 2928, 1726, 1682, 1451, 1238.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.36 (brs, 4 H), 2.10 - 2.25 (m, 4 H), 2.76 (brs, 1 H), 3.20 (brs, 1 H), 3.49 (d, *J*=11.6 Hz, 1 H), 3.62 (brs, 1 H), 3.67 (s, 3 H), 3.86 (s, 1 H), 4.12 - 4.15 (m, 2 H), 4.75 - 4.89 (m, 2 H), 7.19 - 7.40 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 22.4, 24.1, 33.6, 37.7, 46.2, 47.4, 51.5, 56.7, 61.5, 63.5, 127.78, 127.8, 128.0 (2 C), 128.5 (2 C), 128.75 (2 C), 128.83 (2 C), 136.2, 136.8, 160.0, 173.5, 207.6.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{30}O_5N_2Na$ 461.2047, found 461.2045.

Methyl 6-((4*R*,5*R*)-5-((acetylthio)methyl)-1,3-dibenzyl-2-oxoimidazolidin-4-yl)-6-oxohexanoate (3): To a stirred solution of alcohol **16** (630 mg, 1.44 mmol) in dry DCM (10 ml) was added Et_3N (0.3 mL, 2.16 mmol) at 0 ^oC, followed by addition of tosyl chloride (328 mg, 1.73 mmol) and DMAP (cat.). The reaction mixture was stirred for 24 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was washed with saturated solution of sodium bicarbonate (10 mL), water (10 mL) and extracted with DCM (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *O*-tosyl compound, which was used as such for next transformation.



To a solution of crude *O*-tosyl compound in anhydrous DMF (8 mL) and anhydrous THF (12 mL) was added sodium thioacetate (208 mg, 1.83 mmol) and the reaction mixture was stirred at 80 ^oC for 2 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 2:8 EtOAc: Pet. ether) to afford thioacetate **3** as a yellow liquid.

***R_f*:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 502 mg, 83%.

MF: $C_{27}H_{32}N_2O_5S$, **MW:** 496.61.

$[\alpha]_D^{25}$ = + 40.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 2923, 2851, 1728, 1710, 1695, 1451, 1215.

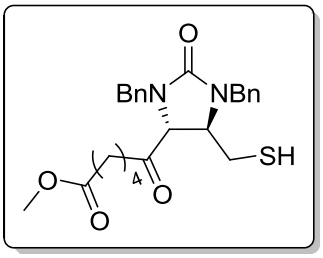
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.31 - 1.42 (m, 4 H), 1.99 - 2.09 (m, 1 H), 2.10 - 2.21 (m, 3 H), 2.24 (s, 3 H), 2.85 (dd, *J*=14.3, 6.3 Hz, 1 H), 3.15 (dd, *J*=14.3, 2.7 Hz,

1 H), 3.30 - 3.33 (m, 1 H), 3.47 (d, *J*=4.6 Hz, 1 H), 3.65 (s, 3 H), 3.95 (d, *J*=15.1 Hz, 1 H), 4.05 (d, *J*=15.1 Hz, 1 H), 4.87 - 4.90 (m, 2 H), 7.21 - 7.41 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 22.4, 24.1, 30.5, 31.4, 33.6, 37.8, 45.9, 47.0, 51.5, 54.2, 64.8, 127.82, 127.84, 128.3 (2 C), 128.72 (2 C), 128.76 (2 C), 128.8 (2 C), 136.2, 136.5, 159.0, 173.4, 194.2, 206.6.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{27}H_{32}O_5N_2NaS$ 519.1924, found 519.1918.

Methyl 6-((4*R*,5*R*)-1,3-dibenzyl-5-(mercaptomethyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate (17): A suspension of **3** (300 mg, 2.5 mM) in phosphate buffer (pH 6.8, 50 mL) was purged with a stream of nitrogen for 5 min, lipase (150 mg) from *Candida rugosa* (706 units/ mg) added, and the contents were stirred vigorously. After 2 h, the reaction mixture was extracted with DCM (3 × 20 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and then evaporated to give thiol **17**. The purification of thiol was effected by flash chromatography (SiO_2, 2:8 EtOAc: Pet. ether) to afford thiol **17** as a yellow liquid.



***R_f*:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 219 mg, 80%.

MF: $C_{25}H_{30}N_2O_4S$, **MW:** 454.58.

$[\alpha]_D^{25}$ = + 17.5 (*c* 2.6, $CHCl_3$).

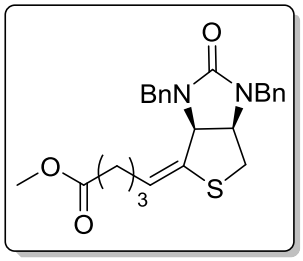
IR ($CHCl_3$, cm^{-1}): νmax 3016, 2923, 2851, 1725, 1695, 1451, 1215.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.11 (dd, *J*=9.2, 7.8 Hz, 1 H), 1.27 - 1.44 (m, 4 H), 2.01 - 2.28 (m, 4 H), 2.47 - 2.71 (m, 2 H), 3.21 - 3.38 (m, 1 H), 3.65 (s, 3 H), 3.77 (d, *J*=4.5 Hz, 1 H), 4.02 (d, *J*=15.2 Hz, 1 H), 4.08 (d, *J*=14.8 Hz, 1 H), 4.85 (d, *J*=14.8 Hz, 1 H), 4.89 (d, *J*=15.2 Hz, 1 H), 7.19 - 7.36 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 22.3, 24.0, 26.8, 33.5, 37.7, 45.7, 47.3, 51.4, 56.2, 64.5, 127.7 (2 C), 127.9 (2 C), 128.0, 128.4, 128.6 (2 C), 128.7 (2 C), 135.9, 136.3, 159.4, 173.4, 207.4.

HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{31}O_4N_2S$ 455.1999, found 455.1993.

(*Z*)-Methyl 5-((3a*S*,6a*R*)-1,3-dibenzyl-2-oxotetrahydro-1*H*-thieno[3,4-*d*]imidazol-4(2*H*)-ylidene)pentanoate (2): Thiol **17** (200 mg, 0.44 mmol) was dissolved in 5 mL toluene and DBU (0.03 mmol) was added drop wise at room temperature under nitrogen atmosphere with continuous stirring. After complete addition, the reaction mixture was heated at 100 º C for 3 h. After the reaction was completed, the toluene was removed under reduced pressure, diluted with ethyl acetate and washed with water (5 mL) and the organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and further it was subjected to elimination.



The crude cyclised hydroxyl compound (200 mg, 0.44 mmol) was dissolved in 5 mL toluene, *p*TSA (0.025 mmol) was added at room temperature and the reaction mixture was stirred continuosly under nitrogen atmosphere. Progress of the reaction was monitored by TLC, which indicated that no unreacted starting material remained after 4 h. Solvent was removed under reduced pressure and ethyl acetate was added. The reaction mixture was neutralized with sodium bicarbonate solution and washed with water (5 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue. The purification of the residue was effected by flash chromatography using silica gel (SiO_2, 2:8 EtOAc: Pet. ether) to afford olefin **2** as a yellow liquid.

***R*$_f$:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 157 mg, 82%.

MF: $C_{25}H_{28}N_2O_3S$, **MW:** 436.56.

$[\alpha]_D^{25}$ = + 194 (*c* 1, $CHCl_3$).

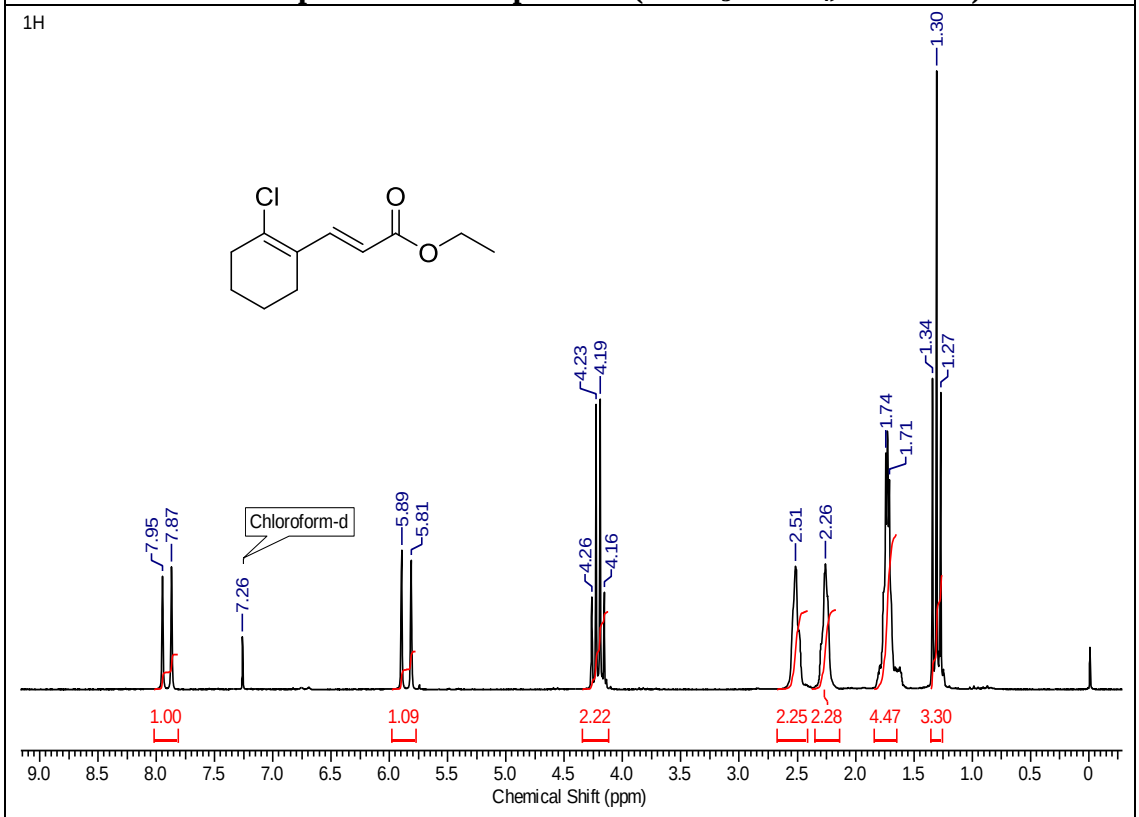
IR ($CHCl_3$, cm^{-1}): νmax 3032, 2928, 1743, 1634, 1440.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.65 - 1.75 (m, 2 H), 2.03 - 2.11 (m, 2 H), 2.27 (t, *J*=7.5 Hz, 2 H), 2.93 - 2.97 (m, 2 H), 3.66 (s, 3 H), 4.01 (d, *J*=15.5 Hz, 1 H), 4.10 (ddd, *J*=9.0, 7.5, 4.0 Hz, 1 H), 4.20 (d, *J*=15.5 Hz, 1H), 4.73 (d, *J*=10.1 Hz, 1H), 4.80 (d, *J*=14.5 Hz, 1 H), 4.95 (d, *J*=15.6 Hz, 1 H), 5.41 (t, *J*=7.0 Hz, 1 H), 7.29 - 7.37 (m, 10 H).

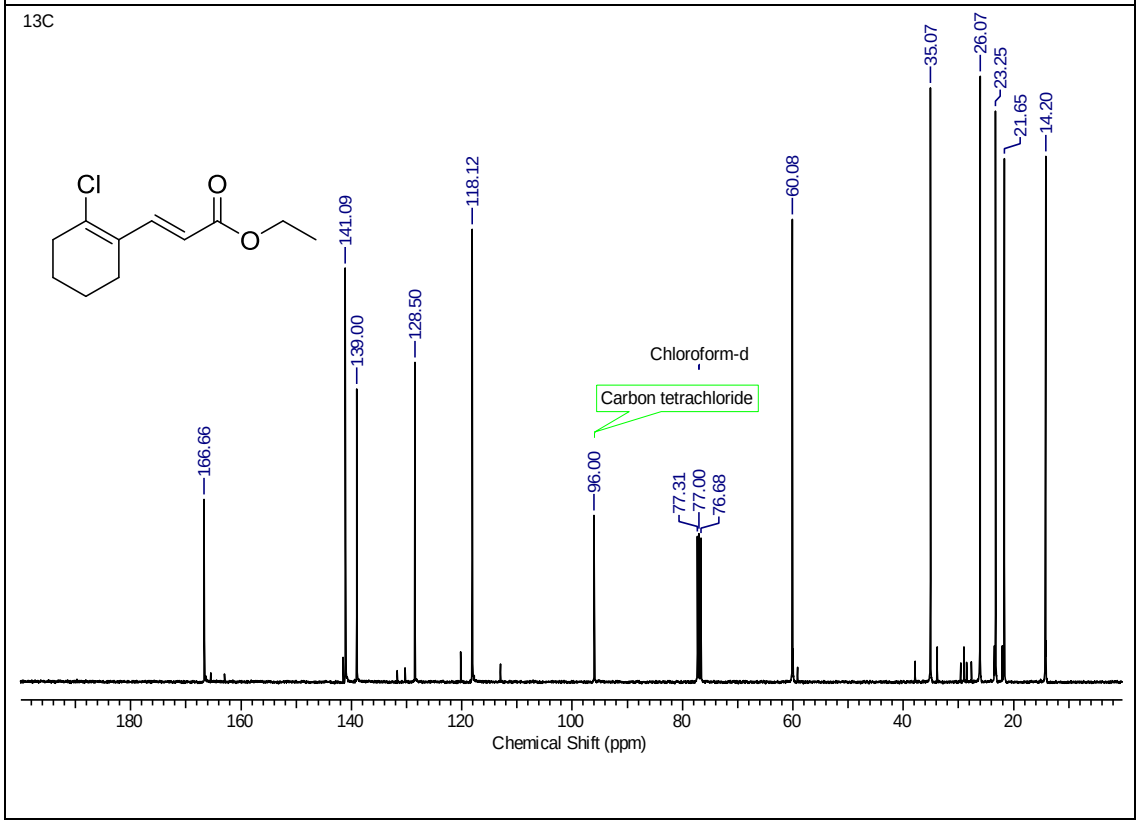
HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{28}O_3N_2NaS$ 459.1713, found 459.1707.

1.2.7 NMR spectra

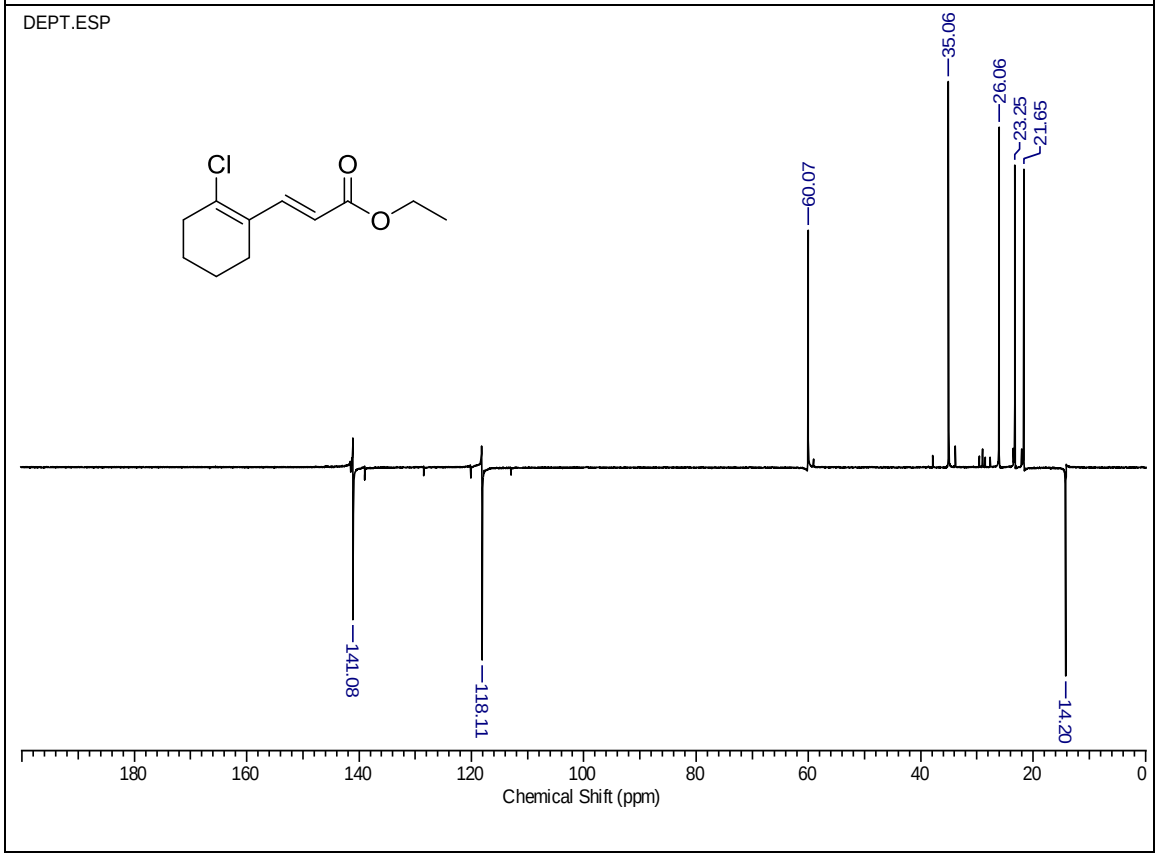
^{1}H NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 200 MHz)



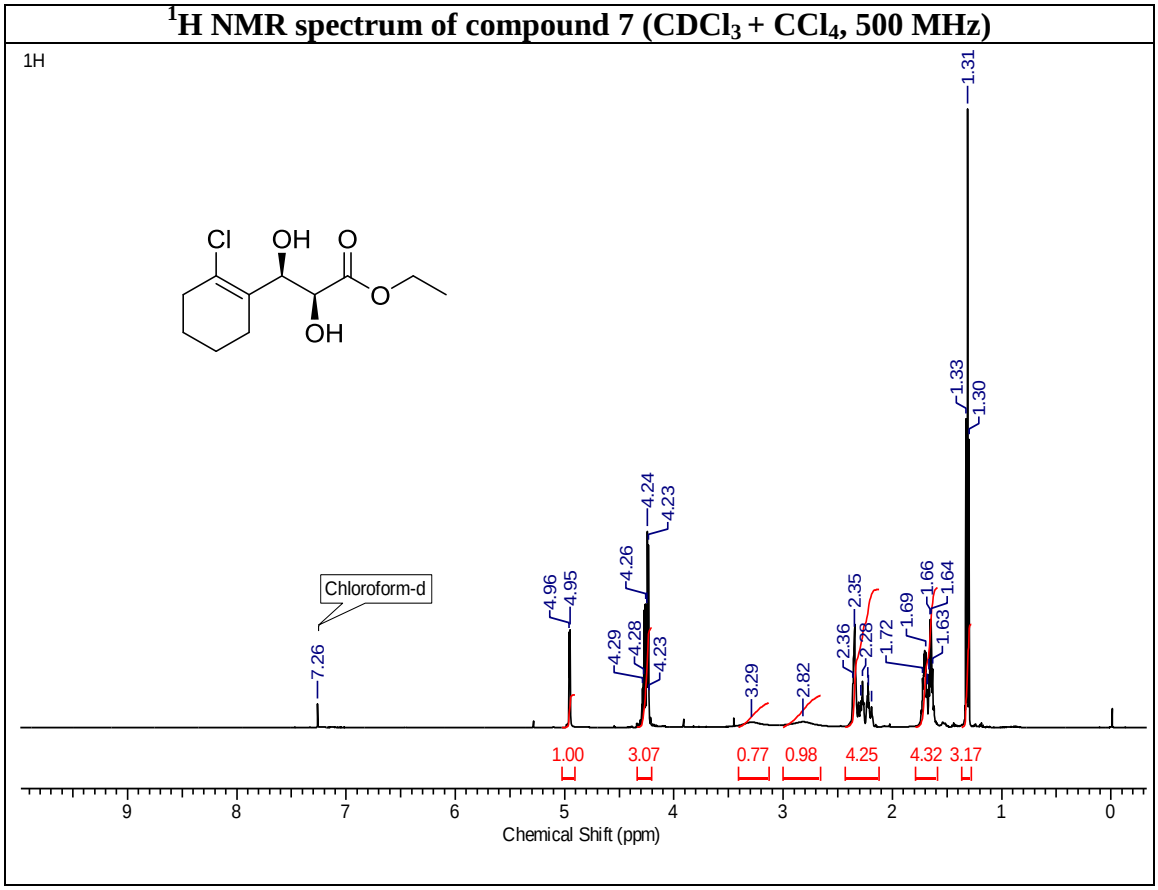
^{13}C NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 100 MHz)



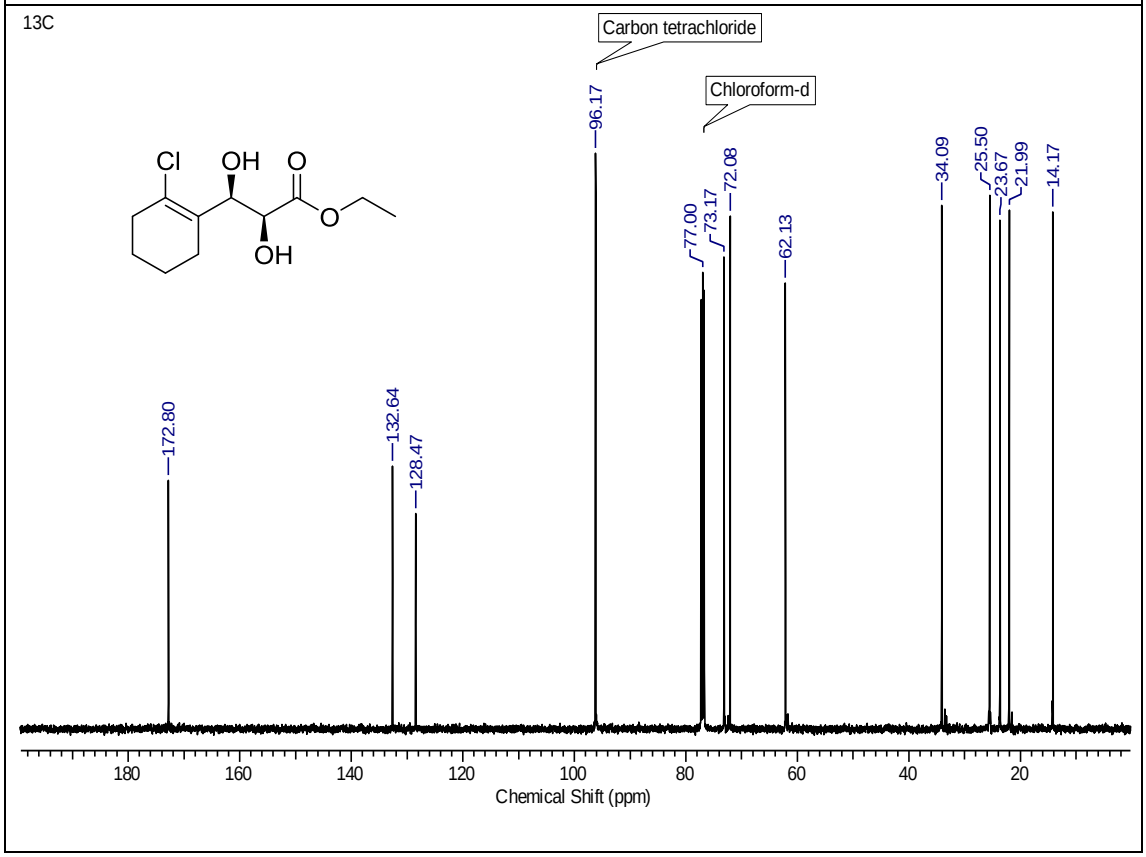
DEPT spectrum of compound 8 ($CDCl_3$ + CCl_4, 100 MHz)



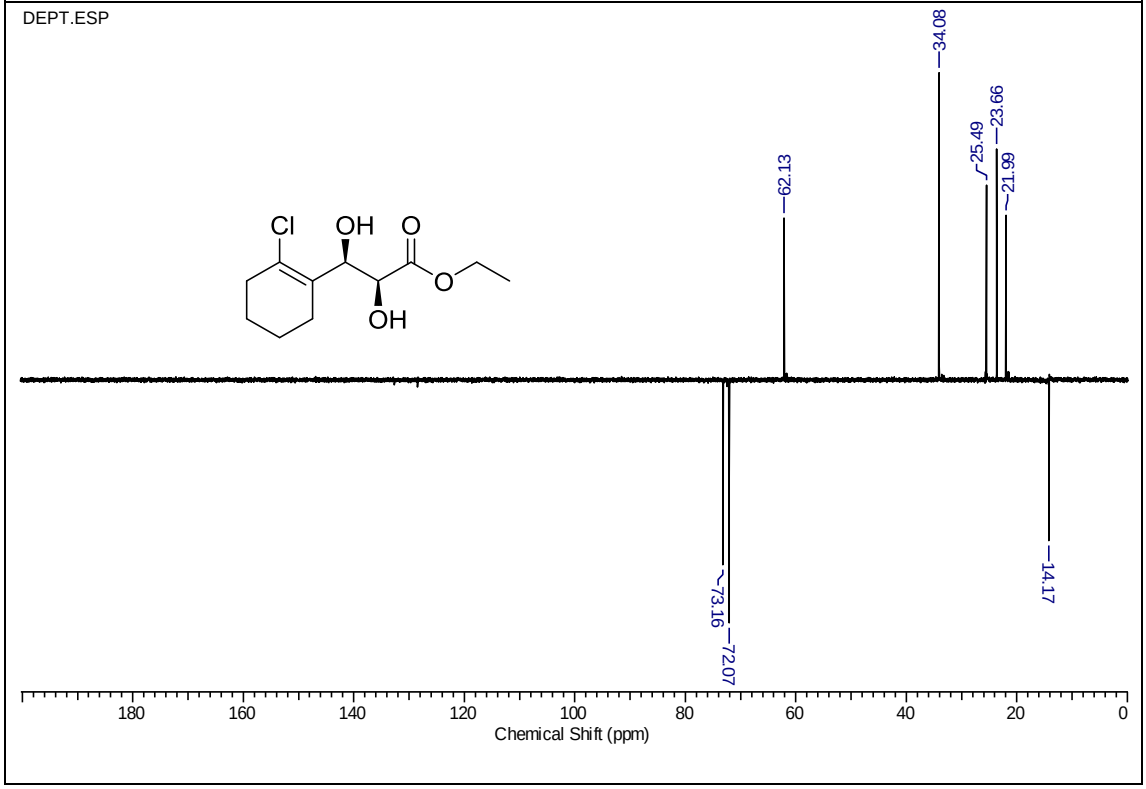
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 500 MHz)



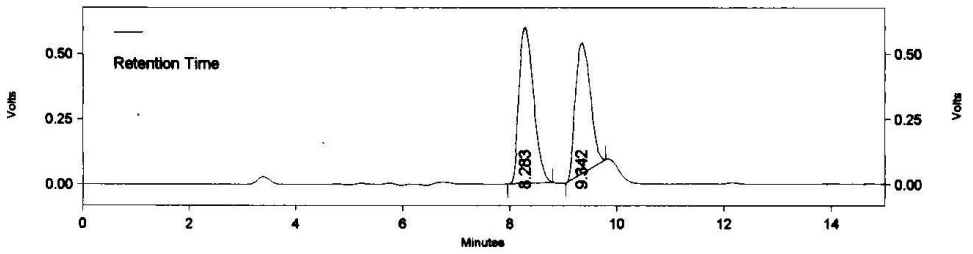
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 125 MHz)

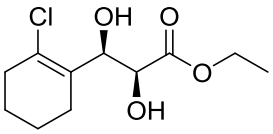


DEPT spectrum of compound 7 ($CDCl_3$ + CCl_4, 125 MHz)



HPLC chromatogram of racemic diol 7



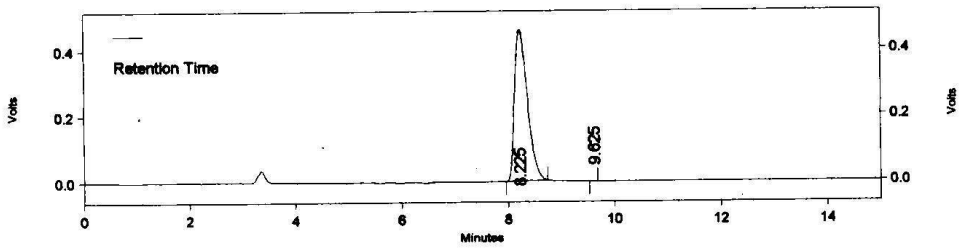


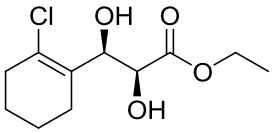
Detector A - 1 (220nm)

Retention Time	C Area	Area %
8.283	11358374	53.848
9.342	9734926	46.152
Totals	21093300	100.000

Project Leader : Dr. S. P. Chavan
Column :Chiracel OJ-H (250 x4.6mm)
Mobile Phase :IPA:PET ETHER (7.5:92.5)
Wavelength : 220 nm
Flow Rate :1 ml/min
Conc. :2 mg/ 1.0 ml
Inj vol- :5 ul.

HPLC chromatogram of chiral diol 7



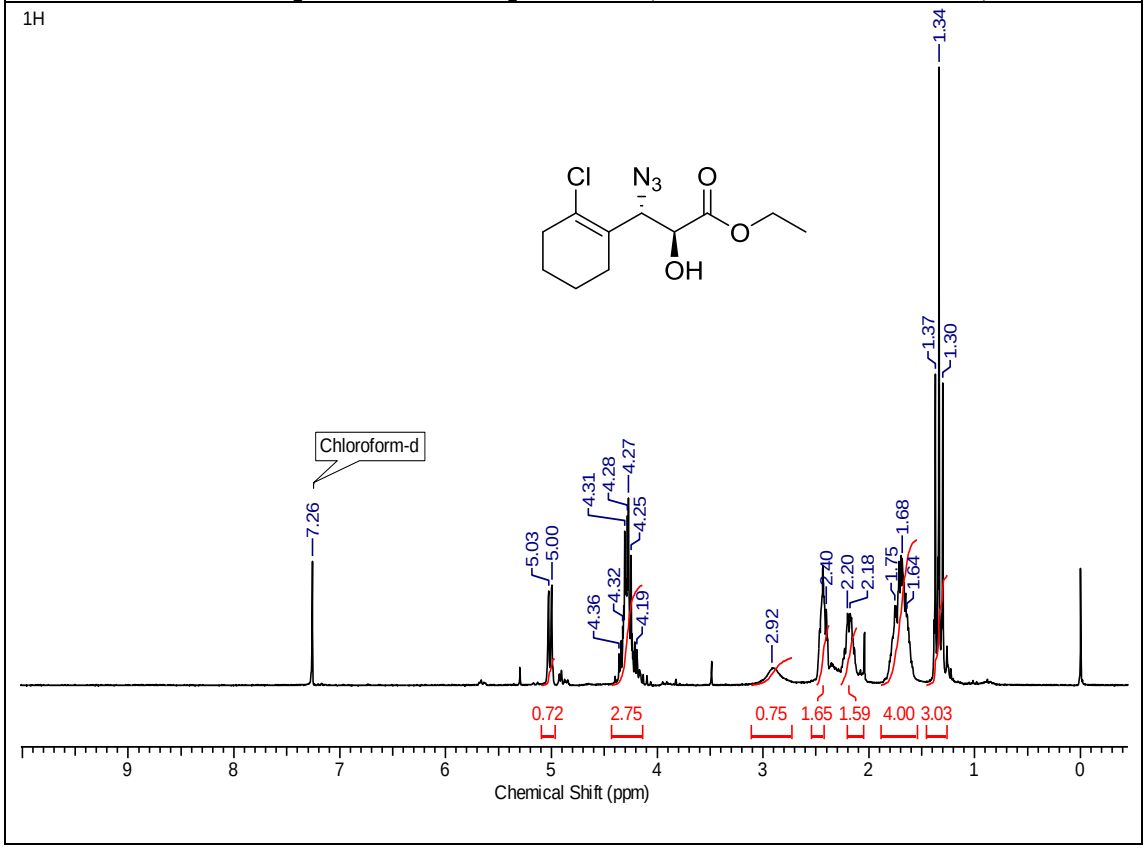


Detector A - 1 (220nm)

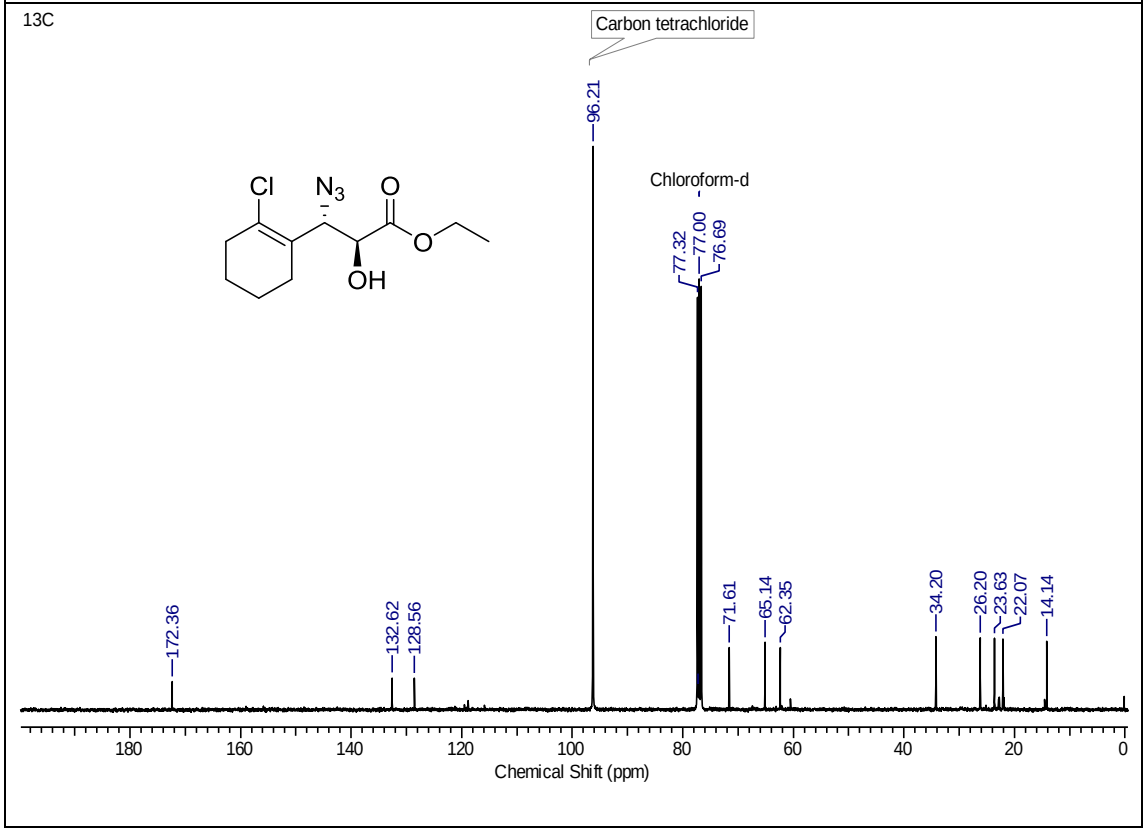
Retention Time	C Area	Area %
8.225	7694779	99.997
9.625	222	0.003
Totals	7695001	100.000

Project Leader : Dr. S. P. Chavan
Column :Chiracel OJ-H (250 x4.6mm)
Mobile Phase :IPA:PET ETHER (7.5:92.5)
Wavelength : 220 nm
Flow Rate :1 ml/min
Conc. :2 mg/ 1.0 ml
Inj vol- :5 ul.

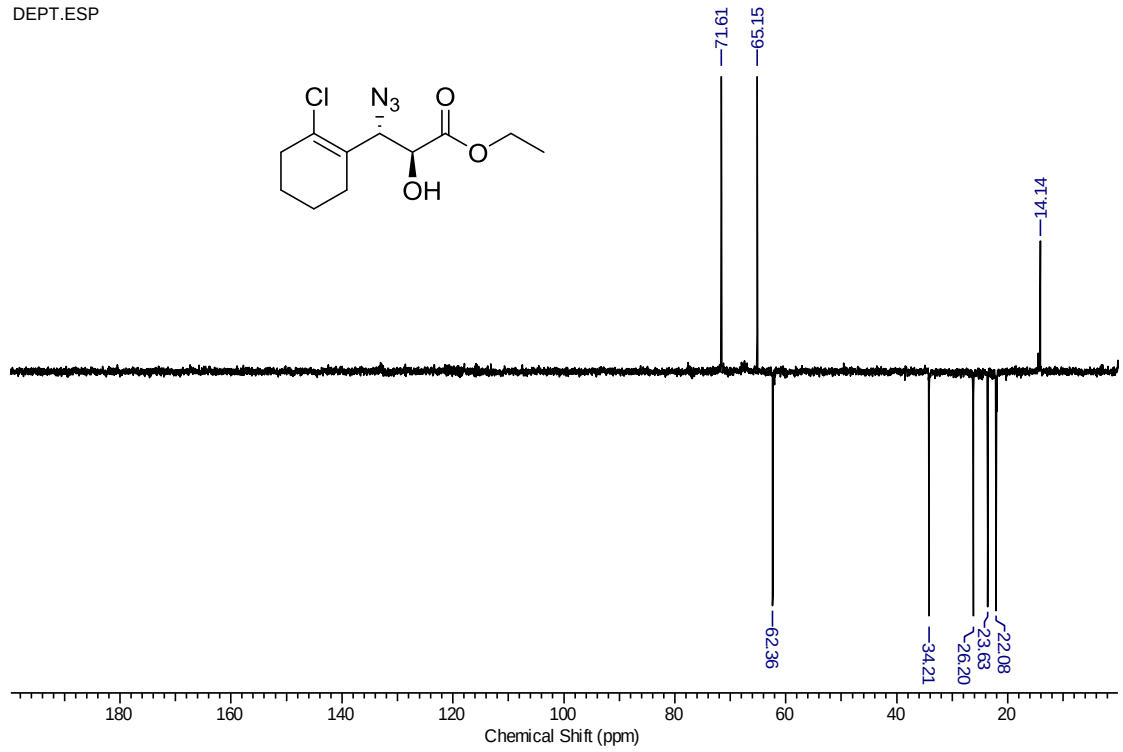
^{1}H NMR spectrum of compound 11 ($CDCl_3$ + CCl_4, 200 MHz)



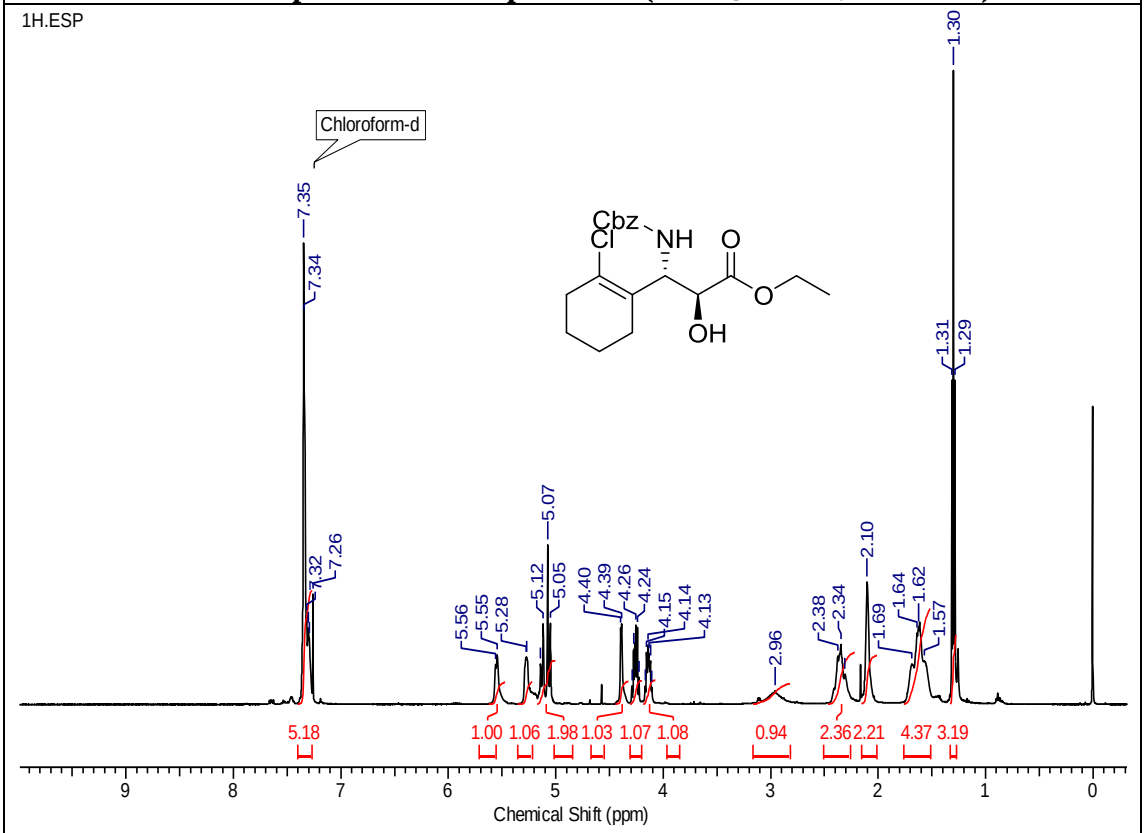
^{13}C NMR spectrum of compound 11 ($CDCl_3$ + CCl_4, 100 MHz)



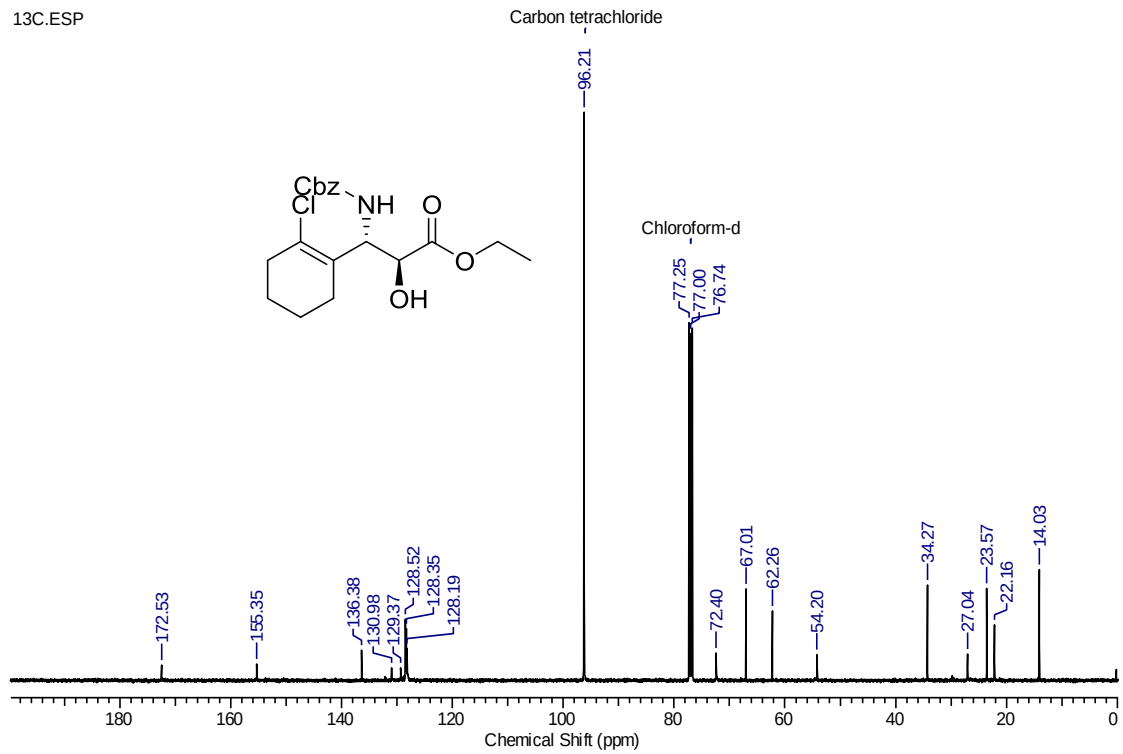
DEPT spectrum of compound 11 ($CDCl_3$ + CCl_4, 100 MHz)



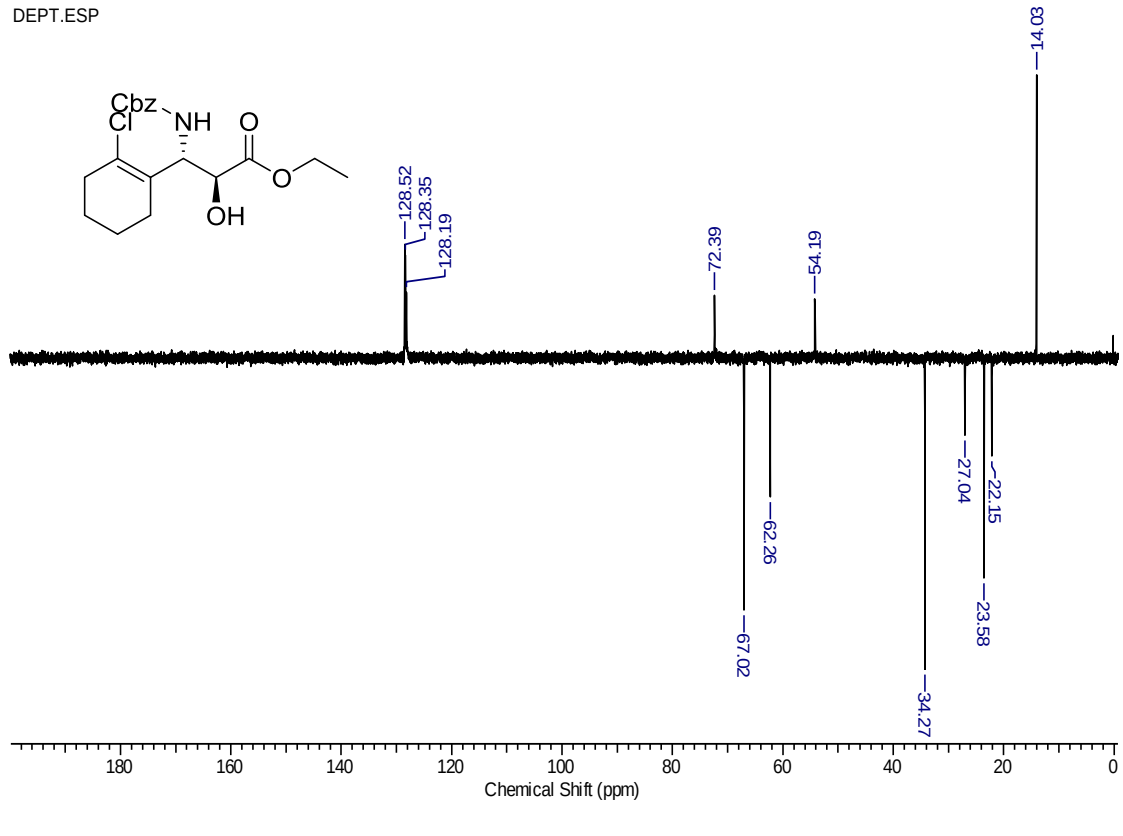
^{1}H NMR spectrum of compound 12 ($CDCl_3$ + CCl_4, 500 MHz)



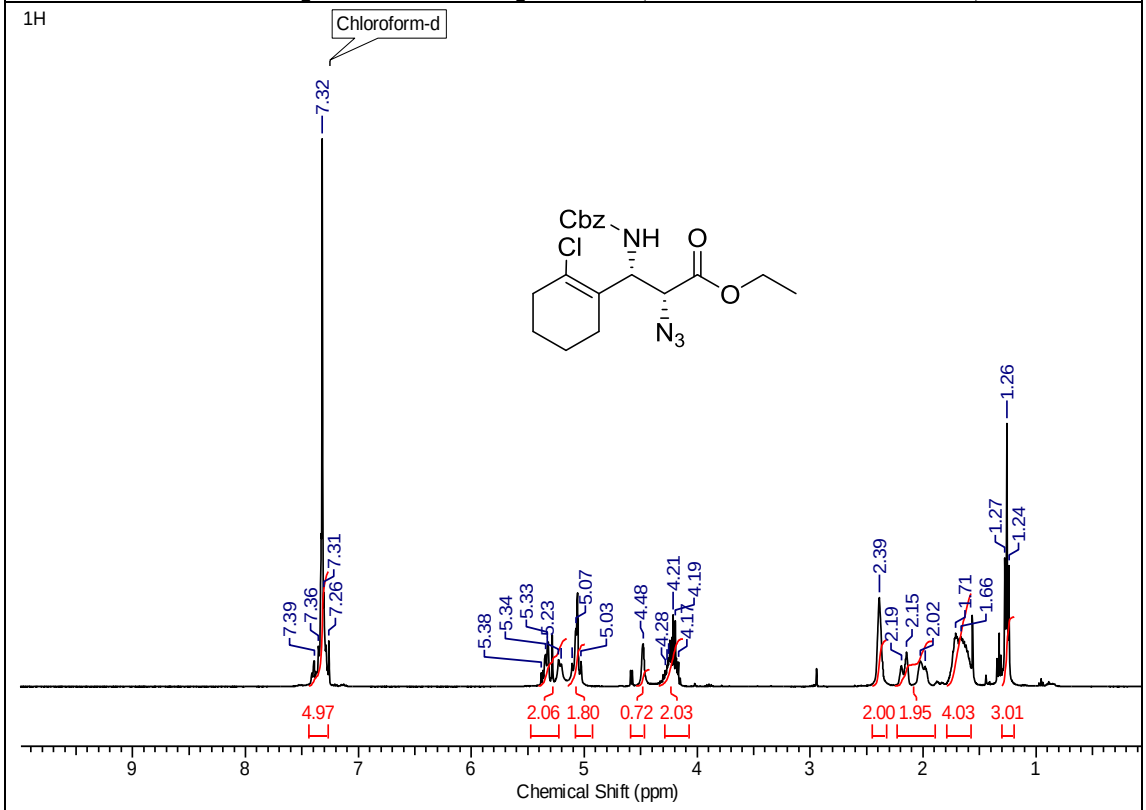
^{13}C NMR spectrum of compound 12 ($CDCl_3$ + CCl_4, 125 MHz)



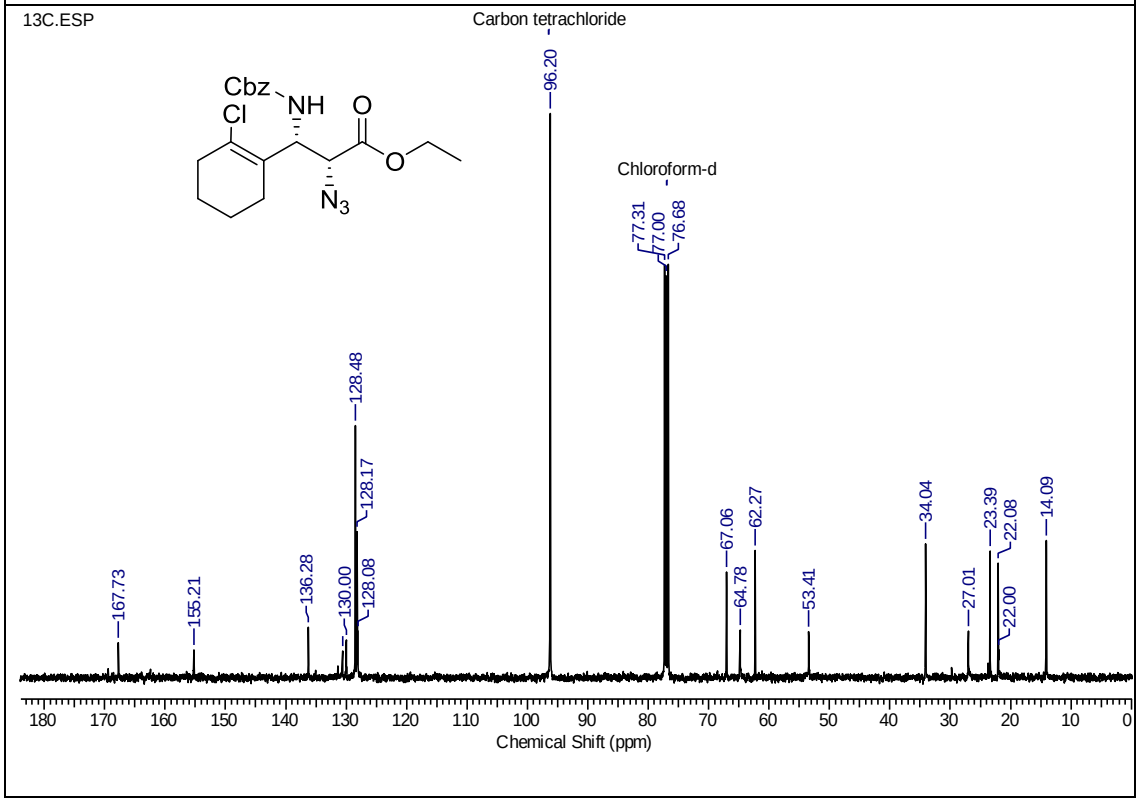
DEPT spectrum of compound 12 ($CDCl_3$ + CCl_4, 125 MHz)



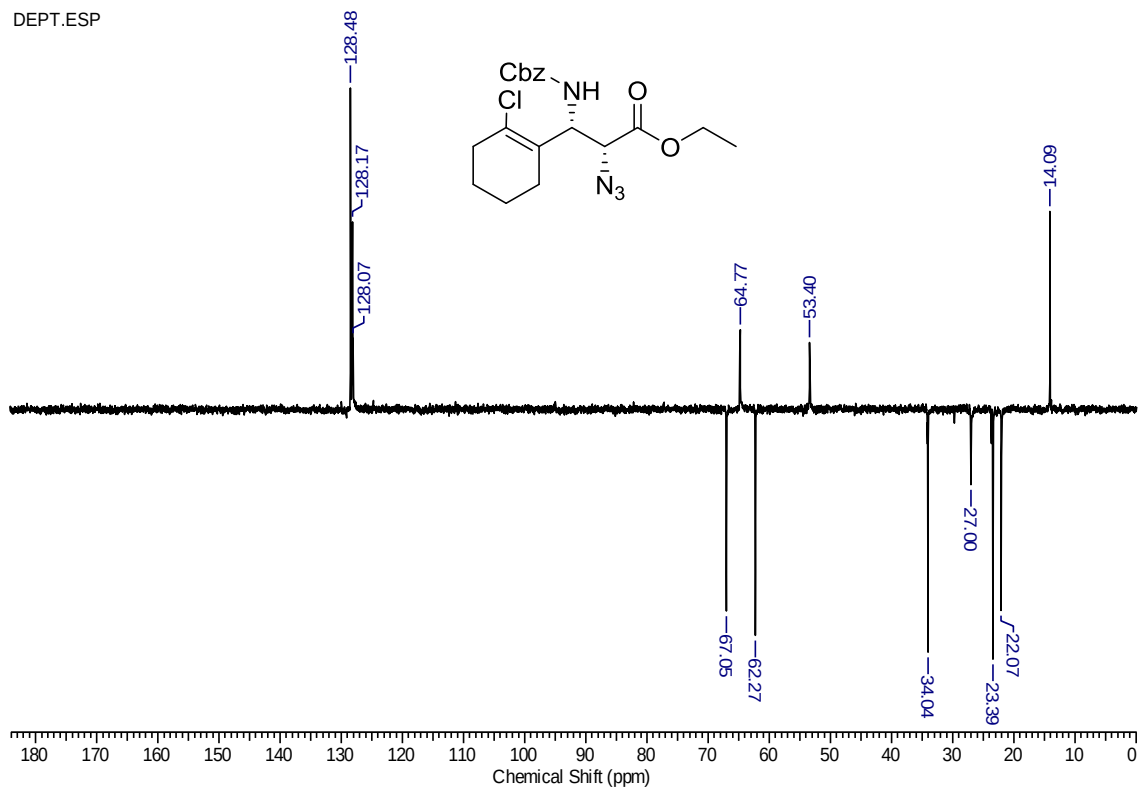
^{1}H NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 400 MHz)



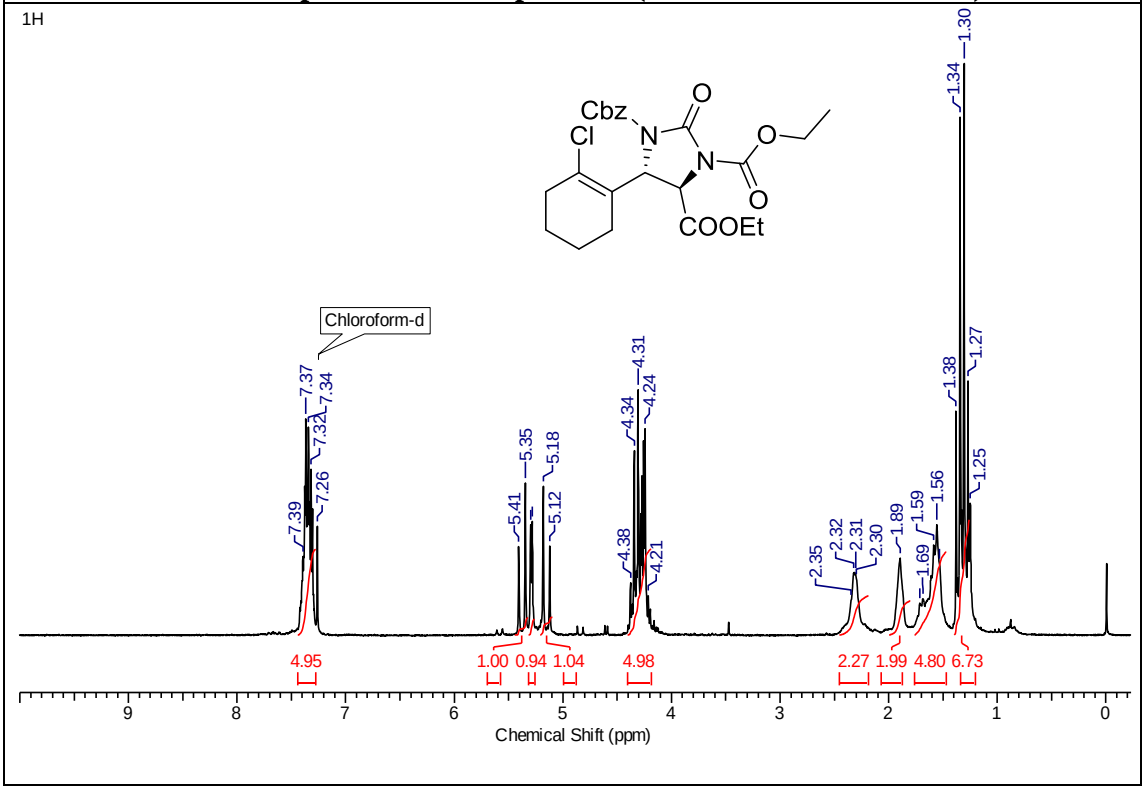
^{13}C NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 100 MHz)



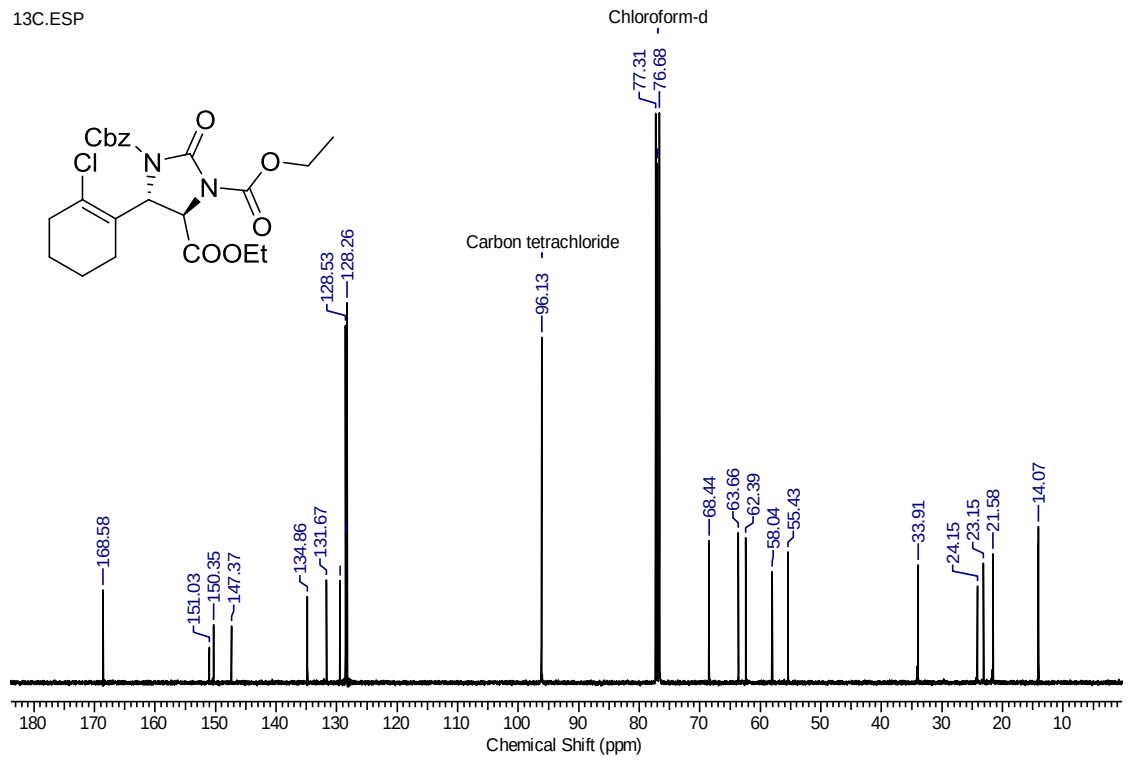
DEPT spectrum of compound 6 ($CDCl_3$ + CCl_4, 100 MHz)



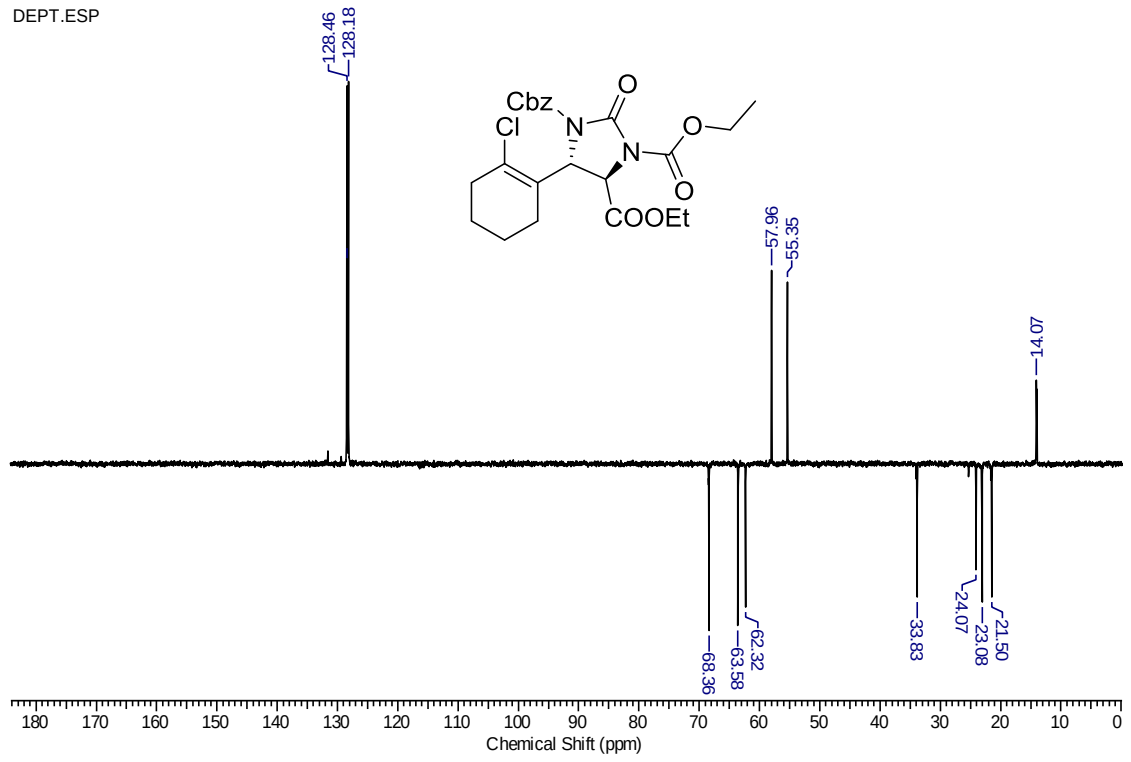
^{1}H NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 200 MHz)



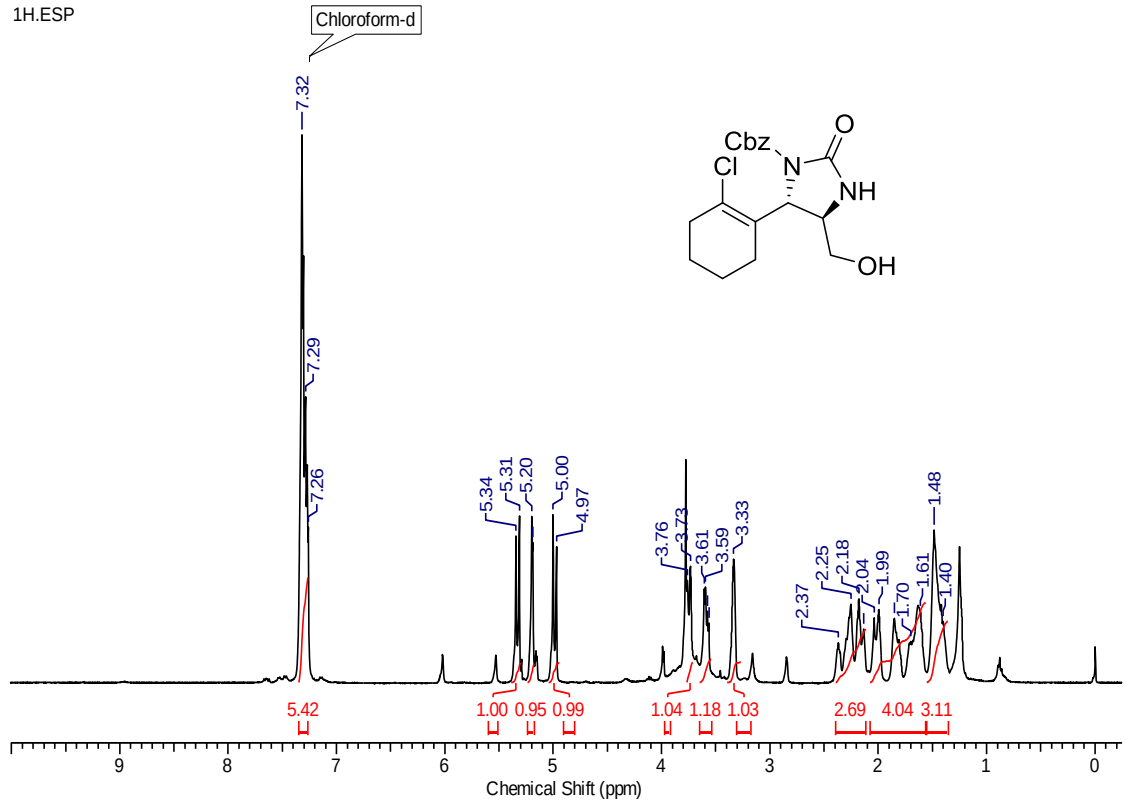
^{13}C NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 100 MHz)



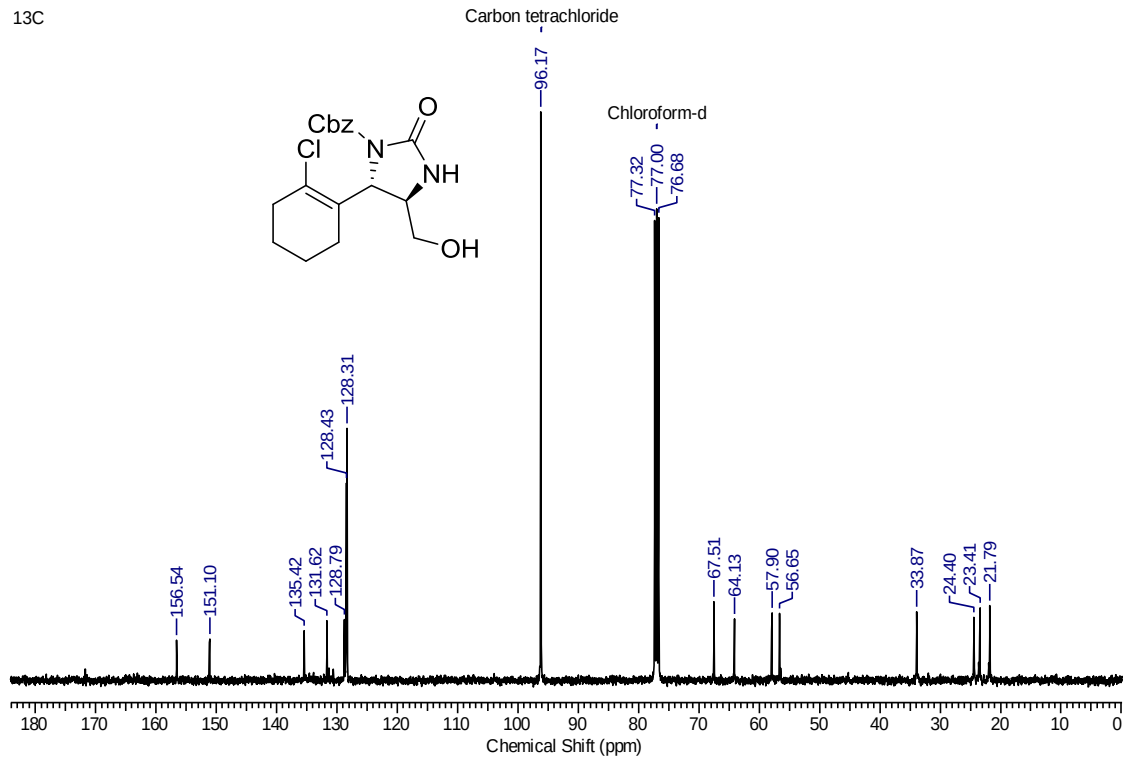
DEPT spectrum of compound 5 ($CDCl_3$ + CCl_4, 100 MHz)



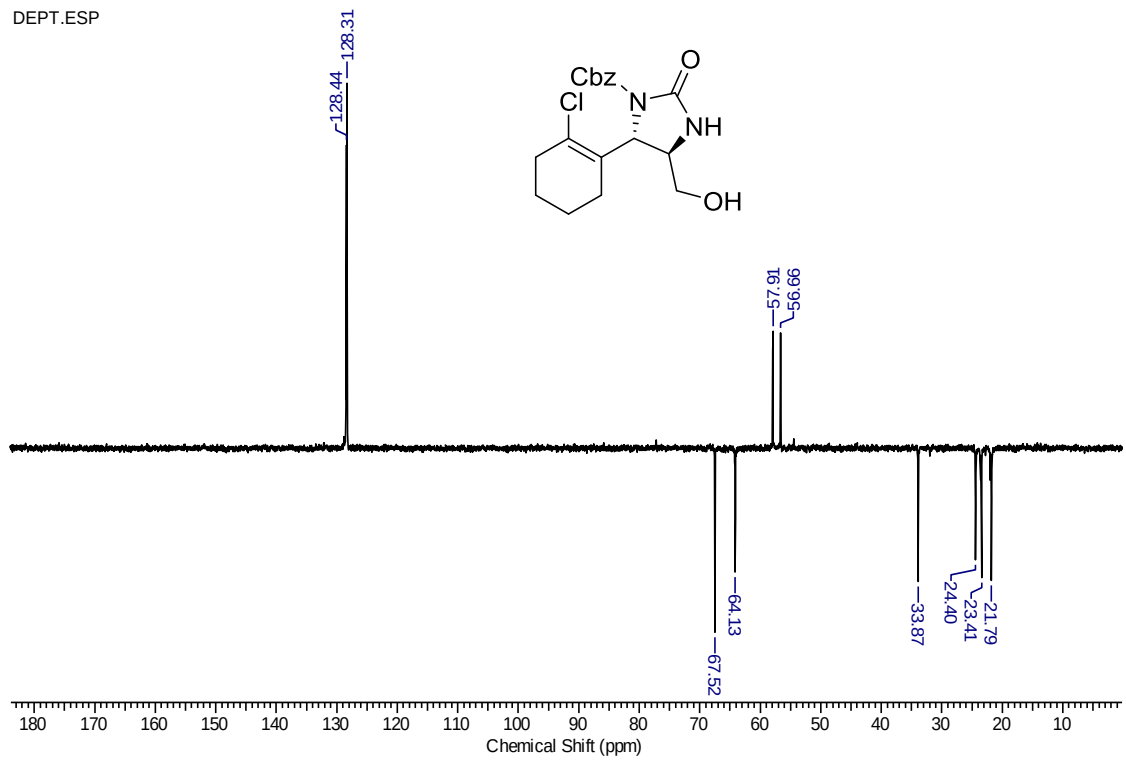
^{1}H NMR spectrum of compound 13 ($CDCl_3$ + CCl_4, 400 MHz)



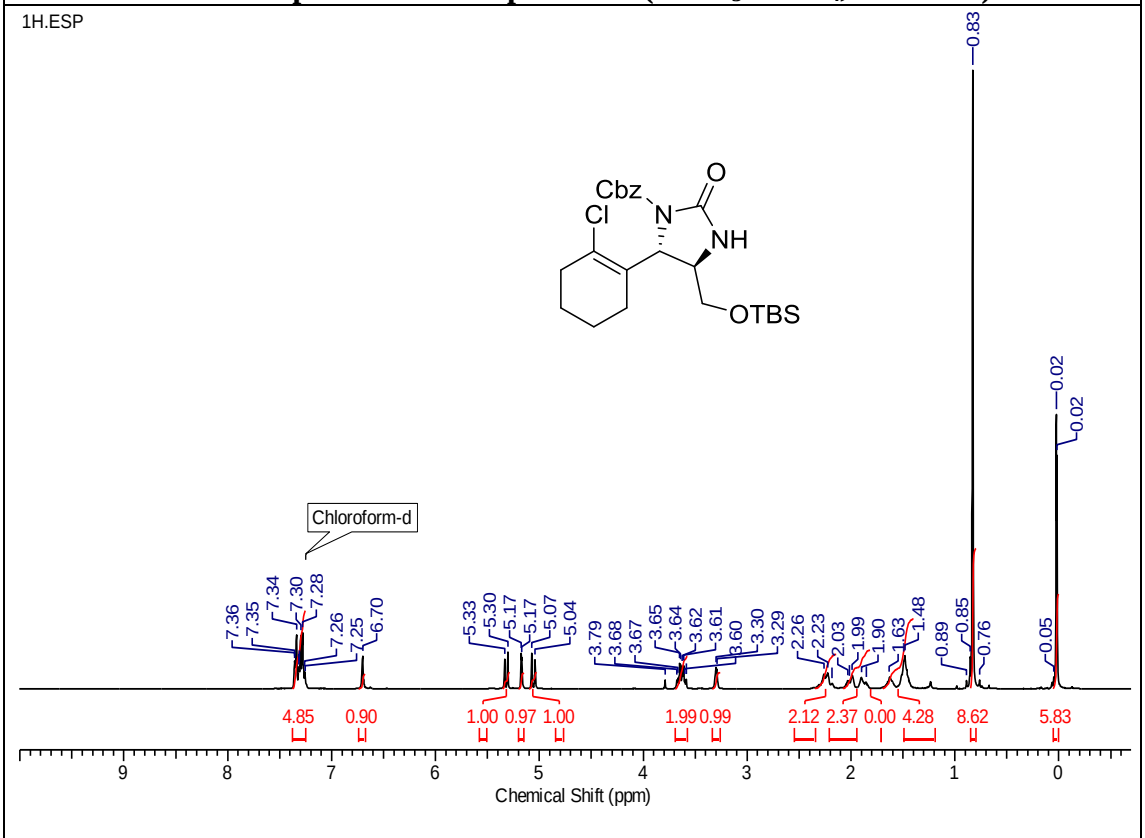
^{13}C NMR spectrum of compound 13 ($CDCl_3$ + CCl_4, 100 MHz)



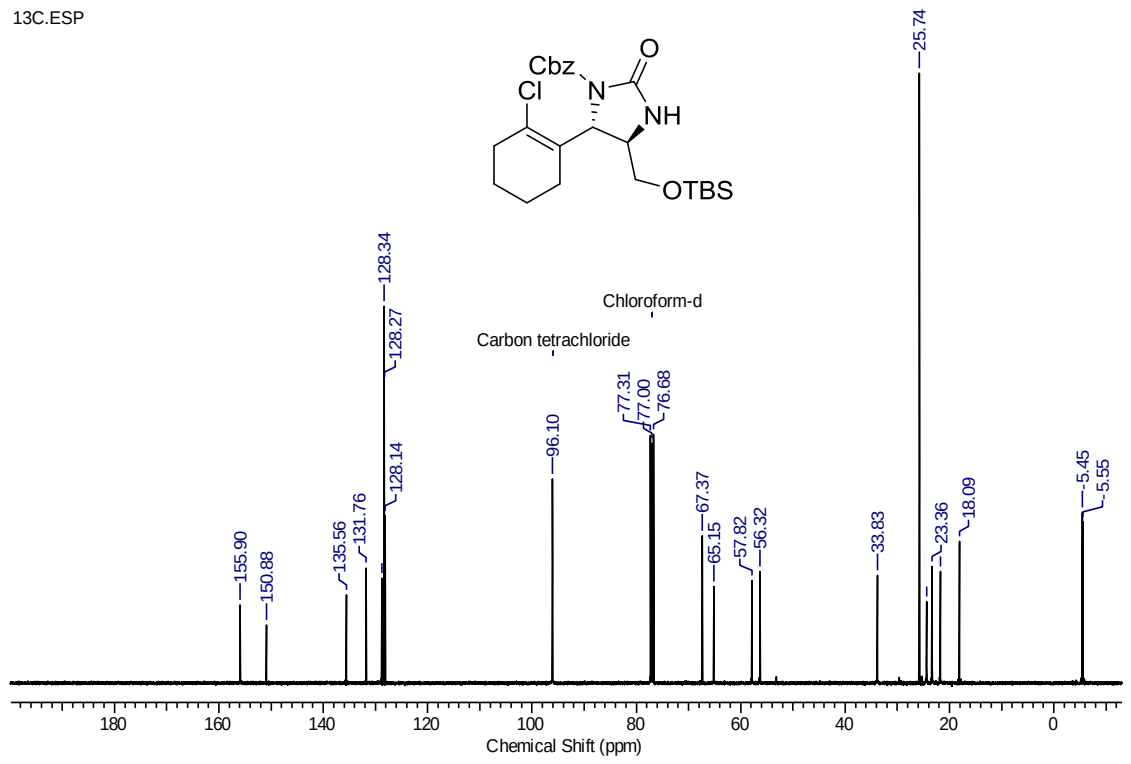
DEPT spectrum of compound 13 ($CDCl_3$ + CCl_4, 100 MHz)



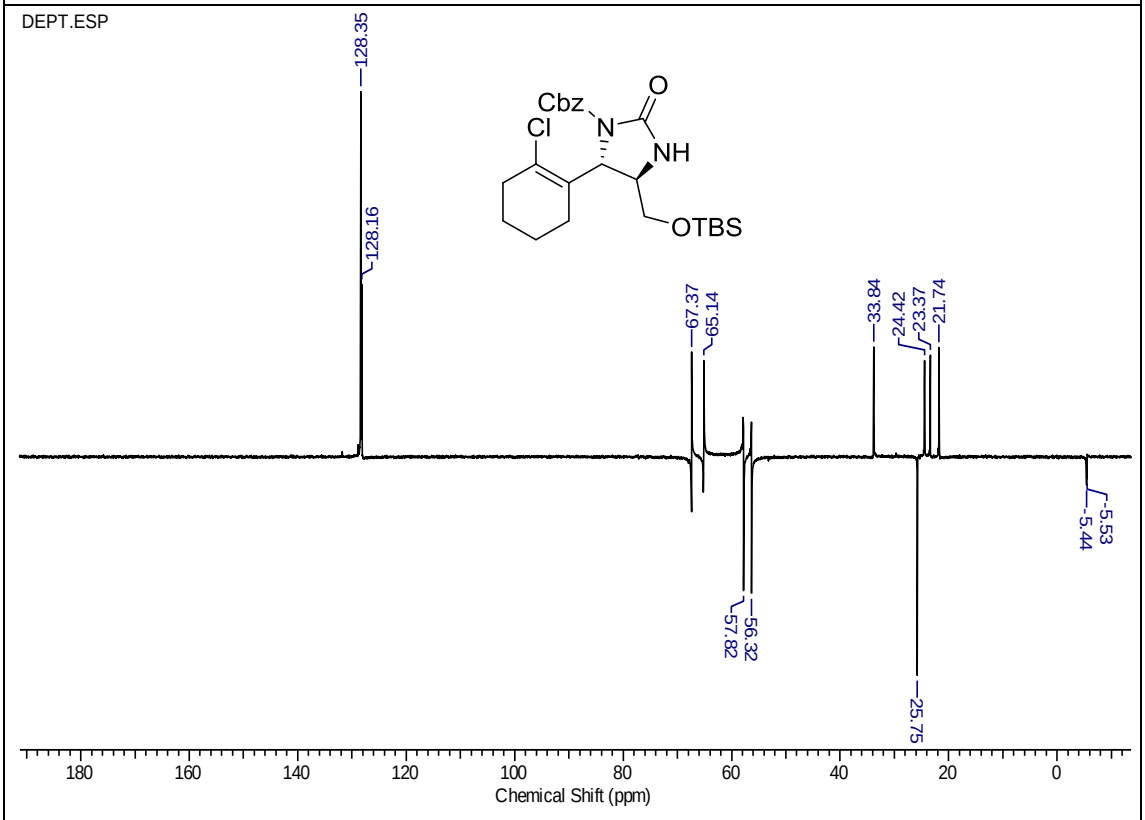
^{1}H NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 400 MHz)



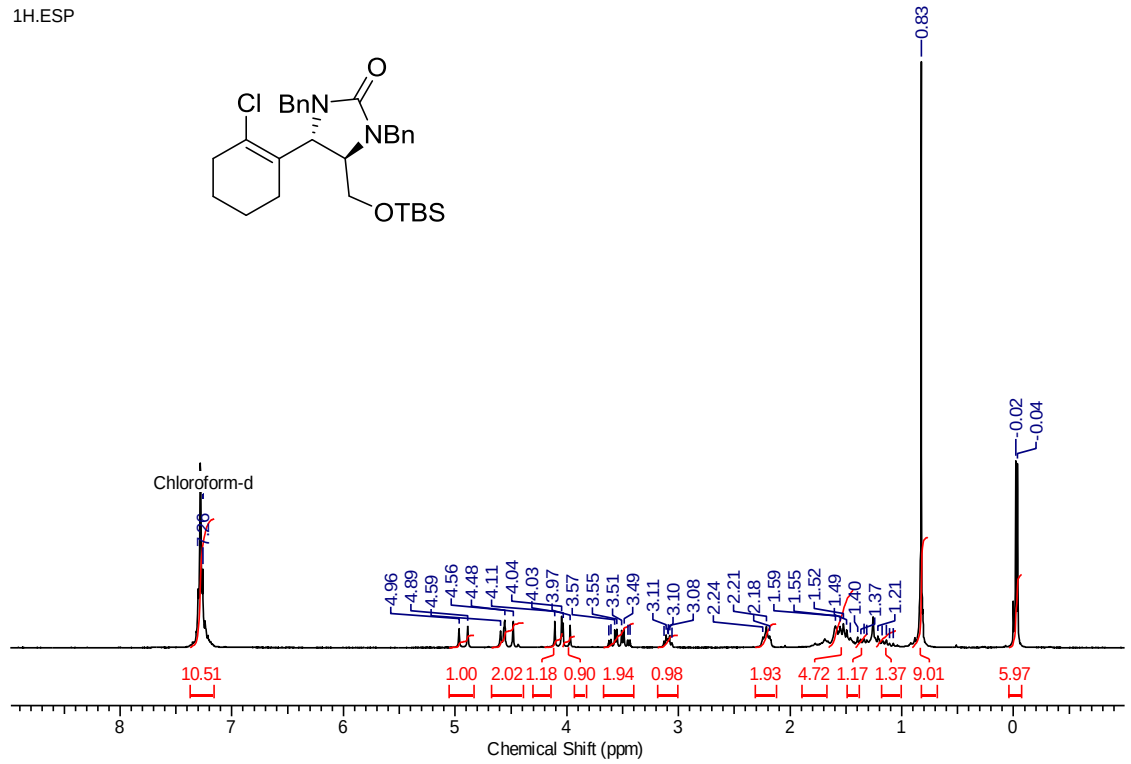
^{13}C NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 100 MHz)



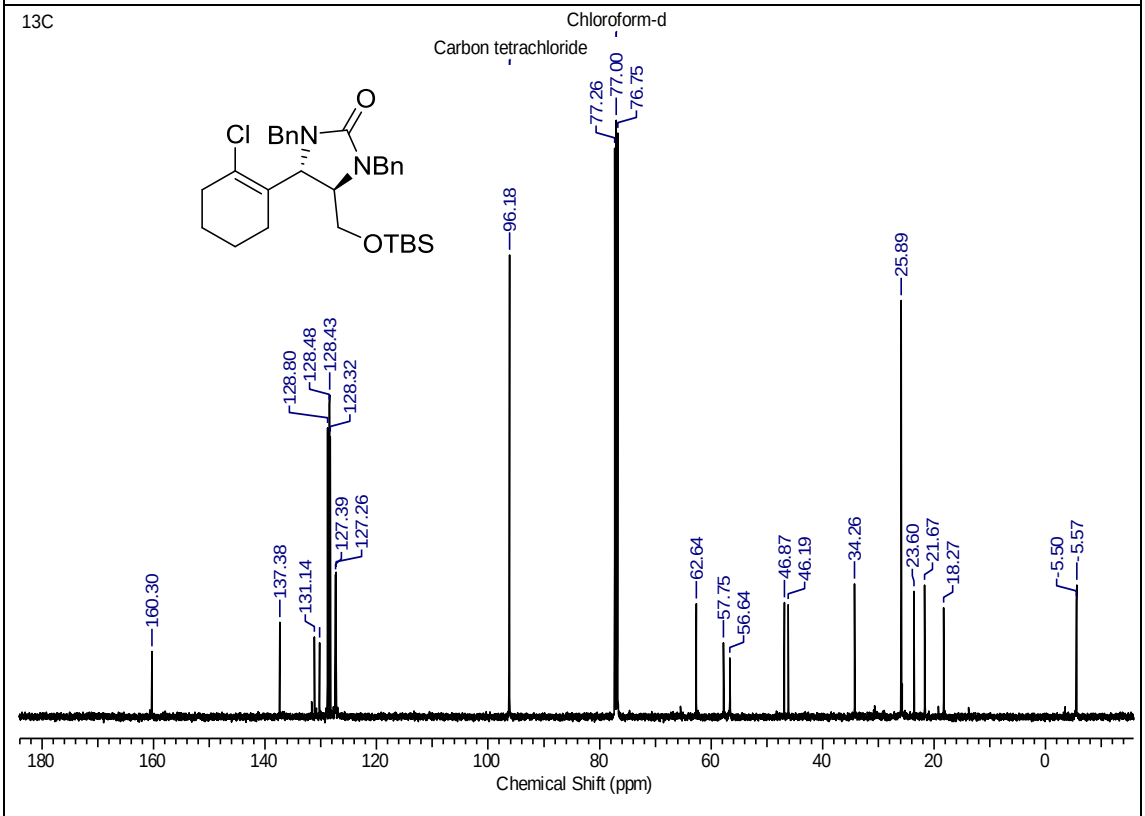
DEPT spectrum of compound 14 ($CDCl_3$ + CCl_4, 100 MHz)



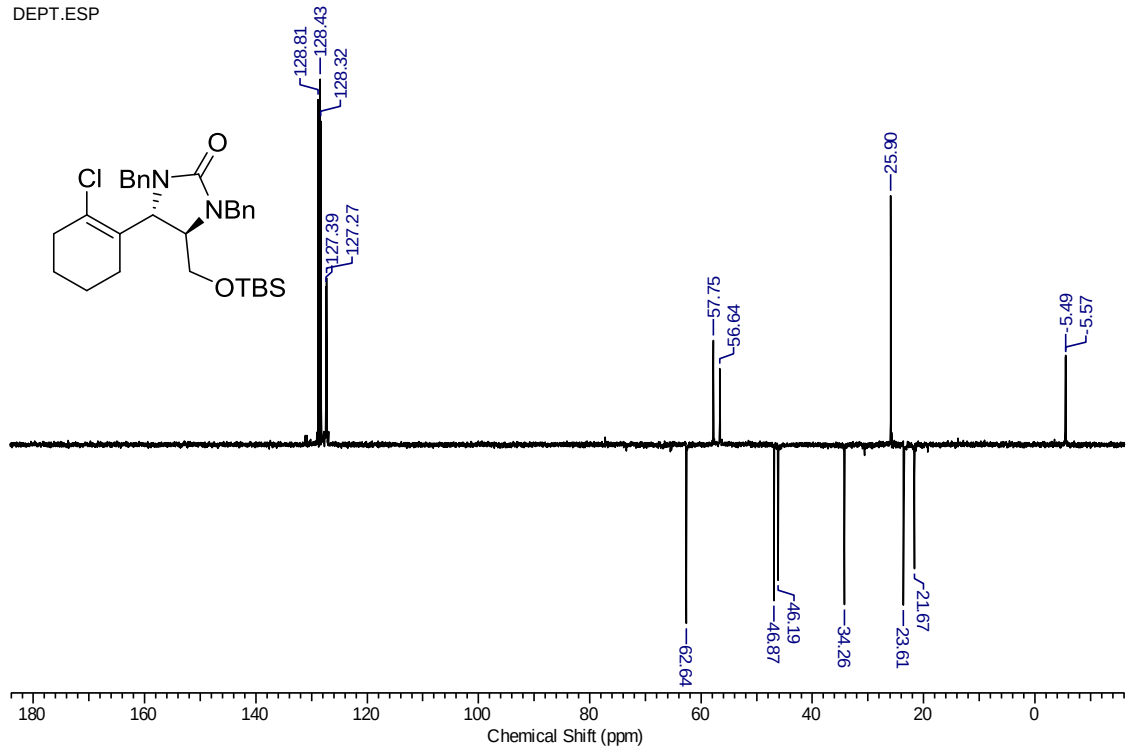
^{1}H NMR spectrum of compound 15 ($CDCl_3$ + CCl_4, 200 MHz)



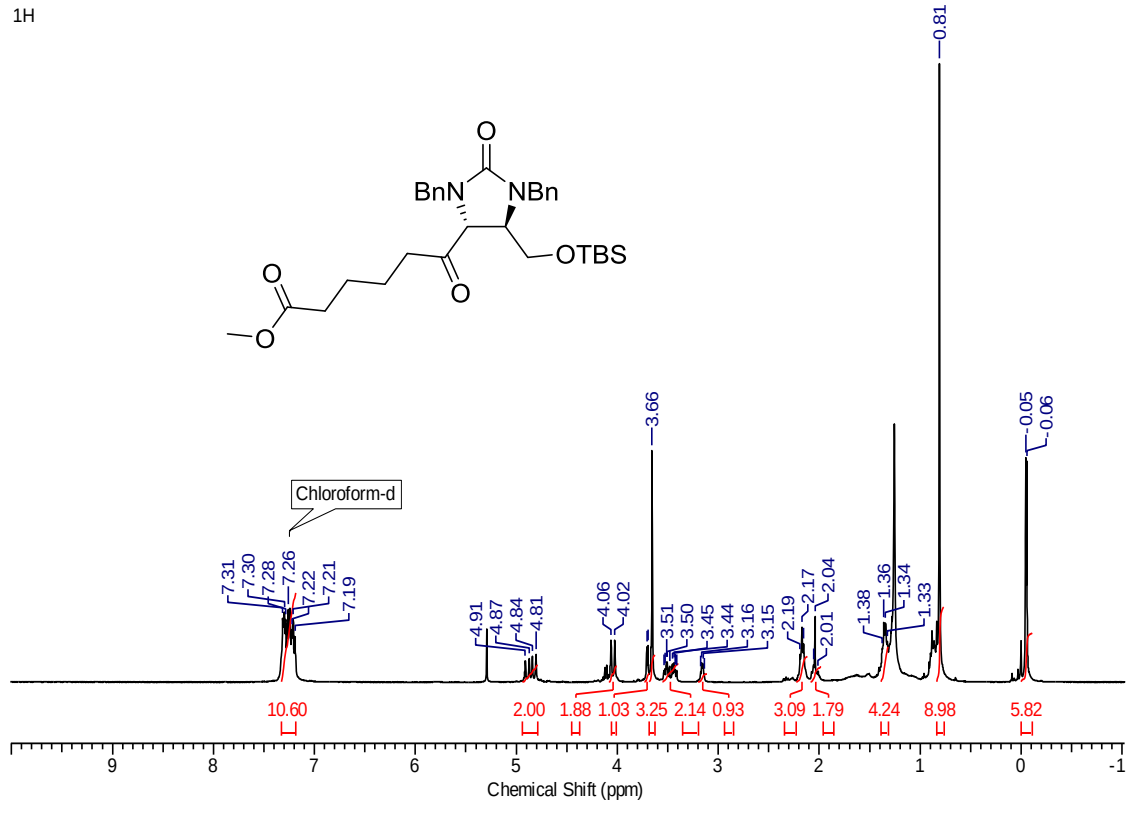
^{13}C NMR spectrum of compound 15 ($CDCl_3$ + CCl_4, 125 MHz)



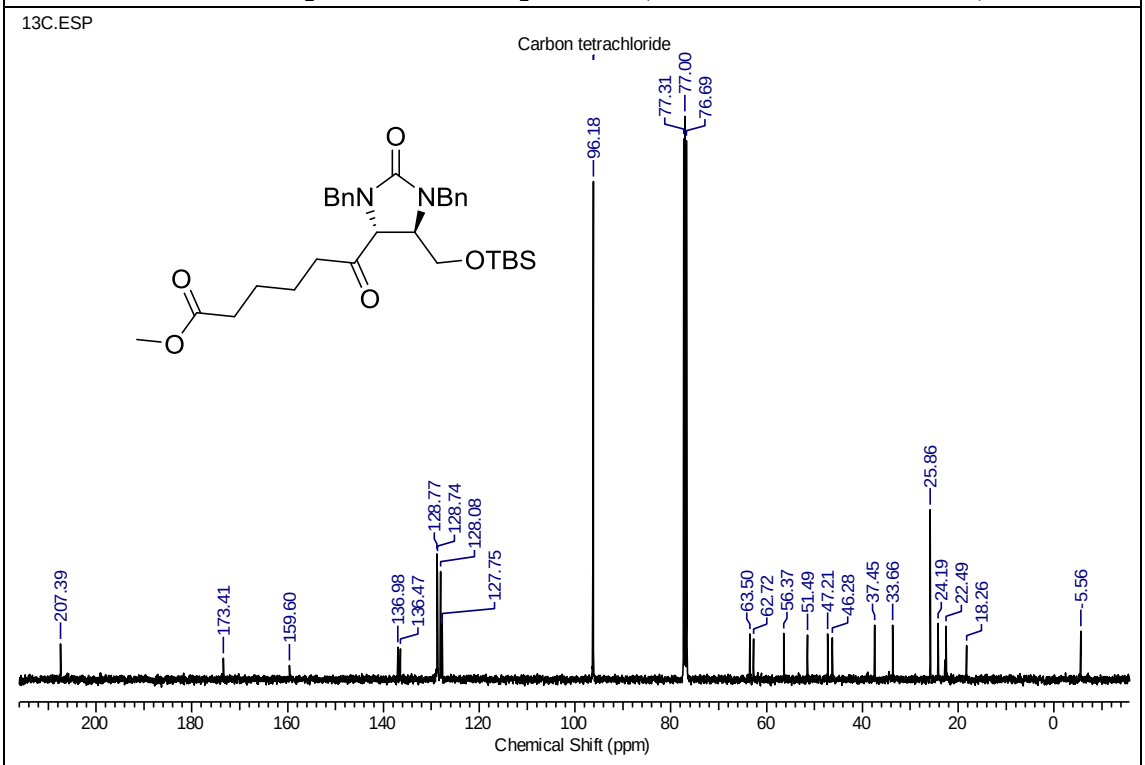
DEPT spectrum of compound 15 ($CDCl_3$ + CCl_4, 125 MHz)



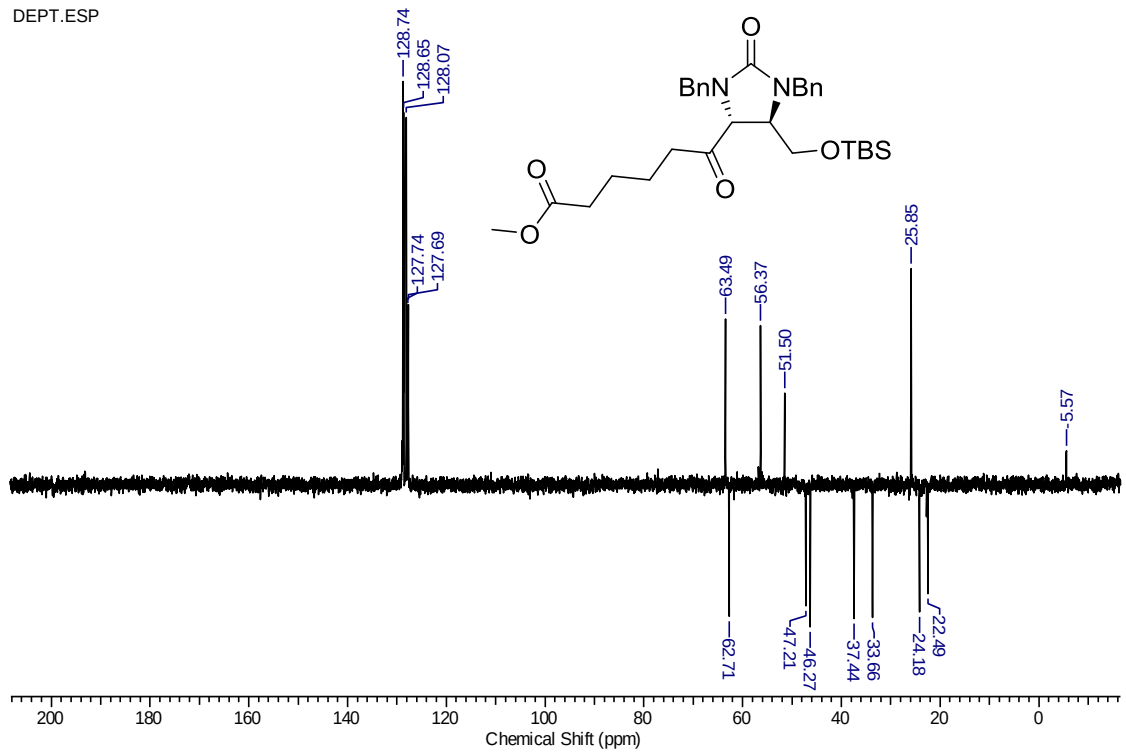
^{1}H NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 400 MHz)



^{13}C NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 100 MHz)



DEPT spectrum of compound 4 ($CDCl_3$ + CCl_4, 100 MHz)



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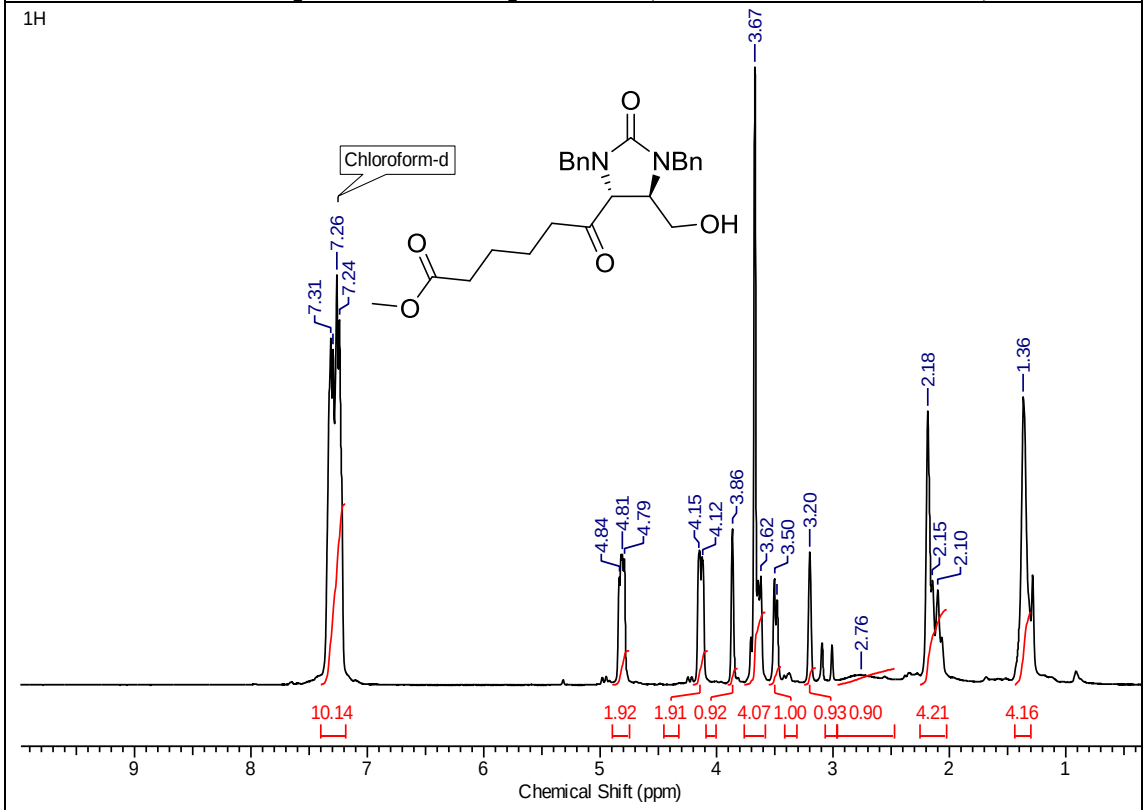
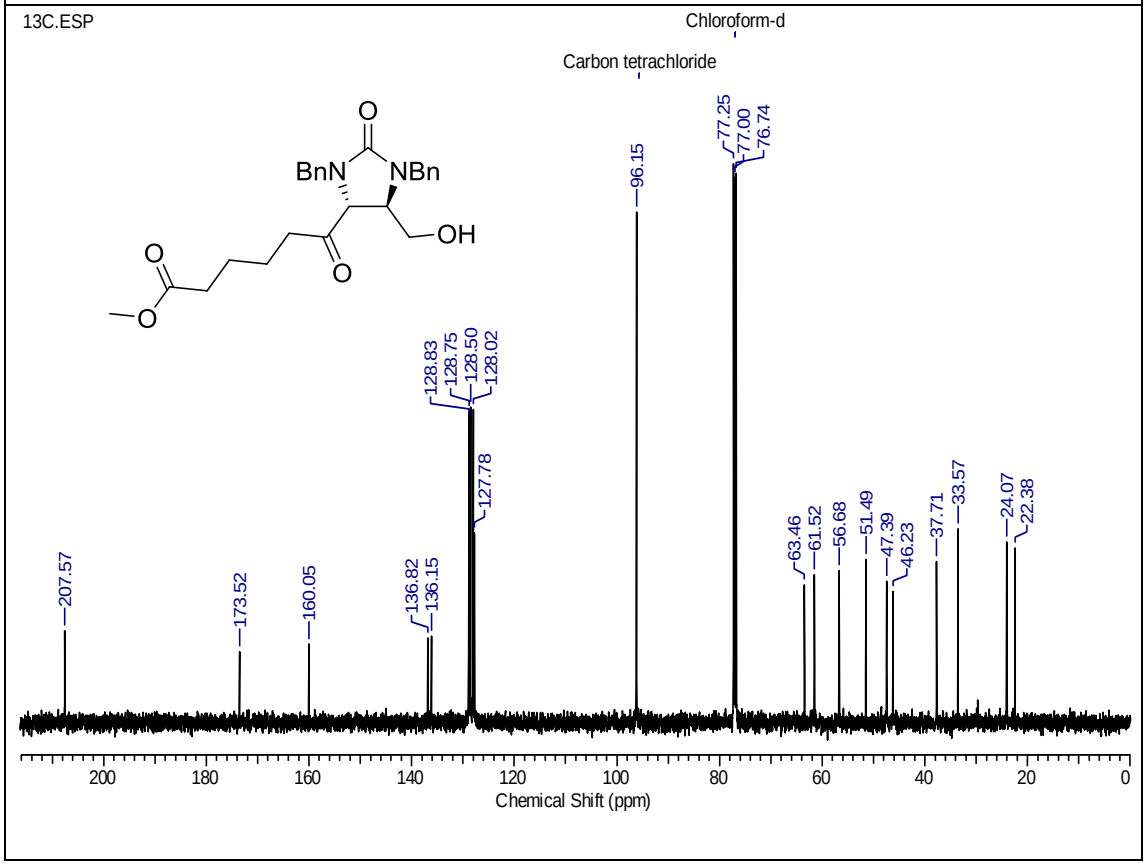
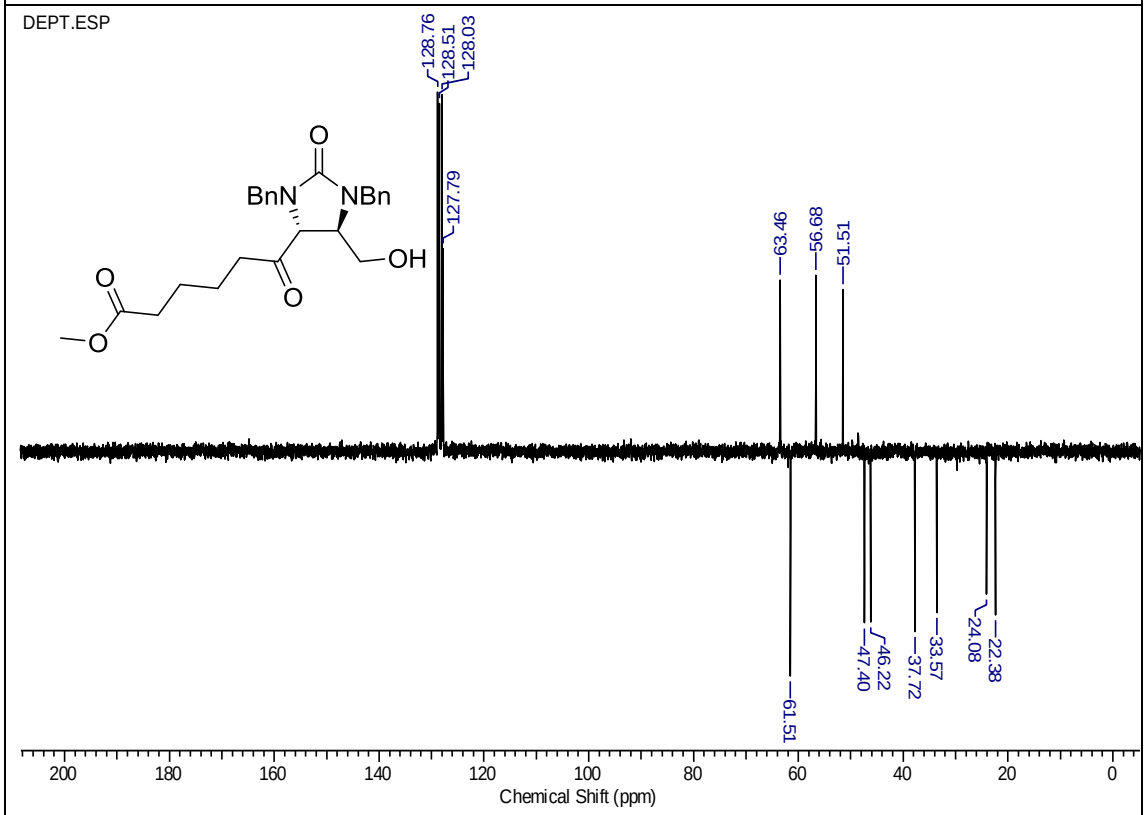


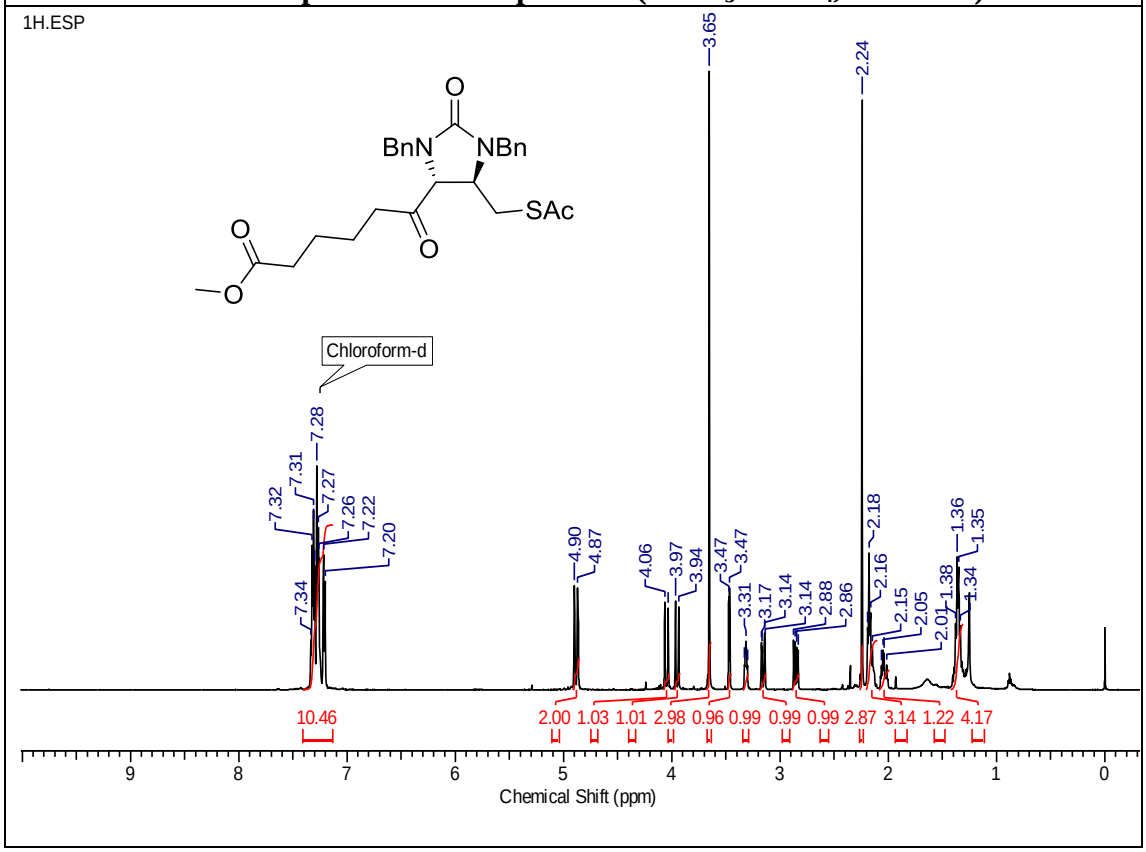
^{13}C NMR spectrum of compound 16 ($CDCl_3$ + CCl_4, 125 MHz)



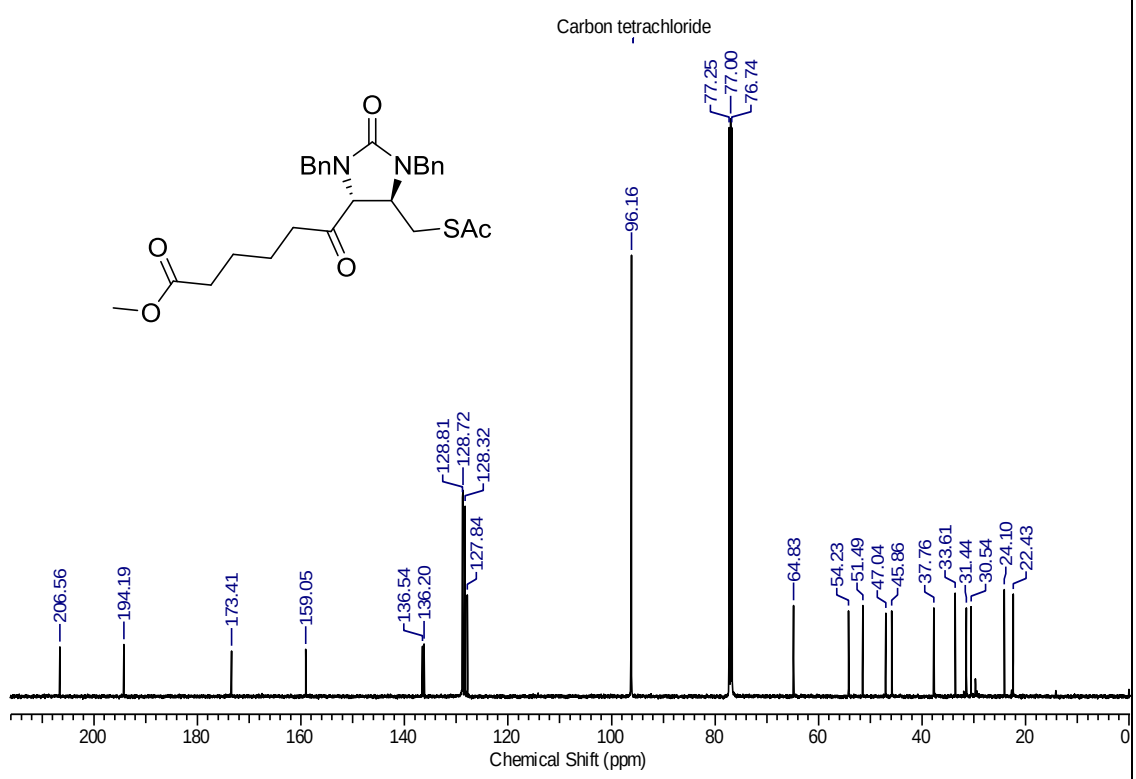
DEPT spectrum of compound 16 ($CDCl_3$ + CCl_4, 125 MHz)



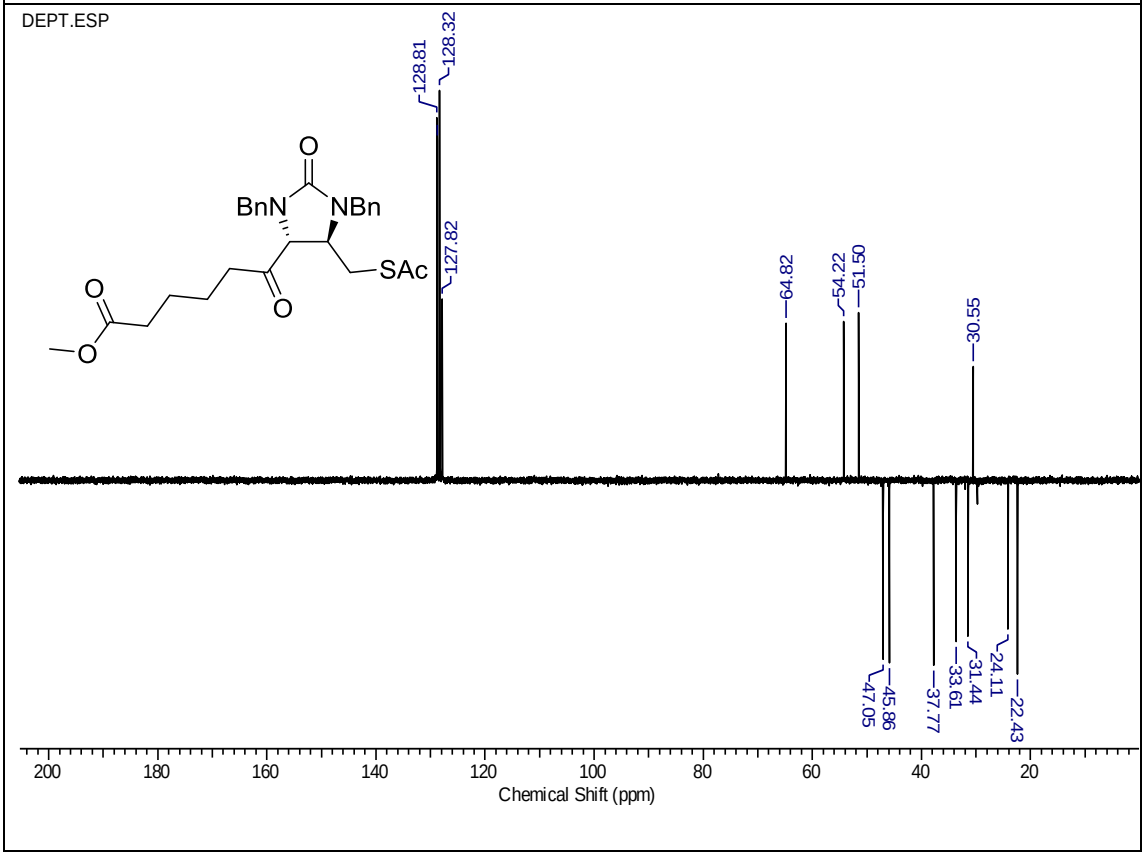
^{1}H NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 500 MHz)



^{13}C NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 125 MHz)



DEPT spectrum of compound 3 ($CDCl_3$ + CCl_4, 125 MHz)



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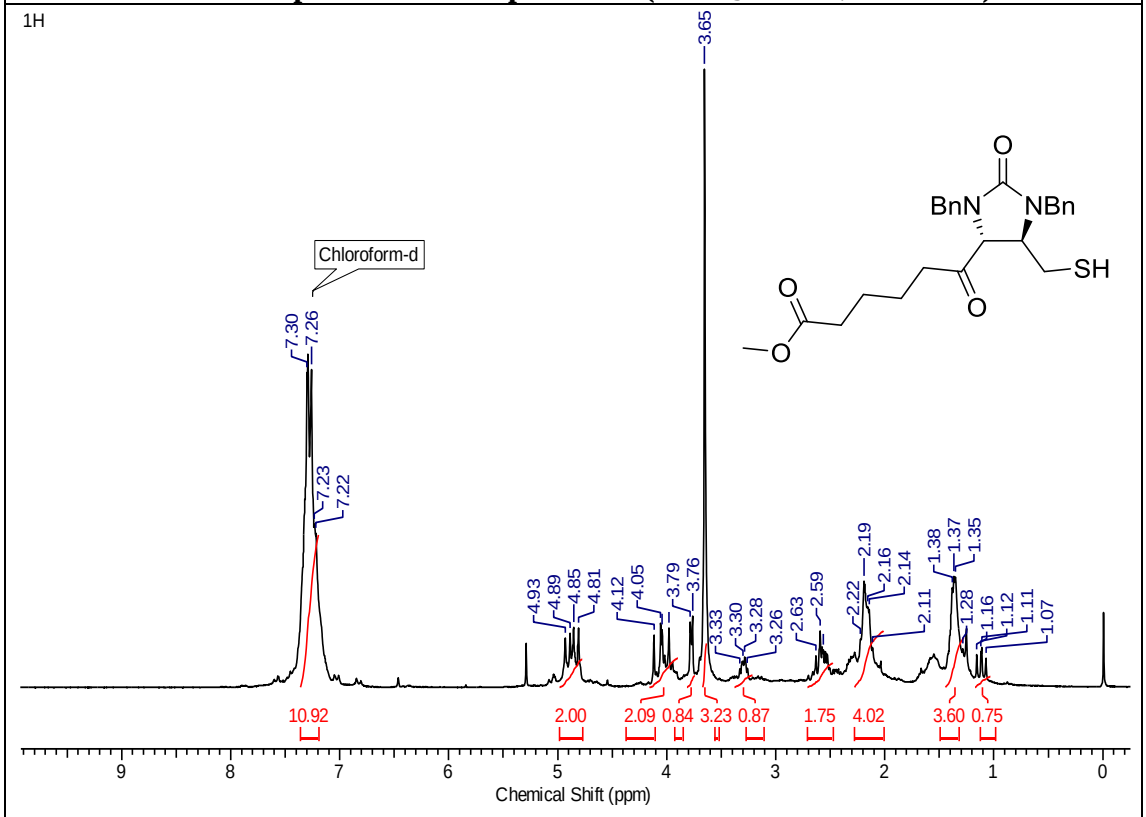
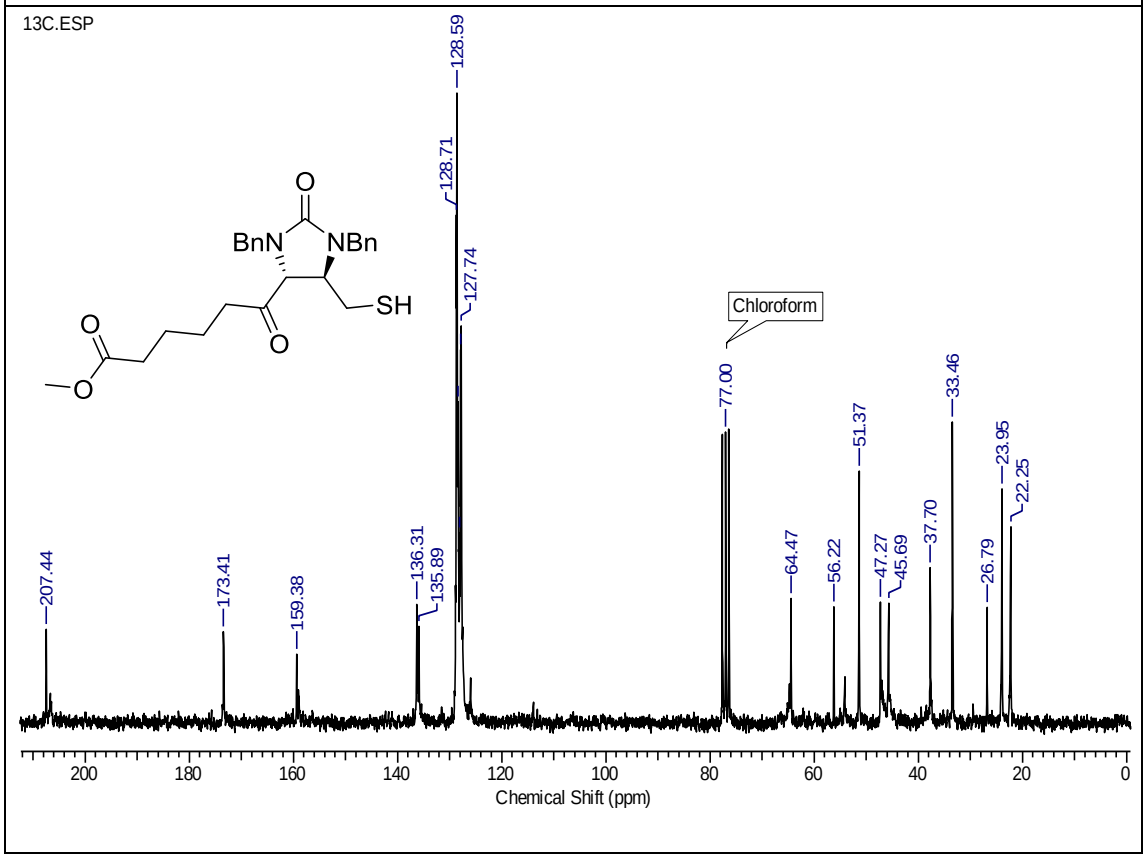
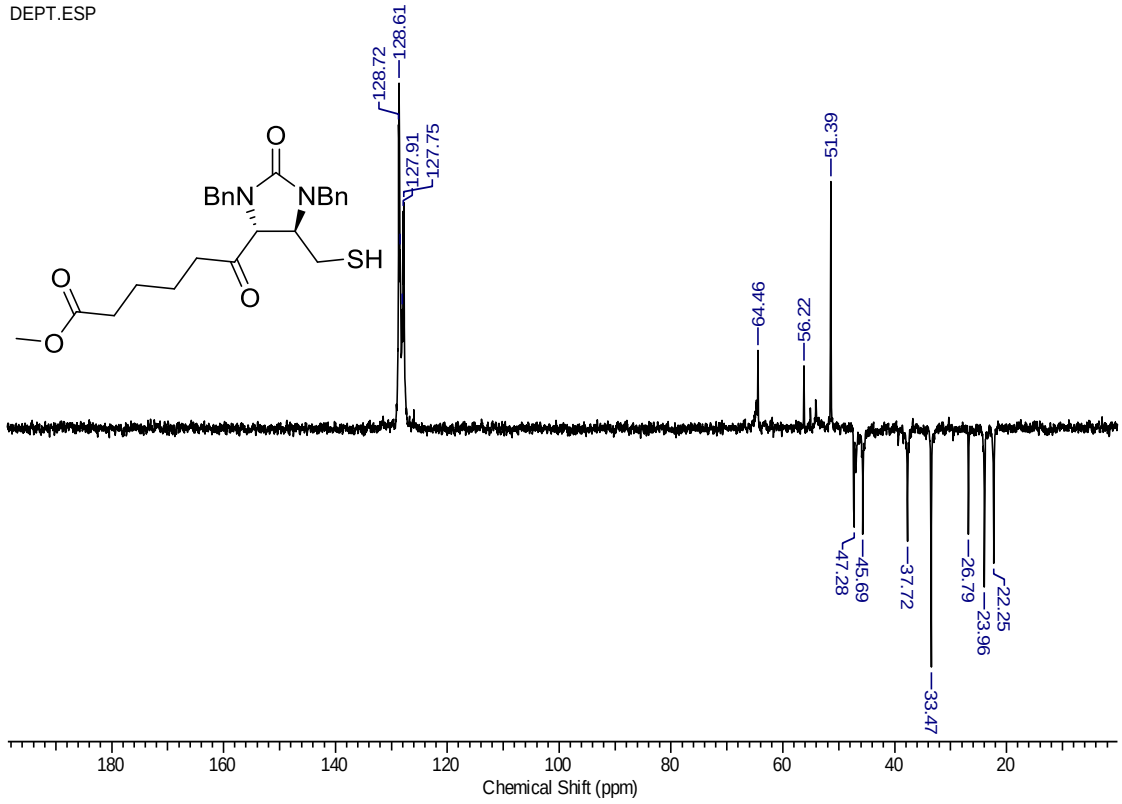


^{13}C NMR spectrum of compound 17 ($CDCl_3$ + CCl_4, 50 MHz)



DEPT spectrum of compound 17 ($CDCl_3$ + CCl_4, 50 MHz)



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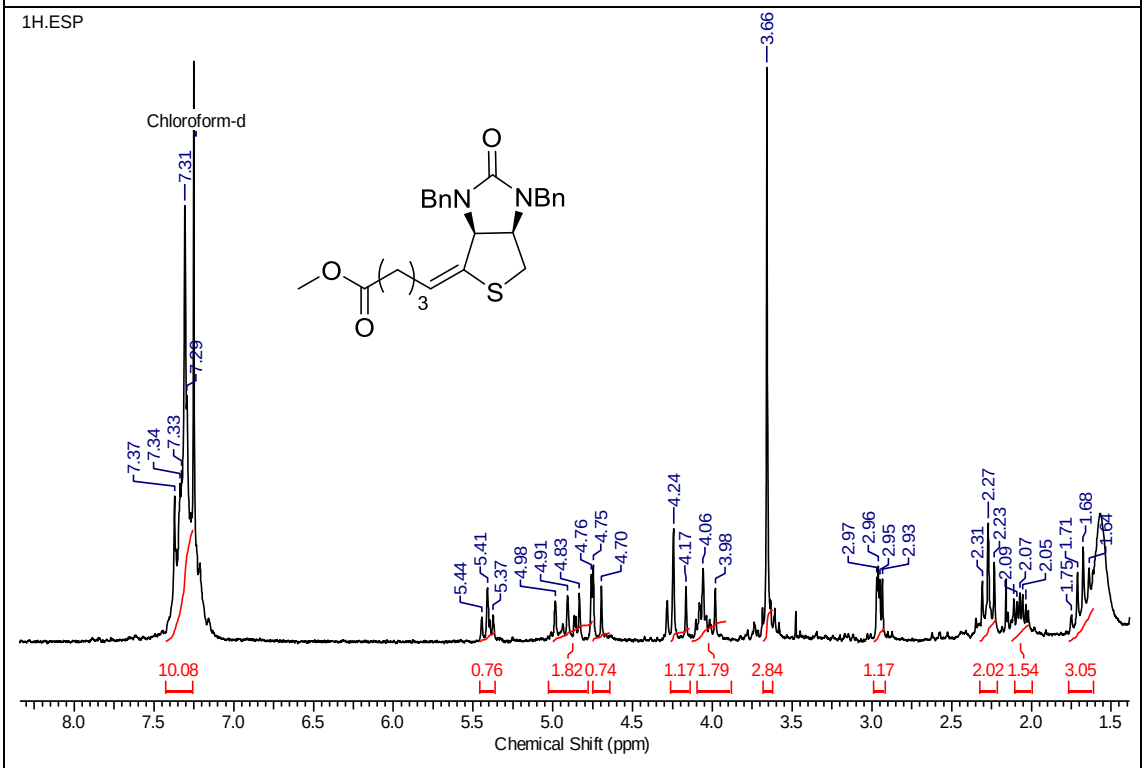

1.2.8 References

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10. Enantiomeric excess (*% ee*) was determined by Chiral HPLC analysis (Chiralcel OJ-H (250×4.6 mm), mobile phase: isopropanol: pet. ether = 7.5: 92.5, wave length = 220 nm, flow rate = 1 ml/min).
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Chapter 1. Synthetic Studies towards D-(+)-Biotin

Section 3

Formal Synthesis of Biotin via Epoxidation

1.3.1 Summary

The present section deals with the formal synthesis of biotin. New expedient and short synthesis of biotin has been achieved from the common starting material *viz* (*E*)-ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate derivative.

1.3.2 Introduction

As described in section I of this chapter the synthesis of biotin is a good synthetic challenge in both industry and academia. Biotin is a large-scale commercial product, hence it was decided to shorten the sequence of reaction and also avoid the use of hazardous chemical like sodum azide to introduce amine functionality. In keeping with the interest in the expedient construction of the ureido ring, it was settled to apply epoxidation and its opening with amine for the efficient synthesis of biotin.

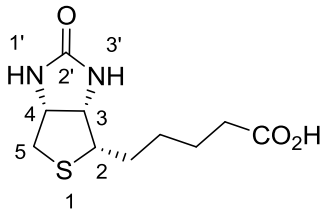


Figure 1. Structure of biotin (**1**)

Epoxides are versatile and important intermediates in organic chemistry.[1] The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. The regio-chemistry in epoxide-opening reactions of 2,3-epoxy alcohols depend on the steric and electronic factors in the substrates and on reaction conditions. Nucleophilic substitution under neutral and basic conditions occurs preferentially from the less substituted side in an S_N2 manner, where the configuration of the attacked carbon is inverted. Nucleophilic attack under acidic conditions occurs at the more substituted side in an S_N2 manner. With sterically unbiased epoxy alcohols or their *O*-protected derivatives, epoxide opening with nucleophiles occurs preferentially at C-3 (Figure 2).[2]

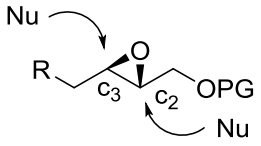
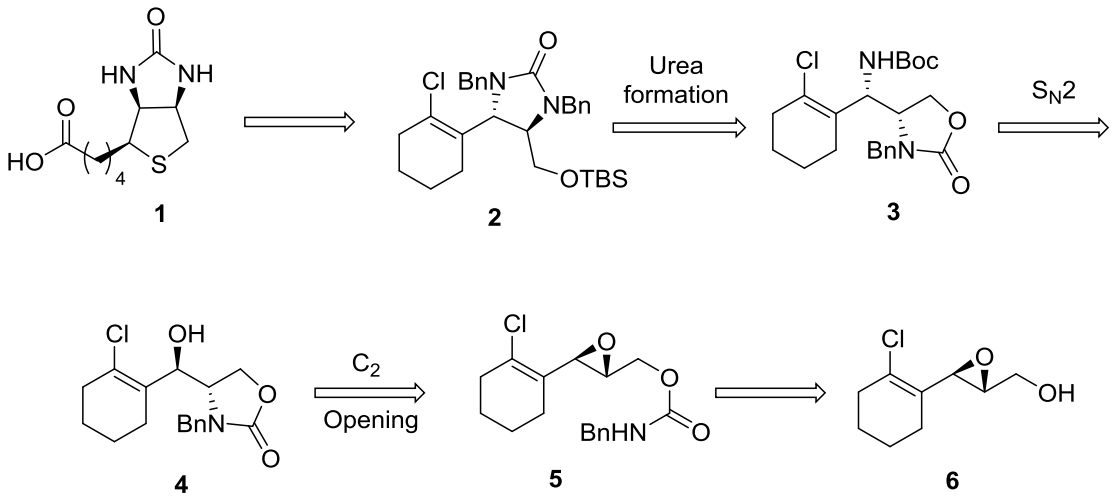


Figure 2

1.3.3 Present work

Owing to their ring strain, epoxides are very prone to nucleophilic ring opening reactions with various nucleophiles.[3] Taking account of this, retrosynthesis for intermediate **2** is as evidenced in Scheme 1. Conversion of **2** to biotin **(1)** was already discussed in previous section of this chapter. The intermediate **2** could be accessed from diamine **3** by urea formation. The diamine could be obtained from hydroxyl compound **4** through S_N2 displacement by nucleophile. The hydroxyl compound **4** in turn could be derived from epoxide **6** through standard synthetic transformations.

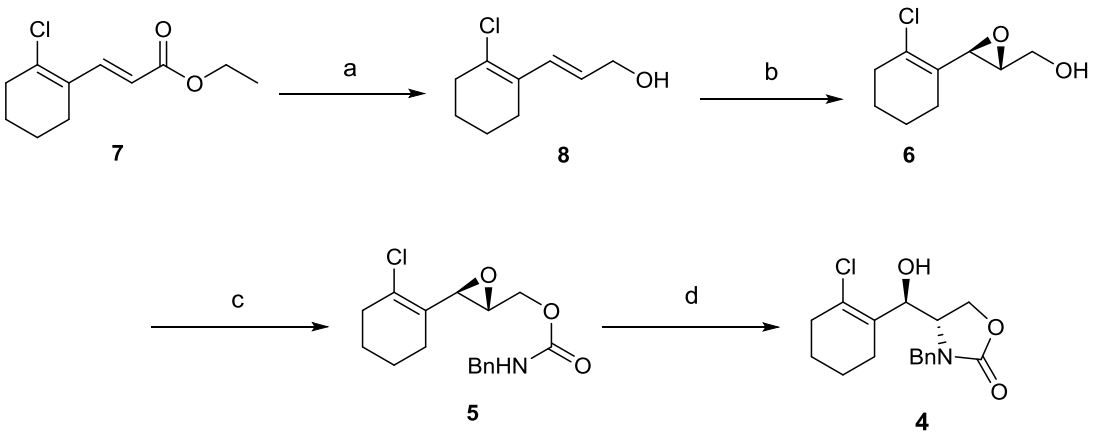


Scheme 1. *Retrosynthetic analysis for biotin **1***

1.3.4 Results and discussion

According to retrosynthetic analysis, the cabamate **5** was synthesized from epoxy alcohol **6** and which in turn synthesized from (*E*)-ethyl 3-(2-chlorocyclohex-1-en-1-yl)acrylate (**7**). The synthesis started from the same unsaturated ester **7** (For preparation refer chapter 1, section 2). Unsaturated ester **7** was reduced by using DIBAL-H to furnish allylic alcohol **8**, followed by epoxidation with *m*-CPBA and NaH_2PO_4 to get epoxy alcohol **6**. The crude epoxide **6** was treated by benzyl isocynate and pyridine in DCM to provide epoxy carbamate **5**. The subsequent intramolecular ring opening of **5** required extensive experimentation.[4,5] Ultimately, the use of sodium hexamethyldisilazide in THF provided the desired oxazolidinone **4** in 63% yield (over four steps).[4] The IR spectrum of compound **4** showed strong bands

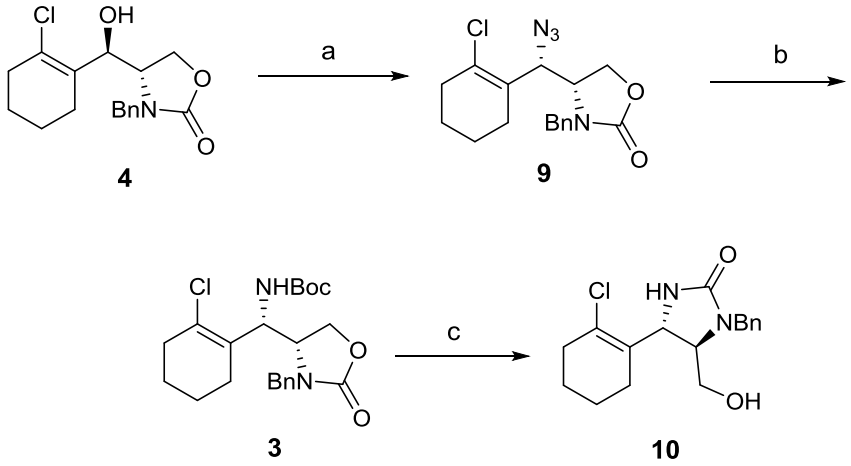
at 3370 and 1749 cm^{-1} indicating the presence of hydroxyl and carbamate functionalities. ^{1}H NMR spectrum of compound **4** showed set of multiplets appeared at δ 1.52 - 1.82 and 2.29 - 2.48 integrating for five protons and three protons which were attributed to cyclohexene ring protons while doublets appeared at δ 4.27 and 4.74 corresponding to methylene protons of -CO-NR-$\underline{CH_2}$-Ph group. ^{13}C NMR spectrum showed the signals that appeared at δ 46.4 and 159.2 corresponding to carbon of (-CO-NR-$\underline{CH_2}$-Ph and -$\underline{CO}$-NR-CH_2-Ph) carbamate functionality. Additionally DEPT experiment also showed the presence of six CH_2 and seven CH supporting the formation of **4**. Finally, peak at *m/z* 343.95 $(M+Na)^+$ in its mass spectrum confirmed the formation of **4** (Scheme 2).



Scheme 2. *Reagents and conditions: a) DIBAL-H, DCM, -20 °C, 2 h; b) m-CPBA, NaH_2PO_4, DCM, 0 °C, 45 min; c) BnNCO, Py, DCM, rt, 12 h; d) NaHMDS, THF, 0 °C, 30 min, 63% (over four steps).*

The hydroxyl group of **4** was activated as the methanesulfonate ester. Displacement with potassium phthalimide was attempted but it failed. Hence it was displaced by sodium azide as nitrogen containing nucleophile to provide azido oxazolidinone **9** in 80% yield over two steps.[6] The IR spectrum of azido oxazolidinone **9** showed strong bands at 2103 and 1755 cm^{-1} indicating the presence of azide and carbamate functionalities respectively. Peak at δ 5.06 in its ^{1}H-NMR spectrum appeared as a doublet accounting for one proton adjacent to azide group. Its ^{13}C-NMR spectrum showed characteristic peak at δ 158.6 which was assigned to carbonyl carbon of cabamate functionality. In its DEPT spectrum CH and CH_2 carbons appeared at chemical shifts in accordance with the structure of **9**. Further, peak at *m/z* 347.41 $(M+H)^+$ in its mass spectrum confirmed the formation of **9**.

Azide was reduced under Staudinger reaction condition and amine was protected with $(Boc)_2O$ anhydride in THF: H_2O system (1:1), gave **3** in 89% yield over two steps. The IR spectrum of **3** displayed a strong absorption bands at 1809 and 1755 cm^{-1} indicating the presence of carbamate functionalities while absence of absorption at 2103 cm^{-1} indicated azide reduction. ^1H NMR spectrum of compound **3** showed the presence of a new singlet which appeared at δ 1.47 integrating for nine protons which was attributed to Boc group. ^{13}C NMR spectrum showed the signals that appeared at δ 28.4, 80.4 and 155.3 corresponding to carbons of Boc group [NH-CO-O-C($\underline{CH_3}$), NH-CO-O-$\underline{C}(CH_3)$ and NH-$\underline{CO}$-O-C(CH_3) respectively]. Additionally, DEPT experiment also showed the presence of six CH_2 and six CH carbons supporting the formation of **3**. Further, peak at *m/z* 443.12 $(M+Na)^+$ in its mass spectrum confirmed the formation of **3**.

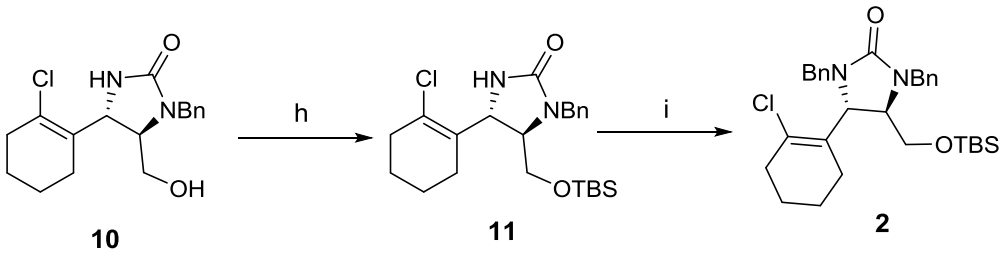


Scheme 3. *Reagents and conditions: a) i) MsCl, Et_3N, DCM, 0 ^oC, 30 min, ii) NaN_3, DMF, RT, overnight, 80% (over two steps); b) i) Ph_3P, THF, RT, 2 h, ii) $(Boc)_2O$, THF:H_2O (1:1), 89% (over two steps) c) NaH, THF, 80 ^oC, 6 h. 92%.*

On treatment with NaH, **3** was converted into uera **10** with free primary hydroxyl in 92 % yield. The IR spectrum of compound **10** showed the absence of bands at 1809 and 1755 cm^{-1} for acyclic *tert*-butyl carbamate and cyclic carbamate indicating the hydrolysis during reaction, also showed broad band at 3337 cm^{-1} indicating the presence of hydroxyl group. The ^1H NMR spectrum of compound **10** showed the absence of singlet at δ 1.47 integrating for nine protons attributed to Boc group indicating the hydrolysis during reaction. ^{13}C NMR and DEPT NMR spectra

were also in good agreement with the structure of compound **10**. Further, peak at *m/z* 343.04 $(M+Na)^+$ in its mass spectrum confirmed the formation of **10** (Scheme 3).

The primary hydroxyl group of **10** was protected as silyl ether by using TBSCl, imidazole and DMAP in DCM gave **11** in 93% yield. The IR spectrum of compound **11** showed the absence of broad band at 3337 cm^{-1} for hydroxyl group indicating the protection of hydroxyl group. Its ^{1}H-NMR spectrum showed peaks as singlets at δ 0.00 and 0.84 for six and nine protons respectively clearly showing the presence of TBS group. Further, peak at *m/z* 436.21 $(M+H)^+$ in its mass spectrum confirmed the formation of **10** (Scheme 4).



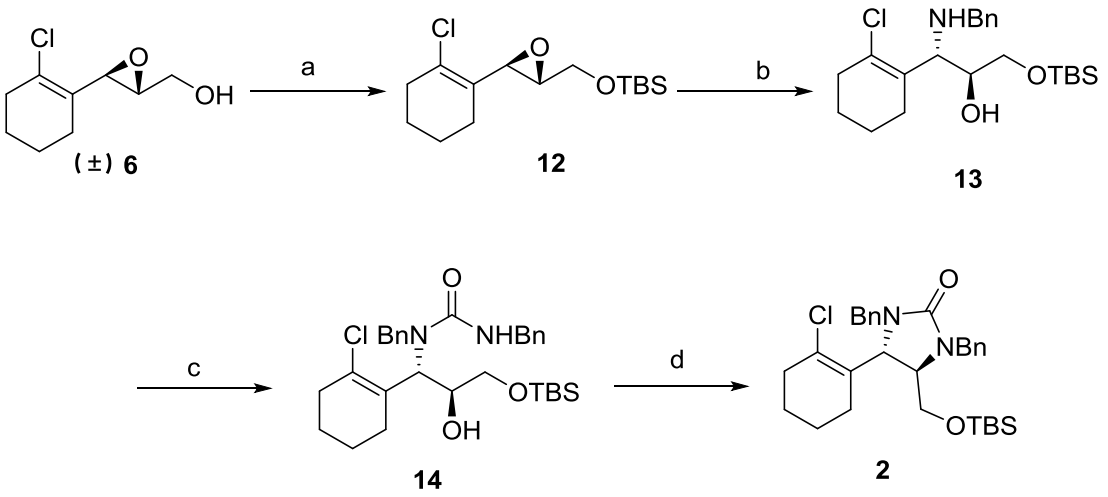
10 **11** **2**

Scheme 4. *Reagents and conditions: a) TBSCl, imdazole, DMAP, DCM, 24 h, 93%; b) NaH, BnBr, THF, 0 ^oC, 3 h, 95%.*

On treatment with sodium hydride, benzyl bromide **11** was converted to dibenzyl protected imidazolidone **2** in 95% yield. The IR spectrum of **2** displayed the strong absorption band at 1698 cm^{-1} indicating the presence of cyclic urea functionality. The ^{1}H NMR spectrum showed four upfield signals at δ 4.00, 4.08, 4.52 and 4.93 for four protons and multiplet at δ 7.24-7.32 for ten protons indicating that the presence of two benzyl groups. This was further confirmed by its ^{13}C NMR and DEPT NMR spectra, which showed a -CH_2- carbon singlets at δ 46.2 and 46.9 for the benzylic carbon. Finally, the structure of compound **2** was confirmed by HRMS analysis (Scheme 4). Fallowing this route, it was able to access biotin in 22 steps and in 7.6% overall yield but this was not an azide free synthesis.

As Biotin has promising biological activity, was an attempt made to reduce number of steps and avoid use of sodium azide to make it a practical method. Keeping these things in mind, synthesis was modified. As depicted in Scheme 5**,** the synthesis began with the same starting material unsaturated ester **7**. Reduction of ester and epoxidation was done by the same procedure as described in Scheme 2. The primary hydroxyl group of epoxy alcohol **6** was protected as its silyl ether by using TBSCl,

imidazole and DMAP in DCM to furnish **12** in 93% yield. The IR spectrum of compound **12** showed the presence of band at 1255 cm^{-1} for C-O-C ether group. Its ^{1}H-NMR spectrum showed peaks as singlets at δ 0.08, 0.09 and 0.91 for three, three and nine protons respectively clearly showing the presence of TBS group. Peaks at δ -5.3, -5.2 and 26.0 in its ^{13}C-NMR spectrum corresponded to TBS group. Further, peak at *m/z* 303.77 $(M+H)^{+}$ in its mass spectrum confirmed the formation of **12** (Scheme 4).



Scheme 5*: Reagents and conditions: a) TBSCl, imidazole, DMAP, DCM, 24 h, 93%; b) $BnNH_2$, $ZrCl_4$, 30 min, RT, 85%; c) BnNCO, DCM, RT, 12 h, 95%; d) KH, TsCl, HMPA, THF, 0 ^{o}C, 1 h, 81%.*

Epoxide **12** on ring opening aminolysis by using zirconium chloride with benzyl amine, afforded aminol **13** in 50% yield.[7] The IR spectrum of **13** showed broad band at 3341 cm^{-1} indicating the presence of hydroxyl group. ^{1}H NMR spectrum of compound **13** showed the presence of a new multiplet which appeared at δ 7.12 - 7.38 integrating for five protons which was attributed to benzyl protons. ^{13}C NMR spectrum showed the signals that appeared at δ 46.9, 127.3, 128.3 and 128.8 corresponding to carbons of Bn group (N-CH_2-Ph). Additionally, DEPT experiment also showed the presence of six CH_2 and eight CH carbons supporting the formation of **13**. Further, peak at *m/z* 411.09 $(M+H)^{+}$ in its mass spectrum confirmed the formation of **13**.

Aminol **13** on treatment with benzyl isocyanate gave acyclic urea **14** in 95% yield. The IR spectrum of compound **14** showed strong bands at 3337 and 1686 cm^{-1} indicating the presence of hydroxyl and urea functionalities. ^{1}H NMR spectrum of

compound **14** showed the presence of a two multiplets which appeared at δ 7.13 - 7.24 and 7.25 - 7.37 integrating for total ten protons which was attributed for two Bn protons. ^{13}C NMR spectrum showed the signals that appeared at δ 45.0 and 50.8 corresponding to carbons of Bn group (N-CH_2-Ph). Additionally, DEPT experiment also support the formation of **14**. Further, peak at *m/z* 565.11 $(M+ Na)^+$ in its mass spectrum confirmed the formation of **14.**

Selective cyclization to the imidazolidone **2** was accomplished under carefully controlled conditions by combining 5 equivalent of potassium hydride and 1.2 equivalent of *p*-toluenesulfonyl chloride in the presence of 30 equivalent of hexamethylphosphoramide in THF which resulted in imidazolidone **2** in 40% yield (Scheme 5).[8]

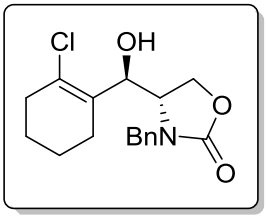
The imidazolidone **2** thus obtained was identical with an authentic sample, with respect to IR, NMR and mass spectra prepared by a different route. Since the conversion of imidazolidone **2** to biotin (**1)** has been reported in previous section, this constitutes a formal synthesis of biotin.

3.3.5 Conclusion

The crucial intermediate for biotin has been accessed from two different strategies to reduce number of steps and avoid use of hazardous sodium azide.

3.2.6 Experimental

3-Benzyl-4-(2-chlorocyclohex-1-en-1-yl)(hydroxy)methyl)oxazolidin-2-one (4):



To a stirred solution of *α,β*-unsaturated ester **7** (3.0 gm, 14.01 mmol) in dry CH_2Cl_2 (30 mL) was added DIBAL-H (28.03 mL, 28.03 mmol, 1 M solution in toluene) at -20 °C slowly over period of 15 min and stirred for another 2 h. TLC showed complete conversion of ester to allylic alcohol **8**. Reaction was quenched by careful addition of pre-cooled MeOH (3 mL) and allowed to warm to 0 °C. Roche's salt (saturated solution of sodium potassium tartarate, 30 mL) was added and stirred for 0.5 h after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and used as such for next reaction.

To a cold (0 °C), magnetically stirred solution of allylic alcohol **8** (2.3 g, 12.36 mmol) in distilled DCM (20 mL), NaH_2PO_4 (2.2 g, 18.54 mmol) was added followed by 60% *m*-CPBA (4.25 g, 14.83 mmol) added portion wise and stirred for 45 min at same temperature. The reaction was quenched with solid $NaHCO_3$ and stirred for further 15 min. The reaction mixture was extracted with DCM (3 × 10 mL) and the combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

To a solution of epoxy alcohol **6** (2.0 g, 10.63 mmol) in anhydrous DCM (20 mL) was added pyridine (1.65 mL, 21.26 mmol) followed by addition of BnNCO (1.69 mL, 12.76 mmol) at room temperature under nitrogen atmosphere. The reaction was allowed to stir at same temperature for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and used as such in the next reaction without further purification.

To a cold (0 °C), magnetically stirred solution of epoxy carbamate **5** (1.00 g, 3.11 mmol) in dry THF (10 mL), NaHMDS (1.95 mL, 3.73 mmol) was added dropwise and sirred for 30 min. The reaction was quenched by addition of aq. NH_4Cl, the

aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the crude residue was purified using flash chromatography (SiO_2, 3:7 EtOAc: Pet. ether) to furnish **4** as a white solid.

***R_f*:** 0.4 (Pet. ether-ethyl acetate, 7:3).

Yield: 0.88 g, 63% (over four steps).

MF: $C_{17}H_{20}ClNO_3$, **MW:** 321.80.

MP: 110-112 ºC.

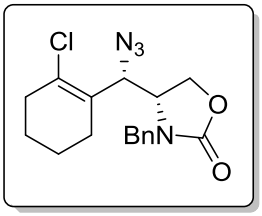
IR ($CHCl_3$, cm^{-1}): νmax 3370 (broad), 2928, 1749, 1416.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.52 - 1.82 (m, 5 H), 2.29 - 2.48 (m, 3 H), 3.30 (brs, 1 H), 3.83 (ddd, *J*=8.8, 6.2, 2.7 Hz, 1 H), 4.18 (t, *J*=8.8 Hz, 1 H), 4.27 (d, *J*=15.1 Hz, 1 H), 4.44 (dd, *J*=8.8, 6.2 Hz, 1 H), 4.74 (d, *J*=15.1 Hz, 1 H), 5.01 (s, 1 H), 7.26 - 7.40 (m, 5 H)**.**

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 22.0, 23.6, 25.8, 34.0, 46.4, 58.0, 62.8, 67.4, 128.0, 128.3 (2 C), 128.9 (2 C), 129.0, 131.8, 136.3, 159.2.

MS (ESI): m/z = 343.95 $(M + Na)^+$.

4-Azido(2-chlorocyclohex-1-en-1-yl)methyl)-3-benzyloxazolidin-2-one (9): To a



stirred solution of carbamate **4** (0.7 g, 2.18 mmol) in dry DCM (10 mL) was added Et_3N (0.9 mL, 6.54 mmol) at 0 ºC, followed by dropwise addition of mesyl chloride (0.35 mL, 4.36 mmol) and the reaction mixture was stirred for 30 min under nitrogen atmosphere. The reaction mixture was diluted with DCM (10 mL) and washed with saturated solution of sodium bicarbonate (20 mL) and water (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *O*-mesyl compound.

To a solution of crude *O*-mesyl compound in anhydrous DMF (10 mL) was added sodium azide (0.71 g, 10.9 mmol) and the reaction mixture was stirred at room temparature for 12 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (75 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography (SiO_2, 1:9 EtOAc: Pet. ether) to afford azide **6** as a gummy liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 8:2).

Yield: 0.6 g, 80%.

MF: $C_{17}H_{19}ClN_4O_2$, **MW:** 346.12.

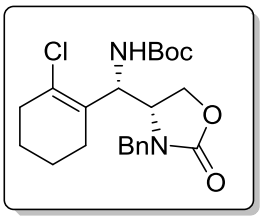
IR ($CHCl_3$, cm^{-1}): νmax 3032, 2859, 2103, 1755, 1496.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 - 1.70 (m, 5 H), 2.20 - 2.55 (m, 3 H), 3.58 - 3.65 (m, 1 H), 3.90 - 3.97 (m, 1 H), 4.07 - 4.15 (m, 1 H), 4.49 (d, *J* = 15.1 Hz, 1 H), 4.89 (d, *J* = 15.1 Hz, 1 H), 5.06 (d, *J* = 9.3 Hz, 1 H), 7.32 - 7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 23.4, 25.5, 34.0, 47.7, 54.6, 64.1, 66.5, 126.8, 127.9, 128.4 (2 C), 128.8 (2 C), 135.3, 136.3, 158.6.

MS (ESI): m/z = 347.41 $(M+H)^+$.

***tert*-Butyl-3-benzyl-2-oxooxazolidin-4-yl)(2-chlorocyclohex-1-en-1-yl)methyl)**



carba- mate (3): To a solution of azide **9** (0.6 g, 1.73 mmol) in diethyl ether (20 mL) was added PPh_3 (1.14 g, 4.33 mmol) and stirred until the evolution of nitrogen gas ceased (2 h). After completion of reaction, the solvent was evaporated under reduced pressure to obtain the amine as thick oil. The crude amine was dissolved in THF:H_2O (1:1, 20 mL) and to this solution was added $(Boc)_2O$ (0.56 mL, 2.57 mmol) and stirred overnight (12 h). The reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified on flash chromatography using silica gel (3:7 EtOAc: Pet. ether 2:8 EtOAc: Pet. ether) to afford carbamate **9** as a solid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 1:1).

Yield: 0.64 g, 89%.

MF: $C_{22}H_{29}ClN_2O_4$, **MW:** 420.93.

MP: 102-104 ºC

IR ($CHCl_3$, cm^{-1}): νmax 3421, 2983,1809, 1755, 1478.

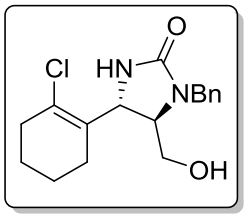
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.47 (s, 9 H), 1.57 - 1.83 (m, 4 H), 2.05 - 2.13 (m, 2 H), 2.42 (brs, 2 H), 3.82 - 3.88 (m, 1 H), 4.00 - 4.26 (m, 3 H), 4.82 (brs, 1 H),

4.99 (d, *J* = 14.9 Hz, 1 H), 5.05 - 5.23 (m, 1 H), 7.17 - 7.26 (m, 2 H), 7.28 - 7.40 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 22.2, 23.3, 27.8, 28.4 (3 C), 34.2, 47.9, 54.9, 55.0, 65.4, 80.4, 128.2 (3 C), 128.9, 129.0 (2 C), 135.7, 155.3, 159.4.

MS (ESI): m/z = 443.12 $(M+Na)^+$.

1-Benzyl-4-(2-chlorocyclohex-1-en-1-yl)-5-(hydroxymethyl)imidazolidin-2-one



(10): To a suspension of NaH (0.1 g, 4.28 mmol) in dry DMF (10 mL) at 0 °C was added a solution of **3** (0.6 g, 1.42 mmol) in DMF (2 mL) and refluxed for 6 h. The reaction mixture was cooled and quenched by addition of water (30 mL) and was extracted with ethyl acetate (3 ×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was removed *in vacuo*. The crude compound was purified by flash column chromatography (SiO_2, 7:3 EtOAc: Pet. ether) to afford **10** as solid.

***R_f*:** 0.4 (Pet. ether-ethyl acetate, 2:8).

Yield: 0.42 g, 92%.

MF: $C_{17}H_{21}ClN_2O_2$, **MW:** 320.82.

MP: 86-88 ºC.

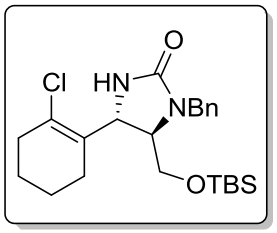
IR ($CHCl_3$, cm^{-1}): νmax 3337 (broad), 2925, 2824, 1676, 1537.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 - 1.71 (m, 5 H), 1.94 (brs, 1 H), 2.11 - 2.22 (m, 1 H), 2.28 - 2.42 (m, 2 H), 3.18 - 3.34 (m, 1 H), 3.60 (d, *J*=11.0 Hz, 1 H), 3.77 (d, *J*=10.0 Hz, 1 H), 4.26 (d, *J*=15.2 Hz, 1 H), 4.59 (brs, 1 H), 4.71 (d, *J*=15.2 Hz, 1 H), 4.97 (d, *J*=6.6 Hz, 1 H), 7.29 - 7.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 23.6, 25.0, 34.2, 45.8, 52.3, 60.9, 61.3, 127.8, 128.2 (2 C), 128.8 (2 C), 130.1, 131.5, 137.2, 161.7.

MS (ESI): m/z = 343.04 $(M+Na)^+$.

1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(2-chlorocyclohex-1-en-1-yl)imidazolidin-2-one (11): To a solution of alcohol **10** (0.4 g, 1.25 mmol) in anhydrous DCM (10 mL) was added imidazole (0.26 g, 3.75 mmol) followed by addition of TBSCl (0.38 g, 2.50 mmol) and DMAP (cat.) at 0 ^{o}C under nitrogen atmosphere. The reaction was allowed to stir at room



temperature for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3:7 EtOAc: Pet. ether) to afford TBS ether **11** as a colorless liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 3:2).

Yield: 0.5 g, 93%.

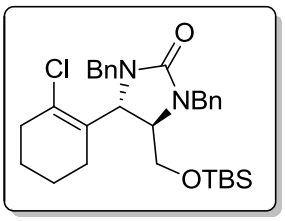
MF: $C_{23}H_{35}ClN_2O_2Si$, **MW:** 435.08.

IR ($CHCl_3$, cm^{-1}): νmax 2925, 2824, 1674, 1514, 1438.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.00 (s, 6 H), 0.84 (s, 10 H), 1.43 - 1.72 (m, 5 H), 1.96 - 2.34 (m, 3 H), 3.09 - 3.27 (m, 1 H), 3.46 - 3.73 (m, 2 H), 4.00 (d, *J*=15.0 Hz, 1 H), 4.42 (s, 1 H), 4.72 (dd, *J*=5.7, 1.9 Hz, 1 H), 4.82 (d, *J*=15.0 Hz, 1 H), 7.09 - 7.37 (m, 5 H).

MS (ESI): m/z = 436.21 $(M+H)^+$.

1,3-Dibenzyl-4-(((tert-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl)imidazolidin-2-one (2): To the suspension of 60% NaH (68 mg, 1.74 mmol)



(washed with dry petroleum ether 2-3 times) in dry THF (10 mL) was added TBS ether **11** (0.5 g, 1.16 mmol) in anhydrous THF (5 mL) at 0 ^oC and stirred for 10 min. Then benzyl bromide (0.17 mL, 1.39 mmol) was added drop wise and reaction mixture was stirred for 3 h at room temperature. On completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (2 × 10 mL) and washed with water followed by brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 1:9 EtOAc: Pet. ether) to afford benzyl protected cyclic urea **2** as a white solid.

***R_f*:** 0.6 (Pet. ether-ethyl acetate, 8:2).

Yield: 0.57 g, 95%.

MF: $C_{30}H_{41}ClN_2O_2Si$, **MW:** 525.19.

Melting Point: 87-89 °C.

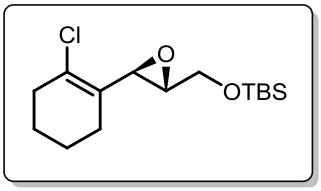
IR ($CHCl_3$, cm^{-1}): νmax 2930, 2857, 1698, 1448, 1252, 1119.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ -0.04 (s, 3 H), -0.02 (s, 3 H), 0.83 (s, 9 H), 1.08 - 1.65 (m, 6 H), 2.18 - 2.24 (m, 2 H), 3.09 (dt, *J*=6.1, 3.9 Hz, 1 H), 3.40 - 3.67 (m, 2 H), 4.00 (d, *J*=12.3 Hz, 1 H), 4.08 (d, *J*=12.3 Hz, 1 H), 4.52 (d, *J*=15.0 Hz, 1 H), 4.56 - 4.59 (m, 1 H), 4.93 (d, *J*=15.0 Hz, 1 H), 7.24 - 7.32 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ -5.6, -5.5, 18.3, 21.7 (2C), 23.6, 25.9 (3C), 34.3, 46.2, 46.9, 56.6, 57.8, 62.6, 127.3, 127.4, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 130.2, 131.1, 137.4, 137.4, 160.3.

HRMS (ESI) $[M+Na]^+$ calcd for $C_{30}H_{41}O_2N_2ClNaSi$ 547.2518, found 547.2523.

***tert*-Butyl-3-(2-chlorocyclohex-1-en-1-yl)oxiran-2-yl)methoxy)dimethylsilane**



(12): To a solution of epoxy alcohol **6** (800 mg, 4.25 mmol) in anhydrous DCM (10 mL) was added imidazole (434 mg, 6.38 mmol) followed by addition of TBSCl (770 mg, 5.10 mmol) and DMAP (cat.) at 0 ^oC under nitrogen atmosphere. The reaction was allowed to stir at room temperature for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 04:96 EtOAc: Pet. ether) to afford TBS ether **12** as a colorless liquid.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 19:1).

Yield: 1.22 g, 93%.

MF: $C_{15}H_{27}ClO_2Si$, **MW:** 302.91.

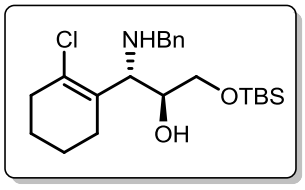
IR ($CHCl_3$, cm^{-1}): νmax 2932, 2883, 1531, 1454, 1255.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.08 (s, 3 H), 0.09 (s, 3 H) 0.91 (s, 9 H), 1.57 - 1.85 (m, 5 H), 1.94 - 2.16 (m, 1 H), 2.29 - 2.45 (m, 2 H), 3.03 - 3.10 (m, 1 H), 3.59 - 3.75 (m, 1 H), 3.81 - 4.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ -5.3, -5.2, 18.4, 21.7, 23.7, 24.2, 26.0 (3 C), 34.2, 54.4, 57.1, 63.4, 77.0, 128.8, 131.9.

MS (ESI): m/z = 303.77 $(M+H)^+$.

1-(Benzylamino)-3-((*tert*-butyldimethylsilyl)oxy)-1-(2-chlorocyclohex-1-en-1-



yl)propan-2-ol (13): $ZrCl_4$ (42 mg, 5 mol%) was added to a magnetically stirred mixture of **12** (1.1 g, 3.64 mmol) and

benzyl amine (0.48 mL, 4.37 mmol) at room temperature under nitrogen. After completion of the reaction (30 min, TLC), the reaction mixture was diluted with Et_2O (15 mL) and the precipitated catalyst was separated by decantation of the supernatant ethereal solution. The catalyst was washed with Et_2O (10 mL) and the combined ethereal solutions were dried (Na_2SO_4) and concentrated in vacuo and the crude residue was directly adsorbed on simple silica gel and was purified using flash chromatography (SiO_2, 1:19 EtOAc: Pet. ether) to furnish the aminol **13** as a colorless liquid.

***R_f*:** 0.6 (Pet. ether-ethyl acetate, 9:1).

Yield: 1.26 g, 85%.

MF: $C_{22}H_{36}ClNO_2Si$, **MW:** 410.07.

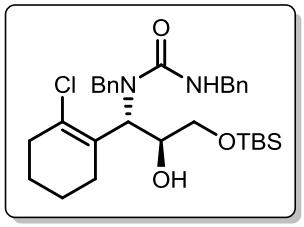
IR ($CHCl_3$, cm^{-1}): vmax 3341 (broad), 2930, 2857, 1683, 1531, 1454.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.00 (m, 6 H), 0.81 (m, 9 H), 1.44 - 1.77 (m, 4 H), 2.25 - 2.94 (m, 4 H), 3.48 - 3.82 (m, 5 H), 4.08 (d, *J*=6.1 Hz, 1 H), 7.12 - 7.38 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ -5.6, -5.5, 18.3, 21.7, 23.6, 25.9 (3 C), 34.3, 46.2, 46.9, 56.6, 57.8, 62.6, 127.3, 128.3 (2 C), 128.8 (2 C), 130.2, 131.1, 137.4.

MS (ESI): m/z = 411.09 $(M+H)^+$.

1,3-Dibenzyl-1-3-((tert-butyldimethylsilyl)oxy)-1-(2-chlorocyclohex-1-en-1-yl)-2-hydroxypropyl)urea (14): To a solution of aminol **13** (1.2 g, 2.93 mmol) in anhydrous DCM (10 mL) was BnNCO (0.47 mL, 3.52 mmol) at room temperature under nitrogen atmosphere. The reaction was allowed to stir at room temperature for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (15 mL) and extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and was purified using flash chromatography (SiO_2, 1:9 EtOAc: Pet. ether) to furnish the urea **4** as a colorless liquid.



***R_f*:** 0.5 (Pet. ether-ethyl acetate, 4:1).

Yield: 1.51 g, 95%.

MF: $C_{30}H_{43}ClN_2O_3Si$, **MW:** 542.21.

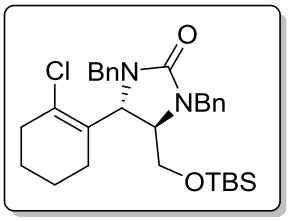
IR ($CHCl_3$, cm^{-1}): vmax 3337, 2925, 2854, 1686, 1537, 1496.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 1.55 - 1.78 (m, 4 H), 2.18 - 2.62 (m, 4 H), 3.56 - 3.74 (m, 2 H), 3.94 (brs, 1 H), 4.24 (d, *J*=4.6 Hz, 1 H), 4.29 - 4.39 (m, 1 H), 4.44 - 4.54 (m, 3 H), 4.96 (d, *J*=4.6 Hz, 1 H), 5.10 (brs, 1 H), 7.17 (m, 2 H), 7.25 - 7.37 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.42, -5.39, 18.2, 22.3, 22.7, 23.6, 25.9 (3 C), 27.8, 34.5, 45.0, 50.8, 61.9, 63.8, 72.6, 126.4 (2 C), 127.1, 127.3 (2 C), 127.3, 128.5 (2 C), 128.8 (2 C), 131.3, 132.1, 139.3, 158.9.

MS (ESI): m/z = 565.11 $(M+Na)^+$.

1,3-Dibenzyl-4-(((tert-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl)imidazolidin-2-one (2): Under an argon atmosphere potassium hydride (35%, 210 mg, 1.84 mmol) was washed with *n*-hexane (10 mL × 2), and to it was added hexamethylphosphoramide (1.8 mL, 11.1 mmol) and solutions of **14** (200 mg, 0.37 mmol) in THF (10 mL) and *p*-TsCl (84 mg, 0.44 mmol) in THF (5 mL) successively at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched by sat. NH_4CI. The entire mixture was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4) and concentrated to leave an oil which was purified by flash chromatography (SiO_2, 1:9 EtOAc: Pet. ether) to afford benzyl protected cyclic urea **2** as a white solid.



***R_f*:** 0.6 (Pet. ether-ethyl acetate, 8:2).

Yield: 157 mg, 81%.

MF: $C_{30}H_{41}ClN_2O_2Si$, **MW:** 525.19.

Melting Point: 87-89 °C.

IR ($CHCl_3$, cm^{-1}): νmax 2930, 2857, 1698, 1448, 1252, 1119.

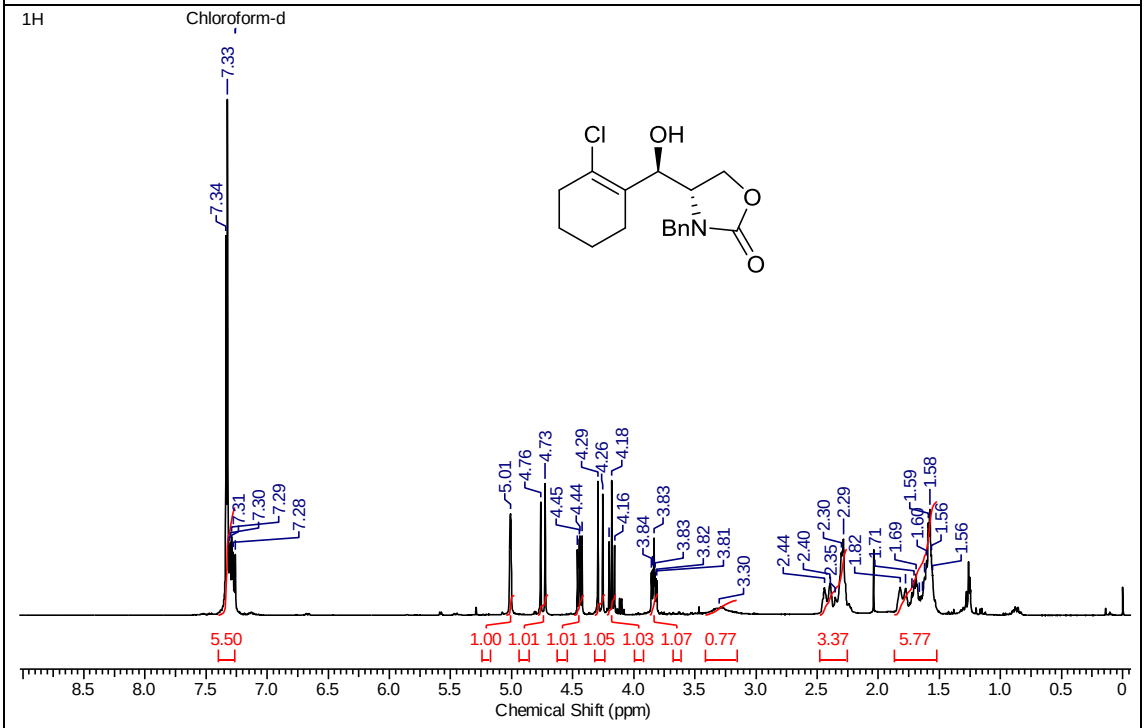
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ -0.04 (s, 3 H), -0.02 (s, 3 H), 0.83 (s, 9 H), 1.08 - 1.65 (m, 6 H), 2.18 - 2.24 (m, 2 H), 3.09 (dt, *J*=6.1, 3.9 Hz, 1 H), 3.40 - 3.67 (m, 2 H), 4.00 (d, *J*=12.3 Hz, 1 H), 4.08 (d, *J*=12.3 Hz, 1 H), 4.52 (d, *J*=15.0 Hz, 1 H), 4.56 - 4.59 (m, 1 H), 4.93 (d, *J*=15.0 Hz, 1 H), 7.24 - 7.32 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ -5.6, -5.5, 18.3, 21.7 (2C), 23.6, 25.9 (3C), 34.3, 46.2, 46.9, 56.6, 57.8, 62.6, 127.3, 127.4, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 130.2, 131.1, 137.4, 137.4, 160.3.

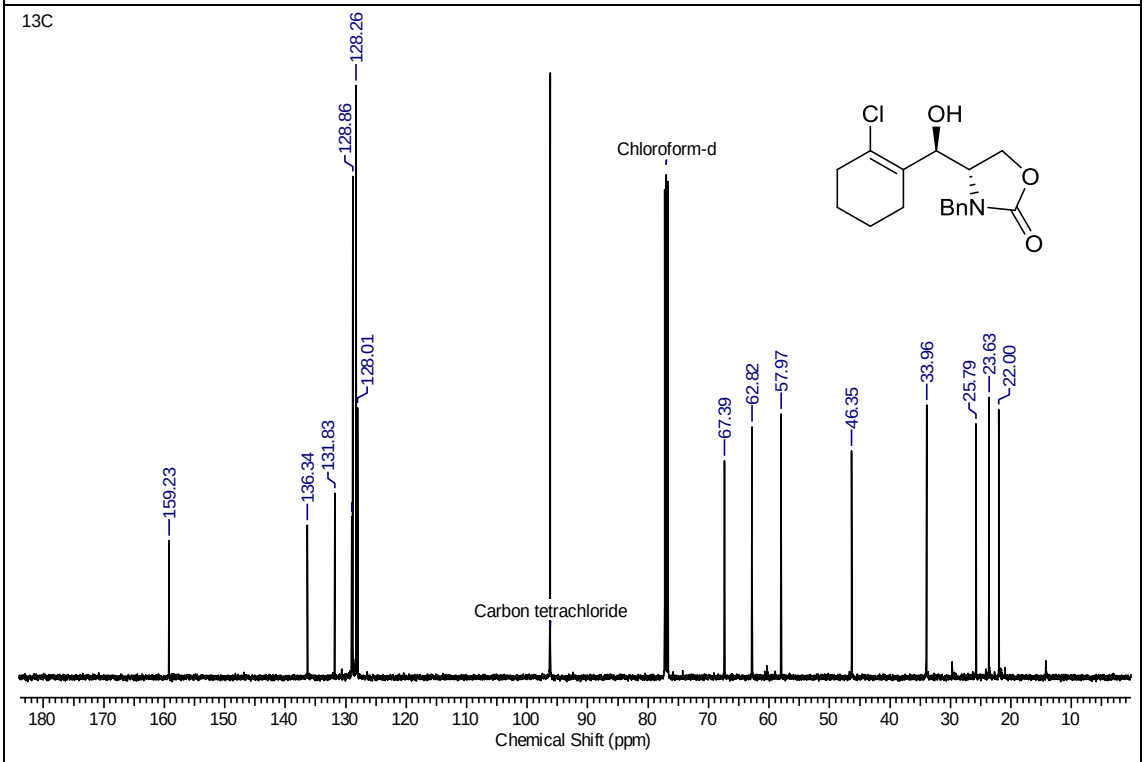
HRMS (ESI) $[M+Na]^+$ calcd for $C_{30}H_{41}O_2N_2ClNaSi$ 547.2518, found 547.2523.

3.3.7 Spectra

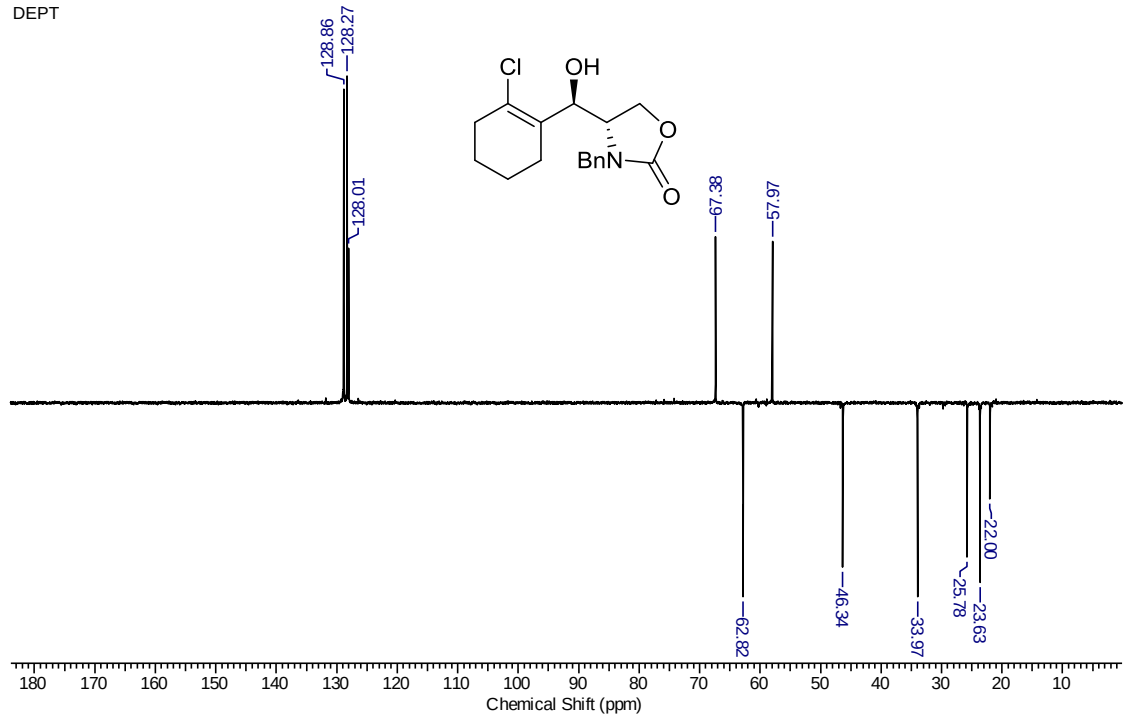
^{1}H NMR spectrum of compound 4 ($CDCl_3$, 400 MHz)



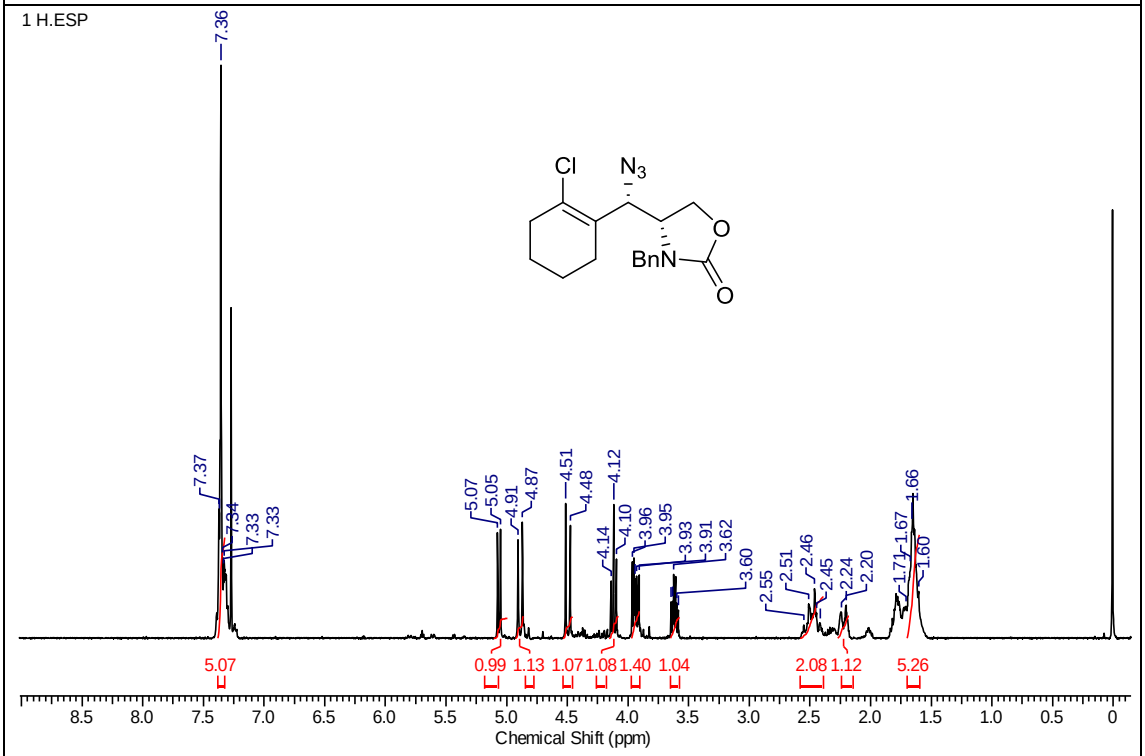
^{13}C NMR spectrum of compound 4 ($CDCl_3$+CCl_4, 125 MHz)



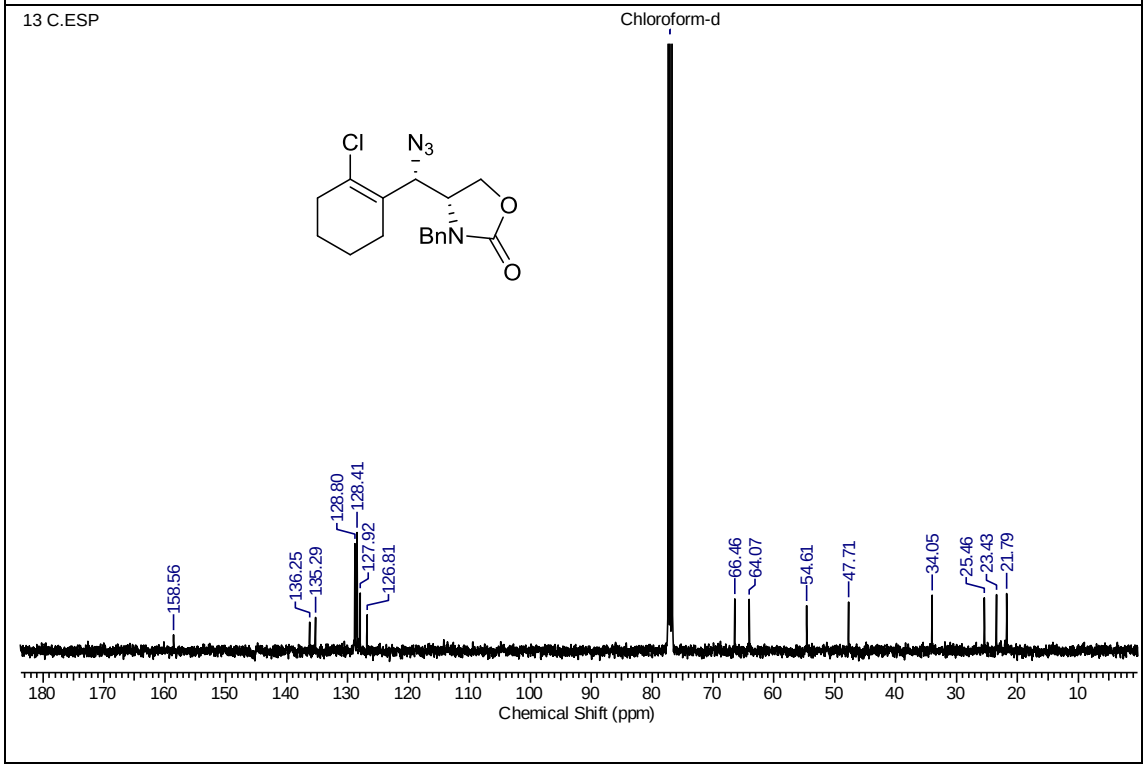
DEPT spectrum of compound 4 ($CDCl_3$+CCl_4, 125 MHz)



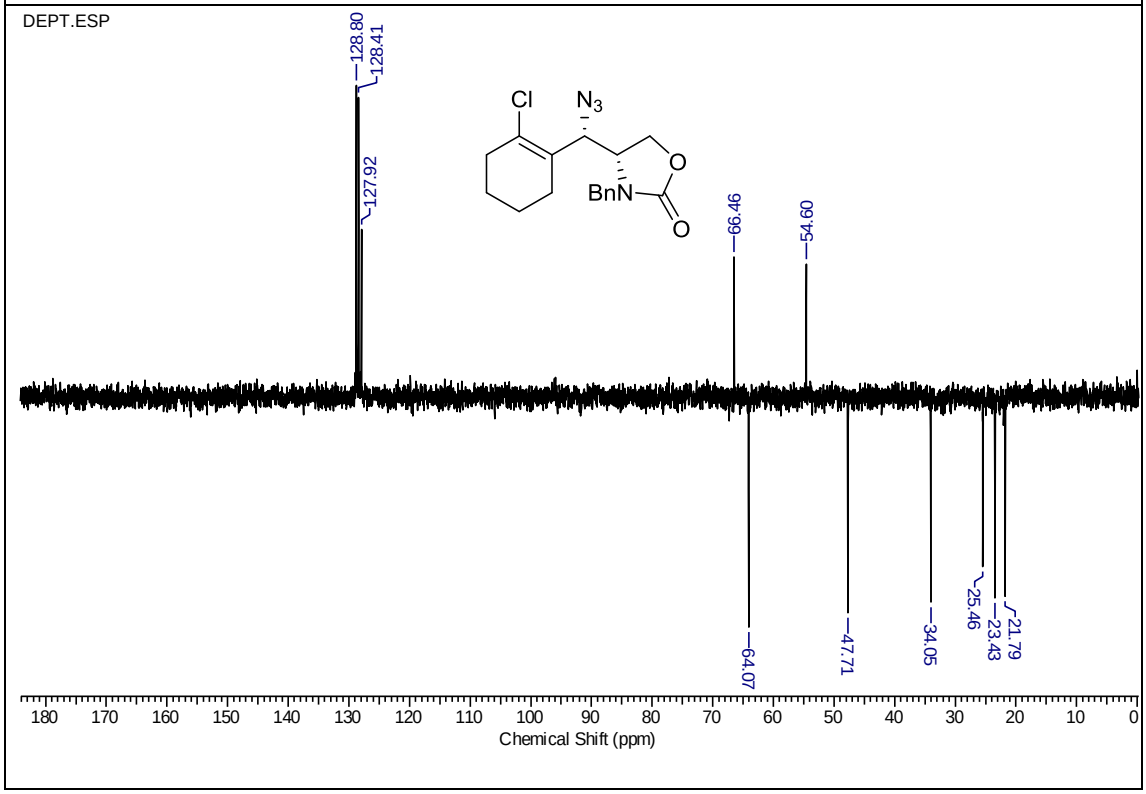
^{1}H NMR spectrum of compound 9 ($CDCl_3$, 400 MHz)



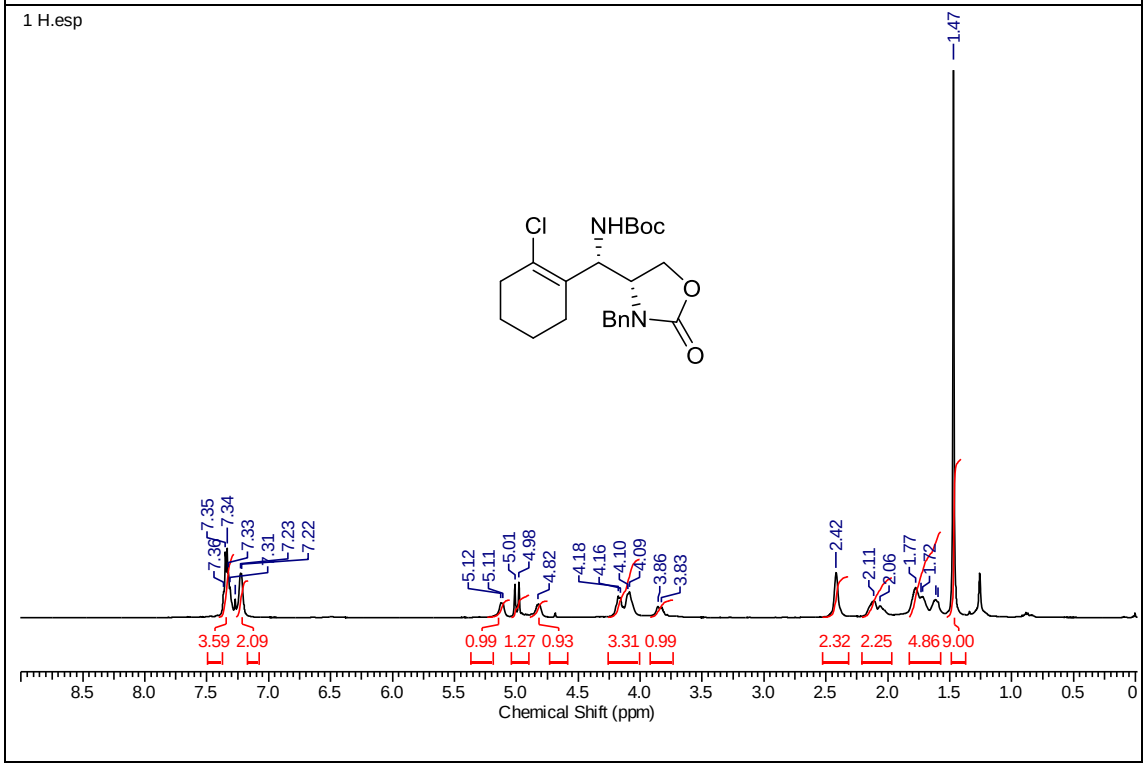
^{13}C NMR spectrum of compound 9 ($CDCl_3$, 100 MHz)



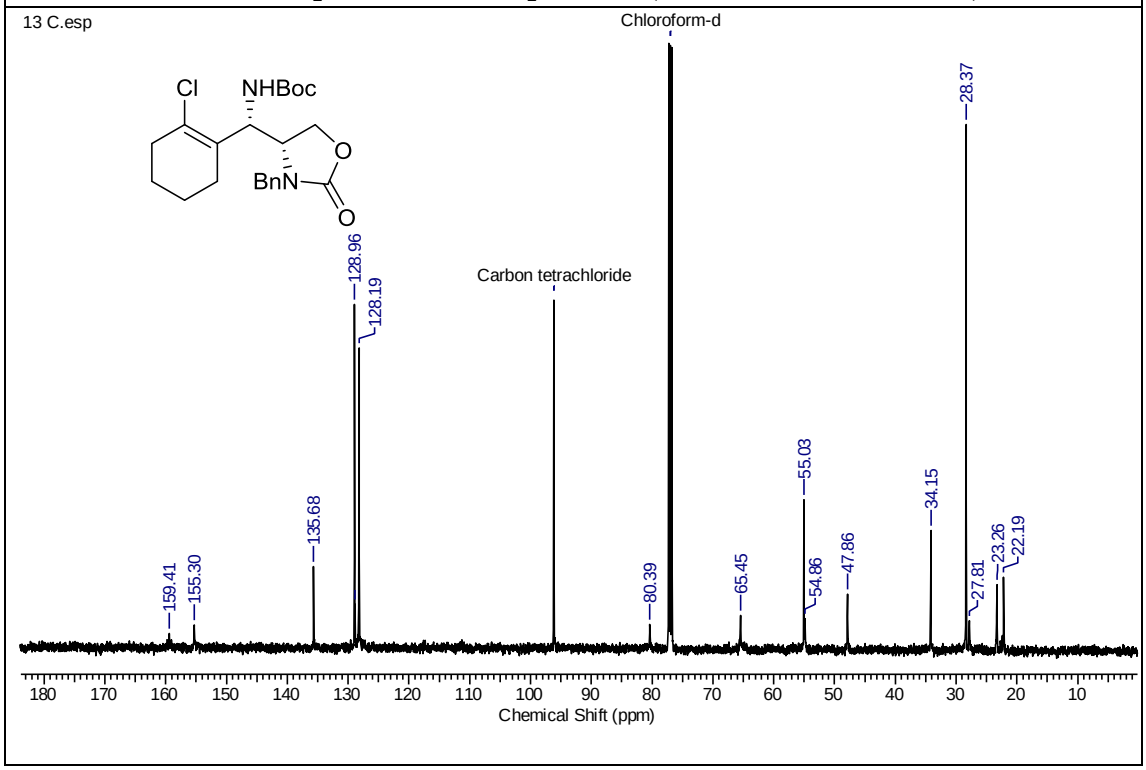
DEPT spectrum of compound 9 ($CDCl_3$, 100 MHz)



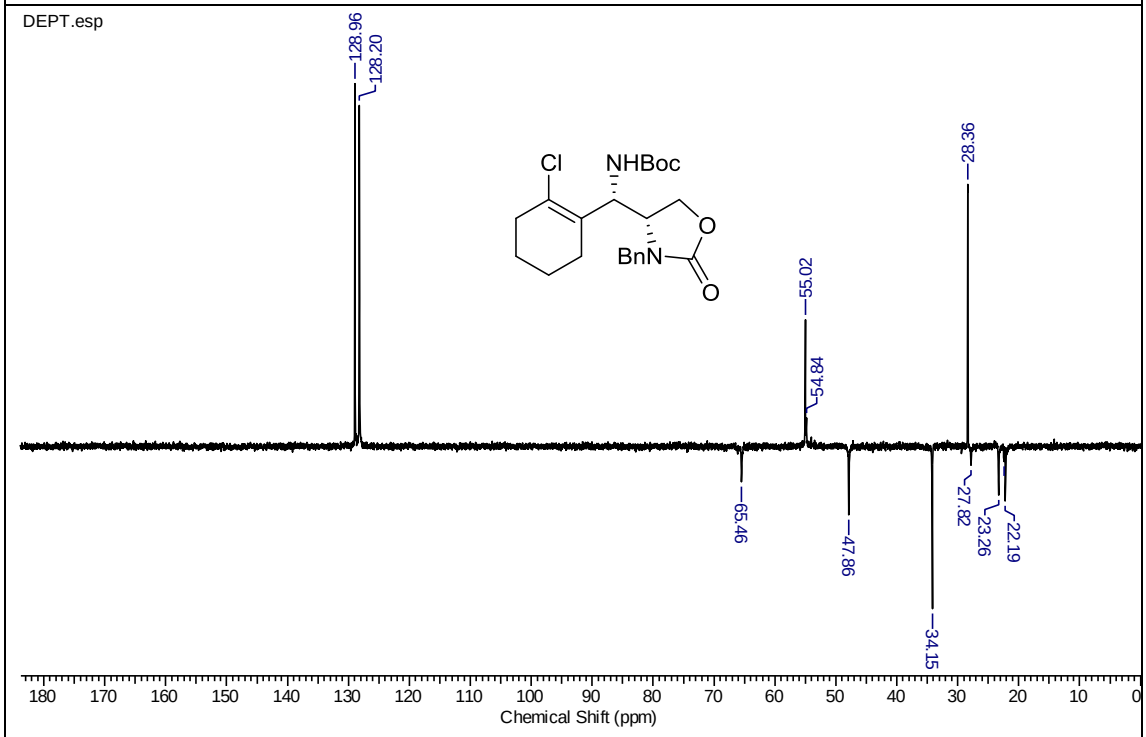
^{1}H NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 500 MHz)



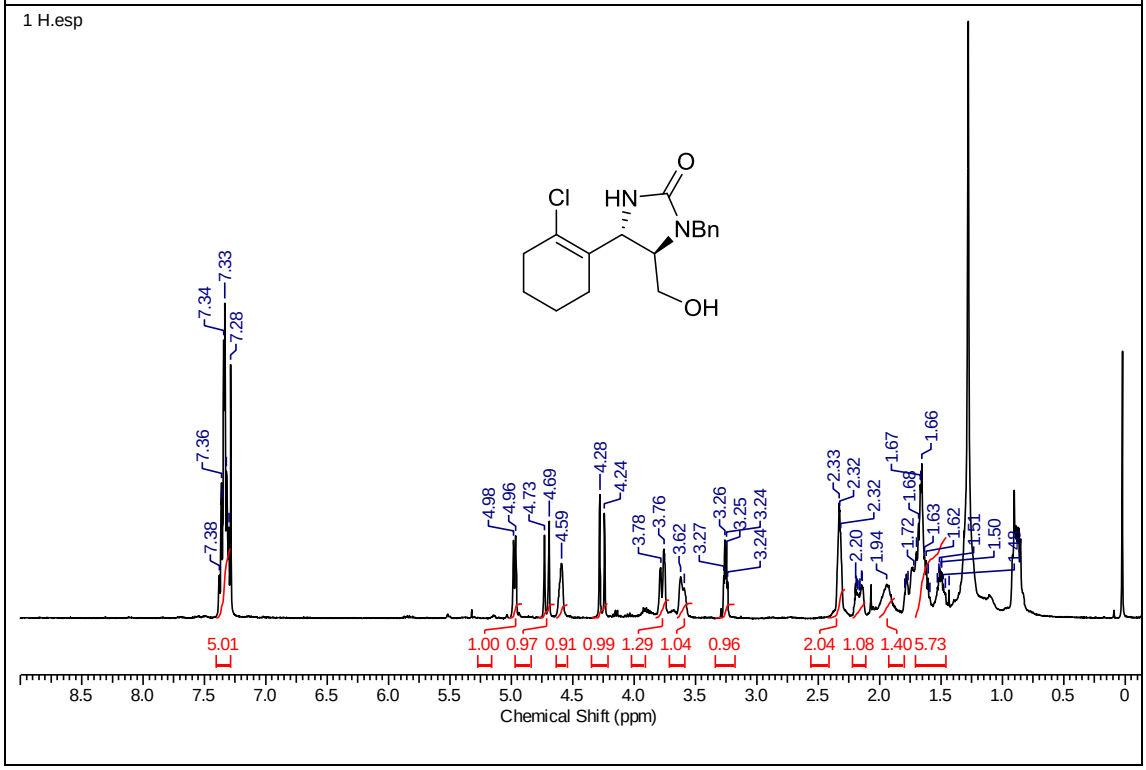
^{13}C NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 125 MHz)



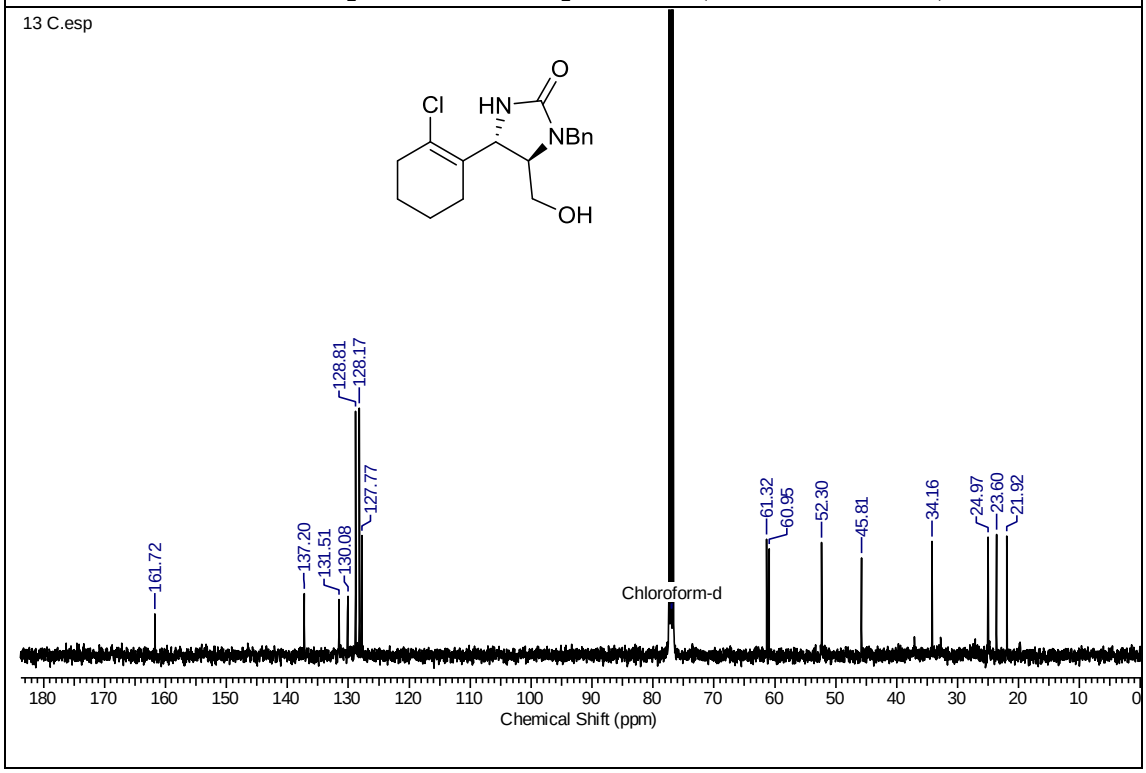
DEPT spectrum of compound 3 ($CDCl_3$+CCl_4, 125 MHz)



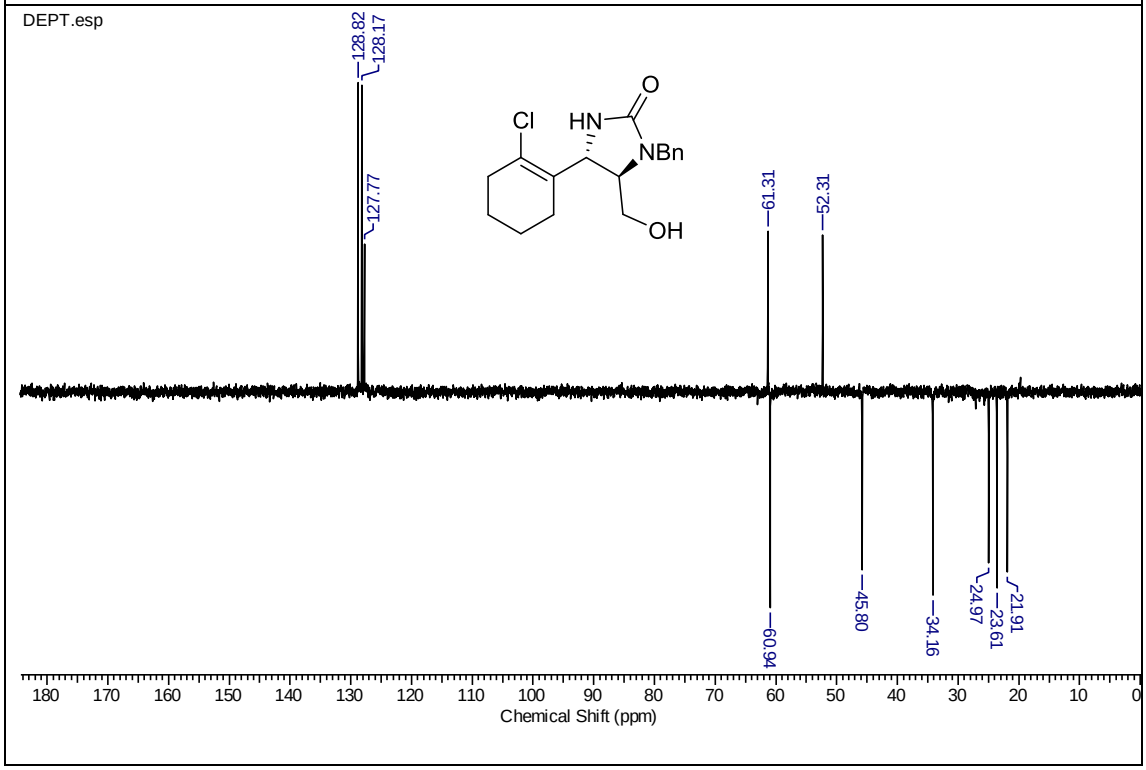
^{1}H NMR spectrum of compound 10 ($CDCl_3$, 400 MHz)



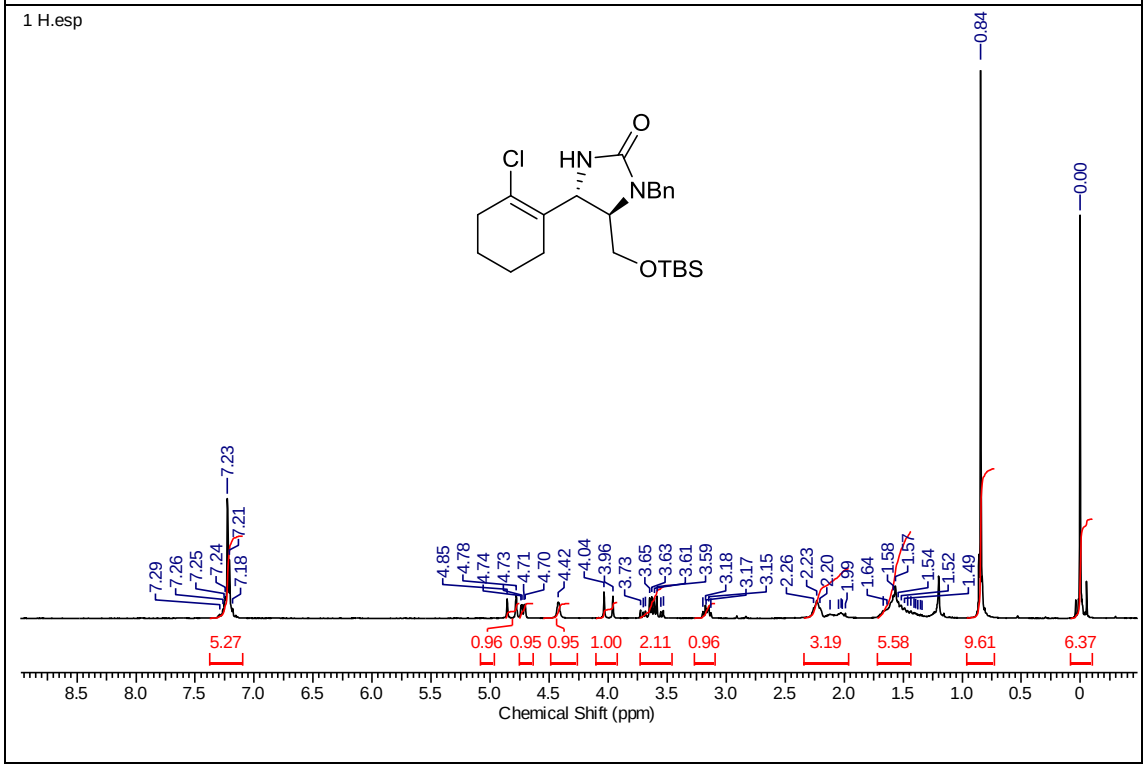
^{13}C NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



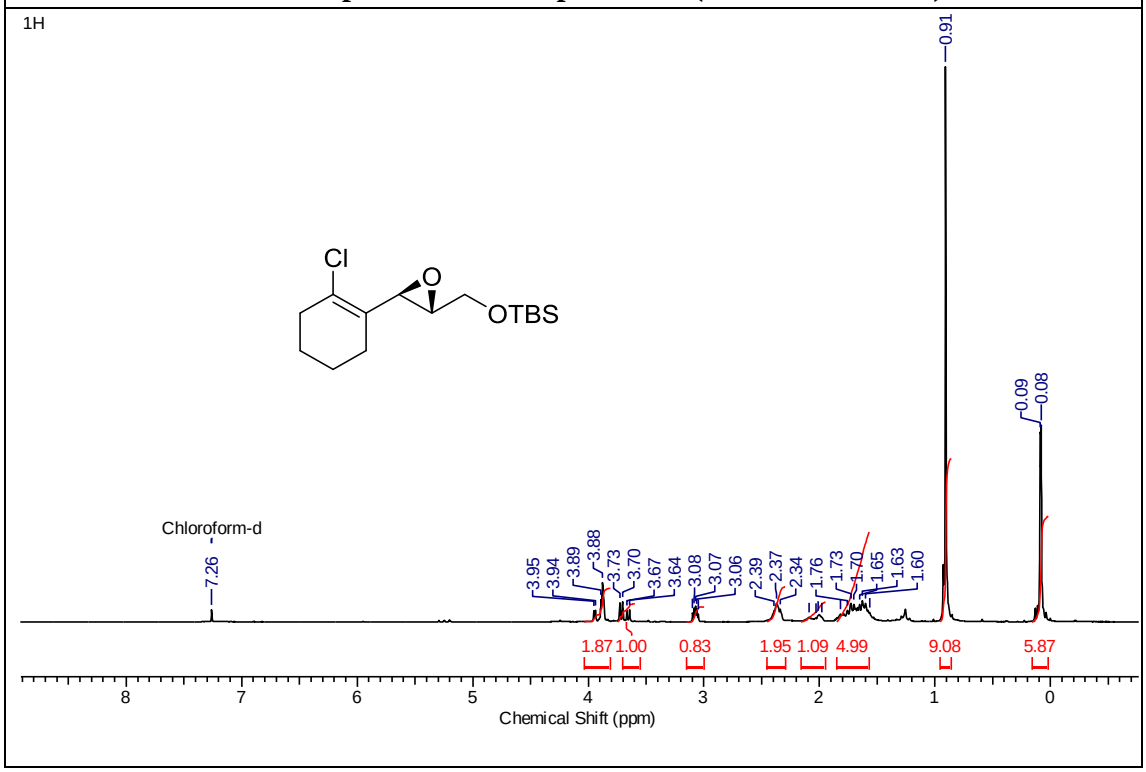
DEPT spectrum of compound 10 ($CDCl_3$, 100 MHz)



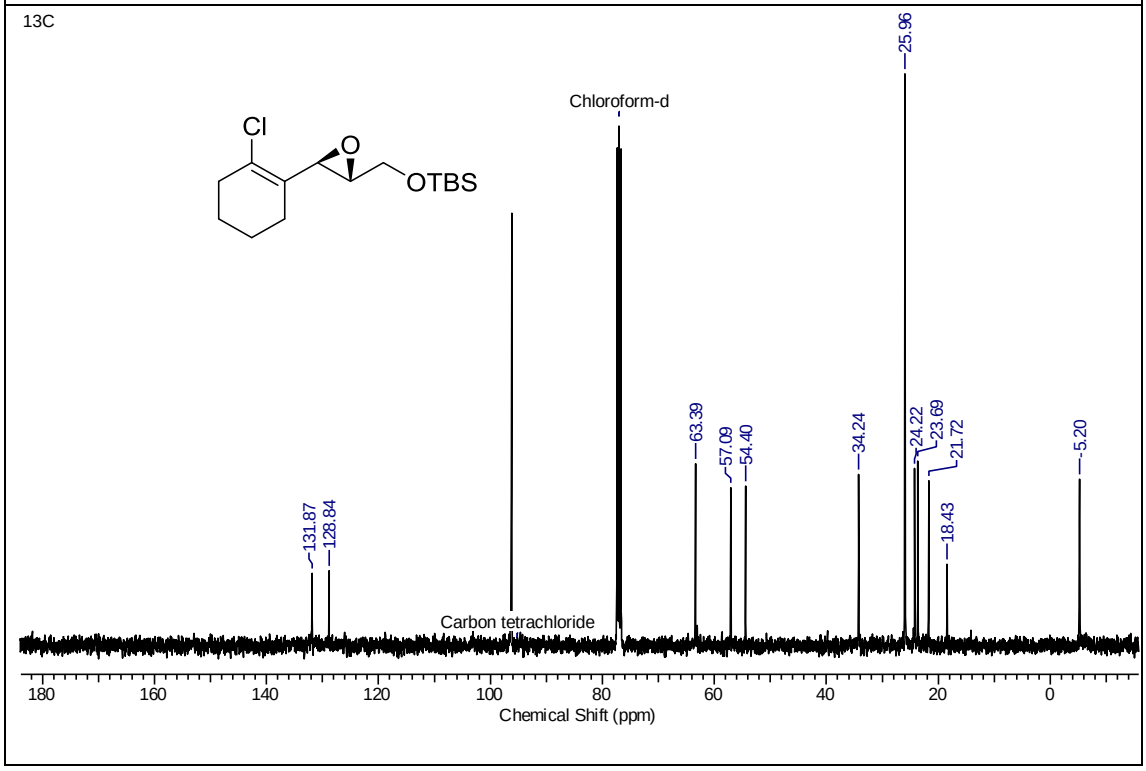
^{1}H NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



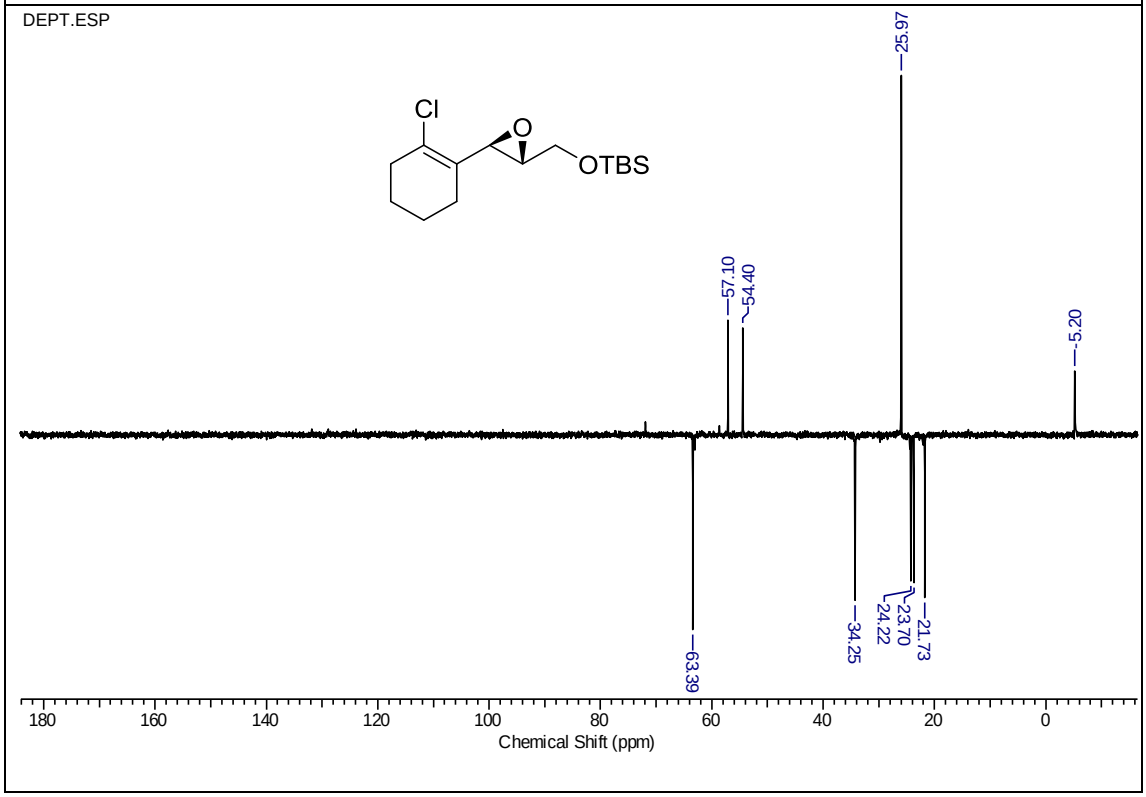
^{1}H NMR spectrum of compound 12 ($CDCl_3$, 200 MHz)



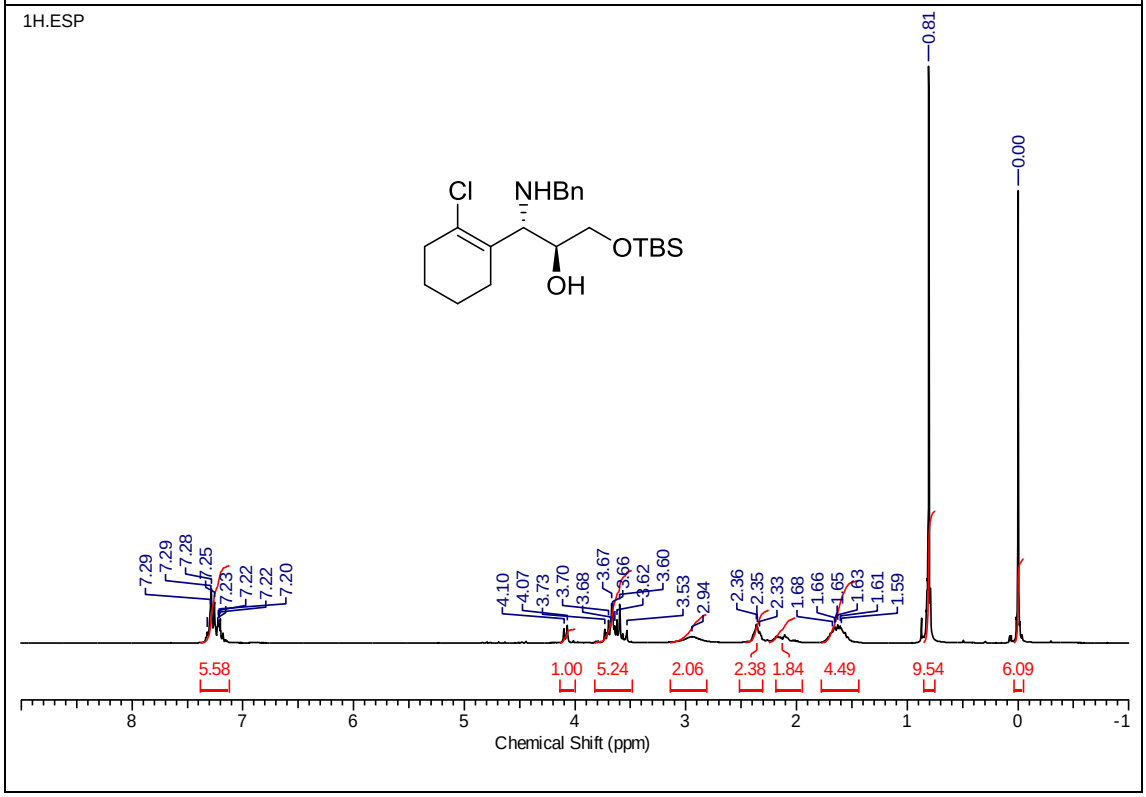
^{13}C NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



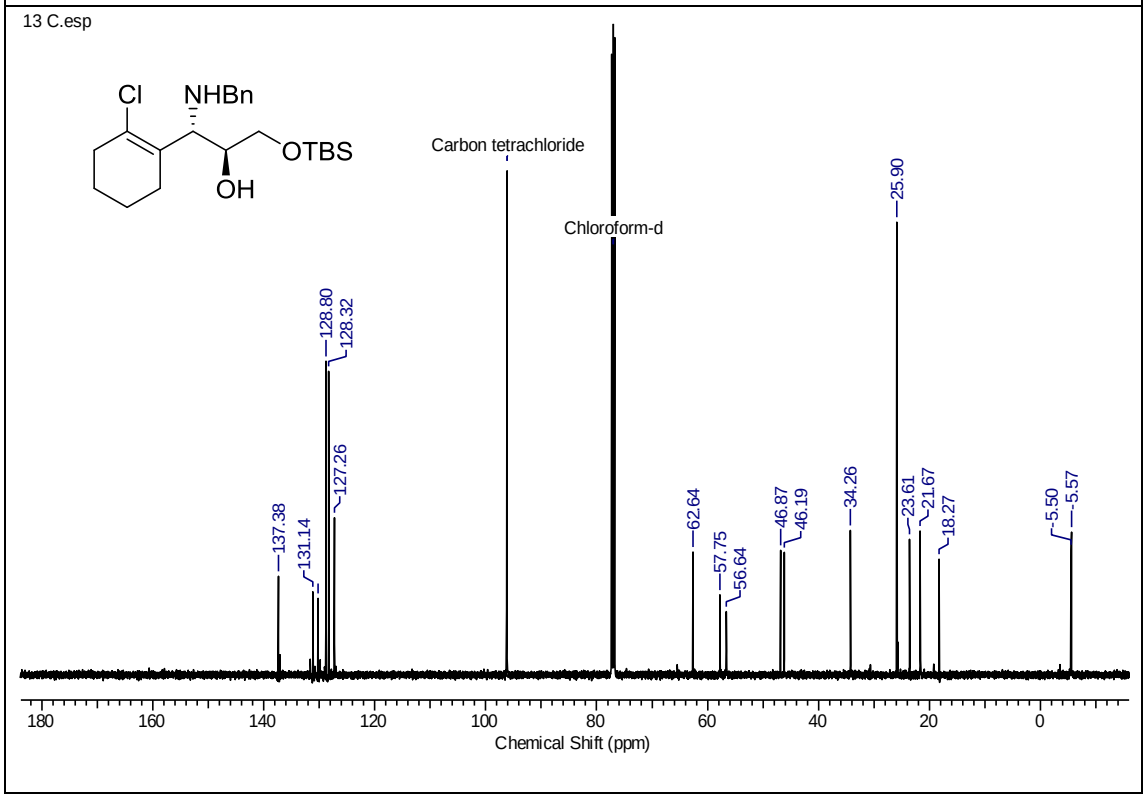
DEPT spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



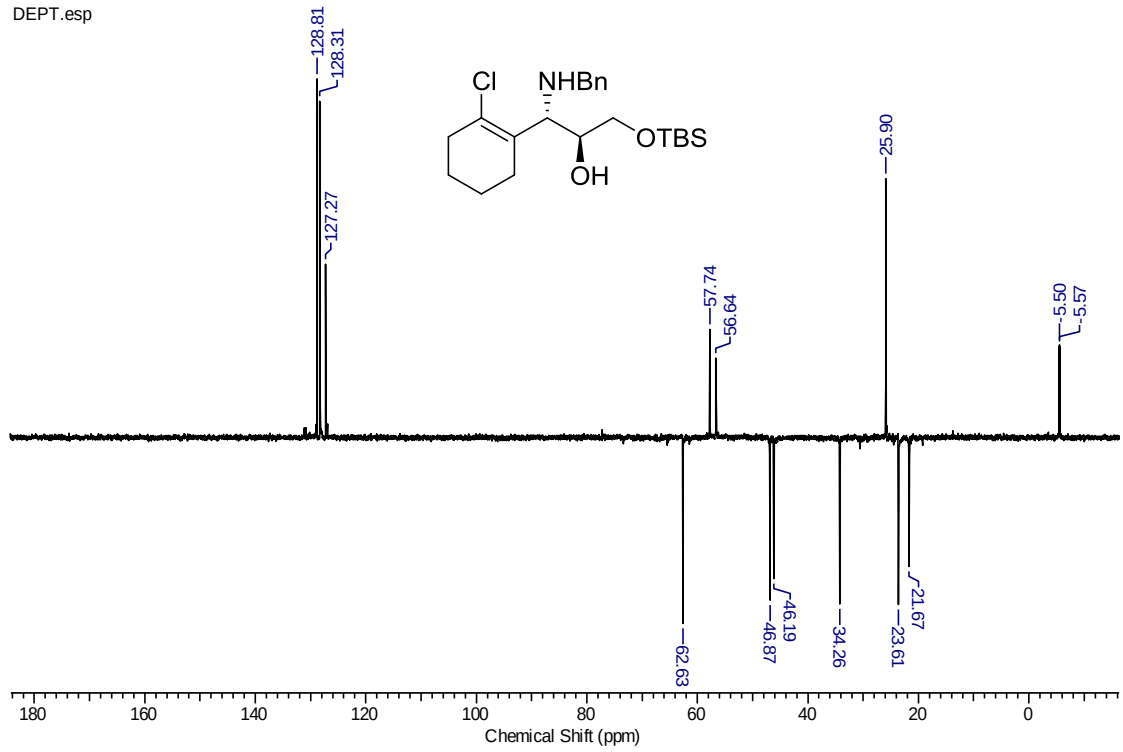
^{1}H NMR spectrum of compound 13 ($CDCl_3$, 200 MHz)



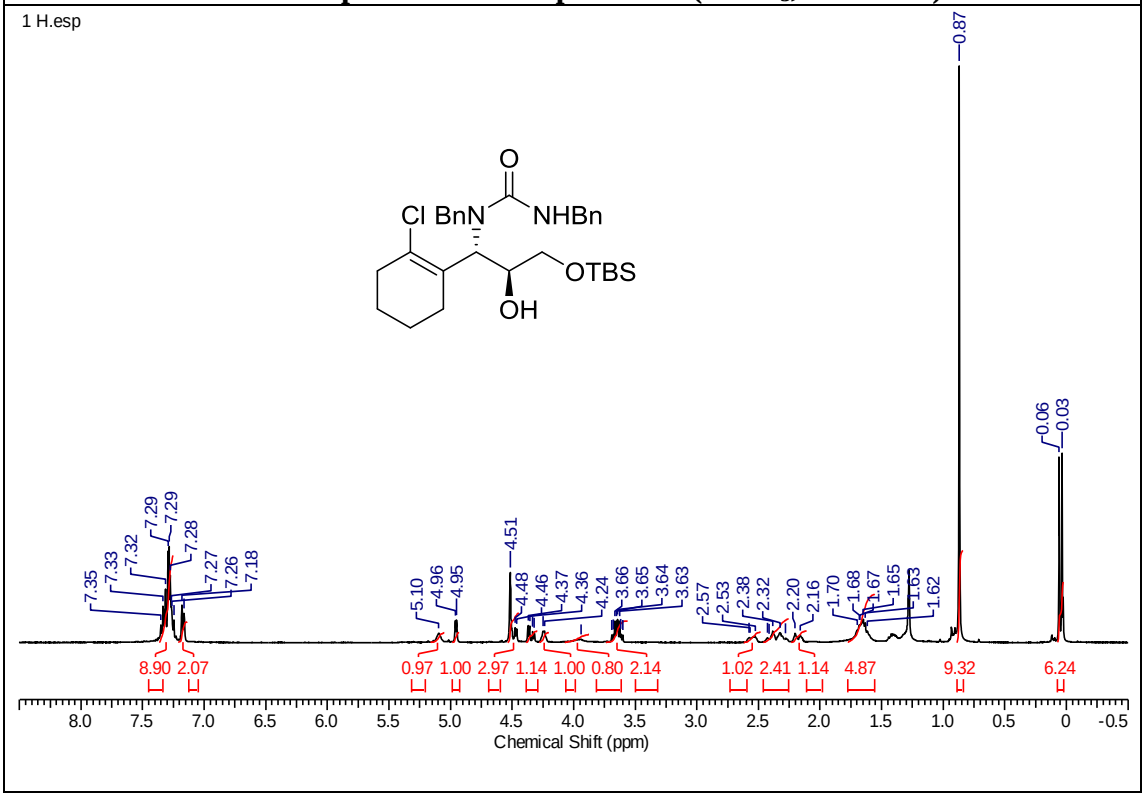
^{13}C NMR spectrum of compound 13 ($CDCl_3$+CCl_4, 125 MHz)



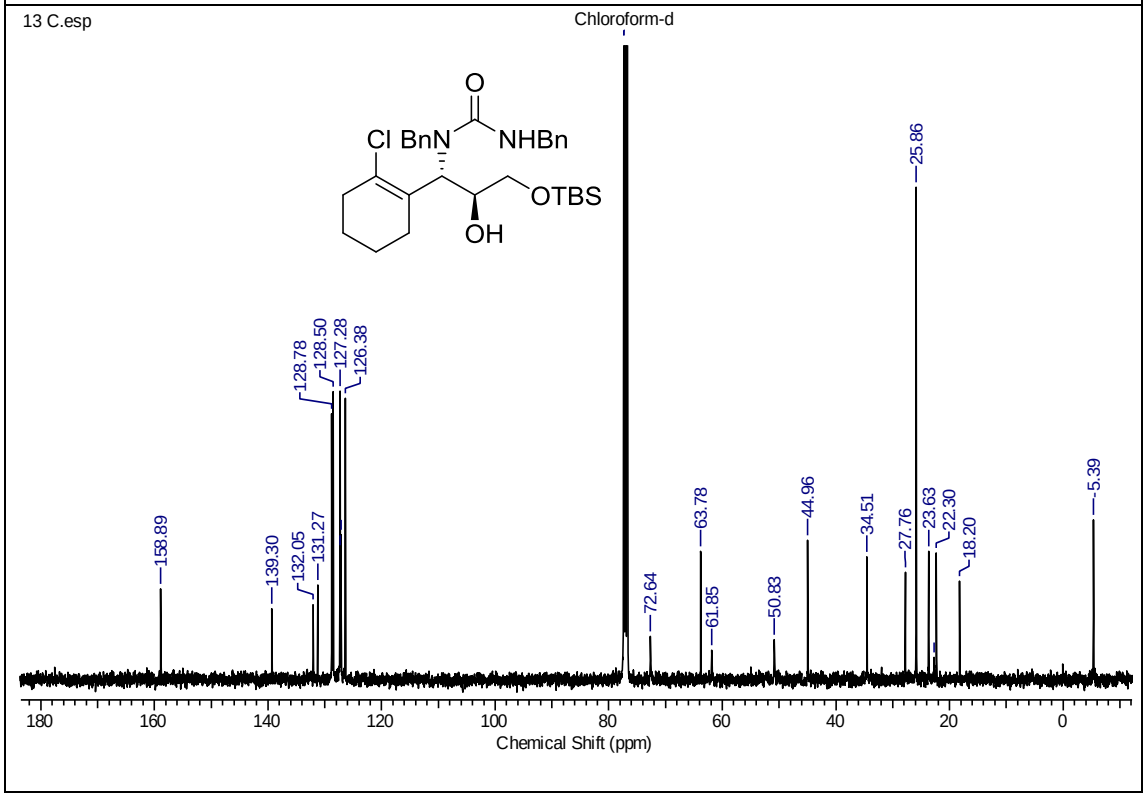
DEPT spectrum of compound 13 ($CDCl_3$+CCl_4, 125 MHz)



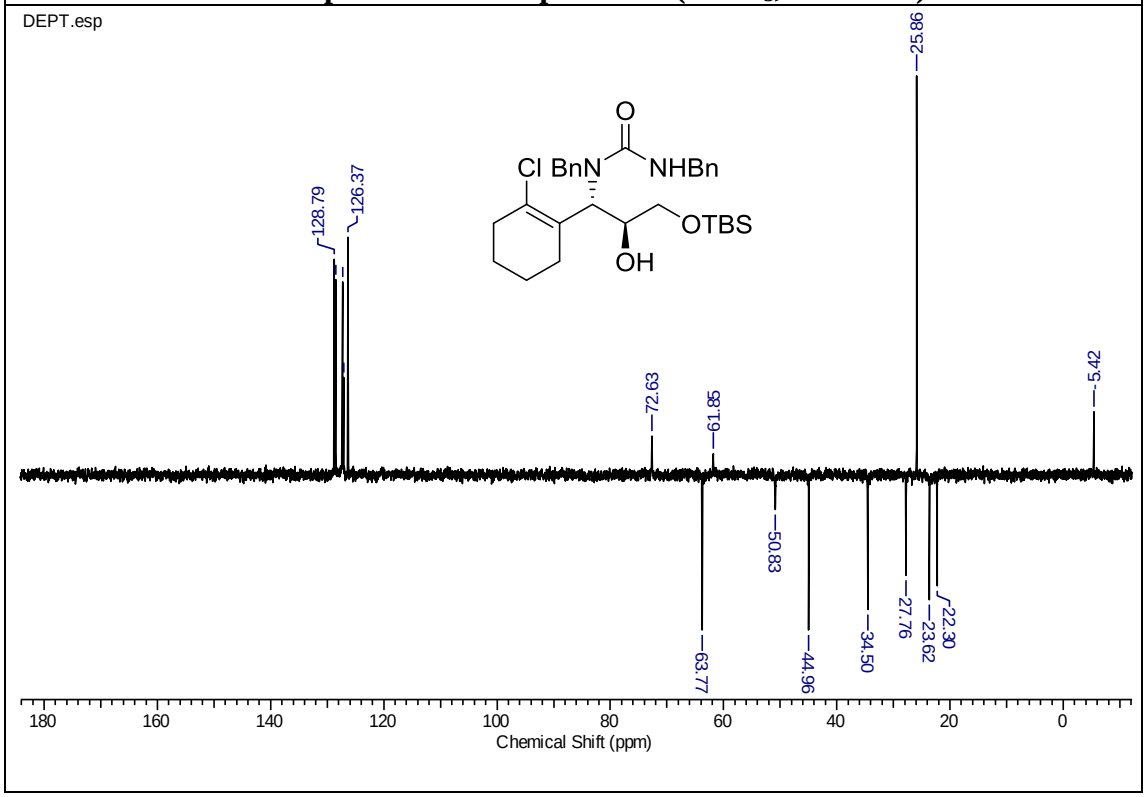
^{1}H NMR spectrum of compound 14 ($CDCl_3$, 400 MHz)



^{13}C NMR spectrum of compound 14 ($CDCl_3$, 100 MHz)



DEPT spectrum of compound 14 ($CDCl_3$, 100 MHz)



3.3.8 References

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Chapter 2. Synthetic studies towards olopatadine and one-pot migration-formylation of benzyl aryl ethers under Duff reaction condition

Section 1

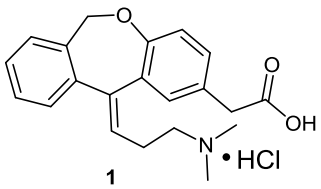
Introduction to olopatadine

2.1.1 Summary

The present section deals with general introduction of olopatadine along with detailed review on the synthetic approaches towards olopatadine, an antihistaminic drug.

2.1.2 Introduction

Olopatadine hydrochloride **1** is an antihistaminic drug ranked in 'Top 200 Brand Name Drugs by total US prescriptions in 2010'.[1] It is selective histamine H_1 receptor antagonist. It also shows mast cell stabilisation property. Olopatadine is used for the treatment of ocular symptoms of seasonal allergic conjunctivitis. The compound may be administered in a solid oral dosage form such as 'allelock®' tablets, as ophthalmic solution form 'pataday®', 'patanol®' and nasal spray 'patanase®'. Olopatadine was developed by Kyowa Hakko Kirin Co. Ltd. and is produced commercially by the synthetic route using Wittig reaction as the key step.[2]



1

Figure 1

Structure-activity relationship studies revealed that the key elements required for enhanced antiallergic activities are a 3-(dimethylamino)propylidene group as the side chain at the 11-position, a terminal carboxyl moiety at the 2-position and a dibenzoxepin ring system.[2a] Although both olopatadine *Z* and *E* isomers show similar H_1R affinities,[3] only the *Z* isomer is the marketed drug. Because of antiallergic activity exhibited by *Z*-isomer of olopatadine (Figure 1), many chemists are involved in developing a better process for it.

The other most commonly prescribed drugs for ocular allergies are epinastine **2**, azelastine **3** and ketotifen **4** (Figure 2).[4b] Epinastine **2** (brand names alesion, elestat, purivist and relestat) is an antihistamine and mast cell stabilizer that is used in eye drops to treat allergic conjunctivitis. Azelastine **3** (brand names Allergodil in Europe, Rhinolast in the UK, Astelin in US, Azep in Australia and Lastin in Finland) is a potent, selective histamine antagonist manufactured by Medapharma. Ketotifen **4** (brand names zaditor, alaway, zyerec itchy-eye drops and claritin eye) is a second

generation noncompetitive H_1-antihistamine and mast cell stabiliser. It is most commonly sold as a salt of fumaric acid, ketotifen fumarate and available in both ophthalmic and oral forms. The main side effects include drowsiness, weight gain, dry mouth, irritability and increased nosebleeds.

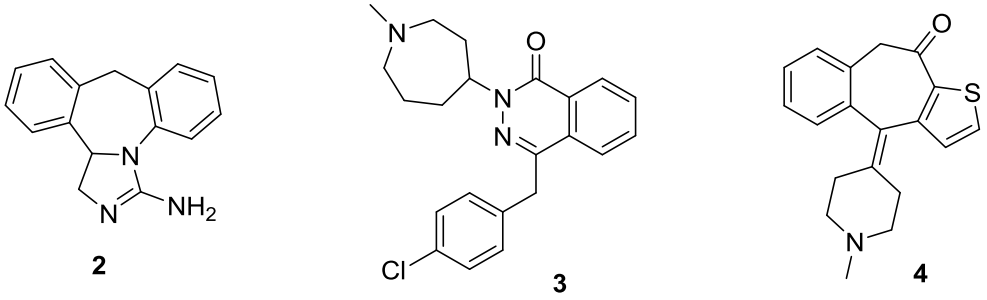
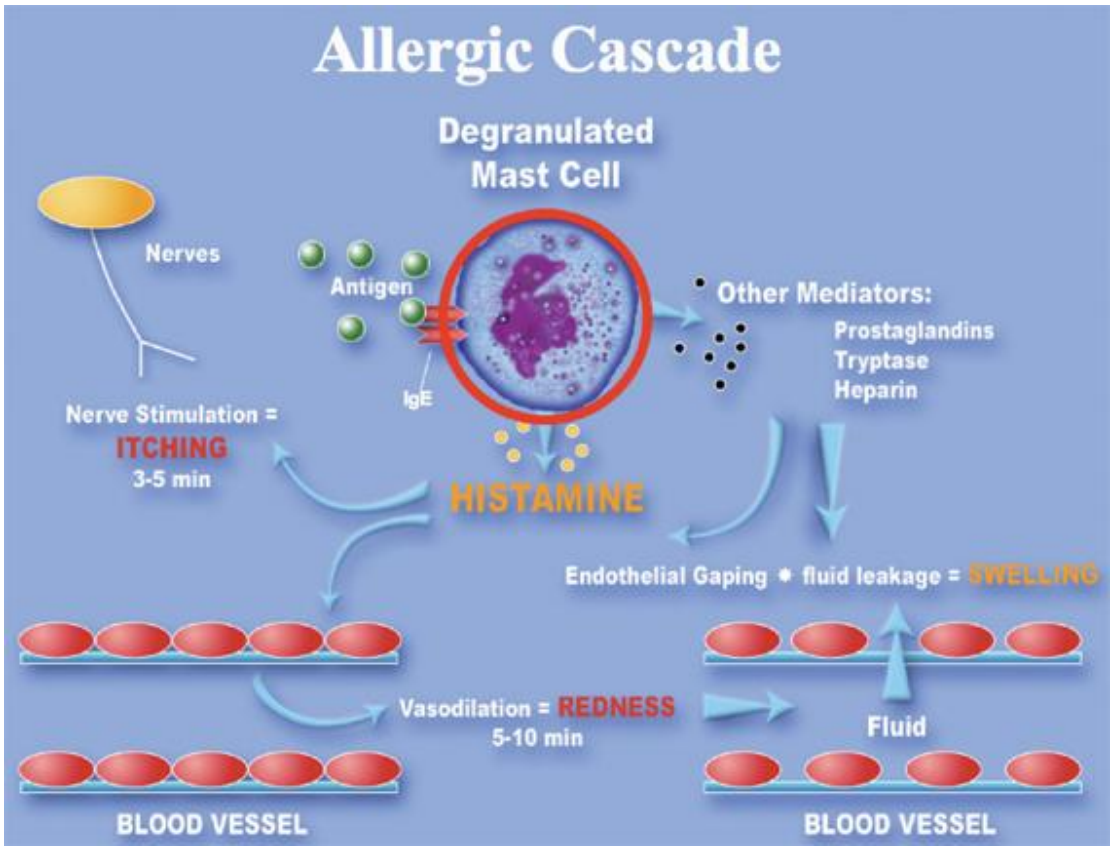


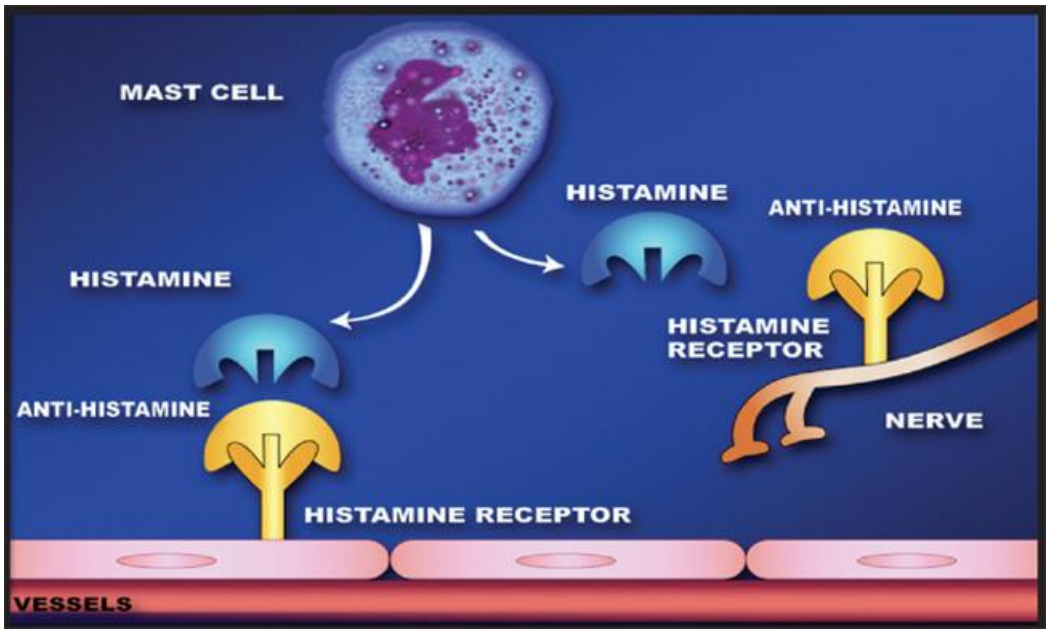
Figure 2

2.1.3 Mode and mechanism of action[4,5,6]



Antigens that cross-link with the IgE antibody on the mast cells trigger the allergic response. This leads to mast cell degranulation and the release of histamines and proinflammatory mediators.

Olopatadine hydrochloride **1** is histamine H_1 receptor antagonist with mast cell stabilizing properties. Olopatadine is used to treat ocular symptoms of allergic conditions, such as inflammation, itching, watering and burning. Allergies cause mast cell degranulation and the release of histamines and proinflammatory mediators. The allergic reaction is triggered by antigens, which cross-link with the immunoglobulin E antibody (IgE) on the mast cells, leading to mast cell degranulation. This, in turn, releases histamines and proinflammatory mediators, such as prostaglandins, tryptase and heparin. The histamine quickly binds with H_1 receptor sites on the nerves and causes itching. It also binds to H_1 receptor sites on the blood vessels, causing redness, chemosis and fluid leakage.



An antihistamine is attracted to the same H_1 receptor sites that histamine seeks. It binds to those sites, effectively blocking the attachment of histamines, thereby preventing ocular itching and redness.

An antihistamine's mechanism of action is simple. It's attracted to the same H_1 receptor sites that histamine seeks. It binds to those sites, effectively blocking the attachment of histamines and preventing itching and redness. Clearly, it's beneficial to put an antihistamine to work early in the inflammatory process.

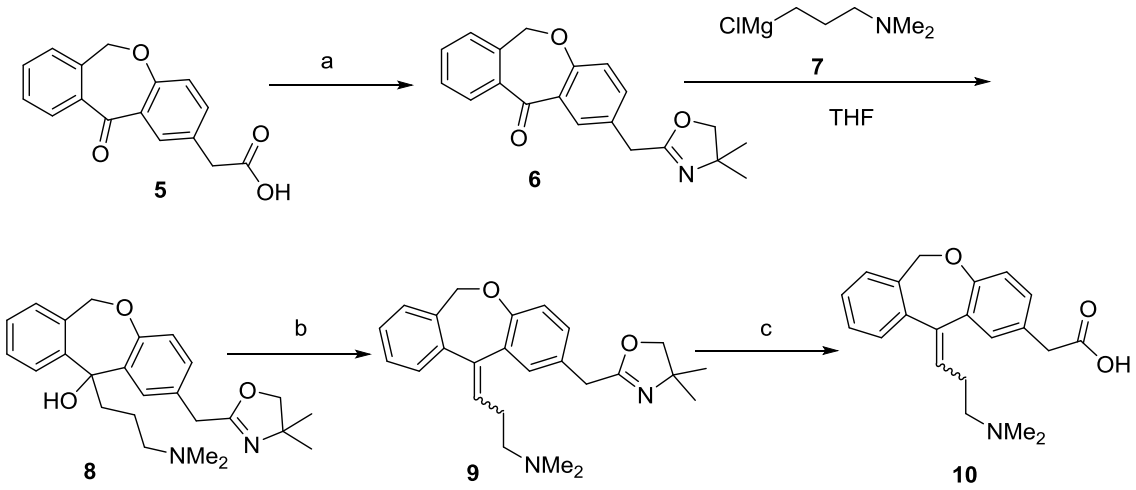
2.1.4 Synthesis of olopatadine: A literature survey[7]

There are original three general routes for the preparation of olopatadine which are described in literature: the first one involves a Grignard reaction followed by a dehydration step, second one involves a Wittig reaction and third one involves a palladium catalyzed Heck coupling.

1. Grignard reaction:

Ohshima's approach[2a] (US005116863, **1992**; *Chem Abstr.* **1988**, *108*, 167330; EP 0235796 B1, *J. Med. Chem.* **1992,** *35***,** 2074)

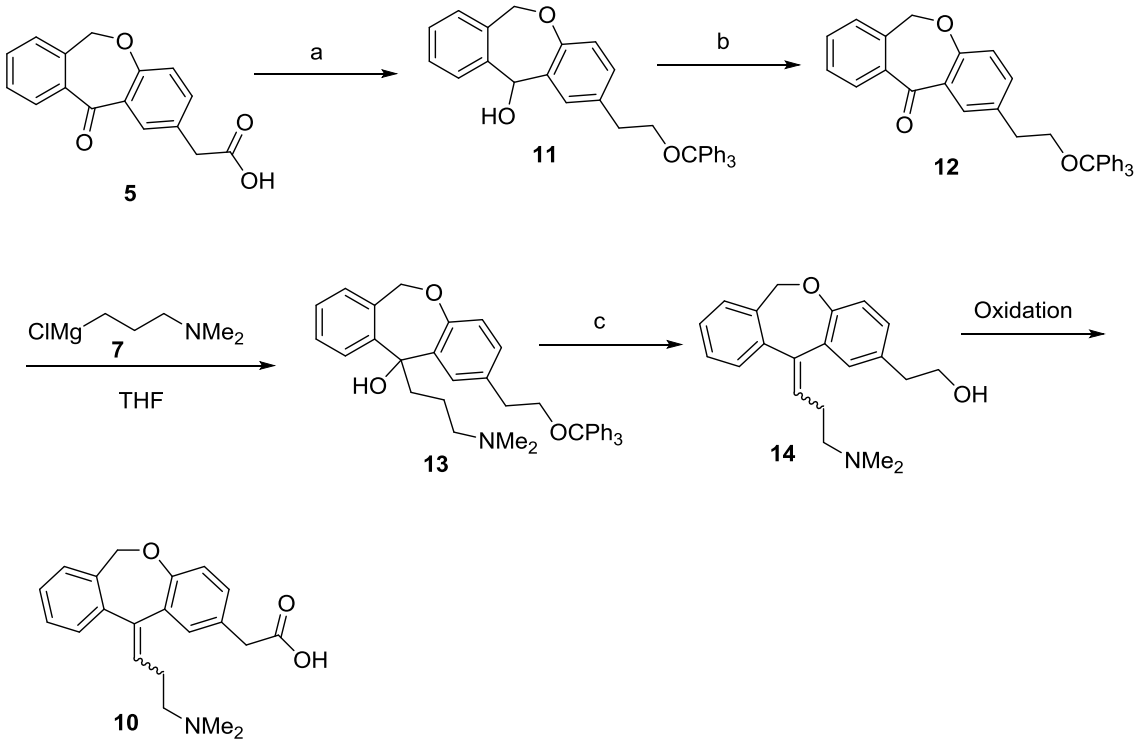
The synthesis started with 2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetic acid (isoxepac) which was prepared by the reported procedure.[8] The carboxyl group of isoxepac **5** was protected as its oxazoline derivative by sequential treatment with thionyl chloride, 2-amino-2-methylpropan-1-ol and finally again with thionyl chloride. The resultant product (protected isoxepac **6)** was allowed to react with Grignard reagent **7** to provide the alcohol **8**. Dehydration was carried out using *p*-TsOH in ethanol-water system to furnish **9** (*E/Z* = 9/1). The cleavage of oxazoline ring of **9** under strong acidic condition in ethanol resulted in olopatadine **10**.



Scheme 1: *Reagents and conditions: a)* i) *$SOCl_2$, Py, CH_2Cl_2; ii) $H_2NC(Me)_2CH_2OH$, toluene; iii) $SOCl_2$, CH_2Cl_2; b) p-TsOH, EtOH, H_2O; c) H_2SO_4, EtOH.*

In the second strategy, reduction of both keto and carboxylic groups in isoxepac **5** was carried out using LAH which resulted in diol **11**. Primary hydroxyl

group was protected selectively as its trityl ether using trityl chloride. Benzylic oxidation was carried out using $KMnO_4$ as a mild oxidizing agent resulting in keto compound **12**. Reaction of Grignard reagent **7** with keto compound **12** furnished alcohol **13**. Simultaneous dehydration and trityl deprotection was carried out using *p*-TsOH in dioxane-water system to furnish **14** (*E/Z* = 9/1). Finally, oxidation of primary alcohol resulted in olopatadine **10**.[2a]



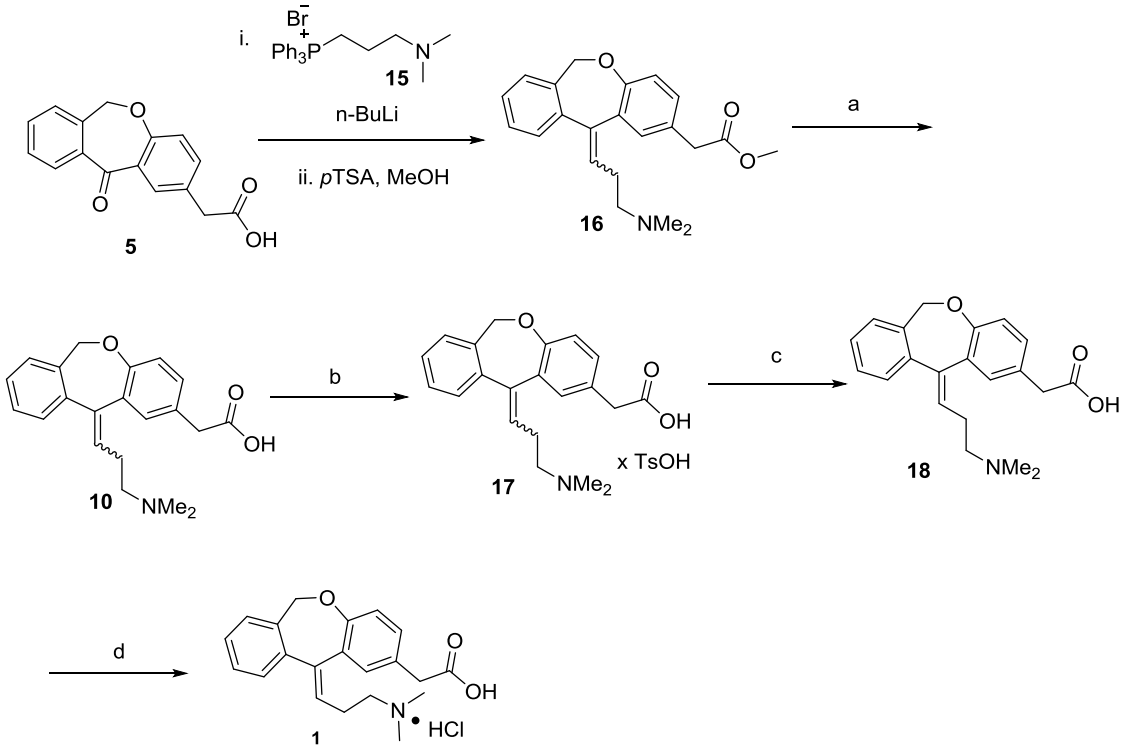
Scheme 2: *Reagents and conditions: a) i) $LiAlH_4$, THF; ii) Ph_3CCl, Py; b) $KMnO_4$, $MgSO_4$, Na_2HPO_3, acetone, H_2O; c) p-TsOH, dioxane, H_2O; d) Oxidation.*

2. Wittig reaction:

Ohshima's approach (US005116863, **1992**; *Chem Abstr*. **1988**, *108*, 167330; EP 0235796 B1, *J. Med. Chem.* **1992,** *35***,** 2074)

Ohshima *et al.*[2a] reported a highly efficient total synthesis of olopatadine hydrochloride. Key step of the synthesis was the Wittig reaction. The ylide, generated by the treatment of wittig reagent **15** with n-BuLi, was allowed to react with isoxepac **5** and the crude product (*E/Z* = 1/2) was esterified to **16** for ease of purification. Saponification was carried out using NaOH and the acid was treated with TsOH to make diastereomers **17**. Separation of diastereomers was carried out by fractional

crystallization and the desired *Z*-isomer was treated with $NaHCO_3$ to make it acid free, resulting in compound **18**. Finally, treatment of olopatadine **18** with 8 N HCl furnish olopatadine hydrochloride **1** as it in marketed salt form.



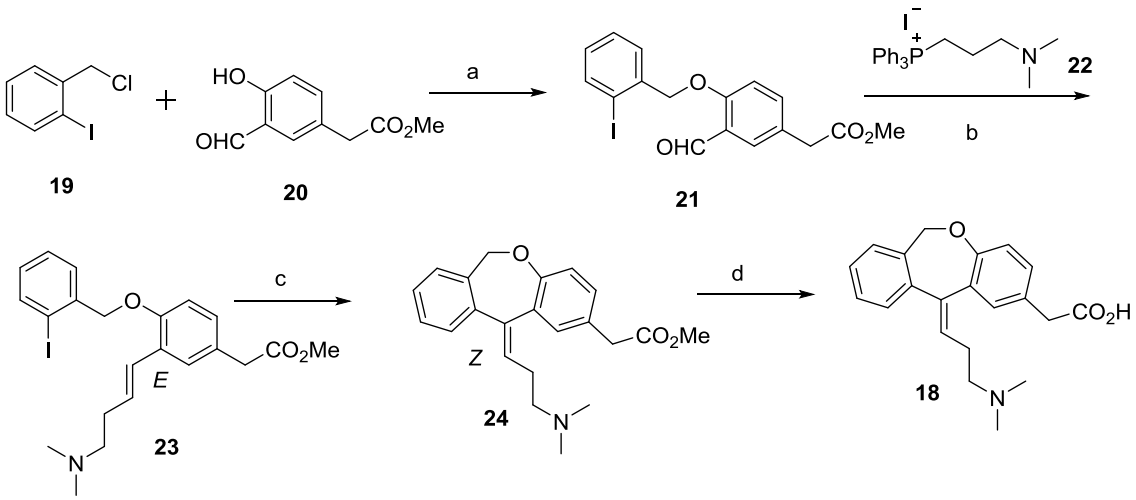
Scheme 3: *Reagents and conditions: a) NaOH; b) TsOH, separation of diastereomers by fractional crystallization; c) $NaHCO_3$; d) 8 N HCl.*

3. Palladium catalyzed Heck coupling:

Bosch's approach (*J. Org. Chem.* **2012,** *77*, 6340)

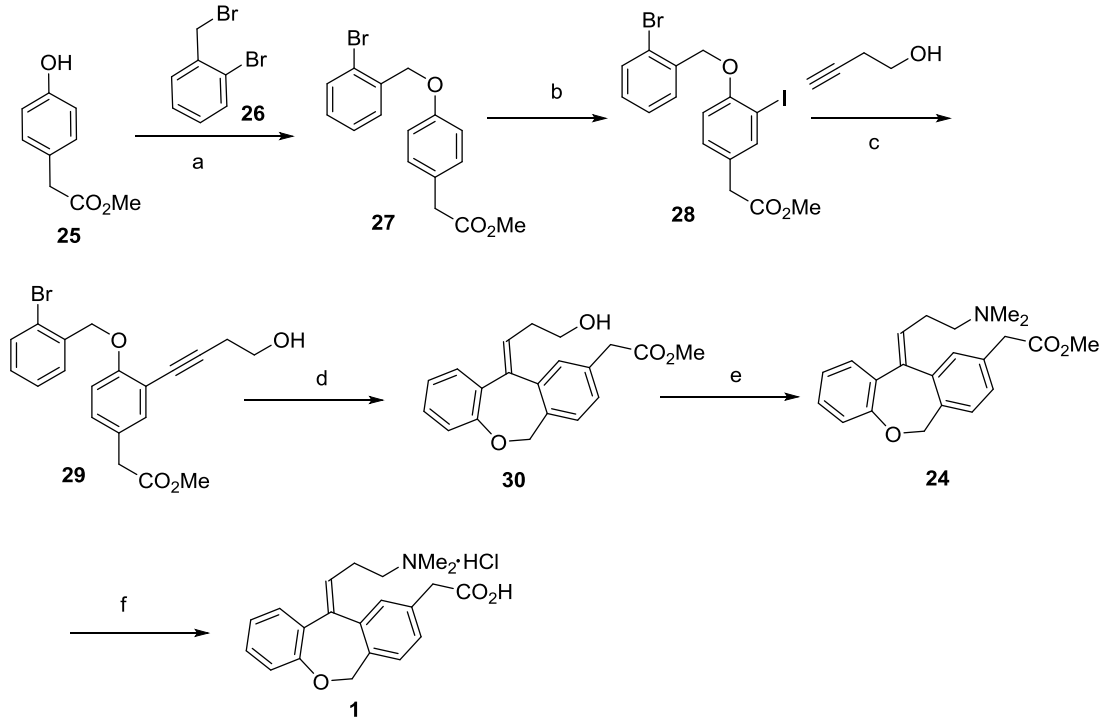
Bosch *et al.*[9] reported stereoselective synthesis of olopatadine involving successive stereoselective Wittig and intramolecular Heck reactions as the key steps. The starting aldehyde **21** was prepared from 2-iodobenzyl chloride **19** and methyl 3-formyl-4-hydroxyphenylacetate **20**. The Wittig reaction of **21** was performed using the ylide generated from commercially available phosphonium iodide **22** by treatment with LiHMDS in toluene giving a mixture of *E/Z* alkenes in a 9/1 ratio. The intramolecular Heck reaction of iodo alkene **23** was performed under solid-liquid phase transfer conditions, using a stoichiometric quantity of Bu_4NCl as the transfer agent and K_2CO_3 as the base, in the presence of a catalytic amount of $Pd(OAc)_2$ in an acetonitrile-water mixture. A single dibenzoxepin derivative **24**, bearing a *Z*-

configurated double bond, was formed with complete stereoselectivity in 60% yield. Finally, alkaline hydrolysis of the cyclised product **24** furnished the target drug olopatadine **18**.



Scheme 4: *Reagents and conditions: a) K_2CO_3, NaI, CH_3CN; b) LiHMDS, THF, rt; c) $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, CH_3CN-H_2O; d) NaOH, EtOH/H_2O.*

Nishimura's approach (*Org. Process Res. Dev*. **2012**, *16*, 225)



Scheme 5: *Reagents and conditions: a) K_2CO_3, DMF; b) I_2, Ag_2SO_4, MeOH; c) $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF; d)$Pd(OAc)_2$, tri-o-tolylphosphine, HCO_2H, piperidine, MeCN; NaOH, EtOH/H_2O; e) i) MsCl; ii) Me_2NH; f) i) NaOH, aq./MeOH; ii) aq. HCl.*

Nishimura *et al.*[10] reported a synthetic route olopatadine *via* the intramolecular stereospecific seven-membered ring cyclization from an alkyne intermediate using palladium catalyst. The key precursor **29** was prepared from **25** through sequence of reaction involving benzylation, iodination and Sonogashira coupling reaction. The seven-membered ring cyclization of **29** using palladium catalyst furnished the *Z*-isomer **30** as a sole product. The substitution reaction of the mesylate prepared from **30** by dimethylamine was performed to afford **24**, and olopatadine hydrochloride **1** was obtained by hydrolysis and hydrochlorination of **24**.

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Chapter 2. Synthetic studies towards olopatadine and one-pot migration-formylation of benzyl aryl ethers under Duff reaction condition

Section 2

A simple synthesis of novel antihistaminic drug olopatadine

2.2.1 Summary

The present section deals with the formal synthesis of olopatadine (**1)**. The key side chain has been introduced *via* three different strategies; a) Dehydrogenation, b) Acid mediated dehydration of diol and c) Lewis acid mediated ring opening of cyclic ether. Where Lewis acid mediated ring opening of cyclic ether gave the best selectivity (*E/Z* 2:3).

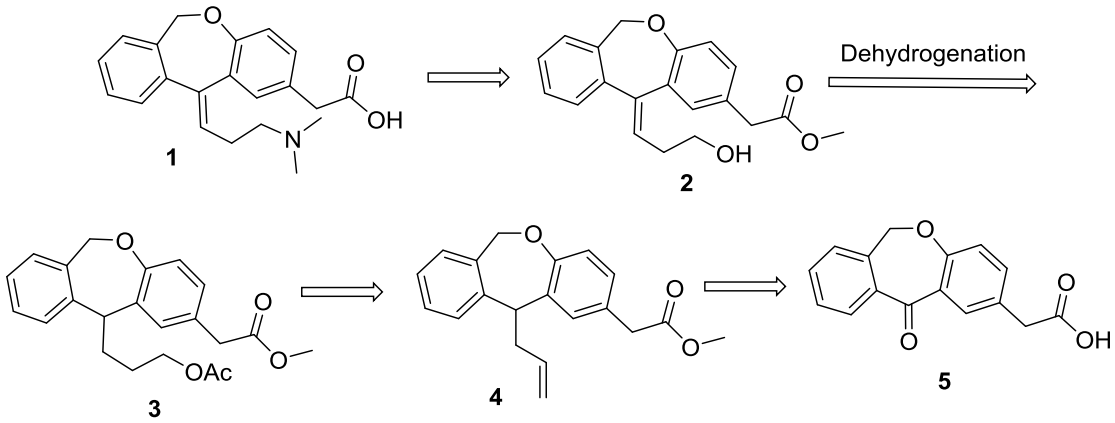
2.2.2 Introduction

Olopatadine hydrochloride is a selective histamine H_1 receptor antagonist *in vitro* and *in vivo* as demonstrated by its ability to inhibit binding and histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscuarinic type 1 and 2, and serotonin receptors. Only cis isomer of olopatadine being useful in treating allergic eyes diseases in humans, which comprises of stabilizing conjuctival mast cells by topical administration to the human eye. Literature review reveals a number of synthetic strategies to access olopatadine, mostly in the form of patents.[1] In most of the synthesis, the key side chain has been introduced *via* 'Grignard reaction' or 'Wittig olefination'.[1d,2] In most of the previous approaches, the main drawback has been the low *E*/*Z* stereoselectivity. Recently, Bosch *et al.* have utilized a stereoselective Heck reaction for the selective generation of *Z*-isomer *via* the intramolecular cyclization of an *E*-alkene intermediate.[3] Nishimura *et al.* too reported a stereospecific route to **1** under palladium catalysis. In their synthetic route, the *Z*-stereoselectivity was controlled by an intramolecular stereospecific seven-membered ring cyclization from an alkyne intermediate using palladium catalyst.[4] Unfortunately most of the reported syntheses involves expensive reagents and harsh reaction conditions which are operationally difficult to perform on a large scale.

2.2.3 Present work

The envisaged retrosynthetic strategy for olopatadine **1** is delineated in Scheme 1. A linear synthetic strategy was invoked wherein homoallyl alcohol **2** was conceived as the ideal precursor to **1**. Elaboration of the intermediate **2** to **1** is well documented in the literature.[4] Homoallyl alcohol **2** upon mesylation, dimethylamination and hydrochlorination would lead to olopatadine hydrochloride salt. In turn the focus was the construction of the key side chain. The homoallyl

alcohol **2** could be accessed from intemediate **3** by DDQ mediated dehydrogenation, which in turn can be synthesized from allyl compound **4** by hydroboration and protection. The allyl compound **4** could be accessed from known intermediate 2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid (**5**, also known as Isoxepac) through reduction followed by allylation.



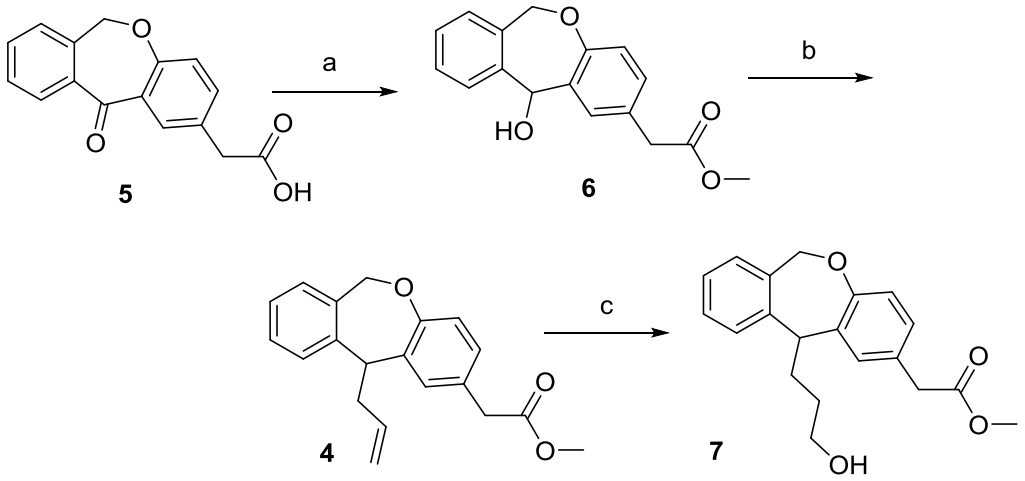
Scheme 1. *Retrosynthetic analysis for olopatadine **1***

1.2.4 Results and discussion

According to retrosynthetic plan (Scheme 1), synthesis of olopatadine (**1)** began from Isoxepac (**5**).[5] **5** on treatment with thionyl chloride in methanol gave the corresponding Isoxepac methyl ester in quantitative yield. This methyl ester was reduced using sodium borohydride in methanol furnished alcohol **6** in 93% yield. The IR spectrum of compound **6** showed strong bands at 3462 and 1739 cm^{-1} indicating the presence of hydroxyl and ester functionalities. The ^{1}H NMR spectrum of compound **6** showed peak at δ 3.64 as singlet corresponding to the three protons indicating the presence of a methyl ester compound. Peak at δ 5.55 appeared as a singlet accounting for one proton adjacent to hydroxyl group. The ^{13}C NMR spectrum showed peak at δ 172.2 corresponding to ester functional group. Its DEPT NMR spectrum showed presence of peak at δ 76.1 corresponding to characteristic benzylic methine carbon. MS spectrum of compound **6** showed signal appearing at *m/z*: 307 (M + Na), further confirmed its molecular formula (Scheme 2).

Alcohol **6** was converted into allyl compound **4** using allyltrimethylsilane and $BF_3 \cdot OEt_2$ in DCM in 83% yield. The IR spectrum of compound **4** showed absence of band at 3462 cm^{-1} indicating the absence of hydroxyl group. ^{1}H NMR spectrum

showed signals that appeared in olefinic region at δ 5.63-5.87 (m, 1 H), as multiplet integrating for one proton (-CH=CH_2) and the multiplet which appeared at 2.78-3.13 (m, 2 H) integrating for two protons (-CH_2-CH=CH_2) was attributed to the allylic methylene protons while rest of the proton peaks associated with the compound resonated at expected positions. ^{13}C NMR and DEPT NMR spectra of compound **4** showed the signals that appeared at δ 136.6 (CH_2-CH=CH_2), 116.3 (CH_2-CH=CH_2) and 43.6 (CH_2-CH=CH_2) corresponding to allyl chain carbons while rest of the carbons associated with the compound resonated at their expected positions. Finally, HRMS analysis (calculated for $C_{20}H_{21}O_3$-309.1485, observed-309.1480) confirmed the formation of **4**.

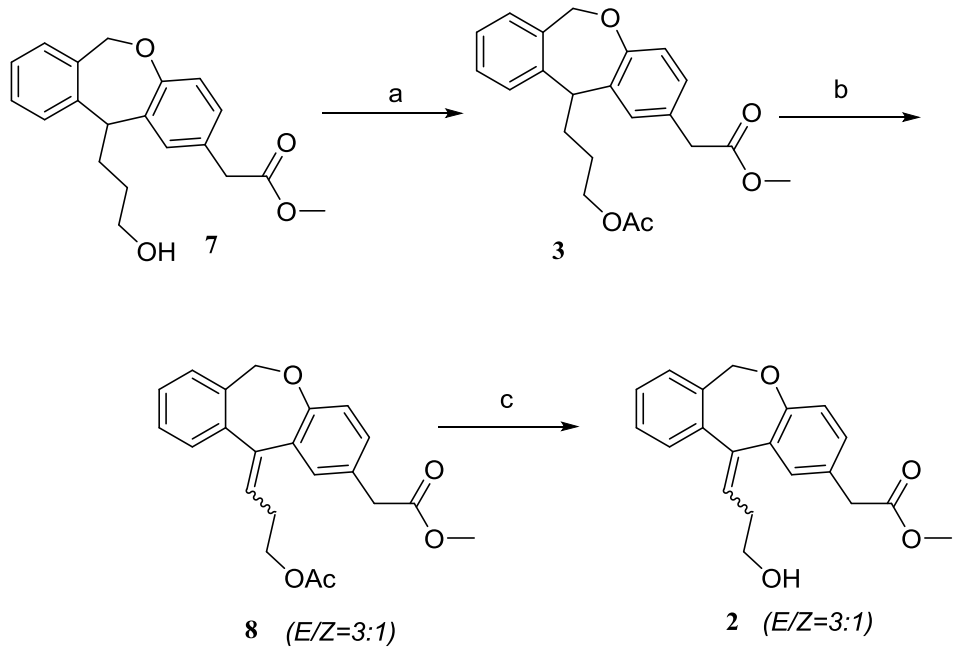


Scheme 2. *Reagents and conditions: a) i) $SOCl_2$, MeOH, 24 h, rt, quent; ii) $NaBH_4$, MeOH, 0 ºC, 2 h, 93%; b) Allyl-TMS, $BF_3{\cdot}Et_2O$, 0 ºC-rt, DCM, 4 h, 83%; c) $BH_3{\cdot}DMS$, NaOH, H_2O_2, THF, 0 ºC-rt, 12 h, 81%.*

Hydroboration was carried out on **4** using $BH_3{\cdot}$DMS which was quenched by sodium hydroxide and hydrogen peroxide, afforded alcohol **7** in 81% yield.[6] IR spectrum of the product **7** indicated the presence of a hydroxyl group by revealing broad absorption at 3444 cm^{-1} confirming hydroboration-oxidation. ^{1}H NMR spectrum showed no peak in the olefinic region corresponding to allyl protons and ^{13}C NMR and DEPT NMR spectra of compound **7** showed signals that appeared at δ 31.6, 35.4, 40.3, 62.5 and 72.7 corresponding to methylene (-CH_2-) carbon confirming hydroboration-oxidation. Finally, the structure of compound **7** was confirmed by HRMS analysis (calculated for $C_{20}H_{23}O_4$-327.1591, observed-327.1584).

The primary hydroxyl group of **7** was protected as its acetate using pyridine and acetic anhydride, afforded acetate **3** in 96% yield. The IR spectrum of compound **3** showed absorption bands at 1742 and 1732 cm^{-1} for the corresponding ester and acetate functionalities respectively. ^{1}H NMR spectrum of compound **3** showed singlet at δ 2.02 which indicated the formation of acetate compound **3**. Its ^{13}C NMR and DEPT NMR spectra showed peaks at δ 170.6 and δ 20.8 corresponding carbonyl group ($CH_3\underline{CO}$-) and methyl group ($\underline{CH_3}CO$-) of acetate respectively. Finally, the structure of compound **3** was confirmed by HRMS analysis.

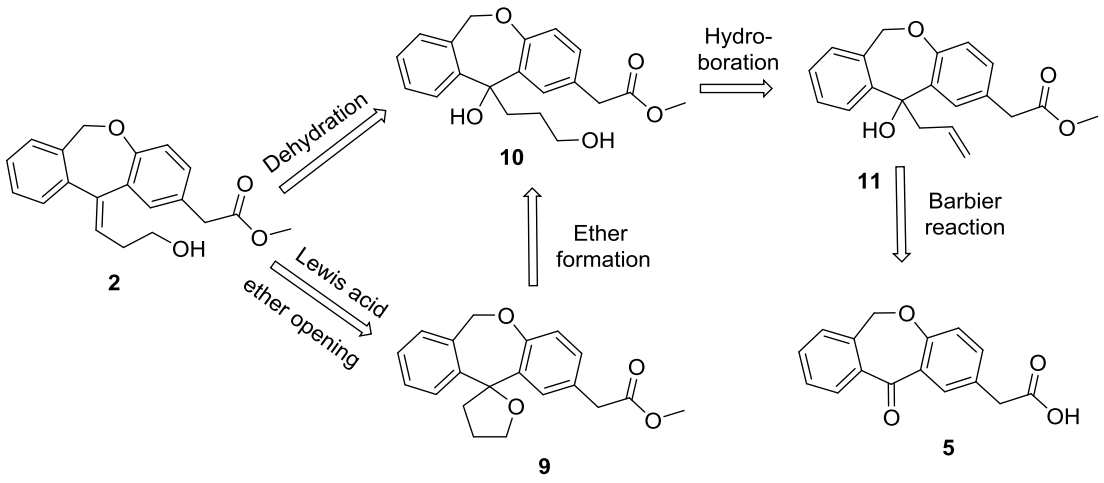
Next job was the introduction of key double bond. Accordingly, compound **3** was subjected to DDQ oxidation.[7] Here although desired compound **8** (*E/Z*=3/1) was obtained, but in low (40%) yield. ^{1}H NMR spectrum of compound **8** showed characteristic triplet at δ 5.69 (t, *J*=7.1 Hz) and 6.02 (t, *J*=7.1 Hz) integrated for 0.25 H and 0.75 H corresponding to *Z*-isomer and *E*-isomer respectively. Interestigly, ^{1}H NMR spectrum of compound **8** showed a broad peak at δ 5.16 (brs, 2 H) as a hump corrosponding to two protons (benzylic proton of oxepin ring) indicating presence of a double bond at C-11. Acetate deprotection smoothly worked in potassium carbonate and methanol in 30 min resulted in the formation of hydroxyl compound **2** (*E/Z*=3/1) in quantitative yield (Scheme 3).



7 **3** **8** *(E/Z=3:1)* **2** *(E/Z=3:1)*

Scheme 3. *Reagents and conditions: a) Py, Ac_2O, 0 ºC-rt, DCM, 4 h, 96%; b) DDQ, Dioxane, Reflux, 12 h, 40%; c) K_2CO_3, MeOH, 30 min, 90 %.*

Having failed in yield improvement in the DDQ oxidation step, resulted in a changed strategy. Accordingly, the homoallyl alcohol **2** in turn could be accessed from cyclic spiro ether **9** by Lewis acid mediated ether ring opening or by direct dehydration of diol **10**. Cyclic spiro ether **9** in turn could be obtained from known compound **5**, through routine functional group manipulations such as Barbier reaction to introduce the allyl group, followed by hydroboration and ether formation (Scheme 4).

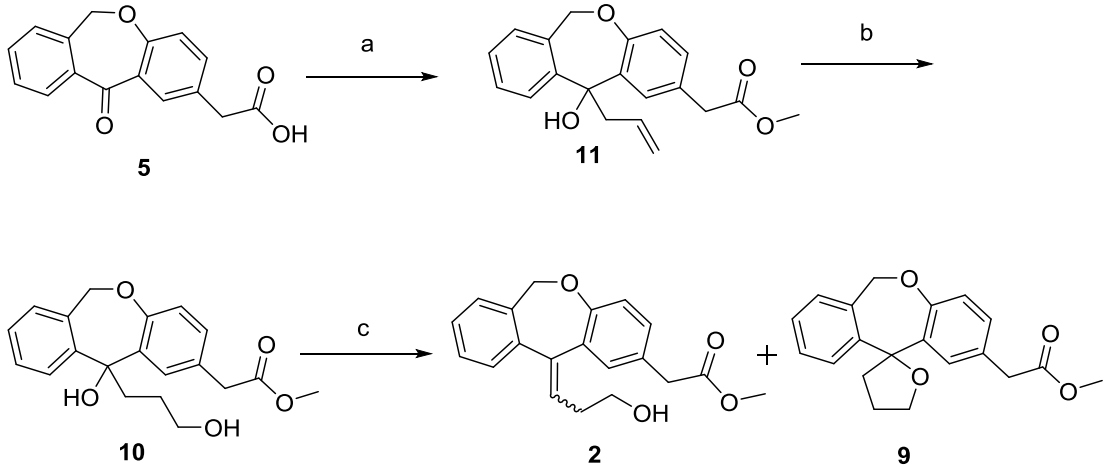


Scheme 4. *Altered retrosynthetic analysis for olopatadine **1***

According to the proposed plan (Scheme 4), synthesis of olopatadine (**1**) started from Isoxepac (**5**).[5] Isoxepac (**5**) on treatment with thionyl chloride in methanol gave the corresponding Isoxepac methyl ester in quantitative yield. Barbier reaction on the methyl ester with allyl bromide in the presence of zinc powder in DMF as the solvent furnished the allylic alcohol **11** in 91% yield.[8] Its IR spectrum showed strong band at 3482 and 1735 cm^{-1} indicating the presence of hydroxyl and ester functionalities respectively. The ^{1}H-NMR spectrum of compound **11** showed multiplets at δ 5.35-5.56 (m, 1 H), 5.09-5.18 (m, 2 H), 3.34-3.44 (m, 1 H) and 2.86-2.97 (m, 1 H) corresponded to the allyl group. Additionally, its ^{13}C NMR and DEPT NMR spectra showed the signals that appeared at δ 133.5 (CH_2-$\underline{CH}$=CH_2), 119.4 (CH_2-CH=$\underline{CH_2}$) and 48.7 ($\underline{CH_2}$-CH=CH_2) attributing to the allyl chain carbons. Finally, the structure of compound **11** was confirmed by HRMS analysis.

Hydroboration of **11** with 9-BBN followed by quenching with sodium hydroxide and hydrogen peroxide afforded the diol **10**.[6] IR spectrum of the product **10** indicated the presence of a hydroxyl group by revealing broad absorption at 3505 cm^{-1}

confirming hydroboration-oxidation. ^{1}H NMR spectrum showed no peak in the olefinic region corresponding to allyl protons and ^{13}C NMR along with DEPT NMR spectra of compound **10** showed signals for downfield seven methine that appeared at δ 129.3, 128.3, 126.9 (2C), 126.2, 125.8 and 121.2 were assigned for aromatic carbons. The signal present at δ 52.0 correspond to methyl carbon of methyl ester, while the five methylene (-CH_2-) signals at δ 73.7, 62.7, 41.9, 40.4 and 27.3 affirming hydroboration-oxidation. Finally, the structure of compound **10** was confirmed by HRMS analysis.



Scheme 5. *Reagents and conditions: a) i) $SOCl_2$, MeOH, 24 h, rt, quent; ii) Zn, Allyl bromide, DMF, 2 h, 0 ºC-rt, 91%; b) 9-BBN, NaOH, H_2O_2, THF, 24 h, 0 ºC-rt, 84%. c) Table 1.*

In order to introduce the exocyclic double bond by acid mediated dehydration of diol **10** several different conditions were screened, as shown in table 1. Almost all the reaction conditions led to the predominant formation of the undesired *E*-olefin along with the generation of the spiro cylic ether **9** (Scheme 5).

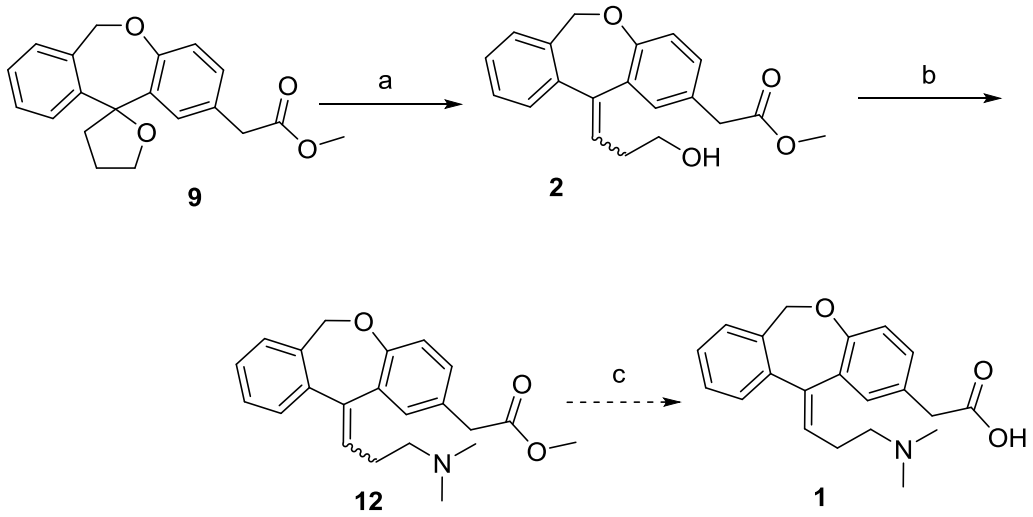
Table 1 Acid mediated dehydration

Entry	Reagent[a]	Time (h)	Temperature	Yield 2 (%)	Yield 3 (%)	*E*/*Z*[b] of 2
1	HCl	24	RT	none	90	-----
2	H_2SO_4	24	RT	30	53	4/1
3	HCOOH	32	RT	45	32	4/1
4	PPTS[c]	14	80 °C	59	10	4/1

5	*p*TSA	1/4	RT	none	99	-----
6	$BF_3{\cdot}Et_2O$	6	0 °C	22	64	3/2
7	$BF_3{\cdot}Et_2O$	1/2	50 °C	95	none	3/2

[a] DCM used as the solvent. [b]*E/Z* ratio was confirmed by ^{1}H-NMR and HPLC. [c] EtOH used as solvent.

The diol **10** was treated with both protic as well as Lewis acids. It was found that inorganic protic acids led to the formation of cyclic ether **9** as the major/exclusive product (Table 1, entries 1, 2), while organic acids furnished the olefin as the major product (Table 1, entries 3, 4). It was observed that treatment of diol **10** with catalytic *p*-TSA at ambient temparature instantly formed a spiro tetrahydrofuran ring **9** in almost quantitative yield (Table 1, entry 5). The IR spectrum of compound **9** showed absence of band at 3505 cm^{-1} indicating the absence of hydroxyl group. ^{1}H NMR spectrum showed absence of signal that appeared at δ 4.84 (brs, 1 H), as a broad singlet integrating for one protons (C-O<u>H</u>) and downfield shifting of the multiplet at δ 3.36-3.64 (m, 2 H) to δ 4.33-4.17 (m, 2 H) indicating the presence of a spiro ether (C-O-<u>CH_2</u>-). ^{13}C NMR along with DEPT NMR spectra of compound **9** displayed downfield quaternary signal at δ 85.1, indicated the formation of spiro ether. Finally, the structure of compound **9** was confirmed by HRMS analysis.



Scheme 6. *Reagents and conditions: a) Table 2; b) i) MsCl, Py, 2 h, 0 ºC-rt; ii) 50 % Me_2NH, MeOH, 3 h, 50 ºC 84% over two steps; c) ref. 4.*

Whereas, **10** on treatment with Lewis acid ($BF_3{\cdot}Et_2O$) at room temparature led to the formation of cyclic ether **9** along with the formation of olefin **2** as the minor

product (Table 1, entry 6). However, when the reaction was carried out at elevated temperature the olefin **2** was the only product formed (Table 1, entry 7). In both the cases the ratio of *E/Z* was 3:2, in the favor of the unwanted isomer. In order to improve the *Z* selectivity, different Lewis acids were screened along with their combination with base as summarized in Table 2. Amongst various Lewis acids screened, it was observed that $AlCl_3$ gave the best result. Thus spiro ether **9** on treatment with 2.5 equivalents of $AlCl_3$ resulted in the formation of homoallyl alcohol **2** in 95% yield with *E/Z* in 2:3 ratio. Attempts to separate the isomers by $AgNO_3$ column chromatography failed. As compound **2** was solid, attempted to separate the isomers by preferential recrystallization. The ratio of *E/Z* isomer could be improved to 1:9 after two crystallization.[9]

Table 2 Lewis acid mediated ether opening

Reagent (s)[a]	Time	Temperature	Yield (%)	E/Z[b]
$BF_3{\cdot}Et_2O$	6 h	0 °C-RT	93	3/2
$AlCl_3$	10 min	RT	96	1/1
$AlCl_3$	7 h	0 °C-RT	95	2/3
$TiCl_4$	12 h	0 °C-RT	39	4/1
$SnCl_4$	5 h	0 °C-RT	81	2/1
SbF_5	30 min	0 °C-RT	82	3/2
$InCl_3$	24 h	0 °C-RT	60	3/2
$AlCl_3$	6 min	MW	83	2/1
$AlCl_3$+$C_6H_5N(CH_3)_2$	18 h	RT	92	1/1
$AlCl_3$ + DBU	30 min	0 °C-RT	91	4/1

[a] DCM used as the solvent; [b] *E/Z* ratio was confirmed by ^{1}H-NMR and HPLC.

IR spectrum showed strong bands at 3446 and 1736 cm^{-1} indicating the presence of hydroxyl and ester functionalities respectively. ^{1}H NMR spectrum of compound **2** showed characteristic triplet at δ 5.73 (t, *J* = 7.8 Hz, 0.9 H, *Z*-isomer), 6.06 (t, *J* = 7.8 Hz, 0.1 H, *E*-isomer) integrated for 0.9 H and 0.1 H corresponding to *Z*-isomer and *E*-isomer respectively. Finally, the structure of compound **2** was confirmed by HRMS analysis.

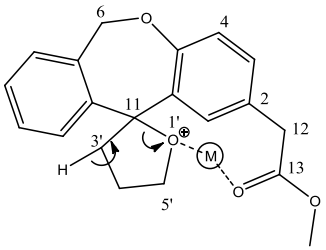


***Figure 1**. Plausible mechanism for the stereoselectivity towards Z-isomer.*

Although the exact mechanism of this reaction remains to be elucidated, the plausible mechanism for the stereoselectivity towards *Z*-isomer (major) could be explained by considering the metal coordination. The Lewis acid first chelates with the 1´-oxygen of furan ring and metal coordinates with oxygen of C-13 at 2-position. Opening of the furan ring results in the formation of *Z*-isomer as the major isomer.

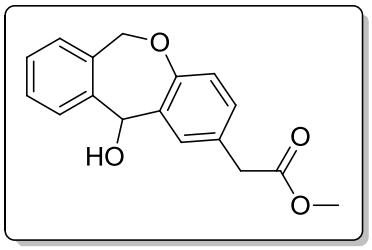
To complete the synthesis, the isomeric mixture (*E*/*Z* 4:6) of homoallyl alcohol **2** was subjected to mesylation and dimethylamination resulting in compound **12** in 84% yield (Scheme 6). IR spectrum of compound showed a strong absorption band at 1740 cm^{-1} indicating the presence of ester functionalities. ^{1}H NMR spectrum of compound **12** showed singlets at δ 2.15 (s, 2 H) and 2.24 (s, 4 H) integrated for 2 H and 4 H corresponding [-N($\underline{CH_3}$)$_2$] to *E*-isomer and *Z*-isomer respectively.[3] Ohshima *et al.* have reported the saponification and *E/Z* isomer separation of the corresponding acid. All the spectroscopic data of **12** was in good agreement with the reported one.[2.]

2.2.5 Conclusion

In conclusion, a novel and concise synthetic route to the antihistaminic drug, olopatadine hydrochloride has been developed, in seven steps with 59% overall yield. Lewis acid mediated ring opening of the cyclic ether resulted in the formation of desired *Z*-isomer (*E/Z* 2:3) as the major component, which could be improved to (*E/Z* = 1:9) after two recrystallization. The present method is operationally simple and have several advantageous compared to the conventional methods of manufacturing,[2] where a large excess of the reagent is required; the reaction has to be performed under strict anhydrous conditions with poor *E/Z* ratio.

2.2.6 Experimental

Methyl 2-(11-hydroxy-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (6):



2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetic acid (5 g, 18.65 mmol) was dissolved in methanol (100 mL) and cooled at 0 °C. Thionyl chloride (2.06 mL, 27.98 mmol) was added dropwise during a half hour period and the solution was stirred at room temperature for 24 h. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane (50 mL) and saturated sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, giving ketoester, which was used without further purification.

Ketoester (5 g, 17.66 mmol) was dissolved in methanol (50 mL) and cooled to 0 °C. Sodium borohydride (0.65 g, 17.66 mmol) was added portionwise over a period of half hour. After complete addition, the reaction mixture was stirred for additional 2 h. After completion of the raction (TLC), the reaction mixture was quenched by addition of 10% HCl solution and evaporated almost to dryness and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine solution were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (silica gel, pet. ether: EtOAc, 7:3) to furnish **6** as colorless liquid**.**

R_f = 0.3 (pet. ether-ethyl acetate, 7:3)

Yield: 4.8 g, 96% over two steps.

MF: $C_{17}H_{16}O_4$, **MW:** 284.30.

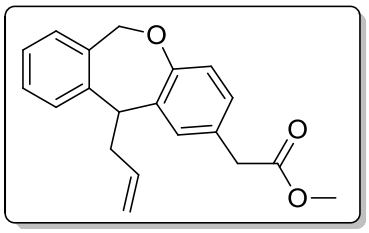
IR ($CHCl_3$, cm^{-1}): νmax 3462, 2951, 1739, 1496.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.01 (brs, 1 H), 3.51 (s, 2 H), 3.64 (s, 3 H), 4.93 (d, *J* = 12.8 Hz, 1 H), 5.55 (s, 1 H), 5.83 (d, *J* = 12.8 Hz, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 8.3 Hz and 2.2 Hz, 1 H), 7.17-7.37 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 39.9, 51.9, 70.6, 76.1, 120.5, 126.5, 127.4, 127.9, 128.4 (2 C), 128.6, 130.6, 131.6, 134.7, 140.6, 155.8, 172.2.

MS (ESI): *m/z*: 307.00 $(M+Na)^+$.

Methyl 2-(11-allyl-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (4):



To a stirred solution of **6** (4 gm, 14.08 mmol) in dry CH_2Cl_2 (40 mL) was added Allyl-TMS (3.34 mL, 3.59 mmol) at 0 °C, after 10 min $BF_3{\cdot}Et_2O$ was added slowly over period of 15 min and stirred for another 15 min. TLC showed complete conversion of hydroxyl to allyl. Reaction mixture was quenched by careful addition of saturated solution of NH_4Cl, after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, to yield colorless oil of **4** which was purified using flash chomatography (silica gel, pet. ether: ethyl acetate, 2:8) furnished allyl compound **4** as colorless liquid.

R_f = 0.6 (pet. ether-ethyl acetate, 2:8)

Yield: 4.03 g, 93%.

MF: $C_{20}H_{20}O_3$, **MW:** 308.37.

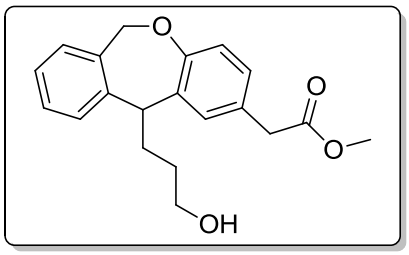
IR ($CHCl_3$, cm^{-1}): νmax 2950, 1732, 1500.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.78-3.13 (m, 2 H), 3.63 (s, 2 H), 3.76 (s, 3 H), 3.90 (t, *J* = 7.8 Hz, 1 H), 4.90-5.14 (m, 3 H), 5.57 (d, *J* = 14.6 Hz, 1 H), 5.63-5.87 (m, 1 H), 6.98-7.08 (m, 1 H), 7.08-7.21 (m, 3 H), 7.21-7.33 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 40.4, 43.6, 51.9, 52.6, 72.8, 116.3, 121.3, 126.7, 127.2, 127.4, 128.4, 128.9, 130.4, 131.5, 133.6, 135.8, 136.6, 140.1, 156.8, 171.8.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{20}H_{21}O_3$-309.1485, observed-309.1480.

Methyl 2-(11-(3-hydroxypropyl)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (7):



The allyl compound **4** (2 g, 6.49 mmol) was dissolved in dry THF (15 mL) in an oven-dried flask under a nitrogen atmosphere, then $BH_3{\cdot}DMS$ (1.31 mL, 12.98 mmol) was added dropwise *via* syringe at 0 °C, stir it for 4 h. Then the reaction mixture was quenched with 3 M NaOH (2.4 mL) at 0 °C, followed by the dropwise addition of 30% H_2O_2 (2.2 mL) and the resulting solution was stirred for additional 6 h at room temperature. The organic phase was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (30

mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 7:3) to obtain primary alcohol **7** as liquid.

R_f = 0.5 (pet. ether-ethyl acetate, 1:1)

Yield: 1.9 g, 90 %.

MF: $C_{20}H_{22}O_4$, **MW:** 326.38.

IR ($CHCl_3$, cm^{-1}): νmax 3444 (broad), 2952, 1738, 1500.

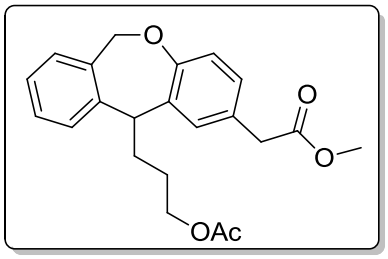
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.35-1.58 (m, 2 H), 1.96-2.35 (m, 3 H), 3.46-3.61

(m, 4 H), 3.68 (s, 3 H), 3.74 (t, *J* = 7.8 Hz, 1 H), 4.95 (d, *J* = 14.5 Hz, 1 H), 5.48 (d, *J* = 14.5 Hz, 1 H), 6.98-6.87 (m, 1 H), 6.99-7.11 (m, 3 H), 7.11-7.23 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 31.6, 35.4, 40.3, 51.9, 52.2, 62.5, 72.7, 121.3, 126.7, 127.2, 127.5, 128.4, 128.9, 130.2, 131.5, 134.0, 135.7, 140.6, 156.7, 172.0.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{20}H_{23}O_4$-327.1591, observed-327.1584.

Methyl 2-(11-(3-acetoxypropyl)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (3):



1 g (3.08 mmol) of alcohol **7** was dissolved in dry DCM (10 mL) and the solution was stirred. To the stirred solution was added 0.49 mL (6.16 mmol) of pyridine at 0 °C and the mixture was stirred for five minutes. Acetic anhydride (0.72 mL, 7.71 mmol) was added dropwise, and stirred well while warming to room temperature for 4 h. Reaction mixture was quenched by saturated solution of $NaHCO_3$ (10 mL), The organic phase was separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 8:2) to obtain acetate **3** as sticky liquid.

R_f = 0.6 (pet. ether-ethyl acetate, 7:3)

Yield: 1.1 g, 98 %

MF: $C_{22}H_{24}O_5$, **MW:** 368.42.

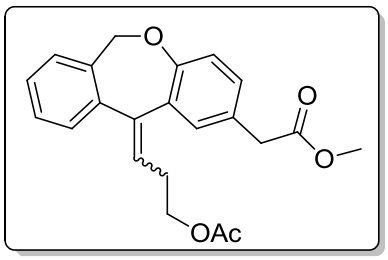
IR ($CHCl_3$, cm^{-1}): νmax 2950, 1742, 1732, 1503.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.49-1.62 (m, 2 H), 2.02 (s, 3 H), 2.05-2.17 (m, 1 H), 2.17-2.30 (m, 1 H), 3.55 (s, 2 H), 3.68 (s, 3 H), 3.74 (t, 1 H), 4.02 (t, 2 H), 4.95 (d, *J* = 14.5 Hz, 1 H), 5.47 (d, *J* = 14.5 Hz, 1 H), 6.96 (d, *J* = 8.7 Hz, 1 H), 7.01-7.11 (m, 3 H), 7.13-7.24 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 20.8, 27.4, 35.2, 40.2, 51.8, 51.9, 64.0, 72.6, 121.3, 126.7, 127.1, 127.3, 128.5, 128.9, 130.1, 131.3, 133.9, 135.6, 140.1, 156.6, 170.6, 171.7.

HRMS (ESI) $[M + H]^+$ Calculated for $C_{22}H_{25}O_5$-369.1697, observed-369.1692.

Methyl 2-(11-(3-acetoxypropylidene)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (8): To a solution of acetate **7** (1 g, 2.71 mmol) in dry dioxane (10 mL), DDQ (2.98 mmol) was added. The reaction mixture was refluxed for 6 h. After completion of the reaction, the precipitated solid $DDQH_2$ was removed by filtration and the filtrate was evaporated. The residue was taken in ethyl acetate (20 mL) and was washed with water (2 × 10 mL), saturated solution of $NaHCO_3$ (2 × 5 mL), brine (2 × 10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford a crude yellow liquid. The crude product was subjected to purification by flash column chromatography (silica gel, pet. ether: ethyl acetate, 8:2) to furnish acetate **8** as an oil (*E/Z* = 3:1).



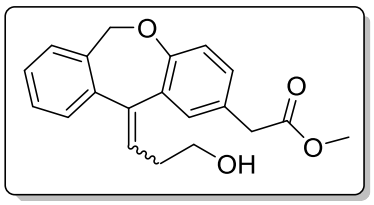
R_f = 0.6 (pet. ether-ethyl acetate, 7:3)

Yield: 0.39 g, 40 %

MF: $C_{22}H_{22}O_5$, **MW:** 366.14.

IR ($CHCl_3$, cm^{-1}): νmax 2950, 1742, 1732, 1503.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) (*E/Z* = 3:1): δ 2.04 (s, 2.25 H, for *E*-isomer), 2.07 (s, 0.75 H, for *Z*-isomer), 2.51 (dt, *J* = 7.1 and 6.7 Hz, for *E*-isomer), 2.77 (dt, *J* = 7.1 and 6.7 Hz, for *Z*-isomer), 3.54 (s, 2 H), 3.69 (s, 3 H), 4.13-4.23 (m, 2 H), 5.16 (brs, 2 H), 5.69 (t, *J* = 7.1 Hz, 0.25 H, for *Z*-isomer), 6.02 (t, *J* = 7.1 Hz, 0.75 H, for *E*-isomer), 6.71 (d, *J* = 8.24 Hz, 0.75 H, for *E*-isomer), 6.81 (d, *J* = 8.24 Hz, 0.25 H, for *Z*-isomer), 7.03-7.40 (m, 6 H).

Methyl 2-(11-(3-hydroxypropylidene)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (2): 

To a stirred solution of acetate **8** (0.3 g, 0.81 mmol) in MeOH was added K_2CO_3 (0.22 g, 1.63 mmol) at room temperature and stirred for 30 min. The MeOH was evaporated, diluted with EtOAc (10 mL) and solid K_2CO_3 was filtered. The filtrate was washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to afford a crude product. The crude product was subjected to flash column chromatography (silica gel, pet. ether: ethyl acetate, 7:3) to obtain homoallyl alcohol **2** as a white solid (*E/Z* = 3:1).

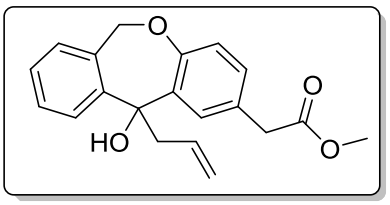
R_f = 0.4 (pet. ether-ethyl acetate, 6:4)

Yield: 0.25 g, 96 %

MF: $C_{20}H_{20}O_4$, **MW:** 324.13.

IR ($CHCl_3$, cm^{-1}): νmax 3446, 2921, 1736, 1463.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.38-2.49 (m,0.8 H, *E*-Form), 2.63-2.73 (m,1.2 H, *Z*-Form), 3.53 (s, 2 H), 3.68 (s, 3 H), 3.75 (m, 0.8 H, *E*-Form), 3.81 (t, *J*=6.3 Hz, 1.2 H), 5.19 (brs, 2 H), 5.73 (t, *J*=7.8 Hz, 0.6 H, *Z*-Form), 6.06 (t, *J*=7.8 Hz, 0.4 H, *E*-Form), 6.70 (d, *J*=8.2 Hz, 0.4 H, *E*-Form), 6.79 (d, *J*=8.2 Hz, 0.6H, *Z*-Form), 7.00-7.34 (m, 6H).

Methyl 2-(11-allyl-11-hydroxy-6,11-dihydrodibenzo [*b,e*]oxepin-2-yl) acetate (11): 

2-(11-Oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetic acid **5** (5.00 g, 18.65 mmol) was dissolved in methanol (100 mL) and cooled at 0 °C. Thionyl chloride (2.06 mL, 27.98 mmol) was added dropwise over 30 min and the resulting solution was stirred at ambient temperature for 24 h. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, giving Isoxepac ester, which was used without further purification.

To a stirred mixture of Isoxepac ester (5.00 g, 17.66 mmol) and zinc (3.44 g, 53 mmol) in DMF (50 mL), allyl bromide (1.66 mL, 19.43 mmol) was added at 0 ºC. After 2 hours, the reaction mixture was filtered to remove the excess zinc. 10%

Hydrochloric acid (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with small portions of EtOAc (3 × 20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting liquid was purified by column chromatography (silica gel, pet. ether- EtOAc, 8:2) to furnish compound **11** as thick colorless liquid.

R_f = 0.5 (pet. ether-EtOAc, 8:2).

Yield: 5.2 g, 91% over two steps.

MF: $C_{20}H_{20}O_4$, **MW:** 324.37.

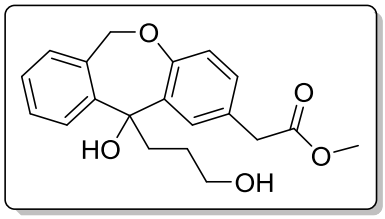
IR ($CHCl_3$, cm^{-1}): νmax 3482, 3073, 2951, 1735, 1490.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ = 2.86-2.97 (m, 1 H), 3.34-3.44 (m, 1 H), 3.60 (s, 2 H), 3.68 (s, 3 H), 5.04 (d, *J* = 15.5 Hz, 1 H), 5.09-5.18 (m, 2 H), 5.47 (d, *J* = 15.5 Hz, 1 H), 5.35-5.56 (m, 1 H), 6.90-7.00 (m, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 7.15-7.31 (m, 3 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 7.94-7.84 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 40.5, 48.7, 51.8, 73.6, 75.7, 119.4, 121.3, 125.8, 125.9, 126.8, 127.0, 127.5, 129.5 (2 C), 133.5, 134.5, 139.0, 142.1, 154.7, 171.9.

HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{21}O_4$: 325.1434, found: 325.1433.

Methyl 2-(11-hydroxy-11-(3-hydroxypropyl)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (10): 9-BBN (1.80 g, 14.81 mmol) was added to a well stirred solution of olefin **11** (4.00 g, 12.34 mmol) in anhydrous THF (40 mL) at ambient temperature and the reaction mixture was stirred for 24 h at 70 ºC. The reaction mixture was quenched with 3 M NaOH solution (0.54 g, 13.50 mmol) at 0 ºC, followed by the dropwise addition of 30% H_2O_2 (3.50 mL, 37.03 mmol). The resulting solution was stirred for 6 h at room temperature to cleave the boron complex. The organic phase was separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pet. ether-EtOAc, 7:3) to obtain diol **10** as colorless liquid.



R_f = 0.4 (pet. ether-EtOAc, 1:1).

Yield: 3.54 g, 84%.

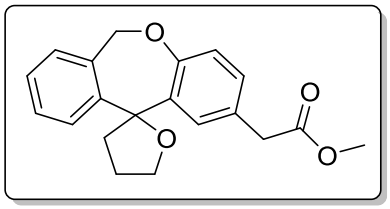
MF: $C_{20}H_{22}O_5$, **MW:** 342.38.

IR ($CHCl_3$, cm^{-1}): νmax 3505, 2949, 1735, 1491.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 1.20-1.56 (m, 2 H), 2.08-2.28 (m, 1 H), 2.64-2.89 (m, 1 H), 3.36-3.64 (m, 4 H), 3.67 (s, 3 H), 4.84 (brs, 1 H), 5.01 (d, *J* = 15.4 Hz, 1 H), 5.43 (d, *J* = 15.4 Hz, 1 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 6.98-7.32 (m, 4 H), 7.62 (d, *J* = 2.2 Hz, 1 H), 7.97 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 27.3, 40.4, 41.9, 52.0, 62.7, 73.7, 76.6, 121.2, 125.8, 126.2, 126.9 (2 C), 128.3, 129.3 (2 C), 134.4, 139.7, 143.4, 154.9, 172.6.

HRMS (ESI) $[M + Na]^+$ calcd for $C_{20}H_{22}O_5Na$: 365.1359, found: 365.1360.

Methyl 2-(4',5'-dihydro-3'H,6H-spiro[dibenzo[*b,e*] oxepine-11,2'-furan]-2-yl)acetate (9):  The diol **10** (3.00 g, 2.50 mmol) was dissolved in dry DCM (30 mL) in an oven-dried flask under a nitrogen atmosphere and *p*-TSA (83 mg, 0.43 mmol) was added at ambient temperature. The solution was stirred for additional 10 min. and then the reaction mixture was quenched by the addition of water (20 mL). Resulting organic mass was extracted with DCM (3 × 20 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was column purified over silica gel (pet. ether:EtOAc, 9:1) to furnish spiro ether **9** as colorless liquid.

R_f = 0.7 (pet. ether-EtOAc, 8:2).

Yield: 2.81 g, 99 %.

MF: $C_{20}H_{20}O_4$, **MW**: 324.37.

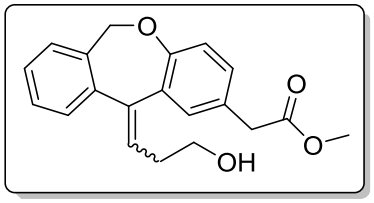
IR ($CHCl_3$, cm^{-1}): νmax 2926, 1738, 1488.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ = 1.87-1.99 (m, 2 H), 2.56-2.72 (m, 2 H), 3.59 (s, 2 H), 3.69 (s, 3 H), 4.33-4.17 (m, 2 H), 5.02 (d, *J* = 15.3 Hz, 1 H), 5.56 (d, *J* = 15.3 Hz, 1 H), 6.97 (d, *J* = 7.2 Hz, 1 H), 7.03 (d, *J* = 8.03 Hz, 1 H), 7.10-7.26 (m, 3 H), 7.51 (s, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ = 25.9, 40.7, 42.6, 51.9, 68.9, 72.9, 85.1, 121.4, 124.5, 126.2 (2C), 126.9, 127.0, 129.21, 129.27, 133.6, 140.2, 143.4, 153.9, 172.0.

HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{21}O_4$: 325.1434, found: 325.1437.

Methyl 2-(11-(3-hydroxypropylidene)-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (2): To an ice cold (0 ºC), magnetically stirred solution of spiro ether **9** (2.00 g, 6.12 mmol) in anhydrous DCM (25 mL), was added anhydrous crystalline aluminium chloride (2.05 g, 15.43 mmol) in one portion under nitrogen. The resulting mixture was warmed to ambient temperature and the red-orange reaction mixture was stirred at ambient temperature until the completion of reaction (7 h, by TLC). The reaction mixture was then poured into an ice cooled 10% aqueous HCl solution and the aqueous layer was extracted with DCM. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (silica gel, pet. ether/EtOAc, 7:3) resulting in allylic alcohol **2** as white solid.



Mp 102-104 °C.

R_f = 0.4 (pet. ether-EtOAc, 6:4).

Yield: 1.9 g, 95 %.

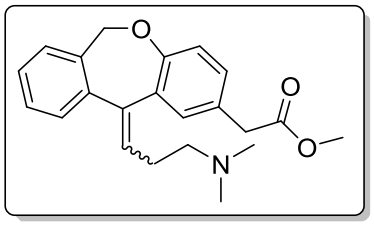
MF: $C_{20}H_{20}O_4$, **MW:** 324.13.

IR ($CHCl_3$, cm^{-1}): νmax 3446, 2921, 1736, 1463.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 2.38-2.49 (m, 0.8 H, *E*-isomer), 2.63-2.73 (m, 1.2 H, *Z*-isomer), 3.53 (s, 2 H), 3.68 (s, 3 H), 3.69-3.75 (m, 0.8 H, *E*-isomer), 3.81 (t, *J* = 6.3 Hz, 1.2 H, *Z*-isomer), 5.19 (brs, 2 H), 5.73 (t, *J* = 7.8 Hz, 0.6 H, *Z*-isomer), 6.06 (t, *J* = 7.8 Hz, 0.4 H, *E*-isomer), 6.70 (d, *J* = 8.2 Hz, 0.4 H, *E*-isomer), 6.79 (d, *J* = 8.2 Hz, 0.6 H, *Z*-isomer), 7.00-7.34 (m, 6 H).

HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{21}O_4$: 325.1434, found: 325.1437.

Methyl 2-(11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenzo [*b,e*]oxepin-2-yl)acetate (12): To allyl alcohol **2** (1.00 g, 3.08 mmol) in pyridine (16 mL) was added methanesulfonyl chloride (0.95 mL, 11.72 mmol) gradually at 0 °C. The reaction mixture was allowed to come to ambient temperature and stirred for further 2 h. The reaction mixture was quenched with water (5 mL) and then extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (10 mL) and concentrated at reduced pressure. To a solution of the resulting oil in MeOH (20 mL) was added 50% aqueous dimethylamine (5.20 mL,



18.0 equiv) and the mixture was stirred under reflux for 3 h. The solvent was evaporated and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (DCM:MeOH, 97:3) to obtain **12** as pale yellow liquid.

R_f = 0.4 (MeOH).

Yield: 0.91 g, 84% over two steps.

MF: $C_{22}H_{25}NO_3$, **MW:** 351.43.

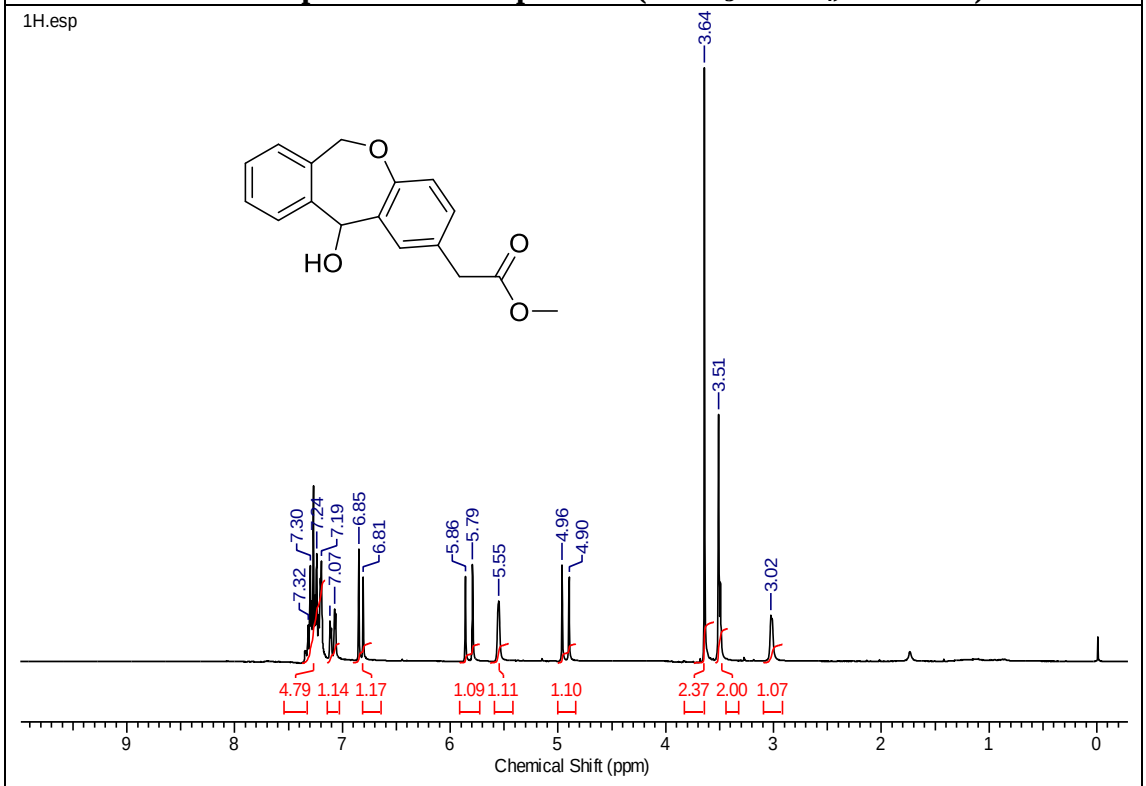
IR ($CHCl_3$, cm^{-1}): νmax 1740, 1495, 1221.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 2.15 (s, 2 H), 2.24 (s, 4 H), 2.31-2.62 (m, 4 H), 3.51 (s, 2 H), 3.67 (s, 3 H), 4.73 (brs, 1 H), 5.45 (brs, 1 H), 5.69 (t, *J* = 7.1 Hz, 0.6 H, *Z*-isomer), 6.02 (t, *J* = 6.9 Hz, 0.4 H, *E*-Form), 6.69 (d, *J* = 8.3 Hz, 0.4 H, *E*-isomer), 6.78 (d, *J* = 8.3 Hz, 0.6 H, *Z*-isomer), 6.98-7.37 (m, 6 H).

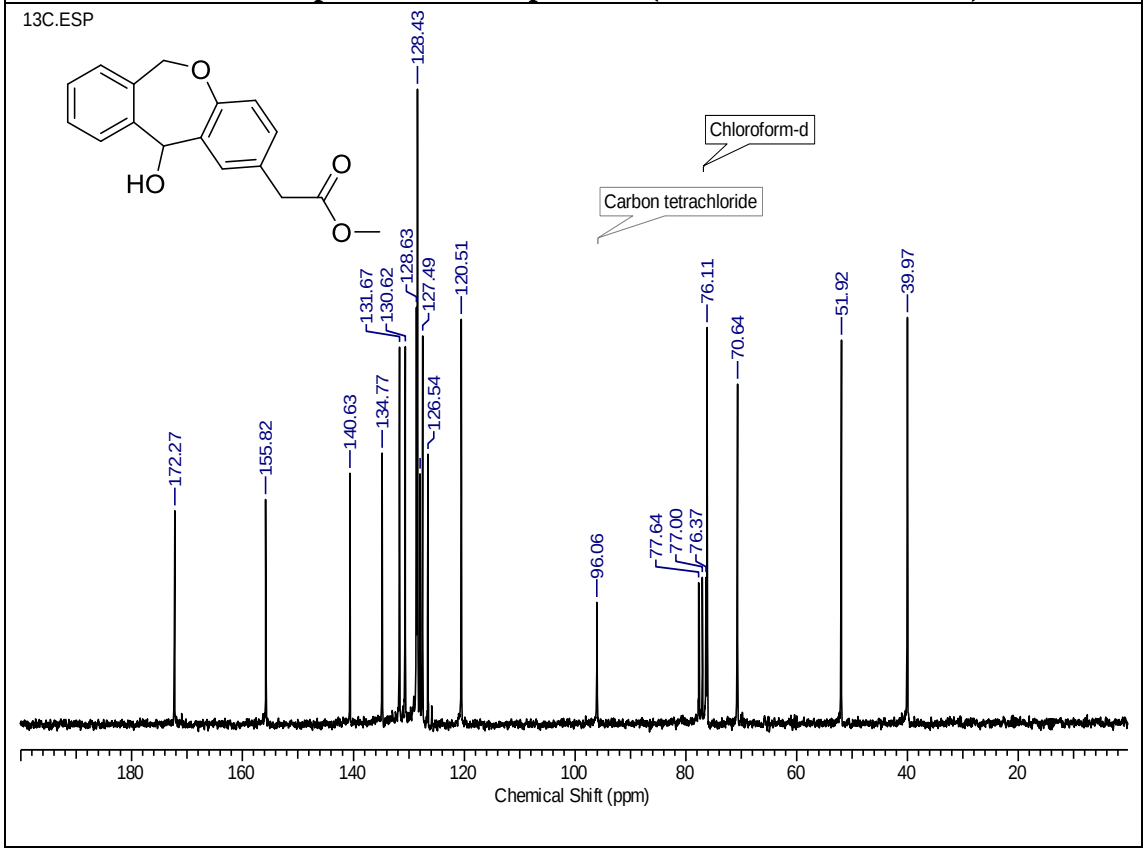
MS (ESI): m/z = 352.14 $(M + H)^+$.

2.2.7 Spectra

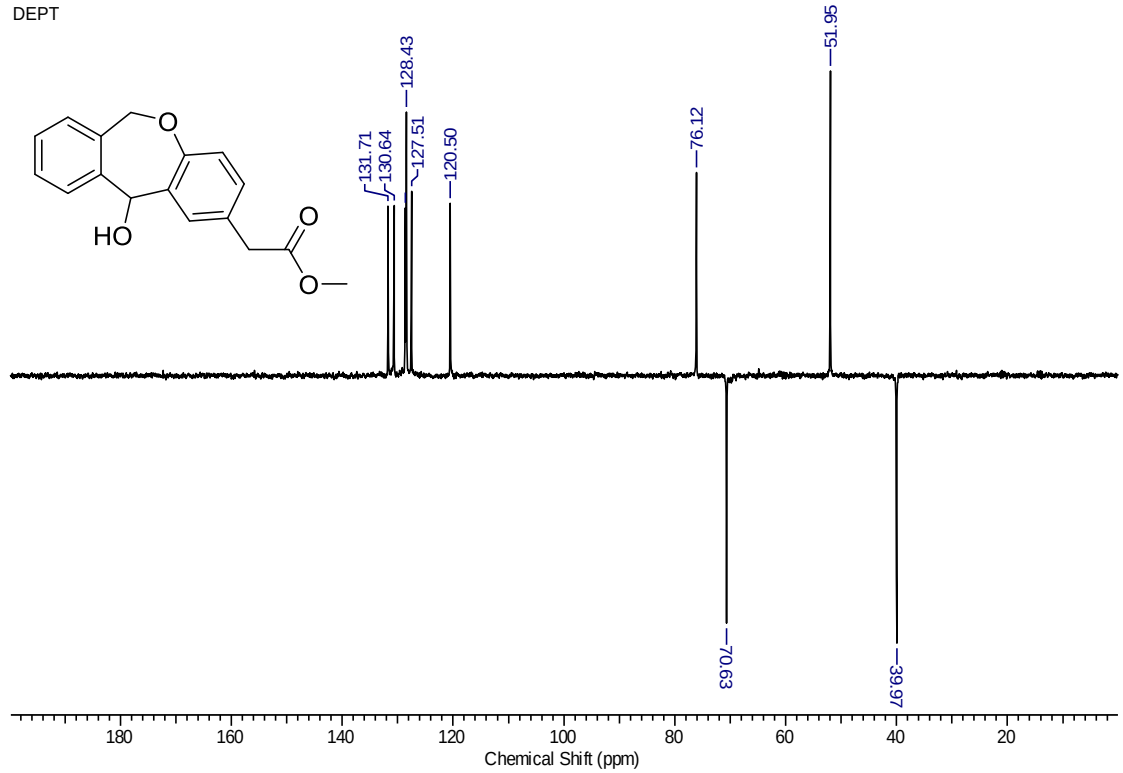
^{1}H NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 200 MHz)



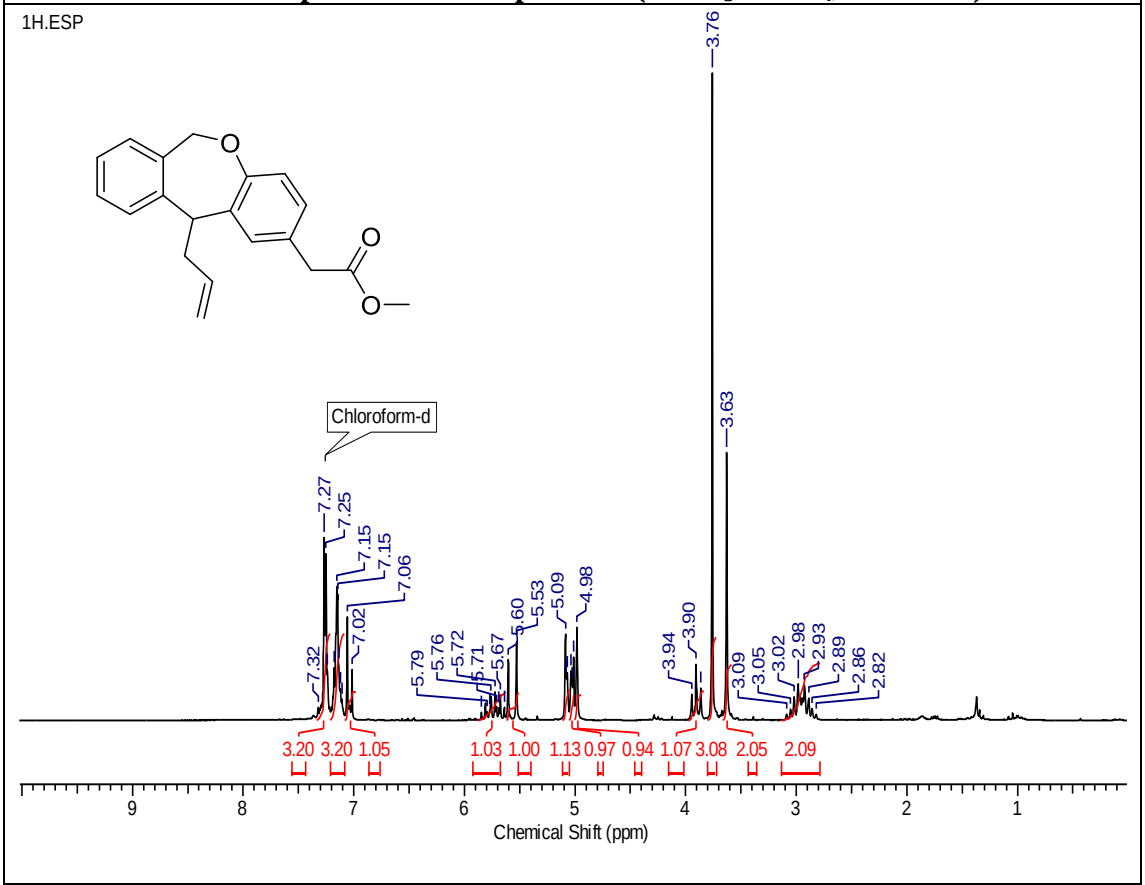
^{13}C NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 50 MHz)



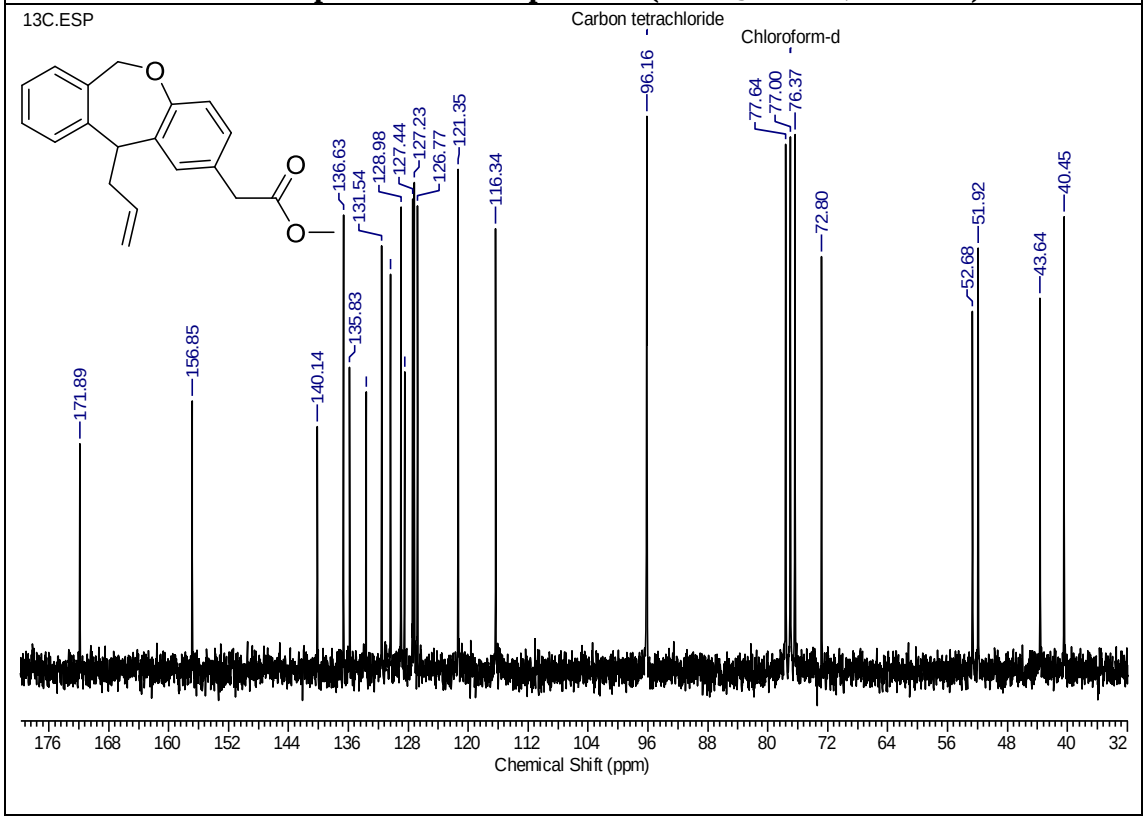
DEPT spectrum of compound 6 ($CDCl_3$ + CCl_4, 50 MHz)



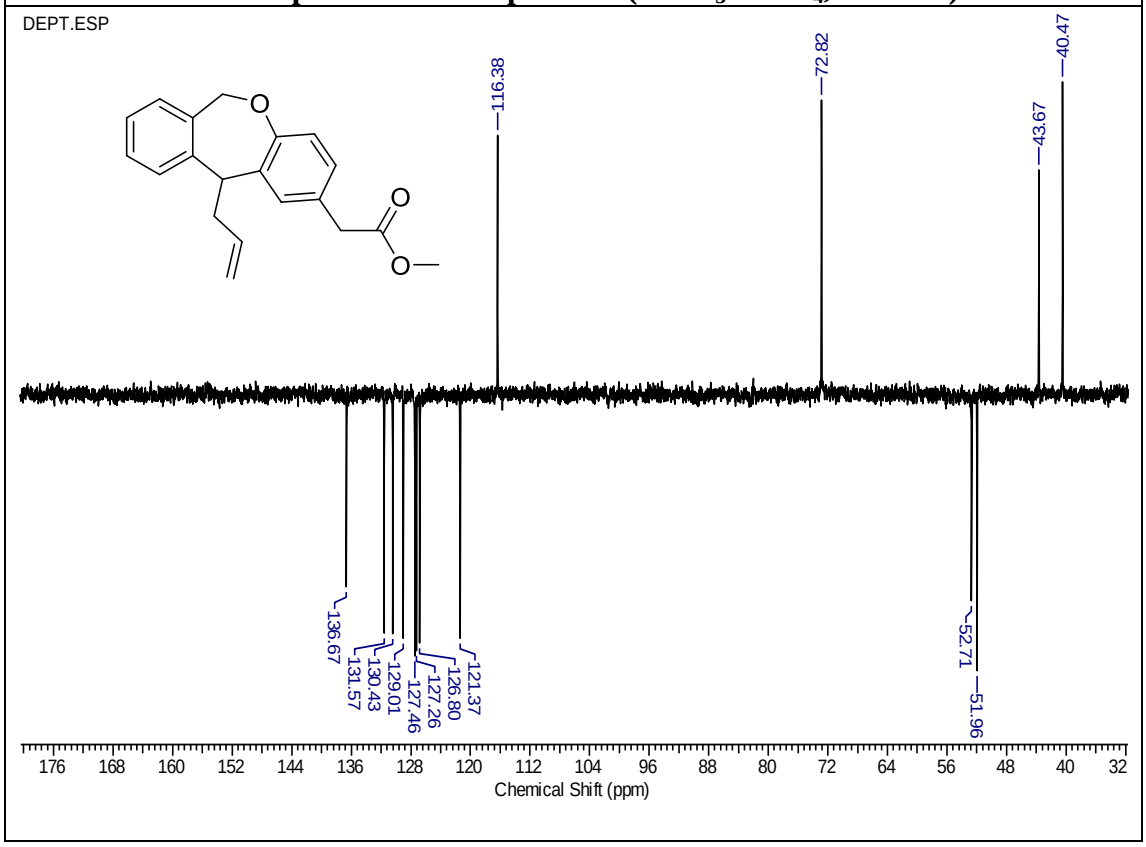
^{1}H NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 200 MHz)



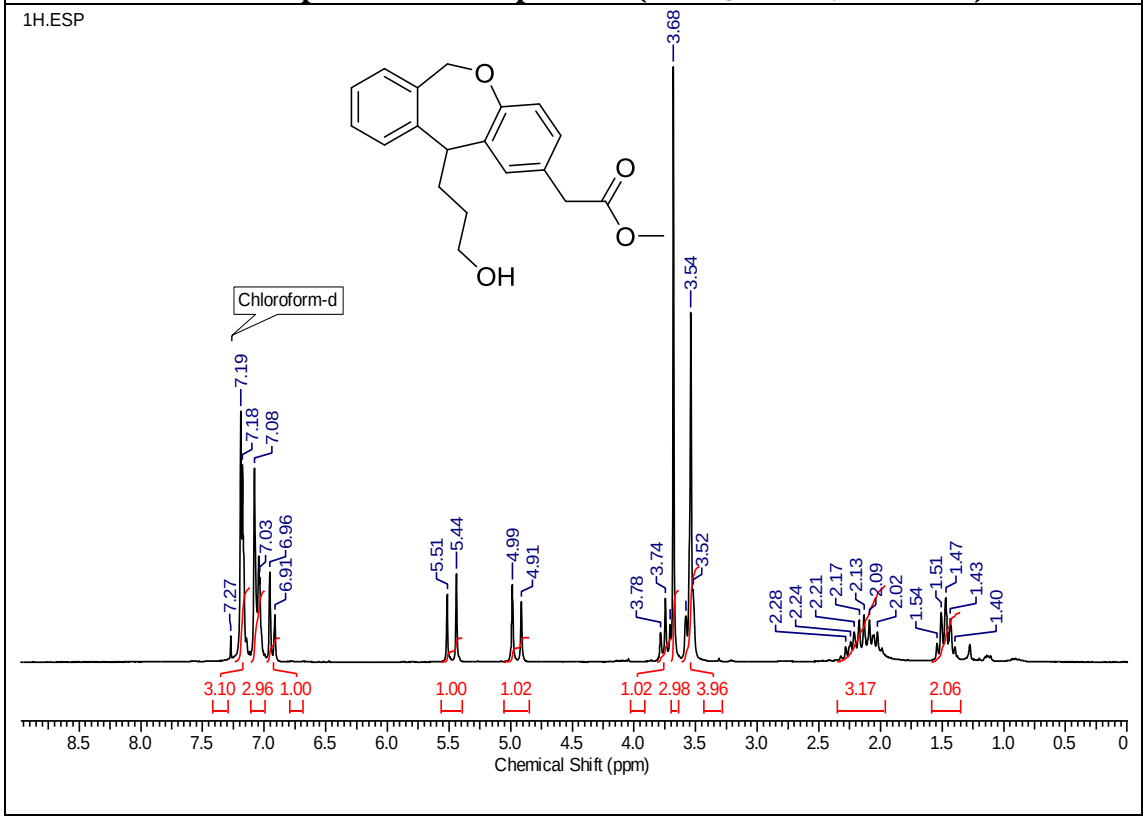
^{13}C NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 50 MHz)



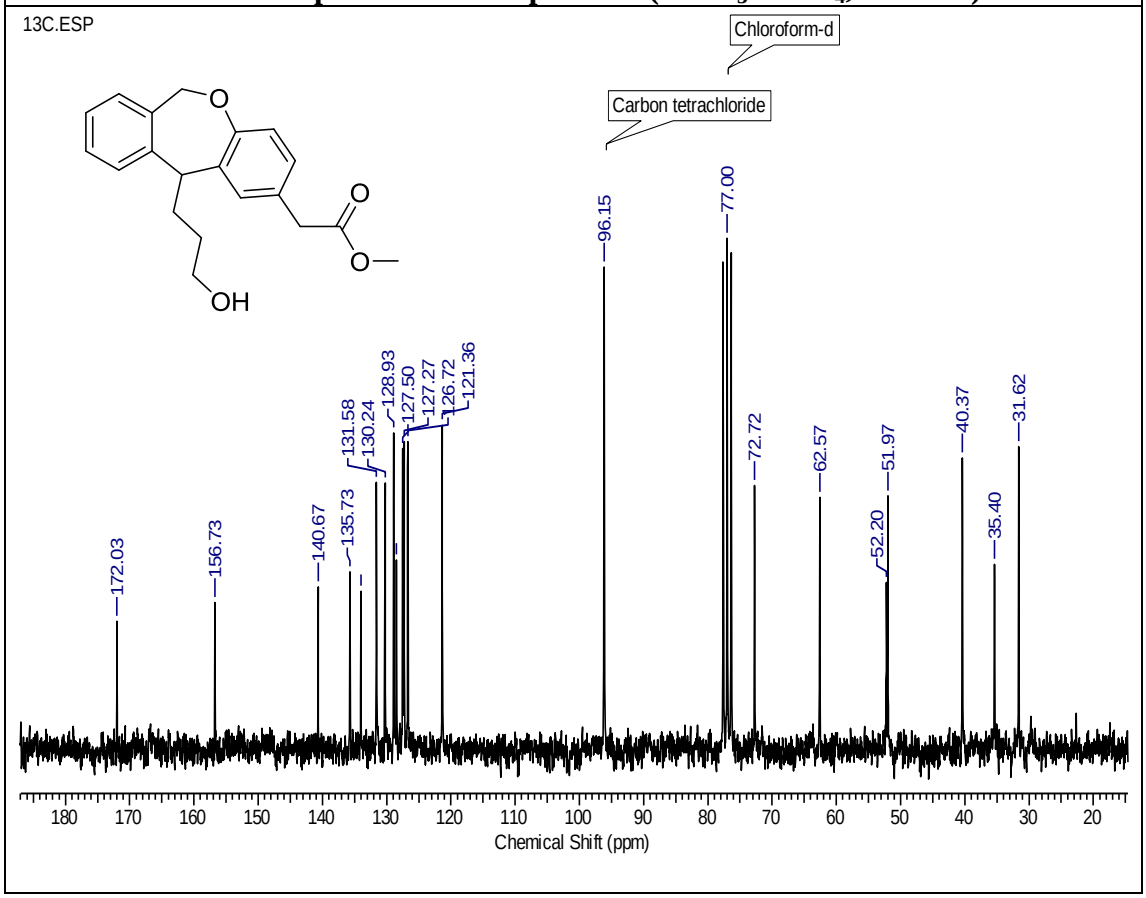
DEPT spectrum of compound 4 ($CDCl_3$ + CCl_4, 50 MHz)



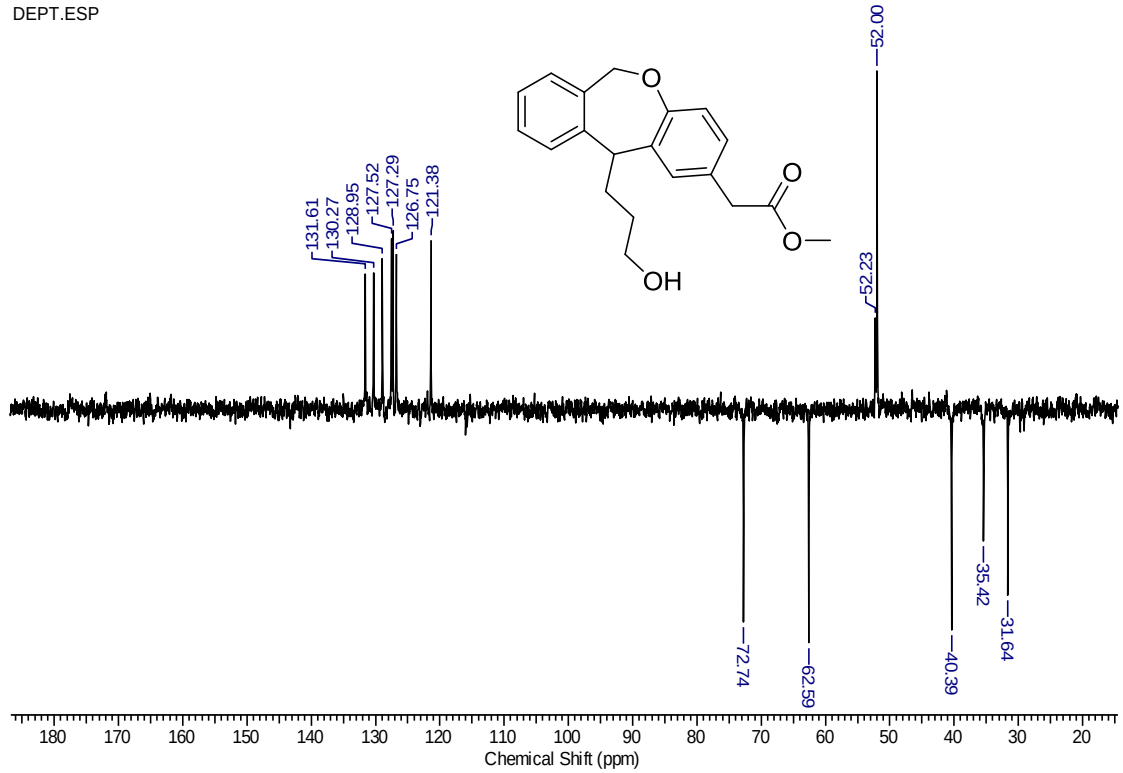
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 200 MHz)



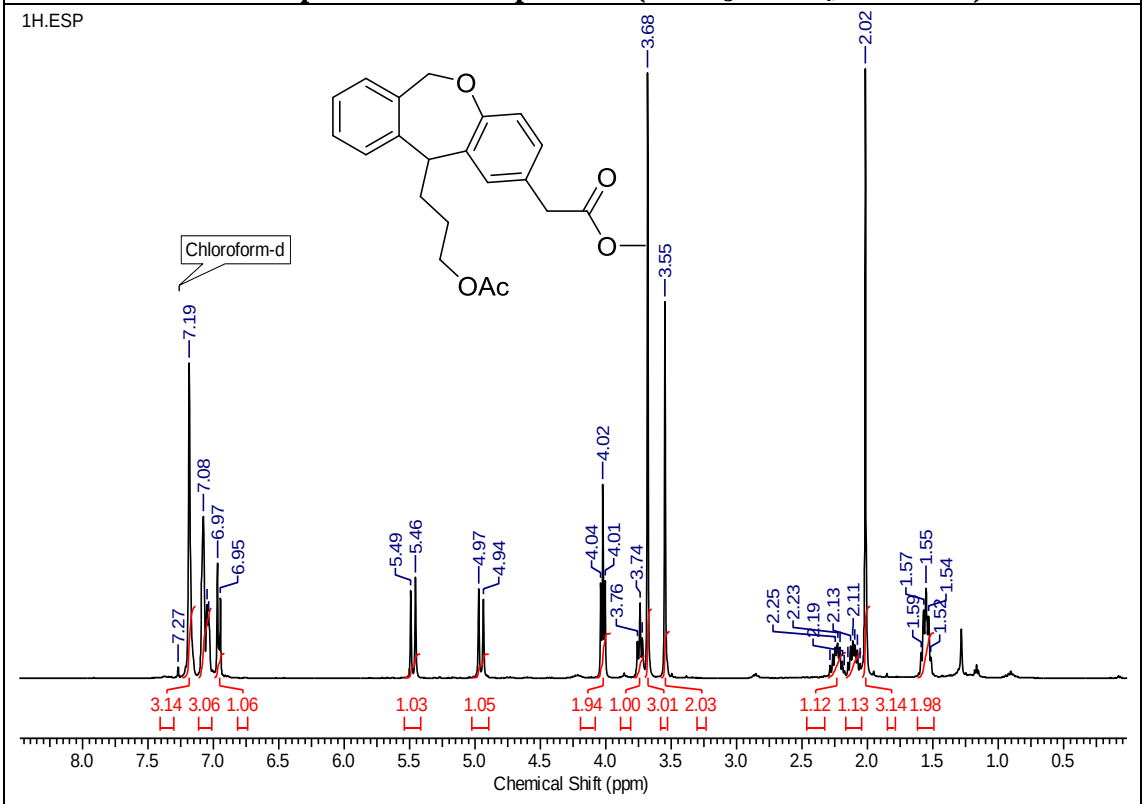
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



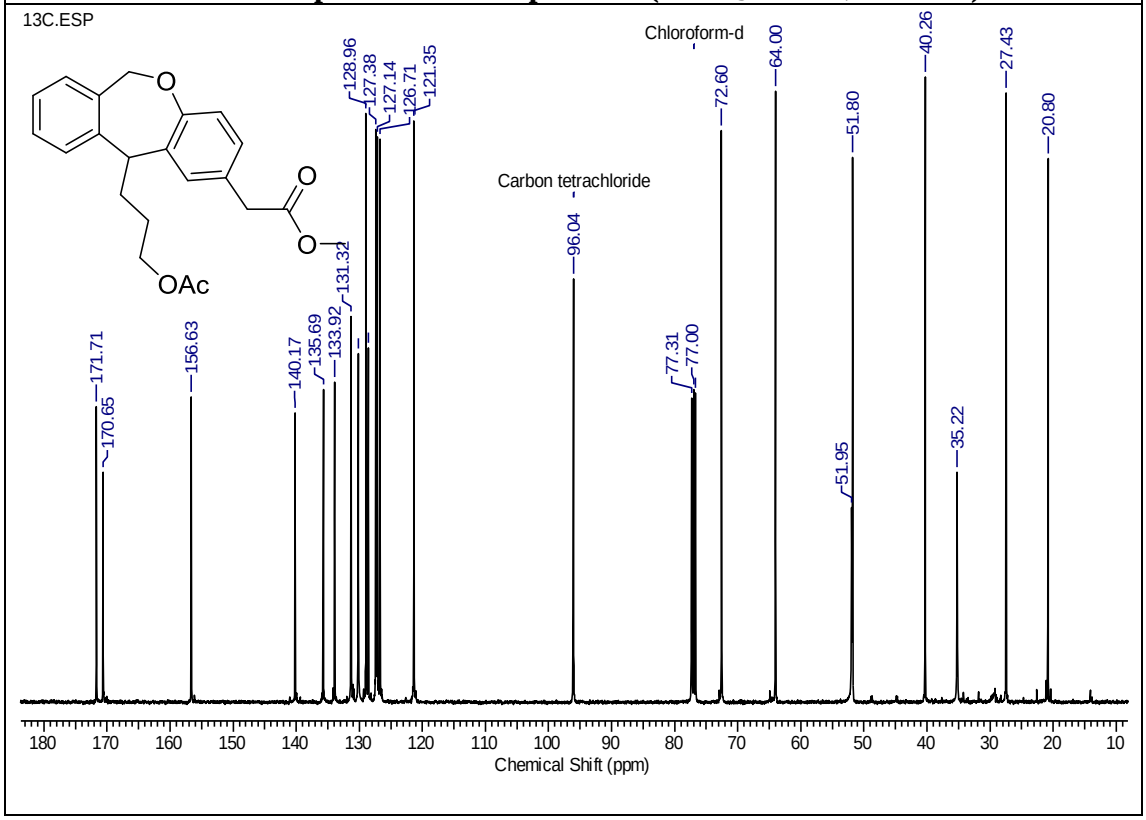
DEPT spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



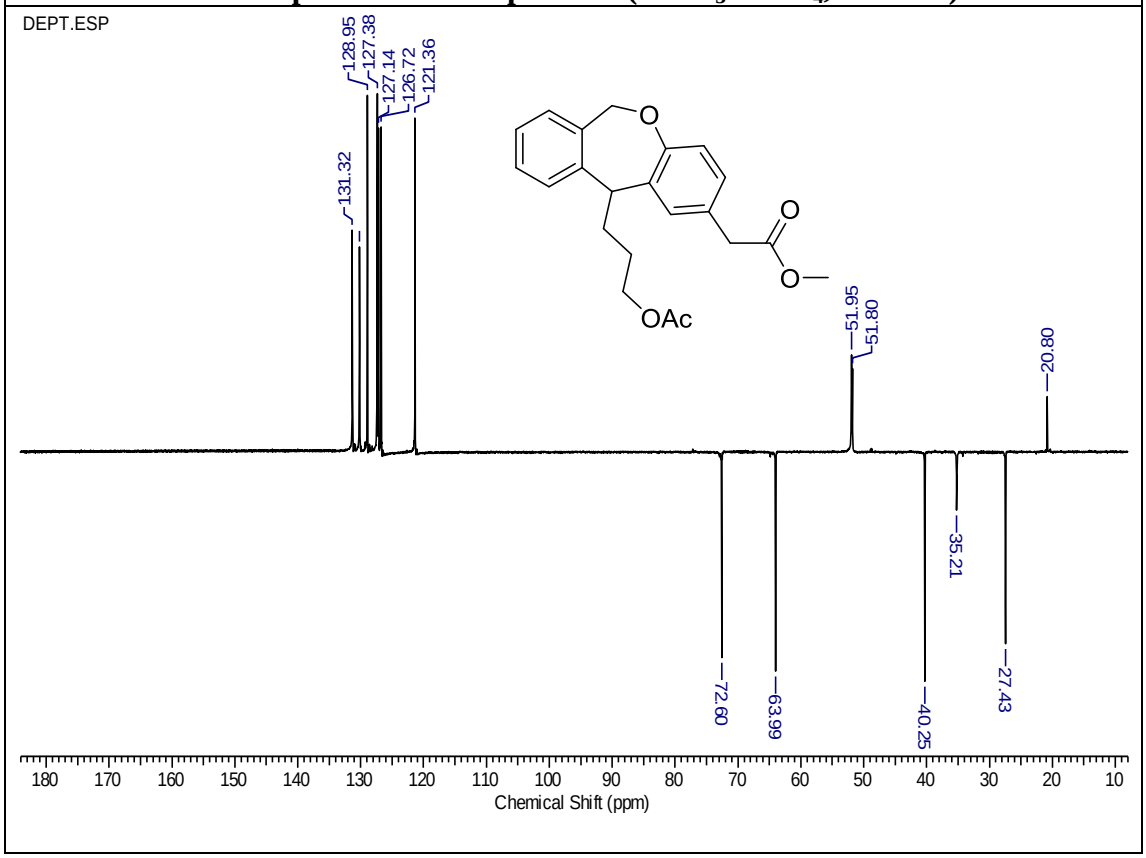
^{1}H NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 200 MHz)



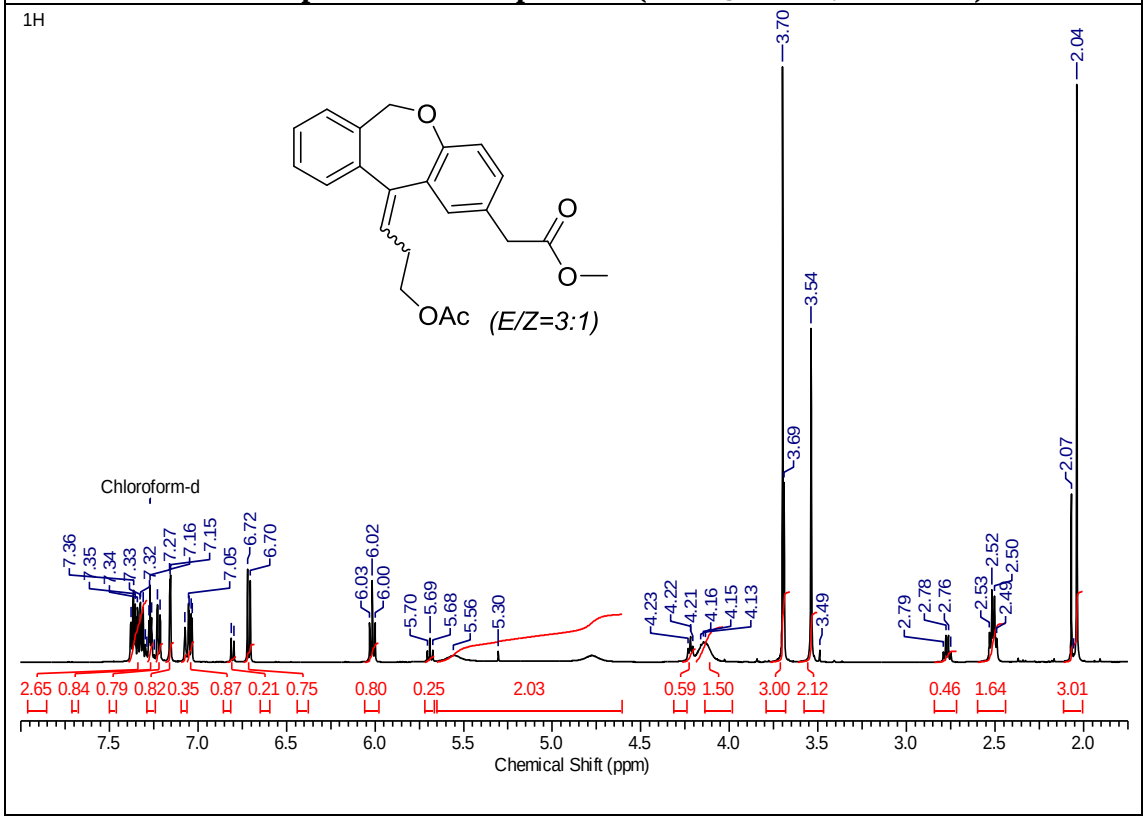
^{13}C NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 50 MHz)



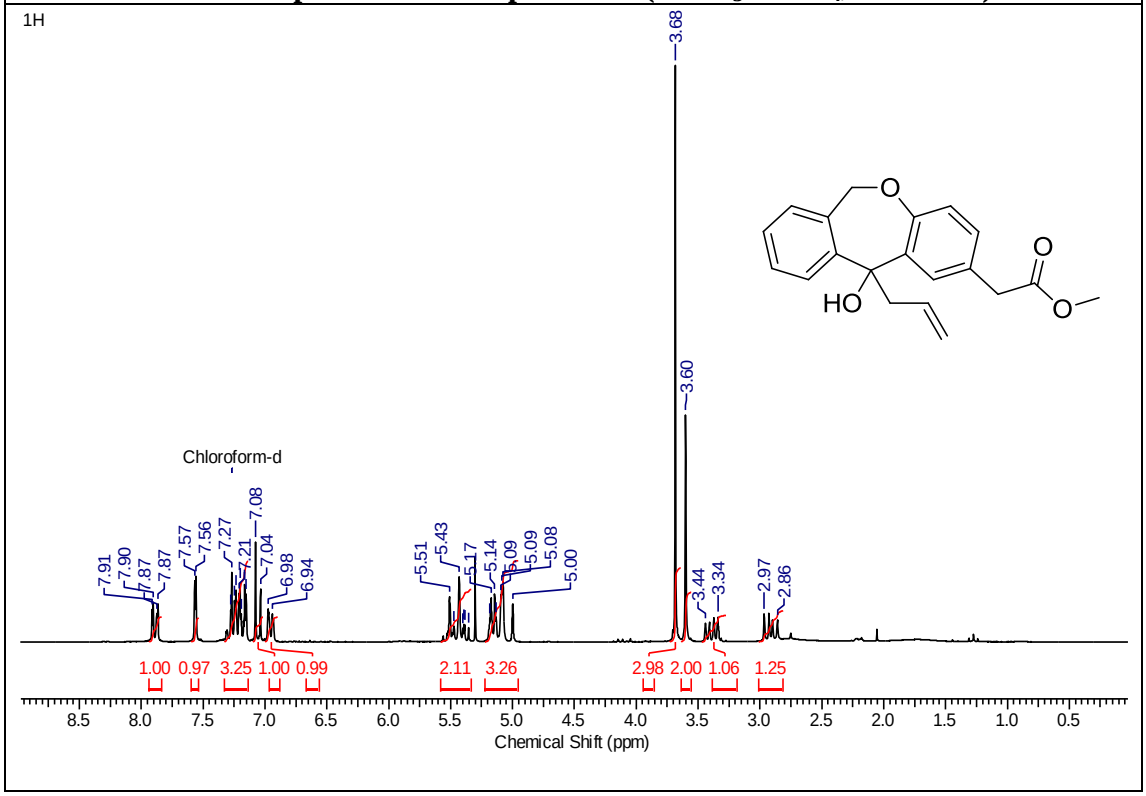
DEPT spectrum of compound 3 ($CDCl_3$ + CCl_4, 50 MHz)



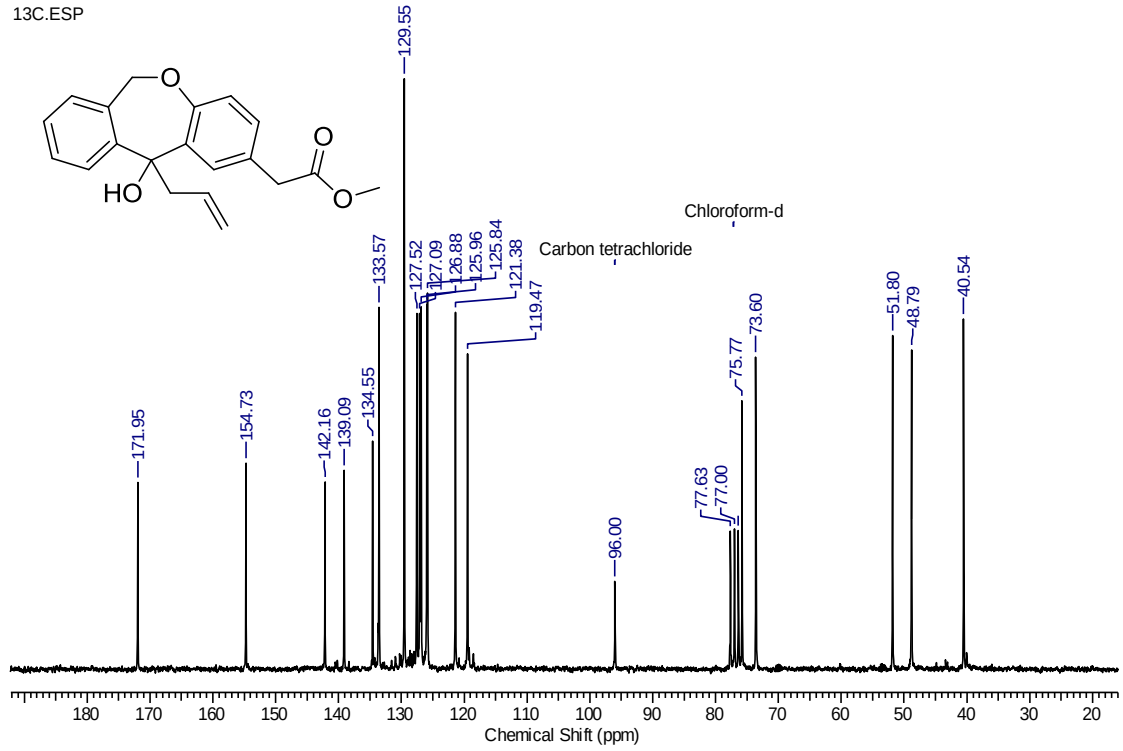
^{1}H NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 400 MHz)



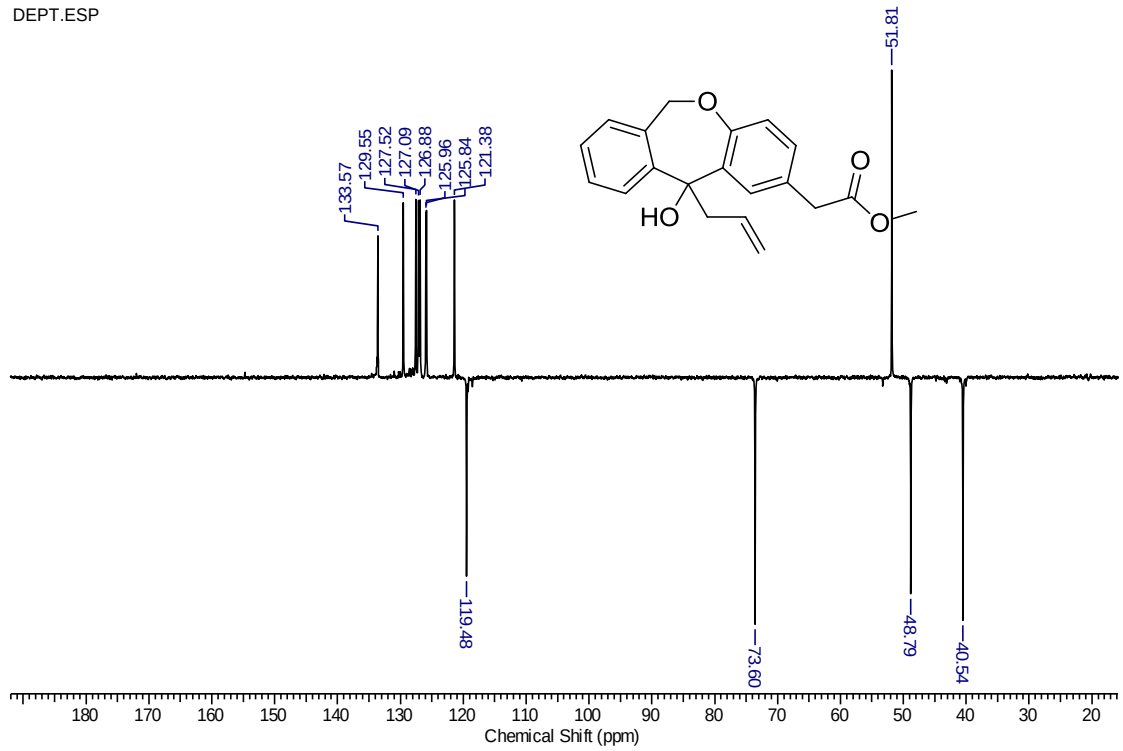
^{1}H NMR spectrum of compound 11 ($CDCl_3$ + CCl_4, 200 MHz)



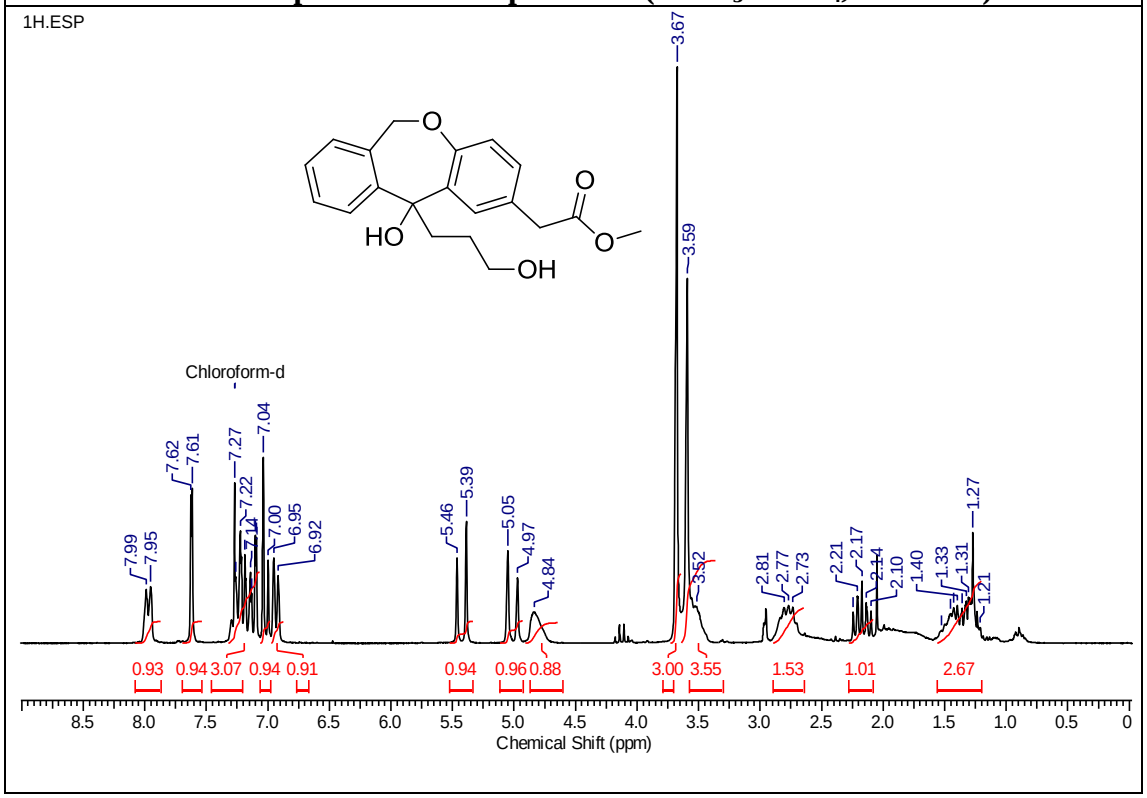
^{13}C NMR spectrum of compound 11 ($CDCl_3$ + CCl_4, 50 MHz)



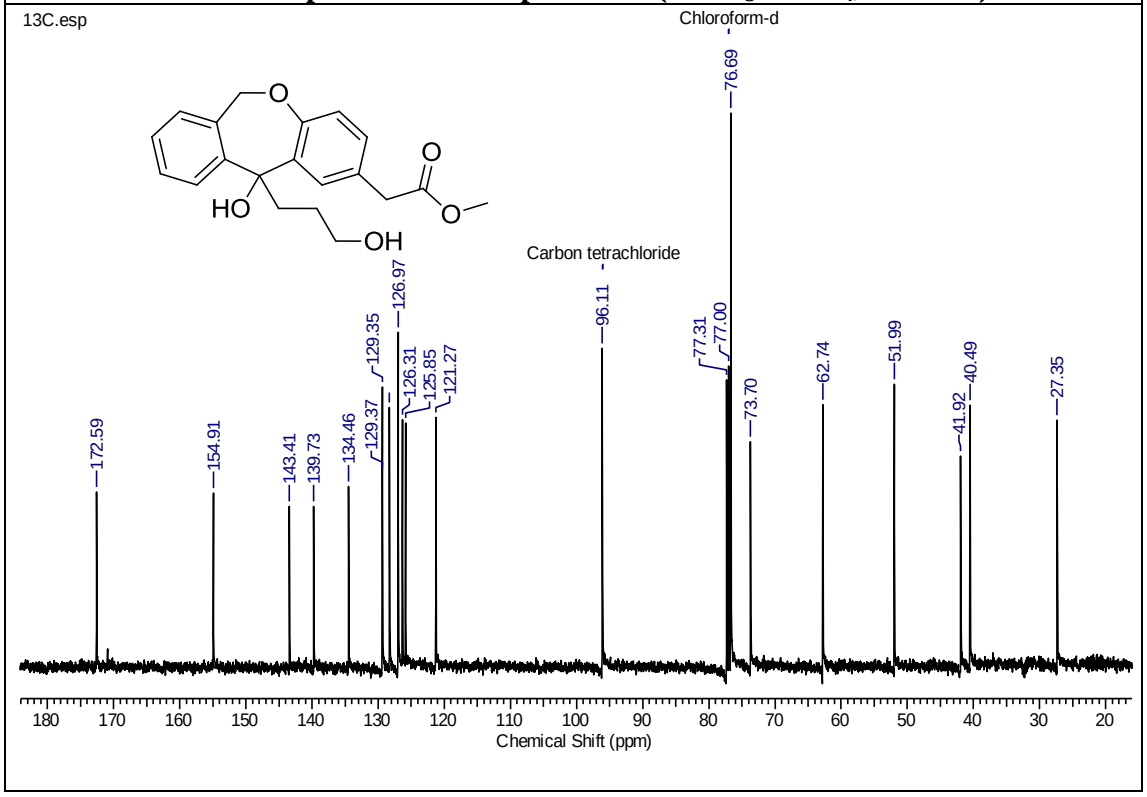
DEPT spectrum of compound 11 ($CDCl_3$ + CCl_4, 50 MHz)



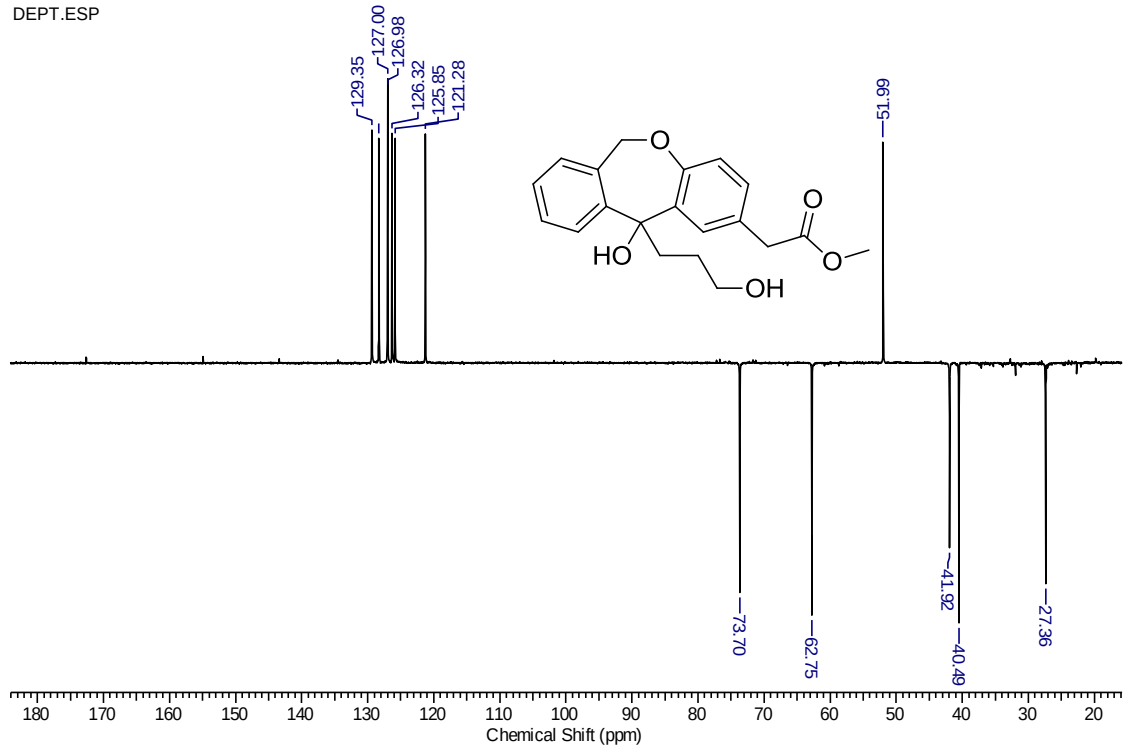
^{1}H NMR spectrum of compound 10 ($CDCl_3$ + CCl_4, 200 MHz)



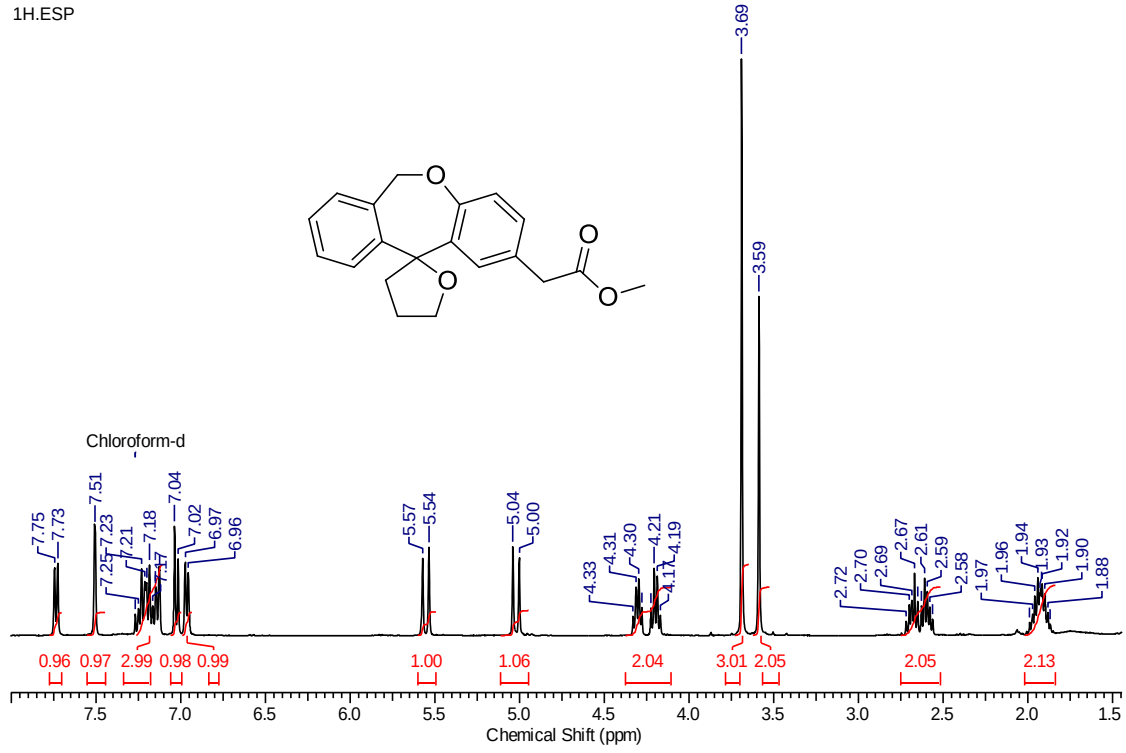
^{13}C NMR spectrum of compound 10 ($CDCl_3$ + CCl_4, 50 MHz)



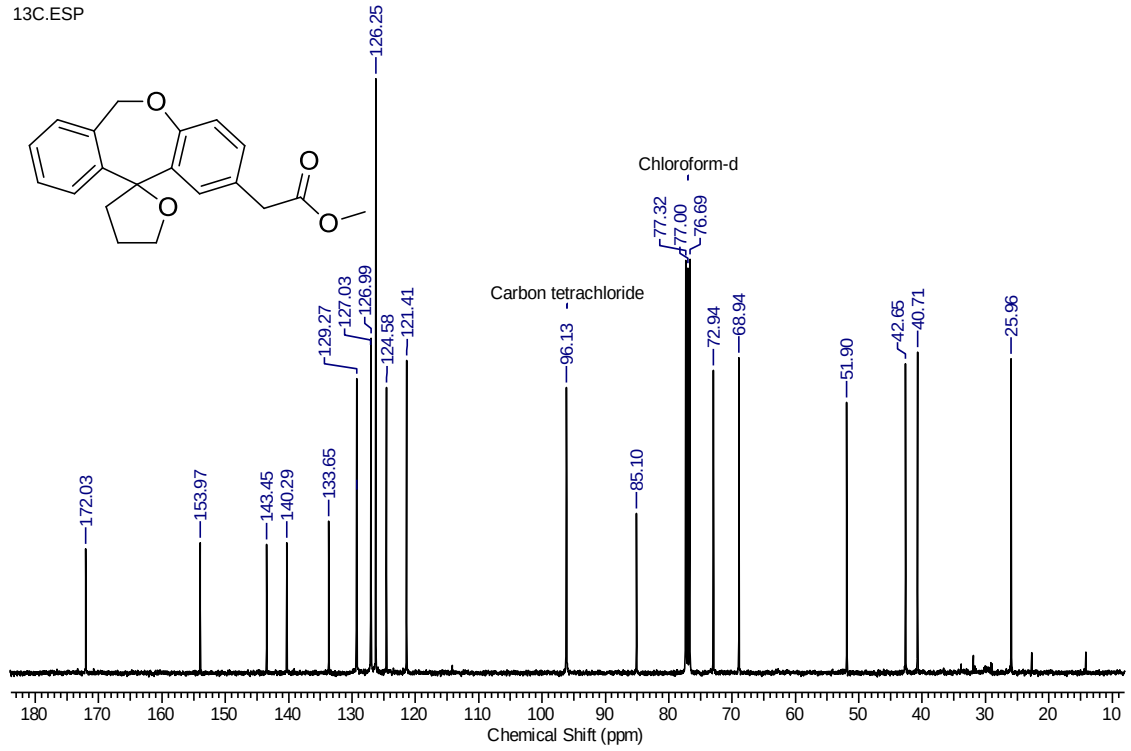
DEPT spectrum of compound 10 ($CDCl_3$ + CCl_4, 50 MHz)



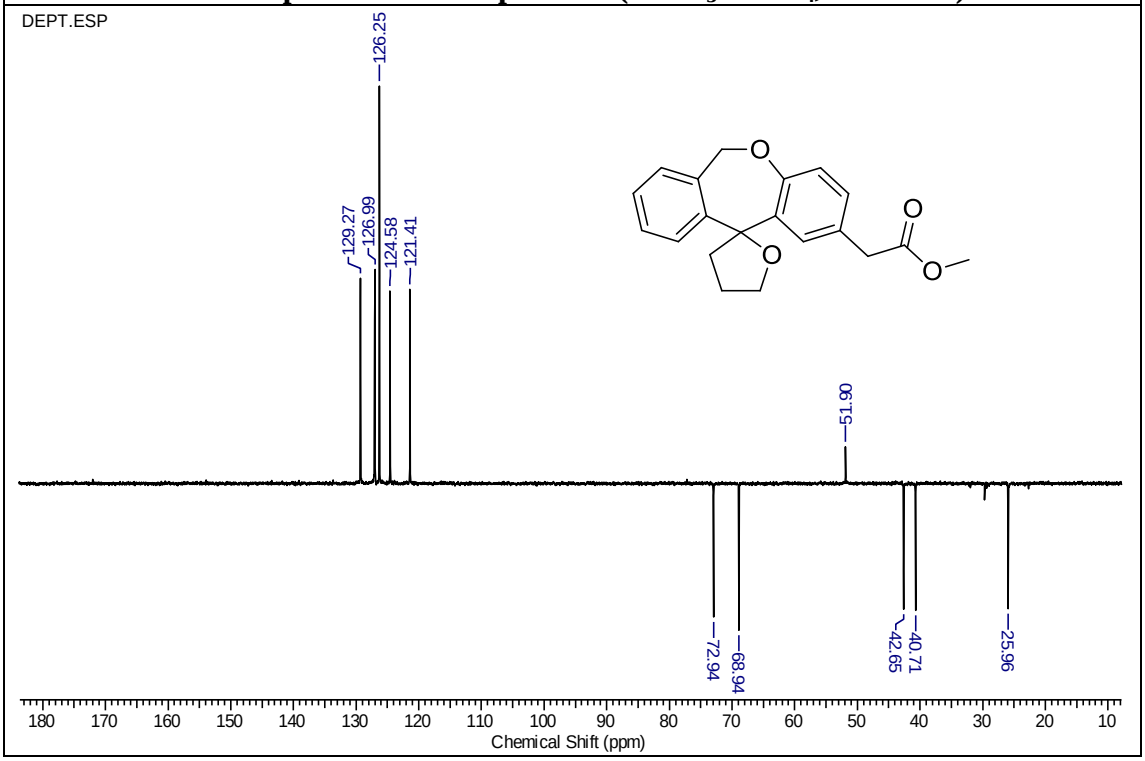
^{1}H NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 400 MHz)



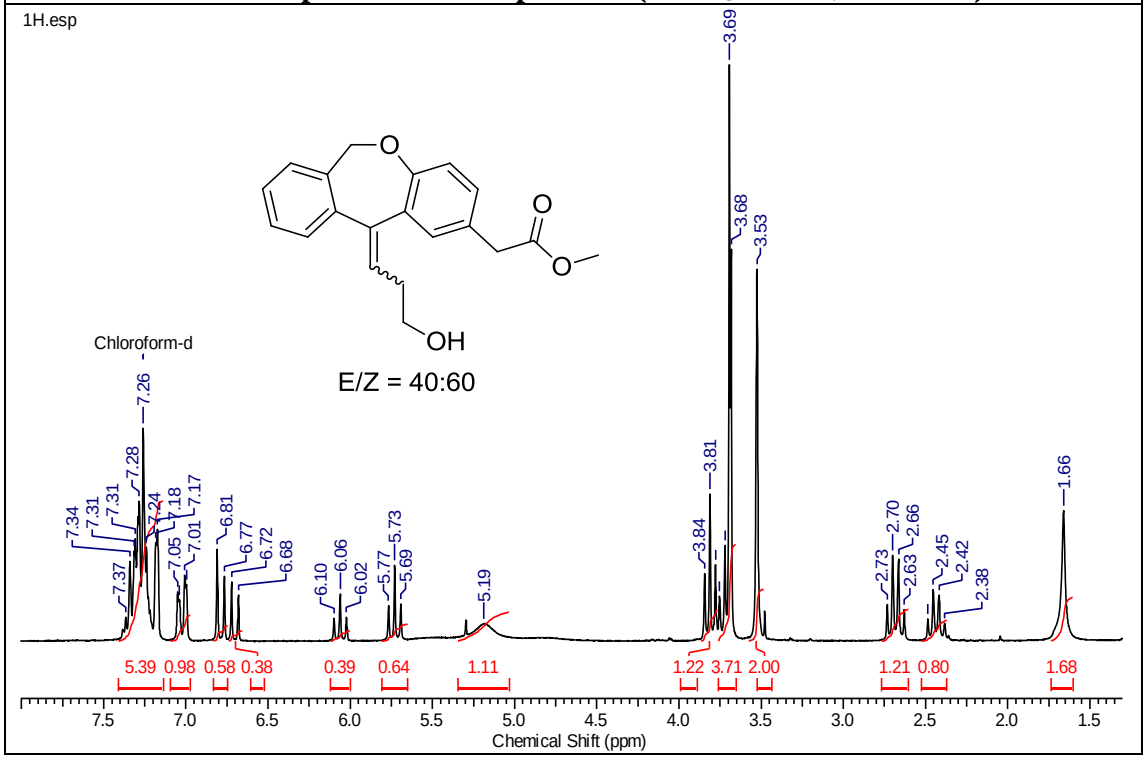
^{13}C NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 100 MHz)



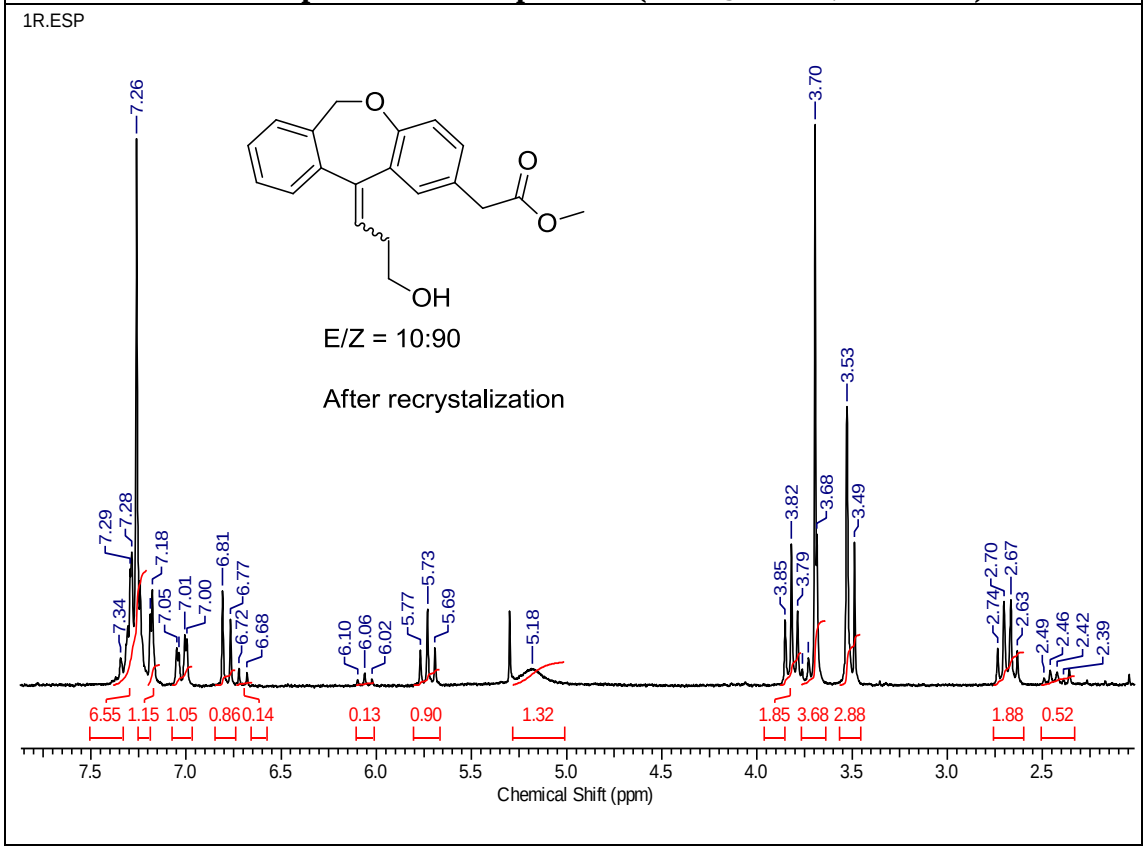
DEPT spectrum of compound 9 ($CDCl_3$ + CCl_4, 100 MHz)



^{1}H NMR spectrum of compound 2 ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 2 ($CDCl_3$ + CCl_4, 200 MHz)



HPLC chromatogram of compound 2

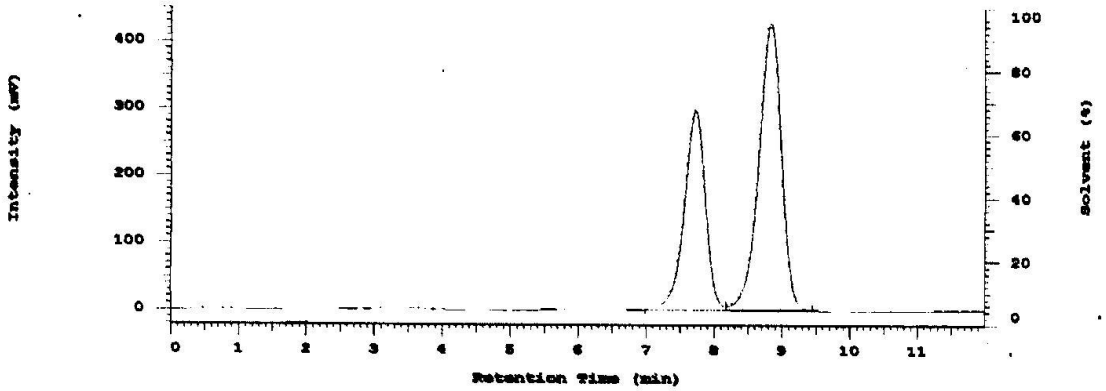
D-7000 HSM: NCLOC Series: 5810 Report: modified System: Sys 1

NATIONAL CHEMICAL LABORATORY

ORGANIC CHEMISTRY TECHNOLOGY

Analyzed: 12/14/12 03:41 PM Reported: 12/14/12 04:11 PM
Data Path: f:\win32app\hsm\NCLOC\DATA\5810\
Processing Method: Lichrosphere RP-18 (250-4) Acquisition Method: Lichrosphere RP-18 (250-4)
System(acquisition): Sys 1 Series:5810
Sample Name: PL-766-2 Vial Number: 4
Injection from vial: 1 of 1 Vial Type: UNK
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	7.72	296332	6386981	39.157
2	8.83	427591	9924438	60.843
		723923	16311419	100.000

Peak rejection level: 0

Group Leader : Dr. S.P.Chavan
Column : Kromasil RP-18(150 x 4.6 mm)
M.P. : MeOH :H2O(60:40)
Flow Rate : 1.5 ml/min (3090 psi)
Sample conc: 1 mg/2.0 ml
Inj vol: 5 ul
WAVELENGTH : 254 nm

2.2.8 References

1. For synthetic processes, see: (a) Oshima, E.; Kumazawa, T.; Otaki, S.; Obase, H.; Ohmori, K.; Ishii, H.; Manabe, H.; Tamura, T.; Shuto, K. US Patent US005116863, **1992**; *Chem Abstr*. **1988**, *108*, 167330. (b) Lever, W.; Leighton, H. European Patent EP0214779, **1990**; *Chem Abstr*. **1987**, *107*, 58673. (c) Bosch, C.; Bachs, R.; Gomez, A.; Alonso, M.; Bessa, A. Patent WO2006/010459, **2006**; *Chem Abstr*. **2006**, *144*, 192128. (d) Tarur, V.; Bhise, N.; Sathe, D.; Naidu, A.; Aher, U.; Patil, S.; Verma, S.; Sawant, K.; Naik, T.; Amre, R. WO2007/105234 A2, **2007**; *Chem Abstr*. **2007**, *147*, 371628. (e) Castellin, A.; Ferrari, C.; Galvagni, M. U.S. Patent US 2011/0065936 A1, **2011**; *Chem Abstr*. **2010**, *153*, 554939.
2. Ohshima, E.; Otaki, S.; Sato, H.; Kumazawa, T.; Obase, H.; Ishii, A.; Ishii, H.; Ohmori, K.; Hirayama, N. *J. Med. Chem.* **1992,** *35*, 2074.
3. Bosch, J.; Bachs, J.; Gómez, A. M.; Griera, R.; Écija, M.; Amat, M. *J. Org. Chem.* **2012**, *77*, 6340.
4. Nishimura, K.; Kinugawa, M. *Org. Process. Res. Dev*. **2012**, *16*, 225.
5. Ueno, K.; Kubo, S.; Tagawa, H.; Yoshioka, T.; Tsukada, W.; Tsubokawa, M.; Kojima, H.; Kasahara, A. *J. Med. Chem.* **1976**, *19*, 941.
6. a) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956,** *78*, 5694; b) Brown, H. C; Zweifel, G. *J. Am. Chem. Soc.* **1959,** *81*, 247.
7. Chauncey, M.A.; Grundon, M.F. *Synthesis* **1990**, *11*, 1005.
8. Barbier, P. *Compt*. *Rend*. **1898**, *128*, 110.
9. Recrystalization details: after two crystallization using pet. ether/EtOAc (9:1) system, compound **2** with *E/Z* 2:3 ratio could be improved to *E/Z* 1:9 ratio.

Chapter 2. Synthetic studies towards olopatadine and one-pot migration-formylation of benzyl aryl ethers under Duff reaction condition

Section 3

One-pot migration-formylation of benzyl aryl ethers under Duff reaction condition

2.3.1 Summary

This section describes a one-pot migration-formylation of benzyl aryl ethers under Duff reaction condition. The reaction was performed with HMTA (hexamethylene tetramine) and TFA (trifluoroacetic acid). Under the optimal reaction conditions, a variety of Bn and PMB ethers underwent *ortho* rearrangement.

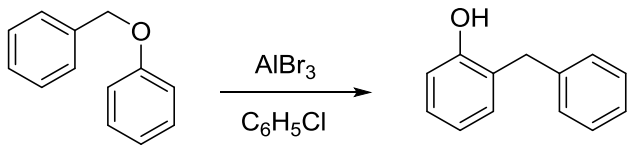
2.3.2 Introduction

3,5-Disubstituted salicylaldehydes have been shown to possess interesting pharmacological properties. They have great significance in synthetic organic chemistry, particularly in the area of asymmetric synthesis as salen ligands, which are combination of amines with 3,5-disubstituted salicylaldehyde.[1] For example, several asymmetric diiron complexes have been synthesized[2] from substituted salicylaldehyde, and these complexes mimic the spectroscopic properties of purple acid phosphatase enzymes. The use of bifunctional ligand systems is an attractive method of simulating the reactivity of natural enzymes.[3] They are also precursors to Schiff-base macrocycles. Duff and Bills reported formylation of phenolic compounds using hexamethylene tetramine,[4] which was later modified by Smith.[5] The Duff protocol for formylation of structurally and electronically demanding phenols has become an important tool in the arsenal of synthetic chemists.[6]

2.3.3 *Ortho* rearrangement of benzyl aryl ethers: A review

A short descriptive presentation of the work reported by different groups is being presented to give a better and comparative view of the different methods for *ortho* rearrangement of benzyl aryl ethers employed so far.

Tarbell's approach[7] (*J. Am. Chem. Soc.* **1952**, *74*, 244)

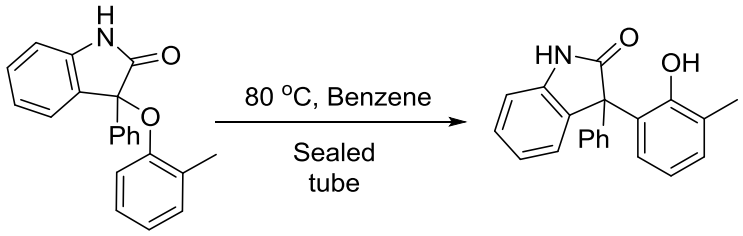


Scheme 1

Tarbell *et al.* observed that when they studied the reaction between benzyl phenyl ether and aluminum bromide, in order to compare the action of this strong Lewis acid on the oxygen ether; benzyl phenyl ether was found to be converted very rapidly by aluminum bromide in chlorobenzene solution to a mixture of phenol and *o*-

benzylphenol (Scheme 1). The ratio of the phenolic products is the same at -40 ºC or at 25 ºC and is unaffected by the use of benzene or nitrobenzene as the solvent.

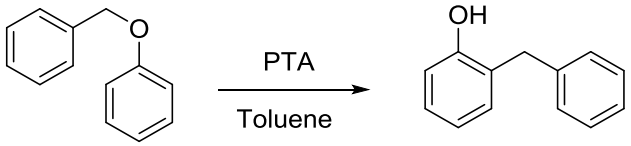
Magnus's approach[8] (*Org. Lett.* **2005**, *7*, 4531)



Scheme 2

Magnus *et al*. reported unusual rearrangement of an *O*-aryl ether to an *ortho*-hydroxyaryl system in good yield (Scheme 2).

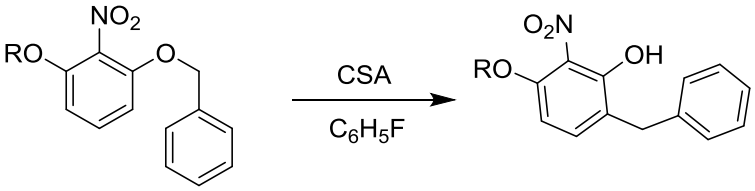
Rode's approach[9] (*Catal. Commun.* **2007**, *8*, 139)



Scheme 3

Rode *et al*. demonstrated that phosphotungstic acid could be used as a solid catalyst for the rearrangement of benzyl phenyl ether to give 2-benzyl phenol as a major product (Scheme 3). A complete conversion of benzyl phenyl ether with 52% selectivity to 2-benzyl phenol was achieved in toluene at reflux conditions and PTA catalyst could be easily recovered and reused without the loss of activity.

Luzzio's approach[10] (Luzzio, F. A.; Chen, J. *J. Org. Chem.* **2009**, *74*, 5629)



Scheme 4

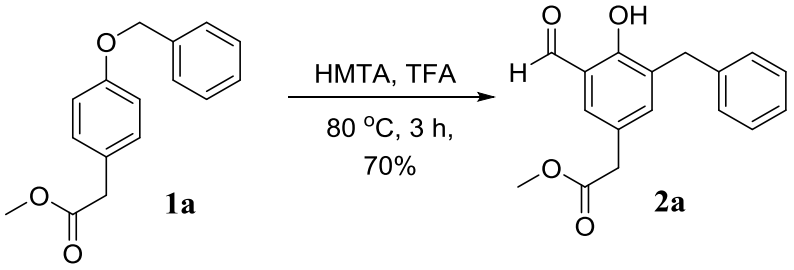
Luzzio *et al*. reported the use of camphorsulfonic acid in warm fluorobenzene to facilitates the *ortho* rearrangement of (alkoxy-substituted) benzyl ethers of 1-(*O*-methyl)-2-nitroresorcinols to the corresponding *o*-(alkoxy-substituted) arylmethylnitrophenols (Scheme 4). Bronsted acids can mediate the *ortho* rearrangement of benzyl phenyl ethers having multiple substituents on both the

migrating and nonmigrating rings. The presence of at least one electron-releasing group on the migrating ring allows the use of the relatively milder camphorsulfonic acid as the mediator.

2.3.4 Results and discussion

In the present work, a facile one-pot migration-formylation protocol is described, when aryl benzyl ethers were subjected to Duff reaction conditions. The rearrangement shown below in Scheme 5 was observed when **1a** (Table 2) was subjected for formylation under Duff reaction condition, wherein **1a** was found to undergo smooth *ortho* rearrangement as well as formylation. The *ortho* rearrangement was mediated by TFA[11] followed by the formylation on the electronically rich phenolic ring.

Literature search reveled that there is no report on ortho rearrangement and formylation in one pot.



Scheme 5

The initial investigation was carried out on the **1c** as a model substrate with HMTA at 80 °C in TFA as solvent. Delightfully, the desired migrated as well as formylated product **2c** was obtained in good yield (74%) by stirring for 3 h at 80 °C (Table 1, entry 3). Encouraged by this excellent result, it was decided to optimize the reaction conditions (Table 1). Accordingly, under the identical reaction conditions different solvents like acetic acid, methanesulfonic acid and triflic acid were tested wherein it was found that in acetic acid starting material was recovered and in comparatively more acidic condition like triflic acid or methanesulfonic acid, starting material got decomposed. In order to optimize the reaction conditions, the formylating agent was also varied and the reaction was performed with paraformaldehyde and formalin but no product formation was observed in the presence of TFA. The stoichiometry of hexamethylene tetramine and also the amount of trifluoroacetic acid used were also varied. It was found that 2 equiv of hexamethylene tetramine and 3–4

mL of trifluoroacetic acid were needed per mmol of the benzyl aryl ethers for optimal results.

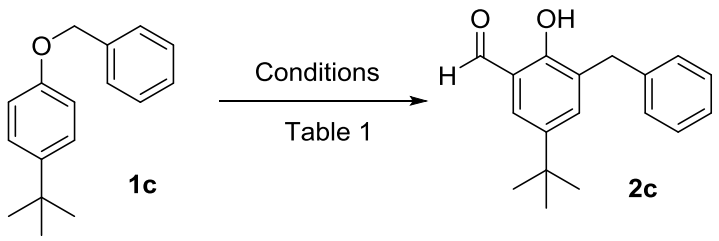


Table 1. Optimization of reaction conditions

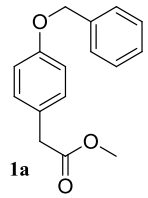
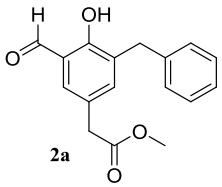
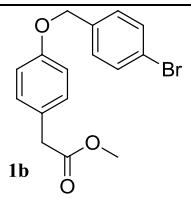
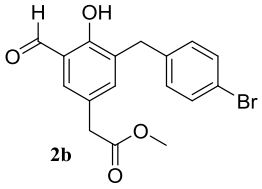
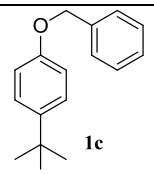
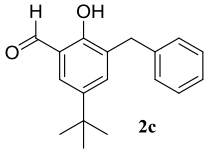
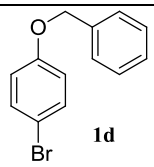
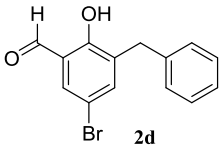
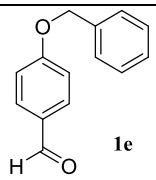
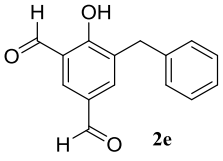
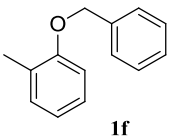
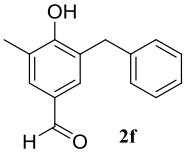
Entry[a]	Solvent[b]	Formylating agent	Time (h)/ temp.(° C)	Yield[c] (%)
1	AcOH	HMTA	8/80	00[d]
2	TFA	HMTA	8/80	51
3	TFA	HMTA	3/80	74
4	CF_3SO_3H	HMTA	1.5/80	00[e]
5	CH_3SO_3H	HMTA	1/80	00[e]
6	TFA	Paraformaldehyde	10/80	00[f]
7	TFA	Formalin	10/80	00[f]

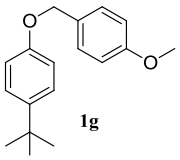
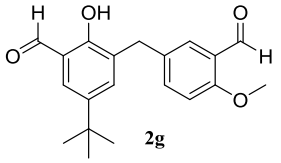
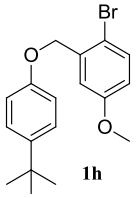
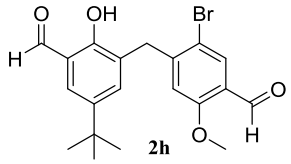
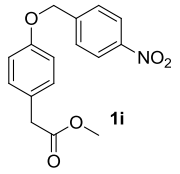
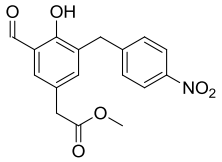
[a]Reactions (entry 1 to 5) were carried out with 2 equiv of HMTA except entry 2 where 1 equiv was used. [b]3-4 mL of solvents were used for 1 mmol of substrate. [c]Isolated yield. [d]Starting material recovered. [e]Starting material decomposed. [f]From GC and ^{1}H-NMR.

After establishing the optimum reaction conditions, the attention was turned to examine the scope of this reaction. The migration–formylation reactions were examined on various types of benzyl aryl ethers and the results are summarized in Table 2. First, it was decided to examine the effect of substitution on phenolic ring. Compound **1a** bearing carbomethoxy methyl group at *para* position to the phenolic group, was found to undergo smooth *ortho* rearrangement and formylation in 3 h in 70% yield after purification by column chromatography. Then the substitution at 4-position to the phenolic group was varied with electron rich as well as electron demanding functional groups. It was observed that compounds with ^{t}Bu and bromo groups at *para* position to the phenolic group (**1c, 1d**) underwent facile migration-formylation; whereas the electron withdrawing group such as formyl at *para* position **1e** gave comparatively lower yield and took longer time for the consumption of starting material. Secondly, it was decided to examine the effect of substitution on migrating benzyl ring. Accordingly, when compound **1g** bearing *para* methoxybenzyl ether (Table 2, entry 7) was subjected to the optimal reaction conditions, it also underwent *ortho* rearrangement and formylation on both the rings to afford compound

2g. Analysis of the ^{1}H-NMR of **2g** showed the presence of two formyl groups in the molecule. After careful examination of NMR it was concluded that the migrating *para*-methoxybenzyl ring also gets formylated. When compound **1i** bearing *para* nitrobenzyl ether (Table 2, entry 9) was subjected under the similar reaction conditions to study the effect of electron withdrawing group on benzyl ring, it was observed that benzyl group gets deprotected leading to the formation of *para* nitrobenzyl alcohol.

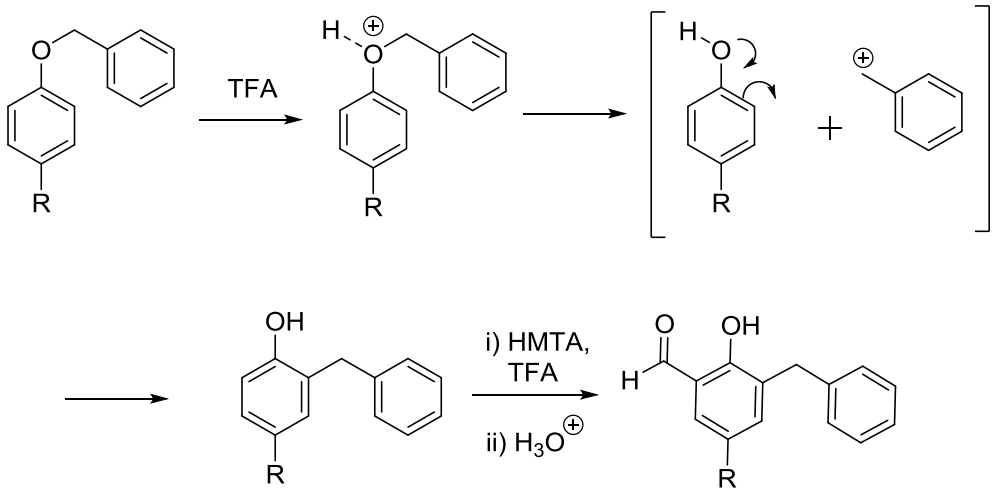
Table 2. Scope of substitution on phenyl and benzyl ring

Entry	Substrate[a]	Time (h)	Product	Yield (%)[b]
1	 **1a**	**3**	 **2a**	**70**
2	 **1b**	**3.5**	 **2b**	**61**
3	 **1c**	**3**	 **2c**	**74**
4	 **1d**	**5**	 **2d**	**59**
5	 **1e**	**6**	 **2e**	**52**
6	 **1f**	**4**	 **2f**	**68**

7	 **1g**	**3.5**	 **2g**	**55**
8	 **1h**	**3**	 **2h**	**52**
9	 **1i**	**6**		**00[c]**

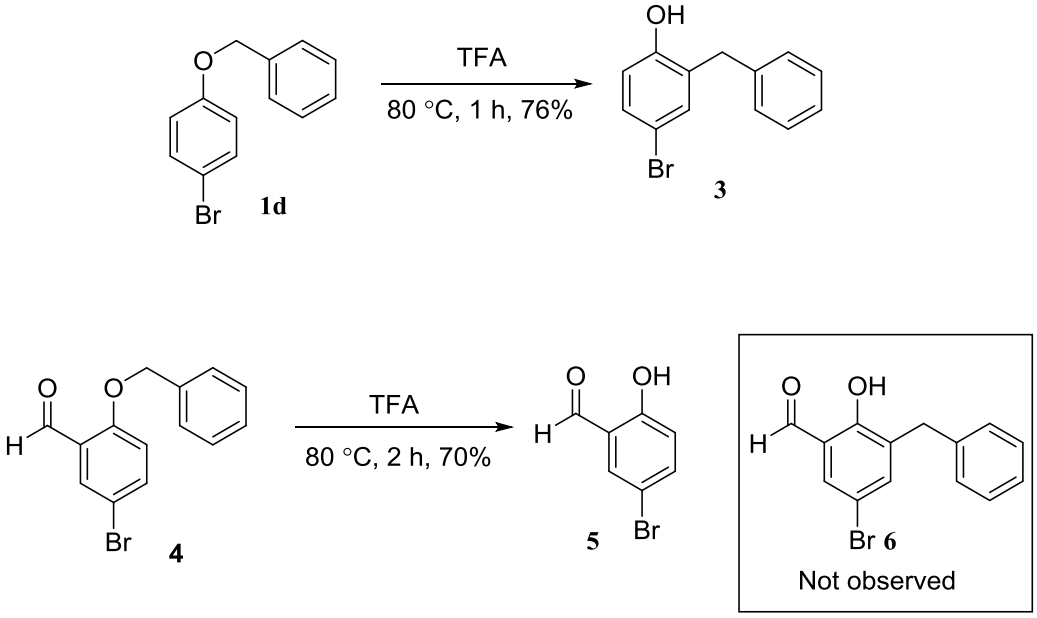
[a] Benzyl aryl ethers were prepared by treating corresponding phenols with the appropriate benzyl bromide in DMF under basic condition (K_2CO_3). [b] Isolated yield. [c]Debenzylated product observed, confirmed by ^{1}H-NMR.

From literature precedence, the migration-formylation proceeds *via* the reaction pathway illustrated in Scheme 6. Under acidic condition, the benzyloxy group gets protonated to form free phenol and benzyl cation. The benzyl cation thus generated is concomitantly captured by phenol in a Friedel-Crafts fashion to form 2-benzyl phenol.[7-10] This mechanism is in good agreement with that proposed by Seoane *et al*.[12] Addition of phenol to imine, which gets generated *in situ* from HMTA and TFA, preferentially undergoes electrophilic substitution reaction at the *ortho*-position of –OH, in a Mannich fashion, followed by hydrolysis to provide the aldehyde.[4-6]



Scheme 6. Plausible reaction mechanism

The reaction pathway was further proven by carrying out a set of reactions as described below. As shown in Scheme 7, treatment of **1d** with TFA at 80 °C resulted in the *ortho*-rearrangement to furnish phenol **3**. Under similar reaction conditions, the 2-(benzyloxy)-5-bromobenzaldehyde **4** resulted only in debenzylated product **5**[13] instead of **6**. Further proof for the mechanism was deduced, when **1f**, where one of the *ortho* positions is already blocked by methyl group (Table 1, entry 6), was subjected to optimal reaction conditions. It underwent *ortho*-rearrangement and *para* formylation, which was confirmed by ^{1}H-NMR spectroscopy. This may be contrasted with the result obtained when **1d** was subjected to Duff reaction conditions as described earlier which led to the formation of compound **2f** which clearly gives credence to the hypothesis that *ortho*-rearrangment precedes the formylation.



Scheme 7. Evidence for mechanism

2.3.5 Conclusion

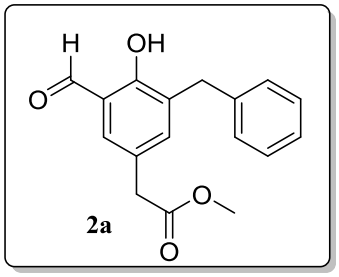
In conclusion, a novel one-pot synthetic route to access substituted salicylaldehyde from benzyl aryl ether involving migration of benzyl group and formylation in moderate to good yields has been developed.

2.3.6 Experimental

General procedure for migration-formylation-

Benzyl aryl ether (1 equiv) was dissolved in TFA (4-5 mL for 1 mmol of benzyl aryl ether) under N_2, and hexamethylenetetramine (2 equiv) was added in one portion. The solution was stirred at 80–100 °C (time required for completion of reaction given in table 2). Subsequently, aq. HCl (10%, 4-5 mL for 1 mmol of benzyl aryl ether) was added and the reaction mixture was kept at the same temperature for additional 1 hour. The mixture was then cooled to room temperature. The product was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with brine (10 mL), then dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel) using Pet. ether/ethyl acetate to furnish benzaldehyde derivatives (Table 2).

Methyl 2-(3-benzyl-5-formyl-4-hydroxyphenyl)acetate (2a):

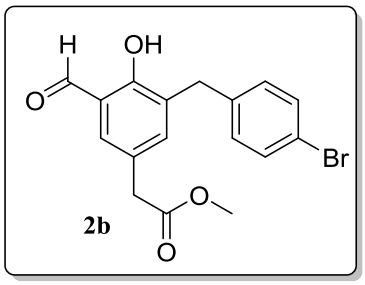


Colorless oil; $\boldsymbol{R_f}$ 0.5 (Pet. ether/EtOAc = 4:1).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 3.46 (s, 2 H), 3.61 (s, 3 H), 3.92 (s, 2 H), 7.05-7.30 (m, 7 H), 9.78 (s, 1 H), 11.19 (s, 1 H).

IR ($CHCl_3$, cm^{-1}): νmax 2919, 2850, 1738, 1656, 1453, 1265; **HRMS** *m/z*: Calculated for $C_{17}H_{17}O_4$- 285.1121, observed- 285.1123.

Methyl 2-(3-(4-bromobenzyl)-5-formyl-4-hydroxyphenyl)acetate (2b):



Colourless oil; $\boldsymbol{R_f}$ 0.4 (Pet. ether/EtOAc = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 3.55 (s, 2H), 3.70 (s, 3H), 3.94 (s, 2H), 7.11 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=2.0 Hz, 1H), 7.36 (d, *J*=2.0 Hz, 1H), 7.39 (d, *J*=8.5 Hz, 2H), 9.87 (s, 1H), 11.27 (s, 1H).

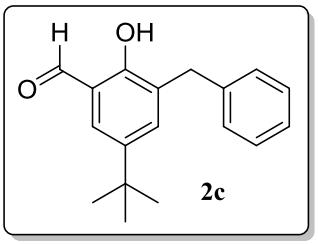
^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 34.3, 39.8, 52.1, 120.3, 125.1, 129.8, 130.0, 130.6 (2), 131.6 (2), 132.4, 138.3, 138.7, 158.7, 171.4, 196.2 .

IR ($CHCl_3$, cm^{-1}): νmax 3058, 2953, 1714, 1651, 1437, 1246.

HRMS *m/z*: Calculated for $C_{17}H_{16}O_4Br$- 363.0226, observed- 363.0226.

3-Benzyl-5-(*tert*-butyl)-2-hydroxybenzaldehyde (2c):

Yellowish oil; $\boldsymbol{R_f}$ 0.6 (Pet. ether/EtOAc = 19:1).



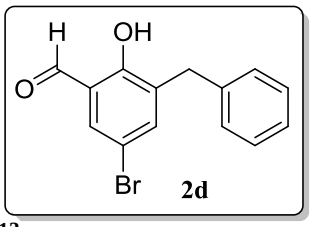
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 1.31 (s, 9 H), 4.03 (s, 2 H), 7.16-7.42 (m, 7 H), 9.87 (s, 1 H), 11.19 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 31.2 (3 C), 34.0, 35.1, 117.2, 119.7, 126.0, 127.9, 128.3 (2 C), 128.8 (2 C), 135.2, 140.0, 142.1, 157.5, 196.5.

IR ($CHCl_3$, cm^{-1}): νmax 2963, 1652, 1454, 1269.

HRMS *m/z*: Calculated for $C_{18}H_{21}O_2$- 269.1536, observed- 269.1536.

3-Benzyl-5-bromo-2-hydroxybenzaldehyde (2d):



Yellow solid; **mp** 87-89 °C; $\boldsymbol{R_f}$ 0.5 (Pet. ether/EtOAc = 9:1).

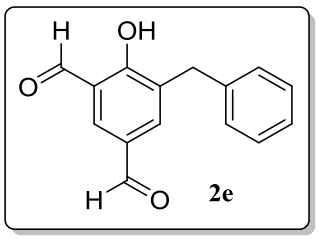
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 3.99 (s, 2 H), 7.21-7.34 (m, 5 H), 7.40 (d, *J*=2.7 Hz, 1 H), 7.53 (d, *J*=2.7 Hz, 1 H), 9.82 (s, 1 H), 11.2 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 34.7, 111.2, 121.4, 126.5, 128.6 (2 C), 128.9 (2 C), 132.9, 133.6, 138.8, 139.7, 158.5, 195.3.

IR ($CHCl_3$, cm^{-1}): νmax 2917, 2849, 1658, 1433, 1274, 1163.

HRMS *m/z*: Calculated for $C_{14}H_{12}O_2Br$- 291.0015, observed- 291.0017.

5-Benzyl-4-hydroxyisophthalaldehyde (2e):



Brownish yellow solid; **mp** 117-119 °C; $\boldsymbol{R_f}$ 0.4 (Pet. ether/EtOAc = 4:1).

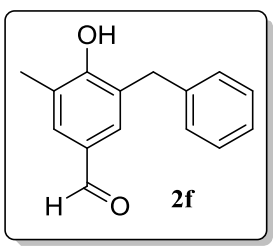
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 4.06 (s, 2 H), 7.21-7.33 (m, 5 H), 7.86 (d, *J*=2.0 Hz, 1H), 8.01 (d, *J*=2.0 Hz, 1 H), 9.87 (s, 1 H), 9.99 (s, 1 H), 11.92 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 34.8, 120.0, 126.6, 128.7 (2 C), 128.9, 129.0 (2 C), 131.8, 134.6, 137.1, 138.7, 164.3, 189.1, 196.1.

IR ($CHCl_3$, cm^{-1}): νmax 2923, 1692, 1653, 1599, 1452, 1271, 1137.

HRMS *m/z*: Calculated for $C_{15}H_{13}O_3$- 241.0859, observed- 241.0860.

3-Benzyl-4-hydroxy-5-methylbenzaldehyde (2f):



Yellow solid; **mp** 104-106 °C; $\boldsymbol{R_f}$ 0.2 (Pet. ether/EtOAc = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 2.34 (s, 3 H), 4.07 (s, 2 H), 6.24 (brs, 1 H), 7.21-7.34 (m, 5 H), 7.53 (s, 1 H), 7.60 (s, 1 H), 9.76 (s, 1 H).

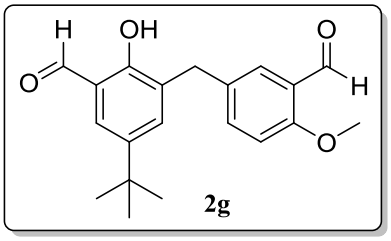
^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 16.0, 36.4, 124.7, 126.7, 127.2, 128.6 (2 C), 128.8 (2 C), 129.2, 131.2, 138.7, 158.3, 191.1.

IR ($CHCl_3$, cm^{-1}): νmax 3311, 3027, 2920, 1660, 1585, 1482, 1128.

HRMS *m/z*: Calculated for $C_{15}H_{15}O_2$- 227.1067, observed- 227.1067.

5-(*tert*-Butyl)-3-(3-formyl-4-methoxybenzyl)-2-hydroxybenzaldehyde (2g):

Yellowish oil; R_f 0.6 (Pet. ether/EtOAc = 9:1).



2g

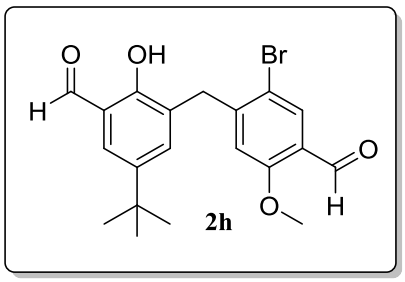
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) : δ 1.30 (s, 9 H), 3.90 (s, 3 H), 3.96 (s, 2 H), 6.90 (d, *J*=8.5 Hz, 1 H), 7.38 (d, *J*=2.4 Hz, 1 H), 7.41 (d, *J*=2.4 Hz, 1 H), 7.45 (dd, *J*=8.5 & 2.4 Hz, 1 H), 7.69 (d, *J*=2.4 Hz, 1 H), 9.87 (s, 1 H), 10.42 (s, 1 H), 11.14 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 31.3 (3 C), 34.1, 34.3, 55.6, 111.6, 119.9, 124.6, 128.2, 128.4, 129.0, 132.6, 135.2, 136.3, 142.4, 157.5, 160.3, 189.4, 196.6.

IR ($CHCl_3$, cm^{-1}): νmax 2961, 2863, 1682, 1651, 1496, 1463, 1268.

HRMS *m/z*: Calculated for $C_{20}H_{23}O_4$- 327.1591, observed- 327.1590.

3-(2-Bromo-4-formyl-5-methoxybenzyl)-5-(*tert*-butyl)-2-hydroxybenzaldehyde



2h

(2h): Brownish solid; **mp** 143-145 °C; R_f 0.4 (Pet. ether/EtOAc = 9:1).

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 1.30, (s, 9 H), 3.84 (s, 3 H), 4.15 (s, 2 H), 7.00 (s, 1 H) 7.43 (d, *J*=2.2 Hz, 1 H), 7.57 (d, *J*=2.2 Hz, 1 H), 7.98 (s, 1 H), 9.90 (s, 1 H), 10.32 (s, 1 H), 11.30 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 31.3 (3 C), 34.2, 36.0, 55.7, 114.7, 115.9, 119.9, 124.6, 126.6, 128.5, 132.3, 135.8, 142.6, 147.3, 157.6, 160.6, 187.6, 196.7.

IR ($CHCl_3$, cm^{-1}): νmax 2961, 2856, 1687, 1651, 1598, 1463, 1386, 1266.

HRMS *m/z*: Calculated for $C_{20}H_{22}O_4Br$- 405.0696, observed- 405.0699.

2.3.7 References

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Chapter 3. Synthetic studies towards α-cuparenone and unusual metal free auto-oxidation by air

Section 1

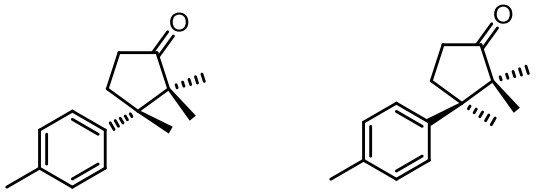
Introduction to α-cuparenone

3.1.1 Summary

The present section deals with general introduction of α-cuparenone along with detailed review on synthesis emphasizing mainly the synthetic approaches towards α-cuparenone, a bicyclic terpene.

3.1.2 Introduction

α-Cuparenone **1** is a bicyclic sesquiterpene which exhibits itself in two isomeric forms (Fig. 1). (+)-α-Cuparenone was isolated from the wood of the *Thuja orientallis* (mayurpankhi) by Sukh Dev and co-workers[1] whereas (-)-α-cuparenone was isolated from the liverwort *Mannia fragrans* by Benesova and co-workers.[2] This sesquiterpene is a synthetic challenge to organic chemists due to presence of two contiguous quaternary centers,[3] one of which is stereogenic in cyclopentane ring.



(+)-1 **(-)-1**

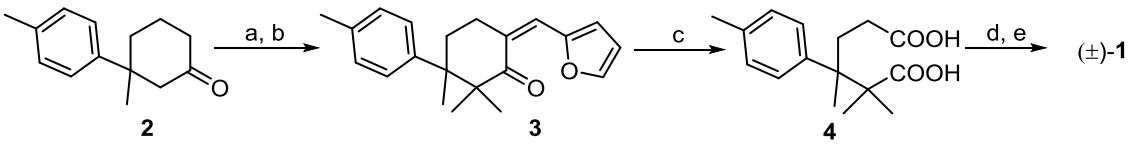
Figure 1

3.1.3 Synthesis of α-cuparenone: Literature survey

Owing to its challenging structure having two contiguous quaternary centers in a cyclopentane ring, several syntheses of α-cuparenone are reported in the literature employing various strategies. In many cases, the synthesis of α-cuparenone has been used as a demonstration of the novelty and efficiency of new methodology. Since review on synthesis of all categories up to 2010 has been covered by Sachindra S. Patil[4a] and Abasaheb N. Dhawane[4b] from this group, only those syntheses of optically pure α-cuparenone reported after 2010 and some representative syntheses have been described in this present section.

Raphael's approach (*J. Chem. Soc.* **1962**, 1558)

Raphael and co-workers[5] have reported the first total synthesis of α-cuparenone in seven steps with overall yield of 18%, employing Dieckmann cyclization as key step .

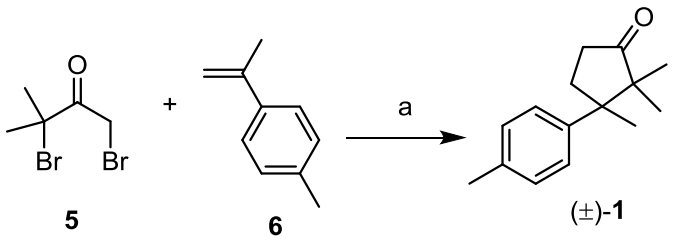


Scheme 1 : *Reagents and conditions: a) Furfuraldehyde, EtOH, aq. NaOH, rt, 2 h; b) t-BuOK, CH_3I, rt; c) O_3, AcOH, H_2O_2, H_2SO_4; d) i) CH_2N_2, ether, 0 ^oC; ii) Benzene, t-BuOK, reflux, 6 h; e) i) AcOH, HCl, H_2O, 4 h; ii) Heat, 100 ^oC, MeOH, NaOH.*

The less hindered methylene of ketone **2** was protected *via* aldol condensation with 2-furfuraldehyde. The resulting enone was subjected to gem-dimethylation reaction to get enone **3**. Ozonolysis of compound **3** afforded substituted adipic acid **4**. The acid **4** on esterification followed by Dieckmann cyclization, hydrolysis and decarboxylation afforded α-cuparenone **1** (Scheme 1).

Noyori's approach (*Tetrahedron Lett.* **1978**, *19*, 993)

In this communication Noyori *et al.*[6] have reported an elegant one-step synthesis of α-cuparenone using transition metal catalyst (Scheme 2).



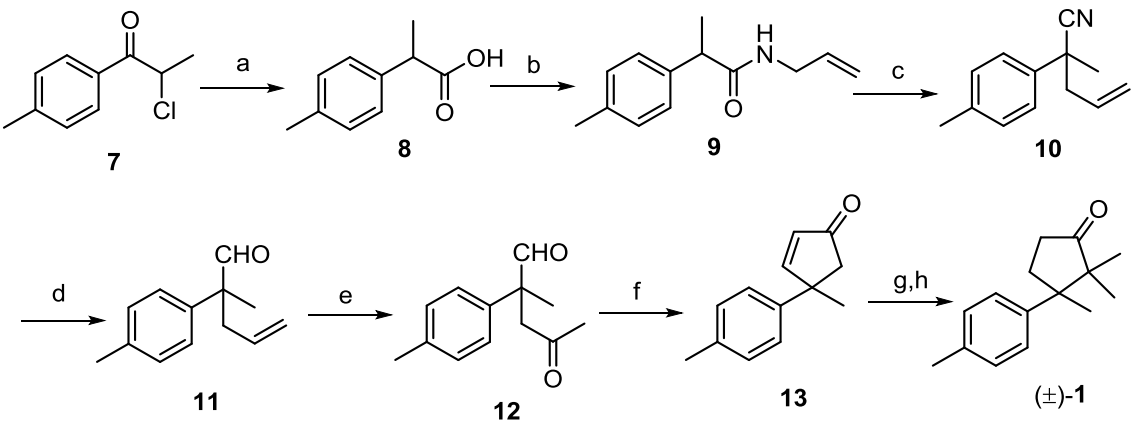
Scheme 2: *Reagents and conditions: a) $Fe_2(CO)_9$, benzene, 55 ^oC, 1 h, argon, 18%.*

Dibromoketone **5** was treated with 2-*p*-tolyl-1-propene **6** in presence of $Fe_2(CO)_9$ directly to afford the α-cuparenone **1**, though in very low yield (18%). This is the shortest and most well-designed synthesis of α-cuparenone involving dipolar cycloaddition of oxa-allyl cation to construct five membered ring.

Chavan's 1st approach (*Tetrahedron Lett.* **1996**, *37*, 2629)

This group[7] synthesized (±)-α-cuparenone employing aza-Claisen rearrangement (Scheme 3). α-Chloro-4-methyl propiophenone **7** was converted to α-*p*-tolyl propionic acid **8** by facile photochemical rearrangement, in the presence of propylene oxide as an acid scavenger. α-*p*-Tolyl propionic acid **8** was converted to allyl amide **9** by reacting it with thionyl chloride followed by allylamine. Aza-Claisen rearrangement of compound **9** mediated by triphenyl phosphine and CCl_4 furnished

unsaturated nitrile **10**, which on partial reduction and hydrolysis afforded aldehyde **11**.

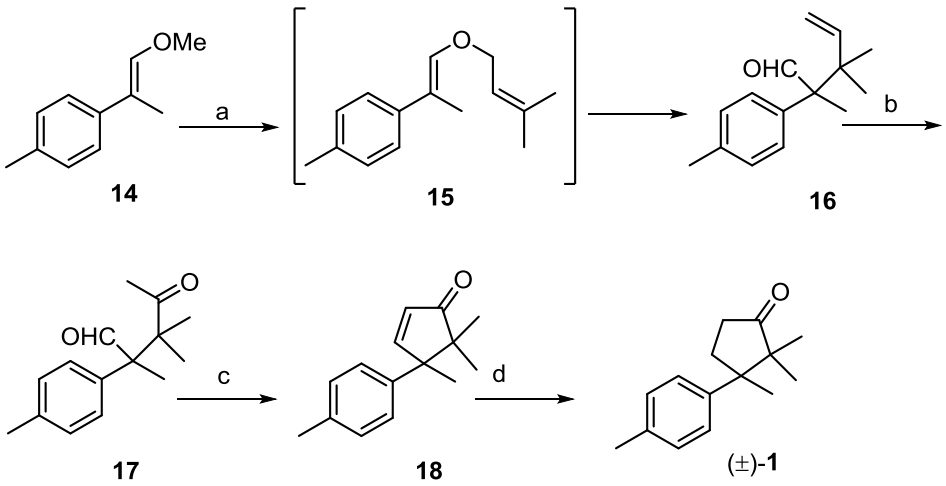


Scheme 3: *Reagents and conditions: a) hν, 2-methyl oxirane, aq. acetone 6 h, 70%; b) $SOCl_2$, benzene, allylamine, Et_3N; c) PPh_3, CH_3CN, CCl_4, Et_3N, 24 h, 80%; d) DIBAL-H, benzene, 70%; e) Wacker oxidation, 63%; f) KOH, EtOH, rt, 98%; g) NaH, MeI (excess), 65%; h) Pd-C, H_2, rt, 98%.*

Wacker oxidation of compound **11** gave ketone **12** which was followed by intramolecular aldol condensation and dehydration to give cyclopentenone **13**. Gem-dimethylation of compound **13** followed by hydrogenation completed the total synthesis of α-cuparenone **1**. Thus the total synthesis was completed in eight steps with an overall yield of 14%.

Kulkarni's approach (*Tetrahedron*, **1997**, *53*, 3167)

Kulkarni *et al.*[8] have reported a short and efficient total synthesis of (±)-α-cuparenone employing a tandem enol ether exchange Claisen rearrangement (Scheme 4). Accordingly, enol ether **15** was prepared by enol ether exchange from **14** and subsequent Claisen rearrangement using trifluoroacetic acid in refluxing toluene gave aldehyde **16** *via* **15**. Wacker oxidation of aldehyde **16** afforded ketoaldehyde **17**, which on aldol condensation gave **18** and hydrogenation of **18** afforded the (±)-α-cuparenone **1**. Thus the total synthesis of (±)-α-cuparenone was completed in four steps with an overall yield of 43%.



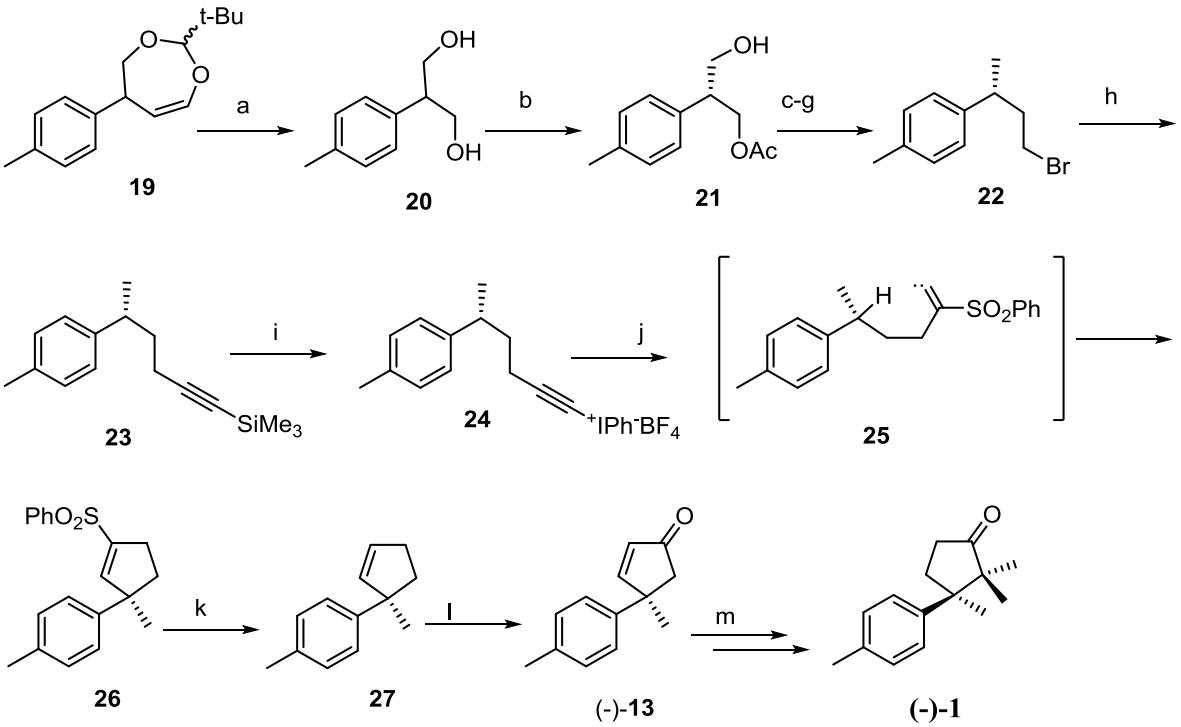
Scheme 4: *Reagents and conditions: a) Prenyl alcohol, TFA (10%), toluene, reflux, 18 h, 69%; b) $PdCl_2$ (10%), $CuCl_2$ (10%), O_2, H_2O:DME (1:9), rt, 2 h, 81%; c) KOH, MeOH, rt, 2 h, 87%; d) Pd/C, AcOEt, H_2, rt, 8 h, 94%.*

Shishido's approach (*Chem. Commun*. **1997**, 1167)

Shishido and coworkers[9] have reported an efficient and enantiocontrolled formal total synthesis of (-)-α-cuparenone by employing an asymmetric construction methodology for formation of the benzylic quaternary stereogenic centre (Scheme 5). Accordingly, treatment of 2-*tert*-butyl-4,5-dihydro-5-(4-methylphenyl)-1,3-dioxepine **19**[10] with ozone followed by reductive workup with $NaBH_4$ gave prochiral 1,3-diol **20**. Diol **20** on asymmetric acetylation using porcine pancreatic lipase (PPL) and vinyl acetate gave monoacetate **21**. Removal of hydroxy moiety in **21** by tosylation and subsequent reduction gave alcohol, which on mesylation and subsequent cyanation, DIBAL-H reduction, and further reduction of the aldehyde thus obtained with $NaBH_4$ gave one carbon elongated alcohol, which was converted to bromide **22** by using CBr_4 and triphenylphosphine. Reaction of bromide with lithium trimehylsilylacetylide produced the alkynylsilane **23** in 69% yield.

The construction of quaternary stereogenic center was carried out *via* [1,5] C-H insertion reaction of the alkylidene carbene. Thus, treatment of **23** with iodosylbenzene in the presence of boron trifluoride diethyl etherate in DCM at 0 ^oC followed by treatment with aq. sodium tetrafluoroborate provided the iodonium tetrafluoroborate **24**, which was exposed to aq. sodium benzenesulfinate at 0 ^oC to give the cyclised vinyl sulfone **26** *via* the alkylidene carbene intermediate **25**. Reductive removal of benzenesulfonyl moiety in **26** under sonication afforded **27**.

Oxidation of allylic methylene was carried out using PDC in presence of *tert*-butylhydroperoxide and celite to furnish enone **13** which is an intermediate in the cuparenone synthesis and can be converted to (-)-α-cuparenone.[11] Thus this synthetic sequence constitutes a formal synthesis of (-)-α-cuparenone.

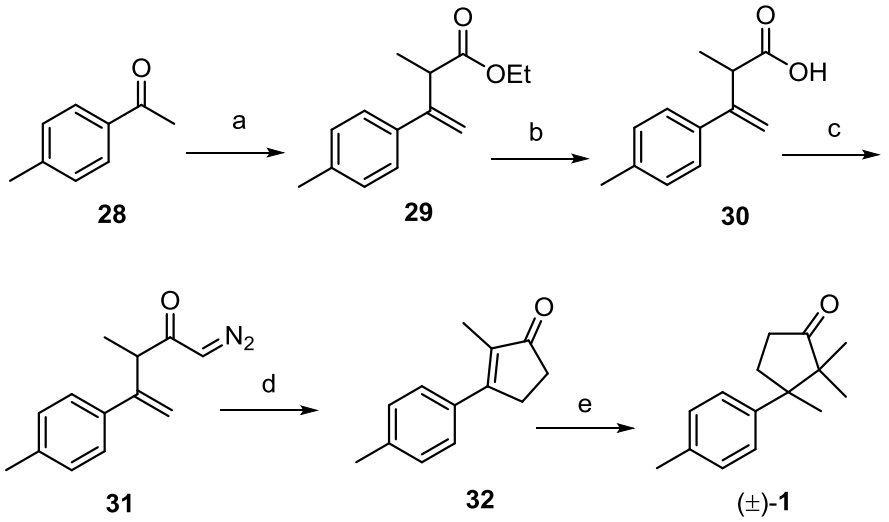


Scheme 5: *Reagents and conditions: a) O_3, $NaBH_4$, CH_2Cl_2, -78 to 0 °C, 84%; b) Vinyl acetate, PPL, Et_2O, rt, 84%; c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, $NaBH_4$, Me_2SO, 60 °C, 73%; d) MsCl, i-Pr_2NEt, CH_2Cl_2, rt, 88%; e) KCN, 18-crown-6, Me_2SO, 60 °C, 90%; f) DIBAL-H, hexane–CH_2Cl_2 (1:1), -78 °C then 1M HCl, $NaBH_4$, MeOH, 75%; g) Ph_3P, CBr_4, CH_2Cl_2, -40 °C, 94%; h) t-BuLi, HC≡$CSiMe_3$, THF, HMPA, -78-0 °C, 69%; i) $(PhIO)_n$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; j) $PhSO_2Na$, H_2O, 0 °C, 83% (over two steps); k) Na–Hg (5%), MeOH, sonication, rt, 70%; l) PDC, t-BuOOH, celite, benzene, 10 °C, rt, 72%; m) Ref. 15.*

Chavan's 2nd approach (*Tetrahedron* **1999,** *55*, 13417)

This is the second short and simple approach from this group (Scheme 6).[12] Central to this approach is construction of a substituted cyclopentenone *via* acid catalyzed decomposition of β,γ-unsaturated-α-diazoketone. Accordingly, Reformatsky reaction of 4-methylacetophenone **28** and ethyl 2-bromopropionate furnished the β,γ-unsaturated ester **29**. Saponification of ester **29** gave acid **30** followed by treatment with $SOCl_2$ to give corresponding acid chloride. Reaction of

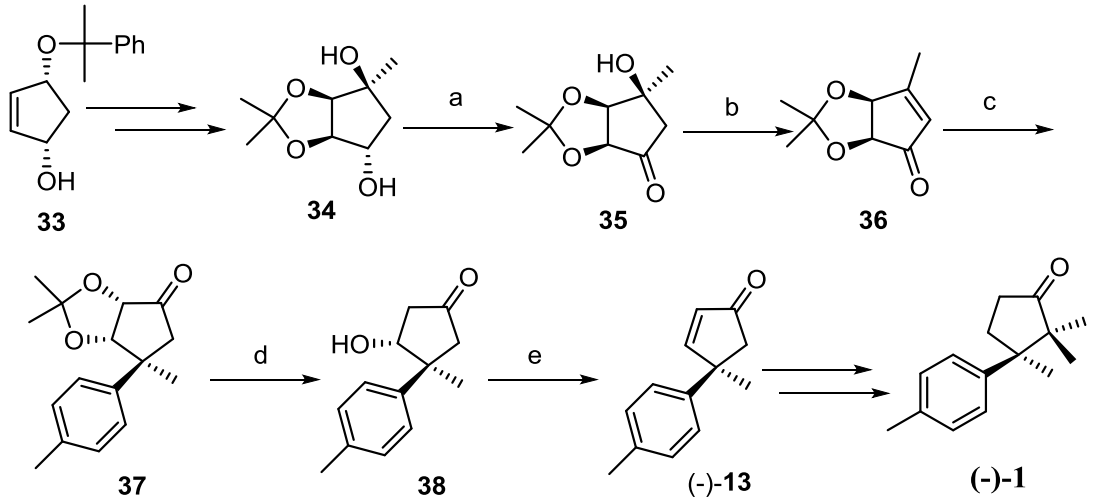
acid chloride with diazomethane gave β,γ-unsaturated-α-diazoketone **31**. Cyclization was carried out by using $BF_3.Et_2O$ to furnish cyclopentanone **32**. 1,4-Conjugate addition with trimethylaluminum[13] followed by alkylation[14] furnished α-cuparenone **1**. Thus total synthesis was achieved in five steps with an overall yield 56%.



Scheme 6: *Reagents and conditions: a) i) Ethyl 2-bromopropionate, Zn, ether; ii) H^+, 97%; b) KOH, EtOH-H_2O; c) i) $SOCl_2$, benzene; ii) CH_2N_2, ether, quant; d) $BF_3.Et_2O$, DCM, 0 ^oC, quant; e) i) Me_3Al, $Ni(acac)_2$, THF, rt, 85%; ii) NaH, diglyme, MeI, 68%.*

Ogasawara's approach (*Tetrahedron Lett.* **2000**, *41*, 2639)

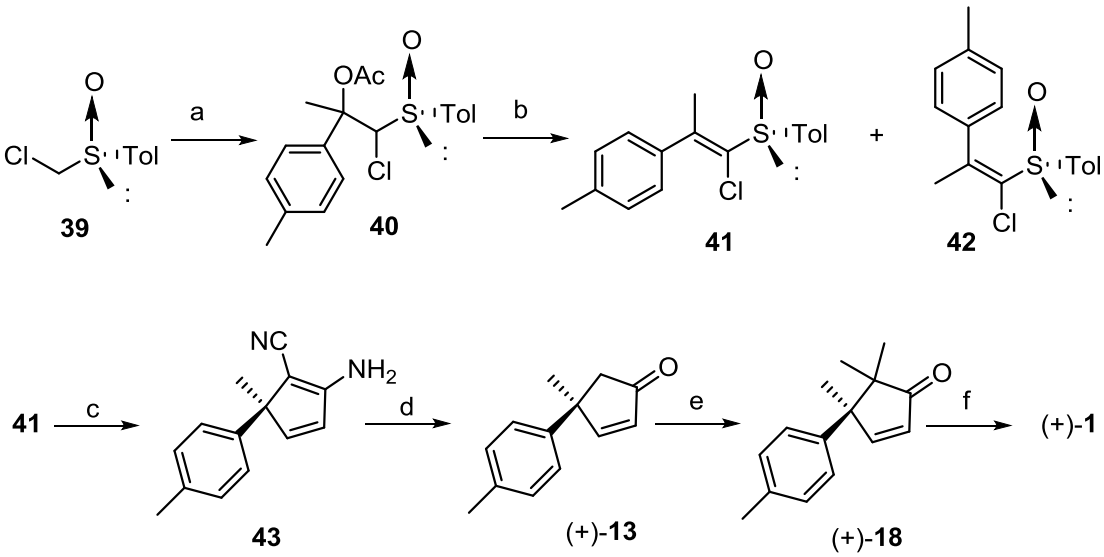
In this communication Ogasawara *et al.*[15] reported an efficient enantioselective route to (-)-α-cuparenone utilizing a chiral cyclopentanoid **33** as a starting material (Scheme 7). Thus, enantiopure diol (-)-**34** was accomplished from **33**[16] by using enantiodivergent functional group transformation. Oxidation of **34** with PCC afforded β-hydroxyketone **35**, which on dehydration gave enone **36**. Treatment of **36** with Grignard reagent in presence of copper (I) bromide and TMS-chloride allowed convex face selective 1, 4-addition to afford cyclopentanone **37** having benzylic quaternary stereogenic center. Conversion of **37** into known key intermediate to synthesis of (-)-α-cuparenone was carried out by reductive cleavage using aluminium amalgam to afford β-hydroxyketone **38** which on treatment with dil. HCl afforded enone **13** from which (-)-α-cuparenone has been obtained in two steps.[11]



Scheme 7: *Reagents and conditions: a) PCC, CH_2Cl_2, 90%; b) AcOH, 40 °C, 93%; c) 4-MeC_6H_4MgBr, $CuBr.SMe_2$, HMPA, TMSCl, THF, -78°C, then TBAF, THF, 87%; d) Al–Hg, EtOH, 91%; e) 10% HCl:dioxane (1:1), 40 °C, 81%.*

Satoh's approach (*Tetrahedron*: *Asymmetry* **2003**, *14*, 281)

Satoh *et al.*[17] reported asymmetric synthesis of 4, 4-disubstituted 2-cyclopentenones from optically active 1-chlorovinyl *p*-tolyl sulfoxides and its application to the asymmetric total synthesis of (+)-α-cuparenone (Scheme 8).

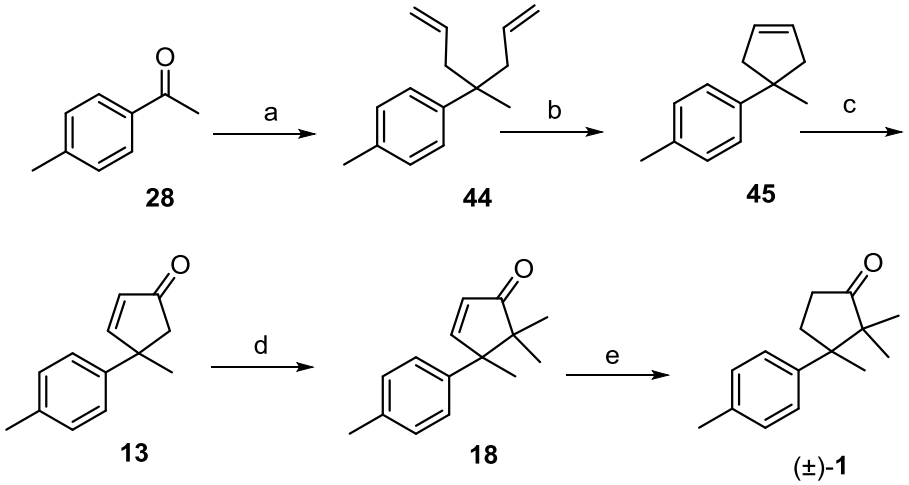


Scheme 8: *Reagents and conditions: a) i) LDA, 4-methyl acetophenone, -50 ^oC, 98%; ii) Acetic anhydride, pyridine, DMAP, 95%; b) $LiNPh_2$, THF, 93%; c) $LiCH_2CN$, THF, 75%; d) H_3PO_4, AcOH-H_2O, 93%; e) NaH, MeI (excess), DMF, 72%; f) Pd-C, H_2, rt, 97%.*

Enantiomerically pure (*R*)-(-)-**39** was treated with LDA at -50 ^{o}C followed by 4-methylacetophenone to afford the hydroxy compound, which was acetylated to afford the acetate **40** in 95% yield. The reaction of the acetate with lithium diphenylamide gave 93% yield of the desired 1-chlorovinyl *p*-tolyl sulfoxides **41** and **42** in 3:1 ratio. The major isomer **41** was treated with cyanomethyllithium to give optically active enaminonitrile **43** in 75% yield. The enaminonitrile **43** was heated under reflux with H_3PO_4 in acetic acid to give the desired cyclopentenone **13** in 93% yield, which was dimethylated followed by hydrogenation in ethyl acetate with catalytic Pd/C to give (+)-α-cuparenone **1**.

Chavan's 3rd approach (*Tetrahedron Lett.* **2007**, *48*, 965)

This is the third, short and concise approach from this group.[18] Central to this approach is $InCl_3$ mediated one-pot diallylation (Scheme 8).

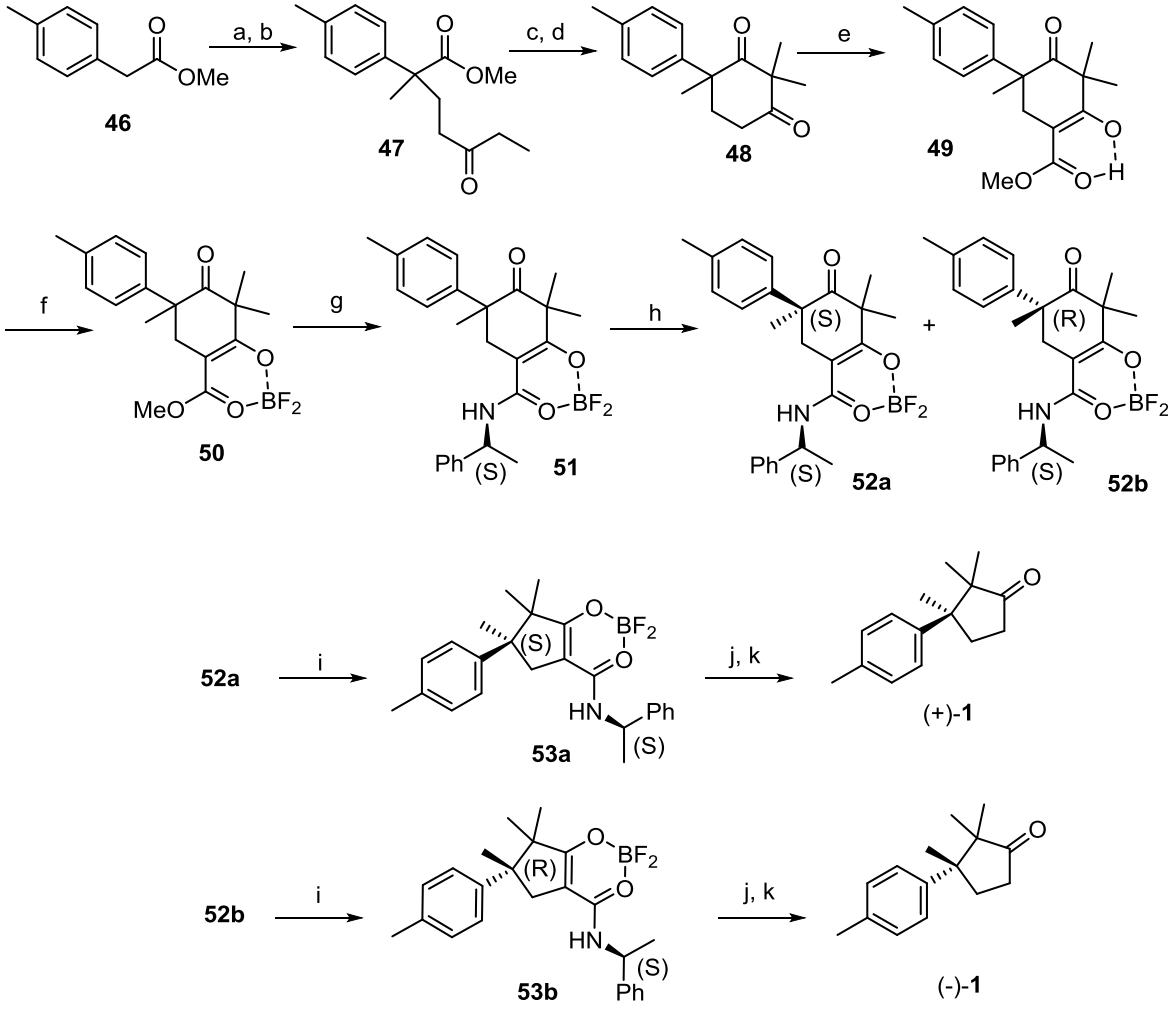


Scheme 9: *Reagents and conditions: a) $InCl_3$, Me_3SiCl, allyltrimethylsilane, EDC, 8 h, 30%; b) Grubbs' cat. 1st generation, DCM, rt, 5 h, 90%; c) PDC, pyridine, 100 ^{o}C, 7 h, 65%; d) NaH, DMF, CH_3I (excess), rt, 12 h, 70%; e) H_2-Pd/C, EtOH, piperidine, 4 h, quantitative yield.*

Accordingly, olefin **44** could be realised by one-pot diallylation of 4-methyl acetophenone (**28**) on treatment with $InCl_3$, allyl trimethylsilane (Scheme 9). Ring closing metathesis of diallyl compound **44** furnished cyclopentene **45**. Treatment of **45** with PDC furnished the rearranged α,β-unsaturated ketone **13**. Dimethylation of **13** furnished compound **18**. Finally hydrogenation of **18** using 10% Pd/C afforded (±)-α-cuparenone **1**.

Garibay's approach (*Angew. Chem. Int. Ed.* **2007**, *46*, 6485)

Garibay and coworkers[19] reported the solid to solid reactions for the stereospecific synthesis of (+) and (-) isomers of α-cuparenone utilizing photo-induced decarbonylation of crystalline hexasubstituted ketones with adjacent stereogenic quaternary centers.

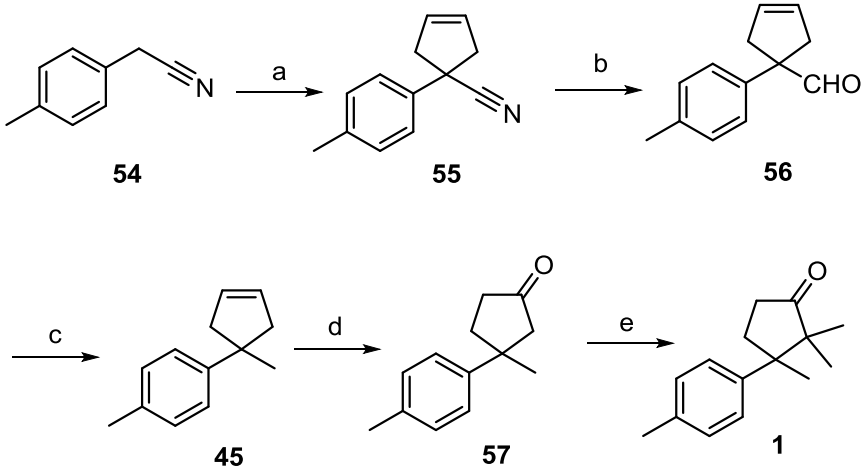


Scheme 9: *Reagents and conditions: a) KH, MeI, THF, 0 ^{o}C, 92%; b) LDA, ethyl vinyl ketone, THF, 0 ^{o}C, 81 %; c) Na, MeOH, reflux, 99%; d) KH, MeI, DMF, 75 ^{o}C, 81%; e) LiHMDS, MeO(CO)CN, 92%; f) $BF_3.OEt_2$, toluene, 100%; g) (S)-(a)-Methylbenzylamine, MeCN, 80%; h) Silica gel chromatography (EtOAc/hexane 2:8); i) hν, suspension of nanocrystals in aq. CTAB solution, 80%; j) $MeCO_2Na$, EtOH, 70 ^{o}C, >98%; k) 6 M HCl, 100 ^{o}C, 90%.*

As a starting point, racemic cyclohexanedione **48** was prepared in four steps from methyl 2-*p*-tolylacetate **46**. To prepare the enantiomerically pure natural

products a classical resolution of (±)-**48** *via* the diastereomeric difluorodioxaborinane complexes of *β*-keto-*(S)*-*(α)*-methylbenzylamide **51** was performed. *β*-Ketoester **49** was obtained in 92% yield by selective C-acylation of (±)-**48** with methyl cyanoformate, and subsequent treatment with $BF_3.OEt_2$ gave difluorodioxaborinane (±)-**50** in 98% yield. Reaction of (±)-**50** with (-)-(*S*)-(*α*)-methylbenzylamine in acetonitrile yielded 80% of diastereomers **51**. Separation by column chromatography (EtOAc/hexane 2:8) led to pure **52a** and **52b**. Finally syntheses of (+)- and (-)-(*α*)-cuparenone were completed by parallel UV/Vis irradiation of suspended nanocrystals of (+)-(*S,S*)-**52a** and (-)-(*S,R*)-**52b** in aqueous cetyltrimethylammonium bromide (CTAB) solutions which led to the clean formation of the α-cuparenone ketoamide derivatives (+)-(*S,S*)-**53a** and (-)- (*S,R*)-**53b** with 100% stereoselectivity in 80% yield. Removal of the BF_2 unit with NaOAc in ethanol followed by amide hydrolysis and decarboxylation gave the (*S*)-(+)-**1** and (*R*)-(-)-**1** each in 90% yield (Scheme 9).

Chavan's 4th approach (*Synthesis* **2007**, *24*, 3827)



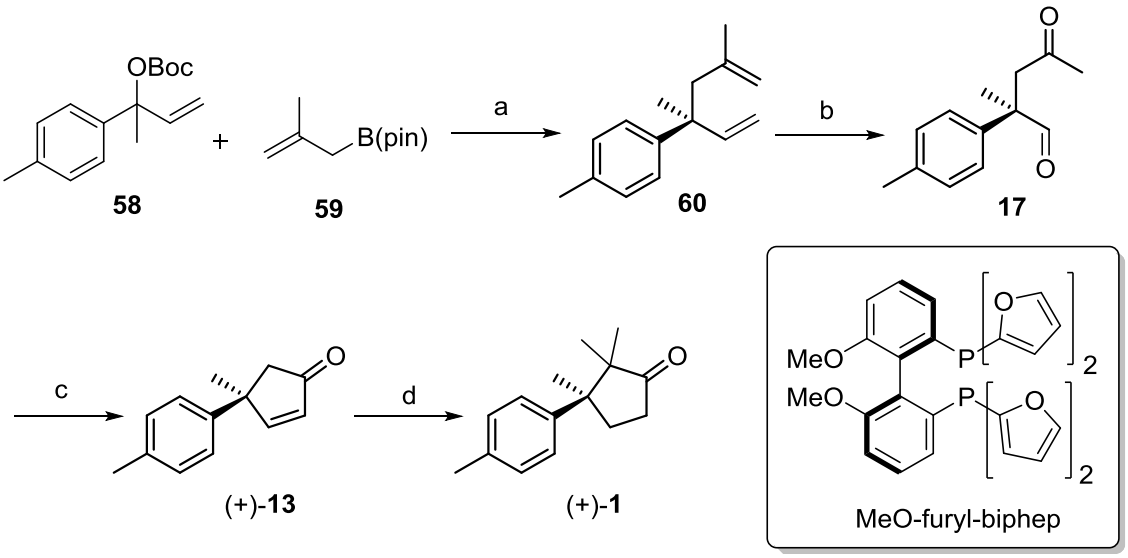
Scheme 10: *Reagents and conditions: a) NaH, cis-1,4-dichlorobutene, THF, rt, 8 h, 80%; b) DIBAL-H, DCM, -78 ^oC, 1 h; c) $NH_2NH_2.H_2O$, NaOH, diethylene glycol, 180 ^oC, 8 h, 60 % (over two steps); d) i) $BH_3.SMe_2$, THF, H_2O_2, 3 N NaOH; ii) IBX, DMSO, 12 h, 85%; e) LiHMDS, MeI, DME, HMPA, 3 h, 70%.*

In this communication Chavan *et al.*[20] reported an efficient and practical total synthesis of (±)-α-cuparenone employing a one-pot cyclopentannulation approach as the key step (Scheme 10). Accordingly, synthesis was initiated from 4-methylbenzyl cyanide **54** which was subjected for cyclopentannulation with *cis*-1,4-dichlorobutene

to furnish cyclopentene **55** (Scheme 2), which on partial reduction and hydrolysis afforded aldehyde **56**. Under Huang-Minlon reaction conditions aldehyde **56** was reduced to furnish the required olefin intermediate **45**. The olefin **45** was subjected to hydroboration-oxidation sequence to furnish cyclopentanone **57** in 85% yield. The ketone **57** on regioselective alkylation afforded the target compound (±)-α-cuparenone **1** in 70% yield.

Morken's approach (*J. Am. Chem. Soc.* **2011**, *133*, 9716)

Morken *et al.*[21] reported the Pd-catalyzed cross-coupling of racemic tertiary allylic carbonates and allylboronates and its application to the asymmetric total synthesis of (+)-α-cuparenone.

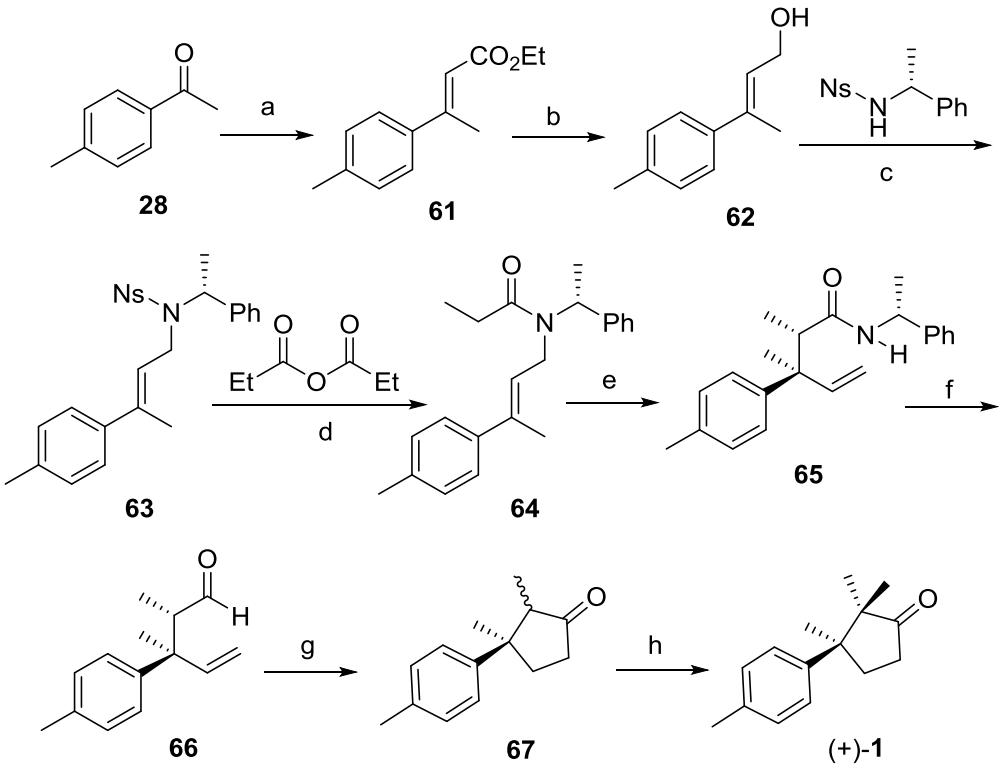


Scheme 11: *Reagents and conditions: a) 2% $(Pd)_2(dba)_3$, 4% MeO-furyl-biphep, CsF, THF/H_2O (5:1), 60 ºC, 12 h, 53%, er 98:3; b) O_3, PPh_3, DCM, 56%; c) KOH, EtOH, 64%; d) i) NaH, CH_3I; ii) Pd/C, H_2, 70%.*

Coupling of carbonate **58** and methallylB(pin) **59** occurred with excellent levels of asymmetric induction (98:2 *er*). As depicted in Scheme 11, ozonolysis delivered ketoaldehyde **17**, which was converted to cyclopentenone **13** by intramolecular aldol condensation. In analogy to a study by Meyers,[11] **13** was converted to *R*-cuparenone. This five-step route from **58** represents the shortest catalytic asymmetric synthesis of this target structure (Scheme 11).

Tsunoda's approach (*Tetrahedron Asymmetry* **2012**, *23*, 739)

Tsunoda *et al.*[22] demonstrated applicability of the asymmetric aza-Claisen rearrangement to asymmetric total synthesis of α-cuparenone. The precursor amide **64** was prepared from *p*-methyl acetophenone **28** as a starting material and converted into the unsaturated ester **61** by the Horner-Wadsworth-Emmons reaction.[23] Alcohol **62**, obtained by reduction with LAH, was subjected to the Fukuyama method[24] using TMAD-PBu_3 **62** to afford allylic amine **63**, which was acylated to give propanamide **64**. Under strong basic condition **64** was converted into **65** by aza-Claisen rearrangement.



Scheme 12: *Reagents and conditions: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, EtOH, reflux, 20 h, 93%; b) $LiAlH_4$, Et_2O, 0 °C to rt, 2 h, quant.; c) TMAD, Bu_3P, toluene, rt, 24 h, 93%; d) i) Cs_2CO_3, PhSH, MeCN, 50 °C, 2 h, 93%; ii) Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 95%; e) i) LHMDS, LiCl, toluene-hexane, -78 °C; ii) 120 °C, 6 h; f) Ph_2SiH_2, Ti(O-iPr)$_4$, rt, 44 h, 85%; g) $RhCl(PPh_3)_3$, ethylene in $CHCl_3$, rt, 3 h, 75%; h) MeI, NaH, diglyme, 0 °C to rt, 24 h, 65%.*

Amide **65**, was reduced to corresponding aldehyde **66** with diphenylsilane-Ti(O-iPr)$_4$[25] followed by cyclization using the Wilkinson complex[26] in an ethylene saturated $CHCl_3$ solution,[27] to afford cyclopentanone derivative **67**, which was subsequently alkylated to afford the desired ketone (+)-**1** (Scheme 12).

3.1.4 References

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Chapter 3. Synthetic Studies Towards α-Cuparenone and Unusual metal free auto-oxidation by air.

Section 2

A chiral pool based approach to antipodes of α-cuparenone

3.2.1 Summary

The present section deals with the total synthesis both the antipodes of α-cuparenone. Novel syntheses of both the antipodes of α-cuparenone employing cyclopentannulation have been achieved starting from commercially available cheap starting materials like 4-methylbenzyl cyanide and L-malic acid as chiral pool templates.

3.2.2 Introduction

Both (+)-α-cuparenone (+)-**1** and (+)-β-cuparenone (+)-**1a** were first isolated from the essential oil of *Thuja orientallis* (Mayurpankhi) by Dev and Chetty in 1964.[1] Benesova reported the isolation of (-)-α-cuparenone (-)-**1** and (-)-β-cuparenone (-)-**1a** from the liverwort *Mannia fragrans* in 1976.[2]

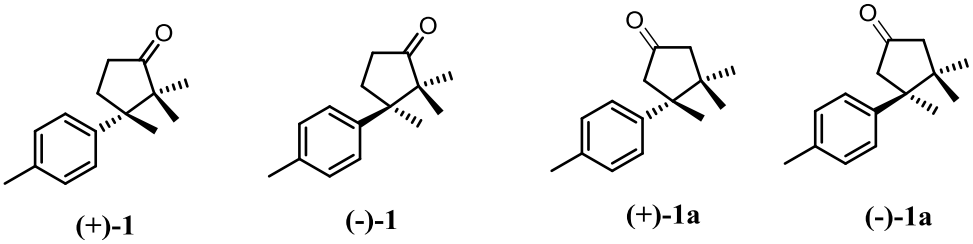


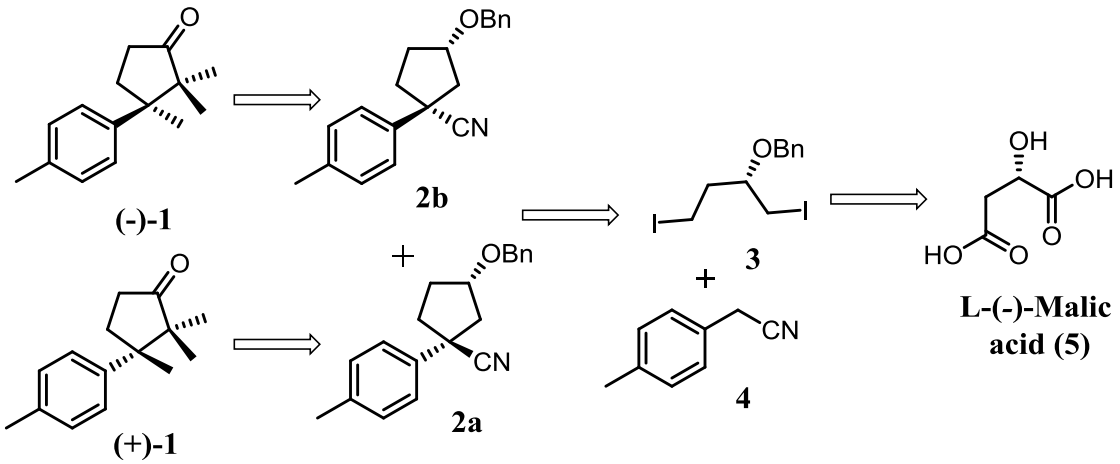
Figure 1

The structure of α-cuparenone is quite interesting as it has a five membered ring having two contiguous quaternary centers. This makes α-cuparenone a good synthetic challenge to organic chemist. Although varieties of approaches have been employed for the synthesis of α-cuparenone, all the reported syntheses have their own advantages and disadvantages and very few of them construct the five membered rings. There still exists need to develop a simple, practical and efficient synthesis of α-cuparenone. Continued interest in synthesis of cyclopentanoid natural products[3] led to the syntheses of both the enantiomers of α-cuparenone employing one-pot cyclopentannulation[4] starting from cheap and commercially available starting material like 4-methylbenzyl cyanide and L-malic acid.

3.2.3 Present work

As is obvious from the retrosynthesis outlined in Scheme 1, the tactic was to prepare key intermediates **2a** and **2b** by dialkylation. From previous results,[4] it was

expected that cyclopentannulation of 4-methylbenzyl cyanide **4** with the help of (*S*)-(((1,4-diiodobutan-2-yl)oxy)methyl)benzene **3** as a chiral auxillary would provide the required stereogenic center of **2**, compound **3** could be accessed from commercially available cheap starting material like L- malic acid.



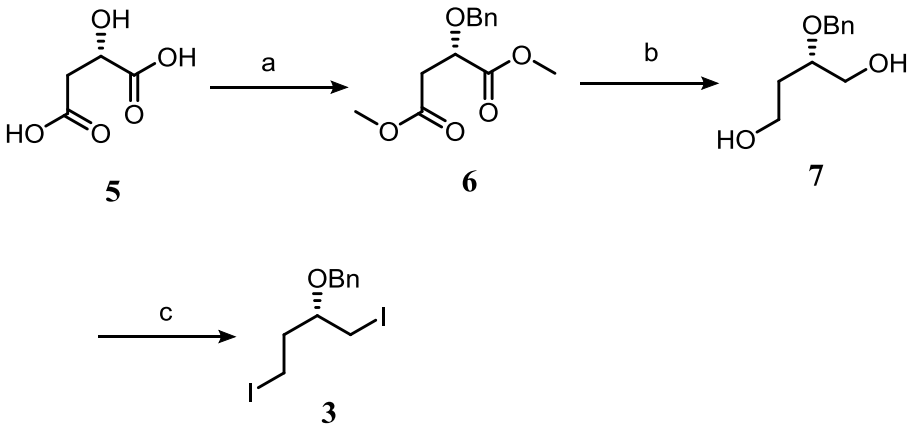
Scheme 1

3.2.4 Results and discussion

The enantiomerically pure (*S*)-(((1,4-diiodobutan-2-yl)oxy)methyl)benzene **3** was obtained in four steps from L-malic acid.[5] Accordingly, L-malic acid **5** on treatment with thionyl chloride and methanol gave methyl ester. Secondary hydroxyl group was protected using benzyl bromide and silver oxide in ethyl acetate as a solvent to furnish its *O*-benzyl ether **6** in 90% yield over two steps. The formation of compound **6** was confirmed by spectroscopic data. IR spectrum of the compound **6** displayed strong absorption band at 1746 cm^{-1} indicating the presence of ester functionality. The ^{1}H NMR spectrum of compound **6** showed peaks at δ 3.69 and 3.78 as singlets corresponding to the three protons indicating dimethyl ester compound. A multiplet at δ 7.29-7.35 integrating for five protons and doublets at δ 4.54 and 4.78 integrating for one proton each were assigned to phenyl ring protons and benzylic protons respectively. ^{13}C NMR spectrum displayed signals at δ 127.8, 128.0 (2 C), 128.3 (2 C) and 137.2 corresponding to aromatic ring carbons and characteristic peaks at δ 170.2 and 171.5 for ester carbonyl

carbons. Formation of **6** was further supported by its mass spectrum which showed the molecular ion peak at m/z 275 $(M+Na)^+$.

The reduction of diester **6** was carried out using calcium borohydride to afford dihydroxy compound **7** in 95% yield. Its IR spectrum showed broad band at 3393 cm^{-1} indicating the presence of hydroxy functionality. The broad peak at δ 3.27 (brs, 2 H) in its ^{1}H-NMR spectrum was assigned to –OH protons. Disapperance of peaks at δ 170.2 and 171.5 in ^{13}C NMR spectrum clearly confirmed the reduction of ester carbonyls. Its DEPT spectrum showed presence of four CH_2 carbons that appeared at δ 34.0, 58.9, 63.6 and 71.5 in accordance with the structure of **7**. Further, the formation of **7** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 219 $(M + Na)^+$.

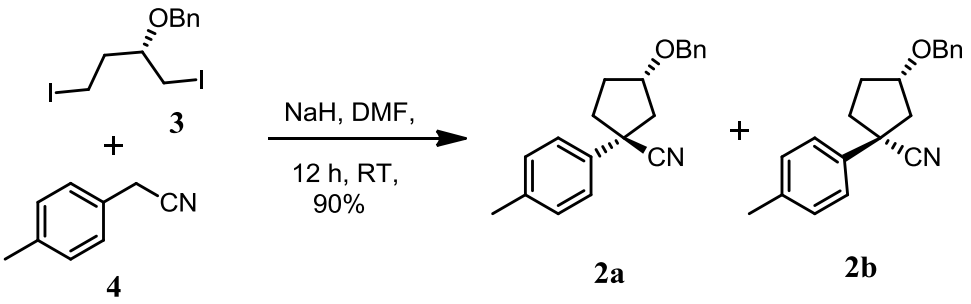


5 **6** **7** **3**

Scheme 2*. Reagents and conditions: a) i) $SOCl_2$, MeOH, RT, 24 h; ii) Ag_2O, BnBr, EtOAc, RT, 6 h, 90% (over two steps); b) $NaBH_4$, $CaCl_2$, EtOH, 2 h, 0 ^oC, 95%; c) i) Et_3N, MsCl, DCM, 0 ^oC, 6 h; ii) NaI, acetone, reflux, 4 h, 85% (over two steps).*

Both the hydroxyl groups were converted to mesylate derivative and mesylate was treated with sodium iodide in acetone at 65 ^{o}C to furnish the corresponding di-iodo compound **3** in 85% yield over two steps (Scheme 2). The IR spectrum of **3** displayed the disapperance of peak at 3393 cm^{-1} indicating the absence of hydroxy functionality. The ^{1}H NMR spectrum showed upfield multiplet at δ 3.25-3.33 integrating for four protons (-$\underline{CH_2}$-I) indicating the formation of **3**. This was further confirmed by its ^{13}C NMR and DEPT NMR spectra, which showed upfield -CH_2- carbon singlets at δ 2.1 and 8.7 for the methylene carbons (-$\underline{CH_2}$-I).

Having di-iodo compound **3** in hand, next job was to construct cyclopentane ring. Thus, 4-methyl benzyl cyanide was treated with sodium hydride in DMF as a solvent at 0 ^{o}C followed by addition of **3** to afford mixture of diastereomers **2a** and **2b** (50:50) in 90% yield, which was separated by column chromatography (SiO_2) using hexane/ethyl acetate (98:2) as eluent to obtain pure **2a** and **2b** (Scheme 3).



Scheme 3. *Key cyclopentannulation*

The formation of compounds **2a** and **2b** was confirmed by spectroscopic data. IR spectrum of the mixture of **2a** and **2b** displayed strong absorption band at 2233 cm^{-1} indicating the presence of -CN functionality. Fortunately, one of these two diastereomers, **2b** was solid (m.p. = 82 ^{o}C). After recrystallization (pet ether/ethylacetate) a colourless X-ray quality crystal was obtained.

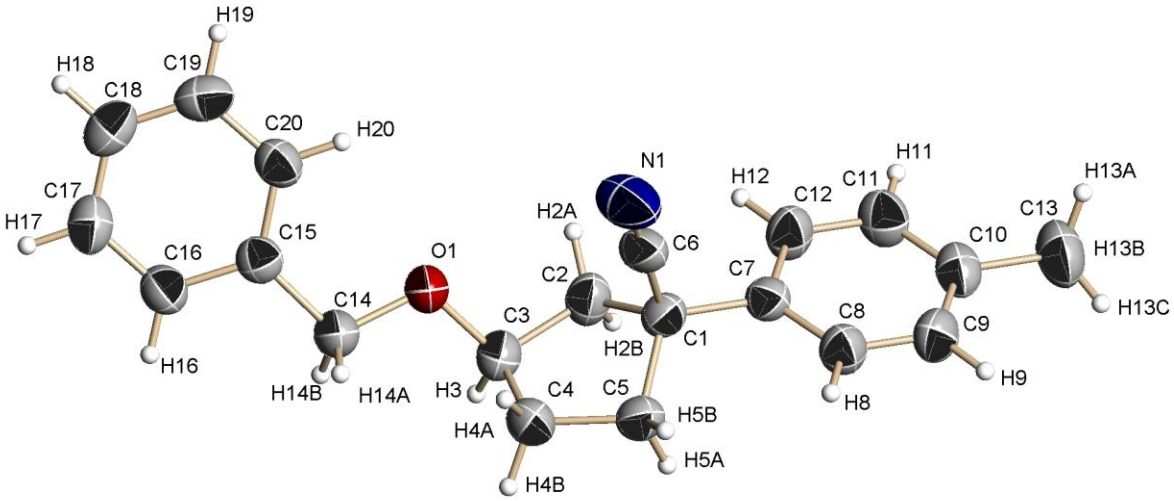
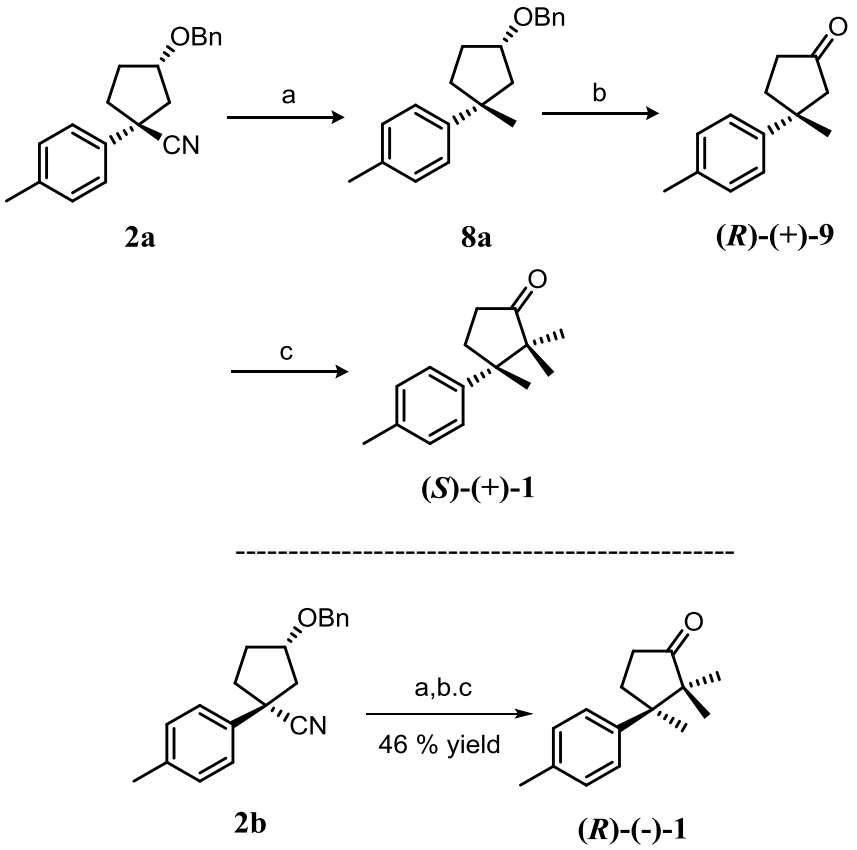


Figure 2. X-ray structure of polar diastereomer **2b**

The absolute configuration of the L-malic acid used is *S*; from single-crystal X-ray diffraction analysis[6] it could be clearly ascertained that absolute stereochemistry of the quaternary carbon of **2b** has the *R* configuration (Figure 2). With the (*R*,*S*) configuration assigned for the polar diastereomer **2b**, the configuration for the other less polar isomer **2a** was assigned as (*S*,*S*). This was again confirmed by nOe experiment (Figure 3).



Scheme 4*. Reagents and conditions: a) i) DIBAL-H, DCM, -78 °C, 1 h; ii) NaOH, NH_2NH_2, ethylene glycol, 180 °C, 24 h, 70%; b) i) Pd-C, H_2, 60 psi, 1 h, MeOH; ii) IBX, dry DMSO, 4 h, 95%; c) LiHMDS, MeI, DME, HMPA, 3 h,70%.*

Further functional group transformations were carried out separately on both diastereomers. Thus, cyanide **2a** was subjected to reduction using DIBAL-H to furnish aldehyde and it was used as such for the next reaction without further purification. The crude aldehyde was subjected to Huang-Minlon[7] reaction conditions to give **8a** in 70% yield. The IR spectrum of **8a** showed no peak corresponding to the –CN functionality. ^{1}H NMR spectrum of compound **8a** showed the presence of a new singlet that appeared at δ

1.29 integrating for three protons which was attributed to methyl protons attached to quaternary center while a singlet integrating for three protons appeared at δ 2.38 which was attributed to aryl methyl protons. ^{13}C NMR spectrum of **8a** also exhibited the absence of signals of nitrile carbons and revealed new signal that appeared at δ 30.2 which was assigned to quaternary methyl carbon. DEPT spectrum of **8a** showed presence of two methyl carbons while rest of the carbon peaks associated with the compound were seen at expected positions and finally the structure of **8a** was confirmed by mass spectrum and elemental analysis. The mass spectrum showed the *m/z* peak at 303 (M + Na) $^{+}$. Elemental analysis was also found to be in good agreement with the calculated values.

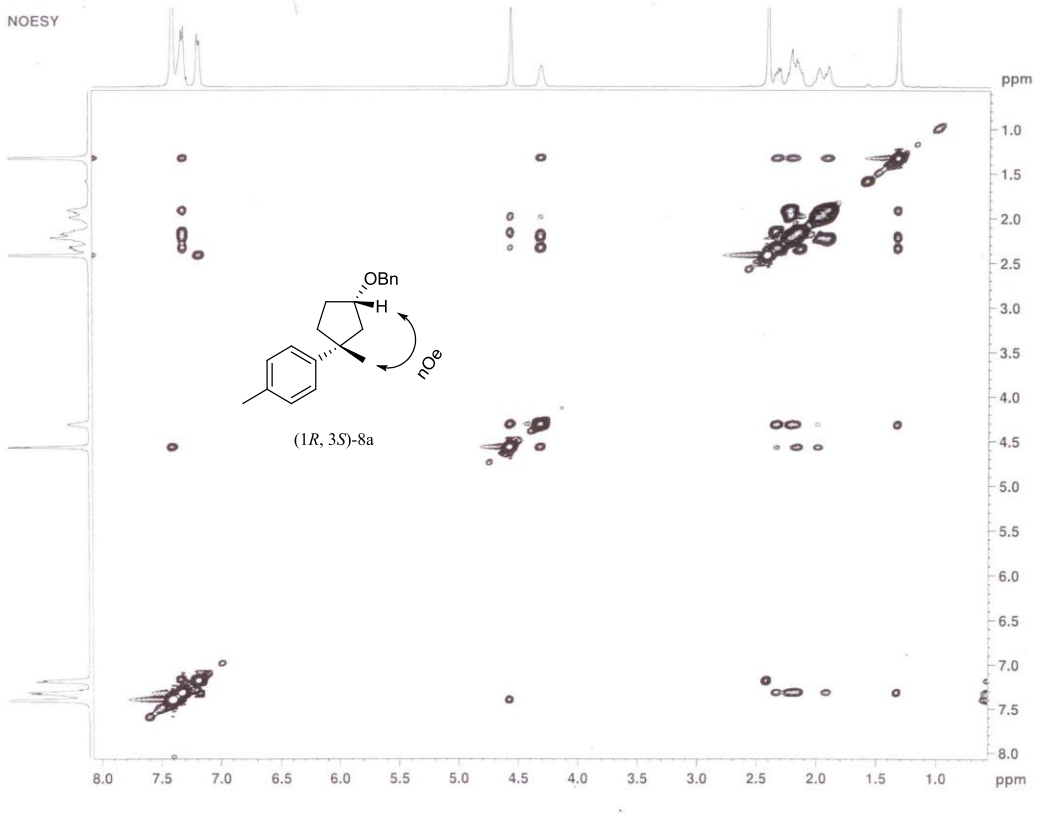


Figure 3. The 2D NOESY spectrum of **8a**

Hydrogenolysis of **8a** was carried out using Pd/C as the catalyst to furnish hydroxyl compound. The hydroxy compound was oxidized by using IBX in dry DMSO

as a solvent to furnish 3,3-disubstituted cyclopentanone **9** in 95% yield.[8,9] IR spectrum of the product **9** indicated the presence of a carbonyl group by revealing absorption at 1720 cm^{-1} confirming debenzylation-oxidation. ^{1}H NMR spectrum showed no peak in the benzylic region (δ 4.00-6.00) while appearance of peaks at δ 2.46 and 2.65 as a doublet integrating for one proton each, having geminal coupling constant 17.7 Hz, was attributed to methylene protons between carbonyl and quaternary center. The methylene protons next to carbonyl and quaternary center showed multiplets at δ 2.21-2.29 and 2.32–2.37 respectively integrating for two protons each. ^{13}C NMR spectrum of compound **9** showed a signal that appeared at δ 217.7 corresponding to carbonyl carbon while rest of the proton and carbon peaks associated with the compound **9** resonated at expected positions. The mass spectrum of **9** showed the *m/z* peak at 211 $(M + Na)^{+}$ which further supported the assigned structure.

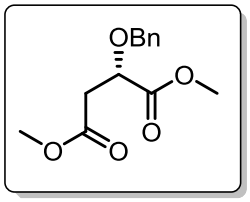
Finally, cyclopentanone **9** on regioselective alkylation using MeI and LiHMDS as a hindered base and cat. HMPA in DME afforded (+)-*α*-cuparenone **1** in 70% yield (Scheme 4).[4,9] The IR spectrum of **1** showed characteristic absorption at 1725 cm^{-1} for the ketone carbonyl. The ^{1}H NMR spectrum displayed all the four methyls as singlets at δ 0.61, 1.17 and 1.26 for methyls on cyclopentanone ring and δ 2.35 for Ar-CH_3. The multiplets at δ 1.86-1.97 integrating for one proton, 2.41-2.52 integrating for one proton and 2.58-2.71 integrating for two protons were assigned to the protons in cyclopentanone ring. Aromatic protons appeared at δ 7.14-7.30 as multiplet integrating for four protons. ^{13}C NMR and DEPT spectra of compound **1** showed the signals at δ 18.4, 20.8, 22.1 and 25.3 which were attributed to four methyl carbons while signals that appeared at δ 29.6 and 33.8 were attributed to methylene carbons in cyclopentanone ring. The rest of the protons and carbons associated with the compound **1** resonated at expected positions. Finally the mass spectrum of **1** showed the *m/z* peak at 216 $(M + H)^{+}$.

3.2.5 Conclusion

In conclusion, the synthesis of both the enantiomers of *α*-cuparenone was achieved in ten steps involving one diastereomeric separation, starting from L-malic acid **5** and 4-methyl benzyl cyanide **4** which led to (*S*)-(+)-**1** and (*R*)-(-)-**1** in ≥99 % *ee* and 15 % overall yield.

3.2.6 Experimental

(*S*)-Dimethyl 2-(benzyloxy)succinate (6):



L-(*S*)-Malic acid (5 g, 37.31 mmol) was dissolved in methanol (100 mL) and cooled at 0 ^{o}C. Thionyl chloride (5.95 mL, 82.08 mmol) was added dropwise during a half hour period and the solution was stirred at room temperature for 24 h. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane (50 mL) and saturated sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, giving colourless oil, which was used without further purification.

To the stirred solution of (*S*)-malate (6 g, 37.03 mmol) in EtOAc was added Ag_2O (12.83 g, 55.55 mmol), benzyl bromide (5.42 mL, 44.44 mmol) was then added drop wise and reaction mixture was stirred for 6 h. After completion, the reaction mixture was filtered through celite pad, the solution was concentrated under reduced pressure and purified by flash column chromatography (SiO_2) using 10% EtOAc /hexane as an eluent to furnish **6** as a colorless oil.

***R*$_f$:** 0.5 (Pet. ether-ethyl acetate, 7:3).

Yield: 8.43 g, 90%.

MF: $C_{13}H_{16}O_5$, **MW:** 252.27.

$[\alpha]_D^{25}$ = -70.37 (c 1.08, $CHCl_3$).

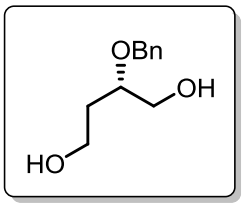
IR ($CHCl_3$, cm^{-1}): νmax 3028, 2954, 1746, 1217, 756.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.78-2.81 (m, 2 H), 3.69 (s, 3 H), 3.78 (s, 3 H), 4.35-4.42 (m, 2 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.78 (d, *J* = 11.4 Hz, 1 H), 7.29-7.35 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 37.7, 51.7, 52.0, 72.9, 74.4, 127.8, 128.0 (2 C), 128.3 (2 C), 137.2, 170.2, 171.5.

MS (ESI): m/z = 275 $(M + Na)^+$.

(*S*)-2-(Benzyloxy) butane-1,4-diol (7):



Compound **6** (8.4 g, 33.20 mmol) was dissolved in ethanol (100 mL) and cooled to 0 ^{o}C. Calcium chloride was added (14.74 g, 132.8 mmol) followed by portion wise addition of sodium borohydride (4.91 g, 132.8 mmol) over a period of half hour. After complete addition, the reaction mixture was stirred for additional 2 h. After completion, the reaction mixture was quenched by 10% HCl solution and evaporated almost to dryness and then extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (SiO_2) using 50% EtOAc/hexane as a eluent to furnish **7**.

***R*$_f$:** 0.3 (Pet. ether-ethyl acetate, 1:1).

Yield: 6.18 g, 95 %.

MF: $C_{11}H_{16}O_3$, **MW:** 196.25.

$[\alpha]_D^{25}$ = -14.28 (c 1.26, $CHCl_3$).

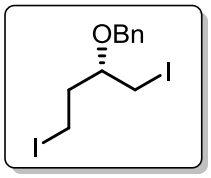
IR ($CHCl_3$, cm^{-1}): νmax 3393, 2933, 2873, 1716, 1278.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.76-1.85 (m, 2 H), 3.27 (brs, 2 H), 3.53-3.77 (m, 5 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 11.6 Hz, 1 H), 7.26-7.34 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 34.0, 58.9, 63.6, 71.5, 77.6, 127.8 (3 C), 128.4 (2 C), 138.2.

MS (ESI): m/z = 219 $(M + Na)^+$.

(*S*)-(((1,4-Diiodobutan-2-yl)oxy)methyl)benzene (3):



To a stirred a solution of **7** (6 g, 30.61 mmol) in dry DCM (60 mL) was added Et_3N (14.37 mL, 101.02 mmol) at 0 ^{o}C, followed by dropwise addition of mesyl chloride (6.23 mL, 76.52 mmol). The reaction mixture was stirred at 0 ^{o}C for 6 h under nitrogen atmosphere. After completion of reaction, the reaction mixture was diluted with dichloromethane and washed with saturated solution of sodium bicarbonate (50 mL) followed by water. The

organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give *O*-mesyl compound (10.8 gm, crude).

To a solution of *O*-mesyl compound (10 g, 28.40 mmol) in anhydrous acetone (150 mL) was added sodium iodide (21.16 g, 142.04 mmol) and the reaction mixture was heated at 70 ^oC for 4 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), it was cooled to room temperature, evaporated almost to dryness and then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (SiO_2) using 20% EtOAc/hexane as eluent to furnish **3**.

***R_f*:** 0.6 (Pet. ether-ethyl acetate, 8:2).

Yield: 10.04 g, 85 %.

MF: $C_{11}H_{14}I_2O$, **MW:** 416.04.

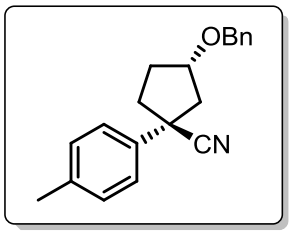
$[\alpha]_D^{25}$ = -62.74 (c 1.02, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 3029, 2861, 1087, 1062, 737, 697.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.08-2.18 (m, 2 H), 3.25-3.33 (m, 4 H), 3.42-3.53 (m, 1 H), 4.50 (d, *J* = 11.2 Hz, 1 H), 4.72 (d, *J* = 11.2 Hz, 1 H), 7.31-7.39 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 2.1, 8.7, 38.7, 71.8, 76.9, 128.00, 128.04 (2 C), 128.5 (2 C), 137.5.

(1*S*,3*S*)-3-(Benzyloxy)-1-(p-tolyl)cyclopentanecarbonitrile (2a):



To the suspension of 60% NaH (458 mg, 19.08 mmol) (washed with dry petroleum ether 2-3 times) in dry DMF was added 4-methyl benzyl cyanide **4** (1 g, 7.63 mmol) in dry DMF (10 mL) at 0 ^oC and stirred for 30 min. 1, 4-Diiodo compound **3** (3.16 g, 7.63 mmol) in DMF (15 mL) was added drop wise over 20 min and reaction was stirred for 12 h at room temperature. On completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (3 × 20 mL) and washed with water followed by brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure to furnish **2a** and **2b** as a diastereomeric mixture (1:1) in 90 % yield, which were separated by column chromatography (SiO_2) using 2% EtOAc/hexane as eluent to afford compound **2a** (0.95 g, 45%) as oil and compound **2b** (0.95 g, 45%) as solid, melting point 82 ^{o}C. R_f (10% EtOAc/hexane) 0.4 and 0.3 for **2a** and **2b** respectively.

***R*$_f$:** 0.4 (Pet. ether-ethyl acetate, 9:1).

Yield: 0.95 g, 45%.

MF: $C_{20}H_{21}NO$, **MW:** 291.39.

$[\alpha]_D^{25}$ = -3.468 (c 1.73, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 2924, 2233, 1274, 813, 755.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.01-2.53 (m, 5 H), 2.37 (s, 3 H), 2.85 (ddd, *J* = 14.2, 6.3, 0.9 Hz, 1 H), 4.26 - 4.43 (m, 1 H), 4.43 - 4.66 (m, 2 H), 7.07 - 7.23 (m, 2 H), 7.28 - 7.49 (m, 7 H).

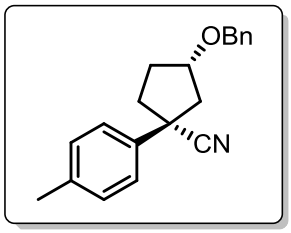
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 21.0, 31.9, 39.5, 46.5, 47.2, 71.1, 79.1, 124.3, 125.9 (2 C), 127.6 (2 C), 127.7, 128.4 (2 C), 129.5 (2 C), 136.8, 137.4, 138.0.

MS (ESI): m/z = 292 $(M + H)^+$, 314 $(M + Na)^+$.

Elemental analysis: Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81%.

Found: C, 83.14; H, 7.74; N, 4.64%.

(1*R*,3*S*)-3-(Benzyloxy)-1-(p-tolyl)cyclopentanecarbonitrile (2b):



***R*$_f$:** 0.3 (Pet. ether-ethyl acetate, 9:1).

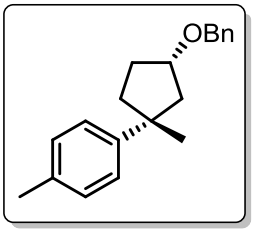
Yield: 0.95 g, 45%.

$[\alpha]_D^{25}$ = +8.38 (c 6.68, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.08-2.39 (m, 4 H), 2.37 (s, 3 H), 2.50-2.86 (m, 2 H), 4.10-4.35 (m, 1 H), 4.52 (d, *J* = 11.9 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 7.16-7.44 (m, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 20.9, 32.2, 38.8, 44.8, 46.1, 70.8, 79.0, 124.3, 125.6 (2 C), 127.5 (2 C), 128.3 (2 C), 129.5 (2 C), 137.3, 137.4, 138.1.

1-((1*R*,3*S*)-3-(Benzyloxy)-1-methylcyclopentyl)-4-methylbenzene (8a):



The compound **2a** (0.9 g, 3.09 mmol) was taken in dry DCM (10 mL) under argon atmosphere and temperature was lowered to -78 ^{o}C. DIBAL-H (6.18 mmol, 6.14 mL, 1M, solution in toluene) was added drop wise and the reaction mixture was left to stir at same temperature till the completion of the reaction (1 h). After completion of reaction, it was quenched at –78 ^{o}C with the drop wise addition of 2N HCl and then warmed to the room temp. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford aldehyde which was used as such without further purification.

To the stirred solution of crude aldehyde (0.9 g, 3.07 mmol) in diethylene glycol (10 mL), was added hydrazine monohydrate (0.59 mL, 12.28 mmol) and sodium hydroxide (0.49 g, 12.28 mmol). The reaction mixture was heated to reflux for 24 h. After completion of the reaction, it was diluted with water (10 mL) and extracted using ethyl acetate (3 × 10 mL). Combined organic layers were then washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue which was purified by flash column chromatography (SiO_2) using 2% EtOAc/hexane as eluent to give compound **8a** as oil.

***R_f*:** 0.2 (Pet. ether-ethyl acetate, 9.5:0.5).

Yield: 0.6 g, 70%.

MF: $C_{20}H_{24}O$, **MW:** 280.41.

$[\alpha]_D^{25}$ = -29.67 (c 1.82, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 2956, 1515, 1454, 815, 734.

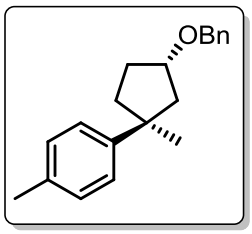
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.29 (s, 3 H), 1.85-2.36 (m, 6 H), 2.38 (s, 3 H), 4.23-4.34 (m, 1 H), 4.54 (s, 2 H), 7.12-7.38 (m, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 20.9, 30.2, 31.2, 38.1, 45.6, 46.8, 70.9, 80.2, 125.7 (2 C), 127.3, 127.5 (2 C), 128.3 (2C), 128.8 (2 C), 134.7, 138.8, 148.1.

MS (ESI): m/z = 303 $(M + Na)^+$.

Elemental analysis: calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63%. Found: C, 85.85; H, 9.03%.

1-((1*S*,3*S*)-3-(Benzyloxy)-1-methylcyclopentyl)-4-methylbenzene (8b):

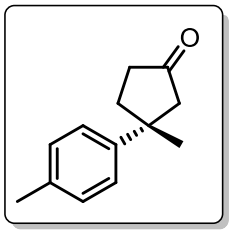


$[\alpha]_D^{25}$ = +18.09 (c 2.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.43 (s, 3 H), 1.93-2.06 (m, 5 H), 2.34 (s, 3 H), 2.28-2.39 (m, 1 H), 4.08-4.15 (m, 1 H), 4.50 (s, 2 H), 7.08-7.22 (m, 4 H), 7.27-7.36 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 20.91 31.0, 31.8, 38.3, 45.8, 46.3, 71.0, 80.4, 125.6 (2 C), 127.4, 127.5 (2 C), 128.3 (2 C), 128.8 (2 C), 134.8, 138.9, 147.7.

(*R*)-3-Methyl-3-(p-tolyl)cyclopentanone (9):



To a well stirred solution of compound **8** (500 mg, 1.78 mmol) in MeOH (10 mL), was added 10% Pd/C (20 mg). The resulting reaction mixture was kept on a shaker at 60 *psi* under a hydrogen atmosphere for 1 h. After the disappearance of starting material, the reaction mixture was filtered on celite and residue was washed with MeOH (3 × 20 mL). The solvent was removed under reduced pressure to afford alcohol which was used as such without further purification.

To the stirred solution of alcohol (330 mg, 1.78 mmol) in dry DMSO (10 mL) was added IBX (982 mg, 3.56 mmol) and left to stir at room temperature for 4 h. After completion of the reaction, the reaction mixture was diluted with water and extracted using diethylether (3 × 20 mL). Combined organic layers were then washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford residue which was purified by flash column chromatography (SiO_2) using 10% EtOAc/hexane as eluent to afford compound **9** as a white solid.

***R_f*:** 0.3 (Pet. ether-ethyl acetate, 9:1).

Yield: 310 mg, 95%.

MP = 56-58 ^oC.

MF: $C_{13}H_{16}O$, **MW:** 188.27.

$[\alpha]_D^{25}$ = +12.34 (c 1.62, $CHCl_3$); lit. $[\alpha]_D^{25}$ = +13.3 (c 4.00, $CHCl_3$).

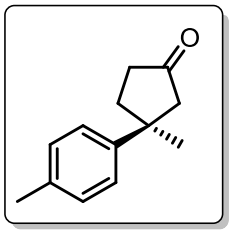
IR ($CHCl_3$, cm^{-1}): vmax 3019, 1720, 1614, 1246, 815.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.39 (s, 3 H), 2.21-2.29 (m, 2 H), 2.35 (s, 3 H), 2.35- 2.37 (m, 2 H), 2.46 (d, *J* = 17. 7 Hz, 1 H), 2.65 (d, *J* = 17.7 Hz, 1 H), 7.12-7.22 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 20.9, 29.4, 35.9, 36.6, 43.4, 52.2, 125.2 (2 C), 129.1 (2 C), 135.6, 145.3, 217.7.

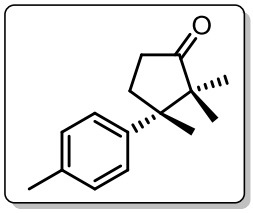
MS (ESI): m/z = 211 $(M + Na)^+$.

(*S*)-3-Methyl-3-(p-tolyl)cyclopentanone (9):



$[\alpha]_D^{25}$ = -10.00 (c 1.05, $CHCl_3$).

(*S*)-2, 2, 3-Trimethyl-3-*p*-tolylcyclopentanone (1):



To the stirred solution of ketone **9** (200 mg, 1.0 mmol) in dry DME (10 mL) was added LiHMDS (371 mg, 2.2 mmol) and catalytic amount of HMPA (0.25 mL) and stirred for few minutes. Then methyl iodide (0.325 mL, 5.0 mmol) in dry DME (2 mL) was added drop wise and reaction mixture was stirred for 3 h. After completion, the reaction mixture was quenched with saturated ammonium chloride solution, extracted with ethyl acetate (3 × 10 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (SiO_2) using 5% EtOAc/hexane as eluent to furnish desired target molecule **1** as white solid.

***R_f*:** 0.4 (Pet. ether-ethyl acetate, 9:1).

Yield: 152 mg, 70%.

MP = 56 ^{o}C (lit. 52-53 ^{o}C).

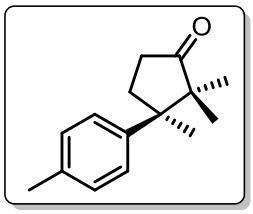
MF: $C_{15}H_{20}O$, **MW:** 216.

$[\alpha]_D^{25}$ = +170.08 (c 1.08, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 2960, 1725, 1510, 1460, 815.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.61 (s, 3 H), 1.17 (s, 3 H), 1.26 (s, 3 H), 1.86-1.97 (m, 1 H), 2.35 (s, 3 H), 2.41-2.52 (m, 1 H), 2.58-2.71 (m, 2 H), 7.14-7.30 (m, 4 H).
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 18.4, 20.8, 22.1, 25.3, 29.6, 33.8, 48.3, 53.2, 126.4 (2 C), 128.9 (2 C), 135.8, 141.9, 222.7.
MS (ESI): m/z = 216 $(M+H)^+$.

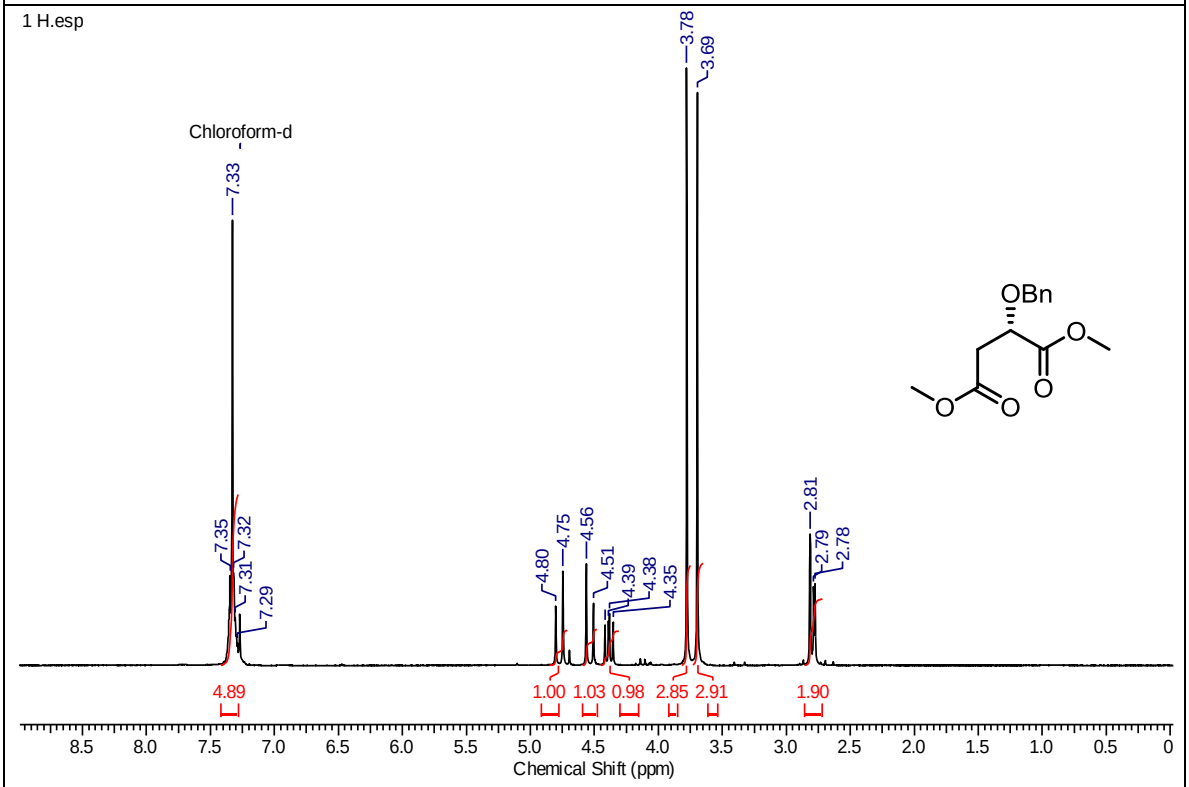
(*R*)-2, 2, 3-Trimethyl-3-*p*-tolylcyclopentanone (1)



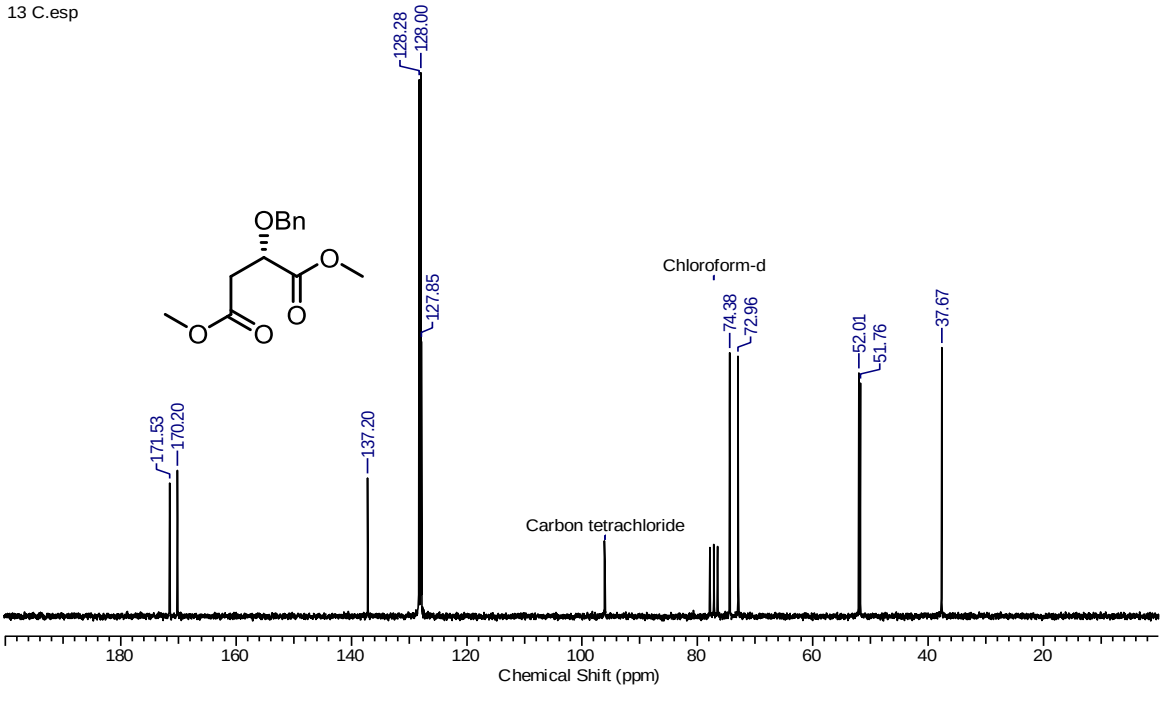
$[\alpha]_D^{25}$ = -162.74 (c 1.02, $CHCl_3$).

3.2.7 Spectra

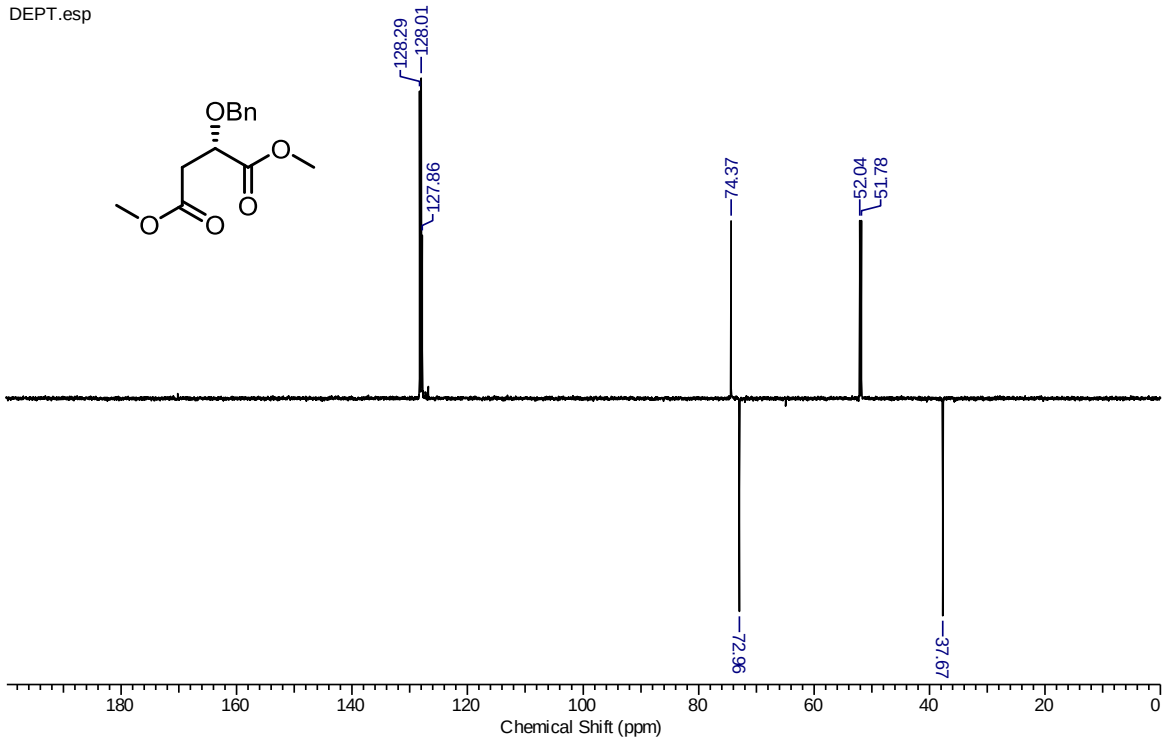
^{1}H NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 200 MHz)



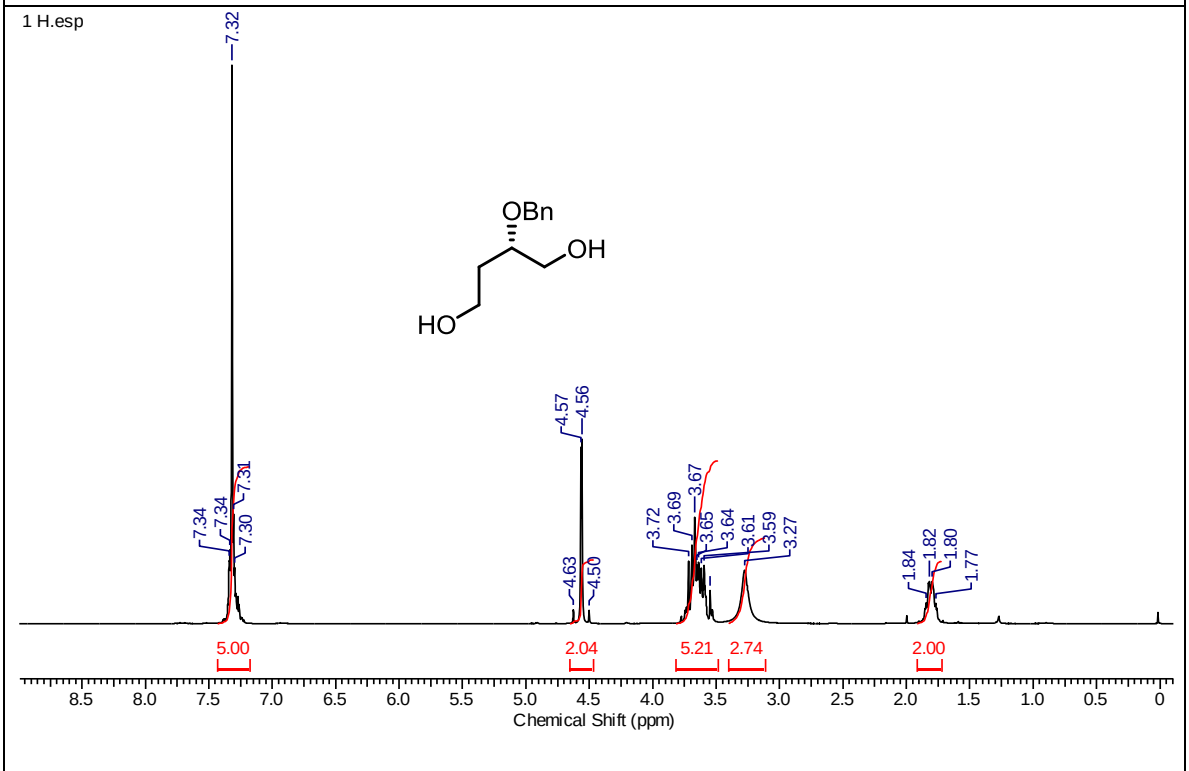
^{13}C NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 50 MHz)



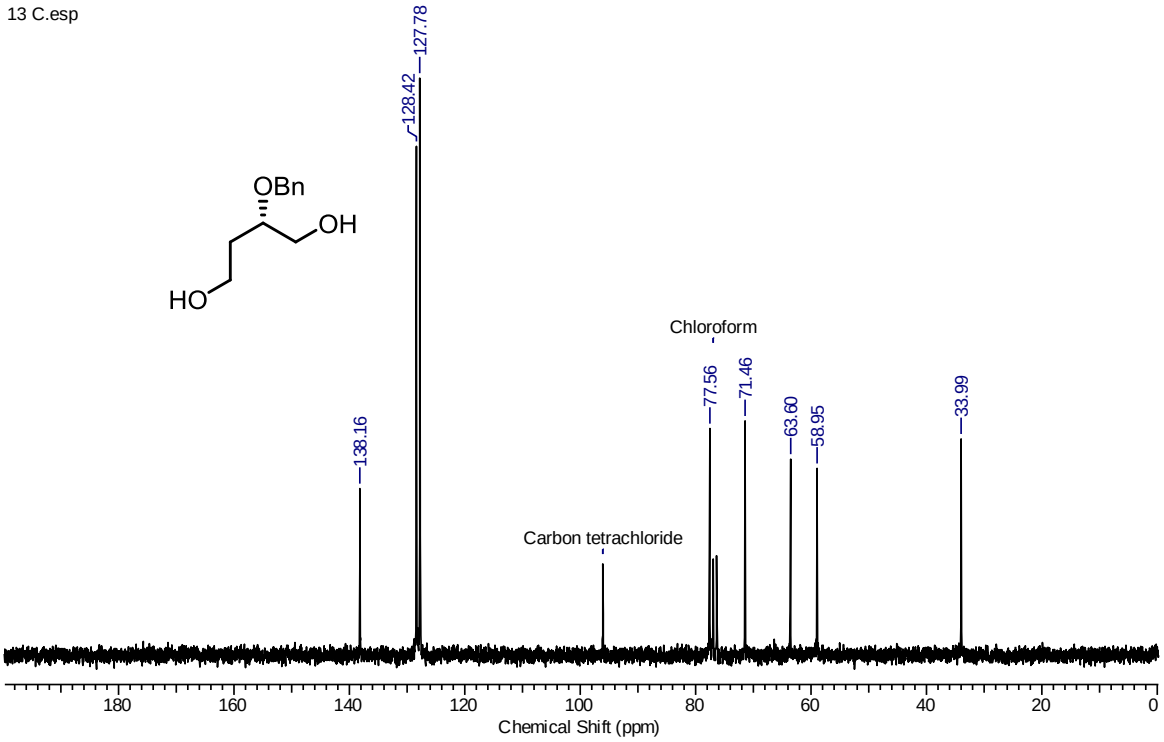
DEPT spectrum of compound 6 ($CDCl_3$ + CCl_4, 50 MHz)



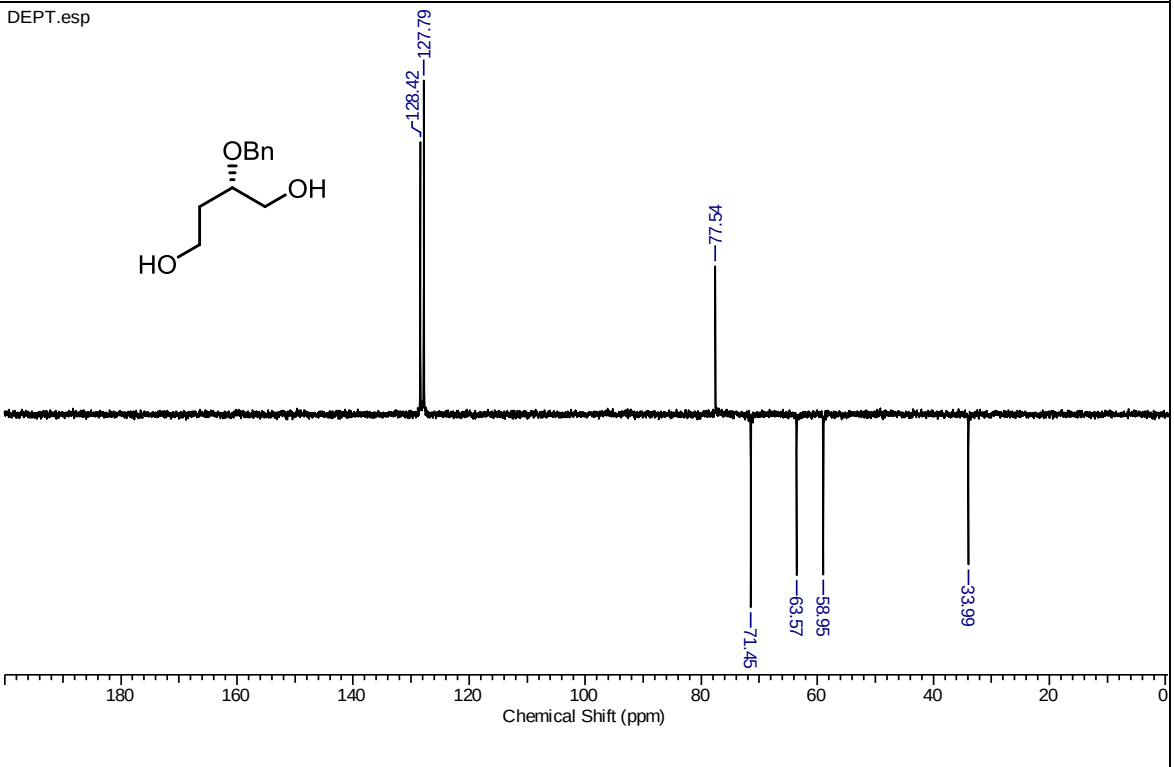
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 200 MHz)



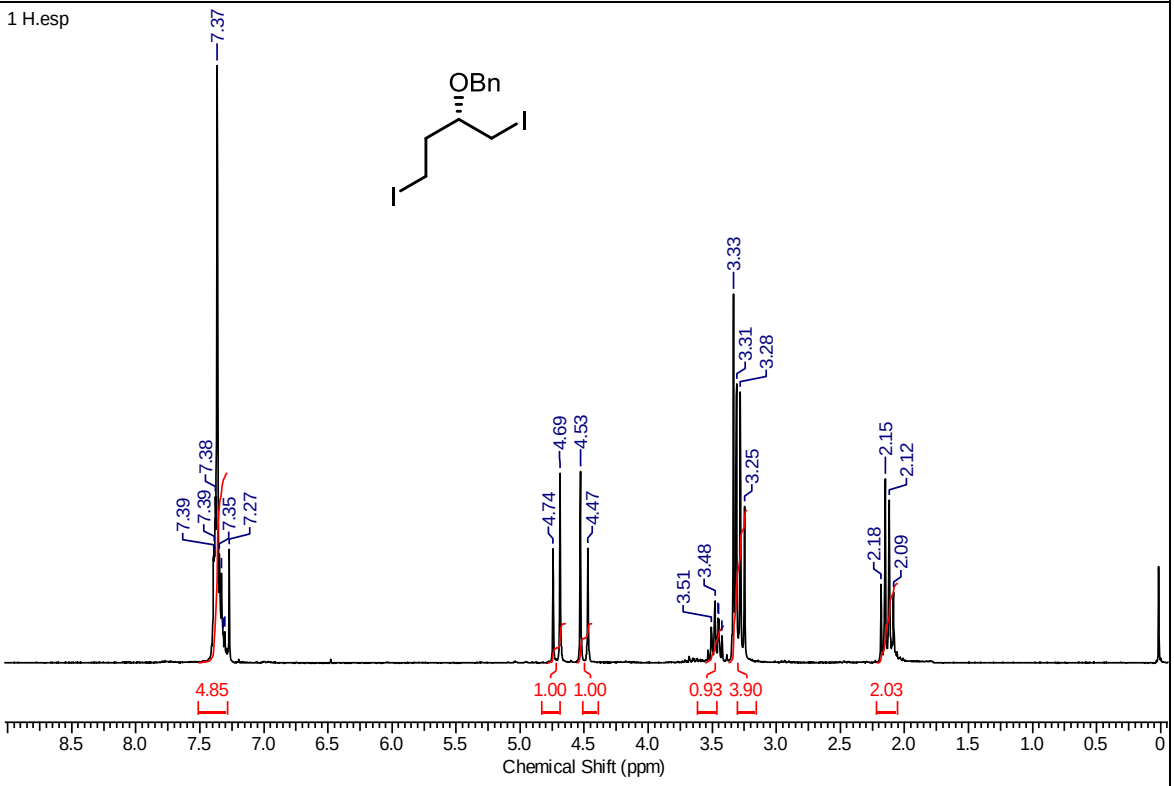
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



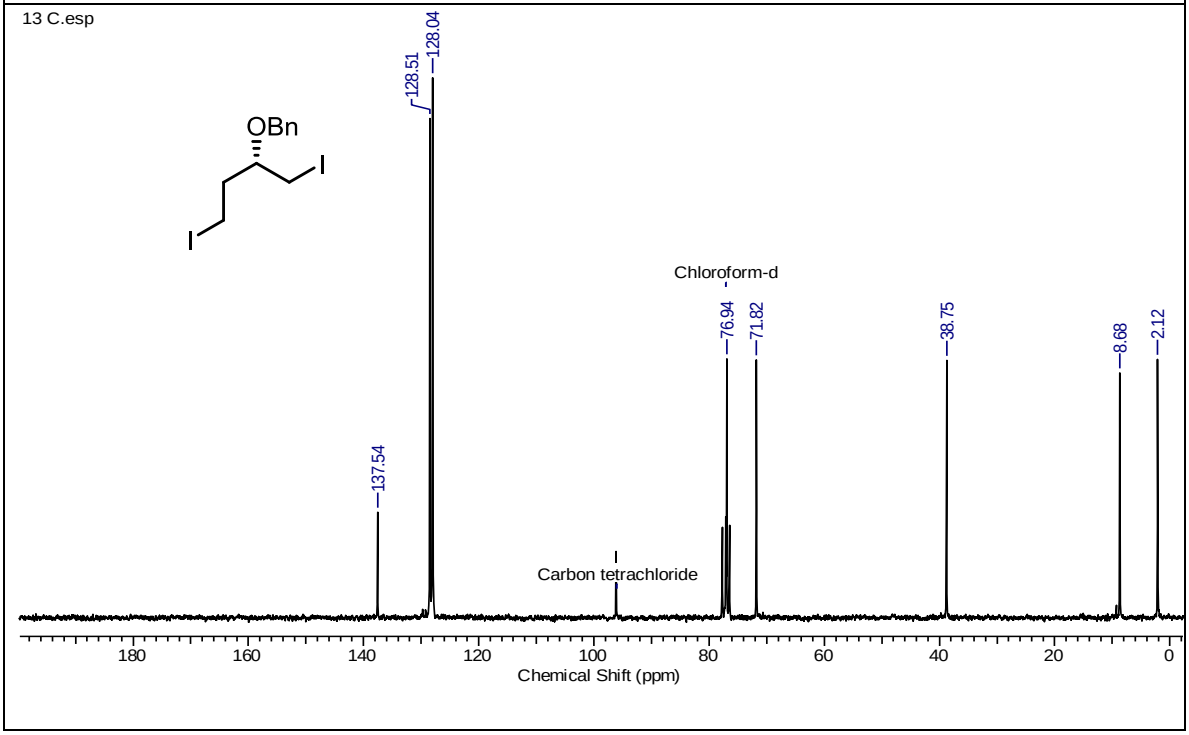
DEPT spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



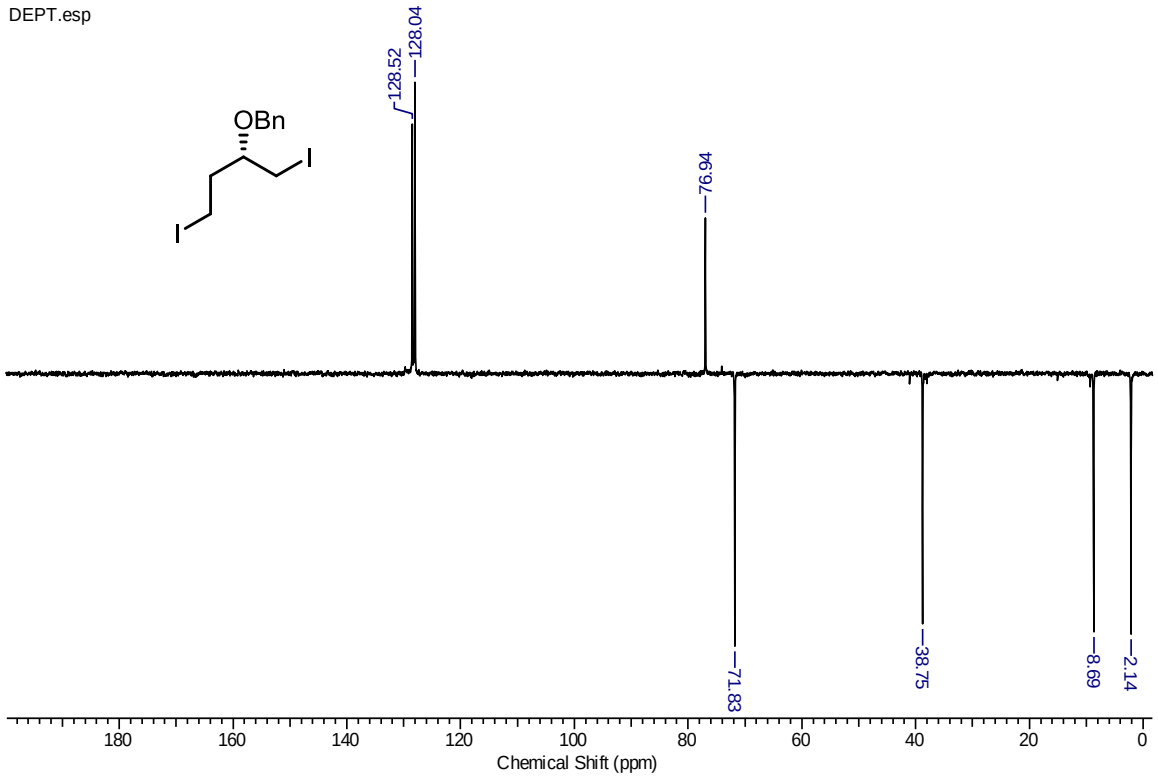
^{1}H NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 200 MHz)



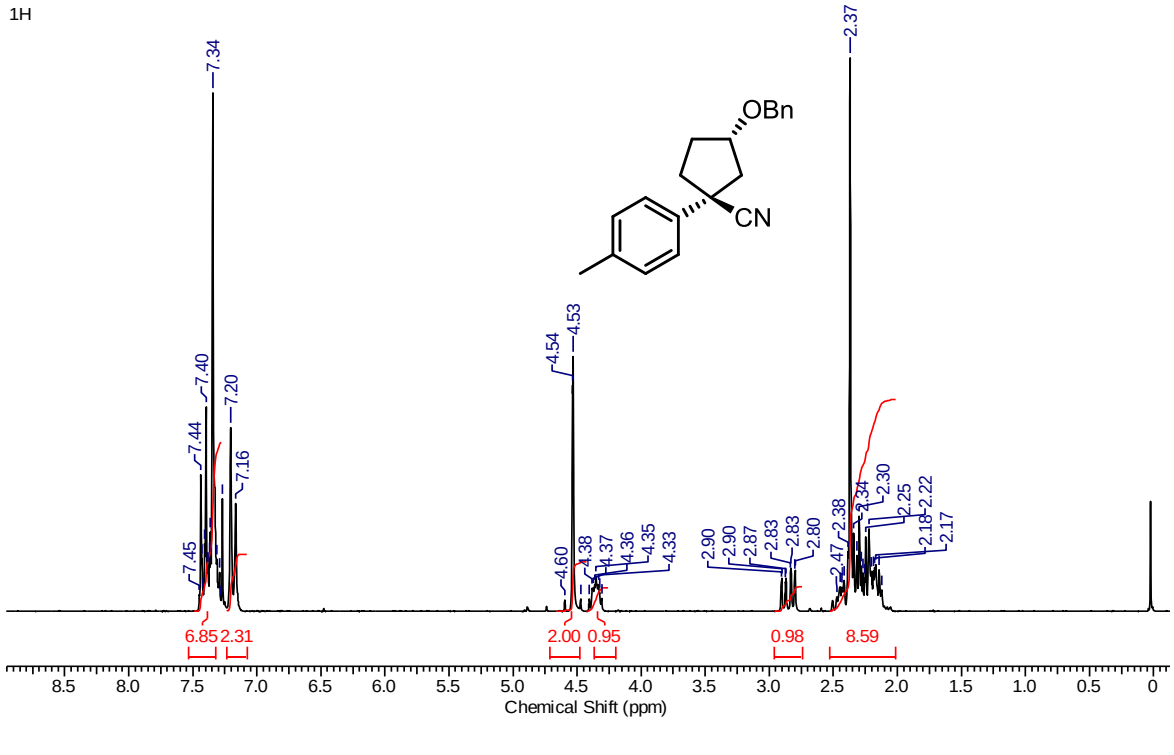
^{13}C NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 50 MHz)



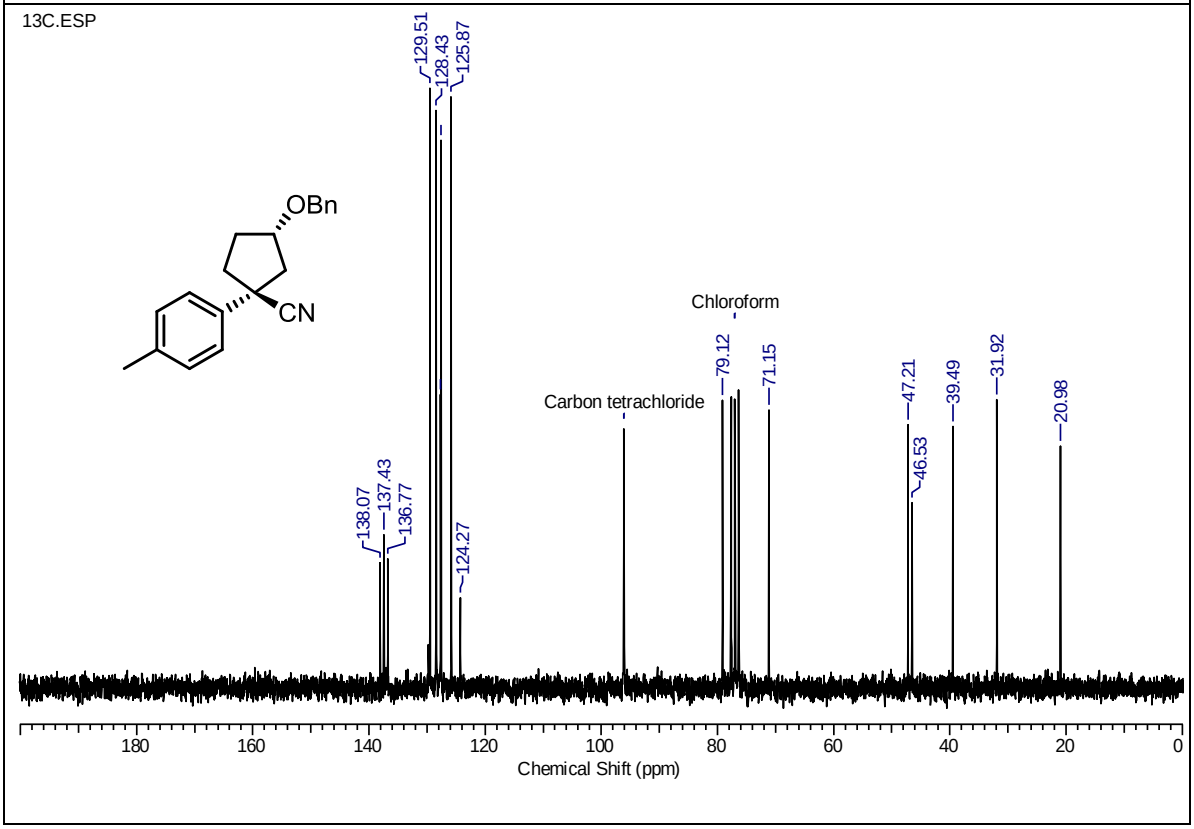
DEPT spectrum of compound 3 ($CDCl_3$ + CCl_4, 50 MHz)



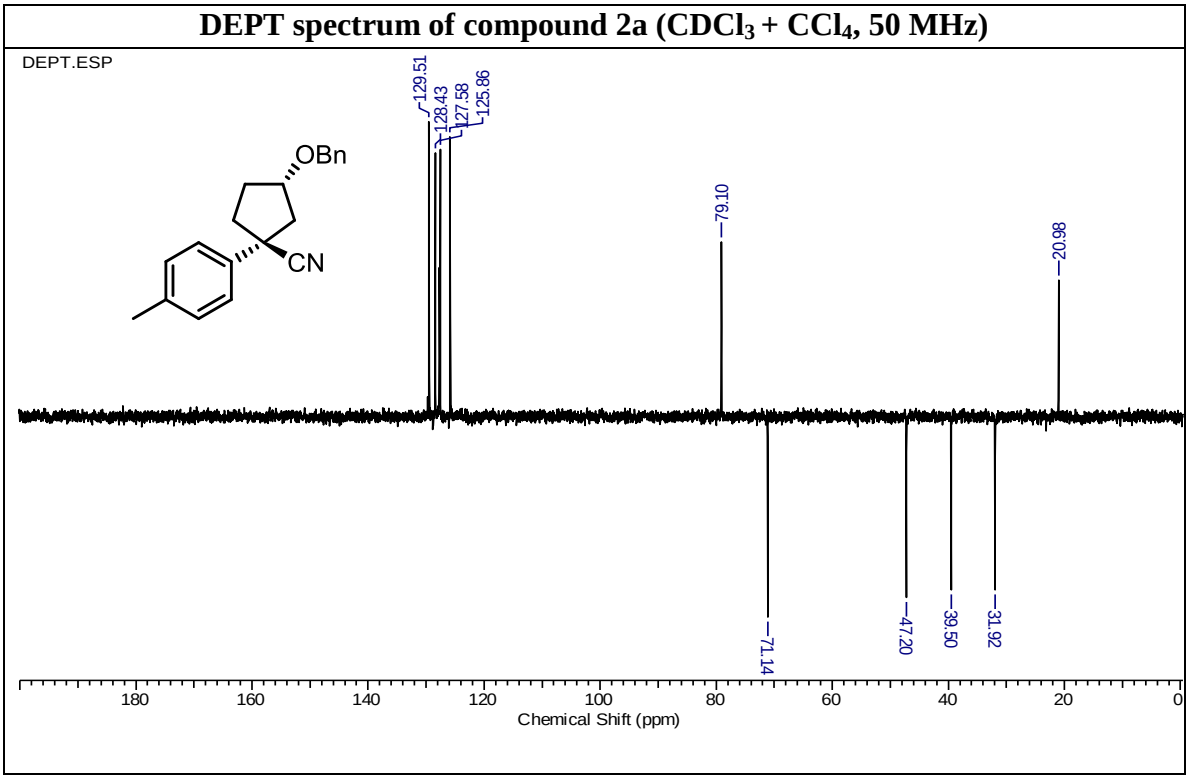
^{1}H NMR spectrum of compound 2a ($CDCl_3$ + CCl_4, 200 MHz)



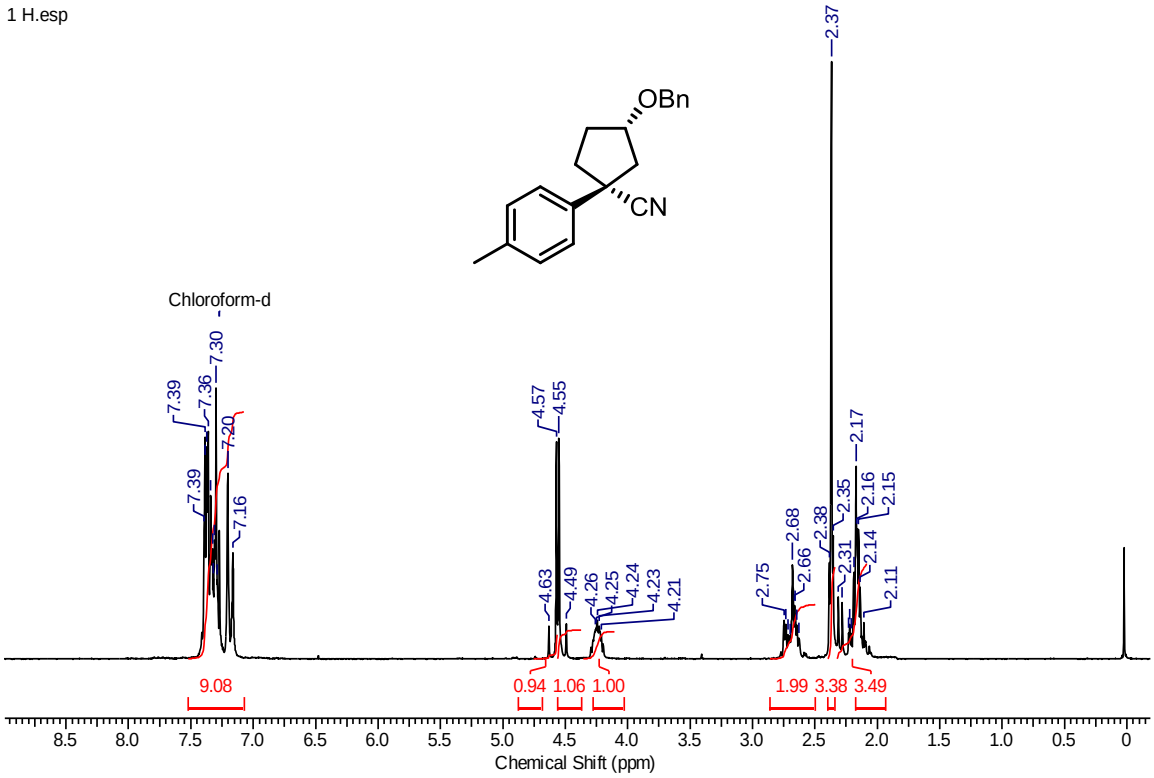
^{13}C NMR spectrum of compound 2a ($CDCl_3$ + CCl_4, 50 MHz)



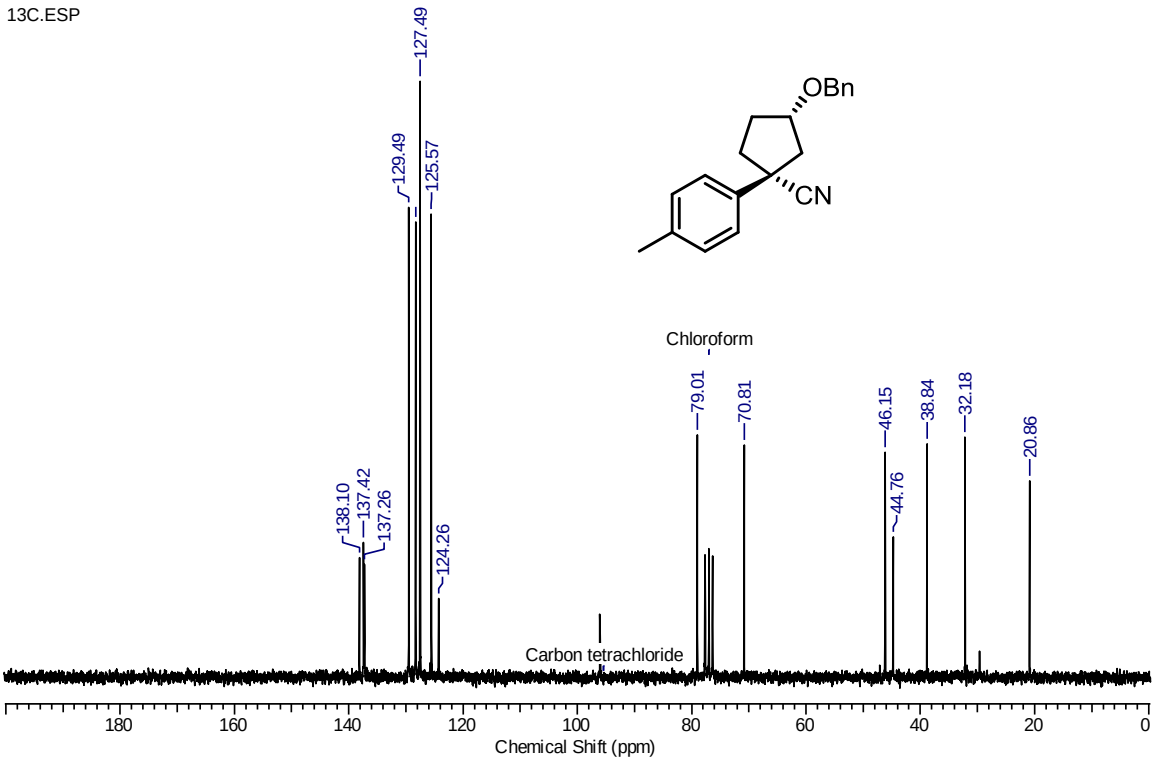
DEPT spectrum of compound 2a ($CDCl_3$ + CCl_4, 50 MHz)



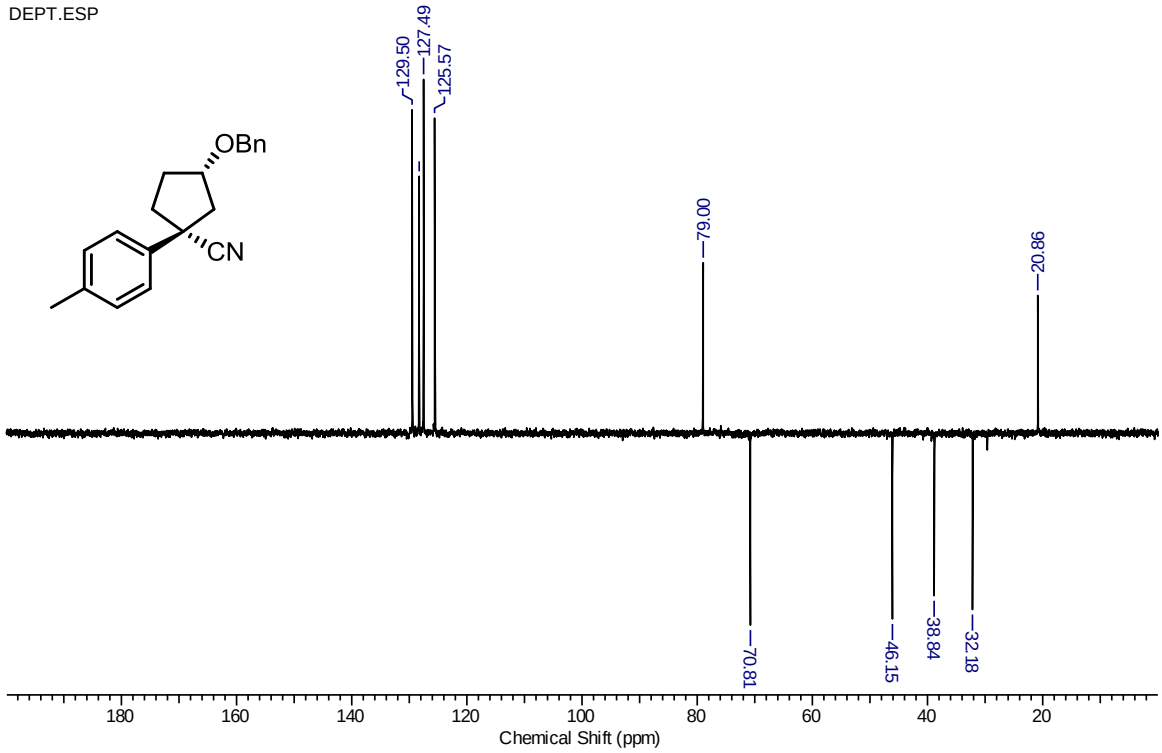
^{1}H NMR spectrum of compound 2b ($CDCl_3$ + CCl_4, 200 MHz)



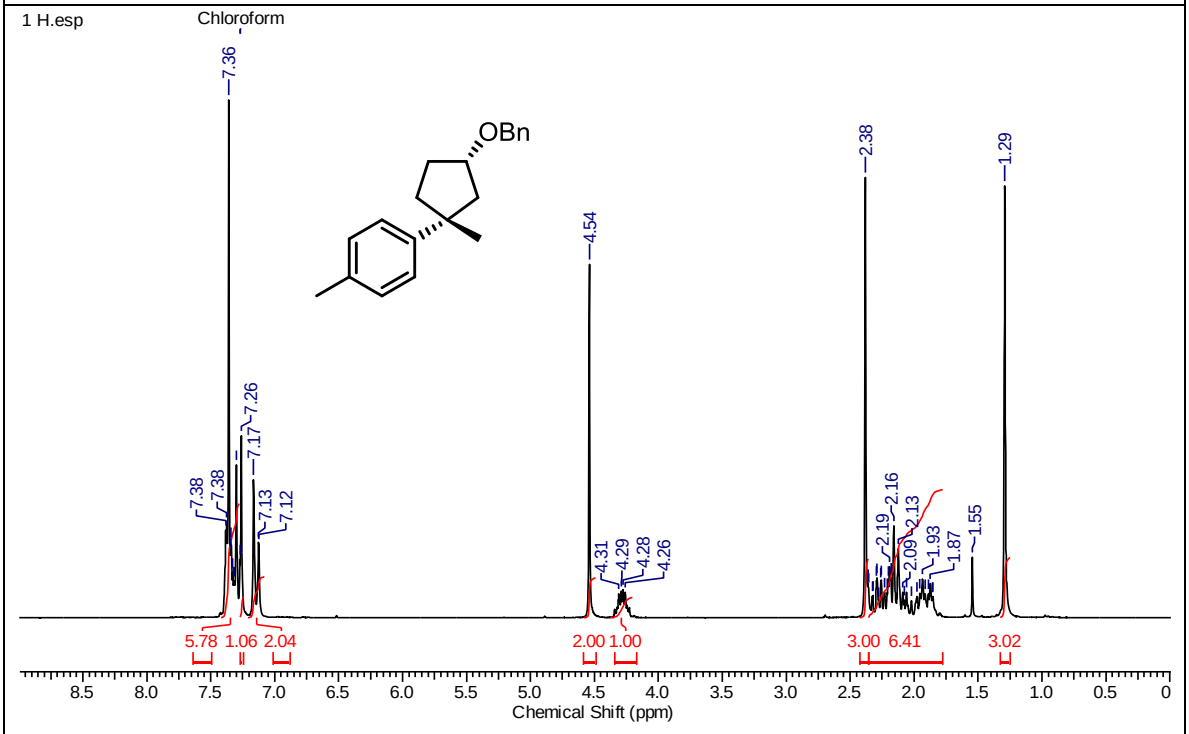
^{13}C NMR spectrum of compound 2b ($CDCl_3$ + CCl_4, 50 MHz)



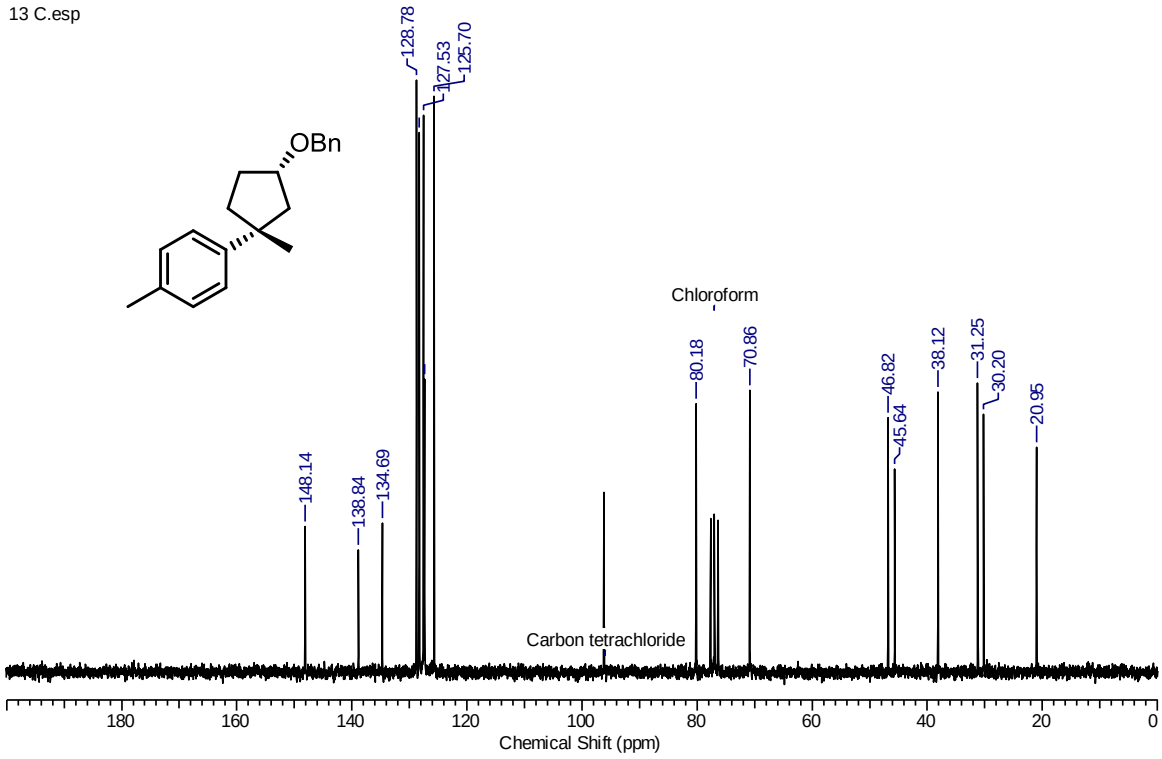
DEPT spectrum of compound 2b ($CDCl_3$ + CCl_4, 50 MHz)



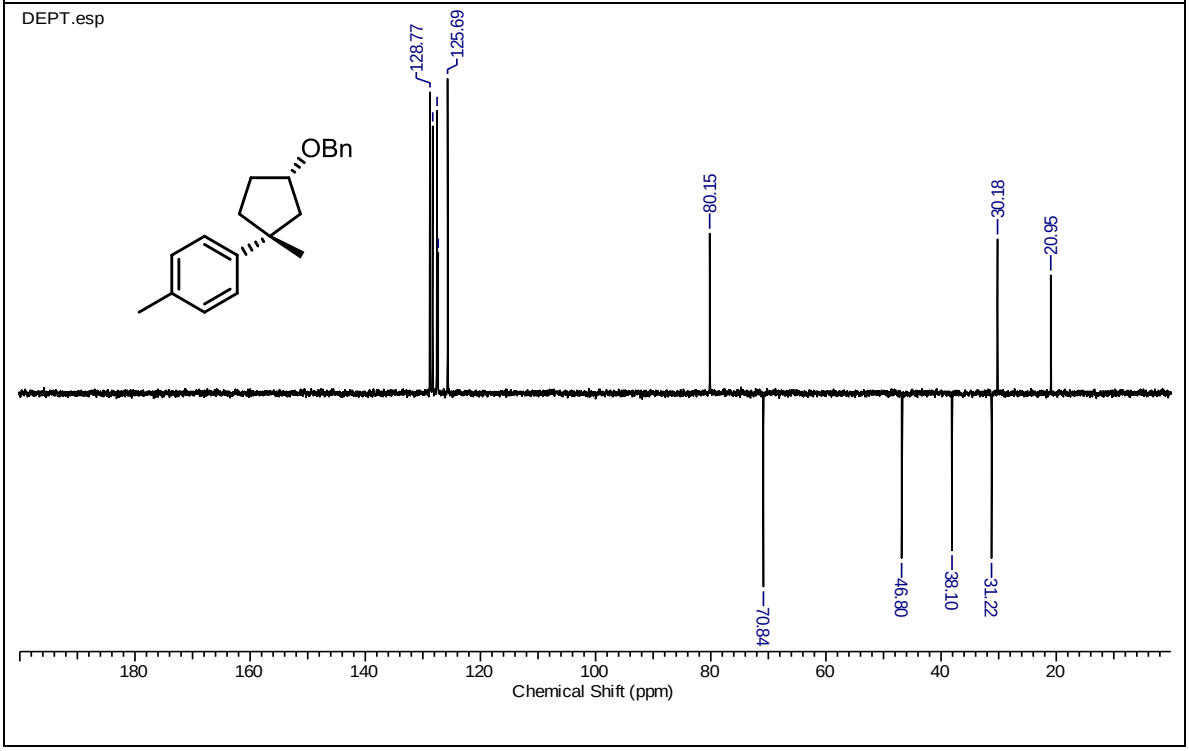
^1H NMR spectrum of compound 8a ($CDCl_3$ + CCl_4, 200 MHz)



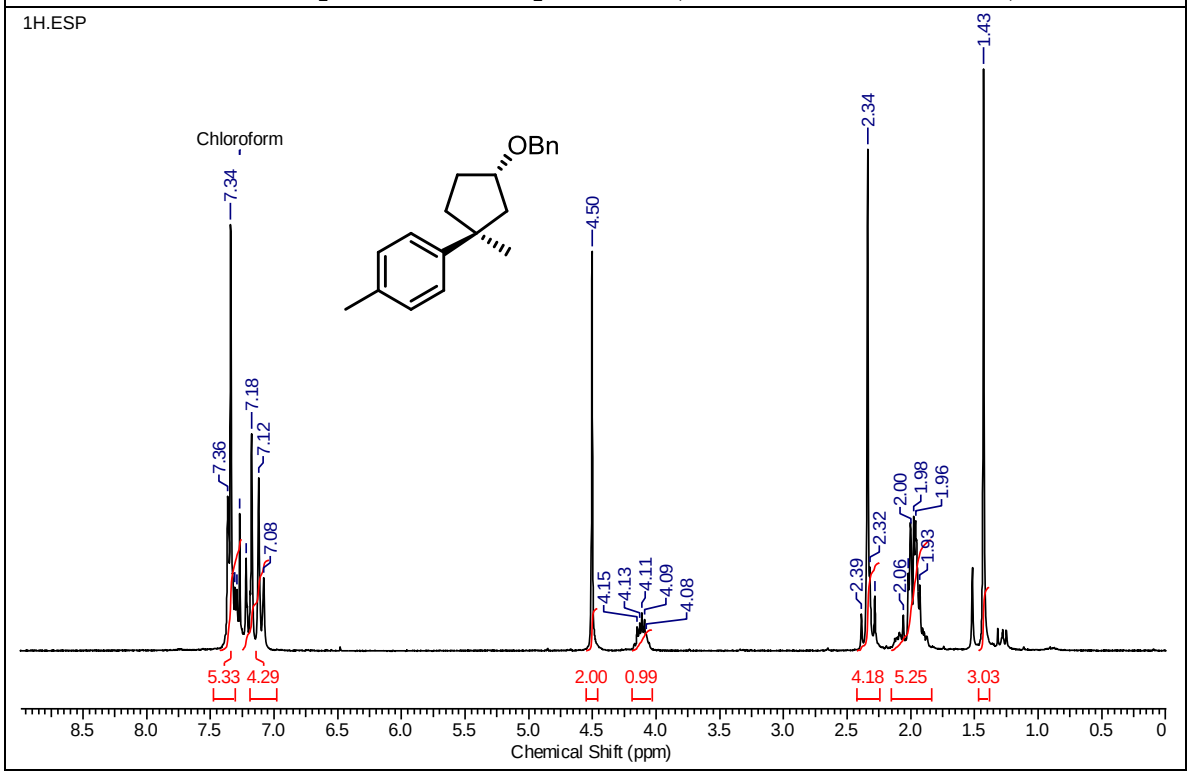
^{13}C NMR spectrum of compound 8a ($CDCl_3$ + CCl_4, 50 MHz)



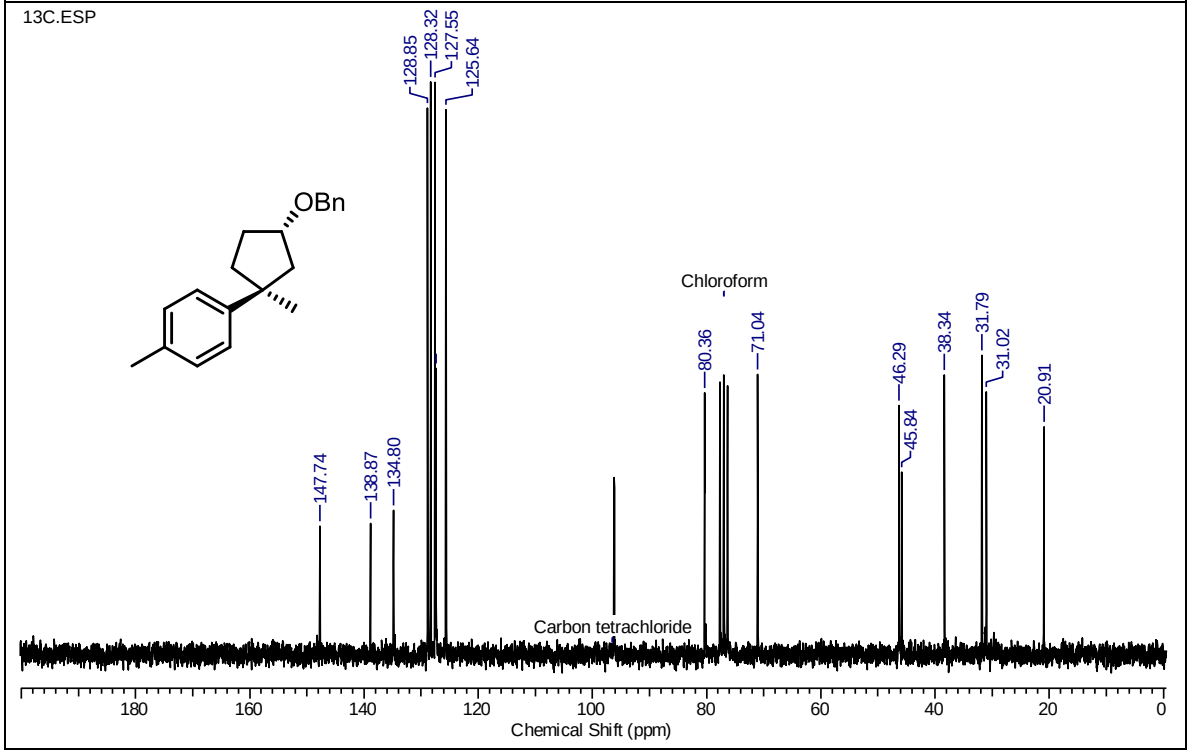
DEPT spectrum of compound 8a ($CDCl_3$ + CCl_4, 50 MHz)



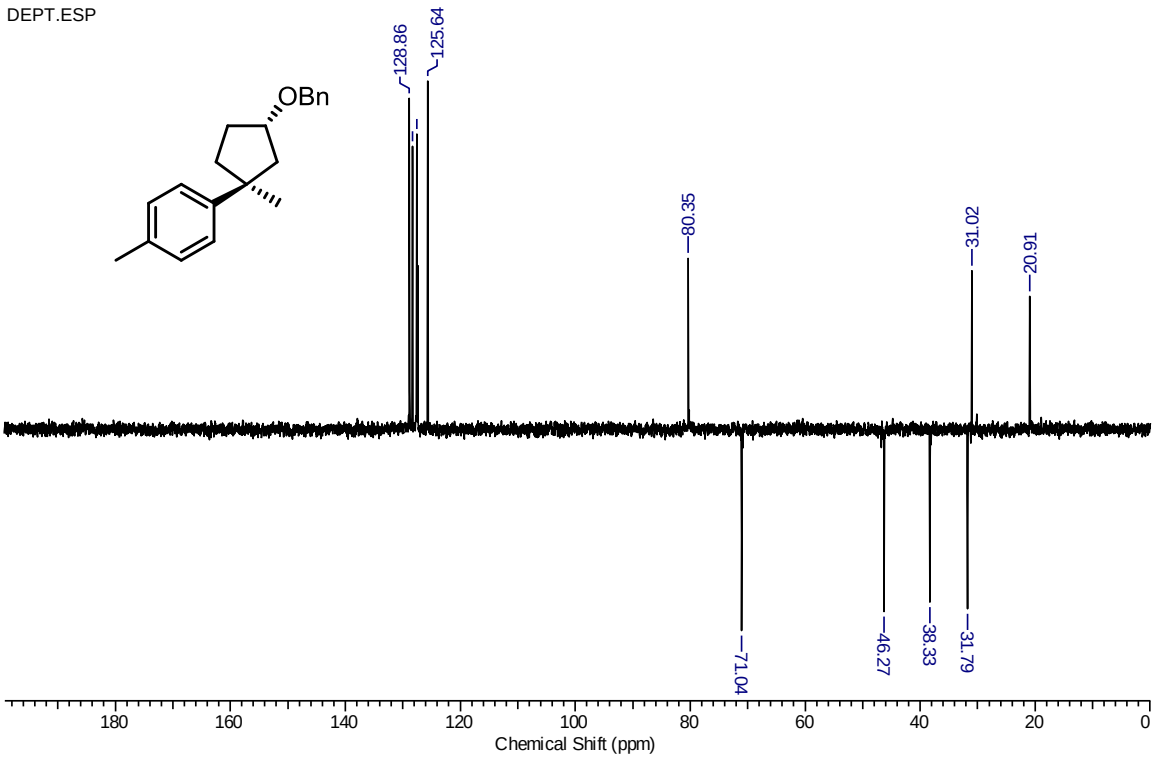
^{1}H NMR spectrum of compound 8b ($CDCl_3$ + CCl_4, 200 MHz)



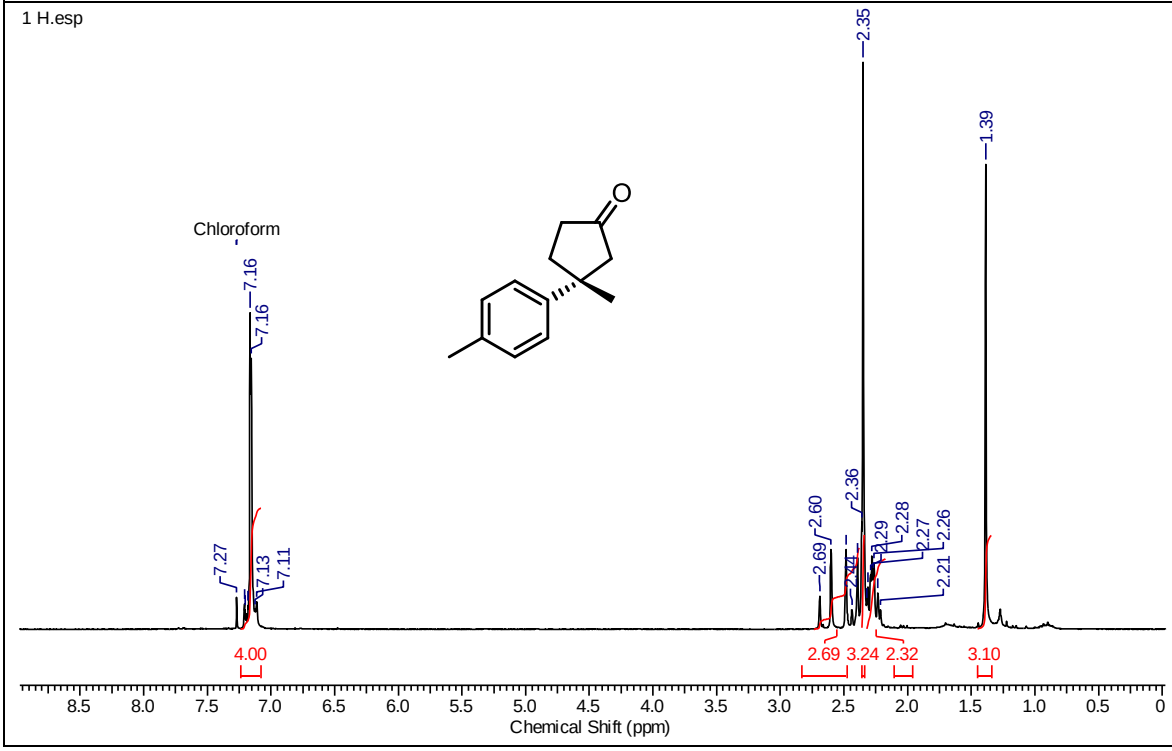
^{13}C NMR spectrum of compound 8b ($CDCl_3$ + CCl_4, 50 MHz)



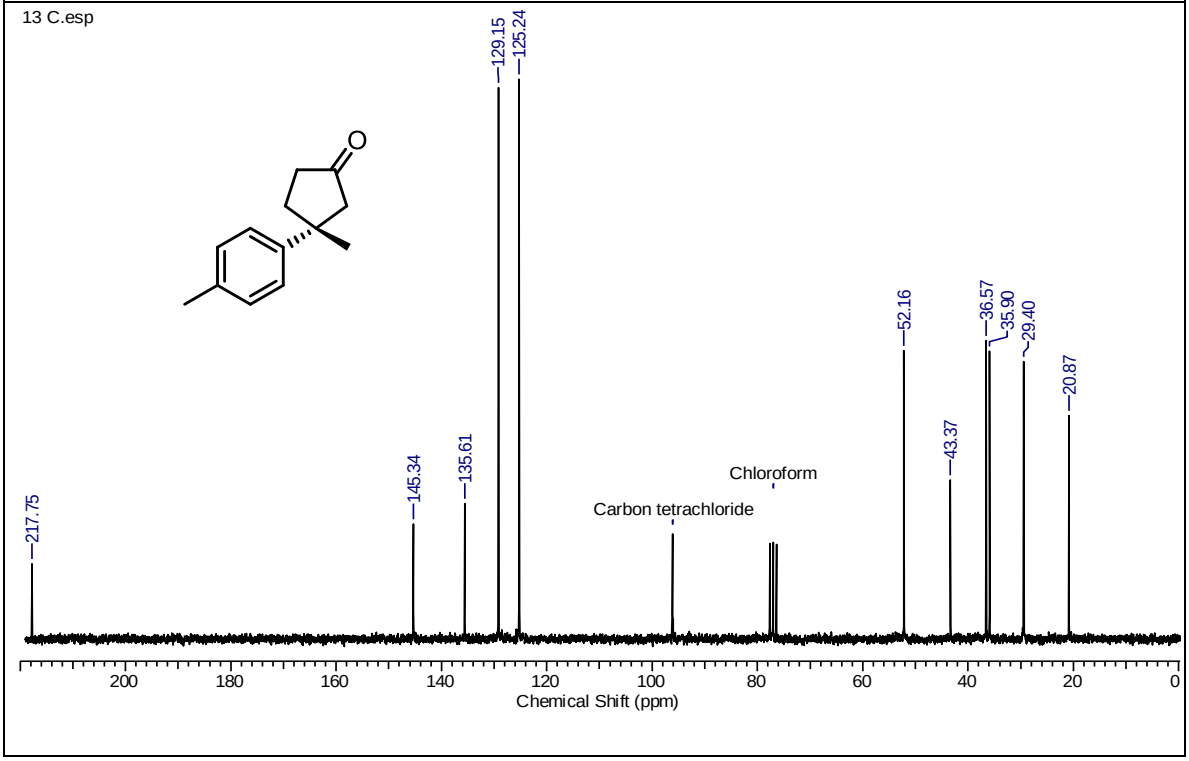
DEPT spectrum of compound 8b ($CDCl_3$ + CCl_4, 50 MHz)



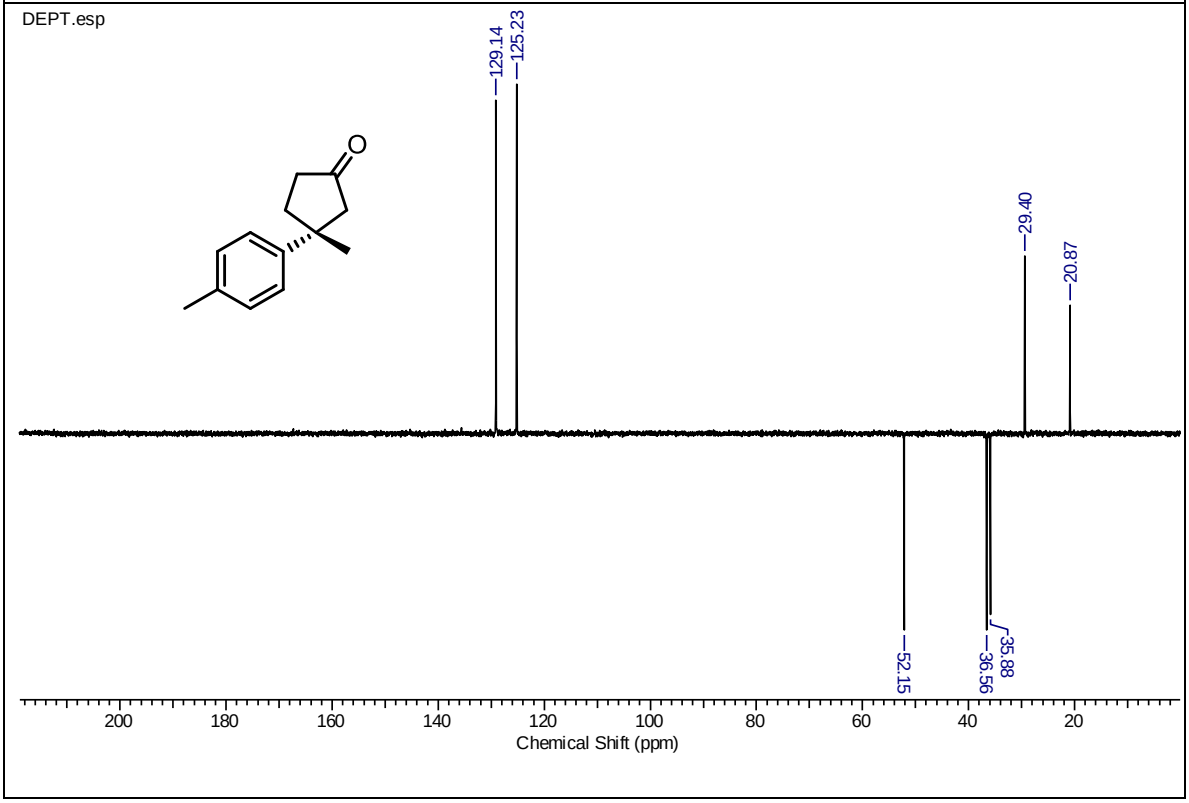
^{1}H NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 200 MHz)



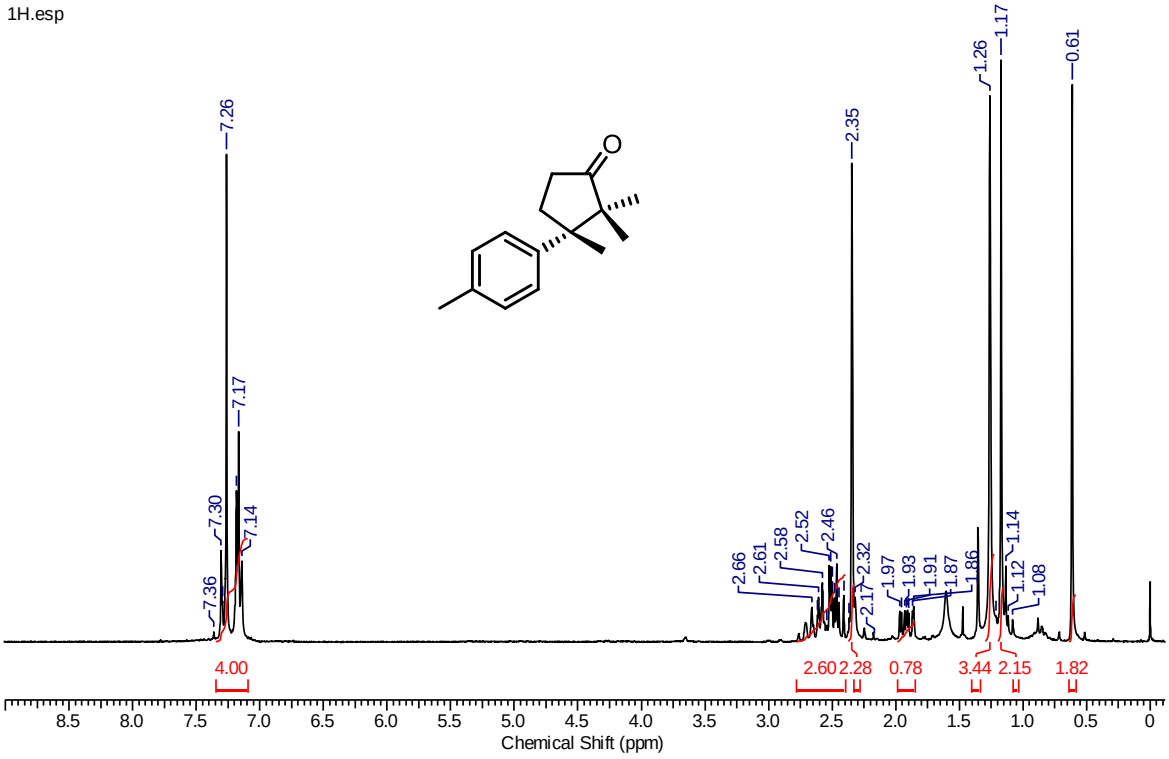
^{13}C NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 50 MHz)



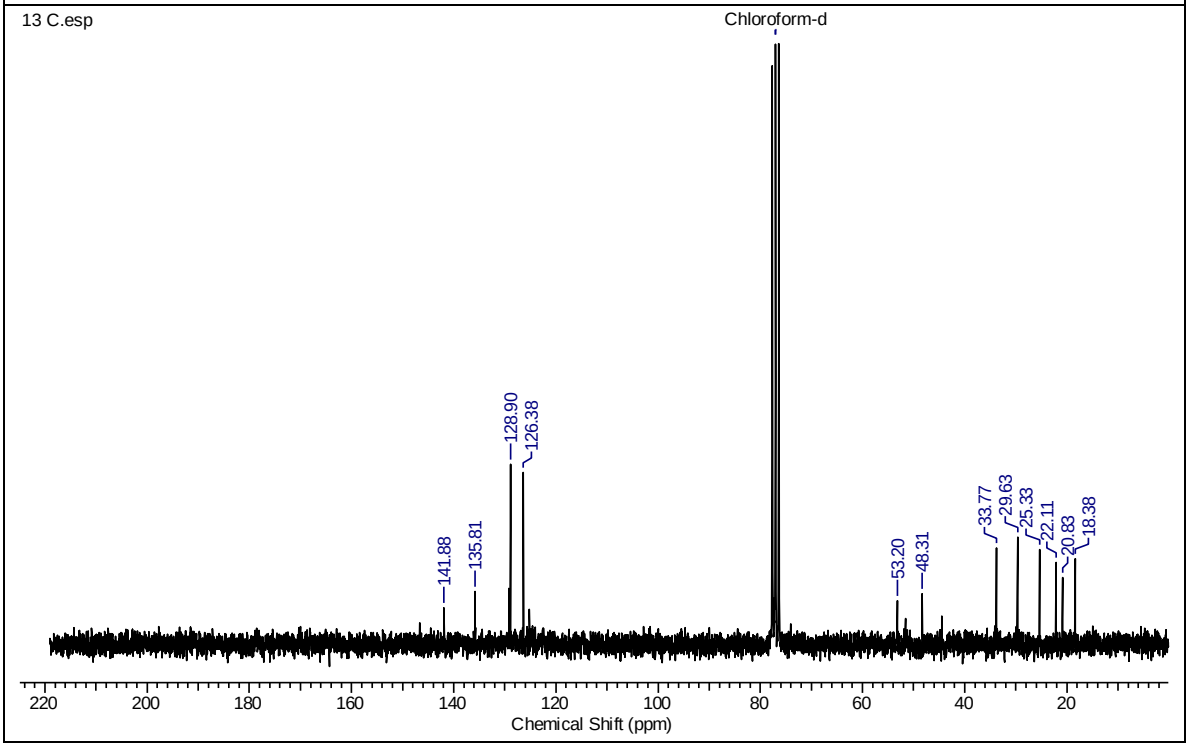
DEPT spectrum of compound 9 ($CDCl_3$ + CCl_4, 50 MHz)



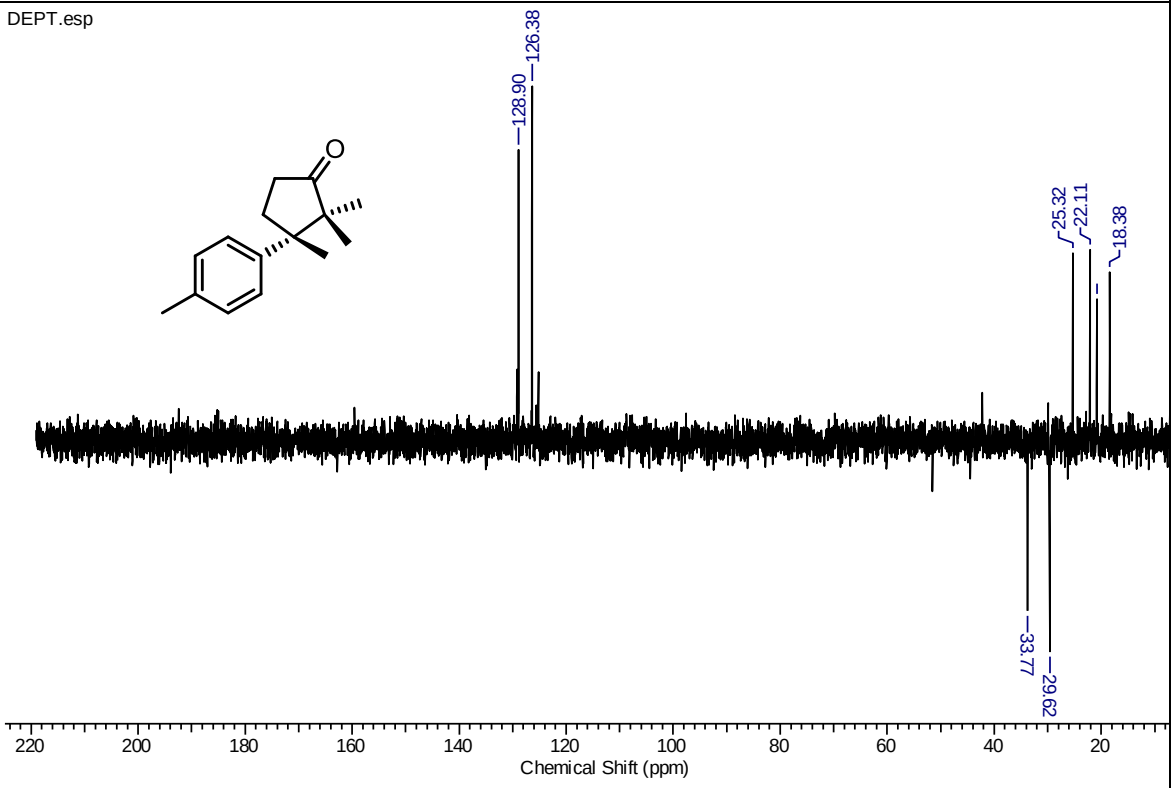
^{1}H NMR spectrum of compound 1 ($CDCl_3$ + CCl_4, 200 MHz)



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



DEPT spectrum of compound 1 ($CDCl_3$ + CCl_4, 50 MHz)



3.2.8 References

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2. Benesova, V.; *Collec. Czech. Chem. Commun.* **1976**, 3812.
3. a) Chavan, S. P.; Ethiraj, K. S. *Tetrahedron Lett.* **1995**, *36*, 2281; b) Chavan, S. P., Ravindranathan, T.; Patil, S. S.; Dhondge, V.; Dantale, S. W. *Tetrahedron Lett.* **1996**, *37*, 2629*;* c) Chavan, S. P., Ravindranathan T.; Patil, S. S. *Tetrahedron* **1999**, *40*, 4733; d) Chavan, S. P.; Kharul, R. K.; Kale, R. R.; Khobragade, D. A. *Tetrahedron* **2003**, *59*, 2737; e) Chavan, S. P.; Thakkar, M.; Kharul, R. K.; Pathak, A. B.; Bhosekar, G. V.; Bhadbhade, M. M. *Tetrahedron* **2005**, *61*, 3873; f) Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Tetrahedron Lett.* **2007**, *48*, 965.
4. Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Synthesis* **2007**, *24*, 3827.
5. Bertus, P.; Zhang, J.-H.; Sir, G.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2003**, *44*, 3391.
6. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 897216. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: þ44-(0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
7. a) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487; b) Huang-Minlon, *J. Am. Chem. Soc*. **1949**, *71*, 3301.
8. Confirmed by comparing specific rotation with the literature values and HPLC on a CHIRALCEL OD-H column to determine enantiomerc purity of (+)-**9** and (-)-**9** by comparison with racemic **9**, which was synthesized using the same reaction sequence using dl-malic acid.
9. Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1988**, *29*, 325.

Chapter 3. Synthetic Studies Towards α-Cuparenone and Unusual metal free auto-oxidation by air.

Section 3

An Unprecedented Method for allylic oxidation

3.3.1 Summary

The present section deals with unusual metal free auto-oxidation of electron deficient cyclohexenes by air. A novel and green protocol for the allylic oxidation has been developed employing atmospheric molecular oxygen alone, devoid of metal catalysts, photo-activation or high oxygen pressure, to give the corresponding ketones as well as phenols in good yields.

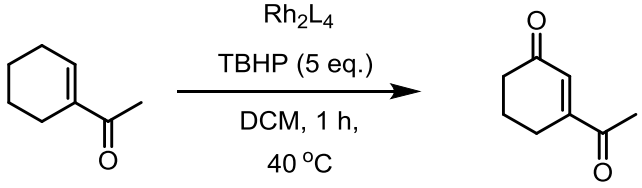
3.3.2 Introduction

The ability to selectively convert a particular molecule by oxidation utilizing the abundant and inexpensive oxidant oxygen often represents a beneficial low-cost method for upgrading the value of a raw material. Oxidation is one of the most fundamental transformations in organic chemistry. Direct oxygenation of allylalkane or alkylarenes to the corresponding carbonyl compounds is a highly important reaction because an oxygen atom can be introduced into organic substrates. Conventionally for these transformations, a stoichiometric amount of an oxidant such as manganese dioxide, chromic acid, potassium dichromate, silver oxide, selenium dioxide and periodic acid have been employed,[1,2] which produce environmentally unacceptable heavy metal wastes. From the perspective of atom efficiency and environmental concerns, however, the development of methods using molecular oxygen or air has attracted much attention.

3.3.3 Allylic oxidation: A review

A short descriptive presentation of the work reported by different groups is being presented to give a better and comparative view of the different methods for allylic oxidation employed so far.

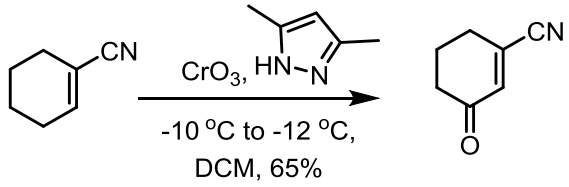
Doyle's approach[3] (*J. Am. Chem. Soc.* **2004**, *126*, 13622)



Scheme 1

Doyle *et al.* developed a novel catalytic allylic oxidation protocol based on dirhodium. The unique reactivity of $Rh_2(cap)_4$ emanates from its ability to undergo facile redox chemistry, namely Rh_2^{4+} / Rh_2^{5+}.

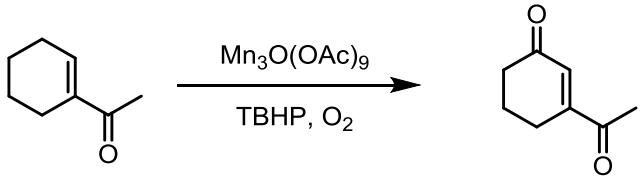
Fleming's approach[4] (*Synthesis*, **2005**, *18*, 31790)



Scheme 2

Fleming *et al.* reported a technically simple, very reliable and one-step oxidation process. The chromium trioxide-3,5-dimethylpyrrazole oxidation of cyclohexenecarbonitrile provides a robust synthesis of gram quantities of 3-oxocyclohex-1-ene-1-carbonitrile.

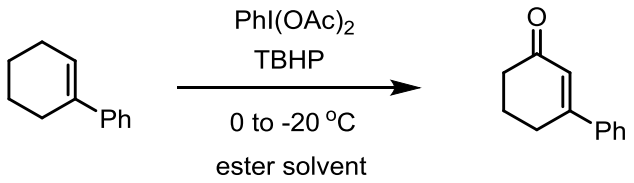
Shing's approach[5] (*Org. Lett.* **2006**, *8*, 3149)



Scheme 3

Shing *et al.* reported a mild, efficient, regioselective, and highly functional group compatible allylic oxidation protocol using manganese(III) acetate dihydrate as the catalyst. The inexpensive and commercially available manganese(III) acetate as the catalyst and *tert*-butylhydroperoxide (TBHP) as the cooxidant were used for mild, efficient, regioselective, chemoselective (functional group compatible), allylic oxidation of simple and complex alkenes.

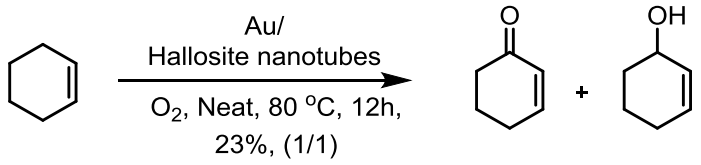
Yeung's approach[6] (*Org. Lett.* **2010**, *12*, 2128)



Scheme 4

Yeung *et al.* developed a mild and efficient allylic oxidation protocol with inexpensive and commercially available DIB/TBHP. The *tert*-butylperoxy radical was generated with $PhI(OAc)_2$ and *t*BuOOH. K_2CO_3 and $Mg(OAc)_2 \cdot 4H_2O$ were found to be important additives and ester solvent played a critical role in the reaction.

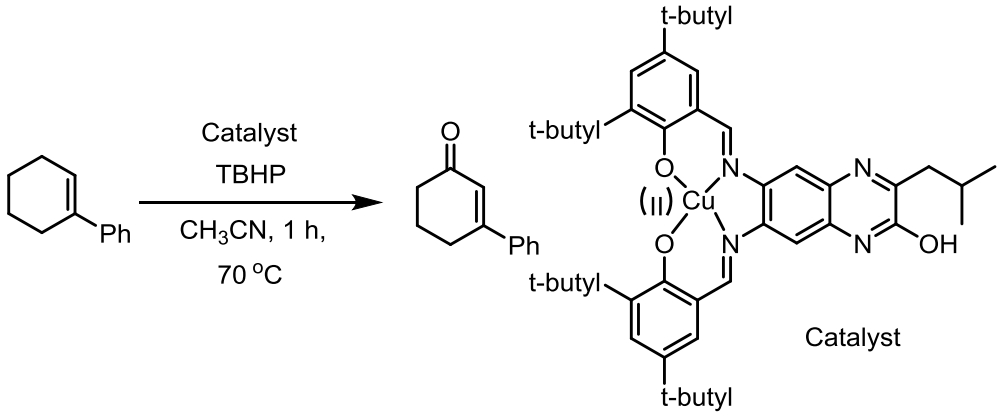
Cai's approach[7] (*Adv. Chem. Engineer. Sci.* **2011**, *1*, 15)



Scheme 5

The selective oxidation of cyclohexene to 2-cyclohexene-1-ol and 2-cyclohexene-1-one has been investigated over Au/HNTs (HNTs: halloysite nanotubes) catalysts with molecular oxygen in a solvent-free system by Cai *et al.* The results show that the catalytic performance of Au/HNTs is quite well and the catalytic activity over recycled catalyst remains high. Moreover, the nano-size effect of gold is also reported for the reaction.

Li's approach[8] (*J. Org. Chem.* **2012**, *77*, 4628)



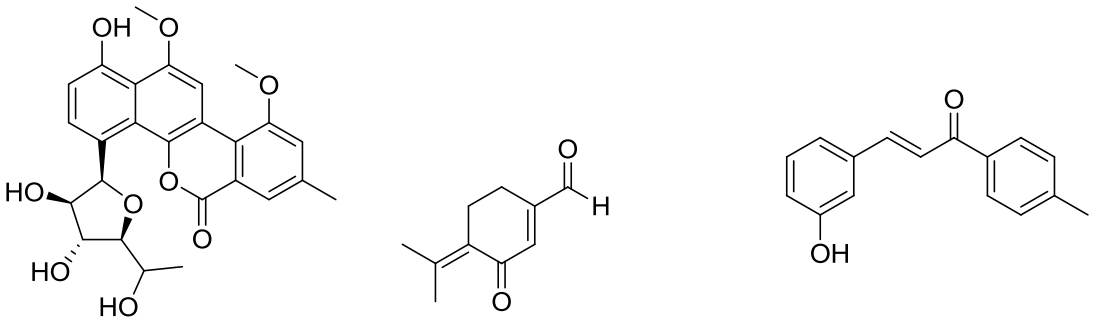
Scheme 6

Li *et al.* reported the first Cu(II) complex catalyzed, regioselective allylic oxidation of olefins to enones and 1,4-enediones. Using a Cu(II) 2-quinoxalinol salen complex as the catalyst and tert-butyl hydroperoxide (TBHP) as the oxidant, allylic activations of olefin substrates resulted in the corresponding enones or 1,4-enediones. Excellent

yields were achieved (up to 99%) within a very short reaction time and with great tolerance for additional functional groups.

3.3.4 Present work

Oxidation of organic compounds should ideally be achieved using molecular oxygen, because of its ready availability, atom-economy, low cost and its distinct environmental advantage. Recently, considerable progress has been made towards realizing this goal including Mukaiyama's oxidation-reduction-hydration reaction using several transition metal catalysts,[9] Ishii's aerobic oxidation using *N*-hydroxyphthalimide,[10] and oxidation of alcohols in the presence of a catalytic amount of palladium,[11] copper,[12] or ruthenium[13] compounds. Due to insufficient reactivity of molecular oxygen, it is not often easy to oxidize organic compounds in practical yields by the use of molecular oxygen alone. One has to resort to metal catalysts or photo-activation to achieve the desired goal.



Gilvocarcin M **Robinal** **3-Hydroxy-4´-methyl chalcone**

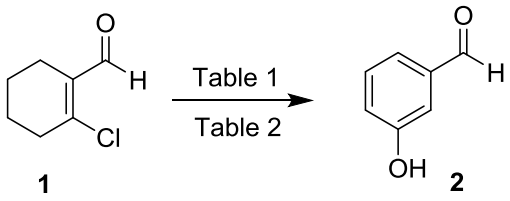
Figure 1. Examples of the benzaldehyde and cyclohexanone motif in natural products.

Hayashi *et al*. reported oxidative cleavage of the carbon-carbon double bond of substituted styrene derivatives to afford the corresponding ketones under an atmospheric pressure of molecular oxygen without the use of transition metal catalysts or photo-activation.[14] Oxidation of fluorene derivatives at the benzylic position to the corresponding carbonyl compounds using molecular oxygen promoted by activated carbon is reported in the literature.[15] The meta hydroxy benzaldehyde is the constituent of many natural products such as Gilvocarcin M[16] which shows significant antitumor activity (Figure 1). Also the highly conjugated monoterpenoid

Robinal[17] is the derivative of cyclohexanone. 3-Hydroxy-4´-methyl chalcone showed potent inhibitory activity in the phosphorylation test, which suggests its antitumorigenic effect.[18]

3.3.5 Results and discussion

In the present work, an unprecedented method for oxidation of electron deficient allylic carbon with molecular oxygen alone is reported. The main feature of the present method is, no requirement of transition metals, no photo-activation or no high oxygen pressure to afford the corresponding ketone derivatives in moderate to good yields. The initial investigation was carried out by examining the allylic oxidation of 2-chlorocyclohex-1-enecarbaldehyde **1**[19] using atmospheric oxygen. It was found to undergo smooth allylic oxidation followed by aromatization in the presence of base.



1 **2**

Table 1. Screening of bases

Entry[a]	**Base**[b]	**time (h)**	**yield (%)**[c]
1	Ph_3P	24	00
2	2,6-Lutidine	24	10
3	DABCO	20	91
4	DMAP	24	87
5	Imidazole	20	65
6	Triethylamine	24	16
7	Pyridine	24	36
8	K_2CO_3	12	92
9	Cs_2CO_3	14	87

[a] all the reactions were carried out at 80 °C in DMF as a solvent. [b] 2 equivalent of base was used.

[c] Isolated yield of the product.

For optimization of bases the solvent used was DMF and the reaction was monitored by TLC. It was observed that (Table 1) use of 2 equivalent of K_2CO_3 in DMF at 80 °C gave the phenol product in better yield. The bases like DABCO, DMAP, Cs_2CO_3 also resulted in the product formation although in similar yields but took longer time period for completion of reaction.

Table 2. Effect of solvent on oxidation

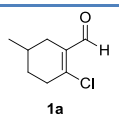
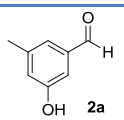
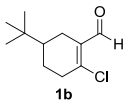
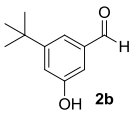
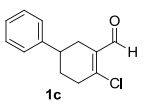
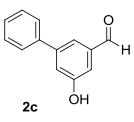
Entry[a]	Solvent	Temp (° C)	Time (h)	Yield (%)[b]
1	Degassed DMF	80	24	00
2	THF:DMF (1:1)	70	24	32
3	H_2O	80	12	<10
4	MeOH	70	18	<10[c]
5	IPA	90	34	50[d]
6	MeCN	90	32	90
7	neat	90	6	00[e]

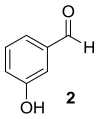
[a] all the reactions were carried out using 2 equivalent of DABCO as base. [b] Isolated yield for product only [c] we found maximum conversion of starting aldehyde as its acetal was observed. [d] 40% starting recovered. [e] starting material decomposed.

Using 2 equiv of K_2CO_3 and atmospheric oxygen, the effect of different solvents on the oxidation of 2-chlorocyclohex-1-enecarbaldehyde **1** was also studied (Table 2). When the reaction was performed in degassed DMF devoid of air/oxygen, we observed that there was no product formation. Also in polar protic solvents like IPA, formation of product took longer time whereas in MeOH there was formation of acetal which decreased the reactivity of allylic proton and resulted in lower yields of the product.

Having arrived at optimal conditions, allylic oxidation of a variety of representative chloro aldehyde was examined using 2 equiv of K_2CO_3, atmospheric oxygen (air) and DMF as solvent at 80 °C (Table 3). It was heartening to note that this reaction was fairly general and most of the substrates could be converted into corresponding phenols in excellent yield.

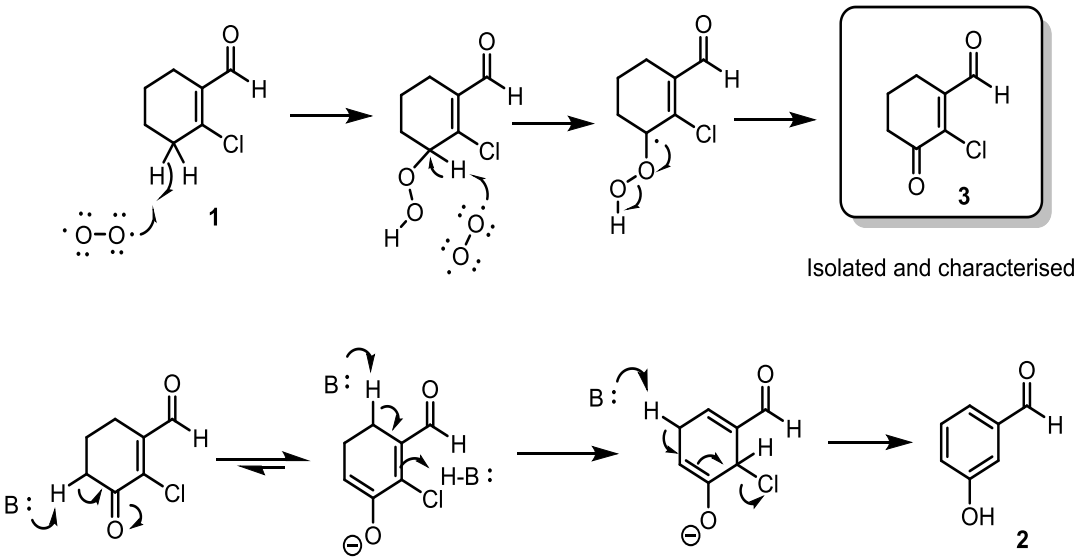
Table 3. Allylic oxidation of representative chloro aldehyde

Entry	substrate[a]	products	Time (h)	Yield (%)[b]
1	 1a	 2a	20	89
2	 1b	 2b	24	77
3	 1c	 2c	21	82

4[c]	 1d	 2	20	84

[a] starting material was prepared using Vilsmeier-Haack reaction from the appropriate cyclohexanone.
[b] Isolated yield for product only. [c] instead of $POCl_3$, PBr_3 was used.

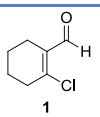
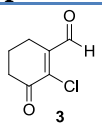
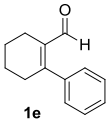
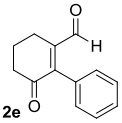
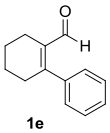
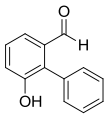
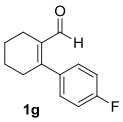
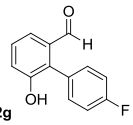
In order to explain the observed oxidation and major product formation, a plausible mechanism was proposed. According to the literature[20] and the analysis of the products obtained during oxidation in the absence of the base (Table 4, entry 1-2), the oxidation of 2-chlorocyclohex-1-enecarbaldehyde **1** with molecular oxygen initially formed 2-chloro-3-hydroperoxycyclohex-1-enecarbaldehyde as shown in Scheme 7. The hydroperoxide being unstable was easily transformed to enone **3** as a relatively stable product. Under basic condition, the enone **3** readily aromatized to a stable phenol product **2**.



Scheme 7. Possible reaction pathway

When 2-chlorocyclohex-1-enecarbaldehyde **1** was subjected to optimal reaction condition without base, enone **3** was isolated as the sole product. Also to probe the role of chloro functionality as a good leaving group, it was replaced by phenyl group using Suzuki coupling with phenyl boronic acid (Table 4, entry 3-4).[21] Interestingly here also the formation of phenol product was observed but it took longer time for completion. Hence it was concluded that the role of chloro group is to accelerate rate of aromatization and its presence is not absolutely necessary for the success of the reaction.

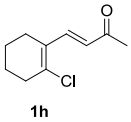
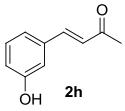
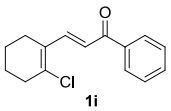
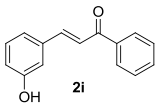
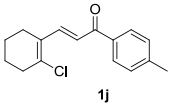
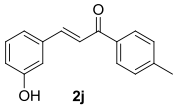
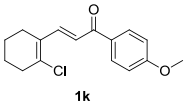
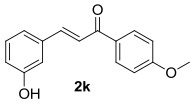
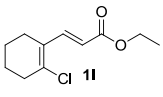
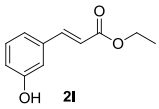
Table 4. Evidences for mechanism

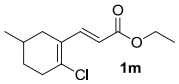
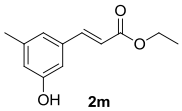
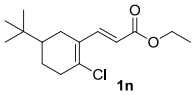
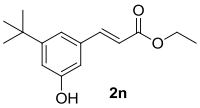
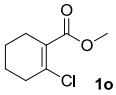
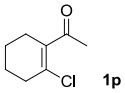
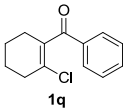
Entry	substratea	products	time (h)	yield (%)[b]
1[c]	 1	 3	12	80
2[c]	 1e	 2e	17	72
3[d]	 1e	 2f	22	75
4[d]	 1g	 2g	24	73

[a]Starting material was prepared using Vilsmeier-Haack reaction from appropriate cyclohexanone.
[b] Isolated yield for product only. [c]Without base. [d]With base.

Having a good protocol in hand, it was decided to screen some more substrates to establish the generality of the protocol. Unsaturated ketones and unsaturated esters resulted in corresponding phenols smoothly, whereas the ester (Table 5, entry 8) initially remained intact even after 48 h but the keto derivatives (Table 5, entry 9-10) decomposed in 8-10 h under the standard conditions.

Table 5. Scope and limitations

Entry	Substrate	Products	Time (h)	Yield(%)[d]
1[a]	 1h	 2h	32	82
2	 1i	 2i	23	71
3	 1j	 2j	30	66
4	 1k	 2k	32	61
5 [b]	 1l	 2l	36	81

6 [b]	 1m	 2m	48	71
7 [b]	 1n	 2n	40	78
8	 1o	------	48	0[e]
9 [c]	 1p	------	10	0[f]
10 [c]	 1q	------	8	0[f]

Starting material was prepared using: [a]aldol condensation, [b]Wittig reaction and [c]Grignard reaction followed by oxidation. [d] Isolated yield for product only. [e]starting material recovered. [f]starting material decomposed.

3.3.6 Conclusion

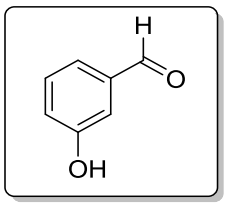
In conclusion, a novel protocol for the allylic oxidation has been developed employing atmospheric molecular oxygen alone, devoid of metal catalysts, photo-activation or high oxygen pressure to give the corresponding ketones as well as phenols in good yields. As only air and heat are employed to convert cycloalkenes to ketones, this is an example of an ecofriendly oxidation.

3.2.7 Experimental

General procedure for allylic oxidation:-

A mixture of cyclohexene (1 molar equiv) and K_2CO_3 (2 molar equiv) in DMF was placed in a two necked RB flask with continuous bubbling of air at 80 °C until the completion of reaction (TLC). The reaction mixture was filtered, the filtrate was then treated with water and extracted with EtOAc. The organic extracts were washed with brine, dried (anhydrous Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel) using pet. ether/ethyl acetate as eluent.

3-Hydroxybenzaldehyde (2):



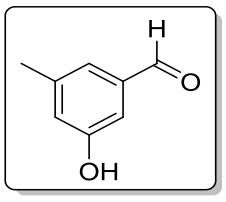
Cyclohexene **1** (200 mg, 1.39 mmol), and K_2CO_3 (383 mg, 2.78 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 12 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the brown solid compound **2** (mp = 100-102 °C, 156 mg, 92% yield). R_f 0.5 (20% Ethyl acetate/pet. ether).

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.09 (d, *J* = 7.6 Hz, 1 H), 7.24 (brs, 1 H), 7.30 - 7.46 (m, 2 H), 9.90 (s, 1 H), 10.03 (brs, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 114.7, 121.3, 122.0, 130.5, 137.8, 158.1, 193.3.

GC-MS (EI): *m/z* =122 $(M)^+$; CAS Registry No: [100-83-4].

3-Hydroxy-5-methylbenzaldehyde (2a):



Cyclohexene **1a** (0.2 g, 1.26 mmol), and K_2CO_3 (0.34 g, 2.53 mmol) in DMF (7 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 20 h. Purification by flash column chromatography (silica gel, 7:3 pet. ether/ethyl acetate) afforded the brown solid compound **2a** (mp = 78-80 °C, 0.15 g, 89% yield).

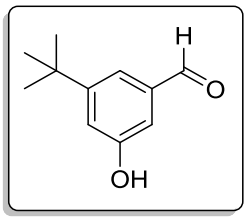
R_f 0.5 (30% Ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (s, 3 H), 6.23 (brs, 1 H), 6.91 – 7.00 (m, 1 H), 7.15 – 7.20 (m, 1 H), 7.21 – 7.25 (m, 1 H), 9.89 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4+ DMSO-d_6): δ 20.5, 112.1, 121.4, 122.0, 137.0, 139.3, 157.4, 191.6.

GC-MS (EI): *m/z* =136 $(M)^+$; CAS Registry No: [60549-26-0].

3-(*tert*-Butyl)-5-hydroxybenzaldehyde (2b):



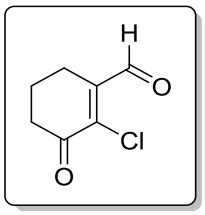
Cyclohexene **1b** (200 mg, 1.00 mmol) and K_2CO_3 (276 mg, 2.00 mmol) in DMF (5 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 24 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the red solid compound **2b** (mp.=70-72 °C, 137 mg, 77% yield). R_f 0.5 (30% Ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 9 H), 7.14 (s, 1 H), 7.21 – 7.29 (m, 2 H), 7.46 (t, *J* = 1.5 Hz, 1 H), 9.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 31.1 (3 C), 34.8, 112.4, 119.8, 120.5, 137.4, 154.2, 156.7, 193.2.

GC-MS (EI): *m/z* =178 $(M)^+$; CAS Registry No: [532966-72-6].

2-Chloro-3-oxocyclohex-1-enecarbaldehyde (3):

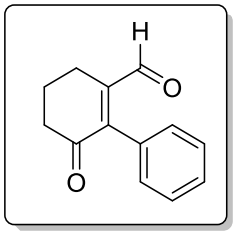


Cyclohexene **1** (200 mg, 1.39 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 12 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the colorless liquid compound **3** (220 mg, 80% yield). R_f 0.3 (10% Ethyl acetate/pet ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.97 – 2.20 (m, 2 H), 2.53 – 2.77 (m, 4 H), 10.45 (s, 1 H). **^{13}C NMR** (50 MHz, $CDCl_3$+ CCl_4): δ 21.1, 24.3, 38.6, 140.6, 145.6, 191.7, 192.2.

GC-MS (EI): *m/z* =158 $(M)^+$, 130, 102, 95, 73, 65.

6-Oxo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (2e):



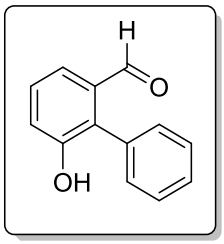
Cyclohexene **1e** (200 mg, 1.07 mmol) in DMF (6 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 17 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the yellow solid compound **2f** (mp = 57-59 °C, 158 mg, 72% yield). R_f 0.6 (20% Ethyl acetate/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08-2.23 (m, 2 H), 2.63 - 2.75 (m, 4 H), 7.19 - 7.21 (m, 2 H), 7.43 - 7.45 (m, 3 H), 9.72 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 21.5, 23.0, 38.8, 128.0 (2 C), 129.1, 130.91, 130.97 (2C), 147.7, 147.9, 195.0, 200.1.

HRMS (ESI) calculated for $C_{13}H_{13}O_2$, 201.0910 $(M+H)^+$; Found, 201.0908.

6-Hydroxy-[1,1'-biphenyl]-2-carbaldehyde (2f):



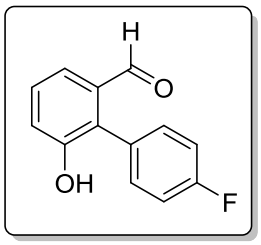
Cyclohexene **1e** (200 mg, 1.07 mmol) and K_2CO_3 (296 mg, 2.15 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 22 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the green solid compound **2f** (mp.=127-129 °C, 159 mg, 75% yield). R_f 0.4 (20% Ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 5.21 (brs, 1 H), 7.23 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.35 – 7.44 (m, 3 H), 7.47 – 7.62 (m, 4 H), 9.70 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+ CCl_4): δ 119.9, 120.9, 129.1, 129.2, 129.5 (2 C), 130.8 (2 C), 131.0, 131.6, 134.8, 153.3, 191.5.

HRMS (ESI) calculated for $C_{13}H_{11}O_2$, 199.0754 $(M+H)^+$; Found, 199.0754.

4'-Fluoro-6-hydroxy-[1,1'-biphenyl]-2-carbaldehyde (2g):



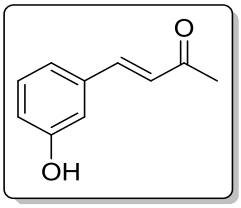
Cyclohexene **1g** (200 mg, 1.02 mmol) and K_2CO_3 (281 mg, 2.04 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 24 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the orange solid compound **2g** (mp.=128-130 °C, 155 mg, 73% yield). R_f 0.3 (20% ethyl acetate/pet. ether).

^{1}H NMR (500 MHz, $CDCl_3$+ CCl_4): δ 7.24 – 7.31 (m, 4 H), 7.37 – 7.42 (m, 2 H), 7.43 – 7.46 (m, 1 H), 7.61 (dd, *J* = 7.7, 1.2 Hz, 1 H), 9.74 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 16.5 (d, Ar-C, $J_{C\text{-}F}$ = 21.9 Hz, 2 C), 120.4, 121.1, 127.5 (d, Ar-C, $J_{C\text{-}F}$ = 3.4 Hz), 129.4, 129.9, 132.6 (d, Ar-C, $J_{C\text{-}F}$ = 8.1 Hz, 2 C), 135.0, 153.4, 163.1 (d, Ar-C, $J_{C\text{-}F}$ = 249.7 Hz), 191.3.

HRMS (ESI) calculated for $C_{13}H_{10}O_2F$, 217.0659 $(M+H)^+$; Found, 217.0661.

(*E*)-4-(3-Hydroxyphenyl)but-3-en-2-one (2h):



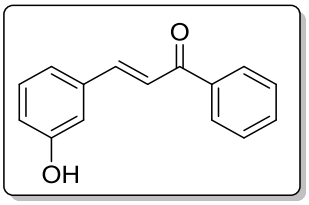
Cyclohexene **1h** (200 mg, 1.08 mmol) and K_2CO_3 (298 mg, 2.16 mmol) in DMF (8 mL) were placed in a two necked RB flask

with continuous bubbling of air at 80 °C for 32 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the white solid compound **2h** (mp.=91-93 °C, 144 mg, 82% yield). R_f 0.3 (20% ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, DMSO-d_6): δ 2.32 (s, 3 H), 6.68 (d, *J* = 16.4 Hz, 1 H), 6.78 – 6.91 (m, 1 H), 6.98 – 7.30 (m, 3 H), 7.52 (d, *J* = 16.4 Hz, 1 H), 9.68 (s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ 27.3, 114.7, 117.7, 119.4, 127.1, 130.0, 135.7, 143.4, 157.7, 198.2. CAS Registry No: [20511-03-9].

(*E*)-3-(3-Hydroxyphenyl)-1-phenylprop-2-en-1-one (2i)



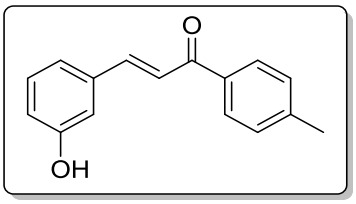
Cyclohexene **1i** (200 mg, 0.81 mmol), and K_2CO_3 (223 mg, 1.62 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 23 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the light green solid compound **2i** (mp.=150-152 °C, lit.[22] 160-161 °C, 129 mg, 71% yield). R_f 0.3 (20% ethyl acetate/pet. ether).

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 6.87 – 6.99 (m, 1 H), 7.09 – 7.19 (m, 2 H), 7.23 (d, *J* = 7.9 Hz, 1 H), 7.46 – 7.64 (m, 4 H), 7.70 (d, *J* = 15.6 Hz, 1 H), 7.97 – 8.08 (m, 2 H), 9.32 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 114.0, 117.1, 118.7, 120.7, 127.3 (2 C), 127.6 (2 C), 128.8, 131.8, 134.9, 137.0, 143.9, 156.8, 189.0.

HRMS (ESI) calculated for $C_{15}H_{13}O_2$, 225.0910 $(M+H)^+$; Found, 225.0907.

(*E*)-3-(3-Hydroxyphenyl)-1-(p-tolyl)prop-2-en-1-one (2j)

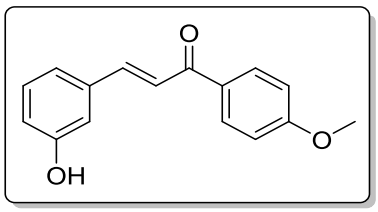


Cyclohexene **1j** (200 mg, 0.76 mmol) and K_2CO_3 (212 mg, 1.53 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 30 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the yellow solid compound **2j** (mp.=137-139 °C, lit.[22] 142-143 °C, 120 mg, 66% yield). R_f 0.3 (10% ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 2.36 (s, 3 H), 6.78 – 6.85 (m, 1 H), 7.00 – 7.06 (m, 2 H), 7.10 – 7.24 (m, 3 H), 7.40 (d, *J* = 15.7 Hz, 1 H), 7.61 (d, *J* = 15.7 Hz, 1 H), 7.81 – 7.85 (m, 2 H), 9.00 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 21.0, 114.3, 117.4, 119.1, 121.2, 127.9 (2C), 128.6 (2C), 129.2, 135.0, 135.4, 142.8, 144.0, 157.2, 189.0.

(*E*)-3-(3-Hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (2k):

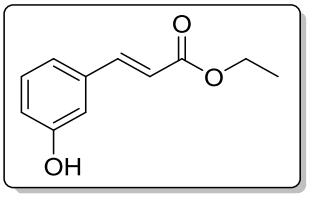


Cyclohexene **1k** (200 mg, 0.72 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 32 h. Purification by flash column chromatography (silica gel, 8:2 pet. ether/ethyl acetate) afforded the yellow solid compound **2k** (mp.=160-162 °C, lit.[22] 163-165 °C, 112 mg, 61% yield). R_f 0.3 (20% ethyl acetate/pet. ether).

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.86 (s, 3 H), 6.80 – 6.90 (m, 1 H), 7.08 (d, *J* = 8.9 Hz, 2 H), 7.19 – 7.22 (m, 1 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 7.27 – 7.31 (m, 1 H), 7.60 (d, *J* = 15.6 Hz, 1 H), 7.82 (d, *J* = 15.6 Hz, 1 H), 8.14 (d, *J* = 8.9 Hz, 2 H), 9.64 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 55.7, 114.2 (2 C), 115.3, 117.8, 119.9, 122.0, 130.0, 130.6, 131.1 (2 C), 136.2, 143.6, 157.9, 163.4, 187.6.

***(E)*-Ethyl 3-(3-hydroxyphenyl)acrylate (2l):**

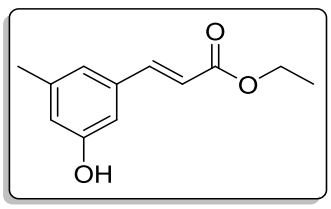


Cyclohexene **1l** (200 mg, 0.93 mmol) and K_2CO_3 (200 mg, 1.87 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 36 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the yellow solid compound **2l** (mp.= 66-68 °C; lit.[23] 70-71 °C, 145 mg, 81% yield). R_f 0.4 (20% ethyl acetate/pet. ether).

^{1}H NMR (200 MHz $CDCl_3$+CCl_4): δ 1.34 (t, *J* = 7.1 Hz, 3 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 6.83 – 6.95 (m, 1 H), 6.97 – 7.11 (m, 2 H), 7.14 – 7.42 (m, 1 H), 7.62 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.2, 60.8, 114.6, 117.7, 117.9, 120.4, 130.0, 135.6, 145.1, 156.5, 167.7.

(*E*)-Ethyl 3-(3-hydroxy-5-methylphenyl)acrylate (2m):



Cyclohexene **1m** (200 mg, 0.88 mmol) and K_2CO_3 (242 mg, 1.75 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C

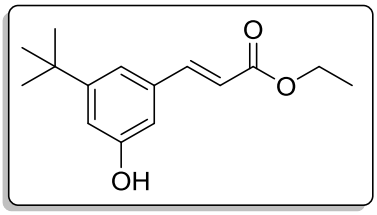
for 48 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the yellow liquid compound **2m** (128 mg, 71% yield). R_f 0.5 (20% ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, DMSO-d_6): δ 1.24 (t, *J* = 7.1 Hz, 3 H), 2.23 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 6.65 (s, 1 H), 6.82 (s, 1 H), 6.94 (s, 1 H), 7.49 (d, *J* = 16.0 Hz, 1 H), 9.56 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 21.1, 60.2, 112.1, 117.9, 118.5, 120.3, 135.2, 139.7, 145.0, 157.8, 166.5.

HRMS (ESI) calculated for $C_{12}H_{15}O_3$, 207.1016 $(M+H)^+$; Found, 207.1015.

(*E*)-Ethyl 3-(3-(*tert*-butyl)-5-hydroxyphenyl)acrylate (2n):



Cyclohexene **1n** (200 mg, 0.88 mmol) and K_2CO_3 (242 mg, 1.75 mmol) in DMF (8 mL) were placed in a two necked RB flask with continuous bubbling of air at 80 °C for 40 h. Purification by flash column chromatography (silica gel, 9:1 pet. ether/ethyl acetate) afforded the yellow liquid compound **2n** (128 mg, 78% yield). R_f 0.4 (20% ethyl acetate/pet. ether).

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.28 – 1.41 (m, 12 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 6.01 (brs, 1 H), 6.38 (d, *J* = 15.9 Hz, 1 H), 6.82 – 6.88 (m, 1 H), 6.88 – 6.94 (m, 1 H), 7.08 (s, 1 H), 7.63 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$+ CCl_4): δ 14.3, 31.2 (3 C), 34.7, 60.6, 111.4, 115.1, 118.0, 118.2, 135.4, 145.3, 153.7, 156.0, 167.2.

HRMS (ESI) calculated for $C_{15}H_{21}O_3$, 249.1485 $(M+H)^+$; Found, 249.1481.

3.3.8 References

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List of publications

1. Subhash P. Chavan,* and **Pradeep B. Lasonkar** "A chiral pool based approach to antipodes of α-cuparenone" *Tetrahedron asymmetry* **2012**, *23*, 1496-1500.

2. Subhash P. Chavan,* and **Pradeep B. Lasonkar**, "One-pot migration–formylation of benzyl aryl ethers under Duff reaction condition" *Tetrahedron Lett.* **2013**, *54*, 4789-4792.

3. Subhash P Chavan, * and **Pradeep B. Lasonkar** "A simple synthesis of novel antihistaminic drug olopatadine hydrochloride" *Synthesis* **2013**, *45*, 3399-3403.

4. Subhash P. Chavan,* **Pradeep B. Lasonkar** and Prakash N. Chavan "A novel and enantioselective synthesis of D-(+)-Biotin *via* Sharpless asymmetric dihydroxylation strategy" *Tetrahedron asymmetry* **2013**, *23*, 1473-1479.

5. Subhash P. Chavan,* and **Pradeep B. Lasonkar** "Unusual metal free auto-oxidation of electron deficient cyclohexenes by air (atmospheric molecular oxygen): Synthesis of meta hydroxy benzaldehydes and cyclohexenones" (communicated).

Patents:

1. Subhash P. Chavan,* and **Pradeep B. Lasonkar** "Improved process for synthesis of olopatadine" Indian Patent. Provisional Filing number: 0803DEL2013-04-08; Provisional filing date: 19.03.2013.

2. Subhash P. Chavan,* and **Pradeep B. Lasonkar** "Metal free allylic oxidation process" Indian Patent. Provisional Filing Number: 2242DEL2013-08-02; Provisional Filing date: 29.07.2013.

Erratum