Progress towards the Stereoselective Synthesis of Warburganal

by

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Declaration

I hereby certify that this research is a result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed.....

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I hereby certify that this statement is correct.

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Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
BuLi / *n*-BuLi	butyllithium
t-$BuMe_2SiCl$	*tert*-butyldimethylsilylchloride
conc.	concentration
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
d	doublet of doublets
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DDVP	2,2-dichlorovinyl dimethyl phosphate
DEPT	distortionless enhancement over polarization transfer
DHP	dihydropyran
DIBAL	diisobutylaluminium chloride
DMD	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EI	electron impact
equiv.	equivalent(s)
Et	ethyl
Et_3N / NEt_3	triethylamine
GC/MS	gas chromatography/mass spectrometry
h	hour(s)
HETCOR	heteronuclear correlation
HMPA	hexamethylphosphoric triamide
Hz	hertz
i	iso

IR	infrared
LDA	lithium diisopropylamide
$LiMe_2Cu$	lithium dimethylcuprate
lit.	literature
m	meta
m	multiplet
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
Me_3N	trimethylamine
MoOPH / MoO_5.Py.HMPA	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
m.p.	melting point
MsCl	methanesulfonyl chloride
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
q	quartet
s	singlet
sat.	saturated
soln.	solution
t	triplet
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
p-TSA	*p*-toluenesulfonic acid

$TsNHNH_2$	*p*-toluenesulfonylhydrazine
UV	ultraviolet

Summary

The aim of the project was to synthesize warburganal, a natural product isolated from the *Warburgia* plants native to Venda, known as a potent molluscicide, in a new, cheaper and more efficient way to be used in the ongoing war against bilharzia.

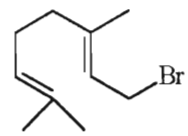
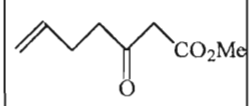
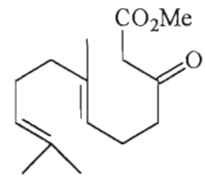
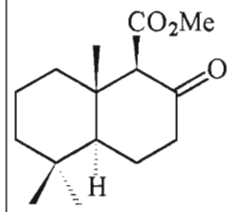
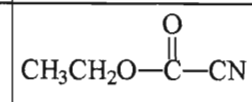
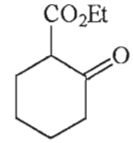
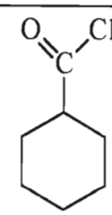
A synthetic pathway beginning with geraniol as the starting material was planned to afford a 7-step route. The first step involved the substitution of a bromine group for a hydroxyl group. Geranyl bromide underwent an alkylation step with the dianion of methyl acetoacetate to afford methyl 3-oxo-7,11-dimethyldodeca-6*E*,10-dienoate. The next Lewis acid-catalyzed step involved formation of the bicyclic decalin ring system, methyl (1*R**,4a*S**,8a*S**)-2-oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate. The next step was to add a hydroxyl group alpha to the ester, the α-OH being vitally important to the biological activity of warburganal. This step proved to be unsuccessful with the methodology used.

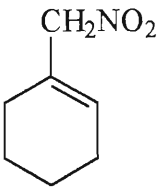
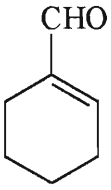
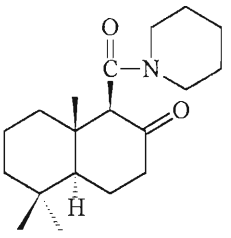
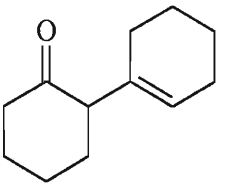
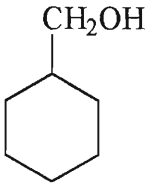
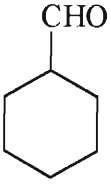
A change in tactics was obviously required and initially protection of the ketone as an acetal was attempted. Instead of the expected acetal product, an epimer of the decalin structure above, namely, methyl (1*S**,4a*S**,8a*S**)-2-oxo-5,5,8a-trimethyldecahydro-naphthalene-1-carboxylate was isolated. This epimer seems to form under acidic as well as basic conditions and was also isolated from an α-hydroxylation reaction that employed KH and MoOPH.

Most of the steps were attempted on model compounds to enable the conditions to be optimized prior to attempting the reaction on the warburganal precursor. It was soon discovered that for reasons as yet unknown, the reactions that worked on the model compounds did not always work on the warburganal precursors, although the model compounds possessed functional groups that best simulated those possessed by warburganal.

The progress reported towards the synthesis of warburganal highlights the many difficulties encountered when introducing the requisite functional groups on to the decalin ring skeleton to afford warburganal *i.e.* the α-hydroxyl and β-aldehyde moieties and the α,β-unsaturated aldehyde. Although the planned synthetic pathway was not entirely successful, the pitfalls encountered are discussed and potential solutions are presented. A number of interesting and unexpected compounds were isolated en route and ideas are discussed that may well culminate in an efficient synthesis of warburganal.

Table of compounds prepared

NAME	NUMBER	STRUCTURE	MOLECULAR WEIGHT	FORMULA
Geranyl bromide	**10**		217.14	$C_{10}H_{17}Br$
Methyl 3-oxo-hept-6-enoate	**50**		156.18	$C_8H_{12}O_3$
Methyl 3-oxo-7,11-dimethyldodeca-6*E*,10-dienoate	**11**		252.35	$C_{15}H_{24}O_3$
Methyl (1*R**,4*aS**,8*aS**)-2-oxo-5,5,8a-trimethyl-decahydronaphthalene-1-carboxylate	**45**		252.35	$C_{15}H_{24}O_3$
Ethyl cyanoformate	**59**		99.08	$C_4H_5NO_2$
Ethyl 2-oxocyclohexyl-carboxylate	**60**		170.20	$C_9H_{14}O_3$
Cyclohexane-carbanoyl chloride	**62**		146.61	$C_7H_{11}ClO$

1-Nitromethane-cyclohexene	**75**		141.16	$C_7H_{11}NO_2$
1-Cyclohexene-carboxaldehyde	**76**		110.15	$C_7H_{10}O$
(1*R*,4aS*,8aS**)-2-Oxo-5,5,8a-trimethyldeca-hydronaphthalene-piperidino-methanone	**78**		305.46	$C_{19}H_{31}NO_2$
2-Cyclohex-1′-enylcyclohexanone	**79**		178.27	$C_{12}H_{18}O$
Cyclohexane-methanol	**81**		114.18	$C_7H_{14}O$
Cyclohexane-carboxaldehyde	**82**		112.17	$C_7H_{12}O$

1. Introduction

Warburganal, a natural product from the *Warburgia* plants and the compound of principal interest in this project, has many varied beneficial properties (these properties are discussed in detail in section 1.3). Warburganal is one of the most potent molluscicides known, a property that proves invaluable in the control of the disease bilharzia, which makes use of a snail in its life cycle. One of the greatest scourges of the modern world today is the increasing occurrence of bilharzia, a disease where the symptoms may include inflammation, cough, late-afternoon fever, skin eruption, swelling and tenderness of the liver. There may be blood in the stools and urine in the more acute stage. The chronic stage of the disease is characterized by the gradual impactment of eggs into the walls of the body organs, leading to their fibrous thickening and loss of elasticity. Liver damage, stone formation in the bladder and secondary bacterial infection, as well as lesions of organs such as the brain and lungs are some of the more serous effects of this disease. The ensuing discussion is intended to give a general background to bilharzia and in particular show the part that certain species of snail play in the life cycle of bilharzia as well as the current methods used for the control of this disease. These introductory paragraphs are included to show the importance of developing efficient syntheses of warburganal for future use in the fight against bilharzia.

1.1 Bilharzia

Bilharziasis or bilharzia, now more commonly called schistosomiasis, is caused by the infestation with one of three species of flukes (parasitic trematode worms) of the genus *Schistosoma*, namely *S. haematobium, S. mansoni,* and *S. japonicum.* The first was discovered by Theodore Bilharz. Recently, bilharzia has been reported in six of the nine provinces of South Africa (Northern Province, North-West, Gauteng, Mpumalanga, KwaZulu-Natal and Eastern Cape) and in every country in Africa except Lesotho.[1]

Bilharzia is very much a social disease of rural people and results from interactions between the individual and the community at large. Water-contact studies have shown that swimming and washing clothes, both of which are usually social activities, pose the greatest risk of infection and thus contribute most to transmission of the disease. Short-term control measures are aimed particularly at these. Bilharzia may also be a recreational disease inasmuch as canoeists sometimes become infected while paddling on rivers and dams contaminated with the bilharzia disease.[1]

1.1.1 Life cycle

Bilharzia is endemic in over 70 countries across the world, and is believed to have affected more than 200 million people. It occurs when low standards of sanitation result in the voiding of faeces and urine into fresh water where certain species of fresh water snails are present, which act as intermediate hosts to the parasites. The adult worms (male and female) are about 3 cm long and inhabit the veins draining the pelvic viscera of human beings, notably the bladder and lower bowel, the females' eggs being excreted in urine and faeces. These release mobile larvae (miracidia) which invade the snail, where further fork-tailed larvae (cercariae) develop which are able to penetrate the intact skin of man, especially after bathing in infested water, where they develop into adults thereby completing the life cycle. The infestation causes chronic ill health, chiefly due to anaemia, with a variety of specific, often serious, complications mentioned previously. See **Figure 1** for a schematic representation of the life cycle of the bilharzia parasites.

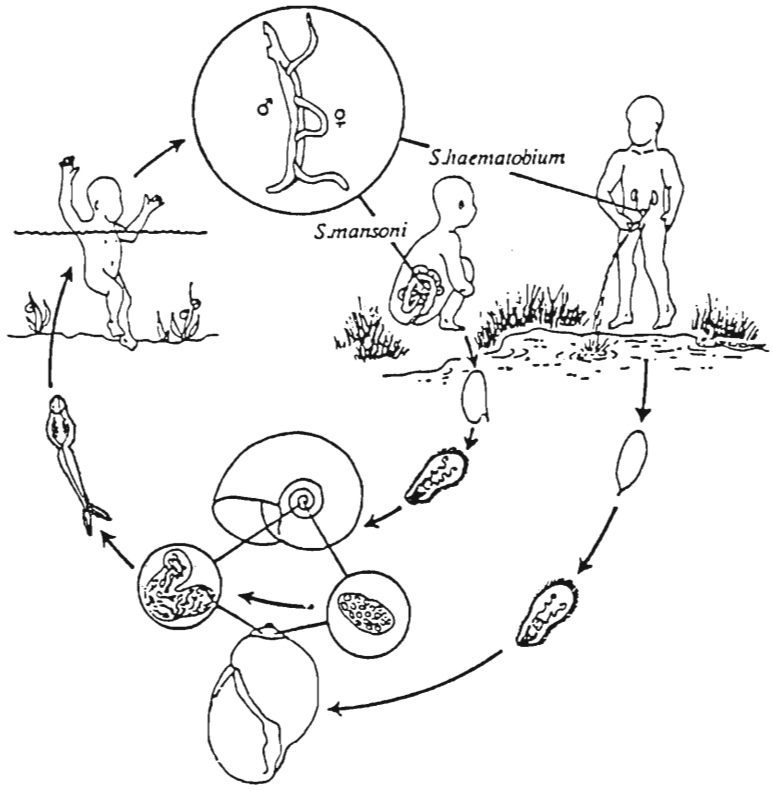


Figure 1. Diagram illustrating the life cycles of the bilharzia parasites, *S. haematobium* (causing urinary bilharzia) and *S. mansoni* (causing intestinal bilharzia)[Drawn by Marlies Tschneuschner].[1]

1.1.2 Control of schistosomiasis (bilharzia)

Control of this disease may be focused on treating the infestation in man (chemotherapy is effective), on snail control (use of molluscicides), on improving personal hygiene and sanitation, or on a combination of all three methods.

Snail control by spraying molluscicides onto waterbodies has changed in recent years from being a major tool in its own right to a supportive one. Molluscicides are generally considered to be environmentally friendly compounds. Although molluscicides may affect other organisms, even when spraying is done focally at water-contact sites only, populations of both target and non-target animals recover quickly due to rapid breeding and immigration from refuges elsewhere.

Synthetic molluscicides are expensive and because treatments need to be repeated two or three times a year, cost has become a key problem. This is made worse by the fact that the countries which suffer most from bilharzia are also those which can least afford to pay for control programmes. Research is therefore bifocal, the development of cheaper molluscicidal compounds derived from plants, and biological control. Some plant molluscicides are extremely toxic to snails and researchers are concentrating on those obtained from plants that are already used in traditional medicine since they are known to rural communities and their value recognised.

A number of predators, parasites and competitors of the bilharzia-carrying snails have been identified as potential biocontrol agents against these snails. The most useful biocontrol agents however, seem to be competitor snails, *i.e.* the competitor snails compete for resources or predate the bilharzia-carrying snails.[1]

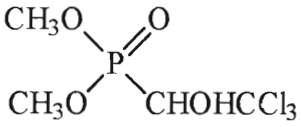
1.1.2.1 Chemotherapy

The primary objective of chemotherapy in schistosomiasis control is the reduction and prevention of morbidity in humans. High cure rates are achieved following treatment with all the new antischistosomal drugs. Even if egg excretion persists after treatment, the intensity of infection is greatly reduced, and the risk of developing disease among those who were previously heavily infected is greatly reduced. Although there is great interest in the antischistosomal drugs, there is also concern about their cost for large-scale use. The cost can be reduced if the drugs are obtained by direct, bulk purchase through the national schistosomiasis control programmes or as part of a national drug policy.

Of the many drugs that display antischistosomal activity, only three can be considered for large-scale chemotherapy: metrifonate **(1)**, oxamniquine **(2)** and praziquantel **(3)**.

1.1.2.1.1 Metrifonate

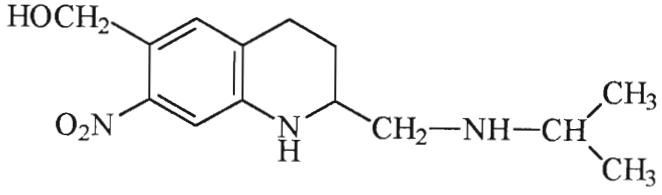
Metrifonate **(1)**, formerly known as trichlorphone and trichlorofone, is an organophosphorus ester that is active only against *S. haematobium*. This cheap drug is rapidly absorbed, metabolised, and excreted. Two metabolic pathways have been identified, both giving rise to DDVP (2,2-dichlorovinyl dimethyl phosphate) a cholinesterase inhibitor that acts directly; this is the active compound and metrifonate acts as a slow-release formulation. The mode of action of metrifonate in schistosomiasis remains unknown.[2] Metrifonate is an extremely well tolerated drug of moderately good therapeutic efficiency.[3]



(1) Metrifonate

1.1.2.1.2 Oxamniquine

Oxamniquine **(2)** is a well-known tetrahydroquinoline drug which proves very useful for the treatment of *S. mansoni* infection including many complicated syndromes.[4] Interestingly, the adult male *S. mansoni* worms are more susceptible to oxamniquine than the female worms. Although the precise mode of action is not known, worm death has been observed to be associated with the formation of large subtegumental vesicles. The early developmental stages of *S. mansoni* are also vulnerable to oxamniquine.



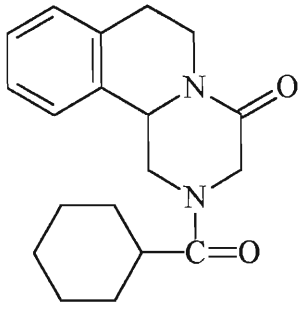
(2) Oxamniquine

It is also the first of the currently used antischistosomal drugs to be implicated in resistance. At present, resistance to oxamniquine is not a major public health problem and

oxamniquine-resistant patients are treated with success by praziquantel. Such findings, however, are cause for concern and should obviously stimulate more studies in this field.[3]

1.1.2.1.3 Praziquantel

Praziquantel **(3)** is a heterocyclic pyrazino-isoquinoline compound. The active substance is an hygroscopic, colourless, almost odourless powder with a bitter taste.[4] It is active against *S. mansoni, S. haematobium* and many other species of bilharzia worm.



(3) Praziquantel

Although considerable research has been carried out to elucidate the mode of action of praziquantel, it cannot yet be explained at the molecular level, but it is known to be associated with strong molecular contraction and tegumental vesicle formation.[2]

Praziquantel remains the drug of choice for all forms of schistosomiasis occurring in man. High therapeutic efficacy, excellent patient tolerance and few and relatively minor side effects all ensure that its use will continue at individual clinical level and expand in epidemiological intervention programmes aimed at controlling community morbidity.[3]

1.1.2.2 Snail control

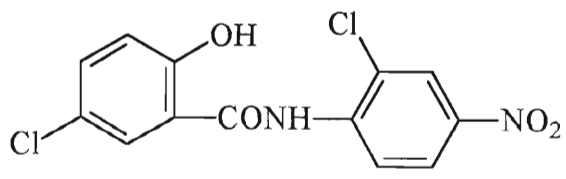
Three methods of snail control: chemical, environmental and biological, have been used in the past to control snail hosts. These methods have been comprehensively reviewed in recent years.[2]

During the past decade numerous control projects in Brazil, Congo, Egypt, Ghana, Jordan, Madagascar, Philippines, Tanzania, Venezuela, Zimbabwe, and elsewhere have shown that snail control by molluscicides, in combination with other methods, can reduce or eliminate transmission of the disease. There is, however, a major need for the development of new synthetic molluscicides to increase the impact of the other advances made in schistosomiasis control. Snail control procedures, including the administration of molluscicides, will therefore remain among the methods of choice for the control of schistosomiasis, even though selective population-based chemotherapy now plays the leading role in integrated control strategies.[2]

1.1.2.2.1 Available molluscicides

Available molluscicides must be safe, *i.e.* non-toxic for mammals and other aquatic organisms; they must not produce unacceptable adverse effects if they enter the food chain; and they must be stable in storage. Other considerations include cost and availability, snail specificity, low toxicity for non-target species, acceptable formulations, simple means of application, and a reliable method of field analysis.

Niclosamide, also known as Bayluscide, is at present the molluscicide of choice.



Niclosamide

A similar chemical product is known in Egypt as Mollutox.

Copper salts have been largely discarded by most snail control programmes since their molluscicidal efficacy, irrespective of method of application (in slow-release matrices, in chemical barriers, in compounds of different anionic nature, *etc.*) has been less than satisfactory. Moreover, the cost-effectiveness of the use of copper sulfate, despite its low purchase price, has been shown to be unacceptably high in comparison with that of niclosamide.[2]

1.1.2.2.2 Molluscicides under development

(1) Organotin compounds: The high molluscicidal activity of a number of organotin compounds is well known. The molluscicidal activity appears to be limited to the trisubstituted molecules, *e.g.* as has been demonstrated against *Bulinus* spp. and *Biomphalaria* spp.. Certain organotin compounds have been incorporated into slow-release rubber formulations that permit low dosing rates to be achieved over long periods. However, insufficient information is at present available to assess the long-term toxicity to man and his domestic animals. Such information is at present being recorded on bis(tri-*n*-butyltin)oxide (TBTO), which shows promising molluscicidal properties.

(2) Amide compounds: The action of fluoracetamide and its analogues (bromoacetamide, chloracetamide) against amphibious and aquatic snails has been investigated. The toxicological effects on man and the environmental impact of these compounds have not been assessed. These compounds have high molluscicidal activity and low toxicity to fish, and are water soluble, stable and easy to apply. The results of small-scale field trials indicate that they are particularly suitable for use in fishponds.

(3) Molluscicides of plant origin: The most promising plant molluscicides available at present available are certain strains of *Phytolacca dodecandra* (endod), and *Jatropha*

curcas from the Philippines. However, they each have their limitations. No plant molluscicide is specific to snails, and few have been adequately tested under simulated field conditions. Long-term toxicological studies have not, as yet, been undertaken on any vegetable molluscicide, and the same toxicological regulations apply to these compounds as apply to synthetic products. Further research in this area can be expected.

Almost all candidate molluscicides have undergone adequate short- and medium-term (90 days) toxicity testing, but few have been subjected to long-term toxicological studies. Niclosamide is the only molluscicide that has undergone carcinogenicity testing.[2]

1.1.2.2.3 Resistance to molluscicides

Observations suggesting that the snail intermediate hosts of *Schistosoma* can develop resistance to molluscicides will require further study. Increased tolerance to niclosamide has been reported. There is still, however, no firm evidence that snail hosts can develop levels of resistance to molluscicides that are high enough to affect snail control operations.[2]

1.1.2.2.4 The market for molluscicides and molluscicidíng costs

Paradoxically, those countries that most need molluscicides are often those that are least likely to be able to afford them. Consequently, the market available for existing or new molluscicides is limited. The development costs of a new synthetic molluscicide from initial laboratory trials to market availability have been estimated to be far above the 10 million US dollars mark.[2] It is not surprising, therefore, that no new molluscicide has become available recently.[2]

Cost-effectiveness of mollusciciding is greatest where the volume of water to be treated per person at risk is small. Molluscicides are particularly well suited to relatively arid areas where transmission sites are relatively small and seasonal. The administration of molluscicides may also be cost-effective in large, flowing, or static waterbodies now that it is recognised that schistosomiasis transmission tends to be focal rather than widespread. Even in some large irrigation schemes, where human population density is high and where water-management mechanisms are sophisticated, area-wide administration of molluscicides can be cost-effective.

1.1.2.2.5 Future role of molluscicides in schistosomiasis control

Population-based chemotherapy combined with health education and focal and seasonal mollusciciding are likely to be the most important features of schistosomiasis control operations in high-priority endemic foci. The application of molluscicides must be carefully planned to take advantage of focal and seasonal patterns of transmissions; it also requires efficient management, well-trained and motivated staff, and sufficient funds for supplies and activities. Better strategies and delivery systems will be needed to improve the cost-effectiveness of administering molluscicides. In particular, there is a great need, at present to add to the single compound, praziquantel, that is commercially available.[2]

These introductory paragraphs have served to describe the disease bilharzia and illustrate the key role that certain snail species play in the life cycle of this disease, as well as describe particular drugs that are currently employed to help combat the disease. Thus research culminating in an efficient synthesis of a molluscicide is a valuable exercise. As mentioned previously, warburganal is one of the most potent molluscicides known. The stage is now set to introduce warburganal and become better acquainted with its origin, isolation, valuable properties and structure-activity relationship.

1.2 Origin and isolation of warburganal

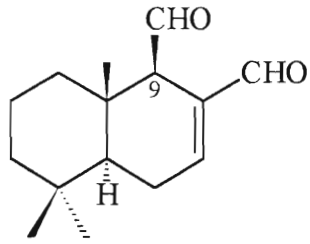
There is little doubt that tropical flora, which are constantly exposed to attack by various parasites such as viruses, bacteria, protozoans, fungi and insects, are confronted with much harsher conditions for survival than their temperate counterparts. This necessarily leads to efficient built-in defence mechanisms and it is for this reason that tropical flora offer a rich and intriguing source for isolating natural products possessing attractive pesticidal or medicinal properties.[5]

Chemical investigation of antifeedant compounds from *Warburgia* plants by Kubo *et al.*[6] in 1976 led to the isolation and characterization of warburganal, a drimane sesquiterpene. The East African genus *Warburgia* (Canellaceae) consists of three species, *W. stuhlmannii*, *W. ugandensis* and *W. salutaris*, ("Muziga" in Swahili), the barks of which are employed widely in folk medicine and as spices in food. Preliminary tests indicated that the bark extract possessed antifeedant activity against army worms *Spodoptera littoralis* and *S. exempta*, widely occurring African crop pests.

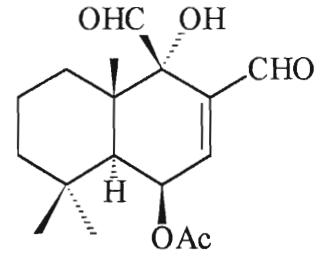
Extracts of the bark were fractionated by using a leaf disc bioassay with corn, containing sucrose and adenosine as feeding stimulants. The test consists of dipping 2 cm diameter leaves into acetone solutions of fractionated extracts for 2 seconds and giving them to insects, with or without control leaves. This led to the isolation of the known sesquiterpenes polygodial **(4)** and ugandensidial **(5),** and hitherto unknown warburganal **(6)**, all of which exhibit very strong antifeedant activities against African army worms.[2] In a separate extraction of the bark of these trees another sesquiterpene was isolated, muzigadial **(7)**, with similar properties to those of warburganal.

As well as the potent anti-feedant properties of warburganal against the African army worm, this compound also exhibits molluscicidal properties. Mentioned in more detail in section 1.3 is how the molluscicidal properties of warburganal were discovered by a routine investigation of a variety of tropical flora which have been known for some time to have molluscicidal properties. The snail test was used in this investigation.

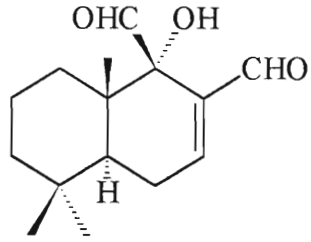
Mashimbye[7] isolated warburganal from the combined petroleum ether and dichloromethane extracts of the bark of *Warburgia salutaris*. Warburganal **(6)** and polygodial **(4)** have also been isolated from other taxonomically unrelated plants, *Polygonum hydropiper* (Polygonaceae) and *Porella vernicosa* (Porellaceae).[7]



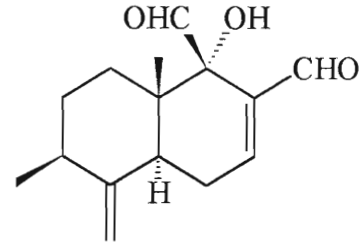
(4) Polygodial



(5) Ugandensidial



(6) Warburganal



(7) Muzigadial

The structure of warburganal **(6)** was elucidated by means of chemical ionization mass spectrometry evidence, UV, IR, ^{13}C & ^{1}H nuclear magnetic resonance (NMR) spectroscopy.[6]

1.3 Applications

Warburganal was discovered to have antifeedant activity against the African army worm, as well as possessing other biological activities such as plant growth regulation, cytotoxic, antimicrobial, antibiotic and molluscicidal properties. Warburganal **(6)** and muzigadial **(7)** are two of the most potent helicocides (snail-killers) isolated from *Warburgia ugandensis* and *W. stulmannii*.[5]

According to electrophysiological tests employing *S. exempta* sensilla (microscopic sensory organs corresponding to taste buds and found at the tip of the maxillary palp), the antifeedant activity of warburganal and muzigadial are comparable. Both warburganal and muzigadial belong to the strongest group of antifeedants against the African army worm found so far.[8]

When guinea pigs were sensitized to polygodial **(4)** by using intradermal injections in Freund's complete adjuvant they showed a high response when the skin was treated with polygodial **(4)**, the primary sensitizer. Moreover, related compounds, e.g. warburganal **(6)**, having the same configuration also resulted in an allergic contact dermatitis. Since it was observed that the reaction was halved when a racemic mixture of warburganal was used; the allergenic response was enantiospecific.[9]

A variety of tropical flora have been known for some time to have molluscicidal properties. For example, *Phytolacca dodecandra, Balanites aegyptica, Polygonum senegalense,* and others, are currently receiving considerable attention as potent molluscicides for the control of bilharzia.[5] The snail test was used to test for molluscicidal activity as it is an extremely simple and rapid assay and snails are known to be hosts to a variety of parasitic nematodes which include schistosomes responsible for the wide-spread occurrence of diseases such as schistosomiasis (discussed in detail in section 1.1). Thus, it is possible that by carrying out a simple molluscicide test, an important lead may be given to agents which could be used to control the schistosomes by killing the schistosome-transmitting snail.[5] Schistosome infection, however, does not necessarily lead to clinical disease. The control of schistosomiasis by use of commercially available molluscicides is increasing in cost; therefore, efforts are underway to find cheaper molluscicides that can be easily obtained from local plant material. The aim is also to try and develop a new and improved method for control of schistosome-transmitting snails without harmful effects on humans, wildlife and vegetation.[10]

1.4 Structure-activity relationship

The fascinating biological activity of warburganal is hardly surprising when one considers the plethora of reactive functionality it possesses. The following studies elucidate the manner in which these functional groups interact with biological systems, focusing on the much-studied anti-feedant activity of warburganal rather than its molluscicidal activity, as the exact biological mode of action linked to the structure of warburganal as a molluscicide has not yet been determined.

The antifeedant activities of compounds **(4)-(7)** were suppressed upon addition of equimolar quantities of L-cysteine to test solutions. This strongly suggests that sulfhydryl groups on the receptors of the army worms are involved in their taste sense. This group will interact with the electrophilic 9β-aldehyde moiety of the antifeedant, in certain cases, irreversibly, thus leading to cessation of feeding.[5] The inhibitory action of L-cysteine suggests that the enal unit acts as a nucleophile (SH) acceptor (Michael fashion) and the 9β-CHO can participate in hydrogen bonding or act as a nucleophilic acceptor which is located at a critical distance from the enal unit.[6] Thus the enal *and* 9β-equatorial CHO moieties (see **Figure 2**) are required for activity. When the 9β-CHO and α-OH groups are swopped, all biological activity is lost. The fact that the axial isomer shown in **Figure 2** is more stable, is presumably due to the unfavourable dipole-dipole interaction between the two equatorial aldehyde groups in the 9β isomer. The oxidation level of the substituents is important, a fact well borne out by a loss of activity incurred when the aldehyde groups are reduced or oxidized. The enhanced activity of warburganal compared to its analogues, suggests that the 9α-OH functionality is also involved, possibly the molecule whose shape best matches the active site on the sensilla. Its mode of biological activity has not yet been determined. In contrast, the weaker activity of ugandensidial **(5)** shows that the acetoxy substituent somehow blocks the fit of the molecule on the sensilla of the army worms.[5] Interestingly, the army worm antifeedants taste 'hot' to humans, whereas all inactive derivatives are devoid of 'hot' taste.[6]

Since interaction with a receptor site sulfhydryl (SH) group appears to be an essential mechanism, at least in the case of the African army worm, it is not surprising to find that these antifeedants exhibit manifold activities, since sulfhydryl groups play crucial roles in many biological systems.

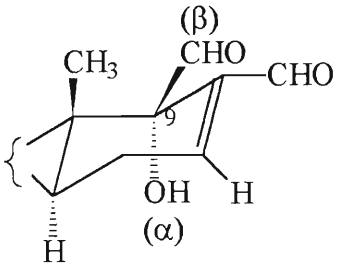
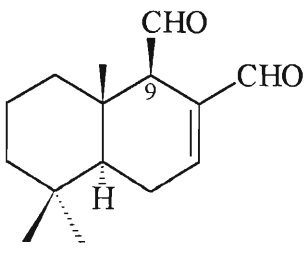


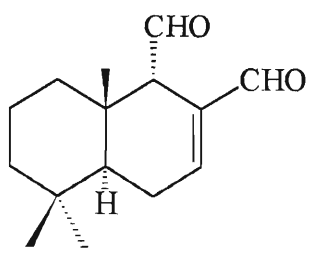
Figure 2. Structure and antifeedant activity correlation.

Based on kinetic data, it has been proposed that the biological activities of the enal-aldehydes are primarily related to their ability to form adducts with amino groups rather than sulfhydryl (SH) groups on the receptors. This was shown when similar reactivity was observed for both polygodial **(4)** and iso-polygodial **(8)** in a reaction with thiols, while the reaction with substrates possessing both amino and sulfhydryl groups was dependent upon the stereochemistry of the 9-aldehyde group, the 9β-isomer exhibiting the higher reactivity. With amines or amino acids, a remarkable difference in reactivity was observed, with the 9α-isomer, iso-polygodial **(8)**, being practically unreactive.[9]

The biological mechanism of 'hot tasting' and antifeedant activity of 1,4-dialdehydes may also result from covalent binding to primary amino groups of the chemoreceptive sites rather than from Michael addition of membrane sulfhydryl groups, even though both are available at the receptor site.[9]



(4) Polygodial



(8) Iso-polygodial

It is hoped that the preceding exposé has served to impress upon the reader the merits of conducting research on warburganal.

1.5 Syntheses of warburganal

There are to date 11 syntheses of warburganal published in the literature.[11-21] However, only those syntheses that involve the use of natural products as starting materials are summarised here, as the attempted synthesis of warburganal described in this dissertation employs a natural product as starting material. There are other syntheses of warburganal which do not begin with natural products and will not be discussed here.[13,14,18] All the above syntheses describe stereoselective preparations of (±)-warburganal, but in two cases, enantioselective syntheses of (-)-warburganal were carried out.[16,17] To put the subject in perspective, the rest of the chapter will be devoted to a review in which published syntheses of warburganal will be described. This review also serves as a means of comparing the synthetic route we employed for the synthesis of warburganal with those of other workers.

1.5.1 Synthesis from geraniol

The following synthesis[21] is of special interest to us as we too decided to capitalize on the functionality vested in geraniol **(9)**. Upon closer inspection, geraniol **(9)** possesses substituents and functionality that seem admirably suited for elaboration into warburganal; namely, the three methyl groups already in position, the reactive hydroxyl moiety, as well as the two double bonds to allow for ring closure and formation of the decalin ring structure.

Geraniol **(9)** (lemonol), is an olefinic terpene alcohol constituting the chief part of rose oil and oil of palmarosa. It is also found in many other essential oils such as citronella,

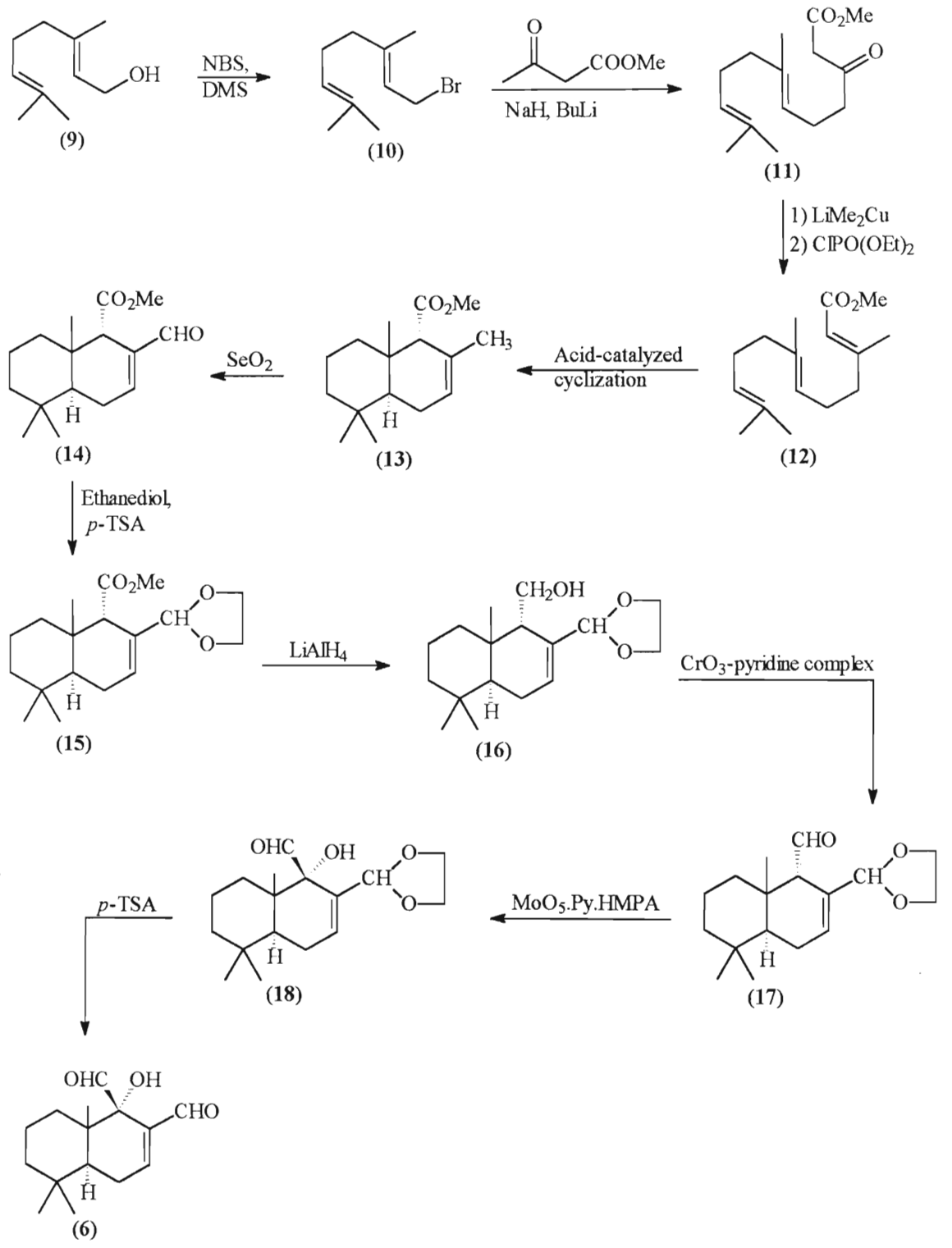
lemon grass, *etc*. It is isomeric with linalool. Geraniol is an oily liquid with a sweet rose odour and it finds most of its use in perfumery and as an insect attractant.

A paper by Oshuka and Matsukawa[21] describes the synthesis of warburganal from methyl (±)-9-epidrimenate **(13)**, which was easily obtained by acid-catalyzed cyclization of methyl farnesoate **(12)**. The methyl farnesoate **(12)** was prepared from geranyl bromide **(10)** and methyl acetoacetate. Geranyl bromide **(10)** was prepared from geraniol **(9)** using *N*-bromosuccinimide.[16] Compound **(11)** was converted into the enol phosphate with diethyl phosphorochloridate and then reacted with lithium dimethylcuprate to give methyl farnesoate **(12)** **(Scheme 1)**.[22]

The 9-epimer **(13)** was oxidized regioselectively with selenium dioxide in dioxane to give an aldehyde ester **(14)** in 61% yield. The aldehyde ester **(14)** was treated with ethanediol and a catalytic amount of *p*-toluenesulfonic acid to give acetal ester **(15)** in 85% yield. Acetal ester **15** was reduced with lithium aluminium hydride in ether at room temperature to give an alcohol acetal **(16)** in almost quantitative yield. The oxidation of **16** with the modified Collin's reagent (chromium trioxide-pyridine complex) gave aldehyde acetal **(17)** in 78% yield.

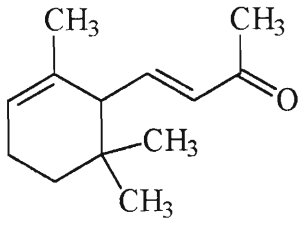
A solution of the lithium enolate, prepared from (±)-isotadeonal 12-monoacetal **(17)** by treatment with one equivalent of lithium hexamethyldisilazide-hexamethyl phosphoric triamide complex, was added to a suspension of oxidoperoxymolybdenum(pyridine)-(hexamethyl phosphoric triamide) (MoO_5.Py HMPA) to give hydroxy aldehyde **(18)** in 24% yield. Since the enolate anion was attacked by the bulky oxidizing agent from the less hindered side, the hydroxy aldehyde **(18)** was obtained stereoselectively. The acetal **(18)** was hydrolyzed to afford racemic warburganal **(6)** in 10 steps and approximately 6% overall yield from geraniol.[21]

Scheme 1

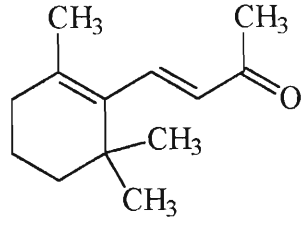

OH
NBS,
DMS
Br
(9)
(10)
O
COOMe
NaH, BuLi
CO2Me
O
(11)
1) LiMe2Cu
2) ClPO(OEt)2
CO2Me
(12)
Acid-catalyzed
cyclization
CO2Me
CH3
H
(13)
SeO2
CO2Me
CHO
H
(14)
Ethanediol,
p-TSA
CO2Me
CH
O
O
H
(15)
LiAlH4
CH2OH
CH
O
O
H
(16)
CrO3-pyridine complex
CHO
CH
O
O
H
(17)
MoO5.Py.HMPA
OHC
OH
CH
O
O
H
(18)
p-TSA
OHC
OH
CHO
H
(6)

1.5.2 Syntheses from β-ionone

Ionone (irisone) is a mixture in which the major constituents are α-ionone **(19)** and β-ionone **(20)**. The latter is a key intermediate in the synthesis of vitamin A. Ionone is isolated from the volatile oil of *Boronia megastigma* Nees., *Rutaceae:* Naves, Parry, a tree indigenous to Australia.



(19)

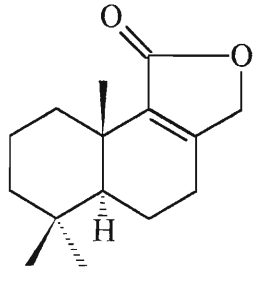


(20)

Ionone is a liquid that has an odour reminiscent of cedar wood and in very dilute alcoholic solution it resembles the odour of violets. Its primary use is in perfumery and it has been known to cause allergic reactions.

β-Ionone again already possesses the three methyl groups on the cyclohexene ring. The double bond in the ring will allow for ring closure to form the second cyclohexane ring of the decalin ring structure as will the ketone group.

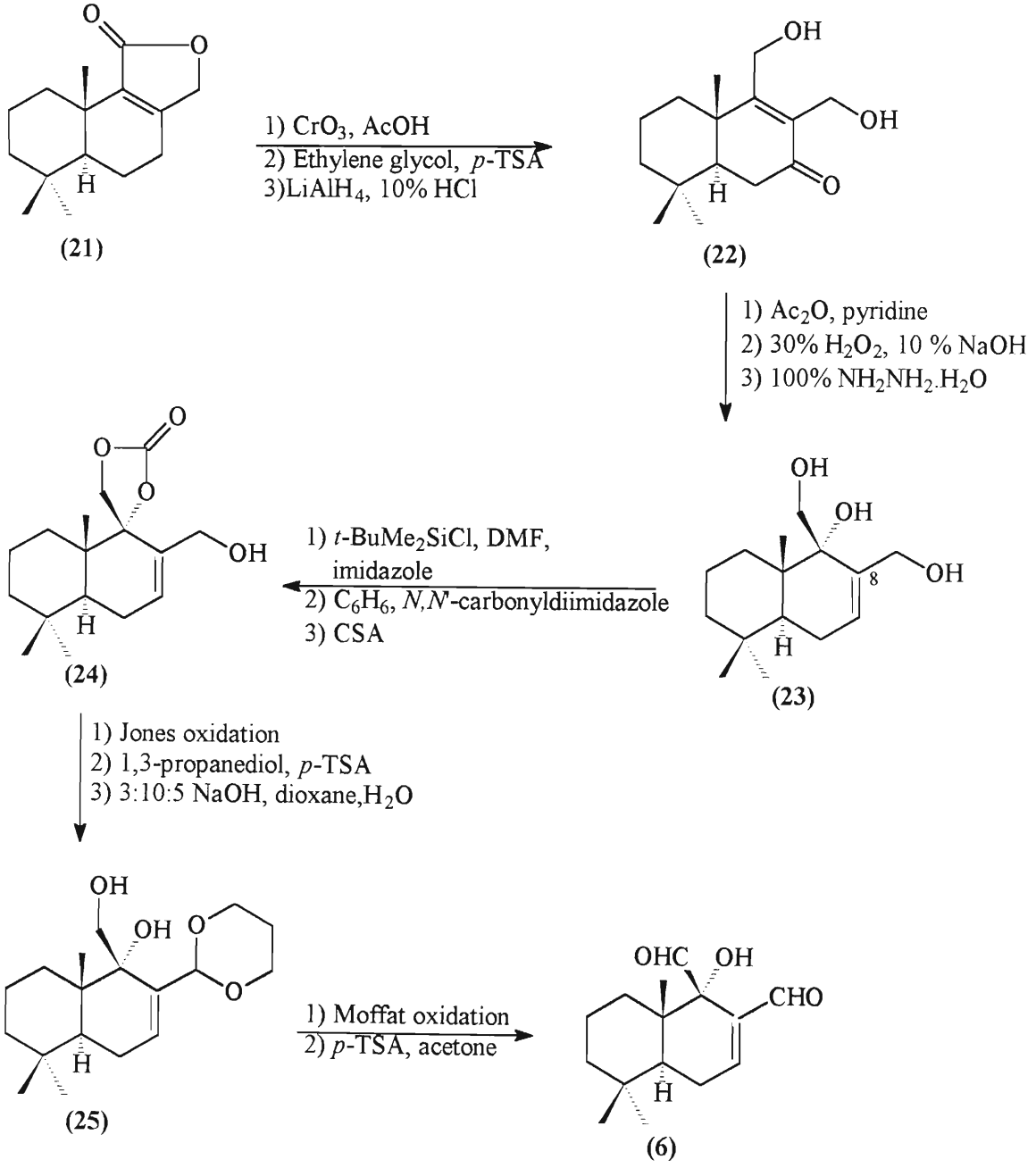
A paper by Nakata, Akita, Naito and Oishi[12] describes the total synthesis of (±)-warburganal **(6)** from readily available (±)- isodrimenin **(21)**. A large-scale preparation of (±)-isodrimenin **(21)** from β-ionone **(20)** was developed in the same laboratory.[24]



(21) Isodrimenin

A number of manipulations were then carried out on isodrimenin **(21)** to introduce the enal moiety as well as the 9β-CHO and 9α-OH moieties onto the decalin ring skeleton to finally reach (±)-warburganal in 14 steps and approximately 7% overall yield from isodrimenin **(21) (Scheme 2)**.[12]

Scheme 2



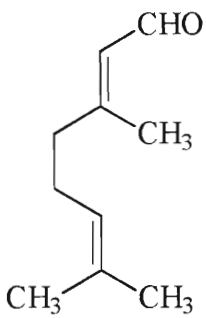
Allylic oxidation of isodrimenin **(21)** with chromium trioxide in acetic acid afforded an α,β-unsaturated ketone, which under standard conditions was protected as a ketal. Reductive opening of the lactone ring with $LiAlH_4$ afforded keto diol **22**. Acetylation of **22** gave the diacetate. Epoxidation of the α,β-unsaturated ketone gave exclusively the α-epoxide. Formation of the allylic alcohol **(23)** was effected by reductive cleavage using hydrazine hydrate. The commendable feature of this synthesis is the methodology developed for selective and effective protection of the three different alcohols present in **23**. Firstly C-8 was protected to give the monosilyl ether. The vicinal alcohols were then protected by being converted into the corresponding carbonate using *N,N'*-carbonyldiimidazole. Treatment with camphorsulfonic acid served to remove the silyl protecting group on C-8 and afforded the allylic alcohol **(24)**. Jones oxidation of **24** gave the enal, the aldehyde group was then protected as an acetal. The carbonate group was cleaved under basic conditions to give the glycol acetal **(25)**. Moffat oxidation produced the desired hydroxy aldehyde and acid hydrolysis of the acetal (*p*-TSA, acetone) gave warburganal **(6) (Scheme 2)**.[12]

These authors have subsequently published an alternative synthesis of warburganal from the same starting material, namely β-ionone.[20] This synthesis is virtually identical to the synthesis presented in **Scheme 2**, *i.e.* the same reagents were used in both cases but in a slightly different order, and therefore this synthesis will not be summarized here. It is suffice to say that warburganal was prepared in 14 steps in 3.2% overall yield from **21** though for comparative purposes.

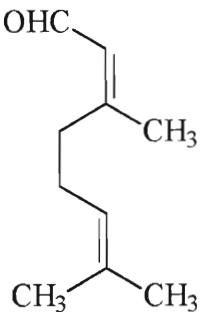
1.5.3 Syntheses from citral

Citral is a major constituent (75-80%) of the volatile oil of lemon grass, *Cymbopogon citratus* (DC.) Stapf, and of *Cymbopogon flexuosus* (Nees) Stapf, *Gramineae*. It is also present to a limited extent in oils obtained from verbena, lemon and orange. Citral from natural sources is a mixture of two geometric isomers, geranial **(26)** and neral **(27)**.

Geranial **(26)** is a pale yellow oily liquid with a strong lemon odour, whereas neral **(27)**, also a pale yellow oily liquid, has an odour that is sweeter but less intense than geranial.



(26)



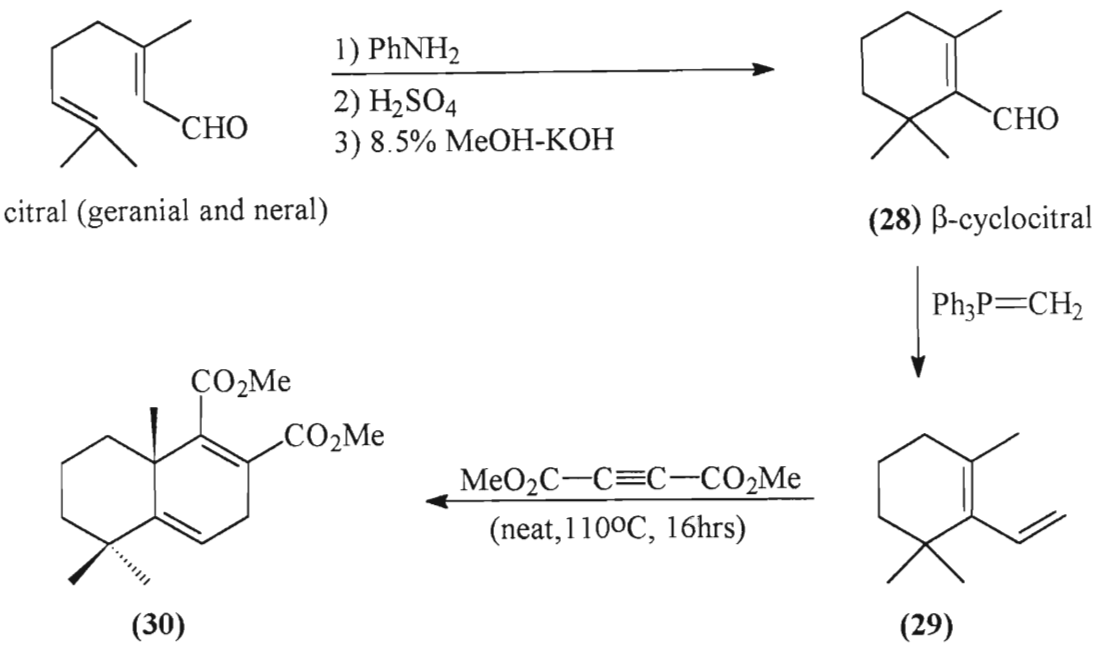
(27)

Citral finds its uses in the synthesis of vitamin A, ionone and methylionone and as a flavour for fortifying lemon oil. It is also used in perfumery for its citrus effect in lemon and verbena scents, in cologne odours and in perfumes for coloured soaps. Citral is unstable in the presence of alkalies and strong acids and will cause discolouration of white soaps and alkaline cosmetics.

Citral, like geranial possesses the three methyl groups required for warburganal as well as the double bonds in suitable positions for the ring closure to form the cyclohexene ring. The aldehyde moiety can also be used as a synthetic handle onto which new functional groups may be added to form the second cyclohexane ring and thus the decalin ring structure common to warburganal.

Tanis and Nakanishi[11] describe a synthesis of warburganal from 1-vinyl-2,6,6-trimethyl-1-cyclohexene **(29)** which is prepared in 92% yield by the addition of methylene triphenylphosphorane to β-cyclocitral **(28)** which in turn is synthesized from citral in three steps. The first step requires the preparation of the Schiff's base using aniline, secondly, cyclization with sulfuric acid and then isomerization of the α- and β-cyclocitral to β-cyclocitral **(28)** using 8.5% methanolic KOH **(Scheme 3)**.[25]

Scheme 3



citral (geranial and neral)

(28) β-cyclocitral

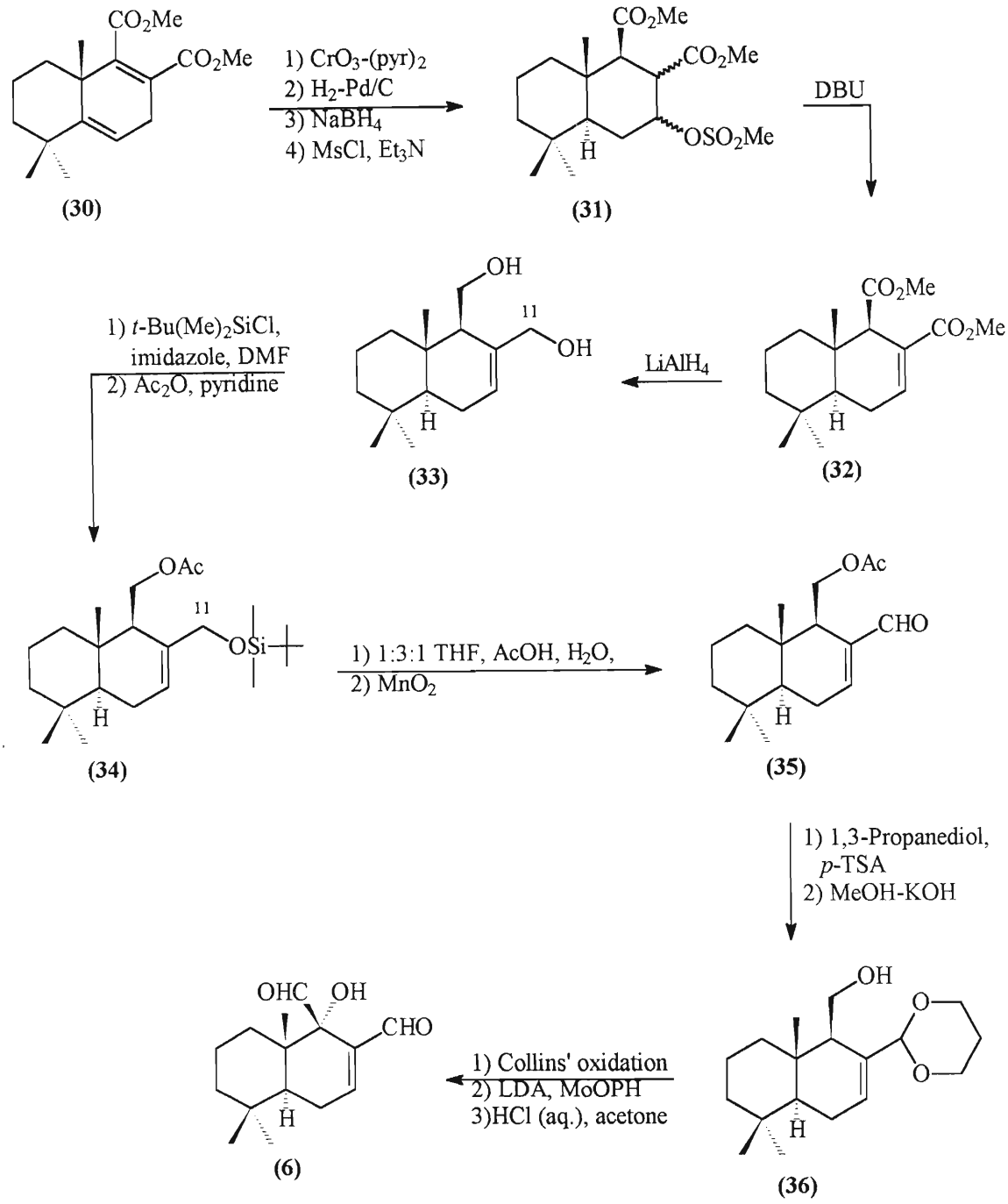
(30)

(29)

The Diels-Alder reaction of dimethyl acetylenedicarboxylate with 1-vinyl-2,6,6-trimethyl-1-cyclohexene **(29)** provided the diester **(30)** in 83% yield **(Scheme 3)**. In this way the decalin ring structure was formed. A further 15 steps were performed to reach warburganal **(6)** in a 20% overall yield from the diene **(29)** **(Scheme 4)**.[11]

The diester **(30)** underwent allylic oxidation with chromium trioxide-pyridine complex to produce a cyclohexadienone that was hydrogenated to give the desired *trans*-fused decalin ring system. The ketone was reduced with sodium borohydride and treatment of the resulting free alcohol with methanesulfonyl chloride provided mesylate **31**.

Scheme 4



Heating of the mesylate **(31)** under reflux in benzene with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) initiated elimination of methanesulfonic acid which gave an allylic ester **(32)**, reduction of which provided diol **(33)**. Fortuitously the C-11 alcohol was selectively protected using *tert*-butyldimethylsilyl chloride and imidazole in DMF to give the

monosilyl ether, leaving the unprotected alcohol free to undergo acetylation with acetic anhydride and pyridine as base. The resultant acetate **(34)** was hydrolyzed to the hydroxy acetate and manganese dioxide oxidation of the allylic hydroxyl function afforded enal **(35).**

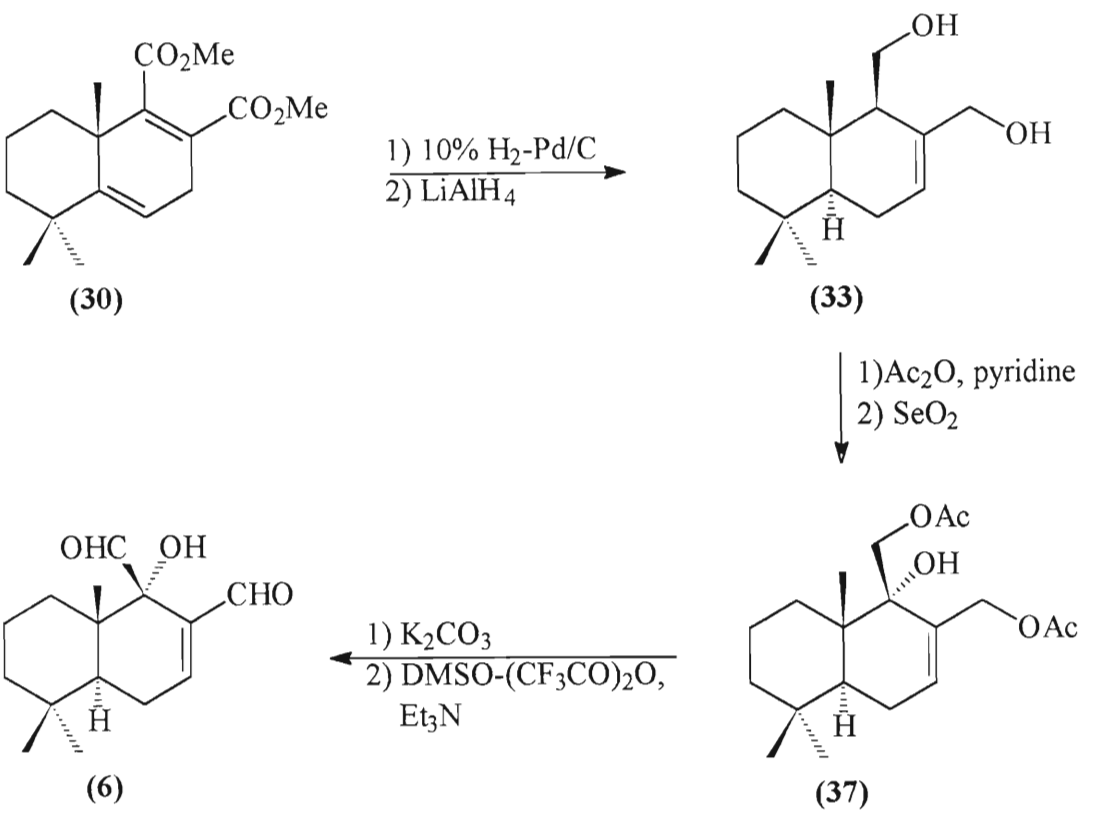
Treatment of enal **35** with 1,3-propanediol and a trace of *p*-TSA gave the acetoxy acetal that was saponified with methanolic potassium hydroxide to produce alcohol **(36)**. Upon Collins' oxidation, the desired monoprotected dialdehyde was formed. Formation of the enolate of the aldehyde using LDA and treatment with MoO_5.pyridine.HMPA provided the hydroxyaldehyde. The acetal group was then removed with 2.5% aq. HCl in acetone to give warburganal **(6) (Scheme 4)** in 16 steps (from **28**) in an overall yield of 20%.[11]

Hollinshead *et al.*[15] also prepared the diester **(30)** as shown in **Scheme 3**. Their conversion of this compound into warburganal required only 6 steps **(Scheme 5)** (*cf.* 16 steps carried out by Tanis and Nakanishi depicted in **Scheme 4**). This comparison lends credence to the fact that the search for shorter, more efficient syntheses is indeed possible and therefore a worthwhile endeavour.

Typical reductive/isomerising conditions (10% H_2-Pd/C in methanol in the presence of acid catalysts) gave smooth conversion of **(30)** into the allylic ester which was reduced with $LiAlH_4$ to diol **(33)**. These two intermediates also appear in **Scheme 4**. The diol **(33)** was protected as the diacetate by treatment with acetic anhydride and pyridine and then allylic oxidation with SeO_2 served to introduce the 9-OH group to give **(37)**. Hydrolysis of the acetate groups of **37** with potassium carbonate in methanol gave the triol in quantitative yield. Oxidation with DMSO-trifluoroacetic anhydride at -50°C, followed by treatment with triethylamine afforded warburganal **(6)** in 7 steps and 20% yield from the diene **(28) (Scheme 3 & 5)**.[15]

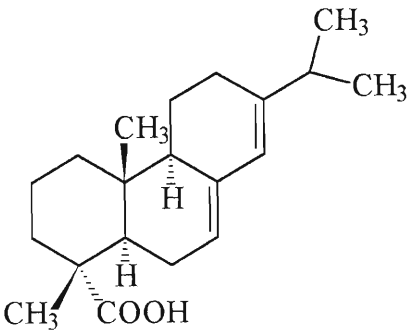
The same synthesis is reported by Ley and Mahon.[19] To date this is the most efficient and shortest route to warburganal with the highest overall yield reported.

Scheme 5



1.5.4 Synthesis from abietic acid

Abietic acid **(38)** (sylvic acid) is a widely available diterpene, prepared by isomerisation of rosin. Rosin is a yellow resin, also known as colophony or abietic anhydride. It is obtained from the residue left behind after distilling off the volatile oil from *Pinus palustris* and other species of *Pinus, Pinaceae.* Rosin is chiefly produced in the USA and is composed of approximately 90% resin acids and 10% neutral matter. Of the resin acids about 90% are isomeric with abietic acid and the other 10% is a mixture of dihydroabietic acid and dehydroabietic acid.

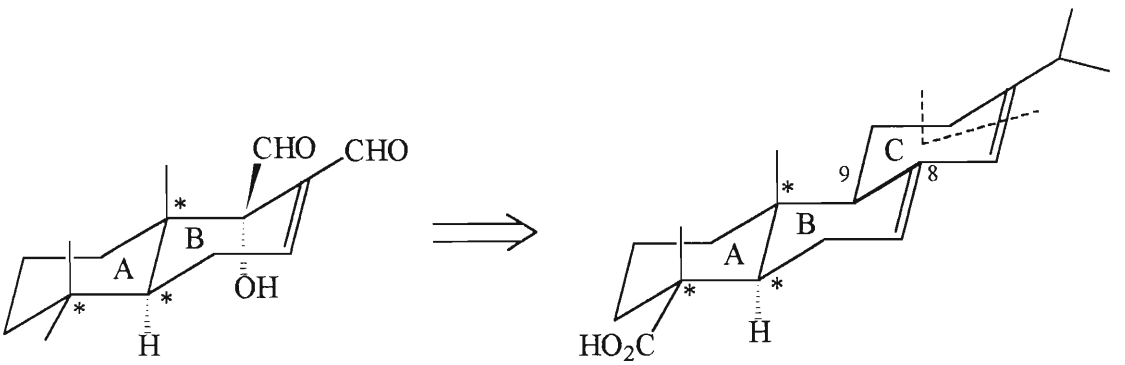


(38) Abietic acid

Abietic acid is used in the manufacture of commercially important esters (ester gums), e.g., methyl, vinyl and glyceryl esters for use in lacquers and varnishes. It is also used in the manufacture of "metal resinates", soaps and plastics. Abietic acid assists the growth of lactic and butyric acid bacteria.

A total synthesis of warburganal has been reported from abietic acid by Okawara *et al.*[16] Since the decalin ring structure is already in place, this synthesis deals with manipulations of the functional groups on the existing skeleton. Abietic acid was considered to be a good chiral template for the elaboration of the warburganal skeleton, since the three chiral centres of L-abietic acid can be incorporated into warburganal by selective and oxidative cleavage of the C ring as shown by the dotted lines in **Scheme 6**.[16] Abietic acid already possess the decalin ring structure and has two of the three methyl groups in position, with the acid moiety easily converted into the third methyl group. Facile opening of the third ring allows installation of the necessary aldehyde and hydroxy groups at positions 8 and 9. The endocyclic double bond of ring B is an added bonus and can be left untouched as it is a structural feature of warburganal **(6)**.

Scheme 6

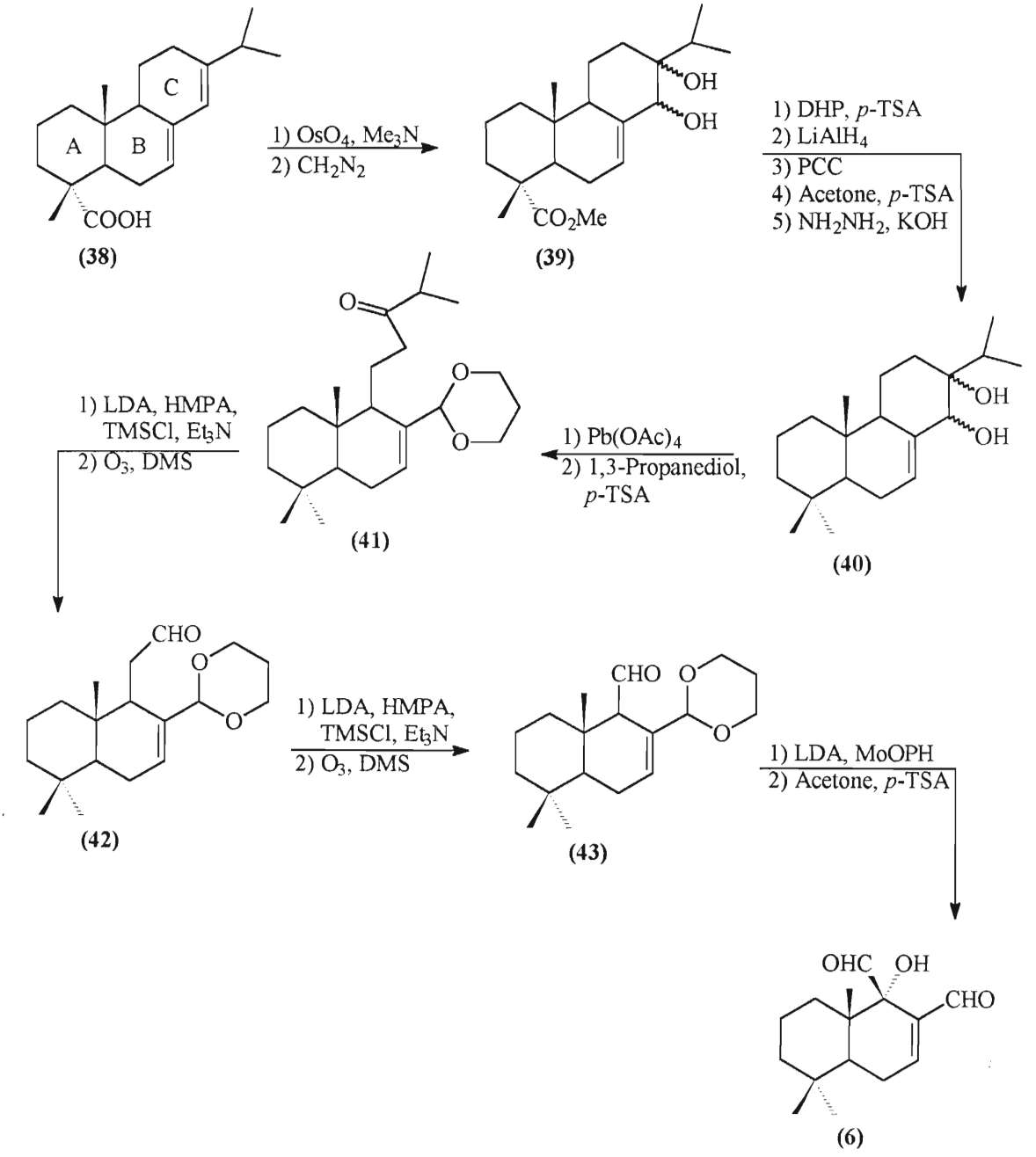


(6) **(38)** Abietic acid

Abietic acid **(38)** was successfully converted into warburganal **(6)** in 15 synthetic steps in 9% overall yield. **(Scheme 7)**.[16]

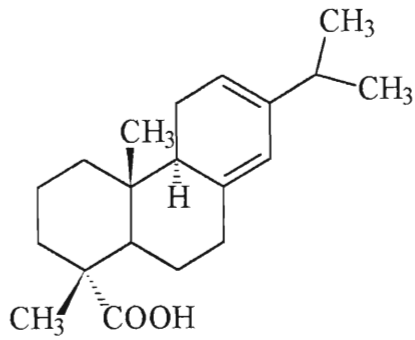
Regioselective osmylation of the double bond of ring C of **38** afforded a mixture of α- and β-diols that were directly converted to the corresponding methyl ester **39** using diazomethane. Thus *gem*-dimethyl β-glycol **(40)** was obtained by the following steps: protection of the glycol **39** with dihydropyran; reduction of the methyl ester with $LiAlH_4$; subsequent oxidation to the aldehyde with PCC; removal of the dihydropyran group and Wolff-Kishner reduction of the aldehyde with NH_2NH_2/KOH. The diol **40** then suffered selective oxidative cleavage affording **43** in seven steps as shown in **Scheme 7** (oxidative ring cleavage with $Pb(OAc)_4$; protection of the aldehyde group gave **41**; regioselective silyl enol ether formation and ozonolysis afforded aldehyde **42**; further silyl enol ether formation, ozonolysis and subsequent treatment with MoO_5.Py.HMPA, provided the penultimate precursor, hydroxy aldehyde **43**). Finally warburganal **(6)** was obtained by unmasking the aldehyde group at C-8 with *p*-TSA **(Scheme 7)**.[16]

Scheme 7


C
A
B
COOH
(38)
1) OsO_4, Me_3N
2) CH_2N_2
OH
OH
CO_2Me
(39)
1) DHP, *p*-TSA
2) $LiAlH_4$
3) PCC
4) Acetone, *p*-TSA
5) NH_2NH_2, KOH
OH
OH
(40)
1) $Pb(OAc)_4$
2) 1,3-Propanediol,
p-TSA
O
O
O
(41)
1) LDA, HMPA,
TMSCl, Et_3N
2) O_3, DMS
CHO
O
O
(42)
1) LDA, HMPA,
TMSCl, Et_3N
2) O_3, DMS
CHO
O
O
(43)
1) LDA, MoOPH
2) Acetone, *p*-TSA
OHC
OH
CHO
(6)

1.5.5 Synthesis from levopimaric acid

Levopimaric acid **(44)** (β-pimaric acid) has been isolated from American pine oleoresin, from French galipot, from *Pinus maritima* and *Pinus palustris.* Galipot is the thick syrupy component of the gum turpentine medium, containing the settled crystalline acids or so-called "galipot".



(44) Levopimaric acid

Levopimaric acid possesses many of the same structural features as abietic acid with the main difference being the absence of the double bond in the second ring which needs to be introduced at some stage in the synthesis.

A paper by Ayer and Talamas[17] describes the transformation of levopimaric acid **(44)** into warburganal **(6)**. A large number of manipulations and reactions were carried out on the tricyclic skeleton to finally reach the desired target molecule, warburganal in 15 steps and 2.7% overall yield. This synthesis is long and complicated with a large number of alternative steps. A summary of this synthesis will therefore not be included because of its length and concomitant inefficiency.

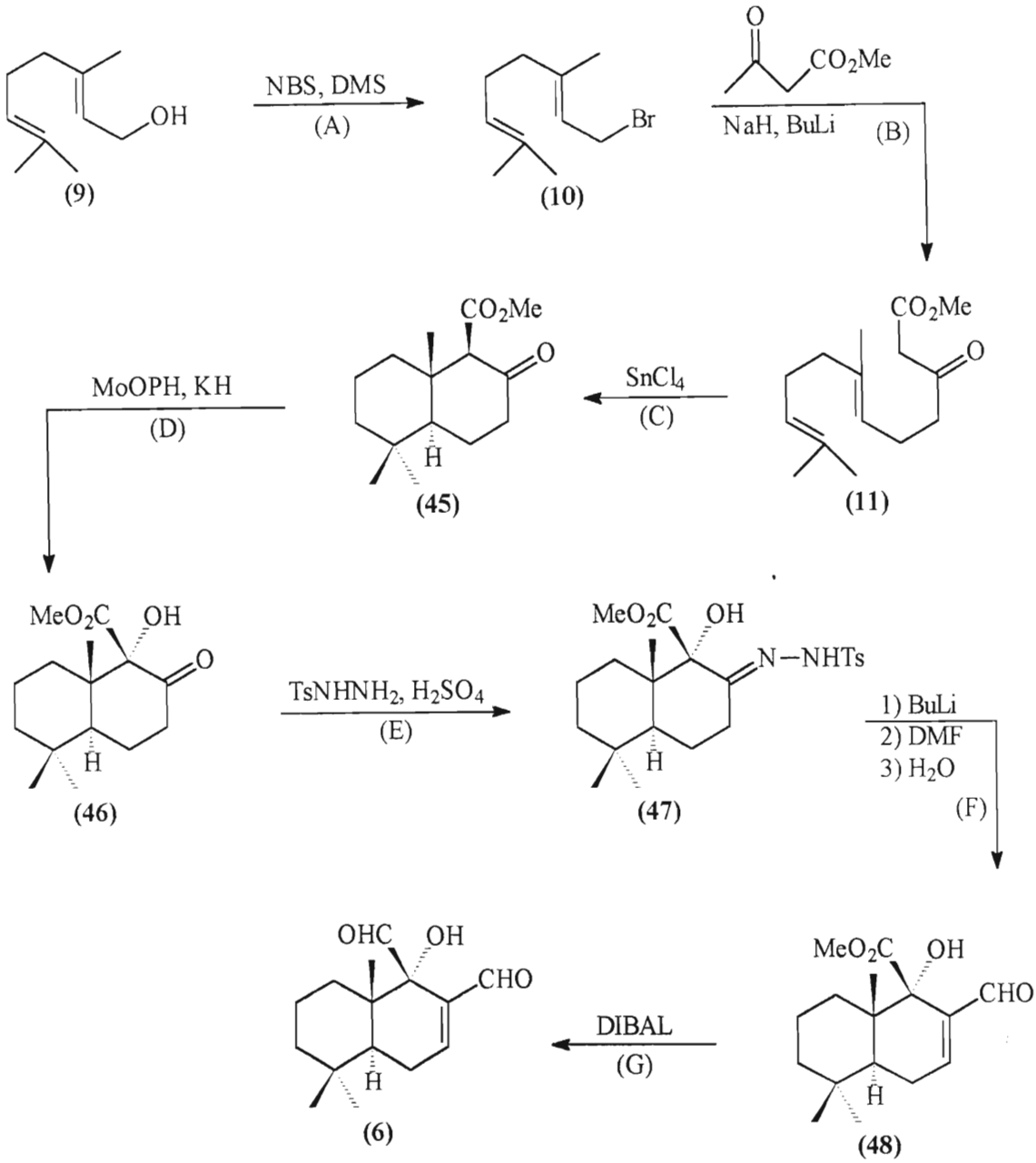
2. Discussion

2.1 Aim

The aim of this project was to synthesise warburganal in as efficient and cost-effective a way as possible. There are various reasons for our choosing warburganal for stereoselective total synthesis. Firstly, warburganal is a comparatively simple target molecule and thus the possibility of completing a synthesis of it within the timeframe of a Masters degree is not unrealistic. You may be asking yourself, why bother with another total synthesis of this compound when we have just seen many examples of published syntheses? The answer to this question lies in the fact that many of the published synthetic routes are relatively long-winded and low-yielding. We thought that our route might prove more efficient and higher yielding and thus justify the endeavour. The third and possibly most important reason draws impetus from the varied and beneficial biological properties of this natural product. Pharmacologists, in order to further assess the biological activity of warburganal, need larger quantities of material. If we can formulate an efficient high-yielding synthesis of this compound, our synthesis could in principle be used to make larger quantities of this intriguing natural product for subsequent testing. Thus we will have made a significant contribution to this branch of science. A final, somewhat more esoteric reason, is that the synthesis of warburganal (and, in general, of sesquiterpenes possessing complex structures and several stereogenic centres) is a very challenging and creative intellectual pursuit.

Scheme 8 shows the proposed synthetic route we envisaged employing for the synthesis of warburganal from geraniol (*c.f.* **scheme 1** from section 1.5.1). The proposed reagents for each step are also included in the scheme. Each of the individual steps will be discussed in the following sections as well as the synthesis of model compounds that were used as 'practice' substrates in order to optimise conditions and verify the feasibility of the reactions on warburganal precursors.

Scheme 8



Geraniol **(9)** was viewed as an ideal starting material, being a terpene and possessing tailor-made double bonds and methyl groups in relative positions for elaboration into warburganal. A nucleophilic substitution of bromide with the bis-enolate derived from methyl acetoacetate would introduce the missing number of carbon atoms **(11)** required for ring closure to form the decalin ring skeleton of warburganal **(45)**. Systematic introduction

of the required groups to this skeleton would then afford warburganal **(6)**. The addition of an α-hydroxyl group to the ester **(45)** would be the first addition and then a Shapiro reaction would be employed to transform the ketone into an enal, passing through the tosylhydrazone intermediate **(47)**, to afford the allylic aldehyde **(48)**. A final reaction required to obtain warburganal is the chemoselective reduction of the ester group of **48** to the aldehyde and thus affording warburganal **(6)**.

It is important to note that the stereochemistry depicted in **Scheme 8** denotes relative stereochemistry only. Therefore, although compounds in the scheme are shown as a specific enantiomer, this synthetic route would produce every compound as a racemate.

What precedents can we draw on in support of the proposed synthetic route outlined in **Scheme 8**? Some of the steps have direct precedents in already well-known published work, but others are relatively unexplored. The following step-by-step analysis gives an account of both the encouraging features and the potential problems that are expected in the proposed synthetic route.

Step A: The synthesis of geranyl bromide **(10)** from geraniol **(9)** involves a straightforward nucleophilic substitution of hydroxyl with bromide. The brominating reagent that we hoped to employ for this is *N*-bromosuccinimide based on work published by Corey *et al.*[23]. No problems were envisaged except for the instability of the geranyl bromide, which would probably have to be prepared immediately prior to use in the subsequent reaction.

Step B: The alkylation of the generated dianion of methyl acetoacetate with geranyl bromide **(10)** to provide keto ester **11** is precedented by a method of White *et al.*[26] and Sum and Weiler.[22] With both published yields being relatively high and the reaction relatively straightforward, no problems were expected for this step.

Step C: Stannic chloride was chosen as the Lewis acid of choice for this most important step involving ring fusion to form the decalin ring skeleton of warburganal **(45)**. The

reason being that this ring fusion carried out by White *et al.*[26] could be effected in one extremely easy step, whereas most other Lewis acid catalysed ring closures involved an additional preparative step before closure could take place, thus lowering yields and increasing the cost and length of the overall synthesis. These alternative methods will be discussed at a later stage.

Step D: There are no literature precedents to be found for this α-hydroxylation of a β-keto ester although α-hydroxylation of esters is well known.[17] MoOPH was chosen to afford the α-hydroxy ester **46** because reactions with this oxidant are generally high yielding and easily performed. The problems envisaged are that the reaction has shown to be troublesome with simpler β-keto ester systems due to interaction between the organic substrate and the bulky molybdenum complex. Enolate oxidations using this reagent are sensitive to the structure of the substrate and by-products are frequently formed.

Steps E and F: Literature precedent for these steps are found in the publications by Hiegel and Burk[27] and Traas *et al.*[28] The formation of the tosylhydrazone **47** ought to be straightforward. The only problem foreseen would be the close proximity of the ester group, which may retard formation of the tosylhydrazone due to steric hindrance. Step F should pose no problem once **47** is prepared. This is not a typical Shapiro reaction where just the alkene is generated, but rather a trapping experiment where a formyl group is introduced by attack of DMF by the intermediate vinylic carbanion to afford **48**. However, because of the acidity of the hydroxyl group, the possibility exists that the OH may need to be protected to prevent formation of unwanted side-products.

Step G: Finally to complete a total synthesis of **6**, all that is required is the chemoselective reduction of the methyl ester of **48** to afford aldehyde **6**. Zakharkin and Khorlina[29] have converted many esters to aldehydes with great success, although the reduction has not been attempted on this particular compound before. Care would have to be exercised to prevent reduction of the enal group. Protection of the aldehyde as an acetal prior to reduction may present a solution to this problem should it arise.

2.1.1 Summary of aims

In brief, the chief aims of this project were:

- To synthesise the relatively simple target molecule warburganal in as few and as high-yielding steps as possible.

- To provide an economical synthetic pathway to warburganal to enable larger quantities of this intriguing natural compound to be made for further testing.

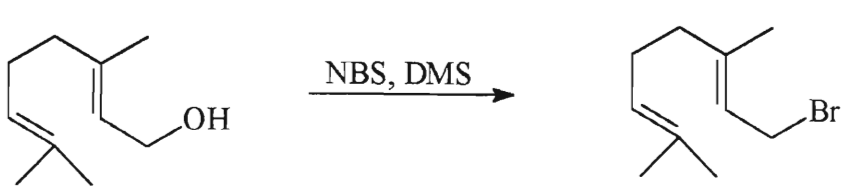
- To provide a very challenging and creative intellectual pursuit.

The following sections will give an account of the successes and failures incurred when applying the proposed methodology I have just discussed. I will also proceed to describe each step in detail as well as the problems encountered, unsuccessful attempts and model reactions carried out to verify the feasibility of certain steps.

2.2 Preparation of geranyl bromide

The first step in our proposed synthesis of warburganal involved the preparation of geranyl bromide **(10)** from geraniol **(9)** **(Scheme 9)**. An adaptation of the method of Corey *et al.*[23] was used which involves the substitution of a hydroxyl group by a bromine atom under neutral conditions.

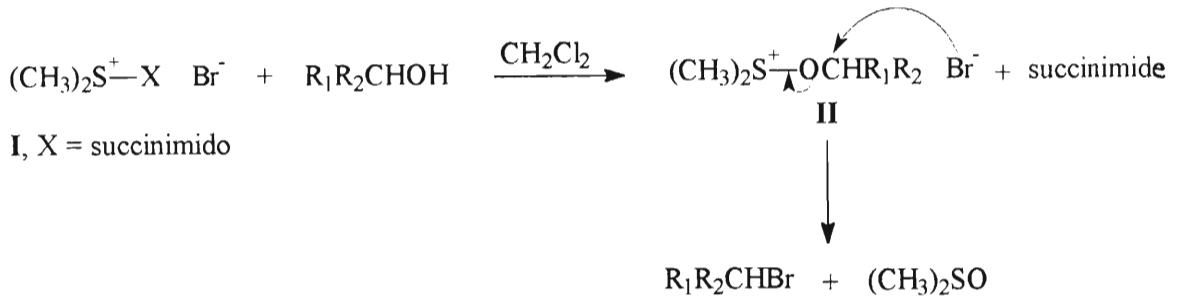
Scheme 9



(9) **(10)**

The use of a 1:1 complex between dimethyl sulfide (DMS) and *N*-bromosuccinimide (NBS) converts alcohols to the corresponding bromides according to the mechanism shown below **(Scheme 10)**.

Scheme 10



I, X = succinimido

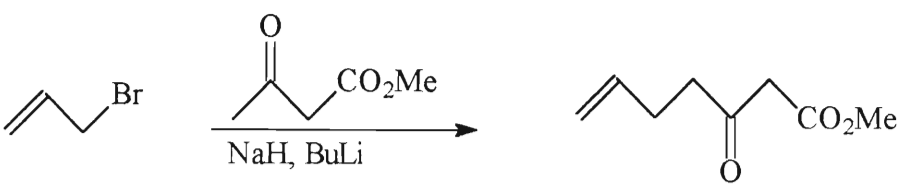
Reaction of sulfonium bromide **I** with the alcohol (geraniol in this case) afford the oxysulfonium derivative **II**. The oxysulfonium intermediate is relatively unstable and suffers nucleophilic attack by bromide to form the corresponding bromide (geranyl bromide). A thermodynamic driving force for the reaction is the formation of the S=O in the resulting DMSO.

The authors reported a yield of 82% of geranyl bromide.[23] Our comparatively moderate yield of 45% may be attributed to the fact that the reported product was used without further purification, whereas in our case we thought it prudent to purify the product prior to further use. It was observed that geranyl bromide readily decomposes and was therefore used shortly after purification. The reported method was performed on a milligram scale whereas we performed the reaction on a 10 g scale which may be another contributing factor for the large difference in yields. The product was characterised by ^{1}H & ^{13}C NMR spectroscopy.

2.3 Model reaction of allyl bromide with methyl acetoacetate

A model reaction using allyl bromide **(49)** instead of geranyl bromide **(10)** was performed as above to test if the dianion of methyl acetoacetate was being generated and that the alkylation was occurring at the terminal locale of methyl acetoacetate **(Scheme 11)** to afford methyl 3-oxo-hept-6-enoate **(50)**. This was confirmed by ^{1}H NMR spectroscopy. The vinyl protons are readily visible in the upfield region (4.95-5.92 ppm) of the ^{1}H NMR spectrum and the alkene carbons at 115.60 & 136.51 ppm in the ^{13}C NMR spectrum.

Scheme 11



(49) **(50)**

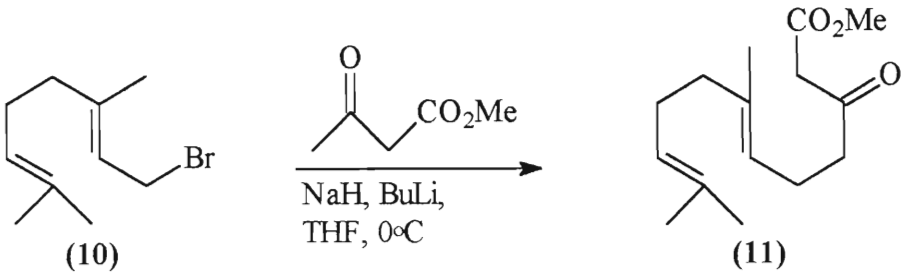
At this stage we were satisfied that the method was sound and we could now investigate the reaction using geranyl bromide to prepare the intermediate required for the cyclization step.

2.3.1 Preparation of methyl 3-oxo-7,11-dimethyldodeca-6*E*,10-dienoate (11)

The dianion of methyl acetoacetate was generated with sodium hydride and *n*-butyllithium and was then alkylated with the geranyl bromide **(10)** to afford **11** in 58% yield **(Scheme 12)** .[26] The sodium hydride abstracts the proton alpha to the two carbonyl groups and the *n*-BuLi abstracts the terminal proton alpha to the keto carbonyl group of the methyl acetoacetate.[30] The reason being that the sodium hydride abstracts the most acidic proton first *i.e.* the proton alpha to the ester and ketone groups. Thus, when *n*-BuLi is added, it

will abstract a terminal acidic proton. For some reason as yet unknown, the yield for this alkylation reaction is rather low, being only 58%, disappointing in comparison with the literature yields of 95%[22] and 61%.[26] Although the method used was identical to that of White *et al.*[26], it was found that it was necessary to purify the crude reaction mixture by distillation as well as by column chromatography to ensure that the resulting product was homogeneous before proceeding to the next synthetic step.

Scheme 12



(10) **(11)**

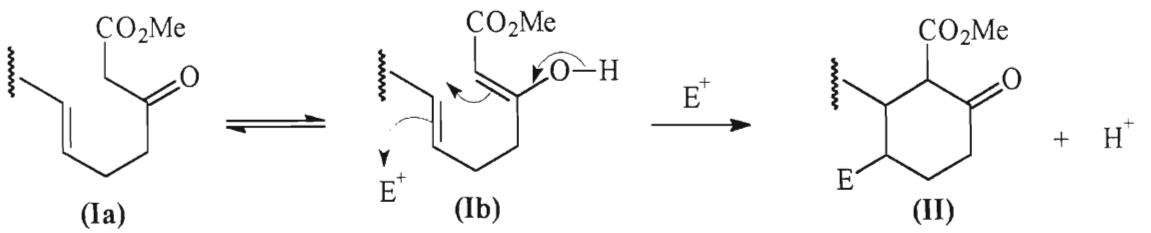
Although distillation produced material sufficiently pure to proceed to the next step of the synthesis, in the interests of obtaining unambiguous NMR spectra it proved advisable to carry out further purification by column chromatography. This extra purification step is optional as no difference in the purity of the cyclized product **(45) (Scheme 8)** was observed upon use of the unpurified product **(11)** or the purified product. This product **(11)** now possesses the necessary number of carbon atoms and double bonds in the appropriate positions to facilitate ring closure and formation of the decalin ring structure. The stage was now set for the next and most important step – ring closure.

2.4 Decalin ring formation

The biomimetic cyclization of polyolefins pioneered by Eschenmoser[31] and by Stork[32], and developed extensively by Johnson[33], has proved to be exceedingly useful for the construction of terpenoid ring systems. Extending this methodology to olefinic β-keto esters is attractive for several reasons, not the least of which are the ready accessibility of

β-keto ester precursors, as well as the favourable prospect of elaboration of residual functionality after cyclization. Moreover, the β-keto ester moiety, *via* its enol tautomer, should be a particularly effective participant in the annulation process.[34] White *et al.*[26] were attracted to olefinic β-keto esters **(Ia)** as the cyclization substrates in the belief that the enol tautomer **(Ib)** would represent a prize candidate for the electrophile-mediated ring closure depicted in **Scheme 13**.

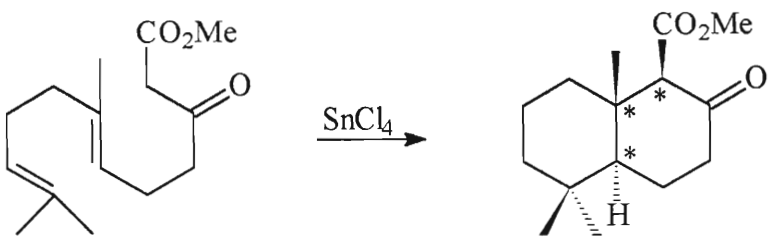
Scheme 13



(Ia) **(Ib)** **(II)**

The following cyclization **(Scheme 14)** of broad potential utility in diterpene synthesis affords direct entry into a decalin system. The method outlined by White *et al.*[26] was followed with the following crucial modification. A few drops of water were added to the reaction mixture prior to addition of the stannic chloride (even though water-saturated dichloromethane was used as the solvent). By trial and error it was found that a failure to add additional water led to no product being formed (contrary to the findings of White *et al.*[26]). However, addition of a few drops of water led to the formation of the required product, which was isolated by column chromatography. However, too much water led to the formation of large amounts of tin salts and sabotaged the reaction. The water probably plays a role in activating the stannic chloride by causing formation of HCl gas. The electrophile could then be considered to be H^+. This is therefore an electrophile-mediated ring closure. It could be that the water-saturated dichloromethane did not contain enough water to allow this process to occur and hence the need for a few drops more in this case.

Scheme 14

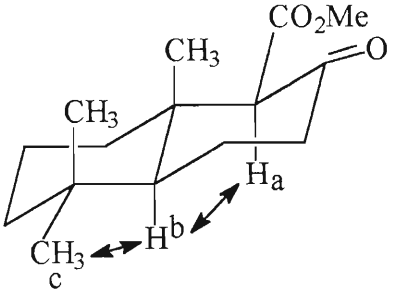


(11) **(45)**

β-Keto ester **(11)**, upon treatment with stannic chloride in dichloromethane, gave the bicyclic product in 41% (*cf.* 53% obtained by White *et al.*[26]). The fact that polymeric by-products were obtained probably accounts for the moderate yield. The melting point obtained of 78-80°C is slightly lower than the literature value of 83-84.5°C[26]. This indicates that the product was not entirely pure although no impurities could be detected using NMR spectroscopy. There was close enough agreement between the NMR spectral data obtained and those of White *et al.*[26] COSY and HETCOR NMR spectra confirmed the structure shown and NOE experiments were run on this product (45) to confirm the relative stereochemistry at the chiral centres (*) **(Scheme 14)**.

A useful feature of the nuclear Overhauser effect (NOE) is that it gives information complementary to that obtained from NMR coupling constants. NMR coupling constants inform one about the bonding relationships in a structure, but the NOE is a direct through-space effect, and helps in the determination of molecular geometry by exposing groups that are in spatial proximity.

By irradiating Ha, a 3-spin system was revealed consisting of the proton irradiated, Hb and CH_3c. This matches the proposed stereochemistry and confirms the *trans* ring fusion and equatorial orientation of the ester substituent.



(45)

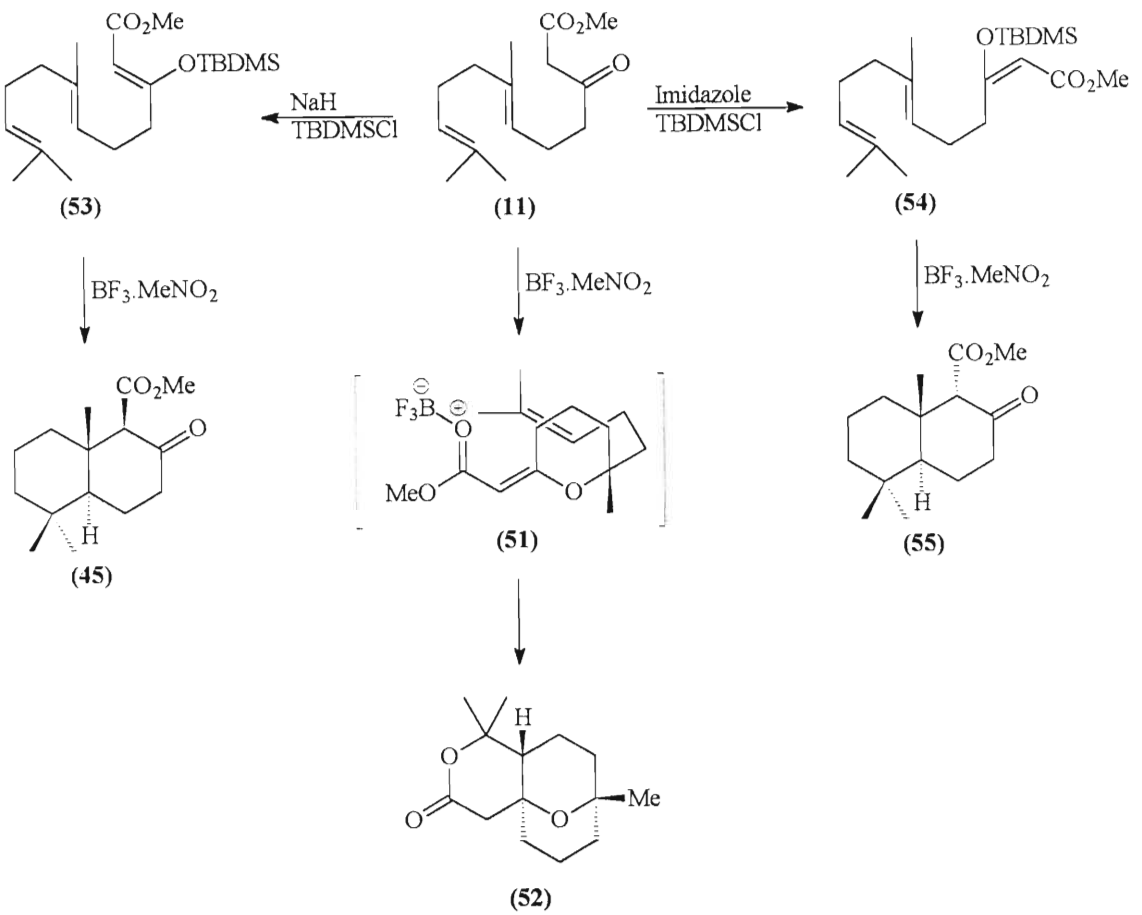
2.4.1 Alternative cyclization procedures

2.4.1.1 Cyclization involving the Lewis acid catalyst $BF_3{\cdot}MeNO_2$

An alternative cyclization procedure for the precursor above **(11)** has been recorded in the literature.[35,36] The method described below has been classified as a cationic sequence and involves a Lewis acid-promoted biomimetic polyene cyclization to form a sesquiterpene.[35] Direct cyclization of the β-keto ester **(11)** with $BF_3.MeNO_2$ at -20°C, furnished the unexpected tricyclic lactone **(52)** in 84% yield by a process that can be formulated as either an inverse electron demand [4 + 2] cycloaddition *via* intermediate **51** or a cationic process. On the other hand, cyclization of the (*Z*)- and (*E*)-siloxyenoates **(53 & 54)** provided the equatorial and axial β-keto esters **45** & **55** in 70% and 90% yield, respectively **(Scheme 15)**.[35]

The first step in this scheme was attempted *i.e.* the synthesis of silyl enol ether **53**. However this reaction proved to be unsuccessful as only starting material was isolated. This alternative cyclization was not pursued further as the previous cyclization with $SnCl_4$ proved to be shorter, involving one step instead of two to give the cyclized product **(45)**, and also avoids working with BF_3 gas which is necessary when preparing $BF_3{\cdot}MeNO_2$.

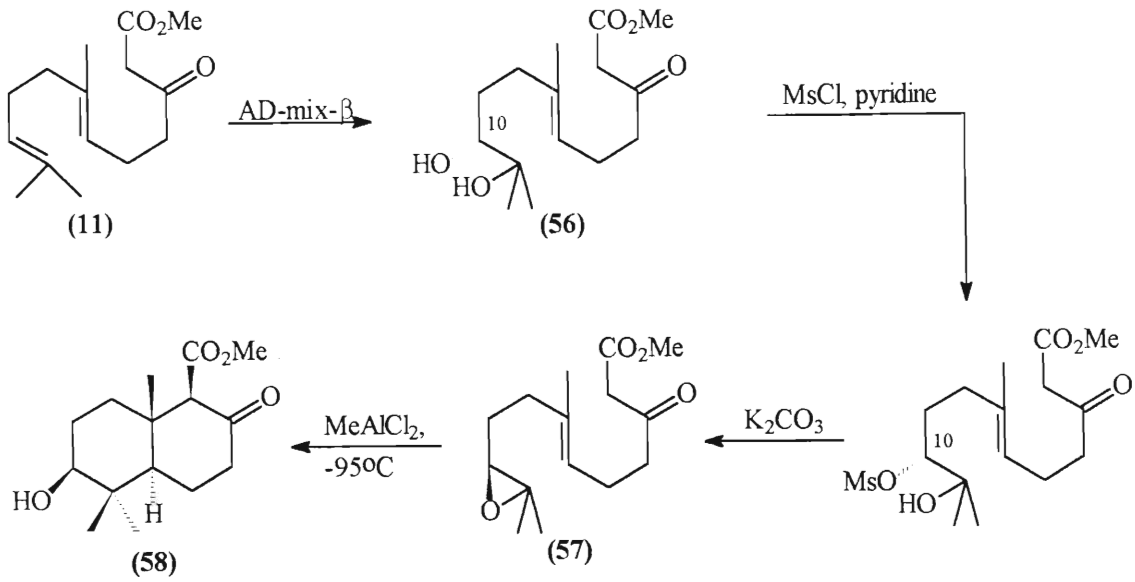
Scheme 15



2.4.1.2 Cyclization involving the Lewis acid $MeAlCl_2$

Corey *et al.*[37] described a short enantioselective synthesis of Dammarenediol II, which contains another procedure that may prove useful for the annelation of **11** to form **45**. This method is much longer than the above two procedures. The first step involves asymmetric dihydroxylation of **11** with AD-mix-β[38] to afford **56** and then epoxide formation by selective mesylation of the 10-hydroxyl group with methanesulfonyl chloride and pyridine, followed by treatment with potassium carbonate to afford **57**. Cyclization of **57** at -95°C with the Lewis acid methyl aluminium dichloride would then afford the cyclized product **58** **(Scheme 16)**.[37]

Scheme 16



The only snag is that there is an unwanted hydroxyl group, which would have to be removed to afford **45**. This pathway requires at least four steps and its lengthy nature detracts from its appeal especially bearing in mind that the shortest possible route to warburganal is a primary goal of this work.

2.5 α-Hydroxylation of the ester

The next step in the synthesis of warburganal as outlined in **Scheme 8** was the α-hydroxylation of the ester **45**. The method employed involved the use of a molybdenum complex: oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), MoOPH or MoO_5.Py.HMPA. This complex was synthesised in a 69% yield compared to a 51-53% yield according to the method of Vedejs and Larsen[39]. This method was chosen in preference to the other methods outlined below:

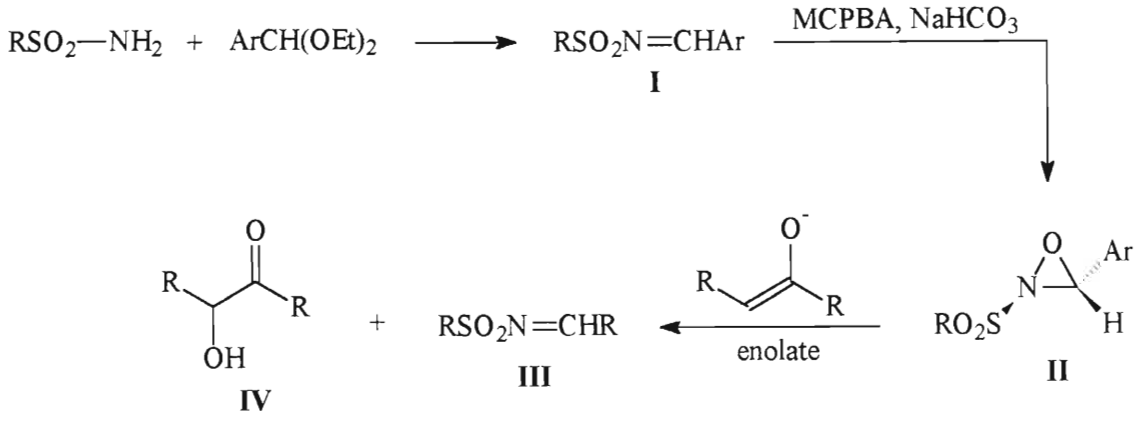
1) The use of molecular oxygen and LDA to afford the α-hydroxyl carboxylic ester derivative[40]. This method seemed outdated by the more recent methods mentioned below and the yields were far lower than those expected for the chosen method. The

enolate oxidations using this reagent are sensitive to the structure of the carbonyl compound and by-products are frequently formed. For example, with O_2 oxidative α-carbon cleavage may occur as well as α-dicarbonyl formation.[41]

2) Dimethyldioxirane (DMD) oxidation of titanium enolates to afford the α-hydroxyl carboxylate derivative.[42,43] Thus this method offers an effective chemo- and diastereoselective preparation of α-hydroxyl carbonyl compounds.[43] It involves 2 steps in that the titanium enolate needs to be prepared prior to the oxidation reaction. The diastereoselectivity of the DMD oxidation appears to be opposite of that of the transition metal oxidant MoOPH and steric affects appear to operate in the DMD oxidation of the titanium enolates. The DMD also needs to be prepared from water, acetone, sodium bicarbonate and solid caroate,[42] thus making this alternative oxidation longer than that using MoOPH.
3) Synthesis of the α-hydroxyl carboxylate using 2-sulfonyloxaziridines.[41,44,45] This method appears to be superior to both the previous methods, in that it results in better yields of α-hydroxy carbonyl compounds. The 2-sulfonyloxaziridine is easily prepared, stable and aprotic and affords high stereoselectivity. **Scheme 17** shows the synthesis of 2-sulfonyloxaziridines and then subsequent α-hydroxylation of the enolate.

An alkane- or arenesulfonamide (RSO_2NH_2) is heated with the diethyl acetal of an aromatic aldehyde to give sulfonimine **I**. Epoxidation of the C=N bond of **I** to sulfonyloxaziridine **II** utilises biphasic conditions and involves the addition of *m*-chloroperbenzoic acid in sodium bicarbonate in a water-chloroform solution.[44] Enolate is then reacted with **II** to afford a sulfonimine **III** and an α-hydroxy ester **IV**.[41]

Scheme 17

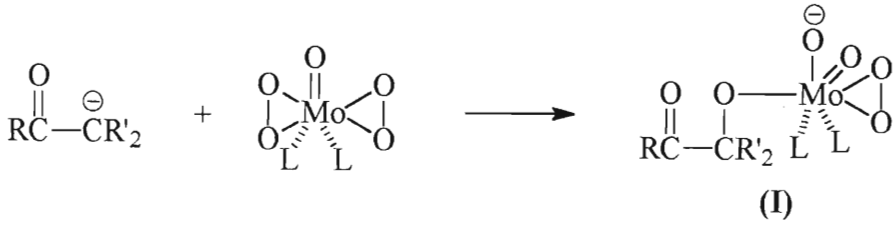


R = Alkyl, Aryl
Ar = Arene, Aromatic

However, MoOPH remains the reagent of choice despite its shortcomings *viz.* sensitivity to the structure of the carbonyl compound and formation of by-products, because it seems to be the oxidant employed by the majority of workers to introduce the α-hydroxyl substituent of warburganal.[21,2,16] In addition this method is facile and requires a single step after preparation of the oxidant.

The reaction pathway that can be written for enolate oxidation with MoOPH is consistent with the known tendency of MoO_5 chelates to transfer one of the peroxidic oxygens rather than the oxo oxygen to potential nucleophiles. This path involves cleavage of the O-O bond and formation of **I (Scheme 18)**.[46] L in this case refers to HMPA and pyridine ligands.

Scheme 18



(I)

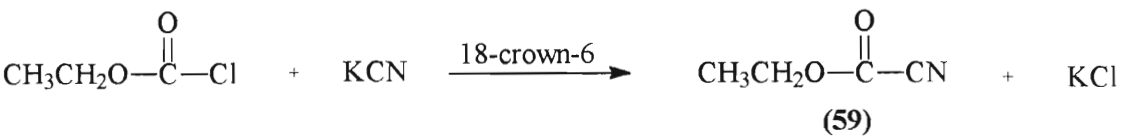
This α-hydroxylation reaction was only attempted on warburganal precursor **45** after trials were carried out on the appropriate model compounds. The preparation and use of these model compounds will be discussed in the next section.

2.5.1 Preparation of model α-hydroxy esters

2.5.1.1 Preparation of an enolizable β-keto ester for α-hydroxylation

The first step in the synthesis of a model compound on which to perform the α-hydroxylation reaction was to prepare a cyanoformate. The cyanoformate would then be used to supply the ester functionality to the ketone to afford a β-keto ester **(Scheme 20)**. Cyanoformate **59** was prepared by reacting ethyl chloroformate with potassium cyanide, using 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) as a phase-transfer catalyst following an established literature procedure **(Scheme 19)**.[47]

Scheme 19



(59)

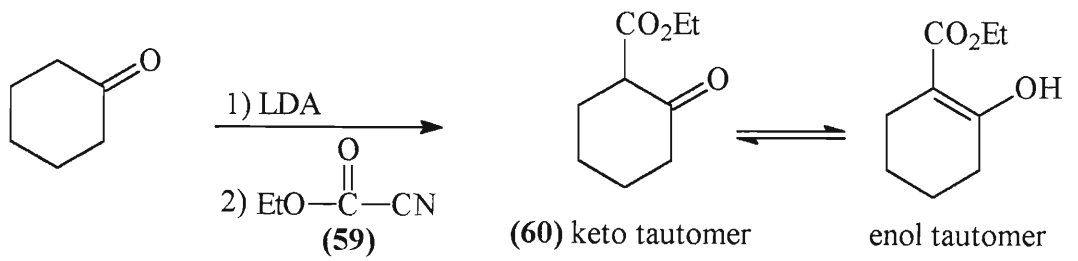
This reaction is an example of a solid-liquid phase transfer catalytic reaction.[48-51] The reaction is free of side reactions, since yield-diminishing dimer formation does not take place. This reaction is quite general and is successful for primary, secondary, benzyl, and phenyl cyanoformates. The NMR spectral data obtained for ethyl cyanoformate **(59)** compare favourably with those in the literature.[47]

Although methyl chloroformate is a desirable starting material in view of its structural similarity to **45**, we settled for ethyl chloroformate, as it was readily available. Also, if the

α-hydroxylation worked on the more sterically hindered model compound possessing the ethyl ester and ketone moiety then it would surely work on methyl ester **45**.

The β-keto ester **(60)** was prepared from cyclohexanone and ethyl cyanoformate **(59)** according to a method reported by Mander and Sethi.[52] These authors purport this method to be an efficient and completely general one for the regiocontrolled preparation of β-keto-esters from the parent ketone. The method is based on the reaction of preformed lithium enolates with methyl cyanoformate as indicated in the following **Scheme 20**. Also shown in **Scheme 20** is the reaction to form the model compound **(60)** on which the α-hydroxylation could be practised to form the α-hydroxy ester **(61) (Scheme 21)**.

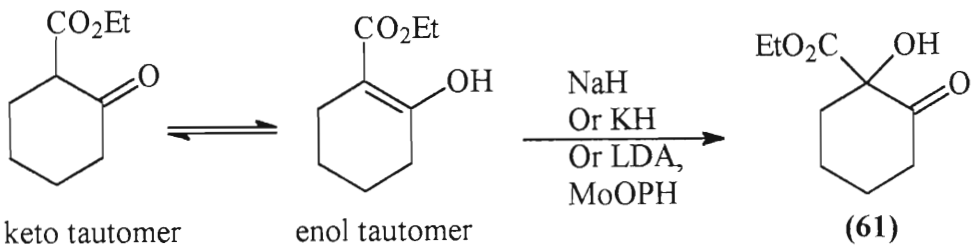
Scheme 20



The yield obtained from this reaction with ethyl cyanoformate was 83% which compares favourably with the reported yield of 86% using methyl cyanoformate as reagent **(Scheme 20)**.[52] The product **(60)** was fully characterised by ^{1}H , ^{1}H D_2O exchange and ^{13}C NMR spectroscopy. The NMR spectra also brought to light the 1:1 ratio of keto/enol tautomers of **60**.

Worthy of note is the stability of the cyanoformate in the presence of diisopropylamine (the by-product of LDA proton abstraction). All reactions appeared completely regioselective, reflecting the specificity of enolization.[52]

Scheme 21



(60) keto tautomer enol tautomer **(61)**

Scheme 21 illustrates the use of **60** as a model compound to test the feasibility of performing a hydroxylation reaction alpha to the ester. This reaction was attempted using the following bases: sodium hydride, potassium hydride and LDA. These were investigated in turn in conjunction with MoOPH as oxidant. However, this was to no avail, as starting material and decomposition products were the only components isolated from the reaction. The smaller bases were initially investigated because it was thought that proton abstraction by LDA would be encumbered due to steric clashes with the substrate. Upon further investigation, it was found that this exact reaction had been attempted by Vedejs *et al.*[46] They found that **61** was not formed and the product mixture was exceedingly complex and the experiment was not pursued. It was at this stage that this model compound was abandoned as a precursor to the α-hydroxy ester. Although this best mimicked the warburganal precursor, the search for an alternative pathway at this point seemed inevitable. However, just to prove that this α-hydroxylation reaction with MoOPH really does work as no success had been reported up to this point regarding this particular reaction, an alternative model compound was prepared.

The alternative model compound is structurally simpler than **60**, possessing an ester group but lacking the ketone group. Although this model compound is a poor analogue of the warburganal precursor, it was prepared to see if the α-hydroxylation reaction with MoOPH as oxidant would work even with just an ester group present. The following section describes the preparation and attempted α-hydroxylation of an alternative model compound.

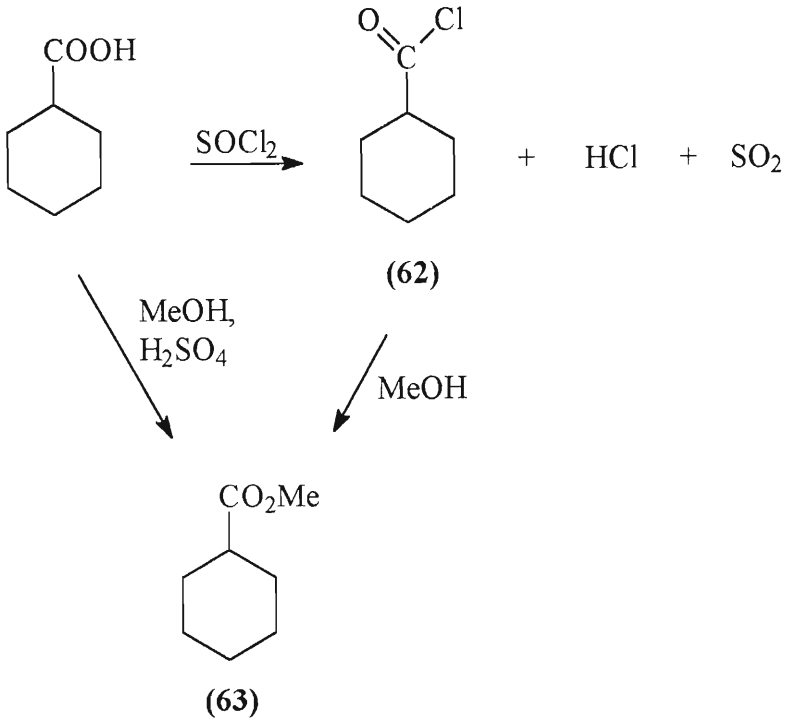
2.5.1.2 Preparation of a cyclic ester as a model compound for α-hydroxylation

With the problems encountered during the use of the previous model compound **(60)** fresh in our minds, a simpler compound, methyl cyclohexanecarboxylate **(63)**, was prepared. This compound is simpler as it lacks the β-ketone functionality. Two methods were used to prepare **63**. The first method, a standard esterification reaction, involved the use of cyclohexane carboxylic acid and methanol in the presence of a catalytic quantity of conc. H_2SO_4. Even after heating under reflux for several days and the addition of activated molecular sieves to remove the water being produced, only a low 15% yield was obtained **(Scheme 22)**.[53] The remaining component was recovered starting material.

An alternative method of synthesising ester **(63)**, involved two steps instead of one. Firstly the acyl halide **(62)** was prepared in 78% yield from cyclohexane carboxylic acid and thionyl chloride.[53] Thionyl chloride is a particularly convenient reagent as the by-products of the reaction (HCl and SO_2) are gaseous and therefore do not contaminate the product and excess thionyl chloride is usually separable by fractional distillation.[53] In the second step **62** to **63**, the acyl chloride reacts readily with methanol to give ester **63**. Thus it appears that preparation of ester **63** is easiest *via* the acid chloride.

Methyl cyclohexanecarboxylate **(63)** was obtained in a gratifying 77% yield by the slow addition of the acyl halide to methanol **(Scheme 22)**.[53] The ^1H and ^{13}C NMR were identical to those obtained from the product in the experiment discussed above.

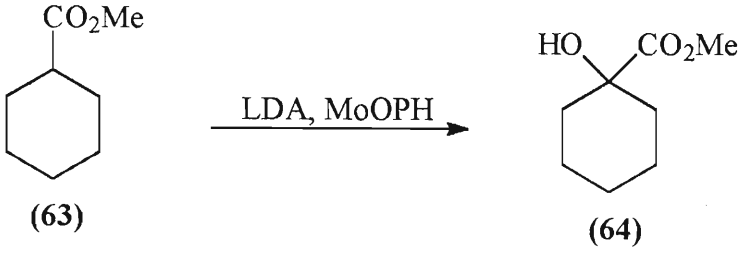
Scheme 22



2.5.1.2.1 α-Hydroxylation of the model compound ***63***

α-Hydroxylation was then attempted on ester **63**. In this case LDA was used as the base to abstract the acidic proton α to the methyl ester, and then MoOPH was used as the oxidant to introduce a hydroxyl group α to the ester. In this manner we had in hand the long awaited α-hydroxy ester **(64) (Scheme 23)**.[45,54] The success of this reaction laid to rest any fears we had concerning the ability of MoOPH to effect α-hydroxylation.

Scheme 23



The existence of the hydroxyl group was proved by D_2O exchange in the ^1H NMR spectrum with the disappearance of the hydroxyl proton peak at 2.95 ppm. The ^{13}C NMR spectrum showed a peak at 73.67 ppm, indicative of the quaternary carbon linked to both the ester and hydroxyl functionalities. The yield was a moderate 45%, disappointingly lower than the 85% yield reported for the α-hydroxylation of a related aldehyde[11]. This may be due to the larger ester group introducing a degree of steric hindrance not present in the aldehyde.

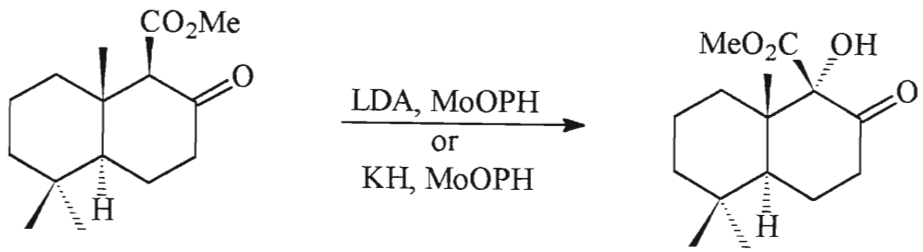
Despite the problems we encountered, it was decided to attempt the α-hydroxylation reaction on the warburganal precursor **45**.

2.5.2 Preparation of α-hydroxy ester 46 from 45

The α-hydroxylation of **45** using MoOPH was then attempted. LDA was initially investigated but after obtaining poor results and recovering only starting material, we resorted to using KH as the base **(Scheme 24)**.

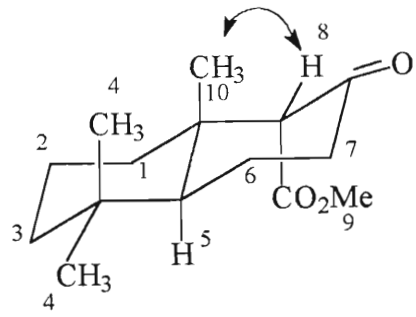
It was thought that LDA being a large base, might be prevented from abstracting a proton because of steric hindrance proffered by the ester group and ketone functionality. Surprisingly, no difference in reactivity was observed when the smaller base KH was employed. Instead an unexpected reaction occurred.

Scheme 24



(45) **(46)**

2.5.2.1 An unusual by-product from α-hydroxylation of **45**

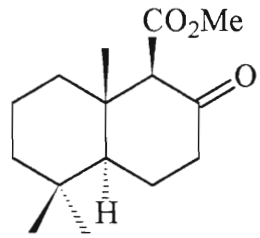


(65)

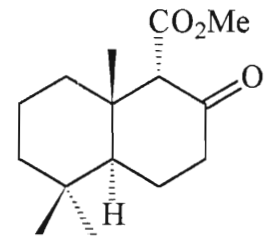
Instead of obtaining compound **46** as shown in **Scheme 24**, the epimer **65** was obtained instead. This reaction appears to violate thermodynamic considerations of conformational stability. No trace of **45** was detected in the isolated product. ^{1}H and ^{13}C NMR spectra, as well as COSY, HETCOR and NOE experiments proved the stereochemistry and purity of the epimer.

The COSY spectrum is complex with a lot of cross coupling and long range coupling evident, but this, together with the NOE spectra enabled a confident assignation of peaks to protons. Methyl group protons 10 were irradiated and a positive correlation showed with methyl group protons 9 and proton 8. When the methyl group protons 9 were irradiated the previous positive correlations were confirmed. The β-proton 8 was irradiated although it overlapped with the axial proton of CH_2 group 7. This gave important evidence for the stereochemistry of the molecule by showing the positive correlations with the equatorial proton of C-7 methylene group, the axial proton of C-6 methylene group and the C-10 methyl group. The ^{1}H NMR spectrum also compares favourably with the reported spectrum[36] with the most important new peak at 3.00 ppm corresponding to H-8, comparing favourably with the reported chemical shift of 2.90 ppm for the same proton. The chemical shift of H-8 of **45** is 3.23 ppm, thus a noticeable difference between these shifts is observed. **(Table 1)**.

The basic environment would enable the epimerization to take place but we are hard-pressed to provide an explanation for preference for the thermodynamically less stable axially disposed ester group. Interestingly Harring and Livinghouse[36] reported that epimerization of the same β-keto ester is favoured under protic conditions. The same product was isolated at a later stage from an acidic environment. This reaction and a proposed mechanism are discussed in section 2.6.1.



(45)



(65)

In conclusion concerning the α-hydroxylation step, employing MoOPH as oxidant, provides the desired hydroxyl compound in a single step. However, hydroxylation of kinetic enolates derived from α,β-unsaturated ketones or methyl ketones, as well as β-keto esters, is also possible, but complications due to enolate attack upon the initial oxidation intermediate are common.[46]

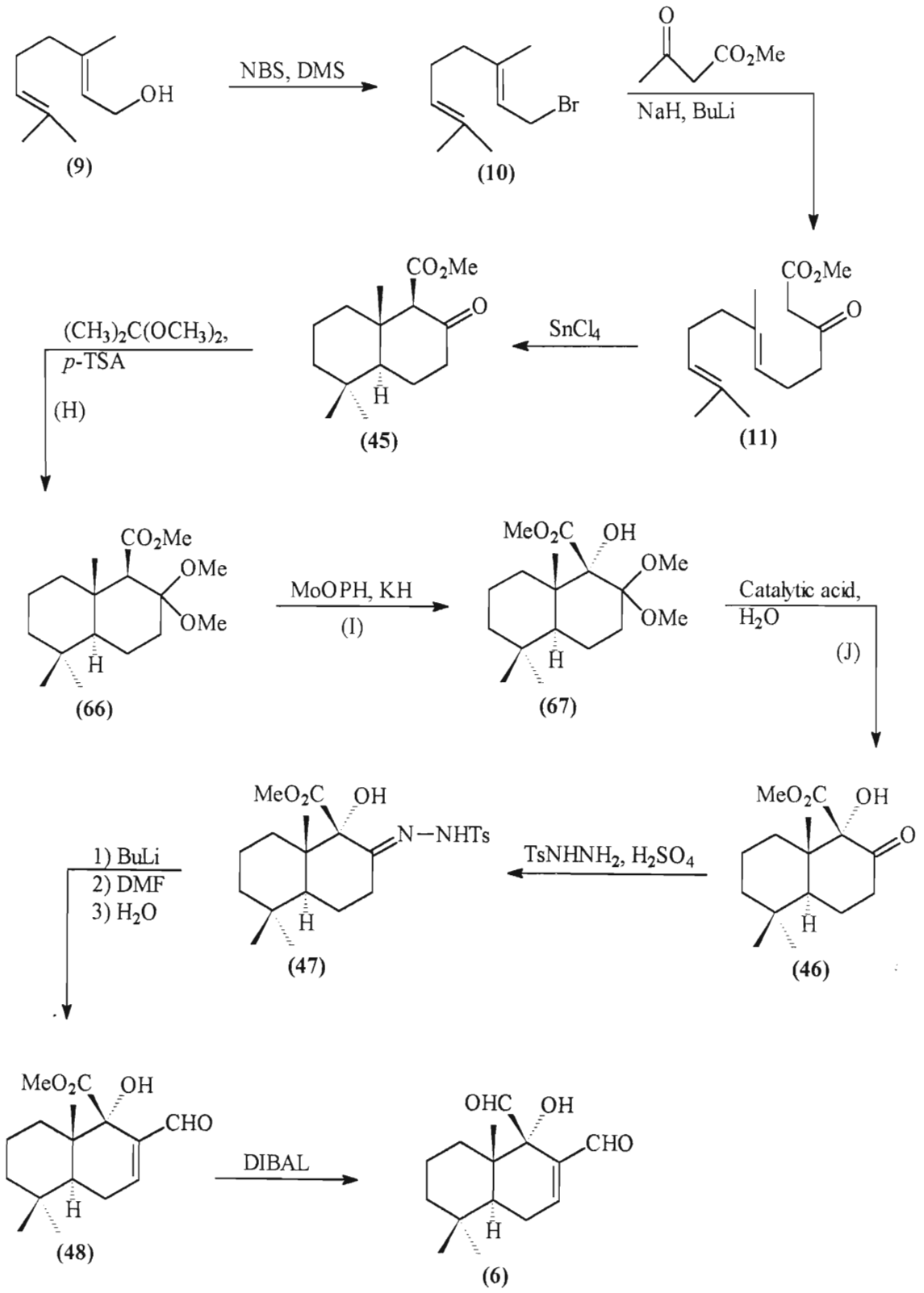
Because of the difficulties we encountered in attempting to prepare α-hydroxy ester **46**, an alternative route to that shown in **Scheme 8** was investigated. Literature precedents suggest that Mo chelates the ketone group and prevents oxidation alpha to the ester group of **45**. We therefore decided to investigate protecting the ketone as an acetal in order to circumvent the problem of molybdenum chelation.

2.6 Protection of the ketone

The slightly modified route is shown in **Scheme 25** with the introduction of three extra steps (steps H, I and J) to overcome the difficulties experienced with the α-hydroxylation of **45** to **46**.

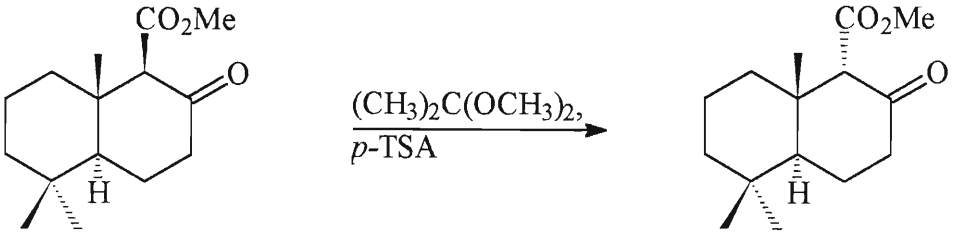
The plan was to protect the ketone group of **45** with 2,2-dimethoxypropane to afford the protected warburganal precursor **(66)**. This acetal ought not to interfere in the subsequent α-hydroxylation of the ester. Once the hydroxyl group is in place, the remaining step entails removing the protecting group by reacting **67** with aqueous acid solution to afford the much sought after α-hydroxy ester **(46)**. Potassium hydride would be the base of choice to abstract the acidic α-proton of **66** because the large amount of steric hindrance introduced by the added protecting group would inhibit the attack of a bulky base such as LDA.

Scheme 25


OH
NBS, DMS
Br
O
CO2Me
NaH, BuLi
(9)
(10)
CO2Me
O
SnCl4
(CH3)2C(OCH3)2,
p-TSA
(H)
H
(45)
(11)
OMe
MoOPH, KH
(I)
MeO2C
Catalytic acid,
H2O
(J)
(66)
(67)
N—NHTs
TsNHNH2, H2SO4
1) BuLi
2) DMF
3) H2O
(47)
(46)
CHO
DIBAL
OHC
(48)
(6)

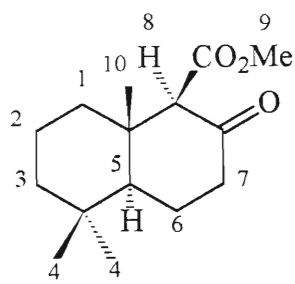
The first step in this alternative pathway was attempted *i.e.* heating the β-keto ester **(45)** in toluene under reflux with 2,2-dimethoxypropane in the presence of a catalytic quantity of *p*-TSA. TLC of the crude reaction mixture showed the presence of starting material, as well as another compound of higher R_f value, conceivably the desired product. However, this was not the case as we soon found out. Rather, a very surprising product resulted, this being the epimer of **45**, namely **65**, in 21% yield from β-keto ester **45 (Scheme 26)**. Although this seemed very unlikely, when comparing the NMR spectral data obtained (^{1}H & ^{13}C NMR spectra), they compare well with the literature values.[36] Refer to **Table 1** for a comparison of the ^{1}H NMR spectral data for compounds **45**, **65** and literature values for **65**.[33] Bear in mind that the numbered **65** below differs from **45** only at the chiral centre with protons H-8 and H-9.

Scheme 26

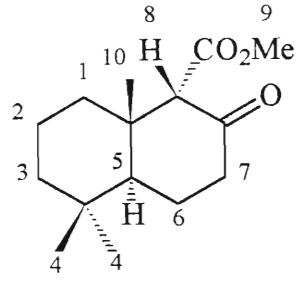


(45) **(65)**

With reference to **Table 1** it is clear that the reported ^{1}H NMR data for compound **65** correspond quite well with those we obtained. The ^{1}H NMR data for compound **45** were included to show the spectral differences between the two epimers. A major difference between the two epimers is the chemical shift of H-5; from being included in the large multiplet extending from 1.20-1.87 ppm for **45** to a doublet of doublets pattern at 2.17 ppm in **65**. Another difference is the upfield shift of the signal for the H-8 proton from 3.23 ppm for **45** to 3.00 ppm for **65**.



(45)



(65)

Table 1 Comparison of ^{1}H NMR data for 45 and 65 and literature values of 65.

Compound 45	Compound 65	Harring and Livinghouse for compound 65[36]
0.90 (3H, s, H_4)	0.86 (3H, s, H_4)	0.81 (3H, s, H_4)
0.97 (3H, s, H_4)	0.97 (3H, s, H_4)	0.91 (3H, s, H_4)
1.16 (3H, s, H_{10})	1.00 (3H, s, H_{10})	0.94 (3H, s, H_{10})
1.20-1.87 (8H, m, $H_{1,2,3,6eq,5*}$)	1.15-1.75 (7H, m, $H_{1,2,3,6eq}$)	1.16 (1H, dd) 1.25 (1H, dd) – {$H_{1,2,3,6eq}$} 1.34-1.63 (5H, cm)
2.04 (1H, m, H_{6ax})	2.03 (1H, m, H_{6ax})	1.96 (1H, m, H_{6ax})
see * above	2.17 (1H, dd, H5)	2.11 (1H, dd, H5)
2.40 (2H, m, H_7)	2.45 (1H, m, H_{7eq}) 2.95 (1H, m, H_{7ax})	2.37 (1H, dm, H_{7eq}) 2.89 (1H, m, H_{7ax})
3.23 (1H, s, H_8)	3.00 (1H, d, H_8)	2.90 (1H, d, H_8)
3.68 (3H, s, H_9)	3.68 (3H, s, H_9)	3.62 (3H, s, H_9)

All the spectra were recorded in $CDCl_3$ as NMR solvent.

NOE experiments as discussed in section 2.5.2.1 also confirm the relative stereochemistry of the epimer, showing that the H-8 proton is in close proximity to the methyl group protons at H-10.

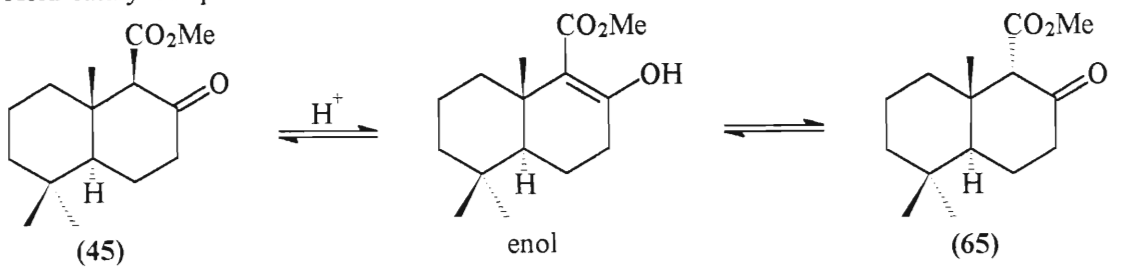
As stated previously in section 2.5.2.1, Harring and Livinghouse[36] report the axial (α) isomer forms more readily under protic conditions. It is highly likely that the acidic environment enables the epimerization to occur. If one recalls our earlier discussion of a similar anomalous result in section 2.5.1.3 for the same compound **65** that was formed under basic conditions. So we have produced additional experimental evidence that β-keto esters are amenable to acid- and base-catalysed epimerization of the ester group. Interestingly the yield of the epimer produced under acidic conditions was greater (21%) than the yield (2%) obtained under basic conditions.

Under basic conditions a possible mechanism most likely proceeds by abstraction of the proton α to the ester to form the enolate **(Scheme 27)**. The sp^2 carbon centre may be reprotonated from the other face with resultant inversion of stereochemistry. Under acidic conditions the mechanism most likely proceeds *via* the enol tautomer where the ester group is now attached to an sp^2 carbon centre, and when the keto tautomer reforms it does so with the opposite stereochemistry thereby affording the epimer *i.e.* the α-ester **5** **(Scheme 27)**. Once again, a plausible thermodynamic rationale for this particular observation is elusive.

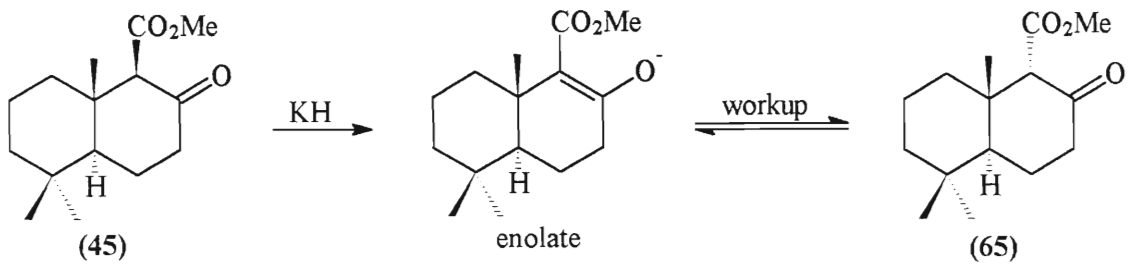
Although this is a very interesting result it did not help in the overall scheme of things. The epimerization circumvented the formation of a protected ketone to allow the α-hydroxylation to occur and places a 'spanner in the works'. Although this prevented us from continuing with the synthesis as planned, it did not deter us from trying out all of the outstanding steps on model compounds. If these reactions prove successful on model compounds then, time permitting, additional methods for effecting the α-hydroxylation on β-keto ester **45** may be attempted.

Scheme 27

Acid-catalyzed epimerization



Base-catalyzed epimerization



2.7 Preparation of the tosylhydrazone for the Shapiro reaction

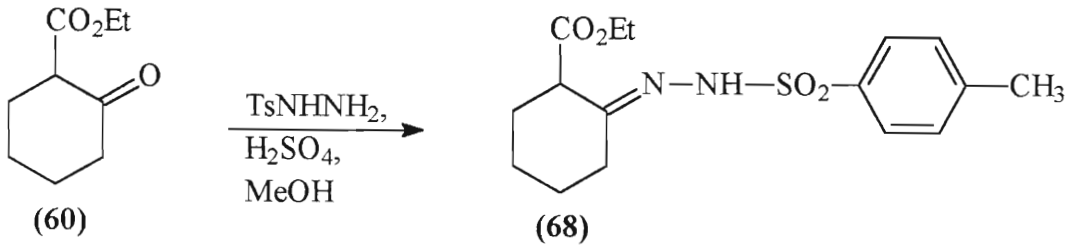
The next step in the synthesis, seen in both **Schemes 8 & 25**, involves the preparation of the tosylhydrazone of the ketone **(46)** in preparation for the Shapiro reaction **(47 → 48)**. The conditions were first optimised on a model compound (section 2.7.1) and then attempted on precursor **45** because of the difficulties in formation of the α-hydroxy ester **46** mentioned in the previous section.

2.7.1 Preparation of a model tosylhydrazone

β-Keto ester **60** was used as a model compound to test the synthetic feasibility of forming a tosylhydrazone. If tosylhydrazone **68** can be prepared this bodes well for a successful reaction on the more complex bicyclic β-keto ester **45.** Several methods were

attempted[53,55,56] before a successful method was found. I will briefly mention these other tosylhydrazone preparations. The first method involves the use of hot acetic acid and tosylhydrazine[55], the second method employs ethanol and tosylhydrazine[53] and the third method uses ethanol, tosylhydrazine and a catalytic quantity of basic or neutral alumina to afford the tosylhydrazone.[56] None of these methods was successful as only starting material was recovered. An alternative method was sought. The successful method involved reacting the β-keto ester **(60)** with *p*-toluenesulfonylhydrazine in methanol with a catalytic quantity of conc. H_2SO_4 to afford hydrazone **68** in 78% yield **(Scheme 28)**.[27]

Scheme 28



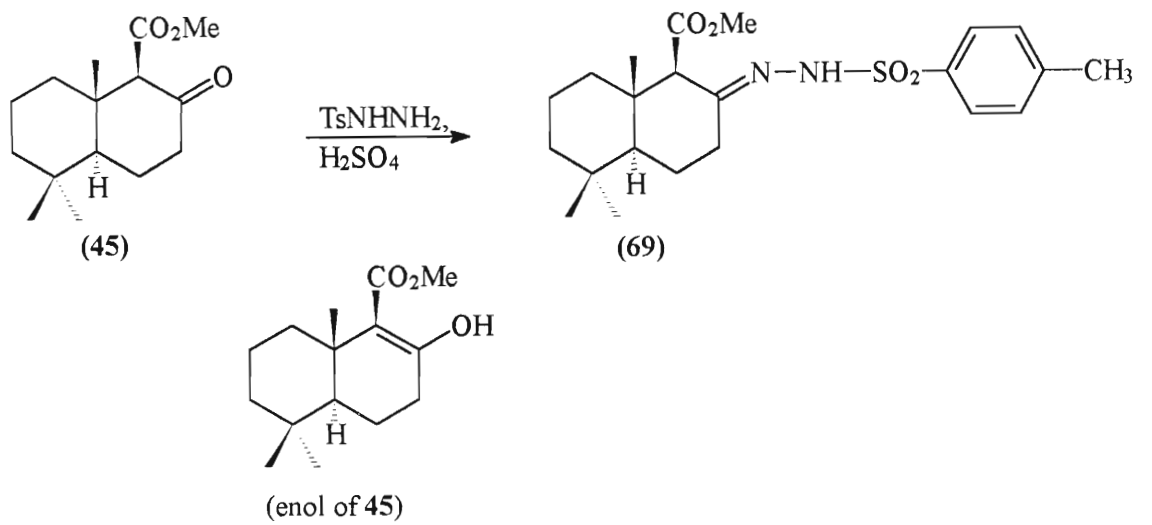
(60) **(68)**

The ^{1}H NMR spectral data compare favourably with those in the literature.[56] In the ^{1}H NMR spectrum only one resonance is visible at 9.71 ppm for the NH signal of the *E*-isomer according to Vinczer *et al.*[56] However, in another spectrum of the same compound before purification by column chromatography, the other isomer (*Z*-isomer) was also visible as a peak at 12.25 ppm, which according to the literature[56] corresponds to the *Z*-isomer. Also clearly evident in the ^{1}H NMR spectrum are the aromatic protons at 7.30 and 7.80 ppm, confirming the presence of the hydrazone moiety. Fortunately the Shapiro reaction was unaffected by the stereochemical integrity or lack thereof of the hydrazone starting material. Also proof that hydrazone formation has occurred, is the disappearance of the C=O shift at 206.31 ppm and the appearance of the C=N shift at 171.75 ppm in the ^{13}C NMR spectrum.

2.7.2 Preparation of tosylhydrazone 69

Unfortunately the reaction of ketone **45** with *p*-toluenesulfonylhydrazine and a catalytic quantity of conc. H_2SO_4 in methanol **(Scheme 29)** failed completely and only starting material was recovered from the reaction mixture. Repeating the reaction with additional acid failed to induce hydrazone formation.

Scheme 29



(45) (69)

(enol of **45**)

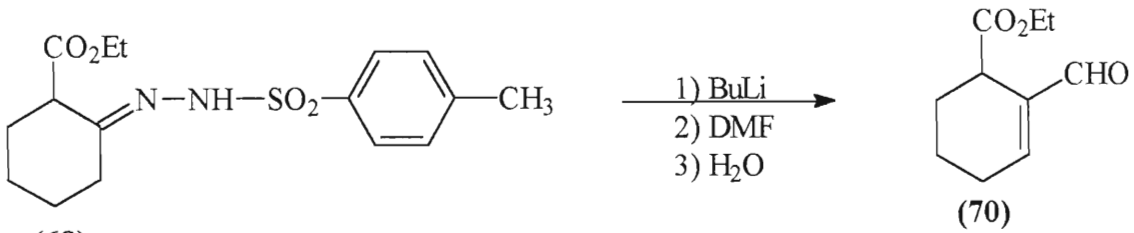
However, as seen in section 2.7.1, this reaction does work and that it is only the sterically demanding nature of the ester group that is preventing the formation of the tosylhydrazone and not a problem in the methodology. There could also be enol formation of **45** under the acidic conditions which is non-reactive and will hinder hydrazone formation.

Even though this reaction did not work, in the next step, the Shapiro reaction was carried out on the model compound **68** prepared previously.

2.7.3 The Shapiro reaction on a model compound

Once the tosylhydrazone **(68)** prepared previously was characterised, it was used in the Shapiro reaction to afford the allylic aldehyde **70** in a dismal 3.7% yield **(Scheme 30)**. This yield was unexpectedly low considering our close compliance with the literature procedure.[28]

Scheme 30

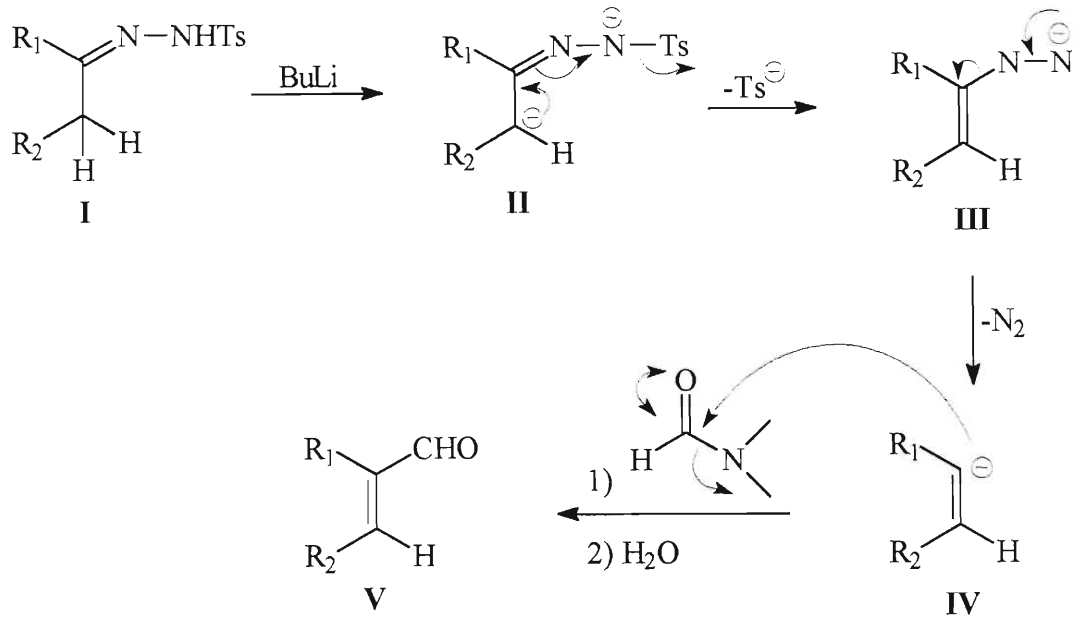


(68) **(70)**

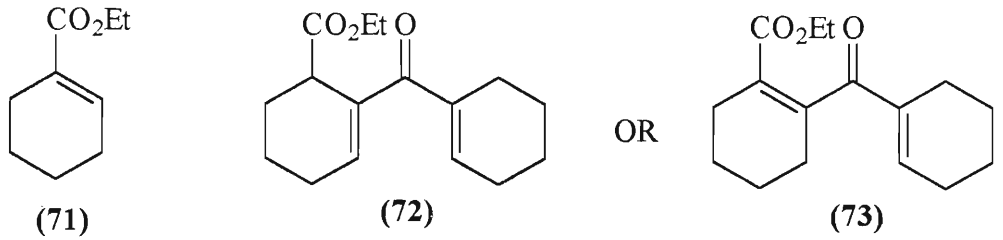
The general mechanism of the reaction is shown in **Scheme 31** as depicted by Traas *et al.*[28]. The *n*-BuLi abstracts the acidic protons on the carbon next to the hydrazone moiety and the proton on the nitrogen in **I**. The tosyl group is eliminated and nitrogen is evolved. The subsequent intermediate alkenyllithium species **IV** is then trapped with DMF to afford the allylic aldehyde **V**.[28] One must however be aware that there are two allylic protons and the double bond could form in two places.

The aldehyde hydrogen atom was clearly visible in the ^{1}H NMR spectrum at 9.45 ppm, as was the aldehyde carbon atom at 193.07 ppm in the ^{13}C NMR spectrum. It was proved by ^{1}H NMR, ^{13}C NMR and HETCOR spectra that the double bond was allylic to the aldehyde as opposed to in-between the ester and aldehyde because of the presence of a vinyl proton at 7.00 ppm in the ^{1}H NMR spectrum and a vinyl carbon at 152.70 ppm in the ^{13}C NMR spectrum which correlate in the HETCOR spectrum.

Scheme 31



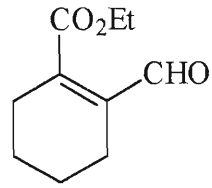
Yield optimisation studies were not performed. However, the low yield may be ascribed to steric hindrance encountered during the approach of DMF. TLC analysis of the crude reaction mixture showed the presence of a very complex mixture. GC/MS's of some of the isolated compounds from this large mixture, although not entirely homogeneous, provided pertinent clues for determination of tentative structures from their masses and fragmentation patterns. These tentative structures are shown below.



(71) **(72)** **(73)**

The mass spectrum of the first by-product exhibited a peak at *m/z* 154 which corresponds to the molecular mass of enoate **71** formed upon removal of the hydrazone moiety. This is the Bamford-Stevens reaction product.[28] Enones **72** and **73** are possible self-condensation

products that may also occur when there is a delay between anion formation and subsequent reaction with DMF. This gives the anion time to perform self-condensation reactions. The GC/MS spectrum of another by-product showed a peak at *m/z* 262, which corresponds to the molecular mass of isomers **72** and **73**. It was most surprising that the thermodynamically most probable fully conjugated enal **74** was not observed in any of the isolated fractions.



(74)

We would have thought that this isomer **(74)** would be far more likely to form, as the proton alpha to the ester is far more acidic than the one next to the ketone and the product would be fully conjugated hence more stable. The *n*-BuLi may have abstracted the proton that it did because it is less sterically hindered than the one between the ester and the ketone substituents.

Although the Shapiro reaction only worked on the model compound, and the problems were probably due to steric hindrance proffered by the ester moiety, I am still convinced that this reaction is a possibility on the warburganal precursor if the steric problems are overcome.

2.8 Direct preparation of the allylic aldehyde

Ho and Wong[57] reported the preparation of α,β-unsaturated 1-cycloalkenecarboxaldehyde from the corresponding 1-nitromethylcycloalkenes by reduction with titanium (III) chloride. The nitroalkenes are readily available from cyclic ketones by condensation with

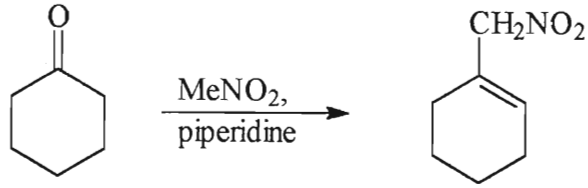
nitromethane.[58] This procedure constitutes a mild and useful route to these conjugated aldehydes.

2.8.1 Preparation of a model allylic aldehyde with nitromethane

In this case cyclohexanone was used as the model compound. The cyclohexanone was first converted into 1-nitromethylcyclohexene **(75)** by heating cyclohexanone, nitromethane and a catalytic amount of piperidine in benzene under reflux for 48 hours. Activated molecular sieves (4Å) were added to remove the water that forms as a by-product and to drive the reaction to completion. This afforded **75** in 41% yield **(Scheme 32)**. The yield did not improve by refluxing the reaction mixture for longer periods of time.

A singlet provided evidence for the presence of the CH_2NO_2 protons at 4.81 ppm in the ^1H NMR spectrum and a signal at 82.85 ppm in the ^{13}C NMR spectrum provided evidence for the presence of the CH_2NO_2 carbon atom. Confirmation of the presence of the vinyl proton was provided by a multiplet at 5.94 ppm in the ^1H NMR spectrum and a signal at 133.29 ppm in the ^{13}C NMR spectrum.

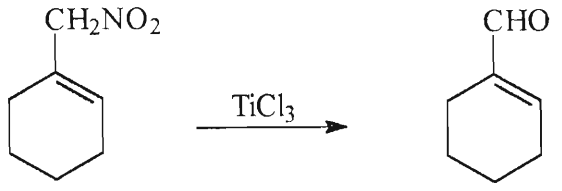
Scheme 32



(75)

1-Nitromethylcyclohexene **(75)** was then used directly in the reduction reaction with $TiCl_3$ by stirring them together under nitrogen for 40 hours to afford conjugated enal **76** in a poor 14% yield **(Scheme 33)**.[57]

Scheme 33



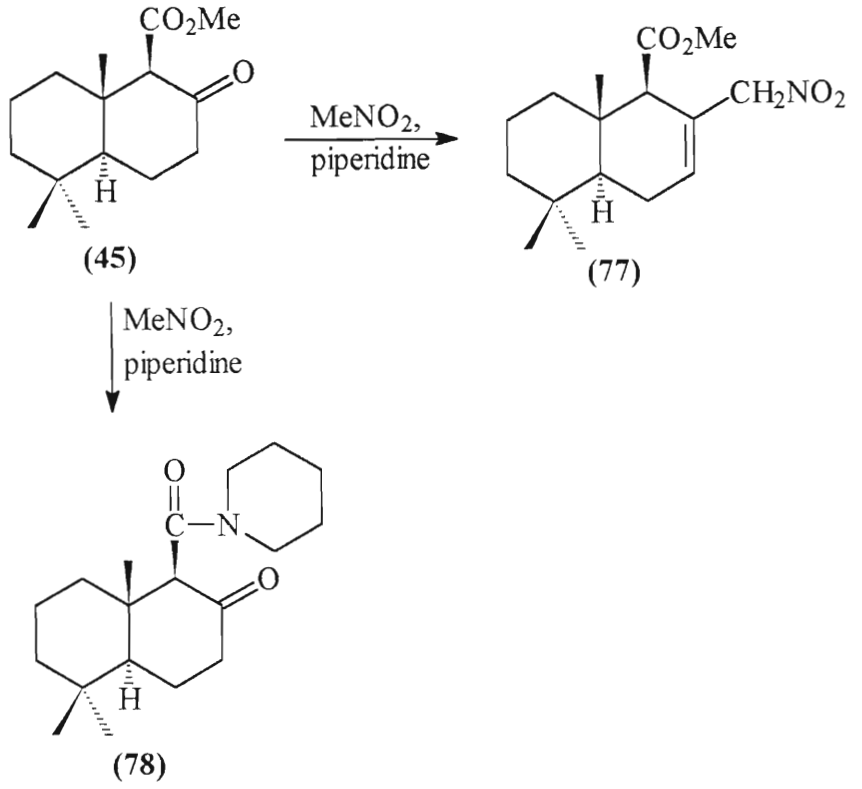
(75) **(76)**

Stirring the reaction mixture for longer periods of time did not improve the yield. The aldehyde proton was clearly visible at 9.41 ppm, as was the vinyl proton at 6.82 ppm in the ^1H NMR spectrum. The aldehyde carbon was also clearly visible at 194.45 ppm in the ^{13}C NMR spectrum.

2.8.2 Preparation of vinyl nitromethane derivatives

Using the successful methodology of the above model reaction, β-ketoester **(45)** was heated under reflux with nitromethane, a catalytic quantity of piperidine and benzene for 72 hours (a longer time was employed than for the model compound) **(Scheme 34)**. Mostly starting material was retrieved from the reaction mixture after work-up and regrettably the desired vinylogous nitromethane **(77)** could not be detected. However, a very interesting by-product **(78)** was isolated instead **(Scheme 34)**.

Scheme 34



This piperidino analogue was a surprise and was also obtained in a control experiment when only piperidine was added to the reaction mixture and nitromethane omitted. This product **(78)** was obtained in 14% yield. First of all the GC/MS peak at *m/z* 305 coincided with the molecular mass of this compound and the fragmentation pattern seemed to confirm the proposed structure with loss of the piperidine moiety corresponding to a molecular mass of 84. The ^{1}H and ^{13}C NMR data as well as COSY and HETCOR spectra provided conclusive evidence for the proposed structure. When the expected methyl ester peak at 3.68 ppm was not present in the ^{1}H NMR spectrum, this prompted investigation into possible addition reactions at the ester carbonyl. The downfield multiplet at 3.54 ppm in the ^{1}H NMR spectrum correlates to some of the piperidine protons. The signal at 3.26 ppm corresponds to the proton adjacent to the ester and ketone and there is a general downfield shift in most of the proton signals due to the electron withdrawing piperidine group. The signals at 2.39 and 3.00 correspond to the equatorial and axial CH_2 protons adjacent to the ketone group. This was proved by the HETCOR spectrum, which showed

both the multiplet and doublet of doublet of doublets correlating to one carbon peak. The signal for the ring-junction proton occurs in-between these two peaks at 2.68 ppm. In the COSY spectrum this couples with the axial CH_2 proton next to it at 2.00 ppm. As expected there was no coupling associated with the signal at 3.26 ppm corresponding to the isolated α-proton of **78**.

The reaction ought to have taken place as follows: the piperidine acts as a base, abstracting protons from nitromethane, leaving the nitromethylene carbanion to attack the ketone group of **45**. In effect a water molecule is lost and the piperidine acts as a proton ferry, redistributing the protons to effect the condensation reaction. However, in this case, instead of the piperidine playing its catalytic role, it has undergone nucleophilic substitution with the ester carbonyl of **45** to afford **78**. In effect the nitrogen atom of piperidine behaves as a nucleophile and substitutes the methoxy group of **45** producing methanol as the side product. The nitromethane is thus only a spectator molecule in this case.

Unfortunately this reaction did not work as it was supposed to, providing another dead-end to the allylic aldehyde, but the piperidino product **(78)** provided an interesting interlude.

Although this reaction worked on the model compound, cyclohexanone, it did not work on the warburganal precursor **45**. Therefore another allylic aldehyde preparation was attempted on the model compound.

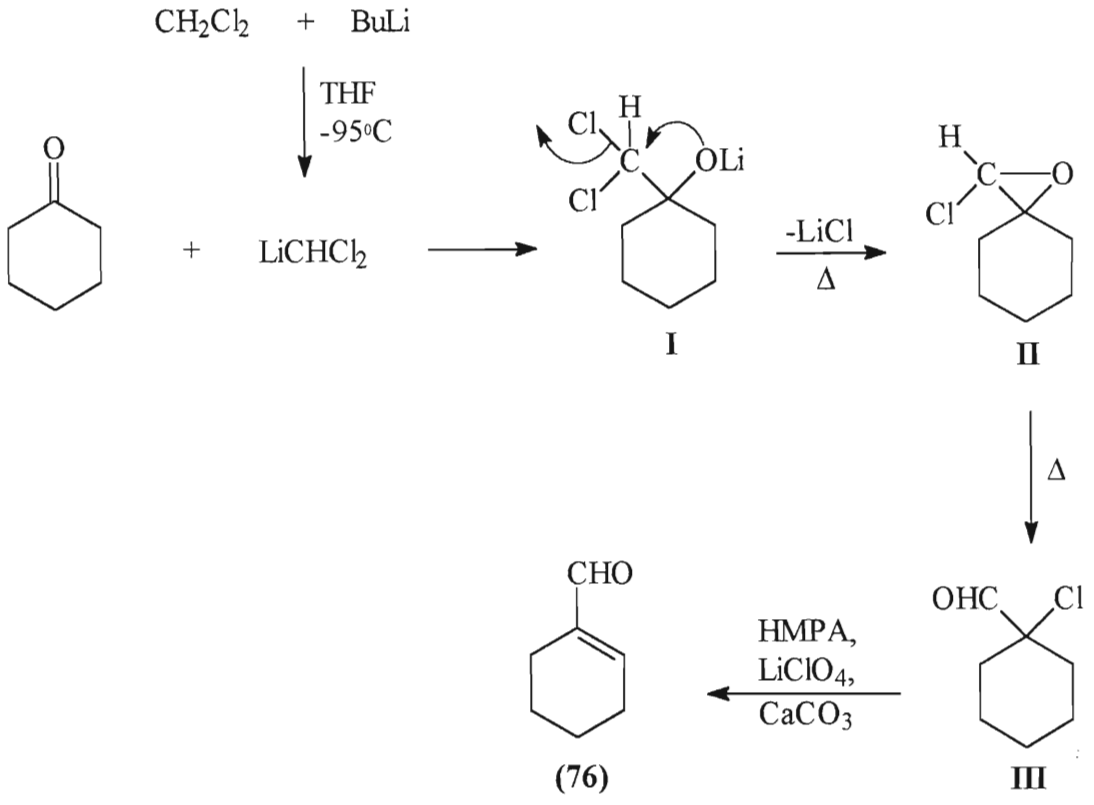
2.8.3 Another preparation of a model allylic aldehyde

Cyclohexanone was once again used as a model compound to see if the method of Taguchi *et al.*[59] would work as well as reported for a related system. This reaction is reported as a 'one-pot' synthesis and advances through two main intermediates, which are not isolated.

This method involves a one-carbon homologation of ketones to the corresponding α,β-unsaturated aldehyde.

The complete sequence is illustrated in the transformation of cyclohexanone to 1-cyclohexenecarboxaldehyde **(76)** **(Scheme 35)**. The first step involves the *in situ* generation of dichloromethyllithium from dichloromethane and *n*-BuLi at -95°C.

Scheme 35

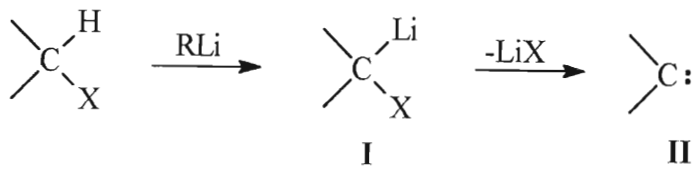


Once the dichloromethyllithium species was prepared, the cyclohexanone is added and this supposedly forms a colourless solution of the nucleophilic addition adduct **I**. This solution is then heated under reflux to produce the intermediate epoxide **II** which rearranges to the α-chloroaldehyde **III**. To this is added HMPA, lithium perchlorate and calcium carbonate and heated to afford 1-cyclohexenecarboxaldehyde **(76)** ostensibly as the sole product

(Scheme 35). The combination of $LiClO_4$-$CaCO_3$-HMPA is reported to be the best cocktail of reagents for the dehydrochlorination of α-chloroaldehydes.[59]

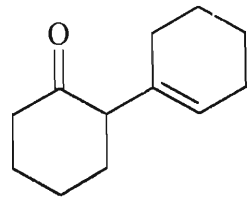
A little bit first needs to be said about the organometallic dichloromethyllithium species. The high tendency of an organometallic compound to decompose is not synonymous with a low formation tendency. On the contrary, because of their electron-attracting inductive and/or mesomeric effect, the functional groups that are responsible for the thermolability mostly increase the acidity of the neutral molecule from which the organometallic compound is derived. One consequence, to which too little attention was given in the past, is that the metal can be introduced under very mild conditions. A large class of thermally unstable substances consists of the α-haloorganolithium compounds **I**, of which dichloromethyllithium is one. They are intermediates of the α-elimination whose general formulation is given in **Scheme 36**, and since they function as latent carbenes **II**, they are known as carbenoids, meaning in this case that they are α-haloorganolithium compounds that have a metal atom and a leaving group on the same carbon atom.[60] The dichloromethyllithium carbenoid can be very easily prepared without decomposition by low-temperature metalation (The term 'metalation' is used to denote the hydrogen-lithium exchange between an organic substrate and an organolithium compound)[60] of the corresponding chlorinated hydrocarbon with *n*-BuLi in THF. The optimum reaction temperature, which is normally between -70 and -120°C, is limited at the lower end of the range by the rate of formation, and at the upper end by the tendency of carbenoids to decompose to carbenes. Both of these factors are strongly and fairly predictably influenced by the hybridization of the carbon and the substituent effects. The metalation proceeds on all sp^3-hybridized carbon atoms carrying at least two chlorine atoms.

Scheme 36

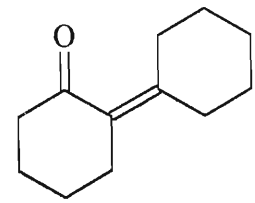


I **II**

Although this method sounds straightforward in theory, it was more complex in practice. First of all the nucleophilic addition adduct **I (Scheme 35)** was not colourless, even upon several repetitions of this reaction, and then the desired 1-cyclohexenecarboxaldehyde **(76)** was not obtained in the final analyses but an unexpected self-condensation product **(79)**.



(79)



(80)

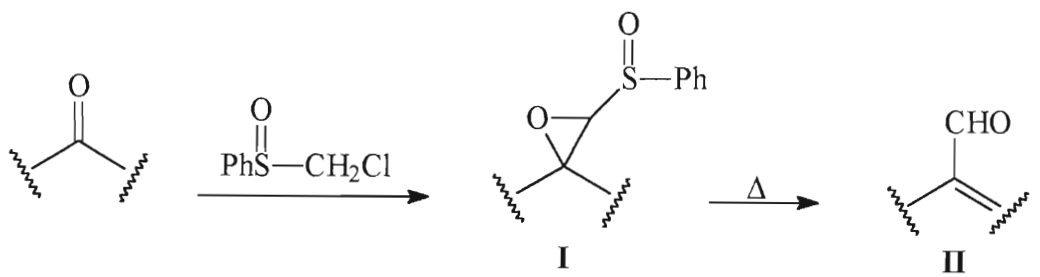
The dichloromethyllithium anion is acting as a base, abstracting an acidic proton from cyclohexanone. This will then facilitate the formation of a self-aldol condensation product. Thus, dehydration took place across the β-γ positions to give an unconjugated enone. The fact that self-condensation took place is not altogether surprising considering the fact that the reaction took place under basic conditions. Compounds **79** and **80** both have the same molecular masses of 178 g/mol but the NMR data prove the product to be **79.** COSY and HETCOR spectra were also used in the determination of **79**.

The signal at 2.90 ppm corresponds to the tertiary CH group, which couples to CH_2 protons at 1.20-2.13 ppm in the COSY spectrum. The multiplet at 5.43 ppm in the ^1H NMR spectrum corresponds to the vinyl proton, which is coupling to one of the CH_2 protons amidst the large multiplet at 1.20-2.13 ppm. Assuming that the isolated compound is **80** instead of **79**, then the downfield signal at 5.43 ppm is difficult to assign to any proton in structure **80**. The four peaks furthest downfield in the ^{13}C NMR spectrum appear to correspond to the two tertiary and two quaternary carbons in the molecule. Thus once again, a rather unusual product was formed in what promised to be a straightforward reaction.

Another method for the synthesis of α,β-unsaturated aldehydes by one-carbon homologation of carbonyl compounds was reported by Reutrakul and Kanghae.[61] This

method was not attempted because several steps were required to prepare the chloromethyl phenyl sulfoxide and α-epoxysulfoxide[62,63] as well as several steps being required to effect the homologation reaction. The overall process represented by **Scheme 37** involves the introduction of both an acyl group, and a double bond at the original carbonyl carbon. The carbon of the chlorosulfoxide functions as a masked nucleophile. This process is based on the rearrangement, followed by the pyrolytic elimination of the derived sulfoxides, of the α-epoxysulfoxides **(I)** to afford the α,β-unsaturated aldehyde **(II)** as indicated in **Scheme 37**.

Scheme 37



2.9 Preparation of a model ester for DIBAL reduction and Swern oxidation

The next step in the overall synthesis of warburganal involves the reduction of the ester **48** to the aldehyde to afford warburganal **(6)**. This may either be achieved in one step by reducing the ester to the aldehyde with DIBAL or, the ester may be reduced to the alcohol with DIBAL and then reoxidized to the aldehyde by the Swern oxidation method. This set of reactions was only attempted on the model compound, namely methyl cyclohexanecarboxylate **(63)**.

2.9.1 Reduction of model ester 63 to the aldehyde with DIBAL

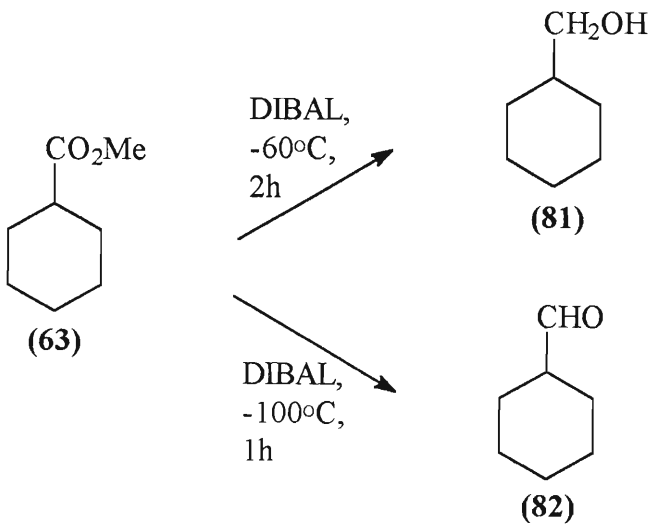
Diisobutylaluminium hydride (DIBAL) has become a common reducing agent, being the reagent of choice in many reduction reactions. DIBAL can react with ethers, both aromatic and aliphatic, oxiranes, aldehydes, ketones, esters, lactones, amides and lactams, nitriles, double bonds and triple bonds.[64]

In the first instance, DIBAL was used to reduce the model ester **63** to the aldehyde. This supposedly facile reaction turned out to be extremely temperamental, preferring to over-reduce the ester to the alcohol. Not surprisingly, this reaction appeared amenable to temperature control. When the temperature was kept very low, the aldehyde was the major product. However, increasing the temperature initiated further reduction to the alcohol.

It was found through trial and error, that if the reaction temperature was allowed to increase above -60°C, then the alcohol was the exclusive product and could be isolated in 85% yield. Even if only one equivalent of DIBAL was used, the intermediate aldehyde being more reactive than the ester, enters competition with the ester for reduction by DIBAL. The reaction was performed at -60, -78 and -100°C. At -60°C no aldehyde was present, but only starting ester and alcohol. At -78°C, a little aldehyde was present and alcohol and ester quantities were about the same. At -100°C, more aldehyde than alcohol or ester was produced. Now that the correct temperature for aldehyde formation had been found, only the reaction time had to be optimised. The optimum reaction time was found to be 1 hour. Shorter reaction times resulted in the isolation of starting material. Longer reaction times favoured the competing aldehyde reduction reaction. Unfortunately this was not as clean a reaction as hoped for and the aldehyde **(82)** was isolated from the reaction mixture by column chromatography in a dismal 12% yield. We can conclude from this reaction that the temperature as well as the length of the reaction is crucial in obtaining the correct reduction product. **Scheme 38** illustrates the conversion of the ester to the alcohol **(81)** and the aldehyde **(82)** at the respective temperatures and reaction times.

The alcohol **(81)** was isolated and characterised by ^{1}H and ^{13}C NMR. The signal at 2.36 ppm disappeared upon addition of D_2O to the NMR tube, providing conclusive evidence for the presence of an alcohol and that this signal corresponded to the hydroxyl proton. The signal at 3.41 ppm, appears suitable for CH_2 protons adjacent to a hydroxyl group. GC/MS analysis showed a clear difference between the alcohol **81** and aldehyde **82**. The aldehyde exhibited a lower retention time than the alcohol with an M^+ peak of 112 compared to an M^+ peak of 114 for the alcohol. This shows clearly the difference of 2 mass units between the aldehyde and the alcohol.

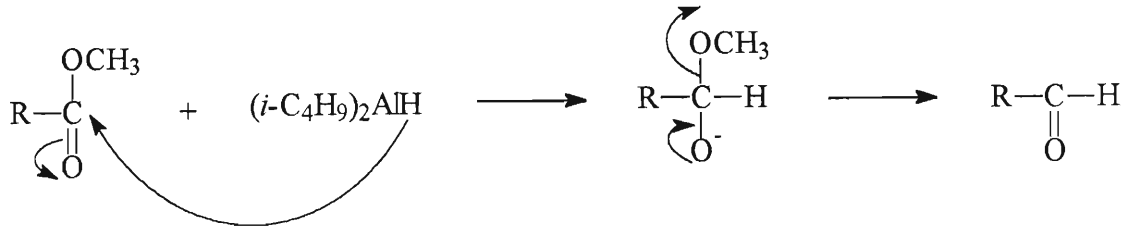
Scheme 38



The aldehyde **(82)** was characterised by ^{1}H & ^{13}C NMR spectroscopy. The aldehyde proton was unmistakable at 9.61 ppm in the ^{1}H NMR spectrum, as was the aldehyde carbon at 205.01 ppm in the ^{13}C NMR spectrum.

The mechanism[64,29] for the reduction of the ester to the aldehyde is illustrated **Scheme 39**. To afford an alcohol, a second DIBAL molecule would attack the aldehyde and another two protons would be added.

Scheme 39



2.9.2 Swern oxidation of alcohol 81 to aldehyde 82

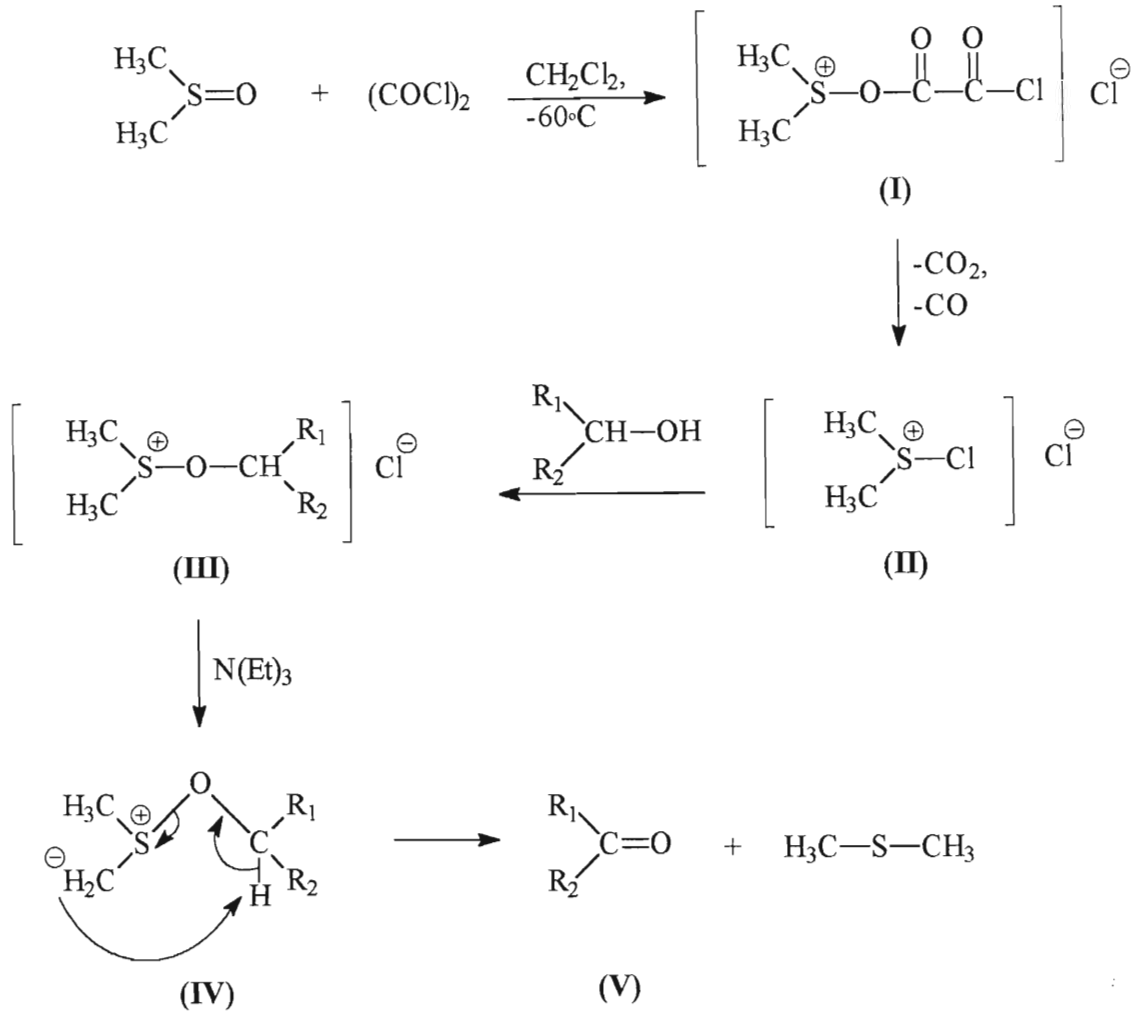
As the reduction of the ester **(62)** directly to the aldehyde **(82)** was not as successful as hoped for, only being formed in 12% yield, we thought that the aldehyde **82** may be obtained by Swern oxidation of the readily accessible alcohol **81**. This is a circuitous route to the desired aldehyde, but well worth it if the aldehyde is formed in a better overall yield than in the DIBAL reduction.

Oxidation of alcohols to the corresponding carbonyl compounds is a very important synthetic procedures and the development of selective and efficient reagents for that conversion, especially when other oxidizable functional groups are also present, has interested organic chemists for a long time. Even though many preparative methods are available, the restrictions that accompany some of them make new, mild and selective procedures attractive. Thus a major breakthrough was achieved with the development of a number of mild and efficient procedures in which alkoxysulfonium salts are reactive intermediates, and hence provide an important addition to the tools available to the synthetic chemist.[65]

Alcohol **81** was oxidized using activated dimethyl sulfoxide. The DMSO was activated with oxalyl chloride. The mechanism detailed in **Scheme 40** illustrates how oxalyl chloride reacts with DMSO; successful activation requires low temperatures (usually -60°C) to form the activated intermediate **II**, obtained from spontaneous loss of carbon dioxide and carbon monoxide from **I**. Nucleophilic substitution of chloride by an alcohol, yields the key

intermediate **III**. The oxidation occurs *via* ylid **IV** and subsequent collapse by an intramolecular cyclic mechanism gives the desired carbonyl compound and dimethyl - sulfide .[65]

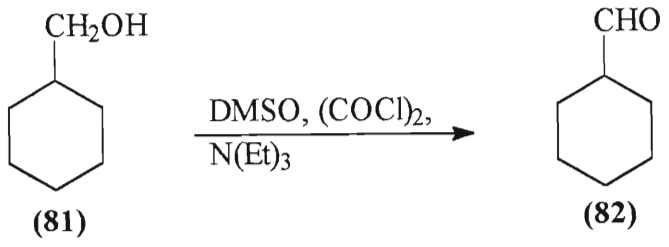
Scheme 40



R_1 and R_2 = aryl

The alcohol **(81)** was oxidized to the aldehyde **(82) (Scheme 41)** in only 12% yield, comparing identically with the 12% yield obtained for the DIBAL reduction in section 2.9.1.

Scheme 41



(81) **(82)**

2.10 Future investigations

With a field as large and diverse as organic chemistry, there are almost always alternative procedures that may be used instead of the one chosen. It is up to the individual to choose those methods most appropriate, cost-effective and in style with the type of synthesis required. With this in mind, the sky is the limit!

The reactions described above lend themselves to further investigations into (i) the optimization of reaction conditions and in some cases yield optimization. (ii) The 'tweaking' of reaction conditions to get the reaction to work on the warburganal precursors, especially those that worked on the respective model compounds, and (iii) attempting the alternative pathways, even if more steps are involved, as a better overall yield may be obtained in the end.

The progress towards the synthesis of warburganal has highlighted the many difficulties encountered when introducing requisite functional groups onto the decalin ring skeleton to afford warburganal *i.e.* the α-hydroxyl and β-aldehyde moieties and the α,β-unsaturated aldehyde. These reactions need to be further investigated to make this proposed synthetic route a viable one.

Even though cyclization to form the decalin ring system of warburganal was successful, an even better route may be found with better yields. The first major hurdle after cyclization is the introduction of the α-hydroxy group to **45** to afford **46 (Scheme 8)**. Optimization of conditions to effect the Shapiro reaction on **46** *via* the tosylhydrazone **47** to afford the enal **48** would also be a large breakthrough for this proposed synthetic route. Finally the reduction of the ester group to an aldehyde is possible when carried out on the model compounds. However, a problem may arise with reduction of the enal functionality being reduced as well under the conditions employed, which would then mean that the enal would need to be protected prior to reduction of the ester to afford warburganal **(6)**. With all of these problematic steps, the chosen reaction conditions would have to be carefully revised and modified to effect the desired reaction and to increase subsequent yields.

2.11 Conclusion

To see the planned synthesis of warburganal work **(Schemes 8** or **25)**, would be the desired conclusion to this project. However, this was not achieved due to time constraints as well as the difficulties mentioned. There is potential and place for a better molluscicide that can be synthesised cheaply and easily in high yields with fewer side effects. The fight against bilharzia still continues as this disease is spreading at a rapid rate throughout Africa. This may sound rather idealistic considering the low yields and difficulties experienced in the synthesis of warburganal, however with serendipity playing such a large role in the development of organic chemistry this far, success may not be so far removed. Some remarkable and unexpected compounds have been isolated from seemingly simple and clean reactions such as the piperidinomethanone **78** and self-condensation product **79**.

3. Experimental

3.1 Index

3.2 Instrumentation and chemicals

3.2.1 Purification of solvents and reagents

All reagents and solvents were dried using standard techniques and distilled prior to use.[66] THF was distilled twice over sodium/potassium alloy and benzophenone. All glassware for butyllithium reactions, sodium hydride and DIBAL reactions were flame dried and all reactions were carried out under a nitrogen atmosphere.

Low temperatures were maintained using dry ice/solvent baths according to the procedure of Phipps and Hume.[67]

3.2.2 Chromatographic separations

Kieselgel 60 F_{254} Merck aluminium backed plates precoated with 0.25 mm silica gel 60 were used for thin layer chromatography. Preparative column chromatography was performed using the technique of Still *et al.*[68] on Merck silica gel (230-400) mesh.

3.2.3 Spectroscopic and physical data

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra and decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 200 instrument at 199.98 MHz and 50.29 MHz respectively. All spectra were recorded in deuterated chloroform ($CDCl_3$). Chemical shifts are reported on the δ scale relative to tetramethylsilane as internal standard. The chemical shifts are reported: value (number of

hydrogens, description of signal, assignment if possible, coupling constant(s) in Hz where applicable). COSY, DEPT and HETCOR spectra were routinely used for the complete assignment of NMR signals.

Gas chromatographic mass spectra were recorded on a Hewlett-Packard gas chromatographic mass spectrometer (HP5988A). Ratios of compounds were calculated based on comparison of peak areas. Analyses were performed under different operating conditions depending on the molecular mass of the compound in question.

Infrared spectra were obtained using a Shimadzu FTIR-4300 spectrophotometer. The liquids were runs as films between sodium chloride plates. The absorptions were reported on the wavenumber (cm^{-1}) scale, in the range 400-4000 cm^{-1}. The signals are reported: value (relative intensity, appearance *i.e.* sharp or broad). Unless specified otherwise, assignments refer to bond stretching deformations. Abbre*via*tions used in quoting spectra are: v ≡ very, s ≡ strong, m ≡ medium, w ≡ weak, sh ≡ sharp, br ≡ broad.

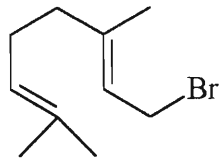
3.2.4. Other general procedures

Concentration or evaporation *in vacuo* refers to the removal of solvent under reduced pressure on a rotary evaporator and final drying on an oil pump.

Yields are calculated from the mass of the immediate synthetic precursor used.

3.3 Preparations

Geranyl bromide **(10)**

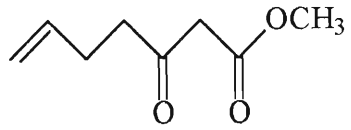


$C_{10}H_{17}Br$
MW = 217.14

(10)

The following procedure is a modification of that reported by Corey *et al.*[23] To a solution of *N*-bromosuccinimide (8.54 g, 48 mmol) in anhydrous dichloromethane (160 ml) (magnetic stirring and nitrogen atmosphere) was added dropwise at 0°C over a period of 3 min, dimethyl sulfide (3.48 g, 57.6 mmol). The mixture was cooled to -20°C and geraniol (4.94 g, 32 mmol) in dichloromethane (16 ml) was added dropwise over a few minutes. The reaction mixture was then warmed to 0°C and stirred for 3 hours, diluted with pentane (75 ml), and poured into ice water (240 ml). The organic phase was washed with a cold sat. NaCl soln., dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was distilled, collecting the geranyl bromide **(10)** at 60-62°C, 4.5 mmHg (lit.[23] b.p. 101-102°C, 12 mmHg) (3.13 g, 45%); **^{1}H** δ 1.60 (3H, s, $C\underline{H}_3C{=}CH$), 1.69 (3H, s, $C\underline{H}_3CCH_3$), 1.73 (3H, s, $CH_3C\underline{H}_3$), 2.12 (4H, s, $(C\underline{H}_2)_2$), 4.03 (2H, d, $C\underline{H}_2Br$), 5.07 (1H, m, $=C\underline{H}CH_2$), 5.53 (1H, m, $=C\underline{H}CH_2Br$); **^{13}C** δ 15.97 ($\underline{C}H_3C{=}CH$), 17.71 ($CH_3\underline{C}H_3$), 25.69 ($\underline{C}H_3CCH_3$), 26.19 ($-\underline{C}H_2CH{=}C(CH_3)_2$), 29.71 ($\underline{C}H_2Br$), 39.53 ($\underline{C}H_2C(CH_3){=}CH$), 120.51 ($\underline{C}HCH_2Br$). 123.51 ($-\underline{C}H{=}C(CH_3)_2$), 131.98 ($=\underline{C}(CH_3)_2$), 143.60 ($=\underline{C}CH_3$); ***m/z*** (EI) 218 (^{81}Br), 216 (^{79}Br) (M^+, <1%), 174 (^{81}Br) (3), 172 (^{79}Br) (4), 137 (40), 121 (5), 93 (17), 81 (41), 69 (100).

Methyl 3-oxo-hept-6-enoate **(50)**

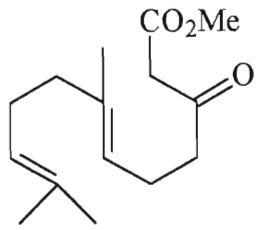


$C_8H_{12}O_3$
MW = 156.18

(50)

The following procedure is a modification of that reported by White *et al.*[26] A suspension of sodium hydride (0.67 g of a 60% mineral oil dispersion, 16.7 mmol) in THF (20 ml) was stirred in an ice-bath as methyl acetoacetate (1.74 g, 15.0 mmol) was added dropwise. The mixture was stirred for 10 min after addition was complete and butyllithium (1.1 equiv.) was slowly added. The resultant solution was stirred in the ice-bath for an additional 10 min, allyl bromide (2.00 g, 16.5 mmol) was added in one portion and then the mixture was stirred at room temperature for 20 min. A solution of conc. HCl (10 ml) in water (25 ml) was added carefully followed by ether (50 ml). The organic layer was separated and washed with 3 x 50 ml portions of water, dried ($MgSO_4$) and evaporated to leave an oil. The crude reaction mixture was purified by distillation (50°C, 4.5 mmHg) to afford a yellow oil **(50)** (1.02 g, 40%); **^{1}H** δ 2.37 (2H, q, $C\underline{H}_2CH{=}CH_2$, J = 7.25 Hz), 2.76 (2H, t, $CH_2C\underline{H}_2CO$, J = 7.23 Hz), 3.47 (2H, s, $COC\underline{H}_2CO$), 3.74 (3H, s, $C\underline{H}_3$), 5.03 (2H, m, $CH{=}C\underline{H}_2$), 5.81 (1H, m, $C\underline{H}$); **^{13}C** δ 27.39 ($CH_2{=}CH\underline{C}H_2$), 42.06 ($CH_2\underline{C}H_2CO$), 49.07 ($COCH_2CO$), 52,37 ($\underline{C}H_3$), 115.60 ($\underline{C}H_2{=}CH$), 136.51 ($\underline{C}H$), 167.59 ($\underline{C}OOCH_3$), 201.90 ($\underline{C}OCH_2$); ***m/z*** (EI) 156 ($M^+$, 11%), 138 (5), 124 (32), 101 (68), 83 (53), 82 (80), 69 (50), 59 (55), 55 (100).

Methyl 3-oxo-7,11-dimethyldodeca-6E,10-dienoate **(11)**

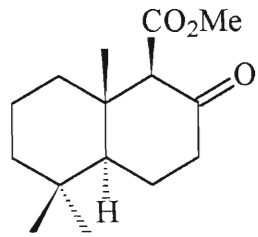


$C_{15}H_{24}O_3$
MW = 252.35

(11)

The following procedure is a modification of that reported by White *et al.*[26] The procedure given for **50** was followed using geranyl bromide **(10)** (2.00 g, 9.21 mmol), methyl acetoacetate (5.88 g, 50.5 mmol), sodium hydride (2.70 g of a 60% mineral oil dispersion, 56.3 mmol) and *n*-BuLi (1.1 equiv.). Distillation (120°C, 4.5 mmHg) (lit.[26] b.p. 140-144°C, 0.6 torr) afforded **11** (8.17 g 58%); **^{1}H** δ 1.61 (6H, s, $(C\underline{H}_3)_2C$), 1.68 (3H, s, $C\underline{H}_3C$), 2.00 (4H, m, $(C\underline{H}_2)_2C(CH_3)$=CH), 2.29 (2H, m, $C\underline{H}_2CH_2COCH_2$), 2.56 (2H, m, $CH_2COC\underline{H}_2$), 3.45 (2H, s, $C\underline{H}_2COOCH_3$), 3.74 (3H, s, $OC\underline{H}_3$), 5.09 (2H, m, 2x C<u>H</u>=); **^{13}C** δ 16.00 and 17.69 ($(\underline{C}H_3)_2C$=), 22.15 ($\underline{C}H_2CH_2CO$), 25.69 ($\underline{C}H_3C$=), 26.59 and 39.64 ($(\underline{C}H_2)_2(CH_3)$=CH), 43.08 ($\underline{C}H_2C$=$OCH_2$), 49.11 ($\underline{C}H_2COOCH_3$), 52.33 ($O\underline{C}H_3$), 122.03 and 124.13 (2x –<u>C</u>H=), 131.46 ($(CH_3)_2\underline{C}$=), 136.78 ($CH_3\underline{C}$=), 167.65 ($\underline{C}OOCH_3$), 202.49 (<u>C</u>O); ***m/z*** (EI) 252 (M^+, 0.8%), 234 (2), 209 (3), 190 (5), 150 (9), 136 (18), 109 (67), 101 (22), 93 (18), 81 (41), 69 (100), 59 (18); ν_{max} (liquid film) 1749 (s, sh), 1716 (s, sh), 1652 (w, br), 1438 (m, sh).

Methyl (1R,4aS*,8aS*)-2-oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate* **(45)**[26]

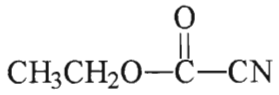


$C_{15}H_{24}O_3$
MW = 252.35

(45)

The following procedure is a modification of that reported by White *et al.*[26] To a cooled solution (0°C) of **11** (1.00 g, 3.96 mmol) in water–saturated dichloromethane (35 ml) under argon, was added a few drops of water followed by anhydrous stannic chloride (5.20 g, 20.0 mmol). The solution was stirred for 30 min at 0°C and then for 20h at room temperature. The mixture was diluted with 5% aqueous HCl (60 ml) and ether (50 ml). The organic phase was washed with 5% aqueous HCl (3 x 10 ml), water and a sat. NaCl soln. and dried ($MgSO_4$). Concentration gave an orange oil that was chromatographed (5:1 hexane, ether) and fractionally distilled (120°C, 4.5 mmHg) to give colourless crystalline **45** upon standing (0.41 g, 41%); m.p. 78-80°C (lit.[26] m.p. 83-84.5); **^{1}H** δ 0.90 (3H, s, $CH_3CC\underline{H}_3$), 0.97 (3H, s, $C\underline{H}_3CCH_3$), 1.16 (3H, s, $C\underline{H}_3CCH$), 1.20-1.87 (8H, m, $((C\underline{H}_2)_3CC\underline{H}_{eq}(H))$), 2.04 (1H, m, $HC\underline{H}_{ax}CH$), 2.40 (2H, m, $C\underline{H}_2CO$), 3.23 (1H, s, $C\underline{H}COOCH_3$), 3.68 (3H, s, $COOC\underline{H}_3$); **^{13}C** δ 14.77 ($\underline{C}H_3CCH_3$), 18.57 ($\underline{C}H_2CH_2C(CH_3)_2$), 21.71 ($CH_3C\underline{C}H_3$), 23.02 ($CH\underline{C}H_2$), 33.47 ($\underline{C}H_3C$), 33.54 ($\underline{C}(CH_3)_2$), 39.13 ($\underline{C}H_2CCH_3$), 41.22 ($\underline{C}H_2C(CH_3)_2$), 41.83 ($\underline{C}H_2CO$), 41.98 ($\underline{C}CH_3$), 51.40 ($COO\underline{C}H_3$), 53.14 ($\underline{C}H(CH_2)_2$), 69.92 ($\underline{C}HCOOCH_3$), 168.67 ($\underline{C}OOCH_3$), 205.55 ($\underline{C}O$); ***m/z*** (EI) 252 ($M^+$, 12%), 234 (28), 219 (31), 205 (26), 177 (13), 163 (14), 149 (14), 145 (21), 137 (62), 136 (100), 129 (56), 123 (54), 116 (91), 109 (44), 95 (41), 81 (31), 69 (35), 55 (18), 41 (13).

Ethyl cyanoformate **(59)**

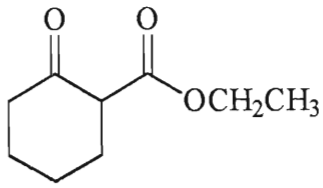


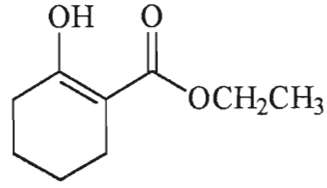
$C_4H_5NO_2$
MW = 99.08

(59)

The following procedure is a modification of that reported by Childs and Weber.[47] Dichloromethane (60 ml), potassium cyanide (7.03 g, 0.11 mol), ethyl chloroformate (10.85 g, 0.10 mol), and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) (0.1 g, 0.04 mmol) were stirred together at room temperature for 4h. The reaction mixture was filtered and concentrated *in vacuo* and distilled at atmospheric pressure collecting the colourless liquid **(59)** boiling at 98°C (lit.[47] b.p. 115-116°C) (4.68 g, 47%); **^{1}H** δ 1.40 (3H, t, C<u>H</u>$_3$, J = 7.15 Hz), 4.40 (2H, q, C<u>H</u>$_2$, J = 7.15 Hz); **^{13}C** δ 13.73 (<u>C</u>H$_3$), 65.27 (<u>C</u>H$_2$), 109.42 (<u>C</u>≡N), 144.29 (<u>C</u>O); ***m/z*** (EI) 99 (M^+, 0.3%), 91 (59), 85 (0.4), 83 (0.6), 73 (7), 63 (100).

Ethyl 2-oxocyclohexylcarboxylate **(60)**



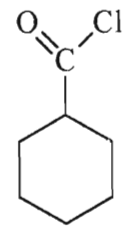


$C_9H_{14}O_3$
MW = 170.20

(60) (keto form) (enolic form)

The following procedure is a modification of that reported by Mander and Sethi.[52] *n*-BuLi (1.2 equiv.) was added to a stirred solution of diisopropylamine (1.7 ml, 12 mmol) in THF (25 ml) at -20°C. After 30 min the temperature was lowered to -78°C and a solution of cyclohexanone (1.0 g, 10 mmol) in THF (10 ml) was added and stirring continued at 0°C for 1h. The temperature was lowered to -78°C and HMPA (1.04 ml, 10.2 mmol) was added followed by ethyl cyanoformate **(59)** (1.21 g, 12.2 mmol). After stirring for 10 min the mixture was poured into cold water (100 ml) and the product extracted into ether (2 x 100ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (10:1 hexane, ethyl acetate) to afford **60** as a colourless liquid (1:1 keto and enol tautomers according to ^{1}H NMR spectroscopy) (3.37 g, 68%); **^{1}H** δ 1.25 (3H, t, C<u>H</u>$_3$, J = 7.14 Hz), 1,47 – 2.60 (9H, m, C<u>H</u>(C<u>H</u>$_2$)$_4$), 4.20 (2H, q, OC<u>H</u>$_2$CH$_3$, J = 7.18 Hz), 12.25 (1H, s, O<u>H</u>); **^{13}C** δ 14.18 and 14.33 (<u>C</u>H$_3$), 21.98, 22.45, 23.34, 27.16, 29.12, 30.01 and 41.58 (cyclohexane <u>C</u>H$_2$'s), 57.25 (<u>C</u>H), 60.16 and 61.07 (O<u>C</u>H$_2$CH$_3$), 97.76 (<u>C</u>COOEt), 172.02 (<u>C</u>OOEt), 172.79 (<u>C</u>OH), 206.31 (<u>C</u>O); ***m/z*** (EI) 170 (M^+, 32%), 142 (12), 141 (15), 125 (37), 124 (100), 123 (22), 114 (18), 96 (30), 86 (13), 68 (86), 67 (20), 55 (43); ν_{max} (liquid film) 1653 (vs, br), 1743 (s, sh).

Cyclohexanecarbanoyl chloride **(62)**

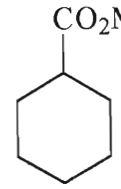


(62)

$C_7H_{11}ClO$
MW = 146.61

The following procedure is a modification of that reported by Furniss *et al.*[53] Cyclohexane carboxylic acid (20.0 g, 0.16 mol) was placed in a flask and heated on an oil bath as thionyl chloride (37.13 g, 0.31 mol) was added dropwise with stirring over 45 min. The reaction mixture was heated under reflux for 2h and then distilled through a Vigreux column collecting **62** as a pure, colourless, lachrymatory fraction at 25°C (4.5 mmHg) (lit.[53] b.p. 76-78°C, 12 mmHg) (17.84 g, 78%); **^{1}H** δ 1.12 - 1.90 (8H, m, C$\underline{H}_2$'s, but only axial H's of C$\underline{H}_2$CH$_2$C$\underline{H}_2$), 2.10 (2H, m, equatorial H's of C$\underline{H}_2$CH$_2$C$\underline{H}_2$), 2.73 (IH, m, C$\underline{H}$); **^{13}C** δ 25.03 (C$\underline{H}_2$CH$_2$C$\underline{H}_2$), 25.45 (CH$_2$C$\underline{H}_2$CH$_2$), 29.19 (C$\underline{H}_2$CHC$\underline{H}_2$), 55.01 (C$\underline{H}$), 176.95 (C$\underline{O}$); ***m/z*** (EI) 146 (M^+, 3%), 111 (37), 83 (100), 67 (11), 55 (61).

Methyl cyclohexanecarboxylate **(63)**



(63)

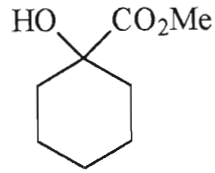
$C_8H_{14}O_2$
MW = 142.19

The following procedures are a modification of that reported by Furniss *et al.*[53]

I) Cyclohexane carboxylic acid (5.0 g, 39 mmol), conc. H_2SO_4 (1 drop) and methanol (20 ml) were heated under reflux for 7 days in the presence of molecular sieves (4 Å). The mixture was filtered and then washed with sat. $NaHCO_3$ soln., extracted with ethyl acetate and the organic layer washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford **63** as a colourless liquid (0.83 g, 15%).

II) Methanol (0.5 ml, 0.1 mol) was cooled to 0°C and cyclohexanecarbanoyl chloride **(62)** (17 g, 0.12 mol) was then added dropwise over 45 min to the methanol with stirring. The ice bath was removed and the mixture was poured into water, washed with a sat. $NaHCO_3$ soln., water once more, dried ($MgSO_4$) and concentration *in vacuo* afforded **63** as a colourless, odiferous liquid (12.66 g, 77%); **^{1}H** δ 1.10 – 1.97 (10H, m, CH_2's), 2.30 (1H, m, C<u>H</u>), 3.66 (3H, s, C<u>H</u>$_3$); **^{13}C** δ 25.48 ($CH_2\underline{C}H_2CH_2\underline{C}H_2CH_2$), 25.78 ($(CH_2)_2\underline{C}H_2(CH_2)_2$), 29.05 ($\underline{C}H_2CH\underline{C}H_2$), 43.13 (<u>C</u>H), 51.47 (<u>C</u>H$_3$), 176.61 (CO); ***m/z*** (EI) 142 (M^+, 57%), 127 (13), 113 (35), 111 (35), 110 (38), 101 (24), 87 (97), 83 (100), 82 (39), 81 (26), 74 (43), 68 (19), 55 (99), 41 (45).

Methyl 1-hydroxycyclohexanecarboxylate **(64)**

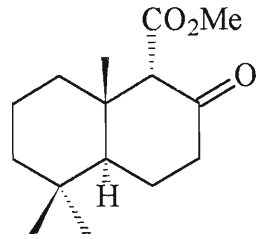


$C_8H_{14}O_3$
MW = 158.19

(64)

The following procedure is a modification of that reported by Vedejs *et al.*[46,54] A solution of diisopropylamine (1.2 ml, 9.3 mmol) in THF (6 ml) was cooled to 0°C. *n*-BuLi (1.2 equiv.) was added *via* syringe and the solution was stirred for 30 min at 0°C. The mixture was then cooled to –78°C and a soln. of the ester **(63)** (1.0 g, 7 mmol) in THF (10 ml) was added dropwise over 2-3 min. After 30 min the MoOPH complex (4.58 g, 11 mmol) was added in one portion by means of an L-shaped tube. After 1h, the cooling bath was removed and the mixture allowed to warm up to 0°C for 30 min before quenching the reaction with sat. Na_2SO_3 soln. (5 ml) and allowing the mixture to reach room temperature. Water was added and the solution left to stir until no colour change in the pale blue aqueous layer was observed. Ether was added, the aqueous layer removed and the ether layer was washed with 5% HCl, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (5:1 hexane, ether) to afford **64** as a colourless oil (0.50 g, 45%); **^{1}H** δ 1.20 – 1.40 (2H, m, $(CH_2)_2C\underline{H}_2(CH_2)_2$)), 1.50 – 1.90 (8H, m, $(C\underline{H}_2)_2CH_2(C\underline{H}_2)_2$), 2.95 (1H, s, O<u>H</u>, D_2O exchange), 3.77 (3H, s, $C\underline{H}_3$); **^{13}C** δ 21.16 ($\underline{C}H_2CH_2\underline{C}H_2$), 25.23 ($(CH_2)_2\underline{C}H_2(CH_2)_2$), 34.72 ($C(\underline{C}H_2)_2$), 52.65 ($\underline{C}H_3$), 73.67 (<u>C</u>), 177.81 (<u>C</u>O); ***m/z*** (EI) 158 (M^+, 0.4%), 99 (100), 81 (83), 79 (19), 55 (21).

Methyl (1S,4aS*,8aS*)-2-oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate* **65** [Epimerization of **45** to **65**]



$C_{15}H_{24}O_3$
MW = 252.35

(65)

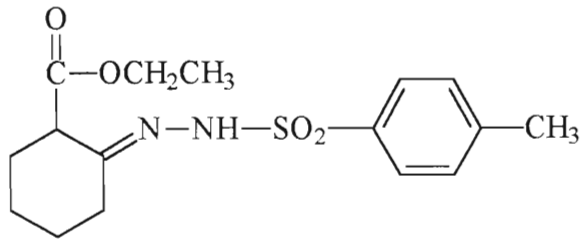
The following procedure is a modification of that reported by Ayer and Talmas.[17]

I) KH (35% in mineral oil dispersion, 0.17 g, 1.5 mmol) was washed with dry hexane. THF (10 ml) was added and the mixture was cooled to 0°C. β-Keto ester **(45)** (0.25 g, 0.99 mmol) in THF (10 ml) was added slowly to the slurry and the mixture stirred for 2h at 5°C. The mixture was cooled to -78°C and MoOPH (0.65 g, 1.5 mmol) was added in one portion. The resulting suspension was stirred vigorously and then warmed to -55°C and stirred for 1h. The mixture was allowed to warm up to 0°C for 30 min and then quenched with 10% Na_2SO_3. The two-phase solution was stirred until no further colour change in the organic layer was observed. Ether was added and the two phases were separated. The organic layer was washed with water, 5% HCl and a sat. NaCl soln., dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (3:1 hexane, ether) to afford **65** as colourless crystals (5 mg, 2%).

II) β-Keto ester **45** (0.20 g, 0.79 mmol), 2,2-dimethoxypropane (0.12 g, 1.2 mmol), *p*-TSA (15 mg, catalytic quantity) in toluene (5 ml) were heated under reflux for 20h. The mixture was concentrated *in vacuo*, ether was added and the mixture was washed with a sat. $NaHCO_3$ soln. The organic layer was washed with water, sat. NaCl soln. and dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by column chromatography (8:1 hexane, ether) to afford **65** as colourless crystals (0.042 g, 21%); m.p. 103-104°C (lit.[36] m.p. 105-106°C); ^{1}**H** δ 0.86 (3H, s, $CH_3CC\underline{H}_3$), 0.97 (3H, s, $C\underline{H}_3CCH_3$), 1.00 (3H, s, $C\underline{H}_3C$), 1.15 – 1.75 (7H, m, $(C\underline{H}_2)_3C(CH_3)_2$ & $\underline{H}_{eq}CHCH_2CO$), 2.03 (1H, m, $HC\underline{H}_{ax}CH_2CO$), 2.17 (1H, dd, $(CH3)_2C\underline{H}$), 2.45 (1H, m, $\underline{H}_{eq}CHCO$), 2.95

(1H, m, $HC\underline{H}_{ax}CO$), 3.00 (1H, s, $C\underline{H}COOCH_3$), 3.68 (3H, s, $COOC\underline{H}_3$); ^{13}**C** δ 18.66 ($\underline{C}H_2CH_2C(CH_3)_2$), 21.02 ($\underline{C}H_3CCH3$), 22.09 ($CH_3C\underline{C}H_3$), 22.82 ($CH\underline{C}H_2$), 33.30 ($\underline{C}H_3C$), 33.35 ($\underline{C}(CH_3)_2$), 38.08 ($\underline{C}H_2CCH_3$), 39.94 ($\underline{C}H_2CO$), 41.73 ($\underline{C}H_2C(CH_3)_2$), 41.81 ($\underline{C}CH_3$), 44.12 ($\underline{C}H(CH_2)_2$), 51.91 ($COO\underline{C}H_3$), 70.85 ($\underline{C}HCOOCH_3$), 169.44 ($\underline{C}OOCH_3$), 207.27 ($\underline{C}O$); ***m/z*** (EI) 252 ($M^+$, 2%), 234 (48), 219 (58), 205 (30), 177 (10), 163 (25), 145 (36), 137 (100), 136 (61), 123 (59), 116 (77), 95 (61), 81 (48), 69 (51), 55 (36), 41 (30).

Ethyl [3-(4-methylphenylsulfonylhydrazone)]-cyclohexane carboxylate **(68)**



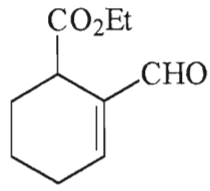
$C_{16}H_{22}N_2O_4S$
MW = 338.42

(68)

The following procedure is a modification of that reported by Hiegel *et al.*[27] and Traas *et al.*[28] β-Keto ester **(60)** (2.00 g, 11.8 mmol), *p*-toluenesulfonylhydrazine (2.25 g, 12.1 mmol), anhydrous methanol (30 ml) and 3 drops of conc. sulfuric acid, were left standing overnight at room temperature. The methanol was removed *in vacuo* and ether and a sat. soln. of $NaHCO_3$ were added. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The orange oil obtained was purified by column chromatography (10:1 chloroform, ethyl acetate) to afford **68** as a white crystalline material (3.10 g, 78%); m.p. 79-80°C (lit[56] 81-82°C); **^{1}H** δ 1.15 (3H, t, $OCH_2C\underline{H}_3$, J = 7.14 Hz), 1.55 (6H, m, $(C\underline{H}_2)_3C{=}N$), 2.30 (2H, m, $C\underline{H}_2CHCO$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 3.30 (1H, t, $C\underline{H}CO$), 4.09 (2H, q, $OC\underline{H}_2CH_3$, J = 7.14), 7.30 (2H, m, $(C\underline{H})_2CH_3$), 7.80 (2H, m, $SO_2C(C\underline{H})_2$), 9.71 (1H, s, NH) (*E* isomer), [12.25 (1H, s, NH) (*Z* isomer)]*; **^{13}C** δ 14.06 ($OCH_2\underline{C}H_3$), 21.60 ($\underline{C}H_2CHCO$), 22.59 ($C_6H_4\underline{C}H_3$), 25,22 ($CHCH_2\underline{C}H_2$), 25.65 ($\underline{C}H_2C{=}N$), 29.26 ($CH_2(CH_2)_2\underline{C}H_2$), 50.02 ($\underline{C}HCO$), 60.83 ($O\underline{C}H_2CH_3$), 128.01 ($SO_2C(\underline{C}H)_2$), 129.42 (($\underline{C}H)_2CCH_3$), 129.89 ($\underline{C}CH_3$), 135.32 ($SO_2\underline{C}$), 158.47 ($\underline{C}O$), 171.75 ($\underline{C}{=}N$).

* Only the *E* isomer has been assigned. The *Z* isomer has been included for comparison.

Ethyl 2-formyl-2-cyclohexenecarboxylate **(70)**

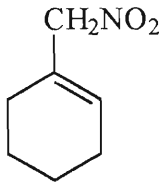


$C_{10}H_{14}O_3$
MW = 182.21

(70)

The following procedure is a modification of that reported by Traas *et al.*[28] *n*-BuLi (4 equiv.) was added at -78°C to a suspension of the tosylhydrazone **(68)** (1.0 g, 3.0 mmol) in TMEDA (10 ml). The clear red solution was allowed to reach room temperature. When evolution of N_2 had ceased (approx. 20 min), DMF (0.26 g, 3.5 mmol) was added at 0°C and the mixture was stirred for an additional hour. The reaction was quenched with a sat. soln. of $NaHCO_3$. The resulting mixture was extracted with ether and the ether layer was separated and washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give a dark orange oil. This oil was purified by column chromatography (2:1 hexane, ether) to afford **70** as a pale yellow oil (0.02 g, 3.7%); **^{1}H** δ 1.25 (3H, t, $C\underline{H}_3$, J = 7.14 Hz), 1.60 – 1.82 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.83 – 2.10 (2H, m, $CHC\underline{H}_2$), 2.15 – 2.58 (2H, m, $C\underline{H}_2CH{=}C$), 3.43 (1H, m, $C\underline{H}CO$), 4.13 (2H, q, $OC\underline{H}_2CH_3$, J = 7.14 Hz), 7.00 (1H, m, $C\underline{H}{=}C$), 9.45 (1H, s, $C\underline{H}O$); **^{13}C** δ 14.14 ($\underline{C}H_3$), 19.50 ($CH_2\underline{C}H_2CH_2$), 25.56 ($\underline{C}H_2CH$), 26.22 ($\underline{C}H_2CH{=}C$), 38.19 ($\underline{C}HCO$), 60.89 ($O\underline{C}H_2CH_3$), 139.27 ($\underline{C}{=}CH_2$), 152.70 ($\underline{C}H{=}C$), 173.58 ($\underline{C}O$), 193.07 ($\underline{C}HO$); ***m/z*** (EI) 182 (M^+, 2%), 154 (47), 137 (37), 136 (47), 109 (76), 108 (66), 81 (100), 79 (97), 53 (19).

1-Nitromethylcyclohexenecarboxylate **(75)**

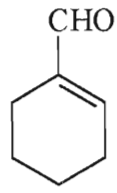


(75)

$C_7H_{11}NO_2$
MW = 141.16

The following procedure is a modification of that reported by Eckstein *et al.*[58] Cyclohexanone (2.00 g, 20.4 mmol), was mixed with nitromethane (2.24 g, 36.7 mmol), benzene (4 ml), piperidine (0.16 ml, catalytic quantity) and activated molecular sieves (4Å). The mixture was heated under reflux for 48h. The reaction mixture was cooled, filtered and washed with a sat. NH_4Cl soln. and extracted with ether. The ether layer was separated and washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography (10:1 hexane, ethyl acetate) to afford **75** as a yellow oil (1.18 g, 41%); **^{1}H** δ 1.63 (4H, m, $CH_2(C\underline{H}_2)_2CH_2$), 2.10 (4H, m, $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 4.81 (2H, s, $C\underline{H}_2NO_2$), 5.94 (1H, m, $C\underline{H}$=C); **^{13}C** δ 21.45, 22.19 ($CH_2(\underline{C}H_2)_2CH_2$), 25.37, 26.54 ($\underline{C}H_2(CH_2)_2\underline{C}H_2$), 82.85 ($\underline{C}H_2NO_2$), 128.51 ($\underline{C}$), 133.29 ($\underline{C}$H); ***m/z*** (EI) 141 ($M^+$, 0.2%), 95 (100), 79 (24), 67 (55), 55 (25).

1-Cyclohexenecarboxaldehyde **(76)**

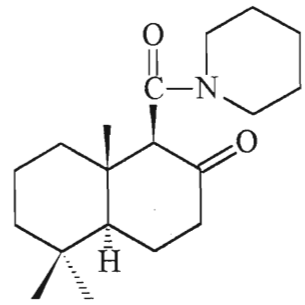


(76)

$C_7H_{10}O$
MW = 110.15

The following procedure is a modification of that reported by Ho and Wong.[57] A mixture of **75** (0.50 g, 3.5 mmol) and titanium (III) chloride (15% soln. in 4% HCl, 21.18 g, 0.14 mol) was stirred under N_2 for 40h. The reaction was quenched with a sat. $NaHCO_3$ soln. The reaction mixture was extracted with ether and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (10:1 hexane, ethyl acetate) to afford **76** as a yellow oil (0.056g, 14%); **^{1}H** δ 1.50 – 1.80 (4H, m, $CH_2(C\underline{H}_2)_2CH_2$), 2.20 (2H, m, $C\underline{H}_2CH$=), 2.35 (2H, m, $C\underline{H}_2C$), 6.82 (1H, m, C<u>H</u>=C), 9.41 (1H, s, C<u>H</u>O); **^{13}C** δ 21.26 ($\underline{C}H_2CH_2CH$), 21.31 ($\underline{C}H_2CH$), 22.03 ($\underline{C}H_2CH_2C$), 26.49 ($\underline{C}H_2C$), 141.58 (<u>C</u>=CH), 151.61 (=<u>C</u>HCH$_2$), 194.45 (<u>C</u>HO); ***m/z*** (EI) 110 (M^+, 88%), 95 (32), 81 (100), 79 (67), 67 (21), 53 (29), 41 (21).

(1R,4aS*,8aS*)-2-Oxo-5,5,8a-trimethyldecahydronaphthalene-piperidinomethanone* **(78)**

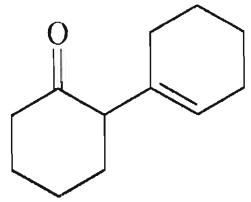


$C_{19}H_{31}NO_2$
MW = 305.46

(78)

The following procedure is a modification of that reported by Eckstein *et al.*[58] β-Keto ester **45** (0.25 g, 99 mmol) was mixed with nitromethane (0.12 g, 1.8 mmol), benzene (3 ml), piperidine (0.14 ml, catalytic quantity) and activated molecular sieves (4Å). The mixture was heated under reflux for 72h before quenching with sat. NH_4Cl soln. and extracting with ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (3:1 hexane, ether) to afford **76** as a yellow oil (0.043 g, 14%); **^{1}H** δ 0.86, 0.99 (6H, 2 x s, $C(C\underline{H}_3)_2$), 1.00 (3H, s, $C\underline{H}_3C$), 1.15 – 1.73 (13H, m, $(CH_3)_2C(C\underline{H}_2)_3$, $HC\underline{H}_{eq}CH_2CO$, $NCH_2(C\underline{H}_2)_3$), 2.00 (1H, m, $\underline{H}_{ax}CHCH_2CO$), 2.39 (1H, M, $HC\underline{H}_{eq}CO$), 2.68 (1H, dd, $C\underline{H}CCH_3$), 3.00 (1H, ddd, $\underline{H}_{ax}CHCO$), 3.26 (1H, d, $C\underline{H}CON$), 3.54 (4H, m, $N(C\underline{H}_2)_2$); **^{13}C** δ 18.76 (decalin $\underline{C}H_2$), 21.88, 22.22 ($(\underline{C}H_3)_2C$), 22.74, 24.53, 25.81 (decalin $\underline{C}H_2$'s), 26,52 (piperidine $\underline{C}H_2$), 33.26 ($\underline{C}(CH_3)_2$), 33.36 ($C\underline{C}H_3$), 37.27 (piperidine $\underline{C}H_2$), 40.53 ($\underline{C}H_2CO$), 41.52 (piperidine $\underline{C}H_2$), 41.88 ($\underline{C}CH_3$), 43.35 (piperidine $\underline{C}H_2$), 44.44 ($\underline{C}HCCH_3$), 47.99 (piperidine $\underline{C}H_2$), 65.82 ($\underline{C}CON$), 166.35 ($\underline{C}ON$), 209.91 ($\underline{C}O$); ***m/z*** (EI) 305 (M^+, 0.3%), 286 (11), 273 (3), 182 (5), 169 (60), 154 (19), 152 (17), 127 (100), 112 (25), 84 (33), 69 (18), 55 (8).

2-Cyclohex-1'-enylcyclohexanone **(79)**

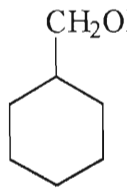


(79)

$C_{12}H_{18}O$
MW = 178.27

The following procedure is a modification of that reported by Taguchi *et al.*[59] and Köbrich.[60] Dichloromethane (1.25 g, 14.7 mmol) and THF (10 ml) were cooled to -95°C and then treated with *n*-BuLi (1.2 equiv.). The reaction mixture was left at -95°C for 10 min and then warmed to -78°C for 2h after which time the mixture was warmed to -20°C. Cyclohexanone (1.0 g, 10 mmol) was added and the mixture left for 30 min. The mixture was heated at reflux under N_2 for 1h then concentrated *in vacuo* at 0°C. HMPA (4 g, excess), $LiClO_4$ (2.17 g, 20.4 mmol) and $CaCO_3$ (2.55 g, 25.5 mmol) were added and the resulting suspension heated at 130°C for 1.5h and then poured onto water. The mixture was diluted with ether and washed with water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (10:1 hexane, ethyl acetate) to afford **79** as a yellow oil (0.098 g, 5.4%); **^{1}H** δ 1.20 – 2.13 (14H, m, C$\underline{H}_2$'s), 2.15 – 2.55 (2H, m, C$\underline{H}_2$CO), 2.90 (1H, m, C$\underline{H}$CO), 5.43 (1H, m, C$\underline{H}$=C); **^{13}C** δ 22.41, 22.84, 24.88, 25.28, 27.26, 27.68 (cyclohexyl $\underline{C}H_2$'s), 31.86 ($\underline{C}H_2$C=), 42.14 ($\underline{C}H_2$CO), 58.75 (CO$\underline{C}$HC=), 123.64 ($\underline{C}$H=C), 135.85 ($\underline{C}$=CH), 211.68 ($\underline{C}$O); ***m/z*** (EI) 178 (M^+, 52%), 149 (100), 135 (26), 121 (15), 107 (15), 93 (25), 91 (28), 79 (46), 67 (29).

Cyclohexanemethanol **(81)**

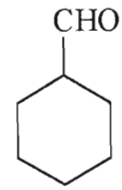


(81)

$C_7H_{14}O$
MW = 114.18

The following procedure is a modification of that reported by Zakharkin *et al.*[29] and Szántay *et al.*.[69] A solution of methyl cyclohexanecarboxylate **(63)** (0.50 g, 3.5 mmol) in toluene (11 ml) was cooled to -60°C and DIBAL (20% in hexane, 1.2 equiv.) was added. The reaction mixture was left to stir for 2h at -60°C before quenching the reaction with sat. NH_4Cl soln. The mixture was extracted with ether and the ether layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford **81** as a colourless oil (0.33 g, 85%); ^{1}**H** δ 0.79 – 1.89 (11H, m, C$\underline{H}_2$C$\underline{H}$), 2.36 (1H, s, O$\underline{H}$, D_2O exchange), 3.41 (2H, d, C$\underline{H}_2$OH); ^{13}**C** δ 25.88 ($CH_2\underline{C}H_2CH_2\underline{C}H_2CH_2$), 26.63 ($(CH_2)_2\underline{C}H_2(CH_2)_2$), 29.62 ($CH_2CH\underline{C}H_2$), 40.46 (<u>C</u>H), 68.60 (<u>C</u>H_2OH); ***m/z*** (EI) 114 (M^+, 0.6%), 96 (49), 83 (93), 82 (43), 81 (86), 67 (57), 55 (100), 41 (33).

Cyclohexanecarboxaldehyde **(82)**



(82)

$C_7H_{12}O$
MW = 112.17

The following procedures are a modification of that reported by Zakharkin *et al.*[29], Mancuso *et al.*[65] and Szántay *et al.*.[69]

I) A solution of methyl cyclohexanecarboxylate **(63)** (0.50 g, 3.5 mmol) in toluene (11 ml) was cooled to -100°C and DIBAL (1.0M in hexane, 1.2 equiv.) was added. The reaction mixture was left to stir for 1h at -100°C before quenching the reaction with sat. NH_4Cl soln. The mixture was extracted with ether and the ether layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (5:1 hexane, ether) to afford **82** as a colourless oil (0.06 g, 12%).

II) Oxalyl chloride (0.14 g, 1.1 mmol) was added dropwise to dichloromethane (20 ml) at -60°C. DMSO (0.14 g, 1.8 mmol) was added and the mixture was stirred for 3 min. The alcohol **(81)** (0.10 g, 0.88 mmol) in dichloromethane (3 ml) was added dropwise and the mixture was stirred for a further 45 min. Triethylamine (0.36 g, 3.5 mmol) was added and after 10 min water was added and the reaction mixture was extracted with dichloromethane. The organic layer was successively washed with 1% HCl (4 ml), water (4 ml), 5% $NaHCO_3$ (4ml) and a sat. NaCl soln. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (5:1 hexane, ether) to afford **82** as a colourless oil (0.012 g, 12%); **^{1}H** δ 1.10 – 2.00 (10H, m, C$\underline{H}_2$'s), 2.23 (1H, m, C$\underline{H}$), 9.61 (1H, s, C$\underline{H}$O); **^{13}C** δ 25.04, 25.94, 25.98 (C$\underline{H}_2$'s), 49.97 (C$\underline{H}$), 205.01 (C$\underline{H}$O); ***m/z*** (EI) 112 (M^+, 26%), 94 (37), 83 (91), 70 (28), 68 (42), 55 (100), 41 (27).

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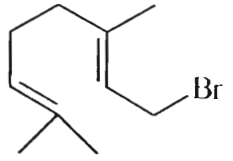
5. Appendix

Selected ^{1}H NMR, ^{13}C NMR and COSY Spectra



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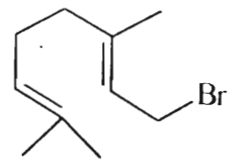

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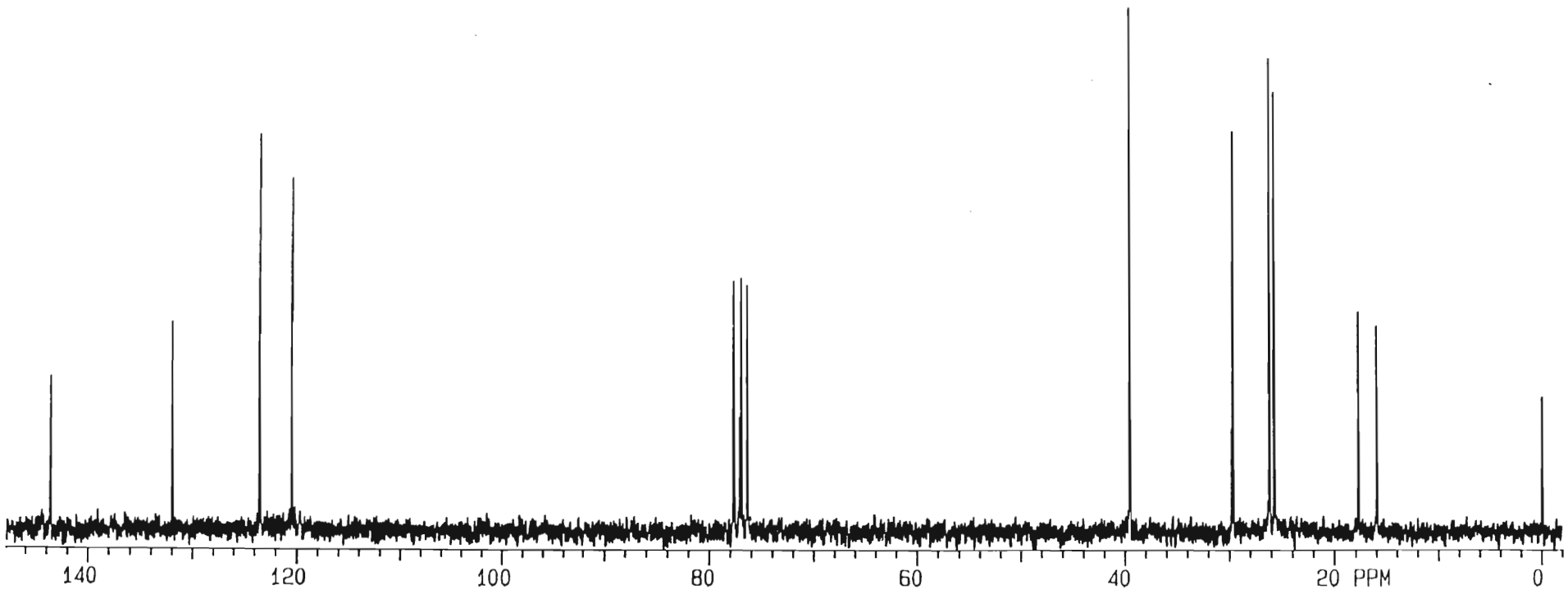

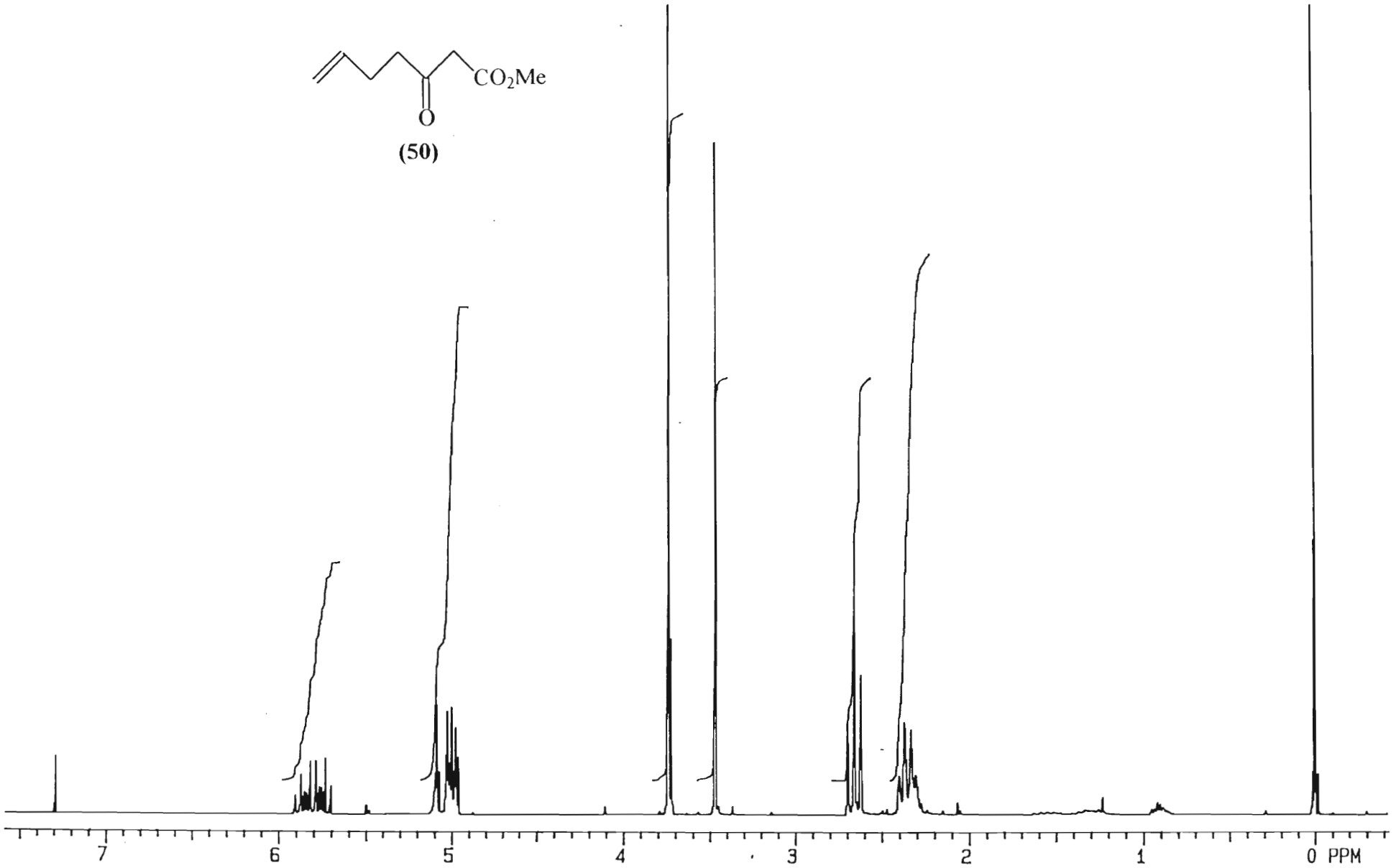

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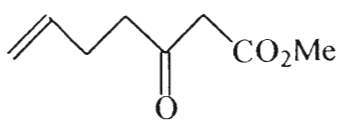

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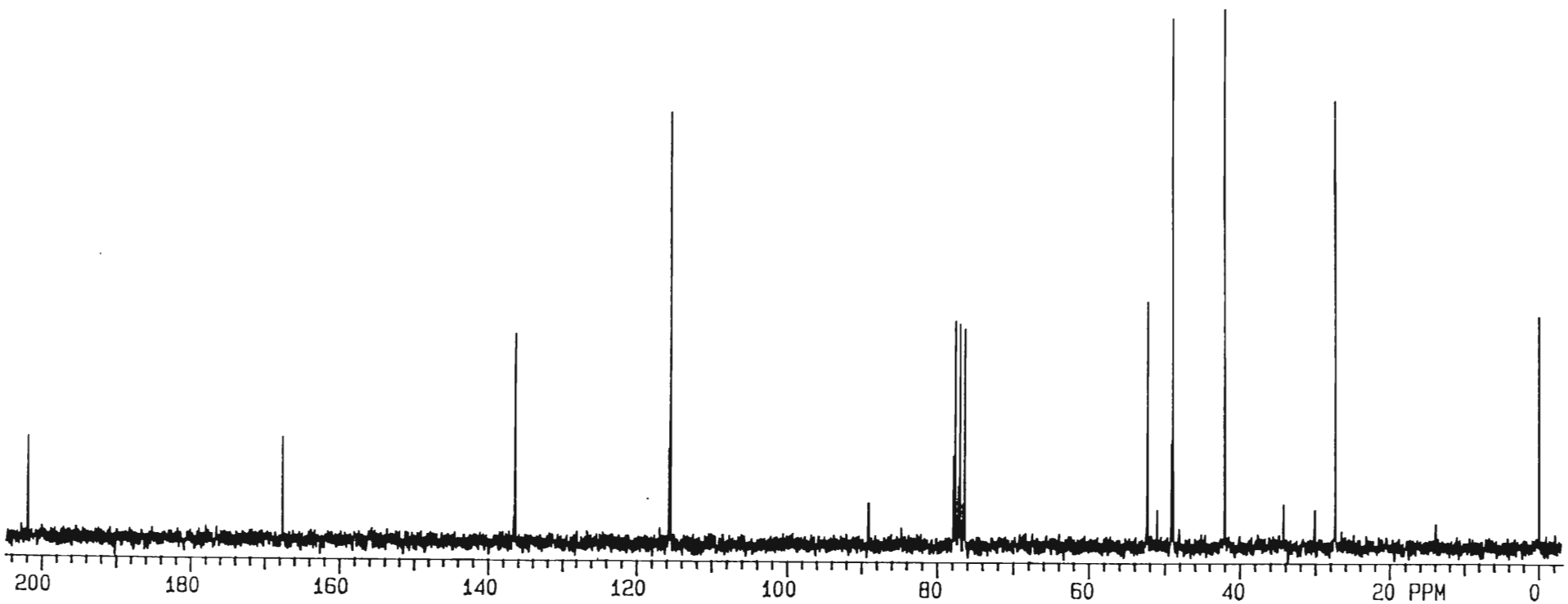

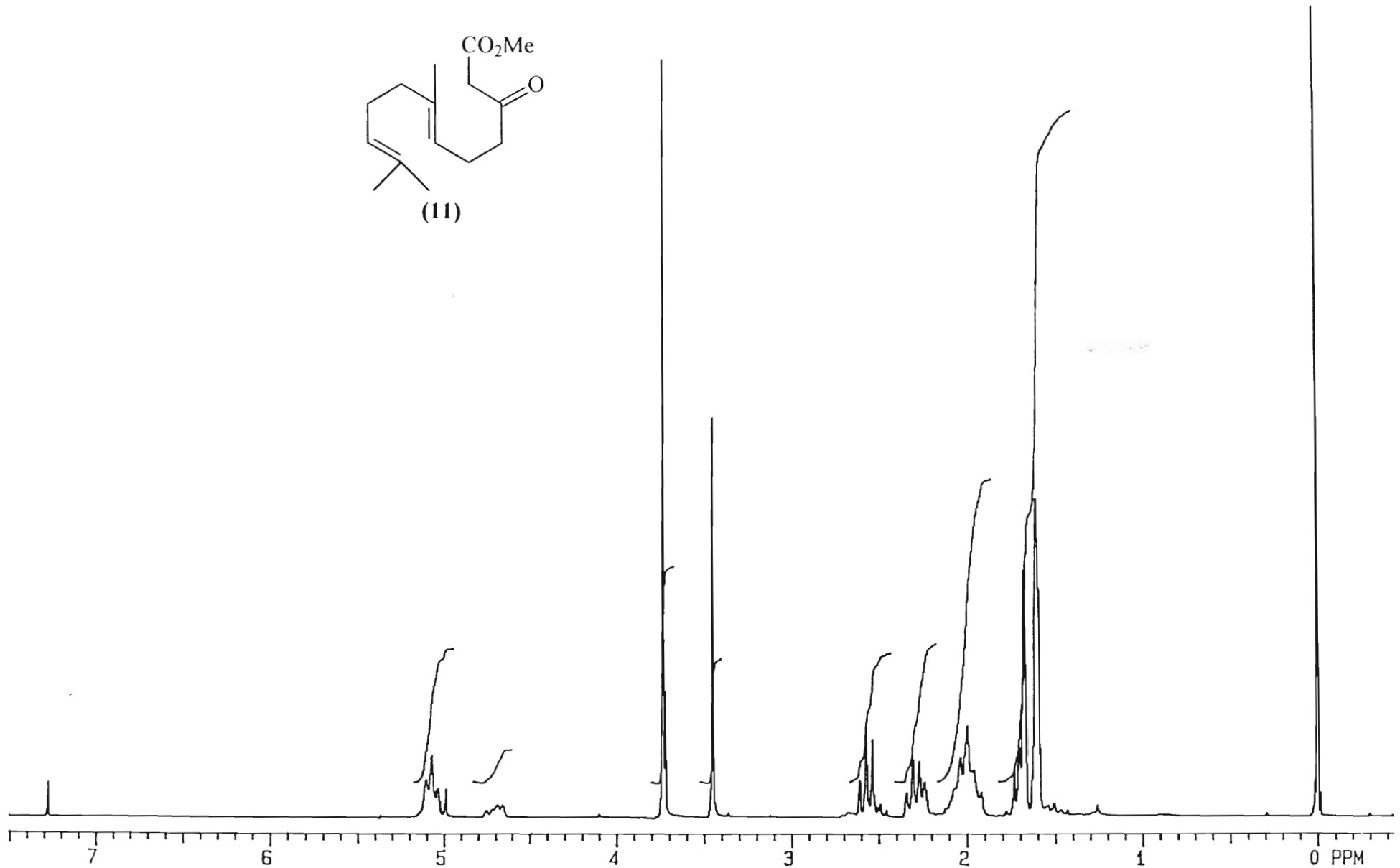

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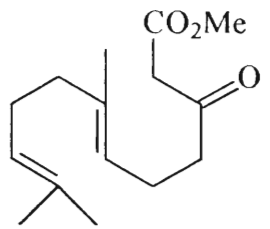

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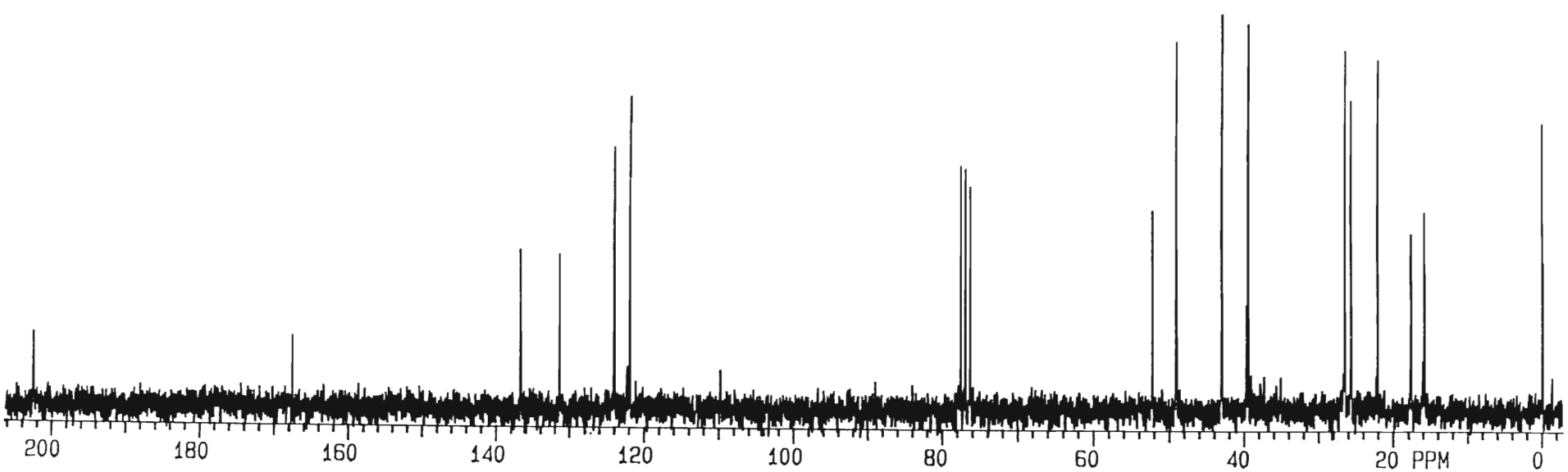

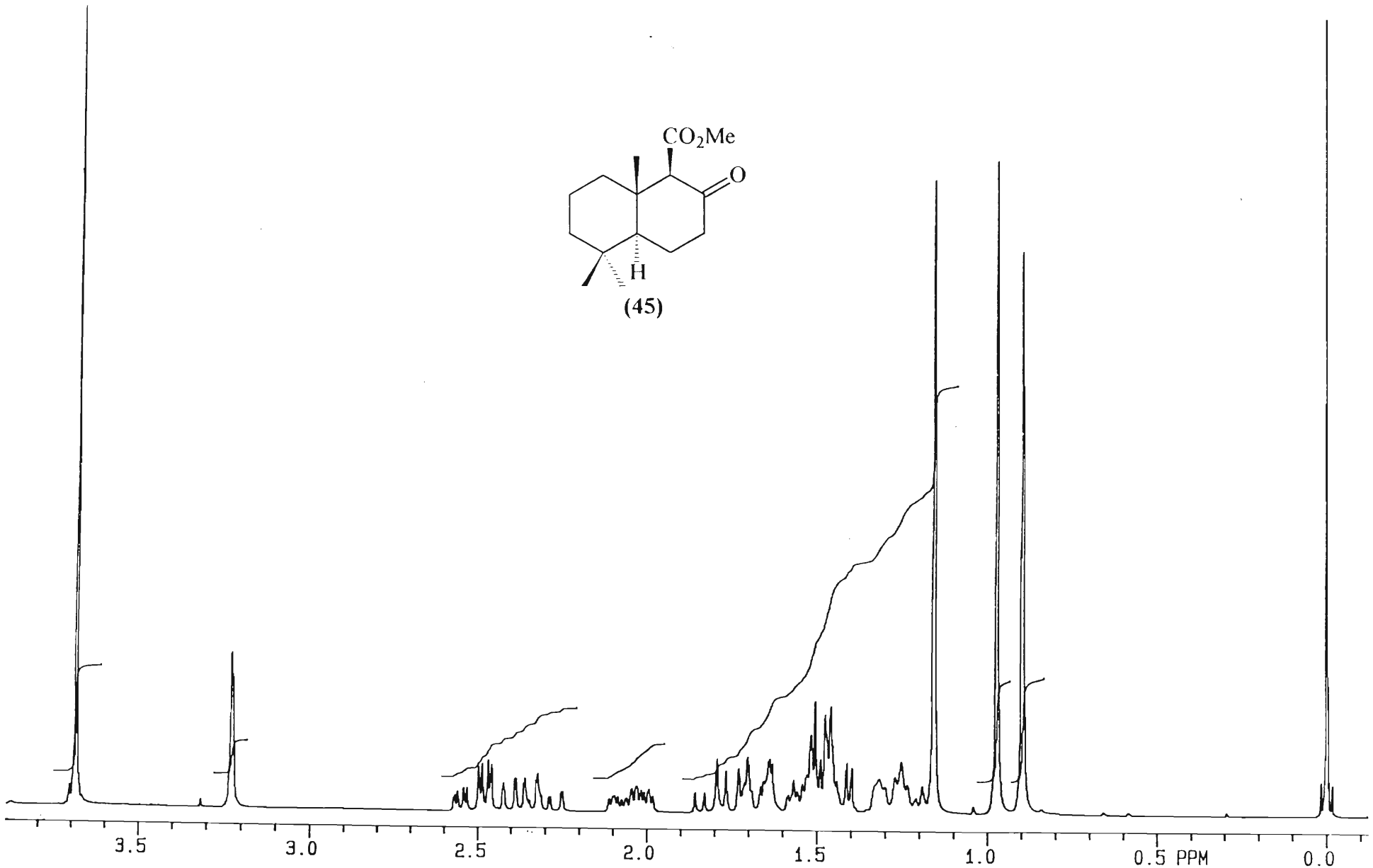

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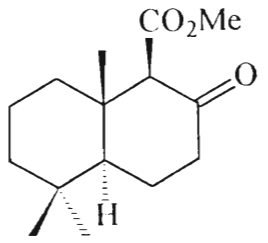

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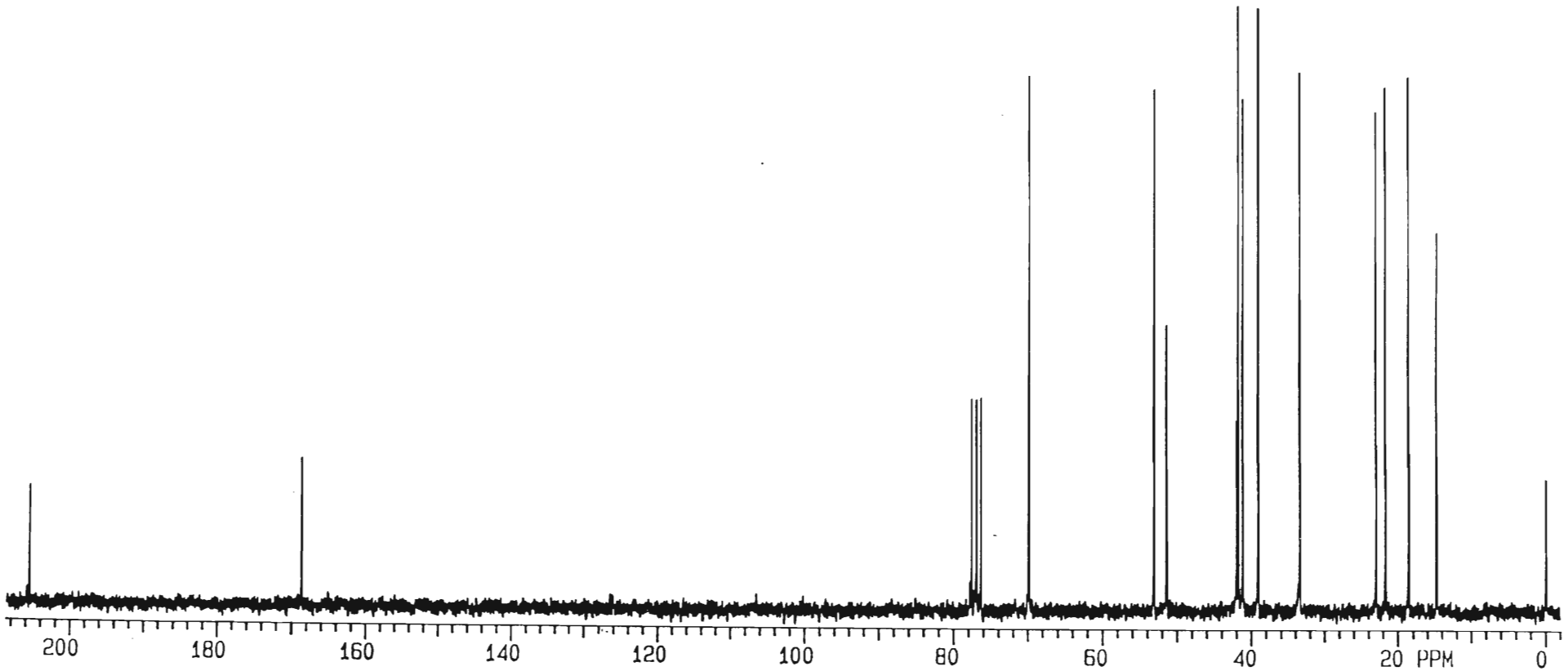

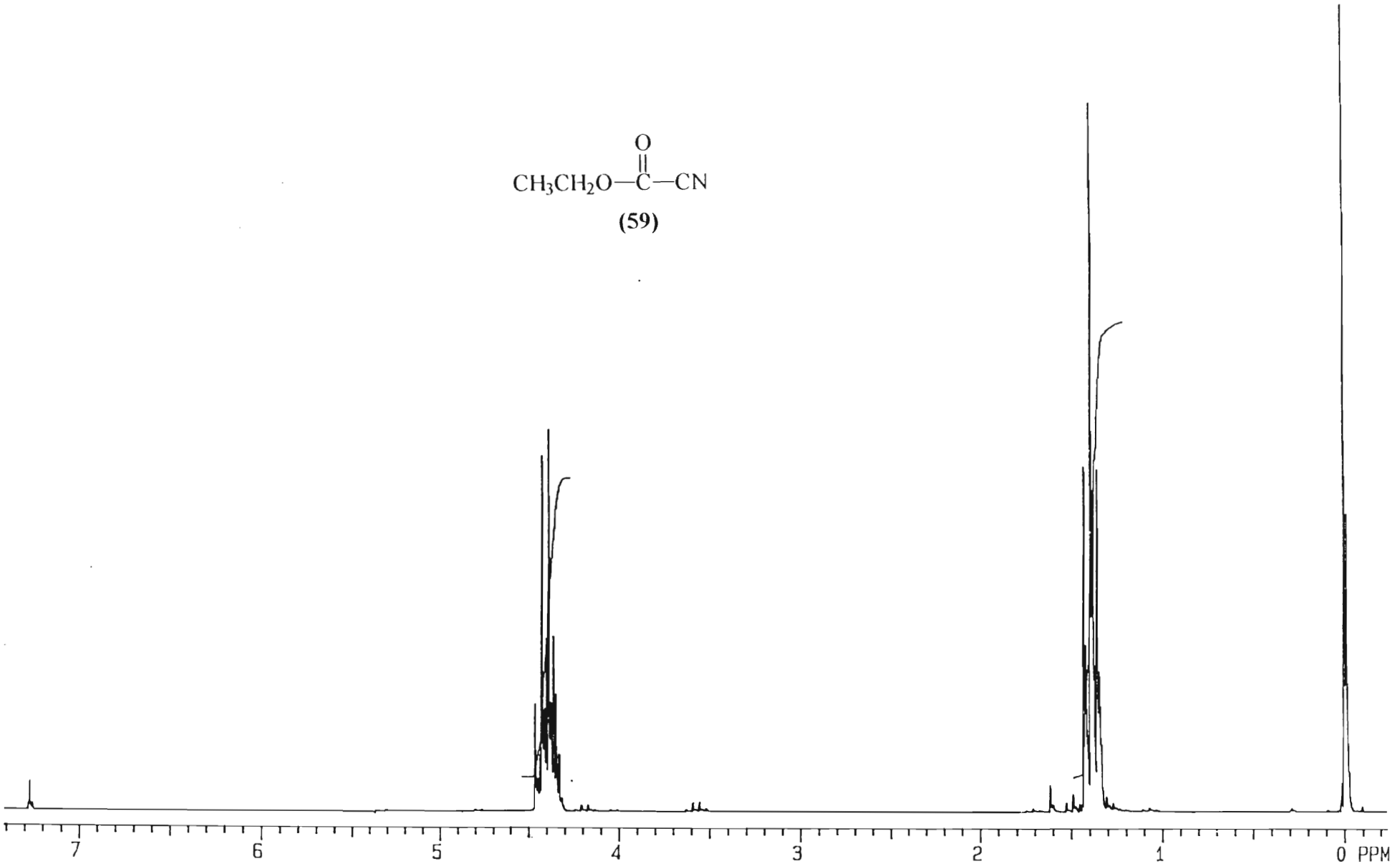

$CH_3CH_2O-\overset{\overset{O}{\|}}{C}-CN$

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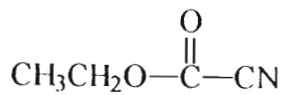

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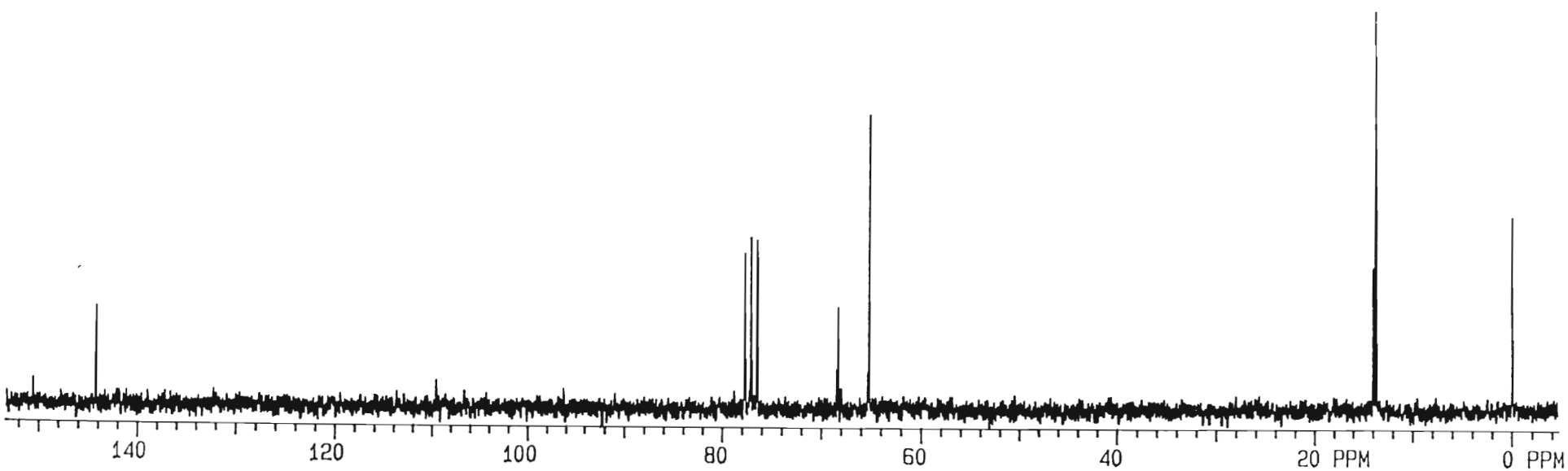

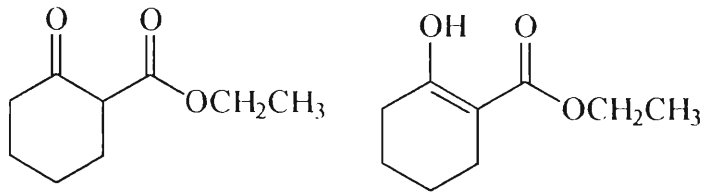

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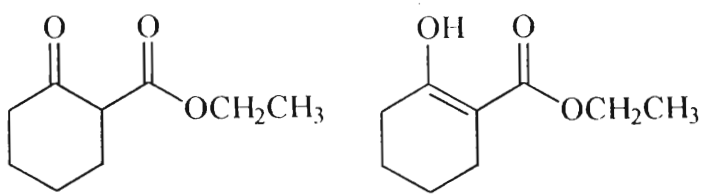

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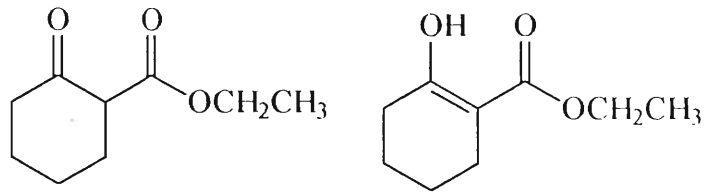

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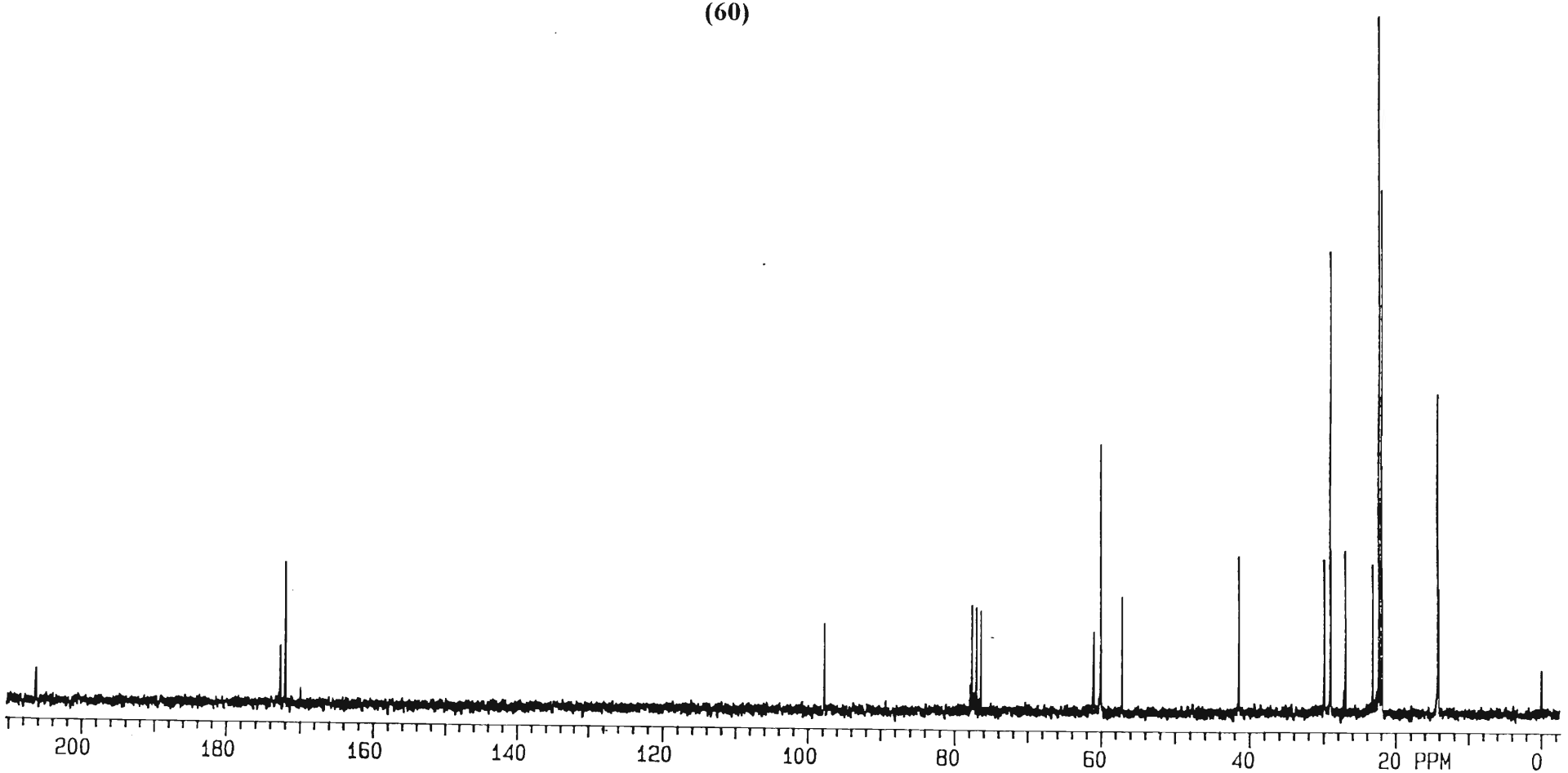

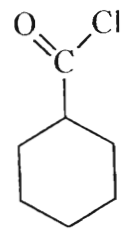

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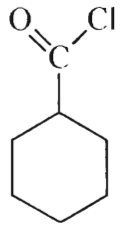

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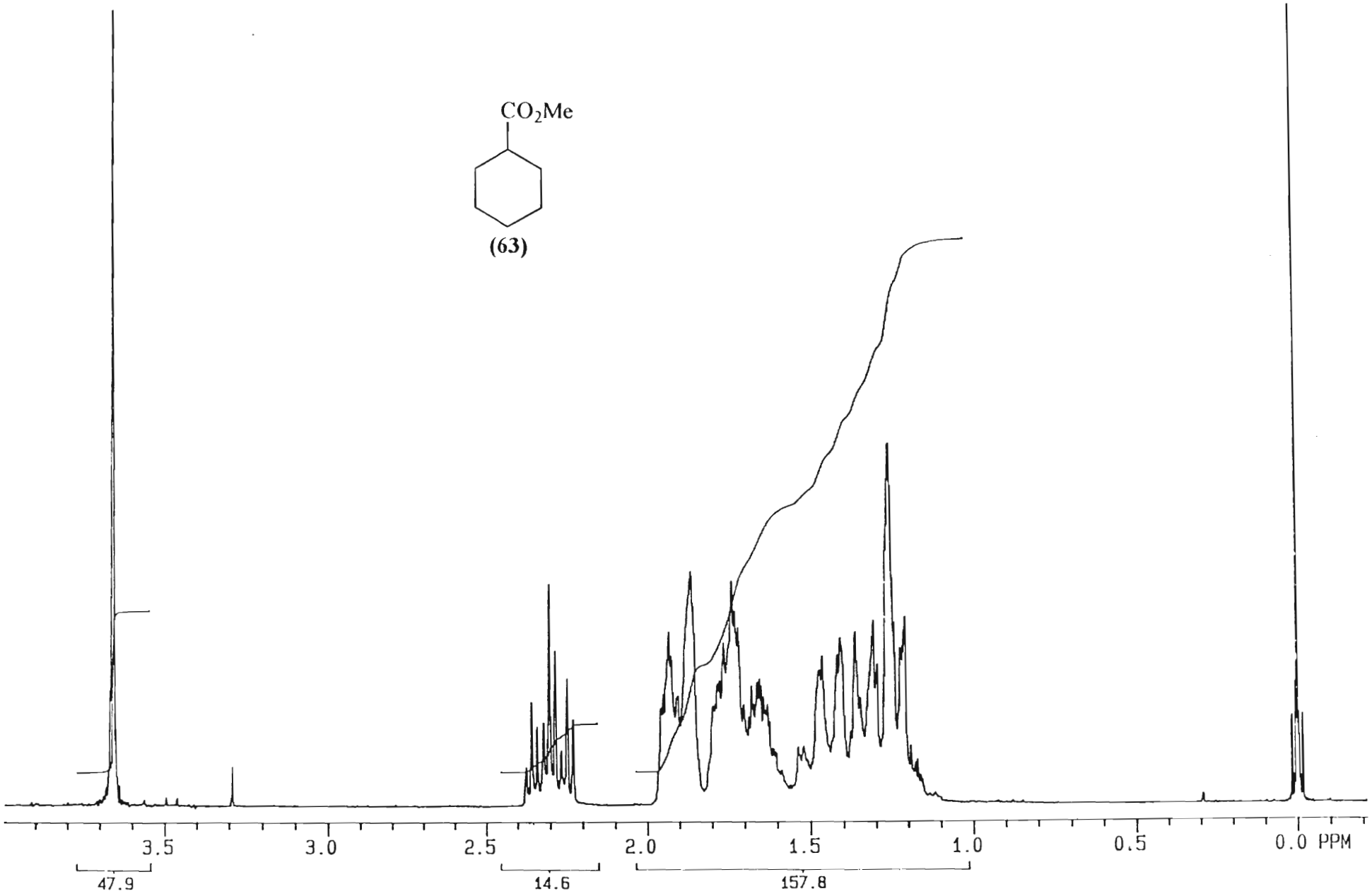
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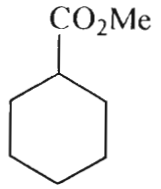
157.8



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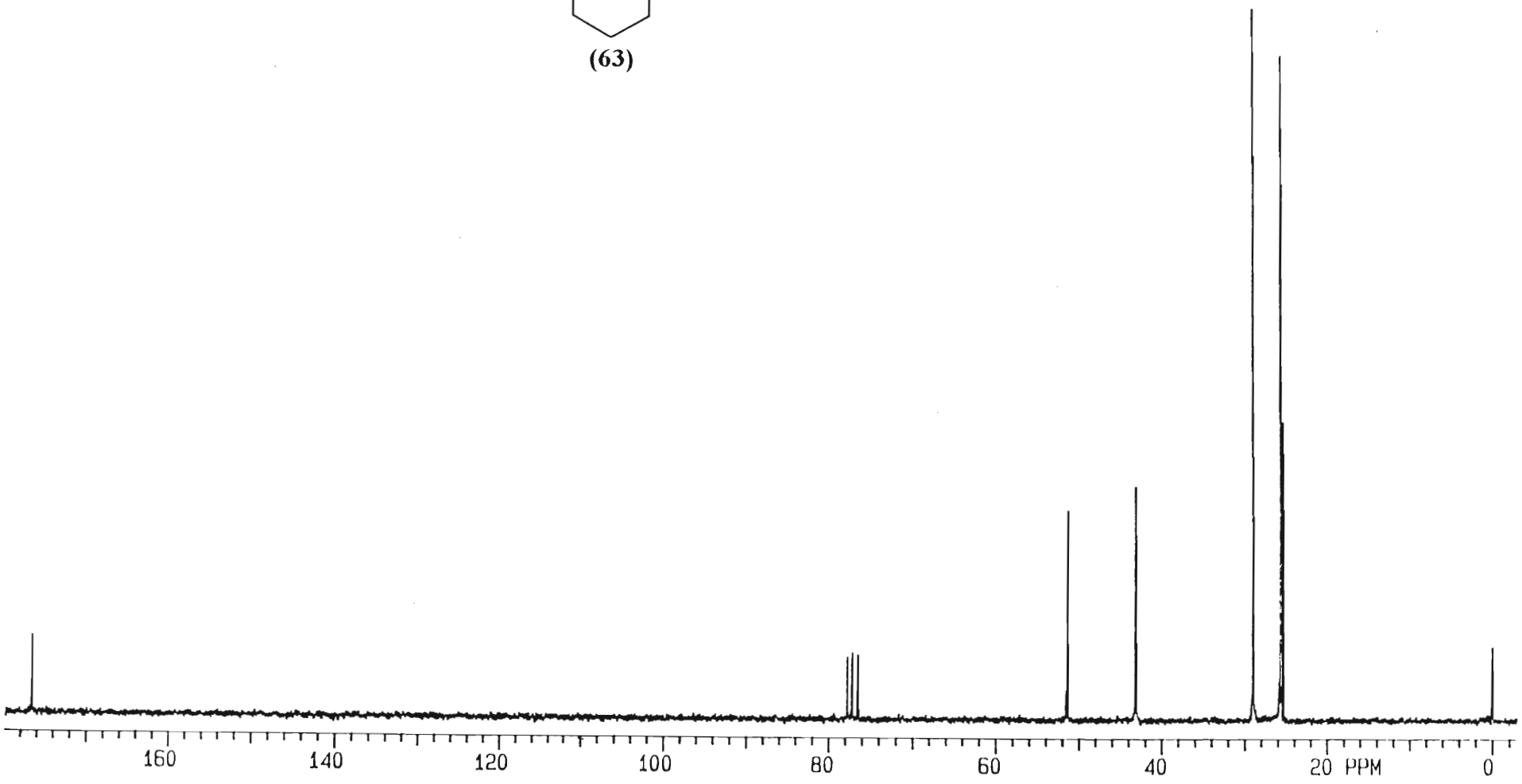

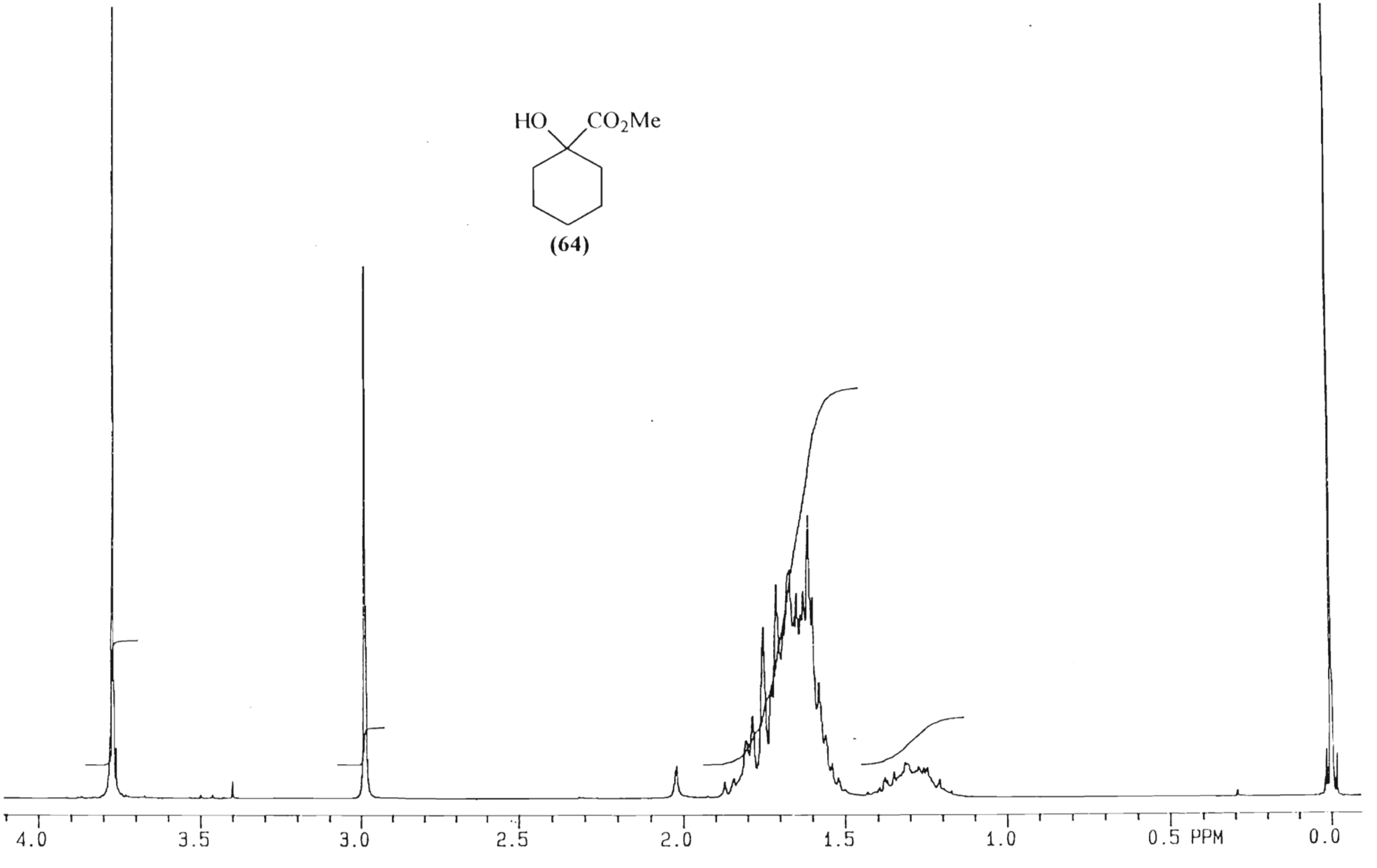

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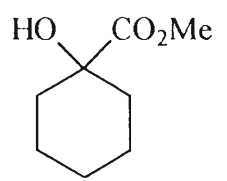

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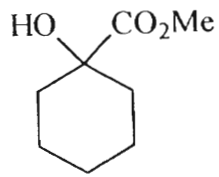

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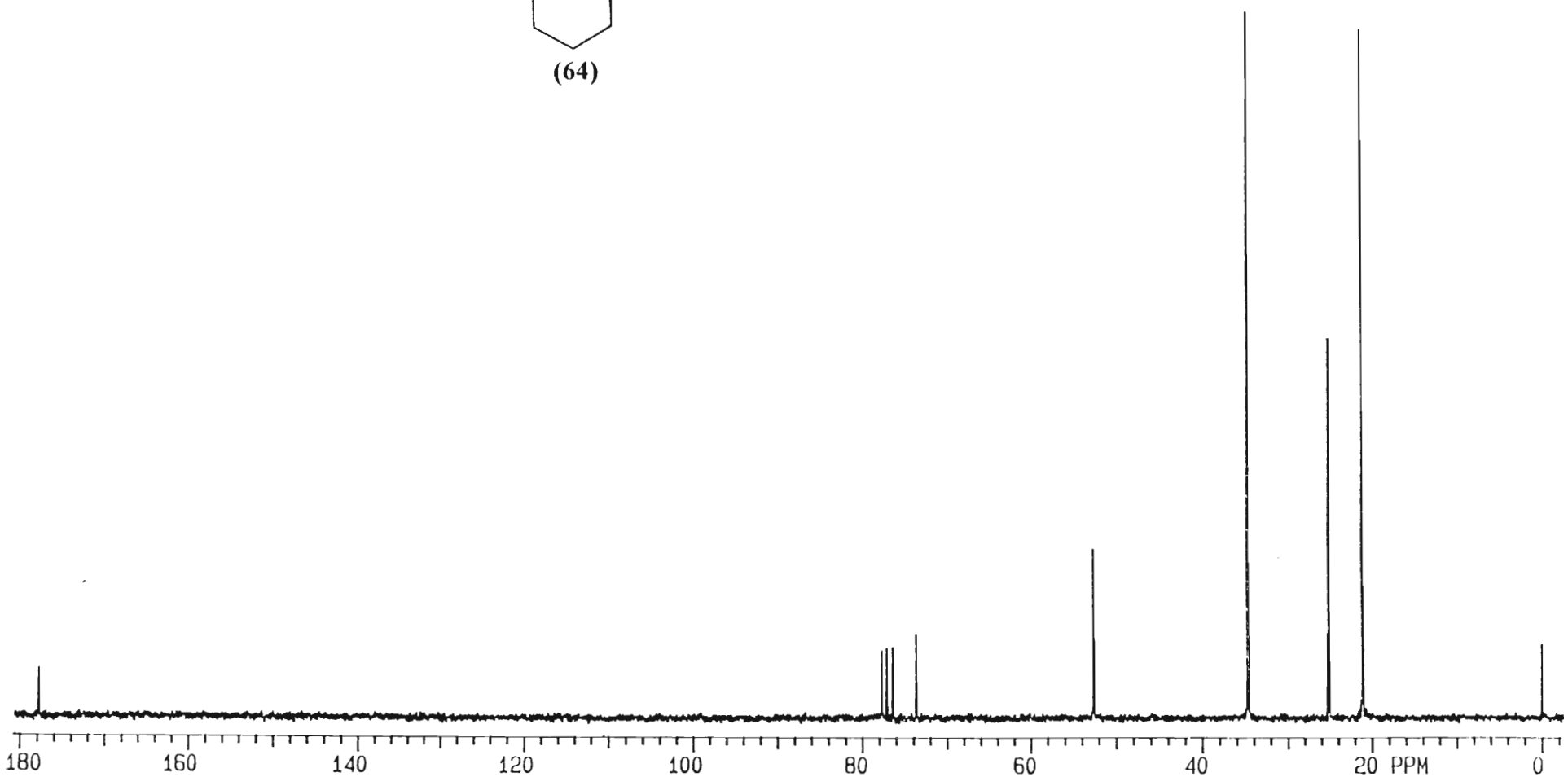

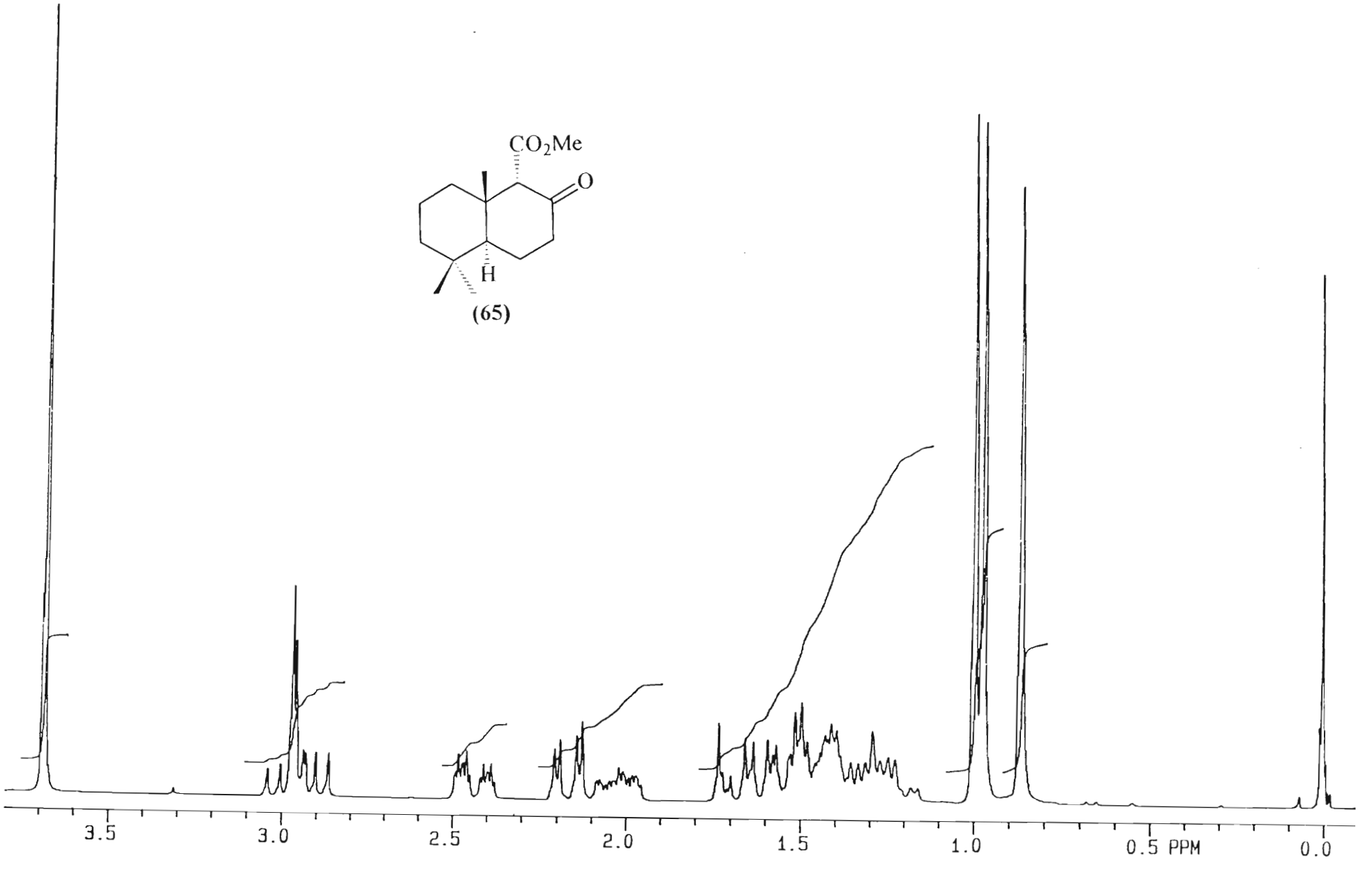

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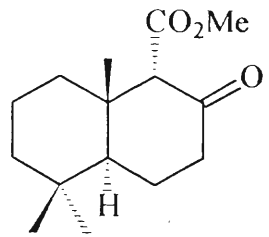

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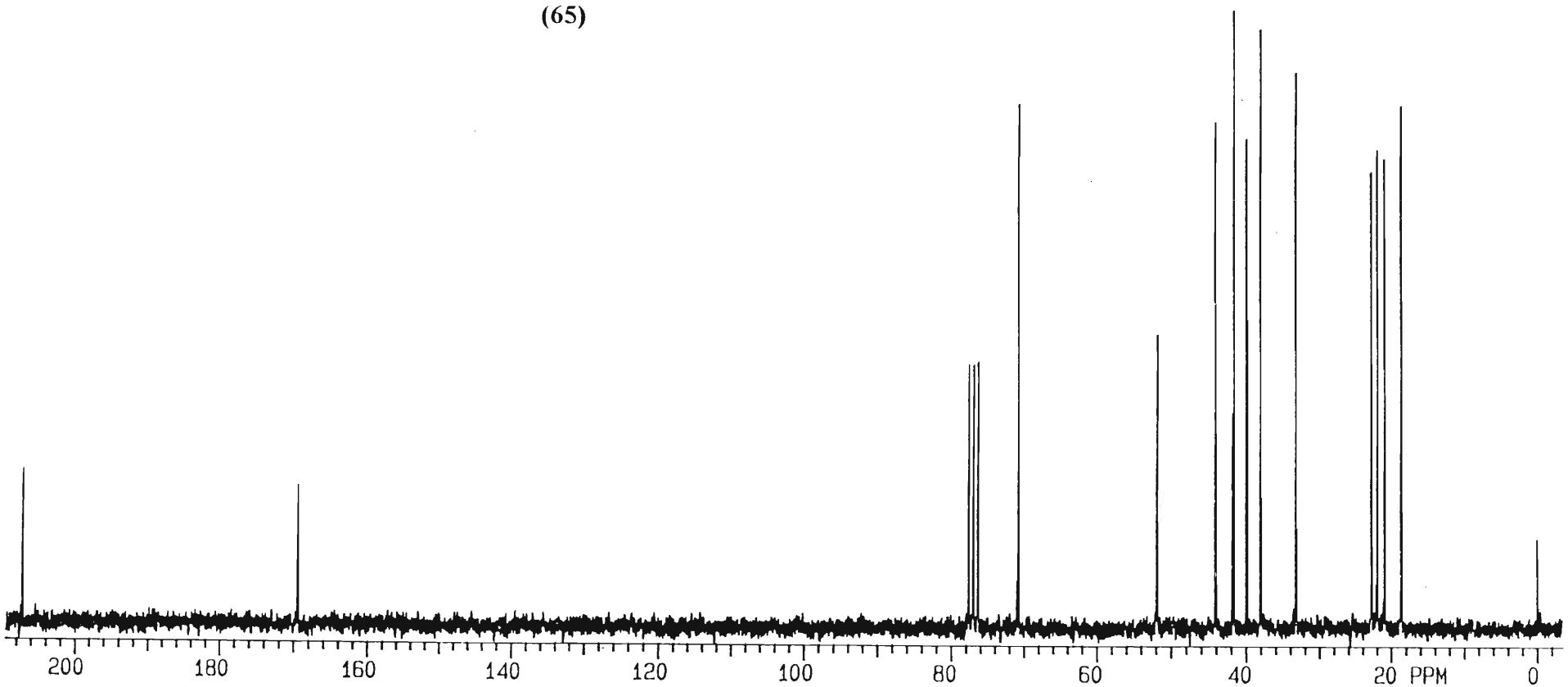

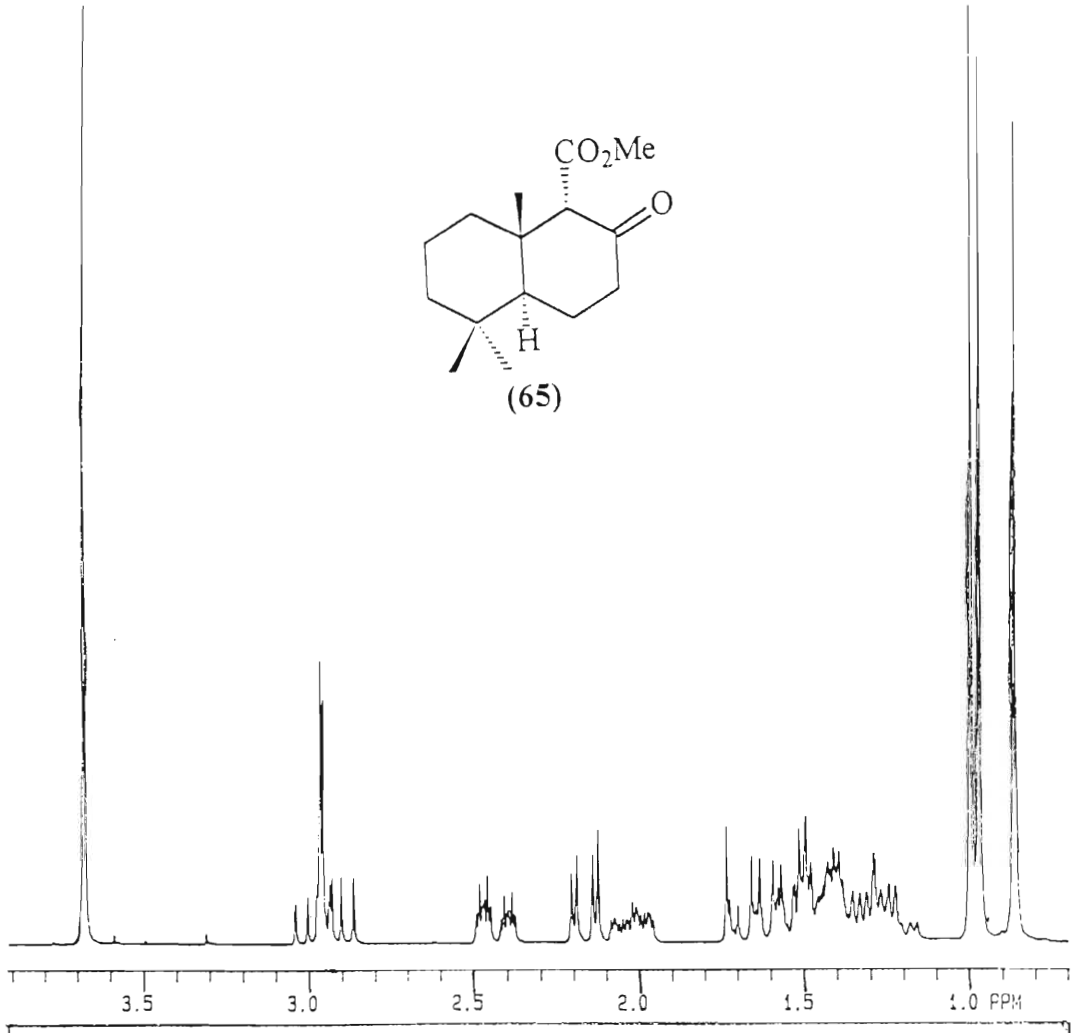

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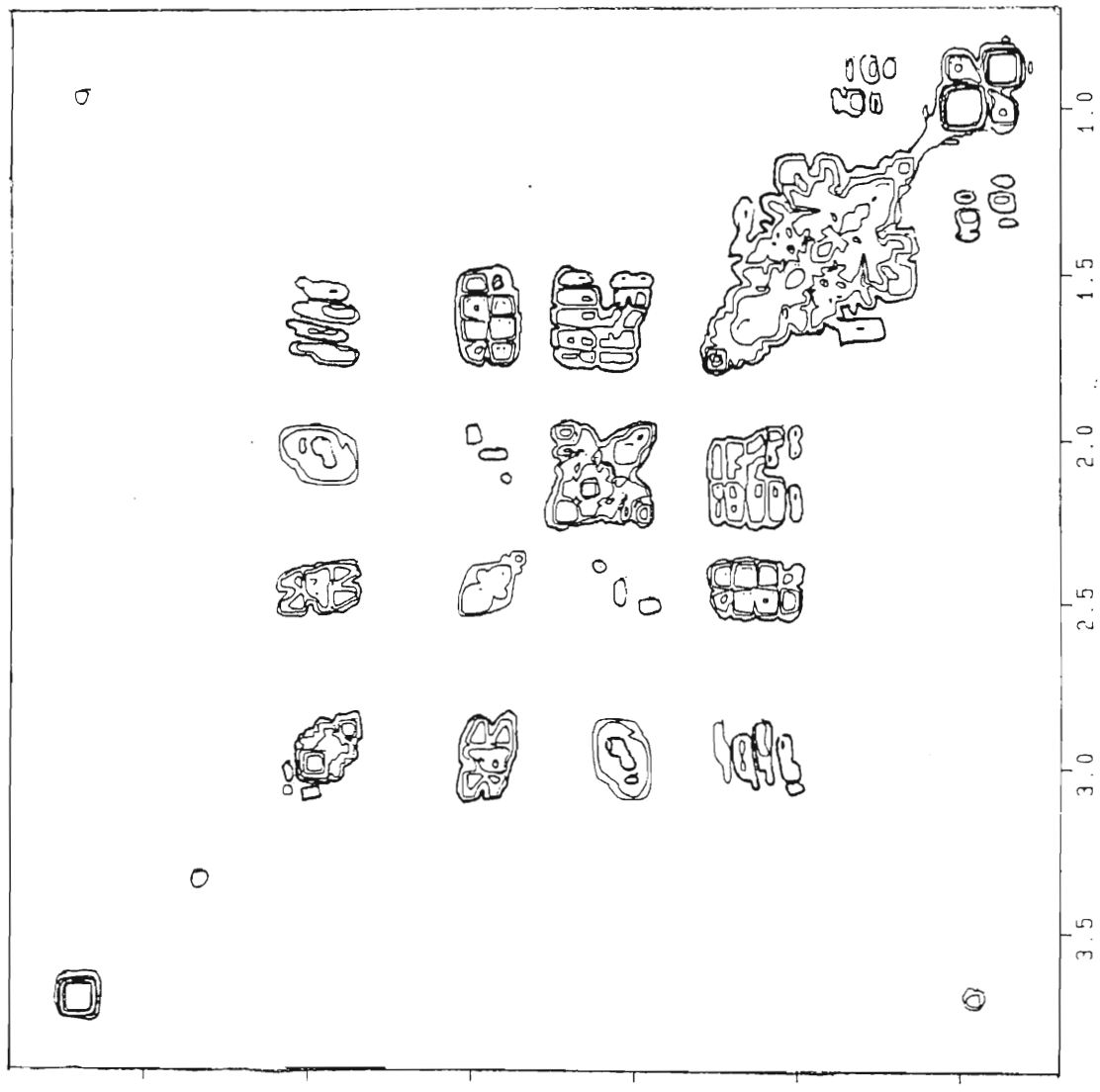

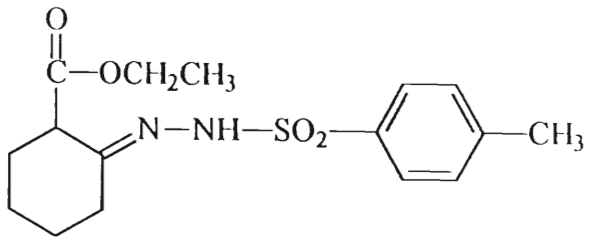

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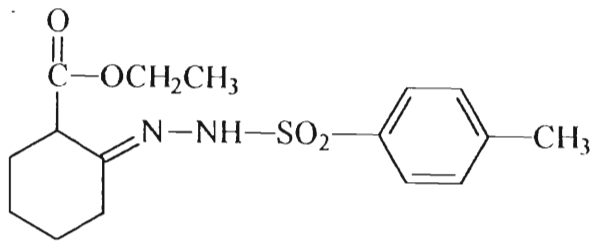

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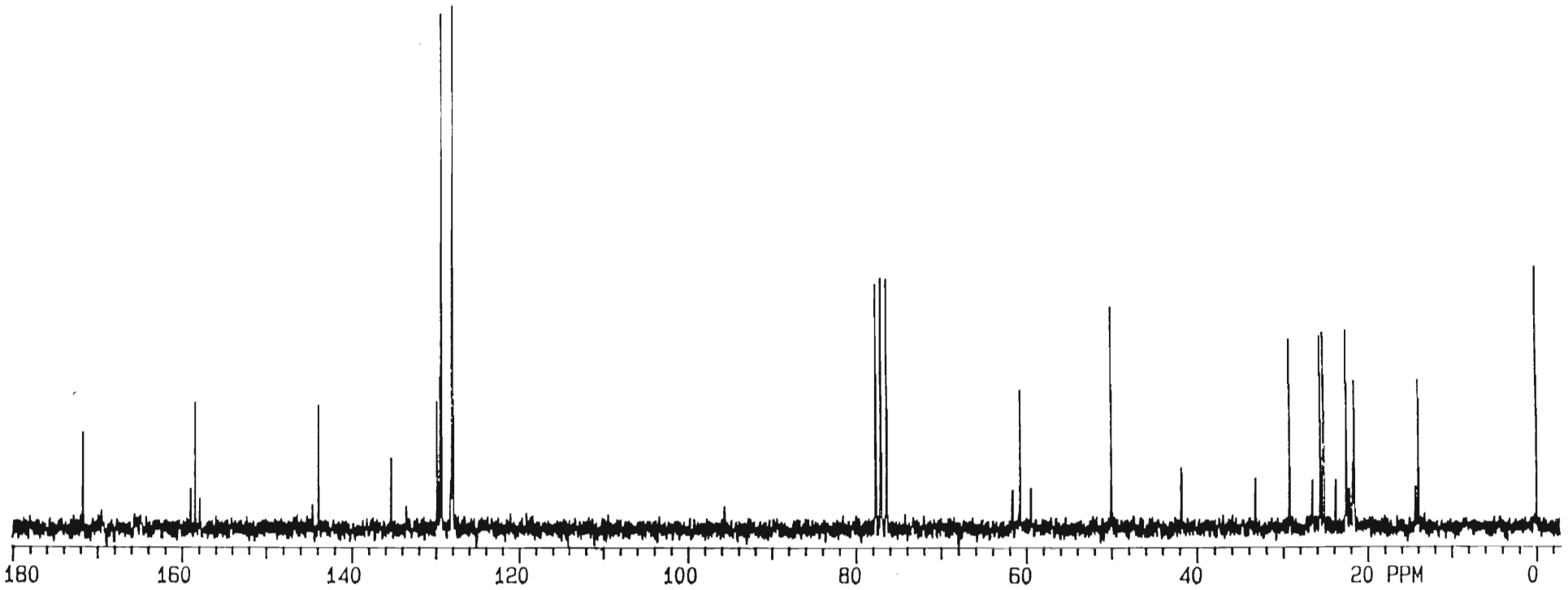

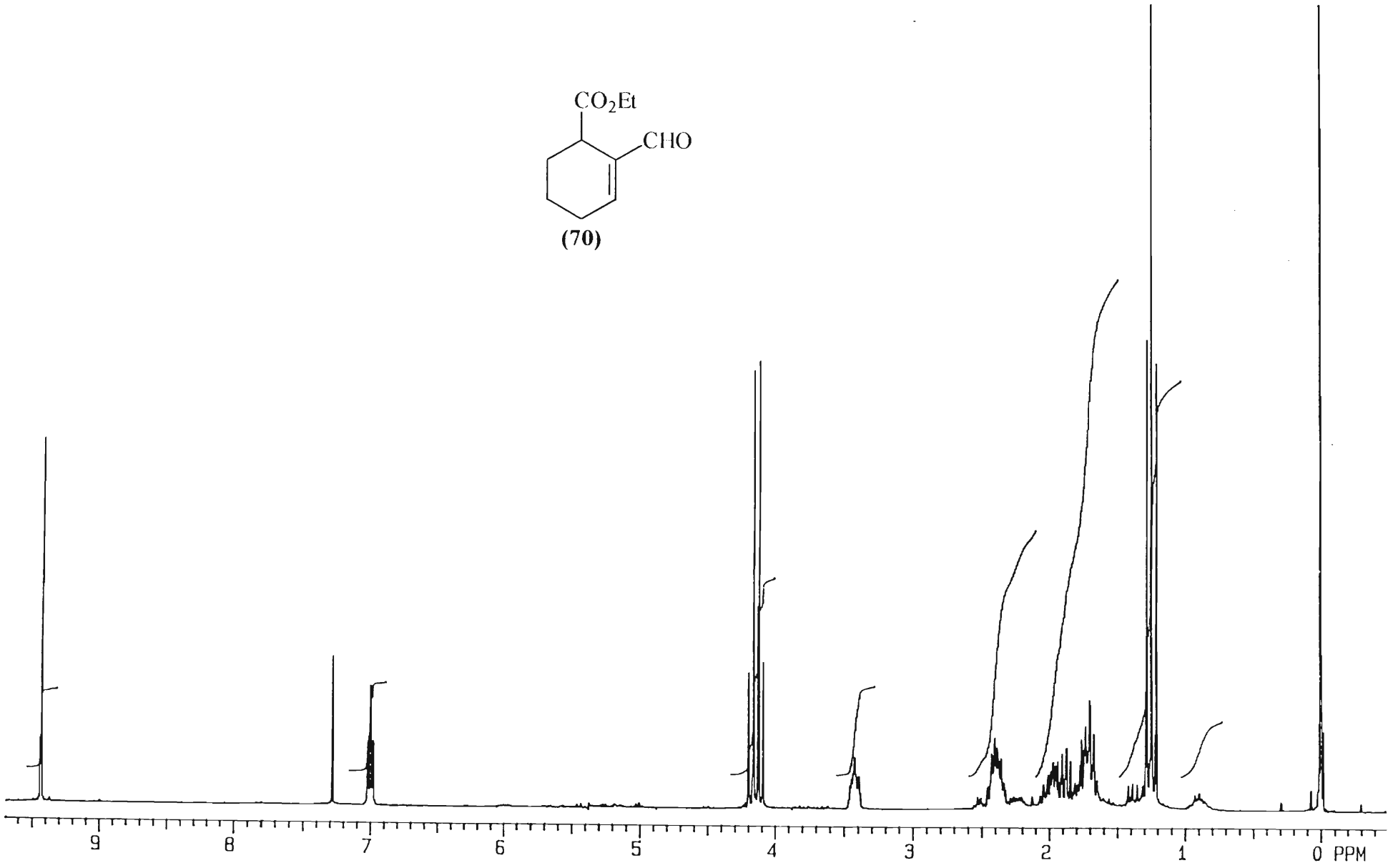
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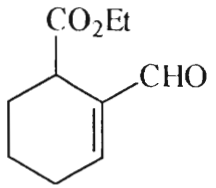

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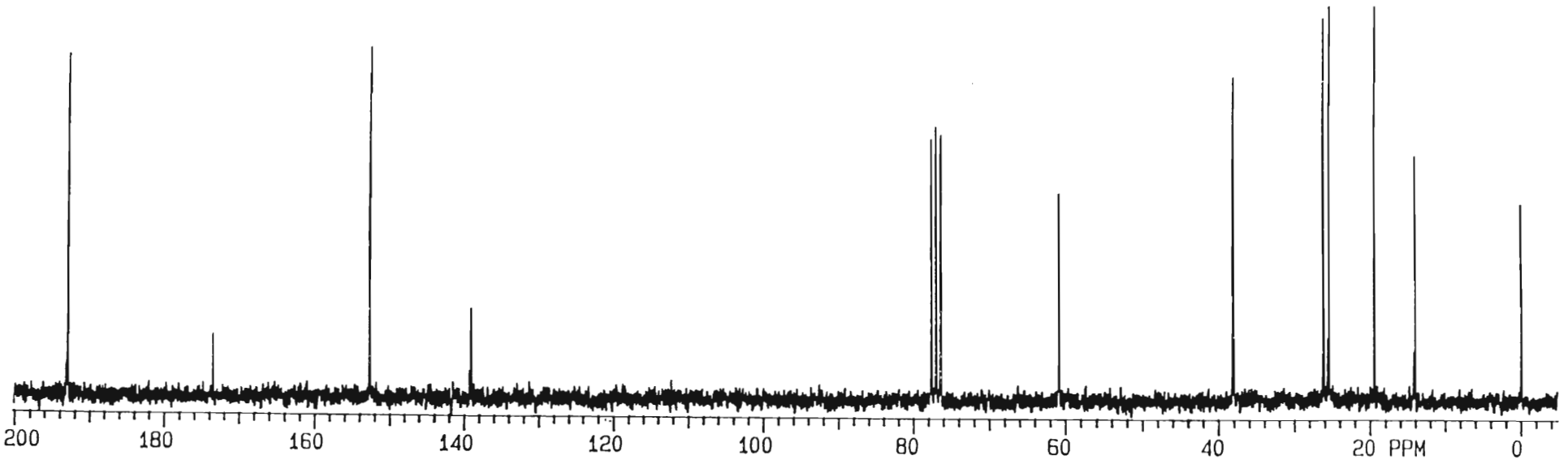

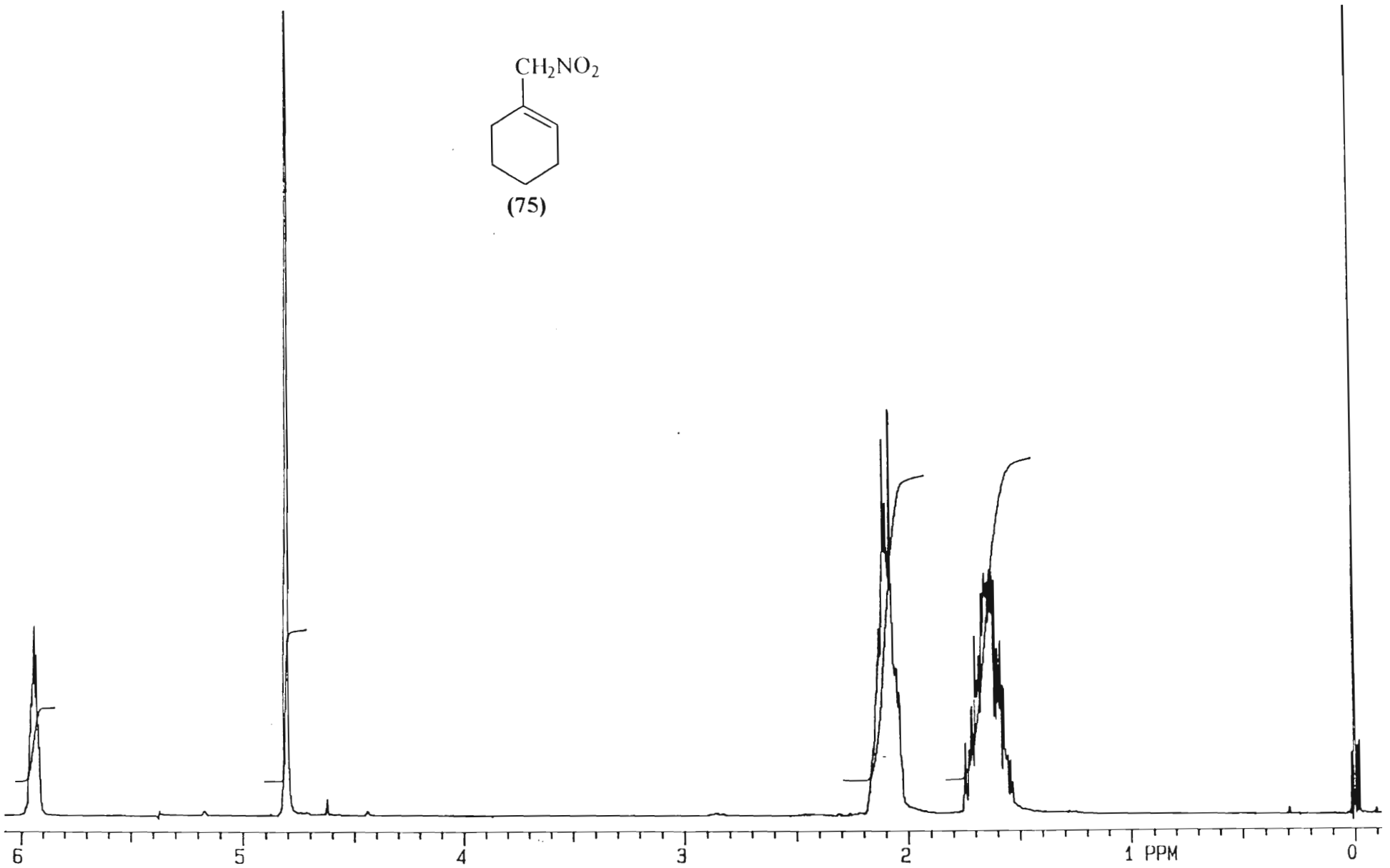

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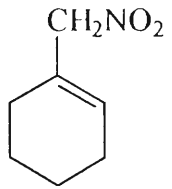

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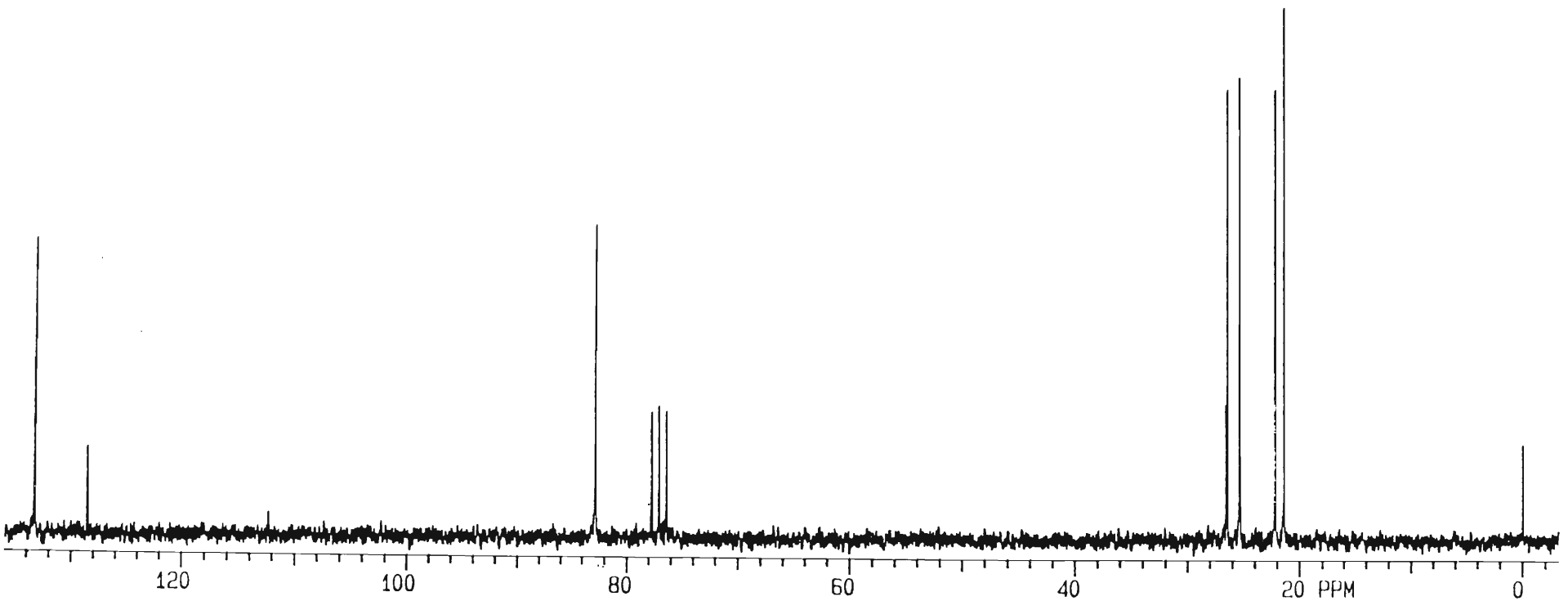

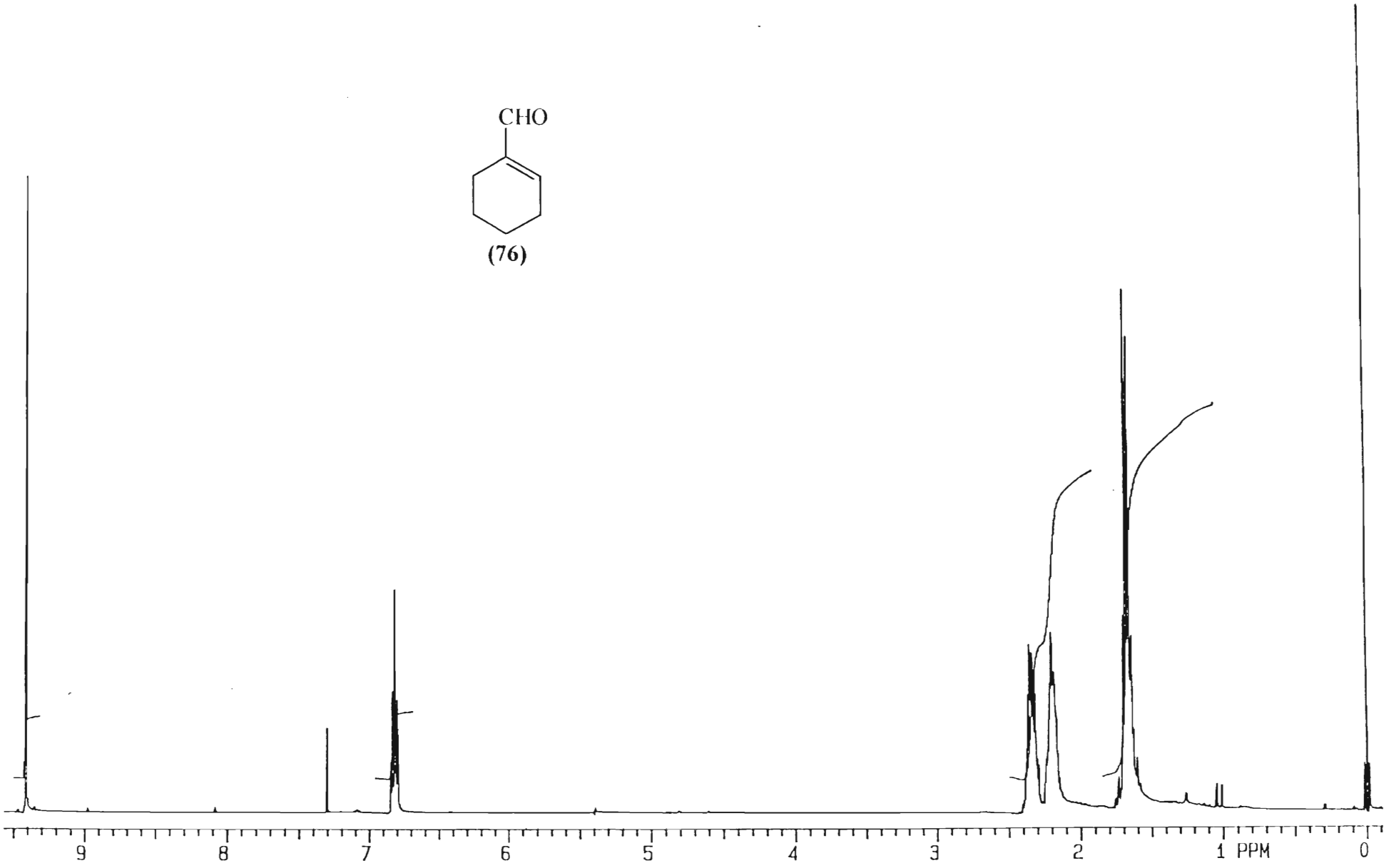

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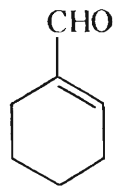

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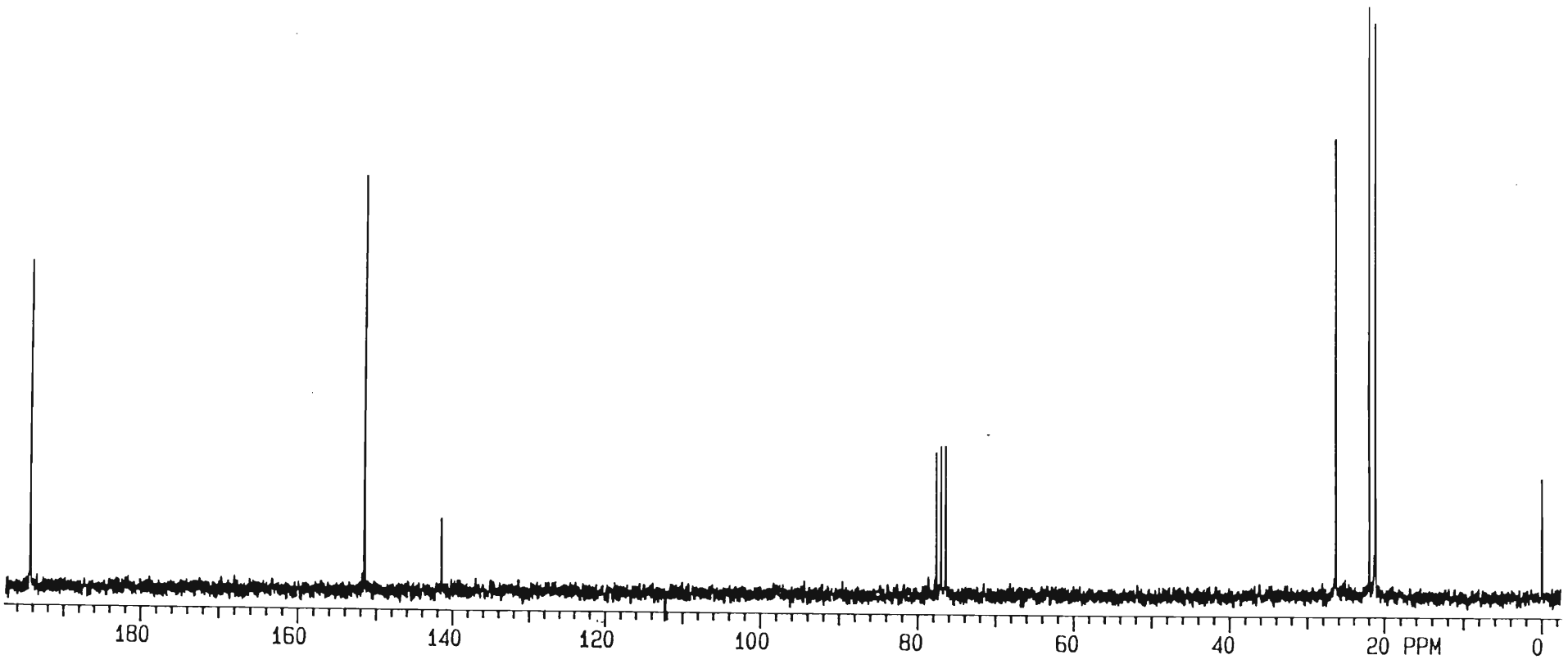

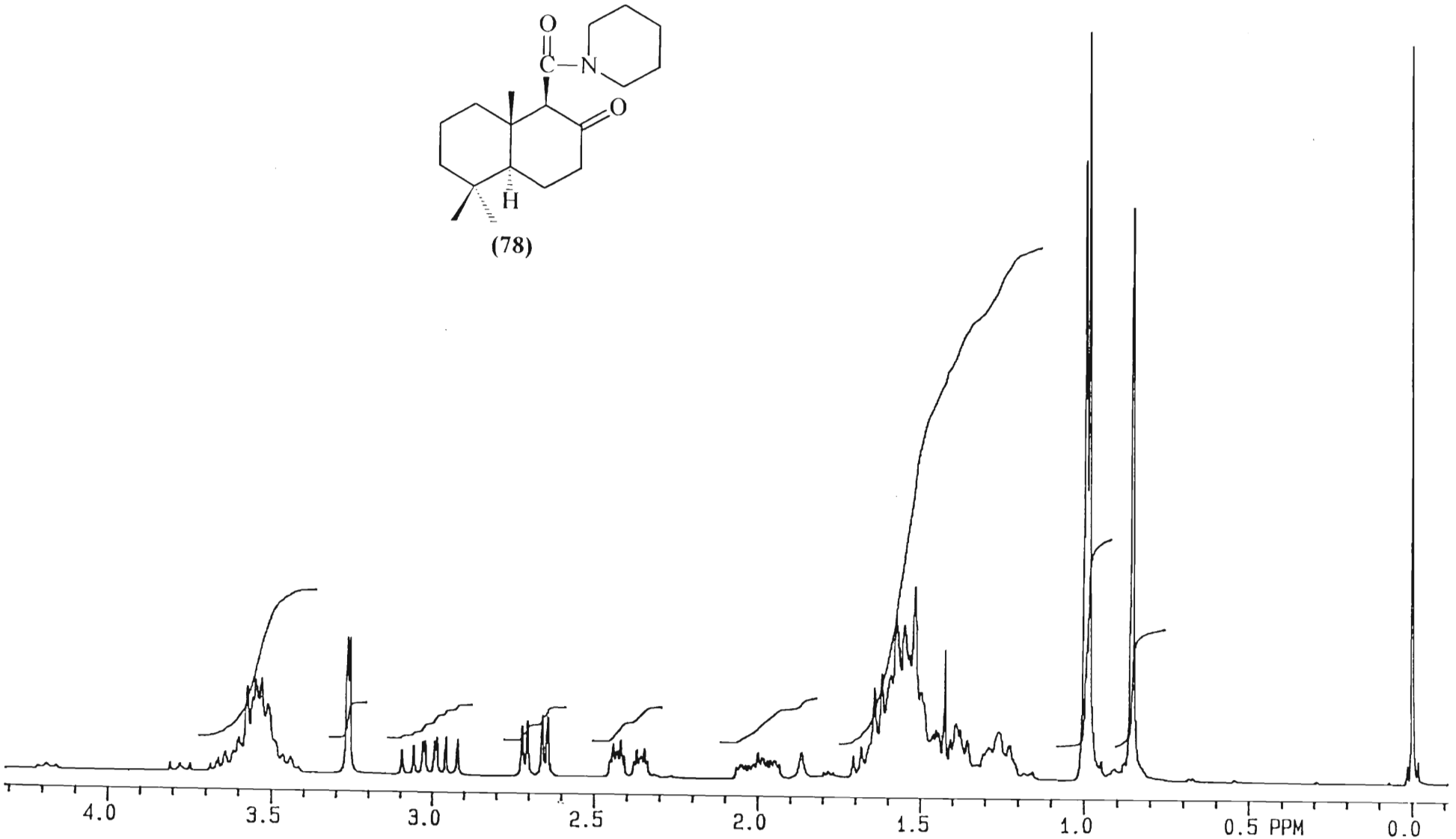

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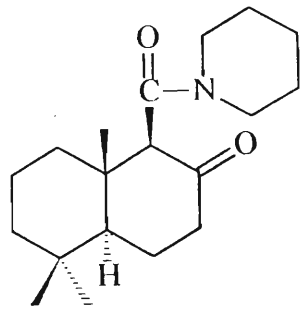

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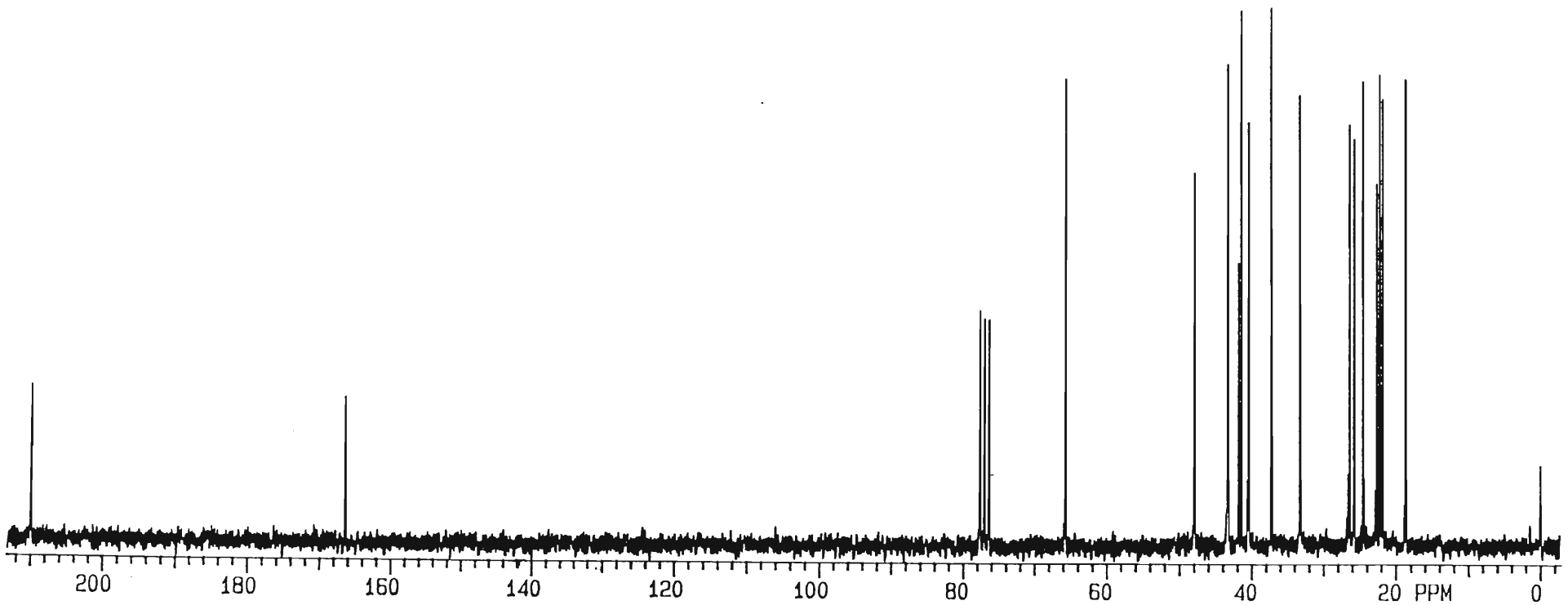

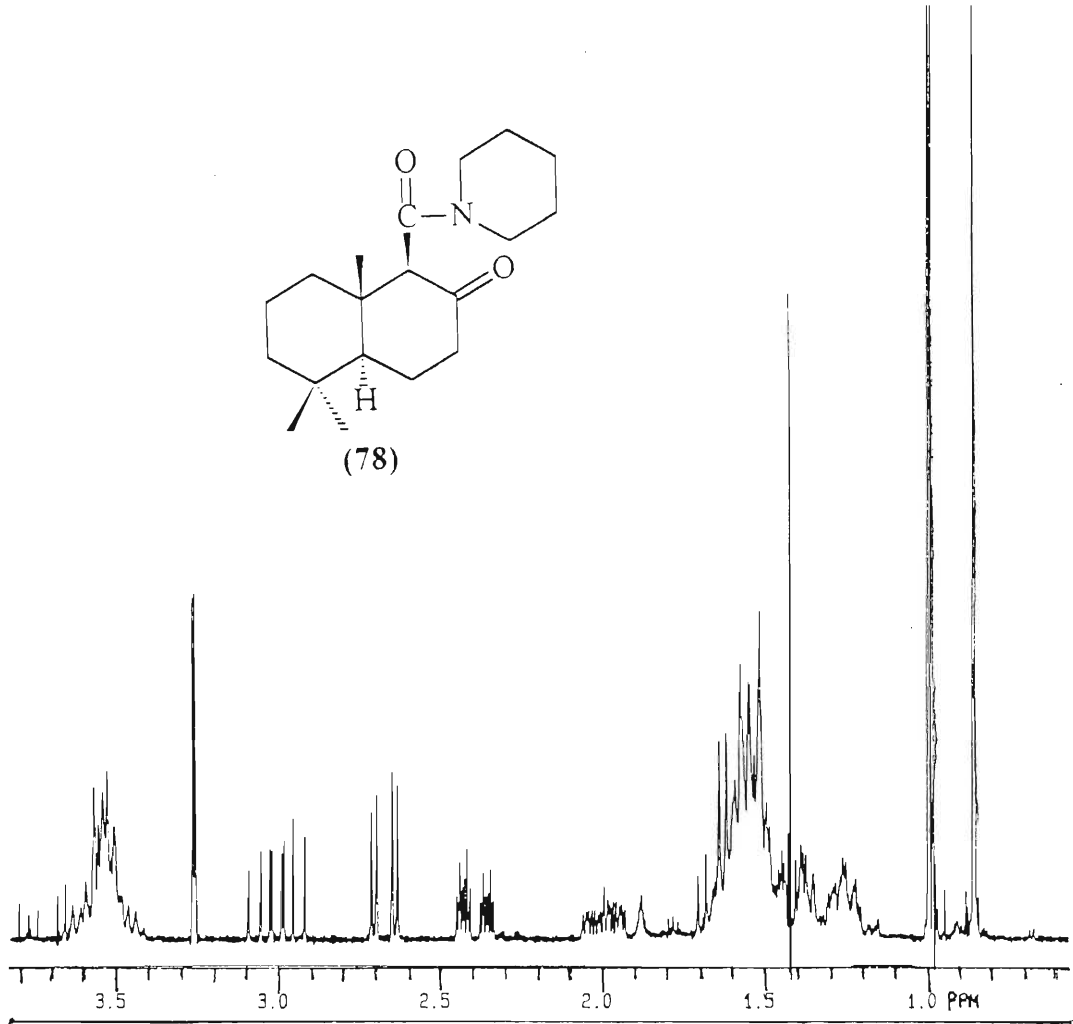

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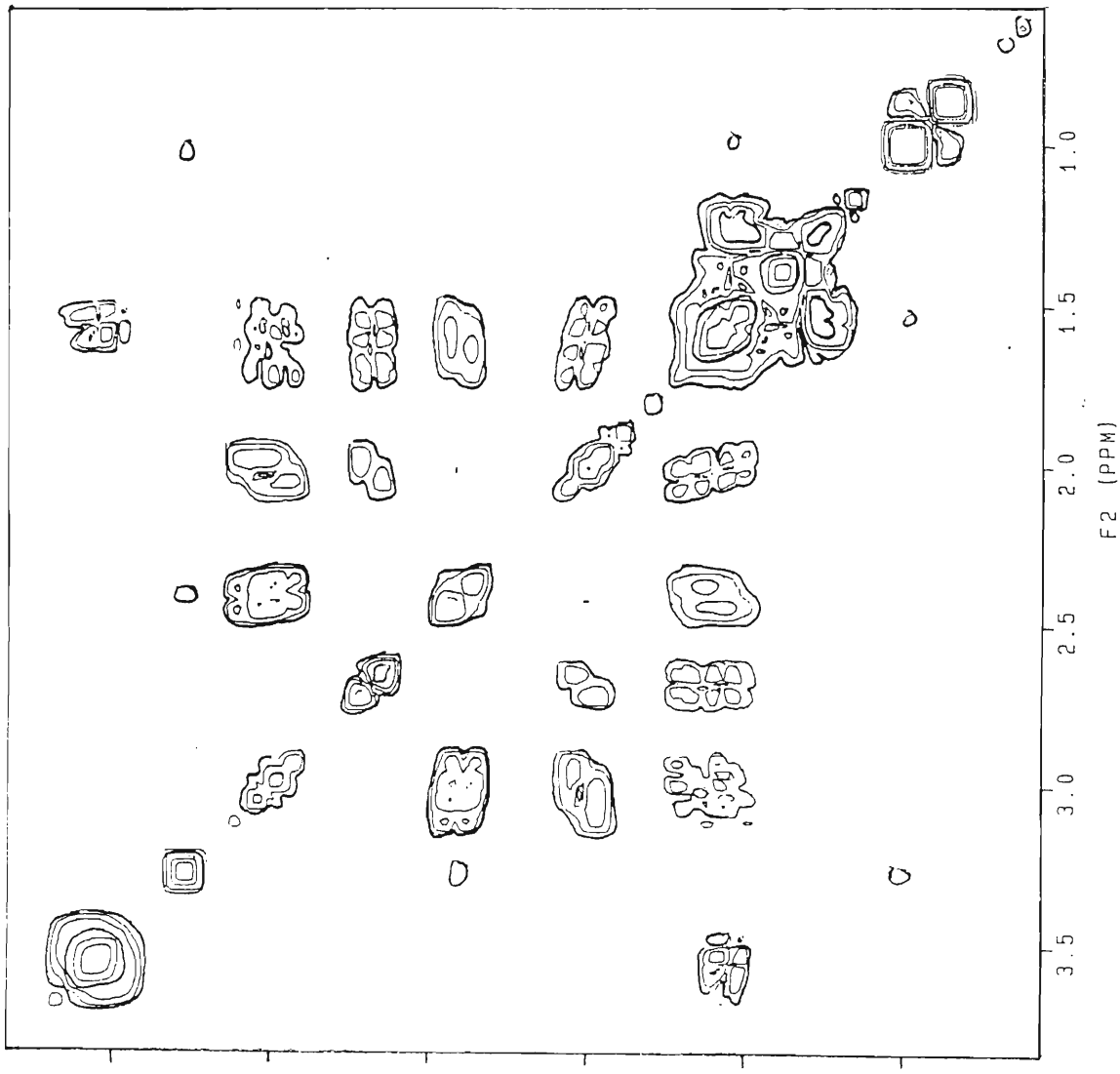

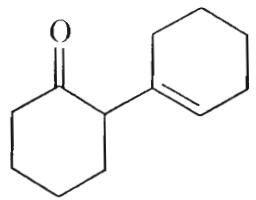

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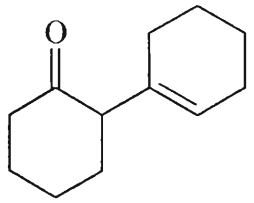

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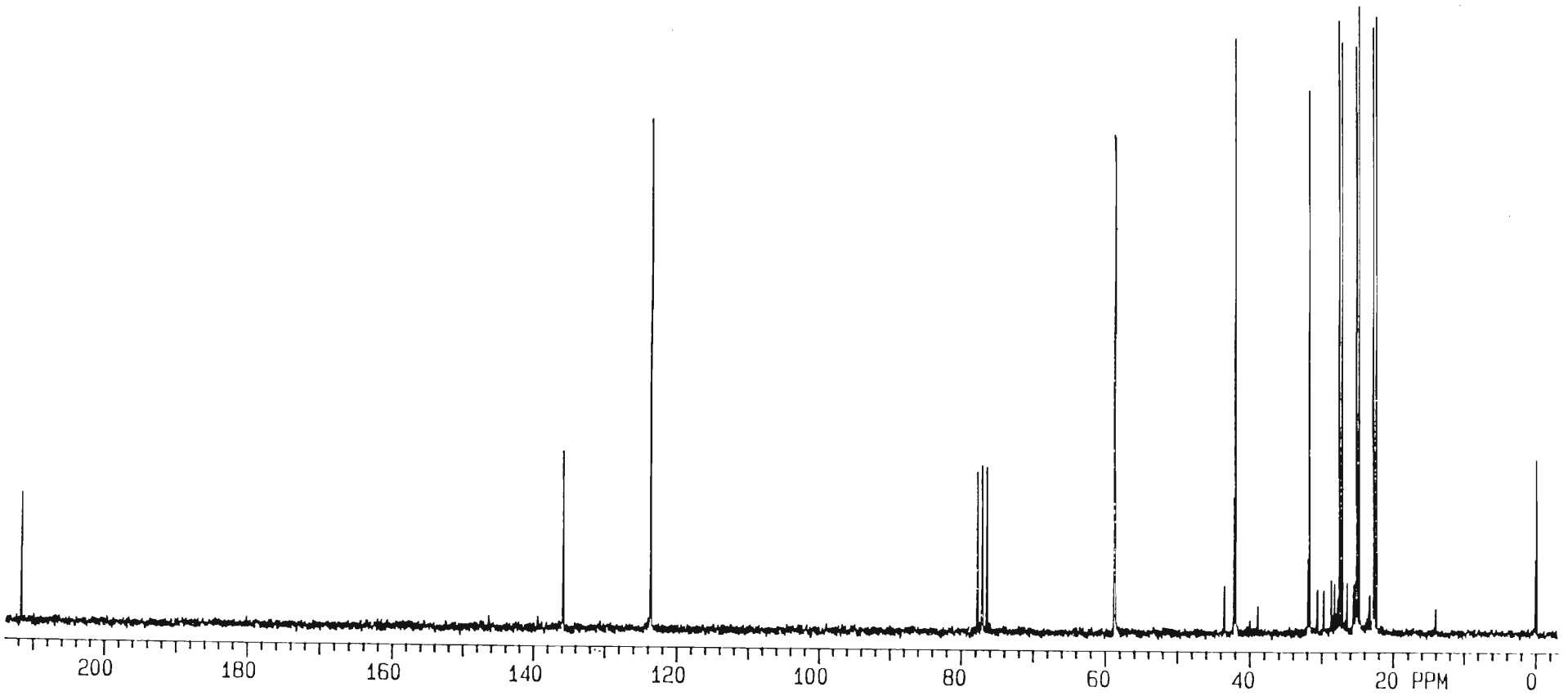

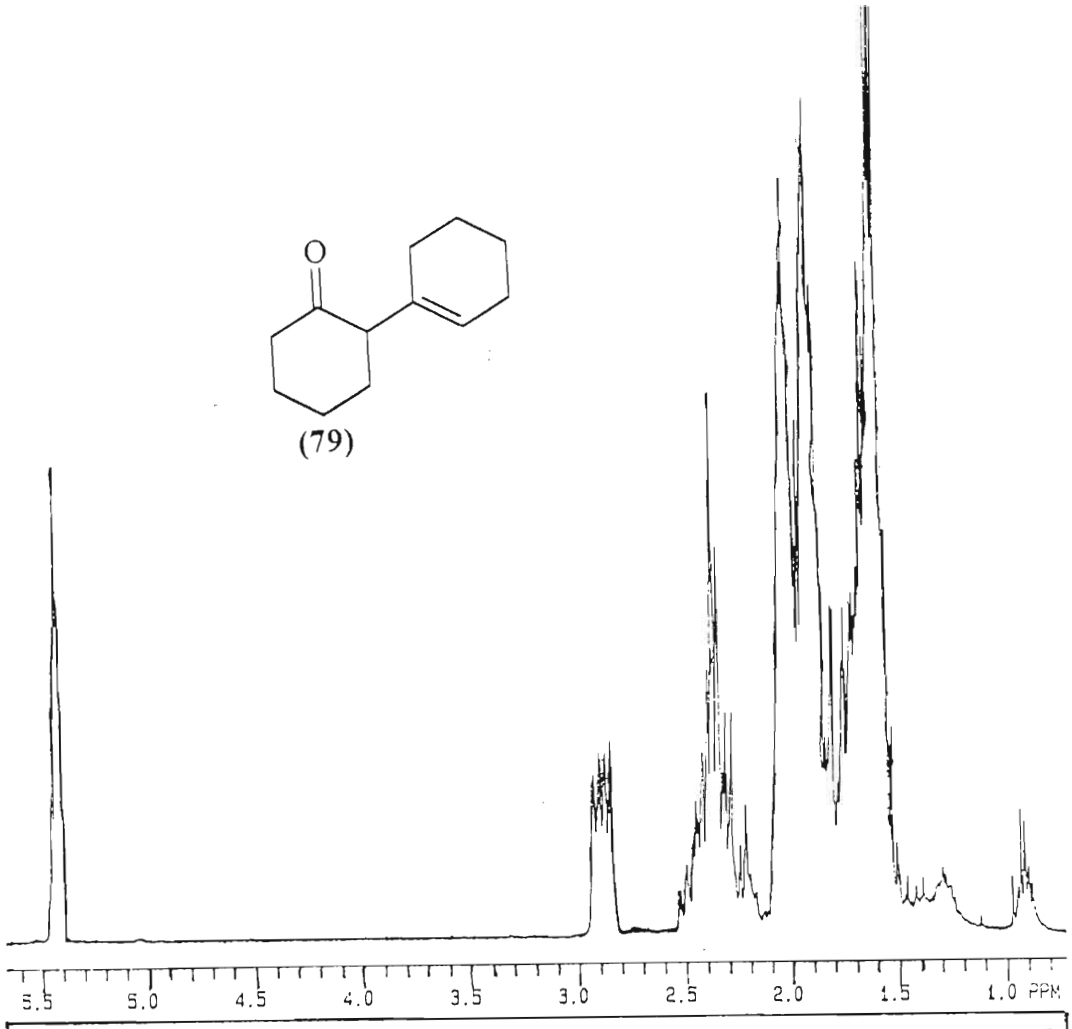

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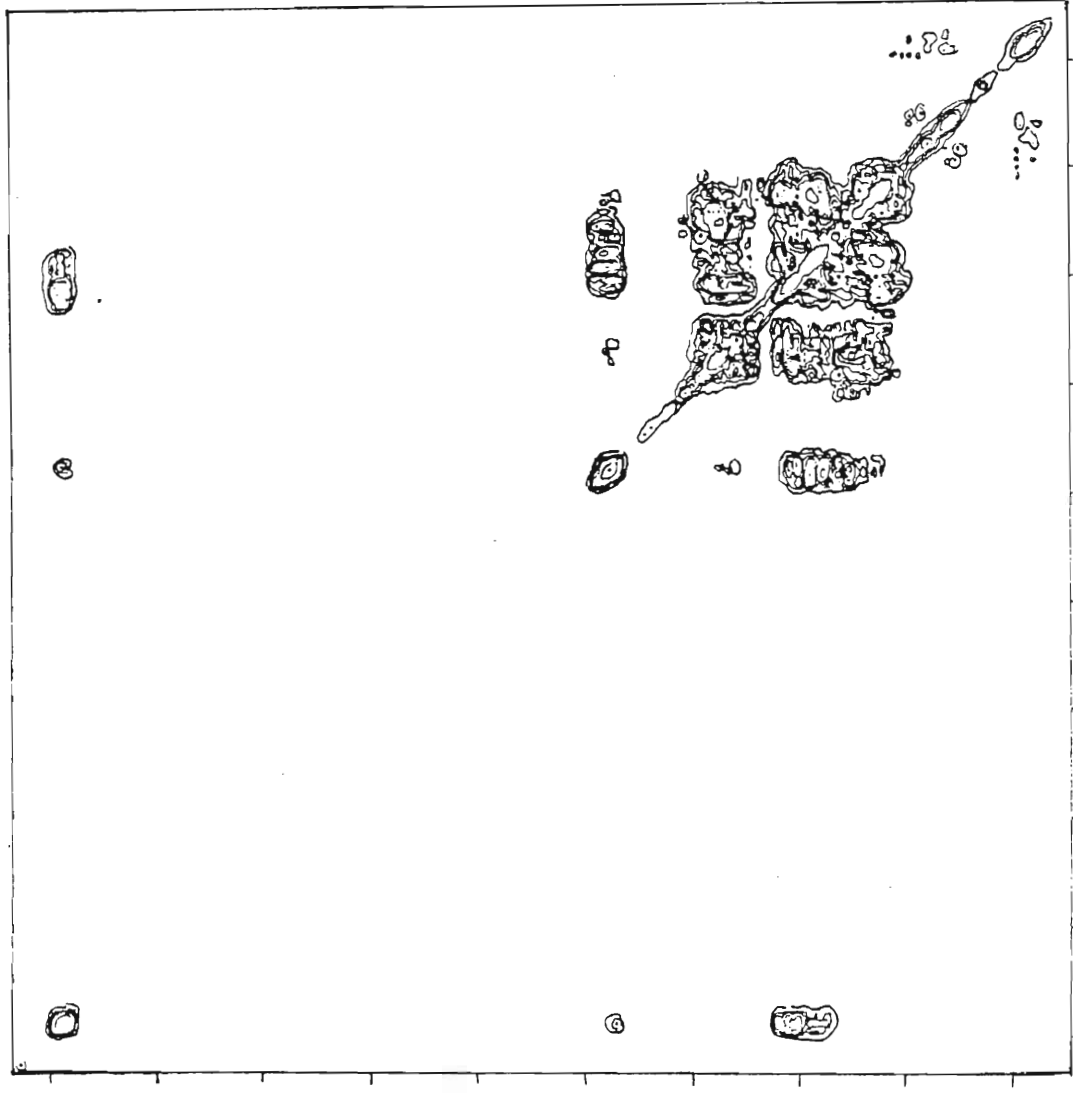

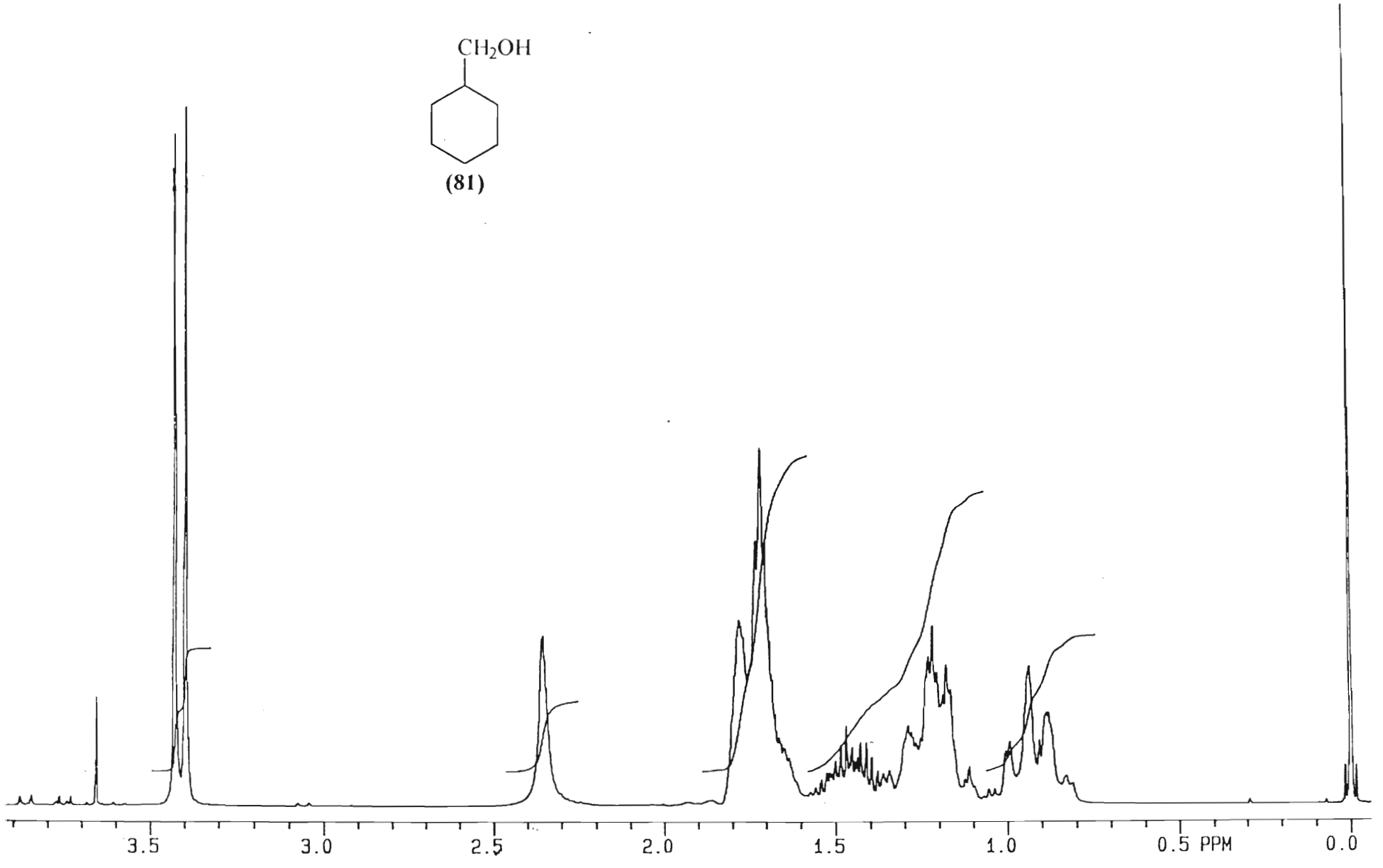

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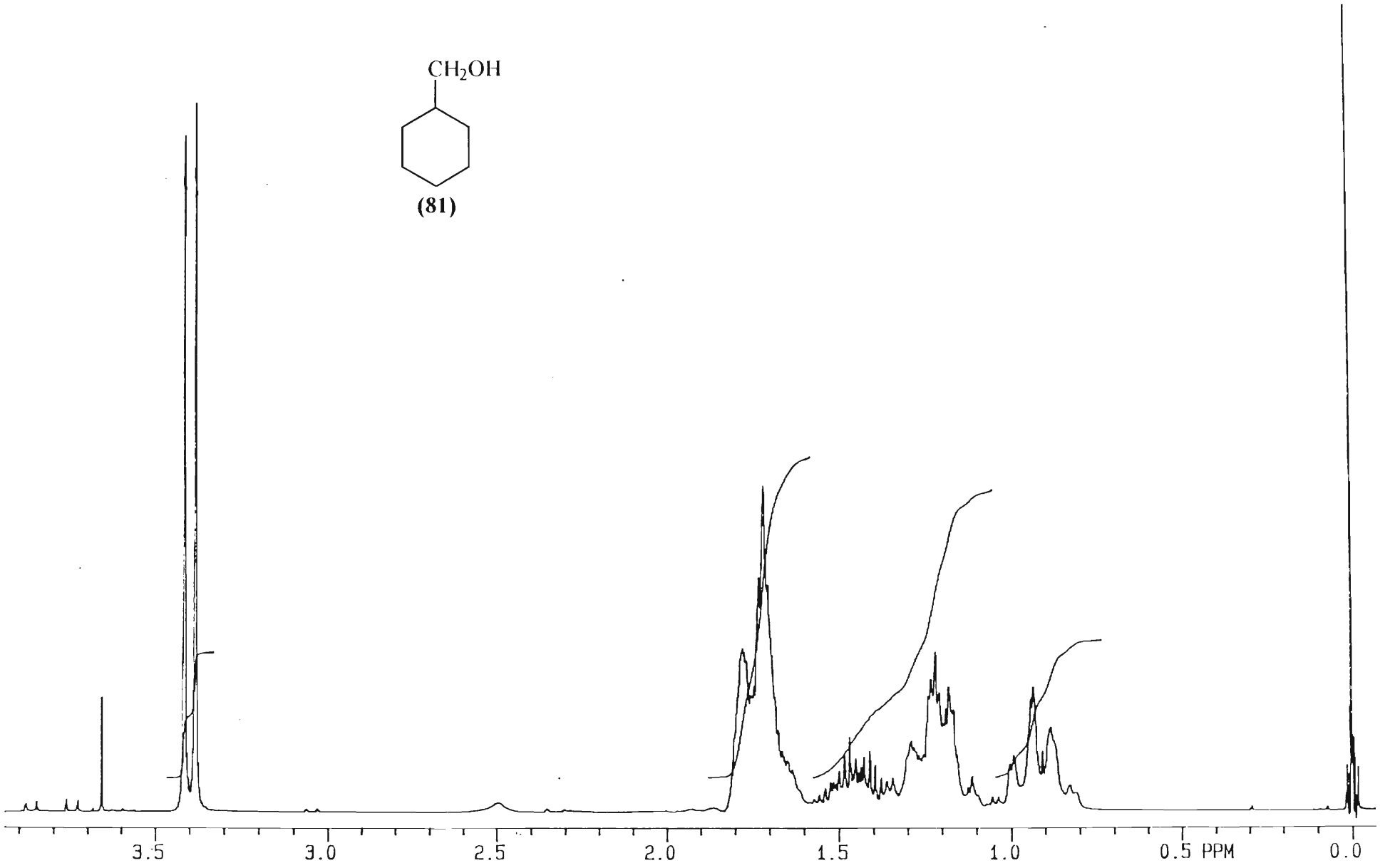

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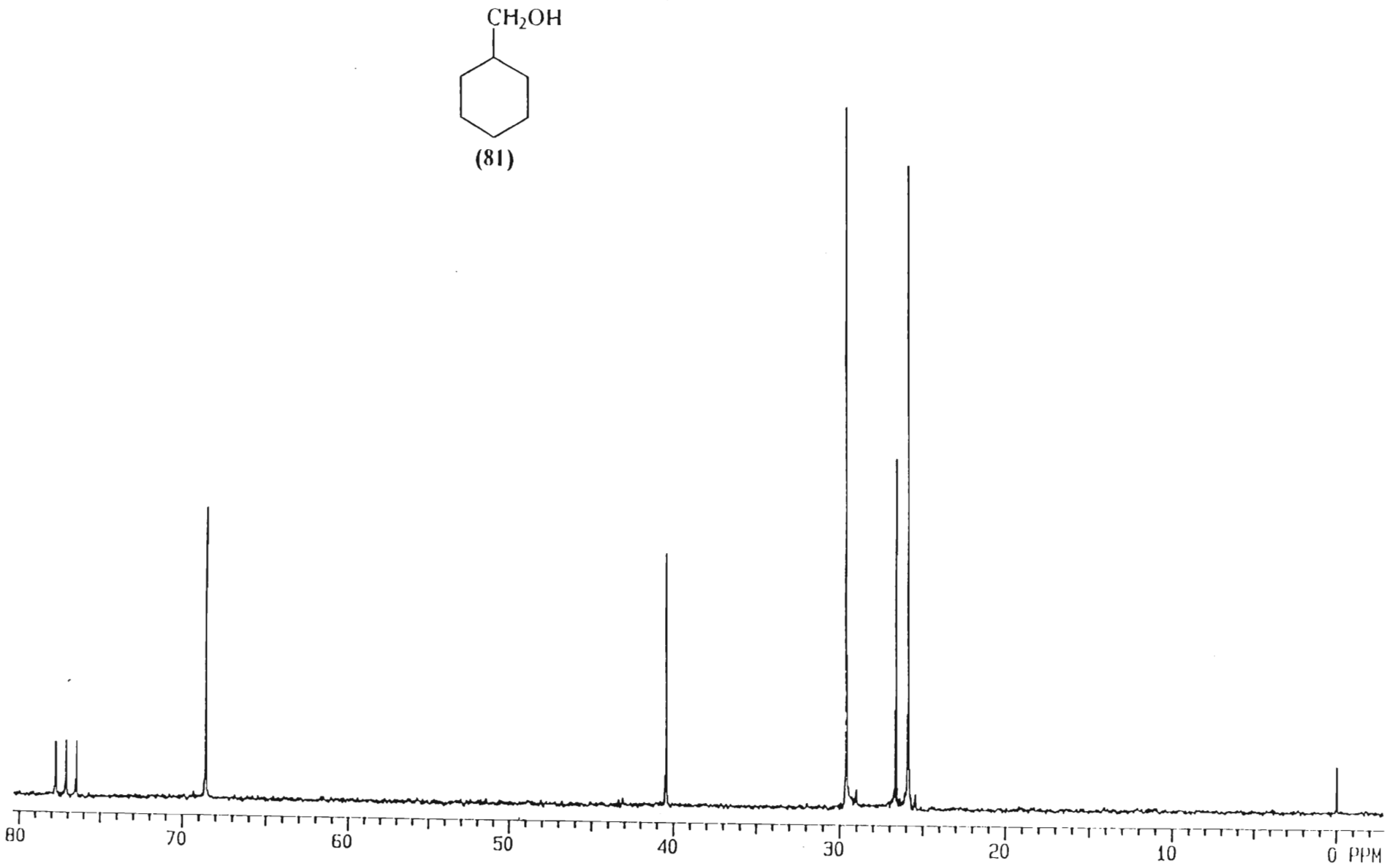

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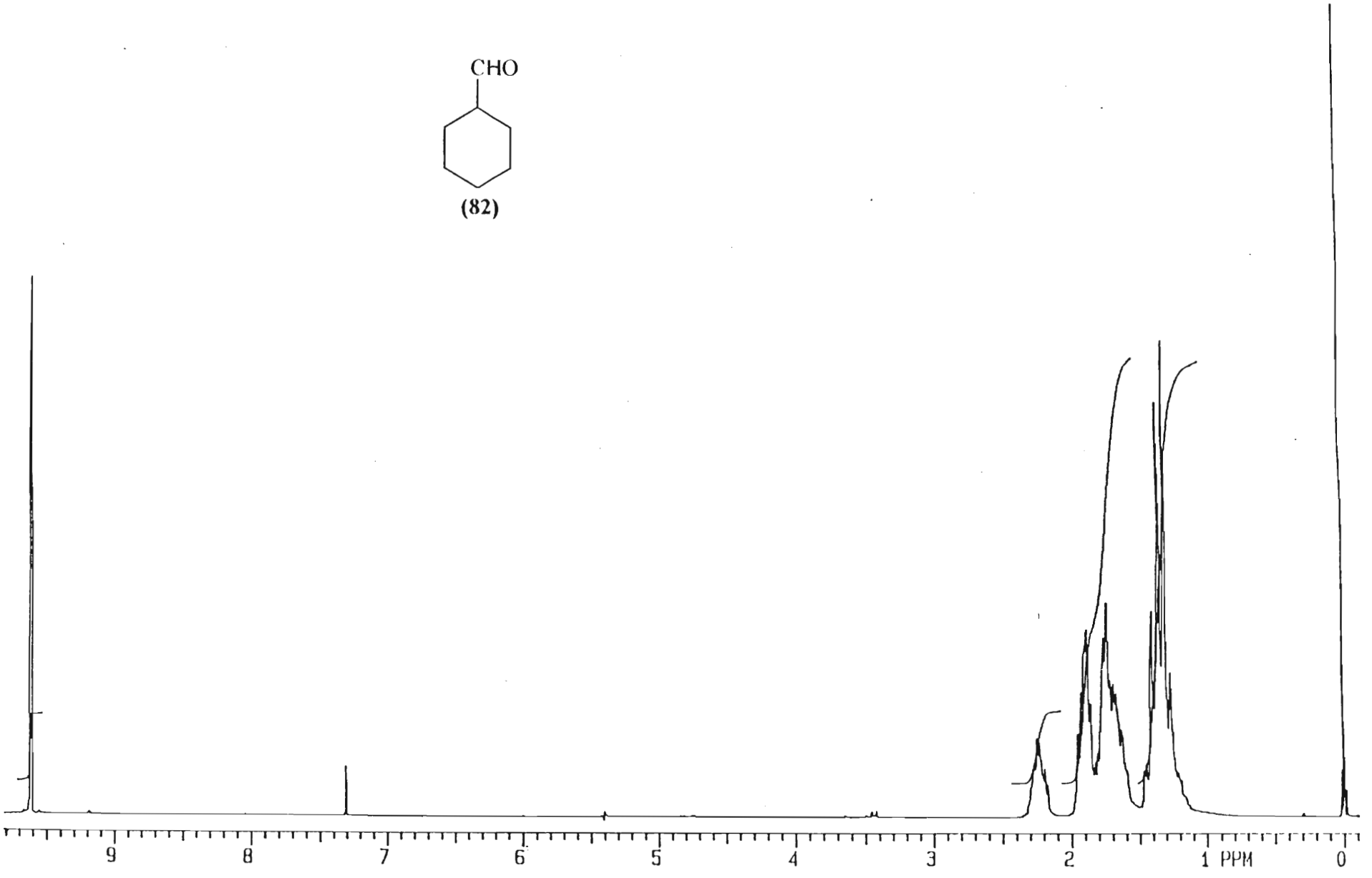
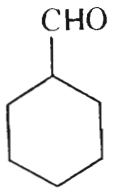


(82)



(82)