SYNTHETIC STUDIES IN AGROCHEMICAL BIOREGULATORS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

BY
G. BHASKAR REDDY
M. Sc.

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE- 411 008.
(INDIA)

JANUARY 1988

Dedicated to
my beloved mother.

C E R T I F I C A T E

Certified that the work incorporated in the thesis entitled "SYNTHETIC STUDIES IN AGROCHEMICAL BIOREGULATORS" by Mr. G. Bhaskar Reddy was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged.

(Dr.R.B. Mitra)
Supervisor

A C K N O W L E D G E M E N T

It is a matter of great pleasure and pride for me to thank Dr. R.B. Mitra, Scientist (Director's grade) and Head, Organic Chemistry Division, National Chemical Laboratory, Pune, for suggesting my research programme, his invaluable guidance and constant encouragement throughout the course of this investigation.

I am indebted to Dr.(Miss) Z. Muljiani, Scientist, for the generous help, valuable suggestions and keen interest.

I am also grateful to Drs. G.H. Kulkarni, S. Krishnappa, B.M. Bhawal, A.R.A.S. Deshmukh and all other members of organic division for the suggestions and co-operation.

The assistance rendered by Microanalysis group, Spectroscopy group, Glass blowing section and Entomology Section of this laboratory is gratefully acknowledged. My thanks are also due to Shri H. Nagarajan for typing my thesis.

Finally I am thankful to Director, National Chemical Laboratory, for allowing me to submit this work in the form of a thesis for Ph.D. and to the CSIR, New Delhi for the award of Research Fellowship.

GBReddy

(G. Bhasker Reddy)

GENERAL REMARKS

1. All melting points and boiling points are uncorrected, in case of boiling points, these refer to bath temperatures.

2. The infrared spectra of liquid were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer infared spectrophotometer model 137-B, and Perkin-Elmer infrared Spectrophotometer model 599-B using sodium chloride optics. Infared bands are expressed in cm^{-1}.

3. The NMR spectra were taken on Varian T-60 MHz Spectrometer (in CCl_4 solution), on Varian FT-80 MHz spectrometer (in $CDCl_3$ solution) and on Bruker WH -90 MHz spectrometer (in $CDCl_3$ solution) and the chemical shifts are measured in δ units.

4. Mass spectra were recorded on a CEC-21-110B mass spectrometer.

5. TLC analysis was carried out on glass plates coated with a mixture of silica gel (200 mesh) and plaster of paris (85:15). The plates were developed by keeping in an iodine chamber or by spraying with H_2SO_4.

6. Numbers given to charts, figures and structures in each chapter of the thesis refer to that particular chapter only.

7. Unless otherwise stated, all solutions were dried over anhydrous sodium sulfate.

C O N T E N T S

A B S T R A C T

The work described in the thesis deals with studies in synthetic pyrethroids and synthesis of naturally ouccurring pheromones. The thesis is divided into two parts: PART A contains a short introduction to pyrethroids and their Syntheses and PART B contains a short introduction to pheromones and Syntheses of some pheromones.

PART A

Natural as well as synthetic pyrethroids are becoming increasingly important as insect control agents as they possess a unique combination of desirable properties such as good insecticidal activity, low mammalian toxicity and rapid biodegradation. In view of this, several synthetic pyrethroids have been reported in literature[1].

Chapter I: Synthesis of spirofused cyclopropane carboxylates

Among the active pyrethroid insecticides containing various substituted cyclopropane carboxylates[2], esters derived from 2,2-dimethyl-5,6-benzospiro[2,4] heptene-1-carboxylic acid (1) and its analogue (2) have been found to have particularly high activity.

This chapter deals with the syntheses[3] of spirofused cyclopropane esters (1 to 8), which involve as the key step, the addition-elimination reaction of stabilised sulfur ylide (9) to appropriately substituted α,β-unsaturated carbonyl compounds (10, 11). Acid catalysed aldol condensation of Silylenol ethers of 1-indanone (12) and α-tetralone (13) with acetone followed by dehydration of the resultant hydroxy compounds (14, 15) gave α,β-unsaturated carbonyl compounds (10, 11) respectively.

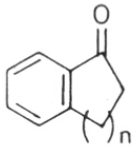
PART B

Insect pheromones are the chemicals secreted by insects used for the communication among the same species of insects[4]. Pheromones serve as sex attractants, stimulants, congregation scents, alarm signals, tracking and marking signs and social signals. These pheromones generally affect only their own species. Thus, in pest control management this specificity of pheromones could be of great advantage.

Chapter I: Syntheses of Z-6-heneicosen-11-one (16), heneicosadien-11-one (17), the sex pheromones of Douglas Fir-Tussock Moth

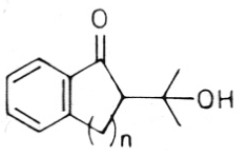
This chapter deals with three different syntheses of (16) and (17).

In the first method[5], one pot successive alkylations



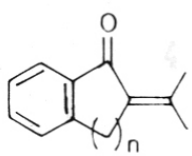
(12), n = 1

(13), n = 2



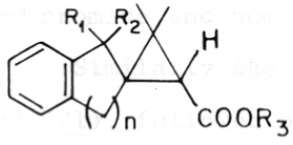
(14), n = 1

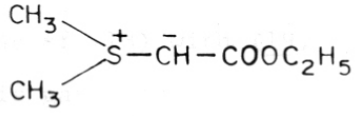
(15), n = 2



(10), n = 1

(11), n = 2





(9)

(1) n = 1, $R_1 = R_2 = R_3 = H$

(2) n = 2, $R_1 = R_2 = R_3 = H$

(3) n = 1, $R_1R_2 = O$, $R_3 = C_2H_5$

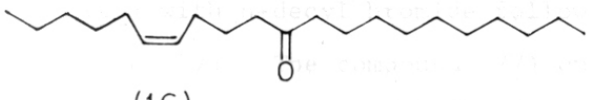
(4) n = 2, $R_1R_2 = O$, $R_3 = C_2H_5$

(5) n = 1, $R_1R_2 = O$, $R_3 = -CH(CN)-C_6H_4-O-C_6H_5$

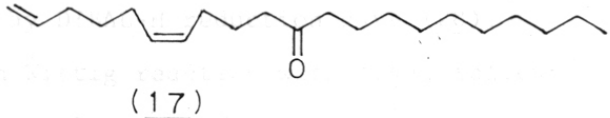
(6) n = 2, $R_1R_2 = O$, $R_3 = -CH(CN)-C_6H_4-O-C_6H_5$

(7) n = 1, $R_1 = OH$, $R_2 = H$, $R_3 = -CH(CN)-C_6H_4-O-C_6H_5$

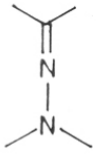
(8) n = 2, $R_1 = OH$, $R_2 = H$, $R_3 = -CH(CN)-C_6H_4-O-C_6H_5$



(16)



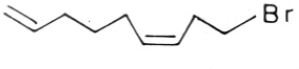
(17)



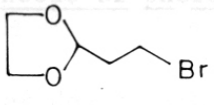
(18)

(19)

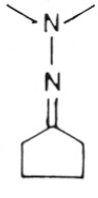
(20)



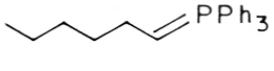
(21)



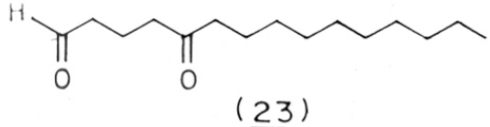
(22)



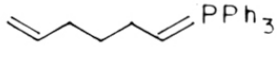
(26)



(24)



(23)



(25)

of hydrazone (18) with n-nonyl bromide (19) and Z-3-nonenyl bromide (20), followed by acid hydrolysis gave (16). Compound (20) was prepared starting from amyl bromide and homopropargyl alcohol.

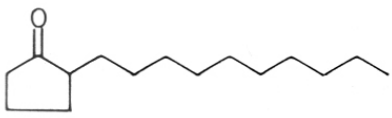
Similarly one pot dialkylations of (18) with (19) and (21), followed by acid hydrolysis gave (17). Compound (21) was prepared from homopropargyl alcohol and 1-bromo-pent-4-ene

In the second method[7], one pot successive alkylations of (18) with (19) and (22), followed by acid treatment gave keto-aldehyde (23). Ketoaldehyde (23) on treatment with Wittig reagent (24) gave (16). Similarly the compound (23) with Wittig reagent (25) gave (17).

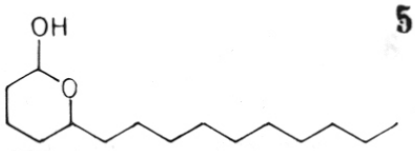
In the third method[6] alkylation of hydrazone (26) with n-decyl bromide followed by acid treatment gave (27). The compound (27) on Baeyer-Villiger oxidation, followed by DIBAL-H reduction gave (28). The compound (28) on Wittig reaction with (24), followed by oxidation of the resultant product gave (16). Similarly (28) with Wittig reagent (25) and followed by the oxidation of the resultant product gave (17).

Chapter II: Synthesis of pheromones having spiroketal functions

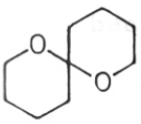
This chapter deals with the synthesis of spiroketal pheromones 1,7-dioxaspiro [5,5] undecane (29),



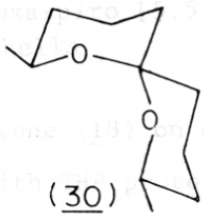
(27)



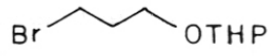
(28)



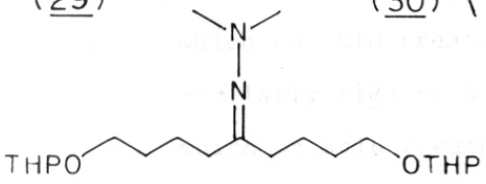
(29)



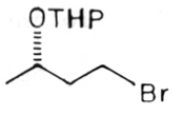
(30)



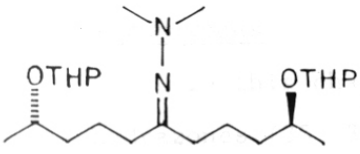
(31)



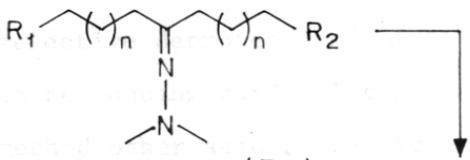
(32)



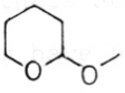
(33)

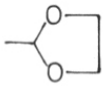
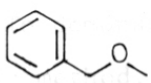


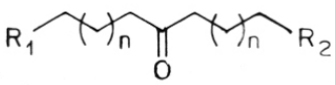
(34)



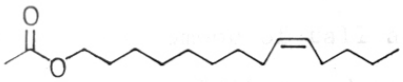
(35)

$R_1 = R_2$ = Alkyl groups or 

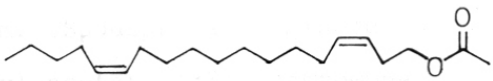
or  or 



n = 1–10 carbons (36)

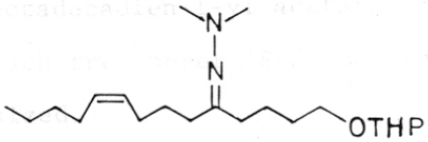


(37)

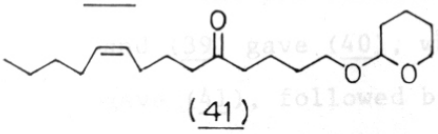


(38)

(39)

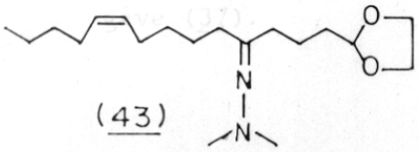


(40)

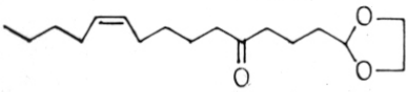


(41)

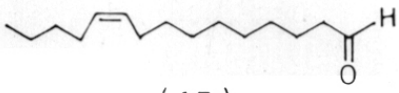
(42)



(43)



(44)



(45)

pheromone of Dacus Oleae Gmelin[5] and (2S, 6R, 8S)-2,8-dimethyl-1,7-dioxaspiro [5,5] undecane (30), pheromone of bee Andrena Wilkella

The hydrazone (18) on one pot successive dialkylations with THP protected bromopropanol (31) gave (32), which on acid treatment afforded (29).

Similarly (18) on bisalkylations with (33) gave (34), which on acid treatment afforded (30).

Chapter III: Selective deprotection of N,N-dimethyl--hydrazones

In this chapter, selective deprotection[9] of hydrazones (35 36) to corresponding carbonyl compounds is discussed. In this method other acid sensitive groups like THP ethers acetals, o-benzyls were intact. Number of examples have been done.

To demonstrate the efficacy and general utility of this method, Z-9-tetradecen-1-yl acetate (37), pheromone of tall army worm. Spodeptera frugiperda[10] and Z-3,13-octadecadien-1-yl acetate (38), pheromone of female peach tree borer 'Sanninoidea exitiosa'[11], were synthesized.

One pot successive alkylations of (18) with (31) and (39) gave (40), which on selective deprotection gave (41), followed by acid treatment and acetylation gave (37).

One pot successive alkylations of (18) with (42) and (22) gave (43), which upon selective deprotection gave (44). Wolff-Fishner reduction of (44) followed by acid hydrolysis gave the important intermediate (45). Wittig reaction of (45) with known procedure and acetylation of the resultant product gave (38).

REFERENCES

1. M. Elliott, Synthetic Pyrethroids, ACS Symposium Series No.42, 1977.

2. K. Tsushima, N. Matsu, N. Itaya, T. Yano and M. Hatakoshi "Pesticide Chemistry Human Welfare and the Environment", Vol. 1, Eds. J. Miyamoto and P.C. Kearney, Pergamon Press, 1983, p.91-94.

3. R.B. Mitra, Z. Muljiani and G. Bhaskar Reddy, Synth. Commun., 16(9), 1099 (1986).

4. K. Mori, The total synthesis of natural products, Vol. 4, Apsimon, p.1-183 (1981).

5. G. Bhaskar Reddy and R.B. Mitra, Synth.Commun., 16(13), 1723 (1986).

6. G. Bhaskar Reddy and R.B. Mitra, Synth.Commun., 17(7), 892 (1987).

7. R.B. Mitra and G. Bhaskar Reddy, Ind.J.Chem.(in press).

8. K. Mori and M. Katsurada, Liebigs Ann.Chem., 157(1984).

9. P. Laszlo, E. Polla, Tetrahedron Lett., 3309 (1984).

10. A.A. Sekul and A.N. Sparks, J.Econ.Entomol., 60, 1270 (1967).

11. T. Ebata and K. Mori, Agric.Biol.Chem., 43, 1567 (1979).

PART A

1. GENERAL INTRODUCTION TO PYRETHROIDS.

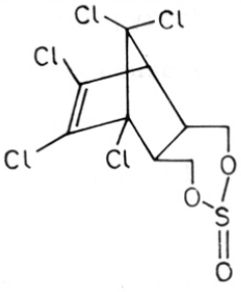
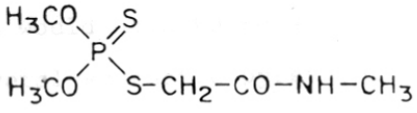
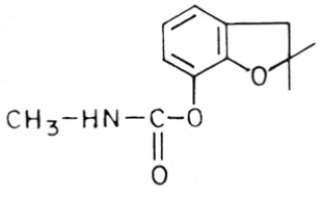
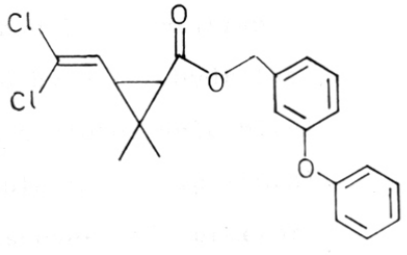
2. CHAPTER: SYNTHESIS OF SPIROFUSED CYCLOPROPANE CARBOXYLATES

INTRODUCTION

Pest control in recent times has been largely achieved by the following group of synthetic organic compounds (Table 1)[1]. Of these the synthetic pyrethroids have come to play the most important and significant role as practical insecticides for crop protection in agriculture. The case history of synthetic pyrethroids dates back to the beginning of this century, when it was discovered that the extracts of flowers from a plant chrysanthemum cinerariefolium possessed extremely useful pesticidal properties[2]. The pioneering work of Ruzicka and Staudinger in Switzerland established the main structural features of the active components present in these extracts. (Fig. 1) shows the structures of the six natural pyrethrins present in these extracts[3]. They are all esters of substituted cyclopropanecarboxylic acids are refered to as pyrethrin I and II, cinerin I and II[4] and Jasmolin I and II[5-7]. The esters of series I are derived from (+)-trans chrysanthemic acid and the esters of series II are derived from (+)-trans pyrethric acid.

These esters were found to be potent knock-down, repellent and antifeeding agents. Combined with this broad range of activity, they were found to

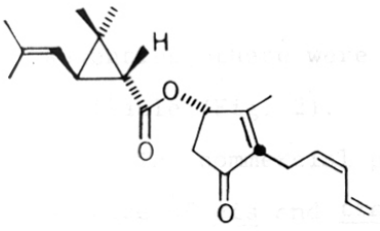
TABLE -1

S.No.	CLASS OF INSECTICIDE	EXAMPLE	STRUCTURE
1	ORGANOCHLORINE	ENDOSULFAN	
2	ORGANO PHOSPHOROUS	ROGOR	
3	CARBOMATES	CARBOFURAN	
4	PYRETHROIDS (Natural and Synthetic)	PERMETHRIN	

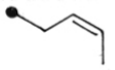
be practically non-toxic to mammals and were rapidly biodegraded leaving no toxic residues. Inspite of possessing such an ideal combination of properties, the practical effectiveness of these natural pyrethrins for crop protection was severely limited, because of the extreme photolability of these compounds.

If a pyrethroid was to be used as an agricultural pesticide, the photolabile zones of the natural pyrethrins would have to be so modified as to give a photostable product and at the same time the critical safety features of detoxification would have to remain unimpaired. Towards this end several synthetic pyrethroids were prepared[8,9] with modification mainly in the alcohol portion, but the final structure that evolved, satisfying the stringent requirements of an agricultural pesticide was that of permethrin (Fig. 2) which is the phenoxybenzyl ester of dichlorovinylcyclopropanecarboxylic acid, and this remarkable success was achieved by M. Elliott[10]. Permethrin was highly photostable and a potent insecticide. Moreover it had low mammalian toxicity being rapidly metabolised by ester hydrolysis and hydroxylation. In permethrin a photostable highly active synthetic pyrethroid suitable for agricultural use was finally obtained. The discovery of permethrin encouraged further research and by the end of the

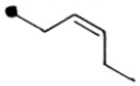
FIG. 1



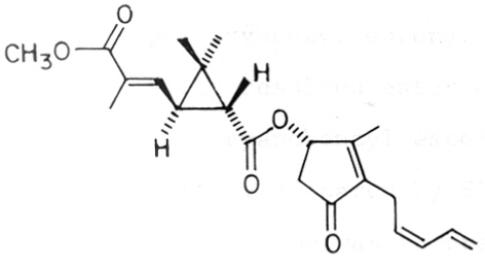
PYRETHRIN I



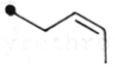
CINERIN I



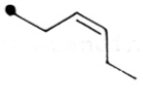
JASMOLIN I



PYRETHRIN II

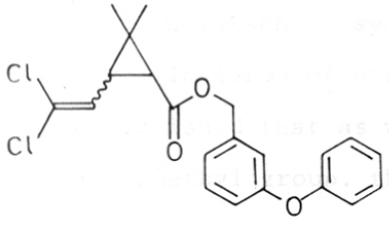


CINERIN II

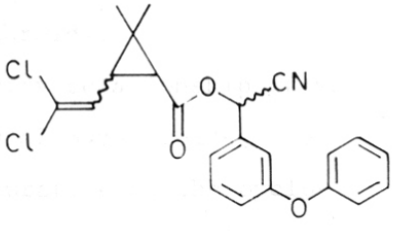


JASMOLIN II

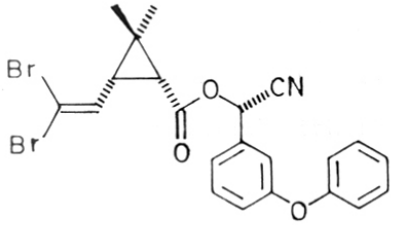
FIG. 2



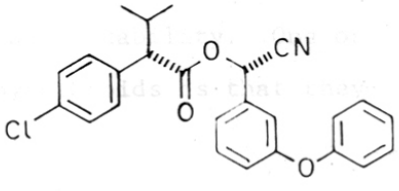
PERMETHRIN



CYPERMETHRIN



DELTAMETHRIN (NRDC 161)



S,S-FENVALERATE

seventies, there were four photostable pyrethroids available (Fig. 2).

The commercial product permethrin is recemic mixture of cis and trans dichlorovinyl acid, and cypermethrin is the ∝-cyano analogue of permethrin[11]. The ∝-cyano-phenoxybenzyl esters were introduced by the Japanese at Sumitomo and were 2-3 times more active than the phenoxybenzyl esters. Deltamethrin[12], which is a fully resolved ester of 1R-cis-dibromovinyl acid and ∝-S-cyanobenzyl ester is a pyrethroid of outstanding potency prepared by Elliott. A novel idea introduced by Sumitomo was to prepare analogues of open chain compounds. The resolved SS-fenvalerate[13] obtained by them is three times as active as permethrin and relatively cheaper. These four compounds can be regarded as the 1st generation synthetic pyrethroids.

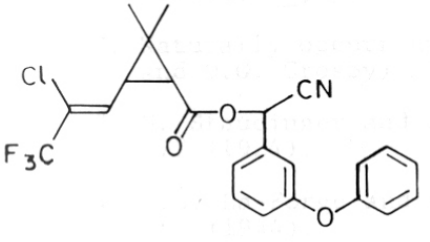
In terms of structure activity relationship it was established that as with the natural pyrethroids, the gemdimethyl group, the 'R' configuration at the cyclo-propane bearing the carboxylic group and the 'S' configuration at the carbon bearing the secondary hydroxy group is essential for activity.

Further research confined to evolve structures with higher activity and greater photostability. One of the problems with the synthetic pyrethroids is that they

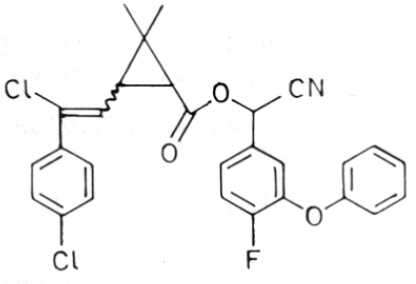
possess poor acaricidal activity. As a result of the efforts put by the big companies like ICI and Bayer, the two new compounds, cyhalothrin[14] and bayticol[15], which gave increased acaricidal activity were introduced in the market (Fig. 3). Replacing the chloro group by CF_3 or by p-chlorophenyl gave increased acaricidal activity.

Further research at FMC concluded that it was not necessary to have a bridging atom between the two unsaturated centres in the alcohol position, to avoid coplanarity (Fig. 3) and that appropriately substitued diphenyl derivative gave excellent insecticides. Detailed quantitative structure activity relationship (QSAR) studies led FMC to develop the new insecticides FMC 54800[16], with entirely different alcohol moiety. The acaricidal activity of this compound against the two spotted spider mite is twice that of any other commercial pesticide. It is also known now that the substituted vinyl group at C_3 is not essential. The tetramethyl compound fenpropathrin[17] (Fig. 3) is a commercial product developed by Sumitomo. The same company has found that the benzospiro compound[18] is also highly active.

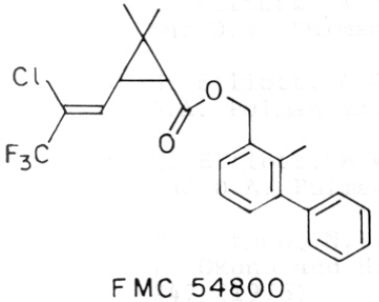
FIG. 3



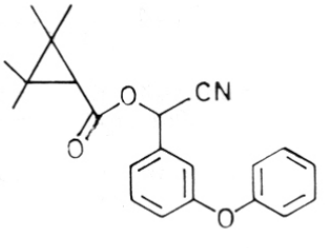
CYHALOTHRIN



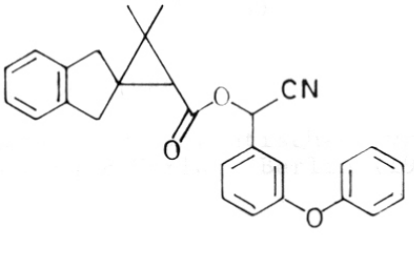
BAYTICOL



FMC 54800



FENPROPATHRIN



SPIRO COMPOUND

REFERENCES

1. M. Elliott, "Synthetic Pyrethroids" ACS-Symposium series, 42, p.2 (1977).

2. Naturally occurring insecticides [Eds. M. Jacobson and D.G. Crosby), Dekker, New Nyork (1971).

3. H. Staudinger and L. Ruzicka, Helv.Chim.Acta., 7, 177 (1924).

4. F.B. La-Forge and W.F. Barthel, J.Org.Chem., 9, 242 (1944).

5. P.J. Godin, R.J. Sleeman, M. Snarey and E.M. Thain, Chem. and Ind., 371 (1964).

6. P.S. Beevor, P.J. Godin and M. Snarey, Chem. and Ind., 1342 (1965).

7. P.J. Godin, R.J. Sleeman, M. Snarey and E.M. Thain, J.Chem.Soc.(C), 332 (1966).

8. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulmann, Nature, 244, 456 (1973).

9. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman and J.H. Sternson, Nature, 246, 169 (1973).

10. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic.Sci., 6, 537 (1975).

11. T. Matsuo, N. Itaya, T. Mizutani, N. Ohno, K.Fujimoto, Y. Okuno and H. Yoshioka, Agric.Biol.Chem., 40, 247 (1976).

12. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Nature, 248, 710 (1974).

13. N. Ohno, Agric.Biol.Chem., 38, 881 (1974).

14. P.D. Bentley Pestic.Sci., 11, 156 (1980).

15. K. Naumann, 'Chemie der Synthetischen Pyrethroid-Insektizide', Springer Verlag, Berlin (1978).

16. E.L. Plumer, ACS meeting at Las Vegas, Nevada, USA (1980).

17. R.D. Verschoyle and J.M. Barnes, Pestic.Biochem. Physiol., 2, 308 (1972), Pestic.Sci., 11, 202 (1980).

18. K.Tsushima, N. Matsuo, M. Hatakoshi, T. Yano and N. Itaya, European Patent 0,056,271-A2, (1982).

CHAPTER I

SYNTHESIS OF SPIROFUSED CYCLOPROPANE CARBOXYLATES

Summary

The spirofused cyclopropanecarboxylates (23) and (24) have been prepared from the α,β -unsaturated carbonyl compounds (21) and (22), by utilising the addition-elimination reaction of stabilised sulfur ylide (33). These cyclopropanecarboxylates finally converted to their corresponding α-cyanophenoxy-benzyl alcohol esters (36 to 39) and tested their activity on houseflies.

INTRODUCTION

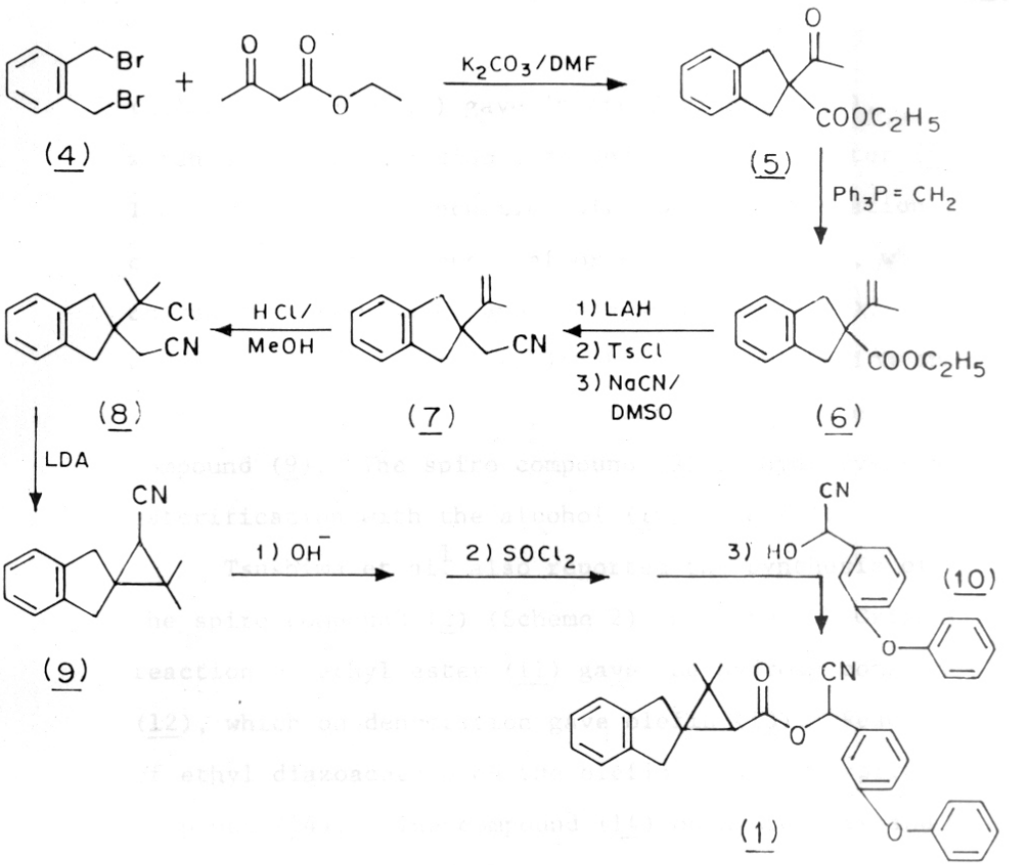
Among the active pyrethroid insecticides containing various substituted cyclopropanecarboxylates, esters derived from 2,2-dimethyl-5,6-benzospiro[2,4]heptene-1-carboxylic acid (1) and its analogue (2) have been found to have high activity[1]. Particularly, the toxicity of the compound (1) against M. domestica is higher than cypermethrin (3) (Table 1). The compound (1) and its analogues were patented for their activity[2]. The first synthesis of these novel spirofused cyclopropane esters have been reported by K. Tsushima et al. in 1983[1].

Table 1: Insecticidal activity of α-cyano-3-phenoxy benzyl esters

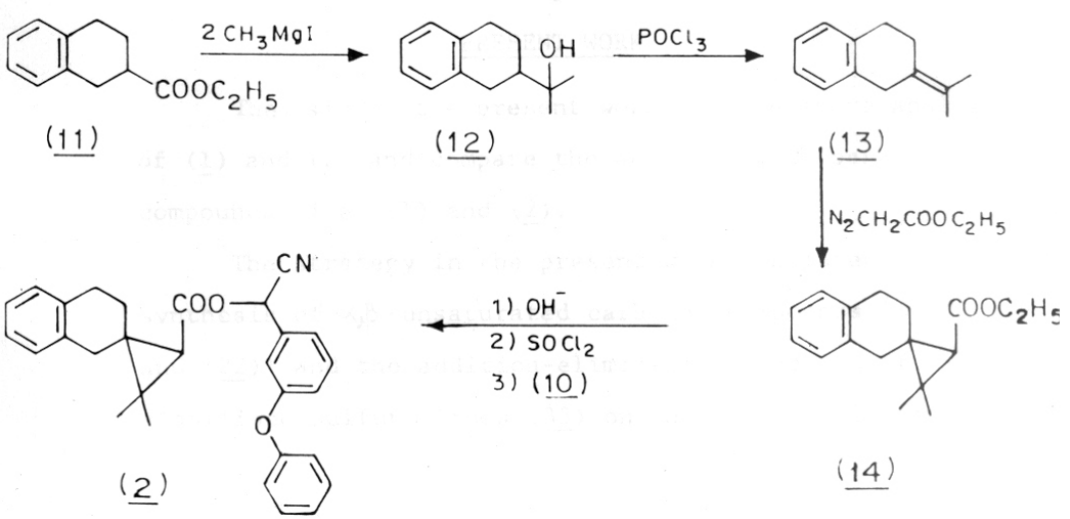
Compound	House fly LD_{50} (µg)	Tobacco cutworm LD_{50} (ppm)	German cockroach LD_{50} (mg/m^2)
(1)	0.0045	2.0	0.60
(2)	0.22	50.15	7.3
(3)	0.0075	0.73	0.17

The spiro compound (1) was synthesized[1] (Scheme 1) in 9 steps, starting from ethyl acetoacetate and dibromo compound (4). Dianion of ethyl acetoacetate on alkylation

SCHEME – 1



SCHEME – 2



with the compound (4) gave indane derivative (5), which on Wittig reaction afforded the olefin ester (6). The compound (6)on reduction with LAH and tosylation of the resultant product, afforded the tosylate, which on reaction with NaCN gave the cyanocompound (7). The compound (7) on treatment with HCl gave (8), which on cyclisation afforded the spirofused cyclopropane compound (9). The spiro compound (9) on hydrolysis and esterification with the alcohol (10) gave (1).

Tsushima et al.[1] also reported the synthesis of the spiro compound (2) (Scheme 2) in 6 steps. Grignard reaction of ethyl ester (11) gave the hydroxy compound (12), which on dehydration gave olefin (13). Reaction of ethyl diazoacetate on the olefin (13) gave spiro compound (14). The compound (14) on hydrolysis and reaction with thionyl chloride gave acid chloride which on eserification with (10)gave (2).

PRESENT WORK

The aim of the present work was to prepare analogues of (1) and (2) and compare the activity with parent compounds, i.e. (1) and (2).

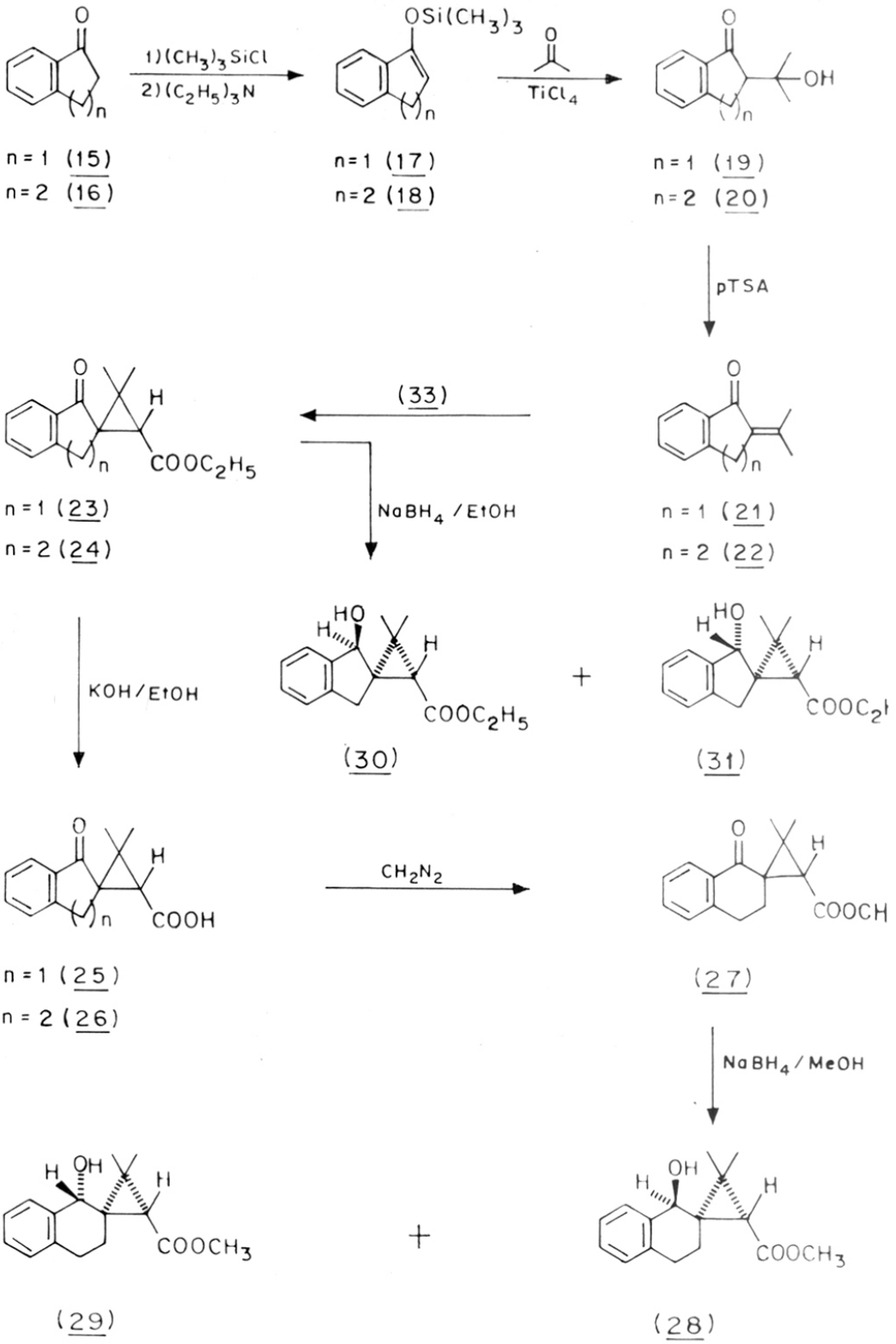
The strategy in the present work consisted of the synthesis of α,β-unsaturated carbonyl compounds [(21) and (22)] and the addition-elimination reaction of stabilised sulfur ylides (33) on these carbonyl compounds

to build up spirofused cyclopropane esters (23) and (24). These were then converted to their cyanobenzyl esters via the acid chloride and tested on houseflies (Musca domestica) for their insecticidal activity.

Synthesis of α,β-unsaturated carbonyl compounds (21) and (22), (Scheme 3)

The reported preparation (crossed aldol condensation of 1-indanone (15) with acetone using KOH as base) of 2-isopropylidene-1-indanone (21) gave the product in very poor yield[3]. Therefore a three step procedure has been developed. The silylenol ether (17) of 1-indanone (15) was prepared using trimethylsilyl chloride and triethylamine in DMF at 90°C. Lewis acid catalysed aldol condensation ($TiCl_4$ catalyst)[4,5] of the silylenol ether (17) with acetone gave the hydroxy compound (19). Dehydration of the compound (19) with pTS acid in benzene gave isopropylidene-1-indanone (21) in an overall yield of 85% from 1-indanone (15). α,β-Unsaturated ketone (21) can be obtained directly from (17) by using excess of $TiCl_4$ (around three equivalents) during the aldol condensation reaction. The compound (21) was crystalline solid, m.p.103°C. IR (Nujol) spectrum showed carbonyl peak at 1680 cm^{-1}. PMR (CCl_4) spectrum showed two singlets at δ 1.80 and 2.27 for two isopropylidine

SCHEME – 3


1)(CH3)3SiCl
2)(C2H5)3N
TiCl4
pTSA
(33)
NaBH4 /EtOH
KOH/EtOH
CH2N2
NaBH4 / MeOH
n=1 (15)
n=2 (16)
n=1 (17)
n=2 (18)
n=1 (19)
n=2 (20)
n=1 (21)
n=2 (22)
n=1 (23)
n=2 (24)
n=1 (25)
n=2 (26)
(27)
(28)
(29)
(30)
(31)

methyl protons. C_3 methylene protons showed as singlet at δ 3.37. Aromatic protons appeared as multiplet between δ 7.0 - 7.58.

Similarly, α-tetralone (16) was converted to 2-isopropyledene-1-tetralone (22) via the intermediates (18) and (20) in approximately 80% yield. The compound (22) was a thick liquid. IR (neat) spectrum showed carbonyl peak at 1675 cm^{-1}. PMR (CCl_4) spectrum showed two singlets at δ1.87 and δ2.13 for two isopropylidene methyl protons. C_3 and C_4 methylene protons showed broad singlet at δ 2.77. Aromatic protons showed multiplet between δ 6.9 - 8.0.

Preparation of EDSA (33), (Scheme 4)

The sulfur ylide (33) was prepared in two steps by a known procedure[6]. Reaction of dimethylsulfide and ethyl bromoacetate at 0°C in acetone gave crystalline solid carbethoxymethyl dimethyl sulfoniumbromide (32), m.p. 78-80°C. Treatment of a vigorously stirred chloroform solution of the salt (32) with saturated K_2CO_3 containing 1 molar equivalent of NaOH afforded ethyl (dimethylsulfuranylidene) acetate (33) in 92% yield.

Synthesis of spirofused cyclopropanecarboxylates[7]
(Scheme 3)

Condensation of (21) with ylide (33) in benzene at relux temperature gave the spirofused compound (23) in quantitative yield. GLC and HPLC analysis showed it to be a single compound and the trans disposition of keto and ester group was assigned on electrostatic consideration. IR (neat) spectrum of (23) showed peaks at 1600 cm^{-1} (aromatic), 1700 cm^{-1} (keto stretching), 1720 cm^{-1} (ester carbonyl stretching). PMR (CCl_4) spectrum indicated the presence of cyclopropane gem-dimethyls at δ 1.35 and 1.45 as singlets. Cyclopropane proton appeared at δ 2.35 as singlet. The C_3 methylene protons appeared as double doublet at δ 3.32 (J=18 Hz) due to the geminal coupling. Rest of the protons appeared at their expected chemical shifts.

Similarly, condensation of (22) with ylide (33) in benzene gave spiroketone (24) in 30% yield. Various reaction conditions were tried to improve the yields. Maximum percentage of yield (30%) was obtained when the compound (22) was refluxed with excess of (around 3 equivalents) ylide (33) in benzene for 4 to 5 hours. As there was little difference in the rf values, chromatographic separation of product (24) from the starting material (22) was difficult. Therefore, chemical method

of separation was adopted. The crude product was treated with 20% aq. KOH. The starting material (22) was separated from the aqueous extract and on neutralisation the aqueous extract gave a white crystalline product, keto acid (26), m.p.174-176°C. The ketoacid (26) was esterified with diazomethane to get ketoester (27). The ketoester was a thick liquid. IR (neat) spectrum of (27) showed peaks at 1600 (aromatic), 1680 (keto stretching) and 1720 cm^{-1} (ester carbonyl). PMR(CCl_4) spectrum showed peaks for gemdimethyl of cyclopropane at δ 1.10 and 1.5 as singlets. C_3 and C_4 methylene protons were seen between δ 1.8 - 3.1 as broad multiplet. Cyclopropane proton was seen at δ 2.7 as singlet. Rest of protons were observed at their expected chemical shfits.

Ketoester (27) was reduced with sodiumborohydride in methanol to give a mixture of two diastereomeric alcohols (28) and (29) in 20:80 ratio. These two alcohols were separated by column chromatography using silica gel (60-120 mesh) and 15% ethyl acetate in pet.ether as eluent. The faster moving compound was the major diastereomer (29), isolated as thick liquid. The slower moving compound (28) was a white crystalline solid, m.p.108°C. PMR ($CDCl_3$) spectra of (28) and (29) were distinctly different from each other. The isomer

(29) (Fig. 3) showed a singlet for cyclopropane proton at δ 1.25. Gemdimethyl protons of cyclopropane ring were seen at δ 1.37 and 1.47 as singlets. In the minor isomer (28) (Fig. 2) cyclopropane ring proton was observed at δ 1.70. Gemdimethyl protons were seen at δ 1.15 and 1.30 as singlets. Stereochemical assignments were done on the basis of attack of the reagent from the least hindered side as indicated by Dreiding models and confirmed by X-ray crystallography of alcohol (28). The compound (28) was crystallised from pet.ether. Crystals belong to monoclinic, space group p 21/n with a = 10.739 (1), b = 22.750 (3) and C= 11.631 (1) Å, β = 97.99 (1) with Z = 8 (two molecules in the asymmetric unit). Intensity data were collected on CAD - 4F - 11 M X-ray diffractometer. The structure has been solved by direct methods using MULTAN-78 and has been refined to R=0.065 for 1850 reflections. Fig. 1 gives the perespective view of the molecules in the assymetric unit. Hydroxy and the dimethyl groups are trans. The hexene moiety has a "half chair" confirmation and hydroxy group is in β configuration. The conformation of both molecules in the assymmetric unit is the same.

Similarly, ketoester (23) was reduced with $NaBH_4$ in ethanol at 0°C to give two diastereomeric alcohols

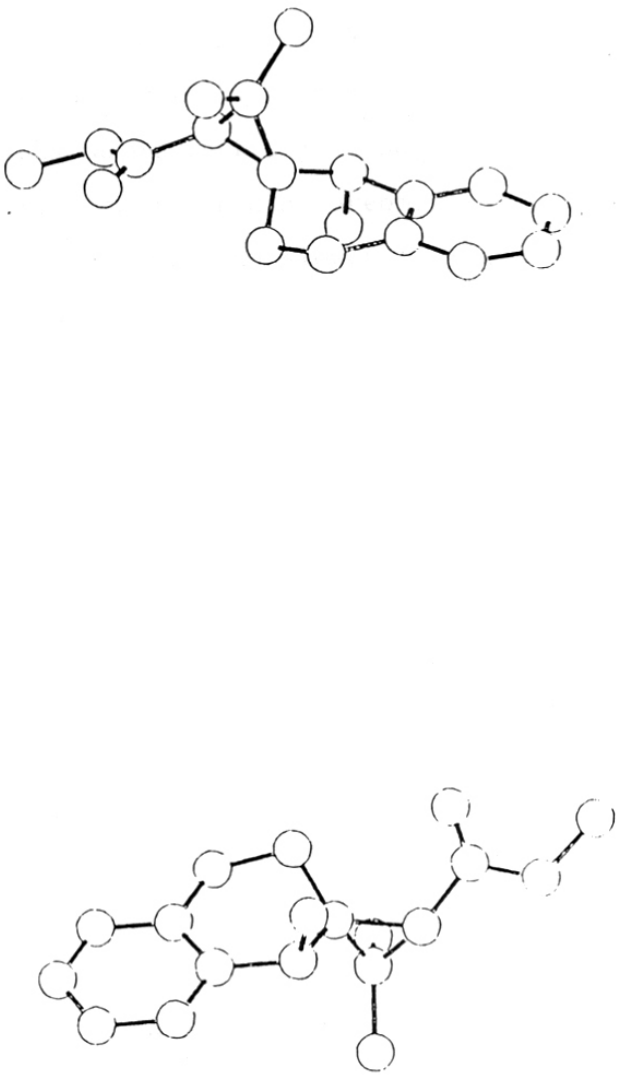


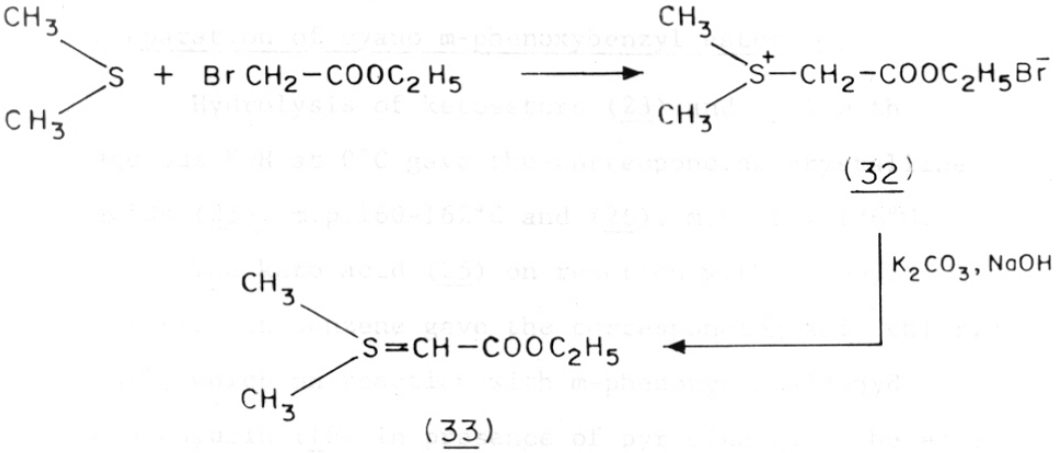
Fig.1 - A perspective view of the two molecules in the asymmetric unit.

(30) and (31) in the ratio of 20:80 (approximately). These two alcohols were also separated by column chromatography using silica gel and 15% ethyl acetate in pet.ether. The major diastereomer (31), a thick liquid eluted faster. The slower moving minor isomer (30) was a white crystalline solid, m.p.78°C.

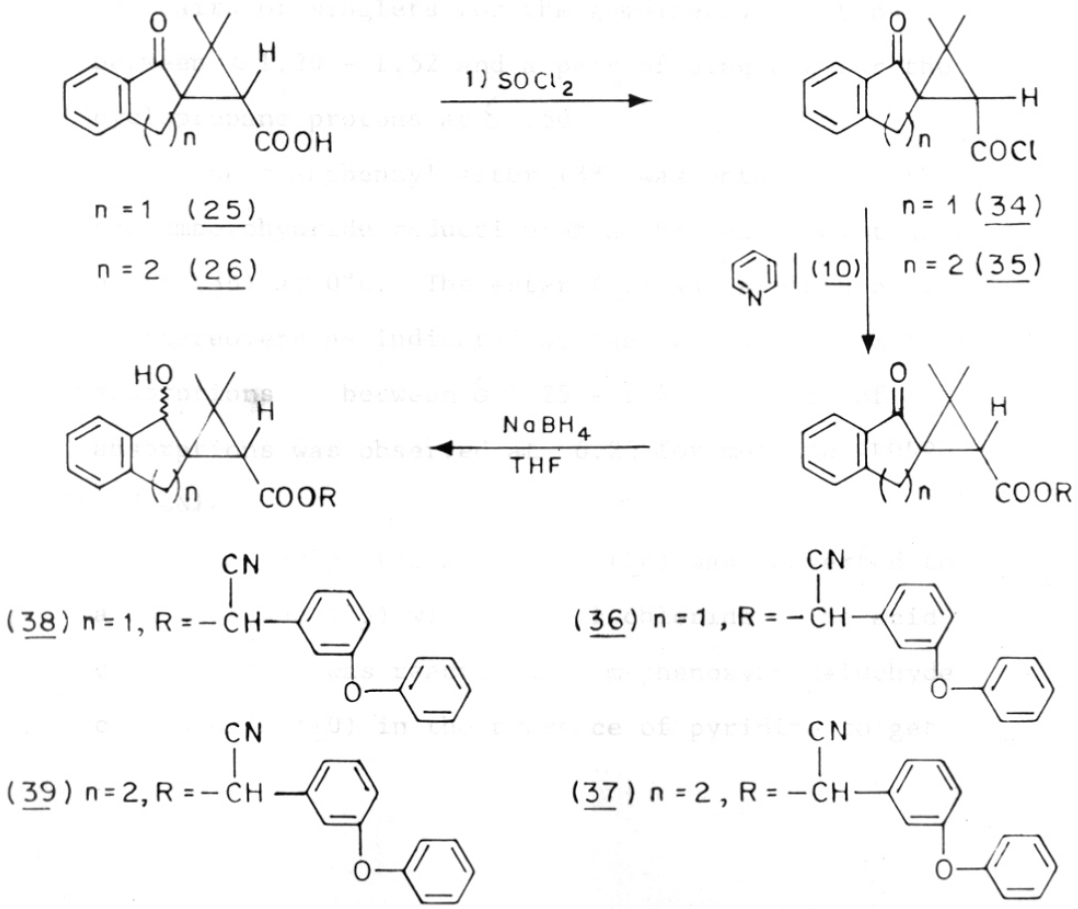
PMR spectra of diastereomers (30) and (31) were distinctly different from each other. PMR (CCl_4) spectrum of (30) (Fig. 4) showed a singlet for cyclopropane ring proton at δ 1.6. Two singlets at δ 1.37 and 1.5 were shown for gemdimethyl protons. PMR (CCl_4) spectrum of (31) (Fig. 5) showed singlet at δ 1.8 for cyclopropane ring proton. Protons of gemdimethyls showed as singlet at δ 1.20. A fine splitting quartet at δ 3.88 (2H, J=7 Hz) was observed for the $-CH_2-$ of alcohol portion. The stereochemical assignments, showing the major isomer (31) with the -OH in α-position and the minor isomer (30) with the -OH in β-position were done on the basis of attack of reagent from the least hindered side as indicated by Dreiding models and by analogy with results obtained on the reduction of ketone (27).

To test the insecticidal activity, the spirocyclopropanecarboxylates have been converted to their

SCHEME-4



SCHEME-5



corresponding cyano m-phenoxy benzyl esters (Scheme 5).

Preparation of cyano m-phenoxybenzyl esters :

Hydrolysis of ketoesters (23) and (24) with aqueous KOH at 0°C gave the corresponding crystalline acids (25), m.p.160-162°C and (26), m.p. 174-176°C.

The keto acid (25) on reaction with thionyl chloride in benzene gave the corresponding acid chloride (34), which on reaction with m-phenoxybenzaldehyde cyanohydrin (10) in presence of pyridine gave the ester (36). The ester (36) was a 50:50 mixture of two diostereomers. This was indicated in PMR ($CDCl_3$) by two pairs of singlets for the gemdimethyl protons between δ 1.20 - 1.52 and a pair of singlets for the cyclopropane protons at δ 2.50.

The cyanobenzyl ester (38) was obtained by the sodiumborohydride reduction of a THF solution of keto-ester (36) at 0°C. The ester (38) was a mixture of diastereomers as indicated by the two pairs of methyl absorptions between δ 1.25 - 1.40. A pair of absorptions was observed at 6.25 for methine proton (-CH-CN).

Similarly, the keto acid (26) was converted to acid chloride (35) with thionyl chloride. The acid chloride (35) was reacted with m-phenoxybenzaldehyde cyanohydrin (10) in the presence of pyridine to get

pyrethroid ester (37). Pyrethroid (37) was obtained as a mixture of two diastereomers as shown in PMR($CDCl_3$) by two pairs of methyl absorptions centered at δ 1.10 and 1.51 and a pair of absorption for the methine proton, -CH-CN at δ 6.25.

The ketoester (37) was reduced with sodium borohydride in THF at 0°C to give pyrethroid ester (39). PMR ($CDCl_3$) showed two pairs of methyl absorptions between δ 1.30 - 1.46 and a pair for methine, -CH-CN, at δ 6.23 for the diostereomeric mixture.

When tested on houseflies (Musca domestica) by topical application, the keto cyano ester (36) gave 100% mortality at 10μg dose/insect, see Table 2. Hydroxy compound (38) was less active as also the tetralone derivatives (37) and (39).

Table 2 Insecticidal activity of α-cyano-3-phenoxy benzyl esters

Compound	Percentage Mortality		
	1 μg/insect	5 μg/insect	10 μg/insect
(36)	20%	60%	100%
(37)	10%	45%	70%
(38)	6%	20%	33%
(39)	5%	15%	24%

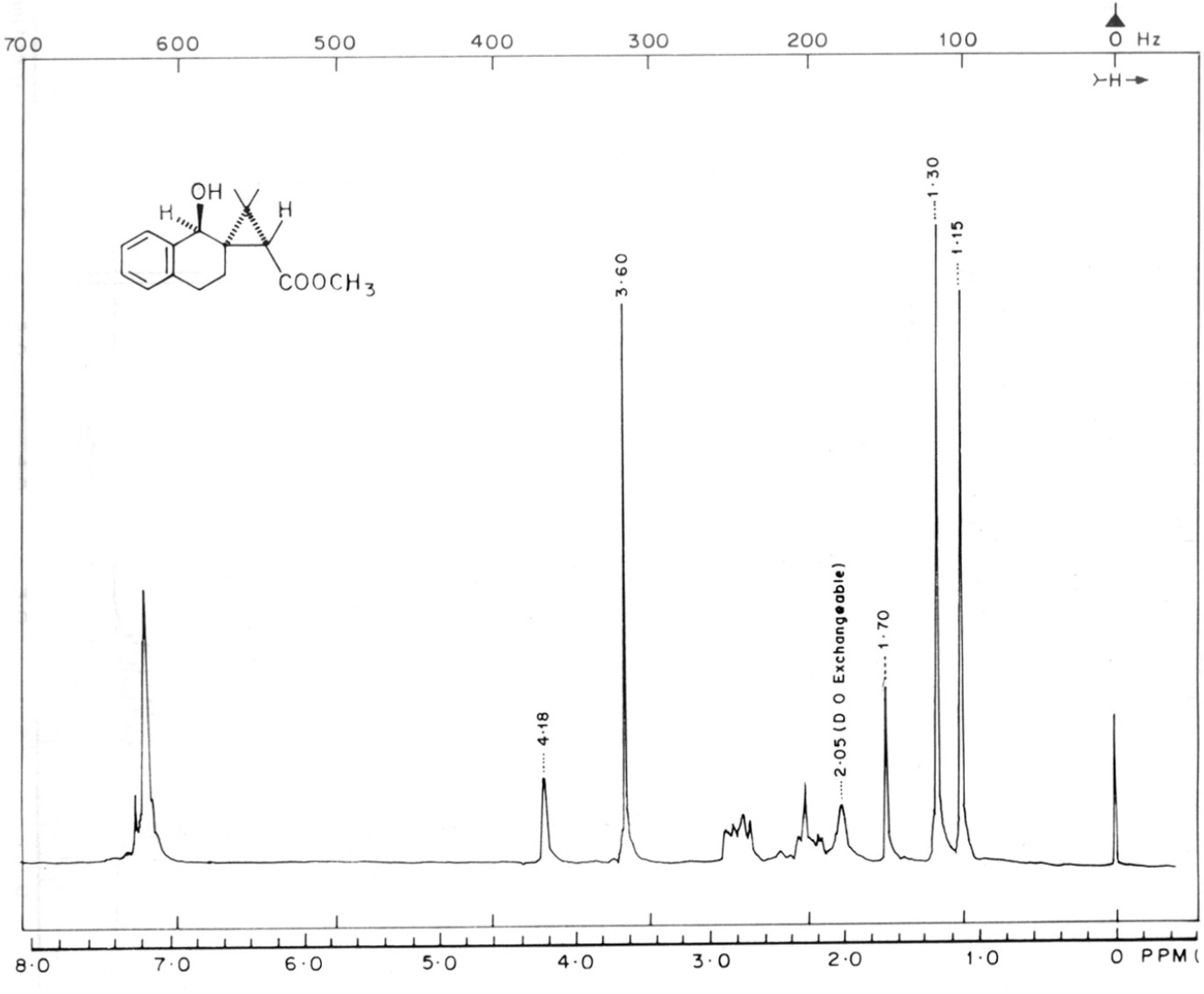


FIG. 2 PMR SPECTRUM OF THE COMPOUND (28) IN $CDCl_3$

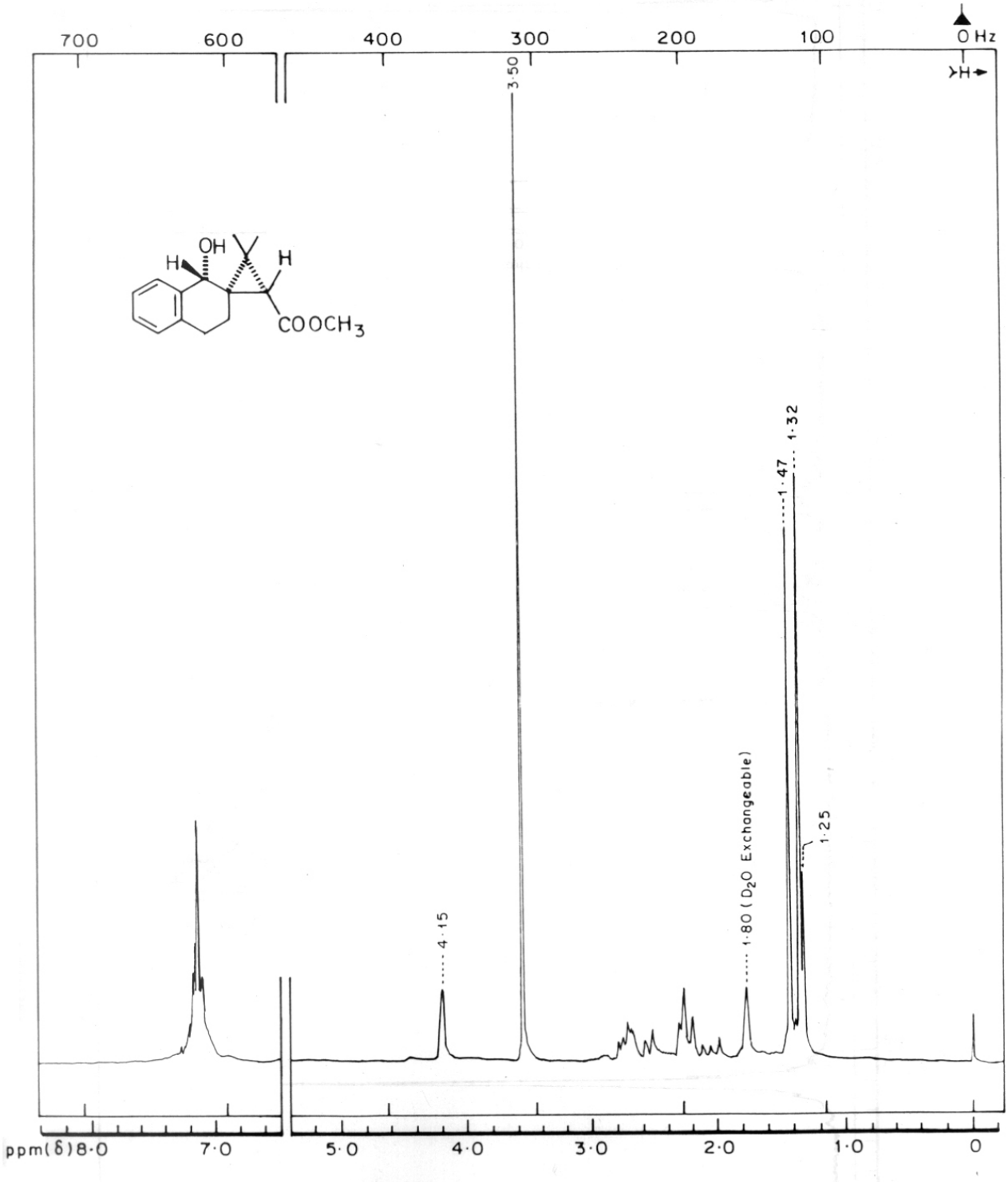


FIG. 3. PMR SPECTRUM OF THE COMPOUND (29) IN $CDCl_3$

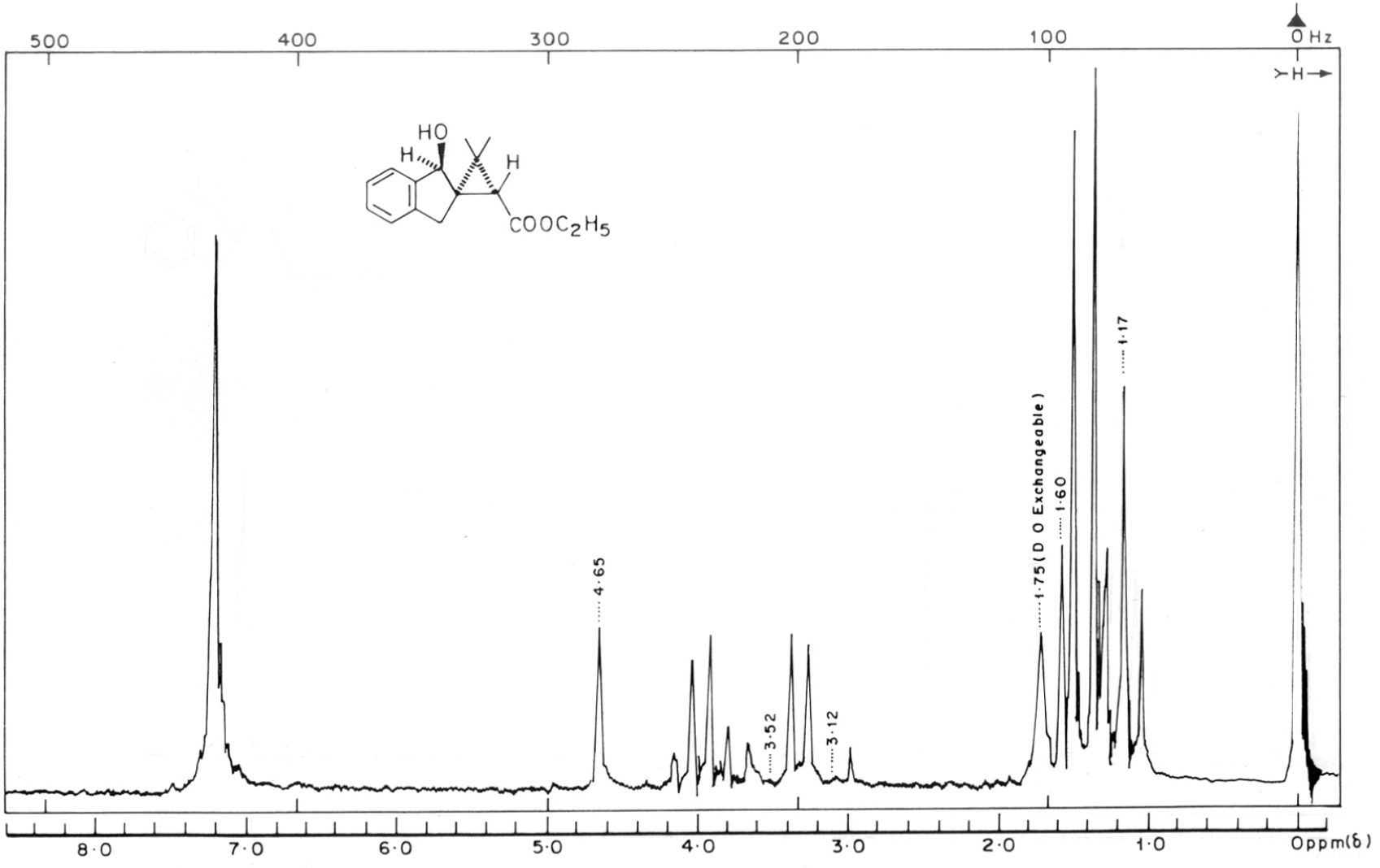


FIG. 4 PMR SPECTRUM OF THE COMPOUND (30) IN CCl_4

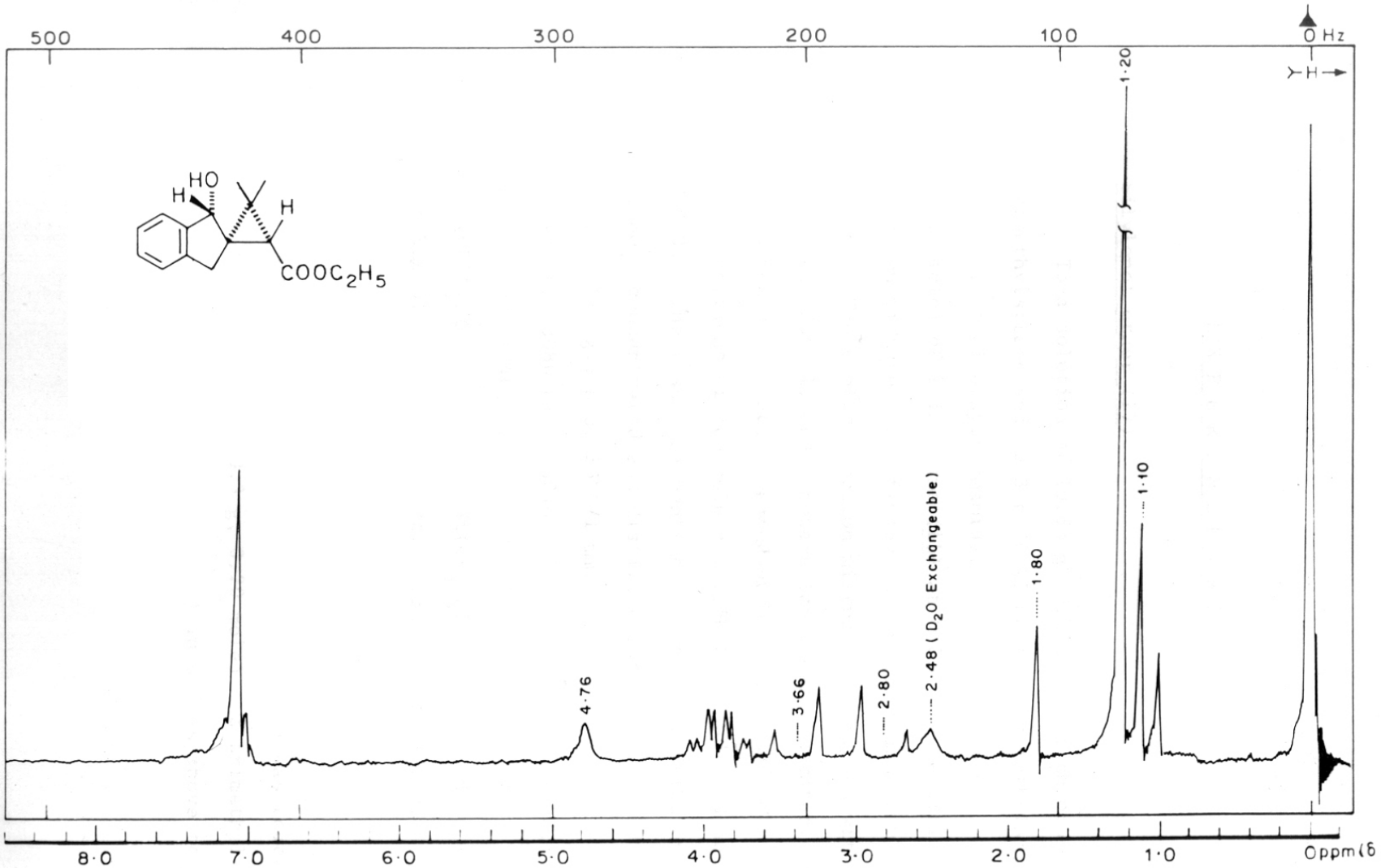


FIG 5. PMR SPECTRUM OF THE COMPOUND (31) IN CCl_4

EXPERIMENTAL

Silylenol ether (17)

To a solution of 10.85 g (0.1 mole) of chlorotrimethylsilane and 20.3 g (0.20 mole) of triethylamine in 50 ml of dimethylformamide, was added 11.9 g (0.09 mole) of 1-indanone (15) at 0°C. The resulting reaction mixture was refluxed for 20 hours and then cooled. The cooled reaction mixture was diluted with n-hexane (200 ml) and n-hexane layer was separated. The n-hexane extract was washed in succession with 50 ml portions of ice cold aq. 1.5M HCl. and cold aq. $NaHCO_3$. The resulting pentane solution was dried over Na_2SO_4, concentrated and distilled to get (17) in 89% yield (16.3 g), b.p.185°C/1 mm.

IR (neat): 3080 cm^{-1}, 3040, 3010, 2955, 2890, 1600, 1570, 1460, 1340, 1255, 1170, 1150, 920, 860, 750, 710.

PMR($CDCl_3$) δ 0.25 [9H, s, $Si(CH_3)_3$], 3.03 (2H, d, J=6 Hz), 5.31 (1H, t, J=2 Hz), 7.31 - 7.75 (4H, m, aromatic).

Silylenol ether (18)

α-Tetralone (16) (13.14 g, 0.09 mole) was reacted with triethylamine (20.3 g, 0.20 mole) and trimethylsilyl chloride (10.8 g, 0.1 mole) in DMF as above to

get (18) in 87% yield (17.1 g).

IR (neat): 3070 cm^{-1}, 3010, 2955, 2880, 1600, 1565, 1440, 1340, 1240, 1170, 1150, 930, 740.

PMR ($CDCl_3$): δ 0.31 [9H, s, $-Si(CH_3)_3$], 2.18 - 2.87 (4H, m), 5.25 (1H, t, J=4 Hz), 7.35 - 7.65 (4H, m, aromatic).

Hydroxy ketone (19)

A methylene chloride (10 ml) solution of (17) (4.5 g, 0.022 mole) was added dropwise into a mixture of acetone (1.74 g, 0.03 mole) and $TiCl_4$ (5.7 g, 0.03 mole) in dry methylene chloride (25 ml) under N_2 atmosphere at 0°C. The reaction mixture was stirred for 5 hours at room temperature. Reaction mixture was then hydrolysed with HCl and the organic layer was extracted with ether. The extract was washed with water, dried over Na_2SO_4 and concentrated to get crude hydroxy ketone (19). This was purified by column chromatography (silica gel, 20% ethyl acetate in pet.ether) to get pure (19) in 91% yield (3.80 g).

PMR (CCl_4): δ 1.13 (3H, s, $-CH_3$), 1.31 (3H, s, $-CH_3$), 2.71 - 2.96 (2H, m, benzylic $-CH_2-$), 3.31 (1H, dd, J=9 Hz), 4.30 (1H, s, D_2O exchangeable), 7.29-7.5 (3H, m, aromatic), 7.77 (1H, d, J=8 Hz).

Analysis: Calculated for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42

Found: C, 75.67; H, 7.48.

Hydroxy ketone (20)

It was prepared as above in 93% yield from the silylenol ether (18). The compound (20) was a white crystalline solid, m.p.65°C.

PMR (CCl_4): δ 1.23 (6H, s, isopropyl methyl protons), 1.6 - 3.13 (5H, m), 4.5 (1H, s, D_2O exchangeable), 7.0 - 7.45 (3H, m, aromatic), 7.8 - 8.0 (1H, d, J=7 Hz, aromatic).

Analysis: Calculated for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90
Found: C, 76.49; H, 7.85.

2-Isopropyledene-1-indanone (21)

Hydroxy ketone (19) (1.90 g, 0.01 mole) was azeotroped in benzene (50 ml) with pTSA (20 mg) for 2 hrs. Then the reaction mixture was washed with water, dried over Na_2SO_4 and concentrated to give (21) in 97% yield (1.67 g). The compound (21) was recrystallised from methanol water mixture to get light yellow colored crystalline solid, m.p.103°C.

IR (Nujol): 3060, 2920, 2840, 1680 (keto carbonyl), 1600, 1300, 1230, 1160, 1130, 1025, 950, 830, 740, 715.

PMR (CCl_4): δ 1.83 (3H, s, $-CH_3$), 2.27 (3H, s, $-CH_3$), 3.37 (2H, s, benzylic $-CH_2-$), 7.0 - 7.4 (3H, m, aromatic), 7.45 - 7.70 (1H, m, aromatic).

Analysis: Calculated for $C_{12}H_{12}O$: C, 83.69; H, 7.02
Found: C, 83.60; H, 7.10.

2-Isopropyledene-α-tetralone (22)

Hydroxy ketone (20) (2.04 g, 0.01 mole) was dehydrated as above to get (22) in 96% yield (1.78 g). It was a colorless thick oil.

IR (neat): 3050, 2930, 2820, 1675 (keto carbonyl), 1600, 1450, 1430, 1370, 1300, 1230, 950, 890, 830, 730, 720.

PMR(CCl_4): δ 1.87 (3H, s, $-CH_3$), 2.13 (3H, s, $-CH_3$), 2.77 (4H, s, 2 X $-CH_2$), 6.9 - 7.4 (3H, m, aromatic), 7.8 - 8.0 (1H, m, aromatic).

Analysis: Calculated for $C_{13}H_{14}O$: C, 83.83; H, 7.58

Found: C, 83.91; H, 7.61.

Carbethoxymethyl dimethylsulfonium bromide (32)

A solution of ethyl bromoacetate (26.5 g, 0.159 mole) and dimethyl sulfide (11.4 g, 1.84 mole) in 50 ml of acetone was stored at 0°C for 4 days. Filtration of reaction mixture gave the (32) in 90% yield (32.6 g), m.p. 78-80°C. The PMR ($CDCl_3$) spectrum showed singlets at δ 3.55 (6H, $S(CH_3)_2$) and 5.36 (2H, $-CH_2$), a triplet at 1.33 (3H, CO_2C-CH_3) and a quartet at 4.34 (2H, CO_2CH_2-).

Ethyl (dimethylsulfuranylidene)acetate (33)

A solution of (32) (16.3 g, 0.71 mole) in 60 ml of $CHCl_3$ was stirred at 5-10°C with ice-bath cooling and treated in one portion with a mixture of 43 ml of saturated K_2CO_3 solution and 58 ml of 12.5 N NaOH.

The reaction mixture was warmed to 15-20°C and was held there for an additional 15 minutes. After removal of salt by filtration, the filtrate was separated and upper chloroform layer was dried over K_2CO_3. Removal of solvent under vacuum at 25°C gave light yellow ylide in 80% yield (8.42 g).

PMR ($CDCl_3$) spectrum: δ 1.21 (3H, t, J=8 Hz, $COOC-CH_3$), 3.95 (2H, q, J=7 Hz, CO_2CH_2-), 2.71 - 2.82 [7H, m $CH=S(-CH_3)_2$].

Spiroketo ester (23)

The keto compound (21) (1.72 g, 0.01 mole) and ylide (33) (1.78 g, 0.012 mole) were refluxed in benzene for 8 hrs. Solvent was distilled off at reduced pressure and the crude product was chromatographed to give (23) in 96% yield (2.47 g) It was a colorless thick liquid.

IR (neat): 2960 cm^{-1}, 2930, 2910, 1720 (ester carbonyl), 1700 (keto carbonyl), 1600 (aromatic), 1460, 1320, 1290, 1210, 1170, 1135, 1100, 740.

PMR (CCl_4): δ 1.23 (3H, t, J=7 Hz, for $COOC-CH_3$), 1.35 (3H, s, for cyclopropane methyl protons), 1.45 (3H, s, for cyclopropane methyl protons), 2.35 (1H, s, cyclopropane proton), 3.32 (2H, dd, J=18 Hz, 8 Hz, for benzyl methylene protons), 4.8 (2H, q, J=7 Hz, $COOCH_2-$), 7.2 - 7.7 (4H, m, aromatic).

Mass: 258 (molecular ion peak), 213, 185 (base peak), 171, 169, 157, 141, 128, 115, 102, 91, 82, 77.

Analysis: Calculated for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02
Found: C, 74.48; H, 7.09.

Spiroketo acid (26) and ester (27)

The keto compound (22) (1.86 g, 0.01 mole) and ylide (33) (4.45 g, 0.03 mole) were condensed (refluxed for 5 hrs) as above to get the ester (24) in 30% yield (GLC yield). Benzene was removed and the crude product was treated with alkaline ethanol at 0°C for 4 hrs. Ethanol was removed and residue diluted with water and extracted with ether. The aqueous layer was acidified with dil.HCl and extracted with ether to give crystalline acid (26) in 25% yield (0.61 g), m.p.174-176°C.

IR (nujol): 3100 (broad peak), 2910, 2860, 1710 (broad peak for carbonyl), 1610 (aromatic), 1380, 1300, 1255, 1230, 1190, 1100, 1010, 930, 740.

PMR ($CDCl_3$): δ1.10 (3H, s, for $-CH_3$), 1.46 (3H, s, $-CH_3$), 2.0 - 3.15 (4H, broad multiplet for C_7 and C_8 methylene protons), 2.8 (1H, s, for cyclopropane protons), 7.10-7.6 (3H, m, aromatic), 8.0 (1H, doublet with fine splitting, J=8 Hz, for aromatic protons).

Analysis: Calculated for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60
Found: C, 73.85; H, 6.49.

Esterification of ether solution of (26) with ether solution of diazomethane gave the ester (27) in 98% as colorless oil.

IR(neat): 2980, 2940, 1720 (ester carbonyl), 1680 (keto carbonyl), 1600 (aromatic), 1430, 1310, 1225, 1200, 1150, 1105, 930, 900, 860, 740

PMR(CCl_4): δ 1.10 (3H, s, $-CH_3$), 1.50 (3H, s, $-CH_3$), 1.8 - 3.10 (4H, m, for C_1 and C_8 methylene protons), 2.71 (1H, s, for cyclopropane protons), 3.60 (3H, s for ester methyl protons), 6.90 - 7.45 (3H, m, aromatic), 7.92 (1H, doublet with fine spitting, J=7 Hz, aromatic).

Analysis: Calculated for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02

Found: C, 74.48; H, 6.93.

Spiroketo acid (25)

The spiroketo ester (23) (2.58 g, 0.01 mole) was stirred at 0°C with KOH (0.56 g, 0.012 mole) in ethanol for 3 hours. Acidification and extractive workup gave (25) in 94% yield (2.15 g) as a crystalline solid, m.p.160-161°C.

IR ($CHCl_3$ solution): 3000 (broad peak), 1710 (broad peak), 1620 (aromatic), 1440, 1390, 1310, 1270, 1220, 1110, 940.

PMR ($CDCl_3$): δ 1.38 (3H, s, for $-CH_3$), 1.44 (3H, s, for $-CH_3$), 2.50 (1H, s, for cyclopropane proton), 3.38 (2H, dd, J=18 Hz, 10 Hz, for benzylic methylene protons), 7.25 - 7.8 (4H, m, for aromatic protons).

Analysis: Calculated for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13

Found : C, 73.12; H, 6.25.

Hydroxy esters (28) and (29)

A methanol (25 ml) solution of keto ester (27) (1.29 g, 0.005 mole) and sodiumborohdyride (0.28 g, 0.006 mole) was stirred at 0°C for 1 hr. Methanol was removed under reduced pessure and the reaction mixture was diluted with water and extracted with ether. Ether layer was washed many times with water and ether layer was concentrated to get crude mixture of (28) and (29). These two compounds were separated by column chromatography (silica gel, 15% ethylacetate in pet.ether). The faster moving isomer (29) was major, weighing 0.944 g (73% yield). The minor isomer (28) weighed 0.221 g (17% yield).

Spectral properties of (28): IR (nujol), 3310 (hydroxy), 3010, 2920, 2850, 1730 (ester carbonyl), 1440, 1380, 1200, 1150, 1100, 985, 950, 860, 750.

PMR ($CDCl_3$): δ 1.15 (3H, s, $-CH_3$), 1.30 (3H, s, $-CH_3$), 1.70 (1H, s, for cyclopropane proton), 2.05 (1H, s, D_2O exchangeable proton), 2.1 - 2.50 (2H, m, for C_8 methylene protons), 2.60 - 2.90 (2H, m, for C_7 methylene protons), 3.60 (3H, s, for ester methyl protons), 4.18 (1H, s, for C_4 benzyl proton linked to oxygen), 7.0 - 7.30 (4H, m, for aromatic protons).

Analysis: Calculated for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74

Found: C, 73.71; H, 7.65.

Spectral properties of (29): IR (neat): 3450 (hydroxy), 3010, 2920, 1720 (ester carbonyl), 1440, 1370, 1210, 1170, 1100, 1000, 880, 750.

PMR ($CDCl_3$): δ1.25 (1H, s, cyclopropane proton), 1.32 (3H, s, for cyclopropane methyl protons), 1.47 (3H, s, for $-CH_3$), 1.80 (1H, s, D_2O exchangeable), 1.95 - 2.35 (2H, m, for C_8 methylene protons), 2.40 - 2.77 (2H, m, for C_7 methylene protons), 3.5 (3H, s, for ester methyl protons), 4.15 (1H, s, for C_4 benzyl proton), 7.0 - 7.3 (4H, m, for aromatic protons).

Mass: 260 (molecular ion), 242, 202, 189, 185, 183, 170, 159, 146 (base peak), 141, 128, 115, 91, 77.

Analysis: Calculated for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74

Found: C, 73.88; H, 7.68.

Hydroxy esters (30) and (31)

Keto ester (23) (1.29 g, 0.005 mole) was reduced with sodiumborohydride (0.28 g, 0.006 mole) in ethanol as above. The product, which is a mixture of (30) and (31) was chromatographed to give the major compound (31) in 75% yield (0.97 g) and the minor compound (30) in 19% yield (0.247 g). The minor compound was a crystalline solid, m.p.78°C, while major compound (31) was a thick liquid.

Spectral properties of (31): IR (neat): 3435 (hydroxy), 2940, 2880, 2820, 1720 (ester carbonyl), 1590 (aromatic), 1450, 1360, 1310, 1280, 1160, 1120, 1030, 730.
PMR (CCl_4): δ 1.10 (3H, t, J=7 Hz, for COO-C-CH_3), 1.20 (6H, s, for cyclopropane gemdimethyl protons), 1.80 (1H, s, cyclopropane proton), 2.48 (1H, bs, D_2O exchangeable), 2.80, 3.66 (2H, dd, J_1= 18 Hz, J_2=34 Hz for C_7 methylene protons), 3.88 (2H, quartet with fine splitting, J=7 Hz, for COO-CH_2-), 4.76 (1H, bs, for C_4 benzylic proton), 6.97 - 7.25 (4H, m, for aromatic protons).
Mass: 260 (molecular ion), 242, 226, 202, 185, 176, 169 (base peak), 143, 132, 120, 115, 91, 83, 77.
Analysis: Calculated for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74
Found: C, 73.91; H, 7.79.
Spectral properties of (30): IR (Nujol): 3420 (hydroxy), 2980, 2920, 1715 (ester carbonyl), 1610 (aromatic), 1470, 1440, 1380, 1340, 1200, 1165, 1010, 750.
PMR (CCl_4): δ1.17 (3H, t, J=7 Hz, for COO-C-CH_3), 1.37 (3H, s, for cyclopropane methyl protons), 1.50 (3H, s, for cyclopropane methyl protons), 1.50 (3H, s, for cyclopropane methyl protons), 1.6 (1H, s, cyclopropane proton), 1.75 (1H, bs, D_2O exchangeable), 3.12, 3.52 (2H, dd, J_1=18 Hz, J_2=25 Hz, for C_7 benzylic methylene protons), 4.00 (2H, q, J=7 Hz, for COO-CH_2-), 4.65 (1H, s, for C_4 benzylic proton), 7.17 - 7.35 (4H, m, aromatic protons)

Analysis : Calculated for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74
Found: C, 73.94; H, 7.68.

Ketoester (36)

To a dry benzene solution (15 ml) of keto acid (25) (0.23 g, 0.001 mole) was added thionyl chloride (0.14 g, 0.0012 mole)in dry benzene (5 ml) at 0°C and stirred for 3 hours. Benzene was distilled off under reduced pressure to get crude acid chloride (34). To the dry benzene (20 ml) solution of acid chloride was added pyridine (0.09 g, 0.0012 mole) at 0°C. To this reaction mixture was added dropwise benzaldehyde cyanohydrin (10) (0.209 g, 0.001 mole) in benzene (5 ml). The reaction mixture was brought to room temperature and stirred for 4 hours. Extractive workup with ether gave a thick oil, purified by the column chromatography to give (36) in 65% yield (0.28 g).

IR (neat): 3020, 2920, 2860, 1740 (ester carbonyl), 1700 (keto carbonyl), 1585 (aromatic), 1480, 1320, 1240, 1210, 1160, 880, 740.

PMR($CDCl_3$): δ1.20 - 1.52 (6H, two pairs of singlets, for the cyclopropane gemdimethyls), 2.50 (1H, fine splitting singlet, for cyclopropane proton), 3.05 - 3.65 (2H, m, for C_7 benzylic protons), 6.25 (1H, s, for —CH-CN), 6.80 - 7.80 (13H, m, for all aromatic protons).

Mass: 437 (molecular ion peak), 411, 383, 355, 339, 326, 311, 298, 285, 257, 229, 209, 185 (base peak), 141, 115, 83, 77.

Keto ester (37)

It was prepared as above starting from the keto acid (26), via the intermediate acid chloride (35) in 69% yield.

IR (neat): 3140, 2920, 1735 (ester carbonyl), 1670 (keto carbonyl), 1580 (aromatic), 1480, 1440, 1310, 1220, 1160, 1120, 1100, 900, 860, 730.

PMR ($CDCl_3$): δ1.10 (3H, a pair of singlets, for one of the gemdimethyl protons), 1.51 (3H, a pair of singlets, for one of the gemdimethyl protons), 1.60 - 3.15 (4H, broad multiplet, for C_7 and C_8 methylene protons), 2.85° (1H, s, for cyclopropane proton), 6.25 (1H, a fine splitting singlet for -CH-CN), 6.81 = 7.56 (12H, m, for aromatic protons). 7.93 (1H, doublet with fine splitting, J=8 Hz, for aromatic protons).

Mass: 451 (molecular ion), 411, 383, 352, 339, 311, 298, 285, 257, 243, 225, 199 (base peak), 181, 141, 139, 115, 92, 77.

Hydroxy ester (38)

A THF (15 ml) solution of keto ester (36) (0.218 g, 0.0005 mole) and sodiumborohydride (0.028 g, 0.0006 mole) was stirred at 0°C for 1 hr. THF was removed under reduced pressure and the reaction mixture

was diluted with water and extracted with ether. Ether layer was washed with water and was concentrated to get the crude compound (38). This crude was chromatographed to get (38) in 76% yield (0.166 g).

IR (neat): 3350 (hydroxy), 2920, 1730 (ester carbonyl), 1585 (aromatic), 1490, 1240, 1205.

PMR ($CDCl_3$): δ1.25 - 1.40 (6H, two pairs of singlets, for gemdimethyl protons), 1.90 (1H, fine splitting singlet for cyclopropane proton), 2.81 - 3.56 (2H, m, for C_7 benzylic protons), 4.59 (1H, a fine splitting singlet for C_4 benzylic proton), 6.25 (1H, fine splitting singlet, for -CH-CN), 6.75 - 7.53 (13H, m, for aromatic protons).

Mass: 439 (molecular ion), 422, 403, 381, 377, 363, 329, 213, 200, 183, 169 (base peak), 141, 132, 115, 91, 83, 77.

Hydroxy ester (39)

It was prepared as above in 79% yield from (37) by $NaBH_4$ reaction in THF.

IR (neat): 3400 (hydroxy), 3120, 2920, 1735 (ester carbonyl), 1590 (aromatic), 1490, 1450, 1245, 1130, 1100, 875, 765.

PMR ($CDCl_3$): δ1.30 - 1.46 (7H, two pairs of singlets for gemdimethyl protons and a peak for cyclopropane proton), 1.84 (1H, bs, D_2O exchangeable), 1.60 - 3.00 (4H, m, for C_7 and C_8 methylene protons), 4.20 (1H, s,

for C_4 benzylic proton), 6.20 and 6.25 (1H, two singlets, for -CH-CN), 6.80 - 7.50 (13H, m, for aromatic protons). Mass: 453 (molecular ion peak, very weak), 436, 422, 396, 383, 365, 356, 336, 245, 227, 209, 183, 181, 141 (base peak), 129, 128, 115, 91, 77.

REFERENCES

1. K. Tsushima, N. Matsuo, N. Itaya, T. Yano and M. Hatakoshi "Pesticide Chemistry Human Welfare and the Environment", Vol. 1, Eds. J. Miyamoto and P.C. Kearney, Pergamon Press, (1983);pp91-94.

2. K. Tsushima, N. Matsuo, M. Hatakoshi, T. Yano and N. Itaya, European Patent No.0,056,271-A 2 (1982).

3. Y. Poriev and N. Lozck, Bull.Soc.Chim.France, 1062 (1966).

4. H.O. House, L.J. Czuba, M. Gall and H.D. Olmstead, J.Org.Chem., 34, 2324 (1969).

5. T. Mukaiyama, K. Banno and K. Naraska, J.Am.Chem.Soc., 96, 7503 (1974).

6. G.B. Payne, J.Org.Chem., 32, 3351 (1967).

7. R.B. Mitra, Z. Muljiani and G. Bhasker Reddy, Synth.Commun., 16(9), 1099 (1986).

PART B

1. GENERAL INTRODUCTION TO PHEROMONES.
2. CHAPTER I: SYNTHESIS OF Z-6-HENEICOSEN-11-ONE AND Z-1,6-HENEICOSADIEN-11-ONE.
3. CHAPTER II: SYNTHESIS OF PHEROMONES HAVING SPIROKETAL FUNCTIONS
4. CHAPATER III: SELECTIVE DEPROTECTION OF N,N-DIMETHYLHYDRAZONES.

INTRODUCTION

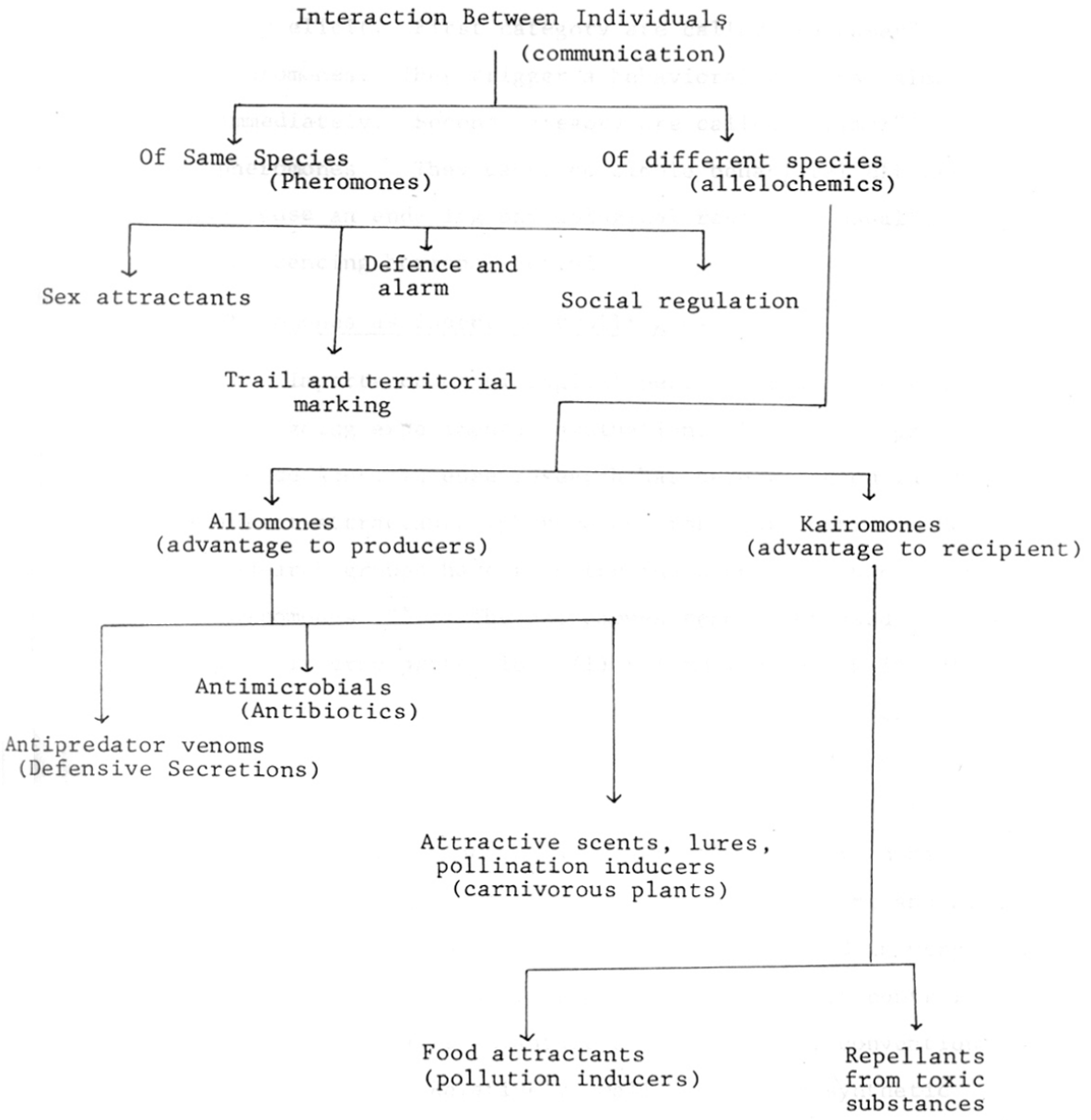
Man has been unable to develop a stable system of agriculture for the expanding world population. This is partly due to the fierce competition of insects for his food and fibre. Insects are constant source of depredation to humans. They devour plants, spread disease and are generally a great nuisance to man. Application of insecticides is still the most generally used approach for controlling insects and other invertibrate pests. These substances have often provided very effective control. Unfortunately the solution has often been only short-term and side effects have sometimes been worse than the original problem. These insecticides are not only harmful to humans but many are very persistent in environment[1]. They show low selectivity to insects and kill harmless and useful insects like honey-bees and predators. Therefore several other longterm approaches, which are more selective and environmentally acceptable to combat the insect pest, have been suggested by many research groups all over the world[2-12]. One of the important approaches depends on an understanding of how insects use chemicals to communicate.

The interdisciplinary investigation of insect kingdom by biologist and chemist have established the

importance and complexity of chemosensory communication among insects. Many facets of insect behaviour have been shown to be regulated by chemical stimuli. There is potential to utilize this information to combat insects in ways that are highly selective and environmentally acceptable. The role of chemicals used for communication in insects and other animals is summarised in flow sheet[13] (page). This form of communication includes attraction between two sexes for mating, alerting members of a colony for the purpose of defence, the use of defensive secretions to fight off predators, territorial marking and trail-marking to assist in gathering food for colony.

The substances which are used for communication between different species are called allelochemics. These include defensive secretions and repellents formed from the toxic substances.

Pheromones are the chemicals used for communication between same species. Pheromones can be defined as substances that are secreted outside by an insect and received by another insect of the same species in which they release a specific reaction, for example, a definite behaviour or developmental process. The term pheromone[14] is derived from the Greek pherein -"to transfer" and hormon -"to excite". Pheromones are classified into two distinct types by Wilson[15] according to the response



Flow sheet of the role of chemicals used for communication in insects and other animals

they elicit. First category are called "releaser" pheromones. They trigger a behavioral response almost immediately. Second category are called "primer" pheromones. They cause no simple behavioral effects but cause an enduring physiological response, usually by influencing hormonal activity.

Pheromones as insect controlling agents

Importance of biological pest control is currently undergoing experimental evaluation. During the past two decades, intense research has been going on in using insect attractants (pheromones) for pest control. Several research groups have reported the successful use of insect pheromones[7-12]. The pheromones tend to be used in three ways in crop protection, (1) for monitoring an insect population to see if it exceeds an economic threshold, when damage of crops becomes significant; (2) for mating disruption, where a male insect may be led to believe that a female is nearby when actually there is none. So no breeding takes place; (3) to attract lure and kill, where a small amount of insecticide is placed in very close proximity to the lure. These methods of pest control have considerable advantage over the use of conventional insecticides. Relatively small amounts of synthetic attractant required minimizes the possibility of

environmental pollution and the species specificity of the natural attractants reduces the risk of destroying beneficial insects such as predators, parasites, and pollinators. The most general application of pheromones probably lies in integrated pest control measures as population survey tools to probe the degree of infestation. Limited application of chemical pesticides could then suffice in areas of intolerable infestation.

Synthetic studies in pheromones

Synthetic approach is very important in pheromone research because of the limited availability of natural pheromoens from insects. Synthetic work in pheromones may be classified into three categories;

(1) Synthesis as the final proof of the proposed structure including olefin geometry and relative as well as absolute stereochemistry ,

(2) Syntheses that provide sufficient material for biological study, such as field tests,

(3) Syntheses of a number of isomers and analogs to clarify the structure-activity relationship. Synthesis thus ensures ample supplies and facilitates the practical use in agriculture and forestry.

Because of the importance of synthetic pheromones, a number of organic chemists from wellknown groups

throughout the world have become involved in this area of research. A large number of papers have been published on pheromones, which includes synthesis and their applications in agriculture and forestry. A number of reviews are available on chemical aspects of pheromones. Rossi reviews the synthesis of both achiral and chiral[16] pheromones. Henrick discusses lepidoptera, coleoptera and diptera pheromones in depth[17]. In 1981, Mori[18] reviewed comprehensively "on the synthesis of insect pheromones", in which he has described the synthesis of as many as ninety six pheromones. Besides references 19-24, number of reviews[25-27] and monographs[28-29] are also available on pheromone biology and their application.

REFERENCES

1. R. Carson, " Silent Spring"; (Houghton-Mifflin Ed.) Boston, (1962).

2. R.L. Ridgway, Ed., "Biological control by augmentation of natural enemies"; proceedings of international conference on entomology, 15th Ed., Washington (1976).

3. P. DeBack, "Biological control of insect pests and weeds" (1964).

4. Chem. Eng. News, (September 30), 20, (1974).

5. J. Calman and R.H. Smith, Science, 182, 775 (1973).

6. C. Djerassi, C. Shih-Coleman and J. Diekman, Science, 186, 596 (1974).

7. J.L. Marx, Science, 181, 736, (1973).

8. R.J. Seltzer, Chem.Eng.News (August 20), 19, (1973).

9. D. Hamilton, J.Econ.Entomol., 64, 150 (1971).

10. D. Hardee, J.Econ.Entomol., 64, 928 (1971).

11. M. Beroza and E.F. Knipling, Science, 177, 19 (1972).

12. M. Beroza, Ed., Pest management with insect sex attractants, ACS Symposium Series No.23, American Chemical Society, Washington (1976).

13. W.R. Stine, J.Chem.Eduction, 63(7), 603 (1986).

14. P. Karlson and M. Lascher, Nature, 183, 55 (1959).

15. E.O. Wilson, Science, 149, 1064 (1960).

16. R. Rossi, Synthesis, 413, 1978.

17. C.A. Henrick, Tetrahedron, 33, 1845 (1977).

18. K. Mori, "Total Synthesis of natural product" Vol. 4, Page 1, [Ed. J. ApSimon), John Wiley and Sons, New York (1981).

19. J.G. MacConnell and R.M. Silverstein, Angew Chem.Int.Ed., 12, 644, 1973.

20. P. Karlson and D. Schneider, Naturwissenschaften, 60, 113 (1973).

21. D.A. Evans and C.L. Green, Chem.Soc.Rev., 3, 74 (1974).

22. K. Eiter, Pure Appl.Chem.,41, 201 (1975).

23. J.P. Vite and W. Francke, Naturwissenschaften, 63, 550 (1976).

24. J.P. Vite and J.A.A. Renwick, Z. Ang.Entomol., 82, 112 (1976).

25. H.Z. Levinson, Naturwissenschaften, 62, 272 (1975).

26. H.Z. Levinson, Z. Angew Entomol. 84, 1, (1977).

27. H.Z. Levinson, Z. Angew Entomol., 84, 337 (1977).

28. M. Jacobson, Insect Sex pheromones, Academic Press, New York (1972).

29. M.C. Birch Ed., Pheromones, North-Holland, Amsterdam, (1974).

CHAPTER I

SYNTHESIS OF Z-6-HENEICOSEN-11-ONE AND Z-1,6-HENEICOSADIEN-11-ONE THE SEX PHEROMONES OF DOUGLAS-FIR TUSSOCK MOTH

Summary

Z-6-Heneicosen-11-one (1) and Z-1,6-Heneicosadien-11-one (2), the pheromones of Gouglas-Fir Tussock moth have been synthesized using different methodologies. In the first method, key step being one pot successive bisalkylations of (39) with appropriately functionalized bromides.

In the second method, one pot successive alkylations of (39) with appropriately functionalised bromides gave ketoaldehyde (26), which upon reaction with appropriately substituted Wittig reagents afforded (1) and (2).

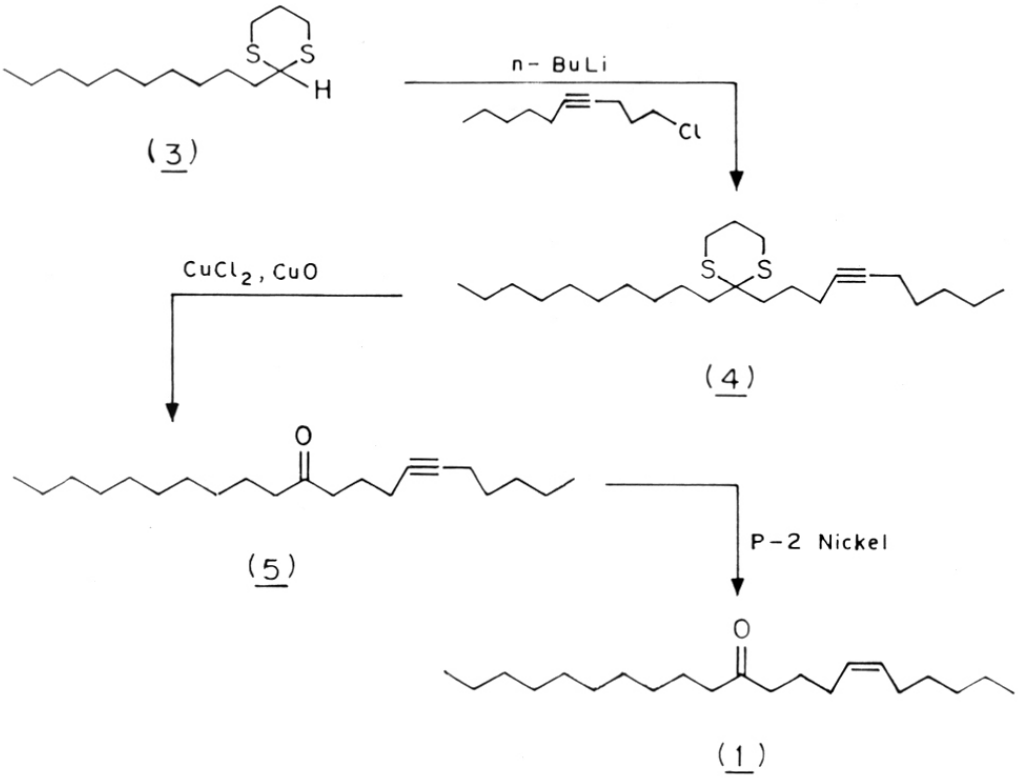
In the third method, Wittig reaction of lactal (66) with appropriately substituted Wittig reagents gave hydroxy olefin (67), which upon oxidation afforded (1) and (2).

INTRODUCTION

The compounds Z-6-Heneicosen-11-one (1) and Z-1,6-Heneicosadien-11-one (2) are the active sex pheromone components of the female Douglas-fir tussock moth "Orgyia Pseudotsugata", which is a severe defoliator of the fir forest of western North America. Compound (1), the major component was isolated by R.G. Smith et al.[1] in 1975 and compound (2), the minor component was isolated by L.M. Smith et al.[2] in 1978. These two pheromones are C_{21} ketones in contrast with other lepidoptera pheromones, which are unsaturated C_{12}-C_{18} primary alcohols or acetates. Tussock moth is capable of dramatic population increase , which can result in severe damage to forest resources. Since these two sex pheromones are potent male attractants and due to their importance in the fir forest protection, several syntheses of these two pheromones have been reported.

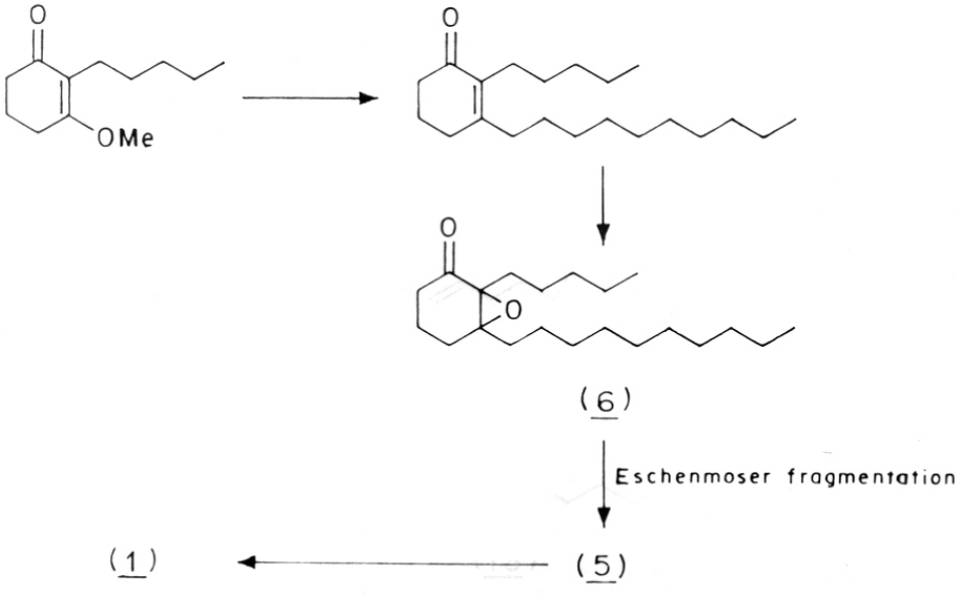
The first total synthesis of (1) was reported by Smith et al.[3] making use of dithiane intermediates (Scheme 1). In this synthesis, dithiane derivative (3) was alkylated with 1-chloro-4-decyne using n-BuLi as base to get alkyl dithiane derivative (4). Carbonyl group was regenerated from (4) with cupric chloride and cupric oxide and partial hydrogenation of resultant keto alkyne (5)

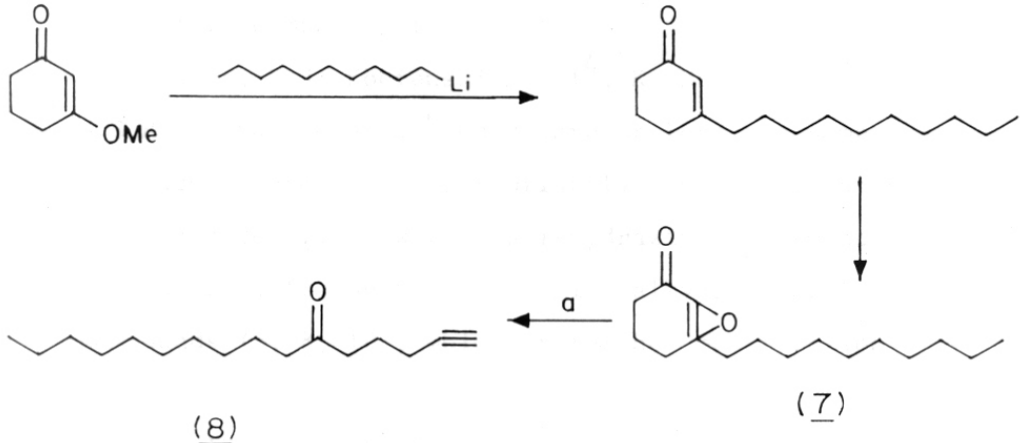
SCHEME - 1



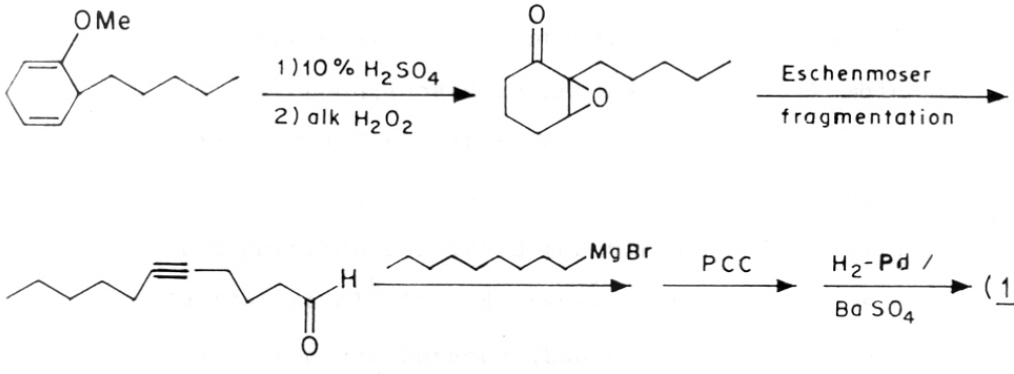
SCHEME - 2

P. J. KOCIENSKI et al

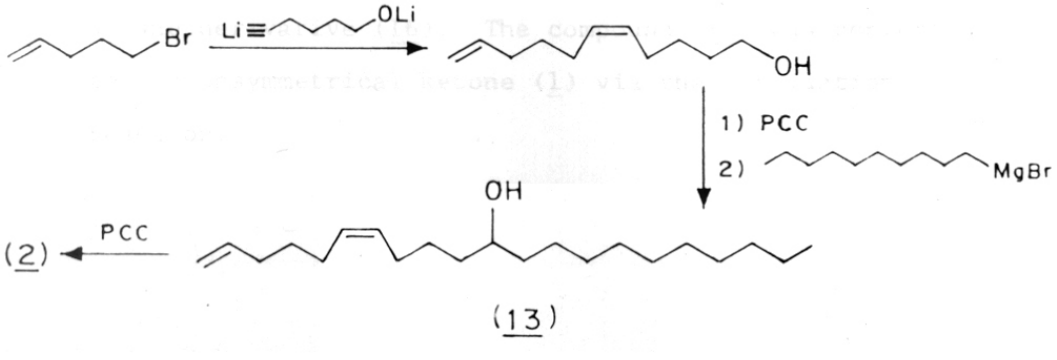




GSR SUBBA RAO et al



SCHEME-3



gave title compound (1).

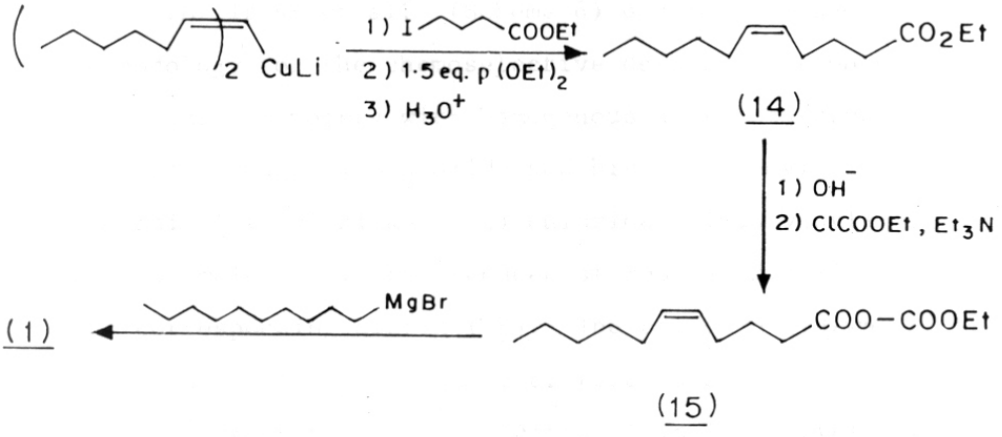
Later, P.J. Kocienski et al.[4], K. Mori et al.[5] and G.S.R. Subba Rao et al.[6] used more or less the same approach (Scheme 2). Appropriately substituted epoxy hexanones (6, 7, 9) with tosyl-hydrazine underwent Eschenmosers fragmentation to give alkyne carbonyl compounds (5, 8, 10), which on further modification gave (1).

In 1978, L.M. Smith et al.[2] synthesised (2) according to the Scheme 3 . The compound (12) on PCC oxidation and Grignard reaction gave (13), which on PCC oxidation afforded (2).

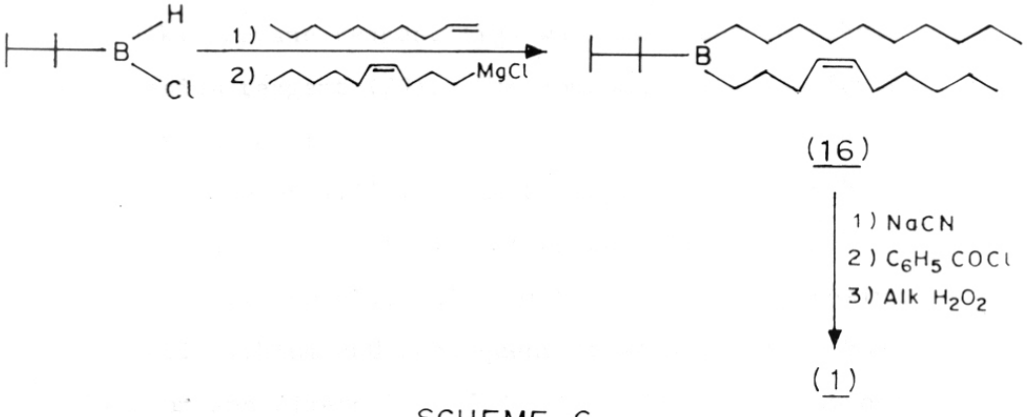
In 1980, Normant et al.[7] reported a synthesis of (1), which was based on the alkylation of Z-dialkenyl cuprates (Scheme 4). Z-diheptenyl cuprate was alkylated with ethy 4-iodobutanoate to get the ester (14), which was saponified and transformed quantitatively into the mixed anhydride (15). Treatment of (15) with n-decyl-magnesium chloride furnished the title pheromone (1).

Zweifel et al.[8] in 1980 reported the synthesis of (1) making use of organoboranes (Scheme 5). Thexyl chloro-borane on treatment with 1-decene followed by alkylation with Z-4-decyl magnesium chloride furnished the alkyl borane derivative (16). The compound (16) was converted to the unsymmetrical ketone (1) via the cyanidation reaction.

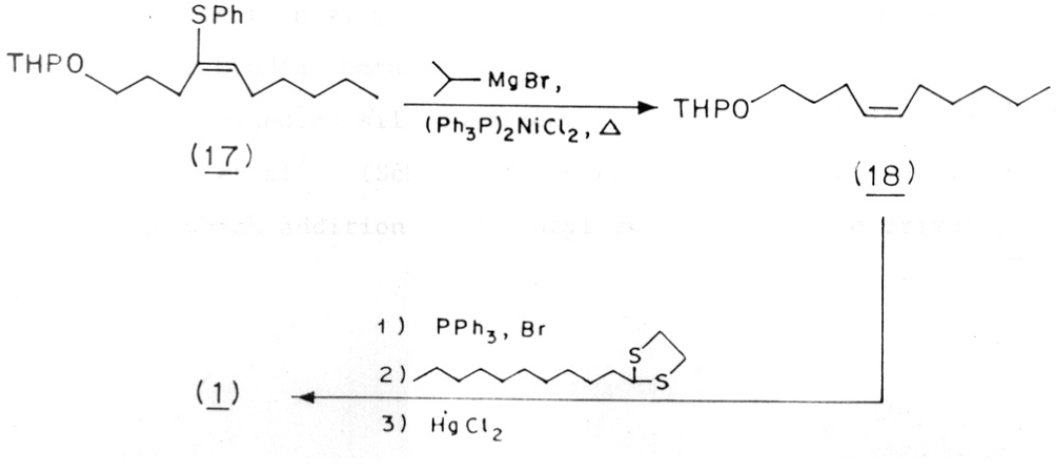
SCHEME-4



SCHEME-5



SCHEME-6



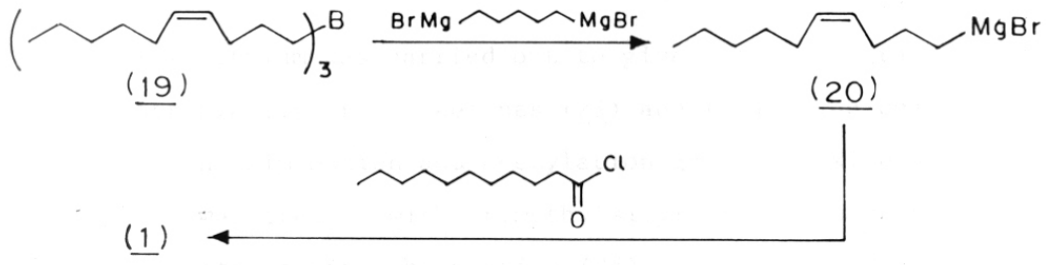
B.M. Trost et al.[9] (Scheme 6) developed a new methodology for the chemoselective desulfurization of vinyl sulfide moiety with homogenous nickel catalyst (isopropyl magnesium bromide and bis-(triphenyl phosphine) vinyl nickel (II) chloride. Thus vinyl-sulfide moiety (17) was reduced stereospecifically to the corresponding olefin (18). The compound (18) was converted to (1) by sequence of reactions.

S. Murahashi et al.[10] (Scheme 7) in 1979 developed a new methodology for the conversion of trialkyl borane to alkyl magnesium compound using pentane-1,5 di(magnesium bromide). Making use of this methodology trialkyl borane reagent (19) was converted to alkyl-magnesium reagent (20). The compound (20) was further converted to (1).

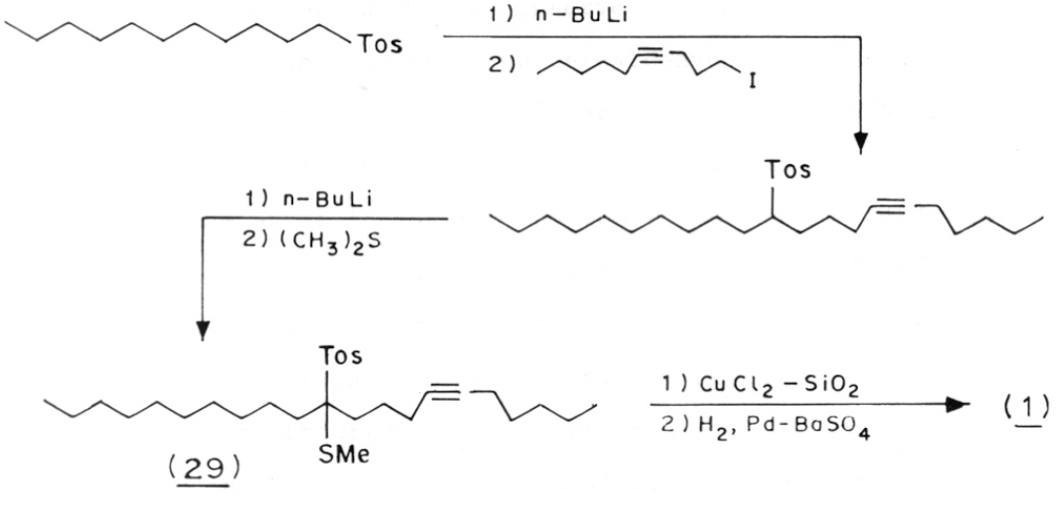
Kotake et al.[11] (Scheme 8) reported the synthesis of (1) making use of alkylation on sulfones. Alkyl sulfone (21) on alkylation with 1-iodo-4-decyne using n-butyl lithium and subsequent treatment with n-butyl lithium and dimethyl sulfide gave (22). The compound (22) on reaction with $CuCl_2$-SiO_2 and partial hydrogenation over Lindlar catalyst gave (1).

Based on silicon-directed Beckmann fragmentation, Itoh et al.[12] (Scheme 9) reported the synthesis of (1), in which addition of 2-pentyl cyclohexenone to trimethyl

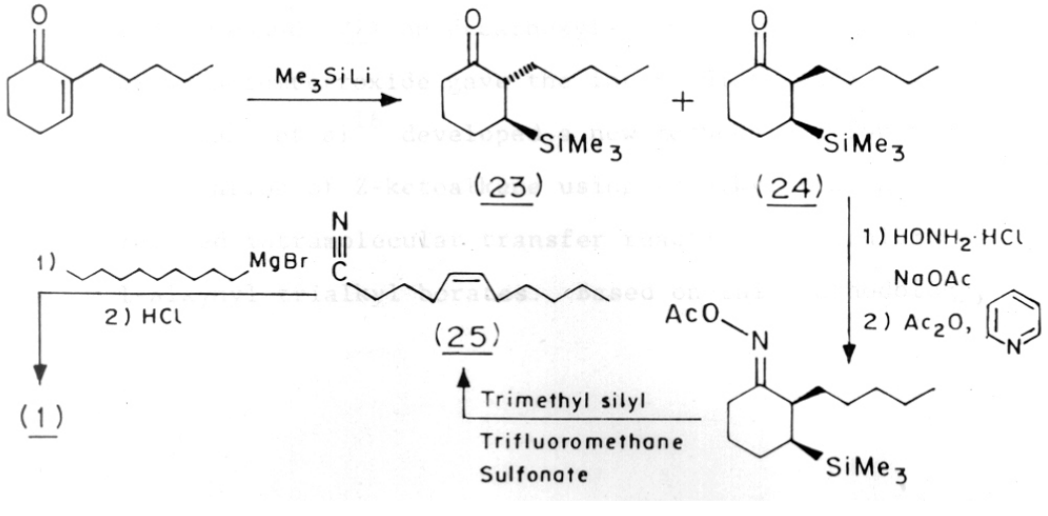
SCHEME-7



SCHEME-8



SCHEME-9

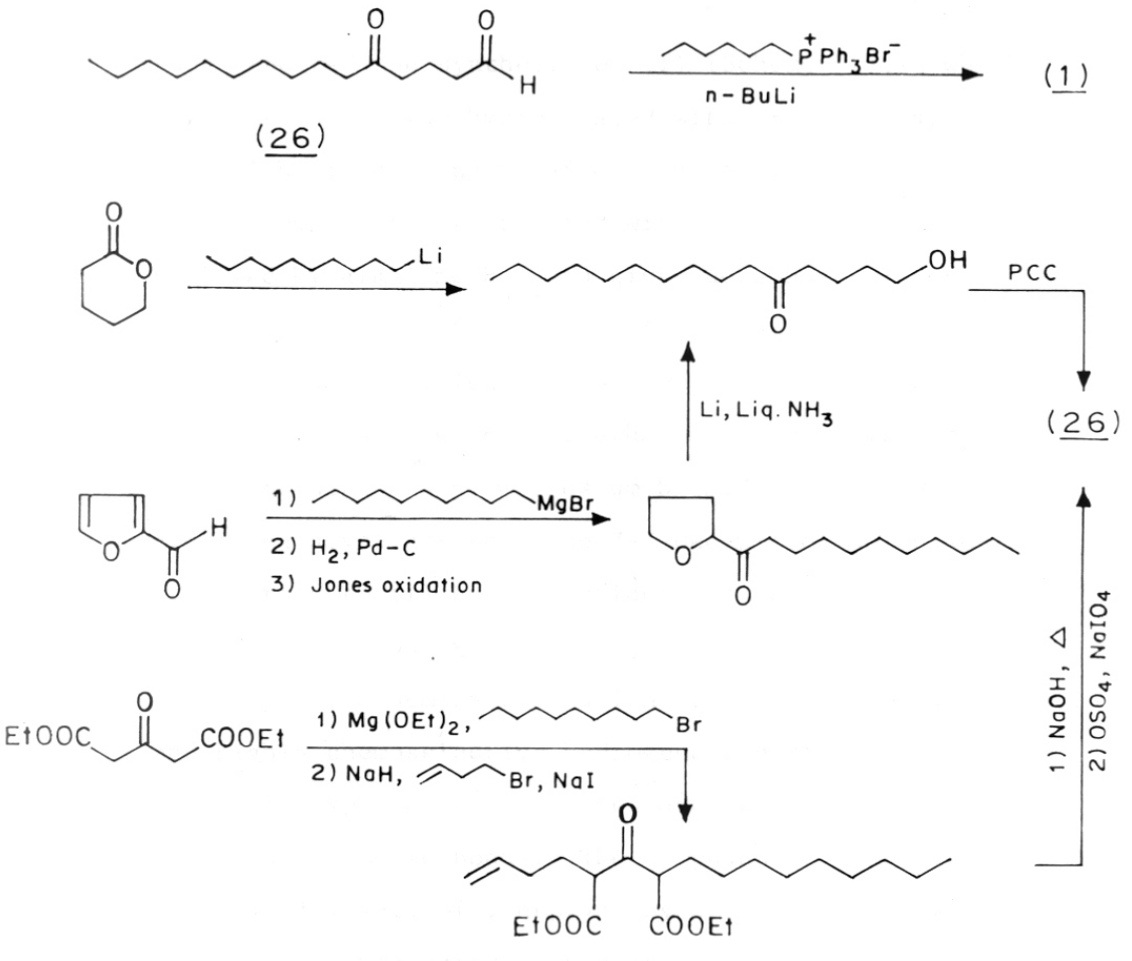


silyl lithium was carried out to give a chromatographically separable mixture of ketones (23) and (24). The compound (24) on oximenation and acetylation gave the oxime acetate, which was treated with trimethylsilyl trifluoro methane-sulfonate to give the nitrile (25). The compound (25) was converted to (1) by conventional methods.

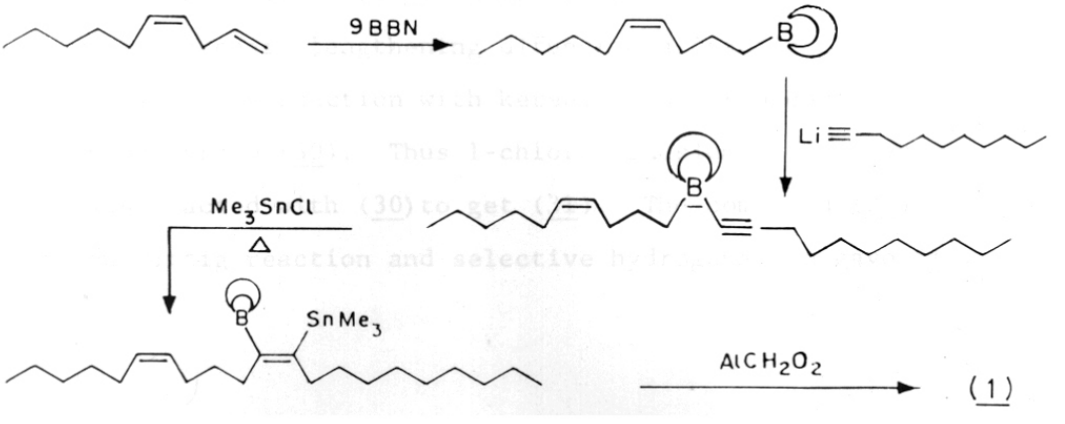
Hernandez et al.[13,14] and Naoshima et al.[15] (Scheme 10) have synthesized the key intermediate ketoaldehyde (26) by different approaches. The ketoaldehyde (26) was converted to pheromone (1) by Wittig reaction with n-hexylidene triphenyl phosphine. In their first synthesis, Hernandez et al.[13] got (26) by the PCC oxidation of 5-oxo-pentadecanol, which in turn was prepared from δ-valerolactone and n-decyl lithium. In the second synthesis[14], 5-oxo-pentadecanol was synthesized by the reductive cleavage of 2-tetrahydrofurfuryl decyl ketone with lithium in liquid ammonia. Naoshima et al.[15] utilized strategy of regio-selective two step alkylation of diethyl-3-oxo-glutarate with appropriately substituted alkyl bromides to get (27). The compound (27) on decarboxylation followed by oxidation with osmiumtetroxide gave the intermediate (26).

Wang et al.[16] developed a new methodology for the preparation of Z-ketoalkene using trialkyl tin chloride induced intramolecular transfer reaction of lithium 1-alkynyl trialkyl borates. Based on this methodology,

SCHEME–10



SCHEME– 11

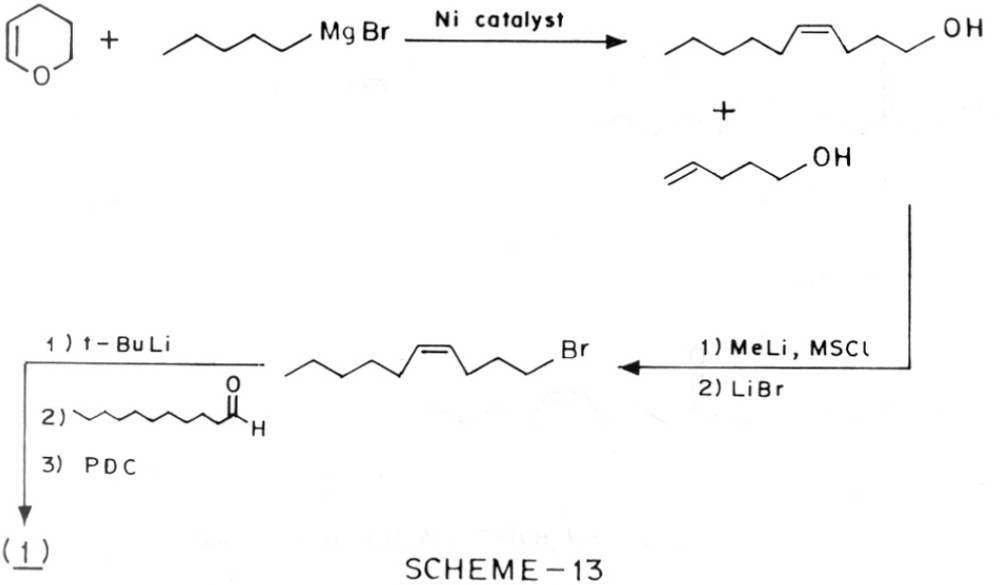


they reported the synthesis of (1) (Scheme 11),in which Z-1,4-decadiene was hydroborated with 9-BBN and alkylated with lithium undecyne to afford the alkyl borane (28). The compound (28) was treated with trimethyl tin chloride followed by alkaline H_2O_2 to give pheromone (1).

Wenkert et al.[17] (Scheme 12) reported the synthesis of (1) using low-valent nickel mediated reactions of Grignard reagents with enol ethers. Dihydropyran on treatment with n-amyl magnesium bromide using low valent nickel catalyst afforded the Z-4-decen-1-ol which was transformed to (1) by conventional reactions. The main strategy in Shibasaki[18] synthesis (Scheme 13) was the stereospecific semihydrogenation of alkynes to Z-alkenes and highly chemoselective hydrogenation of α,β-unsaturated carbonyl compounds to saturated analogues in the presence of isolated double bonds. The compound (29) prepared from lithium salt of 1-heptyne by usual reaction was partially hydrogenated with naphthalenetricarbonyl chromium in THF to furnish (1) with 100% regioselectivity.

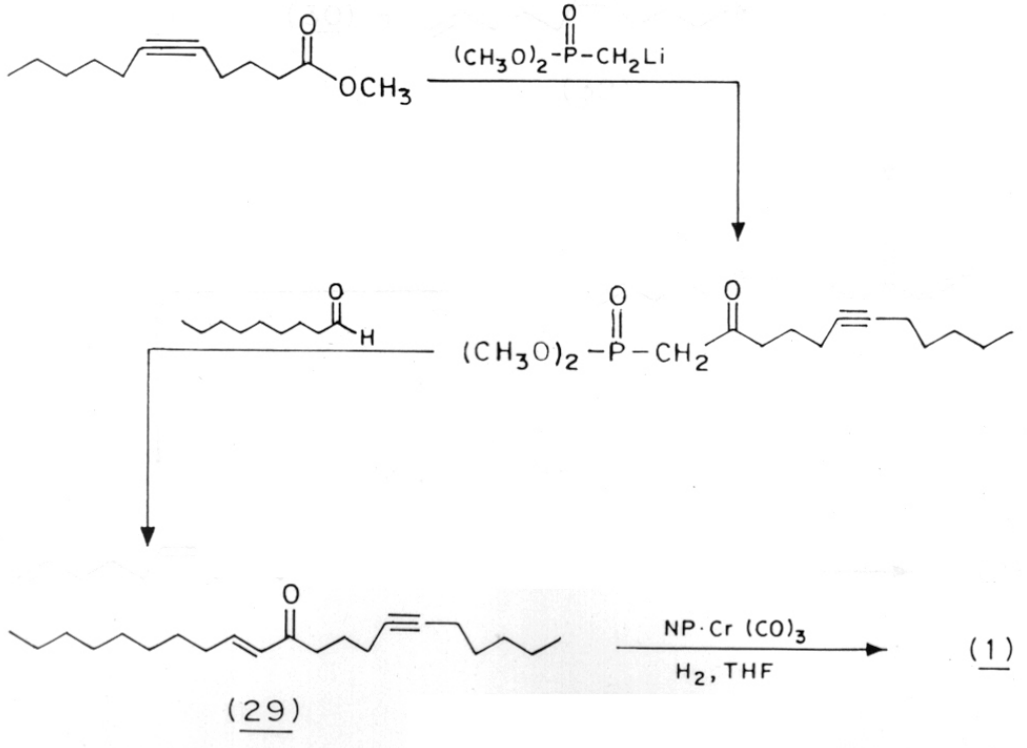
The main strategy in Bestmann[19] (Scheme 14) synthesis was the chain lengthening difunctionalisation of Grignard reagents by reaction with ketenylidene triphenyl phosphorane (30). Thus 1-chloromagnesium Z-dec-4-ene was reacted with (30) to get (31). The compound (31) on Wittig reaction and selective hydrogenation gave (1).

SCHEME – 12



(1)

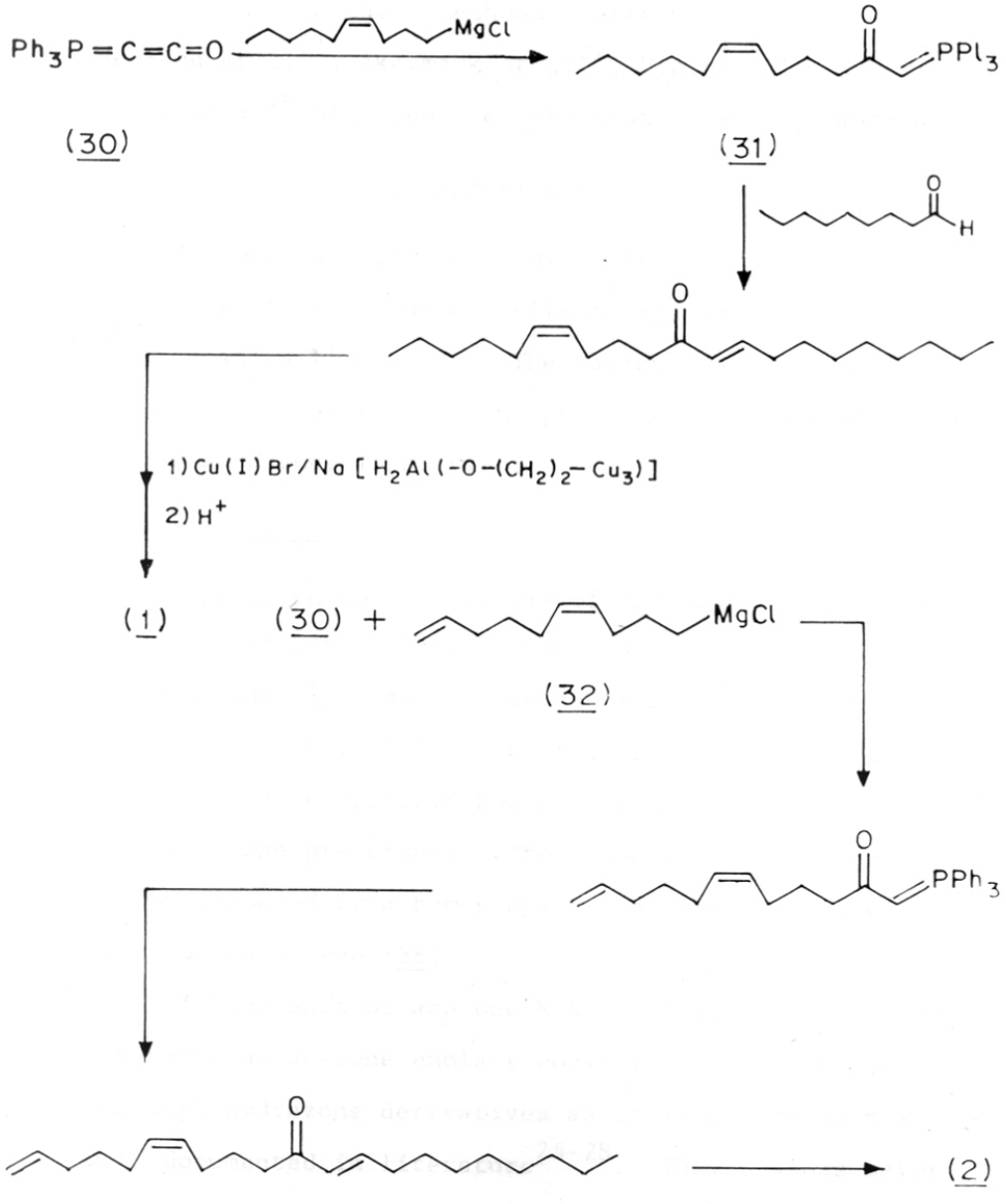
SCHEME – 13



(29)

(1)

SCHEME – 14


Ph3P=C=C=O
MgCl
PPh3
(30)
(31)
O
H
1) Cu(I)Br/Na [H2Al(-O-(CH2)2-Cu3)]
2) H+
(1)
(30) +
MgCl
(32)
PPh3
(2)

Similarly compound (32) was converted to (2) using (30) as key intermediate.

Apart from these methods, Fetizon et al.[20], Henrich et al.[21], Akermark et al.[22], Vig et al.[23] and Yadav et al.[24] also reported the synthesis of pheromone (1).

PRESENT WORK

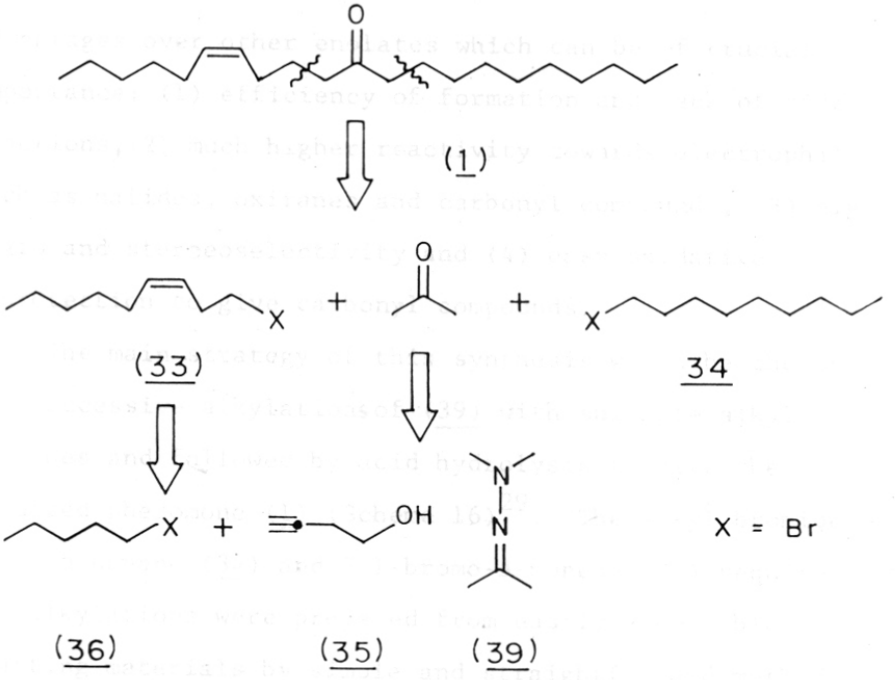
The present work deals with three different syntheses of Z-6-Heneicosen-11-one (1) and Z-1,6-Heneicosadien-11-one (2). The salient features of the molecule (1) and (2) are the presence of ketone and cis double bond functionalities.

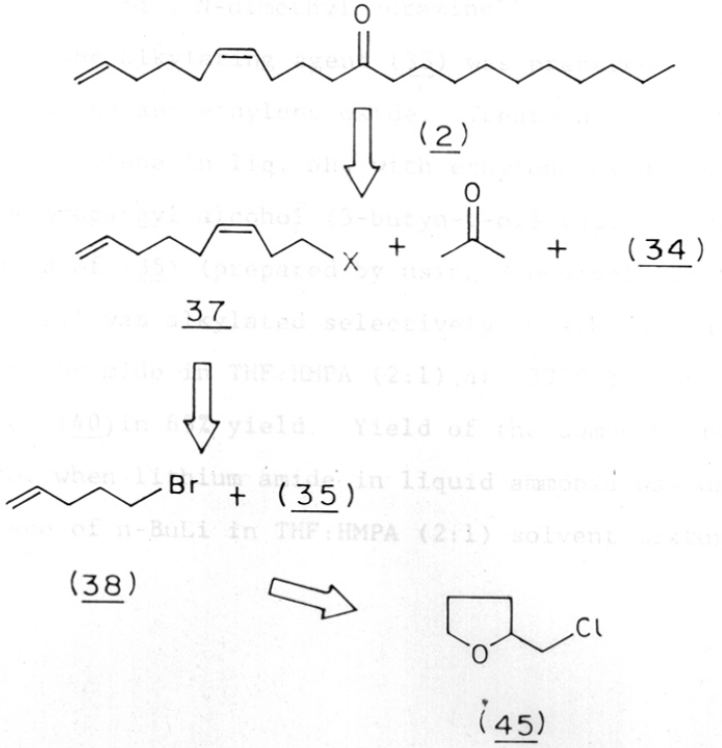
First synthesis

A retrosynthetic analysis of (1) (Scheme 15) would yield a haloolefin (33), acetone and a haloalkane (34). The compound (33) can be obtained starting from homopropargyl alcohol (35) and n-amyl bromide (36). Similarly compound (2) on retrosynthetic analysis would give (37) as one of the precursors. The compound (37) in turn can be prepared from homopropargyl alcohol (35) and 5-bromo-pent-1-ene (38).

Lithium salt of acetone N,N-dimethyl hydrazone (39) can serve as acetone enolate equivalent. Use of N,N-dimethyl hydrazone derivatives as enolate equivalents is well documented in literature[25-28]. They possess several

SCHEME – 15





advantages over other enolates which can be of crucial importance; (1) efficiency of formation and lack of side reactions, (2) much higher reactivity towards electrophiles such as halides, oxiranes and carbonyl compounds, (3) high regio and stereoselectivity and (4) easy oxidative deprotection to give carbonyl compounds.

The main strategy of this synthesis would be the one pot successive alkylations of (39) with suitable alkyl bromides and followed by acid hydrolysis to give the required pheromone (1) (Scheme 16)[29]. The alkyl bromides-1-bromo nonane (34) and Z-1-bromo-3-nonene (33) required for alkylations were prepared from easily accessible starting materials by simple and straightforward method. N,N-Dimethyl acetone hydrazone (39) was prepared from acetone and N,N-dimethylhydrazine[28].

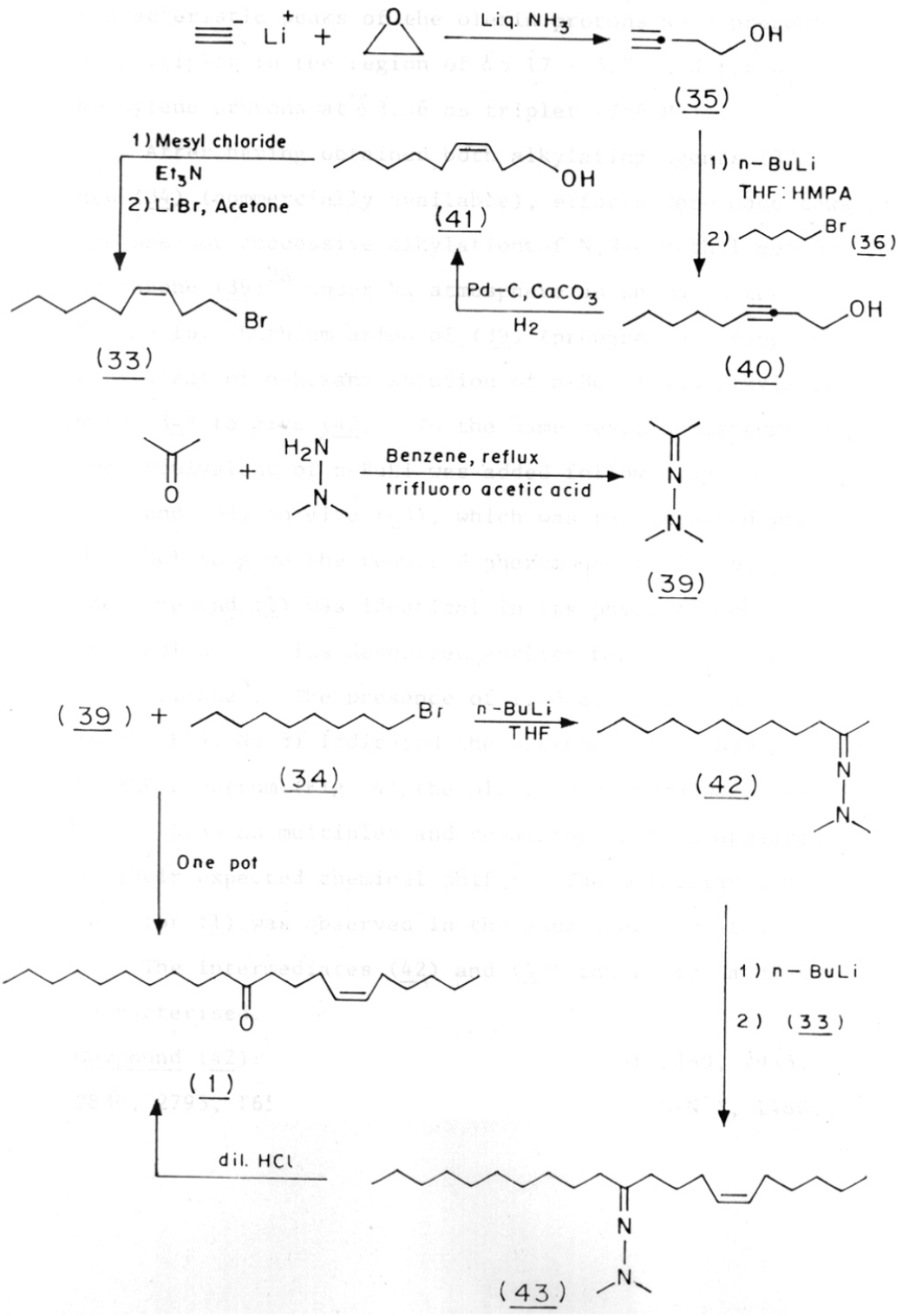
The alkylating agent (33) was prepared starting from acetylene and ethylene oxide. Treatment of lithium salt of acetylene in liq. NH_3 with ethylene oxide gave homopropargyl alcohol (3-butyn-1-ol) (35)[30]. Dilithium anion of (35) (prepared by using 2 equivalents of n-BuLi) was alkylated selectively (C-alkylation) with amyl bromide in THF:HMPA (2:1) at -30°C to get 3-nonyn-1-ol (40) in 65% yield. Yield of the compound (40) was poor when lithium amide in liquid ammonia was used in place of n-BuLi in THF:HMPA (2:1) solvent mixture[31].

The IR spectrum of (40) showed absorption at 3340 cm^{-1} for hydroxyl group and at 1040 cm^{-1} for ether linkage. In the PMR ($CDCl_3$) characteristic distorted triplet peak (coupling constant 6 Hz) for terminal methyl appeared at δ 0.89. Methylene protons adjacent to triple bond apppeared as multiplet in the region δ 2.01 - 2.53 and the C_1 protons appeared at δ 3.66 as triplet (J=6 Hz).

Partial hydrogenation of (40) over Lindlar catalyst[32] at normal pressure and temperature in presence of small amount of quinoline gave Z-3-nonen-1-ol (41) in 95% yield. The IR spectrum of (41) showed characteristic absorption at 730 cm^{-1} for cis double bond and 3340 cm^{-1} for hydroxyl group. In the PMR ($CDCl_3$) spectrum, characteristic peaks for the two olefinic protons showed in the region of δ 5.17 - 5.76 as multiplet and the C_1 protons appeared as triplet at δ 3.64 (J=6 Hz).

The compound (33) was prepared from (41) through its mesylate. Treatment of (41) with methane sulfonyl chloride[33] in presence of triethyl amine at 0°C using dichloromethane as solvent gave the corresponding mesylate, which on reaction with lithium bromide in acetone at room temperature yielded the Z-1-bromo-3-nonene (33) in 85% yield. In the IR spectrum of (33), characteristic absorption at 720 cm^{-1} for cis double bond was present and absorption band at 3350 cm^{-1} due to the hydroxyl group was absent. In the PMR ($CDCl_3$, Fig. No.1) spectrum,

SCHEME-16


Liq. NH3
OH
(35)
1) Mesyl chloride
Et3N
2) LiBr, Acetone
OH
(41)
1) n-BuLi
THF:HMPA
2)
Br
(36)
Br
(33)
Pd-C, CaCO3
H2
OH
(40)
H2N
N
Benzene, reflux
trifluoro acetic acid
(39)
(39) +
Br
(34)
n-BuLi
THF
(42)
One pot
(1)
dil. HCl
1) n-BuLi
2) (33)
(43)

characteristic peaks of the olefin protons were present as multiplet in the region of δ 5.17 - 5.73 and for C_1 methylene protons at δ 3.36 as triplet (J=6 Hz).

After having obtained both alkylating agents (33) and (34) (commercially available), efforts were made towards the one pot successive alkylations of N,N-dimethyl acetone hydrazone (39)[28] under N_2 atmosphere as shown in the Scheme 16. Lithium anion of (39) (prepared by using one equivalent of n-hexane solution of n-BuLi) was alkylated with (34) to give (42). To the same reaction mixture one more equivalent of n-BuLi was added followed by compound (33) to give (43), which was then treated with dil. HCl to give the required pheromone (1) in 75% yield. The compound (1) was identical in its physical and chemical properties described earlier for (Z)-6-heneicosen-11-one[5]. The presence of 1720 cm^{-1} in IR spectrum (neat, Fig. No.5) indicated the presence of carbonyl group. In PMR spectrum (Fig. 4), the olefinic protons were seen at δ 5.1 - 5.33 as multiplet and remaining protons appeared at their expected chemical shifts. The molecular ion peak for (1) was observed in the mass spectrum at 308.

The intermediates (42) and (43) can be isolated and characterised.

Compound (42): IR spectrum showed peaks at 2980, 2945, 2880, 2795, 1655 (characteristic peak for $C=N^-$), 1480,

1370, 1030 and 970 cm^{-1}.

PMR Spectrum ($CDCl_3$): δ 0.89 (distorted triplet, 3H, J=6 Hz), 1.24 (broad singlet for C_4-C_{11} methylenes 16H), 1.93 (s, 3H), 2.02 - 2.31 (m, 2H), 2.42 (for 6H, -N-N$\begin{matrix}CH_3\\CH_3\end{matrix}$)

Mass spectrum: 226 M^+.

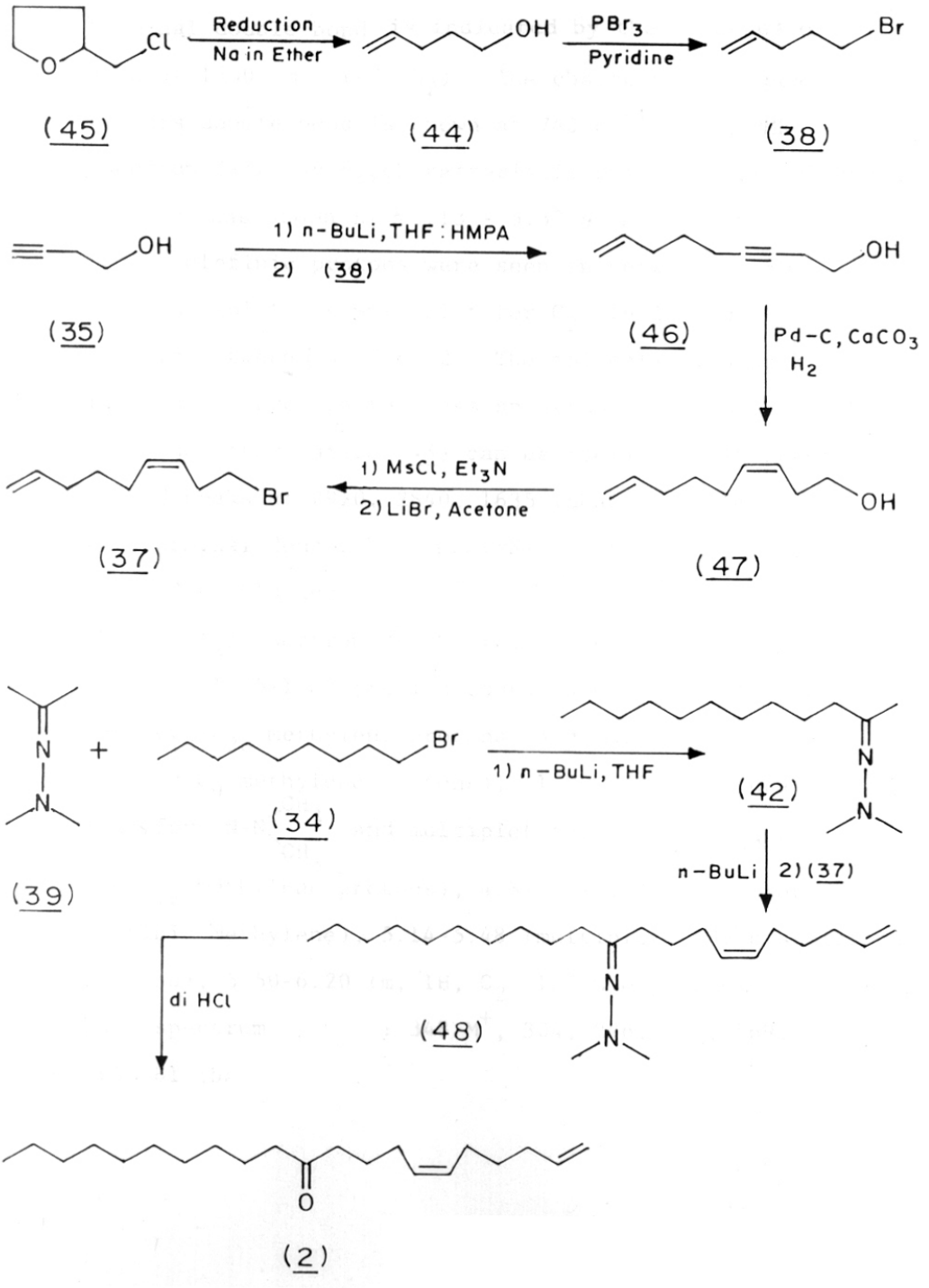
Compound (43): IR spectrum showed peaks at 2910, 2840, 1625 (characteristic peak for -C=N), 1460, 1375, 1260, 1020, 970, 805, 725 cm^{-1} (characteristic peak for cis double bond).

PMR ($CDCl_3$) spectrum: δ 0.9 (distorted triplet for two terminal methyls C_1 and C_{21}, J=6 Hz), 1.25-1.60 [multiplet includes broad singlet for 22 protons (C_2-C_4 and C_{13}-C_{20} methylene protons) and multiplet for C_9 methylene protons], 1.70 - 2.35 (multiplet includes the N-N$\begin{matrix}CH_3\\CH_3\end{matrix}$ and C_5, C_8, C_{10} and C_{12} methylene protons), 5.10 - 5.50 (multiplet for olefinic protons, 2H).

Mass spectrum: 350 M^+, 306, 226, 182, 169, 124, 100 (base peak).

The pheromone (2) was also prepared (Scheme 17) by one pot successive alkyaltions of anion (39), first with (34) and then with Z-1-bromo-3,8-nonadiene (37) to get (48), which on treatment with dilute HCl gave (2). The compound (2) was identical in its physical and chemical properties described earlier for (Z)-1,6-Heneicosadien-11-one[2]. In the IR spectrum,(neat, Fig. No.7) presence

SCHEME – 17


Cl
Reduction
Na in Ether
OH
PBr3
Pyridine
Br
(45)
(44)
(38)
OH
1) n-BuLi, THF : HMPA
2) (38)
OH
(35)
(46)
Pd-C, CaCO3
H2
Br
1) MsCl, Et3N
2) LiBr, Acetone
OH
(37)
(47)
N
N
+
Br
(34)
1) n-BuLi, THF
(42)
(39)
n-BuLi
2) (37)
di HCl
(48)
O
(2)

of carbonyl is shown at 1725 cm^{-1} and presence of terminal double bond is indicated by the presence of peak at 1650 cm^{-1} ($-C=CH_2$). The characteristic peak for cis double bond is shown at 740 cm^{-1}. In PMR spectrum (Fig. No.6), characteristic peaks for cis olefinic protons has shown at δ 5.13 - 5.33 as multiplet. The two C_1 olefinic protons were seen in between δ 4.86-5.11 as a multiplet. A multiplet for C_2 olefinic proton was seen in between δ 5.57-6.02. The molecular ion peak for (2) was observed in the mass spectrum at 306 M^+.

The intermediate (48) can be isolated. IR spectrum showed peaks at 2910, 2840, 1635 (characteristic peak for terminal double bond and C=N- together), 1400, 1020, 990, 910 and 720 cm^{-1}.

PMR ($CDCl_3$) spectrum: δ 0.90 [distorted triplet, C_1 methyl, J=6 Hz), 1.25-1.80 [region contains broad singlet for 16H (C_{13}-C_{20} methylene protons) and multiplet for 4H (C_4 and C_9 methylene protons)], 1.80 - 2.40 (contains peaks for $-N-N(CH_3)_2$ and multiplet for C_3, C_5, C_8, C_{10} and C_{12} methylene protons), 4.8-5.12 (multiplet for C_1 olefinic methylene), 5.14-5.48 (multiplet, 2H, cis olefinic protons), 5.50-6.20 (m, 1H, C_2 olefinic proton).

Mass spectrum : 348 M^+, 304, 226, 182, 169, 122, 100, 81 (base peak).

The alkylating agent (37) was prepared starting from 3-butyn-1-ol (homopropargyl alcohol) (35) and 5-bromo-pent-1-ene (38). The compound (38) was prepared by the bromination of pent-4-ene-1-ol (44)[34], which in turn was prepared by the reduction of tetrahydro-fufuryl chloride (45)[35] with sodium in ether.

The lithium dianion of (35) was alkylated selectively (C-alkylation) with (38) in THF: HMPA (2:1) to get 3-nonyn-8-ene-1 ol (46) in 60% yield. The IR spectrum of (46) showed absorption at 3360 cm^{-1} for hydroxyl group and at 1650 cm^{-1} for exodouble bond. In PMR (Fig. No.2) spectrum,characteristic multiplet for C_9 olefinic protons appeared in the region of δ 4.84-5.13 and for C_8 proton in the region of δ 5.55 - 6.02. The triplet was shown for C_1-methylene at δ 3.64 (J=6 Hz).

Hydrogenation of (46)using Lindlar catalyst[32] at normal pressure and room temperature in presence of small amount of quinoline gave Z-3,8-nonadien-1-ol (47) in 95% yield. The IR spectrum of (47) showed characteristic absorption at 730 cm^{-1} for cis double bond and at 1650 cm^{-1} for exodouble bond. The absorption for the hydroxy was showed at 3350 cm^{-1}. In PMR ($CDCl_3$) spectrum characteristic peaks for the terminal olefinic protons appeared in the region of δ 4.82-5.15 and for cis olefinic

(C_3 and C_4 protons) and C_8 olefinic protons appeared in the region of δ5.15-6.04.

The compound (47) on treatment with methane sulfonyl chloride[33] in presence of triethylamine in dichloromethane gave the corresponding mesylate which on reaction with LiBr in acetone at 0°C afforded the Z-1 bromo-3,8-nonadiene (37) in 70% yield. The IR spectrum of (37) showed absorption at 730 cm^{-1} for cis double bond and showed absorption at 1650 cm^{-1} for exodouble bond. The absorption band at 3350 cm^{-1} due to the hydroxyl group was absent. In the PMR spectrum of the compound (37), C_1 methylene protons appeared at δ 3.34 as triplet (J=6 Hz).

Second Synthesis

In the second synthesis, the pheromones (1) and (2) are synthesized in two steps[37], the key step being of pot dialkylations of N,N-dimethyl acetone hydrazone (39)[28] with 2-(2-bromo ethyl) 1,3-dioxolane (49) and with 1-bromononane (34) (Scheme 18). The compound (49), was prepared[36] by passing dry HBr into acrolein in ethylene glycol at 0°C (Scheme 18).

To the lithium anion of (39) (prepared by using n-BuLi) was added (49) to give (58). To the same reaction mixture, one more equivalent of n-BuLi was added, followed

by addition of (34) to give (59) which was then treated with 10N HCl at 60°C for 2 hours to give keto-aldehyde (26) in 62% yield. In the PMR ($CDCl_3$), aldehyde proton appeared at δ 9.90 as broad singlet, m.p.43°C. All the properties were identical with those reported[14].

The compounds (58) and (59) can be isolated.

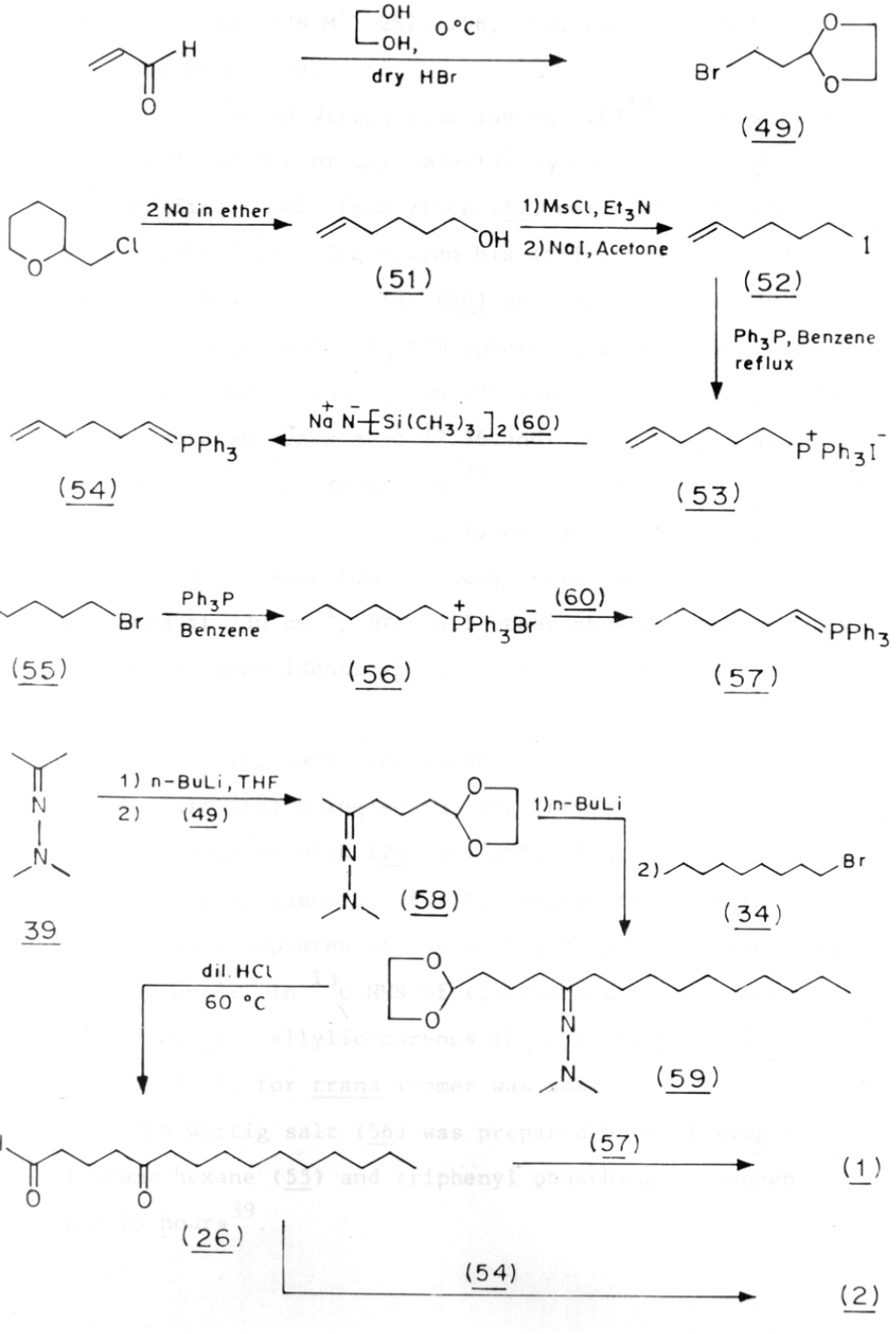
Compound (58): IR spectrum showed peaks at 2940, 2850, 2765, 1640 (characteristic peak for -C=N-), 1470, 1365, 1145, 1030, 945 cm^{-1}.

PMR Spectrum in $CDCl_3$: δ 1.50 - 1.75 (multiplet, 2H), 1.90 (s, 3H), 2.0-2.40 (includes multiplet for C_4 methylene and peak for $-N-N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 3.70 - 4.00 (m, 4H), 4.70-4.95 (m, 1H); Mass: 200 (molecular ion), 156, 128, 113, 99 (base peak) and 73.

Compound (59): IR spectrum showed peaks at 2910, 2840, 1630 (characteristic peak for -C=N-), 1460, 1195, 1140, 1020, 940 cm^{-1}.

PMR spectrum in $CDCl_3$: δ 0.88 (distorted triplet, 3H, 6 Hz), 1.0 - 1.75 [contains broad singlet for C_7-C_{14} (16 protons) methylenes and multiplet for C_2,C_3 methylenes (4 protons)]. 1.80 - 2.50 (contains peak for $N-N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ and multiplet for C_4,C_6 methylene protons), 3.75 - 4.00 (m, 4H, $\begin{smallmatrix}-O-CH_2\\-O-CH_2\end{smallmatrix}$), 4.75 - 4.92 (m, 1H, $H\begin{smallmatrix}O-\\O-\end{smallmatrix}$)

SCHEME – 18


OH
OH,
0 °C
dry HBr
Br
(49)
2 Na in ether
Cl
OH
(51)
1) MsCl, Et3N
2) NaI, Acetone
I
(52)
Ph3P, Benzene
reflux
Na+ N− [Si(CH3)3]2 (60)
PPh3
(54)
P+ Ph3 I−
(53)
Br
Ph3P
Benzene
PPh3Br−
(60)
PPh3
(55)
(56)
(57)
1) n-BuLi, THF
2) (49)
N
N
39
(58)
1) n-BuLi
2)
Br
(34)
dil. HCl
60 °C
(59)
H
O
O
(26)
(57)
(1)
(54)
(2)

Mass spectrum: 326 M^+, 282, 256, 222, 210, 143, 128, 99 (base peak), 73.

The reported Wittig reaction on (26)[13] suffers from low yield andlack of cis selectivity.So the procedure was modified. Salt free ylide (57) was prepared from Wittig salt (56) using sodium bis (trimethyl silyl) amide (60)[38] as base. The ylide (56) was reacted with (26) at -78°C in THF under N_2 atmosphere to give selectively Z-6-Heneicosen-11-one (1) in 79% yield. In the ^{13}C NMR, characteristic peaks at δ 27.36 and 26.78 of cis allylic carbons (C_5, C_8) were present[20]. The peaks reported for allylic carbons of the trans isomer around δ 33.00 were absent. In IR spectrum,characteristic peak for cis appeared at 730 cm^{-1}, and all other physical and chemical properties were identical with those reported for cis compound.

Similarly, salt free ylide (54) was prepared from Wittig salt (53) using sodium bis (trimethyl silyl) amide (60) and reacted with (26) at -78°C to give (2) in 74% yield. In IR spectrum of (2),characteristic peak for cis compound appeared at 730 cm^{-1} and for exodouble bond at 1650 cm^{-1}. In ^{13}C NMR of (2),characteristic peak at δ 26.48 for cis allylic carbons (C_5,C_8) was present[2]. The peak at 31.92 for trans isomer was absent.

The Wittig salt (56) was prepared by refluxing 1-bromo hexane (55) and triphenyl phosphine in benzene for 25 hours[39].

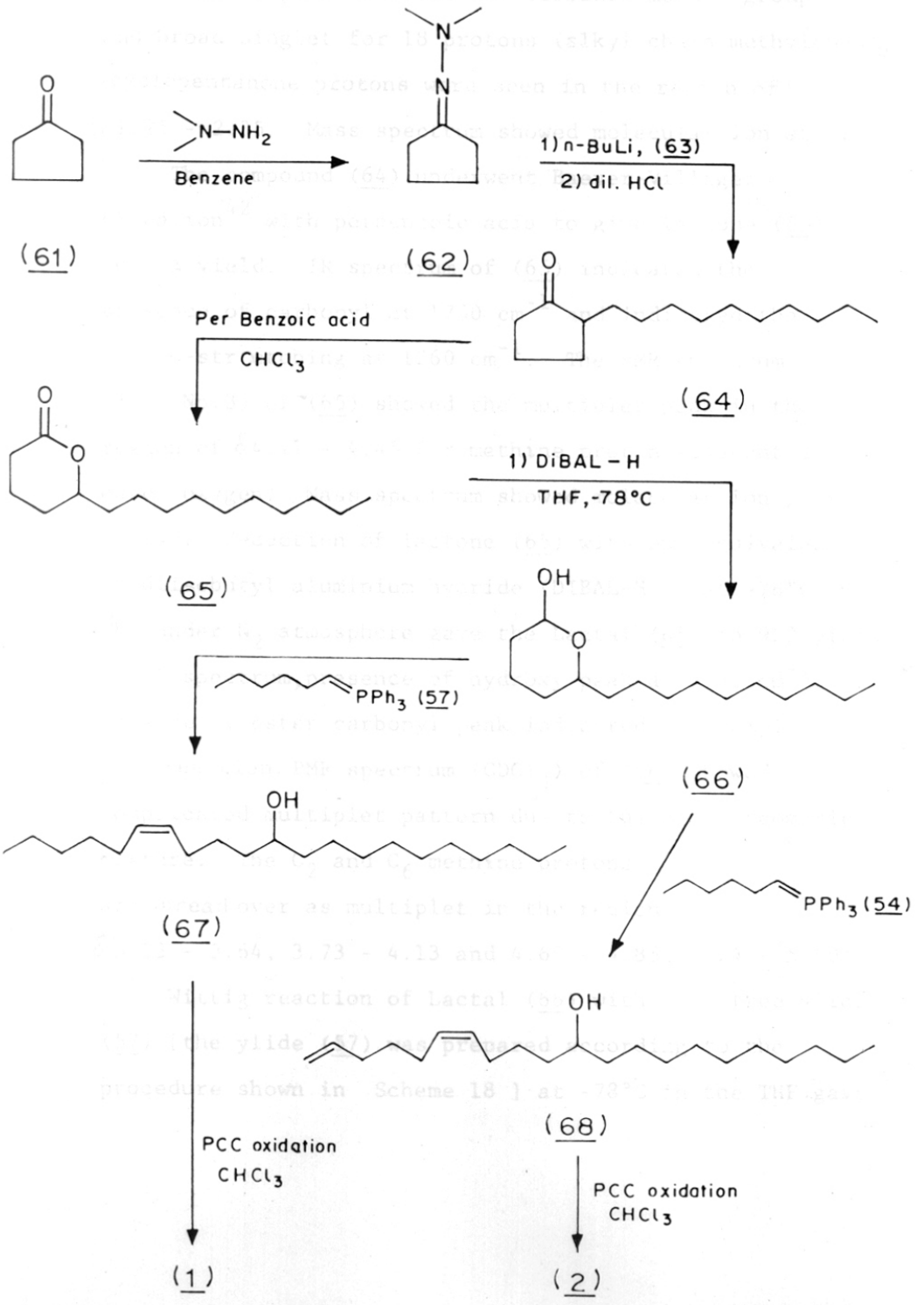
The triphenyl phosphine salt (53) was prepared by following 3 step reaction procedure. Tetrahydropyranyl chloride (50) on reduction with Na in ether gave 5-hexen-1-ol (51) in 70% yield[40]. The compound (51) on treatment with methanesulfonyl chloride[33] in presence of triethylamine at 0°C using dichloromethane as solvent gave mesylate, which on treatment with NaI in acetone afforded 6-iodo-hex-1-ene (52) (72% yield). The compound (52) and triphenyl phosphine refluxed in benzene to give Wittig salt (53)[39].

Third Synthesis

In the third approach,(Scheme 19) the synthesis[41] of Z-6-heneicosen-11-one (1) and Z-1,6- heneicosadien-11-one (2) involves the key step Wittig reaction on substituted lactal (66) and oxidation of resulted hydroxy olefins (67 and 68).

To start with, cyclopentanone (62) was converted to corresponding N,N-dimethyl hydrazone derivative (62) by refluxing it with N,N-dimethyl hydrazine in benzene using small amount of trifluoro acetic acid as catalyst. This on alkylation with n-decylbromide (63) using n-BuLi as base and followed by acid hydrolysis (dil HCl) afforded 2-decylcyclopentanone (64) in 85% yield. IR spectrum of (64) showed peak at 1745 cm^{-1} for carbonyl group. The PMR spectrum ($CDCl_3$) of (64) showed

SCHEME – 19



(61) (62) (64) (65) (66) (67) (68) (1) (2)

distorted triplet at δ 0.88 for terminal methyl group and broad singlet for 18 protons (alkyl chain methylenes). cyclopentanone protons were seen in the region of δ 1.25 - 2.35. Mass spectrum showed molecular ion at 224.

The compound (64) underwent Baeyer-Villiger oxidation[42] with perbenzoic acid to give lactone (65) in 81% yield. IR spectrum of (65) indicated the presence of carbonyl at 1750 cm^{-1} and indicated the -C-O-C-stretching at 1260 cm^{-1}. The PMR spectrum (Fig. No.3) of (65) showed the multiplet peak in the region of δ 4.11 - 4.45 for methine proton adjacent to ester oxygen. Mass spectrum showed molecular ion peak at 240. Reduction of lactone (65) with one equivalent of diisobutyl aluminium hydride (DIBAL-H) at -78°C in THF under N_2 atmosphere gave the Lactal (66) in 92% yield. In IR spectrum, presence of hydroxy peak at 3340 cm^{-1} and absence of ester carbonyl peak indicated the completion of the reaction. PMR spectrum ($CDCl_3$) of (66) showed complicated multiplet pattern due to the diastereomeric mixture. The C_2 and C_6 methine protons are spread over as multiplet in the region δ 3.13 - 3.64, 3.73 - 4.13 and 4.60 - 4.86, 5.24 - 5.40.

Wittig reaction of Lactal (66) with salt free ylide (57) [the ylide (57) was prepared according to the procedure shown in Scheme 18] at -78°C in the THF gave

hydroxy olefin[20] (67) in 83% yield. IR spectrum showed absorption at 3340 cm^{-1} for hydroxy and at 720 cm^{-1} for cis olefinic (-C-H) bending. The PMR spectrum($CDCl_3$) showed multiplet in the region of δ 3.37 - 3.69 for C_{11} hydrogen and showed multiplet in the region δ 5.52 - 5.51 for two olefinic protons. Mass spectrum showed molecular ion peak at 310.

The hydroxy olefin (67) on PCC oxidation gave the required pheromone (1) in 91% yield. All spectral properties were identical with those reported for Z-6-heneicosen-11-one (1)[20].

Similarly, Wittig reaction of lactal (66) with salt free ylide (54) at -78°C in THF under the N_2 atmosphere gave hydroxy diene (68) in 80% yield. IR spectrum of (68) showed peak at 3360 cm^{-1} for hydroxy and at 1650 cm^{-1} for exomethylene group. The characteristic peak for cis olefin showed at 730 cm^{-1}. In the PMR spectrum,multiplet observed in the region δ 3.44-3.73 for C_{11} methine hydrogen. Characteristic peak for terminal olefinic hydrogens (C_1 hydrogens) appeared in the region of δ 4.86 - 5.11 (multiplet) and for cis olefinic hydrogens (C_6 and C_7 hydrogens) in the region of δ 5.13 - 5.33 (multiplet). A multiplet appeared for C_2 hydrogen in the region of δ 5.57 - 6.02. The mass spectrum showed molecular ion peak at 308.

Oxidation of (68) with PCC in methylene chloride at 0°C gave the required pheromone (2) in 86% yield. All spectral properties were identical with those reported for cis compound[2] (2).

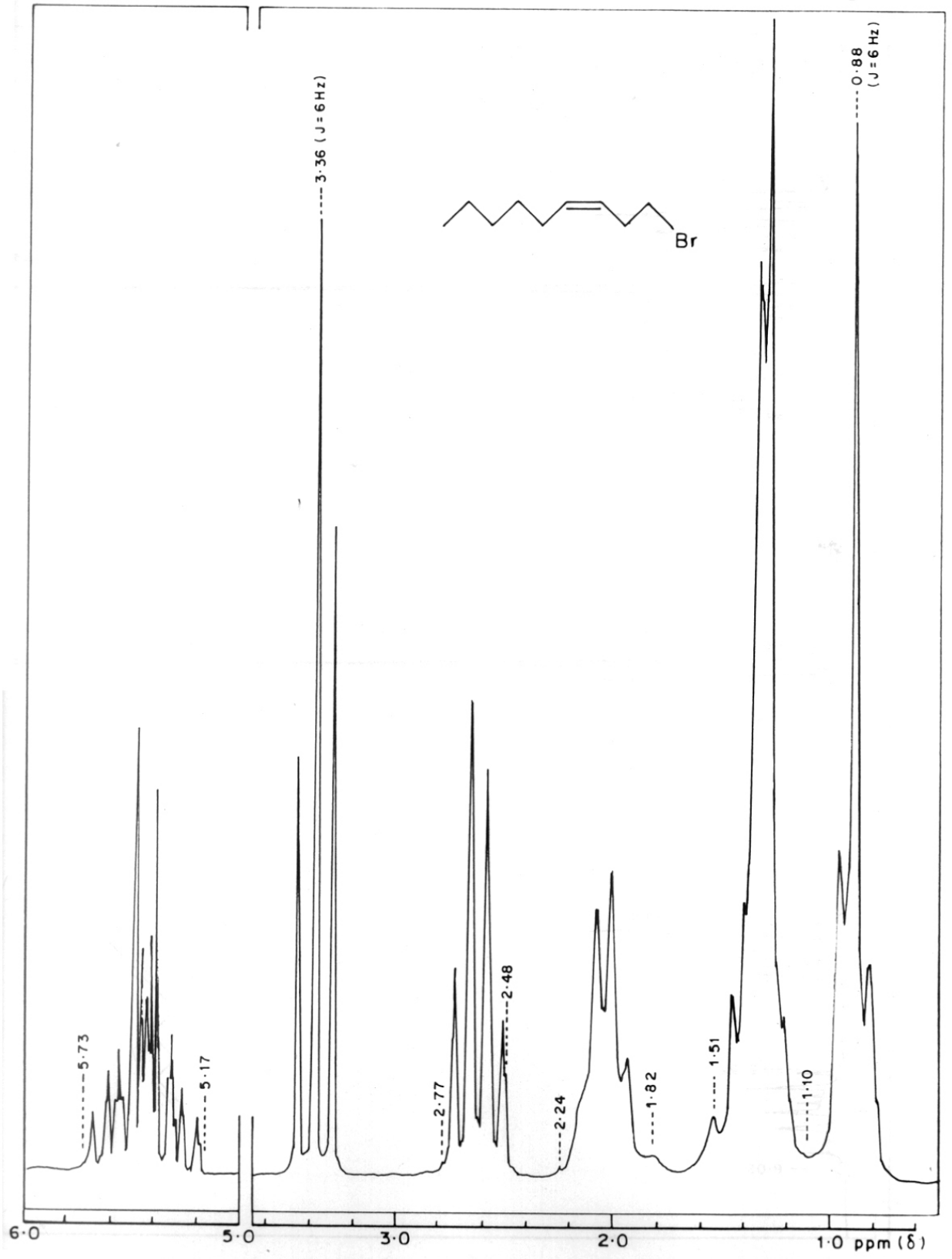


FIG. 1. PMR SPECTRUM OF 1-BROMO-NON-3-ENE (33) IN $CDCl_3$

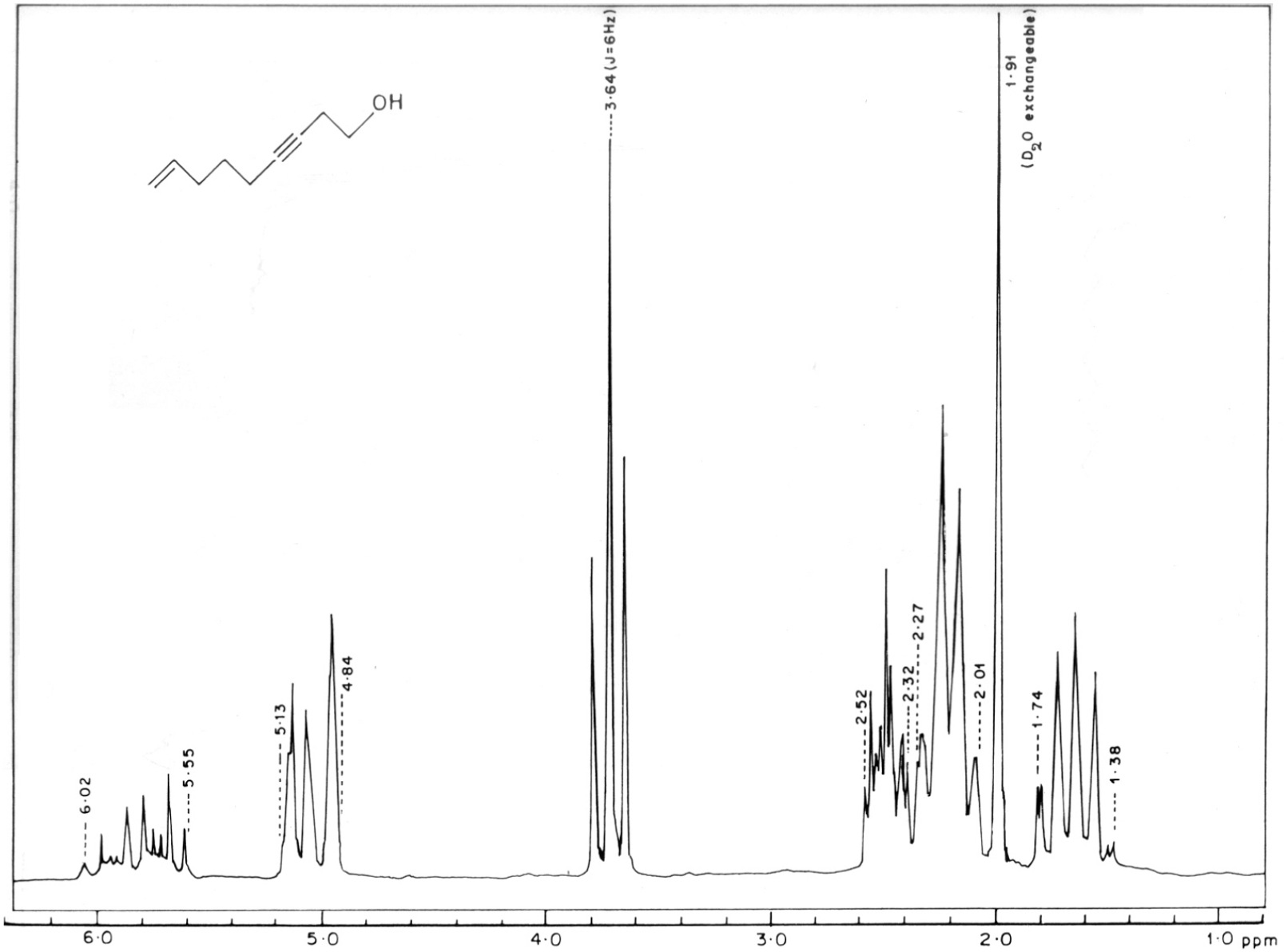


FIG. 2. PMR SPECTRUM OF 3-NONYN-8-ENE-1-OL (46) IN $CDCl_3$

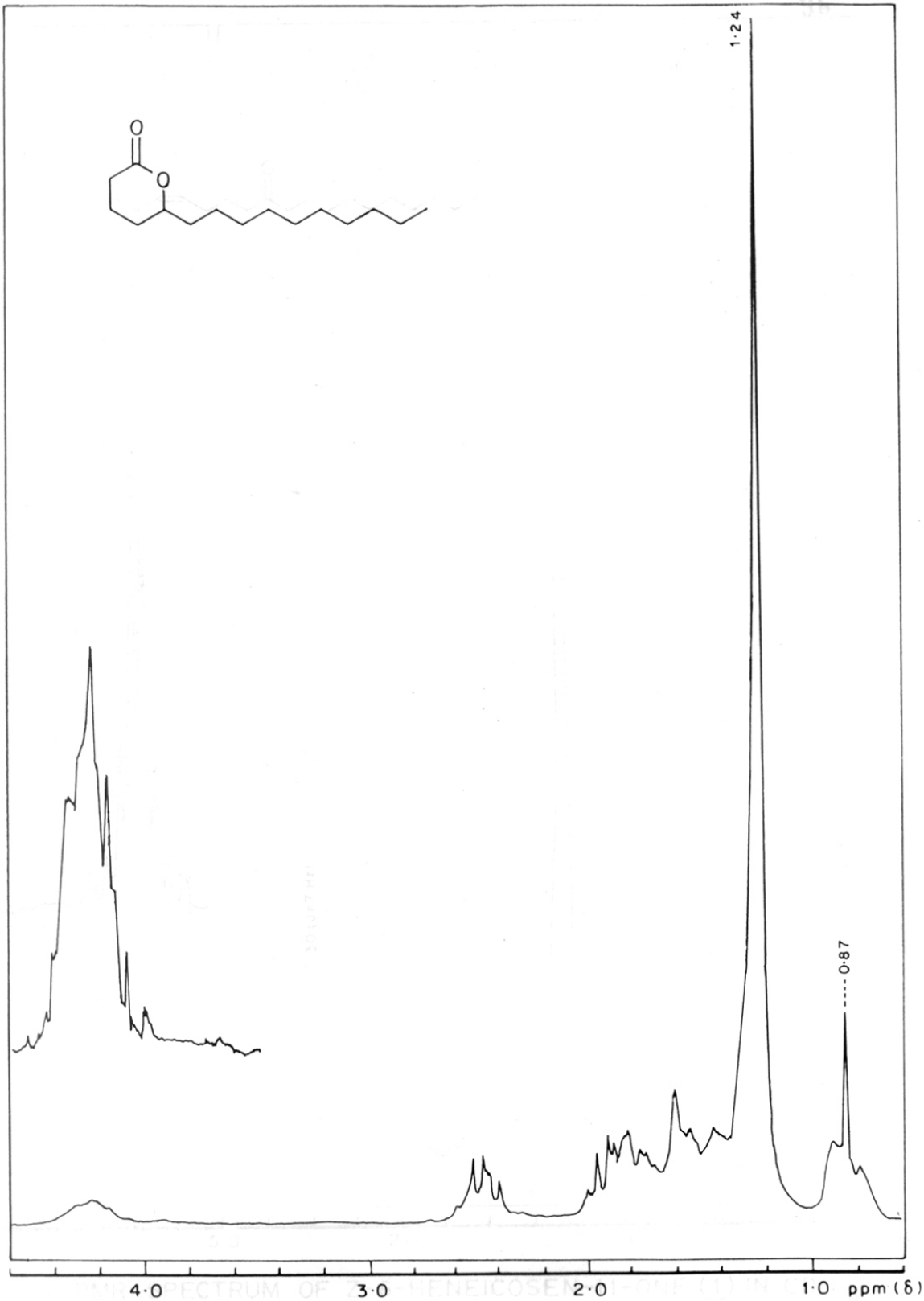


FIG. 3. PMR SPECTRUM OF LACTONE (65) IN $CDCl_3$

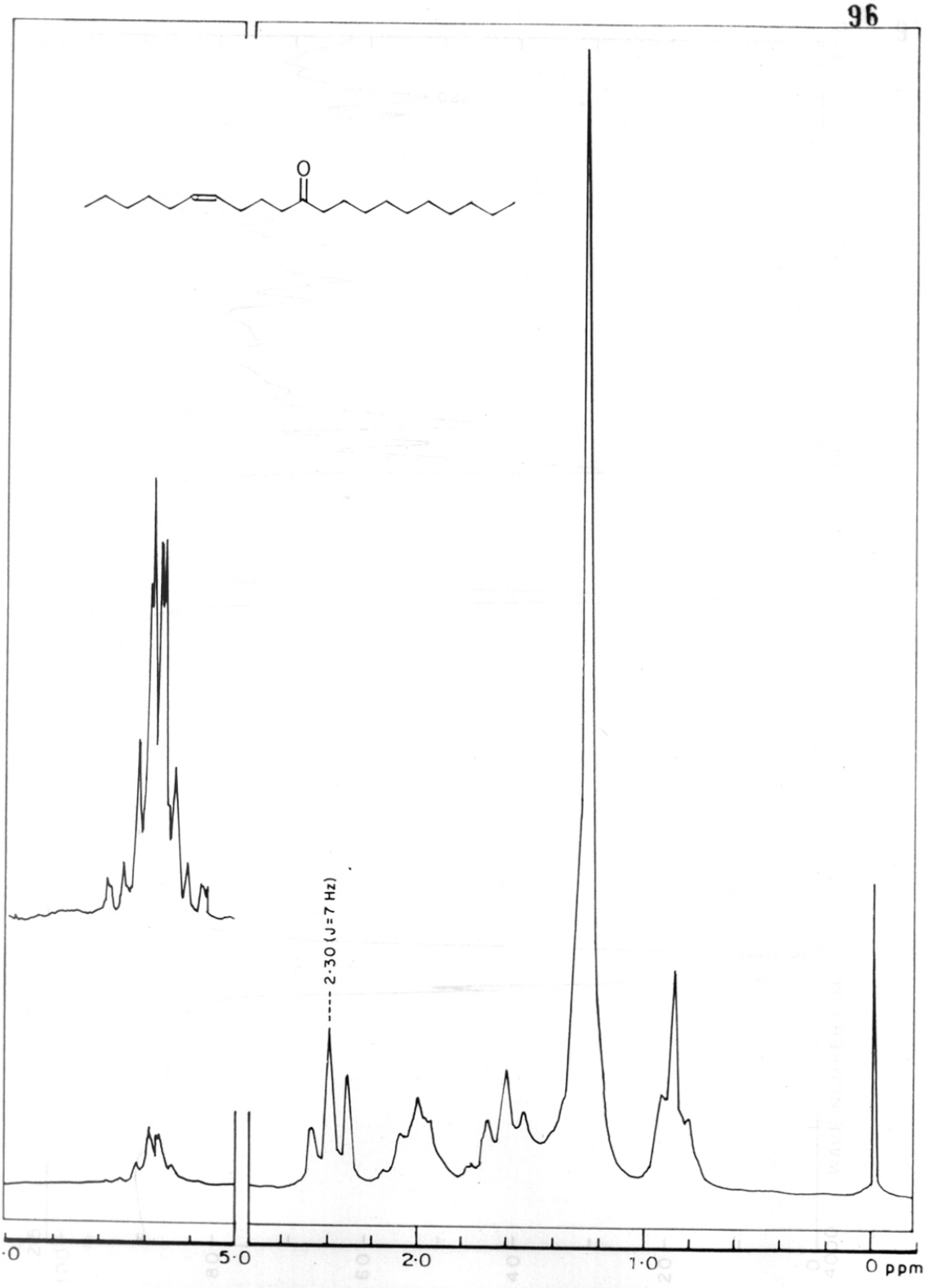


FIG. 4. PMR SPECTRUM OF Z-6-HENEICOSEN-11-ONE (1) IN $CDCl_3$

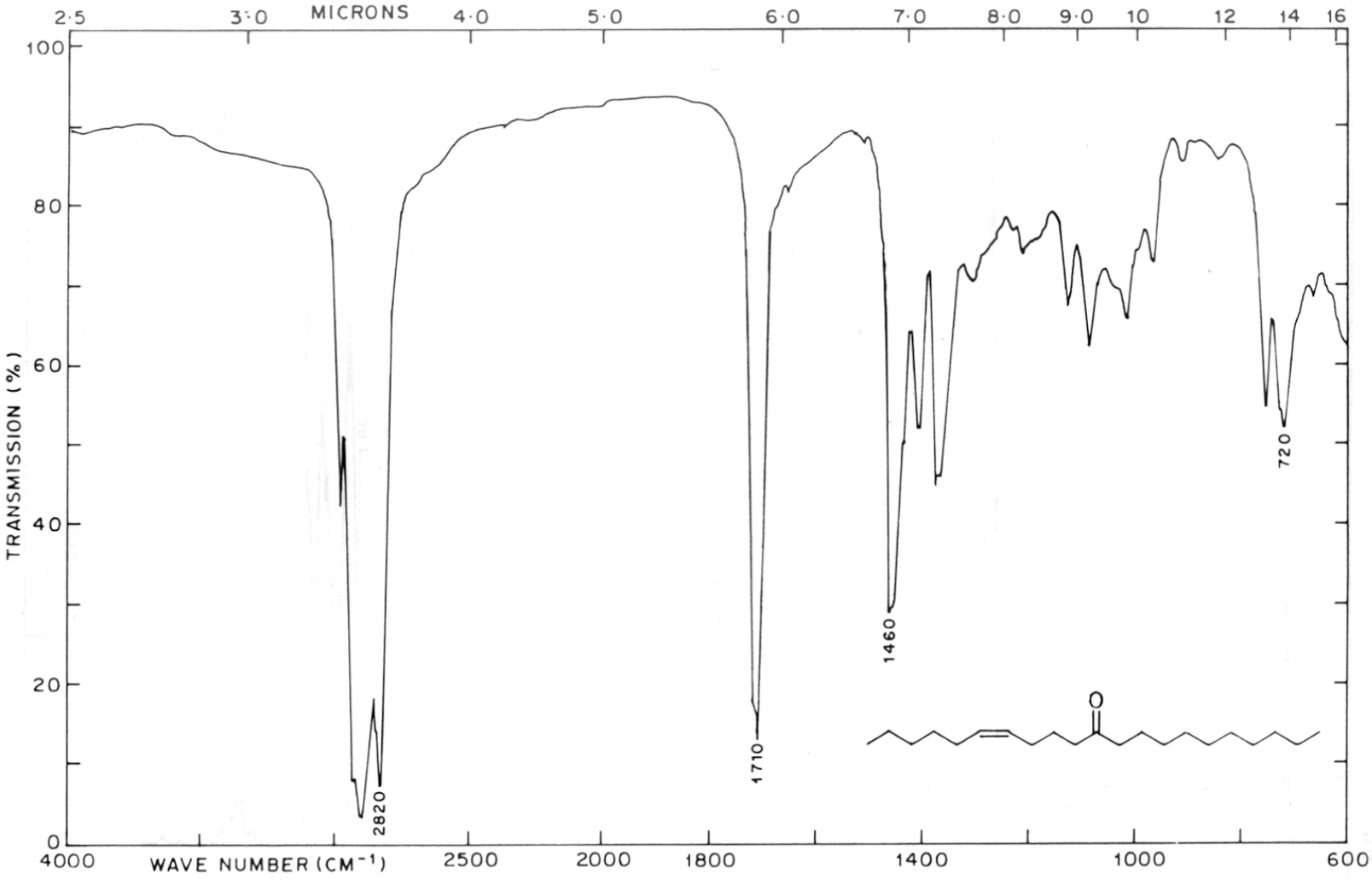


FIG. 5. IR SPECTRUM OF Z-6-HENEICOSEN-11-ONE (1)

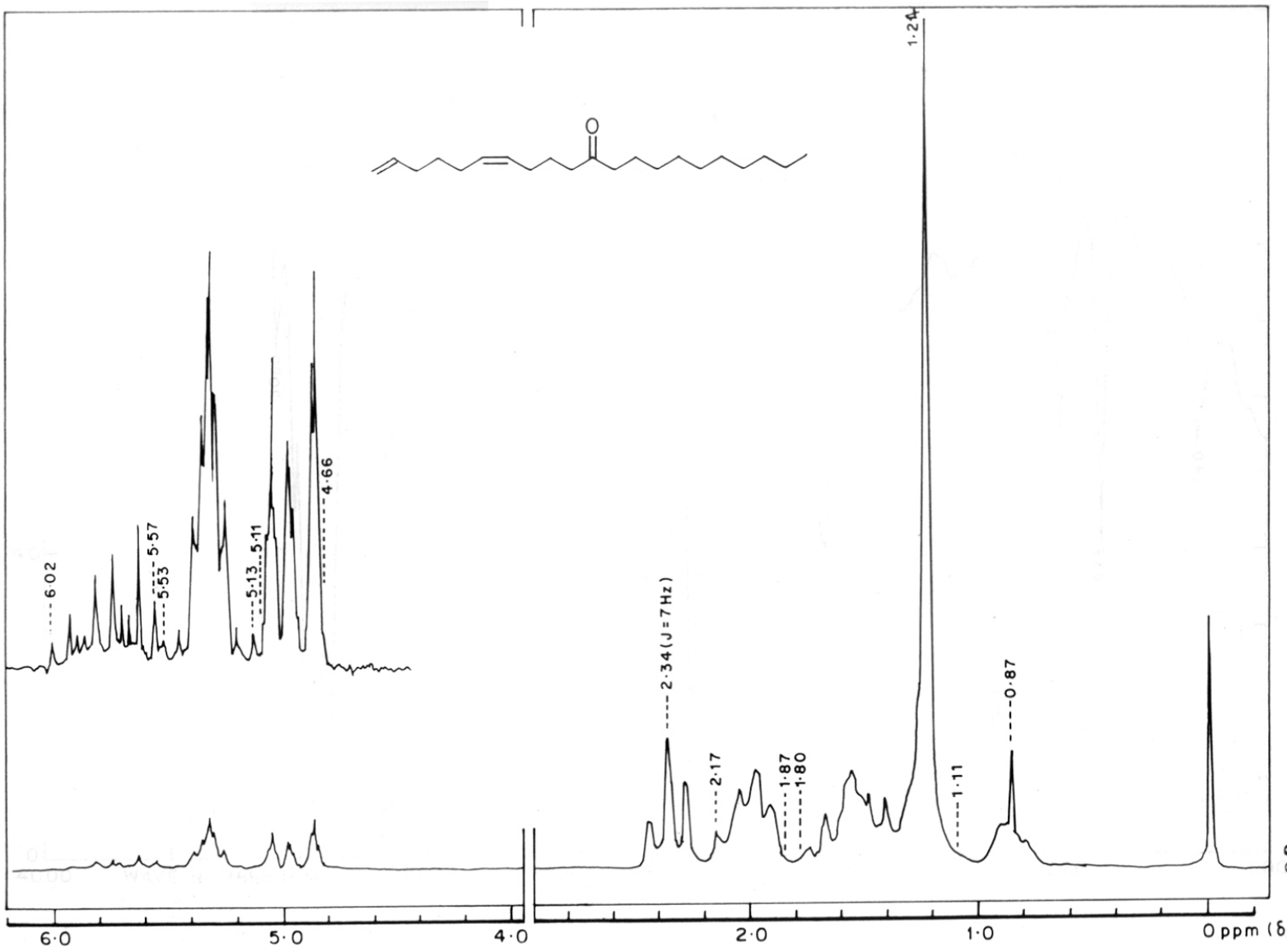


FIG. 6. PMR SPECTRUM OF Z-1,6-HENEICOSADIEN-11-ONE (2) IN $CDCl_3$

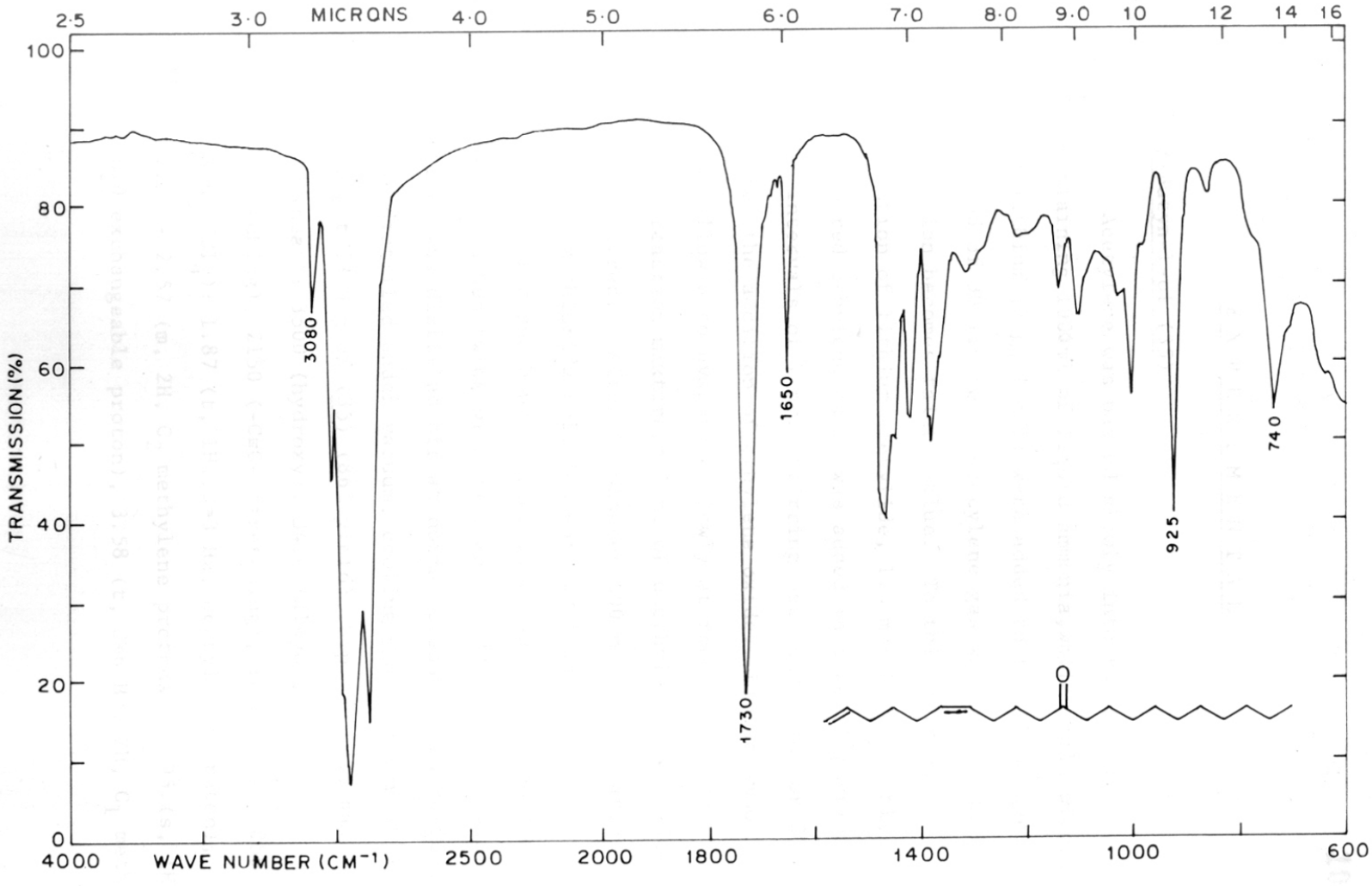


FIG. 7. IR SPECTRUM OF Z-1,6-HENEICOSADIEN-11-ONE (2)

EXPERIMENTAL

3-Butyn-1-ol (35)

Acetylene was passed slowly into the flask containing 1000 ml of liquid ammonia, while small pieces of lithium (7 g, 1 mol) were added to the flask over a period of 30 minutes. Acetylene gas was passed until solution becomes faint blue. To this stirred solution of lithium acetylide, 1.5 moles of freshly prepared ethylene oxide was added in 5 equal portions at intervals of 1 hr. Stirring was continued for 20 hrs after the addition of ethylene oxide. Liquid ammonia was allowed to evaporate slowly at room temperature. To this reaction mixture, 500 ml of diethylether was added and stirred. After 15 minutes 500 ml of saturated ammonium chloride solution was added carefully and stirred for one hour. Ether layer was separated and again washed twice with sat. NH_4Cl (200 ml x 2) solution. Ether was distilled off at normal pressure and residue was distilled under vacuum, cooling the receiver at 0°C to get 58.5 g of (35) (86% yield), b.p. 50°C/15 mm.
IR (neat): 3500 (hydroxy), 3420 (alkyne, ≡ C-H stretching), 2150 (-C≡C- stretching), 1425, 1045, 850.
NMR (CCl_4): 1.87 (t, 1H, J=3 Hz, acetylinic proton), 2.17 - 2.57 (m, 2H, C_2 methylene protons), 2.95 (s, 1H, D_2O exchangeable proton), 3.58 (t, J=6 Hz, 2H, C_1 methylene

protons).

3-Nonyn-1-ol (40)

To a solution of 3-butyn-1-ol (35) (3.4 g, 0.05 mole) in THF (100 ml) under N_2 atmosphere at -30°C, was added n-BuLi (0.1 mole, 52.5 ml of 1.9 N n-hexane solution) with syringe, followed by 50 ml of HMPA. Reaction mixture was slowly allowed to come to room temperature and stirred for 0.5 hr. Reaction mixture was again cooled to -30°C and 1-bromopentane (36) (0.055 mole, 8.3 g) was added dropwise for 1 hr. Reaction mixture was stirred at -30°C for 4 hrs. Saturated NH_4Cl was added to it and stirred for 10 mts. Organic layer was separated and THF was removed under vacuum. Ether (200 ml) was added to the concentrated reaction mixture and washed with water to remove the HMPA. Then ether was evaporated and the residue distilled under vacuum to get (40) in 65% yield (4.6 g), b.p.98°C/2 mm.

IR (neat): 3330 cm^{-1} (hydroxyl stretching), 2930, 2900, 2840 1460, 1430, 1370, 1340 (-C-O stretching).

PMR ($CDCl_3$): δ 0.89 (distored triplet, J=6 Hz, 3H, for C_9 methyl protons), 1.04-1.7 (m, 6H, C_6, C_7 and C_8 methylene protons), 1.19 (s, 1H, D_2O exchangeable), 2.01 - 2.26 (m, 2H, for C_5 methylene protons), 2.31 - 2.53 (m, 2H, C_2 methylene protons), 3.66 (t, J = 6 Hz, 2H, for C_1 methylene protons).

Analysis: Calculated for $C_9H_{16}O$: C, 77.09; H, 11.50

Found: C, 77.02; H, 11.54.

Z-3-Nonen-1-ol (41)

A mixture of (40) (2.8 g, 0.02 mole) and Lindlar catalyst (100 mg) in n-hexane (25 ml) containing one drop of quinoline was stirred in an atmosphere of hydrogen till one mole equivalent of hydrogen was absorbed, the catalyst was filtered off and the filterate washed successively with dil. HCl and 5% $NaHCO_3$. Organic layer was dried, concentrated and residue chromatographed (silica gel, 10% ethyl acetate in pet.ether as eluent) to get pure (41) in 95% yield (2.7 g).

IR (neat: 3330 (hydroxy stretching), 2930, 2900, 2840, 1400, 1255, 1040 (-C-O stretching), 860, 790.

PMR ($CDCl_3$): δ 0.89 (distorted triplet, J=6 Hz, 3H, for C_9 methyl protons), 1.1 - 1.52 (m, 6H, C_6-C_8 methylene protons), 1.6 (s, 1H, D_2O exchangeable), 1.85-2.49 (m, 4H, for C_2, C_5 methylene protons), 3.64 (t, J=6 Hz, 2H, for C_1 methylene protons) and 5.17 - 5.76 (m, 2H, for olefinic protons).

Analysis: Calculated for $C_9H_{18}O$: C, 75.99; H, 12.76
Found: C, 75.94; H, 12.78

Z-1-Bromo-3-nonene (33)

To an ice cooled solution of (41) (1.42 g, 0.01 mole) and triethylamine (1 ml) in dry dichloromethane (25 ml) was added methanesulfonyl chloride (1.35 g, 0.01 mole)

at 0°C and stirred for 3 hrs. Reaction mixture was washed with water, cold dil HCl, followed by 5% $NaHCO_3$ solution and brine. Then organic layer was dried over Na_2SO_4 and concentrated to give mesylate of (41). To the acetone (25 ml) solution of mesylate was added anhydrous LiBr (1.30 g, 0.015 mole) and stirred for 5 hrs. Acetone was removed under reduced pressure and product was extracted with ether. Ether layer was washed with water and brine solution. Ether distilled off and crude was purified by column chromatography (silica gel, pet.ether as eluent) to get (33) in 85% yield (1.74 g).

IR (neat): 2940, 2900, 2840, 1450, 1260, 1200, 1010, 960, 720 (for cis double bond).

PMR ($CDCl_3$): δ0.88 (distorted triplet J=6 Hz, 3H, for C_9 methyl protons), 1.10 - 1.51 (m, 6H, for C_6-C_8 methylene protons), 1.82 - 2.24 (m, 2H, for C_5 methylene protons), 2.48 - 2.77 (m, 2H, for C_2 methylene protons), 3.36 (t, J=6 Hz, 2H, for C_1 methylene protons) and 5.17 - 5.73 (m, 2H, for olefinic protons).

N,N-Dimethyl acetone hydrazone (39)

The mixture of acetone (5.8 g, 0.01 mole), N,N-dimethyl hydrazine (6.0 g, 0.1 mole) and catalytic amount of trifluoroacetic acid in benzene (50 ml) was refluxed for 10 hrs. Water layer was separated and benzene layer was washed with water and dried over Na_2SO_4. Benzene solution

was then subjected to fractional distillation at atmospheric pressure to get (39) in 76% yield (7.6 g).
b.p.94-96°C/760 mm.
IR (neat): 1660, 1170, 1090.
NMR (CCl_4): δ 1.93 (s, 3H), 1.97 (s, 3H), 2.64 (s, 6H, for $N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$).

Z-6-Heneicosen-11-one (1)

To the THF (25 ml) solution of N,N-dimethylacetone-hydrazone (39) (0.5 g, 0.005 mole) under N_2 atmosphere at 0°C was added n-BuLi (3.2 ml of 1.9 N n-hexane solution, 0.006 mole) with syringe. Stirred for 0.5 hr. n-Bromononane (34) (1.03 g, 0.005 mole) was added and stirred for 2 hrs at room temeprature. The reaction mixture was again cooled to 0°C and n-BuLi (3.2 ml) was added. After keeping for 0.5 hr, Z-1-Bromo-3-nonene (33) (1.02 g, 0.005 mole) was added and stirred for 2 hrs at room temperature. It was then treated with 2N HCl (3 ml) and stirred for few minutes. The reaction mixture was diluted with water and extracted with ether (3 x 50 ml). Ether solution was washed with 5% $NaHCO_3$ followed by water, brine and evaporated The crude compound was chromatographed (silica gel, 2% ethylacetate in pet.ether as eluent) to get (1) in 75% yield (1.16 g).
IR (neat): 2980, 2890, 2820, 1725 (carbonyl stretching), 1460, 1405, 1370, 1130, 1090, 1015, 720 (cis olefin).

PMR ($CDCl_3$): δ 0.88 (distorted triplet, J=6 Hz, 6H, for C_1 and C_{21} methyl protons), 1.1 - 1.73 (m, 24H, includes broad singlet for C_2-C_4 and C_{13}-C_{20} methylene protons and multiplet for C_9 methylene protons), 1.86 - 2.15 (m, 4H, for C_5, C_8 allylic methylene protons), 2.30 (t, J=7 Hz. 4H. for C_{10} and C_{12} methylene protons) 5.10 - 5.60 (m. 2H. for olefinic protons).

Mass: 308 M^+, 250, 235, 224, 222, 195, 180, 168, 148, 138, 124 (base peak), 109, 100.

Analysis: Calculated for $C_{21}H_{40}O$: C, 81.75; H, 13.07

Found: C, 81.71; H, 13.10.

Z-1,6-Heneicosadien-11-one (2)

Bis alkylations of (39) (0.5 g, 0.005 mole) was carried out as above [as the synthesis of (1)] with 1-bromononane (34) (1.03 g, 0.005 mole) and Z-1-bromo-3,8-nonediene (37) (1.01 g, 0.05 mole). It was then treated with 2NHCl (5 ml) and worked up as mentioned in the synthesis of (1) to get (2) in 72% yield (1.10 g).

IR (neat): 3080, 3200, 2940, 2265, 1730 (carbonyl stretching), 1650 (terminal CH_2=CH- stretching), 1415, 1380, 1105, 1005, 925, 740 (cis double bond).

PMR ($CDCl_3$): δ 0.87 (distorted triplet 3H, C_{21} methyl protons) 1.11 - 1.80 (m, 20H, this includes broad singlet for C_{13}-C_{20} methylene protons and multiplet for C_4 and C_9 methylene protons), 1.87 - 2.17 (m, 6H, for C_3, C_5

and C_8 allylic methylene protons), 2.34 (t, J=7 Hz, 4H, for C_{10} and C_{11} methylene protons), 4.86 - 5.11 (m, 2H, for C_1 olefinic protons), 5.13 - 5.13 (m, 2H, for C_6 and C_7 olefinic protons), 5.57 - 6.02 (m, 1H, for C_2 olefinic proton).

Mass: 306 (molecular ion), 288, 279, 251, 225, 197, 180, 169, 122 (base peak), 107, 81, 80, 67.

Analysis: Calculated for $C_{21}H_{38}O$; C, 82.28; H, 12.50
Found: C, 82.22; H, 12.53.

Pent-4-ene-1-ol (44)

To powdered sodium (11.2 g, 0.487 moles) in 200 ml of anhydrous ether was slowly added tetrahydrofurfuryl chloride (45) (30 g, 0.25 mole) in 50 ml of ether. Addition was done over a period of 2 hrs. at 0°C. Stirring was continued for 2 more hrs. at room temperature. The reaction mixture was allowed to settle down and ether layer was decanted into dry beaker and decomposed with ice-water to give two layers. The ether layer was separated and dried over Na_2SO_4. Ether was removed and residue was distilled to get 4-pent-1-ol (44) in 76% yield (16.1 g), b.p.134-137°C/760 mm.

IR (neat): 3320 (hydroxy stretching), 3075, 2940, 2860, 1640 (terminal olefin, H_2C=CH- stretching), 1410, 1038, 1010, 904.

PMR ($CDCl_3$): δ 1.44 - 1.80 (m, 2H, for C_2 methylene protons), 1.93 - 2.26 (m, 2H, for C_3 methylene protons), 2.02 (bs, 1H, D_2O exchangeable), 3.62 (t, 2H, J=6 Hz, for C_1 methylene protons), 4.87 - 5.15 (m, 2H, for C_4 olefinic protons), 5.58 - 6.02 (m, 1H, for C_5 olefinic proton).

5-Bromo-pent-1-ene (38)

A mixture of 4-penten-1-ol (44) (13.3 g, 0.155 mole) and pyridine (3.5 g, 0.044 mole) was placed in a flask at -28°C. To this stirred reaction mixture, phosphorous-tribromide (17.4 g, 0.064 mole) was added dropwise over a period of one hr. Stirring continued for 3 more hrs at -28°C. The product was distilled out with an oil bath from the reaction mixture. The distillate was washed with water, dilute NaOH and dried over $CaCl_2$. The yield was 79% (18.3 g), b.p.128-130°C/760 mm.
IR (neat): 3080, 2940, 2850, 1650 (terminal double bond), 1420, 740.
PMR ($CDCl_3$): 1.62 - 2.42 (m, 4H, for C_3 and C_4 methylene protons), 3.46 (t, 2H, J=6 Hz, for C_5 methylene protons), 4.97 - 5.24 (m, 2H, for C_1 olefinic protons), 5.60 - 6.06 (m, 1H, for C_2 olefinic proton).

3-Nonyn-8-ene-1-ol (46)

To the 3-butyn-1-ol (35) (6.8 g, 0.1 mole) in THF (200 ml) at -30°C was added n-BuLi (0.2 mole, 105 ml of

of 1.9N n-hexane solution) under N_2 atmosphere, followed by 100 ml of HMPA. The reaction mixture was stirred for 0.5 hr at 0°C. Reaction mixture again cooled to -30°C and 5-bromo-pent-1-ene (38) (16.39 g, 0.11 mole) was added dropwise for 1 hr. Reaction mixture was stirred at -30°C for 4 hrs and quenched with sat. NH_4Cl (50 ml). Organic layer was separated and THF was removed under vacuum. Crude reaction mixture was then extracted with ether (2 x 200 ml) and washed with water. Ether was evaporated and the crude product was chromatographed (silica gel, 10% ethyl acetate in pet.ether as eluent) to get (46) in 60% yield (8.29 g).

IR (neat): 3360 (hydroxy stretching), 2950, 1650, (terminal olefinic, CH_2=CH- stretching), 1450, 1060, 1010, 930, 860.

PMR ($CDCl_3$): δ 1.38 - 1.74 (m, 2H, for C_6 methylene protons), 1.91 (bs, 1H, D_2O exchangeable), 2.01 - 2.27 (m, 4H, for C_2 and C_5 methylene protons), 2.30 - 2.52 (m, 2H, for C_7 methylene protons), 3.64 (t, 2H, J=6 Hz, for C_1 methylene) 4.84 - 5.3 (m, 2H, for C_9 olefinic protons), 5.53-6.02 (m, 1H, for C_8 olefinic proton).

Analysis: Calculated for $C_9H_{14}O$; C, 78.21; H, 10.21

Found: C, 78.18; H, 10.22.

Z-3,8-Nonadiene-1-ol (47)

A mixture of (46) (6.9 g, 0.005 mole) and 150 mg of Lindlar catalyst (Pd/C - $CaCO_3$) in n-hexane (35 ml) containing one drop of quinoline was stirred in an atmosphere of H_2 till one mole equivalent was absorbed. The catalyst was filtered off and washed with dil. HCl, 5% $NaHCO_3$ and brine. Then organic layer was dried over Na_2SO_4, concentrated and the residue distilled to get pure (47) in 95% yield (6.65 g), b.p. 96°C/2 mm.

IR (neat): 3350 (hydroxyl stretching), 3080, 2940, 2865, 1645 (terminal $-CH_2=CH-$ stretching), 1440, 1055, 1000, 920, 730 (characteristic of cis double bond compound).

PMR ($CDCl_3$): δ 1.17 - 1.84 (m, 2H, for C_6 methylene protons), 1.84 - 2.48 (m, 6H, for C_2, C_5 and C_7 methylene protons), 3.63 (t, 2H, J=6 Hz, for C_1 methylene protons), 4.82 - 5.15 (m, 2H, for C_9 olefinic protons), 5.15 - 6.04 (m, 3H, for C_3, C_4 and C_8 olefinic protons).

Mass: 140 (molecular ion peak), 127, 112 (base peak 81, 67, 55, 41.

Analysis: Calculated for $C_9H_{16}O$: C, 77.09; H, 11.50
Found: C, 77.12: H, 11.48.

Z-1-Bromo-3,8-nonadiene (37)

To a ice cooled solution of (47) (1.40 g, 0.01 mole) and triethylamine (1 ml) in dry dichloromethane (30 ml) was added methanesulfonylchloride (1.35 g, 0.018 mole) at

0°C and stirred for 3 hrs. The reaction mixture was washed with water, cold dil.HCl, followed by 5% $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated to give mesylate of (47). To the acetone solution (25 ml) of mesylate was added anhydrous LiBr (1.30 g, 0.015 mole) and stirred for 5 hrs. Acetone was removed under reduced pressure and the product was extracted with ether. Ether layer was washed with water and brine. Ether was distilled off and crude was purified by column chromatography (silica-gel, pet.ether as eluent) to get (37) in 70% yield (1.42 g)
IR (neat): 3080, 3020, 2940, 2860, 1650 (terminal olefinic, CH_2=CH-, stretching), 1440, 1270, 1215, 1000, 920, 730 (cis double bond).
PMR ($CDCl_3$): δ1.20 - 1.69 (m, 2H, for C_6 methylene protons), 1.89 - 2.24 and 2.44 - 2.78 (two sets of multiplet for C_2, C_5 and C_7 methylene protons, 6H), 3.34 (t, 2H, J=6 Hz, for C_1 methylene protons), 4.84 - 5.15 (m, 2H, for C_9 olefinic protons), 5.15 - 6.04 (m, 3H, for C_3, C_4 and C_8 olefinic protons).

2-(2-Bromoethyl) 1,3-dioxalane (49)

To a stirred solution of HBr (81 g, 1 mole) in ethylene glycol (150 g) at 0°C was added acrolein (44.8 g, 0.8 mole). After stirring for 2 hrs at room temperature, the mixture was extracted twice with

n-hexane. Organic layer was washed with 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated. Distillation of residue afforded (49) in 58% yield (83.9 g), b.p.68-70°C/8 mm.

IR (neat): 2970, 2900, 1490, 1425, 1280, 1125, 1140, 955, 820.

PMR($CDCl_3$): δ 2.08 - 2.33 (m, 2H), 3.46 (t, 2H, J=6 Hz), 3.80 - 4.04 (m, 4H, for $\begin{matrix}CH_2\text{-}O\\CH_2\text{-}O\end{matrix}$), 5.01 (t, 1H, J = 4 Hz).

Ketoaldehyde (60)

To a THF (50 ml) solution of (39) (1 g, 0.01 mole) under N_2 atmosphere at 0°C was added n-BuLi (0.012 mole, 6.3 ml of 1.9 N n-hexane solution) with syringe. The reaction mixture was stirred for 1 hr. 2-(2-Bromoethyl)-1,3-dioxalane (49) (1.81 g, 0.01 mole) was added and stirred for 5 hrs. at room temperature. Reaction mixture was again cooled to 0°C and n-BuLi (0.012 mole was added and stirred for 1 hr. 1-Bromononane (34) (2.07 g, 0.01 mole) was added and stirred for 2 hrs. at room temperature. Then 10 N HCl (15 ml) was added to it and stirred for 2 hrs at 60°C. Reaction mixture was then neutralised with 5% $NaHCO_3$ and diluted with excess of water and extracted with ether. Ether layer was washed with sat. NH_4Cl, dried, concentrated and purified by column chromatography (silica gel, 10% ethyl acetate in pet.ether as eluent)

to get (60) in 62% yield (1.48 g), m.p.43°C.

IR (Nujol): 3000, 2920, 2850, 1720 (both keto and aldehyde gave one broad peak), 1460, 1050.

NMR ($CDCl_3$): δ 0.88 (distorted triplet, 3H, for terminal methyl protons), 0.9 - 2.2 (m, 18H, broad singlet for 16 H and multiplet for C_3 methylene protons, 2H), 2.2 - 2.5 (m, 6H for C_2, C_4 and C_6 methylene protons), 9.9 (broad singlet for aldehyde proton).

Mass: 240 (molecular ion), 184, 169, 114, 99, 95, 86, 81, 71 (base peak).

Analysis: Calculated for $C_{15}H_{28}O_2$: C. 74.95; H, 11.74

Found : C, 74.91; H, 11.76.

Wittig salt (53)

A solution of 6-iodo-hex-1-ene (52) (6.7 g) and triphenylphosphine (7.9 g) in dry benzene (25 ml) was refluxed for 3 hrs, during which two layers separated on being cooled to 0°C, the lower layer crystalised. Then upper layer was decanted. The white crystaline salt (53) was washed with dry ether and dried in high vacuum to yield (53) in 88%(12.5 g), m.p. 165-167°C

Analysis: Calculated for $C_{24}H_{26}IP$: C, 61.00; H, 5.50;I,26.90

Found: C, 61.18; H, 5.42;I,26.81.

Wittig salt (56)

A solution of 1-bromohexane (55) (4.95 g, 0.03 mole) and triphenylphosphine (7.86 g, 0.03 mole) in 50 ml of

benzene was refluxed with stirring for 48 hrs, during which two layers are separated. On being cooled to 0°C. the lower layer crystalised. The upper layer was decanted. The white crystalline solid was washed with dry ether and dried in high vacuum to yield (56) in 75% yield (9.58 g), m.p.197-199°C.

Analysis: Calculated for $C_{24}H_{28}BrP$

C, 67.40; H, 6.60; Br, 18.7

Found: C, 67.51; H, 6.55; Br, 18.61.

Z-6-Heneicosen-11-one (1) [using Wittig reagent (57) and ketoaldehyde]

A solution of sodium bis (trimethyl silyl) amide (61) (1.83 g, 0.01 mole) and n-hexyltriphenylphosphonium bromide (56) (4.27 g, 0.01 mole) in dry THF (30 ml) under N_2 atmosphere, stirred for 30 minutes at room temperature and refluxed for one hr to form dark orange colored ylide (57). This ylide solution was cooled and allowed to Settle down the solid NaBr. The supernatent orange colored ylide (57) solution was taken out with syringe under N_2 atmosphere and added dropwise to precooled (-78°C) THF solution (50 ml) of ketoaldehyde (60) (2.40 g, 0.01 mole) under N_2 atmosphere. Reaction mixture was stirred at -78°C for 3 hrs. THF was evaporated under vacuum and residue was extracted with pet.ether. Pet.ether layer was washed with water,

saturated NH_4Cl solution, dried, evaporated and purified by column chromatography (silica gel, 2% ethyl acetate in pet.ether as eluent) to get (1) in 79% yield (2.42 g).
IR (neat): 2980, 2890, 2815, 1725 (carbonyl), 1460, 1405, 1370, 1130, 1090, 1015, 720 (cis olefin).
PMR ($CDCl_3$): δ0.88 (distorted triplet, 6H, J=6 Hz), 1.1-1.73 (m, 24H, broad singlet for C_2-C_4 and C_{13}-C_{20} methylene protons and multiplet for C_9 methylene protons), 1.86 - 2.15 (m, 4H, for C_5, C_8 allylic methylene protons), 2.30 (t, 4H, J=7 Hz, for C_{10} and C_{12} methylene protons), 5.10 - 5.60 (m, 2H, for olefinic protons).
Mass: 308 (molecular ion), 250, 235, 224, 222, 195, 180, 168, 148, 138, 124 (base peak), 109, 100.
^{13}C NMR ($CDCl_3$): 211.08 (carbonyl carbon), 131.15, 128.94 (olefinic); 42.96, 42.17 (carbons α to carbonyl), 32.04, 31.65, 29.83, 29.70, 29.57, 29.44, 27.36, 26.78, 24.05, 22.68, 14.10.
Analysis: Calculated for $C_{21}H_{40}O$: C, 81.75; H, 13.07
Found: C, 81.71; H, 13.09.

Z-1,6-Heneicosadien-11-one (2) (using ylide (54) and ketoaldehyde (60)

Salt free ylide (54) was prepared as above using Wittig salt (53) (1.21 g, 0.0025 mole). Supernatent ylide (54) solution was added to precooled (-78°C)

THF (25 ml) solution of ketoaldehyde (60) (0.6 g. 0.0025 mole) under N_2 atmosphere. The reaction mixture was stirred for 3 hrs at -78°C. The reaction mixture was then worked up and purified as above to get (2) in 74% yield (0.566 g).

IR (neat): 3080, 3020, 2940, 2265. 1730 (carbonyl), 1650 (terminal, CH_2=CH-, olefinic stretching). 1465, 1380, 1105, 1005, 925, 740 (cis olefin).

^{13}C NMR ($CDCl_3$): 211.15 (carbonyl carbon); 138.88, 130.63, 129.33, 114.64 (olefinic carbons); 42.96, 42.18 (carbons α to carbonyl); 33.40, 32.64, 29.70, 29.57, 29.44, 29.11, 26.78, 24.04, 23.91, 22.75, 14.10.

Analysis: Calculated for $C_{21}H_{38}O$: C, 82.28; H, 12.50
Found: C, 82.24; H, 12.52.

5-Hexene-1-ol (51)

To a stirred dry ether (100 ml) solution of powdered sodium (5.75 g, 0.25 mole) was added tetrahydropyranyl chloride (50) (16.8 g, 0.125 mole) slowly. Addition was done in 1 hr. duration at 0°C. Stirring was continued for 2 more hrs at room temperature. The reaction mixture was allowed to settle down and ether layer was decanted into dry beaker and decomposed with ice water to give two layers. The organic layer was separated and washed with brine. Ether layer was then dried over Na_2SO_4. Ether was evaporated and residue

was distilled to get 5-hexene-1-ol (51) in 70% yield (8.75 g).

IR(neat): 3350 (hydroxyl stretching), 3090, 2940, 2870, 1650 (terminal double bond stretching), 1450, 1040, 1000, 910.

PMR($CDCl_3$): δ 1.10 - 1.87 (m, 4H, for C_2C_3 methylene protons), 1.87 - 2.25 (m, 2H, for C_4 methylene protons), 3.7 (t, 2H, J=6 Hz, for C_1 methylene protons), 4.82-5.13 (m, 2H, for C_6 olefinic protons), 5.52 - 6.10 (m, 1H, for C_5 olefinic proton).

6-Iodo-hex-1-ene (52)

To a stirred solution of (51) (5.0 g, 0.05 mole) in dry dichloromethane (50 ml) containing triethylamine (15.2 g, 0.15 mole) at 0°C, was added solution of methanesulfonyl chloride (6.87 g, 0.06 mole) in dichloromethane (25 ml) over a period of 10 minutes. Stirring was continued for further 2 hrs. and the reaction mixture was washed with ice water followed by 10% HCl, 5% aq. $NaHCO_3$ and brine. Organic layer was dried and concentrated to give mesylate of (51). The mixture of crude mesylate and sodium iodide (15.4 g, 0.01 mole) in dry acetone (50 ml) was refluxed for 3 hrs. Then the reaction mixture was diluted with water and extracted with ether (3 x 100 ml) and ether layer was washed successively with water, sodium thiosufate and brine.

Organic layer was dried, concentrated and distilled to give (52) in 72% yield (7.70 g),

IR (neat): 3070, 2940, 2870, 1645 (terminal double bond), 1450, 730.

NMR ($CDCl_3$): δ 1.30 - 2.25 (m, 6H, for C_3 and C_5 methylene protons), 3.13 (t, 2H, J=6 Hz, for C_6 methylene protons), 4.82 - 5.13 (m, 2H, for C_1 olefinic protons) and 5.52 - 6.10 (m, 1H, for C_2 olefinic proton).

N,N-Diemthylcyclopentanone hydrazone (63)

A solution of cyclopentanone (62) (8.4 g, 0.1 mole) and N,N-dimethylhydrazone (6.0 g, 0.1 mole) in dry benzene (50 ml) was refluxed for 6 hrs. (catalytic amount of trifluoroacetic was used). After cooling, the aqueous layer was separated and benzene layer was washed with water and dried. Benzene was removed under reduced pressure and crude compound was distilled to get (63) in 86% yield (10.8 g), b.p.95/100 mm.

IR (neat): 2955, 2850, 2820, 1660 (C=N- stretching), 1470, 1450, 1430, 1180, 1150, 1020, 970.

PMR ($CDCl_3$): δ 1.62 - 1.88 (m, 4H) and 2.26 - 2.53 (10H, includes singlet for $-N(CH_3)_2$ and multiplet for $N=C(CH_2-)(CH_2-)$).

2-Decyl cyclopentanone (65)

To a dry THF (25 ml) solution of (63) (2.52 g, 0.02 mole) under N_2 atmosphere at 0°C was added n-BuLi (0.025 mole, 12.7 ml of 1.9N n-hexane solution) with syringe and stirred for 1 hr at 0°C. The decyl bromide

(64) (5.52 g, 0.025 mole) was added slowly and stirred for 3 hrs at room temperature. Then 2N HCl (5 ml) was added and stirred for 10 minutes. The reaction mixture was neutralised with 5% aq. $NaHCO_3$, diluted with excess of water and extracted with ether. Ether layer was dried, concentrated and crude product was chromatographed (silica gel, 10% ethyl acetate in pet.ether as eluent) to get (65) in 86% yield (4.81 g).

IR (neat): 2940, 2870,1745 (carbonyl), 1465, 1415, 1160.

PMR($CDCl_3$): δ 0.88 (distorted triplet 3H, J = 6 Hz), 1.25 - 2.35 (m, 26H, includes broad singlet for aliphatic methylene protons, 9 x CH_2, multiplet for cyclopentanone protons, 4 x CH_2).

Mass: 224 (molecular ion), 169, 162, 122, 111, 105, 97, 84 (base peak), 69, 55.

Analysis: Calculated for $C_{15}H_{28}O$: C, 80.29; H, 12.58
Found: C, 80.22; H, 12.60.

Lactone (66)

To a dry chloroform (25 ml) solution of (65) (2.24 g, 0.01 mole) was added chloroform solution of perbenzoic acid (2.07 g, 0.015 mole) at 0°C and stirred for 5 hrs. Reaction mixture was washed with aq. sodium sulfite and with sodiumbicarbonate solution. Chloroform layer was then washed with brine, dried, concentrated. and chromatographed (silica gel, 15% ethyl acetate in

pet.ether as eluent) to get (66) in 78% yield (1.93 g).
IR (neat): 2940, 2865, 1750 (carbonyl stretching), 1480, 1260, 1065, 945.
PMR ($CDCl_3$): δ 0.87 (distorted triplet, 3H), 1.13 - 2.06 (m, 22H, includes broad singlet for aliphatic chain methylene protons, 9 x CH_2 and multiplet for hexane ring methylenes, 2 x CH_2), 2.31 - 2.77 (m, 2H, methylene adjacent to ester carbonyl), 4.11 - 4.45 (m, 1H).
Mass: 240 (molecular ion peak), 222, 178, 114, 99 (base peak), 83, 71, 56.
Analysis: Calculated for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74
Found : C, 74.99; H, 11.71.

Lactal (67)

To a dry THF solution (25 ml) of (66) (1.20 g. 0.05 mole) at -78°C was added diisobutyl aluminium hydride (0.852 g of n-hexane solution, 0.051 mole) solution slowly. Stirred at -78°C for 0.5 hr (reaction was monitered by TLC) and quenched with a few drops of water. Reaction mixture was filtered, dried and concentrated to give (67) in 92% yield (1.11 g). PMR showed complicated multiplet pattern in the region of δ 3.0 - 5.5 due to the diastereomeric mixture.
IR (neat): 3400 (hydroxyl stretching), 2930, 2870, 1470, 1205, 1020, 980.

PMR ($CDCl_3$): δ 0.88 (distorted triplet, 3H, for methyl), 1.28 - 2.13 (m, 24H, includes broad singlet for aliphatic chain methylene protons, 18H, and multiplet for ring methylene protons, 6H), 3.13 - 3.64, 3.73 - 4.31, 4.60 - 4.86 and 5.24 - 5.40 (m, 2H, for protons adjacaent to oxygens).

Analysis: Calculated for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48

Found: C, 74.40; H, 12.45.

Hydroxy olefin (68)

A solution of sodium bis (trimethyl silyl) amide (61) (1.83 g, 0.01 mole) and n-hexyltriphenylphosphonium bromide (56) (4.27 g, 0.01 mole) in dry THF (30 ml) under N_2 atmosphere was stirred for 30 minutes at room temperature and refluxed for one hr to form dark orange colored ylide (57). The ylide solution was cooled and allowed to settle down (solid sodium bromide). The supernatent orange colored ylide (57) solution was taken out with syringe under N_2 atmosphere and was added dropwise to precooled (-78°C) THF solution (50 ml) of lactal (67) (2.42 g, 0.01 mole) under N_2 atmosphere. The reaction mixture was stirred at -78°C for one hour and at room temperature for one more hour. THF was evaporated under vacuum and residue was extracted with pet.ether. Pet. ether layer was washed with water, brine, dried, concentrated and purified by column

chromatography (silica gel, 8% ethyl acetate in pet.ether as eluent) to get (68) in 83% yield (2.57 g).
IR (neat): 3340 (hydroxyl stretching), 2900, 2840, 1460, 1375, 1020, 720 (cis double bond).
PMR ($CDCl_3$): δ 0.88 (distorted triplet, 6H, J=6 Hz, for C_1 and C_{21} methyl protons), 1.11 - 1.71 (m, 28H, includes broad singlet for C_2-C_4 and C_{13}-C_{20} methylene protons and multiplet for C_9, C_{10} and C_{12} methylene protons), 1.82 - 2.20 (m, 4H, for allylic protons), 3.37 - 3.69 (m, 1H, for C_{11} proton), 5.22 - 5.51 (m, 2H, for olefinic protons).
Mass: 310 (molecular ion), 292, 268, 253, 222, 208, 197, 184, 169 (base peak), 151, 137, 124, 109, 95, 82.
Analysis: Calculated for $C_{21}H_{42}O$: C, 81.21; H, 13.63
Found : C, 81.26; H, 13.60.

Hydroxy diene (69)

The ylide (54) was prepared from Wittig salt (53) (1.21 g, 0.0025 mole) by the method used for ylide (57). The ylide (54) was added to the THF solution (25 ml) of lactal (67) at-78°C. The reaction mixture was stirred for one hour at -78°C and at room temperature for one more hour. Worked up in usual way to get (69) in 80% yield (0.62 g).
IR (neat): 3360 (hydroxyl stretching), 2940, 2865, 1650 (terminal CH_2=CH- stretching), 1465, 1000, 920, 730

(cis double bond).

PMR ($CDCl_3$): δ 0.87 (distorted triplet, 3H, for C_{21} methyl protons), 1.11 - 1.88 (m, 24H, includes broad singlet for C_{13}-C_{20} methylene protons, 16H, multiplet for C_4, C_9, C_{10}, C_{12} methylene protons, 8H), 1.92 - 2.20 (m, 6H, allylic protons), 3.44 - 3.73 (m, 1H, for C_{11} proton), 4.86 - 5.11 (m, 2H, for C_1 olefinic protons), 5.13 - 5.53 (m, 2H, for C_6 and C_7 olefinic protons), 5.57 - 6.02 (m, 1H, for C_2 olefinic proton).

Mass: 308 (molecular ion), 290, 279, 251, 237, 225 (base peak), 197, 169, 167, 149, 122, 107, 97, 84, 80, 67.

Analysis: Calculated for $C_{21}H_{40}O$: C, 81.75; H, 13.07

Found: C, 81.69; H, 13.10.

Z-6-Heneicosen-11-one (1) [PCC oxidation of hydroxyolefin (68)]

To a stirred solution of PCC (0.258 g, 0.0012 mole) in dry dichloromethane (15 ml) at room temperature was added hydroxyolefin (68) (0.310 g, 0.001 mole) in dichloromethane (5 ml). Stirring was continued for 2 hrs. After completion of reaction, the dichloromethane solution was passed through silica gel (60-120 mesh) column. It was eluted with (100 ml) dichloromethane. The solvent was removed to get crude product (1). This was purified by column chromatography (silica gel, 2% ethyl acetate

in pet.ether) to get pure (1) in 91% yield (0.280 g). All spectral data and analytical data was identical with those reported for compound (1).

Z-1,6-Heneicosen-11-one (2)[PCC oxidation of hydroxydiene (69)]

PCC (0.258 g, 0.0012 mole) oxidation of (69) (0.308 g, 0.001 mole) was done by the same method which was used for oxidation of (68) to get (2) in 86% yield (0.263 g). All spectral and analytical data were identical with those reported for Z-1,6-heneicosadien-11-one (2).

REFERENCES

1. R.G. Smith, G.E. Daterman and G.D. Daves Jr., Science, 188, 63 (1975).

2. L.M. Smith, R.G. Smith, T.M. Loehr and G.D. Daves Jr., J.Org.Chem., 43, 2361 (1978).

3. R.G. Smith, G.D. Daves Jr., and G.E. Daterman, J.Org.Chem., 40, 1593 (1975).

4. P.J. Kocienski and G.J. Cernigliaro, J.Org.Chem., 41, 2927 (1976).

5. K. Mori, M. Uchida and M. Matsui, Tetrahedron, 33, 385 (1977).

6. K. Pramod, H. Ramanathan and G.S.R. Subba Rao, J.Chem.Soc., Perkin Trans I, 7 (1983).

7. G. Cahiez, A. Alexakis and J.F. Normant, Tetrahedron Lett., 21, 1433 (1980).

8. G.Z. Zweifel and N.R. Pearson, J.Am.Chem.Soc., 102, 5919 (1980).

9. B.M. Trost and Paul L. Ornstein, Tetrahedron Lett., 22, 3463 (1981).

10. K. Kondo and S. Murahashi, Tetrahedron Lett., 1237 (1979).

11. Y. Murata, K. Inomata, H. Kinoshita and H. Kotake, Bull.Chem.Soc., Japan, 56, 2539 (1983).

12. H. Nishiyama, K. Sakuta and K. Itoh , Tetrahedron Lett., 25, 223, (1984).

13. S. Fernandez, R. Quintanilla and J.E. Hernandez, Synth. Comm., 13, 191 (1983).

14. S. Fernandez, A. Cisnerors and J.E. Hernandez, Synth. Comm., 13, 621 (1983).

15. Y. Naoshima, H. Ike, T. Ogawa, T. Nakayama and H. Kondo, Agric. Bio. Chem., 48, 2151 (1984).

16. K.K. Wang and K.H. Chu, J.Org.Chem., 49, 5175 (1984).

17. E. Wenkert, V. Ferreira, E.L. Michelotti and M. Tingoli, J.Org.Chem., 50, 719 (1985).

18. M. Sodeaka and M. Shibasaki, J.Org.Chem., 50, 1147 (1985).

19. H.J. Bestmann and M. Schmidt, Tetrahedron Lett., 26(50), 6171 (1985).

20. M. Fetizon and C. Lazare, J.Chem.Soc., Perkin Trans 1, 18, 842 (1978).

21. C.A. Henrick, Tetrahedron, 33, 1853 (1977).

22. B. Akermark and A. Ljungqvist, J.Org.Chem., 43, 4387 (1978).

23. O.P. Vig, M.L. Sharma, N.K. Verma and N. Malik, Indian J.Chem., 19B, 950 (1980).

24. P.S. Reddy, A.B. Sahasrabudhe and J.S. Yadav, Synth.Comm., 13(5), 379 (1983).

25. E.J. Corey and D. Enders, Tetrahedron Lett., 3,11, (1976) and references cited therein.

26. M.E. Jung and T.J. Shaw, Tetrahedron Lett., 4149(1979).

27. J.D. Morrison, Asymetric Synthesis, Vol. 4, Ed.New York (1984).

28. M. Yamashita, K. Matsumiya, M. Tanabe and R. Suemitsu, Bull.Chem.Soc., Japan, 58, 407 (1985).

29. G.B. Reddy and R.B. Mitra, Synth.Comm., 16(13), 1723 (1986).

30. L. Brandsma, "Preparative acetylenic chemistry" page 60, Elsevier Publishing Co., New York (1971).

31.

32. H. Lindlar and R. Dubuis, Organic Synthesis, 46, 89 (1966).

33. R.K. Crossland and K.L. Servis, J.Org.Chem., 35, 3195 (1970).

34. F.B. Laforge, N. Green and W.A. Gersdorff, J.Am.Chem.Soc., 70, 3707 (1948).

35. L.A. Brooks and H.R. Snyder, Organic Synthesis, Coll.Vol. 3, 698 (1955).

36. G. Buchi and H. Wuest, J.Org.Chem., 34, 1122 (1969).

37. R.B. Mitra and G.B. Reddy, Indian J.Chem. (in press)

38. H.J. Bestmann, W. Stransky and O. Vostrowsky, Chem.Ber., 109, 1694 (1976).

39.a. Ansell and Thomas, J.Chem.Soc., 539, 1961.

b. C.A., 58, 669

40. J. Colonge and P. Lasfargues, Bull.Soc.Chim.(France), 177 (1962).

41. G.B. Reddy and R.B. Mitra, Synth.Comm., 17(7), 893 (1987).

CHAPTER II

SYNTHESIS OF PHEROMONES HAVING SPIROKETAL FUNCTIONS

Summary

This chapter deals with the synthesis of a spiroketal pheromones 1,7-dioxaspiro [5,5] undecane (1) and (2S, 2R, 8S)-2,8-dimethyl-1,7-dioxaspiro [5.5] undecane (2). One pot alkylations of (32) with appropriately substituted bromo-alcohols (34) and (37) and acid catalysed cyclisation gave the compounds (1) and (2) respectively.

INTRODUCTION

The spiroacetal structural unit is widely represented in natural products. It is found in antiparasitic agents such as the avermectins[1] and the milbemycins[2], in polyether antibiotics such as A-23187[3], Salinomycin[4], narasin[5], noboritomycin A and B[6], okadaic acid[7], acanthifolicin[8], aplysiatoxin[9], oligomycin B[10] and botrycidin[11] and in the fungal derived toxins in taloromycin A and B[12]. Pheromones of several insect species also contain substituted 1,6-dioxaspiro (4,4) nonane[13], 1,6-dioxaspiro [4,5] decane[14] and especially 1,7-dioxaspiro [5,5] undecane[15] units.

The 1,7-dioxaspiro [5,5] undecane (1) is the major component of the sex pheromone of olive fly, Dacus oleae (Gmelin) isolated by Raymond Baker et al.[16] in 1980. Racemic mixture of spiroacetal (1) has been shown to be a potent male attractant. Similarly 2,8-dimethyl-1,7-dioxa-spiro [5,5] undecane (2), the analogue of (1) has been isolated as main pheromone component from bee Andrena Wilkella by Francke et al.[15] in 1980. The pheromone (2) has also been isolated[17] from Dacus Cucumis.

Dacus oleae (Gmelin) is the major pest of olives, having its most serious effect in Italy, Spain, Greece and Israel. The bee Andrena Wilkella and Dacus Cucumis are the major pests of cucurbitus and tomatoes in Australia.

Due to the importance in crop protection, many syntheses of (1) and (2) have been reported

Stereochemical aspects of (1) and (2)

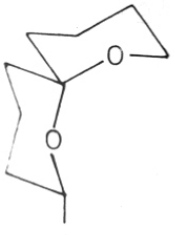
The 1,7-dioxaspiro [5,5] undecane has one asymmetric centre. Therefore two isomers (enantiomeric pair) are possible (Chart 1). The 2,8-dimethyl-1,7-dioxaspiro [5,5] undecane has three asymmetric centres. Out of eight possible stereoisomers (4 enantiomeric pairs), four are [2S, 6R, 8S-(2); 2S, 6S, 8R-(2) and their antipodes] stable. The stereoisomers 2S, 6R, 8R-(2) and 2R, 6S, 8S-(2) are energetically not favoured due to the axial substitution of methyl group and the stereoisomers 2S, 6S, 8S-(2) and 2R, 6R, 8R-(2) are unstable owing to the oxygen anomeric effect[18] (Chart 1).

Synthesis of (1) and (2)

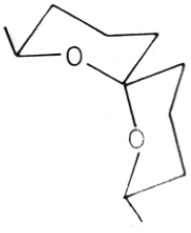
The first synthesis (Scheme 1) of (1) was reported in 1958 (before isolation of (1) and (2) by Stetter and Rauhut[19]. The ethyl 3(2,6-dioxocyclohexyl) propionate (3) was converted to δ-keto-diethyl ester (4) and protection of keto, reduction of diester functionalities gave diol (5) which on cyclisation yielded (1).

In 1969, Micovic et al.[20] (Scheme 2) got (1) by reacting 1,10-decane diol (6) with lead tetraacetate in refluxing benzene (yield 3.3%).

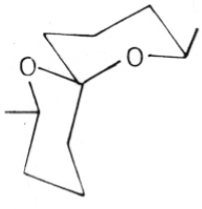
CHART – 1



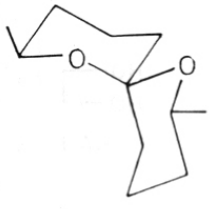
(2R, 6S, 8R)-(2)



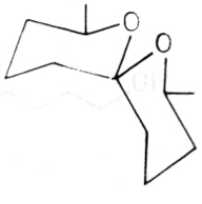
(2S, 6R, 8S)-(2)



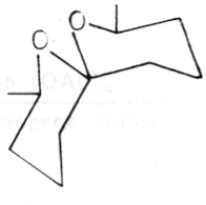
(2R, 6R, 8S)-(2)



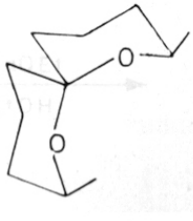
(2S, 6S, 8R)-(2)



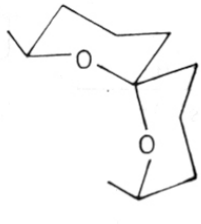
(2R, 6R, 8R)-(2)



(2S, 6S, 8S)-(2)

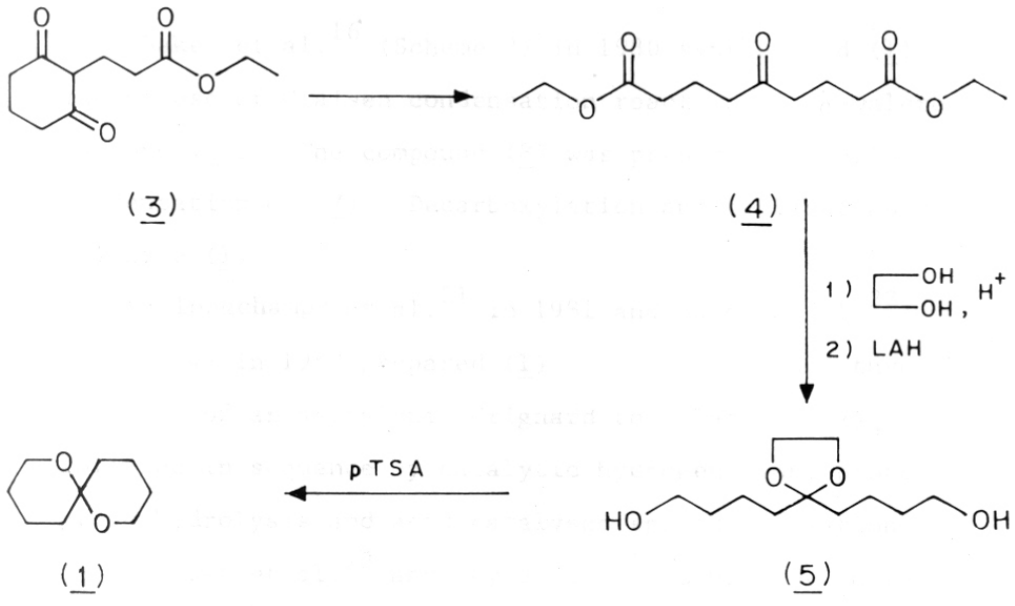


(2R, 6S, 8S)-(2)

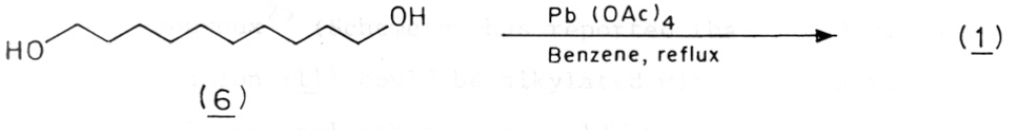


(2S, 6R, 8R)-(2)

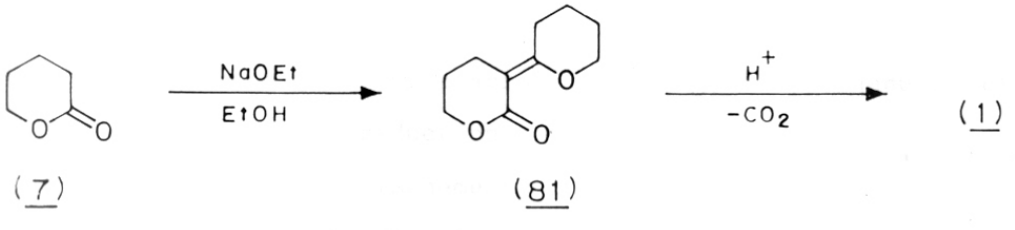
SCHEME –1



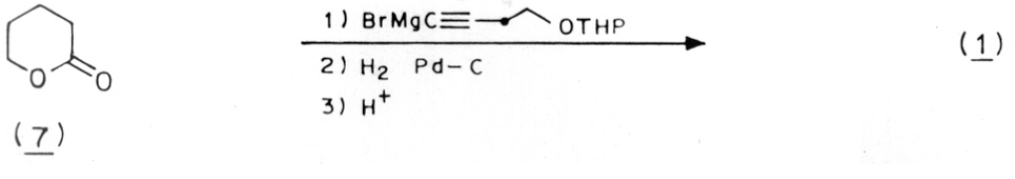
SCHEME – 2



SCHEME – 3



SCHEME – 4



Baker et al.[16] (Scheme 3) in 1980 synthesized (1) making use of Claisen condensation reaction of δ-valerolactone (7). The compound (8) was prepared by self-condensation of (7). Decarboxylation and cyclisation of (8) gave (1).

Deslongchamps et al.[21] in 1981 and Baker et al.[22] (Scheme 4) in 1982 prepared (1) and its analogues through addition of an acetylenic Grignard to lactone (7), followed in sequence by catalytic hydrogenation, protective group hydrolysis and acid catalysed spiroketalisation.

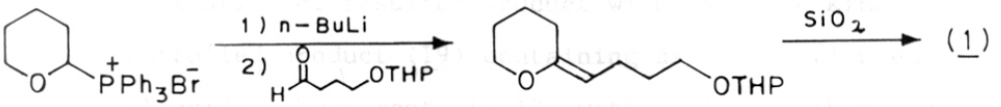
Ousset et al.[23] and Ley et al.[24] (Scheme 5) in 1984 reported that the ylide from phosphonium salt (9) could be condensed with an aldehyde and resulting enol ether (10) could then be transformed into (1).

Amouroux[25] (Scheme 6) has reported that 2-dihydropyranyl anion (11) could be alkylated with alkylhalide (12) and resulting enol ether (13) could then be transformed into (1).

Ireland et al.[26,27] (Scheme 7) have synthesized (1) using Diels-Alder reaction (4 + 2 cycloaddition). Condensation of (14) with acrolein (15) gave cycloadduct (16), which on catalytic reduction gave (1).

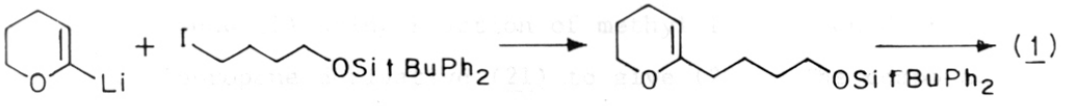
Iwata et al.[28] (Scheme 8) in 1985 synthesized enantiomers of (1) using internal Michael-type addition of vinyl sulfoxide (17) to give (18) upon treatment with PTSA and $MgSO_4$. Deprotection of (18) and

SCHEME – 5



(9) (10)

SCHEME – 6

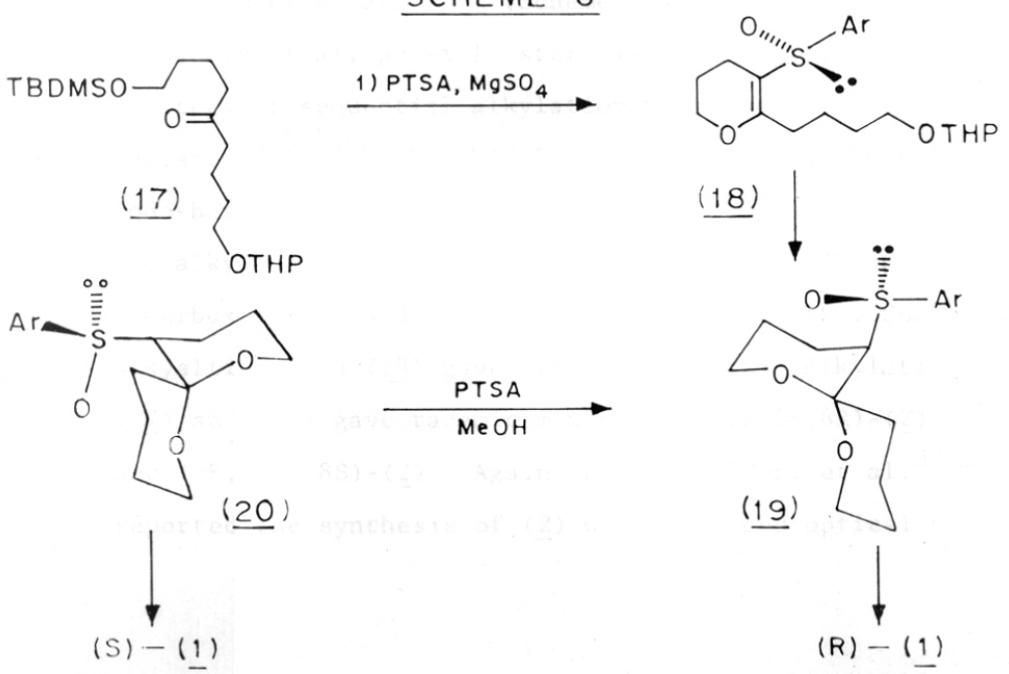


(11) (12) (13)

SCHEME – 7

(14) (15) (16)

SCHEME – 8



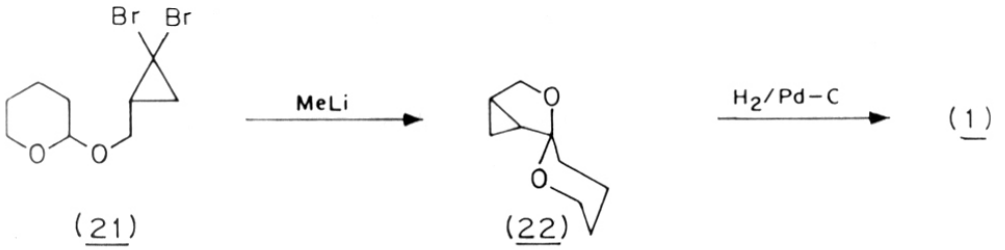
cyclisation of resulted product with NaH gave kinetically controlled product (19) containing axial substituted sulfoxide. Treatment of (19) with pTSA in methanol gave the thermodynamically controlled product (20). Desulfurization of (19) and (20) gave R-(1) and S-(1) respectively.

Brinker et al.[29] (Scheme 9) in 1985 synthesized the compound (1) using reaction of methyl lithium on dibromo-cyclopropane derivative (21) to give (22). The compound (22) on hydrogenation gave (1) as one of the products.

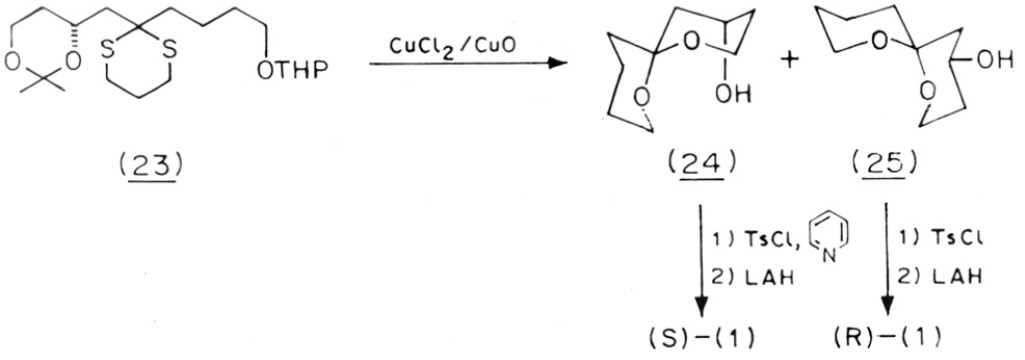
Redlich et al.[30] and K. Mori et al.[31] (Scheme 10) in 1984 reported the synthesis of R and S isoemrs of (1) based on separation of formed diastereomers (24) and (25) from the cyclisation reaction of thioketal derivative (23). Removal of hydroxy of the compound (24) and (25) gave 6S-(1) and 6R-(1) respectively.

K. Mori et al.[18,32] (Scheme 11) in 1981 reported the synthesis of all possible stereoisomers of (2) using strategy of sequential alkylation of methyl aceto-acetate (26) with the chiral 3-tetrahydropyramyloxy-1-iodo-butanes (27) and (28). Thus the compound (26) was alkylated twice with (27) to get (29), which on decarboxylation and cyclisation gave (2S,6R,8S). Similarly alkyaltion with (28) gave (2R, 6S, 8R)-(2). Alkylation with (27) and (28) gave racemic mixture of (2S,6S,8R)-(2) and (2R, 6R, 8S)-(2). Again in 1986 K. Mori et al.[33] reported the synthesis of (2) with enhanced optical purity

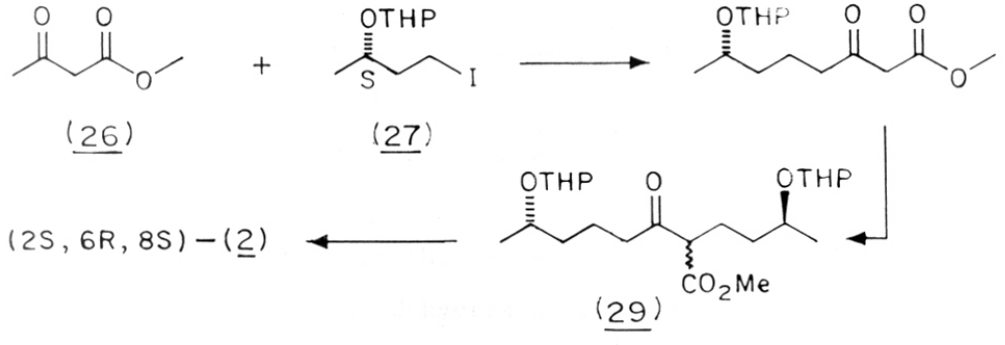
SCHEME – 9

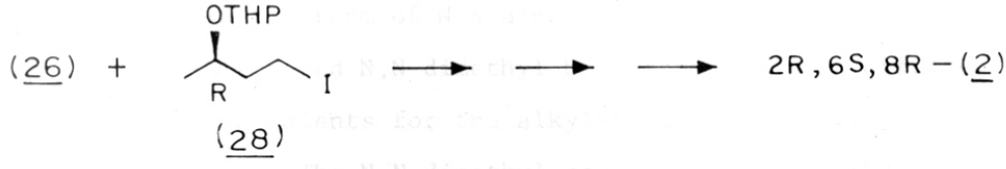


SCHEME – 10



SCHEME – 11





(26) + (27) + (28) → → → (2R, 6R, 8S)–(2)

+

(2S, 6S, 8R)–(2)

by modifying their earlier synthesis[34]. They worked out the synthesis with 100% ee starting materials.

Kitching et al.[34] (Scheme 12) in 1986 reported the synthesis of spiroacetals using the strategy of oxymercuration and cyclisation of dienones. Thus dienone (30) gave dimercury complex (31), which on cyclisation and reductive removal of mercury gave diastereomers of (2).

Oxymercuration strategy was also used by Giese et al.[35] in 1987 to synthesize (2) along with other pheromones having acetal functional group.

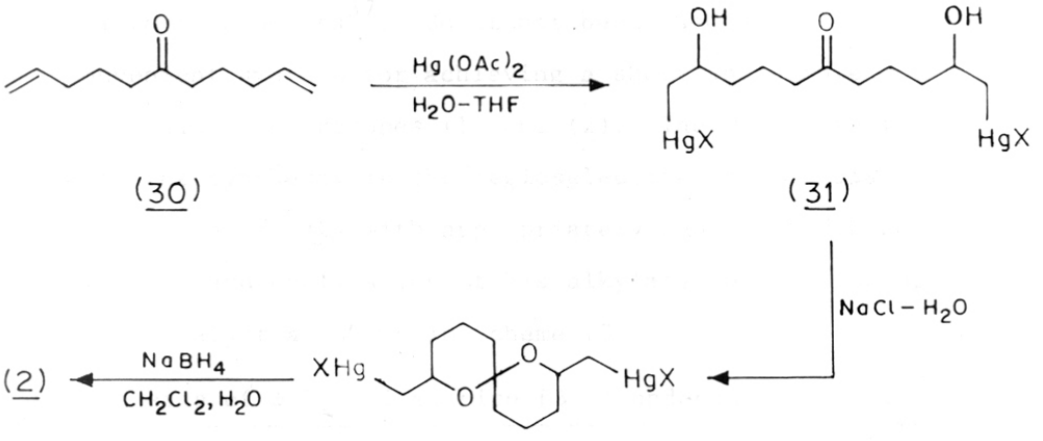
PRESENT WORK

The synthesis of insect pheromones (1) and (2) has attracted the attention of many groups and a number of syntheses have been reported[20-36] because of their practical applicability. A very frequently used strategy for the synthesis of 1,7- dioxaspiro[5,5] undecane system is to build up 1,9-dihydroxy-nonan-5-one system and cyclise it in in acidic medium.

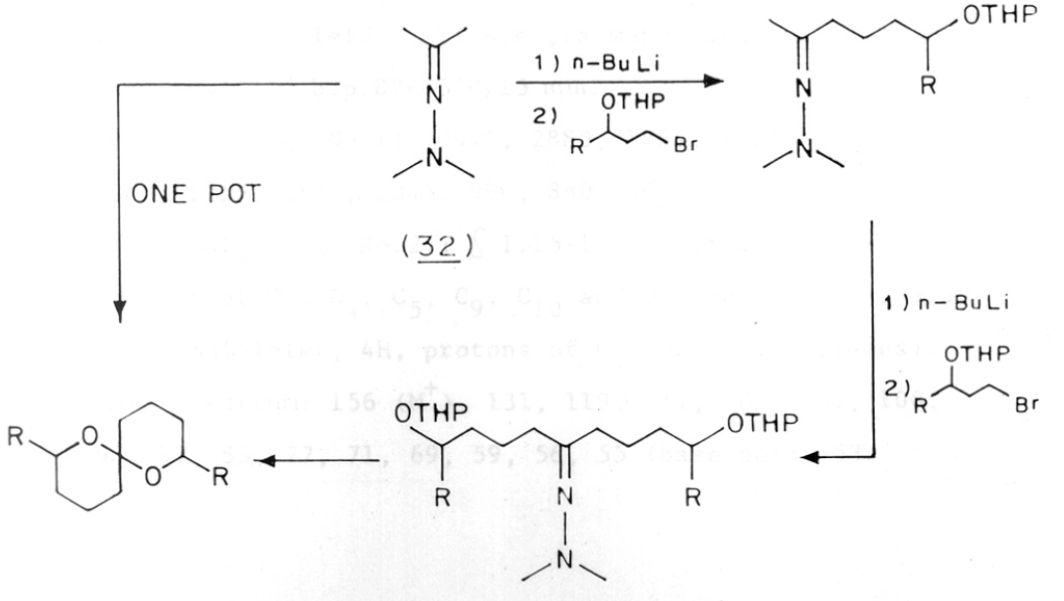
The strategy in the present synthesis also involves construction of 1,9-dihydroxynonan-5-one system in which keto is in the form of N,N-dimethyl hydrazone.

α-Lithiated N,N-dimethyl hydrazones serve as efficient enolate equivalents for the alkylation of carbonyl compounds[36]. The N,N-dimethyl acetone hydrazone (32)

SCHEME-12



SCHEME-13



exhibits regioselectivity towards formation of bis alkylated products[37]. So it has been used as a convenient synthon for achieving a short and simple synthesis of pheromones (1) and (2). The key step in both the syntheses is the regioselective one pot bis alkylation of (32) with appropriately substituted bromo-alcohols and cyclisation of bis alkylated product using acid catalyst as shown in Scheme 13.

Synthesis of ± 1,7-dioxaspiro [5,5] undecane (1) (Scheme 14)

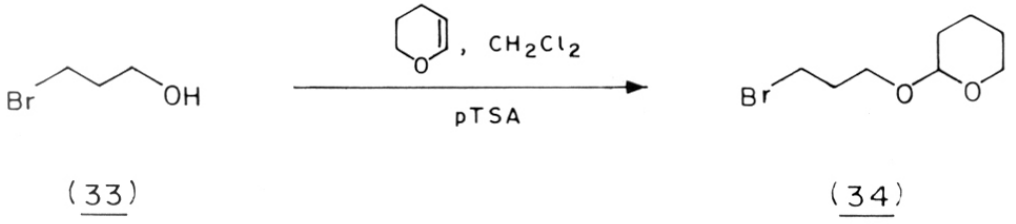
The lithium anion of (32), which was prepared by addition of one equivalent of n-BuLi at 0°C, was alkylated with one equivalent of 5-tetrahydropyranyloxy-1-bromo-propane (34) to get (35). To the same reaction mixture, addition of n-BuLi and (34) was repeated to get (36), which was then treated with conc. HCl at 0°C to get ± (1) in 65% yield. All spectra were identical with those reported[16,20], b.p.82-85°C/15 mm.

IR (neat, Fig. No.1): 2940, 2880, 1460, 1450, 1390, 1290, 1240, 1215, 1185, 1045, 990, 880, 800.

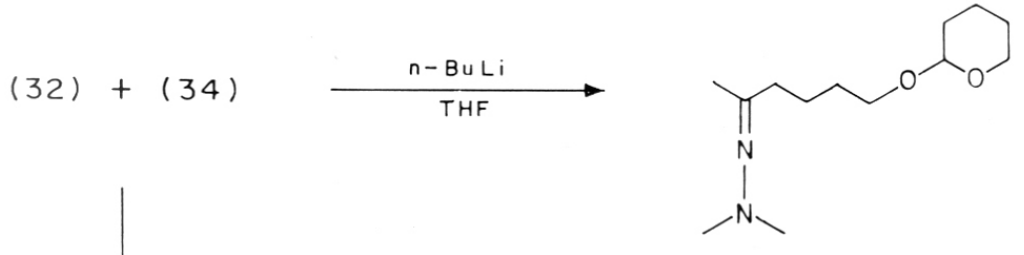
PMR ($CDCl_3$, Fig. No.2): δ 1.15-1.90 (multiplet, 12H, protons of C_3, C_4, C_5, C_9, C_{10} and C_{11} methylenes), 3.35-3.75 (multiplet, 4H, protons of C_2 and C_8 methylenes).

Mass spectrum: 156 (M^+), 131, 119, 111, 105, 101, 100, 98, 91, 83, 77, 71, 69, 59, 56, 55 (base peak) 53.

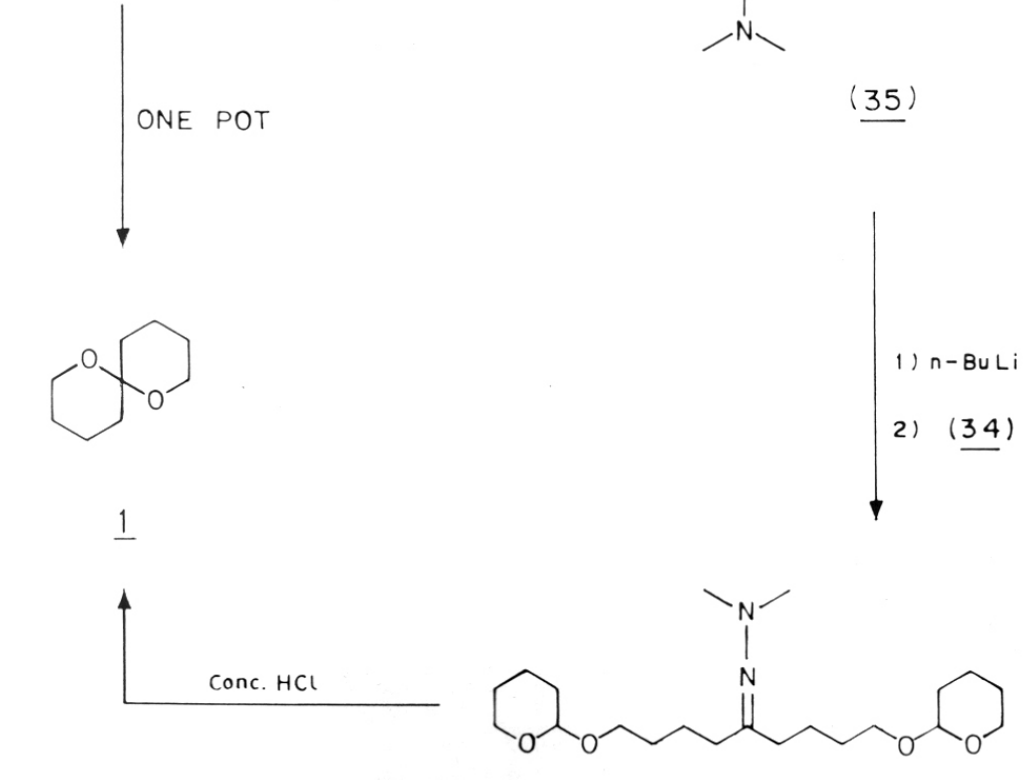
SCHEME - 14



(33) (34)



(35)



(36)

Analysis: Calculated for $C_9H_{16}O_2$: C, 69.19; H, 10.32

Found : C, 69.23; H, 10.30.

The intermediates (35) and (36) can be isolated and characterised.

Compound (35)

IR (neat): 2960, 2880, 1650 (characteristic peak for C=N-stretching), 1450, 1370, 1210, 1130, 1075, 1040, 880.

PMR (CCl_4): δ1.06 - 1.70 (multiplet, 5 x CH_2, 10H), 1.83 (singlet for CH_3-C=N-, 3H), 1.17 - 2.40 (multiplet includes peaks for $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>$N- and multiplet for -$CH_2$-C=N-), 3.06 - 3.93 (multiplet for 2 x CH_2, adjacent to oxygen) and 4.30-4.50 (broad peak for tetrahydropyranyl proton linked to two oxygens, 1H).

Compound (36)

IR (neat): 2940, 2860, 1625 (characteristic peak for C=N-stretching), 1460, 1450, 1440, 1350, 1200, 1140, 1095, 1035, 905, 870.

PMR ($CDCl_3$): δ1.26 - 2.04 (multiplet for 10 x CH_2, 20H), 2.11 - 2.66 (multiplet includes peak of $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>$N- and multiplet for -$CH_2$-$\begin{matrix}C\\CH_2\end{matrix}$=N-), 3.22 - 4.09 (multiplet for 4 x CH_2, linked to oxygen), 4.51 - 4.64 (broad peak for two methine protons linked in between two oxygens).

Mss spectrum: 384 (M^+), 299, 283, 215, 199, 172, 157, 138, 128, 110, 97, 85 (base peak) 82, 67, 59.

Analysis: Calculated for $C_{21}H_{40}N_2O_4$: C, 65.59; H, 10.48; N, 7.29
Found : C, 65.65; H, 10.43; N, 7.32.

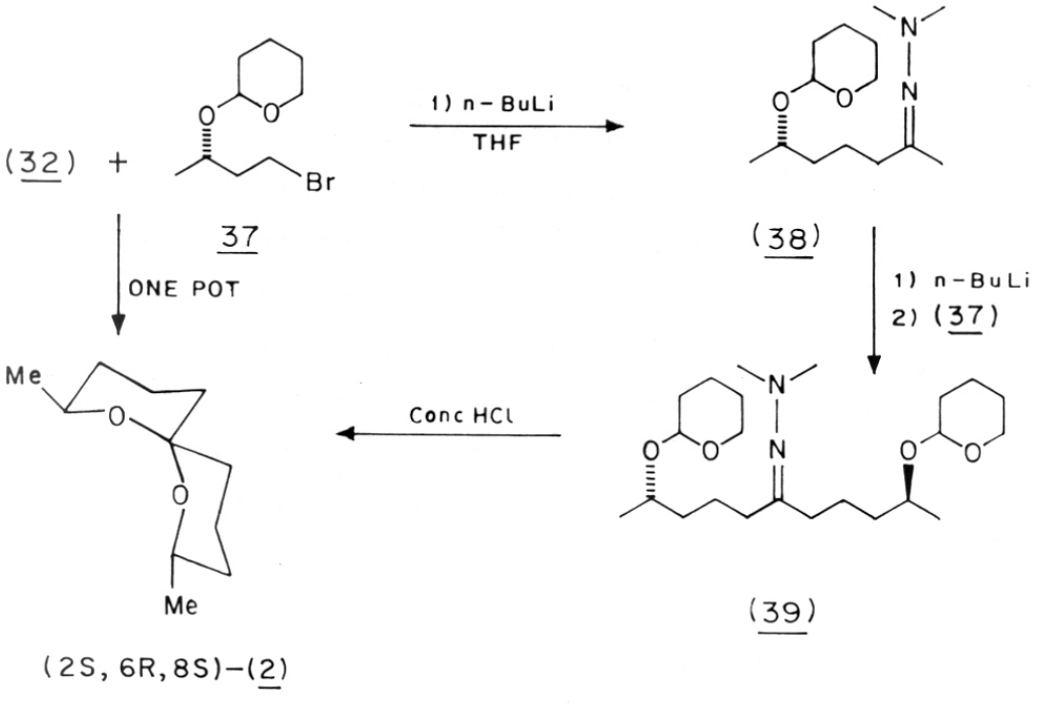
3-Tetrahydropyranyl oxy-1-bromo-propane (34) was prepared (Scheme 14) from 3-bromo propan-1-ol (33) by adding dihydropyran to it in presence of paratoluene sulfonic acid (catalytic amount).

Synthesis of (2S, 6R, 8S) 2,8-dimethyl 1,7-dioxaspiro [5,5] undecane (2)

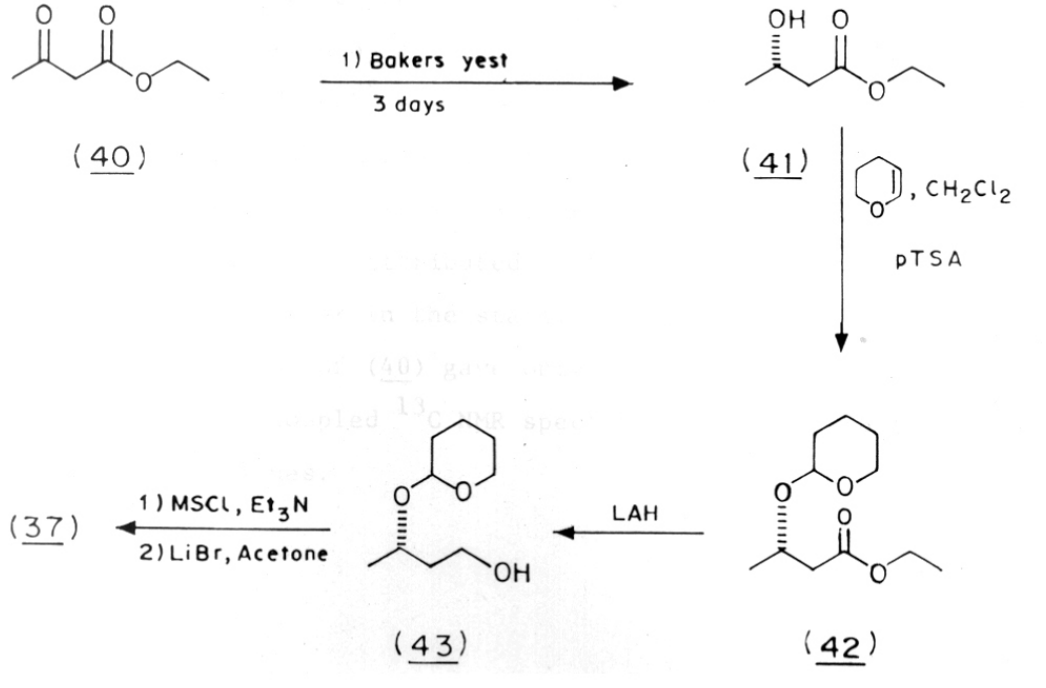
The synthesis of (2) also involves the one pot successive bis alkylations (Scheme 15) of (32) with 3S isomer of 3-tetrahydropyranyloxy-1-bromobutane (37).

The compound 3S-(37) was prepared in 4 steps (Scheme 16) starting from ethyl acetoacetate (40). S-(+)-3-hydroxy-butanoate (41) was obtained by the reduction of ethyl aceto-acetate (40) with baker's yeast. This reaction was previously reported by many research groups[38-41]. They calculated optical purity of S-(41) by the NMR and GLC analysis of its (S)-(-)-α-methoxy-α-trifluoromethyl phenyl acetic acid (MTPA) ester. Meyers et al.[41] found that S-(41) with $[\alpha]_D^{23}$(+) 41.7 in $CHCl_3$ was 97% optically pure. In our experiment optical purity of S-(41) obtained by yeast reduction was ranging from 86% to 92% (showing

SCHEME – 15



SCHEME –16



optical rotation ranging from $[\alpha]_D^{28}$ 32.7° to 37.4° in $CHCl_3$). The best batch which has $[\alpha]_D^{28}$ (+) 37.4° (C=1.10, $CHCl_3$) was utilised for further work.

The compound S(+)(41) was reacted with dihydropyran in methylene chloride at 0°C using catalytic amount of PTS acid to give (42), which on LAH reduction in ether afforded hydroxy compound (43)[18].

The (3S)-3-tetrahydropyranyloxybutan-1-ol (43) was reacted with mesyl chloride and triethylamine in CH_2Cl_2 to form mesylate, which on reaction with LiBr in acetone at 0°C gave (3S)-3-tetrahydropyranyloxy-1-bromo-butane (37) in quantitative yield.

In the final step, synthesis of (2S, 6R, 8S) (2) was achieved by one pot successive bis alkylations (Scheme 15) of (32) with 3S-(37) using n-BuLi as base [reaction sequence goes via the intermediates (38) and (39)] and followed by cyclisation with conc. HCl. The product showed $[\alpha]_D^{28}$ = (-) 50.9 (c = 1.20, n-pentane). Kenji Mori et al.[33] reported the rotation of 2S,6R,8S-(2) as $[\alpha]_D^{21}$ = (-) 56.0 (c = 1.40) n-pentane). The variation in the rotation is attributed to the presence of small amount of R isomer in the starting compound (41) [Baker's Yeast reduction of (40) gave only 92% optically pure S-(41)]. Decoupled ^{13}C NMR spectrum of 2S, 6R, 86-(2) showed six lines.

^{13}C NMR ($CDCl_3$, Fig. No.5); 95.98, 64.80, 35.09, 32.71, 21.68, 18.80.

Kenji Mori et al.[33] reported values;

^{13}C NMR (C_6D_6): 96.06, 65.16, 35.70, 33.70, 22.22, 19.37.

A small difference in the δ values can be attributed to the solvent effect.

All other spectral data were identical with those reported.

IR (neat, Fig. No.3): 2935, 2865, 1450, 1390, 1285, 1230, 1210, 1190, 1130, 1100, 1080, 1040, 1000, 960, 900, 840, 800.

PMR ($CDCl_3$, Fig. No.4): δ 0.82-2.17 (spread out multiplet for 12H, protons of C_3, C_4, C_5, C_9, C_{10} and C_{11} methylenes), 1.13 (doublet, J=7 Hz, for C_2 and C_8 methyl protons, 6H), 3.51-3.91 (multiplet for C_2 and C_8 methine protons, 2H).

Mass spectrum: 184 (M^{+}), 169, 151, 140, 125, 115 (base peak), 114, 112, 97, 83, 73, 69.

Analysis: Calculated for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94

Found: C, 71.71; H, 10.91.

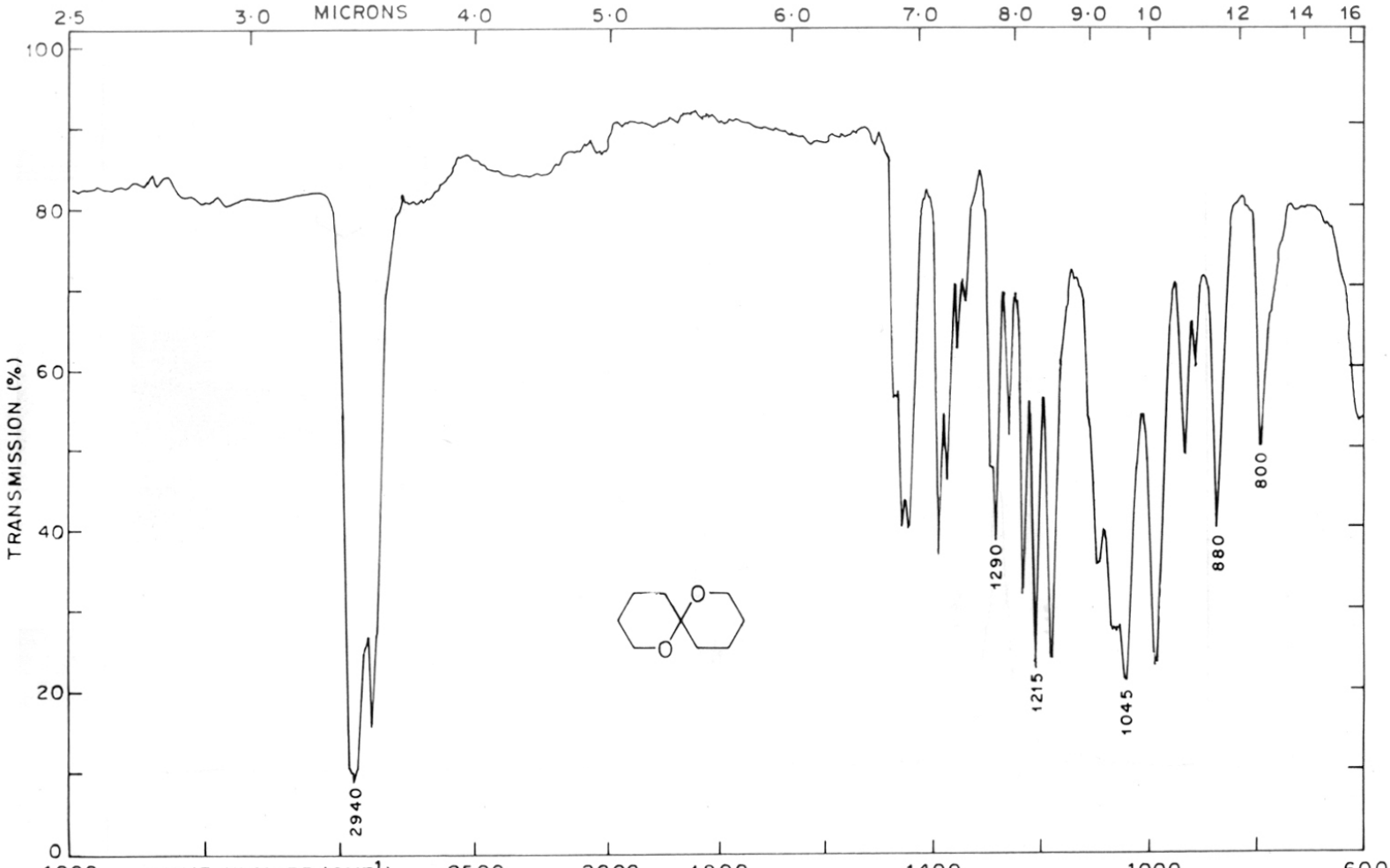


FIG. 1. IR (NEAT) SPECTRUM OF 1,7-DIOXASPIRO [5,5] UNDECANE (1)

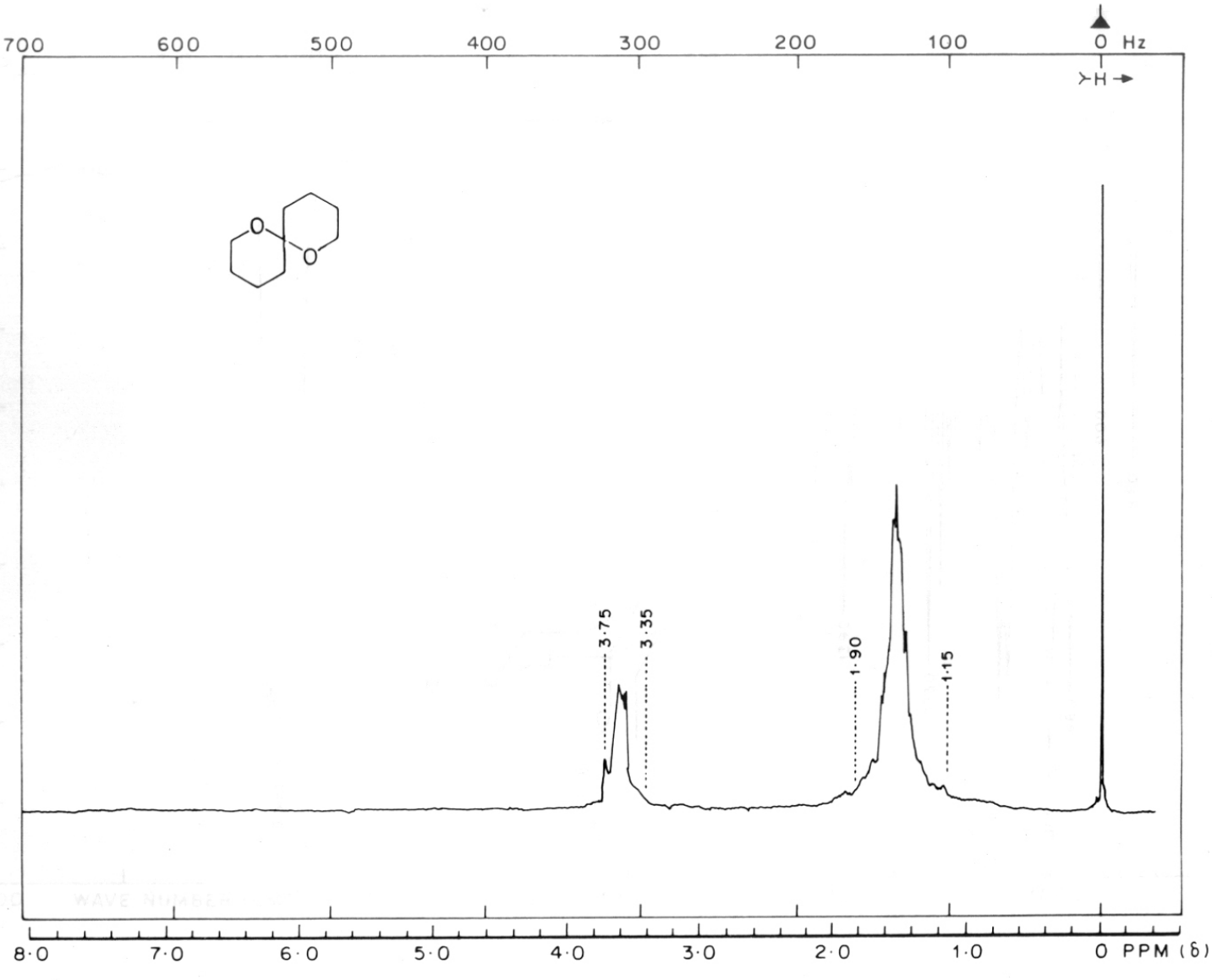


FIG. 2. PMR SPECTRUM OF 1,7-DIOXASPIRO [5,5] UNDECANE (1) IN $CDCl_3$

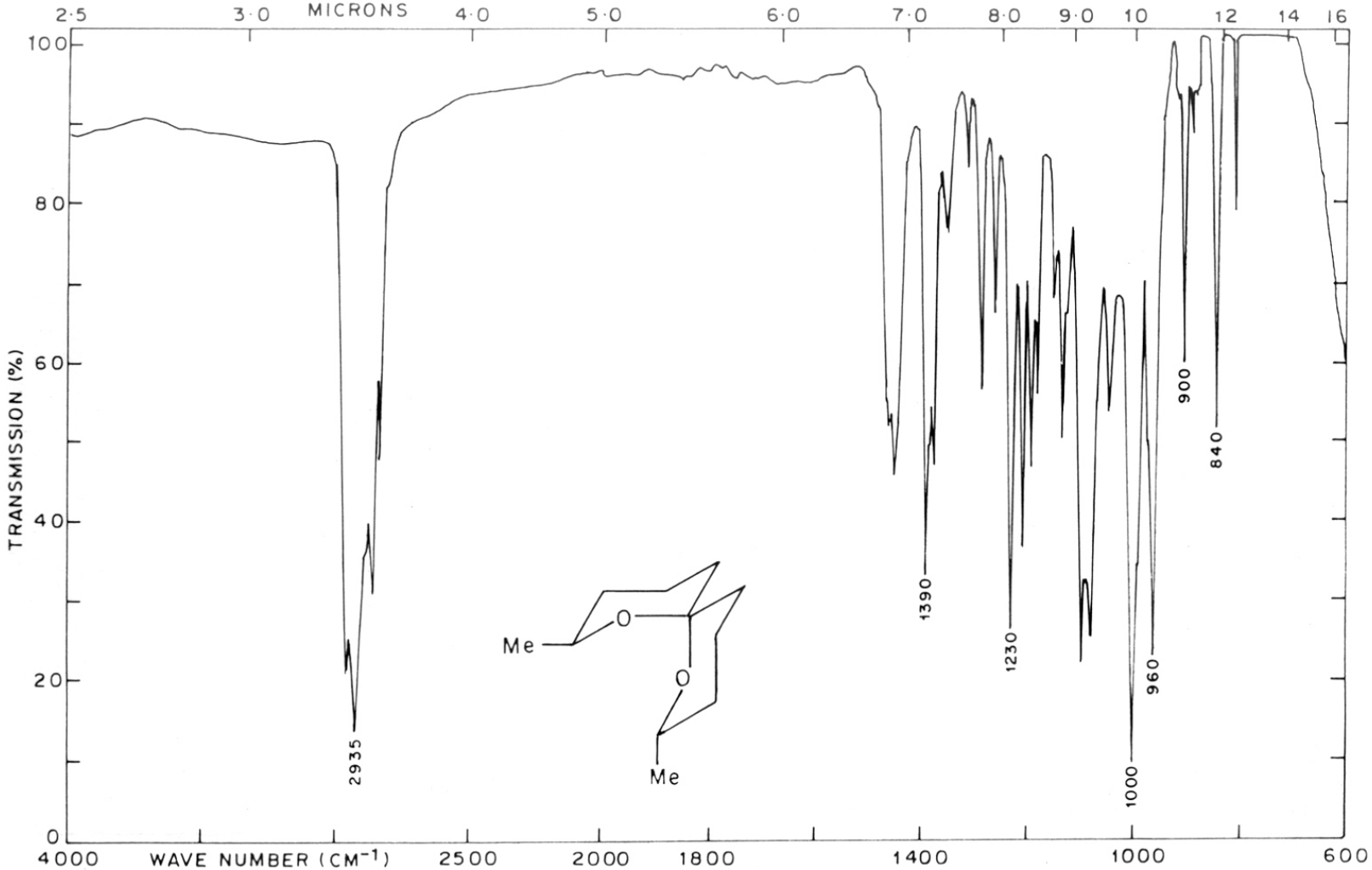


FIG. 3. IR (NEAT) SPECTRUM OF (2S, 6R, 8S)-2,8-DIMETHYL-1,7-DIOXASPIRO [5, 5] UNDECANE (2)

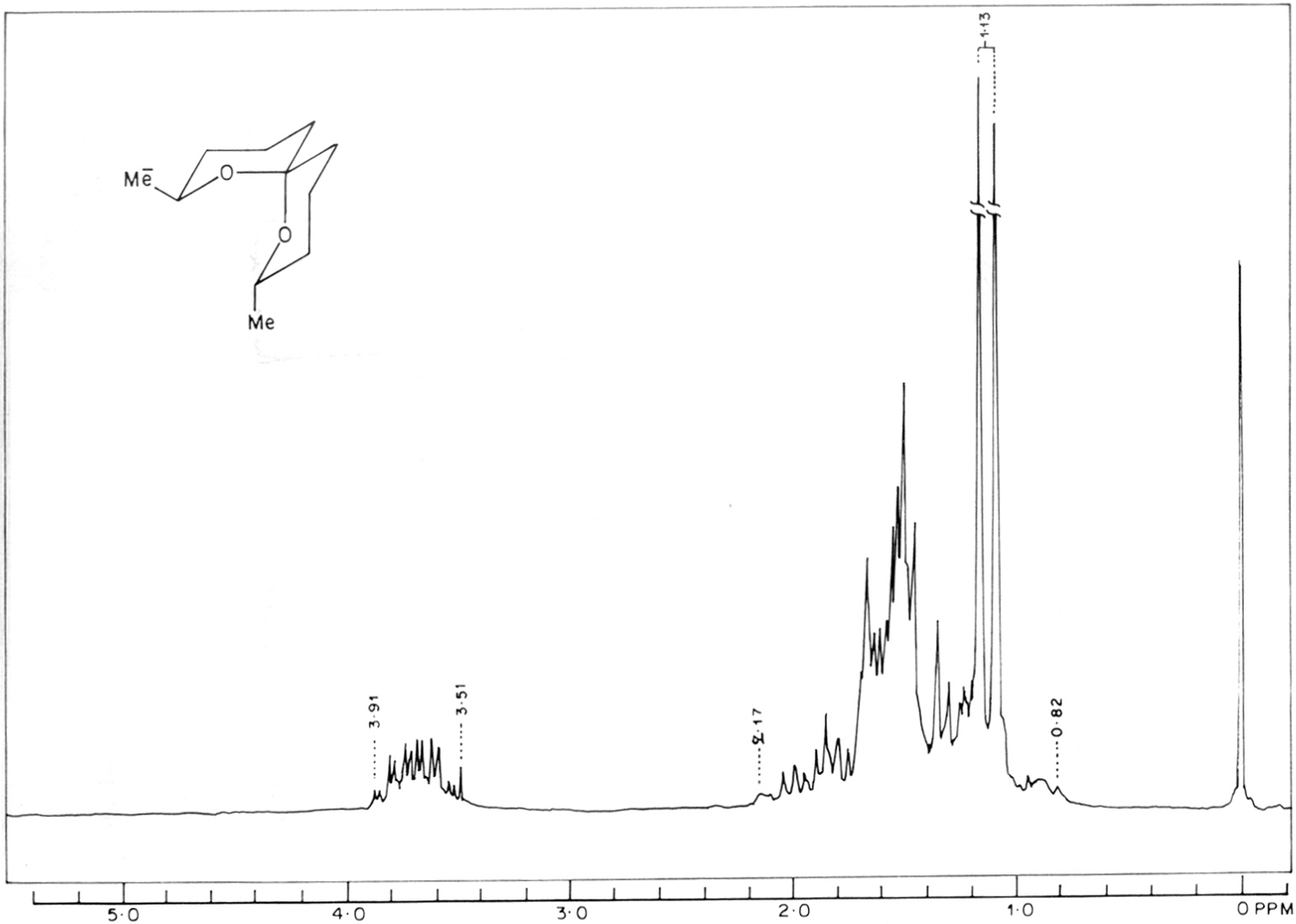


FIG. 4. PMR SPECTRUM OF (2S, 6R, 8S)-2,8-DIMETHYL-1,7-DIOXASPIRO [5, 5] UNDECANE (2) IN $CDCl_3$

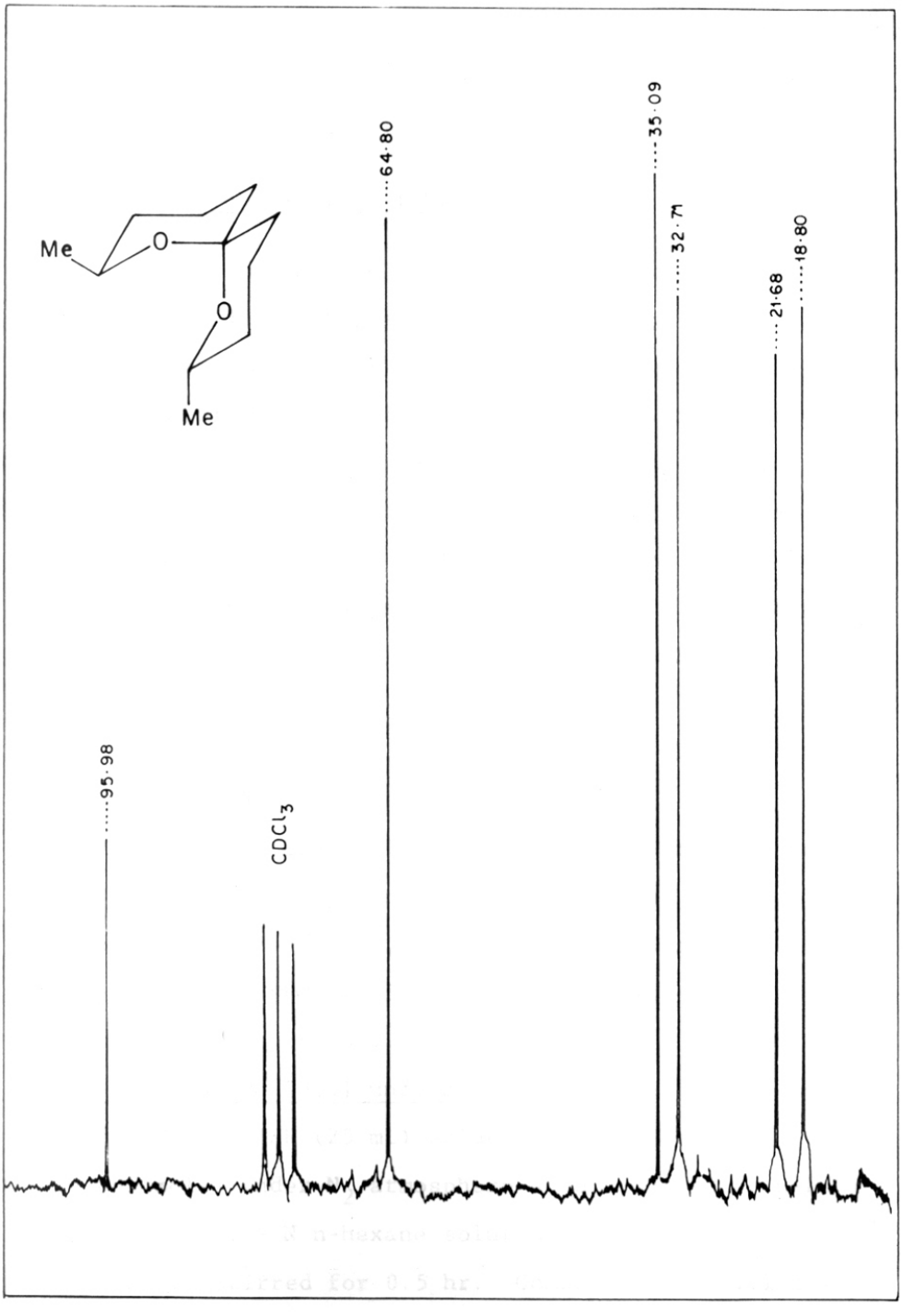


FIG. 5. ^{13}C NMR SPECTRUM OF (2S, 6R, 8S)-2,8-DIMETHYL-1,7-DIOXASPIRO [5, 5] UNDECANE (2)

EXPERIMENTAL

3-Tetrahydropyranyloxy-1-bromopropane (34)

To an ice cooled solution of bromopropanol (33) (1.39 gms, 0.01 mole) and PTS acid (15 mg) in dry dichloromethane (40 ml) was added, dihydropyran (1.0 g, 0.012 mole) and stirred for 2 hrs at room temperature. The reaction mixture was washed with 5% $NaHCO_3$ solution, followed by water and brine. The organic layer was dried over Na_2SO_4 and evaporated to give crude (34). This was chromatographed (silica gel, 10%, ethylacetate in pet.ether as eluent) to give (34) in 86% yield (1.91 g).

IR (neat): 2980, 2900 , 1450, 1360, 1210, 1145, 1130, 1090, 1040, 995, 880.

PMR ($CDCl_3$): δ 1.38-1.93 (m, 6H, three methylene protons of tetrahydropyranyl group), 1.97-2.31 (m, 2H, C_2 methylene protons), 3.38-4.09 (m, 6H, methylene protons linked to oxygens and bromine), 4.53-4.71 (broad peak, 1H, tetrahydropyranyl methine proton).

1,7-Dioxaspiro [5,5] undecane (1)

To the THF (25 ml) solution of (32) (0.50 g, 0.005 mole) under N_2 atmosphere at 0°C, was added n-BuLi (3.2 ml of 1.9 N n-hexane solution, 0.006 mole) with syringe. Stirred for 0.5 hr. Compound (34) (1.115 g,

0.005 mole) was added and stirred for 2 hours at room temeprature. The reaction mixture was again cooled to 0°C and n-BuLi (0.006 mole) was added. After keeping for 0.5 hr, compound (34) (1.115 g, 0.005 mole) was added and stirred for 2 hrs at room temeprature. Then conc.HCl (2 ml) was added and stirred overnight. Reaction mixture was neutralised with 5% $NaHCO_3$ and diluted with excess of water, extracted it with ether. Ether layer was washed with saturated NH_4Cl, dried, evaporated and distilled to get (1) in 65% yield (0.507 g).

(2S, 6R, 8S)-2,8-Dimethyl-1,7-dioxo spiro [5,5] undecane (2)

The N,N-dimethyl acetone hdyrazone (32) (0.5 g, 0.005 mole) was bis alkylated as above with (3S)-3-tetrahydropyranyloxy-1-bromobutane (37) (1.24 g + 1.24 g, 0.005 + 0.005 mole). The dialkylated product was cyclised with conc. HCl (2 ml) and reaction mixture was worked up and distilled in usual manner to get (2) in 26% yield (0.239 g), b.p.150-152°C.

Ethyl (S)-(+)-3-hydroxybutanoate (41)

Dry baker's yeast (20 g) was dispersed in water (350 ml) and sucrose (50 g) was added to it. The flask was shaken at 25°C-30°C for 30 minutes. When brisk fermentation took place, ethyl acetoacetate (40)

(3.5 gm, 0.027 mole) was added and shaking continued for 3 days. Ether (50 ml) was added to the fermentation broth and shaken for 10 minutes. The fermentation broth was filtered through celite. The filtrate was washed two times with ether (50 ml + 50 ml). The ether layer was separated and washed with water, brine, dried over Na_2SO_4 and evaporated to give 2.9 g of crude (41). This was chromatographed (silica gel 20% ethyl acetate in pet.ether as eluent) to give (41) in 51% yield (1.81 g) $[\alpha]_D^{28}$ = (+) 37.8 (c=1.12, $CHCl_3$).

IR (neat): 3440 (hydroxyl), 2980, 2940, 1735 (ester carbonyl stretching), 1465, 1375, 1300, 1185, 1090, 1030, 950.

PMR (CCl_4): 1.17 (d, J=7 Hz, 3H, for C_4 methyl protons), 1.23 (t, J=6 Hz, 3H, for ester methyl protons), 2.32 (d, J=6 Hz, 2H, for C_2 methylene protons), 3.37 (s, 1H, D_2 exchangeable proton), 4.03 (q, J=7 Hz, 2H, for ester methylene proton), 3.86-4.33 (m, 1H, for C_3 methine proton).

Analysis: Calculated for $C_6H_{12}O_3$: C, 54.53; H, 9.15

Found : C, 54.58; H, 9.12.

Compound (42)

To an ice cooled solution of (41) (1.6 g, 0.012 mole) and PTS acid (10 mg) in dry dichloromethane (50 ml) was added, dihydropyran (1.25 g, 0.015 mole) and stirred for 3 hrs at 0°C. Reaction mixture was then washed with

5% $NaHCO_3$ solution, water, brine and dried. Then the organic layer was evaporated and chromatographed (silica gel, 15% ethyl acetate in pet.ether as eluent) to give (42) in 87% yield (2.25 g).

IR (neat): 2960, 2880, 1740 (ester carbonyl), 1460, 1450, 1380, 1360, 1250, 1210, 1130, 1080, 1040, 970, 820, 815.

PMR ($CDCl_3$): δ 1.06-1.87 (m, 12H), 2.12-2.81 (m, 2H, for C_2methylene protons) 3.28-4.34 (m, 5H), 4.53-5.0 (broad peak, 1H).

(3S)-3-Tetrahydropyranyloxy-butan-1-ol (43)

To a suspension of LAH (0.38 g, 0.01 mole) in dry ether (50 ml) at 0°C was added (42) (2.16 g, 0.01 mole) and stirred for 2 hrs at room temperature. Then the reaction mixture was refluxed for 0.5 hr to ensure the completion of reduction. It was cooled to 0°C and unreacted LAH was destroyed by careful addition of MeOH (5 ml) and followed by water (5 ml). The reaction mixture then filtered and organic layer was washed with water, brine, dried, evaporated and distilled to get (43) in 85% yield (1.48 g), b.p.85-90°/1 mm.

IR (neat): 3440 (hydroxyl), 2970, 2900, 1460, 1450, 1360, 1210, 1150, 1130, 1035, 910, 870, 820.

PMR ($CDCl_3$): δ1.09-2.21 (m, 11H, two doublets for C_4 methyl protons, multiplet for C_2 methylene and three methylene protons of tetrahydropyranyl), 3.25-4.16 (m, 5H),

4.43-4.73 (broad peak, 1H, methine protons linked in between two oxygen).

Analysis: Calculated for $C_9H_{18}O_3$: C, 62.04; H, 10.41

Found: C, 62.09; H, 10.39

(3S)-3-Tetrahydropyranyloxy-1-bromobutane (37)

To an ice cooled solution of (43) (1.74 g, 0.01 mole) and triethylamine (1 ml) in dry dichloromethane (30 ml) was added, methanesulfonylchloride (1.35 g, 0.018 mole) at 0°C and stirred for 5 hrs. Then reaction mixture was washed with water, cold dil. HCl, followed by 5% $NaHCO_3$ solution and brine. The organic layer was dried and evaporated to give mesylate of (43). Mesylate was dissolved in dry acetone (30 ml) and anhydrous LiBr (1.30 g, 0.015 mole) was added to it. The reaction mixture was stirred for 5 hrs. Acetone was removed under reduced pressure and product was extracted with ether. Ether layer was washed with water, brine, and dried over Na_2SO_4. Ether evaporated and crude was chromatographed (silica gel 10% ethyl acetate in pet.ether) to get (37) in 72% yield (1.70 g).

IR (neat): 2940, 2895, 1450, 1380, 1270, 1210, 1140, 1080, 1040, 1030, 995, 910, 870.

PMR ($CDCl_3$): δ1.09-2.21 (m, 11H, for C_4 methyl proton, C_2 methylene protons and three methylene protons of tetra-

hydropyranyl), 3.25-4.25 (m, 5H, for C_1 methylene protons, C_3 methine proton and $-CH_2-O$ of tetrahydropyranyl), 4.56-4.78 (broad peak, 1H).

REFERENCES

1. W.C. Campbell, M.H. Fisher, E.O. Stapley, G. Alberg-Schonberg and T.A. Jacob, Science, 221, 823 (1983).

2. H. Mishima, M. Kurabayashi, C. Tamura, S. Sato, H. Kuwano and A. Saito, Tetrahedron Lett., 711 (1975).

3. M.D. Chaney, P.V. Demarco, N.D. Jones and J.L. Occolowitz, J.Amer.Chem.Soc., 96, 1932 (1974).

4. H. Kinashi, N. Otake, H. Yonehara, S. Sato and Y. Saito, Tetrahedron Lett., 4955 (1973).

5. J.L. Occolowitz, D.H. Berq, M. Debono and R.L.Hamill, Biomed.Mass.Spectrosc., 3, 272 (1976).

6. C. Keller-Juslen, H.D. King, M. Kuhn, H.R. Loosli and A. Von wartburg, J. Antibiotics, 31, 820 (1978).

7. K. Tachibana, P.J. Scheuer, Y. Tsukitani, H.Kikuchi, D.V. Engen, J. Clardy, Y. Gopichand and F.Schmitz, J.Amer.Chem.Soc., 103, 2469 (1981).

8. F.J. Schmitz, R.S. Prasad, Y. Gopichand, M.B. Hossain and D. Van der Helm, J.Amer.Chem.Soc., 103, 2467 (1981).

9. Y. Kato and P.J. Scheuer, J.Amer.Chem.Soc., 96, 2245 (1974).

10. M. Von Glehn, R. Norrestam, P. Kierkegaard, L. Maron and L. Ernster, F.E.B.S.Lett., 20, 267 (1972).

11. D. Wuthier, W. Keller-Schierlein and B. Wahl, Helv.Chim.Acta., 67, 1208 (1984).

12. W.C. Hutton, N.J. Phillips, D.W. Graden and D.G. Lynn, J.Chem.Soc.Chem.Comm., 864 (1983).

13. W. Franke, V. Heemann, B. Gerken, J.A.A. Renwick and J.P. Vite, Naturwissenschaften 64, 590 (1977).

14. W. Franke, G. Hindorf and W. Reith, Naturwissenschoften, 66, 618 (1979).

15. W. Francke, W. Reith, G. Bergstrom and J. Tengo, Naturwissenschaften, 67, 149 (1980).

16. R. Baker, R. Herbert, P.E. Howse, O.T. Jones, W. Francke and W. Reith, J.Chem.Soc.Chem.Comm., 52 (1980).

17. W. Kitching, J.A. Lewis, M.T. Fletcher, R.A.I.Drew, C.J. Moore and W. Francke, J.Chem.Soc.Chem.Commun., 853 (1986).

18. K. Mori and K. Tanida, Tetrahedron, 37, 3221 (1981).

19. H. Stetter and H. Rauhut, Chem.Ber., 91, 2543 (1958).

20. V.M. Micovic, S. Stojcic, M. Bralovic, S. Mladenovic, D. Jeremic and S. Stefanovic, Tetrahedron, 25, 985 (1969).

21. P. Deslongchamps, D.D. Rowan, N. Pothier, T. Sauve and J.K. Saunders, Can.J.Chem., 59, 1105 (1981).

22. R. Baker, R.H. Herbert and A.H. Parton, J.Chem.Soc. Chem.Comm., 601 (1982).

23. J.B. Ousset, C. Mioskowski, Y.L. Yang and J.R.Falck, Tetrahedron Lett., 25, 5903 (1984).

24. S.V. Ley and B. Lygo, Tetrahedron Lett., 25, 113 (1984).

25. A. Amouroux, Heterocycles, 22, 1489 (1984).

26. R.E. Ireland and H. Habich, Tetrahedron Lett., 21, 1389 (1980).

27. R.E. Ireland and H. Habich, Chem.Ber., 114, 1418 (1981).

28. C. Iwata, M. Fujita, K. Hattori, S. Uchida and T. Imanishi, Tetrahedron Lett., 26, 2221 (1985).

29. U.H. Brinker, A. Haghani and K. Goman, Angew.Chem.Int.Ed.Engl., 24, 230 (1985).

30. H. Redlich
Angew.Chem.Int.Ed.Engl., 23, 519 (1984).

31. K. Mori, T. Uematsu, H. Watanabe, K. Yanagi and M. Minobe, Tetrahedron Lett., 25, 3875 (1984).

32. K. Mori and K. Tanida, Heterocycles, 15(2), 1171 (1981).

33. K. Mori and H. Watanabe, Tetrahedron, 42(1), 295 (1986).

34. W. Kitching, J.A. Lewis, M.T. Fletcher, J.J.De Voss, R.A.I. Drew and C.J. Moore, J.Chem.Soc.Chem.Comm., 855 (1986).

35. B. Giese, D. Bartmann and T. Hasskerl, Liebigs Ann.Chem., 5, 427 (1987).

36. E.J. Corey and D. Enders, Tetraheddron Lett., 3,11 (1976) and references cited therein.

37. G.B. Reddy and R.B. Mitra, Synth.Comm., 16(13), 1723 (1986) and references cited therein.

38. B.S. Deol, D.D. Ridley and G.W. Simpson, Aust.J.Chem., 29, 2459 (1976).

39. B. Seuring and D. Seebach, Helv.Chim.Acta., 60, 1175 (1977).

40. G. Franter, Helv.Chim.Acta., 62, 2825 (1979).

41. A.I. Meyers and R.A. Amos, J.Am.Chem.Soc., 102, 870 (1980).

CHAPTER III

SELECTIVE DEPROTECTION OF N,N-DIMETHYLHYDRAZONES AND SYNTHESIS OF PHEROMONES UTILISING THIS METHOD

Summary

This Chapter deals with selective oxidative deprotection of N,N-dimethylhydrazones (1 to 10) to corresponding carbonyl compounds (11 to 20).

Utilising this method as one of the steps, pheromones, Z-9-tetradecen-1-yl acetate (31) and Z-3,13-octadecadien-1-yl acetate (58) have been prepared.

INTRODUCTION

N,N-Dimethylhydrazone (DMH) derivatives of enolizable aldehydes and ketones can be metallated cleanely either by lithium diisopropylamide (LDA) in THF at 0°C or with n-butyl lithium in THF at -78°C[1,2,3]. These α-lithiated DMH's can serve as equivalent of enolate ions in synthesis[1] (discussed in Chapter 1 and 2). Hence N,N-dimethylhydrazones (DMH's) have been regarded as widely useful intermediates in natural product synthesis[4-7]. Due to the usefulness of DMH's in synthetic chemistry, there has been considerable interest in the oxidative cleavage (deprotection) of N,N-dimethylhydrazones. Selective oxidative deprotection method is important in organic synthesis[3], because total synthesis of many natural products deals with many other sensitive functional groups. In the past decade there has been tremendous interest in the regeneration of carbonyl compounds from N,N-dimethyl-hydrazones, which resulted in development of a number of methods.

The most widely used method is acid hydrolysis. Dilute HCl[8] peracetic acid[9] other mineral acids are also used in the process.

R.E. Erickson et al.[10] in 1969 developed a method for oxidative deprotection of hydrazones using ozonolysis.

In 1976 Corey et al.[1] reported a novel oxidative hydrolysis of DMH's using aq. sodium periodate at pH 7 (25°C). In the same year Corey et al.[11] developed two more methods using cupric acetate in THF and cupric chloride in a mixture of THF, water and phosphate buffer maintained at pH 7. Advantage of these three methods is that they can be executed at neutral conditions and can be used for selective deprotection of hydrazones in presence of other acid sensitive functionalities in the molecule.

Olah et al. reported 6 different methods for oxidative cleavage of N,N-dimethylhydrazones using organometallic complexes like $Co(III)F_3$[12], $NOBF_4$[13] WF_6[14], MoF_6[15], $MoOCl_3$[15] and UF_6[16].

Gawley et al.[17] reported the oxidative deprotection of DMH's with $BF_3.Et_2O$. The drawback of this procedure is that it is not selective to other acid sensitive functional groups like THP ethers and acetenoid protecting groups.

In 1984 P. Laszlo et al.[18] reported an efficient method for deprotection using less expensive clay-supported ferric nitrate (Clayfen). The reaction was very fast and gave corresponding carbonyl compounds in very good yields.

Quite recently (1986) Moriarty et al.[19] reported the cleavage of phenyl hydrazones with iodosobenzene

diacetate using neutral conditions to give the corresponding carbonyl compounds in fairly good yields.

PRESENT WORK

Present work deals with the selective oxidative cleavage of N,N-dimethylhydrazones with silica gel in THF and synthesis of two pheromones Z-(9)-tetradecen-1-yl acetate and 3,3-octadecadien-1-yl acetate using selective deprotection method as one of the steps.

Selective deprotection of N,N-dimethylhydrazones

There have been a number of important advances in the practical aspects of organic synthesis during the past ten years, and one of these is the use of polymer-bound reagents. The use of insoluble inorganic support for organic synthesis is well documented in literature[20]. One of the reagents used as solid support is silica gel[20]. Silica gel contains substantial amounts of water and retains water tenaciously even after drying. This suggest the presence of hydrates, or silicic acids and these in turn are almost certainly the supported reagents responsible for the organic reactions. Hudlicky[21], Kato et al.[22] and Bachi et al.[23] showed that silica gel can be used as acid catalyst. Conia et al.[24] showed that acidic wet silica gel is excellent medium for deacetalisation of acetals. Hojo et al.[25] used

silica gel/water/SO_2Cl_2 medium for dethioacetalisation of thioacetals. Silica gel is a versatile reagent which is used along with other reagents in the oxidation of nitro compounds and alcohols[26,27]. It is also used in hydroxylation and chlorination of aromatic compounds[28,29].

Now in the present work silica gel with moist THF was used for the selective oxidative deprotection of N,N-dimethylhydrazones (Scheme 1 and Table 1). As shown in Table 1 a number of N,N-dimethylhydrazones [compounds (1) to (10)] having different acid sensitive functionalities were treated with silica gel to get corresponding carbonyl Compounds [(11) to (20)]. The typical experimental procedure is as follows.

Compound (1) (0.384 g, 0.001 mole) dissolved in moist THF (10 ml THF and 1 ml water) and silica gel (3 g, mesh 60-120, Acme make, pH=6.8) was added to it. Reaction mixture (THF-silica gel slurry) was stirred for 3 hrs. at room temperature. Then reaction mixture was concentrated and loaded on column (1:20 ratio of compound to silica gel) and eluted with 15% ethyl acetate in pet.ether to get (2) in 74% yield (0.253 g).

Similar experimental procedure was followed for the compounds (2) to (10). In Table 1 reaction time and percentage yield (isolated) are given. The yields of the

TABLE-1: OXIDATIVE DEPROTECTION OF N,N-DIMETHYL HYDRAZONES

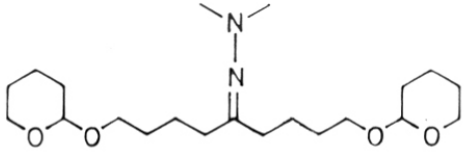
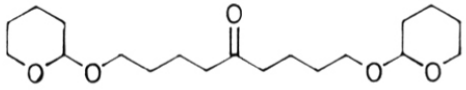
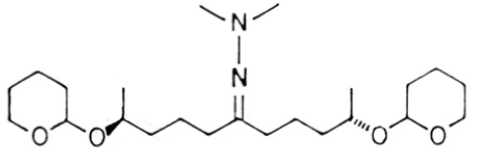
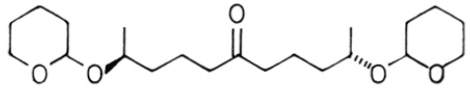
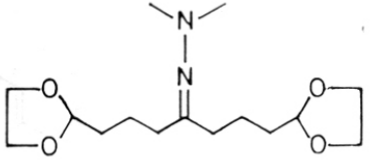
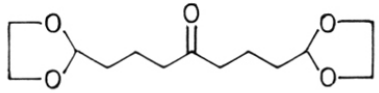
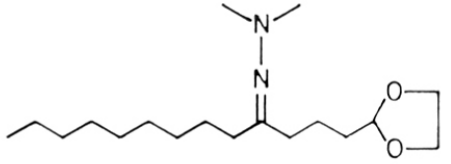
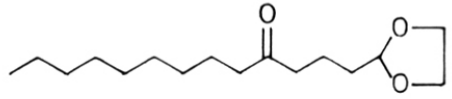
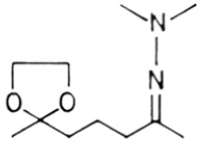
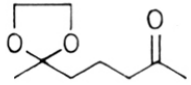
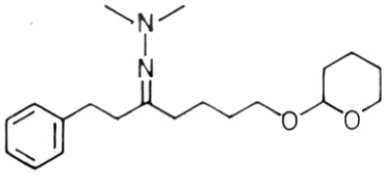
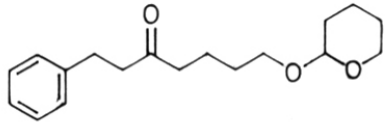
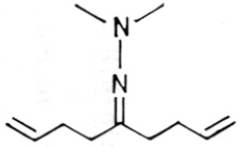
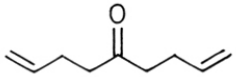
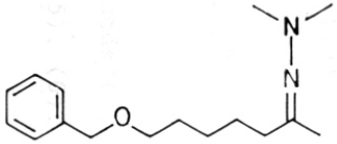
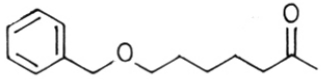
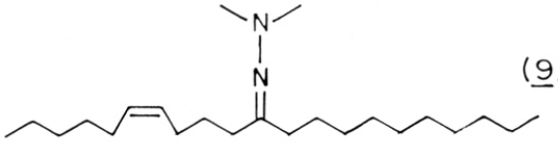
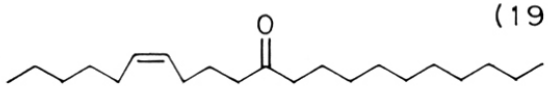
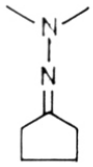
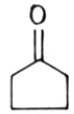
ENTRY	N,N-DIMETHYL HYDRAZONES	PRODUCT (CARBONYL COMPOUND)	TIME IN HOURS	YIELD (ISOLATED)
I	 (1)	 (11)	3	74 %
II	 (2)	 (12)	3·5	71 %
III	 (3)	 (13)	4	66 %
IV	 (4)	 (14)	4	60 %
V	 (5)	 (15)	4	61 %

TABLE-1 (Contd.)...

ENTRY	N, N-DIMETHYL HYDRAZONES	PRODUCT (CARBONYL COMPOUND)	TIME IN HOURS	YIELD (ISOLATED)
VI	 (6)	 (16)	3	65 %
VII	 (7)	 (17)	5	60 %
VIII	 (8)	 (18)	5	69 %
IX	 (9)	 (19)	4·5	75 %
X	 (10)	 (20)	10	20 %

products [(11) to (19)] were fairly good. Percentage of yield varied from 60 to 75%, except in the case of cyclopentanone hydrazone (10), where the yield was 20%. cycloalkanone hdyrazones were resistant to this reaction conditions. In case of the compound (10) reaction mixture was heated upto 60°C for 5 hrs. But there was no significant improvement in the yield (yield was around 30%).

Structure of the compounds (1 to 20) were assigned by their spectral/analytical data and is given in the experimental part.

There are three significant advantages of this method.

(1) Selective deprotection of hydrazones without affecting other acid sensitive functional groups like THP ether [compounds (1), (2) and (6)], acetonide protection [compounds (3), (4) and (5)] and 0-benzyl protection [compound (8)].

(2) Use of inexpensive reagents like silica gel. and (3) simple, mild reaction conditions and fairly good yields.

Preparation of N,N-dimethylhydrazones [(1) to (10)]

Preparation of the compounds (1) and (2) is reported in Chapter 2 and of compounds (9) and (10) in chapter 1. The compounds (3), (4), (5), (6), (7) and (8) are prepared

by alkylation (Scheme 2) of N,N-dimethylacetone-hydrazone (21).

Thus successive bis alkylations (Scheme 2) of (21) with 2-(2-bromoethyl)-1,3-dioxalane (22) gave (3) in 68% yield.

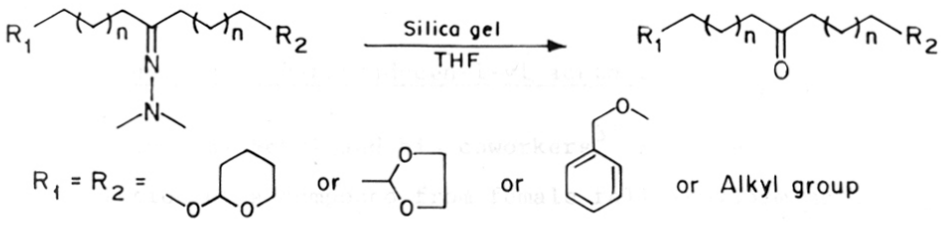
The compound (4) was prepared in 62% yield by alkylation (scheme 2) of (21) with n-octylbromide (23) and (22).

The compound (5) was prepared in 82% yield by alkylation (scheme 2) of (21) with 2-methyl-2-(2-bromo-ethyl)-1,3-dioxalane (24). Addition of dry HBr to the solution of methylvinylketone (25) in ethylene glycol gave the compound (24)[30].

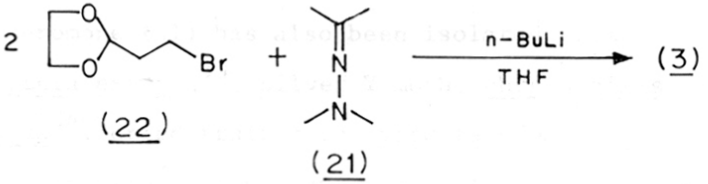
Successive bis alkylations (Scheme 2) of (21) with benzylbromide (26) and THP protected bromopropanol (27) gave compound (6). The compound (27) was prepared according to the procedure reported in Chapter 2. The compound (7) was prepared in 65% yield by successive bis alkylations (scheme 2) of (21) with allylbromide (28).

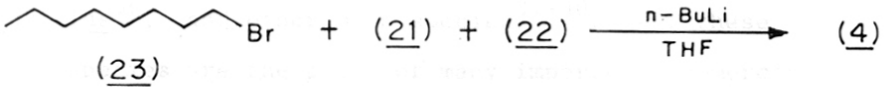
The compound (8) was prepared in 85% yield by alkyaltion (scheme 2) of (21) with the compound (29). The compound (30) on treatment with mesylchloride and Et_3N gave the mesylate, which on reaction with LiBr in acetone gave (29).

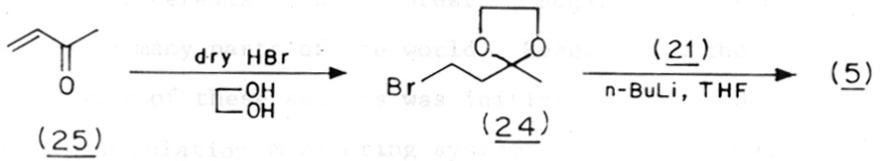
SCHEME-1

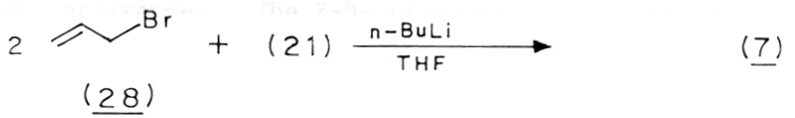


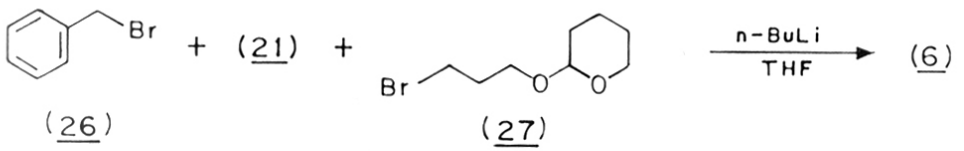
SCHEME-2

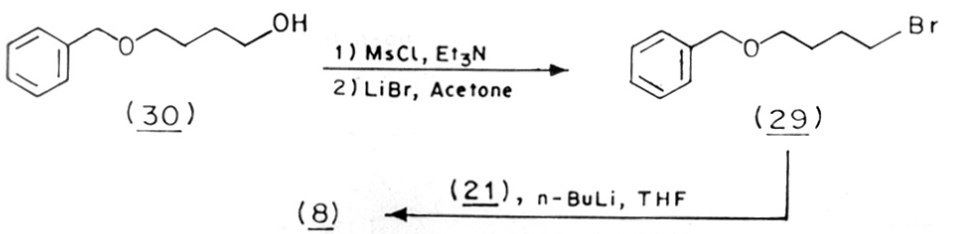










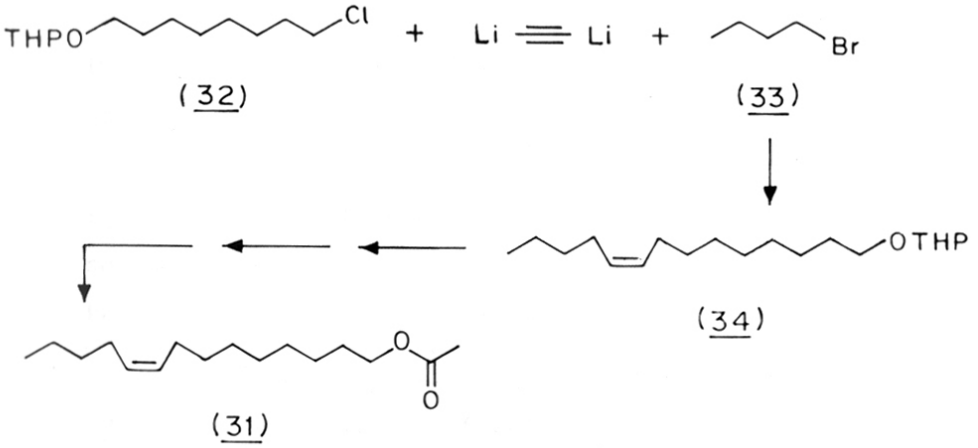


Synthesis of Z-9-tetradecen-1-yl acetate

In 1967 Sekul and his coworkers[31] reported isolation of a compound from female fall armyworm moth spodeptera frugiperda and identified it as Z-9-tetradecen--yl acetate (31) Later in 1973 Minks et al.[32] isolated (31) from two totricid moths, Adoxophyes orana and clepsis spectrana, as one of the pheromone components. The pheromone (31) has also been isolated from Spodoptera exempta[33], silver Y moth, chrysodeixis eriosoma[34], dried-fruit moth, vitulla edmandsae serratilineella[35], sugarcane stalk borer moth, chilo aurilius[36], and other moth species[37-40]. All these moth species are the pests of many important commercial crops like cereals[33], pine forest[40], sugarcane[36], tea crop[32] in many parts of the world. Research on the sex pheromones of these species was initiated to provide a potent population monitoring system and possible mating disruption programmes. The Z-9-tetradecen-1-yl acetate (31) proved to be a potent male attractant either alone or with a mixture of other acetates[31-40]. Because of its practical applicability in controlling the insect population many synthesis of (31) have been reported.

Warthen[41] (Scheme 3) has used the strategy of dialkylation of acetylene with THP ether of 8-chloro-1-octanol (32) and n-butylbromide (33) to get (34).

SCHEME-3

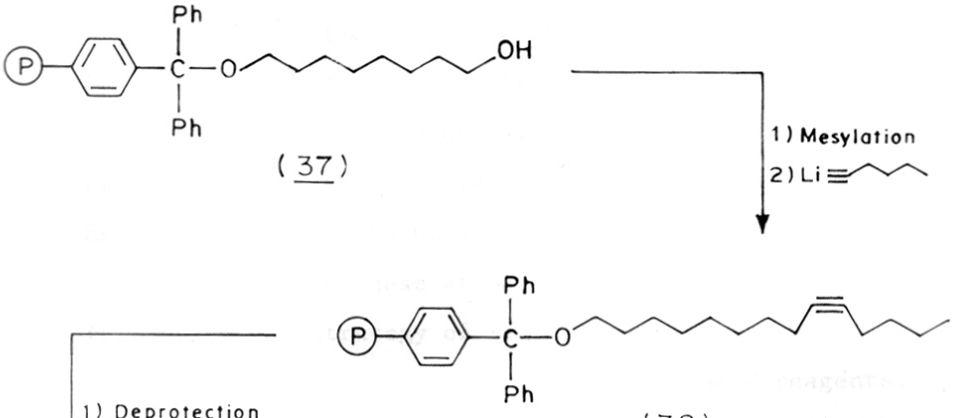


(32) (33) (34) (31)

SCHEME-4

(35) (36) (31)

SCHEME-5



(37) (38)

(39) (31)

The compound (34) was hydrogenated, hydrolysed and acetylated to get (31).

In 1971 Bestmann et al.[42,43] (Scheme 4) synthesized (31) in 8 steps using Wittig reaction between 9-acetoxy-nonanal (35) and salt free solution of ylide (36) as key step to get exclusively cis (31).

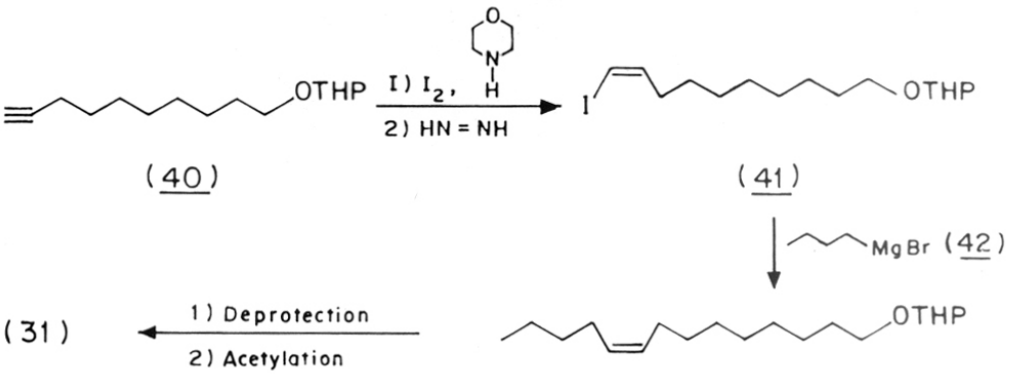
Leznoff et al.[44] (Scheme 5) in 1976 synthesized (31) using the strategy of selective monoprotection of octanediol with polymerbound tritylchloride (37). The compound (37) on mestylation and alkylation with lithium anion of hexyn gave (38), which on deprotection from the polymer and hydrogenation gave alcohol (39). The alcohol (39) was acetylated to get (31).

Michelot[45] (Scheme 6) reported the synthesis of (31) in 1983, based on the alkylation of Z-iodoalkenyl (41) with Grignard reagent (42) in presence of $[(C_6H_5)_3P]_4Pd$ catalyst. The compound (41) was prepared from acetylinic compound (40).

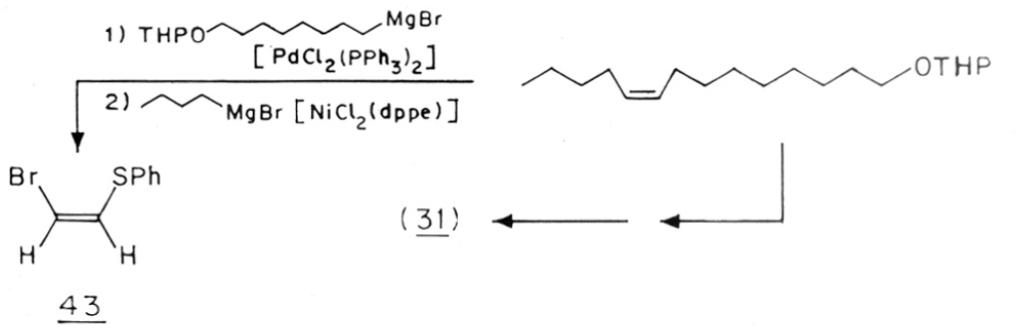
In 1985 Fiandanese et al.[46] (Scheme 7) synthesized (31) using the strategy of sequential alkylation of Z-bromo-2-phenylthioethene (43) with Grignard reagents.

Julia et al.[47] in 1986 (Scheme 8) synthesized (31) using the strategy - aldol condensation of metalated ω-hydroxysulfone (44) with aldehyde, to give (45), which

SCHEME-6

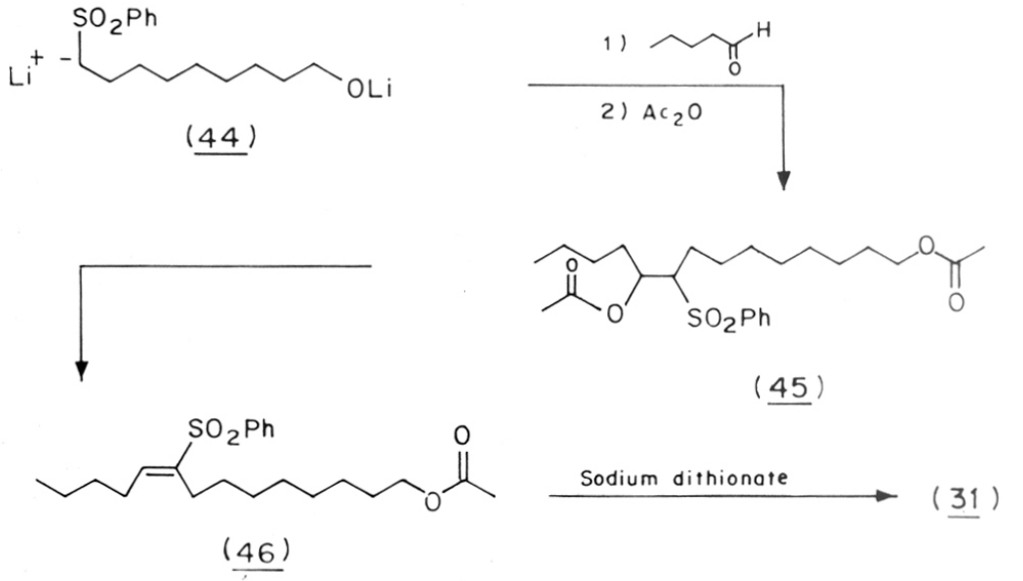


SCHEME-7



43

SCHEME-8



on reaction with sodium hydroxide gave vinylsulfone (46). The vinylsulfone (46) gave (31) on hydrogenolysis with sodiumdithionate.

By following other conventional methods, Sekul et al.[31], Ranganathan et al.[48] Chan et al.[49] and Vig et al.[50] have also synthesized the pheromone (31).

Basic strategy of present work is to build up the C_{14} carbon skeleton of (31) with carbon units (21), (50) and (57). Successive bis alkylations of (21) with the bromides(50) and (57) followed by selective deprotection of resulting product (52) with silica gel gave (53). The carbonyl compound (53) was converted to pheromone (31) by simple and straight forward methods(scheme 9).

The alkylating agent (50) was prepared in three steps starting from homopropargyl alcohol (47) and n-butyl-bromide (33).

The lithium dianion of homopropargyl alcohol (47) was alkylated selectively (C-alkylation) with n-butyl-bromide (33) using (3:1) THF:HMPA solvent mixture to get (48) in quantitative yield. IR (neat) spectrum showed absorption at 3340 cm^{-1} for hydroxy group. The PMR ($CDCl_3$) spectrum of (48) showed a distorted triplet at δ0.88 representing the methyl protons and a triplet at δ3.67 for C_1 methylene protons.

Hydrogenation of (48) over Lindlar catalyst[51] at normal pressure and temeprature in presence of small quantity of quinoline gave the Z-3-octen-1-ol (49) in

almost quantitative yield. IR (neat) spectrum of (49) showed characteristic absorption at 720 cm^{-1} for cis double bond and 3330 cm^{-1} for hydroxyl group. The PMR ($CDCl_3$) spectrum of (49) showed resonance due to the two olefinic protons in the region of δ 5.17 - 5.75 as a multiplet and C_1 methylene protons appeared as triplet at δ 3.63 (J=6 Hz).

Treatment of (49) with methanesulfonylchloride[52] in presence of triethylamine in dichloromethane gave the corresponding mesylate, which on stirring with anhydrous LiBr in acetone for 5 hours afforded Z-1-bromo-3-octene (50). IR (neat) spectrum of (50) showed absorption at 720 cm^{-1} for cis double bond. The absorption band at 3330 cm^{-1} for hydroxyl group was absent.

The alkylating agent 1-tetrahydropyranyloxy-3-bromo-propanol (57) and N,N-dimethylacetonehydrazone (21) was prepared according to the procedure reported in Chapter 2.

After having prepared both alkylating agents (50)and (57), efforts were directed towards one pot bisalkylations of (21) and selective deprotection of resulted hydrazone (52) to get carbonyl compound (53).

Lithium anion of (21) was first alkylated with 1-bromo-3-octene (50) to get (51). To the same reaction mixture one equivalent of n-BuLi was added to generate

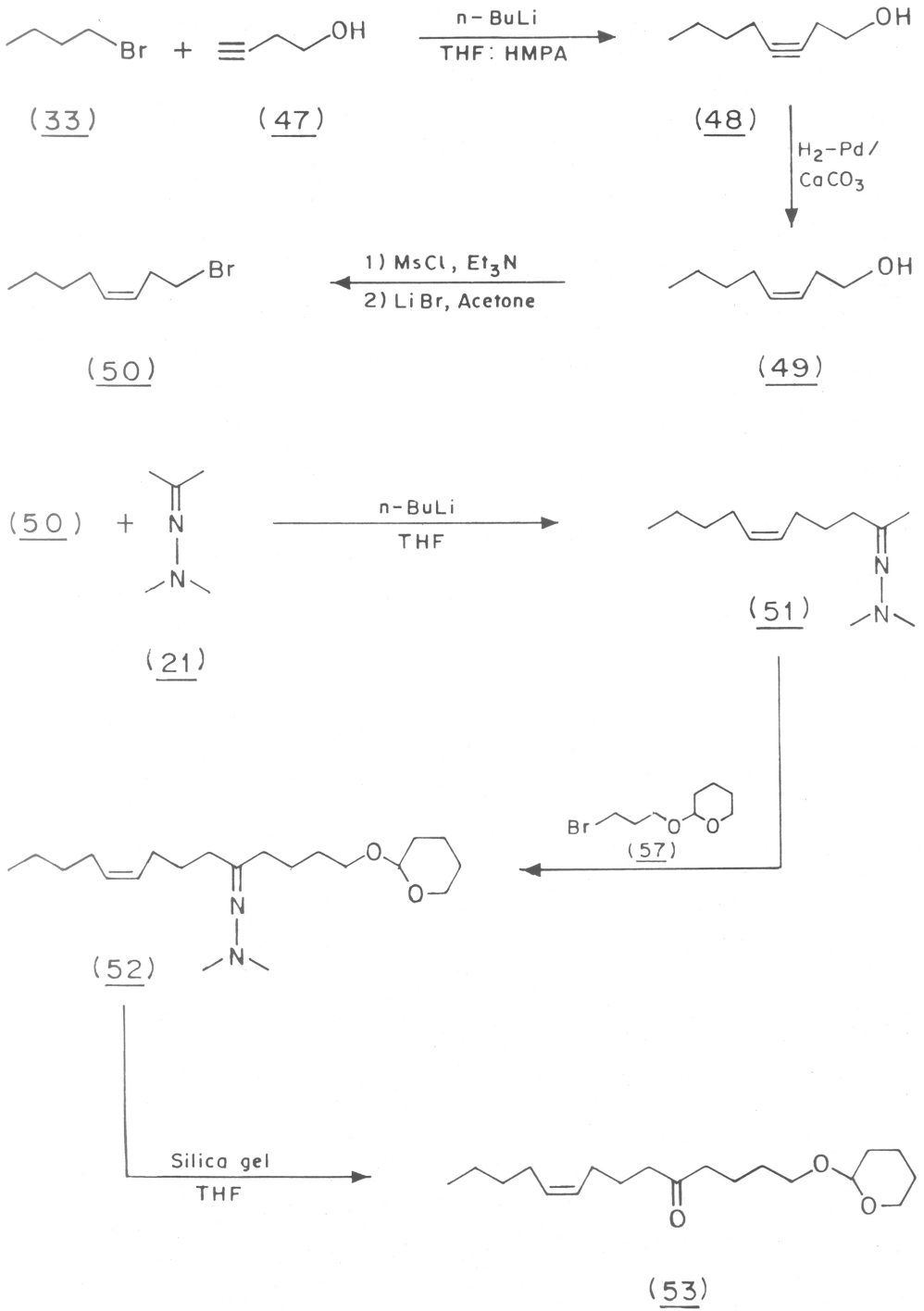
lithium anion of (51) and was alkylated with (57) to get hydrazone (52). IR (neat) spectrum of (52) showed peak at 1640 cm^{-1}, which is characteristic for C=N- stretching. PMR ($CDCl_3$) spectrum showed peak for $-N\langle^{CH_3}_{CH_3}$ at δ 2.36 and showed multiplet for olefinic protons in between δ 5.28 - 5.48. Mass spectrum showed molecular ion peak at 352.

Selective oxidative deprotection of hydrazone function of (52) with silica gel in THF at room temperature gave keto compound (53). IR (neat) spectrum of (53) showed carbonyl peak at 1720 cm^{-1}. In PMR ($CDCl_3$) spectrum (Fig. No.2) C_{14} terminal methyl showed distorted triplet at 0.89 and a multiplet was observed in, between δ 2.29 - 2.58 for α -carbonyl methylene protons. Olefinic protons are seen between δ 5.13 - 5.58 as multiplet.

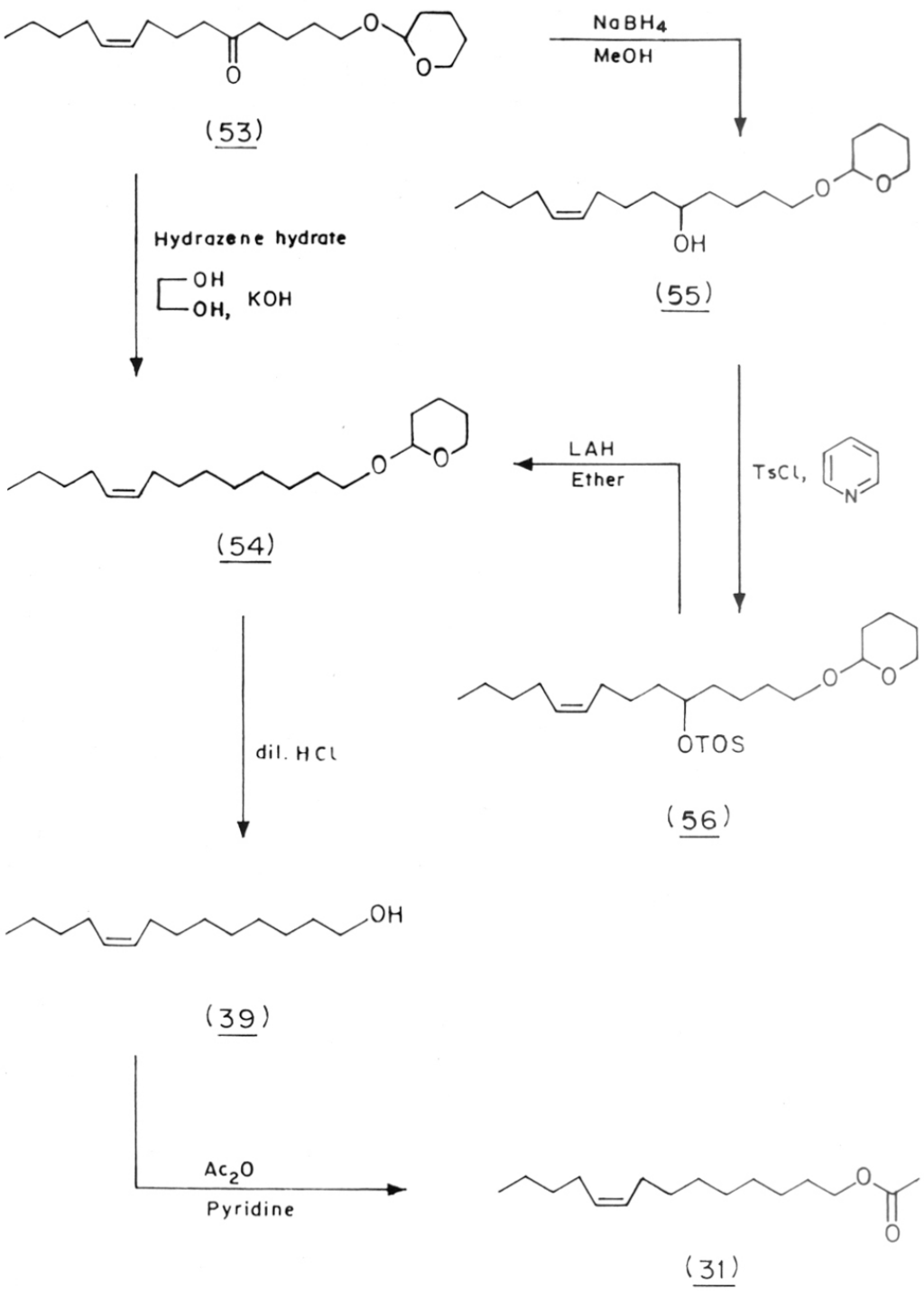
Huang-Minlon reduction[53] of (53) using KOH and ethyleneglycol afforded (54) in low yield (22%). In order to improve the yield, a three step procedure was used for the conversion of (53) into (54).

Reduction of keto compound (53) with $NaBH_4$ in methanol afforded hydroxy compound (55) in 91% yield. IR (neat) spectrum showed hydroxy absorption at 3400 cm^{-1}, and peak at 1720 cm^{-1} for carbonyl group was absent.

SCHEME-9


Br
OH
n-BuLi
THF: HMPA
(33)
(47)
(48)
H_2-Pd/
$CaCO_3$
1) MsCl, Et_3N
2) LiBr, Acetone
(50)
(49)
n-BuLi
THF
(21)
(51)
(57)
(52)
Silica gel
THF
(53)

SCHEME – 9 (Contd.)



Hydroxy compound (55) on reaction with tosyl-chloride in pyridine at 0°C gave tosylate (56) in 95% yield. In IR (neat) spectrum absence of 3400 cm^{-1} peak indicated the complete conversion of hydroxy to tosylate. In PMR ($CDCl_3$) spectrum aromatic protons were seen as two doublets at 7.25 and 7.72 (J=6 Hz).

The tosylate (56) was reduced with $LiAlH_4$ in ether at 0°C to get (54) in 76% yield. Absence of aromatic peaks in PMR ($CDCl_3$) spectrum indicates the completion of reduction

Deprotection of tetrahydropyranyloxy group of compound(54) with dil. HCl in methanol gave alcohol (39), which on acetylation with acetic anhydride in pyridine at 0°C afforded Z-9-tetradecen-1-yl acetate (31)[45] in 86% yield. IR (neat) spectrum (Fig. No.3) of (31) showed peaks at 3000, 2920, 2860, 1745 (acetyl carbonyl), 1470, 1390, 1370, 1240, 1040, 810, 730 (for cis olefinic function). PMR ($CDCl_3$, Fig. No.4) δ 0.89 (distorted triplet, 3H for C_{14} methyl protons), 1.15 - 1.80 (m, 16H, includes broad singlet for 10H and multiplet for 6H), 1.82 - 2.20 (m, 4H, for allyic protons), 2.04 (s, 3H, for acetyl methyl protons), 4.04 (t, 2H, J=7 Hz, for C_1 methylene protons), 5.18 - 5.53 (m, 2H, for olefinic protons).

Mass: 254 (molecular ion), 194 (base peak), 177, 166, 152, 149, 138, 124, 110, 96, 95, 91, 82, 81, 67 and 55.

Analysis: Calculated for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89
Found: C, 75.56; H, 11.83.

Synthesis of 3,13-octadecadien-1-yl acetate

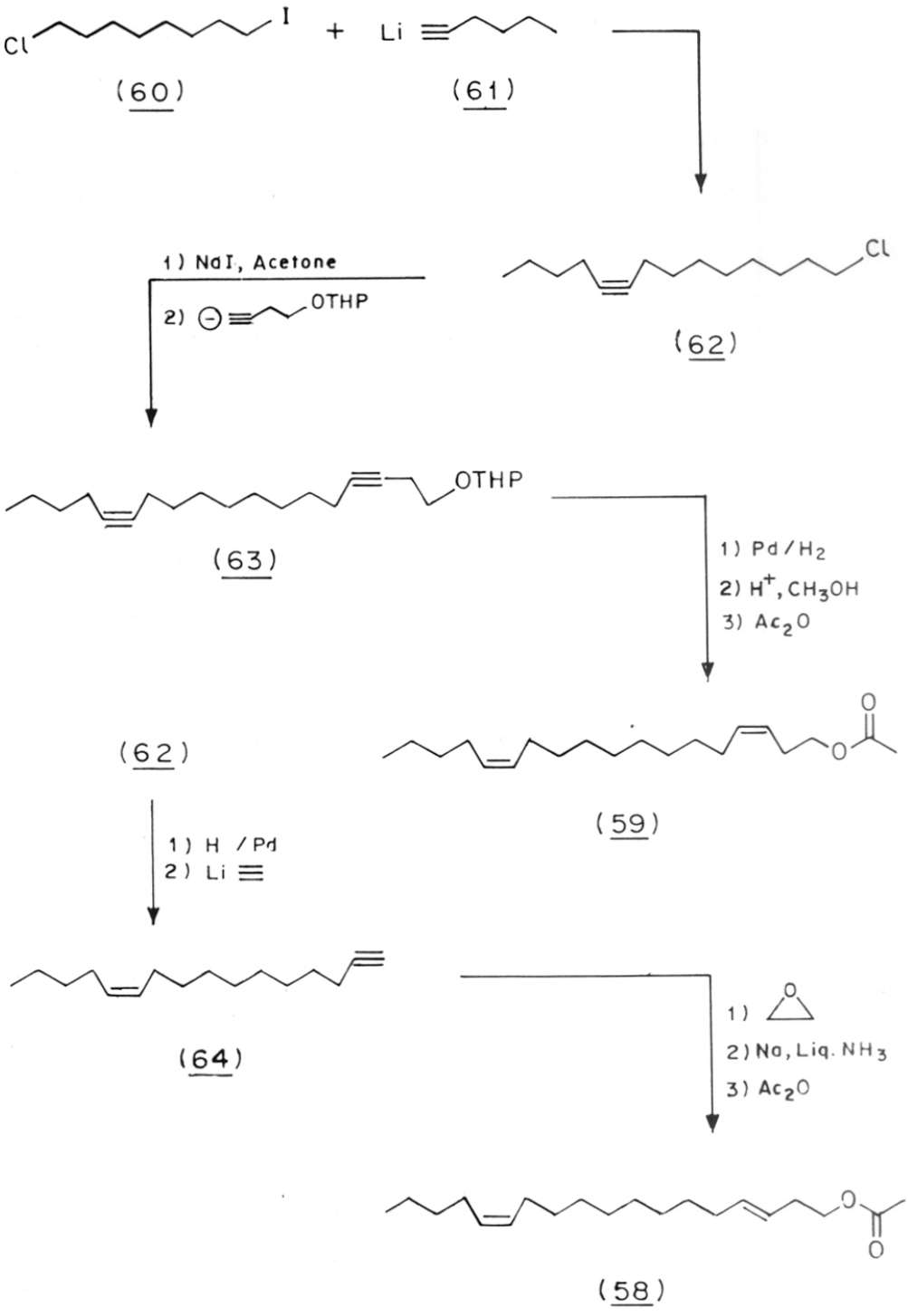
Tumlinson et al.[54] isolated (E,Z)-3,13-octadecadien-1-yl acetate (58) and (Z,Z)-3,13-octadecadien-1-yl acetate (59) from the female lesser peachtree borer, Synanthedon pictipes, and the female peachtree borer, Sanninoidea exitiosa respectively. They strongly attracted the respective males of these species in field biassays. A 1:1 mixture of (58) and (59) has also been shown to be an effective trapbait for the male cherrytree borer, Synanthedon hector, which is a severe pest on peach orchards in Japan[55,56].

Tumlinson et al.[54] (Scheme 10) reported the first synthesis of (58) and its geometrical isomers using acetylenic precursors.

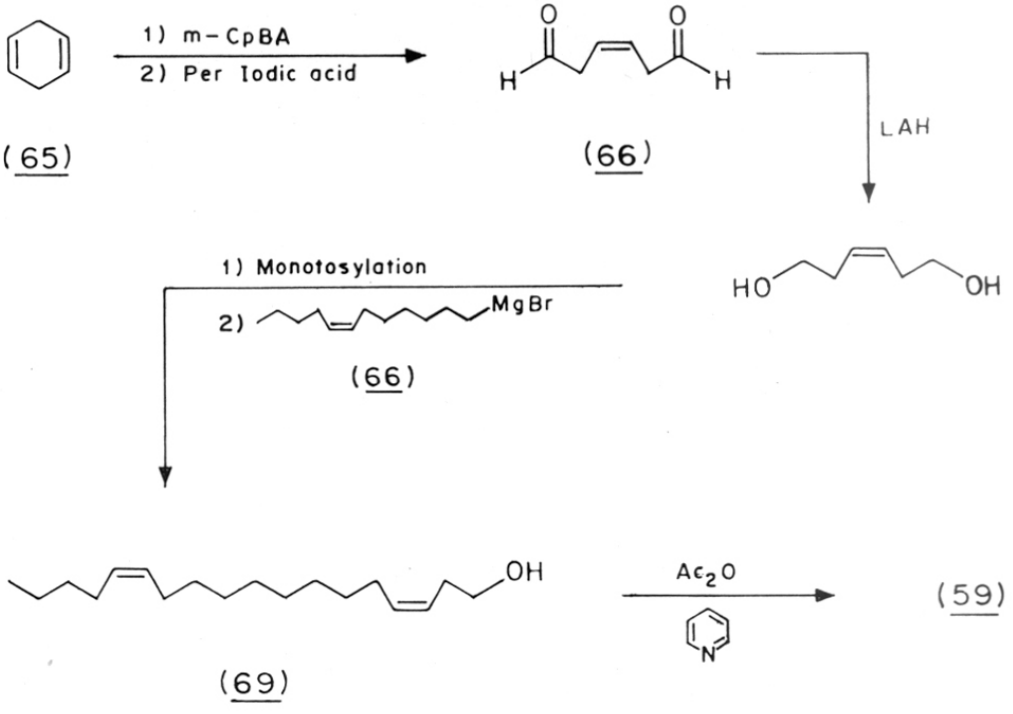
Mori et al.[57] reported the synthesis of (59) (Scheme 11) starting from 1,4-cyclohexadiene (65). The compound (65) on reaction with m-chloroperbenzoic acid and periodic acid gave dialdehyde (66) which on LAH reduction gave diol (67). The diol (67) on mono-tosylation and reaction with bromide (68) gave compound (69), which on acetylation afforded (59).

Apart from these methods, Kenji Mori et al.[56], Dolittle et al.[58], Muchowski et al.[59], M. Gardette et al.[60]

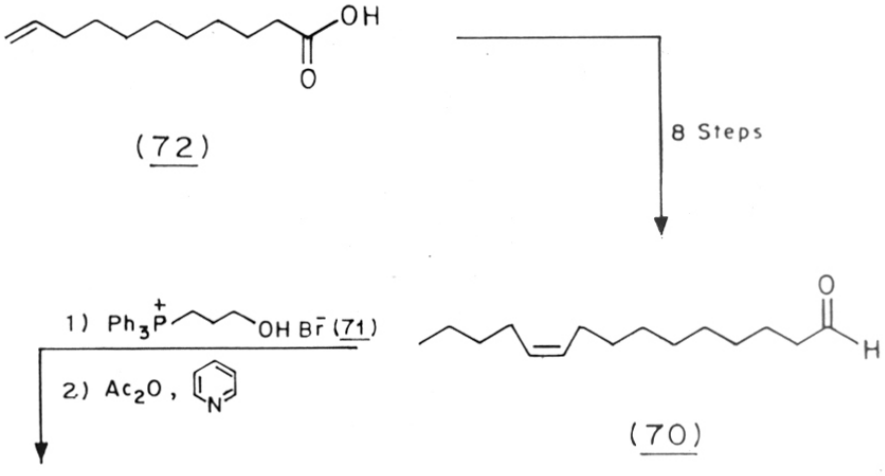
SCHEME-10


Cl
I
+
Li
(60)
(61)
1) NaI, Acetone
2) OTHP
Cl
(62)
OTHP
(63)
1) Pd/H2
2) H+, CH3OH
3) Ac2O
(62)
O
O
(59)
1) H /Pd
2) Li
(64)
O
1)
2) Na, Liq. NH3
3) Ac2O
O
O
(58)

SCHEME-11



SCHEME-12



(58) + (59)

1 : 1

and P.I. Svirskaya et al.[61] also reported the synthesis of (59) and its geometrical isomers either by Wittig or acetylenic approach.

In 1979 Mori et al.[62] (Scheme 12) synthesized 1:1 mixture of (3Z, 13Z)-(59) and (3E, 13Z) - (58), which is effective trapbait for the male cherrytree borer. They employed the Wittig reaction on aldehyde (70) with reagent (71). The aldehyde (70) was prepared starting from commercially available 10-undecenoic acid (72).

Present work involves the synthesis of key intermediate aldehyde (70), which can be converted to a 1:1 mixture of (58) and (59) by following Kenji Mori's method[62] (as shown in the Scheme 12).

The strategy involved in the synthesis of (70) is, bis alkylation of hydrazone (21) with bromide (77) and (22) to get hydrazone (79). The hydrazone (79) on selective deprotection gives (80) which on further transformation gives aldehyde (70)

The alkylating agent (77) was prepared in three steps starting from tetrahydrofurfuryl chloride (73) and(33). (scheme 13)

Tetrahydrofurfuryl chloride (73) on treatment with lithium amide in liq. NH_3 gave the dianion of 4-pentyl-1-ol[63] (74), which was in situ alkylated with n-butylbromide (33) to give 4-nonyn-1-ol[63] (75) in

75% yield. IR spectrum of (75) showed absorption at 3340 cm^{-1} for hydroxy group. The PMR ($CDCl_3$) spectrum showed a distorted triplet at δ 0.89 for terminal methyl and triplet at δ 3.76 for C_1 methylene protons.

Hydrogenation of (75) over Lindlar catalyst[51] at normal pessure gave the Z-4-nonen-1-ol (76) in almost quantitative yield. The PMR ($CDCl_3$) of (76) showed the resonance due to the two olefinic protons in the region of δ 5.13 - 5.48 as multiplet and C_1-methylene protons appeared as triplet at δ 3.67. The remaining proton signals were seen at the expected chemical shfits.

Treatment of (76) with methanesulfonyl chloride[52] in presence of Et_3N and dichloromethane gave the corresponding mesylate, which on stirring with anhydrous LiBr in acetone at 0°C for 4 hours afforded the Z-1-bromo-4-nonene (77). In IR spectrum the absorption band at 3340 cm^{-1} due to the hydroxyl group was absent. In the PMR ($CDCl_3$) spectrum of (77) olefinic protons resonated as multiplet in the region of δ 5.03 - 5.59 and C_1 methylene protons appeared as triplet at δ 3.32 (J=6 Hz).

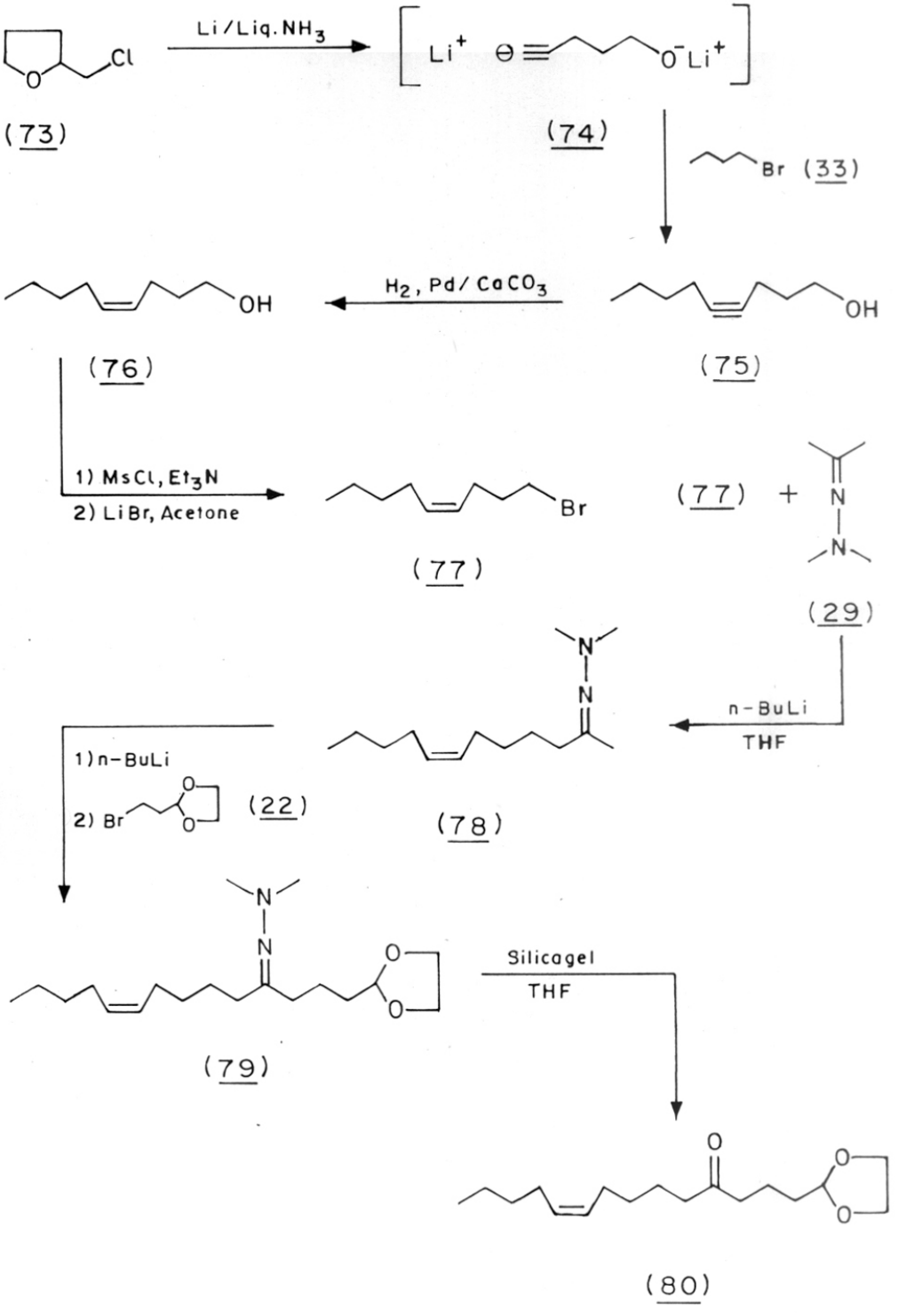
The compounds (29) and (22) were prepared according to the procedure followed in Chapter 1. After having prepared both the alkylating agents (22) and (77), efforts were directed towards bis alkylation

of N,N-dimethyl acetonehydrazone (29). Lithium anion of (21) was alkylated with (77) to get (78). To the same reaction mixture one mole equivalent of n-BuLi was added and alkylated with (22) to get hydrazone (79). IR (neat) spectrum of (79) showed characteristic peak at 1620 cm^{-1} for C=N- stretching. PMR ($CDCl_3$) spectrum showed peak for $N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ at δ 2.16 and for olefinic protons in between δ 5.09 - 5.58 as multiplet. Mass spectrum showed molecular ion peak at 324.

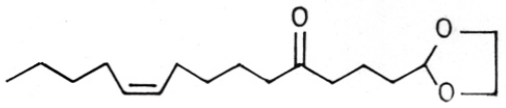
Selective oxidative deprotection of hydrazone (79) with silica gel in THF gave keto compound (80). IR spectrum of (80) showed carbonyl peak at 1720 cm^{-1}. PMR ($CDCl_3$) (Fig. No.5) spectrum of (80) showed multiplet peak in between δ 3.71 - 3.96 for dioxalane methylene protons, 4H and a distorted triplet observed between δ 4.71 - 4.88 for dioxalane methine proton 1H. A multiplet for olefinic protons was seen between δ 5.06 - 5.53 . Mass spectrum showed molecular ion peak at 282.

The compound (80) on reduction with hydrazine hydrate and potassium hydroxide in ethyleneglycol (Huang-Minlon reduction) gave (81) in 25% yield. As the the yield of Huang-Minlon reduction was low, the compound (80) was converted to (81) by a three step reaction sequence in a overall yield of 62%.

SCHEME-13

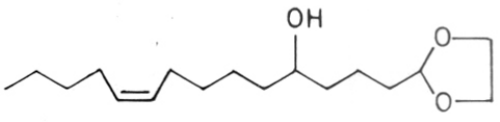

Li/Liq.NH3
Cl
O
(73)
Li+ ⊖ O⁻Li+
(74)
Br (33)
OH
(75)
H2, Pd/CaCO3
OH
(76)
1) MsCl, Et3N
2) LiBr, Acetone
Br
(77)
(77) + N N
(29)
n-BuLi
THF
N N
(78)
1) n-BuLi
2) Br O O
(22)
N N O O
(79)
Silicagel
THF
O O O
(80)

SCHEME-13 (Contd.)



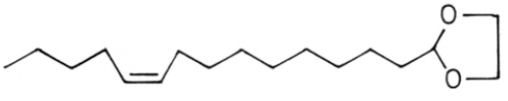
(80)

$NaBH_4$ / MeOH



(82)

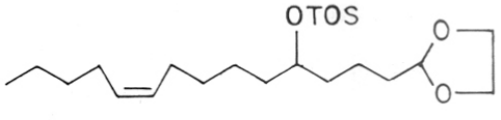
Hydrazine hydrate, OH, OH, KOH



(81)

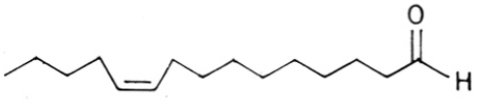
LAH / Ether

TsCl, 



(83)

dil. HCl, MeOH



(70)

ref. 62

(58) + (59)

1 : 1

The keto compound (80) was reduced with $NaBH_4$ in methanol to get hydroxy compound (82) in 92% yield. IR (neat) spectrum of (82) showed peak for hydroxy group at 3410 cm^{-1}. The 1720 cm^{-1} peak of carbonyl group was absent.

The hydroxy compound (82) was tosylated with tosylchloride in pyridine to get (83) in 94% yield. In IR (neat) spectrum the peak at 3410 cm^{-1} representing the hydroxy group was absent. The peak at 1600 cm^{-1} representing the aromatic (-C=C-) stretching was present. In PMR ($CDCl_3$) spectrum two doublets at δ 7.25 and δ 7.72 were seen for aromatic protons. The methyl protons on aromatic ring were seen as singlet at δ 2.43.

The tosylate (83) on reduction with LAH in ether at 0°C gave (81) in 72% yield. In IR (neat) spectrum the peak at 1600 cm^{-1}, respresenting the aromatic (-C=C-) stretching was absent. In PMR ($CDCl_3$) spectrum two doublets at δ 7.25 and δ 7.72 which represent aromatic protons were absent. Mass spectrum showed molecular ion at 268.

The compound (81) on reaction with dil. HCl at room temperature gave the key intermediate aldehyde (70). The IR (neat) spectrum showed carbonyl peak at 1720 cm^{-1}. In mass spectrum molecular ion peak is observed at 224. All other spectral data were identical with those reported[62],

The compound (70) can be utilised for the synthesis of 1:1 mixture of (58) and (59) by the known procedure[62],

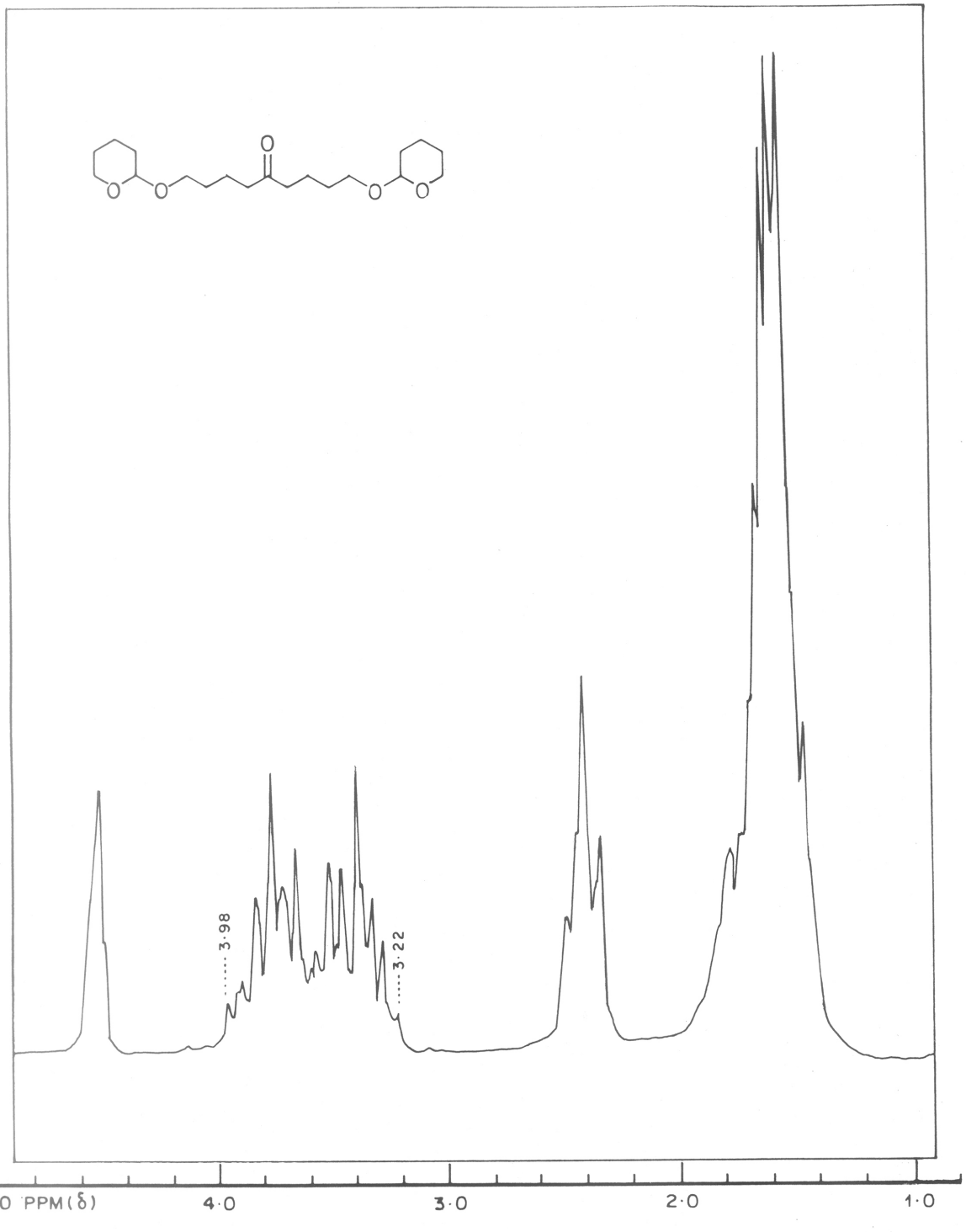


FIG. 1. PMR SPECTRUM OF COMPOUND (11) IN $CDCl_3$

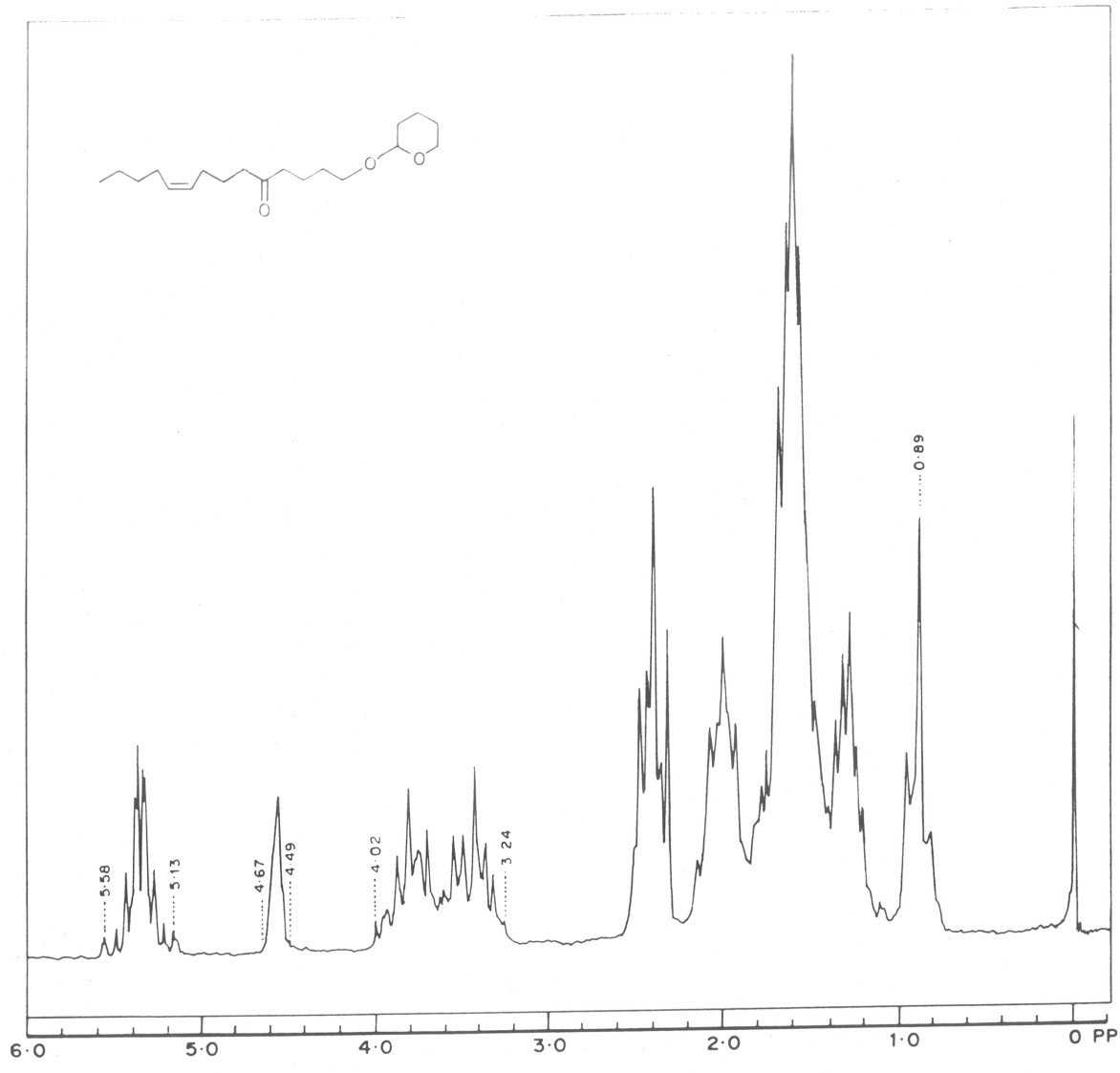


FIG. 2. PMR SPECTRUM OF COMPOUND (53) IN $CDCl_3$

190

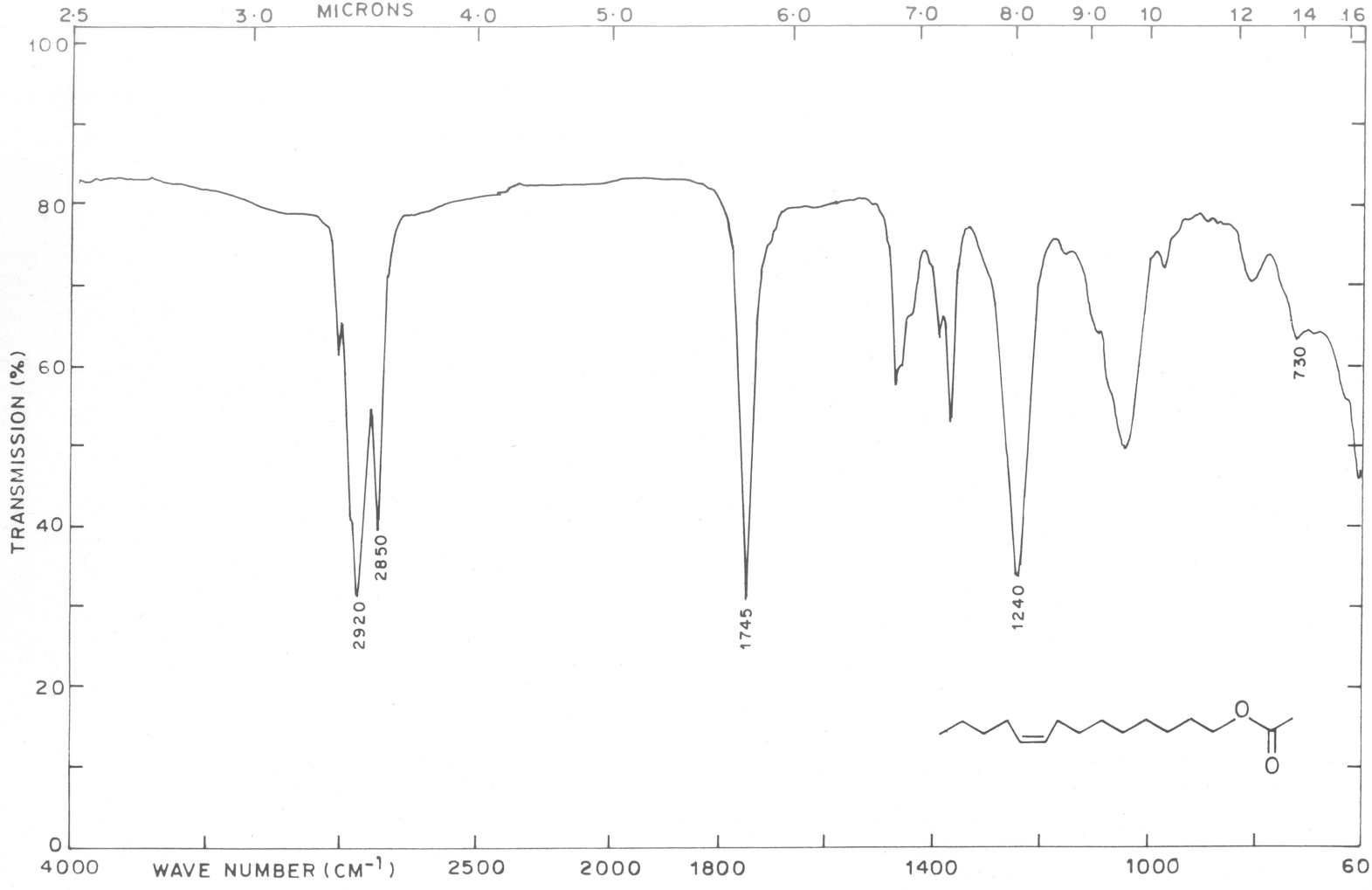


FIG. 3. IR (NEAT) SPECTRUM OF Z-9-TETRADECEN-1-YL ACETATE (31)

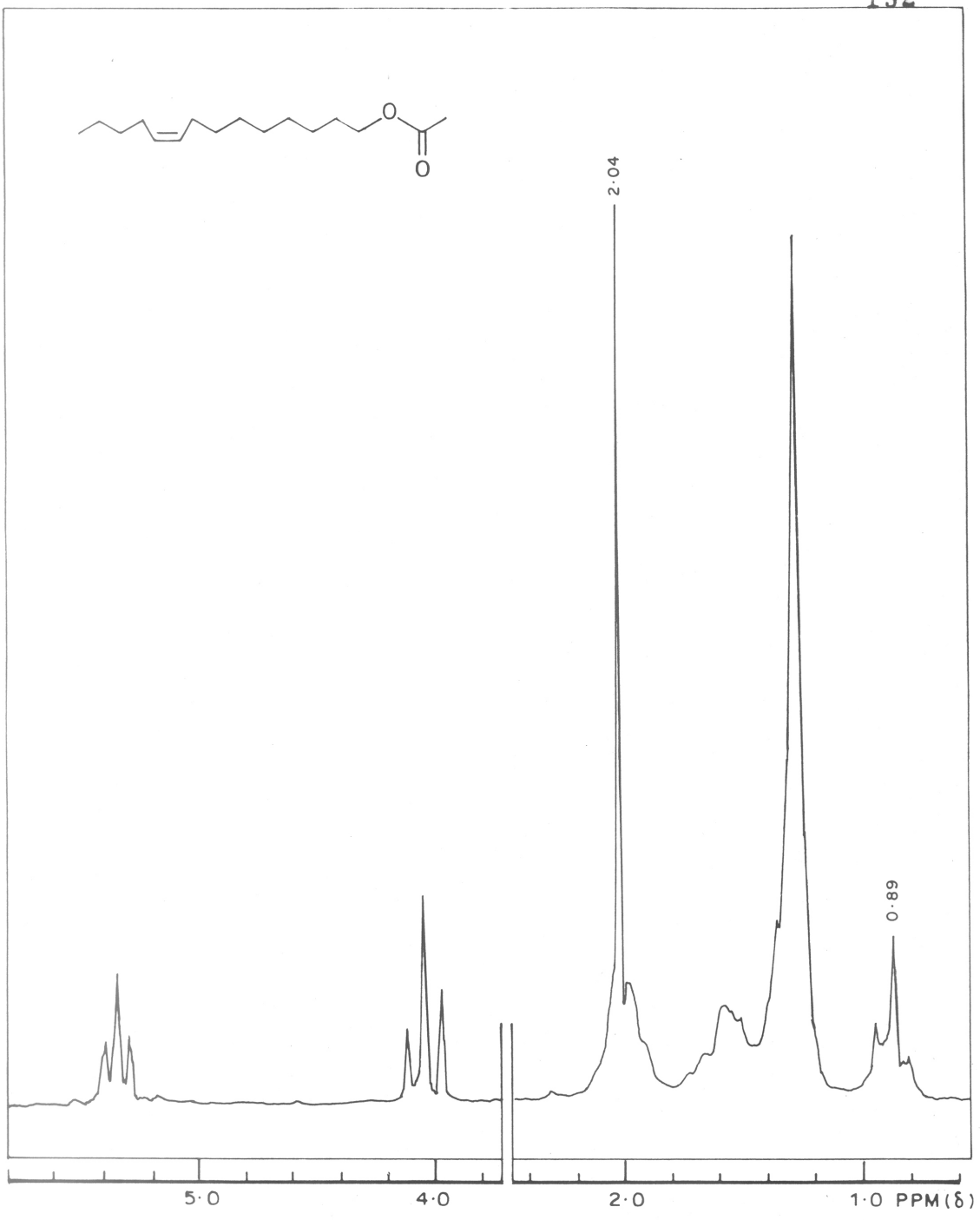


FIG. 4. PMR SPECTRUM OF Z-9-TETRADECEN-1-YL-ACETATE (31) IN $CDCl_3$

193

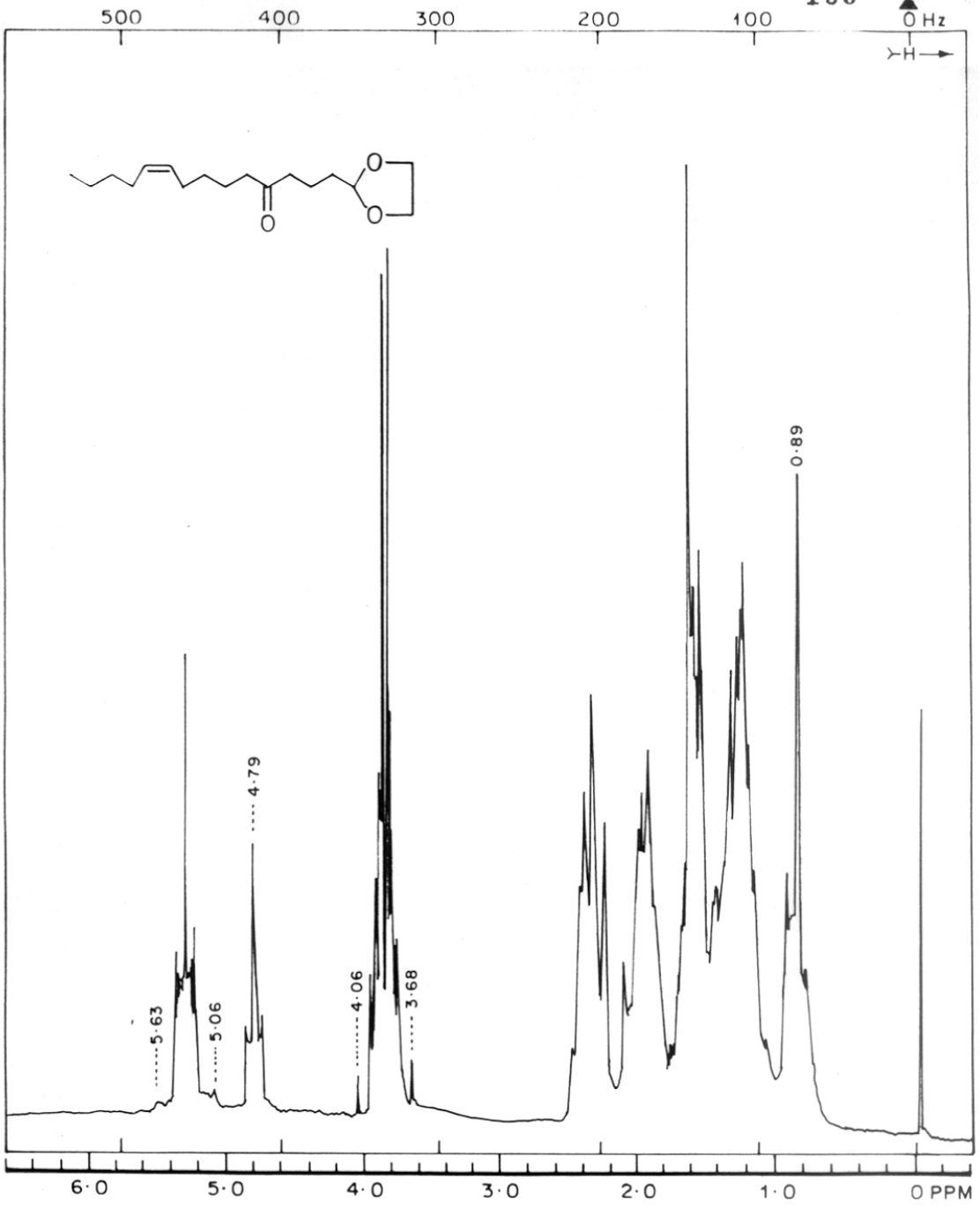


FIG. 5. PMR SPECTRUM OF COMPOUND (80) IN $CDCl_3$

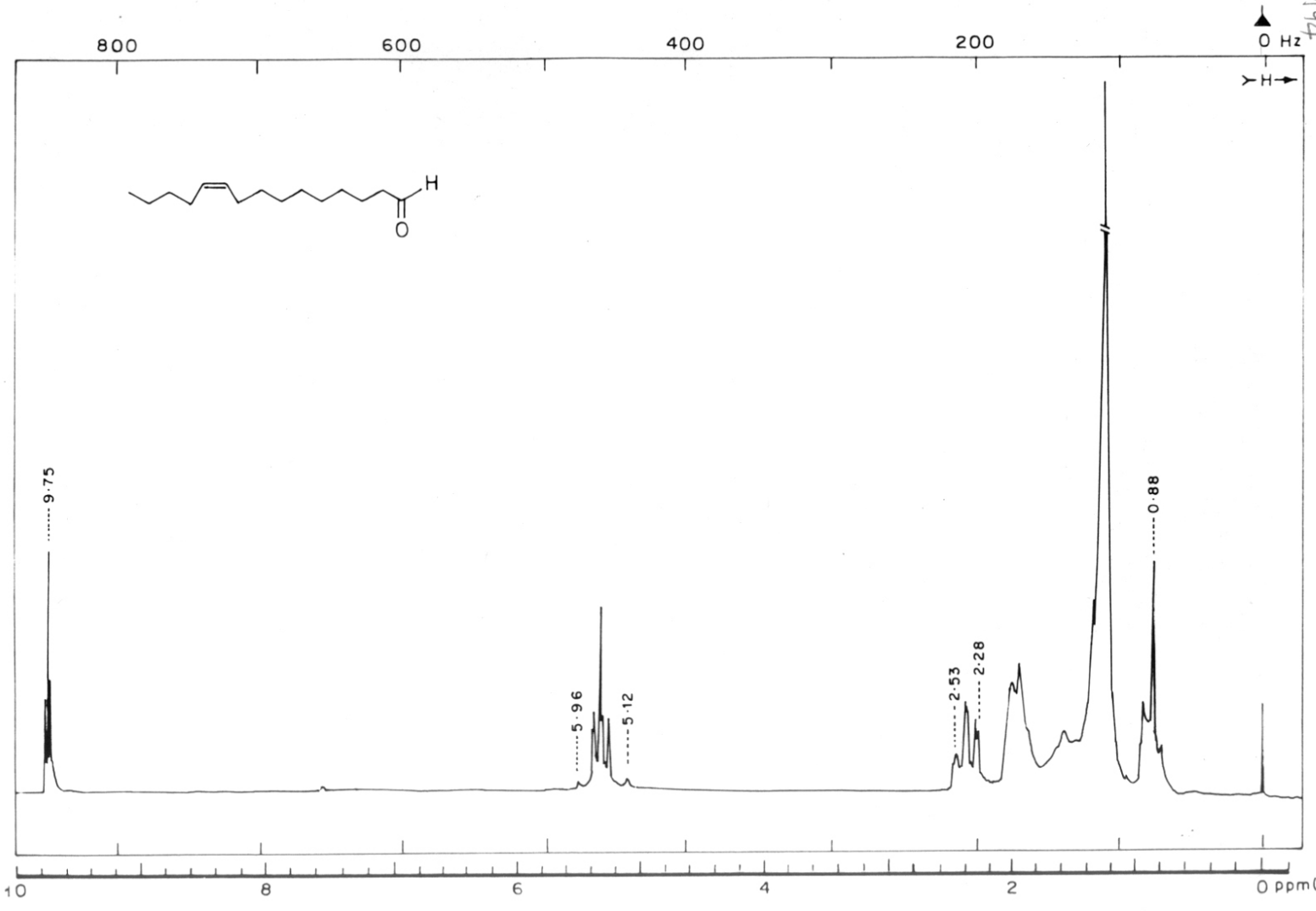


FIG. 6. PMR SPECTRUM OF COMPOUND (70) IN $CDCl_3$

EXPERIMENTAL

Compound (3)

To a THF solution (25 ml) of (21) (0.50 g, 0.005 mole) under N_2 atmosphere at 0°C was added n-BuLi (3.2 ml of 1.9 N n-hexane solution, 0.006 mole) with syringe. Stirred for 0.5 hours. The compound (22) (0.905 g, 0.005 mole) was added and stirred for 2 hrs at room temperature. The reaction mixture was again cooled to 0°C and n-BuLi (0.006 mole) was added. After keeping for 0.5 hr, the compound (22) (0.905 g, 0.005 mole) was added and stirred for 2 hrs at room temperature. Then the reaction mixture was washed with saturated NH_4Cl (3 x 25 ml). The THF layer was then dried over Na_2SO_4 and concentrated to get crude (3). The crude compound was distilled to get the pure compound (3) in 68% yield (1.02 g).

IR (neat): 2930, 2850, 2800, 2750, 1620 (C=N-stretching), 1430, 1400, 1350, 1130, 1020, 940, 810.

PMR ($CDCl_3$): δ 1.51 - 1.80 (8H, m, 4 x $-CH_2-$), 2.08 - 2.55 (10H, m, includes multiplet for methylene protons adjacent to double bond, 4H, and a peak for methyl protons on nitrogen, 6H), 3.70 - 4.08 (8H, m, methylene proton of dioxalane ring), 4.77 - 4.93 (2H, m, methine protons, 2 X CH).

Analysis: Calculated for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.40; N, 9.33

Found: C, 59.91; H, 9.45; N, 9.38.

Compound (4)

Bis alkylation of (21) with (23) and (22) gave the compound (4) in 62% yield.

IR(neat): 2910, 2840, 1630 (-C=N- stretching), 1460, 1370, 1195, 1020, 940.

PMR ($CDCl_3$): δ 0.87 (3H, distorted triplet, for terminal methyl protons), 1.06 - 1.72 (18H, m, 9 X $-CH_2-$), 1.96 - 2.53 (10H, m, includes multiplet for 2 X CH_2 and a peak for methyl protons on nitrogen, 2 X $-CH_3$), 3.72 - 3.96 (4H, m, methylene protons of dioxalane ring), 4.72 - 4.87 (1H, m, for dioxalane methine proton).

Mass: 312 (molecular ion), 280, 268, 196, 168, 156, 141, 128, 113, 99 (base peak), 86, 73, 60.

Analysis: Calculated for $C_{18}H_{30}N_2O_2$:

C, 69.18; H, 11.61; N, 8.97.

Found: C, 69.23; H, 11.63; N, 8.91.

Compound (5)

Alkylation of (21) with (24) gave the compound (5) in 82% yield.

IR (neat): 2970, 2940, 2860, 2800, 2760, 1630 (>C=N- stretching), 1460, 1440, 1370, 1250, 1200, 1130, 1070, 945, 860.

PMR($CDCl_3$): δ 1.28 (3H, s, 1 x $-CH_3$), 1.66 (4H, m, 2 x $-CH_2-$), 1.90 (3H, s, 1 x CH_3), 2.06 - 2.43 (8H, m, includes multiplet for 1 x CH_2 and a peak for methyl protons on nitrogen, 2 x $-CH_3$), 3.90 (4H, s, dioxalane methylene protons, 2 x $-CH_2-$).

Mass: 214 (molecular ion), 199, 171, 127, 112, 108, 99, 87 (base peak), 71, 58, 55, 43.

Analysis: Calculated for $C_{11}H_{22}N_2O_2$

C, 61.65; H, 10.35; N, 13.07

Found: C, 61.60; H, 10.38; N, 13.11.

Compound (6)

Bis alkylation of (21) with benzylbromide (26) and with the bromide (27) gave the compound (6) in 58% yield.

IR (neat): 3120, 2940, 2860, 1630 (C=N- stretching), 1600, 1495 , 1455, 1350, 1200, 1140, 1125, 1080, 1040, 910, 840, 820, 750, 705.

PMR ($CDCl_3$): δ 1.13 - 2.02 (10H, m, 5 x $-CH_2-$), 2.11 - 2.77 (12H, m), 3.22 - 4.08 (4H, m), 4.48 - 4.64 (1H, bs).

Mass: 332 (molecular ion), 247, 231, 215, 204, 189, 175, 157, 141, 132, 118, 105 (base peak), 101, 97, 91, 85, 77.

Compound (7)

Successive bis alkylations of (21) with allyl-bromide (28) gave the compound (7) in 65% yield.

IR (neat): 3100, 3000, 2980, 2880, 2840, 1660 (exodouble bond), 1480, 1460, 1170, 1010, 920.

PMR($CDCl_3$):δ1.93 - 2.65 (14H, m, 4 x CH_2 and $N\text{-}N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ 4.81 - 5.12 (4H, m, for C_1 and C_9 olefinic protons), 5.50 - 6.06 (2H, m, for C_2 and C_8 olefinic protons).

Analysis : Calculated for $C_{11}H_{20}N_2$

C, 73.28; H, 11.18; N, 15.54

Found: C, 73.21; H, 11.21; N, 15.59.

Compound (8)

Alkylation of (21) with the bromide (29) gave the compound (8) in 85% yield.

IR (neat): 2940, 2840, 2800, 2760, 1635 (C=N-stretching), 1500, 1450, 1355, 1200, 1090, 720.

PMR ($CDCl_3$): δ 1.28 - 1.71 (6H, m, 3 x $-CH_2-$), 1.90 (3H, s, 1 x $-CH_3$), 2.03 - 2.46 (8H, m, includes multiplet for $-N{=}C-CH_2-$ and a peak for $-N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ 3.43 (2H, t, J = 7 Hz, for $-CH_2-O-$), 4.44 (2H, s, benzylic methylene protons), 7.26 (5H, s, aromatic protons).

Mass: 262 (molecular ion), 171, 148, 133, 118, 113, 105, 100, 91 (base peak), 77, 70, 65.

Analysis: Calculated for $C_{16}H_{26}N_2O$:

C, 73.24; H, 9.99; N, 10.68

Found:C,73.37; H, 9.86; N, 10.53.

Compound (11)

To the compound (1) (0.384 g, 0.001 mole) dissolved in moist THF (10 ml THF and 1 ml water), was added silica gel

(3 g, mesh 60-120, Acme make, pH = 6.8) was added to it. Reaction mixture (THF - silica gel slurry) was stirred for 3 hours at room temperature. Then the reaction mixture was concentrated and loaded on column (1:20 ratio of compound to silica gel) and eluted with 15% ethyl acetate in pet.ether to get (11) in 74% yield (0.253 g).

IR (neat): 2940, 2860, 1710 (carbonyl), 1450, 1440, 1350, 1200, 1140, 1120, 1080, 1040, 990, 910, 870, 815.

PMR($CDCl_3$): δ 1.35 - 1.95 (20H, m, 10 x $-CH_2-$), 2.28 - 2.53 (4H, m, for the methylene protons α- to carbonyl), 3.22 - 3.98 (8H, m, for the methylene protons adjacent to oxygens), 4.46 - 4.62 (2H, broad singlet, methine protons).

Analysis: Calculated for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01
Found: C, 66.75; H, 10.09.

Compound (12)

The compound (2) was treated with silica gel as above to get (12) in 71% yield.

IR (neat): 2940, 2880, 1715 (carbonyl), 1460, 1450, 1370, 1200, 1140, 1080, 1030, 1000, 910, 870, 820.

PMR ($CDCl_3$): δ 0.97 - 1.97 (20H, m, 10 x CH_2), 1.10, 1.21 (6H, two doublets, J=6 Hz, 2 x $-CH_3$), 2.29 - 2.56 (4H, m, for the methylene protons α to carbonyl), 3.31 - 4.18 (6H, m), 4.51 - 4.78 (2H, m, for methine protons).

Analysis: Calculated for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34

Found: C, 68.01; H, 10.39.

Compound (13)

The compound (3) was treated with silica gel as above to get (13) in 66% yield.

IR (neat): 2960, 2880, 1710 (carbonyl), 1410, 1150, 1040, 945.

PMR ($CDCl_3$): δ 1.43 - 1.90 (8H, m 4 x CH_2), 2.21 - 2.56 (4H, m, for the protons α to carbonyl group), 3.62 - 4.09 (8H, m, 4 x CH_2), 4.81 (2H, distorted triplet).

Mass: 258 (molecular ion), 228, 213, 196, 185, 168, 155, 143, 125, 113, 99, 86, 81, 73 (base peak), 69.

Analysis: Calculated for: $C_{13}H_{22}O_5$: C, 60.44; H, 8.59

Found: C, 60.52; H, 8.48.

Compound (14)

The compound (4) was treated with silica gel as above to get (14) in 60% yield.

IR (neat): 2920, 2850, 1715 (carbonyl), 1460, 1410, 1370, 1130, 1030.

PMR ($CDCl_3$): δ 0.88 (3H, distorted triplet, terminal methyl protons), 1.09 - 1.87 (18H, a multiplet with a broad singlet at δ 1.15), 2.21 - 2.53 (4H, m, 2 x CH_2), 3.65 - 4.06 (4H, m, $\begin{matrix} \text{O-CH}_2 \\ \text{O-CH}_2 \end{matrix}$), 4.81 (1H, distorted triplet).

Mass: 270 (molecular ion), 252, 227, 208, 199, 158, 143, 115, 99, 86, 73 (base peak).

Analysis: Calculated for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18
Found: C, 71.20; H, 11.23.

Compound (15)

The compound (5) was treated with silica gel as above to get (15) in 61% yield.

IR (neat): 2980, 2900, 1730 (carbonyl), 1440, 1390, 1240, 1180, 1140, 1050, 960, 870.

PMR ($CDCl_3$): δ 1.31 (3H, s, $-CH_3$), 1.53 - 1.90 (4H, m, 2 x CH_2), 2.12 (3H, s, $-CO-CH_3$), 2.34 - 2.56 (2H, m, $-CO-CH_2-$), 3.90 (4H, s, $\begin{matrix} O-CH_2 \\ | \\ O-CH_2 \end{matrix}$).

Analysis: Calculated for $C_9H_{16}O_3$ C, 62.76; H, 9.36
Found:C, 62.67; H, 9.31.

Compound (16)

The compound (6) was treated with silica gel as above to get (16) in 65% yield.

IR (neat): 3040, 2880, 1725 (carbonyl), 1600, 1450, 1440, 1380, 1120, 1080, 1040, 990.

PMR ($CDCl_3$): δ 1.31 - 1.90 (10H, m 5 x CH_2), 2.25 - 2.50 (2H, distorted triplet, benzyl methylene protons), 2.56 - 3.03 (4H, m, methylene protons α to carbonyl), 3.21 - 3.93 (4H, m, 2 x $-CH_2-O$), 4.40 - 4.56 (1H, broad singlet).

Analysis: Calculated for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03
Found: C, 74.55; H, 9.12.

Compound (17)

The compound (7) was treated with silica gel as above to get (17) in 60% yield.

IR (neat): 3080, 2980, 2920, 1710 (carbonyl), 1640, (exodouble bond), 1440, 1410, 1360, 1050, 980, 900.

PMR ($CDCl_3$): δ 1.87 - 2.75 (8H, m, 4 x $-CH_2-$), 4.81 - 5.12 (4H, m, for C_1 and C_9 protons), 5.46 - 6.00 (2H, m, for C_2 and C_8 protons).

Analysis: Calculated for $C_9H_{14}O$: C, 78.21; H, 10.21

Found: C, 78.32; H, 10.26.

Compound (18)

The compound (8) was treated with silica gel to get (18) in 69% yield.

IR (neat): 3050, 2960, 2880, 1730 (carbonyl), 1520, 1470, 1380, 1180, 1110, 750, 710.

PMR ($CDCl_3$): δ 1.09 - 1.90 (6H, m, 3 x $-CH_2-$), 2.06 (3H, s, CH_3-CO-), 2.16 - 2.46 (2H, m, for $-CH_2-CO-$), 3.42 (2H, t, J=7 Hz, $-CH_2-O-$), 4.50 (2H, s, benzyl methylene), 7.35 (5H, bs, aromatic).

Mass: 220 (molecular ion), 177, 148, 129, 122, 114, 105, 96, 91 (base peak), 77, 71, 65.

Analysis: Calculated for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15

Found: C, 76.41; H, 9.09.

3-Octyn-1-ol (48)

To a solution of homopropargyl alcohol (47) (6.8 g, 0.1 mole) in THF (200 ml) under N_2 atmosphere at -30°C was added n-BuLi (0.2 mole, 105 ml of 1.9N n-hexane solution) with syringe, followed by 100 ml of HMPA. The reaction mixture was slowly allowed to come to room temperature and stirred for 0.5 hrs. The reaction was again cooled to -30°C and n-butyl bromide (33) (13.7 g, 0.1 mole) was added dropwise for one hr. The reaction mixture was stirred at -30°C for 4 hrs. It was allowed to come to room temperature slowly and quenched with saturated NH_4Cl (300 ml). THF was removed under vacuum and ether was added to the concentrated reaction mixture. Ether layer was washed with water to remove HMPA. Then the ether was evaporated and residue distilled under vacuum to get (48) in 60% yield (7.56 g).

IR (neat): 3340 (hydroxy), 2950, 2920, 2860, 1465, 1430, 1380, 1330, 1085, 850.

PMR ($CDCl_3$): δ 0.88 (3H, distorted triplet, for C_8 methyl protons), 1.08 - 1.74 (4H, m, for C_6 and C_7 methylene protons), 1.74 (s, 1H, D_2O exchangeable), 1.97 - 2.31 (2H, m, for C_5 methylene protons), 2.31 - 2.55 (2H, m, for C_2 methylene protons), 3.67 (2H, t, J=6 Hz, for C_1 methylene protons).

Analysis: Calculated for $C_8H_{14}O$: C, 76.14; H, 11.18
Found: C, 76.18; H, 11.16.

4-Nonyn-1-ol (75)

Lithium (1.05 g, 0.15 mole) in presence of ferric nitrate (25 mg) was dissolved in freshly distilled ammonia (250 ml) (indicated by disappearance of blue colour). To this lithium amide solution was added tetrahydrofurfuryl chloride (73) (6 g, 0.05 mole) during 10 minutes and was stirred for 2 hrs. at -33°C. To this stirred reaction mixture was added n-butylbromide (33) (6.28 g, 0.05 mole) in THF (10 ml) dropwise. It was stirred for additional 0.5 hr. and ammonia was allowed to evaporate by bringing it to room temperature. Ether (200 ml) was added to the residue followed by saturated NH_4Cl solution. The organic layer was separated and again washed with saturated NH_4Cl solution (3 x 50 ml). Ether layer was dried, concentrated and distilled the residue to get pure (75) in 78% yield (5.46 g).

IR (neat): 3340 (hydroxy), 2940, 2920, 2860, 1465, 1430, 1380, 1330, 930, 910.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet, for C_9 methyl protons), 1.18 - 1.89 (6H, m, for C_2, C_7 and C_8 methylene protons), 1.71 (1H, s, D_2O exchangeable), 2.09 - 2.44 (4H, m, for C_3 and C_6 methylene protons), 3.78 (2H, t, J=6 Hz, for C_1 methylene protons).

Analysis: Calculated for $C_9H_{16}O$: C, 77.09; H, 11.50

Found: C, 77.14; H, 11.52.

Oct-3-ene-1-ol (49)

A mixture of (48) (6.30 g, 0.05 mole) and 30 g of Lindlar catalyst ($Pd-CaCO_3$) in n-hexane (100 ml) containing two drops of quinoline was stirred in an atmosphere of hydrogen till one mole equivalent to hydrogen was absorbed. The catalyst was filtered off and the filtrate was washed successively with dil. HCl, 5%sodium bicarbonate, water, brine and dried (Na_2SO_4). The solvent was removed and the residue was distilled to afford (49) in 95% yield (6.08 g), b.p.80-85°C/1 mm.

IR (neat); 3330 (hydroxy), 2990, 2940, 2910, 2860, 1465, 1375, 1050, 870, 720.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet for C_8 methylene protons), 1.06 - 1.71 (4H, m, for C_6 and C_7 methylene protons), 1.51 (1H, s, D_2O exchangeable), 1.88 - 2.46 (4H, m, for allylic protons), 3.63 (2H, t, J=6 Hz, for C_1 methylene protons), 5.17 - 5.75 (2H, m, for olefinic protons).

Analysis: Calculated for $C_8H_{16}O$: C, 74.94; H, 12.58.
Found: C, 74.88; H, 12.54.

Compound (76)

Hydrogenation of (75) over Lindlar catalyst as above gave (76) in 94% yield.

IR (neat): 3500 (hydroxy), 3020, 3010, 2980, 1660, 1480, 1050.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet for C_8 methyl protons), 1.08 - 1.80 (6H, m, for C_2, C_7 and C_8 methylene protons), 1.47 (1H, s, D_2O exchangeable), 1.84 - 2.44 (4H, m, for C_3 and C_6 allylic protons), 3.67 (2H, t, J=6 Hz, for C_1 methylene protons), 5.20 - 5.60 (2H, m, for olefinic protons).

Analysis: Calculated for $C_9H_{18}O$: C, 75.99; H, 12.76

Found: C, 75.92; H, 12.79.

1-Bromo-oct-3-ene (50)

To a cooled solution of (49) (1.152 g, 0.009 mole) in dry dichloromethane (20 ml) containing triethylamine (2 g, 0.02 mole) was added a solution of methanesulfonyl chloride (1.71 g, 0.015 mole) over a period of 15 minutes and stirred for 3 hrs. The reaction was then washed with ice water, followed by 10% HCl, 5% aq. $NaHCO_3$, brine and dried. The solvent was removed under vacuum to get crude mesylate. The crude mesylate was then stirred with LiBr (1 g) in acetone (20 ml) for 5 hrs. at room temperature. Then the acetone was removed under reduced pressure and the residue dissolved in ether (50 ml) and ether layer was washed with water and dried over Na_2SO_4. Ether was evaporated and the crude compound was distilled to get (50) in 72% yield (1.23 g).

IR(neat): 2940, 2900, 2840, 1450, 1260, 1200, 1010, 960, 720.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet, for C_8 methyl protons), 1.06 - 1.51 (4H, m, for C_6 and C_7 methylene protons), 1.89 - 2.20 (2H, m, of C_5 methylene protons) 2.48 - 2.78 (2H, m, for C_2 methylene protons), 3.36 (2H, t, J=6 Hz, for C_1 methylene protons), 5.17 - 5.73 (2H, m, for olefinic protons).

Mass: 190 and 192 (molecular ion), 162, 150, 148, 135, 119, 109, 95, 93, 81, 79, 69, 67 (base peak), 55, 53.

Compound (77)

The compound (77) was prepared from (76) via its mesylate in 78% yield.

IR(neat): 3000, 2940, 2920, 2840, 1450, 1430, 1370, 1240, 1200, 720.

PMR ($CDCl_3$): 0.89 (3H, distorted triplet, for C_9 methylene protons), 1.03 - 1.53 (4H, m, for C_7 and C_8 methylene protons), 1.62 - 2.31 (6H, m, for C_2, C_3 and C_6 methylene protons), 3.32 (2H, t, J=6 Hz, for C_1 methylene protons), 5.03 - 5.59 (2H, m, for olefinic protons.

Compound (52)

The compound (52) was prepared according to the procedure followed for the compound (3). Thus successive bis alkylations of (21) with (50) and (57) gave (52) in 61% yield.

IR (neat): 2960, 2870, 2825, 2780, 1640 (C=N-stretching), 1470, 1360,1210, 1150, 1130, 1090, 1045, 1000, 915, 880, 825.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet, for C_{14} methyl protons), 1.09 - 2.58 (30H, m), 3.27 - 4.07 (4H, m), 4.53 - 4.67 (1H, broad peak), 5.28 - 5.48 (2H, m, for olefinic protons).

Mass: 352 (molecular ion), 267, 242, 224, 210, 167, 158, 139, 126, 114, 100, 98, 85 (base peak), 81, 67, 60, 55.

Compound (79)

Successive bis alkylation of (21) with (77) and (22) gave (79) in 65% yield.

IR (neat): 2940, 2920, 2840, 1620 (C=N-stretching), 1460, 1140, 1020, 960.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet for terminal methyl protons), 1.09 - 1.68 (12H, m, for C_2, C_3, C_7, C_8 C_{13} and C_{14} methylene protons), 1.81 - 2.56 (14H, m, for C_4, C_6, C_9 and C_{12} protons and broad peak for $-N-(CH_3)_2$ protons), 3.75 - 3.98 (4H, m, for dioxalane ring proton), 4.78 - 4.90 (1H, bs, for dioxalane methine proton), 5.09 - 5.56 (2H, m, for olefinic protons).

Mass: 324 (molecular ion), 304, 280, 237, 208, 180, 153, 140, 136, 128, 113, 109, 100, 99 (base peak), 95, 86, 81, 73, 67, 60, 55.

Analysis: Calculated for $C_{19}H_{36}N_2O_2$: C,70.32;H,11.18;N, 8.63

Found : C,70.37;H,11.13;N, 8.68.

Compound (53)

Selective deprotection of (52) with silica gel was done by following the procedure reported for the compound (11). The yield was 73%.

IR (neat): 3000, 2940, 2870, 1720 (carbonyl), 1460, 1415, 1370, 1360, 1210, 1140, 1130, 1080, 1040, 915, 880, 820, 720.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet), 1.09 - 2.20 (20H, m, three sets of multiplets, one for C_{12} and C_{13} methylene protons, one for three methylene protons of THP and C_2, C_3 methylene protons. Third set is for allylic protons), 2.29 - 2.58 (4H, m, α-to carbonyl methylene protons), 3.24 - 4.02 (4H, m), 4.49 - 4.67 (1H, bs), 5.13 - 5.58 (2H, m, for olefinic protons).

Analysis: Calculated for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04
Found: C, 73.45; H, 11.09.

Compound (80)

Selective deprotection of (79) was done by following the procedure reported for the compound (11). The yield was 69%.

IR (neat): 3010, 2940, 2870, 1720 (carbonyl), 1460, 1415, 1380, 1140, 1030, 940, 710.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet, $-CH_3$), 1.05 - 1.78 (12H, m, for C_2, C_3, C_7, C_8, C_{13} and C_{14}

methylene protons), 1.78 - 2.16 (4H, m, for allylic protons), 2.25 - 2.53 (4H, m, for the methylene protons α to carbonyl), 3.68 - 4.06 (4H, m, for dioxalane methylene protons), 4.79 (1H, distorted triplet for dioxalane methine proton), 5.06 - 5.53 (2H, m, for olefinic protons).

Mass: 282 (molecular ion), 264, 239, 220, 211, 198, 193, 178, 171, 163, 158, 153, 148, 143, 136, 122, 109, 101, 99, 95, 81, 73 (base peak), 69, 55.

Analysis: Calculated for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71

Found: C, 72.38; H, 10.79.

Compound (54)

A mixture of diethylene glycol (20 ml), hydrazine hydrate (4 ml, 80%), potassium hydroxide (0.46 g, 0.01 mole) and the compound (53) (1.55 g, 0.005 mole) was refluxed under N_2 atmosphere for 3 hrs. Excess of hydrazine hydrate was distilled off and the temperature raised upto 180°C and kept there for 3 more hours. The reaction mixture was dissolved in ether. Ether layer was washed with water and dried. Ether was evaporated to get crude (54). This was purified by column chromatography (silica gel, 10% ethyl acetate in pet. ether) to get pure (54) in 22% yield (0.33 g).

IR (neat): 3000, 2940, 2860, 1465, 1360, 1270, 1210, 1130, 1080, 1030, 870, 820

PMR($CDCl_3$): δ 0.87 (3H, distorted triplet, $-CH_3$), 1.03 - 2.16 (26H, m, 13 x $-CH_2$), 3.16 - 4.03 (4H, m), 4.46 - 4.59 (1H, bs), 5.06 - 5.53 (2H, m, olefinic protons).

Analysis: Calculated for $C_{14}H_{36}O_2$: C, 76.97; H, 12.24
Found: C, 76.92; H, 12.21.

Compound (81)

The compound (80) was reduced as above to get the compound (81) in 25% yield.

IR (neat): 3000, 2920, 2830, 1460, 1410, 1380, 1260, 1130, 1030, 970, 720 (cis olefin).

PMR ($CDCl_3$): δ 0.88 (3H, distorted triplet, for terminal methyl protons), 1.03 - 1.71 (18H, m, C_2-C_8 and C_{13}, C_{14} methylene protons), 1.78 - 2.09 (4H, m, for allylic protons), 3.68 - 3.90 (4H, m, for dioxalane methylene protons), 4.62 - 4.78 (1H, distorted triplet, for dioxalane methine proton), 5.03 - 5.40 (2H, m, for olefinic protons).

Mass: 268 M^+, 267, 223, 211, 206, 197, 178, 172, 163, 155, 149, 135, 121, 110, 99, 95, 81, 73 (base peak), 67, 55.

Analysis: Calculated for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02
Found: C, 76.00; H, 12.09.

Compound (55)

To a solution of (53) (0.31 g, 0.001 mole) in methanol (10 ml) was added $NaBH_4$ (0.048 g, 0.001 mole)

and stirred at room temperature for 15 minutes. Then acetone (1 ml) was added to destroy the excess of reagent. The reaction mixture then diluted with water and extracted with ether. Ether layer was washed with water, dried and evaporated to give crude (55). This was purified by column chromatography (silica gel, 15% ethyl acetate in pet.ether) to get pure (55) in 91% yield (0.280 g).

IR (neat): 3400 (hydroxyl group), 2930, 2880, 1460, 1355, 1205, 1120, 1070, 1030.

PMR ($CDCl_3$): δ 0.87 (3H, distorted triplet, for C_{14} methyl protons), 1.06 - 2.18 (25H, m, for C_2-C_4, C_6-C_8 and C_{11}-C_{13} methylene protons, three methylene protons of THP and one D_2O exchangeable proton), 3.15 - 4.06 (m, 4H, for C_1 methylene protons and THP methylene protons linked to oxygen), 4.44 - 4.59 (1H, bs), 5.19-5.41 (2H, m, for olefinic protons).

Mass: 312 M^+, 267, 255, 228, 211, 210, 197, 183, 167, 149, 137, 129, 123, 110, 101, 95, 85 (base peak), 81,67.

Compound (82)

The compound (80) was reduced as above with $NaBH_4$ to get (82) in 92% yield.

IR (neat): 3410 (hydroxy), 3000, 2925, 2860, 1470, 1410, 1140, 1030, 940.

PMR($CDCl_3$): δ 0.88 (3H, distorted triplet, for terminal methyl protons), 1.02 - 1.12 (20H, m), 3.43 - 3.65 (1H, m, for C_5 methine proton), 3.71 - 3.93 (4H, m, for dioxalane methylene protons), 1.71 - 4.87 (1H, distorted triplet, for dioxalane methine proton), 5.12 - 5.43 (2H, m, for olefinic protons).

Compounds (56)

The compound (55) (0.312 g, 0.001 mole) in pyridine (3 ml) and tosylchloride (0.23 g, 0.0012 mole) were stored for one day at 0°C. The reaction mixture was then washed with water and pyridine was removed by distillation. The crude compound was chromatographed (silica gel, 20% ethyl acetate in pet.ether) to get pure (56) in 95% yield (0.44 g).

IR (neat): 3000, 2950, 2870, 1600 (aromatic), 1460, 1370, 1195, 1180, 1140, 1130, 1100, 1085, 1040, 910, 820, 735, 670.

PMR($CDCl_3$): δ 0.87 (3H, distorted triplet, for C_{14} methyl protons), 1.06 - 2.02 (24H, m), 2.43 (3H, s, for aromatic methyl protons), 3.09 - 4.06 (4H, m), 4.34 - 4.71 (2H, m, for C_5 methine proton and THP methine proton), 4.93 - 5.50 (2H, m, for olefinic protons), 7.22 - 7.43 and 7.65 - 7.96 (4H, m, two sets of multiplets for aromatic protons).

Compound (83)

The compound (82) was tosylated as above to get (83) in 94% yield.

IR(neat): 3000, 2920, 2850, 1600 (aromatic), 1450, 1355, 1120, 885.

PMR ($CDCl_3$): δ 0.89 (3H, distorted triplet, for terminal methyl protons), 1.03 - 1.68 (16H, m, 1.75 - 2.18 (4H, m, for allylic protons), 2.43 (3H, s, for aromatic methyl protons), 3.71 - 3.93 (4H, m, for dioxalane methylene protons), 4.34 - 4.81 (2H, m, for C_5 methine and dioxalane methine protons), 7.25 (2H, d, J=8 Hz, aromatic protons), 7.72 (2H, d, J=8 Hz, for aromatic protons).

Compound (54)

To the compound (56) (0.466 g, 0.001 mole) in dry ether (25 ml) was added LAH (0.038 g, 0.001 mole) slowly and stirred for 1 hr. at 0°C. Excess LAH was destroyed by adding ethyl acetate (1 ml), followed by water (1 ml) and stirred for a few minutes. The reaction mixture was then filtered. The filrtate was washed with water, dried and ether was evaporated to give the crude compound (54). This was purified by column chromatography (silica gel, 10% ethyl acetate in pet.ether) to get pure (54) in 76% yield (0.22 g). All spectral properties were identical with the product obtained by Huang-Minlon reduction of (53).

Compound (81) (LAH reduction of (83)

The compound (83) was reduced with LAH as above to get (81) in 72% yield. All spectral properties were identical with the product obtained by Huang-Minlon reduction of (80).

Compound (39)

A methanol solution of the compound (54) (0.148 g, 0.0005 mole) and 5% HCL were stirred for 1 hr. at room temperature. The reaction mixture was then neutralised with 5% $NaHCO_3$ and extracted with ether (3 x 10 ml). Ether layer was washed with water, dried and evaporated to get the compound (39) in 92% yield (0.195 g).

IR (neat): 3400 (hydroxyl), 2940, 2860, 1460, 1210, 1190, 1080, 970.

PMR ($CDCl_3$): δ 0.87 (3H, distorted triplet, for C_{14} methyl protons), 1.02 - 1.73 (6H, m, for C_2-C_7 and C_{12}-C_{13} methylene protons), 1.44 (1H, s, D_2O exchangeable), 1.73 - 2.20 (4H, m, for allylic protons), 3.60 (2H, t, J=6 Hz, for C_1 methylene protons), 5.13 - 5.51 (2H, m, for olefinic protons).

Compound (70)

The compound (81) (0.268 g, 0.001 mole) in methanol (5 ml) and 5% HCL (1 ml) were stirred for one

hour at room temperature. The reaction mixture was neutralised with 5% $NaHCO_3$ and extracted with ether. Ether layer was washed with water, dried and evaporated to get crude aldehyde (70). This was purified by column chromatography to get (70) in 72% yield (0.16 g).

IR (neat): 2980, 2400, 2825, 2700, 1720 (carbonyl), 1450, 1440, 1040, 960.

PMR ($CDCl_3$): δ 0.88 (3H, distorted triplet, for C_{15} methyl protons), 1.06 - 2.15 (20 H, m, for C_3-C_9 and C_{12}-C_{14} methylene protons), 2.28 - 2.53 (2H, m, for C_2 methylene protons), 5.12 - 5.96 (2H, m, for olefinic protons), 9.75 (1H, t, for aldehyde proton).

Mass: 224 M^+, 205, 178, 163, 149, 135, 121, 110, 95, 82 (base peak), 67, 55.

Analysis: Calculated for $C_{15}H_{28}O$: C, 80.29; H, 12.58

Found: C, 80.33; H, 12.52.

Z-9-Tetradecen-1-yl acetate (31):

The compound (39) (0.21 g, 0.001 mole), pyridine (0.5 ml), and acetic anhydride (0.5 ml) were stirred together at 0°C for 5 hrs. The reaction mixture was diluted with water and extracted with ether (3 x 10 ml). Ether layer was washed with water, dried and evaporated to get crude (31). This was purified by column chromatography (silica gel, 10% ethyl acetate in pet.ether) to get pure (31) in 86% yield (0.22 g). All spectral properties were identical with those reported.

REFERENCES

1. E.J. Corey and D. Enders, Tetrahedron Lett., 3, (1976).

2. E.J. Corey, D. Enders and M.G. Bock, Tetrahedron Lett., 7,(1976).

3. E.J. Corey and D. Enders, Tetrahedron Lett., 11, (1976).

4. R.E. Gawley, E.J. Termine and J. Aube, Tetrahedron Lett., 45, 3115 (1980).

5. M.E. Jung, T.J. Shaw, R.R. Fraser, J. Banville, and K. Taymaz, Tetrahedron Lett., 4149 (1979).

6. J.W. Ludwig, M. NewComb, and D.E. Bergbreiter, J.Org.Chem., 45, 4666 (1980).

7. G. Bhasker Reddy and R.B. Mitra, Synth.Commun., 16(13), 1723 (1986).

8. M. Yamashita, K. Matsumiya, M. Tanabe and R. Suemitsu, Bull.Chem.Soc., Jpn., 58, 407 (1985).

9. L. Horner and H. Fernekess, Chem.Ber., 94, 712 (1961).

10. R.E. Erickson, P.J. Andrulis Jr., J.C. Collins, M.L. Lungle and G.D. Mercer, J.Org.Chem., 34, 2961 (1969).

11. E.J. Corey and S. Knapp, Tetrhaedron Lett., 3667, (1976).

12. G.A. Olah, J. Welch and M. Henninger, Synthesis, 308 (1977).

13. G.A. Olah and T.L. Ho, Synthesis, 610 (1976).

14. G.A. Olah and J. Welch, Synthesis, 809 (1976).

15. G.A. Olah, J. Welch, G.K. Suryaprakash and T.L. Ho, Synthesis, 808 (1976).

16. G.A. Olah, J. Welch and T.L. Ho, J.Amer.Chem.Soc., 98, 6717 (1976).

17. R.E. Gawley and E.J. Termine, Synth.Commun., 12, 15 (1982).

18. P. Laszlo and E. Polla, Tetrahedron Lett., 3309 (1984).

19. R.M. Moriarty, Omprakash and P.R. VaVilikolanu, Synth.Commun., 16(10), 1247 (1986).

20. Review, A. McKillop and D.W. Young, Synthesis, 401, 481 (1979).

21. M. Hudlicky, J.Org.Chem., 39, 3461 (1974).

22. T. Kato, N. Katagiri, J. Nakano and H. Kawamura, J.Chem.Soc.,Chem.Commun., 645 (1977).

23. M.D. Bachi and J. Vaya, Tetrahedron Lett., 2209 (1977).

24. F. Huet, M. Pellet and J.M. Conia, Tetrahedron Lett., 3505 (1977).

25. M. Hojo and R. Msuda, Synthesis, 678 (1976).

26. E. Keinan and Y. Mazur, J.Am.Chem.Soc., 99, 3861 (1977).

27. J.S. Filippo, Jr. and C.I. Chern, J.Org.Chem. 42, 2182 (1977).

28. Z. Cohen, E. Keinan, Y. Mazur and T.H. Varkony, J.Org.Chem., 40, 2141 (1975).

29. M. Hojo and R. Masuda, Synth.Commun., 5, 169 (1975).

30. T. Sato, T. Kawara, K. Sakata and T. Fujisowa, Bull.Chem.Soc.,Jpn., 54, 505 (1981).

31. A.A. Sekul and A.N. Sparks, J.Econ.Entomol., 60(5), 1270 (1967).

32. A.K. Minks, W.L. Roelofs, F.J. Ritter and C.J. Persoons, Science, 180, 1073 (1973).

33. P.S. Beevor, D.R. Hall, R. Lesster, R.G. Poppi, J.S. Read and B.F. Nesbitt, Experientia, 31, 22 (1975).

34. M.H. Been, R.A. Galbreath, V.A. Holt, H. Young, G. Down and E. Priesner, Z. Naturforsch, C, 37C, 1130 (1982).

35. D.L. Struble and K.W. Richards, J.Chem.Ecol., 9(6), 785 (1983). C.A.: 99, 117793w (1983).

36. B.F. Nesbitt, P.S. Beevor, A. Cork, D.R. Hall, H. David, V. Nandagopal, J.Chem.Ecol., 12(6), 1377 (1986). C.A., 105, 148131a (1986).

37. C. Lofstedt, J.N.C. Vander Pers, J. Lofqvist, B.S. Lanne, A.G. Bergstrom and B. Thelin, J.Chem.Ecol., 8, 1305 (1982).

38. B. Frerot, M. Lettere, J. Einhorn, D. Michelot, and C. Descoins, J.Chem.Ecol., 8, 663 (1982).

39. W. Meyer, G.L. Debbarr, C.W. Berisford, I.R.Barber and W.I. Roelofs, Environ. Entomol., 11, 986 (1982).

40. R. Baker, J.W.S. Brad Shaw and W. Spe, Experientia, 38, 233 (1982).

41. D. Warthen, J.Med.Chem., 11, 371 (1968).

42. H.J. Bestmann, P. Range and R. Kunstmann, Chem.Ber., 104, 65 (1971).

43. H.J. Bestmann, W. Stransky and O. Vostrowsky, Chem.Ber., 109, 1694 (1976).

44. C.C. Leznoff and T.M. Fyles, J.Chem.Soc.Chem.Commun., 251 (1976).

45. D. Michelot, Synthesis, 130 (1983).

46. V. Fiandanese, G. Marchese, F. Naso and L. Ronzini, J.Chem.Soc., Perkin Trans 1, 1115 (1985).

47. M. Julia and J. Stacino, Tetrahedron, 42, 2469 (1986).

48. S. Ranganathan, V. Maniktala, Raajkumar and G.P. Singh, Indian J.Chem., Sect.B 23, 1197 (1984).

49. T. Chan and W. Huang, J.Chem.Soc. Chem.Commun., 909 (1985).

50. O.P. Vig, M.L. Sharma, S. Kumari and N. Vohra, Indian J.Chem., Sect B, 24, 962, (1985).

51. H. Lindlav and R. Dubuis, Organic Synthesis, 46, 89 (1966).

52. R.K. Crossland and K.L. Servis, J.Org.Chem., 35, 3195 (1970).

53.

54. J.H. Tumlinson, C.E. Yonce, R.E. Dolittle , R.R.Heath, C.R. Gentry and E.R. Mitchell, Science, 185, 614 (1974).

55. K. Yaginuma, M. Kumakura, Y. Tamaki, T. Yushima and J.H. Tumlinson, Appl.Entomol. Zoo., 11, 266 (1976).

56. M. Uchida, K. Mori and M. Matsui, Agric.Biol.Chem., 42, 1067 (1978).

57. M. Uchida, K. Nakagawa and K. Mori, Agric.Biol.Chem., 43(9), 1919 (1979).

58. R.E. Dolittle, A.T. Proveaux and R.R. Heath, J.Chem.Ecol., 6(1), 271 (1980).

59. J.M. Muchowski and C.M. Venuti, U.S. Patent, 4,296,042 (1981). C.A. 96, 68361f (1982).

60. M. Gardette, A. Alexakis and J.F. Normant, J.Chem.Ecol., 9(2), 225 (1983).

61. P.I. Svirskaya and C.C. Leznoff, J.Chem.Ecol., 10(2), 321 (1984).

62. T. Ebata and K. Mori, Agric.Biol.Chem., 43(7), 1567 (1979).

63. P.S. Reddy and J.S. Yadav, Synth.Commun., 14, 327 (1984).