Dissertation Report

for

M.Sc degree

on

Attempts Towards Total synthesis of

(±) Spirooliganone-A

Batch-2013- 2015

Submitted By

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Certificate

This is to certify that the THESIS presented and performed experiments in this project entitled "Attempts Towards Total synthesis of(±) Spiroliganone-A" is a bonafide record work done by **Mr. Punarbasu Bhattacharjya,** student of NIT Rourkela, for requirements of the degree of Master of Science for his research project.

He has successfully completed his project work under my guidance in the academic year2014-2015 in this institute. I wish him all the best for his future.

Dr. Debayan Sarkar
Project Guide

ACKNOWLEDGEMENT

It is my privilege to express the feeling of my heart by dedicating this page to people who had been the living inspiration for me for their co-operation and relentless encouragement.

I express my deepest sense of gratitude and to **Dr.Debayan Sarkar,**(Asst. Professor, Department of Chemistry, NIT Rourkela)**,**for his ingenious guidance and constructive criticism throughout the period of projectwork.

I acknowledge the Director and Head of the Chemistry Dept., NIT Rourkela for necessary permission to work and providing departmental infrastructure facilities.

I owe my deep sense of honour and gratitude to my esteemed Nilendri Didi, Monojda, Sagarika Didi, Rahul and friends for their hearty support and cooperation in various stages of preparation of this project work and project report.

I owe my indebtedness to my beloved parents and sister for their encouragement and inspiration throughout the work.

Punarbasu Bhattacharjya

413CY2006

DECLARATION

The work ***"Attempts Towards Total synthesis of (±) Spirooliganone-A"*** embodied in this report and submitted to NIT Rourkela has been carried out by me as a one year Project Fellow during July 2014 – April 2015at NIT Rourkela under the guidance of Dr. Debayan Sarkar . This work is original and has not been submitted for any other degree of this or any other University or Institue.

Punarbasu Bhattacharjya

413CY2006

Contents

Abstract:

The group has recently reported a novel protocol of oxidative dearomatization of napthols using phenyl selenium bromide (PhSeBr). The progress through this process towards the natural product synthesis especially the Spiroliganone system in the different conditions are the main goal for this work .Target was mainly the synthesis of oxa-spirane core through oxidative de-aromatization of the phenolic ring.

Introduction:

Organic synthesis has become the initiation point of interdisciplinary research in Chemistry, Biology as well as in medicine from the last few decades . Synthesis of bioactive molecules has been always the point of attraction, as the natural resources are unable to meet the huge demands of available medicines. Development of the facile routes to accomplish successful multistep organic synthesis, leading to the development of bioactive natural products is one of the most challenging fields in chemistry in academia and industry throughout the world. Useful efforts are being made to develop pathways to shorten the hectic multistep synthesis. Primarily, our interest lies in Oxidative Dearomatization of unprotected systems like phenol, Naphthols, cresols, coumarins etc using cheaper reagents. De-aromatization can lead to the several compounds containing chiral carbons and will provide synthetically useful hydrocarbons and allylic frameworks.

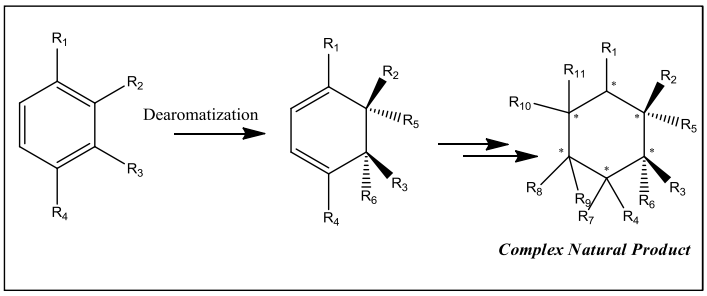


Figure-1

The 3D-framework comprising a bunch of chiral centres can be easily developed from a “Cyclo-hexa dienene intermediate,” (Figure-1) an envisoned one resulting from Oxidative Dearomatization of abundant arenes.

Since, the dearomatization offers unique strategic opportuniety to circumvent the inherent ortho/para selectivity of electron-rich aromatic systems, the dearomatization strategy can also be used in the synthesis of multi-functionalized aromatic compounds that are difficult to prepare by electrophilic substitution reactions.

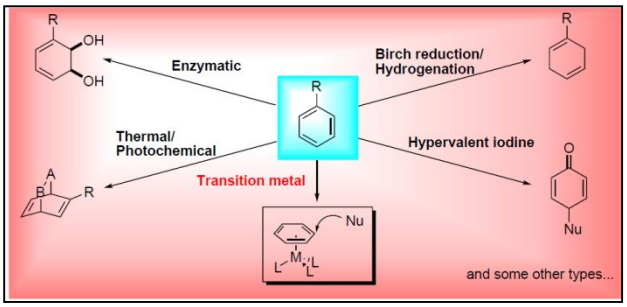


Figure-2

The following scheme illustrates some of the common strategies available (Figire-2).

The Enzymatic, Photochemical, Birch reduction procedures suffer from very low yields and are also not turn out to be generalized methodologies. Transition metal catalysis are very expensive.

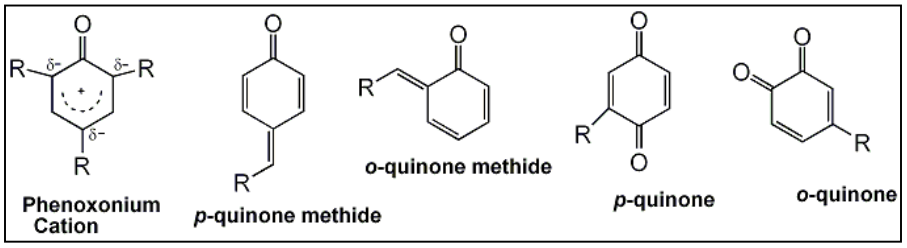


Figure-3

The enzymatic de-aromatization (Figure-2) occurs by the application of monooxygenase eukaryotes, dioxygenase prokaryotes or benzoyl Co-A reducatse by the formation of epoxides, diols, diene derivatives respectively. Although this is advantageous for the synthesis of enantioselective dihydroxylation with the functional group tolerance and aromatic heterocycles but it doesnot lead to any C-C bond formation.

Thermal/photochemical dearomatizations (Figure-2) are done mainly by the Diels-Alder reaction or by the photo induced reactions. The advantage is the atom economic character of the C-C bond formation reaction together with the limitations of the substate scope and harsh conditions.

The birch reduction (Figure-2) can lead to the position selectivity but need to the harsh conditions.

But the most popular de-aromatization process is the oxidative de-aromatizationas per the literature by the hypervalent iodine reagents (Figure-2). It has catalytic, asymmetric as well as mild condition advantage but the main problem of this reaction is that it is only applicable upon the phenolic compounds.

The I(+3) oxidants being cheap and easy to prepare is being used for this purpose exhaustively. The Organic chemists are giving tireless efforts throughout years on oxidative use of hypervalent Iodine compounds such as Phenyl Iodine diacetate (PIDA), $NaIO_4$, *o*-iodoxy benzoic acid(IBX) etc, many of these are compared with "Biomimetic" protocols. The drawbacks associated with the iodine mediated reagents is that phenols on oxidation results into intermediates such as phenoxonium cation, *p*-and *o*- quinone and *p*- and *o*- quinone methide(Figure-3) which are difficult to control, hence resulting into a huge wastage of the substrates and ultimately unsatisfactory yields. One needs an external or internal nucleophile to stabilize the intermediates to deliver a stable product (Figure-4).

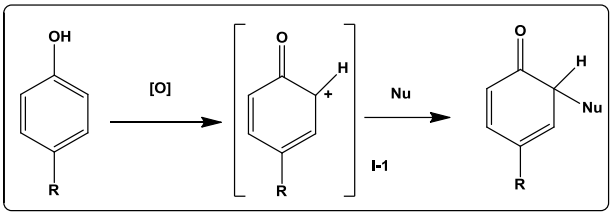


Figure-4

The main (I^{+3}) oxidants utilised for such oxidative de-aromatization reactions are $PhI(OAc)_2$, $PhI(TFA)_2$, F─$PhI(TFA)_2$. A wide variety of natural products has been utilized using such reactions as a key step. In an organic chemist's perseverance, the oxidative dearomatisation phenols proceed through a rapid equilibrium which involves a cyclohexadienone and is stabilized through a nucleophilic attack. However the presence of cyclohexadienyl cation (I-1)(Figure-4) is questionable whether is it a concerted step and can be answered with the formation of suitably substituted diastereomers. Obviously the stability of the Intermediate-1 is also not clearly understood till now.

The cyclohexadienones produces a wide variety of complex 3D organic structures:

- Tandem [4+2] cycloaddition – *Danishefsky , JACS 2006, 128,16440*
- Triggering Diels-Alder cycloaddition (IMDA) -*Liao, Org.lett. 2007, 9, 4563*
- Michael Addition (MEM) – *Porco, Jr.JACS 2007, 129, 12682*
- Retro Diels-Alder / Diels Alder sequence- *Snyder, JACS 2009, 131,1745*
- Claisen Dearomatisation/ Diels- Alder cycloaddition- *Theodorakis, PNAS 2004, 101, 12030*(Figure-5)

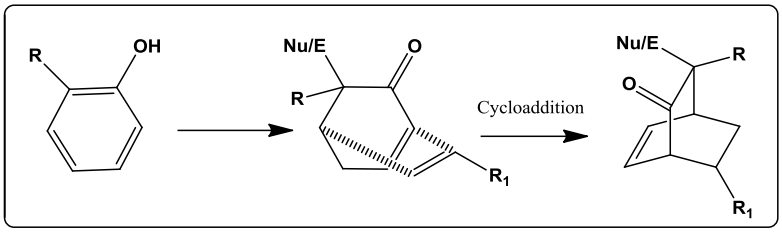


Figure-5

A couple of natural products (Figure-6) has been brought under the purview of synthesis employing the oxidative dearomatisation as a key step.

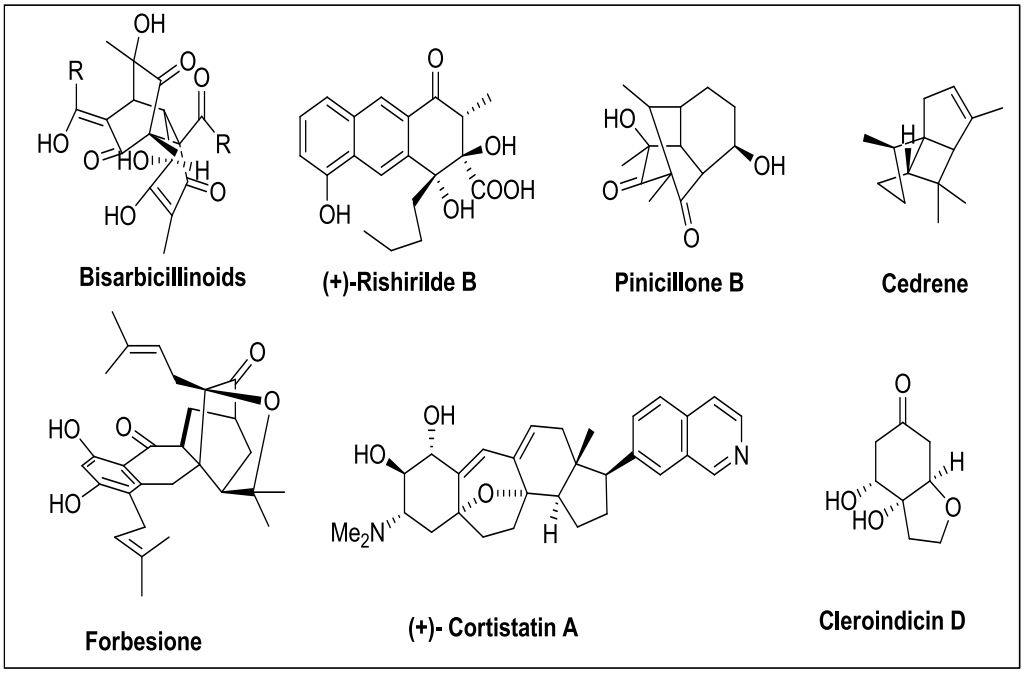


Figure-6

Thus, it acts as a key step for solving molecular intricacy. The oxidative transformations of phenols lead to cyclohexadienones, oxidative coupling, ortho-hydroxylation and ring cleavage reactions. Specifically, the cyclohexadienone is expected to be a suitable scaffold (Figure-7) for different interesting transformations like 1, 2-addition, Diels- Alder Reaction, Cyclopropanation followed by ring expansion etc.

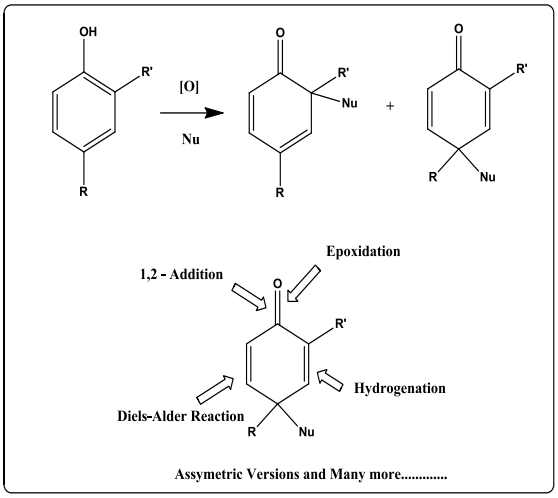


Figure-7

Specifically, attempts have been accomplishing for the synthesis ofmade initiated for synthesing an important natural product namely ***Spirooliganone*** **A**(Figure-8) and so far there is only one report of the total synthesis of this natural product by Xie et.al.(16)

Spiroliganone A(Figure-8) which was found to exhibit potent activities against Coxsackie virus B3 and influenza virus A (H3N2). Spiroologanones possess a cyclopropano pyranose ring.

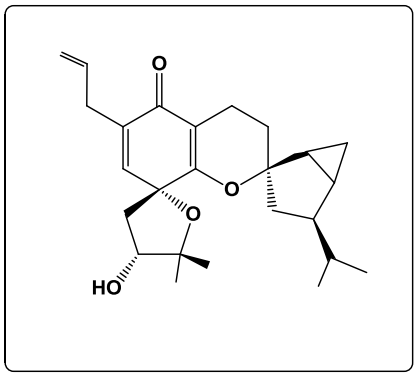


Figure-8

SPIROLIGANONE A

As it has been already hypothesized in proposal of retro-synthesis and biosynthesis that these structural units could be accessed directly and also atom-economically, simply by site-specific de-aromatization of appropriate phenols bearing varieties of functional groups like an olefin side chain and the coumarin groups at the corresponding positions. The structural and functional diversities conferred by such a fascinating ortho and para-fused spiro-bicycles are unusual and highly challenging. Indeed, there are some reports in literature on various methods for dearomatization of phenolic substances, particularly those involving hypervalent iodine reagent - mediated formation of widely useful ortho- and para-quinone monoketals (i.e., de-aromatized rings featuring the formed C-O or C-N bonds). This emerges fully C-C bond formation enabled

phenol dearomatization with the quaternary stereogenic centers exactly at the spiro-ring junctions.

As per the best of our knowledge, there appears to be only two studies by Pettus and Feringa and co-workers, respectively, both reported in 2011,that have successfully realized selective ortho-dearomatization of phenols and naphthols with strategic C-C bonds formation for the targeted construction of spiro-carbocycles. The substrate scope was limited, and phenols have proven to be more challenging motifs than naphthols for the events of oxidative de-aromatization as the aromatic stabilization of the ring single ring is disturbed in this case.

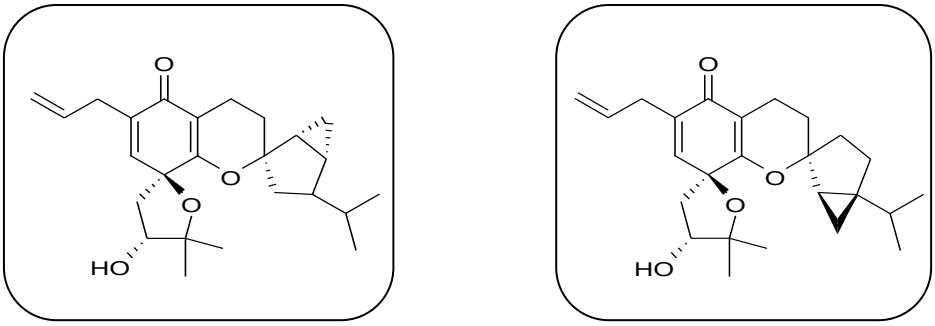
The another retrosynthetic approach for the synthesis of the core of this molecule can suggest an oxidative dearomatization process of coumarins bearing phenolic –OH groups. We have tried first to dearomatize the simple phenolic compounds so that if the process becomes successful it can be feasible with the coumarin derivatives also with consequent generation of our target molecule.

Recently our group has developed a new method for it by the help of selenium through phenyl selenium bromide and published it continuing with lot of substrates like phenols, thiols, napthols, anilines etc. Selenium is efficient and novel and the same oxidative property like hypervalent iodine reminds the diagonal relationship between iodine and selenium in the periodic table. Hence, we have tried for the dearomatization of the compounds serially through this novel method.

Literature survey:

The novel spirooliganone systems have a great antiviral activity, an unprecedented skeleton. Illicium oligandrum was used in Chinese folk medicine for the treatment of rheumatoid arthritis for the centuries. Very few reports are available on this system in literature. In 2013, Yu and co-workers reported the isolation of a pair of spiro carbon epimers, spirooliganones A and B (Figure-9), from the roots of I. oligandrum. The two compounds comprise of unique pentacyclic skeleton containing a rare dioxa-spiro system and a cyclohexadienone moiety together. Their structures were established by X-ray diffraction analysis of their p-bromobenzoyl derivatives, with the absolute configuration being determined by Mosher's method, suggesting that they differ only in the absolute configuration of the spiro carbon (C17). They exhibit potential activities against coxsackie virus (IC_{50} 3.70-33.33 μM) and were the first natural products isolated from I. oligandrum that show antiviral activities. The unprecedented structure of spirooliganones along with the potent antiviral activity B3 and influenza virus A (H3N2) leads to the interest to the organic chemists.

Spirooliganone-B was found to exhibit more potent activities against coxsackie virus B and influenza virus A (H_3N_2) (IC_{50} 3.70_5.05 μM) than spirooliganone- A due to differences in the configuration. Spirooliganone-B was obtained as colorless oil having the molecular formula, $C_{25}H_{34}O$, deduced from HRESIMS and 1D NMR. The UV, IR, CD, and NMR spectral data resmble likely(Figure-9).



Spirooliganone-A **Spirooliganone-B**

Figure-9

Xie and his group in 2014 have presented the first enantioselective total syntheses of (-)-spirooliganones A and B. Yu proposed a biogenetic pathway of spirooliganones A and B (Figure-9); they were derived by hetero-Diels-Alder reaction between monoterpene(-)-sabinene, which could be generated from 5-allylbenzene-1,2,4-triol. Considering the cycloaddition confronting the problematic regioselectivity and possible dimerization of it, they envisioned an earlystage hetero-Diels-Alder cycloaddition of (-)-sabinene and symmetrical 2-methylenecyclohexane-1,3-dione 6 could solve this problem and can give a retrosynthetic analysis of spirooliganones.

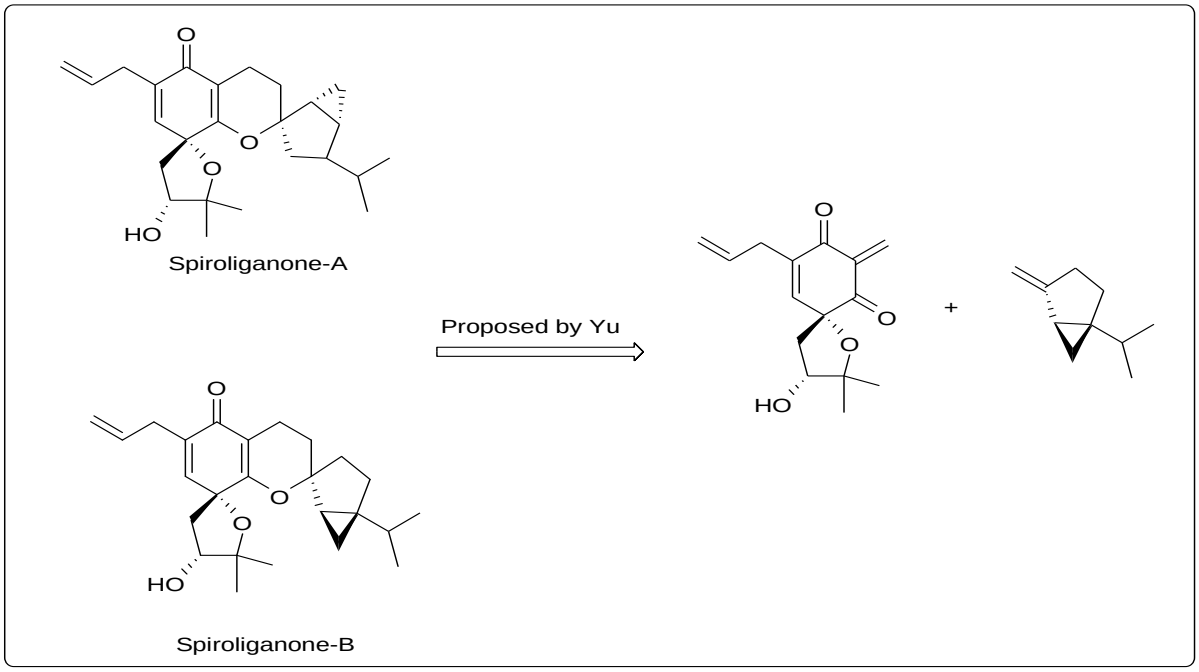


Figure-10

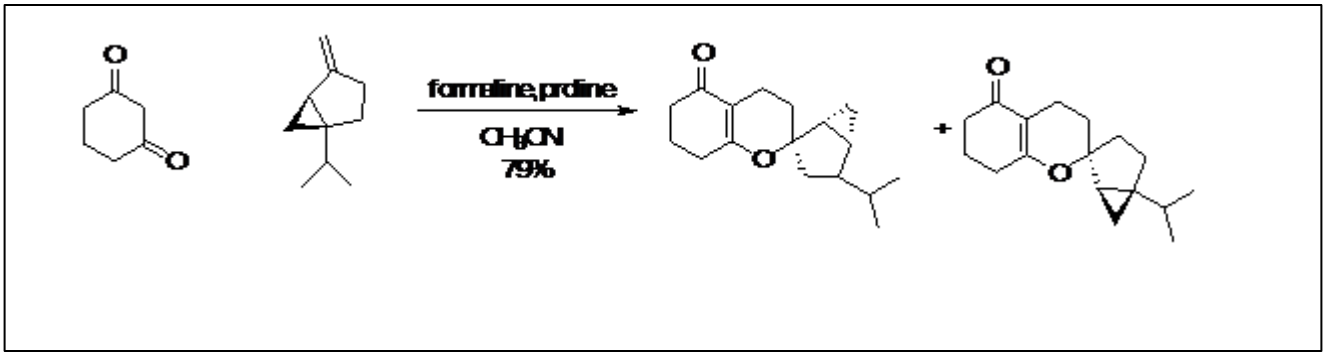


Figure-11(a)

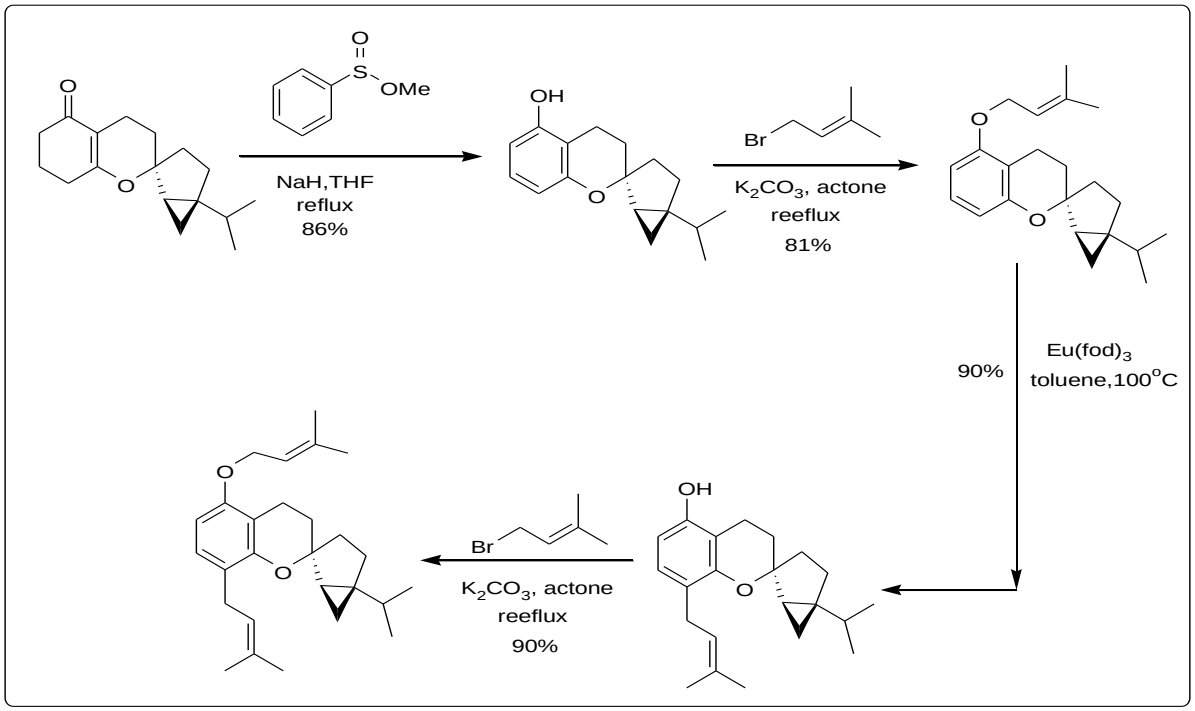


Figure-11(b)

They have focused on the oxa-spiro cyclohexadienone skeletons that could be constructed from diol via tandem oxidative dearomatization/cyclization. The dihydroxy groups at C_{11} and C_{12} could be introduced via an asymmetric dihydroxylation of the prenyl chain. The aromatization of the tetracyclic adducts would give the corresponding phenol, from which the prenyl and allylic side chains could be assembled via twice O-alkylation and Claisen rearrangement sequence(Figure-10(b)). The two stereoisomers , provided via the one-pot Knoevenagel/hetero-DielsAlder reaction from commercially available 1.3-cyclohexanedione, formalin, and (-)-sabinene. The synthesis was begun to prepare the tetracyclic intermediate, at Hoffmann conditions, 1, 3-cyclohexanedione was added slowly to the formalin and (-)-sabinene solution in CH_3CN, and the heteroDiels-Alder reaction went in one pot to afford a 1:1.2 mixture of epimeric tetracyclic adducts with 79% yield. The poor diastereoselectivity could be attributed to the slight steric difference between α and β face of sabinene. The advantage of this is to access both diastereomeric spirooligaones. After preliminary separation by silica gel chromatography, it was successfully isolated as a white solid by recrystallization from ethyl acetate/petroleum ether.

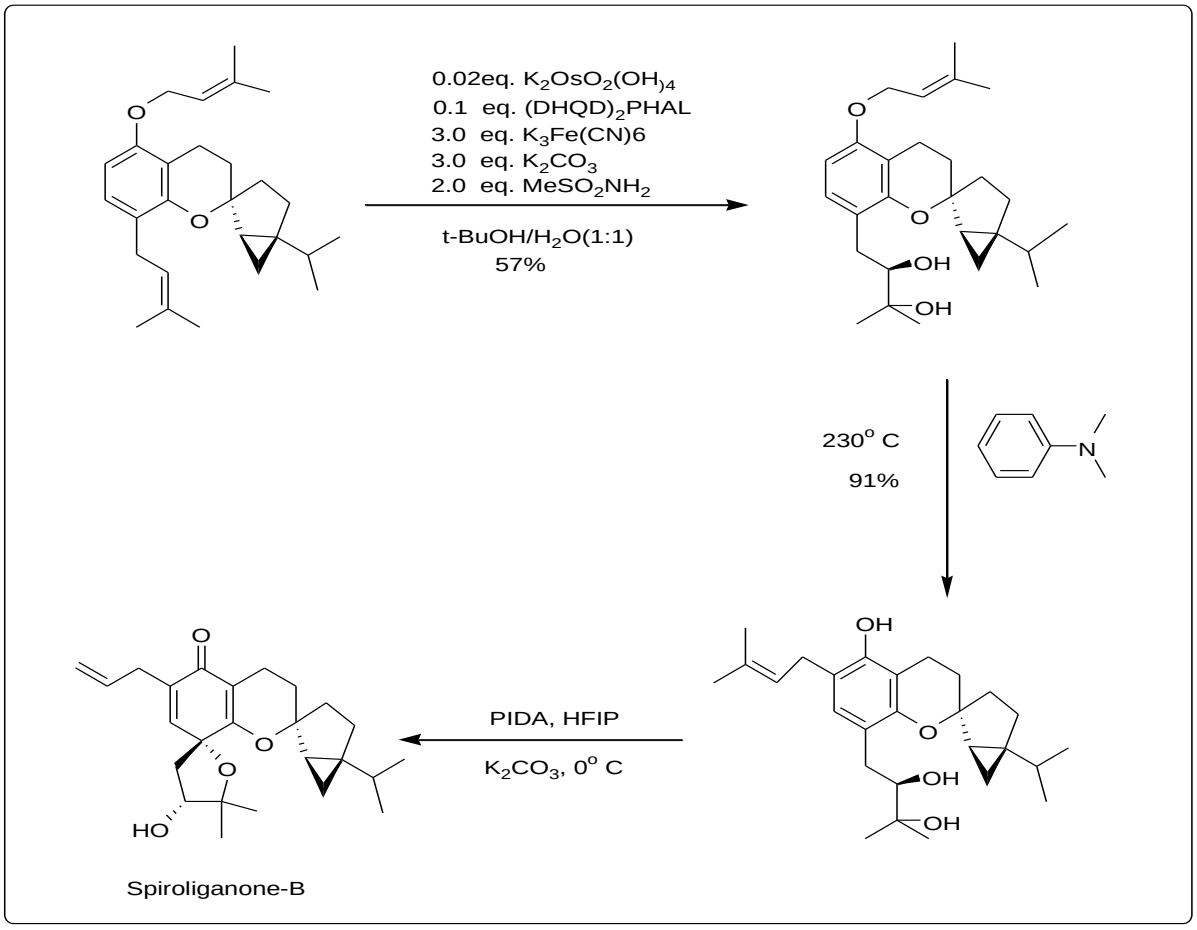


Figure-11(c)

After trying a lot of unsuccessful reactions, DDQ in dioxane solvent alone gave the trace desired product. The yield could not be improved independent on how much the reaction time is and changed the amount of DDQ. Suspecting the sensitivity of phenol derivatives to oxidizing agents, due to the electron-rich nature of resorcinol monoether moiety, they transformed into the corresponding β-keto sulfoxide by use of methylbenzenesulfinate, which was easily converted to the desired one in 86% yield eliminating of the sulfoxide group in one pot. Then the stage was set for introduction of the prenyl and allylic side chains of the phenol ring. A general alkylation/ Claisen rearrangement sequence was adopted. Treatment of phenolic derivative with prenyl bromide and K_2CO_3 in refluxing acetone efficiently delivered prenyl ether, which was heated in toluene in the presence of a catalytic amount of $Eu(fod)_3$ to afford p-prenylated phenol in 88% yield with high regioselectivity together with the retaintion of the acid-sensitive propane ring. Under the sharpless condition then interestingly the decreasing of the amount of $K_2OsO_2(OH)_4$ led to low conversion, and increasing it gave more overoxidation byproduct. The stereochemistry of the formed diol was assigned according to the Sharpless model and eventually verified by the late-stage cyclization of the oxa-spiro B ring in N,N-Dimethylaniline as the optimal solvent (230°C) in Claisen rearrangement of to cleanly furnish O-allyl phenol in 91% yield. The last challenge they have overcome, cyclization of the oxa-spiro B ring using a tandem oxidative

dearomatization/cyclization sequence. The treatment of O-allyl phenol with phenyliodine diacetate(PIDA) in HFIP as optimal solvent.

Experimentals:

Strategy:

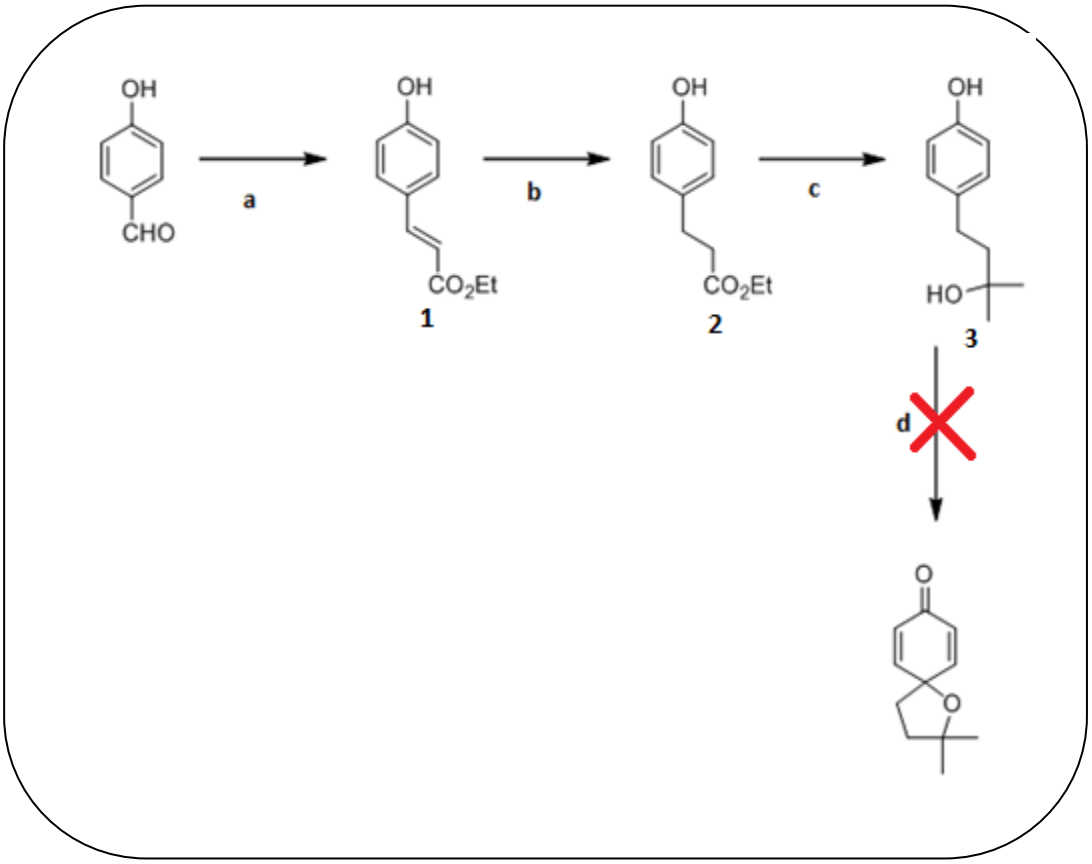


Figure-12

Reagents:- (a)Triethyl phosphonoacetate,NaH,0°C ,(b) H_2,10% Pd charcoal, (c) Mg, diethyl ether, methyl iodide ,

(d)SL.No	Conditions	Result
1	PhSeBr,methanol, triethylamine at rt	Starting left
2	PhSeBr, THF,triethylamine at rt	Starting left
3	PhSeBr, DMSO, Pyridine at rt	Starting left
4	PhSeBr,THF,K_2CO_3 at rt	Starting left
5	PhSeBr, THF,Cs_2CO_3 at rt	Starting left
6	PhSeBr, methanol, triethylamine at refluxing temp.	Starting left
7	PhSeBr, THF,triethylamine at refluxing temp.	Starting left
8	PhSeBr, DMSO, Pyridine at refluxing temp.	Starting left

Procedure:

1. Dry THF was added to oil free 1 eq.NaH in a round bottomed flask and then 1 eq. triethyl phosphonoacetate was added to the solution at 0°C . To the well stirred solution compound i.e. para hydroxyl benzaldehyde (1 gm) was added. The reaction was monitored by TLC for 5 hrs and finally the raction mixture was worked up and purified through column chromatography.

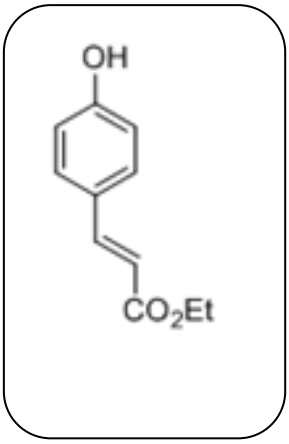
2. The reactant was dissolved in methanol and then paladised charcoal was added in hydrogen atmosphere and kept for 4 hrs. It leads to the 100 % conversion as per TLC monitoring.

3. Activated Mg (excess) was taken in two necked RB and diethyl ether was taken in allowed for stirring then methyl iodide was slowly added so that the refluxing started. The reaction was allowed to stir till a grey color appears which indicates the formation of Grignard then compound was added to it. Then the reaction was quenched using ammonium chloride, worked up and purified through column chromatography.

4. The reactant alcohol is added first and then subsequent addition of the solvent, base and at last the PhSeBr.

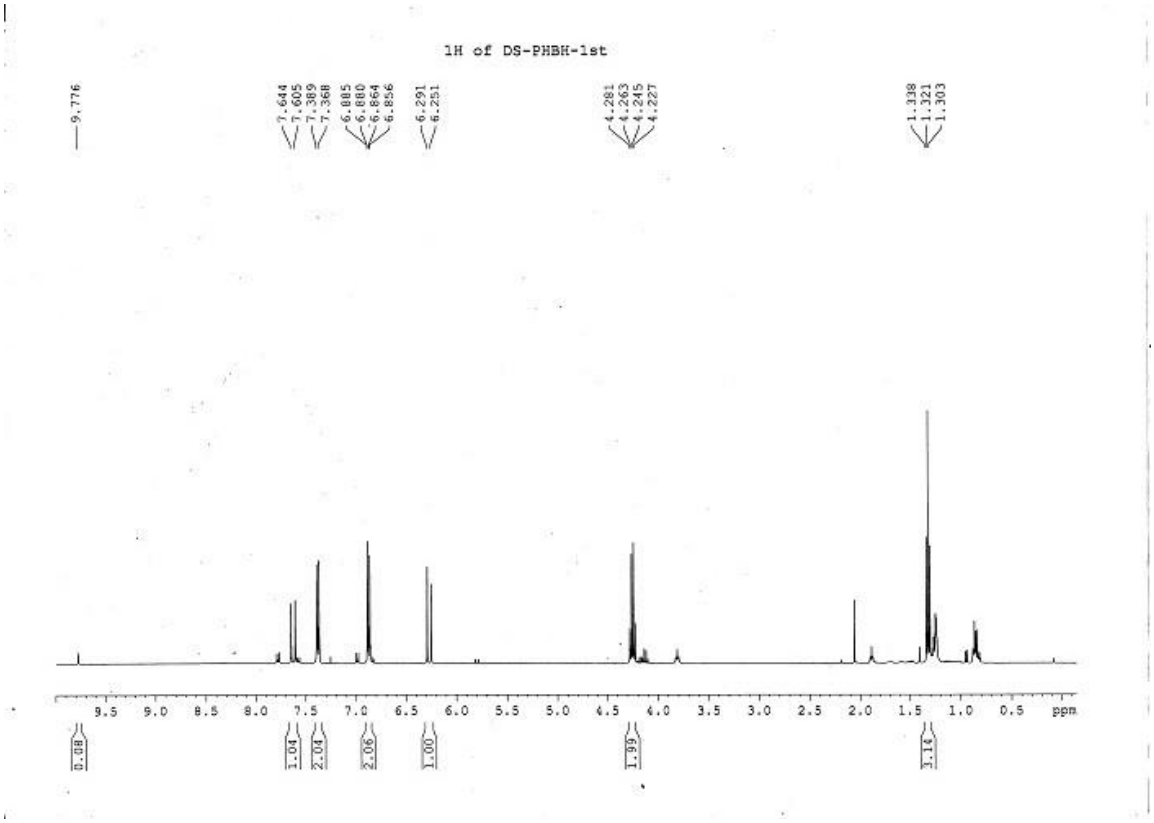
Spectral data:

Compound:

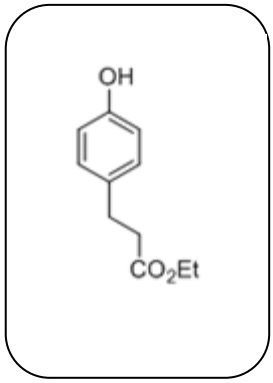


^{1}H NMR ($CDCl_3$, 400 MHz):

δ=1.321(t,3H),4.254(q,2H),6.271(d,1H,J=16Hz),6.872(q,2H,J=6Hz),7.378(d,2HJ=12Hz),7.625(d,1H,J=16Hz) ppm

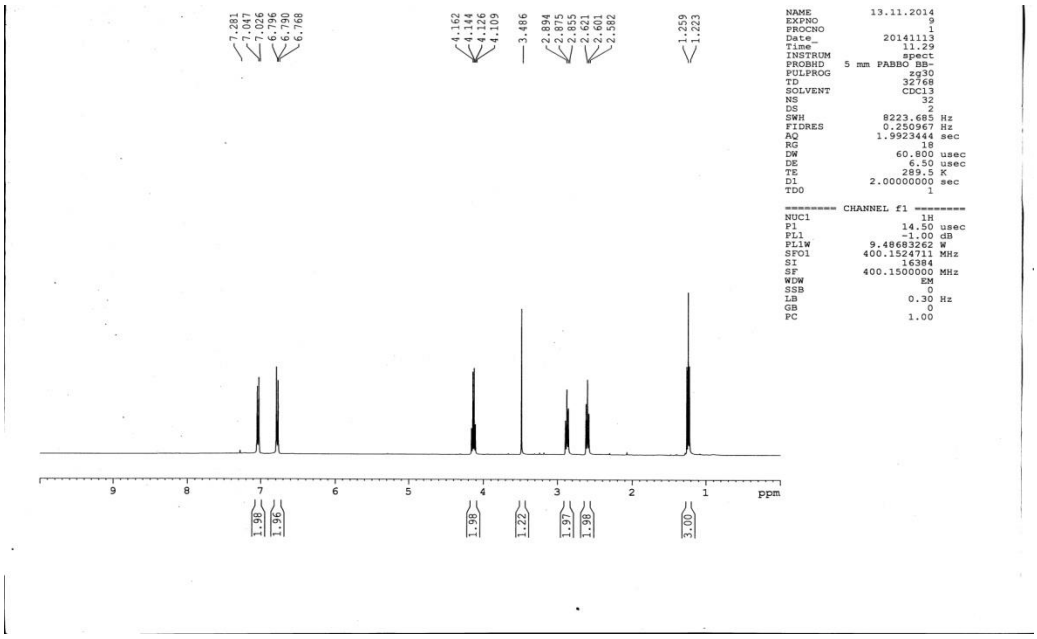


Compound:



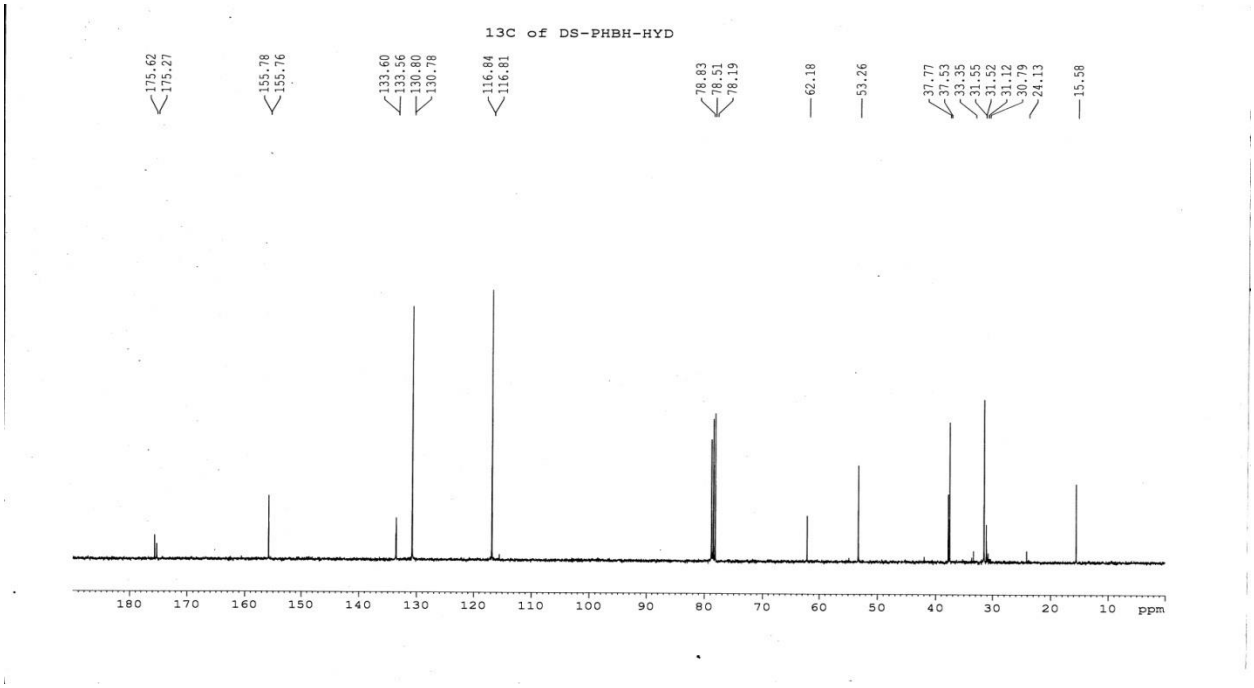
^{1}H NMR ($CDCl_3$, 400 MHz):

=1.236(s,3H),2.601(t,2H),2.875(t,2H),3.486(s,1H),4.135(q,2H,J=7Hz),6.923(dd,4H,J=9Hz)ppm

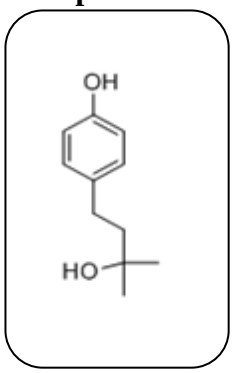


^{13}C NMR ($CDCl_3$,400 MHz):

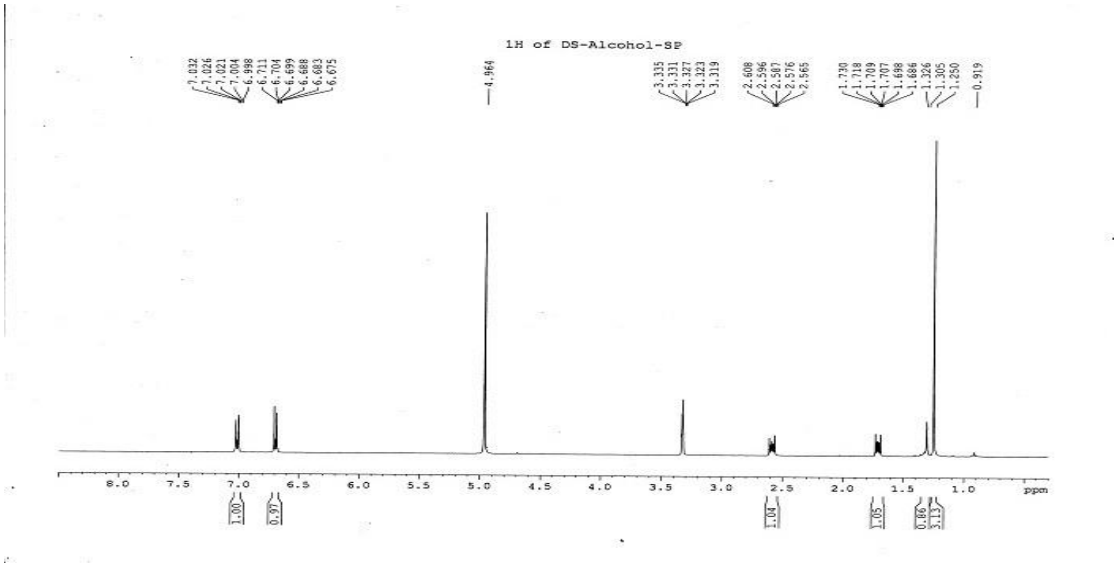
δ=15.58,24.13,30.79,31.12,31.52,31.55,33.35,37.53,37.77,53.26,62.18,78.19,78.51,78.83,116.81,116.84,130.78,130.80,133.56,133.60,155.76,155.78,175.27,175.62 ppm



Compound:

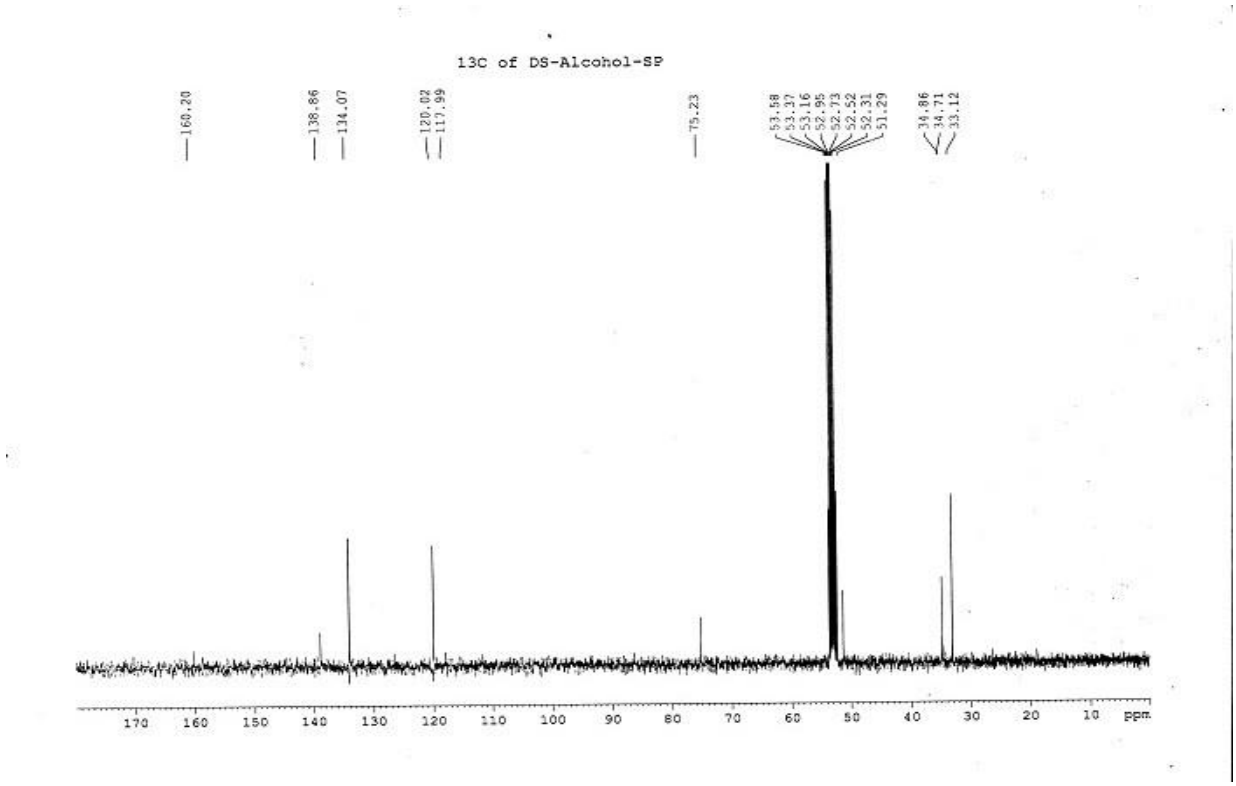


^{1}H NMR (CD_3OD, 400 MHz):
δ=1.250(s,3H),1.326(s,1H),1.708(m,1H),2.587(m,1H),6.693(m,1H,J=2Hz),7.021(m,1H, J=3Hz)ppm



^{13}C NMR (CD_3OD, 400 MHz):

δ=33.12,34.71,34.86,51.29,52.31,52.52,52.73,52.95,53.16,53.37,53.58,75.23,117.99,120.02,134.07,138.86,160.20 ppm



Conclusion and future prospects:

Trials are underway to develop well functionalised oxa-spiranes employing PhSeBr in different experimental conditions. Once the oxa spirane ring system is developed , efforts would be highlighted towards the total synthesis of Spiroliganone .

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