SYNTHETIC STUDIES TOWARDS (±) – SILPHINENE AND (±) – LAURENENE AND SOME REACTIONS OF GEMINAL DISULFONES

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY
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JANUARY, 1988

... to my mother

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Dr. M. Nagarajan.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

YKoteswar Rao

Y. KOTESWAR RAO

Hyderabad

January 1988

CERTIFICATE

Certified that the work contained in this thesis entitled "SYNTHETIC STUDIES TOWARDS (±)-SILPHINENE AND (±)-LAURENENE AND SOME REACTIONS OF GEMINAL DISULFONES" has been carried out by Mr. Y. Koteswar Rao, under my supervision and the same has not been submitted elsewhere for a Degree.

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ACKNOWLEDGEMENTS

I wish to express my deep sense of gratitude to Dr. M. Nagarajan for his help, advice and encouragement during the course of this research. My association with him has been highly instructive and exciting.

I am thankful to Prof. Goverdhan Mehta, Prof. R. Jagannathan, Dean and other faculty members for their help.

I would like to thank Prof. J. Fried, University of Chicago, Chicago, Prof. S. Chandrasekharan, I.I.T., Kanpur and Dr. M. Ravindranathan, I.P.C.L., Baroda for kindly recording mass spectra of some of the compounds. I am thankful to Dr. B. Venugopalan, Hoechst Research Centre, Bombay and Dr. K.K. Balasubramanyan, I.I.T., Madras for getting CHN analysis done for some of the compounds.

It gives me great pleasure to thank all my colleagues and friends, especially Drs. M. Vaman Rao, C. Linga Reddy, J. Mary Elizabeth and Messrs. M. Pulla Reddy, C. Narayana and A. Narayana Murthy for their help and making my stay at University of Hyderabad a memorable one.

All the non-teaching staff of the School of Chemistry, Central Instruments Laboratory and Central Workshop have been extremely helpful and I thank them all. Financial assistance from the UGC and CSIR for pursuing this work is gratefully acknowledged.

Finally, I take this opportunity to express my deepest gratitude and respect to my parents for their constant encouragement throughout my academic career.

Y. KOTESWAR RAO

ABBREVIATIONS

AcOH	acetic acid
n-BuLi	n-butyllithium
DBU	1,5-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DABCO	1,4-diazabicyclo[2.2.2]octane
Et	ethyl
HMPA	hexamethylphosphoric triamide
LAH	lithium aluminium hydride
Me	methyl
MeOH	methanol
PDC	pyridinium dichromate
PCC	pyridinium chlorochromate
Ph	phenyl
Py	pyridine
THF	tetrahydrofuran
$h\nu$	photoirradiation

ABSTRACT

The last decade has witnessed spectacular advances in the isolation and syntheses of polycyclopentanoids or polyquinanes. As many as eighty polyquinanes have been isolated from natural sources which include plants, marine organisms and fungi. Since many of them possess novel structures and significant biological properties ranging from antibiotic action to antitumor activity, they have attracted the attention of the chemical community and many elegant syntheses of several of these molecules have been reported in the last few years.

This thesis deals with the synthetic studies towards (±)-silphinene, (±)-laurenene, (±)-quadrone and some aspects of the chemistry of geminal disulfones. The thesis comprises two parts. In part I, a formal total synthesis of (±)-silphinene along with synthetic studies towards (±)-laurenene and (±)-quadrone are presented, while part II deals with sulfone chemistry. Each part is subdivided into three chapters consisting of introduction, results and discussion and experimental, respectively.

The introduction to Part I briefly covers the synthetic strategies culminating in the synthesis of silphinene and laurenene that have been reported till today.

As both the molecules and as well as quadrone possess a bicyclo[3.3.0]octane skeleton in their structures, efforts were primarily directed towards building a properly functionalized bicyclo[3.3.0]octane

skeleton. Scheme 1.28 depicts the retrosynthetic analysis for obtaining such a framework. Compound **104** was prepared starting from dimedone (**97**), employing the Wolff rearrangement as the key step in obtaining a functionalized cyclopentane ring annelated to a furan ring. Hydrolysis of **104** led to **105** which was considered as a suitable precursor for the functionalized bicyclo[3.3.0]octane skeleton. However, the expected aldol reaction of **105** did not proceed under a variety of conditions. As this reaction that would lead to a common intermediate to a variety of polyquinanes did not work out, the idea of preparing such an intermediate was dropped and efforts were then turned towards the synthesis of silphinene and laurenene.

It was envisaged that as both the molecules possess similar structural features, an attempt could be made towards both the molecules from a common intermediate. For synthesizing this common intermediate, 2,4,4trimethylcyclopentanone (**118**) was identified as the starting material. Compound **118** was alkylated with allyl bromide at the 2-position while the 4-carbon side chain at the 5 position was introduced through an aldol reaction followed by the reduction of the resulting enone leading to **120**. The terminal double bond in **120** was oxidized to a methyl ketone giving **121** which when subjected to the intramolecular aldol reaction gave **122**. However, the stereochemistry of the 4-carbon side chain was found to be opposite to that required for the synthesis of silphinene and laurenene. This was confirmed by single crystal X-ray analysis of **122**. In order to arrive at the molecule possessing the 4-carbon side chain in the required stereochemistry, the terminal double bond in **120** was oxidatively cleaved to an acid which was esterified with diazomethane to furnish **127**. Compound **127** was converted into the β-ketophosphonate **129** which when subjected to the intramolecular Wittig-Horner reaction gave **126** having the 4-carbon side chain in the required stereochemistry. This was confirmed by converting **126** to **125** and then comparing the spectral data of **125** with that reported for the same compound by Crimmins.

Having obtained **126**, the synthesis of silphinene was completed by reducing the ketone in the side chain of **126** to the alcohol **130**, converting the alcohol to a radical source via its thionocarbonate derivative and then adding the radical generated to the enone in an intramolecular Michael reaction type addition. As the intermediate **132** obtained from this operation has been converted to silphinene by Crimmins, this work constitutes a formal total synthesis of silphinene. The work described above involving an intramolecular radical cyclization towards generating a tricyclo[6.3.0.0^{1,5}]undecane skeleton is among the first few approaches towards the tricyclo[6.3.0.0^{1,5}]undecane skeleton using such a method.

As **126** possessess two of the four rings present in laurenene with the methyls and the side chain having the correct stereochemistry, it was envisaged that **126** could also be used in the synthesis of laurenene. A retrosynthetic analysis is given in Scheme 1.22. Although the intramolecular radical cyclization approach and the intramolecular Diels-Alder approach were not successful, the keto-aldehyde **139** required for pursuing the intramolecular Michael reaction approach was synthesized from **126**. It is hoped that **139** would lead to an intermediate like **141** and as **141** has already been converted to laurenene, this work would constitute a formal synthesis of laurenene as well.

In the introductory chapter of part II, some of the salient features of sulfur chemistry in general and sulfone chemistry in particular are discussed. Although the sulfone group has been known to synthetic organic chemists for a long time, the area of geminal disulfones however, remained unexplored. In an attempt to prepare a formaldehyde equivalent, compounds 1,1-bis(phenylsulfonyl)methane (**24**) and 1,1-bis(phenylsulfonyl) ethene (**25**) were synthesized. As very little chemistry of these compounds was known, an indepth study of **24** and **25** was undertaken, which can be grouped under three heads (a) Michael reactions, as shown in Schemes 2.21 and 2.22, (b) Diels-Alder reactions as shown in Scheme 2.23 and (c) phase transfer catalyzed alkylation reactions, as given in Tables 1,2 and 3. Although **24** and **25** have been shown to undergo a variety of reactions, more work is needed to prove their utility in organic synthesis.

Finally, the third Chapter in both Part I and Part II contains all the relevant experimental details, followed in each case by the appropriate references.

PART - I

Synthetic Studies Towards (±)-Silphinene and (±)-Laurenene

INTRODUCTION

Organic synthesis today is a rapidly growing area in which synthesis of complex natural products has become a matter of routine. Indeed, in the past three decades, organic synthesis has registered such a phenomenal growth and achieved such a level of sophistication and finesse that no complex molecule appears to be beyond the reach of synthetic chemists. It would be no exaggeration to point out that organic synthesis as studied under the design of complex molecules, development of new reactions and discovery of new reagents has contributed enormously towards the development and better understanding of organic chemistry as a whole in the past half a century.

There are many motivations for undertaking a synthetic venture. These range from assembling of a complex molecule whose synthesis itself poses a major challenge to the development of practical approaches to the synthesis of molecules which may lack complexity but are of everyday use. A synthetic exercise is also undertaken either to arrive at or for providing unambiguous proof of the structures of natural products.

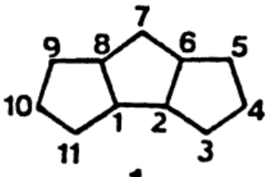
In the evolution of organic synthesis over the years, certain classes of compounds have been in the limelight at each stage of its progress. For example, the premier position occupied by the steroids in the forties and fifties yielded place to the complex terpenoids and alkaloids which were, in turn, displaced by the prostanoids. Today, the emphasis is primarily on polycyclopentanoids, ionophore and anthracycline antibiotics, macrolides and eicosanoids.

In spite of the fact that cyclopentanes have been known in the chemical literature for a long time, interest in their synthesis has remained on a low key until recently. This has been mainly because 1) relatively few cyclopentanes of reasonable complexity were known until the late 60's and 2) the synthetic activity until the late 60's was primarily concerned with the development of rapid and efficient acquisition of annulated cyclohexane rings that formed an integral part of the then important natural products.

However, the scene changed considerably with the arrival of prostaglandins, which were the primary targets for synthesis in the late 60's and 70's. Reasons for their popularity stem from the fact that they have structures of a complex nature which therefore need rigorous stereochemical control, thus posing a challenge to synthetic chemists. They also possess varied biological properties which are of immense significance. Hence, many new synthetic strategies and reagents were developed for the synthesis of functionalized cyclopentane rings which were utilized in the synthesis of several prostaglandins.

With the realization of successful synthesis of several prostaglandins, the attention of synthetic organic chemists shifted in the late 70's from the monocyclopentanoids to the area of polyquinanes or polycyclopentanoids and this interest continues unabated even today.

Among the various naturally occuring polyquinanes, the tricyclopentanoid skeletons **1** and **2** representing linearly and angularly fused five membered rings, respectively, have received maximum attention from synthetic chemists.



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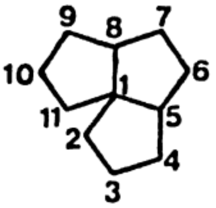

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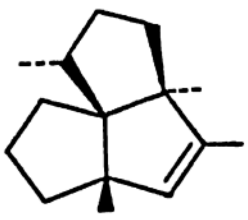
These structural types have been found to be widely distributed among plants, fungal and animal sources. Indeed, as many as eighty polyquinanes have been isolated in the last decade. As many of them possess biological properties which range from simple antibiotic action to antitumor properties, they have become popular targets for synthesis.

Research directed towards the preparation of members of the angular triquinane class of polyquinanes has progressed rapidly over the past few years. This class of compounds is represented by the hydrocarbons isocomene (**3**)[1], pentalenene (**4**)[2], senoxydene (**5**)[3], silphinene (**6**)[4] and silphiperfol-6-ene (**7**)[5]. A variety of oxygenated derivatives are also known. The tricyclo[6.3.0.0^{1,5}]undecane ring system which forms a part of these structures is also embedded in several more complex natural products including laurenene (**8**)[6], retigeranic acid (**9**)[7] and crinipellin A (**10**)[8].

Many synthetic strategies have been worked out to tackle the interesting problems posed by the multiply-fused five membered rings and as a result a number of general solutions have emerged. Most strategies have involved the sequential construction of each five-membered ring in the appropriate angular arrangement. A notable exception to this general strategy is the π-arene olefin meta photocycloaddition of Wender[9]



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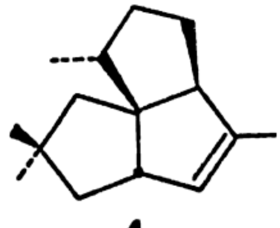

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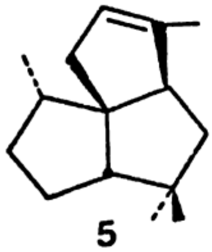

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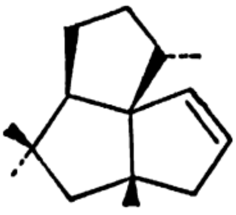

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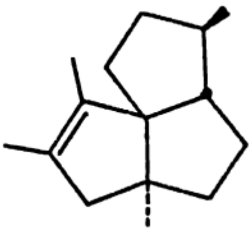

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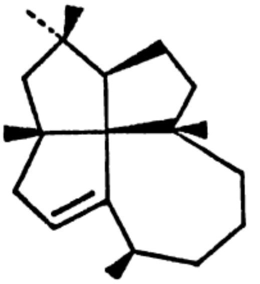

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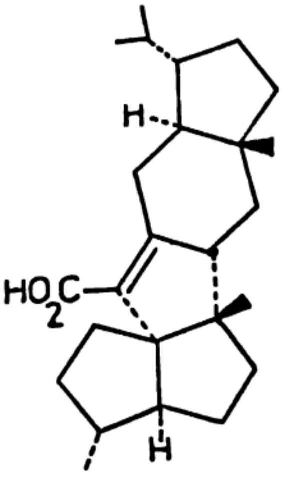

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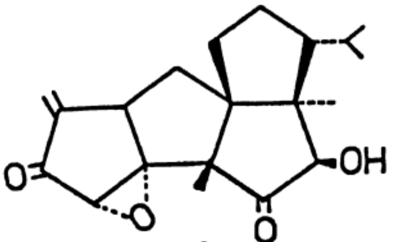

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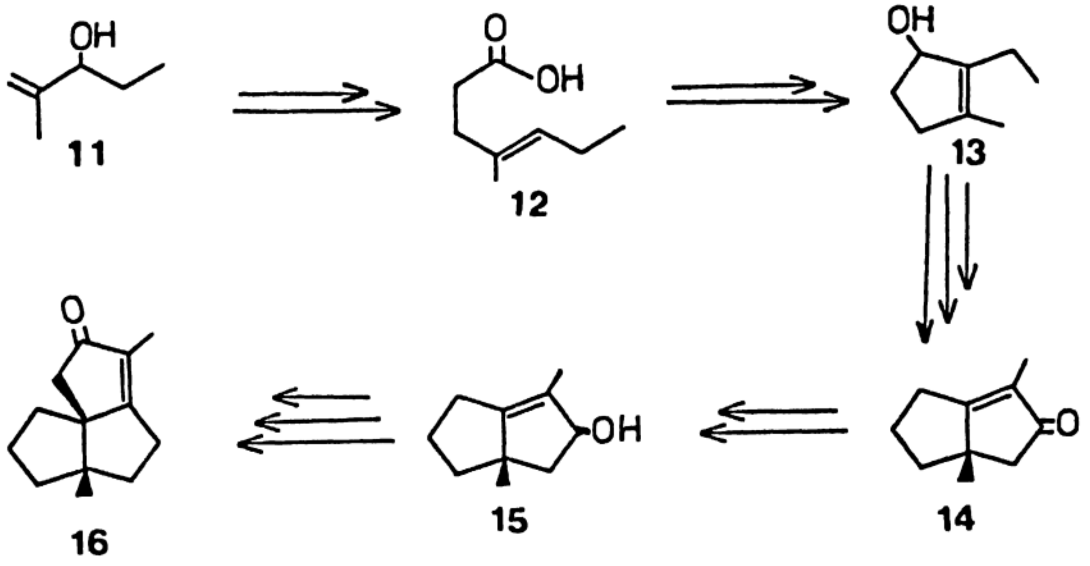
As part of a programme directed towards the synthesis of some of these angularly fused polyquinanes, we were interested in employing free radical reactions for the generation of such systems. Silphinene was chosen as the prototype example to test our strategy because of both its unique structural features as well as its resemblance to three of the four rings that form part of Nature's only fenestrane molecule, laurenene (**8**). Its synthesis, therefore, would give us an opportunity to obtain information regarding a similar synthetic approach to laurenene as well. Before delineating the novel and successful route to silphinene and synthetic approaches to laurenene that have evolved during the course of the present studies, it would be appropriate and instructive to make a quick, schematic survey of the existing approaches to the basic tricyclo[6.3.0.0^{1,5}]undecane skeleton and the syntheses reported to date of silphinene and laurenene. In the past five years, there has been a flurry of synthetic activity in this particular area, around the world, and a look at these endeavours would put our own efforts reported here in proper perspective.

Synthetic Approaches Towards Tricyclo[6.3.0.0^{1,5}]undecane Skeleton

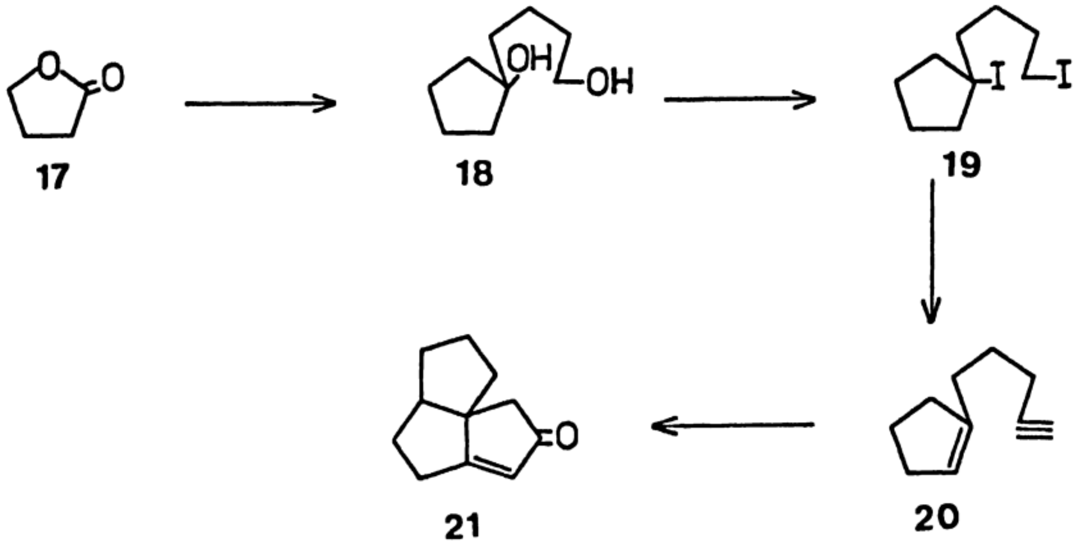
The first systematic approach towards the tricyclo[6.3.0.0^{1,5}]-undecane skeleton was reported by Jager.[10] This three step iterative cyclopentane annulation approach consists of i) preparation of an allylic alcohol from an α, β-enone by LAH reduction or Grignard reaction, ii) Claisen rearrangement of the allylic alcohol involving Johnson's ortho-ester or Ireland's ketene acetal modification followed by hydrolysis to a 4-alkenoic acid and iii) polyphosphoric acid (PPA) induced cyclodehydration to cyclopentenones with appropriate C=C migration.

Thus, 2-methyl-1-penten-3-ol (**11**) on Claisen rearrangement with triethyl orthoacetate followed by hydrolysis gave the acid **12**. This upon treatment with PPA followed by reduction with LAH afforded the alcohol **13**. When subjected to the sequence of Claisen rearrangement followed by PPA cyclization, **13** gave the bicyclo[3.3.0]octenone **14**. This compound was reduced with LAH to furnish the endo alcohol which was inverted by the Mitsunobu reaction and repeating the sequence as described above furnished the triquinane **16**, Scheme 1.10.



Scheme 1.10

A second route, due to Schore,[11] essentially involves utilization of the Pauson-Khand reaction in obtaining the tricyclo[6.3.0.0^{1,5}]-undecane skeleton, Scheme 1.11.

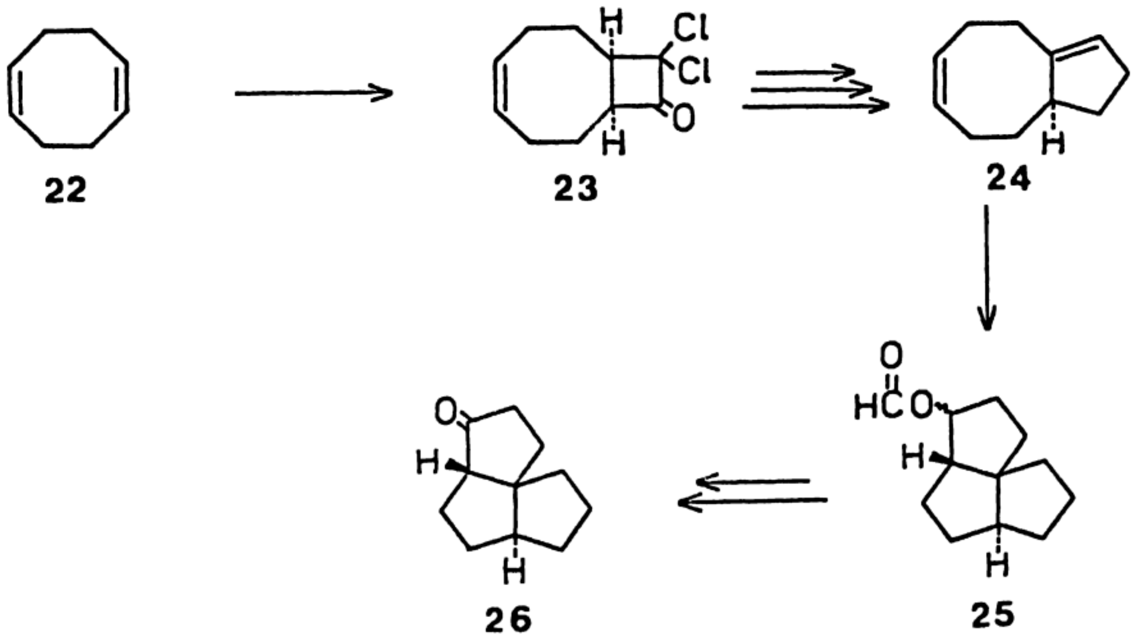


Scheme 1.11

The key intermediate **20** was synthesized as depicted in the scheme starting from Grignard reaction of 1,4-dibromobutane on γ-butyrolactone (**17**). The enyne **20**, upon treatment with $Co_2(CO)_8$/CO yielded tricyclo[6.3.0.0^{1,5}]undec-1-ene-3-one in a reasonable yield. A notable feature of this approach is the tandem formation of two carbocyclic rings in one step. This methodology has been utilized towards the synthesis of bisnorisocomene.

The route described by Mehta[12] to arrive at the tricyclo [6.3.0.0^{1,5}]undecane skeleton utilizes a carbonium ion mediated transannular cyclization of a suitably functionalized bicyclo[6.3.0]undecene derivative as the pivotal step, Scheme 1.12.

The key bicyclic diene **24** was realized from commercially available 1,5-cyclooctadiene (**22**) through the intermediacy of **23**. Formolysis of **24** gave the formate **25** which on base hydrolysis and Jones oxidation



Scheme 1.12

yielded tricyclo[6.3.0.0^{1,5}]undecan-4-one (**26**). This methodology has been exploited for the syntheses of pentalanene and epi-pentalenene.

While the methods described above constitute a general methodology towards the basic tricyclo[6.3.0.0^{1,5}]undecane skeleton, the strategies reported by several active workers in this area like Paquette, Wender, Ito, Crimmins and Hudlicky for the angular triquinanes are unique for the respective molecules and they have been cited in the reference section for each angular triquinane.

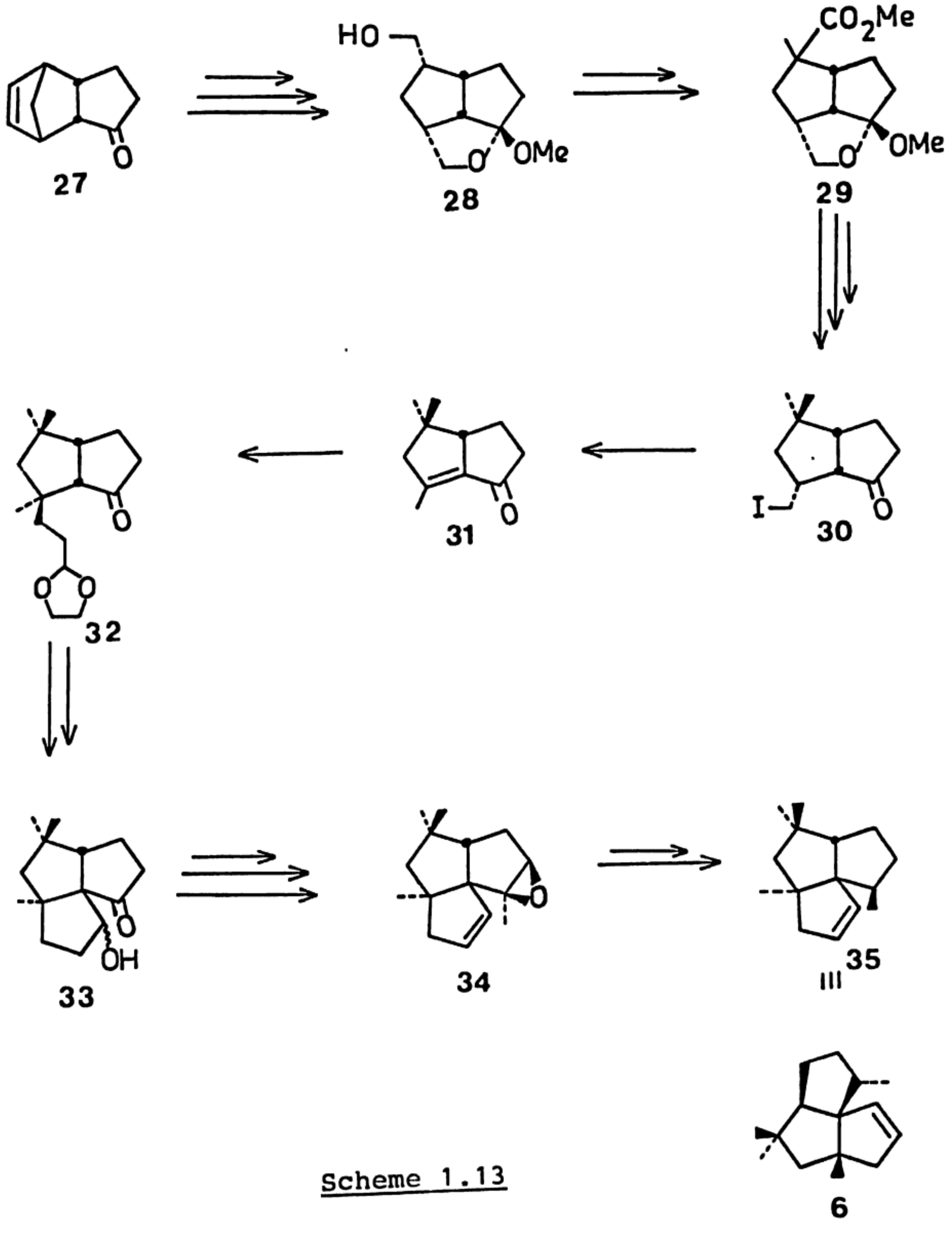
Synthesis of (±)-Silphinene

The first successful total synthesis of (±)-silphinene was reported from the laboratories of Ito,[13] whose regio- and stereoselective synthesis relied on dicyclopentadiene as the starting material, Scheme 1.13.

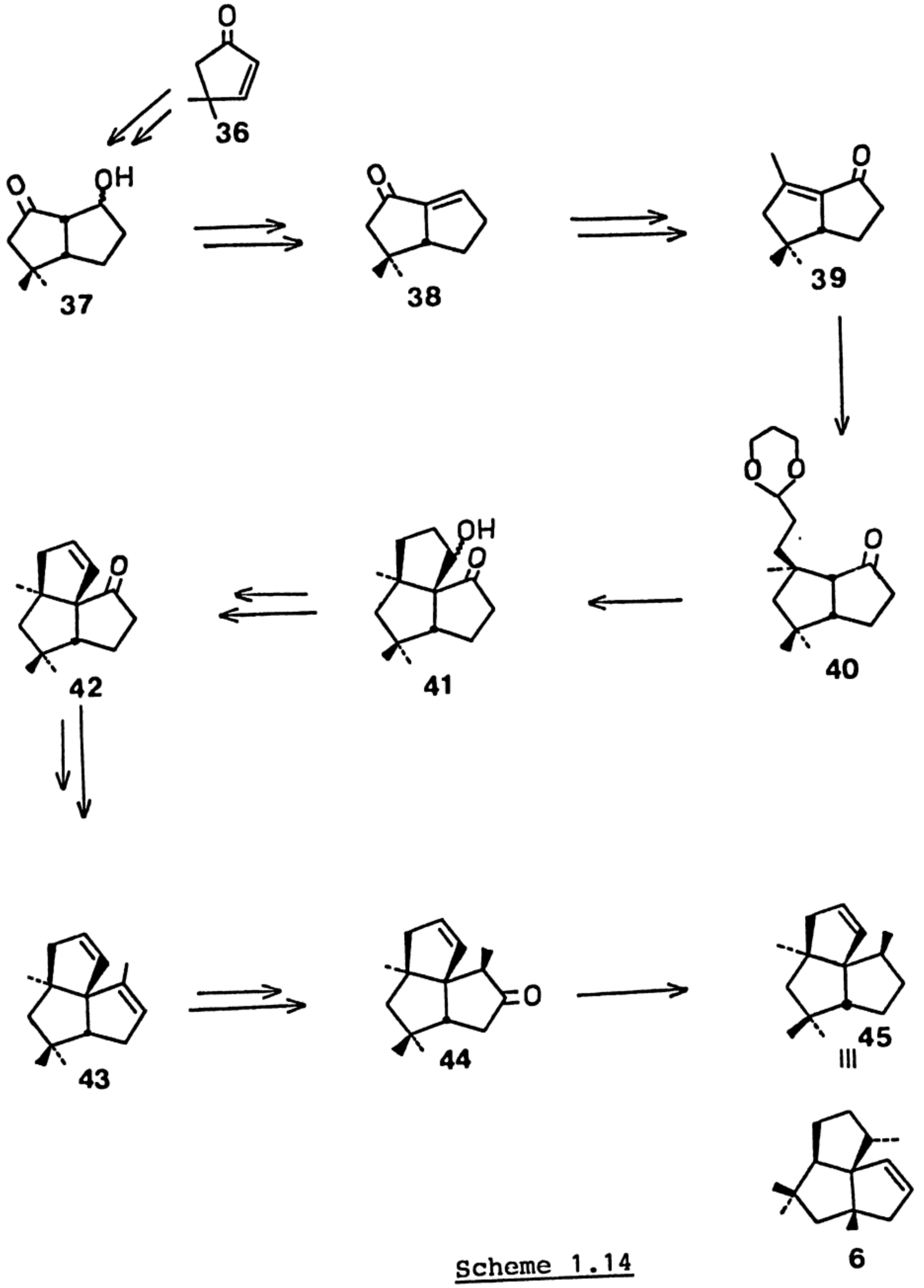
The ketone **27**, obtained readily from dicyclopentadiene, was oxidatively cleaved to provide **28** which was crafted into **29**. Following the reduction of the carbomethoxy group, conversion to the iodo ketone **30** was realized with trimethylsilyl iodide. Reaction of **30** with DBU resulted chiefly in conversion to **31**. Conjugate addition of the Grignard reagent prepared from β-bromopropionaldehyde ethylene acetal to **31** yielded **32**. Deprotection and cyclization of the keto-aldehyde gave the tricyclic aldol **33** which was finally converted to silphinene in another five steps via the epoxide **34**.

The synthesis of silphinene due to Leone-Bay and Paquette[14] makes use of an iterative annulation scheme for fusion of the second and the third five-membered rings, Scheme 1.14.

The bicyclic ketone **37** was obtained in two steps from 4,4-dimethyl-2-cyclopentenone (**36**) using the Helquist-Marfat[15] protocol. Sequential dehydration followed by alkylative carbonyl transposition of **37** provided **39**. This intermediate was subjected to an identical annulation procedure used to prepare **37** and as a result, **41** was obtained exclusively. Dehydration of the alcohol gave **42** which when, treated with methyllithium and acid yielded the diene **43**. Following the methodology used by Ito, **43** was converted to silphinene in another three steps.

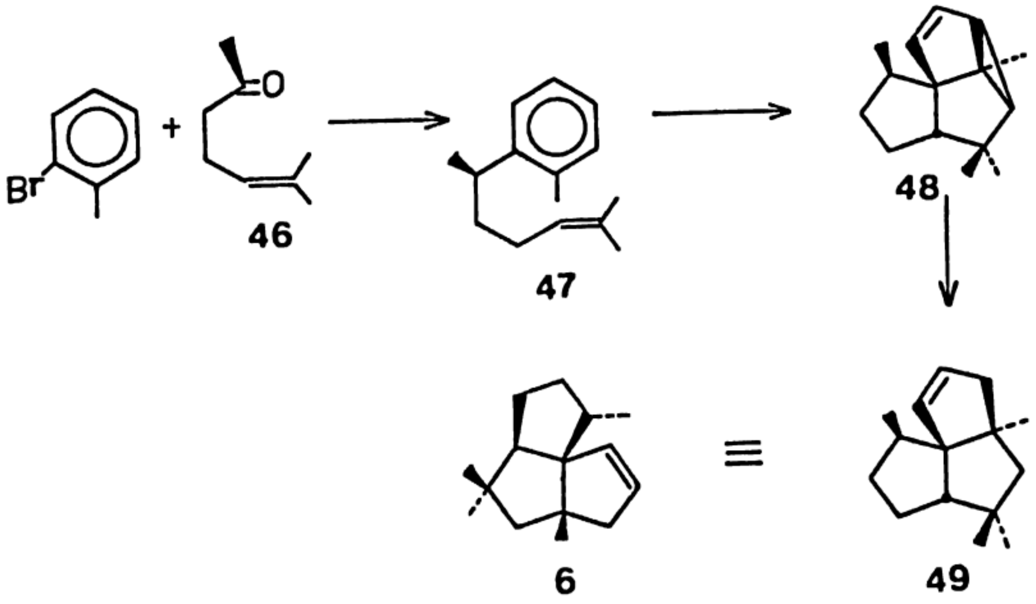


Scheme 1.13



Scheme 1.14

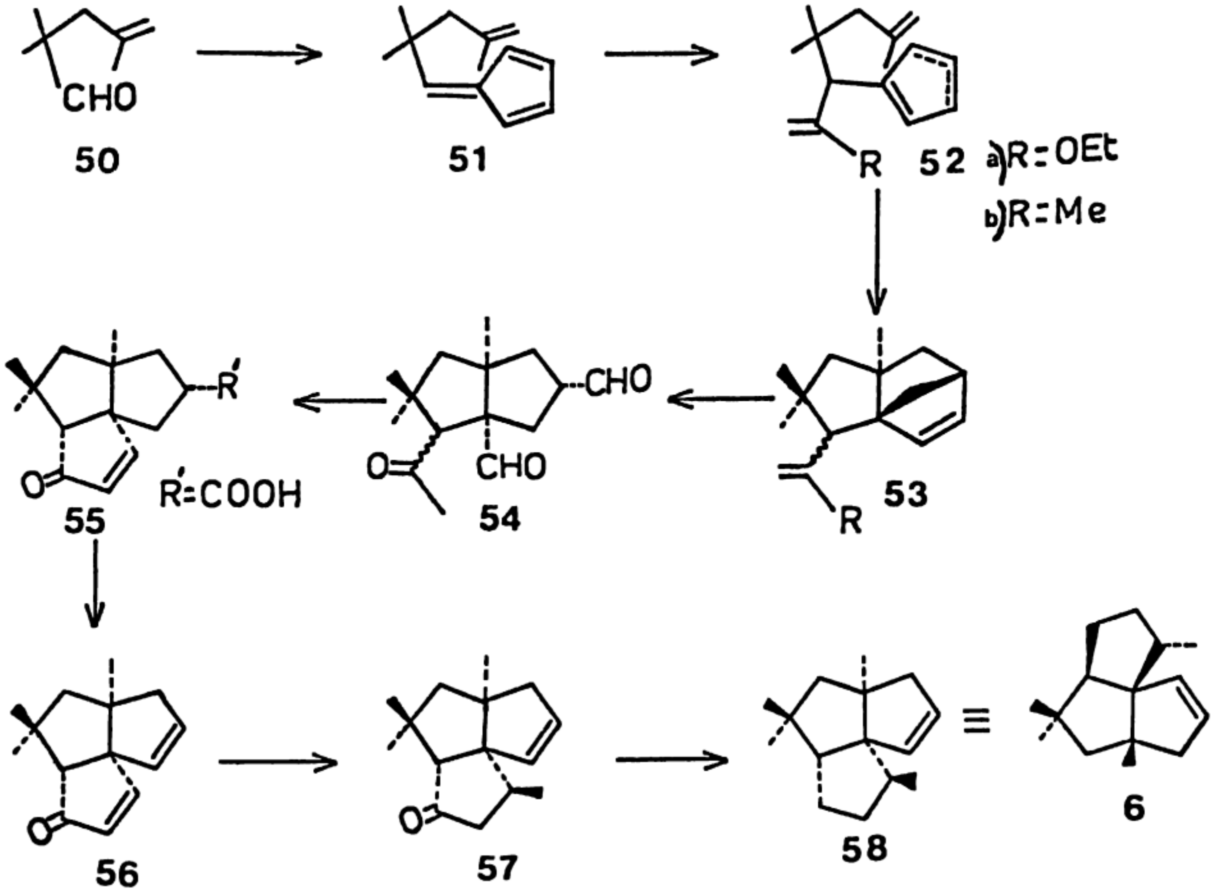
The arene-olefin meta photocycloaddition strategy adopted by Wender[16] differs radically from the earlier two syntheses of silphinene. This is the shortest route towards silphinene and perhaps the shortest ever towards any angular triqinane reported till today. The strategy employed is shown in Scheme 1.15.



Scheme 1.15

6-Methyl-5-hepten-2-one, when treated with phenyllithium generated in situ from bromobenzene and excess lithium gave the corresponding alkoxide which when reduced with lithium-ammonia gave the aromatic hydrocarbon **47**. Irradiation of **47** gave the arene-olefin meta photocycloaddition product **48**. Reductive cleavage of the cyclopropane bond present in **48** employing lithium in methylamine furnished silphinene.

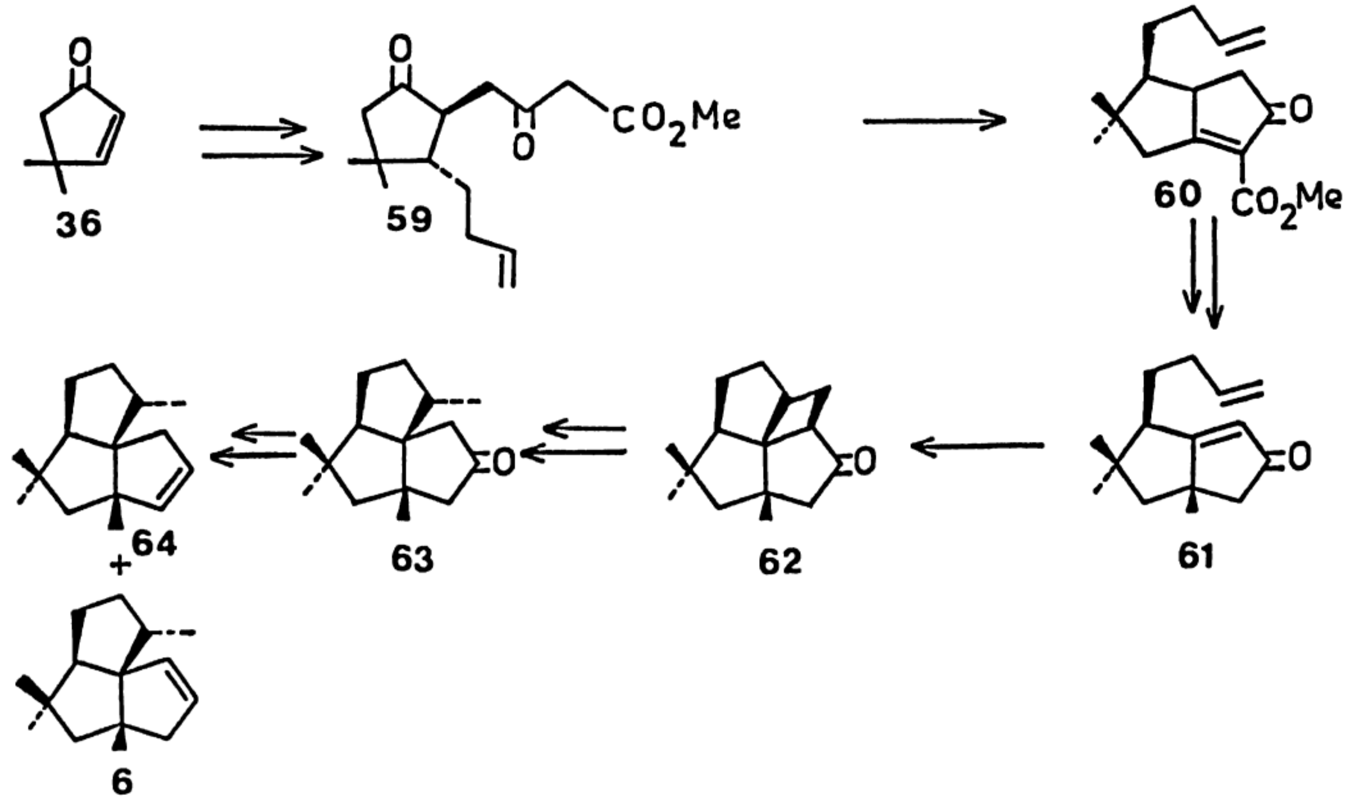
The intramolecular Diels-Alder approach (IMDA) towards silphinene adopted by Sternbach[17] is particularly attractive because of its brevity. The methodology employed is depicted in Scheme 1.16.



Scheme 1.16

The substrate **52b** required for the intramolecular Diels-Alder reaction was obtained by condensing 2,2,4-trimethyl-4-pentenal with cyclopentadienyl sodium followed by addition of isopropenyllithium to the fulvene **51**. Ozonolytic cleavage of the IMDA product **53b** gave the dialdehyde **54**. Aldolization followed by oxidative decarboxylation gave **56** which when exposed to lithium dimethylcuprate followed by Wolff-Kishner reduction produced silphinene.

The last approach towards silphinene, due to Crimmins,[18] employs an intramolecular [2+2] photocycloaddition followed by cyclobutane cleavage of the fenestrane obtained in the photocycloaddition as the key steps, Scheme 1.17.



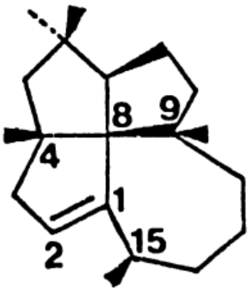
Scheme 1.17

4,4-Dimethyl-2-cyclopentenone (**36**) was converted to **59** by conjugate addition of the Grignard reagent derived from 4-bromo-1-butene followed by regiospecific capture of the generated enolate with methyl 4-iodo-3--methoxycrotonate. Lithium dimethylcuprate addition, removal of the carbomethoxy group and generation of the enone moiety using ethyl (trimethylsilyl)acetate furnished **61** which was subjected to photocycloaddition conditions furnishing the fenestrane **62**. Cleavage of the cyclobutane ring with trimethylsilyl iodide followed by treatment with tributyltin hydride delivered **63**. Enolization of **63**, quenching of the enolate with diethyl chlorophosphonate and reduction of the enol phosphate produced silphinene.

Synthesis of (±)-Laurenene

Only three successful approaches towards (±)-laurenene have been reported till today and that too only in 1987 and 1988.

Laurenene is the only naturally occuring diterpene which is grouped under a new class of compounds called fenestranes and before the strategies that were adopted to arrive at this unique molecule are discussed, it would be worthwhile to consider some of the salient structural features of this molecule.



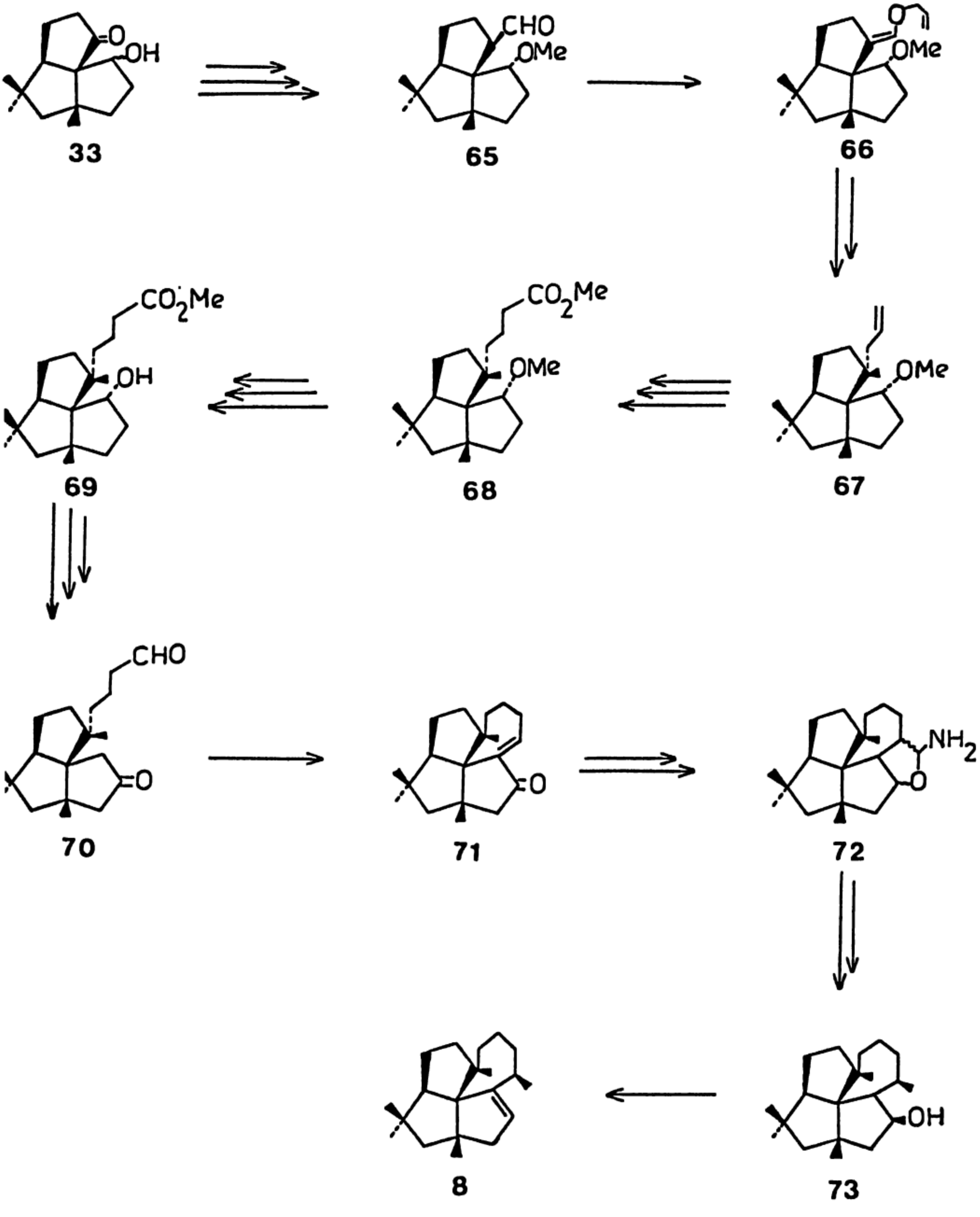
i) It has a tetracyclic skeleton with three five-membered rings and one seven-membered ring attached to a central quaternary carbon atom ii) the stereochemistry of C-15 secondary methyl is β and it is present on the less accessible concave side of the molecule and iii) the three contiguous quaternary centres at C-4, C-8, C-9 create a severely sterically crowded region wherein the two methyl groups at C-4 and C-9 point directly at one another. Any synthesis of laurenene therefore demands that these points be taken into consideration.

The synthesis of laurenene described by Ito[19] utilizes one of the intermediates in his synthesis of silphinene as the starting material, Scheme 1.18.

The aldol **33** was converted into the aldehyde **65** from which the allyl enol ether **66** was obtained. Claisen rearrangement of **66** furnished **67** which possesses the secondary methyl at C-15 in the correct stereochemistry as a result of migration of the allyl group to the less hindered face of the quaternary carbon. At this stage, **67** was transformed into **68** whose conversion to the crucial intermediate **70** proceeded smoothly. The tetracyclic skeleton of laurenene was constructed from this intermediate through a simple aldol reaction which gave **71** in good yield. Hydrocyanation of **71**, reduction of the nitrile group to the amino group, conversion of the amino function to the alcohol followed by Huang-Minlon reduction gave **73** whose dehydration furnished laurenene.

The intermediate **71**, obtained by a totally different route also served Crimmins[20] as the key compound in his synthesis of laurenene, Scheme 1.19.

Starting from 4,4-dimethyl-2-cyclopentenone (**36**), compound **76** was obtained in a manner similar to the strategy adopted for the synthesis of silphinene. Through a series of functional group manipulations, **76** was converted to **78** which when subjected to elevated temperature intramolecular photocycloaddition conditions furnished **79**. This was necessary because of the failure of the photocycloaddition reaction at 25°C due to severe steric interaction in the transition state for cyclization between the two methyls which ultimately reside on carbons 4 and 9 of laurenene. This reaction established the three contiguous quaternary centres required for the sterically congested central position of laurenene. Compound **79** was converted to **81** through the intermediacy of **80**. The tetracyclic skeleton of laurenene was obtained from **81** through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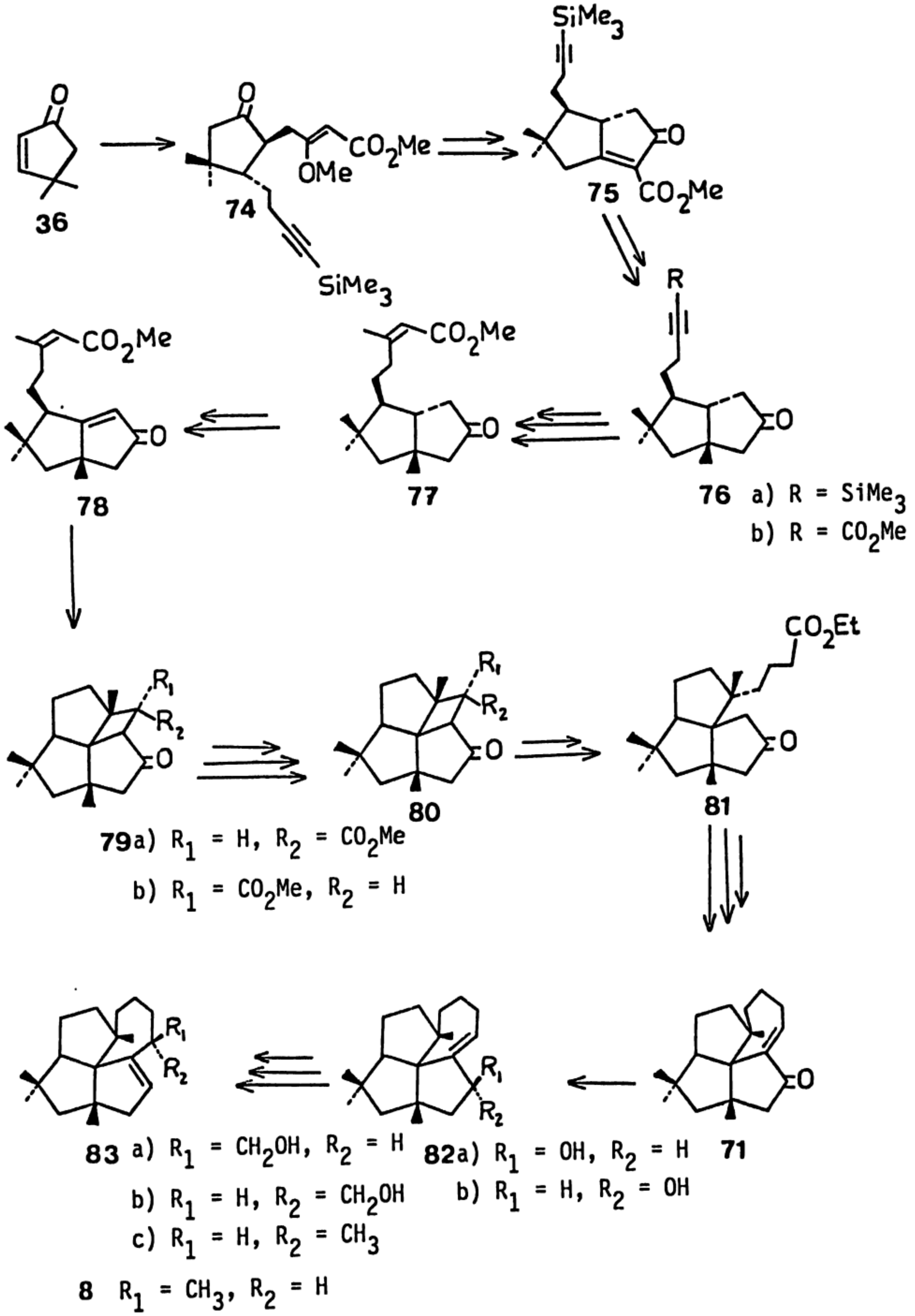
66
OMe
67
CO2Me
OMe
68
CO2Me
OH
69
CHO
O
70
O
71
NH2
O
72
OH
73
8

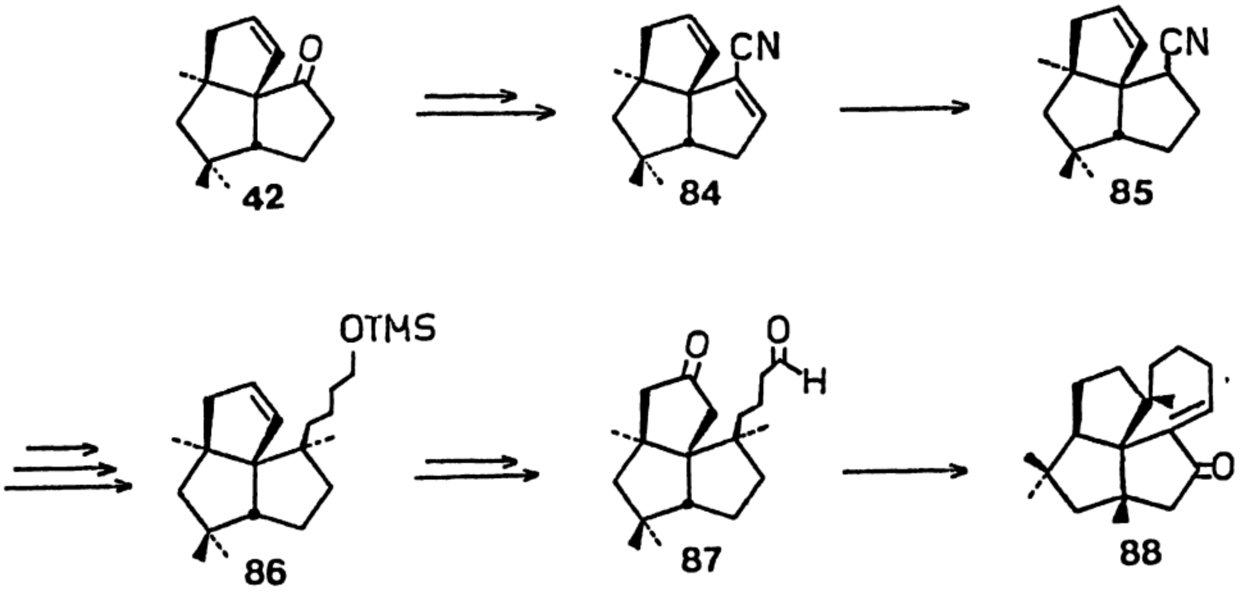
Scheme 1.18


SiMe3
CO2Me
OMe
O
36
74
SiMe3
75
CO2Me
R
CO2Me
CO2Me
78
77
76 a) R = SiMe3
b) R = CO2Me
R1
R2
O
79a) R1 = H, R2 = CO2Me
b) R1 = CO2Me, R2 = H
80
CO2Et
81
83 a) R1 = CH2OH, R2 = H
b) R1 = H, R2 = CH2OH
c) R1 = H, R2 = CH3
8 R1 = CH3, R2 = H
82a) R1 = OH, R2 = H
b) R1 = H, R2 = OH
71

Scheme 1.19

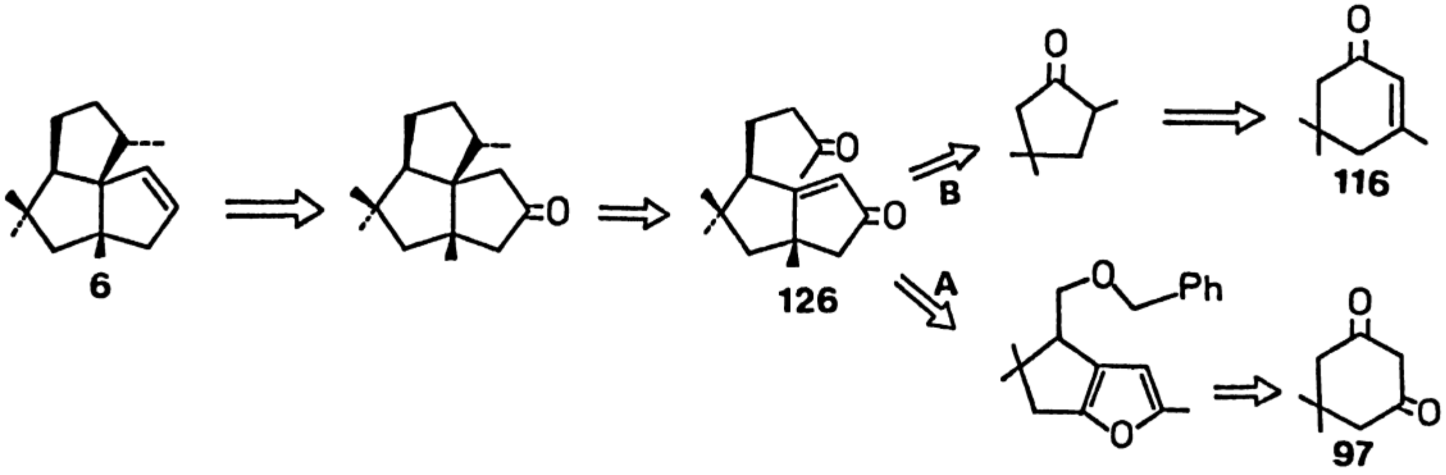
an aldol reaction – in a manner similar to the strategy reported by Ito in his synthesis of laurenene. Reduction of the enone produced the epimeric alcohols **82a** and **82b**. When alcohol **82a** was exposed to the conditions reported by Still,[21] **83a** was obtained whose tosylation followed by reduction of the tosylate produced laurenene.

The third synthesis, reported by Paquette[22] also utilizes one of the intermediates employed in his synthesis of silphinene, Scheme 1.20.

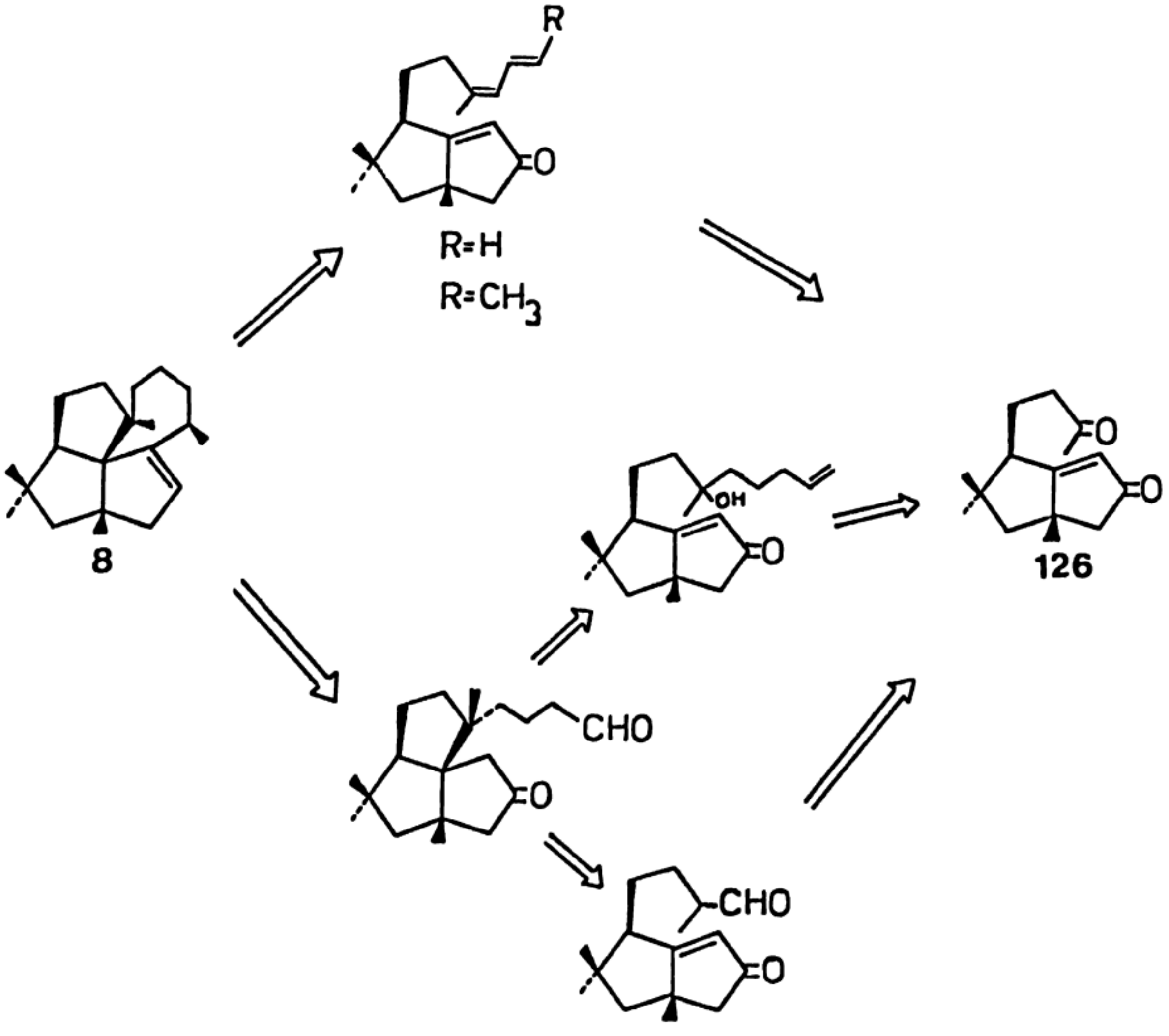


Scheme 1.20

The ketone **42** was transformed into **84** through reaction with trimethylsilyl cyanide and catalytical amounts of zinc iodide followed by treatment with phosphorus oxychloride and DBU. Chemospecific reduction of **84** with magnesium in methanol furnished **85**. Treatment of **85** with 1-bromo-4-[(trimethylsilyl)oxy]butane followed by reduction of the nitrile function gave **86**. Hydroboration-oxidation of **86** gave the keto-aldehyde **87** in a good yield. Closure of the seven-membered ring was achieved



Scheme 1.21



Scheme 1.22

by intramolecular aldolization which provided the intermediate **88**. As **88** has already been converted into laurenene by Ito[19] and Crimmins,[20] this work constitutes a formal total synthesis of laurenene.

It is of interest to point out at this stage that the three syntheses of laurenene reported are very long. This prompted us to synthesize this unique molecule in lesser number of steps.

With the twin objectives of silphinene and laurenene in mind, a careful examination of the problem was undertaken and a retrosynthetic analysis, as depicted in Schemes 1.21 and 1.22, was arrived at.

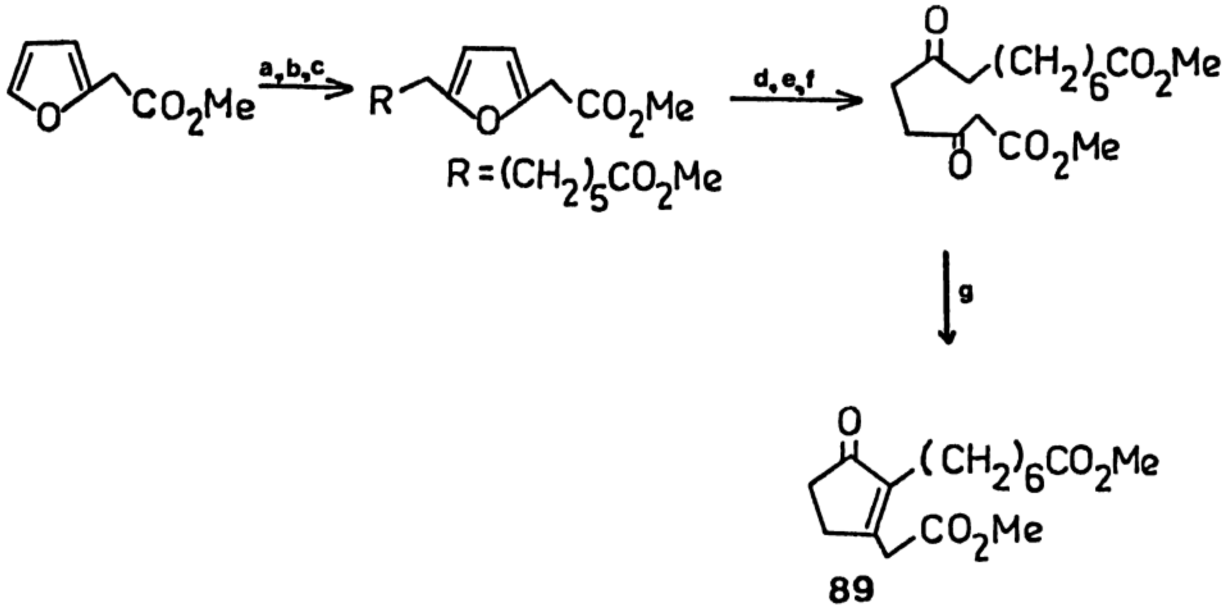
It is evident from the retrosynthetic analysis that the syntheses of silphinene and laurenene can proceed via a common intermediate. Moreoever, there is minimal deployment of protective groups in the entire sequence and the starting materials for providing the common intermediate are both readily available and inexpensive. It is also evident that both the starting materials namely, dimedone and isophorone have a gem dimethyl group in their structures which would ultimately become the gem dimethyl group of the bicyclo[3.3.0]octane skeleton, thereby obviating the need for the introduction of such a group at a later stage in the synthesis.

The operational aspects of these strategies are discussed in detail in the next chapter.

RESULTS AND DISCUSSION

As briefly outlined in the introduction, the main objective of the present study is to synthesize both the molecules, silphinene and laurenene, from a common intermediate and accordingly, efforts were initially directed towards this target i.e., synthesizing a common intermediate possessing the basic bicyclo[3.3.0]octane skeleton with necessary functional groups which can be manipulated in a suitable way so as to arrive at both the molecules in a minimum number of steps. Although a variety of methods are available in the literature to build a bicyclo [3.3.0]octane skeleton,[23] we set out in constructing such a system through the intermediacy of a furan ring, functioning as an equivalent of a 1,4-diketone.

It is known in the literature that furans serve as precursors of 1,4-diketones,[24] to which they are intimately related. The advantages in using a furan as the latent functionality of a 1,4-diketone are worthy of note. Firstly, furans are base resistant. Hence, base catalyzed reactions can be easily performed on them. Secondly, they are easily hydrolyzed to 1,4-diketones, requiring only mild acid conditions for effecting hydrolysis. With these advantages, a classical but economical route to cyclopentenone **89** from commercially available methyl 2-furanacetate has been developed.[25]



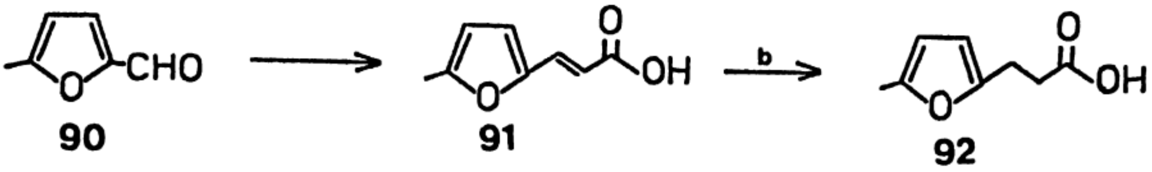
89

a) $SnCl_4$, $ClCO(CH_2)_5CO_2Et$; b) H_2NNH_2, KOH; c) CH_2N_2;
d) Br_2, MeOH; e) Pd-$CaCO_3$, H_2; f) H^+; g) $NaHCO_3$, MeOH.

Scheme 1.23

Taking this aspect into consideration, we felt that if a cyclopentane ring is annelated to a substituted furan, the required bicyclo[3.3.0]octane system could be generated from such a skeleton through hydrolysis of the furan ring to a 1,4-diketone followed by aldol reaction of the resulting 1,4-diketone.

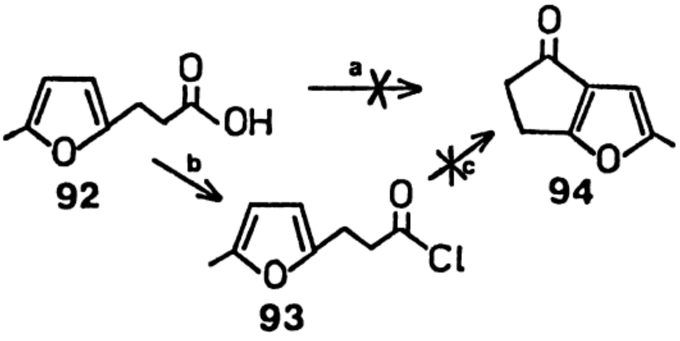
In order to achieve this, 5-methyl-2-furfuraldehyde was condensed with malonic acid in a Doebner fashion to give 3-(5-methyl-2-furyl) acrylic acid (**91**) which was hydrogenated to furnish 3-(5-methyl-2-furyl) propionic acid[26] (**92**).



a) $CH_2(CO_2H)_2$, Py, C_6H_6, 100°C; b) Pd-$SrCO_3$, H_2, r.t.

Scheme 1.24

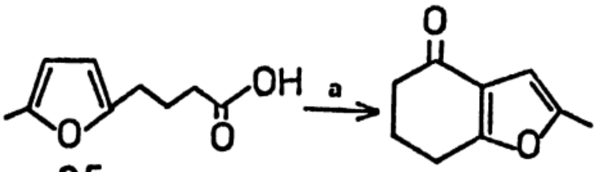
Attempted intramolecular Friedel-Crafts acylation of **92** using $PCl_5/SnCl_4$ to give the corresponding ketone 2-methyl-5,6-dihydro-4H-cyclopenta(b)furan-4-one (**94**) was unsuccessful. Conversion of the acid to the acid chloride 3-(5-methyl-2-furyl)propionyl chloride using oxalyl chloride and subjecting it (**93**) to the intramolecular acylation conditions using $SnCl_4$ as catalyst was also of little use (Scheme 1.25).



a) $SnCl_4$, PCl_5, C_6H_6, 80°C; b) $(COCl)_2$, DCM; c) $SnCl_4$, C_6H_6, 80°C.

Scheme 1.25

Use of different Lewis acids like $BF_3.OEt_2$ and $AlCl_3$ was also unsuccessful in realizing the desired intramolecular acylation. This result was rather surprising since it is known in the literature that 4-(5-methyl-2-furyl)butanoic acid (**95**) cyclizes under similar conditions to give the corresponding compound, 4,5,6,7-tetrahydro-2-methyl-4-benzofuranone (**96**)[26]


95

96

a) $SnCl_4$, PCl_5, C_6H_6, 80°C

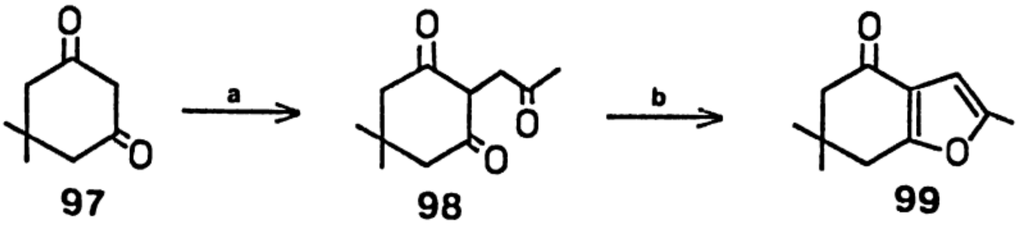
Scheme 1.26

Recently, an observation similar to the one above was also noted by Stone.[27] Reasons for the failure of such a reaction have been advanced in that paper.

With the failure of the intramolecular acylation of the furan ring, it was felt that a system similar to **94** can be generated starting from cyclopentanone or a substituted cyclopentanone by the annelation of the furan ring onto it. Once the required functional groups are incorporated onto the cyclopentane ring, the furan ring could be hydrolyzed and the resulting 1,4-diketone when subjected to aldol conditions would give the desired bicyclo[3.3.0]octane skeleton.

With this objective in mind, 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (**99**) was prepared from 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**97**)[28], Scheme 1.27.

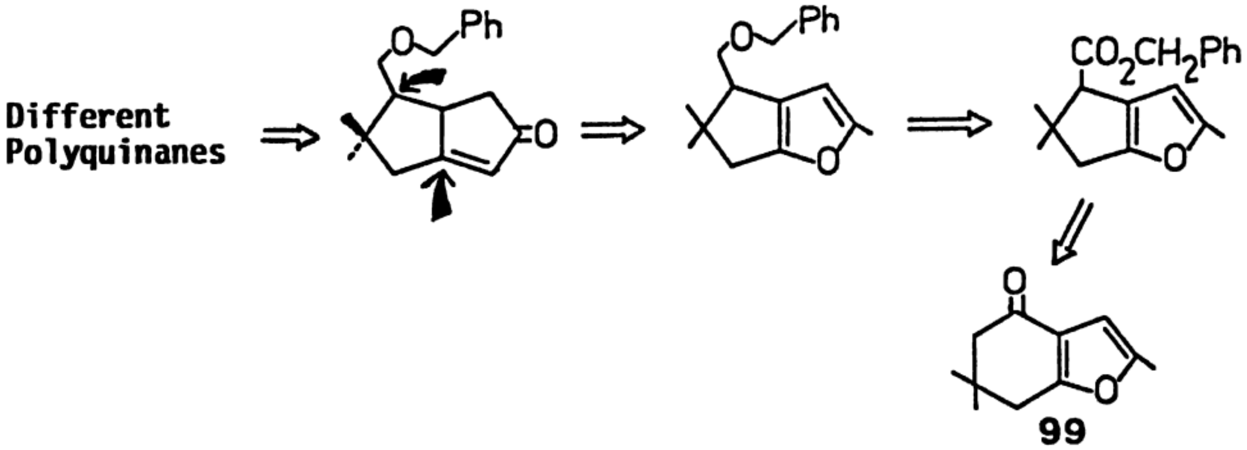
Compound **99** was chosen because (i) it is readily available in two steps from **97**; (ii) it has two methyls in a geminal fashion in the cyclohexane portion which would become gem-dimethyls after contraction of the cyclohexane portion to a cyclopentane, thus incorporating the required



a) NaOEt, MeOH, $ClCH_2COCH_3$, 80°C; b) Conc. H_2SO_4, r.t.

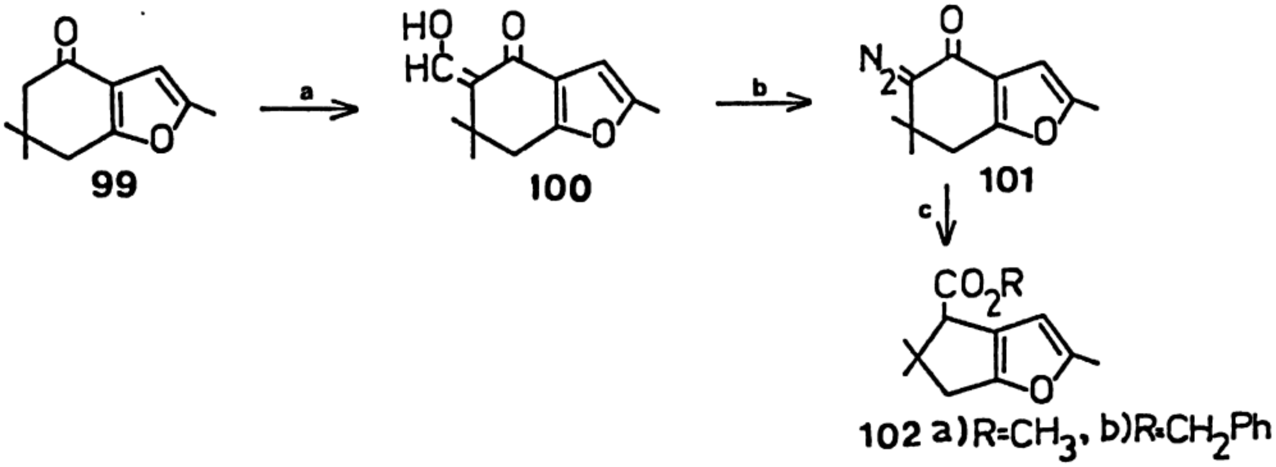
Scheme 1.27

gem dimethyls seen in a variety of polyquinanes; (iii) the cyclohexanone moiety, after ring contraction, would be converted into an ester function on a cyclopentane ring which could be conveniently transformed into a desired functional group. These points can be expressed in a schematic way as follows:



Scheme 1.28

Although the reported procedure employed aqueous hydrochloric acid to prepare **99** from **98**, concentrated sulfuric acid was, however, found to be most suitable among the several dehydrating agents tried to cyclize **98** to **99**. Once **99** was in hand, it was envisaged that ring contraction of the cyclohexanone portion of the molecule would give an intermediate (Scheme 1.28) that could be further transformed into the desired bicyclo-[3.3.0]octane skeleton. In order to effect the ring contraction, the Wolff rearrangement was chosen and accordingly, the substrate required for the Wolff rearrangement was prepared, Scheme 1.29.



a) $C_5H_{11}ONa$, C_6H_6, HCO_2Et; 0°C.
b) DBU, $TosN_3$, DCM, r.t.
c) $h\nu$, MeOH, r.t.; $PhCH_2OH$, 2,4,6-collidine, 180°C.

Scheme 1.29

Attempted formylation of **99** using a variety of bases including NaOMe/MeOH, NaOEt/EtOH, NaH/THF, KOBu*t*/*t*-BuOH and LDA/THF were uniformly unsuccessful and only the starting material was recovered in each case. Finally, the needed formylation was found to proceed with sodium *t*-amyloxide in benzene and after considerable experimentation, the desired product, 6,7-dihydro-5-formyl-2,6,6-trimethyl-4(5H)-benzofuranone (**100**) was obtained in a very good yield of 94%. The structure of **100** was evident from its IR and ^{1}H NMR spectra which displayed bands at 3500, 1680 and 1600 cm^{-1} in the IR spectrum and signals at δ 7.32-7.24 (d, 1H, olefinic) and 6.24 (bs, 1H, furan) in the ^{1}H NMR spectrum. The final proof came from the mass spectrum of **100** which showed a molecular ion peak at m/e = 206.

Reaction of **100** under the usual Regitz conditions[29] with *p*-toluenesulfonyl azide and triethylamine to effect diazo transfer was very slow and did not go to completion even after 24h at 30°C. As **100** is a sterically hindered ketone, modifications of the Regitz reaction employing bases like potassium ethanolate[30] and phase transfer catalyzed method[31] which are known to be effective in such instances, were attempted. However, they too were found to be unsuccessful. Therefore, a systematic investigation of the reaction of **100** with p-toluenesulfonyl azide and various bases was undertaken. While bases like diisopropylethylamine and 4-dimethylaminopyridine (DMAP) were not useful, the reaction of **100** proceeded moderately well in the presence of 1,4-diazabicyclo[2.2.2] octane (DABCO) to give the required 5-diazo-6,7-dihydro-2,6,6-trimethyl -4(5H)-benzofuranone (**101**) in 56% yield after one hour at 30°C. Encouraged by this result, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used and a dramatic improvement in yield (95%) and reduction in reaction time (15 min) was observed.[32] The fact that **101** has indeed formed was apparent from its spectral data. Thus, **101** displayed a strong band at 2100 cm^{-1}, due to the diazo group in the IR spectrum and signals at δ 6.27 (bs, 1H, furan), 2.82 (s, 3H, furan methyl) and 1.38 (s, 6H, gem dimethyl) in the ^{1}H NMR spectrum. The mass spectrum of **101** showed a peak at m/e = 176 (M-28), due to loss of nitrogen in addition to the molecular ion peak at m/e =

204 and finally the elemental analysis was also in keeping with the molecular composition of **101**.

In order to examine the generality of the reaction, a few other substrates shown in Table 1 were reacted with p-toluensulfonyl azide and DBU. It can be readily observed from Table 1 that the yields of the diazo compounds obtained by this procedure are either as good or superior to the ones reported earlier.[32]

The stage was now set for the crucial Wolff rearrangement. When **101** was photolyzed in degassed methanol with a Hanovia 450 W medium pressure mercury lamp using a pyrex filter, the rearranged product, methyl-2,5,5-trimethyl-5,6-dihydro-4H-cyclopenta(b)furan-4-carboxylate (**102a**) was obtained in 67% yield. As this reaction could not be performed on a large scale due to experimental limitations, the Wolff rearrangement was performed under thermolytic conditions employing benzyl alcohol as the medium. Addition of **101** to a mixture of benzyl alcohol and 2,4,6-collidine and heating the mixture to 180°C gave the desired rearranged benzyl ester **102b** in almost quantitative yield. Again, the spectral data of **102a** and **102b** were diagnostic in concluding that the Wolff rearrangement had indeed taken place. A strong carbonyl band at 1720 cm^{-1} and absence of the band at 2100 cm^{-1} due to the diazo group in the IR spectrum and a signal at δ 3.64 (s, 3H, carbomethoxy protons) in **102a** and signals at δ 7.24 (s, 5H, aromatic) and 5.08 (s, 2H, benzylic protons) in **102b** in addition to the usual signals in the ^1H NMR spectra clearly established the proposed structures for **102a** and **102b**, respectively.

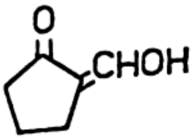
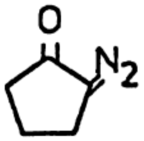
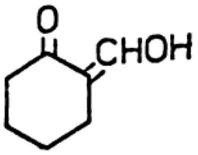
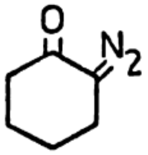
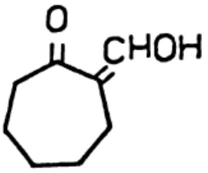
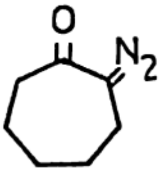
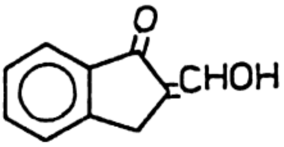
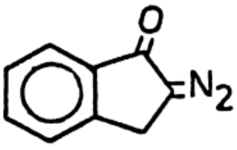
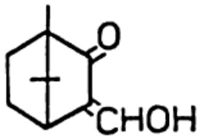
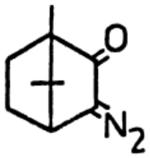
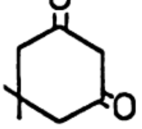
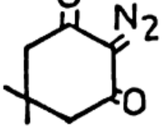
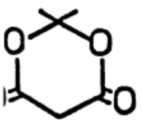
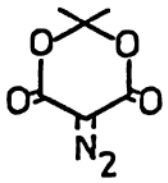
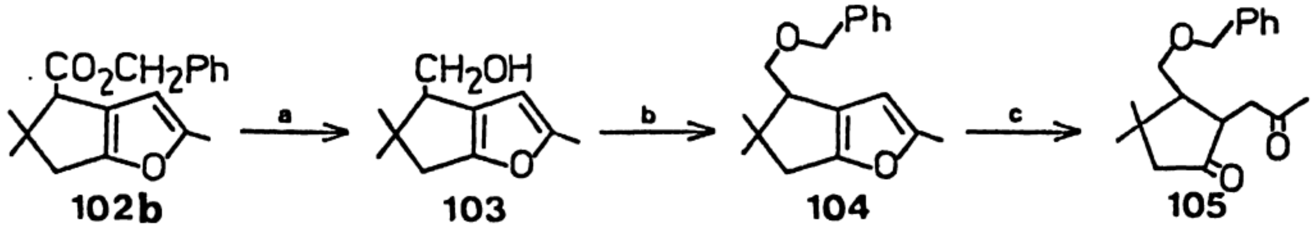
Substrate	Product	Yield (%)	
		Observed	Reported
		82	98
		100	82
		100	83
		73	58
		74	74
		96	78
		76	47
$CH_2(CO_2CH_3)_2$	$N_2C(CO_2CH_3)_2$	81	42
$CH_2(COC_6H_5)_2$	$N_2C(COC_6H_5)_2$	82	81

Table 1

With a servicable route to **102b** in hand, attention was then turned towards building the bicyclo[3.3.0]octane ring system from **102b**. Accordingly, the benzyl ester was reduced by LAH in THF to the alcohol **103**. When **103** was treated with NaH in THF employing benzyl bromide as the alkylating agent, the corresponding benzyl ether **104** was obtained in 88% yield.



102b **103** **104** **105**

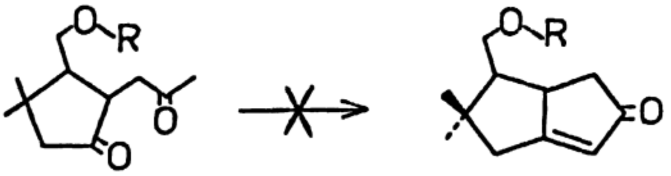
a) LAH, THF, r.t.; b) NaH, THF, $PhCH_2Br$, r.t.; c) Aq.AcOH, Conc.H_2SO_4, 70-80°C.

Scheme 1.30

The spectral data (IR and ^1H NMR) of **103** and **104** were consistent with the proposed structures.

The straight forward preparation of **104** from readily available commercial materials was very encouraging as **104** incorporates the gem dimethyl group and the side chain in the correct position of the desired bicyclo[3.3.0]octane (Scheme 1.28). It only remained to transform the furan ring in **104** to a cyclopentenone. Hydrolysis of **104** with aqueous acetic acid - sulfuric acid at 70-80°C gave the corresponding 1,4-diketone **105** (Scheme 1.30). The structure of **105** is supported by its spectral data: IR : a strong carbonyl band at 1710 cm^{-1}; ^1H NMR : signals at δ7.60 (s, 5H, aromatic), 4.60 (s, 2H, benzylic), 2.08 (s, 3H, acetyl methyl) among other signals. The ^{13}C NMR spectrum of **105** clearly showed two carbon resonances at 217.3 and 205.8 ppm characteristic of cyclopentanone and acetyl carbonyls.

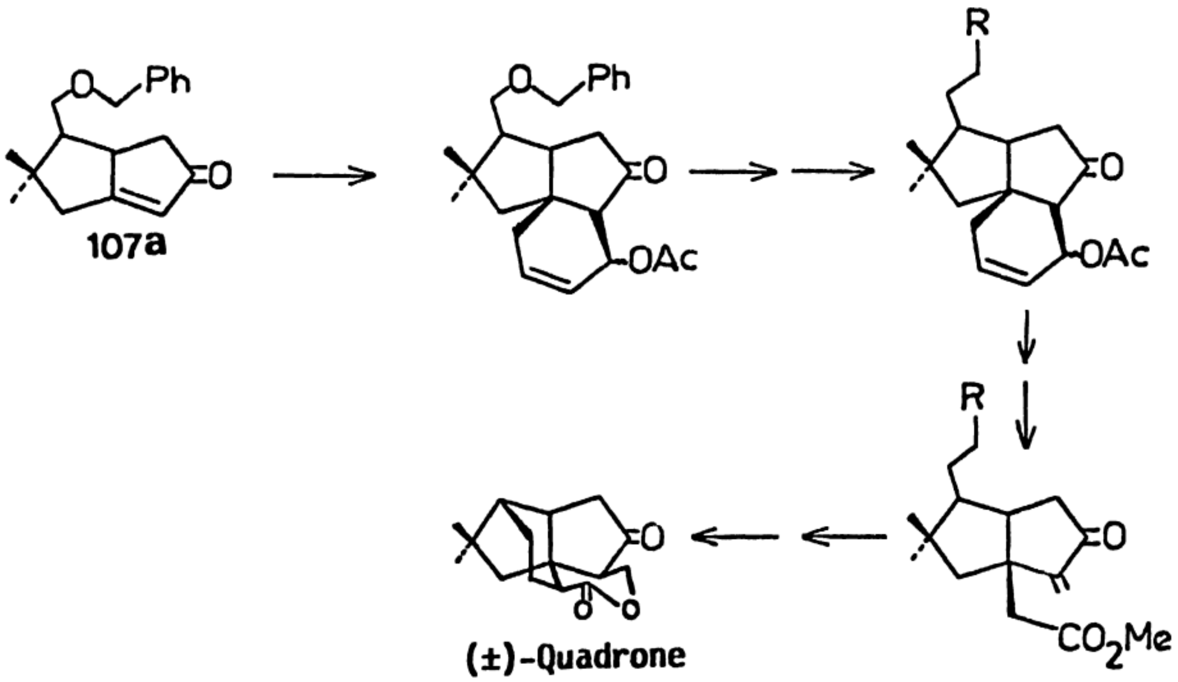
A variety of bases, listed in Table 2, were tried to effect the aldol reaction of the 1,4-diketone of **105** but all the attempts made were futile. Analogues of **105**, with methyl and 2-tetrahydropyranyl as protecting groups of the alcohol were prepared and subjected to the aldol reaction conditions. These were also unsuccessful (Scheme 1.31).



105 R = CH_2Ph **107a** R = CH_2Ph
106a R = CH_3 **b** R = CH_3
b R = THP **c** R = THP

Scheme 1.31

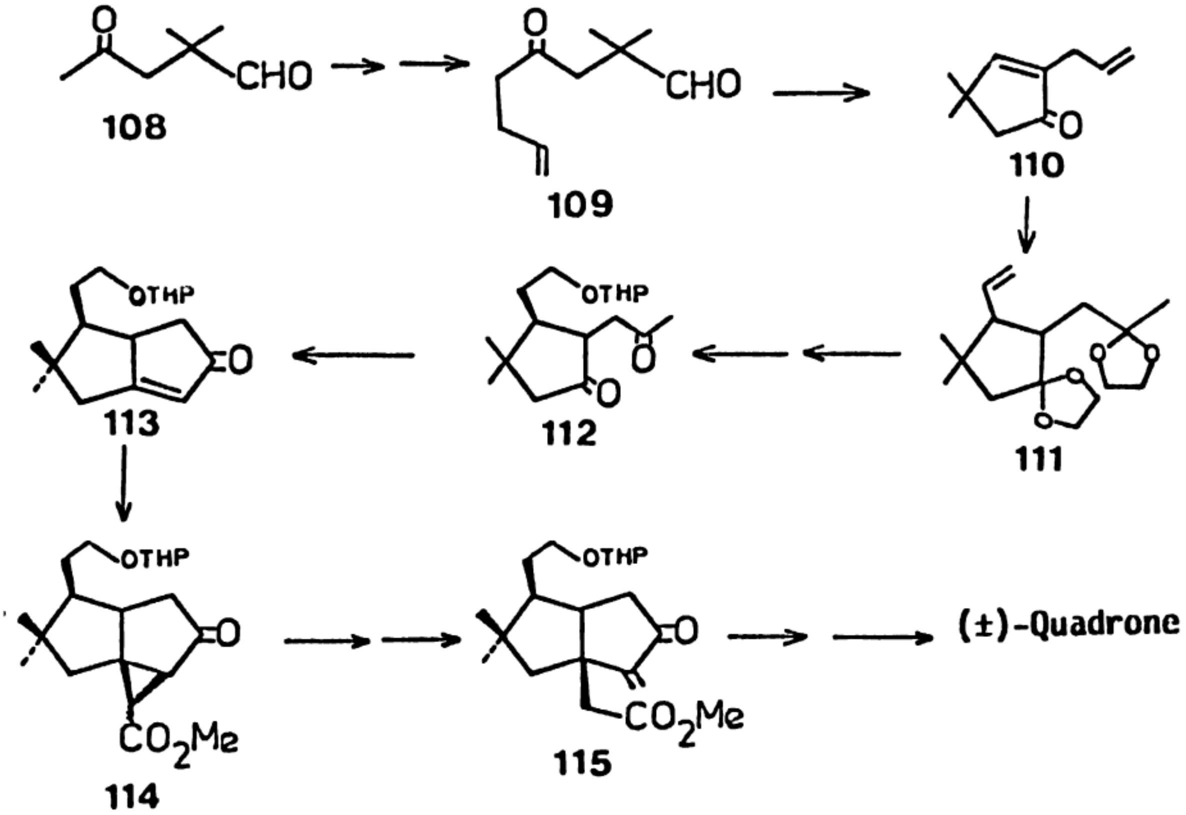
Originally, it was envisaged that the intermediate **107a** would be used not only in the synthesis of silphinene and laurenene [Schemes 1.21 (Path A) and 1.22] but also in that of quadrone, an antitumor fungal metabolite isolated from Aspergillus terreus, as depicted in the following scheme.



S.No.	Substrate	Reaction conditions	Result
1.	**105**	KOH/EtOH at r.t. and at 100°C	No reaction. Starting material recovered
2.	"	NaOMe/MeOH at 60-70°C	No reaction. Starting material recovered.
3.	"	NaH/<u>t</u>-AmOH/C_6H_6 at varied temperatures	Complex mixture
4.	"	NaOAm-<u>t</u>/C_6H_6 at varied temperatures	Complex mixture
5.	"	KOBu-<u>t</u>/<u>t</u>-BuOH/THF at varied temperatures	Complex mixture
6.	"	KH/DME at varied temperatures	Complex mixture
7.	"	KH/THF at varied temperatures	Complex mixture

Table 2

A compound similar to **107a** obtained by a totally different route was utilized by Iwata[33] in his synthesis of quadrone (Scheme 1.33).

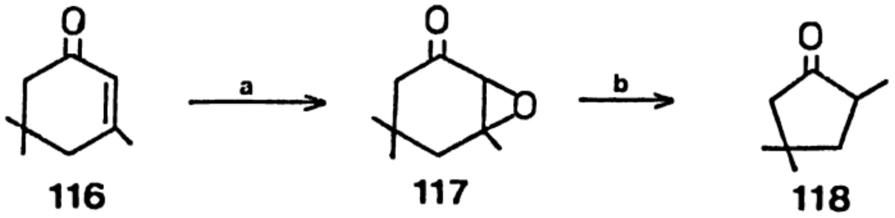


Scheme 1.33

In view of the successful transformation of **112** to **113** reported in this communication, it was rather surprising to us to note that the aldol reaction of **105** could not be effected in our case.

As all the attempts made in constructing the bicyclo[3.3.0]octane skeleton were unsuccessful, the idea of preparing such a system which could be exploited towards a variety of polycyclopentanoids was dropped and efforts were then primarily directed towards the synthesis of silphinene and laurenene.

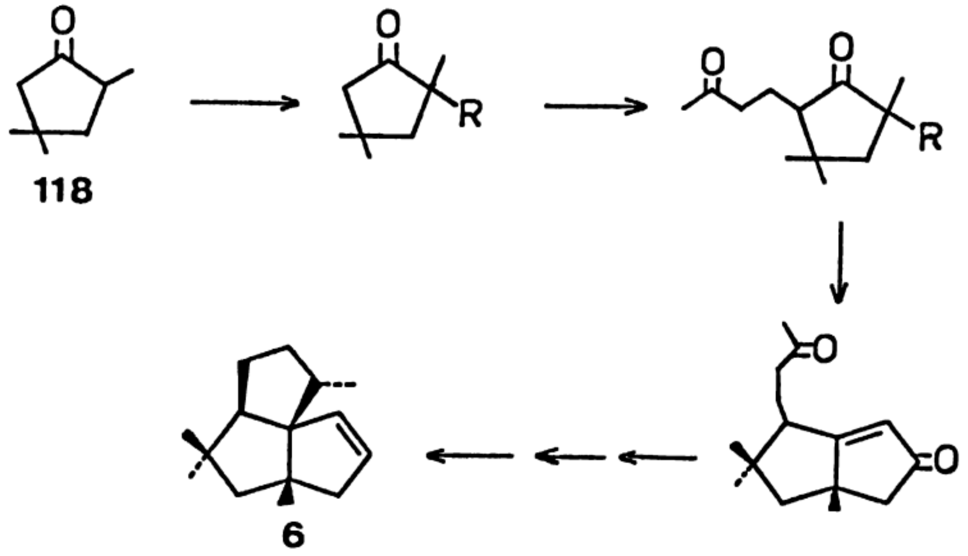
In order to arrive at a common intermediate for the synthesis of silphinene and laurenene, 2,4,4-trimethylcyclopentanone (**118**) was identified as a suitable starting material (Scheme 1.21, Path B). This compound was chosen in view of the fact that it is readily available from 3,5,5-trimethyl-2-cyclohexenone (isophorone)[34] (Scheme 1.34) and secondly, it has three methyls which correspond to the three of the four methyls present in silphinene and three of the five methyls present in laurenene. It was thought that in this way introduction of methyls onto a preformed bicyclo[3.3.0]octane skeleton, which is the usual practice, could be avoided. In this instance as well, the gem dimethyl group is located in the correct position for both silphenene and laurenene.



a) 30% H_2O_2, NaOH, 10-15°C; b) $BF_3.OEt_2$, NaOH, r.t.

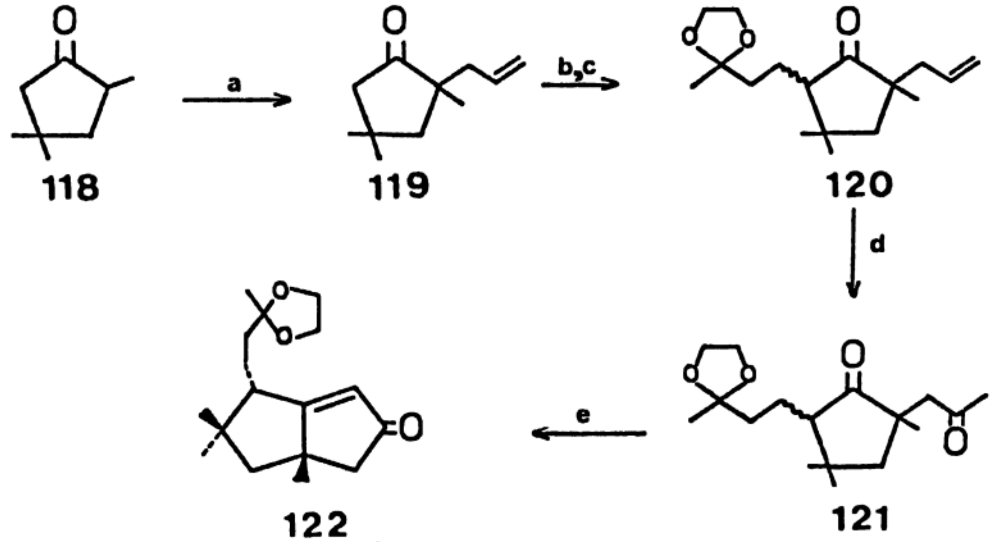
Scheme 1.34

We planned to introduce either an acetonyl side chain or a latent functionality of it at the 2 position of **118**. This was to be followed by the introduction of a four carbon side chain at the 5 position so that once the acetonyl side chain is made use of in obtaining the bicyclo [3.3.0]octane skeleton through an aldol reaction, the four carbon side chain with the necessary functional groups can be cyclized onto the newly formed enone moiety of the bicyclo[3.3.0]octane system, thereby leading to silphinene (Scheme 1.35).



Scheme 1.35

With this objective in mind, **118** was alkylated regiospecifically at the 2 position with allyl bromide under thermodynamically controlled conditions using NaH as the base and THF as the solvent. This particular combination of the base and the solvent was found to be most suitable among a variety of base-solvent combinations tried (NaH/DME, NaH/DMF, KOBu*t*/*t*-BuOH, THF) for effecting allylation. This one step preparation of 2-allyl-2,4,4-trimethylcyclopentanone (**119**) was found to be far superior to a 4 step preparation of the same compound reported in the literature,[35] both in terms of overall yield and the number of steps involved. The identity of **119** was established by comparison of its spectral data (IR, ^{1}H NMR and ^{13}C NMR) with that reported earlier.[35]

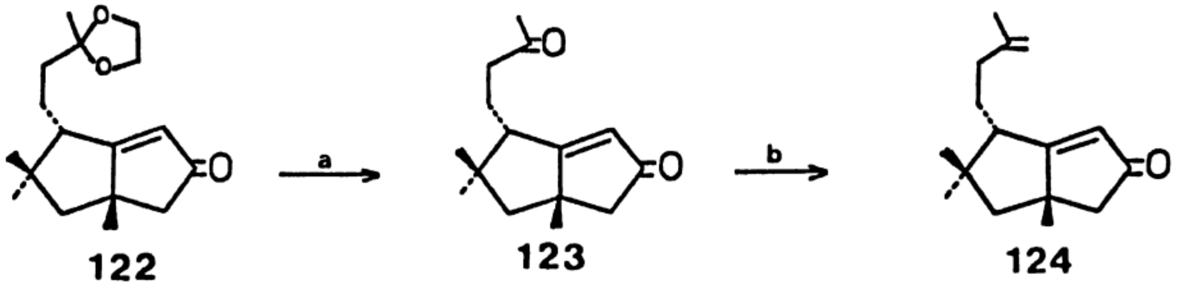


a) NaH, THF, 60°C, $CH_2=CHCH_2Br$. ✓
b) LDA, THF, 0°C, CH_3CCH_2CHO.
c) Li, NH_3, -78°C to r.t., NH_4Cl.
d) $PdCl_2$, CuCl, O_2, DMF, r.t.
e) NaH, C_6H_6, t-AmOH, 80°C.

Scheme 1.36

The next step was to introduce a suitable 4-carbon side chain at the 5 position of **119**. For this purpose, alkylation of **119** with 1-iodo-3,3-ethylenedioxybutane using LDA as the base was attempted but this could not be achieved. However, this problem was overcome by performing an aldol reaction between **119** and 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde using LDA as the base and THF as the medium. As a result, an enone as a mixture of E and Z isomers in the ratio of 60:40 was obtained. The aldol was however, not isolated. The structure of enone was evident from its spectral data : IR: bands at 1710 and 1640 cm^{-1}; ^1H NMR : signals at δ 6.68-6.52 (t, olefinic proton from the enone in the Z isomer), 6.0-5.85 (t, olefinic proton from the enone in the E isomer), (together integrating for one proton), 3.04-2.96 (d, proton coupled to the olefinic proton of the enone of Z isomer), 2.68-2.60 (d, proton coupled to the olefinic proton of the enone of E isomer) (together integrating for two protons). It is known that such a kind of deshielding of the proton in the Z isomer is usually observed in such kind of α, β-unsaturated systems.[36] These assignments were made by decoupling experiments. This enone was reduced by lithium in ammonia at -78°C to furnish 5-(3,3-ethylenedioxybutyl)-2-allyl-2,4,4-trimethylcyclopentanone **(120)** which was also obtained as a mixture. After having obtained **120**, whose structure is fully supported by its spectral (IR, ^{1}H NMR) and analytical data, the terminal olefin in **120** was oxidized to a methyl ketone employing Tsuji's conditions[37] and the product, 2-(2-oxopropyl)-5-(3,3-ethylenedioxybutyl)-2,4,4-trimethylcyclopentanone **(121)** was obtained in a reasonable yield of 54%. The presence of a signal at δ 2.0 (s, 3H, acetyl methyl) and the absence of signals due to the terminal olefin in the ^{1}H NMR spectrum of **121** were particularly diagnostic in characterizing **121**. Moreover, the analytical data of **121** was in complete agreement with that expected for $C_{17}H_{28}O_4$, thus confirming that oxidation of the terminal olefin had indeed taken place.

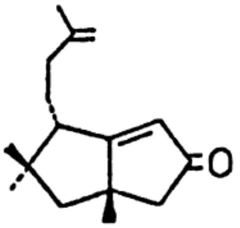
When **121** was subjected to intramolecular aldol reaction using NaH as the base and benzene as the solvent with a catalytic~~al~~ amount of *t*-amyl alcohol, the enone (4SR, 6aRS)-4-(3,3-ethylenedioxybutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)pentalenone **(122)** was obtained as a colorless solid after purification by column chromatography. The presence of a doublet at δ 5.64 in the ^{1}H NMR spectrum and bands at 1710 and 1640 cm^{-1} in the IR spectrum indicated the presence of an enone moiety in **122**. As the stereochemistry of the side chain in **122** has to be established beyond doubt, the ketal in **122** was hydrolyzed to the ene-dione **123**. This was followed by the reaction of **123** with methylene triphenylphosphorane to give **124** (Scheme 1.37).

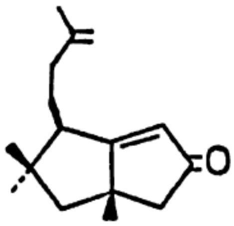


a) Aq.AcOH, r.t.; b) $C_5H_{11}ONa$, C_6H_6, Ph_3PCH_3Br, r.t.

Scheme 1.37

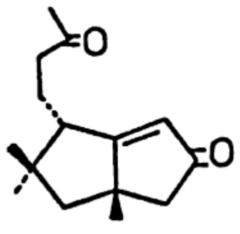
Comparison of **124** with **125**, a similar compound reported by Crimmins,[38] indicated that the side chain in **124** was opposite in stereochemistry to that in **125**.


124

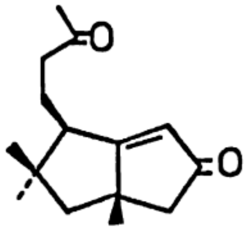

125

Thus, in the ^1H NMR spectrum, while **124** had signals at δ 5.70 (d, 1H, olefinic), 4.72-4.64 (m, 2H, side chain olefinic protons), 1.24 (s, 3H, methyl), 1.20 (s, 3H, methyl), 0.72 (s, 3H, methyl), **125** had the corresponding signals at δ 5.80 (s, 1H, olefinic), 4.76-4.68 (m, 2H, side chain olefinic protons), 1.32 (s, 3H, methyl), 1.18 (s, 3H, methyl) and 0.96 (s, 3H, methyl). This clearly establishes that **124** and **125** are different compounds. As the side chain in **125** is known to be cis to the quaternary methyl group, it is apparent that in **124**, the two substituents are trans to one another. This was further confirmed by a single crystal X-ray analysis of **122**[39] which unequivocally established that the stereochemistry of the side chain is trans with respect to the quaternary methyl. Such a disposition is not of the correct stereochemistry for the synthesis of silphinene and laurenene.

Although a short route (6 steps) to **123** has been devised starting from 2,4,4-trimethylcyclopentanone, the end product in this sequence does not possess the required stereochemistry as far as the four carbon side chain is concerned. Attempted epimerization of the side chain in **122** with bases like NaOMe/MeOH, DBU/C_6H_6, KOBu*t*/*t*-BuOH, KOBu*t*/THF was of little help. Although examination of the ^1H NMR spectrum of the crude reaction mixture obtained in the epimerization reaction of **122** with KOBu*t*/*t*-BuOH indicated that epimerization was taking place as evidenced by signals at δ 5.88 (s) and 5.72 (d) in the ^1H NMR spectrum, preparatively useful amounts of the epimer of **122** could not be isolated from the mixture. In order to obtain an idea of the energy difference between the two epimers, MM2 calculations were performed on **123** and **126** which



123



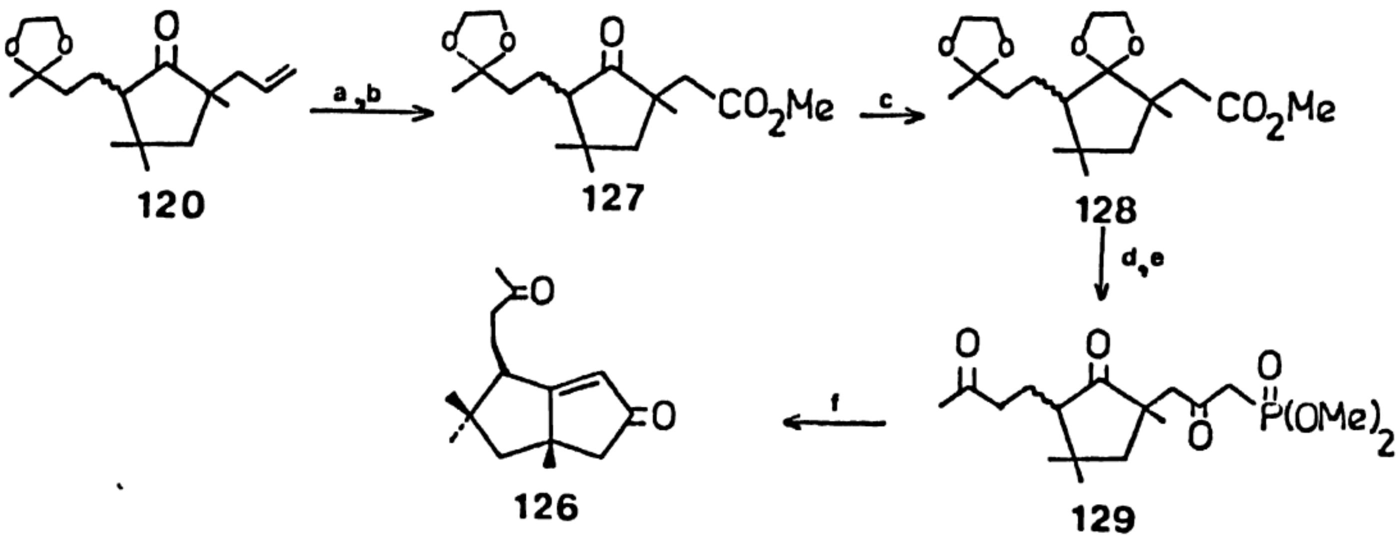
126

indicated that **123** was thermodynamically more stable than **126** by about 2.5 Kcal/mole.[40] Hence, epimerization of the side chain in **122** could at best give a mixture with **122** as the major component.

In view of these results, we were forced to take a fresh look at the synthesis of silphinene, bearing in mind that any route to the bicyclo[3.3.0]octane skeleton should be mild enough so that unwanted epimerization of the side chain can be avoided. With the information gained from the above operations, it was felt that instead of performing the aldol reaction on **121** which involves rather drastic conditions, an intramolecular Wittig-Horner reaction under milder conditions would be preferable. The substrate would now be a β-ketophosphonate instead of the acetonyl group as in **121**. Epimerization of the side chain to the more favourable and less desirable endo face could be avoided (unlike in the earlier instance) due to the milder reaction conditions. Consequently, as a result of such an operation, the possibility of isolating the correct isomer would now be enhanced.

Towards this end, the terminal olefin in **120** was oxidatively cleaved with $RuCl_3/NaIO_4$[41] to an acid which was esterified with diazomethane to give the corresponding keto ester **127** (Scheme 1.38).

Ketalization of **127** using triethyl orthoformate/ethylene glycol/p-toluenesulfonic acid gave **128**. Compounds **127** and **128** were fully characterized by spectral (IR and ^1H NMR) and analytical data. Conversion of the ester to the β-ketophosphonate **129** was achieved by reacting **128** with the lithium salt of dimethyl methylphosphonate followed by hydrolysis of the ketals with aqueous hydrochloric acid.[42] The crude

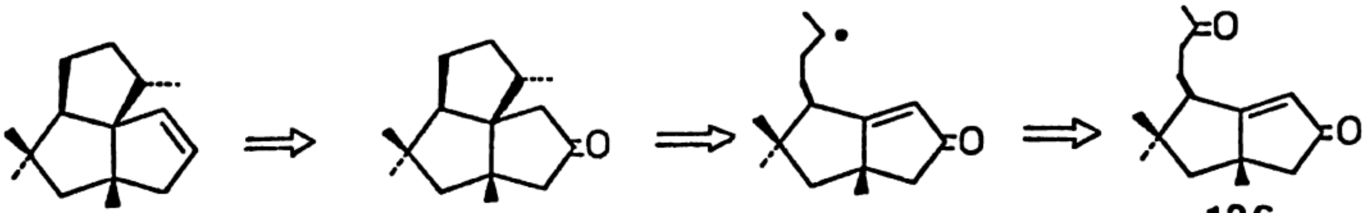


a) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, r.t.; b) CH_2N_2, Et_2O, 0°C.; c) $CH(OEt)_3$, $HOCH_2CH_2OH$, p-TsOH, r.t.; d) $CH_3PO(OMe)_2$, nBuLi, THF, -78°C to r.t.; e) 3NHCl; f) (n-Bu)$_4$NOH, C_6H_6, H_2O, r.t.

Scheme 1.38

material obtained after the two operations was directly subjected to the intramolecular Wittig-Horner reaction employing the recently reported conditions of Heathcock[43] which utilizes the very mild phase transfer catalysis (PTC) conditions involving tetrabutylammonium hydroxide as the base. As per our expectations, the corresponding enone **126** with the side chain in the desired stereochemistry was obtained. That the side chain in **126** indeed had the correct stereochemistry was confirmed by converting **126** into **125** by a simple Wittig olefination and then comparing the spectral data (IR and ^{1}H NMR) with those reported for the same compound by Crimmins.[38]

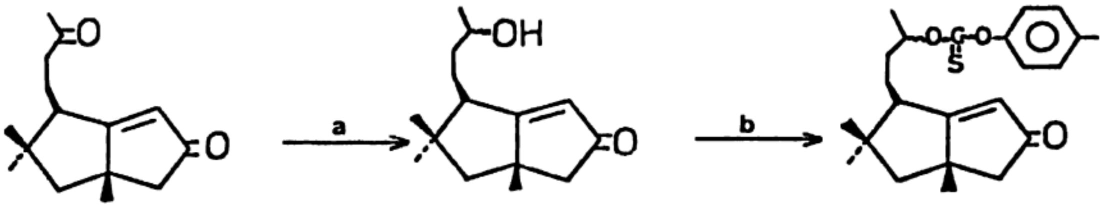
At this stage, conversion of **126** into silphinene proved to be quite simple. As pointed out earlier in the introduction, a strategy based on free radical cyclizations for the synthesis of angularly fused polyquinanes was selected and tested using silphinene as a prototype (Scheme 1.39).



6 **126**

Scheme 1.39

With this objective in mind, the saturated ketone in the side chain of **126** was selectively reduced with sodium borohydride in methanol and the resulting alcohol **130** was converted into the p-tolylthionocarbonate derivative **131** which can be used as a radical source.[44]

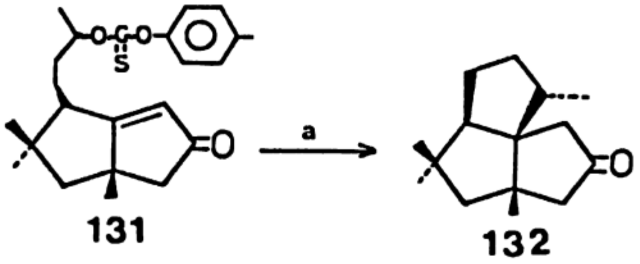


126 **130** **131**

a) $NaBH_4$, MeOH, 0°C; b) Py, DCM, ClCSOC_6H_4-CH_3-p.

Scheme 1.40

Compounds **130** and **131** were fully characterized by IR and ^1H NMR. Treatment of **131** with tributyltin hydride generated a radical which added in a stereospecific fashion to the double bond of the enone giving the angular triquinane **132** exclusively (as shown in Scheme 1.39).

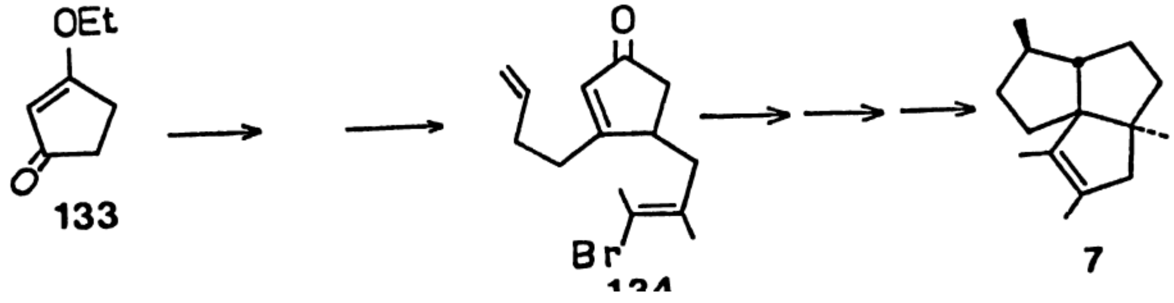


a) n-Bu_3SnH, AIBN, C_6H_6, 80°C.

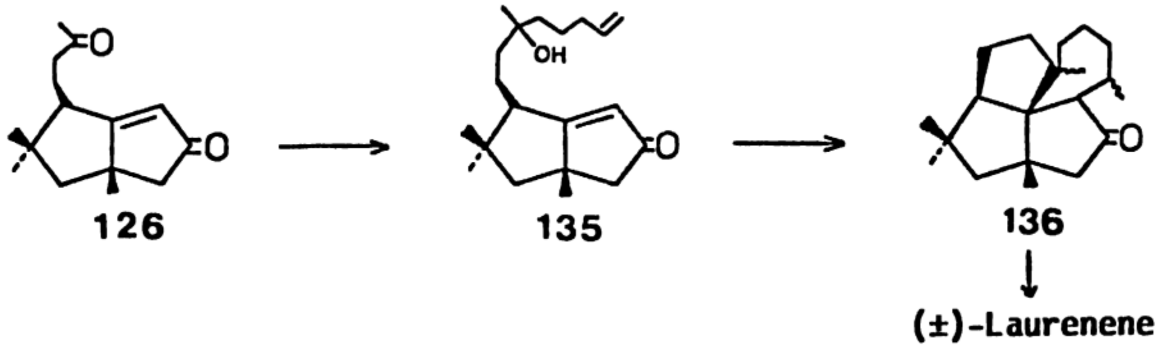
Scheme 1.41

The structure of **132** was unambiguously proved from its spectral data which corresponded with that reported for the same compound by Crimmins.[18] Thus, **132** had a strong carbonyl at 1740 cm^{-1} in the IR spectrum characteristic of a cyclopentanone while the ^1H NMR displayed signals at δ 2.30 (AB, 2H), 2.22 (AB, 2H), 2.18-1.90 (band, 3H), 1.78 (s, 2H), 1.75-1.51 (band 2H), 1.27 (m, 1H), 1.12 (s, 3H), 1.04 (s, 3H), 1.0 (s, 3H) and 0.96 (d, 3H).

As **132** has already been converted to silphinene by Crimmins[18] in another two steps, the above described work constitutes a formal total synthesis of silphinene.[45] This work, involving an intramolecular radical cyclization, is among the first few approaches towards the tricyclo [6.3.0.0^{1,5}]undecane skeleton using such a method. The only other work recorded till today is that of Curran,[5] who has utilized such a radical cyclization approach in obtaining a tricyclo[6.3.0.0^{1,5}]undecane skeleton and has implemented it successfully in the synthesis of silphiperfol-6- ene (**7**) (Scheme 1.42).



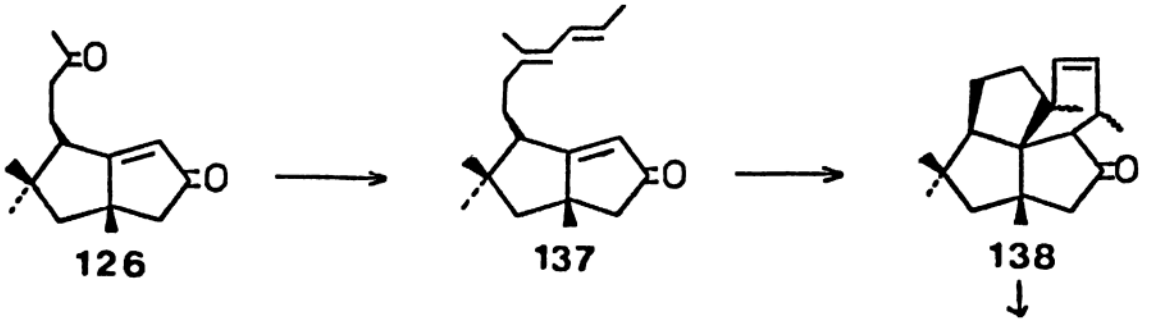
With the successful execution of the methodology involving intramolecular radical cyclization in the synthesis of silphinene, we next turned our attention to the synthesis of laurenene. It was envisaged that a similar type of methodology can as well be utilized in the synthesis of laurenene, as depicted in the following scheme.



Scheme 1.43

Addition of the Grignard derived from 5-bromo-1-pentene to the ketone in the side chain of **126** would give the intermediate **135**, which when subjected to the intramolecular radical cyclization would lead to **135** via a double radical addition. As Curran has already demonstrated the validity of such a double radical addition,[5] **136** would be an advanced intermediate in the synthesis of laurenene. However, the Grignard reaction of **126** with 4-pentenylmagnesium bromide could not be carried out successfully. While the reaction failed with the Grignard reagent derived from 4-bromo-1-butene also, the reaction of **126** with allylmagnesium bromide gave a mixture whose IR spectrum showed no carbonyl band but only the presence of a band at 3300 cm^{-1} due to an alcohol function.

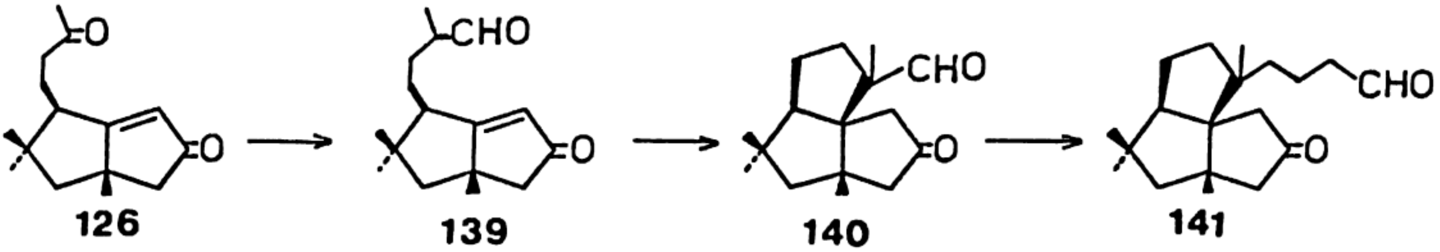
We next turned our attention to pursuing an intramolecular Diels-Alder strategy, Scheme 1.44.


126 137 138

(±)-Laurenene

Scheme 1.44

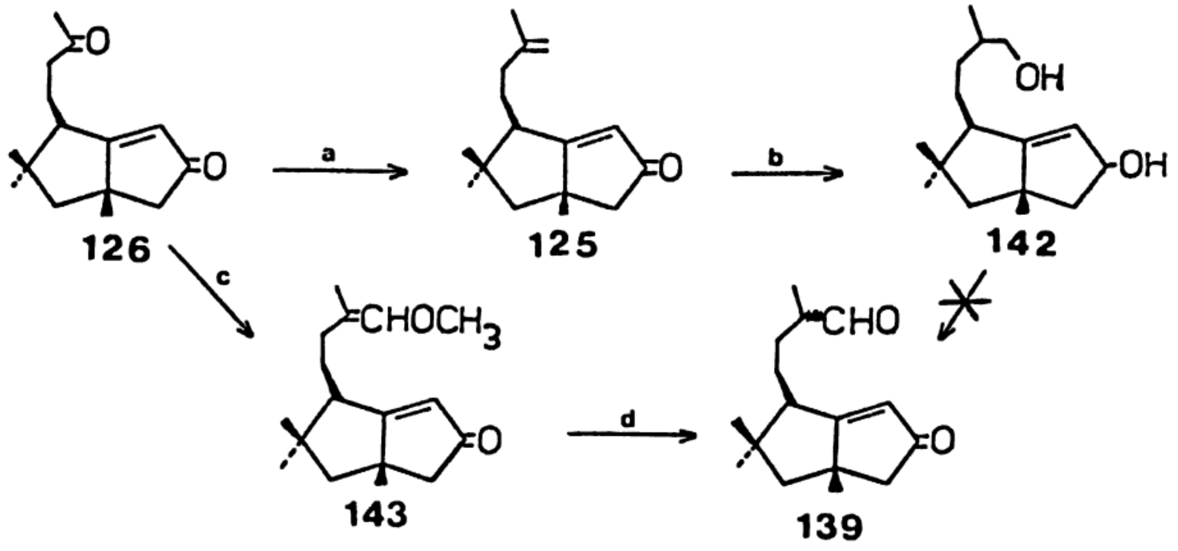
In order to carry out the above strategy, Wittig reaction of **126** with crotyl and allyltriphenylphosphonium bromides was tried. But in both instances, only the starting material was recovered. With the failure of this reaction also, the last approach (as pointed out in Scheme 1.22) i.e., an intramolecular Michael reaction was pursued, Scheme 1.45.



126 139 140 141

Scheme 1.45

To this end, the synthesis of the keto-aldehyde **139** was attempted as shown in scheme 1.46 by two different routes.



a) Ph_3PCH_3I, $C_5H_{11}ONa$, C_6H_6, r.t.; b) 9-BBN, THF, NaOH, H_2O_2, r.t.;
c) $Ph_3PCH_2OCH_3Cl$, $C_5H_{11}ONa$, THF, r.t.; d) $BF_3.OEt_2$, DCM, r.t.

Scheme 1.46

Upon Wittig olefination, **126** gave **125**. Hydroboration of **125** followed by oxidation gave **142**. However, this reaction also reduced the enone present in **125** to an allylic alcohol. The fact that the allyl alcohol **142** was obtained after the hydroboration-oxidation sequence was evident from the ^1H NMR spectrum of **142** in which the signal at δ5.80 (s, 1H, olefinic from enone) was absent and instead, there was a signal at δ5.40 (s, 1H, olefinic). Oxidation of **142** was tried with PCC, PDC and $(COCl)_2$/DMSO (Swern's conditions). In each case, however, only intractable mixtures were isolated. The required keto-aldehyde **139** was obtained from **126** by performing a Wittig reaction on **126** with methoxymethyltriphenylphosphonium bromide and then hydrolyzing the enol ether **143** to **139**. Although the recommended hydrolyzing agents like aqueous perchloric acid and aqueous hydrochloric acid were of little help in this reaction, treatment of **143** with $BF_3.OEt_2$ followed by an aqueous workup gave the keto-aldehyde **139** in almost quantitative yield. Thus, **139** displayed bands at 2750, 1710 and 1640 cm^{-1} in the IR spectrum while the ^1H NMR displayed signals at δ 9.60 (m, 1H, aldehyde), 5.80 (s, 1H, olefinic) in addition to the usual signals. With **139** in hand, it is hoped that **139** would lead to the intermediate **141** via **140** (Scheme 1.45) involving intramolecular Michael reaction of **139** leading to **140**. Wittig reaction on **140** with a 3-carbon Wittig reagent followed by hydrogenation would lead to the intermediate **141**. As **141** has already been converted into laurenene by Ito,[19] Crimmins[20] and Paquette,[22] this work would constitute a formal total synthesis of laurenene.

In conclusion, we have described the strategy leading to the synthesis of (±) silphinene and to an advanced intermediate in the synthesis of laurenene starting from cheap, abundantly available starting materials. More work is needed in extending this strategy to the synthesis of other angular triquinanes.

EXPERIMENTAL

Melting points: Melting points were determined using a Buchi 510 Capillary point apparatus and are uncorrected.

Boiling points: Distillation of liquid samples were done on a Buchi Kugelrohr-GKR 50 apparatus and boiling points indicated are that of the oven air bath.

Elemental Analysis: Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyser.

Infrared Spectra: Infrared spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometers. All spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were prepared as KBr wafers and liquid samples as a film between NaCl plates.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra (100 MHz) and carbon-13-magnetic resonance spectra (25.0 MHz) were obtained using a JEOL-FX-100 spectrometer. All spectra vere recorded in chloroform-<u>d</u> solution with tetramethylsilane as internal standard unless otherwise stated. Spectral assignments are as follows: (1) chemical shift on the δ scale (TMS= δ 0.0); (2) multiplicity : s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, br = broad; (3) number of hydrogens integrated for by the signal; (4) assignment of the signal. Decoupling experiments were carried out by irradiating the frequency of the signal concerned with high power (6-8 watts) and observing the affected signals.

Mass Spectra: Mass measurements were carried out on an AEI-MS 5076 mass spectrometer in the electron impact mode.

Chromatography: GC analysis was done on a Packard instrument equipped with a FID detector, using hydrogen as carrier gas and 20% carbowax or SE-30 columns. Analytical thin layer chromatography (TLC) was performed on (10 x 5 cm) glass plates coated with (250 m μ) Acmes' silica gel G or GF 254 containing 13% calcium sulfate as binder. Visualization of the spots were achieved by exposure to iodine vapour or UV light. Column chromatography was performed using Acmes' silica gel (100-200 mesh) and usually eluted with 20-30% ethyl acetate: hexane, unless otherwise mentioned.

General: As a routine practice, all reactions were monitored by TLC employing appropriate solvent systems for development. All moisture sensitive reactions were carried out using standard syringe-septum techniques under dry nitrogen. All dry solvents were distilled from appropriate drying agents just before use. Pet.ether refers to the fraction boiling between 60-80°C. Hydrogenations were carried out on a Parr hydrogenation apparatus in 250 ml pressure bottles.

All solvent extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated on a Buchi-EL rotary evaporator at reduced pressure. All yields reported are isolated yields of material judged homogeneous by TLC and NMR spectroscopy and for crystalline solids, material having the indicated melting point.

3-(5-Methyl-2-furyl)acrylic acid (91)[26]

To freshly distilled 5-methyl-2-furfuraldehyde (27.5 g, 0.25 mol), malonic acid (26.0 g, 0.25 mol) and pyridine (12 ml, 0.155 mol) were added and the mixture was heated to 80-100°C for 2h. Then the mixture was cooled and diluted with 25 ml of water. The acid was dissolved by addition of concentrated ammonia solution and filtered. Dilute hydrochloric acid (1:1) was added to the mixture till it was acidic to congo-red and then cooled. The crude material obtained was crystallized from pet.ether.

Yield : 34.0 g (90%) mp. : 153-154°C.

3-(5-Methyl-2-furyl)propionic acid (92)[26]

3-(5-Methyl-2-furyl)acrylic acid (13.8 g, 0.1 mol) was dissolved in water (60 ml) containing potassium hydroxide (8.0 g) and palladised strontium carbonate (2.0 g) was added and the mixture was hydrogenated for 3h at room temperature at 4-5 atm. The solution was poured on crushed ice (10.0 g) and vigorously stirred while hydrochloric acid was added until the mixture was acidic to congo-red. The precipitate obtained was filtered and crystallized from pet.ether (40-60°C).

Yield : 12.7 g (91%) mp.: 56-57°C.

Attempted preparation of 2-methyl-5,6-dihydro-4H-cyclopenta(b)furan-4-one (94)

To a solution of **92** (2.0 g, 13 mmol) in 30 ml of benzene, phosphorus pentachloride (2.7 g, 13 mmol) was added and stirred for 15 min at 0°C. At the end of this period, stannic chloride (3.64 g, 14 mmol) in 10 ml of benzene was added dropwise while maintaining the temperature at 0-5°C and then the mixture was stirred for 30 min . The mixture was then added to a mixture of ice-water-toluene. The inorganic layer was washed with cold dil.HCl, aq.potassium carbonate, water, dried and evaporated. Only an intractable mixture was obtained. Use of different Lewis acids like $BF_3.OEt_2$, $AlCl_3$ and $TiCl_4$ instead of $SnCl_4$ also led to only intractable mixtures.

Isolation of the acid chloride (**93**) by using oxalyl chloride instead of phosphorus pentachloride and subjecting it to the same conditions as described above was also unsuccessful. In this operation, lowering the temperature from 0°C to -78°C was also of little consequence.

2-(2-Oxopropyl)-5,5-dimethylcyclohexane-1,3-dione (98)[28]

A mixture of sodium methoxide (11.3 g, 0.210 mol), 5,5-cyclohexane-1,3-dione (30.0 g, 0.214 mol) and chloroacetone (20.3 g, 0.221 mol) in 145 ml of ethanol was heated under reflux for 15 min and then cooled. The sodium chloride which formed was removed by filtration and the filtrate was concentrated under vacuum. The residual syrup was dissolved in a mixture of chloroform (50 ml) and 10% sodium hydroxide (50 ml). The organic phase was removed and the aqueous phase was reextracted with chloroform. The aqueous phase was cooled, made acidic with conc.HCl and extracted with chloroform. The combined organic extracts was dried and evaporated to dryness. Recrystallization of the crude product from hexane provided **98**.

Yield : 30.0 g (71%); mp.: 134-135°C.

2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (99)

Compound **98** (10.0 g, 0.051 mol) was dissolved in 25 ml of conc.

H_2SO_4 and the mixture was stirred at room temperature for 3h. At the end of this period, the mixture was slowly poured into 50 ml of water. The resulting mixture was thoroughly cooled, extracted with chloroform, dried and evaporated. The crude product obtained was purified by distillation.

Yield: 6.53 g (72%); bp.: 60°C/0.2 mm; mp.: 72°C.

6,7-Dihydro-5-formyl-2,6,6-trimethyl-4(5H)-benzofuranone (100)

To a solution of **99** (10.0 g, 0.056 mol) in 25 ml of toluene, sodium _t_-amyloxide (7.4 g, 0.067 mol) in 15 ml of benzene was slowly added and the mixture was stirred for one hour at room temperature. Then, the mixture was cooled with an ice bath and ethyl formate (12.4 g, 0.168 mol) was added dropwise and after the addition was over, the mixture was allowed to come to room temperature and was stirred at room temperature overnight. Water (20 ml) was added to the mixture and it was extracted with dichloromethane. The organic layer was removed, the aqueous layer made acidic with conc.HCl and was extracted with dichloromethane (3x25 ml). The combined organic layers was dried and evaporated. The crude material obtained was crystallized from hexane.

Yield : 10.8 g (94%); mp.: 64-65°C.

IR (KBr, cm^{-1}): 3350 , 1680, 1600, 1600, 1440, 1220.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.32-7.24 (d, 1H, olefinic), 6.24 (br s, 1H, furan proton), 2.68 (s, 2H), 2.28 (s, 3H, furan methyl), 1.24 (s, 6H, gem dimethyl).

Mass : 206 (M^{+}), 178, 163, 135, 94.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.

Found : C, 69.95; H, 7.19.

5-Diazo-6,7-dihydro-2,6,6-trimethyl-4(5H)-benzofuranone (101)

To a solution of **100** (4.0 g, 19.4 mmol) in 25 ml of dichloromethane cooled to 5-10°C, DBU (4.40 g, 29 mmol) was added dropwise followed by the addition of p-toluenesulfonyl azide (3.82 g, 19.4 mmol). The mixture was stirred for 15 min and then washed with water (thrice). The organic layer was dried and evaporated. The crude material obtained was crystallized from hexane.

Yield : 3.76 g (95%); mp.: 102-103°C.

IR (KBr, cm^{-1}): 3000, 2100, 1620, 1420, 1300, 900, 640.

^1H NMR (100 MHz, $CDCl_3$) : δ 6.27 (s, 1H, furan proton), 2.82 (s, 2H), 2.30 (s, 3H, furan methyl), 1.38 (s, 6H, gem dimethyl).

Mass : 204 (M^{+}), 176 (M-28), 161, 148, 133, 105, 79, 43.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92.

Found : C, 65.22; H, 6.36.

The other diazo compounds listed in Table I were prepared by the same procedure.

Methyl-2,5,5-trimethyl-5,6-dihydro-4H-cyclopenta(b)furan-4-carboxylate (102a)

Compound **101** (0.204 g, 1 mmol) was taken in 150 ml of degassed methanol and photolyzed with a Hanovia 450 W medium pressure mercury lamp using a pyrex filter for 1h. At the end of this period, the solvent was evaporated and the crude material was purified by column chromatography, eluting with 5% ethyl acetate-hexane.

Yield : 0.140 g (67%).

IR (neat, cm^{-1}): 2900, 1720, 1460, 1180.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.83 (br s, 1H, furan proton), 3.64 (s, 3H, carbomethoxy), 3.37 (br s, 1H, methine proton), 2.54 (s, 2H, methylene protons adjacent to gem dimethyls), 2.23 (s, 3H, furan methyl), 1.33 (s, 3H, methyl), 1.09 (s, 3H, methyl).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74.
Found : C, 69.10; H, 7.54.

Benzyl-2,5,5-trimethyl-5,6-dihydro-4H-cyclopenta(b)-furan-4-carboxylate (102b)

A mixture of **101** (4.08 g, 20 mmol), benzyl alcohol (6.48 g, 60 mmol) and 2,4,6-collidine (2.42 g, 20 mmol) was heated to 180-190°C for 15 min. During the course of the reaction, vigorous evolution of nitrogen gas was observed. After the reaction was over, the mixture was cooled to room temperature and extracted with dichloromethane. The organic layer was washed with 10% HCl, water, dried and evaporated. The crude material was then purified by fractional distillation.

Yield : 5.60 g (98%); bp. 170-180°C/0.1 mm.

IR (neat, cm^{-1}): 2900, 1730, 1470, 1150, 800.

^1H NMR (100 MHz, $CDCl_3$): δ 7.24 (s, 5H, aromatic), 5.84 (s, 1H, furan proton), 5.08 (s, 2H, benzyl protons), 3.40 (s, 1H, methine proton), 2.48 (s, 2H, methylene protons adjacent to gem dimethyls), 2.20 (s, 3H, furan methyl), 1.28 (s, 3H, methyl), 1.08 (s, 3H, methyl).

^{13}C NMR (25.0 MHz, $CDCl_3$): 172.3, 155.6, 154.9, 135.6, 128.0, 127.8, 127.6, 122.3, 102.8, 65.5, 53.7, 48.5, 40.2, 29.9, 25.0, 13.1 ppm.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.08.

Found : C, 75.88; H, 7.03.

5,6-Dihydro-4-hydroxymethyl-2,5,5-trimethyl-4H-cyclopenta(b)furan (103)

To a suspension of LAH (0.380 g, 10 mmol) in 20 ml of THF, a solution of **102b** (2.84 g, 10 mmol) in 10 ml of THF was added and the mixture was stirred at room temperature overnight. The next day, the mixture was quenched with a saturated solution of aqueous sodium sulfate (10 ml). The mixture was filtered and the filtrate was taken into dichloromethane. The combined organic layers was washed with water, dried and evaporated and the product was distilled.

Yield : 1.54 g (86%); bp.: 100-105°C/0.1 mm

IR (neat, cm^{-1}) : 3350, 2950, 1460, 1400, 1020.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 6.12 (s, 1H, furan proton), 3.80-3.58 (m, 2H, methylene protons adjacent to hydroxy group), 2.76-2.68 (t, 1H, methine proton), 2.60 (s, 2H, methylene protons adjacent to gem dimethyls), 2.36 (s, 3H, furan methyl), 1.28 (s, 3H, methyl), 1.20 (s, 3H, methyl).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.29; H, 8.94.

Found : C, 73.55; H, 8.80.

4-Benzyloxymethyl-5,6-dihydro-2,5,5-trimethyl-4-cyclopenta(b)furan (104)

To thoroughly washed sodium hydride (0.2 g, 4.0 mmol of 50%) in 5 ml of THF, **103** (0.540 g 3 mmol) in 2 ml of THF was added followed by a catalytical amount (30 mg) of tetra-n-butylammonium iodide. The mixture was stirred for 30 min and benzyl bromide (0.684 g, 4 mmol) was added. The mixture was stirred for 14 h at room temperature and then quenched with 10% HCl (2 ml) and extracted with dichloromethane. After drying and evaporation of the solvent, the crude material was purified by column chromatography using 10% ethyl acetate-hexane as eluant.

Yield : 0.710 g (88%); bp. 170-180/0.3 mm.

IR (neat, cm^{-1}) : 2950, 1620, 1070, 890.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.20 (s, 5H, aromatic), 5./2 (s, 1H, furan proton), 4.44 (s, 2H, benzyl protons), 3.48-3.40 (d, 2H, $-C\underline{H}_2OCH_2Ph$), 2.76-2.60 (t, 1H, methine proton), 2.40 (s, 2H, methylene protons adjacent to gem dimethyl), 2.20 (s, 3H, furan methyl), 2.04 (s, 3H, methyl), 1.12 (s, 3H, methyl).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20.
Found : C, 79.66; H, 8.41.

2-(2-Oxopropyl)-3-benzyloxymethyl-4,4-dimethylcyclopentanone (105)

Compound **104** (0.270 g, 1 mmol) was dissolved in 5 ml of 80% aqueous acetic acid and to it, a drop of conc. H_2SO_4 was added and the mixture was heated to 100-120°C for one hour. The mixture was cooled, taken into dichloromethane, washed with saturated aqueous $NaHCO_3$, water, dried and evaporated. The crude material was then subjected to distillation.

Yield : 0.240 g (82%); bp. : 200-210°C/0.3 mm.

IR (neat, cm^{-1}) : 2900, 1730, 1360, 1080, 720.

^1H NMR (100 MHz, $CDCl_3$): δ 7.24 (s, 5H, aromatic), 4.60 (s, 2H, benzyl protons), 3.92-3.48 (m, 2H, $-C\underline{H}_2OCH_2Ph$), 3.0-2.88 (t), 2.72-2.56 (band), (together integrating for 3H), 2.36-2.32 (d, 2H), 2.04 (br s, 4H), 1.28 (s, 3H, methyl), 1.0 (s, 3H, methyl).

^{13}C NMR (25.0 MHz, $CDCl_3$) : 217.3, 205.8, 137.8, 127.9, 127.1, 72.7, 70.3, 53.6, 49.7, 47.4, 42.4, 35.5, 29.4, 28.1, 22.2 ppm.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.96; H, 8.38.
Found : C, 74.89; H, 8.41.

Attempted aldol reaction on 105

To a suspension of NaH (0.150 g, 3 mmol of 50%) in 2 ml of benzene, a drop of _t_-amyl alcohol was added and the mixture was stirred at 80-90°C for 5 min. Then, **105** (0.290 g, 1 mmol) in 1 ml of benzene was added and the mixture was stirred at 80-90°C for 2 h. At the end of this period, the mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated. As the crude mixture was found to contain a series of spots on TLC, its purification was not attempted.

Repeating the reaction on the same scale but at room temperature provided only the starting material.

Use of other base-solvent combinations (Table 2) gave either an intracatable mixture or the starting material.

Isophorone epoxide (117)[34]

To a mixture of isophorone (55.2 g, 0.4 mol) and 30% hydrogen peroxide (115 ml, 1.2 mol) in 400 ml of methanol, 6N aqueous sodium hydroxide (38 ml, 0.2 mol) was added dropwise while cooling the mixture in an ice bath. After the addition was complete, the reaction mixture was stirred at 20-25°C for 3 h. It was then poured into water (500 ml) and extracted with ether. After drying and evaporation of the solvent, the crude mixture was distilled.

Yield : 44.5 g (72%); bp.: 70-73°C/5 mm.

2,4,4-Trimethylcyclopentanone (118)[34]

To a solution of isophorone epoxide (38.6 g, 0.25 mol) in 400 ml of benzene, boron trifluoride etherate (20 ml, 0.16 mol) was added and the mixture was allowed to stand for 30 min and then diluted with 100 ml of ether and washed with 100 ml of water. The organic layer was separated, shaken with aqueous sodium hydroxide (40.0 g, 1 mol, 200 ml of water) and then washed with 100 ml of water. The benzene layer was dried and concentrated and then subjected to distillation.

Yield : 19.8 g (63%); bp. : 61-62°C/21 mm.

2-Allyl-2,4,4-trimethylcyclopentanone (119)[35]

To a suspension of NaH (2.880 g, 0.120 mol of 50%) in 10 ml of THF, compound **118** (7.0 g, 0.056 mol) in 5 ml of THF was added and the mixture was stirred at 55-60°C for 5 h. Then it was cooled to room temperature and allyl bromide (4.8 ml, 0.056 mol) was added dropwise and after the addition was over, the reaction mixture was maintained at 55-60°C overnight. The reaction mixture was quenched with dil. HCl, extracted with dichloromethane, dried and evaporated. The crude mixture was then distilled.

Yield : 8.1 g (88%); bp. : 100°C/0.8 mm.

IR (neat, cm^{-1}): 3080, 1730, 1645, 1000, 920.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.72 (m, 1H), 5.03 (m, 2H), 1.13 (s, 3H), 1.11 (s, 6H).

^{13}C NMR (25.0 MHz, $CDCl_3$): 221.7, 133.8, 118.2, 53.0, 49.0, 48.7, 44.1, 33.0, 30.4, 30.1, 25.0 ppm.

2-Allyl-5(3,3-ethylenedioxybutyl)-2,4,4-trimethylcyclopentanone (120)

To a solution of diisopropylamine (2.525 g, 25 mmol) in 5 ml of THF cooled in an ice bath, n-BuLi (16.6 ml of 1.2 M, 20 mmol) was added dropwise over a period of 30 min. After allowing the mixture to stir for 30 min, compound **119** (3.32 g, 20 mmol) in 2 ml of THF was added slowly and after the addition was over, the mixture was stirred at 5-10°C for 2 h. Then, a solution of 2-(2-methyl-1,3-dioxolan-2-yl)- acetaldehyde (3.2 g, 24.6 mmol) in 2 ml of THF was added and the mixture was stirred for 15 h at room temperature. At the end of this period, water (20 ml) was added and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography.

Yield : 3.04 g (100% based on **119** recovered).

IR (neat, cm^{-1}) : 3000, 1710, 1640, 1460, 1200, 1060.

^1H NMR (100 MHz, $CDCl_3$) : δ 6.68-6.52 (t, olefin proton from enone in Z isomer), 6.0-5.84 (t, olefin proton from enone in E isomer) (together integrating for 1H), 5.72-5.44 (m, 1H, olefinic), 5.08-4.92 (m, 2H, olefinic), 3.92 (s, 4H, ketal protons), 3.04-2.96 (d, proton coupled to olefin proton of the enone in Z isomer), 2.64-2.56 (d, proton coupled to olefin proton of the enone in E isomer), (together integrating for 2H), 2.16-2.08 (d, 2H), 1.96- 1.44 (dd, 2H, methylene protons of cyclopentanone), 1.32 (br s, 6H, 2 methyls), 1.20 (s, 3H, methyl), 1.08 (s, 3H, methyl).

To a suspension of lithium (0.460 g, 66 mmol) in about 250 ml of liquid ammonia at -78°C, the enone obtained from the above operation (3.05 g, 11 mmol) in 5 ml of THF was added dropwise. After the addition was over, the reaction mixture was stirred at -78°C for one hour and then quenched with ammonium chloride (1.06 g, 20 mmol). After the evaporation of ammonia, the crude mixture was extracted with ether, washed once with water, dried and evaporated and purified by column chromatography to give a colourless liquid.

Yield : 1.84 g (60%).

IR (neat, cm^{-1}) : 3000, 1740, 1660, 1480, 1400, 1060.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.92-5.44 (m, 1H, olefinic), 5.08-4.92 (m, 2H, olefinic), 3.92 (s, 4H, ketal protons), 2.12-1.44 (band, 8H), 1.32 (s, 3H, methyl), 1.16 (s, 3H, methyl), 1.08 (s, 3H, methyl), 0.84 (s, 3H, methyl).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06.

Found : C, 72.56; H, 9.98.

2-(2-Oxopropyl)-5-(3,3-ethylenedioxybutyl)-2,4,4-trimethylcyclopentanone (121)

To a suspension of palladium chloride (0.106 g, 0.6 mmol) and cuprous chloride (0.360 g, 3.6 mmol) in 2 ml of DMF, **121** (0.50 g, 1.8 mmol) in 1 ml of DMF was added and the reaction mixture was stirred at room temperature with oxygen bubbling through the reaction mixture for 20 h. The mixture was diluted with dichloromethane, filtered and the filtrate was repeatedly (4 to 5 times) washed with water. After drying and evaporation, the crude material was purified by column chromatography to afford pure **121** as a viscous liquid.

Yield : 0.285 g (54%).

IR (neat, cm^{-1}) : 3000, 1720, 1400, 1220, 1060.

^1H NMR (100 MHz, $CDCl_3$): δ 3.80 (s, 4H, ketal protons), 2.52 (s, 2H), 2.0 (s, 3H, $-COC\underline{H}_3$), 1.80-1.40 (band, 6H), 1.20 (s, 3H, methyl), 1.08 (s, 3H, methyl), 1.0 (s, 3H, methyl), 0.80 (s, 3H, methyl).

Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52.

Found : C, 68.85; H, 9.50.

(4SR, 6aRS)-4-(3,3-Ethylenedioxybutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (122)

To a suspension of NaH (0.20 g, 4 mmol of 50%) in 5 ml of benzene, _t_-amyl alcohol (one drop) was added and stirred at 60-70°C for 15 min. Then, **121** (0.560 g, 1.9 mmol) in 2 ml of benzene was added and the reaction was allowed to stir at 60-70°C for 6 h. The mixture was cooled to room temperature, quenched with water and extracted with dichloromethane.

The organic layer was washed with water, dried and evaporated. The crude material was subjected to purification by column chromatography and then crystallized from pet.ether 40-60°C.

Yield : 0.315 g (60%); mp. : 73-74°C.

IR (neat, cm^{-1}) : 3000, 1710, 1640, 1400, 1060.

^1H NMR (100 MHz, $CDCl_3$): δ 5.68-5.64 (d, 1H, olefin proton from enone), 3.80 (s, 4H, ketal protons), 2.48-2.40 (m, 1H, allyl proton), 2.26 (AB, 2H, methylene proton adjacent to cyclopentanone), 1.68-1.28 (band, 6H), 1.20 (s, 3H, methyl), 1.12 (s, 6H, methyls), 0.60 (s, 3H, methyl).

^{13}C NMR (25.0 MHz, $CDCl_3$): 210.3, 196.7, 121.7, 109.6, 64.5, 53.5, 52.7, 50.0, 46.1, 42.7, 38.7, 30.3, 30.0, 25.1, 23.5, 20.1 ppm.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41.

Found : C, 73.60; H, 9.44.

4-(3-Oxobutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)pentalenone (123)

Compound **122** (0.275 g, 1 mmol) was dissolved in 6 ml of 80% aqueous acetic acid and stirred for 3h at room temperature. The mixture was diluted with dichloromethane, the organic layer washed with saturated aqueous $NaHCO_3$, water, dried and evaporated. The crude material was purified by column chromatography.

Yield : 0.210 g (90%).

IR (neat, cm^{-1}) : 3000, 1710, 1640, 1460, 1400, 860, 840.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 5.68-5.64 (d, 1H, olefin proton from enone), 2.64-2.44 (m, 3H), 2.28-2.24 (AB, 2H, methylene proton adjacent to gem dimethyl), 2.12 (s, 3H, -CO$\underline{H}_3$), 1.80-1.44 (band, 4H), 1.20 (s, 6H, methyls), 0.72 (s, 3H, methyl).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46.
Found : C, 76.80; H, 9.40.

4-(3-Methyl-3-butenyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (124)

To a suspension of methyltriphenylphosphonium iodide (0.215 g, 0.535 mmol) in 2 ml of THF, sodium t-amyloxide (0.047 g, 0.427 mmol) in 1 ml of THF was added and stirred for 15 min. To the deep red solution obtained, compound **123** (0.050 g, 0.213 mmol) in 1 ml of THF was added and the mixture was stirred at room temperature for 15 min. At the end of this period, the mixture was quenched with water (2 ml) diluted with ether, dried and evaporated. The product was purified by column chromatography to give **124** as a clear liquid.

Yield : 0.024 g (50%)

IR (neat, cm^{-1}) : 2900, 1710, 1460, 800, 840.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 5.72-5.70 (d, 1H, olefin from enone), 4.72-4.64 (band, 2H, olefin protons in the side chain), 2.60-2.44 (m, 1H, allyl proton), 2.28-2.24 (AB, 2H), 2.20-1.40 (m, 6H), 1.72 (br s, 3H, methyl), 1.20 (br s, 6H, methyls), 0.72 (s, 3H, methyl).

Methyl-5-(3,3-ethylenedioxybutyl)-2,4,4-trimethylcyclopentanone-2-acetate (127)

To a solution of **120** (0.560 g, 2.0 mmol) in 3 ml of carbon tetrachloride, 3 ml of acetonitrile and 5 ml of water, sodium periodate - (1.070g, 5 mmol) and ruthenium (III) chloride (10 mg, catalytical) were added and the reaction mixture was stirred at room temperature for 3h. The mixture was diluted with dichloromethane, washed repeatedly with water (3-4 times), dried and evaporated.

The material obtained from the above procedure (0.580 g) was esterified with diazomethane, obtained as an ethereal solution from 1.05 g of N-nitroso-N-methylurea (10 mmol) and the resulting product was purified by column chromatography.

Yield : 0.60 g (100%).

IR (neat, cm^{-1}) : 3000, 1740, 1460, 1400, 1080.

^1H NMR (100 MHz, $CDCl_3$) : δ 3.88 (s, 4H, ketal protons), 3.60 (s, 3H, carbomethoxy), 2.08 (s, 2H, $-C\underline{H}_2CO_2Me$), 1.84-1.40 (m, 7H), 1.28 (s, 3H, methyl), 1.12 (s, 6H, methyls), 0.84 (s, 3H, methyl).

Anal. Calcd. for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03.
Found : C, 65.23; H, 8.94.

Methyl 2,2-(ethylenedioxy)-3-(3,3-ethylenedioxybutyl)-1,4,4-trimethylcyclopentaneacetate (128)

To a solution of **127** (0.930 g, 3 mmol) in ethylene glycol (1.86 g, 30 mmol), triethyl orthoformate (2.22 g, 15 mmol) and p-toluenesulfonic acid (10 mg, catalytical) were added and the mixture was stirred at room temperature for 30 h. The mixture was then taken into dichloromethane and washed in succession with saturated aqueous $NaHCO_3$, water, dried and evaporated. Purification of the compound was effected by column chromatography. The title compound was obtained as a colourless liquid.

Yield : 0.630 g (60%).

IR (neat, cm^{-1}) : 2950, 1720, 1460, 1380, 1060.

^1H NMR (100 MHz, $CDCl_3$) : δ3.92 (s, 8H, protons from two ketals), 3.60 (s, 3H, carbomethoxy), 2.40 -1.44 (band, 9H); 1.30 (s, 3H, methyl), 1.16 (s, 6H, methyls), 0.88 (s, 3H, methyl).

Anal. Calcd. for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05.
Found : C, 63.95; H, 9.03.

Dimethyl {2-oxo-3-[1,4,4-trimethyl-3(oxobutyl)-2-oxocyclopentyl]propyl} phosphonate (129)

To a solution of dimethyl methylphosphonate (0.390 g, 3.16 mmol) in 2 ml of THF maintained at -78°C, n-butyllithium (3.16 ml of 1M solution, 3.16 mmol) was added dropwise and after the addition was over the mixture was stirred at -78°C for 30min. Compound **128** (0.450 g, 1.26 mmol) in 2 ml of THF was added to the solution at -78°C over a period of 15 min and after the addition, the reaction mixture was stirred at -78°C for 5 h. The mixture was slowly allowed to come to room temperature and then 3N HCl (4 ml) was slowly added and the contents stirred at room temperature overnight. The mixture was diluted with dichloromethane, washed once with water, dried and evaporated to give crude **129**, which was used directly in the next step.

Yield : 0.450 g (100%).

IR (neat, cm^{-1}) : 2950, 1720, 1740, 1040.

4-(3-Oxobutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)pentalenone (126)

To a solution of **129** (0.450 g, 1.25 mmol) in 15 ml of benzene and 15 ml of water, tetra-n-butylammonium hydroxide (40 wt % in water, 0.9 ml, 1.25 mmol) was added and the mixture was stirred at room temperature for 30 min. The organic layer was removed and the aqueous layer was extracted twice with dichloromethane. The dichloromethane layer was added to the benzene solution, dried and evaporated. The material obtained was purified by column chromatography.

Yield : 0.20 g (70%).

IR (neat, cm^{-1}) : 2950, 1710, 1640, 1460, 1380, 860, 820.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.80 (s, 1H, olefin proton from enone), 2.52-2.36 (m, 5H), 2.16 (s, 3H, $-COC\underline{H}_3$), 2.0-1.52 (m, 4H), 1.32 (s, 3H, methyl), 1.20 (s, 3H, methyl), 1.0 (s, 3H, methyl).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46.
Found : C, 77.10; H, 9.48.

4-(3-Hydroxybutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (130)

To a solution of **126** (55 mg, 0.235 mmol) in 1.5 ml of methanol at 0-5°C, sodium borohydride (12 mg, 0.315 mmol) in 0.5 ml of methanol was added and the reaction mixture stirred for 5 min. The reaction mixture was then quenched with acetone (1 ml) and stirred for another 5 min. The solvent was removed under vacuum and the material obtained was purified by column chromatography.

Yield : 0.040 g (72%).

IR (neat, cm^{-1}) : 3300, 2950, 1710, 1640, 1060.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.80 (s, 1H, olefin from enone), 2.40-2.20 (m, 5H), 1.60-1.40 (m, 4H), 1.32-1.24 (d, 3H, methyl), 1.20 (s, 3H, methyl), 1.04 (s, 3H, methyl), 1.0 (s, 3H, methyl).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23.
Found : C, 76.10; H, 10.22.

4-(p-Tolylthionocarbonato)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H) pentalenone (131)

To a solution of **130** (25 mg, 0.169 mmol) in 5 ml of dichloromethane, pyridine (50 mg, 0.627 mmol) and O-p-tolyl chlorothioformate (37 mg, 0.627 mmol) were added and the mixture was stirred for 1.5 h at room temperature. The solvents were removed under vacuum and the product was purified by column chromatography and used as such in the next step.

Yield : 0.040 g (70%).

IR (neat, cm^{-1}) : 3000, 1710, 1630, 1500, 1440, 1300, 1200, 840, 800.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.20-6.88 (AA'BB', 4H, aromatic), 5.80 (s, 1H, olefin proton from enone), 2.32 (s, 3H), 1.80-1.48 (m, 9H), 1.44-1.36 (d, 3H, methyl), 1.28 (s, 3H, methyl), 1.16 (s, 3H, methyl), 0.96 (s, 3H, methyl).

2,2,4,9-Tetramethyltricyclo[6.3.0.$0^{1,5}$]undecan-6-one (132)

To 60 ml of thoroughly degassed toluene, 2-3 mg of AIBN, compound **131** (35 mg, 0.090 mmol) and tributyltin hydride (31 mg, 0.138 mmol) were added and the mixture was heated to 80-90°C for 3.5 h. The mixture was then cooled to room temperature, washed with 10% potassium fluoride, dried and evaporated.

Yield : 0.016 g (75%).

IR (neat, cm^{-1}) : 3000, 1745, 1460, 1400, 1200.

^1H NMR (270 MHz, $CDCl_3$) : δ 2.30 (AB, 2H), 2.22 (AB, 2H), 2.18-1.90 (band, 3H), 1.78 (s, 1H), 1.75-1.51 (band, 2H), 1.27 (s, 3H, methyl), 1.11 (s, 3H, methyl), 1.05 (s, 3H, methyl), 1.0 (d, 3H, methyl).

^{13}C NMR (25.0 MHz, $CDCl_3$) : 219.1, 96.3, 64.4, 55.3, 53.4, 47.6, 44.5, 38.7, 36.3, 34.0, 29.3, 24.8, 24.0, 17.1 ppm.

High resolution mass : Expected for $C_{15}H_{24}O$: 220.1827;
Found : 220.1822.

4-(3-Methyl-3-butenyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (125)[38]

To a suspension of methyltriphenylphosphonium iodide (0.430 g, 1.07 mmol) in 3 ml of THF, sodium _t_-amyloxide (0.094 g, 0.854 mmol) in 2 ml of THF was added and the mixture was stirred for 15 min. To this, compound **126** (0.10 g, 0.426 mmol) in 2 ml of THF was added and the mixture stirred at room temperature for 5 min. The mixture was then quenched with water, extracted with dichloromethane, dried and evaporated. The material obtained was purified by column chromatography.

Yield : 0.050 g (50%).

IR (neat, cm^{-1}) : 2900, 1700, 1640, 1460.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.80 (s, 1H, olefin proton from enone), 4.76-4.68 (m, 2H, olefin protons in the side chain), 2.36-1.64 (m, 12H), 1.32 (s, 3H, methyl), 1.20 (s, 3H, methyl), 1.0 (s, 3H, methyl).

Attempted preparation of 139

To a solution of 9-BBN (0.038 g, 0.31 mmol) in 0.4 ml of THF, compound **125** (0.020 g, 0.085 mmol) in 0.2 ml of THF was added and the reaction mixture was stirred at room temperature for one hour. At the end of this period, it was quenched with 0.05 ml of 3N NaOH followed by 0.1 ml of 30% H_2O_2. The reaction mixture was diluted with ether, washed with water, dried and evaporated. The crude material was purified by column chromatography.

Yield : 0.019 g (93%).

IR (neat, cm^{-1}) : 3350, 2950, 1700, 1640, 1460, 1020.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.40 (s, 1H, olefin proton from allyl alcohol), 5.20-5.08 (t, 1H), 3.56 -3.44 (t, 2H), 2.48-2.32 (m, 1H), 1.80-1.32 (band, 9H), 1.20 (s, 3H, methyl), 1.08 (s, 3H, methyl), 1.04 (s, 3H, methyl), 1.0-0.96 (d, 3H, methyl).

To a suspension of PDC (0.076 g, 0.2 mmol) in 2 ml of dichloromethane, the compound obtained from the above operation (0.010 g, 0.04 mmol) in 1 ml of dichloromethane was added and stirred for 30 min. When the solvent was removed, a material containing many spots on TLC was obtained. Its purification was therefore not attempted. Replacing PDC by PCC or $(COCl)_2$/DMSO was also of little help in obtaining **139**.

4-(3-Methyl-4-hydroxymethyl-3-butenyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (143)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (0.180 g, 0.534 mmol) in 5 ml of THF, sodium t-amyloxide (0.045 g, 0.425 mmol) in 2 ml of THF was added and the solution stirred for 15 min at room temperature. To this solution, compound **126** (0.050 g, 0.213 mmol) in 1 ml of THF was added and the mixture stirred at room temperature for 2 min. Later on, it was quenched with water, extracted with ether, dried and evaporated. The material obtained was purified by column chromatography.

Yield : 0.024 g (50%).

IR (neat, cm^{-1}) : 3000, 1700, 1640, 1460, 1220, 1160, 1000.

^1H NMR (100 MHz, $CDCl_3$) : δ 5.88-5.84 (d, 1H, olefin proton in the side chain), 5.80 (s, 1H, olefin proton from enone), 3.52 (d, 3H, $CHOC\underline{H}_3$), 2.40-1.52 (m, 12H), 1.32 (s, 3H, methyl), 1.16 (s, 3H, methyl), 0.96 (s, 3H, methyl).

4-(3-Formylbutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1H)-pentalenone (139)

To a solution of **143** (0.024 g, 0.091 mmol) in 5 ml of dichloromethane, boron trifluoride etherate (5 μl) was added and the mixture stirred at room temperature for 30 min. The dichloromethane layer was washed with saturated aqueous $NaHCO_3$, water, dried and evaporated. The material obtained was purified by column chromatography to give **139** as a clear liquid.

Yield : 0.022 g (100%).

IR (neat, cm^{-1}) : 2900, 2750, 1700, 1640, 1460.

^1H NMR (100 MHz, $CDCl_3$) : δ9.60 (m, 1H, aldehyde proton), 5.80

(s, 1H, olefin proton from enone), 2.40-1.50 (band, 10H), 1.32 (s, 3H, methyl), 1.26 (d, 3H, methyl), 1.20 (s, 3H, methyl), 0.96 (s, 3H, methyl).

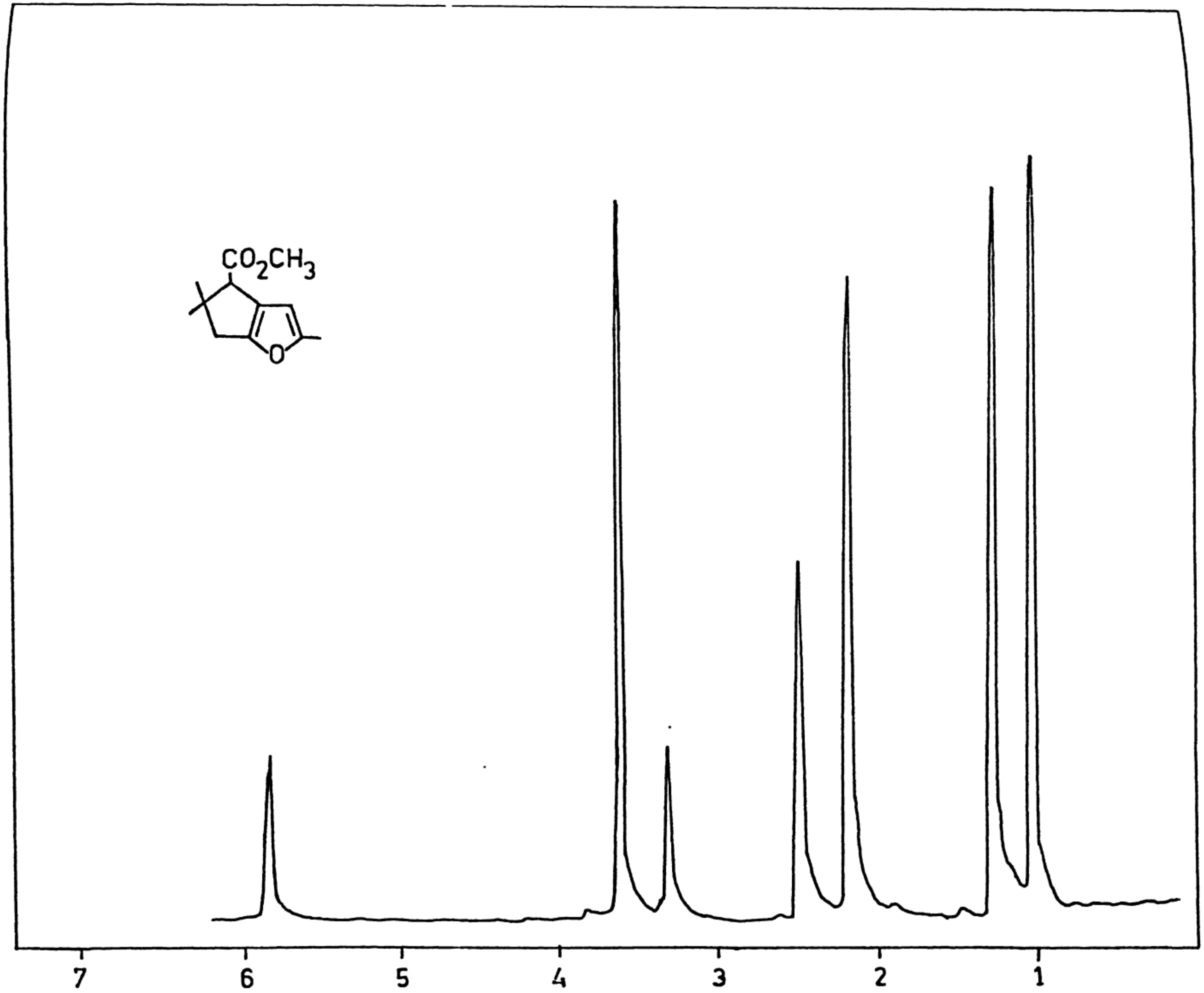


Fig. 1. : ^{1}H NMR spectrum (100 MHz) of **102a**

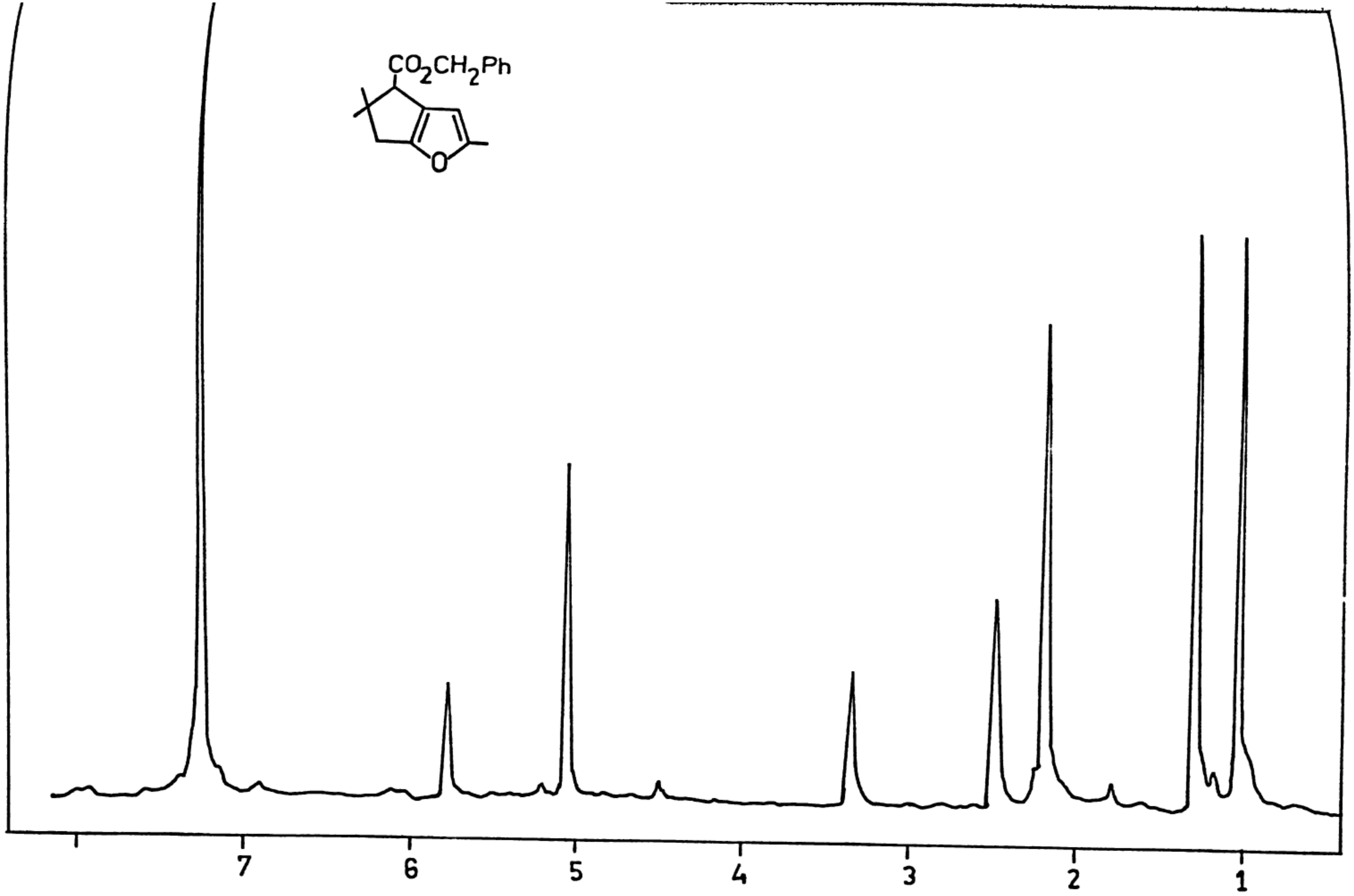


Fig. 2. : ^{1}H NMR spectrum (100 MHz) of **102b**

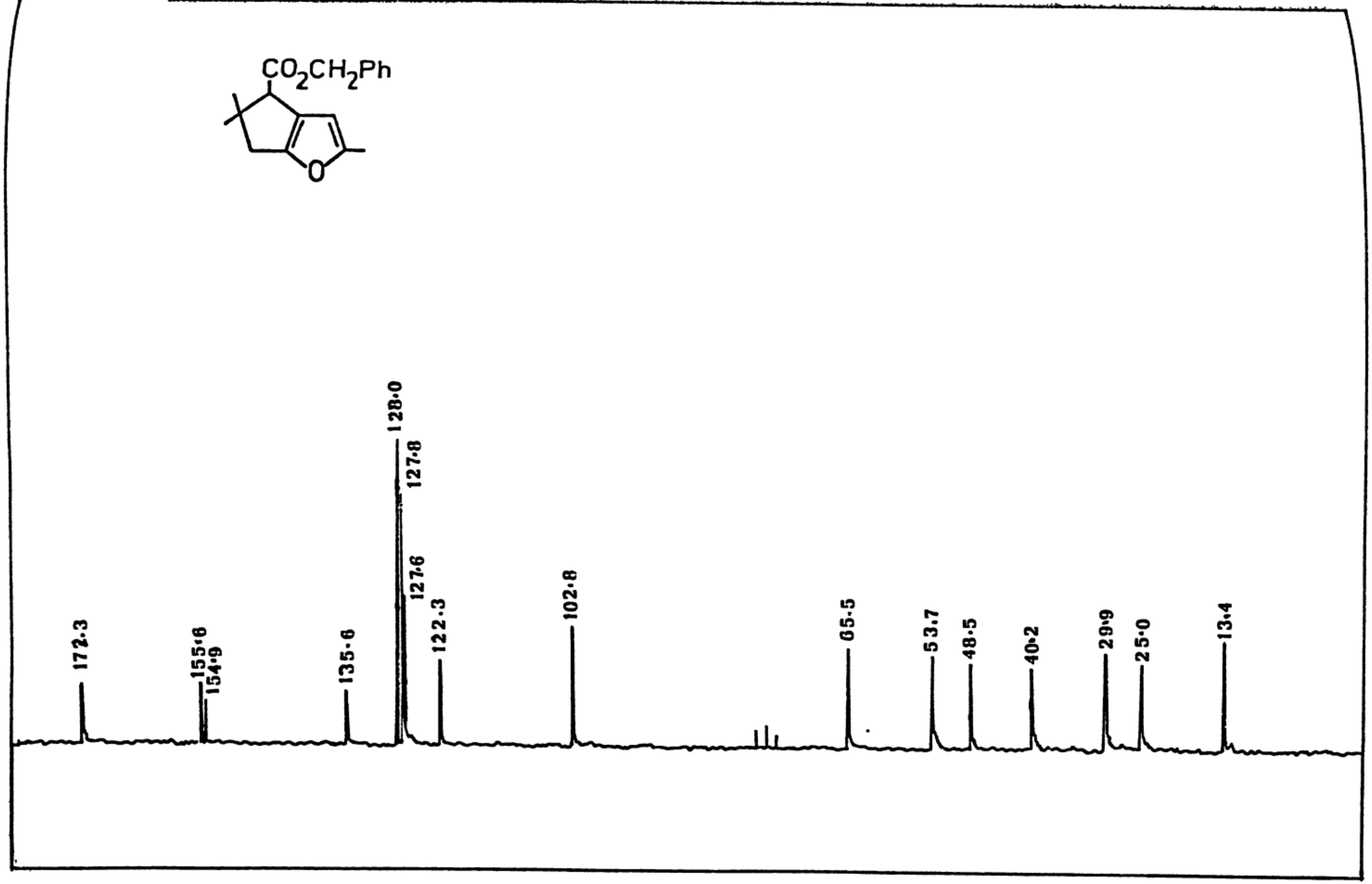


Fig. 3. : ^{13}C NMR spectrum (25 MHz) of **102b**

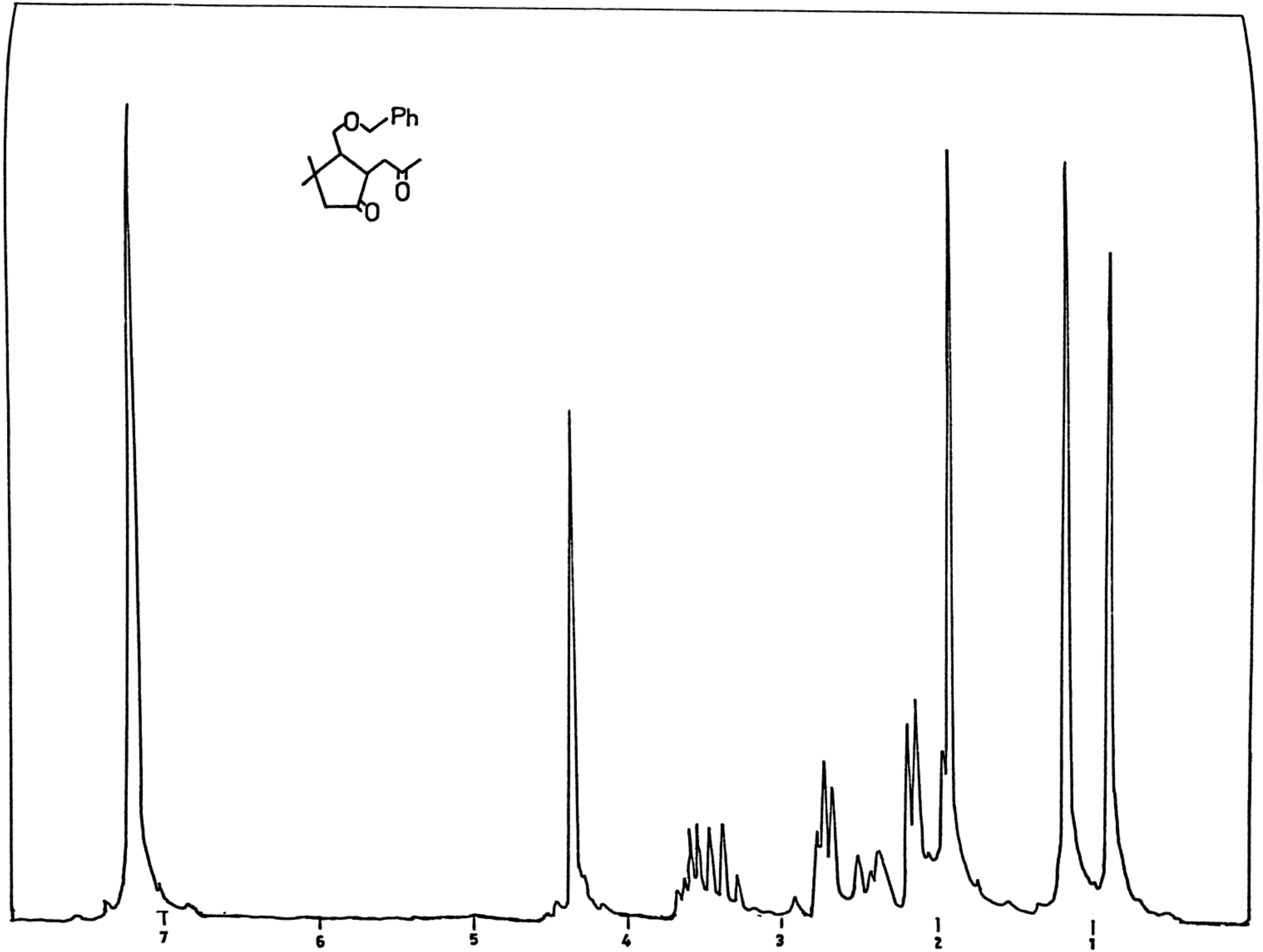


Fig. 4. : ^{1}H NMR spectrum (100 MHz) of **105**

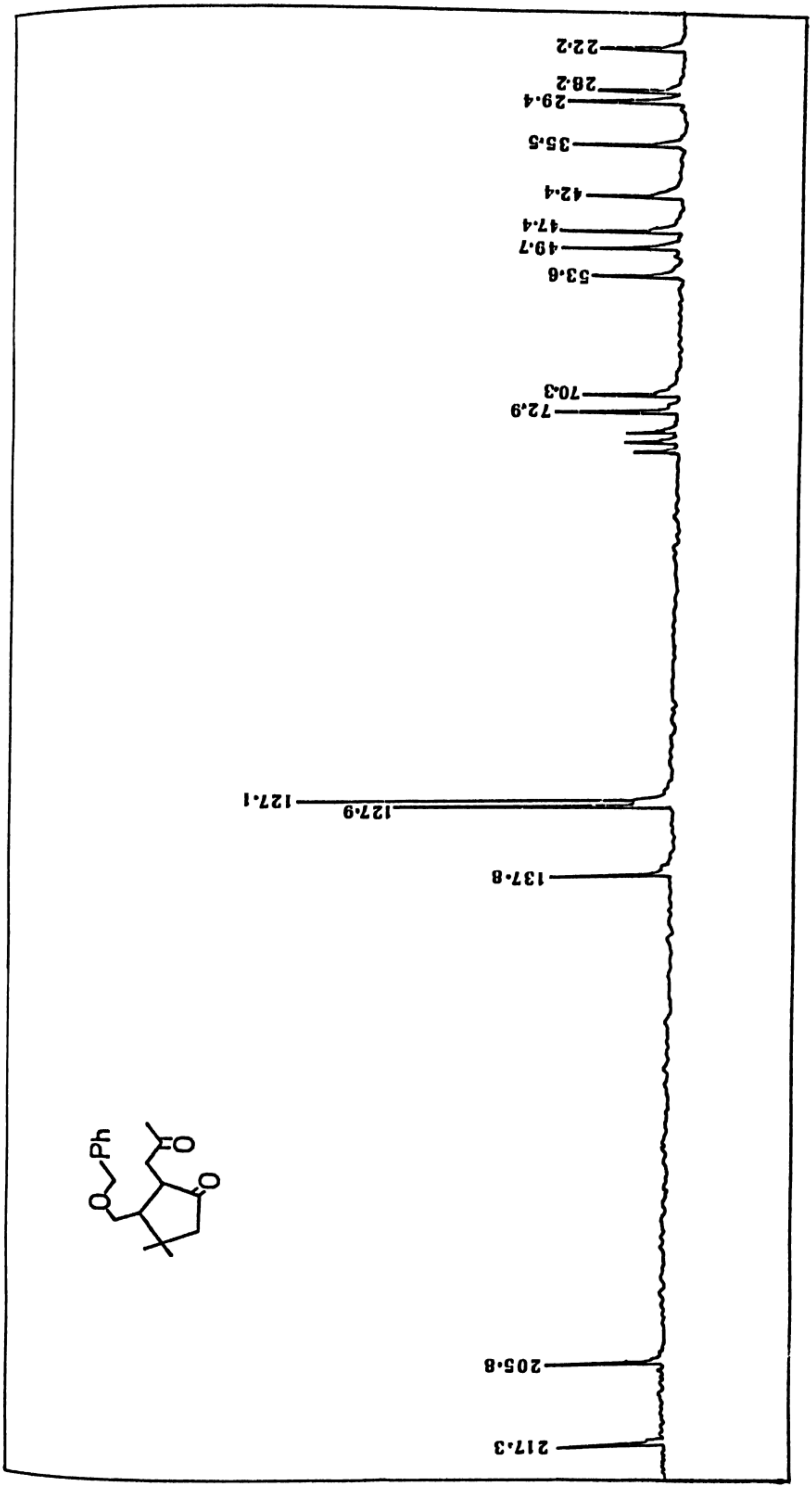
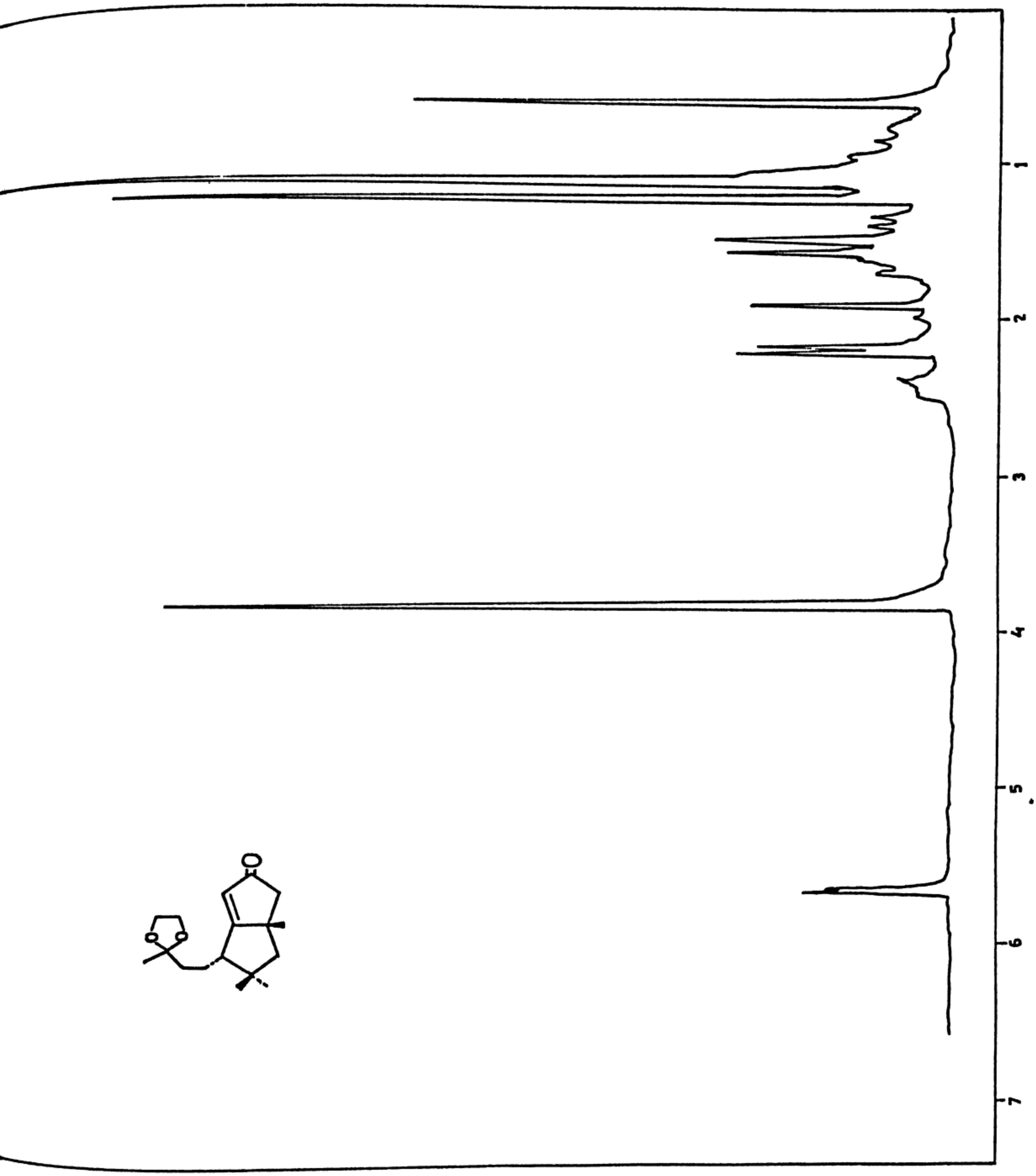


Fig. 5. : ^{13}C NMR spectrum (25 MHz) of 105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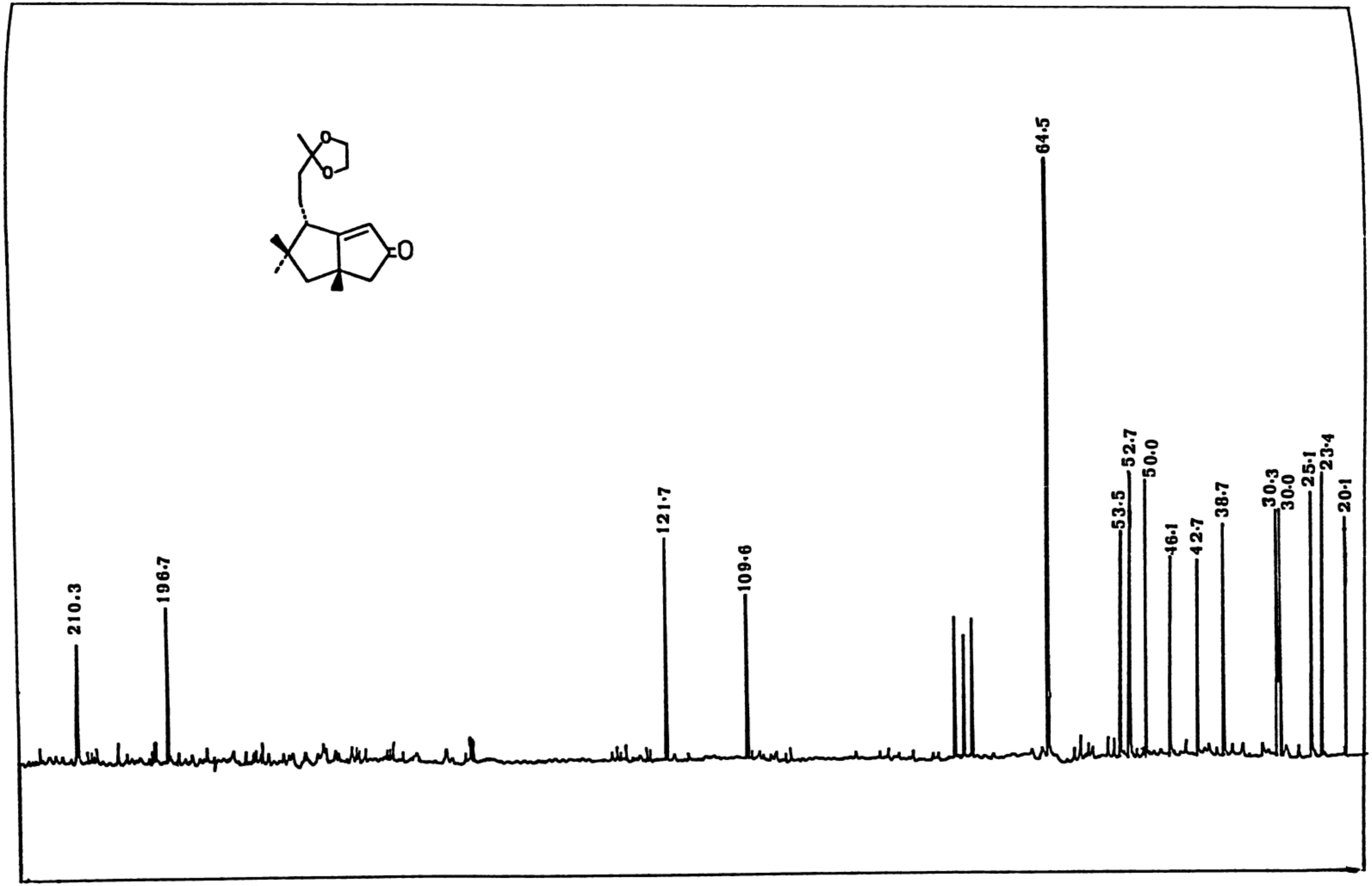

Fig. 7. : ^{13}C NMR spectrum (25 MHz) of **122**

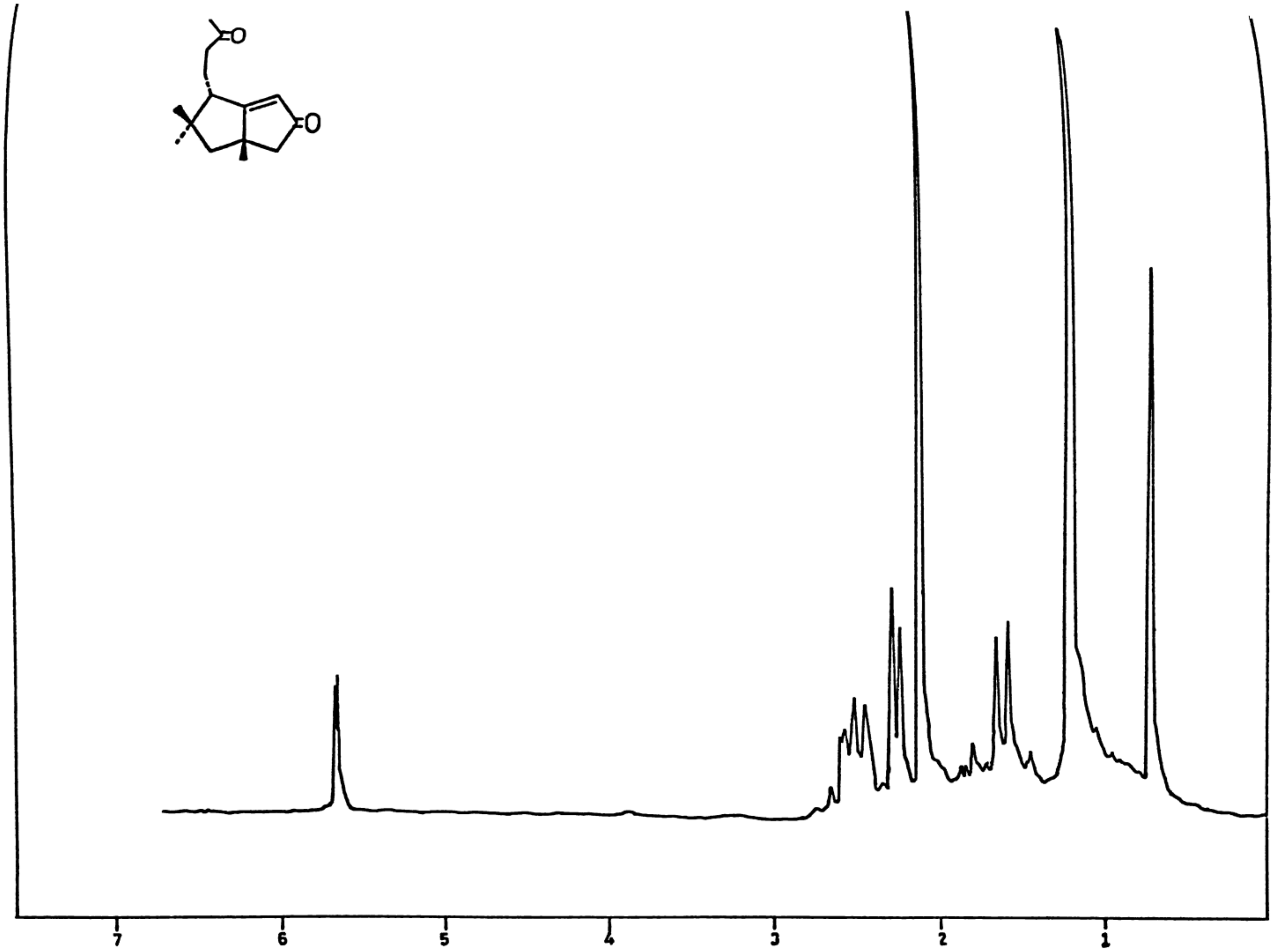

Fig. 8. : ^{1}H NMR spectrum (100 MHz) of **123**

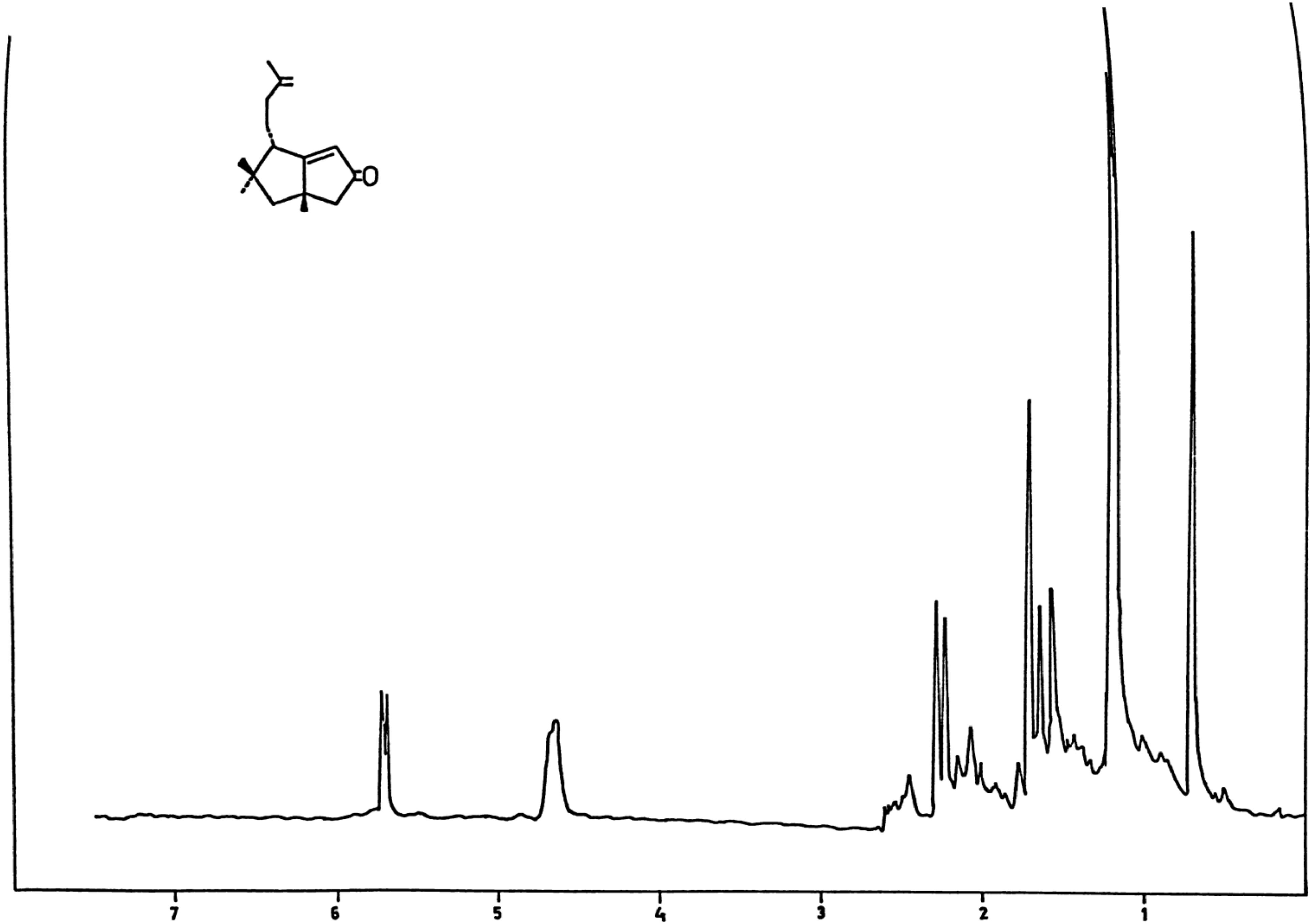

Fig. 9. : ^{1}H NMR spectrum (100 MHz) of **124**

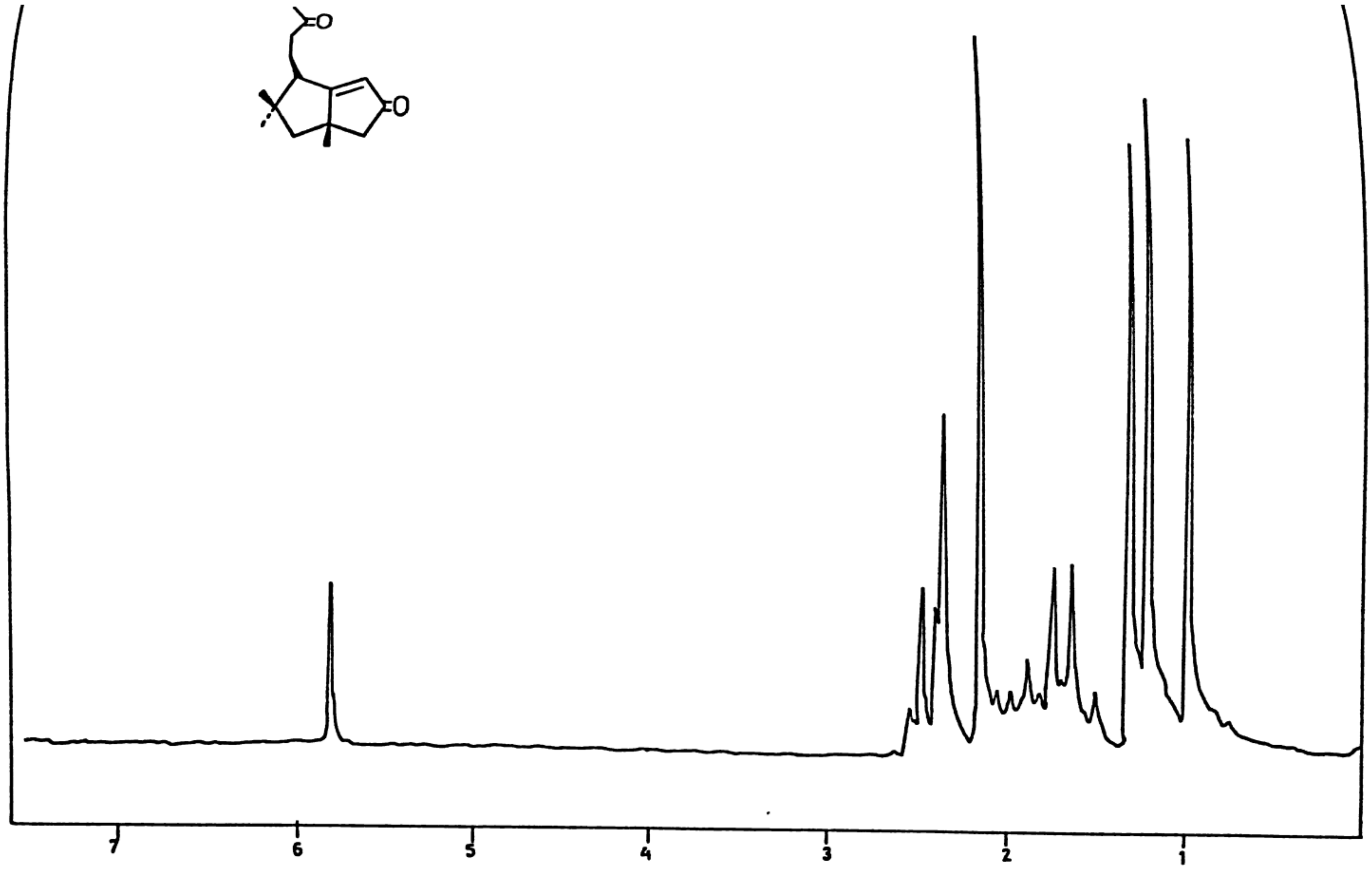

Fig. 10. : ^{1}H NMR spectrum (100 MHz) of **126**

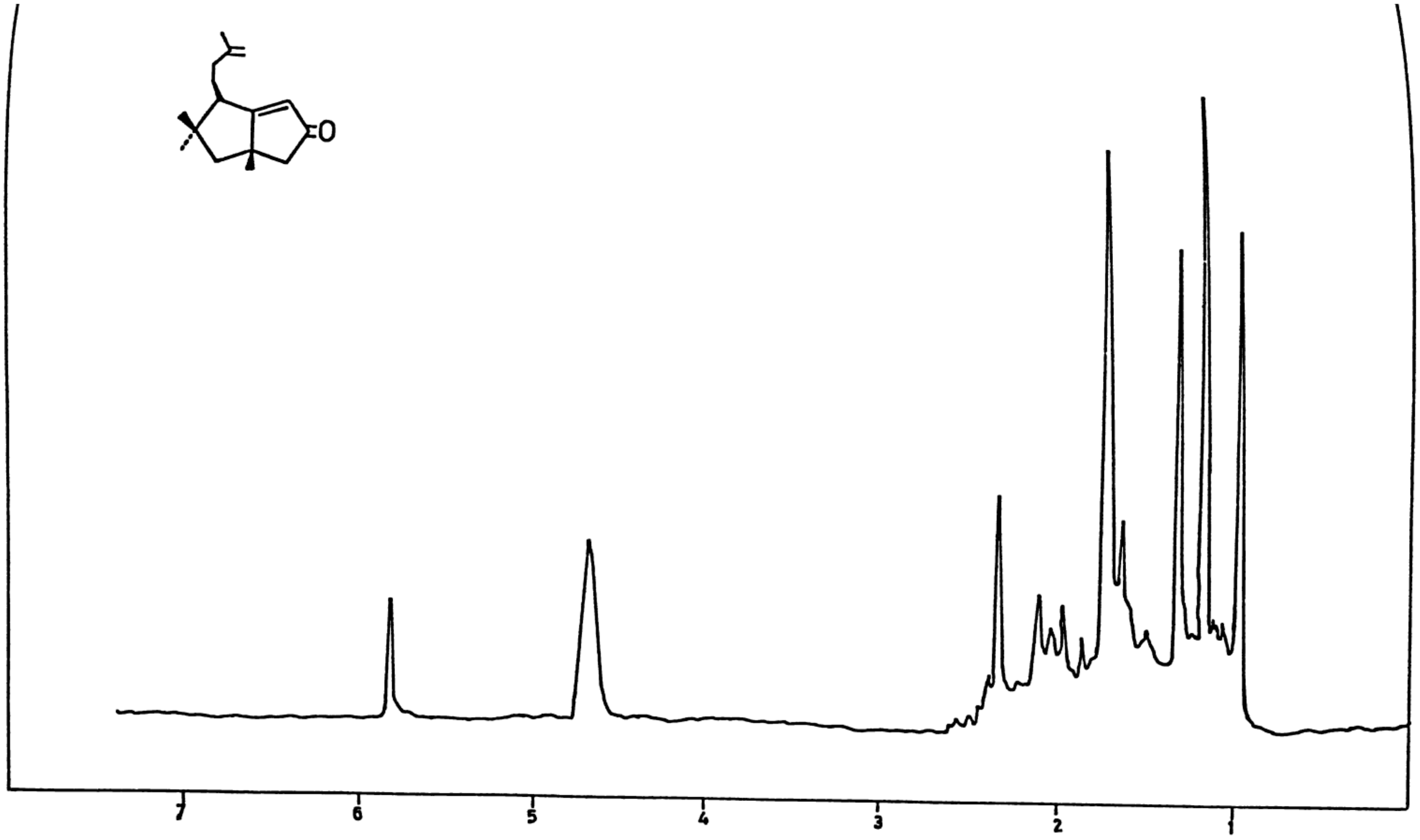

Fig. 11. : ^{1}H NMR spectrum (100 MHz) of 125

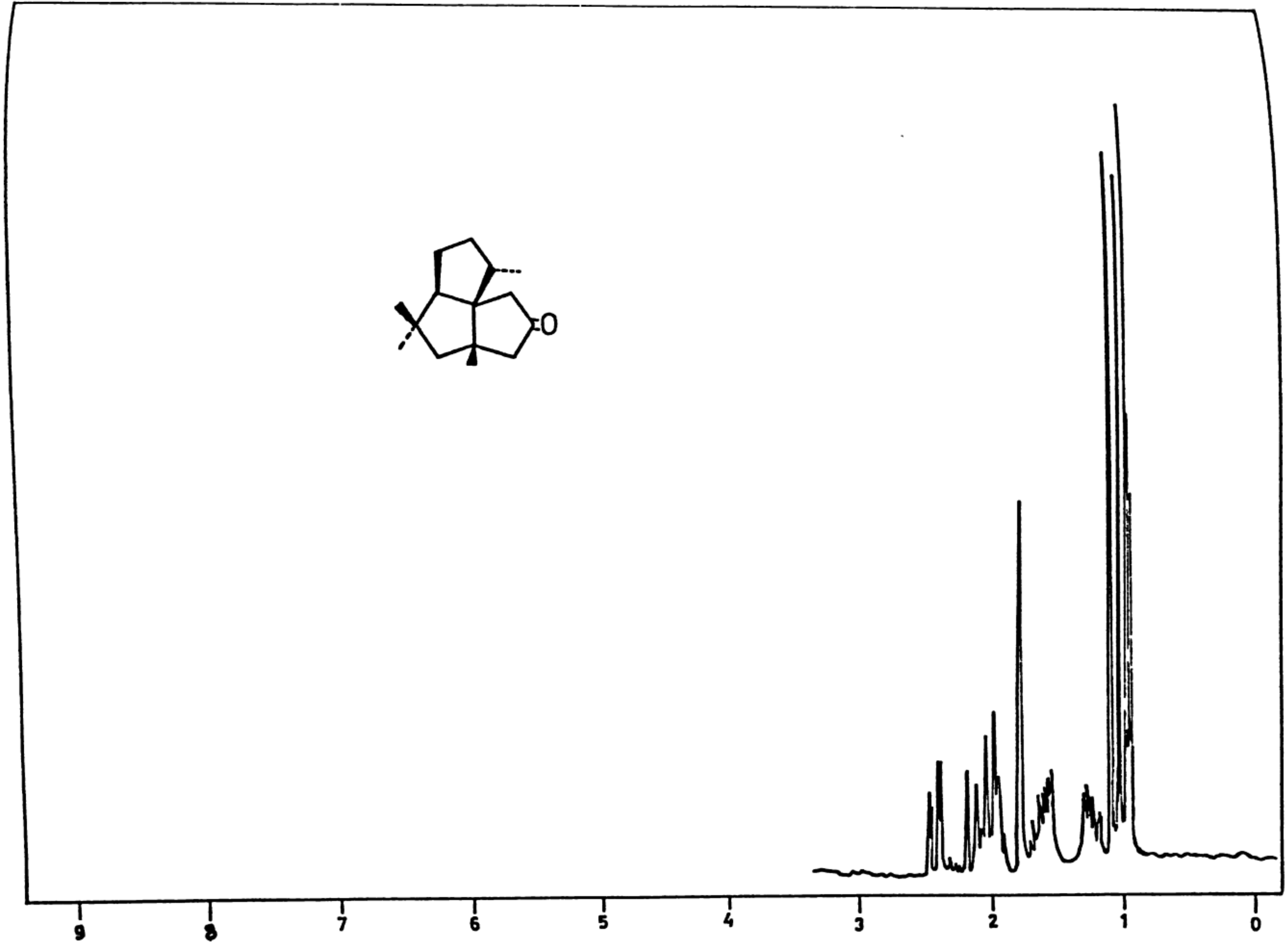

Fig. 12. : ^1H NMR spectrum (270 MHz) of **132**

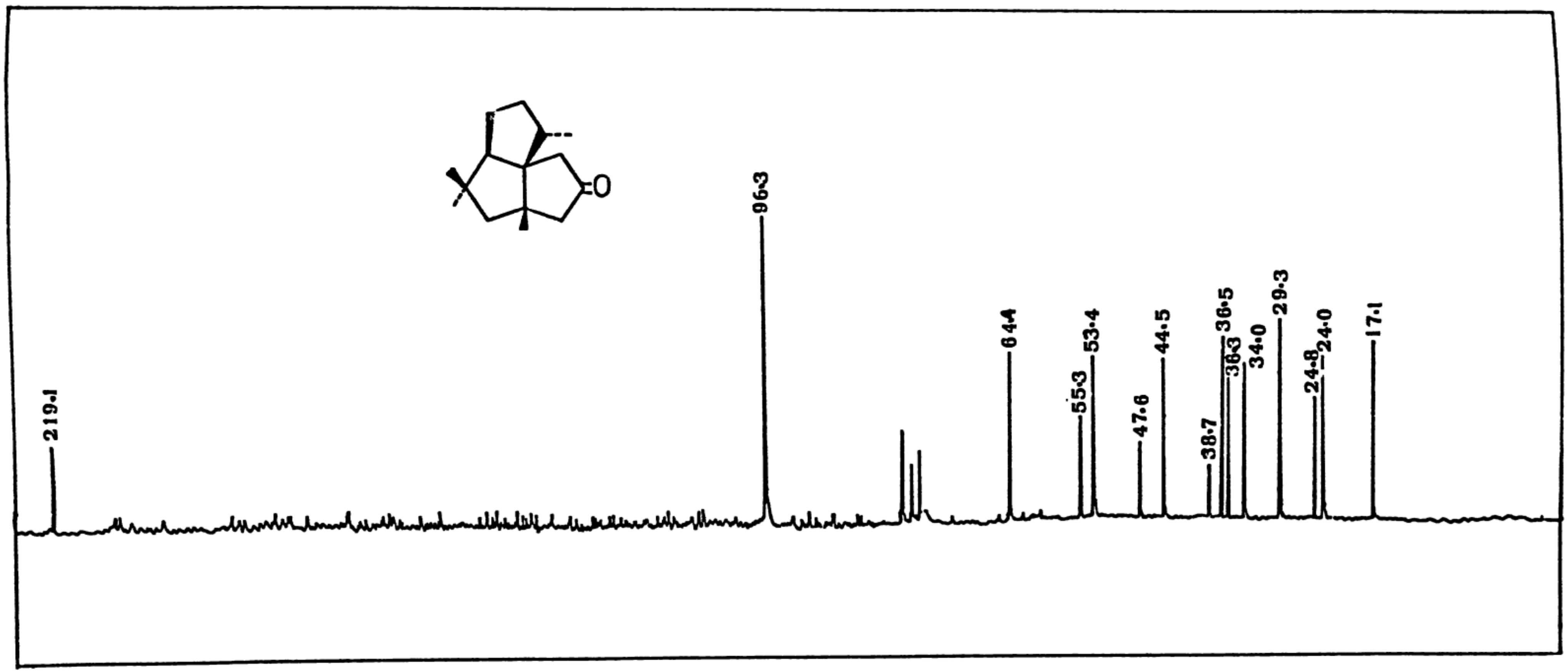

Fig. 13. : ^{13}C NMR spectrum (25 MHz) of 132

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PART - II

Some Reactions of Geminal Disulfones

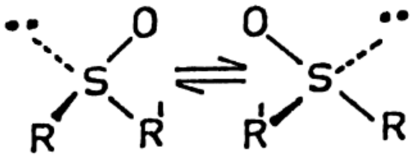
INTRODUCTION

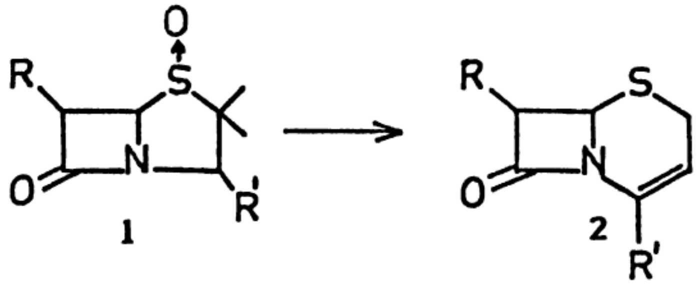
Organosulfur compounds have been known for a long time, more for their unpleasant odours than for their utility and hence importance in organic synthesis. The picture has changed considerably, however, in the last two decades and today organosulfur compounds find wide use as valuable reagents in synthetic organic chemistry, along with organoboron, organophosphorus, organoselenium and organometallic compounds. These developments have come about due to two reasons which are in turn inter-related. The phenomenal growth in synthetic organic chemistry, directed towards the synthesis of diverse complicated molecules, necessitated the development of new strategies and reactions for their successful execution. Simultaneously, the interest in the study of organic compounds containing heteroatoms like sulfur, boron, phosphorus and selenium, among others, led to new and unusual reactions which often find ready application in total synthesis. A measure of the rapid progress of organosulfur chemistry is the appearance of about a dozen books on the subject in the past decade or so. To-day, the chemistry of organosulfur compounds has developed into a well organized and understood branch of chemistry.

The most important feature of organosulfur chemistry is the ability of sulfur to exist in different oxidation states as exemplified by sulfides (II), sulfoxides and sulfonium salts (IV), and sulfones (VI).

Sulfides are stable compounds which are readily prepared by general methods analogous to those used for the synthesis of ethers. However, since higher oxidation states are possible for sulfur compounds, sulfides can also be obtained by reduction of tetravalent and hexavalent organosulfur compounds, unlike in the case of ethers. Sulfides resemble ethers in many ways, but notable differences exist, for example, in the greater stability, in comparison with oxygen analogues, of α-sulfenyl carbanions $-\overset{-}{C}HSR$, sulfonium salts $R_3\overset{+}{S}\,\overset{-}{X}$ and ylides $-\overset{-}{C}H\overset{+}{S}R_2$. Unlike ethers, sulfides can be oxidized to sulfoxides and sulfones. These properties of sulfides, along with the ease of transformation of sulfides into other functional groups like the carbonyl, form the basis for many of the applications of organosulfur compounds in organic synthesis.

Sulfoxides, containing tetravalent sulfur, are obtained by partial oxidation of sulfides, with complete oxidation leading to sulfones. Thus, sulfoxides may be considered as very stable intermediates in the oxidation process. However, since the sulfur oxygen linkage in sulfoxides is polarized and much weaker than that in sulfones, sulfoxides are relatively reactive and undergo many synthetically useful reactions. Sulfoxides have a pyramidal configuration about the sulfur atom and are more stable towards inversion (and hence racemization) than other related compounds like amines and carbanions, except for some benzylic and allylic sulfoxides. Sulfoxides can therefore be readily prepared in enantiomerically pure forms and have been extensively used in asymmetric synthesis. Other synthetically useful reactions of sulfoxides are the Pummerer reaction, employed in the transformation of pencillin S-oxide to cephalexin[1], the





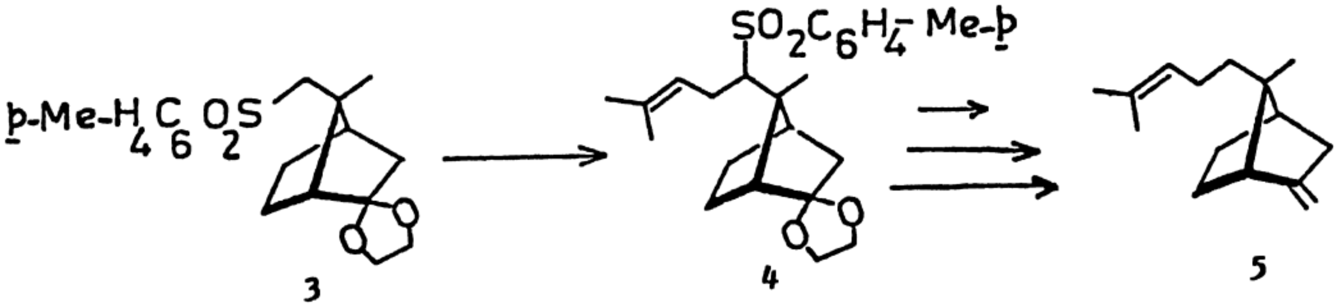
R =-NH-CH_2OPh
R'=-CO_2CH_2Ph-NO_2-p

Scheme 2.10

pyrolytic syn-elimination of sulfenic acids to introduce unsaturation and the reactions of ylides derived from sulfoxides with carbonyl compounds. All these have contributed significantly to the rapid development of the chemistry of sulfoxides.

Sulfones are hexavalent sulfur compounds in which the sulfur atom is bonded to two carbons and two oxygens in a tetrahedral arrangement. The sulfur oxygen bonds are quite polar, giving rise to a large dipole moment relative to the analogous ketones (for eg. $CH_3SO_2CH_3$, 3.22 D; CH_3COCH_3, 2.88 D). This polarity manifests itself in the physical properties of sulphones. They occur as either solids or high boiling liquids. Thermally, the sulfone group is quite stable and this accounts for the use of sulfone containing polymers in high temperature applications.

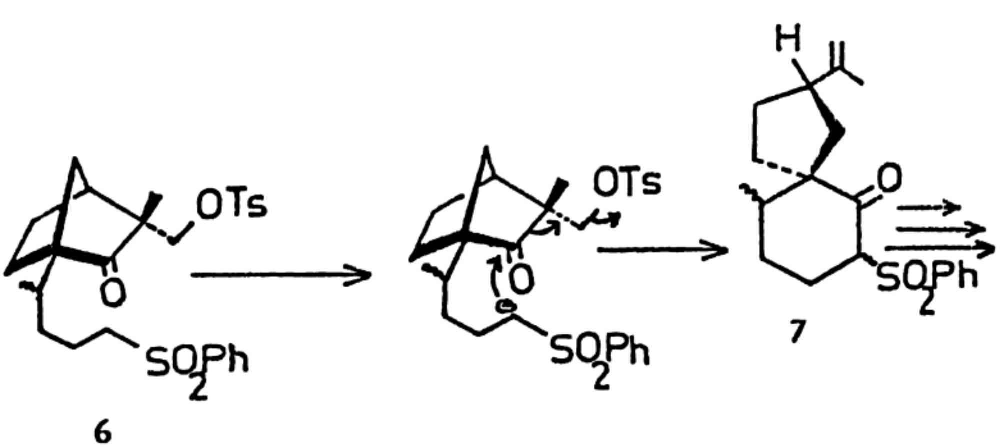
From the synthetic point of view, although the sulfone group has been known for a long time, it is only within the last two decades that a diverse range of chemistry has been discovered. The stability of the sulfone group towards a wide variety of reagents when compared to sulfides and sulfoxides is a distinct advantage in many synthetic transformations. Additionally, the sulfone oxygen is relatively weak in forming hydrogen bonds and in its nucleophilicity, in contrast to the sulfoxide oxygen. These two features coupled with the fact that sulfones are comparable to the corresponding ketones in acidity account for their importance in organic synthesis today. Sulfoxides are considerably less acidic than sulfones. The acidity of the C-H bond in these substances is attributed to a combination of the inductive electron withdrawing ability of the sulfur substituents and their capacity to delocalize the negative charge in the carbanion after deprotanation. β-Ketosulfoxides and β-ketosulfones resemble β-diketones and β-ketoesters in their acidity. Procedures that involve the formation and subsequent reaction of anions derived from such compounds constitute a very important and synthetically useful class of organic reactions, as carbanion mediated C-C bond formation is a dominant process in organic synthesis. A unique advantage with α-sulfonyl carbanions is that they undergo exclusive C-alkylation and O-alkylation is totally absent, in contrast to the reaction of enolates, where O-alkylation is often a serious competing process to C-alkylation. The following few examples illustrate the use of α-sulfonyl carbanions in organic synthesis. It is observed that after carrying out the necessary transformations, the sulfone group is removed either by reductive clevage or by elimination. The synthesis of sesquifenchene reported by Grieco utilizes a sulfone



Scheme 2.11

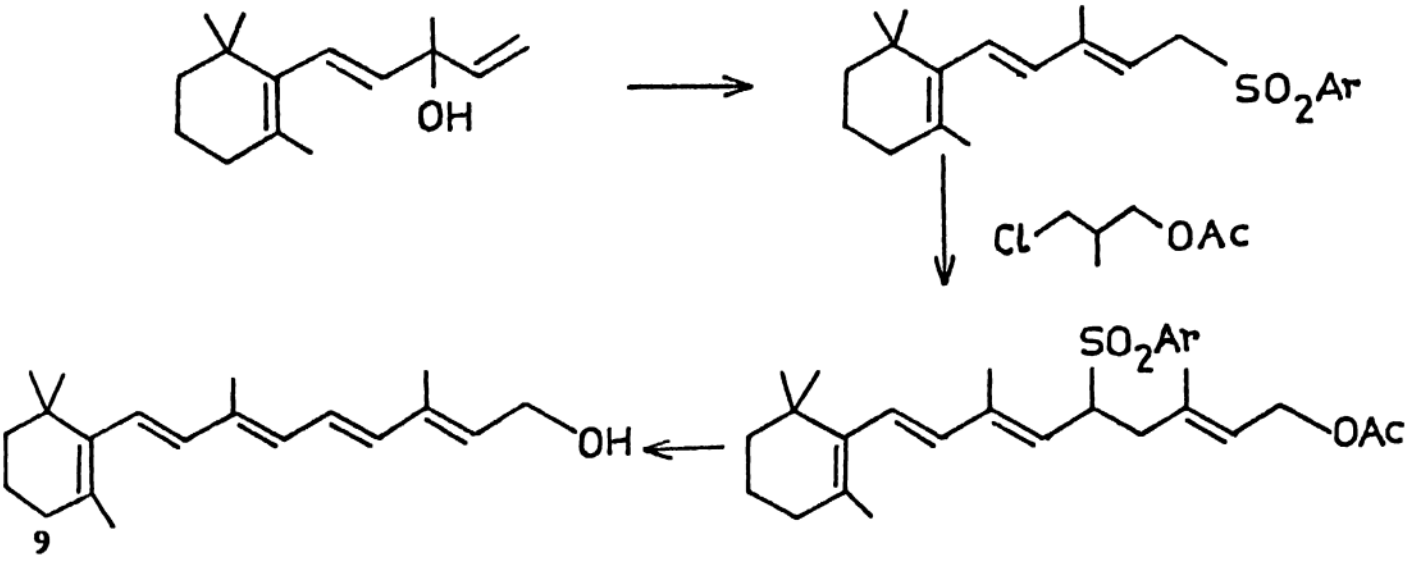
alkylation followed by desulfonylation procedure. The sulfone **3** was alkylated using n-butyl lithium as the base and 3,3-dimethylallyl bromide as the alkylating agent to give **4**. Desulfonylation and subsequent transformations gave sesquifenchene, **5**^{2}.

A similar sequence, namely alkylation followed by desulfonylation, was used to synthesize (±) diumycinol, a sesterpene.[2] The bicyclic sulfone **6** prepared from (-) β-pinene was treated with NaH-DMSO to give



Scheme 2.12

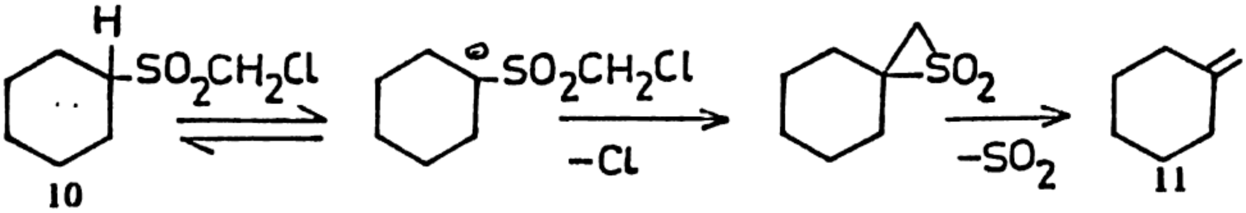
the spiro-[4.5]decane **7** which was converted to (+) hinesol **8**[3]. Vitamin A alcohol **9** has been synthesized via the following route.[4] This type of



Scheme 2.13

chemistry which employs facile elimination of arylsulfinic acid to giv a completely conjugated system was first described by Julia and has been the cornerstone in a number of polyene syntheses.[5]

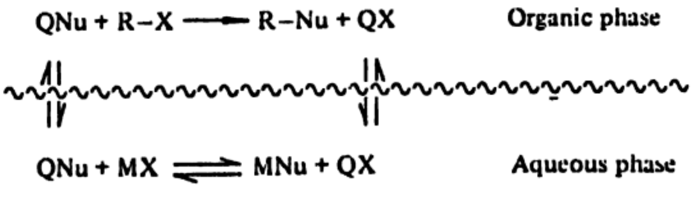
Perhaps the most well known and widely studied reaction involving the sulfone functional group is the famous Ramberg-Bäcklund reaction,[6] in which an α-halosulfone is converted into an alkene. This is illustrated by the following transformation. While this could be treated as a simple example, it has been observed that this reaction can be put to use to arrive at highly strained propellanes[7] which are otherwise very difficult to obtain. A recent use of the Ramberg-Backlund reaction in the natural products area is the synthesis of β-carotene and vitamin A[8] and α, β-unsaturated acids.[9] Although this reaction represented one of the first alkene synthesis in which the position of the double bond was clearly defined, it has lost some of its importance owing to the introduction of many alternative stereo- and regio-selective methods of alkene synthesis.



Scheme 2.14

The usefulness of the sulfone group in organic synthesis, as can be readily understood from the above cited examples, is primarily due to its ability to stabilize carbanions adjacent to it, thereby enabling the C-C bond formation by reaction with an alkylating reagent. Alkylation of carbanions, due to its importance in C-C bond formation, has been extensively studied with respect to the carbanion, its counter cation, the alkylating reagent and the solvent. Very often, the solvent plays a crucial role in the success of an alkylation reaction. While the reaction is frequently unsuccessful in non-polar aprotic solvents due to poor solubility of the carbanion in them, at the other extreme, the use of polar protic solvents results in extensive solvation of the carbanion and the counter-ion, thus lowering the reactivity. This difficulty has been overcome by employing polar, aprotic solvents like N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or hexamethylphosphorictriamide (HMPA), which selectively solvate the cation, thereby leaving the anion free to react. The use of these solvents is not without disadvantages, however. They are expensive, have to be used under anhydrous conditions and they promote O-alkylation at the expense of C-alkylation.[9a]

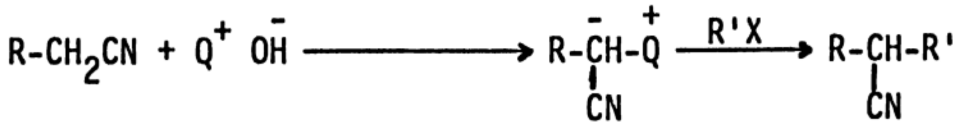
These disadvantages can be overcome to a large extent by performing the alkylation reaction under <u>phase transfer catalysed</u> (PTC) conditions. In this method, a solution of the substrate and the alkylating reagent in a water insoluble solvent is reacted with a strongly basic aqueous solution in the presence of a phase transfer catalyst, which is usually a quaternary ammonium or phosphonium salt (Stark's and Makosza's method)[10].



Starks phase transfer catalytic cycle diagram

<u>Scheme 2.15</u>

A second procedure, due to Brändstrom,[11] employs a stoichiometric amount of a quaternary ammonium salt, in a single solvent, usually strong aqueous sodium hydroxide solution.

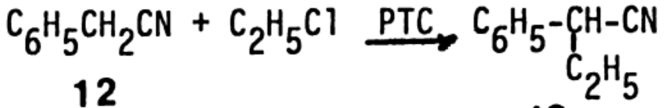


$$\text{R-CH}_2\text{CN} + \overset{+}{\text{Q}}\ \overset{-}{\text{OH}} \longrightarrow \text{R-}\underset{\text{CN}}{\overset{-}{\text{CH}}}\text{-}\overset{+}{\text{Q}} \xrightarrow{\text{R'X}} \text{R-}\underset{\text{CN}}{\text{CH}}\text{-R'}$$

Scheme 2.16

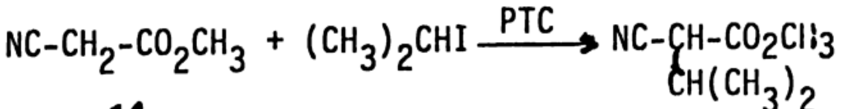
Due to simplicity, convenience and low cost of this method, it has been used extensively and a large number of examples have been reported.

Much of the early alkylation work was performed on nitriles, particularly phenylacetonitrile.[12] This system was chosen because it is reasonably acidic and the nitrile group is not prone to rapid hydrolysis under the strongly basic reaction conditions.



$$\underset{\mathbf{12}}{C_6H_5CH_2CN} + C_2H_5Cl \xrightarrow{\text{PTC}} \underset{\mathbf{13}}{C_6H_5\text{-}\underset{C_2H_5}{CH}\text{-}CN}$$

α-Substituted phenylacetonitriles (α-methyl, α-ethyl, α-ethoxy etc) also underwent facile alkylation giving rise to the respective alkylated products. In addition to these examples, substrates substituted with nitriles and other ancillary functions as ketone or ester have also been alkylated[12].

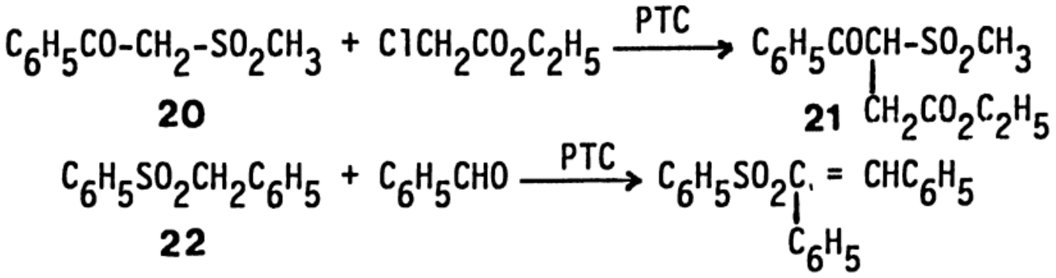


$$\underset{\mathbf{14}}{NC\text{-}CH_2\text{-}CO_2CH_3} + (CH_3)_2CHI \xrightarrow{\text{PTC}} \underset{\mathbf{15}}{NC\text{-}\underset{CH(CH_3)_2}{CH}\text{-}CO_2CH_3}$$

Diactivated substrates such as diesters,[13] dinitriles[14] and ketosulfones.[15] have also been alkylated. The following examples are illustrative.

$$\underset{\mathbf{16}}{CH_2(CO_2C_2H_5)_2} + CH_3I \xrightarrow{\text{PTC}} \underset{\mathbf{17}}{CH_3CH(CO_2CH_5)_2}$$

$$\underset{\mathbf{18}}{CH_2(CN)_2} + \underline{n}\text{-}C_4H_9Br \xrightarrow{\text{PTC}} \underset{\mathbf{19}}{(\underline{n}\text{-}C_4H_9)_2C(CN)_2}$$



$$C_6H_5CO\text{-}CH_2\text{-}SO_2CH_3 + ClCH_2CO_2C_2H_5 \xrightarrow{PTC} C_6H_5CO\underset{CH_2CO_2C_2H_5}{CH}\text{-}SO_2CH_3$$

20 21

$$C_6H_5SO_2CH_2C_6H_5 + C_6H_5CHO \xrightarrow{PTC} C_6H_5SO_2\underset{C_6H_5}{C} = CHC_6H_5$$

22 23

Scheme 2.17

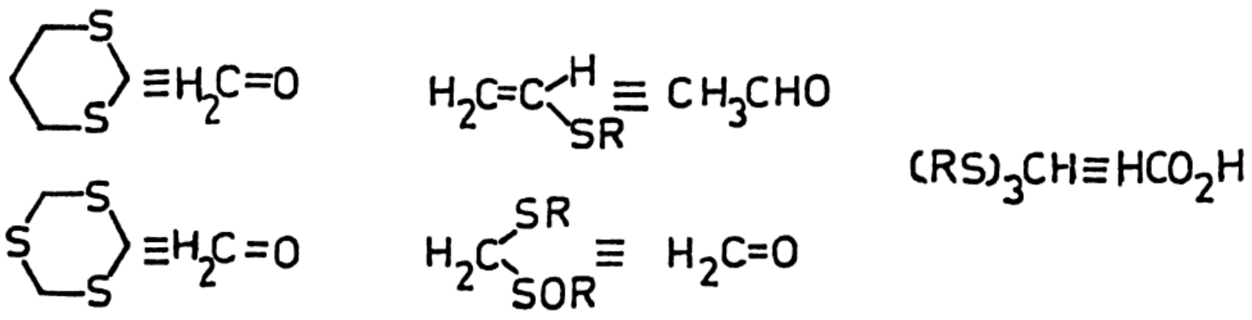
Sulfones are particularly attractive substrates for PTC alkylations as they are unaffected by the strong basic reaction conditions unlike other carbon acids such as aldehydes, ketones and esters which are prone to side reactions.

A perusal of the literature revealed that no systematic examination of the PTC alkylation of geminal disulfones had been carried out. We therefore set out to study in detail the PTC alkylation of the geminal disulfone 1,1-bis(phenylsulfonyl)methane as a function of the alkylating reagent employed, the phase transfer catalyst and the reaction conditions. The results obtained from these investigations are discussed in the next chapter.

A second aspect of organosulfur chemistry which is of current interest is the ability of many sulfur compounds to function as synthetically equivalent groups. A synthetically equivalent group of a functional group can be defined as one which can be easily transformed to that functional group. Thus, a 1,3-dithiane is the synthetic equivalent of a carbonyl group as the latter can be readily obtained from the former by hydrolysis. The development of the concept of synthetically equivalent groups is an important advance in synthetic organic chemistry for it helps in designing a viable strategy for the synthesis of many complex structures.

The advantage in using a synthetically equivalent group lies in the fact that in a sequence of reactions, the synthetically equivalent group can be introduced at the most convenient point in the sequence and later transformed into the desired functional group whose introduction would have been incompatible at that stage.

A variety of organosulfur compounds are known that have the same level of oxidation at carbon as aldehydes and ketones or as carboxilic acids and which are readily converted to them by hydrolysis. The following examples are illustrative:



Scheme 2.18

Thioacetals and thioketals have, of course, long been used as protecting groups for the carbonyl function. While the carbanion forming capacity of certain of these organosulfur carbonyl equivalents had been recognized quite early,[16] it remained for Corey and Seebach[17] to demonstrate with the 1,3-dithiane carbanion the great synthetic utility of nucleophilic acylation, thus opening up an altogether new field as the whole range of reactions characteristic of carbanions could now be effected with these nucleophilic carbonyl equivalents.

While the use of these synthons in organic synthesis can be dated back to the last two to three decades, the use of sulfones as ethylene and acetylene equivalents in Diels-Alder reactions is of recent origin. In this particular context, the pioneering work of Paquette who developed phenyl vinyl sulfoxide[18] and phenyl vinyl sulfone[19] as acetylene equivalents and that of De Lucchi who used [E] and [Z]-1,2-bis(phenylsulfonyl)ethene[20] as acetylene equivalents is worth mentioning.

The use of aldehydes as dienophiles in the Diels-Alder reaction has been studied extensively by Danishefsky[21] and Snider.[22] These reactions provide a ready access to a variety of substituted tetrahydropyrans, which are important in the synthesis of many complex natural products. Unfortunately, the reactions reported by Danishefsky and by Snider proceed well only with reactive, electron rich dienes, activated by Lewis acid catalysts. The successful use of diethyl mesoxolate as a carbon dioxide equivalent in the Diels-Alder reaction[23] prompted us to develop a dienophilic formaldehyde equivalent in the Diels-Alder reaction. An obvious compound for this purpose would be 1,1-bis(phenylsulfonyl)methanone, wherein the two phenylsulfonyl groups would not only polarize the carbon-oxygen double bond in a manner similar to the carboethoxy group in diethyl mesoxolate, but could also be reductively cleaved thereby serving as a formaldehyde equivalent, hitherto unknown. Obvious routes to 1,1-bis(phenylsulfonyl) methanone would be from 1,1-bis(phenylsulfonyl)methane by oxidation and from 1,1-bis(phenylsulfonyl)ethene by oxidative cleavage. Although both the precursors are known and could be readily prepared, they could not be converted to the desired 1,1-bis(phenylsulfonyl)methanone. However, since very little of the chemistry of these two precursor compounds is reported, we undertook a study of them and the results are presented in

pter.

RESULTS AND DISCUSSION

As briefly pointed out in the introduction, the chemistry of the sulfone group has been extensively studied for quite some time. The sulfone group plays a vital role in C-C bond formation to arrive at complex molecules, thus helping the practising synthetic organic chemist in a big way. However, the area of geminal disulfones remains largely unexplored and this attracted our attention to them.

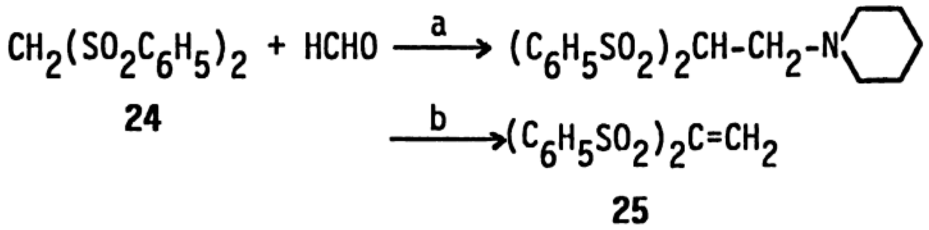
As representative examples, 1,1-bis(phenylsulfonyl)methane (**24**) and 1,1-bis(phenylsulfonyl)ethene (**25**) were chosen, as both are readily available from inexpensive starting materials and hardly any chemistry other than their preparation was known. Compound **24** can be readily prepared by hydrogen peroxide oxidation of formaldehyde diphenyldithioacetal,[24] obtained by reacting thiophenol with dichloromethane under PTC conditions employing sodium hydroxide as base and Aliquat 336 as the phase transfer catalyst[25] (Scheme 2.19).

$$CH_2Cl_2 + 2C_6H_5SH \xrightarrow{a} (C_6H_5S)_2CH_2 \xrightarrow{b} \underset{\mathbf{24}}{(C_6H_5SO_2)_2CH_2}$$

a) Aq.NaOH, Aliquat 336; b) AcOH,Ac_2O, H_2O_2.

Scheme 2.19

Mannich reaction of **24** with formaldehyde and piperidine gives the corresponding Mannich base which upon refluxing in benzene in the presence of HCl gas undergoes quaternisation and elimination to give **25** in good yields[26] (Scheme 2.20).

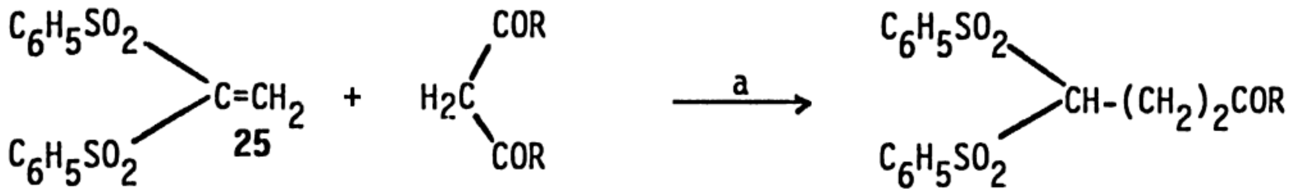


a) Piperidine, 1,4-dioxane; b) HCl(g)/C_6H_6, 100°C

Scheme 2.20

In our search for a formaldehyde equivalent in Diels-Alder reactions, one of the compounds identified was 1,1-bis(phenylsulfonyl) methanone (**26**). As carbonyl groups bearing electron withdrawing groups are known to participate in Diels-Alder reactions[23] and as the phenylsulfonyl groups can be removed either in a single step or in a stepwise fashion, it was thought that **26** would be a satisfactory equivalent for formaldehyde. As **26** is unknown in literature, its preparation was attempted from **24** and **25** by oxidation and oxidative cleavage, respectively. However, these could not be achieved under a variety of conditions.[27] Since very little was known about the chemistry of **24** and **25**, an indepth study of **24** and **25** was undertaken.

It occured to us that **25** could be a potential Michael acceptor. These expectations were soon realized when the corresponding Michael adducts were obtained by reacting **25** with dibenzoylmethane and 2,4-pentanedione (acetyl acetone), employing sodium methoxide as the base and methanol as the medium, respectively. However, this reaction proceeded with concomitant deacylation giving 4,4-bis(phenylsulfonyl)-1-phenyl-1-butanone (**27a**) and 5,5-bis(phenylsulfonyl)-2-pentanone (**27b**). That deacylation had taken place was readily evident from mass and ^1H NMR spectral data. Thus **27a** displayed a molecular ion peak at m/e 428(M^{+}) in the mass



26a) $R = -C_6H_5$ 27 a) $R = -C_6H_5$

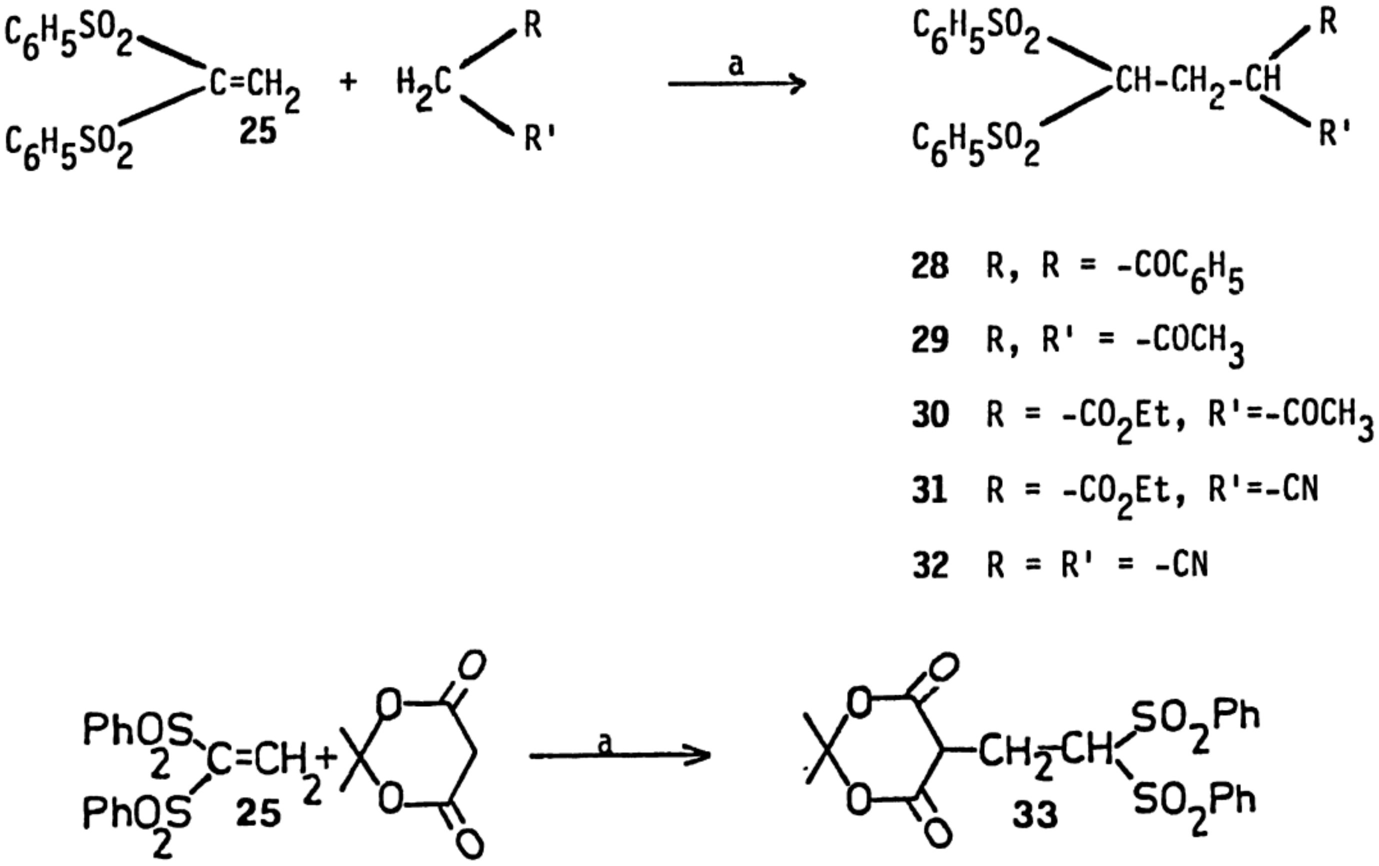
b) $R = -CH_3$ b) $R = -CH_3$

a) NaOMe, MeOH, r.t.

Scheme 2.21

spectrum and signals at δ 5.0-4.80[t,1H,$-C\underline{H}(SO_2C_6H_5)_2$], 3.60-3.40[t,2H,$-C\underline{H}_2-COC_6H_5$] and 2.80-2.60 [q,2H,$-CH_2-C\underline{H}_2-CH-$] besides the usual signals for the aromatic protons in the ^1H NMR spectrum. Similarly, **27b** also showed an $M^{\ddagger}$ peak at m/e 366 and characteristic ^1H NMR signals at δ 4.88-4.72[t,1H,$-C\underline{H}(SO_2C_6H_5)_2$], 3.12-2.96 [t,2H,$C\underline{H}_2COCH_3$] and 2.60-2.40 [q,2H,$-CH_2C\underline{H}_2-CH-$]. No attempts were made to establish whether the deacylation preceded or followed the Michael reaction.

In the Michael reaction, it is a common practice to use relatively weak basic catalysts such as piperidine, pyridine, triethylamine, benzyltrimethylammonium hydroxide (Triton B) or potassium hydroxide in order to minimize side reactions such as the one observed in the above instance, i.e., deacylation.[28] In the above reaction, when sodium methoxide was replaced by Triton B (40% methanolic solution), products of only addition with no deacylation were obtained. Thus, 2-[2,2-bis(phenylsulfonyl)ethyl]-1,3-diphenyl-1,3-propanedione (**28**) and 3-[2,2-bis(phenylsulfonyl)ethyl]-2,4-pentanedione (**29**) were obtained from **25** and dibenzoylmethane and 2,4-pentanedione, respectively.



28 R, R = $-COC_6H_5$

29 R, R' = $-COCH_3$

30 R = $-CO_2Et$, R'=$-COCH_3$

31 R = $-CO_2Et$, R'=$-CN$

32 R = R' = $-CN$

a) Triton B, dioxane, r.t.

Scheme 2.22

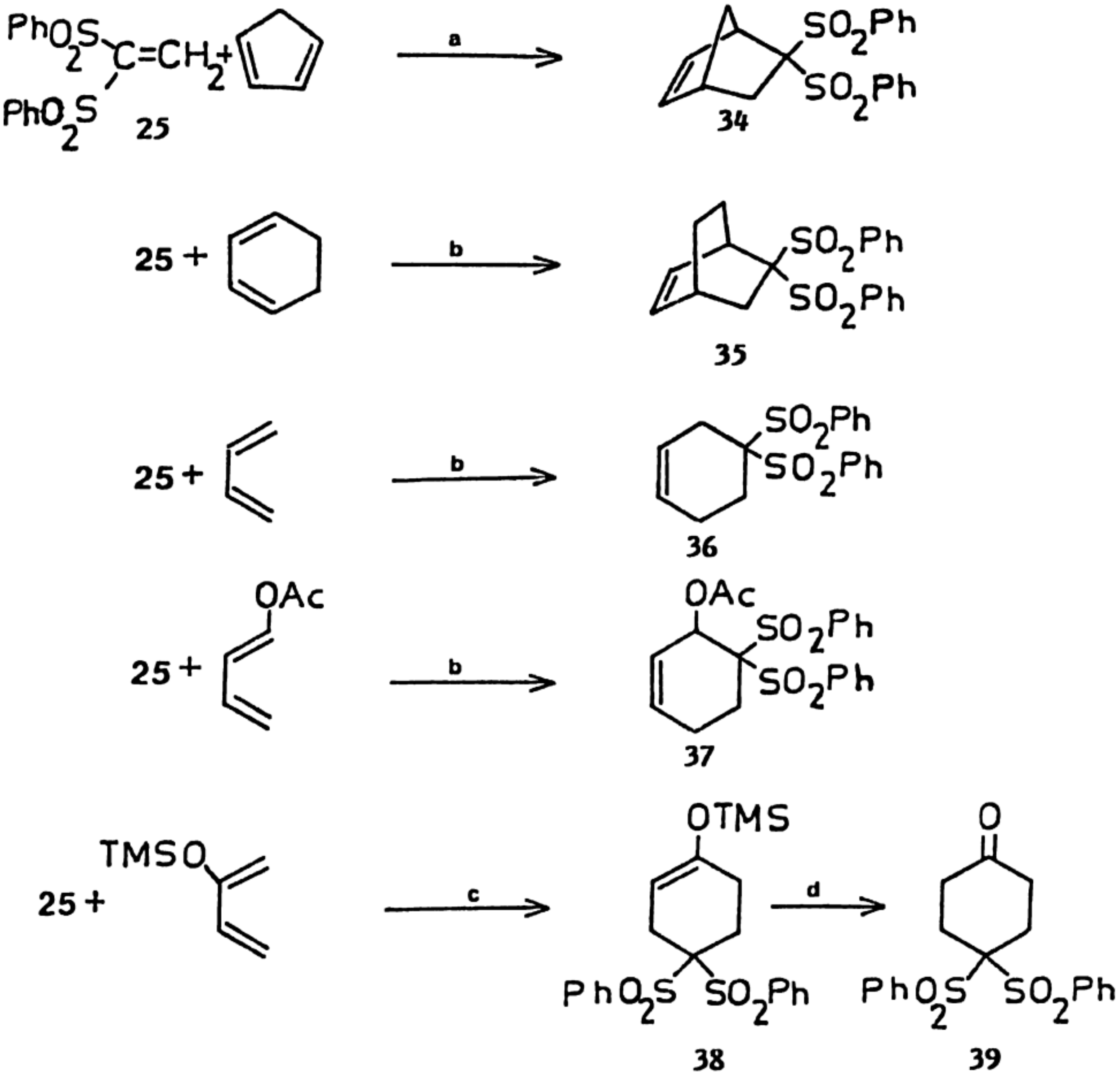
The ^{1}H NMR spectrum of **28** displayed salient signals at δ 6.44-6.32[t,1H,-$C\underline{H}(COC_6H_5)_2$], 5.12-5.0[t,1H,-$C\underline{H}(SO_2C_6H_5)_2$] and 3.12-2.96 [t,2H,-CH-$C\underline{H}_2$-CH-] whereas **29** had appropriate signals at δ 4.60-4.40 [m,2H,-$C\underline{H}(SO_2C_6H_5)_2$ and -$C\underline{H}(COCH_3)_2$] and 2.68-2.52[t,2H,-CH-$C\underline{H}_2$-CH-]. Although the parent ion peaks were absent in the mass spectra of **28** and **29** due to extensive fragmentation, the pattern of fragmentation was in agreement with the proposed structures.

In order to establish the generality of the reaction, **25** was reacted with other Michael donors like ethyl acetoacetate, ethyl cyanoacetate, malononitrile and 2,2-dimethyl-1,3-dioxan-4,6-dione (Meldrum's acid) in 1,4-dioxane using Triton B as base. All of them gave the appropriate adducts, **30-33**, which were fully characterized by ^{1}H NMR, IR and mass spectra as well as elemental analysis. Under identical conditions, no reaction took place between 25 and diethyl malonate. This can be attributed to the fact that the carbanion obtained on addition of diethyl malonate anion to 25 is less basic than diethyl malonate anion itself, thereby leading to the ready reversibility of the adduct.[28]

Around the same time, two groups, one from Russia[29] and another one from Italy[30] also published similar observations utilizing 25 as a Michael acceptor. While the former group employed amines as Michael donors, the latter used enolizable ketones and olefins for the same purpose. These results taken in unison indicate that 25 can be used as the synthetic equivalent of an ethylene 1,2-dipole, in a manner similar to the use of 1,1-bis(phenylsulfonyl) cyclopropane as propylene 1,3-dipole synthon.[31] It has also been suggested that due to ready reaction of 25 with nucleophiles such as alcohols, thiols and amines, it can be used as a convenient protective reagent for these functional groups.[32]

In all the reactions discussed above, the mechanism of addition probably involves attack by the nucleophile at the electron deficient β-carbon of 25 followed by proton transfer. The ^{13}C NMR spectrum of 25 shows the olefinic carbon resonances at 153 and 128 ppm respectively, for C_1 and C_2. Although deshielding at the C_2-carbon (β -carbon) is not evident, the driving force for the reaction is undoubtedly the generation of a highly stabilized carbanion due to the presence of two electron withdrawing phenylsulfonyl groups.

In view of the fact that 25 proved to be a good Michael acceptor it was felt that it could serve as a reasonably good dienophile in Diels-Alder reactions since electron withdrawing groups are known to enhance the reactivity of dienophiles. Accordingly, when 25 was treated with two equivalents of cyclopentadiene in dichloromethane at room temperature, the corresponding [4+2]-cycloadduct, 5,5-bis(phenylsuflonyl)bicyclo[2.2.1]-hept-2-ene (**34**) was obtained in 80% yield as a colorless solid.



a) DCM, r.t.; b) C_6H_6, 100-110°C, sealed tube;
c) DCM, r.t., sealed tube; d) AcOH, THF, H_2O.

Scheme 2.23

The structure of **34** and hence the occurence of a Diels-Alder addition was clearly established from the spectral data of the product.

However, **25** reacted with other dienes like 1,3-cyclohexadiene, 1,3-butadiene (generated in situ from 3-sulfolene) and 1-acetoxy-1,3-butadiene only under more drastic conditions (in a sealed tube), giving the corresponding cycloadducts **35-37** in reasonable yields. ^{1}H NMR, IR and mass spectra of these compounds were in agreement with the proposed structures. The reaction of **25** with 2-trimethylsilyloxy-1,3-butadiene gave the 'para' adduct **38** which upon hydrolysis using acetic acid/tetrahydrofuran/water gave **39** in good yield (78%). This result is in keeping with the previous observation that when a reactive diene like 2-trimethylsilyloxy-1,3-butadiene with an electron donating group at the second position reacts with electron deficient dienophiles, the 'para' adduct is the predominant product.[33] The structure of **39** is further substantiated by the presence of a high degree of symmetry in the ^{1}H NMR and ^{13}C NMR spectra. While the ^{13}C NMR spectrum showed seven lines at 25.1(C-3/5), 36.4(C-2/6), 128.8, 131.4, 134.9, 135.6 (C aromatic) and 207.9(C=O) ppm, the ^{1}H NMR was quite simple displaying just 2 peaks at δ 2.72 (s,8H) and 7.20-8.10 (m, 10H).

These results from our laboratory[34] were further complemented by the results from other laboratories[35]. It has been observed that **25** not only reacts with cyclopentadiene and 1,3-cyclohexadiene but also with other dienes like cycloheptatriene and norbornadiene as well as quadricyclane to give the corresponding cycloadducts in reasonable to good yields. Moreover, reactivity wise, it was found that **25** was less reactive when compared to the isomeric dienophiles, namely [E]-and [Z]-1,2-bis(phenylsulfonyl)ethenes. The explanation offered for this surprising observation (as other dienophiles like 1,1-dicyanoethene react at a much faster rate with dienes than the compounding 1,2-[E] and [Z] isomers) is that the two phenylsulfonyl groups with their bulkiness exert a high degree of steric hindrance when compared to other groups.

The adducts obtained from **25** and various dienes are useful synthetic intermediates. Thus, for example, after the Diels-Alder reaction, if one wishes to perform desulfonylation, it can be achieved either in a protic medium leading to just desulfonylation in which case **25** can be shown as ethylene equivalent or in aprotic medium, leading to the formation of a carbanion centre which can be captured by electrophiles. Identical or different electrophiles can be incorporated into the cycloadducts by making use of the two phenylsulfonyl groups. On the other hand, since it is known that a sulfonyl group can be reduced to a sulfide by DIBAL-H,[36] it can be presumed that by performing such a reduction on these cycloadducts and then hydrolyzing the resulting dithioketal to a ketone, **25** can be used as a ketene equivalent. Alternatively, the ketene equivalence of **25** can also be realized by performing a mono desulfonylation under aprotic conditions and then converting the remaining phenylsulfonyl group into a ketone function by making use of conditions reported by Little.[37] Although phenyl vinyl sulfone has been shown to be ketene equivalent by these manipulations,[37] **25** can be an useful alternative to phenyl vinyl sulfone. These results show that **25** is a useful synthon that can be employed in a variety of ways in synthetic organic chemistry.

In spite of the fact that the two reactions discussed above, namely Michael and Diels-Alder reactions constitute formidable tools in C-C bond formation, new methods to achieve this are being continuously sought. One such method of recent origin which is being used extensively is the phase transfer catalysed (PTC) alkylation. The reason for its popularity stems from the fact that it is quite convenient and economical. Although diactivated substrates like diesters, dinitriles, ketosulfones etc, were alkylated under PTC conditions, it is rather surprising to note that geminal disulfones, which fall under this category have not been studied. Hence we examined the PTC alkylations of **24**.

As a representative example, n-hexyl bromide was chosen as the alkylating reagent and its reaction with **24** using different phase transfer catalysts was studied in a single phase (50% aq. NaOH). Using one equivalent of n-hexyl bromide and tetra-n-butylammonium bromide (TBAB) as the phase transfer catalyst, the monoalkylated product 1,1-bis(phenylsulfonyl)heptane (**40**) was obtained in 73% yield. In an effort to improve the yield, the reaction was repeated using two equivalents of n-hexyl bromide. Gratifyingly, the yield of **40** went upto 95%. Subsequently, all alkylation reactions were carried out using two equivalents of the alkylating reagent unless mentioned otherwise.

$$\underset{\textbf{24}}{(C_6H_5SO_2)_2CH_2} + \underline{n}\text{-}C_6H_{13}Br \longrightarrow \underset{\textbf{40}}{(C_6H_5SO_2)_2\text{-}CH\text{-}(CH_2)_5\text{-}CH_3}$$

Phase Transfer Catalyst	Yield (%) of **40**
1. Tetra-n-butylammonium bromide (TBAB)	95
2. Tetra-n-butylammonium hydrogen sulfate (TBAHS)	75
3. Tricaprylmethylammonium chloride (TCMAC)	70
4. Cetylpyridinium chloride (CPC)	28
5. Cetyltrimethylammonium bromide (CTMAB)	21
6. Benzyltriethylammonium chloride (BTEAC)	20
7. 18-Crown-6	22

Table 1

Table 1 gives the results obtained using different phase transfer catalysts for the alkylation of **24** with n-hexyl bromide. Employing a two-phase system of 50% aqueous sodium hydroxide and dichloromethane as cosolvent did not improve the yield in entries 4-7 in Table 1. As the yields were satisfactory in entries 1-3, these reactions were not carried out using two-phase conditions.

The effect of the leaving group of the alkylating reagent on the reaction is an aspect which has not received much attention in PTC alkylations. Therefore, alkylations of **24** with n-butyl chloride, bromide and iodide in a single phase (50% aq. NaOH) employing TBAB as the phase transfer catalyst were then carried out. While the reaction of **24** with two equivalents of n-butyl chloride did not proceed at all, n-butyl bromide under similar conditions gave an 85% yield of the monoalkylated product, 1,1-bis(phenylsulfonyl)pentane (**41**).[38] Finally, with two equivalents of n-butyl iodide, the dialkylated product of **24**, viz., 5,5-bis(phenylsulfonyl)nonane (**42**),[38] was obtained in 75% yield along with 11% of the monoalkylated product **41**. However, when only one equivalent of n-butyl iodide was used, a mixture of **41** and **42** (61% and 10%, respectively) was obtained. The reaction of **24** with n-butyl iodide in the presence of different phase transfer catalysts led to only **41** with CPC, CTMAB and BTEAC and to a mixture of **41** and **42** with TBAHS and TCMAC. With TBAHS and TCMAC only **41** was obtained when one equivalent of n-butyl iodide was used (Table 2). The results in Table 2 indicate that the course of the reaction (mono or dialkylation) can be controlled by the appropriate choice of the alkylating reagent and/or the phase transfer catalyst.

$$(C_6H_5SO_2)_2CH_2 + C_4H_9I \longrightarrow (C_6H_5SO_2)_2\ CH\text{-}(CH_2)_3CH_3$$

24 **41**

$$(C_6H_5SO_2)_2C[(CH_2)_3CH_3]_2$$

42

PT Catalyst	Yield (%) of **41**	Yield (%) of **42**
1) TBAB	11 (61)	75 (10)
2) TBAHS	21 (91)	54
3) TCMAC	20 (83)	59
4) CPC	57	--
5) CTMAB	62	--
6) BTEAC	63	--

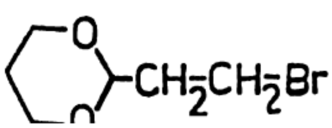
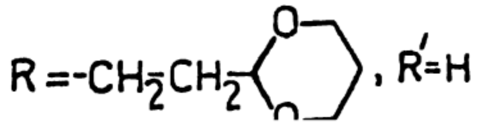
Yields in parenthesis refer to those when one equivalent of n-butyl iodide was used.

TABLE 2

Attention was then focussed on studying the reaction of **24** with n-butyl bromide and n-butyl iodide in a two phase system with dichloromethane and toluene as cosolvents and TBAB as the phase transfer catalyst. Under these experimental conditions only the monoalkylated product **41** was obtained. The use of toluene as cosolvent and n-butyl bromide as the alkylating reagent led to a rather poor yield (45%) of **41**. The yield of **41** when dichloromethane was used as cosolvent was better (57%). With n-butyl iodide, the yields of **41** were 85% and 77% in dichloromethane and toluene as cosolvents, respectively. Hence, further study of the alkylation reaction was limited to n-butyl iodide and dichloromethane. The other phase transfer catalysts showed a behaviour similar to that of TBAB in effecting monoalkylation of **24** to give **41**. However, the yields of **41** Mn the presence of CPC, CTMAB and BTEA were 45%, 62% and 57%, respectively. It is of interest to note that whereas the reaction of **24** with n-butyl iodide in a one-phase system gave either the dialkylated product **42** or the monoalkylated product **41** depending upon the reaction conditions, in a two-phase system, the same reaction always gave only **41**. The reason for this difference in reactivity is not yet clear.

The results presented above indicate that the best conditions for PTC alkylations of **24** would be the use of TBAB as the catalyst and 50% aqueous sodium hydroxide as the medium. A large number of alkylation reactions were successfully performed under these conditions[39] and the results obtained are given in Table 3. It is seen from Table 3 that α, ω-dibromides all give the corresponding cyclized products on reaction with **24**.

$$\underset{\textbf{24}}{(C_6H_5SO_2)_2CH_2} + RX \longrightarrow (C_6H_5SO_2)_2\ CRR'$$

1)	CH_3I	**43** R=R' = $-CH_3$	100 (ref 40)
2)	CH_3CH_2Br	**44** R=R' = $-CH_2-CH_3$	100
3)	$CH_2=CH_2-CH_2Br$	**45** R=R' = $-CH_2\ CH=CH_2$	90
4)	$Br(CH_2)_2Br$	**46** R-R' = $-(CH_2)_2-$	90 (ref 31)
5)	$Br(CH_2)_3Br$	**47** R=R' = $-(CH_2)_3-$	90
6)	$Br(CH_2)_4Br$	**48** R=R' = $-(CH_2)_4-$	100
7)	$Br(CH_2)_5Br$	**49** R=R' = $-(CH_2)_5-$	80
8)	$Br(CH_2)_6Br$	**50** R'=R' = $-(CH_2)_6-$	75
9)	$C_6H_5CH_2Br$	**51** R=$-CH_2-C_6H_5$, R'=H	78
10)	$CH_3CH_2CH_2Br$	**52** R=$-(CH_2)_2-CH_3$, R'-H	100
11)		**53** 	

Incidentally, alkylation under PTC conditions offers the most convenient method for the preparation of 1,1-bis(phenylsulfonyl)cyclopropane (**46**) a compound which has been used as a 1,3-dipole synthon.[31]

Results from other laboratories have shown that **24** can be put to use in a variety of ways. When compared to other diactivated substrates, **24** has been shown to be the substrate of choice to effect cycloalkylation[41] and macrolide formation.[42] Recently it has been shown that **24** serves as a coupling agent whereby alkylation reactions with two different alkylating agents were performed with the removal/ elimination of the two phenylsulfonyl groups to arrive at different pheromones.[43,44] In view of the results obtained, we believe that alkylation of **24** under PTC conditions, which can be performed with greater ease when compared to those reported, would be of use for the synthesis of such compounds.

In conclusion, the reactions described above go to show the utility of geminal disulfones in organic synthesis. More work needs to be done to explore further the chemistry of these interesting compounds.

EXPERIMENTAL

Bis(phenylthio)methane[25]

Thiophenol (5.0 g), sodium hydroxide (3.0 g), water (50 ml), dichloromethane (40 ml), methyltricaprylammonium chloride (Aliquat 336, 100 mg) were combined and stirred vigorously for 15 min at room temperature. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate and evaporated to give a colorless oil. Distillation at 127-128°/0.02 torr gave bis(phenylthio)methane.

Yield : 5.05 g (96%).

Bis(phenylsulfonyl)methane (24)[24]

To 15.0 g of bis(phenylthio)methane in 130 ml of 1:1 acetic acid and acetic anhydride was added with stirring 35 ml of 30% hydrogen peroxide over a two hour period while the mixture was cooled in an ice bath. The mixture was stirred for eight hours at room temperature and then allowed to stand for 3 days. The excess hydrogen peroxide was decomposed by stirring with a small quantity of manganese dioxide and the solvent removed under reduced pressure at room temperature. The solid residue that was obtained was crystallized from a mixture of ethanol and water.

Yield : 18.0 g (94%); m p. : 122°C.

Bis(phenylsulfonyl)ethene (25)[26]

A suspension of 9.0 g of 1-[2,2-bis(phenylsulfonyl)ethyl] piperidine in 150 ml of benzene was treated with a stream of dry HCl gas for 15 min which caused complete solution of the solid. The solution was then refluxed for 2 h, cooled to room temperature, filtered to remove piperidine hydrochloride and the filtrate was evaporated to a volume of about 25 ml. Addition of an equal volume of petroleum ether (60-80°C) gave an oil which soon solidified. This material was crystallized from petroleum ether - benzene mixture.

Yield : 4.75 g (68%); m p. : 126-127°C.

IR (KBr, cm^{-1}) : 1350 and 1140.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.50-7.85 (m, 10H, aromatic), 7.19 (s, 2H, olefinic).

^{13}C NMR (25.0 MHz, $CDCl_3$) : 153.4, 139.0, 138.8, 134.3, 129.1, 128.8 ppm.

General procedure for the preparation of compounds 27a and 27b

To a solution of sodium methoxide (prepared from 0.046 g of sodium, 2 mmol) in 2 ml of absolute methanol, 1 mmol of the active methylene compound in 1 ml of absolute methanol was added followed by 0.5 mmol of **25** in 1 ml. of absolute methanol. The mixture was stirred at room temperature for one hour and then poured into water and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and evaporated to give **27a** and **27b**.

4,4-Bis(phenylsulfonyl)-1-phenyl-1-butanone (27a)

Yield : 0.180 g (60%); m p. (isopropanol): 131-133°C.

IR(KBr, cm^{-1}) : 3020, 2940, 1730, 1450, 1340, 1150.

^1H NMR (100 MHz, $CDCl_3$): δ 7.60-8.08 (m, 15H, aromatic), 4.80-5.0 [t,1H, $-C\underline{H}(SO_2C_6H_5)_2$], 3.40-3.60 (t,2H,$-C\underline{H}_2COC_6H_5$), 2.60-2.80 [q, 2H, $-C\underline{H}_2CH(SO_2C_6H_5)_2$].

Mass : 428 ($M^{+\cdot}$), 323, 287, 223, 196, 141, 105, 77.

Anal. Calcd. for $C_{22}H_{20}O_5S_2$: C, 61.66; H, 4.70.

Found : C, 62.0; H, 4.74.

5,5-Bis(phenylsulfonyl)-2-pentanone (27b)

Yield : 0.160 g (80%); m p. (isopropanol) : 100°-101°C.

IR (KBr, cm^{-1}): 3020, 2940, 1720, 1600, 1450, 1340, 1140.

^1H NMR (100 MHz, $CDCl_3$): δ 7.60-8.0(m, 10H, aromatic), 4.72-4.88 [t,1H,$-C\underline{H}(SO_2C_6H_5)_2$], 2.96-3.12 (t,2H,$-C\underline{H}_2-COCH_3$), 2.40-2.60 [q, 2H, $-C\underline{H}_2CH\ (SO_2C_6H_5)_2$], 2.20(s, 3H, $-COC\underline{H}_3$).

Mass : 366 (M^{+}), 323, 225, 169, 141, 125, 77, 43.

Anal. Calcd. for $C_{17}H_{18}O_5S_2$: C, 55.72; H, 4.95.

Found : C, 56.30; H, 4.95.

General procedure for the preparation of compounds 28-33

To 1 mmol of the active methylene compound in 1 ml of 1,4-dioxane, one drop of 40% methanolic solution of benzyltrimethylammonium hydroxide (Triton B) was added followed by 0.5 mmol of **25** in 1 ml of 1,4-dioxane. The mixture was stirred for 2 h at room temperature. At the end of this period, it was poured into 2 ml of 5% HCl and extracted with ether. The ether layer was washed with water, 2% $NaHCO_3$, water, dried over anhydrous magnesium sulfate and evaporated to give **28-33.**

2-[2,2-Bis(phenylsulfonyl)ethyl]-1,3-diphenyl-1,3-propanedione (28)

Yield : 0.144 g (54%); m p. (isopropanol): 162-164°C.

IR (KBr, cm^{-1}): 3100, 3000, 1720, 1610, 1340, 1150.

^1H NMR (100 MHz, $CDCl_3$): δ 7.32-8.32 (m, 20H, aromatic), 6.32-6.44[t,1H,$-C\underline{H}(COC_6H_5)_2$], 5.0-5.12[t,1H,$-C\underline{H}(SO_2C_6H_5)_2$], 2.96-3.12 (t,2H,$-CH-C\underline{H}_2-CH-$).

Mass : 224, 141, 119, 105, 77.

Anal. Calcd. for $C_{29}H_{24}O_4S_2$: C, 65.39; H, 4.54.

Found : C, 65.77; H, 4.74.

3-[2,2-Bis(phenylsulfonyl)ethyl]-2,4-pentanedione (29)

Yield : 0.150 g (74%); m p. (isopropanol): 125°C.

IR (KBr, cm^{-1}) : 2950, 1740, 1460, 1330, 1160.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.48-7.88 (m, 10H, aromatic), 4.40-4.60 [m, 2H, $-C\underline{H}(COCH_3)_2$ and $-C\underline{H}(SO_2C_6H_5)_2$], 2.52-2.68 (t,2H,$-CH-C\underline{H}_2-CH-$), 2.20(s, 6H, $-COC\underline{H}_3$).

Mass: 267, 141, 125, 119, 77.

Anal. Calcd. for $C_{19}H_{20}O_6S_2$: C, 55.86; H, 4.93.

Found : C, 56.40; H, 5.07.

Ethyl 2-acetyl-4,4-bis(phenylsulfonyl)butyrate (30)

Yield : 0.215 g (100%); m p. (isopropanol) : 92°C.

IR (KBr, cm^{-1}): 3000, 1770, 1720, 1320, 1160.

^1H NMR (100 MHz, $CDCl_3$): δ 7.42-7.92 (m, 10H, aromatic), 4.56-4.72 [t, 1H, $-C\underline{H}(SO_2C_6H_5)_2$], 4.0-4.28 [m, $-C\underline{H}(COCH_3)_2$ and $-CO_2C\underline{H}_2CH_3$], 2.48-2.60 (t, 2H, $-CH-C\underline{H}_2-CH-$), 2.12 (s, 3H, $-COC\underline{H}_3$), 1.04-1.20(t, 3H, $-CO_2CH_2C\underline{H}_3$).

Mass : 439 (M+1), 395, 297, 164, 141, 77, 43.

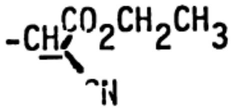
Anal. Calcd. for $C_{20}H_{22}O_7S_2$: C, 54.78; H, 5.05.

Found : C, 54.47; H, 5.26.

Ethyl 2-cyano-4,4-bis(phenylsulfonyl)butyrate (31)

Yield : 0.150 g (72%); m p. (methanol) : 142°C.

IR (KBr, cm^{-1}): 3000, 2270, 1760, 1340, 1160.

^1H NMR (100 MHz, $CDCl_3$): δ 7.52-7.96 (m, 10H, aromatic), 4.80-4.92 [t, 1H, $-C\underline{H}(SO_2C_6H_5)_2$], 4.16-4.48 [m, 3H,  $-C\underline{H}\begin{smallmatrix}CO_2CH_2CH_3\\CN\end{smallmatrix}$ and $-CO_2C\underline{H}_2CH_3$], 2.64-2.84 (t, 2H, $-CH-C\underline{H}_2-CH-$), 1.20-1.36 (t, 3H, $-CO_2CH_2C\underline{H}_3$).

Mass : 422 (M+1), 348, 280, 141, 91, 77.

Anal. Calcd. for $C_{19}H_{19}NO_6S_2$: C, 54.14; H, 4.54; N, 3.32.

Found : C, 53.81; H, 4.52, N, 3.80.

2-[2,2-Bis(phenylsulfonyl)ethyl]propanedinitrile (32)

Yield : 0.10 g (53%); m p. (isopropanol): 153-154°C.

IR (KBr, cm^{-1}): 3000, 2250, 1320, 1160.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.48-7.84 (m, 10H, aromatic), 4.52-4.76 [m, 2H, $-C\underline{H}(SO_2C_6H_5)_2$ and $-C\underline{H}(CN)_2$], 2.76-2.92(t, 2H, $-CH-C\underline{H}_2-CH-$).

Mass : 375 (M+1), 233, 141, 91, 77, 51.

Anal. Calcd. for $C_{17}H_{14}N_2O_4S_2$: C, 54.55; H, 3.76, N, 7.48.

Found : C, 54.50; H, 3.71; N, 7.90.

5-[2,2-Bis(phenylsulfonyl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (33)

Yield : 0.220 g (100%); m p. (isopropanol): 150°C.

IR (KBr, cm^{-1}) : 2950, 1760, 1310, 1160.

^1H NMR (100 MHz, $CDCl_3$): δ 7.48-7.92 (m, 10H, aromatic), 5.32-5.44 (t, 1H), 4.64-4.80 [t, 1H, $-C\underline{H}(SO_2C_6H_5)_2$], 2.76-2.88 (t, 2H, $-CH-C\underline{H}_2-$), 1.76 and 1.84 (2s, 6H, $-C\underline{H}_3$).

Mass: 311, 234, 218, 141, 121, 77, 51.

Anal Calcd. for $C_{20}H_{20}O_8S_2$: C, 53.08; H, 4.45.

Found: C, 53.28; H, 4.63.

5,5-Bis(phenylsulfonyl)bicyclo[2.2.1)hept-2-ene (34)

To a stirred solution of **25** (0.616 g, 2 mmol) in dichloromethane (2 ml), cyclopentadiene (0.264 g, 4 mmol) was added and the mixture stirred for 24 h at room temperature. The solvent was removed and the crude product was purified by crystallization.

Yield : 0.60 g (80%); m p.(benzene) : 157-158°C.

IR (KBr, cm^{-1}) : 3100, 1600, 1450, 1320, 1150.

^{1}H NMR (100 MHz, $CDCl_3$): δ 7.40-7.84 (m, 10H, aromatic), 6.12-6.16 (dd, 2H, olefinic), 3.32 (bs, 1H, H-1), 2.92(bs, 1H, H-4), 2.60-2.80 (dd, 1H, H-6 exo), 2.20 (d, 1H, H-7 syn), 1.16-1.40 (m, 2H, H-6 endo & H-7 anti).

Mass : 374 ($M^{+\cdot}$), 308, 233, 125, 91, 77, 66.

Anal. Calcd. for $C_{19}H_{18}O_4S_2$: C, 60.94; H, 4.84.

Found: C, 60.81; H, 4.24.

General procedure for the preparation of compounds 35-37

A solution of 0.5 mmol of **25** and 0.75 mmol of the diene in dry benzene (2 ml) was heated to 100-110°C in a sealed tube for 3.5 h. The mixture was cooled to room temperature, the seal opened and the solvent removed. The crude material was chromatographed, eluting with hexane : ethyl acetate (90:10), to give **35-37**.

5,5-Bis(phenylsulfonyl)bicyclo[2.2.2]oct-2-ene (35)

Yield : 0.081 g (42%); m p. (benzene) : 148-150°C.

IR (KBr, cm^{-1}): 3000, 1600, 1440, 1300, 1140.

^{1}H NMR (100 MHz, $CDCl_3$): δ 7.44-8.12 (m, 10H, aromatic), 5.76-5.88 (t, 1H, olefinic), 5.44-5.56 (t, 1H, olefinic), 3.36-3.40 (d, 1H), 2.02-2.80 (m, 3H), 1.04-2.12 (m, 4H).

Mass : 388 ($M^{+\cdot}$), 303, 247, 125, 105, 91, 77.

Anal. Calcd. for $C_{20}H_{20}O_4S_2$: C, 61.83; H, 5.18.

Found : C, 61.45; H, 4.90.

4,4-Bis(phenylsulfonyl)cyclohexene (36)

Yield : 0.135 g (75%); m p. (benzene) : 156°C.

IR (KBr, cm^{-1}): 2920, 1460, 1340, 1150.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.60-8.20 (m, 10H, aromatic), 5.64-5.72 (m, 2H, olefinic), 2.84 (bs, 2H), 2.36 (bs, 4H).

Mass : 362 (M+), 221, 219, 141, 125, 77.

Anal. Calcd. for $C_{18}H_{18}O_4S_2$: C, 59.64, H, 5.00.
Found : C, 59.55; H, 4.68.

1-Acetoxy-6,6-bis(phenylsulfonyl)-2-cyclohexene (37)

Yield : 0.120 g (57%); m p. (benzene) : 145-147°C.

IR (KBr, cm^{-1}) : 2950, 1760, 1340, 1160.

^1H NMR (100 MHz, $CDCl_3$): δ 7.52-8.32 (m, 10H, aromatic), 6.16 (bs, 1H), 5.80-5.88 (d, 1H, olefinic), 5.40-5.48 (d, 1H, olefinic), 2.52-2.84 (m, 2H), 2.04-2.20 (m, 2H), 1.92 (s, 3H).

Mass : 420 (M+), 361, 309, 279, 237, 141, 125, 91, 77.

Anal. Calcd. for $C_{20}H_{20}O_6S_2$: C, 57.13; H, 4.79.

Found : C, 57.38; H, 4.73.

4,4-Bis(phenylsulfonyl)cyclohexanone (39)

A solution of **25** (0.154 g, 0.5 mmol) and 2-trimethylsilyloxy-1,3-butadiene (0.284 g, 2 mmol) in dichloromethane (2 ml) was stirred at room temperature in a sealed tube for 3.5 h. At the end of this period, the crude product obtained was hydrolyzed in acetic acid/THF/water (1/50/ 50; 10 ml) to give **39**.

Yield : 0.150 g (79%); m p. (benzene) : 218-220°C.

IR (KBr, cm^{-1}) : 3000, 1720, 1320, 1140.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 7.20-8.10 (m, 10H, aromatic), 2.72 (s, 8H).

^{13}C NMR (25.0 MHz, $CDCl_3$) : 207.7, 135.6, 134.9, 131.4, 128.8, 36.4, 25.1 ppm.

Mass : 378 ($M^{+\cdot}$), 237, 141, 125, 91, 77.

Anal. Calcd. for $C_{18}H_{18}O_5S_2$: C, 57.13; H, 4.79.

Found : C, 56.67; H, 5.20.

General procedure for the preparation of compounds 40 and 44-53

To a mixture of **24** (0.294 g, 1 mmol) and tetrabutylammonium bromide (0.322 g, 1 mmol) in 10 ml of 50% aqueous sodium hydroxide, 2 mmol of the appropriate alkylating agent was added and the mixture was stirred for 3 h at room temperature. The reaction mixture was made acidic (pH 2-3), cooled, extracted with dichloromethane and the organic extract washed with water, dried over anhydrous magnesium sulfate and evaporated to give **40** and **44-53**.

1,1-Bis(phenylsulfonyl)heptane (40)

Yield : 0.360 g (95%); m p. (ethanol) : 80-81°C.

IR (KBr, cm^{-1}) : 2950, 1600, 1320, 1160.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 7.52-8.0 (m, 10H, aromatic), 4.32-4.40 [t, 1H, $-C\underline{H}(SO_2C_6H_5)_2$], 1.08-2.24 (m, 10H), 0.80-0.92 (t, 3H, $C\underline{H}_3$).

Mass : 239 (M-141), 141, 125, 91, 77.

Anal. Calcd. for $C_{19}H_{24}O_4S_2$: C, 59.97; H, 6.35.

Found : C, 60.27; H, 6.30.

3,3-Bis(phenylsulfonyl)pentane (44)

Yield : 0.350 g (100%); m p. (ethanol) : 166°C.

IR (KBr, cm^{-1}) : 3050, 1320, 1160.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.52-8.24 (m, 10H, aromatic), 2.24-2.48 (q, 4H), 1.20-1.32 (t, 6H).

Mass : 352 ($M^{+\cdot}$), 288, 211, 141, 77.

Anal. Calcd. for $C_{17}H_{20}O_4S_2$: C, 57.93; H, 5.71.

Found : C, 57.72; H, 5.32.

4,4-Bis(phenylsulfonyl)-1,6-heptadiene (45)

Yield : 0.338 g (90%); m p. (ethanol) : 95°C.

IR (KBr, cm^{-1}) : 3100, 1650, 1310, 1150.

^1H NMR (100 MHz, $CDCl_3$): δ 7.52-8.16 (m, 10H, aromatic), 5.84-6.20 (m, 2H), 5.12-5.28 (m, 4H), 2.96-3.04 (d, 4H).

Mass : 376 ($M^{+\cdot}$), 251, 235, 141, 125, 93, 77.

Anal Calcd. for $C_{19}H_{20}O_4S_2$: C, 60.61; H, 5.35.

Found : C, 61.02; H, 5.31.

1,1-Bis(phenylsulfonyl)cyclobutane (47)

Yield : 0.300 g (90%); m p. (benzene-hexane) : 117-118°C.

IR (KBr, cm^{-1}) : 3000, 1600, 1320, 1150.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.40-8.0 (m, 10H, aromatic), 2.80-3.0 (t, 4H), 2.0-2.20 (m, 2H).

Mass : 272, 242, 195 (M-141).

Anal. Calcd. for $C_{16}H_{16}O_4S_2$: C, 57.12; H, 4.79.

Found : C, 57.14; H, 4.85.

1,1-Bis(phenylsulfonyl)cyclopentane (48)

Yield : 0.350 g (100%); m p. (benzene-hexane) : 141-142°C.

IR (KBr, cm^{-1}) : 3000, 1450, 1310, 1150.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 7.40-8.0 (m, 10H, aromatic), 2.40-2.52 (m, 4H), 1.60-1.76 (m, 4H).

Mass : 350 ($M^{+\cdot}$), 286, 242, 209, 141, 77.

Anal Calcd. for $C_{17}H_{18}O_4S_2$: C, 58.26; H, 5.17.

Found : C, 58.13; H, 5.23.

1,1-Bis(phenylsulfonyl)cyclohexane (49)

Yield : 0.290 g (80%); m p. (methanol): 158°C.

IR (KBr, cm^{-1}) : 2900, 1320, 1160.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 7.20-7.72 (m, 10H, aromatic), 2.12-2.20 (m, 4H), 1.80-2.0 (m, 4H), 1.40-1.48 (m, 2H).

Mass : 364 ($M^{+\cdot}$), 223, 143, 125, 97, 79, 77.

Anal. Calcd. for $C_{18}H_{20}O_4S_2$: C, 59.31; H, 5.53.

Found : C, 59.45; H, 5.37.

1,1-Bis(phenylsulfonyl)cycloheptane (50)

Yield : 0.280 g (75%); m p. (isopropanol) : 174°C.

IR (KBr, cm^{-1}) : 2950, 1310, 1140.

^{1}H NMR (100 MHz, $CDCl_3$) : δ 7.52-8.04 (m, 10H, aromatic), 2.24-2.36 (m, 4H), 1.80-2.04 (m, 4H), 1.44-1.68 (m, 4H).

Mass : 237 (M-141), 141, 125, 95, 91, 77.

Anal. Calcd. for $C_{19}H_{22}O_4S_2$: C, 60.29; H, 5.85.

Found : C, 59.73; H, 5.73.

1,1-Bis(phenylsulfonyl)-2-phenylethane (51)

Yield : 0.300 g (78%); m p. (ethanol) : 135°C.

IR (KBr, cm^{-1}) : 3100, 1600, 1320, 1150.

^{1}H NMR (100 MHz, $CDCl_3$):δ 7.54-8.0 (m 10H, aromatic), 7.20 (s, 5H, aromatic), 4.68-4.80 (t, 1H), 4.48-4.52 (d, 2H).

Mass : 245 (M-141), 141, 125, 103, 91, 77.

Anal. Calcd. for $C_{20}H_{18}O_4S_2$: C, 62.15; H, 4.69.

Found : C, 62.07; H, 4.59.

1,1-Bis(phenylsulfonyl)butane (52)

Yield : 0.335 g (100%); m p. (methanol-isopropanol) : 128°C.

IR (KBr, cm^{-1}): 2950, 1310, 1140.

^1H NMR (100 MHz, $CDCl_3$): δ 7.48-7.92 (m, 10H, aromatic), 4.28-4.36 (t, 1H), 2.0-2.20 (m, 2H), 1.40-1.68 (m, 2H), 0.72-0.88 (t, 3H).

Mass : 338 ($M^{+\cdot}$), 309, 239, 197, 149, 141, 125.

Anal. Calcd. for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.35.

Found : C, 56.62; H, 5.62.

2-[3,3-Bis(phenylsulfonyl)propyl]-1,3-dioxane (53)

Yield : 0.400 g (100%); m p. (methanol): 140-141°C.

IR (KBr, cm^{-1}): 2950, 1320, 1160.

^1H NMR (100 MHz, $CDCl_3$) : δ 7.28-7.88 (m, 10H, aromatic), 4.48-4.60 (t, 1H), 4.12-4.20 (t, 1H), 2.96-3.60 (m, 6H), 1.40-1.68 (m, 2H), 1.10-1.32 (m, 2H).

Mass : 410 ($M^{+\cdot}$), 369, 141, 125, 87, 77.

Anal. Calcd. for $C_{19}H_{22}O_6S_2$:C, 55.59; H, 5.40.

Found :C, 55.65; H, 5.15.

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5. Synthesis of (±) silphinene
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