SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS

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Dated July 1987

CERTIFICATE

Certified that the work incorporated in the thesis entitled **SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS** by **K Latha Kumari** was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

A V RAMA RAO
Supervisor

SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS

Insects form an integral part of the biological system. However they often serve as a constant source of aggravation to humans by spreading diseases and destroying crops. Food and agricultural products face severe threat due to infestation by pests, especially in the tropical countries where the temperature and other environmental factors favour their growth. Application of chemicals like chlorinated hydrocarbons, organophosphates, carbamates and lately the pyrethroids have played an important role in their control and remained the only remedy for several decades. However the unrestricted use of pesticides have posed several problems for mankind. Use of chemicals like D.D.T. cause severe environmental pollution. Their low selectivity threatens the existence of many useful insects like pollinators and predators etc. which are very important factors of our ecological balance. Besides insects may become resistant to these chemicals. The above factors, combined with the high cost of insecticides have forced researchers all over the world to explore new chemical approaches for pest control.

The chemical and biological investigations carried out in the insect kingdom by many groups have established the importance and complexity of chemosensory communication among insects. The behavioral pattern of many insects are controlled by chemicals. For example, the queensubstance of the bees informs the colony about the presence of the queen. The 'pheromones' or the messenger substances were thus found

to be a group of biologically active compounds produced by insects and moths to attract individuals of the same species. The word 'pheromone', derived from the Greek 'pherein' (to transfer) and 'hormone' (to excite) was coined and defined by Karlson and Luscher[1] as substances secreted to the outside by one individual and received by a second individual of the same species in which they release a specific action. The first of these chemicals was isolated and identified in 1959 from the wing glands of the female silk worm moth. Wilson[2] classified the pheromones into two categories according to the response they elicit on the other organism, namely the 'releasers' and the 'primers'. Chemical stimuli that trigger an immediate and reversible change in the behaviour of the recipient are called releasers whereas those inducing delayed and lasting responses are referred to as primers.

The specificity of their action has been utilised with great advantage in biological pest control. The economic and environmental importance of biological pest control is currently undergoing experimental evaluation and many natural insect attractants have been successfully applied by several groups[3]. These chemicals have been used to reduce the pest populations by employing attractant baited traps and also in the 'confusion technique' whereby the normal mating behaviour is disrupted by permeating the atmosphere with synthetic attractants. Success in the effort could help reduce our dependence on the highly toxic and nonspecific insecticides which are now being used

widely to protect our agricultural products from insect depradation. Pheromones have been widely accepted by farmers all over the world because they are needed in minute quantities which minimises the possibility of environmental pollution. The species specificity of many natural insect attractants more over reduces the risk of destroying beneficial insects such as pollinators.

As more and more of these pheromones are being used for trapping insects there is an increasing demand for particular pheromones. As the natural pheromones are obtained in very minute quantities which are often insufficient for large scale field trials their chemical synthesis has become an important and inevitable tool to acquire the pheromones in sufficient quantities. Chemical synthesis ensures ample supplies and facilitates their practical application in agriculture. Because of the above reasons many organic chemists throughout the world have undertaken the total synthesis of pheromones.

The work mentioned in this thesis describes a successful attempt in the syntheses of two such economically important pheromones viz. (E,E)-10,12-hexadecadien-1-al and (Z)-11-octadecenal which have been applied for destroying the pests affecting the cotton plantations in this country.

SECTION - A

PART I

SYNTHESIS OF (E,E)-10,12-HEXADECADIENAL

(E,E)-1-,12-Hexadecadienal (I) was first isolated, identified and synthesised by Hall et al.[6,7], as a component of the female sex pheromone of the spiny boll worm, Earias insulana (F.Lepidopterae). The spiny bollworm is a serious cotton pest in Africa and the Mediterranean region extending as far as India and the Middle East. The early detection and monitoring is crucial as the larvae spend most of their time inside the boll, thus making control by pesticides impossible. Monitoring by traps baited with synthetic pheromones is the most efficient tool in the hands of the farmer.

It has already been established that the (E,Z) isomer of 10,12-hexadecadienal is the sex pheromone of the female silkworm Bombyx mori[8] and is known as Bombykal.

I

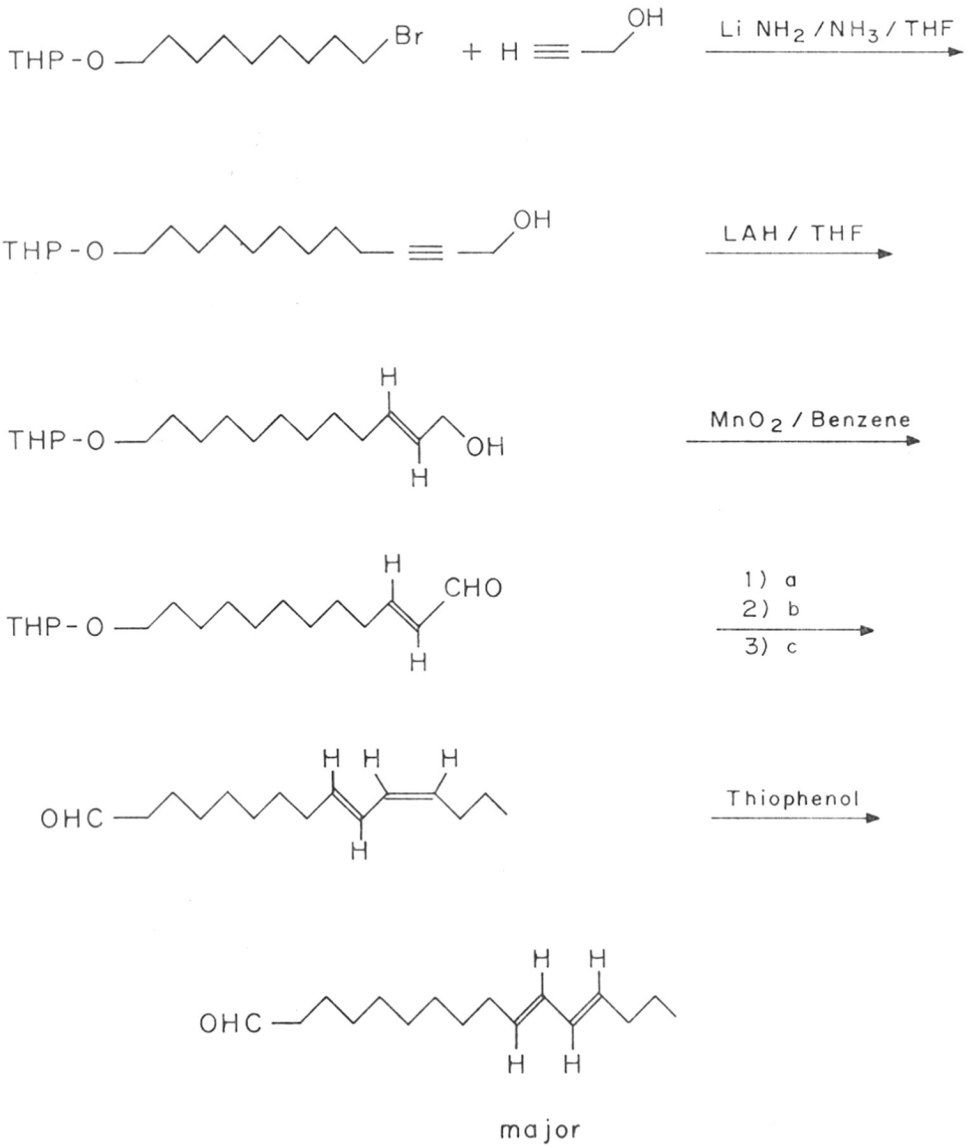
Bombykal

The first synthesis of (I) was reported by Hall et al.[6] (Scheme I). This approach features a Wittig reaction of a trans olefinic aldehyde for the diene formation. The olefin mixture on isomerisation with thiophenol and purification by liquid chromatography gave the pure (E,E) diene (I).

A second synthesis utilising Wittig reaction of a C_{12} aldehyde as key intermediate was reported by K. Daigaku et al.[8]. The

Scheme - 1

D. R. Hall et al. Experientia, 36 152 (1980)



a) $\overset{+}{P}Ph_3\ Br^-$ / NaH / DMSO / THF

b) HCl / MeOH

c) P.C.C. Sodium acetate / $CH_2\ Cl_2$

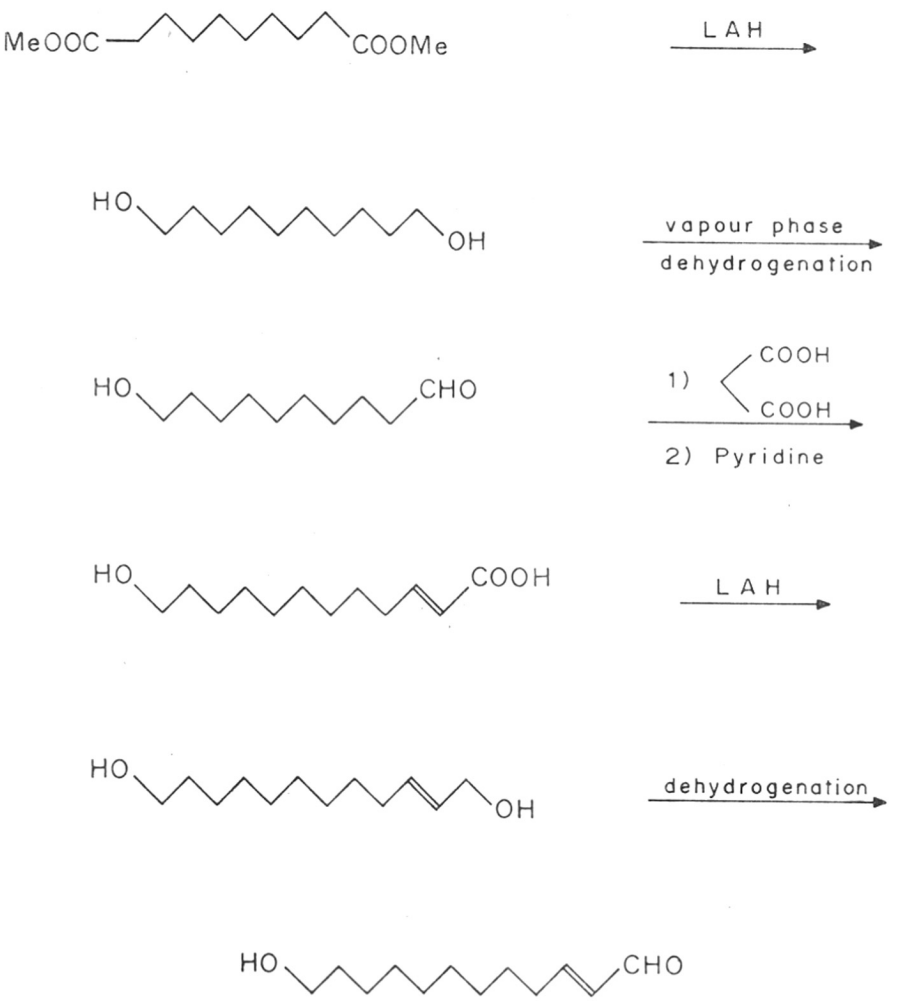
aldehyde was made in six steps from sebacic acid (**Scheme 2**).

A stereospecific synthesis of **1** was reported by Knox and Thom[7] in which the stereochemistry of the double bond was fixed by a suitable protecting group (**Scheme 3**). Iron carbonyl derivatives of suitably substituted butadienes (**3**) on Friedel-Crafts reaction gave the pure dienone complex (**4**). Reduction of **4** followed by cleavage with trimethyl amine N-oxide gave **1**.

Klug et al.[9] reported a short synthesis starting from 1,10-decane diol (**Scheme 4**) in which the Wittig reaction of **5** was performed under thermodynamic equllibrium conditions to yield mainly the trans isomer **6** under Schlosser conditions[10]. **6** on crystallisation gave the pure E,E-isomer which on oxidation using pyridiniumchlorochromate gave **1**.

Scheme - 2

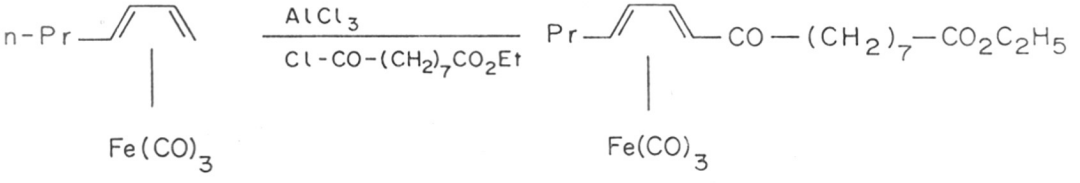
K. Daigaku , Rikogakubu (C.A. 93 25825 f)



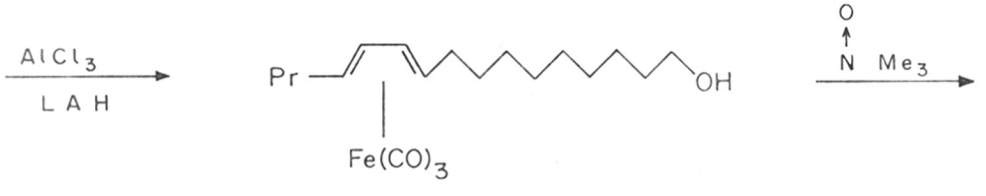
Scheme - 3

Graham. R. Knox and Ian. G. Thom.

J.C.S., Chem. Commun. 373 (1981)



3 4

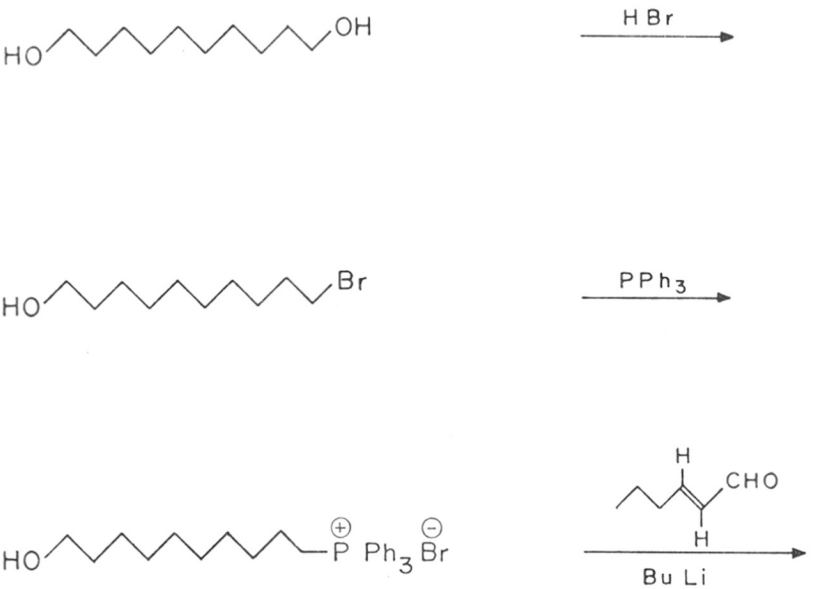


1

Scheme - 4

Jacob. T. Klug . Jacqueline Skarka and Arnon Shani

Chem. Ind. 372 (1982)



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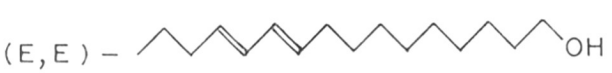


6

1

PRESENT WORK

The chemical structures of many of the known pheromones, particularly those belonging to the Lepiodoptera (moths and butterflies) contain a long carbon chain with a terminal functionality (acetate, aldehyde or alcohol) and which often incorporates an olefinic bond or a conjugated diene system[5] (EE, EZ, ZE or ZZ).

Carbon-carbon double bond formation is a very important tool in synthetic organic chemistry. Acetylenic compounds are very important synthons[11] for the preparation of compounds containing triple bonds which in turn can be utilised for the stereospecific introduction of cis or trans double bonds into the system by employing the desired reagents and reaction conditions. For example, acetylenic compounds on treatment with sodium in liquid ammonia[12,13] organo aluminium compounds[14], organo-zirconium compounds[15] and organoboranes[16] yield the trans olefins whereas hydrogenation with Lindlar's catalyst[17] and P-2 nickel[18] give cis olefins. 2-Alkyn 1-ols on reaction with LAH[19,20] or organotin compounds yield trans-2-alkane-1-ols.

Acetylenic compounds are generally prepared by the alkylation of acetylenes with appropriate halides. In the present synthesis a general method for the preparation of acetylenic alcohols was exploited for the synthesis of **I**. This method, based on the alkylation of the dianion of 4-pentyn 1-ol (generated in situ from tetrahydrofurfuryl chloride by the action of a strong base

(lithium amide))is well documented in literature[21,22]. The synthetic utility of these alkylations for the synthesis of insect pheromones was established by Yadav et al.[23].

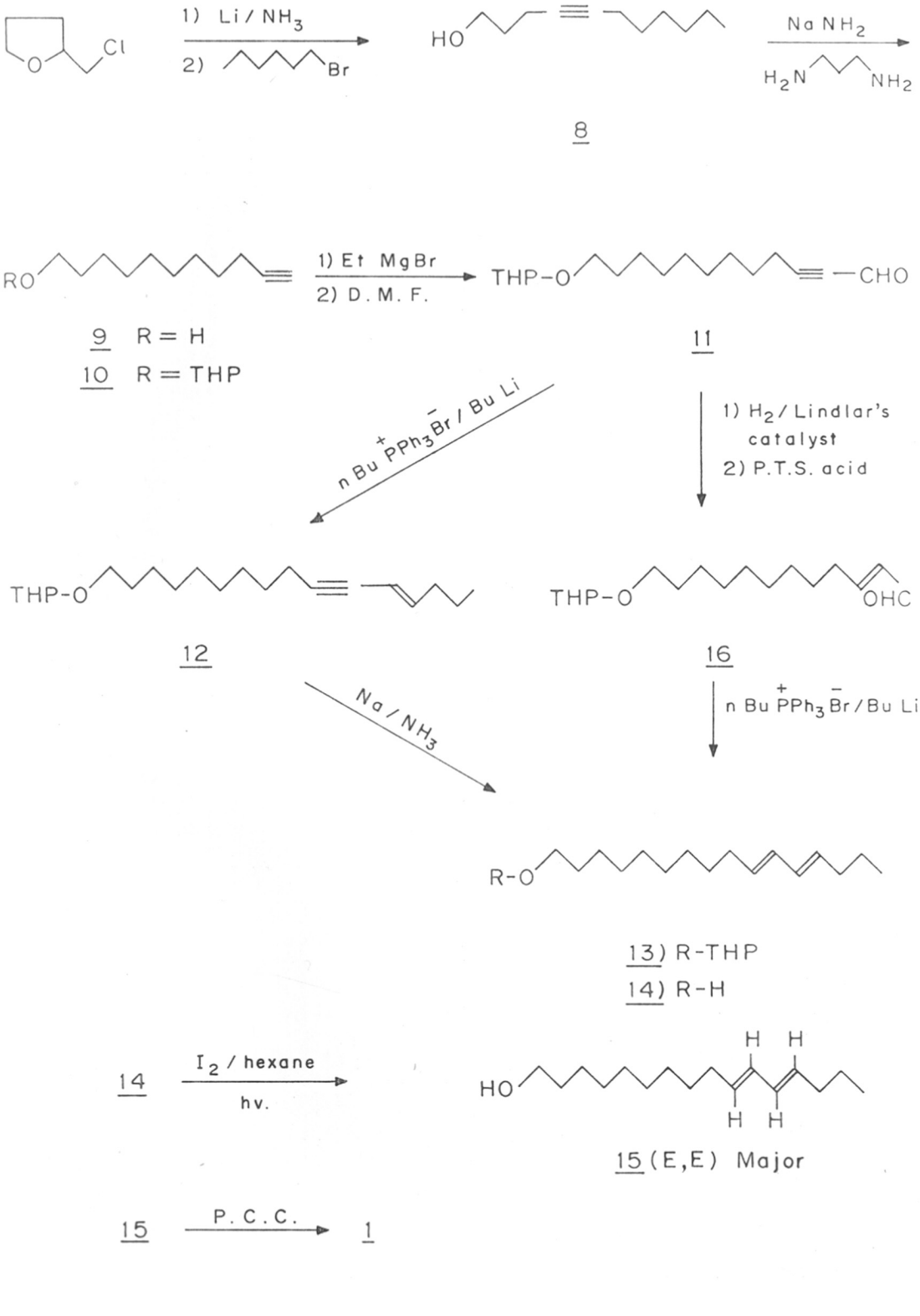
The characteristic features of **I** are (a) a 16-carbon chain with a terminal aldehyde functionality and (b) a trans, trans diene system at C_{10} and C_{12} respectively.

The key step in the present synthesis was therefore the preparation of a suitably substituted acetylenic compound which could be extended further or modified later to the desired carbon chain with the required functionalities.

Thus the present synthesis of **I** was completed in four main steps, consisting of (a) the alkylation of 4-pentyn 1-ol, (b) an acetylenic zipper reaction (c) a formylation and (d) Wittig reaction followed by further modifications (**Scheme 5**).

The synthesis of **I** starts from easily available (commercial) tetrahydrofurfuryl alcohol. Tetrahydrofurfuryl chloride, obtained from tetrahydrofurfuryl alcohol by a known procedure[24] on treatment with lithium in liquid ammonia gave the dianion of 4-pentyn 1-ol which was directly alkylated with hexyl bromide to give the alcohol **8**[25]. The IR spectrum of **8** showed absorptions at 3320 cm^{-1} and 2110 cm^{-1} (weak) for -OH and C≡C respectively. **8** in its PMR spectrum (Fig.1) showed a distorted triplet at δ 0.9 representing the methyl protons. The CH_2-OH protons appeared

Scheme -5


1) Li / NH3
2) Br
HO
Na NH2
H2N NH2
8
RO
1) Et MgBr
2) D.M.F.
THP-O
—CHO
9 R = H
10 R = THP
11
n Bu PPh3Br / Bu Li
1) H2 / Lindlar's catalyst
2) P.T.S. acid
THP-O
THP-O
OHC
12
16
Na / NH3
n Bu PPh3Br / Bu Li
R-O
13) R-THP
14) R-H
14
I2 / hexane
hv.
HO
H H
H H
15 (E,E) Major
15
P.C.C.
1

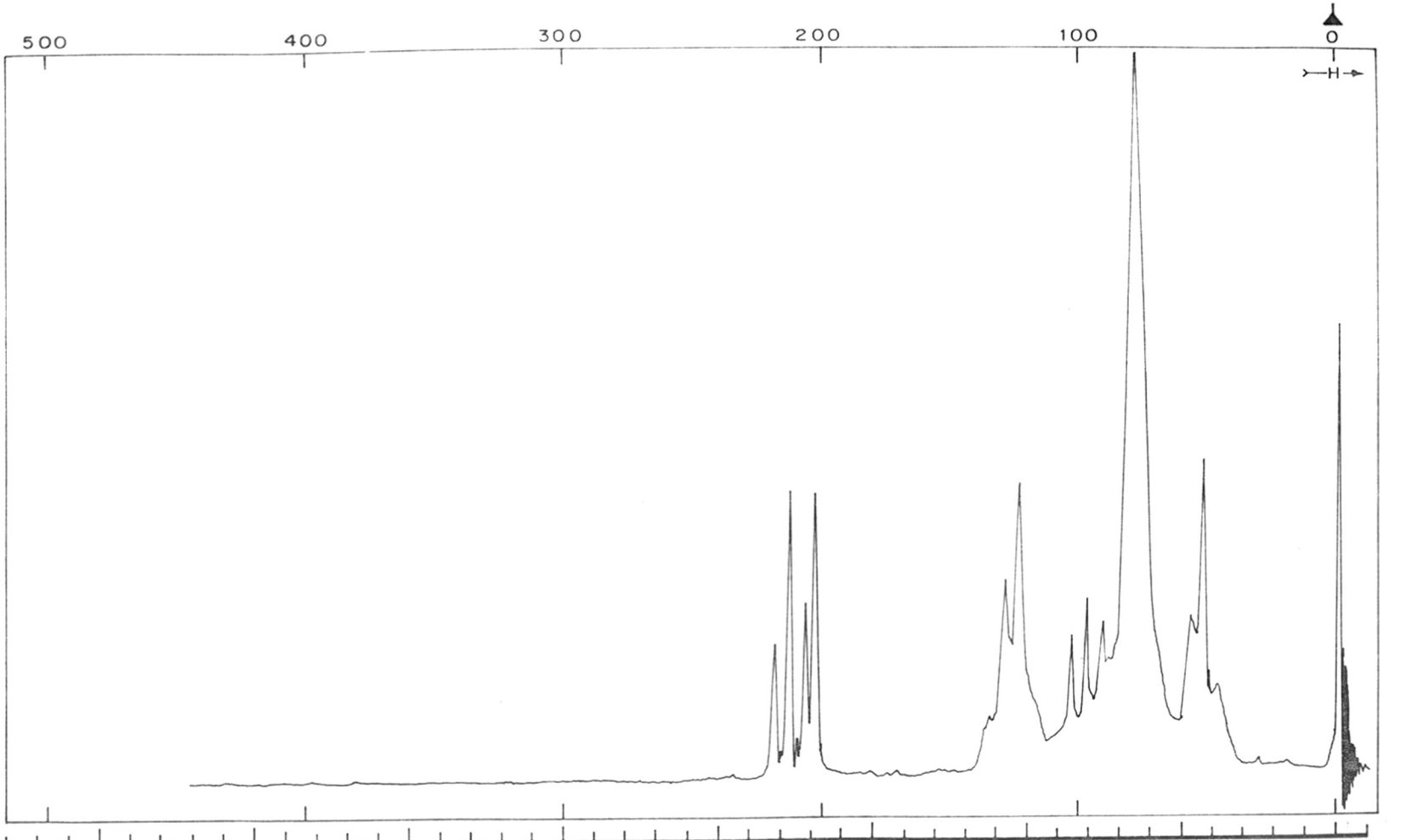


FIG. 1 PMR SECTRUM OF COMPOUND (8) IN $CDCl_3$

as a triplet at δ 3.5 and the rest of the proton signals were observed atthe expected chemical shifts.

In functionalised alcohols such as acetylenic alcohols, the successful multipositional isomerisation[26] of tripple bonds provide a simple and convenient route to long chain aliphatic compounds with different remote functionalities. Migration towards the functional group will produce side reactions. But in the case of acetylenic alcohols, the quantitative conversion of C-OH to $C\text{-}O^-$ would presumably suppress side reactions. Thus the migration of triple bonds of internal acetylenic alcohols to the terminus remote from the hydroxyl group is an attractive and novel synthetic tool for C-C bond formation. The isomerisation of internal acetylenic alcohols is called "acetylene zipper" reaction. The isomerisation is effected using potassium-3-aminopropylamide (KAPA) in 1,3-diaminopropane prepared from potassium hydride at 0°. This isomerisation can also be achieved by employing metal amides such as potassium amide or sodium amide but the reaction requires elevated temperatures.

Accordingly the alcohol **8** was subjected to the acetylene zipper reaction by employing sodium amide in 1,3 diaminopropane at 80-85° for 4 hours, to give the acetylene compound **9**[34] in 80% yield. The IR spectrum of **9** showed strong absorption at 2140 cm^{-1} for terminal C≡C and the C≡C-H stretching as a sharp peak at 3340 cm^{-1} merging with the OH absorption as a clear indication of the isomerisation of the internal triple bond to

the terminal of the carbon chain. The proton spectrum (Fig.2) of **9** in CCl_4 showed the absence of the methyl triplet. The terminal acetylenic proton resonated as a triplet at δ 1.75 and the remaining protons gave the signals at the expected chemical shifts.

The alcoholic function in **9** was protected to a tetrahydropyranyl ether using dihydropyran and catalytic amounts of p-toluenesulfonic acid before subjecting it to the next reaction. The tetrahydropyranyloxy derivative **10** obtained in 85% yield showed the disappearance of OH absorption while terminal acetylenic C-H stretching was noticed clearly at 3320 cm^{-1}. The PMR spectrum showed the characteristic signals for the THP proton at δ 4.55. Acetylenic Grignard compounds or the corresponding organoalkali metal derivatives are important intermediates in many synthesis of acetylenic compounds[27]. The various methods for their formation in organic solvents and in liquid ammonia have been discussed extensively[11].

Deprotonation of terminal acetylenes by organolithium compounds in organic solvents or by alkali metal amides in ammonia is an extremely fast reaction even at very low temperatures and in solvents of relatively low polarity. But Grignardation of terminal acetylenes proceed more slowly and are carried out more easily in THF than in diethyl ether. The acetyl Grignards thus formed react with dimethylformamide at very low temperatures

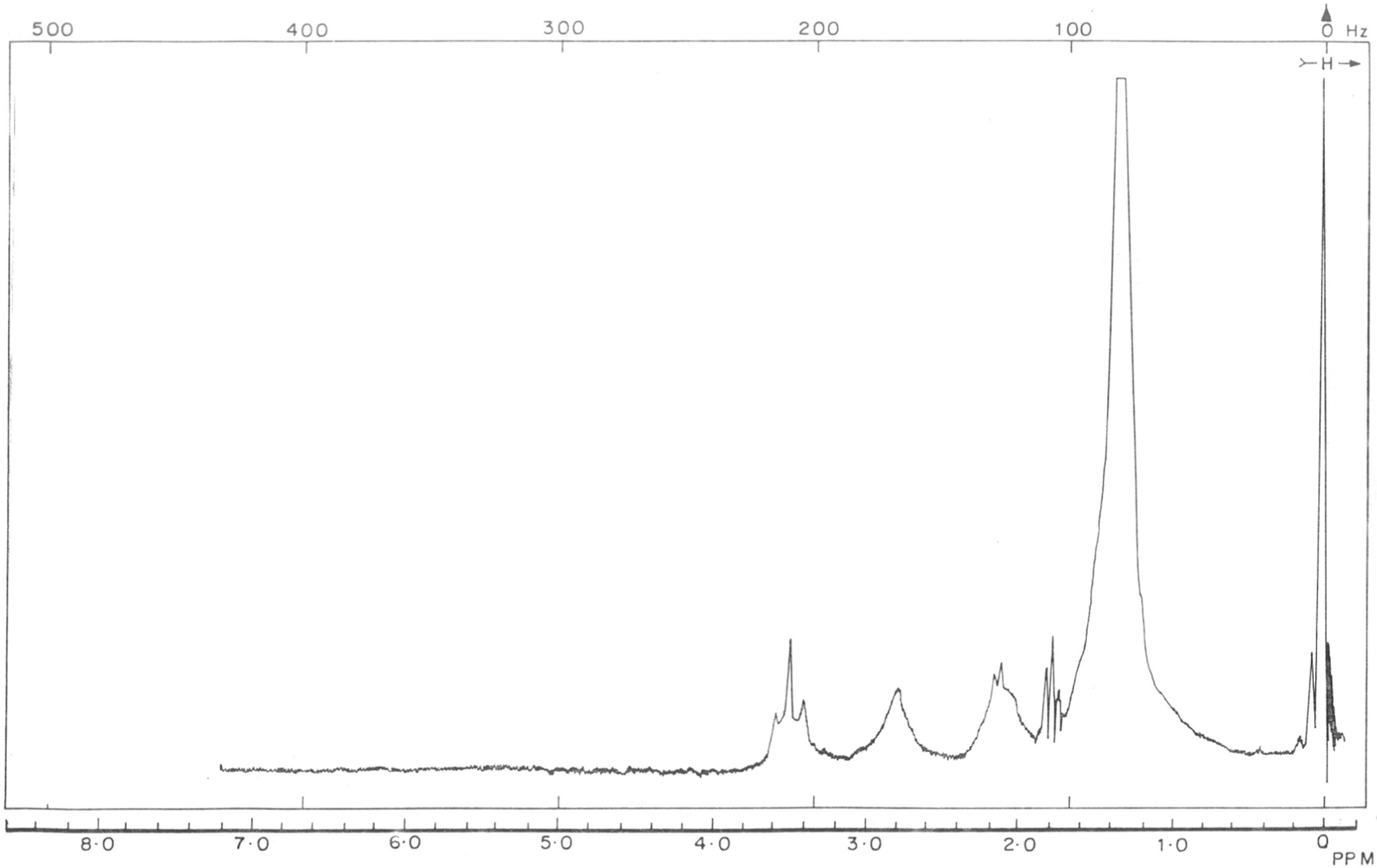


FIG. 2 PMR SPECTRUM OF COMPOUND (9) IN $CDCl_3$

to give ∝ acetylenic aldehydes.

The extension of the C_{11} carbon compound **10** to a chain of 12 carbons was thus achieved by exploiting the reactivity of terminal acetylenic protons towards Grignard reagents. The acetylenic compound **10** obtained bythe zipper reaction was deprotonated with ethyl magnesium bromide and treated at -30° with dimethylformamide to give 12-hydroxy 2-dodecyn-1-al (**11**) in 43% yield. The IR spectrum of **11** showed the carbonyl absorption at 1720 cm^{-1} while the C≡C stretching was observed as a sharp peak at 2200 cm^{-1}. The PMR (**Fig.3**) spectrum of **11** showed the chemical shift for CHO at δ 9.3 as a singlet along with all the other protons at the expected chemical shifts.

Aldehydes serve as excellent synthons for the extension of the carbon chain, and are easily converted to disubstituted olefins when subjected to a Wittig reaction with desired phosphoranes. Thus introduction of a double bond at C-12 along with the extension of the carbon chain to the required C_{16} unit was achieved simultaneously when **11** was made to react with n-butyl triphenylphosphorane liberated in situ by the action of base (n-butyl lithium potassium t-butoxide or sodamide) on n-butyl triphenylphosphonium bromide. The product **12** obtained on almost quantitative yield showed characteristic spectral data. The IR of **12** showed bands at 650 cm^{-1} as well as 970 cm^{-1} for the cis and trans double bonds. The PMR (**Fig.4**) of **12** showed olefinic absorption as a multiplet at δ 6.2. The rest of the protons resonated at the expected chemical shifts.

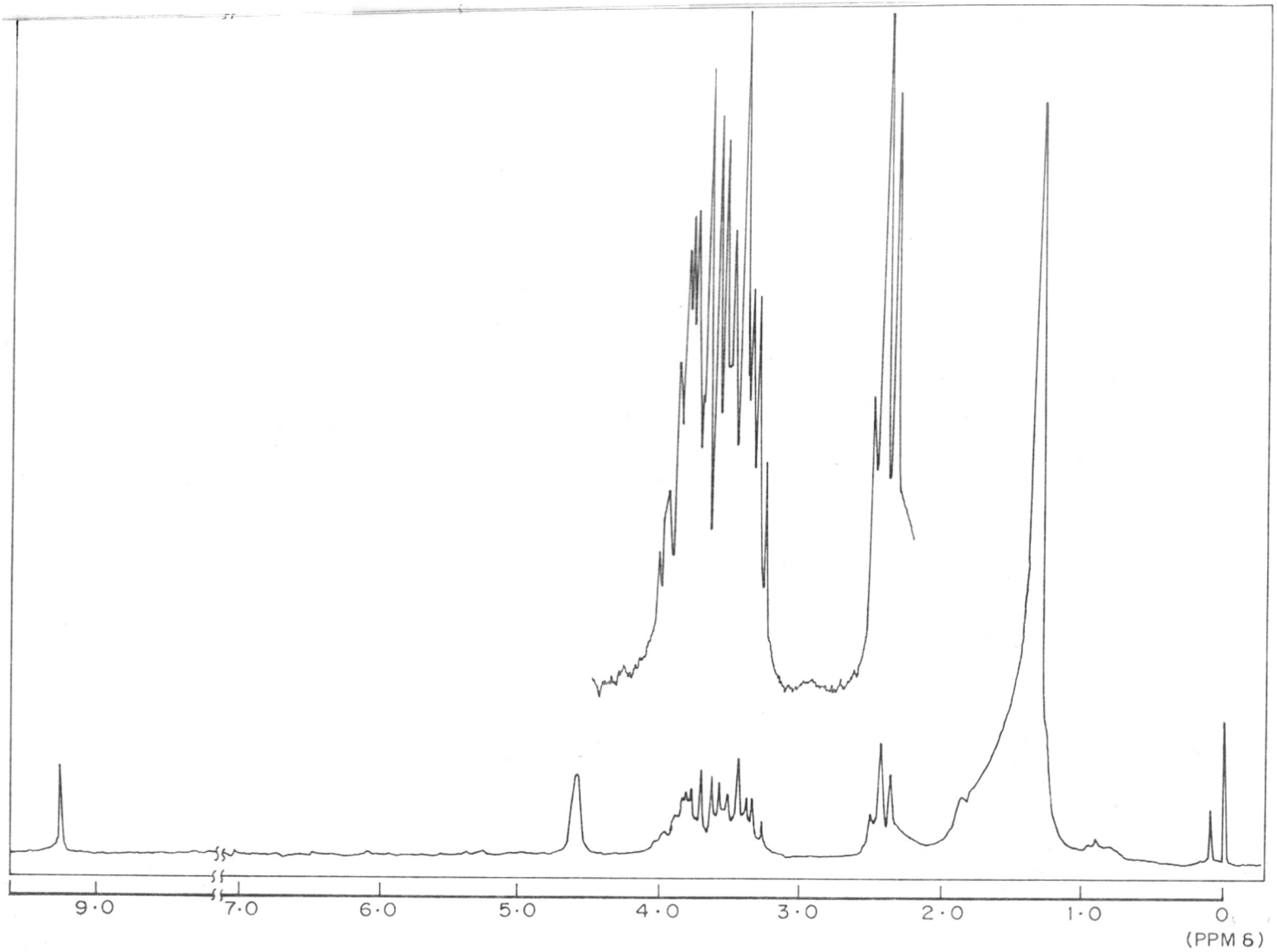


FIG. 3 PMR SPECTRUM OF COMPOUND (11) IN $CDCl_3$

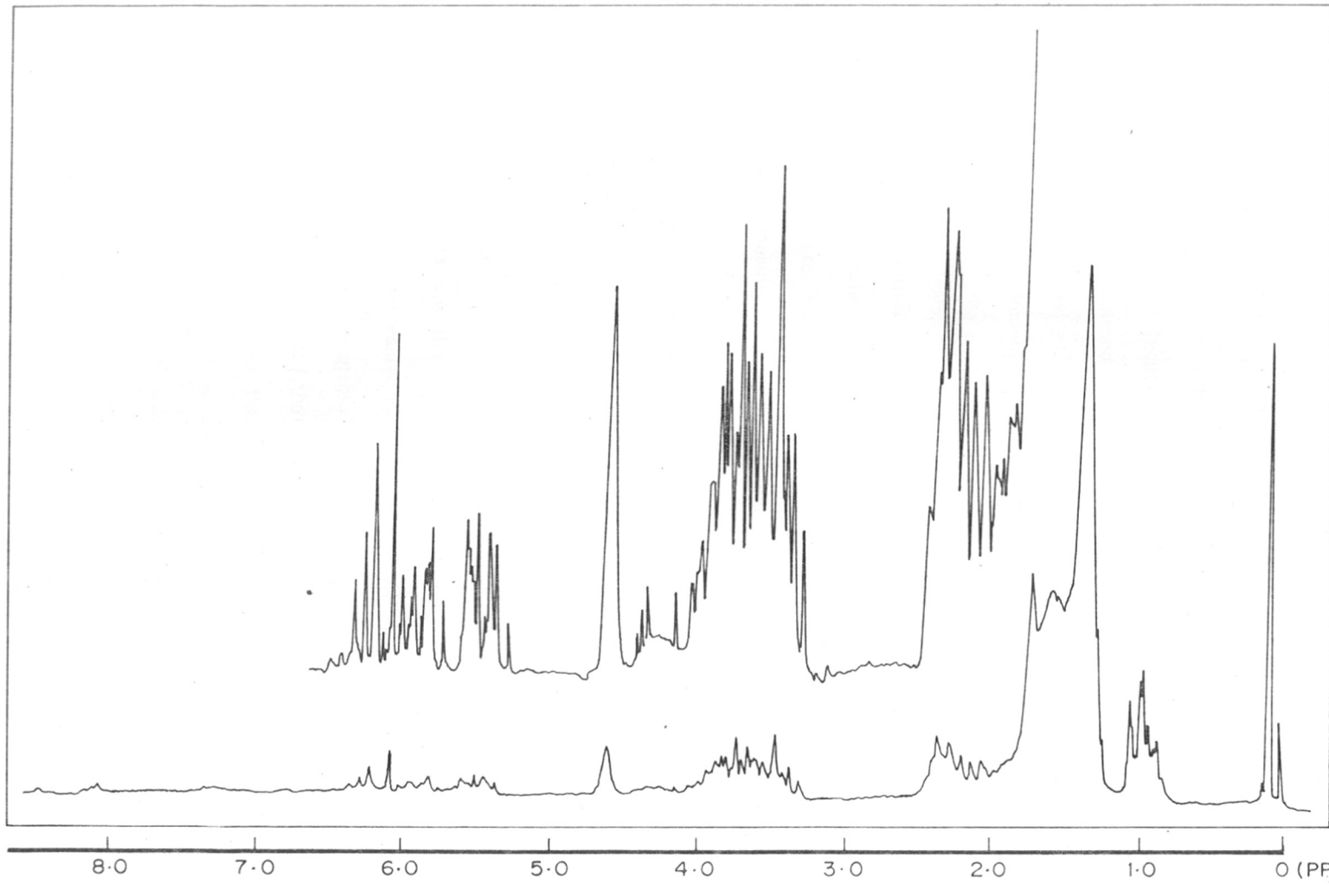


FIG. 4 PMR SPECTRUM OF COMPOUND (12) IN $CDCl_3$

Having achieved the C_{16} carbon skeleton, attention was now diverted to achieve the required stereochemistry of the double bonds. Reduction of triple bonds to trans double bonds is well established in literature[12-16]. Thus a trans-double bond was introduced at C_{10} by subjecting 12 to reduction using sodium in liquid ammonia. The diene system 13 was thus obtained in 70% yield.

Alternatively, aldehyde was hydrogenated using Lindlar's catalyst, when a mixture of cis and trans olefinic aldehydes (16a) were obtained (Fig.5). Treatment of this mixture using p-toluenesulfonic acid in benzene converted the mixture quantitatively to a purely trans-aldehyde 16 (Fig.6) which, when subjected to the same Wittig reaction yielded 13 in 60% yield. The IR of 13 showed absorptions at 970 cm^{-1} (trans double bond) and 670 cm^{-1} (cis double bond). The PMR (Fig.7) of 13 showed the olefinic protons as two broad multiplets δ 6.08 and 6.8 respectively. The rest of the protons resonated at the expected chemical shifts. 13 was thus obtained as a mixture of E,E and E,Z dienes. They could be easily isomerised to a 9:1 mixture of EE and EZ using different reagents[6,28]. In their synthesis of 1, Jacob Klug et al.[9] have reported that the EE isomer of 13 crystallises preferentially than the other three isomers. Separation of the EE isomer was thus achieved by exploiting this behaviour. Accordingly, 13 was deprotected using Amberlite in methanol to the free alcohol 14 which showed IR bands characteristic of the free alcohol at 3300 cm^{-1}. 14 was subjected to isomerisation under

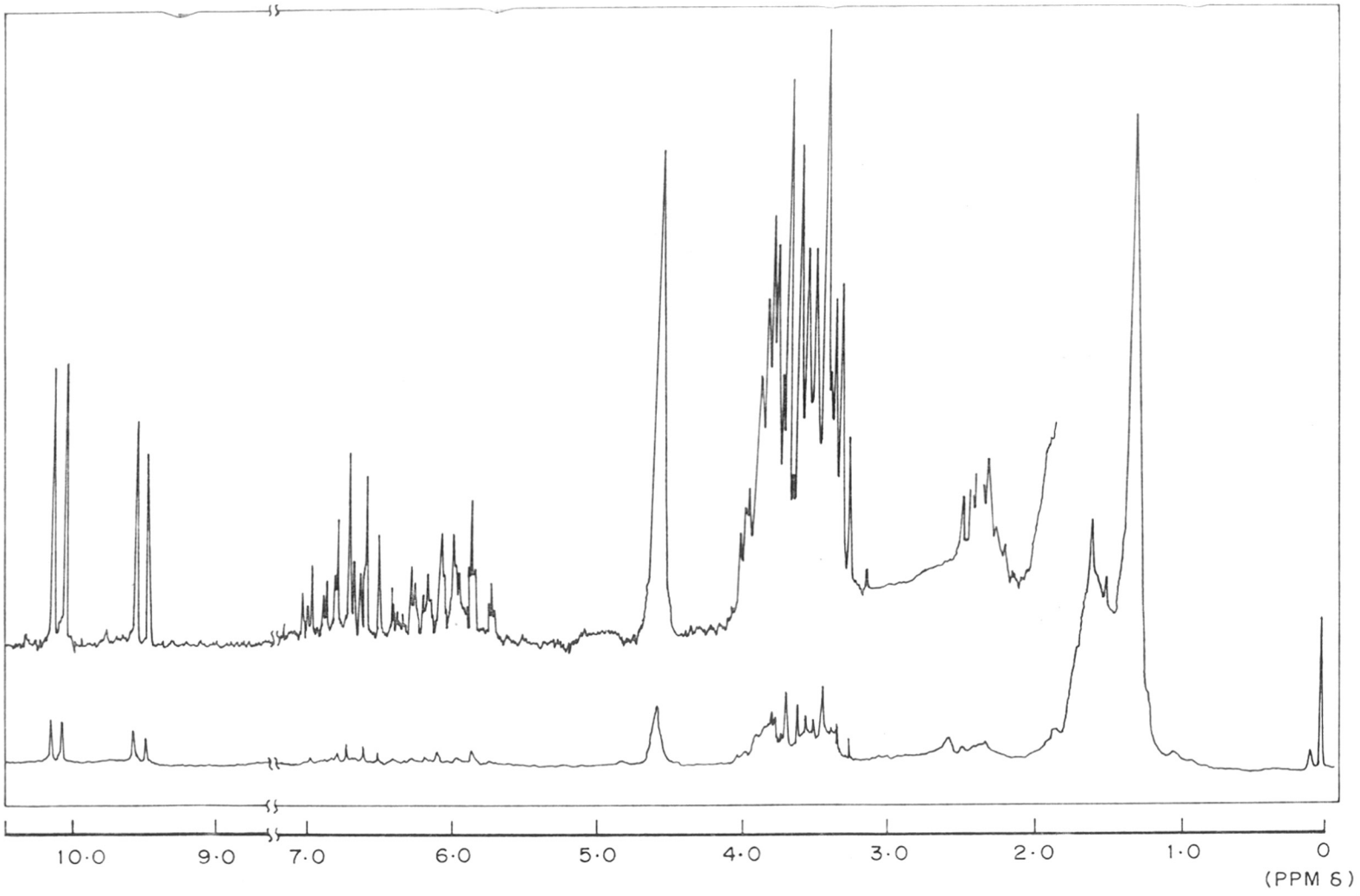


FIG. 5 PMR SPECTRUM OF COMPOUND (16a) IN $CDCl_3$

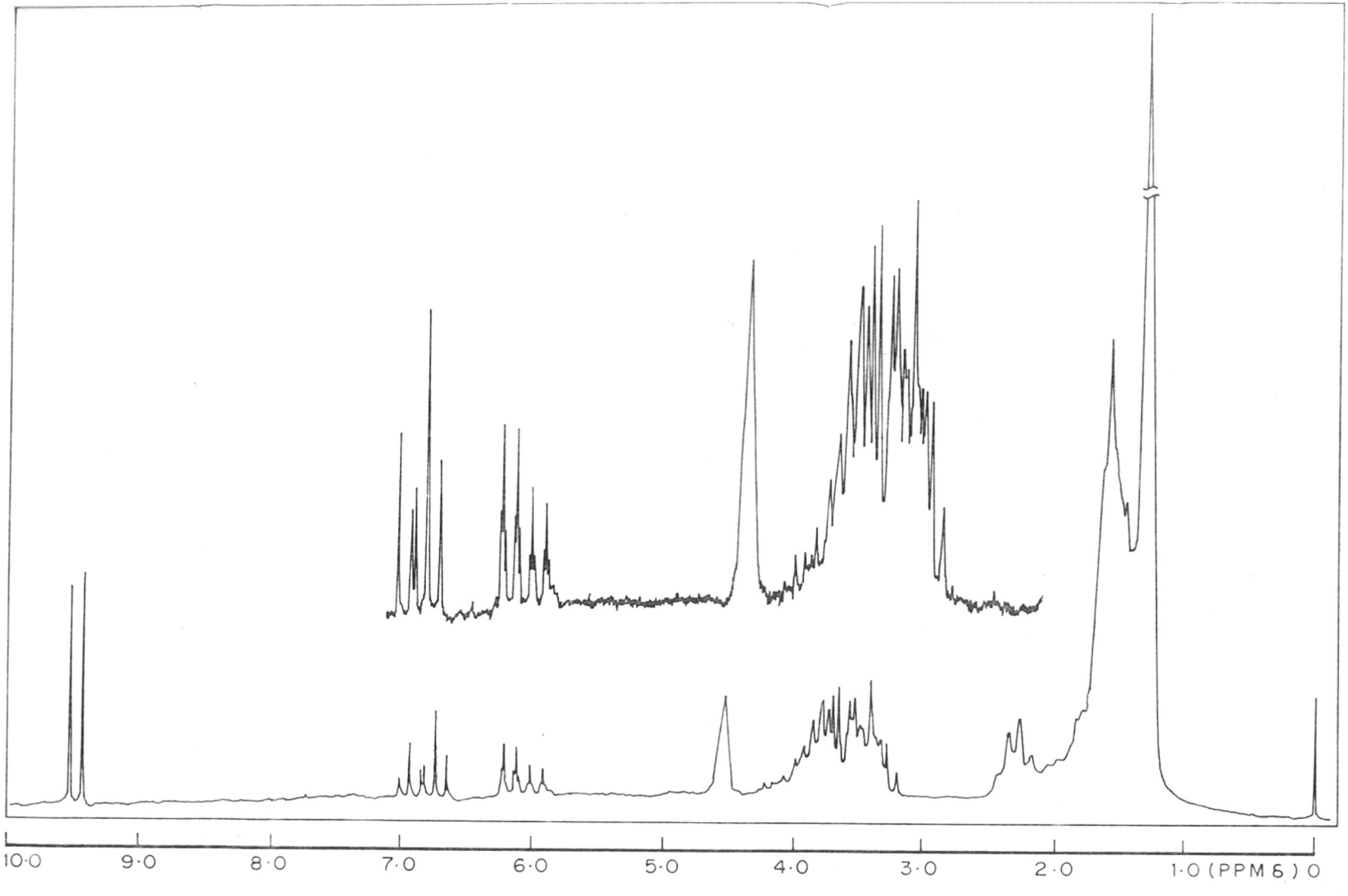


FIG. 6 PMR SPECTRUM OF COMPOUND (16) IN $CDCl_3$

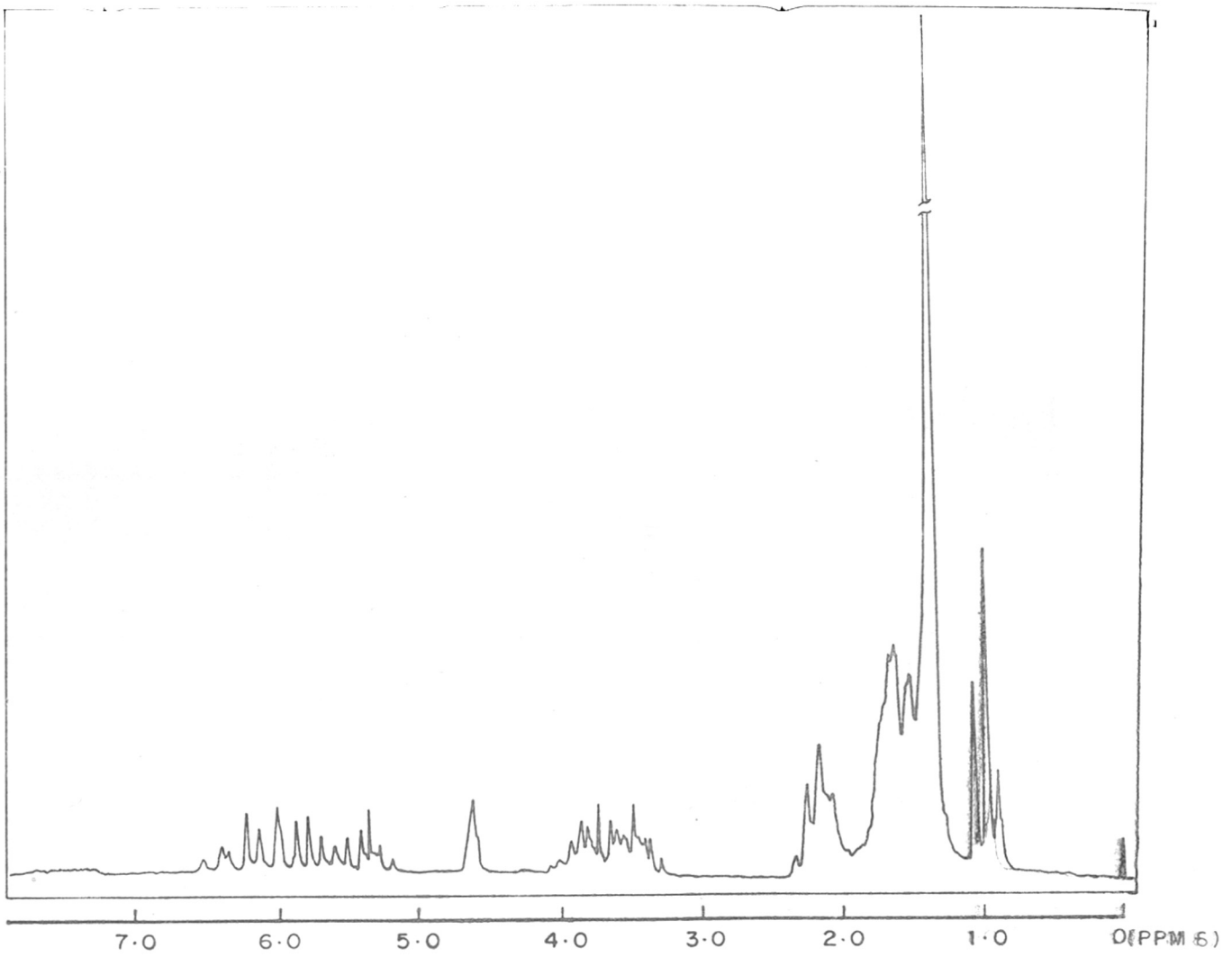


FIG. 7 PMR SPECTRUM OF COMPOUND (13) IN $CDCl_3$

photolytic conditions to a mixture of isomers in which the EE was predominant. Crystallisation of this mixture in hexane at -20° gave the EE isomer 15[35]. The mother liquor was reisomerised and crystallised again to an overall yield of 60%. IR and NMR spectrum of 15 showed a broad absorption at 3300 cm^{-1} for the OH stretching, and sharp absorption at 980 cm^{-1} denoting trans double bonds. In its PMR spectrum 15 showed the olefinic protons as two complex multiplets at δ5.3 - 5.73 and 5.84 to 6.2 respectively.

The successful attempt in obtaining 15 solved the most crucial part of the synthesis namely the required EE stereochemistry of the two double bonds. The goal could be reached very easily bya fast and well known conversion of the hydroxy function in 15 to an aldehyde group through a pyridinium chlorochromate oxidation to 1. The IR spectrum of 1 showed neat absorptions at 1700 cm^{-1} for the carbonyl group and at 970cm^{-1} for trans double bonds. The PMR (**Fig.8**) of 1 showed olefinic protons as two multiplets from δ 5.32 to 6.08 and the aldehyde proton as a triplet atδ9.72. The structure of 1 was further confirmed when the PMR of 1 was shown to be superimposable to the PMR of an authentic sample[29].

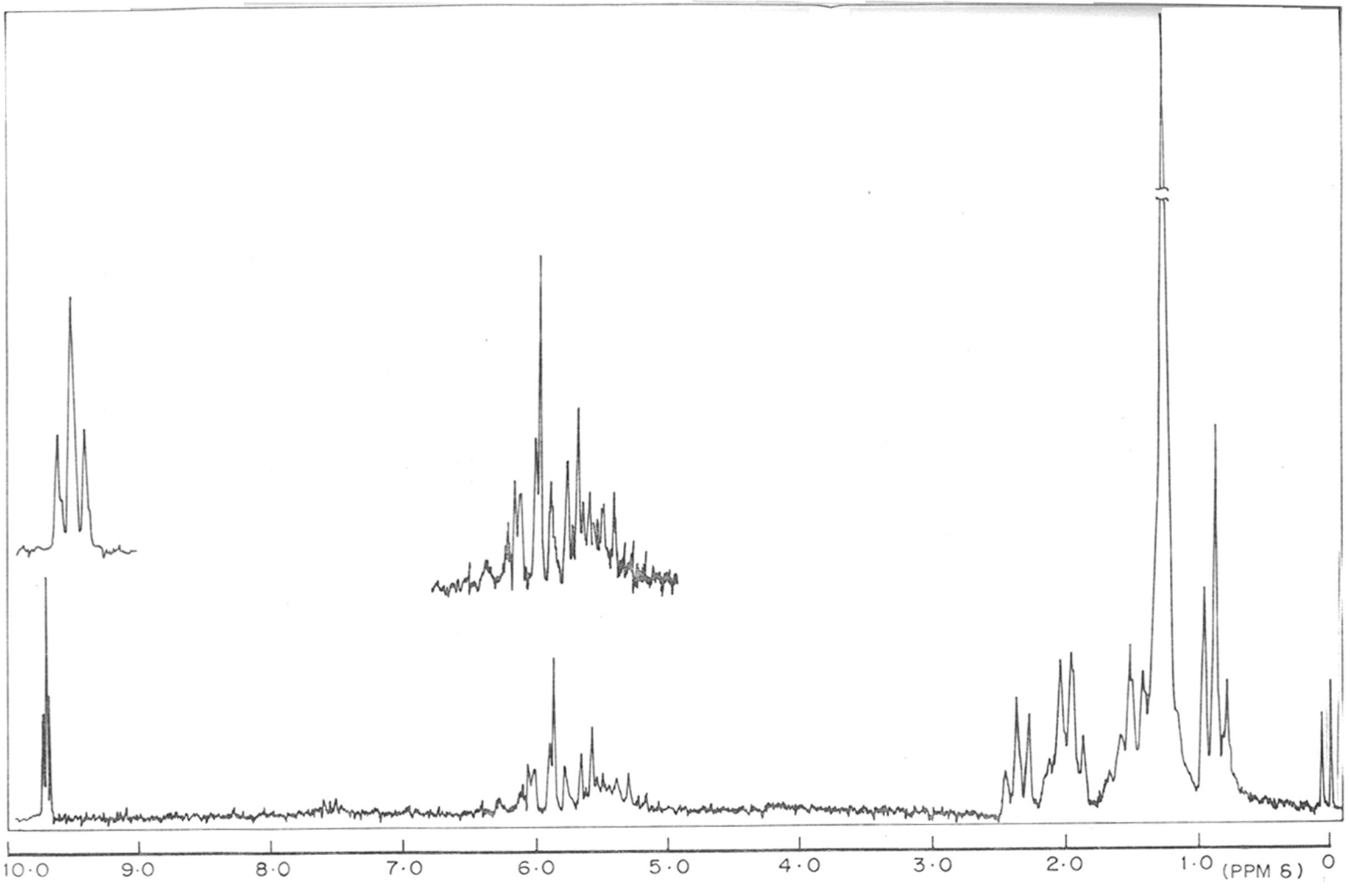


FIG. 8 : PMR SPECTRUM OF COMPOUND (1) IN $CDCl_3$

PART II

SYNTHESIS OF I FROM UNDECENOIC ACID

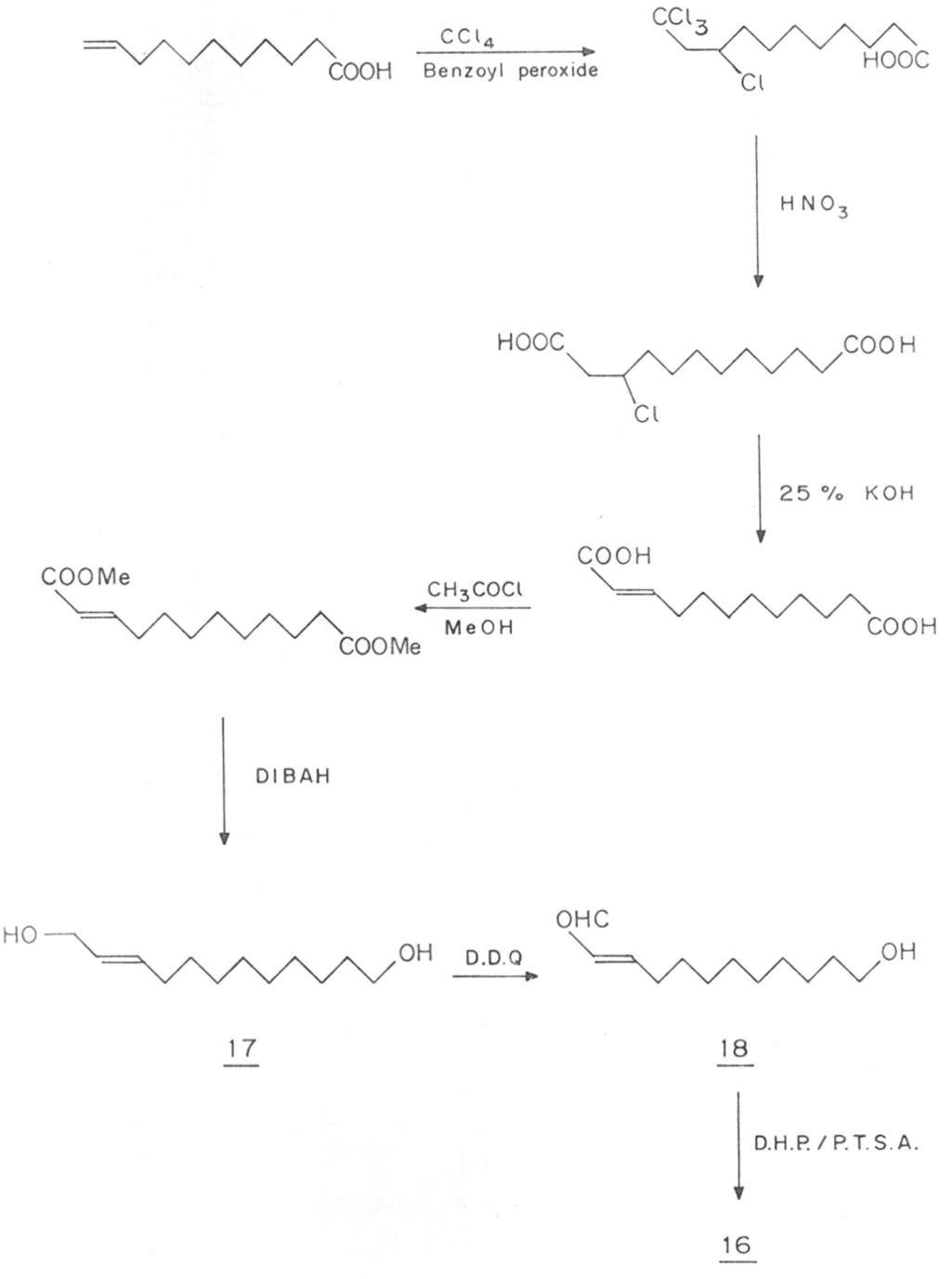
The successful venture to prepare 1 from acetylenic precursors prompted us to explore another route to synthesise this pheromone in a shorter route. This was achieved by synthesising aldehyde 16 mentioned in the earlier Section from undecenoic acid, a cheap and easily available chemical.

Undecenoic acid was converted to trans-2-dodecenoic acid dimethyl ester through a known procedure[30] (**Scheme 6**). DIBAH reduction of the diester provided a 62% yield of 2-dodecene-1-12-diol[33] (17) as a low melting white solid. The IR of 17 showed a broad band at 3340 cm^{-1} denoting the hydroxy groups and a sharp absorption at 970 cm^{-1} denoting a trans olefine. The PMR (**Fig.9**) of 17 showed the olefinic protons as a multiplet at δ 5.66 The rest of the protons were seen at the expected chemical shifts.

The allylic hydroxy function in 17 when oxidised with MnO_2 resulted in very poor yields of aldehyde 18. However a quantitative conversion of 17 to 18 was achieved by replacing MnO_2 with DDQ. Subsequent protection of the hydroxy function using DHP provided 16 which was identical in all respects to the aldehyde obtained by the hydrogenation and subsequent isomerisation of 11 which is already mentioned in the earlier Section.

Wittig reaction of 16 and the phosphorane generated from n-butyl triphenyl phosphonium bromide using n-butyl lithium gave the diene 13 directly.

Scheme - 6


COOH
CCl_4
Benzoyl peroxide
CCl_3
Cl
HOOC
HNO_3
HOOC
COOH
Cl
25 % KOH
COOH
COOH
COOMe
COOMe
CH_3COCl
MeOH
DIBAH
HO
OH
D.D.Q
OHC
OH
17
18
D.H.P. / P.T.S.A.
16

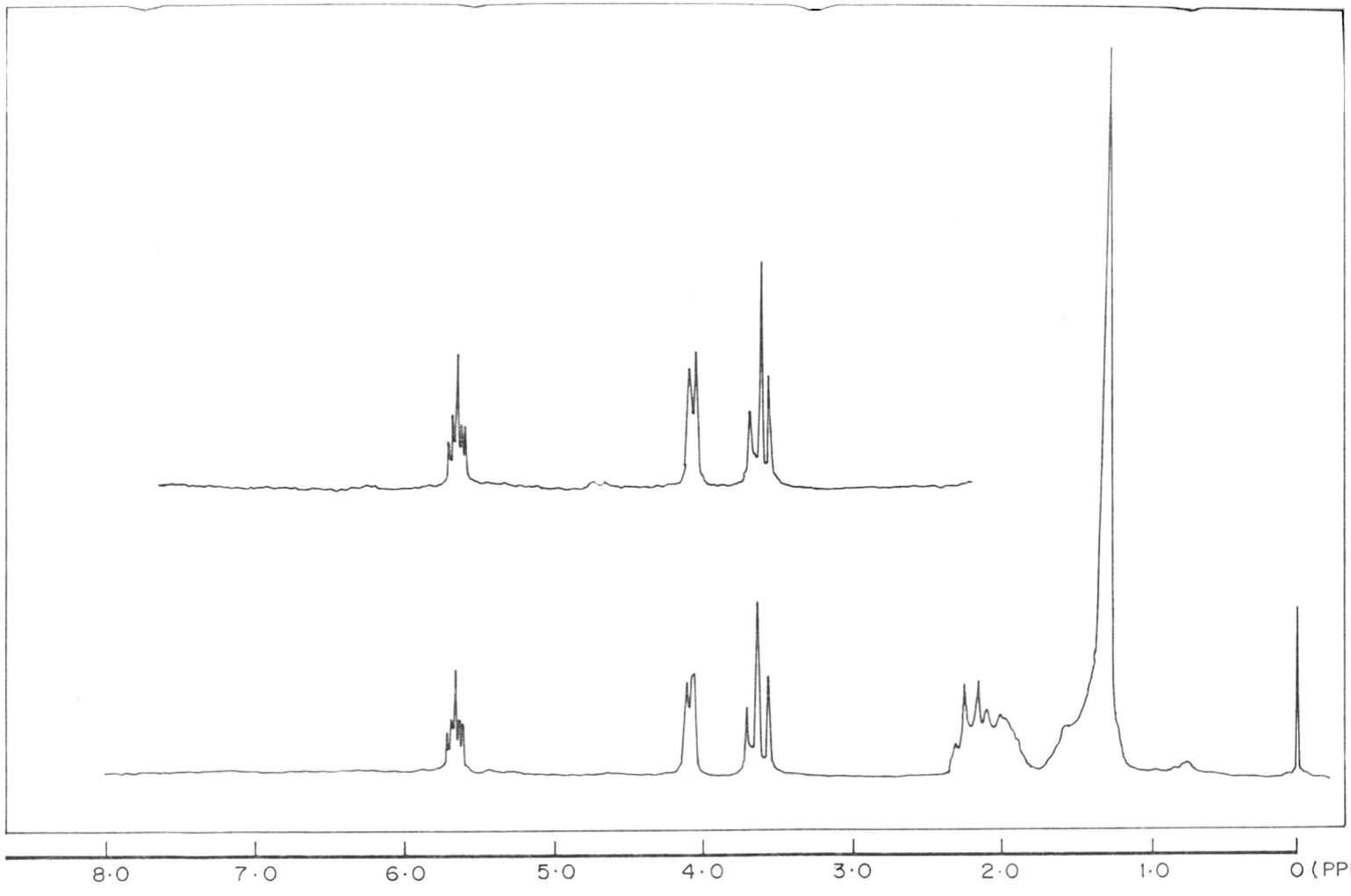


FIG. 9 PMR SPECTRUM OF COMPOUN (17) IN $CDCl_3$

Further modifications and conversions of 13 to 1 has already been discussed in the earlier Section. This route therefore constitutes another simple synthesis of 1.

EXPERIMENTAL

GENERAL REMARKS

Melting points are uncorrected. IR spectra (λ_{max} in cm^{-1}) was recorded in nujol or neat on a Perkin-Elmer Model 683 spectrophotometer with sodium chloride optics.

^1H NMR spectra were obtained on T-60 or Varian FT 80A in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS.

Mass spectra were run on A.E.I.M.S. 30 Doublebeam Mass spectrometer or C.E.C. 21-110B spectrometer.

All solvents and reagents were purified and dried by standard techniques.

Solvents were removed on rotary evaporator at temperature below 50°.

Progress of the reaction was checked by TLC on 0.2 mm layers of silica gel using an iodine chamber for visualisation.

4-Undecyn-1-ol (8)

Lithium (4.2 g, 0.6 mol) in presence of ferric nitrate (50 mg) was dissolved slowly in freshly prepared ammonia (1 lit.) which is indicated by the disappearance of blue colour. To this lithium amide suspension was added, tetrahydrofurfuryl chloride (24 g, 0.2 mol) during 20 min. and the suspension stirred at -33° for 2 hr. A soln. of 1-bromohexane (33 g, 0.2 mol) in tetrahydrofuran (40 ml) was added slowly to the above suspension and stirring continued for an additional 30min. The ammonia was allowed to evaporate and the reaction quenched with ammonium chloride. It was then extracted with ether, the ether layer washed with brine (3 x 100 ml) dried (Na_2SO_4) and concentrated. Distillation of the resulting residue under reduced pressure yielded 8 (13.5 g, 60% b.p. 115-20°/4 mm. lit.[25] $b.p._{20}$ 135°. IR(neat) 3450 cm^{-1} (OH), 2210 cm^{-1} (very weak C≡C). PMR (CCl_4): δ 0.9 (distorted t, 3H, $\underline{CH_3}$-CH_2); 1.36 (m, 10H, 5 x -CH_2-), 2-2.30 (m, 4H, 2 x -$\underline{CH_2}$-C≡C-CH_2-), 3.36 (bs, 1H, OH, D_2O exchangeable), 3.56 (t, J=6 Hz, 2H, $\underline{CH_2}$-OH) M^+ 168.

Analysis: $C_{11}H_{20}O$ requires: C, 78.57; H, 11.90. Found: C, 78.67; H, 11.85%.

1-Undecyn-11-ol (9)

A suspension of sodium amide (6.94 g, 0.178 mol) in dry 1,3 diaminopropane (100 ml) was heated to 80° for 20 min. The suspension was cooled to room temperature and 8 (10 g, 0.059 mol) was added slowly to the stirred mixture during 30 min. The reaction mixture was heated again at 80° for 5 hr. The mixture was cooled to room temperature

and added cautiously to ice-cold water (1 lit.). The mixture was extracted with ether (5 x 100 ml), washed with water (3 x 100 ml), brine (100 ml), dried (Na_2SO_4) and concentrated. Distillation of the residue at reduced pressure yielded pure 9 (6.7 g, 67%) b.p. 115/4 mm. IR (neat) 3400 cm^{-1} (br. OH), 3310 cm^{-1} (C≡C-H), 2100 cm^{-1} (C≡C). PMR (CCl_4): 1.3 (m, 14H, 7x $-CH_2-$), 1.8 (t, 1H, -C≡CH),2-2.3 (m, 2H, C≡C-CH_2), 2.8 (br.s. 1H, OH),3.5 (t,2H,CH_2-OH), M^+ 168.

Analysis: $C_{11}H_{20}O$ requires: C,78.57; H, 11.90; Found: C, 78.37; H, 11.87%.

1-Undecyn-11-ol-tetrahydropyranyl ether (10)

Dihydropyran (5.5 g,0.065 mol) was slowly added within 10 min. to a stirred solution of 9 (10 g, 0.059 mol) and p-toluene sulfonic acid (100 mg) in freshly dried dichloromethane (250 ml). After stirring for 2 hr, the reaction mixture was stirred with solid sodium bicarbonate (200 mg) filtered, the filtrate washed with brine (100 ml), dried (Na_2SO_4) and concentrated. The residue obtained after complete evaporation of the solvent was purified through a column of silica gel using benzene as eluent. Pure 10 was obtained as a colourless liquid (12.5 g, 83%). IR (neat) 3310 (C≡CH), 2210 (C≡C), 1135 cm^{-1}, 1120 cm^{-1}, 1080 cm^{-1}, 1030 cm^{-1} (OTHP). PMR (CCl_4) δ 1.3 (br.s, 20H, 10x $-CH_2-$), 1.8 (t, 1H, C≡CH), 2-2.3 (m, 2H, C≡C-CH_2), 3.12-3.92 (br.m 4H, 2X O-CH_2), 4.6 (br.s THP) M^+ 252.

Analysis: $C_{16}H_{28}O_2$ requires: C, 76.19; H, 11.11; Found: C, 76.53; H, 11.26%.

12-Tetrahydropyranyloxy 2-dodecyn 1-al (11)

Magnesium (0.576 g, 0.024 mol) was suspended in dry tetrahydrofuran (20 ml) under an atmosphere of nitrogen. Ethyl bromide (2.36 g, 0.024 mol) was added dropwise to this, after initiating the reaction by the addition of a small piece of iodine. A vigorous reaction set in and when all the magnesium had reacted, the solution was stirred for another 2 hr and then treated dropwise with 10 (5.04 g, 0.02 mol) in tetrahydrofuran (15 ml). When the evolution of ethane had stopped, the solution was transferred to a dropping funnel and added slowlyto a cooled (-30°) solution of dimethylformamide (8 g, 0.1 mol) in tetrahydrofuran (20 ml). Stirring was allowed to continue at this temperature for 3 hr. The reaction mixture was then warmed slowly to room temperature and acidified with 5% aqueous sulphuric acid. The resulting solution was extracted with ether (5 x 50 ml) the ether layer washed with brine (2 x 25 ml), dried (Na_2SO_4) and concentrated in vacuum to a liquid (5 g). This liquid was loaded on a column of silica gel and eluted with petroleum ether (60-80°) when the starting material (0.2 g) was recovered. Further elution with 1% acetone in petroleum ether provided the required aldehyde 11 as a colourless liquid (2.3 g, 42.5%). IR (neat) 1720 cm^{-1} (C=O), 2200 cm^{-1} (C≡C). PMR ($CDCl_3$) δ 1.31 (bs, 20H, 10xCH_2), 2.3

(m, 2H, $C\underline{H}_2$-C≡C-) 3.3-3.9 (br.m, 4H, 2x O-$C\underline{H}_2$), 4.55 (br.s, 1H, O-THP proton) 9.3 (s, 1H, C<u>H</u>O) M^+ 280.

Analysis: $C_{17}H_{28}O_3$ requires: C, 72.85; H, 10.00; Found: C, 72.66; H, 10.05%.

1-Tetrahydropyranyl 10-yn-12-hexadecene (<u>12</u>)

A 2.7 molar solution (1.05 ml) of n-butyl lithium in petroleum ether was added cautiously to a cooled suspension of n-butyl triphenyl phosphonium bromide (1.2 g) in tetrahydrofuran (10 ml). The mixture was slowly warmed up to room temperature when a red coloured solution denotes the liberation of the ylide. When all the phosphonium bromide had been consumed, the orange red solution is sucked into a syringe leaving the white solid (lithium bromide) behind. The above ylide is added slowly to a stirred and cooled (0°) solution of the aldehyde <u>11</u> (0.560 g, 0.002 mol) in tetrahydrofuran (5 ml). The reaction was checked (TLC) after 5 mins. When all the starting material was consumed (10 min.) the reaction was warmed to room temperature and treated with water (10 ml) and then extracted with chloroform (5 x 30 ml). The chloroform extracts were combined and washed with water (2 x 25 ml), brine (25 ml) dried (Na_2SO_4) and concentrated under reduced pressure. The thick oily syrup thus obtained was chromatographed on silica gel using petroleum ether, and then a mixture of acetone and petroleum ether (2:98) to get <u>12</u> in pure form as a colourless oil (600 mg, 93%). IR (neat) 650 cm^{-1} (<u>cis</u> double bond) and 970 cm^{-1} (<u>trans</u> double

bond). PMR: δ 0.9 (t, J = 7 Hz, 3H, $\underline{CH_3}$-CH_2), 1.2 - 1.6 (m, 16H, 8x CH_2-), 2 - 2.3 (m, 4H, CH_2-C=C and CH_2-HC=CH), 3.4-3.9 (m,4H, 2x O-CH_2), 4.4 (br.s 1H, OTHP), 5.2 -6.2 (m, 2H, $\underline{CH=CH}$). M^+ 320. Analysis: Calculated for $C_{21}H_{36}O_2$: C, 78.75; H, 11.25; Found: C, 78.84; H, 11.73%.

10,12 Hexadecadien-1-ol Tetrahydropyranyl ether (13)

12 (100 mg, 3 m.mol) was added in one lot to freshly distilled ammonia (80 ml) and stirred vigorously. To this solution was added small pieces of sodium (.025 g, 3 equivalents) at intervals till the discharge of blue colour. After half an hour, excess sodium was decomposed by adding NH_4Cl_3 to the disappearance of blue colour. Dilute aqueous ammonia (5 ml) was then carefully added and the solution extracted with ether, washed with water (3 x 10 ml), dried (Na_2SO_4) and concentrated. Purification of the residue over a short column of silica gel using benzene as eluent provided the -unsaturated C_{16} alcohol THP ether 13 (70 mg, 70%) as a colourless oil. IR (neat) 3300 cm^{-1} (OH), 1630 (C=C) 980 cm^{-1} (trans double bond) 670 cm^{-1} (cis double bond). PMR ($CDCl_3$) δ 0.96 (t, 3H, $\underline{CH_3}$-CH_2), 1.28-1.7 (m, 22H, -$\underline{CH_2}$-), 2.20 (2t, 4H, 2($\underline{CH_2}$-CH=)), 3.32-3.9 (m, 4H, 2(OCH_2)), 4.6 (br.s, 1H, O-THP), 5.16-6.5 (m, 4H, olefinic). M^+ 322.

Analysis: Calculated for $C_{21}H_{38}O_2$: C, 78.26; H, 11.80; Found: C, 78.41; H, 11.74%.

12-Tetrahydropyranyloxy trans 2-dodecene-1-al (16)

11 (540 mg, 0.002 moles) was stirred in hexane under

an atmosphere of hydrogen in presence of catalytic amount of (50 mg) Lindlar's catalyst, and a microdrop of quinoline, till the calculated volume of hydrogen (45 ml) was absorbed. The catalyst was filtered off, washed with more hexane and the combined filtrates concentrated to an oily liquid **16** (540 mg quantitative) which contained a mixture of cis and trans products as was evidenced by IR and NMR spectra.

The above mixture was dissolved in dry benzene (5 ml) and stirred at room temperature for 30 minutes. The solution was decanted off washed with 5% aqueous sodium bicarbonate solution (5 ml) water (5 ml) and dried (Na_2SO_4) to pure **16a** (540 mg 100%). IR (neat) 1700 cm^{-1} (C=O), 980 cm^{-1} (trans C=C). PMR ($CDCl_3$) δ 1.1-1.9 (m, 20H, $-CH_2-$), 2.3 (d, 2H, $C\underline{H}_2$-HC=CH), 3.3-4 (br.m, 4H, 2(O-$C\underline{H}_2$-)), 4.5 (br.s, 1H, OTHP), 5.9-6.2 (dt, 1H, H_{10}, J = 16.8 Hz), 6.6-6.9 (dd, 1H, H_{11} J = 8 Hz and 16 Hz, 9.52 (d, 1H, C$\underline{H}$O, J = 8 Hz). M^+ 282. Analysis: $C_{17}H_{30}O_3$ requires: C, 72.34; H, 10.63; Found: C, 72.55; H, 10.42%.

(E,E)and(E,Z)10,12-hexadecadien-1-ol (**14**)

13 (644 mg, 0.002 moles) in dry methanol (5 ml) was stirred with Amberlite (100 mg) for 3 hr.at room temperature. The resin was filtered off,washed with methanol and the combined filtrates concentrated to get a colourless oil **14** (470 mg, 100%). IR(neat) 3300 cm^{-1} (OH), 970 cm^{-1} (trans double bond), 690 cm^{-1} (cis double bond). M^+ 238. PMR ($CDCl_3$) δ 0.93 (t, 3H,

J = 7 Hz, $\underline{CH_3}$-CH_2), 1.2-1.68 (m, 16H, -$\underline{CH_2}$-), 2.13 (m, 4H, $\underline{CH_2}$-CH=CH-), 3.66 (t, 2H, J = 7 Hz, $\underline{CH_2}$OH), 5.3-6.3 (m, 4H, olefinic). M^+ 238.

Analysis: $C_{16}H_{30}O$ requires: C, 80.67; H, 12.60. Found: C, 80.28; H, 12.4%.

(E,E)-10,12-Hexadecadien-1-ol (15)

14 (500 mg,0.0021 moles) was stirred for half hour in hexane (5 ml) in presence of a pinch of iodine. The reaction was kept in front of an illuminated bulb. When the colour disappears the solution was washed with a saturated solution of sodium thiosulphate (5 ml), water (5 ml) and dried (Na_2SO_4). Concentration of the solvent under reduced pressure gave a colourless liquid (500 mg, 100%) which contained the EE isomer as the major product. This liquid was dissolved in hexane (2 ml) and left overnight at -20°. A white crystalline solid was obtained. The hexane was decanted off, and the solid was washed with another 2 ml of cold hexane and dried at room temperature. On warming to room temperature, the solid melts to a colourless liquid 15. The mother liquor was reisomerised and crystallised once again when a second crop of the EE isomer 15 was obtained. (Total yield: 300 mg, 60%). IR (neat) 3300 cm^{-1} (OH), 1630 cm^{-1} (C=C) 980 cm^{-1} trans double bond. PMR ($CDCl_3$)δ 0.93 (t, 3H, J = 8 Hz, $\underline{CH_3}$-CH_2), 1.2-1.68 (m, 16H, -CH_2-), 2.13 (m, 4H, 2×$\underline{CH_2}$-(CH=CH)-), (3.66 (t, 2H, J = 7 Hz, $\underline{CH_2}$-OH), 5.3-5.73 (m, 2H, olefinic), 5.84-6.2 (m, 2H, olefinic). M^+ 238.

Analysis: Calculated for $C_{16}H_{30}O$: C, 80.67; H, 12.60. Found: C, 80.48; H, 12.38%.

EE Hexadecadien-1-al (1)

To a stirred suspension of pyridinium chlorochromate (323 mg, 0.0015 moles) in dry dichloromethane (5 ml) was added in one lot a solution of 15 (238 mg, 0.001 mole) in dichloromethane (1 ml). After 1 hr the reaction mixture was treated with dry ether (50 ml). The solid was filtered off, washed repeatedly with dry ether and the combined filtrates concentrated under vacuum. The crude product (300 mg) was chromatographed on a column of silica gel using benzene as the eluent. Concentration of the required fractions provided the expected pheromone (1) as a colourless liquid (132 mg, 60%). IR (neat) 1700 cm^{-1} (carbonyl), 970 cm^{-1} (trans double bond). PMR ($CDCl_3$) δ 0.9 (t, 3H, CH_2-CH_3); 1.4 (m, 14H, $-CH_2$), 2.0 (m, 4H (CH_2-CH=CH)$_2$), 2.36 (t, 2H, CH_2-CHO) 5.32-6.08 (m, 4H, 2(CH=CH-), 9.72 (t, 1H, CHO). M^+ 236.

Analysis: $C_{16}H_{28}O$ requires: C, 81.35; H, 11.86. Found: C, 80.96; H, 12.08%.

trans-12-Hydroxy 2-dodecene-1-ol (17)

trans 2-dodecenoic acid dimethyl ester (5.12 g, 0.02 moles) was dissolved in methylene chloride (10 ml) and stirred at 0° under an atmosphere of nitrogen. A 25% solution of diisobutyl-aluminium hydride in toluene (21.3 ml, 0.03 moles) was dropped in through a syringe while keeping the temperature within 0-5°. After stirring the mixture for 1 h at this temperature the reaction

mixture was allowed to warm upto room temperature at which it was stirred for another 4 h . When the reaction was complete (TLC) the mixture was treated very cautiously with cold water (10 ml) and conc. hydrochloric acid (5 ml) while cooling the flask externally with ice-salt mixture. More methylene chloride (50 ml) was added and the solution extracted thoroughly. The organic layer was washed with water (4 x 25 ml) and dried (Na_2SO_4). Distillation of the solvent under reduced pressure provided the dialcohol as a semi-solid (3.3 g). Purification of this material on a column of silica gel using chloroform as eluent gave pure trans 12-hydroxy 2-dodecene-1-ol (**17**) as a white crystalline solid m.p. 56-58° (2.5 g, 62.5%). IR (Nujol) 3400 cm^{-1} (br. OH) 970 cm^{-1} (trans double bond). PMR ($CDCl_3$) δ 1.3 (m, 14H, $-CH_2-$); 1.9 (t, 2H, $C\underline{H}_2$-CH=CH-),3.6 (t, 2H, $C\underline{H}_2$-OH); 4.06 (d, 2H, CH=CH-$C\underline{H}_2$-OH) 5.66 (q, 2H, CH=CH). M^+ 200.

Analysis: $C_{12}H_{24}O_2$ requires: C, 72.00; H, 12.00. Found: C, 71.99; H, 12.12%.

trans 12-Hydroxy 2-dodecene-1-al (**18**)

A mixture of **17** (2.00 g, 0.01 moles) and dichloro dicyano-benzoquinone (2.27 g, 0.01 mole) in dichloromethane (20 ml) was stirred at room temperature for 2 h. The solid that separated was filtered off and the solution washed with a dilute aqueous solution of sodium dithionite to destroy the excess of quinone. The solution was further washed with water (3x 20 ml), dried (Na_2SO_4) and concentrated. A thick syrupy liquid of 12-hydroxy

trans-2-dodecene-1-al (**18**) (1.98 g, quantitative) which was pure enough for the next reactions was obtained.

IR (neat) 3400 cm^{-1} (OH), 1700 cm^{-1} (HC=O), 980 cm^{-1} (trans double bond). PMR ($CDCl_3$) 1.4 (m, 14H, $-CH_2-$), 2.36 (q, 2H, $-\underline{CH_2}-CH=CH-$), 3.66 (t, 2H, $-\underline{CH_2}-OH$); 6.31 (dt, 1H, $\underline{CH}=CH-CHO$), 6.71 -7.066 (dd, 1H,$-CH=\underline{CH}-CHO$), 9.5 (d, 1H, $-\underline{CH}O$). M^+ 198.

Analysis: $C_{12}H_{22}O_2$ requires: C, 72.72; H, 11.11. Found: C, 72.55; H, 11.21%.

12-Hydroxy trans 2-dodecene-1-al tetrahydropyranyl ether (**16**)

18 (3.96 g, .02 moles) and p-toluenesulfonic acid (100 mg,catalytic amounts) were stirred in dry dichloromethane (30 ml) for 1 hr at room temperature. Solid sodium bicarbonate (100 mg) was then added to the reaction mixture and stirring continued for 5 minutes. The solution was then decanted from the solid, washed with brine (2 x 25 ml), dried (Na_2SO_4) and concentrated. The syrupy liquid thus obtained was purified by column chromatography (silica gel, benzene). The pure aldehyde **16** thus obtained was identical in all its spectral and analytical data to **16** obtained by the catalytic hydrogenation of **11**.

SECTION B

SYNTHESIS OF (Z)-11-OCTADECENAL

(Z)-11-Octadecenal (2) was identified as one of the sex attractants of the lesser wax moth Achroia grisella (F. Lepidopeterae) by K.H. Dehm et al.[31] from the wing glands of the moth. Achroia grisella are specific enemies of bees. Their caterpillars make silken tunnels in the bee comb under the cover of which they feed upon the bees wax. When the attack is severe, the bees have to abandon the comb. Use of pesticides does limited help sometimes becoming harmful to the bees as well. Attractant baited traps using pheromones remains the only remedy for destroying these pests.

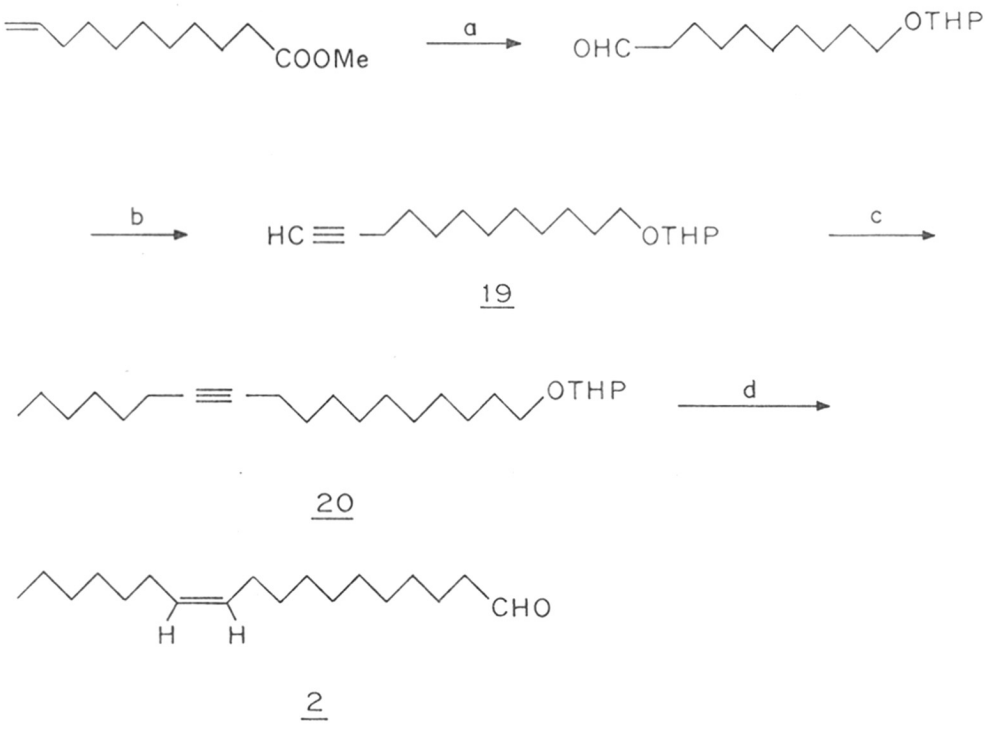
The males of Achroia grisella produce an attractant for the females in a pair of glands located at the base of their wings. This compound was isolated[31] and identified to be a mixture of n-undecenal and n-11-cis-octadecenal(2.)

2 was synthesised in about twelve steps from castor oil by Ranganathan et al.[32] (Scheme 7) in which methyl undecenoate was transformed to 1-dodecyn-12-ol-tetrahydropyranyl ether (19) through a sequence of reactions. 19 was alkylated with 1-bromohexane, using n-butyl lithium in hexamethyl phosphoramide to the acetylenic alcohol 20 which upon partial reduction followed by oxidation of the alcoholic function gave the pheromone 2.

(Z)-11-Octadecenal (2)

Scheme - 7

S. Ranganathan et al. Synth. Commum. 959 (1982)



a) 1) LAH ; 2) DHP, P.P.T.S. ; 3) B_2H_6 , P.C.C.

b) 1) Ph C = CBr_2 ; 2) Li, Hg

c) n Bu Li , HMPT , n-$C_6H_{13}Br$

d) 1) PPTS , EtOH ; 2) $BaSO_4-H_2$; 3) P.C.C.

PRESENT WORK

(Z)-11-Octadecenal (2) is a simple straight chain aldehyde bearing a cis double bond at C-11 position.

Introduction of double bonds in a molecule can be achieved in several ways. But in the present synthesis our attention was again concentrated on the reactivity of acetylenic compounds and the ease with which they undergo different conversions.

Our success in the earlier attempt in carrying out the acetylene zipper reaction prompted us to focus our attention to terminal acetylenic compounds in which the acidity of the terminal proton can be fully exploited. Thus the key step in the present synthesis of 2 was an alkylation involving a 12-carbon acetylenic compound and 1-bromohexane, giving the required 18-carbon chain with a triple bond at C-11 as required. The terminal acetylenic compound was in turn prepared by the "acetylene zipper" reaction of an internal acetylenic compound having the required number of carbon atoms. Since 2 has a terminal aldehyde, the required fragment should also have a hydroxy group at the terminus remote from the triple bond.

A number of such compounds have been prepared and their utility in the synthesis of pheromones have been discussed in detail by J.S.Yadav et al.[23].

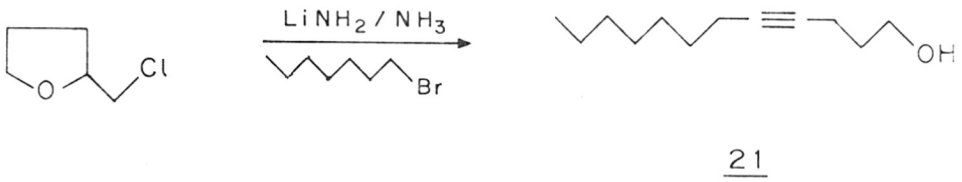
Accordingly, tetrahydrofurfuryl chloride, prepared from tetrahydrofurfuryl alcohol was treated with lithium amide in liquid ammonia and the dianion of 4-pentyn-1-ol thus liberated,

was treated in situ with 1-bromohexane to give 4-dodecyn-1-ol (21)(Scheme 8). The IR spectrum of 21 gave absorption for OH at 3320 cm^{-1} and a very weak absorption at 2110 cm^{-1} for the C≡C. The PMR spectrum (Fig.10) of 21 showed a distorted triplet for methyl at δ 0.9 while the chemical shift for the $\underline{CH_2}$-OH was observed at δ 3.5, as a triplet. The rest of the protons had the expected chemical shifts.

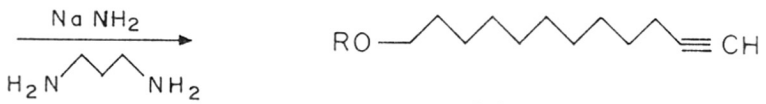
As already discussed in the earlier Section, the conversion of internal acetylenic alcohols to terminal acetylenic alcohols provides a simple and convenient route to long chain aliphatic compounds with differentiated remote functionalities. The acetylene zipper reaction could be carried out in the presence of potassium 3-aminopropyl amide (KAPA) in 3-aminopropylamine (prepared in situ from potassium hydride in 1,3 diamino propane) at 0°. Metal amides such as potassium amide and sodamide also migrate /promote triple bond migration, but requires elevated temperatures.

The internal alcohol 21 was subjected to the "acetylene-zipper" reaction by employing freshly prepared sodamide in 1,3-diaminopropane at 80-85° for 4 hr. to the isomerised product 12-hydroxy 1-dodecyn (22) in 70% yield. In its IR spectrum 22 showed the absorption of OH at 3400 and that for C≡C-H at 3320 cm^{-1} respectively, the former as a broad one while the latter appeared as a sharp one, merging into each other. The C≡C absorption was observed as a sharp peak at 2110 cm^{-1}. The PMR (Fig.11) also showed characteristic absorptions of a terminal acetylenic

Scheme - 8

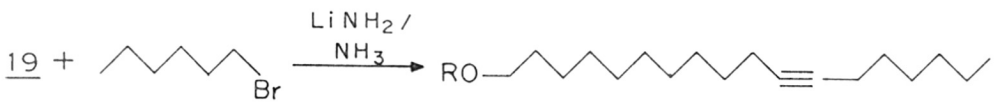


21



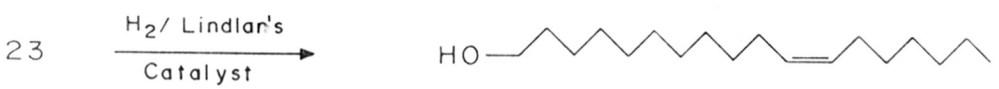
22 - R = H

19 - R = THP



20 - R = THP

23 - R = H



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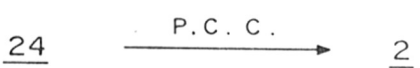

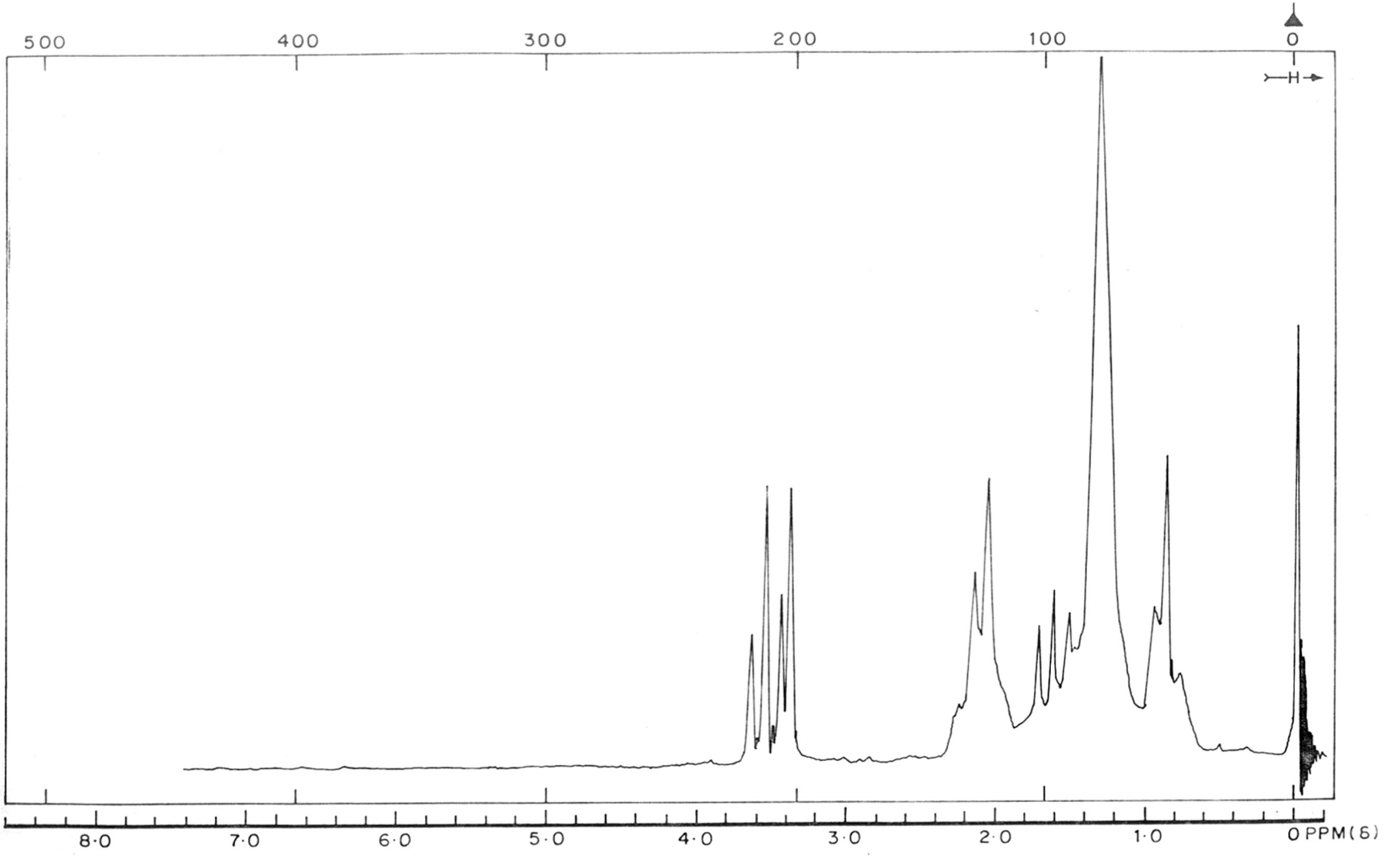

FIG. 10 PMR SECTRUM OF COMPOUND (21) IN $CDCl_3$

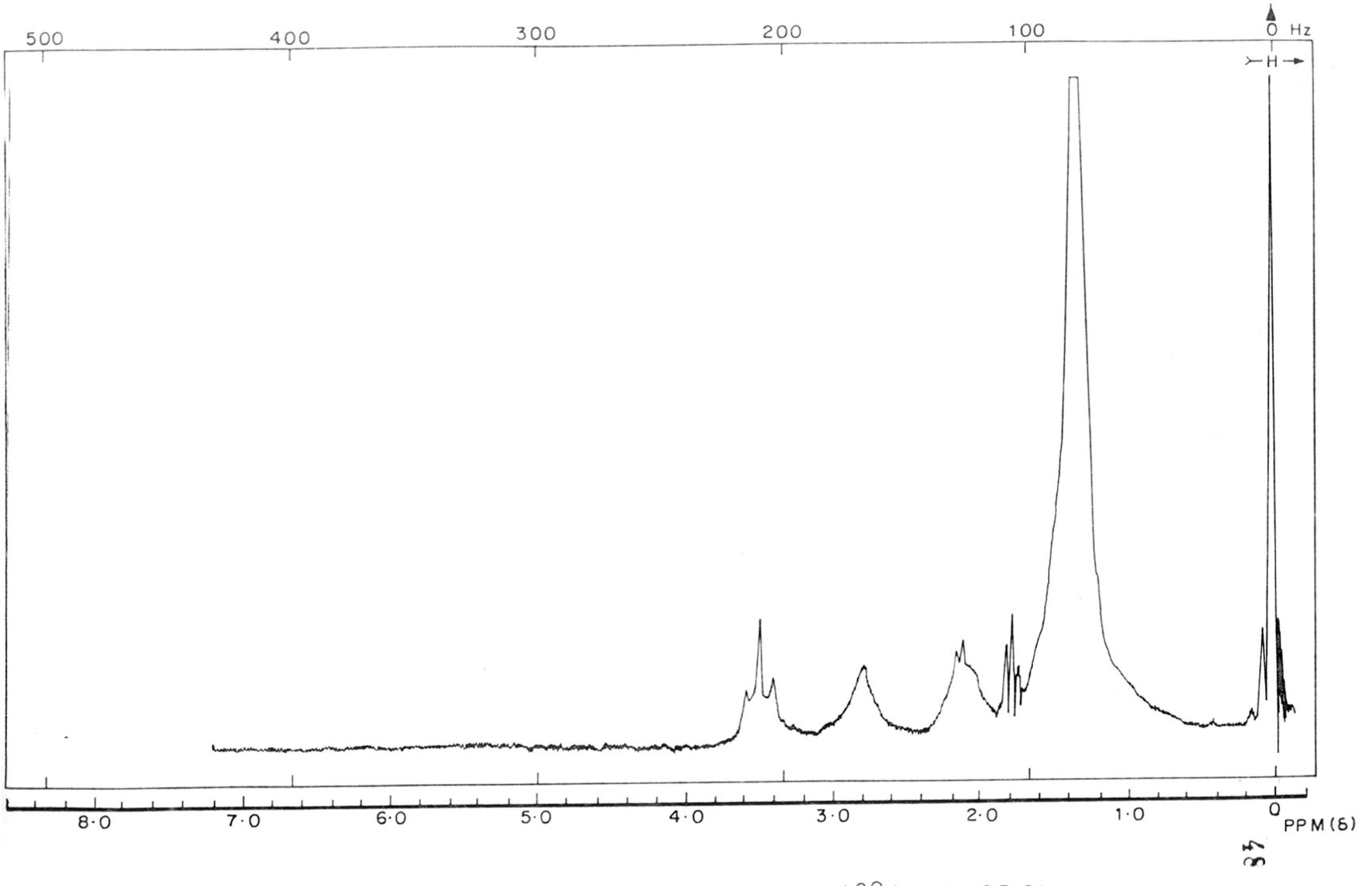

FIG. 11 PMR SPECTRUM OF COMPOUND (22) IN $CDCl_3$

compound with the absence of the methyl triplet at δ 0.9 as a clear indication of the migration. The terminal tripple bond proton resonated at δ 1.75 as a triplet and the remaining protons gave the signals at the expected chemical shifts.

The protection of the alcoholic function in 22 was achieved with dihydropyran in dichloromethane containing catalytic amounts of p-toluenesulfonic acid. The tetrahydropyranyloxy 1-dodecyn (19) was obtained in 85% yield. The IR spectrum of 19 showed the disappearance of the OH absorption, making the C≡CH absorption clearly visible. The PMR spectrum of 19 also showed the characteristic T.H.P. proton at δ 4.6 besides the other expected protons at the respective chemical shifts.

Organo alkali metal derivatives of acetylenic compounds are important intermediates in many synthesis of aliphatic compounds. The various methods for their formation in organic solvents and in liquid ammonia have been discussed extensively[11]. Deprotonation of terminal acetylenes by organo lithium compounds in organic solvents or by alkali metal amides in ammonia is an extremely fast reaction and takes place even at very low temperatures.

The terminal acetylenic compound 19 was subjected to deprotonation by lithium amide in ammonia and reacted subsequently with 1-bromohexane to obtain 1-tetrahydropyranyloxy 11-octadecyn (20) in 70% yield. The IR spectrum of 20 showed the absence of C≡CH absorption and C≡C absorption at 2110 cm^{-1} as a characteristic feature to prove the presence of the

alkylated product. The PMR spectrum showed the methyl protons as a triplet at δ 0.9, C≡C-$\underline{CH}_2$ protons as a multiplet at δ 2.05 and the THP proton at δ 4.6, along with the other protons at the expected chemical shifts.

The extension of the C_{12} fragment to a C_{18} fragment was thus achieved in good yield. Further modifications of 20 to an olefin with cis-geometry and the resulting olefin to an olefinic aldehyde could be easily achieved through simple and known reactions.

Acetylenic compounds can be converted to cis olefins or to trans olefins depending upon the reagents and reaction conditions. For example, when treated with sodium in liquid ammonia, they yield trans olefins whereas hydrogenation using Lindlar's catalyst[17] or P-2 nickel[18] yield exclusively cis olefins. Hydrogenation of acetylenes using Lindlar's catalyst ensures complete formation of cis olefins. The presence of a small drop of quinoline poisons the catalyst, thus preventing further reduction to saturated compounds. This reaction had been exploited for the introduction of the cis double bond in 20. Accordingly 20 was deprotected using catalytic amounts of Amberlite in methanol to the free alcohol 23 which showed characteristic IR and PMR data (presence of OH absorption in the IR spectrum and absence of the THP proton at δ 4.6 in the PMR spectrum).

The free alcohol was hydrogenated in hexane using

Lindlar's catalyst and a micro drop of quinoline, monitoring the reaction by the intake of hydrogen. The cis olefin **24** thus obtained showed the OH absorption at 3400 cm^{-1} and the cis C=C absorption at 670 cm^{-1}. The PMR (Fig.12) showed the olefinic protons as a triplet at δ 5.23 and the CH_2-OH protons as another triplet at δ 3.5 along with the other protons at the expected chemical shifts.

Conversion of the hydroxy group in **24** to an aldehyde completes the synthesis of **2**. Primary alcohols are oxidised to aldehydes by a variety of reagents. But pyridinium chlorochromate is known to be a mild reagent for such oxidations. Thus oxidation of **24** using pyridiniumchlorochromate in dry dichloromethane provided the pure pheromone **2** in 67% yield after usual work up and purification. The IR of **2** showed the aldehyde absorption at 1730 cm^{-1} and the cis C=C absorption at 670 cm^{-1}. The PMR (Fig.13) of **2** showed the methyl protons as a triplet at δ 0.9, the CH_2-CHO protons as a multiplet at δ 2.32. The olefinic protons were observed as a triplet at δ 5.3 and the aldehyde proton resonated at δ 9.7 as a triplet. The IR and NMR values were identical in all respects to the values reported in literature[32].

The synthesis of **2** was thus achieved in an overall 20% yield through a few simple and easy reactions starting from the easily available material viz. tetrahydrofurfuryl chloride.

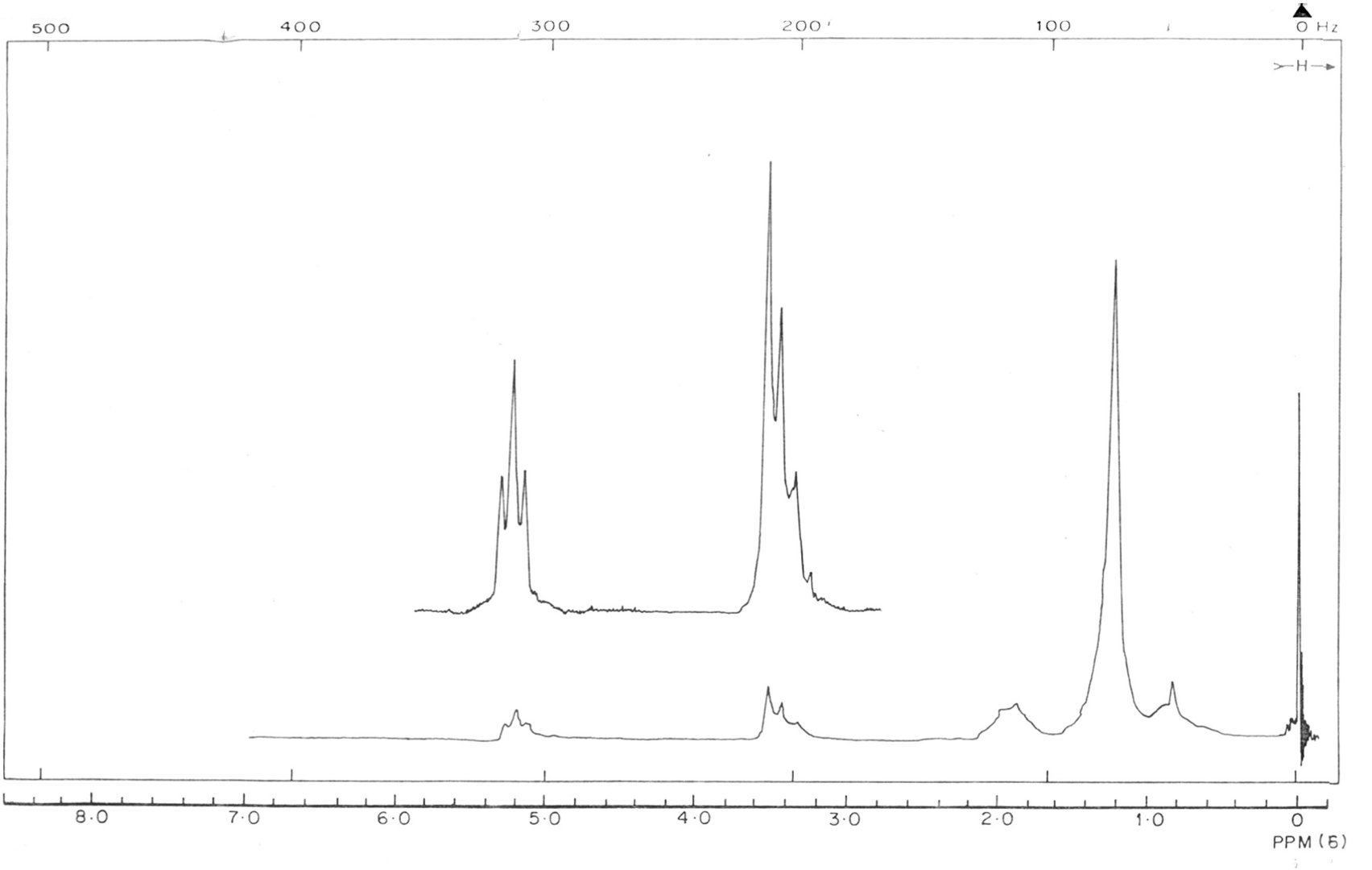

FIG. 12 PMR SPECTRUM OF COMPOUND (24) IN $CDCl_3$

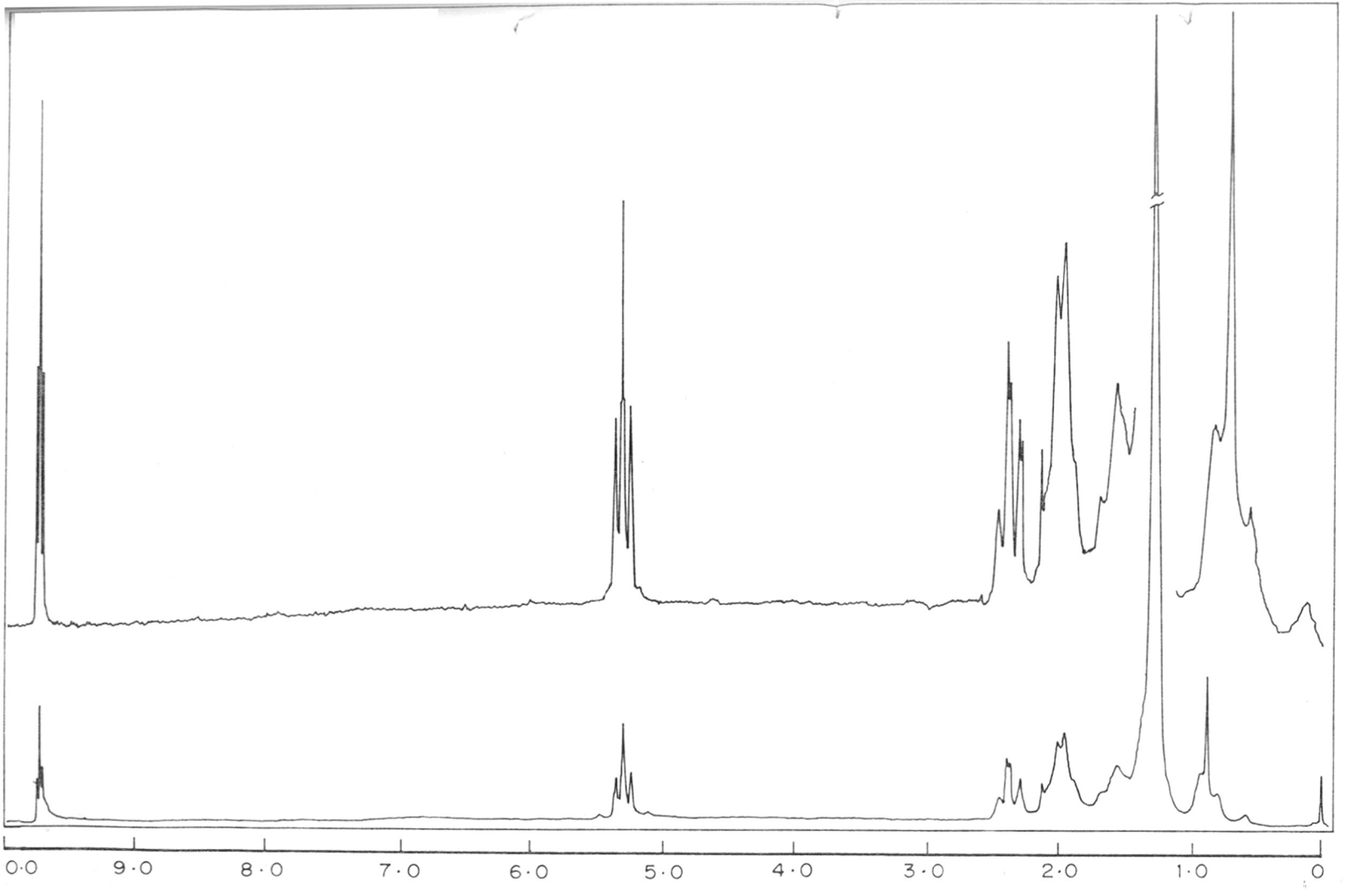

FIG. 13 PMR SPECTRUM OF PHEROMONE (2) IN $CDCl_3$

EXPERIMENTAL

4-Dodecyn-1-ol (21)

Lithium (3 eq. 0.6 g atom) in presence of ferric nitrate (50 mg) was dissolved slowly in freshly collected ammonia (1 lit.). The formation of lithium amide was indicated by the disappearance of blue colour. To this freshly prepared lithiumamide solution was added, tetrahydrofurfuryl chloride (24 g, 0.2 moles) during 30 minutes. The solution was stirred for 2 hr at -33°C. After all the tetrahydrofurfuryl chloride had reacted (TLC) n-heptyl bromide (33 g, 0.2 moles) dissolved in tetrahydrofuran (dry, 30 ml) was added dropwise through a syringe, to the stirred and cooled (-33°) solution. The reaction mixture was stirred at this temperature for another 0.5 hr, and the ammonia was allowed to evaporate. The residue was treated with saturated ammonium chloride solution and extracted with ether (6 x 100 ml). The ether layer was washed with brine (5 x 100 ml) dried (Na_2SO_4) and concentrated. The pure alcohol was obtained by distillation of the crude product. The fraction distilling at 115-120°/4 mm was found to be pure 4-dodecyn-1-ol (21) (18.5 g, 51%). IR (neat) 3450 cm^{-1} (br.OH) 2210 cm^{-1} (very weak, C≡C). PMR (CCl_4) δ 0.9 (t, 3H, $C\underline{H}_3$-CH$_2$) 1.36 (m, 12H, -$C\underline{H}_2$-), 2-2.3 (m, 4H, 2($C\underline{H}_2$-C≡C-)), 3.36 (s, 1H, CH_2-$O\underline{H}$), 3.56 (t,2H, $C\underline{H}_2$OH). M^+ 182.

Analysis: $C_{12}H_{22}O$ requires: C, 79.12; H, 12.08; Found: C, 79.4; H, 12.38%.

11-Dodecyn 1-ol

(12-hydroxy-1-dodecyn) (22)

A suspension of sodium amide (6.94 g,0.178 M) in dry

1,3 diaminopropane (100ml) was heated to 80° for 20 min. The suspension was cooled to room temperature and 21 (10 g, 0.055 moles) was added slowly to the stirred mixture during 30 minutes. The reaction mixture was heated at 80° for 5 hr. The mixture was cooled to room temperature and added slowly over ice-cold wataer (1 lit.). The aqueous solution was then extracted thoroughly with ether (4x 150 ml) washed repeatedly with water (8 x 100 ml), brine (100 ml) dried (Na_2SO_4) and concentrated. Distillation of the residue under reduced pressure gave pure 12-hydroxy 1-dodecynol (22) as a colourless liquid (7 g, 70%) b.p. 120-125°/4 mm (lit.[36] b.p. 83-6/0.05 mm). IR (neat) 3400 cm^{-1} (OH), 3310 cm^{-1} (C≡H) 2110 cm^{-1} (C≡C). PMR (CCl_4)δ 1.09 - 1.8 (m, 16H, a-CH_2-) 1.9 (t, 1H, -C≡C-H) 2.25 (m, 2H, HC≡C-CH_2), 2.8 (s, 1H, OH),3.5 (t, 2H, CH_2-OH) M^+ 182.

Analysis: Calculated for $C_{12}H_{22}O$: C, 79.1; H, 12.08; Found: C, 79.24; H, 12.42%.

12-Tetrahydropyranyloxy-1-dodecyn(19)

Dihydropyran (5.5 g, 0.065 moles) was slowly added within 10 min. to a stirred solution of 22 (10 g, 0.055 moles) and catalytic amounts of p-toluenesulfonic acid (100 mg) in freshly dried dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 2 hr. Solid sodium bicarbonate (200 mg) was added to the reaction mixture, stirred for 10 min. and the solution decanted off. After washing with brine (50 ml) the solution was dried (Na_2SO_4) and concentrated (15.2 g). The residue was purified over a column

of silica gel using benzene as eluent. 12-tetrahydropyranyloxy 1 dodecyn (**19**) was obtained in pure form as a colourless liquid (14 g, 95.8%). IR (neat) 3310 cm^{-1} (-C≡C<u>H</u>, 2110 (C≡C) 1135 cm^{-1}. 1120 cm^{-1}, 1080 cm^{-1}, 1030 cm^{-1} (OTHP). PMR (CCl_4)δ 1.09 - 1.8 (m, 16H, -CH_2-) 1.9 (t, 1H, -C≡C-<u>H</u>) 2.25 (m, 2H, -C≡C-<u>CH_2</u>) 3.2 - 4.0 (m, 4H, -<u>CH_2</u>-O-THP) 4.58 (s, 1H, <u>CH_2</u>-O-THP).

1-Tetrahydropyranyloxy octadec-11-yn (**20**)

Lithium (0.132 g, 3 equivalents) was added at intervals to freshly collected ammonia (100 ml) containing catalytic amount of ferric nitrate (10 mg). The formation of the lithium amide was denoted by the disappearance of blue colour. When all the lithium had reacted, the solution was stirred for another 0.5 hr. to ensure complete formation of the amide. The acetylenic compound **19** (1.7 g, 0.006 moles) in tetrahydrofuran (10 ml) was added dropwise to the reaction mixture within 10 min. and stirring continued at -33° for 3 hr. When all the alcohol had been used up (TLC) n-hexylbromide (2.5 g, 2.5 equivalents) in tetrahydrofuran (10 ml) was added dropwise through a syringe. Stirring was continued for another 1 hr. An additional amount of n-hexylbromide (2.5 g) was added to ensure complete absence of **19** in the reaction mixture. Stirring was continued for another 2 hr and the ammonia was allowed to evaporate. Saturated ammonium chloride solution (10 ml) was cautiously added to the residue and the aqueous solution was extracted thorougly with ether (5 x 25 ml). The ether extracts

were washed several times with water, then brine and dried (Na_2SO_4). Concentration of the solvent provided a light brown liquid (2.3 g) which was loaded on a column of silica gel and eluted with benzene. Tetrahydropyranyloxy 11-octadecyn (20) was obtained in pure form as a colourless liquid (1.7 g, 70%). IR(neat) 1130 cm^{-1}, 1120 cm^{-1}, 1080 cm^{-1}, 1030 cm^{-1} (OTHP). PMR (CCl_4)δ 0.9 (t, 3H, $\underline{CH_3}$-CH_2-) 1-1.8 (m, 30H, -CH_2-), 2.05 (m, 4H, $\underline{CH_2}$-C≡C-$\underline{CH_2}$-) 3.15-4.0 (m, 4H, 2($\underline{CH_2}$-O-) 4.5 (s, 1H, O-THP) M^+ 350.

Analysis: $C_{23}H_{42}O_2$ requires: C, 78.80; H, 12.00% Found: C, 78.50; H, 12.38%.

11-Octadecyn-1-ol (23)

A solution of 20 (1.7 g, 0.05 moles) in dry methanol (15 ml) was stirred at room temperature with Amberlite (150 mg) for 3 hr. When the reaction was complete (TLC) the solution was filtered, the resin washed with more methanol, the filtrates were combined and concentrated to a colourless liquid (1.2 g, 100%). 11-Octadecyn-1-ol (23) thus obtained was used as such for the next step without further purification. IR (neat) 3400 cm^{-1} (free OH). PMR (CCl_4) δ 0.9 (t, 3H, $\underline{CH_3}$-CH_2) 1-1.8 (m, 24H, -CH_2-) 2.05 (m, 4H, $\underline{CH_2}$-C≡C-$\underline{CH_2}$) 3.52 (t, 2H, $\underline{CH_2}$OH) M^+ 266

Analysis: Calculated for $C_{18}H_{34}O$: C, 81.20; H, 12.78. Found: C,81.45; H, 12.92%

(Z) 11-Octadecenol (24)

A solution of 23 (0.266 g, 0.001 mol) in hexane (5 ml)

was stirred under an atmosphere of hydrogen over Lindlar's catalyst ($Pd/BaSO_4$, 30 mg) further deactivated with a small drop of quinoline. The hydrogen uptake was carefully monitored and the reaction was stopped soon after the calculated volume of hydrogen was absorbed (22 ml). The catalyst was filtered off, washed thoroughly with fresh hexane (5 x 5 ml) and the combined filtrates concentrated to a colourless liquid (250 mg). The pure (Z)-11-octadecenol (24) thus obtained was passed through a short column of silica gel to remove small traces of catalyst (240 mg, 89.5%). IR (neat) 3320 cm^{-1} (OH) 670 cm^{-1} (cis double bond). PMR (CCl_4) δ 0.9 (t, 3H, $\underline{CH_3}$-CH_2-) 1-1.8 (m, 24H, -CH_2-) 1.93 (m, 4H, $\underline{CH_2}$-CH=CH-$\underline{CH_2}$) 3.5 (t, 2H, $\underline{CH_2}$-OH) 5.23 (t, 2H, $\underline{H}C=C\underline{H}$) M^+ 268.

Analysis: $C_{18}H_{36}O$ requires: C, 80.6; H, 13.43; Found: C, 80.58; H, 13.44%.

(Z)-11-Octadecenal (2)

To a stirred suspension of pyridinium chlorochromate (325 mg, 0.005 moles) in dry dichloromethane (5 ml) was added 24 (240 mg, 0.0009 moles) in one lot. The mixture was stirred for 30 mins. at room temperature and admixed with ether (20 ml). The residue was decanted off and further extracted with more ether (4 x 20 ml). The combined extracts were concentrated and loaded on a column of silica gel and eluted with benzene. Concentration of the required fractions in vacuo gave the required pheromone 2 in pure form (160 mg, 67%). IR (neat): 1730 cm^{-1} (aldehyde) 670 cm^{-1} (cis double bond). PMR (CCl_4) δ 0.9 (t, 3H,

$\underline{CH_3}$-CH_2). 1.1 (m, 22H, -$\underline{CH_2}$-), 1.98 (m,, $\underline{CH_2}$-CH=CH-$\underline{CH_2}$), 2.32 (m, 2H, -$\underline{CH_2}$-CHO), 5.3 (t, 2H, -$\underline{CH}$=$\underline{CH}$-), 9.65 (t, 1H, -$\underline{C}$HO).

M^+ 266.

Analysis: Calculated for $C_{18}H_{34}O$: C, 81.20; H, 12.78. Found: C, 81.29; H, 12.81%.

REFERENCES

REFERENCES

1a P. Karlson and M. Luscher
Nature 183, 55 (1959).

b P. Karlson and M. Luscher
Naturwissenchaften 46, 63 (1959).

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

3a D. Hamilton
J. Econ.Entomol. 64, 150 (1971).

b D. Hardee
Ibid 64, 928 (1971).

c H.H. Shorey, L.K. Gaston and L.L. Sower
California Agriculture 25, 11 (1971).

d M. Beroza and E.F. Kipling
Science, 177, 19 (1972).

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

5 K. Mori
"Total synthesis of Natural Products" H.P. (Ed.J.ApSimon)
John Wiley & Sons, New York (1981).

6 D.R. Hall, P.S. Beevor, R. Lester and B.F. Nesbitt
Experientia 36, 152-3 (1980).

7 G.R. Knox and I.G.Thom
J.C.S.Chem.Commun. 373 (1981).

8 K. Daigaku, Rikogakubu, Konkyu Hokoku
C.A. 93, 25825

9 J.T. Klug, J. Skarka and A. Shani
Chem. Ind. 372, 1982.

10 M. Schlosser
"The Stereochemistry of the Wittig reaction" in
"Topics in Stereochemistry", Vol.5, 1970. Eds. E.L.Eliel
and N.L.Allinger, Wiley Interscience, pp.1-30.

11 L. Brandsma
'Preparative acetylene chemistry', Elsevier, Amsterdam
(1971).

12 M. Shwarz and R.M. Waters
Syn. 567 (1972).

13 J.D. Warthen Jr. and M. Jacobson
Syn. 616 (1973).

14 S. Baba, D.E. Van Horn and E. Negishi
Tetrahedron Lett. 1927 (1976).

15 N. Okukado, D.E. Van Horn, W.L.Klima and E. Negishi
Tetrahedron Lett. 1027 (1978).

16a H. Yatagai, Y. Yamamoto, K. Maruyamma, A. Sonoda and S. Murabashi
J.C.S. Chem. Commun. 852 (1977).

b E. Negishi and T. Yoshida
J.C.S. Chem. Commun. 606 (1973).

17a H. Lindlar
Helv. Chim. Acta 35, 446 (1952).

b H. Lindlar and R.Dubcies
Org.Syn.Coll. Vol.5, 88 (1973).

18 C.A. Brown and V.K. Ahuja
J.C.S. Chem. Commun. 553 (1973).

19 J. Attenburrow, A.F.B. Cameran, J.H. Chapman, T.M.Evans, B.A. Hems, A.B.A. Janson and T. Walker
J.C.S. 1094 (1952).

20 R.Rossi and A. Carpita
Syn. 561 (1977).

21 E.J. Corey and R.H. Wollenberg
J. O. C., 40, 2265 (1975).

22 G. Ohloff, C. Vial, F.Naf and M. Pawlak
Helv. Chim. Acta 60,1161 (1977).

23 P.S. Reddy, J.S. Yadav
Syn. Commun. 14, 327 (1984).

24a Ref.11, p.20
b Ref.11, p.188

25 D.E. Ames, A.N. Covell and T.G. Goodburn
J. Chem. Soc. 5889 (1963).

26a C.A. Brown and A. Yamashita
J.Am.Chem.Soc., 97, 891 (1975).

b C.A. Brown and A. Yamashita
J. Chem. Soc. Chem.Commun. 959 (1976).

27 L. Brandsma and H.D. Verkruijsse
"Synthesis of acetylenes, allenes and cumulenes"
Elsevier Scientific Publishing Co., New York (1981).

28a William Oroshnik and Alexander D. Mebane
J. Am. Chem. Soc., 76, 5719 (1954).

b K.C. Nicholov et al.
J. Chem.Soc. Chem.Commun. 297 (1985).

29 David Hall
Insect Products Section, Tropical Development and Research Institute, London.

30 A.S.C.Prakasa Rao, U.R. Nayak, Dev.S
Synthesis 608 (1975).

31 K.H. Dehm, D. Mayo
Naturwissenchaften 58, 215 (1971).

32 S. Ranganathan, Maniktala and K. Raajkumar
Synth. Commun. 12(12), 952 (1982).

33 Yasuda Arata, Tanaka Shin, Yamamoto Hisashi, Nozaki Hitosi
Bull.Chem.Soc. Japan 52(6) 1752 (1979).

34 A Chicoisne, G. Dupont and R. Dulou
Bull. Soc. Chim. France 1232-7 (1957).
C.A. 52, 8956 (1958).

35 Noriyo Miyura and Hiroshi Suginome
Tetrahedron 39, 3271 (1983).

36 William W. Christia and Ralph T. Holman
Chem.Phys. Lipids 1(5) 407-23 (1967).
C.A. 68, 39015n (1968).