NEW SYNTHETIC STRATEGY FOR OPTICALLY ACTIVE *trans*-HYDRINDANE: APPLICATION TOWARDS THE SYNTHESIS OF VITAMIN D_3

A THESIS

SUBMITTED TO THE

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DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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To

My Beloved Parents

And

God

DECLARATION

I hereby declare that the work presented in the thesis entitled **"*NEW SYNTHETIC STRATEGY FOR OPTICALLY ACTIVE trans-HYDRINDANE: APPLICATION TOWARDS THE SYNTHESIS OF VITAMIN D_3*"** submitted for Ph. D. degree to the University of Pune, has been carried out by me at The National Chemical Laboratory, Pune, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University. In keeping with the general practice, due acknowledgements have been made, wherever the work described is based on the findings of other investigators. Any inadvertent omissions that might have occurred due to oversight or error in judgment are regretted.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"NEW SYNTHETIC STRATEGY FOR OPTICALLY ACTIVE trans-HYDRINDANE: APPLICATION TOWARDS THE SYNTHESIS OF VITAMIN D_3"*** *submitted by Mr. Sanjay B. Raikar was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

Date:

Dr. Ganesh Pandey

(Research Guide)

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Sanjay B. Raikar

Abstract of the Thesis

"NEW SYNTHETIC STRATEGY FOR OPTICALLY ACTIVE *trans*-HYDRINDANE: APPLICATION TOWARDS THE SYNTHESIS OF VITAMIN D_3"

The thesis deals with the studies directed towards developing a new strategy for the synthesis of optically pure *trans*-hydrindane system and its application towards the total synthesis of 1α,25-dihydrxyvitamin D_3 (1,25-$(OH)_2$-D_3/1,25-D_3/calcitriol) and analogues.

The thesis is divided into four chapters. Chapter I introduces the background literature for undertaking the research work. Chapter II, details our approach for the design and development of a new synthetic strategy for the construction of the optically pure *trans*-hydrindane system, which forms the CD-rings fragment of vitamin D, steroids and various other classes of natural products. Chapter III describes the enantioselective synthesis of CD rings precursors of C-12 and C-16 modified analogues of 1,25-$(OH)_2$-D_3. Chapter IV discusses the new approach towards the synthesis of A-ring synthons of 1,25-$(OH)_2$-D_3 and its enantiomer.

Chapter I. 'Vitamin D: An Overview'

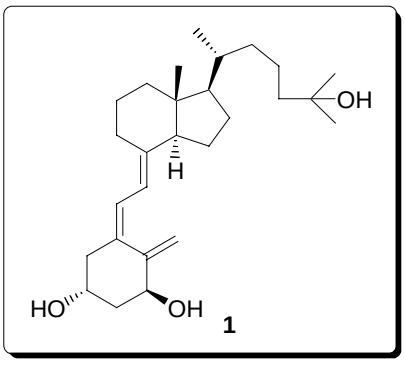


Figure 1. 1α,25-dihydroxyvitamin D_3

1α,25-Dihydroxyvitamin D_3 (Figure 1), is the hormonically active form of vitamin D_3. Besides its classical role in calcium and phosphorous metabolism it has also been shown to be active in the regulation of cell proliferation and differentiation of various

immunological and malignant cells. Thus, calcitriol and its analogues find application in the treatment of diverse array of human disorders. These biomedically important applications continue to stimulate the growing interest in the chemistry, biology and pharmacological applications of vitamin D.

This chapter gives an introduction to various aspects of vitamin D research including biogenesis, metabolism, pharmacology and synthesis. The comparative study of the methods developed for the synthesis of 1,25-D_3 revealed that the A plus CD cross coupling approach originally discovered by Lythgoe and later developed by Mouriño-Castedo is of great advantage in the synthesis of structurally modified analogues of 1,25-D_3 due to its convergent nature and high yields of the coupling reaction. Equally efficient strategies are also available for attachment of side chain to the CD-rings fragment. Thus, with the availability of such an excellent methods for coupling, the efficiency of the synthesis of 1α,25-dihydroxyvitamin D_3 and analogues relies on the efficient production of each of the fragments. Our endeavors in this domain are discussed in subsequent chapters.

Chapter II. 'Design and development of a new synthetic strategy for *trans*-hydrindane system: CD-rings precursor of vitamin D, steroids and related natural products'

This chapter begins with the survey of approaches developed over the years for the synthesis of *trans*-hydrindane skeleton. *trans*-Hydrindane forms a common feature of steroids, vitamin D, higher terpenes and related natural products. These compounds have broad spectrum of biological activities, which makes them synthetically important targets. The main challenge in the synthesis of this moiety has been the construction of *trans* ring junction, which being less stable than the *cis* one.

From the literature precedent it was evident that, although, numerous approaches have been reported for the synthesis of *trans*-hydrindane skeleton, a general strategy leading to large number of functionalized *trans*-hydrindane systems in optically pure form,

starting from cheaply available materials is still lacking. We designed an elegant strategy for the usefully functionalized *trans*-hydrindane system **2**, as depicted in Figure 2, starting from cheaply available aromatic compound **5** (*o*-anisic acid).

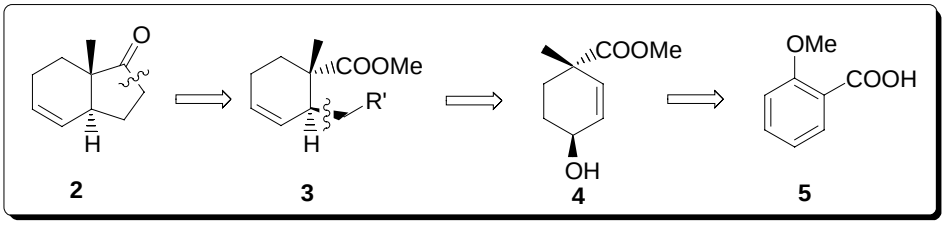


Figure 2. **Retrosynthesis**

For the efficient synthesis of **2** from **5**, in optically active form, two contemporary approaches were visualized, as depicted below, which were envisaged to follow the common path presented in Figure 2.

1) Chiral auxiliary approach
2) Catalytic asymmetric synthesis approach

We began our synthetic explorations with the chiral auxiliary approach, which involved the sequential construction of the two stereocenters in cyclohexyl moiety followed by the annulation of the five-membered ring as depicted in Figure 3.

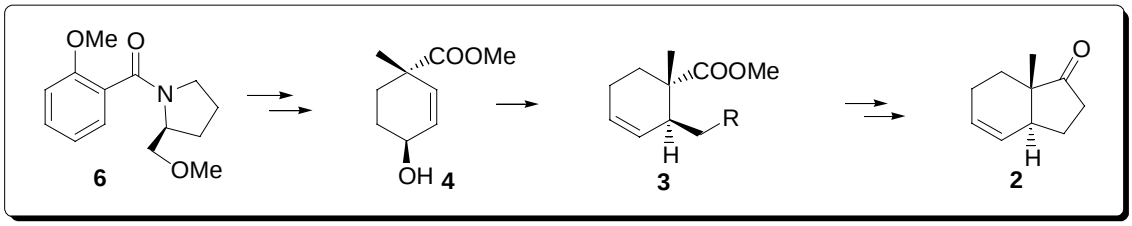
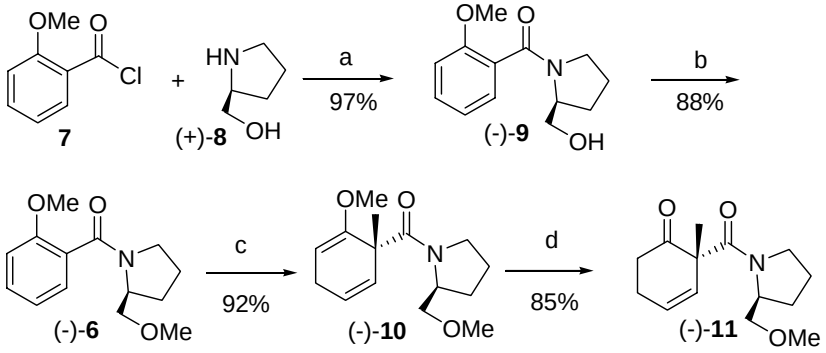


Figure 3. Outline of chiral auxiliary approach

It was conceived that the asymmetric Birch reduction-alkylation strategy could be utilized to construct the quaternary stereocenter present in our system. In this context, the required substrate (-)-**6** was prepared following the literature procedure, which upon Birch reduction-alkylation, followed by hydrolysis of the resulting enol ether (-)-**10** furnished the β-keto amide (-)-**11** as a single diastereomer and in optically pure form (Scheme 1).

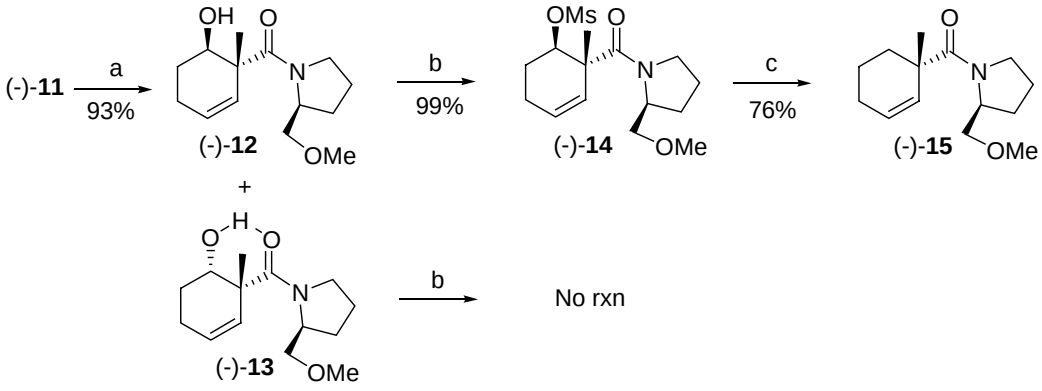
Scheme 1. Construction of quaternary stereocenter



Reagents and conditions: a) Et_3N, DCM, 0 ℃ to rt. b) NaH, MeI, THF, 60 ℃. c) Na, liq. NH_3, THF, ^tBuOH, –78 ℃, MeI. d) 10% HCl, MeOH, rt.

The next task in the planned strategy was to reduce the keto functionality of (-)-**11** to the methylene group. In this regard, the classical methods such as Wolf-Kishner and Clemmensons reductions failed to give required transformation and resulted in complex reaction mixture. The hydride attack on corresponding tosyl hydrazone was also not feasible most probably due to the steric hindrance imparted by quaternary stereocenter. Thus we evaluated Fujimoto's protocol for deoxygenation of alcohols via Zn-NaI reduction of corresponding mesyl derivatives, which was found to produce the desired product (-)-**15**. However the failure of (-)-**13** to undergo mesylation reduced the efficiency of this method (Scheme 2).

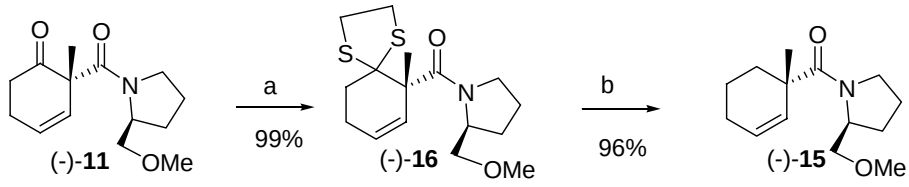
Scheme 2. Application of Fujimoto's deoxygenation protocol



Reagents and conditions: a) $NaBH_4$, MeOH, 0 ℃ to rt. b) MsCl, TEA, DCM, 0 ℃ to rt. c). NaI, Zn, DME, 70 ℃

Continued efforts towards developing a better method for deoxygenation of keto function in (-)-**11**, resulted in a highly efficient protocol for the preparation of (-)-**15**, utilizing chemoselective reduction of the dithiolane derivative (-)-**16** using $^{n}Bu_3SnH$ as depicted in Scheme 3.

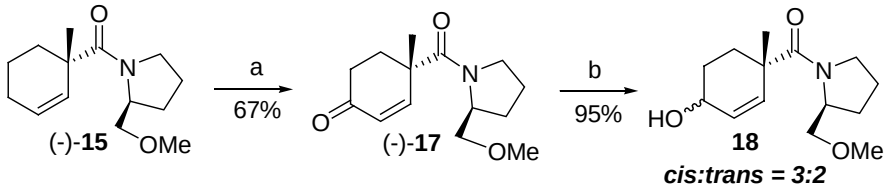
Scheme 3. Deoxygenation via dithiolane derivative



Reagents and conditions: a) ethanedithiol, $BF_3.OEt_2$, DCM, 0 °C to rt. b) $^{n}Bu_3SnH$, AIBN, 120 °C.

With the fully characterized (-)-**15** in hand we moved on to introduce allylic hydroxy group by executing allylic oxidation-reduction sequence to obtain **18** as a 3:2 diastereomeric mixture favoring the *cis* form as indicated by ^{1}H NMR and GC analysis. The poor diastereoselectivity indicated that the chiral auxiliary does not play significant role in influencing stereochemical outcome of the reduction step (Scheme 4).

Scheme 4. Allylic oxidation-reduction

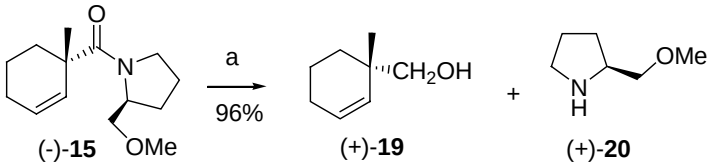


Reagents and conditions: a) PDC, $^{t}BuO_2H$, DCM, 10 °C to rt. b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt.

The diastereomers of **18** or its hydroxyl derivatives could not be separated by TLC and column chromatography. In order to convert the entire material into desired *trans*-diastereomer it was necessary to generate a δ-lactone (-)-**25**, which upon methanolysis and Mitsunobu inversion of the resulting *cis* diastereomer would produce the required *trans*-diastereomer (-)-**4**. For this purpose it was necessary to cleave the chiral auxiliary and to avoid interference by the hydroxy group during the chiral auxiliary cleavage it was decided to proceed with (-)-**15** itself. After considerable experimentation we developed a

successful protocol for detaching the chiral auxiliary in (-)-**15** by LAH reduction (reverse addition) at low temperature (-20 °C) as shown in scheme 5.

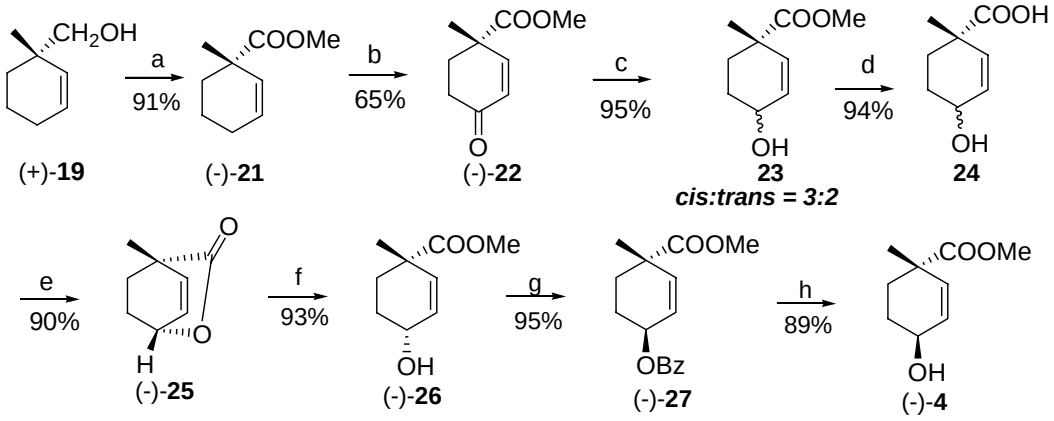
Scheme 5. Cleavage of chiral auxiliary



Reagents and conditions: a) $LiAlH_4$, THF, –20 °C to 0 °C, 2 N H_2SO_4.

At this stage, we proceeded to prepare pure *trans*-diastereomer as planned. The hydroxymethylene group of (+)-**19** was converted to carbomethoxy group by PDC oxidation and diazomethane esterificaton of the resulting carboxylic acid group to produce (-)-**21** in excellent yield. Allylic oxidation-reduction on (-)-**21** produced **23** in 3:2 diastereomeric ratio as indicated by ^{1}H NMR and GC analysis. Consistency in the diastereomeric ratio of the alcohols produced by reduction of (-)-**17** and (-)-**22** confirmed that the chiral auxiliary does not play any role in the stereochemical outcome of the reduction step. The pure *trans* diastereomer (-)-**4** was prepared from mixture following the lactonization strategy discussed above and as depicted in Scheme 6.

Scheme 6. Preparation of *trans*-diastereomer (-)-4

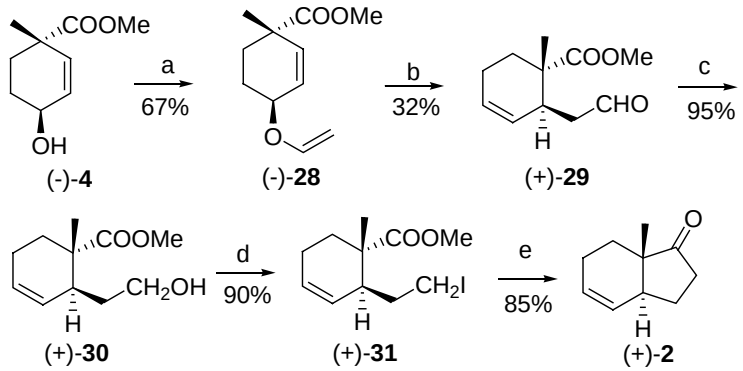


Reagents and conditions: a) i. PDC, DMF, rt. ii. CH_2N_2, Et_2O, 0 °C to rt. b) PDC, $^tBuO_2H$, DCM, 10 °C to rt. c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt. d) LiOH, THF, H_2O, rt. e) $BF_3.OEt_2$, DCM, 0 °C. f) NaOMe, MeOH, reflux. g) DIAD, PPh_3, BzOH, THF, 0 °C to rt. h) 1N NaOH, MeOH, rt.

The next task was to install the tertiary stereocenter vicinal to the quaternary one. As premeditated at the outset we proceeded to evaluate the classical Claisen rearrangement on (-)-**4**

for this purpose. Towards this end it was realized that subjecting (-)-**4** to classical Claisen rearrangement conditions produced the rearranged aldehyde (+)-**29**, but in low yields (32%). Consequently the side arms of (+)-**29** were annulated to form five-membered ring, thus producing the targeted *trans*-hydrindane system (+)-**2** as depicted in Scheme 7.

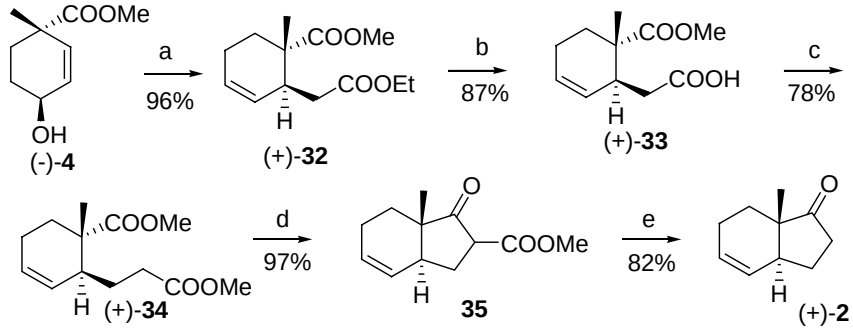
Scheme 7. Classical Claisen rearrangement and annulation



Reagents and conditions: a) Ethyl vinyl ether, $Hg(OAc)_2$, reflux. b) PhH, reflux. c) $NaBH_4$, MeOH, –5 to 10 °C. d) I_2, PPh_3, imidazole, CH_2Cl_2. e) ^tBuLi, THF, –100 °C to –50 °C.

Although the classical Claisen rearrangement-annulation was successful in producing the targeted *trans*-hydrindane system (+)-**2**, low yields of the rearrgement step prompted us to seek a better alternative. In this context, it was remarkable to observe that the Johnson's orthoester Claisen rearrangement on (-)-**4** gave the rearranged product (+)-**32** in very high yield (96%) and short reaction time (3 h). Arndt-Eisteret homologation of the lower sidearm of (+)-**32** followed by Dieckmann condensation-decarboxylation sequence produced the desired *trans*-hydrindane system (+)-**2** in excellent overall yield (Scheme 8).

Scheme 8. Johnson's rearrangement-Dieckmann condensation sequence



Reagents and conditions: a) $CH_3C(OEt)_3$, propionic acid, 137-140 °C. b) 1 eq. NaOH, MeOH, reflux. c) i. $SOCl_2$, Pyridine, PhH, rt. ii. CH_2N_2, Et_2O, 0 °C to rt. iii. Ag_2O, MeOH, reflux. d) NaHMDS, THF, 0 °C to rt. e) DABCO, xylene, 150 °C.

After the successful synthesis of *trans*-hydrindane system (+)-**2** in optically pure form, via chiral auxiliary approach, we moved on to attempt the preparation of same target molecule via catalytic asymmetric synthesis. It was perceived that the intramolecular catalytic asymmetric allylic alkylation on racemic **36** would produce **39** in enantiomerically enriched form, which upon subsequent manipulations would produce targeted **2** in optically active form (Figure 4).

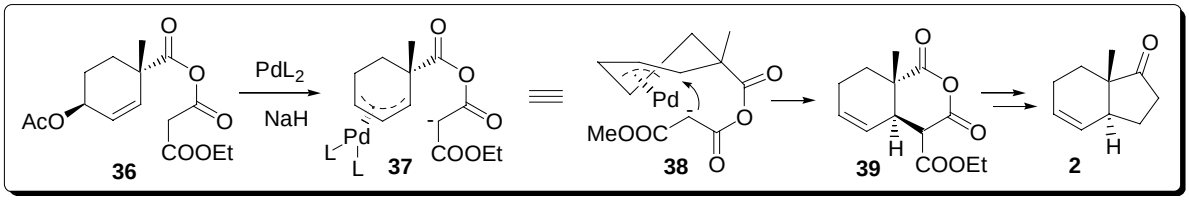


Figure 4. Synthetic design

The designed substrate (±)-**36** was envisaged to be prepared in the racemic form as depicted in Figure 5. The preparation of racemic alcohol (±)-**4** would follow the same path as its optically active congener, but without the use of chiral auxiliary.

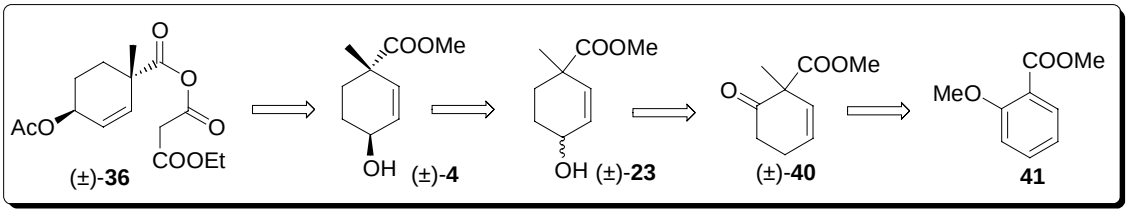
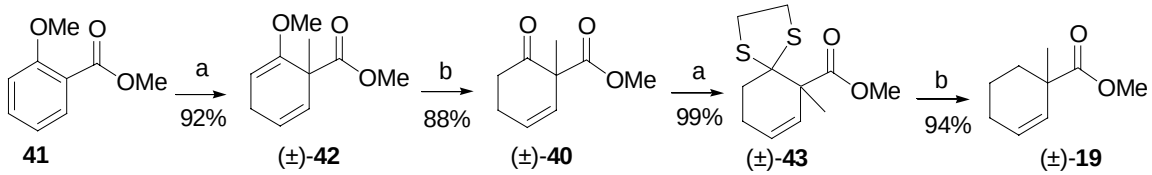


Figure 5. Retrosynthetic analysis of designed substrate (±)-36

The synthesis of (±)-**36** was emanated by Birch reduction-methylation of *o*-anisic acid followed by hydrolysis of the resulting enol ether to produce β-keto ester (±)-**40**, which upon deoxygenation using our standardized protocol gave (±)-**19** in excellent yield (Scheme 9).

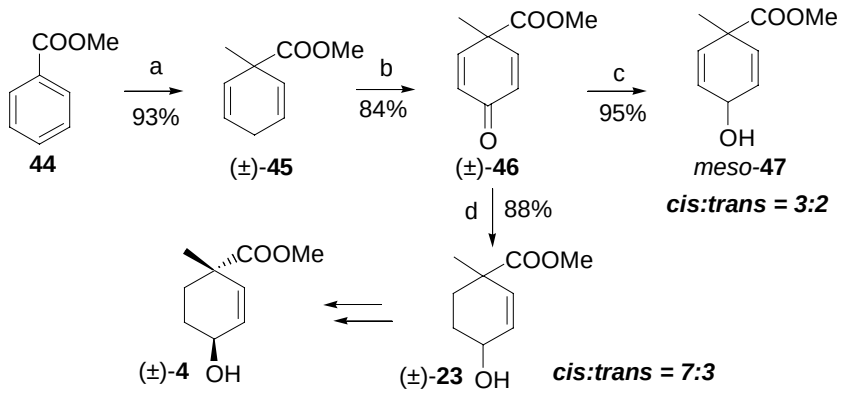
Scheme 9. *o*-Anisic acid route



Reagents and conditions: a) Na, ^{t}BuOH, Liq. NH_3, –78 °C, then MeI. b) 10% HCl, MeOH, rt. c) ethanedithiol, $BF_3(OEt)_2$, DCM, 0 °C to rt. d) $^{n}Bu_3SnH$, AIBN, reflux.

The conversion of (±)-**19** to racemic (±)-**4** was achieved following the same path as described for the preparation of its optically pure congener. At this point, we contemplated that even though the preparation of (±)-**4** from *o*-anisic acid could be achieved in fairly good yield, the length of the synthetic route decreased its efficiency. Thus it was decided to evaluate the preparation of (±)-**4** from benzoic acid. Accordingly, Birch reduction-methylation of methyl benzoate followed by *bis*-allylic oxidation of the resulting diene produced dienone (±)-**46**. During the reduction of dienone (±)-**46** we observed that, when the reduction was carried out under Luche's conditions ($CeCl_3$-$NaBH_4$), *bis*-allylic alcohol *meso*-**47** was produced as a sole product in 3:2 diastereomeric ratio (by GC), while if the reduction was carried out in absence of $CeCl_3$, allylic alcohol (±)-**23** was obtained in 7:3 diastereomeric ratio favoring the *cis* form as indicated by ^{1}H NMR and GC analysis. The conversion of (±)-**23** to (±)-**4** was achieved as usual using lactonization protocol (Scheme 10).

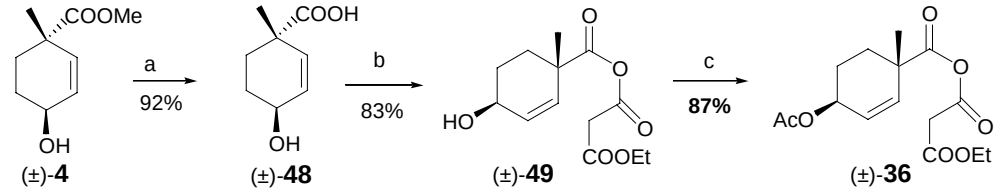
Scheme 10. Benzoic acid route



Reagents and conditions: a) Na, ^{t}BuOH, Liq. NH_3, –78 °C, then MeI. b) PDC, t-BuO_2H, DCM, rt. c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt. d) $NaBH_4$,, MeOH, 0 °C to rt.

With the development of the efficient strategy for the preparation of racemic (±)-**4**, the next task in the planned strategy was to prepare mixed anhydride followed by its *O*-acetylation to obtain the required substrate (±)-**36**. This was achieved as described in Scheme 11.

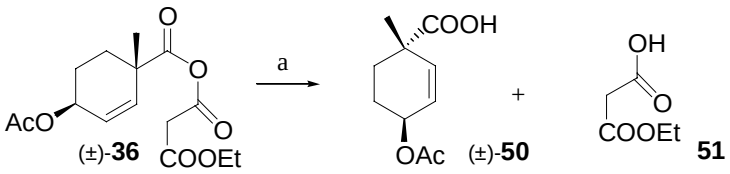
Scheme 11. Preparation of desired substrate 36



Reagents and conditions: a) LiOH, THF, H_2O, rt. b) i. $SOCl_2$, PhH, rt. ii. K-salt of ethyl malonate PhH. c) CH_3COCl, Pyridine, 0 ℃ to rt.

A stage was now set to evaluate the paladium catalyzed allylic alkylation on our designed substrate (±)-**36**. Towards this end, it was quite inopportune that our substrate (±)-**36** could not sustain the basic conditions and broke down to corresponding acids. Various permutations and combinations of reagents and reaction conditions, could not furnish the desired product **39** (Scheme 12).

Scheme 12. Attempted allylic alkylation



Reagents and conditions: a) $Pd_2(dba)_3$, NaH, THF, 0 ℃.

This setback forced us to re-evaluate our strategy and in this regard, detailed study of the reaction conditions as well as design and synthesis of alternative substrates are currently in progress in this laboratory.

The last section of this chapter comprises of experimental details and spectral characterizations of the compounds synthesized as well as copies of ^{1}H NMR, ^{13}C NMR, and mass spectra of some of the key compounds.

Chapter III. 'Enantioselective synthesis of CD-rings precursors of C-12 modified and C-16 modified analogues of 1α,25-$(OH)_2$-D_3'

Although, 1,25-D_3 itself is a potential drug for the treatment of cancer and other hyperproliferation diseases, its calcemic side effects have hampered its use in

therapeutics. Extensive structure function studies have shown that it is possible to modify the calcitriol structure to obtain vitamin D_3 analogues capable of inducing in a selective manner the biological function related to the same molecule. In this regard analogues of 1,25-D_3 with modifications in all the different parts have been prepared and studied for therapeutic value; the CD-rings fragment being the least studied part of the module. The first section of this chapter provides a brief discussion on the importance of the analogues of 1,25-D_3, in particular the C-12 and C-16 modified analogues, which attracted our attention due to their propitious therapeutic profiles.

The second section of this chapter details our design and synthesis of CD-rings precursors of C-12 and C-16 modified analogues of 1,25-D_3. Following figure depicts our designed precursors for C-12 and C-16 modified analogues (Figure 6).

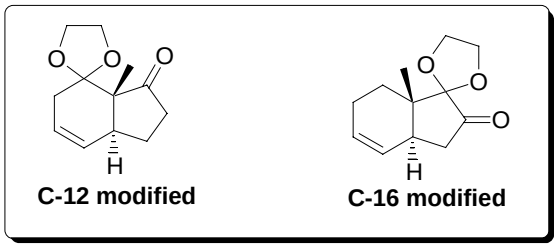
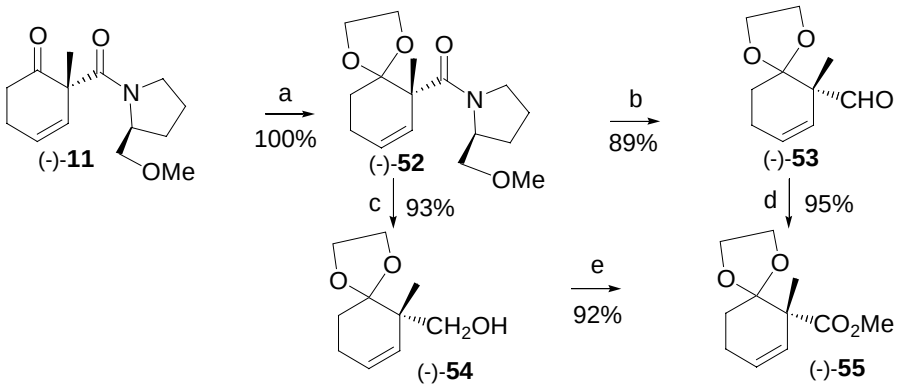


Figure 6

The synthesis of these precursors was envisaged to be carried out using the same starting materials and the strategy developed by us (chiral auxiliary approach) for the CD-rings precursor of parent molecule, so as to demonstrate the versatility of our approach.

Towards this goal, we began by planning the synthesis of C-12 modified precursor, which emanated from β-keto amide (-)-**11**, whose preparation has been discussed in chapter II above. Since the carbon carrying keto functionality in (-)-**11** would form C-12 in the final molecule, it was decided to protect the keto carbonyl as a dioxolane derivative. When the dioxolane derivative (-)-**52** was subjected to chiral auxiliary cleavage it was quite remarkable to observe that either aldehyde (-)-**53** or alcohol (-)-**54** could be selectively obtained by varying the reaction conditions, both of which could be converted to (-)-**55** as depicted in Scheme 13.

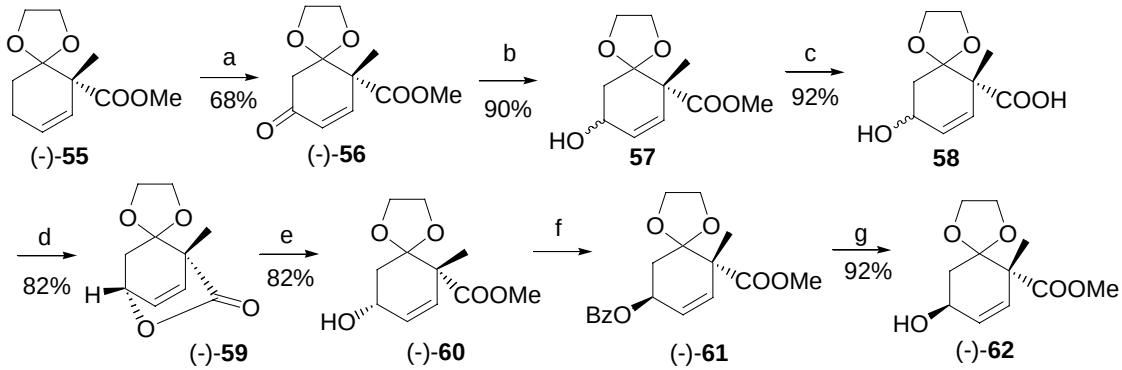
Scheme 13. Preparation of (-)-58



Reagent and conditions: a) $(CH_2OH)_2$, p-TsOH, toluene, reflux. b) LAH, THF, 0 ℃, 3 h. c) LAH, THF, 0 ℃, 4 h then warmed to rt, overnight. d) i. $NaClO_2$, H_2O_2, 0℃ to rt. ii. CH_2N_2, Et_2O, 0 ℃ to rt. e) i. PDC, DMF, rt. ii. CH_2N_2, Et_2O, 0 ℃ to rt.

Next, the *trans* diastereomer (-)-**62** required for the stereospecific installation of the tertiary stereocenter via Claisen rearrangement was procured from (-)-**55** as shown in Scheme 14.

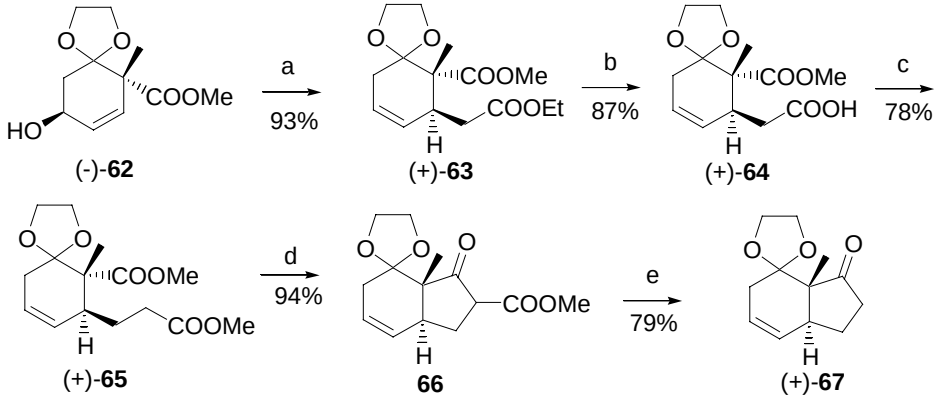
Scheme 14. Preparation of *trans*-diastereomer (-)-62



Reagents and conditions: a) PDC, $^tBuO_2H$, DCM, 10 ℃ to rt. b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ℃ to rt. c) LiOH, THF, H_2O, rt. d) $BF_3.OEt_2$, DCM, 0 ℃. e) NaOMe, MeOH, reflux. f) DIAD, PPh_3, BzOH, THF, 0 ℃ to rt. g) 1N NaOH, MeOH, rt.

With the successful synthesis of *trans*-diastereomer (-)-**62** the stage was now set to install the tertiary stereocenter and annulate the side arms to produce the targeted CD-rings precursor (+)-**67** of C-12 modified analogues of 1,25-D_3. This was achieved as depicted in Scheme 15.

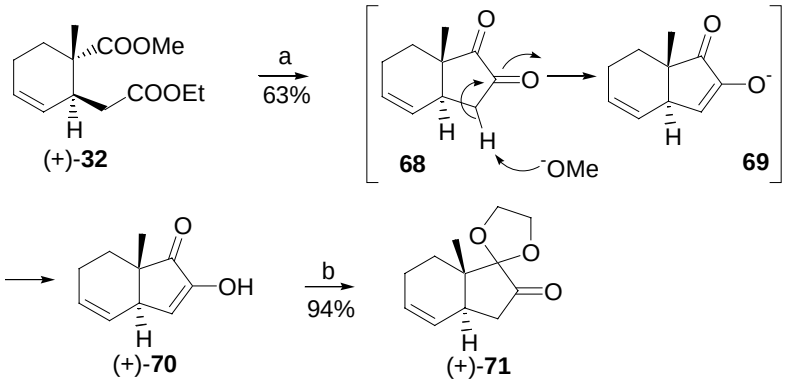
Scheme 15. Preparation C-12 modified precursor (+)-67



Reagents and conditions: a) $CH_3C(OEt)_3$, cat. propionic acid, 137 ºC. b) 1 eq. NaOH, MeOH, reflux,. c) i. $SOCl_2$, Pyridine, PhH, rt. ii. CH_2N_2, Et_2O, 0 ºC to rt. iii. Ag_2O, MeOH, reflux. d) NaHMDS, THF, 0 ºC to rt. e) DABCO, xylene, 150 ºC.

With the successful synthesis of C-12 modified precursor (+)-**67**, we moved on to prepare the C-16 modified precursor (+)-**71**. In this context it was anticipated that the acyloin condensation of diester (+)-**32** would produce the *trans*-hydrindane system with an α-hydroxy ketone in the five-membered ring. However, when (+)-**32** was subjected to the acyloin condensation by treating it with sodium in liquid ammonia at -78 ºC, compound (+)-**70** was obtained as the major product and the expected α-hydroxy ketone was not produced in isolable amounts. Therefore, compound (+)-**70** was subjected to dioxolane protection under controlled conditions (ethylene glycol, *p*-TsOH, toluene, 90 ºC, 6 h) affording (+)-**71** as the sole product (Scheme 16).

Scheme 16. Preparation of C-16 modified precursor (+)-71



Reagents and conditions: a) Na, liq. NH_3, –78 ºC. b) $(CH_2OH)_2$, p-TsOH, toluene, 90 ºC, 6 h.

The last section of this chapter provides detailed experimental procedures and spectral characterizations of all new compounds along with the copies of ^{1}H NMR, ^{13}C NMR and mass spectra of some of the key compounds.

Chapter IV. 'A New approach towards the enantioselective synthesis of A-ring synthons of 1α, 25-Dihydroxyvitamin D_3'

A highly substituted cyclohexyl moiety constitutes the A-ring of calcitriol. The presence of two asymmetric centers along with the typically positioned olefin function makes the synthesis of this moiety particularly challenging This chapter begins with the brief introduction to the synthetic strategies developed for the preparation of various A ring synthons of 1,25-D_3 in optically active form.

The next section begins with the disconnection approach for our designed precursors **78** and **79**, either of which would lead to various A-ring synthons in optically pure form. We envisaged synthesizing **78** and **79** as well as their enantiomers from common starting materials either via *o*-anisic acid route or anthranillic acid route as depicted retrosynthetically in Figure 7.

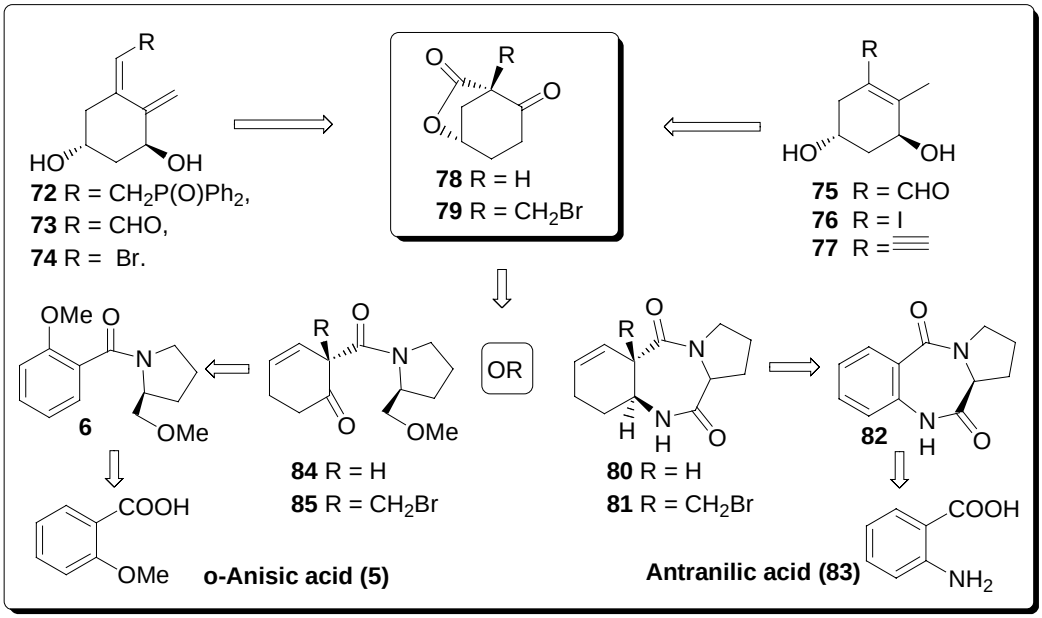
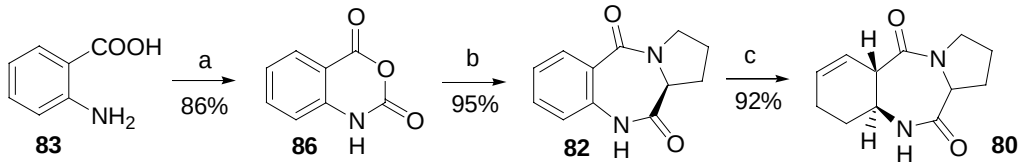


Figure 7. Retrosynthesis

We began our synthetic journey via anthranillic acid route by synthesizing compound **80** (R = H), which was obtained in optically pure form by following the literature procedure (Scheme 17).

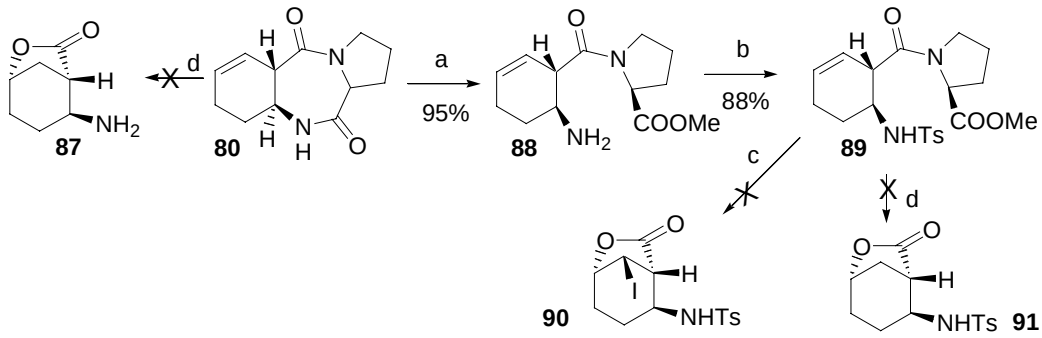
Scheme 17. Initial steps in anthranillic acid route



Reagents and conditions: a) $COCl_2$, 50% HCl. b) L-proline, Py.HCl, pyridine, reflux. c) Na, liq. NH_3, THF, –78 °C, 0.5h, NH_4Cl.

The next step in the planned strategy was to detach the chiral auxiliary, so as to obtain amino lactone, which could be oxidized to the targeted precursor **78**. However, to our dismay, it was not possible to secure the aminolactone by any of the means that we attempted as depicted in Scheme 18.

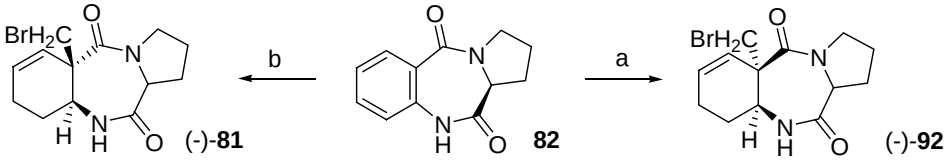
Scheme 18. Attempted preparation of aminolactone



Reagents and conditions: a) cat. H_2SO_4, MeOH, reflux, 30h. b) TsCl, Et_3N, DCM, rt. c) I_2, THF, H_2O, rt. d) 1:1 H_2SO_4, reflux.

At this juncture we realized that the difficulties in procuring the required aminolactone were due to the presence of the enolizable proton vicinal to amide function. Thus we decided to replace it with a group, which could be easily detached later on or would serve as the part of the targeted synthon. In this context, several groups were tried and CH_2Br was found to be most successful. The two diastereomers could be obtained selectively by changing reaction conditions as depicted in Scheme 19.

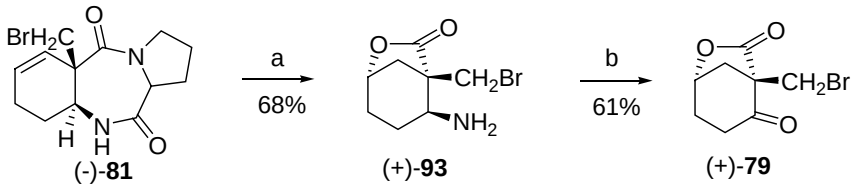
Scheme 19. Modified approach



Reagents and conditions: a) Na, liq NH_3, THF, ^tBuOH –78 °C, then CH_2Br_2. b) Na, liq NH_3, THF, ^tBuOH –78 °C, warm to 25 °C, cool to –78 °C, CH_2Br_2.

The synthesis of targeted precursor (+)-**79** was then successfully achieved from (-)-**81** as shown in Scheme 20.

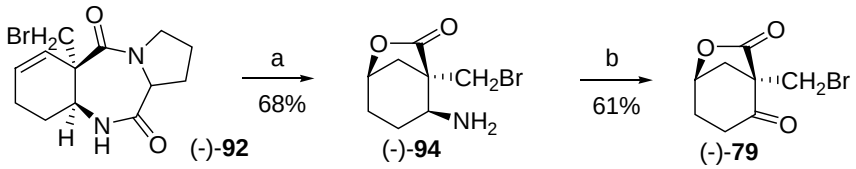
Scheme 20. Synthesis of (+)-79



Reagents and conditions: a) 1:1 H_2SO_4, 100 °C. b) 4-formyl-1-methylpyridinium benzene sulfonate, DCM, DMF, rt., 30 min, DBN, 15 min.

Concomitantly the enantiomer of (+)-**79** was synthesized from (-)-**92** as depicted in Scheme 21.

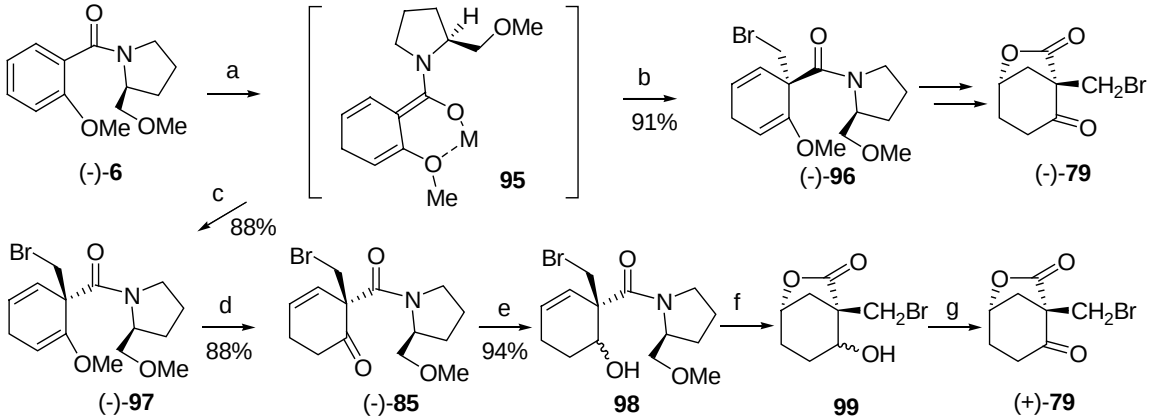
Scheme 21. Synthesis of (-)-79



Reagents and conditions: a) 1:1 H_2SO_4, 100 °C. b) 4-formyl-1-methylpyridinium benzene sulfonate, DCM, DMF, rt., 30 min, DBN, 15 min.

At this stage we realized that the anthranillic acid route suffered from drawbacks such as use of phosgene, lower yields in some of the steps and cost of the oxidizing agent used to convert amino functionality of (+)-**93** and (-)-**94** to a keto carbonyl. Thus in order to enhance the efficiency of our strategy, we decided to evaluate the synthesis of (+)-**79** and (-)-**79** via *o*-Anisic acid route. The success of our endeavors towards this goal is presented in Scheme 22.

Scheme 22. *o*-Anisic acid route



*Reagents and conditions: a) Na, liq NH_3, THF, ^tBuOH –78 °C. b) CH_2Br_2. c) i. Enolate equilibration, ii. CH_2Br_2. d) 10 % HCl, MeOH, rt. e) $NaBH_4$, MeOH, 0 °C to rt. f) 1:1 H_2SO_4, 100 °C, (For **98a**, 6 h, 87%; For **98b**, 32 h, 63%). g) PDC, DCM, rt, 93%.*

Elaboration of the versatility of keto lactone (+)-**79** and its enantiomer *ent*-**79** in the synthesis of various A-ring synthons of 1,25-D_3 and analogues is currently in progress in this laboratory.

CONTENTS

List of abbreviations i

Abstract of the thesis iii

Chapter I **Vitamin D: An Overview**

1. Introduction 1

2. Biogenesis and metabolism of vitamin D_3 5

3. Structural features and conformational behavior of 1α, 25-$(OH)_2$-D_3 8

4. Physiological functions and mode of action of 1α, 25-$(OH)_2$-D_3 10

5. Pharmacology of 1α, 25-$(OH)_2$-D_3 14

6. Literature reports of the Synthetic approaches towards 1α, 25-$(OH)_2$-D_3 17

7. References 31

Chapter II **Design and development of a new synthetic strategy for *trans*-hydrindane system: CD-rings precursor of vitamin D, steroids and related natural products**

1. Introduction 36

2. Retrosynthetic analysis and design 57

3. Enantioselective synthesis of suitably functionalized *trans*-hydrindane system utilizing chiral auxiliary approach 58

4. Attempted construction of optically active *trans*-hydrindane moiety utilizing catalytic asymmetric synthesis approach 88

5. Experimental 103

6. References 138

7. Spectra 141

Chapter III **Enantioselective synthesis of CD-rings precursors of C-12 modified and C-16 modified analogues of 1α,25-$(OH)_2$-D_3**

1. Introduction 155
2. Results and Discussion 159
3. Experimental 178
4. References 193
5. Spectra 194

Chapter IV **A New approach towards the enantioselective synthesis of A-ring synthons of 1α,25-$(OH)_2$-D_3**

1. Introduction 208
2. Results and Discussion 215
3. Experimental 231
4. References 244
5. Spectra 245

1. Introduction

In the course of evolution of the universe, once our sun ignited, it began to emit enormous amounts of energy. This energy bombarded all of its satellite planets. The third planet from the Sun (i.e., Earth) had a huge ocean and a small landmass. In the bubbling, organically rich tide pools, life began to evolve and became dependent on solar energy for its very existence. Early in evolution of life on Earth, organisms captured the sun's energy in the form of carbohydrates through the process of photosynthesis. As organisms evolved, they took advantage of their ocean environment and became dependent on calcium for signal transduction and metabolic functions. In addition, calcium became an important component for organisms that developed exoskeletons. The use of calcium for structural scaffolding became critically important in the evolution of ocean-dwelling vertebrates. The plentiful calcium in the oceans provided the ideal element to incorporate into a collagen-based matrix that gave rise to the structurally rigid vertebrate skeleton. The development of the vertebrate endoskeleton not only provided an opportunity for organisms to grow in size but also gave organisms the opportunity to venture onto land. As vertebrate organisms left their ocean environment for a land-based existence, they needed to develop an efficient method of utilizing the calcium that was absorbed into plants from the calcium-rich soil environment. Remarkably, the sun's energy was again called on to promote the photosynthesis of vitamin D_3 (Figure 1) in the skin of vertebrates that was responsible for enhancing the efficiency of intestinal calcium absorption.[1]

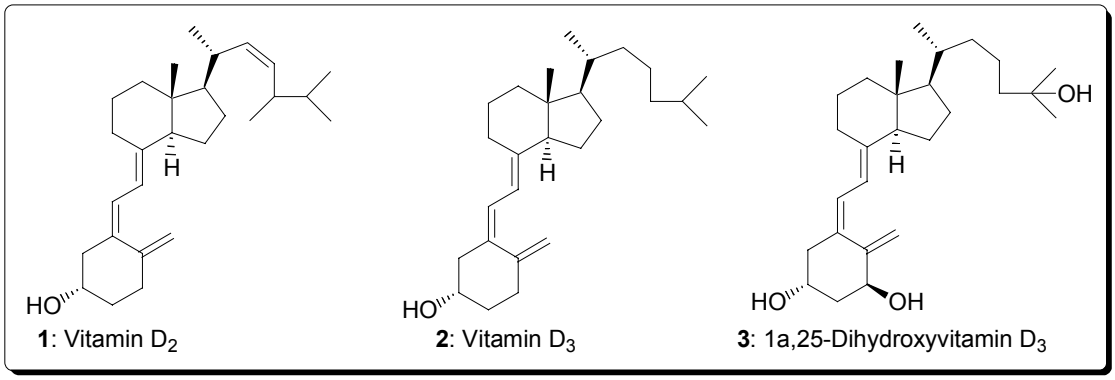


Figure 1. Most common forms of vitamin D

Little is known about when vitamin D made its appearance on Earth and what its function was. However, it is known that some of the earliest phytoplankton and diatom life forms, including *Emiliania huxlei*, which has existed in the oceans for over 750 million years and which has used calcium for its structural support, produces ergosterol (provitamin D_2). Ergosterol, previtamin D_2, vitamin D_2 and their photoproducts efficiently absorb the ultraviolet radiation that is damaging to DNA, RNA and protein i.e. 230-330 nm. Thus, before the ozone layer (which now efficiently absorbs all ultraviolet radiation < 290 nm) evolved, the ergosterol-vitamin D_2 system may have played a critical role in protecting organisms from the high-energy ultraviolet radiation that could have damaged their ultraviolet-sensitive proteins, RNA and DNA.[2]

The disease characterized by improper formation of bone, which later became known as rickets, probably appeared in the human population at the dawn of civilization. Rickets was common in the 19th century, when the industrial revolution caused change of an agrarian society to an industrial society. We now know that, due to scarce exposure to sunlight, the conversion of 7-dehydrocholesterol to vitamin D_3 was no longer occurring in their skin, resulting in the failure of formation of the hormone 1α, 25-dihydroxyvitamin D_3 (1,25-D_3/calcitriol; Figure 1) responsible for maintenance of numerous physiological functions.

The history of vitamin D research can be divided into five distinct phases. The first phase, which might be considered as the recognition of an antirachitic factor, began with an experimental demonstration of the disease rickets by Sir Edward Mellanby[3] and its cure and prevention by the administration of the cod liver oil in 1919. Huldshinsky [4] at the same time demonstrated that this disease could be cured by sunlight or by artificially produced ultraviolet light. Mc Collum *et al*.[5] (1922) established that the antirachitic activity of cod liver oil is due to a new vitamin, which they designated as vitamin D. Steenbock and his coworkers[6] (1924) and almost immediately thereafter Hess and his group[7] (1925)

demonstrated that ultraviolet light induces vitamin D activity in the sterol fraction of the biological material.

The second phase i.e., the isolation and identification of D vitamins was initiated by isolation of Vitamin D_2 (ergocalciferol) from ergosterol by Askew *et al*.[8] in 1931. Subsequently Windaus and his collaborators[9] (1935-1936) established the structure of vitamin D_3 derived from 7-dehydrocholestrol.

The third phase i.e., the delineation of physiologic functions of vitamin D, began, with the conclusive demonstration of its central role in stimulating intestinal calcium absorption by Nicolaysen and coworkers[10] in 1937. Carlson and coworkers[11] (1952-1955) established the role of vitamin D in the mobilization of calcium from bone.

The fourth phase i.e., the functional metabolism of vitamin to its active form(s), began with the demonstration of the highly biologically active metabolites of vitamin D in 1966 by Lund and DeLuca.[12] In 1968 first such metabolite, i.e. 25-hydroxyvitamin D_3 was isolated and identified by Blunt *et al*.[13] and subsequently synthesized[14] (1969). This was followed by isolation and identification of the most potent metabolite i.e., 1,25-dihydroxyvitamin D_3 by Holick *et al*.[15] and Lawson *et al*.[16] (1971) and subsequent report of its synthesis by Semmler *et al*.[17] (1972). In addition, numerous other metabolites were also identified, the enzyme systems involved in some of the conversions were studied and their feed back regulation established.

The fifth phase or the current phase began with the recognition of the molecular or cellular mechanism by which vitamin D carries out its physiological functions. This has led to the development of the vitamin D analogues as sensitive molecular biology probes and new drugs having a favorable therapeutic index (i.e., high efficiency and low toxicity).[18]

Well-known types of vitamin D (D_2-D_7) differ only in the side chain (Figure 2).[19] There is no vitamin D_1 since it was shown that the substance originally designated, as vitamin D_1 was actually the molecular compound of vitamin D_2 and lanosterol. [20] However

only vitamin D_2 and vitamin D_3 occur in considerable amounts and are considered the dietary sources of vitamin D. Vitamin D_2 is commonly called plant vitamin and is commercially produced by irradiation of ergosterol obtained from plants and yeast.

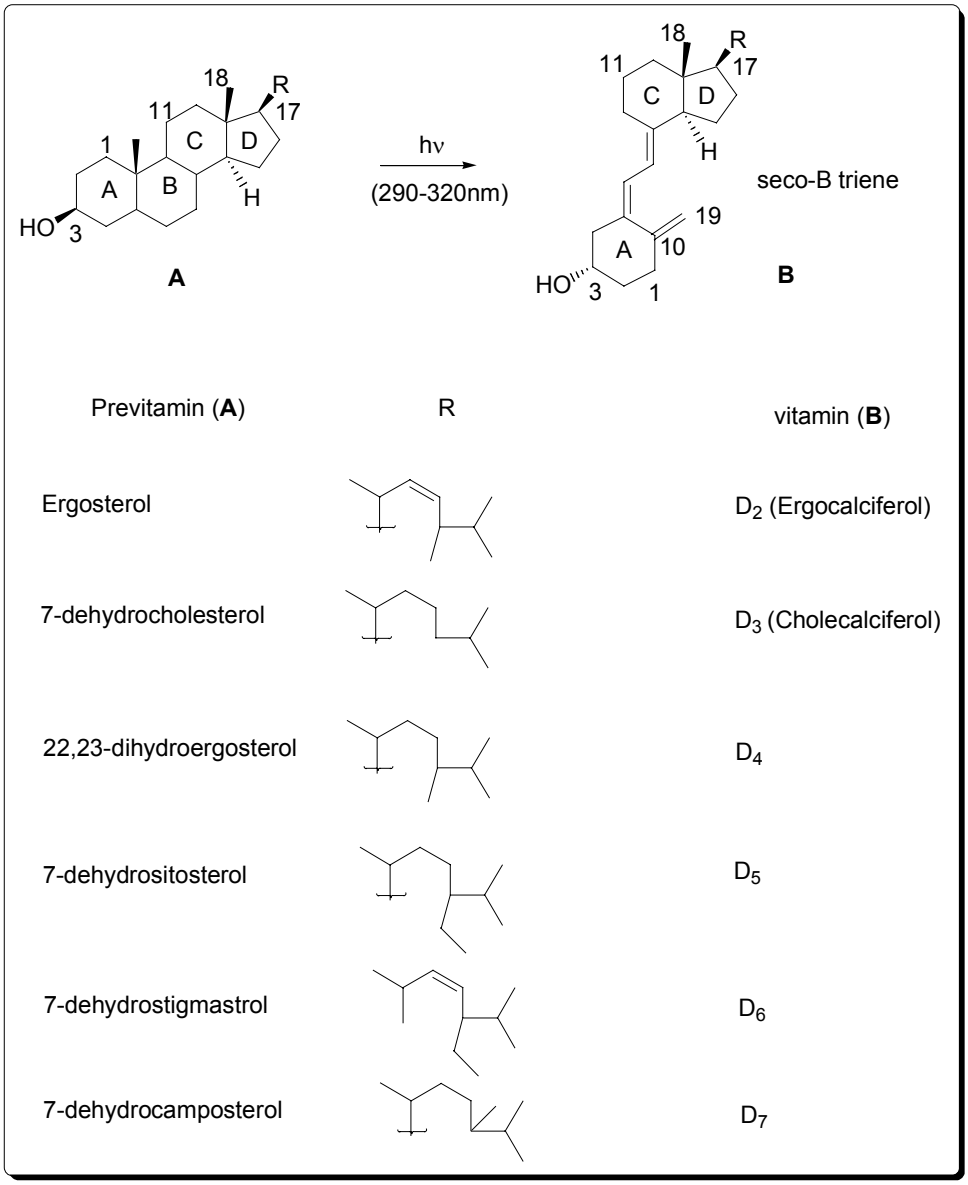


Figure 2. Well-known types of vitamin D

Vitamin D_3 is called animal vitamin since its precursor 7-dehydrcholesterol is produced in relatively large quantities in the skin of many vertebrate animals, including humans. Vitamin D_3 is much more biologically active then vitamin D_2, since the vitamin D binding proteins have weaker affinity for vitamin D_2 metabolites than vitamin D_3. Moreover, unique biologically active metabolites are produced in humans from vitamin D_3, but there are no analogous metabolites derived from vitamin D_2. Thus vitamin D_3 is undoubtedly the most

important form of vitamin D. It can be obtained from the dietary sources[21] or by exposure of skin to sunlight.[22]

Vitamin D research from the viewpoint of its chemistry and pharmacology has expanded enormously in recent years with the discovery that 1α,25-dihydroxyvitamin D_3 exhibits a much broader spectrum of biological activity than originally thought. Its role in calcium and phosphorous metabolism had been established long ago.[23] However, the recent discovery about its ability to inhibit proliferation and to induce differentiation of various cell types such as keratinocytes, tumor cells or lymphocytes, etc., has given rise to renewed interest in this molecule.[24] Thus, the steroid hormone 1α,25-dihydroxyvitamin D_3 and its analogues have been used or have high potential for application as drugs in treating diverse array of human diseases[25] such as rickets,[25(a)] renal osteodystrophy,[25(b)] osteoporosis,[25(c)] psoriasis,[25(d)] leukemia,[25(e)] breast cancer,[25(f)] prostrate cancer,[25(g)] colorectal cancer,[25(h)] hypertension and other cardiovascular ailments,[25(i)] diabetes,[25(j)] rheumatoid arthritis,[25(k)] multiple sclerosis,[25(l)] fracture prevention, brain damage, hyperparathyroidism, acne, ichythyosis, AIDS[25(m)] and Alzheimers disease.[25(n)] These biomedically important applications of 1,25-$(OH)_2D_3$ continue to stimulate the growing interest in research on the chemistry, biology and pharmacological applications of vitamin D. Some of the important aspects of vitamin D research are discussed briefly in the following sections.

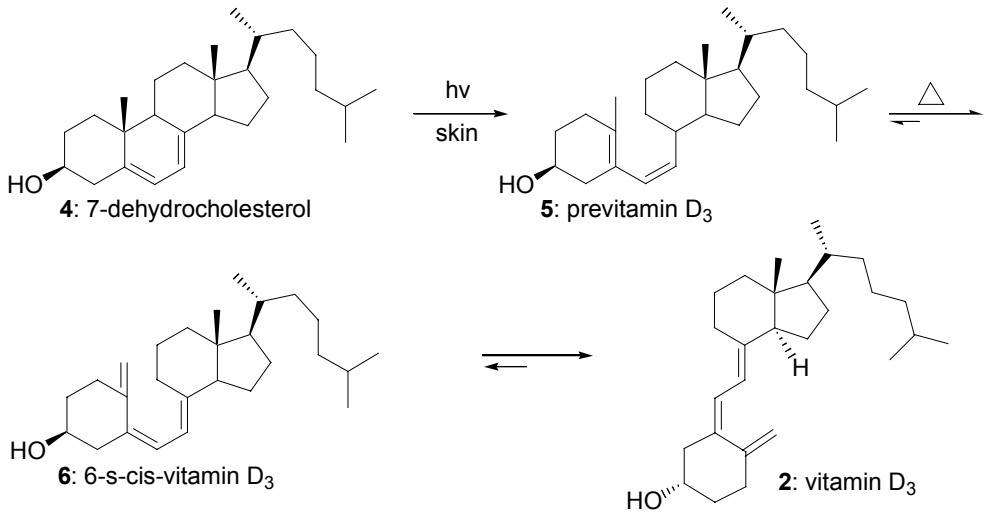
2. Biogenesis and Metabolism of Vitamin D_3

It is well known that vitamin D_3 is synthesized in the skin from 7-dehydrocholesterol (7-DHC / provitamin D_3),[26] which is the immediate precursor of cholesterol in the biogenetic pathway. The elucidation of the actual biosynthetic pathway of cholesterol including the identification of most of the enzymes involved in the process represents a major biochemical achievement. Synthesis of vitamin D_3 from 7-dehydrocholesterol consists of two steps. The first step i.e., the conversion of provitamin D_3 to previtamin D_3 is also called photosynthesis of previtamin D_3. 7-dehydorcholesterol (provitamin D_3) absorbs ultraviolet

light, which effects an electrocyclic rupture of the 9,10 bond to produce previtamin D_3. The efficiency of this transformation depends on the type and amount of UV rays reaching the skin. UV region is divided into three parts viz., UV-A (315-400nm), UV-B (290-315nm) and UV-C (200-280nm). Out of the three types only UV-B radiation, which is also called burning ray can bring about the transformation of provitamin D_3 to previtamin D_3. Thus, the factors such as Melanin (skin pigment),[27] ozone layer,[28] Rayleigh scattering, cloud and aerosol scattering, which absorb the UV light hamper the production of vitamin D.

Previtamin D_3, thus formed is thermodynamically unstable and rearranges its double bonds to form thermodynamically more stable vitamin D_3 structure, initially producing the 6-*s*-*cis* form which rapidly rotates about its 6,7 single bond to its more commonly depicted (and more stable) 6-*s*-*trans* conformer (Scheme 1).

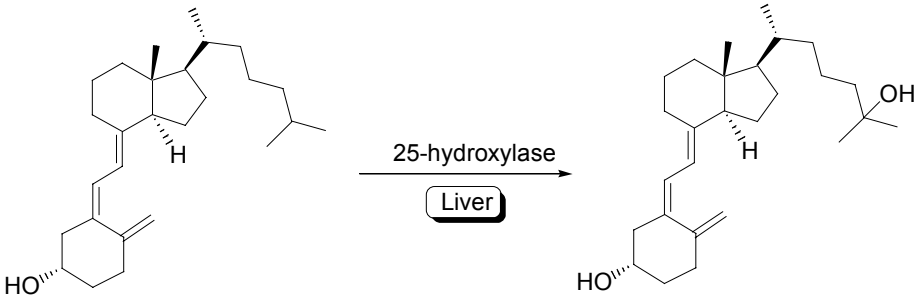
Scheme 1. Biogenesis of vitamin D_3 from 7-DHC



In 1966 the concept that vitamin D must be metabolically activated before it can function was introduced. DeLuca *et al*.[12] demonstrated the existence of polar metabolite(s) of vitamin D, which possessed a high degree of biological activity and identified it to be 25-hydroxy derivative of the parent vitamin. They subsequently showed that this hydroxylation was taking place in the liver (Scheme 2).[29]

25-hydroxyvitamin D_3 represents the major circulating metabolite of vitamin D_3. The conversion of D_3 to 25-hydroxyvitamin D_3 in liver is carried out by a microsomal system requiring NADPH, a flavoprotein, an iron sulfur protein and a cytochrome P-450.[30]

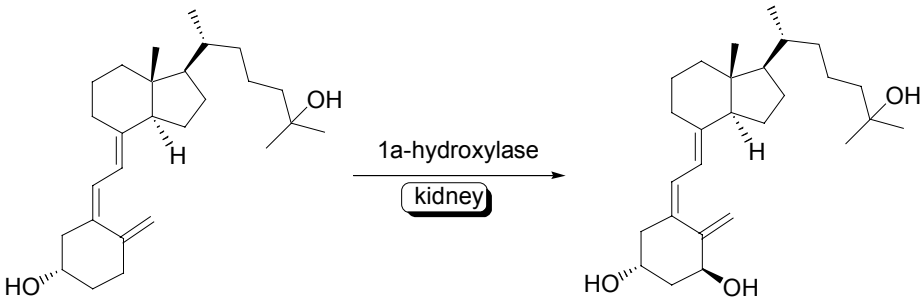
Scheme 2. Enzymatic 25-hydroxylation of vitamin D_3



2: vitamin D_3 **7**: 25-hydroxyvitamin D_3

Subsequently it was shown that 25-OH-D_3 is further metabolized to 1α,25-$(OH)_2$-D_3 which is the actual bioactive form of vitamin D.[15,16] 1α-Hydroxylation occurs exclusively in the renal mitochondrial fraction[31] except in the pregnant mammal in which the placenta can also perform the hydroxylation. 1α-Hydroxylation involves NADPH, a flavoprotein, an iron sulfur protein, and a cytochrome P-450.[32] The hydroxyl residue at C-25 has been shown to play an important role in the introduction of the hydroxyl group at C-1 (Scheme 3).

Scheme 3. Enzymatic 1-hydroxylation of 25-(OH)-D_3



7: 25-hydroxyvitamin D_3 **3**: 1a,25-dihydroxyvitamin D_3

The hormone 1,25-D_3 is most potent among all the other metabolites of vitamin D. Besides 1,25-$(OH)_2$-D_3, 25-OH-D_3 is also metabolized to several other metabolites, which are either biologically inactive or less active than 1,25-$(OH)_2$-D_3. 24,25-$(OH)_2$-D_3 is one such major metabolite which is produced by renal mitochondria when the synthesis of calcitriol is not desired. 23,25-$(OH)_2$-D_3 and 25,26-$(OH)_2$-D_3 are other such metabolites in this series.

Calcitriol, after expression of various biological activities is further metabolized to the inactive forms in the body. There are two major pathways for the metabolism of calcitriol. The first path starts with the hydroxylation at the 24R position followed by further oxidation to the 24-ketone. Further hydroxylation, this time at the 23S position and cleavage of the side chain yields the triol, which is oxidized to calcitrioic acid,[33] which is then excreted out of the body via bile. The second metabolic path proceeds via hydroxylation at the 23S position, hydroxylation at the 26-position and oxidation to the 23*S*, 25*R*-lactone. Very recently[34] it has been revealed that in some of the tissues 1α,25-dihydroxyvitamin D_3 and 24*R*,25-dihydroxyvitamin D_3 are metabolized to their respective epimers of the hydroxyl group at C-3 of the A ring. These epimerized compounds are then metabolized by normal pathways as discussed above.

3. Structural features and conformational behavior of 1,25-$(OH)_2$-D_3

In 1971, two laboratories simultaneously reported the structural identification of 1,25-$(OH)_2$-D_3.[15,16] Conventional chemical methods along with UV and mass spectrometry were used for structure elucidation of this compound. Shortly after the structure was proposed, the solution structures of 1α,25-$(OH)_2$-D_3 were assessed primarily through ^{1}H NMR spectral studies.[35] Together with studies on electronic absorption data and molecular mechanics computations[36] the structure of 1α,25-$(OH)_2$-D_3 was summarized as follows: The A ring exists in dynamic equilibrium between nearly equimolar amounts of the two A-ring chair conformations (α-conformer and the β-conformer) Because of the facile conformational isomerism about single bonds, the flattened twist boat form may be also present in significant amounts (Figure 3).

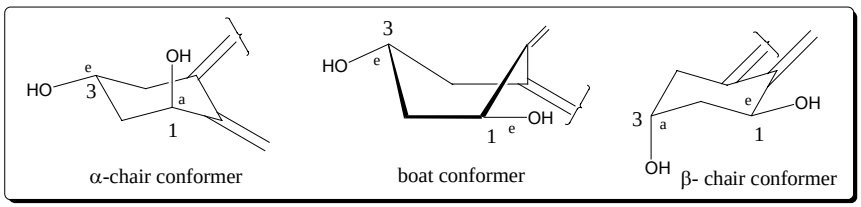


Figure 3. Conformations of A ring

Out of the three double bonds of the triene structure (seco B-ring), only two are fully conjugated as suggested by the electronic spectra. The $\Delta^{5,6}$- and the $\Delta^{7,8}$-double bonds are nearly coplanar and *s-trans*. The exocyclic $\Delta^{10,19}$-double bond is oriented above or below the plane defined by the diene.

The C-ring is chair like, flattened in the vicinity of C-8 due to the presence of the exocyclic double bond, and possesses an unusually large torsion angle at C-13, C-14 due to the CD *trans*-ring junction. The conformation of the D ring may be depicted as the dynamic mixture of envelope and half chair forms (Figure 4).

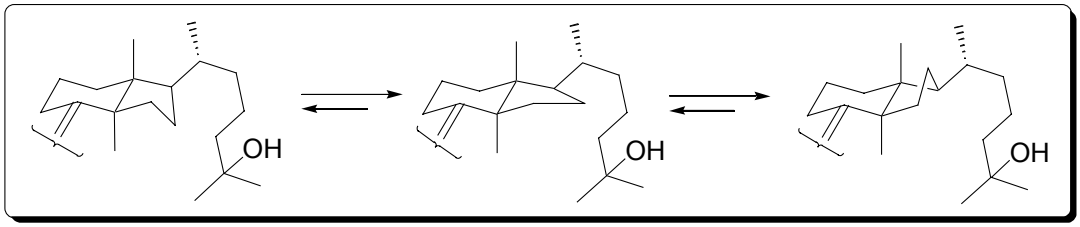


Figure 4. Conformations of CD rings

The 25-hydroxycholesterol side chain is obviously the most flexible structural unit of 1,25-D_3. Six rotatable bonds can lead to the large number of unique staggered conformations (3^6 = 729). Molecular mechanics analyses[36] have been carried out in order to usefully depict the large number of these energy minimized side chain conformers.

The structurally dynamic hormone 1α,25-$(OH)_2$-D_3 involves initial, highly stereoselective binding to a myriad of target proteins including receptors (*n*-VDR and m-VDR) and various enzymes involved in its metabolic production and catabolism. A knowledge of the topology and dynamic behavior of the free steroidal guest molecule (or analogues) in its stereoselective binding to receptor or other protein host is most important to an assessment of intelligible structure-activity correlation. This information is essential in designing yet more effective analogues for therapeutic purposes. Molecular modeling accompanied by semi-empirical calculations is at present one of the leading approaches in this strategy. There was therefore a need to determine x-ray structure of 1α,25-$(OH)_2$-D_3, which might have served as a set of starting parameters for molecular modeling and

quantum chemistry calculations. The crystal structures of the main D vitamins (D_2 and D_3) and some of their analogues were reported over the period of twenty years (1976-1994).[37] However, the x-ray structure of most active form of vitamin D i.e., 1α,25-$(OH)_2$-D_3 was still missing. It was finally achieved by Suwinska and Kutner[38] in 1996 and was of great help in confirming the earlier proposed structure.

4. Physiological functions and mode of action of 1α, 25-$(OH)_2$ D_3

The transportation of vitamin D and its metabolite inside the body constitute an interesting phenomenon. There is in plasma of all animals a protein of the α- or occasionally β-globulin family known as G_c system,[39] with the high affinity for the Vitamin D metabolites. This protein carries the vitamin D metabolites to various sites of metabolism and target tissues. The hydroxyl group at C-1 and C-25 play important role in the binding, whereas the role of C-3 hydroxyl is not very significant. Once 1,25-D_3 is transported from site of synthesis (kidney) to the target tissue it is handed over to another protein[40] present in the cells of the target tissues, which then carries it to the specific cellular moiety (nucleus or mitochondria) where the action of the hormone begins. The hormone is known to act both by genomic as well as non-genomic modes of action. The genomic mode[41] is mediated by the nucleus whereas the non-genomic mode[42] is mediated at the membrane or by extra nuclear sub cellular components.

In the case of genomic mode the first step involves the diffusion of the free hormone across the plasma membrane of the cell, which offers little resistance for entry into the cytoplasm since both the hormone and the membrane are lipophilic. Inside the cell the hormone binds to a receptor protein (vitamin D receptor/VDR),[40] which may be located either in the cytoplasm or in the nucleus. The receptor protein has a high affinity for 1,25-$(OH)_2$-D_3 with a K_d in the range of 1-50 x 10^{-11} M. The specificity of hormonal binding for the receptor has been extensively examined by competitive binding studies with [^{3}H]-1,25-

$(OH)_2$-D_3. The hydroxyl residues at 1α and 25 positions are critical while at 3β is less important for the binding activity.

The hormone receptor complex then interacts with the specific DNA sequences regulating the transcription rates of certain target genes to induce de novo synthesis of mRNA species. These mRNAs are translated into protein which mediate the biological responses initiated by 1,25-$(OH)_2$-D_3 (Figure 5).

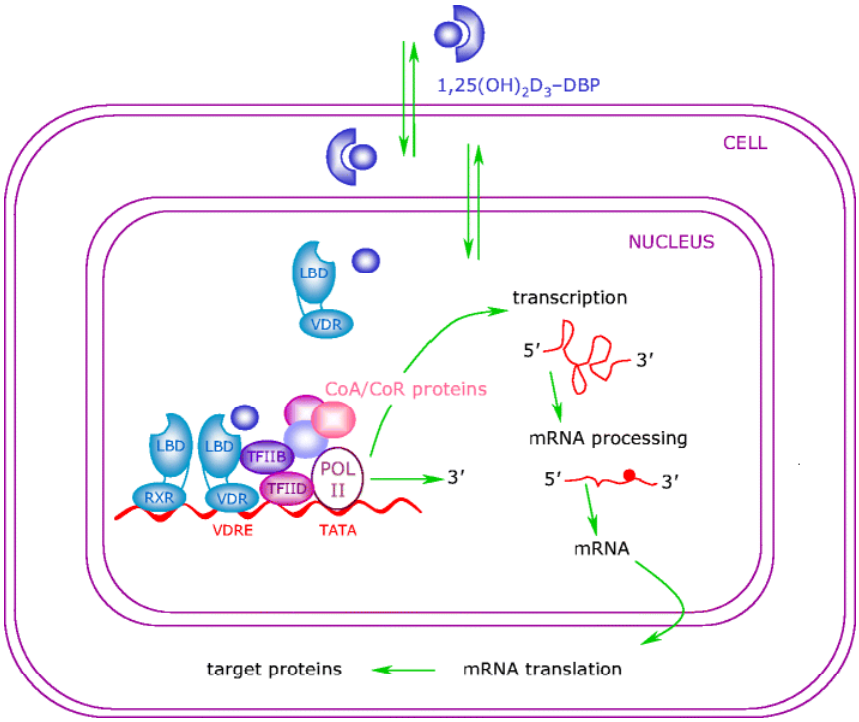


Figure 5. Genomic actions of 1α,25-dihydroxyvitamin D_3. *Molecules of 1,25$(OH)_2D_3$ easily penetrate the plasma membrane and exert their genomic effects by activating the VDR. Ligand binding to the VDR induces a conformational change in the receptor and subsequent heterodimerisation with RXR. The RXR–VDR complex binds to the VDRE, which is located within the 5′ flanking region of target genes. Thereafter, co-repressor (CoR) proteins are released from the surface of the VDR, allowing interaction with co-activator (CoA) proteins. These molecules modulate chromatin structure and allow the interaction of the receptor with the RNA polymerase II transcriptional complex (POL II), thus activating transcription of the target gene. LBD ligand-binding domain; TF transcription factor; RXR retinoic X receptor; VDR vitamin D receptor; VDRE vitamin D response element; DBP vitamin D binding protein.*

The major physiological functions of 1,25-$(OH)_2$-D_3 include the regulation of Calcium and phosphorous metabolism through a direct stimulation of intestinal transport and mobilization of mineral from bone. The classical target tissues for 1,25-$(OH)_2$-D_3 are also those which have been shown to be directly involved in the regulation of mineral homeostasis i.e. the intestine, kidney, bone and parathyroid gland. Besides these classical functions it has also been found to play an important role in cell proliferation and

differentiation. The physiological functions of vitamin D metabolites have been summarized in figure 6.[2(b)]

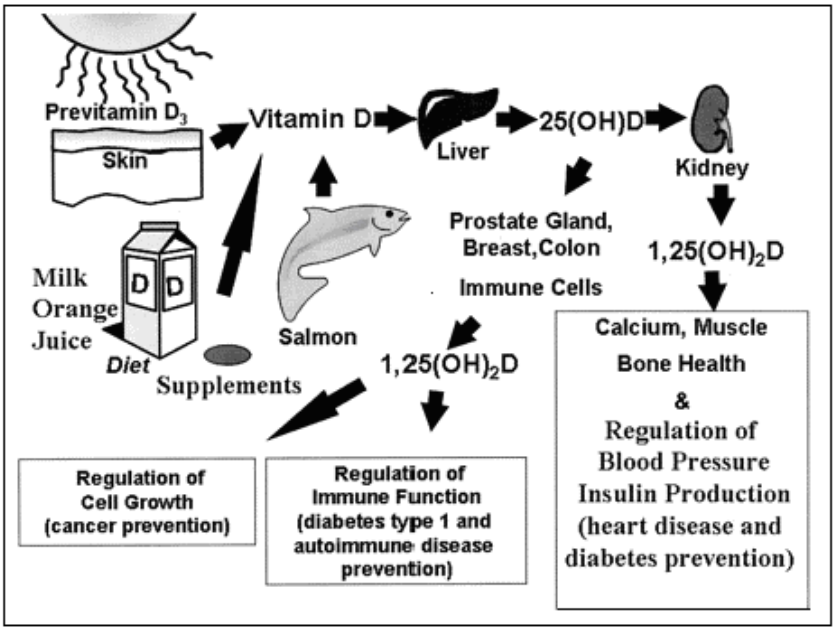


Figure 6. Biosynthesis and physiological functions of 1,25-$(OH)_2$-D_3

The mechanism of regulation of these physiological functions by 1,25-$(OH)_2$-D_3 is discussed briefly in the following section.

4.1 Calcium Homeostasis

Calcium is the fifth most abundant element in vertebrate systems and is the most important structural component of the body.[43] Calcium ions participates in a wide variety of physiological and biochemical processes, including nerve transmission, blood clot formation, maintenance of the membrane integrity, muscle contraction, and bone formation. All these processes are dependent upon an adequate supply of calcium from the diet. It is the integrated action of parathyroid hormone, calcitonin and calciferol (vitamin D), which supplies the required amounts of calcium for all these processes via a smoothly operating calcium homeostatic system.

Intestinal calcium transport occurs via both genomic as well as non-genomic modes of action. In genomic mode, when the concentration of Ca in blood drops below the optimum value 1,25-$(OH)_2$-D_3 interacts with the nucleus resulting in translation of a new

mRNA, which then synthesizes the protein called calcium binding protein (CaBP).[44] Once synthesized CaBP brings about the increased absorption of calcium either by regulation of the intracellular calcium concentration or movement of calcium across the epithilial cell. The non-genomic mode of calcium absorption by 1,25-$(OH)_2$-D_3 is known as transcaltachia,[45] and involves rapid transport of Ca^{+2} across the brush border.

In bone, the primary and most direct effect of 1,25-$(OH)_2$-D_3 is the stimulation of bone resorption[46] leading to the increase in circulating levels of calcium and phosphorous. In contrast with the bone mineral mobilization promoted by 1,25-$(OH)_2$-D_3 , 24,25-$(OH)_2$-D_3 seems to protect bone from demineralization. 24,25-$(OH)_2$-D_3 treatment has therefore been utilized to inhibit excessive 1,25-$(OH)_2$-D_3–dependent bone resorption in some cases of human pathology when high levels of 1,25-$(OH)_2$-D_3 must be administered.[47]

4.2 Phosphorous metabolism

1,25-$(OH)_2$-D_3 is known to have a profound effect on the phosphorous metabolism. Along with calcium it also elevates the phosphorous resorption. The enzyme involved in the process is alkaline phosphatase,[48] whose activity depends the vitamin D status in the body. Whereas the parathyroid hormone acts to increase the excretion of phosphate, 1,25-$(OH)_2$-D_3 facilitates its renal resorption by inhibition of *c*-AMP synthesis. Thus there is fine-tuning of the phosphorous levels in the body.

4.3 Non-classical responses of 1,25-$(OH)_2$-D_3

In the past few years, due to number of technological improvements, 1,25-$(OH)_2$-D_3 receptors were able to be identified in a wide range of tissues and cell lines extending by far the classical limits of the vitamin D actions upon mineral metabolism. Bouquist *et al.*,[49] observed that, administration of 1,25-$(OH)_2$-D_3 increases the insulin release from the pancreas. Thus vitamin D deficiency would lead to the insulin-related diseases like diabetes. Receptors of 1,25-$(OH)_2$-D_3 have also been detected in the limited sections of the brain[50] and heart.[51] In the last few years, considerable evidence has accumulated linking

1,25-$(OH)_2$-D_3 to the heamatopoietic and immunological system. 1,25-$(OH)_2$-D_3 receptors were also found in the non classical target tissues such as thymus and bone marrow, as well as cells derived from these tissues.[52] Early studies using leukemic cell line (HL-60) provided the first line of evidence of the positive effects of 1,25-$(OH)_2$-D_3 upon the heamatopoietic system.

5. Pharmacology of 1,25-$(OH)_2$-D_3

Vitamin D, along with parathyroid hormone and calcitonin, plays a primary role in calcium and phosphorous homeostasis in the body. Intensive research efforts over the past several years have elucidated a role for vitamin D in many other physiological processes as well. The recommended daily allowance (RDA) for vitamin D is 400 IU per day. Inability to supply the minimum requirement of vitamin D leads to deficiency diseases such as rickets in children and osteomalcia in adults. Administration of vitamin D metabolites (analogues of 1,25-$(OH)_2$-D_3) along with calcium intake is the only remedy for such deficiency diseases. After the discovery that VDRs are present in several non-classical tissues it was realized that 1,25-$(OH)_2$-D_3 and its analogues can actually be used as drugs in the treatment of the diseases associated with these tissues. Accordingly the pharmacology of vitamin D metabolites and analogues has expanded enormously over the years. Scientists are slowly realizing that there is no chronic disease where vitamin D cannot serve as a drug. The main diseases, which rely upon vitamin D for treatment, are discussed below.

5.1 Bone disorders (rickets and osteomalacia / osteoporosis)

Vitamin D deficiency develops a distortion of the bone growth that gives rise to soft and distorted skeleton. The primary disturbance responsible for this distortion is the failure to mineralize newly formed osteoid tissue and the cartilage matrix. This in turn is responsible for the unusual softness of the bone, which under the stress and strain of the weight bearing and locomotion gives rise to the characteristic deformities of the disease.

This condition is precisely termed as rickets[25(a)] in children and osteomalacia in adults. Thus rickets prevention depends upon the maintenance of a normal concentration of calcium and inorganic phosphorous in the plasma, which in turn depends upon the absorption of these minerals from the gastrointestinal tract that is stimulated by 1,25-$(OH)_2$-D_3. Thus this disease can be prevented by administration of the 1,25-$(OH)_2$-D_3 along with calcium.

5.2 Autoimmune disorders

Vitamin D_3 is well known for its immunomodulating properties (balancing the immune system). It causes heamatopoietic stem cells to differentiate (grow) into monocytes, the white blood cell (leukocyte) and then it causes these to differentiate (grow) into macrophages[53] and giant cells characteristic of sarcoid granuloma.[54] Without this hormone there would be no formation of granuloma. The hormone is also responsible for maintaining proper operation of the parathyroid, muscle, pancreas, bone, intestine, kidneys, heart and the brain. Many autoimmune disorders, including Graves disease (GD), multiple sclerosis (MS),[25(l)] sarcoidosis[55] and insulin dependent diabetes mellitus, have long been associated with decreased levels of the hormone 1,25-$(OH)_2$-D_3. While vitamin D therapy has not yet been employed as a conventional treatment for the hyperthyroidism of Grave's disease, it is generally a part of most alternative medical protocols for GD. Vitamin D is being currently used in the patients with multiple sclerosis and experimentally in the patients of diabetes.[25(j)]

5.3 Cancers

Cell differentiation is the process by which cells specialize to perform specific functions in different tissues. Loss of cell differentiation can lead to abnormal cell function including uncontrolled cell growth, generally termed as cancer. There are various types of cancers depending on the organ in which they occur. Vitamin D and metabolites are found to be of great use in cancer prevention and treatment.

Prostrate cancer[25(g)] is the leading cause of cancer related deaths in many countries. Vitamin D and retinoids have emerged as leading candidates both to prevent and to treat prostrate cancer. Another cancer whose course may be attenuated by vitamin D is melanoma. Research has shown that, 1,25-$(OH)_2$-D_3 induces cellular death in some types of melanoma. The effect is particularly strong in those cells with high levels of VDRs. Besides these cancers 1,25-$(OH)_2$-D_3 analogues are of great importance in the prevention and treatment of various other types of cancers including the colon cancer, the breast cancer and the lung cancer.

5.4 Cardiovascular diseases

Cardiovascular disease[33] is a wide encompassing category that includes all the conditions that affect the heart and the blood vessels. People with cardiovascular disease generally have high level of LDL cholesterol[56] (known as the 'bad cholesterol') and low levels of HDL cholesterol (known as the 'good cholesterol'). Arteriosclerosis (hardening of arteries) and high cholesterol usually occur together. Exposure to sunlight is effective in lowering the cholesterol, due to genesis of vitamin D_3. Besides this since 1,25-$(OH)_2$-D_3 plays an important role in calcium homeostasis, which in turn is important for proper functioning of heart; 1,25-$(OH)_2$-D_3 and analogues are looked upon as potential drug candidates for the treatment of various cardiovascular diseases.

5.5 Tuberculosis

Research has shown that 1,25-$(OH)_2$-D_3 restricts the growth of *Mycobacterium tuberculosis* in macrophages.[57] Since considerable fraction of the world's population is infected with *M. tuberculosis*, measures that might curtail this infection, such as avoiding vitamin D deficiency, need to be a global priority.

6. Literature reports of the Synthetic approaches towards 1α,25-$(OH)_2$-D_3

1α,25-Dihydroxyvitamin D_3 is the most active natural metabolite of vitamin D. The overwhelming biological activities associated with the molecule have given rise to intense synthetic interest in the molecule, since; the chemical synthesis is the only means to supply sufficient quantities and to create more effective compounds. Several research groups across the world have been involved in the synthesis of this molecule and its analogues and excellent reviews have appeared in the literature. [58] Some of the major synthetic routes utilized to synthesize the hormone 1,25-$(OH)_2$-D_3 and its various analogues are the eight methods depicted in figure below (Figure 7).

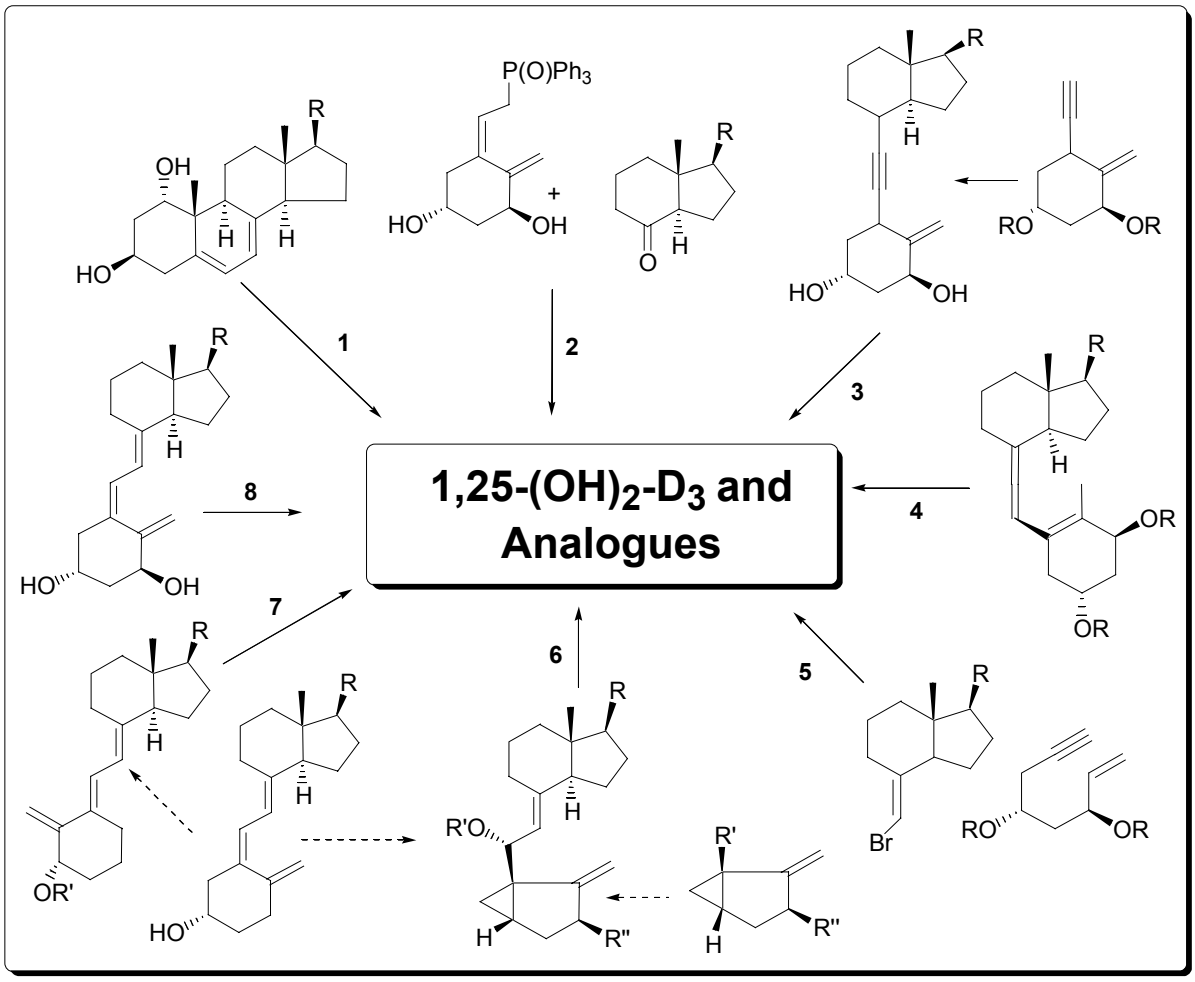
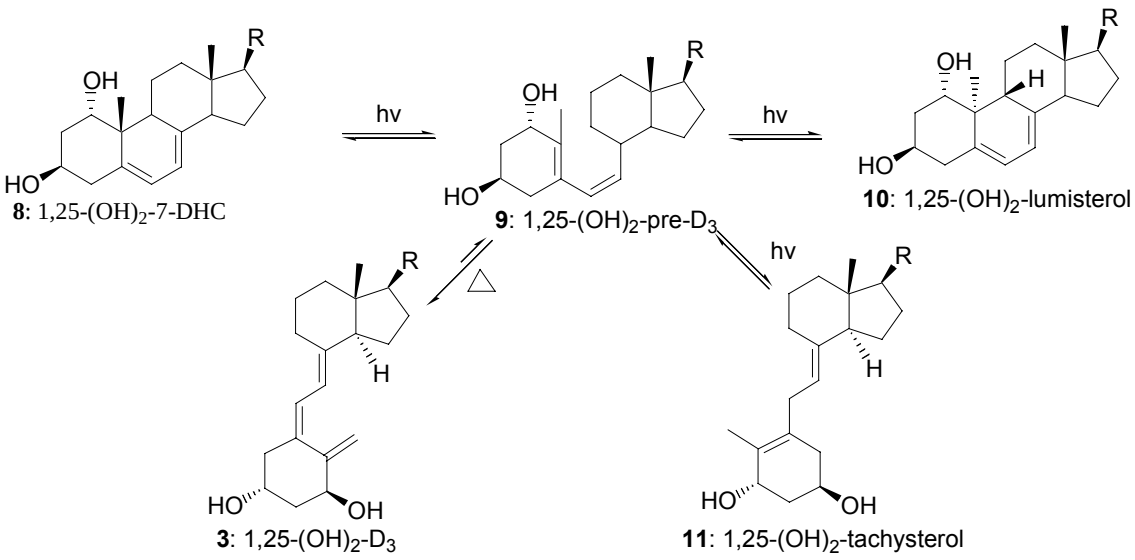


Figure 7. Major synthetic routes to 1,25-$(OH)_2$-D_3

6.1 Biomimetic Photochemical approach

This is the classical approach based on the biosynthesis of vitamin D and still remains the main industrial method for its synthesis.[59] Both Vitamin D_3 and 1,25-$(OH)_2$-D_3 have been prepared by this method. For the synthesis of 1,25-$(OH)_2$-D_3, it entails the photochemical ring opening of a 1α,25-dihydoxylated derivative of 7-dehydrocholesterol (7-DHC itself being used for the synthesis of vitamin D_3), initially producing a previtamin, which is easily thermolysed to the 1,25-$(OH)_2$-D_3. In general the yield of previtamins, and hence the vitamins obtained from the provitamins is low, partly because of the photolytic conversions of the previtamin to tachysterols, lumisterols and other irradiation products (Scheme 4).[60]

Scheme 4. Photochemical synthesis of 1,25-$(OH)_2$-D_3



It was later determined that re-irradiation of the photolysis mixture in the presence of fluorenone as triplet sensitizer afforded previtamin D as a major component.[61]

The influence of wavelength on product distribution has been studied in detail. Initially, it was found that employment of light of 295 nm wavelength afforded the maximum yield of 1,25-$(OH)_2$-pre-D_3, the calculated composition of the mixture being 1% 7-DHC, 70% 1,25-$(OH)_2$-pre-D_3, 26% 1,25-$(OH)_2$-tachysterol, and 3% 1,25-$(OH)_2$-lumisterol. Later, Duben showed that a two step direct irradiation Scheme, first using light of 254 or 300 nm followed by the light of >300 nm, gave an 83% yield of 1,25-$(OH)_2$-pre-D_3 at 95%

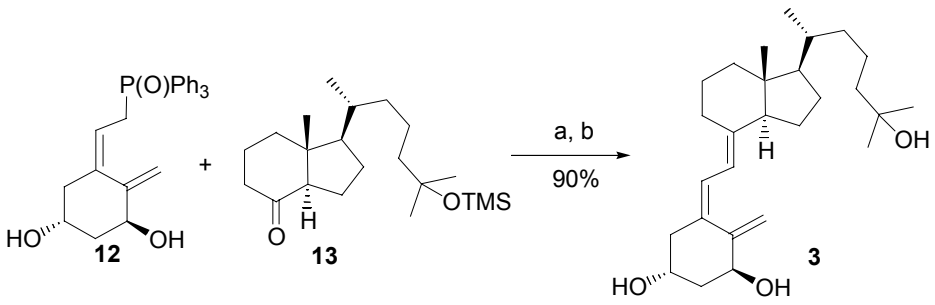
conversion of 1,25-$(OH)_2$-7-DHC.[62] On a preparative scale the two step irradiation, first at 254 nm and then at 350 nm light, gave a 66% isolated yield of 1,25-$(OH)_2$-pre-D_3, which was converted to 1,25$(OH)_2$-D_3 in an overall 50% yield.

6.2 The Horner-Wittig olefination approach

Initial attempts towards the total synthesis of 1,25-$(OH)_2$-D_3 did not involve direct construction of the conjugated triene system.[63] The first approach to the direct construction of the triene was reported by Lythgoe *et al*.,[64] employing Horner-Wittig olefination. The actual synthesis of 1,25-$(OH)_2$-D_3 using this approach was affected later by others by the reaction of the *(Z)*-allylic phosphine oxide and the appropriate bicyclic ketone (Scheme 5).[65]

The reaction proceeds with complete stereoselectivity, the $\Delta^{5,6}$-double bond of the product retaining the natural *Z* geometry of the precursor and the newly formed $\Delta^{7,8}$-double bond assuming natural *E* geometry. An advantage of this coupling approach is its convergency.

Scheme 5. Lythgoe's Horner-Wittig olefination approach

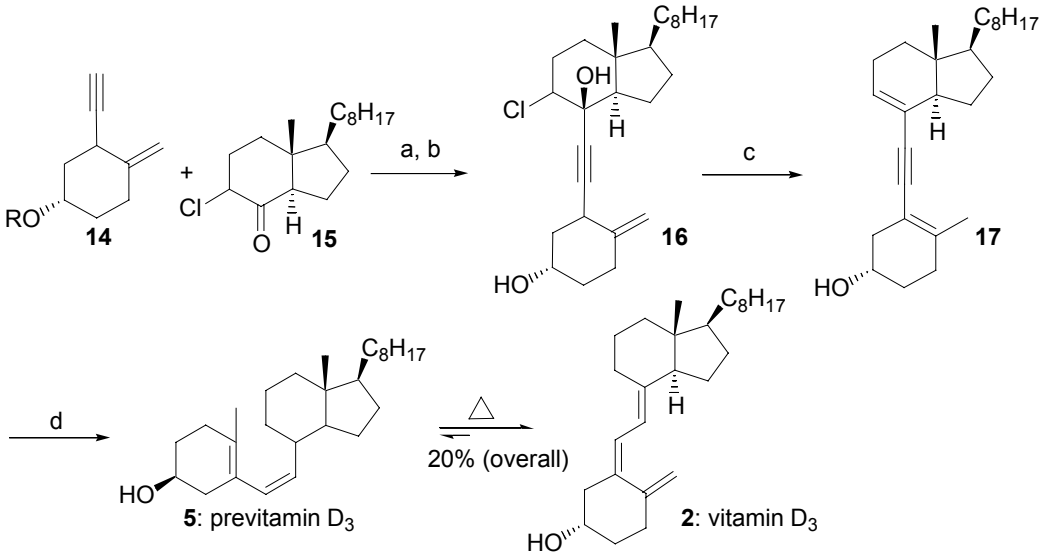


Reagents and conditions: a) n-BuLi, THF, - 78 ℃. b) TBAF, THF, rt.

6.3 A plus CD cross-coupling approach

This is another convergent approach developed by Lythgoe.[66] It involves reacting 8α-chloro hydrindone with the lithium derivative of enyne to give, after deprotection, the vicinal chlorohydrin. Elimination (using Cr^{+2}) generated the $\Delta^{8,9}$-double bond, which was semi hydrogenated over Lindlar's catalyst to give pre-D_3.

Scheme 6. Lythgoe's original cross-coupling approach

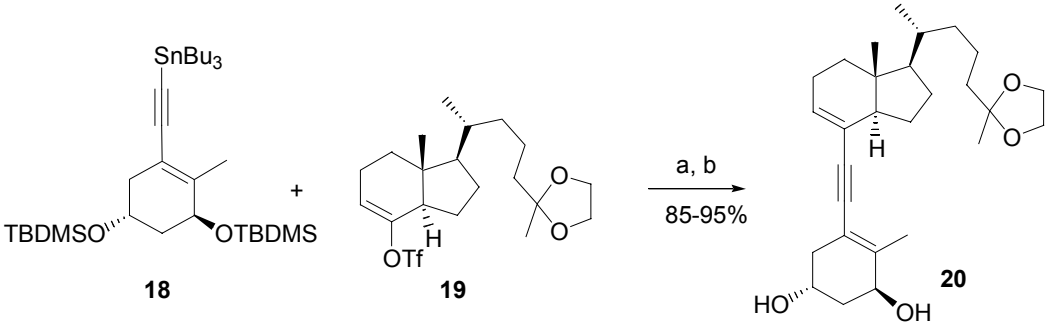


Reagents and conditions: a) n-BuLi, ether, 0 °C. b) TBAF, THF, rt. c) $CrCl_2$, THF, rt. d) H_2, $Pd/BaSO_4$, EtOH, rt

The latter undergoes thermal rearrangement to vitamin D_3. The overall yield was about 20%. The main difficulty with this approach was the troublesome preparation of chloro hydrindone **15** (Scheme 6).

Subsequent developments from the Mouriño-Castedo laboratory, greatly improved the efficiency of this approach. Using Stille's coupling protocol, dienyne was prepared by palladium catalyzed coupling of Grundman's type enol triflate **19** with the A ring enyne or the suitable derivatives. The coupling involves the use of a catalytic amount of $Pd(PPh_3)_2Cl_2$ (2-3 mol %) in DMF (75 °C) in the presence of triethylamine (3-4 eq.) affording dienyne in 85-95% yield (Scheme 7).[67]

Scheme 7. Mouriño's modified cross-coupling approach



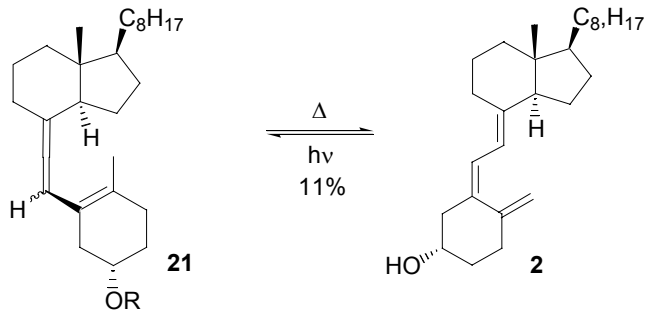
Reagents and conditions: a) $Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 75 °C. b) TBAF, THF, rt

The coupling reaction is quite mild and compatible with the presence of a carbonyl group in the molecule, but the presence of free alcohol considerably decreased the yield of the coupled product.

6.4 The vinylallene approach

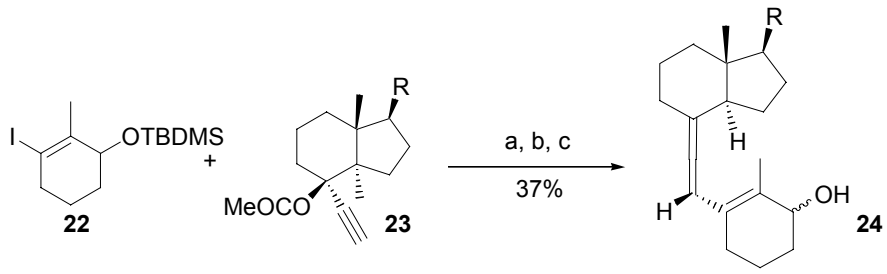
During the study of photochemistry of vitamin D_3, Havinga *et al*.[68] isolated two diastereomeric vinyl allenes as minor photoproducts. They observed that, under gas chromatographic conditions (225 °C), it exhibited a profile characteristic of vitamin D_3. Later Havinga's primary hypothesis that the vinylallenes undergo initial [1,5]-sigmatropic hydrogen shift to vitamin D_3 was investigated in detail in the Okamura laboratory, leading to the novel synthetic approach to vitamin D and its analogues (Scheme 8).[69]

Scheme 8. Vinylallene approach for vitamin D_3



Several approaches leading to the synthesis of vitamin D type vinylallene have been developed over the years. Four general routes have proven useful for effecting coupling of the A and CD fragments. In the first approach known as A-ring vinyl cuprate route (6*R*)-allene was produced essentially exclusively (Scheme 9).[70]

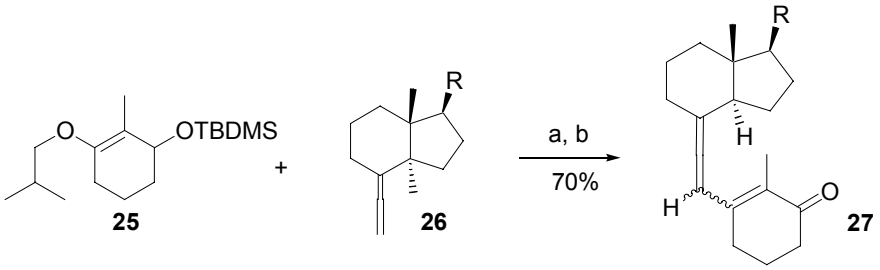
Scheme 9. Synthesis of vinylallene by A-ring cuprate approach



Reagents and conditions: a) t-BuLi (2 eq.), THF, –78 °C. b) CuI.3(n-Bu_3P), THF, –78 °C. c) TBAF, THF, rt.

The second approach known as the allenyllitium method is less capricious than method A but both the diastereomers of the allene were produced (Scheme 10).[71]

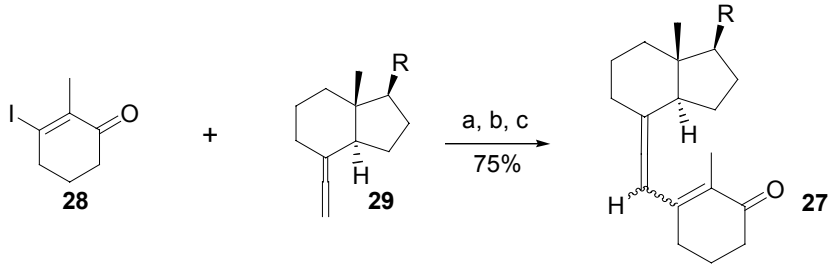
Scheme 10. Synthesis of vinylallene by allenyllitium approach



Reagents and conditions: a) t-BuLi, Et_2O, –78 °C to rt. b) 1 M HCl, rt.

The third approach known as the Pd(0) catalyzed allenylcuperate method was found to be necessary when using A ring iodide, but only 2.2/1 ratio of 6R/6S allenes was observed (Scheme 11).

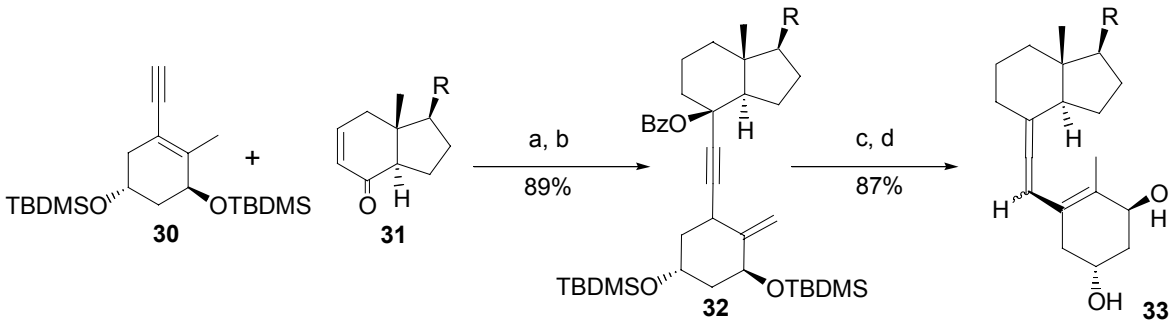
Scheme 11. Synthesis of vinylallene by allenyl cuprate approach



Reagents and conditions: a) t-BuLi, THF, –78 °C. b) CuI, THF, –78 °C. c) $Pd(PPh_3)_4$ (cat.), CH_2Cl_2, rt.

The fourth approach known as the stanylcuprate approach is a three-step sequence with the key step being a triphenylstannyl cyanocuprate SN2' displacement reaction of propargyl benzoate. This approach was anticipated to be the attractive approach for the preparation of (6S)-vinylallene (Scheme 12). [72]

Scheme 12. Synthesis of vinylallene by stanylcuprate approach



Reagents and conditions: a) n-BuLi, Et_2O, –78 °C to rt. b) PhCOCl, –78 °C to rt. c) $(Ph_3Sn)_2Cu(CN)Li_2$, THF, Et_2O, 0 °C. d) TBAF, THF, rt.

6.5 Seco-A-Ring Tandem Palladium-Catalyzed Cyclization Approach

This method was largely developed by Trost *et al*. In order to develop a novel approach to 1,2-dialkyledenecycloalkanes, Trost has explored in detail the palladium catalyzed cycloisomerization of enynes as outlined in the following figure (Figure 8).[73]

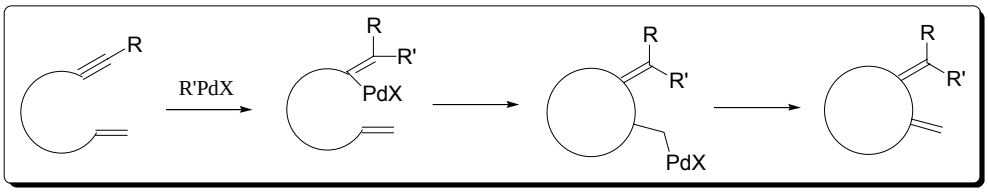
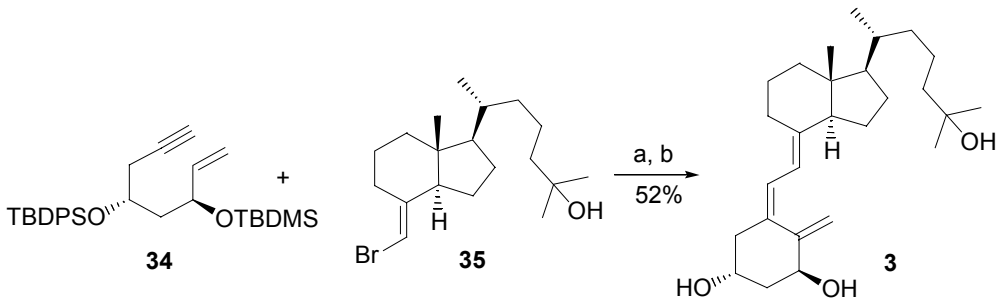


Figure 8. Pd-catalyzed cycloisomerization of enynes

A direct application of this discovery led to a conceptually novel synthetic approach to vitamin D, in which ring A is created from an acyclic unit in which the $\Delta^{5(6),\ 10(19)}$-diene is created from the enyne cyclization and the $\Delta^{7,8}$-double bond with the CD-ring moiety in the alkylative cyclization (R'PdX) (Scheme 13).[74]

Scheme 13. Trost's approach



Reagents and conditions: a) $(dba)_3Pd_2.CHCl_3$, PPh_3, Et_3N, $PhCH_3$, reflux. b) TBAF, THF, reflux.

This concept offers a quite distinct modular approach to the vitamin D system whereby creation of the requisite triene, formation of the A ring, and attachment of this entire unit to the CD fragment occurs in a single reaction (Intramolecular carbometallation). The reaction proceeds through the same common mechanism as depicted in Figure 9.

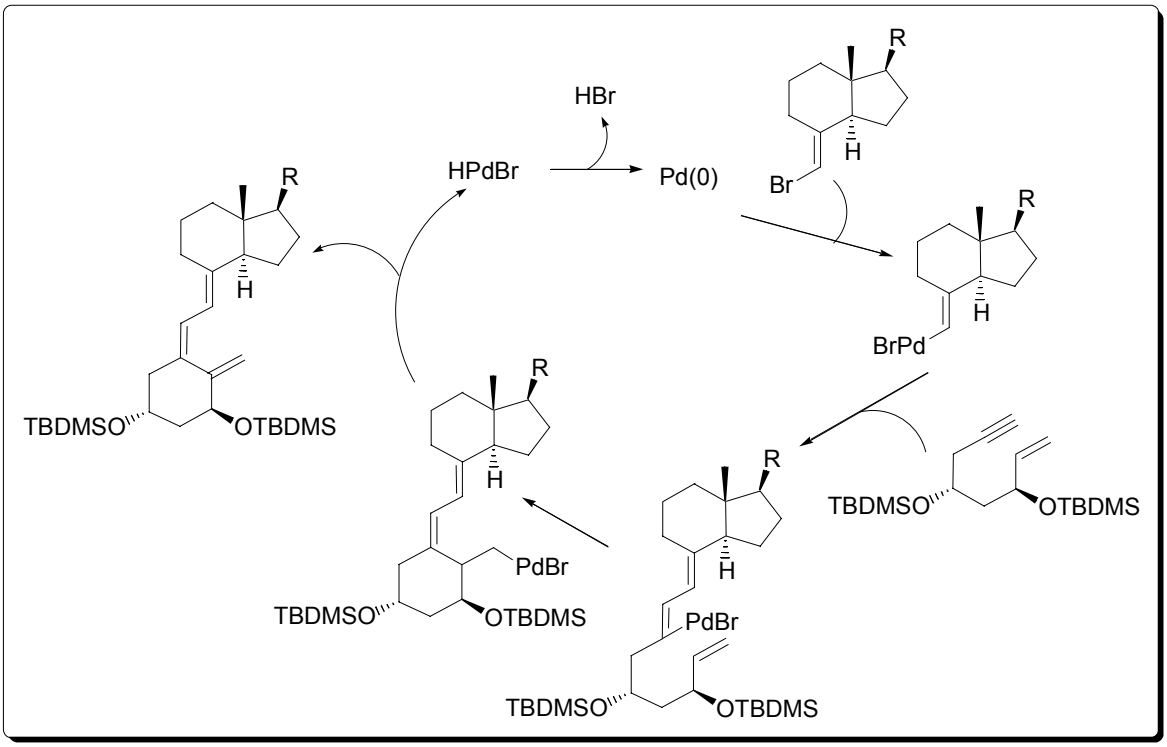


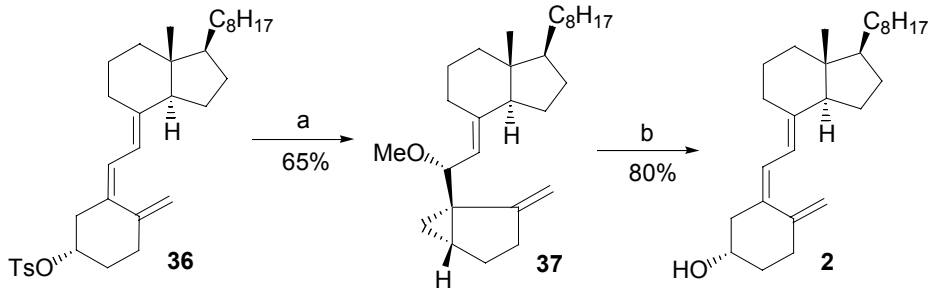
Figure 9. Catalytic cycle of Trost's method

Initial oxidative insertion of Pd(0) to the labile C_7-Br bond is followed by the *cis* addition to the alkyne to give an intermediate with vinyl Pd moiety. Bond formation between C_{10} and C_5 closes the A-ring. Reductive elimination of the HPdBr liberates the product and regenerates the catalyst. The CD-rings vinyl bromide was prepared in high *E* selectivity using Trost`s Wittig Olefination Procedure. This approach was subsequently utilized by other groups, especially to test the feasibility of other metals to catalyze such annulations.

6.6 Mazur's cyclovitamin D solvolysis approach

While attempting to functionalize vitamin D by protecting its reactive triene system, Mazur uncovered the interesting inter conversion between vitamin D and its *i*-steroid form, 3,5-cyclovitamin D.[75] Treatment of vitamin D_3 tosylate with sodium acetate in methanol/acetone gave 6(*R*)-cylovitamin D as the major product. When the cyclovitamin was treated with catalytic amount of *p*-toulenesulfonic acid in aqueous dioxane the conjugated triene system was restored yielding vitamin D_3 as a major product (Scheme 14).

Scheme 14. Mazur's cyclovitamin D approach



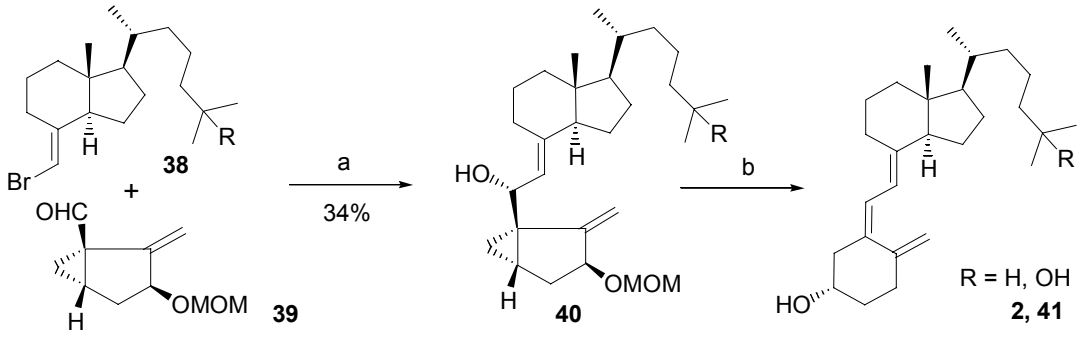
Reagents and conditions:a) NaOAc, MeOH/acetone (4:1), reflux. b) 75% aq. Dioxane, p-TsOH (0.3 eq.), reflux.

On the basis of Mazur's observation on the vitamin-cyclovitamin conversion, several approaches towards vitamin D derivatives hve been developed as outlined below.

6.6.1 Fukumoto-Kametani Method

In this approach the cyclovitamin was constructed as a mixture of stereoisomers in 34% yield by addition of lithio anion to the chiral A-ring aldehyde. The vinyl lithium was generated by *t*-BuLi treatment of the corresponding bromide (Scheme 15).[76]

Scheme 15. Fukumoto-Kametani approach

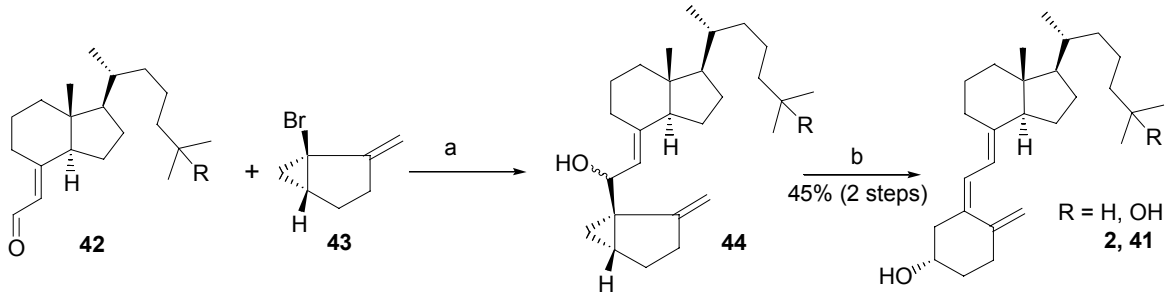


Reagents and conditions: a) t-BuLi, THF, – 78 °C. b) p-TsOH, dioxane, H_2O, reflux.

6.6.2 Wilson's initial approach

The initial method that Wilson adapted was the umpolung version of the Fukumoto-Kametani sequence. The 1-deoxycyclovitamin D was synthesized by addition of the lithiated A ring to the CD-ring aldehyde (prepared from Grundman's ketone) as shown in the scheme below (Scheme 16).[77]

Scheme 16. Wilson's first approach

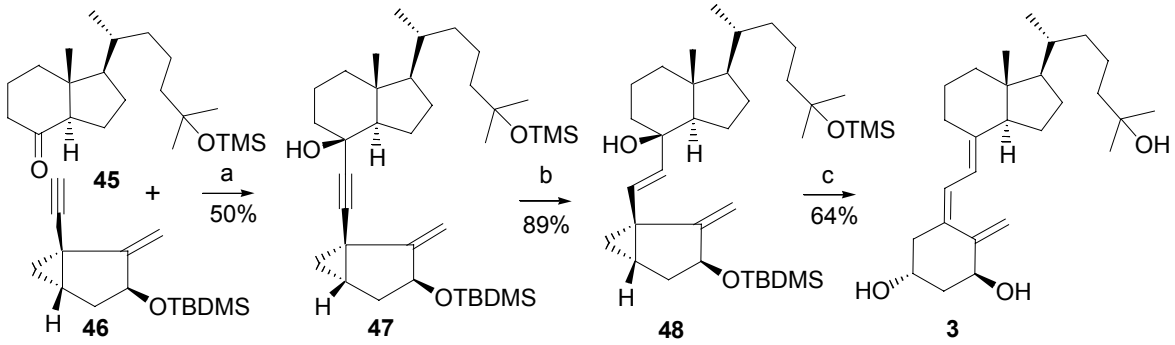


Reagents and conditions: a) t-BuLi, THF, – 78 °C. b) p-TsOH, dioxane, H_2O, reflux.

6.6.3 Wilson's New Approach

Wilson's observation on the acid solvolytic behavior of the vinylogous cyclovitamin established an excellent approach to vitamin D.

Scheme 17. Wilson's second approach



Reagents and conditions: a) n-BuLi, THF, – 78 °C. b) LAH, NaOMe, THF, reflux. c) p-TsOH (1 mol %), dioxane/H_2O (1:1), reflux.

The key step in construction of the cyclovitamin is the coupling of lithium acetalide with the 25-oxygenated Grundman's ketone. 1,25-$(OH)_2$-D_3 was then obtained by reduction-elimination sequence as shown in Scheme 17.[78]

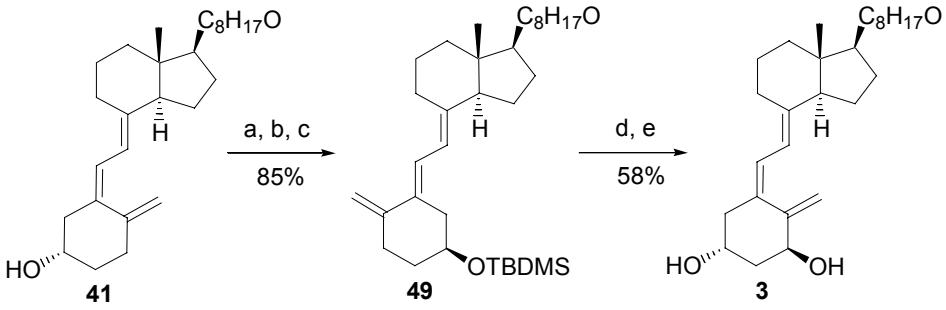
Even though the chemistry involved in the Mazur's method has been explored to a considerable extent, the difficulties in preparation of the desired A ring synthons and cost of the chiral material involved has severely hampered the widespread use of this method.

6.7 Direct Hydroxylation of Vitamin D

This method has gained importance in recent years, due to availability of the methods to prepare the vitamin D skeleton and since the preparation of A ring of vitamin D_3

is easier than that of 1,25-$(OH)_2$-D_3. This method entails regio- and stereoselective C-1 hydroxylation and if necessary, 25-hydroxylation of vitamin D_3 to give 1,25-$(OH)_2$-D_3. For the introduction of the C-1 hydroxyl group, the simple allylic hydroxylation of the triene of D_3 has thus far not been practical because of the difficulty in controlling the site, extent, and stereochemistry of the hydroxylation. However, direct hydroxylation of a TBDMS protected 5,6-trans geometric isomer of vitamin D was reported to be very successful as shown in the scheme below (Scheme 18).[79]

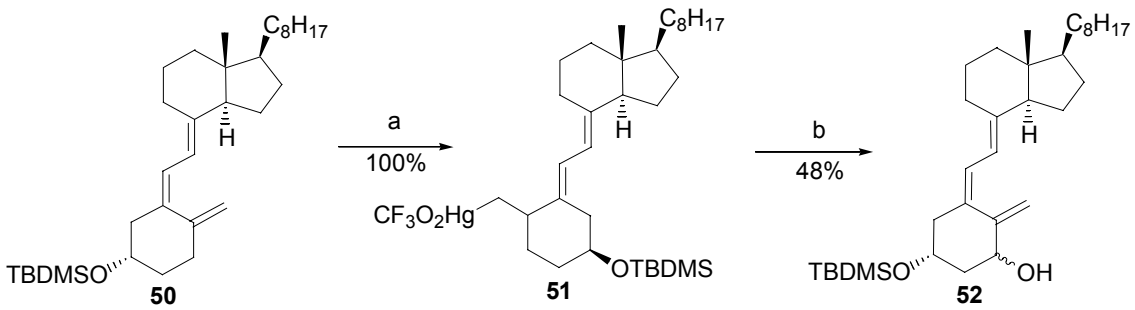
Scheme 18. Synthesis of 1,25-$(OH)_2$-D_3 by hydroxylation of vitamin D_3



Reagents and conditions: a) SO_2, C_6H_6, H_2O, rt. b) EtOH, $NaHCO_3$, reflux. c) TBDMSCl, imidazole, DMF, rt. d) SeO_2 (0.7 eq.), NMO *(4 eq.), CH_3OH, CH_2Cl_2, reflux. d) TBAF, THF, reflux.*

An alternative route to the direct hydroxylation of 5,6-*trans* vitamin D_3 was later reported by Reischl.[80] Treatment of vitamin D_3 with $Hg(OCOCF_3)_2$ in dry THF yields quantitatively, a single organomercurial compound, which on treatment with potassium *tert*-butoxide gave 1-hydroxylated compound with diastereomeric mixture of 5:1 favoring the desired α-OH. It is worthwhile to mention here that 1:1 diastereomeric mixture was obtained when free 3-OH was used instead of TBDMS-protected one (Scheme 19).

Scheme 19. Reischl's approach for direct hydroxylation



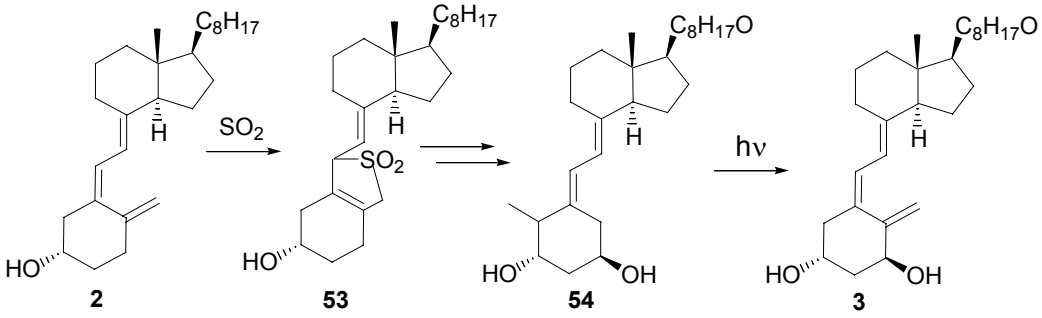
Reagents and conditions: a) $Hg(O_2CF_3)_2$, THF, rt. b) t-BuOK, PhH, reflux.

6.8 Direct modification of vitamin D via triene protection

The primary requirement for such a method is the preparation of the derivative in which the heat-, light-, and air-sensitive triene unit is protected in such a way that the oxidation reaction, or the other transformations, can be performed in ring A as well as the side chain. Secondly the vitamin D triene system should be easily recoverable after such transformations. Various protecting groups have been utilized for this purpose.

The Yamada[81] and Zbiral[82] groups independently established that vitamin D reacts spontaneously and quantitatively with liquid sulfur dioxide at its $\Delta^{5,10(19)}$-diene unit to give α- and the β-face adducts in about 1:1 ratio. After the desired transformations on these sulfur dioxide can be extruded by thermolysis to give 5,6 trans vitamin D_3, which can be photochemically isomerized to the normal vitamin D_3 (Scheme 20).

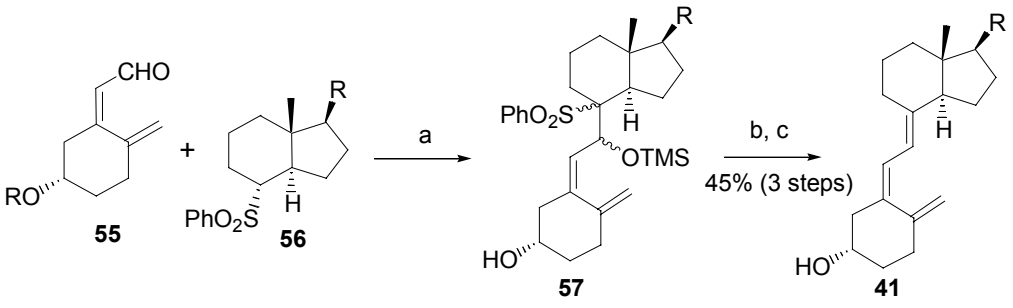
Scheme 20. Synthesis of 1,25-$(OH)_2$-D_3 from vitamin D2 via triene protection



6.9 Other Synthetic Approaches

Besides the common methods discussed above, the synthesis of 1,25-$(OH)_2$-D_3 and derivatives has also been achieved using various other approaches. Most of these approaches are similar to the A plus CD cross coupling approach discussed above.

Scheme 21. Lythgoe's Julia olefination approach

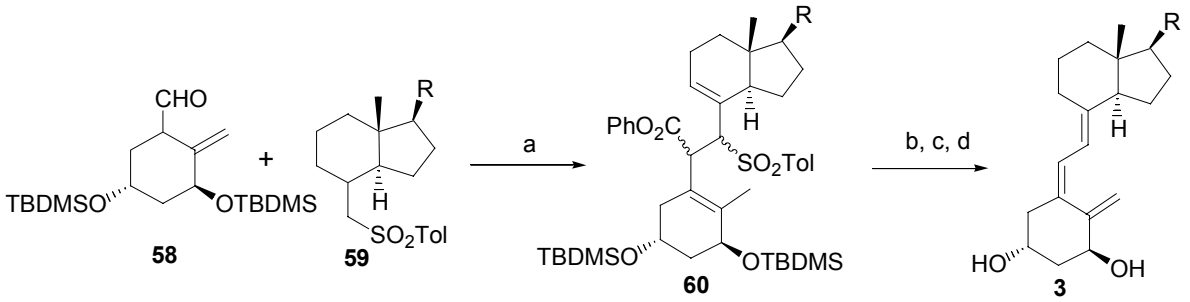


Reagents and conditions: a) n-BuLi, THF, –78 °C, TMSCl, –78 °C to rt. b) 5.7% Li(Hg), MeOH, THF, –20 °C. c) aq. KOH, rt.

The Julia olefination approach, which was first reported by Lythgoe, is the conceptually similar approach to the Horner-wittig olefination approach as depicted by the scheme below (Scheme 21).[83]

The same strategy was later used for the C_6-C_7 bond formation through coupling of CD-ring methylene sulfone with A-ring α,β-unsaturated aldehyde as shown in the scheme below (Scheme 22).[84]

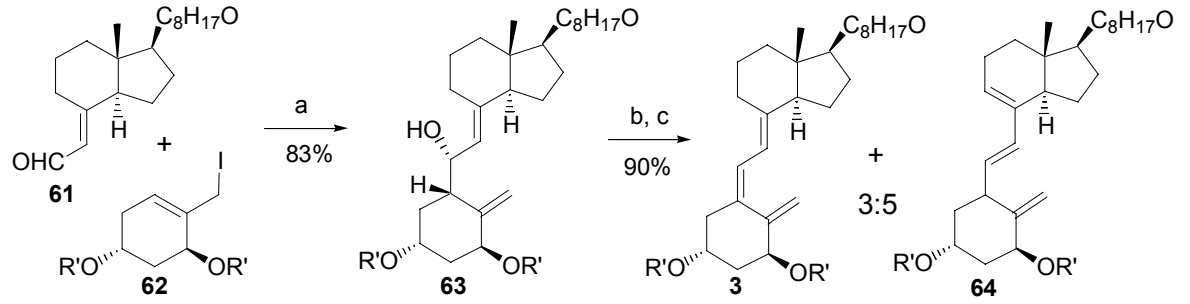
Scheme 22. Alternative Julia olefination approach



Reagents and conditions: a) ^{n}BuLi, THF, –78 °C, BzCl, –78 °C to 0 °C. b) Na(Hg), MeOH, THF, –20 °C. c) 9-fluorenone, PhH, hν, –10 °C.

Takeno *et al*. developed a conceptually novel chromium (II)-mediated coupling of A-ring allyl iodide and CD-ring, α,β-unsaturated aldehyde. The highly diastereoselective Cr(II)-mediated addition of the allylic halide to the aldehyde was thought to give desired compound as a sole product. However, formation of substantial amount of 1,4-elimination product limits the broad applicability of this approach for constructing the triene unit of vitamin D (Scheme 23).[85]

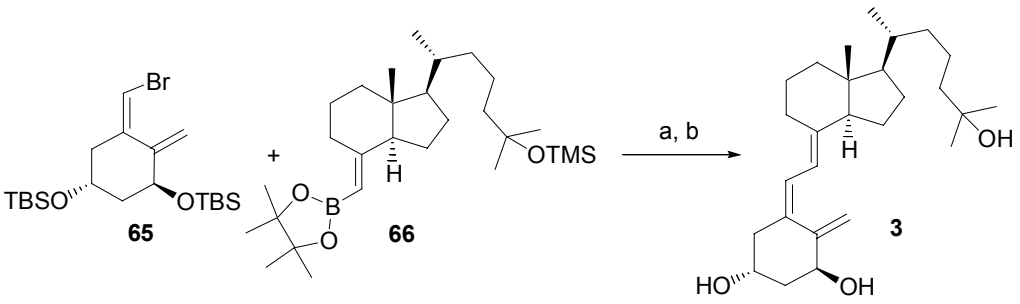
Scheme 23. Takeno's approach



Reagents and conditions: a) $CrCl_2$, THF, 0 °C to rt. b) $CuSO_4$ on silica gel, PhH, –50 °C. c) HF, MeOH, THF, rt.

Recently Sato *et al.* have reported a convergent approach for 1,25-$(OH)_2$-D_3 and analogues utilizing Suzuki-Miyaura coupling protocol (Scheme 24). [86]

Scheme 24. Sato's Suzuki-Miyaura coupling approach



Reagents and conditions: KOH, $PdCl_2$(dppf), THF, H_2O, rt. b) TBAF, THF, rt.

From the survey of the literature precedent, it is clear that the convergent approach involving the coupling of A-ring synthon to the hydrindane moiety, discovered by Lythgoe is one of the best approach for the synthesis of 1,25-$(OH)_2$-D_3 and analogues. The cross coupling approach (Method 6.3) is advantageous than the originally developed Horner-Wittig olefination approach (Method 6.2), since A ring synthon required is easier to prepare. Moreover, subsequent developments in the Mouriño-Castedo laboratory have greatly improved the efficiency of this approach. With the availability of excellent methods for coupling of A and CD-rings fragments the efficiency of the total synthesis depends on the efficient strategy for the preparation of each of the fragments. The subsequent chapters will discuss our endeavors towards developing a new approach for an efficient formal total synthesis of optically active 1,25-$(OH)_2$-D_3 and C-16 and C-12 modified analogues.

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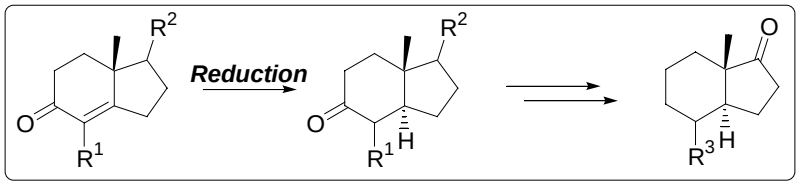
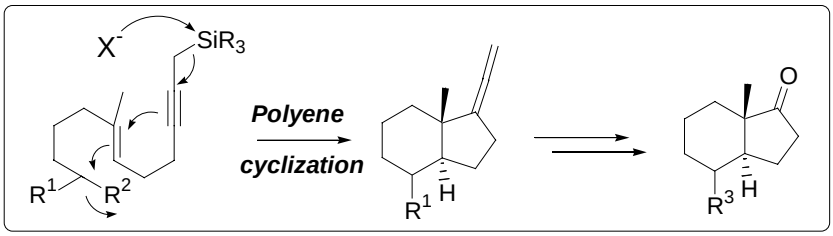
1. Introduction

trans-Hydrindane structural framework forms a common feature of steroids, vitamin D, higher terpenes and related natural products. These compounds have broad spectrum of biological activities, which makes them synthetically important targets. Development of new methodology for the construction of *trans*-hydrindane would be useful in the synthesis of all these compounds and hence is of much value. The main challenge in the synthesis of this moiety has been the construction of *trans* ring junction, which is thermodynamically less stable, compared to *cis* epimer. The importance of this moiety has led to the development of large number of synthetic approaches directed towards its synthesis.[1] In order to put our work in proper perspective it would be appropriate to briefly discuss the literature reports in this domain. The numerous strategies developed over the years for the synthesis of *trans*-hydrindane skeleton can be categorized into four classes based on the protocol used for its construction as shown below:

I. Reduction of the double bond at ring junction in hydrindene skeleton.

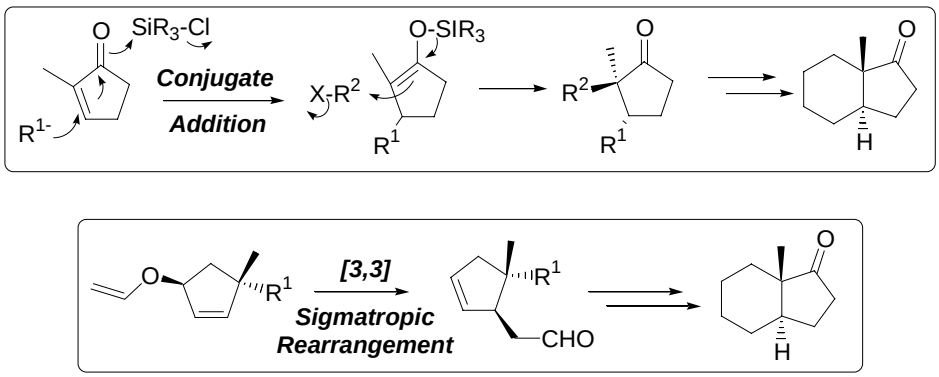


II. Direct one-step construction of the trans-hydrindane skeleton from acyclic precursors.

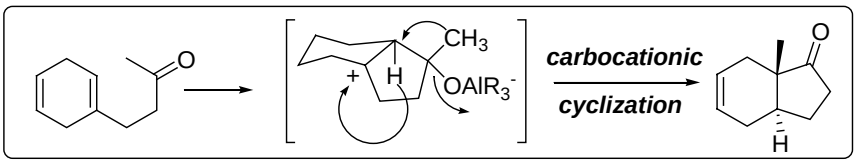


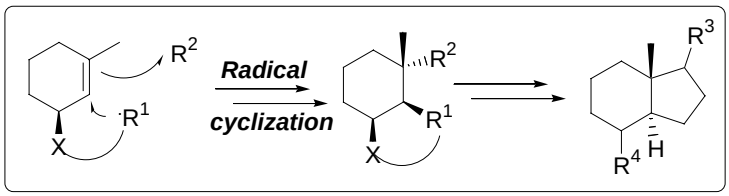
III. Stereoselective annulation approach.

a. Stereoselective annulation of six-membered ring over five-membered one.



b. Stereoselective annulation of five-memebered ring over six-membered one





IV. Miscellaneous approaches.

Some of the noteworthy examples pertaining to each class are briefly discussed in the following section.

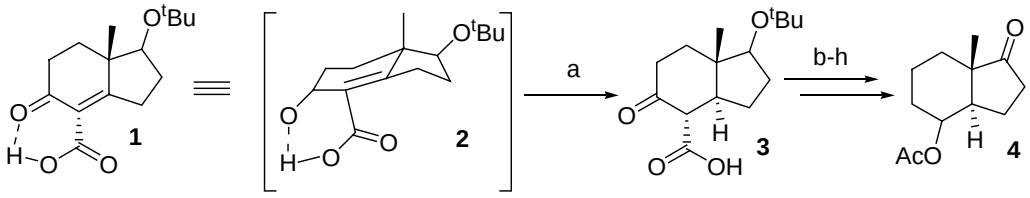
1.1 Reduction of the double bond at ring junction of the hydrindene skeleton

The stereoselective reduction of a double bond present either in the six-membered or five-membered ring of the hydrindene moiety constitutes the most explored approach. The common precursor for such approaches have been Hajos-Parrish-Wiechert (H-P-W) ketone or its derivatives, generally synthesized using the Robinson annulation protocol. The prominent methods utilized for the stereoselective reduction of double bond include the catalytic hydrogenation (heterogeneous and homogeneous), metal hydride reductions and the intramolecular hydrogen transfer.

Although, normal catalytic hydrogenation strategy of H-P-W ketones produces thermodynamically stable *cis* product, the derivatives of these molecules carrying bulky substituent at C-8* position are reported to give higher amounts of *trans* product.[2] Based on this principle, numerous reports have appeared in the literature over the years.

In this context, Uskokovic *et al.,* demonstrated that, the reduction of H-P-W ketone **1**, carrying a carboxylic acid group on C-8 (steroid numbering), leads to the formation of *trans*-hydrindane skeleton **3**. This stereospecificity is explained by considering the transition state **2**, which involves the formation of the pseudo B ring due to the hydrogen bonding between the carbonyl and the carboxyl groups. It is suggested that the hydrogen-bonded structure **2** would most certainly prefer the half chair conformation to relieve steric interactions between the peudo B ring and the five membered ring. Therefore, hydrogenation of the unsaturated β-keto acid **1** having rather planer conformation favors addition of hydrogen from the less hindered bottom side of the molecule opposite to the methyl group. Compound **3**, thus formed, was finally converted to the desired **4** by following series of steps as depicted in Scheme below (Scheme 1).[3]

Scheme 1. Catalytic hydrogenation of C-8 substituted hydrindenone

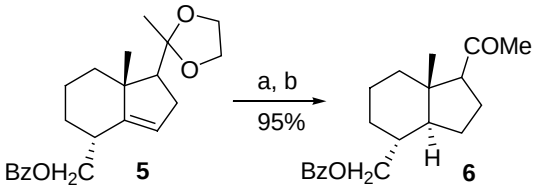


Reagents and conditions: a) H_2, Pd-$BaSO_4$, EtOH, rt. b) $NaBH_4$, EtOH, rt, 72%. c) MeLi, Et_2O, THF, reflux. d) NaI, DMF, pyridine, 100 °C, 96% (2 steps). e) H_2, 10% Rh-C, EtOH, 25 °C, 82%. f) H_2O_2 (90%), F_3CCOOH, CH_2Cl_2, 25 °C, 57%. g) Me_3SiI, CCl_4, 25 °C. h) PCC, CH_2Cl_2, 25 °C, 84%.

Although, similar strategy of catalytic hydrogenation of **5** is also reported to give corresponding *trans* product **6** exclusively, no explanation is offered for the observed selectivity in the hydrogenation step (Scheme 2).[4]

*Steroid numbering has been followed throughout this section.

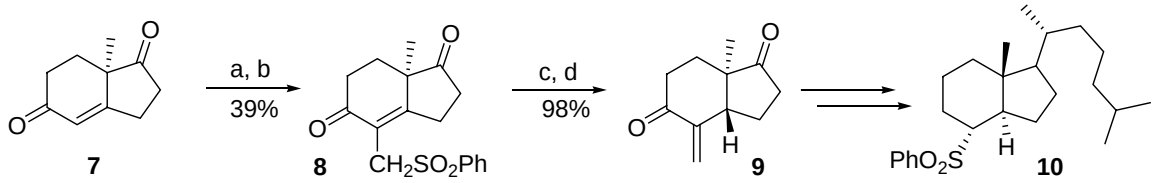
Scheme 2. Catalytic hydrogenation of C-8 substituted 14(15)-hydrindene



Reagents and conditions: a) H_2, Pd/C, $NaHCO_3$, rt. b) cat. p-TsOH, acetone, rt.

Kametani and coworkers have shown that the catalytic hydrogenation of (-)-H-P-W dione derivative **8**, which was obtained from compound **7**, produces the *trans*-hydrindane derivative **9**, however, no explanation is presented for the factors responsible for the exclusive formation of **9** (Scheme 3).[5]

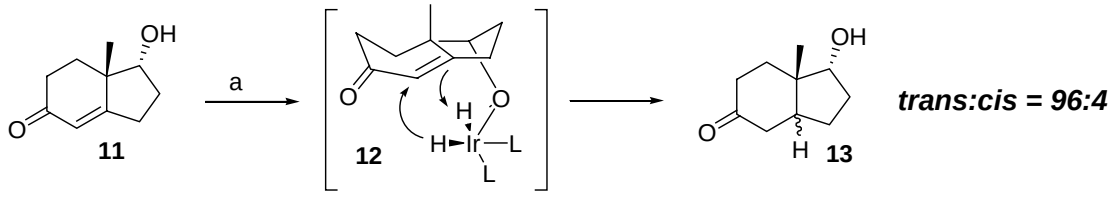
Scheme 3. Catalytic hydrogenation of (-)-H-P-W dione



Reagents and conditions: a) HCHO, PhSH, $N(CH_2CH_2OH)$, 60 ℃. b) m-CPBA, CH_2Cl_2, rt. c) H_2, Pd-C, AcOH, MeOH, rt. D) DBU, PhH, rt.

Homogeneous catalytic hydrogenation using Crabtree catalyst has also been examined for the stereoselective reduction of the double bond of H-P-W ketone derivatives such as **11** by Stork and Kanhe. **13** is produced as a mixture of *trans:cis* in the ratio of 96:4 from **11** by this method. It was also noticed that the substrate lacking 17-α-hydroxy group, or a substrate having a carbonyl or a β-hydroxy group in its place, favored *cis* isomer. The selectivity has been shown to arise due to the coordination of the metal with the hydroxyl group on C-17 as evident from the conformational diagram **12** (Scheme 4).[6]

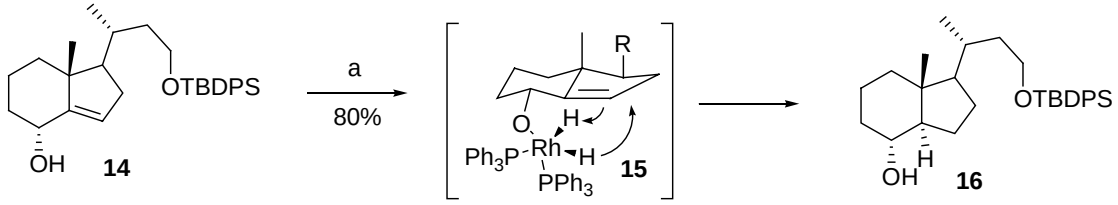
Scheme 4. Homogeneous hydrogenation using Crabtree catalyst



Reagents and conditions: a) H_2, $[Ir(cod)py(Pcy_3)]^+PF_6^-$ (20 mol%), CH_2Cl_2, rt.

Subsequently a Japanese group has found out that the substrate of type **14** in which the hydroxyl group is at C-8 position, on reduction with Wilkinson's catalyst produces exclusive *trans*-product **16**. The selectivity in the hydrogenation step is again attributed to the coordination of the hydroxyl group with the metal (Scheme 5).[7]

Scheme 5. Homogeneous hydrogenation using Wilkinson's catalyst

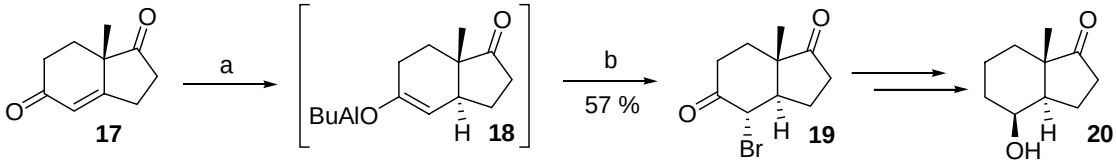


Reagents and conditions: a) H_2, $RhCl(PPh_3)_3$, benzene, rt.

Although, hydrogenation approach has been explored extensively for the synthesis of *trans*-hydrindane system, selectivity is found to depend on the nature of the substituents on C-8 and C-17 of the substrate ketone. Therefore, such approaches do not have general applicability for the synthesis of structurally modified analogues of *trans*-hydrindane system.

Metal hydrides have also been explored for the stereoselective reduction of H-P-W ketone **17** using alkyl copper-DIBAH reducing system which has led to the reductive addition of the hydride with the simultaneous generation of the diisobutylaluminium enolate **18** with *trans* ring junction. Reaction of the enolate **18** with bromine followed by the sequence of steps produced *trans*-hydrindane system **20**. The stereoselectivity was shown to arise from the bulk of the reagent, due to which it preferably attacks from the less hindered bottom face opposite to that of the methyl group (Scheme 6).[8]

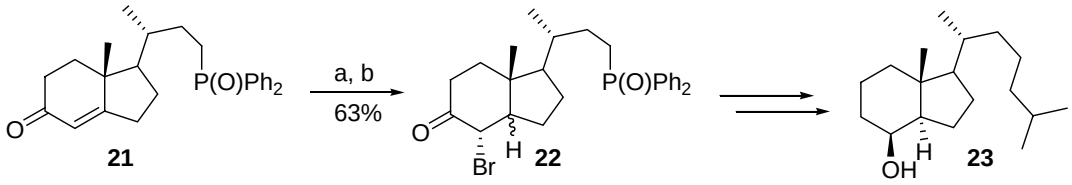
Scheme 6. Hydride reduction using copper-DIBAH reducing system



Reagents and conditions: a) t-BuLi, CuI, DIBAH, HMPA, –50 °C. b) Br_2.

A similar strategy was also adopted by Haynes *et al*. to reduce H-P-W type ketone **21** utilizing MeMgI-CuCN-DIBAH-Br_2 combination which produced **22** in 98:2 ratio of *trans:cis*. Compound **22** was finally converted to the desired *trans*-hydrindane system **23** by a similar procedure as reported by Daniewski *et al.* (Scheme 7).[9]

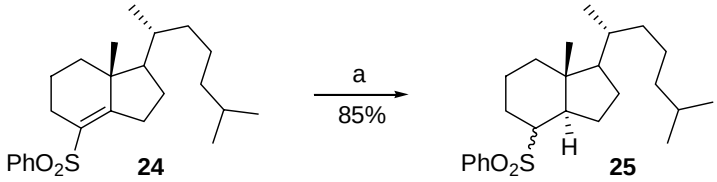
Scheme 7. Hydride reduction using MeMgI-CuCN-DIBAH-Br_2 combination



Reagents and conditions: a) MeMgI, CuCN, DIBAH, THF, HMPA, –78 °C to rt. b) Br_2

Reduction of vinyl sulfone derivative of hydrindene system **24** with LAH in THF at reflux temperature has been shown to yield corresponding saturated sulfone **25** with *trans*-ring junction (Scheme 8).[10] This protocol has been utilized by Wicha *et al.* to synthesize

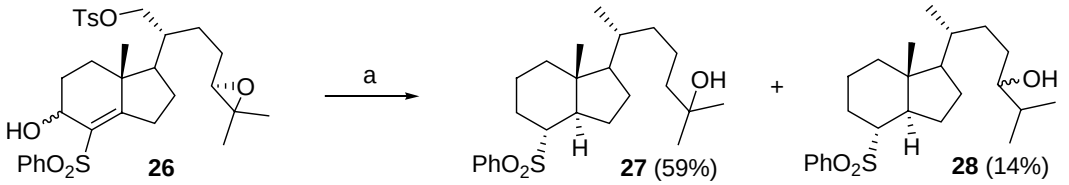
Scheme 8. Hydride reduction using LAH



Reagents and conditions: a) LAH, THF, reflux.

27 from sulfone **26**. The noteworthy feature of the Wicha's approach has been the realization of deoxygenation, olefin reduction and the epoxide opening in a single step, although the mixture of isomers **27** and **28** were obtained in the ratio of 59:14 (Scheme 9).[11]

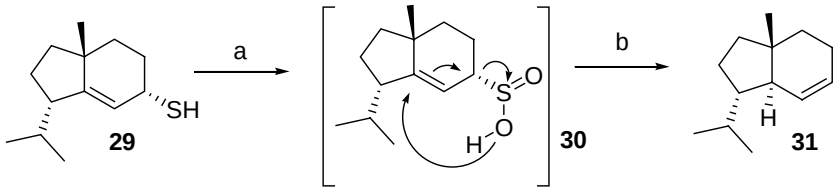
Scheme 9. Wicha's protocol



Reagents and conditions: a) LAH, THF, reflux.

Corey and Engler have reported the synthesis of *trans*-hydrindane derivative **31** via intramolecular hydride transfer in **30** by fragmentation of the sulphinic acid. The stereospecific formation of *trans*- product is due to the cyclic six-membered transition state, which occurs despite strong shielding by the α-isopropyl group as depicted in Scheme 10.[12]

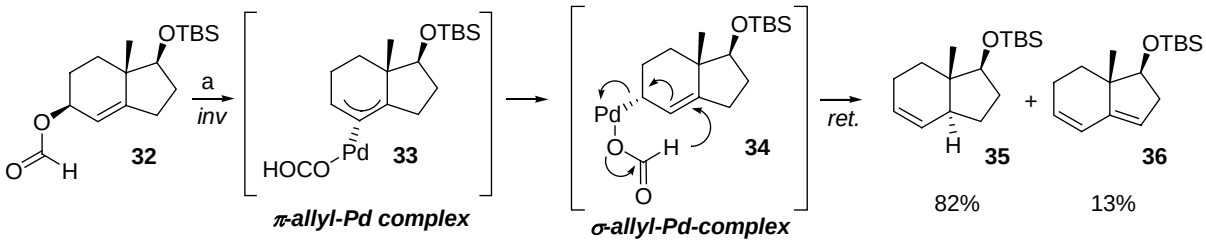
Scheme 10. Intramolecular hydride transfer by fragmentation of sulphinic acid



Reagents and conditions: a) MCPBA, CH_2Cl_2, –90 °C. b) 40-50 °C.

Analogous to above strategy, Mandai, Tsuji and coworkers have developed a general synthetic approach to synthesize *trans*-fused decalin as well as hydrindane system, employing Pd-catalyzed hydrogenolysis of the formate derivatives of the corresponding alcohols. This reaction which is exemplified here by taking **32** as an example, proceeds involving π-allyl-palladium complex **33** followed by σ-allyl-palladium complex **34** and elimination to produce **35** in 82% yield, along with 13% of **36** (Scheme 11).[13]

Scheme 11. Pd-catalyzed intramolecular hydride transfer

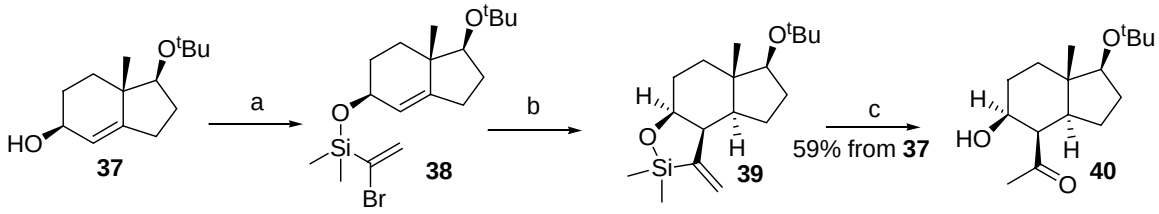


Reagents and conditions: a) $Pd(acac)_2$, PBu_3, THF, rt.

However, it was later realized by other workers that the ratio of **35** and **36** varied with the ratio of $Pd(acac)_2$ and PBu_3 used and also with the purity of PBu_3.[14]

In a similar work, Stork and coworkers have developed a unique strategy utilizing the concept of 'temporary connections' for stereoselective hydride delivery in the reduction of hydrindene **38** to obtain *trans*-hydrindane moiety **40** (Scheme 12).[15]

Scheme 12. Stereoselective hydride delivery by 'temporary connections'

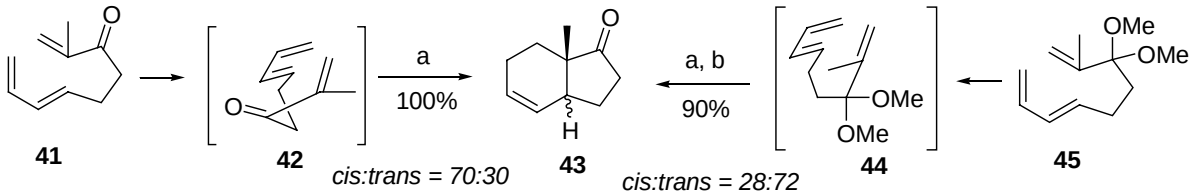


Reagents and conditions: a) $BrC(=CH_2)Me_2SiCl$, Et_3N, rt. b) Bu_3SnH, AIBN, PhH, reflux. c) 30% H_2O_2, KF, $KHCO_3$, MeOH, THF, rt.

1.2 Direct one-step construction of the *trans*-hydrindane skeleton from acyclic precursors.

Intramolecular Diels-Alder cycloaddition (IMDA) strategy has been extensively used for the synthesis of hydrindane derivatives. The important observation in this strategy has been the formation of *cis*-hydrindane as the major product from the IMDA reaction of the trienoic ketone **41** whereas its ketal derivative **45** gives *trans*-hydrindane as the major product (Scheme 13).[16]

Scheme 13. IMDA cycloaddition



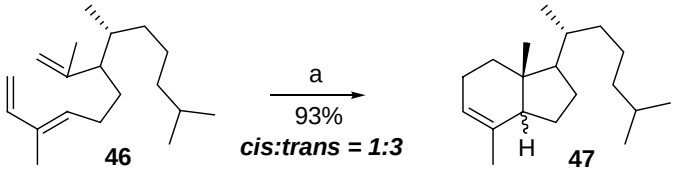
Reagents and conditions: a) hydroquinone, benzene, 190 ℃. b) HCl, H_2O, rt.

The reversal of selectivity in case of **41** and **45** is attributed to the relative bulk of the methyl and the carbonyl group. In the case of **41** the methyl group is bulkier than the carbonyl group, due to which the methyl group controls the stereochemical outcome. Therefore, the favored transition state **42,** having β methyl group is proposed for the formation of *cis* isomer from the cycloaddition of **41**. The transition state similar to **44** also exists for **41**, but is not favored due to interaction between the vinyl methyl group and the

diene portion accounting for the minor product. In the case of **45** where the dimethyl ketal moiety is bulkier than the methyl group favors transition state **44**, leading to the formation of *trans*- isomer predominantly.

Parkar and Iqbal have observed that the trienes lacking substituents on diene moiety upon IMDA reaction produce the hydrindane system in 1:1 mixture, however, trienes with substituents on carbon which becomes C-8 in the product, for example, **46** produces **47** in *cis:trans* ratio of 1:3 (Scheme 14).[17]

Scheme 14. IMDA cycloaddition of substituted triene system

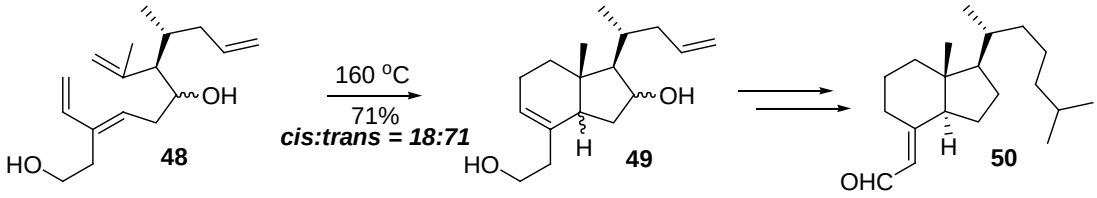


46 **47**

Reagents and conditions: a) Me_2NPh, 200 °C.

Based on this principle, Wilson *et al*. have carried out IMDA reaction of **48** to obtain **49** with *trans:cis* ratio of 71:18 which was ultimately converted to **50** in several steps (Scheme 15).[18]

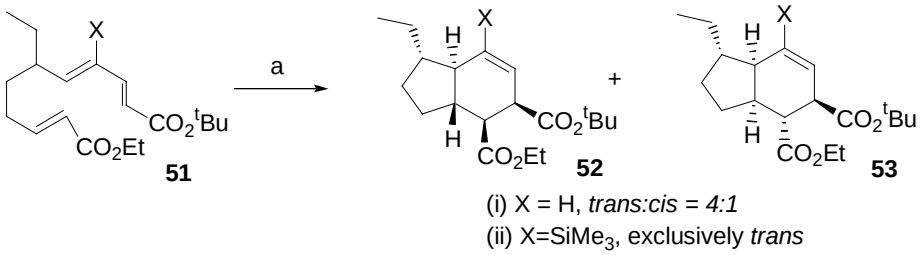
Scheme 15. Wilson's approach



48 **49** **50**

Subsequently, Boeckman and Barta utilized TMS group as removable stereocontrol element in IMDA cycloadditions leading to the formation of *trans*-hydrindane derivatives. For example, IMDA cyclization of the triene **51(ii)** (X = TMS) produced **52** as a sole product, whereas the triene **51(i)** (X = H) gave a mixture of **52** and **53** in the ratio of 4:1 (Scheme 16).[19]

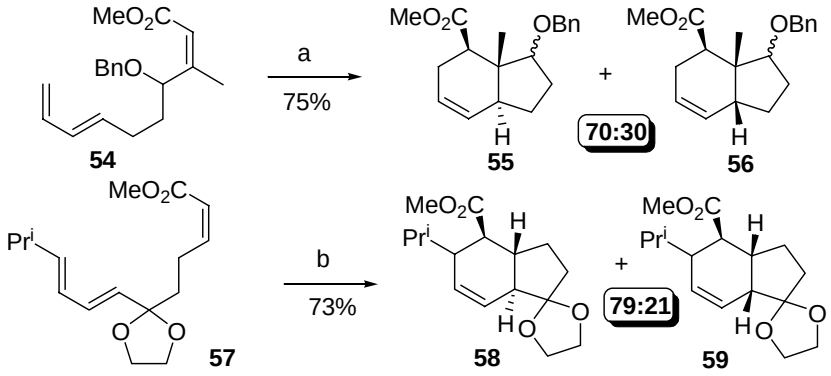
Scheme 16. IMDA cycloaddition using TMS as removable stereocontrol element



Reagents and conditions: a) BHT, Toluene, 165 °C.

Roush's and Martin's group independently investigated the effect of substituents on the positions other than C-8 (in product) on the stereochemical outcome of the IMDA reaction of the trienes. For example, the IMDA reaction of triene **54** produced diastereomeric mixtures of **55**:**56** in 7:3 ratio, whereas the triene **57** gave corresponding diastereomers **58**:**59** in 79:21 ratio (Scheme 17).[20]

Scheme 17. IMDA cycloaddition on substituted triene systems

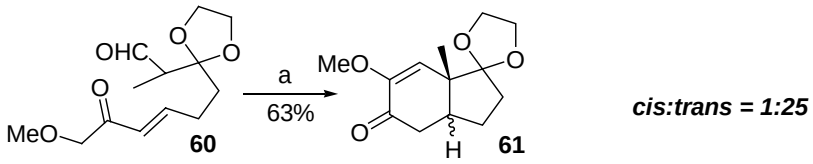


Reagents and conditions: a) 200 °C. b) 180 °C.

Similarly, IMDA cycloadditions have also been carried out with several other substrates.[1] However, stereochemical outcome of such reactions are found to be strongly dependent on the C-8 substituents, akin to the reduction protocol of the substrates of the H-P-W ketone type.

An intramolecular conjugate addition followed by aldol reaction protocol have been used by Stork *et al*. to synthesize *trans*-hydrindane system **61** in 1:25, *cis:trans* ratio. (Scheme 18).[21]

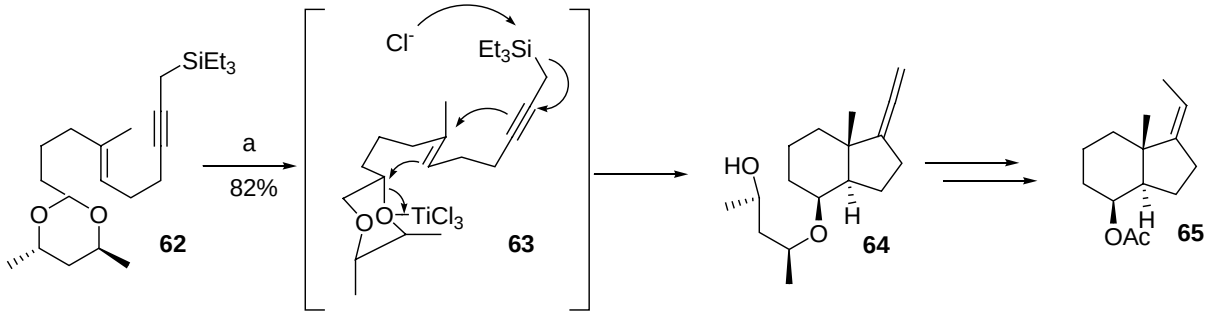
Scheme 18. Intramolecular conjugate addition-aldol reaction protocol



Reagents and conditions: a) $Zr(OPr)_4$, PhH, rt, then MeONa.

In another interesting strategy, Johnson *et al*. have used Lewis acid catalyzed cyclization strategy of polyene **62** to obtain *trans*-hydrindane derivative **65** with 92% *ee* (Scheme 19).[22]

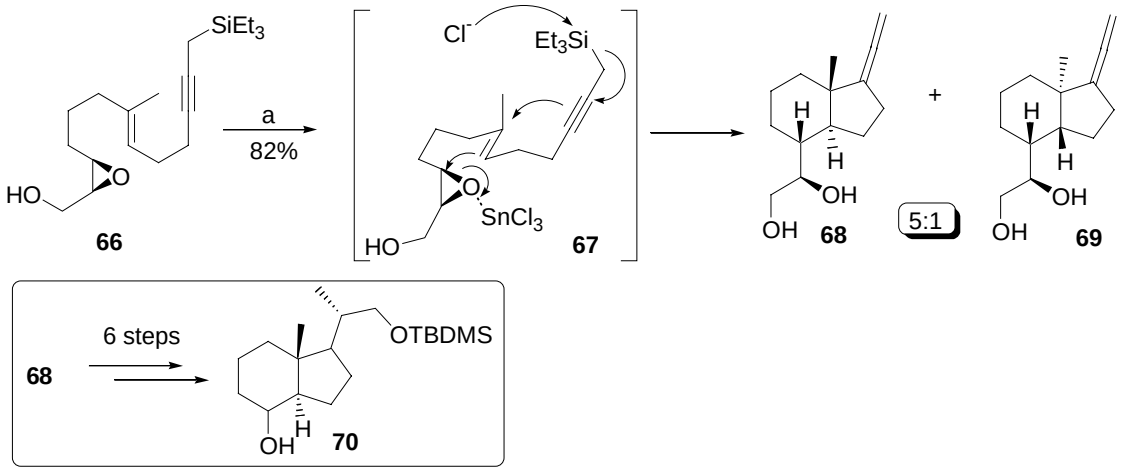
Scheme 19. Johnson's polyene cyclization approach



Reagents and conditions: a) $TiCl_4$, 2,4,6-trimethyl pyridine, CH_2Cl_2, –78 °C.

In a similar approach, Takano *et al*. utilized $SnCl_4$ induced chiral epoxide **66** opening for initiating a polyene cyclization protocol to synthesize *trans*-hydrindane system (Scheme 20).[23]

Scheme 20. Takano's polyene cyclization approach



Reagents and conditions: a) $SnCl_4$, CH_2Cl_2, –95 °C.

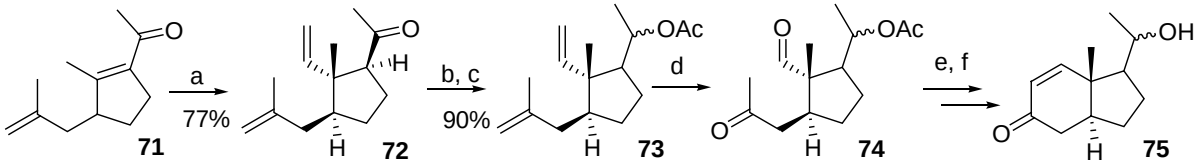
1.3 Stereoselective annulation approach.

The highest stereocontrol in the synthesis of *trans*-hydrindane system has been achieved through this approach. The most challenging task in this approach has been the procurement of the suitably 1,2-*trans* functionalized six or five membered ring precursor. Strategies belonging to this approach can be categorized into two classes based on the size of the ring being annulated.

1.3.1 Annulation of six-membered ring over five-membered one

Stork *et al*. have used stereoselective conjugate addition of vinyllithiumcuperate[24] to α,β-unsaturated ketone **71** for the preparation of 1,2 *trans*-substituted cyclopentyl system **72**, which was converted to *trans*-hydrindane system **75** *via* **74** and following an intramolecular aldol condensation (Scheme 21).[25]

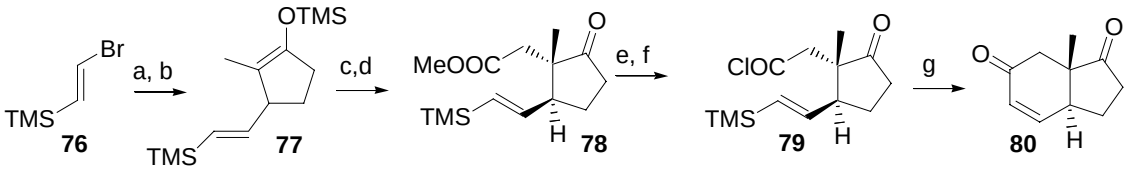
Scheme 21. Stork's conjugate addition-aldol condensation protocol



Reagents and conditions: a) $(CH_2=CH_2)_2CuLi$, Et_2O:THF:DMS (10:1:1.5), –78 °C to 0 °C. b) DIBAH, toluene, 0 °C. c) Ac_2O, pyridine, 25 °C. d) OsO_4 (5%), $NaIO_4$, Et_2O, H_2O, 25 °C. e) O_3, CH_2Cl_2, –78 °C, 75% (2 steps). f) MeONa, Et_2O, 25 °C, 50%.

In another related study, 1,2-*trans*–cyclopentyl system **79**, prepared from **77** by following simple steps, was transformed to *trans*-hydrindane system **80** by $AlCl_3$ catalyzed acylation of vinyl silane moiety as shown in Scheme 22.[26]

Scheme 22. Conjugate addition-vinylsilane acylation approach

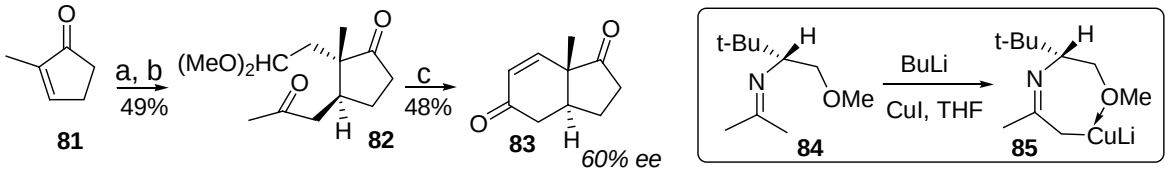


Reagents and conditions: a) Mg, THF, 1.75 h, CuI, then –70 °C, 2-methyl-2-cyclopentenone, THF. b) TMSCl, Et_3N, HMPA, –70 °C to rt. c) MeLi, Et_2O, THF, rt. d) inverse addition to $BrCH_2COOMe$ (5

eq.), HMPA (4 eq.), THF, –20 °C to rt. e) KOH, aq. CH_3OH, rt. f) $COCl_2$, C_6H_6, rt. g) $AlCl_3$ (4.5 eq.), CH_2Cl_2, –30 °C to rt.

Conjugate addition-aldol condensation sequence was also followed by Yamamoto *et al*. in the enantioselective synthesis of dione **83**. Enantioselective conjugate addition of chiral reagent **85** on cyclopentenone **81** was used to prepare key precursor **82** in 60% *ee* (Scheme 23).[27]

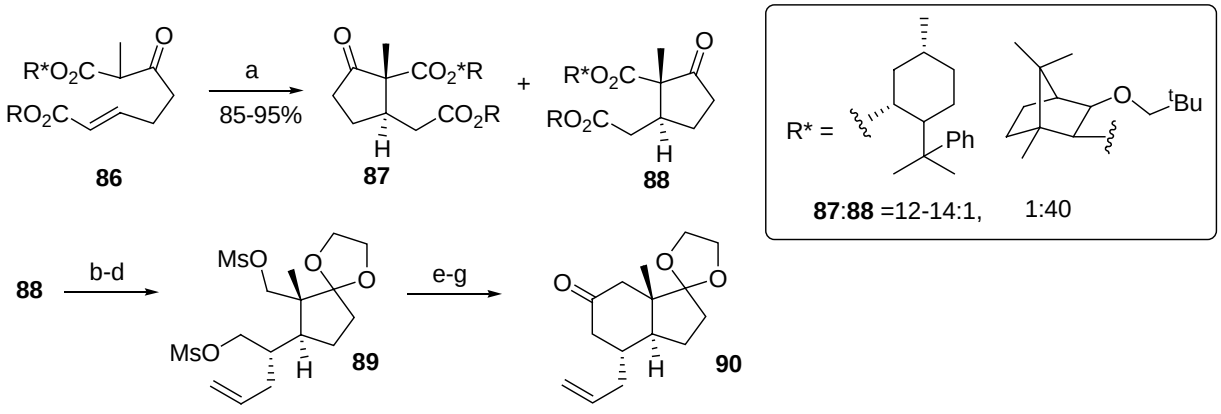
Scheme 23. Yamamoto's optically active version of conjugate addition-aldol condensation



*Reagents and conditions: a) (S) or (R)-**85**, THF, –60 °C to –30 °C, TMSCl, –30 °C. b) $CH(OMe)_3$, $SnCl_4$, CH_2Cl_2, –40 °C to –30 °C. c) $PhCH_2CH_2NH_2$, AcOH, 100 °C.*

Intramolecular displacement of mesylate resulting in the annulation of the six-membered ring (Scheme 24)[28] have been utilized for the synthesis of *trans*-hydrindane derivative **90** from the optically pure 1,2-*trans*-cyclopentane derivative **88,** prepared by the intramolecular addition of chiral enolate to the α,β-unsaturated ester. It was noticed that use of phenylmenthyl chiral auxiliary gave relatively poor diasteroselectivity (**87:88,** 12-14:1) in comparison to neopentyloxybornyl chiral auxiliary, which gave **87:88** (1:40).

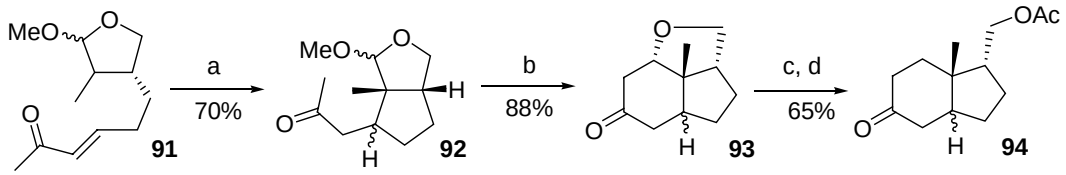
Scheme 24. Intramolecular conjugate addition-annulation approach



Reagents and conditions: a) NaH, PhH, reflux. b) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, rt. c) LDA, THF, –78 °C, then $CH_2=CH_2Br$. d) LAH, THF, rt. d) MsCl, Et_3N, DMPA, CH_2Cl_2, 0 °C. e) $NCCH_2CO_2Me$, KH, NaI, DMSO. f) LiI, DMF, 140 °C. g) i. LDA, THF, –78 °C. ii. O_3. iii. Na_2SO_3, buffer (pH = 7).

In another unique approach, *trans*-hydrindane system **94** with α-oriented substituent at C-17 was presented by Stork *et al*, via tandem conjugate addition-aldol reaction from compound **91** via hydrindane system **93** with *cis:trans* ratio of 1:10 (Scheme 25).[29]

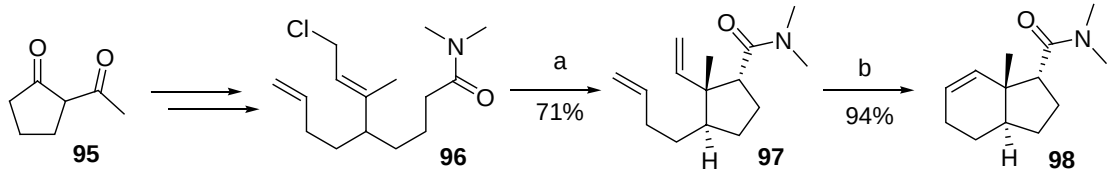
Scheme 25. Tandem conjugate addition-aldol condensation approach



Reagents and conditions: a) cat. p-TsOH, CH_2Cl_2, rt. b) KOH, MeOH, reflux. c) Ac_2O, p-TsOH, PhH, reflux. d) H_2, Pd-C, EtOH, rt.

Recently, Kim *et al.,* have reported a protocol for the racemic synthesis of *trans*-hydrindane system **98** by the ring closing metathesis using Grubb's catalyst from **97**, prepared from **95** as shown in Scheme 26.[30]

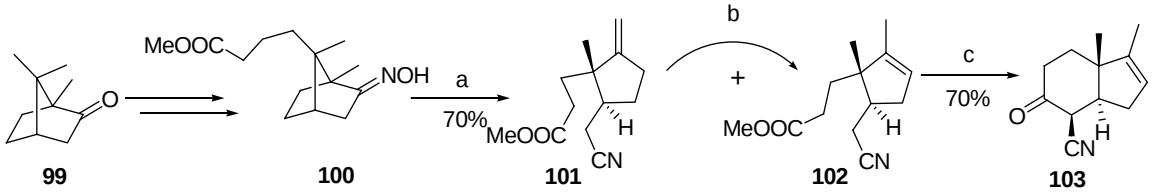
Scheme 26. Kim's approach



Reagents and conditions: a) KHMDS (0.5 M in THF), THF, rt. b) Grubb's catalyst II (2 mol%), CH_2Cl_2, rt.

Stevens *et al.* have used camphor (**99**) to obtain suitably substituted cyclopentane derivative **102** in optically pure form for the synthesis of the hydrindane system **103** as shown in Scheme 27.[31]

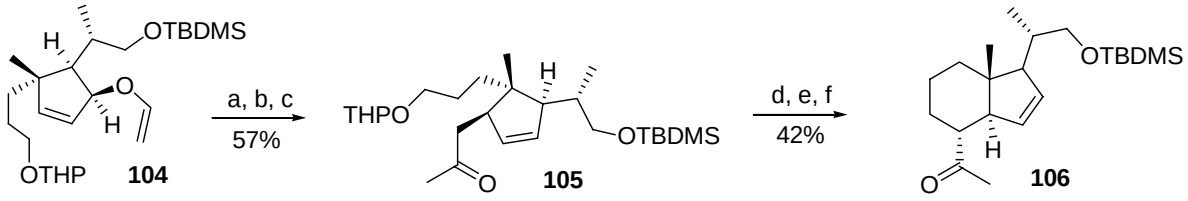
Scheme 27. Steven's approach



Reagents and conditions: a) TsCl, pyridine, rt. b) t-BuOK, THF, reflux. c) CF_3COOH, CH_2Cl_2, rt.

Trost *et al.* have used '1,3-chirality transfer' via Claisen rearrangement strategy on **104** to obtain **105** in order to synthesize *trans*-hydrindane derivative **106** as depicted in the Scheme below (Scheme 28).[32]

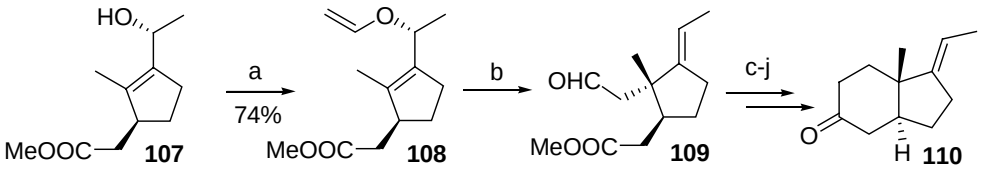
Scheme 28. Trost's approach



Reagents and conditions: a) Flash Vacuum Pyrrolysis (FVP), 500 °C. b) MeLi, Et_2O, THF, reflux. c) PCC, CH_2Cl_2, rt. d) PPTs, PhH, reflux. e) TsCl, Et_3N, CH_2Cl_2, rt. f) t-BuOK, Et_2O, rt.

On similar lines, Takahashi also developed a protocol for the stereoselective construction of suitably substituted cyclopentane moiety **109** from the Claisen rearrangement of **108** and used it for the synthesis of *trans*-hydrindane system **110** as shown in Scheme 29.[33]

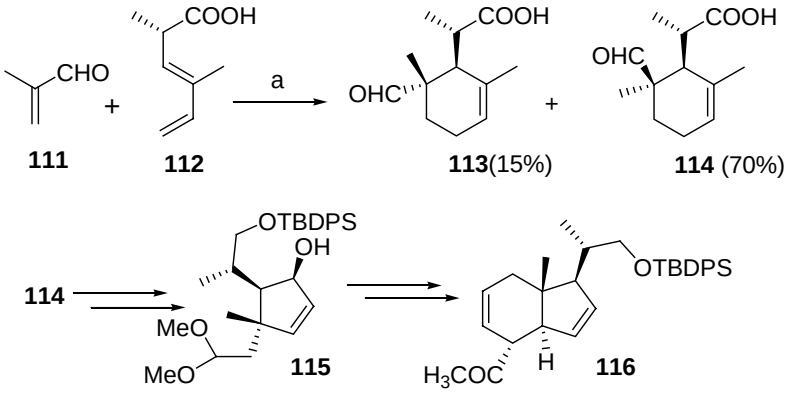
Scheme 29. The Takahashi approach



Reagents and conditions: a) CH_2=CHOEt, $Hg(OAc)_2$, reflux. b) Collidine, 160 °C. c) $NaBH_4$, MeOH, rt. d) TsCl, pyridine, rt 70% (2 steps). e) DIBAH, THF, -78 °C. f) CrO_3, pyridine, CH_2Cl_2, rt. g) $NaHSO_3$, NaCN, H_2O, 0 °C 65% (3 steps). h) CH_2=CHOEt, TsOH. i) NaHMDS, THF, reflux. j) HCl then NaOH, ether 90% (3 steps).

The [4+2]-cycloaddition of dienophile **111** and diene **112** in aqueous medium is reported by Grieco *et al*. to give mixture of diastereomers **113**:**114** in 3:14 ratio. The major diastereomer **114** was converted to the cyclopentane derivative **115** following series of steps. Cyclization using the same protocol as employed by Trost *et al*. produced *trans*-hydrindane system **116** (Scheme 30).[34]

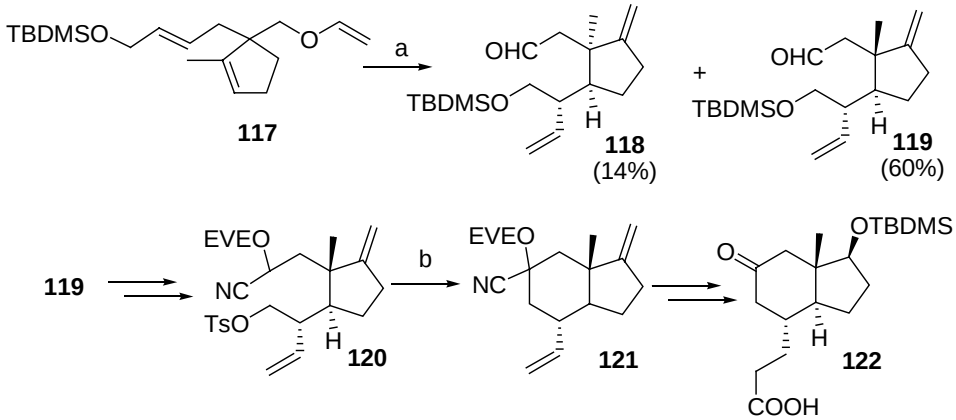
Scheme 30. Grieco`s intermolecular Diels-Alder approach



Reagents and conditions: a) H_2O, 55 ℃.

The tandem Cope-Claisen rearrangement of triene **117** is reported by Ziegler and Lim to produce a mixture of suitably substituted cyclopentanes **118** (14%) and **119** (60%). **119** upon annulation is reported to lead to *trans*-hydrindane system **121** as shown in Scheme 31.[35]

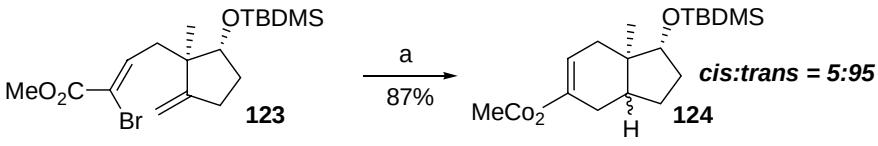
Scheme 31. Tandem Cope-Claisen rearrangement approach



Reagents and conditions: a) Thermolysis, 375 ℃. b) KHMDS, THF.

Satoh et al. have used a free radical cyclization strategy from **123** to synthesize *trans*-hydrindane derivative **124** in *cis:trans* ratio of 5:95 as shown in Scheme 32.[36]

Scheme 32. Satoh's approach

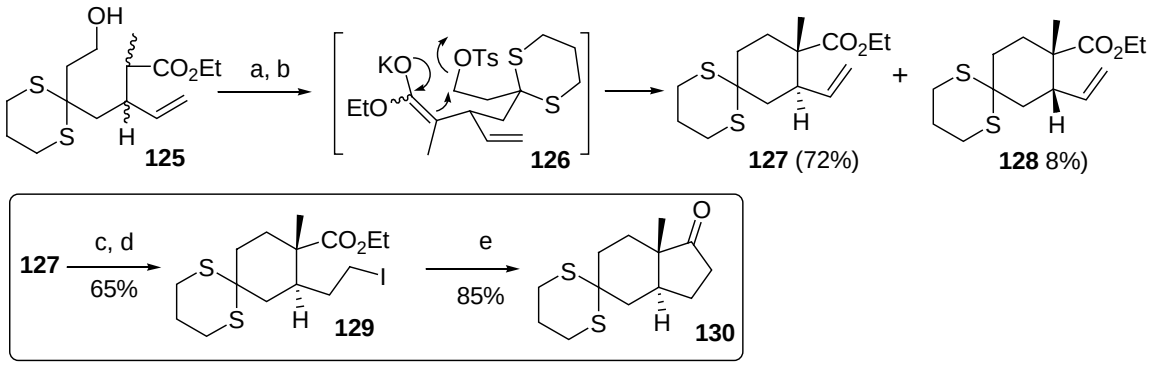


Reagents and conditions: a) n-Bu_3SnH, toluene, − 30 ℃.

1.3.2 Annulation of five-membered ring over six-membered one

Similar to above discussions where six-membered ring is annulated over the suitably substituted cyclopentane rings; there are also several approaches where cyclopentane ring is annulated over the properly substituted cyclohexane ring for the synthesis of *trans*-hydrindane systems. One such example pertains to the cycloalkylation of **125** to obtain *trans*-hydrindane system **130**. Precursor **127** was obtained by stereoselective displacement of the tosylate in **126** by ester enolate in the intramolecular fashion. The selectivity in the formation **127** as the major diastereomer is explained by considering the six-membered chair shaped transition state **126** (Scheme 33).[37]

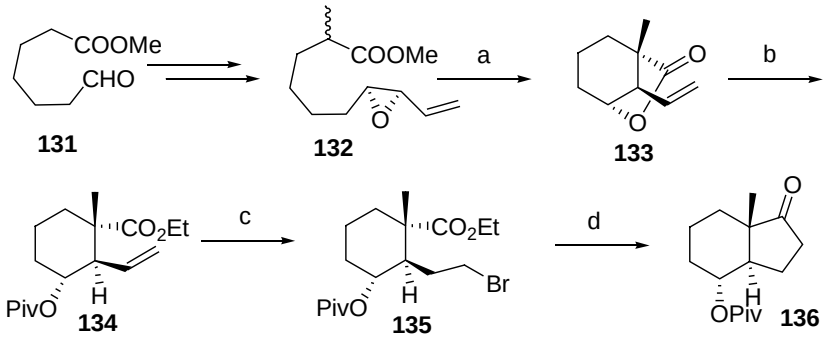
Scheme 33. Claisen rearrangement-intramolecular ester alkylation approach



Reagents and conditions: a) TsCl, pyridine, $CHCl_3$, 0 °C. b) $KN(SiMe_3)_2$, THF, –78 °C to –20 °C. c) dicyclohexyloborane, THF, 0 °C to rt. d) ICl, NaOAc, MeOH, rt. e) t-BuLi, Et_2O, –100 °C to –50 °C.

Stork *et al*. have used an interesting protocol for the stereoselective synthesis of cyclohexane moiety **134** via alkylation of allyl epoxide **132.** Compound **134** was transformed to the *trans*-hydrindane system **136** as shown in Scheme 34.[38]

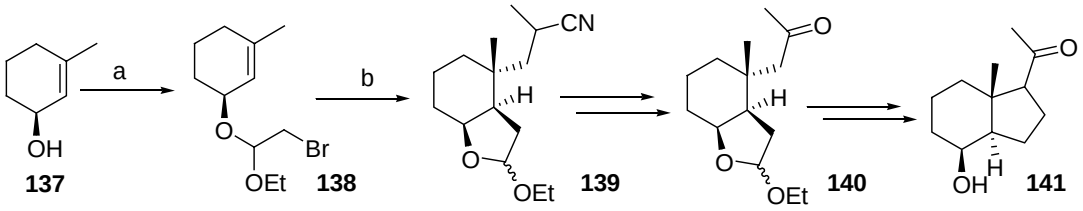
Scheme 34. Stork's epoxidation-cyclization approach



Reagents and conditions: a) LiHMDS, THF. b) i. NaOEt, EtOH, reflux. ii. PivCl, imidazole, CH_2Cl_2, rt. c) HBr, hν (300 nm), n-pentane. d) t-BuLi, THF, –78 °C.

Stork *et al.* have also reported the synthesis of hydrindane unit from optically active 3-methyl cyclohex-2-en-1-ol (**137**). This strategy makes the use of 'temperorary connections', in the key step of free radical addition of bromoacetaldehyde unit attached to the *ene* moiety. The quaternary free radical generated after the free radical cyclization in **138** was trapped with propenyl nitrile to give **139**, which was converted to *trans*-hydrindane derivative **141** following series of steps as shown in Scheme 35.[38]

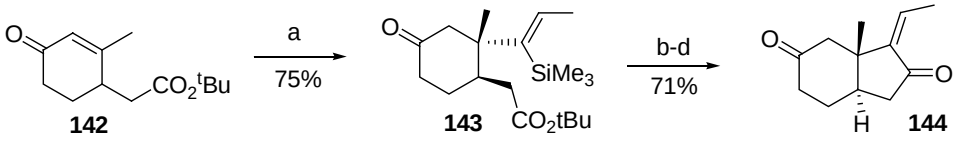
Scheme 35. Stork's radical cyclization approach



Reagents and conditions: a) Ethyl vinyl ether, NBS, CH_2Cl_2, – 30 °C. b) $NaBH_3CN$, AIBN, $CH_3C(CN)=CH_2$, Bu_3SnCl, reflux.

$AgBF_4$ mediated annulation protocol was used for the preparation of *trans*-hydrindane derivative **144**, from **143**, synthesized by the conjugate addition of (1-(trimethylsilyl)-prop-1-enyl)magnesium bromide on cyclohexenone derivative **142** as shown in Scheme 36.[39]

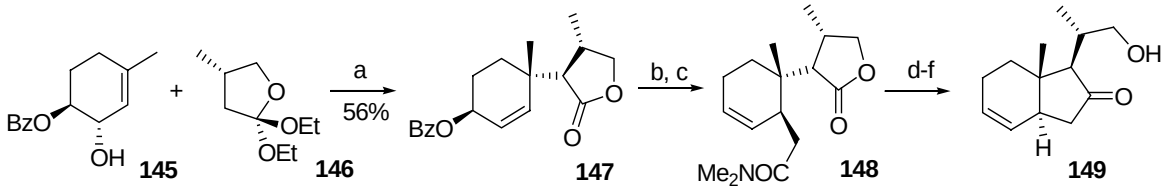
Scheme 36. Conjugate addition-$AgBF_4$ cyclization approach



Reagents and conditions: a) $CH_3CH=C(SiMe_3)MgBr$, CuI, Me_2S, THF, –70 °C. b) Me_3SiCl, NaI, Et_3N, MeCN, 70 °C. c) collidine, DMF, CH_2Cl_2, $(COCl)_2$, 0 °C. d) $AgBF_4$, $MeNO_2$, 0 °C to rt.

Lythgoe *et al*. have applied base catalyzed cyclization of **148,** obtained from **145** by double Claisen rearrangements, to obtain the *trans*–hydrindane derivative **149** as depicted in Scheme 37.[40]

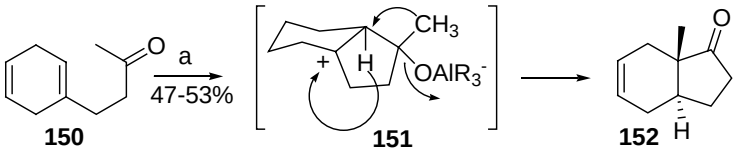
Scheme 37. The Lythgoe approach



Reagents and conditions: a) CH_3CH_2COOH, xylene, reflux. b) NaOMe, MeOH, 20 ℃. c) 1-dimethylamino-1-methoxyethylene, xylene, reflux. d) KOH, EtOH, H_2O, reflux. e) CH_2N_2, Et_2O, 0 ℃ to rt. f) t-BuOK, PhH, reflux.

A racemic synthesis of *trans*-hydrindane system **152** was reported by Fukumoto *et al*., using $MeAlCl_2$ catalyzed carbocationic cyclization the dienone **150** as shown in Scheme 38.[41]

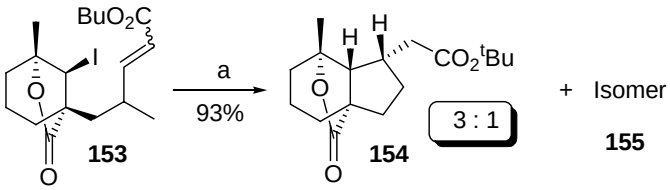
Scheme 38. Lewis acid mediated carbocationic cyclization



Reagents and conditions: a) $MeAlCl_2$, CH_2Cl_2, 90 ℃, (sealed tube).

Chuang and Hart developed a method for the racemic synthesis of *trans*-hydrindane derivative **154** employing radical cyclization approach from iodolactone **153**. The hydrindane derivative was obtained in 3:1 diastereomeric ratio (Scheme 39).[42]

Scheme 39. Annulation of five membered ring by radical cyclization

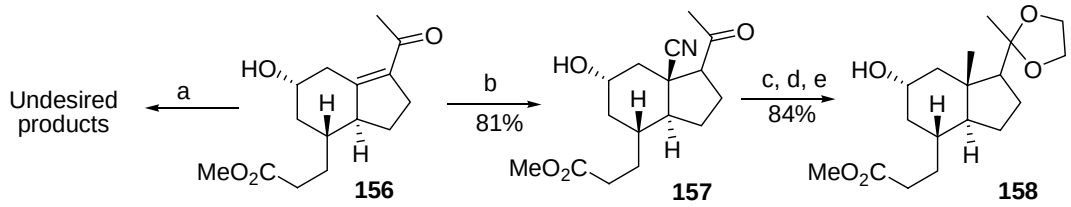


Reagents and conditions: a) $^nBu_3SnH$, AIBN, PhH.

1.4 Miscellaneous Approaches

Hydroxyl directed stereoselective conjugate addition of CN^- to **156** was utilized to produce **157** exclusively which was subsequently used for the synthesis of *trans*-hydrindane derivative **158** as shown in Scheme 40. [43]

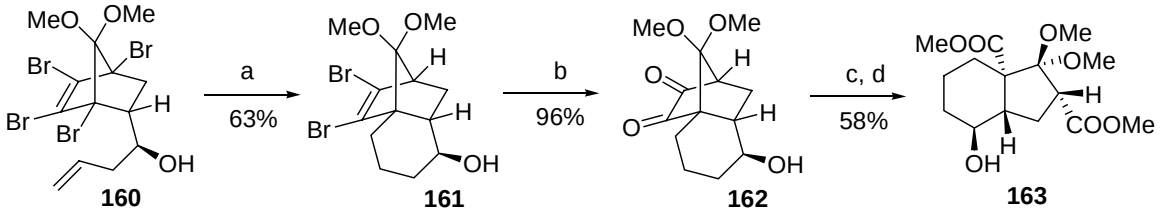
Scheme 40. Stereoselective installation of angular methyl group by CN^- conjugate addition



Reagents and conditions: a) Me_2CuLi, THF. b) Et_2AlCN, PhH, rt. c) $(CH_2OH)_2$, p-TsOH, reflux. d) $LiAlH_4$, THF, reflux. e) N_2H_4, KOH, $(CH_2OH)_2$, reflux.

Very recently, Khan *et al*. have devised an elegant synthesis of *trans*-hydrindane system **163** in the racemic form from bicycloheptane skeleton **160**. Stereoselectivity arises from the *endo*-orientation of the tether chain in **160** due to which the *trans*- stereochemistry at ring junction is established as depicted in Scheme 41.[44]

Scheme 41. Bridgehead functionalization approach



Reagents and conditions: a) Bu_3SnH, AIBN, PhH, reflux. b) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, MeCN-H_2O (6:1), 0 ºC. c) H_2O_2, NaOH, 0 ºC to 10 ºC, H_3O^+. d) CH_2N_2, Et_2O, 0 ºC.

The importance of the *trans*-hydridane system can be gauged from the plethora of synthetic methods discussed above. The main challenge in the synthesis of this moiety still lies in the stereoselective construction of the two chiral centers at the ring junction in the desired *trans*- fashion. Since, *cis* form being more stable, *trans*-hydrindane system is more difficult to synthesize. Despite numerous approaches available, a general method applicable for the synthesis of wide range of structurally modified analogues of *trans*-hydrindane system is still lacking. Most of the earlier approaches devised were for the racemic compounds. Furthermore, the stereoselectivities of some of these methods (especially methods 1.1 and 1.2) strictly depend on the substituents present in the appropriate positions. Thus, it takes extra efforts to introduce these special functionalities and to remove them later on. The chiral approaches developed also suffer from the

drawbacks such as use of costly chiral material, one or more low yielding steps and lengthy synthetic routes. To the best of our knowledge, there is no method to synthesize optically active *trans*-hydrindane system starting from the cheaply available aromatic compounds. Considering the limitations of the literature approaches, we envisaged to design a general strategy for the synthesis of optically pure *trans*-hydrindane system. Details of this endeavor are presented in the following sections.

2. Retrosynthetic analysis and design

We viewed the synthesis of *trans*-hydrindane system **164**, which is equipped with suitable functionalities in appropriate positions for transformation into more complex molecules, through the retrosynthetic analysis as shown in Figure 1.

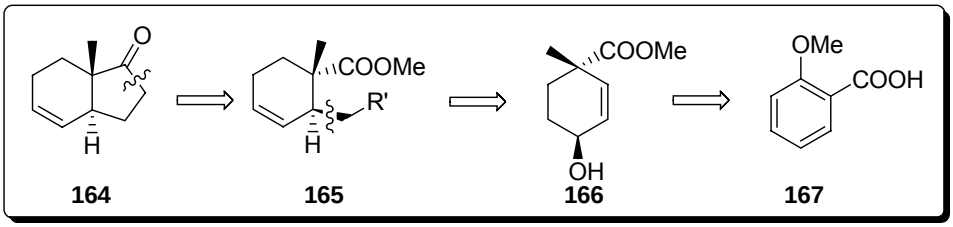


Figure 1. Retrosynthesis

Two contemporary approaches, as depicted below, were visualized for the synthesis of the key precursor **165** in optically active form, from a cheaply available aromatic substrate **167** (*o*-anisic acid) as the starting material.

I. Chiral auxiliary approach (Figure 2).

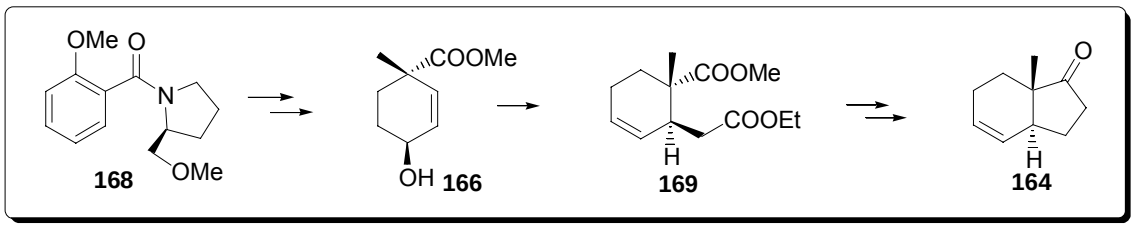


Figure 2. Outline of chiral auxiliary approach

II. Catalytic asymmetric synthesis approach (Figure 3).

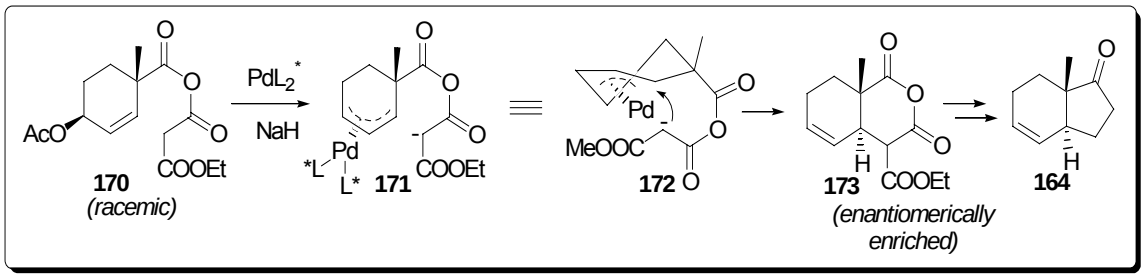


Figure 3. Key step of catalytic asymmetric approach

Following sections would confer our endeavors in detail.

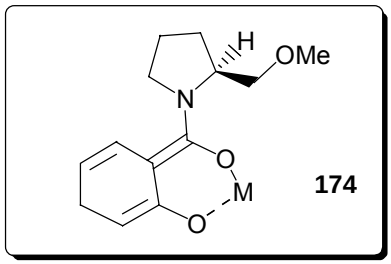
3. Enantioselective synthesis of suitably functionalized *trans*-hydrindane system utilizing chiral auxiliary approach

Synthesis of **164,** as perceived through the retrosynthetic strategy described above, was initiated by planning the synthesis of the key precursor **165**. The synthesis of **165** in optically pure form was envisioned by first constructing a quaternary stereocenter in a cyclohexenyl moiety followed by the installation of the tertiary stereocenter. The annulation of the side arms to form the five membered ring would eventually complete the synthesis of **164**.

3.1 Construction of quaternary stereocenter in a cyclohexyl moiety

Stereoselective construction of an all carbon substituted quaternary stereocenter is a daunting task in organic synthesis.[45] Although, various methods are known for the construction of quaternary stereocenter in which one of the substituent is a heteroatom, the number of methods for the steroselective construction of an all carbon substituted quaternary stereocenter is very limited. One of the most prominent approaches in this domain is the Birch reduction-alkylation strategy. Asymmetric Birch reduction alkylation of benzoic acid derivatives using proline based chiral auxiliaries developed by Schultz *et al*., provides an excellent method for the construction of quaternary stereocenters carrying all carbon substituents.[46] We envisaged to utilize this protocol for constructing the quaternary stereocenter present in our system.

(S)-Prolinol methyl ether as a chiral auxiliary is known to give very good selectivity in the asymmetric Birch reduction-alkylation due to the involvement of chiral enolate **174**, directing the incoming electrophile to approach only from the less hindered side (Figure 4).

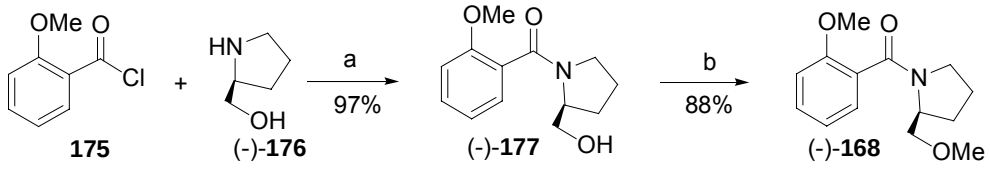


174

Figure 4. Transition state diagram

Our synthesis began with the preparation of substrate (-)-**168** which involved the coupling of prolinol with anisoyl chloride followed by *O*-methylation of the resulting amide (-)-**177** with methyl iodide in the presence of sodium hydride. The optical rotations and spectral data of (-)-**177** and (-)-**168** were found to be in good agreement with those reported in the literature (Scheme 42).[47]

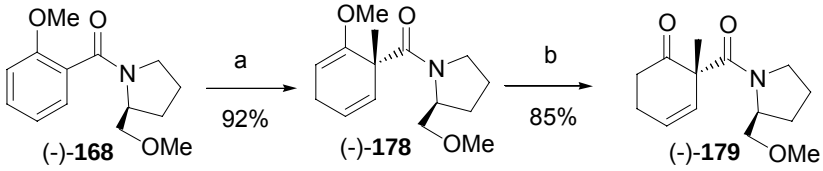
Scheme 42. Preparation of substrate for Birch reduction-alkylation



Reagents and conditions: a) Et_3N, DCM, 0 °C to rt. b) NaH, MeI, THF, 60 °C.

We observed that the Birch reduction-methylation of amide (-)-**168** gives enol ether (-)-**178** as a single diastereomer[*] in 92% yield, which upon hydrolysis with 10% HCl produced corresponding ketone (-)-**179** in 85% yield (Scheme 43).

Scheme 43. Birch-reduction-alkylation and hydrolysis of enol ether



Reagents and conditions: a) Na, liq. NH_3, THF, ^{t}BuOH, –78 °C, MeI. b) 10% HCl, MeOH, rt.

Compounds (-)-**178** and (-)-**179** were characterized by conventional spectroscopic methods. Their spectral data as well as optical rotations were found to be matching well with those reported in the literature.[47]

3.2 Deoxygenation of (-)-179:

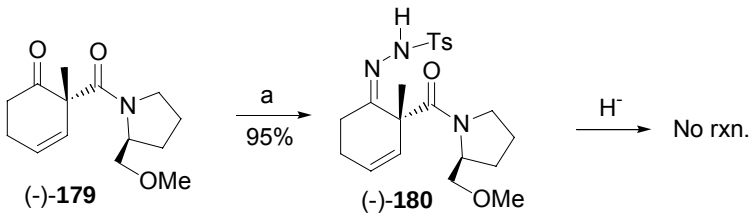
The next task in the planned strategy was the deoxygenation of keto carbonyl group of (-)-**179** and in this context, it was thought that the classical methods such as Clemmensons or Wolf-Kishner reduction should serve the purpose considering the stability

[*] Schultz *et al*., have reported 260:1 diastereomeric mixture by ^{1}H NMR and GC analysis. However, we could observe only one diastereomer both by ^{1}H NMR and GC analysis of **178**.[47]

of the tertiary amides towards the harsh reaction conditions. However, both these methods resulted in the formation of complex reaction mixture and failed to give the desired product by any means.

This observation led us to evaluate the desired transformation via reduction of the tosyl hydrazone derivative of (-)-**179** using various hydride reducing agents.* However, to our dismay this method was found to be inefficient, possibly due to the steric hindrance imparted by the presence of vicinal quaternary carbon (Scheme 44).

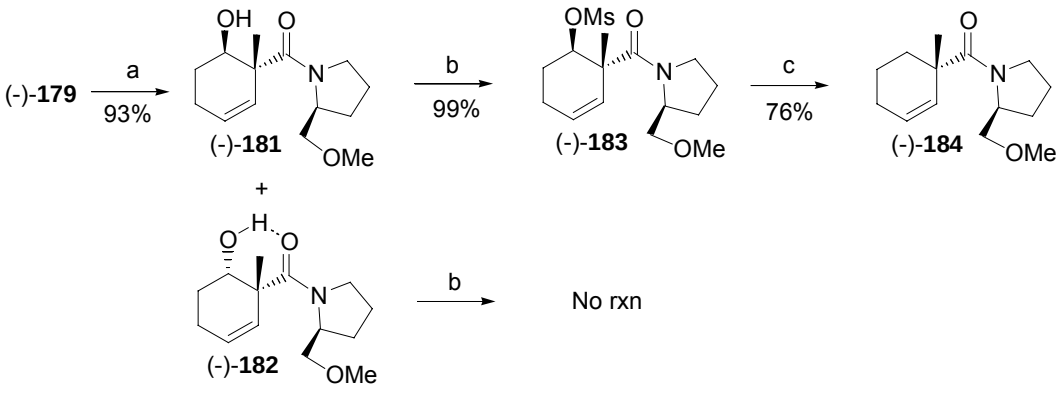
Scheme 44. Attempted deoxygenation via tosyl hydrazone



Reagents and conditions: a) Ts-NHNH$_2$, EtOH, reflux.

These unexpected failures, prompted us to adopt an indirect method of deoxygenation. It was anticipated that a method involving mild conditions and less susceptible to steric factors would best suit our requirement. In this context, we decided to evaluate Fujimoto's protocol for deoxygenation of alcohol via reduction of its mesylate derivative using sodium iodide and zinc.[48] Towards this endeavor, (-)-**179** was reduced to the corresponding alcohol (**181** & **182**) in 1:1 diastereomeric mixture (93% yield) using sodium borohydride.

Scheme 45. Application of Fujimoto's protocol of deoxygenation



* $NaBH_4$, $NaBH_3CN$, $NaBH(OAc)_3$ and catechol borane were tried in solvents such as methanol, ethanol, isoprpanol and sulfolane.

Reagents and conditions: *a) $NaBH_4$, MeOH, 0 °C to rt. b) MsCl, TEA, DCM, 0 °C to rt. c). NaI, Zn, DME, 70 °C.*

These two diastereomers were easily separated and characterized. The diastereomer (-)-**181** in which the hydroxy functionality is *trans* to the amide moiety was found to be solid with m.p. 117-119 °C, while the other isomer, (-)-**182,** was thick liquid. This difference in the physical property was due to the intermolecular hydrogen bonding between the hydroxy hydrogen and the amide oxygen in case of (-)-**181** whereas intramolecular hydrogen bonding dominated in (-)-**182**. Spectral data of (-)-**181** and (-)-**182** were almost identical except for the downfield shift of C<u>H</u>–OH proton of (-)-**182** (δ = 4.70-4.90 in comparison to δ = 4.15 for (-)-**181**) in ^{1}H NMR spectrum.

The IR spectrum of (-)-**181** showed a strong absorption band at ν_{max} = 1677 cm^{-1} indicating the amide carbonyl. The band for keto carbonyl appearing at ν_{max} = 1720 cm^{-1} in the parent ketone had disappeared. The presence of hydroxy group was indicated by a broad band at ν_{max} = 3400 cm^{-1}.

In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**181**, a singlet appearing at δ = 1.25 (3H) was attributed to the methyl group attached to the quaternary carbon (C–CH_3). Two multiplets appearing between δ = 1.60-1.95 (6H) and 2.10-2.30 (2H), integrating for 8 protons altogether, were assigned to the protons of the various methelyene groups except N–CH_2 and O–CH_2. Protons of O–CH_3 group appeared as a sharp singlet at δ = 3.30 (3H). The multiplet appearing between δ = 3.35-3.60 (4H) was assigned to the protons of remaining two methylene groups (N–CH_2 and O–CH_2). The CH–OH proton appeared as a doublet of doublet at δ = 4.15 (*J* = 9.4, 2.3 Hz, 1H). The multiplet appearing between δ = 4.30-4.45 (1H) was attributed to the N–CH proton. The olefinic protons appeared as a multiplet in the region of δ = 5.55-5.80 (2H).

The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**181** displayed a total of 14 signals at δ = 19.0, 23.9, 24.8, 25.4, 26.2, 47.7, 49.4, 57.6, 58.6, 70.2, 72.0, 126.5, 129.5 and 174.4 respectively. DEPT spectrum revealed that peaks appearing at δ = 49.4 and 174.4 belong

to the quaternary carbons of the quaternary stereocenter and the carbonyl group, respectively. The presence of two olefinic methine carbons were indicated by signals at δ = 126.5 and 129.5, respectively. Another signal at δ = 70.2 belonged to the CH-OH carbon and the remaining methine carbon (N–CH) appeared at δ = 57.6. The O–CH_2 carbon appeared at δ = 72.0, whereas the N–CH_2 carbon appeared at δ = 47.7. The remaining four methylene carbons appeared at δ = 23.9, 24.8, 25.4 and 26.2 respectively. The carbon of the methyl group attached to the quaternary carbon (C–CH_3) appeared at δ = 19.0 and the carbon of O–CH_3 group appeared at δ = 58.6.

The mass spectrum of (-)-**181** exhibited a molecular ion peak at *m/z* = 253, along with the base peak at 95.

Our next job was to derivatize the hydroxy function to its mesylate. In this context, when the diastereomers (-)-**181** & (-)-**182** were subjected to mesylation reaction separately, a fact, perhaps not very surprising came to our observation. Due to intramolecular hydrogen bonding, (-)-**182**[*] did not show any change even after prolonged reaction times, whereas (-)-**181** was converted to the corresponding mesyl derivative (-)-**183** within 1 h and in quantitative yield. The structure of (-)-**183** could be easily gleaned from its spectral data, particularly, the disappearance of hydroxy signal in the IR spectrum, the appearance of singlet at δ = 2.95 (3H) belonging to the methyl of mesyl group and downfield shift of the C<u>H</u>–O signal to δ = 5.31 (t, *J* = 4.9 Hz, 1H) in comparison to (-)-**181** in the ^{1}H NMR spectrum. ^{13}C NMR spectrum also provided an additional evidence by displaying an extra peak at δ = 47.5 belonging to the methyl carbon of mesyl group and by downfield shift in the <u>C</u>H–O signal to δ = 76.7.

Application of the Fujimoto's protocol for the reduction of mesylate derivatives to (-)-**183** by heating it with a mixture of zinc and sodium iodide in DME at 70 °C for 4 h produced long awaited compound (-)-**184** ($[\alpha]_D^{25}$ = –92.31, *c* = 0.675, $CHCl_3$) in 76% yield

[*] (-)-**182** had to be recycled by converting it back to ketone (-)-**179** by PDC oxidation.

(Scheme 45). The structure of (-)-**184** was deduced using. IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

The IR spectrum of (-)-**184** showed the presence of tertiary amide function by displaying a strong absorption band at ν_{max} = 1616 cm^{-1}.

In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**184**, the singlet at δ = 1.23 (3H) was assigned to the protons of the methyl group attached to the quaternary carbon (C–CH_3). Protons of the various methylene groups except N–CH_2 and O–CH_2 appeared in the range of, δ = 1.25-1.35 (m, 1H), 1.40-1.51 (m, 2 H), 1.58-1.70 (m, 2H), 1.77-1.86 (m, 3H), 1.92-2.05 (m, 2H) integrating for 10 protons altogether. The singlet appearing at δ = 3.27 (3 H) was assigned to the protons of the O–CH_3 group. Two multiplets appearing in the area of δ = 3.35-3.57 (3H) and 3.59-3.75 (1H) arise from the protons of the methylene group alpha to nitrogen in the pyrrolidine ring (N–$\underline{CH_2}$) and the methylene alpha to OCH_3 group ($\underline{CH_2}$–O–CH_3). A multiplet appearing between δ = 4.20-4.40 (1H) was assigned to the methine proton alpha to nitrogen in the pyrrolidine ring (N–$\underline{CH}$). Finally the olefinic protons appeared as multiplet in the usual range of δ = 5.48-5.80 (2H).

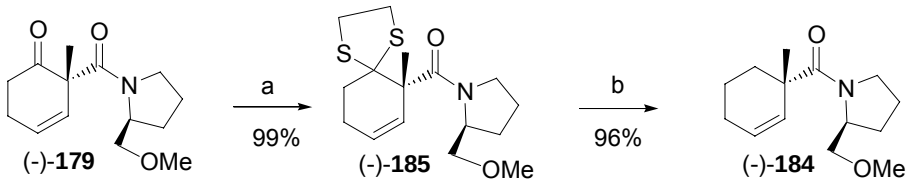
The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**184** displayed a total of 14 signals at δ = 23.8, 25.0, 25.7, 26.2, 27.8, 31.9, 43.5, 46.9, 57.2, 58.0, 71.6, 126.1, 130.8 and 174.1. The DEPT experiment confirmed the presence of two quaternary carbons with signals at δ = 43.5 and 174.1. These were assigned to the quaternary stereocenter and the carbonyl carbon, respectively. It also showed the presence of two olefinic methine carbons at δ = 126.1 and 130.8, respectively, and the N–CH methine carbon at δ = 57.2. The O–CH_2 methylene carbon appeared at δ = 71.6, while the N–CH_2 methylene carbon appeared at δ = 46.9. The remaining five methylene carbons appeared at δ = 23.8, 25.7, 26.2, 27.8 and 31.9, respectively. The two methyl groups present in the molecule appeared at δ = 25.0 (C–$\underline{C}H_3$) and 58.0 (O–$\underline{C}H_3$), respectively.

The mass spectral analysis of (-)-**184** displayed a molecular ion peak at *m/z* = 237 (M^+) along with the base peak at 70.

Although, Fujimoto's protocol of deoxygenation was fairly successful in yielding the deoxygenated compound (-)-**184**, the net conversion of (-)-**179** to (-)-**184** was low. This observation led us to turn our attention to evaluate the deoxygenation of (-)-**179** via reduction of the corresponding dithiolane derivative. Towards this endeavor; the keto group of compound (-)-**179** was converted to the corresponding dithiolane (-)-**185** by treating with ethane dithiol in the presence of $BF_3.OEt_2$. The disappearance of keto carbonyl signals in the IR and ^{13}C NMR spectra of (-)-**185** was consonant with its structure, while the appearance of broad singlet at δ = 3.20 integrating for four protons in its ^{1}H NMR spectrum, along with the characteristic signals corresponding to the carbons of the dithiolane moiety in its ^{13}C NMR Spectrum and a molecular ion peak at *m/z* = 327 in the mass spectrum fully confirmed its structure.

$^{n}Bu_3SnH$ reduction of (-)-**185** by refluxing in benzene in the presence of the catalytic amount of AIBN did not show any sign in the progress of the reaction even after prolonged heating. However, heating of a mixture of (-)-**185** and $^{n}Bu_3SnH$ at 120 °C for 24 h with repeated addition of catalytic amount of AIBN every four hours, produced desired compound (-)-**184** in 96% yield. The reduced product could be obtained in pure form by column Chromatography without much difficulty since there was considerable difference in the R_f values of compound and that of tin-sulfur residues (Scheme 46).

Scheme 46. Deoxygenation via dithiolane



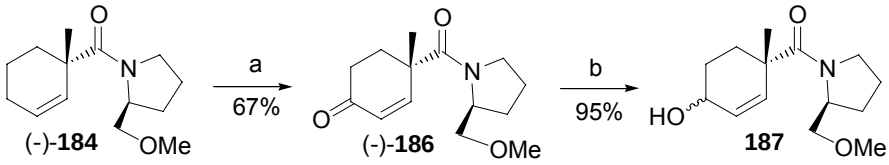
Reagents and conditions: a) ethanedithiol, $BF_3.OEt_2$, DCM, 0 °C to rt. b) $^{n}Bu_3SnH$, AIBN, 120 °C

Thus, having developed an efficient method for the deoxygenation of keto carbonyl in (-)-**179**, the stage was set to functionalize the cyclohexyl moiety in the desired manner.

3.3 Allylic hydroxylation of (-)-184

After successful deoxygenation of (-)-**179**, we moved on to introduce allylic hydroxyl functionality in (-)-**184** required for our planned strategy of installation of the tertiary stereocenter alpha to the quaternary stereocenter via proposed Claisen rearrangement. Initially, we tried direct hydroxylation using SeO_2 and Kharash-Sonvsky reaction,[49] however, these methods were found to be highly unsatisfactory. Therefore, we decided to resort to allylic oxidation-reduction sequence. Accordingly, allylic oxidation of (-)-**184,** using tertiary butyl hydroperoxide–pyridinium dichromate in benzene[50] furnished required ketone (-)-**186**, but in only 30% yield due to the formation of large lumps of PDC and celite causing difficulty in the work-up of the reaction mixture. However, use of DCM in place of benzene solved this problem as PDC has slight solubility in DCM and (-)-**186** could be obtained in 67% yield.

Scheme 47. Allylic oxidation-reduction



Reagents and conditions: a) PDC, $^tBuO_2H$, DCM, 10 ℃ to rt. b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ℃ to rt.

In the IR spectrum of (-)-**186** the amide carbonyl was evidenced by the absorption band at ν_{max} = 1618 cm^{-1} whereas the α,β-unsaturated carbonyl appeared at ν_{max} = 1692 cm^{-1}.

The ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**186** displayed a singlet at δ = 1.45 (3 H) corresponding to the methyl group of the quaternary stereocenter (C–CH_3). Two sets of multiplets appearing in the region of δ = 1.61-2.18 (m, 6H) and 2.42-2.68 (m, 2H) and integrating for eight protons altogether arise from the protons of the methylene groups except the O–CH_2 and N–CH_2 groups. The protons of the O–CH_3, O–CH_2 and N–CH_2 groups appeared as a part of multiplet with an overlapping singlet spanning the area δ = 3.13-3.63 (m, overlapping s at 3.28, 7H). The N–CH proton appeared as a multiplet at δ =

4.19-4.43 (m, 1H). A doublet present at δ = 6.39 (*J* = 9.8 Hz, 1H) was attributed to the olefinic proton on carbon alpha to carbonyl while the doublet exhibited at δ = 6.92 (*J* = 9.8 Hz, 1H) was assigned to the olefinic proton on the carbon beta to the carbonyl group.

In the ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**186**, a total of fourteen signals were displayed at δ = 24.4, 25.2, 26.4, 29.7, 33.9, 34.6, 46.3, 58.5, 58.7, 71.6, 129.2, 150.3, 166.6 and 184.5, respectively. The DEPT experiment confirmed that the signals present at δ = 34.6, 166.6 and 184.5 were of quaternary carbons. These signals were assigned to the quaternary stereocenter (C–CH_3), carbon of amide carbonyl and the carbon of keto carbonyl, respectively. The methine signals of N–CH carbon and the olefinic carbons appeared at δ = 58.5, 129.2 (CO–CH=CH) and 150.3 (CO–CH=CH), respectively. The signals of various methylene groups present in the molecule appeared at δ = 24.4, 26.4, 29.7, 33.9 (CO–CH_2), 46.3 (N–CH_2) and 71.6 (O–CH_2) respectively. Finally, the signal appearing at δ = 25.2 was attributed to the methyl attached to the quaternary stereocenter (C–CH_3) and the one seen at δ = 58.7 was assigned to the carbon of the O–CH_3 group.

Although, the chiral auxiliary in (-)-**186** is 1,4 with respect to the enone carbonyl, owing to its bulk, it was anticipated that it would play a significant role in directing incoming hydride and the reduction of enone carbonyl would occur stereoselectively. However, reduction of enone (-)-**186**, with sodium borohydride in methanol at room temperature gave **187** in 7:3 diastereomeric ratio favoring the *cis* form as indicated by GC and ^1H NMR analysis. Similarly, reduction of enone carbonyl group in (-)-**186** under Luche's conditions[51] by complexing the enone oxygen with $CeCl_3.7H_2O$ prior to addition of sodium borohydride furnished **187** in 3:2 diasteromeric mixture of *cis:trans* (Scheme 47). The structure of **187** followed from the presence of an absorption peak at ν_{max} = 3448 cm^{-1} corresponding to the hydroxyl group and disappearance of the enone carbonyl signal originally present in the parent compound (-)-**186** in the IR spectrum. ^1H and ^{13}C NMR spectra also provided ample evidence for the formation of **187** by displaying a signal for CH-OH proton at δ = 4.18 (td, *J*

= 6.8, 1.4 Hz, 1H) in ^{1}H NMR spectrum, and the corresponding signal for CH-OH carbon at δ = 65.9 in ^{13}C NMR spectrum. The diastereomeric ratios calculated from the peak ratios of OCH_3 signals for two diastereomers in the ^{1}H NMR spectrum were in good agreement with those obtained by GC analysis.

Poor selectivity in the Luche reduction indicated that the chiral auxiliary did not play a significant role in the stereochemical outcome of the reduction. Attempts to improve the diastreoselectivity in the favor of *trans* isomer using bulky reducing agents such as $LiAlH(OEt)_3$ (dr = 7:1) and $LiAlH(O\text{-}^{t}Bu)_3$ (dr = 9:1) also failed, since in both the cases *cis* isomer was found to be the major product. Separation of pure diastereomers by chromatography either directly or through their derivatives (Figure 5) also failed.

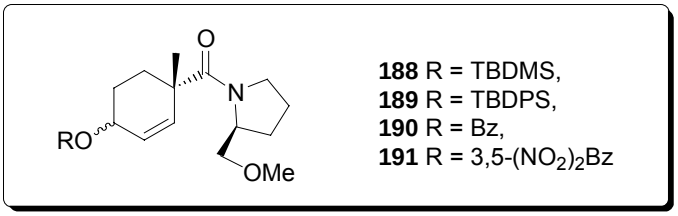


Figure 5. Hydroxy derivatives

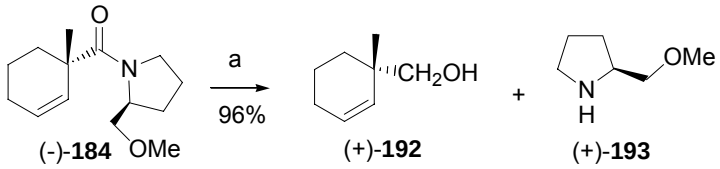
At this stage, we realized that the separation of diastereomers was not necessary since either of the diastereomers could be prepared in pure form via lactonization of the hydroxy group with the carbonyl followed by further manipulations. For this purpose, it was necessary to cleave the chiral auxiliary. Due to possible interference of hydroxy group of **187** during the cleavage of chiral auxiliary it was decided to proceed for auxiliary removal with (-)-**184**.

3.4 Preparation of (1*S*)-4-hydroxy-1-methyl-cyclohex-2-enecarboxylic acid methyl ester (169)

At this point, we focused on developing an efficient protocol for the removal of the chiral auxiliary from the cyclohexyl moiety. Since**,** (-)-**184** could not be subjected to acid catalyzed hydrolysis due to possible lactonization of the carboxyl group with the olefin, we attempted to cleave the chiral auxiliary by subjecting (-)-**184** to the base hydrolysis at

atmospheric pressure. However, it failed to give any product and heating in a steel bomb resulted into the decomposition of the starting material. Therefore, we decided to reduce (-)-**184** to the corresponding alcohol. Refluxing the solution of **184** in THF in the presence of the LAH gave corresponding amine by deoxygenation of the amide carbonyl. However, after some experimentation, we were delighted to obtain (+)-**192** in 96% yield by reverse addition of 1 equivalent of LAH to the stirring mixture of (-)-**184** in dry THF at -20 ºC and then slowly warming it to 0 ºC over a period of 4 h. The chiral auxiliary could also be recovered in 85% yield (Scheme 48).

Scheme 48. Cleavage of chiral auxiliary



Reagents and conditions: *a) $LiAlH_4$, THF, –20 ℃ to 0 ℃, 2 N H_2SO_4.*

Mechanistically, the formation of (+)-**192** can be explained as depicted in figure 6:

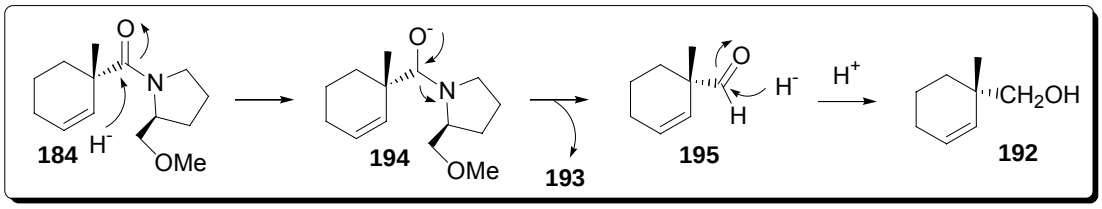


Figure 6. Mechanism of chiral auxiliary cleavage

Alcohol (+)-**192** was characterized using IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

The IR spectrum of (+)-**192** displayed an absorption band at ν_{max} = 3421 cm^{-1} indicating the presence of hydroxy group.

In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**192** a sharp singlet at δ = 0.95 (3 H) was assigned to the protons of the methyl group attached to the quaternary carbon (C–CH_3). The hydroxy proton (OH) along with the six protons of the three methylene groups present in cyclohexyl ring appeared as three sets of multiplets spanning the region of δ = 1.20-1.39 (2H), 1.65-1.79 (3H) and 1.90-2.00 (2H). Each of the $\underline{CH_2}$–OH protons

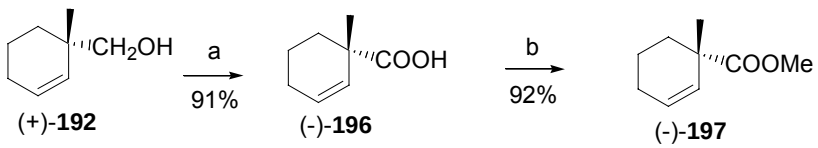
appeared as a doublet at δ = 3.29 (*J* = 11.0 Hz, 1H) and 3.39 (*J* = 11.0 Hz, 1H) respectively. The olefinic protons also appeared separately at δ = 5.36 (dt, *J* = 9.6, 2.2 Hz, 1H) and 5.80 (dt, *J* = 9.8, 3.8 Hz, 1H) respectively.

The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (+)-**192** displayed a total of eight signals at δ = 18.8, 24.0, 24.9, 31.4, 36.8, 71.2, 128.8 and 132.6. The DEPT spectrum showed the presence of a quaternary carbon at δ = 36.8 which was assigned to the quaternary steeocenter. It also revealed the presence of olefinic methine carbons at δ = 128.8 and 132.6, respectively. The methylene carbon of $\underline{C}H_2$–OH group appeared at δ = 71.2, while the carbons of three methylene groups of cyclohexyl moiety appeared at δ = 18.8, 24.9 and 31.4, respectively. The signal at δ = 24.0 was assigned to the carbon of the methyl group attached to the quaternary stereocenter (C–$\underline{CH_3}$).

The mass spectrum of (+)-**192** confirmed its molecular weight by displaying a molecular ion peak at *m/z* = 126.

With the successful cleavage of the chiral auxiliary, we moved on to convert the hydroxy methyl group of (+)-**192** to the carbomethoxy function. Towards this end, the alcohol (+)-**192** was oxidized to the corresponding acid **196** with PDC in DMF and was subsequently converted to its methyl ester (-)-**197** by treating it with the solution of diazomethane in ether (Scheme 49). Appearance of a stretching band at ν_{max} = 1676 cm^{-1} corresponding to carboxyl carbonyl in the IR spectrum and the disappearance of $C\underline{H_2}OH$ protons in ^1H NMR spectrum of **197** clearly indicated the required functional group transformation.

Scheme 49. Conversion of alcohol to ester



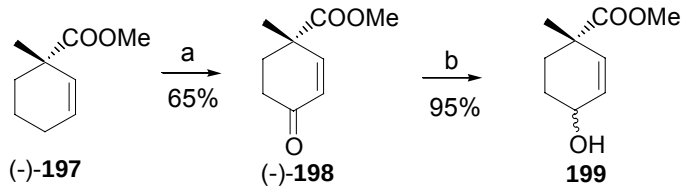
(+)-**192** (-)-**196** (-)-**197**

Reagents and conditions: a) PDC, DMF, rt. b) CH_2N_2, Et_2O, 0 °C to rt.

Spectral data of (-)-**197** displayed all the requisite signals, especially the strong absorption band at ν_{max} = 1730 cm^{-1} in its IR spectrum indicated the presence of ester functionality. The presence of methyl singlet at δ = 3.68 (3H) in the ^{1}H NMR spectrum and the corresponding signal at δ = 52.3 in the ^{13}C NMR spectrum provided ample evidence of the required conversion. In the ^{1}H NMR spectrum of (-)-**197** signal of the methyl group attached to the quaternary stereocenter had also shifted downfield to δ = 1.26 (3H) as compared to (+)-**192** due to electron withdrawing effect of the ester group.

The next step in the synthetic plan was to introduce the allylic hydroxy group. For the reasons discussed earlier, we opted for oxidation-reduction sequence instead of direct hydroxylation. In this context, allylic oxidation of (-)-**197** using PDC and *t*-butylhydroperoxide in DCM furnished α,β-unsaturated ketone (-)-**198** in 65% yield.

Scheme 50. Allylic oxidation-reduction of (-)-197



(-)-**197** (-)-**198** **199**

Reagents and conditions: *a) PDC, $^{t}BuO_2H$, DCM, 10 °C to rt. b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt.*

Compound (-)-**198** was characterized using IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis, which displayed all the requisite signals. The IR spectrum of (-)-**198** exhibited strong absorption bands at ν_{max} = 1730 and 1677 cm^{-1} indicating the presence of ester carbonyl and α,β-unsaturated carbonyl, respectively. In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**198**, a downfield shift in the methyl group attached to the quaternary carbon was observed as compared to (-)-**197** which now appeared as a sharp singlet at δ = 1.43 (3H). There was also a noticeable downfield shift in the protons of the two methylene groups on the cyclohexyl unit which appeared as two sets of multiplets spanning the region of δ = 1.85-2.05 (m, 2H) and 2.35-2.55 (m, 2H). The most significant feature of this spectrum was the appearance of the olefinic protons widely spaced, as

doublets with equal *J* value at δ = 5.96 (d, *J* = 10.2 Hz, 1H, CH=CH–CO) and 6.87 (d, *J* = 10.2 Hz, 1H, CH=CH–CO). Such a pattern is the characteristic feature of the α,β-unsaturated ketone with quaternary carbon in the γ-position. The ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of (-)-**198**, as expected displayed a total of nine signals at δ = 24.9, 32.6, 34.6, 43.9, 52.6, 128.7, 151.7, 174.6 and 198.5, respectively. The appearance of peak at δ = 198.5 arising from the carbonyl carbon of α,β-unsaturated ketone and downfield shift of the β-olefinic carbon to δ =151.7 provided strong support for the required conversion. As expected mass spectrum of (-)-**198** displayed the molecular ion peak at *m/z* = 168 (M^+) and the base peak at *m/z* = 81.

The α,β-unsaturated ketone (-)-**198** upon reduction under Luche's conditions[51] yielded corresponding allylic alcohol **199** in 95% yield and in 3:2 diastereomeric mixture, favoring the *cis* form as indicated by GC and ^1H NMR spectrum. The ratio of the two diastereomers being same as that obtained in the case of **187**, confirmed the fact that the chiral auxiliary does not play any role in the stereochemical outcome of the reduction (Scheme 50). The spectral data of **199** showed all the requisite characteristics. For example, the disappearance of IR absorption signal observed at ν_{max} = 1677 cm^{-1} in case of (-)-**198** for the enone carbonyl, and the appearance of CH-OH proton signal at δ = 4.00-4.15 (m, 1H) in ^1H NMR spectrum along with the hydroxyl stretch at ν_{max} = 3468 cm^{-1} in the IR spectrum of **199** were especially useful in confirming the required functional group conversion.

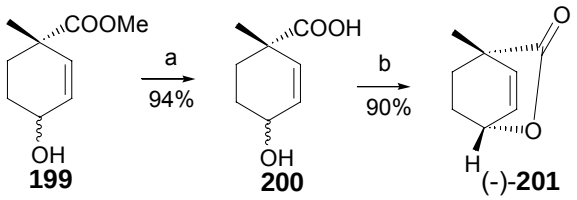
3.4 Preparation of (1*S*,4*S*)-4-Hydroxy-1-methyl-cyclohex-2-enecarboxylic acid methyl ester: A precursor for stereoselective installation of tertiary stereocenter (**174**)

In order to proceed further on our planned strategy of converting the mixture **199** into single diastereomer via lactonization, the carbomethoxy group of **199** was hydrolyzed using LiOH in THF/H_2O (1.3:1), to obtain **200** in 94% yield maintaining the same diastereomeric ratio. Absence of OCH_3 signal in ^1H NMR spectrum and presence of

absorption band at ν_{max} = 3600 cm^{-1} corresponding to the carboxylic acid group in the IR spectrum of **200** provided ample evidence for its structure.

Treatment of **200** with $BF_3.OEt_2$ in DCM converted both the diastereomers of **200** into lactone (-)-**201** in 90% yield (Scheme 51).

Scheme 51. Lactonization



Reagents and conditions: a) LiOH, THF, H_2O, rt. b) $BF_3.OEt_2$, DCM, 0 °C.

Mechanistically, the conversion of **200** to (-)-**201** occurs via allylium cation as depicted in the following figure (Figure 7).

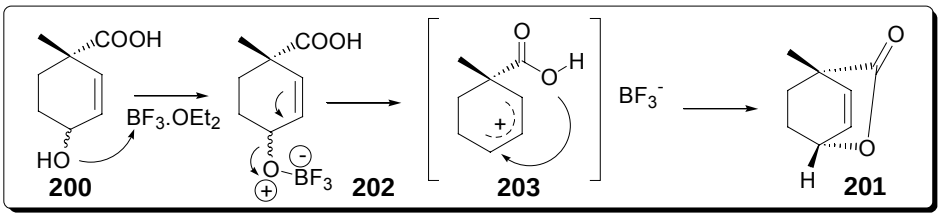


Figure 7. Mechanism of lactone formation

IR spectrum of (-)-**201** displayed a strong absorption band characteristic of lactone carbonyl at ν_{max} = 1743 cm^{-1}.

In the ^1H NMR spectrum ($CDCl_3$, 500 MHz) of (-)-**201,** a sharp singlet at δ = 1.36 (3H) belongs to the protons of the methyl group attached to the quaternary stereocenter (C–$\underline{CH_3}$). The protons of the two methylene groups were found appearing as multiplets at δ = 1.61-1.74 (m, 3H) and 2.14-2.23 (m, 1H) and integrating for four protons altogether. A multiplet observed in the region of δ = 5.07-5.12 (m, 1H) was assigned to the proton on the carbon alpha to oxygen ($\underline{CH}$–O–CO). The two olefinic protons appeared separately as multiplets at δ = 6.18 (dd, *J* = 7.8, 1.4 Hz, 1H) and 6.44 (dd, *J* = 7.8, 5.0 Hz, 1H).

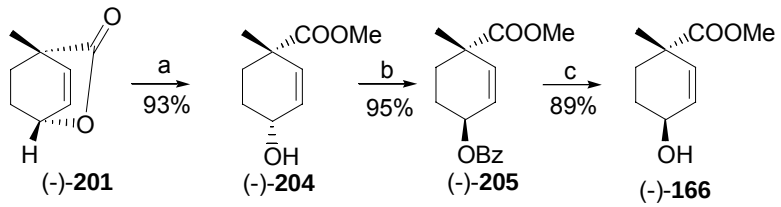
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of (-)-**201** gave a total of eight peaks at δ = 18.5, 26.1, 27.2, 43.6, 73.8, 131.2, 137.7 and 176.4. In the DEPT spectrum the

disappearance of the peaks at δ = 43.6 and 176.4 indicated that they were arising from the quaternary carbons and were assigned to the carbon of the quaternary stereocenter and that of the carbonyl group, respectively. The olefinic methine carbons appeared at δ = 131.2 and 137.7 respectively, while the remaining methine group (CH–O), appeared at δ = 73.8. The signals observed at δ = 26.1 and 27.2 were attributed to the two methylene groups respectively. Finally the signal at δ = 18.5 was assigned to the methyl carbon.

The mass spectrum confirmed the structure of (-)-**201** by displaying the molecular ion peak at *m/z* = 139 (M^++1) and the base peak at 79.

Treatment of (-)-**201** with sodium methoxide provided *cis*-alcohol (-)-**204** in 93% yield.[52]

Scheme 52. Preparation of trans-diastereomer (-)-166



(-)-**201** (-)-**204** (-)-**205** (-)-**166**

Reagents and conditions a) NaOMe, MeOH, reflux. b) i. DIAD, PPh_3, BzOH, THF, 0 °C to rt. ii. 1N NaOH, MeOH, rt.

Characteristic differences in the spectra of (-)-**201** and (-)-**204** established the conversion. For example, the hydroxy and ester functionalities in (-)-**204** were indicated by the presence of absorption bands at ν_{max} = 3440 and 1728 cm^{-1}, respectively, in its IR spectrum.

In the ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**204**, a sharp singlet at δ = 1.22 (3H) was assigned to the protons of the methyl group attached to the quaternary stereocenter (C–C$\underline{H_3}$). Multiplet appearing in the region of δ = 1.32-1.68 (m, 2H) belongs to the protons of the methylene group alpha to the CHOH functionality. The multiplet appearing at δ = 1.86-1.94 (m, 1H) corresponds to one of the proton of the methylene group vicinal to the quaternary stereocenter. The broad singlet present at δ = 2.00-2.07 (1H) was assigned to the proton of the hydroxy group (OH). The muliplet in the region of δ

= 2.17-2.35 (m, 1H) was arising from the remaining proton on the methylene group vicinal to the quaternary stereocenter. A singlet at δ = 3.66 (3H) belongs to the protons of the methyl of OCH_3 group. The proton of C<u>H</u>–OH group appeared as a doublet of doublet at δ = 4.12 (*J* = 6.8, 1.5 Hz, 1H). Finally the olefinic protons appeared as broad singlet in the region of δ = 5.70-5.85 (2H).

The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**204** displayed a total of nine signals appearing at δ = 25.8, 28.7, 29.4, 43.0, 52.2, 64.5, 130.2, 133.1 and 176.7 respectively. The DEPT experiment proved that the signals at δ = 43.0 and 176.7 belonged to the quaternary carbons of quaternary stereocenter and carbonyl group respectively. It also revealed the presence of methine carbon at δ = 64.5, which was assigned to the <u>C</u>H–OH carbon. The two methylene groups appeared closely at δ = 28.7 and 29.4, respectively. The remaining two signals at δ = 25.8 and 52.2 were assigned to the carbons of the methyl group attached to the quaternary stereocenter and that of the carbomethoxy group, respectively.

The mass spectrum of (-)-**204** gave a molecular ion peak at *m/z* = 170, along with the base peak at *m/z* = 110.

Mitsunobu inversion of *cis* alcohol (-)-**204,** provided corresponding *trans* isomer (-)-**166** in excellent yield. Although, the *cis* alcohol was entirely consumed during the inversion reaction, the intermediate benzoyl derivative **205** was isolated in order to ascertain the diastereomeric purity of the *trans* isomer (Scheme 52). The spectral data of (-)-**166,** although having marked similarities with that of (-)-**204,** also showed characteristic differences such as slight downfield shift of most of the peaks in the ^1H NMR spectrum. The difference in the spectral data of (-)-**166** and its preceding benzoyl derivative was obvious from the disappearance of the signals arising from phenyl group in ^1H and ^{13}C NMR spectra of (-)-**166**. The appearance of hydroxy absorption band at ν_{max} = 3433, in the IR spectrum of (-)-**166**, was also a fair indication of the required hydrolysis.

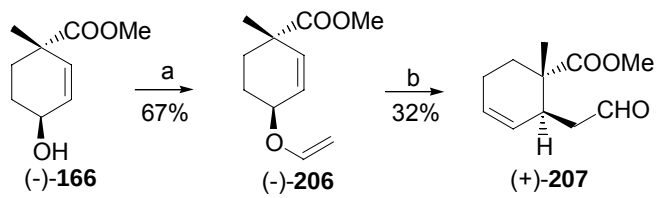
The next step in the planned synthetic route was to subject (-)-**166** to Claisen rearrangement followed by cyclization to obtain the desired *trans*-hydrindane system. Following section describes the successful implementation of this plan.

3.5 Synthesis of *trans*-hydrindane system (+)-164 by installation of tertiary stereocenter using Classical Claisen rearrangement followed by annulation

Construction of two or more vicinal stereocenters is a formidable task in organic synthesis. The difficulties are alleviated when the stereocenters are quaternary or tertiary. As depicted in section 2, it was proposed to make use of stereospecific nature of the Claisen rearrangement reaction for the construction of tertiary stereocenter alpha to the quaternary one. Cyclization of the resulting cyclohexyl moiety carrying vicinal quaternary and tertiary stereocenters should then provide the desired *trans*-hydrindane system (+)-**164**.

Towards this endeavor, *trans*- allylic alcohol (-)-**166** was subjected to classical Claisen rearrangement as depicted in Scheme 53. The reaction sequence involved the initial conversion of (-)-**166** to its vinyl ether derivative (-)-**206** by treatment with ethyl vinyl ether in the presence of the mercuric acetate followed by thermal [3,3]-sigmatropic rearrangement by refluxing in benzene to obtain aldehyde (+)-**207**. The structure of (-)-**206**, followed from the fact that the absorption band arising from the hydroxy group shown by parent alcohol (-)-**166** had disappeared in its IR spectrum. The presence of signals at δ = 4.25-4.40 (m, 2H) and 6.37 (dd, *J* = 9.9, 3.6 Hz, 1H) in the ^{1}H NMR and the signals seen at δ = 149.8 (O–<u>C</u>H=CH_2) and 88.4 (O–CH=<u>C</u>H_2) in the ^{13}C NMR spectrum of (-)-**206**, characteristic of a vinyl ether moiety, were also consonant with its structure.

Scheme 53. Classical Claisen rearrangement



Reagents and conditions: a) Ethyl vinyl ether, $Hg(OAc)_2$, reflux. b) PhH, reflux.

Aldehyde (+)-**207** exhibited requisite spectral characteristics, which assisted in its structure elucidation.

IR spectrum of (+)-**207** evidenced the presence of aldehyde functionality by displaying a strong absorption band at ν_{max} = 1714 cm^{-1}.

^1H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**207** showed a considerable different pattern as compared to (-)-**206** due to skeletal rearrangement. A singlet appearing at δ = 1.35 (s, 3H) arises from the protons of the methyl group vicinal to the quaternary stereocenter (C–CH_3). A multiplet appearing in the region of δ = 1.95-2.10 (m, 2H) was assigned to the protons of allylic CH_2 group (C–CH_2–$\underline{CH_2}$), while another multiplet appearing between δ = 2.25-2.41 (m, 2H) was assigned to the protons of the methylene group alpha to the quaternary stereocenter (C–$\underline{CH_2}$–CH_2). Another multiplet spanning the region between δ = 2.46-2.65 (m, 2H) arises from the protons of the methylene group vicinal to aldehyde function ($\underline{CH_2}$–CHO). A triplet of doublet appearing at δ = 2.91 (*J* = 8.6, 3.9 Hz, 1H) was assigned to the proton of the tertiary stereocenter ($\underline{CH}$–CH=CH). A singlet present at δ = 3.71 (s, 3H) appears from the protons of the methyl group of ester ($COOCH_3$). The olefinic protons appeared as multiplet in the area of δ = 5.75-6.20 (m, 2H, CH=CH). The most significant feature of the ^1H NMR spectrum was the presence of a distinct singlet at δ = 9.67 (s, 1H), which was assigned to the aldehydic proton (CHO).

^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of (+)-**207** confirmed the carbon framework. It exhibited a total of eleven signals at δ = 17.2, 22.1, 33.1, 37.2, 41.1, 43.4, 52.1, 130.2, 131.4, 176.6 and 212.3, respectively. DEPT spectrum revealed that the signals appearing at δ = 43.4, 176.6 and 212.3 belonged to quaternary carbons and were assigned to the carbon of the quaternary stereocenter ($\underline{C}$–CH_3), carbonyl carbon of carbomethoxy group ($\underline{C}OOCH_3$) and the carbonyl carbon of the aldehydic group ($\underline{C}$HO), respectively. Signals at δ = 37.2 ($\underline{C}$H–CH=CH), 130.2 ($\underline{C}$H=CH–CH) and 131.4 (CH=$\underline{C}$H–CH) were arising from the methine carbons of the tertiary stereocenter and the olefin, respectively. Carbons of the three methylene groups present in the molecule appeared at δ = 22.1 ($\underline{C}H_2$–CH_2–CH=CH),

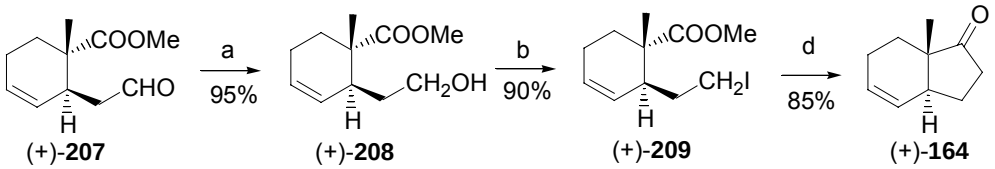
33.1 (CH_2–$\underline{C}H_2$–CH=CH), and 41.1 ($\underline{C}H_2$–CHO), respectively. Methyl groups appeared as usual at δ = 17.2 (C–$\underline{C}H_3$), and 52.1 (COO$\underline{C}H_3$), respectively.

Mass spectral analysis of (+)-**207** revealed a molecular ion peak at *m/z* = 196 (M^+) along with the base peak at *m/z* = 42.

(+)-**207** contains a cyclohexyl moiety carrying vicinal quaternary and tertiary stereocenter with desired *trans* disposition of the groups and with carbomethoxy group and aldehydic group readily available for selective functionalizations.

At this stage, we perceived that in order to convert (+)-**207** to the *trans*-hydrindane system (+)-**164**, annulation by metal halogen exchange would best suit our purpose.[37] Towards this goal, aldehydic group of (+)-**207** was selectively reduced using sodium borohydride in methanol to get alcohol (+)-**208** in excellent yield.

Scheme 54. Annulation of five membered ring



(+)-**207** (+)-**208** (+)-**209** (+)-**164**

Reagents and conditions: a) $NaBH_4$, MeOH, –5 to 10 °C. b) I_2, PPh_3, imidazole, CH_2Cl_2, 6h. c) ^tBuLi, THF, –100 °C to –50 °C 2 h.

As expected, spectral data of (+)-**208** gave all the relevant information, which ascertained the conversion of (+)-**207** to (+)-**208**. The presence of absorption band at ν_{max} = 3426 cm^{-1} belonging to the hydroxyl group and disappearance of the band at 1714 cm^{-1} (displayed by (+)-**207** and arising from the aldehydic carbonyl group) in the IR spectrum of (+)-**208** clearly indicated the required functional group transformation. The absence of aldehydic proton and the appearance of CH_2OH protons at δ = 3.46-3.83 in the ^1H NMR spectrum of (+)-**208** provided additional support. ^{13}C NMR spectrum showed the presence of signal for $\underline{C}H_2OH$ carbon at δ = 71.9 and the disappearance of CHO carbon signal at δ = 212.3 (seen in the case of (+)-**207**). The mass spectrum confirmed these observations by

displaying a molecular ion peak at *m/z* = 198 corresponding to the molecular weight of (+)-**208**.

The iodo precursor (+)-**209** required for cyclization was obtained by substituting the primary hydroxy group of (+)-**208** with an iodo group. This transformation was achieved by treating (+)-**208** with molecular iodine in presence of triphenyl phosphine and imidazole in DCM as a solvent, which furnished (+)-**209** in excellent yield. The spectral data of (+)-**209** exhibited all the requisite characteristics, specially the disappearance of the hydroxy absorption band in the IR spectrum and the upfield shift of the carbon signal of the reaction center in its ^{13}C spectrum provided ample evidence of the required conversion.

Towards the successful annulation of the five-membered ring, we were delighted to observe that the *trans*-hydrindane system (+)-**164** was formed in excellent yield by treatment of (+)-**209** with ^{t}BuLi. A special procedure had to be adopted for this purpose, which involved the addition of ^{t}BuLi (0.52 M solution in *n*-pentane) to a stirred solution of (+)-**209** in THF at −100 °C. The anion that resulted from metal halogen exchange underwent cyclization, by attacking the carbomethoxy group present in the molecule to generate the required five-membered ring. This led to the formation of suitably functionalized hydrindane system (+)-**164**, which had the characteristic camphor like odor (Scheme 54).

The IR spectrum of (+)-**164** gave ample evidence for the presence of cyclopentanone moiety by displaying a strong absorption band at ν_{max} = 1735 cm^{-1}.

In the ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**164** a singlet appearing at δ = 1.05 (3H) was assigned to the protons of the methyl group attached to quaternary stereocenter (C–CH_3). A multiplet appearing at δ = 1.26-1.41 (2H) belongs to the protons of the methylene group in vicinity of the tertiary stereocenter (CH–$\underline{CH_2}$). Two sets of multiplets spanning the region of δ = 1.60-1.80 (m, 2H) and 1.90-2.00 (m, 2H) and integrating for four protons altogether correspond to the four protons of the two methylene groups present in the cyclohexyl moiety. Another multiplet shown in the area of δ = 2.15-

2.40 (3H) arise from the proton at ring junction and the protons of the methylene group vicinal to carbonyl function. The olefin protons appeared as a multiplet at 5.51-5.86 (2H, CH=CH).

The ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of (+)-**164** displayed a total of ten signals at δ = 21.6, 21.8, 26.2, 27.0, 35.9, 43.6, 47.2, 127.5, 129.0 and 223.4 respectively. The DEPT experiment suggested that the peaks appearing at δ = 47.2 and 223.4 arise from quaternary carbons and were assigned to the carbons of the quaternary stereocenter and the carbonyl group. The downfield nature of the carbonyl signal provided additional evidence for cyclopentanone moiety. The signals for methine carbons of tertiary stereocenter and olefin appeared at δ = 43.6 (C̲H–CH=CH), 127.5 (CH–CH=C̲H) and 129.0 (CH–C̲H=CH) respectively. The carbons of the four methylene groups present in the molecule appeared at δ = 21.6 (CH–C̲H$_2$), 26.2 (CH$_2$–C̲H$_2$–CH=CH), 27.0 (C̲H$_2$–CH$_2$–CH=CH) and 35.9 (COC̲H$_2$) respectively. Lastly the signal at δ = 21.8 was assigned to the carbon of the methyl group (C–C̲H$_3$).

The mass spectrum of (+)-**164** as expected, showed fragmentation pattern with prominent fragments at *m/z* = 151 (M^++1), 137, 110, 109, 95, 79, 57 (100) and 41.

The successful synthesis of (+)-**164** was a pleasing moment, since it forms the core structural feature of large number of bioactive natural products and analogues, some of which are already sold in market as efficient drugs for treatment of diverse array of human disorders. However, we were still discontented with the low yields of the classical Claisen rearrangement. This mental agitation resulted in the development of an alternative protocol for the synthesis of (+)-**164** from (-)-**166**, which had been the most fulfilling experience in the entire journey. The success of this endeavor is discussed in the following section.

3.6 Alternative approach for the synthesis of (+)-164 from (-)-166: Use of modified Claisen rearrangement-Dieckmann condensation sequence

At this stage, we closely analyzed the facts responsible for low yields in the classical Claisen rearrangement, which led us to conclude that the absence of activating groups on the reaction centers is primarily responsible for low reaction rates and need for harsh conditions. Literature precedent shows that placing the activating groups on the vinyl unit of the reactant can increase the rate of Claisen rearrangement. The most commonly used modified Claisen rearrangements are summarized in the figure below (Figure 8).

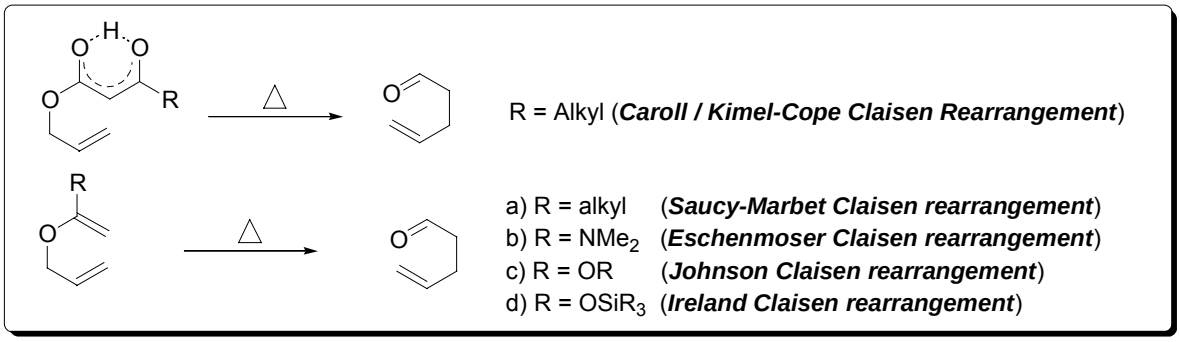
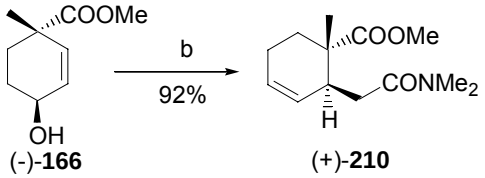


Figure 8. Modified Claisen rearrangements

To begin with, we decided to evaluate the Eschenmoser Claisen rearrangement on (-)-**166**. We reasoned our choice based on the practical proposition of selectively manipulating the resulting amide function in presence of the ester group.

Towards this endeavor, (-)-**166** was also subjected to Eschenmoser Claisen rearrangement by heating it with *N,N*-dimethylacetamide dimethylether in xylene at 150 °C for 5 h, which furnished rearranged product (+)-**210** in very good yield (Scheme 55).

Scheme 55. Eschenmoser Claisen rearrangement



(-)-**166** (+)-**210**

Reagents and conditions: a) $CH_3C(OMe)_2NMe_2$, xylene, 150 °C.

Formation of (+)-**210** can be visualized as depicted in Figure 9.

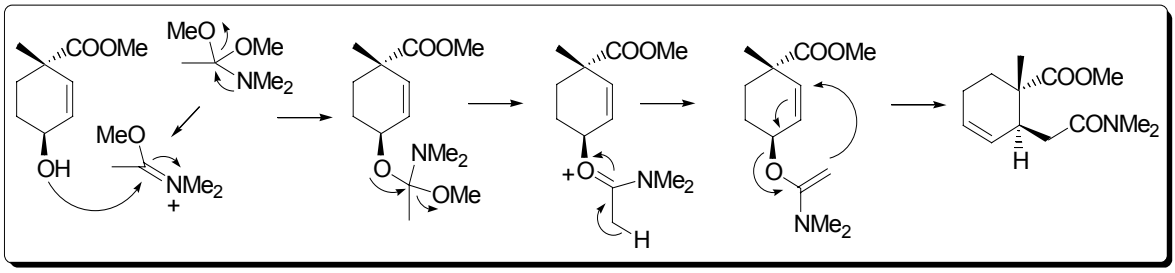
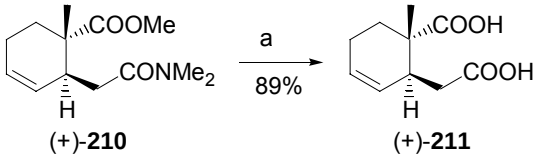


Figure 9. Mechanism of Eschenmoser Claisen rearrangement

The structure of (+)-**210** could be easily gleaned from its spectral data, which disclosed all the relevant information. The presence of Amide ester carbonyls were revealed by the absorption bands at ν_{max} =1682 and 1734 cm^{-1}, respectively in its IR spectrum. The hydroxy absorption band displayed by parent (+)-**166** had also disappeared. This was supported by the presence of two singlets at δ = 2.92 (s, 3H) and 2.96 (s, 3H), corresponding to the *N*-dimethyl group in the ^{1}H NMR spectrum of (+)-**210** and the corresponding signals at δ = 35.2 and 37.0 in its ^{13}C NMR spectrum. The absence of C<u>H</u>-OH proton from ^{1}H NMR of was an additional proof for the depicted skeletal rearrangement.

As per our planned strategy, it was necessary to hydrolyze the amide moiety selectively in order to proceed for the cyclization. Here again, the acid catalyzed hydrolysis could not be used due to probable lactonization and the base catalyzed hydrolysis led to the formation of diacid **211**. Attempts to obtain the desired half ester by a variety of permutations and combinations of reagents and solvents did not yield much success (Scheme 56).

Scheme 56. Attempted selective hydrolysis of amide group



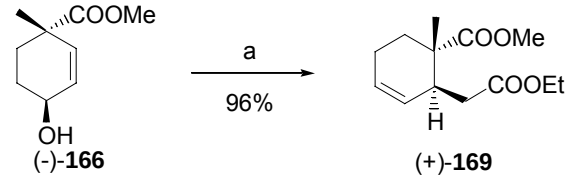
(+)-**210** (+)-**211**

Reagents and conditions: a) KOH, 95% EtOH, reflux.

The structure of (+)-**211** follows from its spectral data, which showed a marked difference as compared to that of (+)-**210**, specially the absence of absorption bands arising from amide and ester carbonyls and the presence of a band corresponding to acid carbonyl in the IR spectrum of (+)-**211.** The absence of methyl groups of carbomethoxy and *N*-dimethyl functionalities in ^{1}H and ^{13}C NMR spectra of (+)-**211** also established the depicted transformation.

At this juncture, we moved on to test the feasibility of Johnson's orthoester Claisen rearrangement, which incidentally became a necessity, since it was not possible to selectively hydrolyze the amide moiety in (+)-**210**. It was a gratifying moment to observe that (-)-**166** underwent Johnson's orthoester Claisen rearrangement when, heated with diethyl orthoacetate in presence of catalytic amount of propionic acid at 137-140 °C to afford diester (+)-**169** in 96% yield (Scheme 57). Very short reaction time of 3 h as compared to that of Classical Claisen rearrangement (95 h) is also quite remarkable and propitious.

Scheme 57. Johnson's orthoester Claisen rearrangement



Reagents and conditions: a) $CH_3C(OEt)_3$, propionic acid, 137-140 °C.

Formation of (+)-**169** can be rationalized by the mechanism depicted in the following figure (Figure 10).

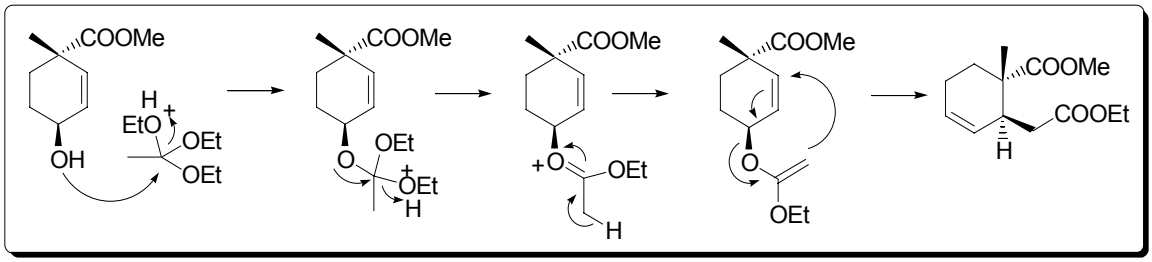


Figure 10. Mechanism of Johnson-Claisen rearrangement

The IR spectrum of (+)-**169** exhibited a strong absorption band at ν_{max} =1730 cm^{-1} indicating the presence of ester functionality.

The ^1H NMR spectrum ($CDCl_3$, 300 MHz) of (+)-**169** displayed a singlet at δ = 1.10 (3H), which belongs to the protons of the methyl group attached to quaternary stereocenter (C–CH_3). A triplet at δ = 1.26 (*J* = 7.0 Hz, 3H) was assigned to the methyl group of the carboethoxy moiety ($COOCH_2\underline{CH_3}$). Two sets of multiplets appearing in the area of δ = 1.55-1.80 (m, 2H) and δ = 1.85-2.20 (m, 4H) and integrating for six protons altogether arise from the protons of the two methylene groups of cyclohexyl moiety and the one attached to the tertiary stereocenter. Another multiplet present in the region of δ = 2.25-2.50 (1H) was assigned to the proton of the tertiary stereocenter (<u>CH</u>–CH=CH). Methyl protons of carbomethoxy group appeared as singlet at δ = 3.7 (3H, $COOCH_3$). A distinct quartet present at δ = 4.13 (q, *J* = 3.0 Hz, 2H) correspond to the methylene protons of carboethoxy group ($COO\underline{CH_2}CH_3$). The olefinic protons appeared separately at δ = 5.50 (dt, *J* = 10.2, 2.4 Hz, 1H, CH–CH=<u>CH</u>) and 5.67 (dd, *J* = 10.2, 2.4 Hz, 1H, CH–<u>CH</u>=CH), respectively.

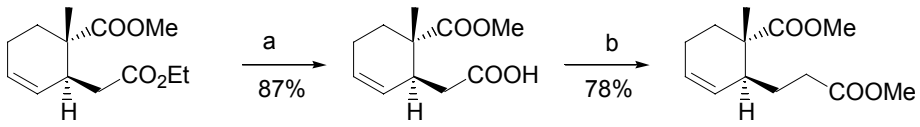
The ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of (+)-**169** exhibited a total of thirteen signals at δ = 13.7, 16.3, 21.6, 31.0, 35.7, 36.8, 43.5, 51.5, 60.0, 125.7, 128.0, 172.0 and 177.1, respectively. The DEPT experiment showed that peaks appearing at δ = 43.5, 172.0 and 177.1 belonged to quaternary carbons and were assigned to the quaternary stereocenter (<u>C</u>–CH_3), carbonyl carbon of carboethoxy (<u>C</u>$OOCH_2CH_3$) group and the carbonyl carbon of the carbomethoxy group (<u>C</u>$OOCH_3$), respectively. The signals present at δ = 36.8, 125.7 and 128.0 arise from the methine carbons of tertiary stereocenter (<u>C</u>H–CH_2–COOEt), and olefin, respectively. The more downfield signal for olefinic methine carbon belongs to the one next to tertiary stereocenter. The methylene carbons were exhibited at δ = 21.6 (CH_2–<u>C</u>H_2–CH=CH), 31.0 (CH–<u>C</u>H_2–COOEt), 35.8 (<u>C</u>H_2–CH_2–CH=CH) and 60.0 ($COO\underline{C}H_2CH_3$), respectively. Finally the signal at δ = 13.6 belongs to the methyl of carboethoxy group ($COOCH_2\underline{C}H_3$), the one at δ = 16.3 belongs to

the methyl group attached to quaternary stereocenter (C–$\underline{C}H_3$), while the other at δ = 51.5 belongs to the methyl carbon of the carbomethoxy group (COO$\underline{C}H_3$).

The mass spectral analysis of (+)-**169** disclosed the molecular ion peak at *m/z* = 240 (M^+) and the base peak at 41.

A stage was now set to evaluate the efficiency of (+)-**169** in producing the desired half ester required for subsequent manipulations. Towards this end, we observed that the selective hydrolysis of the carboethoxy group could be achieved by refluxing it with one equivalent of NaOH in methanol. The structure of (+)-**212**, was evident from its spectral data, which disclosed all the relevant information. The appearance of the absorption band at ν_{max} = 3592 and 1687 cm^{-1} corresponding to the carboxylic acid hydroxy and carbonyl functions respectively as well as the disappearance of the ethyl group signals in ^1H NMR and ^{13}C NMR spectra of (+)-**212**, were especially useful in deducing its structure. As usual the mass spectrum confirmed the information revealed by other spectral techniques by displaying a molecular ion peak at *m/z* = 212 (M^+) and requisite fragmentation pattern.

Scheme 58. Arndt-Eistert homologation



(+)-**169** (+)-**212** (+)-**213**

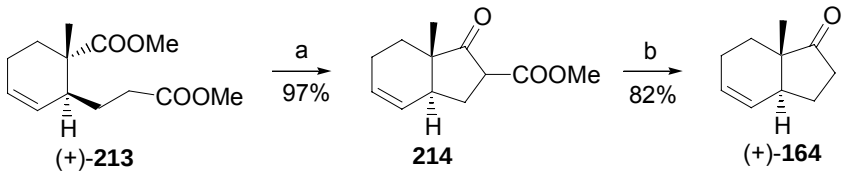
Reagents and conditions: a) 1 eq. NaOH, MeOH, reflux. b) i. $SOCl_2$, Pyridine, PhH, rt. ii. CH_2N_2, Et_2O, 0 ℃ to rt. iii. Ag_2O, MeOH, reflux.

As per our planned strategy, our next task was to homologate the side arm carrying carboxylic acid function using Arndt Eisteret protocol. Towards this objective, the carboxylic acid group of (+)-**212** was converted to acid chloride by treatment with thionyl chloride in benzene at rt. After 6h of stirring the benzene and the excess of thionyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in benzene and was added to the dilute solution of diazomethane in ether at 0 °C. The resulting solution was stirred at room temperature for 5 h to obtain the diazoketone, which was then subjected to Wolf rearrangement by refluxing with silver oxide in methanol to furnish the

homologated diester (+)-**213** (Scheme 58). The structure of (+)-**213**, followed from the presence of two absorptions bands in the carbonyl region at ν_{max} = 1737 and 1730 cm^{-1}, in its IR spectrum, which arise from the two carbomethoxy groups present. Furthermore, the presence of extra methylene signal at δ = 25.6 in the ^{13}C NMR spectrum of (+)-**213**, and the corresponding extra protons in the aliphatic region of ^{1}H NMR spectrum of (+)-**213**, provided strong support for its structure. The presence of molecular ion peak at *m/z* = 240, in the mass spectrum of (+)-**213**, confirmed the data obtained from other spectral techniques.

With the synthesis of diester (+)-**213**, a stage was set to build the five-membered ring over the six-membered ring using Dieckmann condensation. Subjecting (+)-**213** to the Dieckmann condensation yielded β-ketoester **214**. Best results for the Dieckmann cyclization were observed with NaHMDS in THF, which furnished the cyclized product in 97% yield. Other conditions such as NaOMe in PhH, NaH in THF, NaH in DMSO, NaH in DME, LDA, ^{t}BuOK in ^{t}BuOH etc., also produced the desired product, however in the lower yields of 70-80% (Scheme 59).

Scheme 59. Annulation of five-membered ring by Dieckmann condensation



(+)-**213** **214** (+)-**164**

Reagents and conditions: *a) NaHMDS, THF, 0 °C to rt. b) DABCO, xylene, 150 °C.*

In the IR spectrum of **214** the band at ν_{max} = 1753 and 1728 cm^{-1} were assigned to the ester carbonyl and the keto carbonyl, respectively.

In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of **214** a singlet appearing at δ = 1.10 (3H) correspond to the methyl group attached to quaternary stereocenter (C–CH_3). Two sets of multiplets appearing in the region of δ = 1.20-1.50 (m, 2H) and 1.75-2.10 (m, 4H); and integrating for six protons altogether arise from the protons of the three methylene groups present in the molecule. A triplet present at δ = 2.58 (*J* = 8.6 Hz, 1H) was assigned

to the proton on the ring junction (CH–CH=CH), while the triplet at δ = 3.29 (*J* = 8.6 Hz, 1H) was attributed to the proton on the tertiary carbon between the two carbonyl groups (CO–CH–$COOCH_3$). A tall and sharp singlet at δ = 3.72 (3H) belongs to the methyl of the carbomethoxy group ($COOCH_3$). The olefinic proton on the carbon vicinal to ring junction appeared as a doublet of doublet at δ = 5.56 (*J* = 10.1, 1Hz, 1H, CH–CH=CH), whereas the other olefinic proton appeared as a multiplet in the region of δ = 5.69-5.76 (1H, CH–CH=CH).

The ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **214** displayed a total of twelve signals at δ = 21.8, 22.0, 26.4, 27.8, 36.2, 43.9, 48.6, 52.3, 127.7, 129.2, 172.4 and 220.3, respectively. DEPT spectrum of **214** it was realized that the signals appearing at δ = 43.9, 172.4 and 220.3 belonged to the quaternary carbons. These signals were attributed to the quaternary stereocenter, carbonyl carbon of carbomethoxy group and the carbon of the keto carbonyl group respectively. The methine carbons of ring junction, tertiary carbon between the two carbonyl groups and the olefin were exhibited at δ = 36.2, 48.6, 127.7 and 129.2, respectively. The signals appearing at δ = 22.0, 26.4 and 27.8 were proved to be coming from the three methylene groups present in the molecule. The methyl group attached to quaternary stereocenter appeared at δ = 21.8 while the methyl group of carbomethoxy moiety was shown at δ = 52.3.

The mass spectrum of **214** exhibited molecular ion peak at *m*/z = 208 (M^+).

Finally, the target molecule (+)-**164** was obtained from **214** by subjecting it to demethoxycarbonylation by heating it with DABCO in xylene.[53] It may be worth mentioning at this point that the conventional methods for this purpose such as refluxing β-keto ester either with the mixture of acetic acid, conc. HCl and water or with NaCl in DMSO were equally efficient in producing (+)-**164**, but involved tedious workup procedures. The spectral data as well as the optical rotation of (+)-**164** synthesized by this approach matched perfectly with that obtained by the classical Claisen rearrangement-cyclization strategy.

Conclusion

In this section of the thesis, we have accomplished the synthesis of usefully functionalized optically pure *trans*-hydrindane system, present in numerous bioactive natural products, in particular vitamin D and analogues, via chiral auxiliary approach. We have devised a new, simple and flexible strategy towards this moiety starting from cheaply available aromatic compound. The chiral auxiliary was also derived from a cheaply available amino acid L-proline. Although the synthesis of only one enantiomer has been described, the strategy can very well be used for the preparation of both the enantiomers utilizing enolate equilibration protocol developed by Schultz *et al*.

Through this synthesis we have also achieved a daunting task of constructing vicinal quaternary and tertiary stereocenters in cyclohexyl moiety in a stereoselective manner. The versatile precursors (+)-**207**, (+)-**210** and (+)-**169** can in principle serve in the synthesis of large number of bioactive natural products and analogues.

4. Attempted catalytic asymmetric approach for the construction of optically active *trans*-hydrindane system

4.1 Our Plan

Transition metal catalyzed asymmetric allylic alkylation largely developed by Trost *et al*., is a versatile method having great applicability as it permits the formation of plethora of bond types including but not limited to C-C, C-N, C-O, C-S, C-P, and C-H bonds. All the aspects of this reaction have been studied in detail and excellent reviews have appeared in the literature over the years.[54] Despite large number of publications appearing in the literature in this area, the approaches pertaining to stereoselective intramolecular AAA reaction leading to C-C bond formation are very limited.[55] The principal limiting factor in this case had been the steric requirement of the newly forming ring. We decided to work in this least explored area and envisioned the synthesis of *trans*-hydrindane system applying intramolecular AAA reaction as depicted in figure 11.

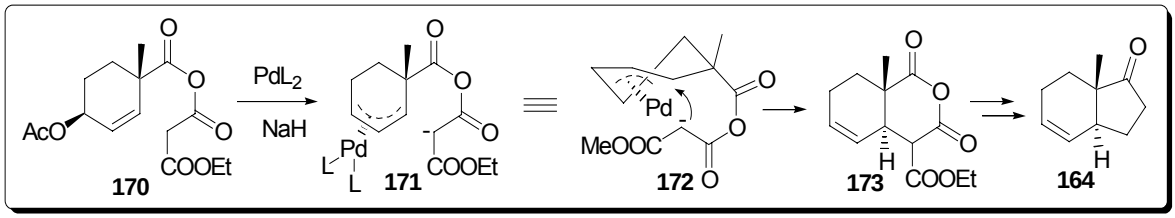


Figure 11. Synthetic design

We designed a racemic substrate **170**, which upon AAA reaction was expected to provide a precursor **173** in enantiomerically enriched form, whose conversion to usefully functionalized *trans*-hydrindane system **164** would involve simple functional group transformations. We reasoned stereo and regioselective formation of **173** based on the molecular architecture of our designed substrate **170**. The relatively flat half-chair conformation of cyclohexene should favor the formation of 1,2-substituted product over 1,4-substituted one, since C-4 would be placed away from the nucleophile. The same factor should ease the formation of *trans* ring junction. It was further anticipated that the use of oxygen as a part of the tether chain carrying nucleophile would bring the nucleophile

closer to C-2, since the C-O bond length is shorter than C-C bond length and also the C-O-C bond angle is smaller than the C-C-C bond angle.

Before, we proceed to discuss the synthesis of our designed precursor and experimental observations regarding palladium catalyzed allylic alkylation reaction, it would be desirable to briefly discuss the principles underlying AAA reaction to justify our choice.

Despite enormous developments in the area of transition metal catalyzed allylic alkylations, the problems concerning the regiochemistry in general have not yet been addressed to a satisfactory limit. The characteristic feature of Pd-catalyzed allylic alkylations using soft nucleophiles is that they involve the retention of configuration and occur at the least hindered site of the π-allyl complex. Therefore, if the substrate is not symmetric, i.e. carrying a substituent on vicinal carbon of one of the end, then 1,4-substituted product is preferred as compared to the 1,2-substituted product. A recent study by DeShong *et al.,* concerning the regioselectivity of the allylic substitution of cyclohexyl and cyclopentyl systems strongly supports this fact.[56] In the case of *cis*-substituted cyclohexyl systems, it was observed that irrespective of whether the substitution is 1,2- or 1,4- with respect to the leaving group, the 1,2-substituted product is formed preferentially (Figure 12).

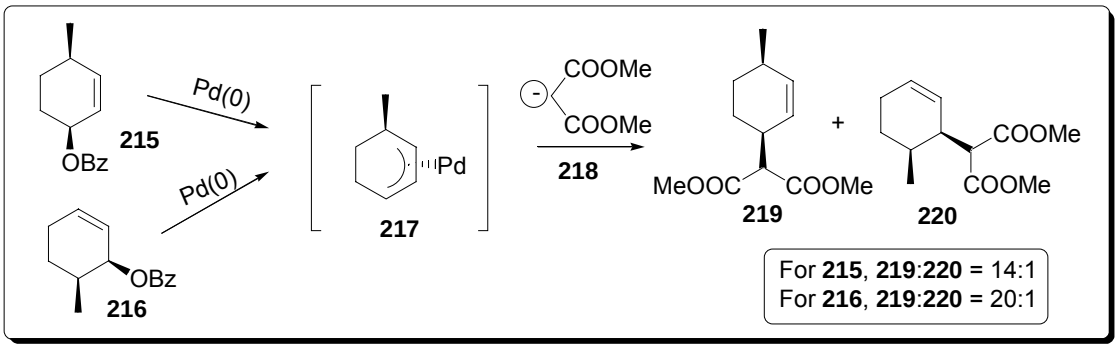


Figure 12. Intramolecular allylic alkylation

Limited formation of 1, 2-substituted product can be attributed to the fact that the nucleophile is external and is free to wander around the substrate. It, thus, attacks the least hindered terminal as a general principle, giving rise to 1,4-substituted product. The corresponding *trans*- benzoates were also tried under similar conditions. In this case, there

is a steric repulsion between the palladium and the methyl group, which are *syn* with respect to each other. The π-allyl complex is thus distorted towards C-4 and favors the attack on C-2, resulting in the formation of *trans*-**219** and *trans*-**220** in the ratio of 1:4. However, these studies were restricted to the tertiary carbon only and the ratio is still not satisfactory. In order to effect the exclusive formation of 1,2-product, the use of internal nucleophile should be desirable.

A great deal of work has been carried out towards the understanding of the transmittance of the stereochemical information by the chiral metal-ligand complex. Thus, chirality can be induced in the racemic or *meso*-starting materials to obtain enantiomerically enriched products. The reaction of the *meso* and the racemic substrates differ in the nature of the enantiodiscrimnating step.

In the case of *meso* starting materials, the formation of the η^3-π-allyl complex (ionization) constitutes the enantiodiscrimnating step. The chiral catalyst (ML_n) promotes the differential ionization of the enantiotopic leaving groups having the metal coordinated to the face of the double bond distal to the leaving groups. The nucleophile ultimately attacks the least hindered allyl terminus from the face opposite to that of the metal resulting in the overall retention in configuration (Figure 13).[54d]

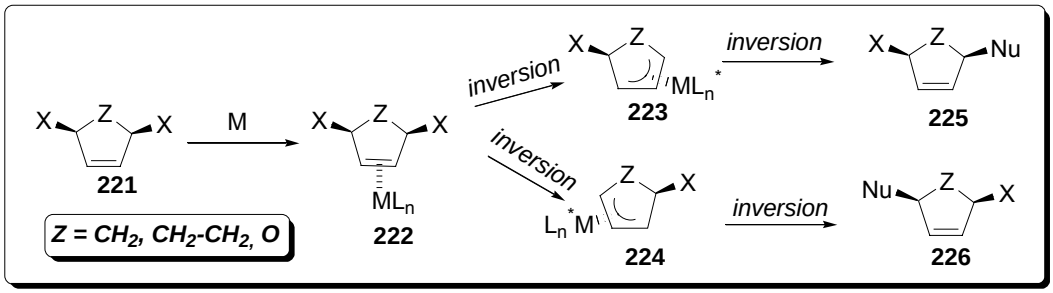


Figure 13. Desymmetrization of meso substrate

Depending on the enantiomer of the chiral ligand used, the formation of either **223** or **224** will be much faster than the other, which in turn leads to the selective formation of either **225** or **226** in higher amounts as compared to the other.

In the case of the racemic substrates, the stereochemical information of the substrate is lost during the formation of the η^3-π-allyl complex. Thus, the enantiodiscrimination in this case occurs during the attack of the nucleophile. Trost has depicted this process of deracemization as a dynamic kinetic asymmetric transformation (DYKAT). The concept can be understood by considering the following figure (Figure 5).[54d]

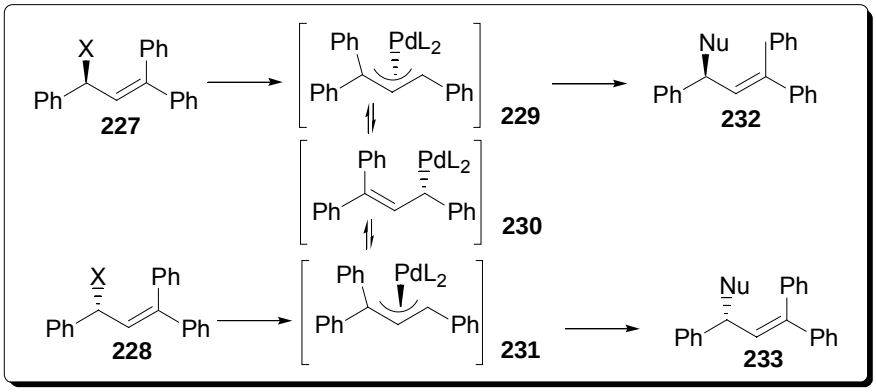


Figure 14. Optical induction in racemic substrate

The η^3-π-allyl complexes derived from each of the enantiomer are diastereomeric and are interconvertable (only when two identical groups are present on one of the termini) by $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ transitions. This process must be fast as compared to the nucleophillic addition, which constitutes the enantiodiscrimnating step. The enantiodiscrimination can be controlled either by the relative stabilities of the two diastereomeric complexes, wherein the attacking nucleophile plays a minimal role or by the ease of approach of the nucleophile wherein it plays a major role. Thus the product is obtained in enantioenriched form.

Research in the area of developing efficient chiral ligands for AAA reaction has also been expanding over the years. Initially, the chiral bidentate phosphines (e.g. **234** and **235**) which had proved to be efficient ligands in the enantioselective hydrogenations were employed for AAA reaction. However, although high *ee* were obtained in certain cases the scope of these ligands was found to be limited when soft nucleophiles are used.[57,54d] The inefficiency of these ligands was attributed to the fact that the crucial bond forming process, the nucleophillic addition to the allyl system, is taking place outside the coordination sphere and, therefore, cannot be controlled by the chiral ligand. Thus, it was

thought that the ligand that can interact with the nucleophile in some way should be more efficient. With this in mind Hayashi *et al*., developed a ferrocene ligand **236** with long side chain to reach over the allyl system and interact with the nucleophile by hydrogen bonding and direct the approach to one of the allylic termini.[58] The concept was fairly successful and respectable *ee* could be obtained for most substrates. However, Trost *et al.* developed a ligand **237**, which demonstrated that the secondary interactions between the ligand and the nucleophile are not prerequisite for high *ee*.[54 c, d] Trost's concept was to increase the P-Pd-P bite angle and, as a consequence, create the chiral cavity in which the allyl system would be embedded. In analogy with functioning of the enzymes, in which primary chirality imposes a folding (a conformational chirality) to create the chiral space of the catalytic active site, the primary chirality of the chiral scaffold (chiral diamine) would induce conformational chirality of the diaryl phosphino moieties and a linker to create the chiral space of the catalytically active site. The experimental demonstration very well proved the model proposed. The ligand has the P-Pd-P bite angle of 110.5°, considerably larger than the bite angle of square planer Pd complexes (~ 90°), due to which the π-allyl unit sits in a chiral pocket defined by the propeller arrangements of the aryl rings which clearly orient in the edge-face relationships.

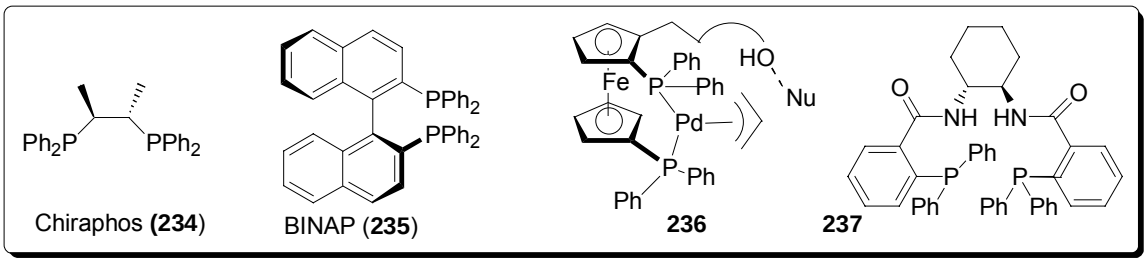


Figure 15. Chiral ligands used in AAA reaction

The Trost's ligand **237** has proved to be highly successful and most versatile for AAA reactions.

The foregoing discussions, besides exposing the principles underlying AAA reaction also justifies the challenges involved in the regio and stereoselective alkylations in the substituted racemic systems, which in turn supports our objective in taking up the

study. The synthesis of our designed precursor and its behavior in palladium catalyzed allylic alkylation reaction are presented in the next section.

4.2 Results and discussion

For an elegant design of the synthetic route to (±)-**170**, we were encouraged to consider its preparation from the racemic alcohol (±)-**166**, whose preparation in optically pure form has already been discussed in the section 3 of this chapter. We envisaged the synthesis of (±)-**166** as depicted in figure 16, which essentially followed the same sequence as its optically active congener but in the absence of a chiral auxiliary.

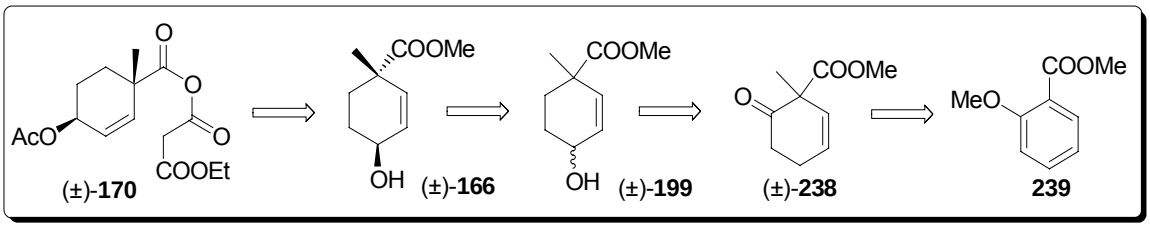
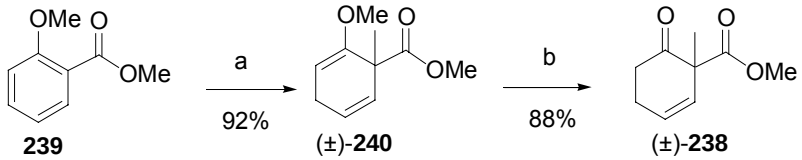


Figure 16. Retrosynthetic analysis of designed substrate 170

Synthesis of (±)-**170** as perceived through the retrosynthetic analysis depicted in figure 16 began with the preparation of β-keto ester (±)-**238**. Towards this end, compound (±)-**240** was obtained in 92% yield by Birch reduction-methylation of methyl anisate (**239)**, which upon hydrolysis with 10% HCl gave (±)-**238** in 88% yield (Scheme 60).

Scheme 60. Preparation of keto-ester 238



Reagents and conditions: a) Na, ^{t}BuOH, Liq. NH_3, –78 °C, then MeI, 1h. b) 10% HCl, MeOH, rt.

Compounds (±)-**240** and (±)-**238** were fully characterized using IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Their spectral data was in very good agreement with that reported in the literature.

The next task was to convert keto carbonyl into a methylene group. Methods of deoxygenation, which were previously tried on (-)-**179**, were also tried on (±)-**238**. However, the observations in case of (±)-**238** were similar to that in case of (-)-**179**.

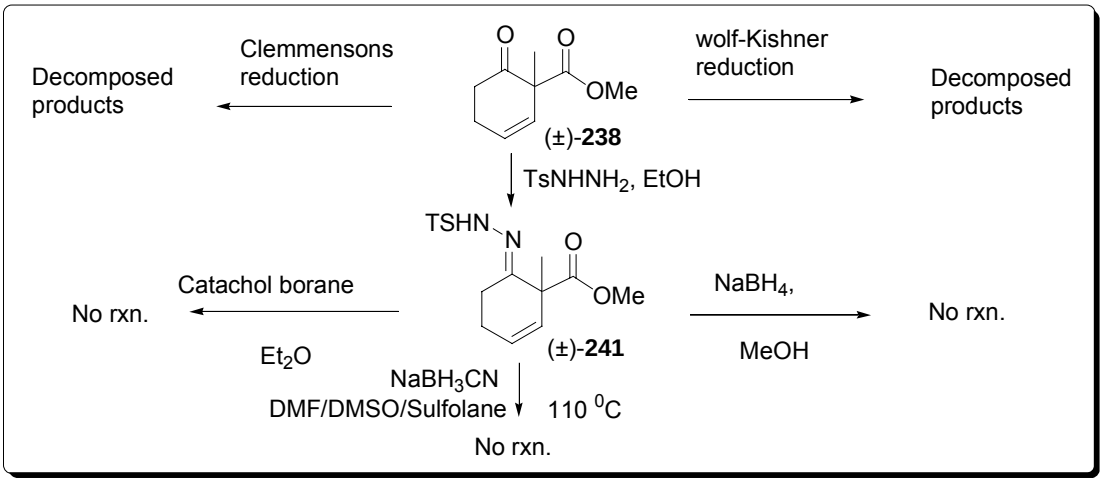
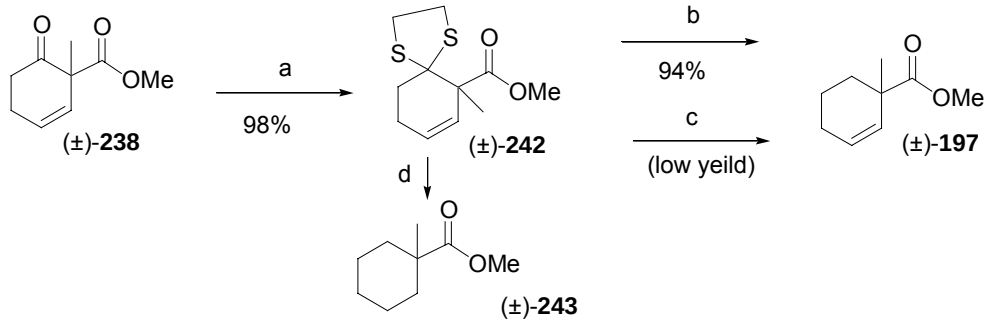


Figure 17. Attempted deoxygenation

Classical methods like Clemmensons and Wolf Kishner reduction gave only decomposed products and the reduction of the corresponding tosyl hydrazone using various hydride reagents also failed (Figure 17). Therefore, we resorted to the reduction of the corresponding dithiolane derivative. Treating (±)-**238** with ethane dithiol in the presence of $BF_3.OEt_2$ effected the conversion of its keto group to the corresponding dithiolane (±)-**242**.

Scheme 61. Deoxygenation via dithiolane



Reagents and conditions: a) ethanedithiol, $BF_3(OEt)_2$, DCM, 0℃ to rt. b) $^nBu_3SnH$, AIBN, reflux. c) Na, Liq. NH_3, –78 ℃. d) Raney nickel, ethanol, reflux.

The IR spectrum of (±)-**242** provided ample evidence of the required conversion since the absorption band corresponding to the keto carbonyl group, which was shown by

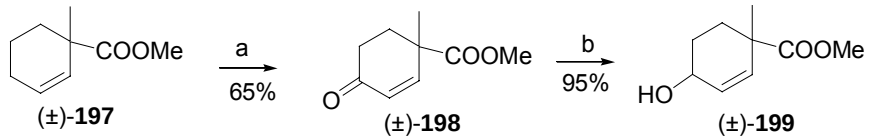
parent ketone (±)-**238** had disappeared, while the signals consonant with the structure of (±)-**242** were observed at ν_{max} = 2952, 2257, 1724, 1460, 1224, 1112, 908, 736 and 649 cm^{-1}. The signals observed in the ^1H NMR spectrum, especially a multiplet seen in the area of δ = 3.10-3.32 and integrating for four protons, indicated the protons of the two methylene groups of the dithiolane moiety. The depicted conversion was also supported by the absence of carbonyl carbon signal and the presence of two methylene carbons indicated by a single signal at δ = 42.3, along with the a quaternary carbon at δ = 66.5 corresponding to dithiolane moiety, in the ^{13}C NMR spectrum of (±)-**242**.

With the dithiolane derivate (±)-**242** in hand, we proceeded for its desulfurization. Towards this end, we observed that the reduction of the dithiolane (±)-**242** with Raney nickel[59] produced compound (±)-**242** in which both the dithiolane as well as olefinic double bonds were reduced. Therefore, we resorted to our previously standardized method of chemoselective reduction with $^nBu_3SnH$. In this regard, compound (±)-**242** was heated with $^nBu_3SnH$ at 120 °C for 24 h with 5 mg of AIBN added every four hours, which resulted in the formation of the desired compound (±)-**197** in 94% yield (Scheme 61). The structure of (±)-**197** was elucidated using conventional spectroscopic means. Its spectral data was found to be matching perfectly with the corresponding optically active compound synthesized earlier.

A stage was now set to introduce allylic hydroxy group, which would serve in the generation of π-allyl palladium complex during our key step. In this context, (±)-**197** was subjected to allylic oxidation with PDC-$^tBu_2OH$ to give α,β-unsaturated ketone (±)-**198** in 65% yield.[50] Structure of (±)-**198** follows from the fact that there is additional carbonyl signal corresponding to α,β-unsaturated ketone in its IR spectrum**.** The remaining peaks in the IR spectrum as well as data obtained from other spectral techniques were consonant with its structure and matched perfectly with its optically active congener synthesized earlier. As expected, (±)-**198** upon reduction under Luche's conditions[51] ($NaBH_4$-$CeCl_3$)

gave allylic alcohol (±)-**199** in 3:2 diastereomeric ratio favoring the *cis* form as indicated by ^{1}H NMR spectrum and confirmed by GC analysis. The spectral data of (±)-**199** displayed all the requisite features and was in very good agreement with the corresponding optically active diastereomeric mixture discussed in preceding section (Scheme 62).

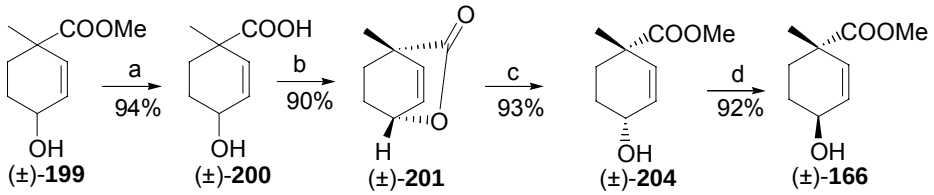
Scheme 62. Allylic oxidation-reduction



Reagents and conditions: *a) PDC, ^{t}BuO$_2$H, DCM, 24h. b) NaBH$_4$, CeCl$_3$.7H$_2$O, 0 ℃, 4h.*

Our next job was to convert the mixture of diastereomers into pure *trans*-diastereomer. This was achieved following the same procedure as described for the optically active congener and is depicted in Scheme 63. The reaction sequence involved, the initial hydrolysis of the carbomethoxy group of diastereomeric mixture (±)-**199** to obtain corresponding acid (±)-**200** in excellent yield, which upon treatment with BF_3.etherate gave desired lactone (±)-**201** in 90% yield. Sodium methoxide opening of the lactone provided us with the *cis* alcohol (±)-**204** in very good yield, which was easily converted to *trans*-isomer (±)-**166** by Mitsunobu inversion. The yields of the steps involved and the spectral data of the intermediate compounds were very much consistent with the earlier observations (Scheme 63).

Scheme 63. Preparation of *trans* diastereomer 238



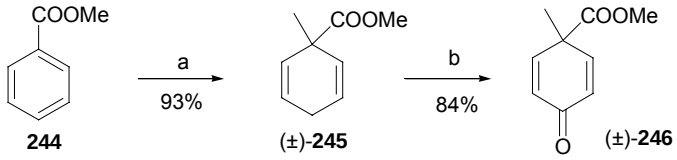
Reagents and conditions: a) LiOH, THF, H$_2$O, rt. b) BF$_3$.OEt$_2$, DCM, 0 ℃. c) NaOMe, MeOH, reflux. d) i. DIAD, PPh$_3$, BzOH, THF, 0 ℃ to rt. ii. 1N NaOH, MeOH, rt.

At this juncture, it was felt that, although the synthesis of desired racemic *trans*-diastereomer (±)-**166** emanating from methyl anisate was quite efficient; the length of the synthetic route prompted us to seek a shorter alternative. The best thing that came to our

mind at this point was to evaluate the preparation of (±)-**166** from methyl benzoate. The practical proposition in making this choice was to shorten the synthetic route by avoiding the deoxygenation step.

We set our sails for exploring this new route for the synthesis of (±)-**166**. As per the logical propagation of transformations required for this purpose, we began by conducting Birch reduction-methylation on methyl benzoate, which resulted in the formation of diene (±)-**245** in excellent yield. The structure of (±)-**245** obliviously followed from the absence of aromatic signals and presence of requisite aliphatic signals in its ^{1}H and ^{13}C NMR spectra. As per the plan, dienone (±)-**246** was prepared by subjecting (±)-**245** to *bis*-allylic oxidation using PDC-$^{t}BuO_2H$. It was quite gratifying to observe that the yield of *bis*-allylic oxidation was reasonably higher than the mono allylic oxidation (Scheme 64).

Scheme 64. Birch reduction alkylation and *bis*-allylic oxidation

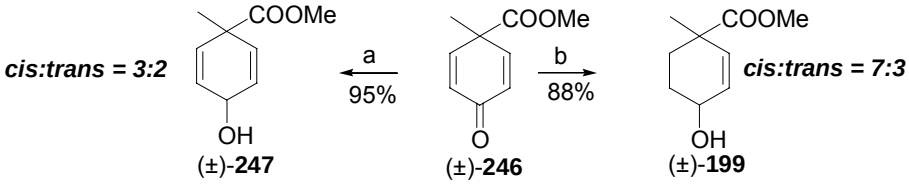


244 (±)-**245** (±)-**246**

Reagents and conditions: a) Na, ^{t}BuOH, Liq. NH_3, –78 °C, then MeI. b) PDC, $tBuO_2H$, DCM, rt.

Our presumption for producing allylic alcohol (±)-**199** from dienone (±)-**246** was based on the fact that $NaBH_4$ can effectively reduce the olefin moiety of the α,β-unsaturated ketone. In this regard it was quite remarkable to observe that, indeed, it was possible to produce selectively either the *bis*-allylic alcohol (±)-**247** or the allylic alcohol (±)-**199** from dienone (±)-**246** by varying the reaction conditions. Thus, when dienone (±)-**246** was subjected to reduction under Luche's condition i.e., with $NaBH_4$ in presence of $CeCl_3.7H_2O$, *bis*-allylic alcohol (±)-**247** was obtained in 95% yield and 3:2 diastereomeric ratio favoring the *cis* form as indicated by GC and ^{1}H NMR analysis. However, when the reduction was carried out in the absence of $CeCl_3$, one of the double bond also was reduced and allylic alcohol (±)-**199** was obtained in 88% yield and 7:3 diastereomeric ratio also favoring the *cis*- form (Scheme 65).

Scheme 65. Reduction of dienone (±)-246



Reagents and conditions: a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt. b) $NaBH_4$,, MeOH, 0 °C to rt.

Compounds (±)-**199** and (±)-**247** were characterized by spectroscopic means. While the spectral data of (±)-**199** obtained from benzoic acid perfectly matched with the one obtained from *o*-anisic acid, the spectral data of (±)-**247** had certain distinguishing features, which led us to its structural elucidation.

The IR spectrum of (±)-**247** provided evidence of the functional groups present by displaying absorption bands at ν_{max} = 3421, 3020, 1728, 1215, 908 and 761 cm^{-1}.

In the ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (±)-**247,** two singlets in the ratio of 3:2 at δ = 1.25 and 1.32, respectively, and integrating for three protons were assigned to the protons of the methyl groups attached to quaternary carbon. The taller peak belongs to the *cis* isomer whereas the shorter one belonged to the *trans*- diastereomer. A broad singlet shown in the area δ = 2.81-2.96 and integrating for one proton is of the hydroxy proton. A tall singlet appearing at δ = 3.60 was attributed to the protons of the methyl group of carbomethoxy functionality. The CH–OH proton appeared as a double δ = 4.41 (d, *J* = 15.6 Hz). A multiplet exhibited in the area δ = 5.87 (d, *J* = 9.3 Hz, 4H), integrating for four protons was assigned to the olefinic protons.

The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (±)-**247**, displayed a total of seven signals at δ = 26.1, 44.3, 52.3, 61.2, 127.9 (2C), 130.7 (2C) and 174.3, respectively. DEPT experiment confirmed that the peaks appearing at δ = 44.3 and δ = 174.3 belonged to the quaternary carbons and were assigned to the quaternary carbon on cyclohexyl moiety and the carbonyl carbon respectively. The signal appearing at δ = 61.2 was attributed to the methine carbon of CH–OH group, while the methine signals of the olefinic carbons were

seen at δ = 127.9 and 130.7, respectively, with each signal corresponding to two carbons. There were no methylene signals as expected. The signal appearing towards the most upfield at δ = 26.1 arise from the methyl group attached to quaternary carbon, while the signal appearing at δ = 52.3 was assigned to the methyl of the carbomethoxy group.

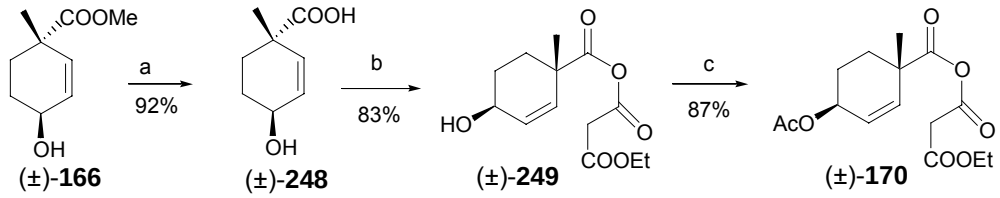
The mass spectrum of (±)-**247** was helpful in confirming its molecular weight by displaying the molecular ion peak at *m/z* = 168.

At this point, we were apprehensive about the lack of diastereoselectivity in the sodium borohydride reduction since the entire material could be converted to the desired *trans*-diastereomer (±)-**166** as discussed earlier.

After developing an efficient protocol for preparing racemic form of *trans*-diastereomer (±)-**166**, we moved on to procure our targeted designed substrate for AAA reaction. For this purpose, it was necessary to hydrolyze the carbomethoxy group of (±)-**166**. This could be easily achieved by treating it with LiOH in the mixture of THF/water (1.3:1) as a solvent to obtain corresponding acid (±)-**248** in reasonably high yield.

The mono-potassium salt of ethyl malonate required for forming mixed anhydride with (±)-**248** was prepared by treatment of diethyl malonate with one equivalent of KOH in ethanol. For the preparation of mixed anhydride from potassium ethyl malonate and (±)-**248,** it was desirable to convert the carboxylic acid group of (±)-**248** to corresponding acid chloride. This was done by conventional method, using thionyl chloride. With both the fragments in hand, the mixed anhydride formation was effected by drop wise addition of acid chloride of (±)-**248** to the solution of mono-potassium salt of ethyl malonate in benzene to obtain the anhydride (±)-**249**.

Scheme 66. Preparation of desired substrate 170



Reagents and conditions: *a) LiOH, THF, H_2O, rt, 4h. b) i. $SOCl_2$, PhH, rt, 6h. ii. K-salt of ethyl malonate PhH. c) CH_3COCl, Pyridine, 0 ℃ to rt, 3h.*

The IR spectrum of (±)-**249** showed five absorption peaks in the carbonyl region at ν_{max} = 1755, 1731 and 1714 cm^{-1} respectively. The absorption band observed at ν_{max} = 1731 cm^{-1} indicates the ester carbonyl while the remaining two bands arise from the symmetric and asymmetric stretch of carbonyl groups of the anhydride function.

The ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (±)-**249** displayed a triplet at δ = 1.22 (t, *J* = 7.2, 3H), which arises from the methyl group on anhydride chain terminal (COO–CH_2–$\underline{CH_3}$). A singlet appearing at δ = 1.31, integrating for three protons, was assigned to the methyl group attached to quaternary carbon (C–$\underline{CH_3}$). The multiplet spanning the region δ = 1.65-2.19, integrating for four protons was attributed to the protons of the two methylene groups present on the cyclohexyl moiety. The protons of the methylene group between the two carbonyls (CO–$\underline{CH_2}$–CO) appeared as a singlet at δ = 3.54 (s, 2H). A quartet shown at δ = 4.14 (q, *J* = 7.1 Hz, 2H) was attributed to the protons of the methylene group vicinal to the terminal methyl group (COO–$\underline{CH_2}$–CH_3). The proton of the $\underline{CH}$–OH group appeared as a multiplet at δ = 4.42-4.57 (m, 1 H). The spectrum was terminated by the olefinic protons appearing as multiplet in the region δ = 5.70-5.93 (m, 2H).

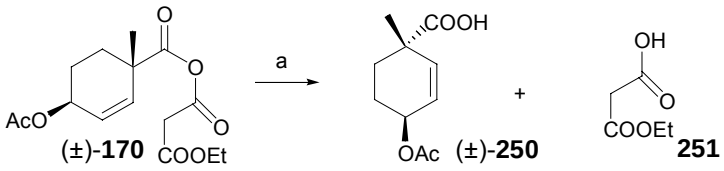
In the ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (±)-**249** a total of thirteen signals at δ = 13.6, 15.3, 23.6, 32.3, 36.6, 40.6, 55.2, 64.6, 12.7, 129.3, 155.3, 159.0 and 172.0, respectively. The carbons were assigned using the DEPT spectrum, which revealed that the signals appearing at δ = 40.6, 155.3, 159.0 and 172.0 arise from the quaternary carbons. These signals were assigned to the quaternary carbon on cyclohexyl ring ($\underline{C}$–CH_3), the carbonyl groups of anhydride, and the carbonyl group of the terminal carboethoxy functionality ($\underline{C}$OO–CH_2–CH_3), respectively. The methine carbons of $\underline{CH}$–OH group and the olefin appeared at δ = 64.6, 122.7 and 129.3, respectively. The signals for the four methylene groups present in the molecule were shown at δ = 23.6

(CH_2–$\underline{C}H_2$–CH–OH), 32.3 ($\underline{C}H_2$–CH_2–CH–OH), 36.6 (CO–$\underline{C}H_2$–CO) and 55.2 (O–CH_2), respectively. Finally the methyl group of the carboethoxy moiety appeared at δ = 13.6 (COO–CH_2–$\underline{C}H_3$) and the quaternary carbon appeared at δ = 15.3 (C–$\underline{C}H_3$).

Consequently, acetylation of the hydroxy group of (±)-**249** using acetyl chloride in presence of pyridine in dichloromethane at 0 °C delivered the desired compound (±)-**170**, eminently poised for palladium catalyzed allylic alkylation (Scheme 10). The structure of (±)-**170** could be easily gleaned from the presence of signals corresponding to acetyl function in its spectral data. The absence of hydroxy absorption band in the IR spectrum of (±)-**170**, appearance of a singlet at δ = 2.12 (3H) and the downfield shifting of C$\underline{H}$-O signal to δ = 5.11-5.33 (m, 1H) in its ^{1}H NMR spectrum were especially useful for this purpose.

A stage was now set to evaluate the paladium catalyzed allylic alkylation on our designed substrate (±)-**170**. In keeping with the common practice, we decided to test the feasibitlity of the reaction by conducting it in absence of the chiral ligand. Our investigations began by applying a standard protocol involving treatment of (±)-**170** with $Pd_2(dba)_3$ and NaH in THF.[55] However, to our great dismay, the outcome was very dicouraging. The anhydride could not survive under basic conditions even at low temperature and broke down to corresponding acids (±)-**250** and **251**, which were eaisily isolated and characterized (Scheme 67).

Scheme 67. Attempted allylic alkylation



Reagents and conditions: a) $Pd_2(dba)_3$, NaH, THF, 0 °C.

In order to avoid the problem of anhydride cleavage, the use of weaker base in place of sodium hydride was thought to be a logical alternative. In this context, it was observed that use of triethylamine in palce of sodium hydride also gave the same result, while the behaviour of pyridine was slightly different. With pyridine as a base there was no

change in the starting material at low temperature, which however broke down to corresponding acids when the temperature was raised. Use of sodium acetate also failed to produce desired products and behaved in close resemblence with pyridine.

Disheartened by the consistent failures, we decided to evaluate an alternative protocol involving *in situ* generation of Pd(0) from $Pd(OAc)_2$ and $^{n}BuLi$ (1 eq) at –78 °C.[55] The resultant π-allyl palladium complex upon treatment with a weak base like LiOAc was expected to produce the desired compound. In this regard, we obsereved that at low teperature there was no change in the starting material, however, decomposition of starting compound was obtained as noticed with other bases on warming the reaction mixture to rt. This led us to conclude that our designed substrate is unsuitable for conducting allylic alkylation reactions. Detailed study of the reaction conditions as well as design and synthesis of alternative substrates for this purpose are currently in progress in this laboratory.

4.3 Conclusion

This section of the chapter describes our efforts towards developing catalytic asymmetric synthetic route for the preparation of optically active *trans*-hydrindane system. We designed and synthesized a precurrsor (±)-**170** for carrying out palladium catalyzed allylic alkyaltion. Instability of our designed substrate towards basic conditions, was primarily responsible for our faliure in acheving our target. However, we forsee the acheviement of our goals in near future which would build on the investigations discussed in this section.

5. Experimental Section:

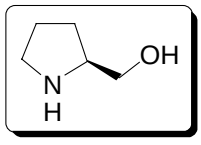
General:

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al*.[60] Benzene, DCM and triethylamine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points.

All commercial reagents were used as supplied. Progress of the reaction was monitored by TLC and gas chromatography. Column chromatography was performed on silica gel 60-120 / 100-200 / 230-400 mesh obtained from S. D. Fine Chemical Co., India or SRL, India.

All melting points were uncorrected in degrees Celsius and were recorded on a Buchi melting point apparatus. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FT-IR. GC analysis was performed on Perkin Elmer 8700 and Varian CP 3800 gas chromatographs using a SGE BP1, BP20 and Varian Chrompack CP-Sil-5CB columns. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300 and Bruker DRX – 500 instruments. Chemical shifts are reported in δ ppm. Optical rotations were measured on JASCO-3010 digital polarimeter using Na lamp.

1. Preparation of (*S*)-(+)-2-Hydroxymethylpyrrolidine [L-prolinol, (+)-176]:



In a 250 ml two-necked round bottom flask, equipped with a reflux condenser, was placed $LiAlH_4$ (2.09 g, 56.5 mmol) under argon atmosphere. The flask was cooled in ice-bath and THF (80 mL) was cautiously added to it. The suspension was heated under reflux for 1 h, the heating stopped and (S)-proline (5.0 g, 43.5 mmol) was added in small portions to the boiling mixture at such a rate as to maintain the gentle

reflux. The addition required ca. 0.5 h. The contents of the flask were refluxed for additional 2 h. Excess $LiAlH_4$ was decomposed by dropwise addition of 30% solution of KOH in water (12 mL) at 0 °C. The mixture containing white precipitate was refluxed for 0.5 h and the hot solution was filtered under vacuum using sintered funnel. The precipitate was washed with CH_2Cl_2; the combined filtrates dried over Na_2SO_4 and concentrated under vacuum to yield pale yellow oil with peculiar odor. The crude mass was purified by distillation under reduced pressure (bp = 76-78 °C / 2 mm) to yield (S)-2-hydroxymethylpyrrolidine (4.01 g, 95%) as viscous colorless oil.

$[\alpha]_D^{25}$	**:**	+ 30.86 (*c* = 2.2, $C_6H_5CH_3$). Literature[61] = +31 (*c* = 1, C_6H_6).
IR ($CHCl_3$)	**:**	ν_{max} = 3365, 2990, 1455, 1050 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.15-1.34 (m, 1H), 1.49-1.82 (m, 3H), 2.66-2.92 (m, 2H), 3.01-3.20 (m, 1H), 3.21-3.33 (m, 1H), 3.46 (m, 1H), 3.67-3.98 (d, *J* = 11.6 Hz, 2H).

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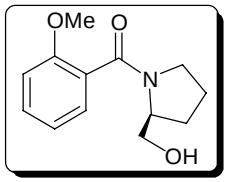
2. Preparation of (*S*)-2-Hydroxymethyl-pyrrolidin-1-yl)-(2-methoxy-phenyl-methanone [(-)-177]:



To a 100 mL two-necked round bottom flask, equipped with a reflux condenser and argon balloon, was added 2-methoxybenzoic acid (5 g, 32.9 mmol) followed by thionyl chloride (15 mL). The resulting solution was heated at 70 °C for 4 h. Excess thionyl chloride was removed by distillation; benzene (15 mL) was added to the crude acid chloride and again distilled. The process of benzene addition and distillation was repeated twice to ensure complete removal of the excess thionyl chloride. The crude mass was distilled under reduced pressure (95-97 °C / 2 mm) to obtain 2-methoxybenzoyl chloride (5.0 g, 89%) as colorless liquid.

2-Methoxybenzoyl chloride (5.0 g, 29.3 mmol) in dry CH_2Cl_2 (15 mL) was added to a stirred solution of L-prolinol [(+)-**176**, 3.26 g, 32.2 mmol) and triethylamine (4.26 g, 42.2

mmol) in dry CH_2Cl_2 (70 mL) at 0 °C. After the addition of the acid chloride was complete, the reaction mixture was warmed to room temperature and stirred for 4 h. A solution of 5% HCl (100 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined and washed with saturated sodium bicarbonate solution (100 mL) and brine (60 mL). The organic layer was dried over sodium sulfate and solvent was removed under vacuum to get off-white solid that upon recrystallization from ethyl acetate and pet-ether (1:4) provided (-)-**177** (6.68 g, 97%) as colorless needles.

$[\alpha]_D^{25}$	**:**	–90.6 (*c* = 1, $CHCl_3$). Literature[47] = –91.0 (*c* = 1.2, $CHCl_3$).
IR ($CHCl_3$)	**:**	ν_{max} = 3483, 2972, 1629, 1461, 1415, 1247, 1111, 1022, 756 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ = 1.53-1.92 (m, 3H), 1.98-2.21 (m, 1H), 3.12-3.3 (m, 2H), 3.60-3.92 (m, overlapping s at 3.80, 5H), 4.22-4.43 (m, 1H), 6.79-7.09 (m, 2H), 7.17-7.45 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 34.6, 38.7, 59.4, 65.9, 71.0, 76.4, 121.5, 131.1, 137.2, 137.8, 140.8, 165.3, 180.0.

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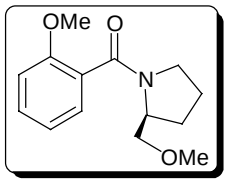
3. Preparation of (*S*)-(2-Methoxymethyl-pyrrolidin-1-yl)-(2-methoxy-phenyl)-methanone [(-)-168]:



Sodium hydride (1.34 g, 34.9 mmol) was taken in a 250 mL 2-necked round bottom flask fitted with a reflux condenser and argon balloon. Dry pet ether (20 mL) was added to the flask; the contents stirred for 2 min and allowed to settle. The supernatant liquid containing grease dissolved in pet ether was withdrawn with the help of syringe and discarded. This process was repeated twice for efficient removal of the grease. The traces of pet ether remaining were also removed under reduced pressure. Dry THF

(50 mL) was introduced into the flask, which was cooled to 0 °C and (-)-**177** (6.68 g, 26.8 mmol) dissolved in dry THF (30 mL) was added to it dropwise. The mixture was stirred at 0 °C for 30 minutes, MeI (2.5 mL, 40.2 mmol) was introduced dropwise and the resulting mixture was stirred at 60 °C for 12 h. Excess NaH was quenched by careful addition of saturated NH_4Cl solution at 0 °C. The layers were separated and the aqueous layer was back extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered under gravity and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to obtain (-)-**168** (6.16 g, 88%) as viscous pale yellow oil.

$[\alpha]_D^{25}$	**:**	−122.7 (*c* = 1.6, $CHCl_3$). Literature[47] = −122.0 (*c* = 1, $CHCl_3$).
IR ($CHCl_3$)	**:**	ν_{max} = 2947, 1595, 1461, 1377, 1245, 1056 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.67-2.13 (m, 4H), 2.96-3.07 (m, 1H), 3.12-3.25 (m, 1H), 3.39 (s, 3 H), 3.45-3.62 (m, 1H), 3.65-3.76 (m, 1H), 3.80 (s, 3H), 4.29-4.46 (m, 1H), 6.80- 7.01 (m, 2H), 7.14-7.39 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 22.0, 27.5, 48.2, 55.4, 56.0, 58.8, 72.1, 111.0, 120.5, 127.4, 130.0, 155.0, 159.5, 167.7.

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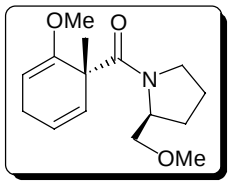
4 Preparation of (*S*)-(2-Methoxy-1-methyl-cyclohexa-2,5-dienyl)-(*S*)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone [(-)-178]:



A solution of (-)-**168** (6.16 g, 24.74 mmol) in dry THF (10 mL) and *t*-butyl alcohol (2.26, mL, 27.27 mmol) was cooled to −78 °C. Liquid ammonia (70 mL, pre-dried over sodium amide and distilled) was added to the reaction mixture. Sodium (1.42 g, 61.74 mmol) was added to the stirred solution in small pieces over a period of ten minutes, upon which the color of the solution turned dark blue. After ten more minutes,

methyl iodide (3.39 mL, 54.43 mmol) was added and the resulting yellow colored solution was stirred for 1 h at −78 °C. After addition of NH_4Cl (~10 g), the mixture was warmed slowly to room temperature while the ammonia was removed with a stream of argon. Water (50 mL) was added and the mixture was extracted with chloroform (3 × 30 mL). The combined organic extracts were washed with 10% sodium thiosulfate (25 mL), water (30 mL), and brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvents under vacuum and subjecting the residue to column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 7:3) yielded (-)-**178** (6.04 g, 92%) as viscous colorless oil.

$[\alpha]_D^{25}$	**:**	−36.23 (*c* = 2.07, CH_2Cl_2).
IR ($CHCl_3$)	**:**	ν_{max} = 2929, 1685, 1633, 1450, 1402, 1382, 1350, 1245, 1207, 1164, 1114, 1093 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.46 (s, 3H), 1.66-2.07 (m, 4H), 2.78-2.96 (m, 2H), 3.19-3.41 (m, overlapping s at 3.39, 5H), 3.55 (s, 3H), 3.60-3.72 (m, 2H), 4.24-4.41 (m, 1H), 4.65 (t, *J* = 3.2 Hz, 1H), 5.50 (dt, *J* = 9.2, 2.1 Hz, 1H), 5.75 (dt, *J* = 9.6, 3.3 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 24.9 (2C), 26.1, 26.4, 46.3, 48.2, 54.2, 58.0, 58.8, 72.0, 90.6, 124.0, 128.7, 155.8, 170.5.

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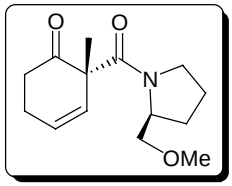
5. Preparation of 2-[(2*S*)-2-methoxymethyl-pyrrolidine-1-carbonyl]-(2*S*)-2-methyl-cyclohex-3-enone [(-)-179]:



To a stirred solution of (-)-**178** (6.04 g, 22.3 mmol) in methanol (100 mL) was added 10% hydrochloric acid (30 mL) at 25 °C. After 24 h at room temperature, the reaction mixture was neutralized by the addition of the concentrated sodium bicarbonate solution (100 mL) and methanol was removed under

reduced pressure. The aqueous mixture was extracted with ethyl acetate (3 × 25 mL) and the combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent under vacuum followed by column chromatography (silica gel, 60-120 mesh; eluent: pet. ether-ethyl acetate = 7:3) gave ketone (-)-**179** (4.87 g, 85%) as colorless oil.

$[\alpha]_D^{25}$	**:**	-55.58 (*c* = 1.2, CH_2Cl_2).
IR (Neat)	**:**	ν_{max} = 2977, 1710, 1631, 1448, 1404, 1113 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.35 (s, 3H), 1.58-1.96 (m, 4H), 2.39-2.62 (m, 4H), 2.87-3.04 (m, 1H), 3.14-3.31 (m, overlapping s at 3.25, 5H), 3.50-3.61 (m, 1H), 4.07-4.25 (m, 1H), 5.57 (d, *J* = 9.8 Hz, 1H), 5.86 (dt, *J* = 9.7, 3.6 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 24.0, 24.4, 25.8, 26.9, 35.8, 37.6, 46.4, 57.7, 58.9, 71.7, 126.9, 130.5, 169.1, 208.8.

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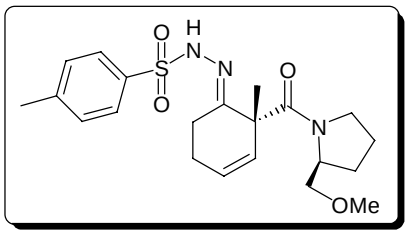
6. Preparation of tosyl hydrazone (-)-180:



A solution of (-)-**179** (0.8 g, 3.19 mmol) and tosyl hydrazine (0.59 g, 3.19 mmol) in absolute ethanol (10 mL) was charged into a 25 mL two-necked RB flask equipped with magnetic stirring bar and argon gas balloon. The flask was fitted with a reflux condenser and the contents were refluxed for 3 h. Cooling the solution afforded crystalline tosyl hydrazone (-)-**180** (1.27g, 95%), which was sufficiently pure to proceed further.

$[\alpha]_D^{25}$	**:**	-122.64 (*c* = 0.9, CH_2Cl_2).
M.p.	**:**	199-201 °C.
IR (Neat)	**:**	ν_{max} = 3020, 2358, 1652, 1608, 1448, 1417, 1332,

1215, 1164, 1112 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.29 (s, 3H), 1.61-2.02 (m, 5H), 2.15-2.74 (m, overlapping s at 2.44, 7H), 3.03-3.46 (m, overlapping s at 3.40, 5H), 3.76 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.21-4.40 (m, 1H), 5.58 (d, *J* = 9.8 Hz, 1H), 5.83 (dt, *J* = 9.5, 3.3 Hz, 1H), 7.32 (d, *J* = 10.7 Hz, 2H), 7.80 (d, *J* = 10.7 Hz, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 21.5, 21.8, 23.8, 24.2, 26.2, 26.9, 46.4, 51.7, 57.5, 58.7, 71.5, 125.9, 128.0, 128.2, 129.3, 129.9, 130.6, 135.6, 143.7, 160.6, 170.6.

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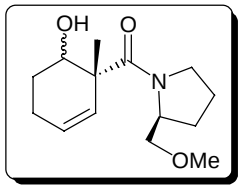
7. Preparation of (1*S*)-(6-Hydroxy-1-methyl-cyclohex-2-enyl)-(2*S*)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone [(-)-181/(-)-182]:



To a solution of (-)-**179** (1.3 g, 5.18 mmol) in methanol (20 mL) was added sodium borohydride (0.26 g, 7.0 mmol) in small portions over a period of ten minutes at 0 °C. The reaction mixture was allowed to warm to room temperature and monitored by TLC. The starting material was consumed after stirring for 2 h at room temperature. Methanol was evaporated under reduced pressure and the residue dissolved in minimum amount of water, acidified to pH 3 with 1N HCl and extracted with ethyl acetate (3 ×15 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (Hexane / EtOAc = 1:1) to give (-)-**181** as white solid and (-)-**182** as highly viscous oil (0.61 g each, 93%). Analytical sample of (-)-**181** was obtained by recrystallization from hexane/acetone (3:1).

Data for diastereomer (-)-181

M.p.	**:**	117-119 °C.
$[\alpha]_D^{25}$	**:**	–71.05 (*c* = 1.3, $CHCl_3$).
IR (film)	**:**	ν_{max} = 3400, 3018.3, 1677, 1596.9, 1450.3, 1407.9, 1215.0 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.25 (s, 3H), 1.60-1.95 (m, 6H), 2.10-2.30 (m, 2H), 3.30 (s, 3H), 3.35-3.60 (m, 4H), 4.15 (dd, *J* = 9.4, 2.3 Hz, 1H), 4.30-4.45 (m, 1H), 5.55-5.80 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 19.0, 23.9, 24.8, 25.4, 26.2, 47.7, 49.4, 57.6, 58.6, 70.2, 72.0, 126.5, 129.5, 174.4.
Mass (GC-MS)	**:**	*m/z* = 253 (M^+), 237, 205, 95 (100%).

Data for diastereomer (-)-182

$[\alpha]_D^{25}$	**:**	–58.83 (*c* = 1.1, $CHCl_3$).
IR (film)	**:**	ν_{max} = 3394, 2931, 1593, 1452, 1406, 1115, 1067 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.30 (s, 3H), 1.63-1.98 (m, 6H), 2.03-2.22 (m, 2H), 3.15-3.64 (m, overlapping s at 3.25, 7H), 4.12-4.33 (m, 1H), 4.70-4.90 (m, 1H), 5.51-5.71 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 18.8, 23.1, 24.7, 25.6, 26.3, 47.7, 48.7, 56.4, 59.2, 70.2, 72.6, 128.8, 130.4, 176.5.
Mass (ESI)	**:**	*m/z* = 271 ($M^+ + H_2O$), 251, 237(100%), 205, 95.

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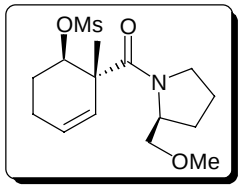
8. Preparation of Methane sulfonic acid 2-[(2*S*)-2-methoxymethyl-pyrrolidine-1-carbonyl]-(2S)-2-methyl-cyclohex-3-enyl ester [(-)-183]:



To a mixture of alcohol (-)-**181** (0.85 g, 3.36 mmol) and triethylamine (0.7 mL, 5.0 mmol) in dichloromethane (15 mL) was added methanesulphonyl chloride (0.29 mL, 3.74 mmol) dropwise at 0 °C. Stirring for an additional 1 h at 0 °C completed the reaction as indicated by TLC. The reaction mixture was transferred to a separating funnel with the aid of more dichloromethane. The mixture was first washed with ice water followed by cold 10% HCl, saturated $NaHCO_3$, and brine. The organic extracts were dried over Na_2SO_4, filtered (gravity) and concentrated to obtain (-)-**183** (1.1 g, 99%).

IR (film)	**:**	ν_{max} = 2956, 1612, 1357, 1146, 1072 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.25 (s, 3H), 1.64-1.87 (m, 4H), 1.92-2.07 (m, 2H), 2.09-2.23 (m, 2H), 2.95 (s, 3H), 3.12-3.72 (m, overlapping s at δ = 3.22, 7H), 4.10-4.35 (m, 1H), 5.31 (t, *J* = 4.9 Hz, 1H), 5.52 (dt, *J* = 10.3, 0.8 Hz, 1H), 5.69 (dt, *J* = 10.3, 3.4 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 23.0 (2C), 24.9, 25.1, 26.5, 28.3, 47.5, 48.1, 58.2, 58.9, 72.4, 76.7, 126.4, 130.4, 176.2.

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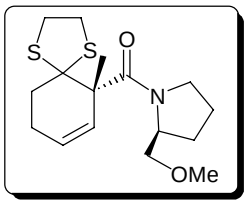
9. Preparation of (2*S*)-(2-Methoxymethyl-pyrrolidin-1yl)-(6*S*)-(6-methyl-1,4-dithia-spiro[4.5]dec-7-en-6-yl-methanone [(-)-185]:



To a solution of (-)-**179** (1.1 g, 4.38 mmol) in ethanedithiol (1 mL, 11.92 mmol) was added boron triflouride etherate (0.6 mL, 4.73 mmol) and contents were stirred at room temperature overnight. The reaction mixture was diluted with ether (30 mL) and washed successively with 1N aqueous NaOH solution (2 × 10 mL) and saturated NaCl solution (10 mL). The organic layer was dried (Na_2SO_4), filtered (gravity) and concentrated to give yellow residue with very unpleasant odor. Recrystallization from a mixture of hexane/ethyl acetate (4:1) furnished (-)-**185** (1.35 g, 99%) as colorless needles.

M.p.	**:**	154-156 °C.
IR ($CHCl_3$)	**:**	ν_{max} = 2950, 2921, 2852, 1606, 1454, 1375, 1112 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.64 (s, 3H), 1.81-1.94 (m, 4H), 2.17-2.28 (m, 2H), 2.36-2.42 (m, 1H), 2.66-2.75 (m, 1H), 3.05-3.20 (br. s, 4H), 3.32 (s, 3H), 3.36 (d, *J* = 2.9 Hz, 1H), 3.42 (d, *J* = 6.8 Hz, 1H), 3.50-3.70 (m, 2H), 4.25-4.45 (m, 1H), 5.75 (s, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 25.2 (2C), 26.6, 29.2, 29.3, 30.3, 44.6, 48.0, 58.2, 59.1 (2C), 65.8, 72.4, 130.7, 133.4, 159.9.
Mass (EI)	**:**	*m/z* = 327 (M^+), 299, 268, 210, 185, 164, 151, 142, 118 (100%),105, 95, 82, 70.

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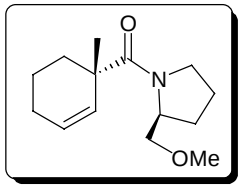
10. Preparation of (2*S*)-(2-Methoxymethyl-pyrrolidin-1-yl)-(1*S*)-(1-methyl-cyclohex-2-enyl)-methanone [(-)-184]:



***a) <u>From compound (-)-183</u>*:** A mixture of mesylate (-)-**183** (0.85 g, 2.57 mmol), sodium iodide (1.95 g, 13.0 mmol) and zinc powder (1.7 g, 26.0 mmol) in dimethoxymethane (8 mL) was heated at 70 °C for 4 h. The reaction mixture was filtered to remove excess sodium iodide and zinc powder. The filtrate was poured into water (15 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:2) to give (-)-**184** (0.45 g, 76%).

***b) <u>From compound (-)-185</u>*:** A solution of (-)-**185** (0.66 g, 2.02 mmol) in $^nBu_3SnH$ (3 mL, 11.01 mmol) containing 0.005 g of AIBN was refluxed at 120 °C for 24 h. Additional

AIBN (0.005 g each time) was added at the intervals of every 4 h. The crude reaction mixture was subjected to column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to yield (-)-**184** (0.44 g, 96%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	–92.31 (*c* = 0.675, $CHCl_3$).
IR (film)	**:**	ν_{max} = 2975, 2931, 2246, 1616, 1406, 1371, 1245, 1114, 910 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.23 (s, 3H), 1.25-1.35 (m, 1H), 1.40-1.51 (m, 2H), 1.58-1.70 (m, 2H), 1.77-1.86 (m, 3H), 1.92-2.05 (m, 2H), 3.27 (s, 3H), 3.35-3.57 (m, 3H), 3.59-3.75 (m, 1H), 4.20-4.40 (m, 1H), 5.48-5.80 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 23.8, 25.0, 25.7, 26.2, 27.8, 31.9, 43.5, 46.9, 57.2, 58.0, 71.6, 126.1, 130.8, 174.1.
Mass (GC-MS)	**:**	*m/z* = 237 (M+), 222, 205, 192, 176, 164, 142, 114, 95, 70 (100), 67, 41.
Elemental analysis	**:**	C_{14} $H_{23}O_2N$ (237.34): Calcd. C 70.85, H 9.77, N 5.90; Found C 71.04, H 9.82, N 5.64.

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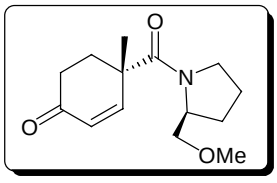
11. Preparation of 4-[(2*S*)-2-Methoxymethyl-pyrrolidine-1-carbonyl]-(4*S*)-4-methyl-cyclohex-2-enone [(-)-186]:



To a stirring mixture of (-)-**184** (0.72 g, 3.04 mmol) and pyridinium dichromate (PDC, 2.86 g, 7.60 mmol) in dichloromethane (15 mL) was added 70% *t*-butylhydroperoxide (1.02 mL, 7.60 mmol) dropwise at 10 °C. After 15 min., the mixture was warmed to room temperature and stirred for the next 12 h. Additional PDC (2.86 g, 7.60 mmol) and *t*-butylhydroperoxide (1.02 mL, 7.60 mmol) were added and the stirring continued for another 12 h. Ethyl acetate (50 mL) was added to the reaction mixture and the content was filtered through a pad of celite. The filtrate was dried

(Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (-)-**186** (0.51 g, 67%) as a colorless liquid.

IR (film)	**:**	ν_{max} = 3051, 1692, 1618, 1448, 1073 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.45 (s, 3H), 1.61-2.18 (m, 6H), 2.42-2.68 (m, 2H), 3.13-3.63 (m, overlapping s at 3.28, 7H), 4.19-4.43 (m, 1H), 6.39 (d, *J* = 9.8 Hz, 1H), 6.92 (d, *J* = 9.8 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 24.4, 25.2, 26.4, 29.7, 33.9, 34.6, 46.3, 58.5, 58.7, 71.6, 129.2, 150.3, 166.6, 184.5.

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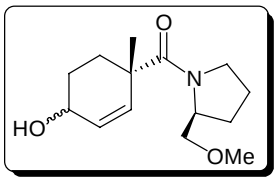
12. Preparation of (1*S*)-(4-Hydroxy-1-methyl-cyclohex-2-enyl)-(2*S*)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (187):



To a stirring solution of (-)-**186** (0.76 g, 3.03 mmol) in methanol was added $CeCl_3.7H_2O$ (1.25 g, 3.33 mmol) at room temperature. The mixture was stirred for 0.5 h at room temperature and cooled to 0 °C. Sodium borohydride (0.15 g, 3.95 mmol) was added in portions over a period of 5 min. The solution was allowed to warm to room temperature. After consumption of the starting material (TLC), the methanol was removed under vacuum. The residual pale pink mixture was dissolved in a minimum amount of water, acidified to pH 3 with 1N HCl and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to afford **187** (0.49 g, 95%) as a colorless liquid in 3:2 diastereomeric mixture, confirmed by GC and ^{1}H NMR spectroscopy.

IR (Neat)	**:**	ν_{max} = 3448, 3032, 1615, 1417, 1109, 1032 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.28 (s, 3H), 1.53-2.19 (m, 8H), 2.31-2.59 (br. s, 1H), 3.28 and 3.31 & 3.33 (2s (3:2), 3H), 3.32-3.73 (m, 4H), 4.18 (td, *J* = 6.8, 1.4 Hz, 1H), 4.26-4.39 (m, 1H), 5.71 (s, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 25.2, 25.3, 26.6, 29.3, 30.3, 44.6, 48.0, 58.2, 59.1, 65.9, 72.4, 130.7, 133.4, 159.9.

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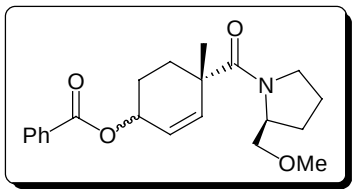
13. Preparation of Benzoic acid 4-[(2*S*)-2-methoxymethyl-pyrrolidine-1carbonyl]-(4*S*)-4-methyl-cyclohex-2-enyl ester (190):



a) <u>By benzoylation of 187</u>: Into a cooled (0 °C) solution of alcohol **187** (0.64 g, 2.53 mmol) in dry DCM (40 mL), was added Et_3N (0.53 mL, 3.79 mmol). BzCl (.39 mL, 3.04 mmol) was added drop-wise to the solution, allowed to warm to room temperature and stirred for 6h. The mixture was diluted with DCM (50 mL), the layers were separated and the water layer was back extracted with DCM (2 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by recrystalization from pet. ether-ethyl acetate (3:1) to obtain benzoyl derivative of **190** (0.82 g, 91%) as a colorless needles and in 3:2 diastereomeric ratio as indicated by GC analysis.

b) <u>By Kharash-Sonvsky reaction on (-)-184</u>: Into a 250 mL, two-necked flask equipped with a magnetic stirring bar and a reflux condenser, was placed a mixture of (-)-**184** (0.60 g, 2.37 mmol) and cuprous bromide (0.73 g, 2.53 mmol) in acetonitrile (10 mL) under argon atmosphere. The mixture was heated to 80 °C and *t*-butyl perbenzoate (0.49 g, 2.53 mmol) was added to it dropwise over a period of 15 min using syringe. The mixture became homogeneous and the color of the solution turned blue during the addition of *t*-butyl perbenzoate. The heating was continued for additional 4 h. The cooled solution was

transferred to a separating funnel with the aid of ethyl acetate and washed with dilute aqueous solution of sodium bicarbonate to remove benzoic acid. The organic layer was washed with water until neutral, followed by brine and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent = pet. ether-ethyl acetate, 3:1) to obtain benzoyl derivative of **190** (0.28 g, 31%) as a white solid in 7:3 diastereomeric ratio favoring the *cis* form as indicated by GC analysis. The starting material (62%) was also recovered.

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.72 (s, 3H), 1.76-2.07 (m, 6H), 3.06-3.71 (m, overlapping s at 3.35, 9H), 4.24-4.47 (m, 1H), 5.56-5.67 (m, 1H), 5.87 (dd, 10.3, 2.0 Hz, 1H), 6.10 (dd, 10.3, 1.7 Hz, 1H), 7.35-7.66 (m, 3H), 7.94-8.16 (m, 2H).

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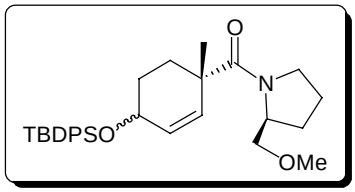
14. Preparation of (1*S*)-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-methyl-cyclohex-2-enyl]-(2*S*)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (189):



Triethyl amine (0.3 mL, 2.16 mmol) was added to a dilute solution of **187** (0.46 g, 1.82 mmol) in dry DCM (10 mL) at 0 °C. To this mixture was added a solution of TBDPSCl (0.51 mL, 2 mmol) in dry DCM (5 mL), over a period of 15 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 30 h. Usual workup and extraction of the reaction mixture with DCM (2 $\times$ 15 mL) followed by washing of the combined organic layers with water (2 $\times$ 15 mL), brine (15 mL), drying over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure furnished crude residue which was subjected to column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to obtain **189** (0.78 g, 87%) as a highly viscous colorless

liquid. The diastereomeric ratio was determined by GC analysis and was found to be same as in the case of parent alcohol (3:2).

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.08 (s, 9H), 1.32 (s, 3H), 1.56-2.13 (m, 8H), 3.16-3.73 (m, overlapping s at 3.26, 7H), 4.08-4.42 (m, 2H), 5.56-5.84 (m, 2H), 7.31-7.49 (m, 6H), 7.62-7.77 (m, 4H).

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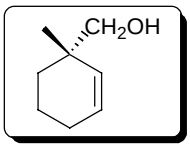
15. Preparation of (1*S*)-(1-Methyl-cyclohex-2-enyl)-methanol [(+)-192]:



To a solution of compound (-)-**184** (1.2 g, 5.06 mmol) in THF (20 mL) was added slurry of LAH (0.19 g, 5.14 mmol) in THF dropwise at –20 °C. The temperature of the mixture was raised to 0 °C over a period of 4 h. The mixture was stirred at 0 °C for an additional hour and was quenched by dropwise addition of 2 N sulfuric acid. The resulting mixture was allowed to warm to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (100-200 mesh; eluent: pet. ether-ethyl acetate = 10:1) to give desired (+)-**192** (0.64 g, 96%) as a colorless liquid.*

$[\alpha]_D^{25}$: +4.6 (*c* = 0.68, $CHCl_3$).

IR (film) : ν_{max} = 3421, 3016, 2927, 2854, 1460, 1215, 1039 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 0.95 (s, 3H), 1.20-1.39 (m, 2H), 1.65-1.79 (m, 3H), 1.90-2.07 (m, 2H), 3.29 (d, *J* = 11.0 Hz, 1H), 3.39 (d, J = 10.8 Hz, 1H), 5.36 (dt, *J* = 9.5, 2.2 Hz, 1H), 5.79 (dt, *J* = 9.8, 3.8 Hz, 1H).

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* The chiral auxiliary was recovered in 85% yield by basifying the mother liquor with 2 N NaOH and extracting with ethyl acetate.

^{13}C NMR (125 MHz,$CDCl_3$) : δ = 18.8, 24.0, 24.9, 31.4, 36.8, 71.2, 128.8, 132.6.

Mass (GC-MS) : *m/z* = 126 (M^+), 96, 95 (100%), 79, 67, 41.

Elemental analysis : $C_8H_{14}O$ (126.20): Calcd. C 76.14, H 11.18; Found C 76.36, H 11.23.

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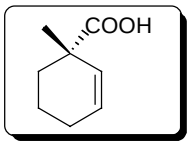
16. Preparation of (1*S*)-1-Methyl-cyclohex-2-enecarboxylic acid [(-)-196]:



A mixture of alcohol (+)-**192** (0.64 g, 5.08 mmol) and pyridinium dichromate (7.64 g, 20.32 mmol) in DMF (15 mL) was stirred overnight. The mixture was poured into a beaker containing water (150 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to furnish (-)-**196** (0.64 g, 91%) as a colorless liquid.

IR ($CHCl_3$) : ν_{max} = 3398, 2972, 1676, 1440, 1380, 1203 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.23 (s, 3H), 1.42-1.49 (m, 1H), 1.53-1.69 (m, 2H), 1.88-2.02 (m, 2H), 2.09-2.21 (m, 1H), 5.71 (dt, *J* = 10.1, 1.7 Hz, 1H), 5.84 (dt, *J* = 10.0, 3.3 Hz, 1H).

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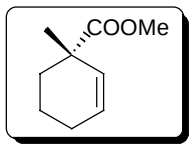
17. Preparation of (1*S*)-1-Methyl-cyclohex-2-enecarboxylic acid methyl ester [(-)-197]:



To a solution of (-)-**196** (0.64 g, 4.57 mmol) in ether (5 mL), a solution of diazomethane in ether (15 mL) prepared from *N*-nitroso-*N*-methyl urea (1.63 g, 18.3 mmol), was added at 0 °C. The mixture was stirred at 0 °C for an additional hour and warmed to room temperature while stirring. The ether was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 19:10) to furnish ester (-)-**197** (0.65 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-44.33 (c = 1, CH_2Cl_2).
IR (film)	**:**	ν_{max} = 3022, 2948, 2891, 1730, 1452, 1240, 1099 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.26 (s, 3H), 1.39-1.51 (m, 1H), 1.55-1.72 (m, 2H), 1.92-2.05 (m, 2H), 2.16 (ddd, 13.1, 7.6, 3.2 Hz, 1H), 3.68 (s, 3H), 5.69 (dt, J = 10.3, 2.1 Hz, 1H), 5.78 (dt, J = 9.9, 3.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 125 MHz)	**:**	δ = 18.6, 23.9, 24.8, 31.6, 36.7, 52.3, 129.3, 131.2, 172.6.
Mass (GC-MS)	**:**	m/z = 154 (M^+), 136, 111, 109, 94, 79, 55, 43.
Elemental analysis	**:**	$C_9H_{14}O_2$ (154.21): Calcd. C 70.10, H 9.15; Found C 70.32, H 9.11.

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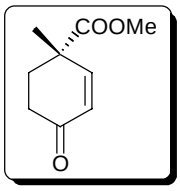
18. Preparation of (1*S*)-1-Methyl-4-oxo-cyclohex-2-enecarboxylic acid methyl ester [(-)-198]:



To a stirring mixture of (-)-**197** (0.72 g, 4.68 mmol) and pyridinium dichromate (PDC, 4.4 g, 11.69 mmol) in dichloromethane (15 mL) was added 70% *t*-butylhydroperoxide (1.57 mL, 11.69 mmol) dropwise at 10 °C. After 15 min., the mixture was warmed to room temperature and allowed to stir for the next 12 h. Additional PDC (4.4 g, 11.69 mmol) and *t*-butylhydroperoxide (1.57 mL, 11.69 mmol) were added and the stirring continued for another 12 h. Ethyl acetate (50 mL) was added to the reaction mixture and the contents were filtered through a pad of celite. The filtrate was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (-)-**198** (0.51 g, 65%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	–20.02 (*c* = 1.73, $CHCl_3$).
IR (film)	**:**	ν_{max} = 3018, 1730, 1677, 1216, 1215 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.43 (s, 3H), 1.85-2.05 (m, 2H), 2.35-2.55 (m, 2H), 3.73 (s, 3H), 5.96 (d, *J* = 10.2 Hz, 1H,), 6.87 (d, *J* = 10.2 Hz, 1H).
^{13}C NMR (125 MHz,$CDCl_3$)	**:**	δ = 24.9, 32.6, 34.6, 43.9, 52.6, 128.7, 151.7, 174.6, 198.5.
Mass (GC-MS)	**:**	*m/z* = 168 (M^+), 153, 140, 125, 109, 82, 81 (100%), 59, 53.
Elemental analysis	**:**	$C_9H_{12}O_3$ (168.19): Calcd. C 64.27, H 7.19; Found C 64.15, H 7.21.

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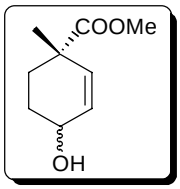
19. Preparation of (1*S*)-4-Hydroxy-1-methyl-cyclohex-2-enecarboxylic acid methyl ester (199):



To a stirring solution of (-)-**198** (0.51 g, 3.04 mmol) in methanol was added $CeCl_3.7H_2O$ (1.3 g, 3.34 mmol) at room temperature. The mixture was stirred for 0.5 h at room temperature and cooled to 0 °C. Sodium borohydride (0.15 g, 3.95 mmol) was added in portions over a period of 5 min. The solution was allowed to warm to room temperature. After consumption of the starting material (TLC), the methanol was removed under vacuum. The residual pale pink mixture was dissolved in a minimum amount of water, acidified to pH 3 with 1N HCl and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to afford **199** (0.49 g, 95%) as a colorless liquid in 3:2 diastereomeric mixture, confirmed by GC and ^{1}H NMR spectroscopy.

IR ($CHCl_3$) : ν_{max} = 3468, 2985, 1731, 1645, 1272, 1250, 1113 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) : δ = 1.18 & 1.25 (2s (3:2), 3H), 1.30-1.70 (m, 2H), 1.72-2.00 (m, 1H), 2.18 (m, 1H), 2.70-2.90 (br. s, 1H), 3.60 (s, 3H), 4.00-4.15 (m, 1H,), 5.60-5.75 (m, 2H).

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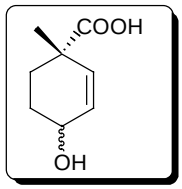
20. Preparation of (1*S*)-4-Hydroxy-1-methyl-cyclohex-2-enecarboxylic acid (200):



To a solution of **199** (0.84 g, 0.49 mmol) in THF (5.5 mL) and water (4.5 mL) was added lithium hydroxide monohydrate (0.48 g, 11.53 mmol) in a single portion. After stirring overnight, THF was removed under vacuum and the residue was acidified with 1N HCl and extracted with ether (3 × 10 mL). The combined ether extracts were dried over sodium sulfate, filtered and concentrated to give viscous colorless oil, which solidified upon standing. Recrystallization from a mixture of hexane:ethyl acetate (3:2) furnished **200** (0.72 g, 94%) as colorless needles.

M.p. : 85-87 °C.

IR (film) : ν_{max} = 3600, 3480, 2600, 1680 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) : δ = 1.25 & 1.35 (s (3:2), 3H), 1.45-2.30 (m, 4H,), 2.36-2.92 (br. s, 1H), 4.15-4.20 (m, 1H), 5.60-5.85 (m, 2H), 9.67-9.92 (br. s, 1H).

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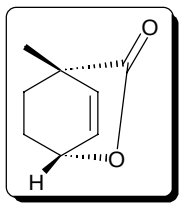
21. Preparation of (1*R*,4*S*)-4-Methyl-2-oxa-bicyclo[2.2.2]oct-5-en-3-one [(-)-201]:



To a solution of **200** (0.42 g, 2.69 mmol) in dichloromethane (20

mL) was added boron triflouride etherate (0.44 mL, 3.7 mmol) dropwise at 0 °C. The pale brown solution was stirred for 3 h and the reaction was quenched by adding 5% sodium bicarbonate solution until the pH of the aqueous phase reached 7. After separation of the layers, the aqueous phase was back extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (-)-**201** (0.33 g, 90%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	–27.28 (*c* = 0.45, $CHCl_3$).
IR ($CHCl_3$)	**:**	ν_{max} = 1743, 1215, 1112 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.36 (s, 3H), 1.61-1.74 (m, 3H), 2.14--2.23 (m, 1H), 5.11-5.23 (m, 1H), 6.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.44 (dd, *J* = 7.8, 5.0 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 18.5, 26.1, 27.2, 43.6, 73.8, 131.2, 137.7, 176.4.
Mass (GC-MS)	**:**	*m/z* = 139 (M^++1), 124, 110, 109, 94, 79 (100%), 65, 44.
Elemental analysis	**:**	$C_8H_{10}O_2$ (138.17): Calcd. C 69.54, H 7.29; Found C 69.32, H 7.36.

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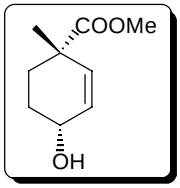
22. Preparation of (1*S*,4*R*)-4-Hydroxy-1-methyl-cyclohex-2-enecarboxylic acid methyl ester [(-)-204]:



To a solution of lactone (-)-**201** (0.62 g, 4.49 mmol) in methanol (20 mL) was added a 25% solution of sodium methoxide in methanol (0.97 mL, 4.49 mmol) and contents were refluxed for an hour. Methanol was removed under reduced pressure. The residue was diluted with ether (40 mL), washed with water (1 × 15 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column

chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to yield (-)-**204** (0.71 g, 93%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	-10.26 (c = 0.835, CH_2Cl_2).
IR ($CHCl_3$)	**:**	ν_{max} = 3440, 2952, 1728, 1650, 1242, 1116 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.22 (s, 3H), 1.32-1.68 (m, 2H), 1.86-1.94 (m, 1H), 2.00-2.07 (br. s, 1H), 2.17-2.35 (m, 1H), 3.66 (s, 3H), 4.12 (dd, J = 6.8, 1.5 Hz, 1H), 5.70-5.85 (br. s, 2H).
^{13}C NMR (125 MHz, $CDCl_3$)	**:**	δ = 25.8, 28.7, 29.4, 43.0, 52.2, 64.5, 130.2, 133.1, 176.7.
Elemental analysis	**:**	$C_9H_{14}O_3$ (170.21): Calcd. C 63.51, H 8.29; Found C 63.38, H 8.16.

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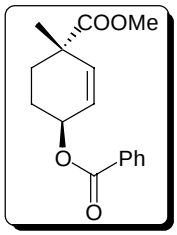
23. Preparation of Benzoic acid (4*S*)-4-methoxycarbobonyl-4-methyl-cyclohex-2-enyl ester [(-)-205]:



To a solution of alcohol (-)-**204** (0.71 g, 4.18 mmol) in THF (15 mL) was added triphenyl phosphine (1.42 g, 5.43 mmol) and benzoic acid (0.76 g, 6.26 mmol). The mixture was cooled to 0 °C and diisopropylazodicarboxylate (1.1 mL, 5.43 mmol) was introduced dropwise over a period of 10 min. After stirring for 4 h at room temperature, the solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (25 mL). The mixture was filtered through a small pad of silica gel; the filtrate concentrated under reduced pressure and the crude benzoate was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to obtain (-)-**205** (1.09 g, 95%) as viscous colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.32 (s, 3H), 1.57-1.65 (m, 1H), 1.78-1.99 (m, 1H), 2.03-2.21 (m, 1H), 2.33-2.41 (m, 1H), 3.74 (s,

3H), 5.45-5.56 (m, 1H), 5.87 (dd, *J* = 10.3, 2.9 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 7.38-7.79 (m, 3H), 7.99-8.34 (m, 2H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ = 25.5, 25.6, 29.6, 42.9, 51.9, 68.4, 126.4, 128.0, 128.2, 129.6, 129.9, 132.7, 133.5, 134.9, 172.0, 176.1.

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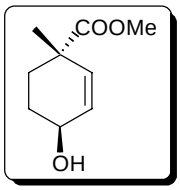
24. Preparation of (1*S*,4*S*)-4-Hydroxy-1-methyl-cyclohex-2-enecarboxylic acid methyl ester [(-)-166]:



To a solution of benzoate (-)-**205** (1.09 g, 3.98 mmol) in methanol (5 mL) was added a solution of 1N NaOH (15 mL) in methanol. The reaction mixture was stirred at room temperature for 2 h, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to give (-)-**166** (0.60 g, 89%) as a colorless liquid.

$[\alpha]^{25}_D$: –29.21 (*c* = 1.13, CH_2Cl_2).

IR (film) : ν_{max} = 3433, 2952, 1728, 1650, 1454, 1269, 1242, 1201, 1116 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 1.30 (s, 3H), 1.61-1.72 (m, 2H), 1.80-2.00 (br. s, 1H), 2.07 (t, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 4.13-4.22 (m, 1H), 5.75-5.85 (br. s, 2H).

^{13}C NMR (125 MHz,$CDCl_3$) : δ = 25.6, 28.9, 29.1, 43.3, 52.0, 64.6, 130.0, 133.3, 176.5.

Mass (GC-MS) : *m/z* = 170 (M^+), 152, 138, 127, 110 (100%), 101, 93, 77, 55, 43.

Elemental analysis : $C_9H_{14}O_3$ (170.21): Calcd. C 63.51, H 8.29;
Found C 63.66, H 8.44.

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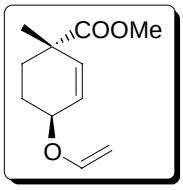
25. Preparation of (1*S*,4*S*)-1-Methyl-4-vinyloxy-cyclohex-2-enecarboxylic acid methyl ester [(-)-206]:



Mercuric acetate (1.03 g, 3.24 mmol) was added to a solution of alcohol (-)-**166** (0.55 g, 3.24 mmol) in ethyl vinyl ether (5 mL). The flask was fitted with a reflux condenser and the mixture was refluxed for 24 h by circulating cold water through the condenser. Additional ethylvinyl ether (3 mL) and benzene (10 mL) were added and the refluxing continued for next 4 h. After cooling to room temperature, glacial acetic acid (0.4 mL) was added to the reaction mixture and stirred for 1 h. The crude reaction mixture was extracted with ethyl acetate (3 × 15 mL), the combined organic layers were washed with 5% aquoeus potassium hydroxide solution (10 mL), water (20 mL) and brine (10 mL). After drying over sodium sulfate the solvent was removed under reduced pressure to yield crude residue which was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 5:1) to furnish allyl vinyl ether (-)-**206** (0.43 g, 67%) as colorless liquid.

IR ($CHCl_3$)	**:**	ν_{max} = 2983, 2360, 1741, 1652, 1463, 1373, 1244, 1047 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.25 (s, 3H), 1.55-2.45 (m, 4H), 3.72 (s, 3H), 4.10 (d, *J* = 9.7 Hz, 1H), 4.25-4.40 (m, 2H), 5.80-6.00 (m, 2H), 6.37 (dd, *J* = 9.9, 3.6 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 27.6, 28.7, 29.8, 44.2, 51.8, 72.2, 88.4, 126.8, 134.1, 149.8, 174.6.

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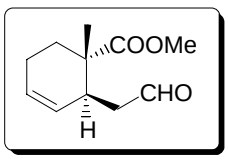
26. Preparation of (1*S*,2*S*)-1-Methyl-2-(2-oxo-ethyl)-cyclohex-3-enecarboxylic acid methyl ester [(+)-207]:



Allyl vinyl ether (-)-**206** (0.63 g, 3.21 mmol) was taken in 50 mL two-necked round bottom flask equipped with a reflux condenser and argon balloon. Benzene (15 mL) was added to the flask and the mixture was refluxed for 95 h. After

cooling to room temperature, the reaction mixture was transferred to a single necked RB flask and benzene was removed under reduced pressure. The crude mass was subjected to column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to yield the desired aldehyde (+)-**207** (0.20 g, 32%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	+14.36 (*c* = 0.8, CH_2Cl_2).
IR ($CHCl_3$)	**:**	ν_{max} = 3034, 1733, 1714, 1373, 1246 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.35 (s, 3H), 1.95-2.10 (m, 2H), 2.25-2.41 (m, 2H), 2.46-2.65 (m, 2H), 2.91 (td, *J* = 8.6, 3.9 Hz, 1H), 3.71 (s, 3H), 5.75-6.20 (m, 2H), 9.67 (s, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 17.2, 22.1, 33.1, 37.2, 41.1, 43.4, 52.1, 130.2, 131.4, 176.6, 212.3.
Mass (GC-MS)	**:**	*m/z* = 196 (M^+), 178, 165, 134, 95, 74, 61, 42 (100).
Elemental analysis	**:**	$C_{11}H_{16}O_3$ (196.25): Calcd. C 67.32, H 8.22; Found C 67.09, H 8.37.

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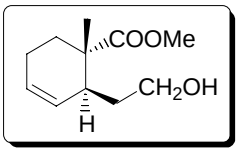
27. Preparation of (1*S*,2*S*)-2-(2-Hydroxy-ethyl)-1-methyl-cyclohex-3-enecarboxylic acid methyl ester [(+)-208]:



This experiment was performed using same procedure as described for the preparation of (-)-**181**/(-)-**182** from (-)-**179**.

Yield	**:**	95%.
IR ($CHCl_3$)	**:**	ν_{max} = 3426, 3019, 1733, 1465, 1217, 1040 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.25 (s, 3H), 1.30-1.41 (m, 2H), 1.57-1.84 (m, 2H), 1.86-2.16 (m, 3H), 3.46-3.83 (m, overlapping s at 3.65, 5H), 5.56-5.93 (m, 2H).

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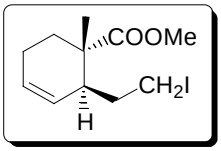
28. Preparation of (1*S*,2*S*)-2-(2-Iodo-ethyl)-1-methyl-cyclohex-3-enecarboxylic acid mthyl ester [(+)-209]:



To a stirred solution of triphenylphosphine (0.56 g, 2.83 mmol) and imidazole (0.19 g, 2.82 mmol) in dry DCM (7 mL) at 0 °C was added iodine (0.72 g, 2.82 mmol) portion wise over a period of ten minutes. The mixture was stirred for additional ten minutes and the solution of alcohol (+)-**208** (0.43 g, 2.17 mmol) in DCM (3 mL) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. It was diluted with DCM (25 mL), washed successively with 20% aqueous sodium thiosulfate solution (15 mL), water (25 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulfate, solvent was removed under reduced pressure and the crude residue was subjected to column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 9:2) to obtain (+)-**209** (0.79 g, 90%) as a colorless liquid, which turned pale yellow upon standing.

IR ($CHCl_3$)	**:**	ν_{max} = 2995, 1736, 1445, 1210, 1035 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.32 (s, 3H), 1.54-1.93 (m, 3H), 1.98-2.49 (m, 4H), 3.30-3.82 (m, overlapping s at δ = 3.70, 5H), 5.62 (dd, *J* = 10.6, 4.2 Hz, 1H), 5.91-6.17 (m, 1H).

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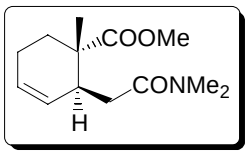
29. Preparation of (1*S*,2*S*)-2-Dimethylcarbamoylmethyl-1-methy-cyclohex-3-enecarboxylic acid methyl ester [(+)-210]:



A mixture of alcohol (-)-**166** (0.52 g, 3.06 mmol) and 1-dimethylamino-1,1-dimethoxyethane (2.03 g, 15.26 mmol) in dry *o*-xylene (15 mL) was heated at 150 ºC for 5 h, under argon atmosphere. After cooling to room temperature the mixture was diluted with ethyl acetate (25 mL) and washed successively with 2 N HCl (15 mL), water (20 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure on rotary evaporator to give crude product which upon

purification by column chromatography (silica gel, 230-400 mesh; eluent: pet. ether-ethyl acetate = 3:1) furnished the desired rearranged amide (+)-**210** (0.67 g, 92%) as pale yellow oil.

IR ($CHCl_3$)	**:**	ν_{max} = 2996, 1734, 1682 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.24 (s, 3H), 1.52-1.72 (m, 1H), 1.77-1.93 (m, 3H), 1.95-2.14 (m, 2H), 2.24-2.48 (m, 1H), 2.92 (s, 3H), 2.96 (s, 3H), 3.68 (s, 3H), 5.51-5.74 (m, 2H).
^{13}C NMR (125 MHz,$CDCl_3$)	**:**	δ = 21.6, 22.0, 26.9, 35.2, 35.9, 37.0, 38.9, 43.9, 51.3, 125.6, 128.6, 171.5, 177.4.
Elemental analysis	**:**	$C_{13}H_{21}O_3N$ (239.32): Calcd. C 65.24, H 8.84, N 5.85; Found C 65.53, H 8.67, N 5. 59.

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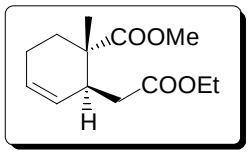
30. Preparation of (1*S*,2*S*)-Methyl-2-(2-ethoxy-2- oxoethyl)-1-methylcyclohex-3-enecarboxylate [(+)-169]:



An RB flask fitted with Claisen adapter was charged with a mixture of (-)-**166** (0.65 g, 3.82 mmol), triethyl orthoacetate (2.8 mL, 15.29 mmol) and propionic acid (0.1 mL) and was heated to reflux at 138-142 ºC for 2 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (230-400 mesh; eluent: pet. ether-ethyl acetate = 9:1) to give (+)-**169** (0.88 g, 96%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	+12.4 (*c* = 1.49, CH_2Cl_2).
IR (film)	**:**	ν_{max} = 3022, 2983, 1730, 1654, 1448, 1373, 1247, 1045 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ = 1.10 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H) 1.55-1.80 (m, 2H), 1.85-2.20 (m, 4H), 2.25-2.50 (m, 1H), 3.7 (s, 3H), 4.13 (q, *J* = 7.0 Hz, 2H), 5.50 (dt, *J* = 10.2, 2.4

Hz, 1H) 5.67 (dd, *J* = 10.2, 2.4 Hz, 1H).

^{13}C NMR (75 MHz,$CDCl_3$) : δ = 13.7, 16.3, 21.6, 31.0, 35.7, 36.8, 43.5, 51.5, 60.0, 125.7, 128.0, 172.0, 177.1.

Mass (GC-MS) : *m/z* = 240 (M^+), 208, 194, 180, 166, 151, 135, 121, 107, 93 (100%), 74, 61, 41.

Elemental analysis : $C_{13}H_{20}O_4$ (240.30): Calcd. C 64.98, H 8.39; Found C 65.23, H 8.24.

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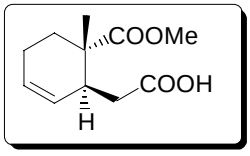
31. Preparation of (1*S*,2*S*)-2-carboxymethyl-1-methyl-cyclohex-3-enecarboxylic acid methyl ester [(+)-212]:



A mixture containing (+)-**169** (0.88 g, 3.67 mmol) and NaOH (0.107 g, 3.67 mmol) in methanol (10 mL) was refluxed for 12 h. The methanol was removed under reduced pressure; the residue was dissolved in water and extracted with ether to remove un-reacted dimethyl ester. Acidification of the aqueous solution with 2N HCl, saturation with common salt and extraction with ether resulted (+)-**212** (0.72 g, 87%) as a colorless liquid.

$[\alpha]^{25}_D$: +12.13 (*c* = 2.095, $CHCl_3$).

IR ($CHCl_3$) : ν_{max} = 3614, 2600, 1735, 1680 1234, 1109 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.27 (s, 3H), 1.50-1.71 (m, 1H), 1.72-1.96 (m, 2H), 2.00-2.20 (m, 2H), 2.28-2.57 (m, 2H), 3.66 (s, 3H), 5.50-5.85 (m, 2H), 9.95 (br. s, 1H).

^{13}C NMR (75 MHz,$CDCl_3$) : δ = 22.2 (2C), 26.8, 37.3, 38.7, 43.5, 51.3, 126.3, 127.2, 176.8, 178.3.

Mass (GC-MS) : *m/z* = 212 (M^+), 184, 169, 152, 149, 137, 121, 107, 93, 77, 67, 41.

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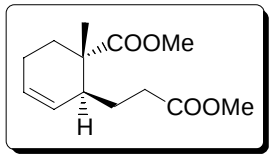
32. Preparation of (1*S*,2*S*)-2-(2-Methoxycarbonyl-ethyl)-1-methyl-cyclohex-3-enecarboxylic acid methyl ester [(+)-213]:



A mixture of (+)-**212** (0.72 g, 3.18 mmol), pyridine (2 drops) and purified thionyl chloride (3 mL) in benzene (10 mL) was stirred at room temperature for 2 h. The solvent and excess thionyl chloride were removed under reduced pressure. Benzene (5 mL) was added to the residue and again evaporated under reduced pressure. The resulting acid chloride was dissolved in benzene (5 mL) and was added to a solution of diazomethane, prepared from *N*-nitroso-*N*-methyl urea (1.42 g, 15.93 mmol) in ether (30 mL) at 0 °C while stirring. The mixture was warmed to room temperature and stirred for additional 5 h. The solvent was removed under reduced pressure. Methanol (10 mL) and silver oxide (0.3 g) were added to the residual diazoketone. After refluxing for 2 h, an additional silver oxide (0.2 g) was added and refluxing continued for the next 10 h. The mixture was filtered through a pad of celite and the filtrate concentrated. The residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (+)-**213** (0.60 g, 78%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	+16.17 (*c* = 0.81, CH_2Cl_2).
IR (film)	**:**	ν_{max} = 2981, 2950, 1737, 1730, 1652, 1434, 1373, 1244, 1166, 1047 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.27 (s, 3H), 1.51-1.72 (m, 2H), 1.78-1.95 (m, 2H), 2.00-2.22 (m, 2H), 2.25-2.50 (m, 2H), 2.58-2.72 (m, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 5.30-5.95 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	**:**	δ = 22.2 (2C), 25.6, 28.4, 31.8, 41.6, 45.0, 51.3 (2C), 126.2, 127.0, 173.7, 177.4.
Mass (GC-MS)	**:**	*m/z* = 240 (M^+), 209, 180, 165, 130, 126, 107 (100%), 93, 79, 59, 41.

Elemental analysis : $C_{13}H_{20}O_4$ (240.30): Calcd. C 64.98, H 8.39;
Found C 65.06, H 8.45.

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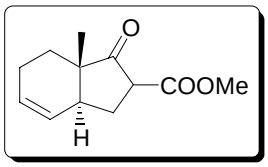
33. Preparation of (3*aS*,7*aS*)-Methyl 7a-methyl-1-oxo-2,3,3a,6,7,7a-hexahydro-1H-indene-2-carboxylate (214):



To a solution of (+)-**213** (0.60 g, 2.5 mmol) in THF (8 mL) was added 2M solution of NaHMDS (1.88 mL, 3.75 mmol) in THF at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 h. Excess NaHMDS was quenched with saturated NH_4Cl solution and the mixture was extracted with EtOAc (3 × 10 mL), washed with water (1 × 10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give **214** (0.50 g, 97%) as a colorless liquid.

IR ($CHCl_3$) : ν_{max} = 3022, 2956, 2931, 1753, 1728, 1434, 1336, 1240, 1157, 1047 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.10 (s, 3H), 1.20-1.50 (m, 2H), 1.75-2.10 (m, 4H), 2.58 (t, *J* = 8.6 Hz, 1H), 3.29 (t, *J* = 8.6 Hz, 1H), 3.72 (s, 3H), 5.56 (dd, *J* = 10.1, 1 Hz, 1H), 5.69-5.76 (m, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ = 21.8, 22.0, 26.4, 27.8, 36.2, 43.9, 48.6, 52.3, 127.7, 129.2, 172.4, 220.3.

Mass (GC-MS) : *m*/z = 208 (M^+), 193, 176, 154, 130, 121, 105, 91, 79, 55, 41.

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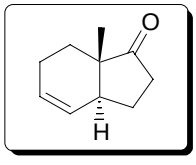
34. Preparation of (3*aS*,7*aS*)-7a-Methyl-3,3a,7,7a-tetrahydro-2H-inden-1(6H)-one [(+)-164]:



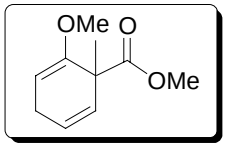
a) From (+)-209: A solution of (+)-**209** (0.55 g, 1.0 mmol) in dry

THF (8 mL) was cooled to –100 °C with the aid of ether-dry ice bath and a 0.52 M (in *n*-pentane) solution of *t*-BuLi (2.12 mL, 1.1 mmol) was added dropwise over a period of 10 minutes. After stirring for additional 30 minutes at –100 °C, the reaction mixture was slowly warmed to –50 °C over period of 45 minutes. The mixture was stirred for 1.5 h and quenched by careful addition of saturated NH_4Cl solution. After the solution had attained room temperature it was transferred to a separating funnel and extracted with ethyl acetate (3 × 10 mL), washed successively with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 9:1) furnished the desired *trans*-Hydrindane system (+)-**164** (0.23g, 85%) as viscous colorless oil having camphor like odor.

b) From 214: An RB flask charged with a solution of **214** (0.32 g, 1.54 mmol) and DABCO (1.03 g, 9.23 mmol) in o-xylene (5 mL) was heated at 150 °C for 10 h. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 9:1) to give (+)-**164** (0.19 g, 82%) as a thick oil with mild camphor like odor.

$[\alpha]^{25}_D$	**:**	+5.63 (*c* = 0.16, CH_2Cl_2).
IR (film)	**:**	ν_{max} = 3020, 2927, 1735, 1217 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.05 (s, 3H), 1.26-1.41 (m, 2H), 1.60-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.15-2.40 (m, 3H), 5.51-5.86 (m, 1H).
^{13}C NMR (125 MHz,$CDCl_3$)	**:**	δ = 21.6, 21.8, 26.2, 27.0, 35.9, 43.6, 47.2, 127.5, 129.0, 223.4.
Mass (GC-MS)	**:**	*m/z* = 151 (M^++1), 137, 110, 109, 95, 79, 57 (100%), 41.
Elemental analysis	**:**	$C_{10}H_{14}O$ (150.22): Calcd. C 79.96, H 9.39; Found C 79.83, H 9.62.

35. Preparation of 2-Methoxy-1-methyl-cyclohexa-2,5-dienecarboxylic acid methyl ester [(±)-240]:



This experiment was performed using same procedure as described for the preparation of (-)-**178** from (-)-**168**.

Yield	**:**	92%
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.41 (s, 3H), 2.73-2.95 (m, 2H), 3.52 (s, 3H), 3.68 (s, 3H), 4.75 (t, *J* = 3.2 Hz, 1H), 5.48 (dt, *J* = 10.1, 1.7 Hz, 1H), 5.79 (dt, *J* = 10.1, 3.3 Hz, 1H).

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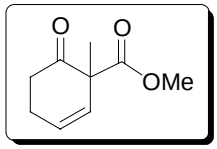
36. Preparation of 1-Methyl-6-oxo-cyclohex-2-enecarboxylic acid methyl ester [(±)-238]:



This experiment was performed using same procedure as described for the preparation of (-)-**179** from (-)-**178**.

Yield	**:**	88%
IR ($CHCl_3$)	**:**	ν_{max} = 2954, 1740, 1720, 1452, 1204 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.35 (s, 3H), 2.36-2.77 (m, 4H), 3.65 (s, 3H), 5.64 (dt, *J* = 9.8, 1.5 Hz, 1H), 5.93 (dt, *J* = 9.8, 3.9 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 23.1, 23.7, 27.2, 48.3, 52.4, 127.4, 128.7, 176.3, 199.7.

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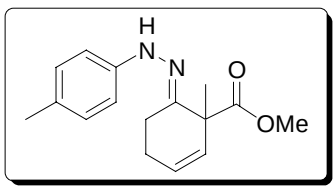
37. Preparation of 1-Methyl-6-(*p*-tolyl-hydrazono)-cyclohex-2-enecarboxylic acid methyl ester [(±)-241]:



This experiment was performed using same procedure as described for the preparation of (-)-**180** from (-)-**179**.

Mp	**:**	163-165 ^{o}C
^{1}H NMR	**:**	δ = 1.41 (s, 3H), 2.12-2.93 (m, 7H), 3.72 (s, 3H), 5.73
(200 MHz, $CDCl_3$)		(d, 9.7 Hz, 1H), 6.01 (dt, 9.7, 2.4 Hz, 1H), 7.35 (d, 10.7 Hz, 2H), 7.81 (d, 10.7 Hz, 2H).

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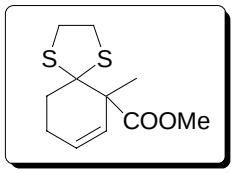
38. Preparation of 6-Methyl-1,4-dithia-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester [(±)-242]:



This experiment was performed using same procedure as described for the preparation of (-)-**185** from (-)-**179**.

Yield	**:**	98%
IR ($CHCl_3$)	**:**	ν_{max} = 2952, 2257, 1724, 1460, 1224, 1112, 908, 736, 649 cm^{-1}.
^{1}H NMR	**:**	δ = 1.57 (s, 3H), 2.09-2.38 (m, 3H), 2.58-2.77 (m,
(200 MHz, $CDCl_3$)		1H), 3.10-3.32 (m, 4H), 3.68 (s, 3H), 5.60 (dt, *J* = 10.3, 1.4 Hz, 1H), 5.76 (dt, *J* = 9.9, 3.4 Hz, 1H).
^{13}C NMR	**:**	δ = 18.7, 21.9, 25.2, 42.3, 43.4 (2C), 51.3, 66.5,
(50 MHz,$CDCl_3$)		131.6, 133.4, 162.3.

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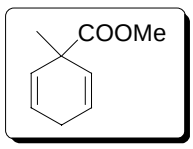
39. Preparation of 1-Methyl-cyclohexa-2,5-dienecarboxylic acid methyl ester [(±)-245]:



This experiment was performed using same procedure as described for the preparation of (-)-**178** from (-)-**168**.

Yield	**:**	93%
^{1}H NMR	**:**	δ = 1.36 (s, 3H), 2.68-2.84 (m, 2H), 3.69 (s, 3H),
(200 MHz, $CDCl_3$)		5.71-5.90 (m, 4H).

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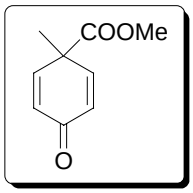
40. Preparation of 1-Methyl-4-oxo-cyclohexa-2,5-diencarboxylic acid methyl ester [(±)-246]:



This experiment was performed using same procedure as described for the preparation of (-)-**186** from (-)-**184**.

Yield	**:**	84%
IR ($CHCl_3$)	**:**	ν_{max} = 3017, 1734, 1667, 1628, 1447, 1238, 1174, 1114, 858, 757 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.52 (s, 3H), 3.71 (s, 3H), 6.25 (d, *J* = 10.3 Hz, 2H), 7.0 (d, *J* = 10.3 Hz, 2H).

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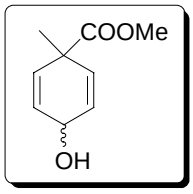
41. Preparation of 4-Hydroxy-1-methyl-cyclohexa-2,5-dienecarboxylic acid methyl ester [(±)-247]:



This experiment was performed using same procedure as described for reduction of (-)-**179** to (-)-**181**/(-)-**182**.

Yield	**:**	95%
IR (film)	**:**	ν_{max} = 3421, 3020, 1728, 1215, 1118, 908, 761 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.25 & 1.32 [2 s (3:2), 3H], 2.81-2.96 (br. s, 1H), 3.60 (s, 3H), 4.41 (d, *J* = 15.6 Hz, 1H), 5.81-5.93 (m, 4H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 26.1, 44.3, 52.3, 61.2, 127.9 (2C), 130.7 (2C), 174.3.

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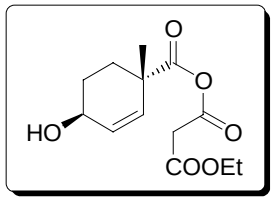
42. Preparation of (±)-249:



To a solution of diethylmalonate (10 g, 62.5 mmol) in absolute ethanol (40 mL) was added a solution of KOH (4 g, 71.43

mmol) in absolute ethanol (40 mL) using dropping funnel at room temperature during a period of 1 h. A white crystalline precipitate appeared during the addition of KOH solution. After all the KOH solution was added, the mixture was stirred for additional 2 h. The stirring was stopped and the mixture was allowed to stand overnight. The mixture was heated on a water bath upon which the precipitate dissolved, while the trace amount of impurities remained undissolved. It was filtered hot under reduced pressure and the filtrate was cooled in ice bath to obtain K-ethylmalonte in pure form and in a quantitative yield.

Acid (±)-**248** was converted to corresponding acid chloride using thionyl chloride and following the same procedure as described for the preparation of anisoyl chloride above. The solution of acid chloride (0.5 g, 2.62 mmol) in dry benzene (2 mL) was added to the stirred suspension of K-ethylmalonate (0.45 g, 2.63 mmol) in dry benzene (5 mL) and the resulting mixture was stirred for 2 h. At the end of this time most of the anhydride had precipitated out of the solution. The mixture was filtered and the filtrate was concentrated to obtain (±)-**249** in 83% yield.

IR (film)	**:**	ν_{max} = 2983, 1755, 1731, 1714, 1514, 1371, 1242 and 1092 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.22 (t, *J* = 7.2, 3H), 1.31 (s, 3H), 1.65- 2.19 (m, 4H), 3.54 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.42-4.57 (m, 1H), 5.70-5.93 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 13.6, 15.3, 23.6, 32.3, 36.6, 40.6, 55.2, 64.6, 12.7, 129.3, 155.3, 159.0, 172.0.

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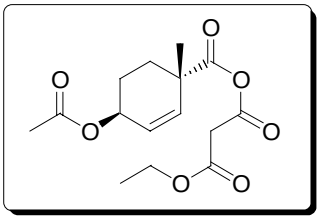
43. Preparation of (±)-170:



To a solution of (±)-**249** (0.7 g, 2.59 mmol) in dry DCM 10 mL) was added pyridine (0.38 mL, 4.71 mmol) at rt. The

mixture was cooled to 0°C and acetyl chloride (0.22 mL, 3.11 mmol), was added to it dropwise with stirring. The solution was allowed to stir for additional 1 h following which it was transferred to a separating funnel and washed successively with saturated $CuSO_4$ solution (10 mL), water (2 × 10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated under vacuum to yield (±)-**170** (0.70, 87%) as a highly viscous pale brown colored oil.

IR ($CHCl_3$)	**:**	ν_{max} = 2995, 1757, 1737, 1730, 1711, 1506, 1392, 1245, 1097 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.22 (t, *J* = 7.3, 3H), 1.33 (s, 3H), 1.59-2.03 (m, 4H), 2.12 (s, 3H), 3.57 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.11-5.33 (m, 1H), 5.57-5.96 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 14.0, 15.7, 17.2, 24.2, 33.7, 36.3, 41.1, 53.6, 74.6, 128.5, 130.2, 156.7, 160.3, 166.8, 171.4.
Elemental analysis	**:**	$C_{15}H_{16}O_3$ (312.32): Calcd. C 57.69, H 6.45; Found C 57.44, H 6.38.

The spectral data of compounds (±)-**197**, (±)-**198**, (±)-**199**, (±)-**200**, (±)-**201**, (±)-**204** and (±)-**166** was identical with corresponding optically active compounds.

6. References

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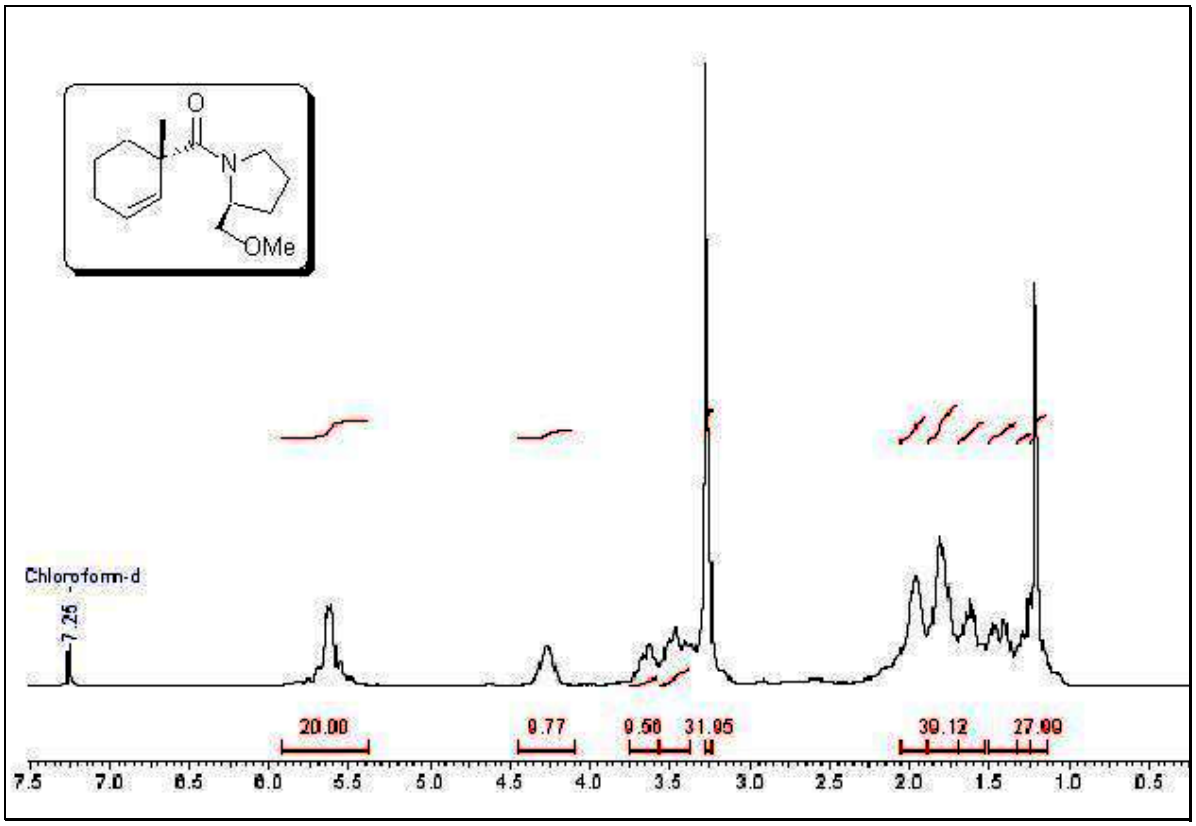


Figure 18. ^{1}H NMR spectrum of (-)-184

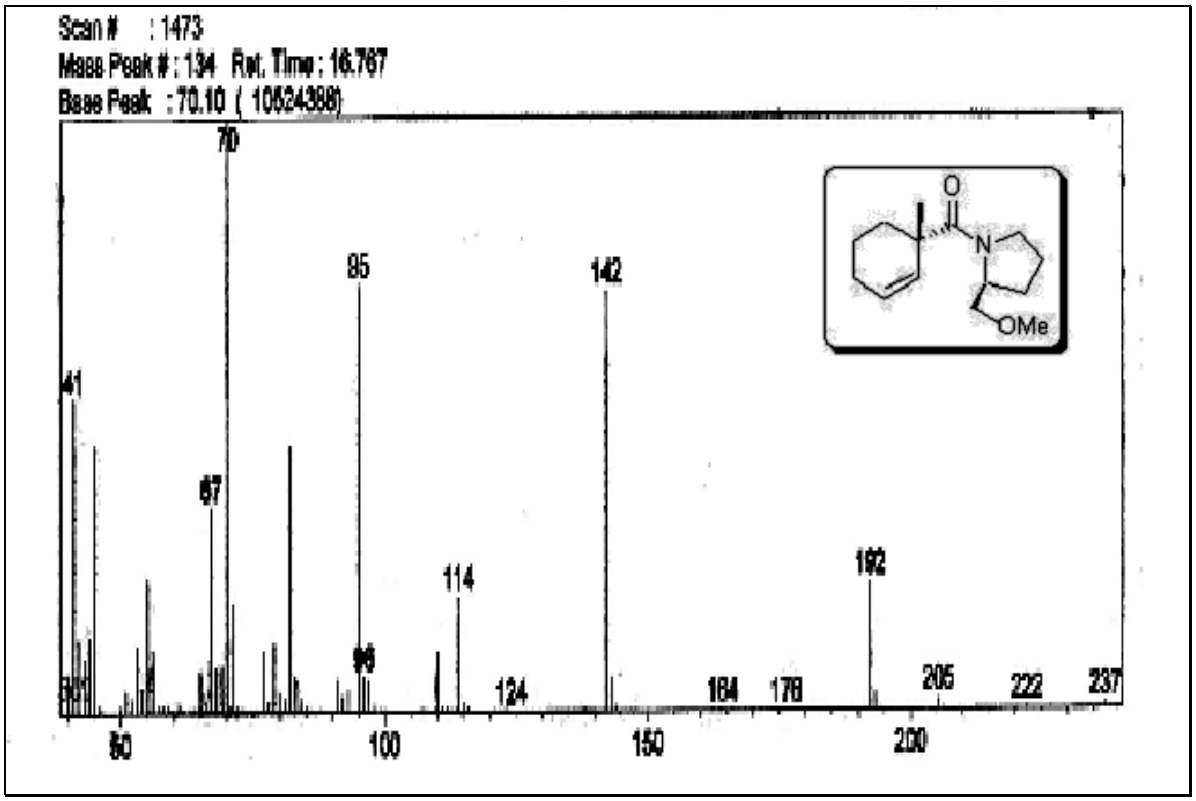


Figure 21. Mass spectrum (GC-MS) of (-)-184

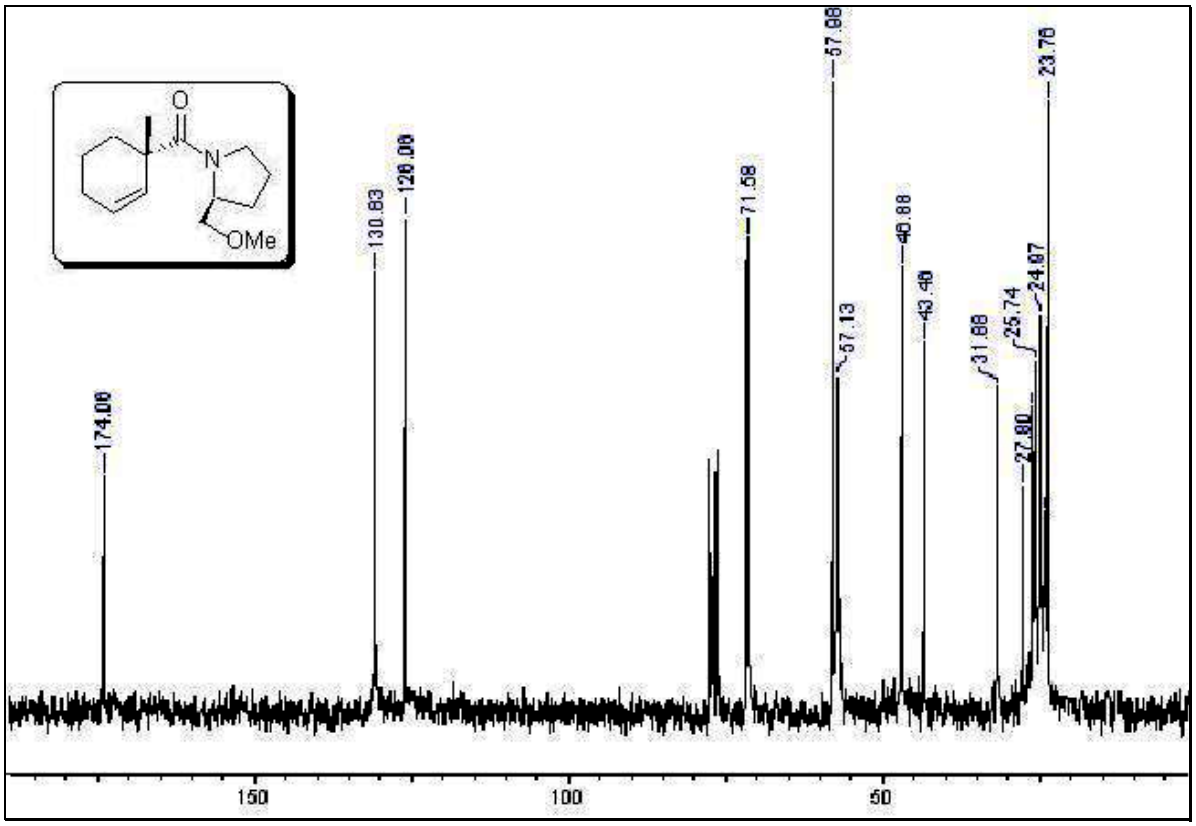


Figure 19. ^{13}C NMR spectrum of (-)-184

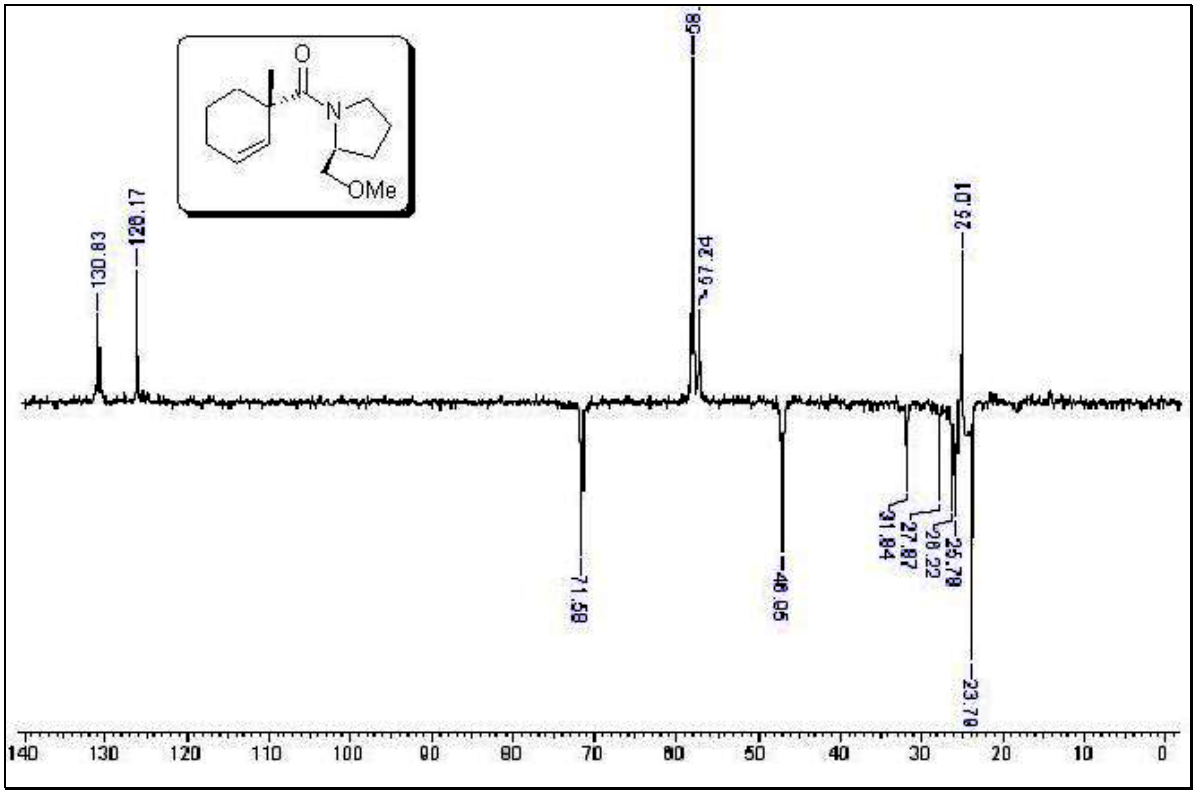


Figure 20. DEPT spectrum of (-)-184

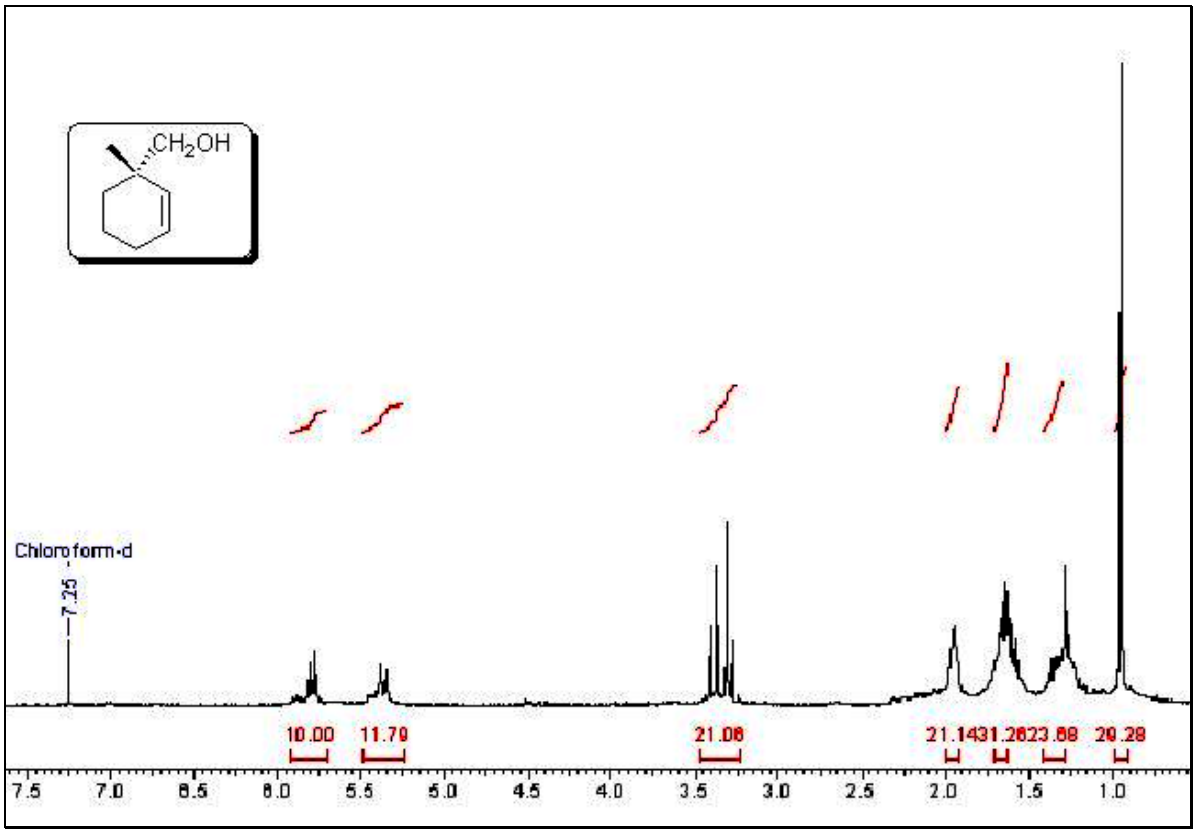


Figure 22. ^{1}H NMR spectrum of (+)-192

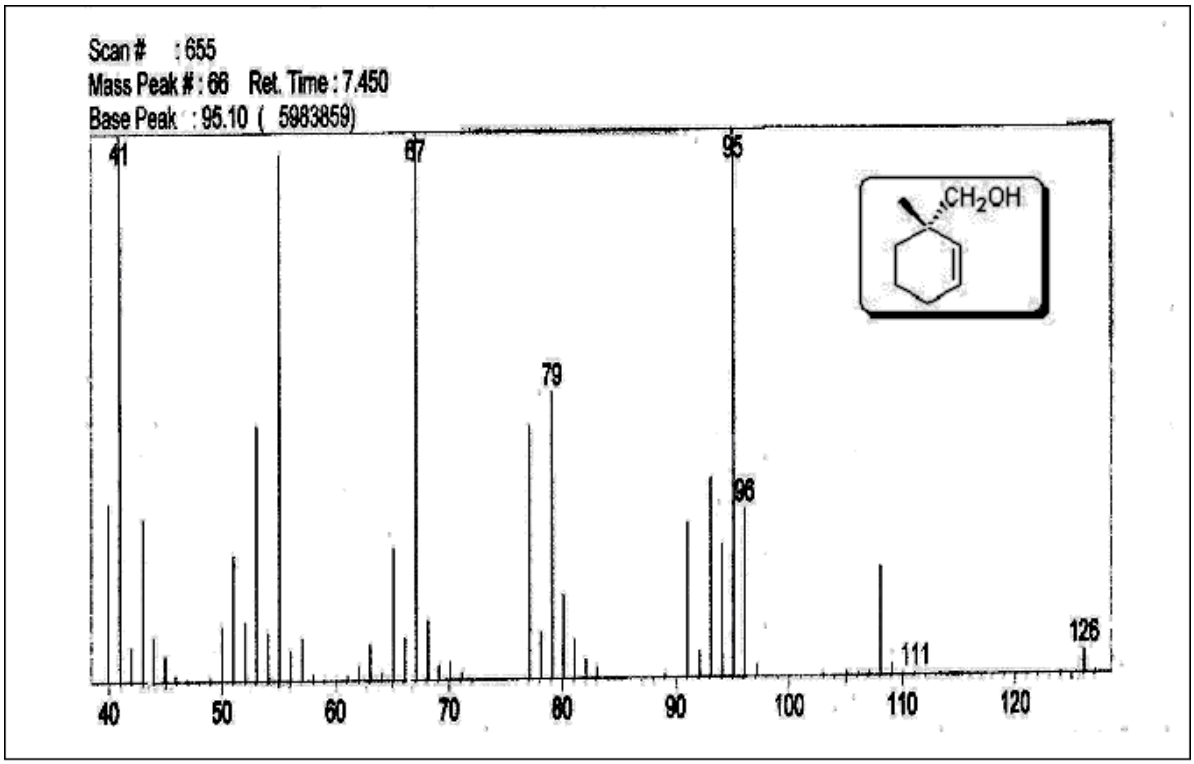


Figure 25. Mass spectrum (GC-MS) of (+)-192

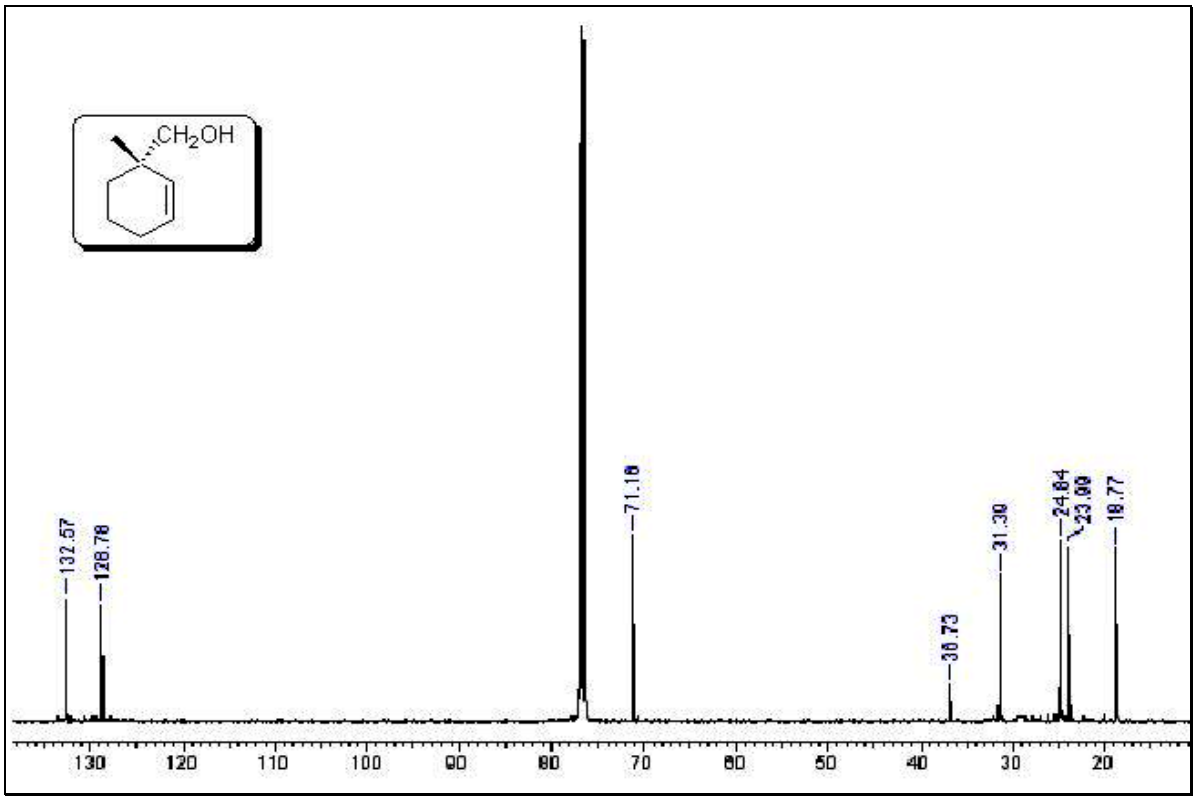


Figure 23. ^{13}C NMR spectrum of (+)-192

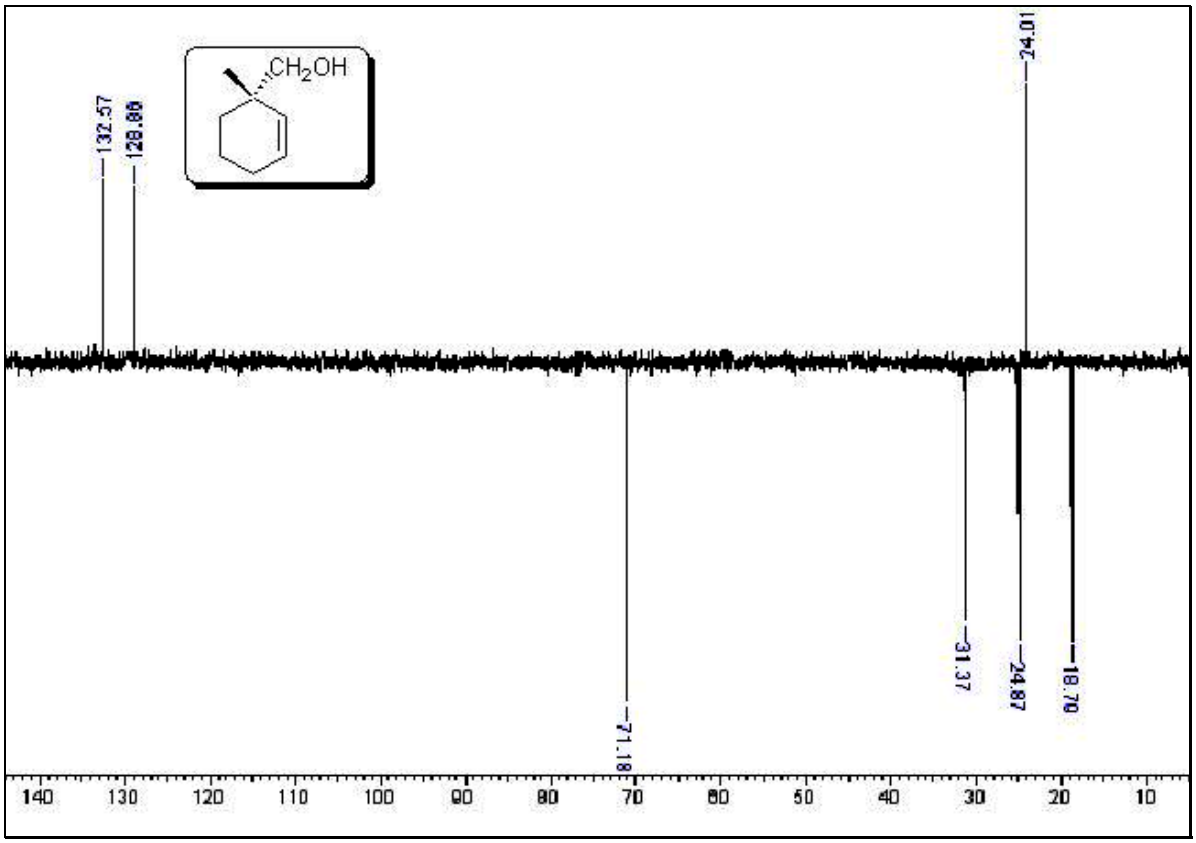
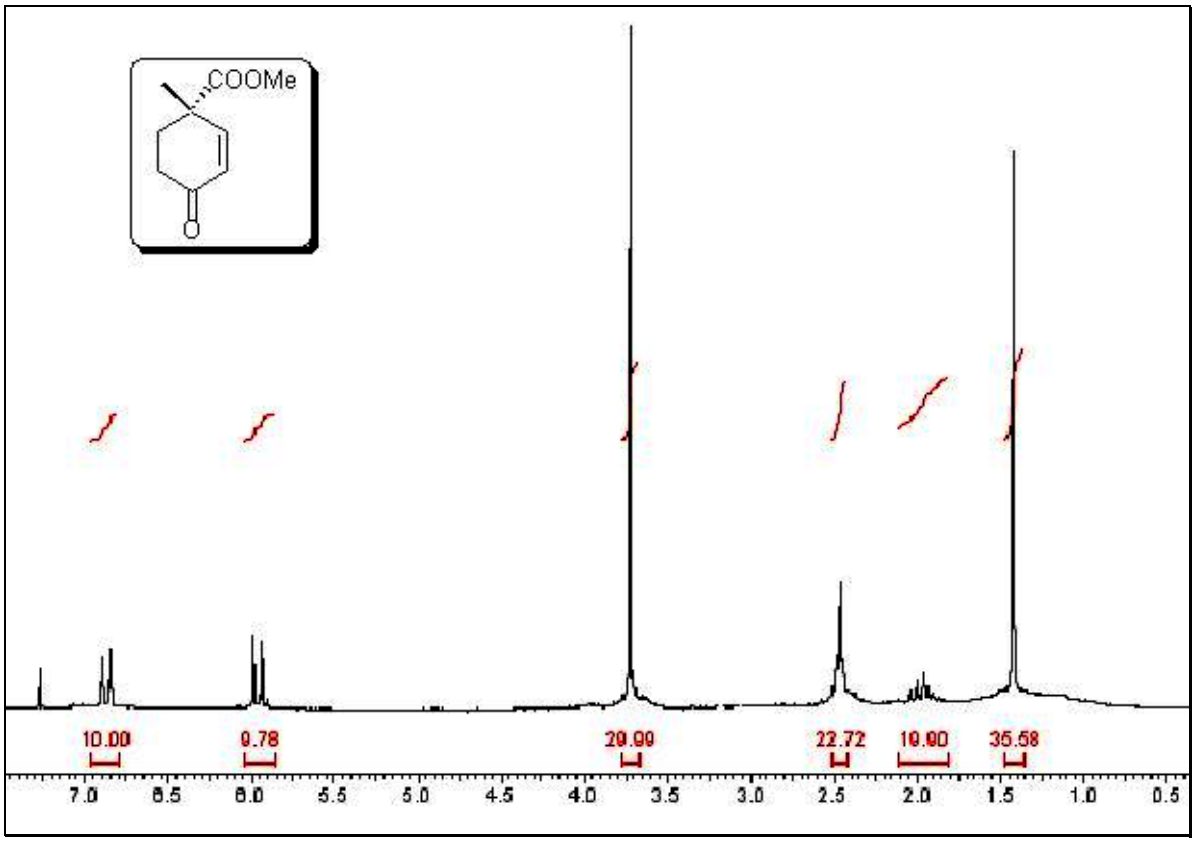


Figure 24. DEPT spectrum of (+)-192



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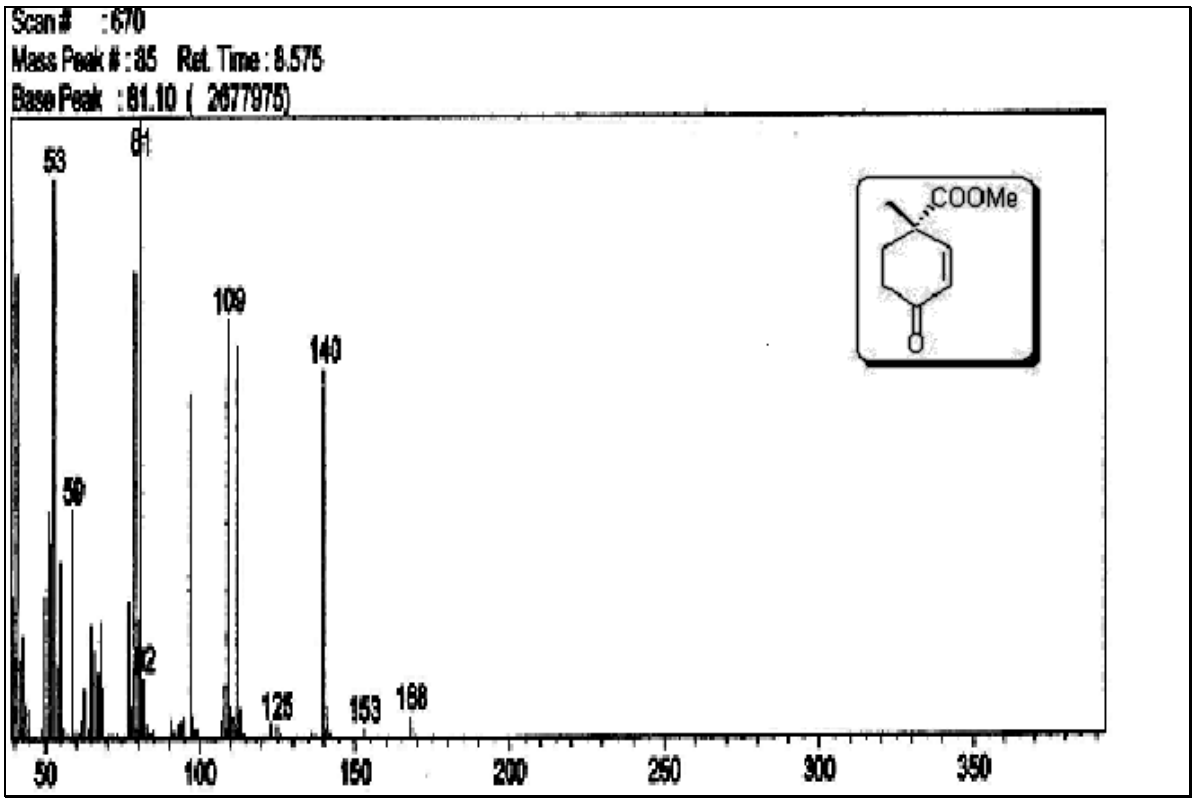


Figure 29. Mass spectrum (GC-MS) of (-)-198

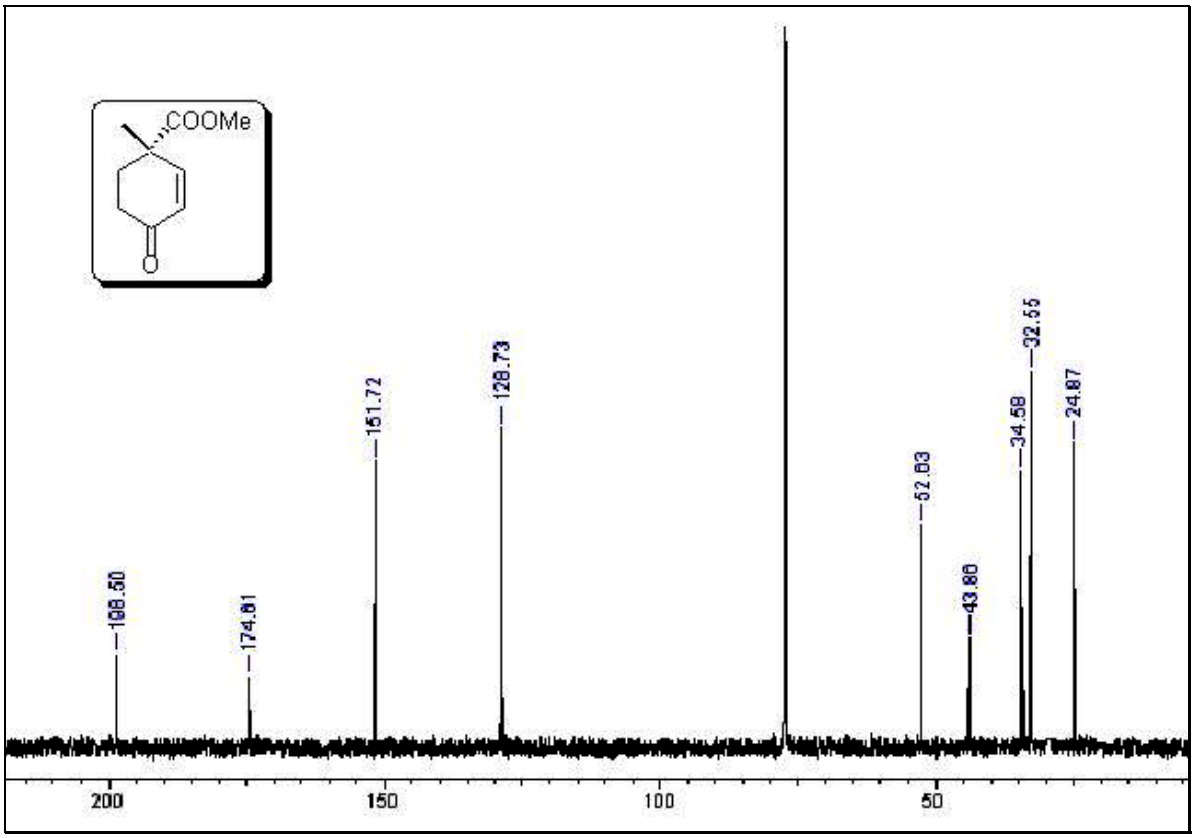


Figure 27. ^{13}C NMR spectrum of (-)-198

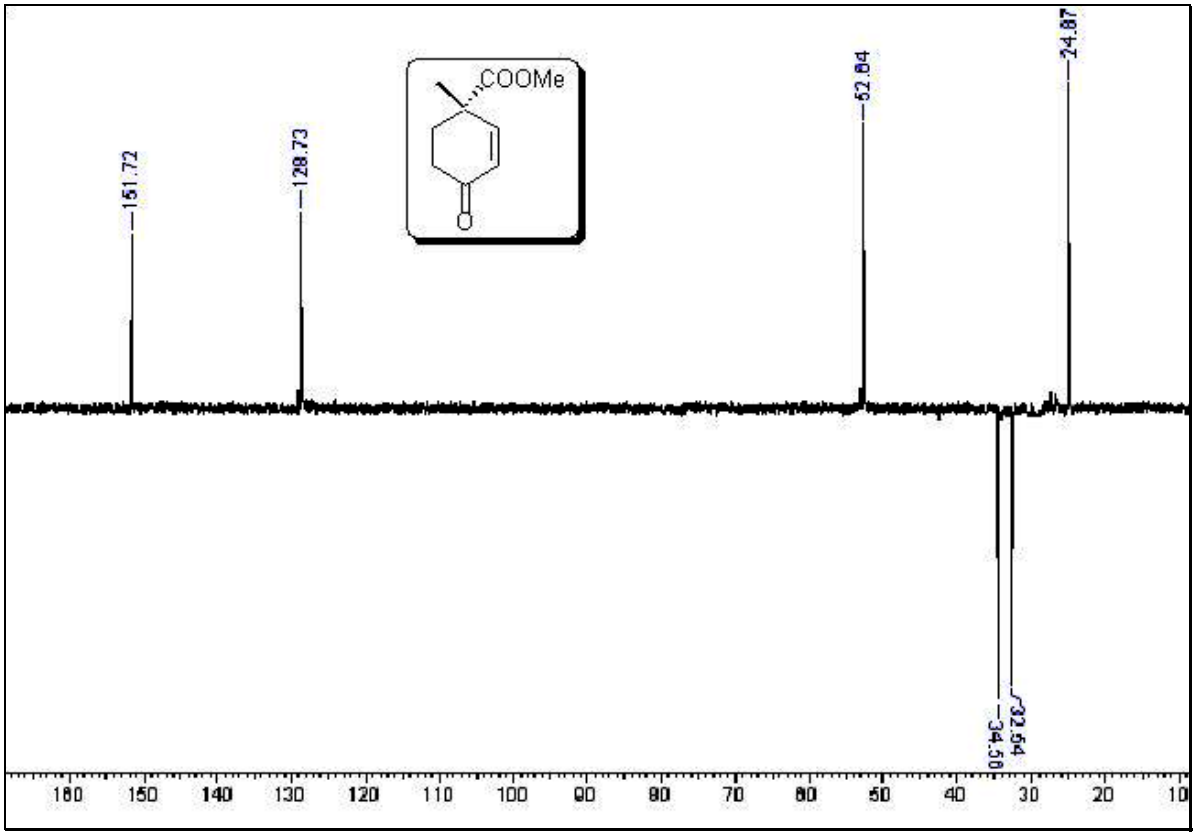


Figure 28. DEPT spectrum of (-)-198

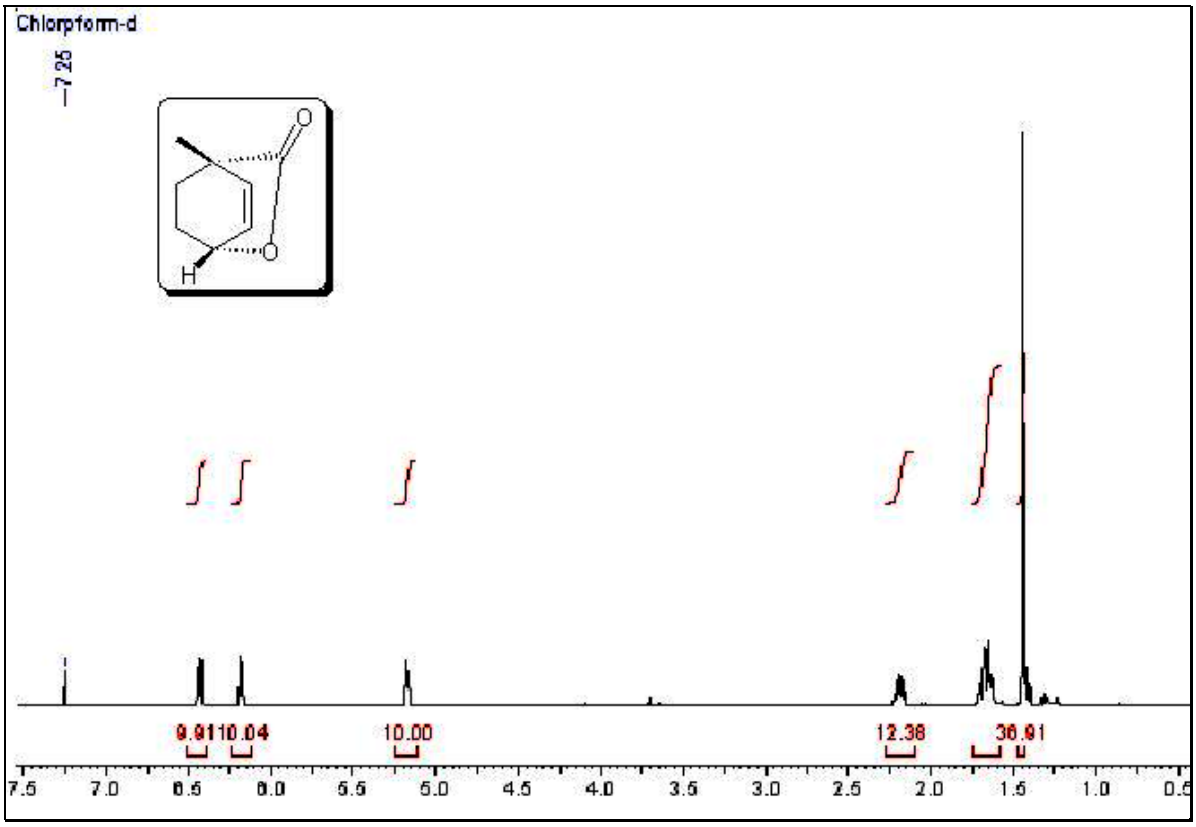


Figure 30. ^{1}H NMR spectrum of (-)-201

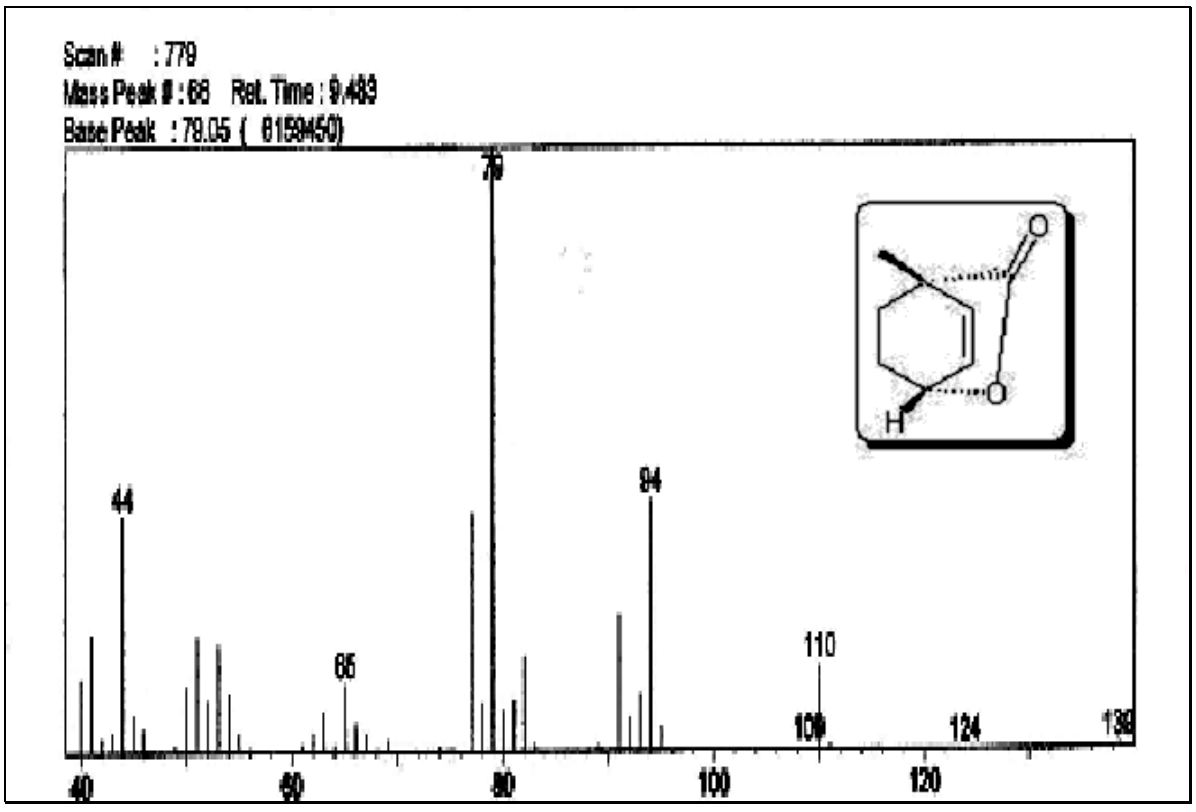


Figure 33. Mass spectrum (GC-MS) of (-)-201

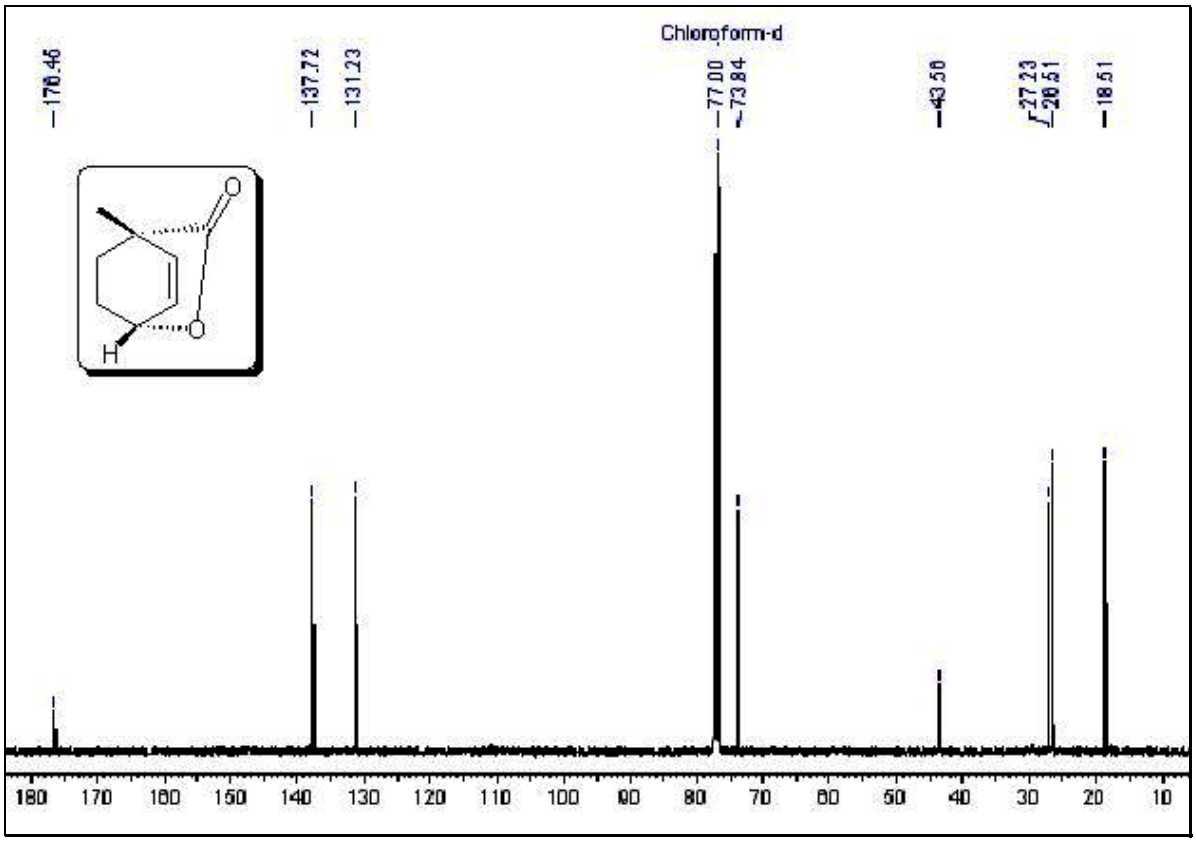


Figure 31. ^{13}C NMR spectrum of (-)-201

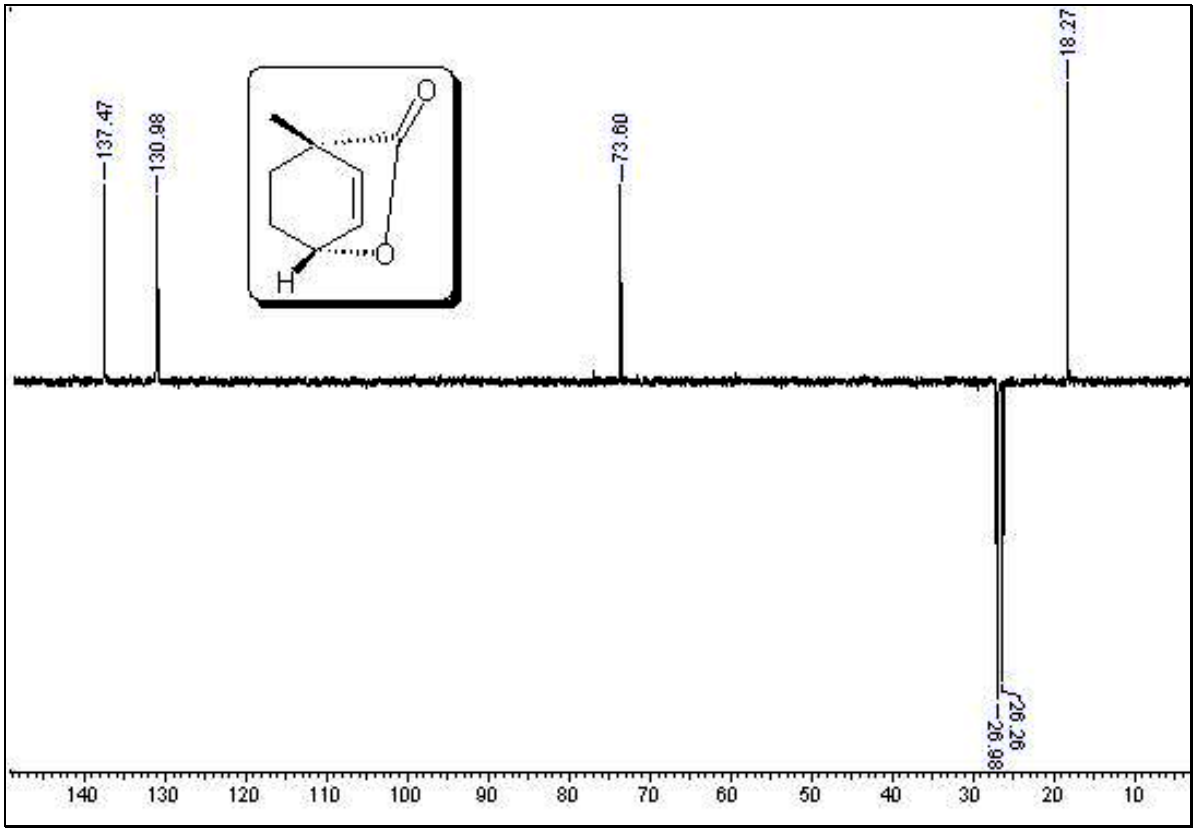


Figure 32. DEPT spectrum of (-)-201

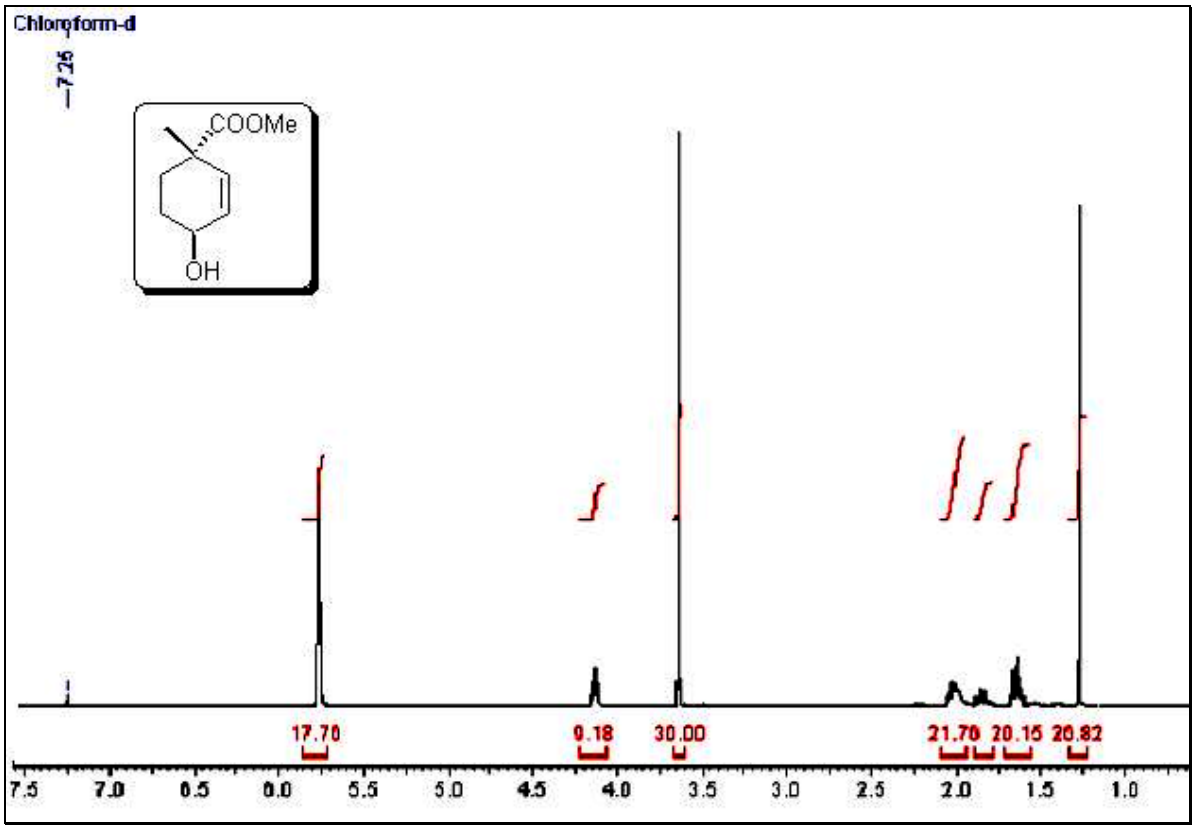


Figure 34. ^{1}H NMR spectrum of (-)-166

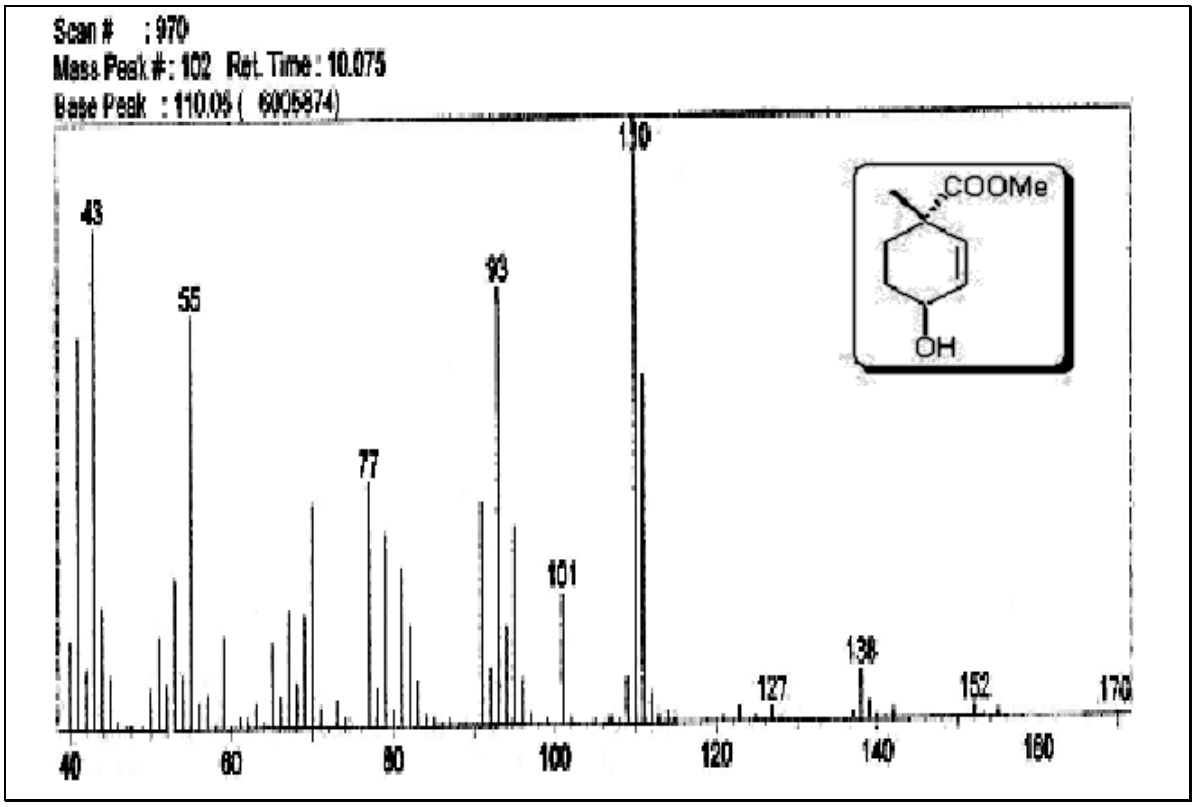


Figure 37. Mass spectrum (GC-MS) of (-)-166

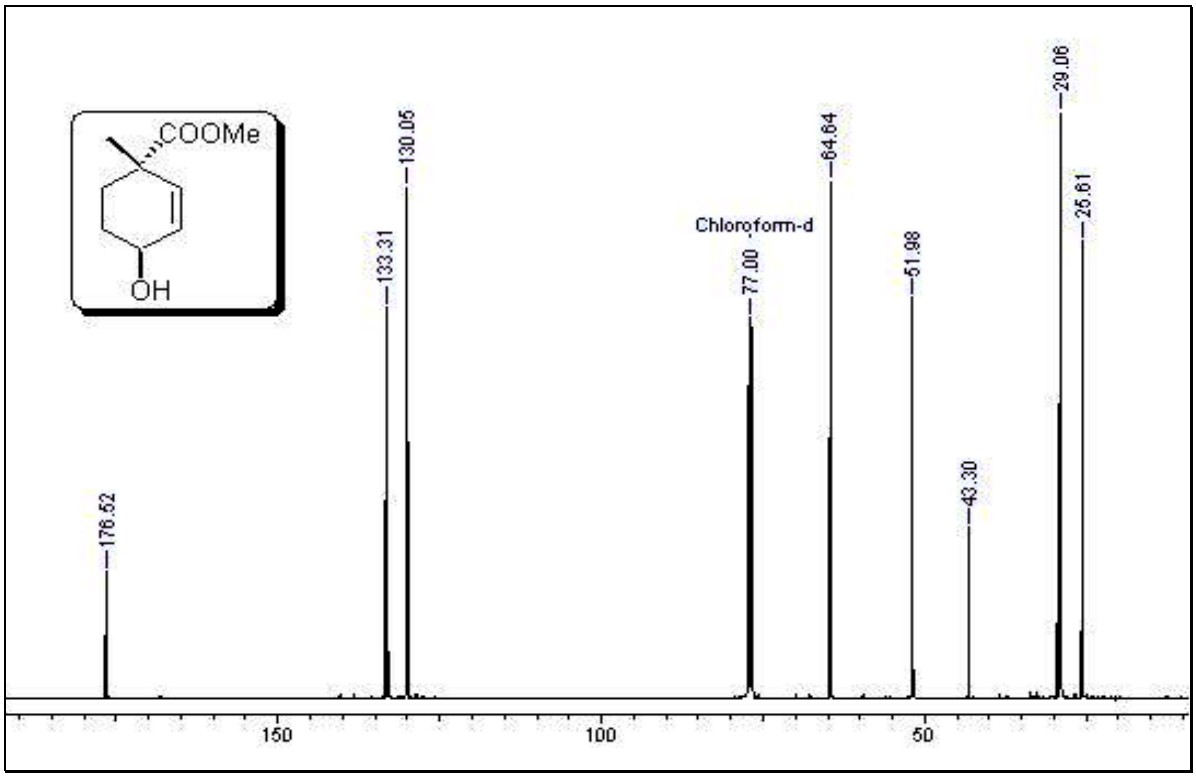


Figure 35. ^{13}C NMR spectrum of (-)-166

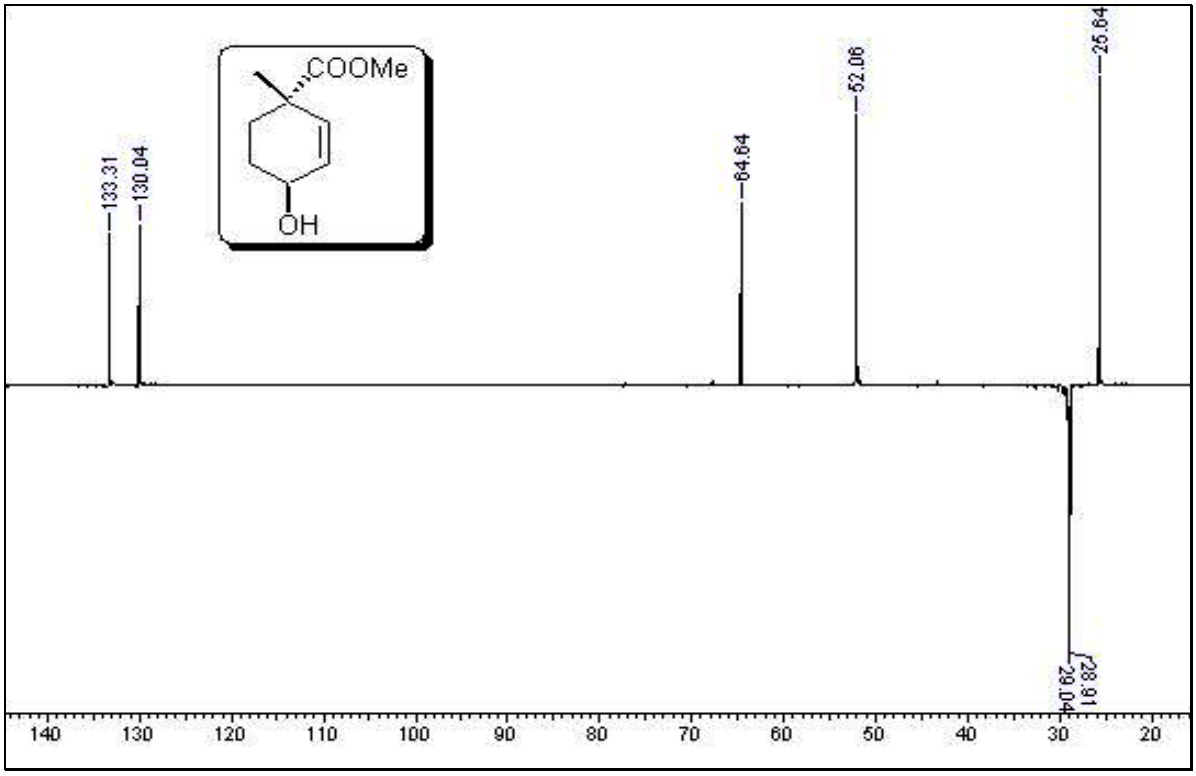


Figure 36. DEPT spectrum of (-)-166

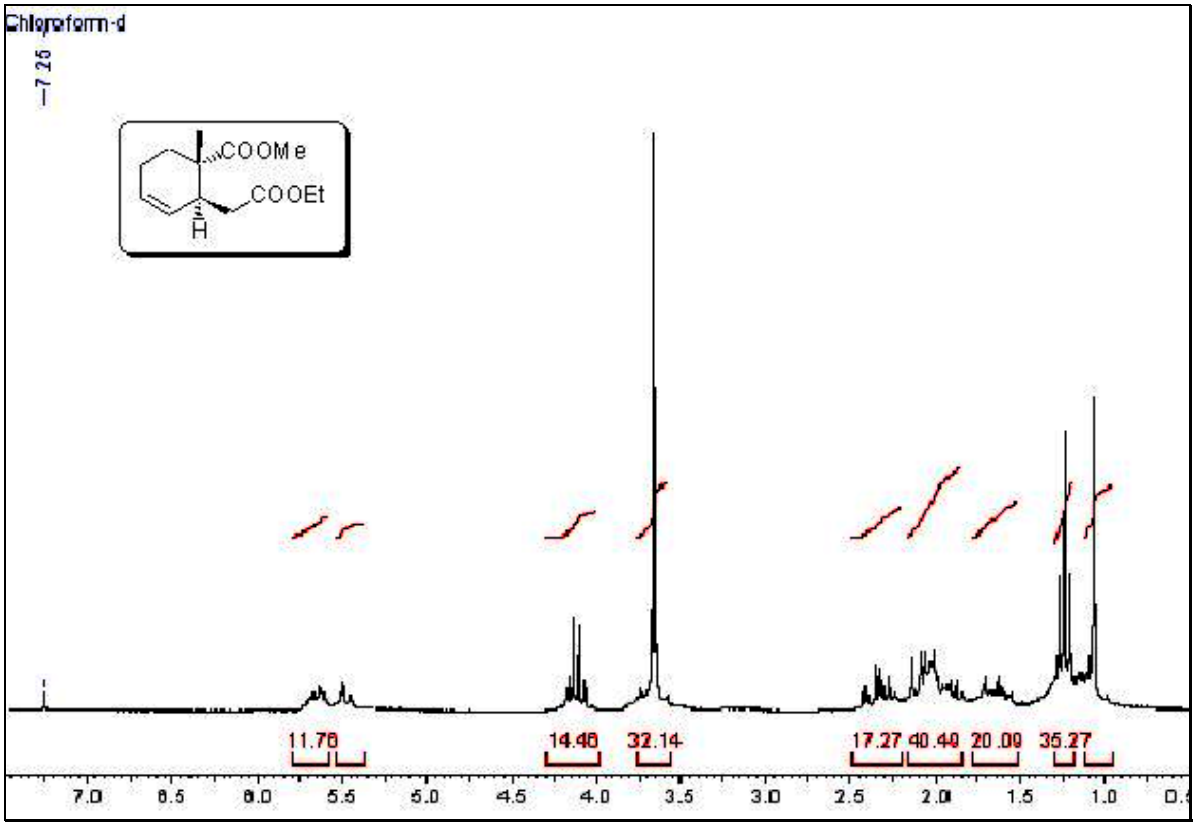


Figure 38. ^{1}H NMR spectrum of (+)-169

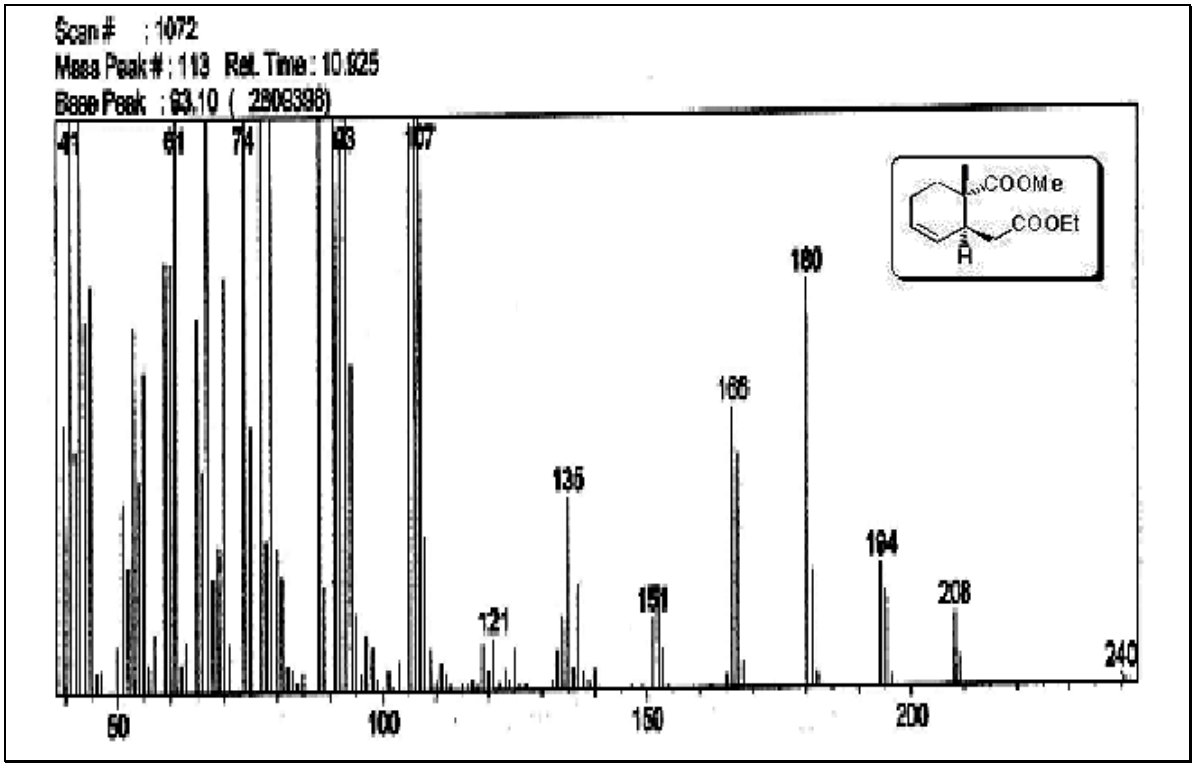


Figure 41. Mass spectrum (GC-MS) of (+)-169

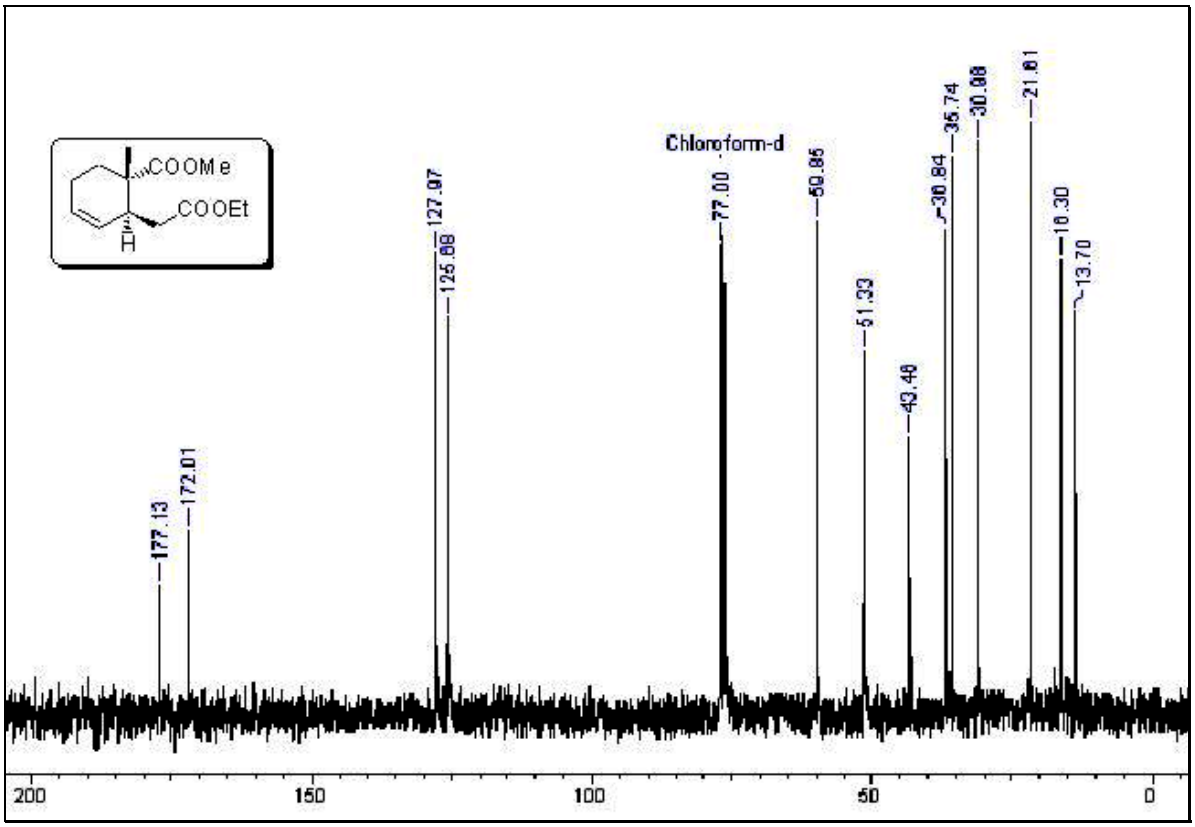


Figure 39. ^{13}C NMR spectrum of (+)-169

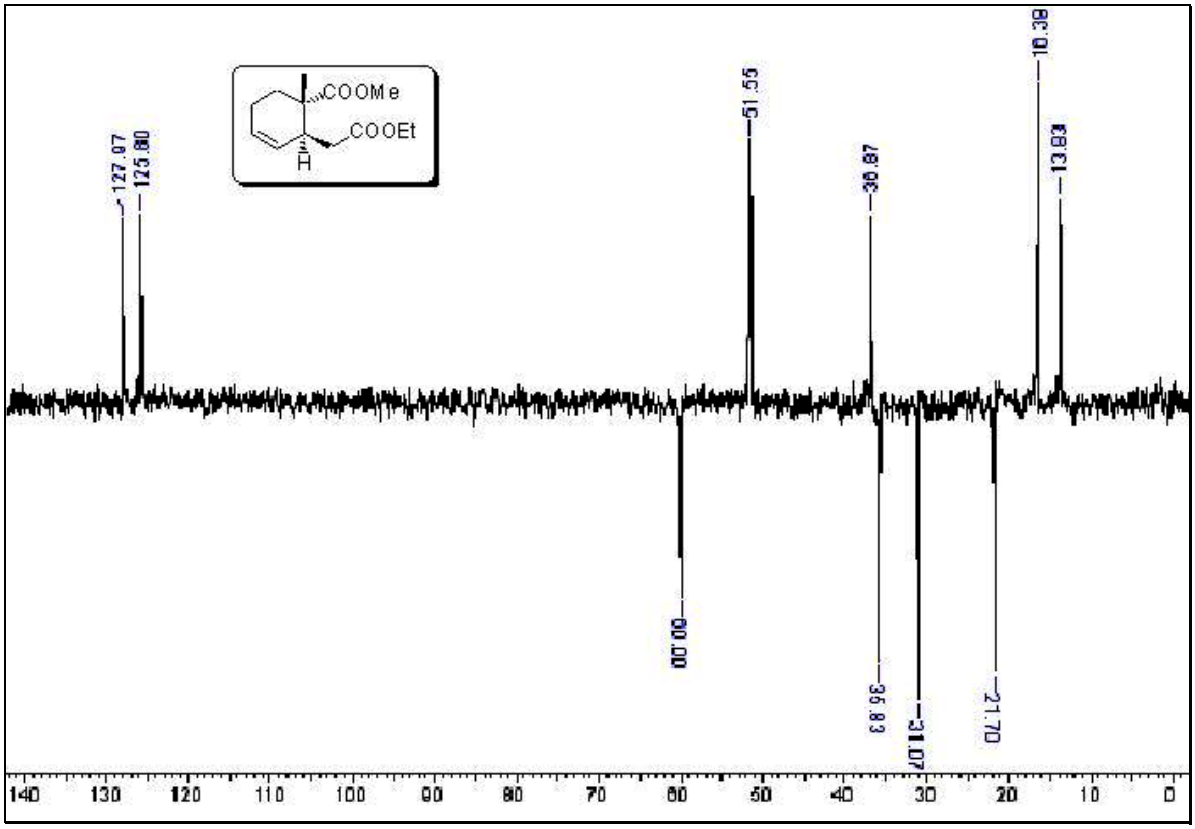


Figure 40. DEPT spectrum of (+)-169

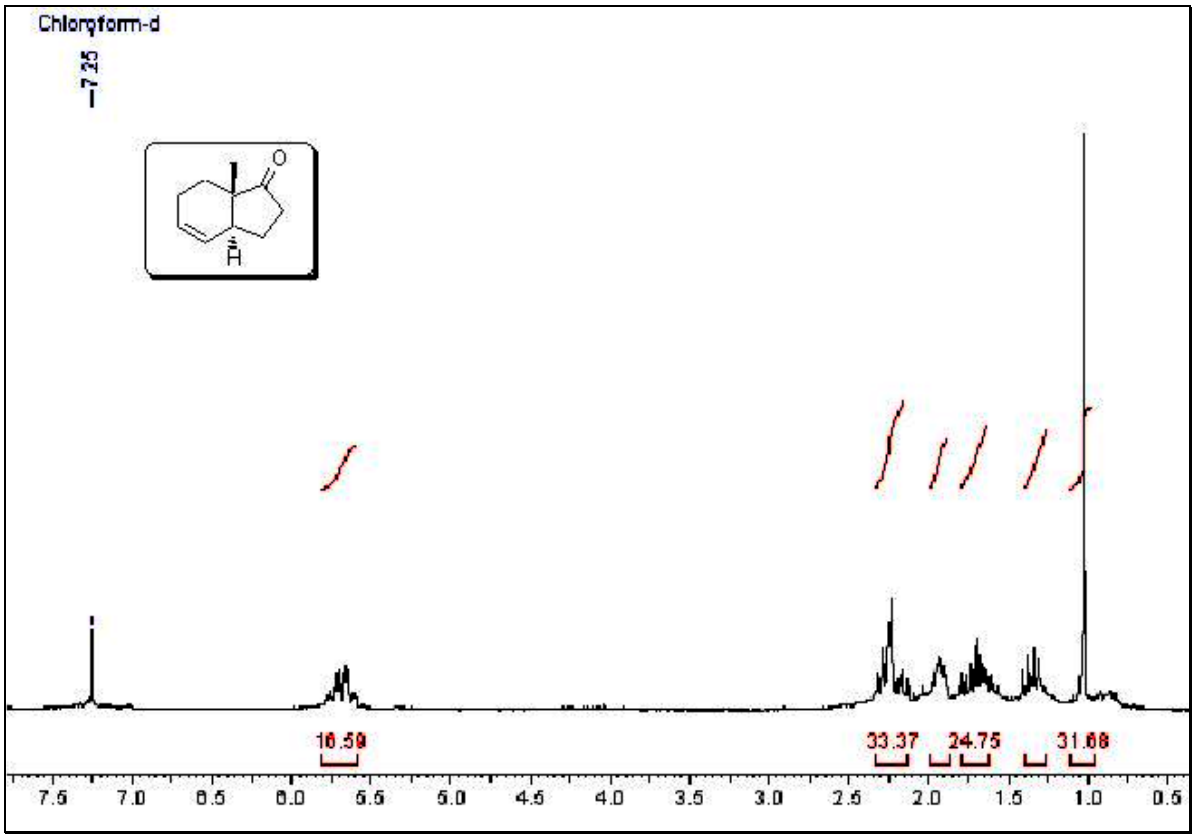


Figure 42. ^{1}H NMR spectrum of (+)-164

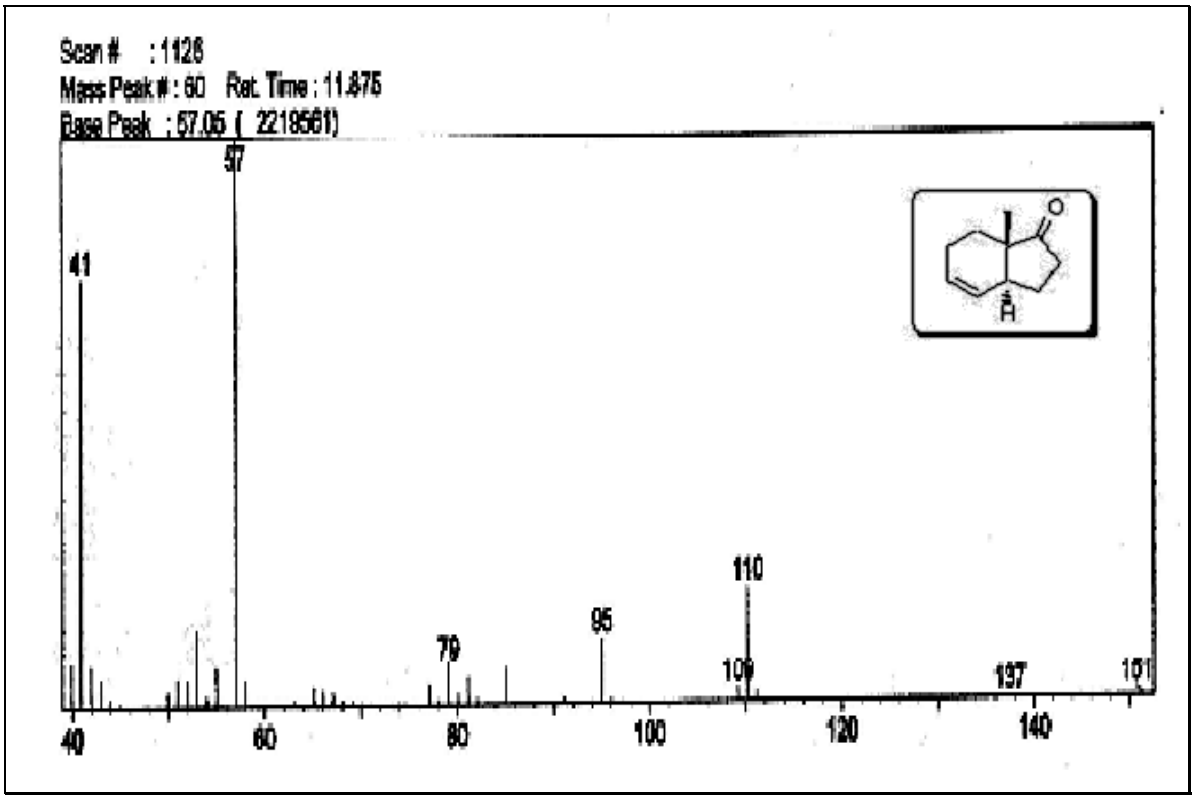


Figure 45. Mass spectrum (GC-MS) of (+)-164

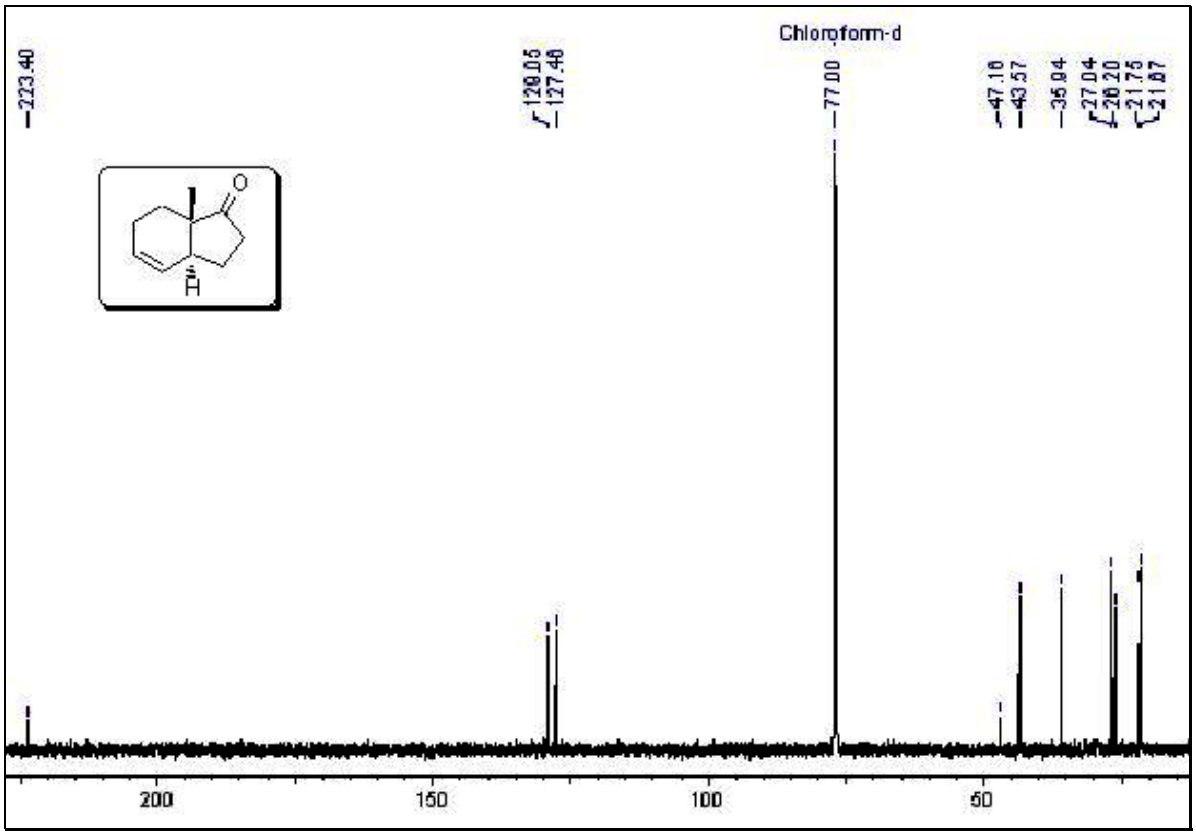


Figure 43. ^{13}C NMR spectrum of (+)-164

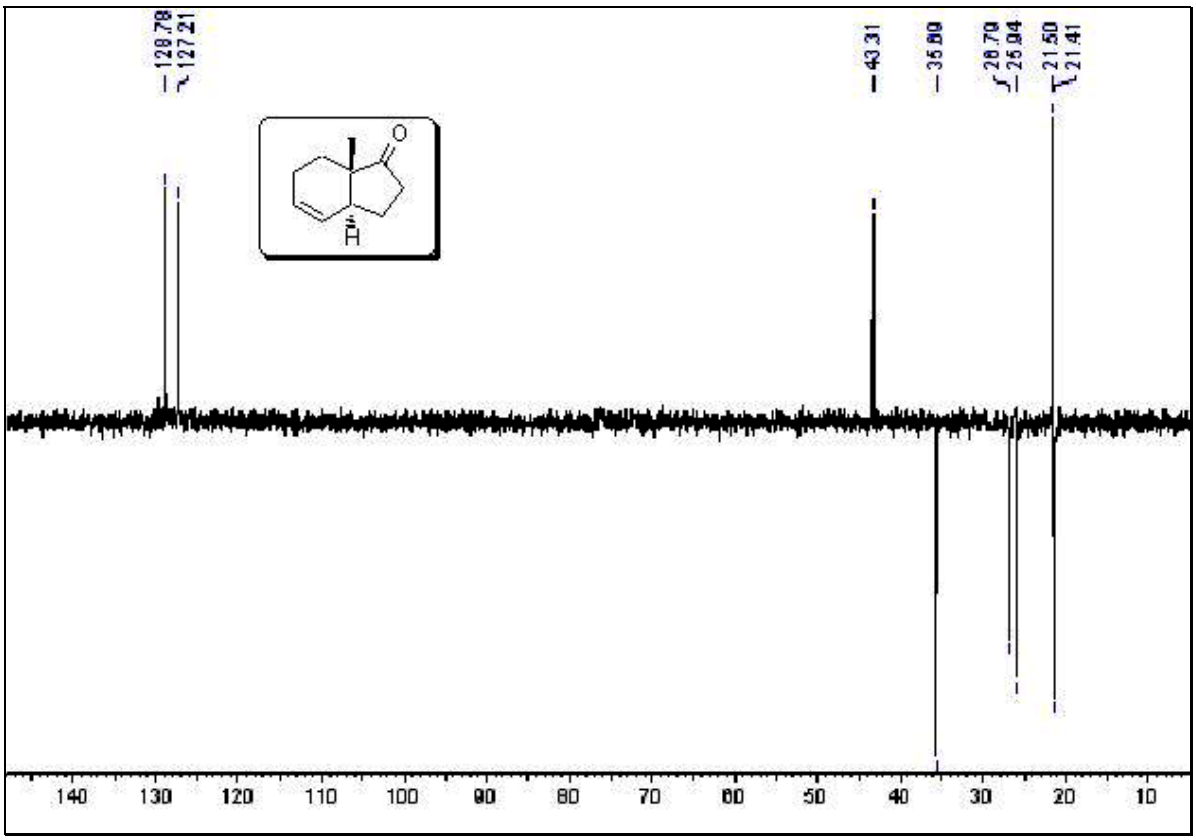


Figure 44. DEPT spectrum of (+)-164

1. Introduction

As discussed in the chapter 1 of this thesis, 1,25-D_3 promotes cell differentiation and inhibits the proliferation of various types of tumor cells, a fact that suggests its possible use in the treatment of cancer and other hyperproliferation diseases. Although, 1,25-D_3 itself is a potential drug for the treatment of these diseases, its calcemic side effects have hampered its use in therapeutics. Research has indicated that high doses of 1,25-D_3 can induce hypercalcemia even in patients with normal calcium balance. Therefore, there have been plenty of efforts focused on developing the structurally related congeners of 1,25-D_3 that are devoid of calcemic activity. Current research in this field is, therefore, aimed not only at the synthesis of analogues with superagonistic potency, but in particular, at the decoupling of the effects on cell differentiation and proliferation from calcemic effects. To put our work in proper perspective, it would be appropriate to summarize various modifications applied to the vitamin D skeleton over the years and their outcome. Some of the important drug design alterations applied to 1,25-D_3 structure have been summarized in Figure 1.[1a]

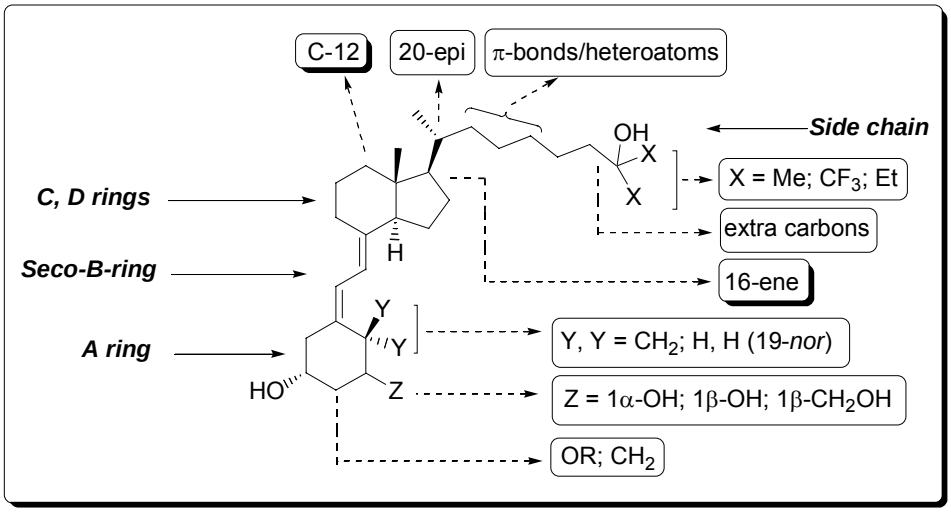


Figure 1. Analogues of 1,25-D_3

Extensive structure function studies have shown that it is possible to modify the calcitriol structure to obtain vitamin D_3 analogues capable of inducing in a selective manner the biological function related to the same molecule. Another reason for developing analogues is to increase the life span of the bioactive molecules, 1,25-D_3 and other active

metabolites. These molecules are converted to the inactive form by side chain oxidation after a certain period of time. Since, the catabolic pathways destroy the biological activity associated with the parent molecule, efforts towards slowing or preventing of such side chain oxidation have given rise to, large number of analogues, which are more potent than the parent molecule. In this context, it has been shown that introduction of the unsaturation in the side chain as well as some remote functionalizations like 16-ene, 1-CH_2OH etc. help to lower the rate of side chain catabolic oxidation.[2]

Thus an increasing number of synthetic vitamin D analogues are now being used as sensitive molecular biology probes and also as new drugs for the treatment of various human diseases.[3] The guiding principle in the synthesis of analogues is to search for the ones that are devoid of calcemic activity but retaining cell differentiating and antiproliferation activities.[4] The earliest analogues were with the modifications in the side chain, since this region of the molecule is most readily accessible for implementing structural and functional variations.[3] It is perhaps not surprising therefore that most of the potentially applicable vitamin D drugs that are being clinically tried and used are side chain analogues of 1,25-D_3. Subsequently analogues with modifications in the other synthetically less accessible parts of the molecule have also been studied.[5] Analogues with modifications in the CD-rings fragment were the last to emerge and constitute the least explored portion of the module due to difficulty in procuring suitably functionalized *trans*-hydrindane derivatives.[6]

The structure of 1,25-D_3 can be considered to consist of central rigid hydrophobic part, the CD-bicyclic system, to which are connected two flexible moieties, i.e., the side chain at C-17 and the seco-B, A-ring part that is attached to the C-ring via a diene in which the 6,7-bond is freely rotatable. Up to 1995 the search for new analogues has mostly concentrated on derivatives possessing structural changes in the flexible parts of the molecule with a strong preference for the side chain. This was obvious since the central CD-rings portion forms the synthetically least accessible part of the molecule. This least studied part of the module, however, has received considerable attention in recent years

since it was realized that analogues with better biological profiles could be obtained by modifications in the central hydrindane system. Analogues with modifications at C-11, C-14 and C-18 were the first to appear in this domain. Some of the earliest ones in this category are summarized in Figure 2.[7]

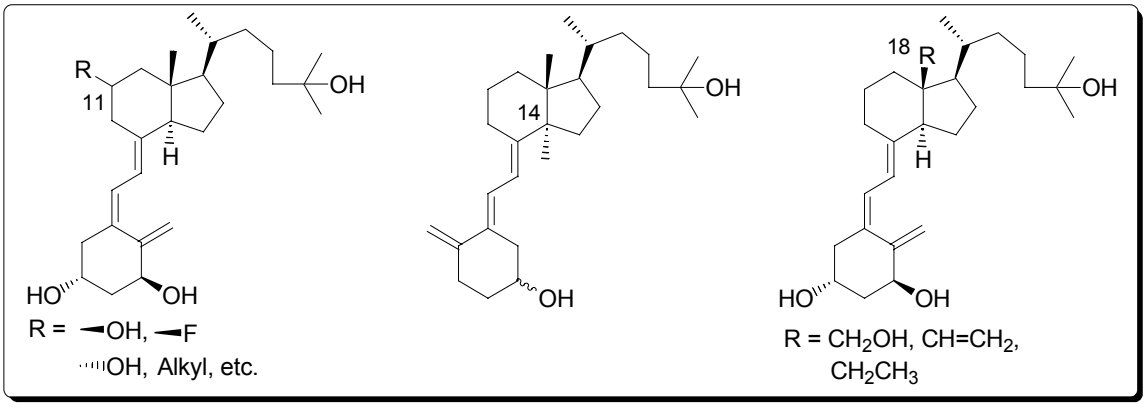


Figure 2. CD-rings modified analogues

Large numbers of analogues with other modifications on these carbons have also appeared in recent years. More recently analogues with modification on the other carbons of the CD rings fragment as well as analogues lacking one of the rings have also been reported.[8]

The search for analogues having functionalities capable of slowing side chain oxidation led to the discovery of analogues having 16-ene modification, which also proved the fact that remote functionalizations are capable of slowing down side chain oxidation. The first report in this domain appeared in 1993, in the form of Hoffman-La Roche's 16-en-24-oxo-1,25-$(OH)_2D_3$.[2a] It has been observed that although 16-ene modification itself is sufficient to check the side chain catabolism to a great extent, 16-ene coupled with other modifications gives best results. Some of the important analogues carrying 16-ene modification are summarized in Figure 3.

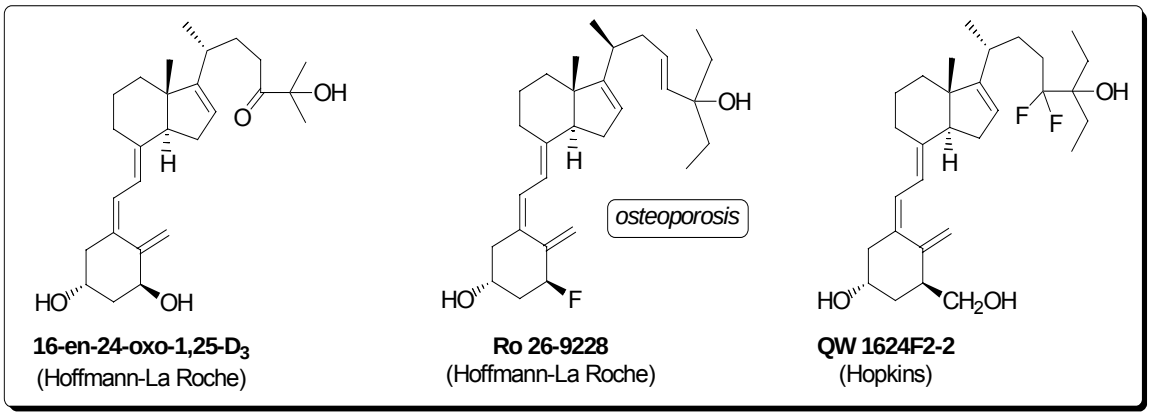


Figure 3. 16-ene analogues

In 2003 Mouriño *et al.* reported the first synthesis of analogues with substituents at C-12 and showed that suitable substitution pattern can lead to very high VDR affinities (Figure 4).[9]

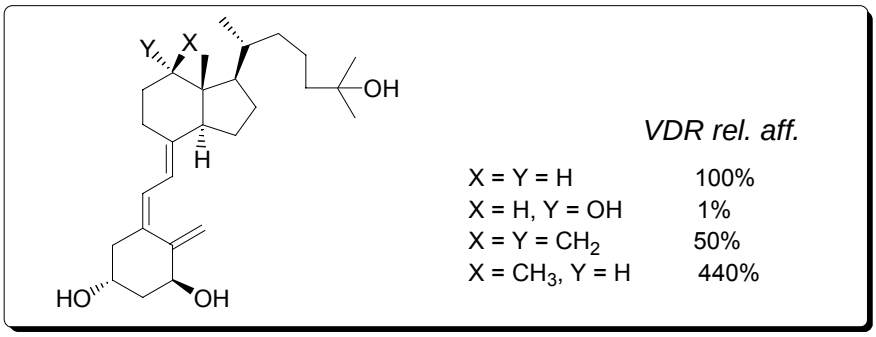
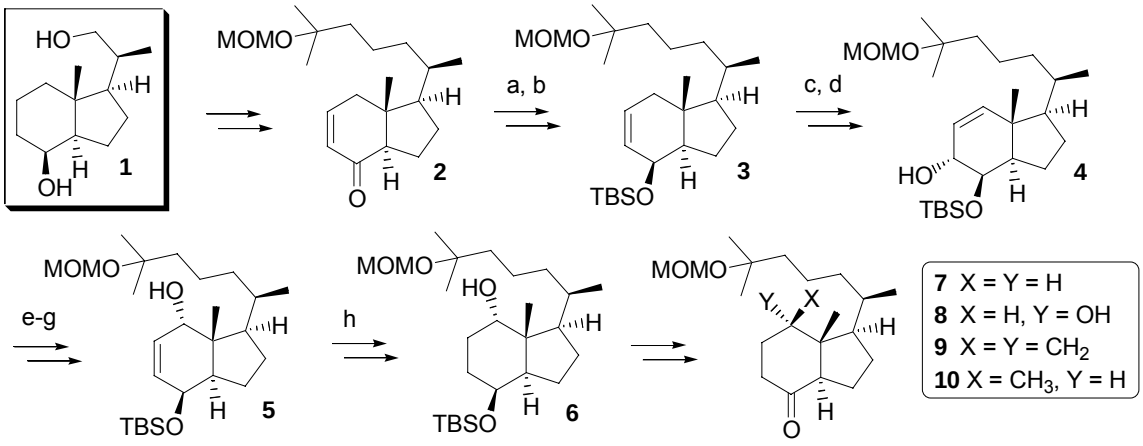


Figure 4. C-12 modified analogues

The synthesis involved the use of Inhoffen-Lythgoe diol to prepare CD-rings precursors which were then coupled with the A ring phosphine oxide (Scheme 1).

Scheme 1. Mouriño approach to C-12 modified analogues



Reagents and conditions: a) $^{i}Bu_2AlH$, THF, -78 °C, 94%. b) TBSCl, imidazole, DMF, 99%. c) m-CPBA, CH_2Cl_2, 94%. d) $LiNEt_2$, Et_2O, HMPA, rt, 97%. e) m-CPBA, CH_2Cl_2, 99%, f) MsCl, Et_3N, CH_2Cl_2, 99%. g) Na-napthalene, THF, rt, 89%. h) H_2, 5% Pd/C, EtOAc, 95%.

With the forgoing background, the importance of analogues of 1,25-D3 in therapeutics becomes evident. Recent studies on the analogues with modifications in the CD-rings fragment of the molecule, which is still the least studied part of the module due to synthetic inaccessibility, have shown propitious results. Recently studied C-12 substituted and clinclically proven C-16 modified analogues attracted our attention due to intriguing structural novelty and impressive biological profiles. We embarked upon designing versatile CD-rings precursors carrying masked substitution on C-12 and C-16 and which would serve to introduce variety of substitutions and modifications on these carbons as well as on the adjacent carbons. Details of our synthetic endeavor are presented in the following section.

2. Results and Discussion

Our approach for the efficient synthesis of CD-rings precursors C-12 and C-16 modified analogues of 1,25-D_3 essentially follow from the methodology developed by us for the synthesis of suitably functionalized *trans*-hydrindane system, discussed in chapter 2. Synthesis of both the precursors emanates from the same starting materials as used for the synthesis of CD-rings precursor of the parent molecule. This fact has great practical proposition, as these materials are cheaply available and it also demonstrates the versatility of our strategy. Following figure depicts our designed precursors for C-12 and C-16 modified analogues (Figure 5).

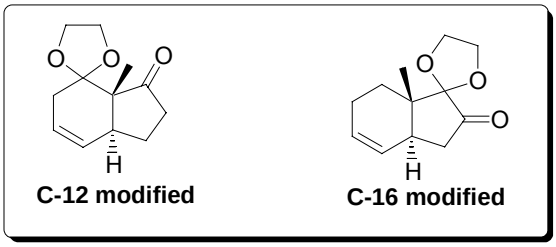


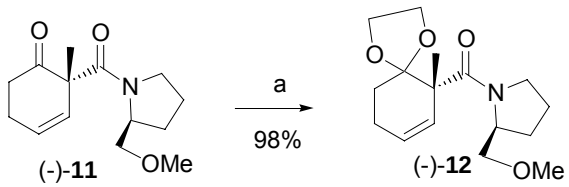
Figure 5. Our designed precursors

2.1 Synthesis of CD ring precursor of C-12 modified analogue

We designed a precursor depicted in figure 5 from which large number C-12 modified analogues can be derived. Towards the synthesis of our designed precursor we envisaged to use readily accessible ketone (-)-**11,** whose preparation has been discussed in chapter 2.

Our synthetic endeavor began with dioxolane protection of the keto group of (-)-**11**. This was achieved by refluxing the solution of (-)-**11**, ethylene glycol and catalytic amount of *p*-TsOH in toluene, which afforded required compound (-)-**12** in quantitative yield (Scheme 2). The spectral data of (-)-**12** showed all the requisite characteristics. Absence of absorption band for keto carbonyl from its IR spectrum and appearance of dioxolane protons in ^{1}H NMR spectrum provided ample evidence of desired conversion. ^{13}C NMR spectrum of (-)-**12** as expected was devoid of keto carbonyl signal and exhibited signals at δ = 71.6 (2C) and δ = 126.6 (1C), corresponding to the methylene carbons and quaternary carbon of dioxolane moiety respectively.

Scheme 2. Dioxolane protection

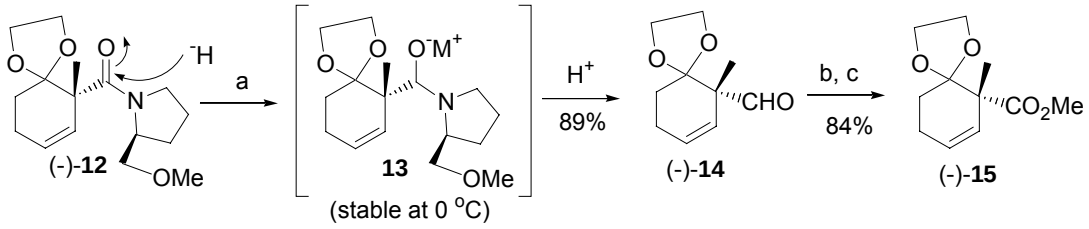


Reagent and conditions: a) $(CH_2OH)_2$, p-TsOH, toluene, reflux.

Our next job was to cleave the chiral auxiliary. As anticipated (-)-**12** was less susceptible towards hydride attack as compared to the corresponding deoxygenated compound used earlier. The protocol devised by us for the removal of chiral auxiliary from the corresponding deoxygenated compound did not work on (-)-**12** as there was no appreciable reaction at low temperature. During the study of reaction conditions for this reaction we observed that when the reaction was carried out by reverse addition of 1 eq. of LAH (slurry in THF) to the stirring solution of (-)-**12** in THF at 0 °C and the reaction was quenched after 3 h of stirring at 0 °C by dropwise addition of 2N H_2SO_4, aldehyde (-)-**14**

was obtained as a sole product and in excellent yield. The chiral auxiliary was also recovered in 88% yield.

Scheme 3. Preparation of 15 via aldehyde



Reagent and conditions: a) LAH, THF, 0 ℃. b) $NaClO_2$, H_2O_2, CH_3CN/H_2O (1:1.7), 0℃ to rt. c) CH_2N_2, Et_2O, 0 ℃ to rt.

The structure of (-)-**14** could be easily gleaned from its spectral data, specially the absence of signals arising from chiral auxiliary and the presence of signals corresponding to aldehyde function provided ample evidence of the depicted conversion. The shifting of carbonyl signal to ν_{max} = 1724 cm^{-1} indicated the aldehyde function. The ^1H and ^{13}C NMR spectrum of (-)-**14** also supported its structure by displaying requisite signals, the most characteristic being presence of aldehydic proton at δ = 9.68 (s, 1 H) in the 1H NMR spectrum and the corresponding signal of aldehydic carbon at δ = 201.3 in the ^{13}C NMR spectrum.

After successful cleavage of the chiral auxiliary the carboxaldehydide moiety of (-)-**14** was converted to carbomethoxy group to obtain (-)-**15**. This functional group transformation was achieved by initial oxidation of the CHO group in (-)-**14** to carboxylic acid group using sodium chlorite followed by esterificaton using diazomethane (Scheme 3).

A strong absorption band at ν_{max} = 1730 cm^{-1} in the IR spectrum of (-)-**15** indicated the presence of ester group.

The ^1H NMR spectrum ($CDCl_3$, 200 MHz) also displayed requisite signals in support of structure of (-)-**15**. The signal for the protons of the methyl group attached to the quaternary stereocenter was exhibited as a singlet at δ = 1.33. The four protons of thee two methylene groups of the cyclohexyl moiety were displayed in the expected region as δ = 1.66-1.83 (m, 1 H), 1.91-2.07 (m, 1 H) and 2.15-2.29 (m, 2 H). A singlet appearing at δ =

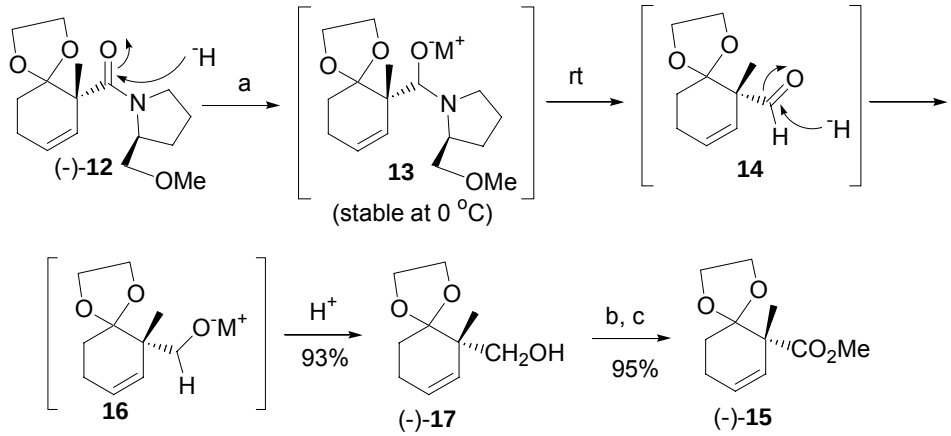
3.67 and integrating for three protons corresponds to the methyl group of the carbomethoxy functionality. A multiplet spanning the region of δ = 3.93-4.01 and integrating for four protons arise from the protons of the two methylene groups of the dioxolane moiety. Two triplets of doublets appearing at δ = 5.56 (dt, *J* = 9.8, 2.0 Hz, 1 H) and 5.74 (dt, *J* = 9.8, 3.9 Hz, 1 H) correspond to the two olefinic protons respectively.

In the ^{13}C spectrum ($CDCl_3$, 200 MHz) of (-)-**15**, 11 signals were observed as desired at δ = 20.3, 23.7, 28.0, 51.8, 64.7, 64.9, 109.5, 126.0, 129.8 and 173.6. The assignment of signals to appropriate carbons was achieved using the DEPT spectrum as usual. The signals at δ = 51.8, 109.5 and 173.6 had disappeared indicating that they belonged to the quaternary carbons and were assigned to the carbon of the quaternary stereocenter, the spiro carbon and the carbonyl carbon respectively. The olefinic methine carbons appeared at δ = 126.0 and δ = 129.8 respectively. The methylene carbons of cyclohexyl unit appeared at δ = 23.7 and 28.0 respectively while the methylene carbons of the dioxolane moiety were displayed at δ = 64.7 and 64.9 respectively. Finally the methyl group attached to quaternary stereocenter was exhibited at δ = 20.3 and the methyl carbon of the carbomethoxy group was shown at δ = 51.8.

The mass spectrum was helpful in confirming the molecular weight of the (-)-**15**, which displayed the molecular ion peak at *m/z* = 212 (M^+).

At this point we were curious to see if the LAH reduction of (-)-**12** can afford corresponding alcohol under any conditions. Further studies in this context, proved that it is in fact possible to synthesize alcohol (-)-**17** from amide (-)-**12** by varying the reaction temperature and using excess of LAH. This conversion was essentially achieved by addition of solution of (-)-**12** in THF to stirred slurry of 2.2 eq. of LAH in THF at 0 °C, warming the reaction mixture to rt and stirring for additional 12 h before working up in the manner similar to that discussed for preparation of (-)-**14**, gave (-)-**17** as a exclusive product (Scheme 4).

Scheme 4. Preparation of 15 via alcohol



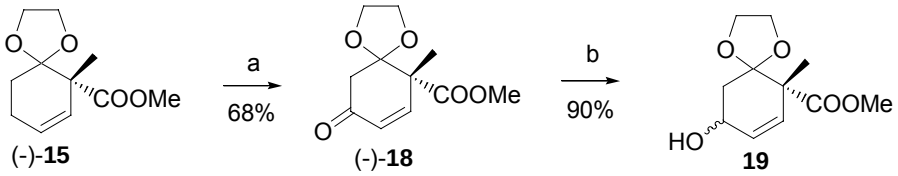
Reagent and conditions: a) LAH, THF, 0 ℃, 2 h then warmed to rt. b) PDC, DMF, rt. c) CH_2N_2, Et_2O, 0 ℃ to rt.

The structure of (-)-**17** was confirmed from its spectral data, which showed characteristic differences from the spectral data of (-)-**14** as expected, specially the absence of carbonyl signals and the presence of signals pertaining to CH_2OH group. The IR spectrum of (-)-**17** exhibited a strong absorption band at ν_{max} = 3444 indicating the presence of hydroxy function, while no peak was seen in the carbonyl region. Similarly, the presence of two singlets at δ = 3.56 and 3.76 respectively and integrating for one protons each, in the ^{1}H NMR spectrum of (-)-**17** were characteristic of the methylene group vicinal to the quaternary carbon and were assigned to the C$\underline{H_2}$OH protons. The ^{13}C NMR spectrum confirmed its carbon framework by displaying ten signals in requisite positions. The absence of carbonyl carbon signal and the appearance of $\underline{C}H_2OH$ methylene carbon at δ = 68.0 in this spectrum were especially useful. Finally the mass spectrum gave the finishing touch to the structure elucidation of (-)-**17** by displaying a molecular ion peak at *m/z* = 184 (M^+).

As anticipated, the preparation of ester (-)-**15** from alcohol (-)-**17** could be easily achieved by PDC oxidation (in DMF) followed by diazomethane esterificaton. The spectral and optical data of (-)-**15** prepared from (-)-**17** matched perfectly with that prepared from (-)-**14** as expected (Scheme 4).

With the successful synthesis of (-)-**15**, we turned our attention to introducing the allylic hydroxy group in (-)-**15** and based on our previous experience decided to opt for allylic oxidation-reduction sequence instead of direct hydroxylation. In this context **15** was subjected to allylic oxidation using PDC in presence *t*-butyl hydroperoxide as a co-oxidant in DCM to provide α,β-unsaturated ketone (-)-**18** in 68% yield.[10]

Scheme 5. Allylic oxidation-reduction



(-)-**15** (-)-**18** **19**

Reagents and conditions: a) PDC, $^{t}BuO_2H$, DCM, 10 °C to rt. b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to rt.

The structure of (-)-**18** followed from the characteristic changes in its spectral data from that of (-)-**15**. Its IR spectrum displayed an additional band in the carbonyl region at ν_{max} = 1685 cm^{-1}, characteristic of α,β-unsaturated ketone, along with the absorption band pertaining to ester carbonyl at ν_{max} = 1733 cm^{-1}. A typical pattern characteristic of olefinic protons of α,β-unsaturated ketone with a quaternary carbon in γ-position was observed in the ^{1}H NMR spectrum of (-)-**18** as expected. Each of the olefinic protons appeared as a doublet at δ = 6.06 (*J* = 10.2 Hz) and 6.82 (*J* = 10.2 Hz) respectively. The protons of the methylene group vicinal to newly incorporated carbonyl function had also shifted downfield to δ = 3.91-4.06 (m, 4 H) as anticipated. These facts attained confirmation from the appearance of eleven signals at the required positions in the ^{13}C NMR spectrum of (-)-**18**. The downfield shifting of one of the olefinic signal to δ = 149.4 indicated α-β unsaturated ketone system, since the β–carbon of such a moiety appears more downfield due to pulling of electrons by the carbonyl group. Appearance of additional carbonyl carbon at δ = 196.4 also indicated the required conversion since it belonged to the newly formed keto-carbonyl. The mass spectrum of (-)-**18** was helpful in confirming its molecular weight and displayed a molecular ion peak at *m/z* = 227 (M^{+}+1), along with the base peak at 87.

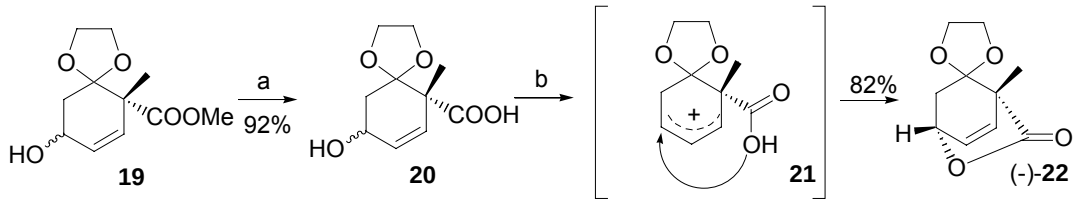
The next step in the planned strategy was to reduce the carbonyl group of the α,β-unsaturated ketone system to the corresponding allylic alcohol. Luche's conditions[11] ($NaBH_4$-$CeCl_3$) were used for this purpose, which resulted in the formation of **19** in 90% yield and 1:1 diastereomeric ratio. The diastereomeric ratio indicated by the ratio of the signals resulting from the methyl group attached to the quaternary stereocenter in the ^1H NMR spectrum of **19** was in good agreement with that determined by GC analysis (Scheme 5). The structure of **19** could be easily gleaned from its spectral data. As expected the IR spectrum of **19** showed a signal for hydroxy function at ν_{max} = 3438 cm^{-1}, while the signal for keto carbonyl displayed by parent (-)-**18** had disappeared. ^1H NMR spectrum of **19** also provided ample evidence of the conversion by displaying a multiplet in the region of δ = 4.20-4.48 (m, 1 H), which corresponds to the newly added proton of C<u>H</u>-OH group. Also the typical pattern of two doublets displayed by olefinic protons in (-)-(-)-**18** was disrupted due to coupling with C<u>H</u>-OH proton and the two olefinic protons now appeared as a doublet and a multiplet respectively at δ = 5.63 (d, *J* = 10.1 Hz, 1 H) and 5.82-6.07 (m, 1 H). The ^{13}C NMR spectrum of **19** was also in complete agreement with its structure and confirmed the transformation by displaying a signal at δ = 69.3 corresponding to the CH-OH carbon. This was also supported by the disappearance of the keto carbonyl signal and the up field shift of the olefinic carbon β to the reaction center.

At this stage, we were not apprehensive about the lack of diastereoselectivity in the reduction step; neither did we attempt the manual separation of two diastereomers, since the mixture can be converted into a single diastereomer by lactonization protocol.[12] Towards this end, the carbomethoxy group of **19** was hydrolyzed to corresponding carboxylic acid **20**, with the aid of lithium hydroxide using the mixture of THF and water (1.3:1) as a reaction medium. The structure of **20** followed from the presence of an absorption band at ν_{max} = 3587 and 1687 cm^{-1} corresponding to the carboxylic hydroxy and carbonyl functions respectively and the absence of the band at ν_{max} = 1736 cm^{-1}

representing the ester functionality in the IR spectrum. This was confirmed by the absence of methyl signal of carbomethoxy group in ^{1}H and ^{13}C NMR spectra of **20**.

Our next step comprised of the lewis acid catalyzed lactonization involving the acyllium ion intermediate. It was quite remarkable at this point to observe that the considerably strained tricyclic lactone (-)-**22** was produced in very good yield by treatment of **20** with $BF_3.OEt_2$ in DCM (Scheme 6).

Scheme 6. Lactonization



Reagents and conditions: a) LiOH, THF, H_2O, rt. b) $BF_3.OEt_2$, DCM, 0 ℃.

The IR spectrum of (-)-**22** displayed the absorption band requisite of the functionalities present at ν_{max} = 2991, 1741, 1217, 1112 cm^{-1}.

The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**22** exhibited a singlet at δ = 1.44 (s, 3 H) belonging to the protons of the methyl group. The two protons of the methylene group in the central cyclohexyl ring appeared separately at δ = 2.06 (dd, *J* = 13.8, 1.4 Hz, 1 H) and 2.44 (dd, *J* = 13.8, 3.8 Hz, 1 H). A multiplet displayed in the region of δ = 3.96-4.09 and integrating for four protons was assigned to the two methylene groups of the dioxolane moiety. As expected the C<u>H</u>-O proton was seen as a multiplet spanning the region δ = 5.20-5.29 (m, 1 H). The spectrum was terminated by the olefinic signals, which appeared at δ = 6.22 (dd, *J* = 7.6, 1.8 Hz, 1 H) and 6.56-6.66 (m, 1 H) respectively.

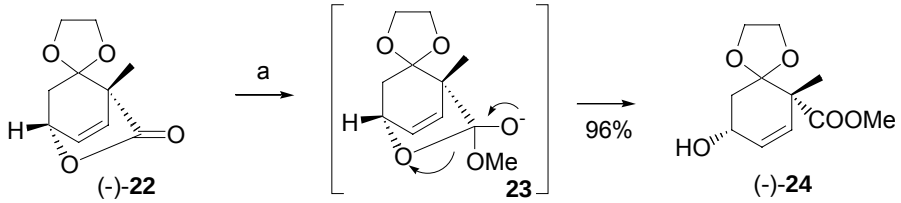
In the ^{13}C NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**22** a total of ten signals were observed at δ = 11.3, 41.6, 56.5, 65.6, 65.7, 72.9, 111.6, 132.2, 135.2 and 158.0 respectively. Peak assignments based on DEPT experiments revealed that the peaks seen at δ = 56.5, 111.6 and 158.0 arise from the quaternary carbons of quaternary stereocenter, spiro carbon and the carbonyl group respectively. The CH-O methine carbon appeared at δ = 72.9 while the olefinic methine carbons were seen at δ = 132.2 and 135.2 respectively.

The signal exhibited at δ = 41.6 belongs to the methylene group of the cyclohexyl rings while the other two signals at δ = 65.6 and 65.7 arise from the methylene carbons of the dioxolane unit. Finally, the most up field signal at δ = 11.3 was assigned to the methyl group.

The mass spectrum of (-)-**22** displayed prominent fragments at *m/z* = 197 (M^++1), 155, 127, 99, 85, 79, 55 and 43 (100%).

Our next job was to open up the lactone to render the system available for further manipulations. Diastereopure *cis* alcohol (-)-**24** was obtained in excellent yield by refluxing the solution of lactone (-)-**22** with a dilute solution of sodium methoxide in methanol (Scheme 7).

Scheme 7. Methanolysis



Reagents and conditions: a) NaOMe, MeOH, reflux.

The IR spectrum of (-)-**24** provided ample evidence of the required transformation by displaying an absorption band at ν_{max} = 3443 cm^{-1}corresponding to the hydroxyl group.

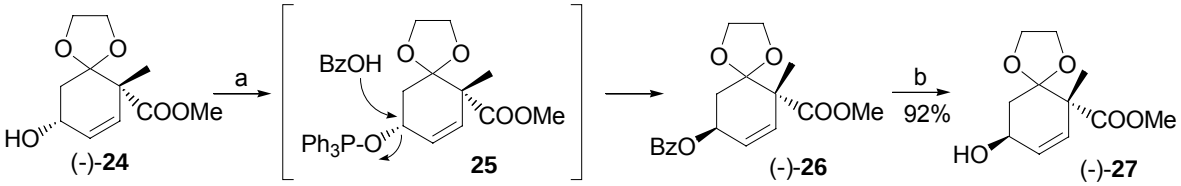
In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**24** a singlet appeared at δ = 1.30 (s, 3 H) as expected and was assigned to the methyl group attached to the quaternary stereocenter. As in the case of lactone (-)-**22** the protons of the methylene group in cyclohexyl ring were exhibited separately at δ = 1.91 (dd, *J* = 13.8, 4.0 Hz, 1 H) and 2.45 (dd, *J* = 13.8, 5.4 Hz, 1 H) respectively. The hydroxyl proton also showed its presence by displaying a signal at δ = 2.33-2.39 (br. s, 1 H). A singlet appearing at δ = 3.67 (s, 3 H) was assigned to the methyl group of the carbomethoxy functionality and the multiplet in the area of δ = 3.81-4.03 (m, 4 H) was attributed to the methylene protons of the dioxolane unit as usual. The CH-OH proton appeared at δ = 4.22 (q, *J* = 4.8 Hz, 1 H), while the olefinic

protons appeared at δ = 5.56 (dd, *J* = 10.0, 0.9 Hz, 1 H) and 5.87 (dd, *J* = 9.7, 3.3 Hz) respectively.

The ^{13}C NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**24** displayed ten peaks as expected at δ = 17.5, 39.2, 51.8, 55.8, 63.9 (2C), 69.2, 111.5, 131.1, 133.3 and 160.4 respectively. The DEPT experiment showed that the peaks appearing at δ = 51.8, 111.5 and 160.4 arise from quaternary carbons. These signals were assigned to the quaternary stereocenter, spiro carbon and the carbonyl carbon respectively. The signal seen at δ = 69.2 belonged to the methine carbon carrying hydroxy function while the signals displayed at δ = 131.1 and 133.3 correspond to the olefinic carbons. The methylene carbon in cyclohexyl ring appeared at δ = 39.2 while those on dioxolane moiety appeared at δ = 63.9 (2C). As usual the signal exhibited at δ = 17.5 was assigned to the methyl group.

With the synthesis of *cis* alcohol the substrate for conducting 1,3 chirality transfer using Johnson's Claisen rearrangement, i.e., the *trans* diastereomer (-)-**21** was already imminent, since its preparation from (-)-**20** involved well established Mitsunobu inversion. The reaction conditions used for this simple transformation involved the addition of DIAD to the mixture of (-)-**24**, triphenyl phosphine and benzoic acid in dry THF at 0 °C, stirring at rt for 3 h and hydrolyzing the resulting benzoate (-)-**26**, having the desired inversion, with 2 N NaOH solution in methanol to furnish (-)-**27** in excellent yield (Scheme 8).

Scheme 8. Preparation of *trans*-diastereomer



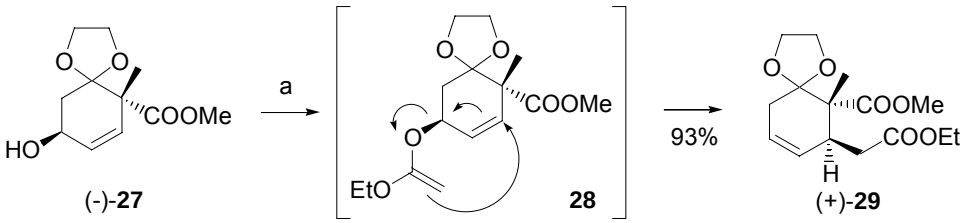
Reagents and conditions: a) DIAD, PPh_3, BzOH, THF, 0 ℃ to rt. b) 1N NaOH, MeOH, rt.

The spectral data of (-)-**27** showed all the requisite characteristics and had close resemblance with that of *cis* diastereomer (-)-**24**. Since the intermediate benzoate (-)-**26** was also isolated and characterized the absence of benzoyl fragment from spectra of (-)-**27** proved the desired hydrolysis. As expected the IR spectrum showed two strong

absorption bands in at ν_{max} = 3447 and 1733 cm^{-1} corresponding to the hydroxyl and ester carbonyl functions respectively. ^{1}H and ^{13}C NMR spectra were also in complete agreement with the structure of (-)-**27**, which was finally confirmed by the appearance of the molecular ion peak at *m/z* = 228 (M^{+}), along with requisite fragmentation pattern in its mass spectrum.

A stage was now set to transform the *trans*-diastereomer (-)-**27** into cyclohexyl moiety carrying vicinal quaternary and tertiary stereocenters, having the stereochemical imprint of the target molecule at both the stereocenters. On the basis of our earlier explorations in the area of 1,3-chirality transfer using Claisen rearrangement we decided to opt for Johnson's Claisen rearrangement to achieve this objective. Accordingly, a neat solution of (-)-**27** in triethyl orthoacetate was heated to 137 °C for 4 h in presence of catalytic amount of propionic acid to afford the desired compound (+)-**29** in excellent yield (Scheme 9). It is interesting to note at this point, that the presence of acid in the reaction mixture did not affect the dioxolane moiety despite the use of considerably high reaction temperature.

Scheme 9. Johnson's orthoester Claisen rearrangement



(-)-**27** **28** (+)-**29**

Reagents and conditions: a) $CH_3C(OEt)_3$, cat. propionic acid, 137 °C.

The IR Spectrum of (+)-**29** gave ample information about the functional groups present by displaying prominent absorption bands at ν_{max} = 2996, 1736, 1730, 1633, 1440, 1371, 1250, 1053, 712 cm^{-1}.

In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**29** the triplet appearing at δ = 1.15 (*J* = 7.1 Hz) and integrating for three protons was assigned to the methyl of the carboethoxy group. The singlet corresponding to the methyl group attached to the quaternary stereocenter was seen at δ = 1.54 (3 H). The signals arising from protons of the

methylene group on cyclohexyl ring, methylene group of the side arm and the methine proton of the tertiary stereocenter were mixed together in the form of a multiplet spanning the region δ = 2.12-2.56 (5 H). The singlet arising from methyl of carbomethoxy group was observed at δ = 3.72 (3H), while the dioxolane methylene protons appeared as a multiplet spanning the region of δ = 3.89-4.08 (4H). The methylene of carboethoxy group was exhibited as a quartet at δ = 4.22 (*J* = 7.0 Hz, 2H), while the olefinic protons appeared in the area of δ = 5.43-5.98 (m, 2 H).

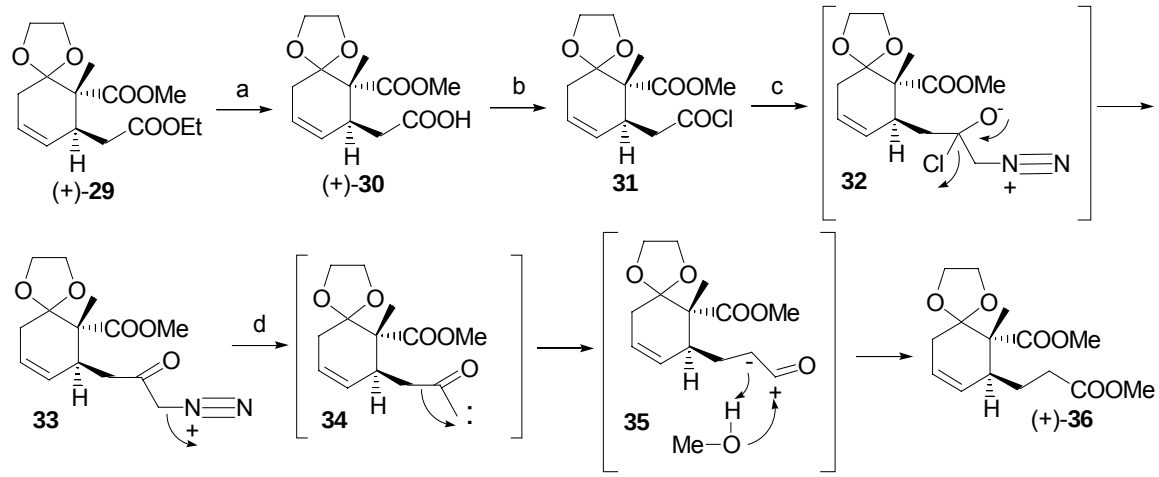
In the ^{13}C NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**29** a total of fourteen signals were observed at δ = 9.07, 22.0, 28.2, 34.4, 36.5, 52.3, 53.0, 63.7, 65.1, 65.4, 112.0, 121.4, 125.6 and 173.9 (2C) respectively. The DEPT spectrum confirmed that the peaks appearing at δ = 52.3, 112.0 and 173.9 (2C) arise from the quaternary carbons. While the first two peaks were assigned to the quaternary stereocenter and the spiro carbon respectively, the third signal was concluded to be a common indication of both the carbonyl groups present. The signal appearing at δ = 34.4 was assigned to the methine carbon of the tertiary stereocenter and the two signals seen at δ = 121.4 and 125.6 were attributed to two olefinic methine carbons respectively. The methylene carbon of the side arm was found appearing at δ = 28.2, whereas the methylene group on the cyclohexyl ring was observed at δ = 36.5. The signals appearing at δ = 63.1 and 65.1 belonged to the remaining two methylene groups present in the dioxolane ring. In the end signal observed most up field at δ = 9.1 was attributed to the carbon of the methyl group attached to the quaternary stereocenter.

The mass spectrum of (+)-**29** was helpful in confirming its structure and displayed prominent fragments at *m/z* = 253 (M^+-OEt), 237, 227, 210, 195, 181, 169, 152, 151, 125, 107, 86, 79, 57 (100) and 43.

After installing the tertiary stereocenter, the next step in the projected synthesis was to increase the chain length of the side arm by one carbon so as to obtain a substrate suitable for annulation of the five-membered ring by Dieckmann condensation. The half

ester required for this purpose was prepared by selective hydrolysis of the carboethoxy group in (+)-**29** using one equivalent of sodium hydroxide in methanol to afford (+)-**30** in very good yield. During the standardization of this reaction, it came to our observation that even the use of slight excess of sodium hydroxide does not affect the carbomethoxy group as long as the reaction is carried out in methanol, most probably due to the presence of vicinal quaternary stereocenter.

Scheme 10. Arndt-Eistert homologation



Reagents and conditions: a) 1 eq. NaOH, MeOH, reflux. b) $SOCl_2$, Pyridine, PhH, rt. c) CH_2N_2, Et_2O, 0 ℃ to rt. d) Ag_2O, MeOH, reflux.

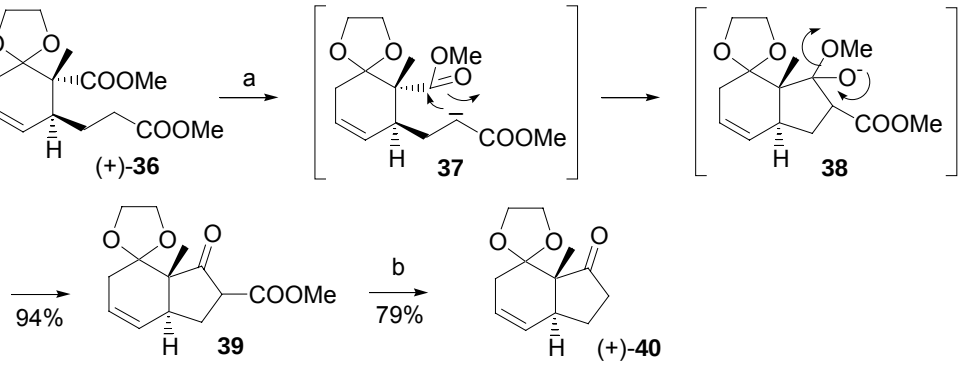
The spectral data of (+)-**30** had all the relevant signals to confirm its structure. The appearance of the carboxyl hydroxy stretching at ν_{max} = 3572 cm^{-1} and the carboxyl carbonyl stretch at ν_{max} = 1688 cm^{-1} in the IR spectrum as well as the disappearance of the ethyl group peaks from the ^1H and ^{13}C NMR spectrum were specially useful for this purpose. Also the presence of a total of 13 signals at the expected positions in the ^{13}C NMR Spectrum further supported its structure.

Subsequently, (+)-**30** was subjected to Arndt-Eistert homologation as depicted in Scheme 10 to obtain diester (+)-**36** in very good overall yield. Detailed spectral and analytical characterization was carried out to confirm its structure. The preliminary investigations using IR spectral technique indicated the presence of two ester groups by displaying two absorption bands at ν_{max} = 1732 and 1737 cm^{-1} respectively. A further support to the depicted structure of (+)-**36** came from ^1H NMR spectrum, which displayed a

additional methyl signal belonging to the methyl group of the carbomethoxy function, and two extra protons in the aliphatic region corresponding to the freshly incorporated methylene group. The appearance of two methyl carbons at δ = 51.8 and 52.7 and an extra methylene carbon signal at δ = 25.9 in the ^{13}C NMR spectrum of (+)-**36** confirmed the information revealed by other spectral techniques.

A stage was now set for the five membered ring closure using Dieckmann condensation. In harmony with our previous experience on this transformation, NaHMDS was found to give best yields of the cyclized product. The conversion was essentially achieved by dropwise addition of NaHMDS (1.5 M solution in THF) to the solution of (+)-**36** in dry THF at 0 °C and stirring the resulting mixture at rt for 10 h, which afforded the desired β-keto ester **39** in excellent yield.

Scheme 11. Dieckmann condensation-demethoxycarbonylation



Reagents and conditions: a) NaHMDS, THF, 0 °C to rt. b) DABCO, xylene, 150 °C.

The structure of **39** follows from the presence of the absorption band at ν_{max} = 1751 cm^{-1} in the IR spectrum, which is the characteristic feature of cyclopentanone carbonyl. The presence of triplet at δ = 3.32 (J = 8.8 Hz) integrating for one proton, which belongs to the methine proton between two carbonyl groups as well as the appearance of keto carbonyl signal at δ = 216 in ^{13}C NMR, provided sufficient support for the intended annulation. The other signals in the ^{1}H and ^{13}C NMR spectrum as well as the fragmentation pattern observed in mass spectral analysis were also in very good agreement with the structure of **39**.

Finally, the decrbomethoxylation of **39** was achieved by refluxing it with DABCO in xylene to reach the desired target molecule (+)-**40** (Scheme 11).[13] The spectral and analytical data of (+)-**40** confirmed its structure unambiguously. It is interesting to note at this point that the entire sequence has been carried out with dioxolane as a protecting group for keto functionality, without any interference from the reaction conditions at any stage.

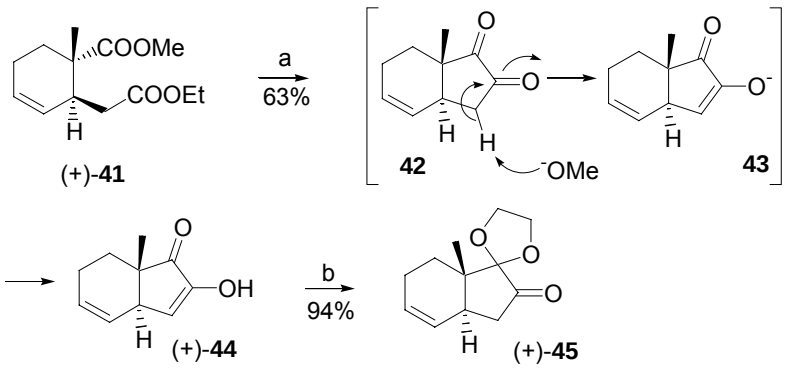
2.2 Synthesis of CD ring precursor of C-16 modified analogue.

As discussed earlier side chain catabolism of the natural hormone $1,25(OH)_2D_3$ usually gives products that are medicinally less useful. Therefore slowing or preventing such catabolic side chain oxidation is an important goal for medicinal chemistry. In 1993 two publications appeared showing that remote functional changes can influence the rate of side chain catabolic oxidation. Hoffman La-Roche showed that 16-en-24-oxo-$1,25(OH)_2D_3$ resists 24-hydroxylation in human leukemic cells under the conditions in which natural $1,25(OH)_2D_3$ is easily 24-hydroxylated.[2a] Such reports indicated that the presence of 16-ene modification sufficiently alter the ligand enzyme interaction and cause significant slowing in the enzymatic side chain oxidation. This observation led to the development of large number of analogues with C-16 *ene* modification which have proved to be potential drug candidates. We designed a CD-rings precursor (Figure 9) which can serve in the preparation of large number of C-16 analogues including those with C-16 *ene* modification. Besides incorporating modifications on C-16, such a precursor would also serve in introducing functionalities at C-15, C-17 and C-20.

Our synthesis of CD-rings precursor of C-16 modified analogs of $1,25(OH)_2D_3$ emanates from a versatile intermediate (+)-**41** designed and developed by us (see chapter 2) starting from cheaply available materials. It was anticipated that (+)-**41** on acyloin condensation would provide the α-hydroxy ketone as is normal for such condensations.[14] However when (+)-**41** was subjected to acyloin condensation with 4 eq. of Na in liq. NH_3,

an extra olefinic proton appearing at δ = 6.6 in the ^{1}H NMR spectrum of the resulting compound baffled us. Since it was exhibited as a doublet it was obvious that there was only one proton in its vicinity. Careful characterization of this compound using IR, ^{1}H NMR, ^{13}C NMR, mass spectra revealed that it was α-hydroxy α,β-unsaturated ketone (+)-**44**.

Scheme 12. C-16 modified precursor



Reagents and conditions: a) Na, liq. NH_3, –78 °C. b) $(CH_2OH)_2$, p-TsOH, toluene, 90 °C.

The IR spectrum of (+)-**44** gave ample evidence of the functionalities present in the proposed structure; especially a strong absorption band at ν_{max} = 1703 cm^{-1}indicated a α,β-unsaturated ketone having electron-donating moiety in its vicinity and the appearance of an absorption band at ν_{max} = 3498 cm^{-1} disclosed the presence of hydroxy function.

The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**44** displayed a singlet at δ = 1.41 integrating for three protons. This signal was assigned to the protons of the methyl group attached to quaternary stereocenter without any ambiguity, since it formed a common feature of ^{1}H NMR spectrum of most of our intermediates. Two sets of multiplets appearing in the region of δ = 1.49-1.72 (2H) and 1.84-2.15 (2H) and integrating for four protons altogether, were attributed to the protons of the two methylene groups present in the cyclohexyl ring. The signal displayed more up field could be arising from the allylic methylene group while the other signal belongs to the methylene group vicinal to the quaternary stereocenter. The proton associated with the ring junction was found appearing as multiplet in the area of δ = 2.81-2.97 (1H). The multiplet integrating for two protons observed at δ = 5.52-5.81 was attributed to the protons of the olefinic double bond embodied in the cyclohexyl unit. The most significant feature of this spectrum was the

appearance of a doublet at δ = 6.45 (d, *J* = 6.4 Hz), integrating for one proton, which suggested the presence of olefinic double bond in newly, formed five-membered ring. On close examination of the entire spectrum it was found that the aliphatic protons pertaining to the five membered ring of the expected α-hydroxy ketone were missing. Thus we proposed the structure for (+)-**44** as depicted above in Scheme 13 and the doublet appearing downfield in the olefinic region was assigned to the proton on the β-carbon of the α-β unsaturated ketone system thus formed in the five membered ring. This structure was confirmed using ^{13}C NMR and mass spectral techniques as discussed below, as well as from elemental analysis.

The ^{13}C NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**44** displayed a total of ten signals as expected at δ = 21.7, 22.1, 31.4, 44.2, 45.3, 126.6, 128.4, 130.2, 149.6 and 209.3 respectively. The presence of four olefinic signals directly pointed to the structure proposed. DEPT experiment was utilized to assign the signals to different carbons. The absence of signals at δ = 45.3, 149.6 and 209.3 indicated that these signals belonged to the quaternary carbons and were assigned to the quaternary stereocenter, quaternary olefinic carbon carrying hydroxy group in the five-membered ring, and the carbonyl carbon respectively. The signal appearing at δ = 44.2 was attributed to the methine carbon at the ring junction, while the signals exhibited at δ = 126.6, 128.4 and 130.2 were ascribed to the remaining three olefinic methine carbons respectively. The two-methylene carbons belonging to cyclohexyl ring were shown at δ = 21.7 and 31.4 respectively. Finally the methyl group was displayed at δ = 22.1.

The mass spectrum fully supported the structure of (+)-**44** by exhibiting a molecular ion peak at *m/z* = 164 (M^+) and the relevant fragmentation pattern with prominent fragments at 149, 136, 121, 107, 91, 77, 55 and 40.

At this point, we projected that since (+)-**44** is the enol form of the corresponding diketone it should be possible to selectively carry out a reaction on the ketone vicinal to ring junction, which would in turn unravel the other ketonic moiety present in the form of

enol. The transformation had to be such that the second ketone after release from the enolic form would not undergo the same transformation. After considerable experimentation, we were finally successful in achieving our target of differentiating the two carbonyl groups by selective protection of the C-17 (steroid numbering) carbonyl group by transforming it into corresponding dioxolane unit under controlled reaction conditions. It was quite remarkable to observe that, when (+)-**44** was heated with slight excess of ethylene glycol and catalytic amount of *p*-TsOH in toluene at 90 °C for 6 h (+)-**45** was produced as a sole product and in excellent yield, while if the reaction mixture was refluxed a compound with both the carbonyl groups protected was produced in considerable amounts depending on reaction time and if the reaction mixture was allowed to reflux for 24 h, this diprotected compound was obtained as a sole product. Formation of (+)-**45** was an additional evidence for the observed abnormal acyloin condensation resulting in the formation of (+)-**44**. The monoprotected compound (+)-**45** was characterized using conventional spectroscopic means and was observed to display all the requisite spectral properties (Scheme 12).

In the IR spectrum of (+)-**45** a strong absorption band appearing at ν_{max} = 1732 indicated the presence of cyclopentanone moiety.

The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**45** displayed a singlet at δ = 1.07 (3H) corresponding to the methyl group attached to the quaternary stereocenter. A multiplet that occurred in the region δ = 1.33-1.62 (2H) was attributed to the protons of the methylene group allylic to olefinic double bond in cyclohexyl ring. Another multiplet spanning the region of δ = 1.99-2.40 (m, 4H) is the combined indication of the protons of the methylene group vicinal to quaternary stereocenter in cyclohexyl ring and the methylene group embodied in the five-membered ring. The proton on the ring junction was shown as a multiplet in the area of δ = 2.61-2.80 (m, 1H). As seen in the case of our CD-rings precursor of C-12 modified analogues, the protons of the dioxolane methylene groups were seen appearing as a singlet at δ = 4.02 (s, 4H). The spectrum was

terminated by the olefinic protons, which appeared as a multiplet spanning the region of δ = 5.48-5.91 (m, 2 H).

In the ^{13}C NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**45** a total of eleven signals were seen appearing at δ = 21.4, 24.0, 29.1, 31.8, 34.5, 37.3, 76.2 (2C), 116.3, 127.5, 128.4 and 218.3 respectively. Peak assignments with the aid of Dept experiment revealed that the signals appearing at δ = 31.8, 116.3 and 218.3 arise from the quaternary carbons and were attributed to the quaternary stereocenter, the spiro carbon and the carbonyl carbon respectively. The methine carbon of the tertiary stereocenter was displayed at δ = 37.3 while the olefinic methine carbons were seen appearing at δ = 127.5 and 128.4 respectively. The signals appearing at δ = 21.4, 29.1 and 34.5 belonged to the carbons of the three methylene groups embodied in the hydrindane skeleton while the signal exhibited at δ = 76.2 was a common indication of the two methylene carbons of the dioxolane moiety. In the end the signal displayed at δ = 24.0 was assigned to the methyl group.

The mass spectrum of (+)-**45** confirmed its molecular weight and structure by displaying a molecular ion peak at *m/z* = 208 (M^+).

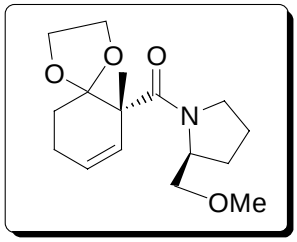
2.3 Conclusion

In this part of the thesis we have achieved the enantioselective synthesis of CD-rings precursors of C-12 modified and C-16 modified analogues of 1,25-D_3.

3. Experimental Section:

For general write up, see the experimental section of chapter 2 of this thesis.

1. Preparation of (2-Methoxymethyl-pyrrolidin-1-yl)-(6-methyl-1,4-dioxa-spiro[4.5]dec-7-en-6yl)-methanone [(-)-(12)]:



A mixture of (-)-**11** (1 g, 3.98 mmol), ethylene glycol (0.3 g, 4.84 mmol) and *p*-TsOH (0.05 g) was refluxed in toluene for 18 h under Dean-Stark condition. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure and column chromatography of the crude residue (silica gel, 60-120 mesh; eluent: pet. ether-ethyl acetate = 3:2) afforded (-)-**12** (1.15 g, 98%) as a viscous colorless oil.

$[\alpha]_D^{25}$	**:**	-66.65 (*c* = 1.2, CH_2Cl_2)
IR ($CHCl_3$)	**:**	ν_{max} = 3027, 1636, 1442, 1411, 1115 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.45 (s, 3H), 1.66-2.04 (m, 6H), 2.41-2.71 (m, 5H), 2.96-3.13 (m, 1H), 3.20-3.44 (m, 6H), 3.64 (dd, 9.4, 3.1 Hz, 1H), 4.17-4.34 (m, 1H), 5.65 (d, 10.2 Hz, 1H), 5.93 (dt, 9.8, 3.1 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ 23.5, 24.1, 25.5, 26.4, 35.4, 46.2, 57.4, 58.6 (2C), 71.6 (2C), 71.9, 126.6, 130.4, 130.8, 168.8.
Mass (GC-MS)	**:**	*m/z* = 295 (M^+), 281, 250, 210, 207, 191, 179, 153, 142, 133, 114, 96, 86, 73, 67, 45 (100%).

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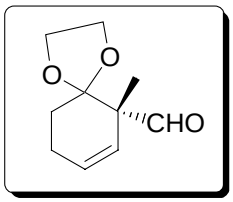
2. Preparation of 6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-carbaldehyde [(-)-14]:



To a solution of compound (-)-**12** (1.15 g, 3.90 mmol) in THF

(20 mL) was added slurry of LAH (0.15 g, 4.05 mmol) in THF dropwise at –20 °C. The temperature of the mixture was raised to 0 °C over a period of 4 h and was quenched by dropwise addition of 2N sulfuric acid. The resulting mixture was allowed to warm to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (100-200 mesh; eluent: pet. ether-ethyl acetate = 10:1) to give the desired compound (-)-**14** (0.63 g, 89%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-30.42 (c = 0.76, $CHCl_3$)
IR ($CHCl_3$)	**:**	ν_{max} = 2957, 1724, 1454, 1361, 1245, 1099, 1026, 756 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.16 (s, 3H), 1.79 (t, *J* = 6.3 Hz, 2H), 2.14-2.33 (m, 2H), 3.84-4.12 (m, 4H), 5.33 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.88 (dt, *J* = 10.2, 3.5 Hz, 1H), 9.68 (s, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 16.4, 24.3, 28.4, 55.5, 64.7, 64.9, 109.4, 127.3, 128.9, 201.3.

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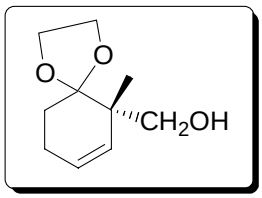
3. Preparation of (6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-yl)-methanol [(-)-17]:



To a solution of compound (-)-**12** (1.20 g, 4.07 mmol) in THF (20 mL) was added slurry of LAH (0.15 g, 4.05 mmol) in THF dropwise at 0 °C. The temperature of the mixture was raised to rt and stirred for 8 h. Excess LAH was quenched by dropwise addition of 2N sulfuric acid. The resulting mixture was allowed to warm to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (100-200 mesh; eluent: pet. ether-ethyl acetate = 10:1) to give the desired compound (-)-**17** (0.70 g, 94%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-2.27 (*c* = 1.1, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 3444, 2935, 1442, 1357, 1236, 1102, 1050, 754 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.08 (s, 3H), 1.73-1.91 (m, 2H), 2.16-.30 (m, 2H), 2.64-2.77 (br. s, 1H), 3.56 (s, 1H), 3.76 (s, 1H), 3.97-4.12 (m, 4H), 5.39 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.77 (dt, *J* = 10.0, 3.7 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 19.2, 24.1, 27.1, 43.9, 64.2, 64.4, 68.0, 112.4, 126.3, 132.1.
Mass (GC-MS)	**:**	*m/z* = 184 (M^+), 166, 154, 139, 125, 110, 99, 86 (100%), 81, 55, 42.

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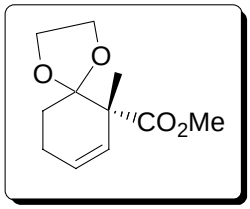
4. Preparation of 6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester [(-)-15]:



a) <u>From aldehyde (-)-14</u>: A solution of $NaClO_2$ (0.54g, 4.85 mmole, 82% purity, by iodometric titration) in water (7 mL) was added dropwise over a period of 10 minutes to a stirred solution of aldehyde (-)-**14** (0.63 g, 3.46 mmol) in acetonitrile (6 mL). This was followed by addition of solution of NaH_2PO_4 (0.2 g) in water (3 mL) and 35% aqueous H_2O_2 solution (0.34 mL, 3.46 mmol), while keeping the temperature at 10 °C using ice-water. After the consumption of starting material, small amount of Na_2SO_3 (0.1 g) was added to destroy the unreacted HOCl and H_2O_2. The resulting mixture was acidified with 10% HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent resulted in acid, which was carried over for next step without further purification.

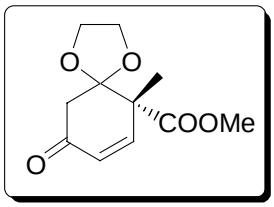
To a solution of acid obtained above, in ether (5 mL), a solution of diazomethane in ether (10 mL), prepared from *N*-nitroso-*N*-methyl urea (0.92 g, 10.38 mmol), was added at

0 °C. The mixture was stirred at 0 °C for an additional hour and warmed to room temperature while stirring. The ether was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 9:1) to furnish ester (-)-**15** (0.62 g, 84%, from (-)-**14**) as colorless liquid.

b) From alcohol (-)-17: A mixture of alcohol (-)-**17** (0.70 g, 3.80 mmol) and pyridinium dichromate (2.15 g, 5.71 mmol) in DMF (5 mL) was stirred overnight. The mixture was poured into a beaker containing water (50 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to furnish acid, in sufficiently pure form, which was esterified using diazomethane as described above to give ester (-)-**15** (0.74 g, 92%, from (-)-**17**) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-77.33 (c = 0.95, CH_2Cl_2)
IR ($CHCl_3$)	**:**	ν_{max} = 2948, 1730, 1452, 1433, 1259, 1240, 1099, 1051, 1027, 950, 788 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ = 1.33 (s, 3H), 1.66-1.83 (m, 1H), 1.91-2.07 (m, 1H), 2.15-2.29 (m, 2H), 3.67 (s, 3H), 3.93-4.01 (m, 4H), 5.56 (dt, *J* = 9.8, 2.0 Hz, 1H), 5.74 (dt, *J* = 9.8, 3.9 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 20.3, 23.7, 28.0, 51.8, 64.7, 64.9, 109.5, 126.0, 129.8, 173.6.
Mass (GC-MS)	**:**	*m/z* = 212 (M^+), 207, 181, 167, 153, 151, 125, 112, 109, 86 (100%), 73, 55, 42.
Elemental Analysis	**:**	$C_{10}H_{14}O_3$ (212.25): Calcd. C 62.23, H 7.60; Found C 62.29, H 7.37.

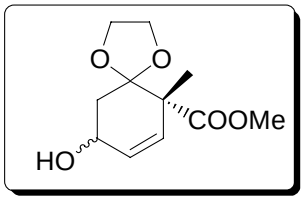
5. Preparation of 6-Methyl-9-oxo-1,4-dioxa-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester [(-)-18]:



To a stirring mixture of (-)-**15** (0.84 g, 3.96 mmol) and pyridinium dichromate (PDC, 3.72 g, 9.9 mmol) in dichloromethane (15 mL) was added 70 % *t*-butylhydroperoxide (1.37 mL, 9.9 mmol) dropwise at 10 °C. After 15 min., the mixture was allowed to warm to room temperature and allowed to stir for the next 12 h. Additional PDC (3.72 g, 9.9 mmol) and *t*-butylhydroperoxide (1.37 mL, 9.9 mmol) were added and the stirring continued for another 12 h. Ethyl acetate (50 mL) was added to the reaction mixture and the content was filtered through a pad of celite. The filtrate was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (-)-**18** (0.61 g, 68%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-53.06 (c = 1.5, CH_2Cl_2)
IR ($CHCl_3$)	**:**	ν_{max} = 2954, 1733, 1685, 1456, 1307, 1255, 1134, 1108, 1026, 914, 732 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.48 (s, 3H), 2.73 (d, *J* = 13.6 Hz, 1H), 2.97 (d, *J* = 13.6 Hz, 1H), 3.74 (s, 3H), 3.91-4.06 (m, 4H), 6.06 (d, *J* = 10.2 Hz, 1H), 6.82 (d, *J* = 10.2 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 18.7, 45.4, 52.4, 52.8, 65.0, 65.3, 110.2, 127.5, 149.4, 171.0, 196.4.
Mass (GC-MS)	**:**	*m/z* = 227 (M^++1), 210, 197, 183, 169, 142, 125, 110, 97, 87 (100%), 79, 55, 43.

6. Preparation of 9-Hydroxy-6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester (19):



To a stirring solution of (-)-**18** (0.61 g, 2.70 mmol) in methanol was added $CeCl_3.7H_2O$ (1.06 g, 2.83 mmol) at room temperature. The mixture was stirred for 0.5 h at room temperature and cooled to 0 °C. Sodium borohydride (0.12 g, 3.24 mmol) was added in portions over a period of 5 min. The solution was allowed to warm to room temperature. After consumption of the starting material (TLC), the methanol was removed under vacuum. The residual pale pink mixture was dissolved in a minimum amount of water, acidified to pH 3 with 1N HCl and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to afford **19** (0.55 g, 90%) as a colorless liquid in 1:1 diastereomeric mixture, confirmed by GC and ^{1}H NMR spectroscopy.

IR (Neat) : ν_{max} = 3438, 2977, 1736, 1456, 1252, 1137, 1035, 915, 732 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.38 (s, 3H), 1.88-2.17 (m, 1H), 2.36-2.59 (m, 2H), 3.70 & 3.75 (2 s [1:1], 3H), 3.91-4.12 (m, 4H), 4.20-4.48 (m, 1H), 5.63 (d, *J* = 10.1 Hz, 1H), 5.82-6.07 (m, 1H).

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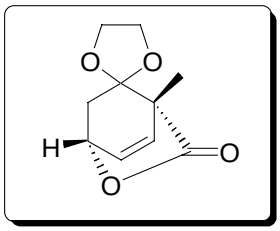
7. Preparation of lactone (-)-22:



To a solution of **19** (0.55 g, 2.57 mmol) in THF (5.5 mL) and water (4.5 mL) was added lithium hydroxide monohydrate (0.32 g, 7.71 mmol) in a single portion. After stirring overnight,

THF was removed under vacuum and the residue was acidified with 1N HCl and extracted with ether (3 × 10mL). The combined ether extracts were dried over sodium sulfate, filtered and concentrated to give **20** (0.48 g, 92%) as a viscous colorless oil.

To a solution of **20** (0.48 g, 2.24 mmol) in dichloromethane (20 mL) was added boron trifluoride etherate (0.37 mL, 3.14 mmol) dropwise at 0 °C. The pale brown solution was stirred for 3 h and the reaction was quenched by adding 5% sodium bicarbonate solution until the pH of the aqueous phase reached 7. After separation of the layers, the aqueous phase was back extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (-)-**22** (0.36 g, 82%) as colorless liquid.

$[\alpha]_D^{25}$	**:**	-44.62 (c = 1.2, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 2991, 1741, 1217, 1112 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.44 (s, 3H), 2.06 (dd, *J* = 13.8, 1.4 Hz, 1H), 2.44 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.96-4.09 (m, 4H), 5.20-5.29 (m, 1H), 6.22 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.56-6.66 (m, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 11.3, 41.6, 56.5, 65.6, 65.7, 72.9, 111.6, 132.2, 135.2, 158.0.
Mass (GC-MS)	**:**	*m/z* = 197 (M^++1), 155, 127, 99, 85, 79, 55, 43 (100%).
Elemental analysis	**:**	$C_{10}H_{12}O_4$ (196.20): Calcd. C 61.22, H 6.16; Found C 61.07, H 6.41.

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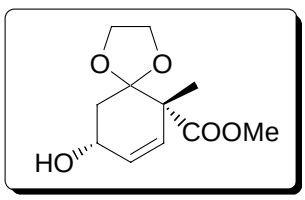
8. Preparation of 9-Hydroxy-6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester [(-)-24]:



To a solution of lactone (-)-**22** (0.88 g, 4.49 mmol) in

methanol (20 mL) was added a 25% solution of sodium methoxide in methanol (0.97 mL, 4.49 mmol) and contents were refluxed for an hour. Methanol was removed under reduced pressure. The residue was diluted with ether (40 mL), washed with water (1 × 15 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to yield (-)-**24** (0.98 g, 96%) as a colorless liquid.

$[\alpha]_D^{25}$	**:**	-18.36 (c = 0.65, CH_2Cl_2)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.30 (s, 3H), 1.91 (dd, *J* = 13.8, 4.0 Hz, 1H), 2.33-2.39 (br. s, 1H), 2.45 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.67 (s, 3H), 3.81-4.03 (m, 4H), 4.22 (q, *J* = 4.8 Hz, 1H), 5.56 (dd, *J* = 10.0, 0.9 Hz, 1H), 5.87 (dd, *J* = 9.7, 3.3 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 17.5, 39.2, 51.8, 55.8, 63.9 (2C), 69.2, 111.5, 131.1, 133.3, 160.4.

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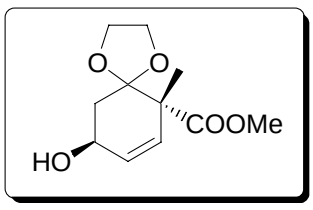
9. Preparation of 9-Hydroxy-6-Methyl-1,4-dioxa-spiro[4.5]dec-7-ene-6-carboxylic acid methyl ester [(-)-27]:



To a solution of alcohol (-)-**24** (0.98 g, 4.30 mmol) in THF (15 mL) was added triphenylphosphine (1.46 g, 5.59 mmol) and benzoic acid (0.78 g, 6.39 mmol). The mixture was cooled to 0 °C and diisopropylazodicarboxylate (1.13 mL, 5.59 mmol) was introduced dropwise over a period of 10 min. After stirring for 4 h at room temperature, the solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (25 mL). The mixture was filtered through a small pad of silica gel; the filtrate concentrated under reduced pressure and the crude benzoate was subjected to silica gel column chromatography to remove traces of unreacted alcohol. The benzoate was hydrolyzed by the addition of 1N NaOH (15 mL) in methanol. The reaction mixture was

stirred at room temperature for 2 h, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) to give (-)-**27** (0.90 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$		-42.73 (c = 0.68, CH_2Cl_2)
IR ($CHCl_3$)	**:**	ν_{max} = 3447, 2985, 1733, 1438, 1255, 1117, 1038 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.33 (s, 3H), 1.91 (dd, J = 13.7, 4.0 Hz, 1H), 2.46 (dd, J = 13.7, 5.2 Hz, 1H), 3.70 (s, 3 H), 3.98-4.07 (m, 4H), 4.28-4.37 (m, 1H), 5.61, (dd, J = 10.0 Hz, 0.9 Hz, 1 H), 5.90 (dd, J = 9.8, 3.1 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 17.9, 38.6, 52.0, 55.7, 63.7 (2 C), 68.9, 111.7, 131.5, 133.4, 165.8.
Mass (GC-MS)	**:**	m/z = 228 (M^+), 180, 166, 152, 137, 112, 107, 93, 74 (100%), 60, 41.

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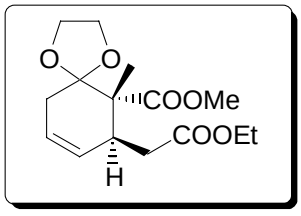
10. Preparation of 7-Ethoxycarbonylmethyl-6-Methyl-1,4-dioxa-spiro[4.5]dec-8-ene-6-carboxylic acid methyl ester [(+)-29]:



A RB flask fitted with a Claisen adapter was charged with a mixture of (-)-**27** (0.90 g, 3.95 mmol), triethyl orthoacetate (2.90 mL, 15.80 mmol) and propionic acid (0.1 mL) and was heated to reflux at 137 ºC for 2 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 9:1) to give (+)-**29** (1.10 g, 93%) as a colorless liquid.

$[\alpha]_D^{25}$		+21.7 (*c* = 0.84, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 2996, 1736, 1730, 1633, 1440, 1371, 1250, 1053, 712 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.15 (t, *J* = 7.1 Hz, 3H), 1.54 (s, 3H), 2.12-2.56 (m, 5H), 3.72 (s, 3H), 3.89-4.08 (m, 4H), 4.22 (q, *J* = 7.0 Hz, 2 H), 5.43-5.98 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 9.07, 22.0, 28.2, 34.4, 36.5, 52.3, 53.0, 63.7, 65.1, 65.4, 112.0, 121.4, 125.6, 173.9 (2C).
Mass (GC-MS)	**:**	*m/z* = 253 (M^+-OEt), 237, 227, 210, 195, 181, 169, 152, 151, 125, 107, 86, 79, 57 (100%), 43.
Elemental analysis	**:**	$C_{15}H_{22}O_6$ (298.34): Calcd. C 60.39, H 7.43; Found C 60.31, H 7.23.

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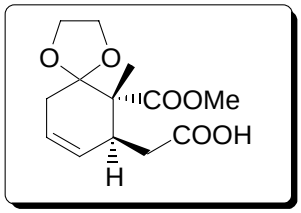
11. Preparation of 7-Carboxymethyl-6-Methyl-1,4-dioxa-spiro[4.5]dec-8-ene-6-carboxylic acid methyl ester [(+)-30]:



A mixture containing (+)-**29** (1.10 g, 3.69 mmol) and NaOH (0.15 g, 3.75 mmol) in methanol (10 mL) was refluxed for 12 h. Methanol was removed under reduced pressure; the residue was dissolved in water and extracted with ether to remove un-reacted dimethyl ester. The aqueous layer was acidified with 6N HCl, saturated with common salt and extracted with ether (3 × 10 mL). The combined ether layer was washed with water (10 mL) followed by brine (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave (+)-**30** (0.87 g, 87%) as a viscous colorless oil.

IR (Neat)	**:**	ν_{max} = 3572, 1734, 1688, 1051 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.29 (s, 3H), 1.74 -1.96 (m, 2H), 2.28-2.57 (m, 3H), 3.61 (s, 3H), 3.97-4.26 (m, 4H), 5.50-5.85 (m, 2H), 9.87 (br. s, 1H).

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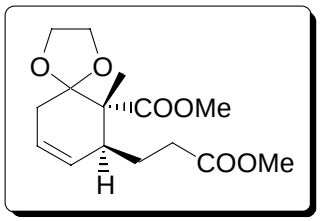
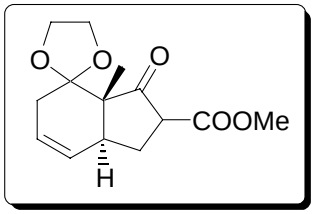
12. Preparation of 7-(2-Methoxycarbonyl-ethyl)-6-Methyl-1,4-dioxa-spiro[4.5]dec-8-ene-6-carboxylic acid methyl ester [(+)-36]:



A mixture of (+)-**30** (0.87 g, 3.22 mmol), pyridine (2 drops), and purified thionyl chloride (3 mL) in benzene (10 mL) was stirred at room temperature for 2 h. The solvent and excess thionyl chloride was removed under reduced pressure. Benzene (5 mL) was added to the residue and again evaporated under reduced pressure. The resulting acid chloride was dissolved in benzene (5 mL) and was added to a solution of diazomethane, prepared from *N*-nitroso-*N*-methylurea (1.42 g, 15.93 mmol) in ether (30 mL) at 0 °C while stirring. The mixture was warmed to room temperature and stirred for additional 5 h. The solvent was removed under reduced pressure. Methanol (10 mL), and silver oxide (0.3 g) were added to the residual diazoketone. After refluxing for 2 h, an additional silver oxide (0.2 g) was added and refluxing continued for the next 10 h. The mixture was filtered through a pad of celite and the filtrate concentrated. The residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 4:1) to give (+)-**36** (0.75 g, 78%) as a colorless liquid.

IR ($CHCl_3$)	**:**	ν_{max} = 2989, 1737, 1732, 1650, 1436, 1367, 1240, 1169, 1045 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.22 (s, 3H), 1.34-1.76 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 2H), 1.91-2.22 (m, 2H), 2.76-2.93 (m, 1H), 3.48 (s, 3H), 3.50 (s, 3H), 3.71-3.94 (m, 4H), 5.16-5.75 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 15.9, 25.9, 29.5, 36.9, 42.0, 48.6, 51.8, 52.7, 68.0 (2 C), 111.2, 126.6, 130.7, 156.1 (2C).
Mass (GC-MS)	**:**	*m/z* = 238 (M^+-COOMe), 228, 213, 197, 193, 179, 161, 151, 134, 119, 106,91, 77, 63 (100%), 51.

13. Preparation of 39:



To a solution of (+)-**36** (0.75 g, 2.52 mmol) in THF (8 mL) was added 2M solution of NaHMDS (1.88 mL, 3.75 mmol) in THF at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 h. Excess NaHMDS was quenched with saturated NH_4Cl solution and the mixture was extracted with EtOAc (3 × 10 mL), washed with water (1 × 10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane / EtOAc = 4:1) to give **39** (0.60 g, 94%) as a colorless liquid.

IR (film) : ν_{max} = 3026, 2947, 1751, 1730, 1438, 1343, 1244, 1162, 1050 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.17 (s, 3 H), 1.75-2.40 (m, 4 H), 2.58-2.71 (m, 1 H), 3.32 (t, *J* = 8.8 Hz, 1 H), 3.74 (s, 3 H), 4.03-4.31 (m, 4 H), 5.56 (dd, *J* = 10.1, 1 Hz, 1 H), 5.69-5.76 (m, 1 H).

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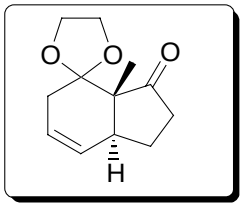
14. Preparation of [(+)-40]:



A 10 mL round bottomed flask, charged with a solution of **39** (0.60 g, 2.38 mmol) and DABCO (1.59 g, 14.29 mmol) in *o*-xylene (5 mL) was heated at 150 °C for 10 h. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 9:1) to give (+)-**40** (0.13 g, 79%) as a thick oil with mild camphor like odor.

$[\alpha]_D^{25}$: +7.38 (*c* = 0.8, CH_2Cl_2);

IR (film) : ν_{max} = 2964, 1736, 1461, 1404, 1178, 1091, 1043, 910, 732 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.06 (s, 3H,), 1.55 (t, *J* = 6.3 Hz, 2H), 1.85-2.11 (m, 3H), 2.17-2.37 (m, 1H), 2.52-2.71 (m, 1H), 4.11 (s, 4H), 5.54-5.82 (m, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 18.2, 21.7, 24.6, 33.6, 38.4, 40.7, 65.8 (2C), 114.3, 125.7, 129.1, 221.7.
Mass (GC-MS)	**:**	*m/z* = 180 (M^+-28), 165, 138, 126, 113 (100%), 94, 79, 67, 41.
Elemental analysis	**:**	$C_{12}H_{16}O_3$ (208.26): Calcd. C 69.21, H 7.74; Found C 69.07, H 7.91.

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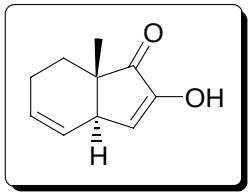
15. Preparation of 2-Hydroxy-7a-methyl-3a-6,7,7a-tetrahydro-inden-1-one [(+)-44]:



A 100 ml 3-necked RB flask equipped with a cold finger condenser was cooled to −78 °C and charged with anhydrous liquid ammonia (40 mL), which was previously dried over sodium for 30 minutes and distilled. Sodium metal (0.36 g, 15.83 mmol) was added to the flask in the form of small pieces over a period of 10 minutes and the resulting deep blue colored solution was swept with argon for 20 minutes. The diester (+)-**41** (0.95 g, 3.96 mmol), dissolved in anhydrous ether (20 mL) was then added over a period of 30 minutes with stirring. After stirring for an additional 40 minutes, the solution changed color suddenly from deep blue to light yellow, indicating complete reaction of the dissolved sodium. The bulk of the ammonia was evaporated within 30 minutes by removing the cooling bath and flushing argon through the flask. Anhydrous ether (15 mL) was added to the residue and flushing of argon continued for another 2 h to ensure complete removal of ammonia. The colorless sodio-enolate of the acyloin was then acidified by addition of 3N HCl (15 mL) over a period of 10 minutes at 0 °C. Until this acidification was complete all traces of oxygen were carefully excluded from the system. The mixture was extracted with ether (3 × 15 mL), the combined organic layer was washed

with water (15 mL), brine 10 mL) and dried over anhydrous sodium sulfate. Evaporation of ether and silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 5:1) of the resulting residue yielded compound (+)-**44** (0.41 g, 63%) as a colorless oil having peculiar odor.

$[\alpha]_D^{25}$	**:**	+5.24 (*c* = 0.76, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 3498, 3020, 1703, 1525, 1398, 1215, 757 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.41 (s, 3H,), 1.49-1.72 (m, 2H), 1.84-2.15 (m, 2H), 2.81-2.97 (m, 1H), 5.52-5.81 (m, 2H), 6.45 (d, *J* = 6.4 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 21.7, 22.1, 31.4, 44.2, 45.3, 126.6, 128.4, 130.2, 149.6, 209.3.
Mass (GC-MS)	**:**	*m/z* = 164 (M^+), 149, 136, 121, 107, 91, 77, 55, 40(100%).
Elemental analysis	**:**	$C_{10}H_{12}O_2$ (164.20): Calcd. C 73.15, H 7.37; Found C 72.91, H 7.55.

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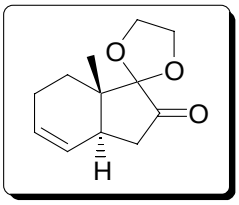
16. Preparation of [(+)-45]:



To a 50 mL round bottomed flask, equipped with a reflux condenser was added a mixture of (+)-**44** (0.41 g, 2.5 mmol), ethylene glycol (0.19 g, 3.1 mmol) and *p*-TsOH (0.02 g) in toluene. The contents of the flask were heated at 90 °C for 6 h. The solvent was evaporated under reduced pressure and the whole residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure and column chromatography of the crude residue (100-200 mesh; eluent: pet. ether-ethyl acetate = 3:2) afforded (+)-**45** (0.49 g, 94%) as viscous colorless oil.

$[\alpha]_D^{25}$	**:**	+6.27 (*c* = 0.35, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 2976, 1732, 1455, 1113, 1077 cm^{-1}
^{1}H NMR	**:**	δ = 1.07 (s, 3H), 1.33-1.62 (m, 2H), 1.99-2.40 (m, 4H),
(200 MHz, $CDCl_3$)		2.61-2.80 (m, 1H), 4.02 (s, 4H), 5.48-5.91 (m, 2H).
^{13}C NMR	**:**	δ = 21.4, 24.0, 29.1, 31.8, 34.5, 37.3, 76.2 (2C), 116.3,
(50 MHz,$CDCl_3$)		127.5, 128.4, 218.3.
Mass (GC-MS)	**:**	*m/z* = 208 (M^+), 180, 178, 165, 151, 126, 113 (100%),
		105, 91, 69, 65, 41
Elemental analysis	**:**	$C_{12}H_{16}O_3$ (208.26): Calcd. C 69.21, H 7.74; Found C
		68.98, H 7.62.

4. References

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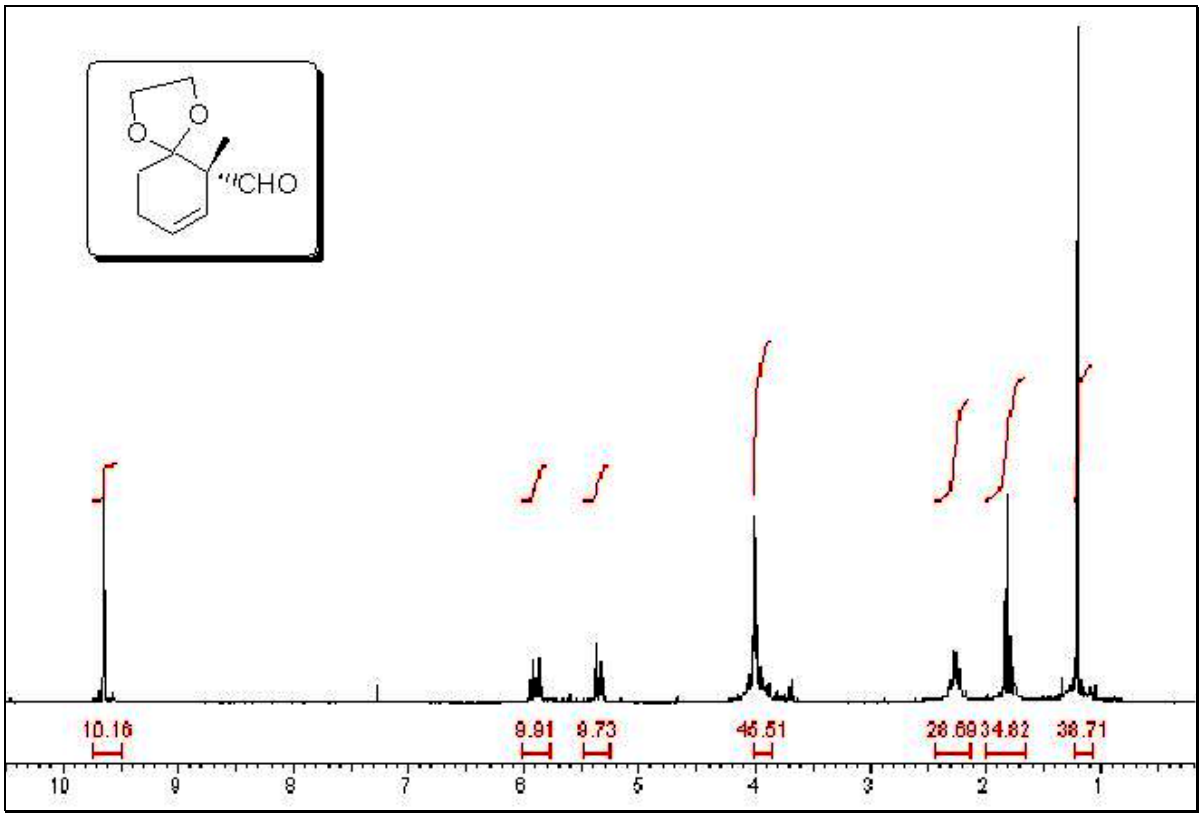


Figure 6. ^{1}H NMR spectrum of (-)-14

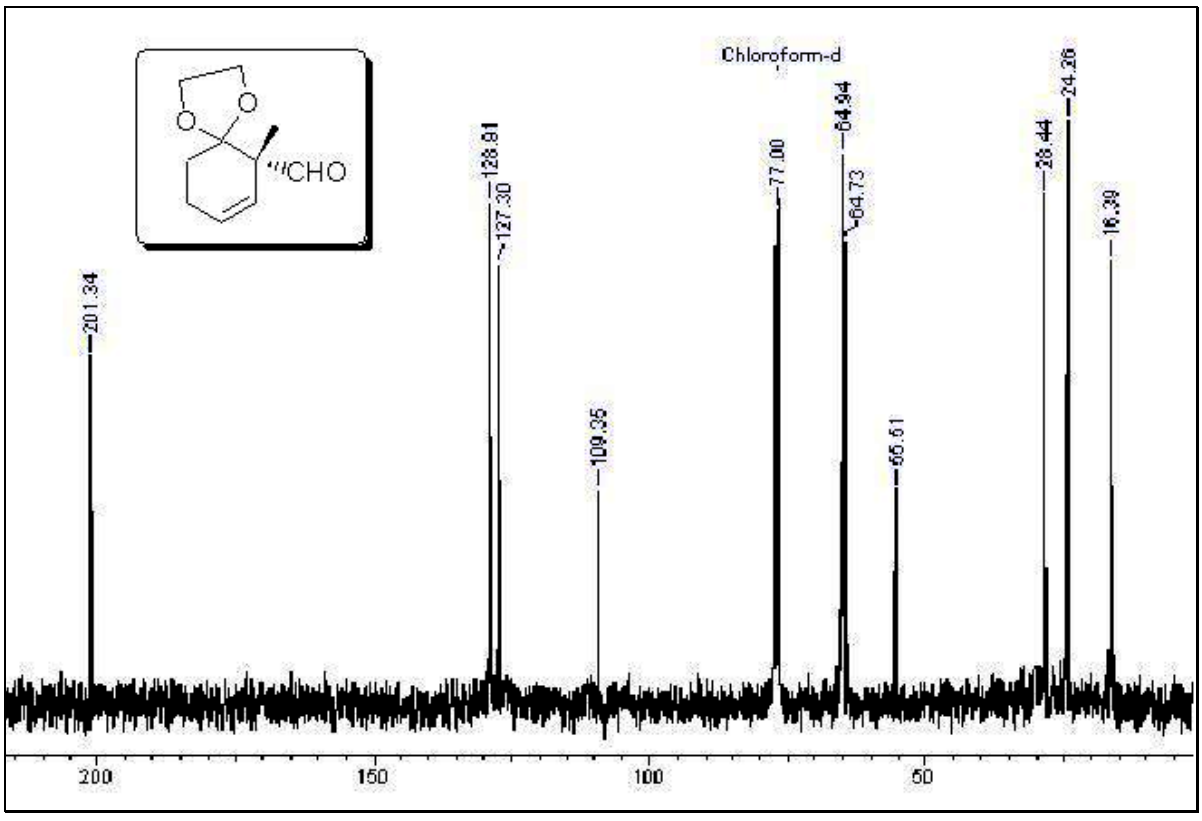


Figure 7. ^{13}C NMR spectrum of (-)-14

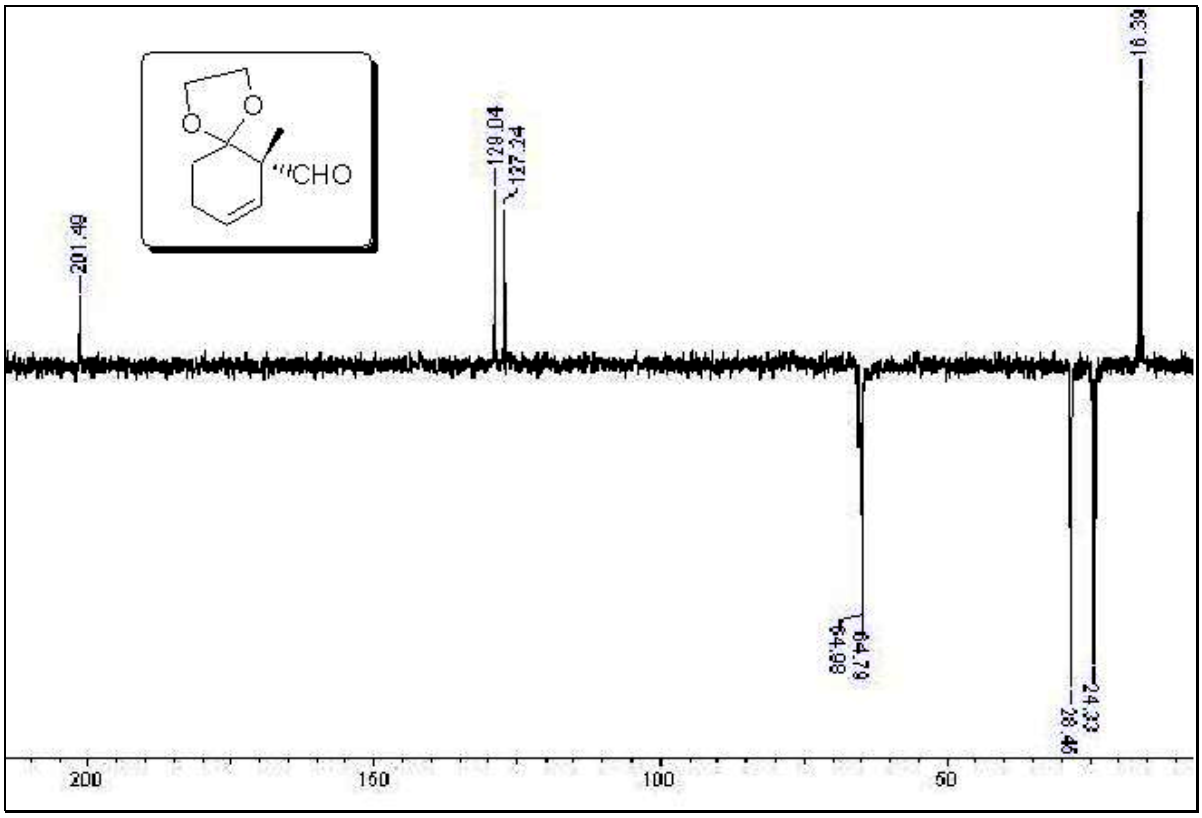


Figure 8. DEPT spectrum of (-)-14

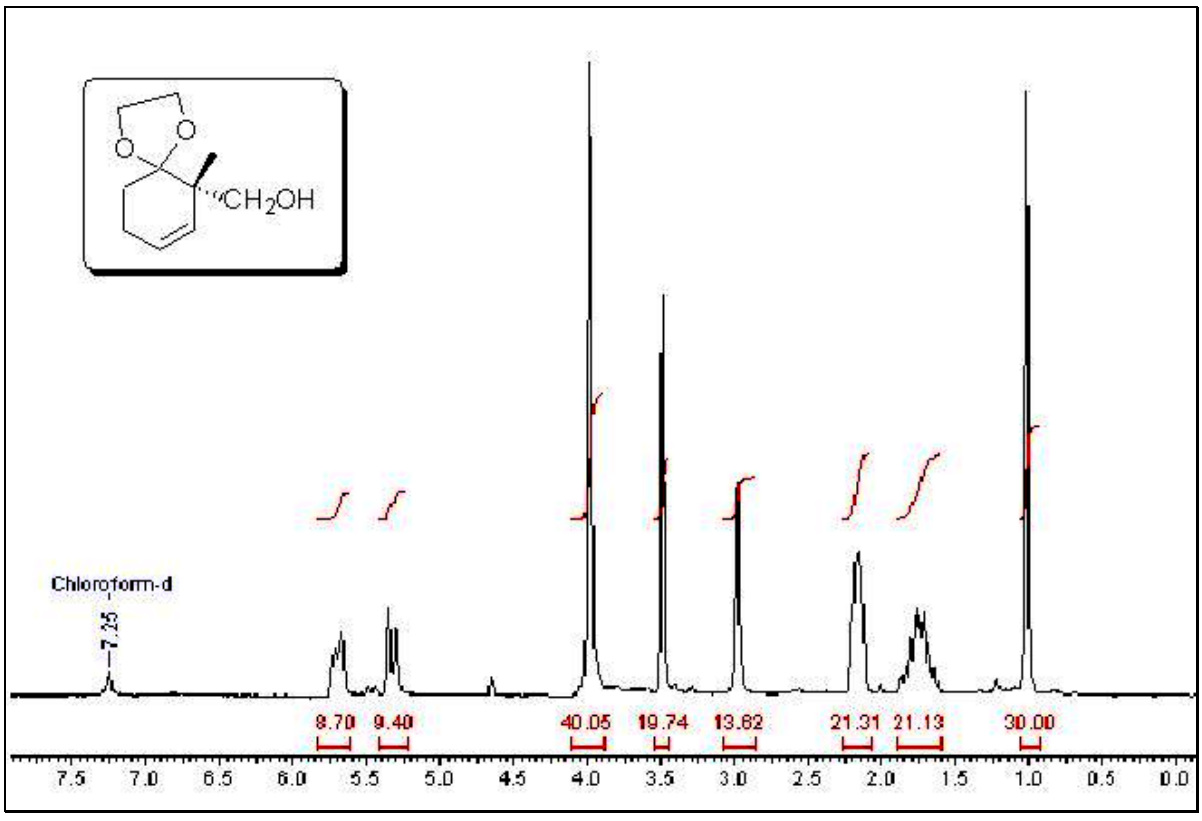


Figure 9. ^{1}H NMR spectrum of (-)-17

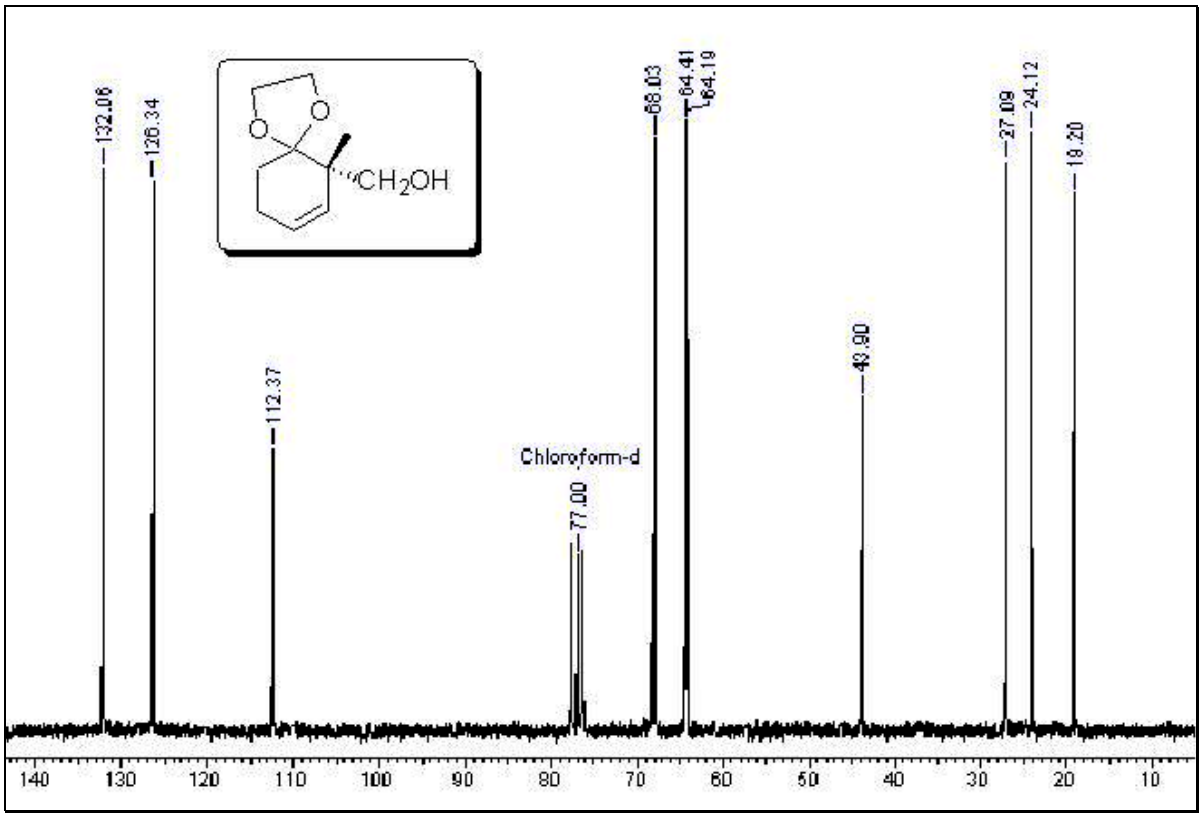


Figure 10. ^{13}C NMR spectrum of (-)-17

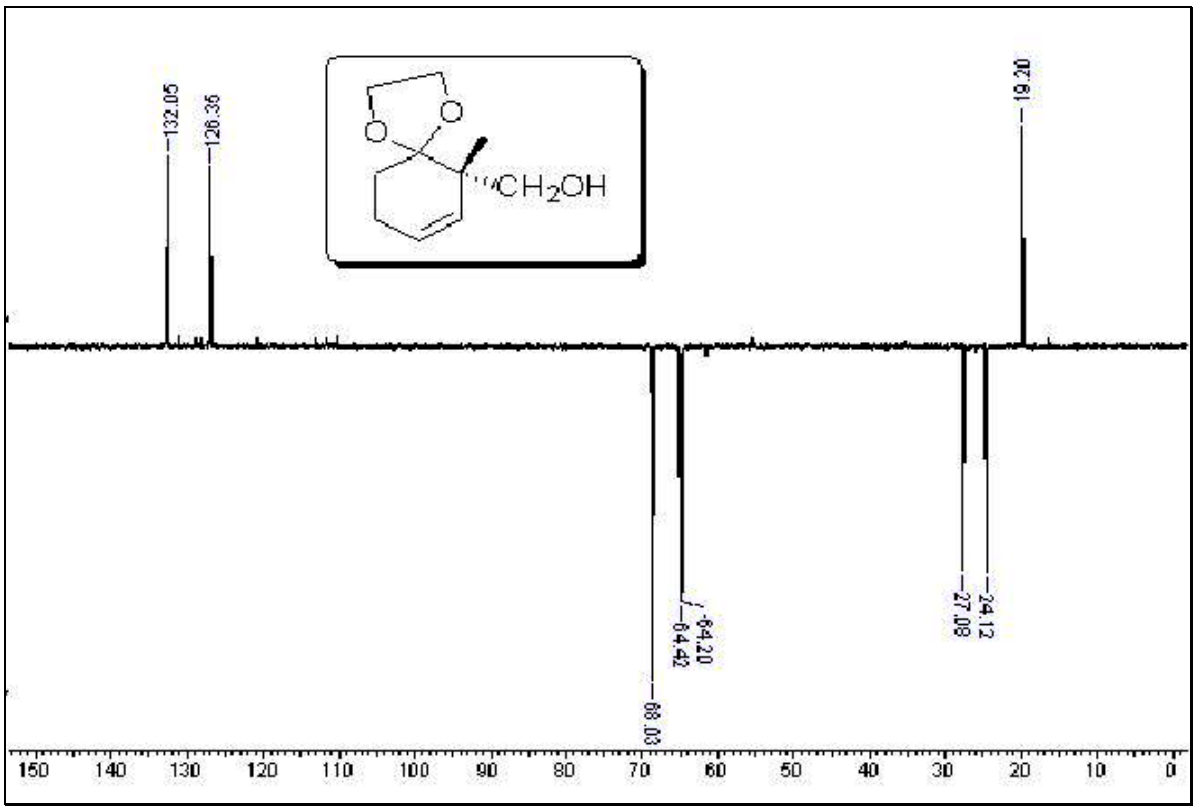


Figure 11. DEPT spectrum of (-)-17

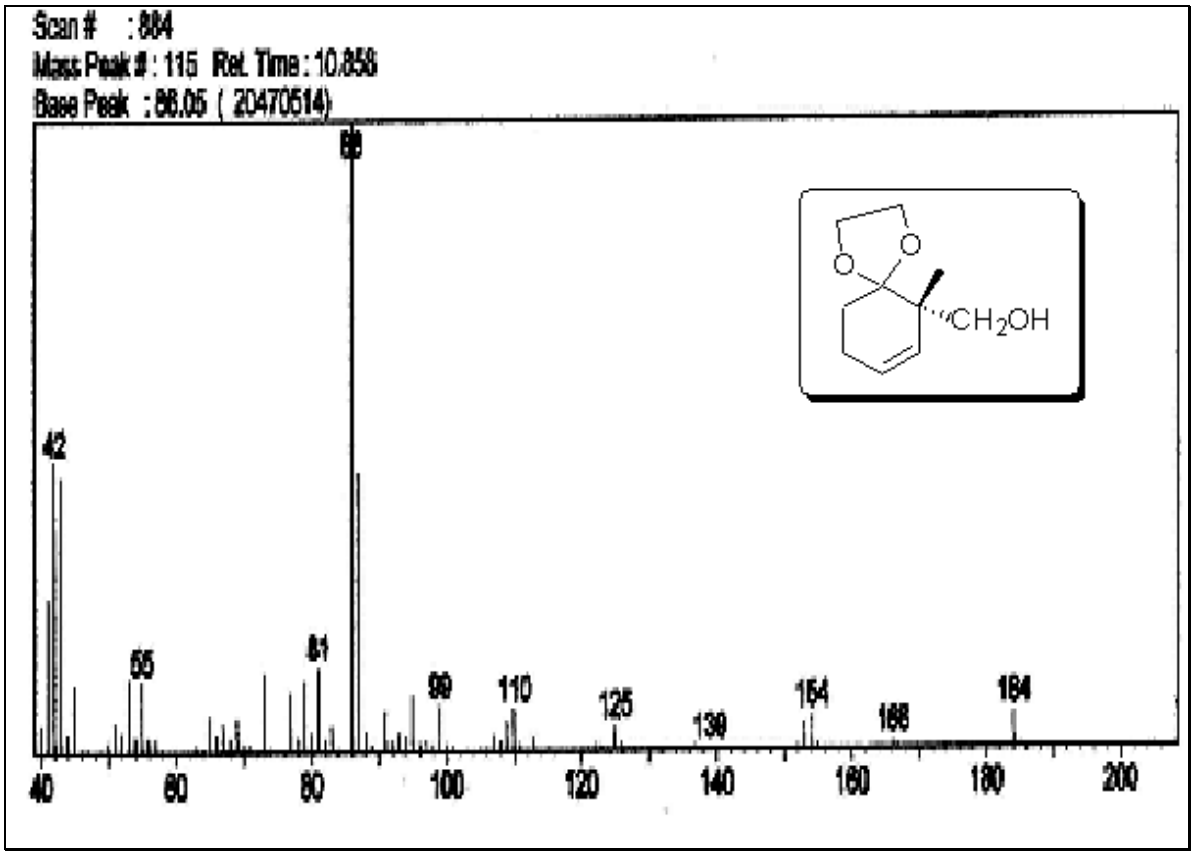


Figure 12. Mass spectrum (GC-MS) of (-)-17

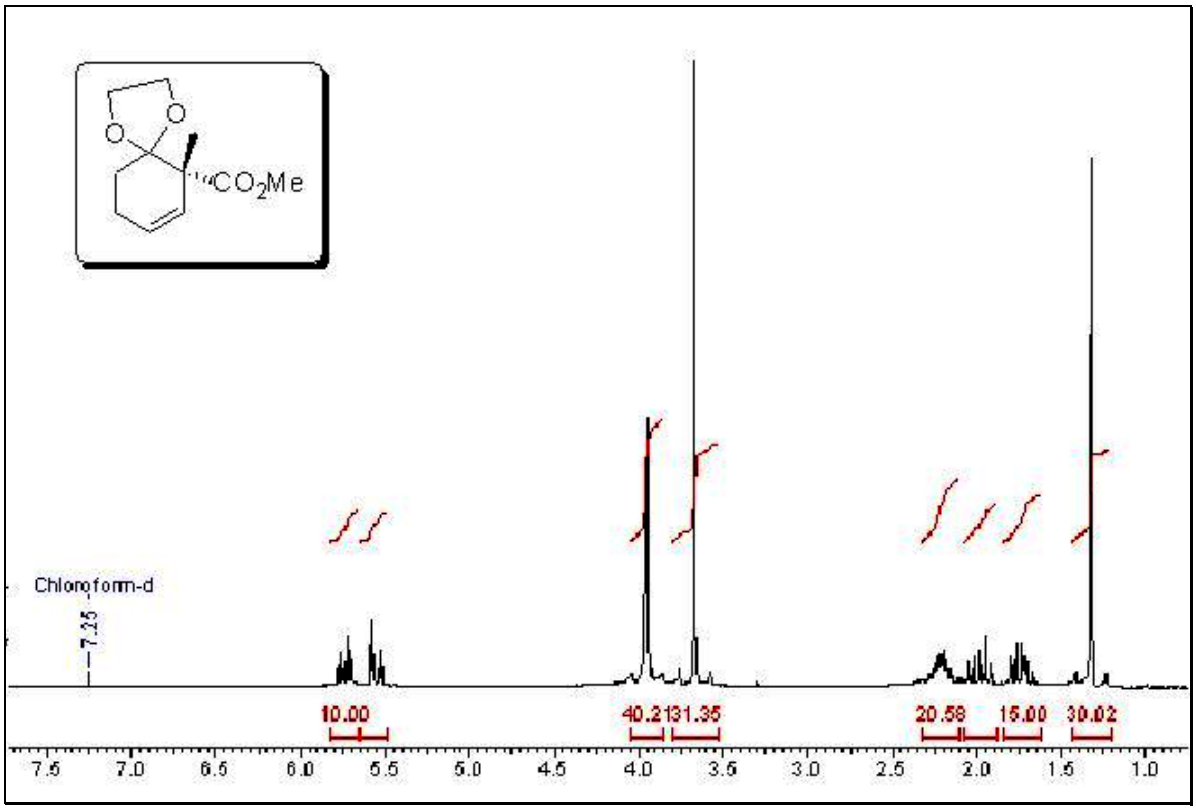


Figure 13. ^{1}H NMR spectrum of (-)-15

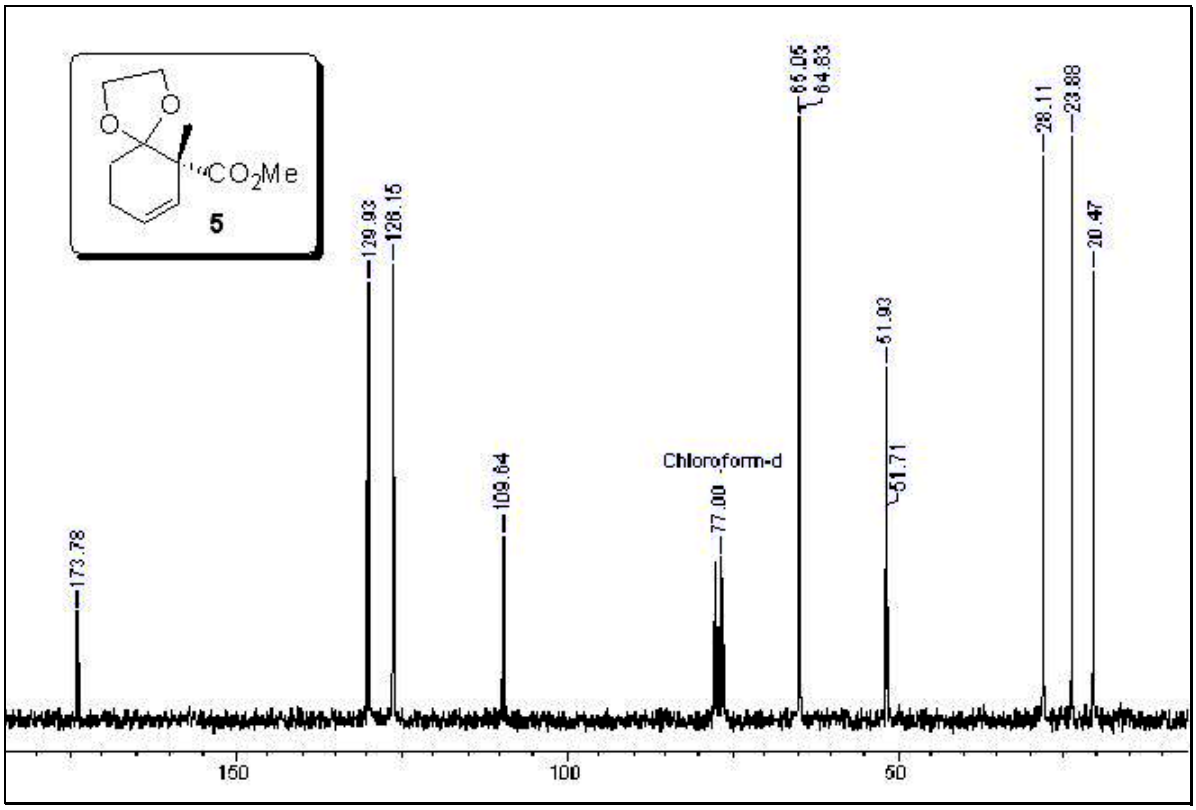


Figure 14. ^{13}C NMR spectrum of (-)-15

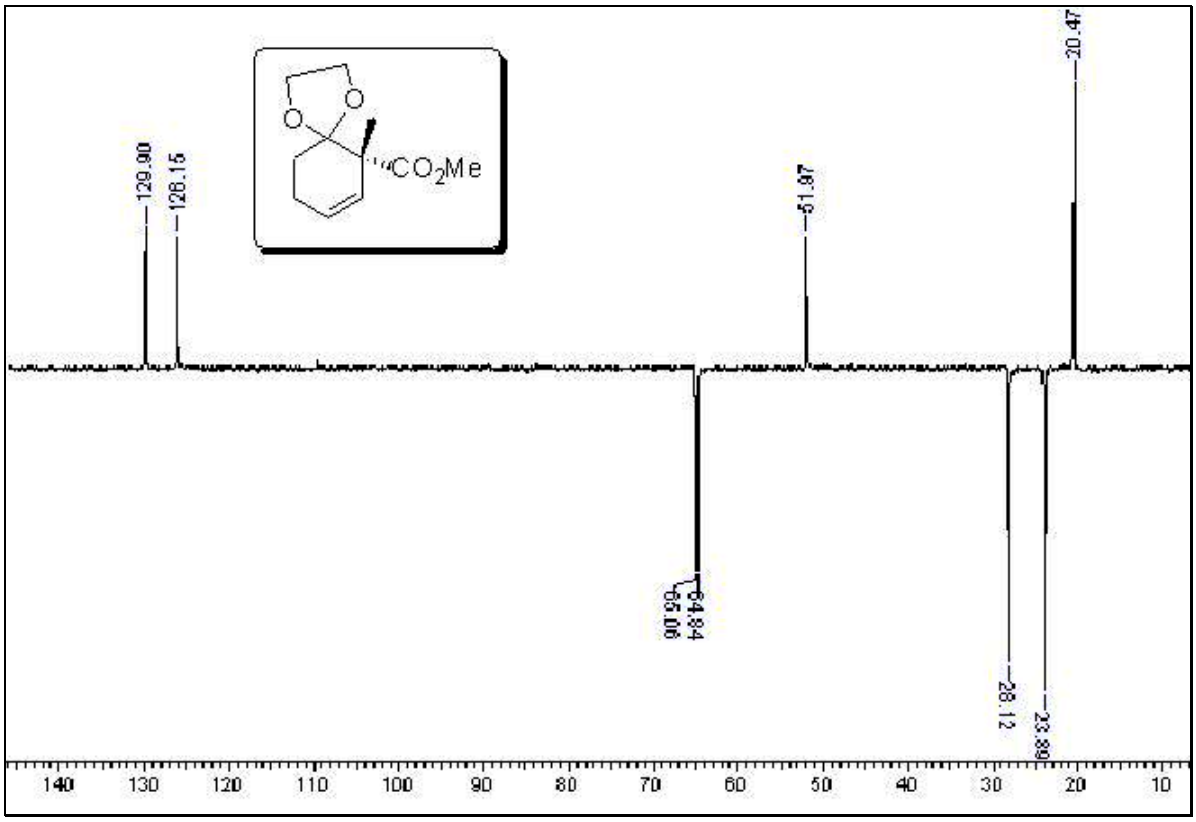


Figure 15. DEPT spectrum of (-)-15

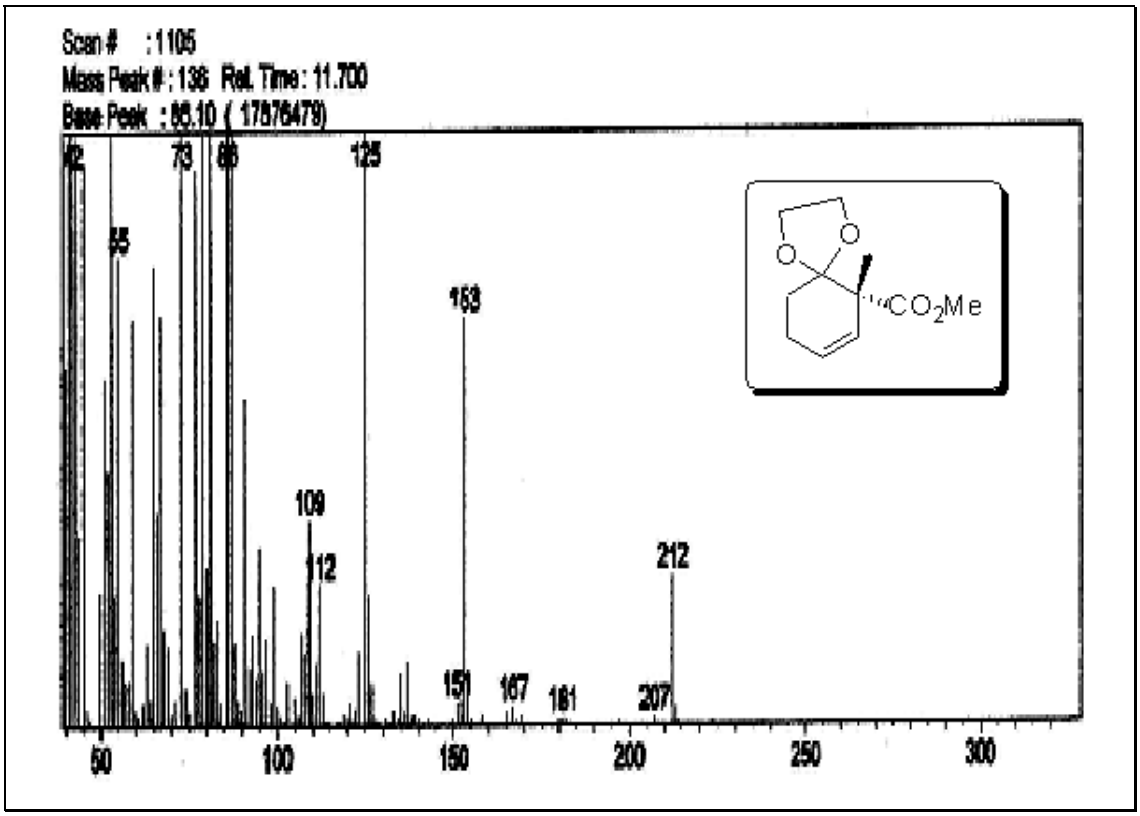


Figure 16. Mass spectrum (GC-MS) of (-)-15

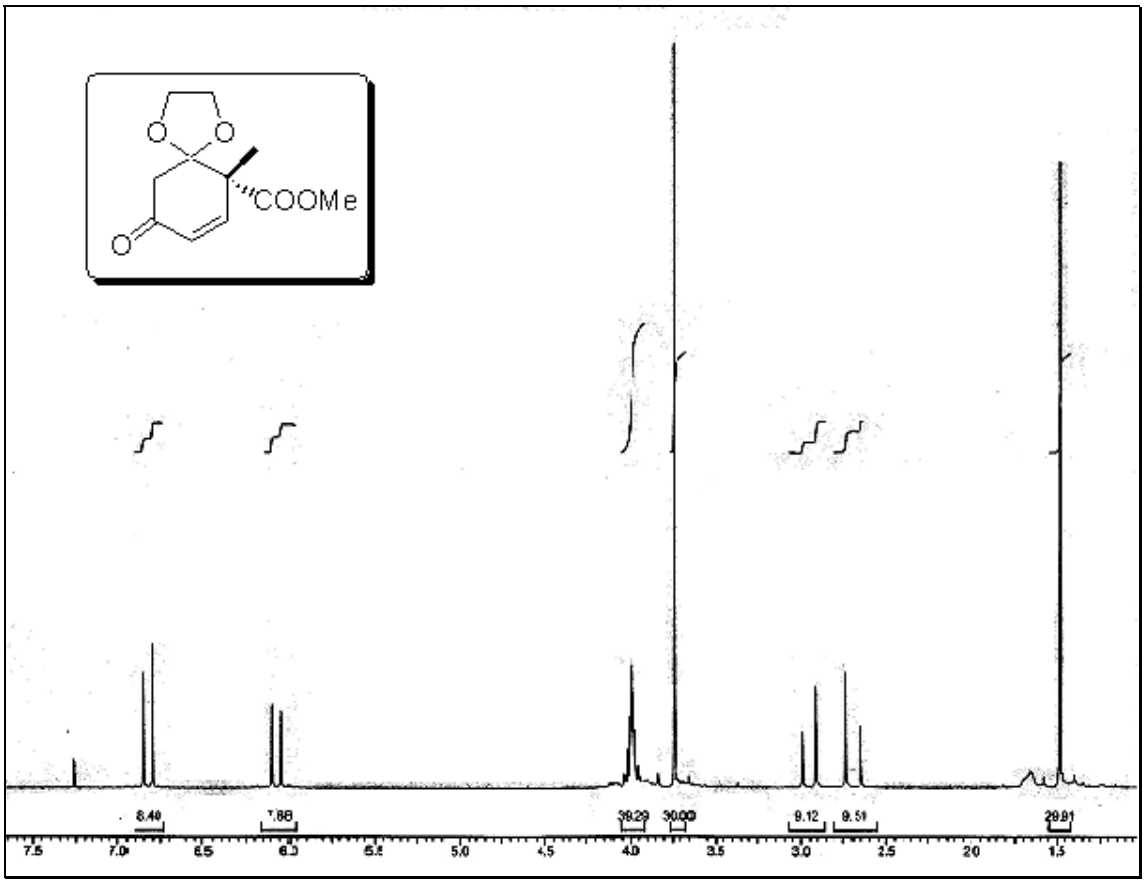


Figure 17. ^{1}H NMR spectrum of (-)-18

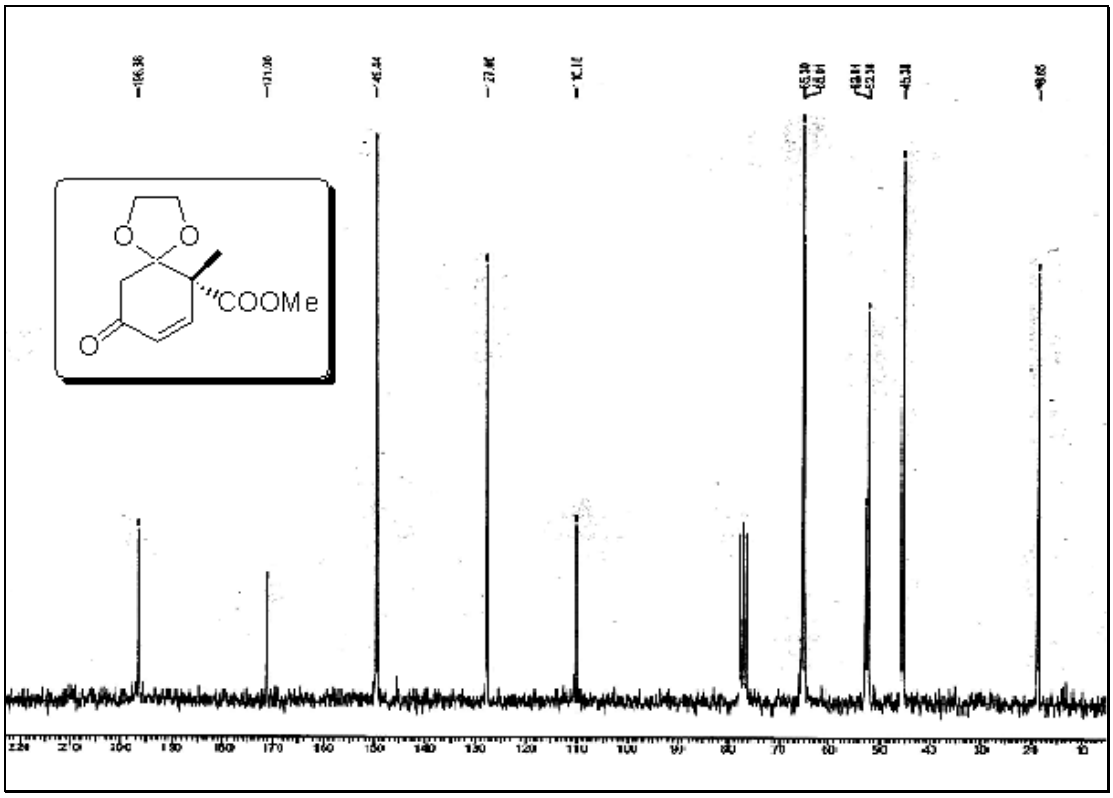


Figure 18. ^{13}C NMR spectrum of (-)-18

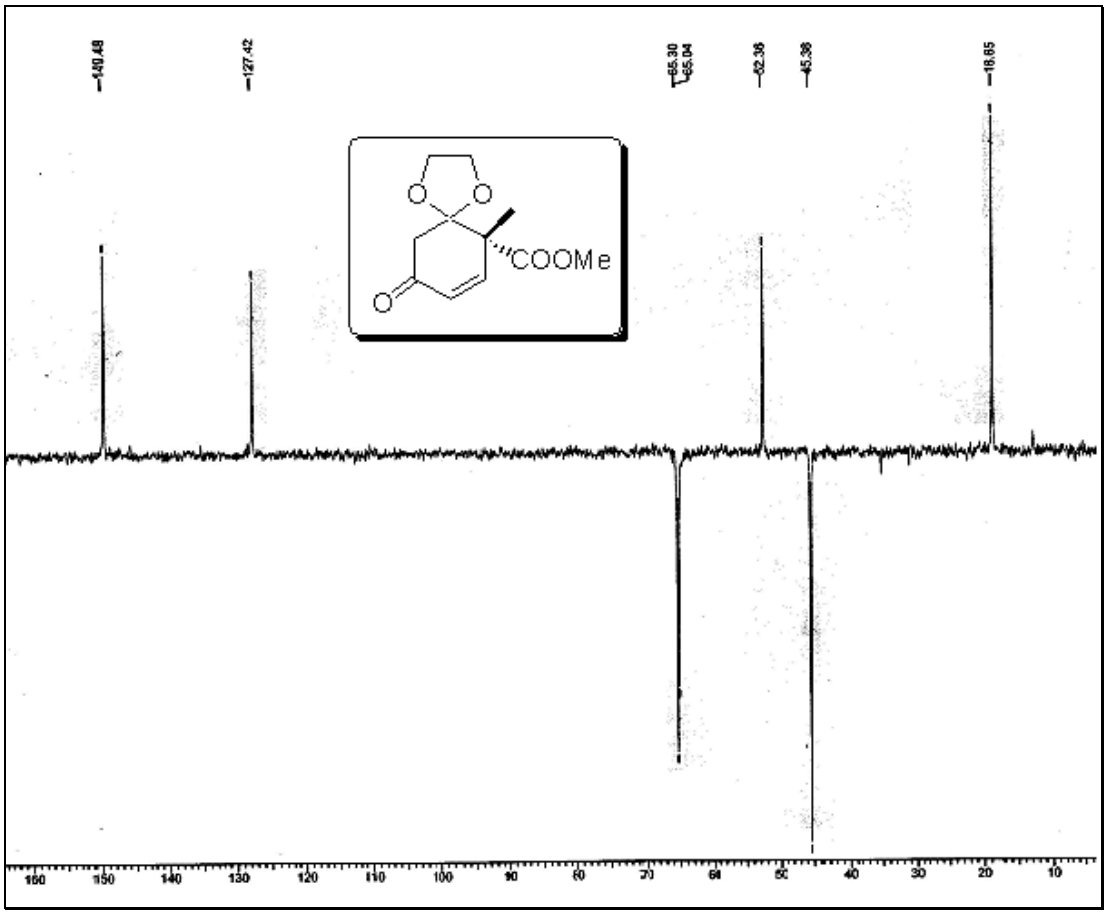


Figure 19. DEPT spectrum of (-)-18

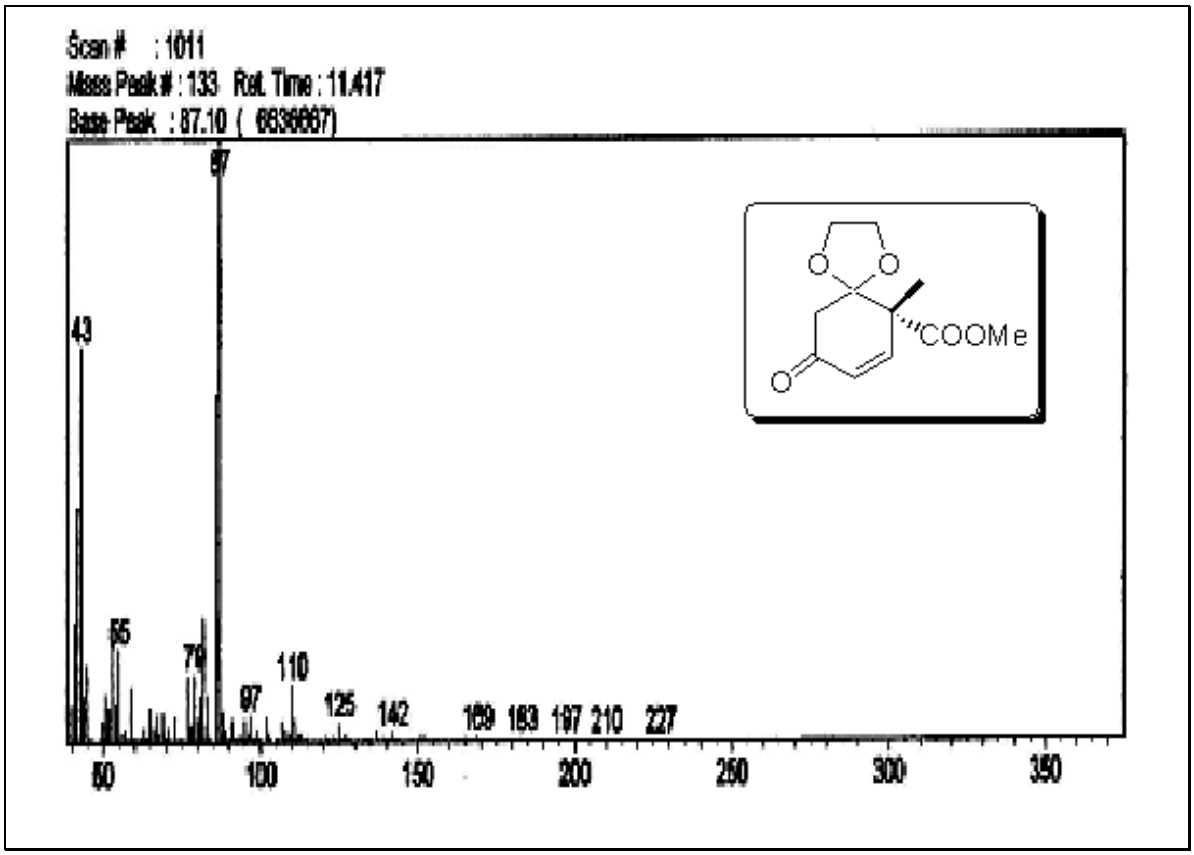


Figure 20. Mass spectrum (GC-MS) of (-)-18

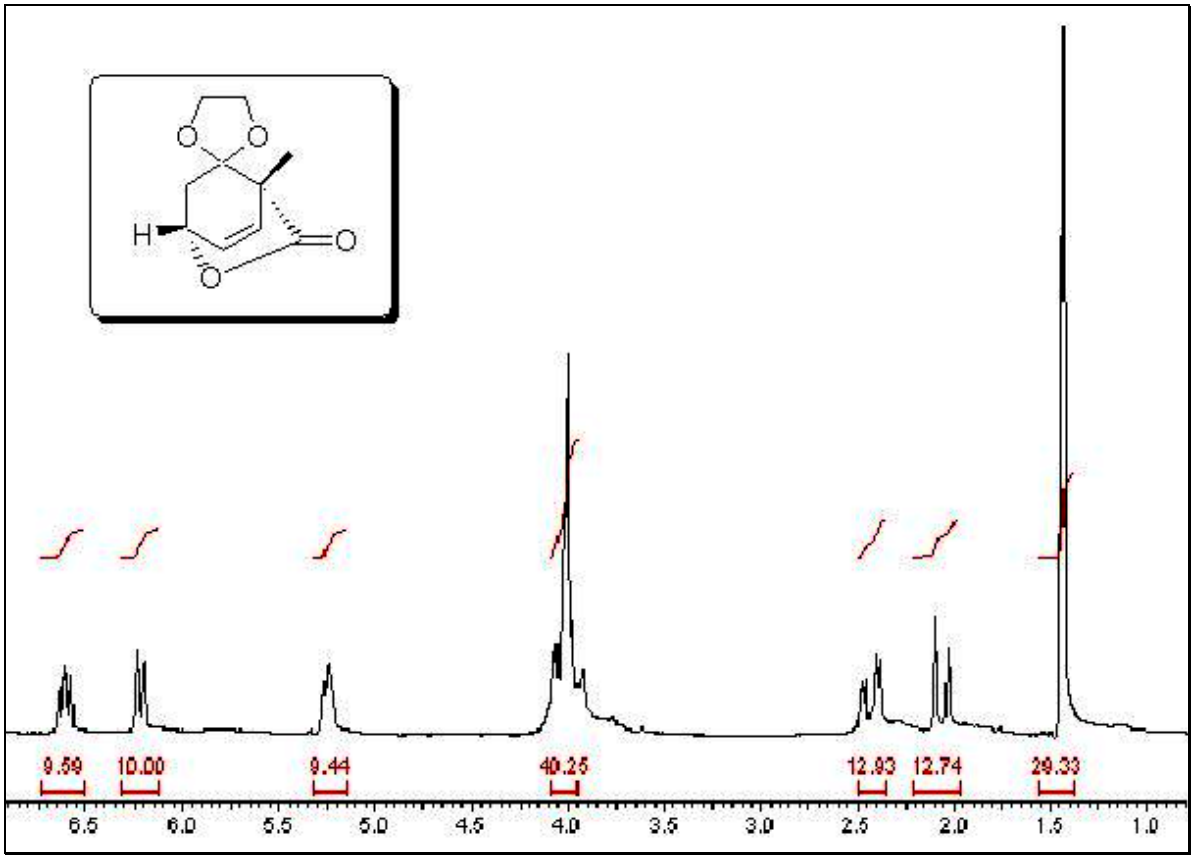


Figure 21. ^{1}H NMR spectrum of (-)-22

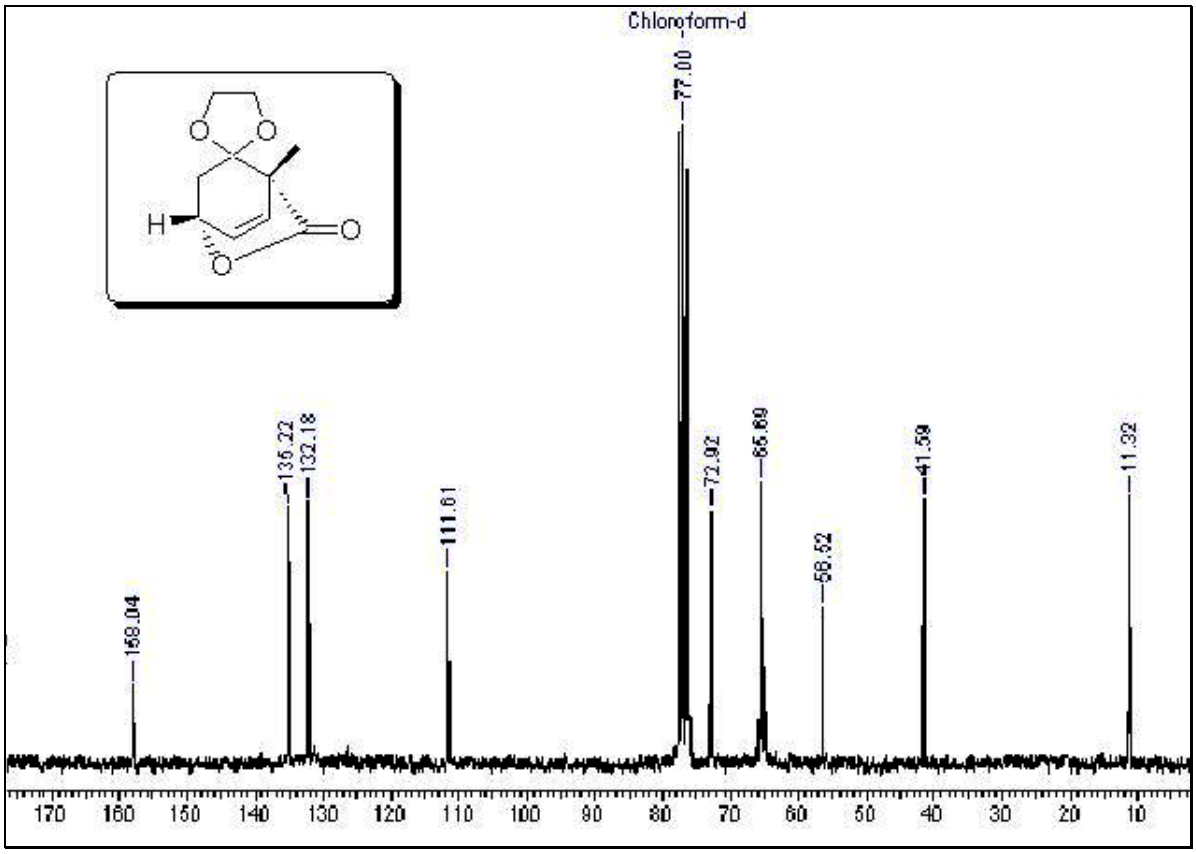


Figure 22. ^{13}CNMR spectrum of (-)-22

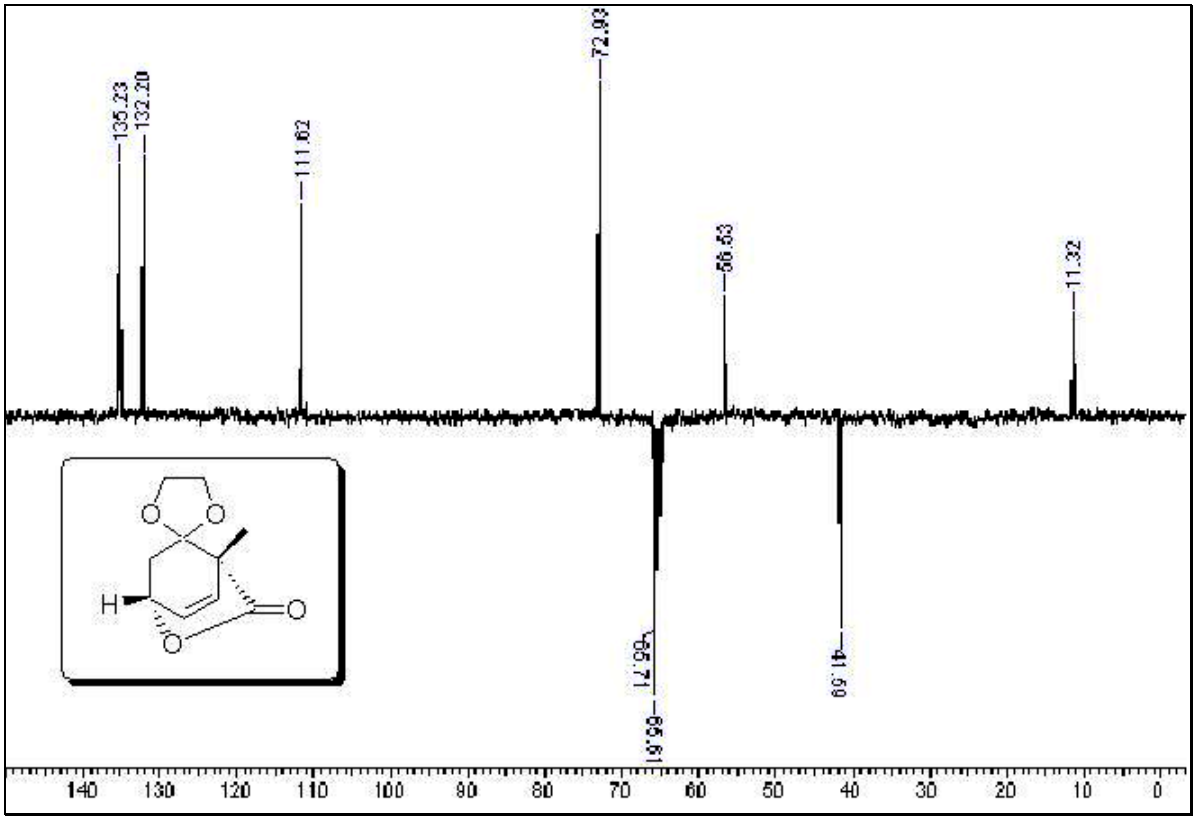


Figure 23. DEPT spectrum of (-)-22

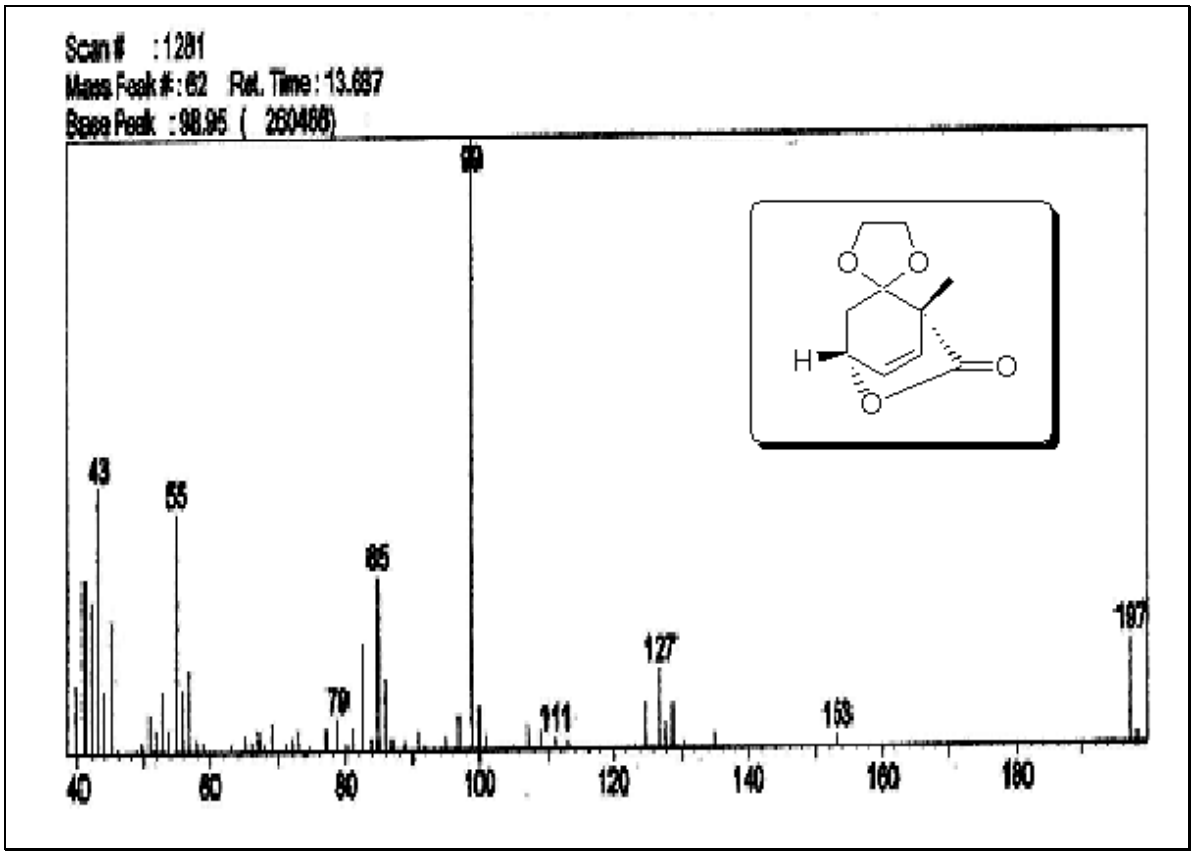


Figure 24. Mass spectrum (GC-MS) of (-)-22

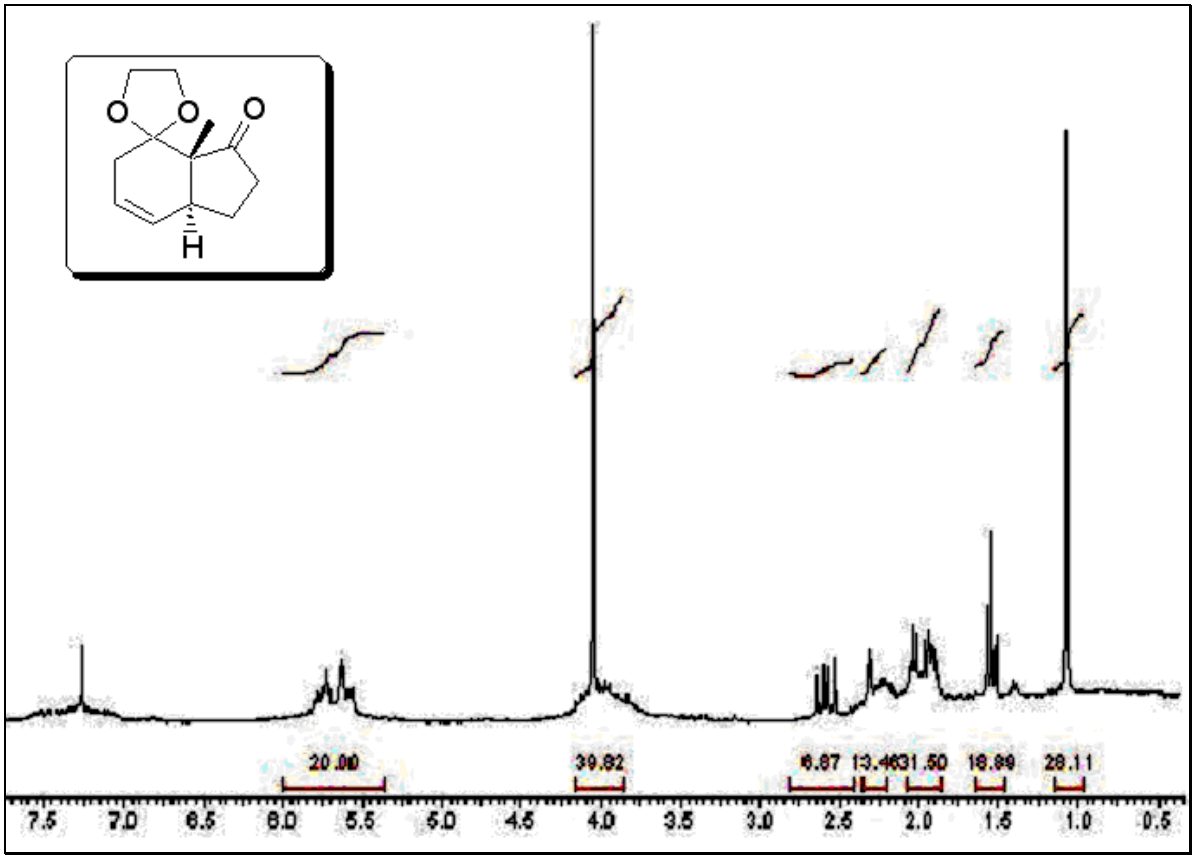


Figure 25. ^{1}H NMR spectrum of (+)-40

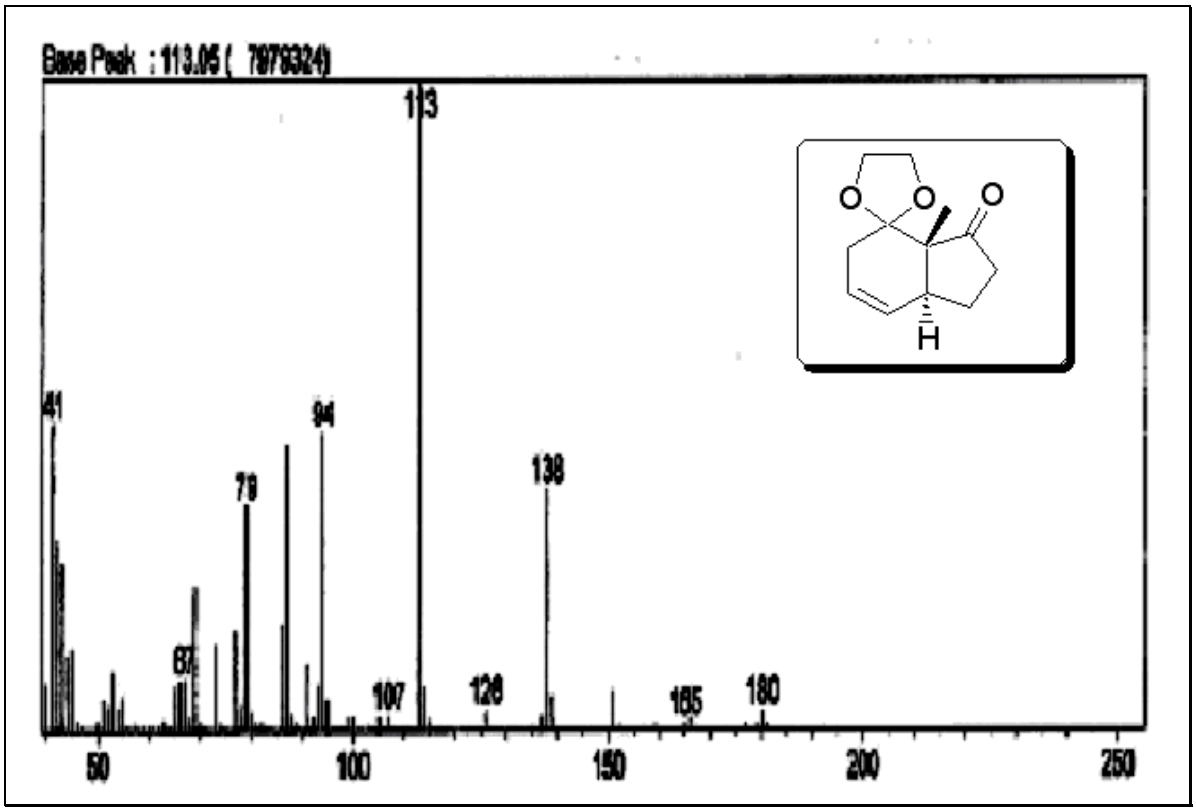


Figure 26. Mass spectrum (GC-MS) of (+)-40

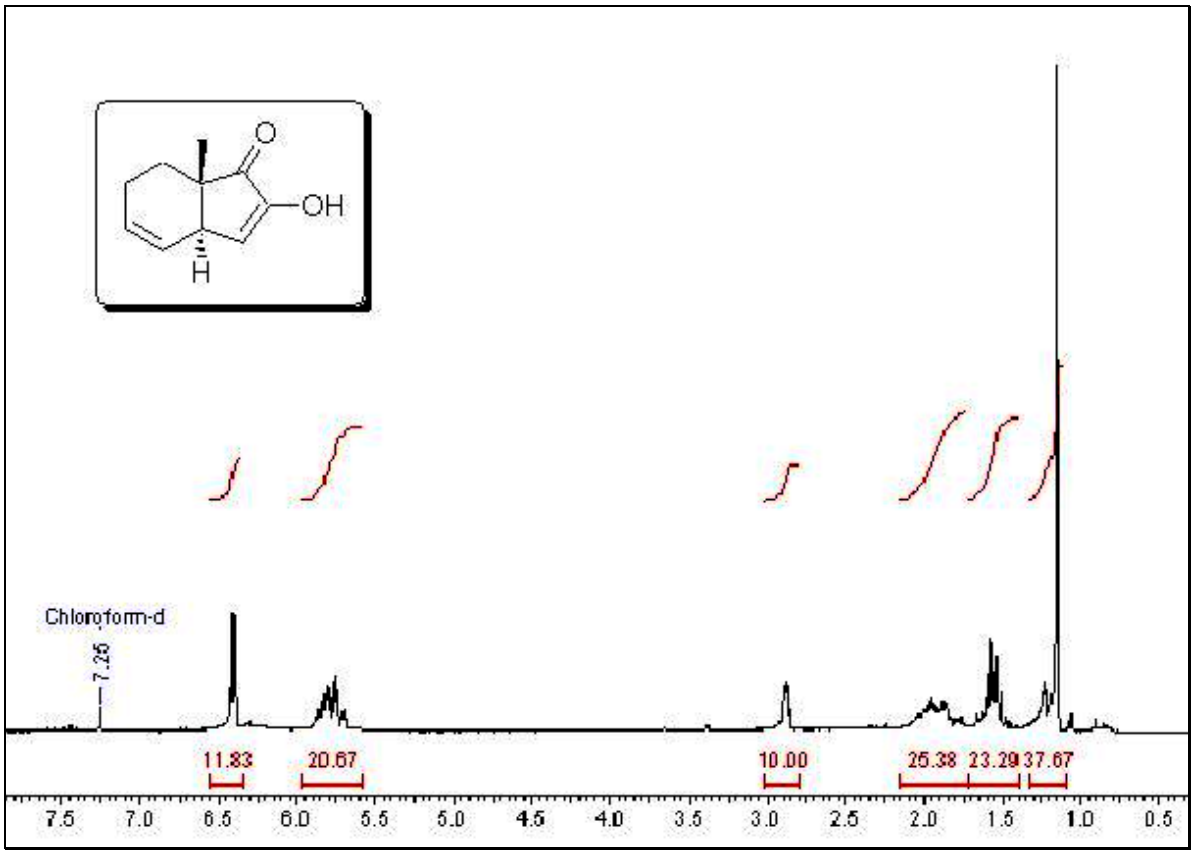


Figure 27. ^{1}H NMR spectrum of (+)-44

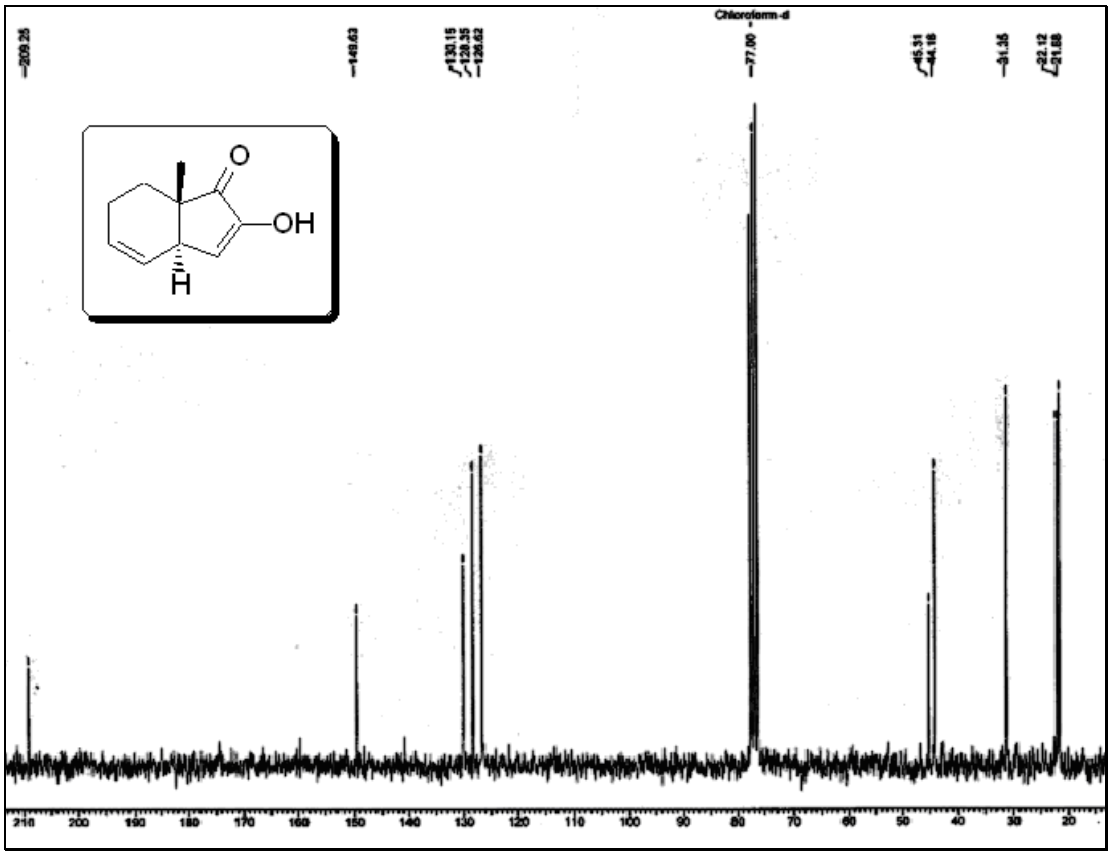


Figure 28. ^{13}C NMR spectrum of (+)-44

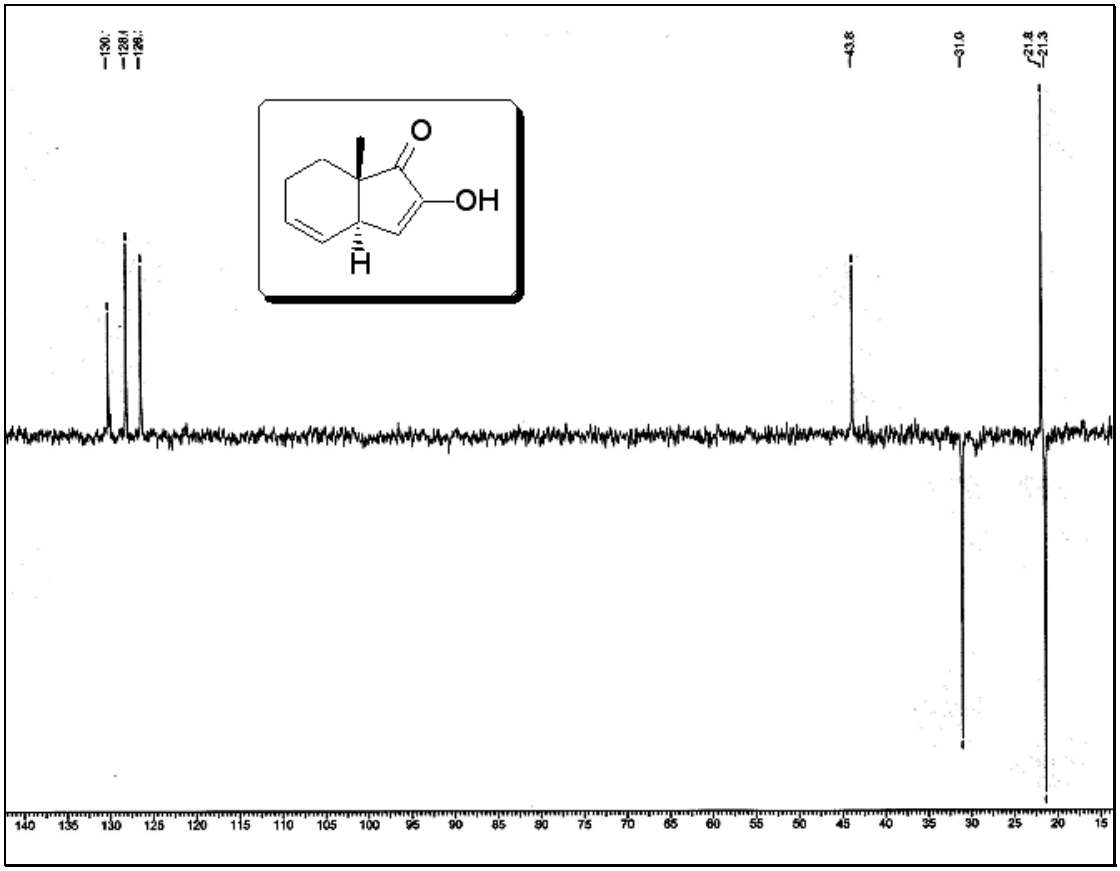


Figure 29 DEPT spectrum of (+)-44

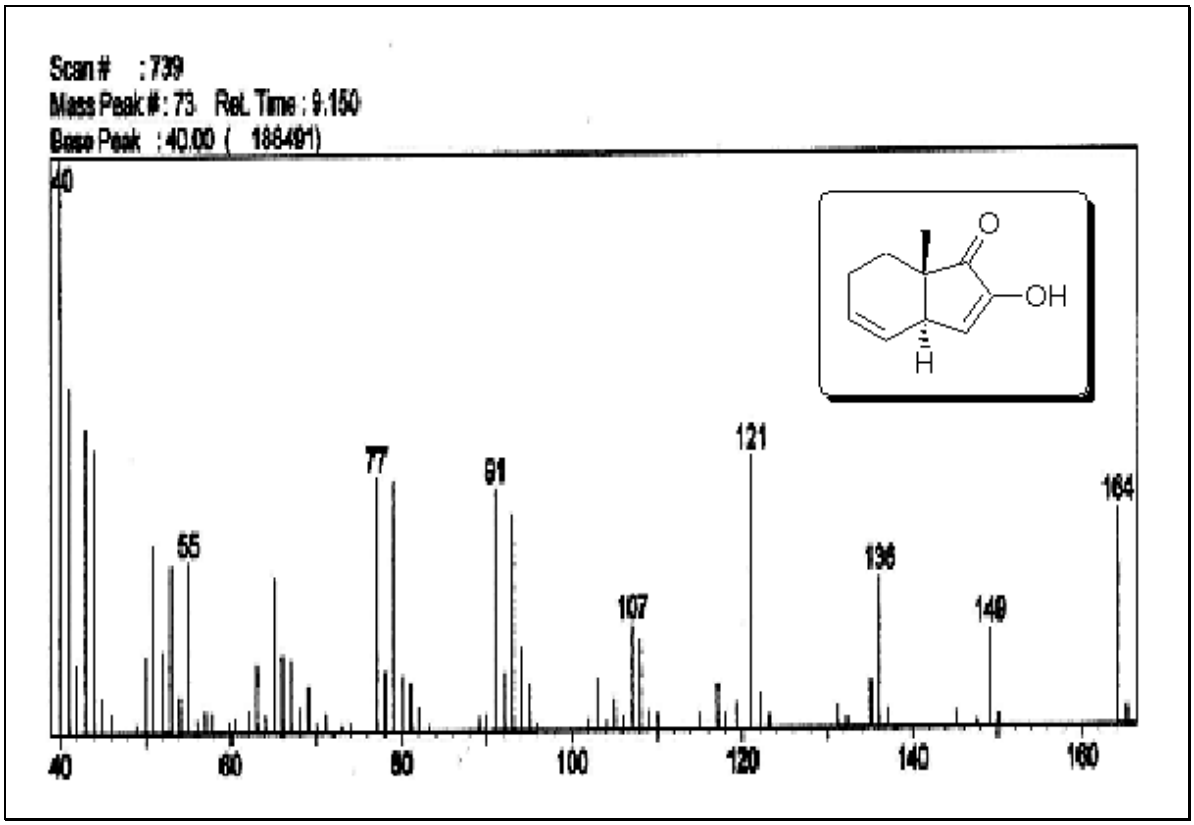


Figure 30. Mass spectrum (GC-MS) of (+)-44

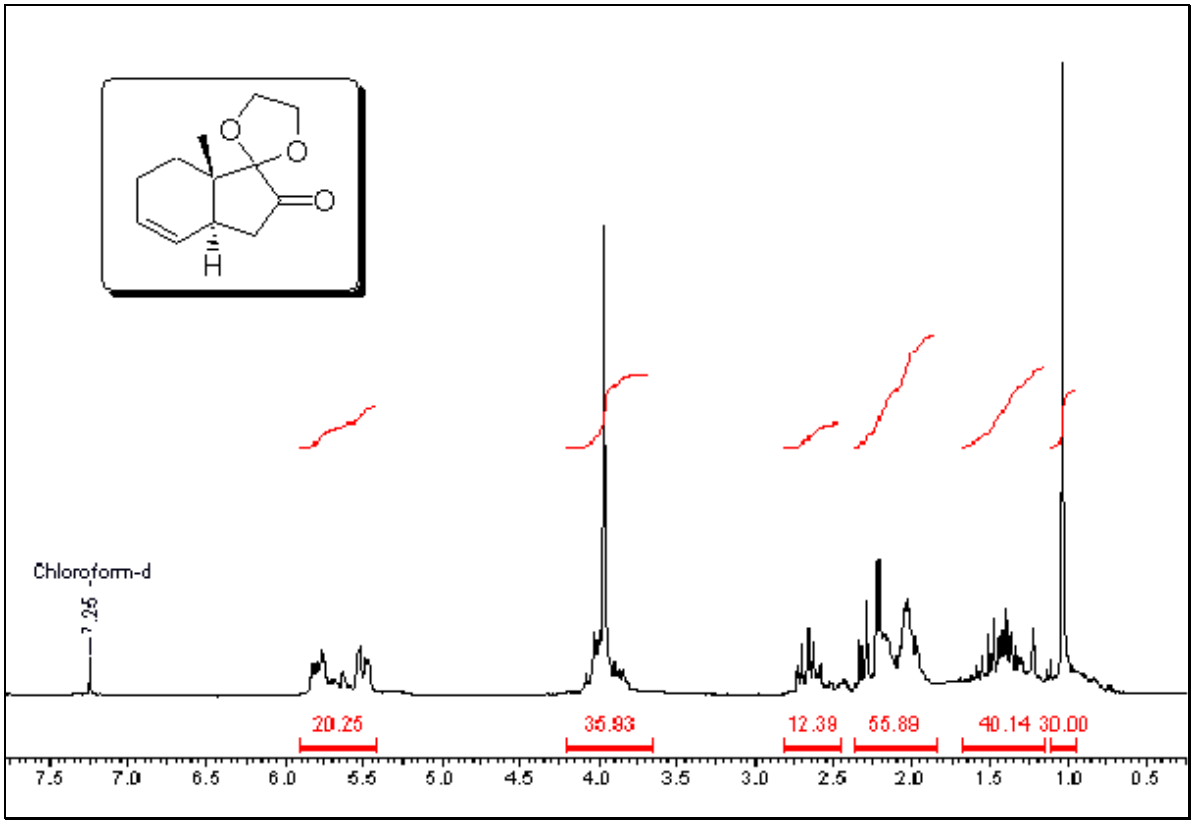


Figure 31. ^{1}H NMR spectrum of (+)-45

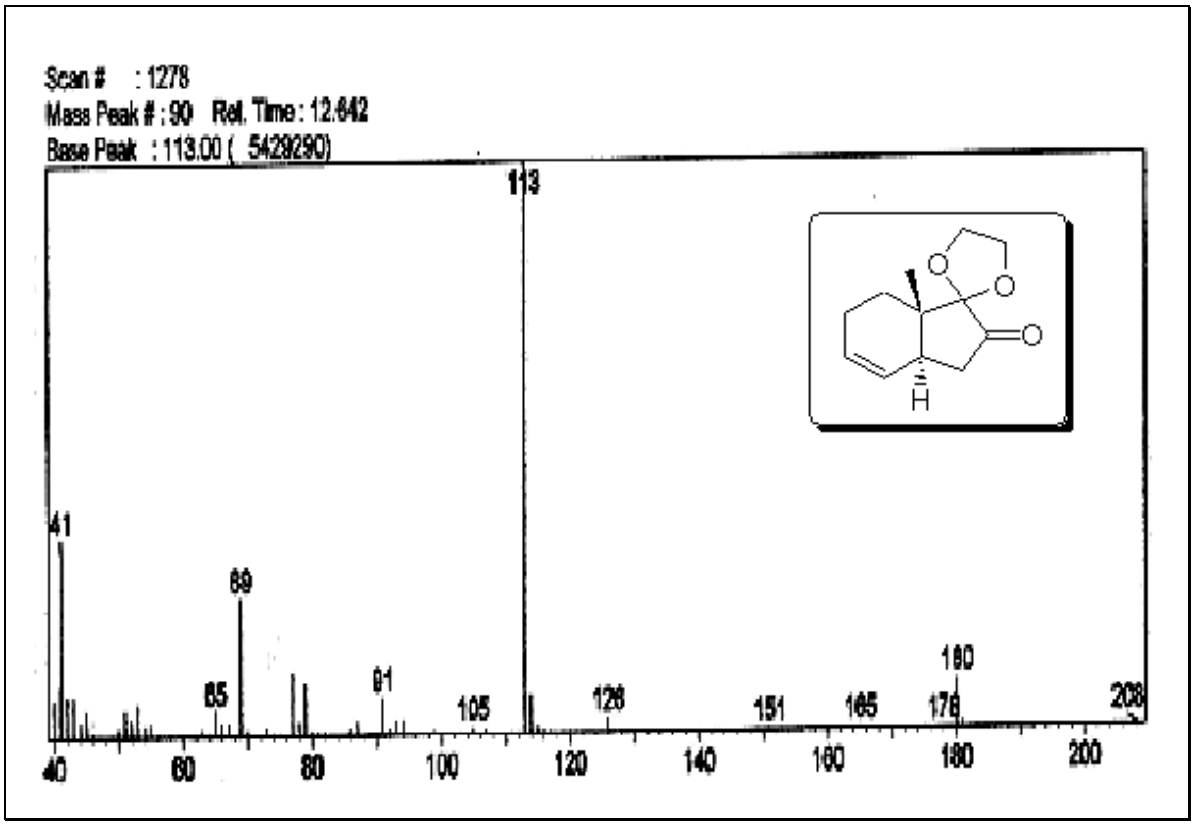


Figure 32. Mass spectrum (GC-MS) of (+)-45

1. Introduction

A highly substituted cyclohexyl moiety constitutes the A-ring of calcitriol. As discussed earlier, the significant biological activities of 1,25-D_3 have given rise to immense synthetic activities focusing on the synthesis of 1,25-D_3 and its analogues. Since the convergent synthesis utilizing coupling of the CD-rings fragment with the A-ring unit has proved to be of great practical significance in producing the parent molecule as well as the therapeutically valuable analogues; the synthesis of individual fragments have aroused intense research interest from the synthetic organic chemists. The A-ring fragment of 1,25-D_3 constitutes an attractive synthetic target due to its highly functionalized nature. The presence of two asymmetric centers along with the typically positioned olefin function makes the synthesis of this moiety particularly challenging. The various protocols developed over the years for the coupling of CD-rings fragment with the A-ring have given rise to various precursors that can be used as A-ring synthons. Some of the common A-ring precursors have been summarized in Figure 1.

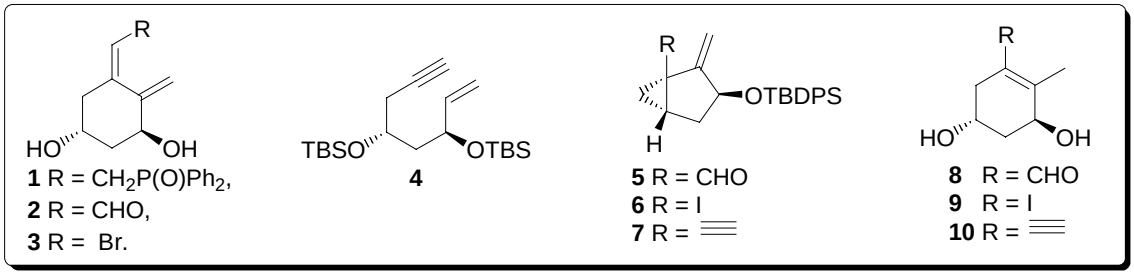


Figure 1. A-ring Synthons

In order to put our efforts towards developing a versatile approach towards the synthesis of A-ring synthons of 1,25-D_3 and analogues, in proper perspective, it would be appropriate to have a birds eye view of the methods reported in the literature in this domain.* The known synthetic approaches for the A-ring synthons can be broadly grouped under two categories based on the origin of the starting material:

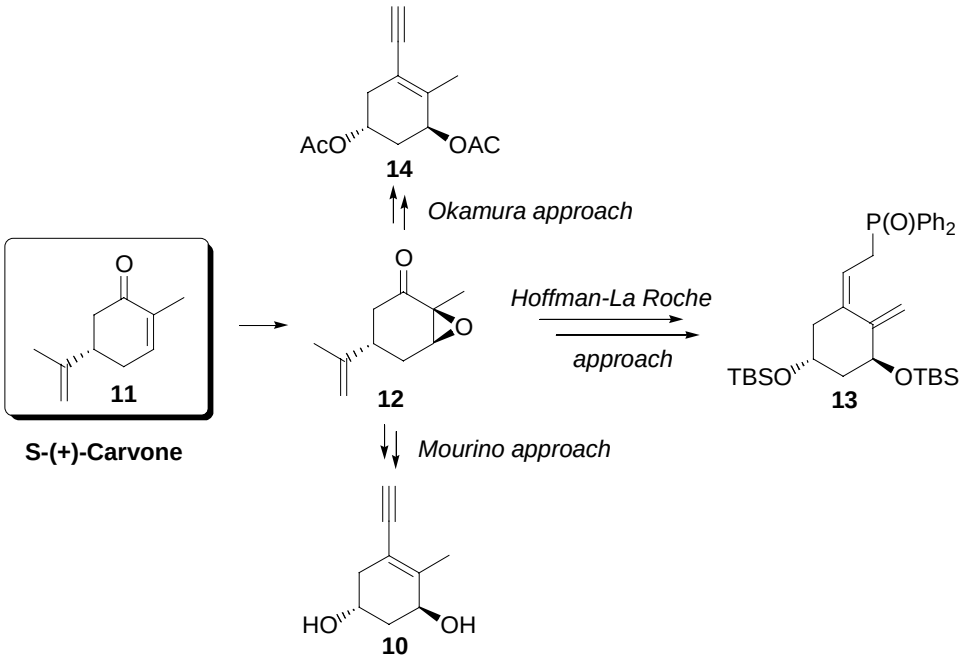
I. Chiral pool approach
II. Synthetic chiral precursor approach

* Racemic approaches as well as recently developed approaches for modified A-ring systems have been excluded

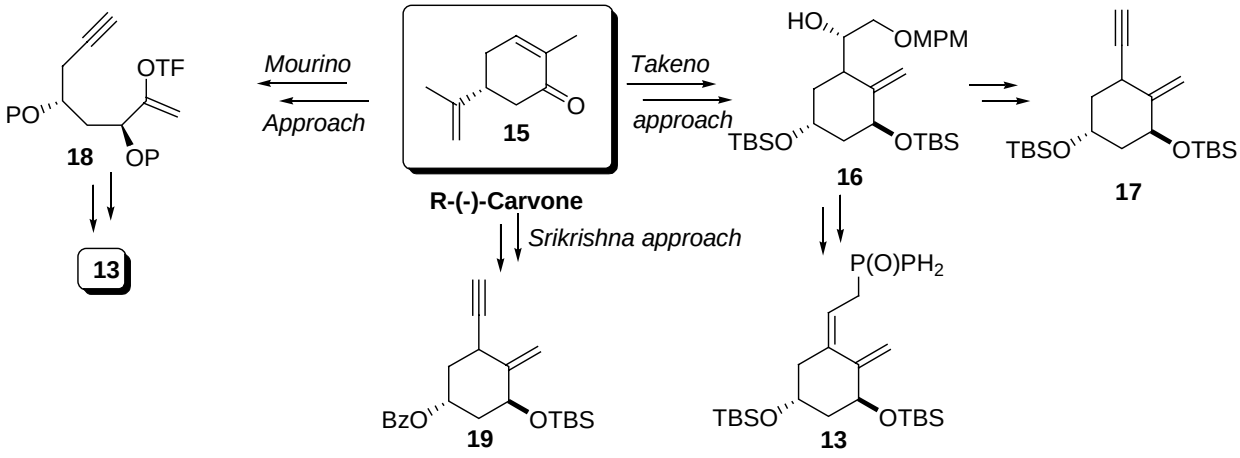
1.1 Chiral pool approach:

1.1.1 The Carvone approach

Scheme 1. Approaches utilizing S-(+)-Carvone[1]

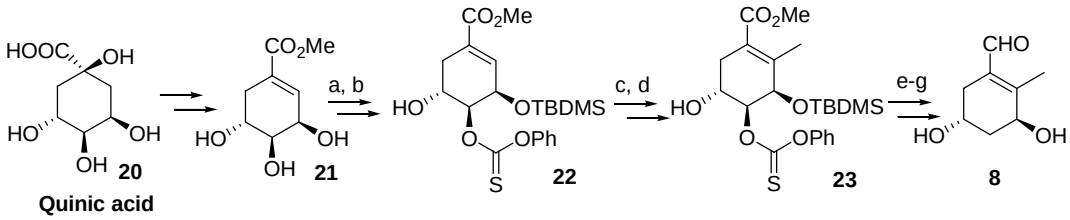


Scheme 2. Approaches utilizing R-(-)-Carvone[2]



1.1.2 The Desmaele quinic acid approach (Tetrahedron Lett. 1985, 4941.)[3]

Scheme 3



Reagents and conditions: a) TBDMSCl, Et_3N, DMAP, 0 ℃. b) PhOC(S)Cl, DMAP, CH_3CN, 20 ℃. c) CH_2N_2, Et_2O, 20 ℃. d) DMSO, 125 ℃. e) DIBAH, toluene –78 ℃ to –30 ℃. f) $^nBu_3SnH$, AIBN, toluene, 100 ℃. g) MnO_2, hexane, 20 ℃.

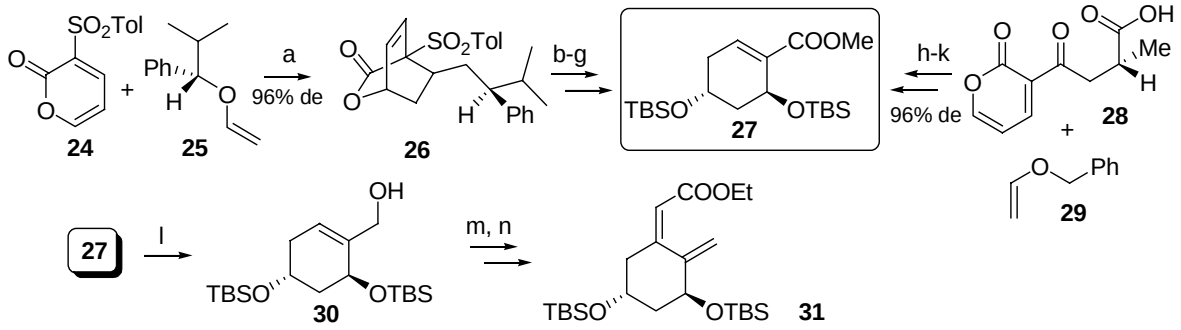
1.2 Synthetic chiral precursor approach

Advancements in developing chiral versions of the existing reactions and commercial availability of optically active compounds have proved to be a useful alternative to the use of optically active natural products and derivatives as starting material. A number of such protocols have been used for the synthesis of chiral precursors, some of which have found application in the synthesis of A-ring synthon of 1,25-D_3. Resolution of racemic material via chiral derivatives is also used to prepare chiral materials, although it can give only up to 50% of the desired isomer. Based on this, approaches in this category are classified into four groups as discussed below:

1.2.1 Precursor synthesized using chiral auxiliary

a) The Posner approach (i. J. Org. Chem. 1991, 56, 6981. ii. J. Org. Chem. 1992, 57, 7012.)[4]

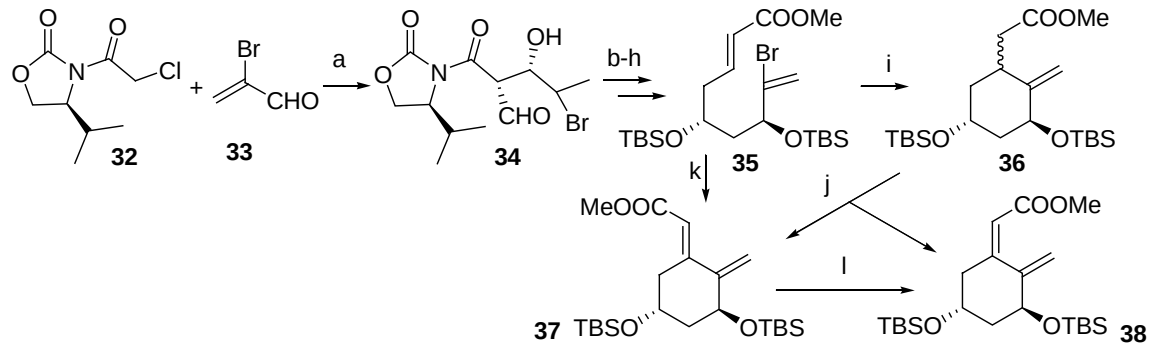
Scheme 4



Reagents and conditions: a) MAD, $PhCH_3$, -40 ℃, 93%, 96% de. b) NaOMe, MeOH-CH_2Cl_2 (6:1 v/v), -78 ℃ to 0 ℃. c) Al(Hg), THF-H_2O, 110 ℃. d) DBU, THF, 0 ℃. e) CF_3COOH, CH_2Cl_2, 0 ℃. f) MeOH, 25 ℃. g) TBDMSCl, imidazole, DMF, 25 ℃. h) (-)-$Pr(hfc)_3$, CH_2=$CHOCH_2Ph$, $PhCH_3$-Et_2O (2.5:1), -20 ℃, 98%, 96% de. i) LiOMe, 100%. j) NMM, CH_3CN-H_2O, 25 ℃. k) $PdCl_2(CH_2CN)_2$, EtOAc-EtOH (1:1), 25 ℃. l) DIBAH, toluene, -78 ℃, 94%. m) $PhS(O)CH_2C(OEt)_3$, H^+, 100 ℃. n) hν, 9-fluorenone, 89%.

b) The Crich approach (J. Chem. Soc., Perkin Trans. I 1991, 2894.)[5]

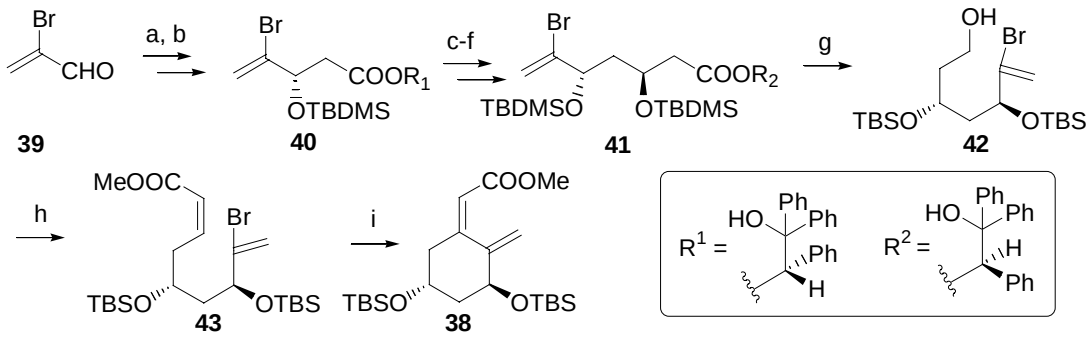
Scheme 5



Reagents and conditions: a) i. Bu_2BOTf, Et_2N^iPr, CH_2Cl_2, -78 °C. ii. aq. H_2O_2. b) Zn, NH_4Cl, MeOH, 96%. c) LiOH, H_2O_2, THF-H_2O (4:1). d) Carbonyl diimidazole (CDI), THF, then $Mg(O_2CCH_2CO_2Et)_2$, 82%. e) $Me_4N(AcO)_3BH$, MeCN, AcOH, -40 °C. f) TBDMS-OTf, py, CH_2Cl_2, 0 °C. g) DIBAH, CH_2Cl_2, -78 °C. h) Ph_3PCHCO_2Et, PhH, rt. i) $^nBu_3SnH$, AIBN, PhH, Δ. j) i. LDA, THF, -78 °C, then PhSeCl in THF, -78 °C to rt, 52%. ii. MMPP, THF, rt, 100%. k) $(Ph_3P)_4Pd$, K_2CO_3, MeCN, Δ, 92%. l) hν, fluorenone.

c) The Shimizu approach (Tetrahedron Lett. 1991, 4937.)[6]

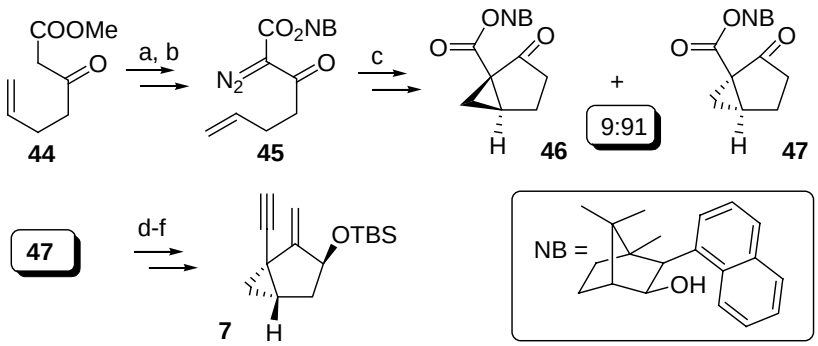
Scheme 6



Reagents and conditions: a) AcO-(-)-R^1, LDA, $MgBr_2$. b) i. TBDMSCl, imidazole, DMF. ii. recrystallization from MeOH-CH_2Cl_2, 57% overall. c) DIBAH, Et_2O, 0 °C. d) PCC, 3A-MS, 84%. e) AcO(+)-R^2, LDA, $MgBr_2$, 85%. f) TBDMSCl, imidazole, DMF, 98%. g) DIBAH, Et_2O, 0 °C, 83%. h) i. PCC, 3A-MS. ii. $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, -78 °C, 74% overall. i) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 90%.

d) The Wilson approach (Tetrahedron Lett. 1984, 3147)[7]

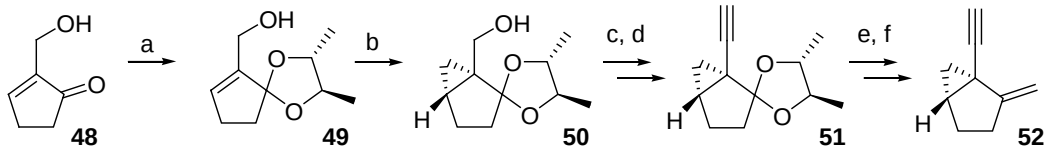
Scheme 7



Reagents and conditions: a) NB, BMAP. b) TsN_3. c) Rh(II)TPPCl, 84% from ***80****. d) $TMSCH_2Li$, 87%-92%. e) i. SeO_2. ii. TBDMSCl, 60%. f) i. $LiALH_4$. ii. PCC. iii. Ph_3P=CHBr. iv. n-BuLi, 84%.*

e) The Uskokovic approach (Tetrahedron Lett. 1991, 2343.)[8]

Scheme 8

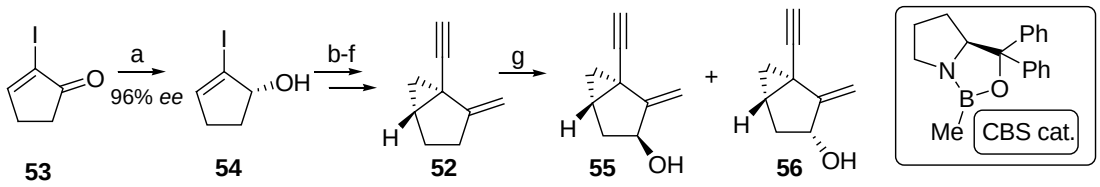


Reagents and conditions: a) R,R-(-)-2,3-butanediol, pyridinium tosylate, 68%. b) Sm, $HgCl_2$, CH_2ICl, THF, 94%. b) $(COCl)_2$, DMSO, 81%. d) $(EtO)_2POCHN_2$, t-BuOK, HF, 98%. e) TsOH, acetone, H_2O, reflux, 80%. f) $Ph_3P^+CH_3I^-$, t-BuOK, 72%.

1.2.2 Precursor synthesized by catalytic asymmetric synthesis approach

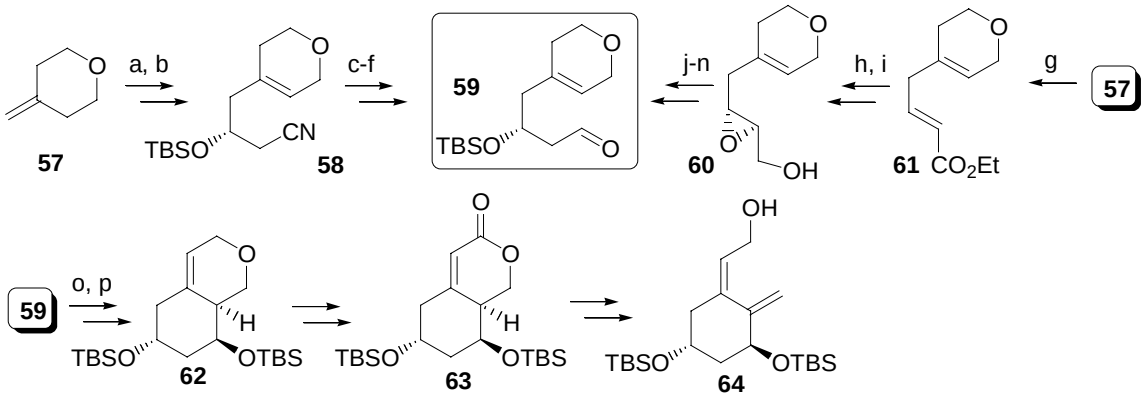
a) The Uskokovic approach (i. Tetrahedron Lett. 1991, 2343. ii. Tetrahedron Lett. 1992, 7701)[8,9]

Scheme 9



Reagents and conditions: a) CBS cat., BH_3·THF, 82%. b) CHCSiMe$_3$, $(Ph_3P)_2PdCl_2$, Et_3N, CuI, 86%, c) Sm, $HgCL_2$, CH_2ICl, 77%. d) PCC, 85%. e) $Ph_3P^+CH_3I^-$, t-BuOK, 92%. f) K_2CO_3, MeOH, 93%. g) SeO_2, t-BuO_2H, CH_2Cl_2, 48%.

Scheme 10

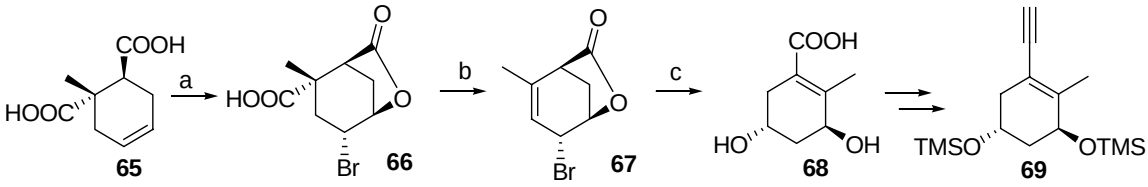


Reagents and conditions: a) MeO_2C-CHO, $TiBr_2(O^iPr)_2$, (R)-BINOL, CH_2Cl_2, -23 °C, 75%. b) TBDMSCl, 91%. c) i. LAH. ii. TsCl, py. iii. KCN, DMSO, 67% overall. d) DIBAH, 79%. e) Ethyl propiolate, $EtAlCl_2$, 81%. f) DIBAH, 94%. g) D-(-)-DIPT, $Ti(O^iPr)_4$, t-BuO_2H, 82%. h) $NaAlH_2(OR)_2$, 88%. i) i. PCOCl, py. ii. TBDMSCl. iii. MeOLi, MeOH, 83%. j) $(COCl)_2$, DMSO, 80%. k) MeAl(OMe)Cl, 87%. l) TBDMSCl, 83%. m) CrO_3, 3,5-dimethylpyrazole, 95%. n) $NaBH_4$, $CeCl_3$, 83%. o) TBDMSCl, imidazole, DMF, 71%. p) i. TsCl, py. ii. NaI, DMF. iii. DBU, DMF, 81% (3 steps). iv. KOH, 79%.

1.2.3 Precursor obtained by resolution of racemic material

a) Lythgoe approach (J. Chem. Soc. Perkin, Trans. 1 1974, 26542657.)[10]

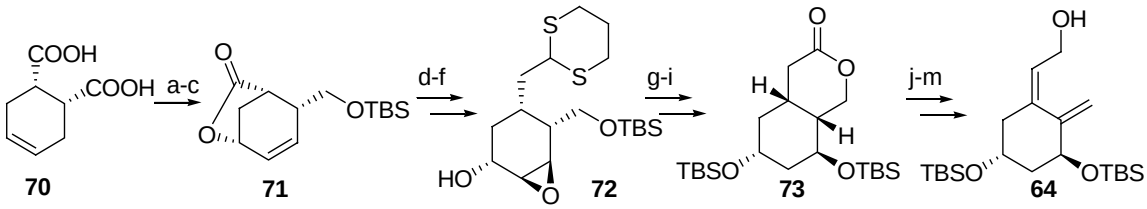
Scheme 11



Reagents and conditions: a) Br_2, $NaHCO_3$, 80%.b) m-CPBA, 81%, 100% de. c) i. NaOMe. ii. H_2O. iii. H^+-resin, 93% (3 steps).

b) Kobayashi approach (Tetrahedron lett. 1990, 1577.)[11]

Scheme 12

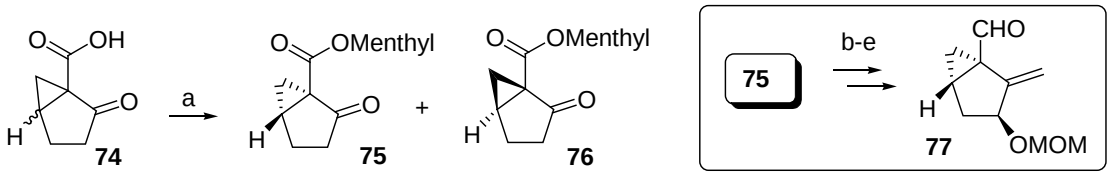


Reagents and conditions: a) i. $ClCO_2Et$, Et_3N, THF, 0 °C, then, $NaBH_4$, THF-H_2O, 0 °C. ii. p-TsOH, PhH, rt. b) i. NaOH, H_2O-THF, rt. ii. I_2, KI, CH_2Cl_2-H_2O, rt. iii. TBDMSCl, imidazole, DMF, rt. c) DBU, toluene, ∆. d) m-CPBA, CH_2Cl_2, rt. e) DIBAH, toluene, -78 °C. f) 2-lithio-2-trimethylsilyl-1,3-dithiane.

g) LAH, THF, rt. h) p-TsOH (cat.), THF. i) i. TBDMSCl, imidazole, DME, rt. ii. NBS, aq. Acetone, -15 °C, 81%. j) i. LDA, PhSeBr, THF, -78 °C. ii. H_2O_2, THF, 0 °C to rt. k) i. NaOH, H_2O-MeOH, rt. ii. CH_2N_2, Et_2O, 0 °C, 81%. l) i. o-NO_2-C_6H_4-SeCN, n-Bu_3P, THF, rt, 84%. ii. H_2O_2, THF, 0 °C to rt, 81%. m) DIBAH, toluene, -78 °C, 87%.

c) Fukumoto-Kametani approach (J. Chem. Soc. Perkin Trans. 1 1986, 1777.)[12]

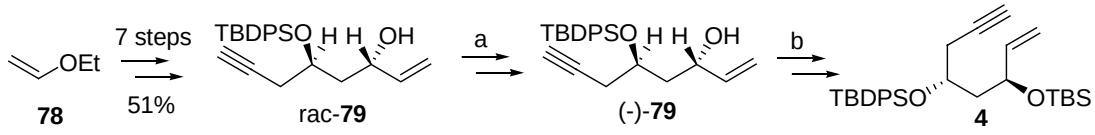
Scheme 13



Reagents and conditions: a) (-)-Menthol, DCC, DMAP, 94%. B) $Ph_3P=CH_2$, 73%. c) t-BuO_2H, SeO_2, 37%. d) MOMCl, 80%. e) i. hydrolysis. ii. DIBAH.

d) Trost approach (J. Am. Chem. Soc. 1992, 114, 1924.)[13]

Scheme 14

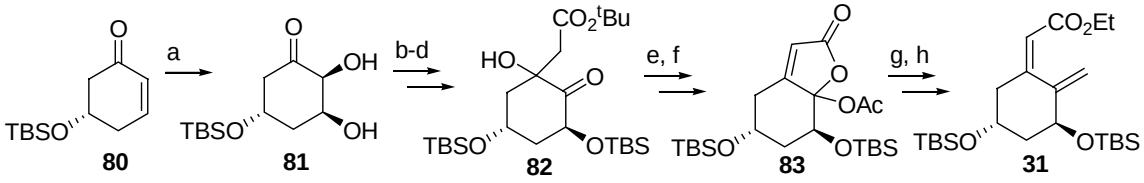


Reagents and conditions: a) t-BuO_2H, D(+)-dicyclohexyl tartarate, Ti $(OiPr)_4$, CH_2Cl_2-isoctane, -20 °C, 92%, separation, 98% ee. b) TBDMSCl, imidazole, DMF, 55 °C, 90%.

1.2.4 Synthesis using commercially available chiral precursors

a) Sato approach (Tetrahedron Lett. 2000, 41, 2385-2388.)[14]

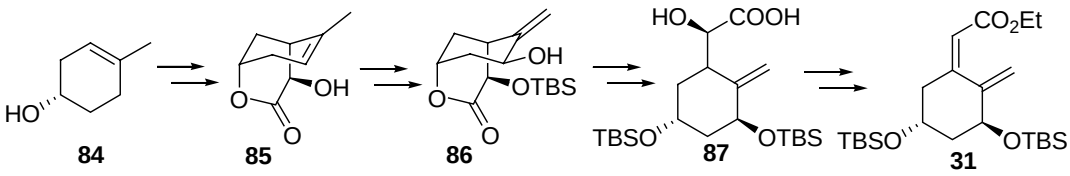
Scheme 15



Reagents and conditions: a) OsO_4, NMO, acetone-water, rt, 80%. b) Zn, $BrCH_2CO_2{}^tBu$, $(MeO)_3B$-THF, rt to reflux to rt, 91%. c) TBSCl, imidazole, DMF, rt, 100%. d) $(COCl)_2$, DMSO, 0 °C to rt, 94%. e) aged Zn-CH_2Br-$TiCl_4$, THF, rt, 37%. f) Ac_2O, $Sc(OTf)_3$, 90%. g) $Pd(PPh_3)_4$, Et_2NH, THF, rt, 90%. h) i. TMSOTf, 2,6-lutidine, THF, reflux. ii. EtI, K_2CO_3, DMF, rt, 95%.

b) Stork approach (Pure Appl. Chem. 1992, 64, 1809-1812)[15]

Scheme 16



From the above survey of literature precedent, it is evident that the A-ring synthons of 1,25-D_3 had been a popular target among synthetic organic chemists as indicated by the immense synthetic efforts directed towards them. Recent years have seen a surge for making these moieties using asymmetric synthesis instead of chiral pool materials or resolution of racemic compounds. Accordingly, numerous approaches have appeared in this domain, however, to the best of our knowledge there had been no approach for the synthesis of these compounds in optically pure form, by asymmetric synthesis, using cheaply available aromatic compounds as starting materials. We envisaged to engineer, the strategy developed by us for CD-rings fragment, for the synthesis of common precursor for a number of A-ring synthons. Following section would discuss this endeavor.

2. Results and Discussion

For an elegant design of a common precursor from which numerous A-ring synthons would be obtained in optically pure form, we closely examined the structures of various A-ring synthons reported in the literature. This led us to envision keto-lactones of the type **88/89**, which were thought to be a versatile precursor for a number of these moieties. Accordingly, we worked out the design for its synthesis as depicted retrosynthetically in Figure 2.

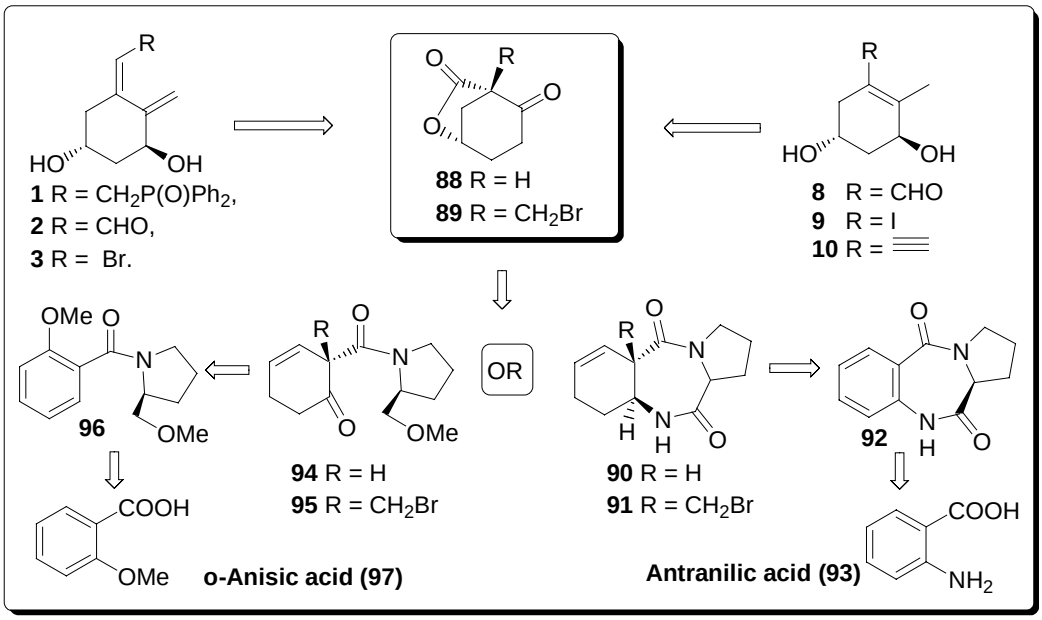
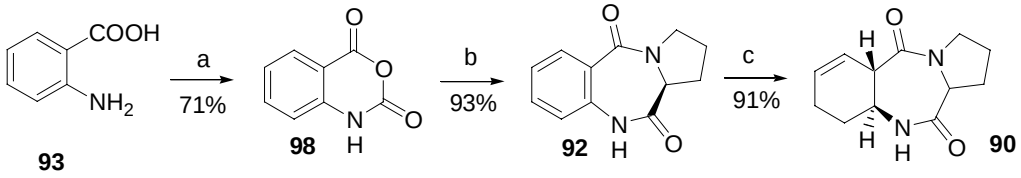


Figure 2. Retrosynthesis of targeted synthons

We began our synthetic journey via anthranillic acid route by synthesizing compound **90** (R = H), which was obtained from **92** by following the procedure reported by Shultz *et al* (Scheme 17).[16]

Scheme 17. Preparation of 90



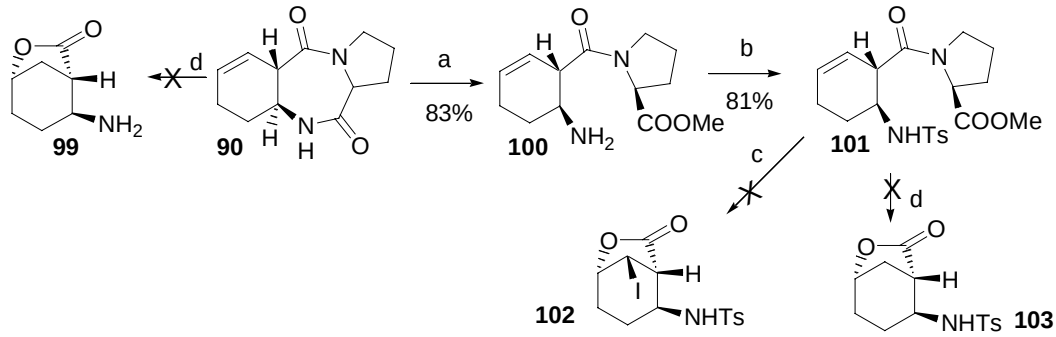
Reagents and conditions: a) $COCl_2$, 50% HCl. b) L-proline, Py.HCl, pyridine, reflux. c) Na, liq. NH_3, THF, –78 ℃, NH_4Cl.

The spectral, physical and analytical data of **98**, **92** and **90** was in good agreement with the literature values.

With compound **90** in hand, we proceeded to cleave the chiral auxiliary to obtain the amino lactone **99**, eminently poised for preparing desired keto-lactone **88**. Towards this end, we initially attempted the cleavage of the chiral auxiliary by heating **90** with 1:1 H_2SO_4/H_2O at 100 °C, which led to the formation of complex reaction mixture. Use of HCl in place of H_2SO_4, varying reaction time and temperature etc., did not furnish the desired amino lactone **99**. It was soon realized that possible interference from the free amino group

is responsible for the failure to achieve this desired transformation. Therefore, we shifted our attention to a milder method involving stepwise cleavage of the two amide bonds of **90** and protecting the amino functionality before lactonization. In this regard, **90** was first subjected to cleavage of the lower amide bond by refluxing with methanol in presence of two equivalents of sulfuric acid to furnish amino ester **100** which was immediately subjected to *N*-tosylation to obtain tosyl protected amino ester **101**.

Scheme 18. Attempted lactonization



Reagents and conditions: a) cat. H_2SO_4, MeOH, reflux. b) TsCl, Et_3N, DCM, rt. c) I_2, THF, H_2O, rt. d) 1:1 H_2SO_4, reflux.

The IR spectrum of **101** indicated the presence of amide and ester functionalities by displaying two strong absorption bands in the carbonyl region at ν_{max} = 1622 and 1739 cm^{-1} respectively.

In the ^1H NMR spectrum ($CDCl_3$, 200 MHz) of **101**, a multiplet spanning the region of δ = 1.76-2.21 and integrating for nine protons belongs to the protons of the two methylene groups in the cyclohexyl ring, two methylene groups (other than the N-CH_2) in the pyrrolidine ring and sulfonamide group (N<u>H</u>-SO_2). A singlet appearing at δ = 2.39 and integrating for three protons was assigned to the methyl group of the tosyl moiety. A multiplet seen in the region of δ = 3.23-3.52 corresponds to two methine protons on the cyclohexyl ring. Another multiplet exhibited at δ = 3.54-3.67 (2H) was assigned to the N-CH_2 protons. The methyl protons of the carbomethoxy functionality were seen as a singlet at δ = 3.70 as expected. A doublet of doublet exhibited at δ = 4.38 (*J* = 7.8, 3.9 Hz), integrating for one proton was attributed to the methine proton of the pyrrolidine ring. The olefinic proton away from the tertiary stereocenter, appeared as multiplet, between δ =

5.29-5.51 (1H), while the other olefinic proton appeared as a doublet of doublet at 5.83 (*J* = 10.2, 2.0 Hz, 1H). The spectrum was terminated by aromatic signals, which appeared as two doublets at δ = 7.22 (d, *J* = 7.9 Hz, 2H) and 7.76 (d, *J* = 8.1 Hz, 2H), respectively.

The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of **101** displayed 18 signals at δ = 21.7, 22.0, 25.1, 25.3, 29.1, 31.8, 47.1, 50.4, 52.4, 59.3, 121.7 (2C), 127.4, 129.8, 130.4 (2C), 138.3, 143.4, 170.8, 172.9. Peak assignments based on DEPT experiment revealed that the signals appearing at δ = 138.3, 143.4, 170.8 and 172.9 belong to the quaternary carbons. While the first two peaks were attributed to the quaternary carbons of the aromatic ring, the other two signals were of the ester carbonyl and the amide carbonyl carbons, respectively. Signal appearing at δ = 47.1 was attributed to the methine carbon vicinal to sulfonamide group, while those observed at δ = 50.4 and 52.4 belonged to the methine carbons vicinal to amide and ester functions, respectively. The two methine carbons of olefinic double bond and the four methine carbons of the aromatic ring appeared at δ = 121.7 (2C), 127.4, 129.8, and 130.4 (2C). The signals appearing at δ = 22.0, 25.1 25.3, 29.1 and 31.8 were revealed to be arising from various methylene groups in the molecule. The methylene signal appearing most downfield was attributed to the N-CH_2 carbon while the two signals appearing most up field belong to the remaining two methylene carbons of the pyrrolidine ring. Finally, the methyl associated with benzene ring of tosyl group was found to appear up field at δ = 21.7.

Spectral data of **101** is fully in support of the depicted structure.

As per our plan, **101** was subjected to lactonization by heating with 1:1 H_2SO4/H_2O at 100 °C. However, to our great dismay a complex reaction mixture was obtained and we could not secure the desired amino lactone by any means. At this point, it was felt that a milder method of lactonization would serve our purpose and in this context we turned our attention to iodo lactonization of **101**. It was anticipated that, it would be possible to get rid of the iodo group from the resulting iodolactone **102** by chemoselective reduction using

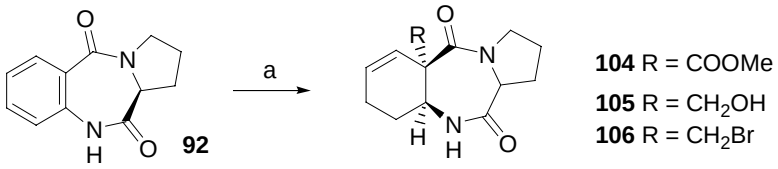
$^{n}Bu_3SnH$. However, this reaction did not work as planned and also gave the complex mixture of products (Scheme 18).

Analysis of the failure of our strategy made us to realize that the enolizable proton present vicinal to amide function in the cyclohexyl ring is the chief troublemaker. Thus, it was felt that, if a group, which can be easily removed at a later stage or which can itself serve as a part of the A-ring synthon, in place of this proton would be most suitable. For stereochemical reasons, it was decided to introduce such a group during Birch reduction itself. Towards this end, we began screening the readily available groups like COOMe, CH_2OH, CH_2I, CH_2Br etc, which fulfilled our criteria. It may be worth mentioning at this point that except for CH_2OH, such groups have not been introduced by Birch-reduction alkylation strategy.

In this context, we initiated our investigations by attempting to introduce COOMe group. Treatment of **92** with 4.5 eq. of Na and 1 eq. of $^{t}BuO_2H$ in liq NH_3 at –78 °C followed by quenching the resulting anion with methyl chloroformate did not yield any alkylated product. Prolonged reaction times and higher temperature also proved futile. Instead of alkylated product, the protonated compound **90** was obtained as a major product. Use of Me_2CO_3 in place of methyl chloroformate gave the alkylated compound **104** in very low yield. Compound **90** was again found to be the major product. Therefore, we turned our attention towards the introduction of CH_2OH using HCHO. Passing the formaldehyde gas through the anion generated at −78 °C did not give any alkylated product **105**. However, when the temperature was raised to −20 °C alkylated product **105** did form but in low yields. Also, the GC analysis revealed a ratio of the two diastereomers as 5:3, which was not acceptable for the synthetic purpose. At this stage, we realized that the slow rates of alkylation in the above cases were due to the weaker electrophilicity of the electrophiles used. Thus, we decided to opt for a stronger and readily available electrophile such as CH_2Br_2. To our delight, when the anion of **92** generated under Birch conditions was

quenched with CH_2Br_2, the corresponding alkylated product (-)-**106** formed in 95% yield and in diastereopure form as indicated by GC analysis* (Scheme 19).

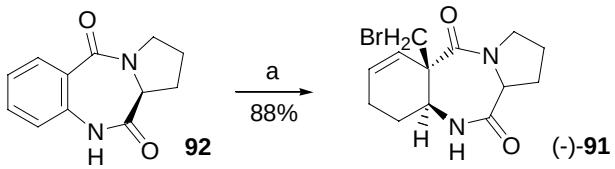
Scheme 19. Birch reduction-alkylation



Reagents and conditions: a) Na, liq NH_3, THF, ^{t}BuOH –78 °C, and then RX (Me_2CO_3/HCHO/CH_2Br).

Compound (-)-**106** obtained under normal conditions of Birch reduction alkylation possess the stereochemistry corresponding to the enantiomer of keto lactone (+)-**89**, at the newly generated quaternary stereocenter. Since we targeted both the (+)-**89** as well as its enantiomer (-)-**89**, we proceeded to synthesize the diastereomer of (-)-**106** having the stereochemical imprint of (+)-**89** at the quaternary stereocenter. For this purpose we resorted to the enolate equilibration protocol, devised by Schultz *et al.*[17] Accordingly the enolate of **92** was generated under Birch conditions as usual, followed by warming up of the reaction mixture to 25 °C, with concomitant removal of ammonia under inert atmosphere, cooling it again to –78 °C and adding CH_2Br_2, which furnished (-)-**91** in diastereopure form (Scheme 20).

Scheme 20. Enolate equilibration protocol



Reagents and conditions: a) Na, liq NH_3, THF, ^{t}BuOH –78 °C, warm to 25 °C, cool to –78 °C, CH_2Br_2.

The structure of (-)-**91** was deduced from its spectral data. The IR spectrum of (-)-**91** displayed two bands in the carbonyl region at ν_{max} = 1638 and 1692 cm^{-1} corresponding to the amide with quaternary nitrogen and the other with tertiary nitrogen, respectively.

* Stereochemical assignments were done based on literature precedent for similar compounds.

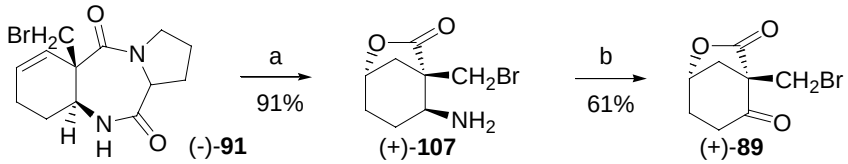
The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**91** displayed at δ = 1.86, integrating for two protons, a multiplet spanning the region of 1.92-2.40 (5H) and a triplet of doublets at δ = 2.62 (*J* = 121, 6.3 Hz, 1H) arising from the protons of the various methylene groups present in the molecule except N-CH_2 and CH_2Br. The CH_2Br protons appeared separately as doublets at δ = 3.33 (*J* = 10.2 Hz, 1H) and 4.02 (*J* = 10.2, 1H), respectively, while the N-CH_2 protons appeared together as a multiplet in the area of δ = 3.55-3.75 (m, 2H). A multiplet exhibited at δ = 4.61-4.76 (m, 1H) was assigned to the methine proton present of the tertiary stereocenter in the cyclohexyl ring while the methine proton of the tertiary stereocenter in the pyrrolidine ring appeared as a doublet of doublet at δ = 4.85 (*J* = 7.8, 5.0 Hz, 1H). The olefinic protons were displayed separately at δ = 5.87 (dt, *J* = 9.9, 3.8 Hz, 1H) and δ = 6.01 (d, *J* = 10.2 Hz, 1H), respectively. The spectrum was terminated by the NH proton which was seen as a broad singled spanning the region of δ = 6.7-6.94 (1H).

In the ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**91**, thirteen signals were observed appearing at δ = 18.8, 21.5, 21.9, 26.9, 39.8, 46.6, 48.5, 52.4, 55.1, 126.2, 129.2, 169.6 and 172.2, respectively. The DEPT experiment confirmed that the peaks exhibited at δ = 52.4, 169.6 172.2, belonged to the quaternary carbons of the quaternary stereocenter and the two amide carbonyls, respectively. The signals observed at δ = 46.6 and 55.1 were attributed to the methine carbons of the tertiary stereocenters present in the cyclohexyl and pyrrolidine rings, respectively. The olefinic methine carbons appeared at δ = 126.2 and 129.2, respectively. The methylene signals appearing most up field at δ = 18.8 and 21.5 belonged to the methylene carbons of the pyrrolidine ring except N-CH_2, while the methylene carbons present on cyclohexyl ring appeared at δ = 21.9 and 26.9 respectively. The signal observed at δ = 39.8 was attributed to the N-CH_2 carbon and the one seen at δ = 48.5 was assigned to the CH_2Br carbon.

The next task in the planned strategy was to prepare amino lactone (+)-**107** by cleaving the chiral auxiliary of (-)-**91**. In this context it was quite remarkable to observe that

unlike in the case of **90**, **100** and **101**, (-)-**91** underwent smooth conversion to amino lactone (+)-**107** in 68% when heated with 1:1 H_2SO_4/H_2O for 7 hours.

Scheme 21. Synthesis of (+)-89



Reagents and conditions: a) 1:1 H_2SO_4, 100 ℃. b) 4-formyl-1-methylpyridinium benzene sulfonate, DCM, DMF, rt., 30 min, DBN, 15 min.

The aminolactone (+)-**107** was sufficiently stable to allow structural elucidation using conventional spectroscopic means. The IR spectrum of (+)-**107** gave ample evidence of the presence of amino and lactone functionalities by displaying strong absorption bands at ν_{max} = 3447 and 1781 cm^{-1} respectively.

The ^1H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**107** displayed two sets of multiplets in the region of δ = 1.27-1.73 (2H) and 1.91-2.35 (4H), integrating for six protons which were assigned to the protons of the three methylene groups of the cyclohexyl ring. The proton attached to the carbon carrying amino functionality appeared as a doublet at δ = 2.42 (*J* = 11.9, 5.7 Hz, 1 H). The broad singlet spanning the region of δ = 2.89-3.22 (2 H) belongs to the protons of the amino group. The CH_2Br protons appeared separately at δ = 3.41 (d, *J* = 10.1 Hz, 1 H) and 3.82 (d, *J* = 10.1 Hz, 1 H), respectively, while the CH-O proton appeared as a triplet at δ = 4.74 (t, *J* = 4.2 Hz, 1 H).

With the amino lactone (+)-**107** in hand, we moved on to procure our targeted keto lactone (+)-**89** by oxidation of the amino functionality of (+)-**107**. The conversion of amino group to keto carbonyl was essentially achieved by treating (+)-**107** with 4-formyl-1-methylpyridinium benzene sulfonate as shown in Scheme 21.[16]

The structure of keto lactone (+)-**89** could be easily gleaned from the disappearance of the absorption band arising from the amino functionality and the

presence of keto carbonyl absorption band at ν_{max} = 1718 cm^{-1} along with lactone carbonyl band at ν_{max} = 1785 cm^{-1} in its IR spectrum.

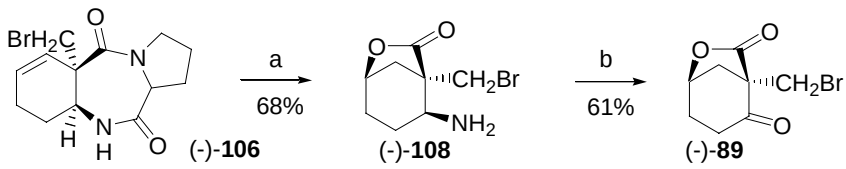
The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (+)-**89** also showed characteristic differences as expected from its parent aminolactone, which assisted in its structure elucidation. For example, the four protons pertaining to the two contiguous methylene groups of the cyclohexyl unit were found as three sets of multiplets spanning the regions of δ = 2.01-2.34 (m, 2H), 2.38-2.57 (m, 1H) and 2.65-2.77 (m, 2H), respectively. The remaining proton of the cyclohexyl ring was exhibited at 3.13 (ddd, *J* = 12.5, 5.9, 2.5 Hz, 1H) respectively. The two singlets appearing at δ = 3.94 and 3.97 and integrating for one proton each were attributed to the protons of the CH_2Br group. Finally the CH-O proton of the lactone unit appeared as multiplet in the area of δ = 5.02-5.11 (m, 1H).

A total of eight signals were disclosed in the ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (+)-**89** as expected at δ = 29.1, 34.5, 36.5, 40.2, 61.6, 75.1, 171.4 and 199.0 respectively. The disappearance of the peaks at δ = 61.6, 171.4 and 199.0 in the DEPT spectrum of (+)-**89** indicated that these signals were arising from the quaternary carbons and were assigned to the carbons of the quaternary stereocenter, lactone carbonyl and the keto carbonyl, respectively. The CH-O methine carbon was observed at δ = 75.1. The remaining four signals displayed at δ = 29.1, 34.5, 36.5 and 40.2 belonged to the four methylene groups present in the molecule.

The mass spectrum of (+)-**89**, finally confirmed its structure by disclosing a molecular ion peak at *m/z* = 233 (M^+) and a relevant fragmentation pattern.

Concurrently, the enantiomer of the keto lactone (+)-**89** was prepared from (-)-**106**, following the same sequence of steps as depicted in Scheme 22.

Scheme 22. Synthesis of *ent*-89



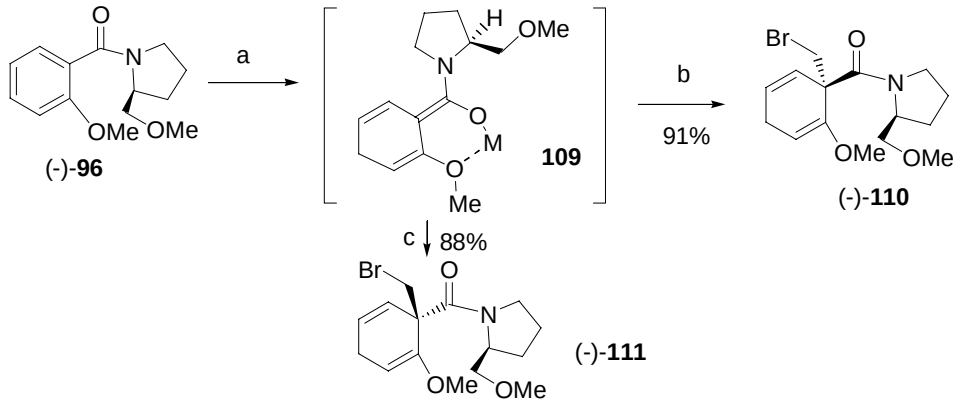
Reagents and conditions: a) 1:1 H_2SO_4, 100 °C. b) 4-formyl-1-methylpyridinium benzene sulfonate, DCM, DMF, rt., 30 min, DBN, 15 min.

The spectral data of (-)-**108** had close resemblance with (+)-**107** and that of (-)-**89** was found to be matching perfectly with (+)-**89**.

Even though, the anthranillic acid route was capable of delivering the desired keto lactone (+)-**89** and its enantiomer (-)-**89**, we were not entirely satisfied with its efficiency. In our view it suffered from a number of drawbacks such as use of phosgene, lower yields in some of the steps and cost of the oxidizing agent used to convert amino functionality of (+)-**107** and (-)-**108** to a keto carbonyl.

Therefore, we took up the studies concerning the preparation of (+)-**89** and (-)-**89** via *o*-anisic acid route. Accordingly compound (-)-**96**, whose preparation has been discussed in the Chapter 2 of this thesis, was subjected to Birch conditions with 2.5 eq of sodium and the enolate was subsequently quenched with dibromomethane by two different methods (normal and enolate equilibration) to obtain (-)-**110** and (-)-**111** as shown in Scheme 23.

Scheme 23. Initial steps in *o*-anisic acid route



Reagents and conditions: a) Na, liq NH_3, THF, ^tBuOH –78 °C. b) CH_2Br_2. c) i. Enolate equilibration, ii. CH_2Br_2.

Compounds (-)-**110** and (-)-**111** were fully characterized using conventional spectroscopic means and while their spectral data was a close match, the optical rotation differed significantly.

The IR spectrum of (-)-**111** indicated the presence of amide functionality by exhibiting an absorption band at ν_{max} = 1637 cm^{-1}.

The ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of (-)-**111** displayed a multiplet between δ = 1.60-1.94 (4H), corresponding to the protons of the two methylene groups of pyrrolidine unit other then N-CH_2. Another multiplet seen in the region of δ = 2.60-3.04 and integrating for two protons was assigned to the protons of the *bis*-allylic methylene group. A signal observed in the region of δ = 3.15-3.35 (m, overlapping s at δ = 3.27, 5H) was a combined indication of the methyl protons of the OCH_3 in chiral auxiliary part and the N-CH_2 protons. Another similar signal spanning the area between δ = 3.43-3.61 (m, overlapping s at δ = 3.49, 5H) arise from the protons of the methyl group of enol ether and the O-CH_2 protons. The protons of the CH_2Br group appeared separately as doublets at δ = 3.71 (*J* = 10.2 Hz, 1H) and 4.02 (d, *J* = 10.2 Hz, 1H) respectively. The proton associated with the tertiary stereocenter of the chiral auxiliary appeared as a multiplet as usual at δ = 4.16-4.31 (1H). The olefinic protons displayed a typical pattern with the signals for all the three protons appearing wide apart. The olefinic proton associated with the enol ether function was the one to appear most upfied due to the electron donating effect of the OMe group and was seen at δ = 4.85 (t, 3.4 Hz, 1H). The proton vicinal to the *bis*-allylic methylene group on the other olefinic double bond appeared at δ = 5.32 (dt, *J* = 9.8, 1.9 Hz, 1H), while the remaining olefinic proton appeared most downfield due to presence of vicinal quaternary center carrying amide function at δ = 5.99 (dt, *J* = 9.7, 3.4 Hz, 1H).

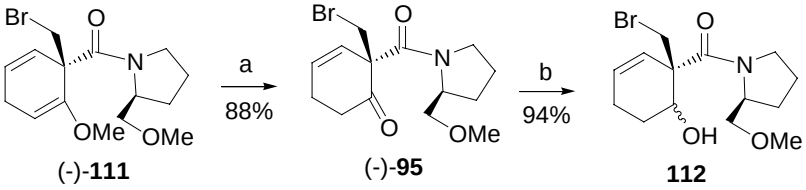
The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of (-)-**111** provided ample information on its carbon framework by displaying fifteen signals in the relevant positions at δ = 24.8, 26.3, 26.9, 41.1, 46.4, 52.8, 54.4, 58.1, 58.9, 71.7, 95.1, 124.1, 128.8, 150.5 and 168.4 respectively. The DEPT experiment revealed that the signals appearing at δ = 52.8, 150.5 and 168.4 belonged to the quaternary carbons of the quaternary stereocenter, enol ether moiety and the carbonyl group respectively. The methine carbon of the tertiary stereocenter appeared at δ = 58.1 while the olefinic methine carbons were displayed at δ =

95.1, 124.1 and 128.8 respectively. Signals appearing at δ = 24.8, 26.3, 26.9, 41.1, 46.4 and 71.7 were revealed to be arising from methylene carbons. The two most up field signals in this group at δ = 24.8 and 26.3 were assigned to the two methylene groups of pyrrolidine moiety other then N-CH_2. The next signal at δ = 26.9 belonged to the *bis*-allylic methylene group, while the two signals at δ = 41.1 and 46.4 belonged to CH_2Br and N-CH_2 carbons respectively. The most downfield methylene carbon shown at δ = 71.7 was assigned to the O-CH_2 carbon. Lastly, the carbon of the methyl group associated with the enol ether moiety was exhibited at δ = 54.4 and the methyl group of auxiliary appeared at δ = 58.9.

With the successful synthesis of both the diastereomers (-)-**110** and (-)-**111**, we moved on towards the synthesis of targeted keto lactone (+)-**89** and its enantiomer. The next step in the projected synthesis of (+)-**89** was to hydrolyze the enol ether and reduce the resulting ketone (-)-**95** to corresponding alcohol **112**, which was envisaged to be a suitable precursor for chiral auxiliary cleavage.

In this regard, (-)-**111** was treated with 10% HCl to obtain ketone (-)-**95** in excellent yield. The structure of (-)-**95** followed from the changes in its spectral data occurring due to conversion of methyl enol ether moiety to a keto function. The presence of keto absorption band at ν_{max} = 1712 cm^{-1} along with the absorption band corresponding to amide carbonyl at ν_{max} = 1633 cm^{-1} provided ample evidence of the required conversion. The absence of methyl and the olefinic proton of the enol ether moiety from ^{1}H NMR spectrum of (-)-**95** and similar disappearance of the methyl and olefinic carbons of this moiety from the ^{13}C NMR spectrum fully supported the depicted transformation. The appearance of signal at δ = 205.9 assignable to keto carbonyl carbon along with the signal corresponding to the amide carbonyl carbon at δ = 166.5 in the ^{13}C NMR spectrum of (-)-**95** also provided sufficient proof for its structure.

Scheme 24. Enol-ether hydrolysis and reduction



(-)-**111** (-)-**95** **112**

Reagents and conditions: a) 10 % HCl, MeOH, rt. b) $NaBH_4$, MeOH, 0 ℃ to rt.

Consequently, the desired alcohol **112** was procured by reduction of the keto carbonyl group of (-)-**95** using sodium borohydride as depicted in Scheme 24. Since the two diastereomers of **112** had sufficiently large difference in R_f values, they could be easily separated by column chromatography. Their spectral data were similar except for the downfield shift of the CH-OH proton and carbon in the ^{1}H NMR and ^{13}C NMR spectrum respectively of the diastereomer with hydroxy *cis* to the amide moiety due to intramolecular hydrogen bonding.

The IR spectrum of **112a** (hydroxy *trans* to amide) showed the presence of hydroxy absorption band at ν_{max} = 3431 and an amide carbonyl absorption band at 1608 cm^{-1}.

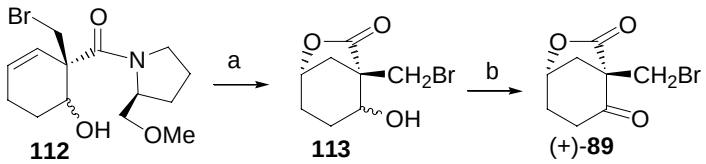
In the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of **112a**, two sets of multiplet appeared in the region of δ = 1.49-1.87 (m, 6H) and 1.98-2.14 (m, 2H) were assigned to the protons of the two methylene groups of cyclohexyl moiety and the two methylene groups (other then N-CH2) on the pyrrolidine ring. The hydroxy proton appeared as a broad singlet in the area of δ = 2.26-2.45 (1H). The singlet seen at δ = 3.18 and integrating for three protons was attributed to the methyl protons of the OCH_3 group. The multiplets arising from OCH_2 protons and NCH_2 protons appeared mixed together between δ = 3.21-3.34 (m, 4H). The proton associated with the tertiary stereocenter of the chiral auxiliary was exhibited at δ = 3.48-3.65 (m, 1H) while the CHOH proton was shown as a triplet at δ = 4.26 (t, *J* = 5.3 Hz, 1H). The two singlets appearing at δ = 4.05 (s, 1H), 4.10 (s, 1H) were assigned to the two protons of the CH_2Br group. The two olefinic protons appeared separately at δ = 5.75 (dt, *J* = 10.1, 3.4 Hz, 1H) and 5.93 (d, *J* = 10.2 Hz, 1H), respectively.

^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of **112a** consisted of fourteen signals at δ = 23.1, 25.1, 25.9, 26.5, 39.2, 48.6, 54.5, 58.5, 59.0, 71.8, 72.0, 127.2, 129.2, and 171.6. Peak assignments using DEPT spectrum conveyed that the peaks at δ = 54.5 and 171.6 belonged to the quaternary carbons of quaternary stereocenter and the carbonyl function, respectively. The methine signals of tertiary stereocenter on pyrrolidine unit and the CH-OH group appeared at δ = 58.5 and 71.8 respectively, while the olefinic methine signals were shown at δ = 127.2 and 129.2 respectively. The various methylene carbons present in the molecule were exhibited at δ = 23.1, 25.1, 25.9, 39.2, 48.6 and 72.0. Closer examination of the spectrum revealed that the two signals appearing most up field at δ = 23.1 and 25.1 belong to the two methylene groups on pyrrolidine ring except N-CH_2. The next two signals in this group seen at δ = 25.9 and 39.2 belong to the methylene carbons of cyclohexyl moiety, while the reaming two signals at δ = 48.6 and 72.0 arise from the methylene carbons of N-CH_2 and O-CH_2, respectively. Finally, the signal at δ = 59.0 was attributed to the OCH_3 methyl carbon.

Mass spectrum was helpful in confirming the structure of **112a** by displaying a molecular ion peak at *m/z* = 333 (M^++1), along with base peak at 70 (100) and a relevant fragmentation pattern.

Next, **112a** and **112b** were subjected to acid catalyzed amide hydrolysis, which resulted in the formation of corresponding hydroxy lactones **113a** and **113b**. At this point it was observed that **112a** in which the hydroxy group is *trans* to the amide moiety underwent hydrolysis and subsequent lactonization smoothly in very short period of time to deliver the desired hydroxy lactone in excellent yield, while **112b** in which the hydroxy is *cis* to the amide function took longer time to undergo the transformation and gave corresponding hydroxy lactone **113b** in slightly lower yields.

Scheme 25. Preparation of (+)-89



112 **113** (+)-**89**

*Reagents and conditions: a) 1:1 H_2SO_4, 100 °C, (For **117a**, 6 h, 87%; For **117b**, 32 h, 63%). b) PDC, DCM, rt, 8 h, 93%.*

As in the case of **112**, the diastereomers of **113** also exhibited the difference in the positions of CH-OH signals in ^1H and ^{13}C NMR spectrum with the signals for this group being more downfield in the case of **113b**, having *cis* disposition of the hydroxy group with respect to amide unit.

The IR spectrum of **113a** provided ample evidence of the functionalities present by displaying absorption bands at ν_{max} = 3461 and 1770 cm^{-1}, which indicated the presence of hydroxy and lactone carbonyl groups respectively.

The ^1H NMR spectrum ($CDCl_3$, 200 MHz) of **113a** displayed a multiplet at δ = 1.68-1.94, integrating for four protons, which was assigned to the protons of the two contiguous methylene groups of cyclohexyl ring. The protons of the remaining methylene group were observed separately at δ = 2.31 (dd, *J* = 11.8, 3.0 Hz, 1H) and 2.46 (dd, *J* = 11.8, 5.8 Hz, 1H) respectively. The proton of the hydroxy group was seen appearing as a broad singlet in the area of δ = 2.65-2.88 (1H). The two signals exhibited at δ = 3.59 (d, *J* = 3.2 Hz, 1H) and 3.74 (d, *J* = 3.1 Hz, 1H) were attributed to the two protons of the CH_2Br group. Finally, the proton of the CH-OH group appeared at δ = 3.85-3.94 (m, 1H) and the proton associated with lactone CH-O was displayed at δ = 4.75-4.86 (m, 1H).

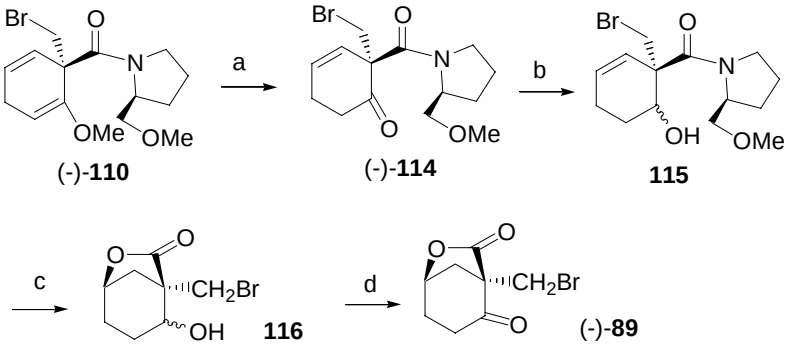
The ^{13}C NMR spectrum ($CDCl_3$, 50 MHz) of **113a** further supported its structure by displaying eight signals at δ = 24.2, 27.7, 32.8, 44.0, 53.4, 67.8, 77.0 and 176.9 respectively. The peak assignments were done on the basis of DEPT experiment, which indicated that the signals observed at δ = 53.4 and 176.9 belong to the quaternary carbons and were easily recognized to be arising from the quaternary stereocenter and the carbonyl function respectively. The methine signal of the CH-OH carbon appeared at δ = 67.8 and that of the CH-O carbon appeared at δ = 77.0. The two contiguous methylene groups of the cyclohexyl ring were displayed most upfied at δ = 24.2 and 27.7 respectively, while the third methylene group of cyclohexyl unit appeared at δ = 33.0. The signal appearing at δ = 44.0 was attributed to the CH_2Br methylene carbon.

The mass spectrum of **113a** confirmed its molecular weight by displaying a molecular ion peak at *m/z* = 235 (M^+) and also provided ample proof for its structure by disclosing relevant fragmentation pattern.

With hydroxy lactone **113** in hand, the desired keto lactone (+)-**89** was already in sight, since its preparation from **113** involved only simple PDC oxidation. It was a pleasing moment to observe that both **113a** and **113b** were smoothly converted to (+)-**89** in excellent yields by stirring with the mixture of PDC and DCM for 12 h at rt (Scheme 25). The optical, spectral and analytical data of (+)-**89** procured by this route matched perfectly with that synthesized earlier using anthranillic acid.

Simultaneously, (-)-**89** was also synthesized from (-)-**110**, following the same route discussed above for the conversion of (-)-**111** to (+)-**89** (Scheme 26).

Scheme 26. Preparation of (-)-89



Reagents and conditions: a) 10 % HCl, MeOH, rt. b) $NaBH_4$, MeOH, 0 ℃ to rt. c) 1:1 H_2SO_4, 100 ℃, 6-30 h. d) PDC, DCM, rt.

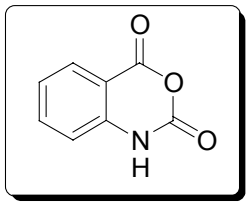
Conclusion

In this part of the thesis we have accomplished the synthesis of a versatile precursor (+)-**89** for large number of A-ring synthons of 1,25-D_3. Furthermore the synthesis of (-)-**89** by same route paves way for the synthesis of corresponding enantiomers of the 1,25-D_3 and analogues, some of which are known to possess excellent biological profiles. Elaboration of the versatility of keto lactone (+)-**89** and its enantiomer (-)-**89** in the synthesis of various A-ring synthons of 1,25-D_3 and analogues is currently in progress in this laboratory.

3. Experimental Section:

For general write up, see the experimental section of chapter 2 of this thesis.

1. Preparation of 1*H*-Benzo[*d*][1,3]oxazine-2,4-dione (Isatoic anhydride; 98):

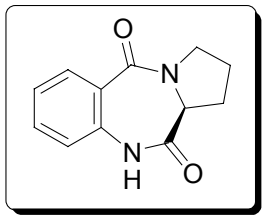


In to a 500 mL 2 necked round-bottomed flask fitted with a gas bubbler at one neck and a stopcock connected to ammonia scrubber at the other, was placed a solution of anthranillic acid (20 g, 145.98 mmol) in concentrated hydrochloric acid (20 mL) and water (150 mL). The solution was stirred vigorously and phosgene (generated by dropwise addition of sulphuric acid to the stirred mixture of CCl_4 and P_2O_5) was passed into it at such a rate that bubbles of gas escape slowly into the ammonia scrubber (about one bubble per second). Isatoic anhydride appeared as an off white precipitate soon after the stream of phosgene was started. The temperature of the solution was maintained below 50 ^oC, throughout, by controlling the rate of flow of phosgene, which was directly proportional to the rate of addition of sulphuric acid. The stream of phosgene was continued for 4 h, the flask was disconnected and residual phosgene was blown out by passing a current of air through the mixture. The product was collected on a Büchner funnel and was washed with cold water (100 mL). The first crop amounted to 12.56 g. The mother liquor was returned to the reaction flask, the apparatus reassembled and the passage of phosgene resumed. After 3 h of passing phosgene the rate of absorption noticeably decreased. The precipitate was collected on a Büchner funnel and washed with cold water to give 5.78 g of Isatoic anhydride. The combined product was dried in air and afterwards at 100 ^oC. Recrystallization from 95% ethanol (about 25 mL per g) resulted in isatoic anhydride (**98;** 16.94 g, 71%) as white needles.

M.p. : 244-247 ^oC (decomposed)

IR ($CHCl_3$) : ν_{max} = 2923, 1697, 1620, 1458, 1377, 756 cm^{-1}.

2. Preparation of 1,2,3,11a-Tetrahydro-10H-benzo [e]pyrrolo[1,2-a][1,4]diazipine-5,11-dione (92):



A mixture of isatoic anhydride (10 g, 56.5 mmol), pyridine hydrochloride (6.53 g, 56.5 mmol) and L-proline (7.15g, 62.2 mmol) was refluxed in pyridine (120 mL) for 6 h. Pyridine was removed under reduced pressure and the remaining semisolid residue was partitioned between water (100 mL) and chloroform (100 mL). The layers were separated and the organic layer was washed with 1N HCl (2 × 25 mL) and brine (20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure and trituration of the solid product with ethyl acetate gave **92** (12.36 g, 93%) as colorless crystals of analytical purity.

M.p.	**:**	221-223 °C
IR ($CHCl_3$)	**:**	ν_{max} = 3552, 3228, 2972, 2877, 2245, 1687, 1620, 1577, 1481, 1415, 1218, 912 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.85-2.21 (m, 3H), 2.63-2.88 (m, 1H), 3.48-3.69 (m, 1H), 3.73-3.90 (m, 1H), 4.08 (d, *J* = 5.9 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.8, 1H), 7.46 (t, *J* = 7.8, 1H), 7.99 (d, *J* = 7.8, 1H), 8.70-8.86 (br. s, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	23.4, 26.1, 47.2, 56.6, 121.1, 124.8, 126.9, 130.8, 132.3, 135.5, 165.4, 171.5.

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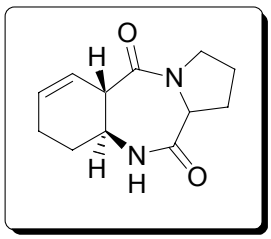
3. 1,2,3,8,9,9a,10,11a-Octahydro-5a*H*-benzo[e] pyrrolo[1,2-a][1,4]diazepine-5,11-dione (90):



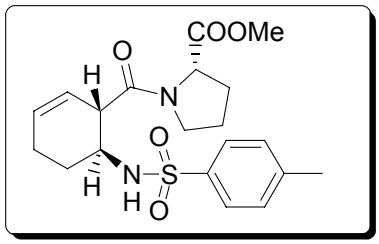
To a mixture of **92** (5 g, 23.15 mmol) and *t*-butyl alcohol (3.85 mL, 46.33 mmol) in dry THF (10 mL) was added ammonia (~

75 mL)* at −78 °C. Sodium (2.13 g, 92.6 mmol) was added in the form of small pieces over a period of 10 min and the resulting mixture was stirred for additional 15 min, upon which its color turned deep blue indicating the generation of anion. After stirring for additional 1.5 h at −78 °C, solid NH_4Cl was added and the ammonia was allowed to evaporate. The resulting residue was partitioned between chloroform (30 mL) and water (30 mL). The layers were separated and the aqueous layer was back extracted with chloroform (2 × 15 mL). The combined organic layer was washed successively with 10% sodium thiosulfate solution (20 mL), water (25 mL) and brine (15 mL). Drying over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure gave crude solid mass, which was purified by recrystallization from a mixture of EtOAc/pet. ether (9:1) to furnish **90** (4.64 g, 91%) as colorless crystals.

M.p.	**:**	124-126 °C
IR (Neat)	**:**	ν_{max} = 3232, 2947, 2243, 1687, 1614, 1415, 910, 731 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.38-1.91 (m, 3H), 1.92-2.12 (m, 2H), 2.12-2.85 (m, 2H), 2.55 (dtd, *J* = 12.9, 6.7, 2.3 Hz, 1H), 3.03 (dt, *J* = 10.6, 2.7 Hz, 1H), 3.59 (t, *J* = 6.7 Hz, 2H), 3.69-3.90 (m, 1H), 4.52 (t, *J* = 7.4 Hz, 1H), 5.71 (dt, *J* = 10.2, 3.1 Hz, 1H), 6.04 (dt, *J* = 9.8, 1.6 Hz, 1H), 6.67-6.92 (br. s, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 21.5, 24.4, 27.2, 27.5, 47.5, 48.3, 50.5, 56.0, 124.8, 126.4, 169.0, 170.6.

* Ammonia was dried over sodium for 30 min and distilled directly into the reaction vessel.

4. 1-[6-(Toluene-4-sulfonylamino)cyclohex-2-enecarbonyl]-pyrrolidine-2-carboxylic acid methyl ester (101):

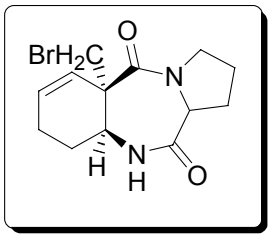


A solution of **90** (4.64 g, 19.19 mmol) and conc. sulphuric acid (2 mL) in dry methanol (75 mL) was refluxed for 20 h. The reaction mixture was cooled and the volume of methanol was reduced to one fourth under reduced pressure. Saturated sodium bicarbonate solution was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). After drying over anhydrous magnesium sulfate, the solution was concentrated to afford crude amino ester, which was subjected to *N*-tosylation without further purification.

To a solution of above amino ester in dry DCM (55 mL) was added triethyl amine (4.16 mL, 29.87 mmol) and tosyl chloride (4.55 g, 23.88 mmol) at rt. The resulting solution was allowed to stir at rt for 48 h. The mixture was taken up in a separating funnel and washed with water (2 × 10 mL) followed by brine (10 mL). Drying the organic layer over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure gave a solid mass, which upon purification by recrystallization from petroleum ether-ethyl acetate (1:4) afforded **101** (7.03 g, 82%) as colorless needles.

M.p.	**:**	79-81 °C
IR ($CHCl_3$)	**:**	ν_{max} = 2923, 1739, 1622, 1456, 1377, 1338, 1157, 1091, 665 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$)	**:**	δ = 1.76-2.21 (m, 9H), 2.39 (s, 3H), 3.23-3.52 (m, 2H), 3.54-3.67 (m, 2H), 3.70 (s, 3H), 4.38 (dd, *J* = 7.8, 3.9 Hz, 1H), 5.29-5.51 (m, 1H), 5.83 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 21.7, 22.0, 25.1, 25.3, 29.1, 31.8, 47.1, 50.4, 52.4, 59.3, 121.7 (2C), 127.4, 129.8, 130.4 (2C), 138.3, 143.4, 170.8, 172.9.

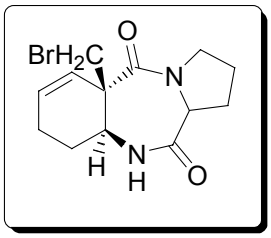
5. 5a-Bromomethyl-1,2,8,9,9a,10,11a-octahydro-5a*H*-benzo[e]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione [(-)-106]:



A solution of **92** (3.5 g, 16.20 mmol) in dry THF (8 mL) and *t*-butyl alcohol (2.69 mL, 32.41 mmol) was cooled to −78 °C. Liquid ammonia (60 mL, pre dried over sodium amide and then distilled) was added to the reaction mixture. Sodium (1.56 g, 67.83 mmol) was added to the stirred solution in small pieces over the period of ten minutes. The resulting mixture was allowed to stir at −78 °C for additional 15 min, upon which the color of the solution turned dark blue. After additional 45 min, dibromomethane (11.84 g, 68.05 mmol) was added and the resulting solution was stirred for 2 h at −78 °C upon which the color of the solution changed from deep blue to yellow. After addition of NH_4Cl (~10 g), the mixture was warmed slowly to room temperature while the ammonia was removed with a stream of argon. Water (50 mL) was added and the mixture was extracted with chloroform (3 × 30 mL). The combined organic extracts were washed with 10% sodium thiosulfate (25 mL), water (30 mL), brine (20 mL) and then dried over anhydrous sodium sulfate. Removal of solvents under vacuum followed by purification of the residue by column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 5:3) yielded (-)-**106** (4.56 g, 95%) as a viscous colorless oil.

IR (Neat)	**:**	ν_{max} = 3053, 1687, 1647, 1596, 1421, 1265, 738 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.52-2.34 (m, 7H), 2.55 (td, *J* = 121, 6.3 Hz, 1H), 3.20 (d, *J* = 10.2 Hz, 1H), 3.46-3.71 (m, 2H), 3.95 (d, *J* = 10.2, 1H), 4.54-4.69 (m, 1H), 4.78 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.80 (td, *J* = 9.9, 3.8 Hz, 1H), 5.94 (d, *J* = 10.2 Hz, 1H). 6.46-6.91 (br. s, 1H).

6. 5a-Bromomethyl-1,2,8,9,9a,10,11a-octahydro-5a*H*-benzo[e]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione [(-)-91]:



To a mixture of **92** (3.5 g, 16.20 mmol) and *t*-butyl alcohol (2.69 mL, 32.41 mmol) in dry THF (10 mL) was added ammonia (~ 60 mL) at –78 °C. Sodium (1.56 g, 67.83 mmol) was added in the form of small pieces over a period of 10 min and the resulting mixture was stirred for additional 15 min, upon which its color turned deep blue indicating the generation of anion. After stirring for additional 0.5 h at –78 °C, the temperature of the reaction mixture was slowly raised to 25 °C with concomitant removal of the ammonia by passing stream of argon though the reaction vessel. The resulting residue of enolate in THF was allowed to stir at 25 °C for 10 min and was again cooled to –78 °C. Dibromomethane (11.84 g, 68.05 mmol) was added to the reaction mixture dropwise, which was then allowed to stir at –78 °C for 1 h. Excess ammonium chloride (~10 g) was dumped in the reaction vessel in one shot and allowed to warm to room temperature. The residue was partitioned between chloroform (30 mL) and water (30 mL). The layers were separated and the aqueous layer was back extracted with chloroform (2 × 15 mL). The combined organic layer was washed successively with 10% sodium thiosulfate solution (20 mL), water (25 mL) and brine (15 mL). Drying over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure gave crude solid mass, which was purified by column chromatography (silica gel 100-200 mesh; eluent: pet. ether-ethyl acetate = 5:3) to obtain (-)-**91** (4.22 g, 88%) as white solid.

M.p.	**:**	108-110 °C
$[\alpha]_D^{25}$	**:**	-10.70 (*c* = 2.5, $CHCl_3$)
IR ($CHCl_3$)	**:**	ν_{max} = 2996, 1692, 1638, 1441, 732 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$)	**:**	δ = 1.86 (t, *J* = 6.8 Hz, 2H), 1.92-2.40 (m, 5H), 2.62 (td, *J* = 12.1, 6.4 Hz, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 3.55-3.75 (m, 2H), 4.02 (d, *J* = 10.2 Hz, 1H), 4.61-4.76 (m, 1H), 4.85 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.87 (dt,

J = 9.9, 3.8 Hz, 1H), 6.01 (d, *J* = 10.3 Hz, 1H), 6.57 – 6.94 (br. s, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ = 18.8, 21.5, 21.9, 26.9, 39.8, 46.6, 48.5, 52.4, 55.1, 126.2, 129.2, 169.6, 172.2.

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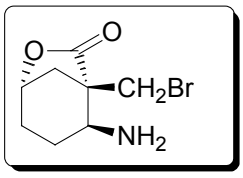
7. 2-Amino-1-bromomethyl-6-oxa-bicyclo[3.2.1]octan-7-one [(+)-107]:



A mixture of **91** (2 g, 6.76 mmol) and water-sulfuric acid (1:1, v/v, 12 mL) was heated to 90 ^{o}C for 7 h. The reaction mixture was cooled, diluted with water (10 mL) and made basic with solid sodium bicarbonate. Extraction with chloroform (3 × 10 mL) followed by drying over anhydrous sodium sulfate and concentration provided amino lactone (+)-**107** (1.35 g, 91%) in sufficiently pure form as a pale brown colored highly viscous oil.

$[\alpha]_D^{25}$: +62.62 (*c* = 0.65, $CHCl_3$)*

IR (Neat) : ν_{max} = 3447, 2985, 1781, 1255, 1118 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.27-1.73 (m, 2H), 1.91-2.35 (m, 4H), 2.42 (dd, *J* = 11.9, 5.7 Hz, 1H), 2.89-3.22 (br. s, 2H), 3.41 (d, *J* = 10.1 Hz, 1H), 3.82 (d, *J* = 10.1 Hz, 1H), 4.74 (t, *J* = 4.2 Hz, 1H).

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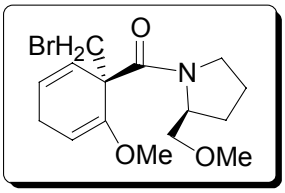
8. (1-Bromomethyl-2-methoxy-cyclohexa-2,5-dienyl)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone [(-)-110]:



This experiment was performed using same procedure as described for the preparation of (-)-**106**, except that 2.5 equivalent of sodium and dibromomethane were used, to obtain (-)-**110** from (-)-**96** in 91% yield.

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* $[\alpha]_D^{25}$ of (-)-108 = -40.0 (*c* = 1.4, $CHCl_3$)

$[\alpha]_D^{25}$		– 32.42 (*c* = 0.6, $CHCl_3$)
IR ($CHCl_3$)	**:**	ν_{max} = 2937, 1623, 1419, 1249, 1110, 757 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.58-2.21 (m, 4H), 2.26-2.73 (m, 2H), 3.11-4.08 (m, 10H), 4.21-4.55 (m, 3H), 4.76-4.93 (m, 1H), 5.57 (dt, *J* = 10.0, 2.1 Hz, 1H), 5.92 (d, *J* = 9.8 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ = 23.2, 24.1, 27.7, 45.8, 48.4, 54.2, 55.6, 56.0, 59.0, 72.3, 92.8, 120.7, 130.3, 155.2, 168.5.

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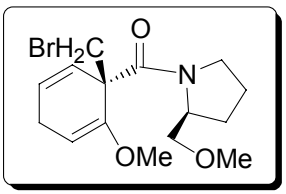
9. (1-Bromomethyl-2-methoxy-cyclohexa-2,5-dienyl)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone [(-)-111]:



This experiment was performed using same procedure as described for (-)-**91**, except that 2.5 equivalent of sodium and dibromomethane were used to obtain (-)-**111** from (-)-**96** in 88% yield

$[\alpha]_D^{25}$	**:**	-74.32 (*c* = 2.15, CH_2Cl_2).
IR ($CHCl_3$)	**:**	ν_{max} = 3014, 1660, 1637, 1600, 1458, 1400, 1218, 1172, 1120 cm^{-1}.
^1H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.60-1.94 (m, 4H), 2.60-3.04 (m, 2H), 3.15-3.35 (m, overlapping s at 3.27, 5H), 3.43-3.61 (m, overlapping s at 3.49, 5H), 3.71 (d, *J* = 10.2 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 4.16-4.31 (m, 1H), 4.85 (t, 3.4 Hz, 1H), 5.32 (dt, *J* = 9.8, 1.9 Hz, 1H), 5.99 (dt, *J* = 9.7, 3.4 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 24.8, 26.3, 26.9, 41.1, 46.4, 52.8, 54.4, 58.1, 58.9, 71.7, 95.1, 124.1, 128.8, 150.5, 168.4.

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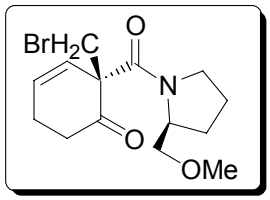
10. 2-Bromomethyl-2-(2-methoxymethyl-pyrrolidine-1-carbonyl)-cyclohex-3-enone [(-)-95]:



To a stirred solution of (-)-**111** (5.7 g, 16.57 mmol) in methanol (80 mL) was added 10% hydrochloric acid (20 mL) at 25 °C. After 24 h at room temperature, the reaction mixture was neutralized by addition of concentrated sodium bicarbonate solution and methanol was removed under reduced pressure. The aqueous mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvents under vacuum followed by column chromatography (silica gel, 100-200 mesh; eluent: pet. ether-ethyl acetate = 5:3) gave ketone (-)-**95** (4.82 g, 88%) as colorless oil.

$[\alpha]_D^{25}$	**:**	– 76.32 (*c* = 1.0, CH_2Cl_2)
IR (Neat)	**:**	ν_{max} = 2976, 1712, 1633, 1404, 1230, 1114, 754 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.69-2.05 (m, 4H), 2.55-2.81 (m, 4H), 3.03-3.21 (m, 1H), 3.30-3.53 (m, overlapping s at 3.38, 5H), 3.62 (dd, 9.5, 2.9 Hz, 1H), 3.86 (s, 1 H), 3.97 (s, 1H), 4.22-4.41 (m, 1H), 5.73 (dt, 9.8, 2.0 Hz, 1H), 6.21 (dt, 9.8, 4.2 Hz, 1H).
^{13}C NMR (50 MHz,$CDCl_3$)	**:**	δ = 24.4, 25.5, 26.5, 36.7, 37.2, 46.6, 58.1, 58.9, 60.9, 71.5, 126.4, 130.1, 166.5, 205.9.
Mass (GC-MS)	**:**	*m/z* = 331 (M+), 297, 284, 250, 240, 218, 204, 187, 176, 161, 142, 135, 107, 87, 70 (100%), 65, 45.

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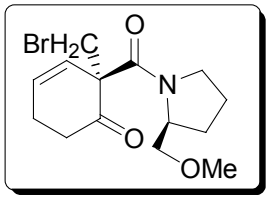
11. 2-Bromomethyl-2-(2-methoxymethyl-pyrrolidine-1-carbonyl)-cyclohex-3-enone [(-)-114]:



This experiment was performed using the same procedure as described for the preparation of (-)-**95**.

$[\alpha]_D^{25}$	**:**	$-$ 50.5 (*c* = 0.695, $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 1.57-1.99 (m, 4H), 2.61-3.11 (m, 5H), 3.34-3.60 (m, 5H), 3.66 (m, 1H), 3.84 (s, 1 H), 3.99 (s, 1H), 4.18-4.33 (m, 1H), 5.78 (dt, 10.0, 2.1 Hz, 1H), 6.07 (dt, 9.8, 3.8 Hz, 1H).
^{13}C NMR (50 MHz, CDCl3)	**:**	δ = 23.4, 24.8, 26.9, 37.3, 37.9, 47.7, 54.9, 55.8, 58.3, 71.3, 126.9, 129.8, 165.9, 194.8.

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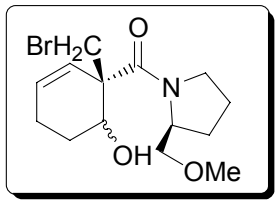
12. 1-Bromomethyl-6-hydroxy-cyclohex-2-enyl)-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (112):



To a solution of (-)-**95** (4.82 g, 14.61 mmol) in methanol (50 mL) was added sodium borohydride (0.65 g, 17.57 mmol) in small portions at 0 °C over a period of ten minutes. The reaction mixture was allowed to warm to room temperature and the progress monitored by TLC. The starting material was consumed after stirring for 4 h at room temperature. Methanol was evaporated under reduced pressure and the residue dissolved in minimum amount of water, acidified to pH 3 with 1N HCl, and extracted with ethyl acetate (3 $\times$ 15 mL.). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. GC analysis indicated a 1:1 diastereomeric ratio. The two diastereomers were easily separated by silica gel column chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 1:1) to give **112a** (2.24 g) as a white solid and **112b** (2.32 g) as viscous colorless oil (combined yield = 94%).

a) Data for 112a (hydroxy trans to amide moiety):

M.p.	**:**	76–78 °C
IR (Neat)	**:**	ν_{max} = 3431, 3008, 1608, 1406, 1394, 1217, 1116, 910, 756 cm^{-1}
^{1}H NMR	**:**	δ = 1.49-1.87 (m, 6H), 1.98-2.14 (m, 2H), 2.26-2.45

(500 MHz, $CDCl_3$) (br. s, 1H), 3.18 (s, 3H), 3.21-3.34 (m, 4H), 3.48-3.65 (m, 1H), 4.05 (s, 1H), 4.10 (s, 1H), 4.26 (t, *J* = 5.3 Hz, 1 H), 5.75 (dt, *J* = 10.1, 3.4 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ = 23.1, 25.1, 25.9, 26.5, 39.2, 48.6, 54.5, 58.5, 59.0, 71.8, 72.0, 127.2, 129.2, 171.6.

Mass (GC-MS) : *m/z* = 333 (M^++1), 297, 284, 250, 240, 218, 204, 187, 176, 159, 142, 135, 107, 82, 70 (100%), 65, 45.

b) Data for 112b (hydroxy cis to amide moiety)

IR ($CHCl_3$) : ν_{max} = 3331, 2929, 1591, 1405, 1267, 1117, 736 cm^{-1}**.**

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.56-2.08 (m, 6H), 2.19-2.36 (m, 2H), 3.34 (s, 3H), 3.45-3.71 (m, 4H), 4.14 (s, 1H), 4.21 (s, 1H), 4.32-4.48 (m, 1H), 4.63-4.74 (m, 1H), 5.77- 6.01 (m, 2H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ = 25.2, 25.4, 26.5, 28.5, 39.7, 49.4, 53.1, 58.9 (2C), 72.0, 74.4, 127.8, 130.3, 173.1.

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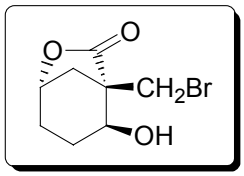
13. 1-Bromomethyl-2-hydroxy-6-oxa-bicyclo[3.2.1]octan-7-one (113a):



This experiment was performed using same procedure as described for the preparation of (+)-**107** from (-)-**91** to obtain **113a** from **112a**.

Yield : 87%

M.p. : 109-111 °C

IR ($CHCl_3$) : ν_{max} = 3461, 2956, 1770, 1452, 1361, 1265, 1184, 1006, 977, 738 cm^{-1}**.**

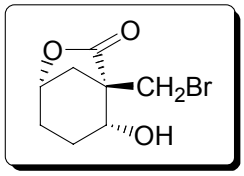
^{1}H NMR : δ = 1.68-1.94 (m, 4H), 2.31 (dd, *J* = 11.8, 3.0 Hz,

(200 MHz, $CDCl_3$) 1H), 2.46 (dd, *J* = 11.8, 5.8 Hz, 1H), 2.65-2.88 (br. s, 1H), 3.59 (d, *J* = 3.2 Hz, 1H), 3.74 (d, *J* = 3.1 Hz, 1H), 3.85-3.94 (m, 1H), 4.75-4.86 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ = 24.2, 27.7, 32.8, 44.0, 53.4, 67.8, 77.0, 176.9.

Mass (GC-MS) : *m/z* = 235 (M^+), 221, 204, 190, 174, 160, 142 (100%), 114, 98, 82, 70, 67, 45.

14. 1-Bromomethyl-2-hydroxy-6-oxa-bicyclo[3.2.1]octan-7-one (113b):



This experiment was performed using same procedure as described for the preparation of (+)-**107** from (-)-**90**, except that the reaction mixture was refluxed for 30 h to obtain **113b** from **112b**.

Yield : 63%

IR ($CHCl_3$) : ν_{max} = 3442, 2995, 1776, 1272, 1181, 980, 735 cm^{-1}.

^{1}H NMR : δ = 1.74-2.02 (m, 4H), 2.37 (dd, 11.5, 2.8 Hz, 1H), 2.53 (dd, 11.6, 5.5 Hz, 1H), 3.68 (d, 3.3 Hz, 1H), 3.87 (d, 3.3 Hz, 1H), 4.21-4.34 (m, 1H), 4.96-5.07 (m, 1H).

(200 MHz, $CDCl_3$)

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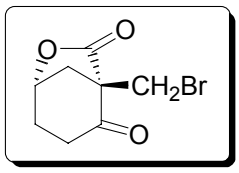
15. 1-Bromomethyl-6-oxa-bicyclo[3.2.1]octane-2,7-dione (89):



A mixture of **113a/b** (0.75 g, 3.19 mmol), pyridinium dichromate (PDC, 1.8 g, 4.79 mmol) and celite (1.5 g) in dichloromethane (12 mL) was stirred for 12 h. Additional PDC (1.8 g, 4.79 mmol) was added and the stirring continued for another 12 h. Ethyl acetate (30 mL) was added to the reaction mixture and the contents were filtered through a pad of celite. The filtrate was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (100-200 mesh; eluent: pet. ether-ethyl acetate = 5:3) to give **89** (0.69 g, 93%) as a colorless liquid.

IR (Neat)	**:**	ν_{max} = 3055, 1785, 1718, 1419, 1353, 1267, 1120, 956, 738 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ = 2.01-2.34 (m, 2H), 2.38-2.57 (m, 1H), 2.65-2.77 (m, 2H), 3.13 (ddd, *J* = 12.5, 5.9, 2.5 Hz, 1H), 3.94 (s, 1H), 3.97 (s, 1H), 5.02-5.11 (m, 1H).
^{13}C NMR (50 MHz, CDCl3)	**:**	δ = 29.1, 34.5, 36.5, 40.2, 61.6, 75.1, 171.4, 199.0.
Mass (GC-MS)	**:**	*m/z* = 233 (M^+), 218, 201, 188, 174, 160, 142, 15, 119, 100, 91, 70 (100%), 65, 45.
Elemental analysis	**:**	$C_8H_9O_3Br$ (233.062): Calcd. C 41.23, H 3.89; Found C 41.07, H 3.96.

4. References

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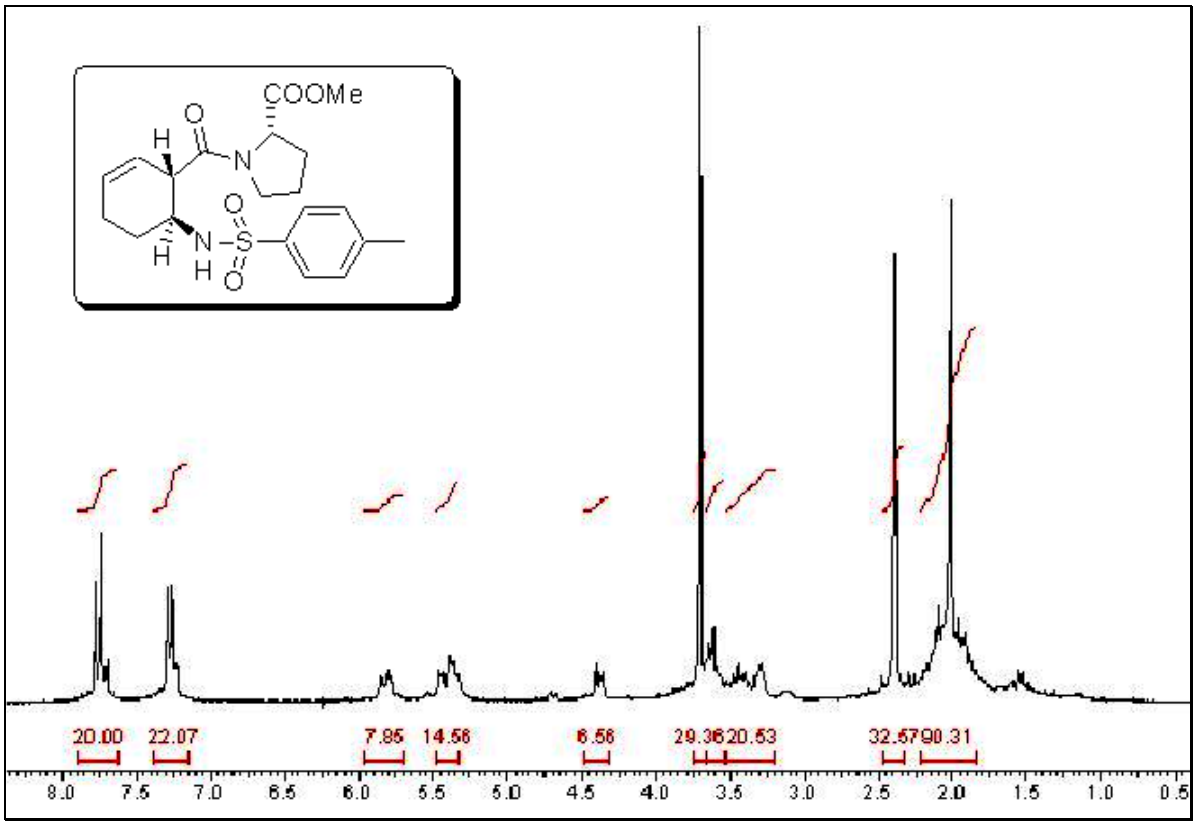

Figure 3. ^{1}H NMR spectrum of 101

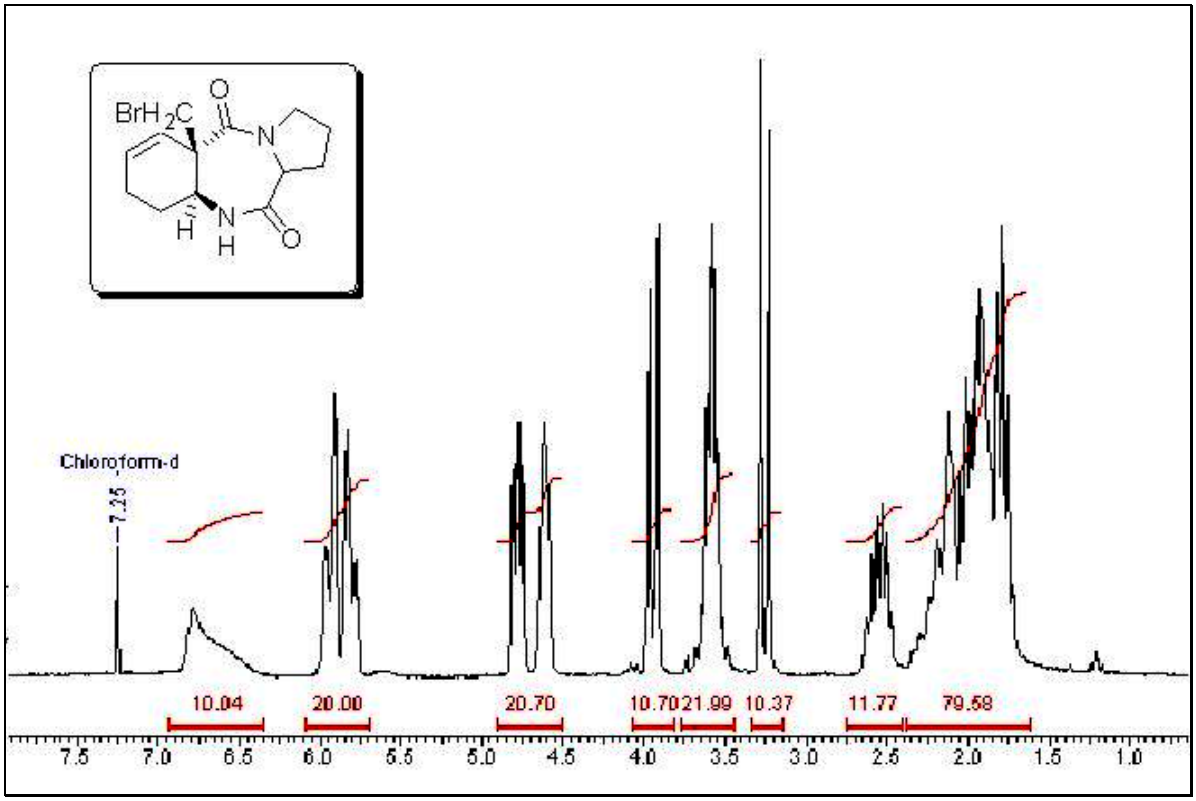

Figure 4. ^{1}H NMR spectrum of (-)-91

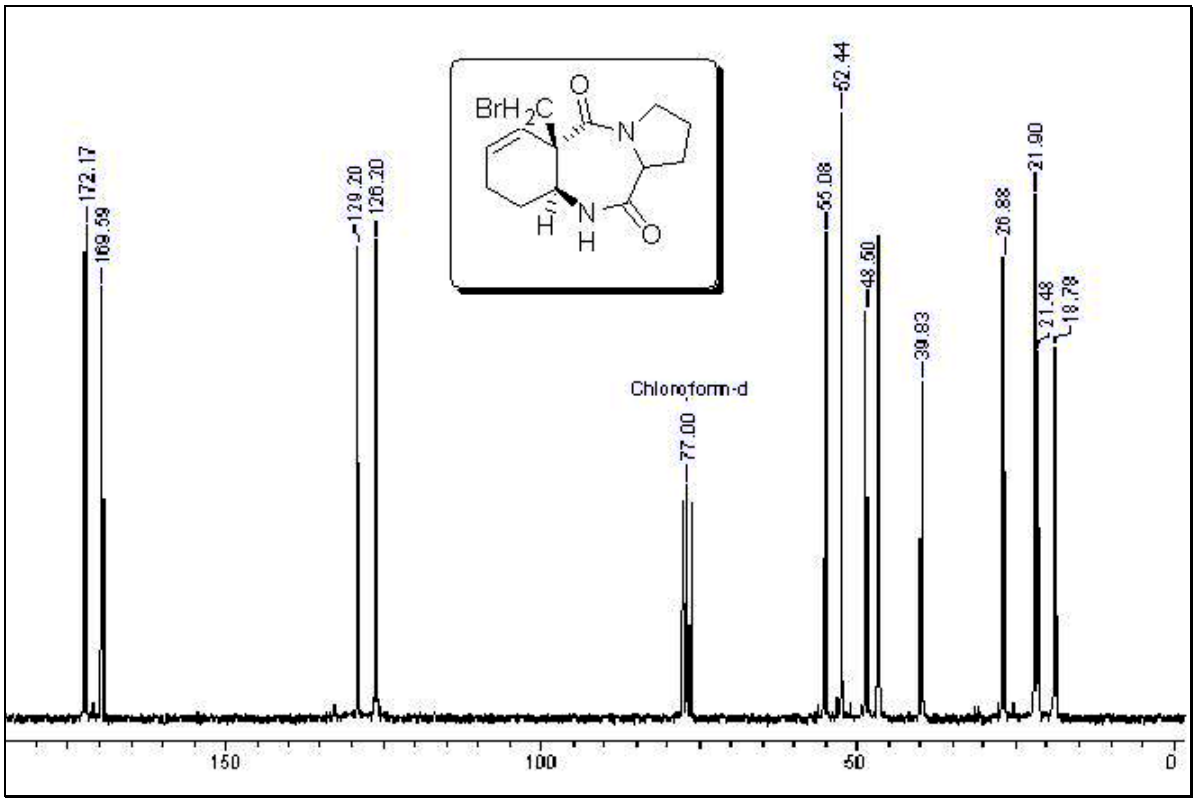

Figure 5. ^{13}C NMR spectrum of (-)-91

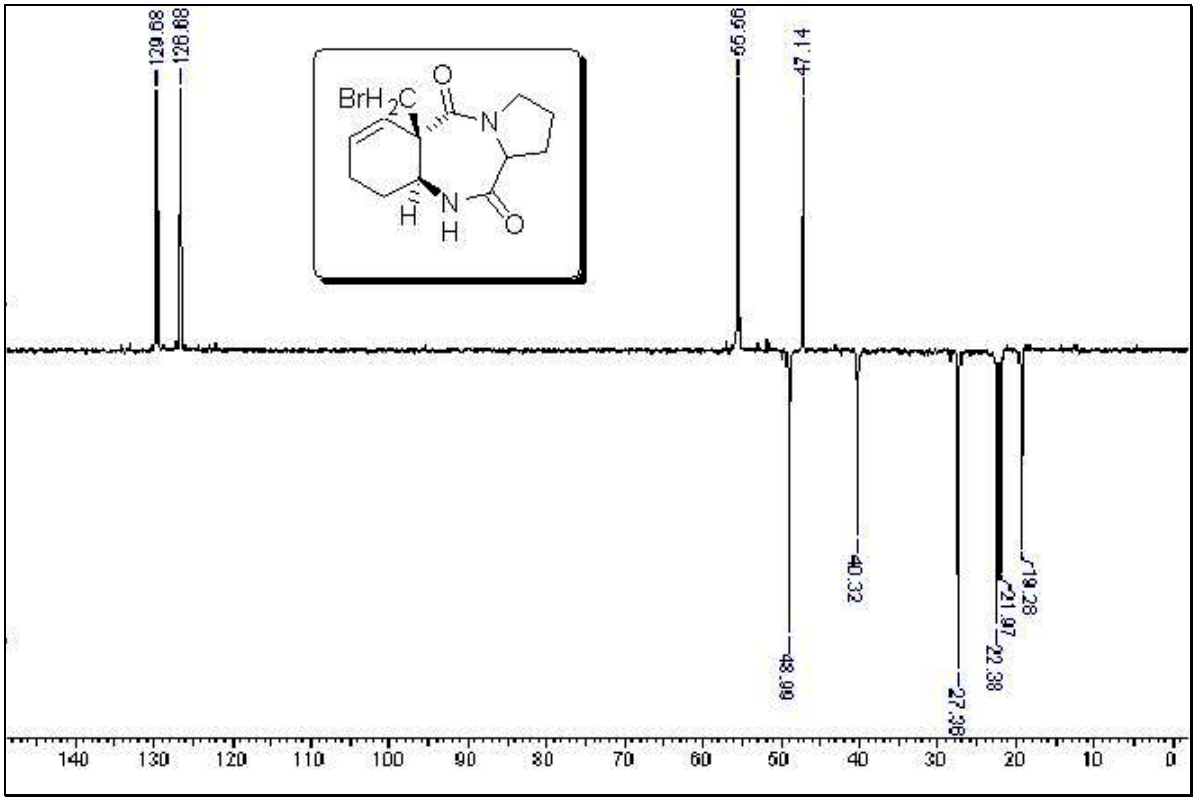

Figure 6. DEPT spectrum of (-)-91

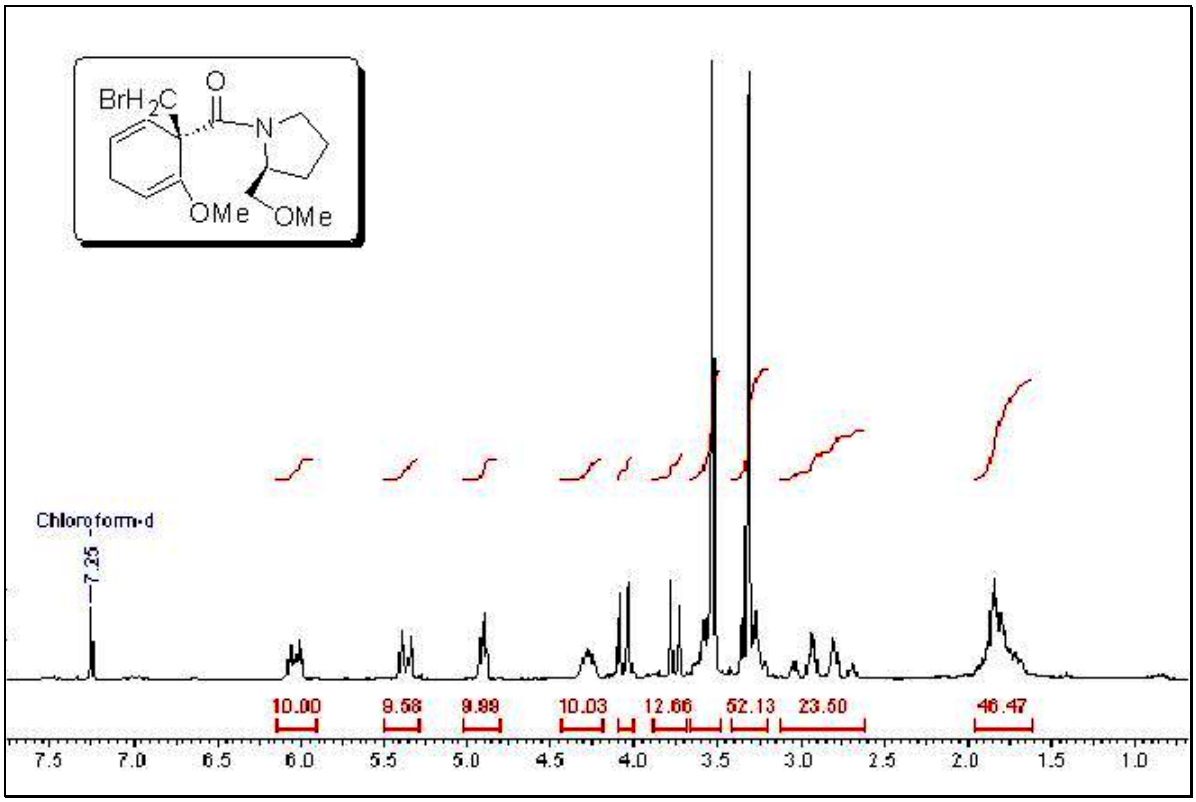

Figure 7. ^{1}H NMR spectrum of (-)-111

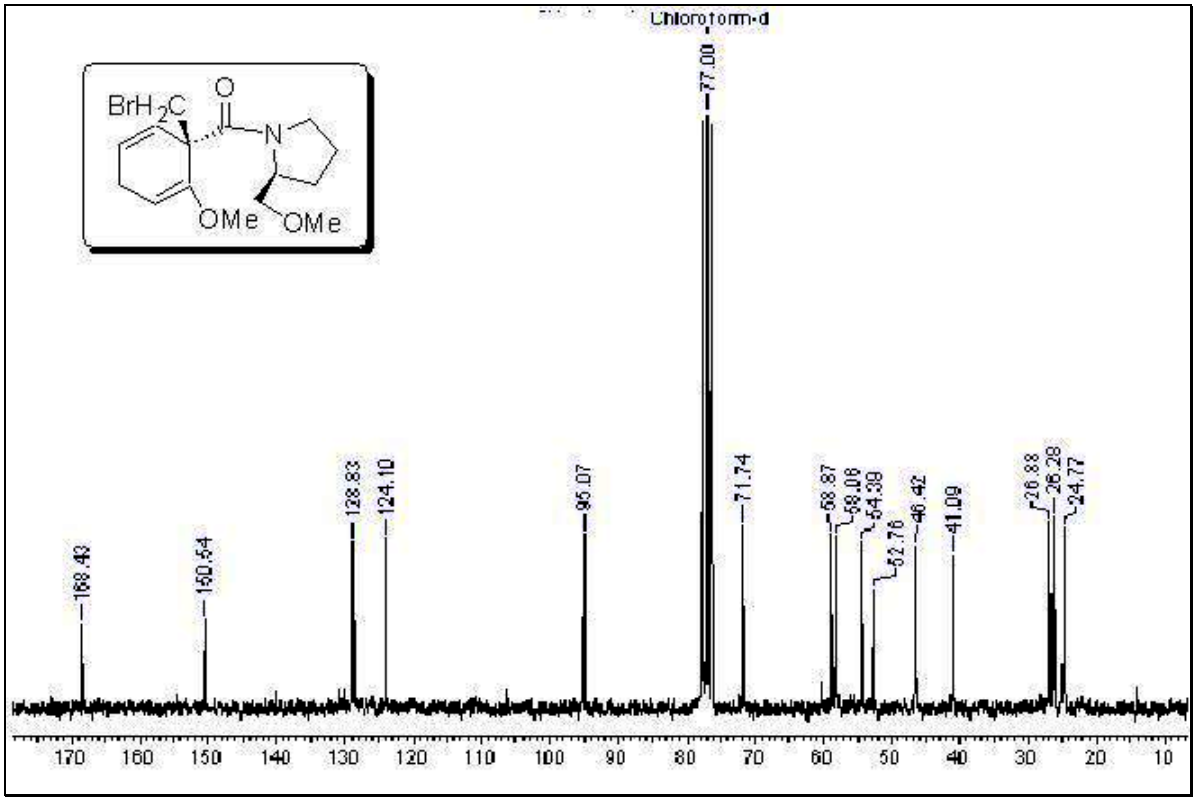

Figure 8. ^{13}C NMR spectrum of (-)-111

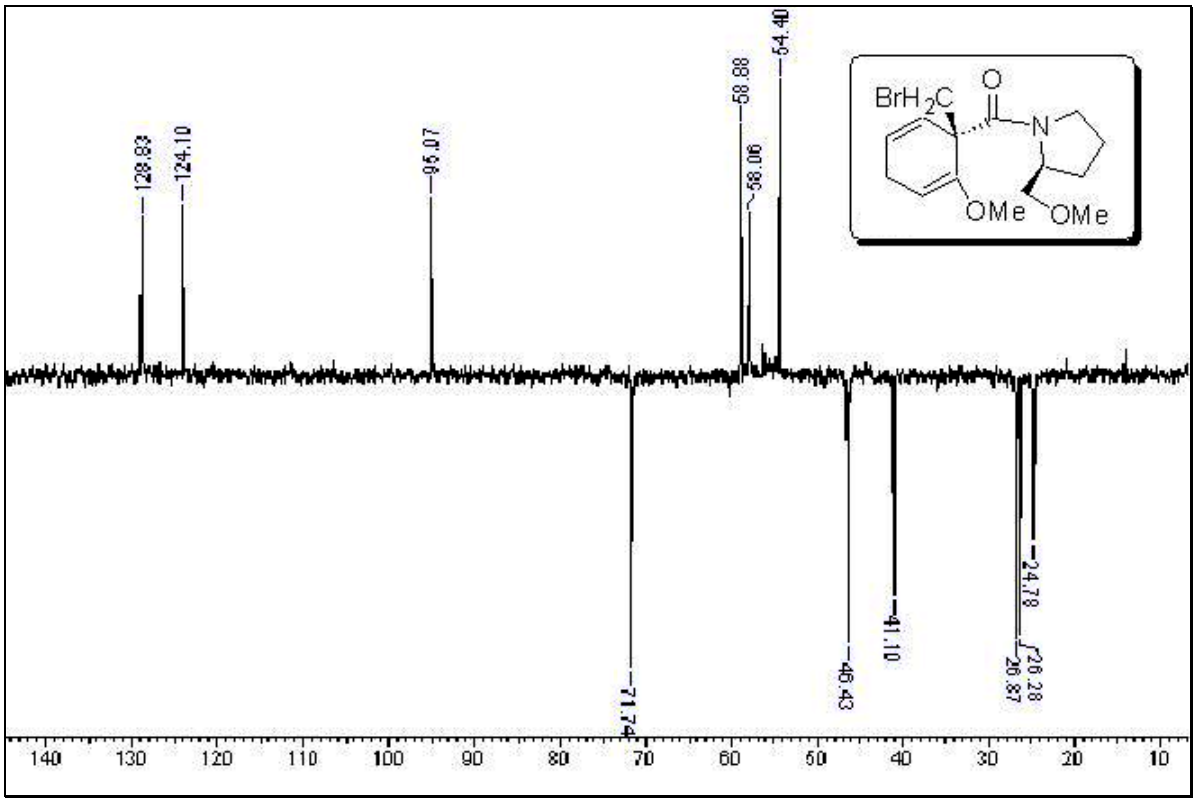

Figure 9. DEPT spectrum of (-)-111

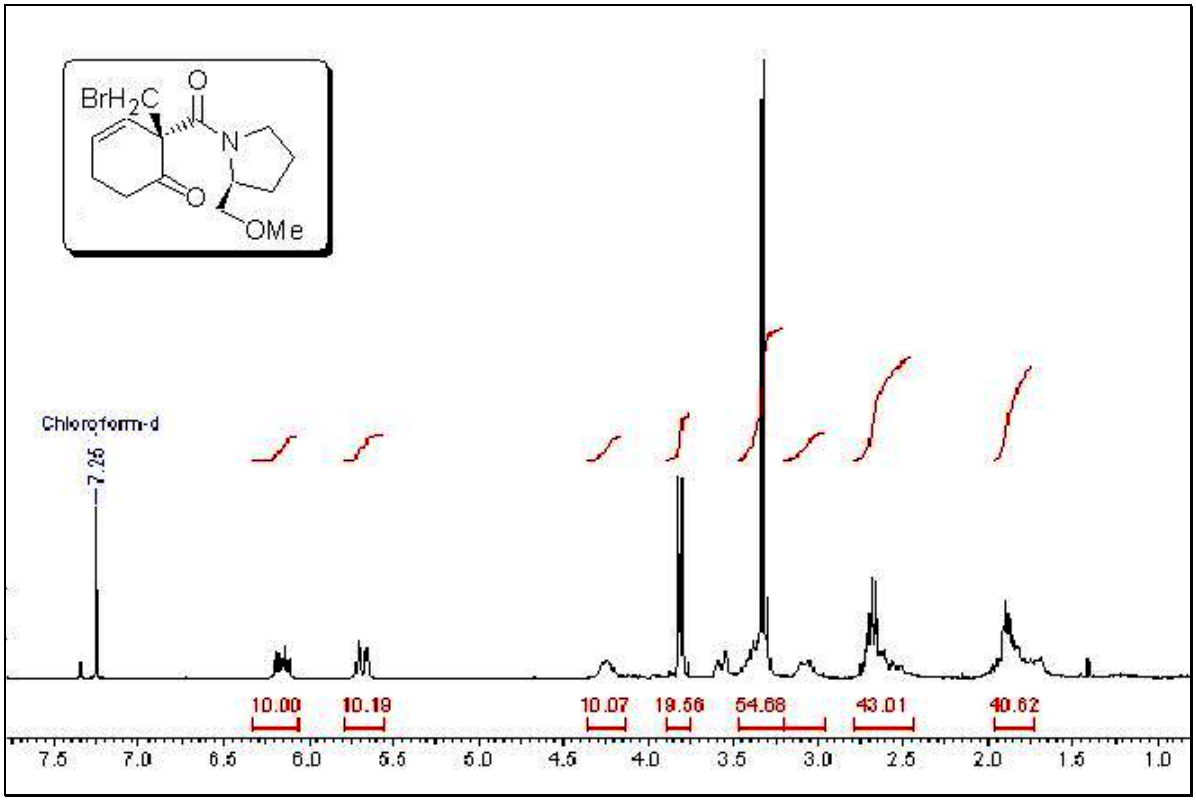

Figure 10. ^{1}H NMR spectrum of (-)-95

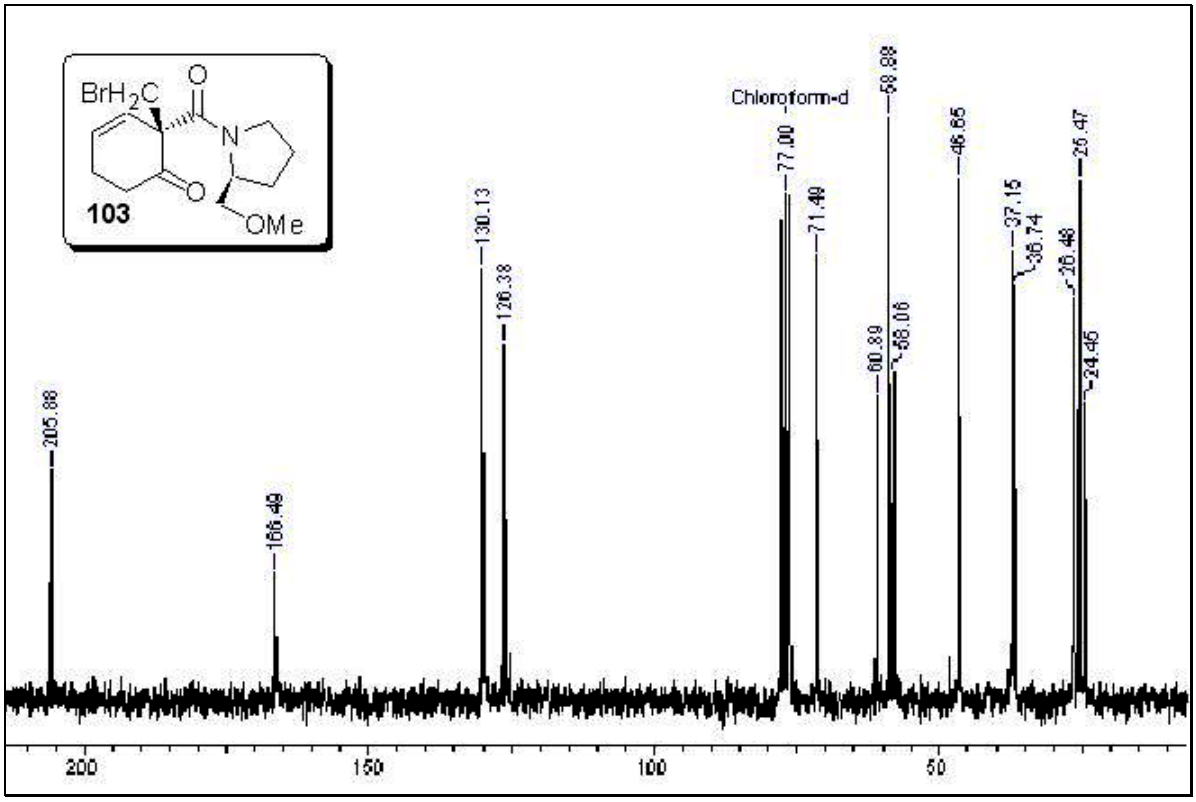

Figure 11. ^{13}C NMR spectrum of (-)-95

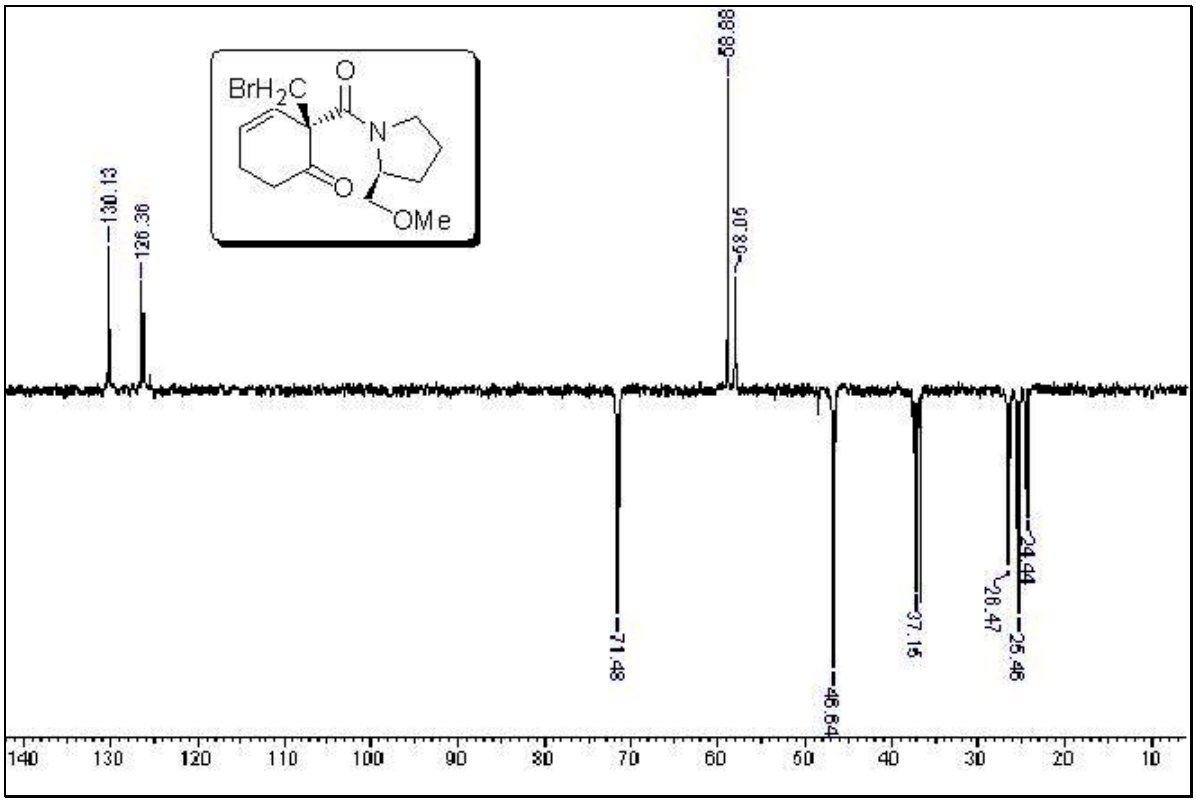

Figure 12. DEPT spectrum of (-)**-95**

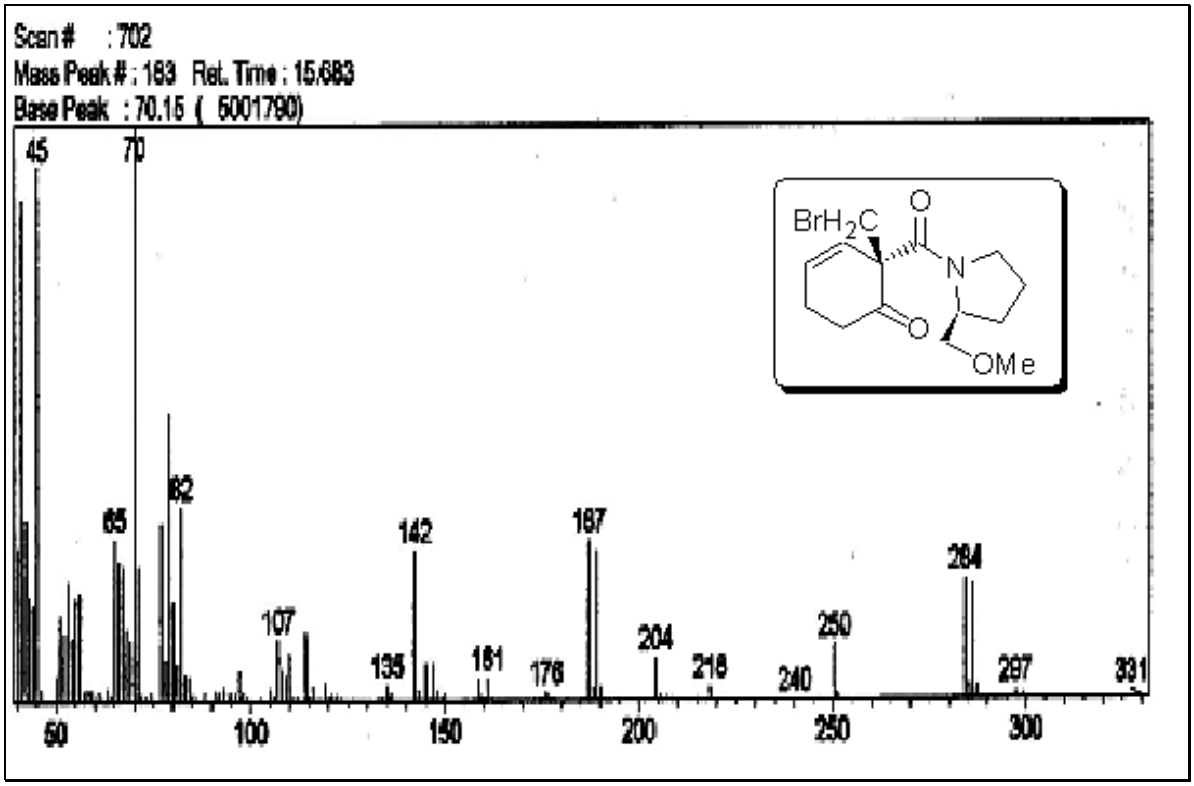

Figure 13. Mass spectrum (GC-MS) of (-)-95

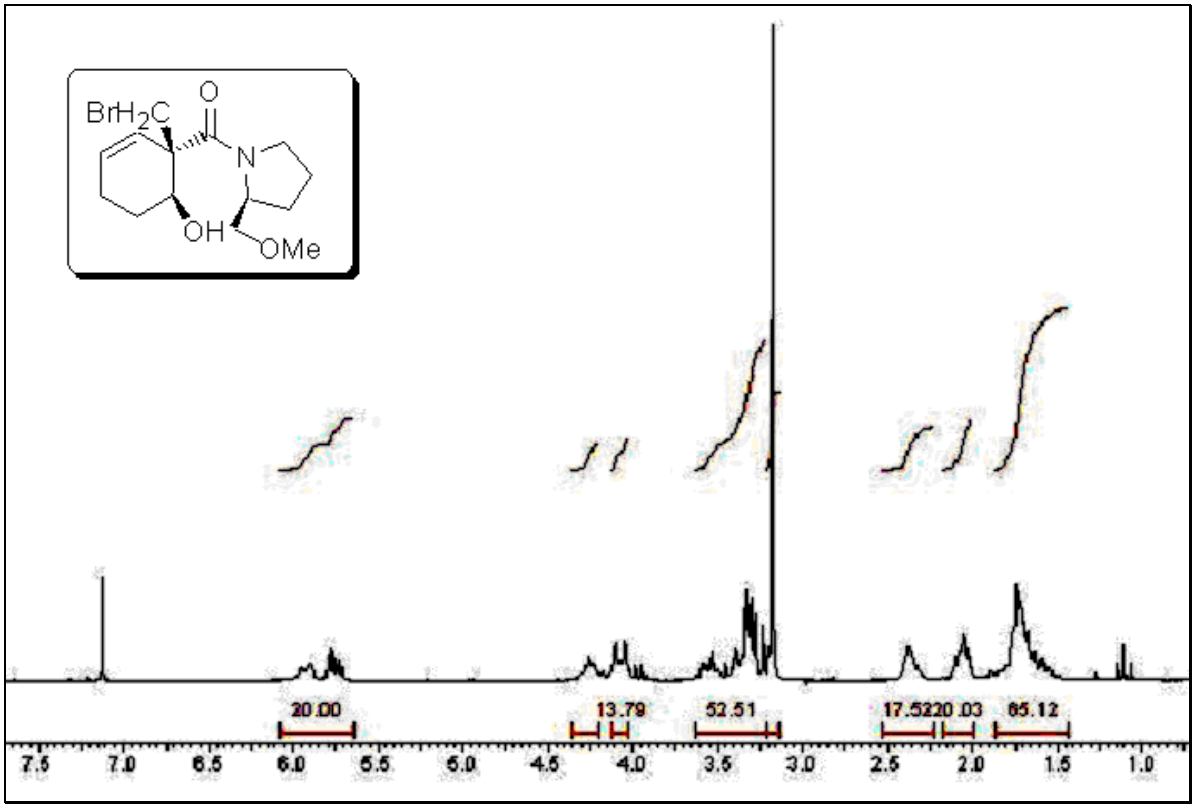

Figure 14. ^{1}H NMR spectrum of 112a

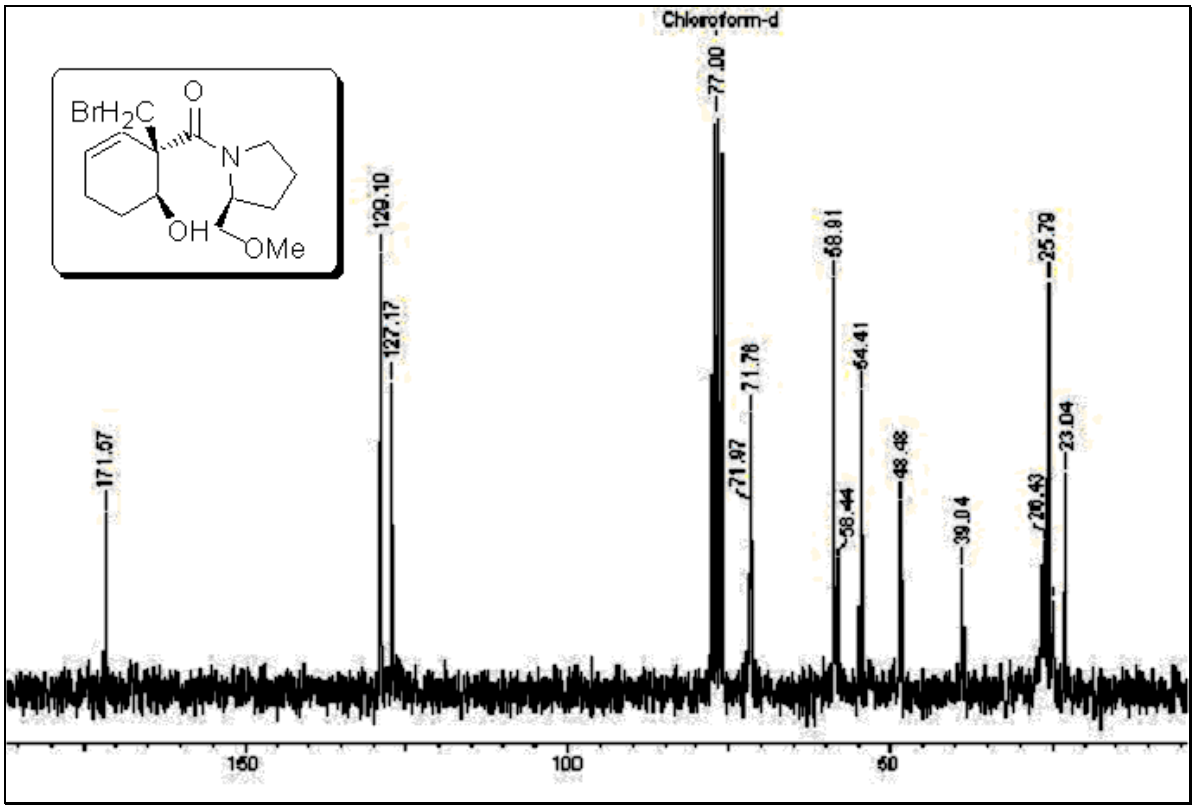

Figure 15. ^{13}C NMR spectrum of 112a

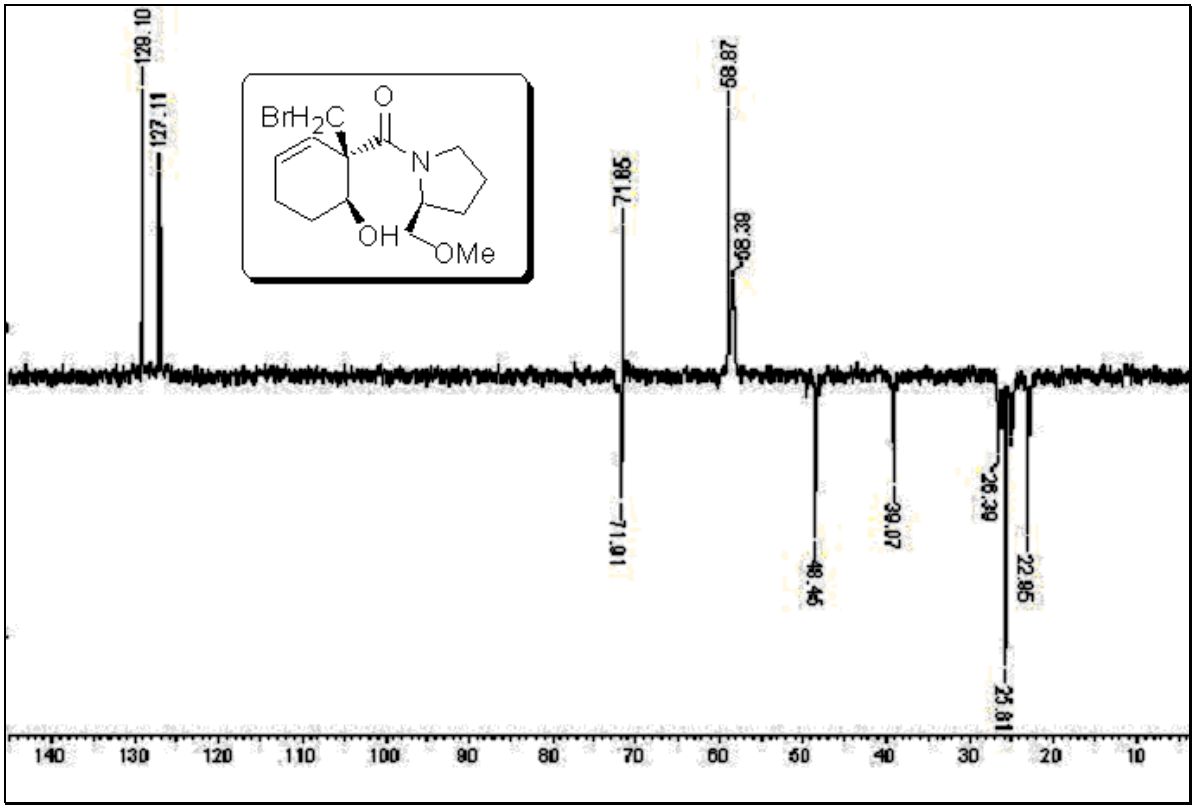

Figure 16. DEPT spectrum of 112a

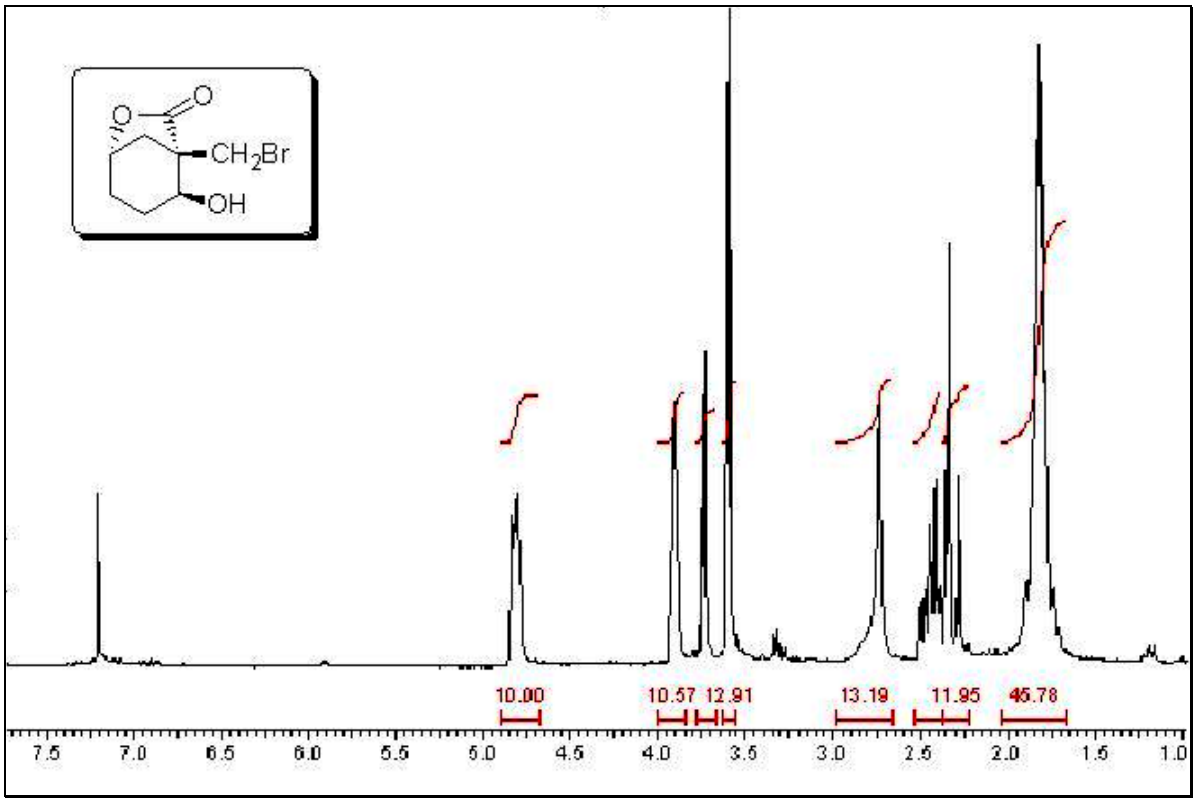

Figure 17. ^{1}H NMR spectrum of 113a

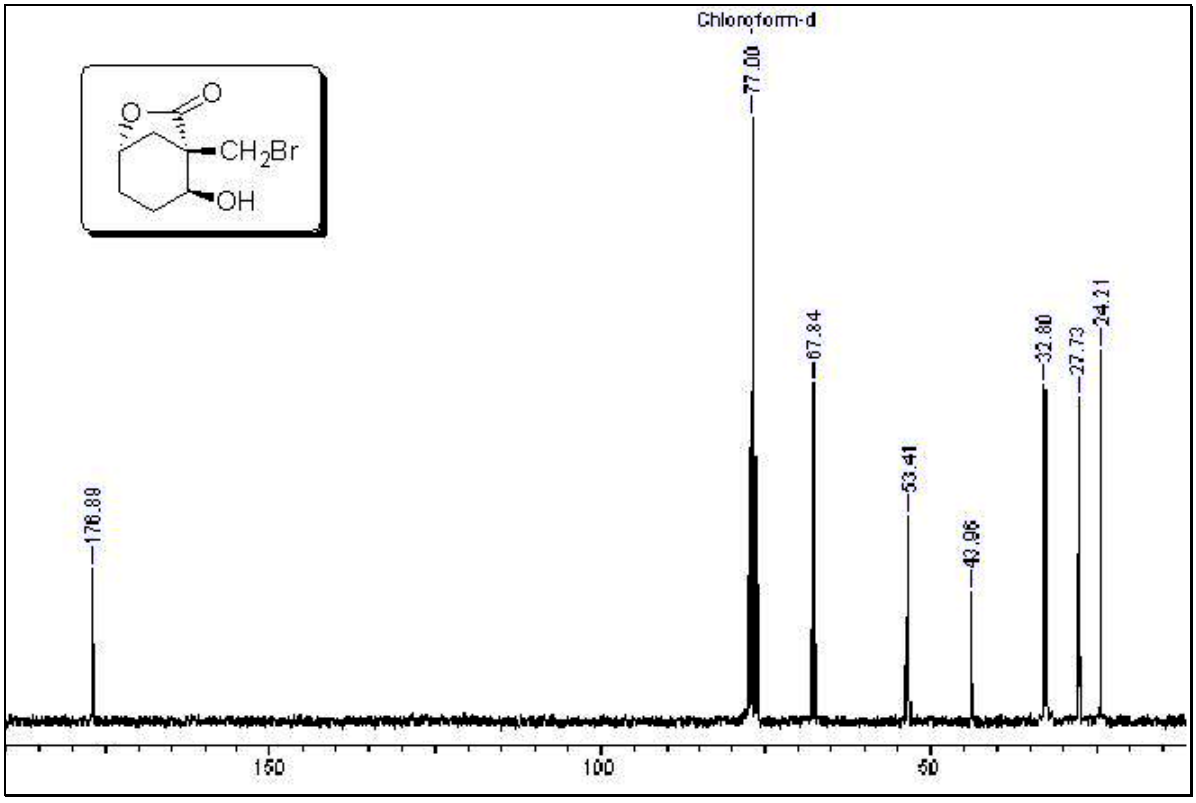

Figure 18. ^{13}C NMR spectrum of 113a

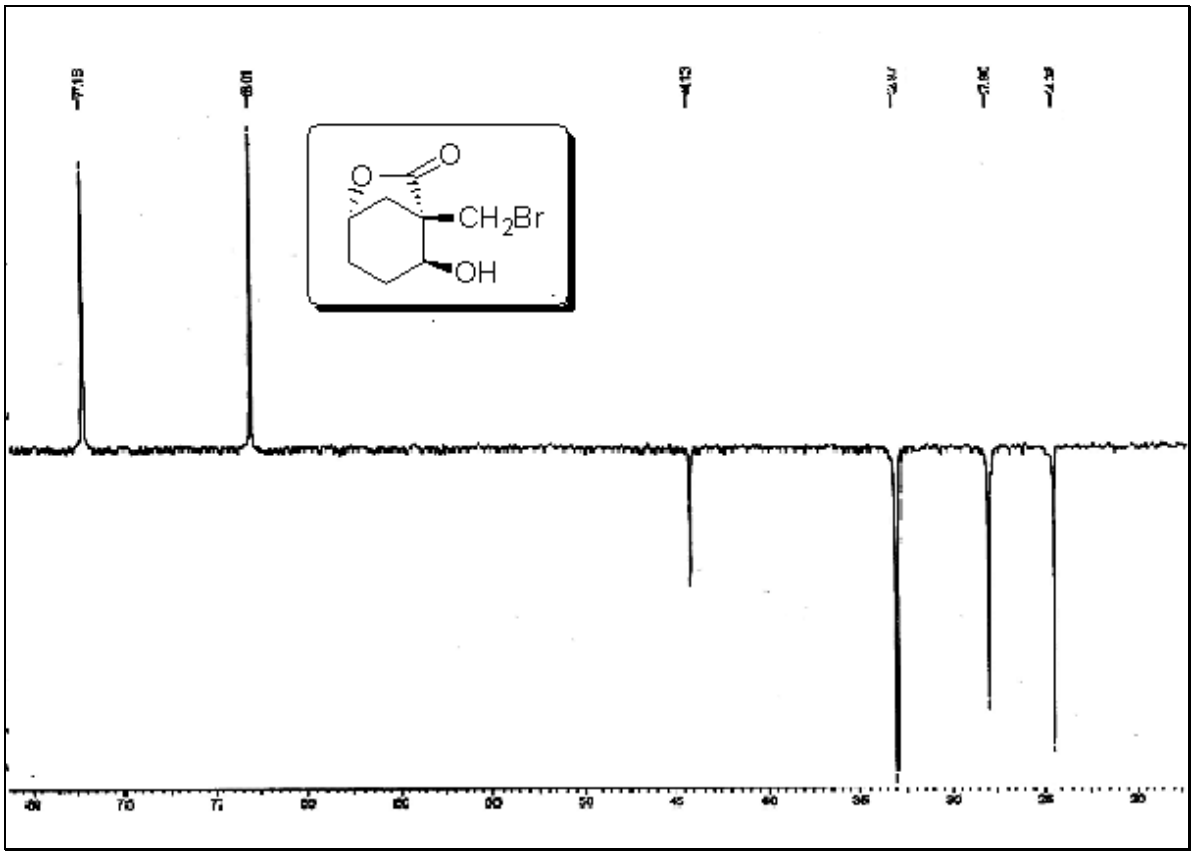

Figure 19. DEPT spectrum of 113a

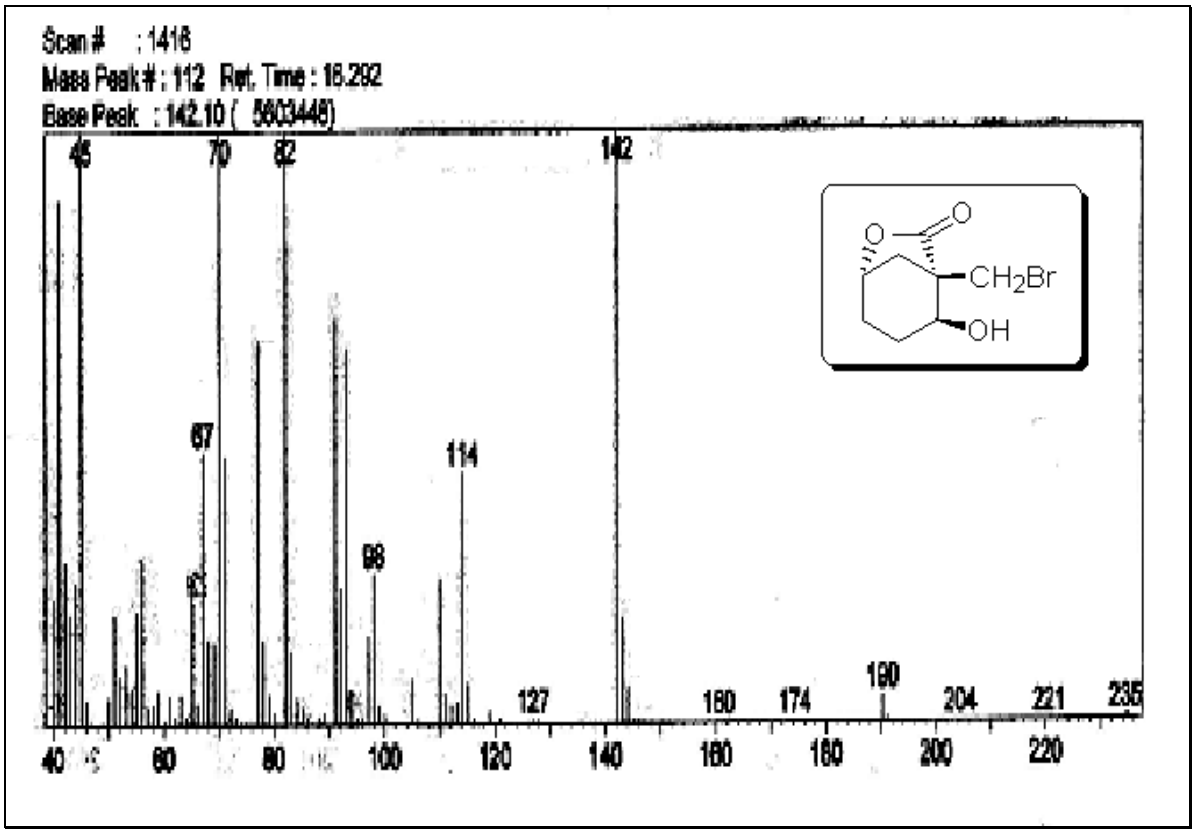

Figure 20. Mass spectrum (GC-MS) of 113a

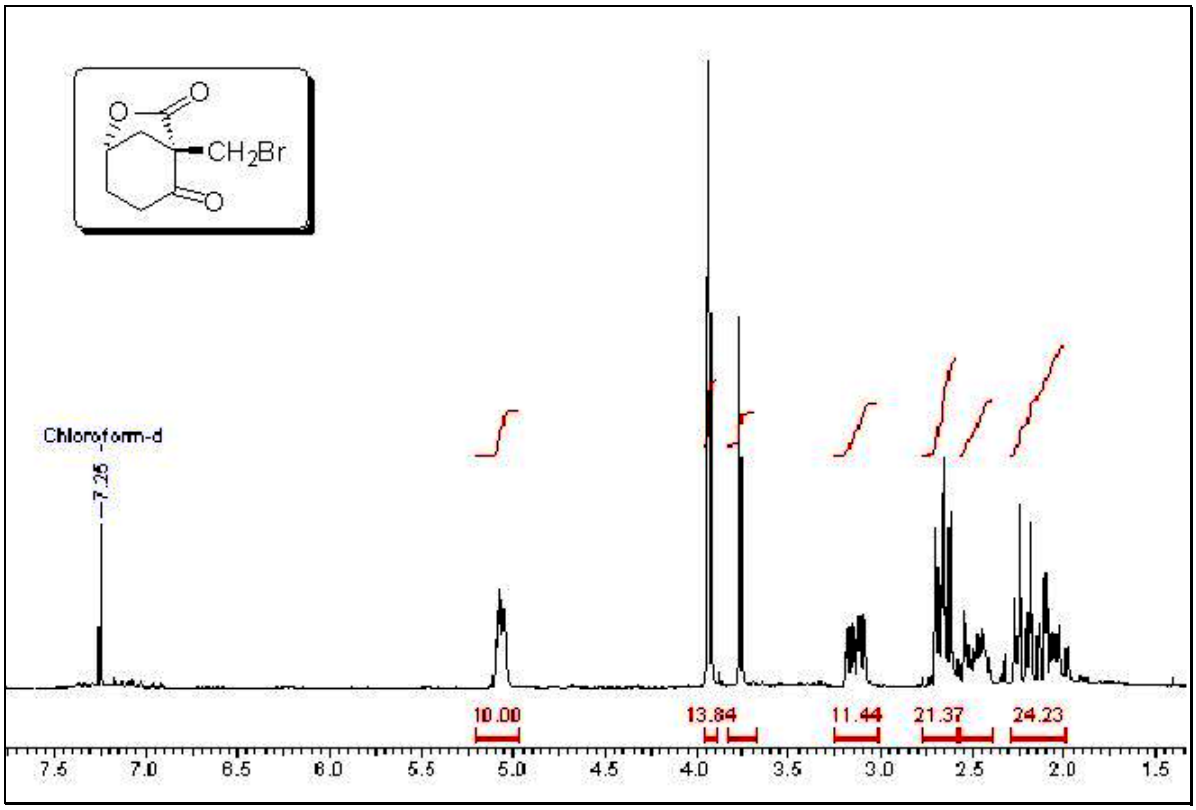

Figure 21. ^{1}H NMR spectrum of (+)-89

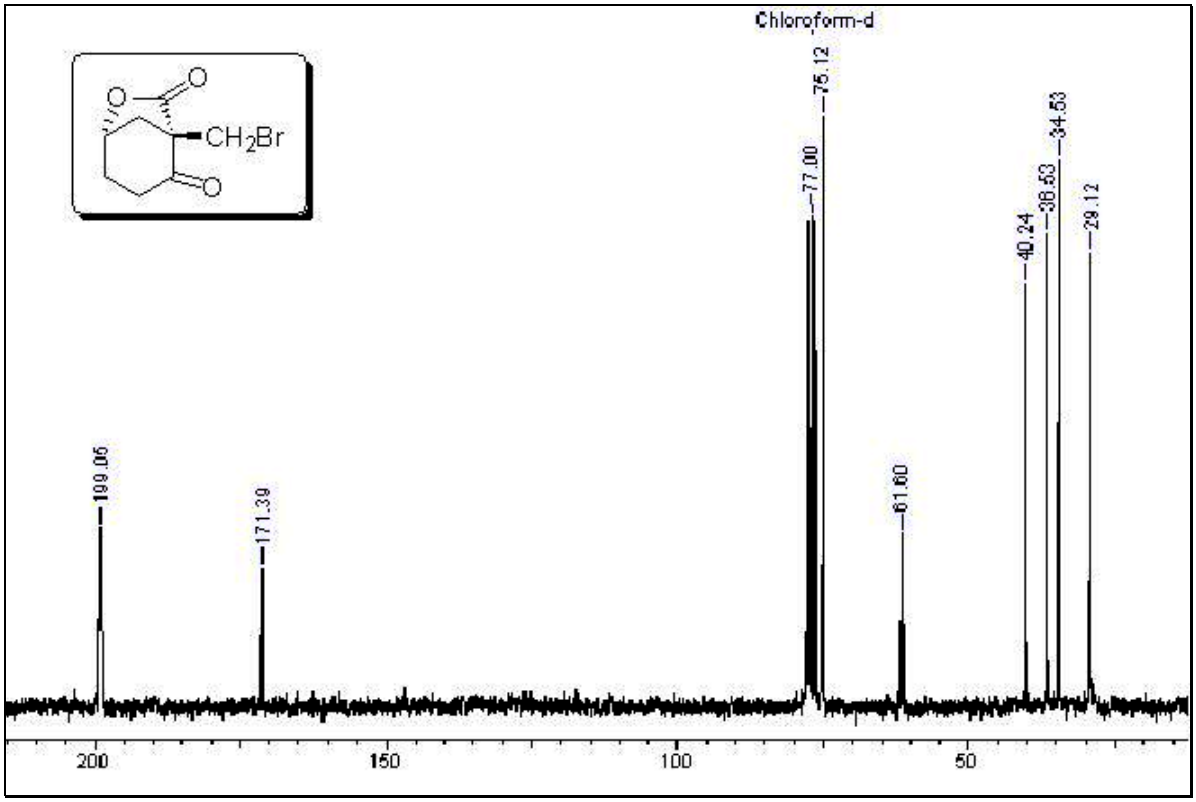

Figure 22. ^{13}C NMR spectrum of (+)-89

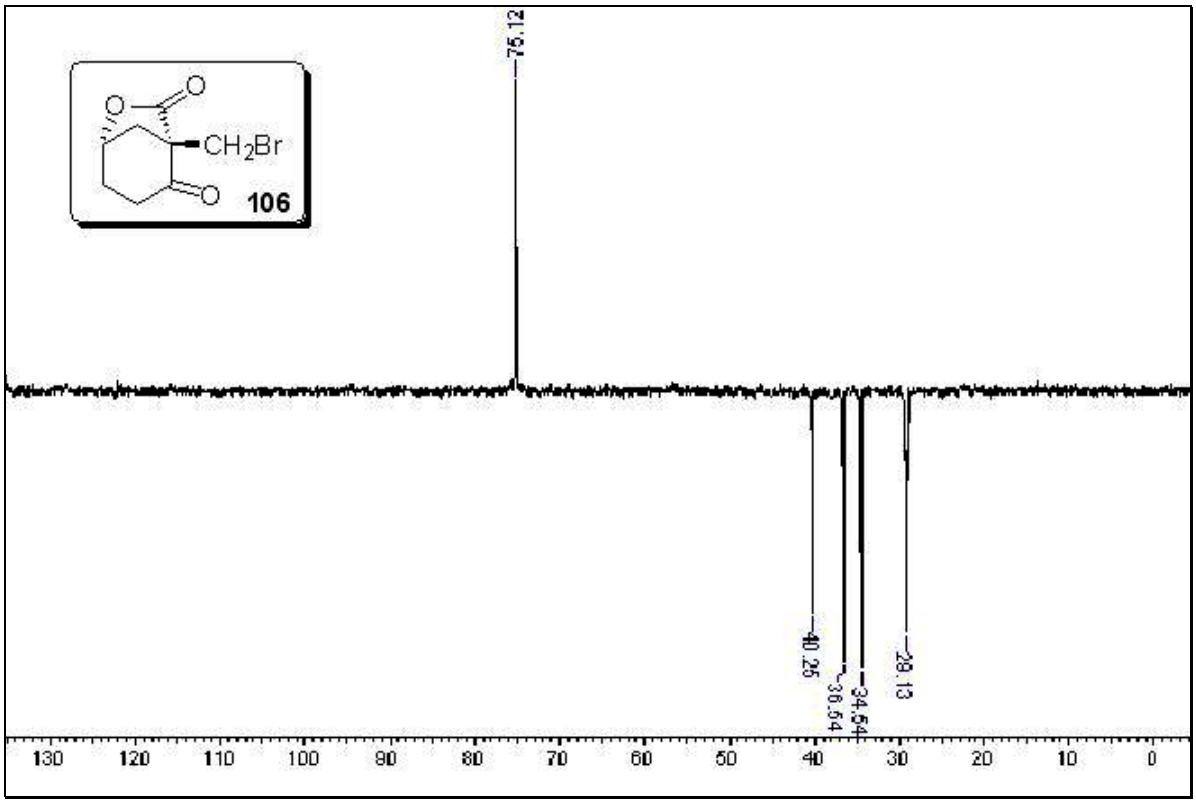

Figure 23. DEPT spectrum of (+)-89

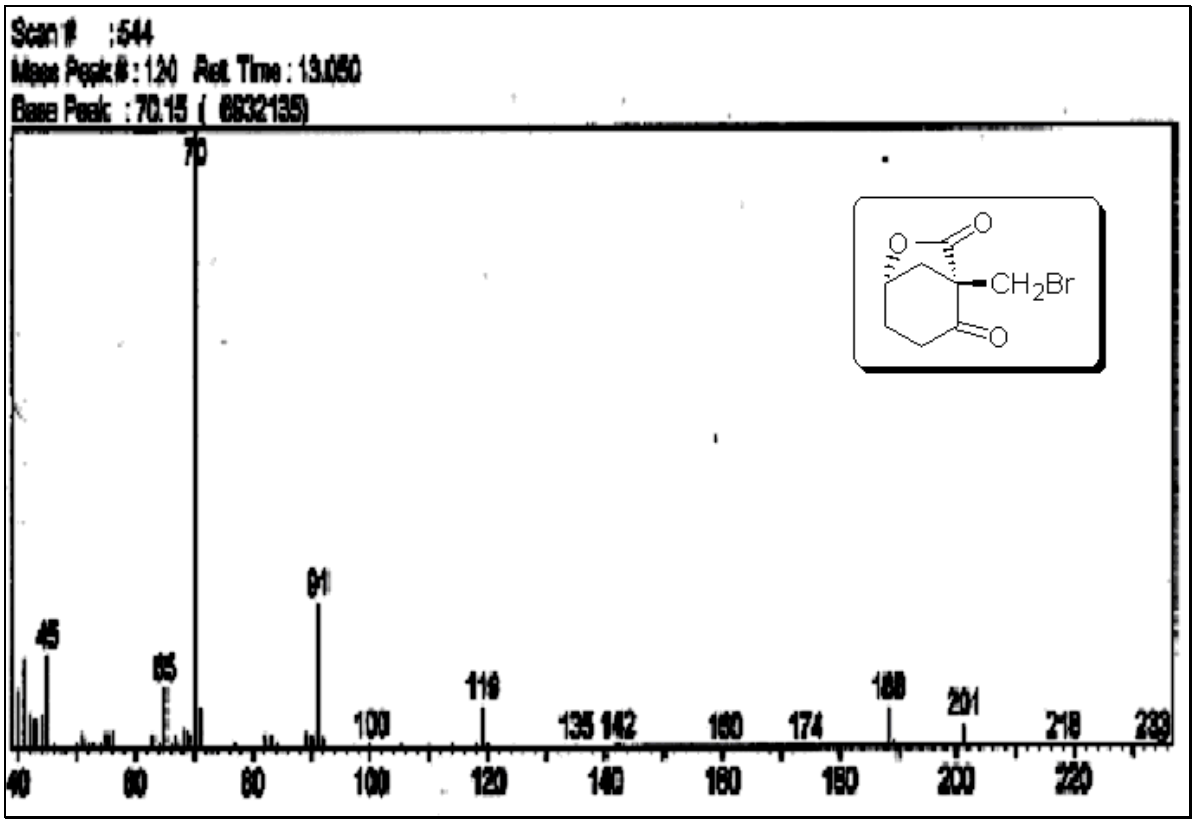

Figure 24. Mass spectrum (GC-MS) of (+)-89

LIST OF ABBREVIATIONS

1,25-$(OH)_2$-D_3 / 1,25-D_3	1α,25-dihydroxy vitamin D_3
Ac	acetyl
Ar	aryl
aq	aqueous
AIBN	2,2'-azobissobutyronitrile
bp	boiling point
n-BuLi	*n*-butyl lithium
t-BuLi	*tert*-butyl lithium
Bz	benzoyl
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAH	diisobutylaluminium hydride
DIAD	diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)-pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
Et_3N	triethyl amine
g	gram
h	hour
HMPA	hexamethylphosphoramide
IR	infra red
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
LAH	lithium aluminium hydride
M	molar

MCPBA / *m*-CPBA	3-chloroperoxybenzoic acid
mL	milliliter
mmol	millimole
mp	melting point
MsCl	methanesulphonyl chloride
NaHMDS	sodium hexamethyldisilazane
NMR	nuclear magnetic resonance
NMU	*N*-nitroso-*N*-methyl urea
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPh_3	triphenyl phosphine
PPTs	pyridinium *p*-toluenesulfonate
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TEA	triethyl amine
p-TsOH	*p*-toluene sulfonic acid
p-TsCl	*p*-toluene sulfonyl chloride

List of Publications

1. A simple strategy for the synthesis of optically pure *trans*-hydrindane systems. Ganesh Pandey* and **Sanjay B. Raikar**. *Tetrahedron Lett*. **2006**, *in press*.

2. Enantioselective synthesis of CD-rings precursors of 1α,25-dihydroxy vitamin D_3 and some of its structurally modified analogues. Ganesh Pandey* and **Sanjay B. Raikar**. (Manuscript under preparation).