DESIGN AND SYNTHESIS OF COMBRETASTATIN A-4 ANALOGUES, SYNTHESIS OF TERREIN AND SYNTHETIC STUDIES TOWARDS KODAISTATIN

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"DESIGN AND SYNTHESIS OF COMBRETASTATIN A-4 ANALOGUES, SYNTHESIS OF TERREIN AND SYNTHETIC STUDIES TOWARDS KODAISTATIN"** submitted by P. D. Shinde was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

Dr. (Mrs.) R. D. WAKHARKAR Date:

Research Supervisor

DECLARATION

I hereby declare that the work presented in the thesis entitled **"DESIGN AND SYNTHESIS OF COMBRETASTATIN A-4 ANALOGUES, SYNTHESIS OF TERREIN AND SYNTHETIC STUDIES TOWARDS KODAISTATIN"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory (Pune), under the supervision of Dr. (Mrs.) R. D. Wakharkar. 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.

P. D. Shinde

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Date:

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Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
B. P.	Boiling point
$BF_3.OEt_2$	Borontrifluoride diethyl etherate
br	Broad (signal)
$CDCl_3$	Deuterated chloroform
d	Doublet
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	Ethylene dichloride
ee	Enantiomeric excess
g	Grams
GC	Gas chromatography
h	Hours
IR	Infra red
m	Multiplet
M. P.	Melting point
M^+	Molecular ion
mg	Milligrams
min	Minutes
ml	Millilitre
mmol	Millimole
n-BuLi	n-Butyllithium
Na_2SO_4	Sodium sulfate
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
$Pd(dba)_2$	Palladium di-benzylidine acetone
PPTS	Pyridinium *p*-toluenesulfonate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
q	Quartet
r. t.	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
$TiCl_4$	Titanium (IV) chloride
TLC	Thin layer chromatography
$ZnCl_2$	Zinc chloride

General remarks

1) All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware.
2) Progress of the reaction was monitored by TLC and was visualized by UV absorption by florescence quenching or I_2 staining or by both.
3) Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi or Heidolph rotary evaporator. Silica gel for column chromatography was 60-120 mesh.
4) Optical measurements were recorded on a JASCO digital polarimeter.
5) All the temperatures are in ^{0}C. All the melting points and boiling points are in ^{0}C and are uncorrected and were recorded on Buchi B-540 melting point apparatus.
6) IR spectra were recorded on a Perkin-Elmer infra-red spectrometer model 599-B and model 1620 FT-IR (υ-max in cm^{-1}).
7) Unless otherwise stated, ^{1}H-NMR spectra were recorded using TMS as internal reference on Bruker AC-200, MSL-300 and 500 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million downfield from TMS. The coupling constants (J values) are reported in Hertz.
8) ^{13}C-NMR spectra were recorded on Bruker AC-200, MSL-300 or 500 instruments operating at 50 MHz, 75 MHz and 125 MHz respectively.
9) Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and are obtained at an ionization potential of 70 eV.
10) GC analysis was carried out on Hewlett Packard 5890; unless otherwise stated.
11) Microanalysis was carried out in the microanalytical section of NCL.
12) The compound numbers, scheme numbers and references given in each chapter refer to that particular chapter only.

Thesis Abstract

Thesis Title

"Design and Synthesis of Combretastatin A-4 Analogues, Synthesis of Terrein and Synthetic Studies Towards Kodaistatin"

Thesis is divided into three chapters.
Chapter 1: Design and Synthesis of Combretastatin A-4 Analogues.
Chapter 2: Some Useful Synthetic Methodologies.
Chapter 3: Synthesis of Terrein and Synthetic Studies Towards Kodaistatin.

CHAPTER 1: Design and Synthesis of Combretastatin A-4 (CA-4) Analogues.

Combretastatins are mitotic agents isolated from the South African tree *Combretum caffrum* by Pettit *et al.*[1] in 1982. Combretastatin A-4 is a potent inhibitor of microtubule assembly having IC_{50} 2-3 μM which binds to tubulin on the colchicine binding site. Among the various antimitotic agents inhibiting tubulin polymerization by interaction with the colchicine site, combretastatin derivatives constitute one of the most extensively investigated groups since the discovery of combretastatin A-4.

Numerous studies on structure-activity relationship of combretastatin A-4 have established that 3,4,5-trimethoxy substituents in the A ring and *cis*-orientation between ring A and B are essential for strong cytotoxicity. However, during storage and administration, *cis* combretastatin analogues are prone to isomerise into *trans*-forms. The *trans*-forms of these compounds show dramatic reduction in both antitubulin activity and cytotoxicity. Also the low aqueous-solubility of CA-4 limited its efficacy *in vivo*. Because of the structural simplicity and potent cytotoxicity, combretastatin A-4 (CA-4) is a very attractive lead compound.

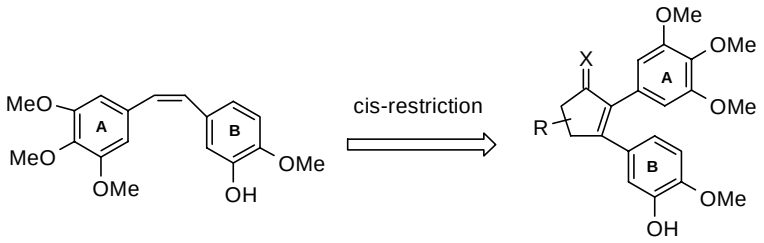
This chapter summarizes the synthesis of *cis* restricted analogues of combretastatin A-4 possessing 2,3-diaryl-4/5-hydroxycyclopentenone ring in place of olefinic double bond and attempts towards the synthesis of 2,3-diaryl-4,5-dihydroxycyclopentenone analogues of CA-4. The resolution of some of the *cis* restricted analogues, which were showing better cytotoxic activity, was carried out by chemical method. This chapter is further divided into five sections.

SECTION I:

Design and synthesis of 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues of CA-4:

Considering the structure activity relationship study of CA-4 3,4,5-trimethoxy substituents on A-ring and 4-OMe group on B-ring of CA-4 are essential for cytotoxic activity. We introduced 4/5-hydroxycyclopentenone ring in place of olefinic double bond between two aryl rings, keeping

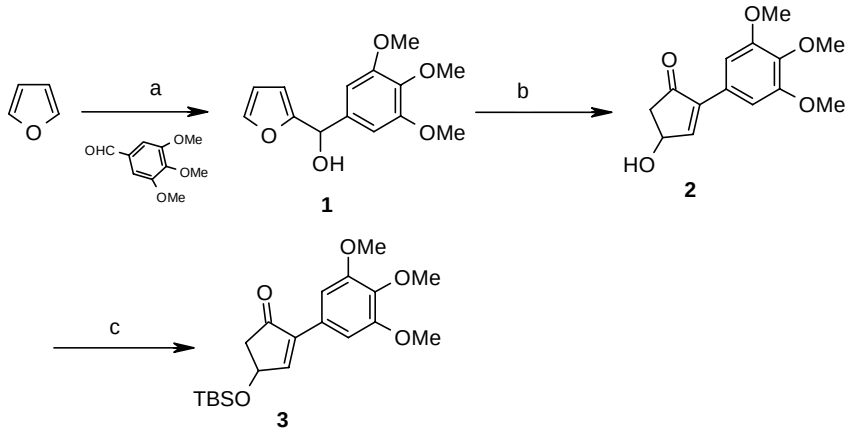
3,4,5-trimethoxy substituents on A ring to obtain compounds with pharmaceutically acceptable properties and improved antitumor activity. The novel molecules were expected to maintain the shape selectivity and were derivatized to increase aqueous solubility.



R = 4/5 OH, OAc, OTBS.
X = O, N-OH

We selected the 5-membered ring with hydroxy group as *cis*-restriction for synthesis of combretastatin A-4 analogues with a view that such a structure will avoid inactivation resulting from *cis*-to-*trans* isomerization of the double bond. Also we can further derivatize these functional groups to obtain the novel analogues of combretastatin A-4.

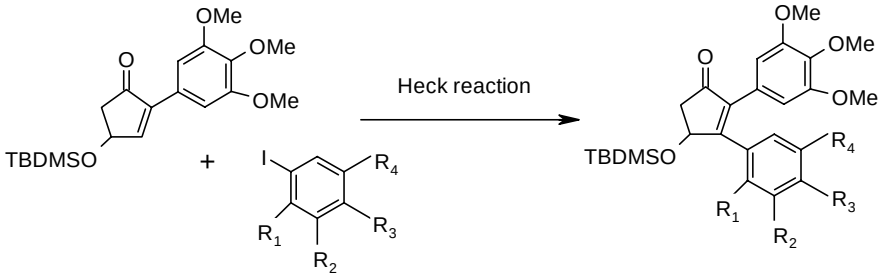
The 2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one (**2**) was envisaged as important common building block for the synthesis of various combretastatin A-4 analogues. The intermediate **2** was prepared from 3,4,5-trimethoxybenzaldehyde as shown in scheme 1. Reaction of furyl magnesium bromide with 3,4,5-trimethoxybenzaldehyde gave the 2-furyl (3,4,5-trimethoxy)phenyl methanol (**1**) which on rearrangement with $ZnCl_2$ in dioxan/water gave the intermediate **2** in excellent yield. The hydroxy group was protected as tert-butyldimethylsilylether to give the intermediate **3**.



Scheme 1

Reagents and conditions: a) i) nBuLi, THF ii) $MgBr_2$, THF, -30^{0}C, 4 h, 93 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 90 % c) TBDMSCl, DMAP, DCM, Et_3N, 3 h, 74 %.

The intermediate **3** was then subjected to the Heck reaction using various aryl iodides as shown in scheme 2.



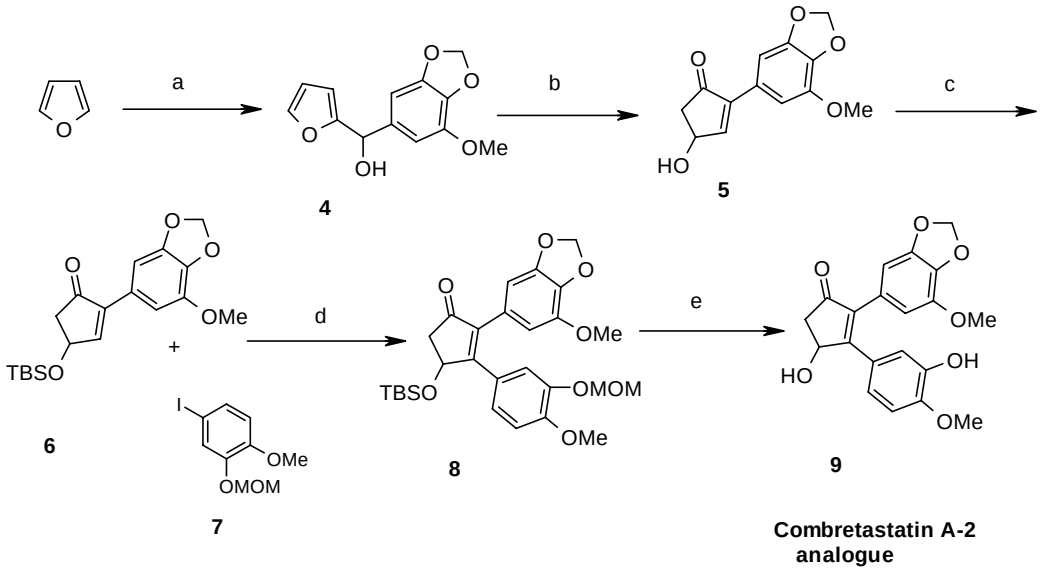
Scheme 2

Heck reaction of various aryl iodides with intermediate **3** in the presence of palladium acetate, triphenyl phosphine and potassium carbonate in acetonitrile using tetrabutylammonium bromide as a catalyst resulted into the expected products. Regeneration of –OH group gave the expected 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues of CA-4. Further derivatization of -OH (hydroxy) and CO (carbonyl) groups resulted into various analogues of combretastatin A-4. Initially we synthesized various B-ring modified analogues of CA-4.

To study the role of 3,4,5-trimethoxy substituents on A-ring and 3-OH and 4-OMe group of B ring, we synthesized the unsubstituted 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues using the same synthetic strategy.

Synthesis of A-ring modified 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues of CA-4: Intermediate **5** was envisaged as a building block for the synthesis of A-ring modified combretastatin A-4 analogues. The intermediate **4** was prepared from 5-methoxypiperonaldehyde as shown in scheme 3. Reaction of furyllithium with 5-methoxypiperonaldehyde gave the furan-2-yl-(7-methoxy-benzo[1,3]dioxol-5-yl)-methanol (**4**) which on rearrangement with $ZnCl_2$ in dioxan/ water gave the intermediate **5** in excellent yield. The hydroxy group was protected as tert-butyldimethylsilyloxyether to get the compound **6**.

The intermediate **6** was then subjected to Heck reaction using aryl iodide **7** to get the expected compound **8** which on regeneration of hydroxy function resulted in the compound **9**.



Scheme 3

Reagents and conditions: a) nBuLi, THF, 0^0C, 5-methoxypiperonaldehyde, 3 h, 80 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 63 % c) TBDMSCl, DMAP, DCM, Et_3N, 73 % d) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), Bu_4NBr, CH_3CN, 36 h. 40 %. e) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 53 %.

SECTION II

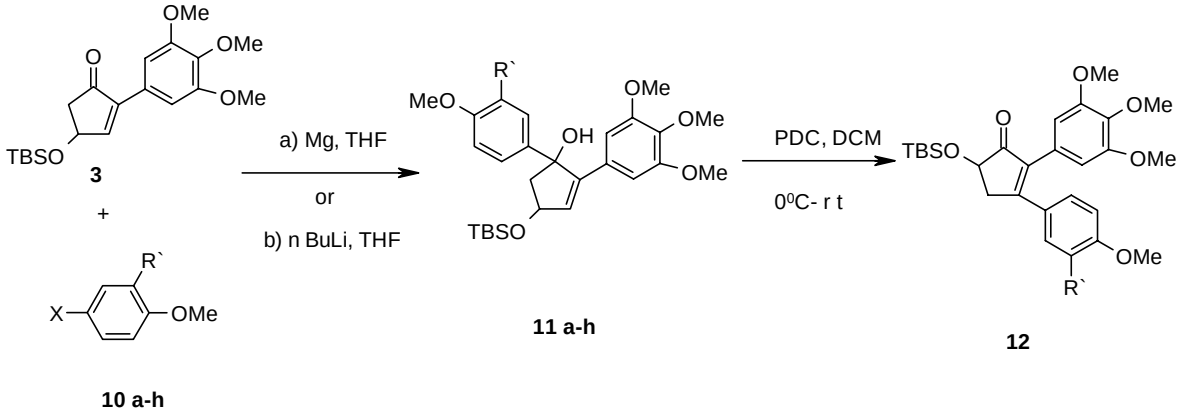
Design and synthesis of 2,3-diaryl-5-hydroxycyclopent-2-en-1-one analogues of CA-4:

We have synthesized 2,3-diaryl-5-hydroxycyclopent-2-en-1-one analogues keeping 3,4,5-trimethoxy substituents on A ring and variable substituents on B-ring. The differenciating factor for these analogues with respect to the compounds described in the section I is the position of hydroxy group in the cyclopentenone ring. The synthetic strategy employed here involves 1,3-oxidative rearrangement of tertiary allylic alcohols by pyridinium dichromate.[2]

In this series we mainly synthesized the B-ring modified analogues of CA-4 in which the –OH at 3-position of B-ring was replaced with variety of substitutents like H, Cl, F, O^iPr, O-allyl, NHAc, NHCOPh, $N(Me)_2$, NHCHO, NMeCHO etc.

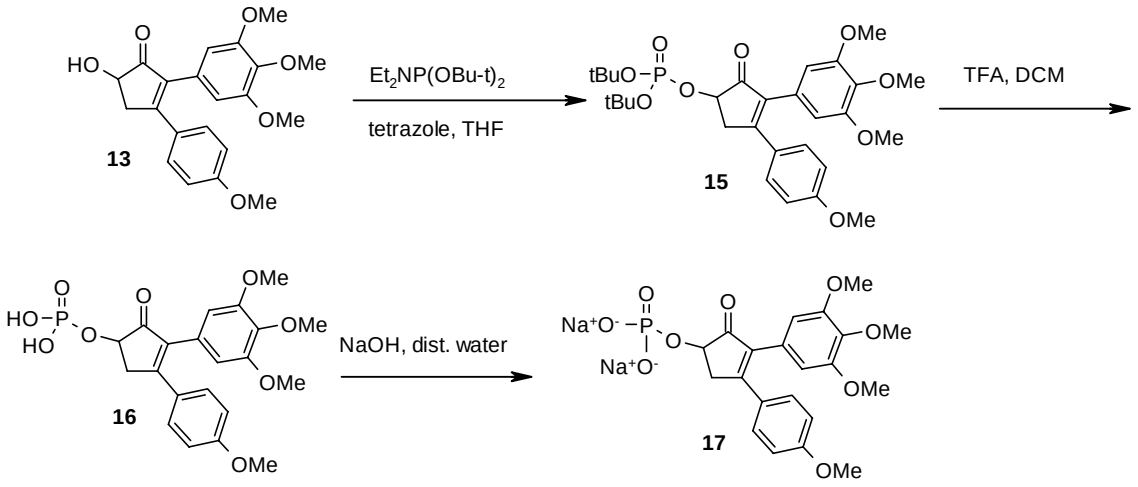
The intermediate **3** was prepared as shown in scheme 1. The addition of Grignard reagent or organolithium reagents in tetrahydrofuran prepared from suitably substituted aryl halides **10** to intermediate **3** afforded the corresponding 1,2-addition products **11** in good to excellent yields. Further treatment of cyclopentenols **11** with pyridinium dichromate (2-3 equivalents) in dichloromethane at 0^0C to room temperature afforded the corresponding 2,3-diaryl-5-tert-butyldimethylsilyloxy-cyclopent 2-en-1-ones **12** (scheme 4).

Regeneration of –OH group resulted in the expected 2,3-diaryl-5-hydroxycyclopent-2-en-1-one analogues of CA-4. Further derivatization of –OH (hydroxy) and CO (carbonyl) resulted in the various analogues of combretastatin A-4.



Scheme 4

From the synthesized analogues in this series some of the analogues showed promising anticancer activity. The compound **13** and its oxime derivative **14** showed cytotoxic activity better than the parent combretastatin A-4 therefore it was converted to water soluble phosphate derivative as shown in scheme 5. The treatment of compound **13** with di-tert-butyl N,N-diethyl phosphoramidite[3] and tetrazole in tetrahydrofuran gave the phosphate derivative **15**. Hydrolysis of tert-butyl group of compound **15** was achieved by treatment with trifluoroacetic acid in dichloromethane[4] to collect compound **16**. The sodium salt of the compound **16** was prepared by treating compound **16** with aqueous NaOH solution to afford compound **17**.



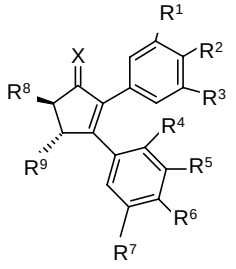
Scheme 5

SECTION III:

Studies towards the synthesis of 2,3-diaryl-4,5-dihydroxycyclopent-2-en-1-one analogues of CA-4:

We have successfully synthesized 2,3-diaryl-4-hydroxycyclopent-2-en-1-one and 2,3-diaryl-5-hydroxycyclopent-2-en-1-one as *cis* restricted analogues of CA-4. The cytotoxicity studies of these compounds indicated that cyclopentenone ring carrying hydroxy group provided a good *cis*-restriction for olefinic double bond of combretastatin A-4 and some compounds from both the series were found to possess more potent cytotoxic activity than the parent compound CA-4.

We further designed and planned to synthesize substituted 2,3-diaryl 4,5-dihydroxycyclopent-2-en-1-one analogues of CA-4. These compounds were expected to be more soluble in biological systems and thereby may impart better cytotoxicity to the human cancer cells.



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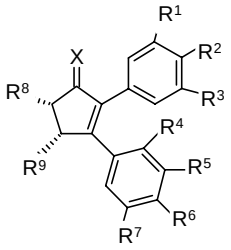
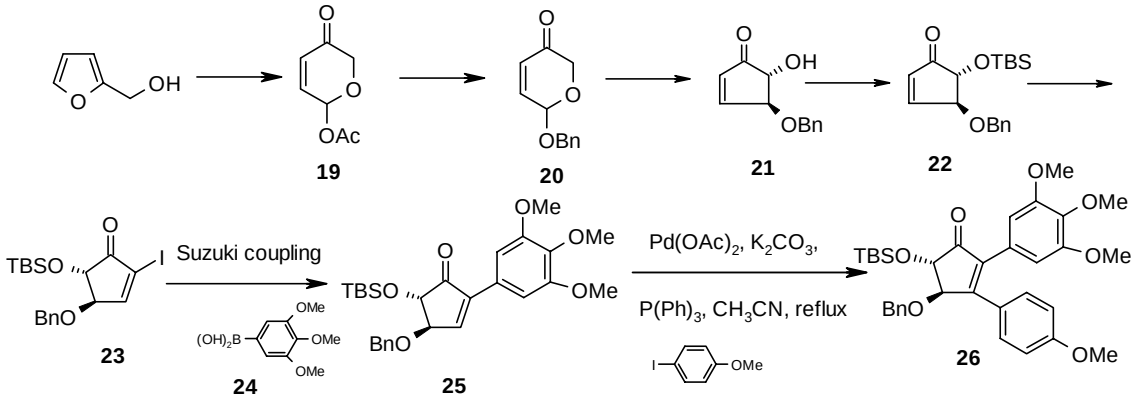


18 b

The synthetic strategy involved Suzuki coupling and Heck reaction as the key steps (scheme 6).



Scheme 6

Reaction of 3,4,5-trimethoxybenzeneboronic acid[5] (**24**) with intermediate **23** using tetrakistriphenylphosphine palladium(0) (4 mol %) in dimethoxyethane and using $NaHCO_3$ as base under reflux resulted in the required intermediate **25** in low yield. Next step was the Heck

reaction of suitably substituted aryl iodide with intermediate **25**. We tried Heck reaction of 4-iodoanisole with intermediate **25** but the required product **26** was not obtained.

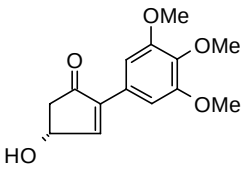
SECTION IV:

Resolution of 4–hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one and substituted-2,3-diaryl 4/5 hydroxycyclopent-2-en-1-one analogues of CA-4

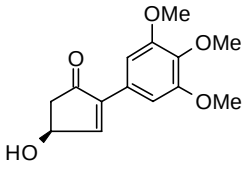
As discussed in sections I and II we have synthesized several *cis* restricted cyclopentenone analogues of combretastatin A-4. The hit compounds in our designed molecules demonstrated remarkable cytotoxic activity against a variety of human cancer cell lines. Initially we screened these compounds in their racemic forms. The resolution of some of these compounds is described in this section.

Resolution of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2):

As 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(2)** was the key intermediate for the synthesis of designed combretastatin A-4 analogues, we carried out the resolution of intermediate **2** by forming a mixture of diastereoisomers with caronaldehyde. Both the isomers **2a** (R) and **2b** (S) were separated with good enantiomeric excess. Absolute configuration of these isomers was assigned by NMR studies of their Mosher esters.



2a (-) (R)

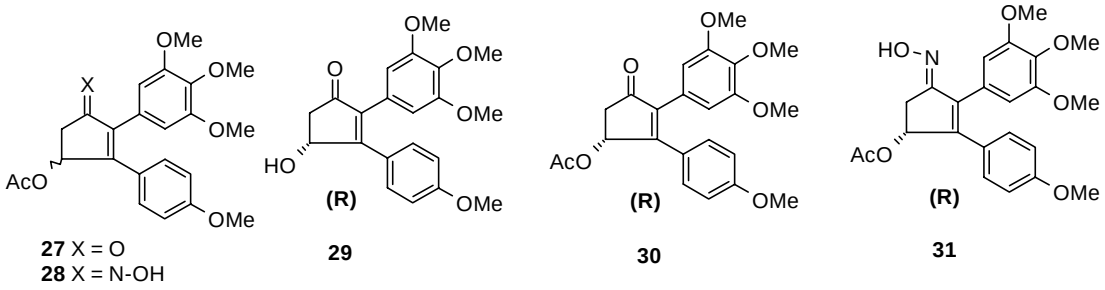


2b (+) (S)

Resolution of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:

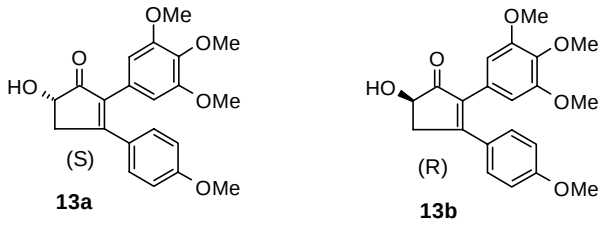
All the novel molecules synthesized in section I and section II possessed one asymmetric center. Most of the biologically active molecules are selective for their activity depending on their chirality. Preliminary screening of our compounds gave encouraging results, therefore it was expected that the particular enantiomers might be more selective towards the cytotoxicity. The resolution of compound **27** was undertaken by forming diastereoisomeric mixture with (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[6] (caronaldehyde). The diastereoisomers were separated by crystallization using chloroform and petroleum ether, which afforded one diastereoisomer in pure form.

The isomer **29** having absolute configuration (R) was separated with good enantiomeric excess (>98 %) and the absolute configuration was assigned by ^{1}H NMR studies of its (R) and (S) Mosher ester derivatives. Further, the chiral analogue **31** was prepared which showed potent cytotoxic activity as compared to its racemic form.



Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (13):

Further, compound **13** from the section II was selected for resolution using caronaldehyde. The compound **13** was treated with (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[6] (caronaldehyde) and PPTS in benzene with azeotropic removal of water to form the mixture of diastereoisomers, which was separated on silica gel column to afford the two diastereomers. Hydrolysis of the diastereomers with dioxan and water afforded pure enantiomers **13a** and **13b** which were having specific rotation of + 23.15° (c 0.55, $CHCl_3$) and - 22.47° (c 0.45, $CHCl_3$) respectively. Both the isomers **13a** (S) and **13b** (R) were separated with good enantiomeric excess (>98 %) and absolute configuration was assigned by NMR studies of their (R) and (S) Mosher esters.



SECTION V:

Biological activity and SAR study of the combretastatin A-4 analogues

The synthesized cyclopentenone analogues (from section I and II) were tested for cytotoxicity against 9 to 12 human tumor cell lines. Out of the 76 new chemical entities (NCEs) submitted for screening 56 NCEs were actually tested for cytotoxicity by plate assay method. A three day MTT

cytotoxicity assay was performed and some of the NCEs synthesized as described in sections I and II displayed cytotoxic activity comparable with combretastatin A-4. The hit molecules selected from the preceding sections should be further optimized for achieving a lead molecule for *in vivo* studies and clinical trials.

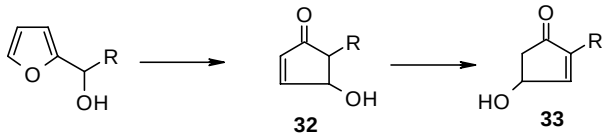
CHAPTER 2: Some Useful Synthetic Methodologies.

SECTION I

A simple procedure for the conversion of 2-aryl-2-furylcarbinols to 2-aryl-4-hydroxycyclopent-2-en-1-ones:

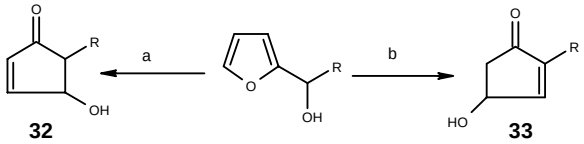
Cyclopent-2-en-1-one and its 4-hydroxy derivatives are present in several biologically active natural products. From the synthetic point of view, 2-substituted-4-hydroxycyclopent-2-en-1-ones **33** are very important intermediates, which can be easily converted to isomeric hydroxycyclopentanones and cyclopentenediones.

The literature survey revealed that most of the methods for synthesis of intermediate **33** involve two steps from 2-furylmethanol. In the first step it forms intermediate **32** which on further rearrangement results into the intermediate **33**.



We have developed a simple and efficient one step method for the preparation of 2-aryl substituted-4-hydroxycyclopent-2-en-1-one from 2-furylmethanol in excellent yield using zinc chloride as a weak Lewis acid (4 equivalent) at 110^0C (reflux temperature of dioxan/water).

Also we have demonstrated that by changing the reaction conditions i.e. by using one equivalent of zinc chloride at lower temperature (60^0C) one can obtain 4-hydroxy-5-aryl substituted cyclopent-2-en-1-ones **32** in good to excellent yields selectively.



Scheme 7

Reagents and conditions: a) $ZnCl_2$ (1 eq.), acetone/water, 60^0C b) $ZnCl_2$ (4eq.), dioxan/water, 110^0C

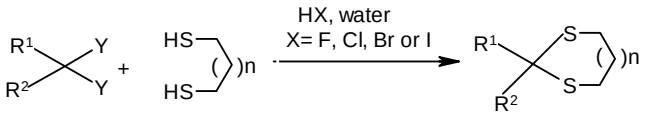
SECTION II:

Thioacetalization of the carbonyl function, transthioacetalization of acetals, ketals, oximes and hydrazones catalyzed by halo acids in aqueous medium:

Functional group protection and deprotection strategies are quite often necessary in the synthesis of multifunctional organic molecules[7]. The protection of carbonyl group as thioacetal is often a necessary step in the synthesis of complex organic molecules due to inbuilt stability of thioacetals for acidic or basic conditions.

Preparation of thioacetals generally involves reaction of carbonyl compounds with thiols in presence of protic or Lewis acids in various dry organic solvents like dichloromethane, chloroform, benzene, n-hexane etc many of which are environmentally hazardous. The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in organic synthesis, have posed a serious threat to the environment. Thus, the design of solvent-free reactions and use of alternative green solvents like water, supercritical fluids and ionic liquids have received a lot of attention in recent years.

We have developed an efficient, mild and environmentally preferred method for the thioacetalization of carbonyl function and transthioacetalization of acetals, ketals, oximes and hydrazones by the use of catalytic amount of halo acids. The advantages of this protocol are that it doesn't need dry/inert conditions and readily available aqueous haloacids are used as catalysts (scheme 8).



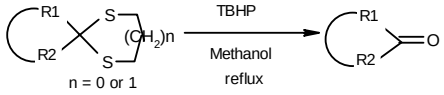
Scheme 8

SECTION III:

A convenient oxidative demasking of 1,3-dithiolanes and dithianes to carbonyl compounds with TBHP:

The carbonyl group, among various functional groups, can be protected as an acetal, oxime, hydrazone, cyclic thioacetal etc. A large number of methods have been developed for the protection and deprotection of carbonyl compounds as 1,3-dithianes and dithiolanes. In view of the oxidative properties of *tert*-butyl hydroperoxide (TBHP, aq. 70%) and its wide spectrum of use, we employed TBHP in methanol for dethioacetalization reactions.[8] We have devised a

simple and convenient method for the demasking of 1,3-dithiolanes and dithianes under neutral conditions in good to excellent yields (scheme 9).



Scheme 9

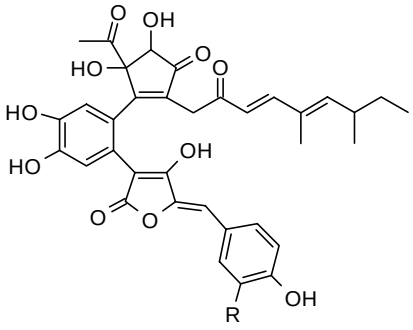
CHAPTER 3: Synthesis of Terrein and Synthetic Studies Towards Kodaistatin.

SECTION I

Synthetic studies towards kodaistatin:

Diabetes is one of the most common diseases in the world. The enzyme system glucose-6-phosphatase (G1-6-Pase) is known to play a major role in the homeostatic regulation of blood glucose. It is responsible for the formation of endogenous glucose originating from gluconeogenesis and glycogenolysis. Glucose-6-phosphate is common end product of glycogenolysis or gluconeogenesis. The glucose-6-phosphate is an enzyme complex made up of glucose-6-phosphate translocase (G6-P-T1), glucose-6-phosphatase and a phosphate translocase. Of these components, G-6-P-T1 is highly selective and is therefore a suitable target for the treatment of diabetes type II by regulating hepatic glucose production.

In recent years, several natural products have been identified as selective inhibitors of G-6-P-T1[9]. The novel inhibitor of G6P-T1, kodaistatin was isolated from cultures of fungus *Aspergillus terreus* Thom DSM 11247, by Vertesy *et al.*[10] in 2000, which inhibits glucose-6-phosphate specifically at submicromolar concentrations. The IC_{50} is 80 nM for kodaistatin A and 130 nM for kodaistatin C.



Kodaistatin A : R = H
Kodaistatin C: R = OH

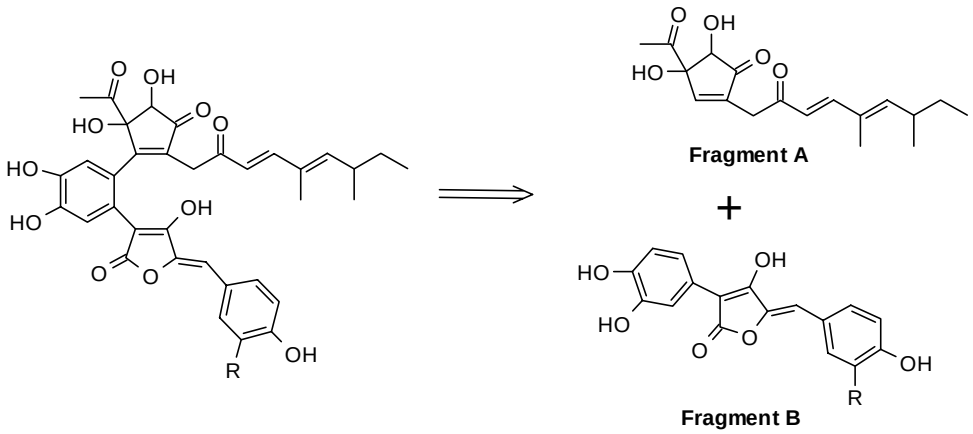
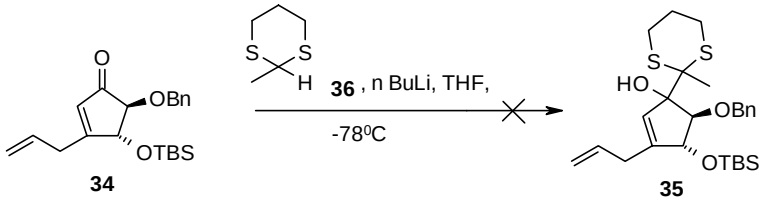


Fig. 1

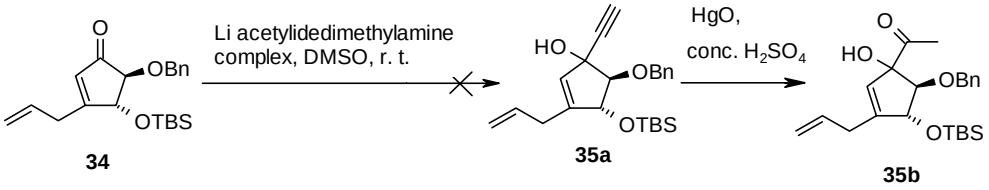
Kodaistatin consists of two main fragments structurally as shown in Fig .1 *viz*. Fragment A and fragment B. The synthesis of fragment B is well reported in literature therefore we planned to undertake the synthesis of fragment A.

For the synthesis of Fragment A, compound **34** was found to be the intermediate which was obtained from compound **22** (scheme 6). After achieving the intermediate **34** successfully, the next step was to introduce -$COCH_3$ group to obtain compound **35**, so we tried the umpolung reaction of 2-methyl 1,3 dithiane **36** with intermediate **34** using n-butyllithium but the required compound **35** could not be obtained (scheme 10).



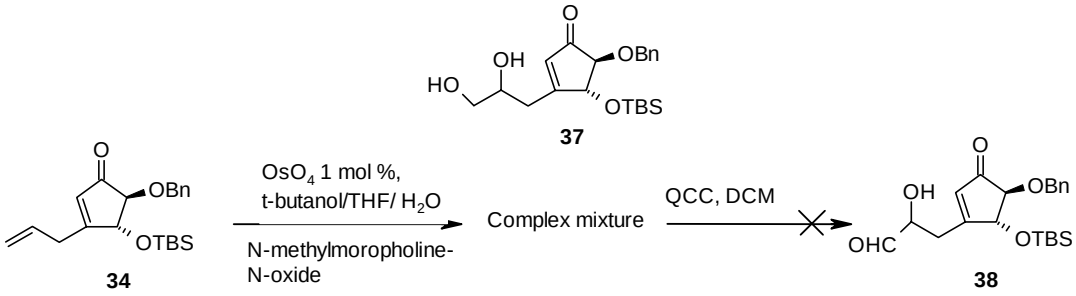
Scheme 10

Alternatively, we carried out reaction of lithium acetylidedimethylamine complex[11] with compound **34** using DMSO at room temperature in order to prepare compound **35a**, which could be converted to compound **35b** using sulfuric acid. However, the spectral data of the product obtained did not match with the expected product.



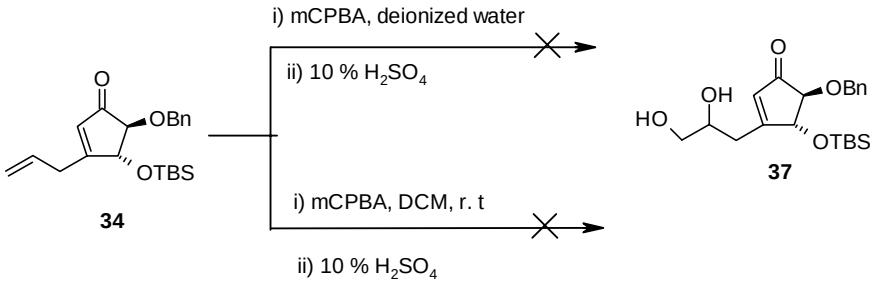
Scheme 11

In our simultaneous efforts to synthesize the aliphatic side chain part of the fragment A, we conducted dihydroxylation of compound **34** with 1 mol % osmium tetroxide and N-methyl morpholine N-oxide as reoxidant in tert-butanol, tetrahydrofuran and water (10:3:1), which resulted in a complex mixture. The purified major component showed a peak at 393 (M+1) in mass spectrum which was in agreement with the expected compound **37**. The selective oxidation of primary -OH group using quinolinium dichromate[12] in dichloromethane was attempted which failed to give the expected product **38**.



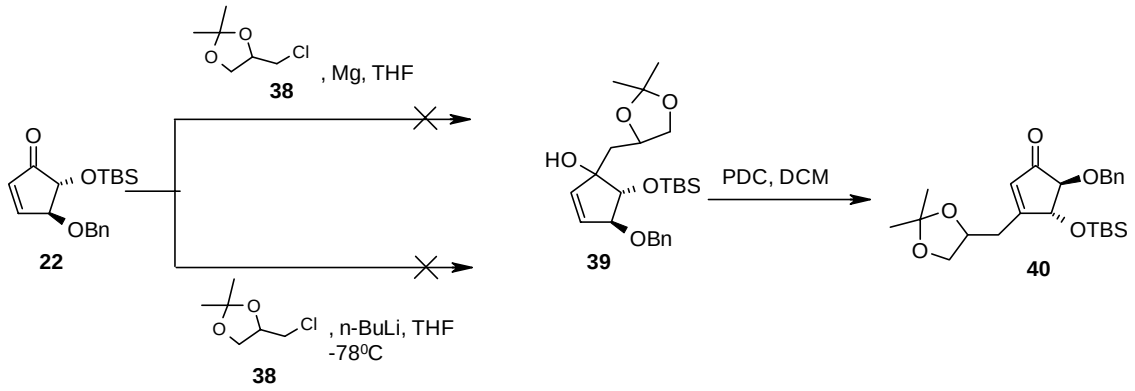
Scheme 12

Since dihydroxylation of compound **34** was problematic, epoxidation of terminal double bond with mCPBA using different solvents was attempted which also gave negative results.



Scheme 13

In an alternative route depicted in scheme 14, it was planned to use the side chain which already possessed a vicinal diol. Accordingly, allyl bromide was replaced by acetonide of 3-chloro-1,2-propanediol for the 1,2-addition on cyclopentenone **22**. However, the chloro compound did not react with magnesium or n-butyllithium to give the expected product **39**.

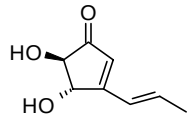


Scheme 14

SECTION II

An efficient synthesis of terrein (*trans*-4, 5-dihydroxy-3-[(E)-1-propenyl]-2-cyclopenten-1-one):

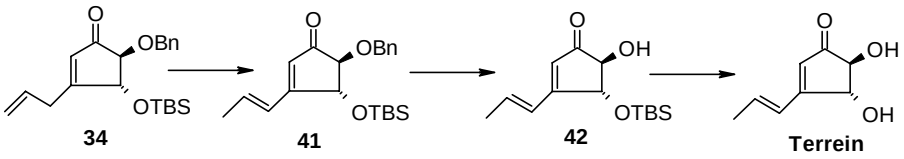
The mould metabolite (+) terrein (*trans*-4, 5-dihydroxy-3-[(E)-1-propenyl]-2-cyclopenten-1-one) was discovered by Raistrick and Smith[13] from *Aspergillus terreus.* (+) Terrein inhibits plant growth, reducing root elongation of lettuce and rice seedings. It has also been shown to have antibacterial activity. Although the structure of terrein is simple, its synthesis is not trivial because of its sensitivity to acids and bases.



Terrein

During our attempts to synthesize kodaistatin, we had obtained the intermediate **34**. It was planned to utilize this intermediate for the synthesis of terrein.

The terminal double bond of compound **34** was isomerized to conjugated double bond by heating compound **34** with rhodium trichloride[14] in ethanol-benzene at reflux temperature to afford the compound **41**. The deprotection of benzyl protection was carried with $TiCl_4$[15] in dry dichloromethane to give compound **42**. The treatment of the compound **42** with tetrabutylammonium fluoride at room temperature afforded the (±) terrein. In our experiments to resolve the intermediate **42** using caronaldehyde it was noteworthy that transetherification took place instead of ether formation with the free hydroxy group.



Scheme 15

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   V. H. Tillu, **P. D. Shinde**, A. V. Bedekar and R. D. Wakharkar, *Synth. Communs.*, 33, 1399, **2003**.
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   N. B. Barhate, **P. D. Shinde**, V. A. Mahajan and R. D. Wakharkar *Tetrahedron Lett.*, 43, 6031, **2002**.
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   V. A. Mahajan**, P. D. Shinde**, A. S. Gajare, M. Karthikeyan and R. D. Wakharkar *Green Chemistry*, 4, 325, **2002**.
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   U. S. Patent Appl. No. NCL-18-2004. (**2004**).
2. A process for the preparation of 2,3-diaryl-5-(tert-butyldimethylsilyloxy)cyclopent-2-en-1-one.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, **P. D. Shinde**, V. A. Mahajan, V. H. Jadhav and A. M. Wagh.
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   M. K. Gurjar, R. D. Wakharkar, H. B. Borate, **P. D. Shinde**, V. A. Mahajan, V. H. Jadhav and A. M. Wagh.
   Ind. Patent No. NF 254-2002 (**2002**).
4. A process for the preparation of 2,3-diaryl-4-(tert-butyldimethylsilyloxy)cyclopent-2-en-1-one.
   M. K. Gurjar, R. D. Wakharkar, H. B. Borate**, P. D. Shinde**, V. A. Mahajan, V. H. Jadhav and A. M. Wagh.
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7 Novel 3-sulfanyl cyclic ketones
   T. Ravindranathan, R. D. Wakharkar, H. B. Borate, **P. D. Shinde**, V. A. Mahajan, S. S. Ghumare and H. S. Jagtap
   Indian Patent Appl. No. NF 80/2000 (**2000**).

CHAPTER 1

Design and Synthesis of Combretastin-A4 (CA-4) Analogues

1.0.1 Cytotoxic Compounds: General Introduction

Cancer as a disease in human population is becoming a larger health problem all over the world. In some areas of the world, cancer has become or shortly will become the leading disease-related cause of death of the human population. The definition of cancer or malignancy is very difficult, but the cancer can be defined[1] as the state in which a family of cells grows progressively with permanent impairment of normal growth control. Tumor is a general term indicating any normal mass or growth of tissues that is not necessarily life threatening. A "cancerous tumor" is malignant neoplasm of potential danger. Cancer can arise in any organ of the body even though some sites are more prone than others. The most dangerous property of cancer cells, which normal cells lack, is their ability to enter other body organs though blood and lymph vessels. This disease has attracted worldwide attention and search for reliable methods, to cure it is continuously going on.

The main curative therapies for cancer can be divided into four types: surgery, radiation, chemotherapy and combined modality therapy, out of which surgery and radiation are generally only successful if the cancer is found at an early localized stage. But once the disease has progressed to local advanced cancer or metastatic cancer, these therapies are less successful. Then the only tool in oncologist's hand to fight against cancer to save the patient is chemotherapy alone or in combination with radiation and surgery.

In early 1940 chemotherapeutic drugs have been developed. Physicians found that "combination of drugs" may cure leukemias, lymphomas and testicular cancers. Unfortunately, the majority of the most common cancers like breast, lung, colorectal and prostate cancers are not yet curable with chemotherapy alone.

Combined modility therapy requires the efforts of wide assortment of specialists, oncologists, surgeons, pathologists and radiologists. Most approaches to cancer chemotherapy have centered around the idea that cytotoxic drugs can be used to eradicate proliferating neoplastic cells. Chemotherapy has curative potentials in patients with various haematologic malignancies, testicular cancer and germ cell tumors. Despite improvements in the treatment of most metastatic solid tumors, these remain largely incurable. Reasons for this are insufficient tumor selectivity of anti-cancer agents and poor penetration within the tumor mass.[2, 3] The main disadvantage of cancer chemotherapy is the toxicity of the drugs used.

A large number of anticancer drugs, possessing diverse molecular structures, are being used presently. Further, many are undergoing clinical trials. Some of the antineoplastic agents although efficient are not specifically cytotoxic to tumor cells as they also kill normal cells. Most of the

anticancer agents in use affect either the function or the synthesis of DNA and are therefore more active in rapidly proliferating cell population.

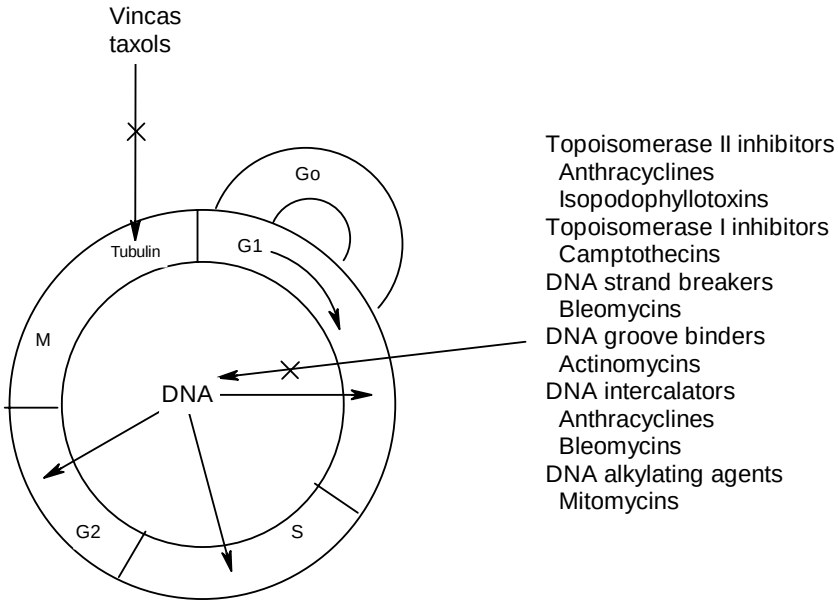
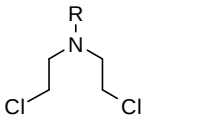


Fig. 1: Synopsis of molecular modes of action of various prominent antitumor natural products.

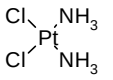
Figure 1 illustrates the various points of attack of prominent natural antitumor agents on growing cells. From the figure 1 it is clear that DNA or tubulin in one way or another (either by direct attack or by interference with enzymes processing these important cellular macromolecules) is the primary target of all of these agents and that most phases of the cell cycle are involved.

All the antineoplastic agents can be classified into six categories namely 1) Alkylating agents 2) Antimetabolites 3) Anthacycline antibiotics 4) Natural products 5) Mitotic inhibitors and 6) Miscellaneous agents.

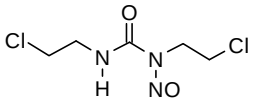
1) Alkylating agents: The compounds that alkylate DNA have long been of interest as anticancer drugs. Alkylating agents behave as electrophiles that can replace a hydrogen atom by alkyl group under physiological conditions. The various alkylating agents are mustards [mechlorethamine (**1**), chlorambucil (**2**), melphalan (**3**), cyclophosphamide, ifosfamide], platinum complexes (cisplatin, carboplatin, tetraplatin etc.), cyclopropylindoles (adozelesin, carzelesin), nitrosoureas (CCNU, BCNU, stroptozotocin) and triazenes (dacarbazine, mitozolomide, temozolomide).



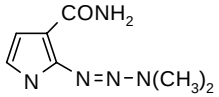
(1) R = CH_3
(2) R = $(CH_2)_3CO_2H$
(3) R = $CH(NH_2)CO_2H$



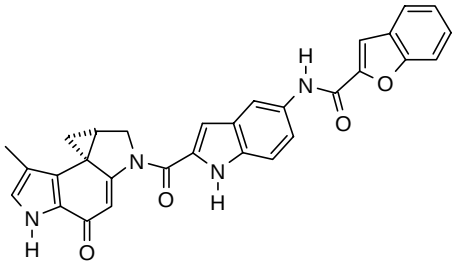
Cisplatin



CCNU

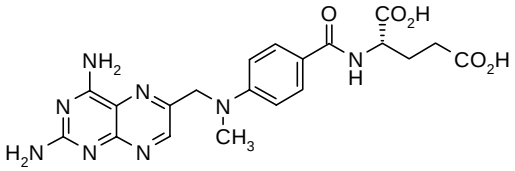


Dacarbazine

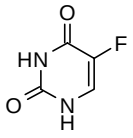


Adozelesin

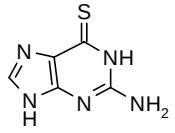
2) Antimetabolites: The compounds which interfere in varying ways with the synthesis of DNA are known as antimetabolites. Various antimetabolites used in cancer chemotherapy are folic acid analogues (methotrexate, edatrexate, raltitrexed, etc.), pyrimidine analogues (5-fluorouracil, cytosine arabinoside, gemcitabine), purine analogues (6-mercaptopurine, 6-thioguanine, fludarabine etc.).



Methotrexate

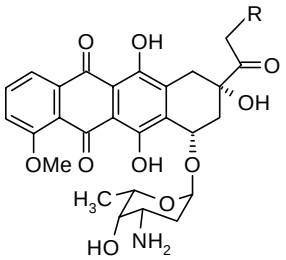


5-Fluorouracil



6-Mercaptopurine

3) Anthracyclines: The anthracyclines are a group of structurally related antitumor antibiotics. The two prototype anthracyclines are adriamycin and daunomycin produced from steptomyces species.[4] Their potent activity was discovered in 1963 when adriamycin and daunomycin,[5] first isolated by Di Marco *et al.*, were found to be effective as antileukemic agents. The tumor cell growth inhibiting property of the anthracyclines has generally been attributed to the interaction of these drugs with DNA. Adriamycin has shown promising results in solid tumors also.



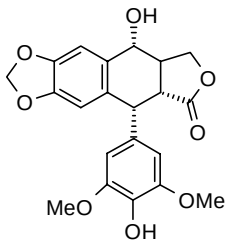
Adriamycin R = OH

Daunomycin R = H

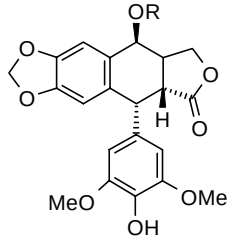
4) Natural products: Drugs derived from plant sources

A wide array of complex terrestrial and marine natural products possess antitumor activity.[6-10] To acquire new anticancer agents a variety of sources have been explored including synthetic compounds, microbial and plant extracts etc. The most important development in the investigation of plant product as potential anticancer agents is the discovery of the dimeric alkaloids *Vinca rosea L*.[11] Two of the alkaloids, vinblastine (**11**) and vincristine (**12**) (VCR), have demonstrated remarkable antitumor activity. They have been the first examples of antitumor agents isolated from plant sources.

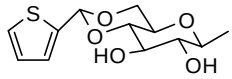
Isopodophyllotoxins: The lignan podophyllotoxin (**4**) is an ancient folk remedy found in the May apple, *Podophyllum peltatum*.[12, 13] The isopodophyllotoxins are semisynthetic analogues resulting from acid catalyzed reaction with suitably protected sugars followed by additional transformations. Teniposide (**5**) and etoposide (**6**) are the most prominent analogues so produced and these are available in the market as antitumor agents.



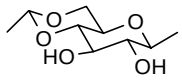
Podophyllotoxin (4)



Teniposide (5) R =

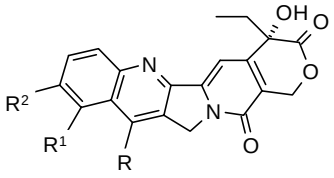


Etoposide (6) R =



Camptothecin: Camptothecin (**7**) a pentacyclic alkaloid was isolated by Wall *et al.*[14] in 1966 from the stem wood of the tree *Camptotheca acuminata* Decne (Nyssaceae), a tree distributed widely and abundantly in the southern part of China. Despite its early promise in laboratory and rodent studies, it was disappointing in clinical studies because of the severe toxicity and so it has not found clinical use as itself. Topotecan (**8**) and Irinotecan (**9**) are two analogues of camptothecin. Irinotecan (**9**) is an analogue hydoxylated in the quinoline ring and further converted to amine-bearing prodrug linker. Topotecan is used for ovarian[15, 16] and small-cell lung cancers.[17, 18] Camptothecins are inhibitors of the action of mammalian topoisomerase I.

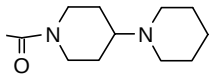
The recent interest in topo inhibitors has been in agents which are capable of simultaneous inhibition of both enzymes topo I and topo II. The anthraquinone saintopin (**10**) is a potent poision of both topo I and topo II[19] but has not been developed as a drug.

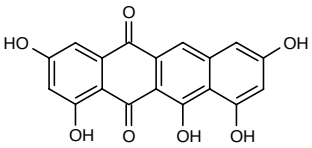


Camptothecin (7) R = H, R^1 = H, R^2 = H

Topotecan (8) R = H, R^1 = $CH_2N(CH_3)_2$, R^2 = OH

Irinotecan (9) R = Et, R^1 = H, R^2 =

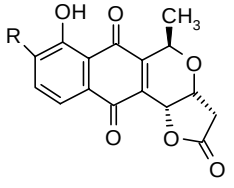




Saintopin (10)

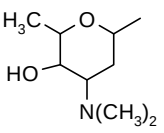
5) Miscellaneous agents:

Miscellaneous agents are the compounds isolated from various sources like bacteria, fungi etc. and their mode of action is not known. During the course of screening programme for new antitumor antibiotics Tanaka *et al.*[20] found that a *Streptomyces* strain IM 8442 T produces a novel antibiotic which inhibits antibiotic resistant cell sublines of L 5178 Y murine lymphoma more markedly than the parent cells. The new agent was named as lactoquinomycin.



Lactoquinomycin

R =



6) Mitotic inhibitors: The cell division cycle regulating chromosome replication/ segregation and cell division is of fundamental importance for any living organism and in disease such as cancer. Limitless replicative potential, self-sufficiency in growth signals and insensitivity to antigrowth signals are acquired capabilities of malignant cancer cells, leading to the uncontrolled cell cycling.[21]

The M-phase or mitosis is the most important part of the cell division cycle and includes condensation of nuclear chromatin and disruption of the nuclear envelope, organization of a mitotic spindle, and chromosome segregation. The key player within cell cycle, namely cyclin-dependent kinase (cdks), cdk inhibitors, microtubules and microtubule associated proteins (MAPs), have been selected as targets for the discovery of new antimitotic cancer drugs.

The microtubule system of eukaryotic cell is an important target for the development of anticancer agents; chemicals which attack microtubules through tubulin disrupt cellular microtubule structure and function resulting in mitotic arrest. The tubulin-binding agents generally exert their effects by microtubule depolymerization or stabilization.

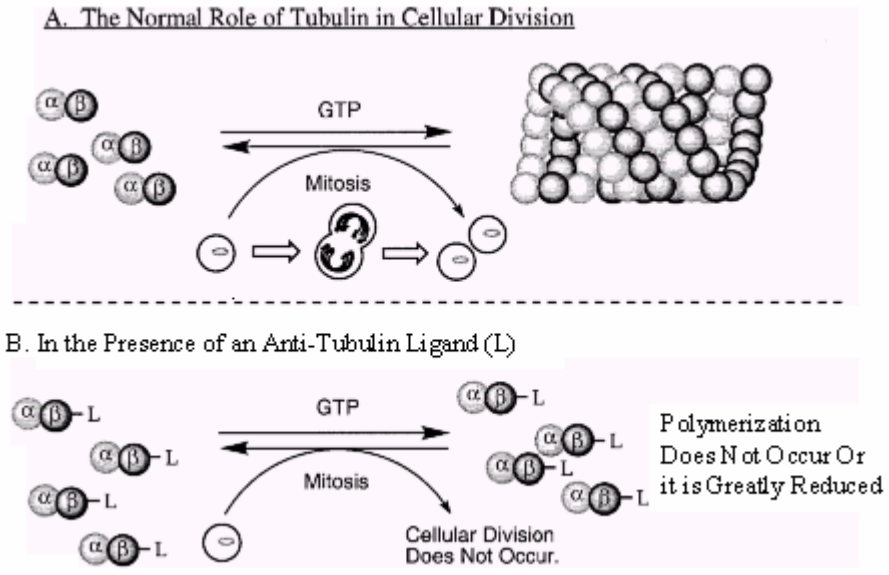


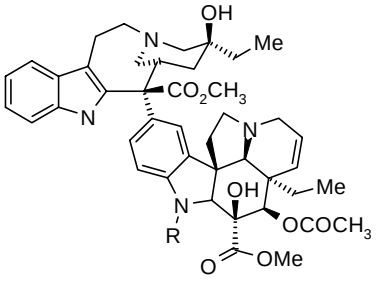
Fig 2: A) Normal tubulin polymerization dynamics in cell division. B) Disruption of dynamic polymerization in the presence of an anti-tubulin ligand (L).

Tubulin is a heterodimeric protein consisting of α and β subunits, each approximately 50 k Da in size.[22, 23] The α and β subunits have a high degree of homology (40-50 %) to each other.[24] Upon binding of GTP, tubulin polymerizes into microtubule which are helical arrays of alternating α and β subunits. The polymerization and subsequent depolymerization of microtubules is

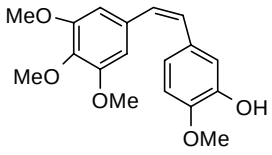
responsible for ciliar and flagellar movement, vesicle movement in secretion, transport of organelles down the axons in nerve cells, chromosome separation during cell division (mitosis) and the generation and maintenance of cell shape.[22-25]

During cellular division, the interphase microtubule array largely disassembles, and the α, β-tubulin repolymerizes to form the microtubule framework of the mitotic spindle, which is essential for chromosome separation and formation of two daughter cells. When ligands that interact with α, β-tubulin or with microtubules are present, a reduction in cellular division is observed. Due to the key role played by tubulin during cell division, ligands that interrupt the dynamic instability inherent to this system have been developed as antimitotic, anticancer drugs.

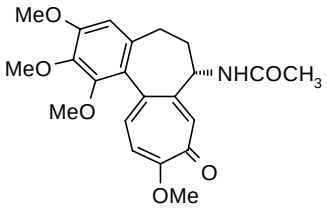
A large number of naturally occurring ligands that inhibit tubulin polymerization have been reported in the literature for many years, and there has been a continuing discovery of new agents with pronounced structural diversity.[26]



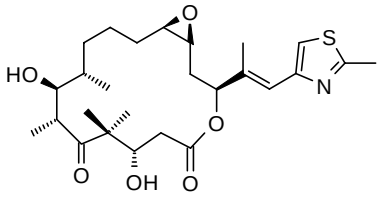
Vinblastine (11) R = CH_3
Vincristine (12) R = CHO



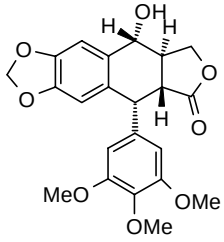
Combretastatin A-4 (13)



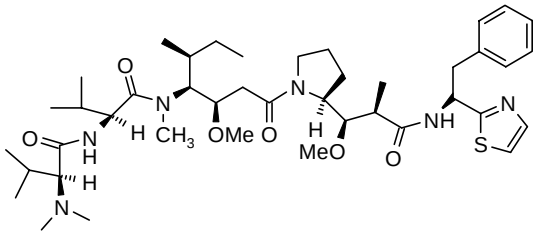
Colchicine (14)



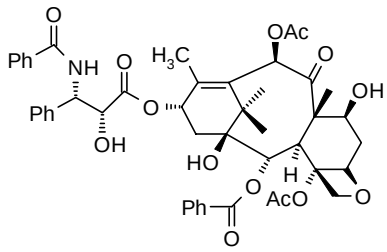
Epothilone A (15)



Podophyllotoxin (4)



Dolastatin 10 (16)



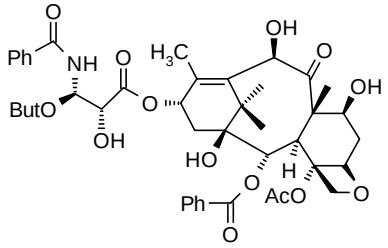
Paclitaxel (17)

Fig.3: Representative antimitotic compounds which interact with tubulin.

There are a variety of synthetic compounds that also demonstrate efficient inhibition of tubulin polymerization.

Some of the semisynthetic and synthetic microtubule inhibitors:

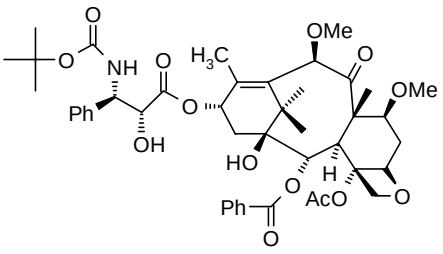
There are number of semisynthetic or synthetic compounds which inhibit microtubule assembly. Paclitaxel (**17**) is one of the ligand, which inhibits microtubule system. Paclitaxel was isolated from the bark of pacific yew *Taxus brevifolia.*[27] The docetaxel (**18**), a semisynthetic analogue of



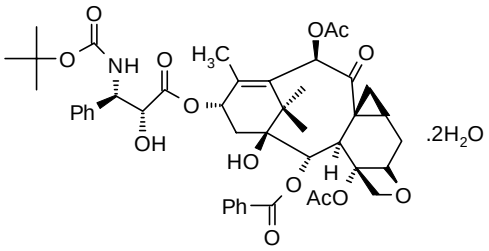
Docetaxel(18)

paclitaxel, vinblastine (**11**) and vincristine (**12**) are standard agents in cancer therapy. The clinical use of paclitaxel (**17**) and docetaxel (**18**), although they are highly potent and effective cancer drugs, is restricted mainly by oral bioavailibility, drug resistance and toxicity related to the mechanism of action. Numerous new semisynthetic analogues of paclitaxel are under clinical study. Bristol-Myers-Squibb, the company which developed paclitaxel, have reported two paclitaxel analogues BMS-184476 and BMS-188797,[28] which are in phase I clinical trials and they displayed similar or superior efficacy in nude mice xenograft models.

Two taxane analogues in clinical development by Aventis Pharma, i. e. TXD-258 (**19**) and RPR-109881A (**20**),[29, 30] have been reported to be effective against various human tumor xenografts, including MDR-positive and taxane-resistant models.



TXD-258 (19)



RPR-109881A (20)

Natural compounds of diverse structures:

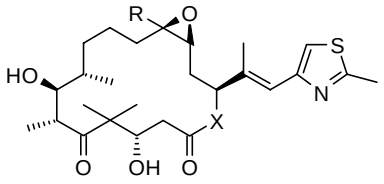
Many tubulin-binding compounds from various natural sources and semisynthetic analogues have been described within the last two decades. Natural compounds like combretastatin A-4 (**13**),

cryptophycin 52, dolastatin 10 (**16**) and dolastatin 15 destabilize tubulin, whereas epothilones, laulimalide, peloruside A, eleuotherobine and (+)-discodermolide, similar to paclitaxel, stabilize microtubules. The various tubulin-binding natural and semisynthetic compounds are shown in table 1.

Table 1: Tubulin-binding natural and semisynthetic compounds of diverse structure

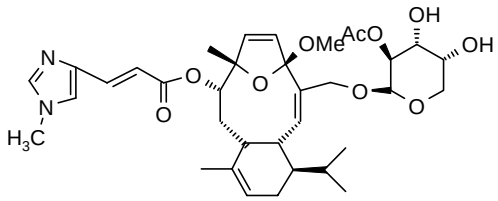
Compound	Source	Toxicity
Epothilone B (**22**) [31]	Novartis	0.2-0.8 μM
BMS-247550 (**23**) [32]	Bristol-Myers Squibb	3.9 nM(mean)
Eleutherobin (**24**) [33]	Bristol-Myers Squibb	10-60 nM
(+)-Discodermolide (**25**) [34]	Novartis	8-36 nM
Vinflunine[35]	Pierre Fabre	18 nM
Cryptophycin 52 (**26**) [36]	Eli Lilly	13-232 pM
Combretastatin A-4 (**13**) [37, 38]	Oxigene	--
ZD-6126 (**27**) [39, 40]	AstraZeneca	n. p.
Dolastatin 10 (**16**) [41, 42]	NCI	0.5 nM (L1210 model)

n. p. = not published.

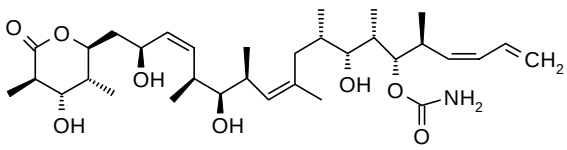


Epothilone B(22) X = O, R = CH_3

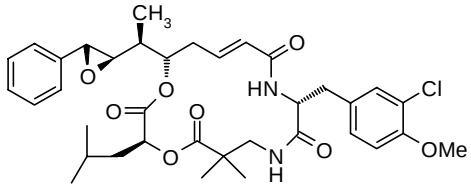
BMS-247550(23) X = NH, R = CH_3



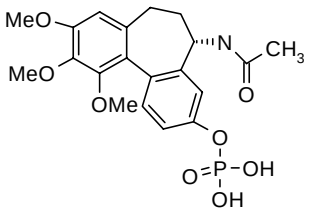
Eleutherobin (24)



Discodermolide (25)



Cryptophycin 52 (26)



ZD-6126 (27)

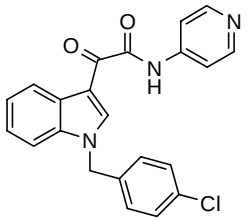
Synthetic low molecular-weight compounds:

From the synthetic point of view, compounds with low molecular weight (small molecules) are very attractive as a drug format. Recently, various synthetic small-molecules as a tubulin inhibitor have been described. Most but not all, compete with colchicine for binding to β-tubulin, thereby acting as destabilizing agents. These compounds have grouped into heterocombretastatins, sulfonamides, phenstatins, indoles and quinones.

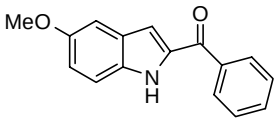
Table 2: Synthetic small molecule tubulin inhibitors

Compound	Toxicity *in vitro* (IC_{50})
D-24851 (**28**) [43]	36-285 nM
D-64131 (**29**) [44, 45]	24-144 nM
A-289099 (**30**) [46]	7 nM
Indanocine (**31**) [47, 48]	< 20 nM (mean)
E-7010 (**32**) [49, 50]	0.2-40 ng/ml
Cl-980 (**33**) [51, 52]	11-165 nM

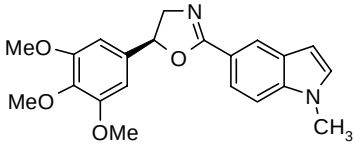
Further, there are number of quinolones and related structures which also represent a promising group of compounds affecting tubulin. The synthetic 2-phenyl-4-quinolones which are structurally related to naturally occurring and antimitotic flavonoids, displayed promising activity and impressive differential cytotoxicity against human tumor cell lines, comparable to that of colchicine.[53, 54-56] The structurally related 2-phenyl-1,8-naphthyridin-4-ones containing additional nitrogen in position 8 of the aromatic system, also exhibited potent cytotoxicity.



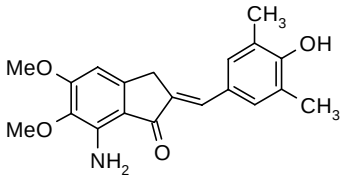
D-24851 (28)



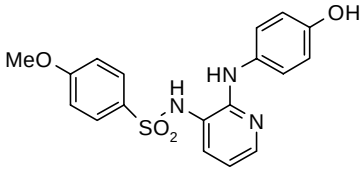
D-64131 (29)



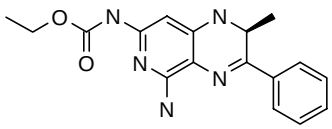
A-289099 (30)



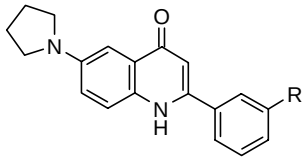
Indanocine
NSC-698666 (31)



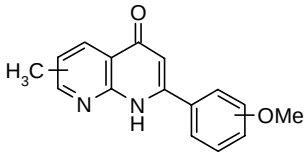
E-7010 (32)



Carbamates, CI-980 (33)

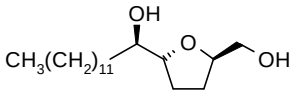


2-Phenyl-4-quinolones
R = OCH_3 or Cl

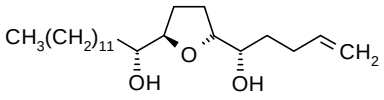


2-Phenyl-1,8-naphthyridin-4-ones

Recently, Jan *et al.*[57] reported COBRA-0 (WHI-261) (**34**) and COBRA-1 (**35**), the compounds containing monotetrahydrofuran moiety attached to a C_{12} aliphatic chain, which were found to bind to α-tubulin and exhibited cytotoxicity at concentrations of 100 μM or higher.



WHI-261 (34)

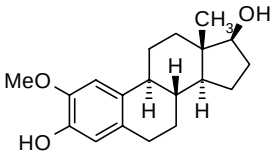


COBRA 1 (35)

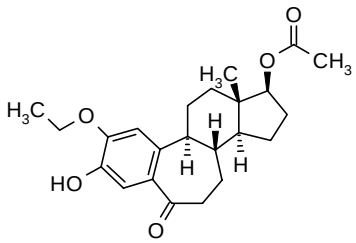
Synthetic steroids with colchicine-type substructure:

2-Methoxyestradiol (NSC-659853) (**36**), a cytotoxic human metabolite developed by Entremed Inc., binds to the colchicine site of tubulin with reasonable affinity (IC_{50} = 4.7 μM). It was shown to have antiproliferative effects on hormone-dependent and hormone-independent breast cancer

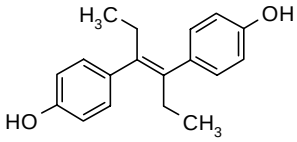
cells as well as antiangiogenic activity.[58] Further, B ring expanded 2-ethoxyestradiol analogue (**37**) were synthesized by Wang *et al.*[59] in which B-ring of the steroid was replaced by the B-ring of colchicine. The resulting analogues showed significant affinity to the colchicine binding site consistent with the proposed structural resemblance.



(36)
2-Methoxyestradiol
(NSC-659853)



(37)
Ring expanded homologues of NSC-659853

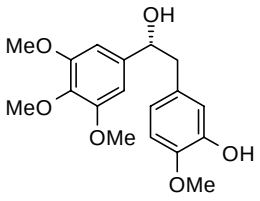


(38)
Diethylstilbestrol

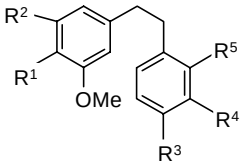
Chaudoreille *et al.*[60] reported another tubulin binding agent diethylstilbestrol (**38**) which was originally developed as an synthetic estrogen. The antineoplastic effect of the diethylstilbestrol was due to the depolymerization of microtubules. Tamoxifen, a stilbene derivative is already in use for the treatment of cancer.

1.0.2 Review of the Literature on Combretastatin A-4 Analogues

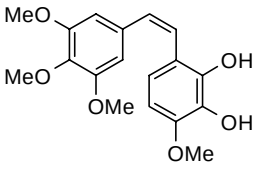
Among the various small molecules, the naturally occuring combretastatins have attracted attention of synthetic organic chemists as well as biologists due to their structural simplicity, biological activity and capacity to bind the cochicine binding sites. Combretastatins are mitotic agents isolated from the South African tree *Combretum caffrum* Kuntze (Combretaceae). Pettit *et al.*[61] in 1982 isolated and characterized the new cell growth inhibitory substance combretastatin (**39**) which showed marginal cytotoxic activity against the murine P388 leukemia as well as the 9ASK system.



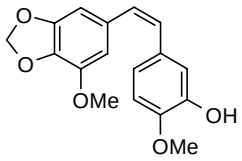
Combretastatin (39)



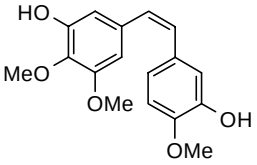
Combretastatin B-1 R^1, R^2, R^3 = OMe;; R^4, R^5 = OH
Combretastatin B-2 R^1, R^3 = OMe; R^2, R^4 = OH; R^5 = H
Combretastatin B-3 R^1, R^2 = OMe; R^3, R^4 = OH; R^5 = H
Combretastatin B-4 R^1, R^5 = H; R^2 = OMe; R^3, R^4 = OH



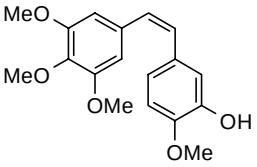
Combretastatin A-1 (40)



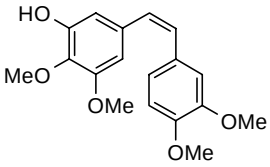
Combretastatin A-2 (41)



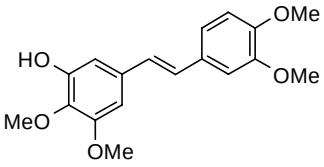
Combretastatin A-3 (42)



Combretastatin A-4 (13)



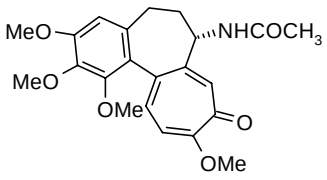
Combretastatin A-5 (43)



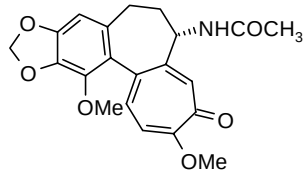
Combretastatin A-6 (44)

They further isolated series of structurally related compounds[62, 63] combretastatin A-1 (**40**) and B-1 and found that combretastatin A-1 is potent inhibitor of tubulin polymerization (IC_{50} 20 μM). Combretastatin A-2 (**41**), A-3 (**42**), A-5 (**43**), A-6 (**44**), B-2, B-3 and B-4 were also having P388 cell growth inhibitory activities. Combretastatin A-2 and A-3 were also found to markedly inhibit tubulin polymerization.

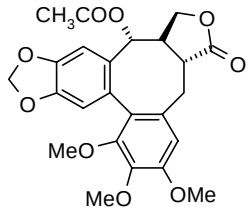
Pettit *et al.*[64] in 1989 isolated combretastatin A-4 (**13**), a potent inhibitor of microtubule assembly from the South African tree *Combretum caffrum*. It was having IC_{50} 2-3 μM. CA-4 binds to tubulin on the colchicine binding site. Many natural products, such as cornigerine (**45**),[65] podophyllotoxin (**4**),[66] steganacin (**46**)[67] and combretastatin (**13**)[68, 69] bind to the colchicine (**14**) site.



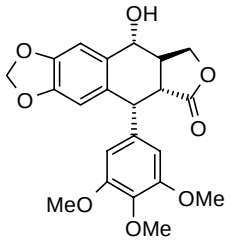
Colchicine (14)



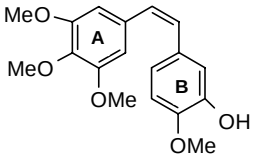
Cornigerine (45)



Steganacin (46)



Podophyllotoxin (4)

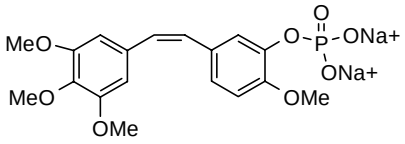


Combretastatin A-4 (13)

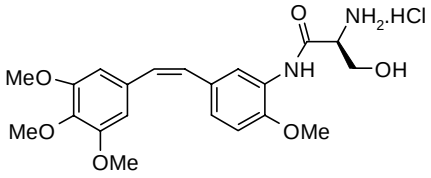
Among the various antimitotic agents inhibiting tubulin polymerization by interaction with the colchicine site, combretastatin derivatives constitute one of the most extensively investigated groups since the discovery of combretastatin A-4.

Numerous studies on structure-activity relationship of combretastatin A-4 have established that 3,4,5-trimethoxy substituents in the A ring and *cis*-orientation between ring A and B are essential for strong cytotoxicity. However, during storage and administration *cis* combretastatin analogues are prone to conversion into *trans* forms. The *trans* forms of these compounds show dramatic reduction in both antitubulin activity and cytotoxicity. Also the low aqueous-solubility of CA-4 limited its efficacy *in vivo.*

Because of the structural simplicity and potent cytotoxicity, CA-4 is a very attractive lead compound. Considerable efforts have gone into modifying CA-4 to improve its *in vivo* efficacy. One example is the water soluble disodium phosphate of combretastatin A-4 (**47**)[70, 71] and another is AC-7700 (**48**) reported by Ohsumi *et al.*[74] These compounds show marked tumor growth suppression against the colon 26 murine tumor model and also exert potent antitumor activity.

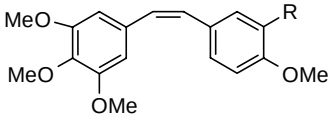


47



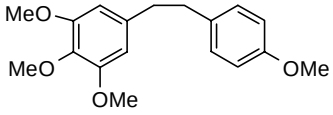
AC-7700 (48)

Cushman *et al.*[72] found that the (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxypheyl) ethane (**49**) acts as a cytotoxic tubulin polymerization inhibitor with potency comparable to that of combretastatin A-4. They also found that dihydro derivative **50** works as a potent cytotoxic tubulin polymerization inhibitor. So they prepared the structural congeners of **49** and **50** in an effort to probe the structural features associated with their antitubulin and anticancer activities and synthesized a conformationally restricted analogues[73] of **50**.

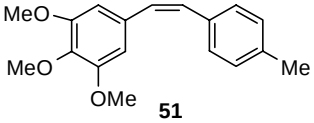


R = H (49)

R = OH (CA-4)



50



51

They replaced 4-OMe group on B-ring of **49** and **50** with variety of substituents like OEt, O^{n}Pr, SMe, Me, Et, ^{i}Pr, ^{t}Bu groups. These studies indicated that substitution with large group like ^{t}Bu resulted in the reduction of cytotoxicity and replacement of 4-OMe of B-ring with -SMe group resulted in the compound which was as cytotoxic as the parent compound **49**. From above studies they noticed that increase in steric bulk at this position results in a decrease in activity. The only compound more effective than the parent compound as an inhibitor of tubulin polymerization was **51**, in which methyl group replaced the 4-methoxy group of CA-4. The potency of this agent as a tubulin polymerization inhibitor was equivalent to combretastatin A-4 (**13**) the natural product, even though it was lacking the adjacent hydroxyl group in the B-ring.

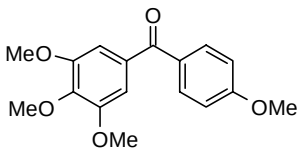
They also found that the *trans* isomers of these compounds were less potent than their corresponding *cis* isomers.

The *cis* stilbenes with substitution on olefinic bridge, substitution at either 1 or 2 position of the olefin reduced the cytotoxicity by atleast 1 to 5 orders of magnitude.

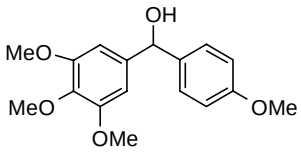
Among the dihydrostilbene analogues of compound **50**, five compounds had ED_{50} values less than 1 μM in atleast four cell lines.

They further prepared several stilbenes and dihydrostilbenes containing acidic and basic groups, in an effort to obtain substances that could be more readily formulated. But none of these compounds inhibited tubulin polymerization nor were they very cytotoxic.

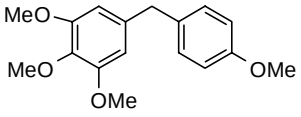
In another set of modification, the two-carbon bridge in **49** and **50** was reduced to one carbon bridge (compounds **52**, **53** and **54**). However, all these compounds were less potent than **51**.



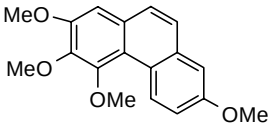
52



53



54



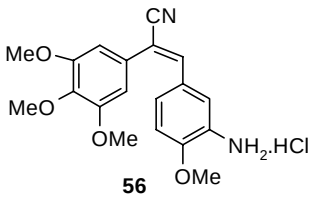
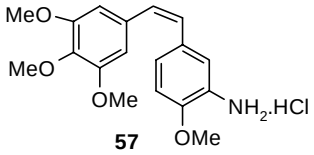
55

They synthesized various conformationally restricted analogues of the stilbene **49** and dihydrostilbene **50**, but they were not potent inhibitors of tubulin polymerization. Particularly striking was that the inactivity of phenanthrene **55** (IC_{50}> 40 μM) in comparison to the antitubulin activity of stilbene **49** (IC_{50}> 2.5 μM). This data indicated that conformation of the stilbene **49** was not planar.

From all above studies they came to the conclusion that only limited modification could be made in structures of combretastatin A-4 (**13**) and its tetrahydro analogue (**49** or **50**) without substantial compromise in cytotoxic and antitubulin activity.

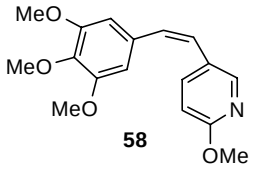
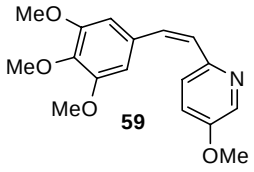
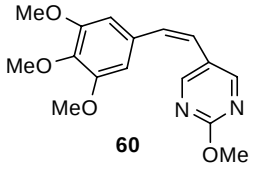
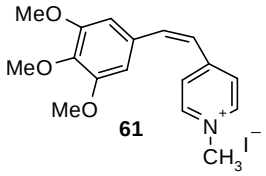
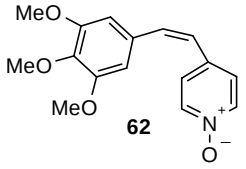
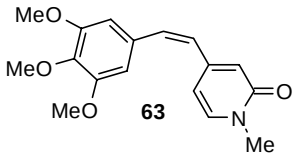
Ohsumi *et al.*[74] synthesized various analogues of combretastatin A-4 to improve aqueous solubility by introduction of nitrogen-containing groups. He replaced phenolic –OH group by amine and obtained the compound with potent cytotoxicity and antitubulin activity. Among the various analogues synthesized, only compounds **56** and **57** showed potent antitumor activity. Compound **57** was superior to cisplatin in three tumor models (colon 38, 3LL and HCT-15).

Table 3: Antitumor activities of CA-4 analogues

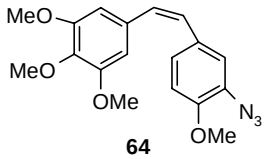
Sr. No.	Compound	Colon 26 IC_{50} (nM)	Antitubulin activity IC_{50} (μM)
1	 **56**	5.9	10
2	 **57**	5.1	4
3	CA-4 (**13**)	18.0	4

B-ring modified heterocombretastatin analogues of CA-4 have been reported by Ohsumi *et al.*[75] in which the B-ring of CA-4 was replaced by a variety of 6-membered heterocycles having substituents on the 4-position. They found that the compounds 2-methoxypyridine **58**, 3-methoxypyridine **59** and pyrimidine derivative **60** showed potent antitubulin activity (IC_{50} 2 μM, 3 μM and 3 μM respectively) and only compound **58** showed strong cytotoxicity (IC_{50} 29.2 nM). They found that N-substituted pyridinium compounds **61** and **62** which were synthesized to improve water solubility, did not show antitubulin or cytotoxic activity. From the above studies they concluded that the cationic center on the 4-position is not appropriate. However 4-substituted pyridine **63** showed strong antitubulin activity (IC_{50} 2 μM) and cytotoxicity (IC_{50} 19.2 nM).

Table 4: Biological activities of B-ring modified combretastatin analogues.

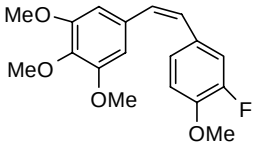
Sr. No.	Compound	Anti-tubulin activity IC_{50} (μM)	Cytotoxicity IC_{50} (nM)
1	Combretastatin A-4 (**13**)	2	8.7
2	 **58**	2	29.2
3	 **59**	3	182
4	 **60**	3	275
5	 **61**	nt.	>3000
6	 **62**	>10	>3000
7	 **63**	2	19.2

Pinney *et al.*[76] synthesized CA-4 analogues having azide group (compound **64**) instead of phenolic OH group on B-ring and the resulting analogue was found to possess potent activity (IC_{50} = 1.4 μM) comparable to that of CA-4 (IC_{50} = 1.2 μM).



64

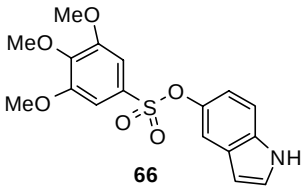
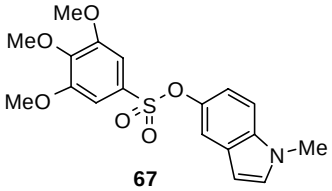
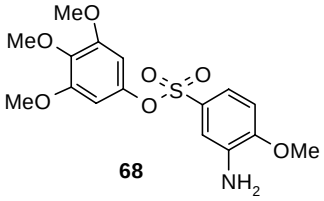
Lawrence *et al.*[77] synthesized the fluorinated analogues of CA-4 wherein they replaced hydrogen or hydroxyl group with fluorine atom and found that compound **65** (IC_{50} = 4 nM) is as active as CA-4 (IC_{50} = 3 nM).



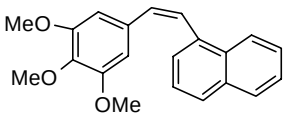
65

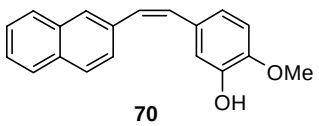
Sulfonate analogues of combretastatin A-4 have been reported by Gwaltney *et al.*[78] These analogues compete with colchicine and combretastatin A-4 for the binding site on tubulin. They found that the orientation of sulfonate group relative to the two aryl rings makes little difference in the antiproliferative activity of these compounds and found sulfonate as effective replacement for the *cis* olefin of CA-4. In an effort to replace the 3-hydroxy-4-methoxyphenyl group (B-ring) of CA-4 with other groups, they found that 5-substituted indole nucleus (as in compound **66**) and especially N-methyl indole (as in compound **67**) are good replacement for the 3-hydroxy-4-methoxyphenyl ring of CA-4 (**13**). One of the sulfonate analogues (compound **68**) was having potent cytotoxicity.

Table 5: Inhibition of tubulin polymerization (IC_{50}) for sulfonate analogues of CA-4

Sr. No.	Compound	IC_{50} (μM)
1	 **66**	6.6 (± 1.3)
2	 **67**	1.4 (± 0.15)
3	 **68**	6.7 (± 3.7)
4	CA-4 (**13**)	1.2 (± 0.76)

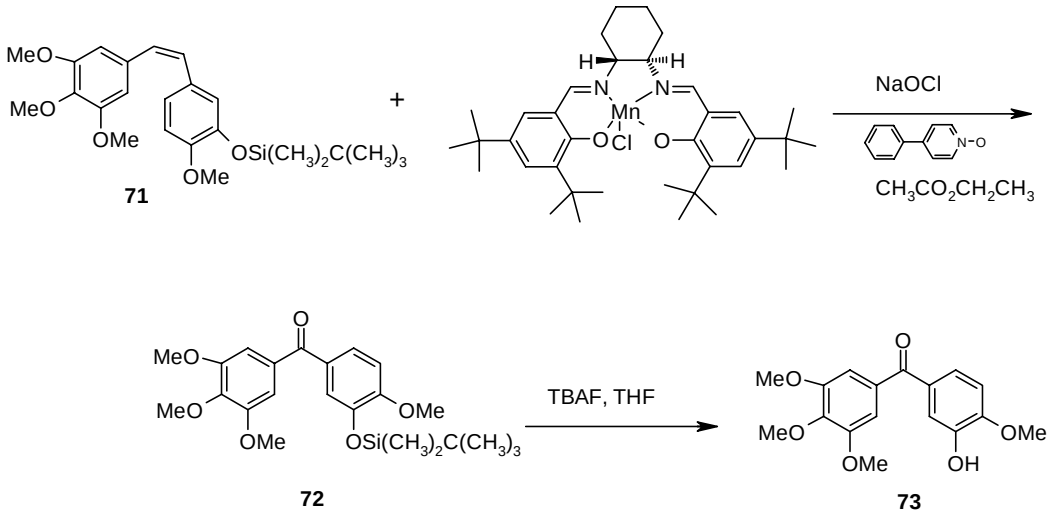
Naphthalene analogues of CA-4 have been reported by Medarde *et al.*[79] As the structure activity relationship study of CA-4 revealed that the 3,4,5-trimethoxyphenyl and 3-hydroxy-4-methoxyphenyl rings of CA-4 are essential for its activity as antimitotic agent, these authors found that the replacement of either one by a naphthalene rings results in compounds (**69** and **70**) with a potency comparable to that of the parent compound. These results showed that the naphthalene ring is a good surrogate for the 3,4,5-trimethoxyphenyl or the 3-hydroxy-4-methoxyphenyl rings of CA-4.


69


70

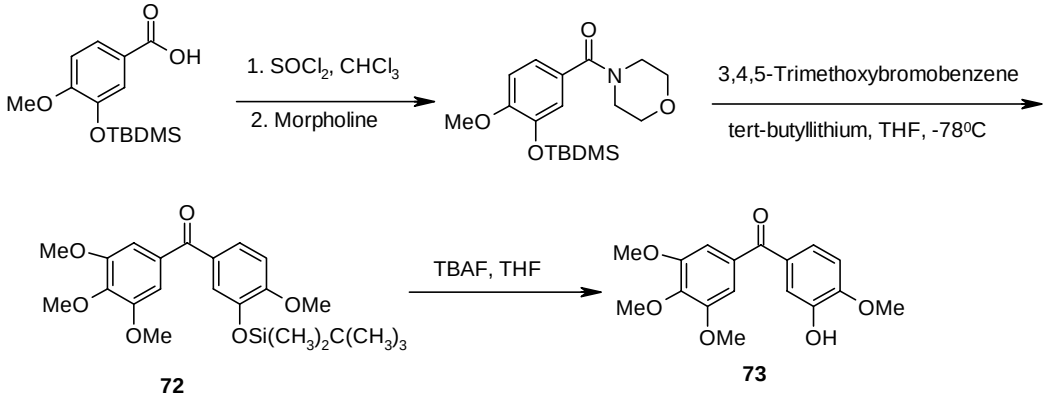
Phenstatin analogues of combretastatin:

Pettit *et al.*[80] reported the phenstatin analogues of combretastatin A-4. Since SAR studies of combretastatin A-4 indicated that the Z-geometry of olefin between two phenyl rings is essential for cytotoxic activity, to maintain *cis* geometry they thought to place epoxide or cyclopropyl group as *cis* restriction in place of olefinic double bond.



Scheme 1

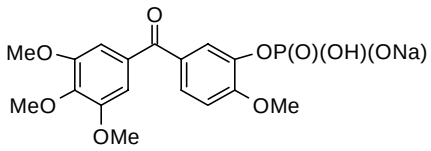
They attempted the epoxidation of combretastatin A-4 silylether **71** using the Jacobsen chiral Mn (salen) complex and obtained a rearranged oxidation product which on further cleavage of silyl protection resulted in the phenstatin **73** but the yield obtained by above method was very low (scheme 1). Compound **73** was showing strong cytotoxicity profile comparable with combretastatin A-4 and also inhibited the growth of Gram-positive pathogenic bacterium *Neissoria gonorrhoeae.* To obtain these compounds on large scale, they synthesized these compounds by another route as shown in scheme 2.



Scheme 2

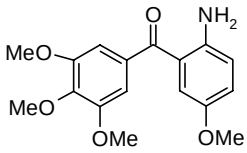
They also synthesized the water-soluble prodrug **74** of phenstatin but found that it was having weak activity in inhibiting microtubule assembly and moderate activity as an inhibitor of colchicine binding.

From the antiproliferative activity data of these compounds, phenstatin **73** was found to be equivalent to combretastatin A-4 (**13**) in its interaction with tubulin.

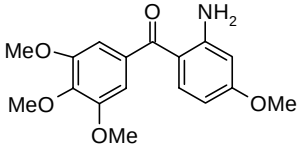


74

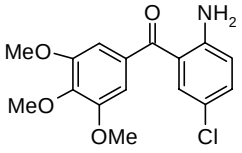
Hsieh *et al.*[81] reported synthesis of aminobenzophenone CA-4 analogues and found that compounds **75** and **76** with amino and methoxy substituents showed more potent cytotoxicity than phenstatin and slightly less potent cytotoxicity than CA-4. Compound **77** with amino and chloro substituents showed good activity against various drug-resistant cell lines. They also found that introduction of an unsubstituted amino group (compounds **75**, **76** and **77**) at the *ortho* position in benzophenone derivatives is important for increased cytotoxicity.



75

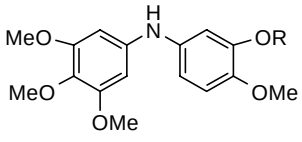


76

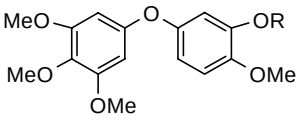


77

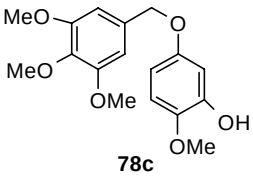
Lawrence *et al.*[82] reported synthesis and anticancer activity of combretastatin A-4 like ethers. They prepared a series of diarylamines, diaryl and arylbenzyl ethers based on combretastatin A-4 and evaluated them for anticancer activity. They found that the compound 2-methoxy-5-(3,4,5-trimethoxyphenoxymethyl)phenol (compound **78c**) was the most active (IC_{50}, K562 20 nM) and caused significant G2/M cell cycle arrest. They found that X-group in the combretastatin A-4 like compounds **78d-m** is important in determining their biological activity (table 6).



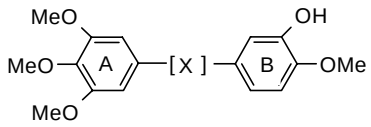
78a



78b



78c



78 d-m

Table 6: Cell growth inhibitory properties of diaryl containing compounds **78d-m**

78	X	$IC_{50}/\mu M$
d	Z –CH=CH-	0.0026[a]
e	E –CH=CH-	0.16[a]
f	-C≡C-	21[b]
g	$-CH_2\ CH_2-$	0.11[a]
h	-CO-	0.01[a]
i	(S, S)-C(OH)HC(OH)-	2[a]
j	(R, R)-C(OH)HC(OH)-	19[a]
k	$-(R, S)-C(OH)HCH_2-$	0.033[a]
l	$-(R, S)-CH_2CH(OH)-$	33[a]
m	-[d]	>50[c]

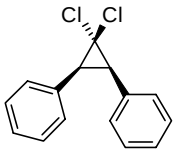
[a]P 388 murine leukemia cell line.

[b]K 562 human chronic myelogenous leukemia cell line.

[c]L 1210 murine leukemia cell line.

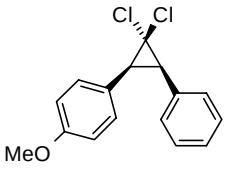
[d] The aryl rings are bonded directly to each other.

Day *et al.*[83] synthesized the 1,1-dichloro-2,3-diarylcyclopropanes as antitubulin and anti-breast cancer agents. They found that the compound Z-1,1-dichloro-2,3-diphenylcyclopropane (**79**) is an effective anti-breast cancer agent in rodents and in cell culture and also inhibits tubulin assembly *in vitro* and causes microtubule loss in breast cancer cells leading to accumulation in the G_2/M portion of cell cycle. Various analogues of the **79** such as aryl ring halogenated, methoxylated and benzyloxylated derivatives of **79**, as well as its E-isomer were synthesized and tested for their ability to inhibit the assembly of tubulin into microtubules. They found that the compound Z-1,1-dichloro-2-(4-methoxyphenyl)-3-phenylcyclopropane (**80**) was more potent than the compound **79** against the breast cancer cells.



79

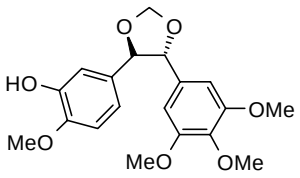
z-1,1-Dichloro-2,3-diphenyl-cyclopropane



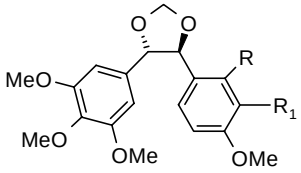
80

1,1-Dichloro-2-(4'-methoxyphenyl) -3-phenylcyclopropane

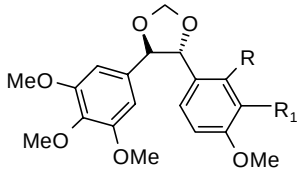
Shirai and co-workers[84] have reported that the *cis* carbon-carbon double bond in CA-4 could be replaced by a dioxolane (**81**). Pettit *et al.*[85] have synthesized and evaluated the 1,3-dioxolanes (S,S) **82a** (designated as dioxostatin) and its prodrugs (S,S) **82b** and (R,R) **83**. The dioxostatin (**82a**) was found to be the most potent inhibitor of microtubule assembly at the colchicine site.



81

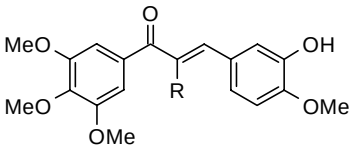


(S,S)-**82a**, $R=R_1$ = OH
(S,S)-**82b**, $R=R_1$ = $OP(O)(ONa)_2$



(R,R)-**83**, $R=R_1$ = OH

Lawrence *et al.*[86] synthesized a library of chalcones by parallel synthesis using the Claisen-Schmidt base catalyzed aldol condensation of substituted acetophenones and benzaldehydes. The cytotoxicity of these chalcones was determined by conventional MTT assay. One of the compounds they prepared, *viz*, α-methyl-substituted chalcone **84**, was highly cytotoxic, its IC_{50} (K 562) was 0.21 nM and the chalcone **85** lacking α-methyl group was also potent (IC_{50} 4.3 nM).

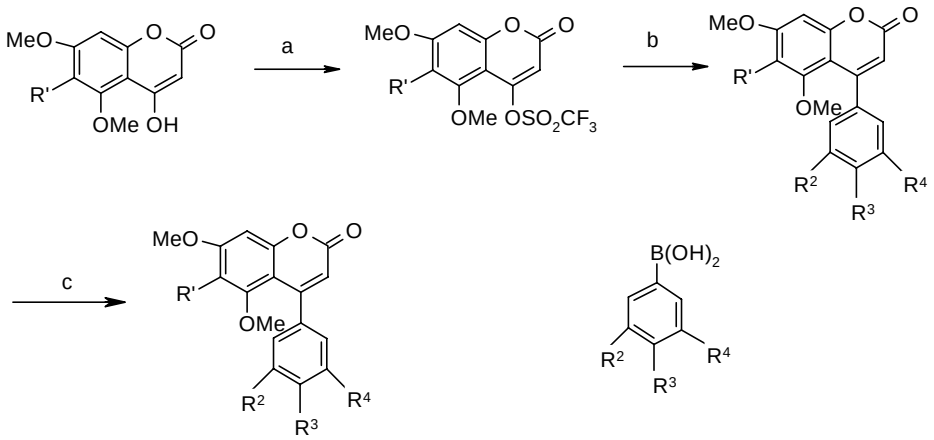


84 R= Me

85 R = H

4-Arylcoumarin analogues of combretastatin A-4 have been reported by Bailly *et al.*[87] In the past recent years, a number of neoflavonoid (4-phenylcoumarin) derivatives isolated from various plant sources have revealed cytotoxic properties.[88] The two aromatic rings of 4-phenylcoumarin derivatives adopt a conformation in which they are not coplanar. The structural similarity between combretastatin and neoflavonoid was expected to lead to a potent 4-arylcoumarin

analogue of combretastatin A-4. So they prepared a series of A-ring polymethoxylated neoflavonoids by coupling reactions involving either Suzuki or Stille reactions as shown in scheme 3. From the various 4-arylcoumarin analogues compounds **86** and **87** were found to have a potent cytotoxic activity.



	R'	R^2	R^3	R^4
86	OMe	H	OMe	OH
87	H	H	OMe	OH

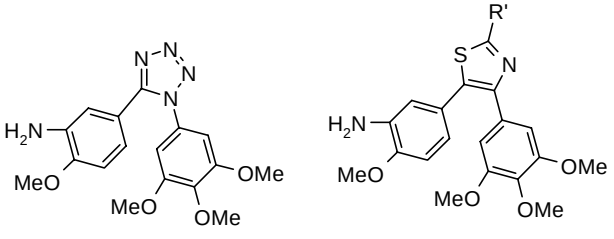
R^2	R^3	R^4
H	OMe	OH

Scheme 3

Reagents and conditions: a) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2 b) $ArB(OH)_2$, $Pd(PPh_3)_4$, CuI, Na_2CO_3, C_6H_6 c) aqueous HBr, H_2O

Wang *et al.*[89] reported five membered heterocycle in place of the *cis*-double bond in comebretastatin A-4. They synthesized 1,2-substituted five-membered aromatic heterocycles in place of olefinic double bond such as imidazole, oxazole and pyrazole to mimic the *cis* double bond. They were interested in the imidazole ring as the basic nitrogen on the imidazole ring may lead to the compounds with decreased lipophilicity that can be formulated into water-soluble salts to give improved physicochemical properties.

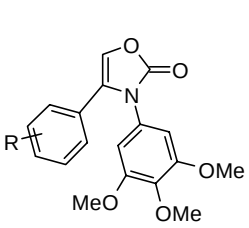
Ohsumi *et al.*[90] demonstrated that a tetrazole (**88**) or a thiazole (**89a** or **b**) ring could replace the *cis* double bond to maintain potent cytotoxicity.



88

89a R' = H
89b R' = NH_2

Nam *et al.* reported the five membered *cis*-restricted heterocycle based analogues of CA-4 including combretooxazolones (**90**, **91**)[91] and furanones (**92**)[92] with very potent cytotoxicity and significant antitumor activity.



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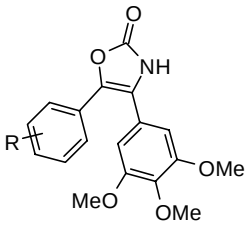

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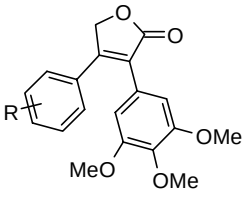

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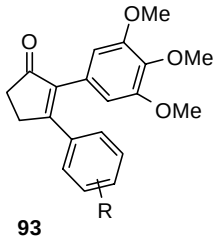
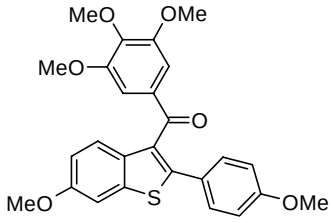


93

Ahn *et al.*[93, 94] reported the synthesis of combretocyclopentenones **93** as *cis* restricted analogues of combretastatin A-4. They synthesized various analogues including pentenone, pentenol, pentene and furan, which were evaluated for cytotoxicity against murine and human tumor cell lines. Some of the compounds from this series showed strong cytotoxicity with IC_{50} values in the range of 8-34 ng/mL.

Flynn and Hessian[95] reported the benzo[b] thiophene analogues of combretastatin A-4 using palladium-mediated coupling approach. Two of the analogues **94** and **95** exhibited greater activity than **96**. These compounds inhibited both the rate and extent of tubulin assembly but again were less active than CA-4.[96]



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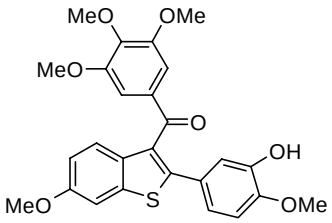

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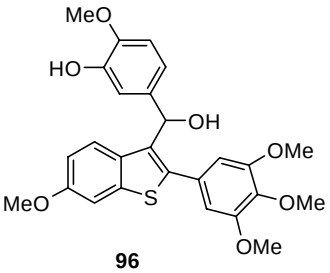
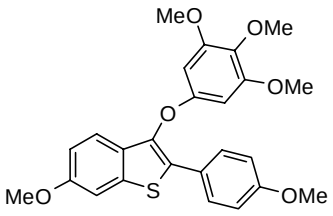


96

Pinney *et al.*[97] prepared alkynyl sulfide type compounds **98** and aryl ether **97**. They found that the aryl ether **97** strongly inhibited tubulin polymerization and was selected for initial *in vivo* evaluation by the NCI in their hollow fiber assay. Alkynyl sulfide **98** was about 3-4 times less active than **97** as an inhibitor of tubulin polymerization.

Various *cis* restricted analogues of combretastatin A-4, such as indole derivatives[98], benzofuran analogues[99] as well as thiophene based[96] analogues of CA-4 have been synthesized and evaluated for their cytotoxic activity.



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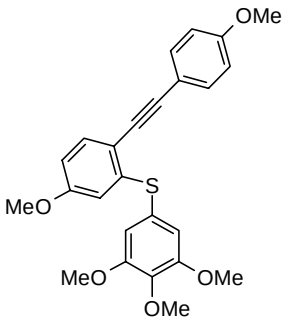


98

Pinney *et al.*[100] further prepared the phosphate ester derivatives of combretastatin A-4 and found them as potential CA-4 prodrugs or stable CA4P analogues after biological evaluation. *In vivo*, CA4P is rapidly enzymatically converted to CA-4.

CONCLUSION:

Interfering with mitosis using tubulin-binding drugs is a clinically validated approach to treat cancer patients. Today, more than 30 new compounds targeting tubulin, either stabilizing or destabilizing microtubule dynamics, are in late preclinical or early clinical development. Many of these are natural or semisynthetic compounds of complex structure, but surprisingly simple synthetic molecules are also potent antimitotic agents.

Combretastatins are the structurally simple stilbenes which showed potent cytotoxicity against multidrug resistant cancer cell lines. In preclinical terms, the combretastatins seem to have advantages over many existing tubulin agents because the observed effects on tumor vasculature occur well below the maximum tolerated dose. Combretastatin A-4 is a tubulin binding agent which has shown to have potential anticancer activity. Number of *cis* restricted analogues of combretastatin A-4 have been synthesized and evaluated for their cytotoxicity. Few water soluble analogues of CA-4 have been synthesized which showed better activity than combretastatin A-4. Many of the analogues are facing problem of poor aqueous solubility, poor bioavailability, low biochemical efficacy *in vivo* and metabolic unstability. Thus there is still a need to approach this problem in a different way and to produce CA-4 analogues which are potent, simple, biocompatible and nontoxic.

CHAPTER 1

DESIGN AND SYNTHESIS OF COMBRETASTATIN A-4 ANALOGUES

SECTION I

Design and Synthesis of 2,3-Diaryl-4-Hydroxycyclopent-2-en-1-one Analogues of Combretastatin A-4

1.1.1 INTRODUCTION:

Modern drug discovery often involves screening small molecules for their ability to bind to a preselected protein target. Target-oriented syntheses of small molecules, individually or as collections can be planned effectively with retrosynthetic analysis and such target oriented syntheses used in drug discovery efforts involve preselected protein targets, whereas diversity-oriented syntheses are used to identify simultaneously therapeutic protein targets and their small-molecule regulators. Our efforts in drug discovery research were focused on combretastatin A-4 as the lead molecule. Combretastatin A-4 is believed to bind at the same site as that of colchicine which is a tubulin binding agent. The designed *cis*-restricted combretastatin A-4 analogues were assumed to be tubulin binding which was further confirmed by the biological activity studies conducted at Dabur Research Foundation, Ghaziabad, Delhi.

Our interest in the field of design and synthesis of biologically active compounds prompted us to undertake the synthesis of *cis* restricted analogues of combretastatin A-4 [*cis*-1-(3,4,5-trimethoxyphenyl)-2-(3'-hydroxy-4'-methoxyphenyl) ethylene].

A number of studies have been reported on structure activity relationship of combretastatin A-4 (**13**). These studies showed that the *cis* orientation of the two benzene rings is essential and 3,4,5-trimethoxy substituents on the A-ring of CA-4 are indispensable for potent cytotoxicity. CA-4 (*cis*) analogues are prone to isomerization to *trans* forms during storage and administration and *trans* forms of these compounds show dramatic reduction in antitubulin and antitumor activity. CA-4 is in phase II clinical trials. Cushman *et al.*[12] reported that the active conformation of the combretastatin A-4 is not planar. Considering the structure activity relationship study of CA-4, the 3,4,5-trimethoxy substituents on A-ring and 4-OMe group on B-ring of CA-4 are essential for cytotoxic activity.

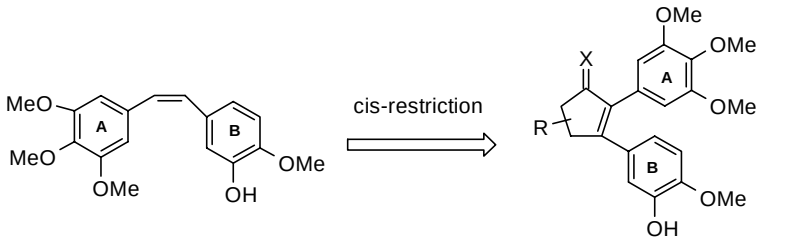
1.1.2 PRESENT WORK:

We planned to introduce 4/5-hydroxy-cyclopentenone ring in place of olefinic double bond between two aryl rings of combretastatin A-4, keep 3,4,5-trimethoxy substituents on A ring, to obtain compounds with pharmaceutically acceptable properties, improved antitumor activity and also to maintain shape selectivity. The hydroxy group at 4/5 of cyclopentenone should also provide a handle for derivatisation required to increase aqueous solubility.

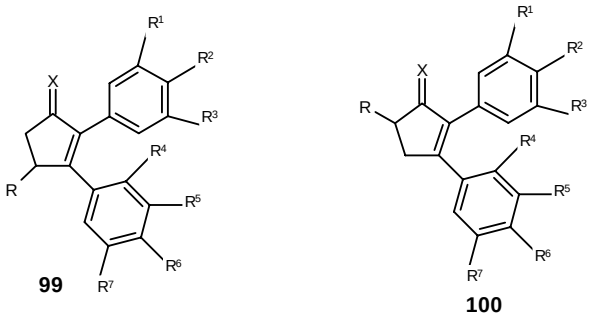
The-4-hydroxy-cyclopent-2-en-1-one is one of the most important intermediate used in synthesis of various natural products like prostaglandins, prostacyclines etc. We selected the 5-membered

ring with hydroxy group to replace the *cis* double bond for synthesis of combretastatin A-4 analogues, as in prostaglandins it is well known that five membered ring having 4-hydroxy group is essential for biological activity. Moreover, such a structure should avoid inactivation resulting from *cis*-to-*trans* isomerization of the double bond of combretastatin A-4 derivatives. We can also further derivatize these functions to obtain the novel analogues of combretastatin A-4. We planned to derivatize these functions as oxime, acetate etc as these groups have polar character and they also effect markedly the transport of the molecule across biological membranes.

Our Strategy

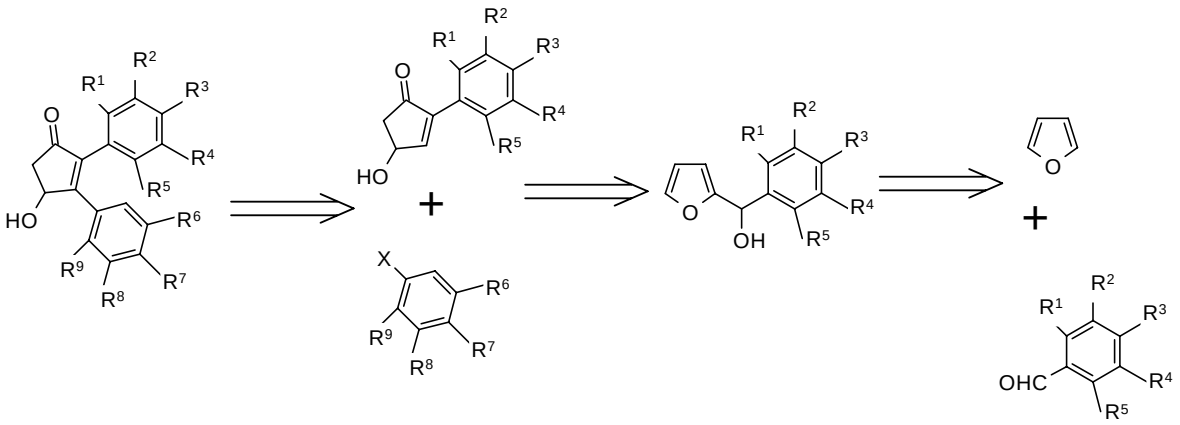


R = 4/5 OH, OAc, OTBS.
X = O, N-OH



Synthesis of substituted 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues (99) using Heck reaction approach:

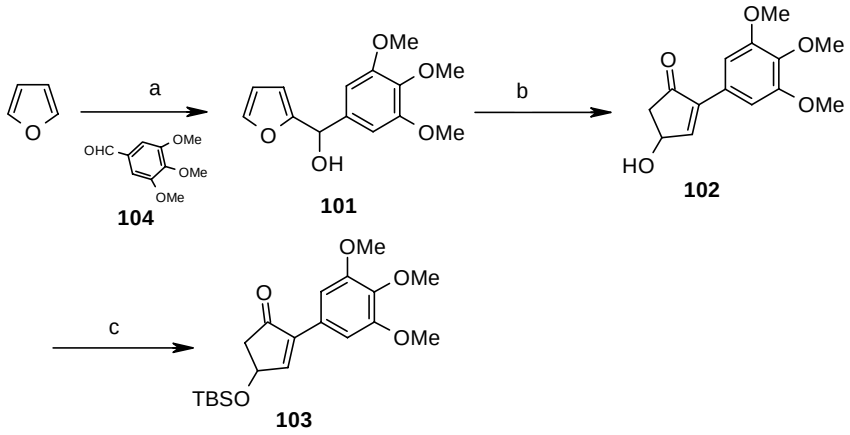
Initially we planned to synthesize compounds of type **99** by applying the Heck reaction approach as shown in retrosynthetic route in scheme 4. The 2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one (**102**) was envisaged as important common building block for the synthesis of various combretastatin A-4 analogues.



Scheme 4

Synthesis of 2-(3,4,5-trimethoxyphenyl)–4–hydroxycyclopent-2-en-1-one (102):

The intermediate **102** was prepared from 3,4,5-trimethoxybenzaldehyde as shown in scheme 5. Reaction of furyl magnesium bromide with 3,4,5-trimethoxybenzaldehyde (**104**) gave the 2-furyl(3,4,5-trimethoxyphenyl) methanol (**101**) which on rearrangement with $ZnCl_2$ in dioxan/water gave the intermediate **102** in excellent yield. The hydroxyl group was protected as tert-butyldimethylsilylether to give intermediate **103**.



Scheme 5

Reagents and conditions: a) i) nBuLi, THF ii) $MgBr_2$, THF, -30^{0}C, 4 h, 93 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 90 % c) TBDMSCl, DMAP, DCM, Et_3N, 3 h, 74 %.

We obtained the compound **102** from furfuryl alcohol **101** in single step using zinc chloride and aqueous dioxan. The reported method for the synthesis of substituted 2-aryl/alkyl-4-hydroxy-cyclopent-2-en-1-one involved two steps from furfuryl alcohol. We developed a simple method

for synthesis of substituted 2-aryl-4-hydroxycyclopent-2-en-1-ones from furfuryl alcohols in one step. The details of this methodology are discussed in Chapter 2 Section I.

The C-C bond forming reactions play a vital role in the synthetic organic chemistry. Among the various C-C bond-forming reactions, Heck reaction has received much attention in recent years as a new method for C-C bond formation. The arylation or alkenylation of alkenes under the influence of a palladium catalyst is commonly referred, as the Heck reaction.[101] The Heck reaction is amenable to a variety of easily available starting materials. It is remarkably chemoselective and most of the functional groups can be tolerated. The regiochemistry found for such transformation was consistent with carbon-carbon bond formation at the least hindered terminus of the alkene, much like in a Michael addition. The stereochemistry of addition usually delivered a *trans* disubstituted alkene.

The traditional mechanism for the Heck reaction[102] proposes that a coordinately unsaturated 14-electron palladium (0) species, usually coordinated with weak ligands (tertiary phosphanes), is assumed to be the catalytically active complex. Tetrakis(triphenylphosphane)palladium(0) generates tris(triphenylphosphane)palladium(0) ***in situ.*** However, palladium (II) salts such as palladium acetate or bis(triphenylphosphane)palladium dichloride, which are reduced in the reaction medium, are more commonly used.

In the first step of the catalytic cycle (**A** in fig. 3) halo alkenes and haloarenes are commonly assumed to oxidatively add to bis(triphenylphosphane)palladium(0), generating a σ-alkenyl or σ-arylpalladium(II) complex. In the next step an alkene molecule is coordinated, probably after elimination of another phosphane ligand. After both ligands have adopted the *cis* orientation necessary for insertion of the alkene into the σ-alkenyl or σ-aryl C-Pd bond, rotation of the alkene leads to in-plane coordination of the alkene. Finally, the alkene inserts into the σ-alkenyl or -arylpalladium bond to give a σ- alkylpalladium complex *via* a four-center transition state (step **B**). After the *cis*-addition of the alkene, the reaction-terminating β-hydride elimination (step **D**) can generally occur only after internal rotation (step **C**) of the generated alkylpalladium species. The catalyst is regenerated after reductive elimination of HX in presence of the base.

Asymmetric Heck reaction has recently emerged as a powerful tool for the enantioselective synthesis of chiral compounds.[103, 104] The intramolecular asymmetric Heck reaction has received particular attention, although intermolecular variants are also known.

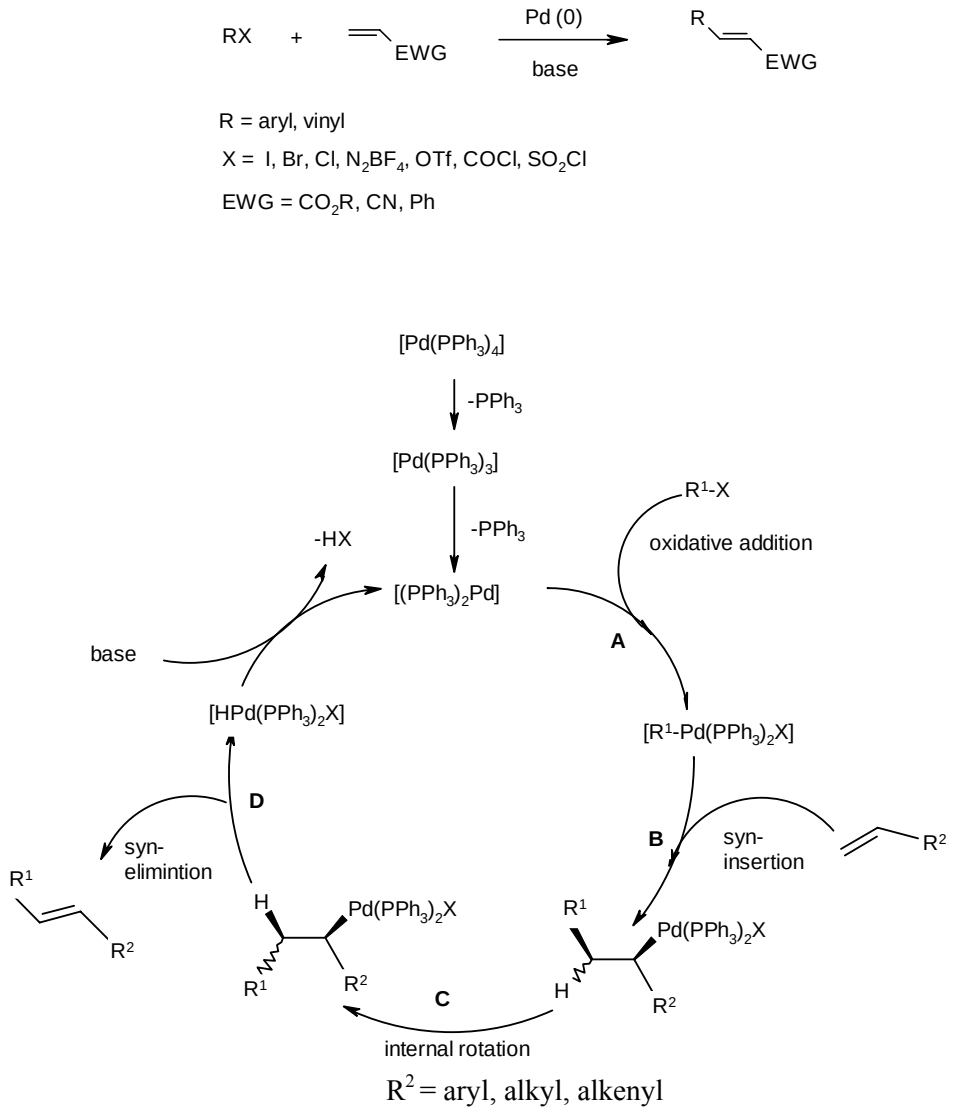
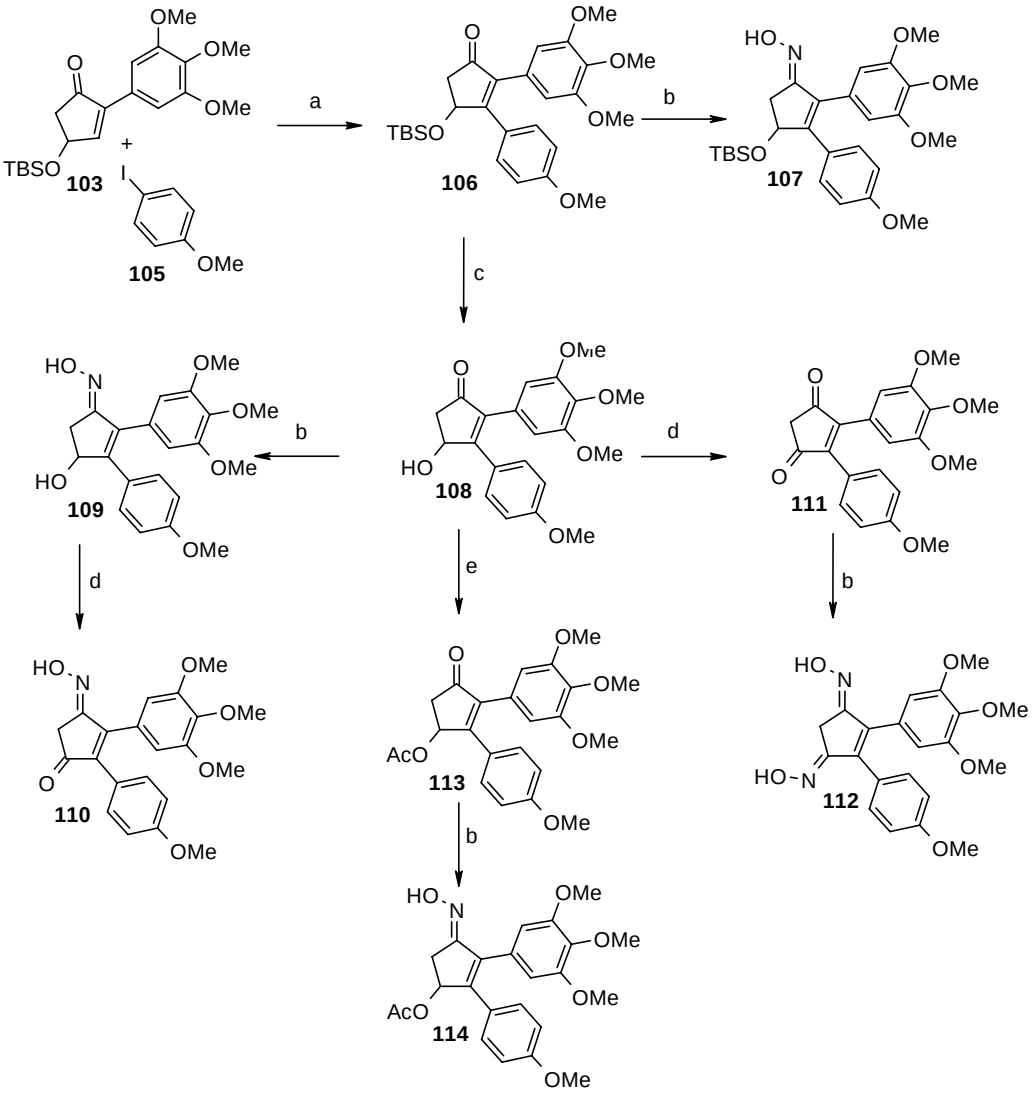


Figure 3: Mechanism of the Heck reaction.

The intermediate **103** was subjected to Heck reaction using various aryl iodides. First we carried out the Heck reaction of 4-iodoanisole (**105**) with intermediate **103** in presence of palladium acetate, triphenyl phosphine and potassium carbonate in acetonitrile using tetrabutylammonium bromide to give 2-(3,4,5-trimethoxyphenyl), 3-(4-methoxyphenyl)-4-tert–butyldimethylsilyloxycyclopent-2-en-l-one (**106**) in 66 % yield (scheme 6).



Scheme 6

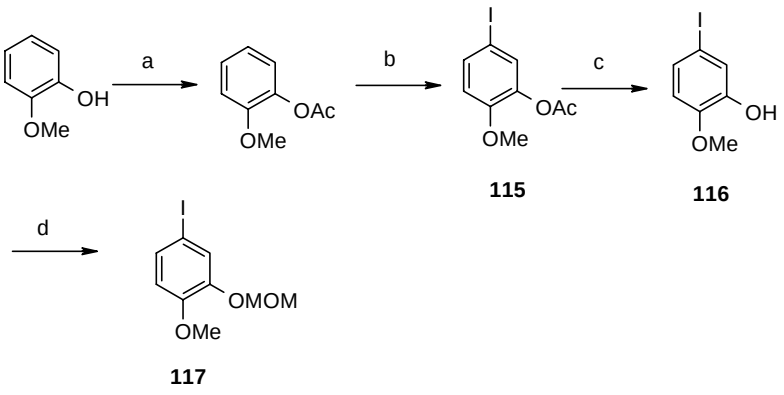
Reagents and conditions: a) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), PPh_3, Bu_4NBr, CH_3CN, 36 h, 66 %. b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h, 75 %. c) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 88 %. d) PCC, CH_2Cl_2, r t, 2 h, 30 %. e) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 85 %.

The compound **106** on oximation with hydroxylamine hydrochloride and sodium acetate in ethanol afforded the compound **107**. The hydroxy group in **106** was regenerated by treating it with acetic acid, tetrahydrofuran and water at ambient temperature to give the compound **108** in 86 % yield, which on oxidation with pyridinium chlorochromate in dichloromethane gave the diketone **111** in 30 % yield. The diketone **111** on oximation gave the dioxime **112** in 51 % yield while compound **108** on oximation afforded **109** in 75 % yield. The compound **110** was obtained

from **109** by oxidation with pyridinium chlorochromate. The compound **108** on acylation gave the compound **113** which on oximation afforded compound **114**.

The yields of the products obtained by Heck reaction of various substituted aryl iodides with the intermediate **103** were not satisfactory since the reaction did not go to completion. Therefore we optimized Heck reaction conditions using 4-iodoanisole **105** and intermediate **103** by changing solvents such as acetonitrile, dimethylformamide, dimethylsulfoxide etc., various bases tried were potassium carbonate, triethylamine, diisopropyl ethylamine etc. but there was not much difference in yields and reaction time. The best result obtained was using acetonitrile as a solvent and potassium carbonate as base at 90^0C. Heck reactions using other aryl iodides were mostly performed under these optimized conditions to generate library of designed new chemical entities.

The synthesis of the analogue **119** possessing 4-methoxy and 3-hydroxy group in B-ring of combretastatin A-4 is depicted in scheme 8. The required iodo compound, 4-iodo-1-methoxy-2-methoxymethyloxybenzene (**117**) was prepared from 2-methoxyphenol as shown in scheme 7.



Scheme 7

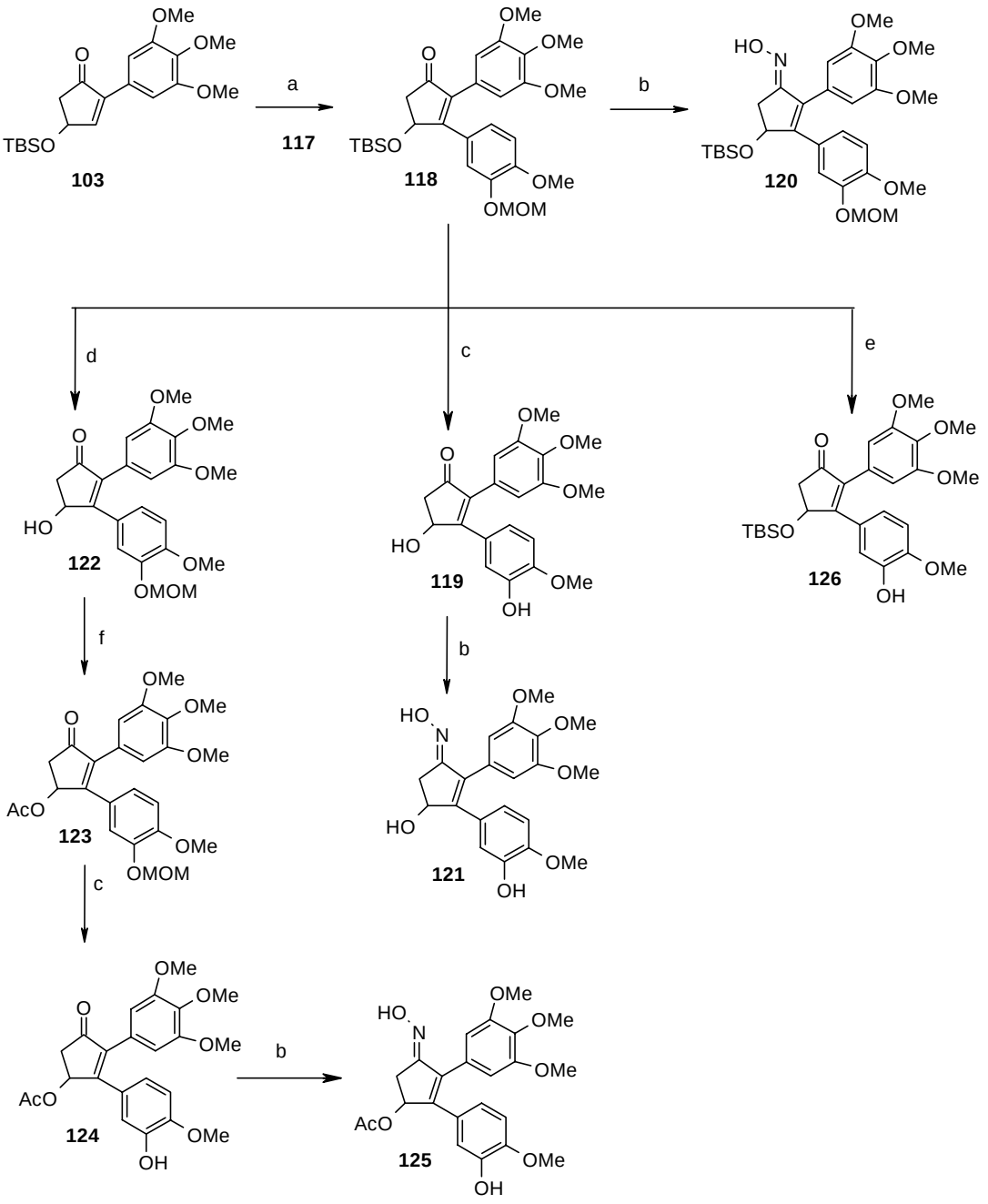
Reagents and conditions: a) Acetic anhydride, pyridine, r t, 20 h, 85 % b) I_2, CF_3COOAg, dry $CHCl_3$, 4 h, 60 % c) Aq. NaOH, r t, 5 h, 73 % d) Mom-Cl, ethyl-diisopropylamine, dichloromethane, 78 %.

Acylation of 2-methoxyphenol with acetic anhydride in pyridine at room temperature for 20 h afforded the 2-methoxyphenyl acetate in excellent yield, which on iodination with iodine and silver trifluoroacetate in dry chloroform afforded the iodo acetate **115**. Hydrolysis of acetate using dilute sodium hydroxide at room temperature afforded the compound **116** in high yield. The phenolic –OH group of compound **116** was then protected as methoxymethylether using MOM-

chloride and Hunnings base (ethyl-diisopropyl-amine) to give the iodo compound **117** in 78 % yield.

The reaction of intermediate **103** with iodo compound **117** using palladium acetate and potassium carbonate in acetonitrile using tetrabutylammonium bromide as a catalyst afforded the compound **118** (scheme 8) and some aryl-aryl coupled product. The compound **118** on oximation with hydroxylamine hydrochloride in ethanol afforded the compound **120** in 75 % yield. The hydroxy group in **118** was regenerated by treating it with acetic acid, tetrahydrofuran and water at ambient temperature to give the compound **119** in 60 % yield. Further oximation of this product with hydroxylamine hydrochloride and sodium acetate in ethanol afforded the oxime derivative **121** in 77 % yield.

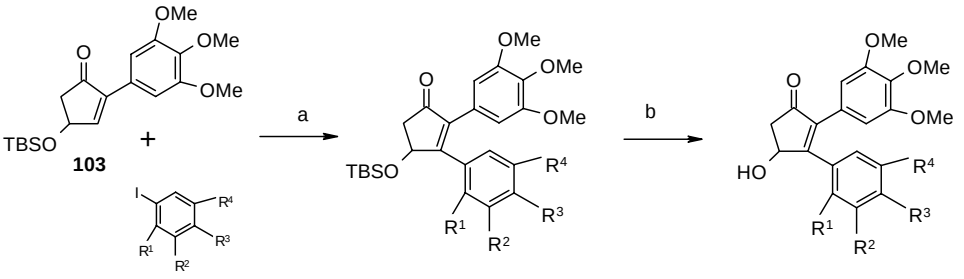
The selective deprotection of tert-butyldimethylsilyloxy group in the compound **118** was achieved by treating it with tetrabutylammonium fluoride in tetrahydrofuran at 0^0C in 88 % isolated yield to get the compound **122**. Further acylation of this compound with acetic anhydride and pyridine afforded the compound **123** in quantitative yield. The cleavage of methoxymethyl protection of this compound was achieved by treating it with acetic acid, tetrahydrofuran and water to collect compound **124** in 77 % yield, which on oximation with hydroxylamine hydrochloride in ethanol afforded the derivative **125**. On the other hand selective deprotection of methoxymethyl ether was achieved by treating the compound **118** with trifluoroacetic acid in dry dichloromethane to give the derivative **126** in fair yield of 56 %. The synthesized derivatives from this series were evaluated for their cytotoxicity.



Scheme 8

Reagents and conditions: a) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), Bu_4NBr, CH_3CN, 36 h, 34 % b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h c) CH_3COOH-THF-H_2O (3:1:1), r. t, 20 h d) TBAF (1 M soln.), THF, 0-r. t, 1 h. e) CF_3COOH, dichloromethane, 20 h f) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 74 %

Synthesis of B ring modified analogues of CA-4:



	R^1	R^2	R^3	R^4
127	OMe	H	H	OMe
128	H	Me	OMe	Me
129	H	H	OMe	OMe
130	H	H	H	H
131	H	H	OMe	COOMe

	R^1	R^2	R^3	R^4
132	OMe	H	H	OMe
133	H	Me	OMe	Me
134	H	H	OMe	OMe
135	H	H	H	H
136	H	H	OMe	COOMe

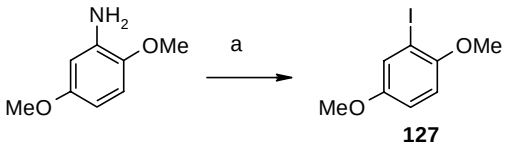
	R^1	R^2	R^3	R^4
137	OMe	H	H	OMe
138	H	Me	OMe	Me
139	H	H	OMe	OMe
140	H	H	OMe	COOMe

Scheme 9

Reagents and conditions: a) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), PPh_3, Bu_4NBr, CH_3CN, 36 h.
b) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h.

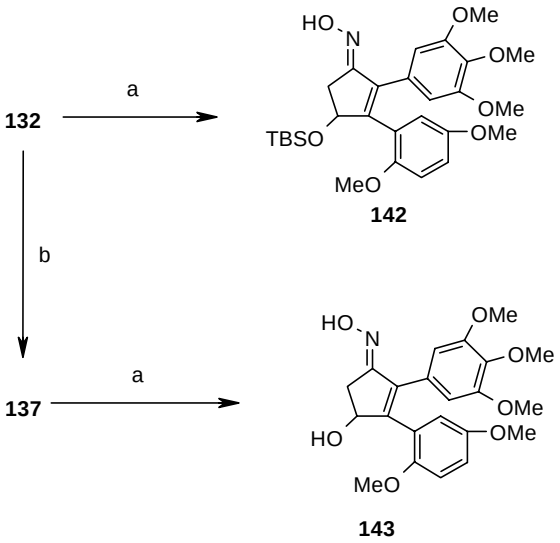
As shown in scheme 9 various B-ring substituted analogues of CA-4 were synthesized by Heck reaction of appropriately substituted aryl iodides (**127-131**) with intermediate **103** to give the corresponding CA-4 analogues (**132-136**) respectively.

The 2-iodo-1,4-dimethoxybenzene (**127**) was prepared from 2,5-dimethoxyaniline by diazotisation followed by Sandmeyer reaction in 63 % yield as shown below.



Reagents and conditions: a) i) Glacial acetic acid, $NaNO_2$, 0^0C, ii) KI, 0^0C, 1 h, 63 %.

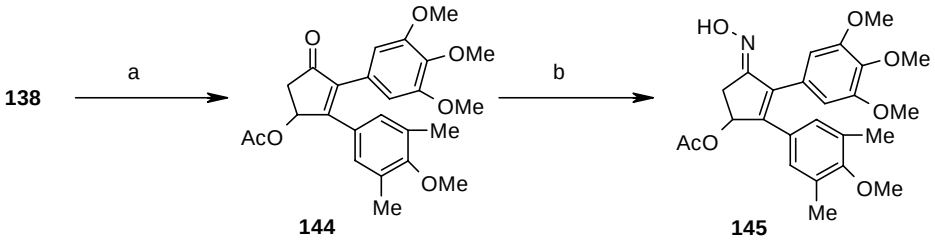
The Heck reaction of the compound **127** with intermediate **103** gave the compound **132** in 56 % yield, which on cleavage of tert-butyldimethylsilyloxy group with acetic acid, tetrahydrofuran and water resulted in the compound **137** in 91 % yield. Similarly compound **132** on oximation gave the compound **142**. While the compound **137** on oximation gave the compound **143** in 86 % yield as a semisolid (scheme 10).



Scheme 10

Reagents and conditions: a) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h b) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h.

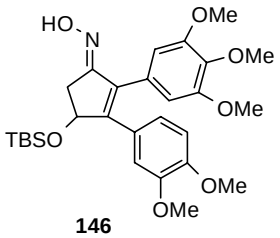
The Heck reaction of compound **128** with the intermediate **103** gave the compound **133** in 26 % yield and the cleavage of tert-butydimethylsilyloxy protection in compound **133** resulted in the compound **138**. Acylation of the compound **138** gave derivative **144** in 85 % yield, which on oximation gave compound **145**.



Scheme 11

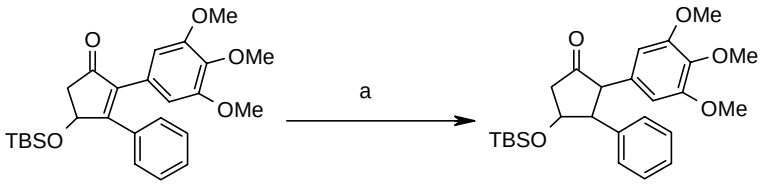
Reagents and conditions: a) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 74 % b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h

Similarly, compound **134** was obtained by Heck reaction of 4-iodo-1,2-dimethoxybenzene (**129**) with intermediate **103**. Compound **134** on oximation using hydroxylamine hydrochloride in ethanol under reflux resulted in the compound **146**. Cleavage of –OTBS protection with acetic acid, tetrahydrofuran and water resulted in the derivative **139** in 76 % yield.



146

The Heck reaction of iodobenzene (**130**) with intermediate **103** resulted in the analogue **135**, which was not having any substituent on the B-ring. Yield obtained in this case was somewhat low (25 %). To see the feasibility of double bond reduction we subjected compound **135** to reduction using 5 % palladium/carbon in ethanol at room temperature to give compound **141** in 40 % yield within 3 h without affecting the carbonyl function (scheme 12).

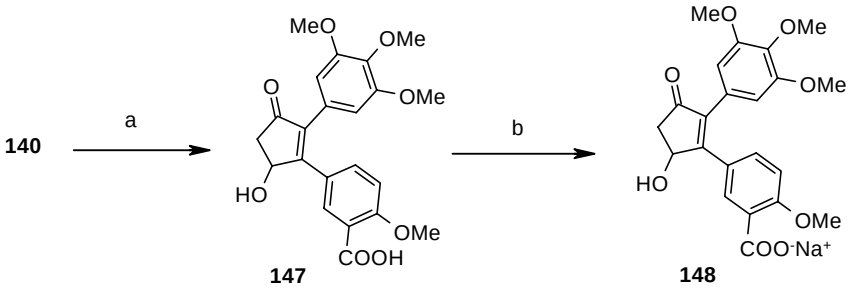


135 **141**

Scheme 12

Reagents and conditions: a) 5 % Pd/C, EtOH, H_2, r t., 3 h, 40 %

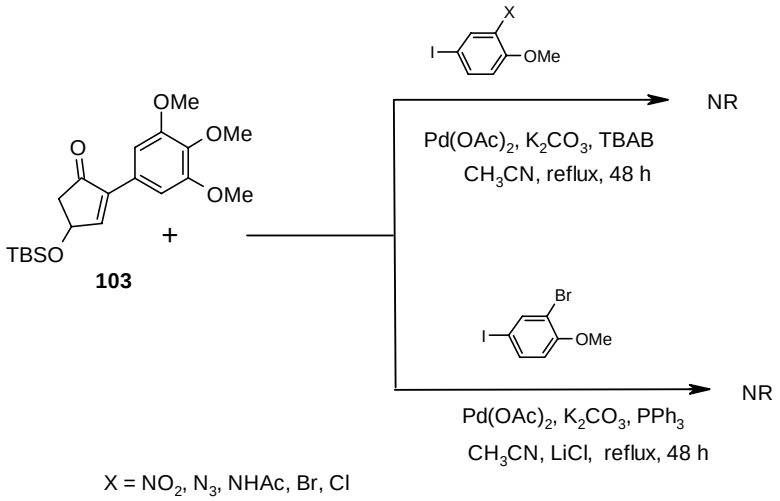
Methyl-5-iodo-2-methoxybenzoate (**131**) under the Heck reaction conditions with intermediate **103** resulted in the formation of the compound **136** in poor yields of 17 %. This compound on cleavage of –OTBS group as in scheme 9 resulted in the compound **140** as semisolid in good yields (76 %). The hydrolysis of the ester function of the compound **140** was achieved with aqueous NaOH, methanol at room temperature which gave the compound **147**. As compound **147** possessed –COOH group in 3-postion of B-ring it was planned to make water soluble sodium salt of that acid. Treatment of the compound **147** with NaOH in distilled water and removal of water under reduced pressure resulted in the compound **148** containing ionizable group (scheme 13).



Scheme 13

Reagents and conditions: a) Aq. NaOH, MeOH, r t, 5 h, 64 % b) NaOH, distilled water

Since some of the compounds from this series showed good cytotoxic activity we planned to prepare analogues having different substitutents such as $–NO_2$, Br, N_3, NH_2, NHAc, Cl, etc. at 3-position of B-ring of CA-4 analogues instead of phenolic –OH group, to improve cytotoxic activity and also to prepare water soluble derivatives by forming salts of amino substitutents. To prepare these analogues we tried Heck reaction approach with appropriately substituted iodo compounds with intermediate **103** as shown in scheme 14 but all these reactions failed to give the required products.

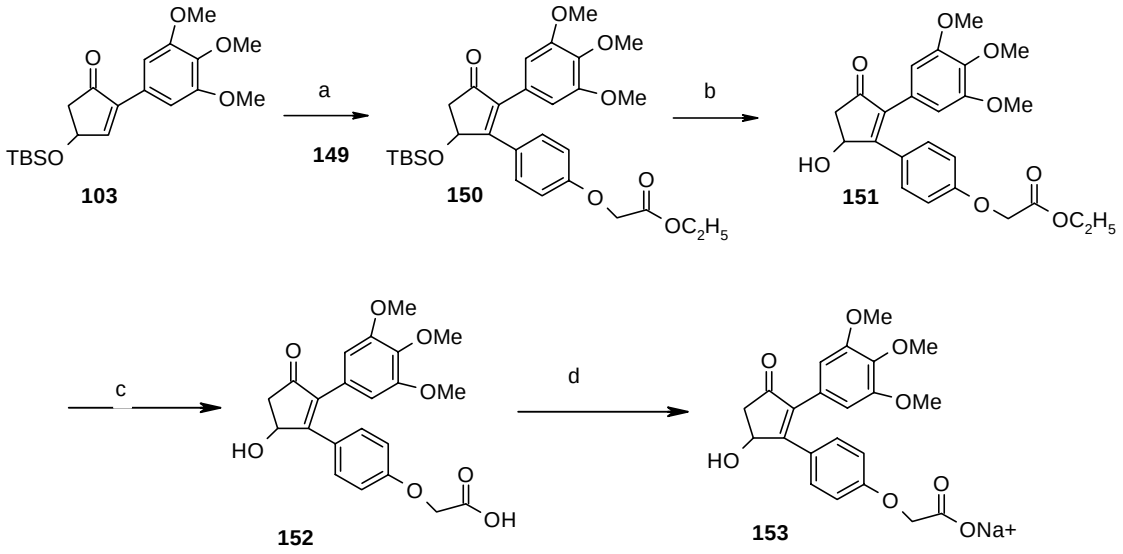


Scheme 14

Biological screening studies of the compounds synthesized at this stage indicated that the compounds exhibiting potent cytotoxicity possessed only 4-OMe group in B-ring of the CA-4 analogues. The compound **114** showed promising cytotoxic activity against various cancer cell lines. It showed better activity than CA-4 under simultaneous studies using various cell lines.

Consequently, to confirm the above finding we planned to synthesize the B-ring modified compounds having ester or acid functionality in place of 4-OMe. The required compound (4-iodo-phenoxy)-acetic acid ethyl ester (**149**) was prepared as follows: phenol on reaction with ethyl bromoacetate and potassium carbonate in acetone resulted in the phenoxy-acetic acid ethyl ester in 78 % yield, which on reaction with iodine monochloride in acetic acid resulted in the formation of compound **149**.

The Heck reaction of the iodo compound **149** with the intermediate **103** using palladium acetate, triphenyl phosphine, potassium carbonate in acetonitrile and catalytic amount of tetrabutylammonium bromide provided {4-[5-(tert-butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-phenoxy}-acetic acid ethyl ester (compound **150**). The removal of tert-butyldimethylsilyloxy group using tetrabutylammonium fluoride in tetrahydrofuran resulted in the compound **151** in excellent yield. Hydrolysis of ester functionality in compound **151** was achieved with 10 % sodium hydroxide in methanol to give compound **152**. The compound **152** on reaction with sodium hydroxide in distilled water provided the compound **153**, a water soluble sodium salt of compound **152** as shown in scheme 15.

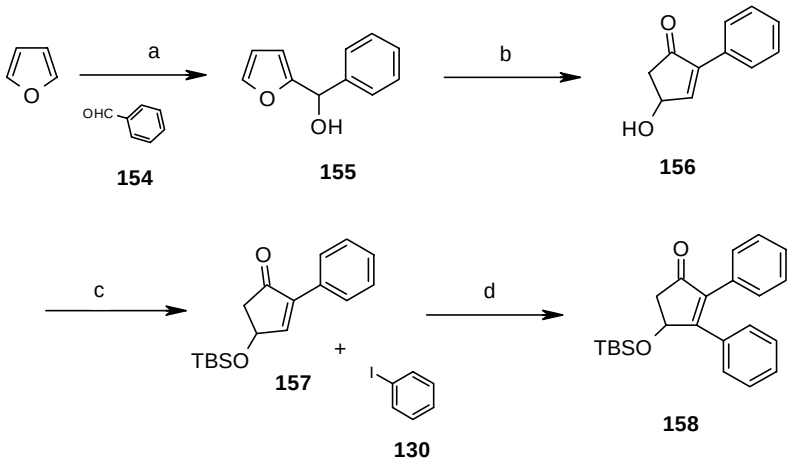


Scheme 15

Reagents and conditions: a) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), Bu_4NBr, CH_3CN, 36 h, 35 % b) TBAF (1 M soln.), THF, 0-r. t., 1 h, 79 % c) 10 % NaOH, MeOH, 75 % d) NaOH, dist. water

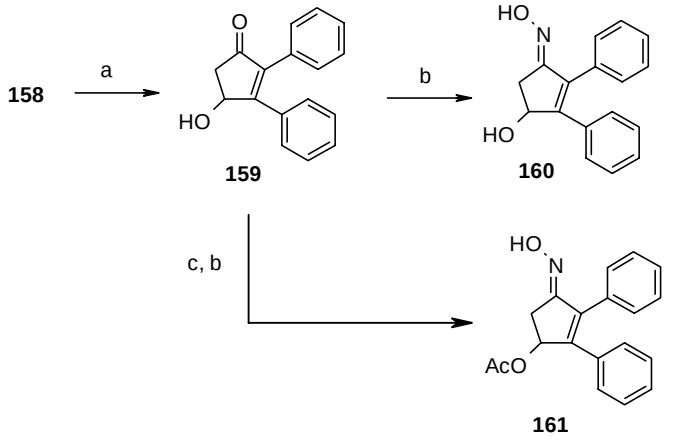
Synthesis of unsubstituted 2,3-diaryl analogues of combretastatinA-4:

In order to study the role of 3,4,5-trimethoxy substitutents on A-ring of combretastatin A-4 and 3-OH and 4-OMe groups of B ring, we planned to synthesize the unsubstituted 2,3-diaryl –4-hydroxy cyclopent-2-en-1-one analogues of combretastatin A-4 as shown in scheme 16 and scheme 17. The intermediate **156** was prepared from benzaldehyde as shown in scheme 16. Reaction of furyl magnesium bromide with benzaldehyde **(154)** gave the furyl-2-phenylmethanol **(155)** which on rearrangement with $ZnCl_2$ in dioxan/ water gave the intermediate **156** in excellent yield in a single step. The free hydroxy group was protected as tert-butyldimethylsilyl ether (**157**). The Heck reaction of iodobenzene (**130**) with intermediate **157** under optimized Heck reaction conditions afforded compound **158**. The hydroxy group was regenerated by treating compound **158** with acetic acid, tetrahydrofuran and water to give the compound **159** in excellent yield. Oximation of the compound **159** using hydroxylamine hydrochloride in ethanol afforded the compound **160** as yellowish solid where as the compound **159** on acylation with acetic anhydride in pyridine followed by oximation provided the derivative **161**.



Scheme 16

Reagents and conditions: a) i) nBuLi, THF ii) $MgBr_2$, THF, -30^{0}C, 4 h, 85 %. b) $ZnCl_2$, dioxan/water, reflux, 24 h, 89 % c) TBDMSCl, DMAP, DCM, Et_3N, 3 h, 74 %. d) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), PPh_3, Bu_4NBr, CH_3CN, 36 h, 25 %.

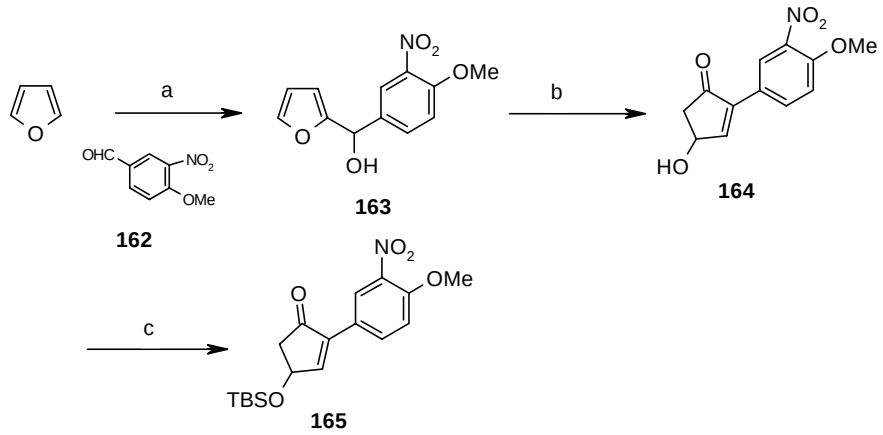


Scheme 17

Reagents and conditions: a) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 88 % b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h, c) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 74 %.

Synthesis of A-ring modified 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues of combretastatin A-4:

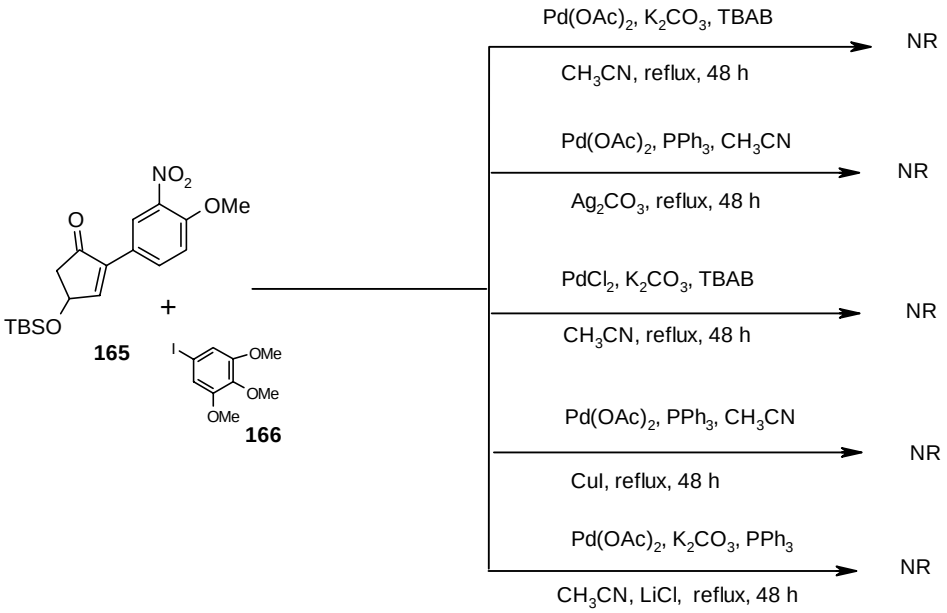
After successful synthesis of B-ring modified analogues of 4-hydroxy-cyclopentenone we planned to synthesize the analogues in which position of A-ring and B-ring was interchanged employing the same synthetic strategy using the corresponding variably substituted benzaldehydes.



Scheme 18

Reagents and conditions: a) i) nBuLi, THF, ii) $MgBr_2$, THF, -30^0C, 4 h, 75 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 65 % c) TBDMSCl, DMAP, DCM, Et_3N , 3 h, 78 %.

The synthesis of intermediate **165** was achieved in three steps starting from lithiation of furan with n-butyllithium at -30^0C and then addition of 4-methoxy-3-nitrobenzaldehyde (**162**) to get the furylmethanol **163** (scheme 18), which on treatment with zinc chloride in dioxan/water under reflux for 24 h gave the compound **164** in high yield. The free hydroxy group was protected as tert-butyldimethylsilyl ether to afford the intermediate **165**. The Heck reaction of 3,4,5-trimethoxyiodobenzene (**166**) was attempted with intermediate **165** using the optimized conditions which failed to give the desired product. Various reaction conditions to get the required product as given in scheme 19, were attempted however required product could not be obtained.

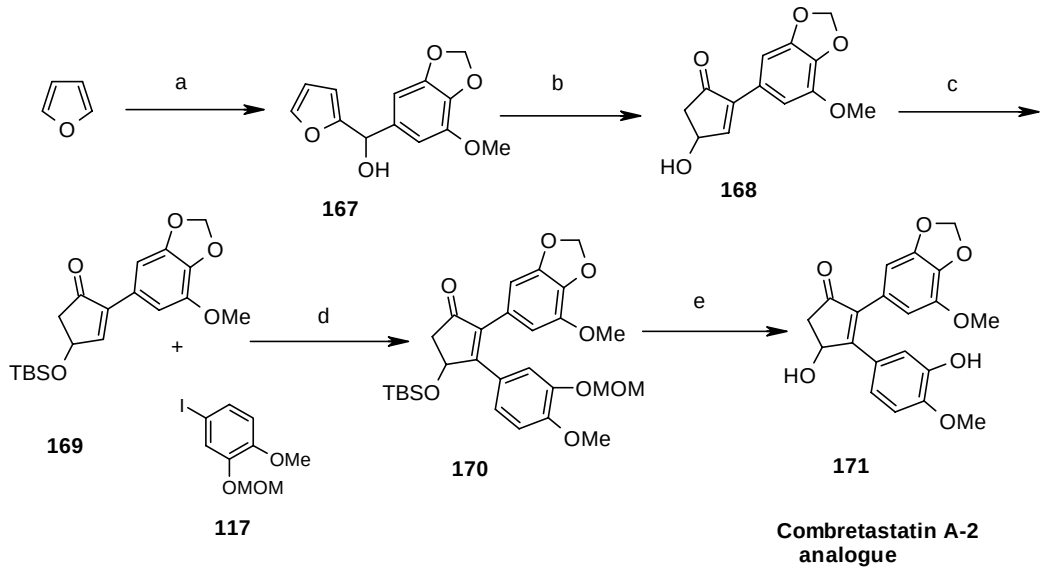


Scheme 19

Further, the intermediate **168** was envisaged as an intermediate for the synthesis of A-ring modified combretastatin A-4 analogues. The intermediate **167** was prepared from 5-methoxypiperonaldehyde as shown in scheme 20. Reaction of furyllithium with 5-methoxypiperonaldehyde gave the furan-2-yl-(7-methoxy-benzo[1,3]dioxol-5-yl)-methanol **(167)** which on rearrangement with $ZnCl_2$ in dioxan/ water gave the intermediate **168** in excellent yield. The hydroxy group was protected as tert-butyldimethylsilyloxyether to give the compound **169**. The intermediate **169** was then subjected to Heck reaction using various aryl iodides.

First we carried out the Heck reaction of 4-iodo-1-methoxy-2-methoxymethyloxybenzene **(117)** with intermediate **169** employing our optimized conditions to give 4-(tert-butyldimethylsilyloxy)-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-3-(4-methoxy-3-methoxymethoxyphenyl)-cyclopent-2-en-

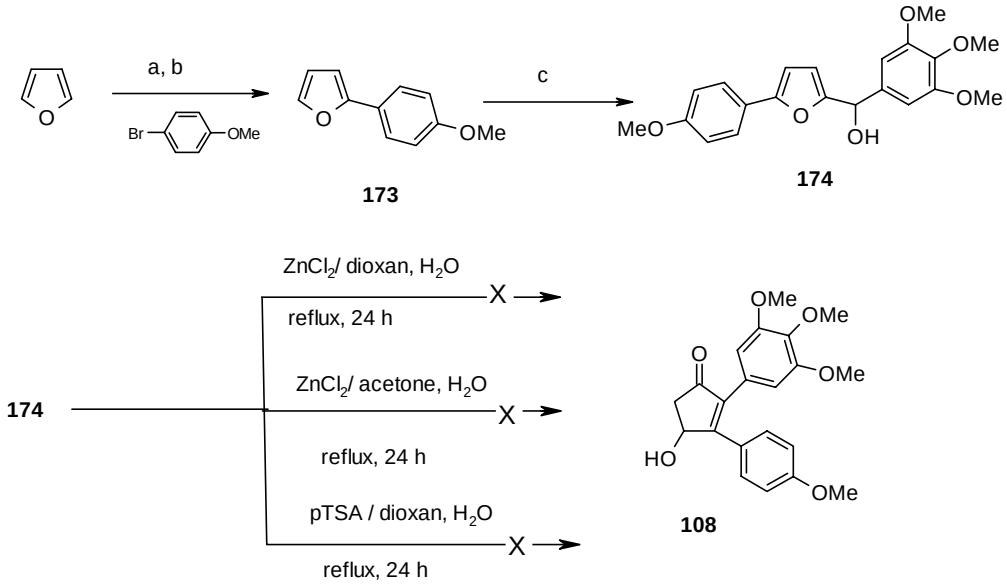
1-one **(170)**. The cleavage of both the protecting groups *viz*. methoxymethyl (-OMOM) and tert-butyldimethylsilyloxy (OTBS) was achieved by treating compound **170** with acetic acid, tetrahydrofuran and water to collect compound **171** which is a *cis* restricted analogue of combretastatin A-2 (scheme 20).



Scheme 20

Reagents and conditions: a) nBuLi, THF, 0^0C, 5-methoxypiperonaldehyde, 3 h, 80 % b) $ZnCl_2$, dioxan/water, reflux, 24 h, 63 % c) TBDMSCl, DMAP, DCM, Et_3N, 73 % d) $Pd(OAc)_2$ (12 mol %), K_2CO_3 (2 eq.), Bu_4NBr, CH_3CN, 36 h, 40 %. e) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 53 %.

Due to the failure of the Heck reaction in many cases and low yields of products, we planned another route for the synthesis of *cis* restricted 4-hydroxycyclopent-2-en-1-ones as shown in scheme 21. Coupling of 4-bromoanisole with furyllithium using tetrakis triphenylphosphine palladium and zinc chloride resulted in the coupling product **173** in 46 % yield.[105] The compound **173** on lithiation using n-butyllithium and reaction with trimethoxybenzaldehye provided the 5-aryl-furfuryl alcohol **174**. This compound **174** was further treated with zinc chloride in dioxan/ water for rearrangement in attempt to get the compound **108**. However, it was observed that under these conditions this rearrangement did not take place. Different Lewis acids were attempted for this reaction which failed to give the expected compound probably due to steric hindrance.



Scheme 21

Reagents and conditions: a) nBuLi, THF b) $ZnCl_2$, $Pd(PPh_3)_4$, 4-bromoanisole, 2 h, 46 % c) nBuLi, THF, 3,4,5-trimethoxybenzaldehyde, 2 h, 92 %.

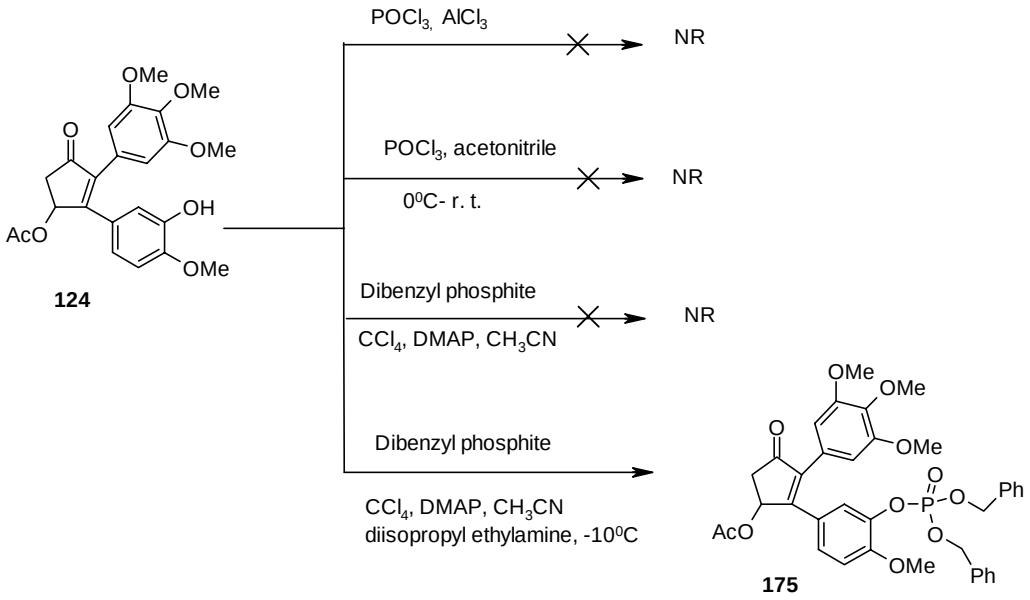
Attempts to improve aqueous solubility of synthesized CA-4 analogues:

The solubility of compound has central importance with respect to the ADME (absorption, distribution, metabolism and excretion) properties. A major hurdle for many small molecules to become drugs is often attributed to poor ADME properties in addition to lack of efficacy.[106, 107] Oral bioavailability is also an important factor for the development of bioactive molecules as therapeutic agents. Lipinski has discussed the molecular properties of compound which predict the drug-likeness features of the given compound. This concept of drug-likeness is known as the rule of five.[108, 109] Lipinskis rule about solubility says that low solubility can be a more limiting factor in drug development.

One of the method to make a compound water soluble is to incorporate ionizable groups in its structure. We have already synthesized two water soluble analogues **148** and **153** as sodium salts of acid, but these compounds showed reduction in the cytotoxicity.

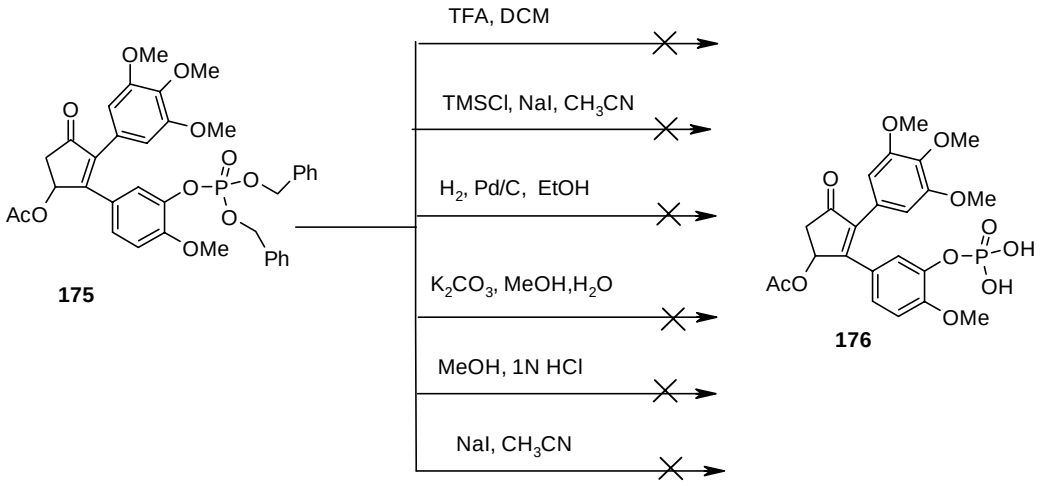
The substitution pattern in two aromatic rings of combretastatin A-4 has been retained in our designed molecule **119** and the biological studies indicated that this molecule showed substancial inhibition of multiplication of cancer cells. In view to improve this activity, it was essential to increase its solubility in water. Our attempts were therefore focused on the synthesis of water soluble derivative like **176**. The treatment of compound **124** with phosphorous oxychloride and

aluminium chloride resulted in failure to give phosphate derivative. Treatment of this compound with phosphorous oxychloride in acetonitrile also did not give required phosphate derivative. The reaction of compound **124** with dibenzyl phosphite, using dimethylamino pyridine, carbontetrachloride and acetonitrile also did not give the required compound. The required phoshphate ester derivative **175** was obtained by the reaction of compound **124** with dibenzyl phosphite, using dimethylamino pyridine, carbontetrachloride, acetonitrile and diisopropyl ethylamine (Hunnings base) at -10^0C as shown in scheme 22.



Scheme 22

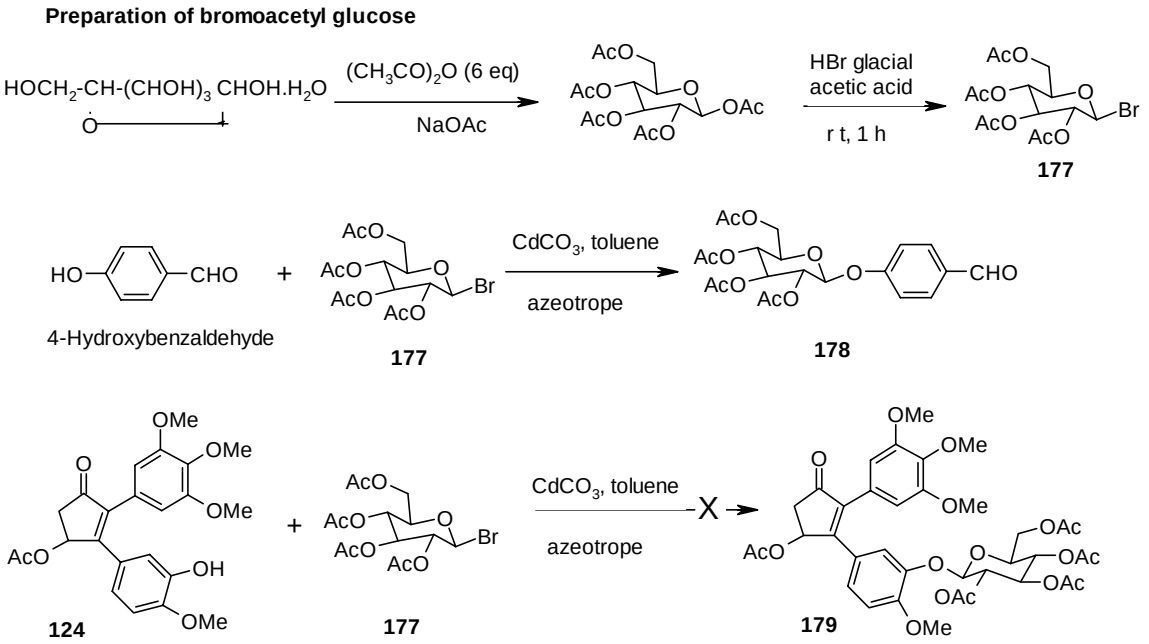
Subsequent debenzylation of phosphate protection of the compound **175** was tried using various conditions to get compound **176**, however the compound **175** could not be debenzylated under the conditions shown in scheme 23.



Scheme 23

We further planned to attach sugar functionality to phenolic –OH group of the compound **124**. We prepared the sugar derivative bromoacetylglucose (**177**) from glucose by reported[110] procedure.

Initially as a model experiment we carried out the reaction of the compound **177** with 4-hydroxybenzaldehyde using cadmium carbonate[111] as a base in toluene, which provided sugar derivative **178** in excellent yields within 6 h. The reaction of the compound **124** with bromoacetylglucose **177** under similar conditions using cadmium carbonate in toluene failed to give the expected derivative **179** (scheme 24) probably due to the steric hindrance of two phenyl rings and adjacent methoxy group.



Scheme 24

Table 2 in section V exhibits the list of 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues synthesized by Heck reaction method. All compounds showed satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra corresponding to their structures. The complete spectral data is given in the experimental section. Their evaluation as anticancer compounds has been discussed in section V.

1.1.3 CONCLUSION:

The *cis*-restricted combretastatin A-4 analogues were designed as a class of 2,3-diaryl-4-hyroxycyclopent-2-en-1-one and synthesized using Heck reaction approach as the key step. The synthetic strategy involved 5 to 7 steps including derivatization. In order to study the structure activity relationship overall 38 compounds of this category were synthesized. All compounds were characterized by spectral and analytical methods.

Some water soluble sodium salts were prepared in view to enhance the activity.

A general protocol for the synthesis of 2,3-diaryl-4-hydroxycyclopent-2-en-1-one has been developed.

1.1.4 EXPERIMENTAL:

Preparation of substituted furfuryl alcohols-General procedure:

Magnesium (1.68 gm, 70 mmol) was taken in three neck R.B. flask equipped with reflux condensor and 100 ml ether followed by dibromoethane (9.5 gm, 51.02 mmol) were added with stirring at 0°C under nitrogen atmosphere. Stirring was continued till all magnesium reacted, then ether was removed under vacuum till slurry was formed (A). In another single neck R.B. flask furan (4.76 gm, 70 mmol) in tetrahydrofuran (100 ml) was cooled with ice-salt mixture, n-butyllithium (2M, 35 ml, 70 mmol) was added dropwise, and stirred at 0°C for 45 min (B).

Furyllithium thus prepared in flask B was added to cold mixture in A though cannula, stirred at 0°C for 5 min, brought to room temperature, stirred at room temperature for 1.5 hs and then cooled to -20°C (dry ice + CCl_4). To this substituted benzaldehyde (51.02 mmol) in tetrahydrofuran (50 ml) was added and stirred at -20°C for 4 h (monitored by TLC). After completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution and the mixture was allowed to warm to room temperature. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect pure substituted furfuryl alcohols.

Furan-2-yl-(4-methoxy-3-nitrophenyl)-methanol (163):

Yield: 75 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.88 (s, 3H), 5.73 (s, 1H), 6.09 (d, *J* = 4 Hz, 1H), 6.26 (d, *J* = 4 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 7.30 (d, *J* = 4 Hz, 1H), 7.53 (dd, *J* = 8 Hz, and 2 Hz, 1H), 7.84 (d, *J* = 2 Hz, 1H); Mass (m/e): 249 (M^+)

Furan-2-yl-(7-methoxy-benzo[1,3]dioxol-5-yl)-methanol (167):

In a 50 ml evacuated two neck round bottom flask, furan (0.81 g, 12.00 mmol) and dry tetrahydrofuran (20 ml) were taken, flask was cooled to 0^0C, n-butyllithium (6 ml of 2M solution, 12.0 mmol) was added slowly with stirring and the reaction mixture was stirred for 30 min. 5-Methoxypiperonaldehyde (2 g, 11.10 mmol) in tetrahydrofuran (5 ml) was then added slowly and allowed to stirr for 2 h (TLC indicated completion of reaction). The reaction mixture was quenched with ammonium chloride, extracted with ethyl acetate (3 x 20 ml), organic layer washed with water followed by brine, dried over sodium sulfate and concentrated under reduced pressure using rotary evaporator. The column purification using silica gel (petroleum ether-acetone as eluent) afforded the furan-2-yl-(7-methoxy-benzo[1,3]dioxol-5-yl)-methanol (2.19 g, 80 %) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.84 (bs, 1H), 3.88 (s, 3H), 5.67 (s, 1H), 5.95 (s, 2H), 6.12 (d, *J* = 2 Hz, 1H), 6.30 (s, 1H), 6.56 (s, 1H), 6.62 (s, 1H), 7.37 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$+CCl_4): δ 56.37, 69.74, 100.84, 101.23, 106.36, 106.91, 110.02, 134.71, 135.60, 142.13, 143.29, 148.66, 155.86; Mass (ESI): 249(M+1).

Preparation of 2-aryl substituted -4-hydroxy-cyclopent-2-en-1-ones-Genereal Procedure:

In a 1 liter round bottom flask, a solution of aryl furfuryl alcohol (25 gm, 94.69 mmol) and $ZnCl_2$ (51.26 gm, 378.7 mmol) in dioxan (309 ml) and water (206 ml) was refluxed for 24 h at which time TLC analysis indicated the complete disappearance of starting material. The mixture was brought to room temperature, acidified to pH 1 with dilute HCl and extracted with ethyl acetate. Organic layer was washed with water followed by brine and dried over sodium sulphate. The organic layer was concentrated under reduced pressure using rotary evaporator and chromatographed on silica gel column to collect the 2-aryl substituted -4-hydroxycyclopent-2-en-1-ones.

4-Hydroxy-2-(4-methoxy-3-nitrophenyl)-cyclopent-2-en-1-one (164):

Yield: 65 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.48 (dd, *J* = 18 Hz and 2 Hz, 1H), 2.93 (dd, *J* = 18 Hz and 6 Hz, 1H), 2.96 (bs, 1H), 3.94 (s, 3H), 4.93-5.01 (m, 1H), 7.07 (d, *J* = 8 Hz, 1H),

7.66 (d, *J* = 2 Hz, 1H), 7.95 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.21 (d, *J* = 4 Hz, 1H); **Mass** (m/e): 249 (M^+); Anal. Calcd. For: $C_{12}H_{11}NO_5$ C 57.83; H 4.45; N 5.62 . Found: C 57.98; H 4.52; N, 5.76 %.

4-Hydroxy-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-cyclopent-2-en-1-one (168):

Yield: 63 %; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1559, 1609, 1702, 2986, 3071, 3538 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 2.50 (dd, *J* = 18 Hz and 3 Hz, 1H), 2.99 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.93 (s, 3H), 5.00-5.08 (m, 1H), 6.00 (s, 2H), 6.89 (s, 1H), 7.08 (s, 1H), 7.53 (d, *J* = 3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 46.09, 56.60, 67.59, 101.66 (2C), 107.58, 124.67, 136.14, 143.34, 143.49, 184.90, 155.51, 204.00; **Mass** (m/e): 249 (M+1); Anal. Calcd. For: $C_{13}H_{12}O_5$ C 62.90; H 4.87 %. Found: C 63.05; H 4.98 %.

General procedure for the preparation of tert-butyldimethylsilyl derivatives:

A solution of 2-aryl-4-hydroxy-cyclopent-2-en-1-one (8.7 mmol) in dry dichloromethane (30 ml) was stirred at 0°C under inert atmosphere (maintained by using nitrogen or argon gas filled in balloon), a solution of tert-butyldimethylsilylchloride (1.5 gm, 9.95 mmol) and dimethylaminopyridine (0.194 gm, 1.5 mmol) in dichloromethane (10 ml) was added drop wise and stirred at same temperature for 15 min. Then triethylamine (1.77 ml, 12.7 mmol) was added and mixture was warmed to room temperature and stirred further for 3 h (monitored by TLC). The reaction mixture was filtered though whatman filter paper, dichloromethane removed under reduced pressure and extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to give the title derivatives.

4-(tert-Butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (103):

Yield: 74 %; m. p. 87-88^{0}C; **IR** (υ_{max}, $CHCl_3$): 1504, 1602, 1704, 2935, 3014 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.16 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 2.47 (bd, *J* = 18 Hz, 1H), 2.92 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.85 (s, 3H), 3.90 (s, 6H), 4.95-5.05 (m, 1H), 6.96 (s, 2H), 7.45 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.97 (2C), 17.82, 25.50 (3C), 46.49, 55.79 (2C), 60.50, 67.81, 104.57 (2C), 125.89, 138.46, 142.61, 152.79 (2C), 156.76, 203.81; **Mass** (m/e): 378 (M^+, 100), 363 (10), 321 (15), 290 (40), 219 (70); Anal. Calcd. For: $C_{20}H_{30}O_5Si$ C 63.46; H 7.99; Si 7.42 %. Found: C 63.58; H 8.12; Si 7.46 %.

4-(tert-Butyldimethylsilanyloxy)-2-phenyl-cyclopent-2-en-1-one (157): Yield: 74 %; m. p. 70-71 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.17 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 2.50 (dd, *J* = 18 Hz and 4 Hz, 1H), 2.94 (dd, *J* = 18 Hz and 6 Hz, 1H), 4.95-5.05 (m, 1H), 7.30-7.45 (m, 3H), 7.54 (d, *J* = 2 Hz, 1H), 7.67-7.76 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.55 (2C), 18.17, 25.89 (3C), 46.73, 68.38, 127.63 (2C), 128.46 (2C), 128.95, 130.83, 143.44, 157.33, 203.90; **Mass** (m/e): 288 (M^+); Anal. Calcd. For: $C_{17}H_{24}O_2Si$ C 70.78; H 8.39; Si 9.74 %;
Found: C 70.89; H 8.30; Si 9.78 %.

4-(tert-Butyldimethylsilanyloxy)-2-(4-methoxy-3-nitrophenyl)-cyclopent-2-en-1-one (165): Yield: 78 %; **^{1}H-NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 0.16 (s, 3H), 0.18 (s, 3H), 2.49 (dd, *J* = 18 Hz and 3 Hz, 1H), 2.93 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.99 (s, 3H), 4.99-5.07 (m, 1H), 7.09 (d, *J* = 9 Hz, 1H), 7.55 (d, *J* = 3 Hz, 1H), 8.03 (dd, *J* = 9 Hz and 3 Hz, 1H), 8.20 (d, *J* = 3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.90 (2C), 17.93, 25.58 (3C), 46.27, 56.42, 67.96, 113.28, 124.31, 132.98, 140.26 (2C), 152.83 (2C), 157.21, 203.34; **Mass** (m/e): 363 (M^+)

4-(tert-Butyldimethylsilanyloxy)-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-cyclopent-2-en-1-one (169): Yield: 73 %; m. p. 98-99^{0}C; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 0.16 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 2.47 (dd, *J* = 18 Hz and 3 Hz, 1H), 2.91 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.93 (s, 3H), 4.87-5.03 (m, 1H), 5.99 (s, 2H), 6.88 (s, 1H), 7.08 (s, 1H), 7.42 (d, *J* = 3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$+CCl_4): δ -4.92 (2C), 17.62, 25.50 (3C), 46.47, 56.28, 67.79, 101.12, 101.34, 107.63, 124.71, 135.74, 142.32, 143.91, 148.62, 155.54, 203.10; **Mass** (ESI): 363(M^+); Anal. Calcd. For: $C_{19}H_{26}O_5Si$, C 62.95; H 7.23; Si 7.75 %. Found: C 63.18; H 7.43; Si 7.83 %.

Preparation of 4-(tert-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (106):

A mixture of *p*-iodoanisole (3.71 g, 15.87 mmol), 2-(3,4,5-trimethoxyphenyl)-4-tert-butyldimethylsilanyloxy -cyclopent-2-en-1-one (3.00 g, 7.93 mmol), palladium acetate (0.23 g, 1.02 mmol), triphenyl phosphine (0.40 g, 1.52 mmol), potassium carbonate (2.20 g, 15.86 mmol) and catalytic amount of tetrabutylammonium bromide (0.03 g) in degassed acetonitrile was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using a

rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect pure product as a yellowish solid (2.53 g, 66 %).

M. p. 106-107^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1582, 1606, 1701, 2957, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.05 (s, 3H), 0.09 (s, 3H), 0.80 (s, 9H), 2.57 (bd, *J* = 16 Hz, 1H), 3.02(dd, *J* = 16 Hz and 6 Hz, 1H), 3.69 (s, 6H), 3.82 (s, 3H), 3.84 (s, 3H), 5.30 -5.40 (m, 1H), 6.44 (s, 2H), 6.82 (d, *J* = 6 Hz, 2H), 7.27 (d, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ -5.22, -4.55, 17.33, 25.37 (3C), 45.33, 54.81, 55.54 (2C), 60.36, 70.03, 106.64 (2C), 113.25 (2C), 126.34 (2C), 130.27 (2C), 137.02, 138.36, 152.70 (2C), 160.00, 167.62, 202.72; **Mass** (m/e): 484(M^+, 5), 427 (30), 369 (32), 353 (100), 325 (61), 294 (47); Anal. Calcd. For: $C_{27}H_{36}O_6Si$ C 66.91; H 7.49; Si 5.79 %. Found: C 66.98; H 7.56; Si 5.85 %.

Preparation of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (108):

In a 50 ml round bottom flask, 4-(tert-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.35 g, 0.72 mmol) was taken in a mixture of acetic acid; tetrahydrofuran and water (3:1:1) (20 ml) and the mixture was heated at 50^{0}C for 20 h (monitored by TLC). The reaction mixture was cooled to 0^{0}C and neutralized by adding sodium bicarbonate and then extracted with chloroform (3 x 20 ml). The organic layer was washed with water followed by brine and dried over sodium sulfate and solvent was removed under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.23 g, 88 %) as yellowish solid.

M. p. 139-140^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1694, 3468 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.65 (bd, *J* = 18 Hz, 1H), 3.11 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.72 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 5.45 -5.50 (m, 1H), 6.46 (s, 2H), 6.87 (d, *J* = 10 Hz, 2H), 7.41 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 44.56, 55.06, 55.82(2C), 60.55, 68.94, 106.76(2C), 113.78(2C), 125.16, 126.84, 130.71(2C), 137.89, 138.28, 153.02(2C), 160.78, 166.76, 203.75; **Mass** (m/e): 370 (M^+, 100), 355 (19), 262 (32), 231 (20), 219 (18), 177 (30), 163 (27), 135 (25); Anal. Calcd. For: $C_{21}H_{22}O_6$ C 68.10; H 5.99 %. Found: C 67.98; H 5.88 %.

Preparation of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (109) :

In a 50 ml single neck round bottom flask, a mixture of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.12 g, 0.40 mmol), hydroxylamine hydrochloride (0.04 g, 0.60 mmol) and sodium acetate (0.05 g, 0.60 mmol) in ethanol (5 ml) was refluxed on water bathe for 3 h. The reaction was monitored by TLC and after completion of reaction the solvent was removed under reduced pressure using rotary evaporator. The residue was extracted with chloroform, the organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure oxime (0.075 g, 75 %) as a yellowish solid.

M. p.175^{0}C; **IR** (υ_{max}, $CHCl_3$): 1583, 1605, 3270, 3580 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.80 (bd, *J* = 18 Hz, 1H), 3.36 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.73 (s, 6H), 3.79 (s, 3H), 3.87 (s, 3H), 5.30-5.40 (m, 1H), 6.47 (s, 2H), 6.80 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 35.52, 55.58, 56.40 (2C), 61.19, 73.64, 107.43 (2C), 114.26 (2C), 126.59, 128.88, 130.71 (2C), 136.09, 138.34, 152.08, 153.63 (2C), 160.10, 164.59; **Mass** (m/e): 385 (M^+, 100), 368 (40), 336 (12); Anal. Calcd. For: $C_{21}H_{23}NO_6$ C 65.44; H 6.02; N 3.63 %. Found: C 65.62; H 6.12; N 3.76 %.

4-(tert-Butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (107): Yield: 83 %; m. p. 164-165^{0}C; **IR** (υ_{max}, $CHCl_3$): 1496, 1582, 2932, 3015, 3263 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ -0.01 (s, 3H), 0.08 (s, 3H), 0.82 (s, 9H), 2.70 (bd, *J* = 18 Hz, 1H), 3.32 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.69 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 5.24-5.30 (m, 1H), 6.46 (s, 2H), 6.76 (d, *J* = 9 Hz, 2H), 7.14 (d, *J* = 9 Hz, 2H), 7.85 (bs, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ -4.88, -4.40, 17.88, 25.64 (3C), 35.92, 55.12, 55.88 (2C), 60.70, 74.34, 107.24 (2C), 113.29 (2C), 127.36, 128.24, 130.41 (2C), 135.38, 137.73, 152.93 (2C), 153.60, 159.34, 163.92; **Mass** (m/e): 499 (M^+, 68), 442 (67), 368 (100), 320 (12), 74 (60); Anal. Calcd. For $C_{27}H_{37}NO_6Si$: C 64.90; H, 7.46; N 2.80; Si 5.62 %. Found: C 64.98; H, 7.56; N 2.87; Si 5.72 %.

4-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione (111):

In a 50 ml two neck round bottom flask, a solution of pyridinium chlorochromate (0.30 g, 1.39 mmol) in dry dichloromethane (20 ml) was cooled to 0^{0}C and stirred for 5 min. Then a solution of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.20 g, 0.54 mmol) in dichloromethane (5 ml) was added and stirred at same temperature for 15 min. The mixture was allowed to warm to room temperature and stirred for 2 hours (reaction monitored by

TLC). The reaction mixture was filtered though celite. The filtrate was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione (0.06 g, 30 %) as yellowish solid.

M. p. 175^{0}C; IR (υ_{max}, $CHCl_3$): 1215, 1701, 1736, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.17 (s, 2H), 3.69 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 6.63 (s, 2H), 6.88 (d, *J* = 6 Hz, 2H), 7.38 (d, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.84, 54.78, 55.54 (2C), 60.31, 107.12 (2C), 113.50 (2C), 120.83, 123.85, 131.29 (2C), 139.29, 150.89, 151.00, 152.66 (2C), 160.56, 198.38, 198.62; **Mass** (m/e): 368 (M^+, 100), 353 (30), 283 (23), 169 (20), 111 (46) 69 (70).

4-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione-1-oxime (110):

In a 25 ml two neck round bottom flask, a solution of pyridinium chlorochromate (0.08 g, 0.38 mmol) in dry dichloromethane (10 ml) was cooled to 0^{0}C, stirred for 5 min, a solution of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (0.07 g, 0.19 mmol) in dichloromethane (5 ml) was added and stirred at same temperature for 15 min. The mixture was allowed to warm to room temperature and stirred for 2 hours (reaction monitored by TLC). The reaction mixture was filtered though celite. The filtrate was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione-1-oxime (0.026 g, 34.8 %) as yellowish semisolid.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.41 (s, 2H), 3.69 (s, 6H), 3.80 (s, 3H), 3.89 (s, 3H), 6.58 (s, 2H), 6.83 (d, *J* = 9 Hz, 2H), 7.24 (d, *J* = 9 Hz, 2H), 8.60 (bs, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$ + CCl_4): δ 42.05, 54.96, 55.69 (2C), 60.51, 107.26 (2C), 113.69 (2C), 121.01, 124.02, 131.56 (2C), 139.43, 151.00, 152.03, 152.88 (2C), 159.46, 160.74, 198.53; **Mass** (m/e): 384 (M^+, 100), 367 (37), 336 (34), 307 (12); Analysis Calculated for $C_{21}H_{21}NO_6$: C 65.79; H 5.52; N 3.65 %; Found: C 65.88; H 5.59; N 3.77 %.

4-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione dioxime (112):

A mixture of diketone **111** (0.060 g, 0.16 mmol), hydroxylamine hydrochloride (0.026 g, 0.40 mmol) and sodium acetate (0.033 g, 0.40 mmol) in ethanol (5 ml) was refluxed on a water bath for 3 h (monitored by TLC). Then the solvent was removed under reduced pressure using a rotary

evaporator and the residue obtained was extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using a rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect pure dioxime **112** (0.033 g, 51.6%).

M. p. 240-241^{0}C; **^{1}H NMR** ($CDCl_3$ + CCl_4): δ 3.42 (s, 2H), 3.47 (s, 6H), 3.61 (s, 3H), 3.64 (s, 3H), 6.36 (s, 2H), 6.60 (d, *J* = 6 Hz, 2H), 7.06 (d, *J* = 6 Hz, 2H); **^{13}C NMR** ($CDCl_3$+ DMSO-d_6): δ 26.82, 54.96, 55.69 (2C), 60.43, 107.70 (2C), 113.00 (2C), 124.76, 127.63, 131.12 (2C), 137.59 (2C), 143.25, 144.20, 152.22 (2C), 159.05 (2C); **Mass** (m/e): 398 (M^+, 100); Anal. Calcd. For $C_{21}H_{22}N_2O_6$: C 63.31; H 5.57; N 7.03 %. Found: C 63.47; H 5.65; N 7.13 %.

4-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (113):

In a 50 ml two neck round bottom flask, a solution of 2-(3,4,5-trimethoxyphenyl)-3-(4-methoxyphenyl)-4-hydroxy-cyclopent-2-en-1-one (0.075 g, 0.20 mmol) in dichloromethane (3 ml) was cooled to 0°C under inert atmosphere. To the cold solution dry pyridine (0.019 gm, 0.24 mmol) was added and stirred at 0°C for 10 min. To the stirred solution, acetic anhydride (0.025 g, 0.024 mmol) was added dropwise while maintaining the temperature below 0°C. The reaction mixture was stirred at room temperature for 15 h (monitored by TLC) and then quenched by cold dilute hydrochloric acid. The organic layer was washed three times with water, 10% sodium bicarbonate solution and finally with brine. The organic layer was dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **113** (0.078 gm, 83.7 %).

M. p. 183-184 ^{0}C; **IR** (υ_{max}, $CHCl_3$): 1216, 1583, 1605, 1705, 1739, 2939, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.01 (s, 3H), 2.52 (bd, *J* = 18 Hz, 1H), 3.15 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.71 (s, 6H), 3.81 (s, 3H), 3.85 (s, 3H), 6.38-6.43 (m, 1H), 6.44 (s, 2H), 6.81 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.88, 41.38, 54.32, 55.09 (2C), 59.80, 69.32, 105.85 (2C), 113.06 (2C), 123.87, 125.67, 129.60 (2C), 137.32, 139.49, 152.39 (2C), 160.18, 161.98, 169.52, 201.31; **Mass** (m/e): 412 (M^+, 100), 397 (8), 352 (13), 337 (17); Anal. Calcd. For $C_{23}H_{24}O_7$: C 66.98; H 5.87 %. Found: C 67.07; H 5.94 %.

4-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (114):

A mixture of 4-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.050 g, 0.12 mmol), hydroxylamine hydrochloride (0.012 g, 0.18 mmol) and sodium acetate (0.015 g, 0.18 mmol) in ethanol (5 ml) was refluxed on water bath for 3 h. The reaction was monitored by TLC and after completion of reaction the solvent was removed under reduced pressure using rotary evaporator. The residue was extracted with chloroform, organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect pure 4-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime **114** (0.040 g, 77 %). M. p. 170-171 ^{0}C; **IR** (υ_{max}, $CHCl_3$): 1583, 1606, 1734, 3019, 3440 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.02 (s, 3H), 2.72 (bd, *J* = 18 Hz, 1H), 3.40 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.72 (s, 6H), 3.78 (s, 3H), 3.87 (s, 3H), 6.25-6.35 (m, 1H), 6.46 (s, 2H), 6.75 (d, *J* = 10 Hz, 2H), 7.12 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 20.81, 33.05, 54.92, 55.80 (2C), 60.65, 74.18, 106.56 (2C), 113.56 (2C), 125.57, 127.96, 129.94 (2C), 136.52, 137.92, 147.81, 153.25 (2C), 159.64, 163.17, 170.34; **Mass** (m/e): 427 (M^+, 100), 412 (7), 369 (47), 351 (25), 320 (31), 305 (7); Anal. Calcd. For $C_{23}H_{25}NO_7$: C 64.63; H 5.90; N 3.28 %. Found: C 64.74; H 5.96; N 3.30 %.

4-(tert-Butyldimethylsilanyloxy)-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (118):

Yield: 34 %; semisolid; **IR** (υ_{max}, $CHCl_3$): 1215, 1700, 2931, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.03 (s, 3H), 0.07 (s, 3H), 0.78 (s, 9H), 2.52 (bd, *J* = 18 Hz, 1H), 2.97 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.34 (s, 3H), 3.67 (s, 6H), 3.79 (s, 3H), 3.85 (s, 3H), 4.90-5.02 (m, 2H), 5.25-5.35 (m, 1H), 6.41 (s, 2H), 6.80 (d, *J* = 8 Hz, 1H), 6.94-7.08 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.25, -4.63, 17.57, 25.33 (3C), 45.33, 55.58 (3C), 60.29 (2C), 69.95, 95.32, 106.60 (2C), 110.86, 117.55, 123.44, 126.49 (2C), 137.62, 138.87, 145.86, 150.60, 152.77 (2C), 167.58, 202.98; **Mass** (m/e): 544 (M^+); Anal. Calcd. For $C_{29}H_{40}O_8Si$: C 63.94; H 7.40; Si 5.16 %. Found: C 64.03; H 7.48; Si 5.25 %.

4-(tert-Butyldimethylsilanyloxy)-2,3-diphenyl-cyclopent-2-en-1-one (158):

In a 250 ml two neck round bottom flask, a mixture of iodobenzene (4.24 g, 20.8 mmol), 4-(tert-butyldimethylsilanyloxy)-2-phenyl-cyclopent-2-en-1-one (3.00 g, 10.4 mmol), palladium acetate

(0.260 g, 1.20 mmol), potassium carbonate (2.88 g, 20.8 mmol) and catalytic amount of tetrabutylammonium bromide (0.05 g) in degassed acetonitrile (60 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using a rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect the pure 4-(tert-butyldimethylsilanyloxy)-2,3-diphenyl-cyclopent-2-en-1-one (0.95 g, 25 %). Yield: 25 %; m. p. 77^0C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ -0.02 (s, 3H), 0.07 (s, 3H), 0.77 (s, 9H), 2.60 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.04 (dd, *J* = 18 Hz and 6 Hz, 1H), 5.27-5.40 (m, 1H), 7.10-7.45 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -4.70 (2C), 17.65, 25.33 (3C), 45.44, 70.43, 127.85 (4C), 128.41 (4C), 129.35 (2C), 134.10, 139.83, 168.50 (2C), 203.05; **Mass** (m/e): 364 (M^+); Anal. Calcd. For $C_{23}H_{28}O_2Si$: C 75.78; H 7.74; Si 7.70 %. Found: C 75.89; H 7.80; Si 7.74 %.

Preparation of 4-(tert-butyldimethylsilanyloxy)-3-phenyl-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (135):

In a 100 ml two neck round bottom flask, a mixture of iodobenzene (3.21 g, 15.87 mmol), 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (3.0 g, 7.92 mmol), palladium acetate (0.230 g, 1.02 mmol), triphenyl phosphine (0.40 g, 1.52 mmol), potassium carbonate (2.20 g, 15.86 mmol) and catalytic amount of tetrabutylammonium bromide (0.03 g) in degassed acetonitrile (60 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using a rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium suflate and concentrated to dryness using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-(tert-butyldimethylsilanyloxy)-3-phenyl-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**135**) (1.26 g, 35.0 %) as a yellowish semisolid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ -0.05 (s, 3H), 0.05 (s, 3H), 0.77 (s, 9H), 2.61 (bd, *J* = 18 Hz, 1H) 3.05 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.63 (s, 6H), 3.82 (s, 3H), 5.27-5.33 (m, 1H), 6.47 (s, 2H), 7.32 (bs, 5H); **13C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ -5.65, -5.07, 17.40, 25.06 (3C), 45.36, 55.36 (2C), 60.21, 70.26, 106.70 (2C), 125.47, 127.72 (2C), 128.03 (2C), 128.49, 134.38, 137.70, 138.99, 152.35 (2C), 168.35, 202.95; **Mass** (m/e): 454 (M^+, 28), 379 (100), 323 (28), 291 (27),

247 (92), 219 (66), 75 (83); Anal. Calcd. For $C_{26}H_{34}O_5Si$: C 68.69; H, 7.54; Si, 6.18 %. Found: C 68.81; H, 7.67; Si, 6.23 %.

4-(tert-Butyldimethylsilanyloxy)-3-(2,5-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (132):

In a 100 ml two neck round bottom flask, a mixture of 2,5-dimethoxy-1-iodobenzene (4.19 g, 15.87 mmol), 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (3.0 g, 7.93 mmol), palladium acetate (0.230 g, 1.02 mmol), triphenyl phosphine (0.45 g, 1.72 mmol), potassium carbonate (2.20 g, 15.86 mmol) and catalytic amount of tetrabutylammonium bromide (0.03 g) in degassed acetonitrile (60 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using a rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-(tert-butyldimethylsilanyloxy)-3-(2,5-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2.28 g, 56 %) as a yellowish solid.

M. p. 113-114^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ -0.19 (s, 3H), -0.04 (s, 3H), 0.74 (s, 9H), 2.55 (bd, *J* = 16 Hz, 1H), 3.02 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.63 (s, 6H), 3.65 (s, 3H), 3.69 (s, 3H), 3.78 (s, 3H), 5.25-5.38 (m, 1H), 6.52 (s, 2H), 6.61 (s, 1H), 6.82 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ - 5.69, -5.36, 17.65, 25.26 (3C), 45.92, 55.47 (4C), 60.36, 70.12, 106.27 (2C), 111.10, 115.00, 115.83, 125.00, 126.12, 137.85, 140.00, 150.14, 152.25 (2C), 135.26, 168.24, 203.27; **Mass** (m/e): 514 (M^+, 71), 458 (87), 443 (30), 384 (40), 154 (70), 75 (100).

4-(tert-Butyldimethylsilanyloxy)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (134): Yield: 45 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.09 (s, 3H), 0.12 (s, 3H), 0.82 (s, 9H), 2.56 (bd, *J* = 18 Hz, 1H), 3.03 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.62 (s, 3H), 3.72 (s, 6H), 3.83 (s, 3H), 3.90 (s, 3H), 5.35-5.45 (m, 1H), 6.47 (s, 2H), 6.80-6.84 (m 2H), 7.02 (bd, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -4.93, -4.31, 17.78, 25.54 (3C), 45.46, 55.46, 55.83 (2C), 60.50 (2C), 70.13, 106.85 (2C), 110.52, 112.47, 122.10, 126.37, 126.77, 137.91, 138.79, 148.35, 150.07, 152.98 (2C), 167.57, 202.93; **Mass** (m/e): 514 (M^+); Anal. Calcd. For $C_{28}H_{38}O_7Si$: C 65.34; H 7.44; Si, 5.46 %. Found: C 65.45; H 7.56; Si, 5.52 %.

4-(tert-Butyldimethylsilanyloxy)-3-(4-methoxy-3,5-dimethylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (133):

In a 100 ml two neck round bottom flask, a mixture of 3,5-dimethyl-4-methoxy-1-iodobenzene (4.15 g, 15.87 mmol), 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (3.0 g, 7.93 mmol), palladium acetate (0.230 g, 1.02 mmol), triphenyl phosphine (0.45 g, 1.72 mmol), potassium carbonate (2.20 g, 15.86 mmol) and catalytic amount of tetrabutylammonium bromide (0.03 g) in degassed acetonitrile (60 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using a rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect the pure 4-(tert-butyldimethylsilanyloxy)-3-(4-methoxy-3,5-dimethylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (1.05 g, 26 %).

M. p. 111-112^{0}C; **IR** (υ_{max}, $CHCl_3$): 1128, 1707, 2857, 2932, 3011, 3400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3 + CCl_4$): δ -0.01 (s, 3H), 0.07 (s, 3H), 0.78 (s, 9H), 2.20 (s, 6H), 2.56 (bd, *J* = 18 Hz, 1H) 3.01 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.68 (s, 6H), 3.70 (s, 3H), 3.83 (s, 3H), 5.20-5.30 (m, 1H), 6.51 (s, 2H), 6.97 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.48, -4.74, 15.59 (2C), 17.57, 25.22 (3C), 45.36, 55.47 (2C), 59.22, 60.32, 70.25, 106.71 (2C), 126.05 (2C), 129.02 (2C), 129.50, 130.16, 137.70, 138.29, 152.47 (2C), 157.47, 168.13 (2C), 202.91; **Mass** (m/e): 512 (M^+, 18), 456 (38), 425 (16), 381 (51), 353 (15), 322 (13), 129 (100). Anal. Calcd. For $C_{29}H_{40}O_6Si$: C 67.94; H 7.86; Si 5.48 %. Found: C 68.12; H 7.94; Si 5.41 %.

5-[5-(tert-Butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid methyl ester (136):

In a 250 ml two neck round bottom flask, a mixture of 5-iodo-2-methoxybenzoic acid methyl ester (4.50 g, 15.30 mmol), 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2.89 g, 7.65 mmol), palladium acetate (0.240 g, 1.07 mmol), potassium carbonate (2.11 g, 15.30 mmol) and catalytic amount of tetrabutylammonium bromide (0.02 g) in degassed acetonitrile (80 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure using a rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium suflate and concentrated to dryness using rotary evaporator. The crude residue was purified by column chromatography using silica

gel (petroleum ether: acetone as eluent) to collect the pure 5-[5-(tert-butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid methyl ester as yellowish semisolid (0.70 g, 17.0 %).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.09 (s, 3H), 0.12 (s, 3H), 0.79 (s, 9H), 2.57 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.03 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.70 (s, 6H), 3.84 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 5.30-5.50 (m, 1H), 6.42 (s, 2H), 6.85 (d, *J* = 8 Hz, 1H), 7.33 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.96 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 542 (M^+); Anal. Calcd. For $C_{29}H_{38}O_8Si$: C 64.18; H 7.06; Si 5.18 %. Found: C 64.31; H 7.18; Si 5.22 %.

{4-[5-(tert-Butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-phenoxy}-acetic acid ethyl ester (150):

Yield: 35 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ -0.03 (s, 3H), 0.08 (s, 3H), 0.78 (s, 9H), 1.30 (t, *J* = 8 Hz, 3H), 2.57 (dd, *J* = 12 Hz and 4 Hz, 1H), 3.00 (dd, *J* = 12 Hz and 6 Hz, 1H), 3.68 (s, 6H), 3.83 (s, 3H), 4.25 (q, *J* = 8 Hz, 2H), 4.62 (s, 2H), 5.28-5.35 (m, 1H), 6.43 (s, 2H), 6.83 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H); **Mass** (m/e): 556 (M^+).

4-(tert-Butyldimethylsilanyloxy)-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-3-(4-methoxy-3-methoxymethoxyphenyl)-cyclopent-2-en-1-one (170)

A mixture of 4-iodo-1-methoxy-2-methoxymethoxybenzene (2.45 g, 8.30 mmol), 4-(tert-butyldimethylsilanyloxy)-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-3-(4-methoxy-3-methoxy-methoxyphenyl)-cyclopent-2-en-1-one (1.5 g, 4.14 mmol), palladium acetate (0.105 g, 0.47 mmol), potassium carbonate (1.14 g, 8.26 mmol) and catalytic amount of tetrabutylammonium bromide (0.03 g) in degassed acetonitrile (30 ml) was refluxed for 36 h. Then the reaction mixture was cooled to room temperature and acetonitrile removed under reduced pressure using rotary evaporator. The residue was acidified with dilute HCl and then extracted with chloroform. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure, using a rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect pure product as a yellowish semisolid (0.92 g, 40.0 %).

IR ($\upsilon_{max,}$ $CHCl_3$): 1240, 1507, 1630, 1701, 2929, 2954 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$ + CCl_4): δ 0.05 (s, 3H), 0.09 (s, 3H), 0.80 (s, 9H), 2.55 (dd, *J* = 15 Hz and 5 Hz, 1H), 2.99 (dd, *J* = 15 Hz and 5 Hz, 1H), 3.41 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 5.02-5.10 (m, 2H), 5.30-5.36 (m, 1H), 5.94 (s, 2H), 6.37 (s, 1H), 6.44 (s, 1H), 6.83 (d, *J* = 10 Hz, 1H), 7.02 (dd, *J* = 10 Hz and 5 Hz, 1H), 7.10 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$+CCl_4): δ -5.18, -4.56, 17.64, 25.38 (3C),

45.28, 55.54, 55.70, 56.08, 70.00, 95.37, 100.99, 103.58, 109.34, 110.91, 117.43, 123.49, 125.18 (2C), 126.46, 134.92, 138.80, 143.28, 146.00, 148.41, 167.26, 202.89; **Mass** (ESI): 529 (M^+); Analysis Calculated for $C_{28}H_{36}O_8Si$: C 63.61; H 6.86; Si 5.31 %. Found: C 63.80; H 6.98; Si 5.40 %.

4-(tert-Butyldimethylsilanyloxy)-3-phenyl-2-(3,4,5-trimethoxyphenyl)cyclopentanone (141) : In a 25 ml two neck round bottom flask compound **135** and ethanol (2 ml) was taken to this 5 % Pd/C added and flask flushed with argon. Then reaction mixture was stirred under atmosphere of hydrogen at room temperature for 2 h (TLC analysis indicated completion of reaction). The reaction mixture filtered though a pad of celite, ethanol removed under reduced pressure using rotary evaporator, the crude residue was extracted with ethyl acetate, washed with water followed by brine and dried over sodium sulfate solvent removed under reduced pressure and residue column purified to collect pure 4-tert-butyldimethylsilanyloxy-3-phenyl-2-(3,4,5-trimethoxyphenyl) cyclopentanone **141** (0.012 g, 40 %) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ -0.40 (s, 3H), -0.20 (s, 3H), 0.77 (s, 9H), 2.60 (bd, *J* = 18 Hz, 1H), 2.73 (dd, *J* = 18 Hz and 3 Hz, 1H), 3.58-3.66 (m, 1H), 3.76 (s, 9H), 4.06 (d, *J* = 12 Hz, 1H), 4.54-4.58 (m, 1H), 6.34 (s, 2H), 7.29 (bs, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.29 (2C), 18.27, 25.96 (3C), 49.52, 55.22, 55.91, 56.24 (2C), 60.95, 71.98, 105.83 (2C), 106.82, 127.37, 128.47 (2C), 129.10 (2C), 132.44, 137.85, 153.36 (2C), 215.70; **Mass** (m/e): 456 (M^+).

4-(tert-Butyldimethylsilanyloxy)-3-(2,5-dimethoxyphenyl)-2-(3,4,5trimethoxyphenyl)-cyclopent-2-en-1-one oxime (142): Yield 71 %; m. p. 146-148^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ - 0.21 (s, 3H), - 0.06 (s, 3H), 0.76 (s, 9H), 2.69 (bd, *J* = 18 Hz, 1H), 3.36 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.64 (s, 3H), 3.66 (s, 6H), 3.70 (s, 3H), 3.80 (s, 3H), 5.20-5.30 (m, 1H), 6.50-6.57 (m, 3H), 6.76 (s, 2H), 7.99 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ -5.45, -5.27, 17.86, 25.50 (3C), 36.13, 55.46 (4C), 60.50, 73.88, 106.48 (2C), 110.93, 114.05, 116.59, 125.37, 127.73, 136.99 (2C), 137.25, 150.99, 152.28(2C), 153.13, 162.98; **Mass** (m/e): 529 (M^+, 63), 512 (71), 472 (100), 398 (68), 75 (60); Anal. Calcd. For $C_{28}H_{39}NO_7Si$: C 63.49; H 7.42; N 2.64; Si 5.30 %. Found: C 63.65; H 7.56; N 2.68; Si 5.41 %.

4-(tert-Butyldimethylsilanyloxy)-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enone oxime (121):

Yield: 73 %; semisolid; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.03 (s, 3H), 0.10 (s, 3H), 0.83 (s, 9H), 2.63 (bd, *J* = 18 Hz, 1H), 3.27 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.36 (s, 3H), 3.71 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 4.96-5.00 (m, 2H), 5.20-5.30 (m, 1H), 6.42 (s, 2H), 6.75 (d, *J* = 8 Hz, 1H),

6.85-7.00 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -4.86, -4.35, 17.86, 25.69 (3C), 35.79, 55.79 (3C), 60.57 (2C), 74.17, 95.56, 107.03 (2C), 111.04, 117.95, 123.50, 127.62, 128.24, 135.85, 137.65, 145.96, 149.74, 152.98 (2C), 159.67, 163.84; **Mass** (m/e): 559 (M^+); Anal. Calcd. For $C_{29}H_{41}NO_8Si$: C 62.23; H 7.38; N 2.50; Si 5.02 %. Found: C 62.34; H 7.48; N 2.59; Si 5.12 %.

4-(tert-Butyldimethylsilanyloxy)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (146):

Yield: 86 %; semisolid; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.13 (s, 3H), 0.16 (s, 3H), 0.87 (s, 9H), 2.64 (bd, *J* = 18 Hz, 1H), 3.08 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.66 (s, 3H), 3.76 (s, 6H), 3.88 (s, 3H), 3.95 (s, 3H), 5.39-5.45 (m, 1H), 6.52 (s, 2H), 6.80-6.89 (m, 2H), 7.06 (bd, *J* = 6 Hz, 1H); **Mass** (m/e): 529 (M^+); Anal. Calcd. For $C_{28}H_{39}NO_7Si$: C 63.49; H 7.42; N 2.64; Si, 5.30 %. Found: C 63.58; H 7.32; N 2.67; Si, 5.43 %.

4-Hydroxy-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (119): Yield 60 %; m. p. 94^{0}C; **IR** (υ $_{max}$, $CHCl_3$): 1215, 1699, 3019, 3333 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.61 (bd, *J* = 18 Hz, 1H), 3.40 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.72 (s, 6H), 3.85 (s, 3H), 3.91 (s, 3H), 5.35-5.46 (m, 1H), 6.45 (s, 2H), 6.78 (d, *J* = 8 Hz, 1H), 6.91 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.03 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 44.30, 55.80 (2C), 60.54 (2C), 69.03, 106.67 (2C), 110.46, 114.83, 121.86, 125.75, 126.56, 137.84, 138.69, 145.42, 148.03, 152.92 (2C), 166.59, 203.71; **Mass** (m/e): 386 (M^+); Anal. Calcd. For $C_{21}H_{22}O_7$: C 65.28; H 5.74 %. Found: C 65.42; H 5.86 %.

3-(2,5-Dimethoxyphenyl)-4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (146): Yield 91 %; m. p. 152^{0}C; **IR** (υ $_{max}$, $CHCl_3$): 1217, 1583, 1698, 2941, 3017, 3501 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.63 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.06 (dd, *J* = 18 Hz and 6 Hz, 1 H), 3.59 (s, 3H), 3.64 (s, 6H), 3.71 (s, 3H), 3.80 (s, 3H), 5.35-5.50 (m, 1H), 6.47 (bs, 2H), 6.66 (bs, 1H), 6.88 (bs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 44.54, 55.31, 55.33 (2C), 55.68, 60.46, 69.80, 106.22 (2C), 112.14, 115.34, 115.52, 123.68, 126.22, 137.65, 140.22, 150.52, 152.43 (2C), 153.35, 167.06, 203.56; **Mass** (m/e): 400 (M^+, 19), 369 (3), 111 (82), 83 (52), 71 (67); Anal. Calcd. For $C_{22}H_{24}O_7$: C 65.99; H 6.04 %. Found: C 66.12; H 6.15 %.

4-Hydroxy-3-(4-methoxy-3,5-dimethylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (138): Yield 78 %; m. p. 130^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.21 (s, 6H), 2.63

(bd, *J* = 18 Hz, 1H), 3.07 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.69 (s, 6H), 3.1 (s, 3H), 3.84 (s, 3H), 5.35-5.45 (m, 1H), 6.47 (s, 2H), 7.06 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 15.91 (2C), 44.47, 55.83 (2C), 59.39, 60.61, 69.13, 106.99 (2C), 126.37 (2C), 28.53, 129.42 (2C), 131.00, 138.13, 138.83, 152.87 (2C), 158.27, 167.24, 203.63; **Mass** (m/e): 398 (M^+, 100), 367 (5), 262 (32), 247 (51), 231 (12), 177 (15), 149 (13); Anal. Calcd. For $C_{23}H_{26}O_6$: C 69.33; H 6.58 %. Found: C 69.47; H 6.62 %.

5-[5-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid methyl ester (140): Yield: 76 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.59 (bd, *J* = 20 Hz, 1H), 3.03 (dd, *J* = 20 Hz and 6 Hz, 1H), 3.45 (bs, 1H), 3.69 (s, 6H), 3.82 (s, 9H), 5.40-5.44 (m, 1H), 6.41 (s, 2H), 6.86 (d, *J* = 10 Hz, 1H), 7.45 (dd, *J* = 10 Hz and 2 Hz, 1H), 8.00 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 44.62, 51.86, 55.86 (3C), 60.53, 68.88, 106.88 (2C), 111.77, 119.90, 125.12, 126.48, 132.43, 134.75, 138.00, 139.16, 153.20 (2C), 159.83, 165.18, 165.92, 203.45; **Mass** (m/e): 428 (M^+); Anal. Calcd. For $C_{23}H_{24}O_8$: C 64.48; H 5.65 %. Found: C 64.57; H 5.61 %.

3-(3,4-Dimethoxyphenyl)-4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (139): Yield 76 %; m. p. 127^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.61 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.08 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.57 (s, 3H), 3.73 (s, 6H), 3.83 (s, 3H), 3.90 (s, 3H), 5.42-5.46 (m, 1H), 6.46 (s, 2H), 6.84 –6.88 (m, 2H), 7.15 (dd, *J* = 8 Hz and 2 Hz, 1H); **Mass** (m/e): 400(M^+), Anal. Calcd. For $C_{22}H_{24}O_7$: C 65.99; H 6.04 %. Found: C 66.19; H 6.15 %.

4-Hydroxy-2,3-diphenyl-cyclopent-2-en-1-one (159): Yield: 88 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.09 (bs, 1H), 2.65 (bd, *J* = 18 Hz, 1H), 3.09 (dd, *J* = 18 Hz and 6 Hz, 1H), 5.20-5.51 (m, 1H), 7.10-7.45 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 44.58, 69.76, 128.39 (2C), 128.87 (6C), 129.60, 129.93, 130.96, 133.20, 140.55, 166.91, 203.26; **Mass** (m/e): 250 (M^+); Anal. Calcd. For $C_{17}H_{14}O_2$: C 81.58; H 5.64 %. Found: C 81.71; H 5.70 %.

{4-[5-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-phenoxy}-acetic acid ethyl ester (151): Yield: 76 %; m. p. 109-110^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 1.28 (t, *J* = 8 Hz, 3H), 2.57 (dd, *J* = 14 Hz and 2 Hz, 1H), 3.01 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.63 (s, 6H), 3.83 (s, 3H), 4.23 (q, *J* = 8 Hz, 2H), 4.60 (s, 2H), 5.33-5.40 (m, 1H), 6.41 (s, 2H), 6.82 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H); **^{13}C NMR** ($CDCl_3$+CCl_4): δ 14.38, 44.89, 56.17 (2C), 61.06,

61.76, 65.21, 69.48, 106.75 (2C), 114.91 (2C), 126.45, 129.93, 131.16 (2C), 138.14, 139.24, 153.47 (2C), 159.28, 166.52, 168.58, 203.97; **Mass** (ESI): 442 (M^+).

4-Hydroxy-3-(3-hydroxy-4-methoxyphenyl)-2-(7-methoxy-benzo[1,3]dioxol-5-yl)-cyclopent-2-en-1-one (171):

In a 50 ml round bottom flask, compound **170** (0.35 g, 0.66 mmol) was taken and to this a mixture of acetic acid; tetrahydrofuran and water (3:1:1; 20 ml) was added and heated at 50^0C for 20 h (reaction monitored by TLC). The reaction mixture was cooled to 0^0C and neutralized by adding sodium bicarbonate and then extracted with chloroform (3 x 20 ml). The organic layer was washed with water followed by brine, dried over sodium sulfate and the solvent was removed under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect 4-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-2-(7-methoxy-benzo[1,3]dioxolyl)cyclopent-2-en-1-one (0.130 g, 53 %) as yellowish semisolid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.60 (dd, *J* = 16 Hz and 4 Hz, 1H), 2.64 (bs, 1H), 3.06 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.80 (s, 3H), 3.93 (s, 3H), 5.30-5.43 (m, 1H), 5.97 (s, 2H), 6.39 (s, 1H), 6.45 (d, *J* = 2 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 6.94 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.03 (d, *J* = 2 Hz, 1H); **Mass** (ESI): 370(M^+); Anal. Calcd. For $C_{20}H_{18}O_7$: C 64.86; H 4.90 %. Found: C 64.91; H 4.97 %.

3-(2,5-Dimethoxyphenyl)-4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (143): Yield 86 %; semisolid; **IR** (υ_{max}, $CHCl_3$): 1607 3272, 3584 cm^{-1}; **^{1}H NMR** ($CDCl_3$ + CCl_4): δ 2.71 (bd, *J* = 18 Hz, 1H), 3.32 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.57 (s, 3H), 3.66 (s, 6H), 3.68 (s, 3H), 3.81 (s, 3H), 5.22-5.28 (m, 1H), 6.44 (s, 2H), 6.57 (bs, 1H), 6.70-6.85 (m, 2H); **Mass** (m/e): 415 (M^+); Anal. Calcd. For $C_{22}H_{25}NO_7$: C 63.60; H 6.07; N 3.37 %. Found: C 63.78; H 6.17; N 3.44 %.

4-Hydroxy-2,3-diphenyl-cyclopent-2-en-1-one oxime (160):

Yield 76 %; m. p. 202 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + Acetone-d_6): δ 2.53 (bd, *J* = 12 Hz, 1H), 3.08 (dd, *J* = 12 Hz and 4 Hz, 1H), 5.05-5.15 (m, 1H), 6.75-7.10 (m, 10H); **Mass** (m/e): 265 (M^+) Anal. Calcd. For $C_{17}H_{15}NO_2$: C 76.96; H 5.70; N 5.28 %. Found: C 77.14; H 5.92; N 5.40 %.

4-Acetoxy-3-(4-methoxy-3,5-dimethylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (144):

Yield 85 %; m. p. 104-105^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.00 (s, 3H), 2.17 (s, 6H), 2.51 (bd, *J* = 18 Hz, 1H), 3.15 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.69 (s, 9H), 6.30-6.40 (m, 1H), 6.45 (s, 2H), 6.94 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 15.74 (2C), 20.44, 42.05, 55.69 (2C), 59.22, 60.40, 70.14, 106.86 (2C), 125.83, 127.88, 128.99 (2C), 130.68 (2C), 152.84 (3C), 159.46, 162.84 (2C), 169.97, 201.77; **Mass** (m/e): 440 (M^+, 100), 398 (7), 365 (15); Anal. Calcd. For $C_{25}H_{28}O_7$: C 68.17; H 6.41 %. Found: C 68.29; H 6.51 %.

4-Acetoxy-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (123):

Semisolid; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.05 (s, 3H), 2.54 (bd, *J* = 18 Hz, 1H), 3.17 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.36 (s, 3H), 3.75 (s, 6H), 3.86 (s, 3H), 3.89 (s, 3H), 4.90-5.10 (m, 2H), 6.40-6.55 (m, 3H), 6.82 (d, *J* = 8 Hz, 1H), 6.95-7.17 (m, 2H); **Mass** (ESI): 472 (M^+)

4-Acetoxy-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (125): Yield 82 %; m. p. 122^{0}C; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.03 (s, 3H), 2.73 (bd, *J* = 20 Hz, 1H), 3.40 (dd, *J* = 20 Hz and 6 Hz, 1H), 3.72 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 6.21-6.28 (m, 1H), 6.45 (s, 2H), 6.68 (bs, 2H), 6.77 (s, 1H); **Mass** (ESI): 443 (M^+); Anal. Calcd. For $C_{23}H_{25}NO_8$: C 62.30; H 5.68; N 3.16 %. Found C 62.46; H 5.81; N 3.22 %.

4-Acetoxy-3-(4-methoxy-3,5-dimethylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (145): Yield 85 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.02 (s, 3H), 2.14 (s, 6H), 2.69 (bd, *J* = 18 Hz, 1H), 3.37 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.68 (s, 3H), 3.71 (s, 6H), 3.86 (s, 3H), 6.22-6.35 (m, 1H), 6.44 (s, 2H), 6.80 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 16.27 (2C), 21.06, 33.43, 56.41 (2C), 59.68, 61.00, 74.89, 107.94 (2C), 128.12, 129.30, 129.52 (2C), 130.73 (2C), 139.04, 142.97, 148.59, 153.56, 157.67, 59.55, 170.50, 198.55; **Mass** (m/e): 455 (M^+, 31), 396 (10), 364 (8), 256 (9), 123 (100); Anal. Calcd. For $C_{25}H_{29}NO_7$: C 65.92; H 6.42; N 3.08 %. Found: C 66.04; H 6.49; N 3.19 %.

4-Acetoxy-2,3-diphenyl-cyclopent-2-en-1-one oxime (161): Yield: 74 %; m. p. 206 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO d_6): δ 2.31 (s, 3H), 2.44 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.11 (dd, *J* = 18 Hz and 6 Hz, 1H), 6.00-6.15 (m, 1H), 6.80-7.15 (m, 10H); **Mass** (m/e): 307 (M^+); Anal. Calcd. For $C_{19}H_{17}NO_3$: C 74.25; H 5.58; N 4.56 %. Found: C 74.20; H 5.69; N 4.46 %.

4-(tert-Butyldimethylsilanyloxy)-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (127):

In a 50 ml dry two neck round bottom flask, 4-(tert-butyldimethylsilanyloxy)-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**118**) (0.100 g, 1.83 mmol) was taken under inert atmosphere, dry dichloromethane (10 ml) was added, the reaction mixture was cooled to 0^0C in which trifluoroacetic acid (0.042 ml, 5.49 mmol) was added and stirring continued at the same temperature for 15 min and then allowed to warm to room temperature and stirred for 4 h. The reaction mixture was diluted with dichloromethane, organic layer was separated and washed with water, followed by brine to give the title compound **127** (51.46 g, 56 %) as a semisolid material.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.05 (s, 3H), 0.09 (s, 3H), 0.81 (s, 9H), 2.56 (bd, *J* = 18 Hz, 1H), 3.01 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.70 (s, 6H), 3.85 (s, 3H), 3.90 (s, 3H), 5.25-5.35 (m, 1H), 6.46 (s, 2H), 6.70-6.85 (m, 2H), 6.96 (bs, 1H); **Mass** (m/e): 500 (M^+, 13), 443 (30), 412 (25), 369 (70), 341 (31), 310 (23), 75 (100); Anal. Calcd. For $C_{27}H_{36}O_7Si$: C 64.77; H 7.25; Si 5.61 %. Found: C 64.81; H 7.37; Si 5.68 %.

4-Hydroxy-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (122):

In a 100 ml dry two neck round bottom flask, 4-(tert-butyldimethylsilanyloxy)-3-(4-methoxy-3-methoxymethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**118**) (3.00 g, 5.51 mmol) was taken under inert atmosphere, tetrahydrofuran (60 ml) was added, the flask was cooled to 0^0C and then tetrabutylammonium fluoride (1 M solution, 5.52 ml, 5.51 mmol) was added slowly. Stirring was then continued at the same temperature for 1 h. The reaction mixture was quenched with brine, stirred vigorously for 30 min and extracted with ethyl acetate (3 x 60 ml). The organic layer was dried over sodium sulfate and solvent was removed on a rotary evaporator. The crude residue was purified by column chromatography to afford pure title compound (**122**) as a semisolid.

Yield 88 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.62 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.07 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.36 (s, 3H), 3.74 (s, 6H), 3.84 (s, 3H), 3.90 (s, 3H), 4.90-5.05 (m, 2H), 5.40-5.52 (m, 1H), 6.43 (s, 2H), 6.88 (d, *J* = 8 Hz, 1H), 7.15-7.25 (m, 2H); **Mass** (ESI): 430 (M^+); Analysis calculated for $C_{23}H_{26}O_8$: C 64.18; H 6.09 %. Found: C 64.42; H 6.23 %.

4-Acetoxy-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (124): Yield 77 %; m. p. 213^0C; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.01 (s, 3H), 2.51 (dd, *J*

= 18 Hz and 2 Hz, 1H), 3.15 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.71 (s, 6H), 3.84 (s, 3H), 3.88 (s, 3H), 6.31-6.39 (m, 1H), 6.44 (s, 2H), 6.70-6.91 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 20.69, 42.12, 55.79 (3C), 60.57, 70.20, 106.41 (2C), 110.27, 114.68, 121.48, 125.26, 126.00, 137.87, 140.55, 145.33, 148.20, 153.02 (2C), 162.94, 170.51, 202.53; **Mass** (ESI): 428 (M^+), 367; Anal. Calcd. For $C_{23}H_{24}O_8$: C 64.48; H 5.65 %. Found: C 64.66; H 5.79 %.

5-[5-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid (147):

In a 50 ml single neck round bottom flask, ester **140** (0.100 g, 0.23 mmol) and 10 % sodium hydroxide solution (1 ml) in methanol (5 ml) was stirred at room temperature for 24 h. Then methanol was removed on rotary evaporator, the reaction mixture was acidified and extracted with ethyl acetate (3 x 10 ml). The extracts was washed with water, followed by brine and dried over sodium sulfate and the solvent was removed on a rotary evaporator. The residue was purified to collect pure 5-[5-hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid **147** (0.062 g, 64 %) as thick semisolid material.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.63 (bd, *J* = 20 Hz, 1H), 3.08 (dd, *J* = 20 Hz and 8 Hz, 1H), 3.71 (s, 6H), 3.38 (s, 3H), 4.03 (s, 3H), 5.40-5.55 (m, 1H), 6.39 (s, 2H), 6.91 (d, *J* = 8 Hz, 1H), 7.45 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.34 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 414 (M^+); Anal. Calcd. For $C_{22}H_{22}O_8$: C 63.76; H 5.35 %. Found: C 63.89; H 5.42 %.

{4-[5-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-phenoxy}-acetic acid (152): Yield 75 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.49 (bd, *J* = 18 Hz, 1H), 2.92 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.61 (s, 6H), 3.73 (s, 3H), 4.50 (s, 2H), 5.23-5.26 (m, 1H), 6.33 (s, 2H), 6.76 (d, *J* = 10 Hz, 2H), 7.35 (d, *J* = 10 Hz, 2H); **Mass** (ESI): 414 (M^+); Anal. Calcd. For $C_{22}H_{22}O_8$: C 63.76; H 5.35 %. Found: C 63.91; H 5.49 %.

Sodium-5-[5-hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxy benzoate (148):

In a 10 ml round bottom flask, 5-[5-hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxybenzoic acid **147** (0.062 g, 0.15 mmol) was dissolved in dichloromethane (0.5 ml). To this solution sodium hydroxide (0.006 g, 0.15 mmol) in distilled water (0.5 ml) was added and stirred well. After 30 min the reaction mixture was diluted with dichloromethane and the organic layer was separated. The aqueous layer was evaporated under reduced pressure to collect pure salt **148** (0.044 g, 67 %) as yellowish solid.

M. p. 207^{0}C; **^{1}H NMR** (200 MHz, D_2O): δ 2.35 (bd, *J* = 20 Hz, 1H), 2.89 (dd, *J* = 20 Hz and 6 Hz, 1H), 3.45 (s, 6H), 3.53 (s, 3H), 3.56 (s, 3H) 5.25-5.35 (m, 1H), 6.30 (s, 2H), 6.67 (dd, *J* = 10 Hz and 2 Hz, 1H), 7.09 (d, *J* = 10 Hz, 1H), 7.23 (d, *J* = 2 Hz, 1H); **Mass** (ESI): 436 (M^+).

{4-[5-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-phenoxy}-acetic acid sodium salt (153): Yield 79 %; m. p. 163^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.29 (bd, *J* = 20 Hz, 1H), 2.78 (dd, *J* = 20 Hz and 4 Hz, 1H), 3.36 (s, 6H), 3.48 (s, 3H), 4.14 (s, 2H), 5.13-5.19 (m, 1H), 6.19 (s, 2H), 6.55 (d, *J* = 10 Hz, 2H), 7.05 (d, *J* = 10 Hz, 2H); **Mass** (ESI): 436 (M^+).

Preparation of 4-iodo-1-methoxy-2-methoxymethoxybenzene (117):

In a 500 ml two neck round bottom flask, 5-iodo-2-methoxyphenol (20 g, 80.00 mmol) was taken in dry dichloromethane (100 ml) under argon atmosphere and cooled to 0^{0}C. Ethyl-diisopropylamine (51.6 g, 69.54 ml, 400.00 mmol) and methoxymethyl chloride (32.2, 30.37 ml, 400.00 mmol) were added with stirring at the same temperature for 30 min. The mixture was allowed to warm to room temperature and stirred for 10 h. Then the reaction mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate (3 x 100 ml). The ethyl acetate extract was washed with water and brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue on column purification afforded the title compound (20.56 g, 78 %).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.52 (s, 3H), 3.86 (s, 3H), 5.21 (s, 2H), 6.64 (d, *J* = 8 Hz, 1H), 7.29 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.42 (d, *J* = 2 Hz, 1H); **Mass** (ESI) 294 (M^+).

Preparation of 2-methoxyphenylacetate:

In a 1 liter two neck round bottom flask, a mixture of o-methoxyphenol (30 g, 241.9 mmol), acetic anhydride (45.60 ml, 483.8 mmol), pyridine (30 ml, 362.8 mmol) and dry dichloromethane (250 ml) were stirred under inert atmosphere for 20 h at room temperature. Then the reaction mixture was poured in ice and extracted with ethyl acetate (3 x 500 ml). The organic layer was washed with water followed by brine and dried over sodium sulfate, the solvent was removed under reduced pressure to collect the pure 2-methoxyphenylacetate (34.13 g, 85 %) as a colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.30 (s, 3H), 3.82 (s, 3H), 6.90-7.06 (m, 3H), 7.10-7.20 (m, 1H); **Mass** (ESI): 166 (M^+).

Preparaion of 5-Iodo-2-methoxyphenyl acetate:

In a flame dried three neck round bottom flask fitted with a sealed stirrer, a dropping funnel and a reflux condensor with drying tube (calcium chloride), were placed silver trifluoroacetate (226.70 g, 1443.90 mmol), and a 2-methoxyphenylacetate (133.15 g, 802.16 mmol) and stirred well. To this stirred suspension iodine (170.05 g, 1604.30 mmol) in chloroform (1000 ml) was added though dropping funnel over a period of 2 h and then stirred for 9 h. The mixture was filtered and the precipitate of silver iodide was washed with chloroform. The solvent was removed from filtrate under vacuum. It gave 5-iodo-2-methoxyphenyl acetate (111.00 g, 47 %) as a solid.

M. p. 89^0C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.31 (s, 3H), 3.82 (s, 3H), 6.72 (d, *J* = 8 Hz, 1H), 7.34 (s, 1H), 7.50 (dd, *J* = 8 Hz and 2 Hz, 1H); **Mass** (ESI): 293 (M^+).

Preparation of 5-iodo-2-methoxyphenol:

In 2 liter round bottom flask, 5-iodo-2-methoxyphenyl acetate (111.00 g, 378.84 mmol) and sodium hydroxide (140 g, 546.00 mmol) in 500 ml water were stirred at room temperature for 8 h. Then the reaction mixture was acidified with dil. HCl and extracted with ethyl acetate (3 x 700 ml). The ethyl acetate extract was washed with water followed by brine and the solvent was removed under reduced pressure to give 5-iodo-2-methoxyphenol (71 g, 74 %) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.88 (s, 3H), 5.50 (bs, 1H), 6.57 (d, *J* = 10 Hz, 1H), 7.14 (dd, *J* = 10 Hz and 2 Hz, 1H), 7.22 (d, *J* = 2 Hz, 1H); **Mass** (ESI): 250 (M^+).

Methyl-5-iodo-2-methoxybenzoate (131):

In a 100 ml two necked round bottom flask, a mixture of 5-iodo salicylic acid (5.00 g, 18.93 mmol), potassium carbonate (6.58 g, 47.34 mmol), dimethyl sulfate (3.42 ml, 47.34 mmol) and acetone was refluxed under inert atmosphere for 5 h. The reaction mixture was cooled to room temperature, filtered though celite and acetone was removed under reduced pressure. To the crude residue, water was added and stirred at room temperature for 2 h. The solid formed was filtered and washed with water to collect pure methyl-5-iodo-2-methoxybenzoate (4.74 g, 86 %) as a white solid.

M. p. 61-62 ^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.86 (s, 6H), 6.73 (d, *J* = 8 Hz, 1H), 7.69 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.03 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 292 (M^+)

Preparation of (4-iodo-phenoxy)-acetic acid ethyl ester:

In a 100 ml two neck round bottom flask phenoxy-acetic acid ethyl ester (1.8 g, 10.00 mmol) was taken and a solution of iodine monochloride (1.62 g, 10.00 mmol) in glacial acetic acid (30 ml)

was added at room temperature dropwise under inert conditions over a period of 15 min. The stirring was continued for further 5 h, the reaction mixture was poured over ice-water, filtered and washed with water to give the title compound (1.4 g, 46 %).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.30 (t, *J* = 8 Hz, 3H), 4.27 (q, *J* = 8 Hz, 2H), 4.60 (s, 2H), 6.70 (dd, *J* = 6 Hz and 2 Hz, 2H), 7.57 (dd, *J* = 6 Hz and 2 Hz, 2H); **Mass** (ESI): 305 (M^+)

1,3-Dimethyl-2-methoxy-5-nitrobenzene:

In a 100 ml two necked round bottom flask, a mixture of 2,6-dimethyl-4-nitrophenol (2.00 g, 11.00 mmol), potassium carbonate (2.47 g, 17.00 mmol), dimethyl sulfate (2.14 g, 17.00 mmol) and acetone (20 ml) was refluxed under inert atmosphere for 12 h. The reaction mixture was cooled to room temperature, filtered though celite and the acetone was removed under reduced pressure. To the crude residue, water was added and stirred at room temperature for 2 h. The residue was extracted with ethyl acetate (3 x 20 ml), washed with water followed by brine and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to collect the crude product which after column purification provided the pure product 1,3-dimethyl-2-methoxy-5-nitrobenzene (1.71 g, 79 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (s, 6H), 3.79 (s, 3H), 7.92 (s, 2H); **Mass** (m/e): 181 (M^+).

4-Methoxy-3,5-dimethylaniline:

In a 25 ml two neck round bottom flask, 2-methoxy-1,3-dimethyl-5-nitrobenzene (1.00 g, 5.52 mmol) and ethanol (10 ml) were taken and to this 5 % Pd/C (100 mg) was added. Then the reaction mixture was stirred under atmosphere of hydrogen at room temperature for 3 h (TLC analysis indicated completion of reaction). The reaction mixture was filtered though a pad of celite and the ethanol was removed under reduced pressure using rotary evaporator. The crude residue thus obtained was extracted with ethyl acetate, washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography to collect pure 4-methoxy-3,5-dimethylphenylaniline (0.40 g, 40 %) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.22 (s, 6H), 3.34 (bs, 2H), 3.67 (s, 3H), 6.37 (s, 2H); **Mass** (m/e): 151 (M^+).

5-Iodo-2-methoxy-1,3-dimethylbenzene (124):

In a single neck round bottom flask, 4-methoxy-3,5-dimethylphenylaniline (2.00 g, 13.24 mmol), was dissolved in glacial acetic acid (3.15 ml) and water (3.15 ml), and cooled to 0^0C. A solution

of sodium nitrite (1.03 g, 15.00 mmol) prepared in water and cooled to 0^0C was added dropwise to the cooled amine solution slowly with shaking. It was stirred for 30 min and then a solution of potassium iodide (2.47 g, 15.00 mmol) in water (4 ml) was added to the diazotised reaction mixture slowly (over 30 min). The mixture was allowed to stand at room temperature for 1 h. The reaction mixture was digested on water bath till evolution of nitrogen stopped and cooled to room temperature when a black oil settled at bottom. The aqueous part was poured out and the black residue was treated with sodium metabisulphate and extracted with ethyl acetate (3 x 40 ml). The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated under reduced pressure. The column chromatography of the crude product afforded 5-iodo-2-methoxy-1,3-dimethylbenzene (1.7 g, 50 %) as a yellowish liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.26 (s, 6H), 3.72 (s, 3H), 7.37 (s, 2H); **Mass** (m/e): 262 (M^+).

2-Iodo-1,4-dimethoxybenzene (127):

2-Iodo-1,4-dimethoxybenzene (**127**) was prepared from 2,5-dimethoxy aniline by diazotization method as described for preparation of compound **124.**

Yield 56 %; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.80 (s, 3H), 6.72 (d, *J* = 8 Hz, 1H), 6.84 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.33 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 264 (M^+).

Preparation of 2-(4-methoxyphenyl)-furan (173):

In a 250 ml two neck round bottom flask a solution of furan (4.68 g, 5 ml, 73.52 mmol) in 30 ml of dry tetrahydrofuran was placed and cooled to -30^0C under argon. n-Butyllithium (2 M solution 50.12 ml, 110.28 mmol) was added and stirred for 1 h. The mixture was treated with solid anhydrous zinc chloride (9.92 g, 73.52 mmol) dissolved in tetrahydrofuran (20 ml). The reaction mixture was stirred at 0^0C for 30 min, recooled to -10^0C and treated successively with 4-bromoanisole (20.62 g, 110.28 mmol) dissolved in 20 ml of tetrahydrofuran and tetrakis(triphenylphosphane)palladium (0) (0.423 g, 0.36 mmol). The reaction mixture was stirred at -10^0C for 1 h and at 0^0C for 1 h and then poured into a mixture of ether and 0.5 N HCl and extracted with ether. The organic layer was washed with water followed by brine, dried over sodium sulfate and the solvent was removed on rotary evaporator to collect a residue which on column purification afforded the compound **173** (5.92 g, 46 %) as a low melting solid.

M. p. 52^0C (lit.[117] 52-53^0C); **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.85 (s, 3H), 6.45 (dd, *J* = 4 Hz and 2 Hz, 1H), 6.52 (d, *J* = 4 Hz, 1H), 6.93 (d, *J* = 10 Hz, 2H), 7.44 (d, *J* = 2 Hz, 1H), 7.62 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 55.34, 103.49, 111.62, 114.34 (2C), 115.92,

125.44 (2C), 132.38, 141.46, 154.10; **Mass** (ESI): 174 (M^+); Anal. Calcd. For $C_{11}H_{10}O_2$: C 75.84 H, 5.79 %. Found: C 75.92 H, 5.86 %.

[5-(4-Methoxyphenyl)-furan-2-yl]-(3,4,5-trimethoxyphenyl)-methanol (174):

In a 100 ml two neck dry round bottom flask, 2-(4-methoxyphenyl)-furan (**173**) (1.15 g, 6.57 mmol) was taken, the flask was evacuated and flushed with argon and 15 ml of dry tetrahydrofuran was added. The flask was cooled to 0^0C when n-butyllithium (1.8 M solution, 5.47 ml, 9.85 mmol) was added and stirred at the same temperature for 30 min. 3,4,5-Trimethoxy benzaldehyde (1.28 g, 6.57 mmol) in dry tetrahydrofuran (5 ml) was added though syringe to the cooled flask and the solution was stirred for 2 h at the same temperature. The reaction mixture was quenched with ammonium chloride and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with water, followed by brine and the organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by column purification to afford compound **174** (1.64 g, 92 %) as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.82 (s, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 5.48 (bs, 1H), 6.13 (d, *J* = 4 Hz, 1H), 6.46 (d, 4 Hz, 1H), 6.57 (s, 2H), 6.88 (d, *J* = 10 Hz, 2H), 7.56 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 54.65, 55.53 (2C), 60.24, 69.50, 103.43, 105.34, 106.33 (2C), 109.41, 113.68 (2C), 124.56 (2C), 127.43, 131.29, 134.78, 136.69, 152.68 (2C), 158.53; **Mass** (ESI): 369 (M^{-1}); Anal. Calcd. For $C_{21}H_{22}O_6$: C 68.10; H 5.99 %. Found: C 68.26; H 6.19 %.

4-Acetoxy-3-[3-(bis-benzyloxy-phosphoryloxy)-4-methoxy-phenyl]-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (175):

In a 50 ml two neck round bottom flask compound **124** (0.40 g, 0.934 mmol) and acetonitrile (10 ml) were cooled to -10^0C then dry carbontetrachloride (10 ml) and N, N-diisopropyl ethylamine (0.25 ml, 1.40 mmol) were added followed by DMAP (0.032 g, 0.29 mmol). After 2 min dibenzyl phosphite (0.490 g, 1.87 mmol) was added dropwise at the same temperature, the reaction mixture was stirred for 1.5 h. The reaction was quenched with aqueous KH_2SO_4 and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure to collect the crude residue which was purified by column chromatography to get compound **175** (0.44 g, 65 %).

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 2.04 (s, 3H), 2.55 (bd, *J* = 15 Hz, 1H), 3.16 (dd, *J* = 15 Hz and 5 Hz, 1H) 3.73 (s, 6H), 3.81 (s, 3H), 3.86 (s, 3H), 5.05-5.25 (m, 4H), 6.31-6.37 (m, 1H), 6.46 (s, 2H), 6.84 (d, *J* = 10 Hz, 1H), 7.11 (d, *J* = 5 Hz, 1H), 7.17 (s, 1H), 7.20-7.45 (m, 10H);

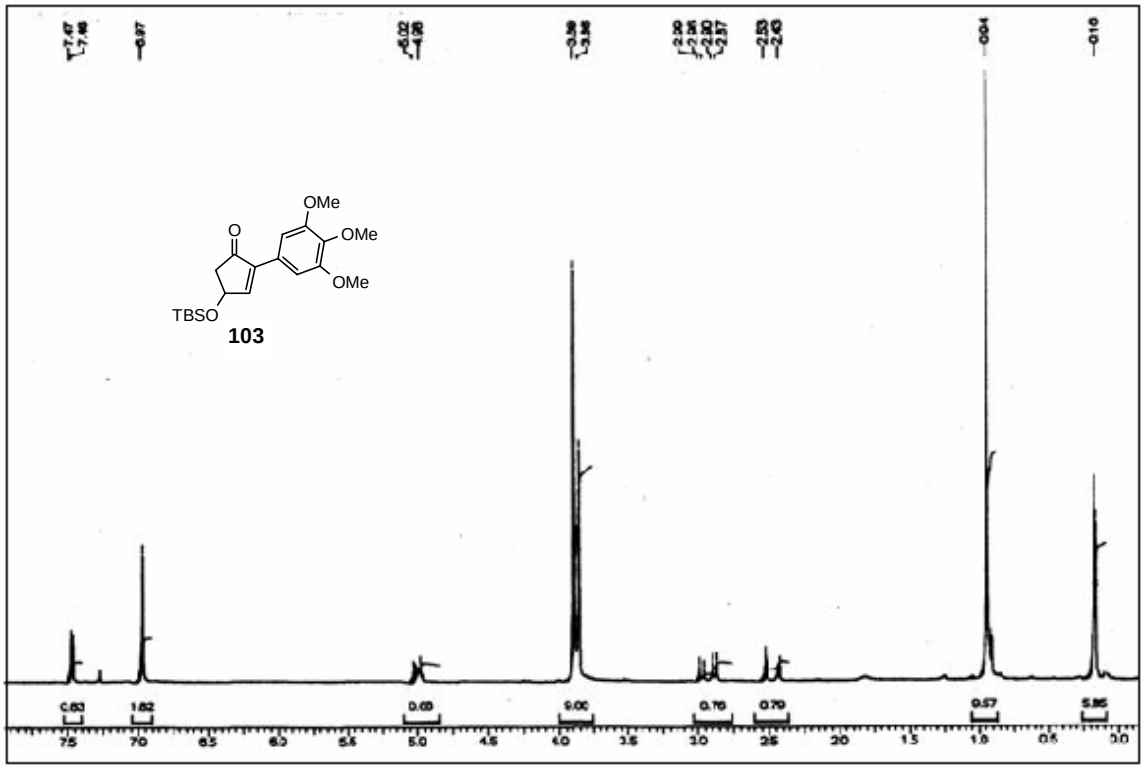
Mass (ESI): 688 (M^+); Anal. Calcd. For $C_{37}H_{37}O_{11}P$: C 64.53; H 5.42; P 4.50 %. Found: C 64.69; H 5.65; P 4.59 %.

3,4,5-Triacetoxy-6-(4-formyl-phenoxy)-tetrahydropyran-2-ylmethyl acetate (178):

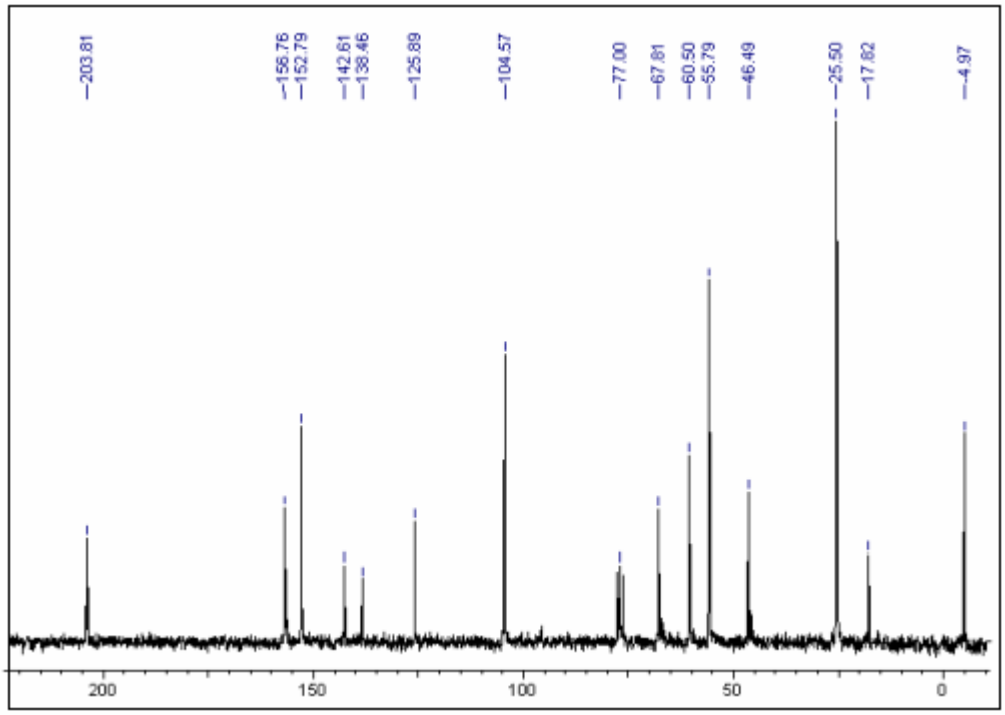
In a 50 ml two neck round bottom flask with Dean-Stark apparatus, the mixture of 4-hydroxy benzaldehyde (0.50 g, 4.09 mmol), cadmium carbonate (1.37 g, 8.18 mmol) and bromo sugar **177** (3.28 g, 8.18 mmol) was taken. Toluene was added to the reaction mixture and heated azeotropically for 5 h. Then the toluene was removed under reduced pressure and the residue was extracted with dichloromethane (3 x 20 ml). The dichloromethane layer was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give compound **178** (0.80 g, 43 %) as a thick liquid.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 1.88 (s, 3H), 1.92 (s, 6H), 2.02 (s, 3H), 3.90-4.15 (m, 3H), 4.69 (dd, *J* = 10 Hz and 4 Hz, 1H), 4.85-5.02 (m, 2H), 5.25-5.37 (m, 1H), 6.98 (d, *J* = 10 Hz, 2H), 7.71 (d, *J* = 10 Hz, 2H), 9.74 (s, 1H); **Mass** (ESI): 452 (M^+); Anal. Calcd. For $C_{21}H_{24}O_{11}$: C 55.75; H 5.35 %. Found: C 55.83; H 5.41 %.

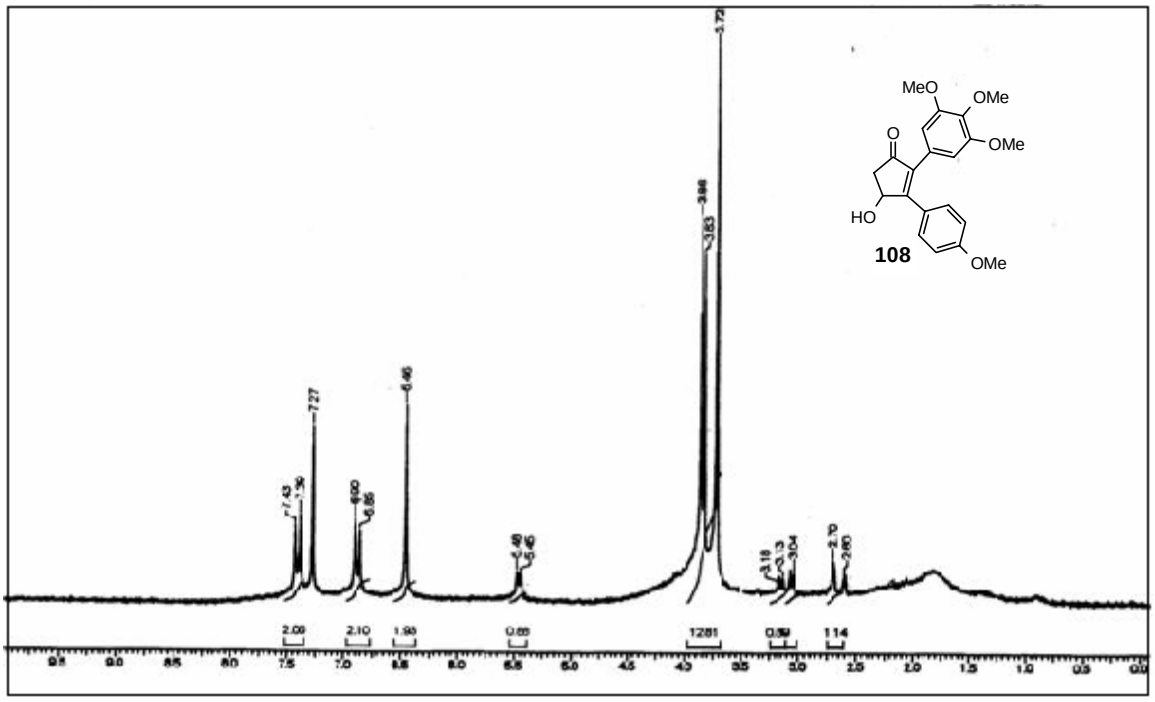
^{1}H NMR spectrum of the compound 103:



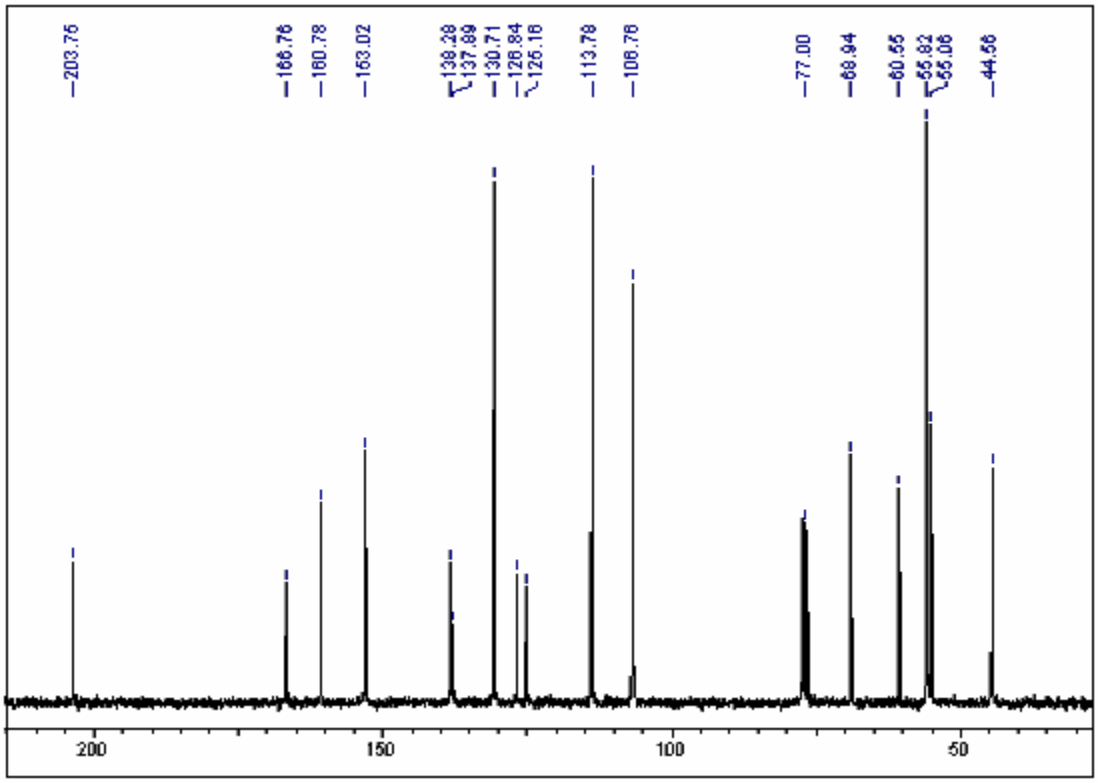
^{13}C NMR spectrum of the compound 103:



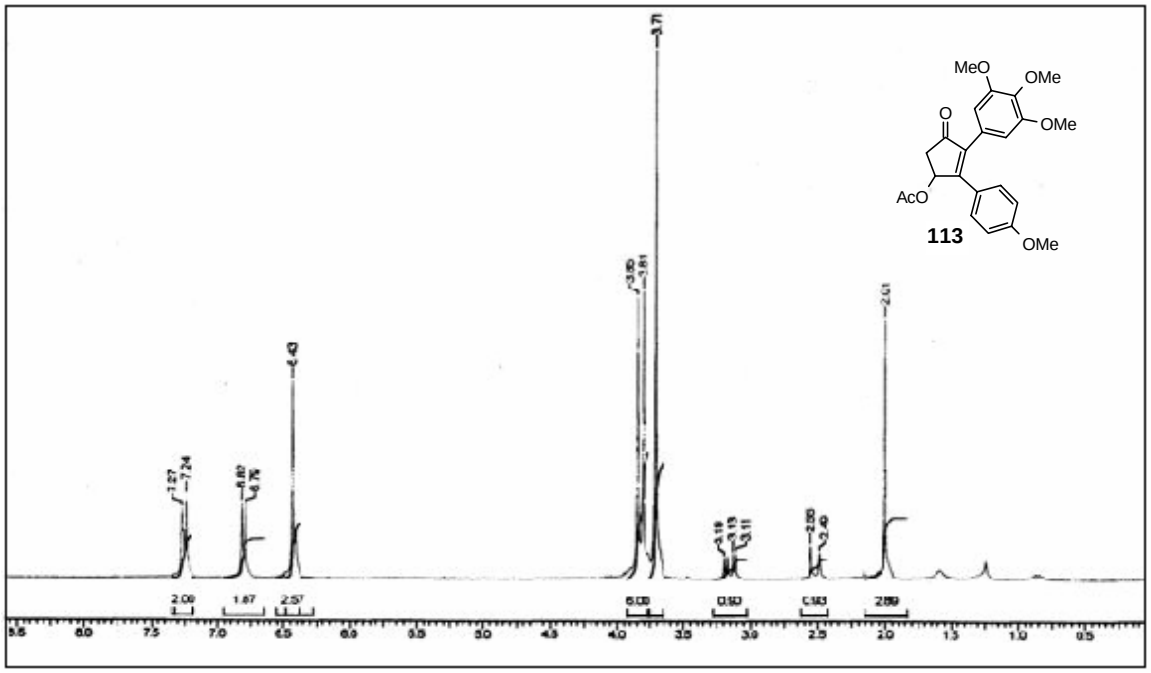
^{1}H NMR spectrum of the compound 108:



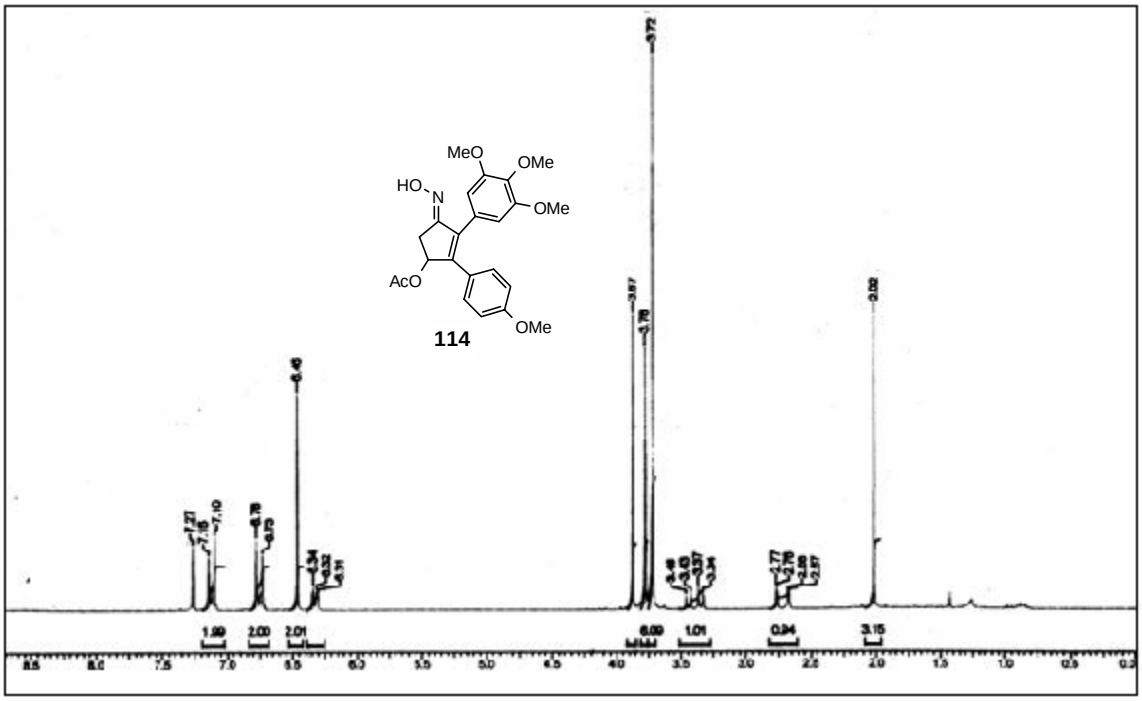
^{13}C NMR spectrum of the compound 108:



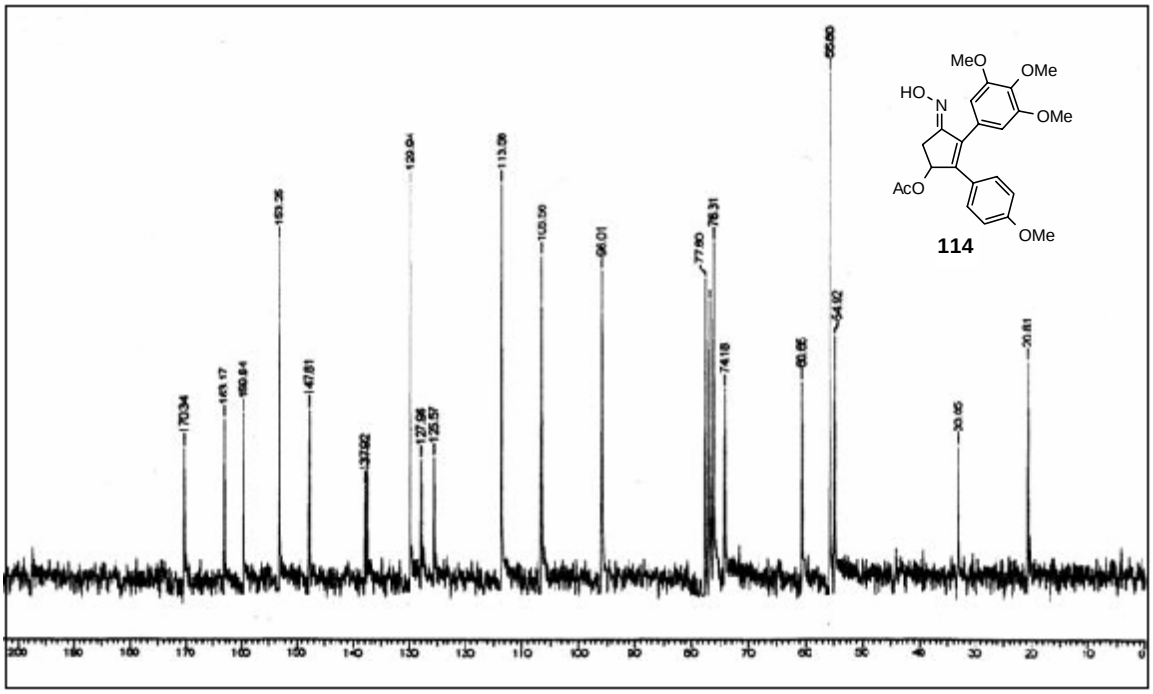
^{1}H NMR spectrum of the compound 113:

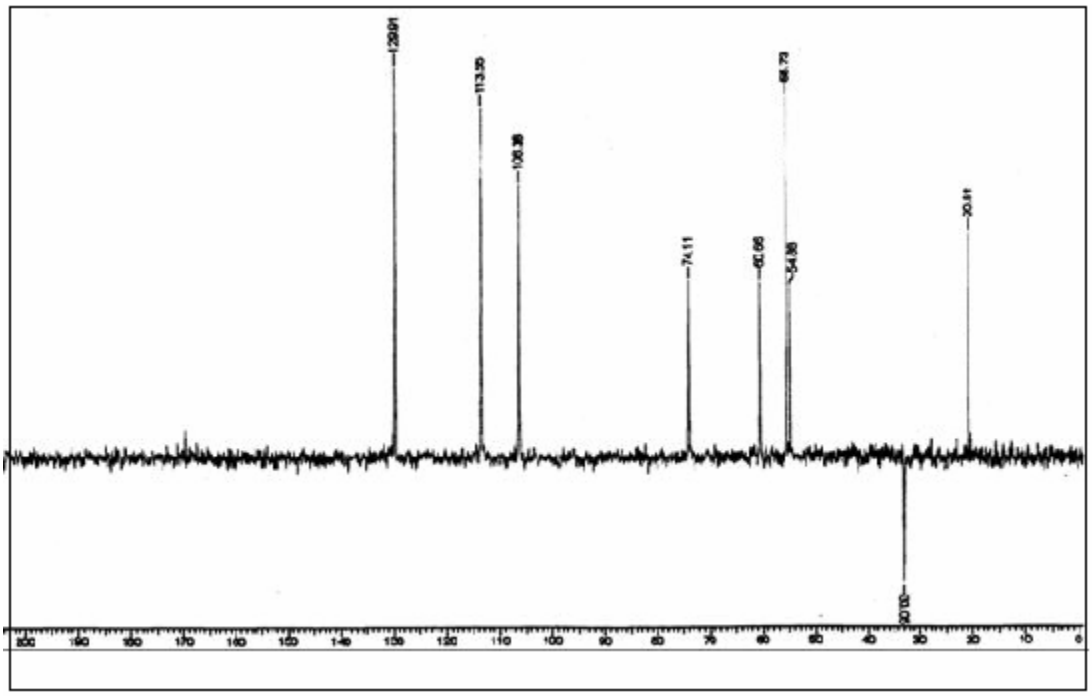


^{1}H NMR spectrum of the compound 114:

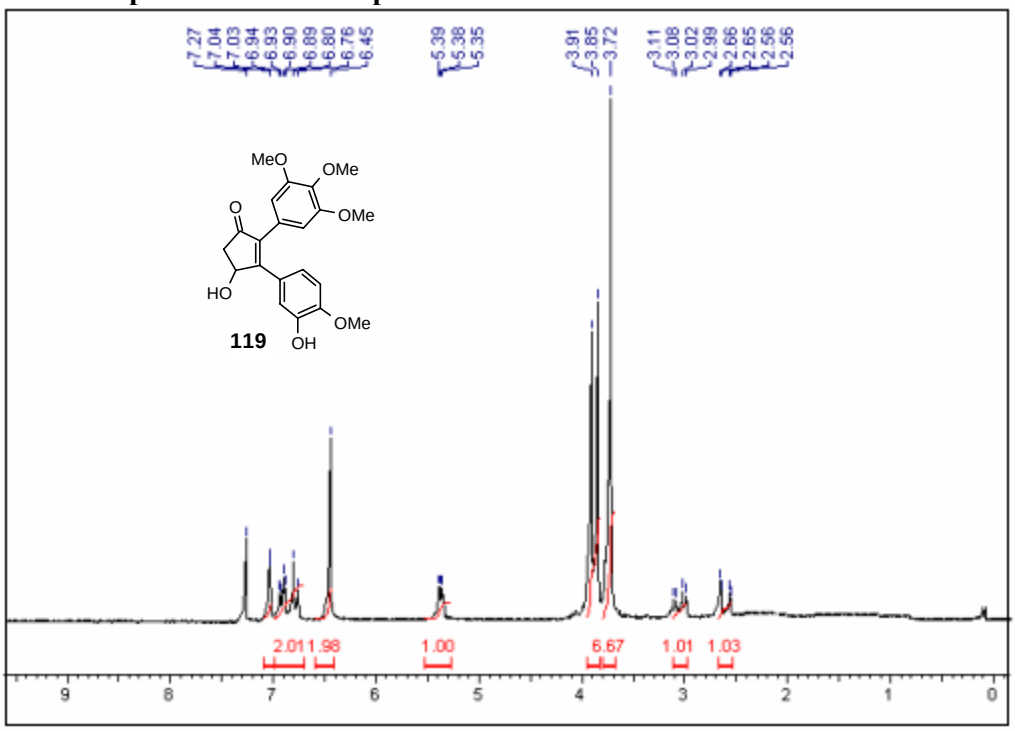


^{13}C NMR spectrum of the compound 114:

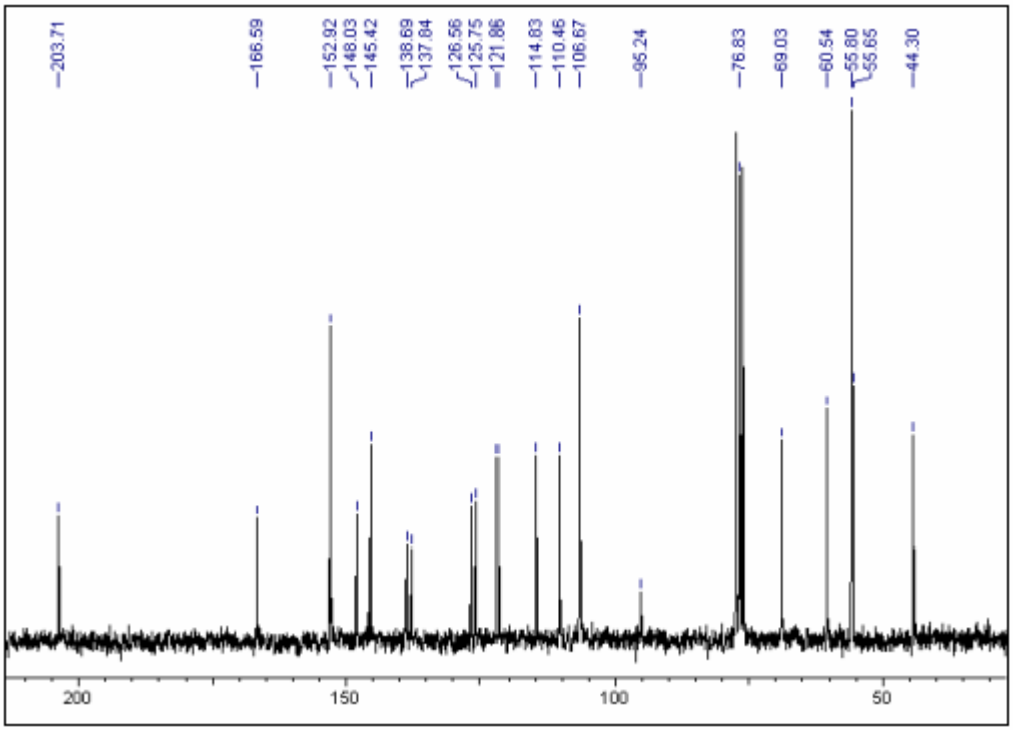




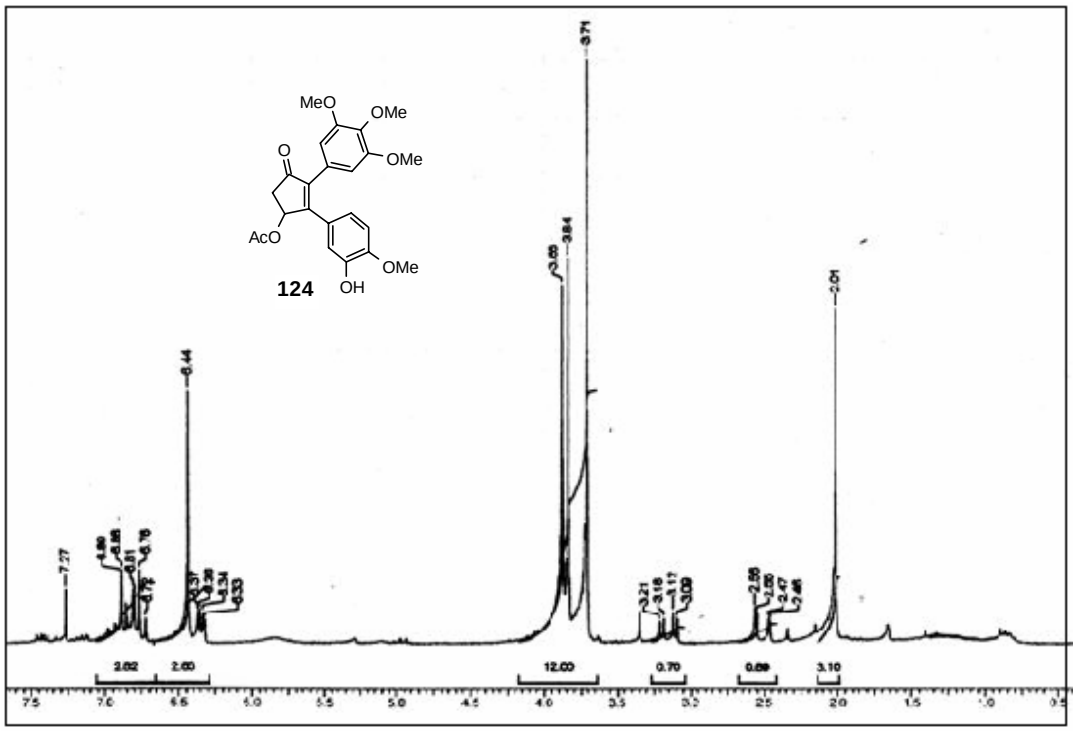
^{1}H NMR spectrum of the compound 119:



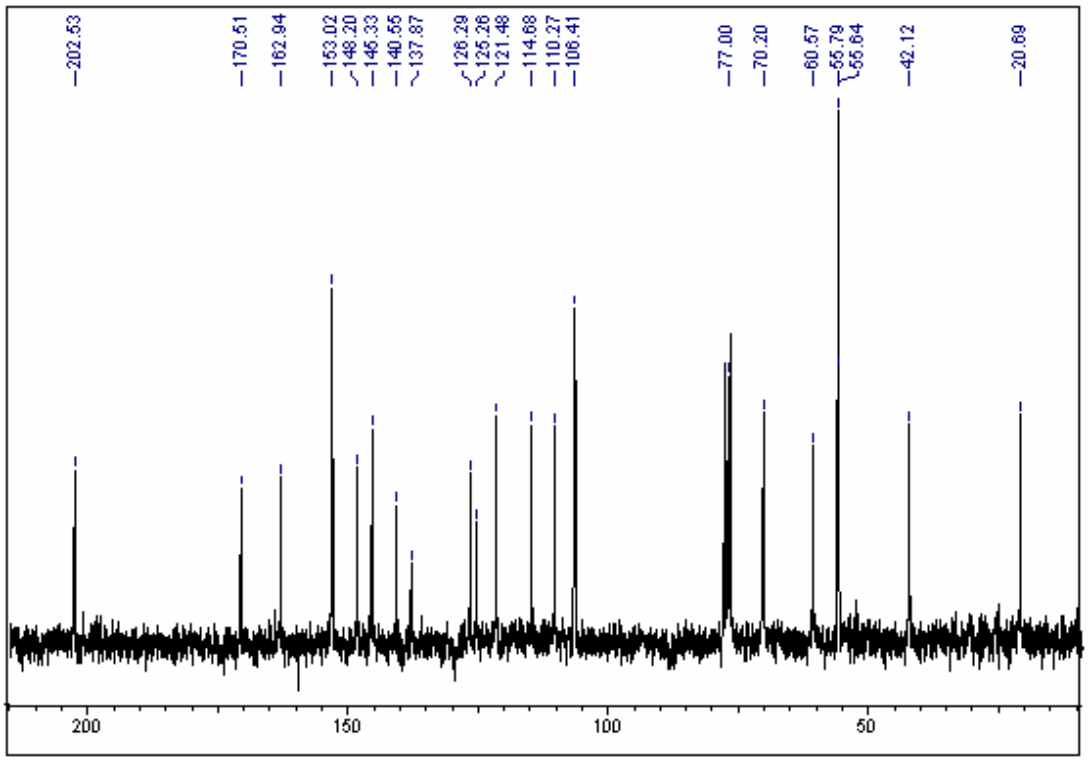
^{13}C NMR spectrum of the compound 119:



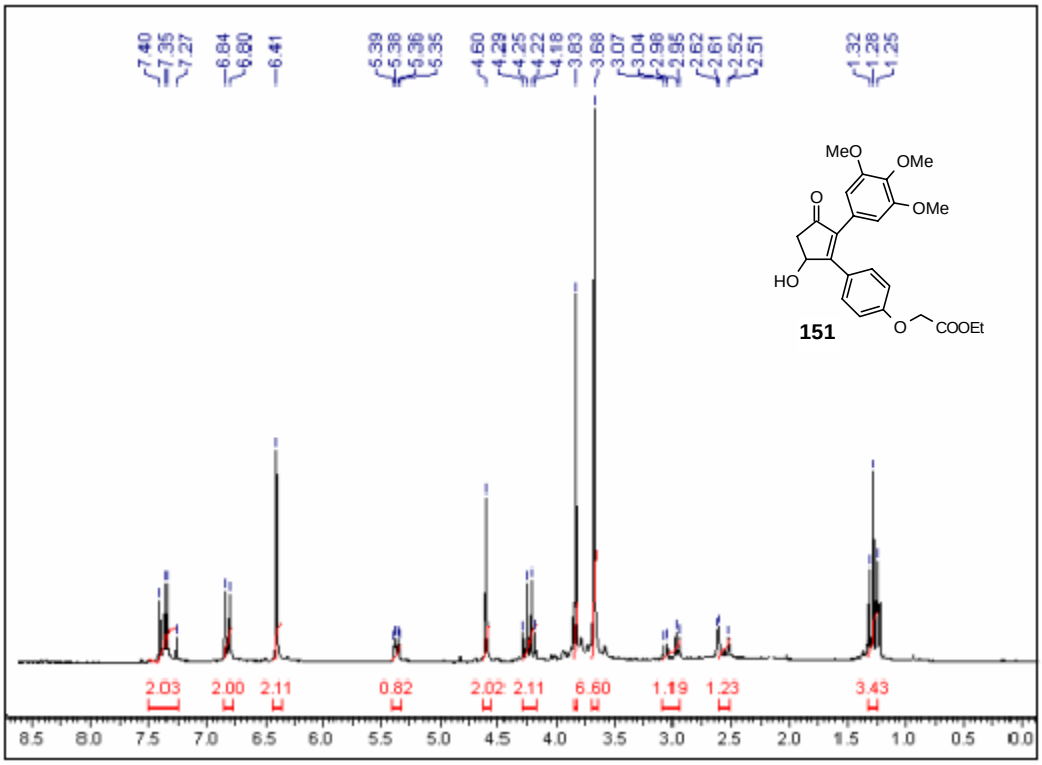
^{1}H NMR spectrum of the compound 124:



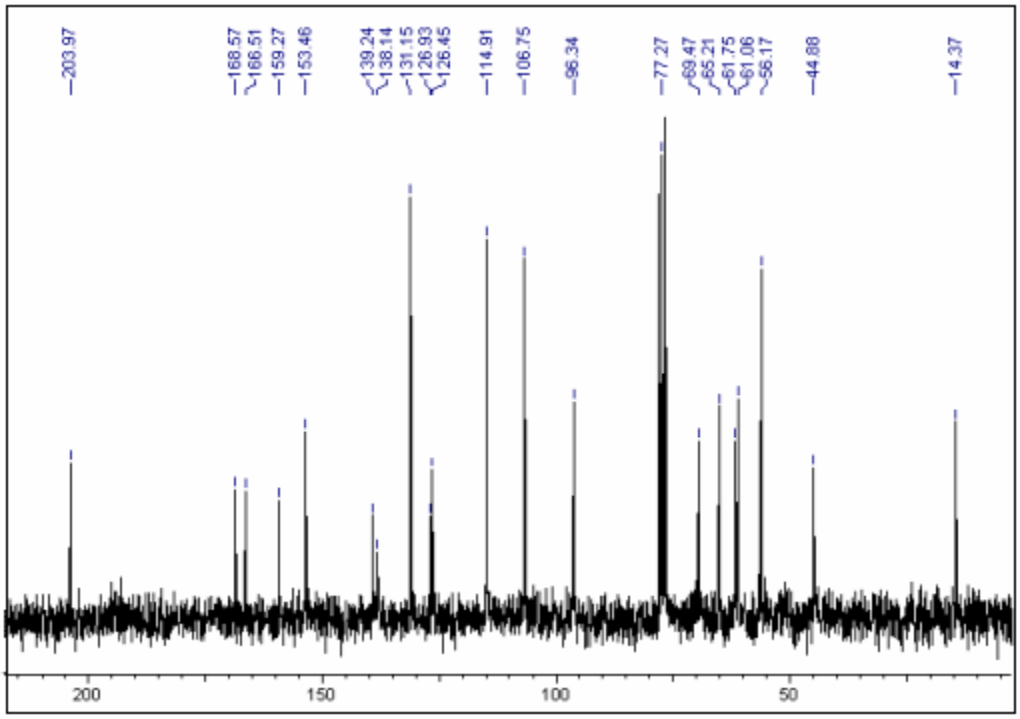
^{13}C NMR spectrum of the compound 124:



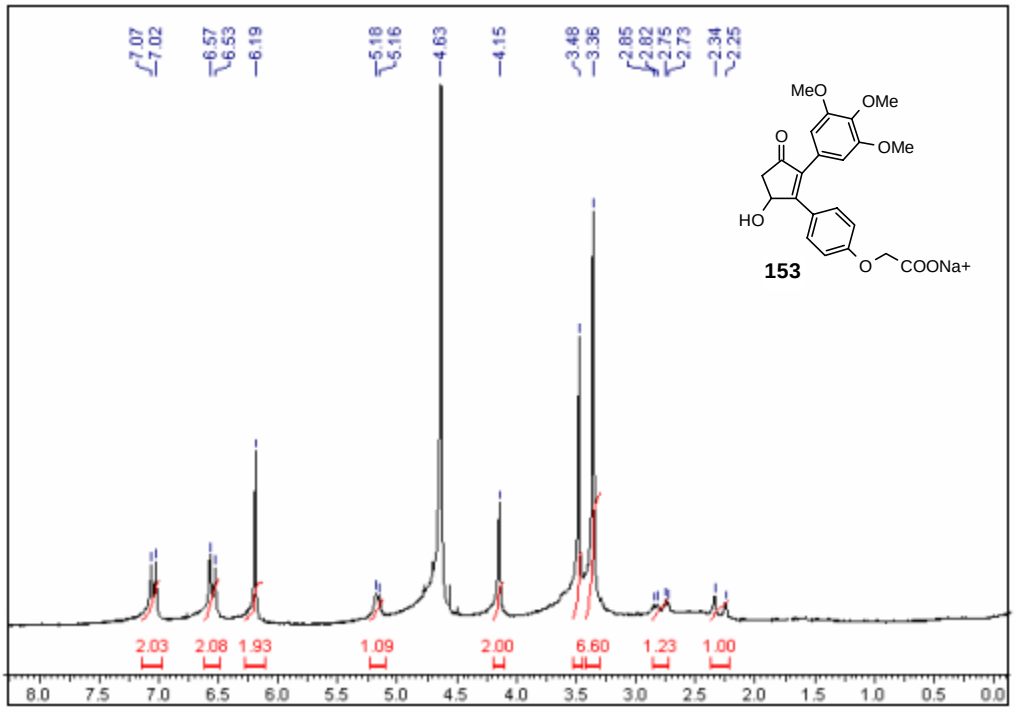
^{1}H NMR spectrum of the compound 151:



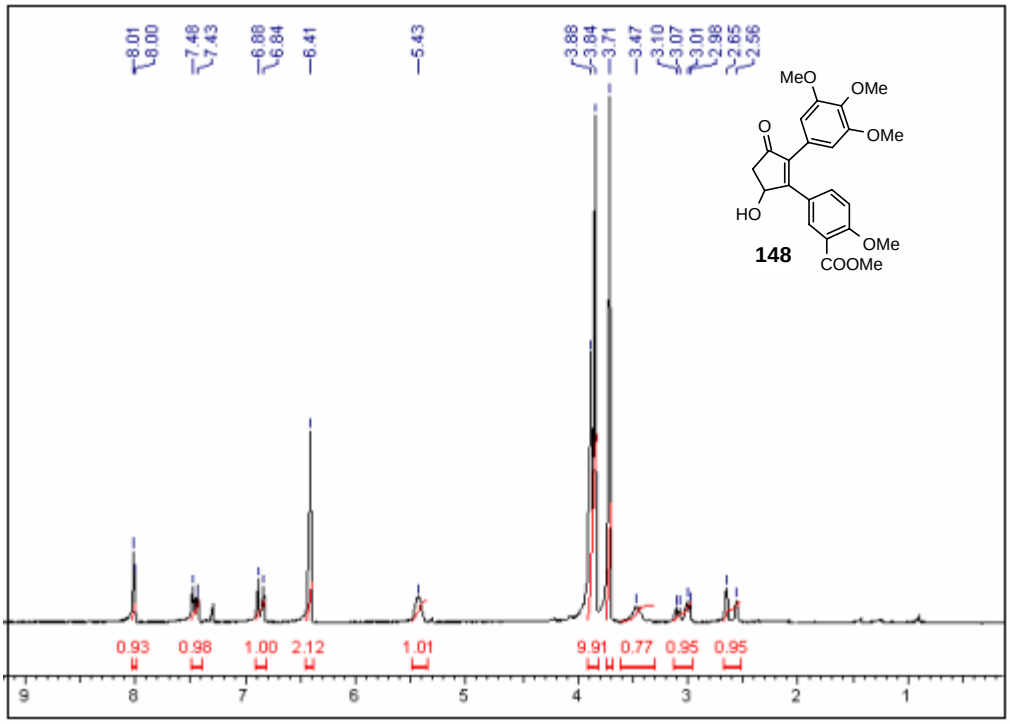
^{13}C NMR spectrum of the compound 151:



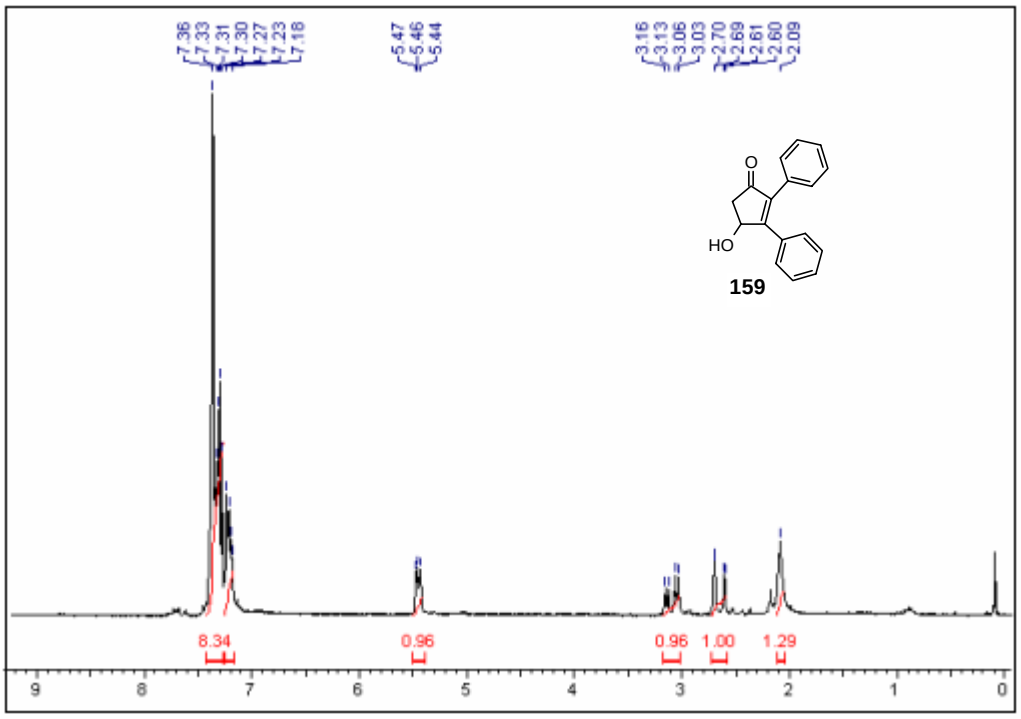
^{1}H NMR spectrum of the compound 153:



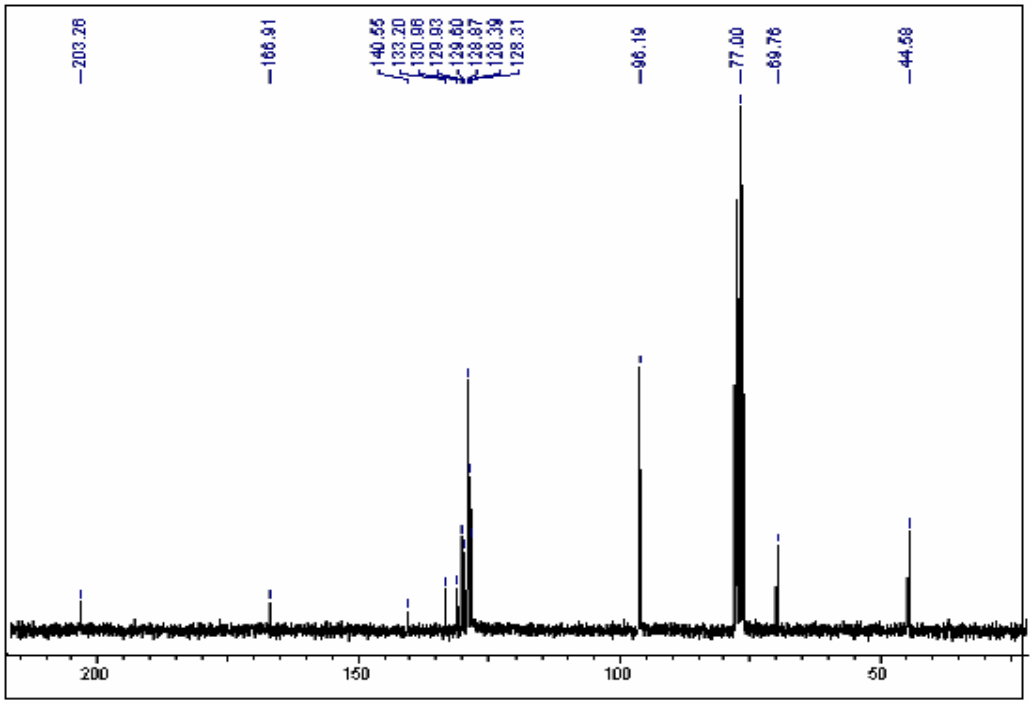
^{1}H NMR spectrum of the compound 148:



^{1}H NMR spectrum of the compound 159:



^{13}C NMR spectrum of the compound 159:



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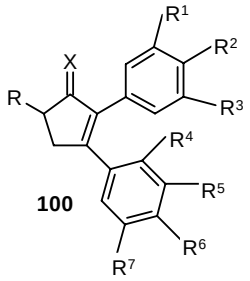
CHAPTER 1

SECTION II

Design and Synthesis of 2,3-Diaryl-5-Hydroxycyclopent-2-en-1-one Analogues of Combretastatin A-4

1.2.1 INTRODUCTION:

The syntheses of 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues (**99**) of CA-4 *via* Heck reaction method achieved successfully have been described in section I. We planned to synthesize 2,3-diaryl-5-hydroxycyclopent-2-en-1-one analogues (**100**) of combretastatin A-4. The position of hydroxy group in the cyclopentenone ring was changed in order to study the effect of these functional group on biological activity of these compounds. It was assumed that the hydroxy group at 5-position in the cyclopentenone ring being adjacent to the carbonyl group should impart hydrogen bonding and provide compounds with better solubility in biocompatible solvents and especially in water.



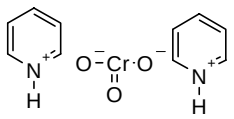
The synthetic strategy employed here involved 1,3-oxidative rearrangement of tertiary allylic alcohols by pyridinium dichomate.[1] The ability to transpose a functional group efficiently from one carbon to another, as in 1,3-carbonyl transposition of α, β-unsaturated ketones, offers a wide degree of latitude in synthetic design of many naturally occurring compounds. Among the methods commonly employed are included allylic interconversion of oxygen with selenoxide[2], sulfoxide[3] and amine oxide[4] *via* 2,3-sigmatropic rearrangements and the Wharton epoxy ketone rearrangement.[5] However, these methods suffer from inferior yields and/or multistep manipulation of delicate intermediates.

Trost[6] in 1975 reported a method by which tertiary allylic alcohols, generated by 1,2-addition of an organometallic reagent to α, β-unsaturated ketones, are converted in several steps to new, transposed β-allyl conjugated ketones.

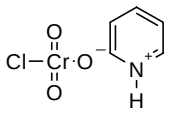
The oxidation of alcohols to corresponding carbonyl compounds is one of the key step reaction in organic synthesis. Among the variety of reagents available for the oxidation of organic compounds, the most commonly used are derivatives of hexavalent chromium (Cr^{VI}) or heptavalent manganese (Mn^{VII}). Chromium trioxide (CrO_3) and sodium dichromate ($Na_2Cr_2O_7$) are converted to the chromium (III) ion (Cr^{3+}) in the course of such oxidations. Jones reagent[7] is a

solution of chromic acid and sulfuric acid in water, which oxidizes secondary alcohols to ketones without disturbing double bonds or triple bonds.

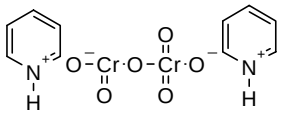
Hexavalent chromium compounds (Cr^{VI}) are very popular for the oxidation of alcohols. They are Cr (VI) oxides (Collins reagent), pyridinium chlorochromate (Corey's reagent) and pyridinium dichromate.



Collins reagent



PCC

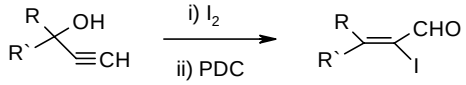


Pyridinium dichromate (PDC)

There are several methods for the oxidation of primary and secondary alcohols to carbonyl compounds but the direct oxidation of tertiary allylic alcohols has received only scant attention. In simpler systems it has been demonstrated that Jones oxidation of substituted tertiary alcohols affords the transposed unsaturated ketone in poor to moderate yields.[8] Pyridinium chlorochromate (PCC) allows the efficient oxidation of a wide range of alcohols to carbonyl compounds in dichloromethane with only a moderate excess of oxidant. However, mildly acidic nature of PCC precludes its use with acid sensitive substrates and same is the case with Collins reagent $(C_5H_5N)_2CrO_3$.

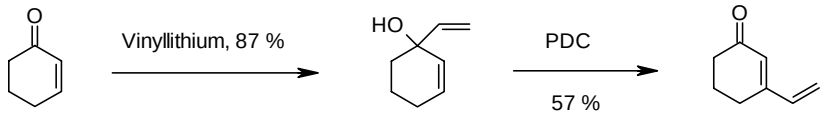
Corey and Schmidt[9] reported a new reagent for the oxidation of alcohols, which was much better than PCC and Collins reagent. They found that oxidations of primary alcohols to aldehydes could be achieved using PDC in dichloromethane but if same reaction was carried out in DMF it gave carboxylic acid. Secondary alcohols were more conveniently oxidized to ketones using DMF-PDC system.

Piancatelli *et al.*[10] reported the use of pyridinium dichromate for the oxidation of ethynyl carbinol using iodine and PDC complex to give α, β-unsaturated-α-iodo-aldehydes under mild conditions. They found that the reaction was regio and stereospecific.

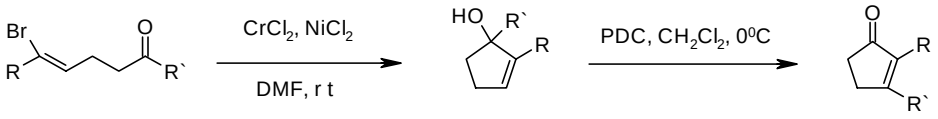


Brian and Just[11] reported the direct method for conversion of aldehydes to methyl esters with pyridinium dichromate using methanol in DMF.

Litto *et al.*[12] found that the pyridinium dichromate induced 1,3-oxidative rearrangement of enynols is completely regiosepecific. Majetich *et al.*[13] studied the 1,3-oxidative rearrangement of dienols and they noticed that oxidation of 1-vinyl-2-cycloalken-1-ols with PDC regiospecifically afforded conjugated dienones in moderate to good yields. They found that PDC was more regiospecific as compared with PCC and CrO_3.



Trost and Pinkerton[14] reported the oxidative rearrangement of cyclopentenols to cyclopentenones using pyridinium dichromate. They prepared cyclopentenols from Z-vinyl bromides under Barbier type conditions, which was oxidatively rearranged to generate cyclopentenone.

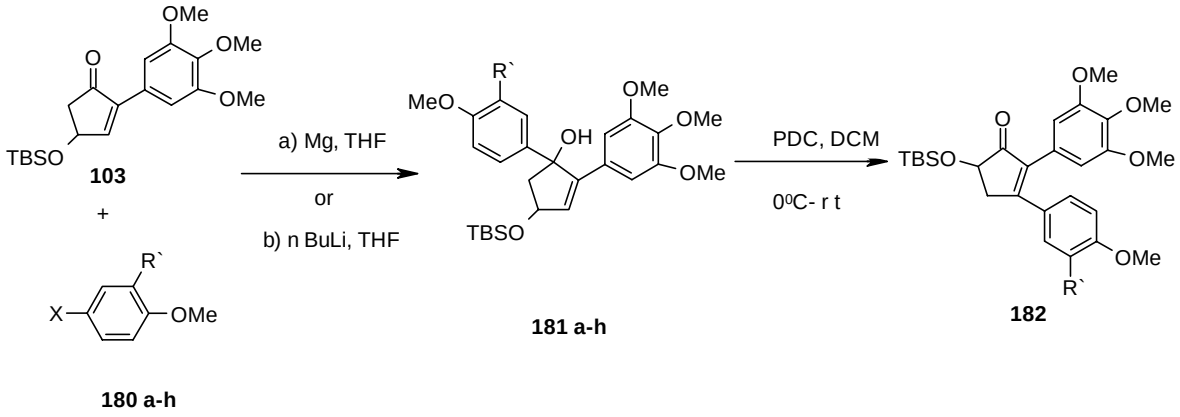


1.2.2 PRESENT WORK:

From the literature survey it was revealed that the synthesis of 2,3-diaryl-cyclopent-2-en-1-one was reported from 1,2-diaryl-cyclopent-2-en-1-ol but reaction of 1,2-diphenyl (substituted)-cyclopent-2-en-1-ol bearing hydroxy or protected hydroxy functionality at 4-position was not reported. We studied the rearrangement of 1,2-diphenyl (substituted)-cyclopent-2-en-1-ols using pyridinium dichromate to achieve the desired 2,3-diaryl-5-tert-butyldimethylsilyloxy-cyclopent-2-en-1-ones, which on deprotection should provide 2,3-diaryl-5-hydroxycyclopent-2-en-1-ones.

In view of the structure activity relationship studies for CA-4 and the finding that the 3,4,5-trimethoxy substituents on A-ring and 4-OMe group on B-ring of CA-4 are essential for cytotoxic activity, we planned to introduce 5-hydroxycyclopent-2-en-1-one ring in place of olefinic double bond between two aryl rings of combretastatin A-4 by keeping 3,4,5-trimethoxy substituents on A ring and to synthesize B-ring modified *cis*-restricted analogues of CA-4.

The synthetic strategy adopted is graphically shown in scheme 1. The 4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**103**) was envisaged as common building block for the synthesis of various 2,3-diaryl-5-hydroxycyclopentenone analogues.

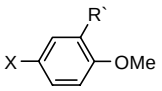


Scheme 1

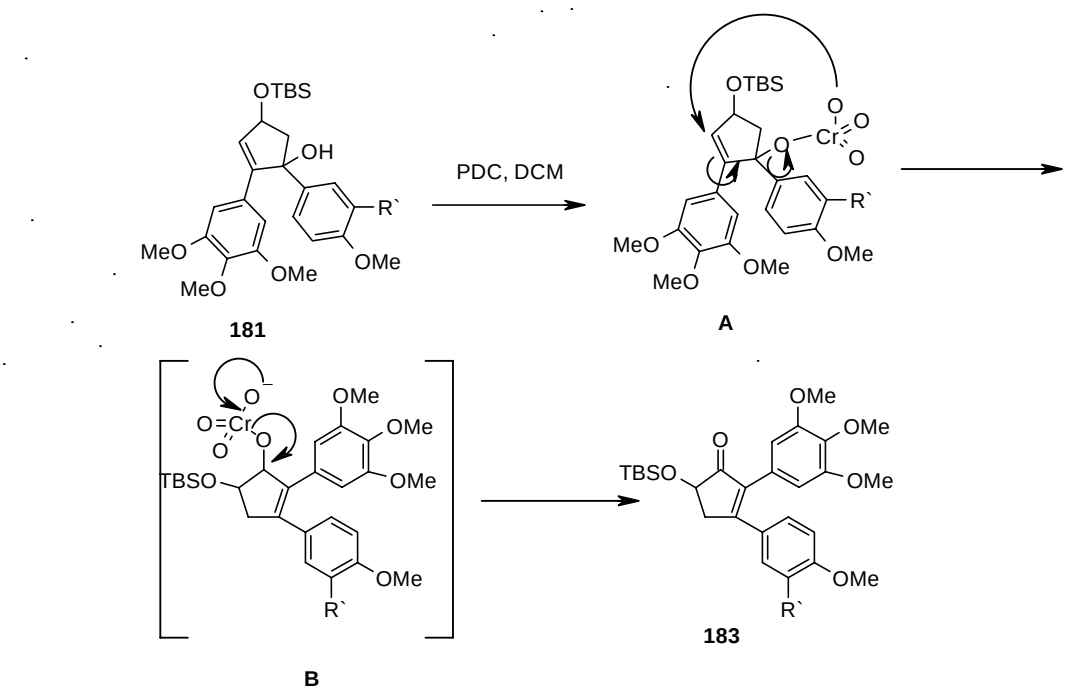
The intermediate **103** was prepared as shown in scheme 5 of section I. The addition of Grignard reagents or organolithium reagents in tetrahydrofuran prepared from suitably substituted aryl halides **180** to intermediate **103** afforded the corresponding 1,2-addition products (**181**) in good to excellent yields. Further treatment of cyclopentenols **181** with pyridinium dichromate (2-3 equivalents) in dichloromethane at 0^0C to room temperature afforded the corresponding 2,3-diaryl 5-tert-butyldimethylsilyloxy-cyclopent-2-en-1-ones (**182**). In this series we mainly synthesized

the B-ring modified analogues of CA-4 in which the –OH at 3-position of B-ring was replaced with substitutents like H, Cl, F, O^{i}Pr, O-allyl, NHAc, NHCOPh, N(Me)$_2$, NHCHO, NMeCHO etc, which could not be obtained by Heck reaction methodology. Table 1 shows the compounds (**183-191**) synthesized by the route captured in scheme 1.

Table 1:

Sr. No.	 **180 a-h**	Cyclopentenol obtained (**181 a-h**)	Cyclopentenone obtained (**182**)
1	**180 a:** X = Br, R` = H	**181 a:** R` = H	**183** R = H
2	**180 b:** X = Br, R` = Cl	**181 b:** R` = Cl	**184** R = Cl
3	**180 c:** X = Br, R` = F	**181 c:** R` = F	**185** R= F
4	**180 d:** X = I, R` = O^{i}Pr	**181 d:** R` = O^{i}Pr	**186** R = O^{i}Pr
5	**180 e:** X = I, R` = O-allyl	**181 e:** R` = O-allyl	**187** R` = O-allyl
6	**180 f:** X = I, R` = N(Me)$_2$	**181 f:** R` = N(Me)$_2$	**188** R = N(Me)(CHO) 189 R = NHCHO
7	180 g: X = I, R` = NHAc	181 g: R` = NHAc	190 R` = NHAc
8	**180 h:** X=I, R`= NHCOPh	**181 h:** R`= NHCOPh	**191** R`= NHCOPh

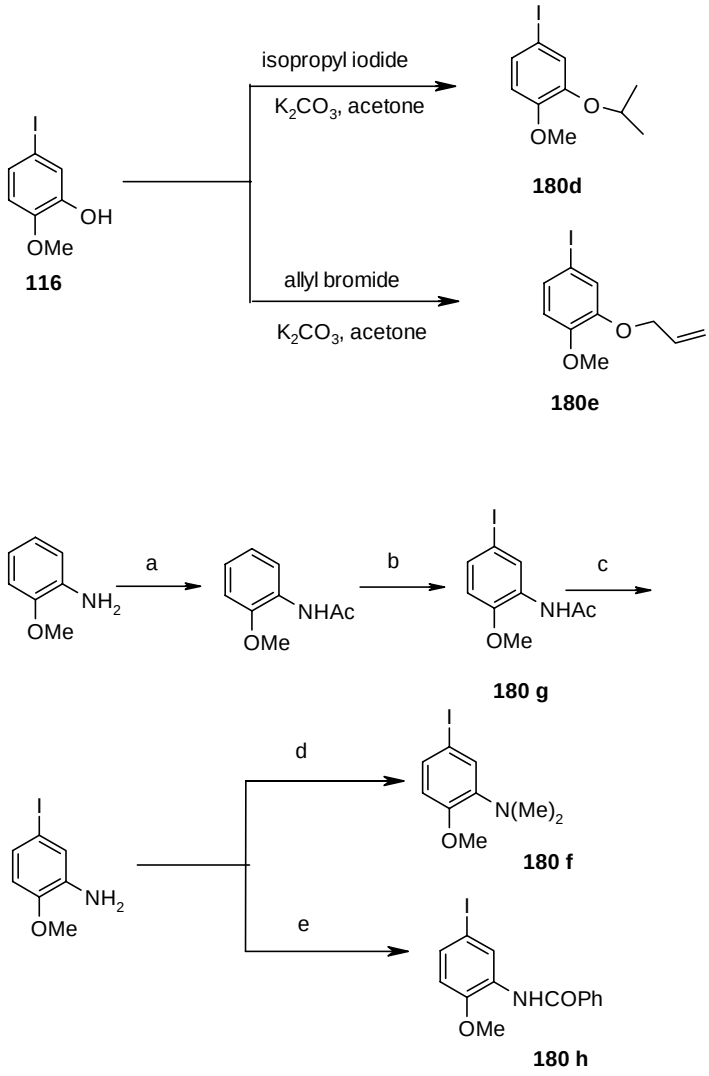
The proposed mechanism for this rearrangement is the initial formation of the chromate ester **A** from the tertiary alcohol followed by allylic rearrangement of the chromate ester of the secondary alcohol. Typical fragmentation of the resultant chromate ester **B** delivers the ketone as shown in scheme 2.



Scheme 2

The substituted aryl halides were prepared as shown in scheme 3. The iodides **180d** and **180e** were prepared by reaction of isopropyl iodide and allyl bromide respectively with 5-iodo-2-methoxyphenol **116** (section I, scheme 8), using potassium carbonate in acetone under reflux.

The aryl iodides **180f**, **180g** and **180h** were prepared from N-(2-methoxyphenyl)-acetamide. Iodination of N-(2-methoxyphenyl)-acetamide with iodine monochloride in glacial acetic acid gave the iodo compound **180g**. Hydrolysis of acetate **180g** with 2.5 N HCl, under reflux resulted in the 5-iodo-2-methoxyaniline, which on methylation with dimethylsulfate[15] afforded compound **180f** (5-iodo-2-methoxy-dimethylaniline). Similarly, 5-Iodo-2-methoxyaniline on benzoylation afforded the compound **180h** as shown in scheme 3.



Scheme 3

Reagents and conditions: a) $(CH_3CO)_2O$, pyridine, DCM, r t b) ICl, glacial acetic acid, 0^0C c) i) 2.5 N HCl, reflux ii) NaOH d) i) DMS, $NaHCO_3$, water ii) $H_2NCH_2CH_2OH$ e) C_6H_5COCl, Py, DCM.

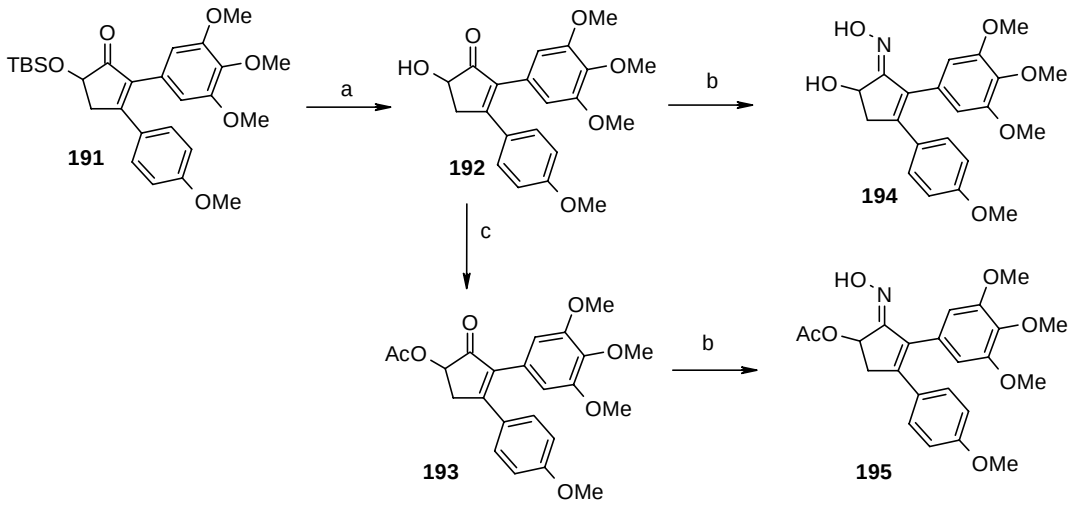
The cyclopentenols **181a**, **181b** and **181c** were obtained by Grignard reaction of 4-bromoanisole, 4-bromo-2-chloroanisole and 4-bromo-2-fluoroanisole respectively with intermediate **103** at 0^0C to room temperature in good yields. The other cyclopentenols **181d-h** were obtained by lithiation of suitably substituted aryl iodides with n-butyllithium at -78^0C in tetrahydrofuran and subsequent 1,2-addition on the intermediate **103**. Grignard reaction approach for the substrates

180d-h gave the corresponding products in lower yields due to poor Grignard reagent formation and formation of side products.

The treatment of these cyclopentenols (**181a-h**) with 2-3 equivalents of pyridinium dichromate in dichloromethane at 0^0C and stirring at room temperature for 10-15 h resulted in the substituted 2,3-diaryl-5-tert-butyldimethylsilyloxy-cyclopent-2-en-1-ones in 25-80 % yields.

The synthesized 5-hydroxy-2,3-diaryl-cyclopentenone analogues shown by the graphical presentation in scheme 1 were characterized by the spectroscopic and analytical methods. The presence of band at 1712 cm^{-1} in IR spectra and methylene peak at δ 39.29 in ^{13}C DEPT experiments were characteristic for these compounds.

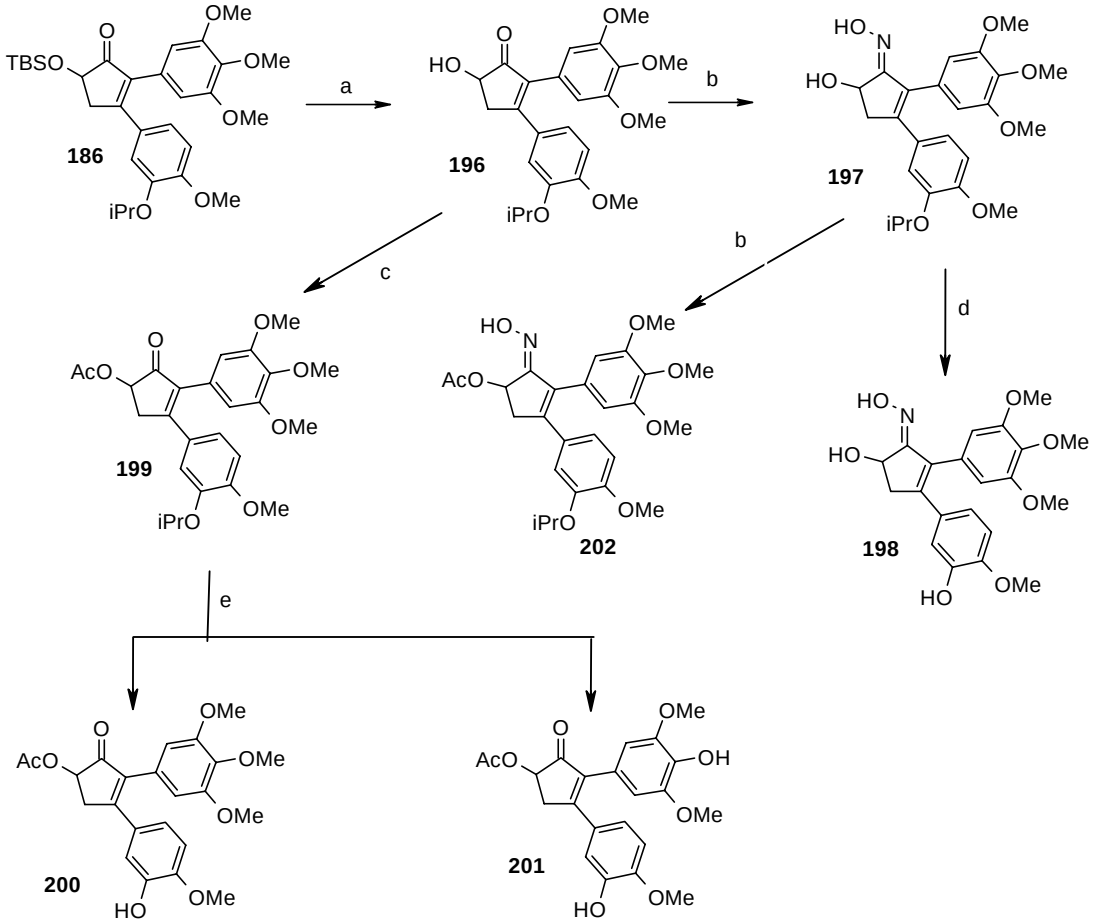
Further treatment of compound **183** with acetic acid, tetrahydrofuran and water at 50^0C provided 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one compound **192** in 84 % yield, which showed the absence of peaks of –OTBS group in NMR spectrum and presence of hydroxy absorption in IR spectrum. Compound **192** on acylation with acetic anhydride in dichloromethane using pyridine resulted in the acetate derivative **193** in 76 % yield, which on oxiamation using hydroxylamine hydrochloride in ethanol under reflux resulted in the oxime derivative **194** in 78 % yield. The IR spectrum of the compound **194** indicated the absence of carbonyl band. The acetate derivative **193** on oxiamation resulted in the compound **195** in 84 % isolated yield as shown in scheme 4.



Scheme 4

Reagents and conditions: a) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 84 % b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h c) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 76 %.

Similar simple organic transformations on compounds **184-191** were performed to achieve several analogues of this basic skeleton. Some of the transformations are outlined in scheme 4 to scheme 6, which efficiently availed the analogues for SAR studies.



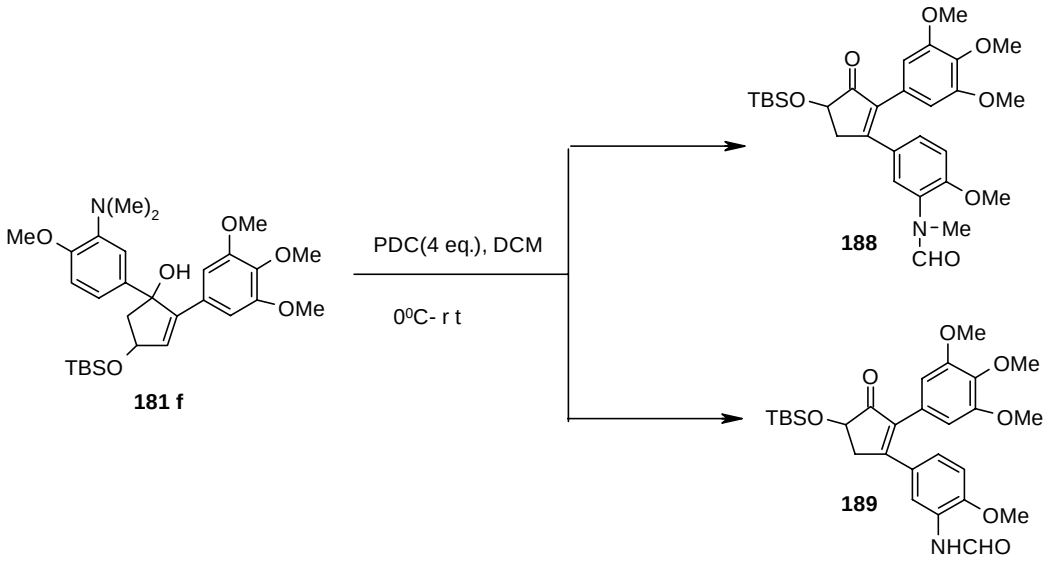
Scheme 5

Reagents and conditions: a) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 80 % b) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h c) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, r t, 15 h, 74 %. d) $AlCl_3$ (2 eq.), C_6H_6, 50^0C, 1 h, 66 % e) $AlCl_3$ (5 eq.), 50^0C, 6 h.

The cleavage of isopropyl group in compound **197** was achieved by treating it with 2 eq. aluminium chloride in benzene at 60^0C which led to the compound **198** in 66 % yield. Compound **197** on acylation with acetic anhydride in dichloromethane and pyridine afforded the acetate derivative **202** while the compound **196** on acylation with acetic anhydride and pyridine in dichloromethane afforded the acetate derivative **199**. The cleavage of isopropyl group in the compound **199** with excess of aluminium chloride afforded a mixture of two compounds. These

two compounds were isolated in pure form by column chromatography techniques. Their NMR and mass spectral studies revealed the presence of compounds **200** and **201**. Compound **201** was obtained due to partial demethylation in the presence of excess of aluminium chloride. NOESY spectral studies of this molecule further confirmed the proposed structure as **201**.

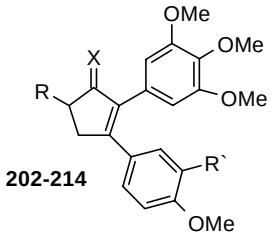
It is noteworthy that when 4-(tert-butyldimethylsilanyloxy)-1-(3-dimethylamino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (**181f**) was treated with pyridinium dichromate (4 equivalents) in dichloromethane at 0^0C it resulted in the formation of two products **188** and **189** where methyl groups were oxidized to aldehyde (scheme 6). The compound **188** showed the presence of one N-methyl and N-CHO (aldehyde) functionality which was indicated from PMR spectrum (N-CH_3 at δ 3.09 for 3 protons) and supported by ^{13}C NMR which showed a peak for carbonyl group at δ 205.14. The mass spectrum and microanalysis further confirmed the structure as **188**.



Scheme 6

In the ^{1}H NMR of compound **189**, peak for N-Me protons was absent whereas the ^{13}C NMR spectrum showed the peak for CHO (aldehyde) functionality at 205.09. IR spectrum of **189** showed two bands at 1674 cm^{-1} (CHO) and 1707 cm^{-1}(C=O). This observation coupled with the microanalysis and mass spectra confirmed the structure as **189**.

Table 2 exhibits other analogues synthesized similarly. All compounds showed satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra corresponding to their structures.

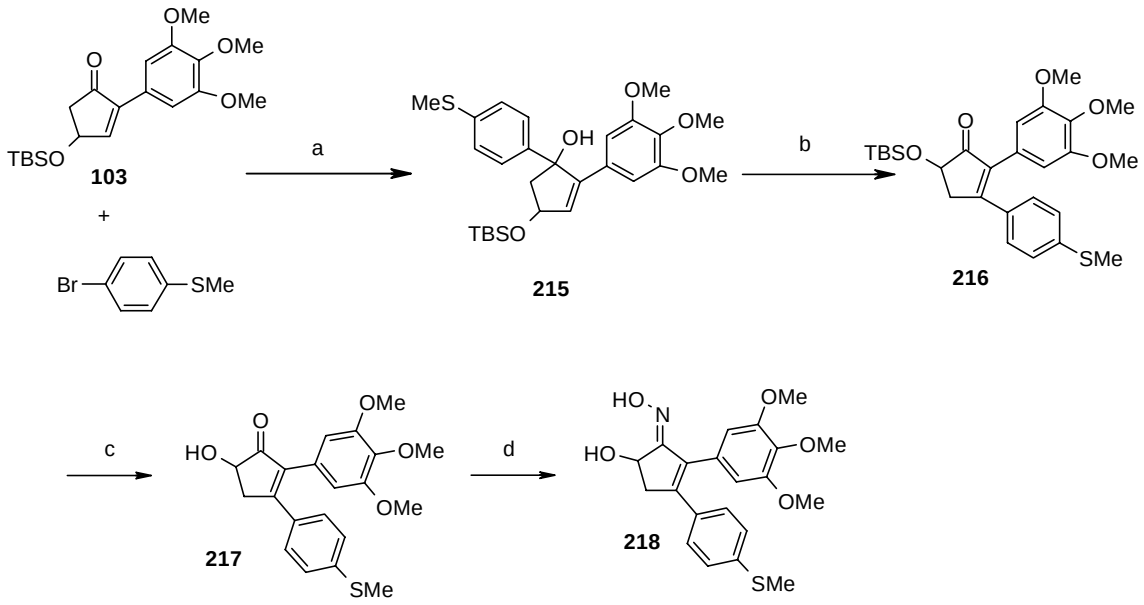


202-214

Table 2

Sr. No.	Compound No.	X	R	R`
1	**202**	O	OH	Cl
2	**203**	O	OAc	Cl
3	**204**	=N-OH	OH	Cl
4	**205**	=N-OH	OAc	Cl
5	**206**	O	OH	F
6	**207**	=N-OH	OH	F
7	**208**	O	OAc	F
8	**209**	O	OH	O-allyl
9	**210**	=N-OH	OH	O-allyl
10	**211**	O	OH	NHAc
11	**212**	O	OH	NHCOPh
12	**213**	O	OH	N(Me)(CHO)
13	**214**	O	OH	NHCHO

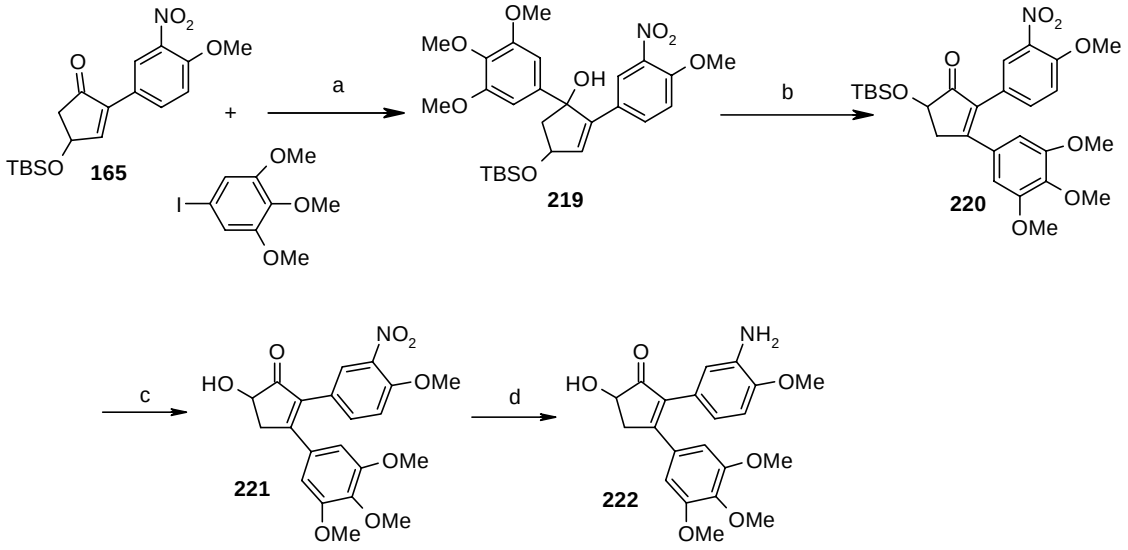
Grignard reaction of 4-bromothioanisole with the intermediate **103** in tetrahydrofuran at room temperature resulted in the compound **215** in 72 % yield. The compound **215** on treatment with pyridinium dichromate (2 equivalents) in dichloromethane resulted in the compound **216** in 46 % yield. Treatment of the compound **216** with acetic acid, tetrahydrofuran and water at 50^0C for 15 h provided the compound **217**. The oximation of the compound **217** using hydroxylamine hydrochloride and sodium acetate in ethanol under reflux resulted in the oxime derivative **218** in 82 % yield as shown in scheme 7.



Scheme 7

Reagents and conditions: a) Mg, THF, 0^0C-r t, 2 h, 72 % b) PDC (2 eq.), DCM, r t, 12 h, 46 % c) CH_3COOH-THF-H_2O (3:1:1), 50^0C, 20 h, 84 % d) $NH_2OH.HCl$, CH_3COONa, EtOH, reflux, 2 h.

It was felt necessary to interchange the substitution pattern in rings A and B for SAR studies and also to introduce electron-withdrawing group in one of the rings. We commenced the synthesis of such analogues as represented in scheme 8. The lithiation of 3,4,5-trimethoxyiodobenzene with n-butyllithium in tetrahydrofuran at -78^0C and treatment with intermediate **165** resulted in the compound **219**. The alcohol **219** on reaction with pyridinium dichromate (2 eq.) in dichloromethane at reflux gave the compound **220**. The cleavage of –OTBS group of the compound **220** was achieved using acetic acid, tetrahydrofuran and water at 50^0C to collect the compound **221** in high yield. The reduction of nitro group of compound **221** was accomplished using $SnCl_2.2H_2O$ at 0^0C in good yield leading to the compound **222**.



Scheme 8

Reagents and conditions: a) n-butyllithium, THF, -78^{0}C, 2 h, 40 % b) PDC (2 eq.), DCM, reflux, 18 h, 52 % c) CH_3COOH-THF-H_2O (3:1:1), 50^{0}C, 20 h, 76 % d) $SnCl_2.2H_2O$, DCM, 0^{0}C

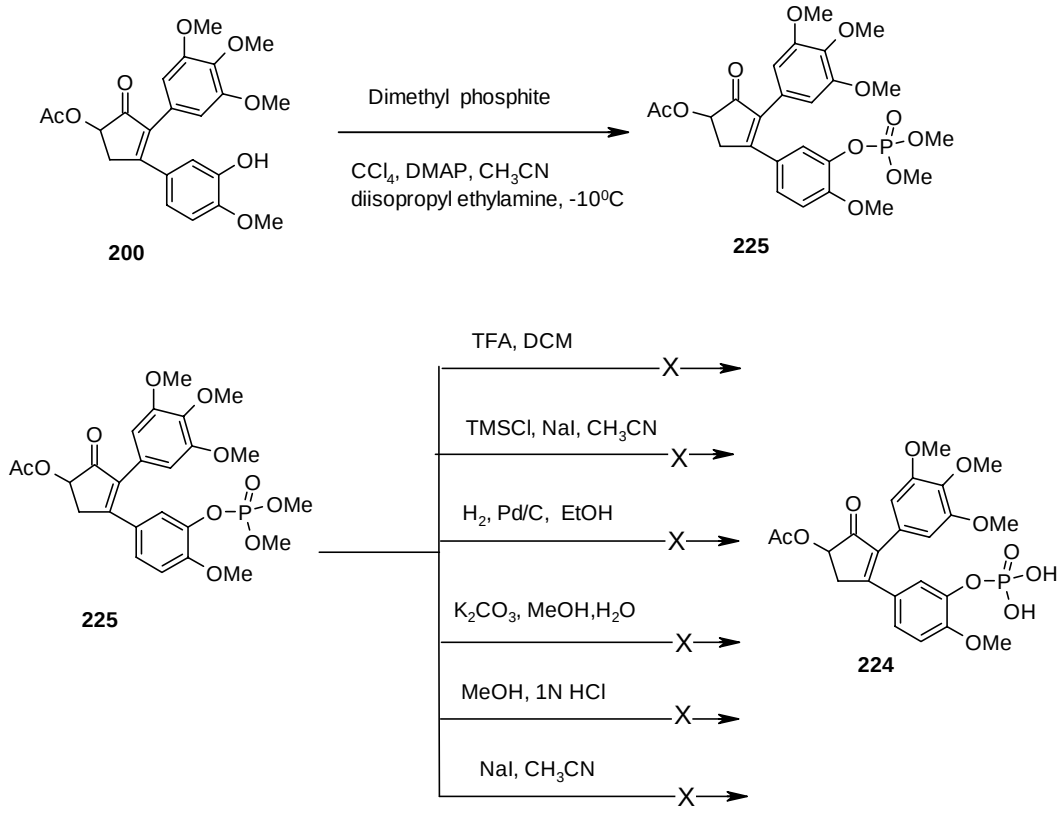
PART B:

Attempts towards improving aqueous solubility of CA-4 analogues:

Biological activity screening data indicated that some of the analogues showed promising anticancer activity. In order to further enhance the potent anticancer activity, one of the effective approach is to increase the water solubility of the molecules and make them more biocompatible. Therefore we tried to prepare phosphate derivatives of compound **200** as shown in scheme 9.

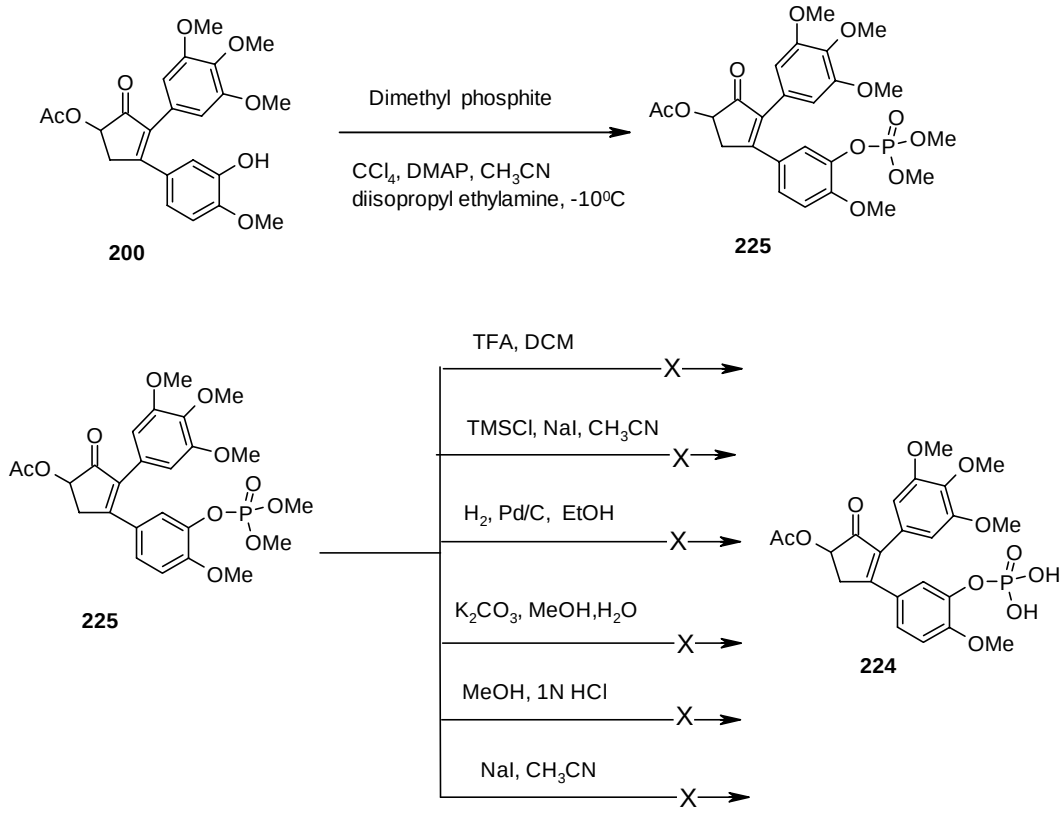
The required phoshphate ester derivative **223** was obtained by reaction of compound **200** with diphenyl phosphorochloridate using dimethylaminopyridine, carbontetrachloride, acetonitrile and diisopropyl ethylamine at –10^{0}C.

Deprotection of the compound **223** was attempted using various conditions to get the compound **224** however it refused to react further. Considering the difficulties faced in cleavage of



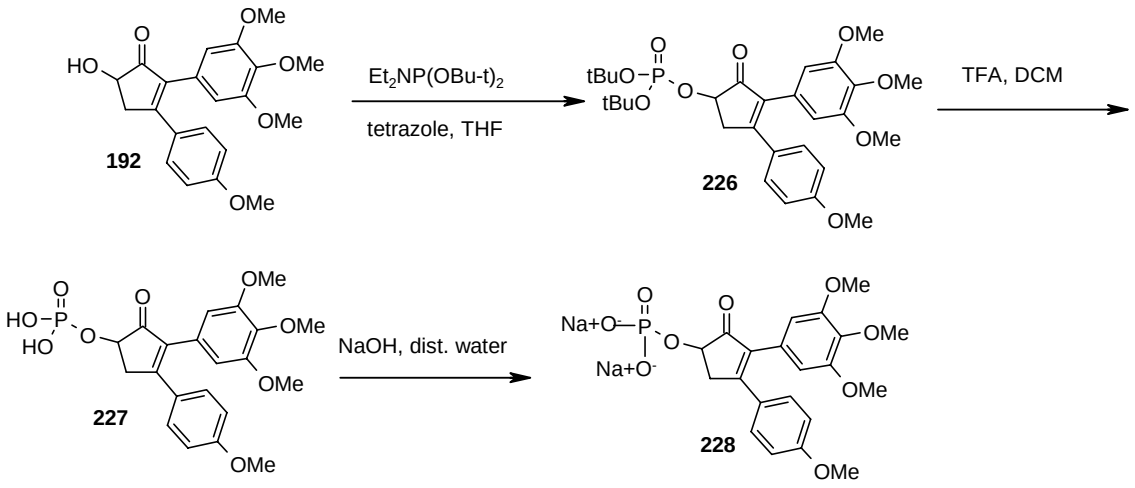
Scheme 9

compound **223**, we planned to make dimethylphosphate derivative **225**. Treatment of the compound **200** with dimethylphosphite, dimethylaminopyridine in carbontetrachloride, acetonitrile and diisopropyl ethylamine (Hunnings base) at -10^0C (scheme 10) smoothly converted it to the compound **225.** ^{31}P spectrum of compound **225** showed a peak at δ -3.46 which confirmed the formation of phosphate derivative. The derivative **225** was further subjected to hydrolysis using various conditions as shown in scheme 10, but the required compound **224** could not be obtained and the derivative **225** remained unreacted.



Scheme 10

The compounds **192** and **194** exhibited better cytotoxic activity than the parent combretastatin A-4 therefore we concentrated our attention to make phosphate derivatives of the compound **192**. In our continued efforts, the compound **192** was treated with di-tert-butyl N,N-diethyl phosphoramidite[16] and tetrazole in tetrahydrofuran (scheme 11) to get phosphate derivative **226**. The mass spectrum of this compound showed molecular ion peak at 564 (M+2) which confirmed the phosphate derivative formation. The hydrolytic cleavage of tert-butyl groups of compound **226** was achieved by treatment of compound **226** with trifluoroacetic acid in dichloromethane.[17] The product thus obtained showed molecular ion peak at 451 (M+1) and the absence of peaks for tert-butyl group in PMR spectrum which confirmed the formation of the compound **227**. The disodium salt of the compound **227** was prepared by treating the compound **227** with aqueous NaOH solution in distilled water to afford the compound **228**, which showed molecular ion peak at 495 (M+1) in its mass spectrum and confirmed the formation of compound **228**. The disodium salt of **227** (compound **228**) thus prepared was highly water soluble and it retained the cytotoxic activity of its parent molecule.



Scheme 11

1.2.3 CONCLUSION:

In conclusion, 2,3-diaryl-5-hydroxy-cyclopent-2-en-1-one analogues were synthesized successfully by the rearrangement of tertiary allylic alcohols using pyridinium dichromate using the same key intermediate which was employed for the Heck reaction approach for the synthesis of the molecules described in the Section 1. Various B-ring substituted analogues at 3-position of cyclopentenone were prepared by this method. Overall a library of 39 compounds of this category was created alongwith generation of their stectral and analytical data.

The water soluble phosphate and its disodium salt of the lead compound **192** were successfully prepared which retained the activity *in vitro*.

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1.2.4 EXPERIMENTAL:

4-(tert-Butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) cyclopent-2-enol (181a):

In 100 ml two neck round bottom flask, magnesium turnings (0.19 g, 7.93 mmol) were taken under nitrogen atmosphere. Dry tetrahydrofuran (30 ml) was added followed by dropwise addition of *p*-bromoanisole (1.48 g, 7.90 mmol) and 4-tert-butyldimetylsilyloxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2.00 g, 5.29 mmol). The reaction mixture was then stirred at room temperature for 2 h (TLC indicated the completion of reaction). It was then quenched with dilute hydrochloric acid (25 ml), tetrahydrofuran was removed under reduced

pressure, the reaction mixture was extracted with ethyl acetate (3 x 25 ml), washed with water, dried over sodium sulfate, concentrated and purified by column chromatography over silica gel (petroleum ether-acetone as eluent) to afford 4-(tert-butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (1.28 g, 52 %) as a thick liquid. **IR** ($\upsilon_{max,}$ $CHCl_3$): 1248, 1509, 1581, 2934, 2955, 3013, 3473 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.12 (s, 6 H), 0.93 (s, 9H), 2.22 (dd, *J* = 16 Hz and 6 Hz, 1H), 2.61 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.66 (s, 6H), 3.76 (s, 6 H), 4.85-4.90 (m, 1H), 6.23 (d, *J* = 2 Hz, 1H), 6.57 (s, 2H), 6.80 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ -4.78 (2C), 17.90, 25.70 (3C), 54.81, 55.54 (3C), 60.36, 73.26, 85.35, 104.80 (2C), 113.33 (2C), 125.71 (2C), 128.88, 131.23, 131.93, 137.22, 149.35, 152.44 (2C), 158.02; **Mass** (m/e): 485 (M^+); Anal. Calcd. For $C_{27}H_{38}O_6Si$: C 66.63; H 7.87; Si 5.77 %. Found: C 66.78; H 7.95; Si 5.80 %.

4-(tert-Butyldimethylsilanyloxy)-1-(3-chloro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (181b): Yield 37 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.19 (dd, *J* = 14 Hz and 4 Hz, 1H), 2.58 (dd, *J* = 14 Hz and 6 Hz, 1H), 2.83 (bs, 1H), 3.69 (s, 6H), 3.77 (s, 3H), 3.85 (s, 3H), 4.81-4.90 (m, 1H), 6.21 (d, *J* = 2 Hz, 1H), 6.59 (s, 2H), 6.79 (d, *J* = 8 Hz, 1H), 7.10 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.45 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$ + CCl_4): δ -5.30 (2C), 17.38, 25.17 (3C), 54.80, 55.02 (2C), 59.69 (2C), 72.70, 84.39, 104.38 (2C), 110.96, 121.62, 123.35, 126.25, 128.02, 129.38, 130.78, 138.05, 148.38, 151.95 (2C), 152.83; **Mass** (m/e): 521 (M^+).

4-(tert-Butyldimethylsilanyloxy)-1-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (181c): Yield 90 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.20 (dd, *J* = 14 Hz and 4 Hz, 1H), 2.60 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.68 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 4.85-4.90 (m, 1H), 6.24 (d, *J* = 2 Hz, 1H), 6.59 (s, 2H), 6.87 (d, *J* = 8 Hz, 1H), 7.00-7.20 (m, 3H); **Mass** (m/e): 504 (M^+).

4-(tert-Butyldimethylsilanyloxy)-1-(4-methylsulfanylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (215): Yield 72 %; Yellowish thick liquid; IR ($\upsilon_{max,}$ $CHCl_3$): 1507, 2931, 2955, 3015, 3468 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.14 (s, 6H), 0.94 (s, 9H), 2.23 (dd, *J* = 14 Hz and 4 Hz, 1H), 2.45 (s, 3H), 2.62 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.67 (s, 6H), 3.78 (s, 3H), 4.85-4.94 (m, 1H), 6.26 (d, *J* = 2 Hz, 1H), 6.58 (s, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.78 (2C), 15.63, 17.90, 25.70 (3C), 55.40, 55.58 (2C),

60.29, 73.30, 85.35, 105.09 (2C), 115.94, 125.16 (2C), 126.49 (2C), 128.77, 131.41, 136.26, 142.48, 148.98, 152.47 (2C); **Mass** (ESI): 502 (M^+).

4-(tert-Butyldimethylsilanyloxy)-1-(3-iso-propoxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (181d):

In a 100 ml two neck round bottom flask, 4-iodo-2-iso-propoxyanisole (1.94 g, 7.90 mmol) in dry tetrahydrofuran (20 ml) was stirred under nitrogen atmosphere at -78^0C and n-butyllithium (3.45 ml, 2.3 M solution, 7.90 mmol) was added dropwise. The reaction mixture was stirred at -78^0C for 1.5 h., 4-tert-butyldimethylsilyloxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (2.00 g, 5.29 mmol) in dry tetrahydrofuran (10 ml) was added and the reaction mixture was stirred at -78^0C for 12 h. It was then quenched with saturated ammonium chloride solution (30 ml), tetrahydrofuran was removed under reduced pressure, extracted with dichloromethane (3 x 50 ml), washed with water followed by brine, dried over sodium sulfate, concentrated and purified by column chromatography over silica gel (petroleum ether-acetone) to afford the 4-(tert-butyldimethylsilanyloxy)-1-(3-iso-propoxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (1.28 g, 45 %) as a reddish thick liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 1215, 3019, 3300 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.11 (s, 6H), 0.92 (s, 9H), 1.19-1.30 (m, 6H), 2.18 (dd, *J* = 8 Hz and 4 Hz, 1H), 2.58 (dd, *J* = 8 Hz and 6 Hz, 1H), 2.77 (bs, 1H), 3.65 (s, 6H), 3.75 (s, 3H), 3.79 (s, 3H), 4.34-4.47 (m, 1H), 4.81-4.90 (m, 1H), 6.20 (d, *J* = 2 Hz, 1H), 6.57 (s, 2H), 6.75 (d, *J* = 8 Hz, 1H), 6.84-6.92 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CCl_4): δ -4.53 (2C), 17.71, 21.53, 25.54 (3C), 30.17, 55.35 (4C), 60.05, 70.86, 73.14, 84.98, 104.90 (2C), 111.41, 113.35, 117.32, 129.01 (2C), 130.92, 137.91 (2C), 146.58, 149.16, 152.28 (2C); **Mass** (m/e): 544 (M^+).

4-(tert-Butyldimethylsilanyloxy)-1-(3-dimethylamino-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (181f): Yield 58 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.12 (s, 6H), 0.92 (s, 9H), 2.19 (dd, *J* = 18 Hz and 4 Hz, 1H), 2.63 (dd, *J* = 18 Hz and 6 Hz, 1H), 2.72 (s, 6H), 3.64 (s, 6H), 3.75 (s, 3H), 3.82 (s, 3H), 4.83-4.91 (m, 1H), 6.20 (d, *J* = 2 Hz, 1H), 6.55 (s, 2H), 6.71 (d, *J* = 8 Hz, 1H), 6.81 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.09 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.09 (2C), 18.18, 25.97 (3C), 26.85, 43.25 (2C), 55.19, 55.67 (2C), 60.49, 73.61, 85.44, 105.04 (2C), 110.84, 114.96, 118.78, 129.37, 131.10, 137.71, 138.04, 141.79, 149.55, 150.84, 152.56 (2C); **Mass** (m/e): 529 (M^+).

1-(3-Allyloxy-4-methoxyphenyl)-4-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (181e):

Yield 68 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.13 (s, 6H), 0.94 (s, 9H), 2.10-2.25 (m, 1H), 2.58 (dd, *J* = 14 Hz and 6 Hz, 1H), 2.65 (bs, 1H), 3.68 (s, 6H), 3.78 (s, 3H), 3.85 (s, 3H), 4.55 (dd, *J* = 8 Hz and 2 Hz, 2H), 4.81-4.90 (m, 1H), 5.18-5.39 (m, 2H), 5.92-6.04 (m, 1H), 6.23 (d, *J* = 4 Hz, 1H), 6.57 (s, 2H), 6.73-6.88 (m, 2H), 6.97 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 542 (M^+).

4-(tert-Butyldimethylsilanyloxy)-2-(4-methoxy-3-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (219): Yield 40 %; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1531, 2955, 3019, 3405 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.14 (s, 6H), 0.94 (s, 9H), 1.58 (bs, 1H), 2.21 (dd, *J* = 14 Hz and 2 Hz, 1H), 2.65 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.79 (s, 6H), 3.82 (s, 3H), 3.91 (s, 3H), 4.86-4.93 (m, 1H), 6.34 (d, *J* = 2 Hz, 1H), 6.55 (s, 2H), 6.88 (d, *J* = 8 Hz, 1H), 7.50 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.02 (d, *J* = 2 Hz, 1H); **Mass** (ESI): 531 (M^+).

N-{5-[4-(tert-Butyldimethylsilanyloxy)-1-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enyl]-2-methoxyphenyl}-benzamide (181h): Yield 54 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.05 (s, 6H), 0.84 (s, 9H), 2.15 (dd, *J* = 14 Hz and 2 Hz, 1H), 2.64 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.60 (s, 6H), 3.65 (s, 3H), 3.81 (s, 3H), 4.82-4.92 (m, 1H), 6.15 (d, *J* = 2 Hz, 1H), 6.59 (s, 2H), 6.73 (d, *J* = 8 Hz, 1H), 7.13 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.28-7.45 (m, 3H), 7.72-7.80 (m, 2H), 8.37 (bs, 1H); **Mass** (ESI): 605 (M^+); Anal. Calcd. For $C_{34}H_{43}NO_7Si$: C 67.41; H 7.15; N 2.31; Si, 4.64 %. Found: C 67.65; H 7.28; N 2.44; Si, 4.86 %.

N-{5-[4-(tert-Butyldimethylsilanyloxy)-1-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enyl]-2-methoxyphenyl}-acetamide (181g): Yield 46 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.16 (s, 6H), 0.92 (s, 9H), 2.17 (s, 3H), 2.20-2.40 (m, 1H), 2.58-2.75 (m, 1H), 3.69 (s, 6H), 3.76 (s, 3H), 3.84 (s, 3H), 4.78-5.00 (m, 1H), 6.23 (d, *J* = 4 Hz, 1H), 6.64 (s, 2H), 6.77 (d, *J* = 8 Hz, 1H), 7.05-7.20 (m, 1H), 7.68 (s, 1H), 8.26 (s, 1H); **Mass** (m/e): 541 (M^+).

Preparation of 5-(tert-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxy phenyl)-cyclopent-2-en-1-one (183):

In a 50 ml two neck round bottom flask, 4-(tert-butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-enol (1.15 g, 2.36 mmol) was taken in dry dichloromethane (20 ml) and cooled to 0^0C. Pyridinium dichromate (1.73 g, 7.38 mmol) was then added and allowed to stir at same temperature for 1 h and then stirred at room temperature for 10

h. It was then filtered through celite (2.00 g) and washed with water (2 x 10 ml) followed by brine (5 ml), dried over sodium sulfate, concentrated on rotary evaporator and column purified using silica gel (2-5 % acetone in pet ether) to afford the 5-(tert-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.52 g, 45 %) as a yellowish solid.

M. p. 104-106 ^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1255, 1280, 1581, 1712, 2933, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.22 (s, 6H), 0.96 (s, 9H), 2.94 (dd, *J* = 16 Hz and 4 Hz, 1H), 3.30 (dd, *J* = 16 Hz and 8 Hz, 1H), 3.71 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 4.45-4.52(m 1H), 6.44 (s, 2H), 6.78 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$ + CCl_4): δ -5.23, -4.49, 18.26, 25.72 (3C), 39.29, 55.02, 55.75 (2C), 60.53, 72.44, 106.30 (2C), 113.57 (2C), 127.14, 127.95, 130.12 (2C), 135.44, 137.54, 153.16 (2C), 161.10, 162.43, 204.88; **Mass** (m/e): 484 (M^+); Anal. Calcd. For $C_{27}H_{36}O_6Si$: C 66.91; H 7.49; Si 5.79 %. Found: C 66.98; H 7.52; Si 5.83 %.

5-(tert-Butyldimethylsilanyloxy)-3-(3-chloro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (184): Yield 34 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.21 (s, 6H), 0.96 (s, 9H), 2.90 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.26 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.84 (s, 3H), 3.90 (s, 3H), 4.44-4.50 (m, 1H), 6.41 (s, 2H), 6.75 (d, *J* = 8 Hz, 1H), 7.19 (dd *J* = 8 Hz and 2 Hz, 1H), 7.46 (d, *J* = 2 Hz, 1H); **Mass** (m/e): 519 (M^+).

5-(tert-Butyldimethylsilanyloxy)-3-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (185): Yield 48 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.19 (s, 6H), 0.94 (s, 9H), 2.89 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.27 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.71 (s, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 4.45-4.57 (m, 1H), 6.41 (s, 2H), 6.78-6.89 (m, 1H), 7.15 (d, *J* = 2 Hz, 1H), 7.16 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.40, -4.63, 18.12, 25.55 (3C), 39.08, 55.69 (3C), 60.40, 72.27, 106.23 (2C), 112.41, 115.53, 115.90, 124.98, 127.19 (2C), 136.34 (2C), 149.13, 153.17 (2C), 159.46, 204.56; **Mass** (m/e): 502 (M^+), 445 (100), 414 (16).

5-(tert-Butyldimethylsilanyloxy)-3-(4-methylsulfanylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (216): Yield 46 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.23 (s, 6H), 0.98 (s, 9H), 2.48 (s, 3H), 2.96 (dd, *J* = 16 Hz and 4 Hz, 1H), 3.30 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.86 (s, 3H), 4.45-4.60 (m, 1H), 6.44 (s, 2H), 7.13 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.23, -4.53, 14.70, 18.22, 25.69 (3C), 39.25, 55.83 (2C),

60.57, 72.84, 106.44 (2C), 125.12 (2C), 127.01, 128.57(2C), 131.11, 136.40, 137.80, 142.06, 153.16 (2C), 162.13, 204.92; **Mass** (m/e): 500 (M^+).

5-(tert-Butyldimethylsilanyloxy)-3-(3-isopropoxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (186): Yield 79 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.21 (s, 6H), 0.96 (s, 9H), 1.13 (d, *J* = 6 Hz, 3H), 1.16 (d, *J* = 6 Hz, 3H), 2.92 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.33 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 4.01-4.06 (m, 1H), 4.45-4.50 (m, 1H), 6.41 (s, 2H), 6.80 (d, *J* = 8 Hz, 1H), 6.83 (d, *J* = 2 Hz, 1H), 7.08 (dd, *J* = 8Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CCl_4): δ -5.19, -4.42, 18.30, 21.61, 21.75, 25.76 (3C), 39.07, 55.61, 55.79 (2C), 60.46, 71.05, 106.33 (2C), 111.04, 115.71, 121.62, 127.21, 128.39, 135.78, 137.65, 146.51, 152.17, 153.42 (2C), 162.39, 204.77, 205.00**; Mass** (m/e): 542 (M^+).

5-(tert-Butyldimethylsilanyloxy)-2-(4-methoxy-3-nitrophenyl)-3-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (220): Yield 52 %; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.23 (s, 6H), 0.97 (s, 9H), 2.95 (bd, *J* = 18 Hz, 1H), 3.30 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.68 (s, 6H), 3.88 (s, 3H), 3.96 (s, 3H), 4.45-4.60 (m, 1H), 6.57 (s, 2H), 7.06 (d, *J* = 8 Hz, 1H), 7.47 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.80 (d, *J* = 2 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -3.52, -4.57, 18.19, 25.65 (3C), 39.76, 56.01 (2C), 56.08, 60.68, 72.52, 106.15 (2C), 113.43, 126.40, 129.60, 133.86, 135.08, 139.98 (2C), 152.13 (2C), 153.13 (2C), 164.04, 206.04. **Mass** (ESI): 529 (M^+).

N-{5-[4-(tert-Butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxyphenyl}-formamide (189): Yield 32 %; m. p. 68-70^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1216, 1583, 1674, 1707, 2935, 2954, 3017 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.20 (s, 6H), 0.94 (s, 9H), 3.04 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.35 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.71 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 4.44-4.54 (m, 1H), 6.41 (s, 2H), 6.72 (d, *J* = 10 Hz, 1H), 7.02 (dd, *J* = 10 Hz and 2 Hz, 1H), 7.81 (s, 1H), 8.46 (s, 1H), 8.54 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.38, -4.72, 18.07, 25.49 (3C), 39.17, 55.63 (3C), 60.41, 72.36, 106.14 (2C), 109.30, 119.81, 125.36, 126.50, 127.68, 129.15, 136.06, 137.35, 148.93, 152.97 (2C), 158.81, 162.75, 205.09; **Mass** (ESI) 527 (M^+).

N-{5-[4-(tert-Butyldimethylsilanyloxy)-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxyphenyl}-N-methyl-formamide (188): Yield 25 %; m. p. 60-62^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$):

1583, 1678, 1706, 2857, 2935, 3014 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.20 (s, 6H), 0.94 (s, 9H), 2.94 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.06 (s, 3H), 3.29 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.72 (s, 6H), 3.83 (s, 3H), 3.84 (s, 3H), 4.46-4.55 (m, 1H), 6.40 (s, 2H), 6.87 (d, *J* = 8 Hz, 1H), 7.13 (d, *J* = 2 Hz, 1H), 7.37 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.37, -4.68, 18.08, 25.54 (3C), 32.27, 38.92, 55.53, 55.72 (2C), 60.50, 72.26, 106.11 (2C), 111.48, 127.36 (2C), 127.76, 129.16, 130.12, 136.33, 137.69, 153.16 (2C), 155.96, 160.95, 162.76, 204.66; **Mass** (m/e): 541 (M^+); Anal. Calcd. For $C_{29}H_{39}NO_7Si$: C 64.30; H 7.26; N 2.59; Si, 5.18 %. Found: C 64.57; H 7.51; N 2.32; Si, 5.39 %.

3-(3-Allyloxy-4-methoxyphenyl)-5-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (187): Yield: 56 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 0.21 (s, 6H), 0.95 (s, 9H), 2.92 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.33 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.73 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 4.24 (d, *J* = 4 Hz, 2H), 4.46-4.55 (m, 1H), 5.11-5.23 (m, 2H), 5.70-5.91 (m, 1H), 6.43 (s, 2H), 6.78-6.88 (m, 2H), 7.09 (dd, *J* = 8 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.56, -4.79, 17.89, 25.39 (3C), 38.70, 55.28, 55.50 (2C), 60.13, 68.84, 72.07, 106.11 (2C), 110.45, 113.43, 117.18, 121.51, 126.73, 127.95, 132.17, 135.37, 137.32, 146.77, 150.96, 152.98 (2C), 161.95, 204.40; **Mass** (m/e): 540 (M^+).

5-Hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (192):

In a 50 ml round bottom flask, 5-(tert-butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.950 g, 2.47 mmol) was taken and to this a mixture of acetic acid, tetrahydrofuran and water (3:1:1) (20 ml) was added and heated at 50^0C for 20 h (reaction monitored by TLC). The reaction mixture was then cooled to 0^0C and neutralized by adding sodium bicarbonate and then extracted with chloroform (3 x 20 ml). The organic layer was washed with water followed by brine and dried over sodium sulfate. The solvent was removed under reduced pressure using rotary evaporator. The crude residue obtained was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect the pure 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.610 g, 84 %) as yellowish solid.

M.p. 205 ^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1215, 1504, 1602, 1697, 3019, 3434 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+ CCl_4): δ 3.06 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.38 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 4.48-4.58 (m, 1H), 6.45 (s, 2H), 6.87 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 38.38, 55.55, 56.24 (2C), 61.06, 72.12, 106.57 (2C), 114.06 (2C), 127.96, 127.69, 130.72 (2C), 135.38, 138.07, 153.73 (2C), 161.78,

164.68, 207.47; **Mass** (m/e): 370 (M^+); Anal. Calcd. For $C_{21}H_{22}O_6$: C 68.10; H 5.99 %. Found: C 68.18; H 6.12 %.

3-(3-Chloro-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (202): Yield 82 %; m. p. 170^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.96 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.33 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.86 (s, 3H), 3.91 (s, 3H), 4.45-4.54 (m, 1H), 6.42 (s, 2H), 6.81 (d, *J* = 8 Hz, 1H), 7.21-7.29 (m, 1H), 7.48 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CCl_4): δ 37.79, 55.87 (2C), 60.58, 71.57, 106.23 (2C), 111.31, 122.41, 126.82, 127.59, 128.58 (2C), 130.05, 135.90, 138.07, 153.36 (2C), 156.48, 162.51, 206.95; **Mass**(m/e): 404 (M^+); Anal. Calcd. For $C_{21}H_{21}ClO_6$: C 62.30; H 5.23; Cl 8.76 %. Found: C 62.42; H 5.38; Cl 8.86 %.

3-(3-Fluoro-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (206): Yield 70 %; m. p. 178^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.93 (dd, *J* = 16 Hz and 4 Hz, 1H), 3.30 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.70 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 4.45-4.60 (m, 1H), 6.40 (s, 2H), 6.78-6.91 (m, 1H), 7.00-7.20 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.86, 55.84 (2C), 60.58, 71.50, 106.16 (2C), 112.56, 115.72, 116.12, 125.35, 127.00 (2C), 136.01, 137.92, 149.28, 149.50, 153.32 (2C), 162.80, 207.17; **Mass** (m/e): 388 (M^+, 100), 373 (37).

5-Hydroxy-3-(4-methylsulfanylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (217): Yield 87 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.46 (s, 3H), 2.63 (bs, 1H), 3.02 (dd, *J* = 20 Hz and 4 Hz, 1H), 3.37 (dd, *J* = 20 Hz and 6 Hz, 1H), 3.73 (s, 6H), 3.87 (s, 3H), 4.50-4.56 (m, 1H), 6.43 (s, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.88, 38.07, 56.08 (2C), 60.86, 72.00, 106.41 (2C), 125.26 (2C), 127.32, 128.87 (2C), 130.85, 136.11, 138.09, 142.87, 153.53 (2C), 164.04, 207.05; **Mass** (m/e): 386 (M^+).

5-Hydroxy-2-(4-methoxy-3-nitrophenyl)-3-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (221): Yield 76 %; semisolid; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.02 (bd, *J* = 16 Hz, 1H), 3.27 (dd, *J* = 16 Hz and 6 Hz, 1H) 3.68 (s, 6H), 3.88 (s, 3H), 3.97 (s, 3H), 4.53 (bs, 1H, D_2O exchangeable), 5.28-5.30 (m, 1H), 6.59 (s, 2H), 7.07 (d, *J* = 8 Hz, 1H), 7.45 (bd, *J* = 8 Hz, 1H), 7.79 (bs, 1H); **Mass** (ESI): 415 (M^+); Anal. Calcd. For $C_{21}H_{21}NO_8$: C 60.72; H 5.10; N 3.37 %. Found: C 60.91; H 5.32; N 3.57 %.

2-(3-Amino-4-methoxyphenyl)-5-hydroxy-3-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (222): In a 50 ml two neck round bottom flask, 5-hydroxy-2-(4-methoxy-3-nitrophenyl)-3-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(221)** (0.100 g, 0.24 mmol) was dissolved in dichloromethane (5 ml) and cooled to 0^0C, then stannic chloride dihydrate ($SnCl_4.2H_2O$) (0.085 g, 0.28 mmol) was added through syringe, the reaction mixture was stirred further for 2 h, then poured over ice and extracted with dichloromethane (3 x 10 ml), the organic layer was washed with water followed by brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue on column chromatographic purification afforded the compound **222** (0.063 g, 68 %) as yellowish semisolid.

Yield 68 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.98 (bd, *J* = 14 Hz, 1H), 3.31 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.65 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 4.47-4.53 (m, 1H), 6.65-6.76 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.11, 55.61, 55.94 (2C), 60.86, 71.93, 106.30 (2C), 110.67, 116.18, 120.23, 124.90, 130.04, 135.04, 136.65, 140.11, 147.58, 152.79 (2C), 163.49, 207.67; **Mass** (ESI): 386 (M^{+1}); Anal. Calcd. For $C_{21}H_{23}NO_6$,: C 65.44; H 6.02; N 3.63 %. Found: C 65.58; H 6.11; N 3.70 %.

3-(3-Allyloxy-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (209): Yield 76 %; m. p. 160^0C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1216, 1262, 1583, 1698, 2855, 2929, 3019, 3439 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.02 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.39 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.76 (s, 6H), 3.86 (s, 3H), 3.91 (s, 3H), 4.27 (d, *J* = 4 Hz, 2H), 4.50-4.59 (m, 1H), 5.14-5.26 (m, 2H), 5.73-5.91 (m, 1H), 6.46 (s, 2H), 6.81-6.92 (m, 2H), 7.13 (dd, *J* = 8 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.76, 55.96, 56.18 (2C), 60.85, 69.53, 71.81, 106.69 (2C), 111.14, 114.04, 117.97, 122.53, 127.09, 128.30, 132.71, 135.62, 138.04, 147.42, 151.90, 153.74 (2C), 164.80, 207.74; **Mass** (ESI): 426 (M^+); Anal. Calcd. For $C_{24}H_{26}O_7$: C 67.59; H 6.15 %. Found: C 67.71; H 6.24 %.

N-{5-[4-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxyphenyl}-benzamide (212): Yield 54 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.57 (dd, *J* = 16 Hz and 2 Hz, 1H), 2.97 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.33 (s, 6H), 3.40 (s, 3H), 3.54 (s, 3H), 4.00-4.09 (m, 1H), 6.04 (s, 2H), 6.44 (d, *J* = 8 Hz, 1H), 6.69 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.06-7.15 (m, 3H), 7.46 (d, *J* = 8 Hz, 2H), 8.18 (bs, 1H), 8.30 (s, 1H); **Mass** 489 (M^+); Anal. Calcd. For $C_{28}H_{27}NO_7$: C 68.70; H 5.56; N 2.86 %. Found: C 68.87; H 5.71; N 2.98 %.

N-{5-[4-Hydroxy-3-oxo-2-(3,4,5-trimethoxyphenyl)-cyclopent-1-enyl]-2-methoxyphenyl}-acetamide (211): Yield 79 %; m. p. 191-192^{0}C; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.21 (s, 3H), 3.03(dd, *J* = 18 Hz and 2 Hz, 1H), 3.45 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.75 (s, 6H), 3.86 (s, 3H), 3.90 (s, 3H), 4.45-4.55 (m, 1H), 6.43 (s, 2H), 6.72 (d, *J* = 8 Hz, 1H), 6.95-7.10 (m, 1H), 7.69 (bs, 1H), 8.59 (bs, 1H); **Mass** (m/e): 427 (M^+); Anal. Calcd. For $C_{23}H_{25}NO_7$: C 64.63; H 5.90; N 3.28 %. Found: C 64.85; H 5.98; N 3.49 %.

5-Hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (194):

In a 50 ml single neck round bottom flask, a mixture of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.18 g, 0.60 mmol), hydroxyl amine hydrochloride (0.06 g, 0.90 mmol) and sodium acetate (0.075 g, 0.90 mmol) in ethanol (8 ml) was refluxed on water bath for 3 h. The reaction was monitored by TLC and after completion of reaction, the solvent was removed under reduced pressure using rotary evaporator. The residue was extracted with chloroform, the organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect the pure 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (0.146 g, 78 %) as a yellowish solid.

M. p. 178 ^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1256, 1504, 1603, 2939, 3017, 3279 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.97 (bd, *J* = 18 Hz, 1H), 3.33 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.79 (s, 3H), 3.89 (s, 3H), 5.29-5.37 (m, 1H), 6.45(s, 2H), 6.76 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 40.72, 55.02, 55.90 (2C), 60.75, 67.19, 106.44 (2C), 113.46 (2C), 127.43, 128.94, 129.71 (2C), 131.07, 137.54, 149.12, 153.31 (2C), 159.85, 168.49; **Mass** (m/e): 385 (M^+); Anal. Calcd. For $C_{21}H_{23}NO_6$: C 65.44; H 6.02; N, 3.63 %. Found: C 65.38; H 5.92 N, 3.68 %.

3-(3-Chloro-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (203): Yield 82 %; m. p. 96^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.92 (bd, *J* = 18 Hz, 1H), 3.26 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.76 (s, 6H), 3.88 (s, 6H), 5.25-5.34 (m, 1H), 6.43 (s, 2H), 6.74 (d, *J* = 8 Hz, 1H), 7.06 (bd, *J* = 8 Hz, 1H), 7.27 (bs, 1H); **Mass** (m/e): 419 (M^+).

3-(3-Fluoro-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (207): Yield 74 %; m. p. 167-168^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.90 (bd, *J*

=16 Hz, 1H), 3.25 (dd, *J* = 16 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 5.15-5.40 (m, 1H), 6.42 (s, 2H), 6.72-6.85 (m, 1H), 6.85-7.05 (m, 2H); **Mass** (m/e) 403 (M^+); Anal. Calcd. For $C_{21}H_{22}FNO_6$: C 62.52; H 5.50; F 4.71; N 3.47 %. Found: C 62.74; H 5.68; F 4.84; N 3.67 %.

5-Hydroxy-3-(4-methylsulfanylphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (218): Yield 63 %; m. p. 167-168^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.45 (s, 3H), 2.97 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.33 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.75 (s, 6H), 3.89 (s, 3H), 5.25-5.35 (m, 1H), 6.43 (s, 2H), 7.07 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H); **Mass** (m/e): 401 (M^+); Anal. Calcd. For $C_{21}H_{23}NO_5S$: C 62.82; H 5.77; N 3.49; S 7.99 %. Found: C 62.98; H 5.87; N 3.68; S 8.08 %.

Preparation of 5-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (198):

In a 50 ml two neck round bottom flask with reflux condensor and two way stopcock, a mixture of the compound **197** (0.30 g, 0.67 mmol), aluminium chloride (0.180 gm, 1.35 mmol) and benzene (10 ml) was stirred at 50^{0}C under argon atmosphere. It was then cooled and quenched with cold dilute hydrochloric acid (10 ml) and extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with water (2 x 15 ml) followed by brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by column chromatography afforded pure compound **198** (0.180 g, 66 %).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.94 (bd, *J* = 18 Hz, 1H), 3.32 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.76 (s, 6H), 3.88 (s, 6H), 5.29-5.40 (m, 1H), 6.44 (s, 2H), 6.65-6.75 (m, 2H), 6.84 (bs, 1H); **Mass** (m/e): 401 (M^+); Anal. Calcd. For $C_{21}H_{23}NO_7$: C 62.83; H 5.78; N 3.49 %. Found C 62.98; H 5.85; N 3.64 %.

5-Hydroxy-3-(3-isopropoxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (205): Yield 76 %; m. p. 89-90^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 1.13 (d, *J* = 6 Hz, 3H), 1.17 (d, *J* = 6 Hz, 3H), 2.96 (bd, *J* = 18 Hz, 1H), 3.31 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.76 (s, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 3.90-4.15 (m, 1H), 5.25-5.40 (m, 1H), 6.46 (s, 2H), 6.65-6.85 (m, 2H), 6.86-6.95 (m, 1H); **Mass** (ESI): 443 (M^+); Anal. Calcd. For $C_{24}H_{29}NO_7$: C 65.00; H 6.59; N 3.16 %. Found: C 65.18; H 6.81; N 3.25 %.

5-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (193):
In a 50 ml two neck round bottom flask, a solution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.150 g, 0.40 mmol) in dichloromethane (6 ml) was cooled to 0°C under inert atmosphere. To the cold solution, dry pyridine (0.038 gm, 0.48 mmol) was added and stirred at 0°C for 10 min. To the stirred solution, acetic anhydride (0.05 g, 0.048 mmol) was added dropwise while maintaining the temperature below 0°C. The reaction mixture was stirred at room temperature for 15 h (monitored by TLC) and then quenched by adding cold, dilute hydrochloric acid. The organic layer was washed three times with water, 10% sodium bicarbonate solution and finally with brine. The organic layer was dried over sodium sulfate and concentrated to dryness under reduced pressure using a rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect the pure 5-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.142 gm, 76 %) as a semisolid.
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.21 (s, 3H), 2.96 (bd, *J* = 18 Hz, 1H), 3.51 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.75 (s, 6H), 3.84 (s, 3H), 3.88 (s, 3H), 5.40-5.45 (m, 1H), 6.46 (s, 2H), 6.82 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H); **Mass** (m/e): 412 (M^+); Anal. Calcd. For $C_{23}H_{24}O_7$: C 66.98; H 5.87 %. Found: C 67.08; H 5.98 %.

5-Acetoxy-3-(3-chloro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (203): Yield 75 %; m. p. 72^{0}C; **^{1}HNMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.21 (s, 3H), 2.95 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.49 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.76 (s, 6H), 3.88 (s, 3H), 3.92 (s, 3H), 5.38-5.44 (m, 1H), 6.45 (s, 2H), 6.81 (d, *J* = 10 Hz, 1H), 7.25 (bd, *J* = 10 Hz, 1H), 7.47 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CCl_4): δ 20.69, 36.31, 56.08 (2C), 60.75, 71.89, 106.59 (2C), 111.84, 122.84, 126.70, 127.00, 128.72 (2C), 130.19, 137.06, 138.46, 153.57 (2C), 156.76, 161.58, 170.22, 200.76; **Mass** (m/e): 446 (M^+).

5-Acetoxy-3-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (208): Yield 78 %; m. p. 66-67^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.19 (s, 3H), 2.93 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.45 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.86 (s, 3H), 3.89 (s, 3H), 5.30-5.55 (m, 1H), 6.43 (s, 2H), 6.80-6.90 (m, 1H), 7.05-7.25 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.48, 36.06, 55.84 (2C), 60.58, 71.72, 106.16 (2C), 112.56, 115.59, 116.05, 125.05, 126.63 (2C), 136.85 (2C), 137.96, 149.39, 153.32 (2C), 161.99, 170.30, 200.99; **Mass** (m/e): 430 (M^+)

5-Acetoxy-3-(3-isopropoxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (199): Yield 72 %; m. p. 89^0C; **^{1}H-NMR** ($CDCl_3$ + CCl_4): δ 1.17 (d, *J* = 6 Hz, 6H), 2.21 (s, 3H), 2.96 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.56 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.77 (s, 6H), 3.85 (s, 3H), 3.88 (s, 3H), 4.00-4.10 (m, 1H), 5.39-5.45 (m, 1H), 6.46 (s, 2H), 6.83 (d, *J* = 8 Hz, 1H), 6.87 (d, *J* = 2 Hz, 1H), 7.09 (dd, *J* = 8 Hz and 2 Hz, 1H); **Mass** (m/e): 470 (M^+); Anal. Calcd. For $C_{26}H_{30}O_8$: C 66.37; H 6.43 %. Found: C 66.37; H 6.43 %.

5-Acetoxy-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (200): Yield 32 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.19 (s, 3H), 2.95 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.48 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.85 (s, 3H), 3.89 (s, 3H), 5.35-5.45 (m, 1H), 6.45 (s, 2H), 6.73 (d, *J* = 8 Hz, 1H), 6.80-7.00 (m, 2H); **Mass** (m/e): 428 (M^+); Analysis calculated for $C_{23}H_{24}O_8$: C 64.48; H 5.65 %. Found: C 64.65; H 5.78 %.

5-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (195): Yield: 84 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.17 (s, 3H), 2.80 (bd, *J* = 18 Hz, 1H), 3.46 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.75 (s, 6H), 3.78 (s, 3H), 3.87 (s, 3H), 6.15-6.20 (m, 1H), 6.45 (s, 2H), 6.74 (d, *J* = 6 Hz, 2H), 7.16 (d, *J* = 6 Hz, 2H); **Mass** (m/e): 427 (M^+); Analysis calculated for $C_{23}H_{25}NO_7$: C 64.63; H 5.90; N 3.28 % Found: C 64.80; H 5.99; N 3.38 %.

5-Acetoxy-3-(3-chloro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one oxime (205):

Yield 84 %; m. p. 179^0C; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.17 (s, 3H), 2.80 (bd, *J* = 18 Hz, 1H), 3.43 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.77 (s, 6H), 3.87 (s, 6H), 6.16-6.24 (m, 1H), 6.44 (s, 2H), 6.73 (d, *J* = 8 Hz, 1H), 7.00-7.10 (m, 1H), 7.27 (bs, 1H), 8.62 (bs, 1H, D_2O exchangeable); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.79, 55.87 (2C), 60.58, 71.57, 106.23 (2C), 111.31, 122.41, 126.82, 127.59, 128.58 (2C), 130.05, 135.90, 138.07, 153.36 (2C), 156.48, 162.51, 206.95; **Mass** (m/e): 461 (M^+).

5-Acetoxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-cyclopent-2-en-1-one (201): Yield 27 %; **^{1}H-NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.18 (s, 3H), 2.94 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.51 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.79 (s, 6H), 3.92 (s, 3H), 5.37-5.46 (m, 1H), 6.49 (s, 2H), 6.74 (d, *J* = 8 Hz, 1H), 6.89-7.03 (m, 2H); **Mass** (m/e): 414 (M^+); Anal. Calcd. For $C_{22}H_{22}O_8$: C 63.76; H 5.35 %. Found: C 63.89; H 5.53 %.

5-Acetoxy-3-[3-(diphenoxy-phosphoryloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (224):

In a 50 ml two neck round bottom flask the compound **200** (0.400 g, 0.934 mmol) and acetonitrile (10 ml) were cooled to -10^0C. Then dry carbontetrachloride (10 ml) and N, N-diisopropyl ethylamine (0.25 ml, 1.40 mmol) were added followed by DMAP (0.032 g, 0.29 mmol). After 2 min. diphenyl phosphorochloridate (0.536 g, 1.87 mmol) was added dropwise at the same temperature and the reaction mixture was stirred for 1.5 h. Then the reaction was quenched with aqueous KH_2SO_4 and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude residue was column purified to collect compound **224** (0.344 g, 54 %).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.21 (s, 3H), 2.87 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.38 (dd, *J* = 18 Hz and 6 Hz, 1H); 3.74 (s, 9H), 3.85 (s, 3H), 5.38-5.45 (m, 1H), 6.45 (s, 2H), 6.83 (d, *J* = 10 Hz, 1H); 7.15-7.42 (m, 12H); **Mass** (ESI): 660 (M^+); Anal. Calcd. For $C_{35}H_{33}O_{11}P$: C 63.63; H 5.04; P 4.69 %. Found: C 63.85; H 5.21; P 4.82 %.

5-Acetoxy-3-[3-(dimethoxy-phosphoryloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (225): Yield 62 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.96 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.52 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.78 (s, 6H), 3.82 (s, 6H), 3.87 (s, 3H), 3.91 (s, 3H), 5.37-5.46 (m, 1H), 6.45 (s, 2H), 6.85-7.02 (m, 2H), 7.41-7.50 (m, 1H); ^{31}P (81 MHz, $CDCl_3$): -3.46; **Mass** (ESI): 536 (M^+); Anal. Calcd. For $C_{25}H_{29}O_{11}P$: C 55.97; H 5.45; P 5.77 %. Found: C 56.14; H 5.468; P 5.87 %.

Phosphoric acid di-tert-butyl ester 2-oxo-3-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-cyclopent-3-enyl ester (226):

In a 50 ml two neck round bottom flask, 1H-tetrazole (0.14 g, 1.62 mmol) was added in one portion to a stirred solution of the compound **192** (0.200 g, 0.54 mmol) and di-tert-butyl N,N-diethylphosphoramidite (0.40 g, 1.60 mmol) in dry THF (3 ml) and the mixture was stirred for 15 min at 20^0C. The mixture was then cooled to -40^0C and a solution of 85 % mCPBA (0.35 g, 1.72 mmol) in dichloromethane (4 ml) was rapidly added such that the reaction temperature was kept below 0^0C. After stirring for 5 min at 20^0C, 10 % aqueous $NaHSO_3$ (8 ml) was added and the mixture was stirred for a further 10 min. The reaction mixture was then transferred to separating funnel and extracted with diethylether (50 ml). The organic layer was washed with 10 % aq. $NaHSO_3$ (2 x 10 ml), 5 % aq. $NaHCO_3$ (2 x 10 ml), dried over sodium sulfate and the solvent was removed under reduced pressure to get the compound **226** as colorless liquid (0.13 g, 60 %)

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 1.58 (s, 18H), 3.21 (dd, *J* = 15 Hz and 5 Hz, 1H), 3.47 (dd, *J* = 15 Hz and 5 Hz, 1H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 5.03-5.10 (m, 1H), 6.45 (s, 2H), 6.83 (d, *J* = 10 Hz, 2H), 7.38 (d, *J* = 10 Hz, 2H); **Mass** (ESI): 564 (M+2), 507, 451, 353; Anal. Calcd. For $C_{29}H_{39}O_9P$: C 61.91; H 6.99; P 5.51 %. Found: C 62.14; H 7.08; P 5.59 %.

Phosphoric acid mono-2-oxo-3-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-cyclopent-3-enyl ester (227):

In a 10 ml round bottom phosphoric acid di-tert-butyl ester 2-oxo-3-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-cyclopent-3-enyl ester (**226**) (0.200 g, 0.35 mmol) was dissolved in dichloromethane (10 ml), cooled to 0^0C and trifluoroacetic acid (0.5 ml) was added and stirred well for 4 h. The reaction mixture was poured over crushed ice, extracted with dichloromethane (3 x 20 ml) the organic layer was separated and dried over sodium sulfate. This extract was concentrated under reduced pressure to collect pure phosphoric acid mono-(2-oxo-3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-cyclopent-3-enyl ester (0.099 g, 62 %) as yellowish solid.

M. p. 168-170^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$ + CCl_4): δ 3.46 (bd, *J* = 15 Hz, 1H), 3.74 (bd, *J* = 15 Hz, 1H), 3.84 (s, 6H), 3.94 (s, 3H), 4.01 (s, 3H), 5.42-5.48 (m, 1H), 6.55 (s, 2H), 6.97 (d, *J* = 10 Hz, 2 H), 7.53 (d, *J* = 10 Hz, 2H); ^{31}P (202 MHz, $CDCl_3$): -1.55; **Mass** (ESI): 451 (M+1); Anal. Calcd. For $C_{21}H_{23}O_9P$: C 56.00; H 5.15; P 6.88 %. Found: C 56.19; H 5.23; P 6.95 %.

Disodium salt of phosphoric acid mono-[4-(4-methoxyphenyl)-2-oxo-3-(3,4,5-trimethoxyphenyl)-cyclopent-3-enyl] ester(228):

In 10 ml round bottom flask, a phosphoric acid mono-(2-oxo-3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-cyclopent-3-enyl ester (0.074 g, 0.15 mmol) was dissolved in dichloromethane (0.5 ml), to this sodium hydroxide (0.006 g, 0.15 mmol) in distilled water (0.5 ml) was added and stirred well. After 30 min, the reaction mixture was diluted with dichloromethane and organic layer was separated. The aqueous layer was evaporated under reduced pressure to collect the compound **228** (0.042 g, 52 %).

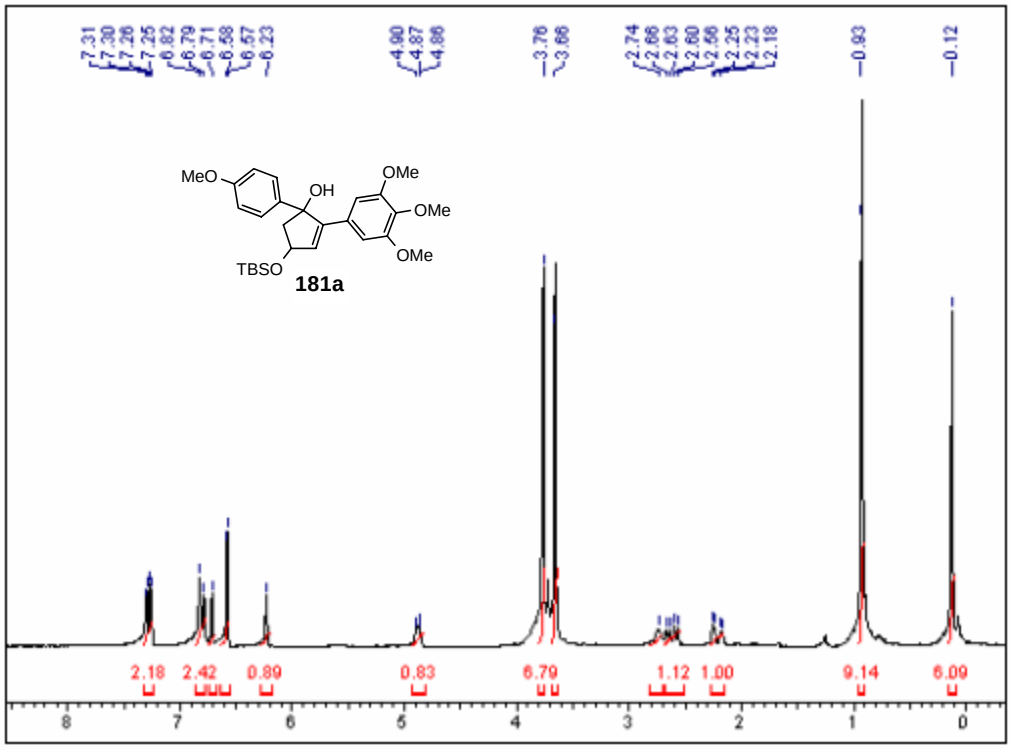
^{1}H NMR (500 MHz, D_2O): δ 3.18 (bd, *J* = 20 Hz, 1H), 3.48 (bd, *J* = 20 Hz, 1H), 3.64 (s, 6H), 3.70 (s, 3H), 3.71 (s, 3H), 4.86 (bs, 1H), 6.49 (s, 2H), 6.75 (bs, 2H), 7.34 (bs, 2H); **Mass** (ESI): 495 (M+1), 473, 451.

(5-Iodo-2-methoxyphenyl)-dimethylamine (180f):

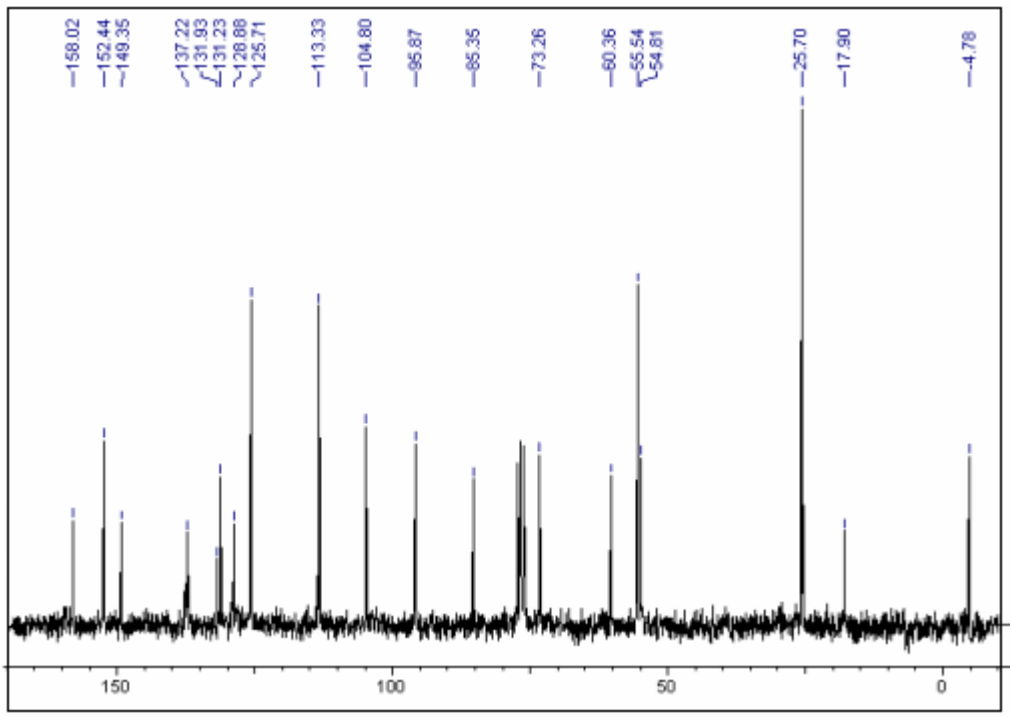
In a 250 ml two necked round bottom flask, 5-iodo-2-methoxyaniline (10 g, 40.16 mmol) was taken to this sodium bicarbonate (20 g, 240.09 mmol) dissolved in (80 ml) water was added slowly with stirring. The reaction mixture was cooled to 0^0C and then dimethyl sulfate (30.36 g, 240.09 mmol) was added dropwise over a period of 1 h. Reaction mixture was heated to 60^0C for 1 h to remove excess dimethyl sulfate and then it was neutralized with ethanolamine (30 ml) and heated at 100^0C. The reaction mixture was cooled to room temperature and extracted with chloroform (3 x 100 ml), washed with water followed by brine. The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to afford the (5-iodo-2-methoxyphenyl)-dimethylamine (9.00 g, 81 %) **(180f)** as a low melting solid.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.88 (s, 6H), 3.94 (s, 3H), 6.68 (d, *J* = 8 Hz, 1H), 7.28 (d, *J* = 2 Hz, 1H), 7.33 (dd, *J* = 8 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.52 (2C), 54.91, 82.92, 112.62, 126.29, 130.30, 143.38, 151.58; **Mass** (m/e): 277 (M^+).

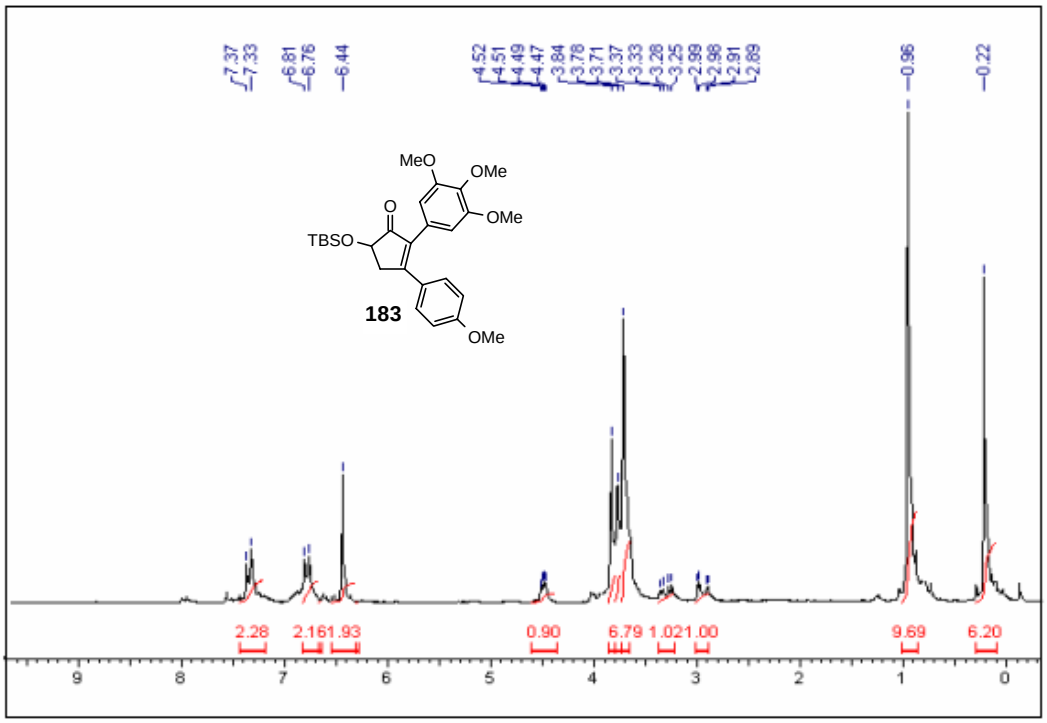
^{1}H NMR spectrum of the compound 181a:



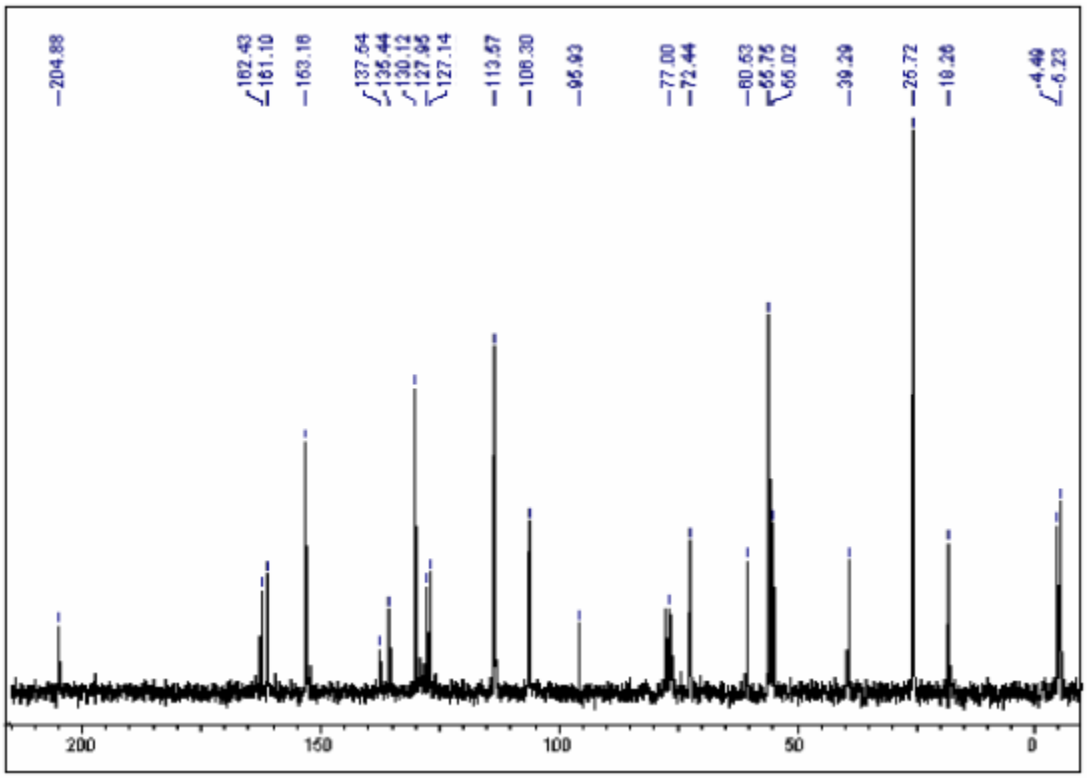
^{13}C NMR spectrum of the compound 181a:



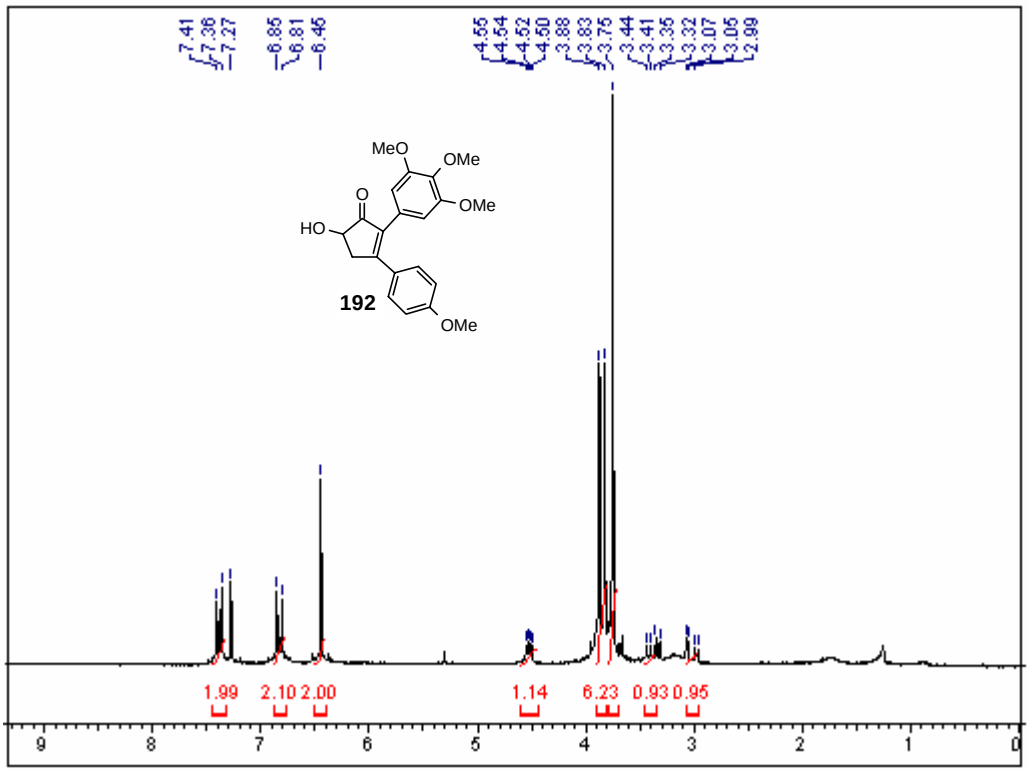
^{1}H NMR spectrum of the compound 183:



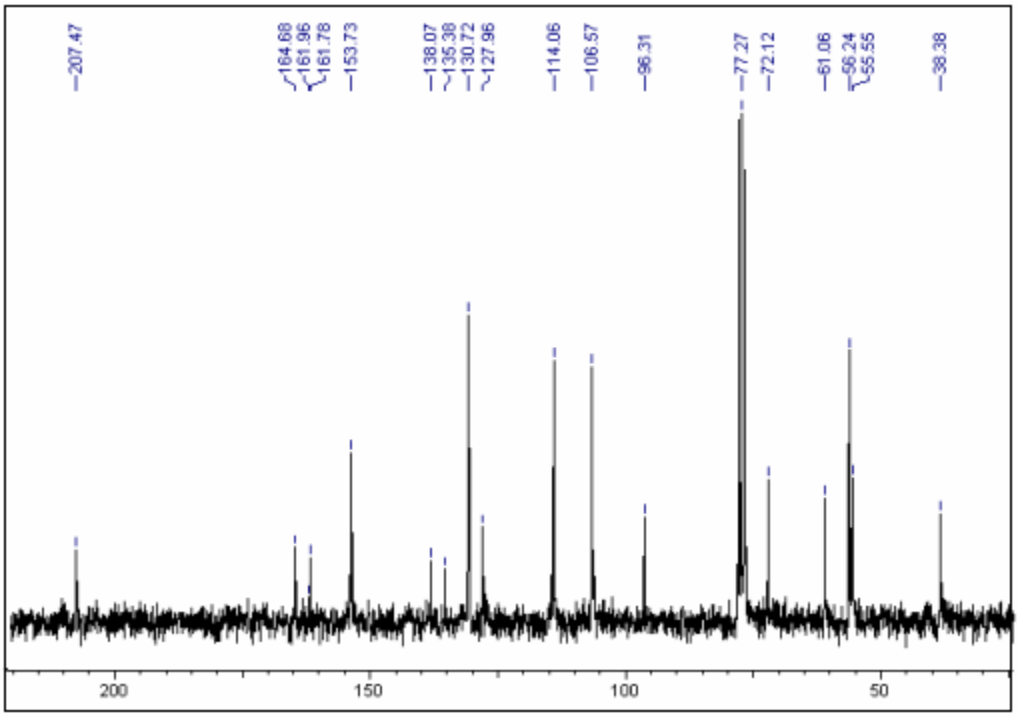
^{13}C NMR spectrum of the compound 183:



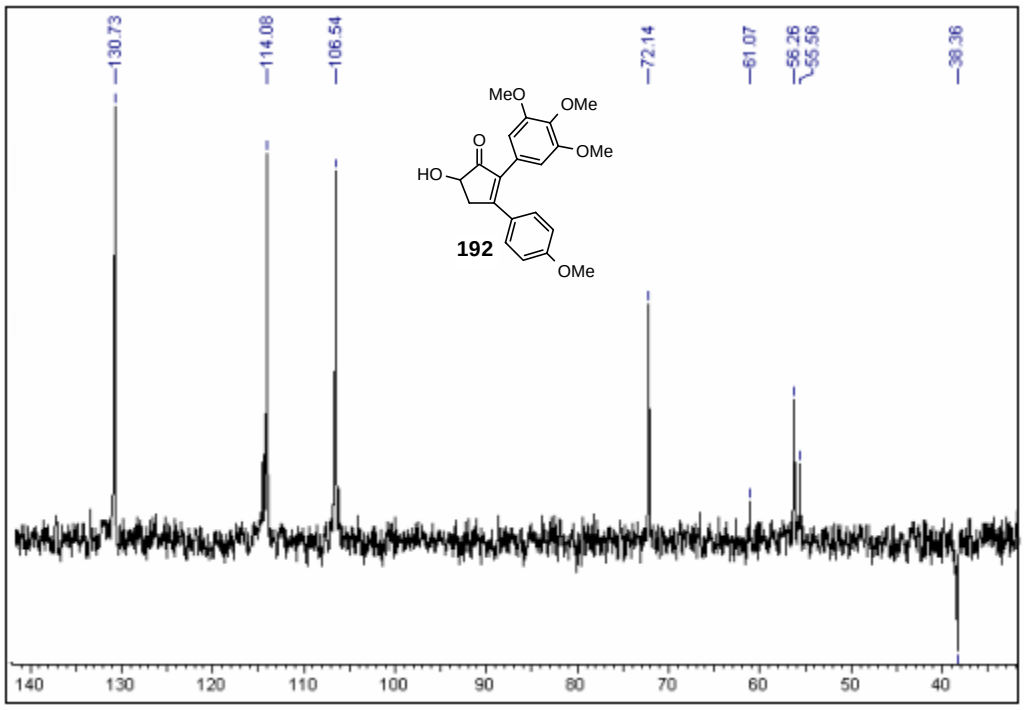
^{1}H NMR spectrum of the compound 192:



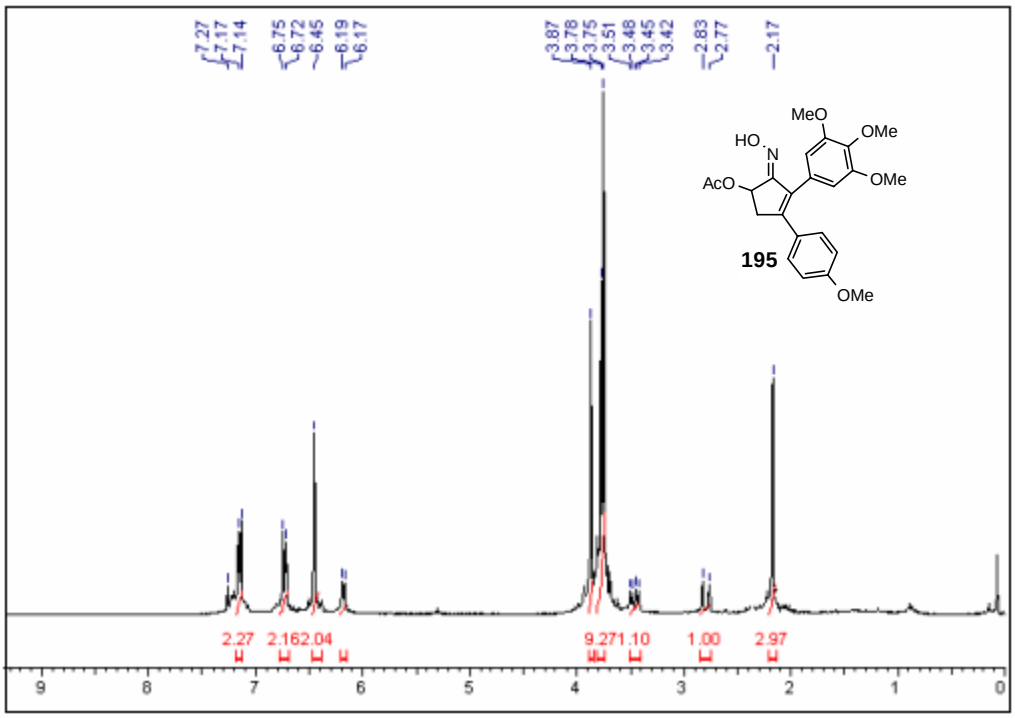
^{13}C NMR spectrum of the compound 192:



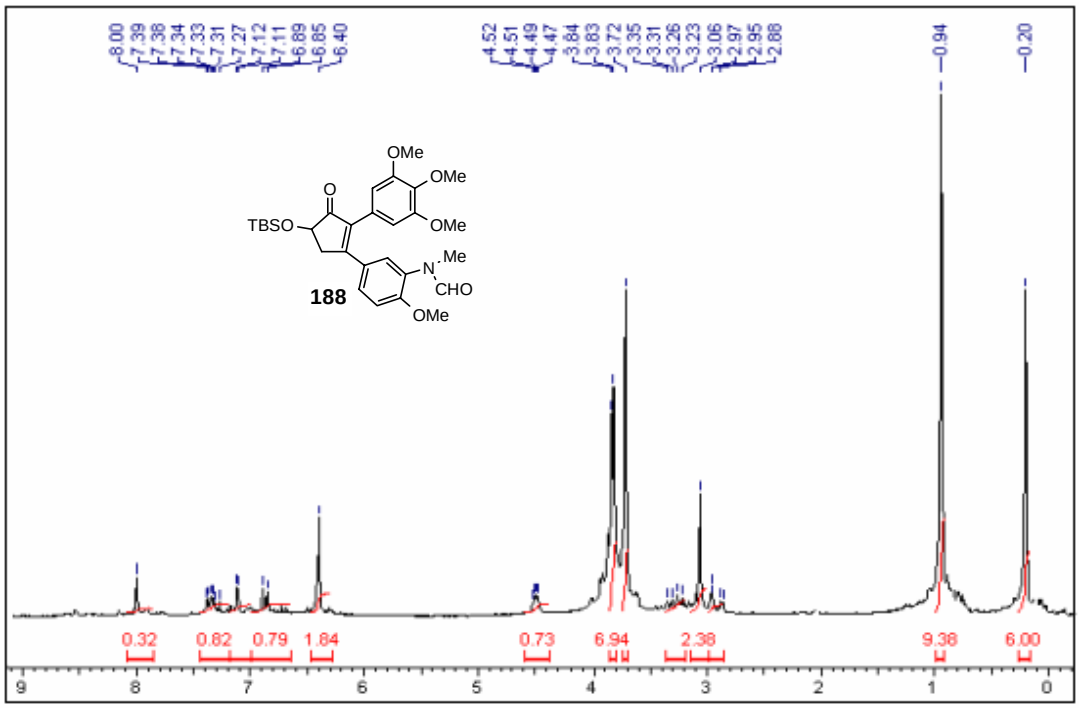
DEPT spectrum of the compound 192:



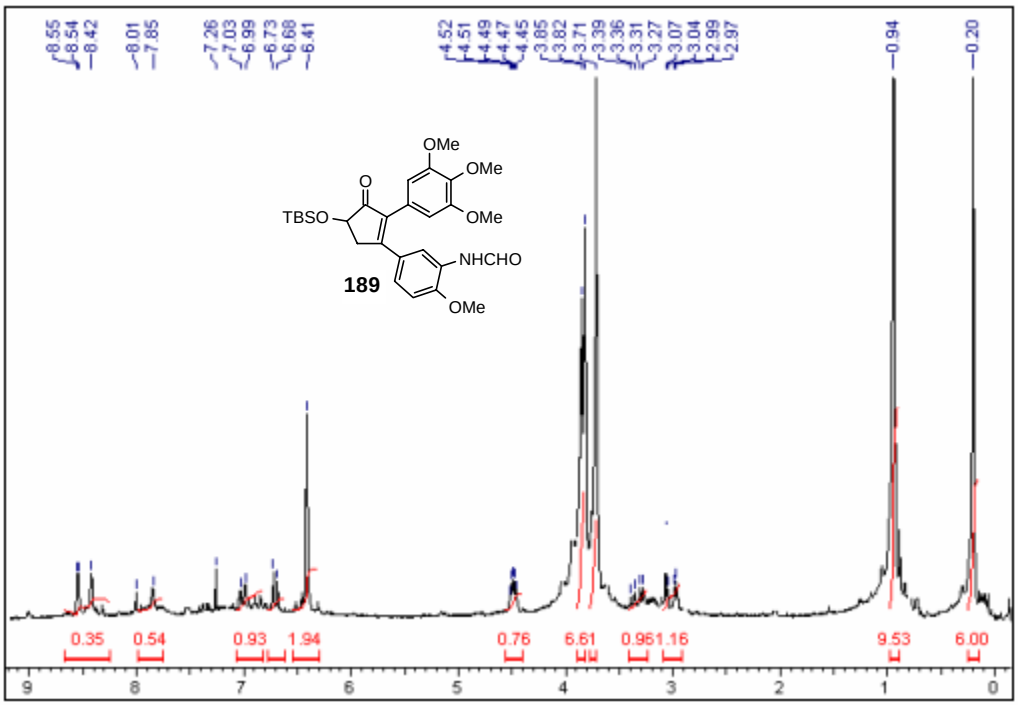
^{1}H NMR spectrum of the compound 195:



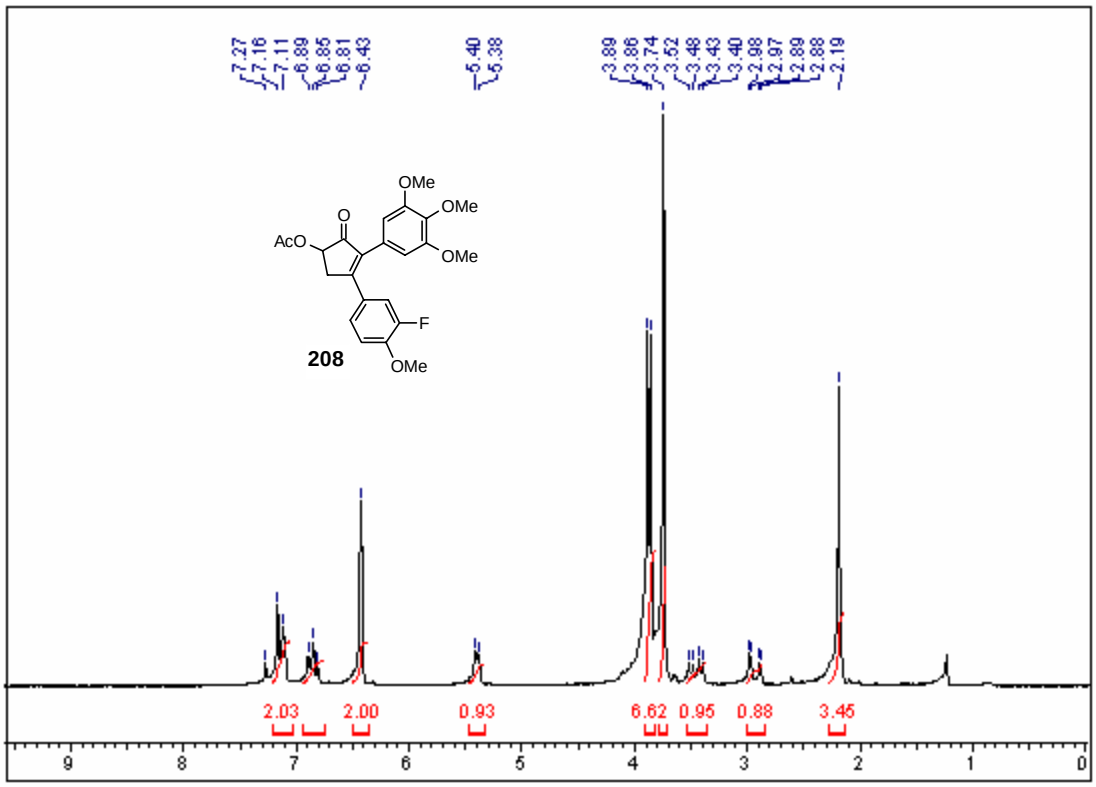
^{1}H NMR spectrum of the compound 188:



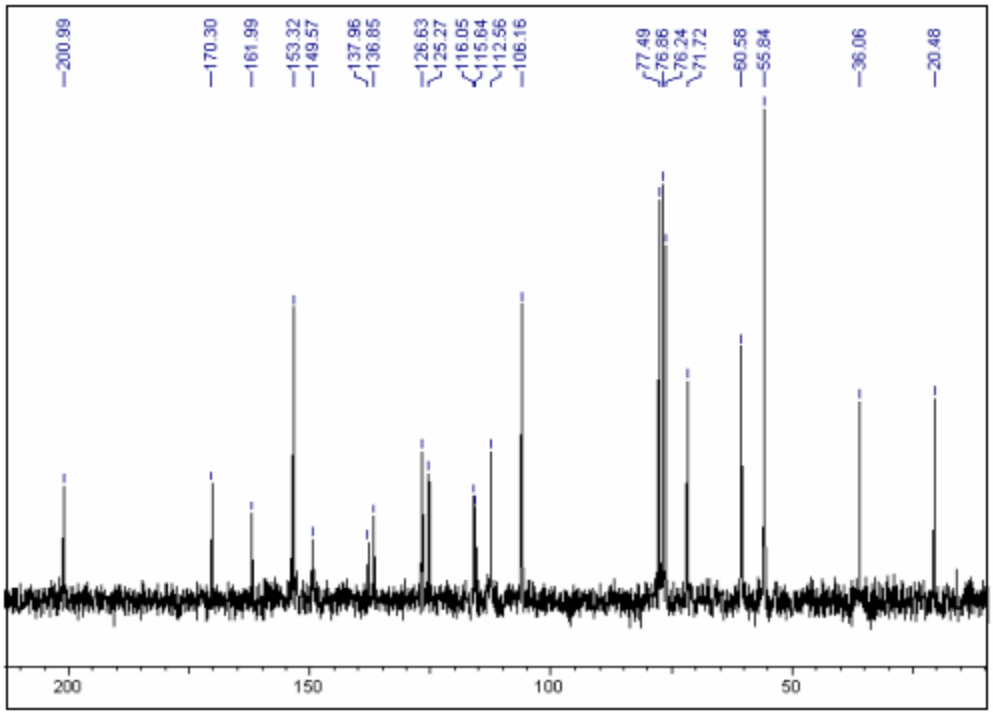
^{1}H NMR spectrum of the compound 189:



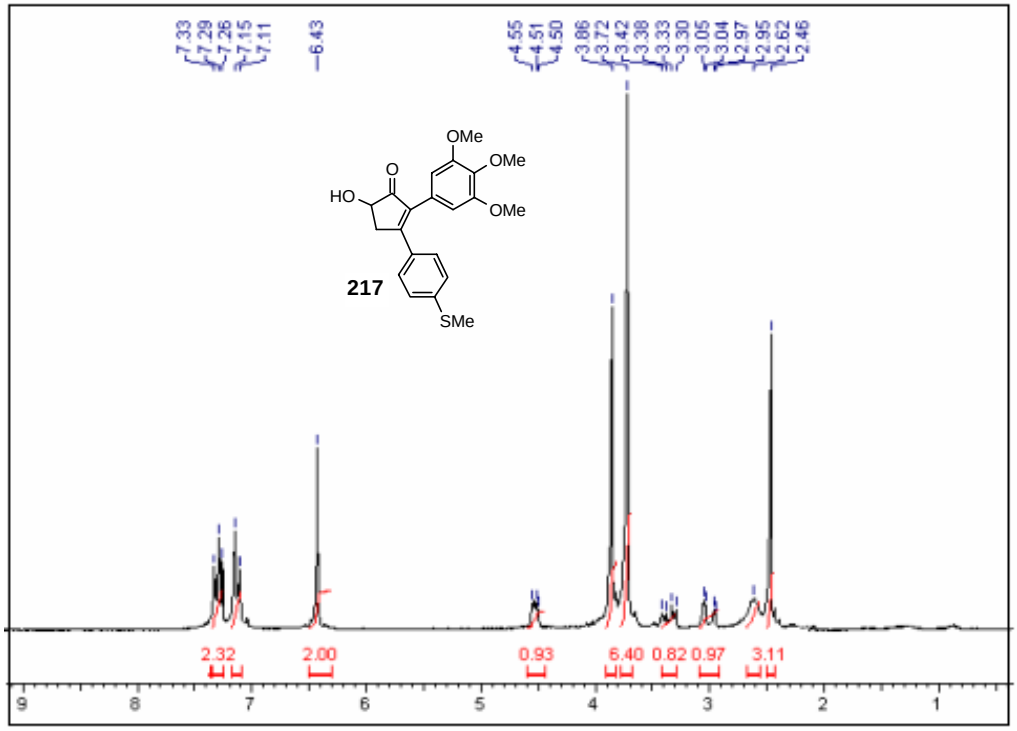
^{1}H NMR spectrum of the compound 208:



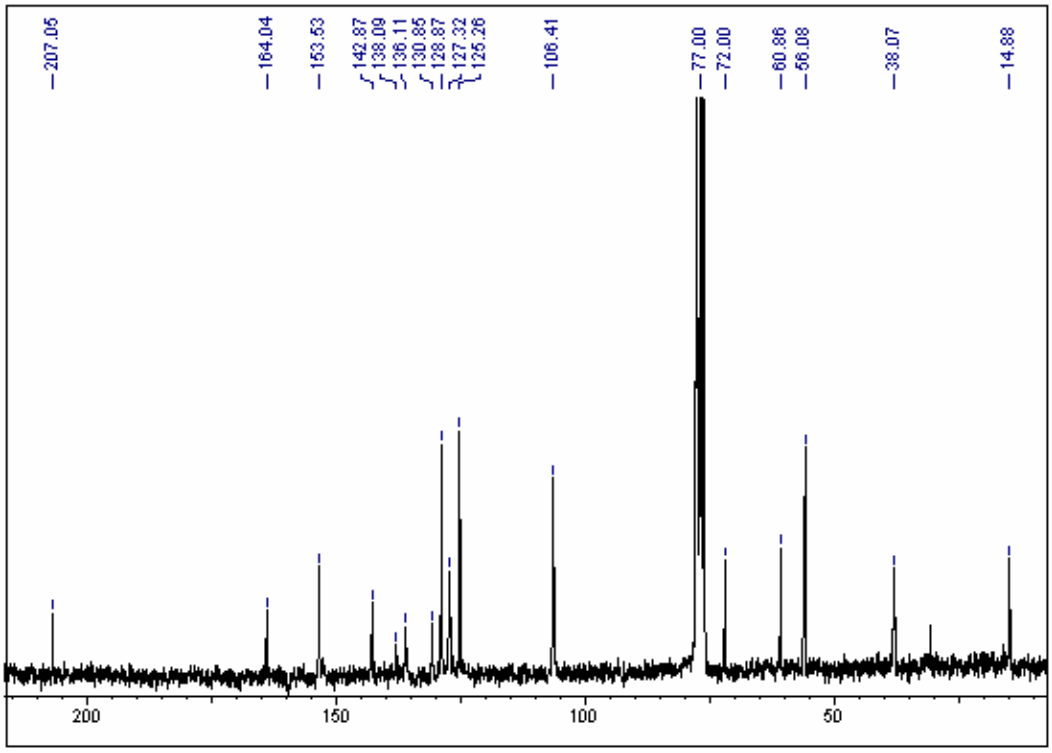
^{13}C NMR spectrum of the compound 208:



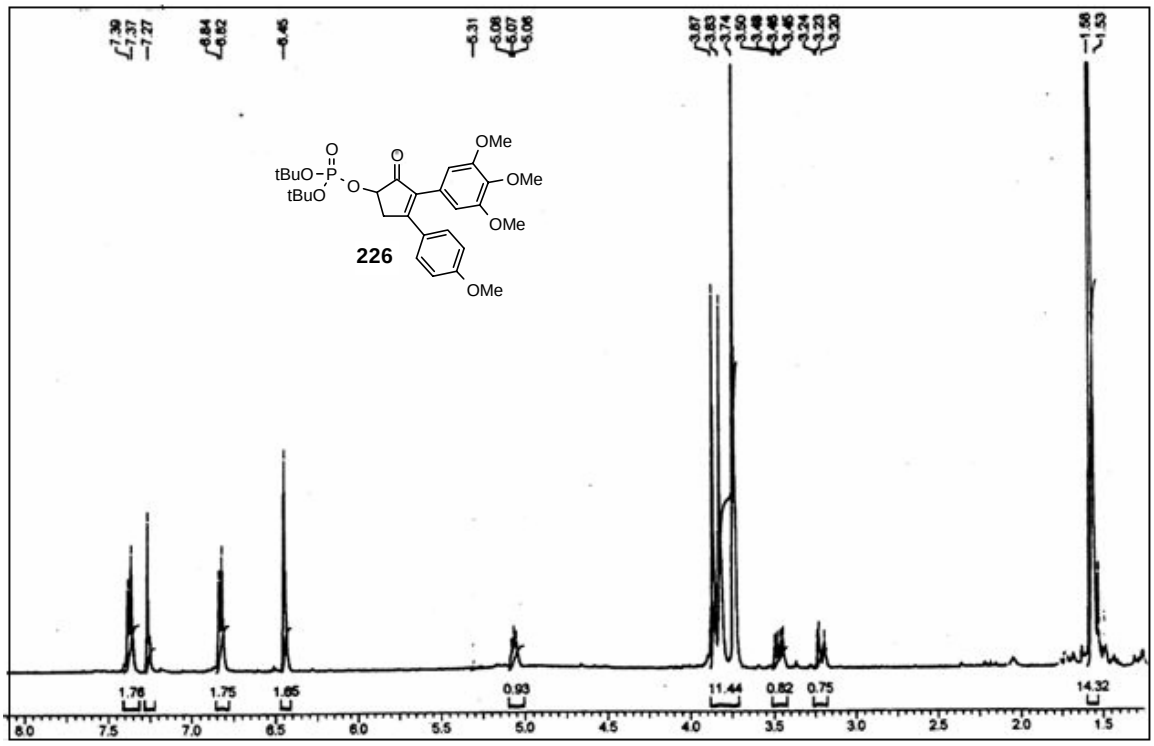
^{1}H NMR spectrum of the compound 217:



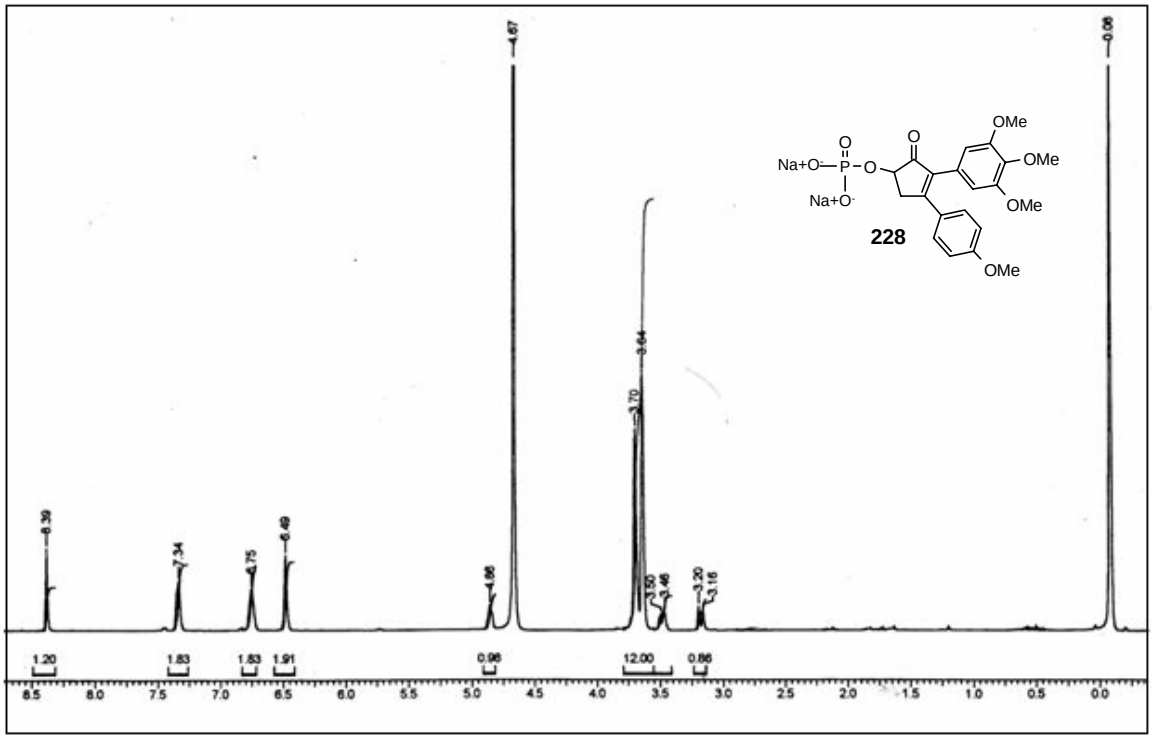
^{13}C NMR spectrum of the compound 217:



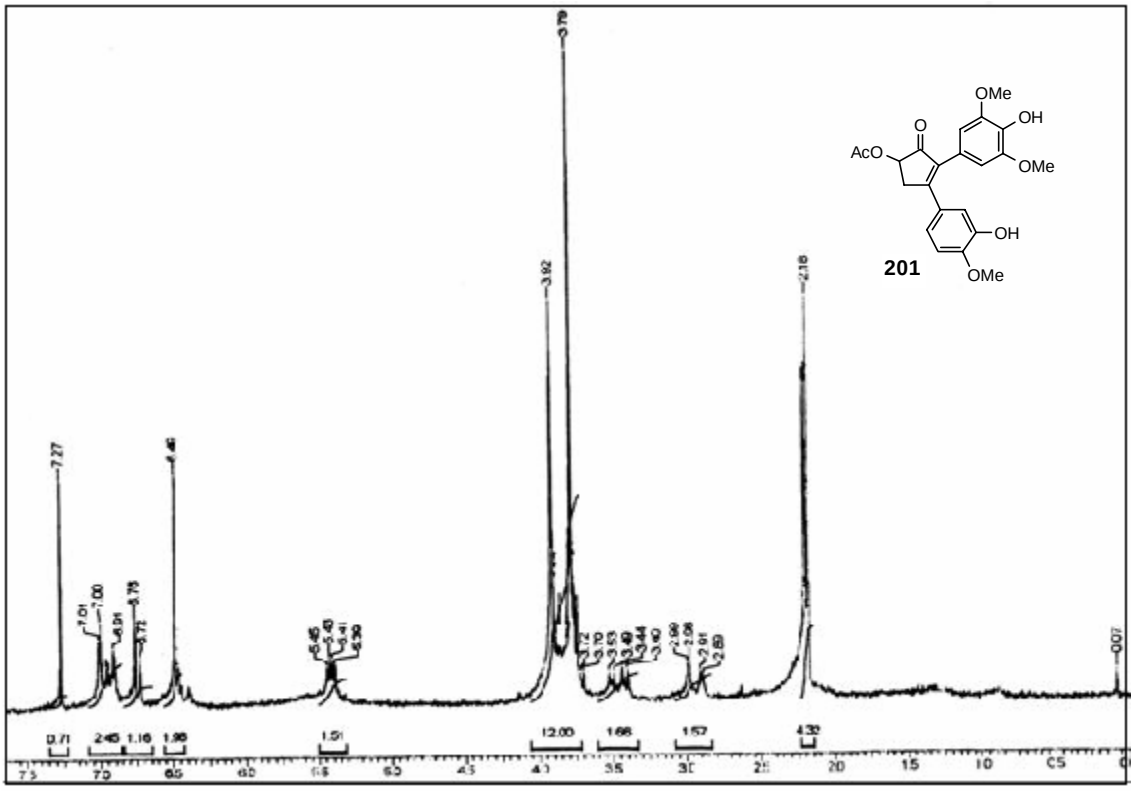
^{1}H NMR spectrum of the compound 226:



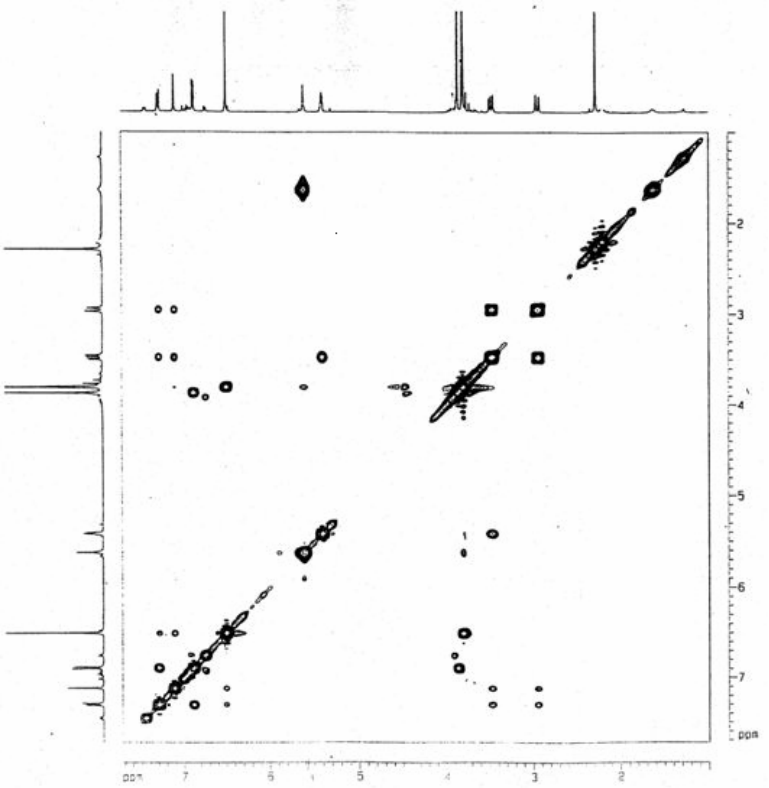
^{1}H NMR spectrum of the compound 228:



^{1}H NMR spectrum of the compound 201:



NOESY spectrum of the compound 201:



1.2.5 REFERENCES:

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CHAPTER 1

SECTION III:

Studies Towards the Synthesis of 2,3-Diaryl-4,5-Dihydroxycyclopent-2-en-1-one Analogues of CA-4

1.3.1 INTRODUCTION:

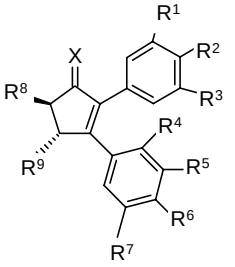
In sections I and II we have described the syntheses of the 2,3-diaryl-4-tert-butyldimethylsilyloxycyclopent-2-en-1-one analogues (**99**) by applying Heck reaction method and 2,3-diaryl-5-tert-butyldimethylsilyloxycyclopent-2-en-1-one analogues (**100**) by oxidative rearrangement of tertiary allylic alcohols as *cis* restricted analogues of CA-4, respectively.

We have also studied the cytotoxic activity of the synthesized compounds and these studies indicated that cyclopentenone ring carrying hydroxy group provided *cis*-restriction for olefinic double bond of combretastatin A-4 and some of the compounds from both series (**99**) and (**100**) were found to have more cytotoxic activity than parent compound CA-4. Our studies also indicated that compounds from 5-hydroxy series (**100**) contributed for better cytotoxic activity than the 4-hydroxycyclopentenone series (**99**).

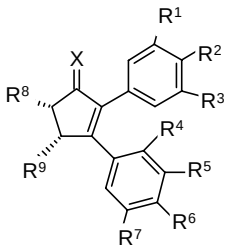
Bearing in mind the structure activity relationship study of CA-4 analogues we designed and planned to synthesize substituted 2,3-diaryl-4, 5-dihydroxy-cyclopent-2-en-1-one analogues. The expectation was that the compounds from this series might show better activity than first two series.

1.3.2 PRESENT WORK:

We designed analogues **229a** in which 4,5-dihydroxy groups are *trans* to each other while in **229b** 4,5-dihydroxy groups are *cis* to each other. The synthetic strategy involved the Suzuki coupling and the Heck reaction as the key steps.

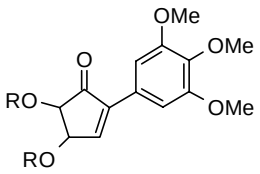


229 a



229 b

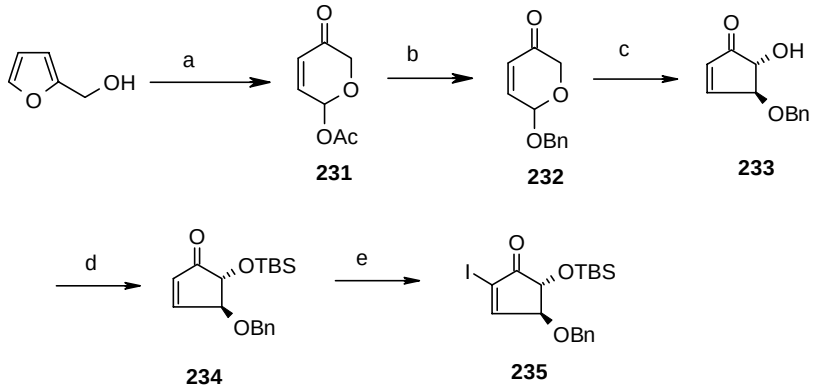
For the syntheses of designed analogues, compound **230** is a key intermediate, which on Heck reaction with suitably substituted aryl halides should result in the designed analogues.



230

Preparation of 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-iodo-cyclopent-2-en-1-one (235):

Synthesis of cyclopentenediol from furfuryl alcohol was achieved as outlined in scheme 1. The synthesis of building block **233** is given in chapter 3 section I (compound no. **7**) by known chemical transformations.[1-4]



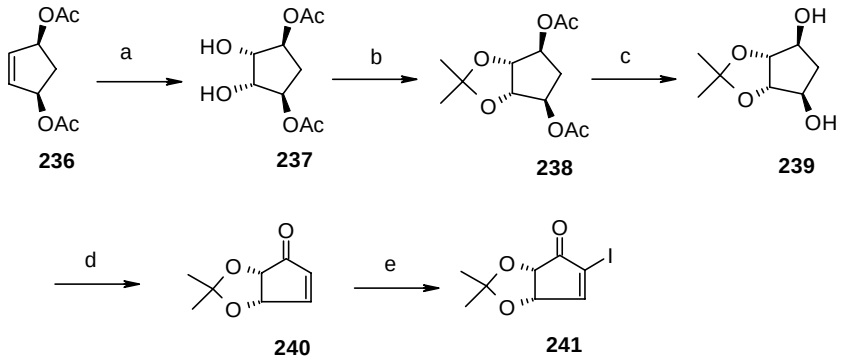
Scheme 1

Reagents and conditions: a) i) NBS, THF-water, 0^0C ii) $(CH_3CO)_2O$, pyridine, r t, 15 h. b) Benzyl alcohol, 30 % montmorillonite K 10, DCM, reflux, 2 h. c) C_6H_5COOH, CH_3COOK, DMF, 80^0C, 3 h. d) TBDMSCl, DMAP, Et_3N, r t, 4 h e) I_2, pyridine, CCl_4.

The free hydroxy group of cyclopentenone **233** was protected as tertiary butyldimethylsilyl ether to give the compound **234** in 76 % isolated yield. α-Iodination of this intermediate was achieved by using iodine, dichloromethane and pyridine[5] to give the intermediate **235** in 80 % isolated yield.

Synthesis of 5-iodo-2,2-dimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (**241**):

Similarly corresponding *cis*-diol intermediate **241** could be synthesized by the synthetic strategy outlined in scheme 2.



Scheme 2

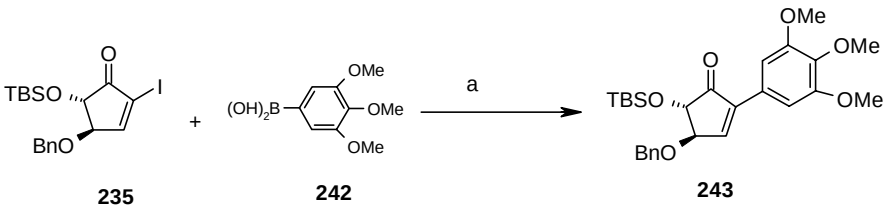
Reagents and conditions: a) 1 mol % OsO_4, Me_3NO, THF, acetone b) Acetone, catalytic TsOH c) KOH, MeOH d) PDC, pyridine e) I_2, pyridine, CCl_4

The *cis* dihydroxylation of diacetate **236**[6] with 1 mol % osmium tetroxide and trimethylamine N-oxide[7] as cooxidant in a mixture of tetrahydrofuran and acetone furnished the diol **237** in 85 % yield. The protection of the free hydroxy groups was achieved by using acetone and sulfonic acid at room temperature in 89 % yield to give the compound **238**. Treatment of the compound **238** with potassium hydroxide in methanol gave the diol **239** in 87 % yield.[8] Oxidation/dehydration of the compound **239** was carried out with pyridinium dichromate[9] in pyridine in 64 % yield to give the compound **240**.

α-Iodination of the intermediate **240** was achieved by using iodine, dichloromethane and pyridine[5] to give the compound **241** in 80 % isolated yield.

Thus after having these α-iodo cyclopentenones (**235** and **241**) in hand, the next step was the coupling of these iodocyclopentenones with 3,4,5-trimethoxyiodobenzene to obtain the required intermediate **230** with *cis* and *trans* configuration of the hydroxy groups at 4 and 5 positions of the cyclopentenone ring.

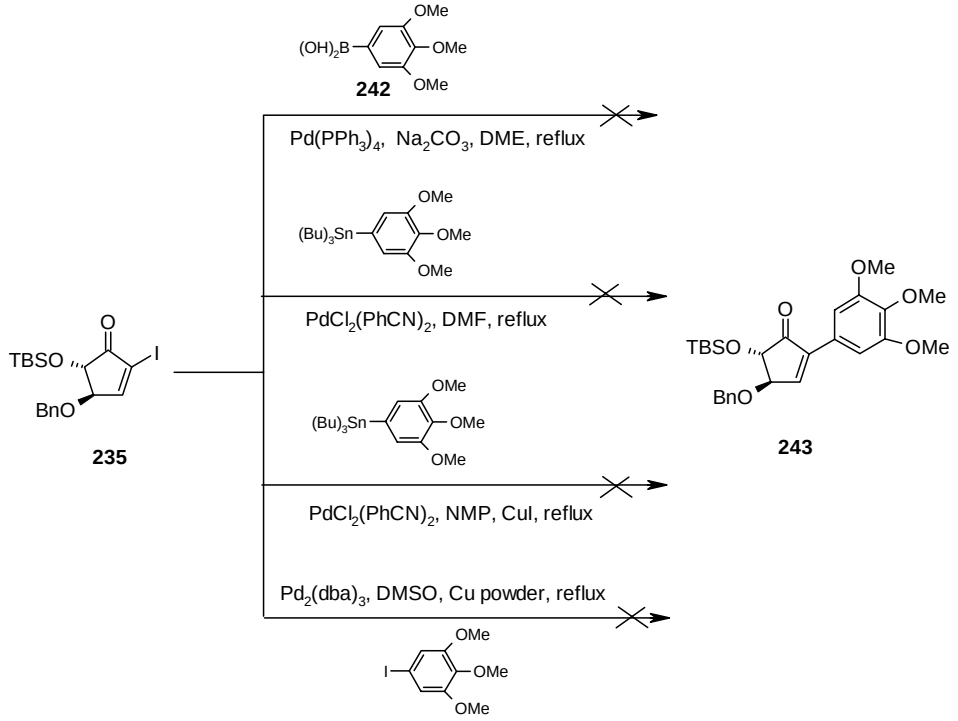
The reaction of 3,4,5-trimethoxybenzeneboronic acid[10] (**242**) with the intermediate **235** was performed using tetrakistriphenylphosphine palladium(0) (4 mol %) in 1,2-dimethoxyethane using $NaHCO_3$ as base under reflux for 24 h to collect the required intermediate **243** (scheme 3). This reaction suffered from low isolated yield of the desired product due to byproduct formation. Therefore, various conditions were tried to improve the yields in Suzuki coupling, however the competitive aryl-aryl coupling reaction product was the major product in all our attempts.[11]



Scheme 3

Reagents and conditions: a) $Pd(PPh_3)_4$ 4 mol %, $NaHCO_3$ (3.5 equiv.), 1,2-dimethoxyethane, reflux, 24 h

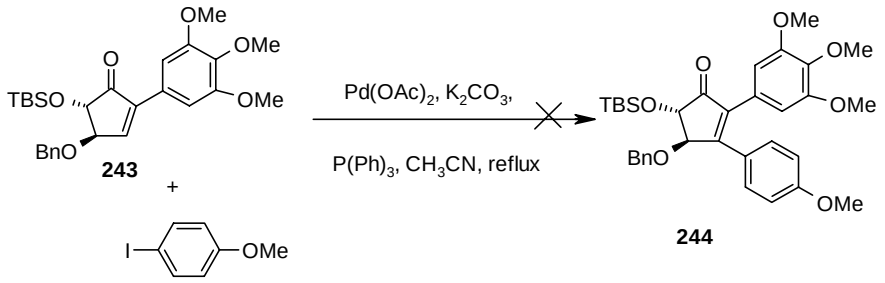
Further, for the Stille coupling[12, 13] reaction of n-tributyl-(3,4,5-trimethoxyphenyl)-stannane with intermediate **235** in the presence of bis(benzonitrile)palladium(II) chloride ($PdCl_2(PhCN)_2$, various conditions were attempted which met with failures. Other palladium reagents like palladium bis (dibenzylideneacetone) ($Pd(dba)_2$), $PdCl_2$ were employed to get the intermediate **243** but the required product (scheme 4) could not be obtained.



Scheme 4

Similar efforts were made using the intermediate **241** to get the *cis*-diol coupled product but the difficulties encountered in getting the required product could not be overcome.

In our continued efforts to complete the synthesis of 2,3-diaryl-4,5-dihydroxy-cyclopentenone of type **244** we carried out the Heck reaction of 4-iodoanisole with the intermediate **243** in the presence of palladium acetate, triphenyl phosphine, tetrabutylammonium bromide and potassium carbonate in acetonitrile, but required compound **244** was not formed (scheme 5).



Scheme 5

Various conditions by changing all parameters like solvents, (DMF, DMSO) and bases (like triethylamine, diisopropylamine, Na_2CO_3) were tried but unfortunately the desired product **244** could not be obtained.

1.3.3 CONCLUSION:

A route for the synthesis of substituted 2,3-diaryl-4,5-dihydroxycyclopent-2-en-1-one has been attempted using Suzuki coupling method. The synthesis of required key intermediate **243** was successfully accomplished. Utilizing this intermediate, various analogues of substituted 2,3-diaryl-4,5-dihydroxycyclopent-2-en-1-one of combretastatin A-4 were anticipated. However, due to negative results in the Suzuki coupling approach further efforts were discontinued owing to shortage of time.

1.3.4 EXPERIMENTAL:

4-Benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-en-1-one (234):

In 100 ml two neck round bottom flask with two way stopcock, 4-benzyloxy-5-hydroxy-cyclopent-2-enone (**233**, synthesized by the reported procedure) (6.00 g, 29.41 mmol) was taken under argon atmosphere, dry dichloromethane (40 ml) was added through syringe and the flask

was cooled to 0^0C. A solution of tert-butyldimethylsilyl chloride (4.87 g, 32.35 mmol) and dimethyaminopyridine (0.78 g, 6.40 mmol) in dichloromethane (20 ml) was added dropwise and stirred at the same temperature for 15 min. Then triethylamine (4.09 ml, 38.23 mmol) was added, the mixture was warmed to room temperature and stirred further for 5 h (reaction monitored by TLC). The reaction mixture was filtered through Whatman filter paper, water was added to the filtrate and extracted with dichloromethane (3 x 50 ml). The combined organic layer was washed with water followed by brine, dried over sodium sulphate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (2 % ethyl acetate in pet ether) to give the 4-benzyloxy-5-(tert-butyldimethylsilyloxy)-cyclopent-2-en-1-one (7.10 gm, 76 %) as a colorless liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 1217, 1253, 1725, 2858, 2930, 3014 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.23 (s, 3H), 0.26 (s, 3H), 1.00 (s, 9H), 4.32 (d, *J* = 4 Hz, 1H), 4.52-4.59 (m, 1H), 4.72 (d, *J* = 10 Hz, 1H), 4.84 (d, *J* = 10 Hz, 1H), 6.21 (dd, *J* = 6 Hz and 2 Hz, 1H), 7.30-7.42 (m, 6H). **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.30, -4.20, 18.15, 25.72 (3C), 72.07, 80.53, 83.73, 127.58 (2C), 127.80, 128.35 (2C), 132.54, 137.43, 156.51, 202.09; **Mass** (m/e): 318 (M^+); Anal. Calcd. For $C_{18}H_{26}O_3Si$: C 67.88; H 8.23; Si 8.82 %. Found: C 67.94; H 8.26; Si 8.96 %.

4-Benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-iodo-cyclopent-2-en-1-one (235):

In 100 ml two neck round bottom flask 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-en-1-one (**234**) (2.00 g, 6.28 mmol) was dissolved in dichloromethane and pyridine(1:1; 20 ml) and cooled to 0^0C. Then a solution of iodine (2.70 g, 10.65 mmol) in dichloromethane and pyridine (1:1; 20 ml) was added dropwise with stirring, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with water, organic layer was separated and washed with water, 1N HCl (2 times) followed by water and then 15 % sodium thiosulfate solution followed by brine. The organic layer was dried over sodium sulfate, concentrated under reduced pressure to give 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-iodo-cyclopent-2-en-1-one (2.23 g, 80 %) as a reddish liquid.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.23 (s, 3H), 0.26 (s, 3H), 0.99 (s, 9H), 4.35 (d, *J* = 2 Hz, 1H), 4.51 (d, *J* = 2 Hz, 1H), 4.71 (d, *J* = 10 Hz, 1H), 4.81 (d, *J* = 10 Hz, 1H), 7.36-7.42 (m, 5H), 7.81 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.30, 4.29, 18.15, 25.65 (3C), 72.29, 78.07, 85.09, 102.22, 127.76 (2C), 128.09, 128.53 (2C), 136.99, 162.61, 197.68; **Mass** (ESI): 445 (M+1); Anal. Calcd. For $C_{18}H_{25}IO_3Si$: C 48.65; H 5.67; I 28.56; Si 6.32 %. Found C 48.84; H 5.87; I 28.71; Si 6.48 %.

5-Iodo-2,2-dimethyl-3a,6a-dihydro-cyclopenta[1,3]dioxol-4-one (241):

Preparation same as for compound **235**.

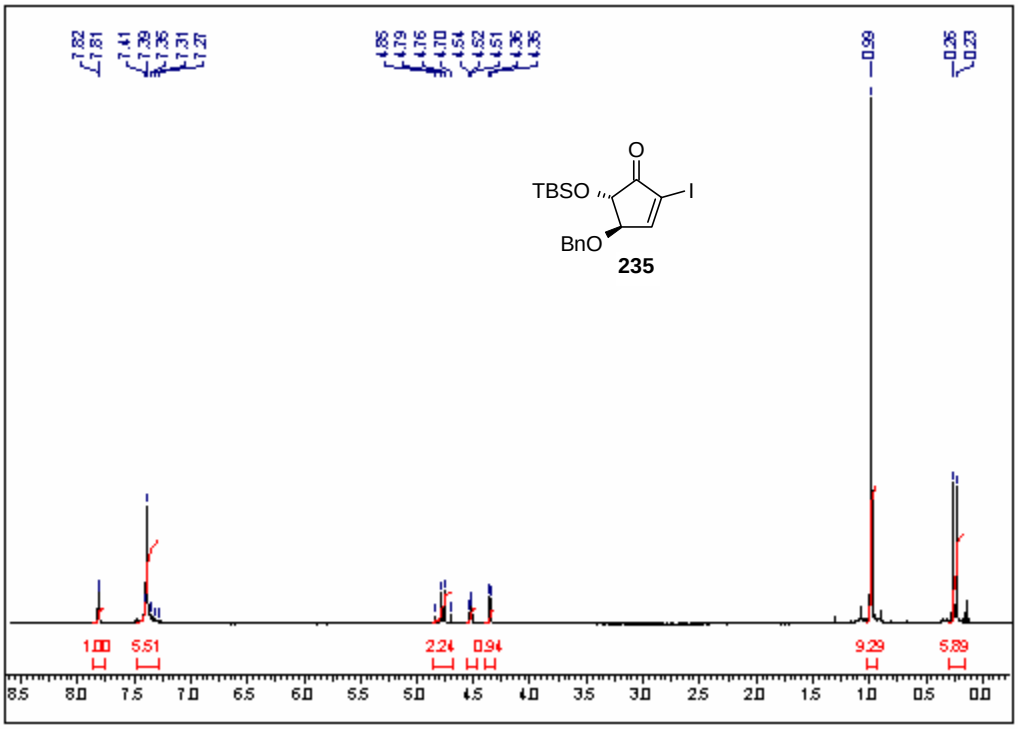
Yield 76 %; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.36 (s, 3H), 1.39 (s, 3H), 4.50 (d, *J* = 6 Hz, 1H), 5.21 (dd, *J* = 6 Hz and 2 Hz, 1H), 7.96 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 26.42, 27.30, 73.69, 79.68, 115.71, 159.71, 164.70, 197.20; **Mass** (ESI): 279 (M^+); Anal. Calcd. For $C_8H_9IO_3$: C 34.31; H 3.24; I 45.31 %. Found: C 34.39; H 3.28; I 45.42 %.

4-Benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (243):

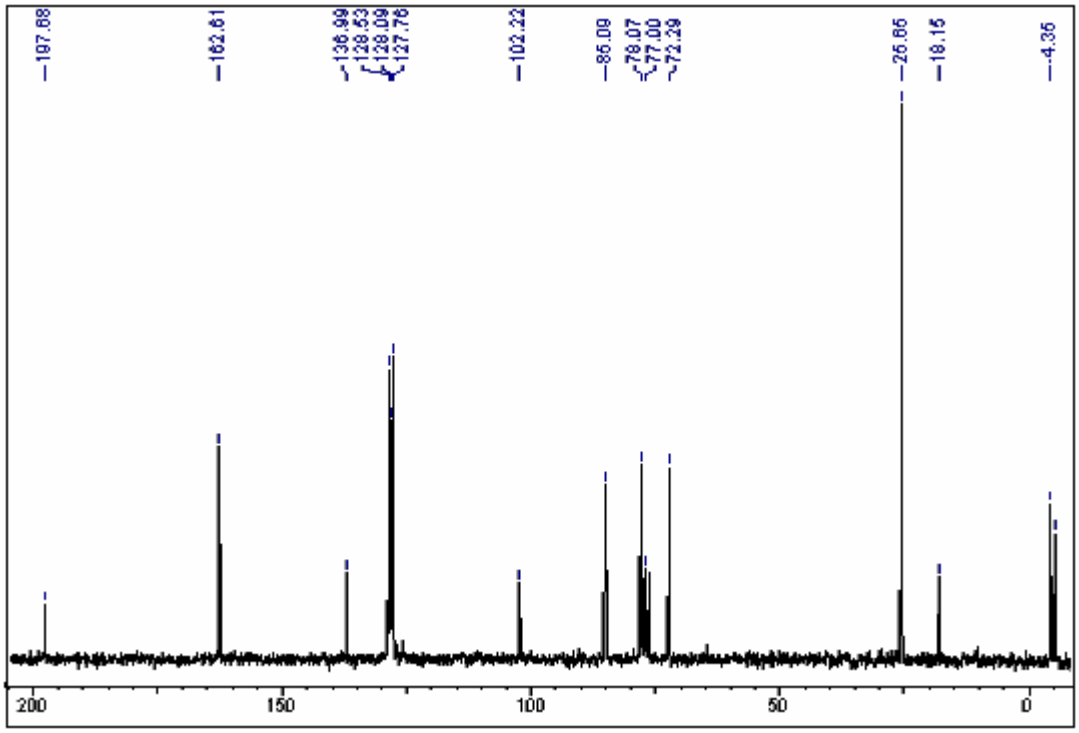
To the solution of 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-iodo-cyclopent-2-en-1-one (**235**) (0.80 g, 1.79 mmol) in dimethoxyethane (20 ml), 3,4,5-trimethoxybenzeneboronic acid (0.531 g, 2.50 mmol), sodium hydrogen carbonate (0.510 g, 6.08 mmol), water (0.86 ml) and tetrakistriphenylphosphine palladium (0.330 g, 0.28 mmol) were added and the reaction mixture was refluxed for 24 h. Reaction mixture was then cooled to room temperature and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated on rotary evaporator. The residue on column purification afforded 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**243**) (0.110 g, 12 %) as colorless thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.24 (s, 3H), 0.27 (s, 3H), 0.99 (s, 9H), 3.87 (s, 6H), 3.89 (s, 3H), 4.47 (d, *J* = 2 Hz, 1H), 4.59 (bd, *J* = 4 Hz, 1H), 4.78 (d, *J* = 10 Hz, 1H), 4.88 (d, *J* = 10 Hz, 1H), 7.00 (s, 2H), 7.32-7.45 (m, 6H); **Mass** (ESI): 486 (M+2); Anal. Calcd. For $C_{27}H_{36}O_6Si$: C 66.91; H 7.49; Si 5.79 %. Found: C 67.03; H 7.65; Si 5.87 %.

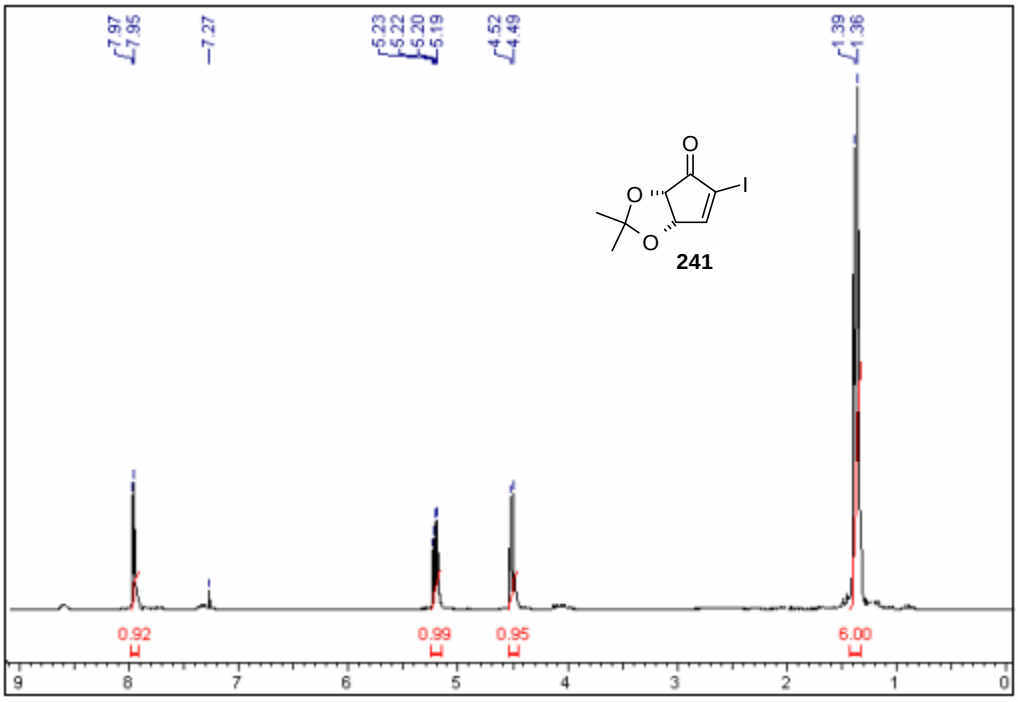
^{1}H NMR spectrum of the compound 235:



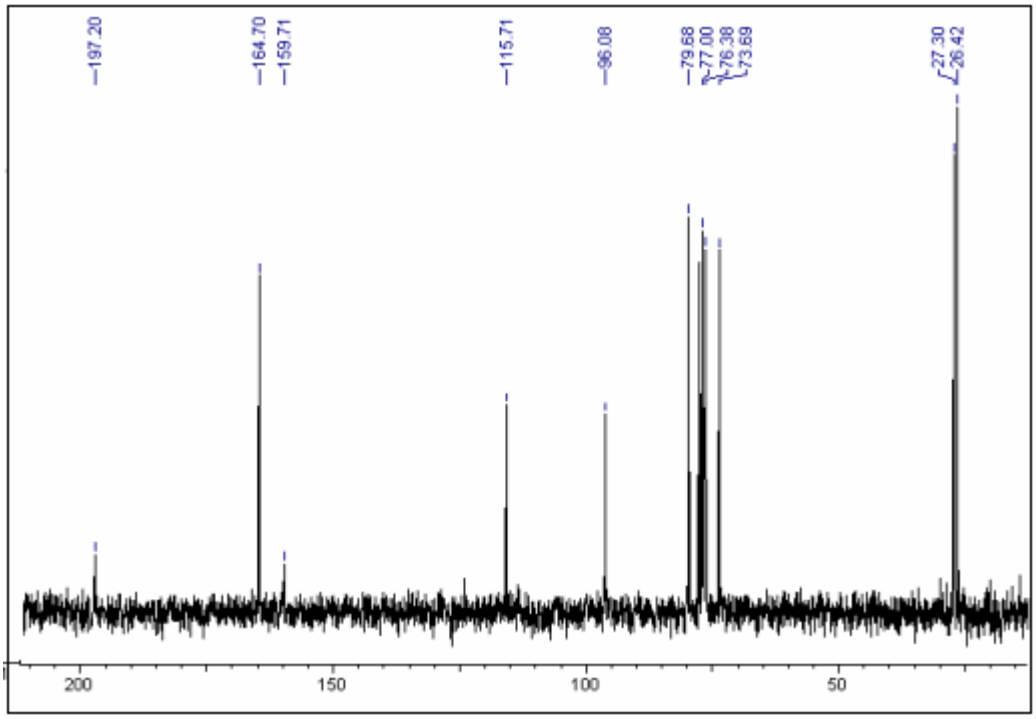
^{13}C NMR spectrum of the compound 235:



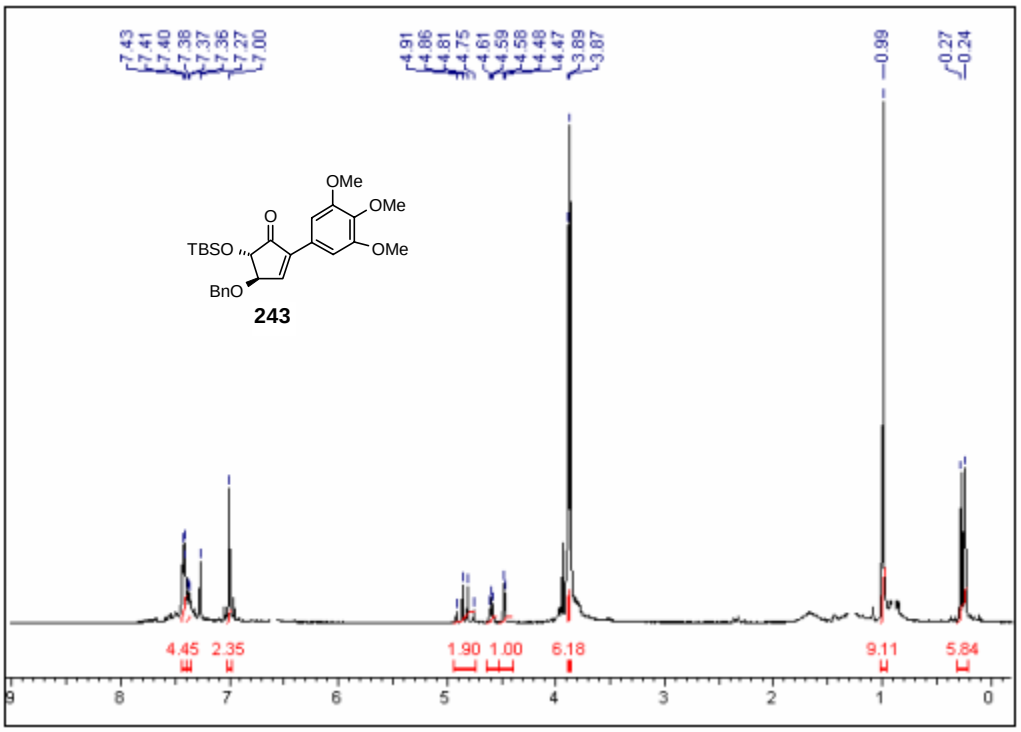
^{1}H NMR spectrum of the compound 241:



^{13}C NMR spectrum of the compound 241:



^{1}H NMR spectrum of the compound 243:



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CHAPTER 1

SECTION IV

Resolution of 4–Hydroxy-2-(3,4,5-Trimethoxyphenyl)-cyclopent-2-en-1-one and Substituted-2,3-Diaryl-4/5-Hydroxycyclopent-2-en-1-one Analogues of CA-4

1.4.1 INTRODUCTION:

The importance of obtaining optically pure materials hardly requires restatement. Manufacture of chemical products applied either for the promotion of human health or to combat pests that otherwise adversely impact on the human food supply is now increasingly concerned with the enantiopurity. A large proportion of such products contain at least one chiral center. To show importance of single-enantiomer drugs, Sujan Ba, Director of Chiral Chemistry Consulting Services at the consulting firm Technology Catalyst International (TCI) measured their appearance among the top-selling drugs[1]. Of the top 100 drugs world wide, 50 are single enantiomers. Their sales were $42.8 billion in 1997 i.e. 51 % of the total sales of $85.2 billion for these top 100 drugs. Single enantiomers remain important among the top 300, with 158 drugs accounting for $64.7 billion out of total sales of $124.4 billion. There is a move towards increasing single enantiomer use, wherever possible as a matter of choice as well as by dictates of regulates in bioactive materials for different reasons including the biological ones.

The reasons for producing optically pure materials include the following: (i) biological activity is often associated with only one enantiomer (ii) enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable (Fig.1). Racemic thalidomide consumed by expectant mothers as sedative in the early sixties created a generation of maltransformed babies because of teratogenicity of the (S)-isomer[2] which made the company to close down for ever and opened the eyes of scientist against the potential harm from the wrong isomer usage. Production of only one enantiomer allows the separation of the effects; (iii) the unwanted isomer is at best 'enantiomeric ballast[3] gratuitously applied to the environment (iv) the optically pure compound may be more than twice as active as the racemate because of antagonism, for example the pheromone of the Japanese beetle **245** where, as little as 1 % of the (S, Z)-isomer inhibits the (R, Z) isomer;[4] (v) registration consideration;[5] production of materials as the required enantiomer is now a question of law in certain countries, the unwanted enantiomer being considered as an impurity; (vi) where the switch from racemate to enantiomer is feasible, there is the opportunity effectively to double the capacity of an industrial process; alternatively, in some cases, where the optically active component of the synthesis is not very expensive, it may allow significant savings to be made in some other achiral but very expensive process intermediate; vii) improved cost benefit ratio; viii) the physical characteristics of enantiomers versus racemates may confer processing or the formulation advantages.

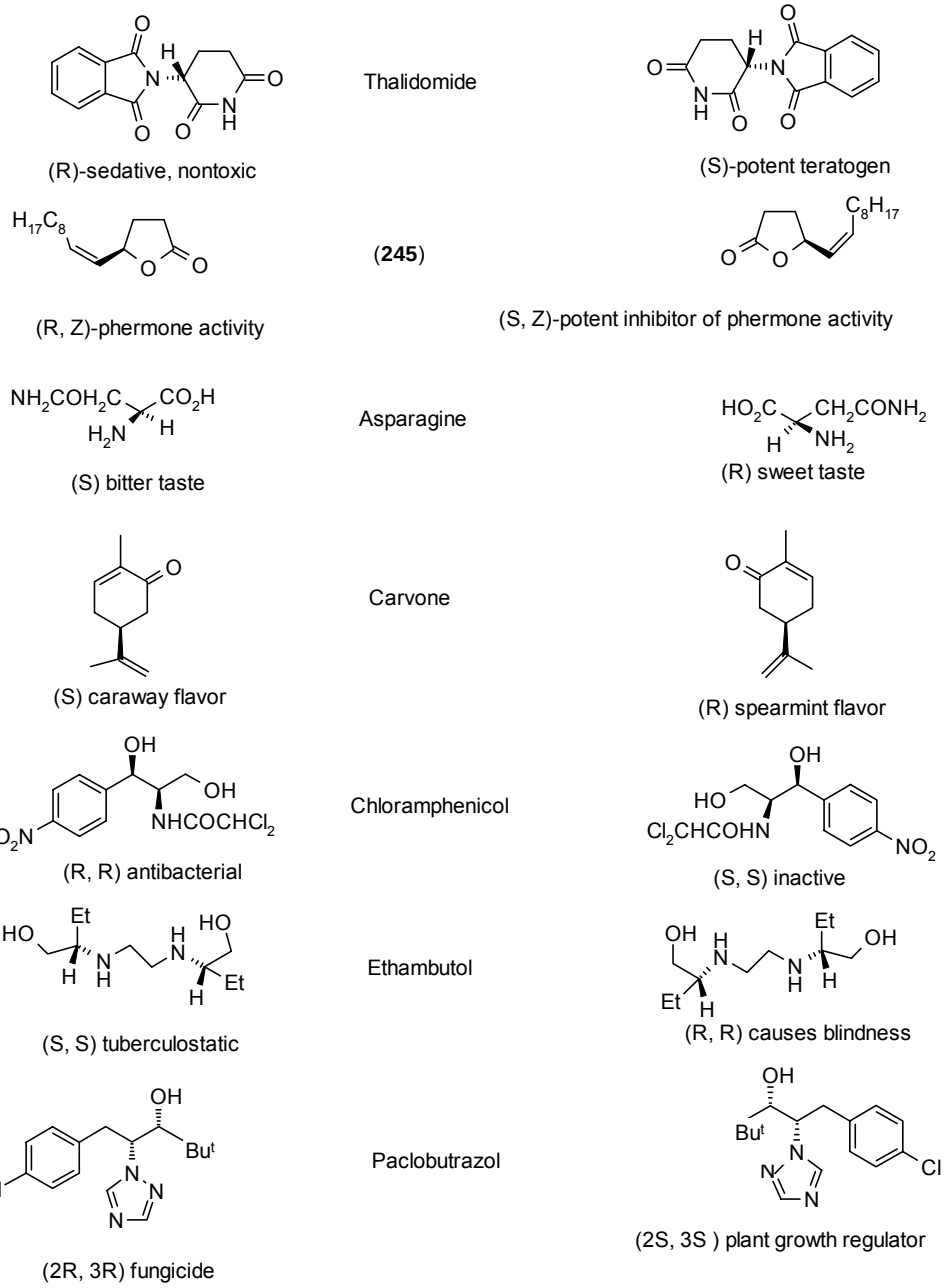


Fig. 1

The development of the various strategies for the synthesis of optically active compounds in high enantiomeric excess has made great advances over the last decade. All conceivable methods for the production of optically pure materials are being actively researched. All these methods are summarized in Figure 2. The enzymes can play their role in the production of single enantiomer either by kinetic resolution of racemates or by asymmetric synthesis from prochiral substrates.

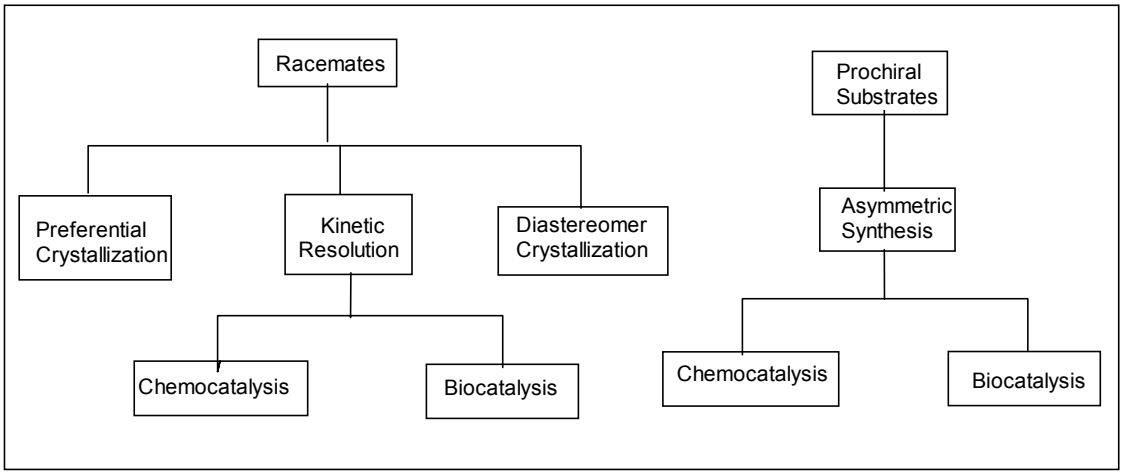


Fig 2

Nevertheless, resolution is still necessary to prepare optically pure chiral auxiliaries, to purify products of low enantiomeric excess and as a valid strategy for chiral synthesis in its own right. The most important general procedure for such resolutions, originally proposed and explored by Pasteur, involves the conversion of the mixture of enantiomers into a pair of diastereoisomeric derivatives by reaction with a pure, optically active reagent, as shown in following equation.

$$2(\pm)\text{-X} + 2(+)\text{-Y} \rightarrow (+)\text{-X}(+)\text{-Y} + (-)\text{X}(+)\text{-Y}$$

(a) (b) (c)

It should be noted that the enantiomers in the mixture (or racemate) (a) have identical physical properties (except for their action on the plane of polarised light), the diastereomers (b) and (c) have physical properties (e.g. solubility, boiling points, chomatographic behavior, etc.) which are frequently significantly different. Resolution of the mixture (or racemate) can then be achieved provided that one of the diastereomers may be obtained in a pure state, and that regeneration from it of the pure enantiomorphous form is not accompanied by any degree of racemization.

The most important development in the last decade for the resolution of mixtures of enantiomers is in the application of g.l.c, h.p.l.c and NMR techniques. These techniques have been used in the analytical mode to determine the ratio of enantiomers, for example in the case of products arising from an asymmetric synthesis. The chromatographic methods may also be used in the preparative mode for the realistic isolation of the pure enantiomers. Furthermore, by a close study of the chromatographic behaviour (i.e. elution times) of a series of enantiomeric pairs of compounds having like functionality and known configurations, some judgement is possible for the assignment of configuration to a similar member of the series but of unknown configuration.

Methods for determination of absolute configuration of organic substances:

The determination of absolute configurations of organic compounds has become an important task of the natural products chemist as well as the synthetic chemist. There are a few physical methods, e.g. exciton chirality method[6] and X-ray crystallography that fill this need. The heavy-atom phase-shifted X-ray crystallographic analysis being the most general and reliable is nevertheless limited by the necessity to get adequate monocrystals and requires specialized equipment. There are also several chemical methods used to predict the absolute configurations of organic substances[7]. Mosher`s method[8] involving study of NMR spectra of 2-methoxy-2-phenyl-2(trifluoromethyl) acetic acid (MTPA) esters has been found very useful in many cases.

In recent years there has been a marked increase in the number of papers describing the use of NMR for the assignment of absolute stereochemistry of organic compounds. The general procedure consists of the derivatization of the substrate of unknown configuration with the two enantiomers of an auxiliary reagent. The proton NMR spectra of the resulting diastereoisomeric derivatives are compared and the difference in chemical shifts is measured to give a $\Delta\delta^{RS}$ values. Mosher proposed a configuration correlation model to assign the configuration of unknown compound from the shift difference of two diastereoisomeric derivatives as given in figure 4 (C). The specification of the carbinyl moiety as R or S follows from the application of the Cahn-Ingold-Prelog configurational nomenclature rules. Several auxiliary reagents (Fig 3) have been described for this purpose[9]. But very few have been subjected to detailed theoretical or experimental studies. There are many publications which guide the factors governing the efficiency of arylmethoxyacetic acids (AMAAs) for the determination of absolute configuration of alcohols by NMR.[10, 11] Among them, Mosher`s method[8] using 2-methoxy-2-phenyl-2(trifluoromethyl) acetic acid (MTPA) esters has been most frequently used. Mosher proposed

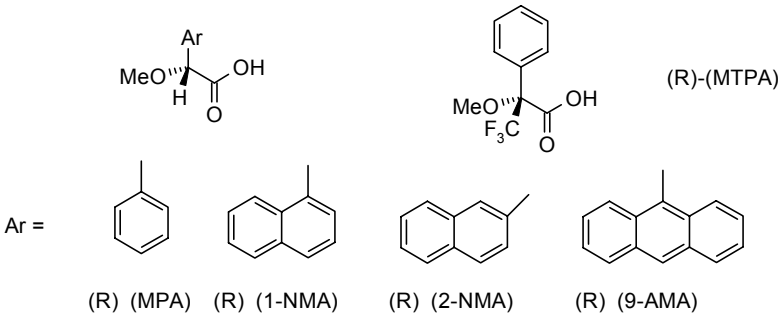


Fig 3

that, in solution, the carbinyl proton and ester carbonyl and trifluoromethyl groups of the MTPA moiety lie in the same plane (Fig 4 A). When the MTPA group is in the hypothesized conformation, Mosher pointed out that the ^{1}H NMR signal of L^2 of the (R) MTPA ester will appear upfield relative to that of the (S)-MTPA ester due to the diamagnetic effect of the benzene ring. When Mosher first put forward this analysis, the NMR instruments most commonly available were 60-100 MHz instruments and the complete assignment of protons of complex organic molecules was practically impossible.

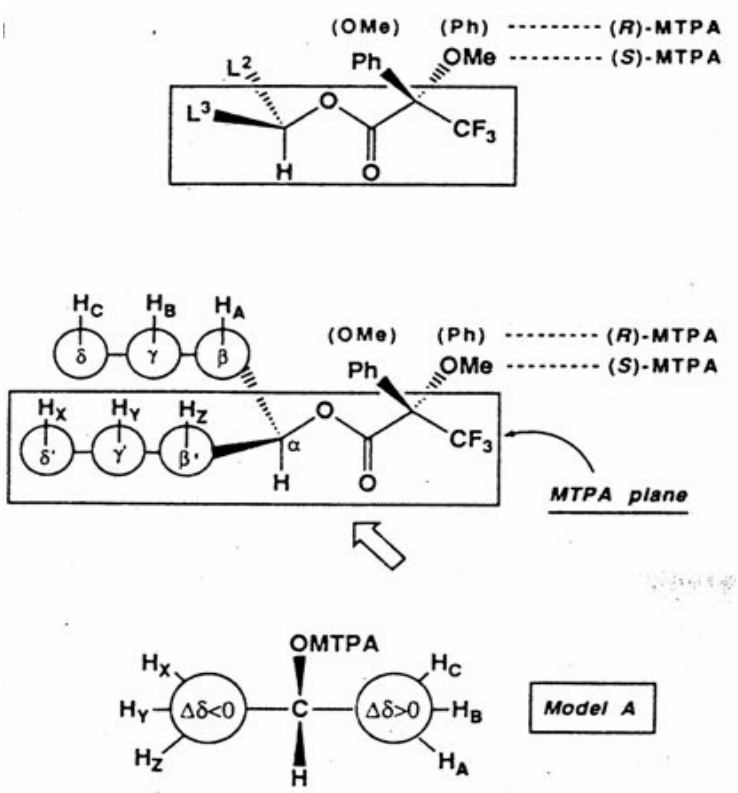


Fig 4

(A) Configurational correlation model for the (R)-MTPA derivatives and the (S)-MTPA derivatives proposed by Mosher. (B) MTPA plane of an MTPA ester is shown. $H_{A, B,C}$ and $H_{X, Y, Z}$ are on the right and left sides of the plane, respectively. (C) Model A to determine the absolute configurations of secondary alcohols is illustrated. Model A is a view of the MTPA ester drawn in (B) from the direction indicated by the outlined arrow.

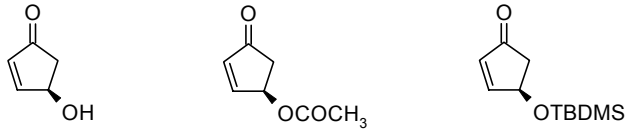
The most important factor in use of these modified methods is the difference in steric bulkiness on the β-and β`-carbons (Fig 4 B); the steric repulsion between the phenyl group of the MTPA moiety and the β-substituents is essential to bring about the chemical shift difference of the CF_3 (^{19}F) or OMe (^{1}H) group.[12]

The advanced Mosher method reported by Ohtani *et al.*[12] provided a major breakthough in the field of absolute stereochemical determination.

Methods for the preparation of optically pure 4-(R)-hydroxycyclopentenone or its OH-protected derivatives:

Large amount of literature is available for the preparation of optically pure 4-hydroxy-cyclopentenone building block **(246)**, its O-acetate derivative **247** and its O-silylated derivative **248**. The various methods reported for the synthesis of **246** and its derivatives **247** and **248** are mainly of two types *viz.* chemical methods and enzymatic methods.

Chemical methods include classical resolution of the racemic **246**, preparation from chiral natural products or *via* resolved synthetic intermediates, by asymmetric synthesis and by kinetic resolution of (±)-**246** using chiral catalysts.

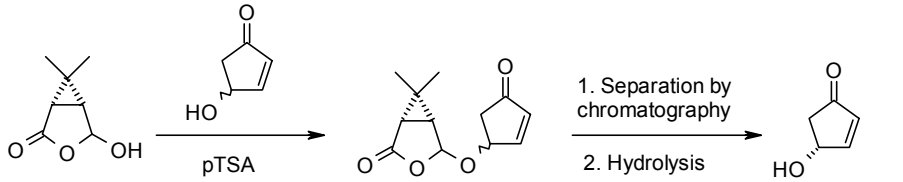


246 **247** **248**

The (R) cyclopentenone derivative **246**, is obtainable by chemical[13] or chromatographic resolution,[14] transformation from D-tartaric acid (2S,3S)-(-)-tartaric acid),[15] chemical kinetic resolution of racemic 4-hydroxycyclopent-2-en-1-one,[16] enzymatic kinetic resolution of the acetate[17] and asymmetric reduction of 2-cyclopentene-1,3-dione[18] etc.

Noyori *et al.*[19] resolved (±)-**246** using bicyclic species caronaldehyde (**249**), derived from (1S, 3S)-*trans* chysanthemic acid proved to be an efficient resolving agent. They found that diastereomeric adducts **250** of racemic **246** with caronaldehyde could be easily separated on a silica gel column. The desired (R)-**246** of 97 % ee was obtained in 88 % overall yield (scheme 1).

Scheme 1



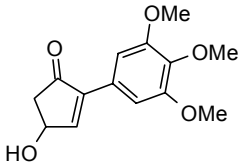
249 **250** (R)- **246**
e.e.> 97%

The use of caronaldehyde for the resolution of substituted 2-aryl/2,3-diaryl-4/5-hydroxy cyclopentenone is not known. So we explored the methods for resolution of these compounds.

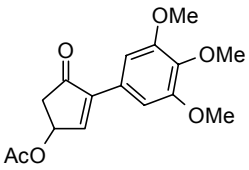
1.4.2 PRESENT WORK:

As discussed in section I and II of chapter 1 we have synthesized several cyclopentenone analogues of combretastatin A-4. The hit compounds in our designed molecules demonstrated remarkable cytotoxic activity against a variety of human cancer cell lines. Initially we screened these compounds in their racemic forms. These cyclopentenone analogues possess one asymmetric center therefore resolution of these compounds was undertaken to obtain two enantiomers in pure form so that one enantiomer may exhibit improved potent activity or both of which may be beneficial or one may be beneficial and the other may be undesirable.

1.4.3: Resolution of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (102):



102



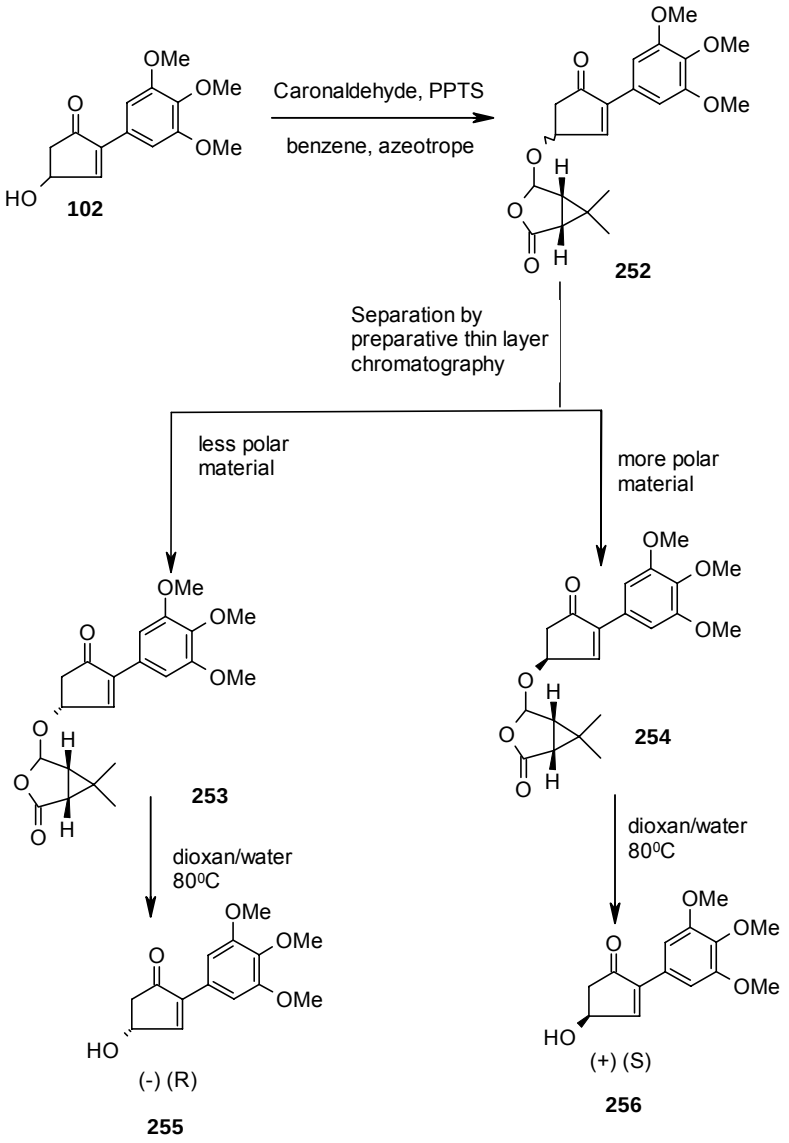
251

As 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**102**) was the key intermediate for the synthesis of designed combretastatin analogues we attempted the resolution of intermediate **102** so that we could synthesize chiral CA-4 analgoues.

Initially we tried to resolve intermediates **102** and **251** by enzymatic methods. First we tried the ester hydrolysis of compound **251** using commercially available enzymes like Porcine Pancreatic Lipase (PPL), Pig Liver Acetone Powder (PLAP) and Chicken Liver Acetone Powder (CLAP) in buffer at pH 7, but selective ester hydrolysis was not observed.

Since enzymatic ester hydrolysis did not work in this case, we attempted lipase catalysed transesterification of compound **102**. The various enzymes like PPL, PLAP, CLAP, chirazyme and *Candida cylindracea* (CCL) were tried in various acyl donar solvents like vinyl acetate, ethyl acetate etc. Using *Candida cylindracea* and vinyl acetate, the transesterification of compound **102** was observed with poor selectivity. Moreover the results were not reproducible and consistant.

Therefore, the chemical method for resolution of intermediate **102** by forming mixture of diastereoisomers with caronaldehyde, separation of the diastereoisomers and hydrolysis of the purified diastereoisomers to the corresponding alcohol was adopted as captured in the graphical presentation in scheme 2.



Scheme 2

The compound **102** was treated with (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[20] (caronaldehyde) and PPTS in benzene with azeotropic removal of water to form the diastereoisomeric mixture **252**. The diastereoisomers were then separated by preparative thin layer chromatography, to afford pure diastereoisomers **253** and **254** which on hydrolysis with dioxan and water afforded pure enantiomers **255** and **256** respectively (scheme 2).

The next task was to assign absolute configuration to enantiomers **255** and **256** and to determine ee of **255** and **256**.

NMR chiral shift reagent: Tris[3-(trifluoromethylhydroxymethylene)-(+)camphorato] europium (III) was used as chiral shift reagent and its effect on the NMR spectra of racemic **102** as well as optically enriched **255** was studied. Few overlapping peaks in the spectra were shifted and resolved, but separation of enantiomeric peaks was not observed at various concentrations of shift reagent used. Therefore this method was not useful for identification of asymmetry at 4 position of 2-aryl-4-hydroxy-cyclopentenone.

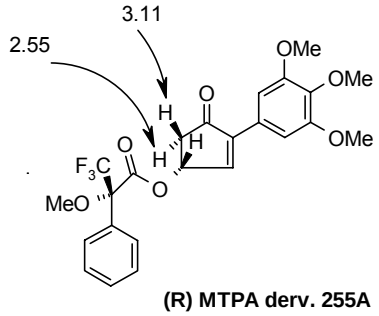
We prepared various derivatives of resolved enantiomers to get crystals in attempt to assign absolute stereochemistry by X-ray crystallography but we were unable to get good crystals of compounds **255** and **256** under various conditions.

Mosher ester method: Assignment of absolute configuration:

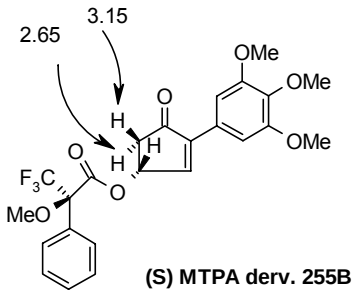
Mosher esters of racemic as well as optically enriched **255** and **256** were prepared by treating them with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane. The spectra of both Mosher esters were studied. Peaks of the -OMe of Mosher esters were resolved in both ester derivatives. From the comparison of peak areas ee of **255** was >98 % and ee of **256** was >97 %.

Still the problem of determining absolute configuration was not solved. So we studied Mosher esters **255A** and **255B** prepared from the enantiomer **255** by reacting it with (R)-Mosher acid and (S)-Mosher acid respectively in order to determine the absolute configuration by study of ^{1}H NMR spectra.[8]

From the chemical shift differences of β-substituents (CH_2) in both ester derivatives and following Mosher's model, the absolute configuration for **255** was assigned as (R) and the other enantiomer **256** was assigned the (S) configuration as shown below.



(R) MTPA derv. 255A



(S) MTPA derv. 255B

$\Delta\delta = (\delta s - \delta r) \times 1000$

For 5 H β = (3.15-3.11) x 1000

= (0.04) x 1000

= +40

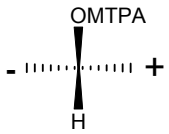
$\Delta\delta = (\delta s - \delta r) \times 1000$

For 5 Hα = (2.65-2.55) x 1000

= (0.10) x 1000

= +100.

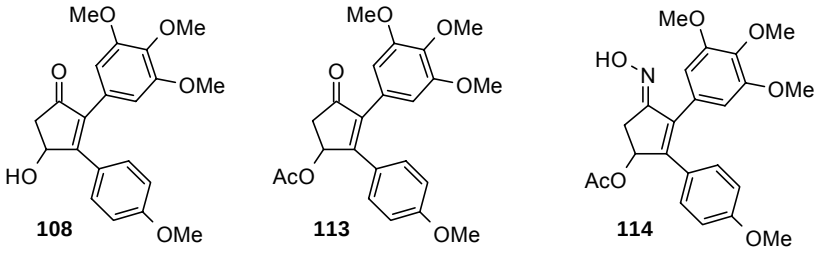
Mosher's configurational correlation model



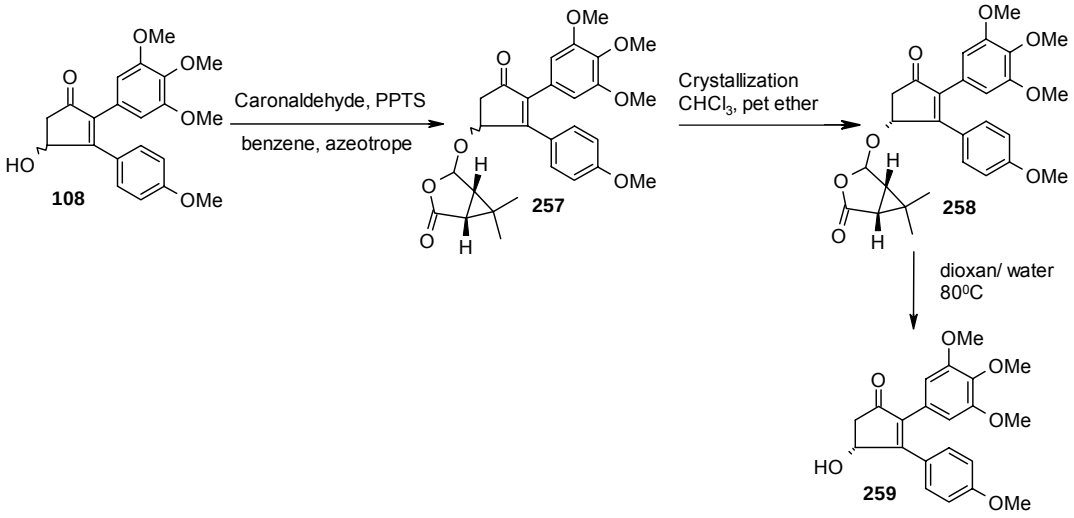
According to Mosher's method, the groups showing + $\Delta\delta$ value are placed on the right hand side of this model and the groups showing -$\Delta\delta$ value are placed on the left hand side. As in our case the $\Delta\delta$ value was positive for the 5 Hβ and 5 Hα, we placed the methylene group on the right hand side of Mosher's model and followed the priority rules to come to the conclusion that the enantiomer **255** showing rotation $[\alpha]_D^{25}$ -14.76^0 (c 1.00, $CHCl_3$) had (R)-configuration and the other enantiomer i.e. **256** had (S) configuration.

1.4.4: Resolution of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**108**):

Our achievement in the resolution of (R) and (S) enantiomers of the key intermediate **102** and the assignment of their absolute configuration by NMR studies of their Mosher esters; encouraged us to repeat this protocol for the cytotoxic molecule **108**. The optical isomers thus obtained can further be derivatised to get the analogue **114** in optically active form.



The preparation of the compound **108** is given in section I of the chapter 1. The compound **108** was treated with (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[20] (caronaldehyde) and PPTS in benzene with azeotropic removal of water to form the mixture of diastereoisomers of the compound **257**. This mixture of diastereoisomers of compound **257** on crystallization using chloroform and petroleum ether afforded the diastereomer **258** in pure form. Another diasteroisomer could not be obtained in pure form (scheme 3).

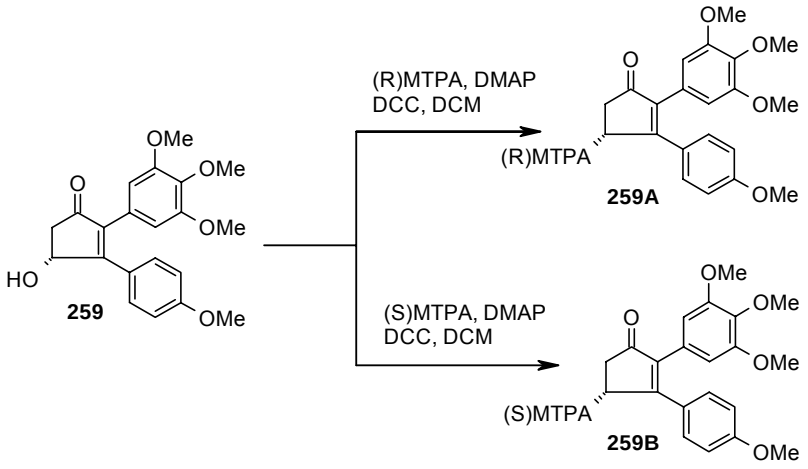


Scheme 3

The compound **258** on hydrolysis with dioxan and water afforded pure enantiomer **259** having specific rotation +17.18° (c 1.00, $CHCl_3$). As the absolute configuration of the compound **259** was not known in the literature, our next aim was to assign absolute configuration and to determine enantiomeric excess (ee) of the compound **259**.

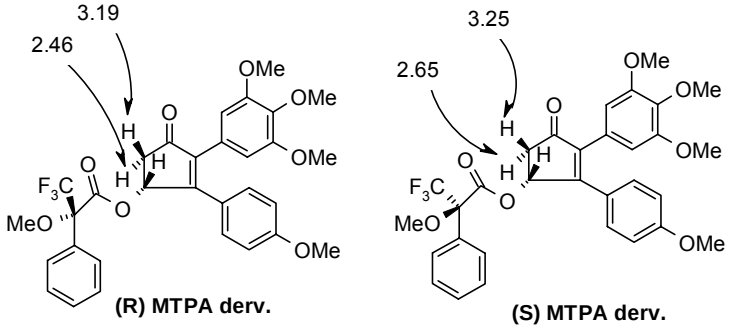
Mosher ester method: Assignment of absolute configuration:

Mosher ester of **259** was prepared by treating it with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane to form derivative **259A**. Similarly (S) Mosher ester was prepared by treating **259** with (S) Mosher acid under similar conditions and derivative **259B** was obtained as shown in scheme 4.



Scheme 4

The spectra of both Mosher esters were studied. From the the chemical shift differences of β-substituents (CH_2) in both ester derivatives **259A** and **259B** and following Mosher's model the absolute configuration for **259** was assigned as (R).



$\Delta\delta = (\delta s - \delta r) \times 1000$

For 5 Hβ = (3.25-3.19) x 1000

= (0.06) x 1000

= +60

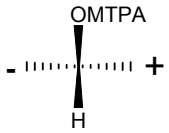
$\Delta\delta = (\delta s - \delta r) \times 1000$

For 5 Hα = (2.65-2.46) x 1000

= (0.19) x 1000

= +190.

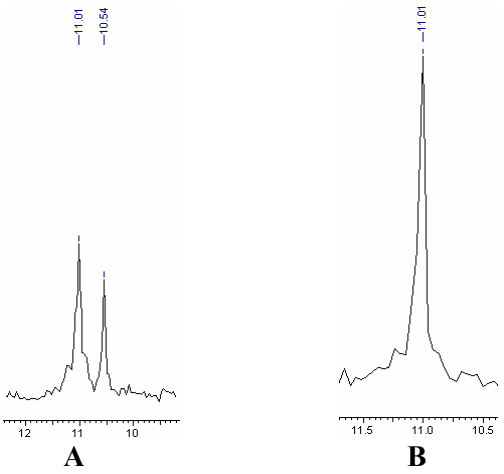
Mosher's configurational correlation model



As in our case the Δδ value was positive for the 5 Hβ and 5 Hα, we placed these groups on the right hand side of Mosher's model and following priority rules, the (R) configuration was assigned to the isomer **259** which was showing rotation $[\alpha]_D^{25}$ +17.18° (c 1.00, $CHCl_3$).

Mosher ester method: Mosher ester of racemic (**108**) as well as optically enriched **259** was prepared by treating with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane. The ^1H NMR spectra of both the Mosher esters were studied. Peaks of the -OMe of Mosher esters were resolved in both ester derivatives. The enantiomeric excess of compound **259** was determined from the comparison of peak area in ^1H NMR and it was found to be >98 %.

Similarly the ^{19}F spectra of (R) Mosher ester of racemic **108** as well as optically enriched **259**

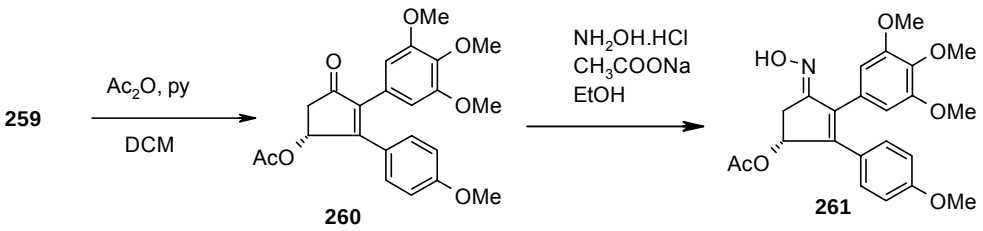


A) ^{19}F NMR spectrum of the (R) MTPA ester derivative of the compound **108**

B) ^{19}F NMR spectrum of the (R) MTPA ester derivative of the compound **259**

were studied. The (R) Mosher ester of racemic **108** showed two peaks in its ^{19}F spectra at δ 10.54 and 11.01, while (R) Mosher ester derivatives of **259** showed single peak δ 11.01 in ^{19}F spectra which confirmed the ee> 98 %.

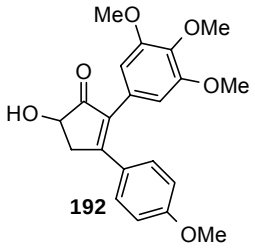
The acylation of compound **259** with acetic anhydride and pyridine in dichloromethane afforded acetate derivative **260** in 83 % yield having specific rotation +16.1° (c 1.00, $CHCl_3$). Oximation of compound **260** using hydroxylamine hydrochloride and sodium acetate afforded oxime derivative **261** in 77 % isolated yield which was having specific rotation +25.8° (c 1.00, $CHCl_3$) (scheme 5).



Scheme 5

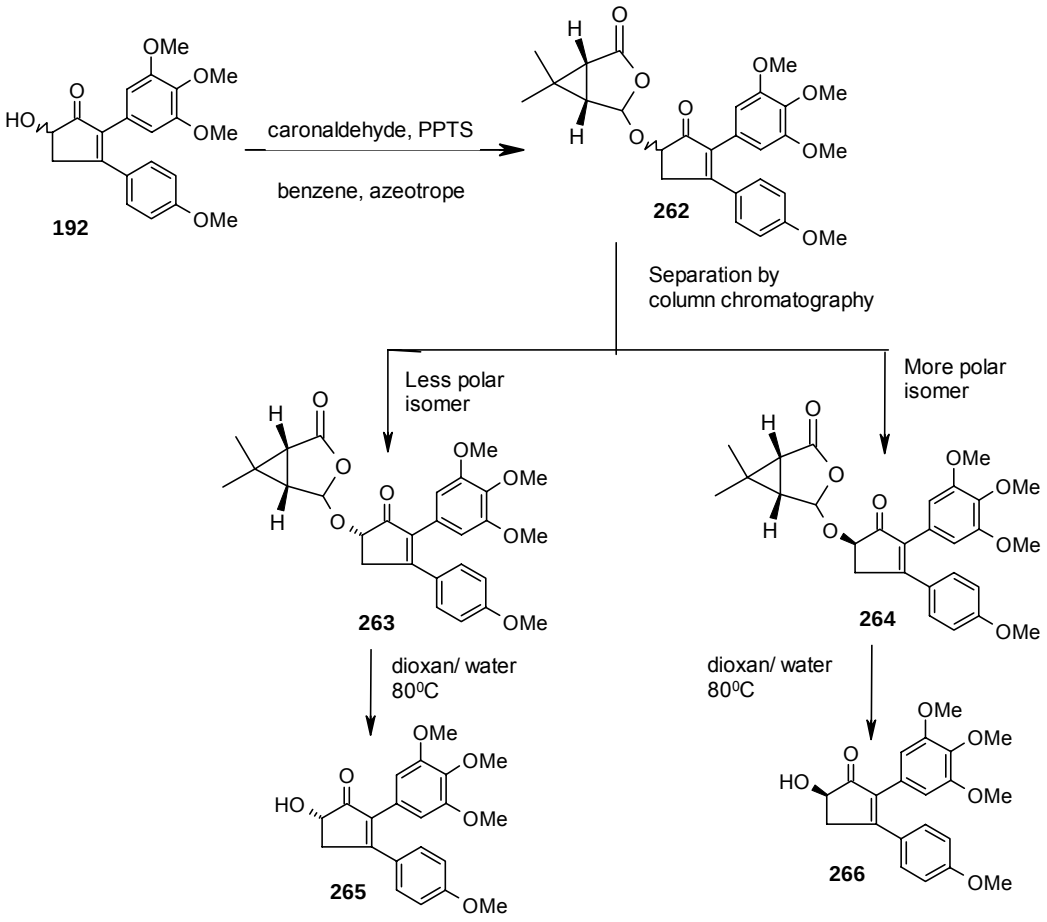
1.4.5: Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (192):

In continuation with our efforts to resolve the designed and synthesized molecules which demonstrated promising cytotoxic activity, the compound **192** was selected for resolution to its optical isomers. The compound **192** as well as its oxime derivative **194** showed high potential for inhibition of tubulin polymerization even in their racemic forms. Consequently, resolution of the compound **192** was highly desired.



The preparation of compound **192** is given in section II of the chapter 1. When compound **192** was treated with (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[20] (caronaldehyde) and PPTS in benzene with azeotropic removal of water, the mixture of diastereoisomers represented as the compound **262** was obtained. The column chromatographic purification of this mixture using silica gel afforded two compounds **263** and **264**. The compounds **263** and **264** on hydrolysis with dioxan and water afforded pure enantiomers **265** and **266** which were having specific rotation of + 23.15° (c 0.55, $CHCl_3$) and - 22.47° (c 0.45, $CHCl_3$)

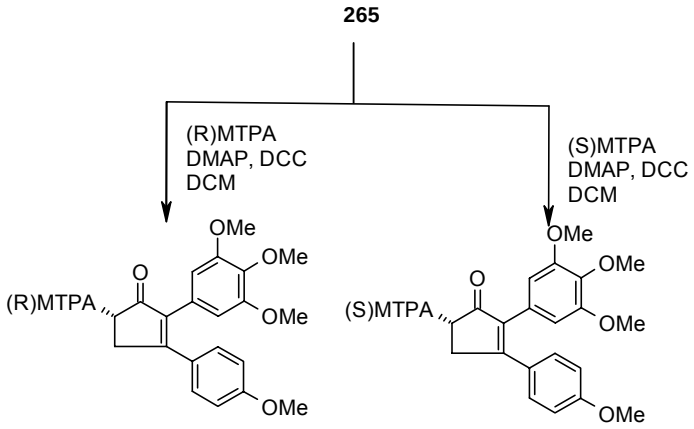
respectively (scheme 6). The absolute configuration of compounds **265** and **266** is not known in the literature, therefore assignment of absolute configuration and determination of enantiomeric excess of the compounds **265** and **266** was undertaken, which is described below.



Scheme 6

Mosher ester method: Assignment of absolute configuration:

Mosher ester of **265** was prepared by treating with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane. Similarly Mosher ester of **265** was prepared by treating with (S) Mosher acid under similar conditions. The spectra of both Mosher esters were studied. From the chemical shift differences of β-substituents (CH_2) in both ester derivatives and following Mosher's model, the absolute configuration for **265** was assigned as (S) and the configuration of another isomer **266** was assigned as (R**)**.



$\Delta\delta = (\delta s - \delta r) \times 1000$

For 4 Hβ = (3.03-3.23) x 1000

= (- 0.20) x 1000

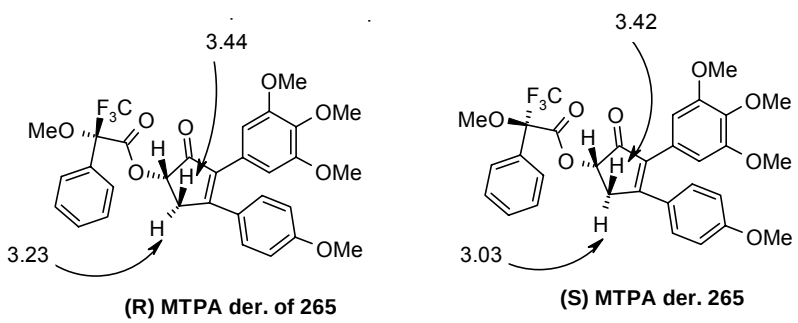
= - 200

$\Delta\delta = (\delta s - \delta r) \times 1000$

For 4 Hα = (3.42-3.44) x 1000

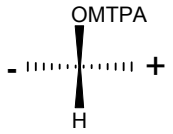
= (-0.02) x 1000

= -20.



(R) MTPA der. of 265 **(S) MTPA der. 265**

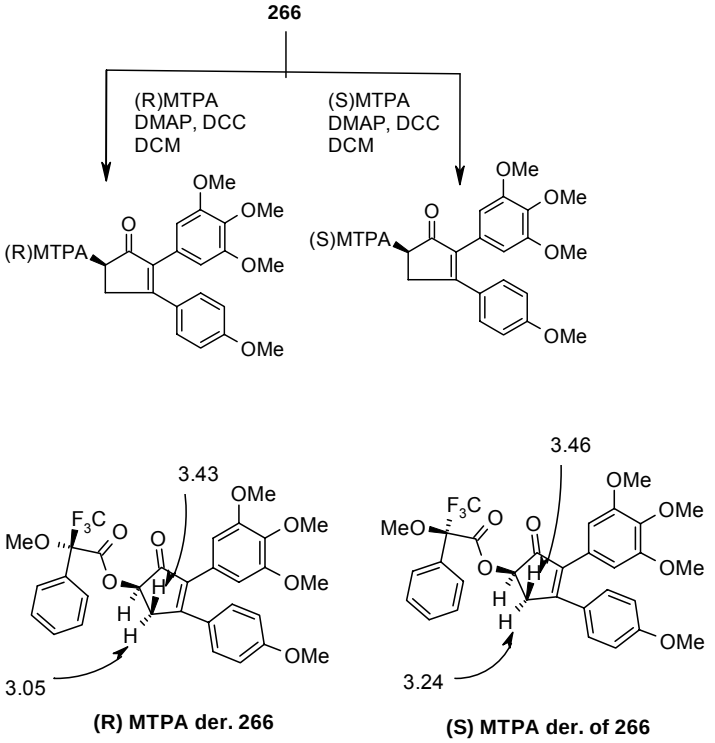
Mosher's configurational correlation model



According to Mosher's model, as in our case the Δδ value was negative for the 4 Hβ and 4 Hα, we placed these groups on the left hand side of Mosher's model and followed the priority rules to

assign the (S) configuration to the isomer **265** which showed rotation $[\alpha]_D^{25}$ + 23.15° (c 0.55, $CHCl_3$, ee > 98).

Under similar conditions Mosher ester of **266** was prepared by treating with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane. Similarly Mosher ester of **266** was prepared by treating with (S) Mosher acid under similar conditions. The spectra of both Mosher esters were studied. From the the chemical shift differences of β-substituents (CH_2) in both ester derivatives and following Mosher's model the absolute configuration for **266** was assigned as (R) configuration.



$\Delta\delta = (\delta s - \delta r) \times 1000$

For 4 Hβ = (3.46-3.43) x 1000

= (0.30) x 1000

= + 30

$\Delta\delta = (\delta s - \delta r) \times 1000$

For4 Hα = (3.24-3.05) x 1000

= (0.19) x 1000

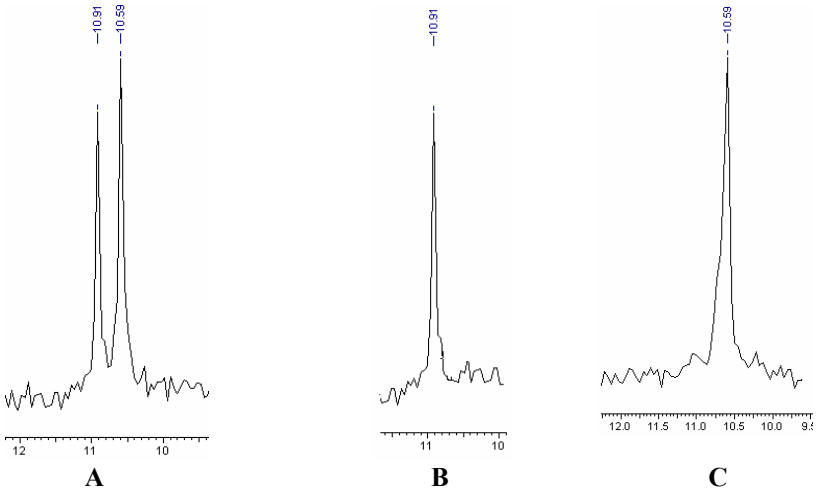
= + 190.

As calculated above, the Δδ value was positive for the 4 Hβ and 4 Hα, so we placed these groups on the right hand side of Mosher's model. Following the priority rules, the (R) configuration was assigned to the isomer **266** which showed rotation -22.47° (c 0.45, $CHCl_3$, ee>98).

Mosher ester method for determination of enantiomeric excess:

Mosher esters of racemic **192** as well as the optically enriched **265** and **266** were prepared by treating them with (R) Mosher acid and dicyclohexylcarbodiimide in dichloromethane. The spectra of both Mosher esters were studied. Peaks of the -OMe of Mosher esters were resolved in both ester derivatives. The enantiomeric excess of compound **265** and **266** was determined from the comparison of peak area in ^{1}H NMR it was found to be >98 %.

Similarly the ^{19}F spectra of (R) Mosher ester of racemic **192** as well as optically enriched **265** and **266** were studied. The (R) Mosher ester of racemic **192** showed two peaks in its ^{19}F spectra at δ 10.59 and 10.91, while (R) Mosher ester derivative of **265** showed single peak at δ 10.91 and (R) Mosher ester derivative of **266** showed peak at δ 10.59 as single peaks. These ^{19}F spectral studies confirmed the optical purity of our resolved compounds.



A) ^{19}F NMR spectrum of the (R) Mosher ester derivative of the compound **192**

B) ^{19}F NMR spectrum of the (R) Mosher ester derivative of the compound **265**

C) ^{19}F NMR spectrum of the (R) Mosher ester derivative of the compound **266**

1.4.6: CONCLUSION:

Resolution of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**102**) was carried out successfully by chemical method. Both the enantiomers (R)-**(255)** and (S)-**(256)** were separated with good enantiomeric excess and the absolute configurations of these isomers were assigned by ^{1}H NMR studies of Mosher esters.

Similarly, 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**108**) was resolved using caronaldehyde. One of the isomers **259** having absolute configuration (R) was separated with good enantiomeric excess (>98 %), absolute configuration was assigned by NMR studies of its (R) and (S) Mosher esters. Further, the chiral analogue **261** was prepared which showed better inhibition of tubulin polymerization than its racemic form.

Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (**192**) into its (R) and (S) isomers was achieved successfully. Both the isomers (S) (**265)** and (R) (**266**) were separated with good enantiomeric excess (>98 %), absolute configuration was assigned by NMR studies of its (R) and (S) Mosher ester derivatives of both the isomers independently.

1.4.7 EXPERIMENTAL:

Procedure for the resolution of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (102):

In a 100 ml single neck round bottom flask equipped with a Dean-Stark apparatus, were placed racemic 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(102)** (0.50 g, 1.89 mmol), (1R, 2S)-*cis*-2-formyl-3,3-dimethycyclopropane-1-carboxylic acid (a cyclic hemiacylal form) (0.191 g, 1.35 mmol, $[\alpha]_D^{25}$ –105°, c 0.5 C_2H_5OH), pyridinium *p*-toluenesulfonate (0.16 g, 0.67 mmol) and dry benzene (20 ml). The mixture was heated at reflux under stirring for 12 h. The TLC analysis indicated completion of the reaction. Then the benzene was removed under reduced pressure, the residual material was dissolved in ethyl acetate (50 ml) and washed twice with water followed by saturated $NaHCO_3$ solution (20 ml) and three times with water. The organic solution was dried and concentrated on rotary evaporator to give crude mixture of condensation product (0.60 g, 81 %). The diastereomers (0.05 g) were separated by preparative thin layer chromatography using 20 % ethyl acetate and petroleum ether (>15 times run). It afforded the

less polar material (0.018 g, 36 %) and more polar material (0.014 g, 28 %) as yellowish thick liquids.

The less polar material (253):

Yield 36 %; $[\alpha]_D^{25}$ -92.43^0 (c 0.2, $CHCl_3$); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1580, 1715, 1777, 2937, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.19 (s, 3H), 1.23 (s, 3H), 2.09 (dd, *J* = 8 Hz and 6 Hz, 2H), 2.59 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.00 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.86 (s, 3H), 3.89 (s, 6H), 5.01-5.10 (m, 1H), 5.35 (s, 1H), 6.98 (s, 2H), 7.67 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.31, 24.98, 25.60, 30.16, 35.60, 43.39, 56.41 (2C), 61.11, 74.64, 101.18, 105.11 (2C), 125.88, 139.33, 144.70, 153.41, 154.14 (2C), 173.11, 203.00;**Mass** (m/e): 388 (M^+).

More polar material (254):

Yield 28 %; $[\alpha]_D^{25}$ -49.56^0 (c 0.2, $CHCl_3$); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1580, 1715, 1777, 2937, 3016 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.20 (s, 3H), 1.23 (s, 3H), 2.10 (dd, *J* = 10 Hz and 6 Hz, 2H), 2.71 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.03 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 6H), 5.00-5.08 (m, 1H), 5.41 (s, 1H), 7.00 (s, 2H), 7.62 (d, *J* = 4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.06, 24.66, 25.36, 29.91, 35.32, 44.40, 56.20 (2C), 60.90, 74.24, 100.06, 104.90 (2C), 125.63, 139.75, 145.08, 151.54, 153.20 (2C), 172.46, 203.01; **Mass** (m/e): 388 (M^+).

Hydrolysis of less polar material:

A mixture of less polar material **253** (0.018 g, 0.046 mmol) obtained above by preparative thin layer chromatography, dioxan (0.5 ml) and water (1.0 ml) was placed in 10 ml single neck round bottom flask and heated at 80^{0}C for 4 h under stirring. The TLC showed the disappearance of starting material. The reaction mixture was cooled to room temperature, and then the dioxan was removed under reduced pressure. To the residual aqueous layer saturated $NaHCO_3$ solution (1 ml) was added followed by the addition of $NaHCO_3$ powder until the reaction mixture was basic to pH paper. The aqueous layer was extracted three times with ethyl acetate (3 x 5 ml). The combined extracts were dried and evaporated on a rotary evaporator to afford (R)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one (**255**) (0.011 g, 90 %).

$[\alpha]_D^{25}$ -14.76° (c 1.00, $CHCl_3$, ee> 98); m. p. 85-86^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1709, 3464 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.50 (dd, *J* = 18 Hz and 2 Hz, 1H), 2.98 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 6H), 4.98-5.08 (m, 1H), 6.96 (s, 2H), 7.56 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 45.78, 55.88 (2C), 60.58, 67.02, 104.59 (2C), 125.92 (2C),

138.34, 142.80, 152.75, 156.66, 204.48; **Mass** (m/e): 264 (M^+, 100); Anal. Calcd. For $C_{14}H_{16}O_5$: C 63.63; H 6.10 %. Found: C 63.71; H 6.18 %.

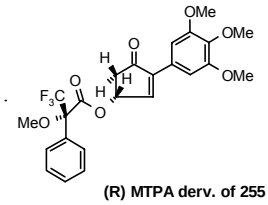
Hydrolysis of more polar material:

A mixture of more polar material **254** (0.014 g, 0.036 mmol) obtained above by preparative thin layer chromatography, dioxan (0.5 ml) and water (1.0 ml) was placed in 10 ml single neck round bottom flask and heated at 80^0C for 4 h under stirring. The TLC showed disappearance of starting material. The reaction mixture was cooled to room temperature, and then the dioxan was removed under reduced pressure. To the aqueous residue saturated $NaHCO_3$ solution (1 ml) was added followed by the addition of $NaHCO_3$ powder until the reaction mixture became basic. The aqueous mixture was extracted with ethyl acetate (3 x 5 ml). The combined extracts were dried and evaporated on rotary evaporator to afford (S)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one (**256**) (0.007 g, 74 %).

$[\alpha]_D^{25}$ +15.24° (c 0.60, $CHCl_3$, ee >98); m. p. 87^0C.

Assignment of absolute configuration by NMR using α-methoxy-α-trifluoro-methylphenyl acetate (MTPA) ester:

Preparation of (R)-MTPA derivative of (R)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one:

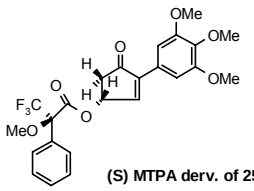


(R) MTPA derv. of 255

To the solution of (R)-Mosher acid (0.007 g, 0.021 mmol), (R)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one **(255)** (0.005 g, 0.018 mmol) and DMAP (cat.) in dry dichloromethane (2 ml), was added a solution of DCC (0.005 g) in dry dichloromethane (1 ml) at 0^0C. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The dicyclohexylurea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using 15 % ethyl acetate in petroleum ether gave the MTPA-ester in quantitative yield.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.55 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.11 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.59 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 6.06-6.14 (m, 1H), 7.00 (s, 2H), 7.34-7.66 (m, 6H).

Preparation of (S) MTPA derivative of (R)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one:



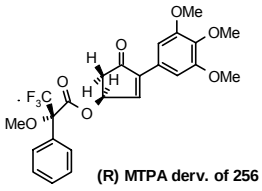
(S) MTPA derv. of 255

To the solution of (S) Mosher acid (0.007 g, 0.021 mmol), the (R)-2-(3,4,5-trimethoxyphenyl)-4-hydroxycyclopent-2-en-1-one **(255)** (0.005 g, 0.018 mmol) and DMAP (cat.) in dry dichloromethane (2 ml), was added a solution of DCC (0.005 g) in dry dichloromethane (1 ml) at 0^0C. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The dicyclohexylurea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using 15 % ethyl acetate in petroleum ether gave the MTPA-ester in quantitative yield.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.65 (dd, *J* = 20 Hz and 2 Hz, 1H), 3.15 (dd, *J* = 20 Hz and 6 Hz, 1H), 3.58 (s, 3H), 3.87 (s, 3H), 3.90 (s, 6H), 6.04-6.14 (m, 1H), 6.98 (s, 2H), 7.40-7.59 (m, 6H).

.

(R) MTPA derivative of compound 256:



(R) MTPA derv. of 256

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.63 (dd, *J* = 20 Hz and 2 Hz, 1H), 3.06 (dd, *J* = 20 Hz and 2 Hz, 1H), 3.65 (s, 3H), 3.87 (s, 3H), 3.90(s, 6H), 6.04-6.16 (m, 1H), 6.98 (s, 2H), 7.41-7.56 (m, 6H).

Resolution of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (108):

In a 100 ml single neck round bottom flask equipped with a Dean-Stark apparatus, were placed racemic 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(108)** (0.50 g, 1.35 mmol), (1R, 2S)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid (a cyclic hemiacylal form) (0.137 g, 0.94 mmol, $[\alpha]_D^{25}$ –105°, c 0.5 C_2H_5OH), pyridinium *p*-toluenesulfonate (0.121 g, 0.48 mmol) and dry benzene (20 ml). The mixture was heated at reflux under stirring for 12 h. The TLC analysis indicated the completion of reaction, when benzene was

removed under reduced pressure, the residual material was dissolved in chloroform (50 ml) and washed twice with water followed by the saturated $NaHCO_3$ solution (20 ml) and three times with water. The organic solution was dried and concentrated on rotary evaporator to give crude mixture of condensation product **265** (0.605 g, 91 %). The diastereomers were separated by fractional crystallization method using chloroform and petroleum ether (two times) afforded 0.25 g as one isomer which was again recrystallized to afford the pure material **258** (0.22 g, 36 %).

M. p. above 220^0C (gets charred); $[\alpha]_D^{25}$ -21.25° (c 1.1, $CHCl_3$); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1216, 1605, 1702, 1773, 2841, 2938, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.16 (s, 3H), 1.26 (s, 3H), 1.99 (bs, 2H), 2.65 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.05 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 5.34 (bs, 1H), 5.59-5.66 (m, 1H), 6.45 (s, 2H), 6.81 (d, *J* = 10 Hz, 2H), 7.40 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 15.27, 24.94, 25.53, 29.68, 35.42, 41.48, 55.41, 56.15 (2C), 60.96, 73.06, 99.19, 106.62 (2C), 114.00 (2C), 124.59, 127.02, 131.39 (2C), 138.19, 139.96, 153.56 (2C), 161.35, 163.52, 172.78, 202.37; **Mass** (m/e): 494 (M^+).

(R)-4-Hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (259): The mixture of crystallized isomer **258** (0.145 g, 0.293 mmol), dioxan (6 ml) and water (12 ml) was placed in 50 ml single neck round bottom flask and heated at 80^0C for 15 h under stirring. When TLC showed disappearance of starting material the reaction mixture was cooled to room temperature and dioxan was removed under reduced pressure. To the aqueous residue was added saturated $NaHCO_3$ solution (10 ml) and then $NaHCO_3$ powder until the reaction mixture became basic. The aqueous mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were dried and evaporated on rotary evaporator to afford (R) 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(259)** as yellowish solid (0.095 g, 87 %).

M. p. 161^0C; $[\alpha]_D^{25}$ +17.18° (c 1.00, $CHCl_3$, ee> 98); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1694, 3468 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.65 (d, *J* = 18 Hz, 1H), 3.11 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.72 (s, 6H), 3.83 (s, 3H), 3.86 (s, 3H), 5.45 -5.50 (m, 1H), 6.46 (s, 2H), 6.87 (d, *J* = 10 Hz, 2H), 7.41 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 44.54, 55.09, 55.79(2C), 60.64, 68.99, 106.44(2C), 113.87(2C), 125.01, 126.84, 130.85(2C), 137.69, 138.39, 153.09(2C), 160.84, 166.69, 203.78; **Mass** (m/e): 370 (M^+, 100), 355 (19).

(R)-4-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (260): In a 50 ml two neck round bottom flask, a solution of (R) 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(259)** (0.075 g, 0.20 mmol) in dichloromethane (3 ml) was cooled to 0°C under inert atmosphere. To the cold solution, dry pyridine (0.019 gm, 0.24 mmol) was added and stirred at 0°C for 10 min. To the stirred solution, acetic anhydride (0.025 g, 0.024 mmol) was added dropwise while maintaining the temperature below 0°C. The reaction mixture was stirred at room temperature for 15 h (monitored by TLC) and then quenched by adding cold, dilute hydrochloric acid. The organic layer was washed three times with water, 10 % sodium bicarbonate solution and finally with brine. The organic layer was dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect the pure (R)-4-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(260)** (0.078 gm, 83.7 %).

M. p. 175^{0}C; $[\alpha]_D^{25}$ +16.1° (c 1.00, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.01 (s, 3H), 2.52 (d, *J* = 18 Hz, 1H), 3.15 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.71 (s, 6H), 3.81 (s, 3H), 3.85 (s, 3H), 6.38-6.42 (m, 1H), 6.44 (s, 2H), 6.81 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.88, 41.38, 54.32, 55.09 (2C), 59.80, 69.32, 105.85 (2C), 113.06 (2C), 123.87, 125.67, 129.60 (2C), 137.32, 139.49, 152.39 (2C), 160.18, 161.98, 169.52, 201.31; **Mass** (m/e): 412 (M^+, 100).

(R)-4-Acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one-oxime (261): A mixture of (R)-4-acetoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (260) (0.050 g, 0.12 mmol), hydroxylamine hydrochloride (0.012 g, 0.18 mmol) and sodium acetate (0.015 g, 0.18 mmol) in ethanol (5 ml) was refluxed on water bath for 3 h. The reaction was monitored by TLC and after completion of reaction the solvent was removed under reduced pressure using rotary evaporator. The residue was extracted with chloroform, organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether-acetone as eluent) to collect pure (R)-2-(3,4,5-trimethoxyphenyl)-3-(4-methoxyphenyl)-4-acetoxy-cyclopent-2-en-1-one-oxime (261) (0.040 g, 77 %).

M. p. 162-163^{0}C; $[\alpha]_D^{25}$ +25.8° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + CCl_4): δ 2.02 (s, 3H), 2.72 (bd, *J* = 18 Hz, 1H), 3.40 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.72 (s, 6H), 3.78 (s, 3H), 3.87 (s, 3H), 6.25-6.35 (m, 1H), 6.46 (s, 2H), 6.75 (d, *J* = 10 Hz, 2H), 7.12 (d, *J* = 10 Hz, 2H); ^{13}C NMR (50

MHz, $CDCl_3$+CCl_4): δ 20.81, 33.05, 54.92, 55.80 (2C), 60.65, 74.18, 106.56 (2C), 113.56 (2C), 125.57, 127.96, 129.94 (2C), 136.52, 137.92, 147.81, 153.25 (2C), 159.64, 163.17, 170.34; Mass (m/e): 427 (M^+, 100).

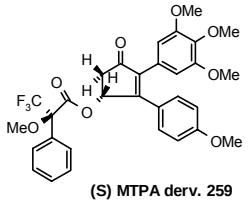
Assignment of absolute configuration by NMR using α-methoxy-α-trifluoro-methylphenyl acetate (MTPA) ester:

Preparation of (R)-α-methoxy-α-trifluoro-methylphenyl acetate (MTPA) ester of 4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:

To a solution of (R)-Mosher acid (0.019 g, 0.081 mmol), (R)-4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.030 g, 0.081 mmol) and DMAP (cat.) in dry dichloromethane (4 ml) was added a solution of DCC (0.02 g) in dry dichloromethane (2 ml) at 0^0C. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The dicyclohexylurea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using 15 % ethyl acetate in petroleum ether gave the MTPA-ester in quantitative yield.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.46 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.19 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.21 (s, 3H), 3.70 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 6.44 (s, 2H), 6.74-6.80 (m, 1H), 6.84 (d, *J* = 8 Hz, 2H), 7.24-7.45(m, 7H).

Preparation of (S)-MTPA ester derivative of (R)-4-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one: As described above, using (S)-MTPA.



(S) MTPA derv. 259

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.65 (dd, *J* = 18 Hz and 2 Hz, 1H), 3.25 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.42 (s, 3H), 3.70 (s, 6H), 3.81 (s, 3H), 3.86 (s, 3H), 6.44 (s, 2H), 6.64-6.69 (m, 1H), 6.73 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H), 7.24-7.40 (m, 5H).

Resolution of 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (192):

In a 100 ml single neck round bottom flask equipped with a Dean-Stark apparatus, were placed racemic 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(192)**

(0.350 g, 0.95 mmol), (1R, 2S)-*cis*-2-formyl-3,3-dimethycyclopropane-1-carboxylic acid (a cyclic hemiacylal form) (0.096 g, 0.60 mmol, $[\alpha]_D^{25}$ –105°, c 0.5 C_2H_5OH), pyridinium *p*-toluenesulfonate (0.085 g, 0.34 mmol) and dry benzene (20 ml). The mixture was heated at reflux under stirring for 12 h. TLC analysis indicated completion of reaction. Benzene was then removed under reduced pressure, the residual material was dissolved in ethyl acetate (50 ml) and washed twice with water, saturated $NaHCO_3$ solution (20 ml) and three times with water. The organic solution was dried and concentrated on rotary evaporator to give crude mixture of condensation product **262** (0.419 g, 89 %). The diastereoisomers were separated by silica gel column chromatography using 10 %, 15 %, 20 % ethyl acetate in petroleum ether. It afforded the less polar material **263** (0.121 g, 28 %) and more polar material **264** (0.103 g, 25 %) as yellowish solids.

Less polar material (263):

M. p. 150-152^{0}C; $[\alpha]_D^{25}$ -47.04° (c 1.0, $CHCl_3$); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1216, 1603, 1703, 1775, 2938, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.19 (s, 3H), 1.24 (s, 3H), 2.06 (d, *J* = 6 Hz, 1H), 2.23 (d, *J* = 6 Hz, 1H), 3.07 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.43 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 4.56-4.65 (m, 1H), 5.84 (bs, 1H), 6.44 (s, 2H), 6.81 (d, *J* = 10 Hz, 2H), 7.37 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 14.95, 24.36, 25.24, 29.58, 35.28, 37.01, 55.06, 55.86 (2C), 60.57, 75.82, 101.15, 106.55(2C), 113.76 (2C), 126.70, 127.25, 130.30(2C), 135.37, 138.05, 153.35 (2C), 161.54, 164.01, 172.57, 203.34; **Mass** (m/e): 494 (M^+).

More polar material (264)

M. p. 82-83^{0}C; $[\alpha]_D^{25}$ -88.24° (c 1.3, $CHCl_3$); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1216, 1603, 1703, 1775, 2938, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.21 (s, 3H), 1.22 (s, 3H), 2.11 (d, *J* = 6 Hz, 1H), 2.34 (d, *J* = 6 Hz, 1H), 3.15 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.40 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 4.71-4.80 (m, 1H), 5.48 (bs, 1H), 6.45 (s, 2H), 6.82 (d, *J* = 10 Hz, 2H), 7.37 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 15.06, 24.40, 25.32, 30.06, 35.32, 36.57, 55.13, 55.94 (2C), 60.61, 74.72, 99.02, 106.74 (2C), 113.79 (2C), 126.92, 127.25, 130.30 (2C), 136.03, 138.20, 153.42 (2C), 161.54, 163.23, 172.17, 201.87; **Mass** (m/e): 494 (M^+).

(S)-5-Hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (265):

A mixture of less polar material **263** (0.100 g, 0.20 mmol), dioxan (6 ml) and water (12 ml) was placed in a 50 ml single neck round bottom flask and heated at 80^{0}C for 15 h under stirring. The

TLC showed disappearance of starting material. Reaction mixture was cooled to room temperature and the dioxan was removed under reduced pressure. To the aqueous residue was added saturated $NaHCO_3$ solution (10 ml) and then $NaHCO_3$ powder until the reaction mixture became basic. The aqueous mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were dried and evaporated on rotary evaporator to afford (S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(265)** (0.065 g, 87 %).

M. p. 173-174^{0}C; $[\alpha]_D^{25}$ + 23.15° (c 0.55, $CHCl_3$, ee > 98); **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.01 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.39 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.75 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 4.48-4.57 (m, 1H), 6.45 (s, 2H), 6.83 (d, *J* = 10 Hz, 2H), 7.39 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 38.11, 55.28, 55.97 (2C), 60.79, 71.85, 106.30 (2C), 113.79 (2C), 126.95, 127.69, 130.45 (2C), 135.11, 137.80, 153.46 (2C), 161.51, 164.41, 207.20.

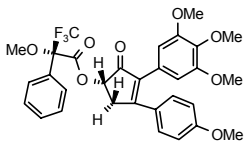
Mass (m/e): 370 (M^+).

(R)-5-Hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (266): The mixture of more polar material **264** (0.088 g, 0.18 mmol), dioxan (3 ml) and water (6 ml) was placed in 50 ml single neck round bottom flask and heated at 80^{0}C for 15 h under stirring. The TLC showed disappearance of starting material. The reaction mixture was cooled to room temperature and then dioxan was removed under reduced pressure. To the aqueous residue, was added saturated $NaHCO_3$ solution (5 ml) and then $NaHCO_3$ powder until the reaction mixture became basic. The aqueous mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were dried and evaporated on rotary evaporator to afford (R)- 5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(266)** (0.053 g, 80.4 %).

M. p. 194^{0}C; $[\alpha]_D^{25}$ - 22.47° (c 0.45, $CHCl_3$, ee > 98).

Assignment of absolute configuration by NMR using α-methoxy-α-trifluoro-methylphenyl acetate (MTPA) ester:

Preparation of (R) MTPA derivative of (S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(265)**:

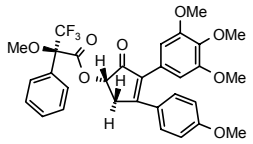


(R) MTPA der. of 265

To a solution of (R)-Mosher acid (0.013 g, 0.054 mmol), (S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one **(265)** (0.020 g, 0.054 mmol) and DMAP (cat.) in dry dichloromethane (4 ml), was added a solution of DCC (0.010 g) in dry dichloromethane (2 ml) at 0^0C. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. The dicyclohexylurea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using 15 % ethyl acetate in petroleum ether gave the MTPA-ester in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.23 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.44 (dd, *J* = 18 Hz and 9 Hz, 1H), 3.61 (s, 3H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 5.63-5.71 (m, 1H), 6.46 (s, 2H), 6.83 (d, *J* = 9 Hz, 2H), 7.38 (d, *J* = 9 Hz, 2H), 7.42-7.47 (m, 3H), 7.65-7.72 (m, 2H); **Mass** (m/e): 588 (M+2).

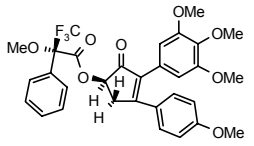
Preparation of (S)-MTPA ester derivative of (S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (265):



(S) MTPA der. of 265

To a solution of (S)-Mosher acid (0.010 g, 0.042 mmol), (S)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (0.015 g, 0.04 mmol) and DMAP (cat.) in dry dichloromethane (4 ml), was added a solution of DCC (0.010 g) in dry dichloromethane (2 ml) at 0^0C. The reaction mixture was allowed to warm at room temperature and stirred for 15 h. The dicyclohexylurea formed was filtered off and the organic layer was concentrated *in vacuo*. Silica gel column chromatographic purification of the residue using 15 % ethyl acetate in petroleum ether gave the MTPA-ester in quantitative yield. **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.03 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.42 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.70 (s, 3H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 5.80-5.90 (m, 1H), 6.45 (s, 2H), 6.82 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.36-7.48 (m, 3H), 7.63-7.72 (m, 2H); **Mass** (m/e): 588 (M+2).

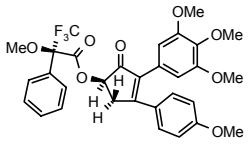
Preparation of (R)-MTPA derivative of (R)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (266):



(R) MTPA der. of 266

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.05 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.43 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.69 (s, 3H), 3.73 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 5.80-5.90 (m, 1H), 6.45 (s, 2H), 6.82 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.40-7.48 (m, 3H), 7.64-7.70 (m, 2H).

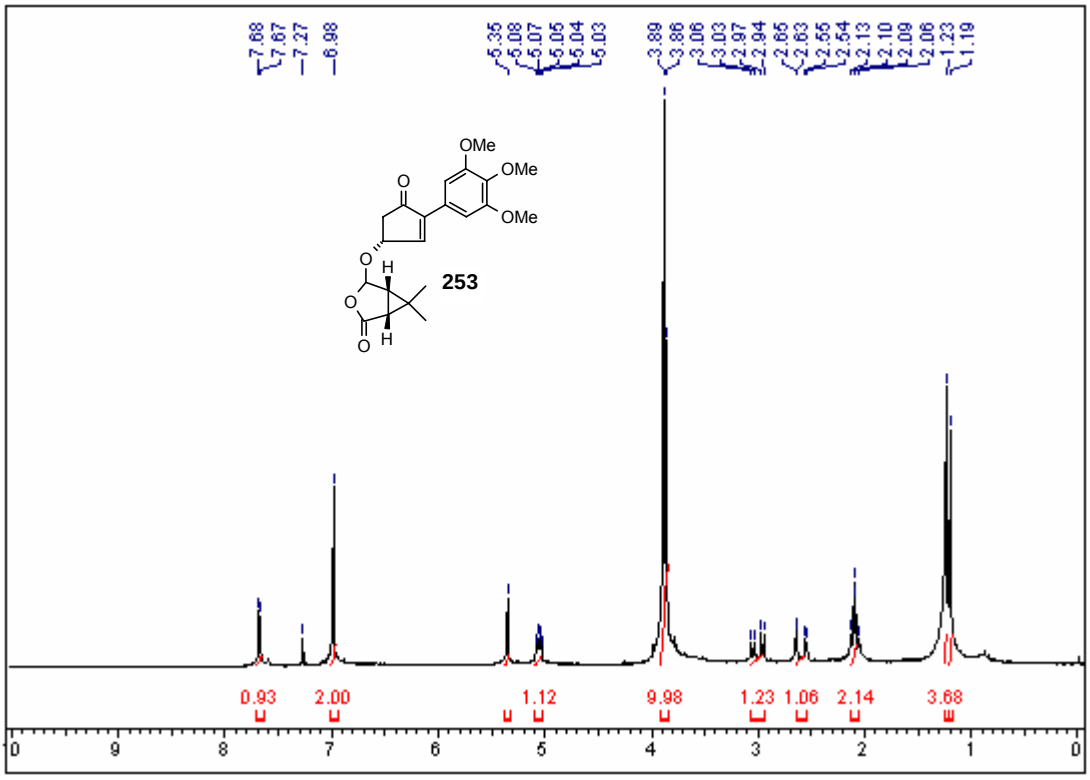
Preparation of (S)-MTPA derivative of (R)-5-hydroxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one (266):



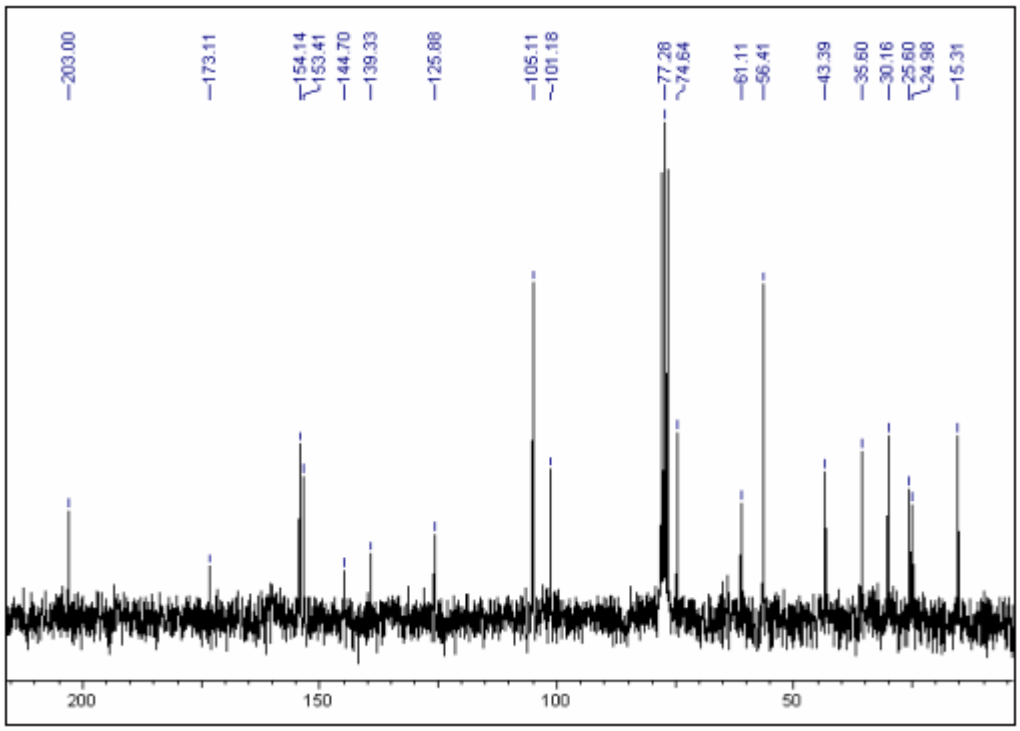
(S) MTPA der. of 266

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.24 (dd, *J* = 18 Hz and 4 Hz, 1H), 3.46 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.60 (s, 3H), 3.74 (s, 6H), 3.83 (s, 3H), 3.87 (s, 3H), 5.63-5.72 (m, 1H), 6.47 (s, 2H), 6.83 (d, *J* = 10 Hz, 2H), 7.38 (d, *J* = 10 Hz, 2H), 7.41-7.45 (m, 3H), 7.64-7.70 (m, 2H).

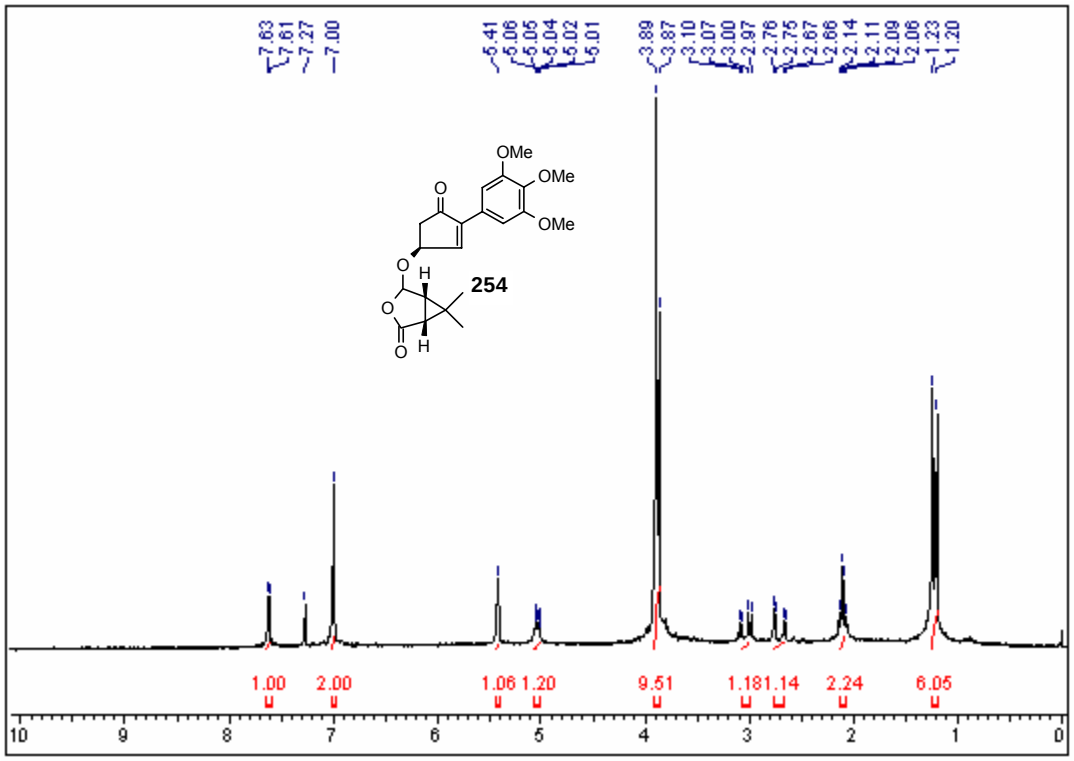
^{1}H NMR spectrum of the compound 253:



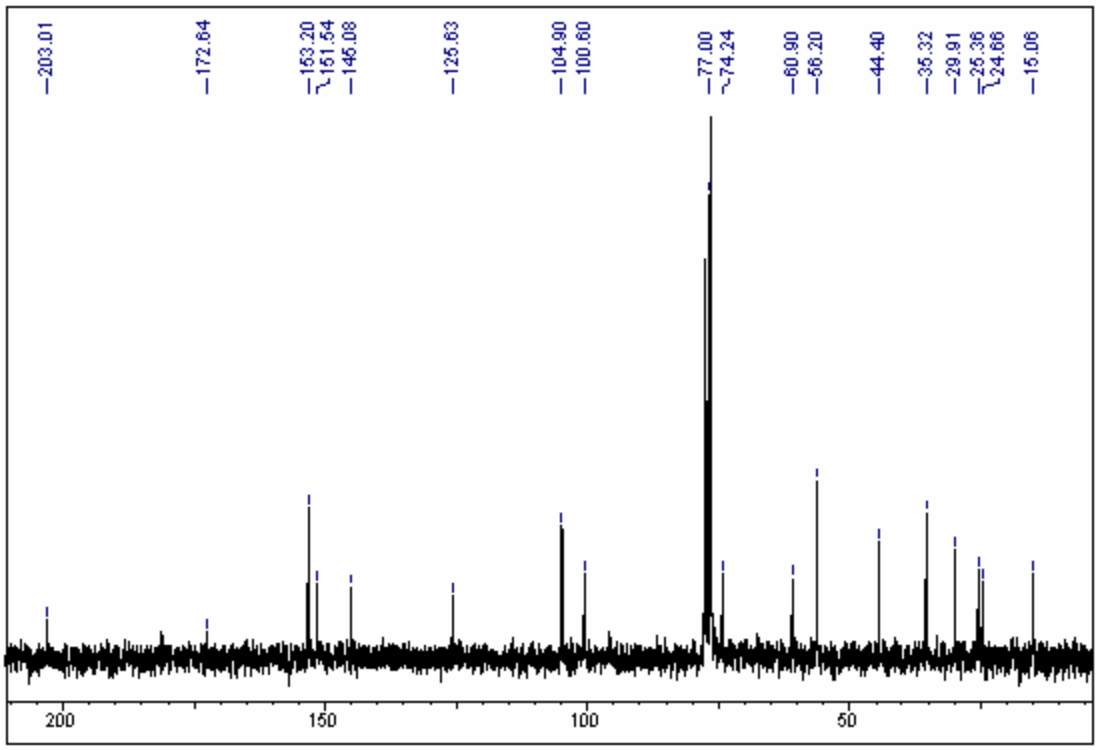
^{13}C NMR spectrum of the compound 253:



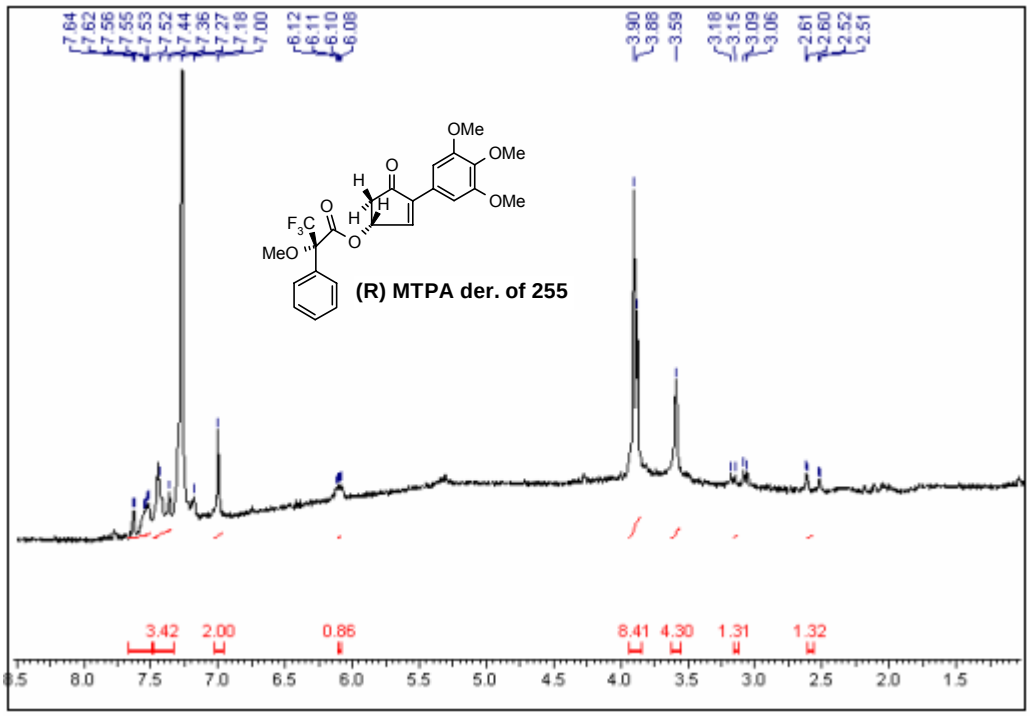
^{1}H NMR spectrum of the compound 254:



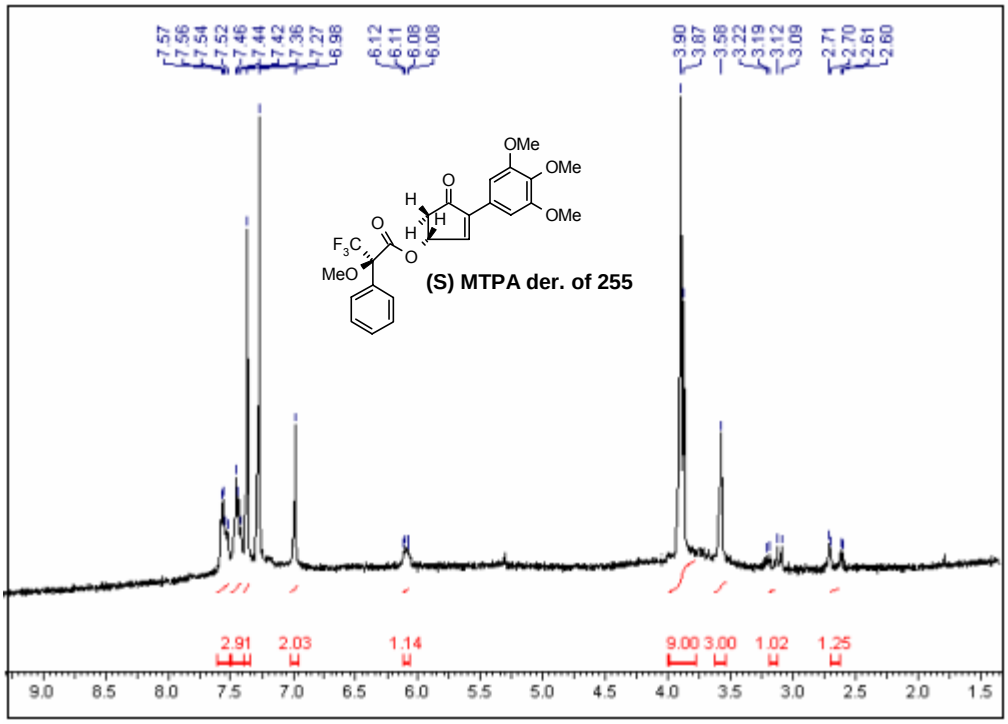
^{13}C NMR spectrum of the compound 254:



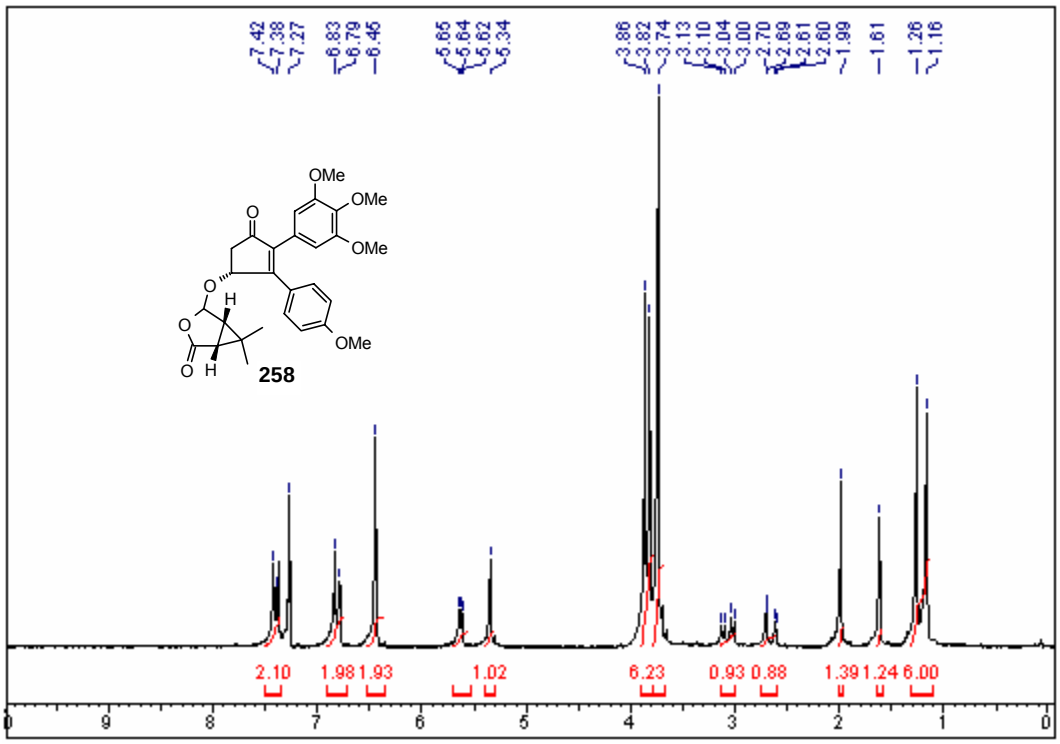
^{1}H NMR of the (R) MTPA derivative of the compound 255:



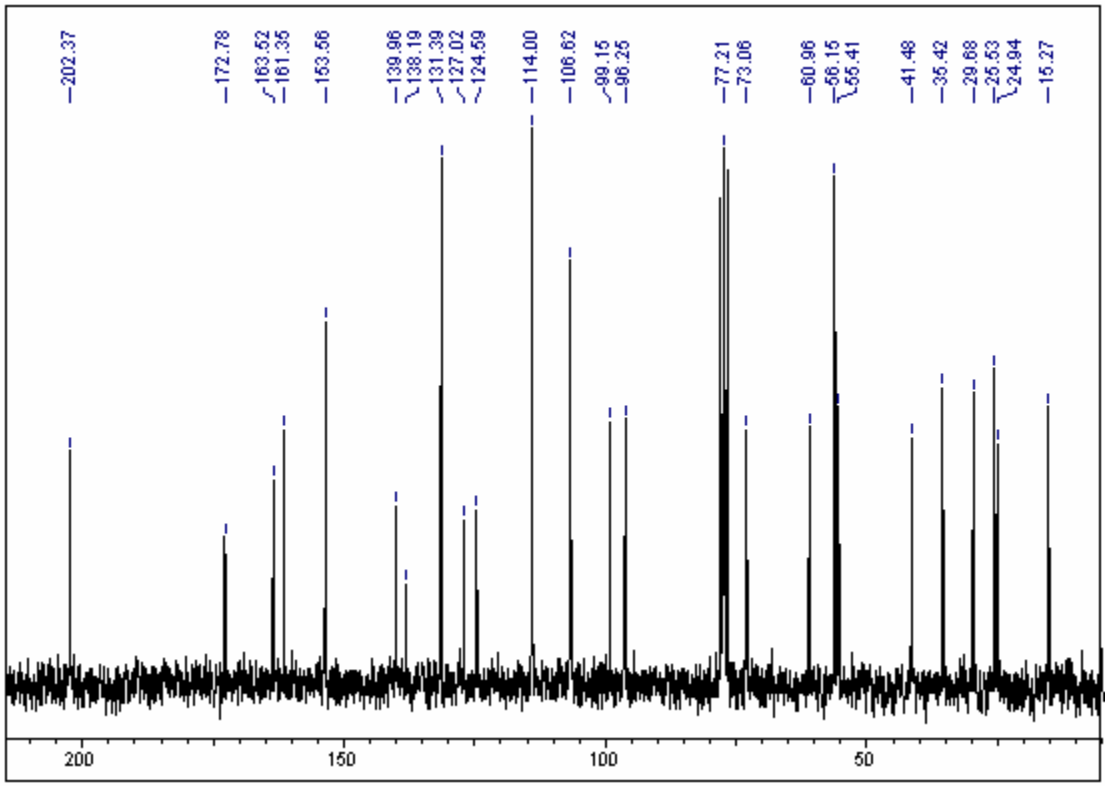
^{1}H NMR of the (S) MTPA derivative of the compound 255:



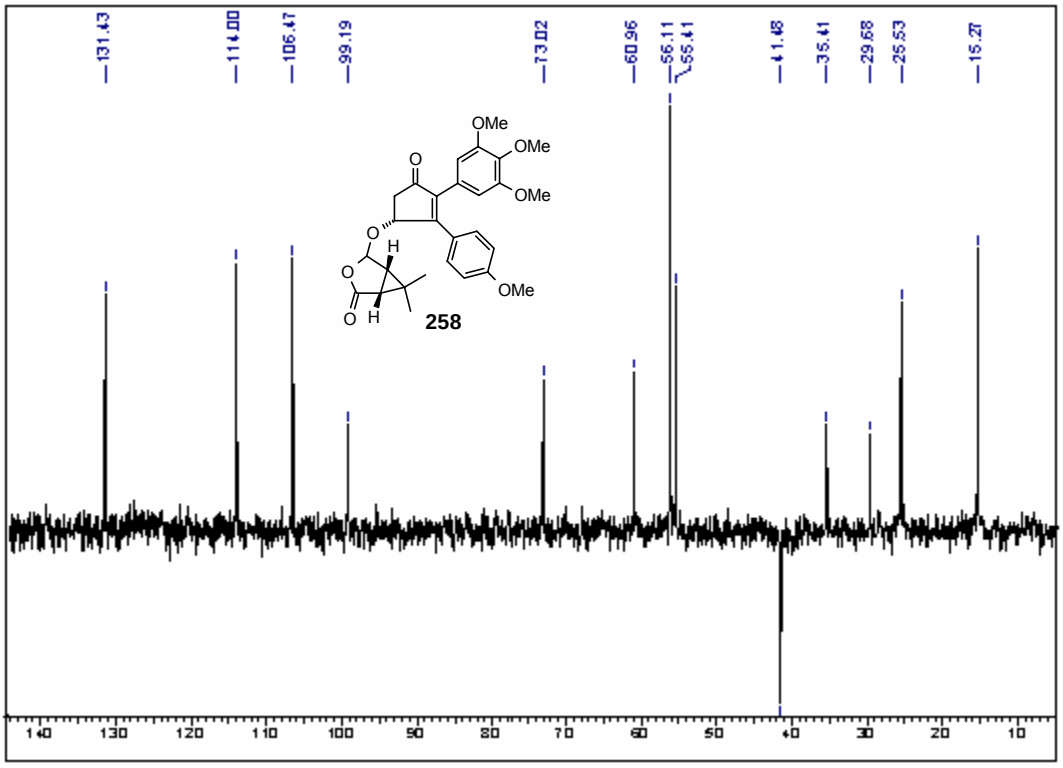
^{1}H NMR spectrum of the compound 258:



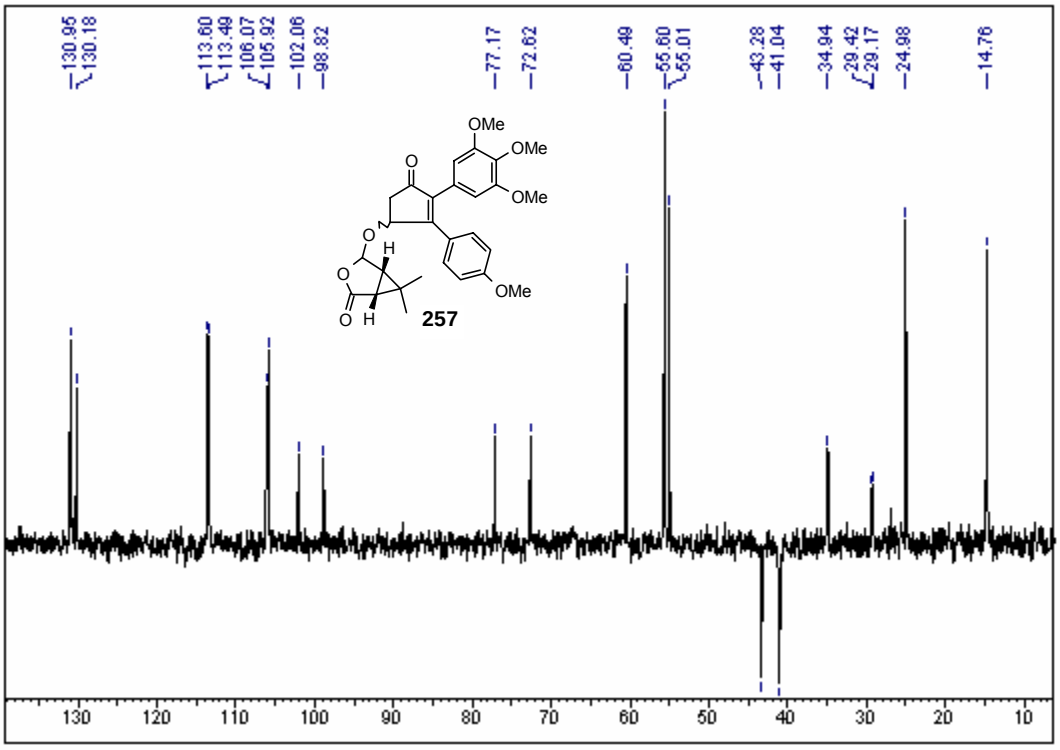
^{13}C NMR spectrum of the compound 258:



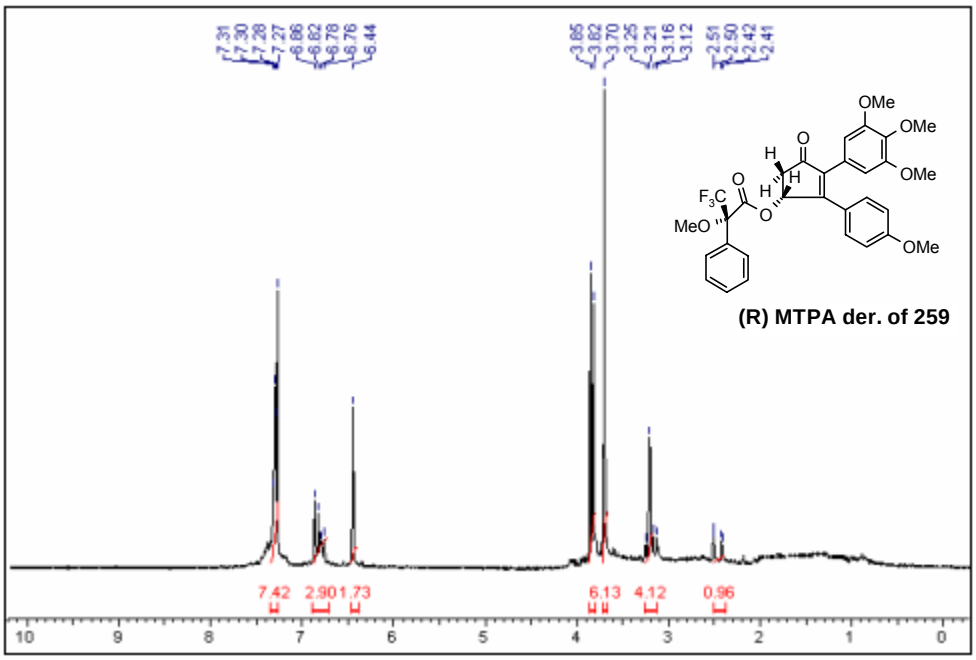
DEPT NMR spectrum of the compound 258:



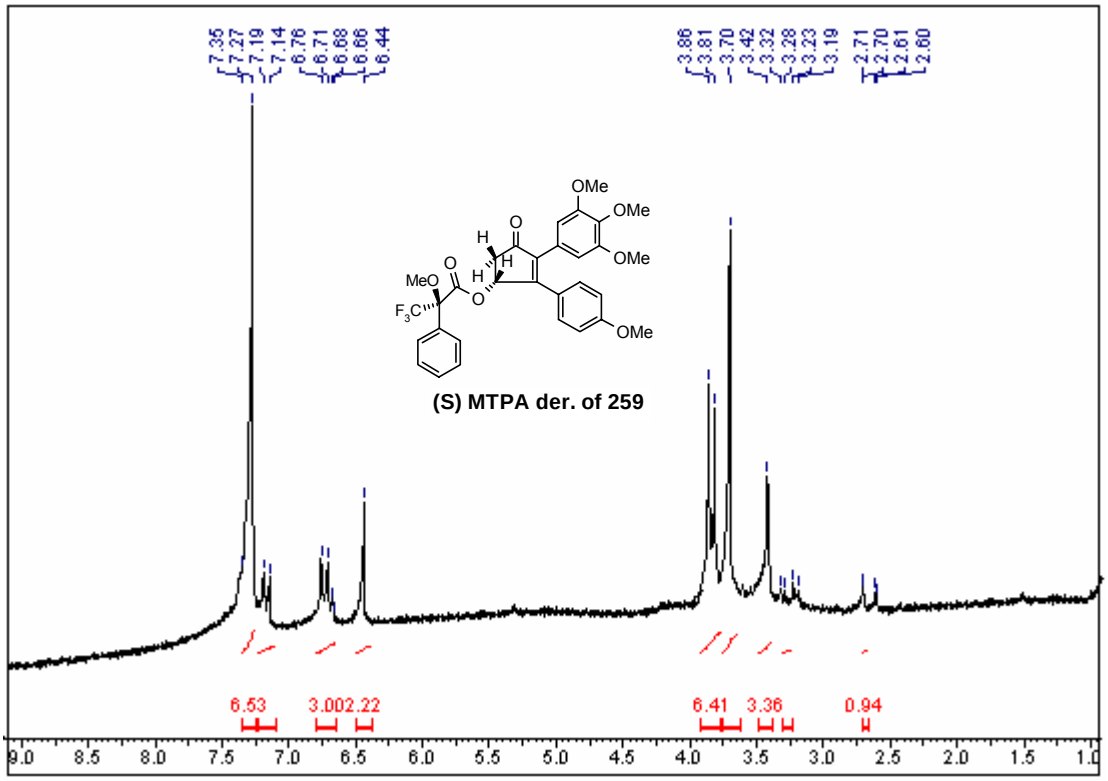
DEPT NMR spectrum of the compound 257:



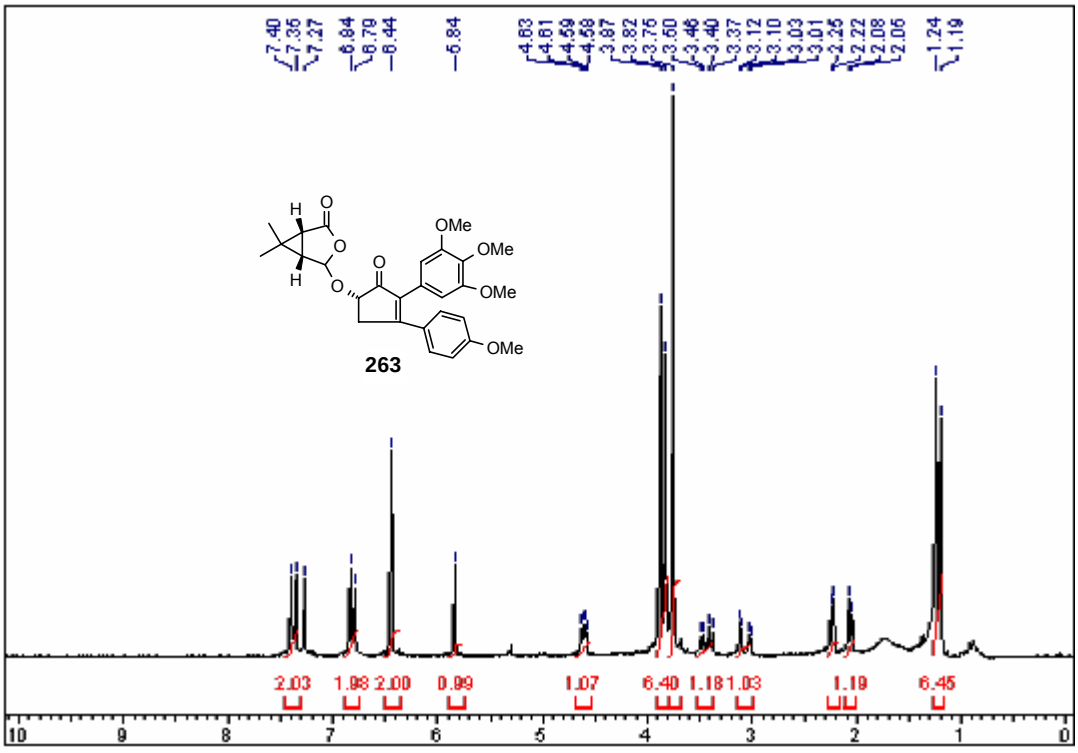
^{1}H NMR spectrum of the (R) MTPA derivative of the compound 259:



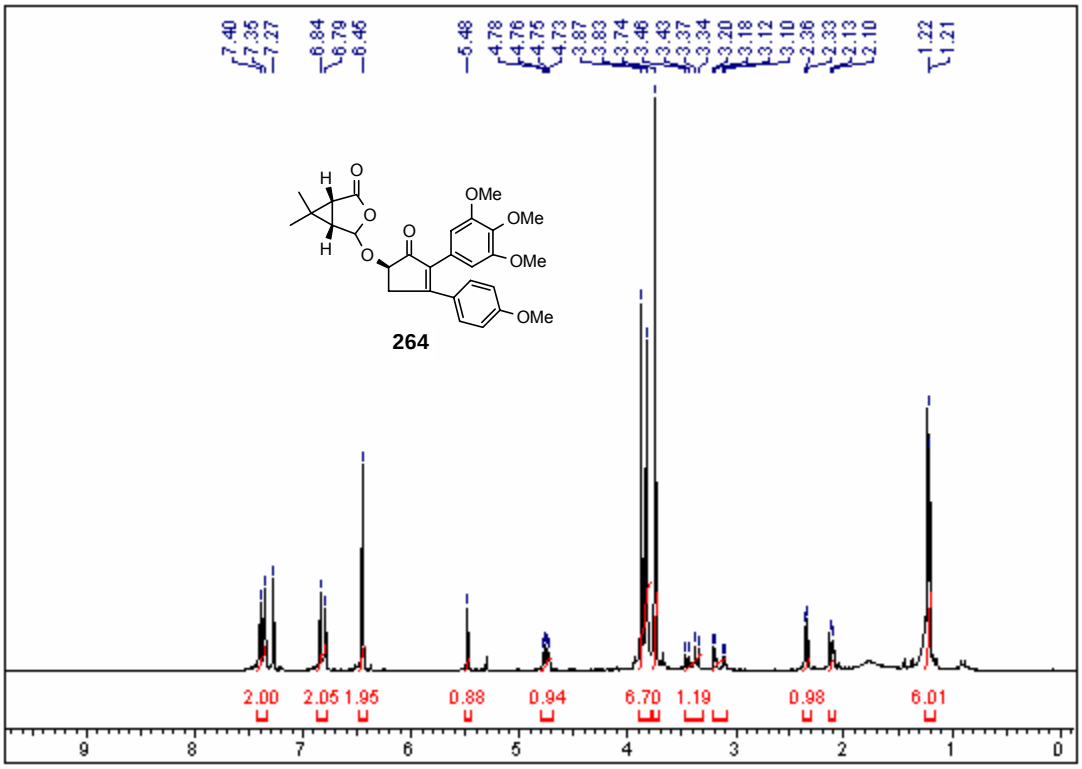
^{1}H NMR spectrum of the (S) MTPA derivative of the compound 259:



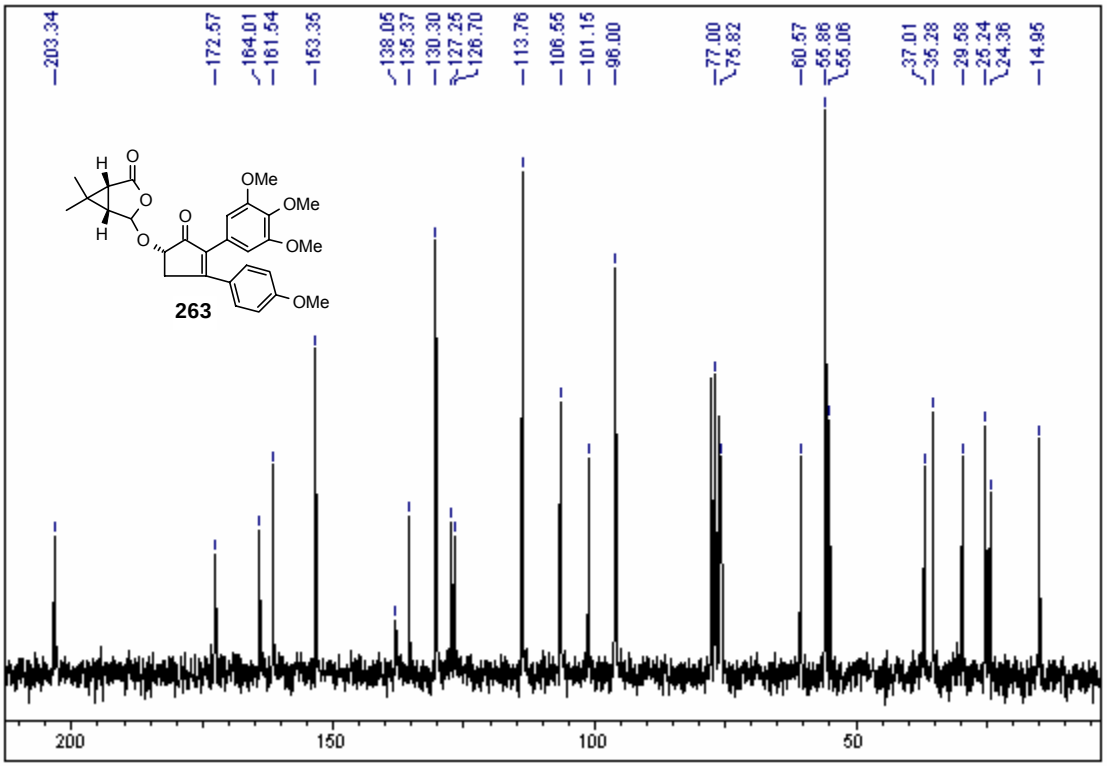
^{1}H NMR spectrum of the compound 263:

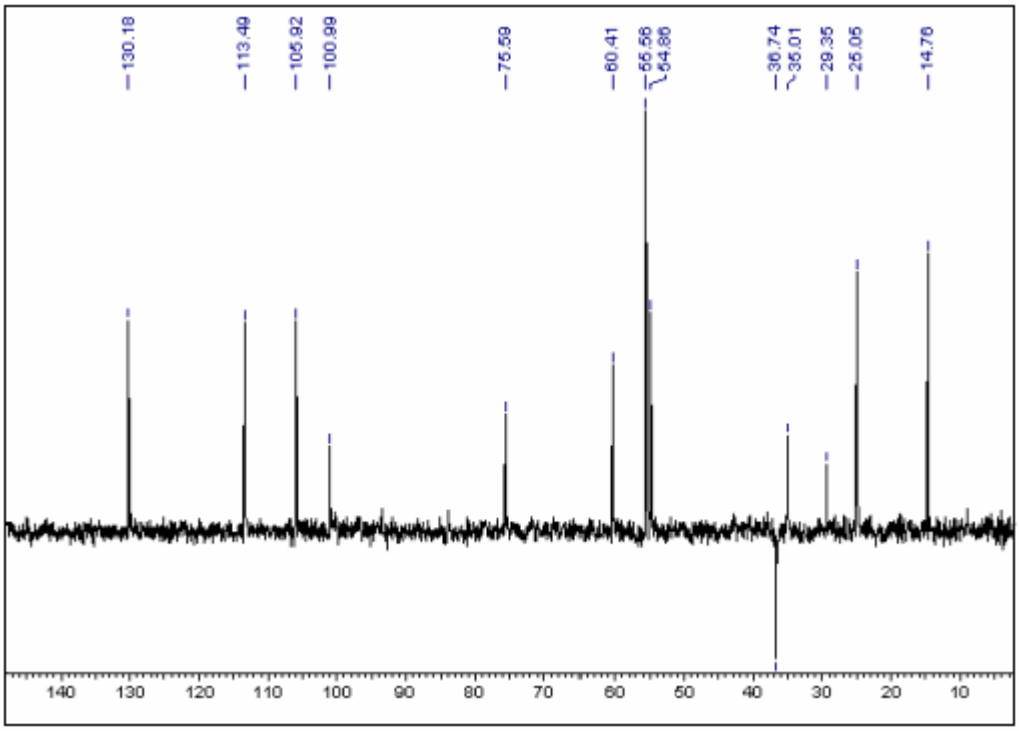


^{1}H NMR spectrum of the compound 264:

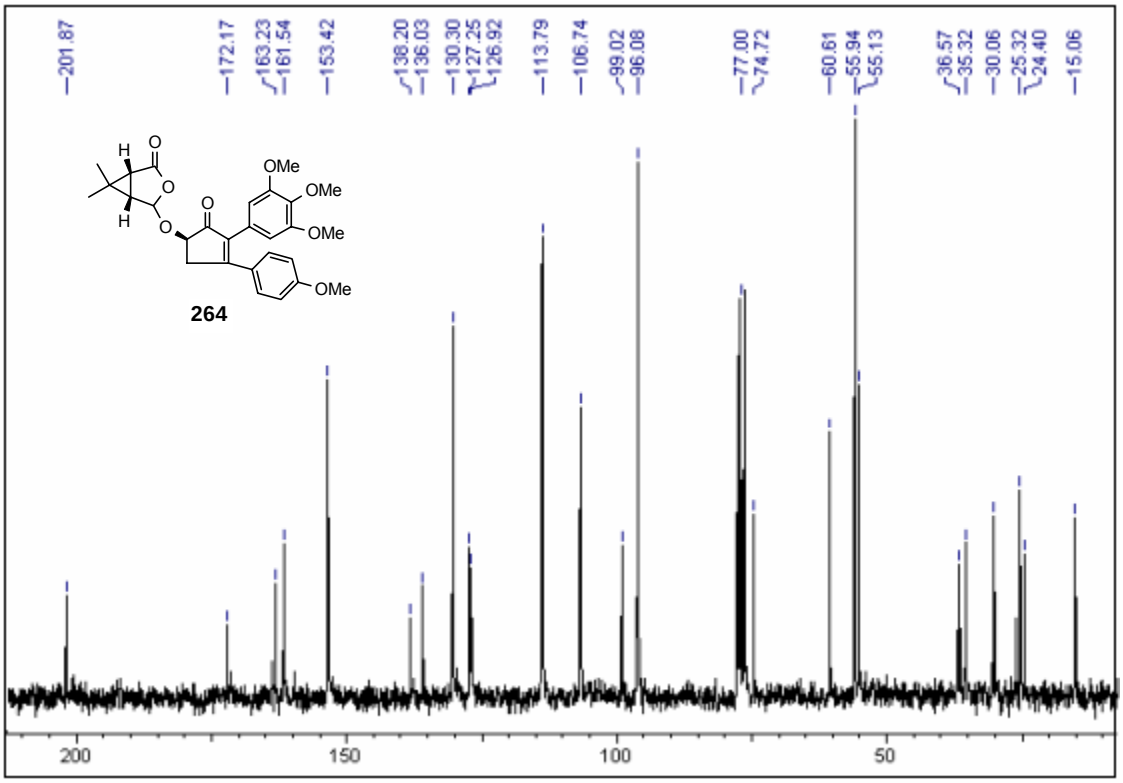


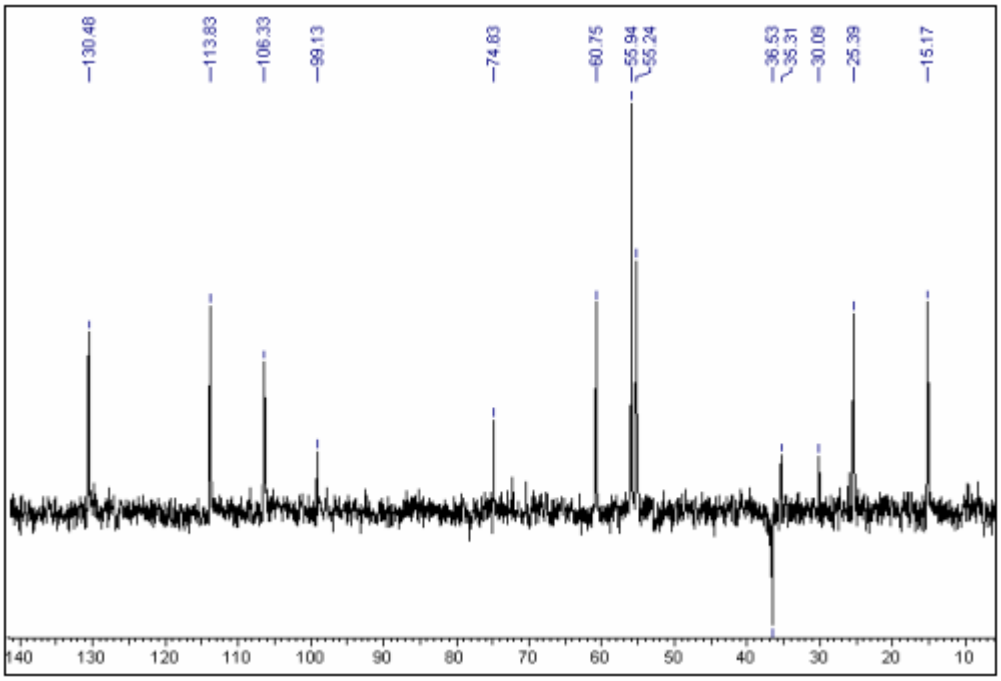
^{13}C NMR spectra of the compound 263:



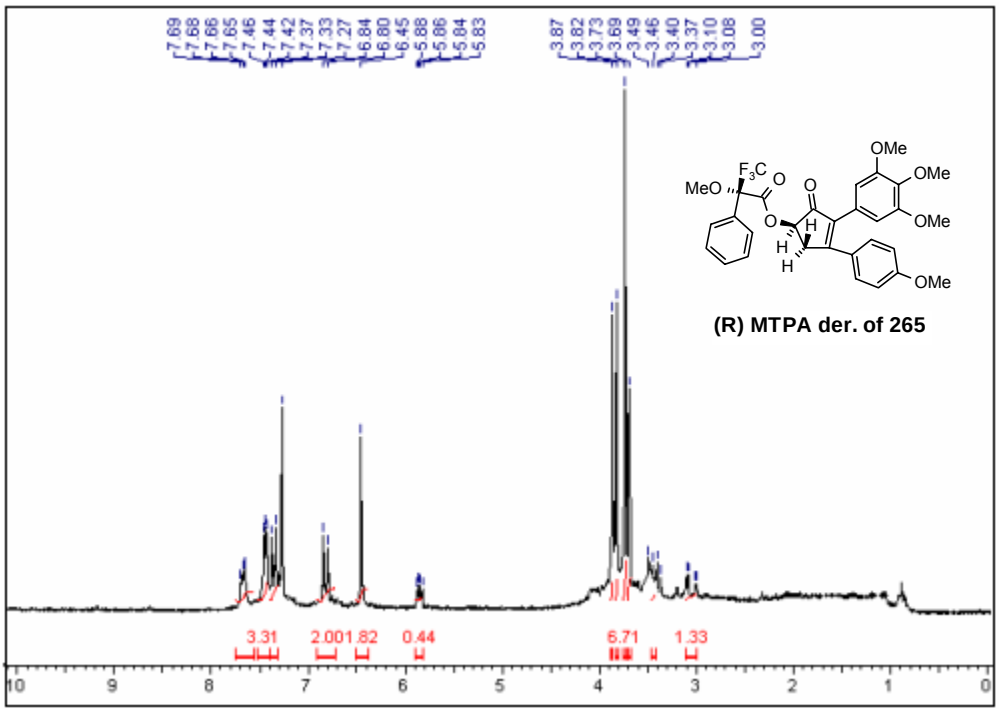


^{13}C NMR spectrum of the compound 264:

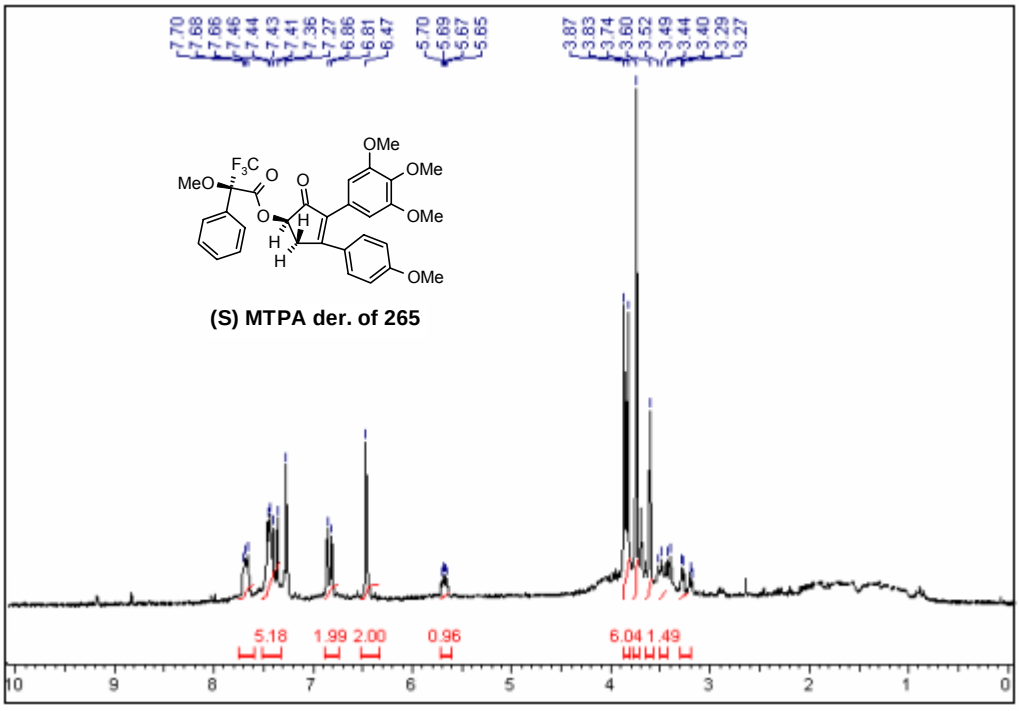




^{1}H NMR spectrum of the (R) MTPA derivative of the compound 265:



^{1}H NMR spectrum of the (S) MTPA derivative of the compound 265:



1.4.8 REFERENCES:

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CHAPTER 1

SECTION V

Biological Activity and SAR Study of the Combretastatin A-4 Analogues

1.5.1 Biological Activity Study:

The synthesized cyclopentenone analogues were tested for cytotoxicity against 9 to 12 human tumor cell lines such as PTC (all colon), MOLT-4 (leukemia), SW620 (ovary), DU145 (prostate), KB (oral squamous cell), L132 (lung), MiaPaca2 (pancreas), Hep2 (larynx), PA-1 (ovary), HuTu80 (duodenum), ECV304 (endothelial) and 293 (kidney). The cytotoxicity screening was carried out by plate assay method at Dabur Research Foundation, Ghaziabad, New Delhi. For the relevance of this chapter the methodology used for screening is briefly described herein. A three day MTT cytotoxicity assay[1] was performed, which is based on the principle of uptake of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] a tetrazolium salt, by the metabolically active cells where it is metabolized by active mitochondria into a blue colored formazan product that is read spectrophotometrically.

MTT was dissolved in phosphate buffered saline with a pH of 7.4 to obtain an MTT concentration of 5 mg/ml; the resulting mixture was filtered through a 0.22 micron filters to sterilize and remove a small amount of insoluble residue. For each type of tumor cell 10000 to 15000 cells were seeded in 96 well culture plate and incubated with the individual cyclopentenone derivatives in a CO_2 incubator for a total of 72 hours. Control cells not treated with the cyclopentenone derivatives were similarly incubated. The assay was terminated by adding 100 μg of MTT to each well and then incubating for additional one hour and finally adding 50 μl of 10 % SDS-0.01 N HCl to each well to lyse the cells and dissolve formazan. After incubating for one hour, the plates were read spectrophotometrically at 540 nm and the percentage of cytotoxicity calculated using the following formula

Cytotoxicity percentage = $100 \times [1-(X/R_1)]$

Where X = (absorbance of treated sample at 540 nm)-(absorbance of blank at 540 nm)

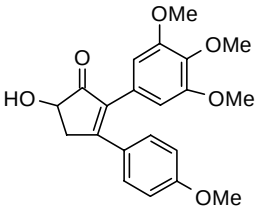
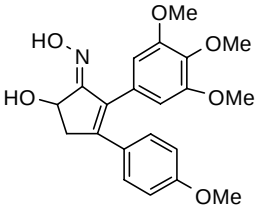
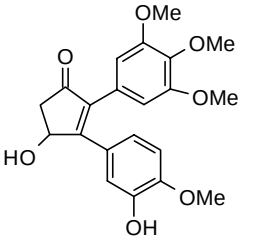
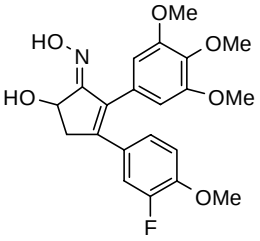
R_1 = absorbance of control sample at 540 nm.

The cyclopentenone derivatives were checked for their effects on tubulin polymerization *in vitro*. The tubulin assembly reaction was performed at 37^0C in buffer containing 80 mM PIPES, 1mM EGTA, 1.0 mM GTP and 1 mM $MgCl_2$ (pH 6.9) at a tubulin concentration of 1 mg/ml in the presence or absence of the cyclopentenone derivatives. The final concentration of the cyclopentenone derivatives in the reaction mixture varied from 1-5 μM. The derivatives were dissolved in 0.1 % DMSO. The control experiments were carried out with 0.1 % DMSO. The

tubulin polymerization was followed by measurement of the absorbance of the solution at 340 nm every 30 seconds. The IC_{50} values (molar concentration) for the inhibition of tubulin polymerization by the cyclopentenone derivatives are shown in table 1.

Table 1:

IC_{50} values for inhibition of tubulin polymerization by cyclopentenone derivatives

Sr. No.	Compound No.	Structure	IC_{50} values μM
1	**192**		2.1 ± 0.1
2	**194**		2.3 ± 0.5
3	**119**		1.4 ± 0.6
4	**207**		2.0 ± 0.6

The cyclopentenone derivatives inhibited tubulin polymerization with IC_{50} values ranging from 1.4-2.9 μM *in vitro*. Thus it was confirmed that the cyclopentenone derivatives mediated their observed anticancer activities by tubulin depolymerization as expected.

1.5.2 Structure Activity Relationship Studies of CA-4 Analogues:

The QSAR analysis of the combretastatins (natural as well as synthetic analogues) studied earlier revealed that the *cis* isomer is comparatively more active than the *trans* isomer. The bridge length between the two-phenyl rings is critical and the compounds with an ethyl or ethylene were more active than those with a longer bridge. The A and B rings of combretastatins have two separate binding sites on α and β chains of tubulin respectively. Therefore if the two rings are far apart the affinity for the binding site decreases, resulting in a reduced cytotoxicity of the compounds.
In view of the prior knowledge available in the literature, *cis* restricted combretastatin analogues were designed and synthesized. The *cis* restriction of the ethylene bridge between the two rings was achieved by replacing it with a cyclopentenone ring. The functionalities like ketone and hydroxy group in the cyclopentenone ring provided the handles required for the derivatization and manipulation of the hydrophilicity of the molecules. The synthetic aspects of these new chemical entities (NCEs) have been discussed in the preceding sections of this chapter.
All the new chemical entities (NCEs) were screened by the plate assay method briefly described in the "Biological Activity" above. The data compilation of the *in vitro* studies has been depicted in table 3 and table 5, for the compounds synthesized in section I and section II respectively. The corresponding compounds are listed in the tables 2 and 4 for the discussion in this section.

2,3-Diaryl-4-hydroxycyclopent-2-en-1-one analogues:

Section I dealt with the synthesis of 2,3-diaryl-4-hydroxycyclopent-2-en-1-one analogues (table 2) and overall 39 NCEs were submitted for screening. In the designed molecules ring A possessed 3,4,5-trimethoxy substitution, which was considered to be essential for the tubulin binding activity, whereas variations were made in the ring B. For every variation in the B-ring we achieved 4 to 6 samples for SAR study by simple organic transformations like 1) removal of tert butyldimethylsilyl (-OTBDMS) protecting group, 2) derivatisation of this free hydroxy group by acylation, 3) oximation of the ketone group etc. Other derivatizations leading to molecules with more than 500 molecular weight were avoided to maintain the rule of five. Some of the samples

could not be screened due to their poor solubility in the solvent used for the plate assay method. From the screening data of 27 samples the following observations are noteworthy:

Some of the samples were purposely synthesized with absence of a methoxy group at 4-position in the B-ring, such samples e.g. the compounds **135**, **137** and **142** showed reduced cytotoxicity which confirmed that the presence of a methoxy group at position 4 in the ring-B is mandatory for the activity.

In order to increase the solubility of these molecules in water it was thought that a carboxylic acid group attached to B-ring which can also be converted to its sodium salt should be a better choice than only a methoxy functional group. We synthesized compounds with –COOH at the 3 position of B-ring e.g. the compounds **136**, **140**, **147** and **148**. This option was not found beneficial as it lowered the cytotoxic activity. Similarly the methoxy at 4-position in the ring B was replaced by carboxymethyloxy (-OCH_2COOH) group e. g. the compounds **150** to **153** which were atleast 10-50 fold less active than the active compounds in the list.

The combretastatin mimic i.e. the compound **119** and the compound **114** displayed comparable or even better cancer cell growth inhibition. In most of the examples studied, oximation of the ketone in cyclopentenone ring did not influence the ED_{50} values significantly. The oxime derivatives were preferred in some cases due to their higher solubility.

The ED_{50} values obtained for methyl derivatives clearly indicate that the position of the substituents on the phenyl ring greatly affected the cytotoxic activity. All compounds methylated on 3 and 5 position (e. g. **133**, **138**, **144**, **145**) were inactive.

The tert-butyldimethylsilyl derivatives (products obtained after the Heck reaction) were also screened for cytotoxicity. Although there is no precedence of using silylated compounds for biological activity, to our surprise some of our samples displayed enhanced activity compared with the corresponding hydroxy compounds. The role of -TBS group in such examples (e. g. **133**, over **138**, **142** over **137**, **158** over **159**) is unknown.

It is noteworthy that the compound **158** possessing unsubstituted phenyl rings A and B, exhibited ED_{50} values comparable with the hit molecules. This example appears to be an exception to all the SAR studied for combretastatins and the behavior is inexplicable.

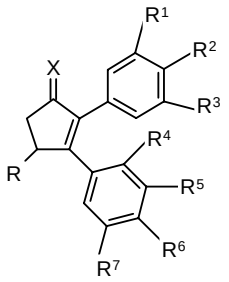


Table 2: 2,3-Diaryl-4-hydroxycyclopent-2-en-1-one analogues of CA-4

Sr. No.	Comp No.	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X
1	**108**	OH	OMe	OMe	OMe	H	H	OMe	H	O
2	**138**	OH	OMe	OMe	OMe	H	Me	OMe	Me	O
3	**137**	OH	OMe	OMe	OMe	OMe	H	H	OMe	O
4	**106**	OTBS	OMe	OMe	OMe	H	H	OMe	H	O
5	**135**	OTBS	OMe	OMe	OMe	H	H	H	H	O
6	**133**	OTBS	OMe	OMe	OMe	H	Me	OMe	Me	O
7	**132**	OTBS	OMe	OMe	OMe	OMe	H	H	OMe	O
8	**113**	OAc	OMe	OMe	OMe	H	H	OMe	H	O
9	**111**	O	OMe	OMe	OMe	H	H	OMe	H	O
10	**109**	OH	OMe	OMe	OMe	H	H	OMe	H	N-OH
11	**110**	O	OMe	OMe	OMe	H	H	OMe	H	N-OH
12	**112**	N-OH	OMe	OMe	OMe	H	H	OMe	H	N-OH
13	**107**	OTBS	OMe	OMe	OMe	H	H	OMe	H	N-OH
14	**114**	OAc	OMe	OMe	OMe	H	H	OMe	H	N-OH
15	**142**	OTBS	OMe	OMe	OMe	OMe	H	H	OMe	N-OH
16	**158**	OTBS	H	H	H	H	H	H	H	O
17	**136**	OTBS	OMe	OMe	OMe	H	COOMe	OMe	H	O
18	**134**	OTBS	OMe	OMe	OMe	H	OMe	OMe	H	O
19	**144**	OAc	OMe	OMe	OMe	H	Me	OMe	Me	O
20	**145**	OAc	OMe	OMe	OMe	H	Me	OMe	Me	N-OH

Sr. No.	Comp No.	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X
21	**146**	OTBS	OMe	OMe	OMe	H	OMe	OMe	H	N-OH
22	**139**	OH	OMe	OMe	OMe	H	OMe	OMe	H	O
23	**160**	OH	H	H	H	H	H	H	H	N-OH
24	**161**	OAc	H	H	H	H	H	H	H	N-OH
25	**159**	OH	H	H	H	H	H	H	H	O
26	**118**	OTBS	OMe	OMe	OMe	H	OMOM	OMe	H	O
27	**119**	OH	OMe	OMe	OMe	H	OH	OMe	H	O
28	**120**	OTBS	OMe	OMe	OMe	H	OMOM	OMe	H	N-OH
29	**126**	OTBS	OMe	OMe	OMe	H	OH	OMe	H	O
30	**121**	OH	OMe	OMe	OMe	H	OH	OMe	H	N-OH
31	**122**	OH	OMe	OMe	OMe	H	OMOM	OMe	H	O
32	**124**	OAc	OMe	OMe	OMe	H	OMOM	OMe	H	O
33	**150**	OTBS	OMe	OMe	OMe	H	H	OCH_2COOEt	H	O
34	**151**	OH	OMe	OMe	OMe	H	H	OCH_2COOEt	H	O
35	**152**	OH	OMe	OMe	OMe	H	H	OCH_2COOH	H	O
36	**153**	OH	OMe	OMe	OMe	H	H	OCH_2COONa	H	O
37	**140**	OH	OMe	OMe	OMe	H	COOEt	OMe	H	O
38	**147**	OH	OMe	OMe	OMe	H	COOH	OMe	H	O
39	**148**	OH	OMe	OMe	OMe	H	COONa	OMe	H	O

Table 3: Cytotoxicity data of cyclopentenone CA-4 analogues from 2,3-diaryl-4-hydroxycyclopent-2-en-1-one series.

Sr No	Comp.of formula No	ED50 (ug/ml)											
		PTC	MOLT4	SW620	DU145	KB	L132	MiaPaca	Hep2	PA1	HuTu80	ECV304	293
1	**CA-4**	**ND**	**<1**	**5**	**57**	**10**	**10**	**<1**	**5**	**<1**	**72**	**50**	**72**
2	**106**	ND	ND	>5	>100	>100	>100	40	>100	80	>100	>100	>100
3	**108**	ND	ND	15	-	-	10	>100	-	-	-	-	-
4	**109**	-	-	15	-	-	11	>100	-	-	-	-	-
5	**114**	**-**	**<1**	**1.5**	**20**	**5**	**20**	**1.0**	**3**	**20**	**20**	**4**	**32**
6	**118**	33	-	43	34	33	32	50	12	13.5	36	40	>100
7	**119**	**78**	**-**	**<1**	**8**	**<1**	**<1**	**>100**	**<1**	**<1**	**1.5**	**>100**	**>100**
8	**126**	37.6	-	38	75	6.5	<1	55	14.5	14	9.5	30	42
9	**121**	>100	-	9	23	10	8	>100	<1	3.7	23.5	>100	>100
10	**120**	14.2	-	<1	30	27	28	6	13.7	8	14	16.5	18
11	**132**	-	-	5	100	10	100	>100	19	17	20	6.5	9.5
12	**137**	-	-	75	>100	90	>100	>100	>100	>100	>100	>100	>100
13	**142**	-	-	50	>100	>100	>100	**1**	**7**	**8.5**	**8.5**	**6**	**7**
14	**134**	>100	--	>100	>100	>100	>100	>100	>100	-	>100	>100	>100
15	**146**	53	-	20	60	15	60	15	32	-	72	36	70
16	**136**	>100	-	>100	>100	-	>100	>100	>100	-	-	>100	>100
17	**148**	-	-	-	>100	>100	>100	>100	-	-	>100	-	>100
18	**135**	11	-	75	>100	>100	>100	40	>100	80	>100	>100	>100

Sr No	Comp.of formula No	ED50 (ug/ml)											
		PTC	**MOL T4**	**SW6 20**	**DU14 5**	**KB**	**L132**	**MiaP aca**	**Hep2**	**PA1**	**HuTu 80**	**ECV 304**	**293**
19	**133**	12	-	10	>100	40	>100	-	26	32	>100	15	29
20	**138**	63	-	50	100	50	60	100	>100	>100	>100	>100	>100
21	**144**	80	-	60	>100	-	>100	>100	>100	-	-	>100	>100
22	**145**	>100	-	>100	>100	-	>100	>100	>100	-	-	>100	>100
23	**151**	-	-	-	>100	>100	>100	>100	>100	-	>100	-	>100
24	**153**	-	-	-	>100	>100	>100	>100	>100	-	>100	-	>100
25	**158**	**-**	**-**	**1**	**1.5**	**-**	**40**	**1**	**4**	**-**	**-**	**4**	**5**
26	**160**	-	-	>100	>100	>100	>100	71	71	>100	-	100	-
27	**161**	-	-	>100	>100	9	>100	4.5	>100	>100	-	>100	-

2,3-Diaryl-5-hydroxy-cyclopent-2-en-1-one analogues:

All the compounds described in section II (table 4) of this chapter belong to this category. The biological activity screening data of this group of molecules was in agreement with our observations for the group studied in section I.

Out of the 37 samples submitted only 28 samples could be screened for the cytotoxic activity. One of the additional feature studied in this group of molecules is the halogenated B-ring compounds. The enhanced inhibition of tubulin polymerization exhibited by this group is noteworthy. The 3-chloro and 3-fluoro substituted B-ring compounds **202** to **208** displayed marked tumor growth suppression (IC_{50} <1μg/ml) selectively against SW620 (ovary), L132 (lung) and Hep2 (larynx) cell lines.

On the contrary the free hydroxy group as well as the methoxy group at 3-position of the B-ring decreased the cytotoxic activity. Other alkyl ethers at 3-position of ring B like allyl ether and isopropyl ether also abolished activity e. g. compounds **186, 196**, **197**, **199**, **209** and **210.**

The potent efficacy has been attributed to the replacement of the phenolic OH of CA-4 with an amino group in the literature. We investigated the compounds with NHAc, NMeCHO, NHCHO

group in place of phenolic OH at 3-position in the B-ring. These groups were well tolerated and the compounds **213** and **214** were highly toxic to the tumor cells. The compound **214** in particular was highly cytotoxic with ED_{50} values of <1 μg/ml against 5 cell lines *viz*. KB, L132, MiaPaca, Hep2 and PA1.

By interchanging the substitution pattern of rings A and B we had synthesized the compounds **220-222**. It was noteworthy that this pattern destroyed the efficacy of the compound to inhibit the growth of cancer cells especially in case of the compounds with an electron-withdrawing (nitro) group in place of phenolic OH (in ring A in this example). The presence of primary amine instead of phenolic OH in the ring A (compound **222**) was effective for inhibition of atleast two cell lines *viz*. SW620 and KB (<1μg/ml).

Finally, the 4-methoxy in the B-ring was replaced by 4-thiomethyl group and it was observed that the compound **216** still retained the cytotoxicity. However, this activity was lost to some extent when the TBS protection was removed (similar to other compounds with TBS as discussed earlier).

The overall biological activity studies of the compounds in this group indicated that the compound with A-ring possessing 3,4,5-trimethoxy system and B-ring with 4-methoxy substitution was the most potent cytotoxic compound. A water-soluble phosphate derivative of this molecule was prepared which retained the activity shown by the parent molecule.

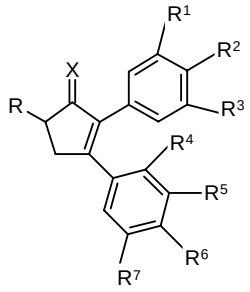


Table 4: 2,3-Diaryl-5-hydroxycyclopent-2-en-1-one analogues of CA-4

Sr. No.	Comp. No.	R	X	R^1	R^2	R^3	R^5	R^6	R^7
1	**192**	OH	O	OMe	OMe	OMe	H	OMe	H
2	**193**	OAc	O	OMe	OMe	OMe	H	OMe	H
3	**194**	OH	N-OH	OMe	OMe	OMe	H	OMe	H
4	**195**	OAc	N-OH	OMe	OMe	OMe	H	OMe	H
5	**196**	OH	O	OMe	OMe	OMe	OiPr	OMe	H
6	**197**	OH	N-OH	OMe	OMe	OMe	OiPr	OMe	H
7	**183**	OTBS	O	OMe	OMe	OMe	H	OMe	H
8	**186**	OTBS	O	OMe	OMe	OMe	OiPr	OMe	H
9	**216**	OTBS	O	OMe	OMe	OMe	H	SMe	H
10	**220**	OTBS	O	NO_2	OMe	H	OMe	OMe	OMe
11	**221**	OH	O	NO_2	OMe	H	OMe	OMe	OMe
12	**222**	OH	O	NH_2	OMe	H	OMe	OMe	OMe
13	**218**	OH	N-OH	OMe	OMe	OMe	H	SMe	H
14	**204**	OH	N-OH	OMe	OMe	OMe	Cl	OMe	H
15	**206**	OH	O	OMe	OMe	OMe	F	OMe	H
16	**208**	OAc	O	OMe	OMe	OMe	F	OMe	H
17	**207**	OH	N-OH	OMe	OMe	OMe	F	OMe	H
18	**202**	OH	O	OMe	OMe	OMe	Cl	OMe	H
19	**199**	OAc	O	OMe	OMe	OMe	OiPr	OMe	H
20	**203**	OAc	O	OMe	OMe	OMe	Cl	OMe	H
21	**205**	OAc	N-OH	OMe	OMe	OMe	Cl	OMe	H
22	**200**	OAc	O	OMe	OMe	OMe	OH	OMe	H
23	**211**	OH	O	OMe	OMe	OMe	NHAc	OMe	H
24	**198**	OH	N-OH	OMe	OMe	OMe	OH	OMe	H

Sr. No.	Comp. No.	R	X	R^1	R^2	R^3	R^5	R^6	R^7
25	**201**	OAc	O	OMe	OH	OMe	OH	OMe	H
26	**188**	OTBS	O	OMe	OMe	OMe	NMeCHO	OMe	H
27	**189**	OTBS	O	OMe	OMe	OMe	NHCHO	OMe	H
28	**209**	OH	O	OMe	OMe	OMe	O-allyl	OMe	H
29	**210**	OH	N-OH	OMe	OMe	OMe	O-allyl	OMe	H
30	**212**	OH	O	OMe	OMe	OMe	NHCOPh	OMe	H
31	**190**	OTBS	O	OMe	OMe	OMe	NHAc	OMe	H
32	**191**	OTBS	O	OMe	OMe	OMe	NHCOPh	OMe	H
33	**185**	OTBS	O	OMe	OMe	OMe	F	OMe	H
34	**184**	OTBS	O	OMe	OMe	OMe	Cl	OMe	H
35	**187**	OTBS	O	OMe	OMe	OMe	O-allyl	OMe	H
36	**213**	OH	O	OMe	OMe	OMe	NMeCHO	OMe	H
37	**214**	OH	O	OMe	OMe	OMe	NHCHO	OMe	H

Table 5: Cytotoxicity data of cyclopentenone CA-4 analogues from 2,3-diaryl-5-hydroxycyclopent-2-en-1-one series.

Sr. No	Comp. of formula No	ED50 (ug/ml)											
		PTC	MOLT4	SW620	DU145	KB	L132	MiaPaca	Hep2	PA1	HuTu80	ECV304	293
1	CA-4	ND	<1	5	57	10	10	<1	5	<1	72	50	72
2	183	16	-	5	28	7	9	<1	16	7	-	16	-
3	186	>100	-	9	6.3	7.5	7	>100	7.1	7.1	-	>100	>100
4	196	71	-	>100	87	>100	>100	>100	84	100	-	>100	-
5	197	55	-	69	81	95	75	98	40	61	-	96	-
6	198	>100	-	69	10	90	81	>100	20	26	-	>100	>100
7	199	83	-	47	93	>100	77	>100	>100	>100	-	81	94
8	200	>100	-	-	>100	35	6	18.5	>100	6	-	>100	92
9	202	30	-	<1	40	2.5	<1	>100	<1	>100	-	20	>100
10	203	-	-	<1	64	64	<1	24	<1	>100	-	3.5	60
11	204	15	-	<1	16	9.8	<1	33	<1	>100	-	18.5	50
12	205	-	-	<1	17	50	<1	10	<1	37.5	-	8	32
13	206	20	-	<1	27	4.5	<1	64	<1	>100	-	19.5	>100
14	207	27	-	<1	10	<1	<1	94	<1	>100	-	43	>100
15	208	80	-	<1	16	33	<1	39.5	<1	>100	-	41	59
16	209	>100	-	>100	45	90	>100	38	>100	>100	-	-	>100
17	210	82	-	>100	67	>100	82	62	>100	>100	-	-	>100
18	212	>100	-	>100	25	75	93	56	>100	>100	-	-	>100
19	213	62	-	>100	8	2	2	-	5	-	-	-	>100

Sr. No	Comp. of formula No	ED50 (ug/ml)											
		PTC	**MOLT4**	**SW620**	**DU145**	**KB**	**L132**	**MiaPaca**	**Hep2**	**PA1**	**HuTu 80**	**ECV 304**	**293**
20	**214**	**>100**	**-**	**-**	**21**	**<1**	**<1**	**<1**	**<1**	**<1**	**-**	**60**	**22**
21	**192**	**6.0**	-	**<1**	>100	**8**	**9**	79	**<1**	**<1**	-	>100	-
22	**193**	**6**	-	**<1**	>100	**72**	>100	**<1**	**18**	**<1**	-	18	-
23	**194**	**<1**	-	**<1**	>100	**<1**	**<1**	**24**	**<1**	**<1**	-	>100	-
24	**195**	**1.5**	-	**1**	>100	69	-	**<1**	100	**<1**	-	>100	-
25	**216**	**14**	-	**<1**	**>100**	**10**	**<1**	**<1**	**>100**	**<1**	-	**>100**	-
26	**218**	68	-	36	**2.5**	15	>100	40	**<1**	25.3	-	57	27
27	**220**	41	-	84	46	74.5	>100	75	37	73.8	-	100	41
28	**221**	48	-	98	>100	>100	>100	>100	74	77	-	50	-
29	**222**	>100	-	**<1**	41	**<1**	54	>100	16	20	-	>100	>100

1.5.3 CONCLUSION:

Out of the 76 NCEs submitted for screening 56 NCEs were actually tested for cytotoxicity against 9 to 12 human cancer cells. The overall cytotoxicity data revealed that in addition to the 3,4,5-trimethoxy system in the A ring, 4-methoxy in the B-ring is essential for the cytotoxic activity. The electron withdrawing groups like nitro and carboxyl reduced the potency of the molecules whereas the presence of halogen in place of phenolic OH of CA-4 enhanced the inhibition of cancer cell growth. Some of the NCEs synthesized as described in sections I and II displayed cytotoxic activity comparable with combretastatin A-4. The hit molecules selected from the preceding sections were the compounds **114, 119, 192, 193, 194, 195, 214, 216** which should be further optimized for achieving a **LEAD** molecule for *in vivo* studies and clinical trials.

1.5.4 REFERENCES:

1. Edondson, J. M.; Armstrong, L. S.; Martinez, A. O. *J. Tissue Cult. Methods.* **1988**, 11, 15.

CHAPTER 2

Some Useful Synthetic Methodologies

CHAPTER 2

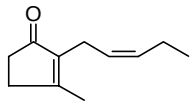
SOME USEFUL ORGANIC METHODOLOGIES

SECTION I

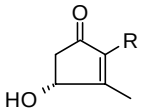
A Simple Procedure for the Conversion of 2-Aryl-2-Furylcarbinols to 2-Aryl-4-Hydroxycyclopent-2-en-1-ones

2.1.1 INTRODUCTION:

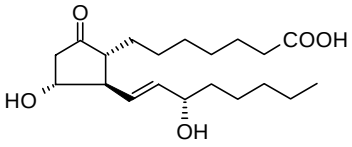
Cyclopent-2-en-1-one and its 4-hydroxy derivatives are present in several biologically active natural products like *cis*-jasmone (**1**), an important perfumery constituent[1] and the rethrolones (**2**), the ester components of the insecticidal pyrethins[2] and are important intermediates in the synthesis of the prostaglandins, a family of mammalian hormones[3].



cis-Jasmone (1)

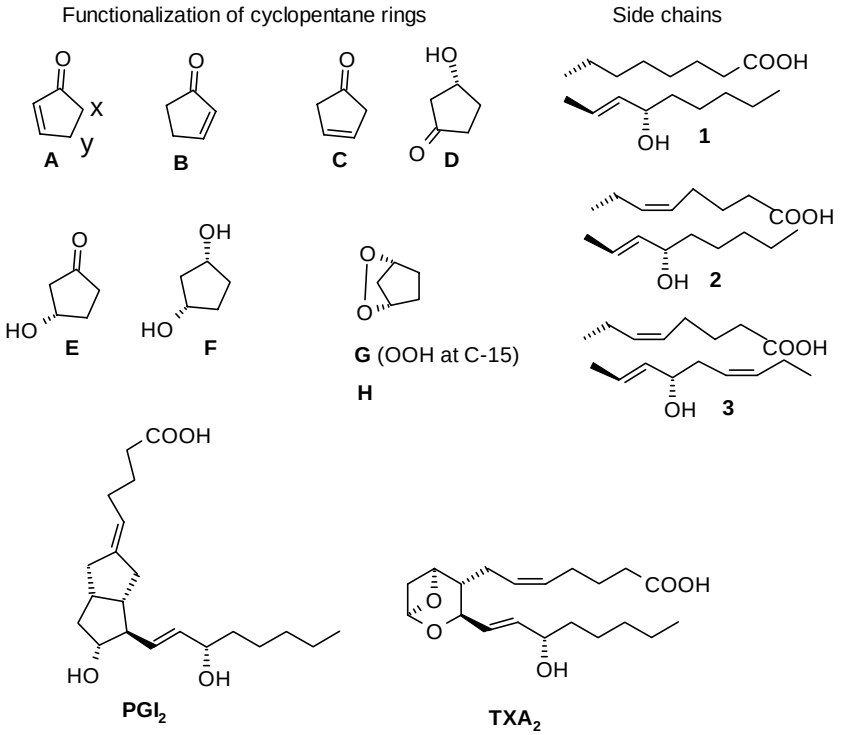


Rethrolones (2)



Prostaglandin E1 (3)

Prostaglandins exhibit diverse pharmacological properties and are now recognized as local hormones that control a multitude of important physiological processes[4]. Structural variation and classification of prostaglandins (PGs) and related compounds are explained as shown in scheme 1. PGs are classified based upon the double bond in cyclopentane ring and α, β side chains.[5]

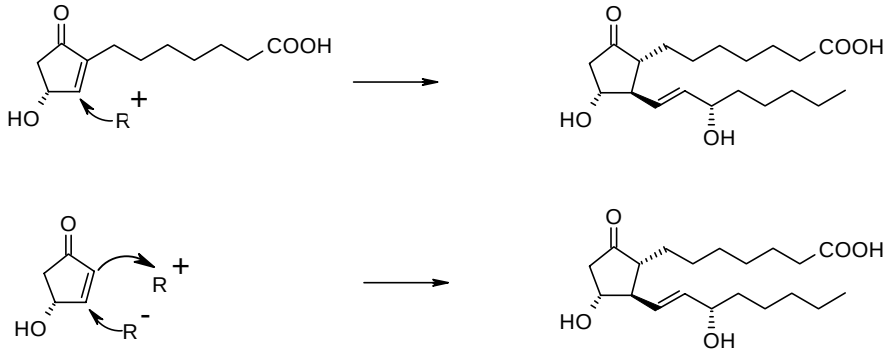


PGI_2 and TXA_2 are prostacyclin and thromboxane A_2 respectively

Scheme 1

Characteristically PGs contain a functionalized cyclopentane or cyclopentenone ring with two side chains (α and β) *trans* disposed at x and y position. There are series of prostaglandins generally abbreviated as PGSx, where 'S' denotes A, B, C to H and 'x' the subscript for the three different series 1, 2 or 3 denoting the number, location and type of double bonds in α and β side chains of the PGs structure.

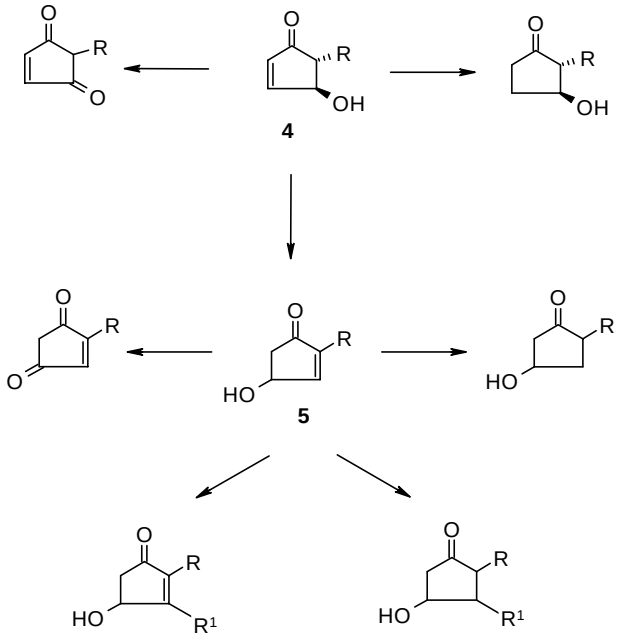
The intense interest in the prostaglandins has contributed to the more recent synthetic activity of these molecules.[6] There are many routes for the synthesis of prostaglandins but one of the approaches involving "conjugate addition" is most attractive and extensively studied. The two routes for the conjugate addition are 1) introduction of the lower side chain commonly called as β side chain into a 4-hydroxy-2-cyclopentenone, which already possesses the upper side chain which is generally, called as α-side chain, and 2) the consecutive linking of β and α side chains to cyclopentenones (scheme 2).



Scheme 2

In both routes 4-hydroxycyclopentenone is the key intermediate for prostaglandin syntheses. Various routes are available for the syntheses of 4-hydroxycyclopentenone or suitably 2-substituted 4-hydroxy cyclopentenone.

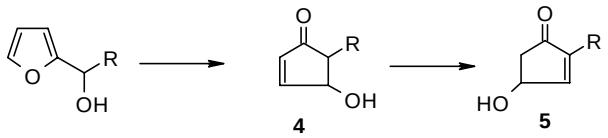
From the synthetic point of view 2-substituted-4-hydroxycyclopent-2-en-1-ones (**5**) are very important intermediates, which can be easily converted to isomeric hydroxycyclopentanones and cyclopentenediones as shown in scheme 3.



Scheme 3

BRIEF REVIEW OF LITERATURE:

There are many reagents reported in the literature for the preparation of 2-substituted-4-hydroxycyclopent-2-en-1-ones (**5**) by the molecular rearrangement of 2-furylcarbinol but most of the methods for preparation of 2-substituted-4-hydroxycyclopent-2-en-1-one involve two steps from 2-furyl carbinols as shown below.

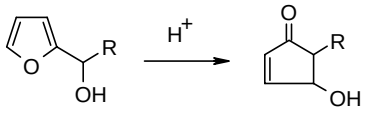


As discussed in chapter 1, for our synthetic work on *cis* restricted substituted 2,3-diaryl 4/5 hydroxy-cyclopent-2-en-1-one analogues of combretastatin A-4, we envisaged substituted 2-aryl-4-hydroxycyclopent-2-en-1-one (**5**) as the key intermediate. So it was necessary to prepare these intermediates on large scale, in shorter routes and good yields.

The literature survey revealed that most of the methods for synthesis of intermediate **5** involve two steps from 2-furylmethanol. In the first step it forms intermediate **4**, which on further rearrangement results in intermediate **5**.

There are various methods reported in the literature for the synthesis of 4-hydroxy-5-substituted-cyclopent-2-en-1-ones (**4**) some of which are discussed below.

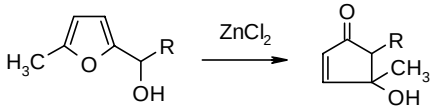
Piancatelli *et al.*[7] reported the utility of formic acid, polyphosphoric acid and *p*-toluenesulfonic acid for the preparation of 4-hydroxy-5-substituted-cyclopent-2-en-1-ones (**4**) from 2-furylcarbinol in acetone-water at ambient temperature (scheme 4).



Scheme 4

The rearrangement proceeded stereospecifically to give *trans* arrangement of the substituents (R and OH). The yields were good when the furylcarbinol contained R group as aromatic substituent while when furylcarbinol contained R as alkyl substituent, the reaction rate was extremely slow, giving poor yields and formation of unidentified side products.

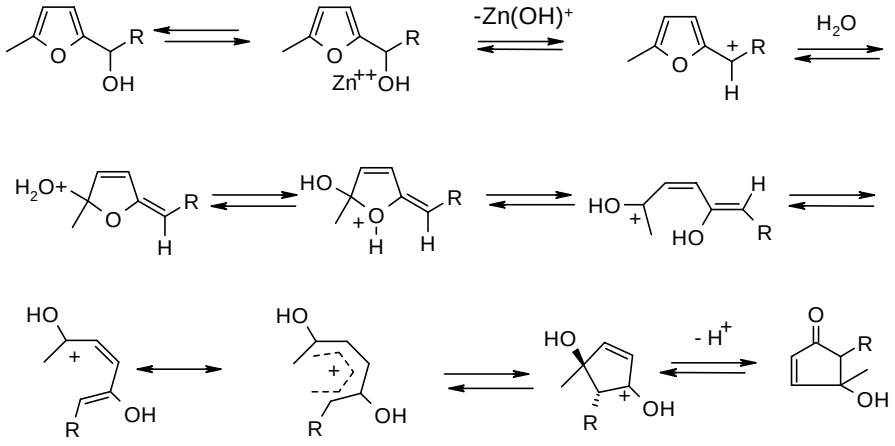
Piancatelli *et al.*[8] further reported zinc chloride as weak Lewis acid catalyst for the conversion of 5-methyl-2-furylcarbinol to 4-hydroxy-4-methyl-5-substituted-cyclopent-2-en-1-one in acetone-water mixture at 60^0C, the other methods failed in this case giving a mixture of products which were showing the absence of any carbonyl (CO) function in the IR spectrum.



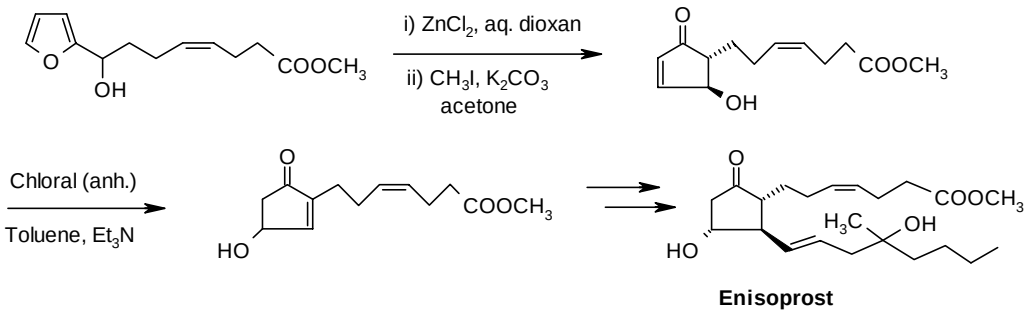
Scheme 5

They also found that when the furylcarbinol contained an alkyl group as substituent R, the reaction rate was extremely slow, poor yields and unidentified byproducts were formed. When R was an aromatic substituent, the reaction was much faster and yields were excellent.

They proposed the underlying mechanism for the reaction in terms of thermal electrocyclic reaction of 4π electrons system that is conrotatory.

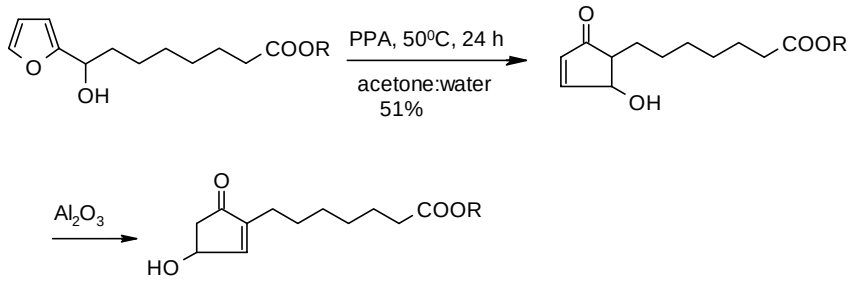


Dygos *et al.*[9] synthesized antisecretory prostaglandin Enisoprost (scheme 6) using zinc chloride and aqueous dioxan for rearrangement which on further treatment with chloral in toluene afforded the required intermediate.



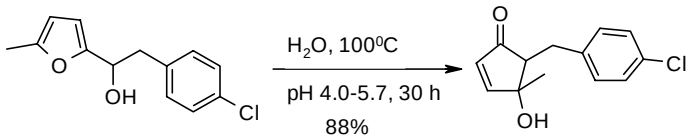
Scheme 6

Piancatelli and Scettri[10] reported polyphosphoric acid (scheme 7) in acetone-water (2:1) at 50^0C for the conversion of substituted 2-furylmethanol to 4-hydroxy-5-alkyl- cyclopent-2-en-1-one which was further treated with alumina to give the 2-alkyl-4-hydroxycyclopent-2-en-1-one, an important intermediate for prostaglandin synthesis.



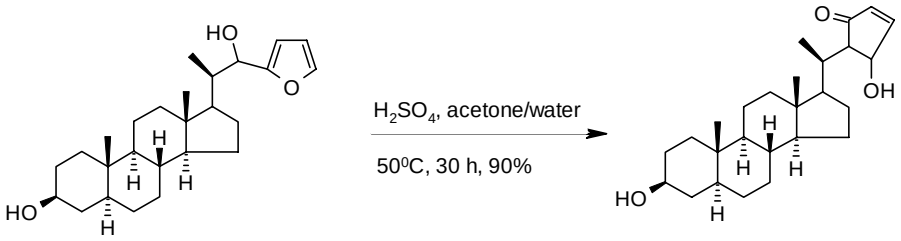
Scheme 7

Saito and Yamachika[11] found that when furancarbinol was heated in aqueous medium at controlled pH 4.0-5.7 in boiling buffered medium it gave the isomerized product in good yields (scheme 8). They found that when the side chain was an alkyl or cycloalkyl group, reaction rate was slower.



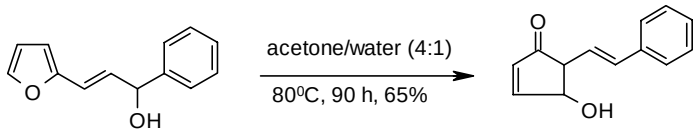
Scheme 8

Piancatelli and Scettri[12] reported concentrated sulfuric acid catalyzed rearrangement of steroid 2-furylcarbinol to cyclopentenone in excellent yields (scheme 9).



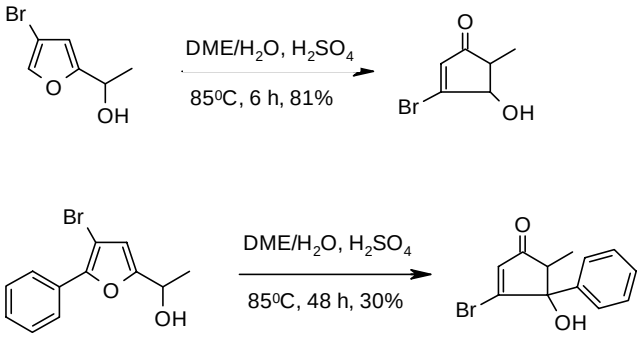
Scheme 9

The isomerization of 2-furylidenecarbinol to cyclopentenone (scheme 10) was reported by Antonioletti *et al.*[13] in acetone-water without an acid catalyst at 80^0C in 65 % yield but the reaction time was somewhat longer.



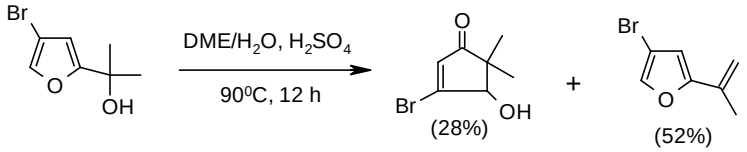
Scheme 10

D`Auria *et al.*[14] studied substituent effect on furan ring on the rearrangement. They noticed that 2-furylcarbinols with a bromo substituent at position 3 and/or 4 of furan ring are unusually stable and they yield the corresponding rearranged compounds under more drastic conditions by using concentrated sulfuric acid in dimethoxyethane/water (2:1) at 85^0C. They noticed that when 2-furyl methanol having phenyl group as substituent at position 5 was subjected to rearrangement there was remarkable decrease in yield and reaction time was longer (scheme 11).



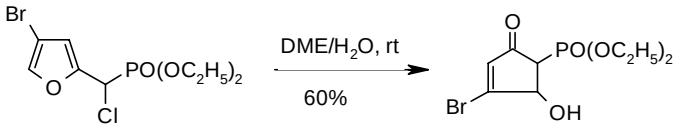
Scheme 11

They also reported that furanoid compounds with tertiary carbinol side chain underwent side reaction such as formation of dehydration product along with the formation of cyclopentenone (scheme 12).



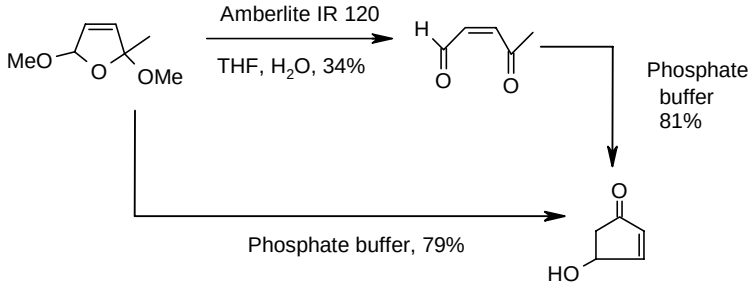
Scheme 12

The rearrangement of compound having chloro in place of hydroxyl group of 2-furylmethanol was reported by Castagnino *et al.*[15] with dimethoxyethane-water without catalyst (scheme 13). The reaction was complete at room temperature as chloro is efficient leaving group, which enhances the reactivity of the furan.



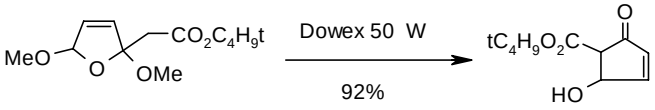
Scheme 13

Teijin Ltd. Japan[16] reported (scheme 14) the preparation of cyclopent-2-en-1-one from dimethoxydihydrofuran using phosphate buffer (pH 6) in 79 % yield whereas when dimethoxydihydrofuran was treated with an acidic ion exchange resin the dicarbonyl compound was isolated in low yield of 34 % which on further treatment with phosphate buffer gave cyclopentenone in 81 % yield.



Scheme 14

Use of strong acid resin Dowex 50 (H^+) for the conversion of dimethoxydihydrofuran to cyclopentenone (scheme 15) was reported by Shono *et al.*[17]

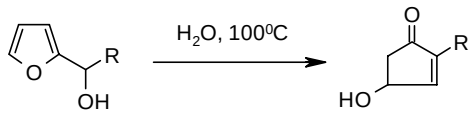


Scheme 15

Synthesis of 2-substituted-4-hydroxycyclopent-2-en-1-ones:

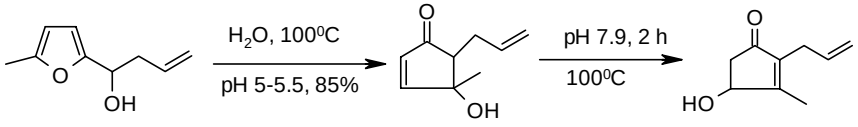
There are a few methods reported in the literature, which give 2-substituted-4-hydroxycyclopent-2-en-1-one from 2-furylcarbinols in one step. Some of the methods are discussed below.

D` Auria[18] found that when 2-furylcarbinol was treated with boiling water under inert atmosphere (scheme 16) 2-aryl or 2-alkyl-4-hydroxycyclopent-2-en-1-one was obtained in single step. The reaction is stereospecific and general for aliphatic as well as arylfurylcarbinols.



Scheme 16

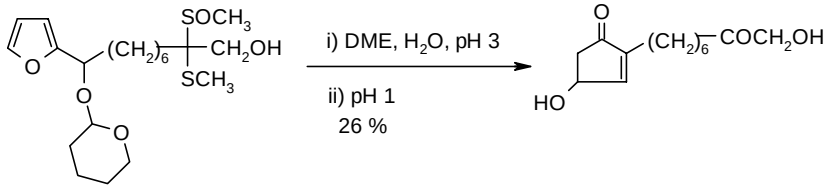
Saito and Yamachika[19] reported preparation of 2-substituted-4-hydroxycyclopent-2-en-1-ones from 2-furylcarbinols in one-pot operation without isolating the intermediate merely by changing acidic (pH 5) to basic conditions (pH 7.9) after the first intramolecular cyclization as shown in scheme 14.



Scheme 17

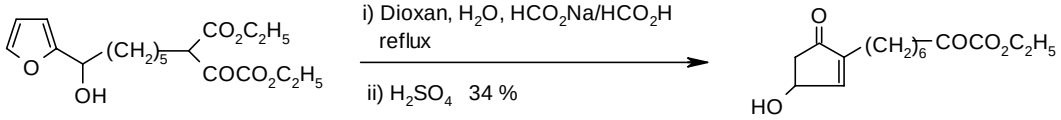
It was also reported by Saito *et al.*[20] that rearrangement of 2-furylcyclohexylcarbinol into cyclopentenone could be achieved by heating in an autoclave at 150^0C (pressure 2 Kg/ cm^2) at pH 6.2. Collins *et al.*[21] reported zinc chloride in dioxan-water system at high temperature (180^0C) for the rearrangement of 2-furylcarbinol to cyclopentenone in single step but the yields obtained were poor and the method was not generalized.

Peake S. L.[22] reported the one step process to prepare cyclopentenone (scheme 18) first by acid catalyzed rearrangement of 2-furylcarbinol with polyphosphoric acid, followed by addition of concentrated sulfuric acid.



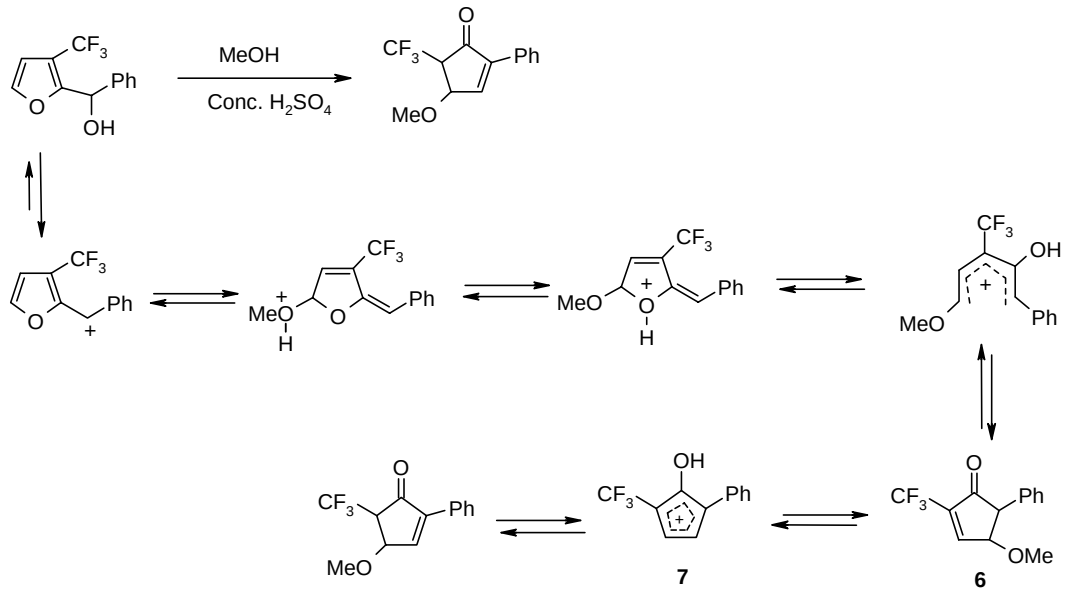
Scheme 18

Floyd [23] reported one step procedure (scheme 19) for the preparation of cyclopentenones from 2-furylcarbinols using buffer (sodium formate/ formic acid) at reflux temperature.



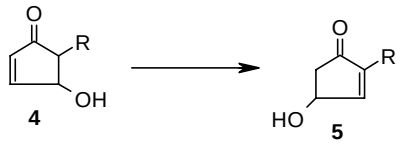
Scheme 19

Kobayashi *et al.*[24] found that when phenyl-(3-trifluoromethyl-furan-2-yl)-methanol was treated with conc. sulfuric acid in methanol at room temperature they directly obtained the 4-methoxy-2-phenyl-5-trifluoromethyl-cyclopent-2-en-1-one (scheme 20). They proposed mechanism for this reaction that the cyclopentenone derivative **6** may be formed initially and the subsequent conversion to **6** to the final product may involve the cationic intermediate **7**.



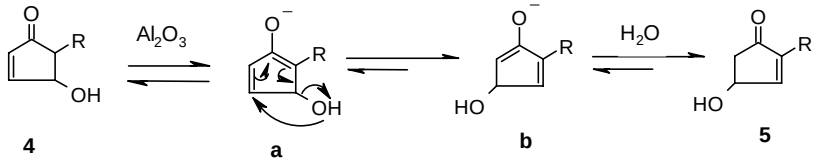
Scheme 20

Synthesis of 2-substituted-4-hydroxycyclopent-2-en-1-one (**5**) from 4-hydroxy-5-substituted cyclopent-2-en-1-one (**4**) (scheme 21) was achieved by alumina (neutral or basic),[25] chloral and triethylamine[26] or by adjusting pH to basic value.[27] Alternatively same reaction was carried out in acidic conditions.[20-22]



Scheme 21

The mechanism for conversion of **4** to **5** using neutral alumina was proposed by Piancatelli *et al.*[24] as given below.

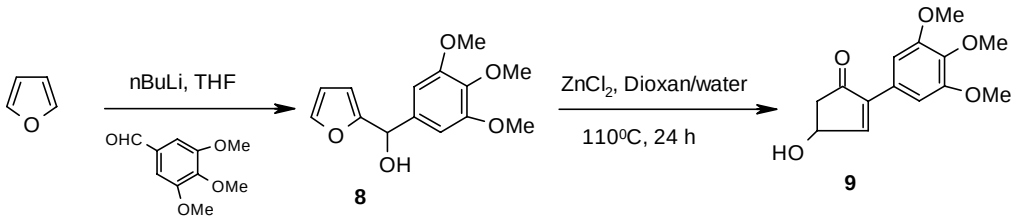


Initial formation of the enolate **a** takes place, which rapidly rearranged into the isomeric, thermodynamically more stable enolate **b** by migration of alcoholic function which on protonation results in intermediate **5**.

2.1.2 PRESENT WORK:

From the literature survey it was evident that there are many methods for the synthesis of 2-substituted-4-hydroxycyclopent-2-en-1-one from 2-furylcarbinol and most of the methods involve two steps. A few reports revealed a single step method.

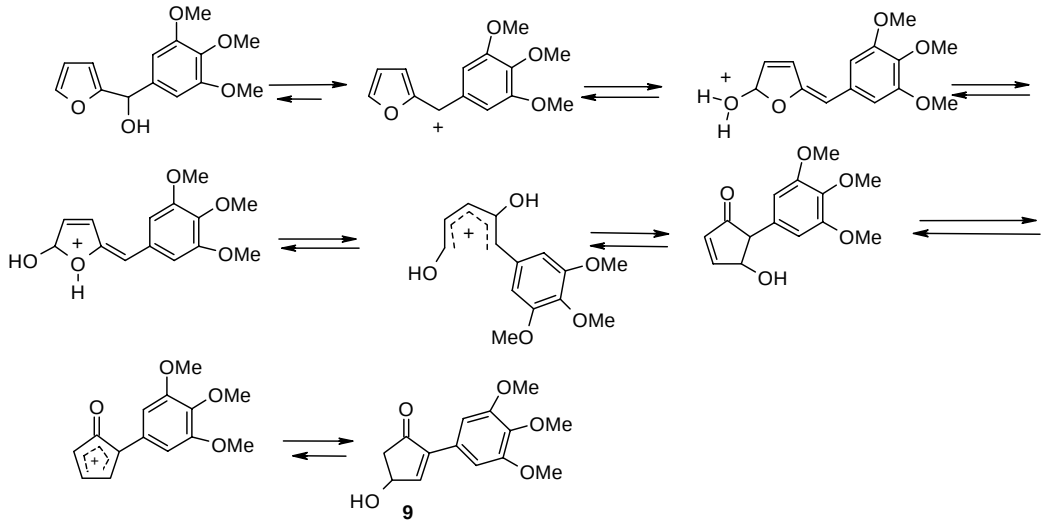
During our studies on synthesis of novel *cis* restricted combretastatin analogues we wanted to prepare 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one from 2-(3,4,5-trimethoxy phenyl) furylmethanol (scheme 22). The 2-(3,4,5-trimethoxyphenyl) furylmethanol was prepared by lithiation of furan at -20^0C, which was treated with 4 equivalent of zinc chloride in dioxan-water mixture at reflux temperature for 24 hours and it was observed that the 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one was formed exclusively in 90 % of isolated yield.



Scheme 22

The formation of compound **9** was confirmed by ^{1}H NMR, which showed doublet at δ 2.52 for one proton with coupling constant 18 Hz and doublet of doublet at δ 3.00 for one proton showing coupling constant 18 Hz and 6 Hz, which is characteristic of 4-hydroxycyclopent-2-en-1-one ring. Also the ^{13}C DEPT of this compound showed the presence of methylene (CH_2) at δ 45.78. In IR spectrum the peak at 1709 cm^{-1} confirmed the presence of carbonyl function. The mass spectrum and microanalysis were also in agreement with the structure of the compound **9**.

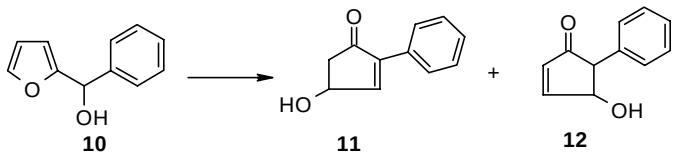
The proposed mechanism for this reaction may be as given in scheme 20. The initial formation of carbocation and its relative stability is the key factor in this rearrangement. Initially the 4-hydroxy-5-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one may be formed, it may involve cationic intermediate which then gets converted to the final product 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one. At low temperature and if less quantity of zinc chloride was used in the reaction it gave mixture of products which were identified as 4-hydroxy-5-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one and 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one.



Scheme 23

D` Auria[18] reported the isomerization of substituted 2-furylcarbinols to 2-substituted 4-hydroxy cyclopent-2-en-1-ones by heating in distilled water but we observed that in case of our compounds this method did not work satisfactorily especially on large scale (10-50 g), which was necessary to collect these intermediates for further transformations.

We studied the reaction using variable amount of zinc chloride and effect of temperature on the isomerization of phenyl-2-furylmethanol and the results are shown in table 1.



It was observed that 4 equivalents of zinc chloride in dioxan-water as a solvent and reflux temperature (110^0C) were necessary to get good yields of 2-aryl-4-hydroxycyclopent-2-en-1-one (**11**). With lesser quantity of zinc chloride (either 2 or 3 equivalents) the yields were less and reaction gave mixture of products (**11+12**) in different proportion.

Table 1: Effect of temperature and quantity of zinc chloride on the rearrangement of phenyl-2-furylmethanol

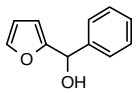
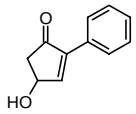
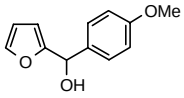
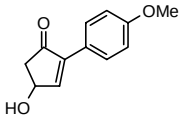
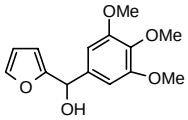
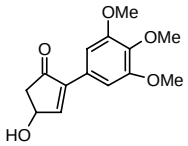
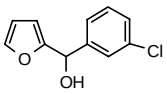
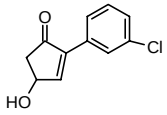
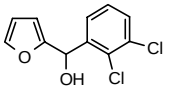
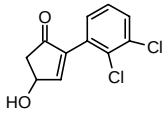
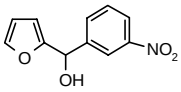
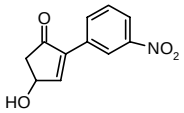
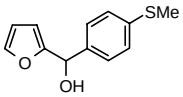
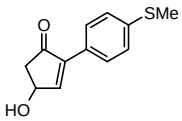
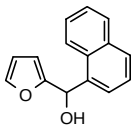
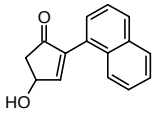
Entry	$ZnCl_2$ (eq.)	Temp. (^0C)	Solvent	Time (h)	Product	Yield (%)
1	1	60	Acetone/water	40	12	70
2	1	60	Dioxan/water	24	12	65
3	1	110	Dioxan/water	24	11+12 (2:3)	62
4	4	110	Dioxan/water	24	11	89
5	4	60	Dioxan/water	24	11+12 (3:2)	58
6	4	60	Acetone/water	70	11+12 (3:2)	52

When phenyl-2-furylmethanol was treated with 1 equivalent of zinc chloride in acetone/water system at 60^0C, exclusive formation of 4-hydroxy-5-phenyl-cyclopent-2-enone (**12**) in good yield was observed while when dioxan/water was used as a solvent under similar conditions product **12** was obtained with lower yields. When 1 equivalent of zinc chloride was used in dioxan/water at reflux temperature the reaction proceeded to give a mixture of products (**11+12**) in 2:3 ratio as confirmed by GC. It was observed that this rearrangement was highly sensitive to solvent and temperature used and it was possible to get the desired product selectively in high yield by manipulating the reaction conditions.

After standardization of reaction conditions, in order to study the scope of this methodology different aryl 2-furylmethanols were reacted with 4 equivalents zinc chloride using dioxan/water at 110^0C for 24 h or 1 equivalent of zinc chloride in acetone/water at 60^0C for 24 h and the results obtained for different substrates are given in table 2 and table 3 respectively.

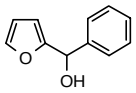
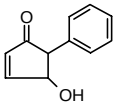
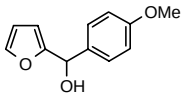
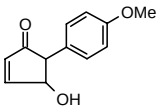
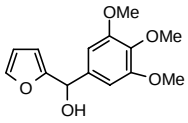
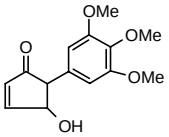
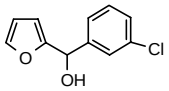
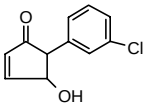
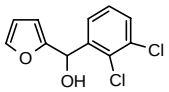
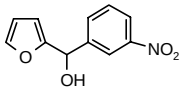
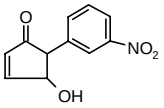
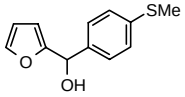
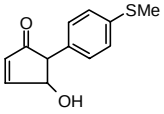
From the tables 2 and 3 it is clear that the electronic nature of substituents as well as their position on aromatic ring has strong influence on the conversion of 2-furylcarbinol to 2-aryl substituted 4-hydroxycyclopent-2-en-1-one. The electron donating substituents on aromatic ring strongly favor the rearrangement and excellent yields are obtained from these substrates (entry **1**, **2**, **3;** table 2). The electron withdrawing substituents like nitro and substitution at ortho position afforded low yields (entry **4**, **5**, **6;** table 2), larger aryl groups like napthalenyl also gave good yields of rearranged product (entry **8,** table 2).

Table 2: Reaction of substituted aryl 2-furylcarbinols with 4 eq. $ZnCl_2$ in dioxan/water at 110^0C

Entry	Substrate	Product [a]	Yield (%) [b]
1			89
2			90
3			90
4			80
5			76
6			72
7			84
8			85

a: Characterized by usual spectroscopic methods; b: isolated yield.

Table 3: Reaction of substituted aryl 2-furylcarbinols with 1 eq. $ZnCl_2$ in acetone/water at 60^0

Entry	Substrate	Product [a]	Yield (%)
1			70
2			69
3			77
4			54
5		No reaction	-
6			52
7			76

a: Characterized by usual spectroscopic methods; b: isolated yield.

From the table 3 it is clear that 4-hydroxy-5-aryl (substituted)-cyclopent-2-en-1-one can be obtained exclusively by using one equivalent zinc chloride in acetone/water at 60^0C. It is also clear that electron-donating substituents give better yields (entry **1**, **2**, **3**; table 3). In case of electron withdrawing substituents the yields are poor (entry **4**, **6**; table 3) and when two

electronegative groups are present on aromatic ring there is no formation of product (entry **5**, table 3).

2.1.3 CONCLUSION:

A simple and efficient single step method for the preparation of 2-aryl-substituted-4-hydroxycyclopent-2-en-1-one in excellent yield was developed using zinc chloride as a weak Lewis acid (4 equivalent) at elevated temperature (reflux temperature of dioxan/water). It was also demonstrated that by changing the reaction conditions i.e. by using one equivalent of zinc chloride at lower temperature (60^0C) one can obtain 4-hydroxy-5-arylsubstituted cyclopent-2-en-1-ones selectively in good to excellent yields.

2.1.4 EXPERIMENTAL:

Preparation of substituted furfuryl alcohols-General procedure:

Magnesium (1.68 gm, 70 mmol) was taken in three neck R.B. flask equipped with reflux condensor and 100 ml ether followed by dibromoethane (9.5 gm, 51.02 mmol) were added with stirring at 0°C under nitrogen atmosphere. Stirring was continued till all magnesium reacted, then ether was removed under vacuum till slurry was formed (A). In another single neck R.B. flask furan (4.76 gm, 70 mmol) in tetrahydrofuran (100 ml) was cooled with ice-salt mixture, n-butyllithium (2M, 35 ml, 70 mmol) was added dropwise, and stirred at 0°C for 45 min (B).

Furyllithium thus prepared in flask B was added to cold mixture in A though cannula, stirred at 0°C for 5 min, brought to room temperature, stirred at room temperature for 1.5 h and then cooled to -20°C (dry ice + CCl_4). Substituted benzaldehyde (51.02 mmol) in tetrahydrofuran (50 ml) was added and stirred at -20°C for 4 h (monitored by TLC). After completion of reaction, the reaction mixture was quenched with saturated ammonium chloride solution and the mixture was allowed to warm to room temperature. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried over sodium sulfate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (petroleum ether: acetone as eluent) to collect pure substituted furfuryl alcohols.

1) Furan-2-yl-(3,4,5-trimethoxyphenyl)-methanol:
Yield 93 %; m. p. 77-78^{0}C; **IR** (υ_{max}, $CHCl_3$): 1216, 1595, 3017, 3433 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.72 (bs, 1H), 3.84 (s, 9H), 5.75 (bs, 1H), 6.15(d, *J* = 6 Hz, 1H), 6.27-6.32 (m, 1H), 6.66 (d, *J* = 2 Hz, 2H), 7.40 (bs, 1H); **Mass** (m/e): 264 (M^+, 80), 247 (60), 233 (12), 214 (15), 189 (20), 169 (70), 161 (25), 95 (100); Anal. Calcd. For $C_{14}H_{16}O_5$: C 63.63; H 6.10 %. Found: C 63.78; H 6.22 %.

2) Furan-2-yl-phenyl-methanol: Yield 85 %; **IR** (υ_{max}, $CHCl_3$): 1200, 1492, 1590, 3410, 3620 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.78 (s, 1H), 5.81 (s, 1H), 6.12 (d, *J* = 4 Hz, 1H); 6.33 (m, 1H), 7.28-7.55 (m, 6H); **Mass** (m/e): 174 (M^+).

3) Furan-2-yl-(4-methoxyphenyl)-methanol: Yield 89 %; **IR** (υ_{max}, $CHCl_3$): 1303, 1512, 1611, 3013, 3436 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.79 (s, 3H), 5.72 (s, 1H), 6.12 (d, *J* = 2 Hz, 1H), 6.32 (t, *J* = 2 Hz, 1H), 6.89 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.41 (dd, *J* = 6 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 55.02, 69.54, 106.81, 110.01, 113.72 (2C), 127.80 (2C), 128.64, 133.39, 142.02, 156.47; **Mass** (m/e): 204 (M^+).

4) Furan-2-yl-(3-nitrophenyl)-methanol: Yield 78 %; **IR** (υ_{max}, $CHCl_3$): 1479, 1530, 3407 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.26-2.93 (bs, 1H), 4.49 (s, 1H), 4.76 (d, *J* = 4 Hz, 1H), 4.91 (t, *J* = 4 Hz, 1H), 5.96 (s, 1H), 6.10 (t, *J* = 8 Hz, 1H), 6.34 (d, *J* = 8 Hz, 1H), 6.70 (d, *J* = 8 Hz, 1H), 6.87 (s, 1H); **Mass** (m/e): 219 (M^+).

5) (3-Chlorophenyl)-furan-2-yl-methanol: Yield 69 %; **IR** (υ_{max}, $CHCl_3$): 1597, 1704, 3416 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.18 (bs, 1H), 5.78 (s, 1H), 6.13 (d, *J* = 4 Hz, 1H), 6.32 (d, *J* = 2 Hz, 1H), 7.20-7.45 (m, 5H); **Mass** (m/e): 208 (M^+), 191, 180, 139.

6) (2,3-Dichlorophenyl)-furan-2-yl-methanol: Yield 51 %; **IR** (υ_{max}, $CHCl_3$): 1707, 3383 cm^{-1}**; ^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.63 (bs, 1H), 6.02 (d, *J* = 2 Hz, 1H), 6.13 (s, 1H), 6.27 (d, *J* = 2 Hz, 1H), 7.20-7.45 (m, 3H), 7.59 (d, *J* = 8 Hz, 1H); **Mass** (m/e): 242 (M^+), 225, 176,141.

7) Furan-2-yl-(4-methylsulfanylphenyl)-methanol: Yield 60 %; **IR** (υ_{max}, $CHCl_3$): 1599, 3416 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.44 (s, 3H), 3.00 (bs, 1H), 5.68 (s, 1H), 6.06 (d, *J* = 2 Hz, 1H), 6.26 (d, *J* = 2 Hz, 1H), 7.05-7.60 (m, 5H); **Mass** (m/e): 220 (M^+), 203, 173, 151.

8) Furan-2-yl-naphthalen-1-yl-methanol: Yield 83 %; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.48 (bs, 1H), 6.04 (d, *J* = 4 Hz, 1H), 6.29 (dd, *J* = 4 Hz and 2 Hz, 1H), 6.48 (s, 1H), 7.39 (d, *J* = 2 Hz, 1H), 7.45-7.58 (m, 3H), 7.72 (d, *J* = 8 Hz, 1H), 7.91-8.03 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 67.16, 107.74, 110.20, 123.51, 124.04, 125.20, 125.38, 125.90, 128.43, 128.51, 130.49, 133.58, 136.30, 142.07, 155.71; **Mass** (m/e): 224 (M^+).

Preparation of 2-aryl substituted-4-hydroxy-cyclopent-2-en-1-ones:

In a 1 liter round bottom flask a solution of aryl furfuryl alcohol (25 gm, 94.69 mmol) and $ZnCl_2$ (51.26 gm, 378.7 mmol) in dioxan (309 ml) and water (206 ml) was refluxed for 24 h at which time TLC analysis indicated the complete disappearance of starting material. The mixture was brought to room temperature, acidified to pH 1 with dilute HCl and extracted with ethyl acetate. Organic layer was washed with water, followed by brine and dried over sodium sulphate. The organic layer was concentrated under reduced pressure using rotary evaporator and chromatographed on silica gel column to collect the 2-aryl substituted -4-hydroxy-cyclopent-2-en-1-ones as shown in table 2.

1) 4-Hydroxy-2-phenyl-cyclopent-2-en-1-one: M. p. 58-59 ^{0}C (lit.[24] 58-59^{0}C); **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.48 (bd, *J* = 20 Hz, 1H), 2.73 (bs, 1H), 2.97 (dd, *J* = 20 Hz and 6 Hz, 1H), 4.90-5.58 (m, 1H), 7.25-7.50 (m, 3H), 7.55-7.80 (m, 3H); **Mass** (m/e): 174 (M^+); Anal. Calcd. For $C_{11}H_{10}O_2$: C 75.84; H 5.79 %. Found: C 75.98; H 5.85 %.

2) 4-Hydroxy-2-(4-methoxyphenyl)-cyclopent-2-en-1-one: **IR** (υ_{max}, $CHCl_3$): 1250, 1708, 3019, 3442 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.50 (bd, *J* = 14 Hz, 1H), 2.99 (dd, *J* = 14 Hz and 6 Hz, 1H), 3.83 (s, 3H), 4.95-5.10 (m, 1H), 6.92 (d, *J* = 6 Hz, 2H), 7.55 (d, *J* = 2 Hz, 1H), 7.69 (d, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 45.66, 54.74, 66.64, 113.47 (2C), 122.99, 128.40; (2C), 142.11, 155.60, 159.72, 204.49; **Mass** (m/e): 204 (M^+); Anal. Calcd. For $C_{12}H_{12}O_3$: C 70.57; H 5.92 %. Found: C 70.79; H 6.22 %.

3) 4-Hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one: M. p. 93-94^{0}C; **IR** (υ_{max}, $CHCl_3$): 1709, 3464 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.46 (dd, *J* = 18 Hz and 4 Hz, 1H), 2.91 (dd, *J* = 18 Hz and 8 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 6H), 4.93-4.98 (m, 1H), 6.91 (s, 2H), 7.51 (d, *J* = 4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 45.78, 55.88 (2C), 60.58, 67.02, 104.59 (2C), 125.92 (2C), 138.34, 142.80, 152.75, 156.66, 204.48; **Mass** (m/e): 264 (M^+, 100), 249 (57), 233 (10), 221 (22), 205 (32), 189 (70), 177 (20), 161 (40); Anal. Calcd. For $C_{14}H_{16}O_5$: C 63.63; H 6.10 %. Found C 63.71; H 6.18 %.

4) 2-(3-Chlorophenyl)-4-hydroxy-cyclopent-2-en-1-one: IR (υ_{max}, $CHCl_3$): 1711, 3019, 3442 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 2.43 (bd, *J* = 18 Hz, 1H), 2.90 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.62 (bs, 1H), 4.96 (d, *J* = 6 Hz, 1H), 7.26 (d, *J* = 6 Hz, 2H), 7.48 (d, *J* = 3 Hz, 1H), 7.59 (d, *J* = 3 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$ + CCl_4): δ 45.71, 67.41, 125.58, 127.41, 129.12, 129.73, 132.05, 134.34, 142.40, 158.15, 204.32; **Mass** (m/e): 208 (M^+).

5) 2-(2,3-Dichlorophenyl)-4-hydroxy-cyclopent-2-en-1-one: IR (υ_{max}, $CHCl_3$): 1707, 3383 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 2.42 (bd, *J* = 18 Hz, 1H), 2.89 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.69 (s, 1H), 5.01 (bs, 1H), 7.05-7.25 (m, 2H), 7.42 (d, *J* = 9 Hz, 1H), 7.57 (d, *J* = 3 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$ + CCl_4): δ 44.93, 68.41, 127.34, 127.90, 129.18, 132.52, 133.99, 134.17, 143.99, 161.30, 203.13; **Mass** (m/e): 242 (M^+), 207, 172.

6) 4-Hydroxy-2-(3-nitrophenyl)-cyclopent-2-en-1-one: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.52 (dd, *J* = 18 Hz and 4 Hz, 1H), 2.99 (dd, *J* = 18 Hz and 6 Hz, 1H), 3.40 (bs, 1H), 5.05-5.20 (m, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.80 (d, *J* = 2 Hz, 1H), 7.98 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.11 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.46 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 45.33, 67.23, 122.00, 123.29, 129.28, 131.82, 133.25, 141.12, 147.81, 159.13, 203.79; **Mass** (m/e): 219 (M^+).

7) 4-Hydroxy-2-(4-methylsulfanylphenyl)-cyclopent-2-en-1-one: M. p. 137-138^{0}C; **IR** (υ_{max}, $CHCl_3$): 1215, 1711, 3019, 3386 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$ + CCl_4): δ 2.13 (bs, 1H), 2.43-2.55 (m, 4H), 2.98 (dd, *J* = 18 Hz and 6 Hz, 1H), 7.23 (d, *J* = 6 Hz, 2H), 7.58 (d, *J* = 3 Hz, 1H), 7.64 (d, *J* = 6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$ + CCl_4): δ 15.18, 45.73, 67.49, 126.05 (2C), 127.00, 127.55 (2C), 139.94, 143.17, 154.86, 203.42; **Mass** (m/e): 220 (M^+), 145; Anal. Calcd. For $C_{12}H_{12}O_2S$: C 65.43; H 5.49; S 14.56 %. Found: C 65.56; H 5.54; S 14.70 %.

8) 4-Hydroxy-2-naphthalen-1-yl-cyclopent-2-en-1-one: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 2.36 (dd, *J* = 16 Hz and 2 Hz, 1H), 2.75 (dd, *J* = 16 Hz and 8 Hz, 1H), 3.64 (bs, 1H), 4.68-4.78 (m, 1H), 7.16-7.50 (m, 5H), 7.62 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.73 (d, *J* = 6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 44.70, 67.71, 124.80, 124.94, 125.83, 126.12, 126.89, 128.32, 128.40, 128.91, 130.97, 133.36, 144.76, 161.59, 205.37; **Mass** (m/e): 224 (M^+); Anal. Calcd. For $C_{15}H_{12}O_2$: C 80.34, H 5.39 %. Found: C 80.48, H 5.48 %.

Preparation of 4-hydroxy-5-aryl substituted-cyclopent-2-en-1-ones:

In a 50 ml. round bottom flask, a solution of aryl furfuryl alcohol (0.5 gm, 1.89 mmol) and $ZnCl_2$ (0.257 gm, 1.89 mmol) in acetone (14.2 ml) and water (0.5 ml) was heated at 60-65^{0}C for 24 h at which time TLC analysis indicated the complete disappearance of starting material. The mixture was brought to room temperature, acidified to pH 1 with dilute HCl and extracted with ethyl acetate. Organic layer was washed with water, followed by brine and dried over sodium sulphate. The organic layer was concentrated under reduced pressure using rotary evaporator and chromatographed on silica gel column to collect the 4-hydroxy-5-aryl substituted-cyclopent-2-en-1-ones.

1) 4-Hydroxy-5-phenyl-cyclopent-2-en-1-one: IR (υ_{max}, $CHCl_3$): 1602, 1714, 3400 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.78 (bs, 1H), 3.43 (d, *J* = 2 Hz, 1H), 4.96 (s, 1H), 6.32 (d, *J* = 4 Hz, 1H), 7.09-7.16 (m, 2H), 7.25-7.50 (m, 3H), 7.61 (bd, *J* = 4 Hz, 1H); **Mass** (m/e): 174 (M^+).

2) 4-Hydroxy-5-(4-methoxyphenyl)-cyclopent-2-en-1-one: IR (υ_{max}, $CHCl_3$): 1334, 1710, 3016, 3418 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.23 (s, 1H), 3.72 (s, 3H), 4.70 (s, 1H), 6.13 (d, *J* = 6 Hz, 1H), 6.79 (d, *J* = 6 Hz, 2H), 6.91 (d, *J* = 6 Hz, 2H), 7.44 (d, *J* = 6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 55.02, 60.86, 78.43, 114.16 (2C), 129.00, 129.09 (2C), 133.46, 158.64, 162.50, 206.17; **Mass** (m/e): 204 (M^+).

3) 4-Hydroxy-5-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one: IR (υ_{max}, $CHCl_3$): 1591, 1710, 3017, 3442 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 3.25 (d, *J* = 2 Hz, 1H), 3.71 (s, 9H), 3.80 (d, *J* = 6 Hz, 1H), 4.85 (s, 1H), 6.19 (s, 2H), 7.54 (dd, *J* = 6 Hz and 2 Hz, 1H); **^{13}C NMR** ($CDCl_3$+CCl_4): δ 55.84 (2C), 60.36, 61.86, 78.37, 105.53 (2C), 132.40, 133.54, 137.11, 153.10 (2C), 162.03, 204.93; **Mass** (m/e): 264 (M^+).

4) 5-(3-Chlorophenyl)-4-hydroxy-cyclopent-2-en-1-one: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 3.39 (d, *J* = 2 Hz, 1H), 4.89 (s, 1H), 6.29 (d, *J* = 6 Hz, 1H), 6.97 (t, *J* = 6 Hz, 1H), 7.10 (s, 1H), 7.26 (d, *J* = 6 Hz, 2H), 7.60 (dd, *J* = 6 Hz and 2 Hz, 1H). **Mass** (m/e): 208 (M^+).

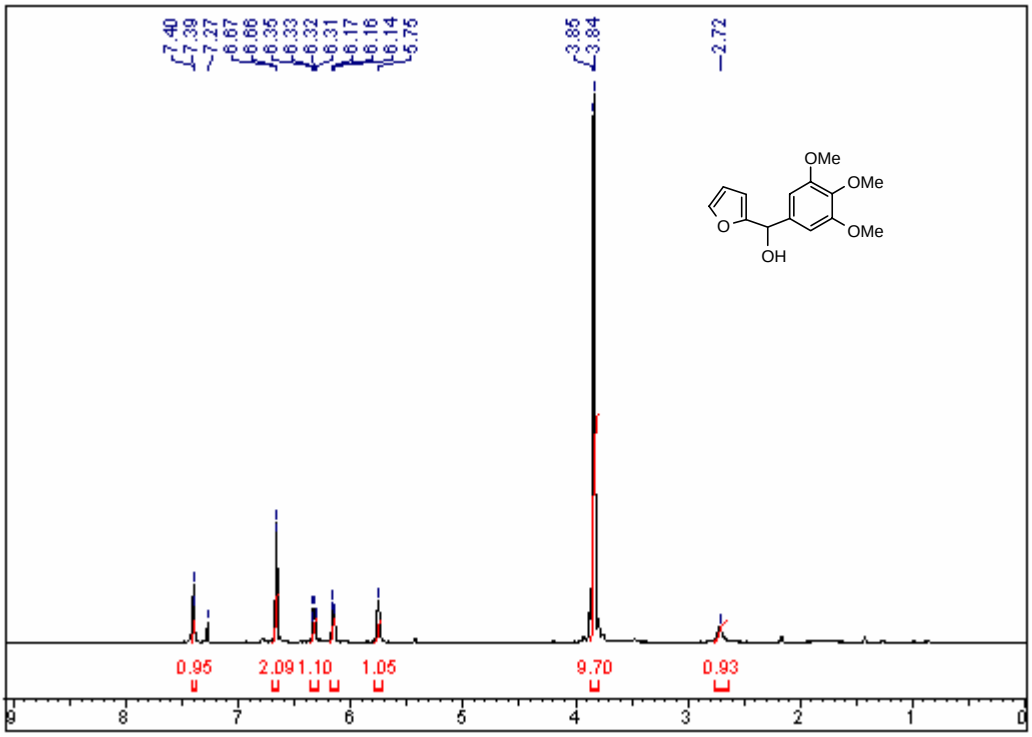
5) 5-(2,3-Dichlorophenyl))-4-hydroxy-cyclopent-2-en-1-one: No reaction

6) 4-Hydroxy-5-(3-nitrophenyl)-cyclopent-2-en-1-one: ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4):δ 3.60 (bs, 1H), 5.04 (s, 1H), 6.37 (d, *J* = 4 Hz, 1H), 7.44-7.90 (m, 3H), 8.00-8.48 (m, 2H); **Mass** (m/e): 219 (M^+).

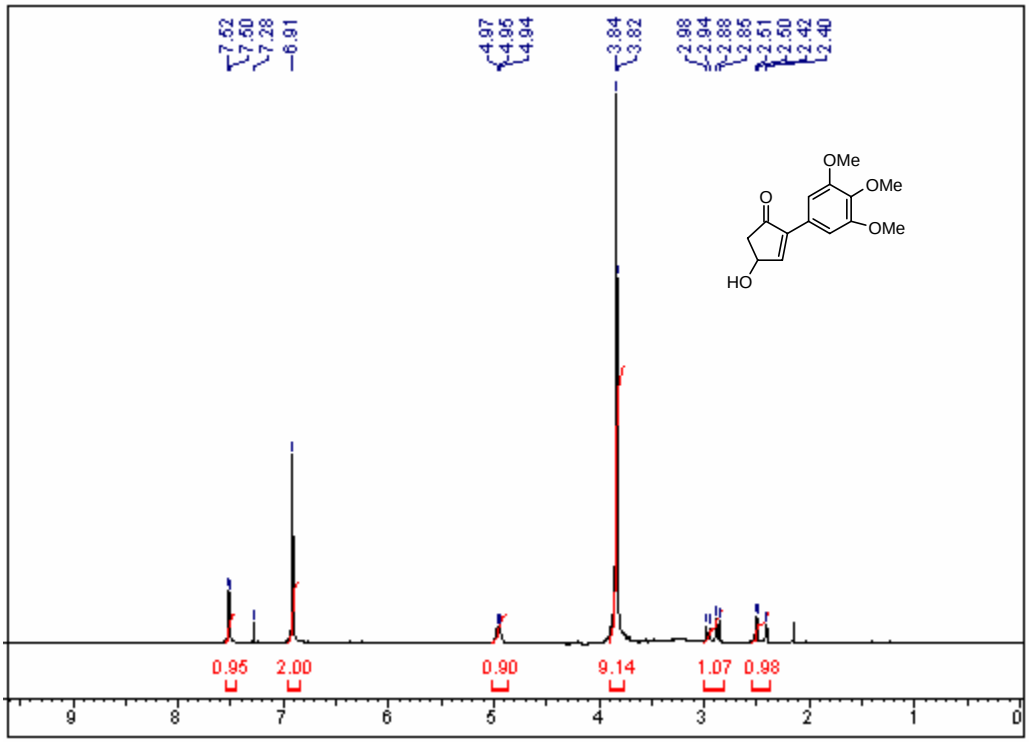
7) 4-Hydroxy-5-(4-methylsulfanylphenyl)-cyclopent-2-en-1-one:

IR (υ_{max}, $CHCl_3$): 1706, 3018, 3441 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + CCl_4): δ 2.55 (s, 3H), 3.30 (bs, 1H), 3.39 (d, *J* = 2 Hz, 1H), 4.90 (s, 1H), 6.32 (d, *J* = 6 Hz, 1H), 7.07 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.61 (dd, *J* = 6 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + CCl_4): δ 14.01, 59.77, 62.34, 124.91 (2C), 126.96, 128.25 (2C), 135.12, 161.22, 164.57, 205.96; **Mass** (m/e): 220 (M^+); Anal. Calcd. For $C_{12}H_{12}O_2S$: C 65.43; H 5.49; S 14.56 %.
Found: C 65.50; H 5.59; S 14.70 %.

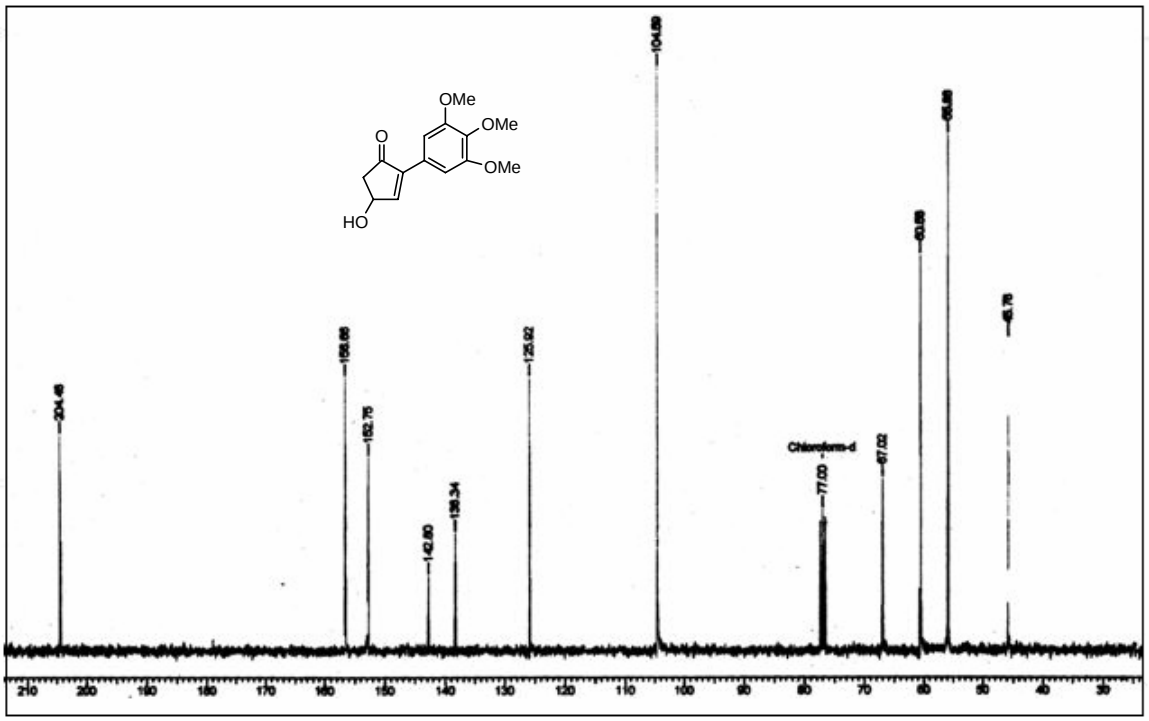
^{1}H NMR spectrum of the furan-2-yl-(3,4,5-trimethoxyphenyl)-methanol:

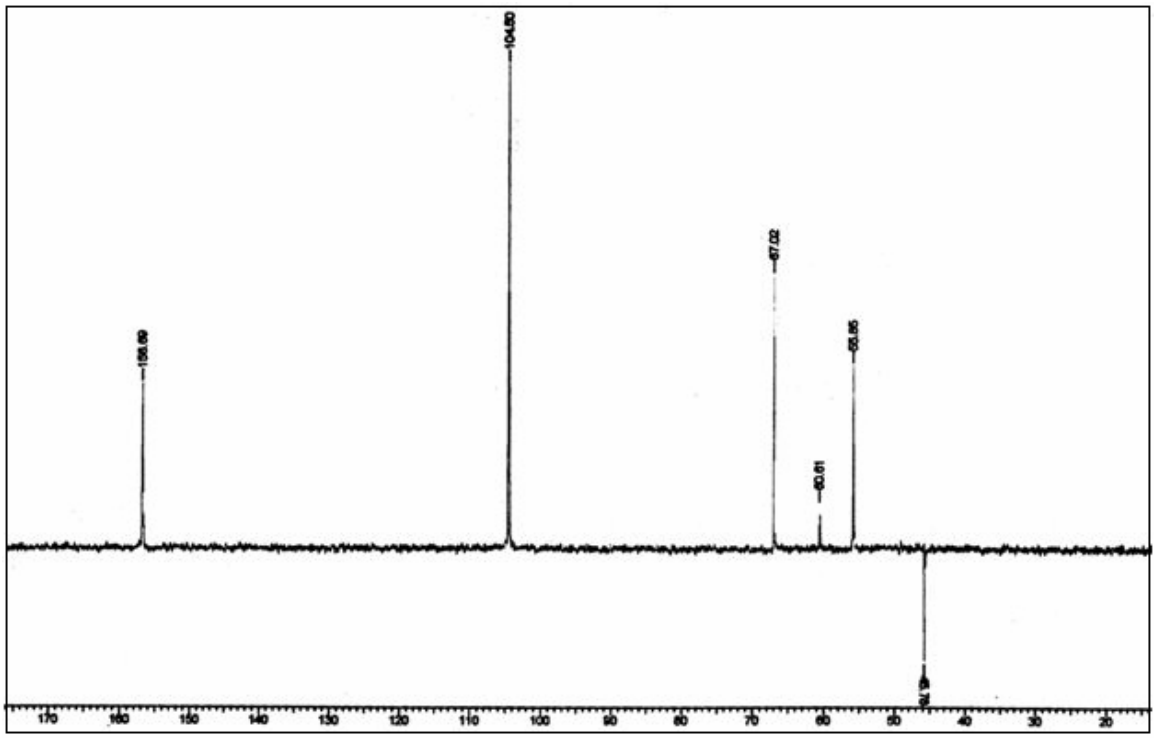


^{1}H NMR spectrum of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:

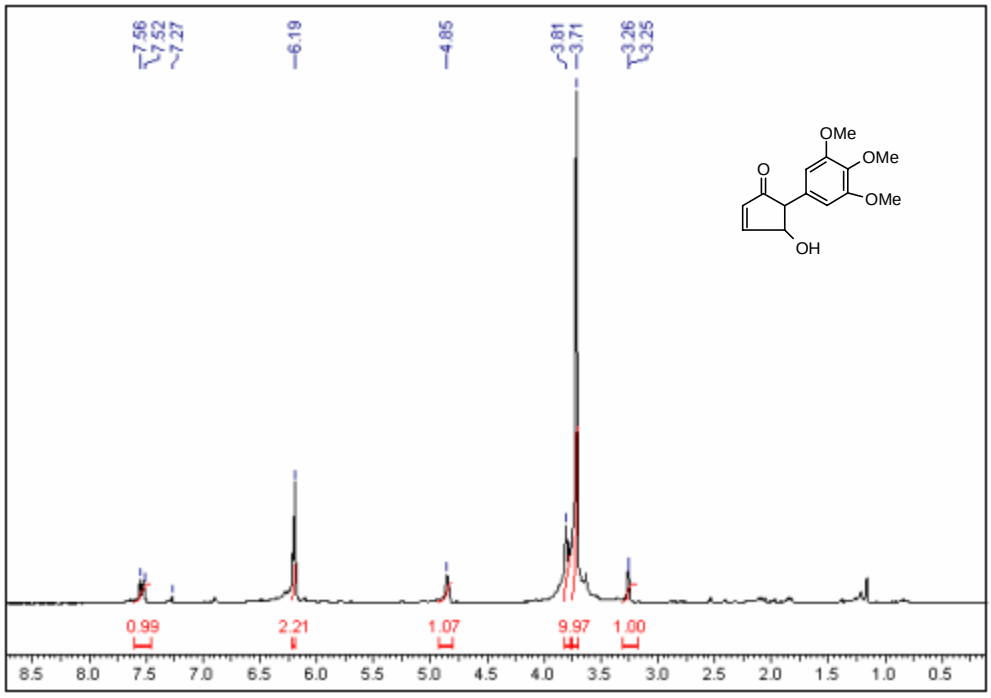


^{13}C NMR spectra of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:

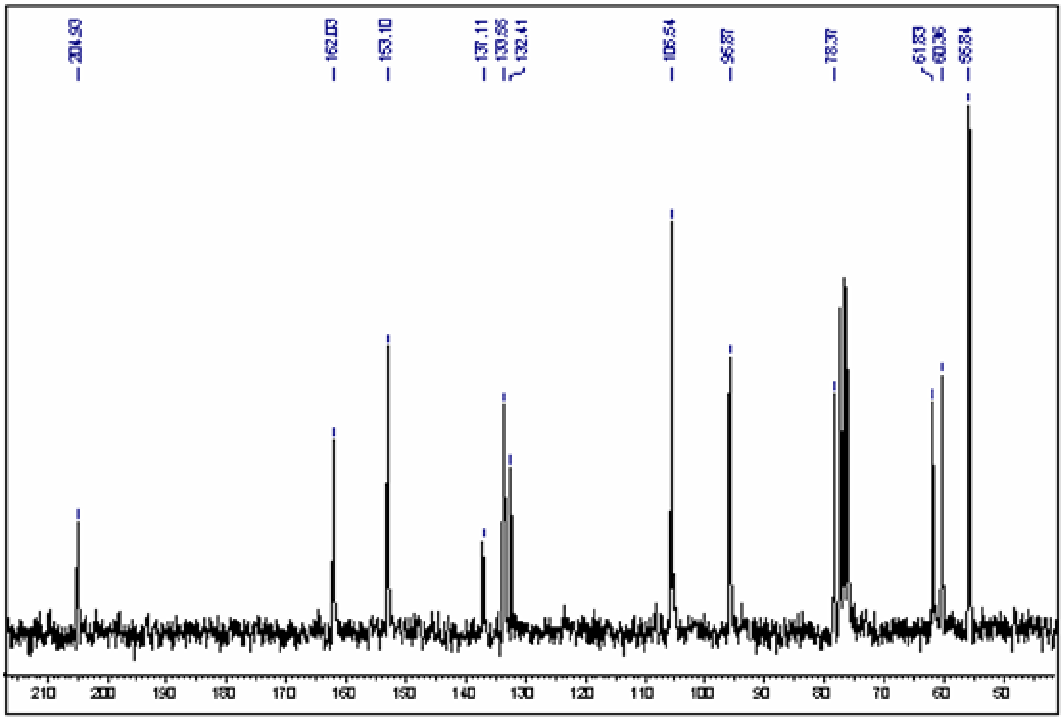




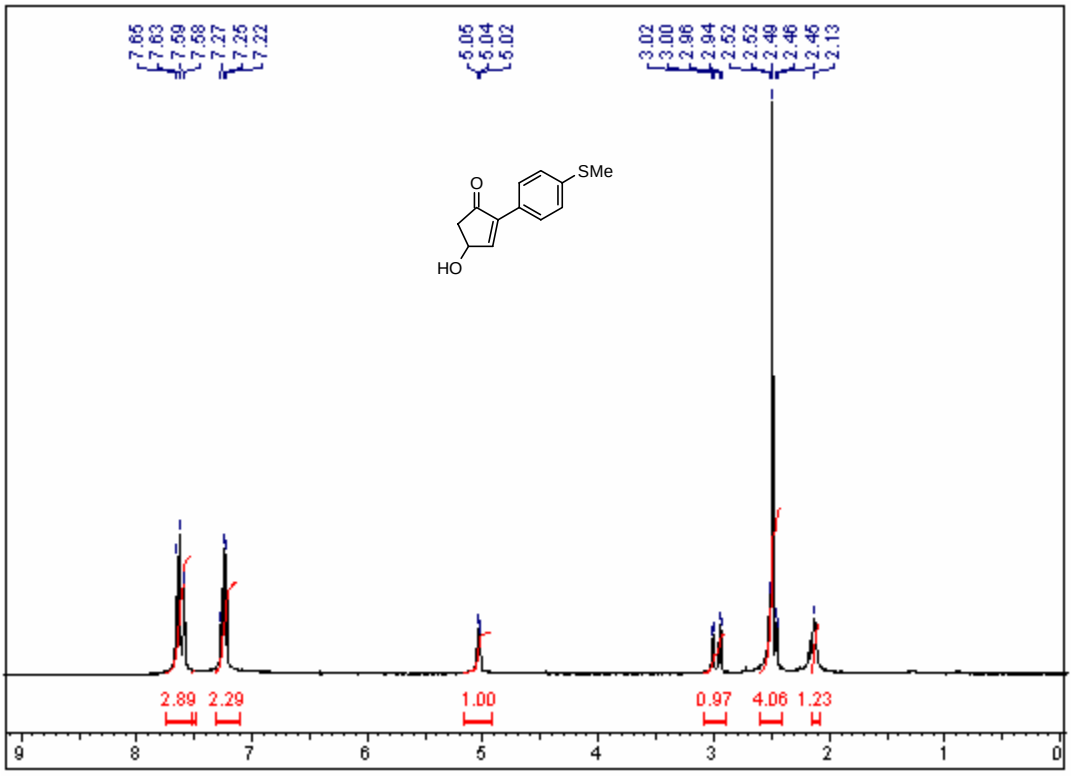
^{1}H NMR spectrum of 4-hydroxy-5-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:



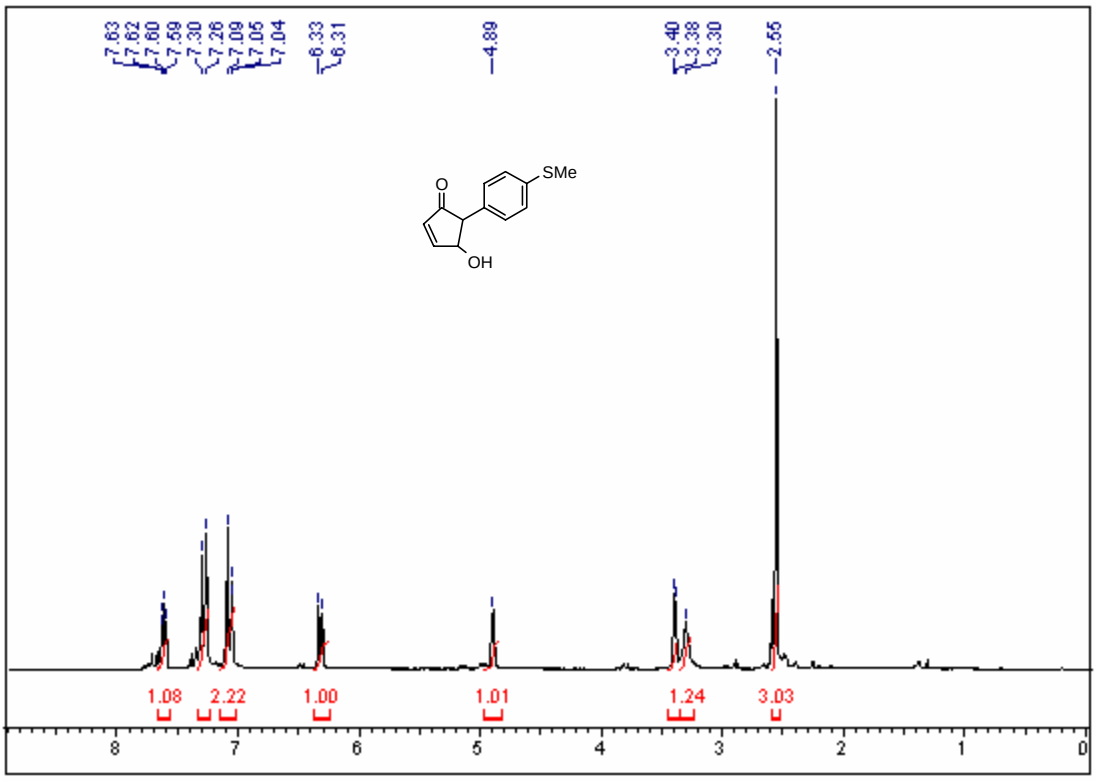
^{13}C NMR spectrum of 4-hydroxy-5-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one:



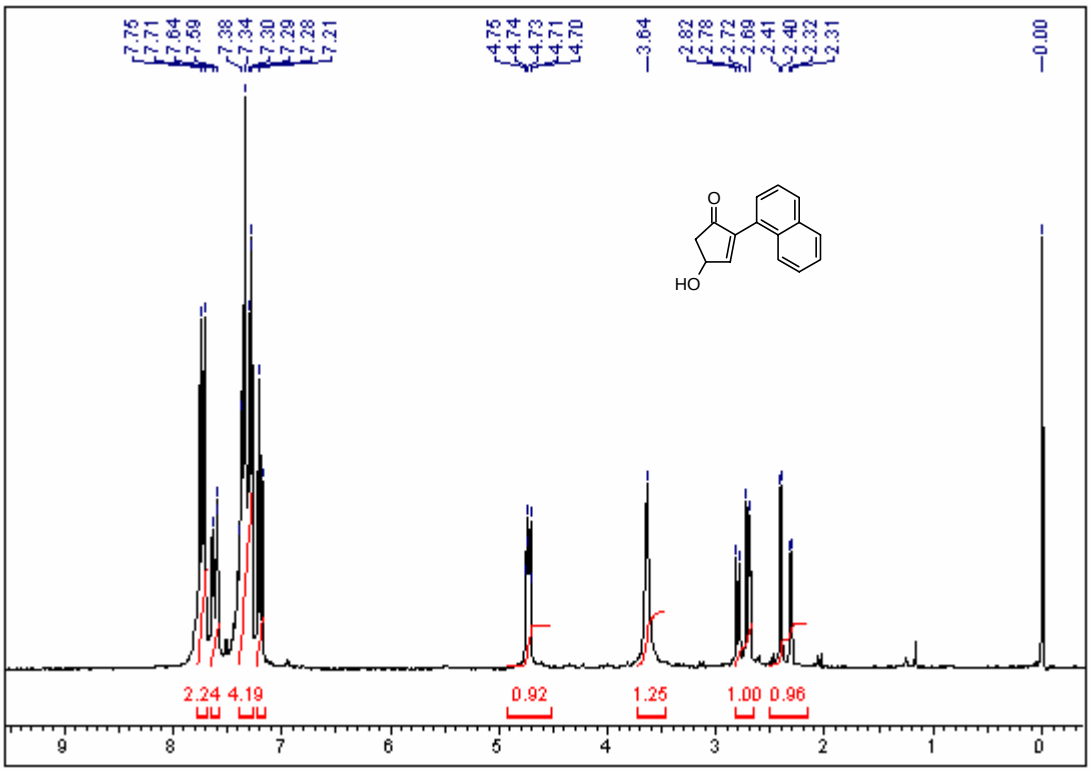
^{1}H NMR spectrum of 4-hydroxy-2-(4-methylsulfanylphenyl)-cyclopent-2-en-1-one:



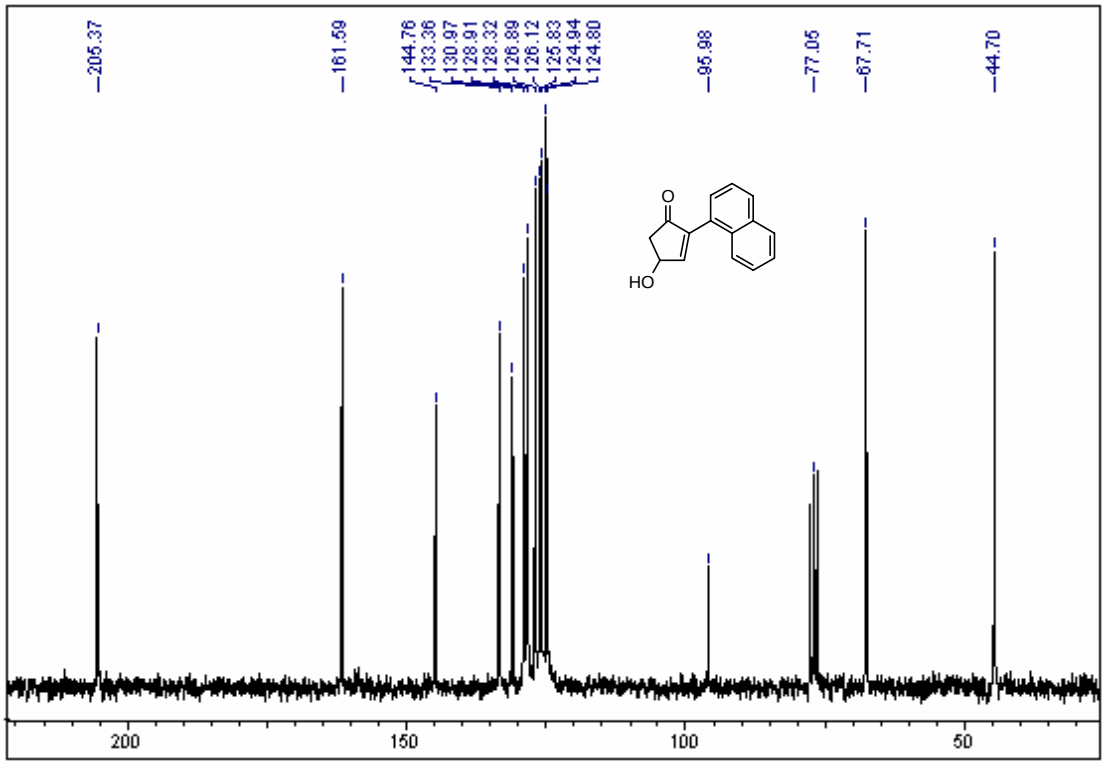
^{1}H NMR spectrum of 4-hydroxy-5-(4-methylsulfanylphenyl)-cyclopent-2-en-1-one:

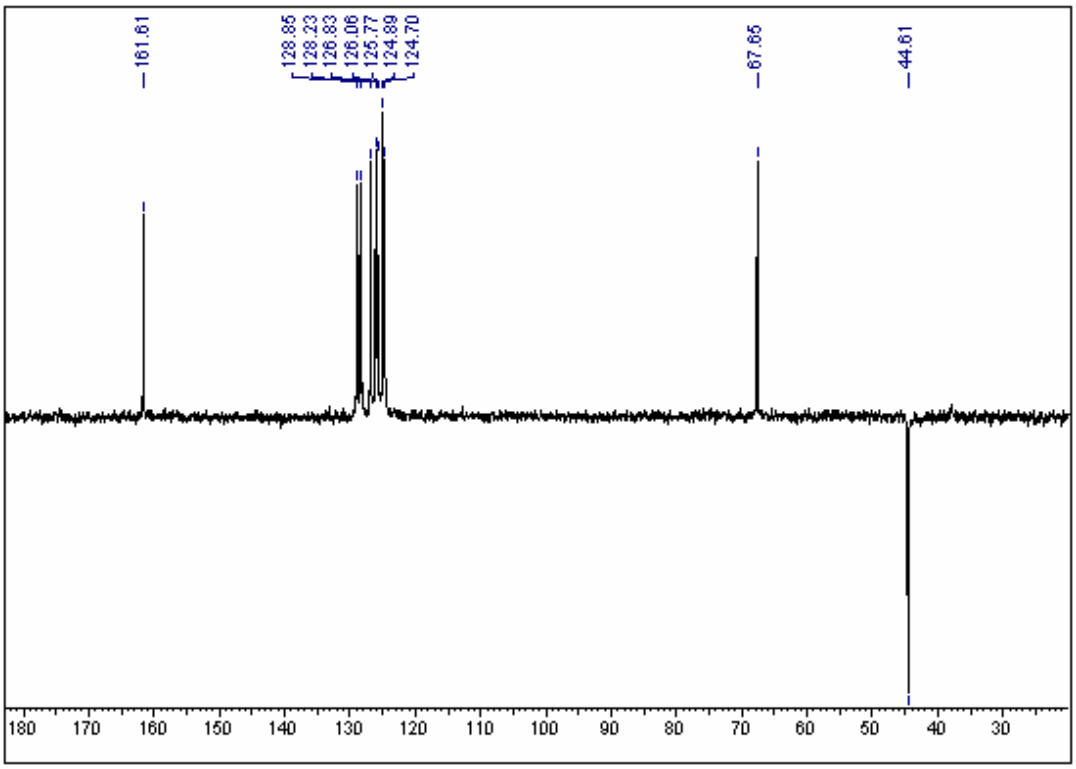


^{1}H NMR spectrum of 4-hydroxy-2-naphthalen-1-yl-cyclopent-2-en-1-one:



^{13}C NMR spectrum of 4-hydroxy-2-naphthalen-1-yl-cyclopent-2-en-1-one:





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CHAPTER 2

SECTION II:

Thioacetalization of the Carbonyl Function, Transthioacetalization of Acetals, Ketals, Oximes and Hydrazones Catalysed by Halo Acids in Aqueous Medium

2.2.1 INTRODUCTION:

Functional group protection and deprotection strategies are quite often necessary in the synthesis of multifunctional organic molecules[1]. The protection of carbonyl group as thioacetal is often a necessary step in the synthesis of complex organic molecules due to inbuilt stability of thioacetals for acidic or basic conditions. Thioacetals are also useful in organic synthesis as acyl carbanion equivalent in C-C bond forming reactions[2-6]. Preparation of thioacetals generally involves reaction of carbonyl compounds with thiols in presence of protic or Lewis acids in various dry organic solvents like dichloromethane, chloroform, benzene, n-hexane etc many of which are environmentally hazardous. The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in organic synthesis have posed a serious threat to the environment. Currently, due to the environmental concerns, industries are interested in moving away from toxic or environmentally damaging solvents. Thus the design of solvent-free reactions and use of alternative green solvents like water, supercritical fluids and ionic liquids have received a lot of attention in recent years.

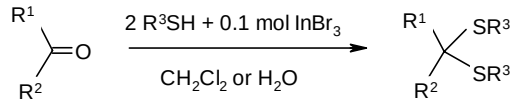
Recently, water[7] is reported to be used as solvent in organic transformations like pericyclic reaction, cross aldol and Reformatsky type reaction etc. as water is cheap and non-toxic. Water promoted reactions lead to improvements in terms of yield and selectivity. Water can facilitate ligand exhange in transition-metal catalyzed reactions and water-soluble catalyst can be reused after filtration, decantation or extraction of the water insoluble products.

There are various methods reported in the literature for the thioacetalization of carbonyl compounds[8-21]. Also the transthioacetalization of acetals, ketals, oximes and hydrazones is important process in organic synthesis as it leads to a novel and direct method for thioacetal preparation.

Some of the recent methods for the thioacetalization and transthioacetalization are discussed below.

A BRIEF REVIEW OF LITERATURE:

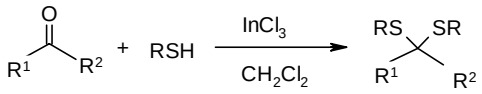
Peppe *et al.*[22] reported protection of aldehydes as dithioacetal with indium tribromide in non-aqueous and aqueous medium. The reaction is general for aliphatic and aromatic carbonyl compounds. The method is chemoselective for aldehydes in non-aqueous media for acyclic dithioacetals (scheme 1).



Scheme 1

Indium(III)chloride catalyzed thioacetalization of carbonyl compounds has been reported by Muthusamy *et al.*[23]. This method is effective for aldehydes as well as ketones.

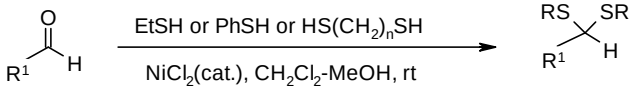
Yadav and coworkers[24] reported the indium(III) chloride (scheme 2) as efficient catalyst for the protection of carbonyl compounds as thioacetals. The method is effective for aliphatic or aromatic aldehydes as well as ketones.



Scheme 2

Perni[25] reported Amberlyst-15 as efficient catalyst for the thioacetalization of aldehydes at room temperature while ketones also can be protected at elevated temperature.

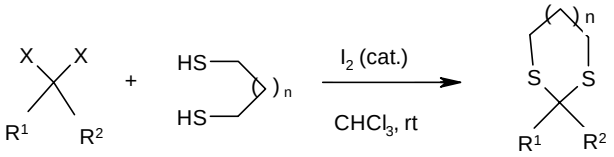
Khan *et al.* [26] reported nickel (II)chloride as catalyst for thioacetalization of aldehydes in presence of ketone (scheme 3).



Scheme 3

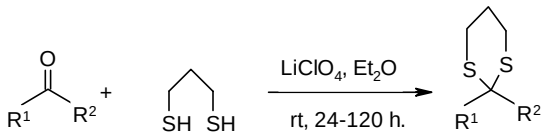
Indium triflate as catalyst for thioacetalization of aldehydes and ketones and transthioacetalization of oxyacetals has been reported by Muthusamy *et al.*[27].

Firouzabadi *et al.*[28] achieved thioacetalization of carbonyl function and transthioacetalization of O, O- and S, O- acetals with iodine (Scheme 4). This method is chemoselective and requires catalytic amount of iodine.



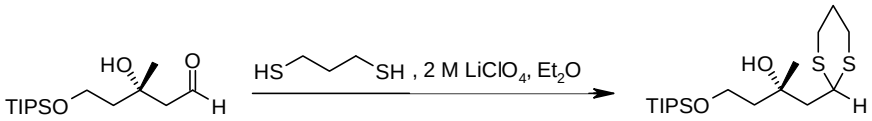
Scheme 4

Sankararaman and Saraswathy[29] reported chemoselective protection of aldehydes as dithiolanes using lithium perchlorate-diethyl ether medium at ambient temperature in high yields (scheme 5). This method works satisfactorily for aromatic as well as aliphatic aldehydes.



Scheme 5

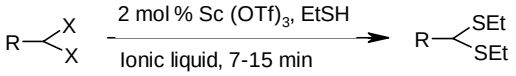
By using this method, Tietze L. F.[30] protected the sensitive hydroxyaldehyde into the corresponding dithiane by using 2M solution of lithium perchlorate in anhydrous diethyl ether (Scheme 6).



Scheme 6

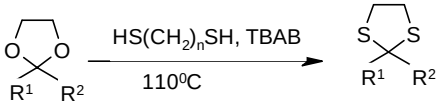
Natural kaolinitic clay for the efficient transthioacetalization of acetals, ketals, oximes and tosylhydrazones has been reported by Sudalai *et al.*[31]. This method has advantage that the catalyst is removed by filtration and can be reused.

Kamal and Chouhan[32] reported the immobilized scandium(III)triflate in ionic liquids for the thioacetalization and transthioacetalization of various aromatic, aliphatic aldehydes and ketones (scheme 7). This method has advantage that the catalyst can be reused three times without any change in catalytic activity.



Scheme 7

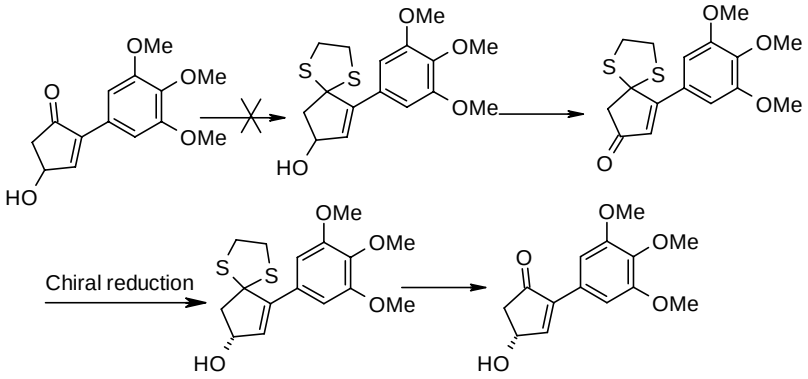
Ranu *et al.*[33] achieved solvent free efficient transthioacetalization of acetals by molten tetrabutylammonium bromide, a cheap ionic salt (scheme 8). Various acetals derived from aliphatic, aromatic and conjugated aldehydes undergo transthioacetalization with variety of aliphatic and aromatic thiols.



Scheme 8

2.2.2 PRESENT WORK:

During the synthesis of *cis*-restricted combretastatin analogues, we wanted to protect the carbonyl function of 4-hydroxy-2-(3,4,5-trimethoxyphenyl)-cyclopent-2-en-1-one as dithiolane as shown in scheme 9. We tried various reagents like $BF_3.OEt_2$, iodine in chloroform etc. which resulted in the formation of complex mixture. Zinc triflate is known as a mild reagent for protection of α, -β-unsaturated ketones and also it prevents β-elimination, but in our case it did not work. To overcome this problem we tried the various conditions for thioacetalization.

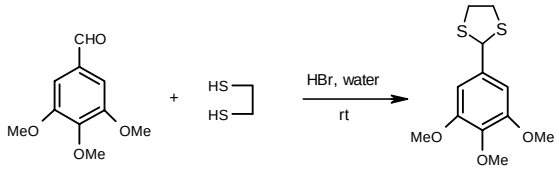


Scheme 9

From the literature survey it was revealed that the use of aqueous medium for the thioacetalization or transthioacetalization is not much explored. So we developed this methodology for thioacetalization of carbonyl compounds and transthioacetalization of acetals, ketals, oximes and hydrazones.

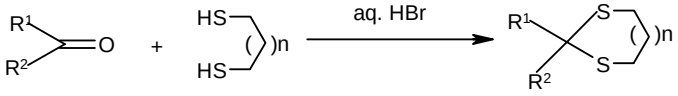
Part I) Thioacetalization of aldehydes and ketones in the presence of aqueous hydrobromic acid:

Initially we tried the commercially available aqueous hydrobromic acid in water for the protection of carbonyl function of 3,4,5-trimethoxybenzaldehyde with ethanedithiol and found that corresponding thioacetal was obtained within 15 minutes in 94 % isolated yield (scheme 10).



Scheme 10

Generality of this transformation was confirmed by reacting various carbonyl compounds with dithiols under similar conditions. Table 1 shows the results of thioacetalization of various carbonyl compounds including variably substituted aldehydes.



Scheme 11

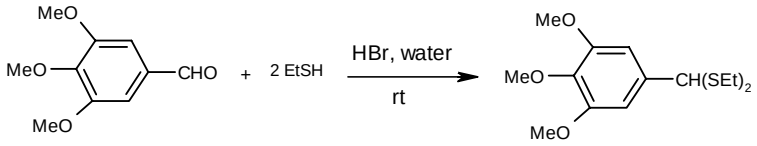
Table1. Thioacetalization of aldehydes and ketones in the presence of aqueous hydrobromic acid

Entry No.	Substrate	n	Time in minutes	Yield[a] %
1	3,4,5-Trimethoxybenzaldehyde	0	15	94
2	3,4,5-Trimethoxybenzaldehyde	1	15	92
3	n-Butyraldehyde	0	60	85
4	3-Nitrobenzaldehyde	0	60	94
5	2,3-Dichlorobenzaldehyde	0	90	92
6	3-Nitrobenzaldehyde	1	60	90
7	4-Methoxybenzaldehyde	0	20	93
8	Benzaldehyde	0	15	96
9	2-Furaldehyde	0	15	92
10	1-Naphthaldehyde	0	60	81
11	Cinnamaldehyde	0	60	89
12	Syringaldehyde	0	120	74
13	Ethyl levulinate	0	60	94
14	Cyclohexanone	0	90	90
15	Chomone-3-carboxaldehyde	0	60	87

a: The figures indicate yield of product after isolation and the products were characterized by spectroscopic methods *viz*. IR, ^{1}H NMR, ^{13}C NMR.

Various substituted aldehydes under these conditions were converted into corresponding dithiolanes (entries **1, 4, 5, 7, 8, 9, 10, 11, 12** and **15**; Table 1) and dithianes (entries **2** and **6)** in excellent yields. Aliphatic aldehyde (entry **3**) was also smoothly converted into corresponding dithiolane in excellent yield. Ketones were also smoothly and cleanly converted to dithiolanes (entries **13** and **14**).

Similarly 3,4,5-trimethoxybenzaldehyde when treated with ethanethiol under similar conditions resulted into the corresponding thioacetal in high yield (scheme 12).

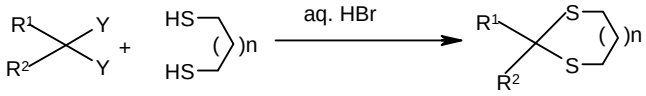


Scheme 12

In view to examine the utility of other halo acids in thioacetalization, 3,4,5-trimethoxybenzaldehyde was reacted with ethanedithiol in presence of 0.2 mole equivalents of commercially available aqueous hydrochloric acid, hydrofluoric acid or hydriodic acid under identical conditions and it was observed that the corresponding thioacetal was obtained in comparable yields.

Part II) Transthioacetalization of oximes, hydrazones and ketals:

Due to the stability of thioacetals, they have been of great interest to organic chemists and there are a number of reports of transthioacetalization of acetals, ketals or O, S-acetals, oximes and hydrazones. The results obtained in case of thioacetalization prompted us to study the scope of the utility of halo acids for transthioacetalization. Accordingly, acetals, ketals, oximes and hydrazones were reacted with dithiols in presence of aqueous hydrobromic acid (scheme 13) and it was found that the thioacetals were obtained in high isolated yields.



Scheme 13

Transthioacetalization of acetals and ketals (entries **14, 15** and **16**; Table 2) was achieved at room temperature while oximes (entries **1-5**; Table 2) and hydrazones (entries **6-13**; Table 2) required refluxing temperature and somewhat longer reaction time. It is evident from the Table 2 that the transthioacetalization using aqueous hydrobromic acid can be achieved successfully in case of oximes and hydrazones irrespective of electronic nature of functional groups.

Table 2. Transthioacetalization of oximes, hydrazones and ketals

Entry No.	Substrate	Y, Y	n	Time in hours	Yield[a]
1	3,4,5-Trimethoxybenzaldehyde	=N-OH	0	2	92
2	2,3-Dichlorobenzaldehyde	=N-OH	0	2	88
3	Cyclohexanone	=N-OH	0	4	90
4	3-Nitrobenzaldehyde	=N-OH	0	2	90
5	3-Nitrobenzaldehyde	=N-OH	1	6	86
6	2-Nitrobenzaldehyde	=NNHPh	0	6	90
7	3-Nitrobenzaldehyde	=NNHPh	0	4	92
8	4-Methoxybenzaldehyde	=NNHPh	0	4	76
9	2-Furaldehyde	=NNHPh	0	2	94
10	4-Hydroxyacetophenone	=NNHPh	0	2	90
11	2,3-Dichlorobenzaldehyde	=NNHPh	0	8	84
12	3,4,5-Trimethoxybenzaldehyde	=NNHPh	0	2	94
13	n-Butyraldehyde	=NNHPh	0	0.25	94
14	2-Acetylfuran	$-OCH_2CH_2O-$	0	1	89
15	3,4, 5-Trimethoxybenzaldehyde	$-OCH_2CH_2O-$	0	0.25	94
16	Cyclohexanone	$-OCH_2CH_2O-$	0	2	83

a: The figures indicate yield of product after isolation and the products were characterized by spectroscopic methods *viz*. IR, ^{1}H NMR, ^{13}C NMR

2.2.3 CONCLUSION:

An efficient, mild and environmentally preferred method for the thioacetalization of carbonyl function and transthioacetalization of acetals, ketals, oximes and hydrazones was developed by using catalytic amount of halo acids in water as the medium. The advantages of this protocol are that it doesn't need dry/inert conditions and easily available aqueous halo acids are used as reagent. The generality of the protocol was confirmed by conducting the transformation on various substrates described in this section.

2.2.4 EXPERIMENTAL:

General experimental procedure for thioacetalization and transthioacetalization:

The oximes, phenylhydrazones and O, O-acetals of carbonyl compounds were prepared by reported procedures[40].

To the appropriate starting compound (1 mmol) and dithiol (1.2 mmol) or thiol (2.1 mmol) in water (5 ml) was added commercially available halo acid (0.2 mmol). The reaction mixture was stirred at appropriate temperature and monitored by thin layer chomatography until starting material disappeared (Tables 1 and 2). The reaction mixture was then extracted with chloroform (2 x 15 ml) and combined organic layer was washed with 10 % sodium hydroxide solution (10 ml) followed by water (10 ml) and brine (5 ml). Concentration of organic layer under reduced pressure and purification of residue by passing though silica gel column furnished pure products which were characterized by spectroscopic methods and comparison with data reported in the literature.

1) 2-(3,4,5-Trimethoxyphenyl)-[1,3] dithiolane:

Pale yellow solid; m. p. 53-54^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.22-3.47 (m, 4H), 3.77 (s, 3H), 3.81 (s, 6H), 5.53 (s, 1H), 6.72 (s, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 39.81 (2C), 55.80 (2C), 56.61, 60.40, 104.87 (2C), 134.98, 137.59, 152.81 (2C); **Mass** (m/e): 272 (M^+).

2) 2-(3,4,5-Trimethoxyphenyl)-[1,3] dithiane[31]:

White solid; m. p. 85-86^{0}C; **IR** (υ $_{max,}$ $CHCl_3$): 760 and 1600 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.75-2.30 (m, 2H), 2.80-3.15 (m, 4H), 3.81 (m, 3H), 3.86 (s, 6H), 5.06 (s, 1H), 6.67 (s, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$): δ 25.04, 32.20 (2C), 51.87, 56.10 (2C), 60.77, 104.73 (2C), 134.80, 137.81, 153.29 (2C); **Mass** (m/e): 286 (M^+).

3) 2-Propyl-1,3-dithiolane:

Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.93 (t, *J* = 7 Hz, 3H), 1.35-1.55 (m, 2H), 1.70-1.90 (m, 2H), 3.00-3.45 (m, 4H), 4.46 (t, *J* = 7 Hz, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 13.45, 22.19, 38.00 (2C), 41.20, 53.14; **Mass** (m/e): 147 (M^+).

4) 2-(3-Nitrophenyl)-1,3-dithiolane:

Pale yellow solid; m. p. 62^{0}C; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1215, 1352, 1532 and 3020 cm$^{-1;}$ **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.30-3.60 (m, 4H), 5.63 (s, 1H), 7.47 (t, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 8.09 (dd, *J* = 8 Hz and 2 Hz, 1H), 8.37 (s, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 40.18 (2C), 54.66, 122.70 (2C), 129.06, 133.80, 143.25, 147.95; **Mass** (m/e): 227 (M^+).

5) 2-(2,3-Dichlorophenyl)-1,3-dithiolane:

White solid; m. p. 58-59^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.35-3.45 (m, 4H), 6.07 (s, 1H), 7.21 (t, *J* = 8 Hz, 1H), 7.38 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.78 (dd, *J* = 8 Hz and 2Hz, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 38.00 (2C), 54.03, 127.90, 128.56, 128.90, 134.50, 134.89, 141.00; **Mass** (m/e): 250 (M^+).

6) 2-(3-Nitrophenyl)-1,3-dithiane:

Yellowish solid; m. p. 110-111^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.75-2.05 (m, 1H), 2.10-2.25 (m, 1H), 2.80-3.15 (m, 4H), 5.20 (s, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 8.13 (d, *J* = 8 Hz, 1H), 8.31 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 24.90, 31.85 (2C), 50.30, 123.23, 123.45, 129.85, 134.18, 141.39. 148.52; **Mass** (m/e): 241 (M^+).

7) 2-(4-Methoxyphenyl)-1,3-dithiolane:

White solid; m. p. 60^{0}C (lit[29] 59-60^{0}C); **IR** ($\upsilon_{max,}$ $CHCl_3$): 1050, 1250, 1500, 1600, 2895 and 2925 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.25-3.55(m, 4H), 3.79 (s, 3H), 5.65 (s, 1H), 6.85 (d, *J* = 10 Hz, 2H), 7.47 (d, *J* = 10 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 39.96 (2C), 55.03, 55.91, 113.62 (2C), 128.99 (2C), 131.56, 159.20; **Mass** (m/e): 212 (M^+).

8) 2-Phenyl-1,3-dithiolane[24, 29]:

Colorless thick oil; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.19-3.50 (m, 4H), 5.59 (s, 1H), 3.81 (s, 6H), 7.18-7.32 (m, 3H), 7.45-7.55 (m, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 40.49 (2C), 56.59, 128.27 (4C), 128.71, 140.62; **Mass** (m/e): 182 (M^+).

9) 2-(1,3-Dithiolan-2-yl)-furan[35, 36]: Thick oil; **IR** ($\upsilon_{max,}$ neat): 1149, 1498, 1650 and 2900 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.25-3.50 (m, 4H), 5.61 (s, 1H), 6.28 (d, *J* = 2 Hz, 2H), 7.36 (dd, *J* = 6 Hz and 2 Hz, 1H), 8.24 (d, *J* = 6 Hz, 1H), 8.32 (s, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 39.28 (2C), 47.66, 107.20, 110.55, 142.68, 154.55; **Mass** (m/e): 172 (M^+).

10) 2-Napthalen-1-yl-1,3-dithiolane[21]:

Thick colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.30-3.60 (m, 4H), 6.54 (s, 1H), 7.42-7.70 (m, 3H), 7.75-7.90 (m, 2H), 8.08 (d, *J* = 8 Hz, 1H), 8.22 (d, *J* = 8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 39.46 (2C), 52.73, 123.19, 124.66, 125.22, 125.62, 126.17, 128.71, 130.99, 133.71, 135.54; **Mass** (m/e): 232 (M^+).

11) 2-Styryl-1,3-dithiolane:

Pale yellow solid; m. p. 56-58^{0}C (lit.[29] 58-59^{0}C); **IR** (υ $_{max,}$ $CHCl_3$): 760 and 2560 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.20-3.50 (m, 4H), 5.24 (d, *J* = 8 Hz,1H), 6.24 (dd, *J* = 16 Hz and 8 Hz, 1H), 6.51 (d, *J* = 14 Hz, 1H), 7.25-7.55 (m, 5H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 39.86 (2C), 54.75, 126.91 (2C), 128.05, 128.78 (2C), 129.41, 130.33, 136.32; **Mass** (m/e): 208 (M^+).

12) 4-(1,3-Dithiolan-2-yl)-2, 6-dimethoxylphenol:

White solid; m. p. 65^0 C; **IR** (υ $_{max,}$ $CHCl_3$): 1215, 1515, 1615 and 3533 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.21-3.49 (m, 4H), 3.82 (s, 6H), 5.54 (s, 1H), 6.73 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 40.23 (2C), 56.41 (2C), 57.29, 104.96 (2C), 130.40, 134.77, 146.94 (2C); **Mass** (m/e): 257 (M^+).

13) Ethyl 3-(2-methyl-1,3-dithiolan-2-yl)-propionate:

Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.20 (t, *J* = 8 Hz, 3H), 1.72 (s, 3H), 2.12-2.25 (m, 2H), 2.45-2.60 (m, 2H), 3.27 (s, 4H), 4.07 (q, *J* = 8 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 13. 85, 31.60, 32.38, 39.32, 39.84 (2C), 59.87, 65.53, 172.50;
Mass (m/e): 119 (M^+).

14) 1, 4-Dithia-spiro-4,5-decane[37, 38]:

Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.30-1.50 (m, 2H), 1.55-1.75 (m, 4H), 1.90-2.08 (m, 4H), 3.27 (s, 4H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 24.84, 25.94 (2C), 38.15 (2C), 42.67 (2C), 68.51; **Mass** (m/e): 174 (M^+).

15) 3-(1,3-Dithiolan-2-yl)-chromen-4-one:

White solid; m. p. 113-114^{0}C; **IR** (υ $_{max,}$ $CHCl_3$): 1216, 1644, 2400 and 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.32 (s, 4H), 5.79 (s, 1H), 7.35-7.50 (m, 2H), 7.67 (m, 1H), 8.24 (d, *J* =

6Hz, 1H), 8.32 (s, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 38.95 (2C), 46.44, 118.20, 123.60, 125.33, 125.90, 126.13, 133.85, 153.85, 156.35, 176.46; **Mass** (m/e): 249 (M^+); Anal. Calcd. For $C_{12}H_{10}O_2S_2$: C 57.61; H 4.12; S 25.68 %. Found C 57.57; H 4.03; S 25.62 %.

16) 2-(2-Methyl-1,3-dithiolan-2-yl)-furan:

Colorless liquid; **IR** (υ $_{max,}$ $CHCl_3$): 1498, 1645 and 2920 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.13 (s, 3H), 3.45 (s, 4H), 6.24-6.35 (m, 2H), 7.37 (d, *J* = 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 29.41, 40.22 (2C), 60.91, 105.90, 109.87, 141.96 (2C); **Mass** (m/e): 186 (M^+).

17) 4-(2-Methyl-1,3-dithiolan-2-yl)-phenol:

White solid; m. p. 82-84^{0}C; **IR** (υ $_{max,}$ $CHCl_3$): 1216, 1508, 1608 and 3368 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.13 (s, 3H), 3.30-3.60 (m, 4H), 5.22 (s, 1H), 6.75 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 33.71, 40.07 (2C), 68.12, 114.54 (2C), 128.10 (2C), 137.55, 154.35; **Mass** (m/e): 212 (M^+).

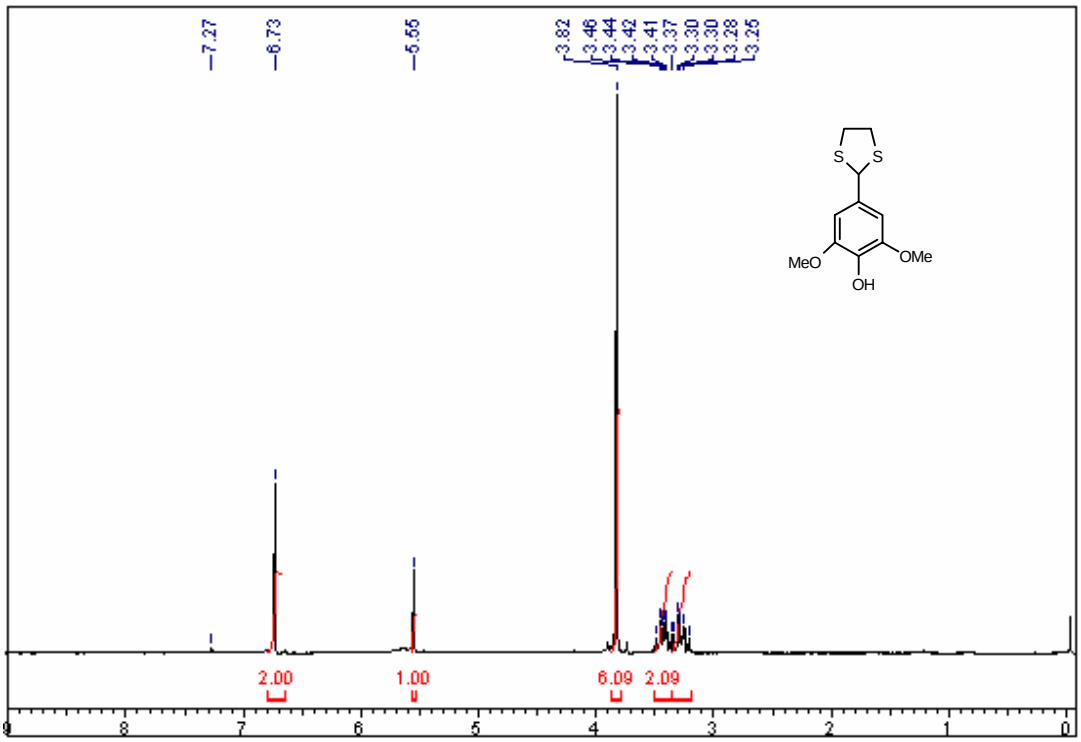
18) 2-(2-Nitrophenyl)-1,3-dithiolane[39]:

Yellow solid; m. p. 61-62^{0}C; **IR** (υ $_{max,}$ $CHCl_3$): 760, 1210 and 2120 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.25-3.60 (m, 4H), 6.20 (s, 1H), 7.28-7.50 (m, 1H), 7.55-7.67 (m, 1H), 7.87 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.90 (dd, *J* = 8 Hz and 2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 39.79 (2C), 50.47, 124.36 (2C), 128.31, 130.30, 133.02, 136.94, 148.34; **Mass** (m/e): 227 (M^+).

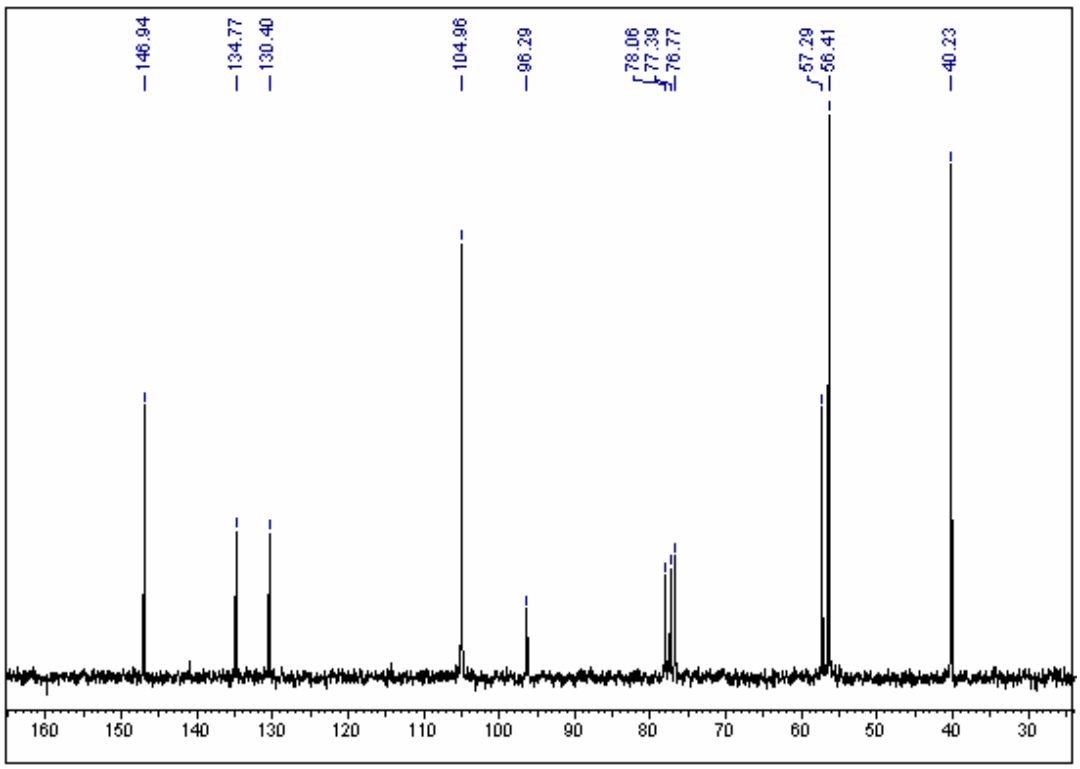
19) 5-(Bis-ethylsulfanyl-methyl)-1,2,3-trimethoxybenzene:

Colorless thick liquid; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 1.22 (t, *J* = 7 Hz, 6H), 2.57 (m, 4H), 3.30-3.81 (s, 3H), 3.85 (s, 6H), 4.82 (s, 1H), 6.66 (s, 2H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 13.63 (2C), 25.61 (2C), 52.34, 55.39 (2C), 59.83, 104.31 (2C), 135.41, 136.99, 152.47 (2C); **Mass** (m/e): 302 (M^+).

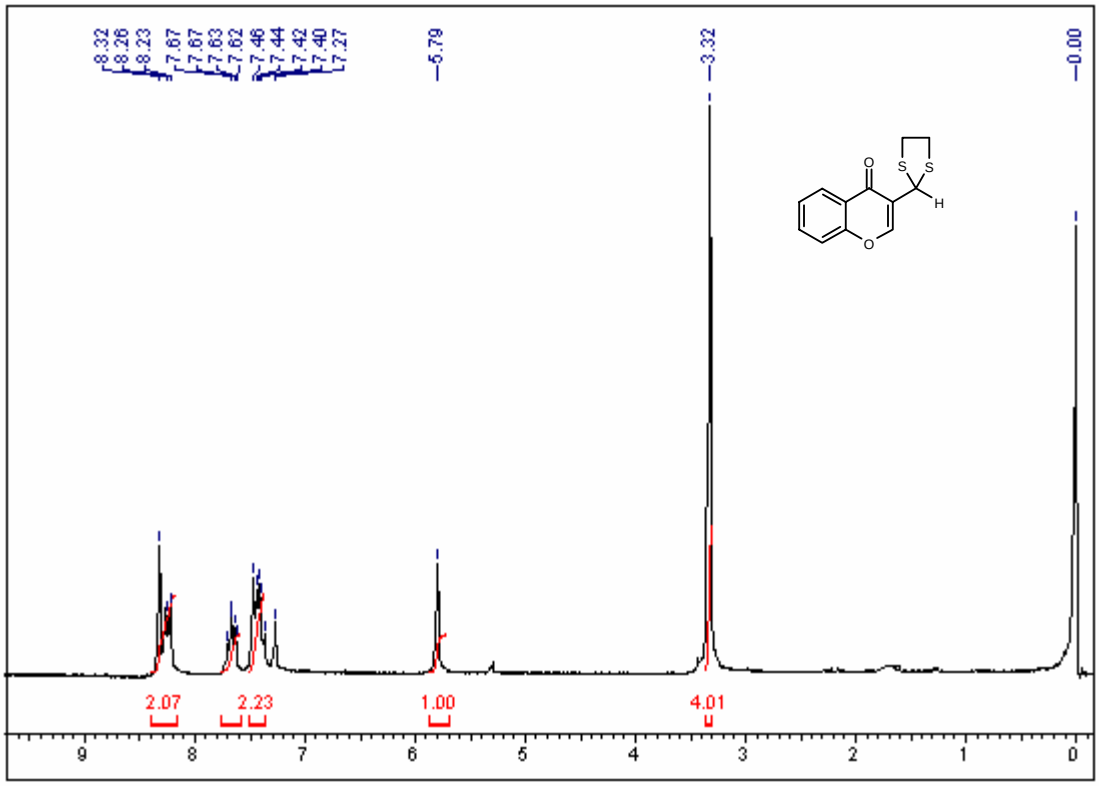
^{1}H NMR spectrum of 4-(1,3-dithiolan-2-yl)-2, 6-dimethoxylphenol:



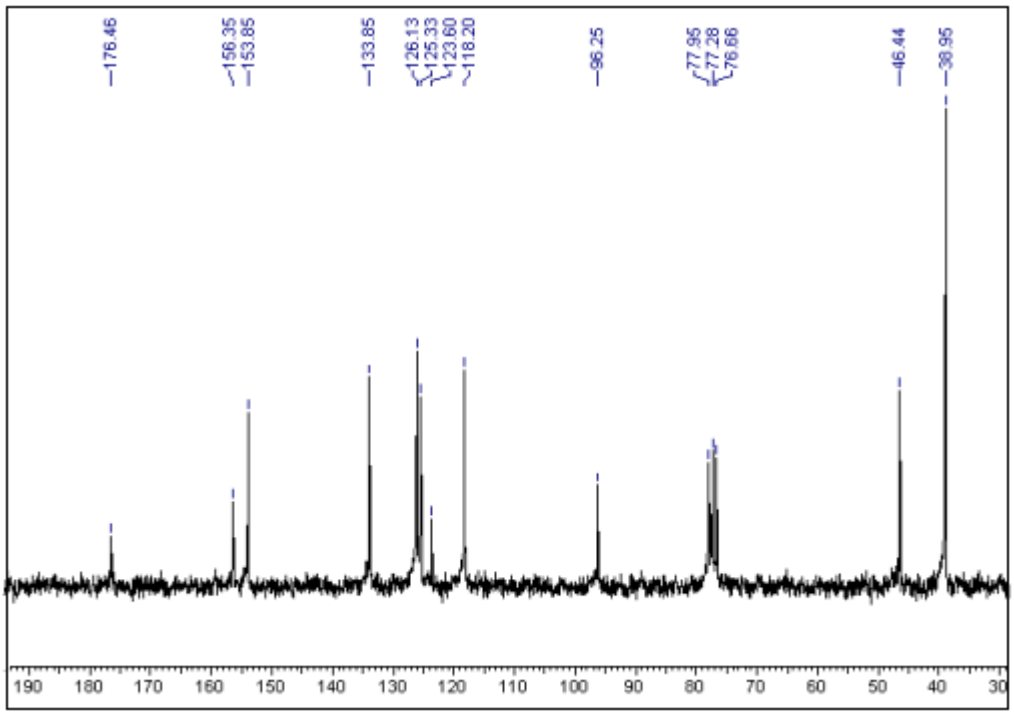
^{13}C NMR spectrum of 4-(1,3-dithiolan-2-yl)-2, 6-dimethoxylphenol:



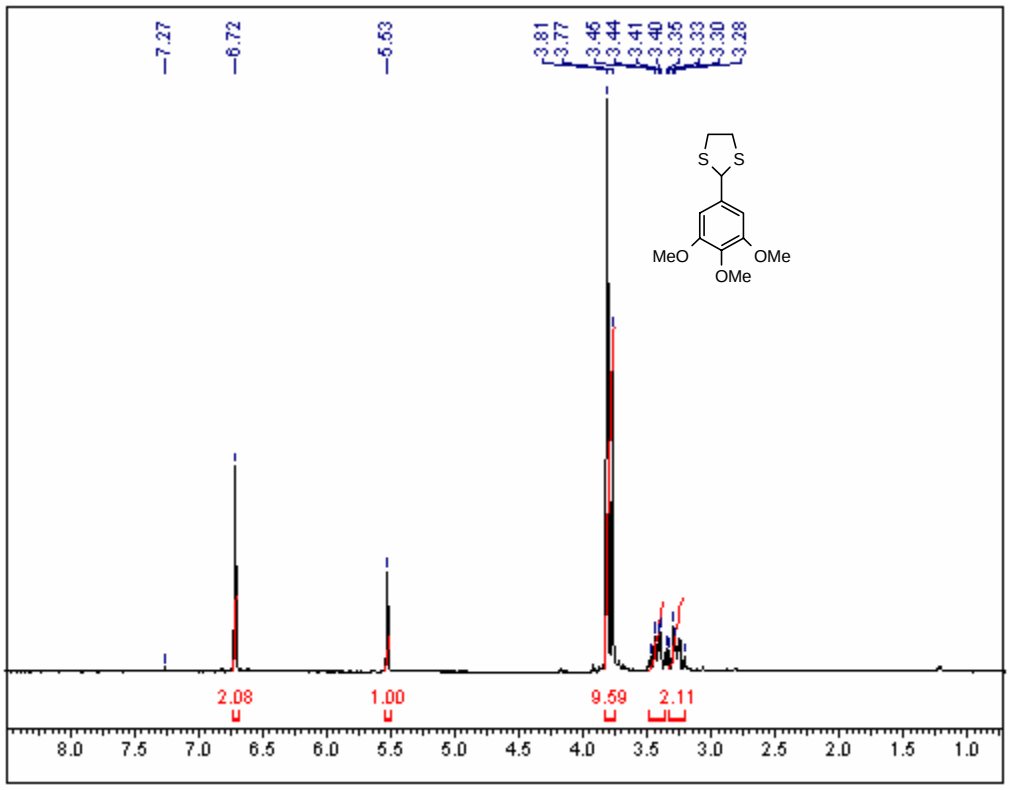
^{1}H NMR spectrum of 3-(1,3-dithiolan-2-yl)-chromen-4-one:



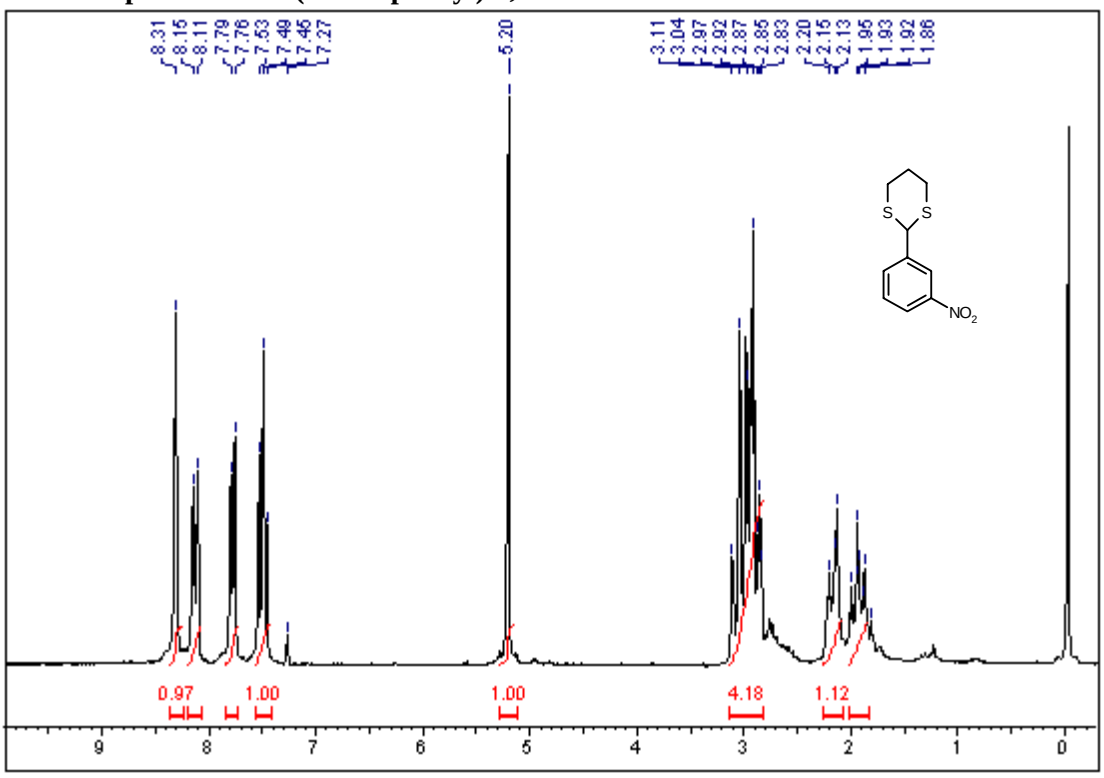
^{13}C NMR spectrum of 3-(1,3-dithiolan-2-yl)-chromen-4-one:



^{1}H NMR spectrum of 2-(3,4,5-trimethoxyphenyl)-[1,3] dithiolane:



^{1}H NMR spectrum of 2-(3-nitrophenyl)-1,3-dithiane:



2.2.5 REFERENCES:

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CHAPTER 2

SECTION III:

A Convenient Oxidative Demasking of 1, 3-Dithiolanes and Dithianes to Carbonyl Compounds With TBHP

2.3.1 INTRODUCTION:

The protection of functional groups and their regeneration constitute important and essential processes in the synthesis of poly-functional molecules and complex natural products. The carbonyl group, among various functional groups, can be protected as an acetal, oxime, hydrazone, cyclic thioacetal etc. Cyclic thioacetals have been widely used as carbonyl protecting groups mainly due to their stability both in acidic and basic reaction conditions. Also 1,3-dithianes play an important role in the development of the synthon concept and their role in Umpolung[1] is well established. Dithianes can be efficiently used as acyl carbanion equivalents for C-C bond forming reactions.

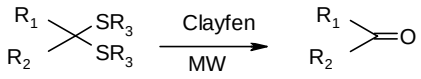
A large number of methods have been developed for the deprotection of 1,3-dithianes and dithiolanes[2-11] to the corresponding carbonyl compounds**.** However, selective removal often requires trial and error. Considerable effort has been made for the development of methods for demasking of 1,3-dithianes and dithiolanes and the search for a new reagent/catalyst is still actively pursued. Chemical procedures are widely used, as they are more accessible for synthetic chemists than other methods involving photolytic[12] or electrochemical[13] techniques. However, chemical procedures require heavy metal salts which are toxic to the environment. Other methods like photolytic and electrochemical techniques are safe to the environment but require expensive equipments.

There is still a need to develop improved, mild and neutral reagent for accomplishing this transformation.

A BRIEF REVIEW OF LITERATURE:

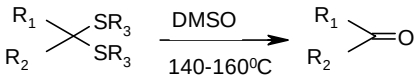
There are several methods reported for the cleavage of dithianes and dithiolanes to the corresponding carbonyl compounds. Some of the recent methods are discussed below.

Varma and Saini[14] reported cleavage of dithiolane and dithianes with clayfen (montmorillonite K 10 clay-supported NH_4NO_3) in microwave (scheme 1). The reaction is general for dithiolanes and dithianes of aromatic and arylaliphatic carbonyl compounds.



Scheme 1

H. Junjappa and coworkers[15] achieved the deprotection of dithiolanes and dithianes to corresponding carbonyl compounds using dimethylsulphoxide by carrying out reaction at high temperature (140-160^{0}C).

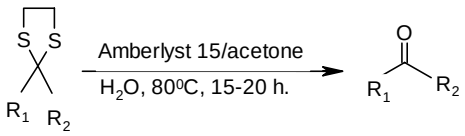


Scheme 2

The cleavage of dithianes with trimethylsilyl halide and dimethylsulfoxide as depicted in scheme 3 was reported by Olah and coworkers[16]. The reaction is general for dithiolanes of aliphatic, arylaliphatic and aromatic carbonyl compounds.

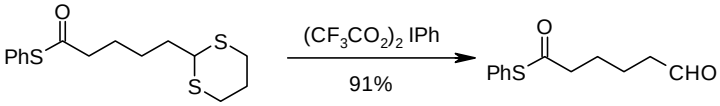
Scheme 3

Billini and Petrini[17] reported the deprotection of dithiolanes to corresponding carbonyl compounds *via* equilibrium exchange with aqueous acetone, paraformaldehyde and Amberlyst 15, as acidic catalyst at 80^0 C (scheme 4). This method was proven to be efficient even for acid sensitive groups such as esters or ethers but the reaction time required was slightly more.



Scheme 4

Another efficient method reported for the dethioacetalization of thioacetals and thioketals to the corresponding carbonyl compounds was reported by Stork and Zhao[18], which involved treatment with bis (trifluoroacetoxy) iodobenzene at room temperature for a short time (scheme 5).



Scheme 5

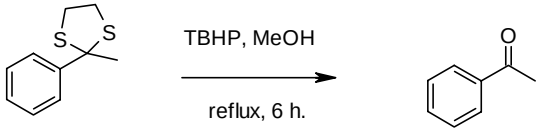
Aldehydes were obtained by treating thioacetals with bis (trifluoroacetoxy)-iodobenzene in aqueous acetonitrile.

Liu and Wiszniewski[19] reported that the combination of phenyldichlorophosphate, DMF and sodium iodide could efficiently deprotect dithioacetals to the corresponding carbonyl compounds.

2.3.2 PRESENT WORK:

From the brief review of the recent literature of the dethioacetalization methodology, it was felt encouraging to develop new method for the same reaction. Recently the utility of *tert*-butyl hydroperoxide (TBHP, aqueous 70%) for halogenations of arenes, alkenes and alkynes [20, 21], regeneration of carbonyl compounds from their corresponding oximes, phenyl hydrazones and tosylhydrazones [22] and oxidation of benzylic alcohols [23] has been reported from our laboratory. In view of the oxidative properties of this reagent and its wide spectrum of use we employed TBHP in methanol for dethioacetalization reactions.

When acetophenone dithioacetal in methanol was stirred with TBHP (2 eq.) under reflux for six hours, smooth formation of acetophenone (Scheme 6) was observed in 90% yield. Methanol was found to be the best solvent as in other solvents, such as carbon tetrachloride and dichloromethane, the reaction was sluggish and did not go to completion. Dithioacetals under these conditions are expected to undergo oxidative cleavage by formation of disulfoxides that eventually promote hydrolytic cleavage to the corresponding carbonyl compound, which explains the requirement of 2 eq. of TBHP for completion of the reaction. To study the scope of this transformation different dithioacetals were treated with TBHP in methanol.

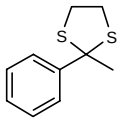
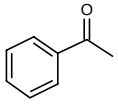
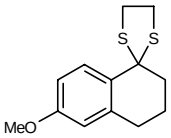
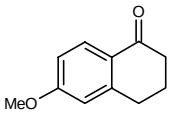
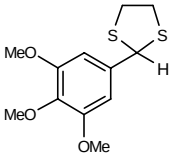
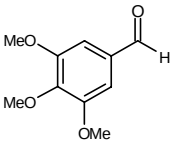
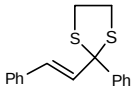
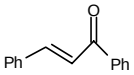
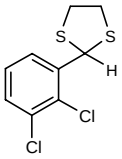
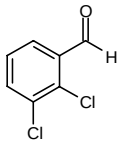
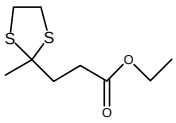
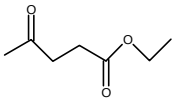
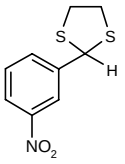
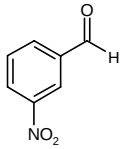
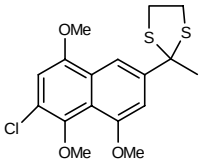
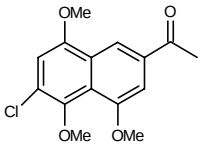
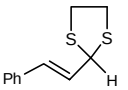
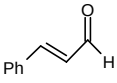
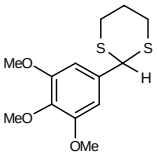
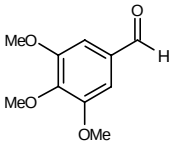
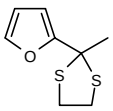
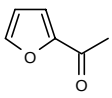
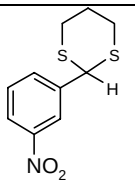
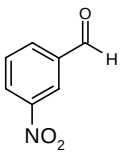


Scheme 6

The results summarized in **Table 1** clearly demonstrate the efficiency of TBHP for cleavage of dithioacetals for various substrates. 1,3-Dithiolanes of aryl ketones (entries **1, 6, 10**), tetralone (entry **7**), aliphatic ketones (entry **9**), an α,β-unsaturated ketone (entry **8**) and substituted benzaldehydes (entries **2**, **3, 4**, **11**) were successfully converted to the corresponding carbonyl compounds in good to excellent yields.

It is noteworthy that the conversion was effective even in the presence of a carboxylic ester (entry **9**). As exemplified by benzaldehydes **2, 3, 4, 11** and compounds **7** and **10**, substituents and their position on the aromatic ring did not alter the efficacy of the cleavage. The yields of dithiolane deprotection of benzaldehydes were on the lower side probably due to overoxidation of the aldehyde. It is significant that cinnamaldehyde dithiolane (**5**) and chalcone dithiolane were

Table 1: Dethioacetalization of various 1,3-dithiolanes and 1,3-dithianes using

Ent. No.	Substrate	Product	Yield[a] (%)	Ent. No.	Substrate	Product	Yield[a] (%)
1			90	7			95
2			75	8			88
3			80	9			92
4			77	10			93
5			83	11			76
6			85	12			80

a: The figures indicate yield of product after isolation and the products were characterized by spectroscopic methods as well as direct comparison with authentic samples

smoothly cleaved to cinnamaldehyde and chalcone wherein no epoxidation was observed. The corresponding 1,3-dithianes of 3,4,5-trimethoxybenzaldehyde and 3-nitrobenzaldehyde (entry **11** and **12**) on treatment with TBHP in methanol also furnished the cleavage products in good yields, indicating the generality of the reagent for dithiolanes as well as dithianes.

2.3.3 CONCLUSION:

In conclusion, we have developed a simple and convenient method for the demasking of 1,3-dithiolanes and dithianes under neutral conditions in good to excellent yield. The advantages of this protocol are that it provides an economically viable, non-hazardous and efficient methodology using a readily available reagent. Application of commercially available TBHP (aqueous 70%) offers experimentally simple conditions wherein no special precautions (inert atmosphere etc.) are necessary. On environmental grounds the use of methanol as the solvent provides added advantage because it is preferred over chlorinated solvents. Present method works better in case of thioketals as well as for thioacetals.

2.3.4 EXPERIMENTAL:

General experimental procedure for deprotection of dithianes and dithiolanes to carbonyl compounds:

The dithioacetals were prepared by reported procedures[24].

In a typical procedure for deprotection the dithioacetal (10 mmol) was dissolved in methanol (10 ml) and TBHP (20 mmol, 2 eq.) was added to the reaction mixture, which was refluxed until completion of reaction. After completion of reaction (4-6 h as monitored by TLC), methanol was removed under reduced pressure. The residue was taken up in ethyl acetate, washed with water, dried over sodium sulfate and concentrated to collect the crude product which was purified by column chomatography (silica gel; petroleum ether: ethyl acetate) to furnish the pure products in yields as shown in **Table 1**. All compounds in **Table 1** were characterized by direct comparison with authentic samples as well as IR and NMR spectroscopy.

1) 1-Phenylethanone: Pale yellow liquid; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1640, 1710 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.40-7.60 (m, 3H), 7.90 (d, J = 6 Hz, 2H).

2) 3,4,5-Trimethoxybenzaldehyde: White solid; m. p. 3-75^{0}C; **IR** ($\upsilon_{max,}$ nujol): 1125, 1540, 1610, 1710 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.94 (s, 9H), 7.13 (s, 2H), 9.87 (s, 1H).

3) 2,3-Dichlorobenzaldehyde: White solid; m. p. 65-67^{0}C; **IR** ($\upsilon_{max,}$ chloroform): 1596, 1693, 2854 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45 (t, *J* = 8 Hz, 1H), 7.69 (dd, *J* = 8 Hz and 2 Hz, 1H), 7.83 (dd, *J* = 8 Hz and 2 Hz, 1H), 10.70 (s, 1H).

4) 3-Nitrobenzaldehyde: Yellowish solid; m. p. 57-59^{0}C; **IR** ($\upsilon_{max,}$ chloroform): 1606, 1701, 3024, 3104 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.80 (t, *J* = 8 Hz, 1H), 8.26 (d, *J* = 8 Hz, 1H), 8.50 (d, *J* = 8 Hz, 1H), 8.72 (s, 1H), 10.40 (s, 1H).

5) 3-Phenylpropenal: Pale yellow liquid; **IR** ($\upsilon_{max,}$ $CHCl_3$): 750, 1130, 1670, 1710 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.70 (m, 2H), 7.40-7.60 (m, 5H), 9.70 (d, *J* = 3 Hz, 1H).

6) 1-Furan-2-ylethanone: Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 6.46 (d, *J* = 2 Hz, 1H), 7.10 (d, *J* = 2 Hz, 1H), 7.51 (d, *J* = 2 Hz, 1H).

7) 6-Methoxy-3,4-dihydro-2H-naphthalen-1-one: Colorless solid; m. p. 77-79^{0}C; **IR** ($\upsilon_{max,}$ neat): 1580, 1660 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.05-2.27 (m, 2H), 2.60 (t, *J* = 4 Hz, 2H), 2.92 (t, *J* = 4 Hz, 2H), 3.85 (s, 3H), 6.70 (s, 1H), 6.82 (d, *J* = 8 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H).

8) 1,3-Diphenylpropenone: Yellowish solid; m. p. 55-57^{0}C; **IR** ($\upsilon_{max,}$ neat): 1606, 1664, 3016, 3062 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.37-7.72 (m, 9H), 7.83 (d, *J* = 16 Hz, 1H), 8.00-8.10 (m, 2H).

9) Ethyl 4-oxopentanoate: Colorless liquid; **IR** ($\upsilon_{max,}$ neat): 1216, 1719, 3019 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 8 Hz, 3H), 2.20 (s, 3H), 2.47 (m, 2H), 2.55 (m, 2H), 4.14 (q, *J* = 8 Hz, 2H).

10) 1-(6-Chloro-4,5,8-trimethoxynaphthalen-2-yl)-ethanone: White solid; m. p 182^{0}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73 (s, 3H), 3.87 (s, 3H), 4.02 (s, 3H), 4.07 (s, 3H), 6.88 (s, 1H), 7.49 (s, 1H), 8.43 (s, 1H).

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CHAPTER 3

Synthesis of Terrein and Synthetic Studies Towards Kodaistatin

CHAPTER 3

SYNTHESIS OF TERREIN AND SYNTHETIC STUDIES TOWARDS KODAISTATIN

SECTION I

Synthetic Studies Towards Kodaistatin

3.1.1 INTRODUCTION:

Diabetes is one of the most common diseases in the world. More than 200 million people are afflicted worldwide with *diabetes mellitus,* the most common endocrine disease. One characteristic of diabetes is the increased blood glucose concentration. Active substances which can reduce the formation of glucose in the liver are therefore of particular interest in the treatment of diabetes.

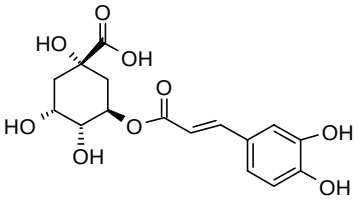
The insulin-dependent or type I diabetes is caused by the death of insulin-producing β-cells of pancreas. So the treatment involves administration of insulin. On the contrary, non-insulin dependent or type II diabetes is characterized by reduced insulin activity in the muscle and fatty tissue and increased glucose concentration in liver[1]. Most of the patients (almost 90 %) are suffering from type II diabetes, the non-insulin dependent diabetes mellitus (NIDDM)[2] while the type I diabetes and some of the type II patients need insulin.

The enzyme system glucose-6-phosphatase (G1-6-Pase) is known to play a major role in the homeostatic regulation of blood glucose[3]. It is responsible for the formation of endogenous glucose originating from gluconeogenesis and glycogenolysis. Glucose-6-phosphate is common end product of glycogenolysis or gluconeogenesis. The glucose-6-phosphate is an enzyme complex made up of glucose-6-phosphate translocase (G6-P-T1), glucose-6-phosphatase and a phosphate translocase. Of these components, G-6-P-T1 is highly selective and is therefore a suitable target for the treatment of diabetes type II by regulating hepatic glucose production.

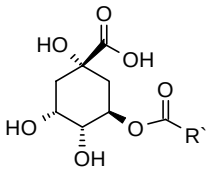
In recent years, several natural products have been identified as selective inhibitors of G-6-P-T1[4]. The chlorogenic acid[5] has been reported to be a weak but selective inhibitor of G-6-P-T1.

Hemmerle *et al.*[6] synthesized various derivatives of chlorogenic acid which were potent G6P-T1 inhibitors.

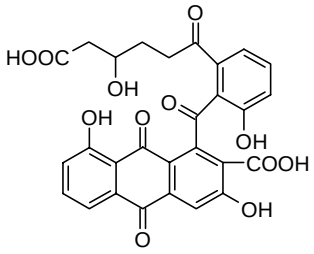
Ramakrishna *et al.*[7] in 1997 isolated mumbaistatin, most powerful natural inhibitor of G6P-T1 (IC_{50} = 5 nM), from the culture of *Streptomyces sp*. DSM 11641. Subsequently, structure of it was disclosed in 2001[8].



Chlorogenic acid

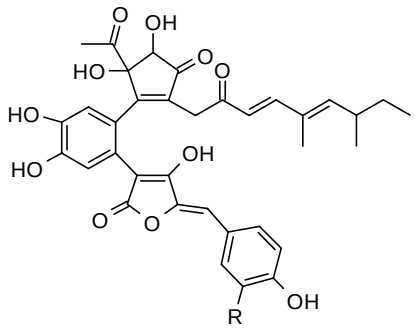


Synthetic chlorogenic acid derivative



Mumbaistatin

Kodaistatins, the novel inhibitors of G6P-T1, were isolated from cultures of fungus *Aspergillus terreus* Thom DSM 11247 by Vertesy *et al.*[9] in 2000, which inhibit glucose-6-phosphate specifically at submicromolar concentrations. The IC_{50} is 80 nM for kodaistatin A and 130 nM for kodaistatin C.



Kodaistatin A : R = H
Kodaistatin C: R = OH

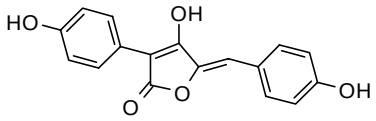
Isolation and structure determination:

The kodaistatin A having molecular formula $C_{35}H_{34}O_{11}$ is a yellow solid having specific rotation $[\alpha]_D^{21}$ -86º (c 0.04, MeOH) while kodaistatin C has molecular formula $C_{35}H_{34}O_{12}$ and specific rotation $[\alpha]_D^{21}$ -20º (c 0.04, MeOH).

The elemental analysis showed that kodaistatin A consists only of carbon, hydrogen and oxygen. The mass spectral analysis using High-resolution fast atom bombardment yielded m/e = 631.2174 $(M+H)^+$. The structure of kodaistatin A was determined by wide range of NMR studies like DQF-COSY, NOESY, HMQC, HMBC spectra. But the structural analysis did not clarify the stereochemical arrangement of the OH groups.

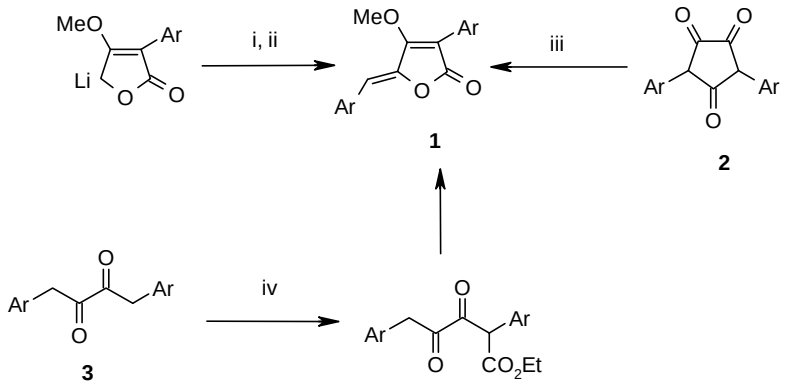
The structure of the kodaistatins includes two characteristic units out of which one is made up of the aromatic substituted aspulvinone and the other one consists of the highly substituted cyclopentenone ring.

The aromatic part consists of aspulvinone E[10] which is a member of a group of closely related natural products, the substituted 4-hydroxy-3-(4-hydroxyphenyl)-5-[(4-hydroxyphenyl)-methylene]-2(5H) furanones. The pulvinone is a generic name used to designate a new family of substituted 4-benzylidene-2-phenyl-tetranoic acid.



Aspulvinone E

The syntheses of aromatic part i.e. aspulvinone and pulvinone are well reported in literature. Pattenden and Knight[11, 12] reported various routes for the synthesis of pulvinone and aspulvinone as shown in scheme 1. They generated the pulvinone carbon skeleton by thermal Claisen rearrangement of dimethoxycyclopentanetrione **(2)** and in another approach, they used the method of the acylation of 1,4-diphenylbutane 2,3-dione **(3)**, by methyl chloroformate, as a key step.



Scheme 1

Reagents and conditions: i) 4-$MeOC_6H_4CHO$; ii) 4-$MeC_6H_4SO_3H$; iii) heat; iv) K_2CO_3, $ClCO_2Et$

3.1.2 PRESENT WORK:

The practice of total synthesis, particularly with reference to natural products, continues to flourish and expand. The organic synthetic community is constantly gifted by the nature with the new challenges of increasingly complex synthetic targets, which opens limitless horizons of achievement. Moreover the biological activity of the novel natural products demands more quantity for their further biological studies for which the scientists depend on organic synthetic approaches. The synthesis of such complex targets greatly depends upon the availability of chemicals, starting materials or building blocks. The structural features of kodaistatin especially the presence of cyclopentenone moiety as a part of the molecule prompted us to undertake the synthesis as this complex molecule. As mentioned in the introduction, kodaistatin consists of two main fragments structurally as shown in Fig. l *viz*. Fragment A and fragment B. The synthesis of fragment B is well reported in literature therefore we planned to undertake the synthesis of fragment A.

Retrosynthetic analysis of kodaistatin:

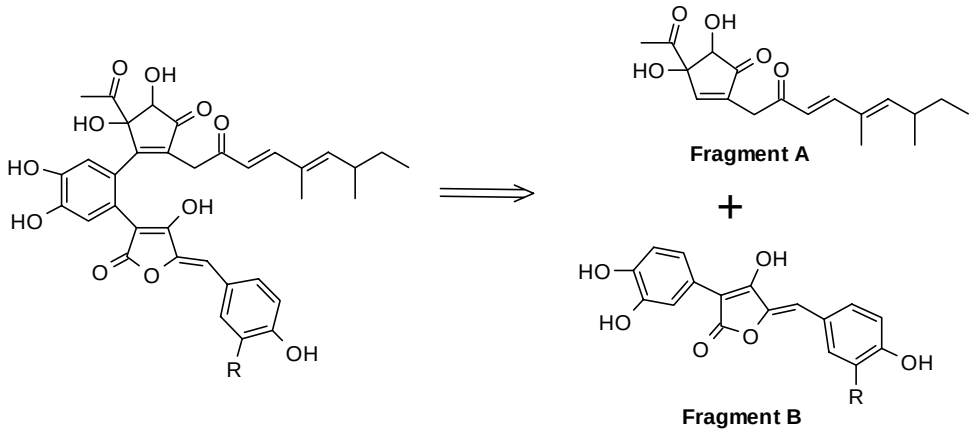
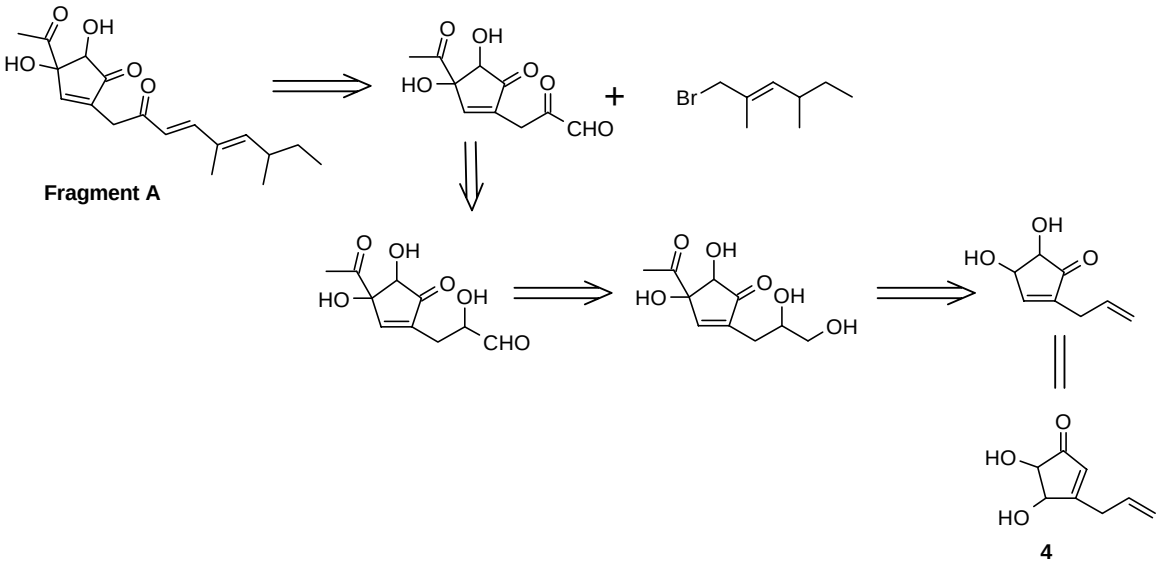


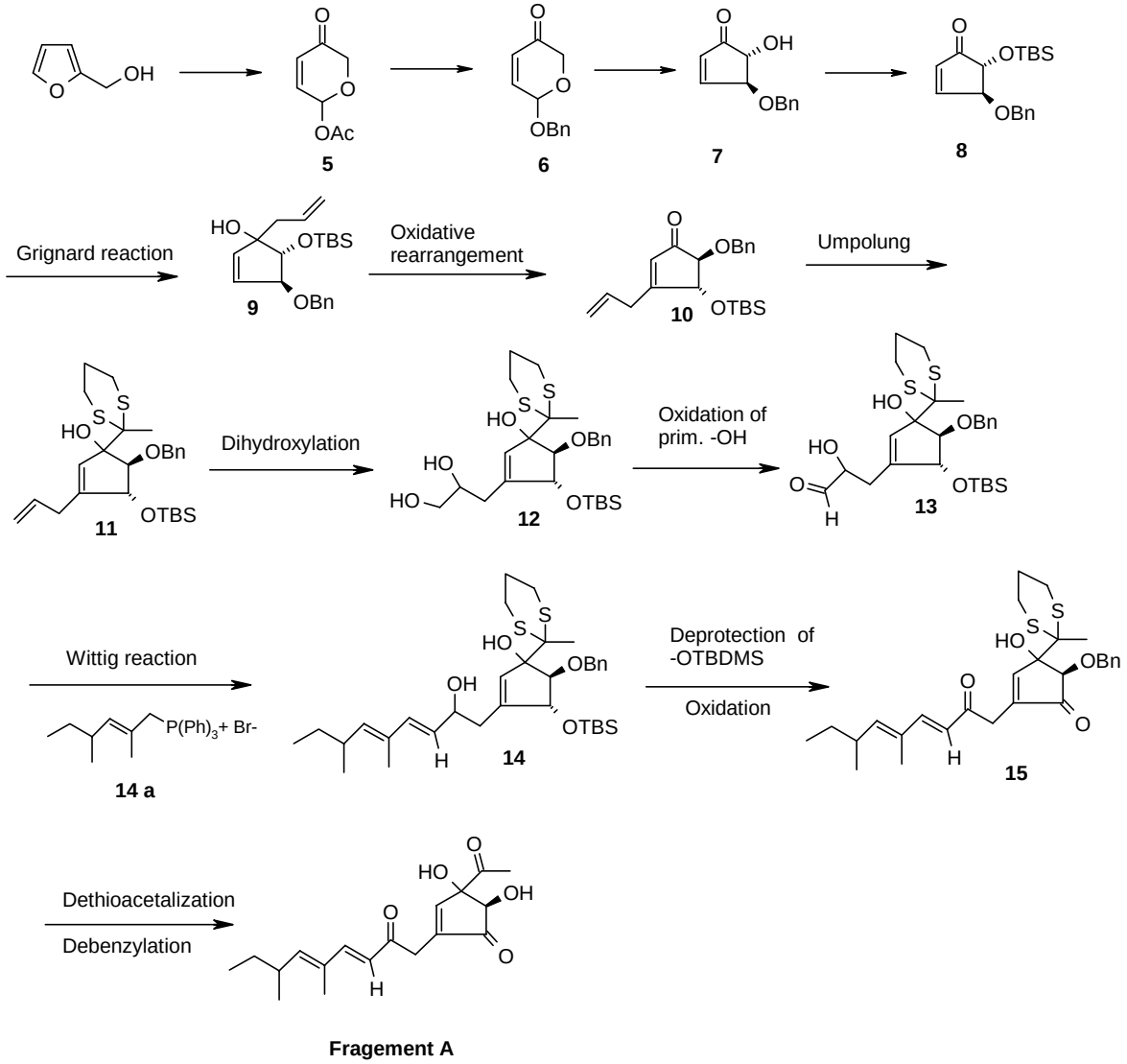
Fig. 1

The retrosynthetic analysis of fragment A revealed that the substituted cyclopentenone and the aliphatic C-6 unit are two main parts. Further analysis indicated that the cyclopentendiol **4** is the key intermediate for the synthesis, which could even be a common building block for the synthesis of compounds described in the section 2 of this chapter.

Retrosynthetic analysis of fragment A:



The synthetic scheme planned for the fragment A of kodaistatin is given in scheme 2. The synthesis of compound **8** from furfuryl alcohol is discussed in chapter 1 section III, which could be elaborated to fragment A of kodaistatin by appropriate chemical conversions as shown in the scheme 2.

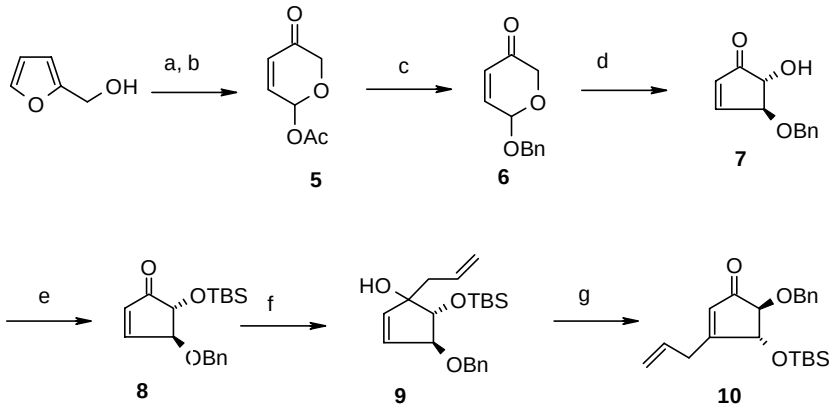


Scheme 2

Synthetic scheme for fragment A:

The synthesis of building block **8** was achieved as discussed in chapter 1, section III using readily available furfuryl alcohol. Treatment of furfuryl alcohol with N-bromosuccinimide in tetrahydrofuran and water (4:1) at 0^0C afforded hemiketal[13, 14] which was further treated with acetic anhydride and pyridine to afford the compound **5**[15] as a white solid in 41 % yield. The IR spectrum of compound **5** exhibited two bands in carbonyl region; one band at 1705 cm^{-1} for keto carbonyl and another at 1756 cm^{-1} for ester carbonyl function. The trans-glycosidation of the compound **5** was carried out using benzyl alcohol and montmorillonite K-10 clay in dichloromethane to give the compound **6** in 81 % yield as a colorless liquid. The ring

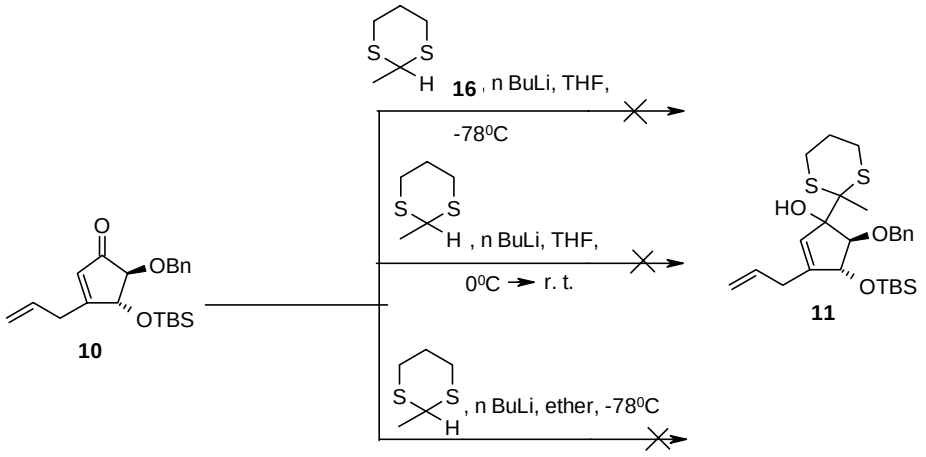
contraction[16] of pyranone **6** was accomplished with benzoic acid and potassium acetate in DMF at 80^0C within 3 h to give the cyclopentenone **7** in 42.7 % yield and recovery of some starting material. The free hydroxy group of cyclopentenone **7** was protected as tertiary-butyl dimethylsilyl ether to give the compound **8** in 76 % isolated yield. Further reaction of compound **8** with allyl magnesium bromide afforded the 1,2- addition product, alcohol **9** in 80 % yield as yellowish thick liquid. IR spectrum exhibited a band at 3452 cm^{-1} and ^{1}H NMR as well as ^{13}C NMR spectra supported the structure. The alcohol **9** on reaction with pyridinium chlorochromate (PCC) in dichloromethane at room temperature afforded the rearranged cyclopentenone **10** in 60 % yield as yellowish thick liquid. Its IR spectrum showed a band at 1710 cm^{-1} and absence of band at 3452 cm^{-1}, indicating the formation of carbonyl compound **10**.



Scheme 3

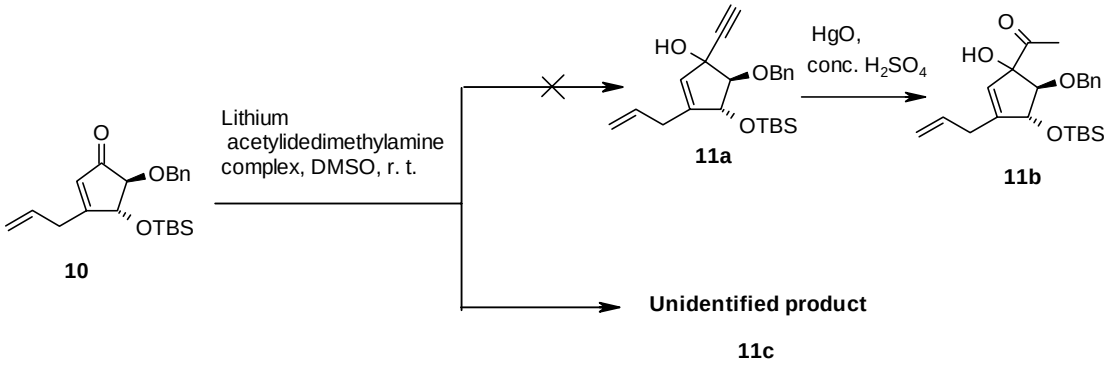
Reagents and conditions: a) NBS, THF-water, 0^0C b) $(CH_3CO)_2O$, Py, r t, 15 h. c) Benzyl alcohol, 30 % Montmorillonite K 10, DCM, reflux, 2 h. d) C_6H_5COOH, CH_3COOK, DMF, 80^0C, 3 h. e) TBDMSCl, DMAP, Et_3N, r t, 4 h. f) Mg, THF, allyl bromide, 0^0C-r t, 14 h g) PCC, DCM, r t, 8 h

After achieving successful synthesis of intermediate **10**, the next step was to introduce -$COCH_3$ group to form compound **11**. The umpolung reaction[17] of 2-methyl 1,3 dithiane **16** with intermediate **10** using n-butyllithium was attempted to achieve this goal as shown in scheme 4.



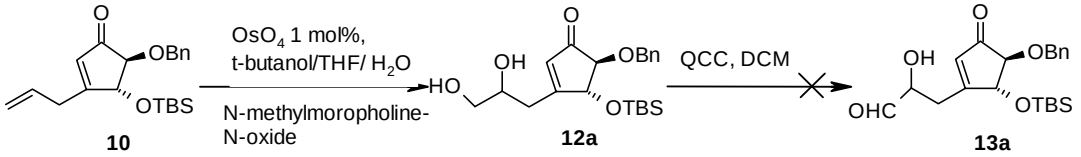
Scheme 4

The reaction was carried out under various conditions (scheme 4), but the required compound **11** was not obtained. Further attempts to introduce acetyl group at the ketone carbon involved introduction of acetylene which eventually could be converted to acetyl group as shown in scheme 5. To our surprise when compound **10** was treated with lithium acetylidedimethylamine complex[18] in DMSO at room temperature the required product **11a** was not obtained but it formed the compound **11c**. In IR spectrum compound **11c** exhibited the presence of carbonyl group at 1725 cm^{-1} and the mass spectrum showed peak at 269 (M^+), indicating cleavage of tert-butyldimethylsilyl protection (scheme 5), which was further confirmed by the ^1H NMR spectrum. The ^1H NMR spectrum did not match with the expected product although the mass spectrum [m/e 269 (M^+)] indicated the addition of acetylene and the product could not be identified further.



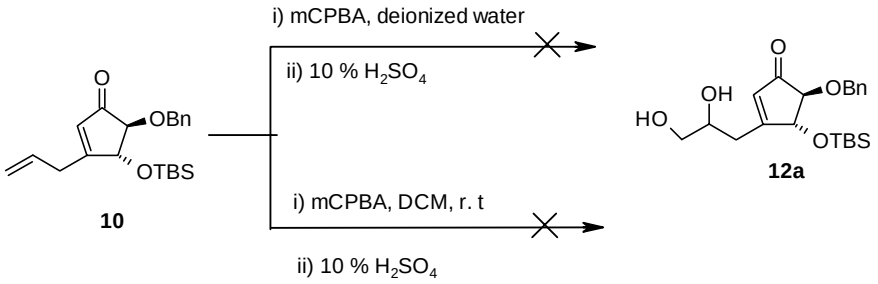
Scheme 5

In our simultaneous efforts to synthesize the aliphatic side chain part of the fragment A, we carried out the dihydroxylation[19] of compound **10** with 1 mol % osmium tetroxide and trimethylamine N-oxide as cooxidant in tert-butanol, tetrahydrofuran and water (10:3:1), which resulted in a complex mixture. The mass spectrum of the major product showed M+1 at 393 which was in accordance with the expected compound **12a**. The selective oxidation of primary –OH group using quinolinium chlorochromate[20] in dichloromethane was attempted but expected compound **13a** could not be obtained.



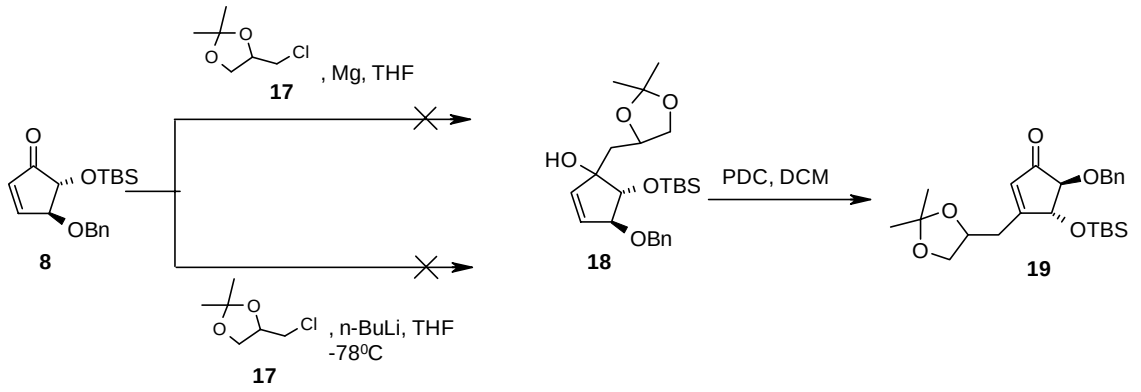
Scheme 6

Considering the failures in dihydroxylation of the compound **10**, we concentrated our efforts in epoxidation of the terminal double bond using m-chloroperbenzoic acid. Fringuelli *et al.*[21] reported the epoxidation of olefin with m-CPBA in deionized water which on further hydrolysis with 10 % sulfuric acid resulted in the trans diol. When we treated compound **10** with m-CPBA in deionized water under Fringuelli condition as well as with m-CPBA in dichloromethane, the expected epoxidation did not proceed to give **12a** (Scheme 7).



Scheme 7

Alternatively, the allyl bromide was replaced by 4-chloromethyl-2,2-dimethyl-[1,3] dioxolane[22] (scheme 8) for the 1,2-addition reaction on the compound **8** in order to achieve the already protected dihydroxylated compound **19**. Unfortunately, none of the above efforts were successful to complete the synthesis of fragment A of kodaistatin during the allotted time span and further efforts were discontinued.



Scheme 8

3.1.3 CONCLUSION:

The synthesis of fragment A of kodaistatin was attempted which could not be completed successfully. However, the key intermediate **10** which can be used for the synthesis of other naturally occurring biologically active compounds was efficiently synthesized.

3.1.4 EXPERIMENTAL:

Preparation of 6-hydroxy 2,3-dihydro-6H-pyran-3-one:

In a 1 liter single neck round bottom flask a solution of furfuryl alcohol (20.00 g, 204.00 mmol) in THF: H_2O (4:1, 400 ml) at 0^0C was taken and NBS (37.50 g, 220.00 mmol) was added in small portions with constant stirring over about 1 h. Then the solution was allowed to stir at the same temperature for 0.5 h. The reaction mixture was extracted with ether (4 x 200 ml) and the ether layer was washed successively with 10% KI (50 ml), 15% $Na_2S_2O_3$ (50 ml), 10% sodium bicarbonate, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent *in vacuo* at 35^0C afforded the 6-hydroxy 2,3-dihydro-6H-pyrane-3-one which was used for the next step without purification.

Preparation of 6-acetoxy-2,3-dihydro-6H-pyran-3-one (5):

In 250 ml two neck round bottom flask, crude 6-hydroxy 2,3-dihydro -6H-pyrane-3-one (19.00 g, 166.66 mmol) was taken and cooled to 0^0C. Acetic anhydride (40 ml) was then added followed by catalytic amount (1 ml) of pyridine. The solution was allowed to stir at the same temperature for 1 h and then allowed to warm to room temperature and stirred for 24 h at the same

temperature. The reaction mixture was then neutralized with sodium bicarbonate and extracted with dichloromethane (2 x 250 ml). The organic phase was washed with saturated $CuSO_4$ (50 ml), water (50 ml) and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a thick brown mass which upon column purification (silica gel, eluent 5% ethyl acetate in hexane) afforded compound **5** (10.80 g, 41.53 %) as colorless oil which crystallized on standing.

White solid; m. p. 41-43^{0}C (lit.[14, 15] 41-45^{0}C); **IR** ($\upsilon_{max,}$ KBr): 1221, 1634, 1705, 1756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 2.12 (s, 3H), 4.18 (d, *J* =16 Hz, 1H), 4.48 (d, *J* = 16 Hz, 1H), 6.24 (d, *J* = 12 Hz, 1H), 6.45 (d, *J* = 4 Hz, 1H), 6.90 (dd, *J* = 10 Hz and 4 Hz, 1H); **^{13}C NMR** (50.3 MHz, $CDCl_3$+CCl_4): δ 20.61, 67.11, 86.37, 128.50, 142.13, 169.26, 193.15; **Mass** (m/e): 156 (M^+); Anal. Calcd. For $C_7H_8O_4$: C 53.85; H 5.16 %. Found: C 53.95; H 5.27 %.

Preparation of 6-benzyloxy-2,3-dihydro-6H-pyran-3-one (6):

In 250 ml two neck round bottom flask with condensor and two-way stopcock, compound **5** (15.00 g, 96.15 mmol) and benzyl alcohol (12.46 g, 115.38 mmol) were taken and dry dichloromethane (80 ml) was added through syringe. The solution was cooled to 0^{0}C and then Montmorillonite K-10 (4.50 g, 30%w/w) was added. The mixture was allowed to stir for about 5 min at the same temp and then at 40^{0}C until TLC showed the absence of starting material (2 h). The reaction mixture was filtered and concentrated *in vacuo*. Purification of crude material by column chromatography (silica gel with 5% ethyl acetate in pet ether) afforded the desired product (16.00 g, 81%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 4.10 (d, *J* = 16 Hz, 1H), 4.48 (d, *J* = 16 Hz, 1H), 4.66 (d, *J* = 10 Hz, 1H), 4.85 (d, *J* = 10 Hz, 1H), 5.27 (d, *J* = 4 Hz, 1H), 6.15 (d, *J* = 10 Hz, 1H), 6.87 (dd, *J* = 10 Hz and 4 Hz, 1H), 7.30-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 66.08, 70.46, 91.92, 126.77, 127.69, 127.98 (2C), 128.42 (2C), 136.84, 144.12, 194.18; **Mass** (m/e): 204 (M^+); Anal. Calcd. For $C_{12}H_{12}O_3$: C 70.57; H 5.92 %. Found: C 70.69; H 6.06 %.

4-Benzyloxy-5-hydroxy-cyclopent-2-enone (7):

In 1 liter two neck round bottom flask with condensor and two way stopcock, 6-benzyloxy-6H-pyran-3-one **(6)** (11.00 g, 53.92 mmol) was taken and dry DMF (350 ml), benzoic acid (3.28 g, 26.92 mmol) and potassium acetate (5.28 g, 53.92 mmol) were added under nitrogen atmosphere. The mixture was stirred at 80^{0}C for 2.5 h and then concentrated *in vacuo* at the same temperature. The residue was taken up in ethyl acetate (500 ml) and the mixture was washed with aqueous sodium bicarbonate solution (5%, 200 ml). After extraction of the aqueous phase with ethyl

acetate (3 x 200 ml) the combined organic layers were washed with brine (200 ml), dried over Na_2SO_4 and solvent removed under reduced pressure on rotary evaporator. Column chromatography on silica gel (10% ethyl acetate in pet ether) afforded cyclopentenone (3.88 g, 42.70 %).

IR (υ_{max}, neat): 1210, 1455, 1500, 1590, 1725, 2880, 3040, 3420 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 3.56 (bs, 1H), 4.31(d, *J* = 2 Hz, 1H), 4.58 (bs, 1H), 4.75 (d, *J* = 10 Hz,1H), 4.90(d, *J* = 10 Hz, 1H), 6.28 (d, *J* = 6 Hz, 1H), 7.30-7.50 (m, 6 H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ 72.10, 80.00, 82.25, 127.75 (3C), 128.19 (2C), 131.87, 137.05, 158.67, 204.14; **Mass**(m/e):204 (M^+); Anal.Calcd.For $C_{12}H_{12}O_3$: C, 70.57; H, 5.92 %.Found: C, 70.72; H, 5.99 %.

4-Benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-enone (8):

In a 100 ml two neck round bottom flask with two way stopcock, 4-benzyloxy-5-hydroxy-cyclopent-2-enone **(7)** (6.00 g, 29.41 mmol) was taken under argon and then dry dichloromethane (40 ml) was added through syringe and the flask was cooled to 0^0C. A solution of tert-butyldimethylsilyl chloride (4.87 g, 32.35 mmol) and dimethyamino pyridine (0.78 g, 6.40 mmol) in dichloromethane (20 ml) was added dropwise and stirred at the same temperature for 15 min. Then triethylamine (4.09 ml, 38.23 mmol) was added and mixture was warmed to room temperature and stirred further for 5 h (monitored by TLC). The reaction mixture was filtered through Whatman filter paper, water was added to the filtrate and extracted with dichloromethane (3 x 50 ml). The combined organic layer was washed with water followed by brine, dried over sodium sulphate and concentrated to dryness under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using silica gel (2 % ethyl acetate in pet ether) to give the 4-benzyloxy-5-(tert-butyldimethylsilyloxy)-cyclopent-2-enone (7.10 gm, 76 %) as a colorless liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 1217, 1253, 1725, 2858, 2930, 3015 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.23 (s, 3H), 0.26 (s, 3H), 1.00 (s, 9H), 4.32 (d, *J* = 4 Hz, 1H), 4.52-4.59 (m, 1H), 4.72 (d, *J* = 10 Hz, 1H), 4.84 (d, *J* = 10 Hz, 1H), 6.21 (dd, *J* = 6 Hz and 2 Hz, 1H), 7.30-7.42 (m, 6H). **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.30, -4.20, 18.15, 25.72 (3C), 72.07, 80.53, 83.73, 127.58 (2C), 127.80, 128.35 (2C), 132.54, 137.43, 156.51, 202.09; **Mass** (m/e): 318 (M^+); Anal. Calcd. For $C_{18}H_{26}O_3Si$: C 67.88; H 8.23; Si 8.82 %. Found: C 67.94; H 8.26; Si 8.96 %.

1-Allyl-4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-en-1-ol (9):

In 100 ml flame dried two neck round bottom flask, magnesium metal (0.80 g, 33.58 mmol) and 4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-enone **(8)** (5.34 g, 16.79 mmol) were

placed under inert atmosphere, tetrahydrofuran (40 ml) was added through syringe and the reaction mixture was cooled to 0^0C. Allyl bromide (4.06 g, 33.58 mmol) was then added slowly, reaction mixture was stirred at same temperature for 30 min and allowed to warm to room temperature and stirred for 12 h (TLC showed completion of reaction). Then the reaction was quenched with saturated ammonium chloride (20 ml), tetrahydrofuran was removed under reduced pressure and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over Na_2SO_4. Removal of solvent under reduced pressure and column purification over silica gel (10% ethyl acetate in pet ether) afforded 1-allyl-4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-en-1-ol (4.84 g, 80.66%) as yellowish thick liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 869, 1126, 1252, 1361, 2857, 2954, 3452 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$+CCl_4): δ 0.17 (s, 3H), 0.18 (s, 3H), 0.97 (s, 9H), 2.25 (dd, *J* = 15 Hz and 9 Hz, 1H), 2.43 (dd, *J* = 15 Hz and 9 Hz, 1H), 2.74 (bs, 1H), 4.12-4.20 (m, 2H), 4.60 (d, *J* = 8 Hz, 1H), 4.66 (d, *J* = 8 Hz, 1H), 5.10 (d, *J* = 6 Hz, 1H), 5.15 (s, 1H), 5.77-5.88 (m, 3H), 7.28-7.40 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$+CCl_4): δ -4.64, -4.35, 18.15, 25.94(3C), 40.79, 71.85, 82.77, 87.40, 87.62, 118.72, 127.65 (3C), 128.35 (2C), 129.97, 133.75, 137.21, 138.42; **Mass** (ESI): 343 (M-OH)); Anal. Calcd. For $C_{21}H_{32}O_3Si$: C 69.95; H 8.95; Si 7.79 %. Found: C 70.05; H 8.99; Si 7.81 %.

3-Allyl-5-benzyloxy-4-(tert-butyldimethylsilanyloxy)-cyclopent-2-enone (10):

In 50 ml two neck round bottom flask, 1-allyl-4-benzyloxy-5-(tert-butyldimethylsilanyloxy)-cyclopent-2-en-1-ol (9) (2.10 g, 5.83 mmol) was taken, flushed with argon, dry dichloromethane (15 ml) was added with syringe, A-4 molecular sieves were added and the flask was cooled to 0^0C. Then pyridinium chlorochromate (3.00 g, 13.29 mmol) was added in small portions. After addition, reaction mixture was stirred at same temperature for 1 h, allowed to warm to room temperature and stirred for 20 h. Reaction mixture was diluted with ether and filtered though a pad of celite. The organic layer was washed with water followed by brine, concentrated under reduced pressure and column purified using silica gel (5% ethyl acetate in pet ether) to give 3-allyl-5-benzyloxy-4-(tert-butyldimethylsilanyloxy)-cyclopent-2-enone (1.17 g, 60 %) as yellowish thick liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 1620, 1710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 0.14 (s, 3H), 0.16 (s, 3H), 0.93 (s, 9H), 3.03 (dd, *J* = 10 Hz and 5 Hz, 1H), 3.23 (dd, *J* = 10 Hz and 5 Hz, 1H), 3.97 (bs, 1H), 4.66-4.74 (m, 2H), 5.16-5.25 (m, 3H), 5.80-5.90 (m, 1H), 5.94 (s, 1H), 7.28-7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ -5.37, -4.77, 17.73, 25.47 (3C), 35.55, 72.48, 76.89, 86.14,

118.33, 127.51, 127.87, 128.02 (2C), 128.09 (2C), 132.34, 137.34, 174.91, 202.12; Mass (ESI): 359 (M+1); Anal. Calcd. For $C_{21}H_{30}O_3Si$: C 70.35; H 8.43; Si 7.83 %. Found: C 70.49; H 8.60; Si 7.96 %.

4-Chloromethyl-2,2-dimethyl-[1,3]dioxolane (17):

In a 100 ml two neck round bottom flask, epichlorohydrin (4.00 g, 43.47 mmol) and dry acetone (60 ml) were taken under argon, catalytic amount of $BF_3.Et_2O$ etherate was added and reaction mixture was stirred at room temperature for 2 h. It was then quenched with water, acetone was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layer was dried over sodium sulfate and concentrated to give compound **17** (5.47 g, 84) as colorless liquid.

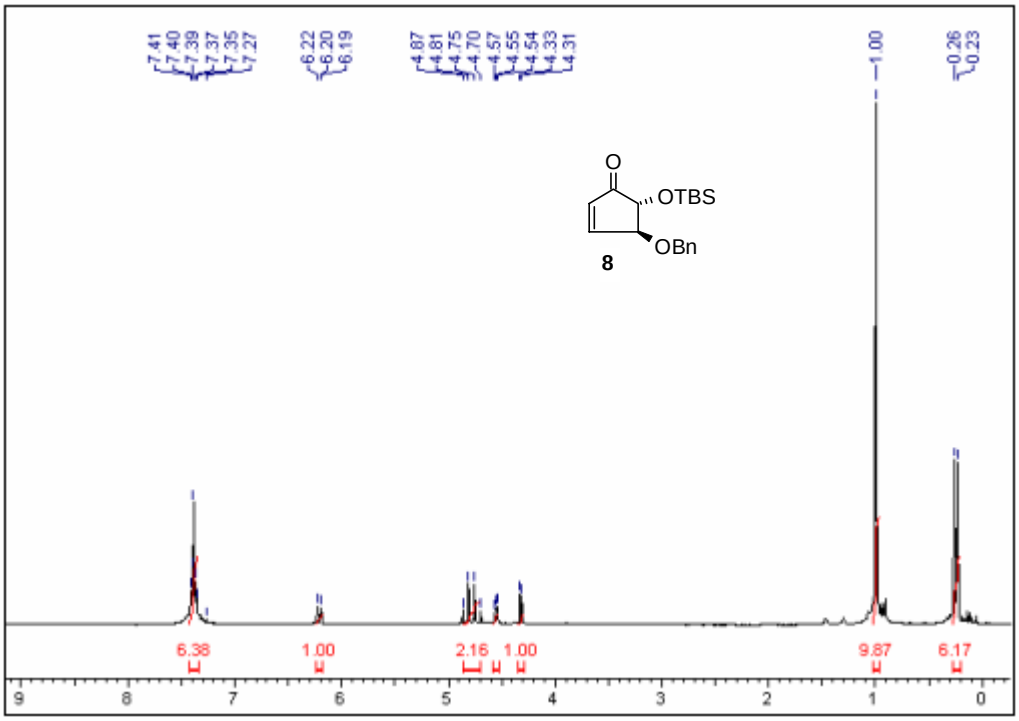
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.43 (s, 3H), 3.45 (dd, *J* = 4 Hz and 2 Hz, 1H), 3.57 (dd, *J* = 4 Hz and 2 Hz, 1H), 3.85-3.89 (m, 1H), 4.07-4.14 (m, 1H), 4.28-4.34 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 25.15, 26.70, 44.37, 67.36, 75.32, 109.93; **Mass** (ESI): 150 (M^+).

Preparation of 2-methyl-[1,3]dithiane:

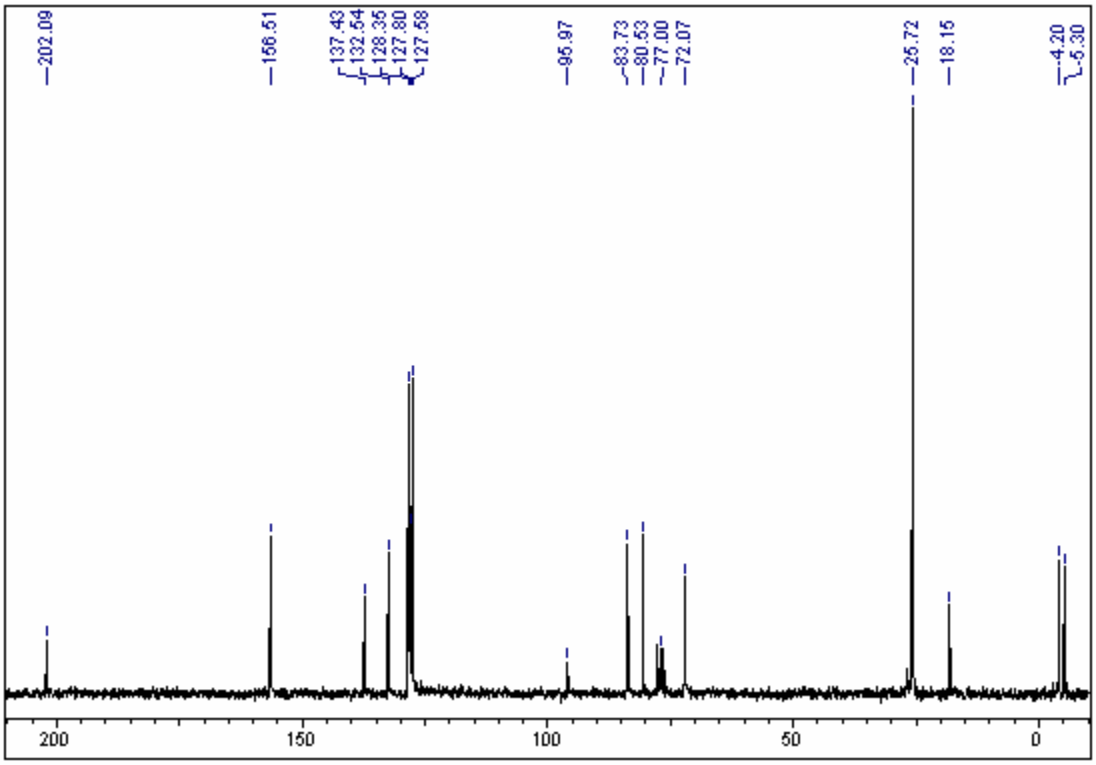
A stirred solution of acetaldehyde (6 ml of 20 % aq. solution, 1.53 g, 30.22 mmol) and 1, 3 propanedithiol (3.91 g, 36.26 mmol) in chloroform (60 ml) was treated with moderate stream of HCl gas for 1 h during which the temperature rose to 60^0C. The aqueous phase was then separated, the organic phase was washed with water, 2.5 M aqueous sodium hydroxide, water followed by brine and dried over sodium sulfate. Solvent was removed under reduced pressure using rotary evaporator. The column chromatography of this material afforded the 2-methyl-[1,3]dithiane (3.37 g, 72.5 %) as colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.44 (d, *J* = 6 Hz, 3H), 1.75-1.91 (m, 1H), 2.00-2.14 (m, 1H), 2.70-2.90 (m, 4H), 4.08 (q, *J* = 8 Hz, 1H); **Mass** (ESI): 134 (M^+).

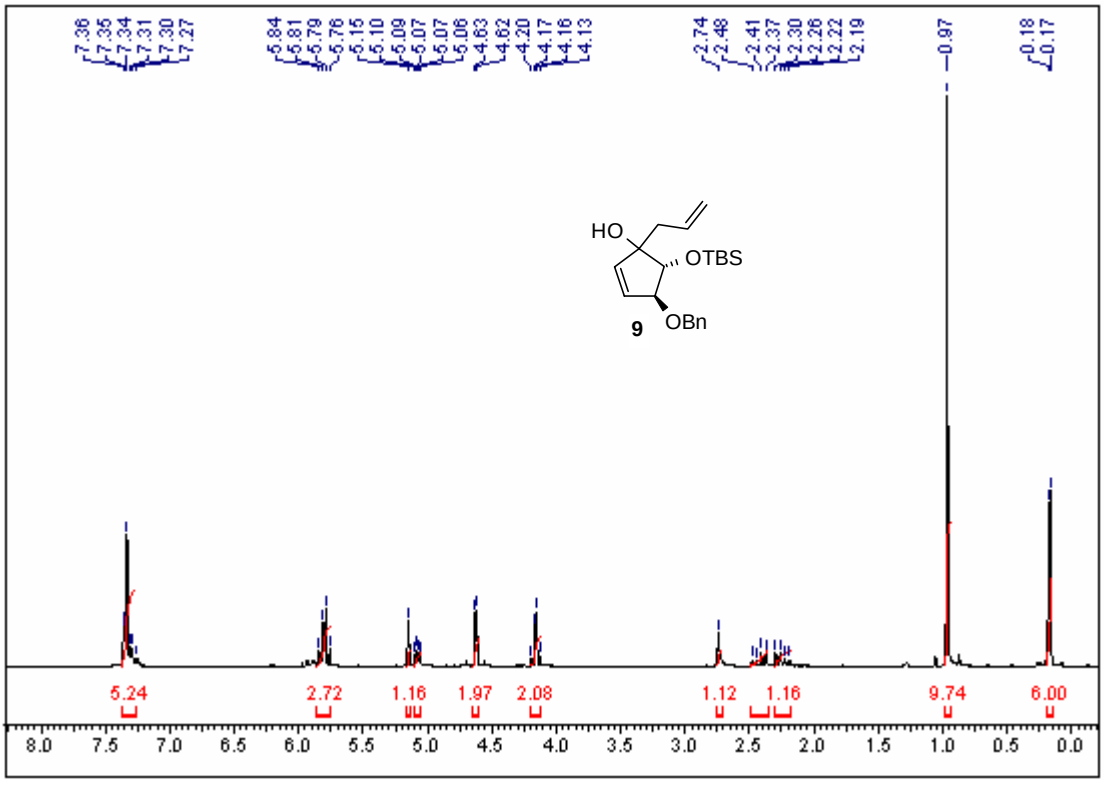
^{1}H NMR spectrum of the compound 8:



^{13}C NMR spectrum of the compound 8:



^{1}H NMR spectrum of the compound 9:


7.36
7.35
7.34
7.31
7.30
7.27
5.84
5.81
5.79
5.76
5.15
5.10
5.09
5.07
5.07
5.06
4.63
4.62
4.20
4.17
4.16
4.13
2.74
2.48
2.41
2.37
2.30
2.26
2.22
2.19
0.97
0.18
0.17
HO
OTBS
OBn
9
5.24
2.72
1.16
1.97
2.08
1.12
1.16
9.74
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
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2.0
1.5
1.0
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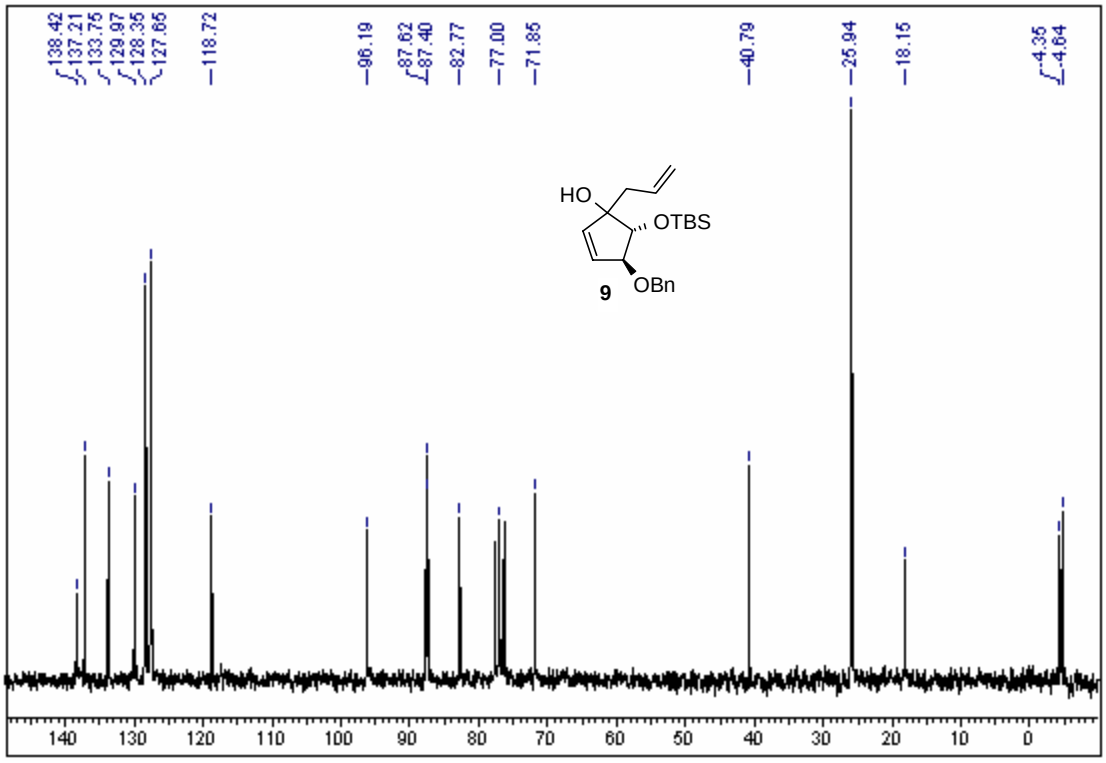
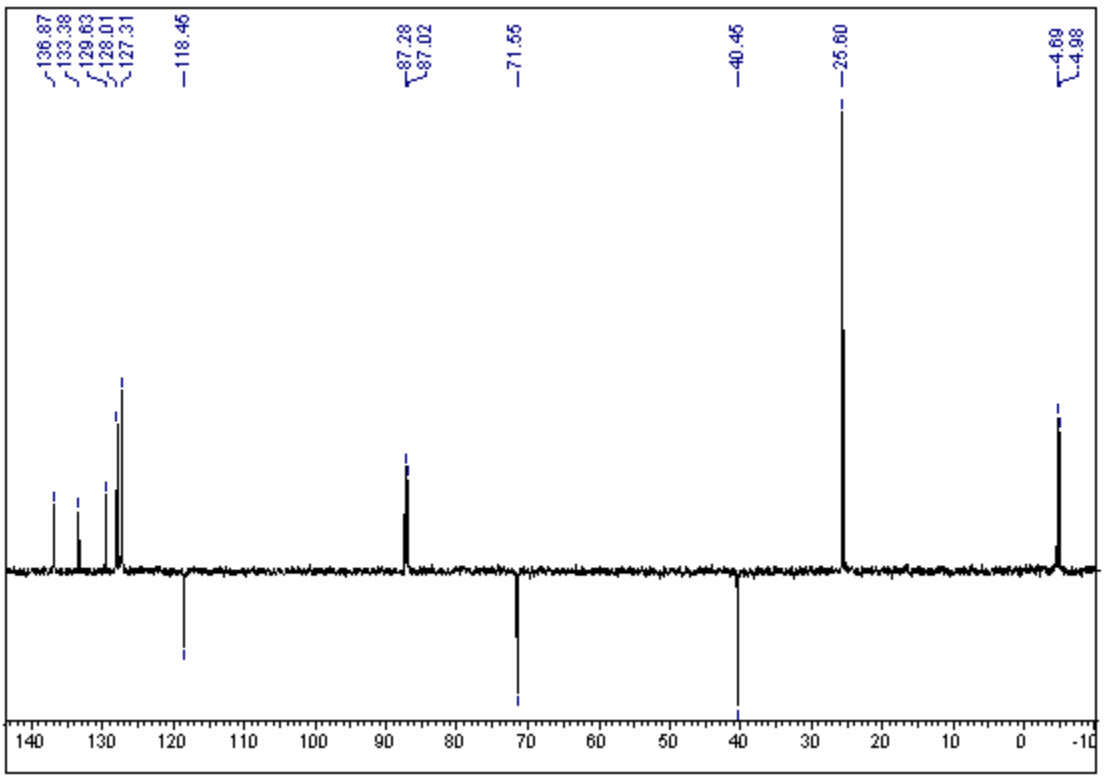
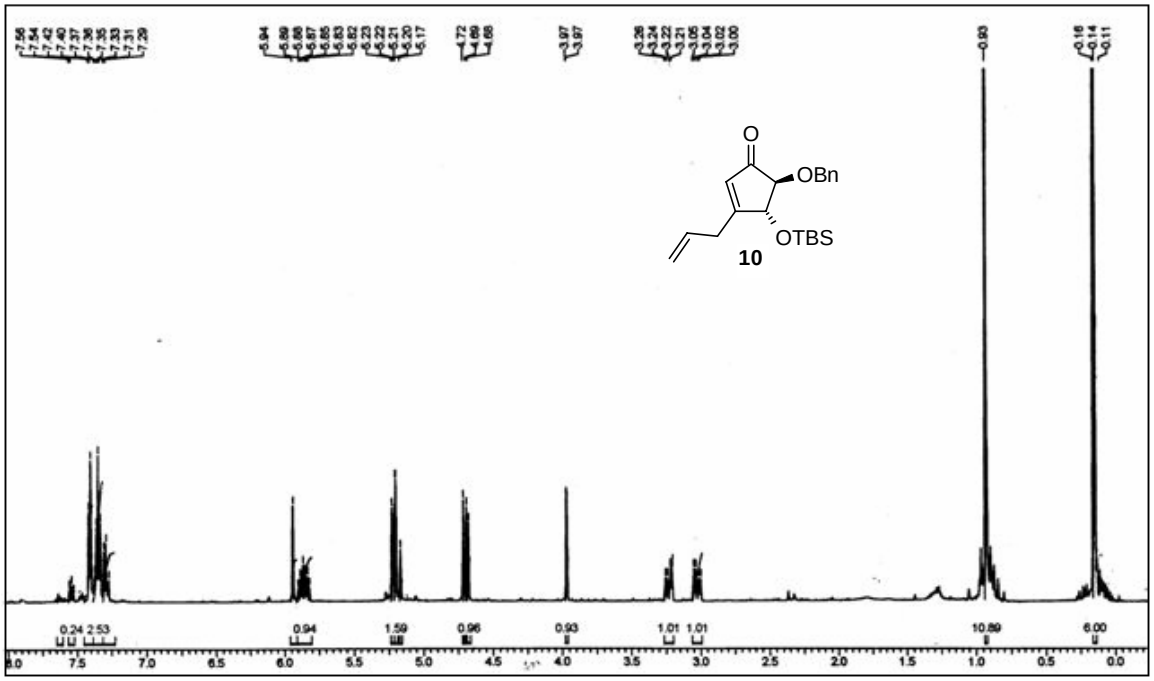
^{13}C NMR spectra of the compound 9:

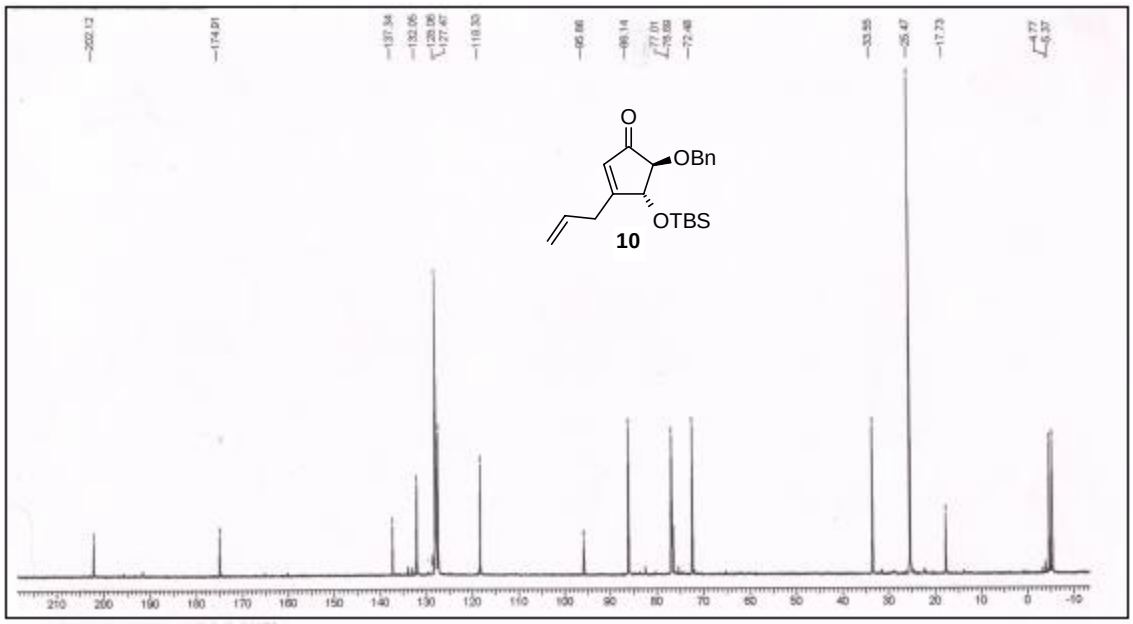


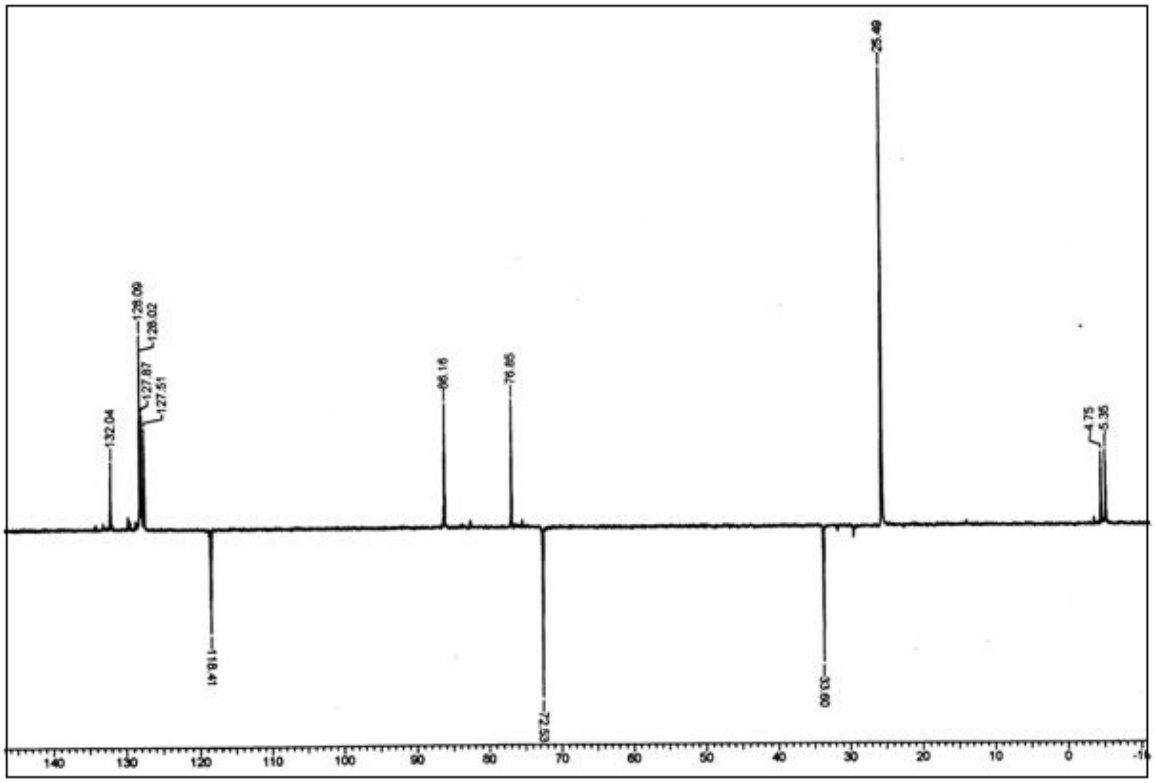


^{1}H NMR spectrum of the compound 10:



^{13}C NMR spectra of the compound 10:





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CHAPTER 3

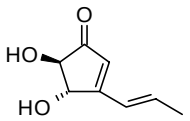
SECTION II

An Efficient Synthesis of Terrein

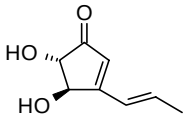
(trans-4, 5-Dihydroxy-3-[(E)-1-propenyl]-2-cyclopenten-1-one)

3.2.1 INTRODUCTION:

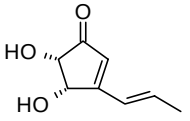
The mould metabolite (+) terrein (trans-4, 5-dihydroxy-3-[(E)-1-propenyl]-2-cyclopenten-1-one) was discovered by Raistrick and Smith[1] which was isolated from *Aspergillus terreus* in 1935. It is a metabolic product of several types of fungi like *Aspergillus fischeri*, [2] *Aspergillus stellatus*, [3] *Aspergillus pulvinus*[4] and *Penicillum raistrickii*[5]. Early work on the structure was carried out by Raistrick *et al.*[6] but the correct structure **20** was proposed in 1954 by Grove and also by Barton and Miller[7]. Japanese workers[8] have shown that (+) terrein inhibits plant growth, reducing root elongation of lettuce and rice seedlings. It has also shown to have antibacterial activity.[4]



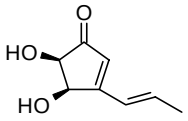
(+)-terrein (+)- **20**



(-)-terrein (-)- **20**



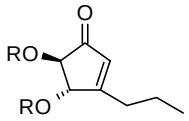
(-)-isoterrein (-)- **21**



(+)-isoterrein (+)- **21**

The molecular formula of terrein determined from elemental analysis and high-resolution mass spectrum was found to be $C_8H_{10}O_3$ and molecular weight 154.0588. In IR ($\upsilon_{max,}$ KBr) spectrum it shows bands at 3350, 1675, 1620, 1210 cm^{-1}. It consists of trans-4, 5-dihydroxycyclopentenone ring having E-propenyl group at 3 position.

Recently Barrero *et al.*[9] reported the isolation of dihydroterrein from the fungus *Emericella variecolor*. They isolated dihydroterrein (**22a**) as diacetyl derivative **22b** having molecular formula $C_{12}H_{16}O_5$.



Dihydroterrein
22a, R = H
22b, R = Ac

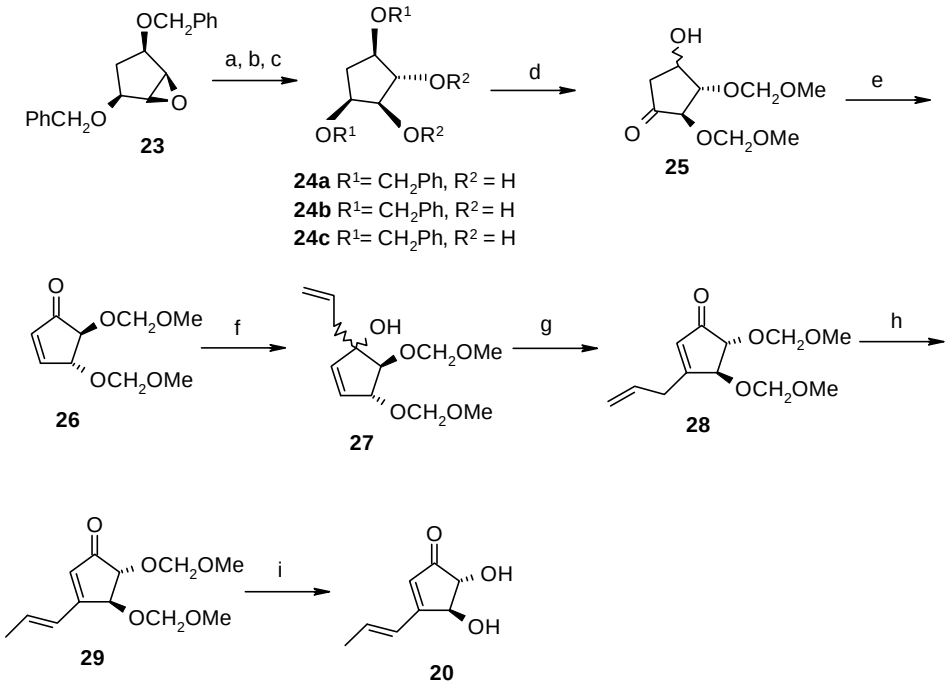
Although the structure of terrein is simple, its synthesis is not tri*via*l because of its sensitivity to acids and bases. Therefore, only after a lapse of twenty years from determination of its structure three approaches to racemic terrein **20** were reported. Barton and Hulshof reported racemic synthesis of terrein and also isoterrein **21**, the more stable isomer of **20**, in which the hydroxyl

groups are *cis* oriented. Only recently, two research groups have succeeded in synthesizing optically active terrein **20**.

BRIEF REVIEW OF LITERATUTE:

In literature three syntheses of (±) terrein and two syntheses of optically active terrein are reported. These syntheses are briefly discussed in the following schemes.

Auerbach and Weinreb[10] in 1974 reported the synthesis of (±) terrein in a multistep sequence and in overall low yield.



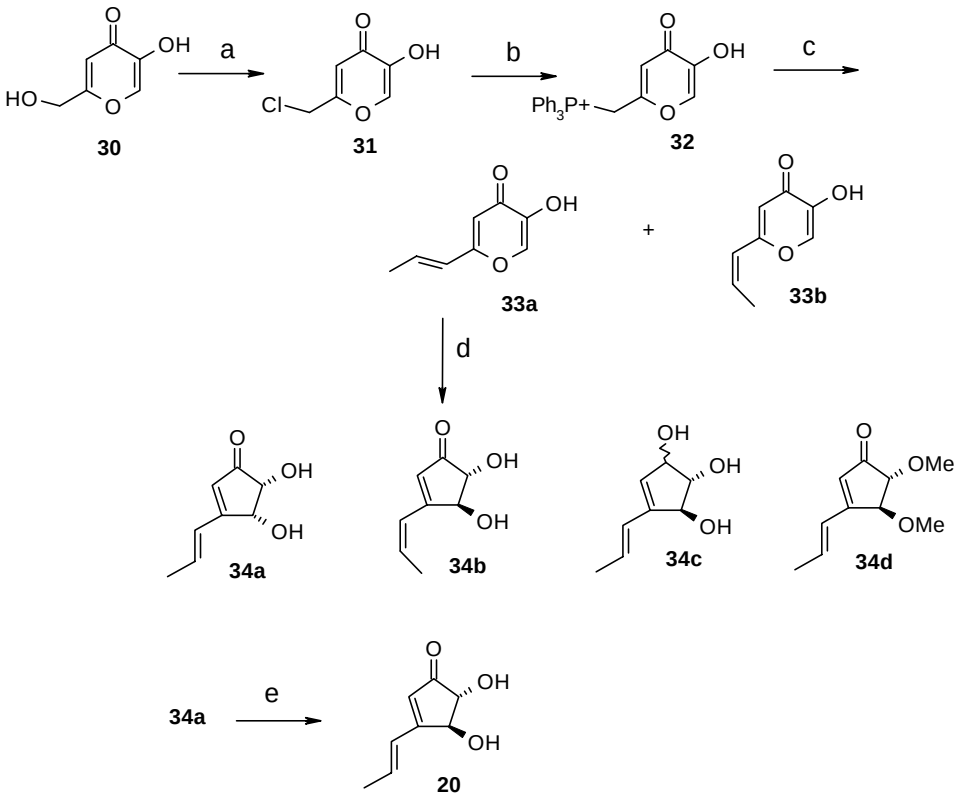
Scheme 1

Reagents and conditions: a) Dimethoxyethane-4 % H_2SO_4 (3:1), 22 h, 86 % b) NaH, chloromethyl methyl ether/ DMF, r t, 85 % c) Na-liq. NH_3, 62 %. d) Jones reagent, acetone, 0^0C, 60 min. e) Ac_2O, pyridine, -20^0C, 12 h, 66 % f) allylmagnesium bromide, ether, -78^0C, 58 % g) Jones reagent, acetone, 22^0C, 2 h, 30 % h) NaOH in MeOH, r t, 50 %. i) Conc. HCl in MeOH, 62^0C, 15 min.

The epoxide **23**[11] was converted to cyclopentenone **26** by series of reactions. Treatment of **26** with allylmagnesium bromide in ether at –78^0C gave mixture of alcohols **27** in 58 % yield which on treatment with Jones reagent[12, 13] in acetone afforded cyclopentenone **28** in 30 % yield. On reaction with NaOH in MeOH at room temperature, **28** was instantaneously converted into fully

conjugated cyclopentadienone **29** in 50 % isolated yield. The alcohol protecting groups were cleaved by treating **29** with concentrated hydrochloric acid in methanol at ambient temperature to give racemic terrein (**20**).

In 1977 Barton and Hulshoff[14] obtained racemic terrein *via* a photochemical ring contraction of 5-hydroxy-4-pyrone as the key step starting from kojic acid in overall yield of 4.5 %. Accordingly,

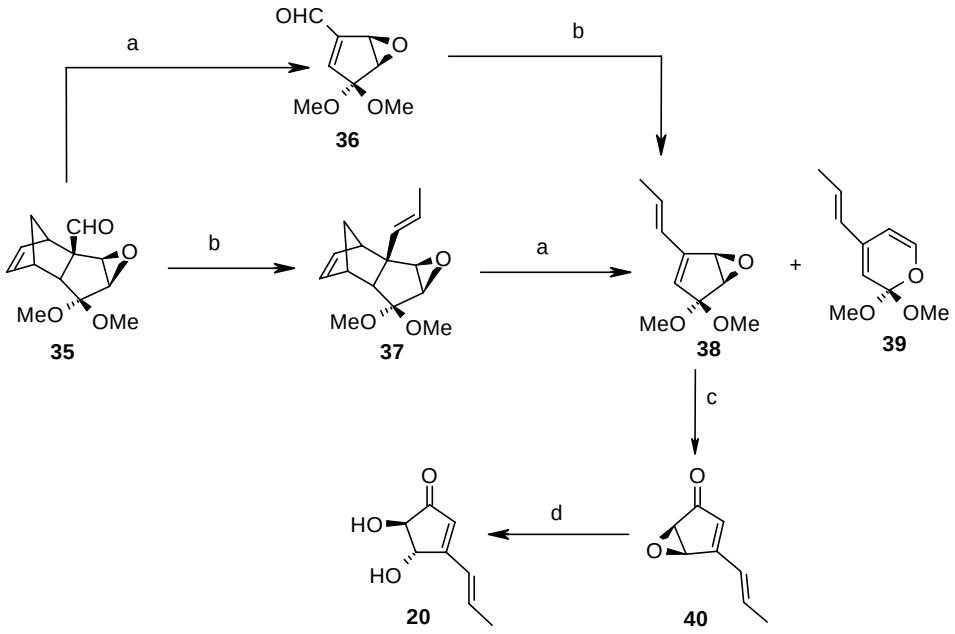


Scheme 2

Reagents and conditions: a) $SOCl_2$, reflux, 5 h. b) PPh_3, THF, 89 % c) acetaldehyde, anhyd. K_2CO_3, THF, dicyclohexyl-18-crown-6, 95 % d) Sodium cyanoborohydride (2 mol. equiv), irradiation, 0^0C, 33 min., 37 % e) Et_3N, water, 26 %

kojic acid (**30**) was converted into the compounds **33a** and **33b** in 5:1 ratio and the pure E-isomer (**33a**) in 60 % yield (schmeme 2). They found that when dilute solution of **33a** in water was irradiated at 0^0C for 33 min in presence of 2 mol. equiv. of sodium cyanoborohydride the mixtue of four products (**34a, 34b, 34c, 34d**) was obtained in 37 % yield as shown in scheme 2. Treatment of compound **34a** with triethylamine in water converted it into (±) terrein (26 % maximum yield) and recovery of some starting material.

Although this is a very short approach, it has the drawback of being non-stereoselective with respect to the configuration of the double bond and the *trans* arrangement of the hydroxy groups. Zwanenburg *et al.*[15] reported the synthesis of (±) terrein starting from functionalized tricyclo [5.2.1.0] decanone as shown in the scheme 3. The key step of the synthesis was the retro Diels-Alder reaction of the mono epoxycyclopentenone adduct which on careful hydrolysis afforded the (±) terrein.

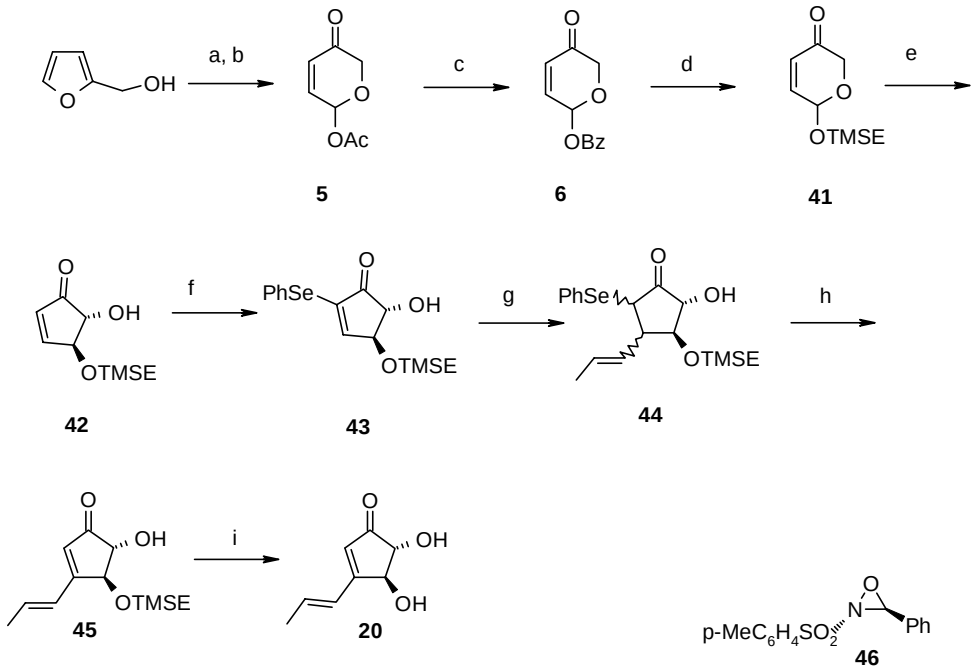


Scheme 3

Reagents and conditions: a) FVP (flash vacuum pyrolysis), 420^0C, 2 x 10^{-2} torr. b) $CH_3CH{=}PPh_3$ c) dil. HCl, r t, quantitative. d) H_2SO_4, acetone

Kolb and Hoffmann[16] reported the first chiral synthesis of (+) terrein by employing the ring contraction of 6-alkoxy-2,3-dihydro-6*H*-pyran-3-one (**41**). The precursor **41,** prepared from furfuryl alcohol as shown in scheme 4, on sequence of reactions afforded the racemic terrein (scheme 4 and 5) which was resolved with camphanic acid.

Approach A:

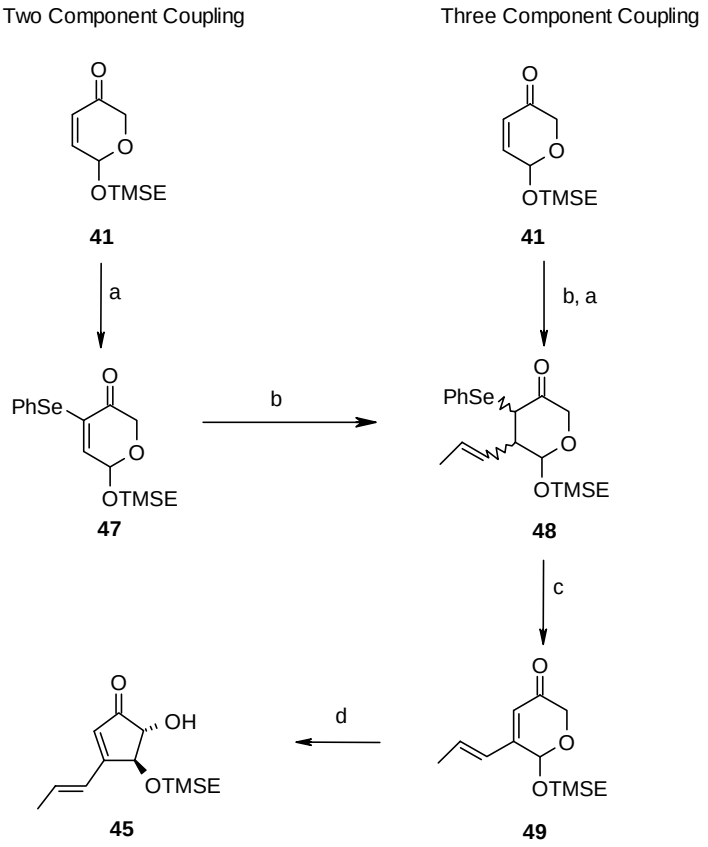


Scheme 4

Reagents and conditions: a) i) Br_2/MeOH/Et_2O ii) aq. H_2SO_4, 49 % b) $(CH_3CO)_2O$, Py c) PhCOCl, pyridine, 66 % d) $Me_3SiCH_2CH_2OH$, $ZnCl_2.OEt_2$, 84 % e) BzOH(0.5 eq), KOAc (1 eq), DMF, 80^0C, 56 % f) PhSeBr, pyridine, 81 % g) E-1-propenyllithium, $CuBr.SMe_2$, Me_2S, 70 % h) Oxaziridine (46), pyridine, 40-55 % i) $ZnCl_2$. OEt_2, 99 %.

This method involved the Michael addition of E-1-propenyllithium to compound **43**, so the double bond was lost during this step. To retain the double bond they treated compound **44** with various oxidative reagents like hydrogen peroxide, m-chloroperbenzoic acid etc. but under these conditions they obtained compound **45** in poor yields. They found that when compound **44** was treated with chiral oxaziridine **46**, the compound **45** was obtained in 40-55 % yield.

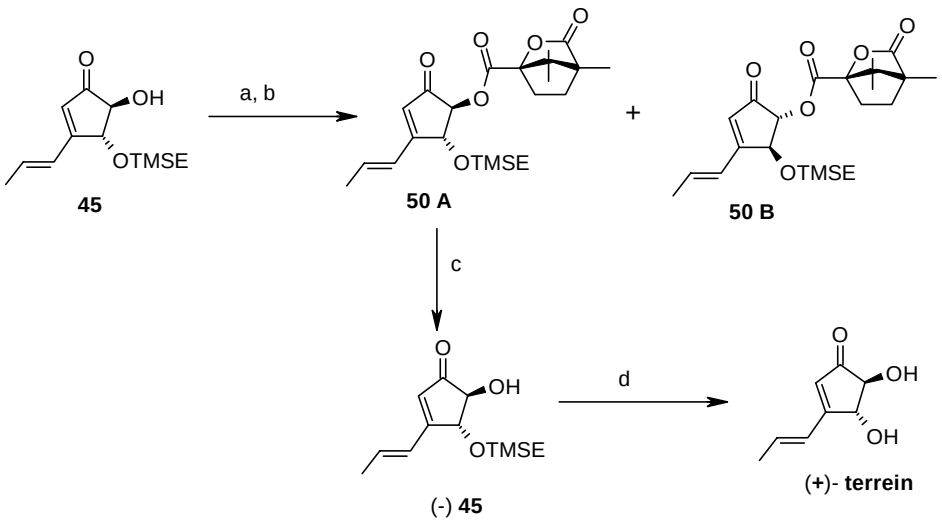
Approach B



Scheme 5

Reagents and conditions: a) PhSeCl, pyridine, 64 % b) E-1-propenyllithium, $CuBr.SMe_2$, Me_2S, -78^0C, c) Oxaziridine (46), pyridine, 57 % d) BzOH (0.5 eq), KOAc (1 eq), DMF, 80^0C, 13.5 %.

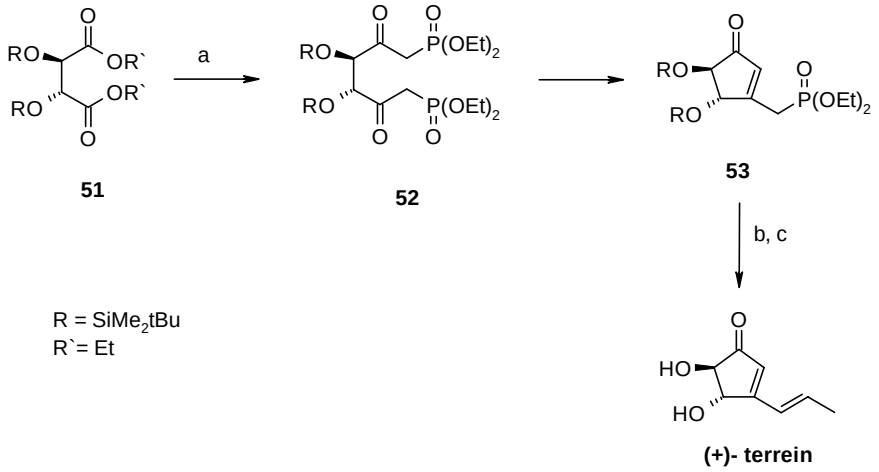
In order to obtain the chiral (+) terrein they carried out resolution of intermediate **45** with camphanic acid chloride. The diastereomers formed **(50A** and **50B** in scheme 6) were separated by column chromatography. Saponification of ester **50A** resulted in the optically active dienone (-) **45** and deprotection of the alcohol function with zinc chloride etherate afforded the naturally occouring (+) terrein [(+)-**20**].



Scheme 6

Reagents and conditions: a) Camphanic acid chloride, pyridine b) Diastereomer separation (column chromatography). c) n-Bu_4NOH, H_2O/CH_2Cl_2, 0^0C, 2 min, 39 % d) $ZnCl_2$. OEt_2, 86 %

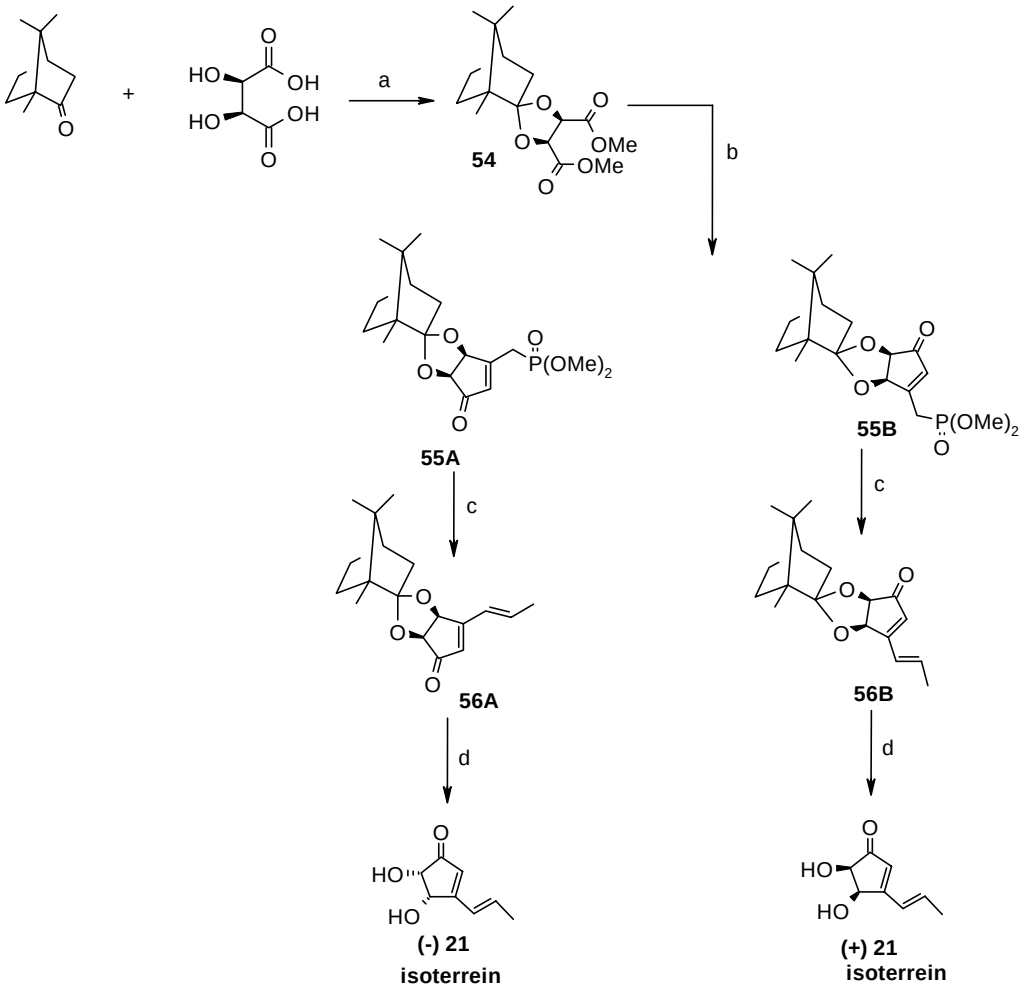
Altenbach and Holzapfel[17]synthesized (+) terrein starting from L-tartaric acid utilizing the chemistry of bis(β-oxophosphonates) as shown in scheme 7.



Scheme 7

Reagents and conditions: a) $LiCH_2PO(OEt)_2$ (4 equiv.), THF, $-78^0 \rightarrow -20^0C$, 1 h, AcOH (2 equiv.), 20 h, room temperature (RT); flash chromatography. b) NaH, THF, CH_3CHO (monomeric), 18 h, r. t.; medium-pressure liquid chromatography (MPLC): silica gel, CH_2Cl_2. c) Et_4NCl (6.5 equiv.), $KF.2H_2O$ (6 equiv.), CH_3CN, 30 h, r. t., MPLC: silica gel, CH_2Cl_2.

Mikolajczyk *et al.*[18] reported the synthesis of (+) and (-) isoterrein, the more stable isomers of terrein in which the hydroxyl groups are *cis* oriented, starting from meso-tartaric acid (scheme 8).



Scheme 8

Reagents and conditions: a) (+) Camphor, $(MeO)_3CH$, MeOH, H_2SO_4 cat., r. t., 5 d. b) $(MeO)_2P(O)CH_2Li$ (4 equiv), THF, -78^{0}C → r. t.; benzene-H_2O, reflux 3 h. c) BuLi, THF, -78^{0}C, CH_3CHO, r. t., 12 h. d) H_2O/dioxan, aq. HCl (36 %), 50^{0}C, 3-4 h.

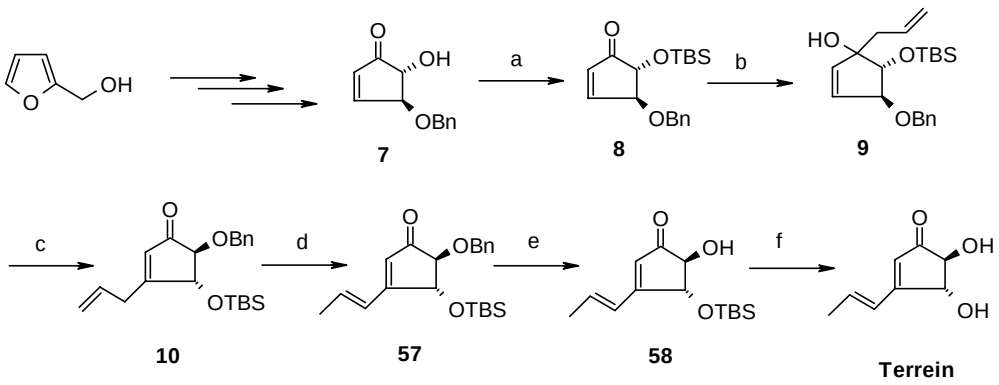
The reaction of meso-tartaric acid with (+)-camphor and methyl orthoformate resulted in the single diastereoisomer **54**. The reaction of **54** with dimethyl lithiomethanephosphonate resulted in the 3-phosphonomethylcyclopentenone **55** in 59 % yield. Fractional crystallization from hexane/acetone led to diastereoisomers **55A** and **55B**. The Horner-Wittig reaction of **55A** and **55B** with acetaldehyde furnished the protected isoterreins **56A** and **56B**. Deprotection of the diol moiety in **56A** and **56B** by acid hydrolysis afforded (-) and (+) isoterrein **21**.

3.2.2 PRESENT WORK:

Substituted cyclopentenone moiety has been of great interest to us during our research under new drug discovery programme, which is described in chapter 1 of this thesis. The structural features of these small molecules terrein and isoterrein attracted our attention.

As described in chapter 1 we have already synthesized 4/5-hydroxy cyclopentenone synthons. Consequently the synthesis of terrein and isoterrein was undertaken.

We planned the synthesis of terrein using the ring contraction of 6-alkoxy-2,3-dihydro-6*H*-pyran-3-one. Kolb and Hoffmann[16] reported the synthesis of terrein using this intermediate but the key step in their synthesis involved Michael addition of E-1-propenyllithium to cyclopentenone so that the double bond in cyclopentenone ring was lost during this step and to retain the double bond they had to use chiral oxaziridine. To overcome the drawbacks of above method, we used the chemistry of rearrangement of tertiary allylic alcohol **9** using pyridinium chlorochromate (Corey's reagent) and then isomerization of terminal double bond with rhodium trichloride, to get the conjugated cyclopentenone **57** as shown in scheme 9.

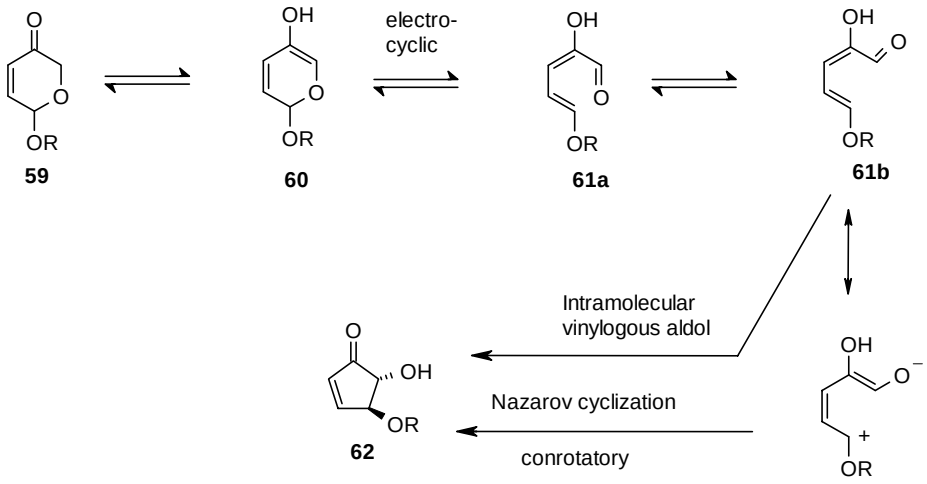


Scheme 9

Reagents and conditions: a) TBDMSCl, DMAP, Et_3N, r. t., 4 h. b) Mg, THF, allyl bromide, 0^0C-r.t., 14 h c) PCC, DCM, r. t., 8 h d) $RhCl_3.3H_2O$ 4 mol %, benzene: EtOH, reflux, 20 h. e) $TiCl_4$, DCM, r. t., 30 min. f) TBAF, THF, r. t., 2 h.

The synthesis of building block **8** was carried out as described in the section I of this chapter by known chemical transformations[19-22] which on further chemical transformations resulted in the intermediate **10.**

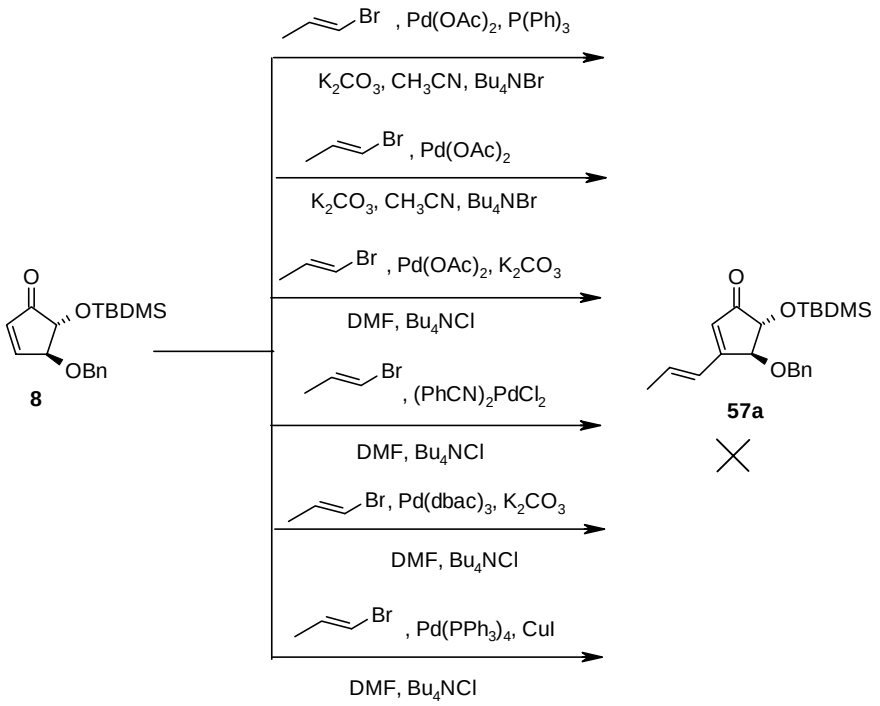
Kolb and Hoffmann proposed a mechanism for the ring contraction involving specific acid catalysis. They prosposed that the enolization of the compound **59** is faster than subsequent electrocyclic opening of oxacyclodiene **60**. Ring closure of **61b** can be either an aldol or Nazarov type process as shown in scheme 10.



Scheme 10

The terminal double bond of compound **10** was isomerized to conjugated double bond by heating with rhodium trichloride[23] in ethanol-benzene at reflux temperature to afford the compound **57** in 52.5 % yield. A doublet at δ 1.93 for 3 protons in the ^{1}H NMR spectrum and a band at 1700 cm^{-1} in the IR spectrum indicated the formation of compound **57**, ^{13}C NMR spectrum also confirmed the formation of the compound **57**. The deprotection of benzyl protection was carried out with $TiCl_4$[24] in dry dichloromethane to give compound **58** in 62 % yield. The treatment of the compound **58** with tetra-butylammonium fluoride at room temperature afforded the (±) terrein **20** in 60 % yield.

After achieving the synthesis of (±) terrein (**20**) by above route we planned to synthesize it by shorter route using Heck reaction method. We tried Heck reaction of 1-bromopropene with intermediate **8** under various conditions as shown in scheme 11 but the expected product **57a** was not obtained.

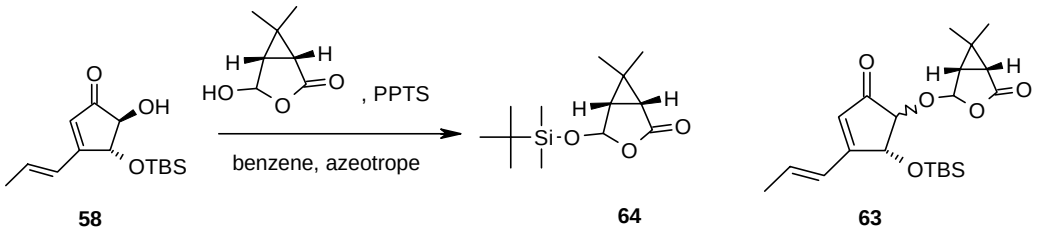


Scheme 11

ATTEMPTED RESOLUTION OF THE COMPOUNDS 58 AND 7:

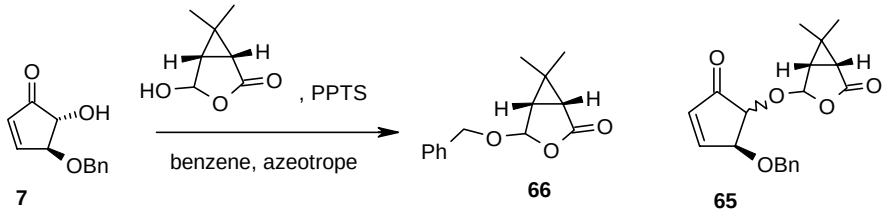
We attempted the resolution of the intermediate **58** in order to get optically active terrein. Treatment of the intermediate **58** with (1R, 2S)-cis-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[25] (caronaldehyde) and PPTS in benzene azeotropically, was expected to form the diasteroisomeric mixture of compound **63**, the diastereoisomers of which were to be separated. The compound **58** was very sensitive to these conditions and it did not give the expected compound **63,** but it formed compound **64** (scheme 12).

We thought that the cleavage of –OTBS group may be due to the acidic nature of PPTS used for the reaction. Therefore we planned to resolve the intermediate **7**. Treatment of the intermediate **7** with (1R, 2S)-cis-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid[25] (caronaldehyde) and PPTS in benzene with azeotropic removal of water was expected to form the diasteroisomeric mixture of compound **65**, but it resulted in the formation of compound **66** (scheme 13).



58 **64** **63**

Scheme 12



7 **66** **65**

Scheme 13

It is noteworthy that the tert-butyldimethylsilyl as well as benzyl ether in the intermediates **58** and **7** respectively underwent transetherification with caronaldehyde almost quantitatively leading to the products **64** and **66**. In the above experiments, the free hydroxy group did not participate in the reaction.

The resolution of (±) terrein derivative **45** was reported[16] using camphanic acid chloride as the resolving agent wherein the protecting group was trimethylsilyl ethyl.

To our knowledge transetherification observed in our experiments is unprecedented and needs further exploration. The diastereomer formation was attempted at room temperature wherein the starting materials (the intermediates **58** and **7**) remained unreacted and at the elevated temperature transetherification was observed. Considering the limitations in using caronaldehyde as resolving agent resolution of (±) terrein derivatives was not persued further.

3.2.3 CONCLUSION:

Synthesis of the racemic terrein was accomplished from intermediate **9** by the method of PCC mediated rearrangement and double bond isomerization in good yields.

The coupling of 1-bromopropene with the intermediate **8** under Heck reaction conditions was unsuccessful in our hands.

Resolution of (±) terrein using caronaldehyde as resolving agent resulted in the transetherification instead of the expected ether formation with the free hydroxy group.

3.2.4 EXPERIMENTAL:

5-Benzyloxy-4-(tert-butyldimethylsilanyloxy)-3-propenyl-cyclopent-2-enone (57):

In a 50 ml two neck round bottom flask with reflux condensor and two way stopcock, 3-allyl-5-benzyloxy-4-(tert-butyldimethylsilanyloxy)-cyclopent-2-enone (0.40 g, 1.11 mmol) was taken and the flask was flushed with argon. 20% Ethanol-benzene (32 ml) and catalytic amount of rhodium chloride trihydrate (ca. 0.008 g) were added and the reaction mixture was refluxed for 16 h. TLC showed the completion of the reaction. Then the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (5% ethyl acetate in pet ether) to afford 5-benzyloxy-4-(tert-butyldimethylsilanyloxy)-3-propenyl-cyclopent-2-enone (0.21 g, 52.50%) as a colorless liquid.

Colorless liquid; **IR** ($\upsilon_{max,}$ $CHCl_3$): 1640, 1700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$+CCl_4): δ 0.14 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 1.93 (d, *J* = 5 Hz, 3H), 3.98 (bs, 1H), 4.69 (d, *J* = 10 Hz, 1H), 4.85 (bs, 1H), 5.22 (d, *J* = 10 Hz, 1H), 6.01 (s, 1H), 6.27 (d, *J* = 15 Hz, 1H), 6.50-6.60 (m, 1H), 7.28-7.44 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$+CCl_4): δ -5.07, -4.18, 18.02, 19.20, 25.78 (3C), 72.62, 76.54, 86.14, 124.94, 125.48, 127.77 (2C), 128.33 (3C), 137.75, 139.08, 168.58, 203.00; **Mass** (m/e): 358 (M+1); Anal. Calcd. For $C_{21}H_{30}O_3Si$: C 70.35; H 8.43; Si 7.83 %. Found: C 70.49; H 8.60; Si 7.96 %.

4-(tert-Butyldimethylsilanyloxy)-5-hydroxy-3-propenyl-cyclopent-2-enone (58):

In a 50 ml two neck round bottom flask, 5-benzyloxy-4-(tert-butyldimethylsilanyloxy)-3-propenyl-cyclopent-2-enone (0.50 g, 1.40 mmol) was taken under argon, dry dichloromethane (15 ml) was added though syringe and was stirred for 15 min. $TiCl_4$ (0.20 ml) was then added slowly and the reaction mixture was stirred for 2 h. The TLC showed completion of reaction. The reaction mixture was poured into ice-water (50 ml) and the organic layer was successively washed with saturated $NaHCO_3$ and water. The organic layer was dried over sodium sulphate and the solvent was removed under reduced pressure. Silica gel column chromatography purification (10% ethyl acetate in pet ether) afforded 4-(tert-butyldimethylsilanyloxy)-5-hydroxy-3-propenyl-cyclopent-2-enone (0.23 g, 62.0 %) as yellowish liquid.

IR ($\upsilon_{max,}$ $CHCl_3$): 1718, 3423 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$+CCl_4): δ 0.21 (s, 3H), 0.22 (s, 3H), 0.92 (s, 9H), 1.91 (d, *J* = 4 Hz, 3H), 3.47 (bs, 1H), 4.14 (d, *J* = 2 Hz, 1H), 4.75 (d, *J* = 2 Hz, 1H), 6.04 (s, 1H), 6.25 (d, *J* = 18 Hz, 1H), 6.50-6.71 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CCl_4): δ -5.68, -4.61, 17.66, 18.95, 25.42 (3C), 77.32, 81.33, 123.38, 124.41, 139.81, 169.51, 203.25;

Mass (ESI): 269 (M-1); Anal. Calcd. For $C_{14}H_{24}O_3Si$: C 62.64; H 9.01; Si 10.46 %. Found: C 62.75; H 9.13; Si 10.56 %.

4,5-Dihydroxy-3-propenyl-cyclopent-2-enone (20):

In a 25 ml two neck round bottom flask with two way stopcock, 4-(tert-butyldimethylsilanyloxy)-5-hydroxy-3-propenyl-cyclopent-2-enone (0.055 g, 0.20 mmol) was taken under argon, dry tetrahydrofuran was added though syringe and the flask was cooled to 0^0C. TBAF (1 M., 0.05ml, 0.21 mmol) was then added slowly and the reaction mixture was stirred at the same temperature for 15 min. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The TLC showed completion of reaction. The reaction was quenched with saturated brine solution and stirred vigorously for 30 min. It was then extracted with ethyl acetate (3 x 15 ml), organic layer was washed with water, dried over sodium sulphate, solvent removed under reduced pressure and the residue purified by chromatography over silica gel (10 % acetone in pet ether) to give the 4,5-dihydroxy-3-propenyl-cyclopent-2-enone (0.020 g, 60 %) as a white solid.

M. p. 94-96^{0}C (lit.[16] 94-95^{0}C); **IR** ($\upsilon_{max,}$ KBr): 1685, 3420 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.92 (d, *J* = 6 Hz, 3H), 4.30 (d, *J* = 2 Hz, 1H), 4.86 (bs, 1H), 5.97 (s, 1H), 6.37 (d, *J* = 16 Hz, 1H), 6.65-6.95 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ acetone d_6): δ 19.78, 76.44, 81.94, 125.09, 125.42, 141.82, 169.27, 203.83; **Mass** (ESI): 155 (M+1); Anal. Calcd. For $C_8H_{10}O_3$: C 62.33; H 6.54 %. Found: C 62.46; H 6.63 %.

Attempted resolution of the 4-benzyloxy-5-hydroxy-cyclopent-2-enone (7):

In a 100 ml single neck round bottom flask equipped with a Dean-Stark apparatus, were placed racemic 4-benzyloxy-5-hydroxy-cyclopent-2-enone **(7)** (1.50 g, 7.35 mmol), (1R, 2S)-*cis*-2-formyl-3,3-dimethycyclopropane-1-carboxylic acid (a cyclic hemiacylal form) (1.26 g, 8.87 mmol, $[\alpha]_D^{25}$ –105°, c 0.5 C_2H_5OH), pyridinium *p*-toluenesulfonate (0.922 g, 3.67 mmol) and dry benzene (40 ml). The mixture was heated at reflux under stirring for 20 h. The TLC analysis indicated completion of the reaction. Then the benzene was removed under reduced pressure, the residual material was dissolved in ethyl acetate (50 ml) and washed twice with water followed by saturated $NaHCO_3$ solution (20 ml) and three times with water. The organic solution was dried and concentrated on rotary evaporator to give crude mixture of condensation product (2.33 g, 84 %). The purification of the condensation product with column chromatography afforded the 4-benzyloxy-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one (**66**) (1.23 g, 63 %) as colorless thick liquid.

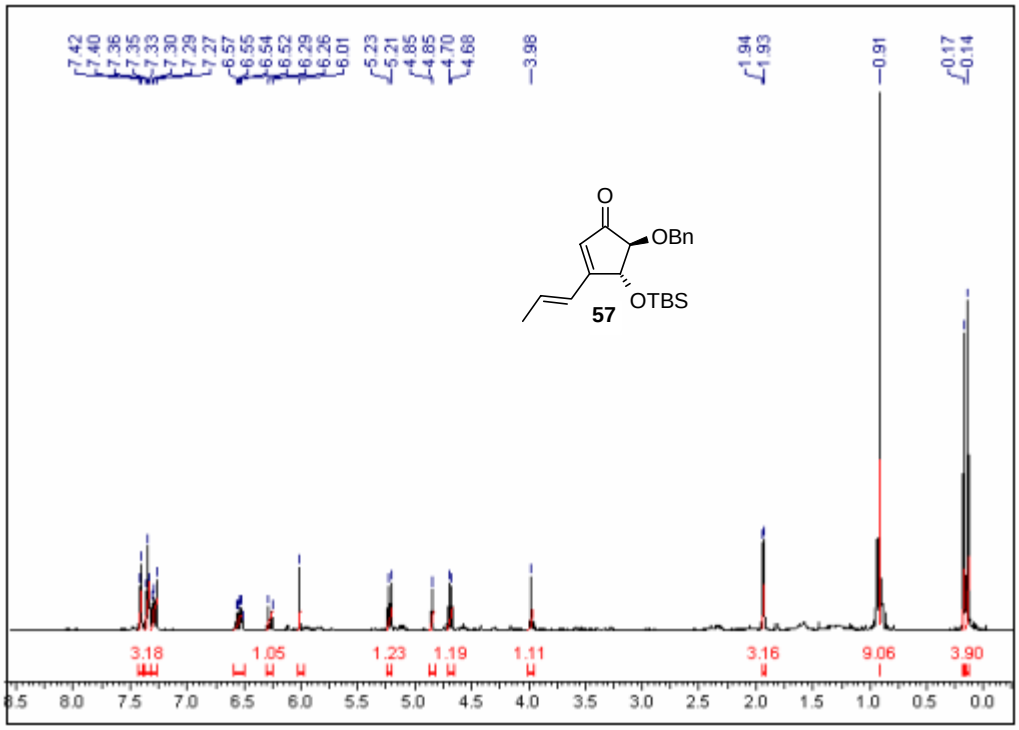
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.07 (s, 3H), 1.92 (d, *J* = 6 Hz, 1H), 2.01 (d, *J* = 6 Hz, 1H), 4.53 (d, *J* = 10 Hz, 1H), 4.78 (d, *J* = 10 Hz, 1H), 5.16 (s, 1H), 7.10-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.47, 23.92, 24.69, 29.29, 34.77, 70.02, 99.94, 127.36, 127.58 (2C), 128.02 (2C), 136.07, 172.64; **Mass** (m/e): 232 (M^+); Anal. Calcd. For $C_{14}H_{16}O_3$: C 72.39; H 6.94; Found: C 72.51; H 7.08.

Attempted resolution of 4-(tert-butyldimethylsilanyloxy)-5-hydroxy-3-propenyl-cyclopent-2-enone (58)

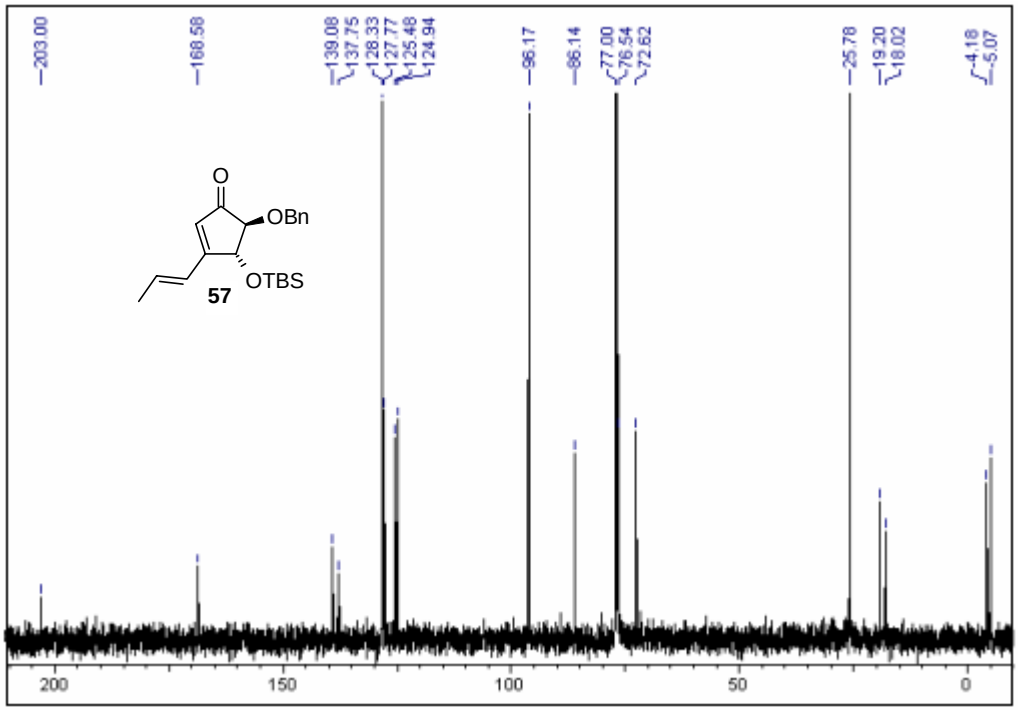
Under similar conditions as described above, treatment of the compound **58** with caronaldehyde resulted in the formation of the 4-(tert-butyldimethylsilanyloxy)-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one **(64)** (0.079 g, 79 %) as colorless liquid.

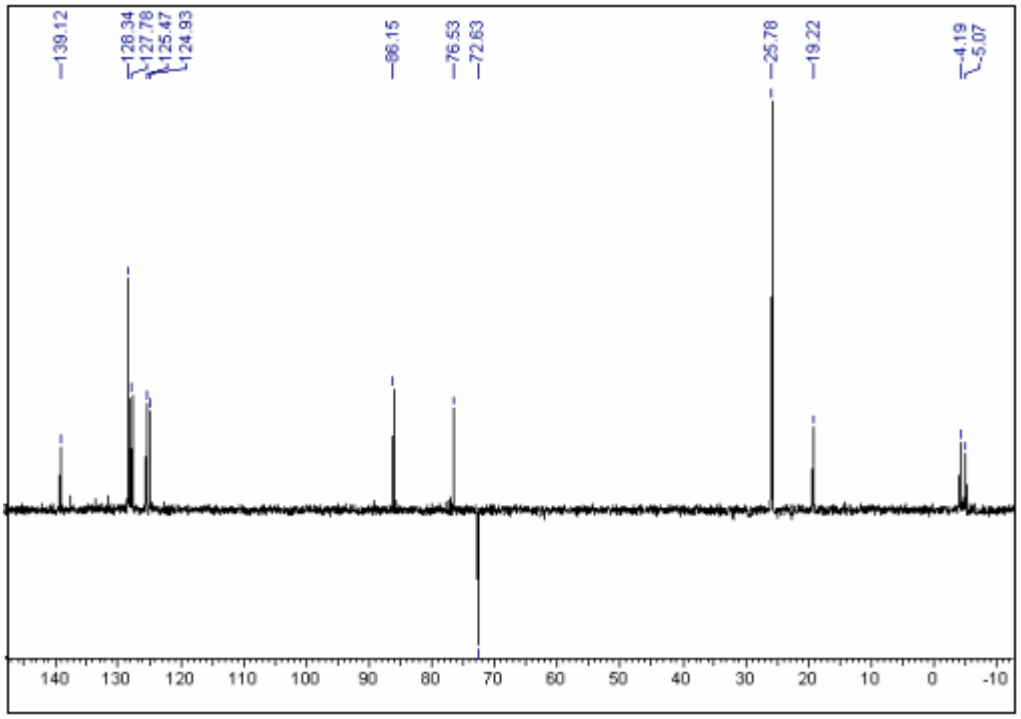
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.17 (s, 6H), 0.92 (s, 9H), 1.16 (s, 3H), 1.19 (s, 3H), 2.01-2.05 (m, 2H), 5.43 (s, 1H); **Mass** (m/e): 256 (M^+).

^{1}H NMR spectrum of the compound 57:

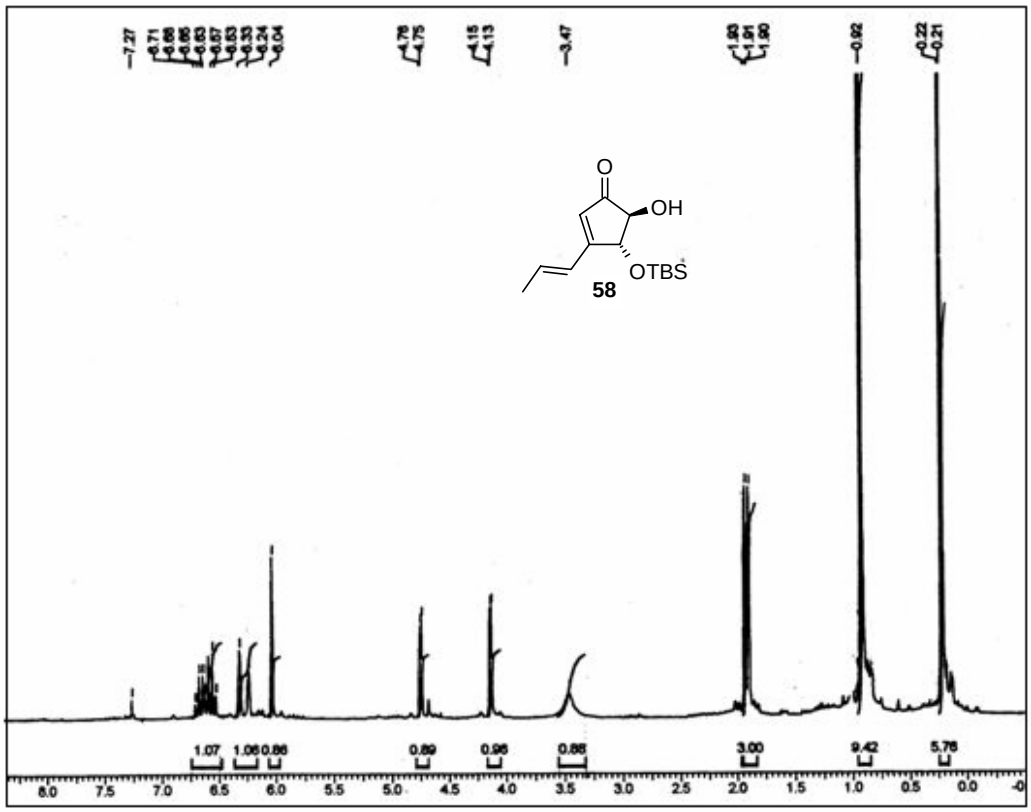


^{13}C NMR spectra of the compound 57:

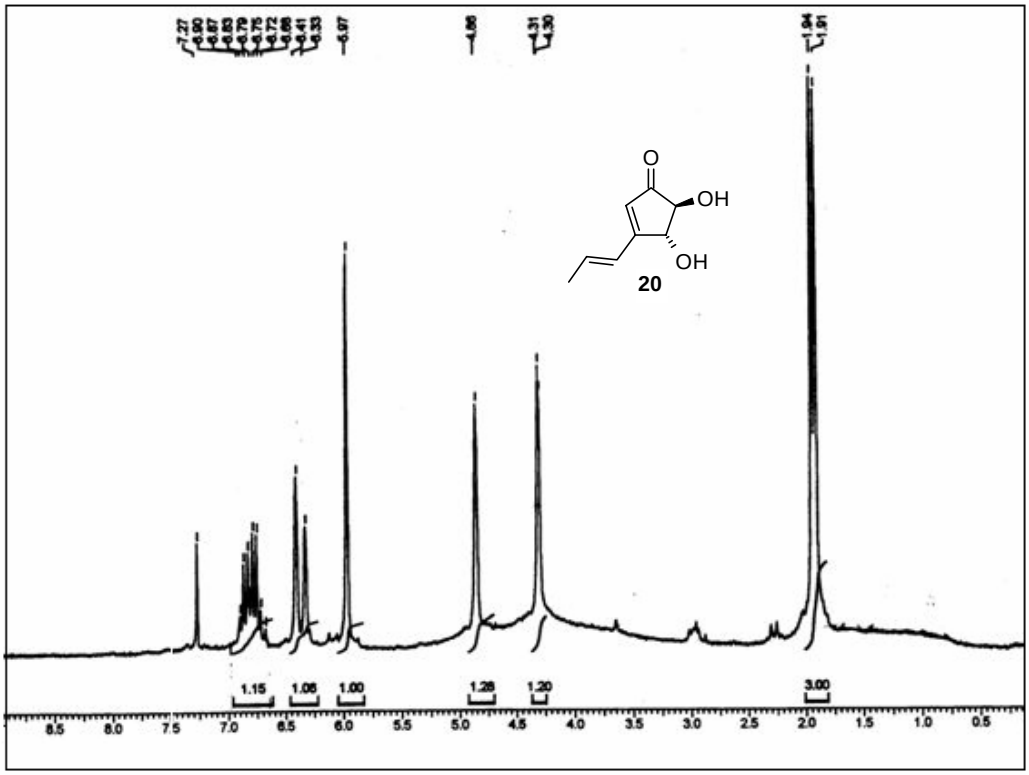




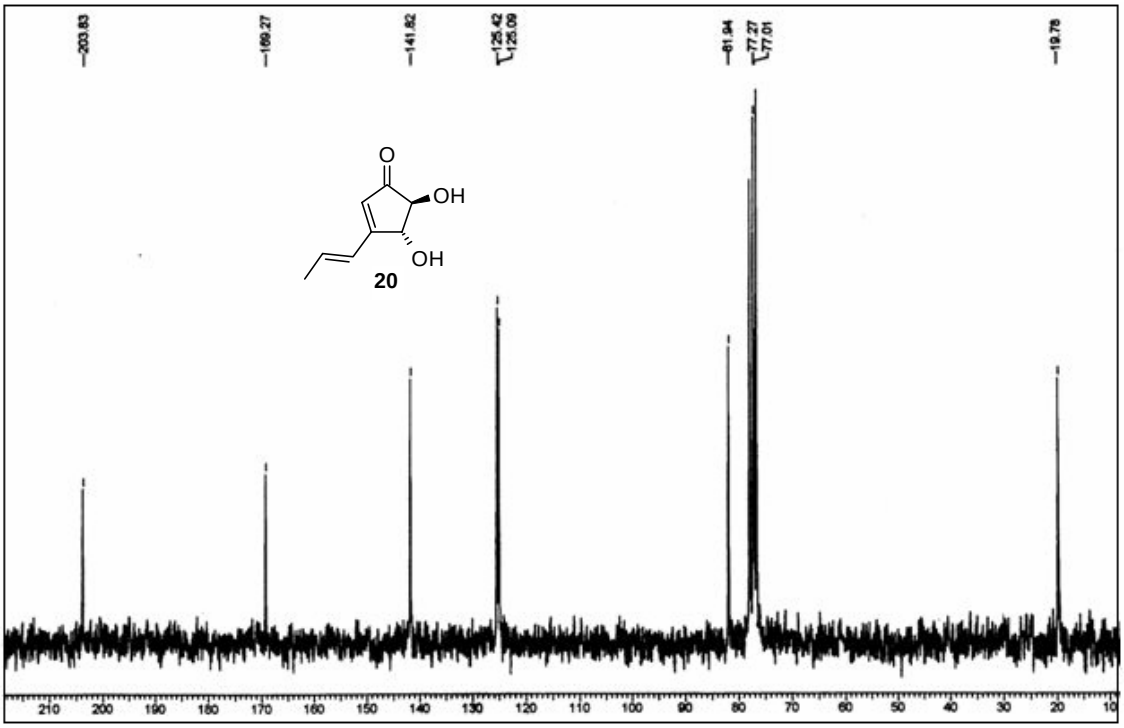
^{1}H NMR spectrum of the compound 58:

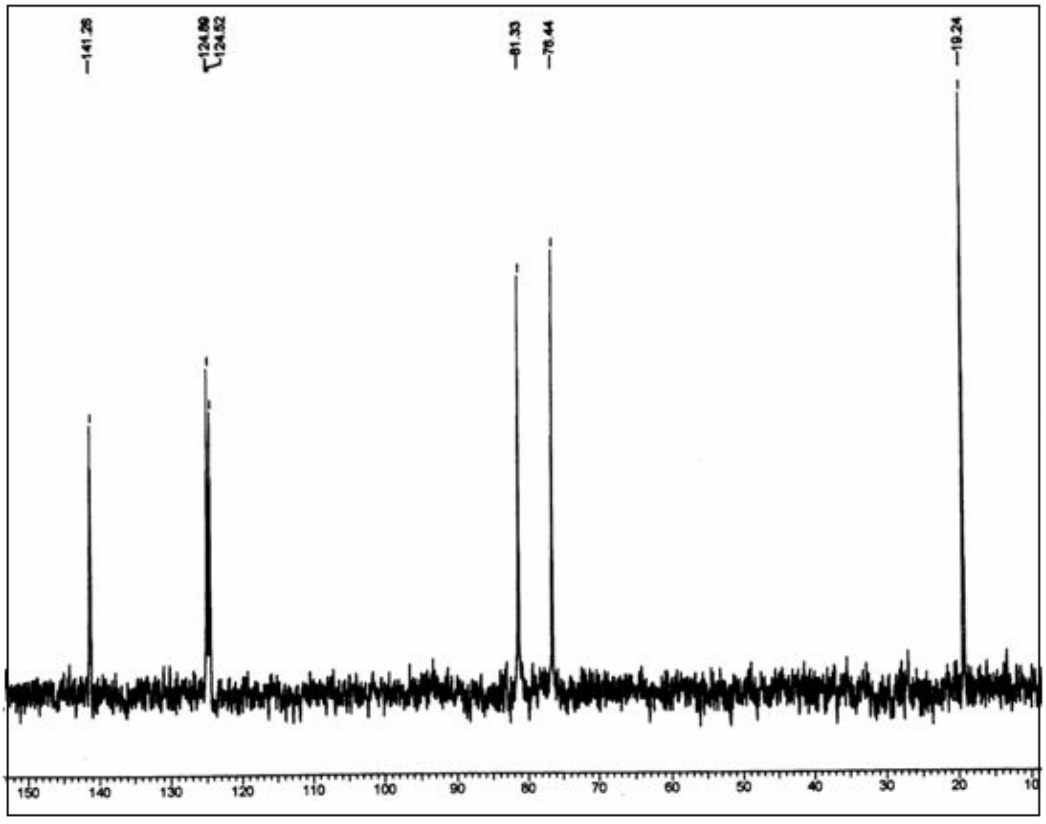


^{1}H NMR spectrum of the compound 20:

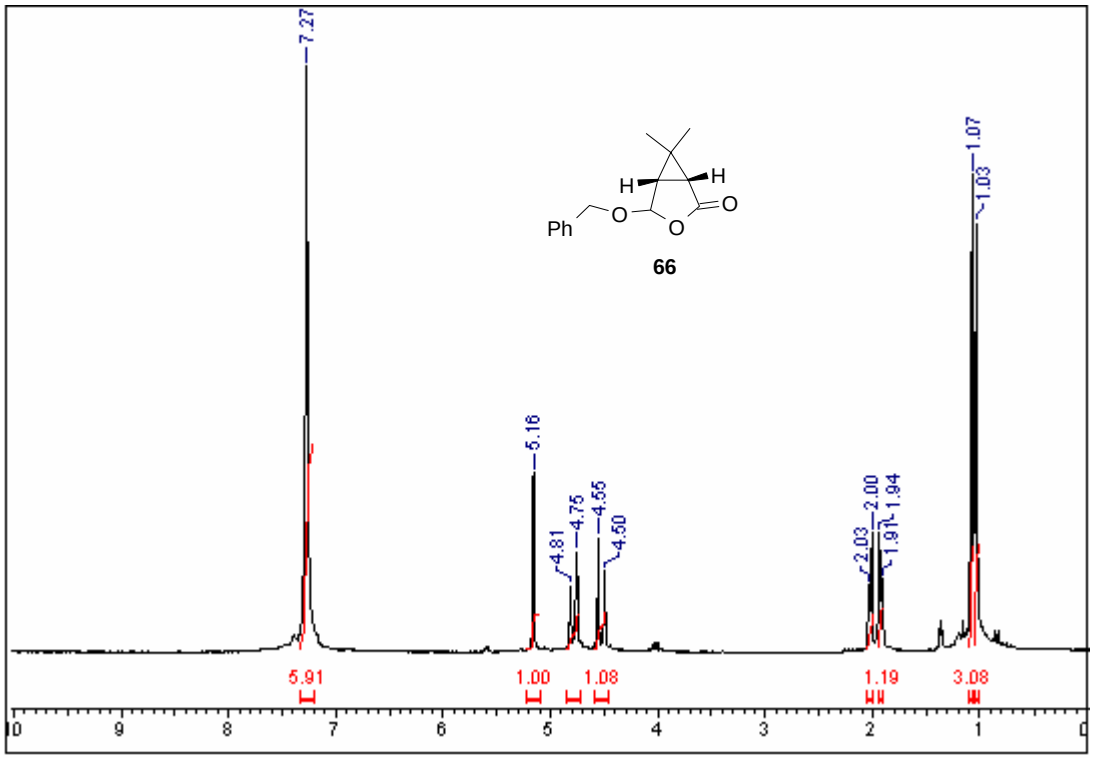


^{13}C NMR spectra of the compound 20:

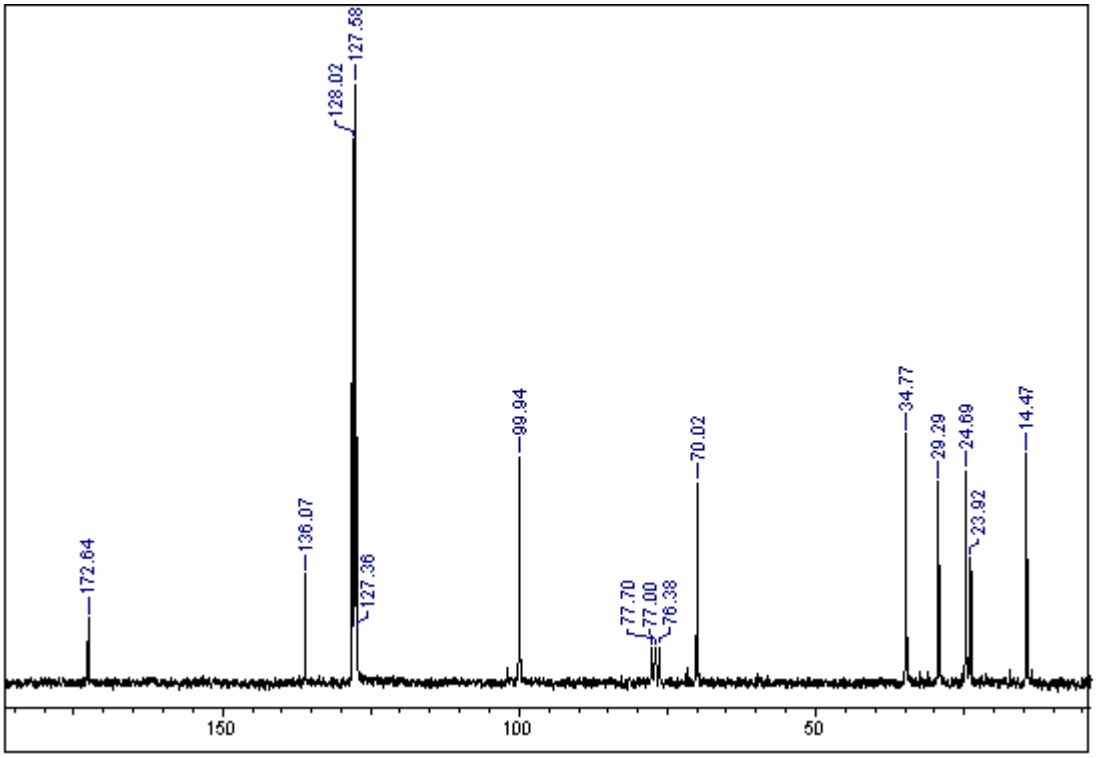




^{1}H NMR spectrum of the compound 66:



^{13}C NMR spectrum of the compound 66



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