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Novel Strategy for the Synthesis of Allenes.

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Novel Strategy for the Synthesis of Allenes

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by

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ABSTRACT

Novel Strategy for the Synthesis of Allenes

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Allenes are very important chemical reagents in organic synthesis. Due to their high reactivity, they have been extensively used to carry out a variety of unique and effective chemical transformations including but not limited to ionic and free radical additions and transition metal catalyzed cyclizations. As the chemistry of this group of compounds is explored further and their applications expanded there is a need to develop alternative and cost effective methods for their synthesis. Our approach involves the synthesis of allenes from oxa-bicyclo-alkan-2-ones by methyllithium induced Eschenmoser fragmentation of the bicyclotosylhydrazone derivatives.

DEDICATION

This thesis is dedicated to my late father: Mr. Peters Meange Kamga. Your strength of character and dedication are my source of inspiration.

ACKNOWLEDGMENTS

I render immense thanks to God Almighty for seeing me through each day.

I would like to extend a heartfelt ‘thank you’ to my supervisor, Dr. David Young, for his patience and dedication. I have learnt so much from him in so little time and I am confident that his example of an excellent teacher would remain with me always. I am proud to have known him and been his student. I equally want to thank Dr. Jeffrey Wardeska and Dr. Yu-Lin Jiang for being on my committee and revising my thesis.

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Lastly I would like to extend my appreciation to my entire family: My mother, Mrs. Francisca Kamga for all her love. My sister and her husband Mr. and Mrs. Kwankam and all my siblings, Nelson, Linda, Manuela and Ndassi. Thank you for being there always.

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LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
AIBN	2,2'-azobisisobutyronitrile
^{n}BuLi	*n*-butyllithium
$CDCl_3$	chloroform-*d*
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
i-Pr	iso-propyl
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
NMR	nuclear magnetic resonance
Ph	phenyl
t-Bu	tert-butyl
Bu	butyl

THF	tetrahydrofuran
TMS	trimethylsilyl

CHAPTER 1

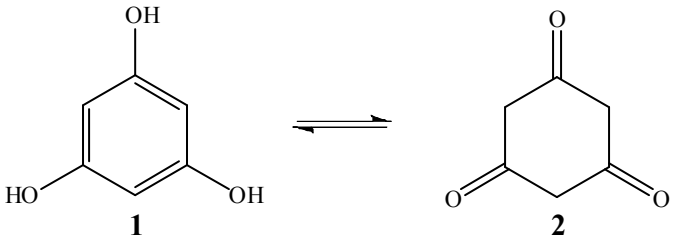
INTRODUCTION AND BACKGROUND

Introduction

In this thesis we shall discuss research attempts to synthesize allenes from tosylhydrazones with the aim of synthesizing hyperforin, a phloroglucinol. In order to provide the reader with enough background, we shall provide a brief introduction to the phloroglucinol family of biologically active molecules. Then, we shall discuss our approach toward the synthesis of hyperforin. Previous studies relevant to our approach will precede the discussion on the results obtained this far.

Introduction to Phloroglucinols: Structure and Biological Activity

The term phloroglucinols is used to describe a group of organic compounds having the phloroglucinol (**1**) moiety as the key structural feature. The molecule phloroglucinol (**1**) exists in two tautomeric forms: 1,3,5-trihydroxybenzene (**1**) and 1,3,5-cyclohexanetrione (**2**) that exist in equilibrium with each other.



1 **2**

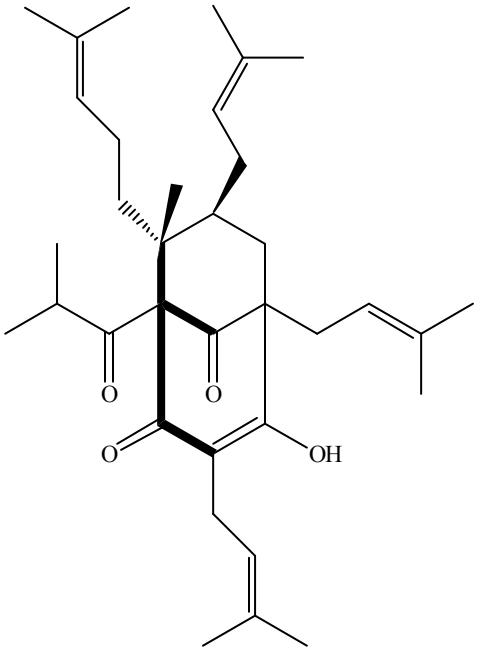
Scheme 1: Tautomers of phloroglucinol

The polyfunctionality of phloroglucinol makes it an important intermediate in the synthesis of pharmaceuticals.

Phloroglucinol based natural products have recently gained a lot of attention for their unique features and important medicinal properties. They have been isolated from natural sources including members of plant genus *Hypericum* and *Garcinia*. Many of the biologically active metabolites of these phloroglucinol based species are polycyclic polyprenylated acylphloroglucinol (PPAP) derivatives. These contain prenyl or geranyl appendages and have been characterized by a densely substituted bicyclo[3.3.1]nonane-2,4,9-trione. Let us examine some phloroglucinols.

Hyperforin

Interest in PPAP natural products increased when it was discovered that hyperforin (**3**) was the primary active ingredient in St. John's wort, a drug used to treat depression. The structure of hyperforin was first elucidated by Gurevich and coworkers in 1971who carried out X-ray diffraction and spectroscopic methods to analyze the structure.



3

Figure 1: Hyperforin

Hyperforin (**3**), which is found in some members of the *Hypericum* plant genus, has been shown to have multiple antibacterial properties. It is active against methicillin resistant *Staphyloccoccus aureus* and has also shown some anticancer activity.

The mechanism of action for biological activity of hyperforin (**3**) has been studied. Hyperforin (**3**) acts as a reuptake inhibitor in synapses by inhibiting monoamines such as dopamine, serotonin, and epinephrine. It also inhibits GABA and glutamate. Its mode of action differs from other antidepressants because instead of inhibiting proteins, it activates the transient receptor potential ion channel (TRPC6), inducing the entry of sodium and calcium into the cell. This changes intracellular H^+ and Na^+ concentrations that cause inhibition of monoamine reuptake.

The mechanism for the biological synthesis of hyperforin (**3**) was proposed by Wolfgang and coworkers. They used carbon-13 labeling experiments to show that the core acylphloroglucinol **10** is prepared from pyruvate. Though some of the intermediates shown can be prepared from valine, self condensation of pyruvate (**4**) followed by decarboxylation to form α-hydroxyketone **5** that transforms to ketocarboxylate **6** could explain the formation of **10**. Oxidative decarboxylation of **6** affords acetyl-CoA (**7**) that condenses with three malonyl-CoA (**8**) units to generate the triketone **9**. Intramolecular cyclization yields acylphloroglucinol **10**.

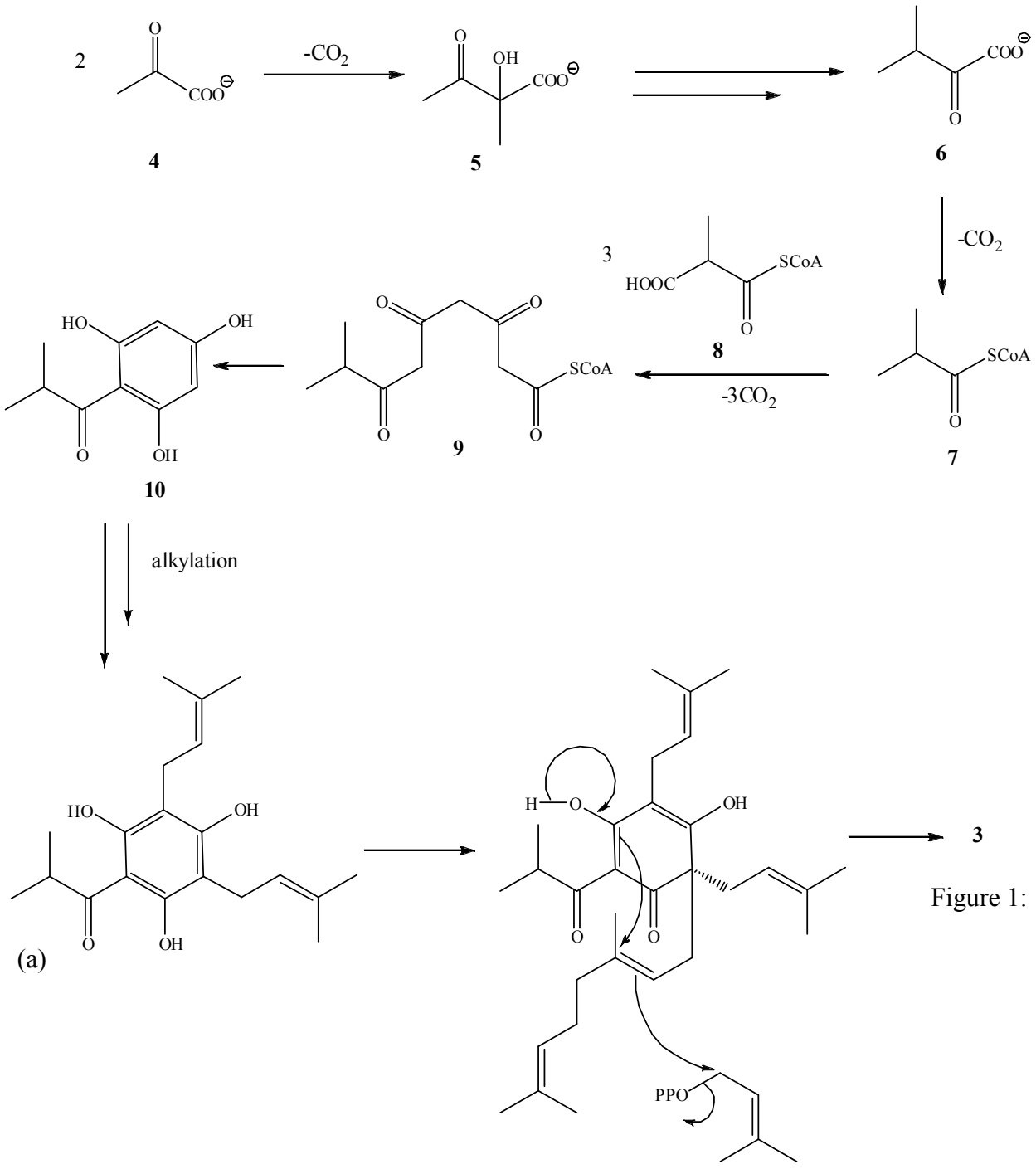
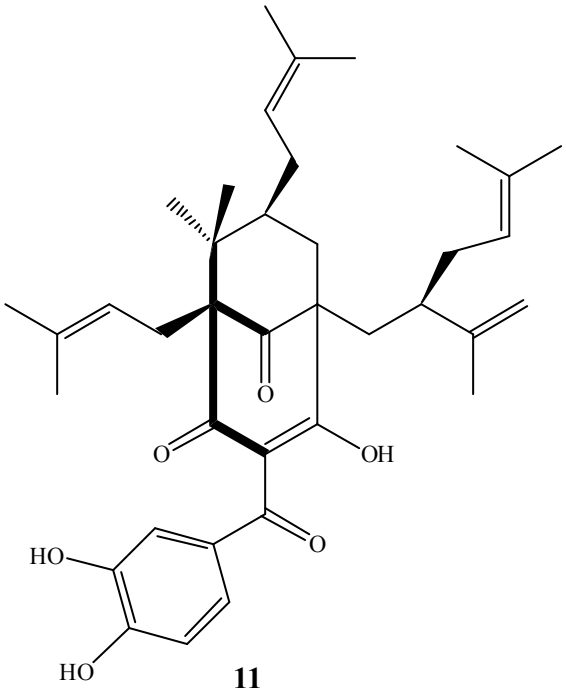


Figure 1:

Scheme 2: Proposed mechanism for the biological synthesis of hyperforin (**3**)

Guttiferone E

Guttiferone was first identified from a sample of *Garcinia ovalifolia* from Central African Republic in 1988.



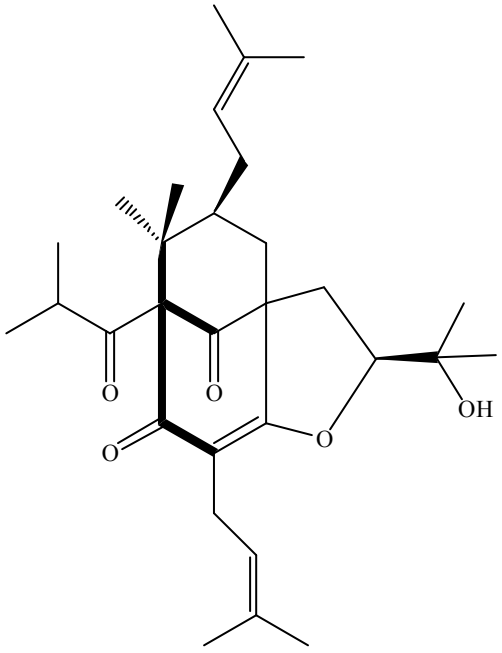
11

Figure 2: Guttiferone E

Guttiferone (**11**) has been found to be active against HIV. It works by inhibiting the cytopathic effects of *in vitro* HIV infection. HIV causes the cytopathic effect by binding to and penetrating a helper T cell. When HIV replication is initiated, the helper T cell is destroyed and immunodeficiency results. Guttiferone inhibits HIV-1 reverse transcriptase that is responsible for transcribing RNA to DNA during reproduction.

Garsubellin A

The structure of garsubellin A (**12**) was first reported by Fukuyama and coworkers in 1997. Garsubellin A (**12**) is extracted from the wood of *Garcinia subelliptica* a tree that grows in Japan. It is a potent inducer of acetyltransferase (ChAT). This enzyme is responsible for the biosynthesis of the neurotransmitter acetylcholine (ACh).



12

Figure 3: Garsubellin A

One of the hypotheses proposed for the causes of Alzheimer's disease is the reduced synthesis of acetylcholine. Therefore, garsubellin A (**12**) can be a potent candidate for the treatment of Alzheimer's. Studies on rats has already shown that garsubellin A (**12**) increases ChAT activity by 154% at a 10 μM concentration.

Garsubellin A (**12**) has been successfully synthesized by Kuramochi and coworkers.

Garcinol

Garcinol (**13**) is extracted from *Garcinia indica*. It is a potent inhibitor of histone acetyltransferases (HATs) both *in vitro* and *in vivo*. The inhibition of this enzyme inhibits the acetylation of histones that is believed to directly facilitate DNA transcription. This process can be applied for the treatment of cancer. Studies have shown that garcinol (**13**) can cause apoptosis in HeLa cells by causing down-regulation of global gene expression. It also down-regulates several proto-oncogenes, therefore, it is potent for the treatment of cancer.

However, inhibition of histone acetylation has also been associated with other disease conditions such as AIDS and so further research still has to be done in order to find if garcinol (**13**) or its derivatives can be used for designing therapeutic agents for the treatment of other diseases.

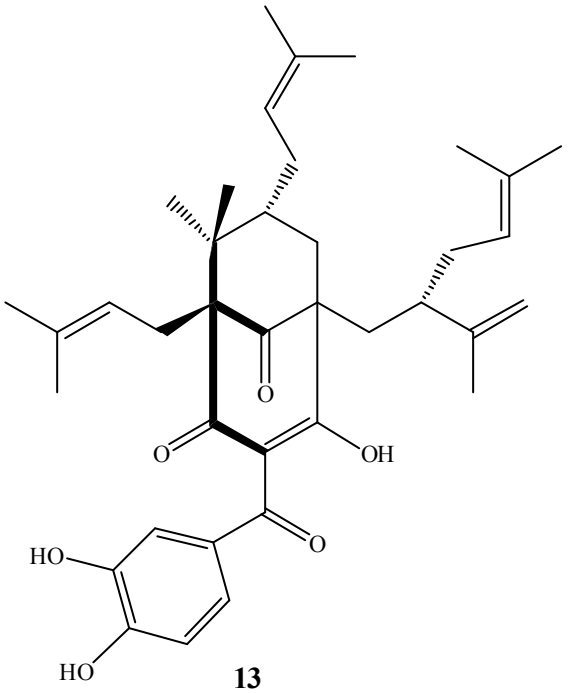


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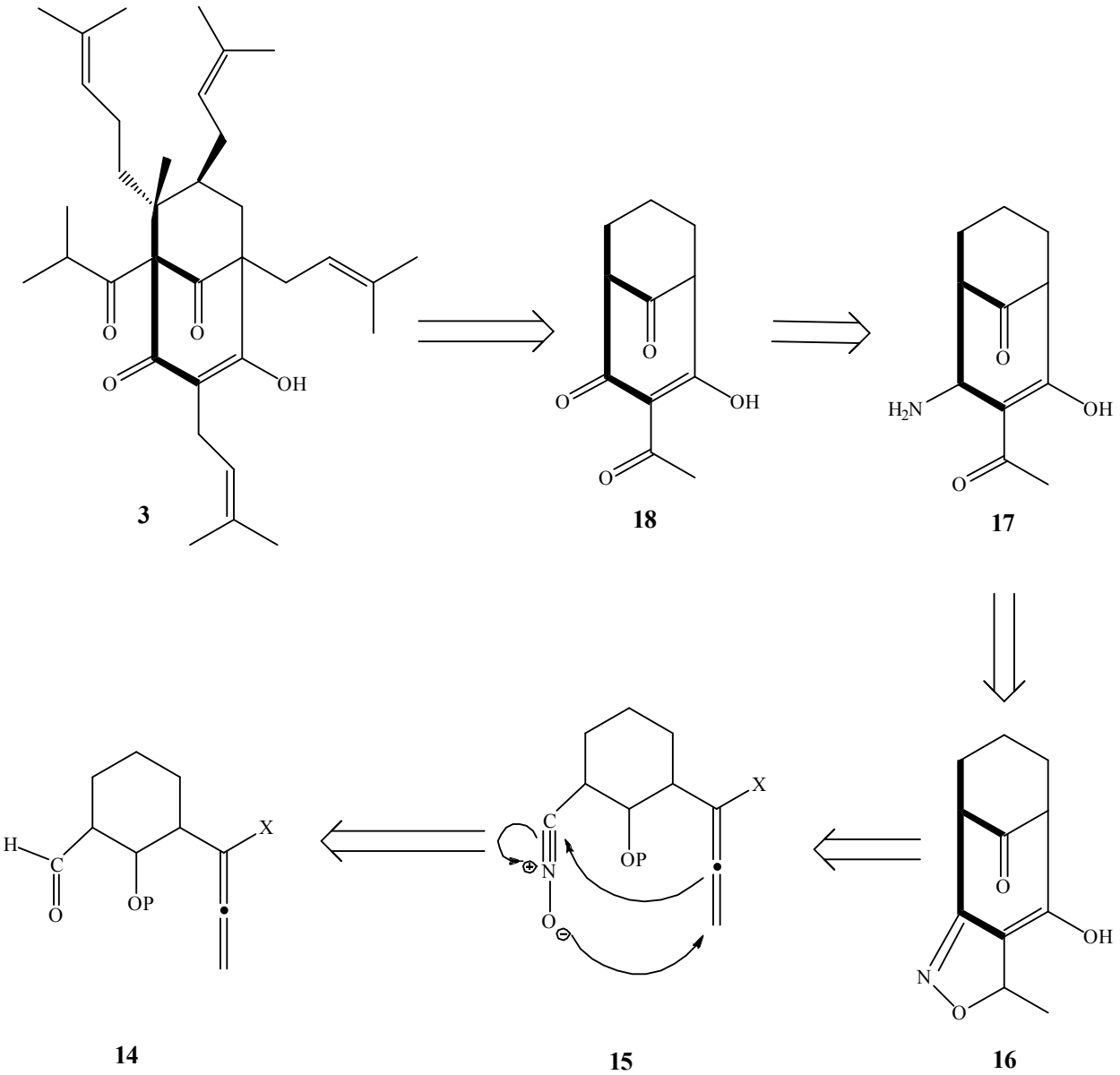
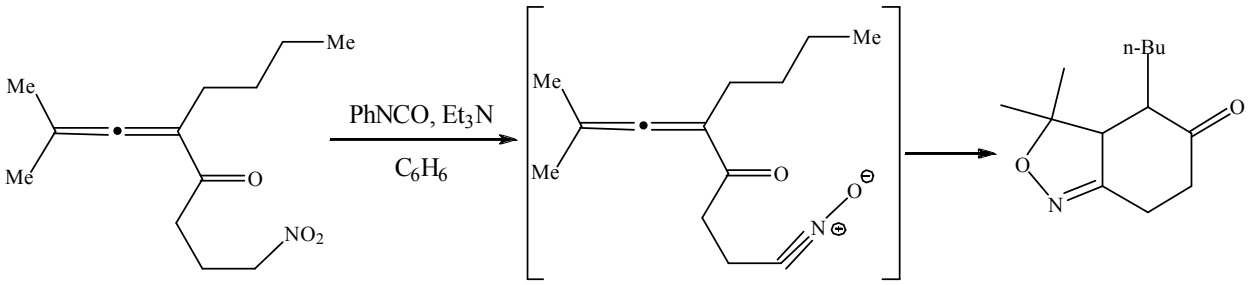
Figure 4: Garcinol

The focus of our research is to synthesize hyperforin (**3**). Although this synthesis has been attempted by several research groups, there has been no published total synthesis of hyperforin (**3**). Our approach toward the synthesis of hyperforin (**3**) involves a nitrile oxide allene cycloadditions. We began with the following retrosynthetic analysis



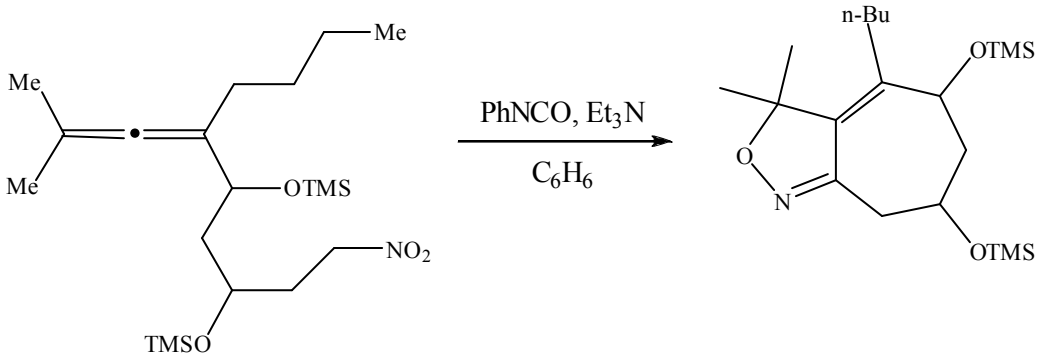
Scheme 3: Retrosynthetic analysis for hyperforin (**3**)

We projected that the nitrile oxide allene cycloaddition would take place regioselectively at the external π-bond rather than the internal. This is in line with previous studies by Young and Zeng[1] as seen below. The studies concluded that in the presence of a bulky group α to the allene, allene-intramolecular nitrile oxide cycloadditions would take place at the external π-bond.



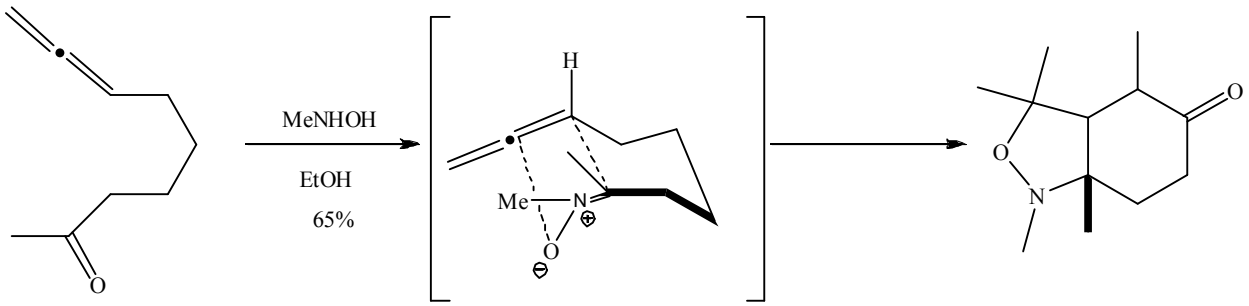
19 **20** **21**

Scheme 4: Allene-intramolecular nitrile oxide cycloadditions presence of bulky group



22 **23**

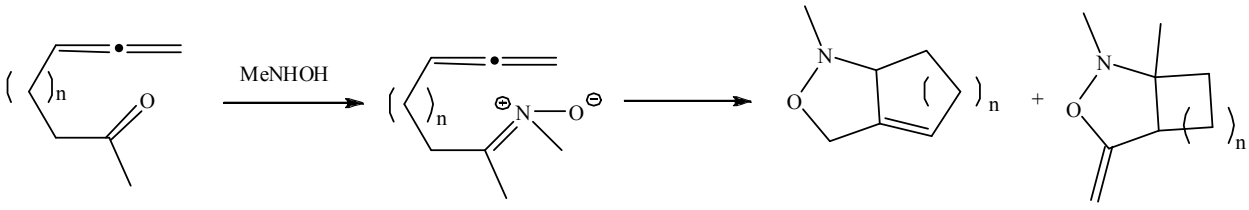
Scheme 5: Allene-intramolecular nitrile oxide cycloadditions in presence of bulky group



24 **25** **26**

Scheme 6: Allene-intramolecular nitrile oxide cycloadditions in absence of bulky group

These results obtained seemed to be in disagreement with previous studies by Norman A. LeBel[6] who showed that the product distribution seemed to follow the thermodynamics of ring formation. Formation of five and six-membered rings are favored and the formation of four and seven-membered rings are not observed suggesting that the internal π-bond of the allene is more reactive in many cases.



27 **28** **29** **30**

Scheme 7: Intramolecular nitrone-allene cycloadditions

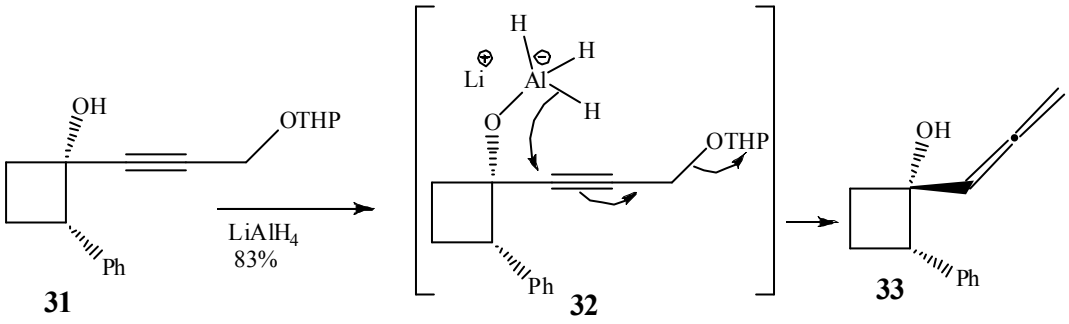
Our objective, therefore, is to synthesize an allene similar in structure to **14**. Let us first examine some of the current methods that have been used for the synthesis of allenes.

Current Methods of Allene Synthesis

Brummond and DeForrest from the University of Pittsburg published a comprehensive paper in 2007 detailing methods that have been used for the synthesis of allenes since 1982. Though their paper was not exhaustive, it gave an overall idea of the synthetic methods and protocols that have stood the test of time. We shall examine some of these general methods that have been employed and our classification of the methods shall be based on the initial material from which the allene is obtained.

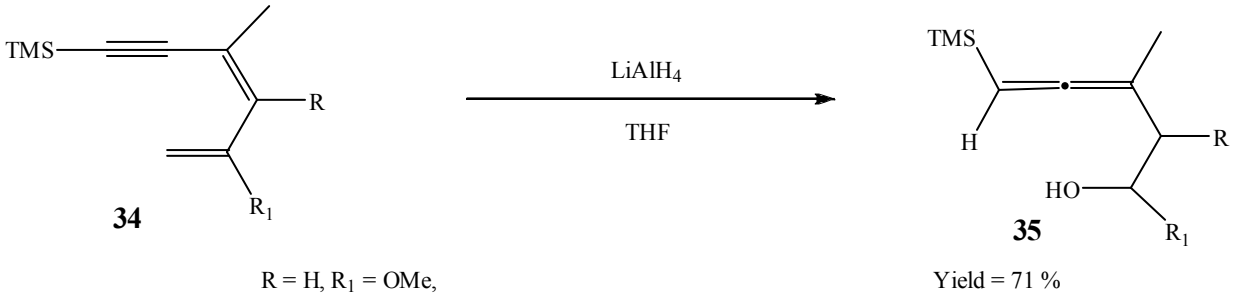
Allenes from Alkynes

Reduction of Propargyl Electrophiles. Allenes have been synthesized from propargyl electrophiles such as ethers, alcohols, and epoxides by employing reducing agents such as lithium aluminum hydride ($LiAlH_4$) and diisobutylaluminum hydride. A hydride is delivered from the reducing agent to the electrophile via an S_N2' attack leading to a new carbon-hydrogen bond and generating a new carbon-carbon double bond. The mechanism is stereospecific and can lead to the syn or anti species depending on the identity of the substrate, reducing agent, and reaction conditions.



Scheme 8: Synthesis of allenes by reduction of propargyl electrophiles

Allenes from Reduction of Enynes. Conjugated enynes have also been converted to allenes by treatment with aluminum hydride reagents. This method has been used since 1973, and in 1988 Bovicelli and co-workers employed this method in the synthesis of β-allenyl alcohols by treating a variety of 1-silyl-enyne-ketones and esters with $LiAlH_4$.

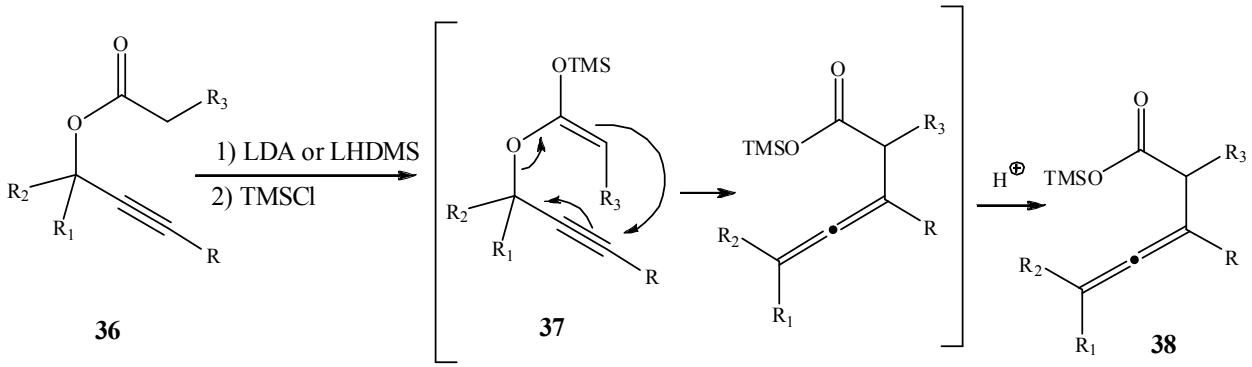


34 **35**

R = H, R_1 = OMe, Yield = 71 %

Scheme 9: Allenes from oxygenated enynes

Allenes from Claisen Rearrangements. Allenes have been synthesized from the Claisen rearrangement and its variants such as the Claisen-Ireland and ortho-ester Claisen. The substrates for these rearrangements include molecules such as the propargyl vinyl esters, propargyl alcohols, and propargylic esters. The mechanism involves a [3,3]-sigmatropic rearrangement.

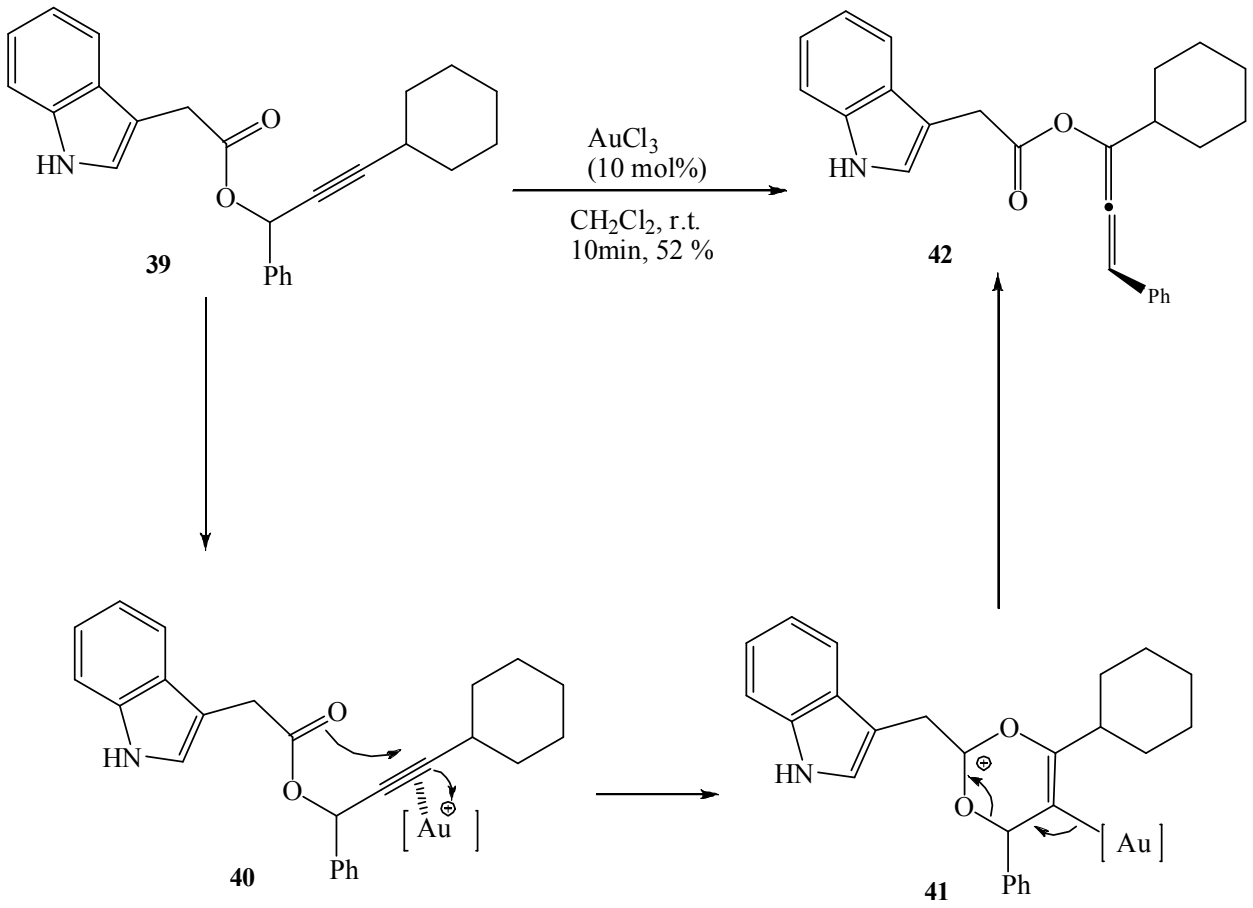


36 **37** **38**

R = alkyl; R_1 = alkyl, aryl, H; R_2 = H, alkyl; R_3 = alkyl, H

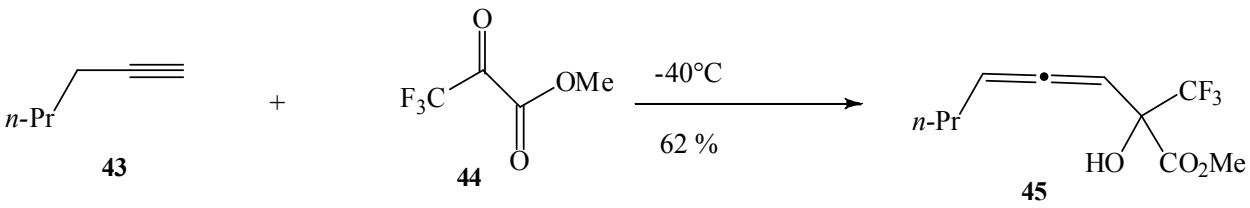
Scheme 10: Synthesis of an allene by Claisen-Ireland rearrangement

Allene Synthesis via Other [3,3]-sigmatropic Rearrangements. There exist other [3,3]-sigmatropic rearrangements that can be employed for the synthesis of allenes from propargyl substrates. Examples include the Saucy-Marbet rearrangement. Other methods include the metal catalyzed [3,3]-sigmatropic rearrangements. This method has been done successfully with silver, gold, platinum, and copper catalysts. A recent example is shown below where gold(III) chloride is used to catalyze the [3,3] rearrangement of a propargyl ester.



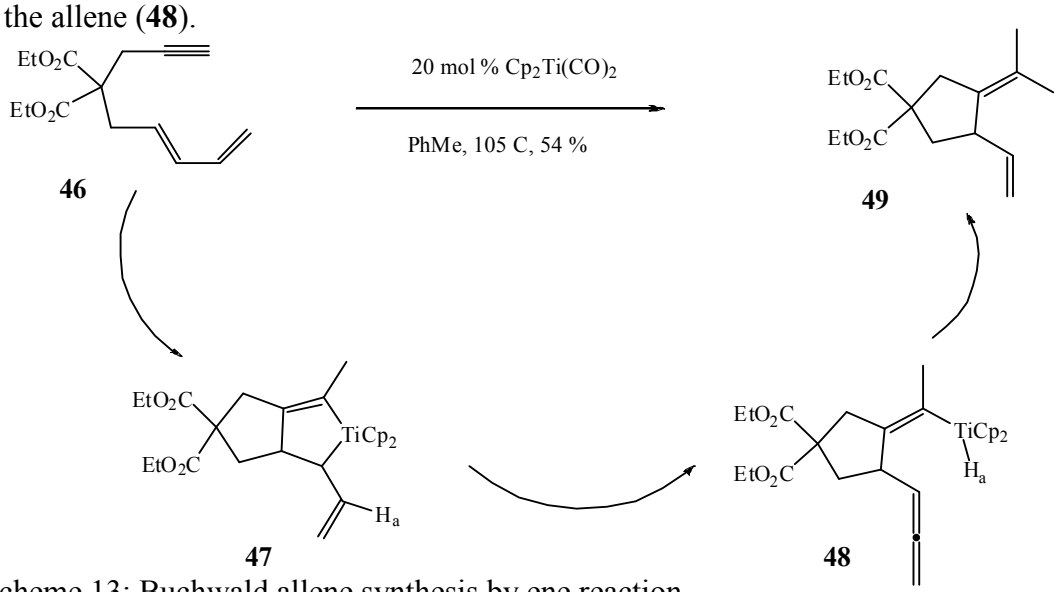
Scheme 11: Metal catalyzed synthesis of allene by [3,3] rearrangement

Allenes from Ene Reactions. The ene reaction has been extensively used in the construction of carbon-carbon bonds and has now found application in the synthesis of allenes. Burger and co-workers showed that that trifluoropyruvate (44) can function as the enophile component in the carbonyl-ene reaction.



Scheme 12: Allene synthesis by ene reaction

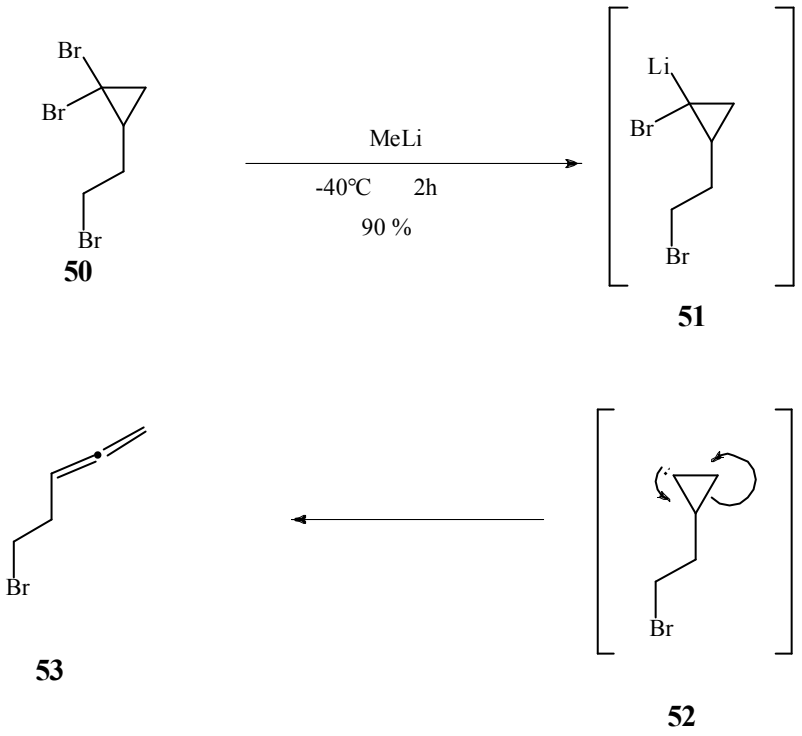
Ene reactions have also been used by Buchwald who showed that titanocene catalyst systems can be used in the synthesis of allenes appended to a ring from acyclic dienynes. The reaction is an ene reaction in which the cycle begins with a loss of CO from the catalyst, then the reaction of the resulting species with a dienyne substrate (**46**). This results in a titanacyclopentane (**47**) that undergoes hydride elimination and subsequent reductive elimination to afford the allene (**48**).



Scheme 13: Buchwald allene synthesis by ene reaction

The Doering-Moore-Skatteböl Reaction

Reactions of geminal dibromocyclopropanes with alkyllithium reagents such as methyllithium and butyllithium produced the desired allene in high yields.

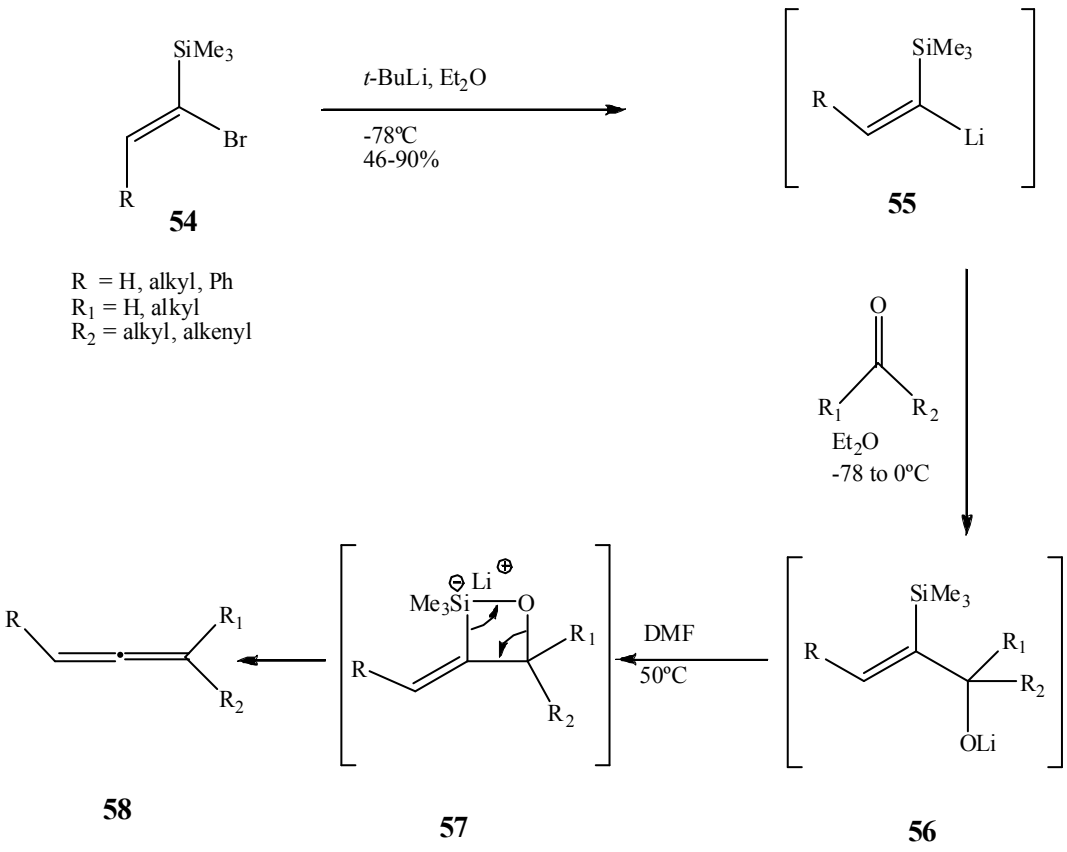


Scheme 14: Allene synthesis from carbene

Peterson Allenation (Allenes from Alkenyl Silanes)

In this procedure, a bromoalkenyl silane undergoes a halogen-metal exchange reaction to produce the vinyl carbanion by treatment with BuLi. Subsequent addition of a ketone results in a lithium alkoxide that undergoes rearrangement and elimination at moderate temperatures of about 50ºC to yield the allene.

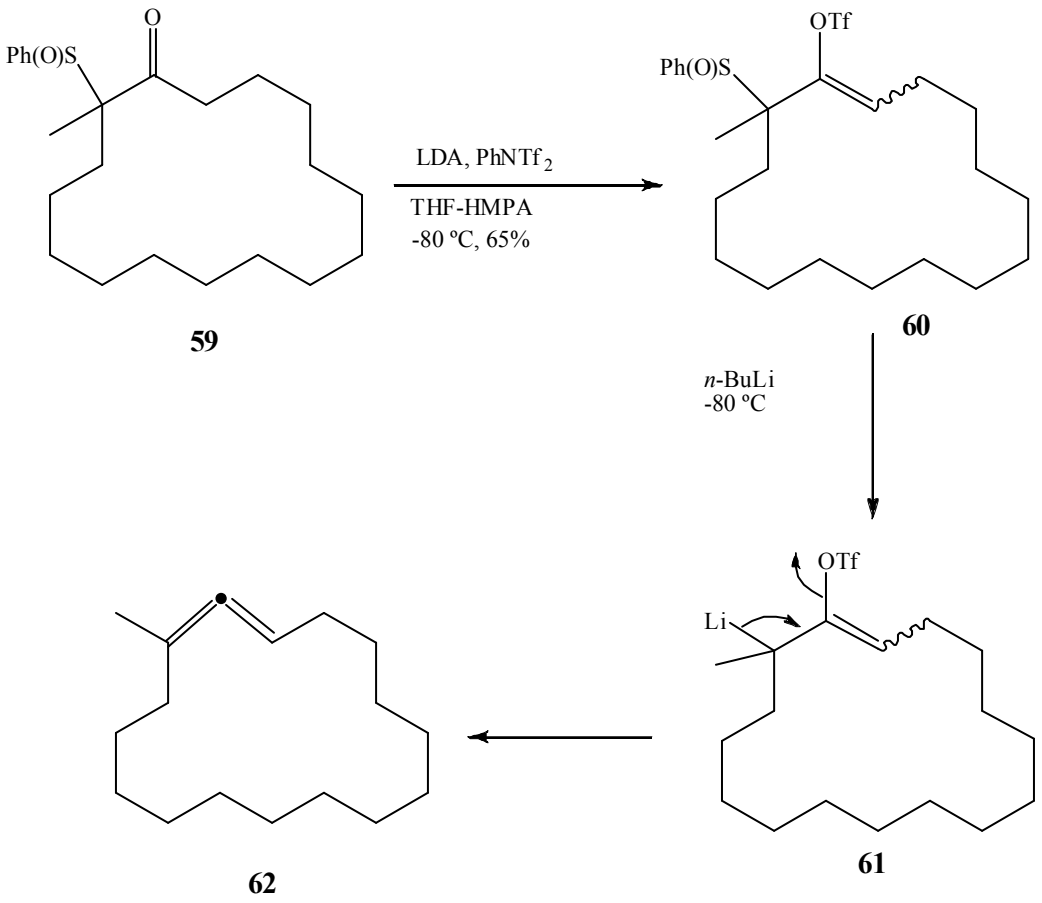
This reaction was found to be solvent sensitive because the yields obtained were higher when diethyl ether was used in contrast to tetrahydrofuran.



Scheme 15: Peterson Allenation

Allenes by β-elimination of Sulfoxide Derivatives

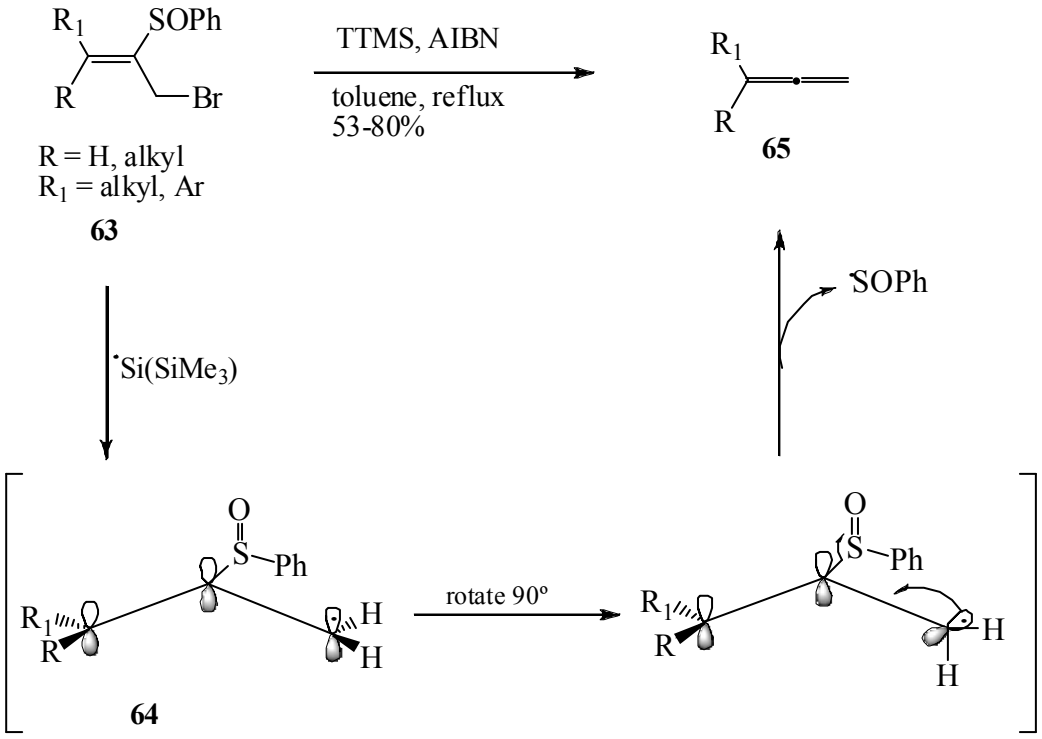
As shown in the scheme below, trisubstituted allenes have been successfully synthesized from β-ketosulfones. This method was developed by Satoh and co-workers. The sulfone is treated with lithium diisopropylamide and phenyl triflimide to obtain the enol triflate (**60**). Further treatment of the enol triflate (**60**) with n-butyllithium at low temperatures causes a sulfoxide-metal exchange to afford a reactive intermediate which undergoes β-elimination to produce a cyclic allene (**62**) in good yield.



Scheme 16: Allene synthesis by β-elimination of sulfoxide derivatives

Allene Synthesis via Radical Intermediates

Another method of allene synthesis based on β-elimination of sulfinyl radicals was designed by Malacria and co-workers. An allyl bromide is treated with excess amount of tris(trimethyl)silane (TTMS) and 2,2´-azobisisobutyronitrile (AIBN) to give a conjugated radical. Orbital rotation in the intermediate produces a species that undergoes β-elimination to afford the allene. When tin hydride is used in the place of TTMS, the final allene product obtained is contaminated with traces of tin hydride.



Scheme 17: Allene synthesis via radical intermediates

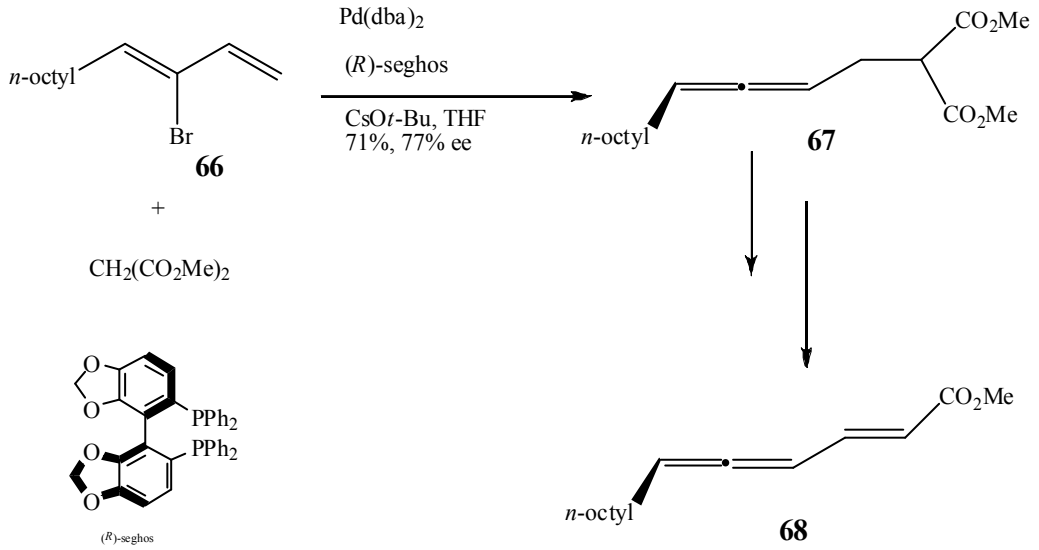
Transition-metal-catalyzed Allene Synthesis

One of the most recent methods that has been used in the synthesis of allenes is the application of transition metal catalysts. Common metals used include palladium, indium, chromium, ruthenium, rhodium, zinc, titanium, and copper. Of all these, Pd is by far the most widely used. The reason for this is that Pd allows for the formation of allenes under very mild conditions.

A major protocol used in Pd catalyzed allene formation is the S_N2' substitution of conjugated dienes. The most common substrate used is 2-bromo-1,3-butadienes. The scope of this method was extended by Hayashi. He showed that hard nucleophiles tend to give the 1,3-

diene products and that a chiral palladium catalyst generates the allene product with high enantioselectivity.

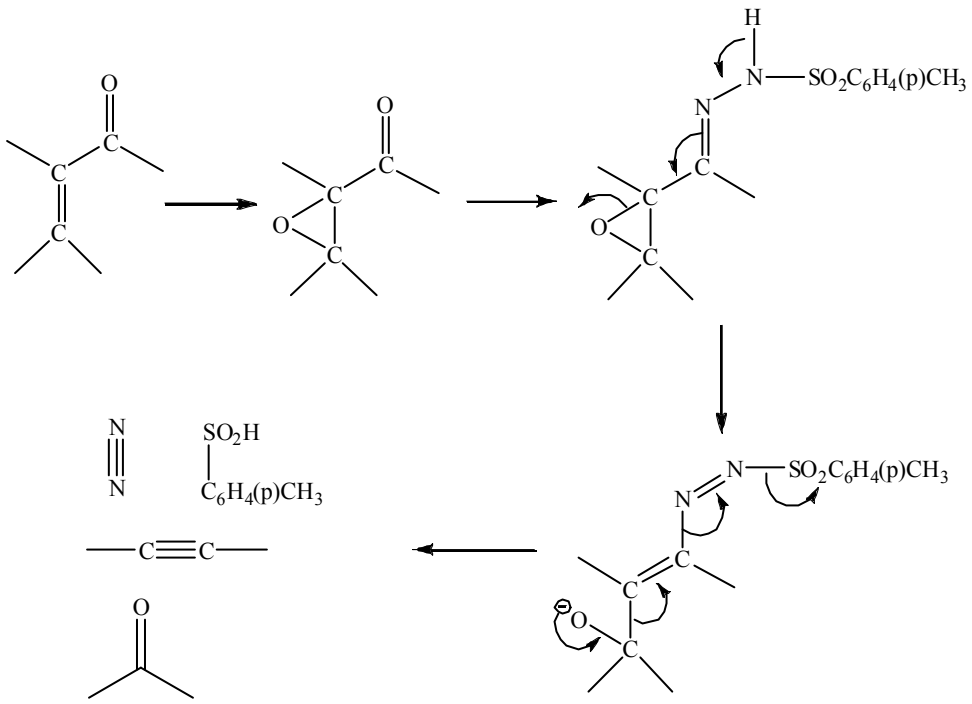
This method was used in the asymmetric synthesis of methyl (R,E)-(–)-tetradeca-2,4,5-trienoate, a sex pheromone of male dried beans beetle.



Scheme 18: Allene synthesis by Pd catalyzed S_N2' substitution of conjugated dienes

All these schemes designed for the synthesis of allenes proved to be insufficient in satisfying our objectives. The final allene products either do not have the desired functionality or do not provide efficient means of converting the allene product to the desired compound.

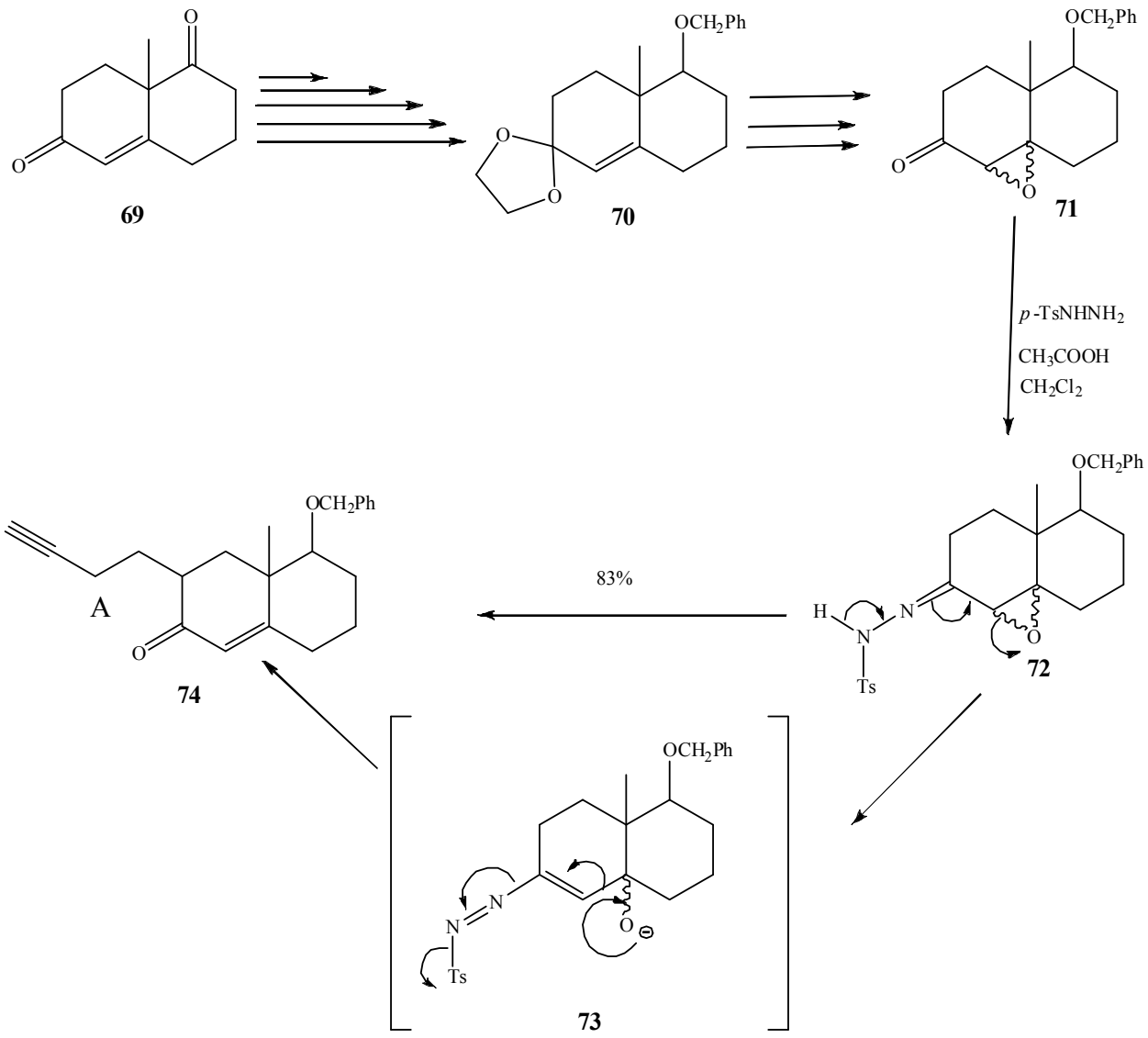
We, therefore, turned to the Eschenmoser fragmentation designed in 1967 and explored further by Masato and coworkers. Eschenmoser showed that fragmentation of α, β-epoxyketones by the reaction with *p*-toluenesulfonylhydrazine occurred readily to afford both terminal and internal acetylenic ketones.



Scheme 19: Mechanism of Eschenmoser fragmentation

Soon after Eschenmoser's publication, Tanabe and coworkers explored this protocol for the synthesis of secosteroid acetylenic ketones and also showed that the mechanism is not limited to aromatic sulfonylhydrazine derivative.

This approach was used by Kane in the synthesis of (±)-zoapatanol. A mixture of diastereomeric epoxides was converted to the monocyclic ω-acetylenic ketone via tosylhydrazone by using an Eschenmoser fragmentation under acidic conditions. The intermediates and mechanism of interest are shown below.



Scheme 20: Synthesis of an alkyne from tosylhydrazone (from Kane synthesis)

Objective of the Research

Our research is focused on developing a novel method for the synthesis of allenes. In order to do this we have developed a theory and our objectives can be presented in two steps.

- Synthesize an oxa-bicyclo-alkan-2-ones and transform it to the corresponding bicyclotosylhydrazone

- Convert the tosylhydrazone to the allene by the methyllithium induced nitrogen gas elimination and rearrangement reaction.

Approach

The first part of our approach was to synthesize an oxa-bicyclo-alkan-2-one.

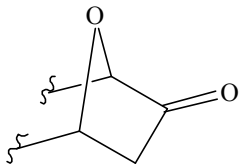
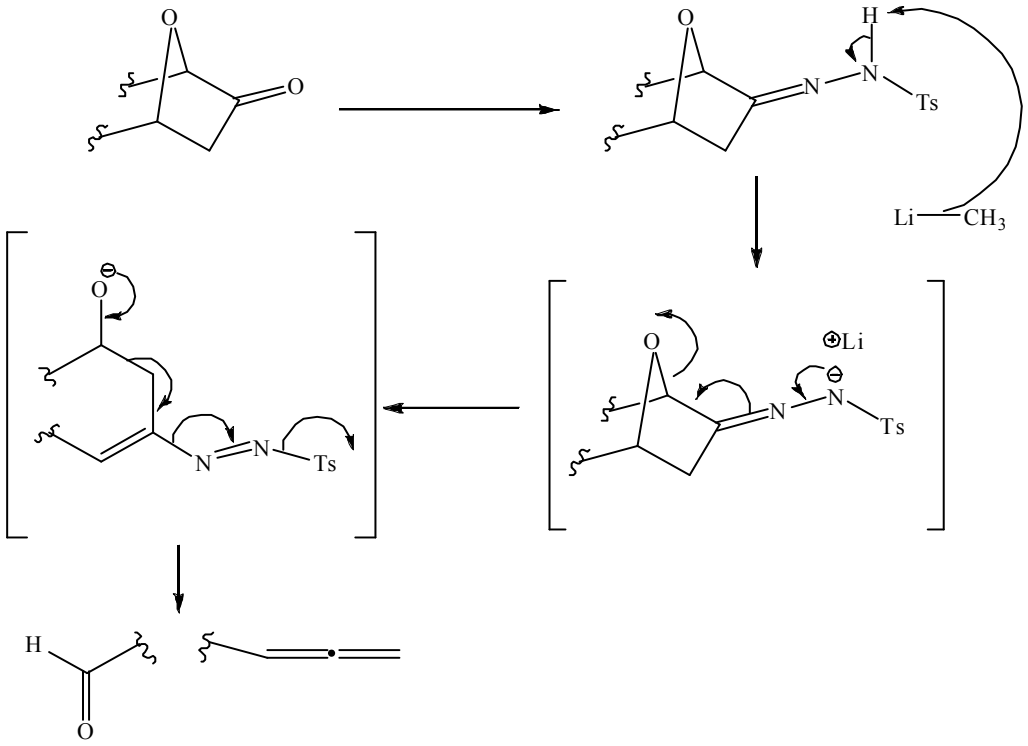


Figure 5: Model oxa-bicyclo-alkan-2-one

The second part was to convert this ketone to the tosylhydrazone and do a methyllithium induced nitrogen gas elimination and rearrangement as shown below.

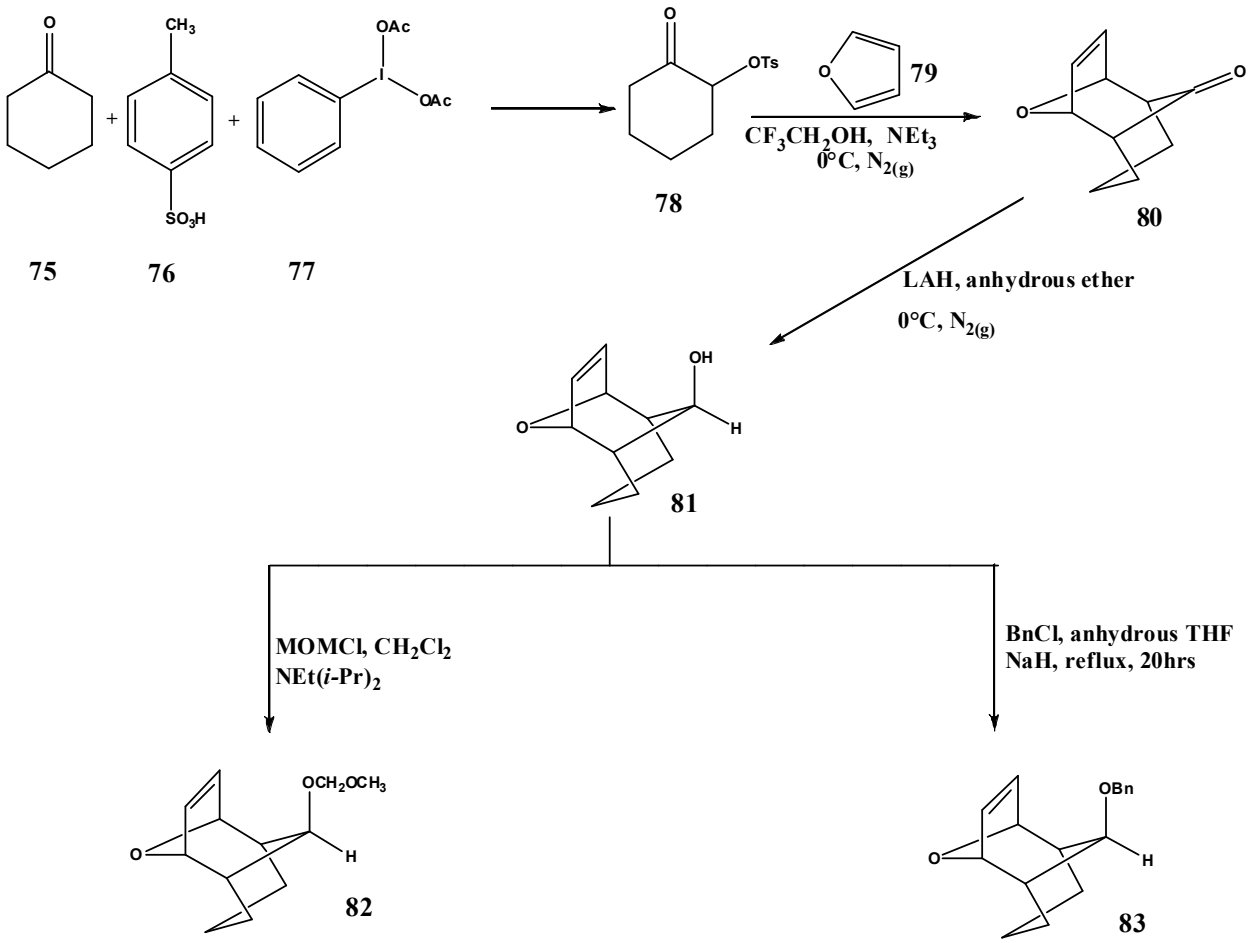


Scheme 21: Novel strategy for allene synthesis

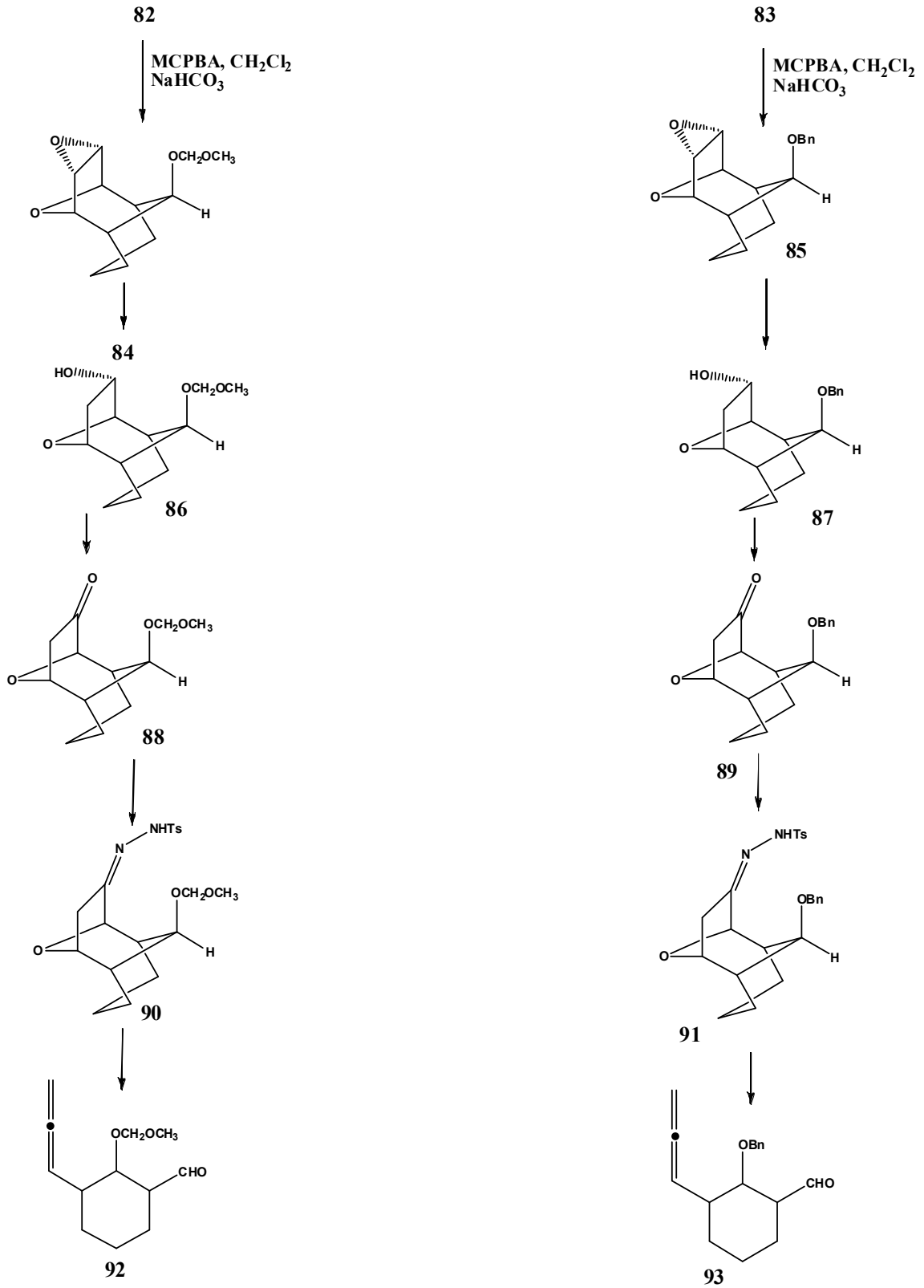
We recognize that in Eschenmoser fragmentation, the ring strain in the three-membered epoxide ring enhances ring opening. However, our molecule contains a five-membered epoxide

ring that does not have as much ring strain and so our conjugated anion generated by base treatment may or may not open the epoxide ring. If the ring opens, then fragmentation should occur exactly as observed for the classic Eschenmoser reaction.

Based on this strategy, we designed an approach for the synthesis of our required allene.



Scheme 22: Strategy for allene synthesis

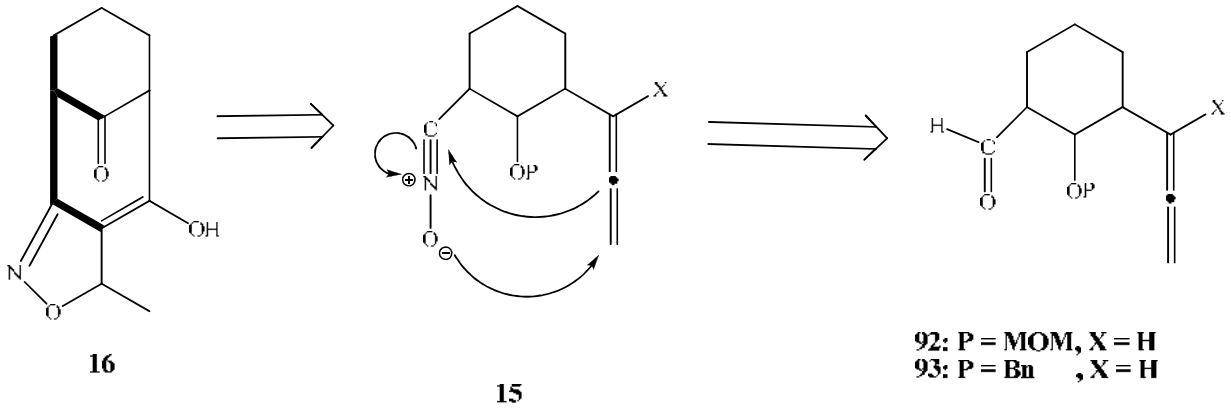


Scheme 22 (continued): Strategy for allene synthesis

CHAPTER 2

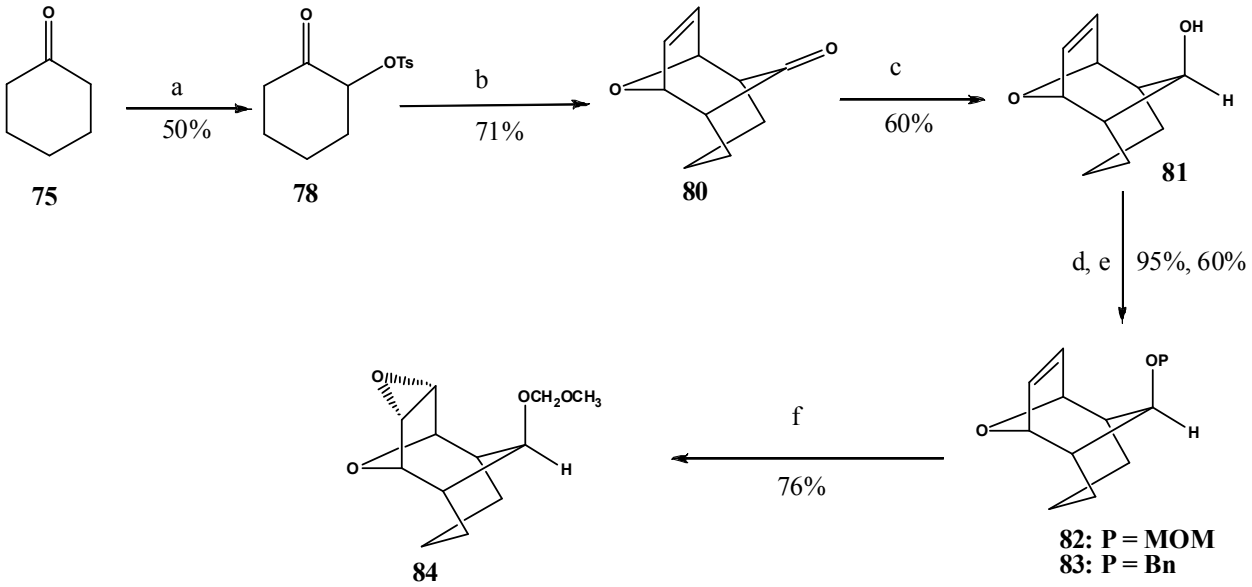
RESULTS AND DISCUSSION

Our overall objective is to synthesize hyperforin and our retrosynthetic analysis involves a step requiring an intramolecular nitrile oxide allene cycloadditions as seen in the scheme below. We hypothesized that we could synthesize **15** from **92** or **93**. The objective of this study is aimed at synthesizing **92** and/or **93** by the application of Eschenmoser fragmentation.



Scheme 23: Retrosynthetic analysis for allene synthesis

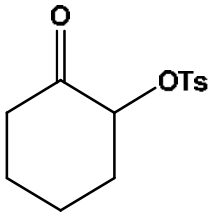
Successful reactions carried out, together with reagents used in completing transformations are shown below (Scheme 24). The percentage yield in each reaction is also indicated.



a) 1.1 eq *p*-toluenesulfonic acid, 1 eq iodobenzene diacetate (b) Furan, CF_3CH_2OH, NEt_3 (c) $LiAlH_4$, anhydrous ether, 0°C (d) MOMCl, $N(i\text{-}Pr)_2Et$, CH_2Cl_2 (e) BnCl, NaH, THF, Δ (f) MCPBA, $NaHCO_3$, CH_2Cl_2.

Scheme 24: Toward novel allene synthesis

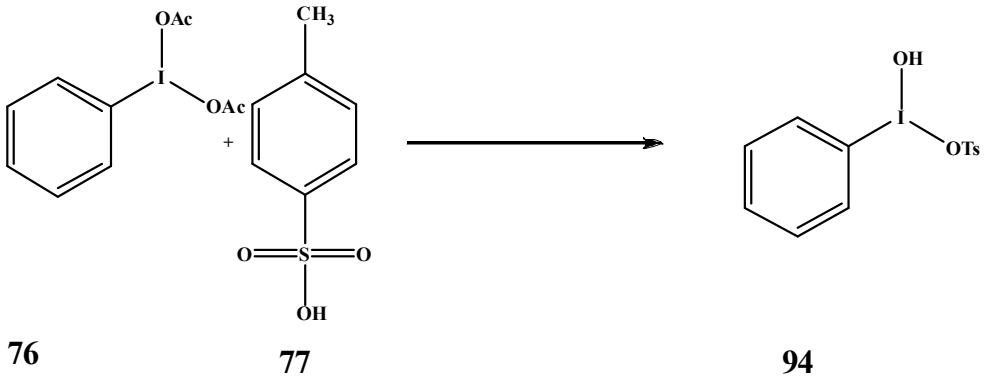
Synthesis of Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (Tosyloxycyclohexanone)



78

Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (**78**) was synthesized using a known procedure developed by Koser and co-workers. The reaction involves a two-step process. The first step is a ligand exchange process. Iodobenzene diacetate (**77**) reacts with toluenesulfonic

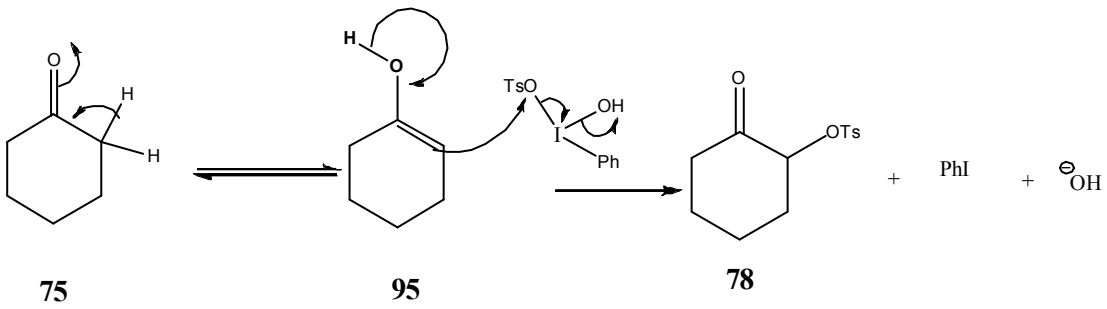
acid (**76**) and undergoes ligand exchange to generate (hydroxytosyloxyiodo)benzene (**94**) in a reaction whose mechanism is not fully understood.



76 **77** **94**

Scheme 25: First mechanistic step in the synthesis of tosyloxycyclohexanone (**78**)

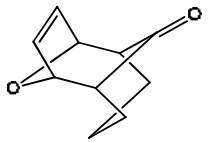
Under the reaction conditions, cyclohexanol undergoes tautomerization to the enol that reacts with the intermediate to form the tosyloxyketone (**78**) with yields ranging between 40%-50%.



75 **95** **78**

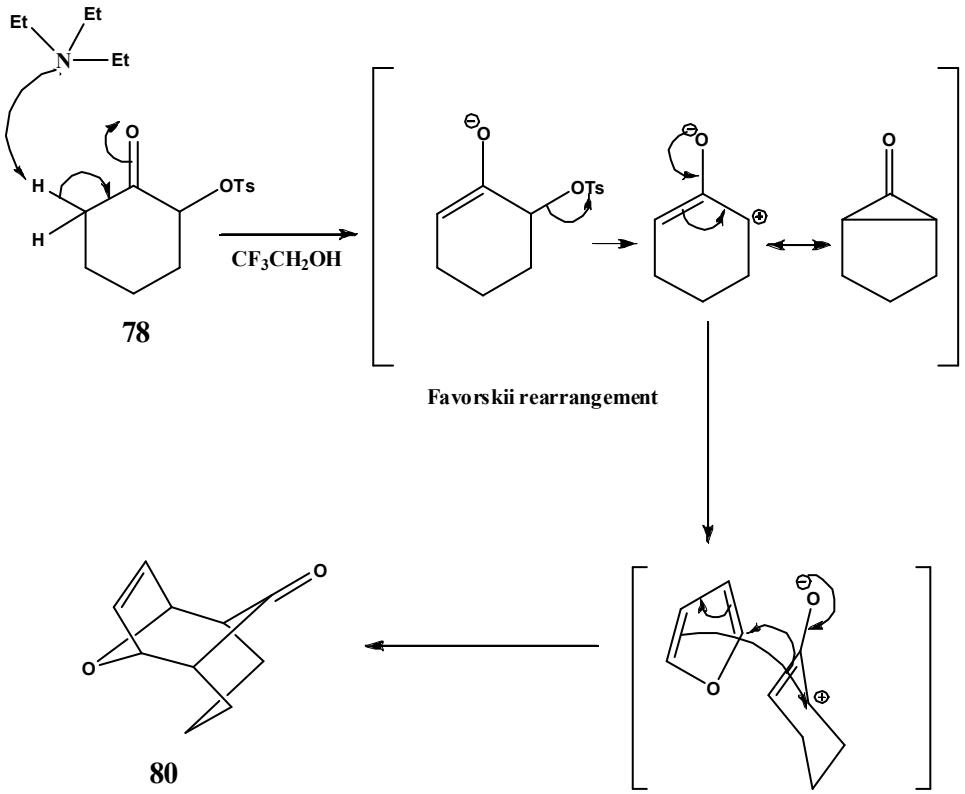
Scheme 26: Second mechanistic step in the synthesis of tosyloxycyclohexanone (**78**)

Synthesis of 11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-one



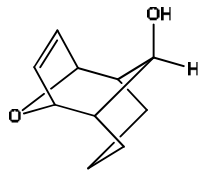
80

The cyclization reaction between tosyloxycyclohexanone (**78**) and furan (**79**) is carried out in trifluoroethanol that enables the cyclization process. The reaction is done under kinetically controlled conditions involving dropwise addition of base to the ketone (**78**) at 0° C. The orientation of the molecules prior to the transition state of the cyclization, results in compound **80** as shown on the scheme below.



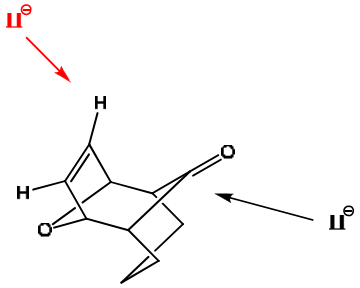
Scheme 27: Mechanism of cyclization

Synthesis of 11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-ol



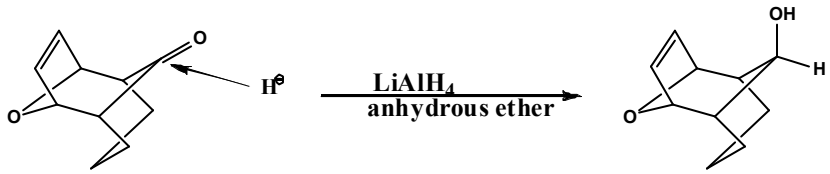
81

From the structure of **80**, we expect that there are two modes of attack by the hydride ion from the reducing agent.



80

In a paper published by Camps, he observed that reduction of ketone **80** using $LiAlH_4$, would result in the stereoselective reduction to the *syn*-alcohol involving attack of the hydride ion from the less hindered side.



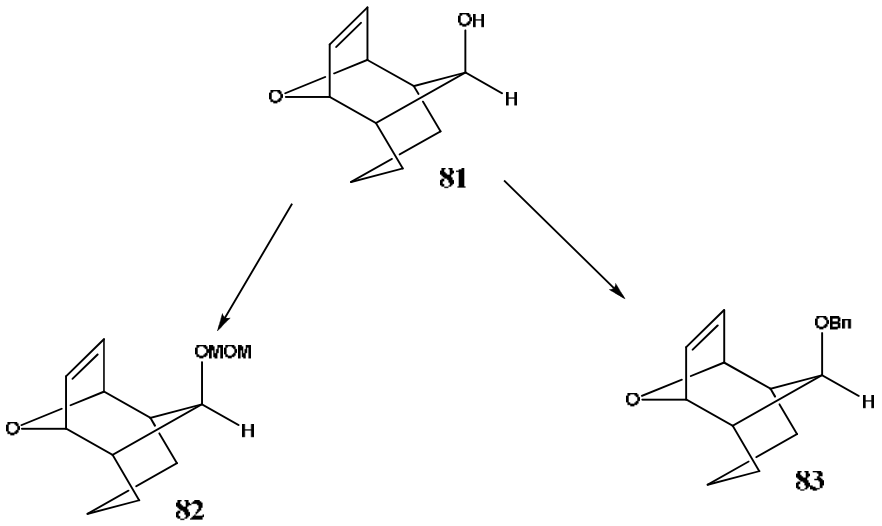
80 **81**

Scheme 28: Reduction of ketone **80** with lithium aluminum hydride

A solution of the ketone in anhydrous ether was added dropwise to a solution of the reducing agent in ether at 0°C. The reaction proved to be temperature sensitive because attempts

to run the reaction at room temperature were unsuccessful. The yields of this reaction were low. We registered a 40%-50% yield in most cases.

Alcohol **81** was used to synthesize two new compounds involving protection of the alcohol **82** and **83**. Protection with MOMCl gave significantly higher yields (80%-95%). The benzyl ether had a characteristic bright yellow color and this was helpful in purification by chromatography because progress of the product could be visually monitored.

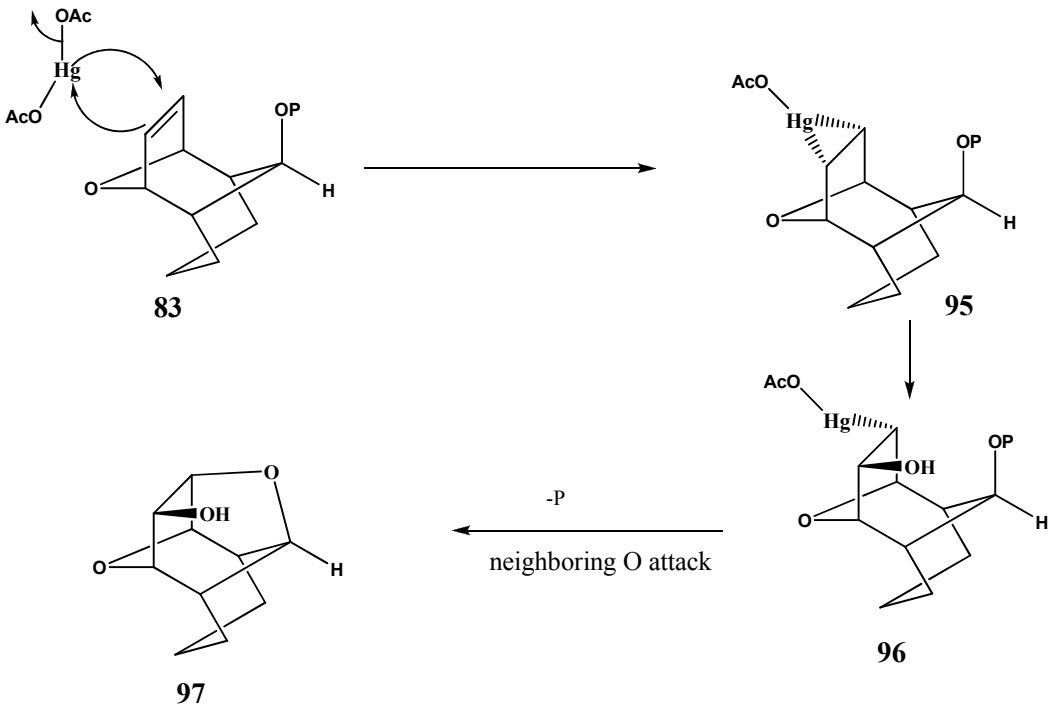


Scheme 29: Alcohol protection by MOMCl and BnCl

This product was characterized by ^{1}H and ^{13}C NMR, GC-MS and IR analysis and the results are recorded in the experimental section.

Attempts to convert **82** and **83** into alcohols by oxidation of the olefin with mercuric acetate failed to produce the desired product. The ^{1}H NMR analysis showed alcohol coupling but the ^{13}C was not consistent with structure **84** or **85**. The first observation was that in both cases the protecting group was lost and the ^{13}C NMR showed 10 peaks.

An IR spectrum showed that a cyclization process had occurred leading to an alcohol. We then hypothesized that the oxygen molecule from the protected alcohol was close enough to the mercurinium ion and opened this ion by neighboring group participation to generate the alcohol as shown in the scheme below. However, we are yet to prove the mechanism involved.

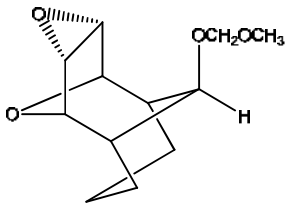


Scheme 30: Proposed mechanism of reaction of **82** and **83** with mercuric acetate.

Since the *syn*-alcohol was proving to be a problem, we tried to reduce ketone **80** by Wolf-Kishner reduction but the reaction failed to give the required product.

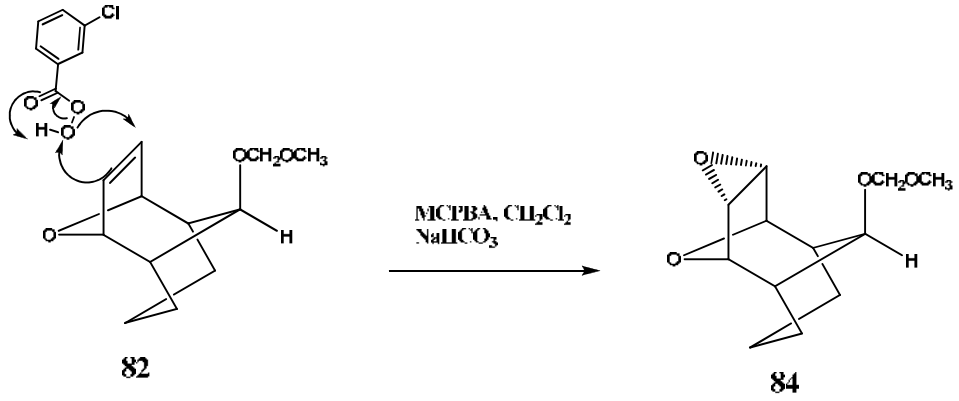
Rather than doing a direct oxidation to the alcohol, we attempted to convert the olefin to the epoxide **84** and then do a reduction of the epoxide **84** to the corresponding alcohol **84**.

Synthesis of Epoxide of **84**



84

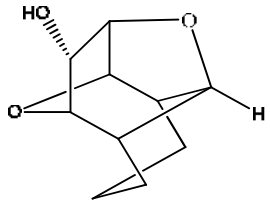
Epoxide **84** was successfully prepared using a known procedure by adding *m*-chloroperoxybenzoic acid to a solution of **82** in dichloromethane and 0.5M $NaHCO_3$ as buffer. Epoxide **84** was obtained in moderate yields of 50%-70% with minimal purification.



82 **84**

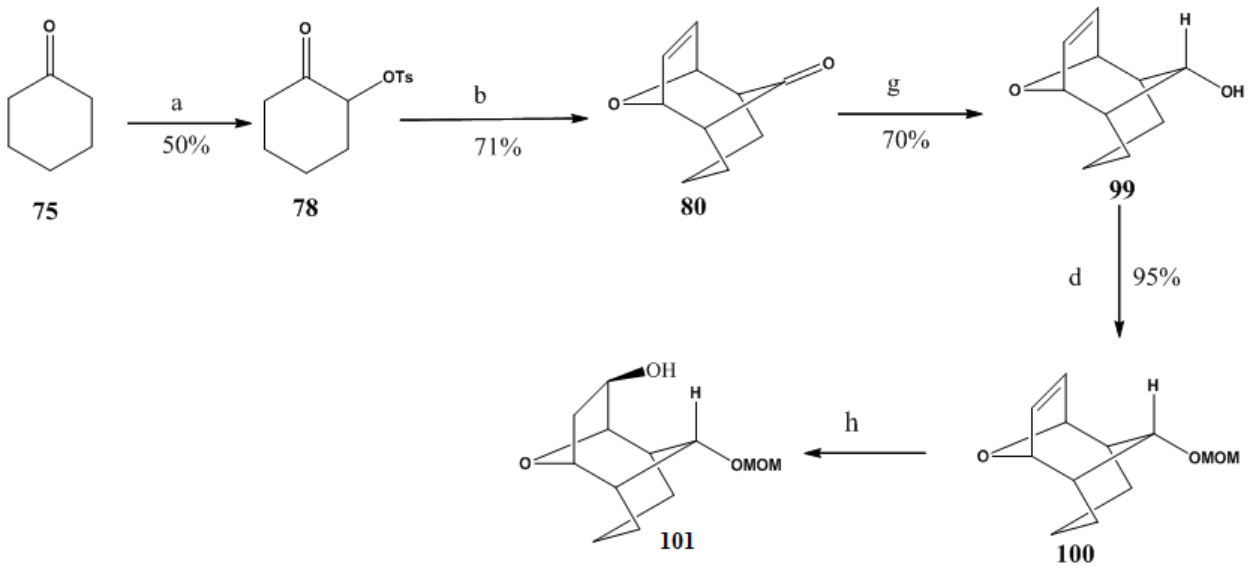
Scheme 31: Mechanism of synthesis of epoxide by MCPBA

However, attempts to reduce **84** to the corresponding alcohol (**86**) were unsuccessful. The protecting group was lost and the ^{13}C NMR did not correspond to the expected compound. The spectrum was similar to that obtained during oxymercuration, but the positions of the peaks were not exactly the same. We proposed that this difference could be as a result of the difference in the orientation of the alcohol function. We think the structure obtained during the reduction of the epoxide is actually:



98

Because the orientation of the alcohol was posing a problem, we decided to modify our procedure so as to change the orientation of the reduction of ketone **80**. In the same paper by Camps mentioned earlier, he noted that in order to obtain the *trans*-alcohol by reduction of **80**, aluminum triisopropoxide should be used in the place of $LiAlH_4$. The structure of the alcohol (**99**) would therefore not permit cyclization during oxymercuration or during epoxide reduction.



75 **78** **80** **99** **101** **100**

(a) 1.1 eq *p*-toluenesulfonic acid, 1 eq iodobenzene diacetate (b) Furan, CF_3CH_2OH, NEt_3 (g) Al(*i*-OPr)$_3$, xylene Δ (d) MOMCl, N(*i*-Pr)$_2$Et, CH_2Cl_2 (h) $Hg(OAc)_2$, THF:H_2O, $NaBH_4$

Scheme 32: Toward novel allene synthesis via *trans*-alcohol (**99**)

The *trans*-alcohol was successfully synthesized using the procedure published by Camps. We, however, noticed lower yields than those published.

The alcohol (**99**) was successfully protected with MOMCl using the same procedure as for the *syn*-alcohol. We have equally succeeded in oxidizing the olefin to the alcohol (**101**) by oxymercuration and are currently attempting to oxidize the alcohol to the ketone. Our assumption that neighboring group participation would not work here due to orientational limitations is therefore true.

Conclusion

Despite the initial setbacks owing to the neighboring O-participation, we have made significant progress towards achieving our overall objective. The problem of this neighboring group participation has been resolved by synthesizing the *syn*-alcohol. This has led to the successful oxymercuration of the olefin to yield the alcohol. Oxidation of this secondary alcohol should not pose any real problem because several protocols exist for such reactions.

With the ketone produced, the tosylhydrazone can be generated and our hypothesis can be tested for the synthesis of allenes.

CHAPTER 3

EXPERIMENTAL SECTION

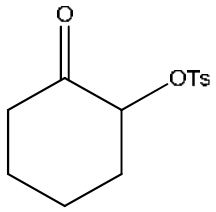
General Methods

^{1}H NMR and ^{13}C NMR data were recorded on a JOEL Oxford AS 400 instrument. ^{1}H NMR spectra are reported as follows: chemical shift [integration, multiplicity (s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet) coupling constants in hertz. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The Infrared data were obtained using a Fourier Transformed Infrared Resonance (FTIR) Spectrometer, Shimadzu (IRPrestige-21). A Shimadzu GCMS-QP2010 Plus instrument was used for all mass spectral analysis.

Analytical thin-layer chromatography was conducted using Whatman K5F 150Å 250µm silica gel plates. Column chromatography was performed in ICN Silitech silica gel (63-200 mesh, 60 Ä).

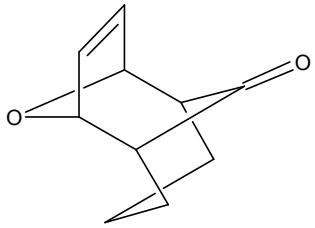
All commercial grade reagents were used without further purification except as otherwise stated in the procedure. All reactions requiring inert conditions were carried out in flame-dried glassware under dry $N_{2(g)}$ atmosphere. Tetrahydrofuran was dried by distillation from benzophenone ketyl.

Experimental Procedures



78

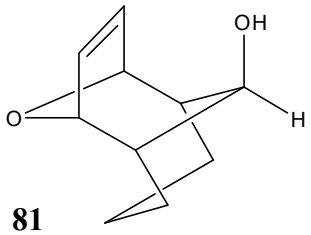
Toluene-4-sulfonic acid 2-oxo-cyclohexyl ester (78). Iodobenzene diacetate (7.13 g, 22.1 mmol), p-toluene sulfonic acid (4.42 g, 23.2 mmol) and cyclohexanone (2.28 g, 23.2 mmol) were ground for 20 min. Chromatography of the residue over 200 g of silica gel (eluted with EtOAc-hexane, 1:1), afforded a pale yellow oil that was subsequently recrystallized in hexane to afford 2.94 g (50%) of a white solid (**78**): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.57-2.60 (m, 8H), 2.42 (s, 3H), 4.89 (dd, 1H, J = 5.88 Hz), 7.32 (d, 2H, J = 8.08 Hz,), 7.82 (d, 2H, J = 8.08 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.78 (s), 23.23 (s), 27.01 (s), 34.71 (s), 40.67 (s), 81.91 (s), 128.03 (s), 129.82 (s), 144.99 (s), 202.86 (s).



80

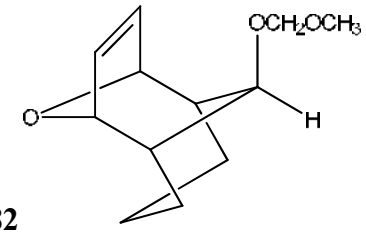
11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-one (80). To 5.36 g (20.0 mmol) of tosyloxyketone **78** in 20.0 mL of furan at 0°C under nitrogen was added 20.0 mL of 2,2,2-trifluoroethanol. To the resulting solution was added dropwise 5.20 mL (37.5 mmol) of

triethylamine over 15 min. The reaction was warmed to room temperature, stirred for 4 h, diluted with 50.0 mL of water, and extracted with four 75-mL portions of ether. The combined organic layers were washed with 100 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue obtained was chromatographed over silica gel (EtOAc-hexane, 1:1 as eluent). Concentration yielded 2.32 g (71%) of the cycloadduct **80** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400MHz,) δ 1.45-2.70 (m, 8H), 4.94 (s, 2H), 6.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz,) δ 215.13 (s), 135.54 (s), 83.63 (s), 53.15 (s), 31.15 (s), 20.92 (s).



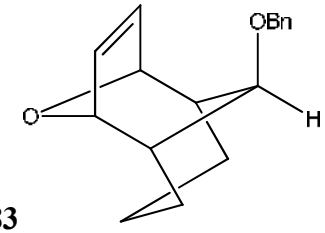
81

***Syn*-11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-ol (81)**. To a slurry of 1.52 g (40.0 mmol) of lithium aluminum hydride in 100 mL of anhydrous ethyl ether was added dropwise 3.28 g (20 mmol) of the cycloadduct **80** in a solution of 100 mL of anhydrous ethyl ether at 0°C. The reaction was stirred 3 h. The reaction was quenched by careful addition of 25 mL of ethyl acetate and washed with five 100-mL portions of ammonium chloride and two 100-mL portions of water. The organic layer was dried ($MgSO_4$) *in vacuo*. The resulting residue was chromatographed over 160 g of silica gel (EtOAc-hexane, 1:1 as eluent) to afford 1.99 g (60%) of alcohol **81** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400MHz,) δ 1.45-1.51 (m, 2H), 1.76-2.11 (m, 4H), 2.32-2.55 (m, 2H), 2.72 (d, 1H, J = 11.36 Hz, O-H), 3.60 (d, 1H, J = 10.64 Hz), 4.76 (s, 2H), 6.65 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.09 (s), 30.42 (s), 40.53 (s), 75.99 (s), 83.12 (s), 137.92 (s).



82

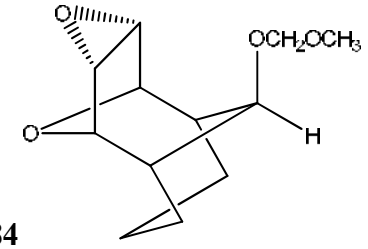
***Syn*-10-Methoxymethoxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (82)**. To a solution of 3.32 g (20.0 mmol) of alcohol **81** dissolved in 100 mL of dichloromethane was added 2.50 g (31.1 mmol) of chloromethyl methyl ether (MOMCl), followed by 3.88 g (30.0 mmol) of N,N-diisopropylethylamine over 5 min. The reaction was stirred 12 h. The reaction was quenched with 50 mL of water, the layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residue over 200 g of silica gel (EtOAc-hexane, 1:2 as eluent) afforded 4.02 g (95%) of a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.61 (m, 2H), 1.72-2.08 (m, 4H), 2.42-2.58 (m, 2H), 3.28 (s, 3H), 3.54 (s, 1H), 4.51 (s, 2H), 4.63 (s, 2H), 6.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.27 (s), 30.19 (s), 37.86 (s), 55.25 (s,), 81.41 (s) 82.91 (s), 95.87 (s), 135.02 (s).



83

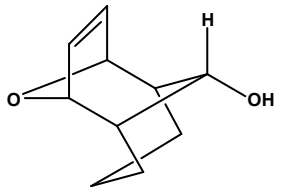
10-Benzyloxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (83). To a solution of 100 mL of anhydrous THF, 0.58 g of sodium hydride and 3.17 g (25.0 mmol) of benzyl bromide was added 3.32 g (20.0 mmol) of alcohol **81** as a solution in 100 mL of anhydrous THF dropwise at room temperature. The resulting solution was heated under reflux for 20 h. The reaction was quenched by addition of 100 mL of saturated NH_4Cl, extracted with four 50-mL portions of ether, dried

($MgSO_4$), concentrated in vacuo. Chromatography of the residue (Hexanes : EtOAc, 2:1 as eluent) afforded 3.07 g of benzylether **83** as a bright yellow oil (60%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.45-1.61 (m, 2H), 1.72-2.08 (m, 4H), 2.42-2.58 (m, 2H), 3.48 (s, 1H), 4.41 (s, 2H), 4.69 (s, 2H), 6.39 (s, 2H), 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.55 (s), 30.24 (s), 36.58 (s), 66.99 (s), 82.48 (s), 83.07 (s), 127.24 (s), 127.36 (s), 128.40 (s), 135.10 (s,), 139.17 (s).



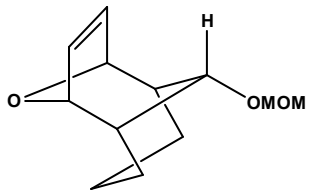
84

To a solution of protected alcohol **82** (2.10 g, 10.0 mmol) in 100 mL of CH_2Cl_2 and 20 mL of 0.5 M aqueous $NaHCO_3$, was added 1.08 g (5.0 mmol) of *m*-chloroperoxybenzoic acid. Additional *m*-chloroperoxybenzoic acid and 0.5 M aqueous $NaHCO_3$ was added after 9 h (1.08 g, 5.0 mmol) and after 18 h (0.54 g, 2.5 mmol). The mixture was stirred for 48 h and the two phases were separated. The organic portion was washed with three 50.0-mL portions of 1 M NaOH and one 100-mL portion of H_2O and dried ($MgSO_4$). Concentration by rotary evaporation followed by high vacuum to give a 1.72 g of a colorless oil (76%): IR (acetone): 2935 cm^{-1} (m), 1033 (m); ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.40-1.51 (m, 2H), 1.77-2.08 (m, 4H), 2.32-2.51 (m, 2H), 3.31 (s, 3H), 3.48 (s, 1H), 3.60 (s, 2H), 4.14 (s, 2H), 4.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 20.77 (s), 30.72 (s), 35.74 (s), 54.13(s), 55.62 (s), 76.84 (s), 79.16 (s), 95.34 (s).



99

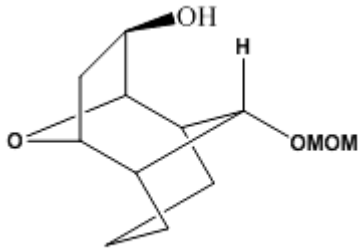
***trans*-11-Oxa-tricyclo[4.3.1.12,5]undec-3-en-10-ol (99)**. A mixture of ketone **80** (25.0 mmol), aluminum triisopropoxide (12.24 g, 60.0 mmol), and 200 mL of *o*-xylene was heated to reflux in a moisture free atmosphere, then 0.5 mL of acetone was added and heating continued for 12 h. The reaction was quenched by addition of 100 mL of 10% NaOH and stirred for a further 30 min. The layers were separated, the aqueous layer extracted with 100 mL of *o*-xylene, dried ($MgSO_4$), and concentrated *in vacuo*. The *o*-xylene solvent was distilled at reduced pressure and the crude product was chromatographed over 200 g of silica gel (EtOAc-hexane, 1:4 as eluent) to afford 2.99 g (70%) of alcohol (**99**) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400MHz,) δ 1.41-1.74 (m, 2H), 1.90-2.11 (m, 4H), 2.15, (s, 1H), 2.22-2.41 (m, 2H), 3.98 (s, 1H), 4.75 (s, 2H), 6.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 19.73 (s), 21.14 (s), 34.20 (s), 66.26 (s), 83.86 (s), 132.65 (s).



100

***trans*-10-Methoxymethoxy-11-oxa-tricyclo[4.3.1.12,5]undec-3-ene (100)**.To a solution of 3.32 g (20.0 mmol) of alcohol **99** dissolved in 100 mL of dichloromethane was added 2.50 g (31.1 mmol) of chloromethyl methyl ether (MOMCl), followed by 3.88 g (30.0 mmol) of N,N-diisopropylethylamine over 5 min. The reaction was stirred 12 h. The reaction was quenched

with 50 mL of water, the layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residue over 200 g of silica gel (EtOAc-hexane, 1:2 as eluent) afforded 4.02 g (95%) of **100** as a yellow oil: IR (acetone): 3942 cm^{-1} (m), 1041 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.60 (m, 2H), 1.91-2.05 (m, 4H), 2.22-2.48 (m, 2H), 3.31 (s, 3H), 3.80 (t, 1H, J = 4.4 Hz), 4.57 (s, 2H), 4.70 (s, 2H), 6.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 20.09 (s), 21.95 (s), 32.85 (s), 55.46 (s,), 72.02 (s) 83.87 (s), 94.62 (s), 132.78 (s); GCMS (*m/z*) 210, 148, 81.



101

To 0.21 g (1.0 mmol) of olefin **100** was added a solution of mercuric acetate (0.38g, 1.2 mmol) in a 1:1 mixture of THF:H_2O (4.0 mL). The mixture was stirred for 48 h, diluted with 3.0 mL of 15% KOH, and treated with 0.04 g $NaBH_4$ in 3.0 mL of 15% KOH. After 1 h the mixture was filtered and the aqueous layer was extracted with three 10-mL portions of CH_2Cl_2, dried ($MgSO_4$), and chromatographed (Hexane:EtOAc as eluent) to afford the alcohol **101** as a colorless oil (60%): IR (acetone): 2943 cm^{-1}, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz,) δ 1.35-1.45 (m, 2H), 1.55-1.1.65 (m, 2H), 1.67-1.85 (m, 2H), 2.21-2.40 (m, 2H), 2.18 (d, 1H) 3.36 (s, 3H), 3.54 (t, 1H), 4.16 (s, 1H), 4.28 (s, 1H), 4.53 (td, 1H), 4.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz,) δ 94.38 (s), 88.85 (s), 81.15 (s), 74.59 (s), 69.82 (s), 55.59 (s), 41.47 (s), 37.91 (s), 36.54 (s), 23.16 (s), 19.65 (s); GCMS (*m/z*) 228, 71, 57.

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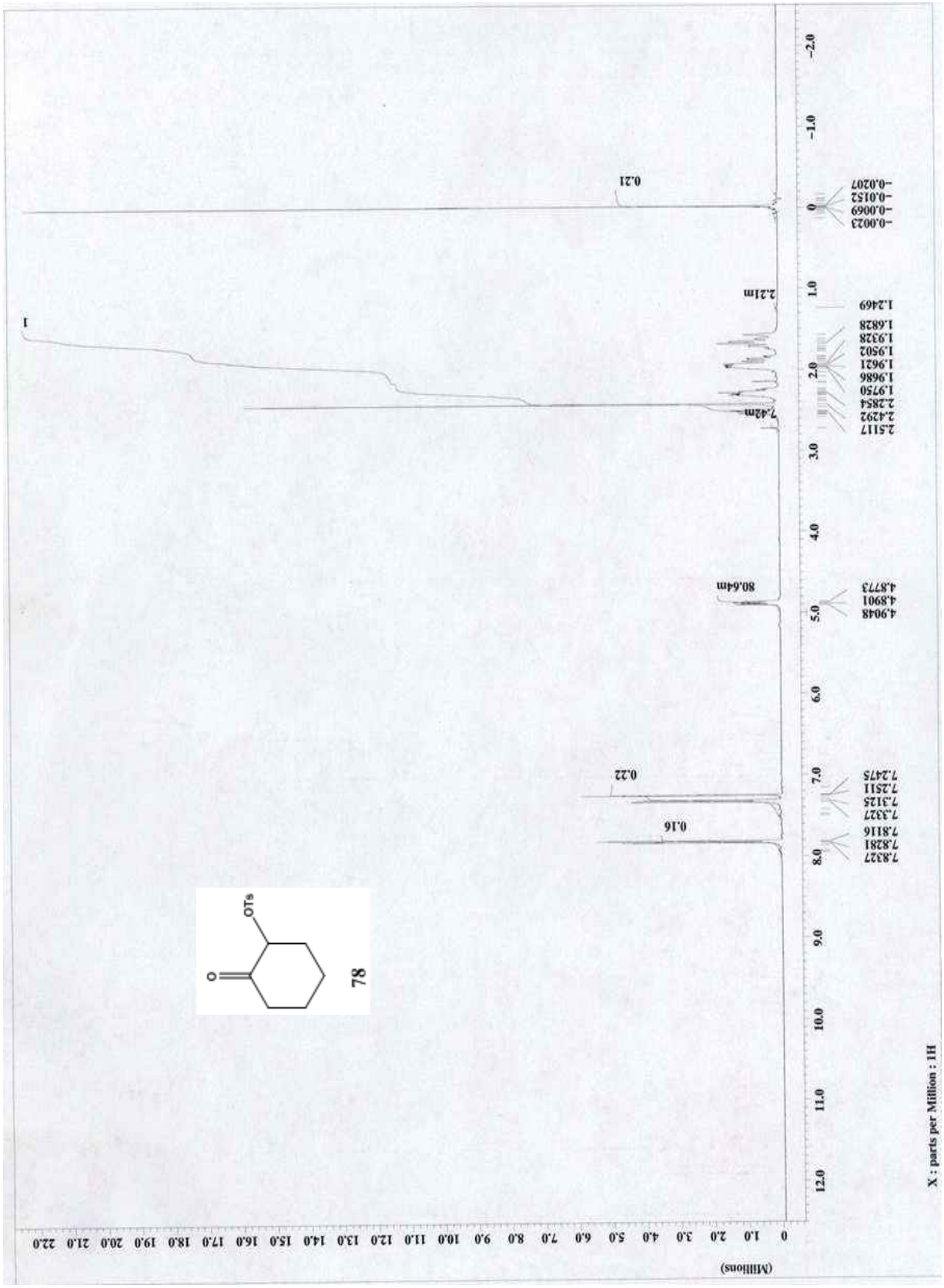
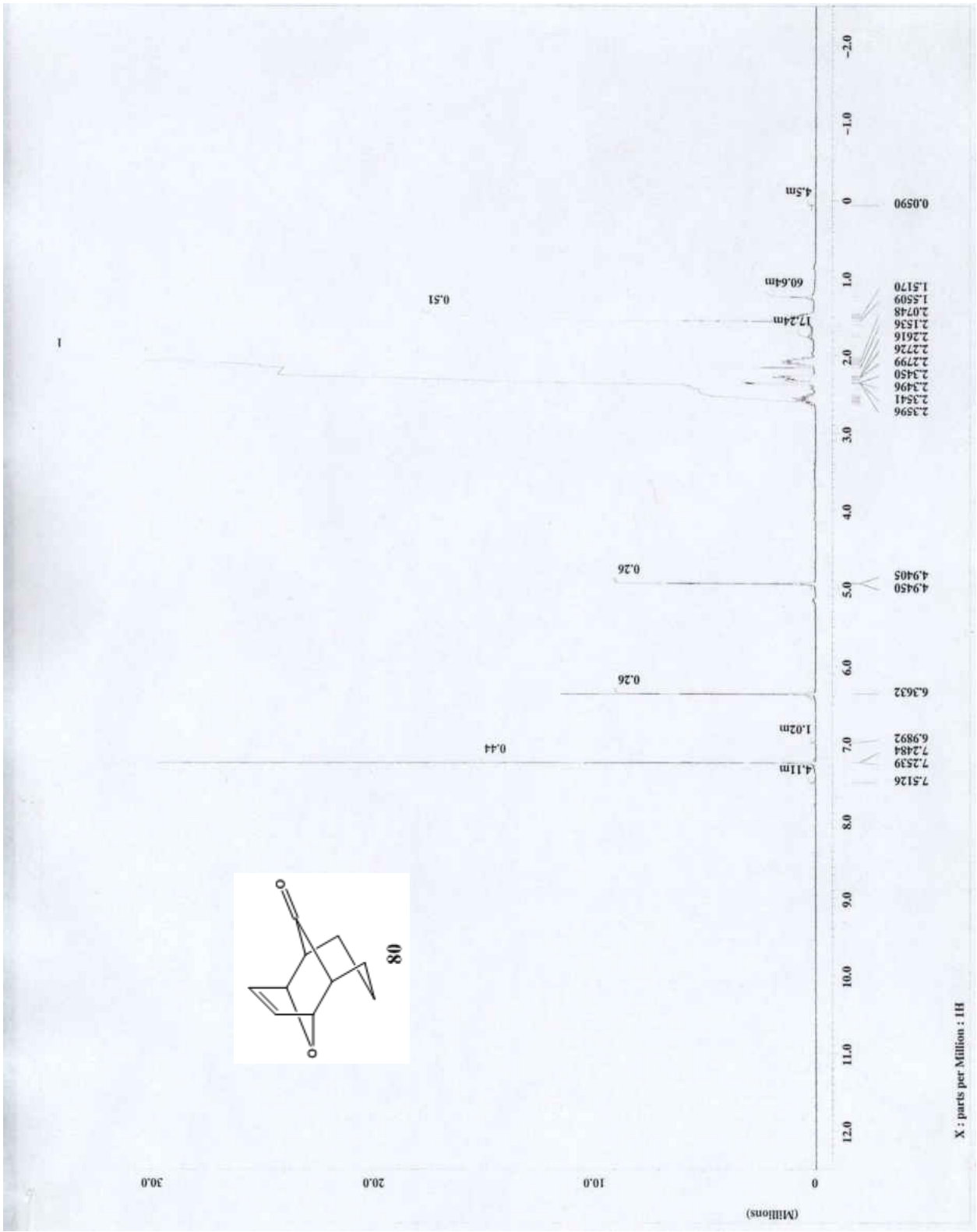
APPENDIX

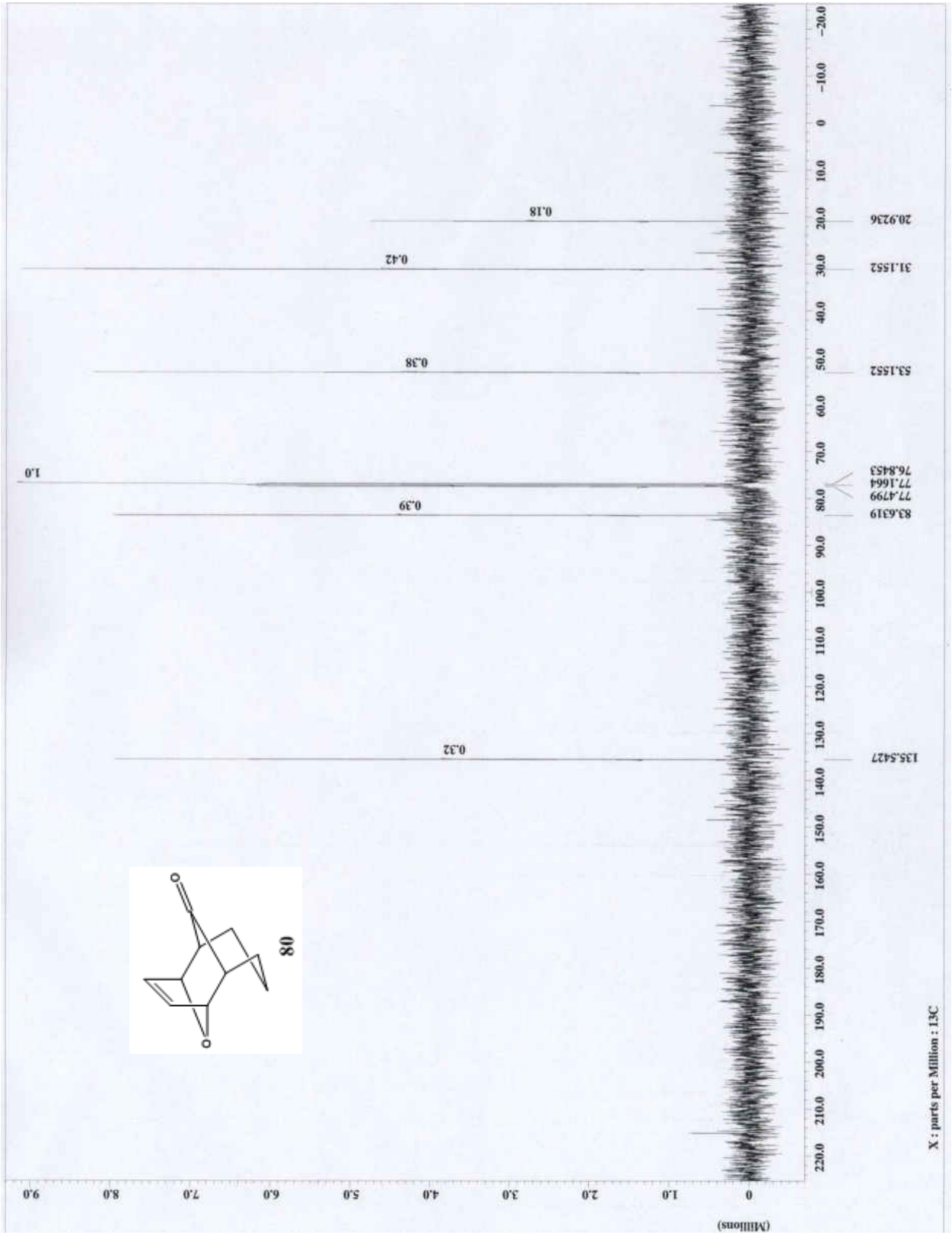
^{1}H NMR and ^{13}C NMR of Compounds Prepared

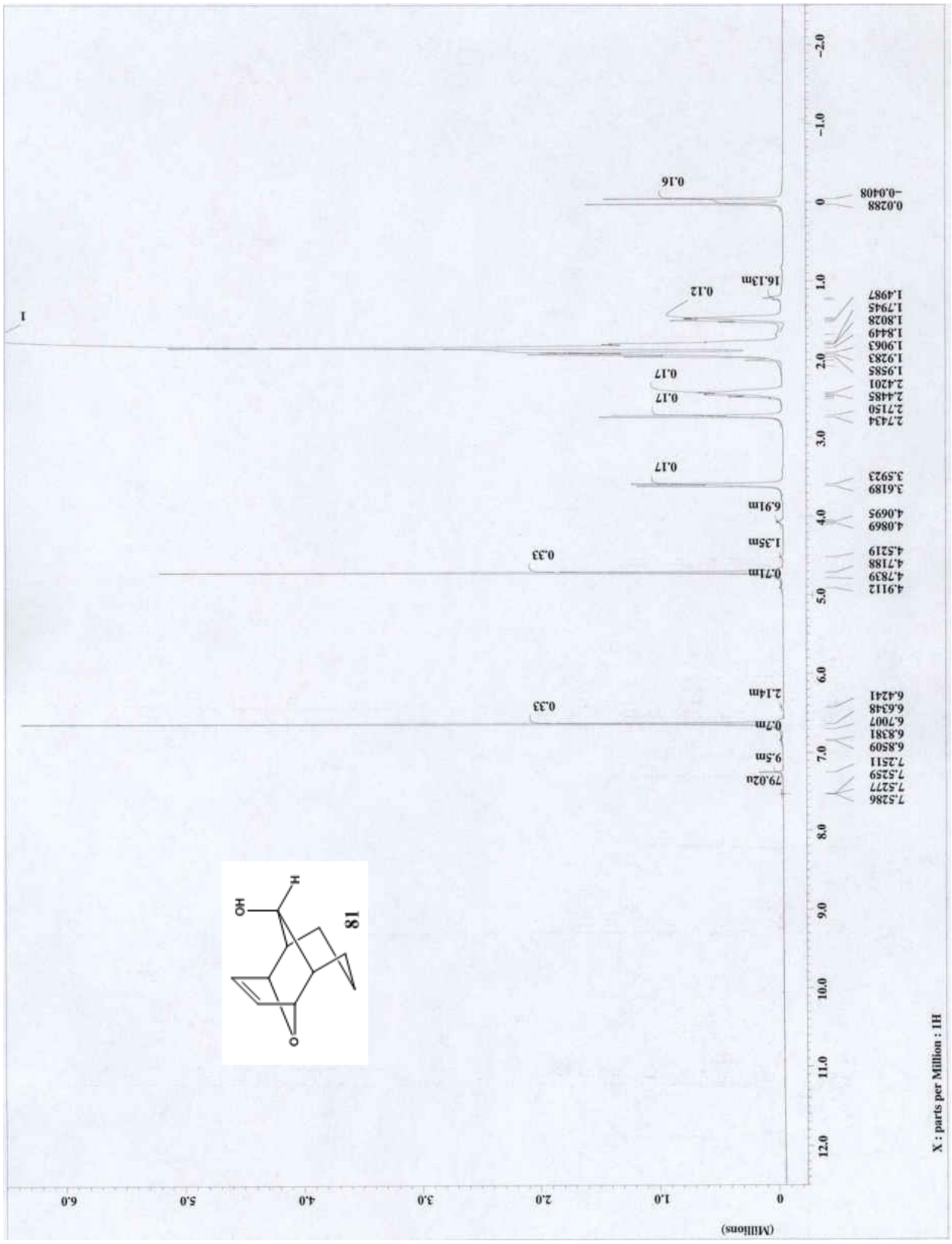
Solvent: d-$CDCl_3$/ TMS

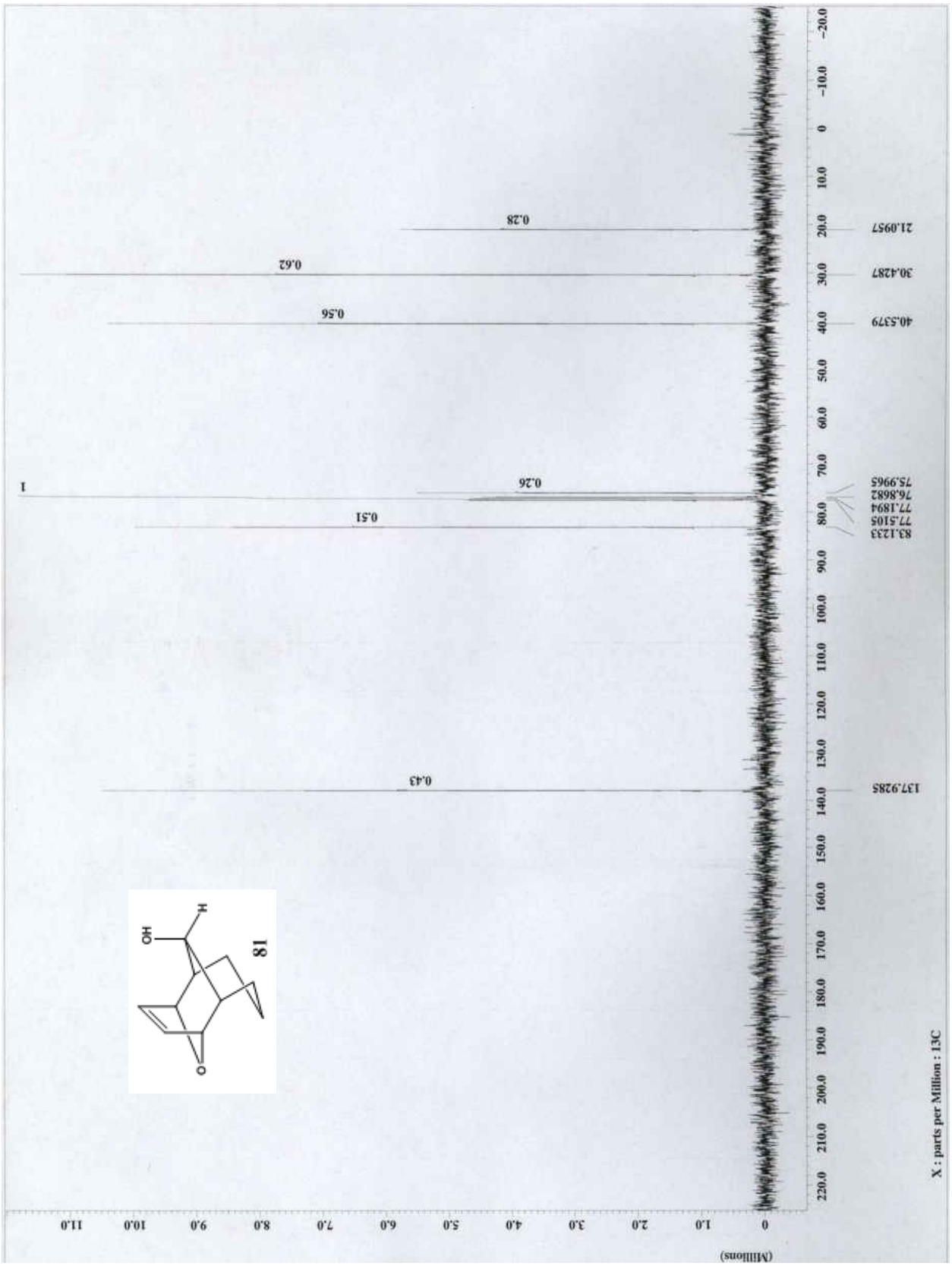

78
OTs
O
X : parts per Million : 1H
(Millions)
0.21
0.16
0.22
80.64m
7.42m
2.21m
1
7.8327
7.8281
7.8116
7.3327
7.3125
7.2511
7.2475
4.9048
4.8901
4.8773
2.5117
2.4292
2.2854
1.9750
1.9686
1.9621
1.9502
1.9328
1.6828
1.2469
-0.0023
-0.0069
-0.0152
-0.0207

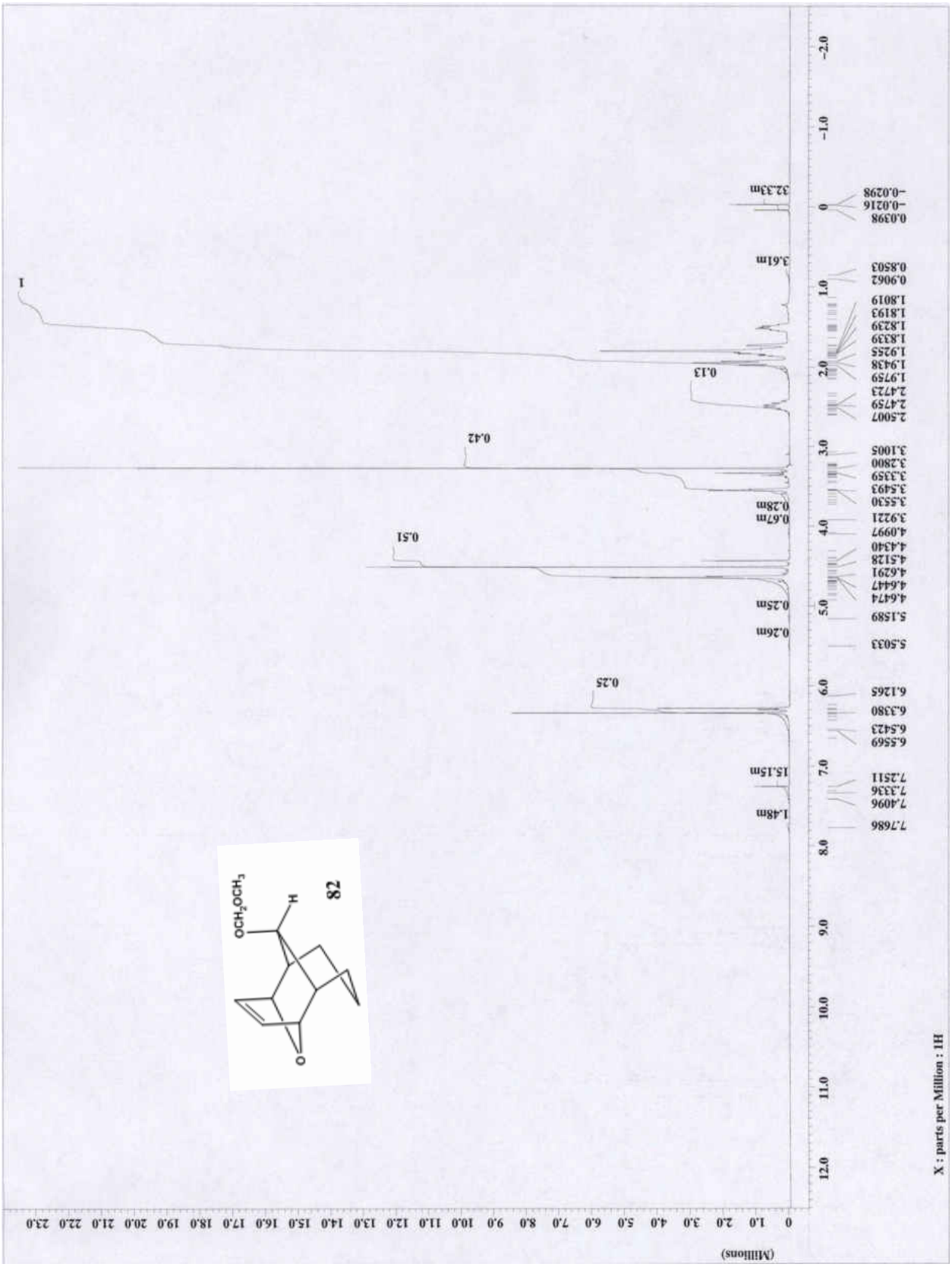
OTs
O
78
(Millions)
X : parts per Million : 13C
202.8658
144.9942
129.8228
128.0335
81.9151
77.4264
77.1052
76.7917
40.6755
34.7110
27.0182
23.2330
21.7801
0.0859


80
X : parts per Million : 1H
(Millions)
7.5126
7.2539
7.2484
6.9892
6.3632
4.9450
4.9405
2.3596
2.3541
2.3496
2.3450
2.2799
2.2726
2.2616
2.1536
2.0748
1.5509
1.5170
0.0590
4.11m
1.02m
17.24m
60.64m
4.5m
0.44
0.26
0.26
0.51

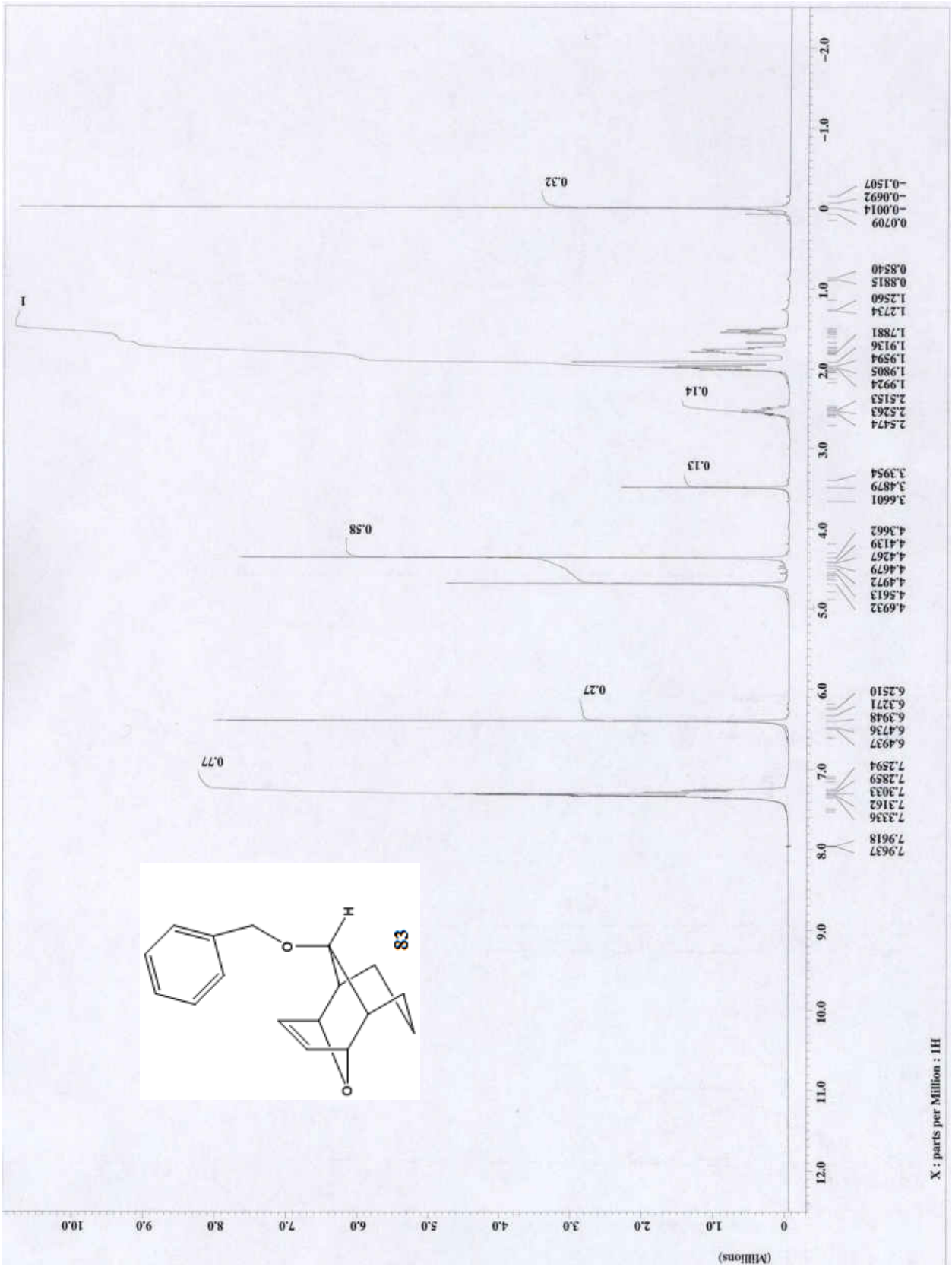

80
1.0
0.39
0.32
0.38
0.42
0.18
135.5427
83.6319
77.4799
77.1664
76.8453
53.1552
31.1552
20.9236
X : parts per Million : 13C
(Millions)

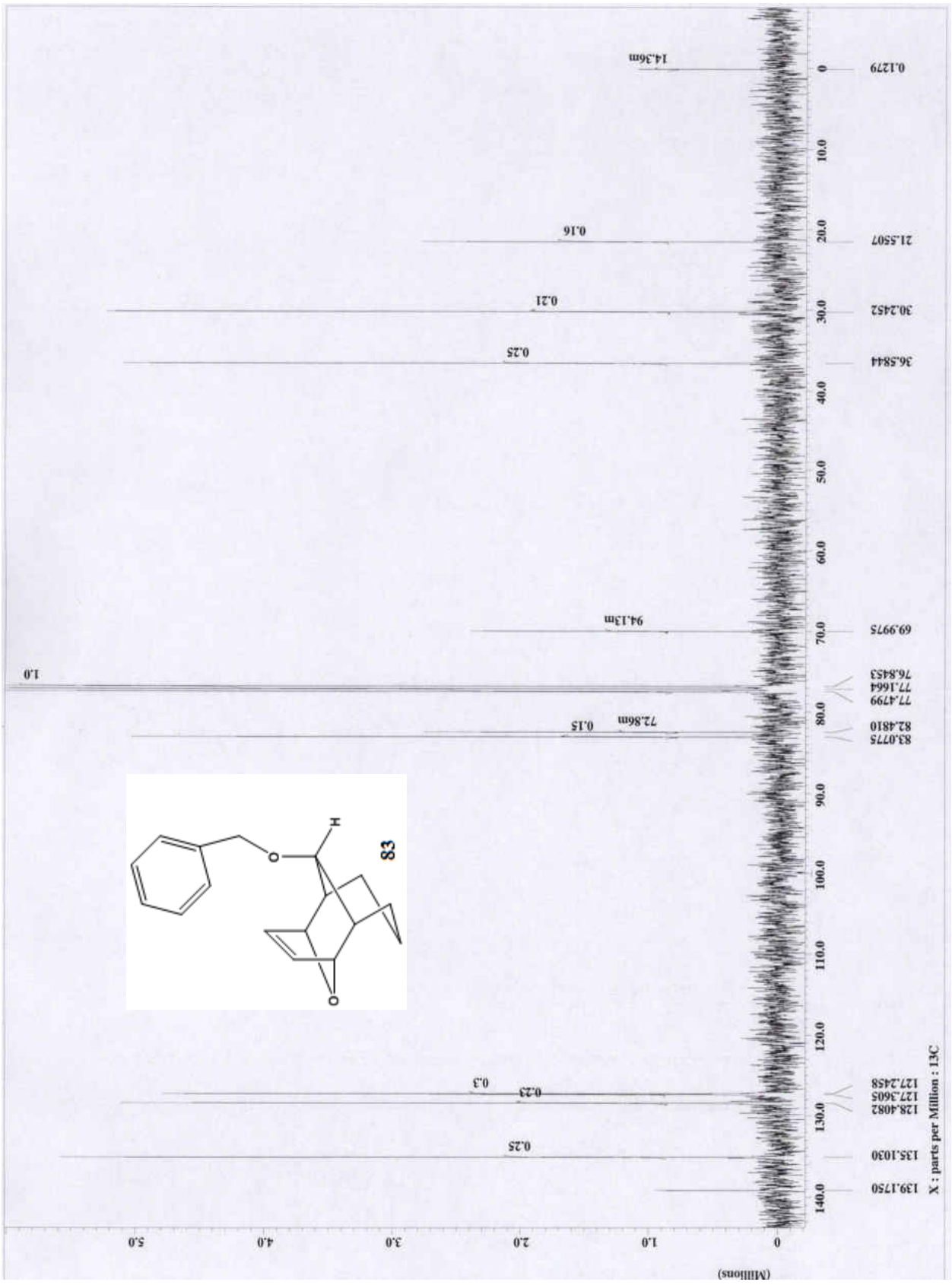

18
OH
H
O
(Millions)
X : parts per Million : 1H
7.5286
7.5277
7.5259
7.2511
6.8509
6.8381
6.7007
6.6348
6.4241
4.9112
4.7839
4.7188
4.5219
4.0869
4.0695
3.6189
3.5923
2.7434
2.7150
2.4485
2.4201
1.9585
1.9283
1.9063
1.8449
1.8028
1.7945
1.4987
0.0288
-0.0408
79.02u
9.5m
0.7m
2.14m
0.71m
1.35m
6.91m
16.13m
0.33
0.17
0.12
0.16
1

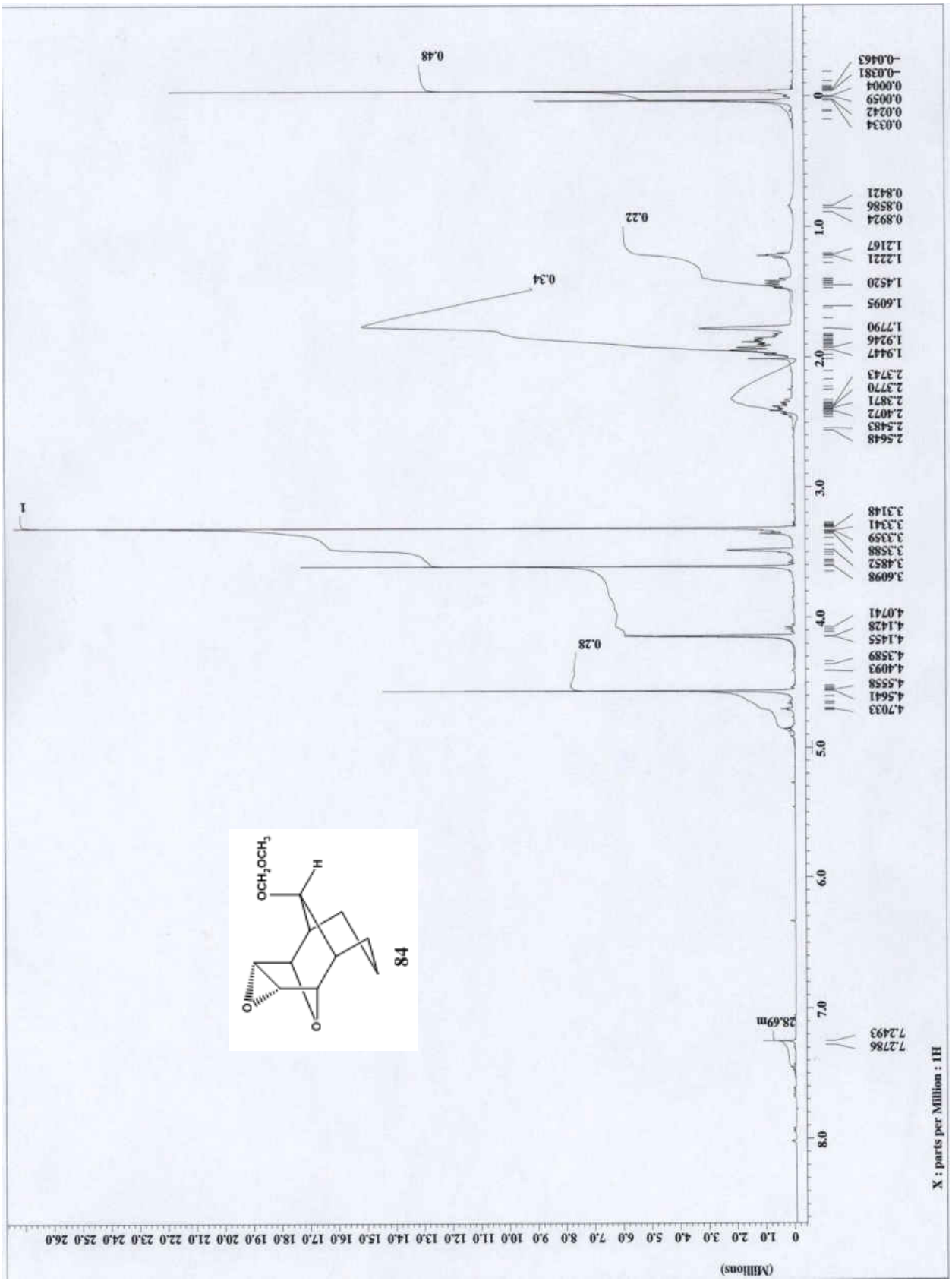

18
OH
H
O
X : parts per Million : 13C
(Millions)
137.9285
83.1233
77.5105
77.1894
76.8682
75.9965
40.5379
30.4287
21.0957
0.43
0.51
0.26
1
0.56
0.62
0.28

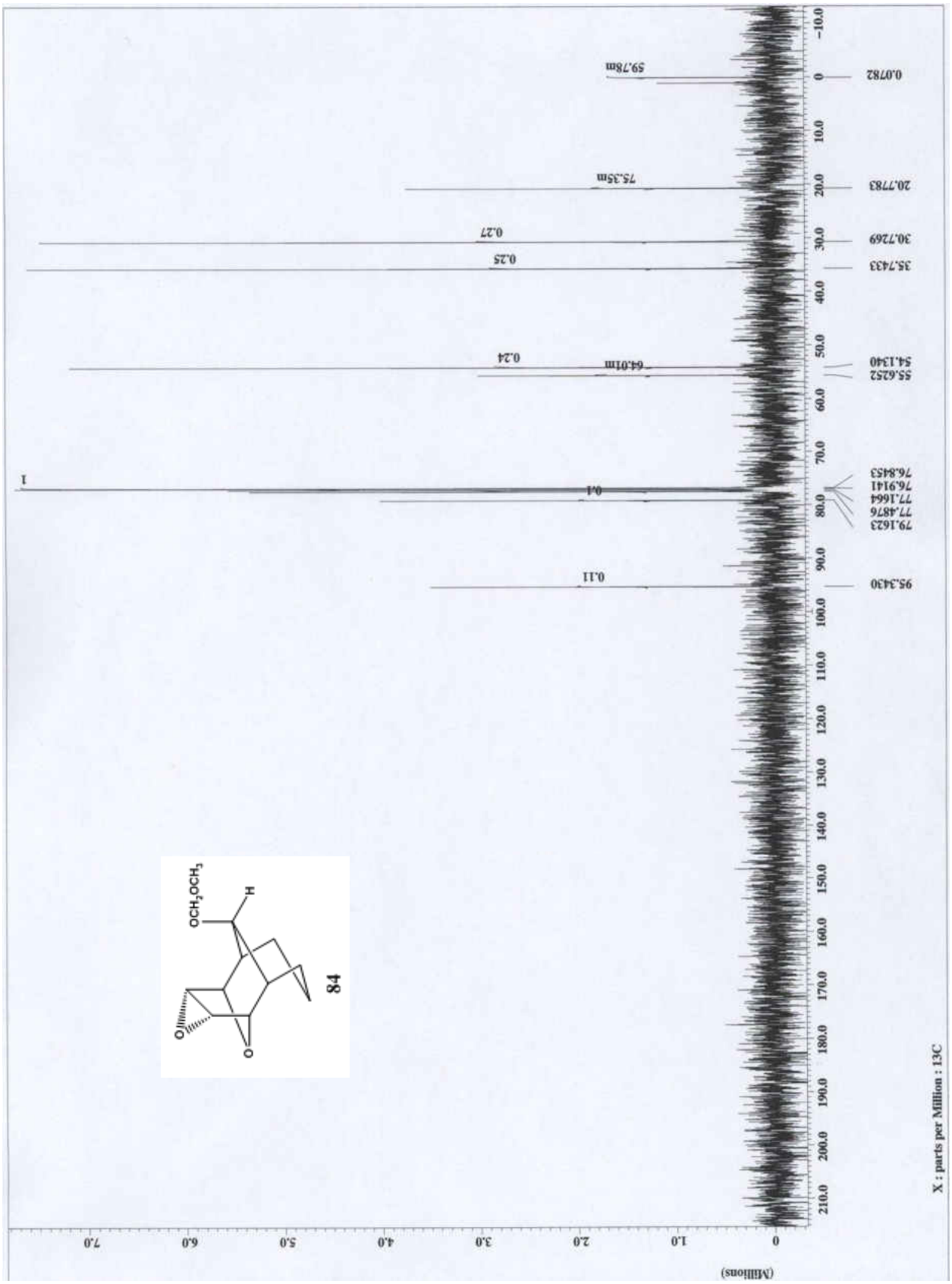

82
OCH2OCH3
H
O
X : parts per Million : 1H
(Millions)
7.7686
7.4096
7.3336
7.2511
6.5569
6.5423
6.3380
6.1265
5.5033
5.1589
4.6474
4.6447
4.6291
4.5128
4.4340
4.0997
3.9221
3.5530
3.5493
3.3359
3.2800
3.1005
2.5007
2.4759
2.4723
1.9759
1.9438
1.9255
1.8339
1.8239
1.8193
1.8019
0.9062
0.8503
0.0398
-0.0216
-0.0298
1.48m
15.15m
0.25
0.26m
0.25m
0.51
0.67m
0.28m
0.42
0.13
3.61m
32.33m
I

82
OCH2OCH3
H
O
135.0227
95.8707
82.9169
81.4104
77.3270
77.0135
76.6923
55.2581
37.8691
30.1917
21.2754
-0.0212
1.0
0.11
57.2m
0.13
58.67m
46.73m
0.12
0.13
57.58m
27.6m
X : parts per Million : 13C


83
O
O
H
X : parts per Million : 1H
(Millions)
0.32
0.14
0.13
0.58
0.27
0.77
1


83
X : parts per Million : 13C
(Millions)
139.1750
135.1030
128.4082
127.3605
127.2458
83.0775
82.4810
77.4799
77.1664
76.8453
69.9975
36.5844
30.2452
21.5507
0.1279
14.36m
94.13m
72.86m
0.25
0.23
0.3
0.25
0.21
0.16
0.15
1.0


84
OCH2OCH3
H
O
O
(Millions)
X : parts per Million : 1H
28.69m
7.2786
7.2493
4.7033
4.5641
4.5558
4.4093
4.3589
4.1455
4.1428
4.0741
3.6098
3.4852
3.3588
3.3359
3.3341
3.3148
2.5648
2.5483
2.4072
2.3871
2.3770
2.3743
1.9447
1.9246
1.7790
1.6095
1.4520
1.2221
1.2167
0.8924
0.8586
0.8421
0.0334
0.0242
0.0059
0.0004
-0.0381
-0.0463
1
0.28
0.34
0.22
0.48


OCH2OCH3
H
O
O
84
(Millions)
X : parts per Million : 13C
95.3430
79.1623
77.4876
77.1664
76.9141
76.8453
55.6252
54.1340
35.7433
30.7269
20.7783
0.0782
1
0.1
0.11
64.01m
0.24
0.25
0.27
75.35m
59.78m

97
OH
O
O
H
X : parts per Million : 1H
(Millions)
7.8016
7.2521
7.2493
6.72m
4.7362
4.5824
4.5338
4.0869
4.0713
3.9587
3.9358
3.8644
3.8543
3.8433
3.5017
2.3761
2.1911
2.1581
2.0089
2.0070
1.8504
1.8339
1.8211
1.8156
1.7945
1.7030
1.6956
1.2203
1.2185
0.8393
0.8073
0.0261
-0.0408
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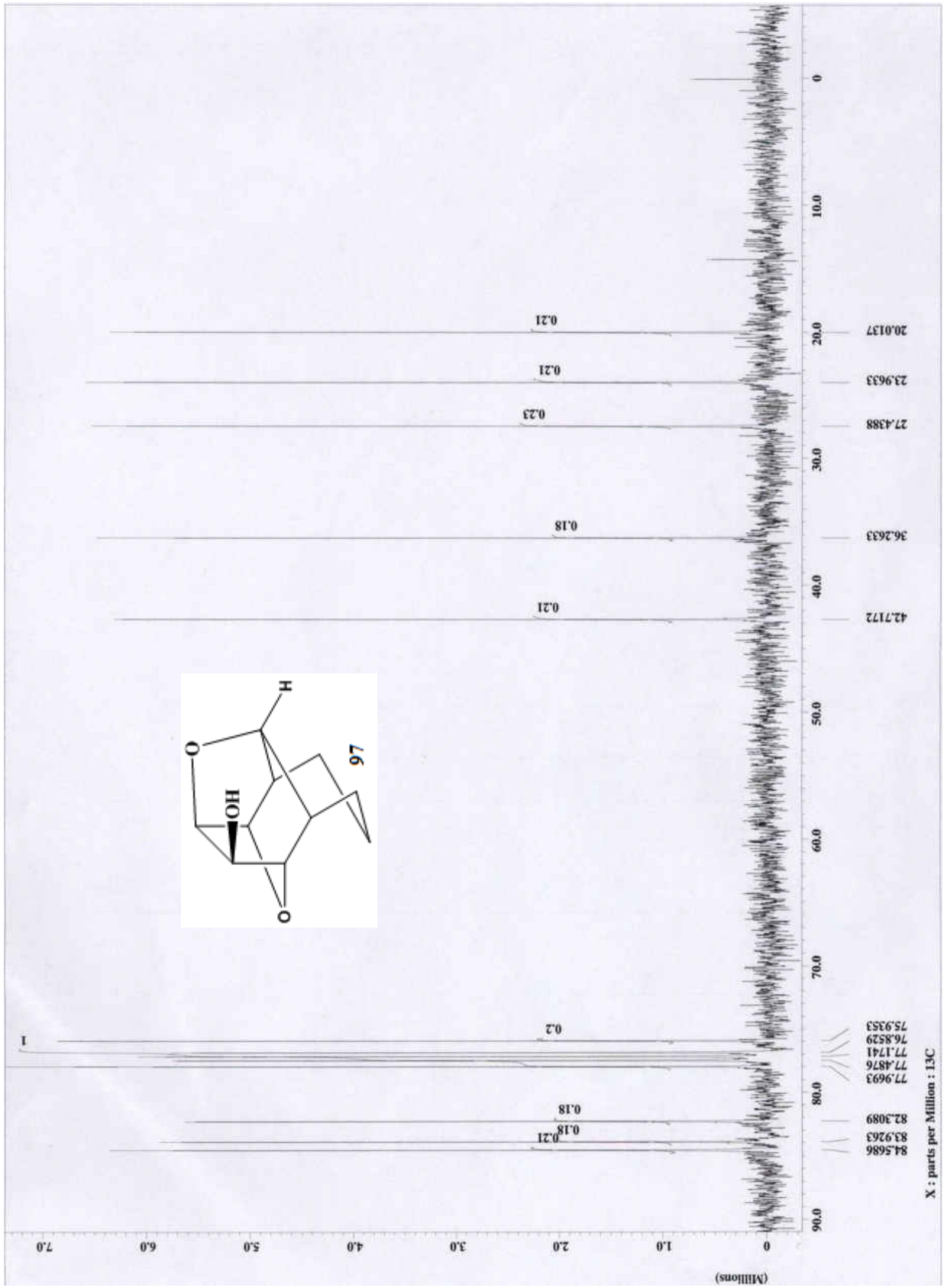
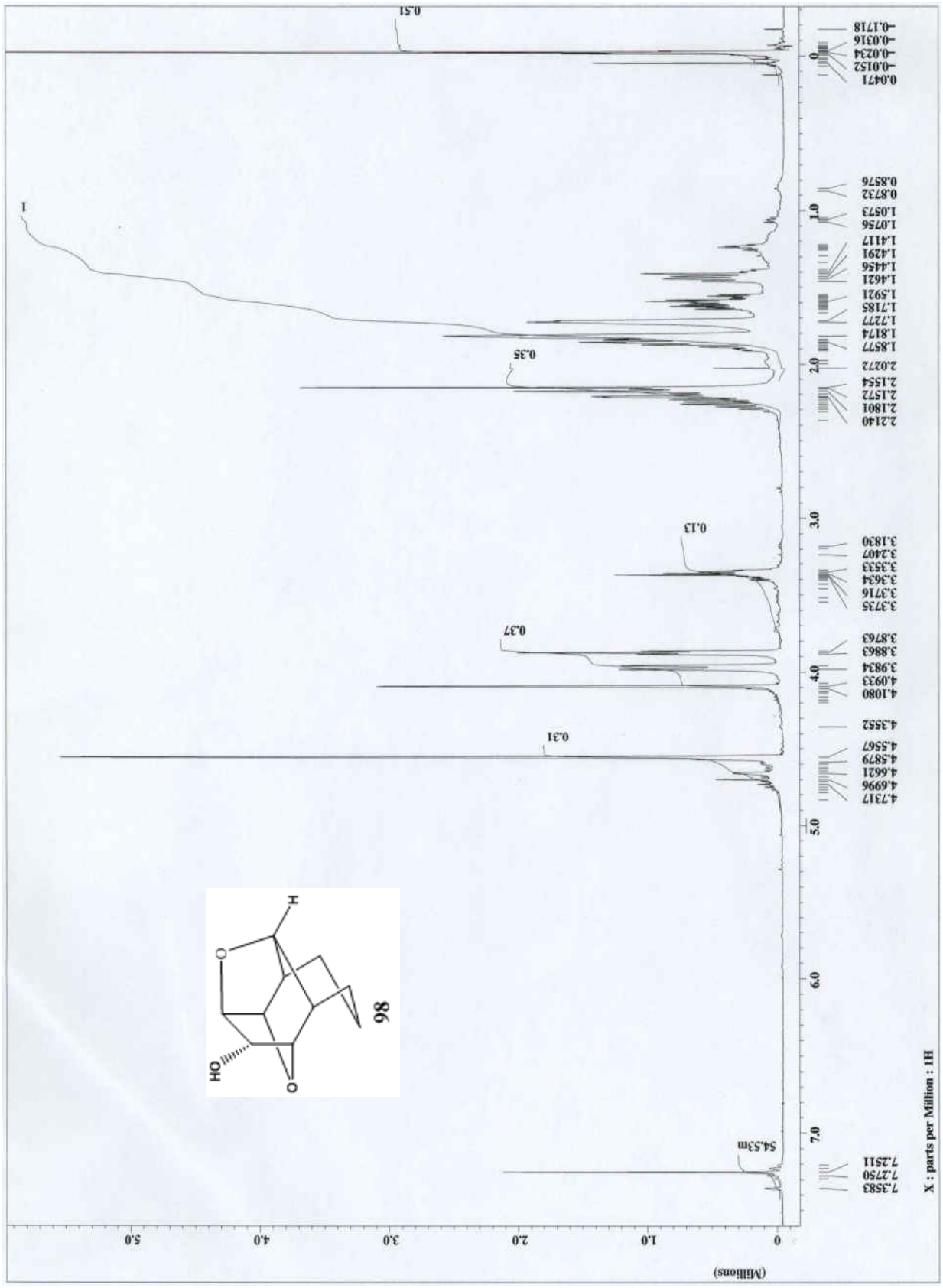
-0.1928
66.26m
0.19
0.31
1

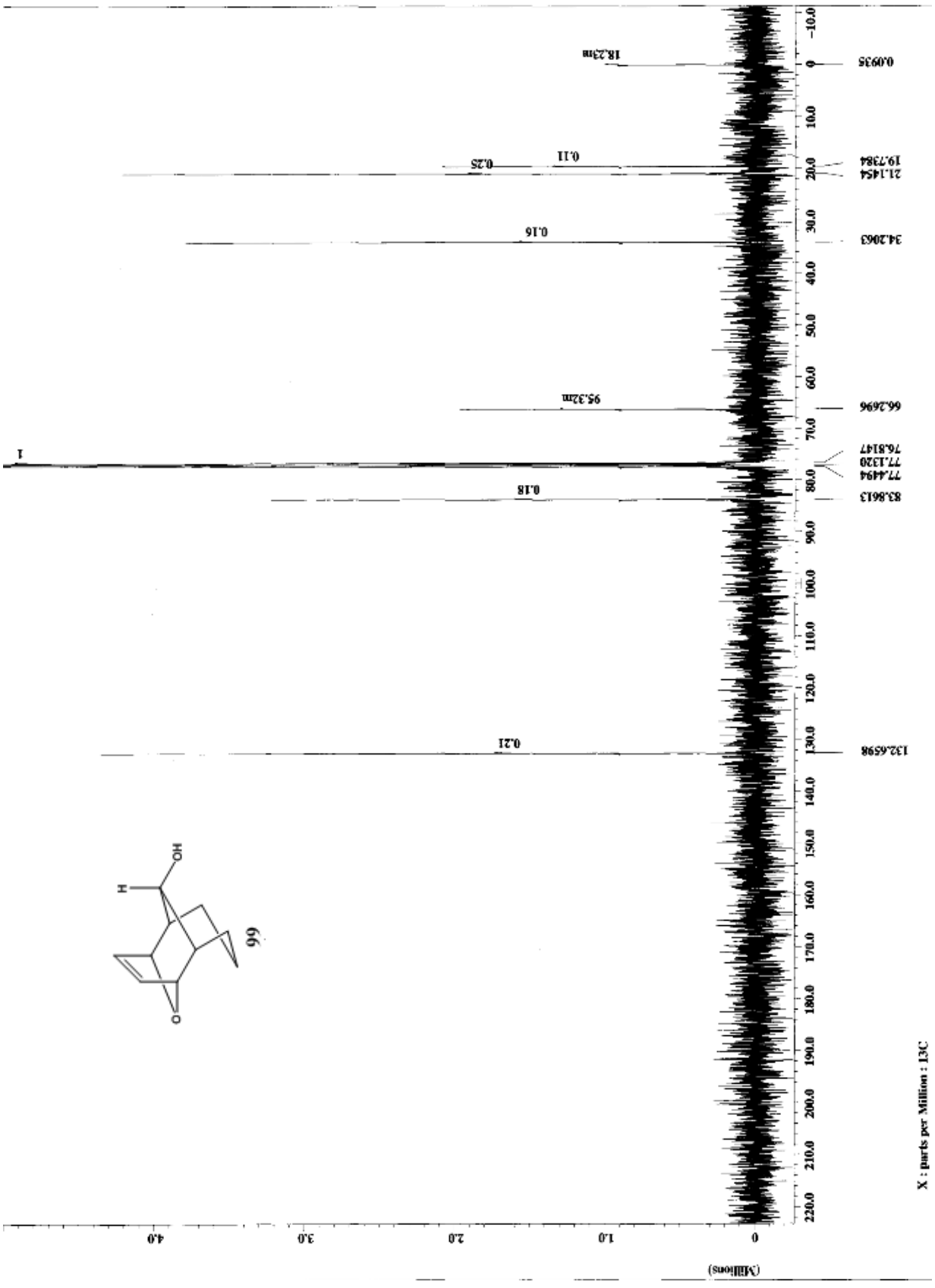

97
OH
O
O
H
X : parts per Million : 13C
(Millions)
84.5686
83.9263
82.3089
77.9693
77.4876
77.1741
76.8529
75.9353
42.7172
36.2633
27.4388
23.9633
20.0137
0.2
0.18
0.21
0.18
0.21
0.23
0.21
0.18
0.21
I

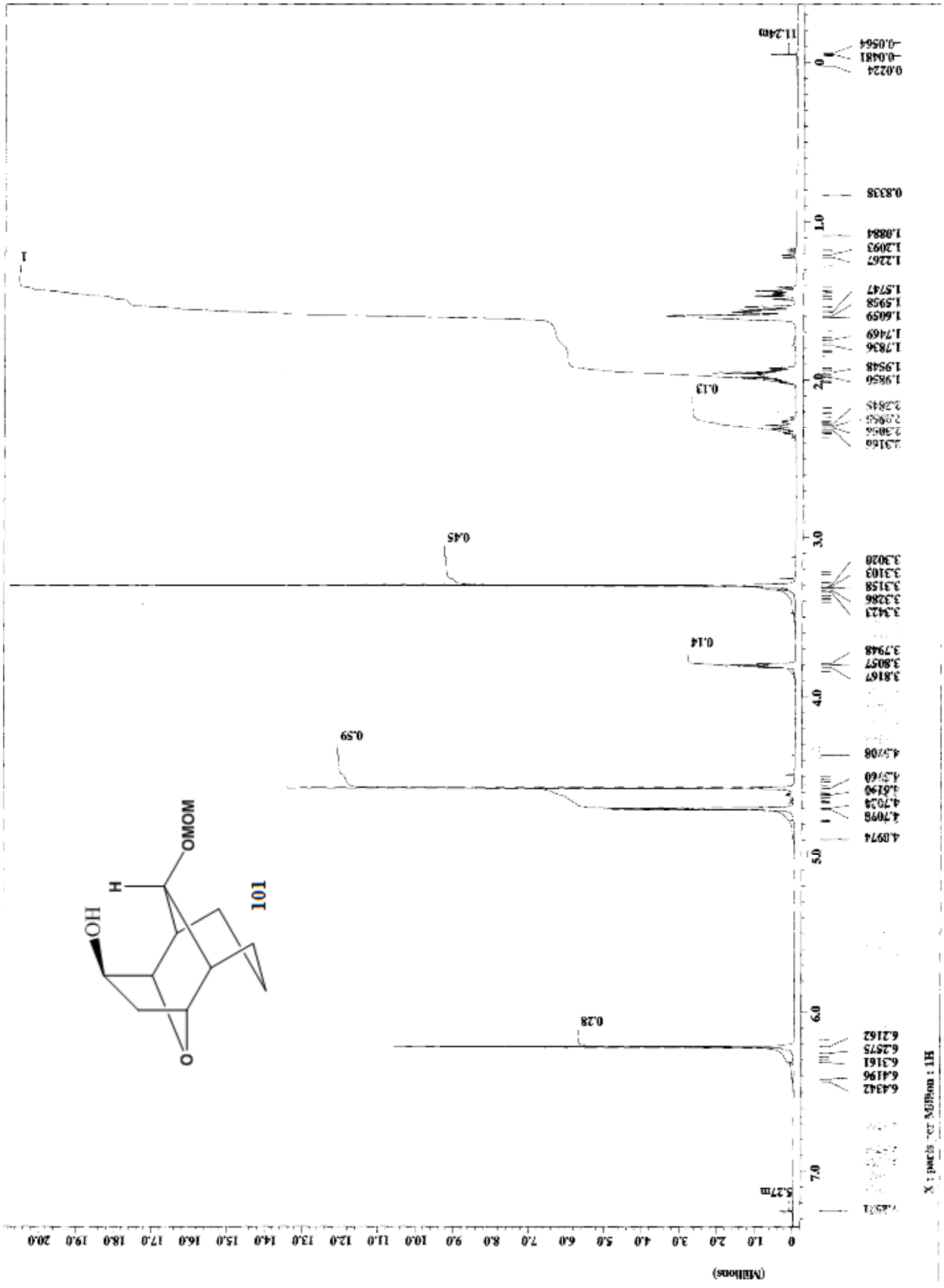

98
OH
O
H
O
54.53m
0.51
0.31
0.13
0.37
0.35
1
X : parts per Million : 1H
(Millions)

s

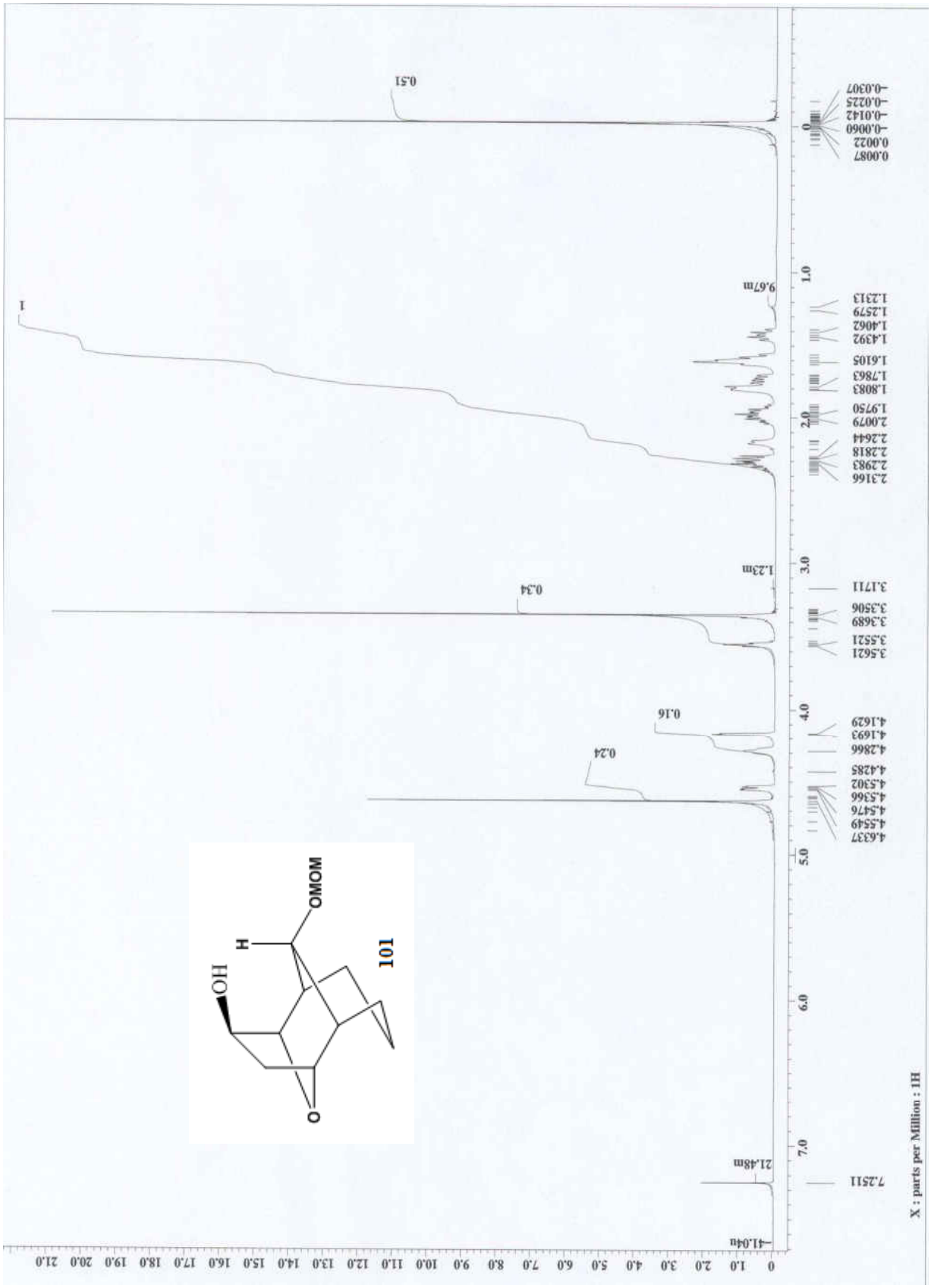
98
X : parts per Million : 13C
(Millions)

OH
H
O
66
X : parts per Million : 1H
(Millions)
7.2521
6.2703
6.2300
6.2190
4.8361
4.7582
4.7518
3.9889
2.3761
2.3679
2.3386
2.3221
2.1563
1.9768
1.9631
1.9484
1.9429
1.7423
1.6608
1.6389
1.6260
1.6022
1.5848
1.4951
1.4621
1.0600
1.0426
0.0480
-0.0133
-0.0216
-0.0298
17.644m
0.18
0.18
88.91m
0.45m
1


66
X : parts per Million : 13C
(Millions)
132.6598
83.8613
77.4494
77.1320
76.8147
66.2696
34.2063
21.1454
19.7384
0.0935
18.23m
95.32m
1
0.21
0.18
0.16
0.25
0.11


OMOM
H
OH
O
101

OMOM
H
HO
O
101
132.7898
94.6242
83.8727
77.5182
77.1970
76.8835
72.0201
55.4646
32.8528
21.9598
20.0939
0.88
0.42
0.89
0.96
0.44
0.37
0.93
0.51
1.0
X : parts per Million : 13C
(Millions)


OMOM
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OH
O
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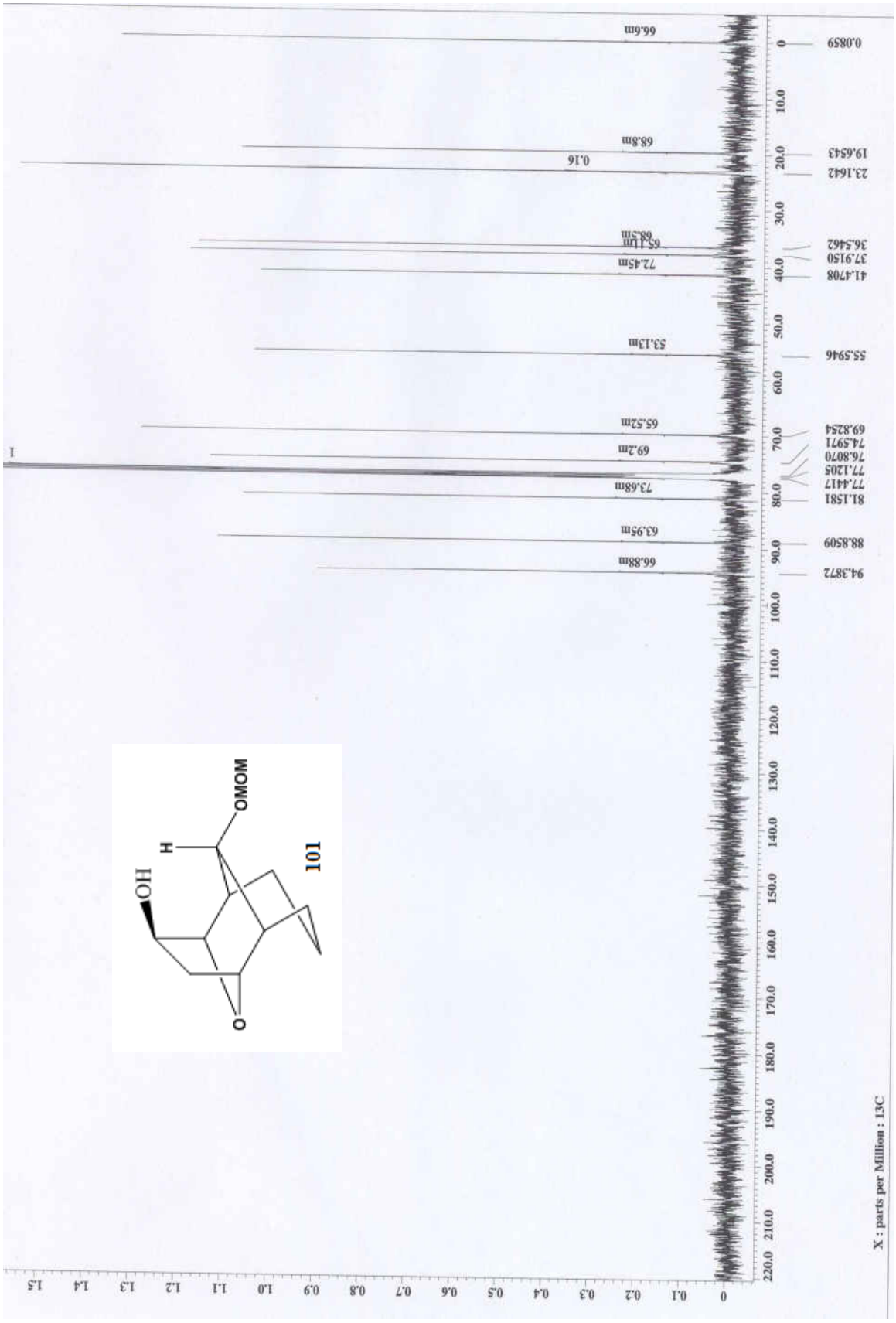
OMOM
H
OH
O
101
X : parts per Million : 13C

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